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THE RESUSCITATION ACADEMY

10 Steps for Improving Survival from Sudden Cardiac Arrest

based on the book "Resuscitate! How Your Community Can Improve Survival from Sudden Cardiac Arrest" by Mickey Eisenberg, M.D.
and inspired by the Faculty of the Resuscitation Academy

Can We Do Better?

A BRIEF INTRODUCTION BY MICKEY EISENBERG, MD

As a medical emergency there is nothing more dramatic than sudden cardiac arrest. A person at home or in the community, suddenly *(often with no symptoms)* collapses. Consciousness is lost in a matter of seconds and there is instantaneous loss of pulse and blood pressure. At the moment of cardiac arrest the person is clinically dead. Within 10 minutes clinical death will progress to irreversible biological death and another statistic will be notched in the tally of deaths from heart disease. This cold "statistic" cannot possibly reveal the reality of a vital person engaged in the community, with family and friends, children and grandchildren. Yet there is a small window of opportunity, measured in minutes, for life literally to be snatched from the closing jaws of death. If CPR, defibrillation, and advanced medical care can arrive at the scene quickly, there is a decent chance of successful resuscitation. Though the national survival rate for cardiac arrest is in the single digits, some communities are able to achieve a survival rate of 50% or higher from cardiac arrest associated with ventricular fibrillation – the rhythm with the best chance of resuscitation.

Mickey Eisenberg, MD, PhD
Medical Program Director, King County EMS
Professor of Medicine, University of Washington

VIDEO

How these communities do it, and how your community can do it, is what this guide is all about. Achieving success in resuscitation does not entail an understanding of quantum physics – the factors leading to success are known. This has been the constant refrain of the Resuscitation Academy since its founding in 2009. Lives are saved not just by highly trained EMS professionals, but also by highly efficient EMS systems. Individuals and systems save people. And both can perform smarter and better. This guide lays out 10 steps that will lead to an increase in cardiac arrest survival in your community. It is a practical guide, full of concrete suggestions and specific training tools. The faculty of the Resuscitation Academy and I hope you embrace these ideas and steps. Though each step may require some adaptation so that it can fit and work in your community, we have little doubt that these steps can transform your system.

For those of us in the emergency medical services business, ***there can be nothing more gratifying than saving a human life.***

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The Resuscitation Academy

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NOTE: Some pages of this PDF include video & 911 audio.
Look for the AUDIO VIDEO icons. Click to view on YouTube.
An internet connection is required.

Improvement is Possible

Improving Cardiac Survival Rates, One Community at a Time

This guide is intended for EMS directors, medical directors, fire department chiefs, EMS service officers, EMS training officers, and dispatch center directors. It is written specifically for you, and with that in mind, jumps right to the practical information. There is little in the way of background or scholarly discussions of the latest scientific finding. (More extensive discussion of the topics in this guide may be found in the University of Washington Press publication, 'Resuscitate! How Your Community Can Improve Survival From Sudden Cardiac Arrest' - Second Edition).

Not every step in this guide will apply to your community, but many of them will. Think of this guide more as a menu, from which you can choose practical programs that *(we believe)* will improve cardiac arrest survival in your community. There are 10 steps and they are divided into low-hanging and high-hanging fruit. The 4 steps designated as low-hanging fruit are those that can deliver the biggest bang *(in terms of improved cardiac arrest survival)* with the least expenditure of resources. The 6 steps, designated as higher-hanging fruit will also improve survival but may require more resources to implement. Whatever step*(s)* you choose to implement in your community, realize that these are called steps for more than metaphorical reasons. One step at a time, so long as you are on the right path and however long it may take, will get you to your goal.

A Few Words of Wisdom

The Seven Mantras

This guide gives you ten steps to improve cardiac arrest in your community. These steps comprise the core teachings of the Resuscitation Academy. At every Academy class the faculty sets the stage with a few pithy expressions which we hope encapsulate a tiny bit of wisdom. We call them 'the Resuscitation Academy Mantras.'

Tom Rea, MD MPH
Medical Program Director, King County Medic One
Associate Professor of Medicine,
University of Washington/Harborview Medical Center VIDEO

MANTRA

1 Measure, Improve

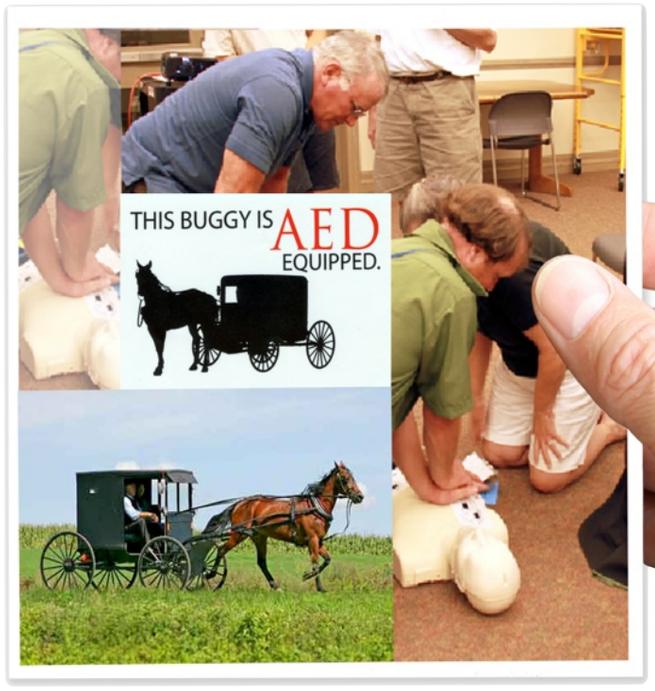
"Measure improve, measure, improve..." defines the essence of ongoing quality improvement. If you don't measure something you can't improve it. And once you measure it you will reveal things that need improving. And once you improve the system, measure it again to see if it has improved. And so on, and so on. Measurement and improvement can apply to many elements of an EMS system. First and at the most basic level, it refers to measuring cardiac arrest events and outcomes *(death, survival, neurological recovery)*. But it also applies to components of the EMS system such as time metrics *(time for dispatch, time for response, time for scene arrival, time for patient arrival)*, high-performance CPR metrics *(CPR density, depth of compression, full recoil, duration of pauses)*, and dispatcher assisted CPR metrics *(recognition of agonal breathing, time to recognition of cardiac arrest, time to delivery of chest compression instructions)*.

MANTRA

2 If You've Seen One EMS System...

"If You've Seen One EMS System, You've Seen One EMS System"

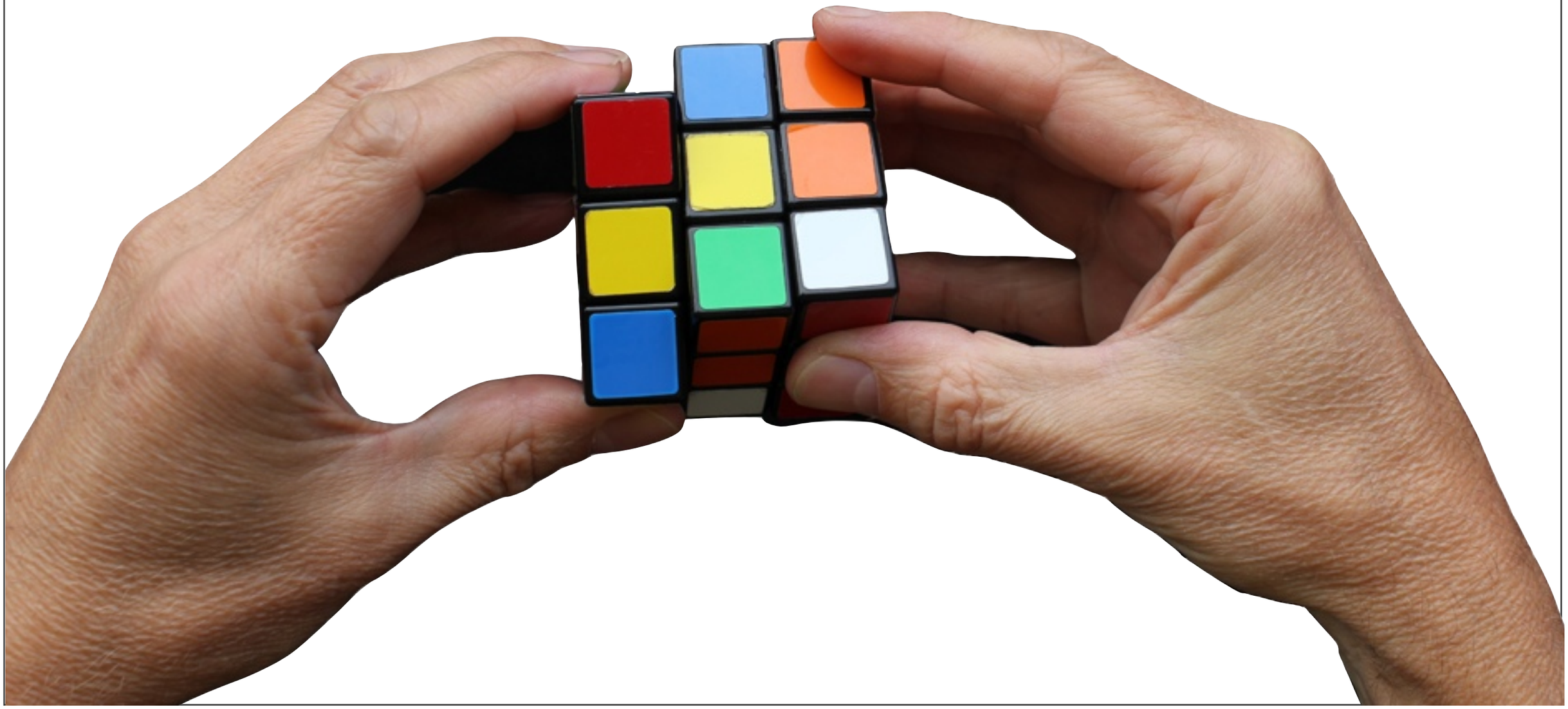
There exists incredible variety and diversity among EMS systems. No two systems are the same. What may be easy to accomplish in one system may be difficult if not downright impossible in another. One example – in some Washington State counties, the EMS medical director has no authority in setting dispatch standards or guidelines for dispatching of EMS. Thus, even if the medical director wishes to establish a dispatcher-assisted CPR program it would be impossible without the full cooperation of the dispatch director. If the dispatch center does not welcome physician involvement *(unfortunately too commonly true)* an impasse exists, unlikely to be brokered. But that same community may have a mandatory CPR training program for high school students – a program other EMS systems wished they had. The differing strengths and limitations of every EMS community are legion.



MANTRA

3 It's Not Complicated, But It's Not Easy

The science behind the steps to improve survival is not difficult to understand and the program requirements are fairly straight-forward. An understanding of nuclear physics is not required. But there may be logistical, cultural, political, resource, union and a variety of other obstacles that block easy implementation. We believe very strongly that change must start at the local level. It is the local medical, administrative, training, operations, and other personnel who are most accountable and can best decide how to bring about change. Ultimately they must decide first what is doable and second how much effort will it take.

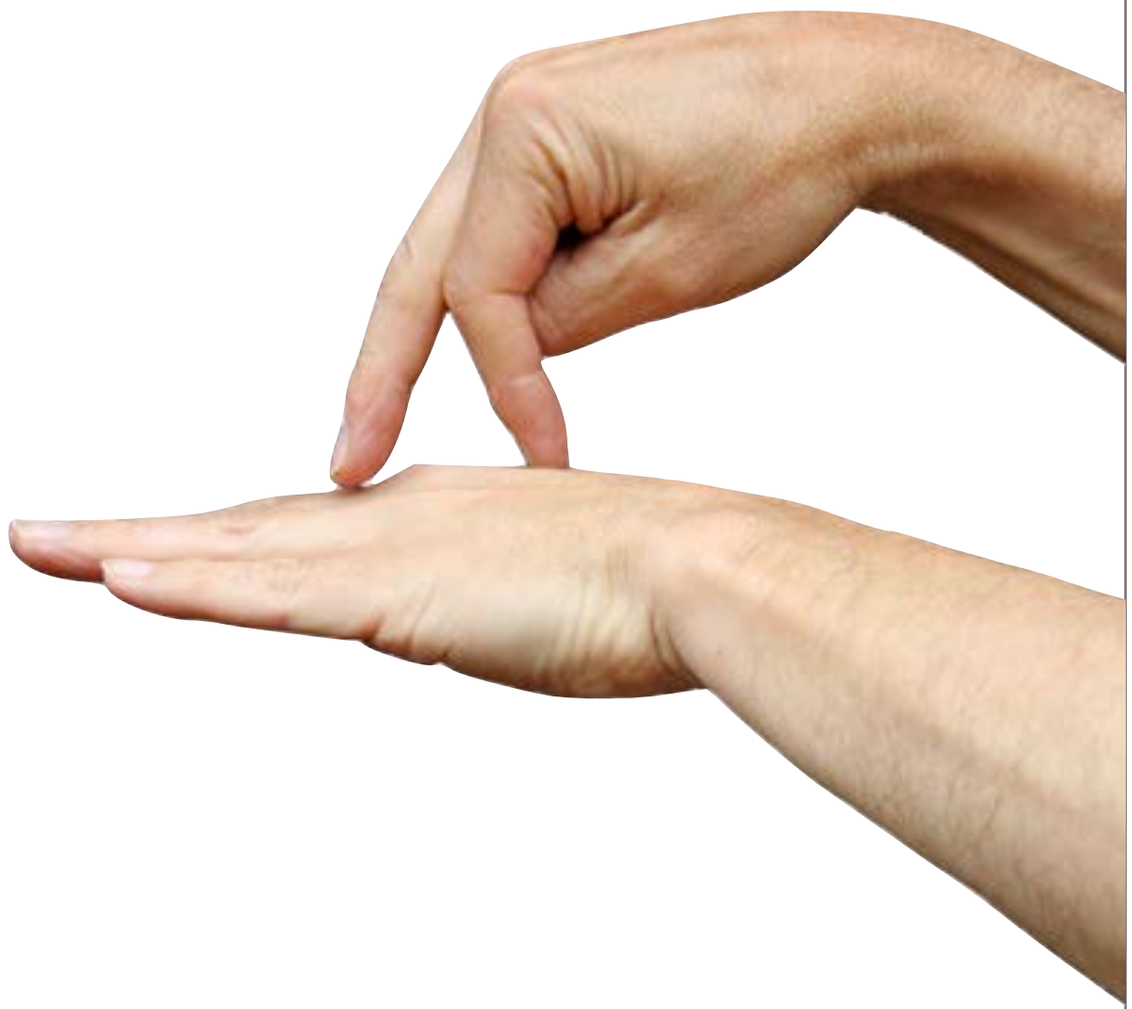


MANTRA

4 Change Occurs Step-By-Step

EMS systems are complex organizations and not likely to be transformed overnight, no matter what the leadership may wish. A good analogy is that of not trying for a home run on your first at bat in the Majors. A single would do just fine. Even a walk will move the effort forward. With each change *(improvement)*, one should remember the first mantra and continue to measure to see if the change really improved matters.

Step by step also refer to the steps in this guide. Don't try to take on everything at once. Start with one step, gain some success and confidence, and then move on to another.



MANTRA

5 Performance Not Protocol

What counts during a resuscitation is the actual performance of the dispatchers, EMTs, and paramedics. A perfect example is dispatcher-assisted CPR. Most dispatch centers claim to have protocols for telephone CPR, but in fact when you measure their performance they come up lacking. There is either infrequent recognition of cardiac arrest or delay in its recognition or both. The bottom line is that these dispatch centers may have the protocols, but are lacking in performance. Another example might be EMS systems that have protocols defining a standard of high-performance CPR. But unless the system trains and requires its EMTs to achieve letter-perfect performance, the protocol will be just so many empty words. Of course the best way to identify and correct poor performance is through ongoing QI – which circles back to the first mantra: Measure, Improve.

MANTRA

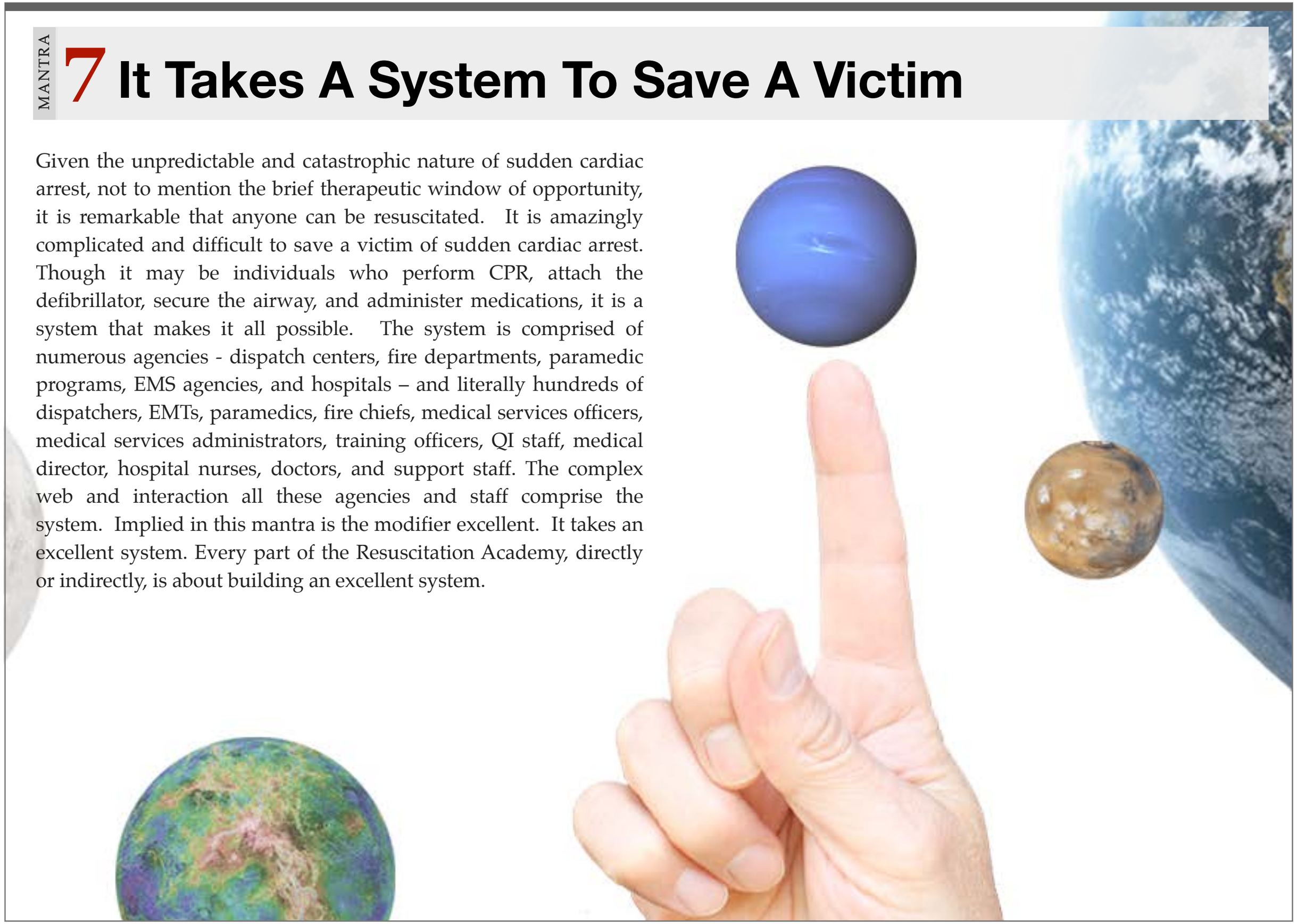
6 Everyone In VF Survives

Expectations become reality. Of course not everyone in VF will survive out of hospital cardiac arrest, but if there is a mindset that they will, behavior will subtly be altered to make it happen. The crew will work a little harder and not give up. They will assume the patient will make it to the hospital alive. In our EMS system, losing a patient in VF is simply unacceptable. I have seen patients receive over 20 defibrillatory shocks with the resuscitation lasting over an hour before achieving a sustaining pulse and blood pressure. A cardiologist once quipped that VF is a benign rhythm? His tongue was in his cheek, since VF means a patient is clinically dead. But he was also making the important point that all that is needed to treat this rhythm is quickly applied electricity. Therein lies the challenge. Quickly applied defibrillation is easy for a cardiologist in a cath laboratory, but a bit more difficult in the community. Nevertheless, if one keeps the mantra in mind – everyone in VF survives – it will create an expectation, a kind of self-fulfilling prophecy. Another aspect to this slogan is that medical directors and EMS directors will begin to scrutinize cases more closely, particularly those in which survival did not occur. The relevant question to ask is: Why did this patient in VF not survive? Asked this way it forces one to look at the system factors that may have contributed to the patient not surviving. Was there a delay in responding? Was there a delay in dispatcher recognition of cardiac arrest? Were telephone CPR instructions provided? Was there bystander CPR? Were there excessive pauses in chest compression? Were there delays in defibrillation?

MANTRA

7 It Takes A System To Save A Victim

Given the unpredictable and catastrophic nature of sudden cardiac arrest, not to mention the brief therapeutic window of opportunity, it is remarkable that anyone can be resuscitated. It is amazingly complicated and difficult to save a victim of sudden cardiac arrest. Though it may be individuals who perform CPR, attach the defibrillator, secure the airway, and administer medications, it is a system that makes it all possible. The system is comprised of numerous agencies - dispatch centers, fire departments, paramedic programs, EMS agencies, and hospitals – and literally hundreds of dispatchers, EMTs, paramedics, fire chiefs, medical services officers, medical services administrators, training officers, QI staff, medical director, hospital nurses, doctors, and support staff. The complex web and interaction all these agencies and staff comprise the system. Implied in this mantra is the modifier excellent. It takes an excellent system. Every part of the Resuscitation Academy, directly or indirectly, is about building an excellent system.



The Perfect Resuscitation

Peter A. had been doing fine, considering. He and his wife, Joanna, had been enjoying his retirement. Their yard was big enough for Joanna to pursue her hobby of butterfly- and bird-attractive gardening.

For Peter, on this afternoon, lifting heavy bags of steer manure for Joanna's garden had triggered another episode of the vague, intermittent ache that he had been experiencing in his upper left arm, mostly when he climbed stairs. This episode, though, was more severe than previous ones, and Peter felt somewhat nauseated. He also felt the ache radiating into the left side of his jaw. But it was his overwhelming sense of fatigue that prompted him to go back inside and lie down on the couch in the living room.

One month before, Peter's doctor had told him that his cholesterol had crept up to the "needing treatment" point, and that his blood glucose now placed him in the prediabetic range. But more disturbing had been his doctor's concern that the ache in Peter's left arm might be related to his heart. Peter's cardiogram had been normal, a result in which he had taken some solace, so he had continued to put off the treadmill test recommended by his doctor. He wanted to believe that the statin medication he had started taking to lower his cholesterol must be working - it certainly cost enough! And though he hadn't lost any weight, as his doctor had also recommended, it seemed to him that the ache in his arm had become less frequent.

Joanna, from her vantage in the den, saw Peter enter the house, and she knew from his slow gait and the way he half collapsed into the couch that something was wrong. She rushed to his side and tried to control her panic as she noted his limp body, the pasty coloring on his face and the bluish cast of his lips.

"Peter!" she shouted, shaking him by the shoulders.

He didn't respond.

With great presence of mind, Joanna brought the portable phone to Peter's side as she called 911.

"911 operator," came the voice on the other side of the line. "What are you reporting?"

"My husband has collapsed. He's not moving."

The emergency dispatcher quickly asked Joanna where she was calling from. Thanks to his training, he knew right away that he should send a full medic response, which he accomplished by typing the directions to Peter's house into his computer console and pressing several buttons on a "tone out" dispatching machine. As he did all this, the dispatcher continued to ask questions.

"Is he conscious?"

"No," Joanna replied.

"Is he breathing normally?"

Joanna looked at her husband. Peter was taking breaths that were more like slow grunts - definitely not normal. She told the dispatcher what she was seeing and hearing. From Joanna's description, the dispatcher knew that she was reporting agonal respirations - the kind of breathing associated with cardiac arrest, a sign of the brain's last-gasp effort to send breathing signals to the lungs. He also knew that there was little air moving in or out.

"Do you know CPR?" he asked Joanna.

"Cardiopulmonary resuscitation?"

Joanna did not.

"OK," the dispatcher said. "I'm going to give you some instructions. First, pull on his feet, and drag him onto the floor. Put your hands to the center of his chest, one hand on top of the other, right between the nipples, and press down firmly, fifteen times. I'll count for you. That's it. Keep doing it, now. Two more breaths."

In the background, over the phone, the dispatcher heard the fire department's sirens, and he told Joanna to open her front door. She did, and she saw three fire fighters already running up the driveway, carrying heavy suitcases. An large fire department pumper was parked on the street.

It had seemed like an eternity to Joanna, but the three fire fighter-emergency medical technicians, or EMTs, had arrived within four minutes of the dispatcher's "tone out." The regional Medic Unit, staffed by paramedics, was also on the way.

It was obvious to the EMTs that Peter was in cardiac arrest the pulse check confirmed the situation. The EMTs placed their cases next to Peter and knelt down, one on each side of his head. One of the EMTs started high-performance CPR. He positioned Peter's head, placed a face mask attached to an air bag over Peter's mouth and nose, compressed the bag to push two deep breaths into Peter's lungs, while his partner positioned himself to deliver thirty chest compressions. Meanwhile, the third EMT unzipped the automated external defibrillator (AED) case and attached two pads to Peter's chest. After the thirty compressions he told her partners he was ready to analyze. The AED "spoke" in a firm, but not harsh voice.

Assessing rhythm. Do not touch the patient.

Both EMTs moved back. After ten seconds, the voice spoke again.

Shock required. Stand back. Press the flashing orange button.
An orange button, labeled with a bolt of lightning icon, began to flash insistently.

Again the EMT followed the instructions. Joanna was startled to see her husband's chest jump up an inch as electricity flowed

from the AED and passed between the two pads. Immediately the EMTs began CPR and continued for two minutes. The EMT asked his partners to stop and the AED assessed the rhythm again. This time the machine's message was different.

No shock required. Check pulse. Check breathing. If needed, begin CPR.

The EMT who had been doing CPR placed his fingers on Peter's neck. "I've got a pulse," he said.

Joanna finally allowed herself to take a breath. One minute later, two paramedics arrived, and the EMTs briefed them on what had happened. The paramedics began an intravenous line and because the patient was still comatose they inserted an endotracheal tube. A study of randomly assigned field induced hypothermia was in progress and so the lead paramedic called his control hospital. The doctor on the phone said the patient was randomized to cold fluid. A second IV line was started and 2 liters of ice-cold saline was infused. Peter was placed onto a stretcher and loaded into the paramedic rig. By the time they reached the hospital almost all of the two liters had been provided.

Later the same day the EMT crew and the paramedic crew uploaded via computer the rhythm and voice recordings from their respective AED and manual defibrillators to the King County EMS Division along with copies of their run reports. The information was logged into the cardiac registry system and along with the dispatch voice recording, formed the case file for the event. This information was used by staff at the EMS Division to provide a quality improvement summary to the firefighters, paramedics, and dispatchers. This report contained performance standards on the time to recognition of cardiac arrest and delivery of chest instructions for the dispatchers and summaries of CPR percentage (for every two minute interval) and pauses in CPR for the EMTs. There was also a clinical summary from the paramedic's medical director with feedback. In this case it was all laudatory.

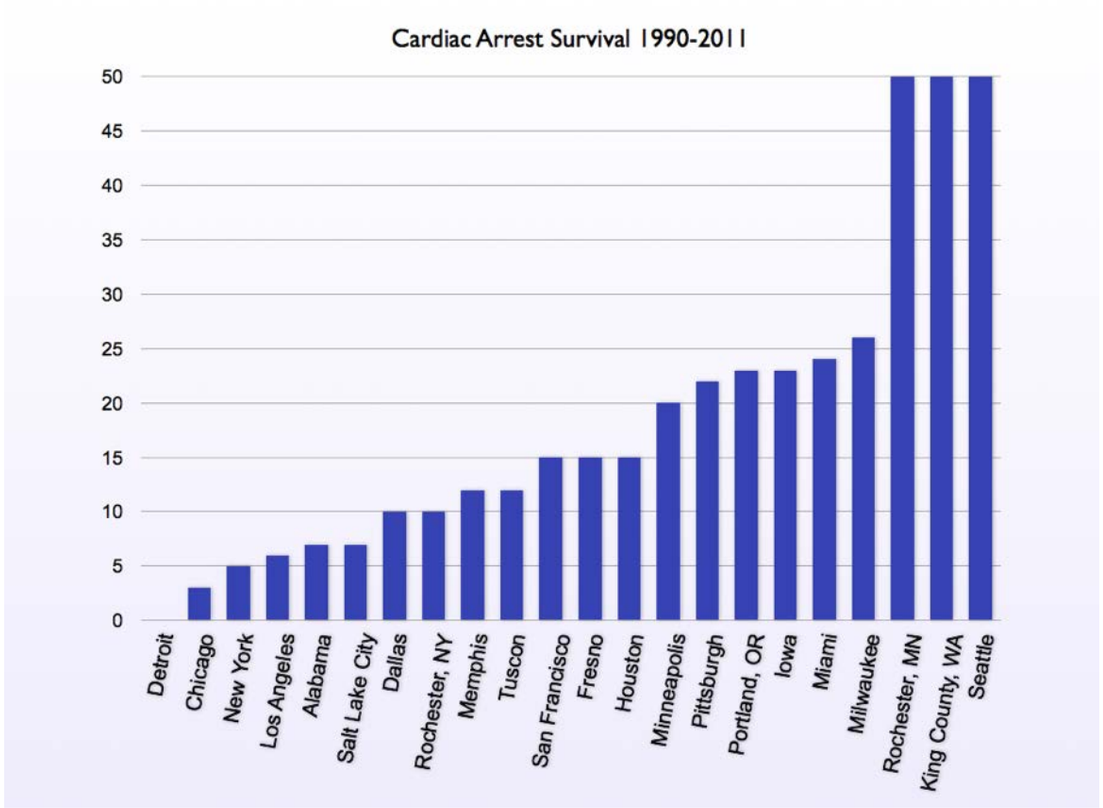
Ten days later Peter was discharged home with a brand new implantable cardioverter defibrillator (ICD) in his left upper chest. He made a full neurological recovery. And two week later an email was sent from the EMS Division to the EMS crews and the dispatchers with the good news.

Embracing the Challenge

Key Challenges

Why Do Some Communities Succeed In Treating Cardiac Arrest While Others Fail?

The survival rate from cardiac arrest in the United States and Canada varies all over the map – literally. In some communities the rate is zero *(yes, no one survives)* and in others it is as high as 50% for ventricular fibrillation. Most communities are on the low end of this range with survival rates in the single digits. Why do some communities succeed in treating cardiac arrest while others fail? It would be convenient if one variable could explain the wide difference in survival rates for cardiac arrest between those communities that are most successful in treating this major public health problem and those that are least successful. But that would imply an easy fix, or at least clarity of direction about what needs to change. Regrettably, there is no single variable and no easy fix. Instead there are multiple variables, each important in itself but insufficient as a single explanation.



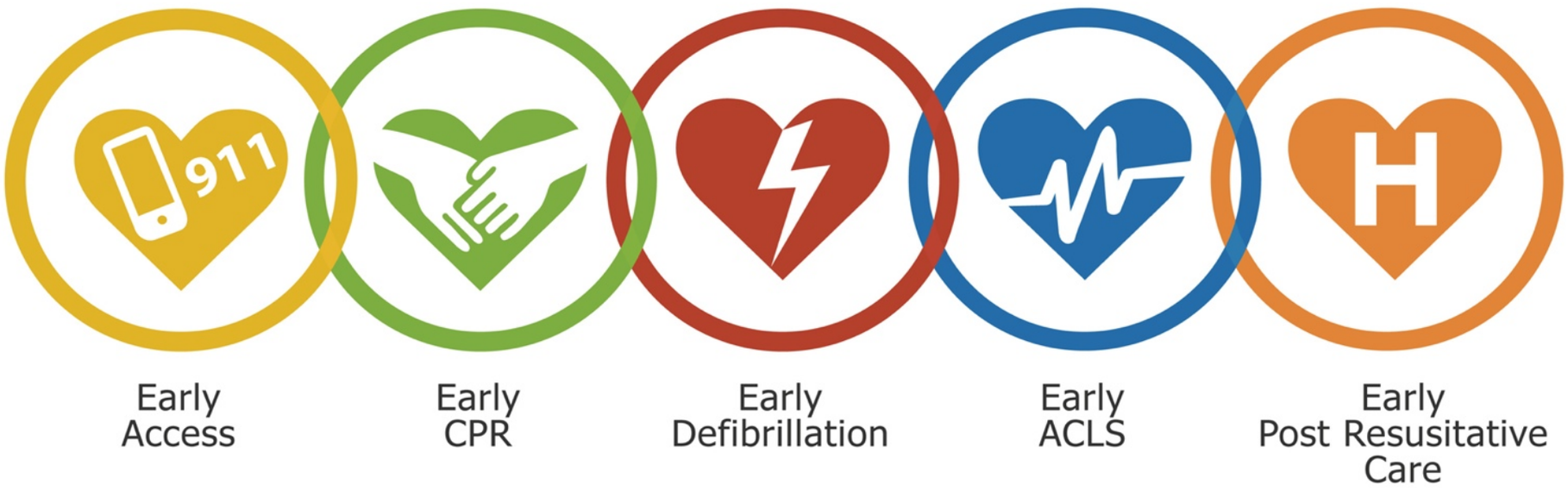
Life Or Death

The many factors which determine whether a patient lives or dies following cardiac arrest may conveniently be divided into patient factors, event factors, EMS system factors, and therapy factors. Certainly patient factors, such as age and co-morbidity, and event factors, such as witnessed collapse and cardiac rhythm, are strongly associated with outcome. But the patient factors and the event factors, although they are undoubtedly important in determining who will live and who will die, cannot be altered by changes made to an EMS program or to the types of therapy it delivers. They are powerful factors, but they are factors of fate of good or bad luck. But the system factors can all be affected by a community's decisions. The chain of survival describes the key system and therapy factors that insure rapid delivery of care.

The Chain Of Survival

What we do know is that successful treatment of cardiac arrest and particularly ventricular fibrillation, is associated with an EMS systems ability to deliver care quickly. The chain of survival, with its five links of early access, early CPR, early defibrillation, early advanced care, and early post resuscitative care illustrates the most critical elements of addressing sudden cardiac arrest.

The system and therapy factors that comprise the links in the chain of survival are quantitative in nature, meaning they have a specific value and can be measured. Some are time related *(time to CPR, time to defibrillation)*; others can be measured by their presence *(dispatcher-assisted CPR, community CPR training, community PAD, hypothermia)* and two can be scored *(quality of CPR can be determined by compressions per minute of CPR and duration of pauses, and the interaction of CPR and defibrillation can be determined by the duration of pauses before and after defibrillation)*. All can be measured in one way

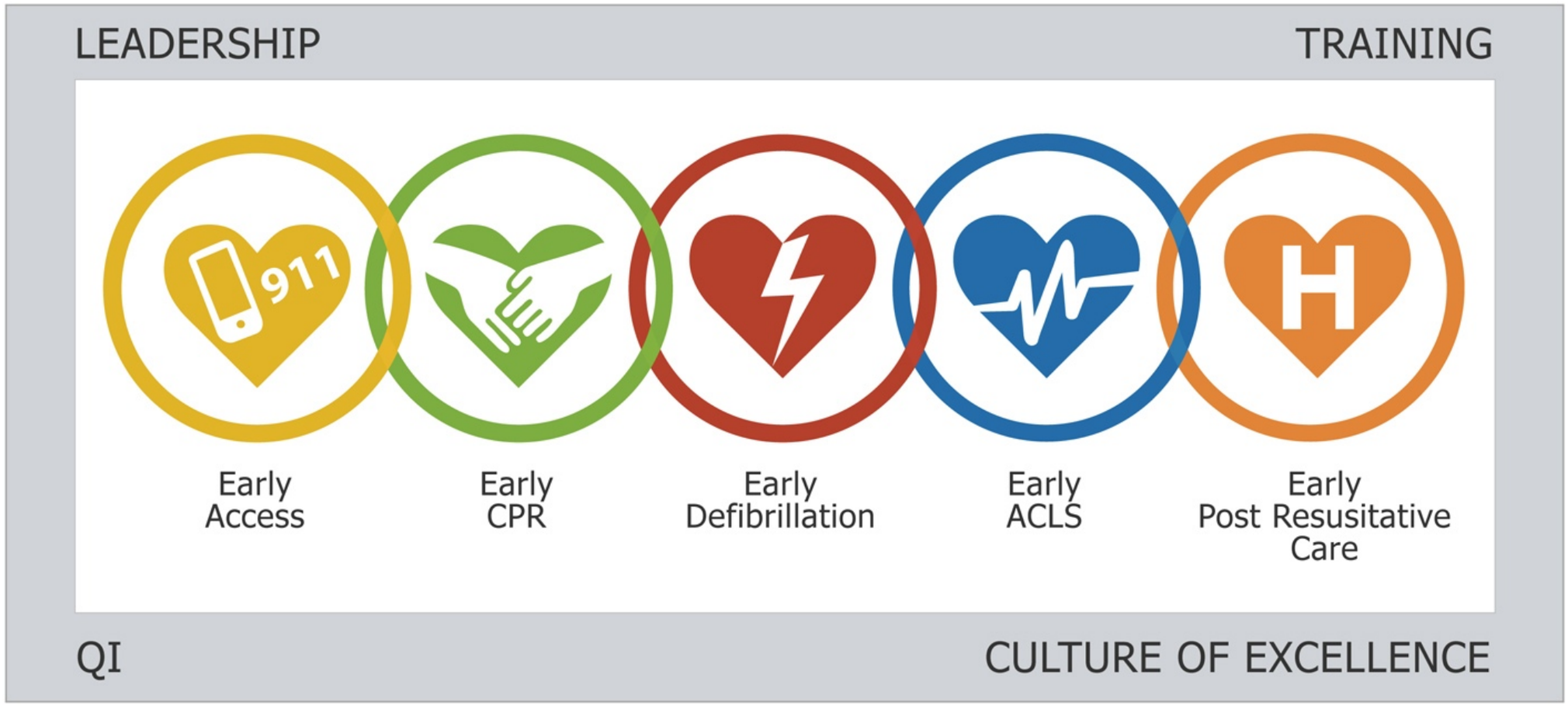


or another. Does this mean that a community merely has to put these system and therapy factors in place in order to see its rate of survival rise? It would certainly be convenient if this were the key to fully understanding the disparity in cardiac arrest survival, but, although one can measure these factors they do not fully explain a systems success or lack thereof. Every community's EMS system already incorporates some if not all of them at least to some degree – but even these factors, although they're necessary, are not sufficient. After all, a baseball team can have nine players but still lose every game. What else, then, is needed?

The Frame Of Survival

To fully understand an EMS system's success *(or lack of success)* we need to address the qualitative factors that also determine the system's performance. The qualitative factors are far more difficult to measure or score. These factors though lacking in hard numbers are just as or more important than the hard metrics.

The links in the chain cannot stay connected unless they are embedded in a context of strong medical and administrative leadership, continuous medical QI, a culture of excellence, and stellar training and continuing education for dispatchers, EMTs, and paramedics. These four elements literally frame, surround, and embed the core links of care. These elements are termed the frame of survival. Together the chain of survival and frame of survival form a complete and comprehensive system of care. Together they nurture, sustain, and define a high-quality EMS system. Just as important to the success of a champion baseball team that starts with nine excellent players are sustained practice, superb managing and coaching, continuous review and fine-tuning, and team spirit. In sum, the frame surrounding the chain of survival can be reduced to a single word: accountability. It is accountability, achieved through leadership, quality improvement, training, and excellence, that holds the chain of survival in place and ensures that its links are as strong as they need to be.



An EMS system that cannot be accountable to the citizens it serves will at best be mediocre. The elements comprising the frame are far more difficult to measure than those inside the frame. As opposed to the quantitative chain of survival, the frame is purely qualitative. Qualitative elements like leadership, culture of excellence, and accountability are softer and less scientific than the quantitative tools that directly contribute to the chain of survival. Nevertheless, these elements are the keys to success in managing cardiac arrest involving VF, and their relative absence is the reason why some EMS systems fail.

Outstanding leaders can instill in their organizations their vision of high expectations and relentless striving for excellence. They also continuously ask the question, "How can the system be improved?" Ongoing quality improvement *(QI)* is the mechanism by which they know where and how to improve. And training and continuing education are the vehicles by which expertise and professionalism are brought to every cardiac arrest.

Public Expectations

Is there a public expectation for high-quality emergency medical services? Before you answer, 'of course', consider the evidence. The average citizen of the average city has no idea what his or her community's EMS systems performance is, as measured by survival rates for cardiac arrest. Furthermore, the average citizen has no idea how his or her community's EMS system works, or who provides the services. Are the services contracted? Are they public? Does the EMS program use a tiered-response system? Are the rest-in personnel EMTs or paramedics? Who is the medical director? Is there an academic connection? Is there a cardiac arrest registry? Is there assertive dispatcher-assisted CPR? These and countless other questions would never enter the mind of the average citizen. For most people, the local EMS system, whatever it is, seems to work: dial 911, and several minutes later one or more vehicles arrive to whisk the patient off to the hospital. But what if concerned citizens in Detroit realized that virtually no one survives cardiac arrest in the Motor City? What if citizens in New York, Chicago, and Los Angeles realized that very few survive in those cities? What if concerned citizens everywhere understood that most communities, their own included, don't track survival rates for cardiac arrest? How can a problem be fixed if it can't be measured? How will the problem even be revealed?

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VIDEO

Nothing will change if the status quo continues to be tolerated. And the status quo in virtually every community is indifference combined with insufficient data a powerful duo on the side of inaction. The catalyst for change will probably vary from community to community.

It may come from an external group or organization, or it may come from within the EMS system or from the political structure of the community. In some communities, a citizens group or a civic action group may take the lead, or a group of physicians may agitate for change. Coalitions may take shape among the local medical society, the chamber of commerce, health care organizations, chapters of the American Heart Association or the Red Cross, local newspapers or TV stations.

Their united voices, especially on behalf of a mission as clearly and widely accepted as improving the community's survival rates for cardiac arrest, can go along way toward prompting politicians to

review the community's EMS services and create an action plan for their improvement.

The media can also play a large role in galvanizing awareness of sudden cardiac arrest and the potential for successful resuscitation. A news media *(paper, TV, radio or local web story)* might conduct an investigative report to determine the survival rate in its community. The reporter will likely discover how difficult it is to determine his or her community's survival rate and, assuming it can be determined, how poorly it likely fares compared to other communities. That's part one of the report. Part two could be what "best practices" the community does or doesn't have in place. Cardiac arrest registry? Assertive dispatcher-assisted CPR? High-performance CPR? Rapid dispatch? Detailed review of every cardiac arrest? Feedback to EMTs and paramedics? Voice recording of the event? Etc... And, part three could be a prescription for improvement.

It is probable that most people also view cardiac arrest fatalistically – sure, there are all those dramatic saves in the movies and on TV – but for the rest of us cardiac arrest is simply the end. This is certainly true for cardiac arrest associated with asystole and pulseless electrical activity *(PEA)*. What is not appreciated, however, is the good prognosis for ventricular fibrillation. When VF is treated quickly, the prognosis is very favorable. If EMS systems began to view VF as a condition with an excellent prognosis, they would both celebrate their successes and investigate every death. Why did the death occur? What could have been done to prevent it?

Leadership

Change is unlikely to happen without leadership. The medical director, paramedics or EMTs, the administrative director of EMS, the mayor, the city council – any of these parties, regardless of their official roles, can take the lead to improve the system. For example, the medical director can unilaterally form an advisory group, create a cardiac arrest registry, rewrite the protocols for cardiac arrest, partner with an academic medical center, establish requirements for training and continuing education, obtain follow-up information on patients, and provide feedback to EMTs and paramedics. Leadership can take many forms and may as likely start in the middle or bottom of an organization, as from the top.

A simple first step is to ask " Why did this patient with witnessed VF not survive?" Detailed answers are likely to facilitate a local action plan leading to improvement. Paramedics and EMTs can work to record times and interventions accurately, improve teamwork, train in high-performance CPR, synchronize AEDs with dispatch centers, suggest ways to speed up response times, and collaborate with dispatch centers to institute rapid dispatch. The administrative director and the medical director can work together to revamp the protocols for dispatcher-assisted CPR. The mayor or the city council can mandate a QI program for cardiac arrest, increase the extent of medical control, and synchronize the operations of the dispatch center with those of the EMS agency. There is no limit to what can be accomplished by motivated individuals working within an organization. Changing an organization's culture is hard work. It would be naive to think that you, the reader of this guide, could simply shout, "Eureka!", and then instantly set about implementing radical changes within your organization. Nevertheless, whatever your role in your EMS system, you can take or contribute to some relatively resource-light actions that are likely to raise your community's survival rate for cardiac arrest, actions whose short-term dividends can encourage

Russ McCallion, Asst. Chief EMS & Training Divisions
East Pierce Fire and Rescue

VIDEO

EAST PIERCE FIRE & RESCUE ALUMNI

"We would tear our department apart and rebuild it step by step, if we thought we were losing 4 to 6 citizens per year that should have been rescued from fires. So, when we know that we can save 4 to 6 additional people every year from cardiac arrest--are we as an agency going to step up and put the same energy into saving these CPR patients? Whether it is a person dying in a house fire or a person dying from cardiac arrest—to the family—dead is dead, and equally tragic, so why would we spend any less effort saving these patients?"

— Russ McCallion
Assistant Chief, East Pierce Fire & Rescue

and reinforce the will to engage in longer-term, more difficult change efforts.

The Will And The Way

The following pages provides a game plan with 10 specific steps to achieve improvements in both the chain and the frame of survival. It takes determination to incorporate these steps into an existing EMS system. Some individual or some group needs to want it to happen. But change can occur, and survival rates for cardiac arrest can improve. Two-hundred and fifty years ago, community leaders in Amsterdam decided to improve survival rates for drowning, the sudden death of their time, and they established the worlds first rescue society. But resuscitation science at that time was primitive, and therapy was not very effective; the leaders of Amsterdam had the will for resuscitation, but not the way. The sudden death of our time is cardiac arrest due to heart disease. Science has made great strides, and therapy can be effective. We now have the way; all we need is the will. Is it possible to change an EMS system in fundamental ways? Can a community's survival rate for cardiac arrest be dramatically and permanently improved? We believe the answer is an emphatic **YES!**

If you don't believe us, **take a moment to see what our alumni have to say...**

Cindy Hambly, Training/Quality Improvement Manager
Thurston County Medic One

VIDEO

THURSTON COUNTY, WA ALUMNI

"Success breeds success: we had immediate, positive results when we rolled out the "High-Density CPR" training. News of this success spread rapdily through the ranks, and the providers were motivated to be part of the success".

— Cindy Hambly, Thurston County Medic One

HOWARD COUNTY, MARYLAND ALUMNI

"The concepts needed to succeed are simple; converting knowledge into ACTION and changing culture are the true challenges. Our approach was to view cardiac arrest survival improvement as a "team" effort. The Academy Faculty's guidance is "spot on!" Great leadership among our field personnel, those who live and breathe life safety, made the true difference in changing the culture of our department when it comes to improving survival through CPR. Giving ownership of HP CPR to the field EMTs and allowing them to gain the critical buy-in from their officers is our greatest accomplishment.

The medical director committed to reviewing all VF arrests and sending feedback; this created a system of measurement of where we were, so that we could assess the impact of each intervention on neurologically-intact patient survival.

We took full advantage of a Fire Chief who has come to realize that EMS is the specialty that this Fire Department does best and a County Executive who personally and closely realized that Sudden Cardiac Arrest can affect anyone, importantly, those people close to you, to accomplish much more: CPR training for students in our school system, AEDs on police cars and hands-only CPR training for the community. All of our successes are a product of the hard work of a team coupled with support from leadership both in the Fire Department and in the government of Howard County, Maryland."

— *Kevin G. Seaman, M. D., FACEP*
Medical Director

HOWARD COUNTY, MARYLAND ALUMNI

"Rushing to the scene doing as much as we can, as fast as we can, and rushing to the hospital only does one thing, and that is moving dead people quickly from here to there. If this sounds like you, I hope at least everyone looked good doing it! In a sudden out of hospital cardiac arrest, we the EMS providers are the definitive care. If we do not resuscitate these patients there is nearly a 100% probability they will not be walking out of the hospital because they are dead. In cases of cardiac arrest specifically, good quality care is more important than shortest on scene time possible if you except patients to survive, and walk out of the hospital."

— Captain Dale Becker,
Howard County, Maryland EMS

YAKIMA COUNTY, WA ALUMNI

"People have a false belief that one person can not make any changes but those are probably the same people that are afraid of change. Should people be afraid of change? I say not. Sinking your head in the sand hoping that the cardiac issues are going away just because we have the most sophisticated equipment in the world is very mistaken.

I feel proud to say that our department of EMS with your help is trying to make changes one step at a time.

I know and believe that we will start seeing VF as a condition with excellent prognosis. Thank you for all you have done and continue to do for our patients."

— Juan F. Acosta, DO, MS, FACOEP, FACEP
MPD, Yakima County EMS

"We were already providing the training programs, we just needed to change the message being delivered. Once that happened, we saw improvements in patient outcomes."

— Candace Hamilton

Plan of Action: Grab The Low Hanging Fruit

The plan to improve a community's survival rate consists of 10 specific but diverse steps. Four of the steps are relatively easy and do not require much in the way of resources. These may be considered the low-hanging fruit. There are six steps that are more difficult and require either modest to considerable equipment or resources – the higher-hanging fruit. It is unrealistic to presume that all 10 local steps can be implemented in any given community; an EMS director and medical director have to decide what is doable in their community. Furthermore what we consider easy steps, may be very challenging in some communities and vice versa. All the recommended steps are cognizant of the fact that real change requires addressing quantitative as well as qualitative factors. The total picture must entail the chain of survival as well as the frame of survival. This guide closes with some thoughts on how to implement change.

FOUR STEPS TO IMPROVE CARDIAC ARREST: THE LOW-HANGING FRUIT

STEPS	LEVEL OF DIFFICULTY
Cardiac arrest registry	Low
Dispatcher Assisted CPR: Training, Implementation & QI	Low
High Performance CPR: Training, Implementation & QI	Low
Rapid Dispatch	Moderate

A disclaimer: The recommendations put forward in this section cannot simply be used as a template and applied to any emergency medical system. Every community has its own constellation of resources, history, culture, and personalities. Indeed, this variety, which makes every EMS system unique, is a strength, offering a crucible for new ideas and new programs, which is why every community can become a source of innovation as well as a testing ground for new ideas. For some communities implementing even one of the recommendations offered here may prove challenging. For others, they may implement several steps in the first year.

The attendees at the Resuscitation Academy, by the end of the two-day training course, are fired up to return home and begin to make changes. It is clear that they are bursting with ideas big and small for their home communities. What should they tackle first? What will give the biggest bang for the buck? The faculty tell them to pick the low-hanging fruit first. Our advice is to reach for the largest, tastiest, juiciest, and closest pear before climbing the tree. Get some success under your belt and keep plugging away, small step by small step until there is a culture of change, allowing one to pick some of the higher-hanging fruit.

The steps that can achieve the quick results are: 1) to establish a cardiac arrest registry, 2) to begin a program in dispatcher-assisted CPR, 3) to begin a program in high-performance CPR, and 4) to begin rapid dispatch. These steps are neither complicated nor costly, but they are not without challenges.

Three of them require ongoing QI if they are to reach their potential. High-performance CPR, dispatcher-assisted CPR, and rapid dispatch all require continuous maintenance and nurturing. To do otherwise would be like planting a vineyard and assuming it would do fine without watering and pruning. Programs without ongoing QI and ongoing training will result at best in mediocre and lackluster performance and at worst in no improvement at all.

STEP 1 Establish a Cardiac Arrest Registry

Randi Phelps, MPH
Program Manager, King County EMS
Washington CARES, Coordinator

VIDEO

A cardiac arrest registry is the first step to improving survival. It is the essence of measurement. One of the mantras at the Resuscitation Academy is "measure, improve, measure, improve…,"encapsulating the concept of documenting cardiac arrest events *(measuring)* and then implementing changes for improvement. In turn, continued measurement will determine if the improvement has had an effect and will identify further steps

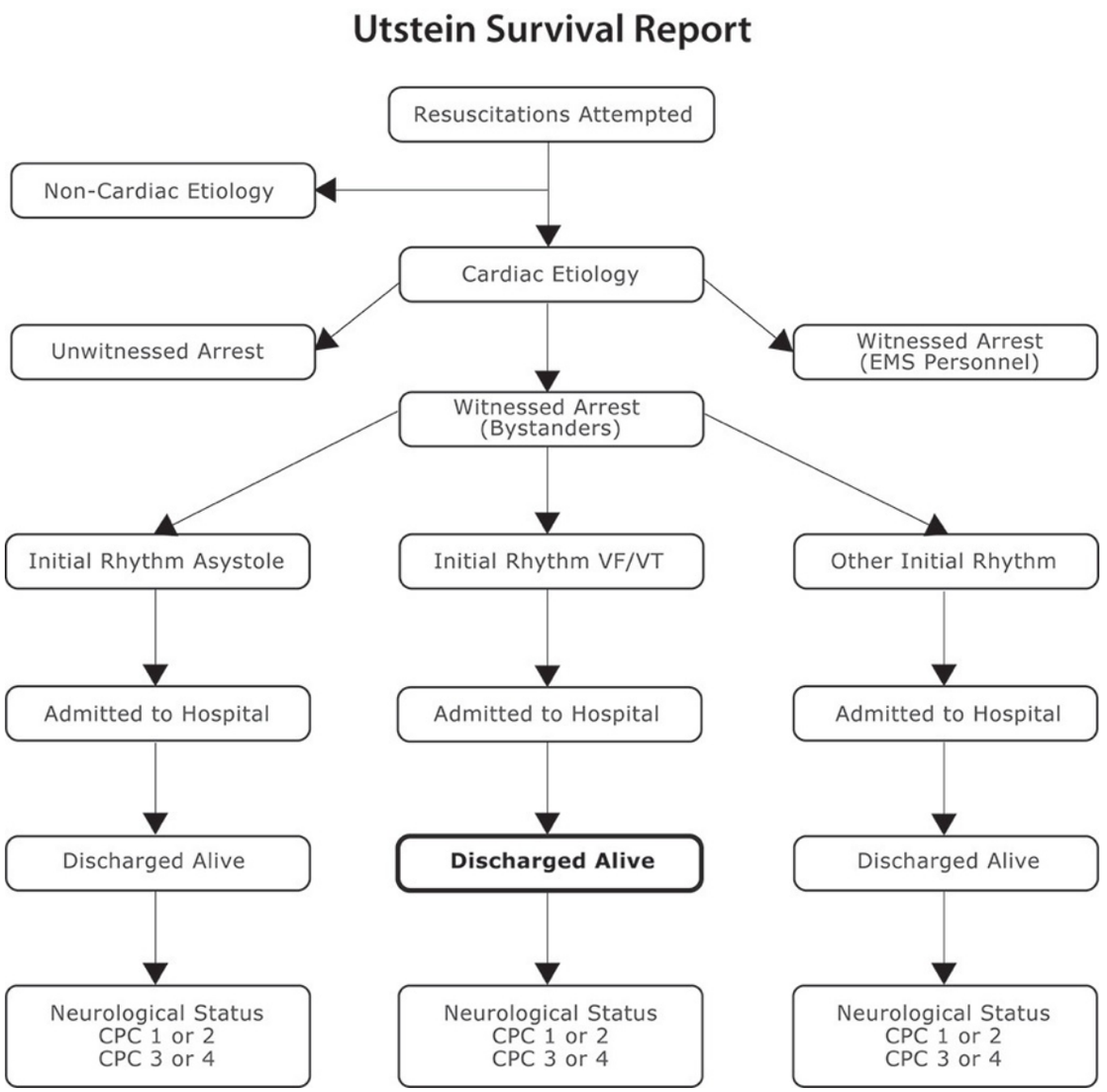
the improvement has had an effect and will identify further steps for improvement. And so on... This is the most important mantra of the Academy since it pithily describes the bedrock upon which all programmatic change springs forth.

A registry is a means of taking the entire EMS system's temperature. If a cardiac arrest is well managed, it's more than likely that all other conditions will be well managed, too. In this sense, cardiac arrest stands for the whole system. A registry measures more than whether the patient lives or dies, but all aspects related to the care. Was bystander CPR performed? Did the dispatcher provide telephone CPR instructions? How good was the EMT CPR? Were there unacceptable pauses in CPR? Did the paramedics intubate successfully? Given enough cardiac arrests, a profile begins to emerge of where the system is succeeding and where it is failing. This information then informs the specific elements that need improvement.

The cardiac arrest registry's efforts must be viewed as a core function, and the registry itself must not be threatened with funding cuts or elimination during lean times. It must have sufficient resources and the full support of the medical and administrative directors. Necessary resources include staff time for gathering information from run reports *(electronic or paper)*, dispatch center reports, AED recordings, hospital records, and ideally death certificates. Clearly, a small community will not have the volume of events to justify full-time dedicated staff, but several small communities can join together to establish a registry at the county or regional level. Investigators from Emory University have established, with funding from the Centers for Disease Control and Prevention, a national cardiac arrest registry: The Cardiac Arrest Registry to Enhance Survival (myCARES.net). The registry is open to EMS systems throughout the nation. As of 2013, there were 50 communities from 17 states participating, plus 6 entire statewide EMS programs. The registry entails having the EMS system and local hospitals submit data via a web-based system. CARES overcomes a major obstacle in most well intentioned registries, namely obtaining outcome data from hospitals. Did the patient live or die and what was the neurological condition on discharge? The CARES project is based on voluntary participation, and all the participants receive summaries of their own community as well as a national summary.

myCares website

CARES can be customized for the needs of the local community. CARES also provides templates so communities can review their statistics sliced and diced in any way they wish. The main template is the Utstein reporting template, which provides the survival *(discharged alive)* rate for witnessed cases of VF in which the collapse occurs before the arrival of EMS personnel. For agencies participating in CARES, the Utstein template is automatically generated. Utstein survival report for reporting cardiac arrest survival *(also known as the Utstein Template).*



The main metric is discharged alive survival from bystander witnessed cases of ventricular fibrillation of cardiac etiology. The survival is expressed as a percentage of all cases meeting this definition. When possible the neurological status of the survivors should also be determined from the hospital record. CPC scores of 1 and 2 indicted good to moderately good neurological outcomes and CPR scores of 3 and 4 indicate poor to terrible outcomes. To maintain a cardiac arrest registry *(whether in CARES or as a free-standing registry)* at its basic level, probably a quarter-time person is needed for a community of one million to gather incident data and obtain follow-up information from hospitals. If the tasks associated with maintaining the cardiac arrest registry are combined with those of collecting and managing data for high-performance CPR and the dispatcher-assisted CPR program, there will be enough work for one half-time employee. This estimate assumes that the EMTs and paramedics are assisting in the data collection such as forwarding run reports and defibrillator downloads. It also assumes that the dispatch center is providing CAD reports and recordings on CPR calls.

The registry should collect information on all cardiac arrests for which EMS care has been provided – in other words, when resuscitation was attempted. The major emphasis, however, should be on cardiac arrests in which VF was the presenting rhythm. For communities with limited resources, restricting the

registry to cases of VF or witnessed VF is a reasonable measure. Implicit in the concept of a cardiac arrest registry is the assumption that time intervals will be measured accurately. The most important time intervals are those between the patients collapse and the start of CPR, and between the collapse and the first shock. Admittedly it is not usually possible to know the exact time of collapse. Therefore, the first accurate time is the time the 911 call is answered, and this should be the precise moment the EMS clock starts ticking. For cases involving bystander CPR, the initiation of CPR can be arbitrarily defined as having occurred halfway between the time of the call to 911 and the time of the first-in units arrival. Ideally, all the systems AEDs will be synchronized automatically or manually to an accurate clock.

YAKIMA COUNTY, WA ALUMNI

"After providing the facts from our new data entry program through CARES, we saw marked increase in interest and participation from local EMS and Fire administrators
- Candace Hamilton
Yakima County EMS

It is important to be realistic about what a cardiac arrest registry includes.

To be fully functional a registry must have the following three elements:

1. **Full capture of all arrests meeting the case definition:** The case definition we use in King County for an event is a cardiac arrest in which EMS personnel initiate or continue CPR. Patients who receive AED shocks and subsequently do not require EMS CPR, are also considered cases. Trauma cases are excluded from the registry unless the trauma involves a low speed motor vehicle accident or other situation in which the cardiac arrest may have preceded the trauma. Patients who are dead on arrival or have a "do not resuscitate (DNR)" order and those who did not receive EMS CPR do not qualify under the "case: definition. But we do include cases in which EMS CPR is started and then stopped after a DNR order is clarified. However, since these cases are invariably non-VF cases, they do not affect the VF survival rate.

2. **Measurement of critical variables:** Measurement of critical variables: Witnessed collapse, collapse before EMS arrival, first rhythm obtained, shockable rhythm, bystander CPR, telephone CPR, time of call to dispatch center, time of EMS CPR, estimated time of bystander CPR, time of first compression for dispatch-assisted CPR, time of first defibrillation.

3. **Measurement of outcome**: death at scene, death in hospital, discharge alive *(ideally with a determination of neurological outcome)* To obtain critical information on the outcome of all patients admitted to the hospital, a good working relationship with area hospitals is essential. A registry is part of ongoing quality improvement and is considered protected information in most states *(and consent from the patient to release medical information is not required)*. The completeness of the registry can of course vary from the bare minimum of information to

hundreds of variables. In King County, we have a registry that is comprehensive and serves as the basis for many studies. The 300 variables we collect from CAD reports, incident reports, defibrillation downloads, voice recordings, hospital records, autopsy reports and death certificates, would be considered excessive for routine quality improvement. A good basic registry can be achieved with 14 event and 3 outcome variables.

CARDIAC ARREST TRACKING SYSTEM	
EVENT VARIABLES	**OUTCOME VARIABLES**
Demographic information	Died at scene
Age, sex	Admitted to hospital
Collapse before EMS arrival	Discharged alive
Witnessed collapse	Discharge location *(optional)*
Time of call to 911	CPC score on discharge *(optional)*
Resuscitation stopped because of DNR orders	
Rhythm on arrival *(or shockable rhythm on arrival)*	
PAD shock	
Dispatcher-assisted CPR	
Bystander CPR without dispatcher-assisted CPR	
Estimated time from call to 911 and bystander CPR *(half of interval from 911 call to scene arrival)*	
Time from call to 911 to time to dispatcher-assisted CPR *(first compression)*	
Time from call to 911 to time to EMS CPR	
Time from call to 911 to time to first shock	

The list of variables in in the preceding page exhibits a minimal data set.

For communities not participating in CARES, information about a free-standing registry may be obtained by contacting the Resuscitation Academy. This free-standing registry, called CATS *(Cardiac Arrest Tracking System)*, includes 14 event variables and 3 outcome variables. It comes with a data dictionary and is a simple to use registry which collects only essential variables. Though CATS is not linked to a national registry, it will allow any EMS system to monitor its own performance in managing cardiac arrest and to track changes in survival over time. CATS uses an Access data base in which to record information, and thus, should be readily available within most organizations. CATS can display the data in an Utstein template and can be exported to Excel to allow for customized displays.

STEP 2 Implement Dispatcher Assisted CPR with Ongoing Training & QI

Linda Culley
Section Manager
Community Programs, King County EMS

VIDEO

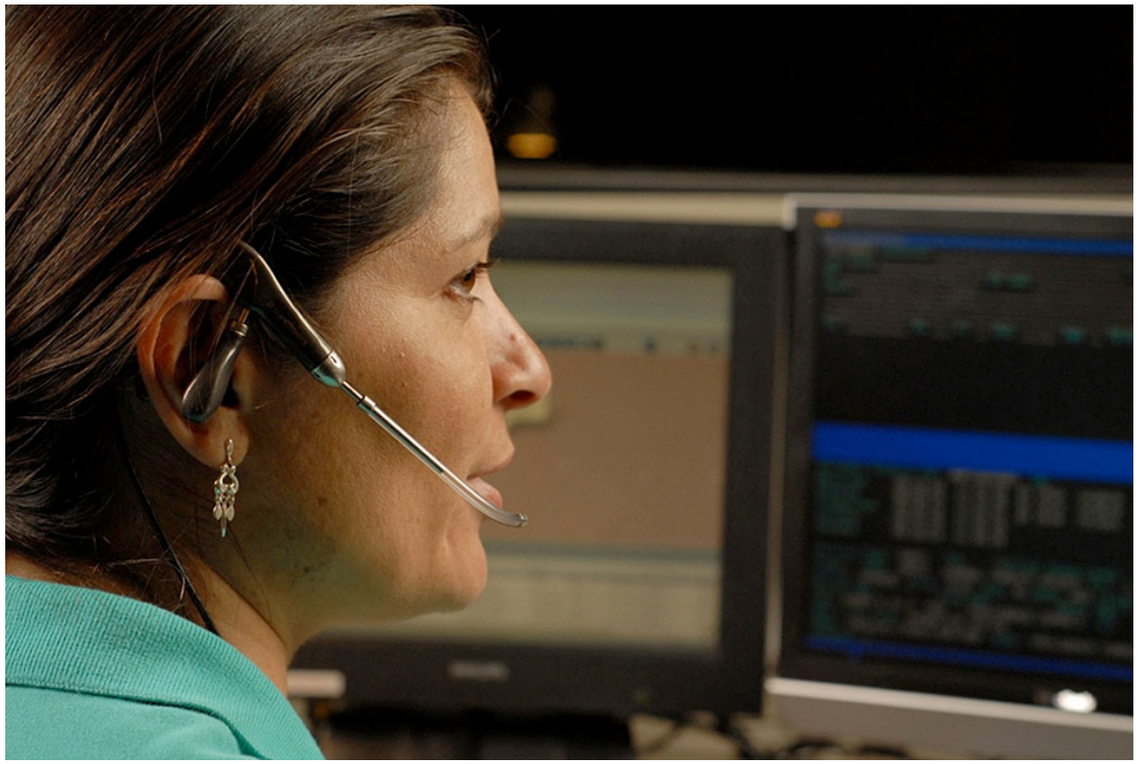
Most dispatch centers claim to have dispatcher-assisted CPR protocols in place, but in practice they don't offer CPR instructions very often. *(Synonymous terms are telephone CPR, dispatcher CPR, and dispatcher-assisted telephone CPR)* Admittedly, it is difficult and stressful for dispatchers to determine the presence of cardiac arrest and provide CPR instructions; it is far easier simply to reassure the caller that help is on the way. But the center whose culture supports it's dispatchers to assertively offer callers CPR instructions over the telephone, is a center that has the chain of survival firmly in it's grasp. This kind of culture can exist only if

someone has responsibility for teaching dispatcher-assisted CPR, monitoring the program, and watching it like a hawk. Someone has to listen to recorded information from all cardiac arrest calls and give feedback to individual dispatchers, as well as to the entire staff. It is just as important to review the calls in which instructions were provided *(how could it be done faster, better?)* as it is to review the calls in which cardiac arrest was not recognized *(how can we do a better job identifying cardiac arrest?)*

The adjective "assertive" describes a useful mindset for dispatchers when fielding possible cardiac arrest calls. A take charge attitude that moves ahead with CPR instructions, when there is reasonable likelihood that cardiac arrest is present, is the attitude needed for this program to succeed. If the dispatcher is overly cautious or holds back in the face of uncertainty, the instructions will seldom be given or there will be considerable delay in their implementation.

One element of any successful dispatcher-assisted CPR program is training, which should include continuing education. Dispatchers in King County receive an initial forty hours of training in emergency medical dispatching, and are thereafter required to complete eight hours of continuing education every year. Special emphasis is placed on recognizing cardiac arrest and delivering CPR instructions.

AUDIO 911 Audio Excerpt:
Great CPR For Over 8 Minutes



AUDIO 911 Audio Excerpt:
Quick to Identify Need for CPR

AUDIO 911 Audio Excerpt:
Great CPR & Good Coaching

Recently a five-year randomized clinical trial in King County, and Thurston County *(south of King County)* in Washington State and London *(England)* looked at whether dispatcher-assisted CPR achieved better survival with standard CPR *(mouth-to-mouth with compressions)* instructions than with chest compressions only instructions. The trial found no difference overall in survival but there were non-statistical improvements in survival and neurological recovery with chest compression only. As a result we

now provide chest-compressions only instructions for all adult cardiac arrests. *(Chest compression only instructions for adults is also recommended by The American Heart Association).* The dispatchers provide standard CPR instructions *(mouth to mouth combined with chest compression)* for cardiac arrest in children and infants *(fortunately rare events)* and when there is an obvious respiratory cause of arrest such as drowning, hanging, or smoke inhalation.

AUDIO 911 Audio Excerpt: Need for CPR Missed Despite Many Signals

AUDIO 911 Audio Excerpt: Unnecessary Questions

Prior to delivering these instructions the dispatcher has determined the likely presence of cardiac arrest. This is achieved by asking two critical screening questions: Is the patient conscious *(awake)*? Is the patient breathing normally? Note that the instructions call for chest compression only CPR. If respiratory arrest is the suspected cause of cardiac arrest then ventilation instructions are provided. There are slightly different protocols for children and infants as well as protocols for choking patients.

In King County, there is an expectation that "every call is a cardiac arrest until proven otherwise". *(We think of this as a step specific mantra for dispatcher assisted CPR).* Though only 1 percent of the calls will actually be a cardiac arrest, nevertheless this expectation primes the dispatcher to always ask the **two screening questions** *(unless the caller is the patient)* as quickly as possible. These two questions must be asked of every caller *(unless the caller is the patient):*

- **Is the patient conscious *(awake)* ?**
- **Is the patient breathing normally ?**

If the answer is no to both, the dispatcher immediately begins instructions. *(Thus, giving us the second step specific mantra "**No**, **No, Go**": **No** Not Conscious, **No** Not Breathing Normally, **Go** - Begin CPR.)*

Dispatchers learn the significance of agonal respirations and how to recognize them. It is particularly important that they offer CPR instructions when there are agonal respirations, since these patients are the ones most likely to be resuscitated and discharged from the hospital. Agonal breathing is present in approximately 60 percent of patients with VF cardiac arrest. Yet the presence of agonal breathing will often confuse the caller and/or dispatcher into thinking the patient is not in cardiac arrest.

Despite our considerable training on how to recognize agonal breathing, it remains a challenge. When asked, "Is the patient

AUDIO 911 Audio Excerpt: Agonals Example - Gargling

AUDIO 911 Audio Excerpt: Agonals Example - Moaning

breathing normally?" the caller often responds with "a little" or "sometimes" or "I'm not sure" or "I think so." The dispatcher is seeking a yes or no response to the question and instead receives an ambiguous reply. When the dispatcher asks the caller to describe the breathing, the replies are varied and include gasping,

AUDIO

911 Audio Excerpt:
Good Example -
Breathing Normally

snoring, slow, grunting, groaning, and gurgling. Often the agonal breathing can be heard in the background but if not the dispatcher may ask the caller to bring the phone to the patient in order to better hear the breathing. In terms of training and motivation, the director of a dispatch center should do whatever is necessary to ensure that the center achieves a 50 percent rate of offering dispatcher-assisted CPR instructions in cases of cardiac arrest. This is not an unrealistic target. Achieving such a target will require a sponsor – someone who takes charge of the desired change, has the authority to mandate it, and establishes training, professional expectations, and ongoing audits to see that the change is fully implemented. Once dispatchers realize how vital they are to the chain of resuscitation, and especially when they see concrete evidence of their success, they will become the staunchest advocates of dispatcher-assisted CPR.

As with high-performance CPR the quality of dispatcher-assisted CPR can be measured. At a minimum every call of cardiac arrest must be reviewed with the following elements measured:

- Was cardiac arrest recognized?
- Were the two basic questions asked:
  - Is the patient conscious *(awake)*?
  - Is the patient breathing normally?
- Were agonal respirations *(if present)* recognized?
- Were telephone CPR instructions offered? We believe ongoing QI of dispatcher-assisted CPR should include the following attainable goals:

1. Recognition cardiac arrest by the dispatcher in 75% of all cardiac arrests treated by EMS.
2. Recognition of cardiac arrest within one minute *(on average)*.
3. Provision of dispatcher-assisted CPR in 50 percent of all cardiac arrests calls treated by EMS *(excluding the calls in which bystanders are performing CPR at the time of the call)*.
4. First compression started within two minutes *(on average)*.

AUDIO

911 Audio Excerpt:
Dispatcher Does Not
Get Sidetracked

AUDIO

911 Audio Excerpt:
Well Handled
Breathing Question

Feedback must be provided to the dispatcher following every event. View DA CPR QI Form (Sample)

The American Heart Association in 2012 issued a Scientific Statement strongly endorsing dispatcher-assisted CPR, including the importance of asking the two identifying questions, special training in the recognition of agonal respirations, and a vigorous ongoing QI program.

DISPATCHER ALL CALLER INTERVIEW ***Only use bulleted phrase if caller does not understand bolded instruction***

9-1-1
- What is your emergency?
- Do you need police, fire, or medical help?
- What are you reporting?

What is the address?
- Are you at (prompt with location on screen)?
- Where are you?

Are you the patient?
- Who is hurt?
- Who needs help?

Are they conscious? (Awake?) – If **NO:** ask next question (breathing). – If **YES**: "Bring the phone to the patient so I can speak with them."
- Can they talk to you?
- Can they respond to you?
- Can you wake them up?

Are they breathing normally?
- Tell me what their breathing sounds like
- Is their chest rising and falling?
- Is their stomach going up and down?

If patient is not conscious and not breathing normally, begin CPR instructions.
- Dispatch Police AED unit
- Be alert for premise/radius information indicating AED
- Send second rescuer to retrieve AED or send lone rescuer ONLY if AED is nearby and easily accessible

About how old is the patient?
- Adult, child, baby?
- 20's, 40's, 60's?
- Skip the following all-caller questions until later in the call if the patient needs CPR

Is the person a man or a woman?
What is the phone number you are calling from?
What is your name?

ADULT CPR INSTRUCTIONS

Only use bulleted phrase if caller does not understand bolded instruction

1. "I've notified the dispatcher, talking to me won't cause a delay. Follow my instructions"

If caller does not understand, say something like this:

- "We need to help the heart work."
- If caller asks, confirm that they will be doing CPR.

2. "Get them on their back on the floor." *(Confirm position, if any doubt that patient is on floor.)*

If caller does not understand, say something like this:

- "Lay them down"
- "On the ground"
- "Face up"

3. "Kneel by their side. "

If caller does not understand, say something like this:

- "Get down on the floor"
- "Next to/close to/near them"

4. "Put your hand on the center of their chest, right between the nipples, and put your other hand on top of that hand."

If caller does not understand, say something like this:

- "Middle of the chest"
- "Between the breasts"
- "Use palm/heel/bottom of your hand"

5. "With straight arms push down as hard as you can, just like you're pumping the chest. Let's start: push, push, push, push, 1, 2, 3, 4, 1, 2, 3, 4, 1, 2, 3, 4… Push and count out loud 1, 2, 3, 4, 1, 2, 3, 4, 1, 2, 3, 4… Keep going! Do not pause. "

TIPS: Count with the caller!
When it sounds like caller is confident counting, stop counting to listen to rate. Jump back in counting with them to speed up or slow down rate, or eliminate pauses. Don't interrupt them with unnecessary questions.

COACHING: Give reassurance and coach caller after chest compressions have been going for awhile:

- "You're doing great! Keep going!
- "Push as hard as you can
- "Don't stop until they tell you to stop"

TROUBLESHOOTING

- If caller worries they are hurting them, reassure them that they are not in pain.
- If caller is tired, ask if they are keeping their arms straight, or suggest a short break.
- If caller mentions phone is interfering with CPR, suggest using speaker phone or putting the phone down during compressions.
- If another person is present, suggest that this person do compressions (take turns).
- If caller feels weak or unable to do compressions, ask if there's a neighbor you can call to come help.

NOTE: IF CALLER REPORTS VOMITING, INSTRUCT CALLER TO:

- Turn patient's head to one side.
- Sweep out contents with your fingers before you resume.

VENTILATION INSTRUCTIONS *(for use when suspected cardiac arrest is secondary to respiratory arrest)*
START with **30 compressions**, then:
PINCH the **NOSE**, with your other hand, **LIFT** the **CHIN** so the head tilts/bends back
Completely **COVER** their **MOUTH** with your **MOUTH**
GIVE 2 BREATHS OF AIR
Continue with cycles of **30 COMPRESSIONS,** followed by **2 BREATHS**

FOREIGN BODY AIRWAY OBSTRUCTION INSTRUCTIONS *(confirmed choking, now unconscious)*
Look for item after 30 compressions: **"Look inside mouth and remove any obvious obstruction."**
If object is removed, give 2 ventilations between each set of 30 compressions.
If object is not seen, continue with compression. Look for item after each set of 30 compressions.

Download PDF File

ADDITIONAL INFORMATION

Dispatchers CPR Coaching Saves Lives When Every Minute Counts
NPR - KPLU

Dispatcher Assisted CPR Toolkit
Resuscitation Academy

STEP **3** **Implement High Performance CPR with Ongoing Training & QI**

Peter Kudenchuk, MD
Professor of Medicine, Division of Cardiology
University of Washington
Associate Medical Director, King County EMS

VIDEO

Recent studies demonstrate the connection between quality CPR and survival from cardiac arrest. Not only is the time interval from collapse to onset of CPR predictive of survival, but also the quality of the CPR is just as important. The better the CPR, the better the outcome. Since 2005, when we trained every EMT in our system how to perform high-performance CPR, we have seen a dramatic increase in survival. Resuscitations that go on for 50 or 60 minutes with a pharmacy of medications and 10-20 defibrillatory shocks and a patient who survives – with excellent neurological recovery – used to be the exception, but now seems commonplace. It is as though the onset of high-performance CPR suspends death and gives a better opportunity for the defibrillatory shocks and medications to work their magic.

High-performance CPR is as much a construct as a measurable skill. The construct says that letter-perfect CPR is the goal of all resuscitations. This skill can be achieved in training, as well as through review of real events. We believe training on manikins with "paper strip recorders" is the best teaching tool as it provides

High Performance CPR - BLS - Continuous Compressions

VIDEO

instant feedback *(tangible, quantifiable, etc.)* about the quality of CPR.

Elements of High-Performance CPR include:

- Correct hand position
- Compression rate of 100-120 beats per minute
- Depth of compression of 2 inches
- Full recoil on the upstroke
- 50:50 duty cycles
- Ventilations of one second each
- Minimal interruptions of CPR *(no pause to exceed 10 seconds)*
- Intubation and IV start without pausing chest compressions

Last, and perhaps most important, is that there is an ongoing QI program that provides feedback with specifics about CPR performance to EMTs following every cardiac arrest? A QI program should among other things measure the percentage of time chest compressions are performed during each two-minute interval between rhythm assessments. Well-trained EMTs should be able to provide chest compressions for at least 90 percent of the available time. Most defibrillators allow digital downloads following the resuscitation, including precise measurements of CPR percentage and quality.

Another aspect to high-performance CPR is the choreography between the EMTs and the paramedics. Other terms used to describe this flawless team performance are the "dance of resuscitation", the "CPR ballet" and the "pit-stop approach to CPR".

Observing well-trained rescuers engaged in high-performance CPR it is indeed like watching a well-choreographed dance. The term pit-stop refers to the pre-defined role of each rescuer and the very minimal waste of time. Like a professional race car pit crew, each member of the team knows exactly what to do and does it with the minimal wastage of time and effort. This choreography means the members switch or rotate roles with minimal interruptions – current protocols call for rhythm analysis every two minutes. Thus, the chest compressor and the ventilator can switch roles every two minutes. With sufficient personnel at the scene, one EMT can start compression, the second EMT can attach the AED pads, the third EMT can provide ventilation, while the fourth EMT can feel the femoral pulse *(in order to define the location*

Captain Jonathan Larsen, Firefighter/Paramedic
Seattle Fire Department

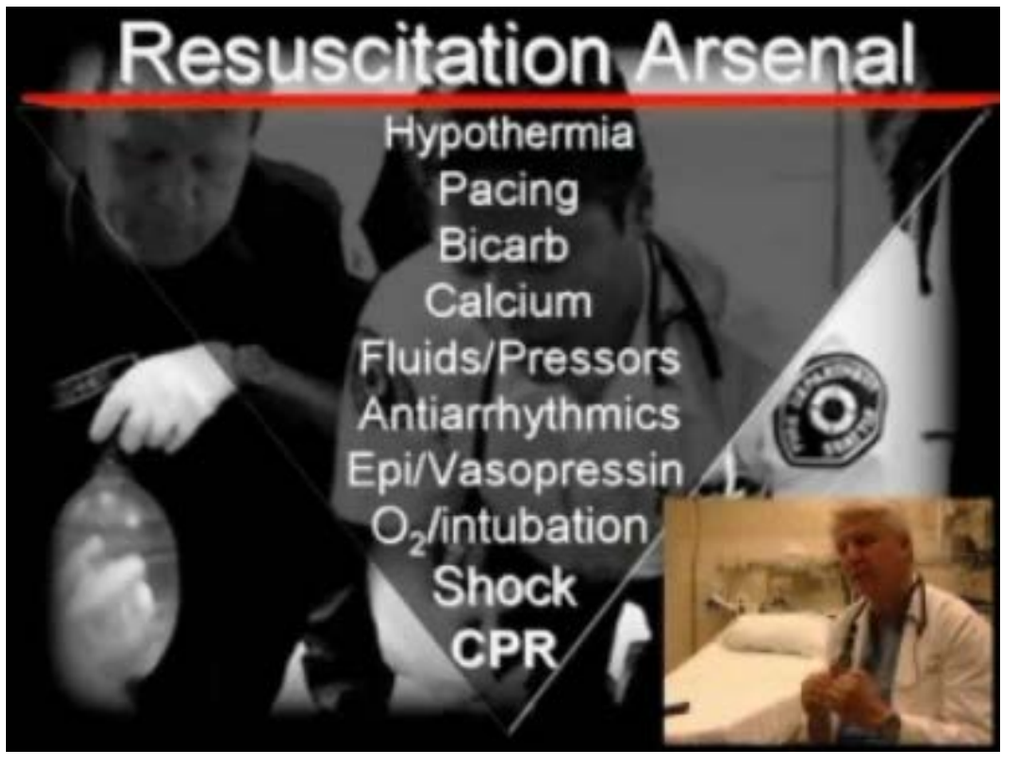
VIDEO

vof the artery and determine if a shock leads to a perfusing rhythm). A fifth EMT, if present, could be the "captain" of CPR and provide direction to the crew *(typically the person providing overall direction is the one who operates the automated external defibrillator).* Paramedics should optimally intubate and place the IV with no interruption in chest compression. Clearly if there are fewer rescuers the responsibilities must be aggregated. In our system, we think of the EMT crew as owning CPR, meaning that they are responsible for the quality and directing assignments. The paramedics own advanced life support, meaning they are responsible for intubation, starting an IV, and administering medications. Upon arrival paramedics become the overall team captains, but they know to delegate CPR to the EMTs. The EMT team not only keeps track of the quality of CPR, but also keeps track of the timing of interventions. Since there is a rhythm analysis every two minutes, an EMT is the official timekeeper, literally using a stopwatch. *(In King County we go slightly beyond two minutes of CPR in order to end with 30 chest compressions prior to every rhythm analysis.)*

For the EMTs and paramedics to understand why high-performance CPR is so critical, part of our training includes instruction in the science of CPR. My colleague, Dr. Peter Kudenchuk, has developed a compelling 30-minute video on the science of CPR and why letter-perfect CPR is so important. This video is part of every King County EMT's training. The video below, is an excerpt:

Norm Nedell, Paramedic, EMT Instructor & Dispatcher
Seattle Fire Department

VIDEO



Excerpt from The Science of CPR, with Peter Kudenchuk, MD

VIDEO

High Performance CPR &
The American Heart Association

The American Heart Association guidelines emphasize the need for high quality CPR *(proper depth, rate and full recoil)* and minimizations of pauses while performing CPR. This is exactly what HP CPR focuses on and strives to achieve.

Michael Sayre, MD
Professor, School of Medicine
University of Washington

VIDEO

Russ McCallion, Asst. Chief, EMS & Training Divisions
East Pierce Fire and Rescue

VIDEO

STEP **4** **Implement Rapid Dispatch**

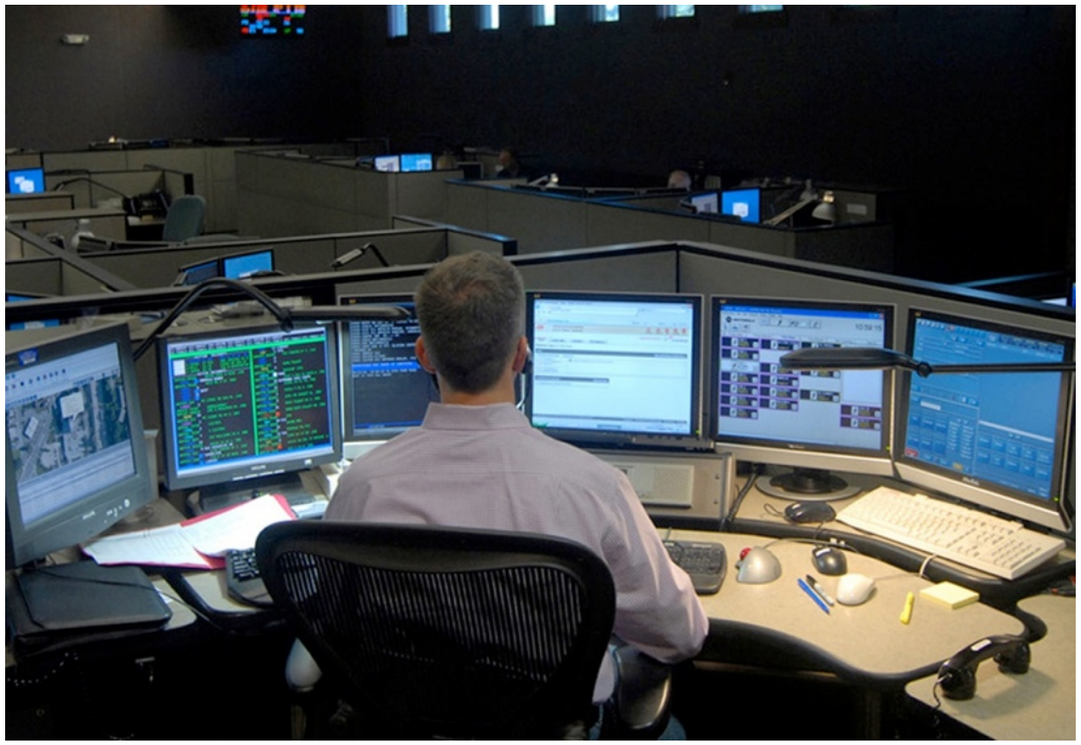
Cleo Subido, EMD Training/QI Coordinator
King County EMS

VIDEO

With rapid dispatch, the closest EMT-staffed vehicle is dispatched within seconds, when specific medical emergencies are reported to the 911 dispatcher. The dispatch should occur even while additional information is being gathered from the caller. The quick arrival of at least an EMT vehicle, allows the EMTs to perform CPR and deliver the first defibrillatory shock. On the other hand, it may be immediately clear that both EMTs and paramedics are required *(such as a report of ongoing CPR)* and thus, both vehicles can be rapidly dispatched. If additional information from the caller suggests that paramedics will not be needed after all, the dispatcher can call off the paramedic unit with a code green message.

The symptoms or complaints that should trigger a rapid dispatch are: unconscious or suspected cardiac arrest, chest pain, difficulty breathing, stroke symptoms, ongoing seizure, and significant trauma. A community should carefully measure its current time interval from first ring into the alarm center to specific dispatch of the first responding unit *(EMT or paramedic unit or EMT/paramedic unit)*. This time interval is variously labeled but will be called "dispatch time" here. The National Fire Protection Association *(NFPA)* sets a dispatch time standard of 60 seconds for critical events. Rapid dispatch can do much better than that. The rapid dispatch target time in King County dispatch centers is 15 seconds or less, especially when the address is auto populated into the dispatcher CAD *(computer aided dispatch)* system. The first mention

SYMPTOMS TRIGGERING RAPID DISPATCH
Unconscious
Difficulty breathing
Stroke symptoms
Chest Pain
Seizure
Major Trauma
Diabetic hypoglycemia



of a critical symptom mandates an immediate dispatch. Dispatch centers that place priority on a rigid, predefined protocol over rapid dispatch are doing their communities a disservice and in the case of cardiac arrest are delaying life-saving therapy.

The concept of rapid dispatch applies to tiered-response EMS systems as well as single response systems. Many EMS systems dispatch protocols require full information before even a single rescue vehicle can be sent. That may be an acceptable procedure for the majority of calls, but speed is of the essence in a life-or-death situation, and in those cases usual dispatching protocols must be short-circuited. In Seattle and King County, we train dispatchers to use rapid dispatch when they hear certain key words and phrases from callers - either the short list of symptoms in the preceding paragraph or words such as "collapsed," "unconscious," "can't breathe" and "heart attack." We also urge the dispatcher to use common sense and immediately send EMTs whenever a caller otherwise conveys the likelihood of a critical event. In King County rapid dispatch is used in approximately 30 percent of EMS calls. We believe rapid dispatch saves 30-60 seconds in dispatch time for the most critical medical emergencies.

Given the fact that survival falls about 10 percent for every minute of delay in CPR and defibrillation, rapid dispatch can add 5-10 percent to a community's survival rate. All of this can happen with no additional staffing or resources. Not bad. Now you see why this is one of the low-hanging fruits.

One more point to be made – EMS dispatch centers *(whether stand-alone centers or part of larger combined centers such as fire and police)* must have protocols authorized by medical directors. Medical expertise is necessary to provide pre-arrival instructions as well as determine the urgency of the callers complaints and thus how quickly units must be dispatched. The logical person to fill this roll is the EMS medical director. Unfortunately many dispatch centers still do not involve the EMS medical director in the writing or approval of protocols for medical emergencies, a bizarre disconnect between the patient and the EMS system.

COMMUNITY SCORECARD

CARDIAC REGISTRY	SCORE	ASSERTIVE DA CPR	SCORE	HIGH PERFORMANCE CPR	SCORE	RAPID DISPATCH	SCORE
Ongoing registry of every cardiac arrest that receives EMS care *(1 point)*		Specific training including recognition of agonal breathing *(1 point)*		Specific training and testing with a printout strip *(1 point)*		Rapid dispatch program with first-in unit dispatched within 30 seconds of the call for 90% of cardiac arrests *(1 point)*	
Determination of outcomes *(primarily discharged alive)* *(1 point)*		Dedicated person who listens to all cardiac arrest tapes and measures performance, such as: Was cardiac arrest recognized *(two questions asked)*? When was it recognized? What was the time to first compression? *(1 point)*		Dedicated person to measure performance from real events *(1 point)*			
Ability to calculate the Utstein metric *(survival from witnessed VF)* *(1 point)*		Provides feedback to dispatchers *(1 point)*		Provide feedback to EMTs *(1 point)*			

There are a total of 10 points. This scorecard is neither validated nor linearly scaled *(A score of 8 is not necessarily twice as good as a score of 4)*. Rather it offers a simple metric that anyone can quickly apply to his or her own EMS system. It would be an interesting study to correlate a community's VF survival rate with its number of points. There is likely a strong correlation. We are confident that if the above four easy steps are taken, there will be a measurable improvement in survival

Plan of Action: Reach For The Higher Hanging Fruit

Overcoming Challenges

Now it is time to go after the higher hanging fruit. These six more difficult steps will also likely lead to improved survival but their implementation is more challenging and resource intensive.

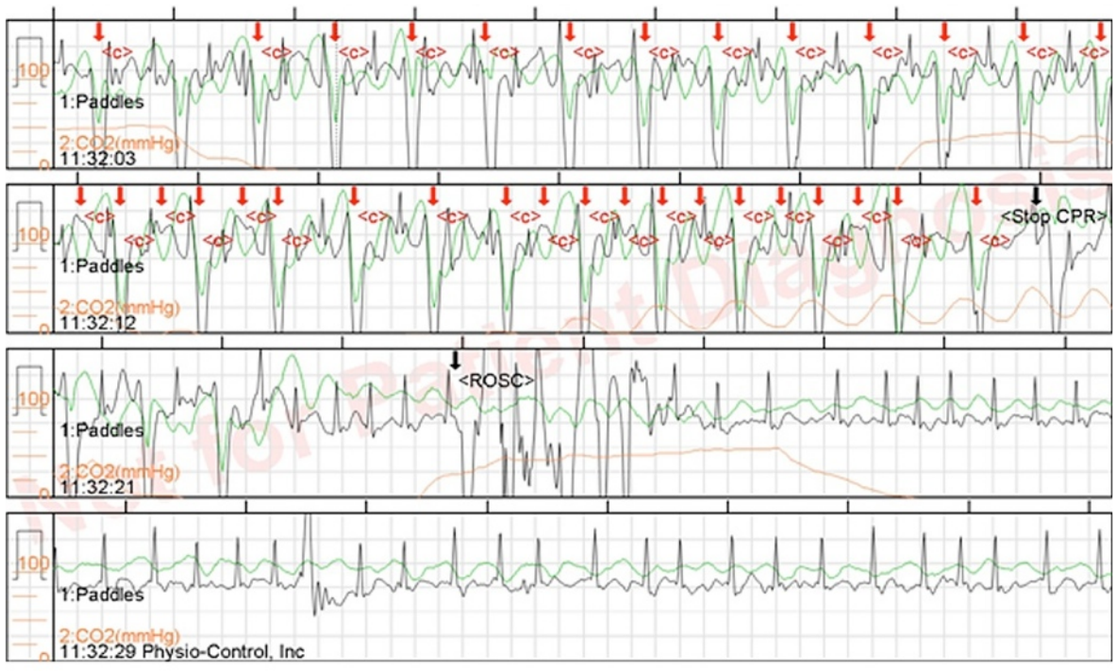
SIX MORE DIFFICULT STEPS TO IMPROVE CARDIAC ARREST: THE HIGH-HANGING FRUIT	
STEPS	**LEVEL OF DIFFICULTY**
Voice record all attempted resuscitations	Middle - High
Begin a program in police defibrillation	Middle - High
Establish a public access defibrillation program	Middle - High
Establish or partner with local foundation to raise funds for training and QI	Middle - High
Institute hypothermia in all receiving hospitals	Middle - High
Culture of excellence	High

STEP **5** **Voice Record All Attempted Resuscitations**

Steve Perry
Paramedic,
King County Medic One

VIDEO

All voice recordings in Seattle and King County are part of an ongoing cardiac arrest QI. Though some EMTs and paramedics may think that the recorded information will be used for disciplinary purposes, the goal of recording is simply to reconstruct the actual events of the resuscitation with accuracy. We have analyzed thousands of voice and ECG recordings and have never used them for any disciplinary action. Listening to a voice recording while viewing the patients cardiac rhythm makes the event vivid. You can tell the moment when the AED was attached and when ventilations were given. You can piece together the sequence and timing of events and deduce the reason for any delays *(the dog was growling at the EMT, the patient had to be moved from the bathroom to the hallway, the oxygen tank ran out, and so on)*. A post-event digital readout of the heart rhythm, with the timing of the shocks, is clearly useful, however nothing beats a voice recording of the event. Some people believe that the only thing better might be a video recording, like those made by police cams, but this suggestion is problematic. Such a recording would be logistically challenging and intrusive, not to mention a violation of privacy. It would be only a matter of time before resuscitation videos began appearing on YouTube. Frankly, though, the most important objection to video recording is that they are not needed. A voice recording is enough to allow adequate reconstruction of the event.



Cardiac Arrest QI

Voice and ECG recordings provide the crucial data allowing for the event to be accurately reviewed. When shared with EMTs and paramedics it provides beneficial QI and teaching material. And it makes everyone want to do better the next time. As an example, in one recording of cardiac arrest the paramedic asked the EMT to stop CPR so he could intubate. Then a long pause ensued that lasted 65 seconds *(with no CPR)* before the paramedic asked the EMT to resume chest compression. The paramedic, when the tape was reviewed with him, could not believe how long the pause was. You can be sure this paramedic will do better the next time. Many training officers in King County fire departments use the recordings for internal teaching. There is nothing like a real event to grab your attention – to make one breathe a sigh of relief when things go well and to cringe when they don't.

STEP **6**

Begin A Program in Police Defibrillation

Ann Doll, Executive Director, Resuscitation Academy
Manager, Medical QI, Seattle/King County EMS

VIDEO

Providing police officers with CPR skills and training in the use of an AED has the potential to increase survival rates from cardiac arrest. Though the promise exists, law enforcements role in resuscitation and early defibrillation has been modest and inconsistent. Yet some communities that have embraced police defibrillation have seen dramatic improvements in survival. Perhaps the most notable community is Rochester, Minnesota. Our system in King County has also seen benefit with police response to cardiac arrest.

Embarking on a police defibrillation program is not without challenges, and some communities that have tried, have not seen much benefit. There are many issues to address: support from the police chief and buy-in from the rank and file, support from the fire-department and or EMS agency, initial and ongoing training and its costs, cost of AEDs, supervision, QI, and integration with EMS dispatching. In early 2010, we undertook police AED programs in Bellevue and Kent, two cities in suburban King County, Washington, each with approximately 100,000 residents. The program has contributed to the successful resuscitation of a handful of lives; and we believe further training *(both for police and dispatchers)* will lead to even more successful police defibrillations.

A few critical lessons we have learned might help other communities as they embark on police defibrillation. First, there

must be total support from the police and EMS agencies. Ideally every police officer should be taught in person (*rather than solely with video or web based training)* and given the chance to practice with the AED device. Second, the training message must be simple and involve two checks: "If the **person does not respond** and **is not breathing normally**, attach the AED." Let it analyze and or shock and then follow the CPR prompt. Third, we teach the police to provide chest compression only *(most are relieved that they do not have to perform mouth to mouth ventilation).* Fourth, we do not

use voice recordings for police AEDs. The police find this a huge relief. Fifth, the dispatch center is key to achieving rapid police response. The police must be dispatched simultaneously with the first responding EMS agency. This is perhaps the most challenging issue in achieving a successful police defibrillation program. Our goal is for police to be dispatched only for true cardiac arrest events. Many times it is clear that the caller is reporting a cardiac arrest, but other times it takes some seconds *(or longer)* to confirm an arrest *(remember that the EMT unit has already been dispatched under rapid dispatch).* When the dispatcher waits to confirm cardiac arrest before dispatching police, the fire department will have had enough of a jump start to arrive before police. How to send police quickly, but not over send, is a challenge we continue to work on.

Russ McCallion, Asst. Chief EMS & Training Divisions
East Pierce Fire and Rescue

VIDEO

ADDITIONAL INFORMATION

Bellevue Police Defibrillation *(youTube video)*

Automated External Defibrillator Use by Police Responders Where Do We Go From Here? *(article)*
American Heart Association, Circulation
José A. Joglar, MD, Richard L. Page, MD

Only a Third of U.S. State Police Agencies Equip Cars With AEDs, Penn Research Shows *(article)*
Perelman School of Medicine, Penn State

Resuscitation Academy Police Defibrillation Toolkit (PDF)

STEP 7

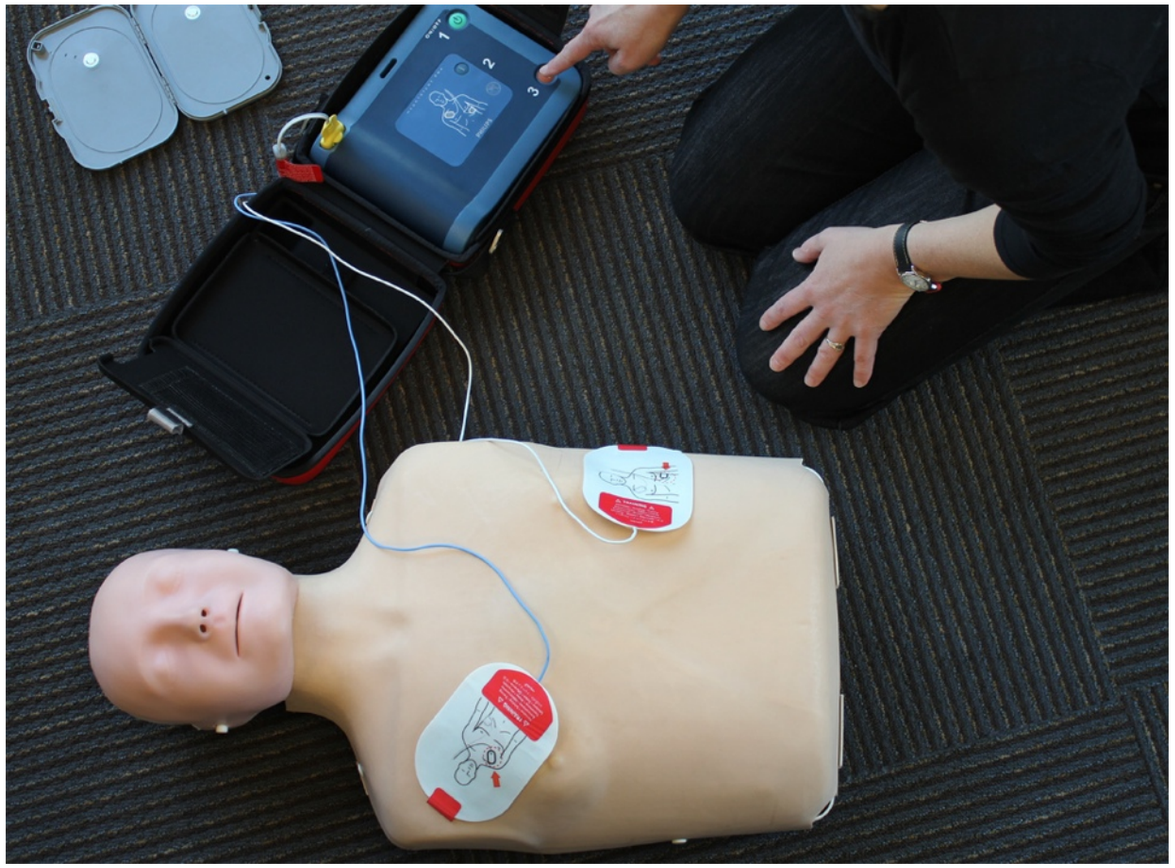
Establish a Public Access Defibrillation Program

Megan Bloomingdale, Dispatch QI, EMT, EMT Instructor
King County EMS / North Seattle Community College VIDEO

Public access defibrillation *(PAD)* refers to placing AEDs in public locations and using them as elements of a community's resuscitation chain. PAD is a difficult step, not necessarily because it is technically challenging, but rather because the it involves widespread community effort and its effects are likely to be modest. Even with widespread dissemination of AEDs in public locations there will be only a small increase in survival. The Public Access Defibrillation Trial was a multi-center trial demonstrating that sites with AEDs on the premises, and with staff trained in their use, had higher survival rates for VF than comparable sites without AEDs *(the non-AED sites relied on the fire department or an EMS agency to bring an AED to the scene)*. Other studies, reporting the use of AEDs in casinos and on airplanes, also showed benefit.

There is an active PAD program in Seattle and King County, with more than 3,000 AEDs registered with EMS, as of 2012. Sites with

AEDs include such places as the airports, health clubs, jails, community centers, senior centers, shopping malls, office buildings, and ferryboats. The number of AEDs has increased significantly over the past decade. A study from Seattle and King County reporting on eight-years' experience with PAD, found that in 1999, 1.8 percent of VF arrests had an AED applied compared to 8.8 percent of VF arrests in 2006. Survival among PAD cases was approximately 60 percent. The strategy of using public AEDs has merit, but enthusiasm must be tempered with awareness on the relatively small number of cardiac arrests – only 15 percent – that occur in public places *(approximately 150 of 1,000 arrests per year in King County)*. Though the absolute number is small, these are great saves. A cardiac arrest in public usually befalls an active person who is out in the community, and since most collapses in public are witnessed, CPR is often started quickly. The fact that these arrests have everything going for them – they are witnessed, they usually involve VF, CPR and defibrillation are started quickly and there is probably less comorbidity – explains the excellent survival rate *(and the typically good neurological recovery)*.



Residential facilities offer great potential for PAD programs. As incentives, an EMS agency could provide free training to residents and personnel and could offer to register the facility's AED with the local dispatch center. The agency could also offer advice on where in the facility to place the AED. A residential community or an apartment or condominium building could establish an AED security system. In such a system, the AED would be placed in a locked box *(all the residents would know the combination)* in a central accessible location. This location would be registered with the dispatch center, and if a cardiac arrest occurred on the premises, someone at the scene would be instructed to get the AED.

Existing computer-aided dispatch programs allow dispatch centers to identify AEDs at particular locations *(assuming that these AEDs are registered with the dispatch center)* as well as any in close proximity. Wouldn't it be amazing if a caller to 911 were informed

that the doorman in the next building had an AED in his buildings lobby and was being called to bring it over? This idea is currently being tested in the King County NorCom Communications Center, and though this is not a formal test, it is offered as one idea for how a community can be creative with AEDs. And what if the dispatcher could automatically alert all staff responsible for AEDs within a certain radius? Thus a security guard in an adjoining building would get a phone text telling him or her that there was a cardiac arrest next door. This technology is commercially available and deployed in a few cities. New smart phone applications can pinpoint *(registered)* AED locations. Clearly, AEDs in the community have the potential to save lives. The challenge is to maximize this potential.

There is interest on the part of some national sudden cardiac arrest foundations and prevention advocacy groups to revise building codes to mandate placement of AEDs in multiple occupancy dwellings and business establishments. The reasoning is that an AED is a lifesaving technology that should be built into the structure of the building, just like a sprinkler system. Another innovative idea is to use social networking and crowd sourcing *(using the public to engage in community data collection)* both to identify the locations of AEDs and to volunteer to respond to a cardiac arrest event if notified by the dispatch center. Dr. Raina Merchant, in a recent commentary in Circulation Cardiovascular Quality and Outcomes, describes both the challenges and potential benefits of crowd sourcing and the potential ability to retrieve AED location information on smart phone mobile apps. With over 1 million AEDs sold in the United States, wouldn't it be nice to determine the precise location of these AEDs and then have this information readily available for witnesses at a cardiac arrest? Perhaps future AEDs could have embedded geographic transponders.

ADDITIONAL INFORMATION

Community PAD Toolkit
Resuscitation Academy

MyHeart Map
Pennsylvania, USA

AED Locator
United Kingdom

STEP 8

Supplemental Funding & Support for Training & QI

Jan Sprake, Executive Director
Medic One Foundation

VIDEO

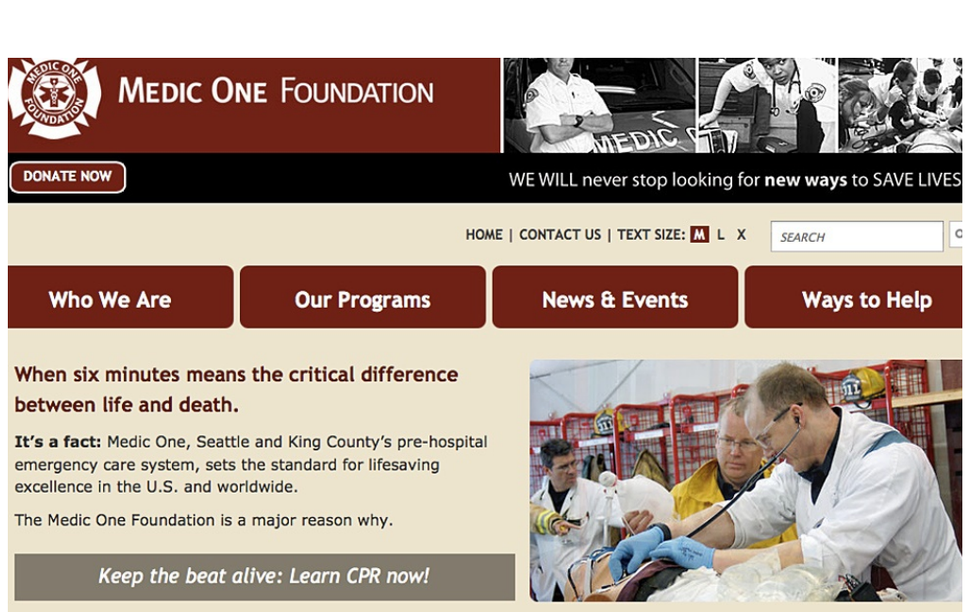
When times are tight financially, usually the first things to be eliminated or reduced are budgets for training and QI. While these decisions may be penny wise and pound foolish, they nevertheless reflect the harsh realities and the need to preserve basic operational personnel. Thus, it is important to find additional sources of revenues. Charitable gifts can provide needed funds to support activities such as training and QI. These in turn provide the margin of excellence to boost a program to a higher level of performance.

The Medic One Foundation is an example of how fundraising can supplement a public EMS system. This foundation supports 100 percent of paramedic training for communities throughout King County and cardiac arrest QI for the Seattle Fire Department. In addition, it funds paramedic training for other agencies outside of King County, as well as provides equipment and research grants.

In order to solicit charitable gifts, EMS agencies can establish a separate nonprofit foundation or find an existing nonprofit that is willing to serve as a fiscal sponsor of your fundraising activities.

For example, an EMS agency could partner with a hospital foundation or auxiliary, fire department auxiliary or benevolent fund, or with a local community foundation.

Such an arrangement saves the local fire department the expense and effort establishing a nonprofit charitable organization.



Medic One Foundation website

STEP

9 Institute Hypothermia in All Receiving Hospitals

Peter Kudenchuk, MD
Professor of Medicine, Division of Cardiology,
University of Washington
Associate Medical Director, King County EMS

VIDEO

Hypothermia is the standard of care for resuscitated VF patients when they arrive at the hospital in a coma. Cooling the patient's body for twenty-four hours after resuscitation, offers the promise of a modest improvement in chances of survival, and to date there is no indication of harm from this practice. The American Heart Association and the International Liaison Committee on Resuscitation have both endorsed it. Like any complex hospital procedure proficiency requires written protocols, practice, and accountability.

As of 2013 most hospitals, that receive resuscitated patients, have hypothermia protocols in place. Lance Becker, director of the Center for Resuscitation Science at the University of Pennsylvania Perelman School of Medicine, is a leading proponent of hypothermia. He and his colleagues, on the basis of laboratory studies, have come to believe that the cells of vital organs do not die from insufficient oxygen; rather, they say, the harm occurs when oxygen is reintroduced. The benefit of cooling is that it inhibits many of the destructive reactions associated with reperfusion of blood and with the reintroduction of oxygen. The University of Pennsylvania Hypothermia and Resuscitation Training (HART) Institute offers an annual two-day "boot camp" designed to educate care providers on in-hospital care of cardiac arrest patients.

Hypothermia is a relatively recent addition to the armamentarium of resuscitation therapy. In 2002, two studies of hypothermia were published in the New England Journal of Medicine. Both studies randomized patients either to receive hypothermia or to not receive hypothermia *(called normothermia)*, for VF patients who had been successfully defibrillated but were comatose when they arrived at the hospital. One of the studies, reporting data obtained from several centers in Europe, demonstrated favorable neurological outcomes six months after cardiac arrest when hypothermia treatment had been delivered: 55 percent of patients in the hypothermia group had favorable outcomes, compared to 39 percent in the control group. Mortality was also significantly lower in the hypothermia group than in the control group: 41 percent and 55 percent, respectively. The other study, this one from Australia, did not demonstrate a significant difference in survival *(the main outcome of the study)* among the hypothermia and normothermia groups, though the authors did report better neurological outcomes in the hypothermia group. This was a smaller study, with only 77 patients as opposed to the 275 patients in the European study. On the basis of these two studies, several national and international organizations, including the International Liaison Committee on Resuscitation and the American Heart Association, now recommend hypothermia for patients who have suffered ventricular fibrillation and are initially resuscitated but are still in a coma when they reach the hospital.

Unresolved issues are whether patients should receive hypothermia in the prehospital setting and whether only VF patients should be eligible for hypothermia therapy. It is for this reason that hypothermia is placed in the difficult-steps category. Though the therapy is reasonably straightforward, the difficult part comes in knowing whether it is beneficial for prehospital use. There is currently no data to clarify whether hypothermia should begin in the field, either after return of spontaneous circulation or in the middle of a resuscitation – in other words, prior to return of a pulse and blood pressure. Dr. Francis Kim at the University of Washington is currently studying the potential benefits of prehospital hypothermia for resuscitated VF patients. This is a randomized trial, and the results will not be known until mid-2013. Also unresolved is whether hospital hypothermia benefits patients who are resuscitated from asystole or pulseless electrical activity. Stay tuned on this issue.

ADDITIONAL INFORMATION

Institutional Protocols for Therapeutic Hypothermia
Perelman School of Medicine

Therapeutic Hypothermia Links
Perelman School of Medicine

Cardiac Arrest, Hypothermia, and Resuscitation Science
with Benjamin Abella, MD, MPhil (Coursera course)

STEP 10 Work Toward A Culture of Excellence

Leonard Cobb, MD,
Medic One Founder, Professor Emeritus,
University of Washington
Harborview Medical Center/Seattle Medic One

VIDEO

Creating and nurturing a culture of excellence is perhaps the most difficult step. What is a culture of excellence? It is an implicit awareness perceived by most or all members of the organization that high expectations and high performance define the standard of care. A culture of excellence requires a leader *(or leaders)* with an uncompromising vision. Ideally, the administrative director and the medical director should share this vision. Practically they should meet regularly – perhaps weekly – to jointly administer and plan all aspects of the EMS program. The two of them, together, should establish a long-term plan to create and maintain a culture of excellence. Some people would argue that a high-quality EMS system demands such a culture. An equal number would claim that creating a culture of excellence is extremely challenging. No doubt it is. Nevertheless, a culture of excellence, hard though it may be to define or measure, is probably a key factor separating great systems from those that are merely satisfactory.

Administrative and medical leadership together must enhance training and continuing education and make medical QI the means of constant improvement. Excellence also requires buy-in from the extended EMS family of dispatchers, EMTs, and paramedics. When

Michael K. Copass, MD, Professor, University of Washington
Harborview Medical Center/Seattle Medic One

VIDEO

EMS providers recognize the presence of sincere, mission-driven leadership, as opposed to lip service, they respond to the positive culture and contribute to it as well.

The Medical Model

A culture of excellence can be achieved in any organization model. However, we believe such a culture can more easily be accomplished in a system that is based on a medical model. What is meant by a medical model? It is a system in which a medical director plays a large role in determining and supervising the quality of medical care. Specifically, a medical model of EMS is a system in which the medical director is responsible for the following seven areas:

Medical Director - Areas of Responsibility

- protocols for dispatchers, EMTs, and paramedics
- medical supervision online and offline
- evidence-based practice
- ongoing medical QI
- training and continuing education
- controlled substance policies
- medical discipline

There is an eighth optional area of responsibility, namely, ongoing research studies. Continuous studies *(to push the envelope of knowledge)* create a sense of being part of a larger enterprise and helps foster a desire to contribute new evidence-based knowledge to the world of EMS. These studies do not have to be randomized clinical trials. One can embark on small-scale projects and still make a contribution. The studies need not necessarily be published in peer-reviewed journals – merely sharing the findings with the personnel, can be rewarding and help to achieve a sense of pride.

A medical model does not require that the physician director run the entire system. In fact, the less administrative involvement by the medical director, the better. The medical director should be responsible for the quality of medical care and establish high expectations and see that they are being met. The EMTs and paramedics must be accountable to the medical director for the quality of their care. The ideal system would have the administrative director responsible for budget, operations and personnel matters and the medical director responsible for patient care. And in the best of all words the two would work closely in partnership since their responsibilities complement each other. The medical director should not deal with hiring, though he or she should have a say in who is hired. And we don't expect the doctor to directly fire anyone, though we expect him or her to work with the administrative director to limit, suspend or terminate an EMT or paramedic whose medical care is substandard. In Seattle and King County, there is a phrase that encapsulates the critical role of the medical director: The EMT or paramedic practices under the medical license of the medical director. In essence, the clinical buck stops with the medical director.

How does one create a medical model? Certainly there is no guidebook to follow and probably many if not most EMS programs think they have a medical model. The test is whether

the medical director has responsibility for all the seven areas above. Why stress the concept of the medical model? Because the medical director is so importantly involved in every link in the chain of survival and every piece of the frame of survival.

Medical directors are appointed in various ways. Whatever the process, the medical director must have the authority to supervise a system that uses a medical model of EMS care. The medical director must clearly state and constantly promote high expectations, and the EMTs and paramedics must be accountable to the medical director for their patient care.

It is desirable *(though not always possible)* that the medical director have an academic appointment and be jointly appointed by the EMS administrative director and by the academic dean or department chair. An academic appointment ensures accountability. Moreover, an academic physician is generally one who is committed to furthering learning, and one who probably has knowledge about epidemiological principles and research methodologies. This is not to say that every medical director must conduct research – far from it, but only that the director must understand the benefits and limitations of data, and know how to interpret *(and not over interpret)* this information. An academic medical director has access to all the expertise of an academic medical center and can turn to colleagues in cardiology, anesthesiology, pediatrics, obstetrics, trauma surgery, endocrinology, biostatistics, epidemiology, preventive medicine, health services, and toxicology to get answers about clinical issues and to seek help in guiding policy.

What can a community do if it is geographically distant from an academic medical center? Many centers offer clinical appointments to individuals who are in service roles in the community, or who help with the teaching mission of the university. Many deans and department chairs in emergency medicine would welcome a conversation with a community's elected officials or its EMS administrative director and would be pleased to help establish a clinical appointment for the community's medical director. It is also advantageous for a community to partner with an academic medical center, which probably already serves as the regions trauma center.

A partnership between a local community and an academic medical center can be a win-win proposition.

The EMS program can provide training opportunities for emergency medical residents and help partner with the medical school on EMS fellowships. The medical center can provide clinical expertise, communications expertise, database management, and managerial experience and can cooperate with local medical directors to establish regional consortia of EMS medical directors and programs. An academic medical center, after all, has a mission to serve the larger community, and the goodwill and reciprocity generated by this kind of effort can reap big dividends.

Continuous Quality Improvement

A culture of excellence also demands ongoing quality improvement. The medical director, with the support of the administrative director, is responsible for conducting QI audits of the EMS system. The cultural norm says we (*all of us who provide care)* are measuring how we perform in order to perform even better.

Medical QI can involve any aspect of EMS care. As it relates to cardiac arrest, however, the substrate for continuous QI is the cardiac arrest registry. Without QI, the cardiac arrest registry is just a collection of facts. With QI, the registry becomes the basis for improvement.

QI can occur at the macro level *(system level)* or micro level (*components of the system)* and even at the level of an individual resuscitation. At the system level one should be able to determine the survival rate for witnessed VF. For the micro level, QI bores down to the components of the system.

For example:

What is the average time to...

- CPR? Defibrillation? What percentage of arrests have bystander CPR?
- Telephone CPR? What is the average time to deliver CPR instructions? The time intervals from the 911 call to CPR and defibrillation are critical to measure. Measuring these time

intervals can be challenging but without this information it will be like trying to solve a puzzle with several key pieces missing.

Most EMS systems report response time *(time from call to arrival at scene).* However, in many centers the actual call occurs seconds *(sometimes a minute or more)* before being keyed as an EMS call. Thus the actual call occurred before the response time clock starts ticking. And arrival at scene occurs a minute or several minutes before someone touches the patient. Measuring time intervals in EMS is a maze. The point, however, is that there are unmeasured time intervals prior to the so-called response time and unmeasured time intervals after the response time.

What really matters is the interval from the first ring in the primary PSAP to contact with the patient including who starts CPR, when it starts, and the exact time of the first defibrillatory shock. At the level of individual cases QI should routinely try to piece together the key interventions. This is particularly important for VF cases when the patient did not survive.

If one starts with a mindset that every case of VF should survive, then, when the patient does not survive, the question becomes,

Why not?

Important Questions

- Who started CPR?
- What was the time to CPR?
- What was the time to first defibrillation? (total number of defibrillatory shocks)
- Were telephone CPR instructions offered?
- Did the dispatcher recognize agonal respirations?
- `Was there rapid dispatch? (What was the time to dispatch the first-in unit?)
- What was the interval between EMTs arrival at the patients side and delivery of the first shock?
- What was the density of CPR between two shocks?
- After the first defibrillatory shock, how long did it take to resume chest compressions?
- Did CPR occur for two minutes between shocks?
- Was the patient intubated? (How many attempts were required for intubation?)
- Was an alternate airway used? (Such as laryngeal mask airway)
- Was an intravenous line started? (Was it peripheral, central, or interosseous?)
- When was hypothermia started?

Every link and every sub link in the chain of survival can be studied; the number of possible QI projects is limited only by resources and by the accuracy of the registry's data. An EMS system should never become complacent. There are always opportunities for improvement, and continuous QI is the way to bring it about.

Improve Skills among Paramedics, EMTs, and Dispatchers

Improvement in skills, is another part of a culture of excellence. Training for excellence. The cultural norm says that we *(again all of us who provide care)* train in order to improve our skills. Paramedic's skills improve with a combination of training, continuing education, and actual performance. In Seattle and King County, paramedics are required to perform 12 intubations and 36 IVs every year to maintain certification. Paramedic staffing correlates directly with opportunities to perform critical skills. There are strong advocates for various types of paramedic staffing in EMS programs. In Seattle and King County, a tiered response system is utilized and paramedics are sent only to the most serious calls. Thus, they are able to maintain critical skill such as endotracheal intubation and central vein IV placement. In other systems, a paramedic is sent to all EMS calls. These programs assume that service is thereby improved, since every call, regardless of the seriousness of the emergency, will have a paramedic in attendance. But the unintended consequence is less opportunity for any single paramedic to practice critical skills. It is unclear whether a high or low ratio of paramedics to total population served, is associated with community cardiac arrest survival.

As for EMTs, the care provided by these personnel is the foundation for all subsequent care delivered during an attempted resuscitation. If that foundation is of poor quality, the entire care structure is jeopardized. EMTs can do a great deal to treat ventricular fibrillation definitively, or to prime the patients body with high-performance CPR for further intervention by paramedics. The details of CPR and defibrillation often determine the outcome, and the key to positive outcomes is training.

Emergency dispatchers are also members of the EMS team. They have the critical role of mobilizing the EMTs and paramedics and seeing that telephone CPR begins before EMS personnel show up. Dispatchers training, practice and skill review are as important to positive outcomes as are high-performance CPR and defibrillation. A highly trained dispatcher can, with rapid dispatch, easily save thirty to sixty seconds in the initial dispatch and, by offering telephone CPR instructions, can significantly increase the likelihood of the patients survival.

Putting Plans into Action

Overcoming Challenges

This guide lists 10 steps that will lead to improved survival. There are four easy steps *(the low-hanging fruit)* and six more difficult steps (*the higher-hanging fruit)*. But one community's easy, may be another community's difficult. An EMS director or manager, partnering with the medical director, must decide what can be achieved in his or her own community. Whether one selects an easy or more challenging step the key is to begin. Success with one step will create momentum for tackling others. The steps listed above provide the overview and general approach to implementation. Missing are detailed game plans as well as the specific tools to implement the programs. Reading a short description of high-performance CPR, or dispatcher-assisted CPR, or rapid dispatch may convince you of the importance and need of such programs but how do you bring them about?

The Resuscitation Academy began in 2009 with the goal to improve cardiac arrest survival. Its tag line is "Improving cardiac arrest survival, one community at a time." It was apparent from the first Resuscitation Academy class in 2009 that the lectures, breakout sessions and workshops could only go so far. We, the faculty, needed to spell out the details of how to implement the various programs we were talking about. The Resuscitation Academy Tool Kits were developed to do just this. They provide a how to guide, for setting up various programs within local communities. But even tool kits have limitations and we realize how hard it can be for local communities to implement the various programs. We think more attention must be focused on the challenges of implementation and the need to mobilize local community resources. Thus the last portion of this chapter tries to shine a beacon on the difficult topic of implementation.

Implementation

Hendrika Meischke, PhD
Professor of Health Services, University of Washington VIDEO

Hendrika Meischke, PhD is a Professor of Health Services at the University of Washington. We have been colleagues in the world of resuscitation research for over 20 years. We both wonder what it takes for communities to implement some of the recommendations in this guide as well as the lessons and programs of the Resuscitation Academy. The question is also gaining attention at the national level – the American Heart Association recently published a consensus statement in 2011 appropriately called "Implementation strategies for improving survival after out-of-hospital cardiac arrest in the United States." Why does community A embrace these recommendations and transform their system and why does community B, given the same information, do very little to improve resuscitation? What is the secret sauce? Definitive answers are elusive, though there is no end to possible explanations. Is it individual charisma? Is it leadership? Is it complementary personalities? Is it legislative mandates *(funded or not)*? Is it adequate resources? Certainly some or all of these may provide part of the explanation. Common sense says that an effective leader can be a catalyst for change *(I have seen very strong county medical directors almost single handedly make substantive and dramatic changes in their EMS system)* but such individuals are relatively rare and often the changes evaporate when that individual leaves or retires. Thoughtful implementation will facilitate meaningful change.

Three complementary features can enhance the likelihood of successful implementation.

First, the core components (*cardiac arrest registry, assertive dispatcher-assisted CPR, high-performance CPR, rapid dispatch)* must be in place.

Second, there must be fidelity to the core components. The best way to achieve fidelity is to define performance standards and use QI to measure the actual performance. This makes sense since, as is all too common, there is a large gap between perceived performance and actual performance.

Third, the EMS program must adapt to the local situation. Again, this makes sense since only through mobilization of local resources can there be any chance of undertaking new initiatives. Change, always difficult, is best smoothed with local buy in and support.

Implementation is not easy and this guide concludes with 5 specific actions on how to implement changes in your local community.

The Four Actions

Action 1: Form an advisory board: We believe the most important ingredient in the sauce of implementation is a team effort with a shared vision. The vision can be as simple as Improving survival from out of hospital cardiac arrest. The advisory board or steering committee *(or whatever term you use),* should ideally be led or co-led by the EMS director *(or fire chief or chief of EMS operations)* and the medical director with a core group consisting of the dispatch director, the head of EMT and paramedic training, the QI officer *(if one exists),* a representative of the local hospital (or local hospital association) and ideally a political leader *(mayor or council member)* and a citizen. The latter could be the head of a local philanthropic organization such as the Kiwanis or Rotary club. This core group may be ad hoc or formal *(in other words commissioned by the mayor or council with formal appointments),* and all it takes is one fired-up individual to catalyze the initiative. Large communities should have a full or at least a part time staff person who is accountable to the advisory board and can keep everyone on task and maintaining forward momentum. The staff person should be thought of as the site coordinator who works on behalf of the advisory board.

Action 2: Determine how to make it happen in your community. Every step in this chapter must be customized to the local system and its strengths. There is no one pattern. Rochester, MN has a completely different EMS system from Seattle and King County. And yet both achieve high survival rates proving that there is no ONE system. Each EMS leader must mobilize and strategize based on what is possible locally.

Action 3: Set specific goals. This group must be realistic. they will not transform their system overnight and they should set attainable goals achieved by plucking the low hanging fruits. Progress will likely be slow and iterative *(step by step).* But once on the path to improvement there is no stopping that community.

Action 4: Establish performance standards. For example earlier in this guide possible performance standards for dispatcher-assisted CPR and high-performance CPR were listed. Let everyone know what the standards are why they matter. Then provide the training and support to meet these standards. Constant *(and timely)* feedback is also part of the equation.

There are regrettably few, if any, national performance standards for resuscitation. A 2011 consensus paper from the American Heart Association calls for specific benchmarks and quality improvement goals for out of hospital cardiac arrest. These goals span the spectrum from medical leadership to dispatch to EMS and hospital care. Whether one agrees with the specific goals, is in some way less important than the fact that performance standards are becoming part of the national dialogue on how to improve survival rates. The following are possible standards for an urban EMS system and are meant to complement the 10 specific steps at the beginning of this guide. Note how the standards are weighted heavily toward bystander CPR *(whether by a trained person or as a result of dispatcher assistance)* and the rapid delivery of CPR and defibrillation standards that will surely lead to improved survival.

One might consider different standards for urban and rural EMS systems. But whatever the standards are, adherence to them should be mandatory, and reported to the members of the EMS agency and governing board.

- Bystander CPR in more than 60 percent of witnessed cardiac arrests
- Dispatcher-assisted CPR in more than 50 percent of all cardiac arrests *(excluding arrests when bystander CPR is in progress at the time of call)*
- Less than five minutes between pickup of the call to 911 and the arrival of EMTs at the patients side more than 90 percent of the time
- Less than six minutes between pickup of the call to 911 and the first defibrillatory shock more than 90 percent of the time
- Less than ten minutes between pickup of the call to 911 and the arrival of paramedics at the patients side 90 percent of the time Use of voice and heart rhythm recordings in all resuscitations
- Medical directors review and critique of all resuscitations
- A community survival rate *(discharge from hospital)* of 25 percent for patients with witnessed VF

Action 5: Measure and improve. Ongoing measurement of survival and ongoing QI are vital. A cardiac arrest registry need not be onerous. It can take as little as 10-15 minutes to register the data. Similarly analysis of cardiac arrest CPR performance or dispatch performance need not be exhaustive. Ten to fifteen minutes should provide the vital elements of QI and will certainly provide the information needed to monitor the system and allow for feedback to the individual EMS personnel and individual dispatchers. Praise is given for good performance, and for the less than good performance, we always stress the challenges of the task and ask how it can be done better the next time. We have never used QI information in a punitive or disciplinary manner.

These five implementation actions help define the frame of resuscitation. The metaphor of a chain of survival and a frame of survival fit nicely with the concepts of resuscitation. The chain of survival is all about the specific therapy, particularly providing CPR and defibrillation as rapidly as possible and with as much fidelity as possible. The frame of survival is all about the qualitative factors leadership, culture, ongoing training and QI. These are the stuff of implementation: establish an advisory board *(leadership)*, set specific goals *(vision)*, establish performance standards *(culture)*, determine how to make it happen *(training)*, measure and improve *(QI)*.

Clearly, the links in the chain and the qualities in the frame are integrally linked. Put them together and lives can be saved.

A Vision Of The Future

We believe that survival from VF in many communities could reach 60 percent. Some communities are already near 50 percent. In King County we will approach 60 percent in the near future with meticulous application of high-performance CPR and intensive training in recognition of cardiac arrest and delivery of dispatcher-assisted CPR. For communities currently at the 10, 20, 30, or 40 percent survival rates, we cannot guarantee a sudden surge to 60 percent, but we do think dramatic increases in survival are possible. From the many inspiring success stories alumni have shared since attending the Resuscitation Academy, clearly this is evidence that improving survival rates from cardiac arrest is not only a possibility for the future, but can, with focused and concerted effort, be possible now.

Finding Your Own Path

Remember two of the opening mantras: "Change occurs step by step" and "It's not complicated but it's not easy". Those are good reminders as you embark on the difficult but rewarding journey to improve cardiac arrest survival in your community. We hope this guide will motivate you, not only to start the process of improvement in your community, but also to attend a future Resuscitation Academy class. The classes are offered tuition-free twice a year, typically in March and October. Each class is 2 days long. We also offer one day focused Academies on Dispatch-assisted CPR and High-performance CPR. Information about future classes and how to register, as well as free downloads of the toolkits, may be found at the Resuscitation Academy website.

Mickey Eisenberg, MD, PhD
Medical Program Director, King County EMS
Professor of Medicine, University of Washington

VIDEO

Hope to see you in Seattle!

The Resuscitation Academy

The tag line for the Resuscitation Academy is, "improving cardiac arrest survival, one community at a time." Since the first Academy class in 2009, we have been trying to do just that. The Resuscitation Academy, held twice a year in Seattle, is a joint effort of King County EMS *(Public Health – Seattle and King County),* Seattle Medic One *(Seattle Fire Department),* and the Medic One Foundation.

Additional support comes from Harborview Medical Center, University of Washington, Asmund S. Laerdal Foundation for Acute Medicine, Life Sciences Discovery Fund and the Medtronic Foundation HeartRescue Program. The faculty members are veterans in directing EMS programs as well as distinguished researchers in resuscitation science. My back of the envelope calculation says that the faculty members collectively represent 300 years of EMS experience.

> *"The Academy broadened my awareness & knowledge of the science of cardiac resuscitation. It convinced me that measuring outcomes is absolutely required for improving system performance."*
>
> *— Resuscitation Academy Alumnus*

The Resuscitation Academy is offered tuition-free and attendees come from throughout the country *(and world)*. The small class size allows for a two-way exchange of Information – the faculty provides evidence-based information and tools to improve cardiac arrest survival and the attendees share the real-life challenges they face. Every community has a different constellation of culture, leadership, resources, and opportunity. Above all we *(the faculty)* have learned that change is very challenging and one should never assume that just because someone comes along with a good idea that it will be embraced and implemented. Impediments to change, whether they stem from habit, inertia, malaise, or lack of resources, will overwhelm the best of intentions. We have also learned that no system will transform itself overnight. Change is not only difficult, it occurs slowly – tiny step by tiny step.

Resuscitation Academy Website

Information about the Academy may be found at: www.resuscitationacademy.org. The most recent curriculum is posted on the site as well as upcoming Academy classes and registration information. Though we have experimented with different lengths for the Academy ranging from one to five days, we have settled into the 2-day length that works well for us, and allows a nice mixture of lectures, small group discussions, workshops and breakout sessions. We expect every student to

Resuscitation Academy website
http://www.resuscitationacademy.org

select a project to implement in his or her home community upon return from the Academy. We limit each Academy to 35-40 students in order to maintain a small group seminar feel to the class. Plus, the small class allows the faculty to get to know the individuals and vice versa.

The Academy's Main Message

The Academy encapsulates the collective experience of decades of running the Seattle Medic One and King County EMS programs. Quantitative and qualitative factors explain a system's success or failure in managing cardiac arrest. The combination of measurable and "softer" factors was conveyed in the figure of the chain of survival *(measurable quantitative factors)* surrounded by a frame of survival *("softer" qualitative factors).* The operant message is that the chain of survival and the frame of survival provide a complete package for success. The Academy obsesses on that message and takes it further by offering concrete instruction on how to implement change.

Resuscitation Academy Tool Kits

The Resuscitation Academy provides toolkits on the following topics:

- Cardiac Arrest Registry
- High Performance CPR: Training, Implementation, and QI
- Dispatcher Assisted CPR: Training, Implementation, and QI
- Community CPR - Community Public Access Defibrillation
- Police Defibrillation
- End of Life Issues
- Foundation and Fundraising

Download Resuscitation Academy toolkits

The tool kits are not exactly recipe books with specific steps for each program. Rather, they provide the information, background, training materials, sample letters, sample forms, references and resources, and a general approach to achieving buy in from directors and managers, as well as the dispatchers, EMTs, paramedics, and police. While they provide important tools, the contents of each kit must be applied and/or modified based upon resources and leadership within the attendee's community.

While most of the kits are directed toward the chain and frame of survival there are two kits that provide supplemental information. One is on End of Life Issues, and the other tackles the challenging matter of raising funds. Most EMS programs face increasing demand for services and programs while grappling with decreasing resources. When EMS personnel are being laid off it seems hardly the right time to take on new programs requiring new staff or additional resources. But we think there are ways to create additional resources. Call it the margin of excellence to make the system better, even in the face of difficult economic conditions. One of the tool kits specifically addresses how to establish a local foundation or partner with an existing foundation and engage in fundraising. Several communities have used the information in this kit to find resources for new equipment and fund additional staff time for QI activities.

The tool kits are publicly available on the Resuscitation Academy website. Tool kits *(pdf format)* may be downloaded free of charge. All the information on the website is free.

The faculty considers the Resuscitation Academy to be a work in progress. We strive to make each Academy better than the one before. In addition to the two-day Academy, we offer one-day mini Academies focused on dispatcher-assisted CPR and high-performance CPR. Such mini Academies can better reach the folks directly responsible for training and QI. We continually learn from attendees on what works best and what needs to be modified. We have welcomed the opportunity to partner with EMS leaders in other states to assist with starting up regional Resuscitation Academies.

Acknowledgements & Resources

Over 500 people, from the United States and the World have attended the Resuscitation Academy. The faculty would like to thank the Academy alumni for teaching us about their EMS systems and the enlightening us on the unique challenges they face. We thank them all for serving as change agents in their community, and for their willingness and passion to be catalysts for improving cardiac arrest survival. We think this small army of believers will do wonders in their community.

Acknowledgements

Sponsors

The Resuscitation Academy would like to thank the following organizations for their deep commitment to the program and for their ongoing support:

Public Health Seattle & King County

City of Seattle Fire Dept.

Medic One Foundation

King County Medic One

King County Training

Harborview Medical Center UW Medicine

Life Sciences Discovery Fund

The Laerdal Foundation for Acute Medicine

HeartRescue Project

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Book Acknowledgement & Credits

The content of this book is based in part on Chapter 10 of the book, "Resuscitate! How Your Community Can Improve Survival from Sudden Cardiac Arrest" (Second Edition) by Mickey Eisenberg, MD, published by University of Washington Press. It is also inspired by the Resuscitation Academy Faculty.

eBook Production

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Resources

Websites

Resuscitation Academy

Resuscitation Academy Toolkits

Resuscitation Academy Alumni Facebook Page

'Resuscitate! How Your Community Can Improve Survival From Sudden Cardiac Arrest' (Second Edition)

Learn CPR

Learn AED

King County EMS

King County Medic One

Seattle Medic One

Medic One Foundation

EMS Online

Harborview Medical Center / University of Washington

Harborview Paramedic Training

Resuscitation Outcomes Consortium (ROC)

MyCARES (Cardiac Arrest Registry to Enhance Survival)

Seattle/King County Public Health

International Liason Committee on Resuscitation

Laerdal Foundation for Acute Medicine

Life Sciences Discovery Fund

Medtronic HeartRescue Project

Perelman School of Medicine - Therapeutic Hypothermia

New Stories & Articles

The Resuscitation Academy
EMSWorld, July 1, 2010
James Weber, EMT / AS

Dispatchers' CPR Coaching Saves Lives
When Every Minute Counts
NPR – Your Health with Keith Seinfeld, KPLU
May 25, 2012

If your heart stops, be in Seattle (but help's coming for the rest)
NPR – Your Health with Keith Seinfeld, KPLU
March 25, 2011

Why are the odds of surviving a heart attack better in the NW?
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David Baumrind

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Northwest Center for Public Health Practice , November 2011
University of Washington

Maryland Firefighters Take CPR to the Next Level
Firehouse.com News
Susan Nicol, May 11, 2012

2017 ESC Pocket Guidelines

Committee for Practice Guidelines

AMI-STEMI

2017 ESC Guidelines for thh Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation

ESC
European Society of Cardiology

www.escardio.org/guidelines

Introduction

Overview

Updates on the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) should be based on sound evidence, derived from well-conducted clinical trials whenever possible, or motivated expert opinion when needed. It must be recognized that even when excellent clinical trials have been undertaken, the results are open to interpretation, and treatments may need to be adapted to take account of clinical circumstances and resources.

Definition of acute MI

The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia. For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms suggestive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI.

Epidemiology of STEMI

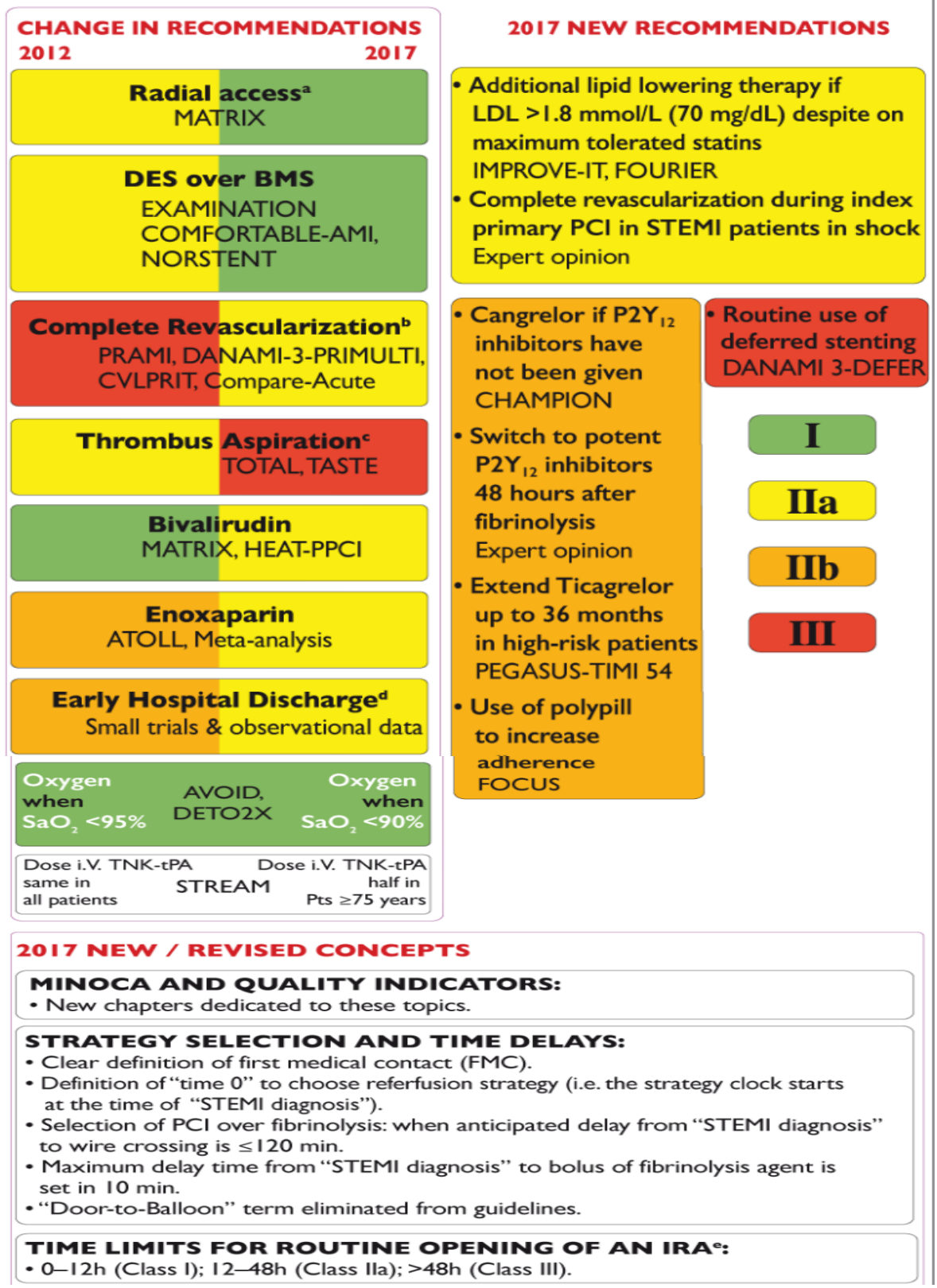
Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. However, in Europe there has been an overall trend for a reduction in ischaemic heart disease mortality during the past three decades. Ischaemic heart disease now accounts for almost 1.8 million annual deaths, or 20% of all deaths in Europe, although with large variations between countries.

The relative incidences of STEMI are decreasing and NSTEMI are increasing. There is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women.

Several recent studies have highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention. Still, mortality remains substantial: the in-hospital mortality of unselected patients with STEMI in the national registries of the ESC countries varies between 4% and 12%, while reported one-year mortality among STEMI patients in angiography registries is approximately 10%.

Although ischaemic heart disease develops on average 7–10 years later in women compared with men, myocardial infarction remains a leading cause of death in women. Acute coronary syndrome (ACS) occurs three to four times more often in men than in women below the age of 60, but after the age of 75, women represent the majority of patients. There is an ongoing debate on whether outcomes are poorer in women, with several studies indicating that a poorer outcome is related to older age and more comorbidities among women suffering myocardial infarction. Some studies have indicated that women tend to undergo fewer interventions than men and receive reperfusion therapy less frequently. These guidelines aim to highlight the fact that women and men receive equal benefit from a reperfusion strategy and STEMI-related therapy, and both genders must be managed in a similar fashion.

Figure 1 What is new in 2017 Guidelines on AMI-STEMI



2017 NEW / REVISED CONCEPTS

MINOCA AND QUALITY INDICATORS:
- New chapters dedicated to these topics.

STRATEGY SELECTION AND TIME DELAYS:
- Clear definition of first medical contact (FMC).
- Definition of "time 0" to choose reperfusion strategy (i.e. the strategy clock starts at the time of "STEMI diagnosis").
- Selection of PCI over fibrinolysis: when anticipated delay from "STEMI diagnosis" to wire crossing is ≤120 min.
- Maximum delay time from "STEMI diagnosis" to bolus of fibrinolysis agent is set in 10 min.
- "Door-to-Balloon" term eliminated from guidelines.

TIME LIMITS FOR ROUTINE OPENING OF AN IRA[e]:
- 0–12h (Class I); 12–48h (Class IIa); >48h (Class III).

ELECTROCARDIOGRAM AT PRESENTATION:
- Left and right bundle branch block considered equal for recommending urgent angiography if ischaemic symptoms.

TIME TO ANGIOGRAPHY AFTER FIBRINOLYSIS:
- Timeframe is set in 2–24h after successful fibrinolysis.

PATIENTS TAKING ANTICOAGULANTS:
- Acute and chronic management presented.

BMS = bare metal stent; DES = drug eluting stent; IRA = infarct related artery; *i.v.* = intravenous; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SaO2 = arterial oxygen saturation; STEMI = ST-elevation myocardial infarction; TNK-tPA = Tenecteplase tissue plasminogen activator. For explanation of trial names, see list of abbreviations and acronyms.

[a]Only for experienced radial operators.

[b]Before hospital discharge (either immediate or staged)

[c]Routine thrombus aspiration (bailout in certain cases may be considered).

[d]In 2012 early discharge was considered after 72h, in 2017 early discharge is 48–72h.

[e]If symptoms or haemodynamic instability IRA should be opened regardless time from symptoms onset. In left and mid panels, below each recommendation, the most representative trial (acronym) driving the indication is mentioned.

Management – including diagnosis and treatment – of STEMI starts from the point of first medical contact (FMC). It is recommended to establish a regional reperfusion strategy to maximize efficiency.

A working diagnosis of STEMI (called the "STEMI diagnosis" throughout this document) must first be made. This is usually based on symptoms consistent with myocardial ischaemia (i.e. persistent chest pain) and signs (i.e. 12-lead ECG).

When a STEMI is suspected, a 12-lead ECG must be acquired and interpreted as soon as possible at the time of FMC to facilitate early STEMI diagnosis and triage. In patients with a clinical suspicion of myocardial ischaemia and ST-segment elevation, reperfusion therapy needs to be initiated as soon as possible.

ECG criteria are based on changes of electrical currents of the heart (measured in miliVolts). Standard calibration of the ECG is 10mm/mV. Therefore 0.1 mV equals to 1 mm square on the vertical axis. For simplicity, in this document ECG deviations are expressed in mm following the standard calibration.

In the proper clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: ≥2 contiguous leads with ST-segment elevation ≥2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V_2 –V_3 and/or ≥1 mm in the other leads. In patients with inferior myocardial infarction, it is recommended to record right precordial leads (V_3R and V_4R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction. Likewise, ST-segment depression in leads V_1–V_3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation ≥0.5 mm recorded in leads V_7 –V_9 should be considered as a means to identify posterior myocardial infarction. The presence of a Q wave on the ECG should not necessarily change the reperfusion strategy decision.

Blood sampling for serum markers is routinely carried out in the acute phase. This is indicated, but should not delay the reperfusion strategy/treatment. If in doubt regarding the possibility of acute evolving myocardial infarction, emergency imaging aids the provision of timely reperfusion therapy to these patients.

Recommendations for initial diagnosis		
Recommendations	**Class[a]**	**Level[b]**
ECG monitoring		
12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.	I	B
The use of additional posterior chest wall leads (V_7–V_9) in patients with high suspicion of posterior myocardial infarction (circumflex occlusion) should be considered.	IIa	B
The use of additional right precordial leads (V_3R and V_4R) in patients with inferior myocardial infarction should be considered to identify concomitant RV infarction.	IIa	B
Blood sampling		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.	I	C

Table 3 Atypical electrocardiographic presentations that should prompt a primary percutaneous coronary intervention strategy in patients with ongoing symptoms consistent with myocardial ischaemia

Bundle branch block

Criteria that can be used to improve the diagnostic accuracy of STEMI in LBBB:

- Concordant ST-segment elevation ≥1 mm in leads with a positive QRS complex
- Concordant ST-segment depression ≥1 mm in V_1–V_3
- Discordant ST-segment elevation ≥5 mm in leads with a negative QRS complex

The presence of RBBB may confound the diagnosis of STEMI.

Ventricular paced rhythm

During RV pacing, the ECG also shows LBBB and the above rules also apply for the diagnosis of myocardial infarction during pacing; however, they are less specific.

Isolated posterior myocardial infarction

Isolated ST depression ≥0.5 mm in leads V_1–V_3 and ST-segment elevation (≥0.5 mm) in posterior chest wall leads V_7–V_9.

Ischaemia due to left main coronary artery occlusion or multivessel disease

ST depression ≥1 mm in eight or more surface leads, coupled with ST-segment elevation in aVR and/or V1, suggests left main-, or left main equivalent- coronary obstruction, or severe three vessel ischaemia.

Relief of hypoxaemia and symptoms		
Recommendations	**Class[a]**	**Level[b]**
Hypoxia		
Oxygen is indicated in patients with hypoxaemia (SaO_2 <90% or PaO_2 <60 mmHg).	I	C
Routine oxygen is not recommended in patients with SaO_2 ≥90%.	III	B
Symptoms		
Titrated *i.v.* opioids should be considered to relieve pain.	IIa	C
A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.	IIa	C

i.v. = intravenous; PaO2 = partial pressure of oxygen; SaO2 = arterial oxygen saturation.

Many deaths occur very early after STEMI onset, due to ventricular fibrillation (VF). As this arrhythmia frequently occurs at an early stage, these deaths usually happen out of hospital.

In patients following cardiac arrest and ST-segment elevation on the ECG, primary PCI is the strategy of choice. Given the high prevalence of coronary occlusions and potential difficulties in interpreting the ECG in patients after cardiac arrest, urgent angiography (within 2 hours) should be considered in survivors of cardiac arrest, including unresponsive survivors, having a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, history of established CAD, and abnormal or uncertain ECG results). However, in patients without ST-segment elevation, a quick evaluation at the emergency department or intensive cardiac care unit to exclude non-coronary causes and to perform an urgent echocardiography is reasonable. Unfavourable pre-hospital settings indicating a remote likelihood for neurological recovery should be strongly considered and argued against an invasive coronary strategy.

Prevention and improved treatment of out-of-hospital cardiac arrest is crucial for reducing the mortality related to CAD.

Cardiac arrest		
Recommendations	**Class[a]**	**Level[b]**
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.	I	B
Targeted temperature management[c] is indicated early after resuscitation of cardiac arrest patients who remain unresponsive.	I	B
It is indicated that healthcare systems implement strategies to facilitate transfer of all patients in whom a myocardial infarction is suspected directly to the hospital offering 24/7 PCI-mediated reperfusion therapy via one specialized EMS.	I	C
It is indicated that all medical and paramedical personnel caring for suspected myocardial infarction have access to defibrillation equipment and are trained in basic cardiac life support.	I	C
Urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST- segment elevation but with a high suspicion of ongoing myocardial ischaemia.	IIa	C
Pre-hospital cooling using a rapid infusion of large volumes of cold *i.v.* fluid immediately after return of spontaneous circulation is not recommended.	III	B

24/7 = 24 hours a day, 7 days a week; ECG = electrocardiogram; EMS = emergency medical system; *i.v.* = intravenous; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation.

[b]Level of evidence.

[c]Targeted temperature management refers to active methods (i.e. cooling catheters, cooling blankets, and application of ice applied around the body) to achieve and maintain a constant specific body temperature between 32°C and 36°C in a person for a specific duration of time (most commonly used ≥24 hours).

To minimize patient delay, it is recommended to increase public awareness of how to recognize common symptoms of AMI and to call the emergency services. All components of the system delay represent the quality of care and it is recommended to measure them as quality indicators.

System delay is more readily modifiable by organizational measures than is patient delay, and it is a predictor of outcomes. When STEMI diagnosis is made in the pre-hospital setting (EMS), activation of the catheterization laboratory not only reduces treatment delays but may also reduce patient mortality.

Optimal treatment of STEMI should be based on implementation of networks between hospitals. The goal of these networks is to provide optimal care while minimizing delays, thereby improving clinical outcomes. Cardiologists should actively collaborate with all stakeholders, particularly emergency physicians, in establishing such networks.

The main features of such a network are:

- Clear definition of geographic areas of responsibility.
- Shared written protocols.
- Pre-hospital triage of STEMI patients to the appropriate institution, bypassing non-PCI hospitals or hospitals without a 24/7 primary PCI programme.
- On arrival at the appropriate hospital, the patient should immediately be taken to the catheterization laboratory, bypassing the emergency department.
- Patients presenting to a non–PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriate monitored and staffed area.
- If the diagnosis of STEMI has not been made by the ambulance crew, and the ambulance arrives at a non–PCI-capable hospital, the ambulance should await the diagnosis and, if a STEMI diagnosis is made, should continue to a PCI-capable hospital.

Logistics of pre-hospital care		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that the pre-hospital management of STEMI patients is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.	I	B
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay.	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory.	I	B
It is recommended that ambulance teams are trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including fibrinolysis when applicable.	I	C
It is recommended that all hospitals and EMS participating in the care of patients with STEMI record and audit delay times and work to achieve and maintain quality targets.	I	C
It is recommended that EMS transfer STEMI patients to a PCI-capable centre, by-passing non-PCI centres.	I	C
It is recommended that EMS, emergency departments, and CCU/ ICCU have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C
It is recommended that patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI are attended in an appropriately monitored area (e.g. the emergency department, CCU/ICCU, intermediate care unit).	I	C

24/7 = 24 hours a day, 7 days a week; CCU = coronary care unit; ECG = electrocardiogram; EMS = emergency medical system; ICCU = intensive cardiac care unit; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

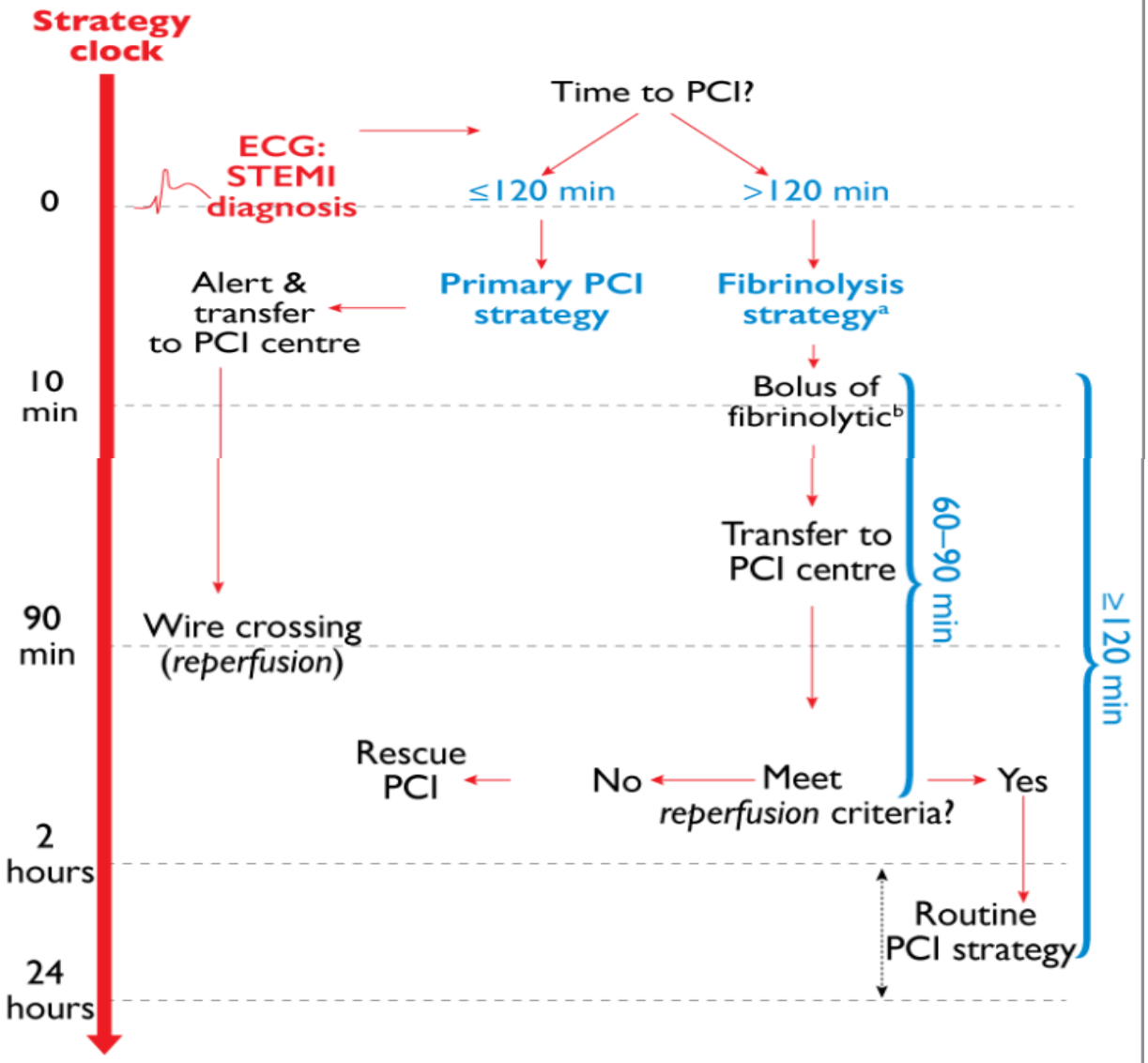
Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset, provided it can be performed expeditiously (i.e. 120 min from STEMI diagnosis) by an experienced team. An experienced team includes not only interventional cardiologists but also skilled support staff.

The extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis has been widely debated. There is a lack of contemporaneous data to set the limit to choose PCI over fibrinolysis. For simplicity, an absolute time (120 min) from STEMI diagnosis to PCI-mediated reperfusion (i.e. wire crossing of the infarct-related artery (IRA)) rather than a relative PCI-related delay over fibrinolysis has been chosen. If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytic within 10 min from STEMI diagnosis.

Table 4 Definitions of terms related to reperfusion therapy

Term	Definition
FMC	The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (e.g. defibrillation). FMC can be either in the pre-hospital setting or upon patient arrival at the hospital (e.g. emergency department).
STEMI diagnosis	The time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent.
Primary PCI	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment.
Primary PCI strategy	Emergent coronary angiography and PCI of the IRA if indicated.
Rescue PCI	Emergent PCI performed as soon as possible in the case of failed fibrinolytic treatment.
Routine early PCI strategy after fibrinolysis	Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis.
Pharmacoinvasive strategy	Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis).

Figure 3 Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non-PCI centre



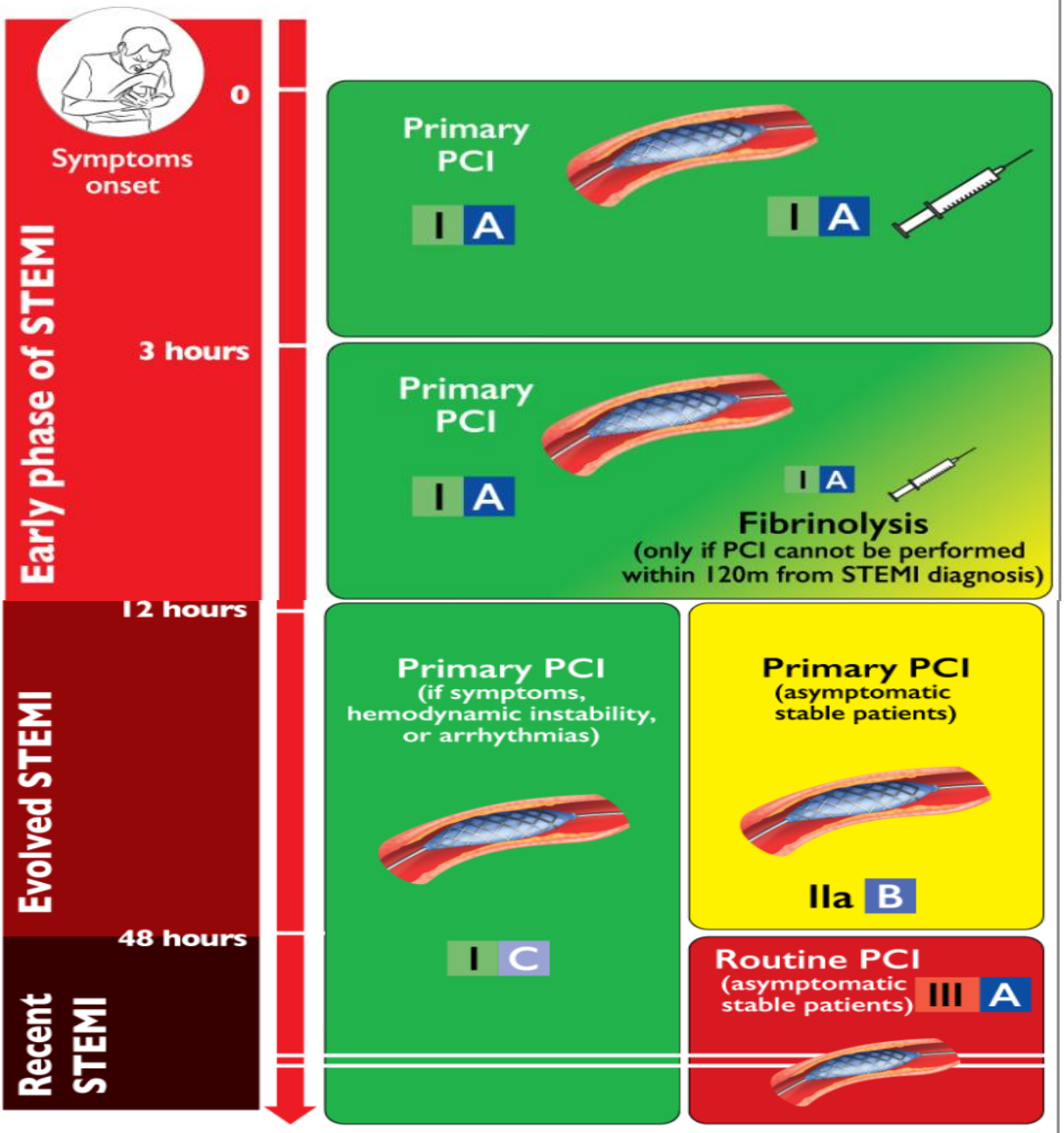
ECG = electrocardiogram; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction.

STEMI diagnosis is the time 0 for the strategy clock. The decision for choosing reperfusion strategy in patients presenting via EMS (out-of-hospital setting) or in a non-PCI centre is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion. Target times from STEMI diagnosis represent the maximum time to do specific interventions.

[a]if fibrinolysis is contra-indicated, direct for primary PCI strategy regardless of time to PCI.

[b]10 min is the maximum target delay time from STEMI diagnosis to fibrinolytic bolus administration, however, it should be given as soon as possible after STEMI diagnosis (after ruling out contra-indications).

Figure 4 Reperfusion strategies in the infarct-related artery according to time from symptoms onset.

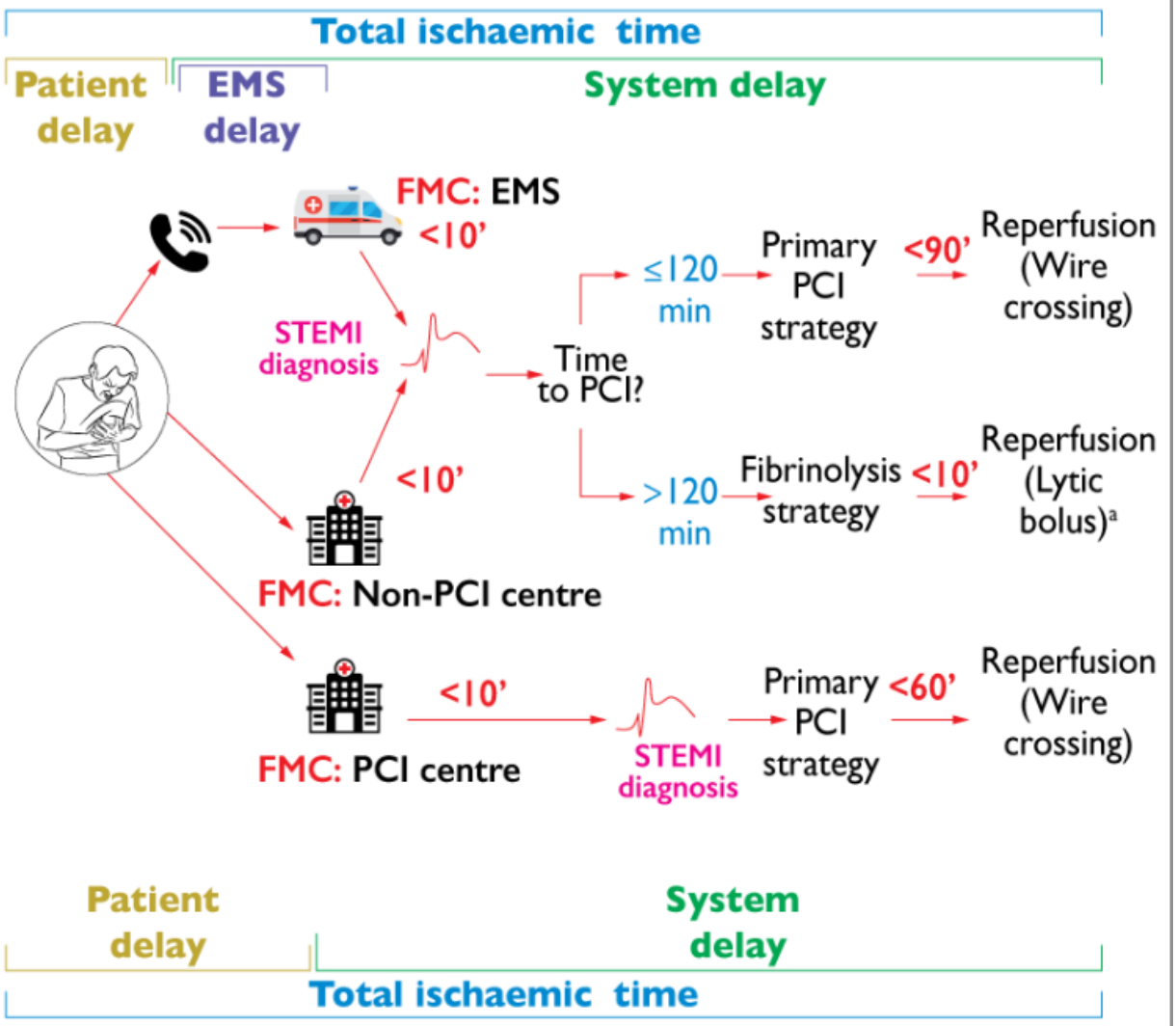


IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

In early presenters (i.e. those with STEMI diagnosis within 3 hours from symptoms onset), a primary PCI strategy is the reperfusion strategy of choice. If the anticipated time from STEMI diagnosis to PCI-mediated reperfusion is >120 min, then immediate fibrinolysis is indicated. After 3 hours (and up to 12 hours) of symptoms onset, the later the patient presents, the more consideration should be given to a primary PCI strategy as opposed to administering fibrinolytic therapy. In evolved STEMI (12–48 hours after symptoms onset), a routine primary PCI strategy (angiography and subsequent PCI if indicated) should be considered in all patients. After 48 hours (recent STEMI) angiography should be performed but routine PCI of a total occluded IRA is not recommended. Regardless of the time from symptoms onset, the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias is an indication for a primary PCI strategy.

Recommendations for reperfusion therapy		
Recommendations	**Class[a]**	**Level[b]**
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤12 hours duration and persistent ST-segment elevation.	I	A
A *primary PCI strategy* is recommended over fibrinolysis within indicated timeframes.	I	A
If timely primary PCI cannot be performed timely after STEMI diagnosis, fibrinolytic therapy is recommended within 12 hours of symptom onset in patients without contra-indications.	I	A
In the absence of ST-segment elevation, a *primary PCI strategy* is indicated in patients with suspected ongoing ischaemic symptoms suggestive of myocardial infarction and at least one of the following criteria present: • haemodynamic instability or cardiogenic shock • recurrent or ongoing chest pain refractory to medical treatment • life-threatening arrhythmias or cardiac arrest • mechanical complications of myocardial infarction • acute heart failure • recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.	I	C
Early angiography (within 24 hours) is recommended if symptoms are completely relieved and ST-segment elevation completely normalized spontaneously or after nitroglycerin administration (provided there are no recurrence of symptoms or ST-segment elevation).	I	C
In patients with time from symptom onset >12 hours, a *primary PCI strategy* is indicated in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.	I	C
A routine *primary PCI strategy* should be considered in patients presenting late (12–48 hours) after symptom onset.	IIa	B
In asymptomatic patients, routine PCI of an occluded IRA >48 hours after onset of STEMI is not indicated.	III	A

Figure 2 Modes of patient presentation, components of ischaemic time and flowchart for reperfusion strategy selection



The recommended mode of patient presentation is by alerting the EMS (call national emergency number: 112 or similar number according to region). When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or in a non-PCI centre, the decision for choosing reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when EMS arrives to the scene (see table 4 for definition of terms).

'denotes minutes.

[a]Patients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus.

Table 5 Summary of important time targets	
Intervals	**Time targets**
Maximum time from FMC to ECG and diagnosis[a]	≤10 min
Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis).	≤120 min
Maximum time from STEMI diagnosis to wire crossing in patients presenting at primary PCI hospitals.	≤60 min
Maximum time from STEMI diagnosis to wire crossing in transferred patients.	≤90 min
Maximum time from STEMI diagnosis to bolus or infusion start of fibrinoly sis in patients unable to meet primary PCI target times.	≤10 min
Time delay from start of fibrinolysis to evaluation of its efficacy (success or failure).	60–90 min
Time delay from start of fibrinolysis to angiography (if fibrinolysis is successful).	2–24 hours

There is robust evidence in favour of the radial approach as the default access site in ACS patients undergoing primary PCI by experienced radial operators. Second generation DES are the stent of choice in primary PCI setting. Revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge. As the optimal timing of revascularization (immediate vs. staged) has not been adequately investigated, no recommendation in favour of immediate versus staged multivessel PCI can be formulated.

Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class[a]	Level[b]
IRA strategy		
Primary PCI of the IRA is indicated.	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI.	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.	I	A
Routine use of thrombus aspiration is not recommended.	III	A
Routine use of deferred stenting is not recommended.	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

Patients undergoing primary PCI should receive DAPT (dual anti-platelet therapy), a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant. Routine post-procedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation.

Periprocedural and post-procedural antithrombotic therapy[c] in patients undergoing primary percutaneous coronary intervention		
Recommendations	**Class[a]**	**Level[b]**
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.	IIb	A
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin *i.v.* should be considered.	IIa	A
Routine use of bivalirudin should be considered.	IIa	A
Fondaparinux is not recommended for primary PCI.	III	B

Table 6 Doses of antiplatelet and anticoagulant co-therapies in patients undergoing primary percutaneous coronary intervention or not reperfused	
Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally or of 75–250 mg *i.v.* if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day In patients with body weight ≤60 kg, a maintenance dose of 5 mg/day is recommended. Prasugrel is contra-indicated in patients with previous stroke. In patients ≥75 years, prasugrel is generally not recommended, but a dose of 5 mg/day should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg *b.i.d.*
Abciximab	Bolus of 0.25 mg/kg *i.v.* and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 hours.
Eptifibatide	Double bolus of 180 μg/kg *i.v.* (given at a 10-min interval) followed by an infusion of 2.0 μg/kg/min for up to 18 hours.
Tirofiban	25 μg/kg over 3 min *i.v.*, followed by a maintenance infusion of 0.15 μg/kg/min for up to 18 hours.
Parenteral anticoagulant therapies	
UFH	70–100 IU/kg *i.v.* bolus when no GP IIb/IIIa inhibitor is planned 50–70 IU/kg *i.v.* bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg *i.v.* bolus.
Bivalirudin	0.75 mg/kg *i.v.* bolus followed by *i.v.* infusion of 1.75 mg/kg/hour for up to hours after the procedure.
Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day.
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally.
Parenteral anticoagulant therapies	
UFH	Same dose as with fibrinolytic therapy (see Table 7).
Enoxaparin	Same dose as with fibrinolytic therapy (see Table 7).
Fondaparinux	Same dose as with fibrinolytic therapy (see Table 7).

Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner. In the presence of contra-indications for fibrinolytic treatment it is important to weigh the potentially lifesaving effect of fibrinolysis against potentially life-threatening side effects taking into account alternative treatment options such as delayed primary PCI.

If trained medical or paramedical staff are able to analyse the ECG on-site or to transmit the ECG to the hospital for interpretation, it is recommended to initiate fibrinolytic therapy in the pre-hospital setting. The aim is to start fibrinolytic therapy within 10 min from STEMI diagnosis.

Following initiation of lytic therapy, it is recommended to transfer the patients to a PCI centre. In cases of failed fibrinolysis, or if there is evidence of reocclusion or reinfarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI is indicated. Re-administration of fibrinolysis should be discouraged. Even if it is likely that fibrinolysis will be successful, a strategy of routine early angiography (2-24h after fibrinolysis) is recommended if there are no contraindications.

Weight-adjusted *i.v.* tenecteplase, aspirin and clopidogrel given orally, and enoxaparin *i.v.* followed by *s.c.* administration until the time of PCI (revascularization), comprise the antithrombotic cocktail most extensively studied.

Fibrinolytic therapy		
Recommendations	**Class[a]**	**Level[b]**
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, reteplase) is recommended.	I	B
A half-dose of tenecteplase should be considered in patients ≥75 years of age.	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or *i.v.* aspirin is indicated.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
DAPT (in the form of aspirin plus a $P2Y_{12}$ inhibitor[c]) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days.The anticoagulant can be:	I	A
• Enoxaparin *i.v.* followed by *s.c.* (preferred over UFH).	I	A
• UFH given as a weight-adjusted *i.v.* bolus followed by infusion.	I	B
• In patients treated with streptokinase: fondaparinux *i.v.* bolus followed by a *s.c.* dose 24 hours later.	IIa	B
Transfer after fibrinolysis		
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.	I	A

Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (< 50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 hours after successful fibrinolysis.	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I	B

DAPT = dual antiplatelet therapy; IRA = infarct-related artery; *i.v.* = intravenous; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; *s.c.* = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

[a]Class of recommendation - [b]Level of evidence.

[c]Clopidogrel is the $P2Y_{12}$ inhibitor of choice as co-adjuvant and after fibrinolysis, 48 hours after fibrinolysis, switch to prasugrel/ticagrelor may be considered in patients who underwent PCI.

Doses of agents at fibrinolysis

Doses of fibrinolytic agents and antithrombotic co-therapies are listed in Table 7.

Table 7 Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Streptokinase	1.5 million units over 30–60 min *i.v.*	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg *i.v.* bolus 0.75 mg/kg *i.v.* over 30 min (up to 50 mg) then 0.5 mg/kg *i.v.* over 60 min (up to 35 mg)	
Reteplase (rPA)	10 units + 10 units *i.v.* bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single *i.v.* bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU) if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥ 90 kg It is recommended to reduce to half-dose in patients ≥75 years of age.	

Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day.	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
Doses of anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg *i.v.* bolus followed 15 min later by 1 mg/kg *s.c.* every 12 hours until revascularization or hospital discharge for a maximum of 8 days.The first two *s.c.* doses should not exceed 100 mg per injection.	
	In patients ≥ 75 years of age: no *i.v.* bolus; start with first *s.c.* dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two *s.c.* doses. In patients with eGFR <30 mL/min/1.73 m^2, regardless of age, the *s.c.* doses are given once every 24 hours.	
UFH	60 IU/kg *i.v.* bolus with a maximum of 4000 IU followed by an *i.v.* infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24–48 hours. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	2.5 mg *i.v.* bolus followed by a *s.c.* dose of 2.5 mg once daily up to 8 days or hospital discharge.	

aPTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; *i.v.* = intravenous; IU = international units; rPA = recombinant plasminogen activator; *s.c.* = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin.

Table 8 Contra-indications to fibrinolytic therapy
Absolute
Previous intracranial haemorrhage or stroke of unknown origin at anytime.
Ischaemic stroke in the preceding 6 months.
Central nervous system damage or neoplasms or arteriovenous malformation.
Recent major trauma/surgery/head injury (within the preceding month).
Gastrointestinal bleeding within the past month.
Known bleeding disorder (excluding menses).
Aortic dissection.
Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture).
Relative
Transient ischaemic attack in the preceding 6 months.
Oral anticoagulant therapy.
Pregnancy or within 1 week postpartum.
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg).
Advanced liver disease.
Infective endocarditis.
Active peptic ulcer.
Prolonged or traumatic resuscitation.

AV = arteriovenous; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Emergent CABG should be considered for patients with a patent IRA but with unsuitable anatomy for PCI and either a large myocardial area at jeopardy or with cardiogenic shock. In patients with myocardial infarction-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair.

Optimal timing for non-emergent CABG in stabilized post- myocardial infarction patients should be determined individually. Patients with haemodynamic deterioration or who are at high-risk of recurrent ischaemic events (i.e. patients with large area of myocardium at jeopardy due to critical coronary stenoses or recurrent ischaemia) should be operated on as soon as possible without waiting for the full recovery of platelet function following discontinuation of DAPT. For all other patients, a waiting period of 3–7 days may be the best compromise, while it is recommended to continue aspirin. The first aspirin administration post-CABG is recommended 6–24 h after surgery in the absence of ongoing bleeding events.

Logistical issues for hospital stay		
Recommendations	**Class[a]**	**Level[b]**
It is indicated that all hospitals participating in the care of STEMI patients have a CCU/ICCU equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.	I	C
Transfer back to a referring non-PCI hospital		
Same-day transfer should be considered appropriate in selected patients after successful primary PCI, i.e. those without ongoing myocardial ischaemia, arrhythmia, or haemodynamic instability, not requiring vasoactive or mechanical support, and not needing further early revascularization.	IIa	C
Monitoring		
It is indicated that all STEMI patients have ECG monitoring for a minimum of 24 hours.	I	C
Length of stay in the CCU		
It is indicated that patients with successful reperfusion therapy and uncomplicated clinical course are kept in the CCU/ICCU for a minimum of 24 hours whenever possible, after which they may be moved to a step-down monitored bed for an additional 24–48 hours.	I	C
Hospital discharge		
Early discharge (within 48–72 hours) should be considered appropriate in selected low-risk patients[c] if early rehabilitation and adequate follow-up are arranged.	IIa	A

CCU = coronary care unit; ICCU = intensive cardiac care unit; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation - [b]Level of evidence - [c]For example, Second Primary Angioplasty in Myocardial Infarction (PAMI-II) criteria: age <70 years, LVEF >45%, one- or two-vessel disease, successful PCI and no persistent arrhythmias.

Special patient subsets

Patients taking oral anticoagulation

Many patients presenting with STEMI are previously on oral anticoagulation or require long-term anticoagulation afterwards.

Management during STEMI: Patients taking oral anticoagulation should be triaged for primary PCI strategy regardless of the anticipated time to PCI-mediated reperfusion. Patients should receive additional parenteral anticoagulation, regardless of the timing of the last dose of oral anticoagulant. Loading of aspirin should be done as in all STEMI patients, and clopidogrel is the $P2Y_{12}$ inhibitor of choice (600 mg loading dose) before or at the latest at the time of PCI. Chronic anticoagulation regimen should not be stopped during admission. Gastric protection with a proton pump inhibitor (PPI) is recommended.

Maintenance after STEMI: Triple therapy (oral anticoagulation, aspirin and clopidogrel) should be considered for 6 months. Then, oral anticoagulation plus aspirin or clopidogrel should be considered for additional 6 months. After 1 year it is indicated to maintain only oral anticoagulation.

Elderly patients

Owing to the ageing of the population, a higher proportion of elderly patients is expected to present with STEMI. As these patients may present with atypical symptoms, the diagnosis of myocardial infarction may be delayed or missed. Elderly patients are also at particular risk of bleeding and other complications. It is, therefore, key to treat them as recommended and using specific strategies to reduce bleeding risk; these include paying attention to proper dosing of antithrombotic therapies.

Renal dysfunction

The type and dose of antithrombotic agent and the amount of contrast agent should be considered based on renal function. ACS patients with chronic kidney disease (CKD) receive frequently excess dosing with antithrombotics, contributing to the increased bleeding risk. Ensuring proper hydration during and after primary PCI and limiting the dose of contrast agents, preferentially low - osmolality contrast agents, are important steps in minimizing the risk of contrast-induced nephropathy.

Table 9: Recommended doses of antithrombotic agents in the acute care of patients with chronic kidney

Aspirin	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	No dose adjustment
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	No dose adjustment
Clopidogrel	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Loading dose of 300–600 mg orally followed by 75 mg/day.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	No dose adjustment
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	No information available

Ticagrelor	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Loading dose of 180 mg orally followed 90 mg twice a day.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	No dose adjustment
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended
Prasugrel	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Loading dose of 60 mg orally followed by 10 mg/ day.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	No dose adjustment
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended
Enoxaparin	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	1 mg/kg *s.c.* twice a day, 0.75 mg/kg *s.c.* twice daily in patients ≥75 years old.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	1 mg/kg *s.c.* once a day
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended
UFH	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	*Before coronary angiography:* Bolus 60–70 IU/kg *i.v.* (maximum 5000 IU) and infusion (12–15 IU/kg/hour, maximum 1000 IU/ hour), target aPTT 1.5–2.5 x control. *During PCI:* 70-100 IU/kg *i.v.* (50-70 IU/kg if concomitant with GP IIb/IIIa inhibitors).
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	No dose adjustment
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	No dose adjustment
Fondaparinux	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	2.5 mg *s.c.* once a day.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	Not recommended if eGFR <20 mL/min/1.73 m^2 or dialysis
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended

Bivalirudin	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Bolus 0.75 mg/kg *i.v.*, infusion 1.75 mg/kg/hour. *If eGFR ≥30 and ≤60 mL/min/1.73m^2 reduce infusion dose to 1.4 mg/kg/hour.*
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	Not recommended
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended
Abciximab	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Bolus of 0.25 mg/kg *i.v.* followed by 0.125 µg/kg/min infusion (maximum 10 µg/min).
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	Careful consideration of bleeding risk
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Careful consideration of bleeding risk
Eptifibatide	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Bolus[a] of 180 µg/kg *i.v.* followed by an infusion of 2.0 µg/kg/min for up to 18 hours. If eGFR <50 mL/min/1.73 m^2 reduce infusion dose to 1.0 µg/kg/min.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	Not recommended
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended
Tirofiban	
Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m^2)	Bolus 25 µg/kg *i.v.* followed by 0.15 µg/kg/min.
Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m^2)	Reduce infusion rate to 50%
Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)	Not recommended

aPTT = activated partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; IU = international units; *i.v.* = intravenous; PCI = percutaneous coronary intervention; *s.c.* = subcutaneous; UFH = unfractionated heparin.

[a]Double bolus if administered during primary PCI.

Management of hyperglycaemia

Recommendations	Class[a]	Level[b]
It is recommended to measure glycaemic status at initial evaluation in all patients, and perform frequent monitoring in patients with known diabetes or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥200 mg/dL).	I	C
In patients on metformin and/or SGLT2 inhibitors, renal function should be carefully monitored for at least 3 days after coronary angiography/PCI.[c]	I	C
Glucose-lowering therapy should be considered in ACS patients with glucose levels >10 mmol/L (>180 mg/dL), while episodes of hypoglycaemia (defined as glucose levels ≤ 3.9 mmol/L or ≤70 mg/dL) should be avoided.	IIa	C
Less stringent glucose control should be considered in the acute phase in patients with more advanced cardiovascular disease, older age, longer diabetes duration, and more comorbidities.	IIa	C

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; SGLT2 = sodium-glucose cotransporter-2.

[a]Class of recommendation - [b]Level of evidence.

[c]A short withdrawal of metformin may be considered after an invasive coronary procedure.

All STEMI patients should have an early assessment of short-term risk, including an evaluation of the extent of myocardial damage, the occurrence of successful reperfusion, and the presence of clinical markers of high-risk of further events.

Routine echocardiography after primary PCI is recommended to assess resting LV function, as well as RV and valve function, to exclude early post-infarction mechanical complications and LV thrombus.

Summary of indications for imaging and stress testing in ST-elevation myocardial infarction patients		
Recommendations	**Class[a]**	**Level[b]**
At presentation		
Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography.	I	C
Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain.	IIa	C
Routine echocardiography that delays emergency angiography is not recommended.	III	C
Coronary CT angiography is not recommended.	III	C
During hospital stay (after primary PCI)		
Routine echocardiography to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients.	I	B
Emergency echocardiography is indicated in haemodynamically unstable patients.	I	C
When echocardiography is suboptimal/inconclusive, an alternative imaging method (CMR preferably) should be considered.	IIa	C
Either stress echo, CMR, SPECT, or PET may be used to assess myocardial ischaemia and viability, including in multivessel CAD.	IIb	C
After discharge		
In patients with pre-discharge LVEF ≤40%, repeat echocardiography 6–12 weeks after MI, and after complete revascularization and optimal medical therapy, is recommended to assess the potential need for primary prevention ICD implantation.	I	C
When echo is suboptimal or inconclusive, alternative imaging methods (CMR preferably) should be considered to assess LV function.	IIa	C

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; PET = positron emission tomography; RV = right ventricular; SPECT = single-photon emission computed tomography.

Key lifestyle interventions include cessation of smoking, optimal blood pressure control, diet advice and weight control, and encouraging physical activity. Low treatment adherence is an important barrier to achieving optimal treatment targets and is associated with worse outcomes. Delayed outpatient follow-up after AMI results in worse short- and long-term medication adherence. Healthcare professionals and patients should be aware of this challenge and optimize communication by providing clear information, simplify treatment regimens, aim at shared decision-making, and implement repetitive monitoring and feedback. DAPT is recommended in STEMI patients who underwent primary PCI or fibrinolysis with subsequent PCI. For patients undergoing fibrinolysis without subsequent PCI and for those not reperfused, one month DAPT is recommended and prolongation up to 12 months should be considered.

Behavioural aspects after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine-replacement therapies, varenicline, and bupropion individually or in combination.	I	A
Participation in a cardiac rehabilitation programme is recommended.	I	A
A smoking-cessation protocol is indicated for each hospital participating in the care of STEMI patients.	I	C
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.	IIb	B

Maintenance antithrombotic strategy after ST-elevation myocardial infarction		
Recommendations	**Class[a]**	**Level[b]**
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contra-indicated) is recommended for 12 months after PCI unless there are contra-indications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high-risk of gastrointestinal bleeding[c].	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.	I	C
In patients who are at high-risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy[d] should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contra-indications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.	IIa	C
In high ischaemic-risk patients[e] who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered.	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.	III	C

AMI = acute myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy;
eGFR = estimated glomerular filtration rate; LV = left ventricular; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]History of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/ corticosteroid user, and ≥2 or more of the following: age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use.
[d]Oral anticoagulant, aspirin and clopidogrel.
[e]Defined as age ≥50 years, and ≥1 of the following additional high-risk features: age ≥65 years, diabetes mellitus on medication, a prior spontaneous AMI, multivessel CAD, or chronic renal dysfunction (eGFR <60 ml/min/1.73 m^2).

Routine therapies in the acute, subacute and long-term phases: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and lipid-lowering treatments after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Beta-blockers		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contra-indicated.	I	A
Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contra-indications, with no signs of acute heart failure, and with an SBP >120 mmHg.	IIa	A
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contra-indications.	IIa	B
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block or severe bradycardia.	III	B
Lipid lowering therapies		
It is recommended to start high-intensity statin therapy[c] as early as possible, unless contra-indicated, and maintain it long-term	I	A
An LDL-C goal of <1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.	I	B
It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation.	I	C

In patients with LDL-C ≥1.8 mmol/L (≥70 mg/dL) despite a maximally tolerated statin dose who remain at high-risk, further therapy to reduce LDL-C should be considered.	IIa	A
ACE-inhibitors/ARBs		
ACE-inhibitors are recommended, starting within the first 24 hours of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct.	I	A
An ARB, preferably valsartan, is an alternative to ACE-inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE-inhibitors.	I	B
ACE-inhibitors should be considered in all patients in the absence of contra-indications.	IIa	A
MRAs		
MRAs are recommended in patients with an LVEF ≤40% and heart failure or diabetes, who are already receiving an ACE-inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia.	I	B

AV = atrioventricular; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation - [b]Level of evidence - [c]High intensity statin defined as atorvastatin 40–80 mg and rosuvastatin 20–40 mg.

Mostly prescribed interventions (Class I, green, and IIa, yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered.

[1]Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous (in patients not already on an aspirin maintenance dose).

[2]Prasugrel loading dose: 60 mg.Ticagrelor loading dose: 180 mg. If there are contra-indications for prasugrel/ticagrelor or these are not available, a loading dose of clopidogrel (600 mg) is indicated.

[3]If the interventional cardiologist is not expert in radial access, the femoral route is then preferred.

[4]Enoxaparin or bivalirudin are alternatives to unfractionated heparin (Class IIa A).

[5]Aspirin maintenance dose: 75–100 mg oral.

[6]Prasugrel maintenance dose: 10 mg once daily.Ticagrelor maintenance dose: 90 mg twice daily. If there are contra-indications for prasugrel/ticagrelor or these are not available, clopidogrel maintenance (75 mg daily) is indicated.

[a]90 min represents the maximum target time to PCI-mediated reperfusion. For patients presenting in a PCI-centre, this target time is 60 min.

[b]Prolongation of ticagrelor (60 mg twice daily) in addition to aspirin may be considered for up to 36 months in patients at high ischaemic risk who have tolerated DAPT without a bleeding complication.

Figure 5 "Do not forget" interventions in STEMI patients undergoing a primary PCI strategy

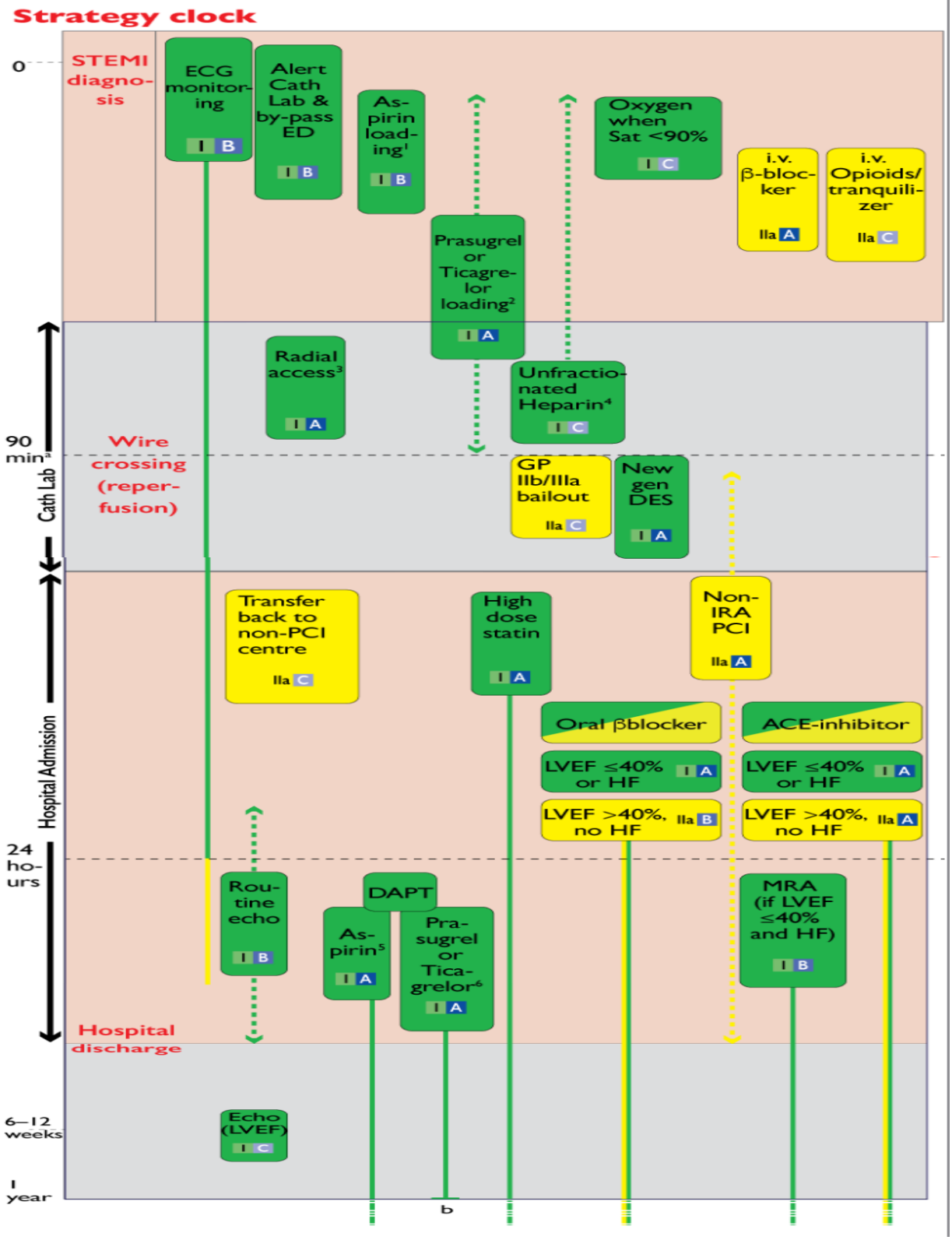
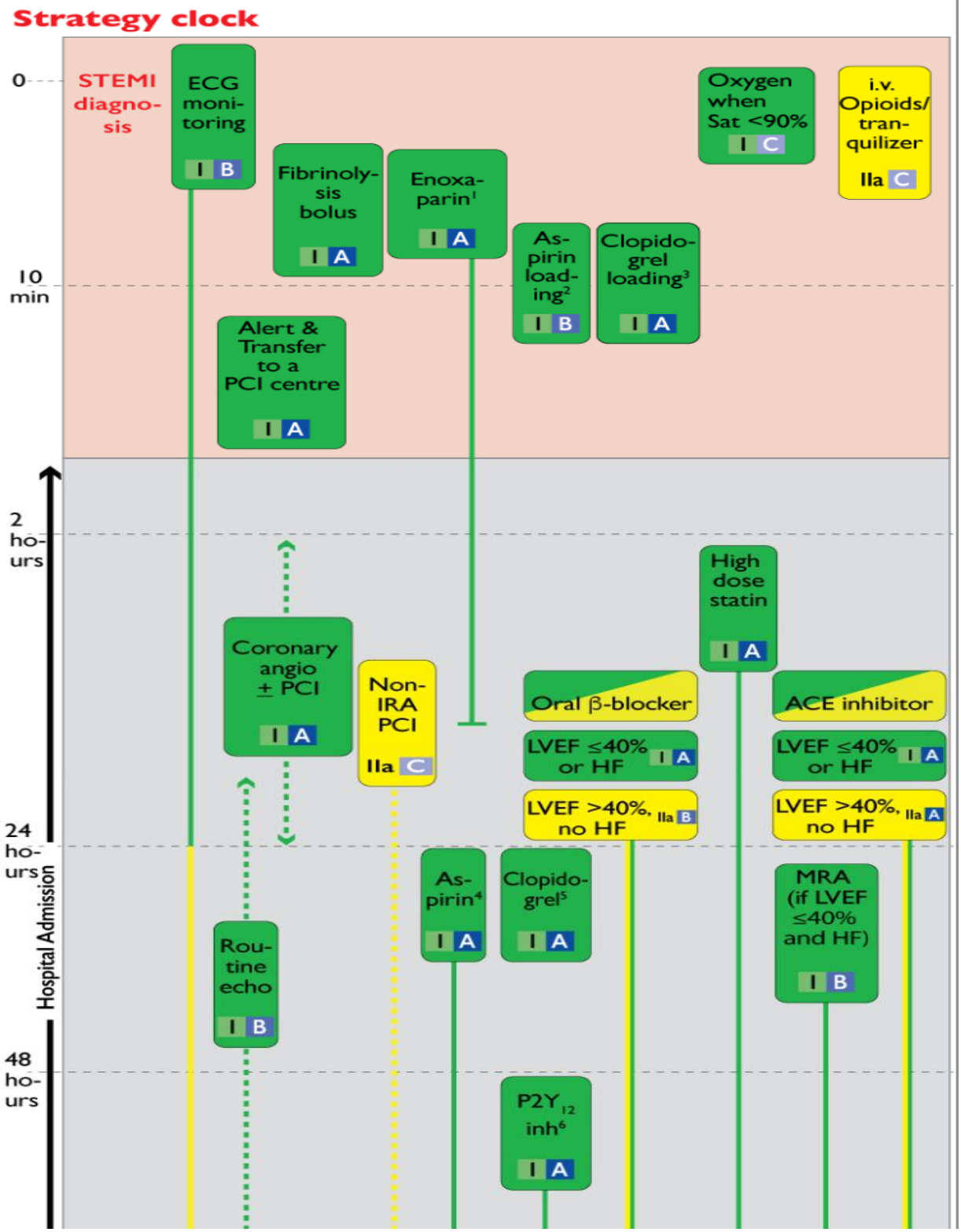
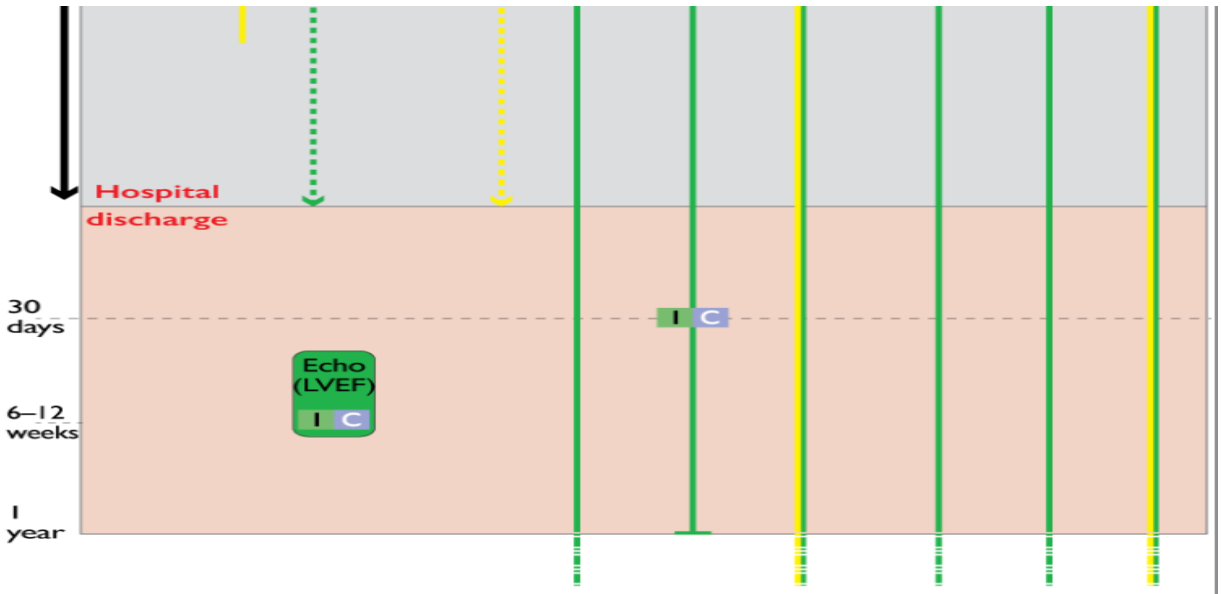


Figure 6 "Do not forget" interventions in STEMI patients undergoing a successful fibrinolysis





Mostly prescribed interventions (Class I, green, and IIa, light yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered.

[1]Enoxaparin dose: 30 mg *i.v.* bolus followed by 1 mg/kg subcutaneous every 12 hours (dose adjustment for ≥75 years and renal insufficiency is presented in Table 9).Unfractionated heparin is an alternative to enoxaparin.

[2]Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous.

[3]Clopidogrel loading dose: 300 mg oral (75 mg in ≥75 years).

[4]Aspirin maintenance dose: 75–100 mg oral.

[5]Clopidogrel maintenance therapy: 75 mg daily.

[6]48 hours after fibrinolysis, switch to prasugrel/ticagrelor may be considered in PCI-treated patients.

Recommendations for the management of left ventricular dysfunction and acute heart failure in ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
ACE-inhibitor (or if not tolerated,ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF ≤40% and/or heart failure to reduce the risk of hospitalization and death.	I	A
Beta-blocker therapy is recommended in patients with LVEF ≤40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.	I	A
An MRA is recommended in patients with heart failure and LVEF ≤40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.	I	B
Loop diuretics are recommended in patients with acute heart failure with symptoms/signs of fluid overload to improve symptoms.	I	C
Nitrates are recommended in patients with symptomatic heart failure with SBP >90 mmHg to improve symptoms and reduce congestion.	I	C
Oxygen is indicated in patients with pulmonary oedema with SaO_2 <90% to maintain a saturation >95%.	I	C
Patient intubation is indicated in patients with respiratory failure or exhaustion, leading to hypoxaemia, hypercapnia, or acidosis, and if non- invasive ventilation is not tolerated.	I	C
Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SaO_2 <90%) without hypotension.	IIa	B
Intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated SBP to control blood pressure and improve symptoms.	IIa	C
Opiates may be considered to relieve dyspnoea and anxiety in patients with pulmonary oedema and severe dyspnoea. Respiration should be monitored.	IIb	B
Inotropic agents may be considered in patients with severe heart failure with hypotension refractory to standard medical treatment.	IIb	C

Recommendations for the management of cardiogenic shock in ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended.	I	B
Invasive blood pressure monitoring with an arterial line is recommended.	I	C
Immediate Doppler echocardiography is indicated to assess ventricular and valvular functions, loading conditions, and to detect mechanical complications.	I	C
It is indicated that mechanical complications are treated as early as possible after discussion by the Heart Team.	I	C
Oxygen/mechanical respiratory support is indicated according to blood gases.	I	C
Fibrinolysis should be considered in patients presenting with cardiogenic shock if a primary PCI strategy is not available within 120 min from STEMI diagnosis and mechanical complications have been ruled out.	IIa	C
Complete revascularization during the index procedure should be considered in patients presenting with cardiogenic shock.	IIa	C
Intra-aortic balloon pumping should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa	C
Haemodynamic assessment with pulmonary artery catheter may be considered for confirming diagnosis or guiding therapy.	IIb	B
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.	IIb	B
Inotropic/vasopressor agents may be considered for haemodynamic stabilization.	IIb	C
Short-term mechanical support[c] may be considered in patients in refractory shock.	IIb	C
Routine intra-aortic balloon pumping is not indicated.	III	B

CABG = coronary artery bypass graft surgery; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation - [b]Level of evidence - [c]Percutaneous cardiac support devices, ECLS, and ECMO.

Management of atrial fibrillation		
Recommendations	**Class[a]**	**Level[b]**
Acute rate control of AF		
Intravenous beta-blockers are indicated for rate control if necessary and there are no clinical signs of acute heart failure or hypotension.	I	C
Intravenous amiodarone is indicated for rate control if necessary in the presence of concomitant acute heart failure and no hypotension.	I	C
Intravenous digitalis should be considered for rate control if necessary in the presence of concomitant acute heart failure and hypotension.	IIa	B
Cardioversion		
Immediate electrical cardioversion is indicated when adequate rate control cannot be achieved promptly with pharmacological agents in patients with AF and ongoing ischaemia, severe haemodynamic compromise or heart failure.	I	C
Intravenous amiodarone should be considered to promote electrical cardioversion and/or decrease risk for early recurrence of AF after electrical cardioversion in unstable patients with recent onset AF.	I	C
In patients with documented de novo AF during the acute phase of STEMI, long-term oral anticoagulation should be considered depending on CHA_2DS_2-VASc score and taking concomitant antithrombotic therapy into account.	IIa	C
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control.	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm.	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated.	III	B

AF = atrial fibrillation; CHA2DS2-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female); STEMI = ST-segment elevation myocardial infarction. [a]Class of recommendation - [b]Level of evidence.

Management of ventricular arrhythmias and conduction disturbances in the acute phase		
Recommendations	**Class[a]**	**Level[b]**
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contra-indicated.	I	B
Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF.	I	C
Intravenous amiodarone is recommended for treatment of recurrent polymorphic VT.	I	C
Correction of electrolyte imbalances (especially hypokalaemia and hypomagnesemia) is recommended in patients with VT and/or VF.	I	C
In cases of sinus bradycardia with haemodynamic intolerance or high degree AV block without stable escape rhythm:		
• *i.v.* positive chronotropic medication (epinephrine, vasopressin and/or atropine) is indicated	I	C
• temporary pacing is indicated in cases of failure to respond to positive chronotropic medication	I	C
• urgent angiography with a view to revascularization is indicated if the patient has not received previous reperfusion therapy.	I	C
Intravenous amiodarone should be considered for recurrent VT with haemodynamic intolerance despite repetitive electrical cardioversion.	IIa	C
Transvenous catheter pace termination and/or overdrive pacing should be considered if VT cannot be controlled by repetitive electrical cardioversion.	IIa	C
Radiofrequency catheter ablation at a specialized ablation centre followed by ICD implantation should be considered in patients with recurrent VT, VF, or electrical storm despite complete revascularization and optimal medical therapy.	IIa	C
Recurrent VT with haemodynamic repercussion despite repetitive electrical cardioversion may be treated with lidocaine if beta-blockers, amiodarone, and overdrive stimulation are not effective/applicable.	IIb	C
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful.	III	B
Asymptomatic and haemodynamically irrelevant ventricular arrhythmias should not be treated with antiarrhythmic drugs.	III	C

Long-term management of ventricular arrhythmias and risk evaluation for sudden death		
Recommendations	**Class[a]**	**Level[b]**
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (NYHA Class II–III) and LVEF ≤35% despite optimal medical therapy for >3 months and ≥6 weeks after MI, who are expected to survive for at least 1 year with good functional status.	I	A
ICD implantation or temporary use of a wearable cardioverter defibrillator may be considered <40 days after MI in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias >48 hours after STEMI onset, polymorphic VT or VF).	IIb	C

MINOCA

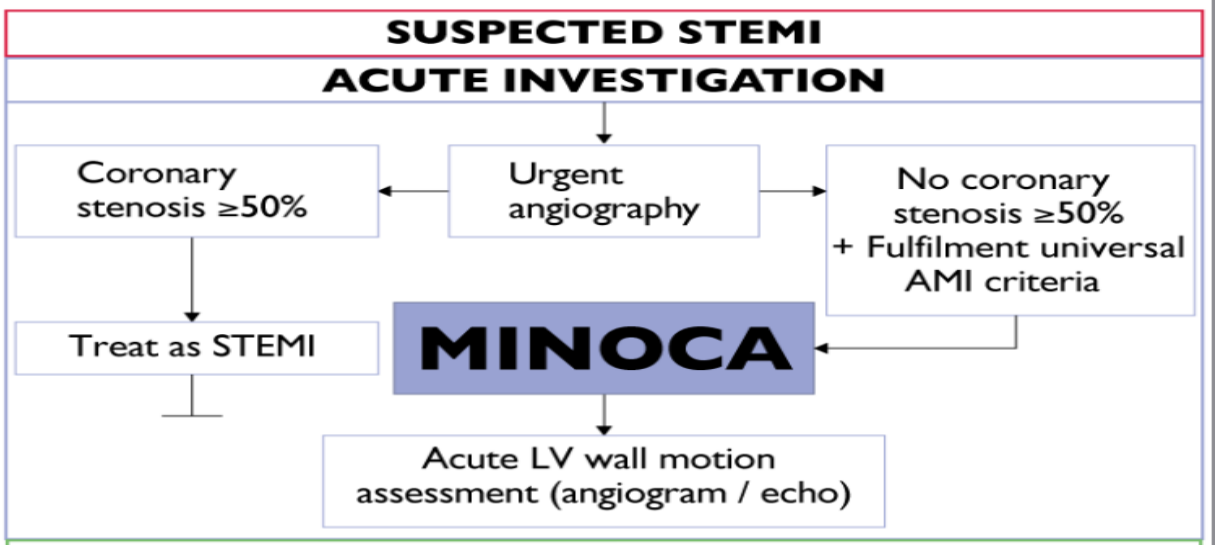
In 1–14% of MI patients there is absence of obstructive CAD. The demonstration of non-obstructive CAD in a patient presenting with symptoms suggestive of ischaemia and ST-segment elevation or equivalent does not preclude an atherothrombosis aetiology. MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes.

The identification of the underlying cause of MINOCA should lead to specific treatment strategies. Although the outcome of MINOCA strongly depends on the underlying cause, its overall prognosis is serious, with a 1-year mortality of about 3.5%.

Table 10 Diagnostic criteria for myocardial infarction with non- obstructive coronary arteries
The diagnosis of MINOCA is made immediately upon coronary angiography in a patient presenting with features consistent with an AMI, as detailed by the following criteria:
(1) Universal AMI criteria.
(2)Non-obstructive coronary arteries on angiography, defined as no coronary artery stenosis ≥50% in any potential IRA.
(3) No clinically overt specific cause for the acute presentation.

AMI = acute myocardial infarction; IRA = infarct-related artery;
MINOCA = myocardial infarction with non-obstructive coronary arteries.

Figure 7 Diagnostic test flowchart in MINOCA



SUSPECTED DIAGNOSIS AND FURTHER DIAGNOSTIC TESTS

	Non-invasive	Invasive
Myocarditis	**TTE Echo** (pericardial effusion) **CMR** (myocarditis[2], pericarditis)	**Endomyocardial biopsy** (myocarditis)
Coronary (epicardial/ microvascular)	**TTE Echo** (Regional wall motion abnormal-ities, embolic source) **CMR** (small infarction) **TOE/Bubble Contrast Echo** (Patent foramen ovale, atrial septal defect	**IVUS/OCT** (plaque disruption /dissection) **Ergonovine/ Ach test**[1] (spasm) **Pressure/ Doppler wire** (microvascular dysfunction)
Myocardial disease	**TTE Echo** **CMR** (Takotsubo, others)	
Pulmonary Embolism	**D-dimer** (Pulmonary embolism) **CT scan** (Pulmonary embolism) **Thrombophilia screen**	
Oxygen supply/ demand imbalance- Type 2 MI	**Blood tests, Extracardiac investigation**	

CMR = Cardiac Magnetic Resonance; IVUS = IntraVascular UltraSound; LV = Left Ventricle; MINOCA = Myocardial Infarction with Non-Obstructed Coronary Arteries; OCT = Optical Coherence Tomography; STEMI = ST segment Elevation Myocardial Infarction; TOE = Trans-Oesofageal Echocardiography; TTE = Trans-Thoracic Echocardiography.

Takotsubo syndrome cannot be diagnosed with certainty in the acute phase as the definition requires follow up imaging to document recovery of left ventricular function. IVUS and OCT frequently show more atherosclerotic plaque than may be appreciated on angiography.They also increase sensitivity for dissection. If intracoronary imaging is to be performed, it is appropriate to carry out this imaging at the time of the acute cardiac catheterization, after diagnostic angiography. Patients should be made aware of the additional information the test can provide and the small increase in risk associated with intracoronary imaging.

[1]Provocative testing for coronary artery spasm might be considered in selected patients with a recent AMI with suspected vasospastic angina. Provocative manoeuvres have to be always performed by operators with experience and not necessarily in the acute phase of STEMI.

[2]Clinically suspected myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus non ischemic pattern on CMR. Definite myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus endomyocardial biopsy confirmation (histology, immunohistology, polymerase-chain reaction based techniques to search for genome of infectious agents, mainly viruses).

It is recommended that STEMI networks and their individual components establish measurable quality indicators, systems to measure and compare these indicators, perform routine audits and implement strategies to ensure that every patient with STEMI receives the best possible care according to accepted standards and has the best possible outcomes. Quality indicators are intended to measure and compare the quality of health-service provision and serve as a foundation for quality improvement initiatives.

Table 11 Quality indicators

Type of indicator and process	Quality indicator
Structural measures (organization)	1) The centre should be part of a network specifically developed for the rapid and efficient management of STEMI patients with written protocols covering the following points: • *Single emergency telephone number* for patients to contact the emergency services • *Pre-hospital interpretation of the ECG* for diagnosis and strategy decision • *Pre-hospital activation* of the catheterization laboratory • *Transportation* (ambulance-helicopter) equipped with ECG defibrillators. 2) Key times to reperfusion are systematically recorded and periodically reviewed for quality assessments by the centre or network participants.

Performance measures for reperfusion therapy	1) Proportion of STEMI patients arriving in the first 12 h receiving reperfusion therapy. 2) Proportion of patients with timely reperfusion therapy, defined as: • For patients attended to in the pre-hospital setting: – <90 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI – <10 min from STEMI diagnosis to lytic bolus for reperfusion with fibrinolysis • For patients admitted to PCI centres: – <60 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI • For transferred patients: – <120 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI – <30 min door-in-door-out for patients presenting in a non- PCI centre (en route to a PCI centre)
Performance measures for risk assessment in hospital	1) Proportion of patients having LVEF assessed before discharge.
Performance measures for antithrombotic treatment in hospital	1) Proportion of patients without a clear and documented contra-indication for aspirin and/or a $P2Y_{12}$ inhibitor, discharged on DAPT.
Performance measures for discharge medication and counselling	1) Proportion of patients without contra-indications with a statin (high-intensity) prescribed at discharge. 2) Proportion of patients with LVEF ≤40% or clinical evidence of heart failure and without contra-indications with a beta-blocker prescribed at discharge. 3) Proportion of patients with LVEF ≤40% or clinical evidence of heart failure without contra-indications with an ACE-inhibitor (or ARB if not tolerated) prescribed at discharge. 4) Proportion of patients with smoking cessation advice/counselling at discharge. 5) Proportion of patients without contra-indications enrolled in a secondary prevention/cardiac rehabilitation programme at discharge.
Patient-reported outcomes	• Availability of a programme to obtain feedback regarding the patient's experience and quality of information received, including the following points: – Angina control. – Explanations provided by doctors and nurses (about the disease, benefit/risk of discharge treatments, and medical follow-up). – Discharge information regarding what to do in case of recurrence of symptoms and recommendation to attend a rehabilitation programme (including smoking cession and diet counselling).
Outcome measures	1) 30-day adjusted mortality (e.g. GRACE risk score-adjusted). 2) 30-day adjusted readmission rates.
Opportunity-based composite quality indicators	• Proportion of patients with LVEF >40% and no evidence of heart failure receiving at discharge low-dose aspirin and a $P2Y_{12}$ inhibitor and high-intensity statins. • Proportion of patients with LVEF ≤40% and/or heart failure receiving at discharge low-dose aspirin, a $P2Y_{12}$ inhibitor, high-intensity statins, an ACE-inhibitor (or ARB), and a beta-blocker

ESC European Society of Cardiology

European Heart Journal (2017) **00**, 1–66
doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

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Keywords Guidelines • Acute coronary syndromes • Acute myocardial infarction • Antithrombotic therapy • Antithrombotics • Emergency medical system • Evidence • Fibrinolysis • Ischaemic heart disease • Primary percutaneous coronary intervention • Quality indicators • MINOCA • Reperfusion therapy • Risk assessment • Secondary prevention • ST-segment elevation.

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Abbreviations and acronyms

ACE	angiotensin-converting enzyme
ACCA	Acute Cardiovascular Care Association
ACS	acute coronary syndrome
AF	atrial fibrillation
ALBATROSS	Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up
AMI	acute myocardial infarction
ARB	angiotensin II receptor blocker
ASSENT 3	ASsessment of the Safety and Efficacy of a New Thrombolytic 3
ATLANTIC	Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery
ATLAS ACS 2–TIMI 51	Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51
ATOLL	Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up
AV	atrioventricular
b.i.d.	bis in die (twice a day)
BMI	body mass index
BMS	bare-metal stent
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CAPITAL AMI	Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction
CCNAP	Council on Cardiovascular Nursing and Allied Professions
CCP	Council for Cardiology Practice;
CCU	coronary care unit
CHA_2DS_2-VASc	Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female)
CI	confidence interval
CKD	chronic kidney disease
CMR	cardiac magnetic resonance
CPG	Committee for Practice Guidelines
CRISP AMI	Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocardial Infarction
CT	computed tomography
COMFORTABLE-AMI	Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with acute myocardial infarction trial;
Compare-Acute	Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease trial
CURRENT-OASIS 7	The Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events–Seventh organization to assess strategies in ischaemic syndromes
CvLPRIT	Complete Versus Lesion-Only Primary PCI Trial
DANAMI	DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction
DANAMI 3-DEFER	DANAMI 3 – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction

DANAMI-3–PRIMULTI	DANAMI 3 – Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
EACVI	European Association of Cardiovascular Imaging
EAPC	European Association of Preventive Cardiology
EAPCI	European Association of Percutaneous Cardiovascular Interventions
EARLY-BAMI	Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
eGFR	estimated glomerular filtration rate
EHRA	European Heart Rhythm Association
EMS	emergency medical system
EPHESUS	Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study
ESC	European Society of Cardiology
EXAMINATION	Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction
ExTRACT–TIMI 25	Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction
FFR	fractional flow reserve
FMC	first medical contact
FOCUS	Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk trial.
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Events
GRACIA	Grupo de Análisis de la Cardiopatía Isquémica Aguda
HDL-C	high-density lipoprotein cholesterol
HFA	Heart Failure Association
HR	hazard ratio
IABP	intra-aortic balloon pump
ICCU	intensive cardiac care unit
ICD	implantable cardioverter defibrillator
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IRA	infarct-related artery
IU	international units
i.v.	intravenous
LBBB	left bundle branch block
LDL-C	low-density lipoprotein cholesterol
LGE	late gadolinium enhancement
LV	left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	left ventricular ejection fraction
MACE	major adverse cardiac event
MATRIX	Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX
METOCARD-CNIC	Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction
MI	myocardial infarction
MINOCA	myocardial infarction with non-obstructive coronary arteries
MRA	mineralocorticoid receptor antagonist
MVO	microvascular obstruction
NORSTENT	Norwegian Coronary Stent
NSTEMI	non-ST-segment elevation myocardial infarction
NT-proBNP	N-terminal pro B-type natriuretic peptide
OASIS-6	Organization for the Assessment of Strategies for Ischemic Syndromes
o.d.	omni die (once a day)
PAMI-II	Second Primary Angioplasty in Myocardial Infarction
PaO_2	partial pressure of oxygen
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin/kexin type 9
PEGASUS-TIMI 54	Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54
PET	positron emission tomography
PIONEER AF-PCI	Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention
p.o.	per os (orally)
PPI	proton pump inhibitor
PRAMI	Preventive Angioplasty in Acute Myocardial Infarction
PRODIGY	PROlonging Dual Antiplatelet Treatment After Grading stent-induced Intimal hyperplasia studY
RBBB	right bundle branch block
REMINDER	A Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction
RIFLE-STEACS	Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome
RIVAL	Radial Versus Femoral Access for Coronary intervention
RV	right ventricle/ventricular
SaO_2	arterial oxygen saturation

SBP	systolic blood pressure
s.c.	subcutaneous
SGLT2	sodium-glucose co-transporter-2
SPECT	single-photon emission computed tomography
STEMI	ST-segment elevation myocardial infarction
STREAM	STrategic Reperfusion Early After Myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
TNK-tPA	Tenecteplase tissue plasminogen activator
TOTAL	Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI
tPA	tissue plasminogen activator
UFH	unfractionated heparin
VALIANT	VALsartan In Acute myocardial iNfarcTion
VF	ventricular fibrillation
VT	ventricular tachycardia
24/7	24 h a day, seven days a week

1. Preamble

Guidelines summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for an individual patient with a given condition. Guidelines and their recommendations should facilitate decision making of health professionals in their daily practice. However, the final decisions concerning an individual patient must be made by the responsible health professional(s) in consultation with the patient and caregiver as appropriate.

A great number of guidelines have been issued in recent years by the European Society of Cardiology (ESC), as well as by other societies and organisations. Because of the impact on clinical practice, quality criteria for the development of guidelines have been established in order to make all decisions transparent to the user. The recommendations for formulating and issuing ESC Guidelines can be found on the ESC website (https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Guidelines-development/Writing-ESC-Guidelines). ESC Guidelines represent the official position of the ESC on a given topic and are regularly updated.

Members of this Task Force were selected by the ESC, including representation from its relevant ESC sub-specialty groups, in order to represent professionals involved with the medical care of patients with this pathology. Selected experts in the field undertook a comprehensive review of the published evidence for management of a given condition according to ESC Committee for Practice Guidelines (CPG) policy. A critical evaluation of diagnostic and therapeutic procedures was performed, including assessment of the risk–benefit ratio. The level of evidence and the strength of the recommendation of particular management options were weighed and graded according to predefined scales, as outlined in *Tables 1* and *2*.

The experts of the writing and reviewing panels provided declaration of interest forms for all relationships that might be perceived as real or potential sources of conflicts of interest. These forms were compiled into one file and can be found on the ESC website (http://www.escardio.org/guidelines). Any changes in declarations of interest that arise during the writing period were notified to the ESC and updated. The Task Force received its entire financial support from the ESC without any involvement from the healthcare industry.

The ESC CPG supervises and coordinates the preparation of new ESC Guidelines. The Committee is also responsible for the endorsement process of these Guidelines. The ESC Guidelines undergo extensive review by the CPG and external experts. After appropriate revisions the Guidelines are approved by all the experts involved in the Task Force. The finalized document is approved by the CPG for publication in the European Heart Journal. The Guidelines were developed after careful consideration of the scientific and medical knowledge and the evidence available at the time of their dating.

Table 1 Classes of recommendations

Classes of recommendations	Definition	Suggested wording to use
Class I	**Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.**	**Is recommended/is indicated**
Class II	**Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.**	
Class IIa	***Weight of evidence/opinion is in favour of usefulness/efficacy.***	**Should be considered**
Class IIb	***Usefulness/efficacy is less well established by evidence/opinion.***	**May be considered**
Class III	**Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.**	**Is not recommended**

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Table 2 Levels of evidence

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

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The task of developing ESC Guidelines also includes the creation of educational tools and implementation programmes for the recommendations including condensed pocket guideline versions, summary slides, booklets with essential messages, summary cards for non-specialists and an electronic version for digital applications (smartphones, etc.). These versions are abridged and thus, if needed, one should always refer to the full text version, which is freely available via the ESC website and hosted on the EHJ website. The National Societies of the ESC are encouraged to endorse, translate and implement all ESC Guidelines. Implementation programmes are needed because it has been shown that the outcome of disease may be favourably influenced by the thorough application of clinical recommendations.

Surveys and registries are needed to verify that real-life daily practice is in keeping with what is recommended in the guidelines, thus completing the loop between clinical research, writing of guidelines, disseminating them and implementing them into clinical practice.

Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies. However, the ESC Guidelines do not override in any way whatsoever the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient or the patient's caregiver where appropriate and/or necessary. It is also the health professional's responsibility to verify the rules and regulations applicable to drugs and devices at the time of prescription.

2. Introduction

Updates on the management of patients presenting with ST-segment elevation myocardial infarction (STEMI) should be based on sound evidence, derived from well-conducted clinical trials whenever possible, or motivated expert opinion when needed. It must be recognized that, even when excellent clinical trials have been undertaken, the results are open to interpretation and treatments may need to be adapted to take account of clinical circumstances and resources.

The present Task Force has made an important effort to be as aligned as possible with the other ESC Guidelines[1–6] and consensus documents, including the simultaneously published update on dual antiplatelet therapy (DAPT),[7] for consistency in the ESC Guidelines strategy. The levels of evidence and the strengths of recommendation of particular treatment options were weighed and graded according to pre-defined scales, as outlined in *Tables 1* and 2. Despite recommendations with a level of evidence being based on expert opinion, this Task Force decided to add references to guide the reader regarding data that were taken into consideration for these decisions in some cases.

2.1 Definition of acute myocardial infarction

The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia.[8] For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms suggestive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated as having a non-ST-segment elevation myocardial infarction (MI) (NSTEMI) and separate guidelines have recently been developed for these.[2] Some patients with MI develop Q-waves (Q-wave MI), but many do not (non-Q-wave MI).

In addition to these categories, MI is classified into various types, based on pathological, clinical, and prognostic differences, along with different treatment strategies (see the Third Universal Definition of MI document,[8] which will be updated in 2018). Despite the fact that the majority of STEMI patients are classified as a type 1 MI (with evidence of a coronary thrombus), some STEMIs fall into other MI types.[8] MI, even presenting as STEMI, also occurs in the absence of obstructive coronary artery disease (CAD) on angiography.[9–12] This type of MI is termed 'myocardial infarction with non-obstructive coronary arteries' (MINOCA) and is discussed in Chapter 9 of this document.

2.2 Epidemiology of ST-segment elevation myocardial infarction

Worldwide, ischaemic heart disease is the single most common cause of death and its frequency is increasing. However, in Europe, there has been an overall trend for a reduction in ischaemic heart disease mortality over the past three decades.[13] Ischaemic heart disease now accounts for almost 1.8 million annual deaths, or 20% of all deaths in Europe, although with large variations between countries.[14]

The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively.[15,16] Probably the most comprehensive European STEMI registry is found in Sweden, where the incidence rate of STEMI was 58 per 100 000 per year in 2015.[17] In other European countries, the incidence rate ranged from 43 to 144 per 100 000 per year.[18] Similarly, the reported adjusted incidence rates from the USA decreased from 133 per 100 000 in 1999 to 50 per 100 000 in 2008, whereas the incidence of NSTEMI remained constant or increased slightly.[19] There is a consistent pattern for STEMI to be relatively more common in younger than in older people, and more common in men than in women.[17,20]

The mortality in STEMI patients is influenced by many factors, among them advanced age, Killip class, time delay to treatment,

presence of emergency medical system (EMS)-based STEMI networks, treatment strategy, history of MI, diabetes mellitus, renal failure, number of diseased coronary arteries, and left ventricular ejection fraction (LVEF). Several recent studies have highlighted a fall in acute and long-term mortality following STEMI in parallel with greater use of reperfusion therapy, primary percutaneous coronary intervention (PCI), modern antithrombotic therapy, and secondary prevention.[14,21,22] Nevertheless, mortality remains substantial; the in-hospital mortality of unselected patients with STEMI in the national registries of the ESC countries varies between 4 and 12%,[23] while reported 1-year mortality among STEMI patients in angiography registries is approximately 10%.[24,25]

Although ischaemic heart disease develops on average 7–10 years later in women compared with men, MI remains a leading cause of death in women. Acute coronary syndrome (ACS) occurs three to four times more often in men than in women below the age of 60 years, but after the age of 75, women represent the majority of patients.[26] Women tend to present more often with atypical symptoms, up to 30% in some registries,[27] and tend to present later than men.[28,29] It is therefore important to maintain a high degree of awareness for MI in women with potential symptoms of ischaemia. Women also have a higher risk of bleeding complications with PCI. There is an ongoing debate regarding whether outcomes are poorer in women, with several studies indicating that a poorer outcome is related to older age and more comorbidities among women suffering MI.[26,30,31] Some studies have indicated that women tend to undergo fewer interventions than men and receive reperfusion therapy less frequently.[26,32,33] These guidelines aim to highlight the fact that women and men receive equal benefit from a reperfusion strategy and STEMI-related therapy, and that both genders must be managed in a similar fashion.

3. What is new in the 2017 version?

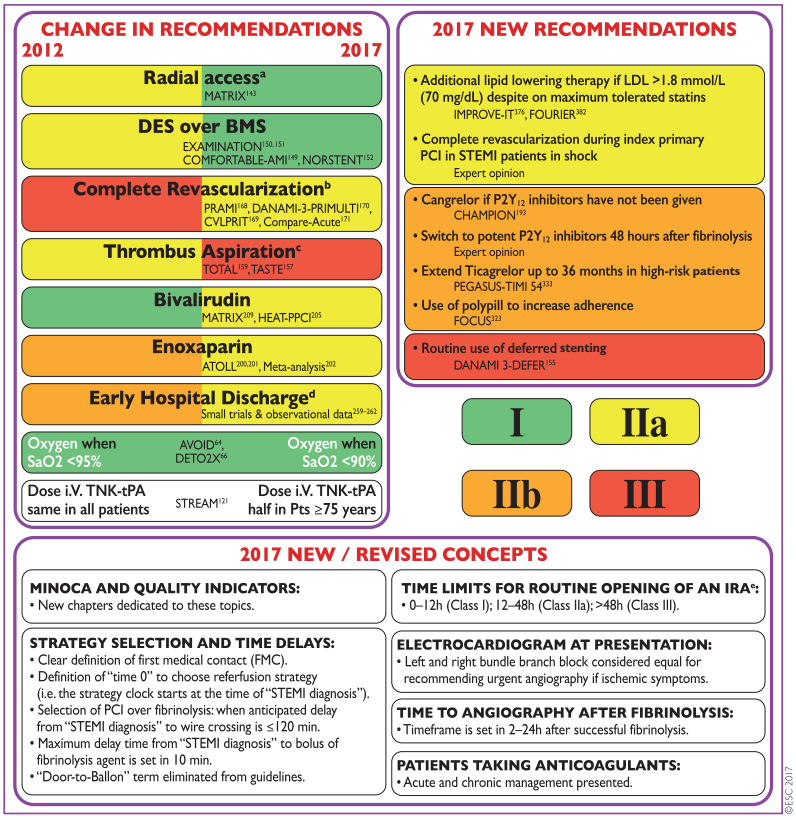

Figure 1 What is new in 2017 STEMI Guidelines. BMS = bare metal stent; DES = drug eluting stent; IRA = infarct related artery; i.v. = intravenous; LDL = low-density lipoprotein; PCI = percutaneous coronary intervention; SaO2 = arterial oxygen saturation; STEMI = ST-elevation myocardial infarction; TNK-tPA = Tenecteplase tissue plasminogen activator. For explanation of trial names, see list of.
[a]Only for experienced radial operators.
[b]Before hospital discharge (either immediate or staged).
[c]Routine thrombus aspiration (bailout in certain cases may be considered).
[d]In 2012 early discharge was considered after 72h, in 2017 early discharge is 48–72h.
[e]If symptoms or haemodynamic instability IRA should be opened regardless time from symptoms onset.
In left and mid panels, below each recommendation, the most representative trial (acronym and reference) driving the indication is mentioned.

4. Emergency care

4.1 Initial diagnosis

Management—including diagnosis and treatment—of STEMI starts from the point of first medical contact (FMC, defined in *Table 4*). It is recommended that a regional reperfusion strategy should be established to maximize efficiency.

A working diagnosis of STEMI (called the 'STEMI diagnosis' throughout this document) must first be made. This is usually based on symptoms consistent with myocardial ischaemia (i.e. persistent chest pain) and signs [i.e. 12-lead electrocardiogram (ECG)]. Important clues are a history of CAD and radiation of pain to the neck, lower jaw, or left arm. Some patients present with less-typical symptoms such as shortness of breath, nausea/vomiting, fatigue, palpitations, or syncope.[34] A reduction in chest pain after nitroglycerin (glyceryl trinitrate) administration can be misleading and is not recommended as a diagnostic manoeuvre.[35] In cases of symptom relief after nitroglycerin administration, another 12-lead ECG must be obtained. A complete normalization of the ST-segment elevation after nitroglycerin administration, along with complete relief of symptoms, is suggestive of coronary spasm, with or without associated MI. In these cases, an early coronary angiography (within 24 h) is recommended. In cases of recurrent episodes of ST-segment elevation or chest pain, immediate angiography is required.

It is recommended to initiate ECG monitoring as soon as possible in all patients with suspected STEMI in order to detect life-threatening arrhythmias and allow prompt defibrillation if indicated. When a STEMI is suspected, a 12-lead ECG must be acquired and interpreted as soon as possible at the time of FMC to facilitate early STEMI diagnosis and triage.[36–40]

In patients with a clinical suspicion of myocardial ischaemia and ST-segment elevation, reperfusion therapy needs to be initiated as soon as possible.[41] If the ECG is equivocal or does not show evidence to support the clinical suspicion of MI, ECGs should be repeated and, when possible compared with previous recordings. If interpretation of pre-hospital ECG is not possible on-site, field transmission of the ECG is recommended.[42]

ECG criteria are based on changes of electrical currents of the heart (measured in millivolts). Standard calibration of the ECG is 10mm/mV. Therefore 0.1 mV equals to 1 mm square on the vertical axis. For simplicity, in this document ECG deviations are expressed in mm following the standard calibration.

In the proper clinical context, ST-segment elevation (measured at the J-point) is considered suggestive of ongoing coronary artery acute occlusion in the following cases: at least two contiguous leads with ST-segment elevation $\geq$ 2.5 mm in men < 40 years, $\geq$2 mm in men $\geq$ 40 years, or $\geq$ 1.5 mm in women in leads V_2–V_3 and/or $\geq$ 1 mm in the other leads [in the absence of left ventricular (LV) hypertrophy or left bundle branch block LBBB)].[8] In patients with inferior MI, it is recommended to record right precordial leads (V_3R and V_4R) seeking ST-segment elevation, to identify concomitant right ventricular (RV) infarction.[8,43] Likewise, ST-segment depression in leads V_1–V_3 suggests myocardial ischaemia, especially when the terminal T-wave is positive (ST-segment elevation equivalent), and confirmation by concomitant ST-segment elevation $\geq$ 0.5 mm recorded in leads V_7–V_9 should be considered as a means to identify posterior MI.[8] The presence of a Q-wave on the ECG should not necessarily change the reperfusion strategy decision.

Recommendations for initial diagnosis

Recommendations	Class[a]	Level[b]
ECG monitoring		
12-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.[36,38]	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.[44,45]	I	B
The use of additional posterior chest wall leads (V_7–V_9) in patients with high suspicion of posterior MI (circumflex occlusion) should be considered.[8,46–49]	IIa	B
The use of additional right precordial leads (V_3R and V_4R) in patients with inferior MI should be considered to identify concomitant RV infarction.[8,43]	IIa	B
Blood sampling		
Routine blood sampling for serum markers is indicated as soon as possible in the acute phase but should not delay reperfusion treatment.[8]	I	C

ECG = electrocardiogram; FMC = first medical contact; MI = myocardial infarction; RV = right ventricle; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

The ECG diagnosis may be more difficult in some cases, which nevertheless deserve prompt management and triage. Among these:

Bundle branch block. In the presence of LBBB, the ECG diagnosis of AMI is difficult but often possible if marked ST-segment abnormalities are present. Somewhat complex algorithms have been offered to assist the diagnosis,[50,51] but they do not provide diagnostic certainty.[52] The presence of concordant ST-segment elevation (i.e. in leads with positive QRS deflections) appears to be one of the best indicators of ongoing MI with an occluded infarct artery.[53] Patients with a clinical suspicion of ongoing myocardial ischaemia and LBBB should be managed in a way similar to STEMI patients, regardless of whether the LBBB is previously known. It is important to remark that the presence of a (presumed) new LBBB does not predict an MI per se.[54]

Patients with MI and right bundle branch block (RBBB) have a poor prognosis.[55] It may be difficult to detect transmural ischaemia in patients with chest pain and RBBB.[55] Therefore, a primary PCI strategy (emergent coronary angiography and PCI if indicated) should be considered when persistent ischaemic symptoms occur in the presence of RBBB.

Ventricular pacing. Pacemaker rhythm may also prevent interpretation of ST-segment changes and may require urgent angiography to confirm diagnosis and initiate therapy. Reprogramming the pacemaker—allowing an evaluation of ECG changes during intrinsic heart rhythm—may be considered in patients who are not dependent on ventricular pacing, without delaying invasive investigation.[56,57]

Non-diagnostic ECG. Some patients with an acute coronary occlusion may have an initial ECG without ST-segment elevation, sometimes because they are seen very early after symptom onset (in which case, one should look for hyper-acute T-waves, which may precede ST-segment elevation). It is important to repeat the ECG or monitor for dynamic ST-segment changes. In addition, there is a concern that some patients with acute occlusion of a coronary artery and ongoing MI, such as those with an occluded circumflex coronary artery,[58,59] acute occlusion of a vein graft, or left main disease, may present without ST-segment elevation and be denied reperfusion therapy, resulting in a larger infarction and worse outcomes. Extending the standard 12-lead ECG with V_7–V_9 leads may identify some of these patients. In any case, suspicion of ongoing myocardial ischaemia is an indication for a primary PCI strategy even in patients without diagnostic ST-segment elevation.[8,38,46–49] *Table 3* lists the atypical ECG presentations that should prompt a primary PCI strategy in patients with ongoing symptoms consistent with myocardial ischaemia.

Isolated posterior MI. In AMI of the inferior and basal portion of the heart, often corresponding to the left circumflex territory, isolated ST-segment depression $\geq$ 0.5 mm in leads V_1–V_3 represents the dominant finding. These should be managed as a STEMI. The use of additional posterior chest wall leads [elevation V_7–V_9 $\geq$ 0.5 mm ($\geq$1 mm in men, 40 years old)] is recommended to detect ST-segment elevation consistent with inferior and basal MI.

Left main coronary obstruction. The presence of ST depression $\geq$ 1 mm in six or more surface leads (inferolateral ST depression), coupled with ST-segment elevation in aVR and/or V_1, suggests multivessel ischemia or left main coronary artery obstruction, particularly if the patient presents with haemodynamic compromise.[60]

Blood sampling for serum markers is routinely carried out in the acute phase. This is indicated, but should not delay the reperfusion strategy/treatment.

If in doubt regarding the possibility of acute evolving MI, emergency imaging aids the provision of timely reperfusion therapy to these patients. Recommendations for the use of echocardiography for initial diagnosis are described in section 6.6.2. If echocardiography is not available or if doubts persist after echo, a primary PCI strategy is indicated (including immediate transfer to a PCI centre if the patient is being treated in a non-PCI centre).

In the STEMI emergency setting, there is no role for routine computed tomography (CT). Use of CT should be confined to selected cases where acute aortic dissection or pulmonary embolism is suspected, but CT is not recommended if STEMI diagnosis is likely.

Some non-AMI conditions can present with symptoms and ECG findings similar to STEMI. An emergency coronary angiography is therefore indicated in these cases (Chapter 9 expands on this topic).

Table 3 Atypical electrocardiographic presentations that should prompt a primary percutaneous coronary intervention strategy in patients with ongoing symptoms consistent with myocardial ischaemia

Bundle branch block Criteria that can be used to improve the diagnostic accuracy of STEMI in LBBB[50]: • Concordant ST-segment elevation ≥1 mm in leads with a positive QRS complex • Concordant ST-segment depression ≥1 mm in V_1–V_3 • Discordant ST-segment elevation ≥5 mm in leads with a negative QRS complex The presence of RBBB may confound the diagnosis of STEMI
Ventricular paced rhythm During RV pacing, the ECG also shows LBBB and the above rules also apply for the diagnosis of myocardial infarction during pacing; however, they are less specific
Isolated posterior myocardial infarction Isolated ST depression ≥0.5 mm in leads V_1–V_3 and ST-segment elevation (≥0.5 mm) in posterior chest wall leads V_7–V_9
Ischaemia due to left main coronary artery occlusion or multivessel disease ST depression ≥1 mm in eight or more surface leads, coupled with ST-segment elevation in aVR and/or V_1, suggests left main-, or left main equivalent- coronary obstruction, or severe three vessel ischaemia

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ECG = electrocardiogram; LBBB = left bundle branch block; RBBB = right bundle branch block; RV = right ventricular; STEMI = ST-segment elevation myocardial infarction.

4.2 Relief of pain, breathlessness, and anxiety

Relief of pain is of paramount importance, not only for comfort reasons but because the pain is associated with sympathetic activation, which causes vasoconstriction and increases the workload of the heart. Titrated intravenous (i.v.) opioids (e.g. morphine) are the analgesics most commonly used in this context. However, morphine use is associated with a slower uptake, delayed onset of action, and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagrelor, and prasugrel), which may lead to early treatment failure in susceptible individuals.[61–63]

Relief of hypoxaemia and symptoms

Recommendations	Class[a]	Level[b]
Hypoxia		
Oxygen is indicated in patients with hypoxaemia (SaO_2 < 90% or PaO_2 < 60 mmHg).	I	C
Routine oxygen is not recommended in patients with SaO_2 $\geq$ 90%.[64–66]	III	B
Symptoms		
Titrated i.v. opioids should be considered to relieve pain.	IIa	C
A mild tranquillizer (usually a benzodiazepine) should be considered in very anxious patients.	IIa	C

i.v. = intravenous; PaO_2 = partial pressure of oxygen; SaO_2 = arterial oxygen saturation.
[a]Class of recommendation.
[b]Level of evidence.

Oxygen is indicated in hypoxic patients with arterial oxygen saturation (SaO_2) < 90%. There is some evidence suggesting that hyperoxia may be harmful in patients with uncomplicated MI, presumably due to increased myocardial injury.[64–67] Thus, routine oxygen is not recommended when SaO_2 is ≥ 90%.

Anxiety is a natural response to the pain and the circumstances surrounding an MI. Reassurance of patients and those closely associated with them is of great importance.

A mild tranquillizer (usually a benzodiazepine) should be considered in anxious patients.

4.3 Cardiac arrest

Many deaths occur very early after STEMI onset due to ventricular fibrillation (VF).[68] As this arrhythmia frequently occurs at an early stage, these deaths usually happen out of hospital. It is indicated that all medical and paramedical personnel caring for patients with suspected MI have access to defibrillation equipment and are trained in cardiac life support, and that, at the point of FMC, ECG monitoring must be implemented immediately for all patients with suspected MI.

Patients with chest pain suggestive of MI should be directed through public awareness programmes to contact the EMS and wait to be transferred to the hospital by the EMS.

In patients following cardiac arrest and ST-segment elevation on the ECG, primary PCI is the strategy of choice.[69–74]

Given the high prevalence of coronary occlusions and the potential difficulties in interpreting the ECG in patients after cardiac arrest, urgent angiography (within 2 h)[2] should be considered in survivors of cardiac arrest, including unresponsive survivors, when there is a high index of suspicion of ongoing infarction (such as the presence of chest pain before arrest, a history of established CAD, and abnormal or uncertain ECG results).[73,74] However, in patients without ST-segment elevation, a quick evaluation at the emergency department or intensive cardiac care unit (ICCU) to exclude non-coronary causes (cerebrovascular event, respiratory failure, non-cardiogenic shock, pulmonary embolism, and intoxication), and to perform urgent echocardiography, is reasonable. The decision to perform urgent coronary angiography and PCI if indicated should also take into account factors associated with poor neurological outcome. Unfavourable pre-hospital settings indicating a remote likelihood for neurological recovery [i.e. unwitnessed cardiac arrest, late arrival of a pre-hospital team without lay basic life support (>10 min), presence of an initial non-shockable rhythm, or more than 20 min of advanced life support without return to spontaneous circulation][75] should be taken strongly into consideration to argue against an invasive coronary strategy.[73]

Unconscious patients admitted to critical care units after out-of-hospital cardiac arrest are at high risk for death, and neurologic deficits are common among those who survive.[76] Targeted temperature management (also called therapeutic hypothermia), aiming for a constant temperature between 32 and 36 °C for at least 24 h, is indicated in patients who remain unconscious after resuscitation from cardiac arrest (of presumed cardiac cause).[73,77–82] However, hypothermia conditions are associated with slow uptake, delayed onset of action, and diminished effects of oral antiplatelet agents (i.e. clopidogrel, ticagrelor, and prasugrel). Moreover, metabolic conversion of clopidogrel in the liver may be reduced in hypothermia conditions.[83] Cooling should not delay primary PCI and can be started in parallel in the catheterization laboratory. Close attention to anticoagulation needs to be paid in patients reaching low temperatures.[84]

Prevention and improved treatment of out-of-hospital cardiac arrest is crucial to reduce the mortality related to CAD. For a more detailed discussion of these issues, refer to the recent European Resuscitation Council Guidelines for resuscitation.[74]

Cardiac arrest

Recommendations	Class[a]	Level[b]
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.[69–71,85]	I	B
Targeted temperature management[c] is indicated early after resuscitation of cardiac arrest patients who remain unresponsive.[77,78,80–82]	I	B
It is indicated that healthcare systems implement strategies to facilitate transfer of all patients in whom a MI is suspected directly to the hospital offering 24/7 PCI-mediated reperfusion therapy via one specialized EMS.	I	C
It is indicated that all medical and paramedical personnel caring for patients with suspected MI have access to defibrillation equipment and are trained in basic cardiac life support.	I	C
Urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST-segment elevation but with a high suspicion of ongoing myocardial ischaemia.[69–71,73]	IIa	C
Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended.[86]	III	B

24/7 = 24 h a day, 7 days a week; ECG = electrocardiogram; EMS = emergency medical system; i.v. = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Targeted temperature management refers to active methods (i.e. cooling catheters, cooling blankets, and application of ice applied around the body) to achieve and maintain a constant specific body temperature between 32 and 36 °C in a person for a specific duration of time (most commonly used ≥ 24 h).

4.4 Pre-hospital logistics of care

4.4.1 Delays

Treatment delays are the most easily audited index of quality of care in STEMI; they should be recorded in every system providing care to STEMI patients and be reviewed regularly, to ensure that simple quality of care indicators are met and maintained over time (see Chapter

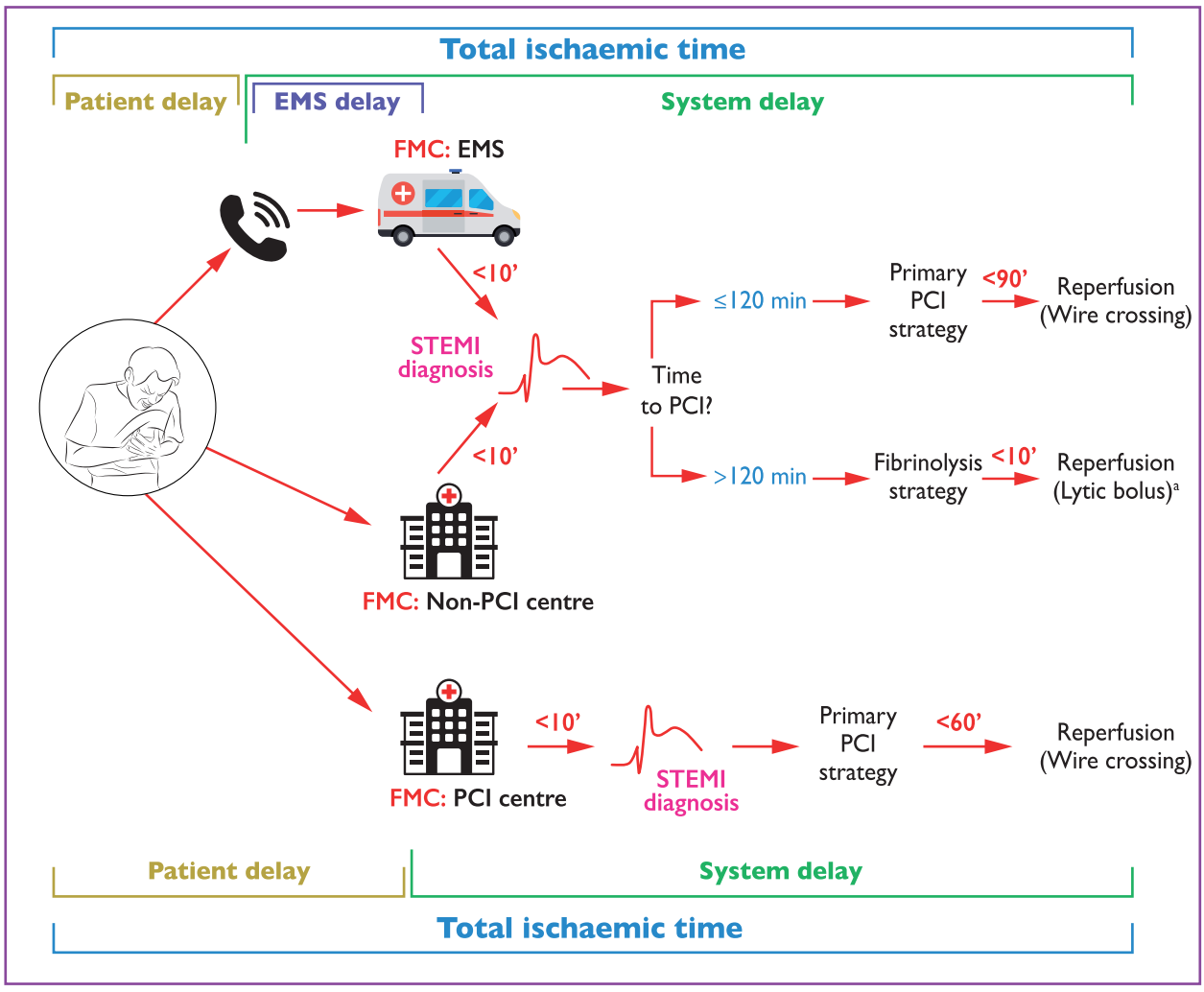

Figure 2 Modes of patient presentation, components of ischaemia time and flowchart for reperfusion strategy selection. EMS = Emergency Medical System; FMC = First Medical Contact; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. The recommended mode of patient presentation is by alerting the EMS (call national emergency number: 112 or similar number according to region). When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or in a non-PCI centre, the decision for choosing reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when EMS arrives to the scene (see *Table 4*). ′denotes minutes. [a]Patients with fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus.

10). If projected target times are not met, then interventions are needed to improve performance of the system. Components of the ischaemic time, delays of initial management, and selection of reperfusion strategy are shown in *Figure 2*.

To minimize patient delay, it is recommended to increase public awareness of how to recognize common symptoms of AMI and to call the emergency services. All components of the system delay represent the quality of care and it is recommended to measure them as quality indicators (see Chapter 10).

In hospitals and EMS participating in the care of STEMI patients, the goal is to reduce the delay between FMC and STEMI diagnosis to ≤ 10 min. STEMI diagnosis refers to the time when the ECG is interpreted as ST-segment elevation or equivalent and it is the time zero to guide appropriate therapy.

System delay is more readily modifiable by organizational measures than is patient delay, and it is a predictor of outcomes.[87]

When STEMI diagnosis is made in the pre-hospital setting (EMS), immediate activation of the catheterization laboratory not only reduces treatment delays but may also reduce patient mortality.[88–91] When a STEMI diagnosis is made by the EMS in the pre-hospital setting and the patient is triaged for a primary PCI strategy, it is indicated to bypass the emergency department and bring the patient straight

to the catheterization laboratory. Bypassing the emergency department is associated with a 20 min saving in the time from FMC to wire crossing.[92] For patients presenting in a non-PCI centre, door-in to door-out time, defined as the duration between arrival of the patient at the hospital to discharge of the patient in an ambulance en route to the PCI centre, is a new clinical performance measure, and ≤30 min is recommended to expedite reperfusion care.[93]

4.4.2 Emergency medical system

An EMS with an easily recalled and well publicized unique medical dispatching number (112 for most medical emergencies across Europe) is important to speed up activation. Parallel circuits for referral and transport of patients with a STEMI that bypass the EMS should be avoided. The ambulance system has a critical role in the early management of STEMI patients and it is not only a mode of transport but also a system to enhance early initial diagnosis, triage, and treatment.[87,94]

It is indicated that all ambulances in the EMS are equipped with ECG recorders, defibrillators, and at least one person trained in advanced life support. The quality of the care provided depends on the training of the staff involved. It is indicated that all ambulance personnel are trained to recognize the symptoms of an AMI, administer oxygen when appropriate, relieve pain, and provide basic life support.[95] Ambulance staff should be able to record an ECG for diagnostic purposes and either interpret or transmit it, so that it can be reviewed by experienced staff in a coronary care unit (CCU)/ICCU or elsewhere and establish a STEMI diagnosis. Paramedics trained to administer fibrinolytics do so safely and effectively.[96] As pre-hospital fibrinolysis is indicated in patients presenting early when anticipated STEMI diagnosis to PCI-mediated reperfusion time is > 120 min,[97–99] ongoing training of paramedics to undertake these functions is recommended, even in the current setting of primary PCI.

4.4.3 Organization of ST-segment elevation myocardial infarction treatment in networks

Optimal treatment of STEMI should be based on the implementation of networks between hospitals ('hub' and 'spoke') with various levels of technology, linked by a prioritized and efficient ambulance service. The goal of these networks is to provide optimal care while minimizing delays, thereby improving clinical outcomes. Cardiologists should actively collaborate with all stakeholders, particularly emergency physicians, in establishing such networks. The main features of such a network are:

- Clear definition of geographic areas of responsibility.
- Shared written protocols, based on risk stratification and transportation by a trained physician, nurse, or paramedic staff in appropriately equipped ambulances or helicopters.
- Pre-hospital triage of STEMI patients to the appropriate institution, bypassing non-PCI hospitals or hospitals without a 24 h a day, 7 days a week (24/7) primary PCI programme.
- On arrival at the appropriate hospital, the patient should immediately be taken to the catheterization laboratory, bypassing the emergency department.
- Patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI must be attended in an appropriately monitored and staffed area.
- If the diagnosis of STEMI has not been made by the ambulance crew and the ambulance arrives at a non-PCI-capable hospital, the ambulance should await the diagnosis and, if a STEMI diagnosis is made, should continue to a PCI-capable hospital.

To maximize staff experience, primary PCI centres should perform the procedure systematically on a 24/7 basis for all STEMI patients. Other models, although not ideal, may include weekly or daily rotation of primary PCI centres or multiple primary PCI centres in the same region. Hospitals that cannot offer a 24/7 service for primary PCI should be allowed to perform primary PCI in patients already admitted for another reason who develop STEMI during their hospital stay. However, these hospitals should be discouraged from initiating a service limited to daytime- or within-hours primary PCI, as this may generate confusion with the EMS operators and may affect the STEMI diagnosis-to-reperfusion time and the quality of intervention of focused 24/7 true primary PCI centres. Therefore, it is indicated that the EMS transports STEMI patients to hospitals with an established interventional cardiology programme available 24/7, if necessary bypassing a non-PCI-capable hospital (if the transfer time is within the recommended time-windows for primary PCI; see *Figure 3*).

Geographic areas where the expected transfer time to the primary PCI centre makes it impossible to achieve the maximal allowable delays indicated in the recommendations (*Figure 2*) should develop systems for rapid fibrinolysis, at the place of STEMI diagnosis, with subsequent immediate transfer to primary PCI centres. Such networks increase the proportion of patients receiving reperfusion with the shortest possible treatment delay.[100–102] The quality of care, time delays, and patient outcomes should be measured and compared at regular intervals for improvement.

4.4.3.1. General practitioners

In some countries, general practitioners play a role in the early care of patients with AMI and are often the first to be contacted by the patients.

If general practitioners respond quickly they can be very effective, as they usually know the patient and can perform and interpret the ECG. Their first task after the STEMI diagnosis should be to alert the EMS. In addition, they can administer opioids and antithrombotic drugs (including fibrinolytics, if that management strategy is indicated), and can undertake defibrillation if needed. However, in most settings, consultation with a general practitioner—instead of a direct call to the EMS—will increase pre-hospital delay. Therefore, in general, the public should be educated to call the EMS rather than the primary care physician for symptoms suggestive of MI.

Logistics of pre-hospital care

Recommendations	Class[a]	Level[b]
It is recommended that the pre-hospital management of STEMI patients is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.[100]	I	B
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay.[18,103,104]	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory.[92,107–110]	I	B
It is recommended that ambulance teams are trained and equipped to identify STEMI (with use of ECG recorders and telemetry as necessary) and administer initial therapy, including fibrinolysis when applicable.[95]	I	C
It is recommended that all hospitals and EMS participating in the care of patients with STEMI record and audit delay times and work to achieve and maintain quality targets.[105–107]	I	C
It is recommended that EMS transfer STEMI patients to a PCI-capable centre, bypassing non-PCI centres.	I	C
It is recommended that EMS, emergency departments, and CCU/ICCU have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C
It is recommended that patients presenting to a non-PCI-capable hospital and awaiting transportation for primary or rescue PCI are attended in an appropriately monitored area (e.g. the emergency department, CCU/ICCU, or intermediate care unit).	I	C

24/7 = 24 h a day, 7 days a week; CCU = coronary care unit; ECG = electrocardiogram; EMS = emergency medical system; ICCU = intensive cardiac care unit; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

5. Reperfusion therapy

5.1 Selection of reperfusion strategies

Table 4 lists the definitions of terms relating to reperfusion therapy.

Table 4 Definitions of terms related to reperfusion therapy

Term	Definition
FMC	The time point when the patient is either initially assessed by a physician, paramedic, nurse or other trained EMS personnel who can obtain and interpret the ECG, and deliver initial interventions (e.g. defibrillation). FMC can be either in the prehospital setting or upon patient arrival at the hospital (e.g. emergency department)
STEMI diagnosis	The time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent
Primary PCI	Emergent PCI with balloon, stent, or other approved device, performed on the IRA without previous fibrinolytic treatment
Primary PCI strategy	Emergent coronary angiography and PCI of the IRA if indicated
Rescue PCI	Emergent PCI performed as soon as possible in the case of failed fibrinolytic treatment
Routine early PCI strategy after fibrinolysis	Coronary angiography, with PCI of the IRA if indicated, performed between 2 and 24 hours after successful fibrinolysis
Pharmacoinvasive strategy	Fibrinolysis combined with rescue PCI (in case of failed fibrinolysis) or routine early PCI strategy (in case of successful fibrinolysis)

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ECG = electrocardiogram; EMS = emergency medical system; FMC = first medical contact; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset, provided it can be performed expeditiously (i.e. 120 min from STEMI diagnosis, *Figures 2* and *3*) by an experienced team. An experienced team includes not only interventional cardiologists but also skilled support staff. Lower mortality rates among patients undergoing primary PCI are observed in centres with a high volume of PCI procedures.[111] Real-life data confirm that primary PCI is performed faster and results in lower mortality if performed in high-volume centres.[112] Randomized clinical trials in high-volume, experienced centres have repeatedly shown that, if delay to treatment is similar, primary PCI is superior to fibrinolysis in reducing mortality, reinfarction, or stroke.[113–116] However, in some circumstances, primary PCI is not an immediate option and fibrinolysis could be initiated expeditiously. The extent to which the PCI-related time delay diminishes the advantages of PCI over fibrinolysis has been widely debated. Because no specifically designed study has addressed

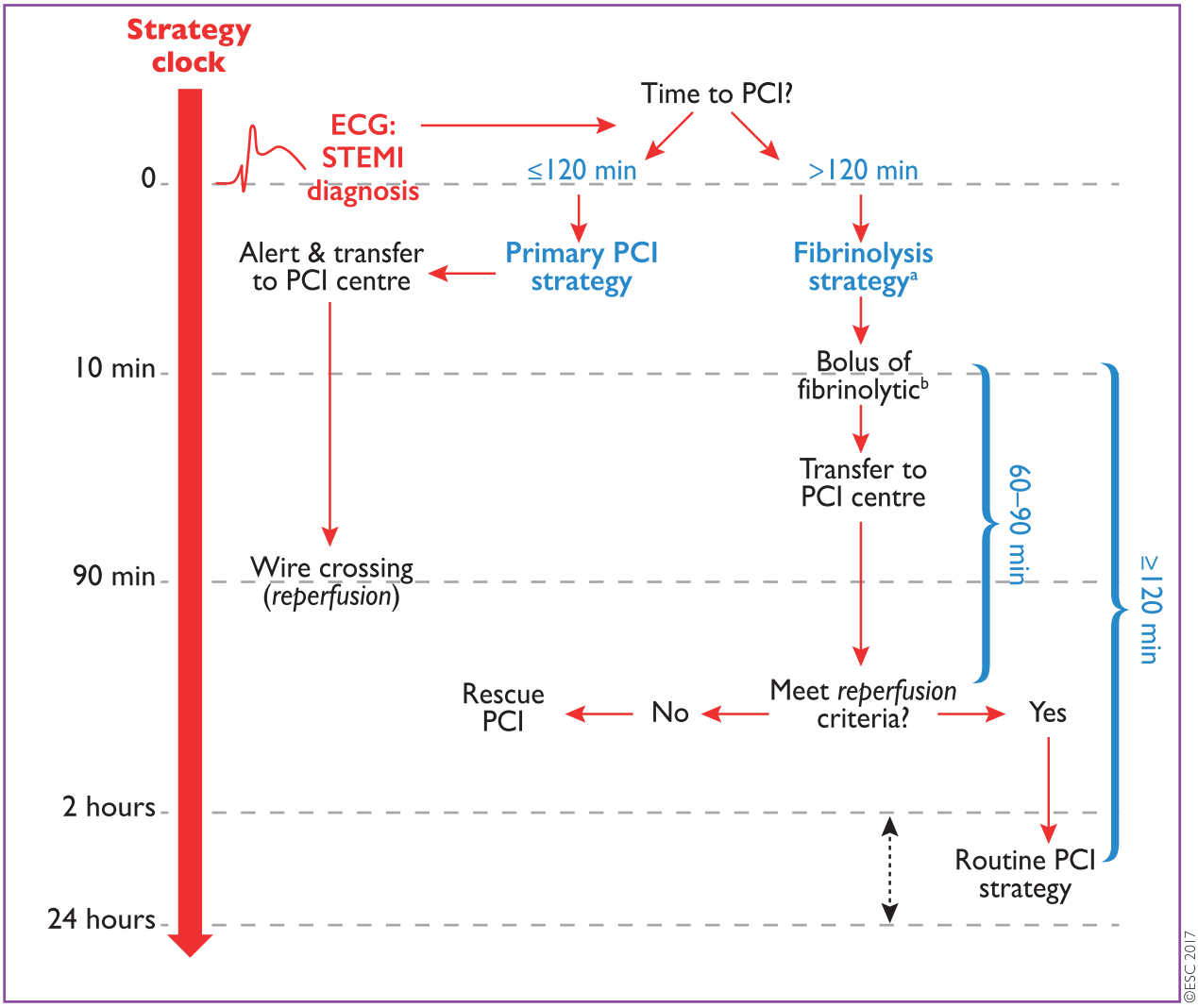

Figure 3 Maximum target times according to reperfusion strategy selection in patients presenting via EMS or in a non-PCI centre. ECG = electrocardiogram; PCI = Percutaneous Coronary Intervention; STEMI = ST-segment elevation myocardial infarction. STEMI diagnosis is the time 0 for the strategy clock. The decision for choosing reperfusion strategy in patients presenting via EMS (out-of-hospital setting) or in a non-PCI centre is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion. Target times from STEMI diagnosis represent the maximum time to do specific interventions.

[a]if fibrinolysis is contra-indicated, direct for primary PCI strategy regardless of time to PCI.

[b]10 min is the maximum target delay time from STEMI diagnosis to fibrinolytic bolus administration, however, it should be given as soon as possible after STEMI diagnosis (after ruling out contra-indications).

this issue, caution is needed when interpreting available data from *post hoc* analyses. A PCI-related time delay potentially mitigating the benefits of PCI has been calculated as 60 min[117], 110 min,[118] and 120 min[119] in different studies. Registry data estimated this time limit as 114 min for in-hospital patients[107] and 120 min in patients presenting in a non-PCI centre.[120] All these data are old and patients undergoing fibrinolysis did not undergo routine early angiography, which improves outcomes in patients receiving fibrinolysis. The recent STrategic Reperfusion Early After Myocardial infarction (STREAM) trial randomized early STEMI presenters without the possibility of immediate PCI to immediate fibrinolysis (followed by routine early angiography) or transfer to primary PCI.[121] The median PCI-related delay in this trial was 78 min, and there were no differences in clinical outcomes. This Task Force recognizes the lack of contemporaneous data to set the limit to choose PCI over fibrinolysis. For simplicity, an absolute time from STEMI diagnosis to PCI-mediated reperfusion [i.e. wire crossing of the infarct-related artery (IRA)] rather than a relative PCI-related delay over fibrinolysis has been chosen. This limit is set to

120 min. Given the maximum limit of 10 min from STEMI diagnosis to bolus of fibrinolytics (see below), the 120 min absolute time would correspond to a PCI-related delay in the range of 110–120 min, being in the range of the times identified in old studies and registries as the limit delay to choose PCI.[107,117–120]

If the reperfusion strategy is fibrinolysis, the goal is to inject the bolus of fibrinolytics within 10 min from STEMI diagnosis. This time is selected based on the median time from randomization to bolus recorded in the STREAM trial, which was 9 min.[121] In previous ESC STEMI guidelines,[122] the target time was 30 min, but this was calculated from FMC (as opposed to STEMI diagnosis). STEMI diagnosis should occur within 10 min from FMC.

Figure 3 summarizes target times for patients presenting in the pre-hospital setting or in a non-PCI centre.

To shorten time to treatment, fibrinolysis should be administered in the pre-hospital setting if possible[98,121,123] (*Figures 2* and *3*). Patients should be transferred to a PCI-capable facility as soon as possible after bolus of lytics administration. Rescue PCI is indicated in the case of failed fibrinolysis (i.e. ST-segment resolution < 50% within 60–90 min of fibrinolytic administration), or in the presence of haemodynamic or electrical instability, worsening ischaemia, or persistent chest pain,[121,124] while a routine early PCI strategy is indicated after successful fibrinolysis (preferably 2–24 h after fibrinolysis) (see section 5.3).[125–130]

Patients with a clinical presentation compatible with AMI and a non-interpretable ST-segment on the ECG, such as those with bundle branch block or ventricular pacing,[55,131,132] should undergo a primary PCI strategy.

There is general agreement that a primary PCI strategy should also be followed for patients with symptoms lasting >12 h in the presence of: (1) ECG evidence of ongoing ischaemia; (2) ongoing or recurrent pain and dynamic ECG changes; and (3) ongoing or recurrent pain, symptoms, and signs of heart failure, shock, or malignant arrhythmias. However, there is no consensus as to whether PCI is also beneficial in patients presenting >12 h from symptom onset in the absence of clinical and/or electrocardiographic evidence of ongoing ischaemia. In asymptomatic patients without persistent symptoms 12–48 h after symptom onset, a small (n = 347) randomized study showed improved myocardial salvage and 4 year survival in patients treated with primary PCI compared with conservative treatment alone.[133,134] However, in stable patients with persistent occlusion of the IRA 3–28 days after MI, the large (n = 2166) Occluded Artery Trial (OAT) revealed no clinical benefit from routine coronary intervention with medical management, beyond that from medical management alone.[135,136] A meta-analysis of trials testing whether late recanalization of an occluded IRA is beneficial showed no benefit of reperfusion.[137] Therefore, routine PCI of an occluded IRA in asymptomatic patients >48 h after onset of symptoms is not indicated. These patients should be managed like all patients with chronic total occlusion, in which revascularization should be considered in the presence of symptoms or objective evidence of viability/ischaemia in the territory of the occluded artery.[1]

Recommendations for reperfusion therapy

Recommendation	Class[a]	Level[b]
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤ 12 h duration and persistent ST-segment elevation.[119,138]	I	A
A primary PCI strategy is recommended over fibrinolysis within indicated timeframes.[114,116,139,140]	I	A
If timely primary PCI cannot be performed after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.[107,120,122]	I	A
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present: - haemodynamic instability or cardiogenic shock - recurrent or ongoing chest pain refractory to medical treatment - life-threatening arrhythmias or cardiac arrest - mechanical complications of MI - acute heart failure - recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.	I	C
Early angiography (within 24 h) is recommended if symptoms are completely relieved and ST-segment elevation is completely normalized spontaneously or after nitroglycerin administration (provided there is no recurrence of symptoms or ST-segment elevation).	I	C
In patients with time from symptom onset >12 h, a primary PCI strategy is indicated in the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or life-threatening arrhythmias.[141]	I	C
A routine primary PCI strategy should be considered in patients presenting late (12–48 h) after symptom onset.[133,134,142]	IIa	B
In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated.[135,137]	III	A

IRA = infarct-related artery; MI, myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

Table 5 Summary of important time targets

Intervals	Time targets
Maximum time from FMC to ECG and diagnosis[a]	≤10 min
Maximum expected delay from STEMI diagnosis to primary PCI (wire crossing) to choose primary PCI strategy over fibrinolysis (if this target time cannot be met, consider fibrinolysis)	≤120 min
Maximum time from STEMI diagnosis to wire crossing in patients presenting at primary PCI hospitals	≤60 min
Maximum time from STEMI diagnosis to wire crossing in transferred patients	≤90 min
Maximum time from STEMI diagnosis to bolus or infusion start of fibrinolysis in patients unable to meet primary PCI target times	≤10 min
Time delay from start of fibrinolysis to evaluation of its efficacy (success or failure)	60–90 min
Time delay from start of fibrinolysis to angiography (if fibrinolysis is successful)	2–24 hours

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ECG = electrocardiogram; FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction
[a]ECG should be interpreted immediately.

Table 5 summarizes the important time targets in acute STEMI.

5.2 Primary percutaneous coronary intervention and adjunctive therapy

5.2.1 Procedural aspects of primary percutaneous coronary intervention

5.2.1.1 Access route

Over recent years, several studies have provided robust evidence in favour of the radial approach as the default access site in ACS patients undergoing primary PCI by experienced radial operators. The Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX)[143] trial recruited 8404 ACS patients (48% STEMI) who were randomly allocated to transradial or transfemoral access. Radial access was associated with lower risks of access site bleeding, vascular complications, and need for transfusion. Importantly, there was a significant mortality benefit in patients allocated to the transradial access site, which reinforced previous observations from the Radial Versus Femoral Access for Coronary Intervention (RIVAL) access for coronary intervention trial,[144] and the Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome (RIFLE-STEACS) trial.[145] No significant interaction was observed in the MATRIX trial between the type of ACS and treatment benefit, suggesting that the results of this investigation can be extended with confidence to the treatment of patients with STEMI.

5.2.1.2 Stenting in primary percutaneous intervention

Coronary stenting is the technique of choice during primary PCI. Compared with balloon angioplasty alone, stenting with a bare-metal stent (BMS) is associated with a lower risk of reinfarction and target vessel revascularization but is not associated with a reduction in the mortality rate.[146,147] In primary PCI, drug-eluting stents (DES) reduce the risk of repeated target vessel revascularization compared with BMS.[148]

New-generation DES have shown superior safety and preserved or even improved efficacy compared with first-generation DES, in particular with respect to lower risks of stent thrombosis and recurrent MI. In two recent trials—the Effect of biolimus-eluting stents with biodegradable polymer vs. bare-metal stents on cardiovascular events among patients with AMI (COMFORTABLE AMI) trial[149] and the Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trial[150]—new-generation DES have been shown to be superior to BMS in patients with AMI, mostly in terms of need for reintervention. In the latter trial, the recently released 5 year follow-up results showed a reduction in all-cause mortality by DES as compared to BMS.[151] In the Norwegian Coronary Stent (NORSTENT) trial,[152] 9013 patients undergoing PCI (26% with STEMI) were randomized to DES or BMS. There were no differences in the incidence of the primary endpoint (composite of death from any cause or non-fatal spontaneous MI) after a median follow-up of 5 years. However, DES were associated with lower rates of definite stent thrombosis (0.8% vs. 1.2%; $P = 0.0498$) and of target lesion and any repeat revascularization (16.5% vs. 19.8%; $P < 0.001$).[152]

Deferring stenting in primary PCI has been investigated as an option to reduce microvascular obstruction (MVO) and preserve microcirculatory function. Two small studies recently found opposite results in the effect of deferred stenting on cardiac magnetic resonance (CMR) imaging-measured MVO.[153,154] In the larger DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction – Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER) trial,[155] in 1215 STEMI patients, deferred stenting (48 h after the index procedure) had no effect on the primary clinical outcome (composite of all-cause mortality, non-fatal MI, or ischaemia-driven revascularization of non-IRA lesions). Routine deferred stenting was associated with a higher need for target vessel revascularization. Based on these findings, routine use of deferred stenting is not recommended.

5.2.1.3 Thrombus aspiration

A number of small-scale or single-centre studies and one meta-analysis of 11 small trials[156] suggested that there could be benefits from routine manual thrombus aspiration during primary PCI. Recently, two large (>10 000 and >7000 patients) randomized controlled trials, which were adequately powered to detect superiority of routine manual thrombus aspiration versus conventional PCI, showed no benefit on clinical outcomes of routine aspiration strategy overall.[157–160] A safety concern emerged in the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) trial (n = 10 732), with an increase in the risk of stroke.[161] In the subgroup with high thrombus burden [TIMI (Thrombolysis in Myocardial Infarction) thrombus grade $\geq$ 3], thrombus aspiration was associated with fewer cardiovascular deaths [170 (2.5%) vs. 205 (3.1%); hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.65–0.98; $P = 0.03$] and with more strokes or transient ischaemic attacks [55 (0.9%) vs. 34 (0.5%); odds

ratio 1.56, 95% CI 1.02–2.42, P =0.04]. However, the interaction P values were 0.32 and 0.34, respectively.[162]

In the Taste[157] and TOTAL trials[159], 1–5% of randomized patients crossed over from PCI alone to thrombus aspiration. Based on these data and the results of a recent meta-analysis,[162] routine thrombus aspiration is not recommended, but in cases of large residual thrombus burden after opening the vessel with a guide wire or a balloon, thrombus aspiration may be considered.

5.2.1.4 Multivessel coronary revascularization

Multivessel disease is common (in approximately 50%) in patients with STEMI.[163,164] While it is recommended to always treat the IRA, evidence supporting immediate (preventive) revascularization of additional significant coronary stenoses is conflicting. It has been reported that patients with extensive CAD in vessels remote from the IRA have lower rates of ST-segment recovery and an adverse prognosis following primary PCI.[163] Data from the US National Cardiovascular Data Registry and New York State's Percutaneous Coronary Interventions Reporting System suggested an increase in adverse events, including mortality, in patients treated with immediate multivessel revascularization versus IRA PCI only, while patients in cardiogenic shock were excluded from the analysis.[165,166]

Randomized clinical trials addressing this issue have been small (each of them included from 69 to 885 patients). One study allocated 214 STEMI patients with multivessel disease to three arms: IRA angioplasty-only, simultaneous treatment of non-IRA lesions, and staged revascularization of the non-IRA. At a mean follow-up of 2.5 years, patients allocated to IRA angioplasty-only had more major adverse cardiac events (MACE) (i.e. death, reinfarction, rehospitalization for ACS, and repeat coronary revascularization) than the patients treated with other strategies.[167] After this study, four randomized clinical trials have compared PCI of the IRA only vs. complete revascularization: the Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial (n = 465, 23 months follow-up),[168] the Complete Versus Lesion-Only Primary PCI Trial (CvLPRIT) (n = 296, 12 months follow-up),[169] the Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3–PRIMULTI) trial (n = 627, 27 months follow-up),[170] and the Comparison Between FFR Guided Revascularization Versus Conventional Strategy in Acute STEMI Patients With Multivessel disease (Compare-Acute, n = 885, 12 months follow-up) trial.[171] PCI of non-IRA was done either during the index procedure (PRAMI and Compare-Acute), staged during hospital admission (DANAMI-3–PRIMULTI), or any time before discharge (immediate or staged) (CVLPRIT). Indication for PCI in non-IRA was angiography-guided in lesions with ≥50% stenosis (PRAMI), >70% stenosis (CVLPRIT), or fractional flow reserve (FFR)-guided (DANAMI-3–PRIMULTI and Compare-Acute). Primary outcome (composite of different endpoints) was significantly reduced in the complete revascularization group in all four trials. Total mortality was not statistically different in any of the four trials. Repeat revascularization was significantly reduced in the complete revascularization arm in the PRAMI, DANAMI-3–PRIMULTI, and Compare-Acute trials. Non-fatal MI was reduced in the non-IRA PCI group only in PRAMI. The lack of significant treatment effect of non-IRA lesion intervention on death or MI was confirmed by three meta-analyses[172–174] (none of these meta-analyses included the Compare-Acute trial, and one[173] did not include the DANAMI-3–PRIMULTI). Based on these data, revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge. As the optimal timing of revascularization (immediate vs. staged) has not been adequately investigated, no recommendation in favour of immediate vs. staged multivessel PCI can be formulated.

5.2.1.5 Intra-aortic balloon pump

The Counterpulsation to Reduce Infarct Size Pre-PCI-Acute Myocardial Infarction (CRISP AMI) trial showed no benefit from a routine intra-aortic balloon pump (IABP) in anterior MI without shock,[175] but there was increased bleeding, which is consistent with previous data regarding the role of IABP in high-risk STEMI without cardiogenic shock.[176] In addition, a recent randomized trial showed that IABP did not improve outcomes in MI with cardiogenic shock.[177] Haemodynamic support in patients with cardiogenic shock is discussed in Chapter 8.

Procedural aspects of the primary percutaneous coronary intervention strategy

Recommendations	Class[a]	Level[b]
IRA strategy		
Primary PCI of the IRA is indicated.[114,116,139,140]	I	A
New coronary angiography with PCI if indicated is recommended in patients with symptoms or signs of recurrent or remaining ischaemia after primary PCI.	I	C
IRA technique		
Stenting is recommended (over balloon angioplasty) for primary PCI.[146,147]	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.[148–151,178,179]	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.[143–145,180]	I	A
Routine use of thrombus aspiration is not recommended.[157,159]	III	A
Routine use of deferred stenting is not recommended.[153–155]	III	B
Non-IRA strategy		
Routine revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease before hospital discharge.[167–173]	IIa	A
Non-IRA PCI during the index procedure should be considered in patients with cardiogenic shock.	IIa	C
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

5.2.2 Periprocedural pharmacotherapy

5.2.2.1 Platelet inhibition

Patients undergoing primary PCI should receive DAPT, a combination of aspirin and a $P2Y_{12}$ inhibitor, and a parenteral anticoagulant. Aspirin can be given orally including chewing, or i.v. to ensure complete inhibition of thromboxane A2-dependent platelet aggregation. The oral dose of plain aspirin (non-enteric-coated formulation) should preferably be 150–300 mg. There are few clinical data on the optimal i.v. dosage. Given a 50% oral bioavailability of oral aspirin, a corresponding dose is 75–150 mg. Pharmacological data suggest that this lower dose range avoids inhibition of cyclooxygenase-2-dependent prostacyclin. A recent randomized study showed that a single dose of 250 or 500 mg acetylsalicylic acid i.v. compared to 300 mg orally was associated with a faster and more complete inhibition of thromboxane generation and platelet aggregation at 5 min, with comparable rates of bleeding complications.[181]

There is limited evidence with respect to when the $P2Y_{12}$ inhibitor should be initiated in STEMI patients. The Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial[182] is the only randomized study testing the safety and efficacy of different timings of $P2Y_{12}$ inhibitor initiation in STEMI. In this trial, patients were randomized to receive ticagrelor either during transfer to a primary PCI centre or immediately before angiography.[182] The median difference between the two tested loading treatment strategies was only 31 min. This study failed to meet the pre-specified primary endpoint in terms of improved ST-segment elevation resolution or TIMI flow before intervention. Rates of major and minor bleeding events were identical in both treatment arms. While the evidence of a clinical benefit of $P2Y_{12}$ inhibitor pre-treatment in this setting is lacking, early initiation of a $P2Y_{12}$ inhibitor while the patient is being transported to a primary PCI centre is common practice in Europe and is consistent with the pharmacokinetic data. Furthermore, early treatment with high-dose clopidogrel was superior to in-catheterization laboratory treatment in observational studies and one small randomized trial.[183–185] In all, the data suggest that the earliest administration may be preferable to achieve early efficacy, particularly for long delays. However, in cases in which the STEMI diagnosis is not clear, delaying $P2Y_{12}$ inhibitor loading until the anatomy is known should be considered.

The preferred $P2Y_{12}$ inhibitors are prasugrel [60 mg loading dose and 10 mg maintenance dose once daily per os (*p.o.*)] or ticagrelor (180 mg *p.o.* loading dose and 90 mg maintenance dose twice daily). These drugs have a more rapid onset of action, greater potency, and are superior to clopidogrel in clinical outcomes.[186,187] Prasugrel is contraindicated in patients with previous stroke/transient ischaemic attack, and its use is generally not recommended in patients aged $\geq$75 years or in patients with lower body weight (<60 kg) as it was not associated with net clinical benefit in these subsets. In case prasugrel is used in these patients, a reduced dose (5 mg)[188] is recommended. Ticagrelor may cause transient dyspnoea at the onset of therapy, which is not associated with morphological or functional lung abnormalities, and which rarely leads to permanent discontinuation.[189] Neither prasugrel nor ticagrelor should be used in patients with a previous haemorrhagic stroke, in patients on oral anticoagulants, or in patients with moderate-to-severe liver disease.

When neither of these agents is available (or if they are contraindicated), clopidogrel 600 mg *p.o.* should be given instead.[190] Clopidogrel has not been evaluated against placebo in any large outcomes studies in the setting of primary PCI, but a higher regimen of a 600 mg loading dose/150 mg maintenance dose in the first week was superior to the 300/75 mg regimen in the subset of patients undergoing PCI in the Clopidogrel and aspirin Optimal Dose usage to reduce recurrent events–Seventh organization to assess strategies in ischaemic syndromes (CURRENT-OASIS 7) trial,[190] and use of high clopidogrel loading doses has been demonstrated to achieve more rapid inhibition of the adenosine diphosphate receptor. All $P2Y_{12}$ inhibitors should be used with caution in patients at high risk of bleeding or with significant anaemia.

Cangrelor is a potent i.v. reversible $P2Y_{12}$ inhibitor with a rapid onset and offset of action. It has been assessed in three randomized controlled trials enrolling patients with PCI for stable angina or ACS against clopidogrel loading or placebo.[191–193] A pooled analysis of these three trials showed that cangrelor reduced periprocedural ischaemic complications at the expense of an increased risk of bleeding.[194] The fact that no potent $P2Y_{12}$ inhibitors (prasugrel or ticagrelor) were used in patients with an ACS, and only about 18% of the enrolled patients presented with STEMI,[193] limits the applicability of the results to current practice of management of STEMI patients. Nevertheless, cangrelor may be considered in patients not pre-treated with oral $P2Y_{12}$ receptor inhibitors at the time of PCI or in those who are considered unable to absorb oral agents.

The pre-hospital routine upstream use of glycoprotein (GP) IIb/IIIa inhibitors before primary PCI has not been demonstrated to offer a benefit and increases bleeding risk compared with routine use in the catheterization laboratory.[195,196] Procedural use of abciximab plus unfractionated heparin (UFH) showed no benefit compared to bivalirudin.[197] Using GP IIb/IIIa inhibitors as bailout therapy in the event of angiographic evidence of a large thrombus, slow- or no-reflow, and other thrombotic complications is reasonable, although this strategy has not been tested in a randomized trial. Overall, there is no evidence to recommend the routine use of GP IIb/IIIa inhibitors for primary PCI. The intracoronary administration of GP IIb/IIIa inhibitors is not superior to its i.v. use.[198]

5.2.2.2 Anticoagulation

Anticoagulant options for primary PCI include UFH, enoxaparin, and bivalirudin. Use of fondaparinux in the context of primary PCI was associated with potential harm in the Organization for the Assessment of Strategies for Ischemic Syndromes 6 (OASIS 6) trial and is not recommended.[199]

There has been no placebo-controlled trial evaluating UFH in primary PCI, but there is a large body of experience with this agent.

Dosage should follow standard recommendations for PCI (i.e. initial bolus 70–100 U/kg). There are no robust data recommending the use of activated clotting time to tailor dose or monitor UFH, and if activated clotting time is used, it should not delay recanalization of the IRA. An i.v. bolus of enoxaparin 0.5 mg/kg was compared with UFH in the randomized open-label Acute myocardial infarction Treated with primary angioplasty and inTravenous enOxaparin or unfractionated heparin to Lower ischaemic and bleeding events at short- and Long-term follow-up (ATOLL) trial, including 910 STEMI patients.[200] The primary composite endpoint of 30 day death, MI, procedural failure, or major bleeding was not significantly reduced by enoxaparin (17% relative risk reduction, $P = 0.063$), but there was a reduction in the composite main secondary endpoint of death, recurrent MI or ACS, or urgent revascularization. Importantly, there was no evidence of increased bleeding following the use of enoxaparin over UFH.[200] In the per-protocol analysis of the ATOLL trial (87% of the study population), i.v. enoxaparin was superior to UFH in reducing the primary endpoint, ischaemic endpoints, mortality, and major bleeding.[201] In a meta-analysis of 23 PCI trials (30 966 patients, 33% primary PCI), enoxaparin was associated with a significant reduction in death compared to UHF. This effect was particularly significant in the primary PCI context and was associated with a reduction in major bleeding.[202] Based on these considerations, enoxaparin should be considered in STEMI.

Five dedicated randomized controlled trials have compared bivalirudin with UFH with or without planned use of GP IIb/IIIa inhibitors in patients with STEMI.[197,203–207] A meta-analysis of these trials showed no mortality advantage with bivalirudin and a reduction in the risk of major bleeding, but at the cost of an increased risk of acute stent thrombosis.[208] In the recent MATRIX trial including 7213 ACS patients (56% with STEMI), bivalirudin did not reduce the incidence of the primary endpoint (composite of death, MI, or stroke) compared to UFH. Bivalirudin was associated with lower total and cardiovascular mortality, lower bleeding, and more definite stent thrombosis.[209] The recently published STEMI subanalysis confirmed a lack of statistical interaction between the type of ACS and outcomes within the study.[210] The MATRIX trial showed that prolonging bivalirudin infusion after PCI did not improve the outcomes compared with bivalirudin infusion confined to the duration of PCI.[209] However, a *post hoc* analysis suggested that prolonging bivalirudin with a full-PCI dose after PCI was associated with the lowest risk of ischaemic and bleeding events, which is in accordance with the current label of the drug.[209] Based on these data, bivalirudin should be considered in STEMI, especially in patients at high bleeding risk.[197,211,212] Bivalirudin is recommended for patients with heparin-induced thrombocytopenia.

Routine post-procedural anticoagulant therapy is not indicated after primary PCI, except when there is a separate indication for either full-dose anticoagulation [due, for instance, to atrial fibrillation (AF), mechanical valves, or LV thrombus][2] or prophylactic doses for the prevention of venous thromboembolism in patients requiring prolonged bed rest.

Periprocedural and post-procedural antithrombotic therapy[a] in patients undergoing primary percutaneous coronary intervention

Recommendations	Class[b]	Level[c]
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.[186,187]	I	A
Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications.[213,214]	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.[192–194]	IIb	A
Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.[200–202]	IIa	A
Routine use of bivalirudin should be considered.[209,215]	IIa	A
Fondaparinux is not recommended for primary PCI.[199]	III	B

GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.
[a]Dose regimens are specified in *Table 6*.
[b]Class of recommendation.
[c]Level of evidence.

Table 6 Doses of antiplatelet and anticoagulant cotherapies in patients undergoing primary percutaneous coronary intervention or not reperfused

Doses of antiplatelet and parenteral anticoagulant cotherapies in primary PCI	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally or of 75–250 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day In patients with body weight ≤60 kg, a maintenance dose of 5 mg/day is recommended Prasugrel is contra-indicated in patients with previous stroke. In patients ≥75 years, prasugrel is generally not recommended, but a dose of 5 mg/day should be used if treatment is deemed necessary
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg *b.i.d.*
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 hours
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to 18 hours
Tirofiban	25 µg/kg over 3 min i.v., followed by a maintenance infusion of 0.15 µg/kg/min for up to 18 hours
Parenteral anticoagulant therapies	
UFH	70–100 IU/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned 50–70 IU/kg i.v. bolus with GP IIb/IIIa inhibitors
Enoxaparin	0.5 mg/kg i.v. bolus
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/hour for up to 4 hours after the procedure
Doses of antiplatelet and parenteral anticoagulant therapies in patients not receiving reperfusion therapy	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day orally
Parenteral anticoagulant therapies	
UFH	Same dose as with fibrinolytic therapy (see Table 7)
Enoxaparin	Same dose as with fibrinolytic therapy (see Table 7)
Fondaparinux	Same dose as with fibrinolytic therapy (see Table 7)

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b.i.d. = twice a day; GP = glycoprotein; i.v. = intravenous; IU = international units; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

5.2.2.3 Therapies to reduce infarct size and microvascular obstruction

Final infarct size and MVO are major independent predictors of long-term mortality and heart failure in survivors of STEMI.[216,217] MVO is defined as inadequate myocardial perfusion after successful mechanical opening of the IRA, and is caused by several factors.[218] MVO is diagnosed immediately after PCI when post-procedural angiographic TIMI flow is < 3, or in the case of a TIMI flow of 3 when myocardial blush grade is 0 or 1, or when ST resolution within 60–90 min of the procedure is < 70%. Other non-invasive techniques to diagnose MVO are late gadolinium enhancement (LGE) CMR (the current state of the art for MVO identification and quantification), contrast echocardiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET).[218] Different strategies, such as coronary post-conditioning, remote ischaemic conditioning, early i.v. metoprolol, GP IIb/IIIa inhibitors, drugs targeting mitochondrial integrity or nitric oxide pathways, adenosine, glucose modulators, hypothermia, and others, have been shown to be beneficial in pre-clinical and small-scale clinical trials,[217,219] but still there is no therapy aimed at reducing ischaemia/reperfusion injury (MI size) that is clearly associated with improved clinical outcomes. The reduction of ischaemia/reperfusion injury in general, and MVO in particular, remains an unmet need to further improve long-term ventricular function in STEMI.

5.3 Fibrinolysis and pharmacoinvasive strategy

5.3.1 Benefit and indication of fibrinolysis

Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner, and prevents 30 early deaths per 1000 patients treated within 6 h after symptom onset.[220] The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2 h after symptom onset.[138,221] Fibrinolytic therapy is recommended within 12 h of symptom onset if primary PCI cannot be performed within 120 min from STEMI diagnosis (see *Figure 3*) and there are no contraindications. The later the patient presents (particularly after 3 h),[98,120,121] the more consideration should be given to transfer for primary PCI (as opposed to administering fibrinolytic therapy) because the efficacy and clinical benefit of fibrinolysis decrease as the time from symptom onset increases.[120] In the presence of contraindications for fibrinolytic treatment, it is important to weigh the potentially life-saving effect of fibrinolysis against potentially life-threatening side effects, taking into account alternative treatment options such as delayed primary PCI.

Fibrinolytic therapy

Recommendations	Class[a]	Level[b]
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.[96,98,123,222]	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.[223,224]	I	B
A half-dose of tenecteplase should be considered in patients ≥75 years of age.[121]	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Oral or i.v. aspirin is indicated.[213]	I	B
Clopidogrel is indicated in addition to aspirin.[225,226]	I	A
DAPT (in the form of aspirin plus a $P2Y_{12}$ inhibitor[c]) is indicated for up to 1 year in patients undergoing fibrinolysis and subsequent PCI.	I	C
Anticoagulation co-therapy with fibrinolysis		
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days.[199,224,227–233] The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH).[227–232]	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.[224]	I	B
• In patients treated with streptokinase: fondaparinux i.v. bolus followed by an s.c. dose 24 h later.[199,233]	IIa	B
Transfer after fibrinolysis		
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.[121,124,126–130,234]	I	A
Interventions following fibrinolysis		
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.[124, 235]	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.[121,124,236]	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2 and 24 h after successful fibrinolysis.[125–128,234]	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.[124]	I	B

DAPT = dual antiplatelet therapy; IRA = infarct-related artery; i.v. = intravenous; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; s.c. = subcutaneous; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.
[a]Class of recommendation.
[b]Level of evidence.
[c]Clopidogrel is the $P2Y_{12}$ inhibitor of choice as co-adjuvant and after fibrinolysis, but 48 h after fibrinolysis, switch to prasugrel/ticagrelor may be considered in patients who underwent PCI.

Doses of fibrinolytic agents and antithrombotic co-therapies are listed in *Table 7*.

5.3.2 Pre-hospital fibrinolysis

In a meta-analysis of six randomized trials (n = 6434), pre-hospital fibrinolysis reduced early mortality by 17% compared with in-hospital fibrinolysis,[123] particularly when administered in the first 2 h of symptom onset.[138] These and more recent data support pre-hospital initiation of fibrinolytic treatment when a reperfusion strategy is indicated.[97,99,100,237] The STREAM trial showed that pre-hospital fibrinolysis followed by an early PCI strategy was associated with a similar outcome as transfer for primary PCI in STEMI patients presenting within 3 h after symptom onset who could not undergo primary PCI within 1 h after FMC.[121,238]

If trained medical or paramedical staff are able to analyse the ECG on-site or to transmit the ECG to the hospital for interpretation, it is

Table 7 Doses of fibrinolytic agents and antithrombotic co-therapies

Drug	Initial treatment	Specific contra-indications
Doses of fibrinolytic therapy		
Streptokinase	1.5 million units over 30–60 min i.v.	Previous treatment with streptokinase or anistreplase
Alteplase (tPA)	15 mg i.v. bolus 0.75 mg/kg i.v. over 30 min (up to 50 mg) then 0.5 mg/kg i.v. over 60 min (up to 35 mg)	
Reteplase (rPA)	10 units + 10 units i.v. bolus given 30 min apart	
Tenecteplase (TNK-tPA)	Single i.v. bolus: 30 mg (6000 IU) if <60 kg 35 mg (7000 IU) if 60 to <70 kg 40 mg (8000 IU) if 70 to <80 kg 45 mg (9000 IU) if 80 to <90 kg 50 mg (10000 IU) if ≥90 kg It is recommended to reduce to half-dose in patients ≥75 years of age.[121]	
Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
Doses of anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 hours until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection. In patients ≥75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 mL/min/1.73 m^2, regardless of age, the s.c. doses are given once every 24 hours.	
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24–48 hours. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.	

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[a]PTT = activated partial thromboplastin time; eGFR = estimated glomerular filtration rate; i.v. = intravenous; IU = international units; rPA = recombinant plasminogen activator; s.c. = subcutaneous; tPA = tissue plasminogen activator; UFH = unfractionated heparin.

recommended to initiate fibrinolytic therapy in the pre-hospital setting. The aim is to start fibrinolytic therapy within 10 min from STEMI diagnosis.

5.3.3 Angiography and percutaneous coronary intervention after fibrinolysis (pharmacoinvasive strategy)

Following initiation of lytic therapy, it is recommended to transfer the patients to a PCI centre (*Figure 3*). In cases of failed fibrinolysis, or if there is evidence of reocclusion or reinfarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI is indicated.[124] In this setting, re-administration of fibrinolysis has not been shown to be beneficial and should be discouraged.[124] Even if it is likely that fibrinolysis will be successful (ST-segment resolution > 50% at 60–90 min; typical reperfusion arrhythmia; and disappearance of chest pain), a strategy of routine early angiography is recommended if there are no contraindications. Several randomized trials[126–128,234,239,240] and meta-analyses[129,130] have shown that early routine angiography with subsequent PCI (if needed) after fibrinolysis reduced the rates of reinfarction and recurrent ischaemia compared with a 'watchful waiting' strategy, in which angiography and revascularization were indicated only in patients with spontaneous or induced severe ischaemia or LV dysfunction, or in those with a positive outpatient ischaemia test. The benefits of early routine PCI after fibrinolysis were seen in the absence of an increased risk of adverse events (stroke or major bleeding), and across patient subgroups.[241] Thus, early angiography with subsequent PCI if indicated is also the recommended standard of care after successful fibrinolysis (see *Figure 3*).

A crucial issue is the optimal time delay between successful lysis and PCI; there was a wide variation in delay in trials, from a median of 1.3 h in the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics ALone in Acute Myocardial Infarction (CAPITAL AMI) trial[240] to 17 h in the Grupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA)-1[234] and STREAM trials.[121] In a pooled patient-level analysis of six randomized trials, very early angiography (<2 h) after fibrinolysis was not associated with an increased risk of 30 day death/reinfarction or in-hospital major bleeding, and a shorter time from symptom onset to angiography (<4 h) was associated with reduced 30 day and 1 year death/reinfarction and 30 day recurrent ischaemia.[125]

Based on this analysis, as well as on trials having a median delay between start of lysis and angiography of 2–17 h,[121,126–128] a time-window of 2–24 h after successful lysis is recommended.

5.3.4 Comparison of fibrinolytic agents

A fibrin-specific agent should be preferred.[224] Single-bolus weight-adjusted tenecteplase tissue plasminogen activator (TNK-tPA) is equivalent to accelerated tPA in reducing 30 day mortality, but is safer in preventing non-cerebral bleeds and blood transfusion, and is easier to use in the pre-hospital setting.[223]

5.3.5 Adjunctive antiplatelet and anticoagulant therapies

An early study showed that the benefits of aspirin and fibrinolytics (i.e. streptokinase) were additive.[213] The first dose of aspirin should be chewed or given i.v. and a low dose (75–100 mg) given orally daily thereafter. Clopidogrel added to aspirin reduces the risk of cardiovascular events and overall mortality in patients treated with fibrinolysis[225,226] and should be added to aspirin as an adjunct to lytic therapy. Prasugrel and ticagrelor have not been studied as adjuncts to fibrinolysis. There is no evidence that administration of GP IIb/IIIa inhibitors improves myocardial perfusion or outcomes in patients treated with fibrinolysis, and bleeding may increase.[242]

Parenteral anticoagulation should preferably be given until revascularization (if performed). Otherwise, it should be given for at least 48 h or for the duration of hospital stay, up to 8 days. In spite of an increased risk of major bleeding, the net clinical benefit favoured enoxaparin over UFH in the ASsessment of the Safety and Efficacy of a New Thrombolytic 3 (ASSENT 3) trial (n = 6095).[227] In the large Enoxaparin and Thrombolysis Reperfusion for Acute myocardial infarction Treatment–Thrombolysis In Myocardial Infarction 25 (ExTRACT–TIMI 25) trial (n = 20 506), a lower dose of enoxaparin was given to patients ≥75 years of age and to those with impaired renal function (estimated creatinine clearance <30 mL/min). Enoxaparin was associated with a reduction in the risk of death and reinfarction at 30 days when compared with a weight-adjusted UFH dose, but at the cost of a significant increase in non-cerebral bleeding complications. The net clinical benefit (i.e. absence of death, non-fatal infarction, and intracranial haemorrhage) favoured enoxaparin.[229,230] Finally, fondaparinux was shown in the large OASIS-6 trial to be superior in this setting to placebo or UFH in preventing death and reinfarction,[199,233] especially in patients who received streptokinase.

In a large trial with streptokinase,[243] significantly fewer reinfarctions were seen with bivalirudin given for 48 h compared with UFH, though at the cost of a modest and non-significant increase in non-cerebral bleeding complications. Bivalirudin has not been studied with fibrin-specific agents. Thus, there is no evidence in support of direct thrombin inhibitors as an adjunct to fibrinolysis.

Weight-adjusted i.v. tenecteplase, aspirin, and clopidogrel given orally, and enoxaparin i.v. followed by s.c. administration until the time of PCI (revascularisation), comprise the antithrombotic cocktail most extensively studied as part of a pharmacoinvasive strategy.[121,126,128,242,244]

5.3.6 Hazards of fibrinolysis

Fibrinolytic therapy is associated with a small but significant excess of strokes, largely attributable to cerebral haemorrhage, with the excess hazard appearing on the first day after treatment.[220] Advanced age, lower weight, female sex, previous cerebrovascular disease, and systolic and diastolic hypertension on admission are significant predictors of intracranial haemorrhage.[245] In the latest trials, intracranial bleeding occurred in 0.9–1.0% of the total population studied.[121,223,246] In the STREAM trial, the initial excess in intracranial haemorrhage in patients ≥75 years was reduced after the protocol amendment to reduce the dose of tenecteplase by 50%. Data from a number of studies suggest that major non-cerebral bleeds occurred in 4–13% of the patients treated.[121,223,224,246] Administration of streptokinase may be associated with hypotension, but severe allergic reactions are rare. Re-administration of streptokinase should be avoided because of antibodies that can impair its activity, and because of the risk of allergic reactions.

5.3.7 Contraindications to fibrinolytic therapy

Short successful resuscitation does not contraindicate fibrinolytic therapy. In patients in refractory cardiac arrest, lytic therapy is not effective, increases the risk of bleeding, and is therefore not recommended. Prolonged, or traumatic but successful, resuscitation increases bleeding risk and is a relative contraindication to fibrinolysis.[247] *Table 8* lists the absolute and relative contraindications to fibrinolytic therapy.

Table 8 Contra-indications to fibrinolytic therapy

Absolute
Previous intracranial haemorrhage or stroke of unknown origin at anytime
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or arteriovenous malformation
Recent major trauma/surgery/head injury (within the preceding month)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

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DBP = diastolic blood pressure; SBP = systolic blood pressure.

5.4 Coronary artery bypass graft surgery

Emergent coronary artery bypass graft surgery (CABG) should be considered for patients with a patent IRA but with unsuitable anatomy for PCI, and either a large myocardial area at jeopardy or with cardiogenic shock.[248] In patients with MI-related mechanical complications who require coronary revascularization, CABG is recommended at the time of repair. In STEMI patients with failed PCI or coronary occlusion not amenable to PCI, emergent CABG is infrequently performed because the benefits of surgical revascularization in this setting are uncertain. As the delay to reperfusion is long, the probabilities of myocardial salvage affecting prognosis are low and the surgical risks are elevated.

In the absence of randomized data, optimal timing for non-emergent CABG in stabilized post-MI patients should be determined individually. A review of California discharge data compared patients who underwent early (<3 days, n = 4676) versus delayed (≥3 days, n = 4800) post-MI CABG.[249] Patients who underwent early CABG had a higher mortality rate (unadjusted mortality 5.6% *vs.* 3.8%; propensity-adjusted odds ratio 1.40, 95% CI 1.12–1.74; P < 0.001), with the highest mortality observed in patients on whom surgery was performed on the day of the MI (8.2%). However, no differentiation was made between NSTEMI and STEMI, and higher-risk patients were more likely to be treated rapidly. Patients with haemodynamic deterioration or who are at high risk of recurrent ischaemic events (i.e. patients with a large area of myocardium at jeopardy due to critical coronary stenoses or recurrent ischaemia) should be operated on as soon as possible without waiting for the full recovery of platelet function following discontinuation of DAPT. For all other patients, a waiting period of 3–7 days may be the best compromise (at least 3 days following interruption of ticagrelor,[187,250] 5 days for clopidogrel, and 7 days for prasugrel),[7] while it is recommended that aspirin is continued.[251] The first aspirin administration post-CABG is recommended 6–24 h after surgery in the absence of ongoing bleeding events.[252,253]

6. Management during hospitalization and at discharge

6.1 Coronary care unit/intensive cardiac care unit

Following reperfusion, it is recommended to admit STEMI patients to a CCU/ICCU or equivalent unit where continuous monitoring and specialized care can be provided. The staff should be thoroughly familiar with the management of ACS, arrhythmias, heart failure, mechanical circulatory support, invasive and non-invasive haemodynamic monitoring (arterial and pulmonary artery pressures), respiratory monitoring, mechanical ventilation, and targeted temperature management. The unit should also be able to manage patients with serious renal and pulmonary disease. The desirable organization, structure, and criteria of the CCU/ICCU have been described in an ESC-Acute Cardiovascular Care Association (ACCA) position paper.[254]

6.2 Monitoring

ECG monitoring for arrhythmias and ST-segment deviations is recommended for at least 24 h after symptom onset in all STEMI patients. Longer monitoring should be considered in patients at intermediate- to high-risk for cardiac arrhythmias (those with more than one of the following criteria: haemodynamically unstable, presenting major arrhythmias, LVEF <40%, failed reperfusion, additional critical coronary stenoses of major vessels, or complications related to PCI). Further monitoring for arrhythmias depends on estimated risk. When a patient leaves the CCU/ICCU or equivalent, monitoring may be continued by telemetry. It is recommended that personnel adequately equipped and trained to manage life-threatening arrhythmias and cardiac arrest accompany patients who are transferred between facilities during the time-window in which they require continuous rhythm monitoring.

6.3 Ambulation

Early ambulation (day 1) is recommended in the majority of patients and is facilitated by using the radial access for PCI. Patients with extensive myocardial damage, heart failure, hypotension, or arrhythmias may initially rest in bed before assessment of myocardial function and achievement of clinical stabilization. Prolongation of bed rest and limitation of physical activity may occasionally be needed for patients with large infarcts or with severe complications depending on symptoms and ability.

6.4 Length of stay

The optimal length of stay in the CCU/ICCU and hospital should be determined on an individual basis, according to the patient's cardiac risk, comorbidities, functional status, and social support. Generalization of successful reperfusion and knowledge of coronary anatomy has led to progressive reductions in length of stay after STEMI, with significant reductions in 30 day mortality, suggesting that earlier discharge is not associated with late mortality.[255,256] Several studies have shown that low-risk patients with successful primary PCI and complete revascularization can safely be discharged from hospital on day 2 or day 3 after PCI.[256–262] Candidates for early discharge after STEMI can be identified using simple criteria [e.g. the Second Primary Angioplasty in Myocardial Infarction (PAMI-II) criteria, the Zwolle primary PCI Index, or other criteria].[257,258] The PAMI-II criteria designate as low risk patients aged <70 years, with an LVEF >45%, one- or two-vessel disease, successful PCI, and no persistent arrhythmias. A short hospital stay implies limited time for proper patient education and up-titration of secondary prevention treatments. Consequently, these patients should have early post-discharge consultations with a cardiologist, primary care physician, or specialized nurse scheduled and be rapidly enrolled in a formal rehabilitation programme, either in-hospital or on an outpatient basis.

Early (i.e. same day) transfer to a local hospital following successful primary PCI is routine practice. This can be done safely under adequate monitoring and supervision in selected patients, i.e. those without signs or symptoms consistent with ongoing myocardial ischaemia, without arrhythmia, who are haemodynamically stable, not requiring vasoactive or mechanical support, and are not scheduled for further revascularization.[263]

Logistical issues for hospital stay

Recommendations	Class[a]	Level[b]
It is indicated that all hospitals participating in the care of STEMI patients have a CCU/ICCU equipped to provide all aspects of care for STEMI patients, including treatment of ischaemia, severe heart failure, arrhythmias, and common comorbidities.	I	C
Transfer back to a referring non-PCI hospital		
Same day transfer should be considered appropriate in selected patients after successful primary PCI, i.e. those without ongoing myocardial ischaemia, arrhythmia, or haemodynamic instability, not requiring vasoactive or mechanical support, and not needing further early revascularization.[263]	IIa	C
Monitoring		
It is indicated that all STEMI patients have ECG monitoring for a minimum of 24 h.	I	C
Length of stay in the CCU		
It is indicated that patients with successful reperfusion therapy and an uncomplicated clinical course are kept in the CCU/ICCU for a minimum of 24 h whenever possible, after which they may be moved to a step-down monitored bed for an additional 24–48 h.	I	C
Hospital discharge		
Early discharge (within 48–72 h) should be considered appropriate in selected low-risk patients[c] if early rehabilitation and adequate follow-up are arranged.[257,259–262,264,265]	IIa	A

CCU = coronary care unit; ICCU = intensive cardiac care unit; LVEF = left ventricular ejection fraction; PAMI-II, Second Primary Angioplasty in Myocardial Infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]For example, PAMI-II criteria: age <70 years, LVEF >45%, one- or two-vessel disease, successful PCI and no persistent arrhythmias.

6.5 Special patient subsets

Several specific patient subsets deserve particular consideration.

6.5.1 Patients taking oral anticoagulation

Many patients presenting with STEMI are previously on oral anticoagulation or require long-term anticoagulation afterwards. The addition of DAPT to oral anticoagulation increases the risk of bleeding complications two- to three-fold compared to anticoagulation alone.[266–269]

Management during STEMI: Given that oral anticoagulation is a relative contraindication for fibrinolysis, when these patients present with a STEMI, they should be triaged for primary PCI strategy regardless of the anticipated time to PCI-mediated reperfusion. Patients should receive additional parenteral anticoagulation, regardless of the timing of the last dose of oral anticoagulant. GP IIb/IIIa inhibitors should be avoided. Loading of aspirin should be done as in all STEMI patients, and clopidogrel is the $P2Y_{12}$ inhibitor of choice (600 mg loading dose) before or at the latest at the time of PCI. Prasugrel and ticagrelor are not recommended. Ideally, a chronic anticoagulation regimen should not be stopped during admission. Gastric protection with a proton pump inhibitor (PPI) is recommended.

Maintenance after STEMI: In general, continuation of oral anticoagulation in patients with an indication for DAPT (e.g. after STEMI) should be evaluated carefully and continued only if compelling evidence exists. Ischaemic and bleeding risks should be taken into consideration. While there is a considerable overlap of risk factors associated with ischaemic with bleeding outcomes, multiple bleeding risk scores outperform CHA_2DS_2-VASc [Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female)] in predicting bleeding risk.[270,271]

For most patients, triple therapy (in the form of oral anticoagulation, aspirin, and clopidogrel) should be considered for 6 months. Then, oral anticoagulation plus aspirin or clopidogrel should be considered for an additional 6 months. After 1 year, it is indicated to maintain only oral anticoagulation. In cases of very high bleeding risk, triple therapy can be reduced to 1 month after STEMI, continuing on dual therapy (oral anticoagulation plus aspirin or clopidogrel) up to 1 year, and thereafter only anticoagulation.[5,7]

The dose intensity of oral anticoagulation should be carefully monitored with a target international normalized ratio in the lower part of the recommended target range. When non-vitamin K antagonist oral anticoagulants are used, the lowest effective tested dose for stroke prevention should be applied. In general, dose reduction below the approved dose is not recommended. Recently, the Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) study randomized 2124 patients with non-valvular AF, who had undergone PCI with stenting (~12% STEMI patients), to receive low-dose rivaroxaban [15 mg *o.d.* (once a day)] plus a $P2Y_{12}$ inhibitor (93% clopidogrel) and no aspirin for 12 months, very-low-dose rivaroxaban (2.5 mg *b.i.d.*) plus DAPT (95% clopidogrel) for 1, 6, or 12 months, or standard therapy with a dose-adjusted vitamin K antagonist plus DAPT (96% clopidogrel) for 1, 6, or 12 months.[272] The primary safety endpoint (TIMI clinically significant bleeding) was lower in the two groups receiving rivaroxaban. No difference in major bleeding or transfusion was observed across groups. However, this study was underpowered for assessing differences in ischaemic events such as stent thrombosis or stroke rates. Therefore, uncertainty remains regarding the comparative performance of three tested antithrombotic regimens in patients at high stroke and/or stent thrombosis risk.

6.5.2 Elderly patients

Owing to the ageing of the population, a higher proportion of elderly patients is expected to present with STEMI. As these patients may present with atypical symptoms, the diagnosis of MI may be delayed or missed.[27] In addition, the elderly have more comorbidities and are less likely to receive reperfusion therapy compared with younger

Table 9 Recommended doses of antithrombotic agents in the acute care of patients with chronic kidney disease

Agent	Normal renal function and stage 1–3 CKD (eGFR ≥30 mL/min/1.73 m²)	Stage 4 CKD (eGFR 15 to <30 mL/min/1.73 m²)	Stage 5 CKD (eGFR <15 mL/min/1.73 m²)
Aspirin	Loading dose of 150–300 mg orally followed by a maintenance dose of 75–100 mg/day	No dose adjustment	No dose adjustment
Clopidogrel	Loading dose of 300–600 mg orally followed by 75 mg/day	No dose adjustment	No information available
Ticagrelor	Loading dose of 180 mg orally followed 90 mg twice a day	No dose adjustment	Not recommended
Prasugrel	Loading dose of 60 mg orally followed by 10 mg/day	No dose adjustment	Not recommended
Enoxaparin	1 mg/kg s.c. twice a day, 0.75 mg/kg s.c. twice daily in patients ≥75 years old	1 mg/kg s.c. once a day	Not recommended
UFH	*Before coronary angiography:* Bolus 60–70 IU/kg i.v. (maximum 5000 IU) and infusion (12–15 IU/kg/hour, maximum 1000 IU/hour), target aPTT 1.5–2.5 x control *During PCI:* 70-100 IU/kg i.v. (50-70 IU/kg if concomitant with GP IIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73 m² or dialysis	Not recommended
Bivalirudin	Bolus 0.75 mg/kg i.v., infusion 1.75 mg/kg/hour *If eGFR ≥30 and ≤60 mL/min/1.73m² reduce infusion dose to 1.4 mg/kg/hour*	Not recommended	Not recommended
Abciximab	Bolus of 0.25 mg/kg i.v. followed by 0.125 µg/kg/min infusion (maximum 10 µg/min)	Careful consideration of bleeding risk	Careful consideration of bleeding risk
Eptifibatide	Bolus[a] of 180 µg/kg i.v. followed by an infusion of 2.0 µg/kg/min for up to 18 hours If eGFR <50 mL/min/1.73 m² reduce infusion dose to 1.0 µg/kg/min	Not recommended	Not recommended
Tirofiban	Bolus 25 µg/kg i.v. followed by 0.15 µg/kg/min	Reduce infusion rate to 50%	Not recommended

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aPTT = activated partial thromboplastin time; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GP = glycoprotein; IU = international units; i.v. = intravenous; PCI = percutaneous coronary intervention; s.c. = subcutaneous; UFH = unfractionated heparin.
[a]Double bolus if administered during primary PCI.

patients.[273,274] Elderly patients are also at particular risk of bleeding and other complications from acute therapies because bleeding risk increases with age, renal function tends to decrease, and the prevalence of comorbidities is high. Observational studies have shown frequent excess dosing of antithrombotic therapies in elderly patients.[275] Furthermore, they have a higher risk of mechanical complications.

It is key to maintain a high index of suspicion for MI in elderly patients who present with atypical complaints, treating them as recommended, and using specific strategies to reduce bleeding risk; these include paying attention to proper dosing of antithrombotic therapies, particularly in relation to renal function, frailty, or comorbidities, and using radial access whenever possible. There is no upper age limit with respect to reperfusion, especially with primary PCI.[276]

6.5.3 Renal dysfunction

Renal dysfunction [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²] is present in approximately 30–40% of patients with ACS and is associated with a worse prognosis and increased risk of in-hospital complications.[277] Owing to differences in presentation (less frequent presentation with chest pain and fewer typical ECG signs) diagnosis may be delayed.

Although decisions on reperfusion in patients with STEMI have to be made before any assessment of renal function is available, it is important to estimate the GFR as soon as possible. The type and dose of antithrombotic agent (see *Table 9*) and the amount of contrast agent should be considered based on renal function.[277] ACS patients with chronic kidney disease (CKD) receive frequently excess dosing with antithrombotics, contributing to the increased bleeding risk.[275] Consequently, in patients with known or anticipated reduction of renal function, several antithrombotic agents should either be withheld or their doses reduced appropriately. Ensuring proper hydration during and after primary PCI and limiting the dose of contrast agents, preferentially low-osmolality contrast agents, are important steps in minimizing the risk of contrast-induced nephropathy.[1]

6.5.4 Non-reperfused patients

Patients who, for specific reasons (e.g. long delay), fail to receive reperfusion therapy within the recommended time (first 12 h) should immediately be evaluated clinically to rule out the presence of clinical,

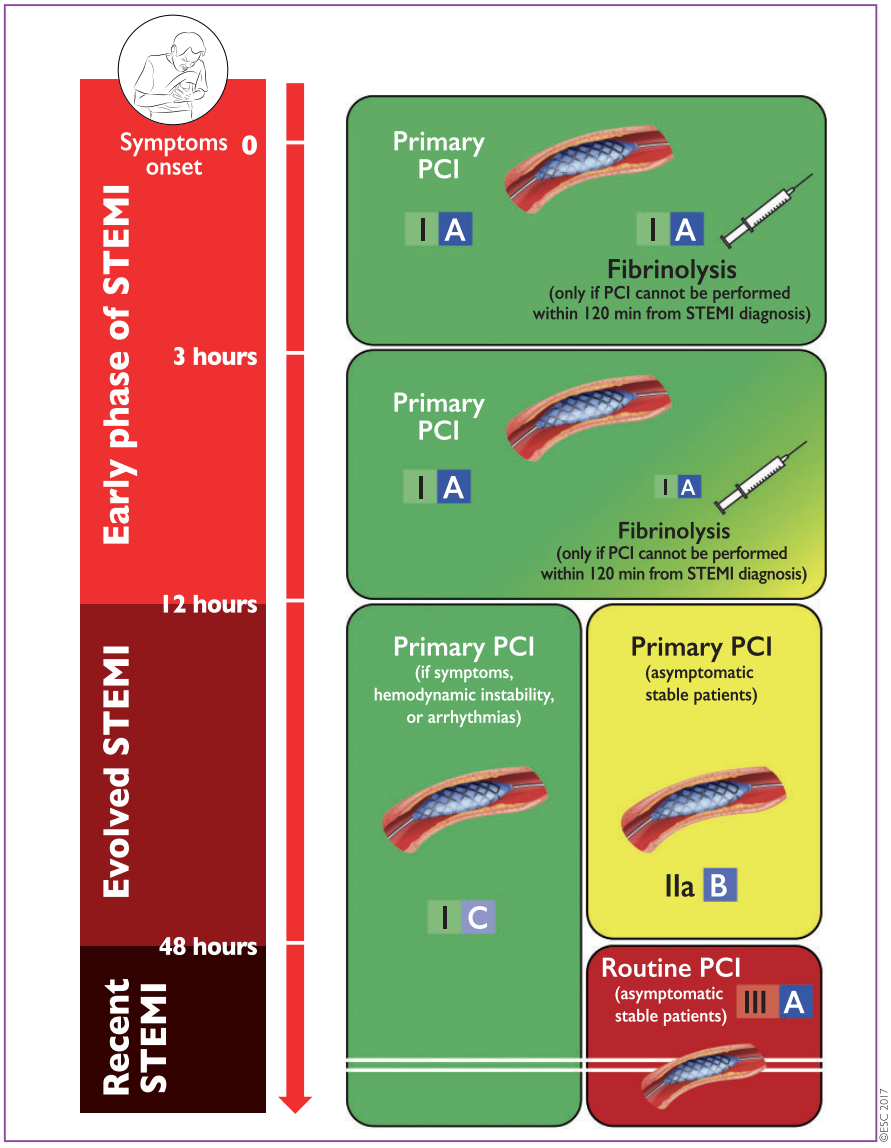

Figure 4 Reperfusion strategies in the infarct-related artery according to time from symptoms onset. PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
In early presenters (i.e. those with STEMI diagnosis within 3 hours from symptoms onset), a primary PCI strategy is the reperfusion strategy of choice. If the anticipated time from STEMI diagnosis to PCI-mediated reperfusion is > 120 min, then immediate fibrinolysis is indicated. After 3 hours (and up to 12 hours) of symptoms onset, the later the patient presents, the more consideration should be given to a primary PCI strategy as opposed to administering fibrinolytic therapy. In evolved STEMI (12–48 hours after symptoms onset), a routine primary PCI strategy (urgent angiography and subsequent PCI if indicated) should be considered in all patients. After 48 hours (recent STEMI) angiography should be performed but routine PCI of a total occluded IRA is not recommended. Regardless of the time from symptoms onset, the presence of ongoing symptoms suggestive of ischaemia, haemodynamic instability, or lifethreatening arrhythmias is an indication for a primary PCI strategy.

haemodynamic, or electrical instability. A primary PCI strategy is indicated in the presence of signs or symptoms suggestive of ongoing myocardial ischaemia, heart failure, haemodynamic instability, or life-threatening arrhythmias,[141] and should be considered in stable asymptomatic patients between 12–48 h after symptom onset.[133,142] After that time, either a non-invasive test for the presence of residual myocardial ischaemia/viability to decide a late invasive strategy or elective coronary angiography should be considered. However, routine PCI is not indicated in totally occluded IRA beyond the first 48 h from symptom onset due to the increased risk of late complications (see *Figure 4*).[135,137]

Early echocardiography with LVEF assessment is indicated in all patients. Medical therapy should include DAPT, anticoagulation, and

secondary prevention therapies. In patients in whom PCI is finally performed, ticagrelor or prasugrel are preferred,[186,187] while in patients who do not undergo PCI, clopidogrel is indicated.[225] Anticoagulation, preferably with fondaparinux, is indicated until coronary revascularisation is done or hospital discharge.[199] These patients are often undertreated. Therefore, it is important to emphasize that they should receive all the same secondary prevention medical therapies as those who receive timely reperfusion.

6.5.5 Patients with diabetes

Patients with diabetes are known to present with atypical chest pain more frequently than patients without diabetes and consequently may receive delayed initiation of treatment.[278] In addition, diabetic patients are characterized by a more diffuse atherosclerotic disease.[279] Although patients with diabetes are at higher risk of death and complications (including repeat revascularization after PCI), selection of antithrombotic therapies and reperfusion therapy is the same as in patients without diabetes. Regarding the use of antiplatelet drugs, the more potent oral $P2Y_{12}$ receptor inhibitors (prasugrel or ticagrelor) have consistently shown increased relative benefits with higher absolute risk reductions in patients with diabetes compared with clopidogrel.[280] On admission, it is recommended to evaluate glycaemic status in all STEMI patients with and without a known history of diabetes or hyperglycaemia, and to monitor it frequently in diabetic patients and patients with hyperglycaemia. In critically ill patients, there is a high risk of hypoglycaemia-related events when using intensive insulin therapy.[281] In the absence of robust data to guide the optimal glucose management (e.g. treatment thresholds and glucose targets) in STEMI patients, a close but not too strict glucose control seems the best approach. In the acute phase, it is reasonable to manage hyperglycaemia (i.e. maintain a blood glucose concentration ≤11.0 mmol/L or 200 mg/dL) but absolutely avoid hypoglycaemia.[282] To assess the risk of renal insufficiency, it is recommended to measure eGFR in patients on metformin and/or sodium-glucose co-transporter-2 (SGLT2) inhibitors.

6.6. Risk assessment

6.6.1 Clinical risk assessment

All patients with STEMI should have an early assessment of short-term risk, including an evaluation of the extent of myocardial damage, the occurrence of successful reperfusion, and the presence of clinical markers of high risk of further events including older age, fast heart rate, hypotension, Killip class >I, anterior MI, previous MI, elevated initial serum creatinine, history of heart failure, or peripheral arterial disease. Several risk scores have been developed, based on readily identifiable parameters in the acute phase before reperfusion.[264,283] The Global Registry of Acute Coronary Events (GRACE) risk score is recommended for risk assessment and adjustment.[283,284] All patients should also have an evaluation of long-term risk before discharge, including LVEF, severity of CAD and completeness of coronary revascularization, residual ischaemia, occurrence of complications during hospitalization, and levels of metabolic risk markers, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting triglycerides, and plasma glucose, as well as renal function. As LDL-C levels tend to decrease during the first days after MI, they should be measured as soon as possible after admission.

Patients who do not get successful reperfusion are at higher risk of early complications and death. These patients should have an assessment of the presence of residual ischaemia and, if appropriate, myocardial viability. Because the risk of events decreases with time, early risk assessment is indicated.

6.6.2 Non-invasive imaging in management and risk stratification

LV dysfunction is a key prognostic factor. Therefore, it is recommended that the LVEF is determined before hospital discharge in all STEMI patients. Emergency echocardiography at presentation is indicated in patients with cardiac arrest, cardiogenic shock, haemodynamic instability or suspected mechanical complications, and if the diagnosis of STEMI is uncertain. Routine echocardiography after primary PCI is recommended to assess resting LV function, as well as

Management of hyperglycaemia

Recommendations	Class[a]	Level[b]
It is recommended to measure glycaemic status at initial evaluation in all patients, and perform frequent monitoring in patients with known diabetes or hyperglycaemia (defined as glucose levels ≥11.1 mmol/L or ≥ 200 mg/dL)	I	C
In patients on metformin and/or SGLT2 inhibitors, renal function should be carefully monitored for at least 3 days after coronary angiography/PCI.[c]	I	C
Glucose-lowering therapy should be considered in ACS patients with glucose levels >10 mmol/L (>180 mg/dL), while episodes of hypoglycaemia (defined as glucose levels ≤3.9 mmol/L or ≤ 70 mg/dL) should be avoided.	IIa	C
Less stringent glucose control should be considered in the acute phase in patients with more advanced cardiovascular disease, older age, longer diabetes duration, and more comorbidities.	IIa	C

ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; SGLT2 = sodium-glucose co-transporter-2.
[a]Class of recommendation.
[b]Level of evidence.
[c]A short withdrawal of metformin may be considered after an invasive coronary procedure.

RV and valve function, to exclude early post-infarction mechanical complications and LV thrombus. This assessment is usually performed with echocardiography, but in the limited cases in which echocardiography may be suboptimal or inconclusive, CMR may be a good alternative. Patients with multivessel disease in which only the IRA lesion has been treated, or patients with late-presenting STEMI, may benefit from additional assessment for residual ischaemia or viability. Treatment of non-IRA lesions in patients with multivessel disease is discussed in section 5.2.1.4. In patients presenting days after the acute event with a completed MI, the presence of recurrent angina or documented ischaemia and proven viability in a large myocardial territory may help define a strategy of planned revascularization of an occluded IRA,[135,285,286] although the evidence is controversial.

The timing of and best imaging technique (echocardiography, SPECT, CMR, or PET) to detect residual ischaemia and myocardial viability remains to be determined, but will also depend on local availability and expertise. The best validated and widely available tests are stress echocardiography and SPECT (both used in combination with exercise or pharmacological stress), but PET and CMR are equally indicated. However, in post-MI patients, the detection of residual ischaemia by echocardiography is challenging due to existing wall motion abnormalities.[287] LGE-CMR imaging has a high diagnostic accuracy for assessing the transmural extent of myocardial scar tissue.[288] However, the ability to detect viability and predict recovery of wall motion is not significantly superior to other imaging techniques.[289] The presence of dysfunctional viable myocardium by LGE-CMR is an independent predictor of mortality in patients with ischaemic LV dysfunction.[290]

More recently, the presence of wall thinning with limited scar burden was shown to be associated with improved contractility and resolution of wall thinning after revascularization, emphasizing the importance of viability beyond wall thickness and myocardial revascularization to improve prognosis.[291] PET is also a high-resolution technique but its use is limited by cost and availability. A randomized clinical trial with PET imaging demonstrated that patients with a substantial amount of dysfunctional but viable myocardium are likely to benefit from myocardial revascularization and may show improvements in regional and global contractile function, symptoms, exercise capacity, and long-term prognosis.[292] The association between viability and improved survival after revascularisation was also demonstrated by a meta-analysis.[293]

In patients with a pre-discharge LVEF ≤40%, re-evaluation of LVEF 6–12 weeks after complete revascularization and optimal medical therapy is recommended to assess the potential need for primary prevention implantable cardioverter defibrillator (ICD) implantation.[3] Additional parameters that are measured by imaging in these patients and that could be used as endpoints in clinical trials are: (1) infarct size (CMR, SPECT, and PET); (2) myocardium at risk (SPECT, CMR); (3) MVO (CMR); and (4) intramyocardial haemorrhage (CMR). Infarct size and MVO are predictors of long-term mortality and heart failure in STEMI survivors.[216,217,294]

Summary of indications for imaging and stress testing in ST-elevation myocardial infarction patients

Recommendations	Class[a]	Level[b]
At presentation		
Emergency echocardiography is indicated in patients with cardiogenic shock and/or haemodynamic instability or suspected mechanical complications without delaying angiography.[295]	I	C
Emergency echocardiography before coronary angiography should be considered if the diagnosis is uncertain.[295]	IIa	C
Routine echocardiography that delays emergency angiography is not recommended.[295]	III	C
Coronary CT angiography is not recommended	III	C
During hospital stay (after primary PCI)		
Routine echocardiography to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients.[296,297]	I	B
Emergency echocardiography is indicated in haemodynamically unstable patients.[295]	I	C
When echocardiography is suboptimal/inconclusive, an alternative imaging method (CMR preferably) should be considered.	IIa	C
Either stress echo, CMR, SPECT, or PET may be used to assess myocardial ischaemia and viability, including in multivessel CAD.[1,298–300]	IIb	C
After discharge		
In patients with pre-discharge LVEF ≤40%, repeat echocardiography 6–12 weeks after MI, and after complete revascularization and optimal medical therapy, is recommended to assess the potential need for primary prevention ICD implantation.[3,296]	I	C
When echo is suboptimal or inconclusive, alternative imaging methods (CMR preferably) should be considered to assess LV function.	IIa	C

CAD = coronary artery disease; CMR = cardiac magnetic resonance; CT = computed tomography; ICD = implantable cardioverter defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; PET = positron emission tomography; RV = right ventricular; SPECT = single-photon emission computed tomography.
[a]Class of recommendation.
[b]Level of evidence.

7. Long-term therapies for ST-segment elevation myocardial infarction

7.1 Lifestyle interventions and risk factor control

Key lifestyle interventions include cessation of smoking, optimal blood pressure control, diet advice and weight control, and encouraging physical activity. Detailed recommendations are available from the ESC Guidelines on prevention.[4] During hospitalization, the time for implementing secondary prevention is limited and a close collaboration between the cardiologist and the general practitioner, specialist rehabilitation nurses, pharmacists, dieticians, and physiotherapists is critically important. Habits of a lifetime are not easily changed, and the implementation and follow-up of these changes are a long-term undertaking.

7.1.1 Smoking cessation

Smoking has a strong pro-thrombotic effect, and smoking cessation is potentially the most (cost) effective of all secondary prevention measures.[301] Smoking cessation interventions should start during hospitalization, when smoking is not allowed, and continue during the post-discharge follow-up period.[302,303] The beneficial effect of smoking cessation in patients with CAD, including a majority suffering an MI, has been shown in a meta-analysis (20 observational studies, including 12 603 patients) reporting a 36% reduction of mortality in quitters.[304]

A significant number of CAD patients continue or restart smoking, illustrating the addictive nature of the smoking habit.[305] There is a strong evidence base for brief interventions, with a combination of behavioural support and pharmacotherapies including nicotine replacement therapy, bupropion, and varenicline.[305,306] Electronic cigarettes may also be helpful in achieving smoking cessation, as there is some evidence from two pooled randomized clinical trials (662 patients) showing that electronic cigarettes with nicotine had higher quit or reduced smoking rates when compared with placebo.[307]

7.1.2 Diet, alcohol, and weight control

Current guidelines on prevention recommend: (i) a diet similar to the Mediterranean diet, which includes a maximum of 10% of total energy intake from saturated fat, by replacing it with polyunsaturated fatty acids and as little as possible of trans fatty acids; (ii) salt intake of < 5 g per day; (iii) 30–45 g fibre per day; (iv) ≥200 g fruits and 200 g vegetables per day; (v) fish 1–2 times per week (especially oily varieties); (vi) 30 g unsalted nuts daily; (vii) limited alcohol intake [maximum of 2 glasses (20 g of alcohol) daily for men and 1 for women]; and (viii) discouraging sugar-sweetened drinks.[4] Moderate alcohol consumption in abstainers is not recommended.

Overweight and obesity [body mass index (BMI) ≥25 kg/m^2] is associated with higher all-cause mortality compared with a healthy weight (BMI between 20 kg/m^2 and <25 kg/m^2). Abdominal fat is particularly harmful and weight loss has beneficial effects on cardiovascular disease risk factors. Consequently, maintaining a healthy weight or losing weight is recommended for all subjects,[308] including patients with STEMI. However, it has not been established that weight reduction *per se* reduces mortality.

7.1.3 Exercise-based cardiac rehabilitation

All AMI patients should participate in an exercise-based cardiac rehabilitation programme,[309] taking into account their age, pre-infarction level of activity, and physical limitations. A cardiac rehabilitation programme preferably includes exercise training, risk factor modification, education, stress management, and psychological support.[309] In a large meta-analysis, exercise training as part of a cardiac rehabilitation programme was associated with a 22% reduction in cardiac mortality rate in patients with CAD.[309] The benefit of cardiac rehabilitation appears to be through direct physiological effects of exercise training and through cardiac rehabilitation effects on risk factor control, lifestyle behaviours, and mood.[310] An additional benefit in the context of a short hospital stay is to ensure proper titration and monitoring of key, evidence-based therapies after STEMI. Nowadays, most rehabilitation is offered as an outpatient programme of 8–24 weeks' duration.[311,312]

7.1.4 Resumption of activities

Return to work after AMI represents an important indicator of recovery. Younger women in particular are at greater risk of not returning to work, given evidence of their worse recovery after MI than similarly aged men.[313] Decisions should be individualized, based on LV function, completeness of revascularization and rhythm control, and the job characteristics. Extended sick leave is usually not beneficial and light-to-moderate physical activity after discharge should be encouraged. Sexual activity can be resumed early if adjusted to physical ability.

Guidance on air travel including repatriation for patients suffering an MI abroad is constrained by limited data. Factors related to the clinical circumstances as well as length of travel, whether accompanied, and the degree of anxiety also play a role. For uncomplicated completely revascularized MI with LVEF >40% the risk is low and travelling is regarded as safe after hospital discharge (from day 3 onwards). In complicated STEMI, including patients with heart failure, LVEF <40%, residual ischaemia, and arrhythmia, travelling should be deferred until the condition is stable.[314]

7.1.5 Blood pressure control

Hypertension is a prevalent risk factor in patients admitted with STEMI and, consequently, blood pressure should be well controlled. In addition to lifestyle changes, including reduced salt intake, increased physical activity, and weight loss, pharmacotherapy with a systolic blood pressure (SBP) target of < 140 mmHg should be initiated. In elderly, frail patients, the target can be more lenient, whereas in patients at very high risk who tolerate multiple blood pressure-lowering drugs, a target of < 120 mmHg may be considered.[4,315,316] Despite the proven efficacy of this treatment, non-adherence to lifestyle interventions and medications may affect treatment effect.

7.1.6 Adherence to treatment

Low treatment adherence is an important barrier to achieving optimal treatment targets and is associated with worse outcomes.[317] Delayed outpatient follow-up after AMI results in worse short- and long-term medication adherence.[318] In a meta-analysis of 376 162

patients, adherence to cardiovascular medications was estimated to be about 57% after a median of 2 years.[319]

It is generally recognized that adherence is determined by the interplay of socioeconomic, medication-related, condition-related, health system-related, and patient-related factors.[320] A strategy to reduce poor adherence is the use of a fixed-dose combination or polypill, including key medications to reduce cardiovascular risk, as a once-daily dose pill.[321,322] The only study dedicated to post-MI patients is the recent phase 2 Fixed-Dose Combination Drug for Secondary Cardiovascular Prevention (FOCUS) trial,[323] in which 695 patients post-MI were randomized to usual care or to a polypill-based strategy [polypill containing aspirin, an angiotensin-converting enzyme (ACE) inhibitor, and a statin]. In this trial, after 9 months of follow-up, the polypill group showed improved adherence compared with the group receiving separate medications. Larger trials are needed to confirm a clinical benefit in secondary prevention.

Although low adherence has been qualified as an ubiquitous problem,[324] healthcare professionals and patients should be aware of this challenge and optimize communication by providing clear information, simplify treatment regimens, aim at shared decision-making, and implement repetitive monitoring and feedback.

Behavioural aspects after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.[4,302,303,325–327]	I	A
Participation in a cardiac rehabilitation programme is recommended.[4,309,328]	I	A
A smoking cessation protocol is indicated for each hospital participating in the care of STEMI patients.	I	C
The use of the polypill and combination therapy to increase adherence to drug therapy may be considered.[4,322,323]	IIb	B

STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

7.2 Antithrombotic therapy

Full text about long-term antithrombotic therapy can be found in the online Web Addenda. In addition, this topic is covered in great detail in the ESC Focused Update on DAPT in CAD published simultaneously with these guidelines.[7]

7.2.1 Aspirin

Aspirin is recommended indefinitely in all patients with STEMI.[329,330] For long-term prevention, low aspirin doses (75–100 mg) are indicated due to similar anti-ischaemic and less adverse events than higher doses, as demonstrated in the CURRENT-OASIS 7 trial.[330]

7.2.2 Duration of dual antiplatelet therapy and antithrombotic combination therapies

DAPT, combining aspirin and a $P2Y_{12}$ inhibitor (i.e. prasugrel, ticagrelor, or clopidogrel), is recommended in patients with STEMI who are undergoing primary PCI (for up to 12 months).[186,187] Clopidogrel is recommended for 1 month in patients treated with fibrinolysis without subsequent PCI.[225,226] Expanding the duration of DAPT up to 12 months should be considered in these patients.

For patients undergoing fibrinolysis and subsequent PCI, DAPT is recommended for 12 months. Clopidogrel is the $P2Y_{12}$ inhibitor of choice as co-adjuvant and after fibrinolysis. Potent $P2Y_{12}$ inhibitors have not been properly tested in patients undergoing fibrinolysis, and safety (i.e. bleeding complications) is not well established. However, in patients who underwent PCI after fibrinolysis, after a safety period (arbitrarily considered 48 h), there are no biological grounds to consider that potent $P2Y_{12}$ inhibitors will add risk and not exert a benefit over clopidogrel as in the primary PCI setting.

Whereas no dedicated study exists on optimal DAPT duration in patients at high bleeding risk, multiple studies have shown that shortening DAPT to 6 months, compared with 12 months or longer, reduces the risk of major bleeding complications, with no apparent trade-off in ischaemic events.[331,332]

Two major studies have shown the benefit towards reduction of non-fatal ischaemic events in patients receiving longer than 12 months of DAPT.[333,334] The DAPT Study included only roughly 10% of STEMI patients and no information has so far been provided with respect to the benefit of prolonging clopidogrel or prasugrel from 12 to 30 months in this patient subset. Hence, no formal recommendations are possible for the use of clopidogrel or prasugrel beyond 1 year.[334]

More recently, the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial examined two doses of ticagrelor (60 mg and 90 mg *b.i.d.*) vs. placebo in patients with a history of MI 1–3 years previously and with high-risk features; the study showed a reduction in MACE with 90 mg ticagrelor.[333] There was no reduction in total mortality, but there was a borderline signal towards reduced cardiovascular mortality (when both doses were pooled) consistent with the reduction in non-fatal outcomes.[333] The 60 mg (but not the 90 mg) ticagrelor (plus aspirin) regimen also significantly reduced the stroke risk compared with aspirin monotherapy. The ticagrelor regimen was associated with a significantly increased bleeding risk. Patients with previous STEMI comprised more than 50% of the overall PEGASUS-TIMI 54 population, and subgroup analysis has shown consistent results in patients with previous STEMI vs. NSTEMI.[333] According to the available data, extension of DAPT beyond 1 year (up to 3 years) in the form of aspirin plus ticagrelor 60 mg *b.i.d.* may be considered in patients who have tolerated DAPT without a bleeding complication and having one additional risk factor for ischaemic events.

Gastric protection with a PPI is recommended for patients with a history of gastrointestinal bleeding and is appropriate for patients with multiple risk factors for bleeding, such as advanced age, concurrent use of anticoagulants, steroids or non-steroidal anti-inflammatory drugs including high-dose aspirin, and *Helicobacter pylori* infection.[335–337]

In the Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial (n = 15 526, 50% STEMI), a low dose of rivaroxaban (2.5 mg twice daily), on top of aspirin plus clopidogrel, reduced the composite primary endpoint of cardiovascular death, MI, or stroke, but also all-cause mortality, over a mean follow-up of 13 months.[338] Stent thrombosis was reduced by one-third. However, this was associated with a three-fold increase in non-CABG-related major bleeding and intracranial haemorrhage.[338] Based on the ATLAS ACS 2–TIMI 51 trial, in selected patients at low bleeding risk, the 2.5 mg dose of rivaroxaban may be considered in patients who receive aspirin and clopidogrel after STEMI.

(METOCARD-CNIC) trial (n = 270) showed that the very early administration of i.v. metoprolol (15 mg) at the time of diagnosis in patients with anterior STEMI, no signs of heart failure, and SBP >120 mmHg was associated with a reduction in infarct size measured by CMR at 5–7 days (25.6 g vs. 32.0 g; P = 0.012), and higher LVEF at 6 months CMR (48.7% vs. 45.0%; P = 0.018) compared with control treatment.[347,348] All patients without contraindications received oral metoprolol within 24 h. The incidence of MACE (composite of death, admission as a result of heart failure, reinfarction, or malignant ventricular arrhythmias) at 2 years was 10.8% vs. 18.3% in the i.v. metoprolol and control

Maintenance antithrombotic strategy after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.[329]	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contraindicated), is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.[186,187]	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding[c].[335–337]	I	B
In patients with an indication for oral anticoagulation, oral anticoagulants are indicated in addition to antiplatelet therapy.[5]	I	C
In patients who are at high risk of severe bleeding complications, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.[332,339,340]	IIa	B
In STEMI patients with stent implantation and an indication for oral anticoagulation, triple therapy[d] should be considered for 1–6 months (according to a balance between the estimated risk of recurrent coronary events and bleeding).[5]	IIa	C
DAPT for 12 months in patients who did not undergo PCI should be considered unless there are contraindications such as excessive risk of bleeding.	IIa	C
In patients with LV thrombus, anticoagulation should be administered for up to 6 months guided by repeated imaging.[341–343]	IIa	C
In high ischaemic-risk patients[e] who have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.[333]	IIb	B
In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered.[338]	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and oral anticoagulation.	III	C

AMI = acute myocardial infarction; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; LV = left ventricular; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]History of gastrointestinal bleeding, anticoagulant therapy, chronic non-steroidal anti-inflammatory drug/corticosteroid user, and ≥2 or more of the following: age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, *H. pylori* infection, and chronic alcohol use.
[d]Oral anticoagulant, aspirin, and clopidogrel.
[e]Defined as age ≥50 years, and at least one of the following additional high-risk features: age ≥65 years, diabetes mellitus on medication, a prior spontaneous AMI, multivessel CAD, or chronic renal dysfunction (eGFR <60 ml/min/1.73 m^2).

7.3 Beta-blockers

7.3.1 Early intravenous beta-blocker administration

In patients undergoing fibrinolysis, early i.v. beta-blocker treatment reduces the incidence of acute malignant ventricular arrhythmias, although there is no clear evidence of long-term clinical benefit.[344–346]

In patients undergoing primary PCI, the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction

arms (P = 0.065).[348] Metoprolol treatment was associated with a significant reduction in the incidence and extent of MVO.[349] The Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention (EARLY-BAMI) trial randomized 683 patients with STEMI within 12 h of onset to i.v. metoprolol (5 mg at recruitment and an additional 5 mg immediately before PCI) or placebo.[350] All patients without contraindications

received oral metoprolol within 12 h. Early i.v. metoprolol administration did not show any benefit in reducing CMR-based infarct size, the trial primary endpoint, available only in 342 patients (55%), or the level of cardiac biomarker release. Early i.v. metoprolol was associated with a borderline reduction of malignant ventricular arrhythmias (3.6% vs. 6.9%; $P = 0.050$). Patients treated with i.v. metoprolol showed no increased risk of haemodynamic instability, atrioventricular (AV) block, or MACE at 30 days. *Post hoc* analyses from primary PCI trials testing other hypotheses have suggested that early i.v. beta-blocker administration might be associated with a clinical benefit, but a selection bias cannot be excluded even after correction for imbalances in baseline characteristics.[351,352] Based on the current available evidence, early administration of i.v. beta-blockers at the time of presentation followed by oral beta-blockers should be considered in haemodynamically stable patients undergoing primary PCI.

7.3.2 Mid- and long-term beta-blocker treatment

The benefit of long-term treatment with oral beta-blockers after STEMI is well established, although most of the supporting data come from trials performed in the pre-reperfusion era.[353] A recent multicentre registry enrolling 7057 consecutive patients with AMI showed a benefit in terms of mortality reduction at a median follow-up of 2.1 years associated with beta-blocker prescription at discharge, although no relationship between dose and outcomes could be identified.[354] Using registry data, the impact of newly introduced beta-blocker treatment on cardiovascular events in 19 843 patients with either ACS or undergoing PCI was studied.[355] At an average of 3.7 years of follow-up, the use of beta-blockers was associated with a significant mortality reduction (adjusted HR 0.90, 95% CI 0.84–0.96). The association between beta-blockers and outcomes differed significantly between patients with and without a recent MI (HR for death 0.85 vs. 1.02; $P_{int} = 0.007$). Opposing these results, in a longitudinal observational propensity-matched study including 6758 patients with previous MI, beta-blocker use was not associated with a lower risk of cardiovascular events or mortality.[356] Based on the current evidence, routine administration of beta-blockers in all post-STEMI patients should be considered as discussed in detail in the heart failure guidelines;[6] beta-blockers are recommended in patients with reduced systolic LV function (LVEF ≤40%), in the absence of contraindications such as acute heart failure, haemodynamic instability, or higher degree AV block. Agents and doses of proven efficacy should be administered.[357–361] As no study has properly addressed beta-blocker duration to date, no recommendation in this respect can be made. Regarding the timing of initiation of oral beta-blocker treatment in patients not receiving early i.v. beta-blockade, a retrospective registry analysis on 5259 patients suggested that early (i.e. <24 h) beta-blocker administration conveyed a survival benefit compared with a delayed one.[362] Therefore, in haemodynamically stable patients, oral beta-blocker initiation should be considered within the first 24 h.

7.4 Lipid-lowering therapy

The benefits of statins in secondary prevention have been unequivocally demonstrated,[363] and trials have shown the benefits of early and intensive statin therapy in ACS.[364,365] A meta-analysis of trials comparing more- vs. less-intensive LDL-C lowering with statins indicated that more-intensive statin therapy produced greater reductions in the risks of cardiovascular death, non-fatal MI, ischaemic stroke, and coronary revascularization.[366] For every 1.0 mmol/L reduction in LDL-C, these further reductions in risk were similar to the proportional reductions in the trials of statins vs. control. Therefore, statins are recommended in all patients with AMI, irrespective of cholesterol concentration at presentation. Lipid-lowering treatment should be started as early as possible, as this increases patient adherence after discharge, and given as high-intensity treatment, as this is associated with early and sustained clinical benefits.[4] The intensity of statin therapy should be increased in those receiving a low- or moderate-intensity statin treatment at presentation, unless they have a history of intolerance to high-intensity statin therapy or other characteristics that may influence safety.[366–368] The treatment goal is an LDL-C concentration of < 1.8 mmol/L (<70 mg/dL) or at least 50% reduction in LDL-C if the baseline LDL-C level is 1.8–3.5 mmol/L.[4,367,369] The use of lower-intensity statin therapy should be considered in patients at increased risk of side effects from statins (e.g. elderly, hepatic or renal impairment, previous side effects, or a potential for interaction with essential concomitant therapy). Following MI, the lipid profile goes through phasic changes, with small reductions in total cholesterol, LDL-C, and HDL-C, and increases in triglycerides within the first 24 h.[370,371] A lipid profile should be obtained as early as possible after admission for STEMI and can be non-fasting, as total and HDL-C show little diurnal variation and LDL-C variation is within 10%.[372] Lipids should be re-evaluated 4–6 weeks after the ACS to determine whether the target levels have been reached and regarding safety issues; the lipid lowering therapy can then be adjusted accordingly. Trial results with high doses of atorvastatin and simvastatin[366,373–375] favour a high-intensity statin.

In patients known to be intolerant of any dose of statin, treatment with ezetimibe should be considered. In the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), 18 144 patients with a recent ACS (29% with STEMI) were randomized to either ezetimibe 10 mg/simvastatin 40 mg or simvastatin 40 mg alone (simvastatin was up-titrated to 80 mg if LDL-C was >79 mg/dL or 2.04 mmol/L).[376] Over a period of 7 years, the composite primary endpoint of cardiovascular death, MI, hospital admission for unstable angina, coronary revascularization, or stroke was significantly lower in the combined treatment arm compared with the statin-only arm (32.7% vs. 34.7%; HR 0.94, 95% CI 0.89–0.99).

Recent data from phase I–III trials show that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors decrease LDL-C up to 60%, either as monotherapy or in addition to a statin dose, and also have beneficial effects on triglycerides and HDL-C.[377–380] Meta-analyses of existing trials with more than 10 000 patients indicate a significant mortality benefit (HR 0.45, 95% CI 0.23–0.86) but are based on relatively few endpoints.[378,381] In the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial consisting of 27 564 patients with atherosclerotic cardiovascular disease, additional risk factors, and LDL ≥70 mg/dL (1.8 mmol/L), who

were already receiving moderate or high intensity statin therapy as compared to placebo, evolocumab injections reduced the primary composite endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 15% in relative rate and by 1.5% in absolute rate. There were no differences in all-cause mortality or cardiovascular mortality and no significant differences in adverse events.[382] Given the moderate effect over 2 years and the absence of mortality reduction, its use should still be restricted to selected high-risk patients.

Based on this relatively limited body of evidence, clinicians should consider adding a non-statin treatment to patients at high risk who do not reach treatment targets after STEMI despite the maximum tolerated dose of statin.

7.5 Nitrates

The routine use of nitrates in STEMI was of no benefit in a randomized controlled trial against placebo and is therefore not recommended.[383] Intravenous nitrates may be useful during the acute phase in patients with hypertension or heart failure, provided there is no hypotension, RV infarction, or use of phosphodiesterase type 5 inhibitors in the previous 48 h. Following the acute phase, nitrates remain valuable agents to control residual angina symptoms.

7.6 Calcium antagonists

A meta-analysis of 17 trials involving calcium antagonists early in the course of STEMI showed no beneficial effect on death or reinfarction, with a trend of higher mortality for patients treated with nifedipine. Therefore, routine use of calcium antagonists in the acute phase is not indicated.[384,385] In the chronic phase, a randomized controlled trial allocating 1775 patients with MI not on beta-blockers to verapamil or placebo found that the risk of mortality and reinfarction was reduced with verapamil.[386] Thus, in patients with contraindications to beta-blockers, particularly in the presence of obstructive airway disease, calcium antagonists are a reasonable option for patients without heart failure or impaired LV function. Routine use of dihydropyridines, on the other hand, has failed to show benefit after STEMI,[387] and they should therefore only be prescribed for clear additional indications such as hypertension or residual angina.[388]

7.7 Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers

ACE inhibitors are recommended in patients with an impaired LVEF (≤40%) or who have experienced heart failure in the early phase.[383,389–392] A systematic overview of trials of ACE inhibition early in STEMI indicated that this therapy is safe, well tolerated, and associated with a small but significant reduction in 30-day mortality, with most of the benefit observed in the first week.[383,393] Treatment with ACE inhibitors is recommended in patients with systolic LV dysfunction or heart failure, hypertension, or diabetes, and should be considered in all STEMI patients.[394,395] Patients who do not tolerate an ACE inhibitor should be given an angiotensin II receptor blocker (ARB). In the context of STEMI, valsartan was found to be non-inferior to captopril in the VALsartan In Acute myocardial iNfarcTion (VALIANT) trial.[396]

7.8 Mineralocorticoid/aldosterone receptor antagonists

Mineralocorticoid receptor antagonist (MRA) therapy is recommended in patients with LV dysfunction (LVEF ≤40%) and heart failure after STEMI.[397–400] Eplerenone, a selective aldosterone receptor antagonist, has been shown to reduce morbidity and mortality in these patients. The Eplerenone Post-AMI Heart failure Efficacy and SUrvival Study (EPHESUS) randomized 6642 post-MI patients with LV dysfunction (LVEF ≤40%) and symptoms of heart failure/diabetes to eplerenone or placebo within 3–14 days after their infarction.[397] After a mean follow-up of 16 months, there was a 15% relative reduction in total mortality and a 13% reduction in the composite of death and hospitalization for cardiovascular events.

Two recent studies have indicated a beneficial effect of early treatment with MRA in the setting of STEMI without heart failure. The Double-Blind, Randomized, Placebo-Controlled Trial Evaluating The Safety And Efficacy Of Early Treatment With Eplerenone In Patients With Acute Myocardial Infarction (REMINDER) trial randomized 1012 patients with acute STEMI without heart failure to eplerenone or placebo within 24 h of symptom onset.[401] After 10.5 months, the primary combined endpoint [CV mortality, re-hospitalization, or extended initial hospital stay due to diagnosis of heart failure, sustained ventricular tachycardia or fibrillation, ejection fraction ≤40%, or elevated B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic peptide (NT-proBNP)] occurred in 29.4% of the active group vs. 18.2% in the placebo group ($P < 0.0001$), with the difference primarily driven by BNP levels.[401] The Aldosterone Lethal effects Blockade in Acute myocardial infarction Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) trial randomized 1603 patients with acute STEMI or high-risk NSTEMI to a single i.v. bolus of potassium canrenoate (200 mg) followed by spironolactone (25 mg daily) vs. placebo. Overall, the study found no effect on the composite outcome (death, resuscitated cardiac arrest, significant ventricular arrhythmia, indication for implantable defibrillator, or new or worsening heart failure) at 6 months. In an exploratory analysis of the STEMI subgroup ($n = 1229$), the outcome was significantly reduced in the active treatment group (HR 0.20, 95% CI 0.06–0.70).[402] Future studies will clarify the role of MRA treatment in this setting.

Routine therapies in the acute, subacute, and long-term phases: beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and lipid-lowering treatments after ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Beta-blockers		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contraindicated.[357–361]	I	A
Intravenous beta-blockers should be considered at the time of presentation in patients undergoing primary PCI without contraindications, with no signs of acute heart failure, and with an SBP >120 mmHg.[346–348,350,403]	IIa	A
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.[344,354–356,404,405]	IIa	B
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure or AV block, or severe bradycardia.[344]	III	B
Lipid lowering therapies		
It is recommended to start high-intensity statin therapy[c] as early as possible, unless contraindicated, and maintain it long-term.[364,366,368]	I	A
An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.[367,369,376,382]	I	B
It is recommended to obtain a lipid profile in all STEMI patients as soon as possible after presentation.[369,406]	I	C
In patients with LDL-C ≥1.8 mmol/L (≥70 mg/dL) despite a maximally tolerated statin dose who remain at high risk, further therapy to reduce LDL-C should be considered.[376,382]	IIa	A
ACE inhibitors/ARBs		
ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct.[383]	I	A
An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.[396,407]	I	B
ACE inhibitors should be considered in all patients in the absence of contraindications.[394,395]	IIa	A
MRAs		
MRAs are recommended in patients with an LVEF ≤40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia.[397]	I	B

AV = atrioventricular; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]High-intensity statin defined as atorvastatin 40–80 mg and rosuvastatin 20–40 mg.

When using MRA, care should be taken with reduced renal function [creatinine concentration >221 mmol/L (2.5 mg/dL) in men and >177 mmol/L (2.0 mg/dL) in women] and routine monitoring of serum potassium is warranted.

Figures 5 and *6* present the mostly prescribed interventions (class I and IIa) in patients undergoing primary PCI or fibrinolysis strategies.

8. Complications following ST-segment elevation myocardial infarction

Expanded information about complications following STEMI is presented in the Web Addenda.

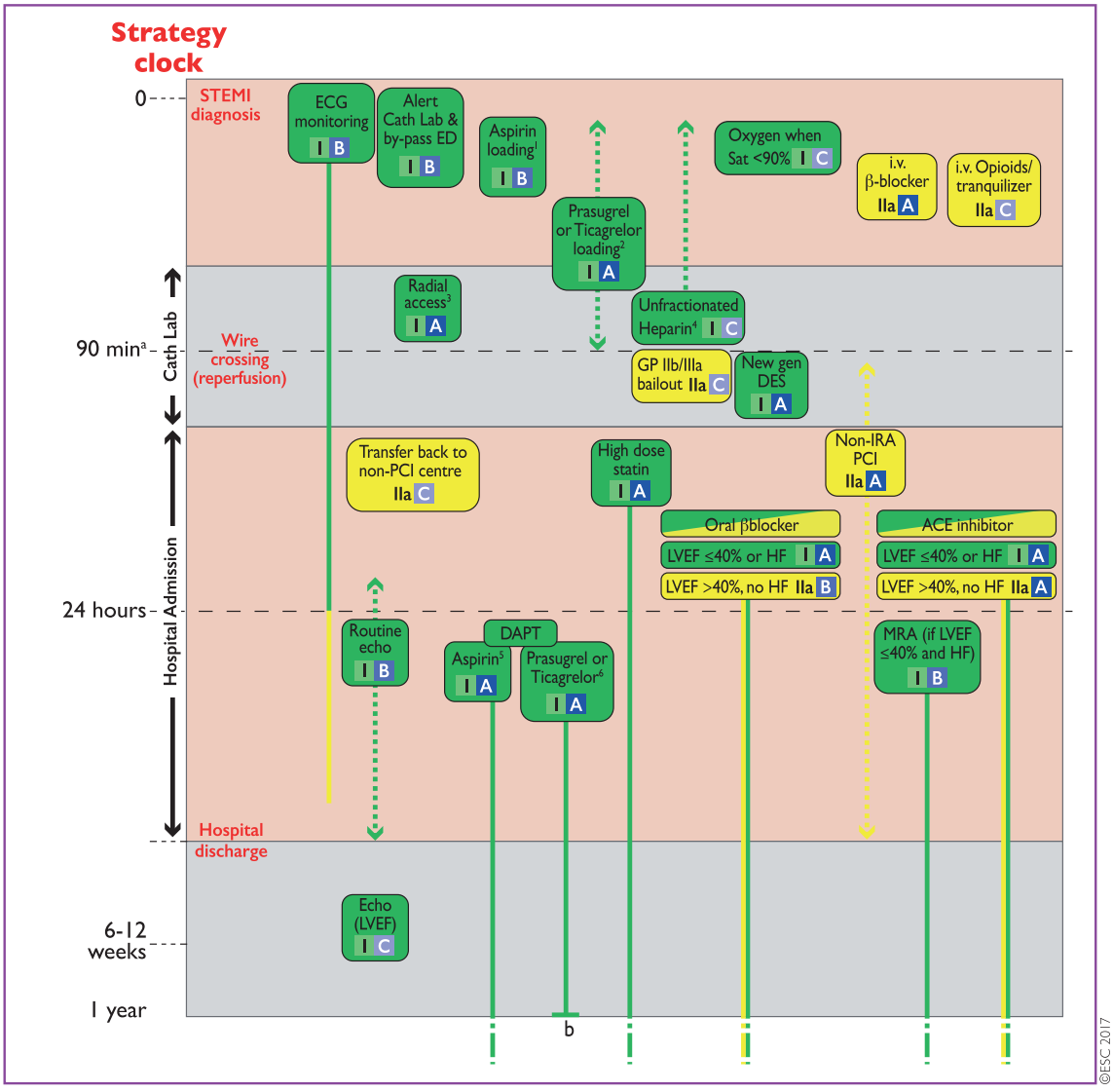

Figure 5 "Do not forget" interventions in STEMI patients undergoing a primary PCI strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; ED = emergency department; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptor antagonist; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin.

Mostly prescribed interventions (class I, green, and IIa, yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered.

[1]Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous (in patients not already on an aspirin maintenance dose).

[2]Prasugrel loading dose: 60 mg. Ticagrelor loading dose: 180 mg. If there are contra-indications for prasugrel/ticagrelor or these are not available, a loading dose of clopidogrel (600 mg) is indicated.

[3]If the interventional cardiologist is not expert in radial access, the femoral route is then preferred.

[4]Enoxaparin or bivalirudin are alternatives to unfractionated heparin (Class IIa A).

[5]Aspirin maintenance dose: 75–100 mg oral.

[6]Prasugrel maintenance dose: 10 mg once daily. Ticagrelor maintenance dose: 90 mg twice daily. If there are contra-indications for prasugrel/ticagrelor or these are not available, clopidogrel maintenance (75 mg daily) is indicated.

[a]90 min represents the maximum target time to PCI-mediated reperfusion. For patients presenting in a PCI-centre, this target time is 60 min.

[b]Prolongation of ticagrelor (60 mg twice daily) in addition to aspirin may be considered for up to 36 months in patients at high ischaemic risk who have tolerated DAPT without a bleeding complication.

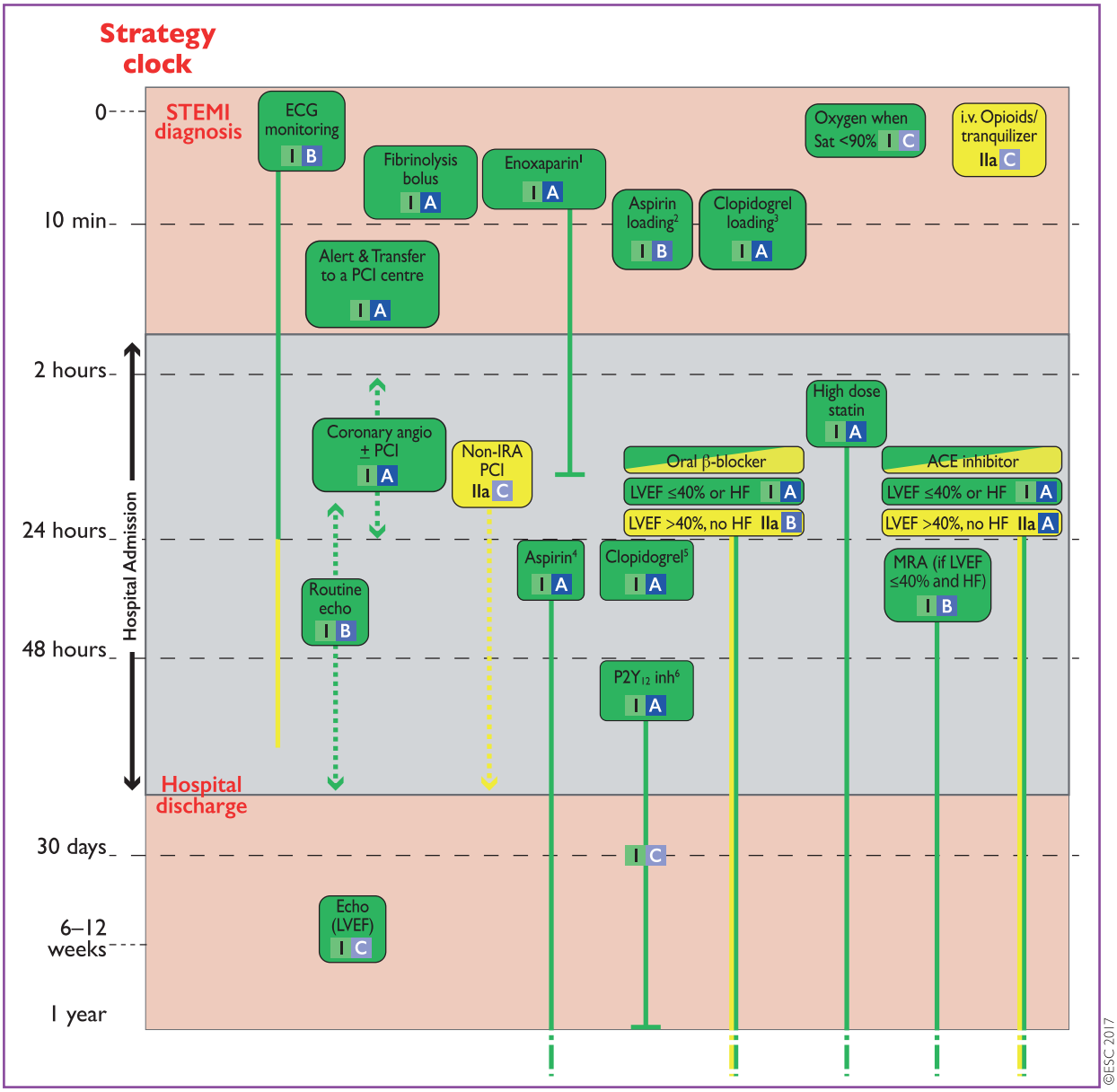

Figure 6 "Do not forget" interventions in STEMI patients undergoing a successful fibrinolysis strategy. ACE = angiotensin-converting enzyme; DAPT = dual antiplatelet therapy; DES = drug eluting stent; ECG = electrocardiogram; echo = echocardiogram; HF = heart failure; i.v. = intravenous; IRA = infarct related artery; LVEF = left ventricular ejection fraction; MRA = mineralcorticoid receptor antagonist; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; UFH = Unfractionated heparin.

Mostly prescribed interventions (class I, green, and IIa, light yellow) are presented along with the expected timing of delivery. Solid lines represent recurrent (daily) intervention. Double-arrowed dashed lines represent a time-window in which the intervention can be delivered.

[1]Enoxaparin dose: 30 mg i.v. bolus followed by 1 mg/kg subcutaneous every 12 hours (dose adjustment for ≥75 years and renal insufficiency is presented in *Table 9*). Unfractionated heparin is an alternative to enoxaparin.

[2]Aspirin loading dose: 150–300 mg chewed or 75–250 mg intravenous.

[3]Clopidogrel loading dose: 300 mg oral (75 mg in ≥ 75 years).

[4]Aspirin maintenance dose: 75–100 mg oral

[5]Clopidogrel maintenance therapy: 75 mg daily.

[6]48 hours after fibrinolysis, switch to prasugrel/ticagrelor may be considered in PCI-treated patients.

8.1 Myocardial dysfunction

8.1.1 Left ventricular dysfunction

See Web Addenda.

8.1.2 Right ventricular involvement

See Web Addenda.

8.2 Heart failure

8.2.1 Clinical presentations

See Web Addenda.

8.2.2 Management

Patients with heart failure should be under continuous monitoring of heart rhythm, blood pressure, and urinary output. The mechanism of heart failure should be assessed early by physical examination, ECG, echocardiography, and (when not rapidly controlled) with invasive haemodynamic monitoring, and corrected as soon as possible.

Patients with pulmonary congestion and SaO_2 <90% or partial pressure of oxygen (PaO_2) <60 mmHg (8.0 kPa) require oxygen therapy and SaO_2 monitoring to correct hypoxaemia, with a target of 95%, and may require periodic blood-gas assessment. Initial pharmacological treatment includes i.v. loop diuretics (e.g. furosemide 20–40 mg i.v. with repeated doses at intervals as needed according to clinical evolution and diuresis) and, if blood pressure allows it, i.v. nitrates, avoiding hypotension or excessive falls in blood pressure. The early use of beta-blockers, ACE inhibitors/ARBs, and MRA is recommended in the absence of hypotension, hypovolaemia, or renal dysfunction. Causal treatment is essential. Coronary revascularization should be performed early when significant CAD is still present. Rhythm disturbances, valvular dysfunction, and hypertension should be corrected as soon as possible. Hypertension should be treated promptly with oral ACE inhibitors/ARBs and i.v. nitrates. In very severe cases, sodium nitroprusside infusion may be necessary. Persistent myocardial ischaemia should be treated with early coronary revascularization. Atrial and ventricular dysrhythmias, and valvular dysfunction or

Recommendations for the management of left ventricular dysfunction and acute heart failure in ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF ≤40% and/or heart failure to reduce the risk of hospitalization and death.[390,396,412,413]	I	A
Beta-blocker therapy is recommended in patients with LVEF ≤40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.[358–361,414–416]	I	A
An MRA is recommended in patients with heart failure and LVEF ≤40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.[397]	I	B
Loop diuretics are recommended in patients with acute heart failure with symptoms/signs of fluid overload to improve symptoms.	I	C
Nitrates are recommended in patients with symptomatic heart failure with SBP >90 mmHg to improve symptoms and reduce congestion.	I	C
Oxygen is indicated in patients with pulmonary oedema with SaO_2 <90% to maintain a saturation >95%.	I	C
Patient intubation is indicated in patients with respiratory failure or exhaustion, leading to hypoxaemia, hypercapnia, or acidosis, and if non-invasive ventilation is not tolerated.	I	C
Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SaO_2 <90%) without hypotension.[410,411,417–419]	IIa	B
Intravenous nitrates or sodium nitroprusside should be considered in patients with heart failure and elevated SBP to control blood pressure and improve symptoms.	IIa	C
Opiates may be considered to relieve dyspnoea and anxiety in patients with pulmonary oedema and severe dyspnoea. Respiration should be monitored.[6,408]	IIb	B
>Inotropic agents may be considered in patients with severe heart failure with hypotension refractory to standard medical treatment.	IIb	C

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; SaO_2 = arterial oxygen saturation; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction.

[a]Class of recommendation.

[b]Level of evidence.

mechanical complications, should be treated as appropriate (see specific sections in this document).

Severely symptomatic patients with pulmonary congestion may also need i.v. morphine to reduce dyspnoea and anxiety, but routine use is not recommended due to concerns about its safety, as it may induce nausea and hypopnea.[408,409] Non-invasive positive pressure ventilation (continuous positive airway pressure, biphasic positive airway pressure) or high-flow nasal cannula is effective in treating pulmonary oedema and should be considered in patients with respiratory distress (respiratory rate >25 breaths/min, SaO_2 <90%) and started soon.[410,411] Endotracheal intubation and ventilatory support may be required in patients unable to achieve adequate oxygenation, or in those with excess respiratory work or evidence of hypercapnia due to respiratory exhaustion. Ultrafiltration to reduce fluid overload may be considered in patients who are refractory to diuretics, especially in patients with hyponatraemia.

In patients with heart failure and adequate blood pressure (SBP >90 mmHg), but a severe reduction in cardiac output resulting in compromised vital organ perfusion not responding to standard therapy, treatment with dobutamine or levosimendan may be considered. However, the clinical evidence of levosimendan in cardiogenic shock is limited. Further details on the management of acute heart failure can be found in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.[6]

8.2.2.1 Management of hypotension

In patients with hypotension and normal perfusion without evidence of congestion or volume overload (i.e. collapsible inferior vena cava), gentle volume loading should be attempted after ruling out complications such as mechanical or severe mitral regurgitation, with central pressure monitoring. Bradycardia or tachyarrhythmias should be corrected or controlled. In patients with RV infarction, volume overloading should be avoided because it might worsen haemodynamics.[420] If hypotension persists, inotropic therapy, preferably with dobutamine, may be considered.[420]

8.2.2.2 Management of cardiogenic shock

Cardiogenic shock is defined as persistent hypotension (SBP <90 mmHg) despite adequate filling status with signs of hypoperfusion. It complicates 6–10% of all STEMI cases and remains a leading cause of death, with in-hospital mortality rates ≥50%.[421] Shock is also considered to be present if i.v. inotropes and/or mechanical support are needed to maintain an SBP >90 mmHg. In STEMI patients presenting with cardiogenic shock in which PCI-mediated reperfusion is estimated to occur >120 min, immediate fibrinolysis and transfer to a PCI centre should be considered. In these cases, upon arrival at the PCI centre, emergent angiography is indicated, regardless of the ST resolution and the time from fibrinolysis administration. It is usually associated with extensive LV damage, but may occur in RV infarction. Cardiogenic shock characterization and management do not necessarily need invasive haemodynamic monitoring, but ventricular and valve function should be urgently evaluated by transthoracic echocardiography and associated mechanical complications ruled out.[422–426]

The first step in patients with cardiogenic shock is to identify the mechanism and to correct any reversible cause such as hypovolaemia, drug-induced hypotension, or arrhythmias; alternatively, initiate the treatment of potential specific causes, such as mechanical complications or tamponade.

Treatments include immediate reperfusion, with primary PCI whenever possible,[248,427] and complete revascularisation if multivessel disease is present. In addition, patients at the highest risk for development of shock might benefit from an early transfer to tertiary centres before the onset of haemodynamic instability. Antithrombotic therapy does not differ from that in any STEMI patient. The specificities of the management of low-output cardiogenic shock associated with RV infarction are mentioned in the Web Addenda.

Invasive monitoring with an arterial line is recommended.[6] A pulmonary artery catheter may be considered, in order to perform a careful adjustment of filling pressures and assessment of cardiac output or in cases of shock of unexplained cause. Hypovolaemia should be ruled out first and corrected with fluid loading. Pharmacological therapy aims to improve organ perfusion by increasing cardiac output and blood pressure. Diuretic therapy is recommended when adequate perfusion is attained. Intravenous inotropic agents or vasopressors are usually required to maintain an SBP >90 mmHg, and to increase cardiac output and improve vital organ perfusion. Dobutamine is the initial therapy for patients with predominant low cardiac output, whereas norepinephrine may be safer and more effective than dopamine in patients with cardiogenic shock and severe hypotension.[428] Levosimendan may be considered as an alternative, especially for patients on chronic beta-blocker therapy, because its inotropic effect is independent of beta-adrenergic stimulation. Phosphodiesterase III inhibitors are not recommended in STEMI patients.

IABP counterpulsation does not improve outcomes in patients with STEMI and cardiogenic shock without mechanical complications,[177] nor does it significantly limit infarct size in those with potentially large anterior MIs.[175] Therefore, routine IABP counterpulsation cannot be recommended, but may be considered for haemodynamic support in selected patients (i.e. severe mitral insufficiency or ventricular septal defect). A small exploratory trial studying the Impella CP percutaneous circulatory support device did not find any benefit compared with IABP in AMI complicated by cardiogenic shock.[429]

Mechanical LV assist devices (LVADs), including percutaneous short-term mechanical circulatory support devices (i.e. intra-cardiac axial flow pumps and arterial-venous extracorporeal membrane oxygenation), have been used in patients not responding to standard therapy, including inotropes, fluids, and IABP, but evidence regarding their benefits is limited.[430] Therefore, short-term mechanical circulatory support may be considered as a rescue therapy in order to stabilize the patients and preserve organ perfusion (oxygenation) as a bridge to recovery of myocardial function, cardiac transplantation, or even LV assist device destination therapy on an individual basis.[431,432]

Recommendations for the management of cardiogenic shock in ST-elevation myocardial infarction

Recommendations	Class[a]	Level[b]
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended.[248]	I	B
Invasive blood pressure monitoring with an arterial line is recommended.	I	C
Immediate Doppler echocardiography is indicated to assess ventricular and valvular functions, loading conditions, and to detect mechanical complications.	I	C
It is indicated that mechanical complications are treated as early as possible after discussion by the Heart Team.	I	C
Oxygen/mechanical respiratory support is indicated according to blood gases.	I	C
Fibrinolysis should be considered in patients presenting with cardiogenic shock if a primary PCI strategy is not available within 120 min from STEMI diagnosis and mechanical complications have been ruled out.	IIa	C
Complete revascularization during the index procedure should be considered in patients presenting with cardiogenic shock.	IIa	C
Intra-aortic balloon pumping should be considered in patients with haemodynamic instability/cardiogenic shock due to mechanical complications.	IIa	C
Haemodynamic assessment with pulmonary artery catheter may be considered for confirming diagnosis or guiding therapy.[433]	IIb	B
Ultrafiltration may be considered for patients with refractory congestion, who failed to respond to diuretic-based strategies.[434–436]	IIb	B
Inotropic/vasopressor agents may be considered for haemodynamic stabilization.	IIb	C
Short-term mechanical support[c] may be considered in patients in refractory shock.	IIb	C
Routine intra-aortic balloon pumping is not indicated.[177,437]	III	B

CABG = coronary artery bypass graft surgery; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Percutaneous cardiac support devices, ECLS, and ECMO.

8.3 Management of arrhythmias and conduction disturbances in the acute phase

Arrhythmias and conduction disturbances are common during the early hours of STEMI and are also important prognostic factors.[438] Despite increased awareness and improved basic and advanced life support, the incidence of sudden cardiac death, mainly due to fast ventricular tachycardia (VT) and VF in the pre-hospital phase, remains high.[438,439] Early reperfusion therapy reduces the risk of ventricular arrhythmias and cardiovascular death.[440,441] The presence of life-threatening arrhythmias requires an urgent need for a fast and complete revascularization in STEMI.[438,442] The evidence for benefits of antiarrhythmic drugs in STEMI patients is limited and negative effects of antiarrhythmic drugs on early mortality have been demonstrated.[439] Careful use of antiarrhythmic drugs is generally recommended and alternative treatment options such as electrical cardioversion, a 'wait and see' strategy for arrhythmias with no or moderate haemodynamic relevance, or in selected cases cardiac pacing and catheter ablation, should be considered. Correction of electrolyte imbalances and early treatment with beta-blockers, ACE inhibitors/ARBs, and statins is recommended.[438,443]

8.3.1 Supraventricular arrhythmias

The most frequent supraventricular arrhythmia is AF, with up to 21% of STEMI patients affected.[444] AF may be pre-existing, first-time detected, or of new onset. Patients with AF have more comorbidities and are at higher risk for complications.[445] In many cases, the arrhythmia is well tolerated and no specific treatment is required, other than anticoagulation.[5] Prompt treatment is required in acute haemodynamic instability. There is scarce information indicating preferences for rate control over rhythm control in this situation.[446] Electrical cardioversion should be considered but early recurrence of AF is frequent after successful cardioversion. Acute rhythm control with antiarrhythmic drugs is limited to the use of amiodarone.[5,444] Adequate rate control can be accomplished by administration of beta-blockers.[438,446] In patients with extensive myocardial damage or severe LV dysfunction, rate control is more safely achieved with i.v. digoxin with or without concomitant administration of i.v. amiodarone. When co-administering i.v. digoxin and amiodarone, close monitoring for digoxin toxicity is necessary as digoxin serum concentrations may be increased. Several, but not all, studies have suggested that new-onset AF may be reduced by beta-blockers, ACE inhibitors/ARBs, and also early-onset statin therapy.[444] Patients with AF and risk factors for thromboembolism should be adequately treated with chronic oral anticoagulation.[5] STEMI patients with documented AF have worse short- and long-term prognoses when compared with patients in sinus rhythm.[445,447] Presence of AF is associated with a higher reinfarction rate, higher stroke rate, higher risk for heart failure, and may also increase the risk for sudden cardiac death.[444,445,448] Of note, also transient, self-terminating AF during STEMI relates to a significantly higher stroke rate during long-term follow-up.[445,448]

Management of atrial fibrillation

Recommendations	Class[a]	Level[b]
Acute rate control of AF		
Intravenous beta-blockers are indicated for rate control if necessary and there are no clinical signs of acute heart failure or hypotension.[449]	I	C
Intravenous amiodarone is indicated for rate control if necessary in the presence of concomitant acute heart failure and no hypotension.[450]	I	C
Intravenous digitalis should be considered for rate control if necessary in the presence of concomitant acute heart failure and hypotension.[451]	IIa	B
Cardioversion		
Immediate electrical cardioversion is indicated when adequate rate control cannot be achieved promptly with pharmacological agents in patients with AF and ongoing ischaemia, severe haemodynamic compromise, or heart failure.	I	C
Intravenous amiodarone is indicated to promote electrical cardioversion and/or decrease risk for early recurrence of AF after electrical cardioversion in unstable patients with recent onset AF.	I	C
In patients with documented *de novo* AF during the acute phase of STEMI, long-term oral anticoagulation should be considered depending on CHA_2DS_2-VASc score and taking concomitant antithrombotic therapy into account.[5,444]	IIa	C
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control.[452,453]	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm.[453]	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated.[438,444]	III	B

AF = atrial fibrillation; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 (Doubled), Diabetes, Stroke (Doubled) – VAScular disease, Age 65–74 and Sex category (Female); STEMI = ST-segment elevation myocardial infarction.
[a]Class of recommendation.
[b]Level of evidence.

8.3.2 Ventricular arrhythmias

The incidence of VT and VF has declined over recent decades, most probably due to the uptake of reperfusion strategies and the early use of beta-blockers.[3] However, 6–8% of patients still develop haemodynamically significant VT or VF during this phase.[439] The typical arrhythmia presentation is unstable, frequently polymorphic, and relatively fast VT, often degenerating into VF. Urgent reperfusion is most important as ischaemia often triggers these arrhythmias.[72] Beta-blockers are recommended if no contraindications exist.[346,347,350,454] Repetitive electrical cardioversion or defibrillation may be necessary.[455] If there is no sufficient control, i.v. administration of amiodarone should be considered.[439,456] In case of contraindications to amiodarone, i.v. lidocaine may be considered, although no studies comparing superiority of either drug in STEMI patients are available. The prognostic role of early VT/VF within the first 48 h of STEMI is still controversial. Available data suggest that patients with early VT/VF have increased 30-day mortality but no increased long-term arrhythmic risks.[442,457,458]

VT or VF may occur at the time of restoration of coronary blood flow (reperfusion arrhythmias). No specific antiarrhythmic drug therapy is necessary due to the benign long-term course. Ventricular premature beats are very frequent on the first day of the acute phase and complex arrhythmias (multiform complexes, short runs, or the R-on-T phenomenon) are common. Their value as predictors of VF is questionable and no specific therapy is required. Sustained VT or VF outside the early phase (usually 48 h after STEMI onset) not triggered by recurrent ischaemia has a poor prognostic implication, and evaluation for ICD implantation for secondary prevention of sudden cardiac death is recommended according to current guidelines.[3] Primary prevention of sudden cardiac death with the ICD within 40 days after MI in the absence of VT/VF is generally not indicated.[3] Patients should be re-evaluated for ICD implantation 6–12 weeks after revascularization, although those with pre-existing impaired LVEF may be considered for ICD implantation for primary prevention even within the early post-infarction period.[3,438]

Some patients may develop electrical storm and/or incessant VT despite complete revascularization and treatment with antiarrhythmic drugs. Overdrive stimulation may help to control this situation; however, recurrence of VT/VF upon cessation of stimulation is frequent and catheter ablation of such triggers appears to be the only treatment option. Successful radiofrequency ablation has been shown to abolish recurrent VT/VF.[459–461]

Management of ventricular arrhythmias and conduction disturbances in the acute phase

Recommendations	Class[a]	Level[b]
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated.[462,463]	I	B
Prompt and complete revascularization is recommended to treat myocardial ischaemia that may be present in patients with recurrent VT and/or VF[71,72]	I	C
Intravenous amiodarone is recommended for treatment of recurrent polymorphic VT.[3]	I	C
Correction of electrolyte imbalances (especially hypokalaemia and hypomagnesemia) is recommended in patients with VT and/or VF.[3]	I	C
In cases of sinus bradycardia with haemodynamic intolerance or high degree AV block without stable escape rhythm:		
• i.v. positive chronotropic medication (epinephrine, vasopressin, and/or atropine) is indicated	I	C
• temporary pacing is indicated in cases of failure to respond to positive chronotropic medication	I	C
• urgent angiography with a view to revascularization is indicated if the patient has not received previous reperfusion therapy.	I	C
Intravenous amiodarone should be considered for recurrent VT with haemodynamic intolerance despite repetitive electrical cardioversion.[438]	IIa	C
Transvenous catheter pace termination and/or overdrive pacing should be considered if VT cannot be controlled by repetitive electrical cardioversion.	IIa	C
Radiofrequency catheter ablation at a specialized ablation centre followed by ICD implantation should be considered in patients with recurrent VT, VF, or electrical storm despite complete revascularization and optimal medical therapy.	IIa	C
Recurrent VT with haemodynamic repercussion despite repetitive electrical cardioversion may be treated with lidocaine if beta-blockers, amiodarone, and overdrive stimulation are not effective/applicable.[438]	IIb	C
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful.[464,465]	III	B
Asymptomatic and haemodynamically irrelevant ventricular arrhythmias should not be treated with antiarrhythmic drugs.	III	C

AV = atrioventricular; i.v. = intravenous; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

Long-term management of ventricular arrhythmias and risk evaluation for sudden death

Recommendations	Class[a]	Level[b]
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (NYHA class II–III) and LVEF ≤35% despite optimal medical therapy for >3 months and ≥6 weeks after MI, who are expected to survive for at least 1 year with good functional status.[3,466,467]	I	A
ICD implantation or temporary use of a wearable cardioverter defibrillator may be considered <40 days after MI in selected patients (incomplete revascularization, pre-existing LVEF dysfunction, occurrence of arrhythmias >48 h after STEMI onset, polymorphic VT or VF).	IIb	C

ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; STEMI = ST-segment elevation myocardial infarction; VF = ventricular fibrillation; VT = ventricular tachycardia.
[a]Class of recommendation.
[b]Level of evidence.

8.3.3 Sinus bradycardia and atrioventricular block

Sinus bradycardia is common in the first hours of STEMI, especially in inferior MI. In some cases, opioids are responsible.[468] It often requires no treatment. If accompanied by severe hypotension, sinus bradycardia should be treated with i.v. atropine. Second-degree type I (Mobitz I or Wenckebach) AV block is usually associated with inferior wall MI and seldom causes adverse haemodynamic effects. If so, atropine should be used first; if it fails, pacing should be instituted. Agents that slow AV conduction (such as beta-blockers, digitalis, verapamil, or amiodarone) should be used with caution. Second-degree type II (Mobitz II) AV block and complete AV block may be indications for pacing. AV sequential pacing should be considered in patients with complete AV block, RV infarction, and haemodynamic compromise. Revascularization should be considered in patients with AV block who have not yet received reperfusion therapy (e.g. late arrival).

AV block associated with inferior wall infarction is usually supra-Hisian and usually resolves spontaneously or after reperfusion. AV block associated with anterior wall MI is usually infra-Hisian and has a high mortality rate due to the extensive myocardial necrosis. The development of a new bundle branch block or hemiblock usually indicates extensive anterior MI. A transvenous pacing electrode should be inserted in the presence of advanced AV block with a low escape rhythm, as described above, and considered if bifascicular or trifascicular block develops. Indications for pacing are outlined in detail in the ESC Guidelines for cardiac pacing and cardiac resynchronization therapy.[469]

8.4 Mechanical complications

Mechanical complications may occur in the first days following STEMI, although incidence has fallen significantly in the era of primary PCI. Mechanical complications are life-threatening and need prompt detection and management. Sudden hypotension, recurrence of chest pain, new cardiac murmurs suggestive of mitral regurgitation or ventricular septal defect, pulmonary congestion, or jugular vein distension should raise suspicion. Immediate echocardiographic assessment is needed when mechanical complications are suspected. A full section describing mechanical complications can be found in the Web Addenda.

8.4.1 Free wall rupture

See Web Addenda.

8.4.2 Ventricular septal rupture

See Web Addenda.

8.4.3 Papillary muscle rupture

See Web Addenda.

8.5 Pericarditis

Three major pericardial complications may occur: early infarct-associated pericarditis, late pericarditis or post-cardiac injury (Dressler syndrome), and pericardial effusion. These are expanded upon in the Web Addenda.

8.5.1 Early and late (Dressler syndrome) infarct-associated pericarditis

See Web Addenda.

8.5.2 Pericardial effusion

See Web Addenda.

9. Myocardial infarction with non-obstructive coronary arteries

A sizeable proportion of MIs, ranging between 1–14%, occur in the absence of obstructive (>50% stenosis) CAD.[10,11] The demonstration of non-obstructive (<50%) CAD in a patient presenting with symptoms suggestive of ischaemia and ST-segment elevation or equivalent does not preclude an atherothrombosis aetiology, as thrombosis is a very dynamic phenomenon and the underlying atherosclerotic plaque can be non-obstructive.

The diagnostic criteria of MINOCA are presented in *Table 10*. MINOCA is a working diagnosis and should lead the treating physician to investigate underlying causes. Failure to identify the underlying cause may result in inadequate and inappropriate therapy in these patients.

The description of the pathophysiology of the different aetiological entities leading to MINOCA is beyond the scope of the present document, and has been extensively described and defined in position papers from the ESC[12] and in dedicated review papers.[10,11] MINOCA patients can fulfil the criteria for both MI type 1 and type 2 according to the universal definition of MI.[8] There are disparate aetiologies causing MINOCA and they can be grouped into: (1) secondary to epicardial coronary artery disorders (e.g. atherosclerotic plaque rupture, ulceration, fissuring, erosion, or coronary dissection with non-obstructive or no CAD) (MI type 1); (2) imbalance between oxygen supply and demand (e.g. coronary artery spasm and coronary embolism) (MI type 2); (3) coronary endothelial dysfunction (e.g. microvascular spasm) (MI type 2); and (4) secondary to myocardial disorders without involvement of the coronary arteries (e.g. myocarditis[470] or Takotsubo syndrome). The last two entities may mimic MI but are better classified as myocardial injury conditions. The identification of the underlying cause of MINOCA should lead to specific treatment strategies. Although the outcome of MINOCA strongly depends on the underlying cause, its overall prognosis is serious, with a 1 year mortality of about 3.5%.[10]

To determine the cause of MINOCA, the use of additional diagnostic tests beyond coronary angiography is recommended. In general, after ruling out obstructive CAD in a patient presenting with STEMI, an LV angiogram or echocardiography should be considered in the acute setting to assess wall motion or pericardial effusion. In addition, if any of the possible aetiologies described above is suspected, additional diagnostic tests may be considered.

CMR is a very helpful imaging technique due to its unique non-invasive tissue characterization, allowing the identification of wall motion abnormalities, presence of oedema, and myocardial scar/fibrosis presence and pattern. Performance of CMR within 2 weeks after onset of symptoms should be considered to increase the diagnostic accuracy of the test for identifying the aetiological cause of MINOCA.[471–473]

Table 10 Diagnostic criteria for myocardial infarction with non-obstructive coronary arteries (adapted from Agewall *et al*[12])

The diagnosis of MINOCA is made immediately upon coronary angiography in a patient presenting with features consistent with an AMI, as detailed by the following criteria:
(1) Universal AMI criteria[8]
(2) Non-obstructive coronary arteries on angiography, defined as no coronary artery stenosis ≥50% in any potential IRA
(3) No clinically overt specific cause for the acute presentation

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AMI = acute myocardial infarction; IRA = infarct-related artery; MINOCA = myocardial infarction with non-obstructive coronary arteries.

10. Assessment of quality of care

There is a wide practice gap between optimal and actual care for patients with STEMI in hospitals around the world.[474,475] To reduce this gap and improve quality of care, it is recommended that STEMI networks and their individual components establish measurable quality indicators, systems to measure and compare these indicators, perform routine audits, and implement strategies to ensure that every patient with STEMI receives the best possible care according to accepted standards and has the best possible outcomes

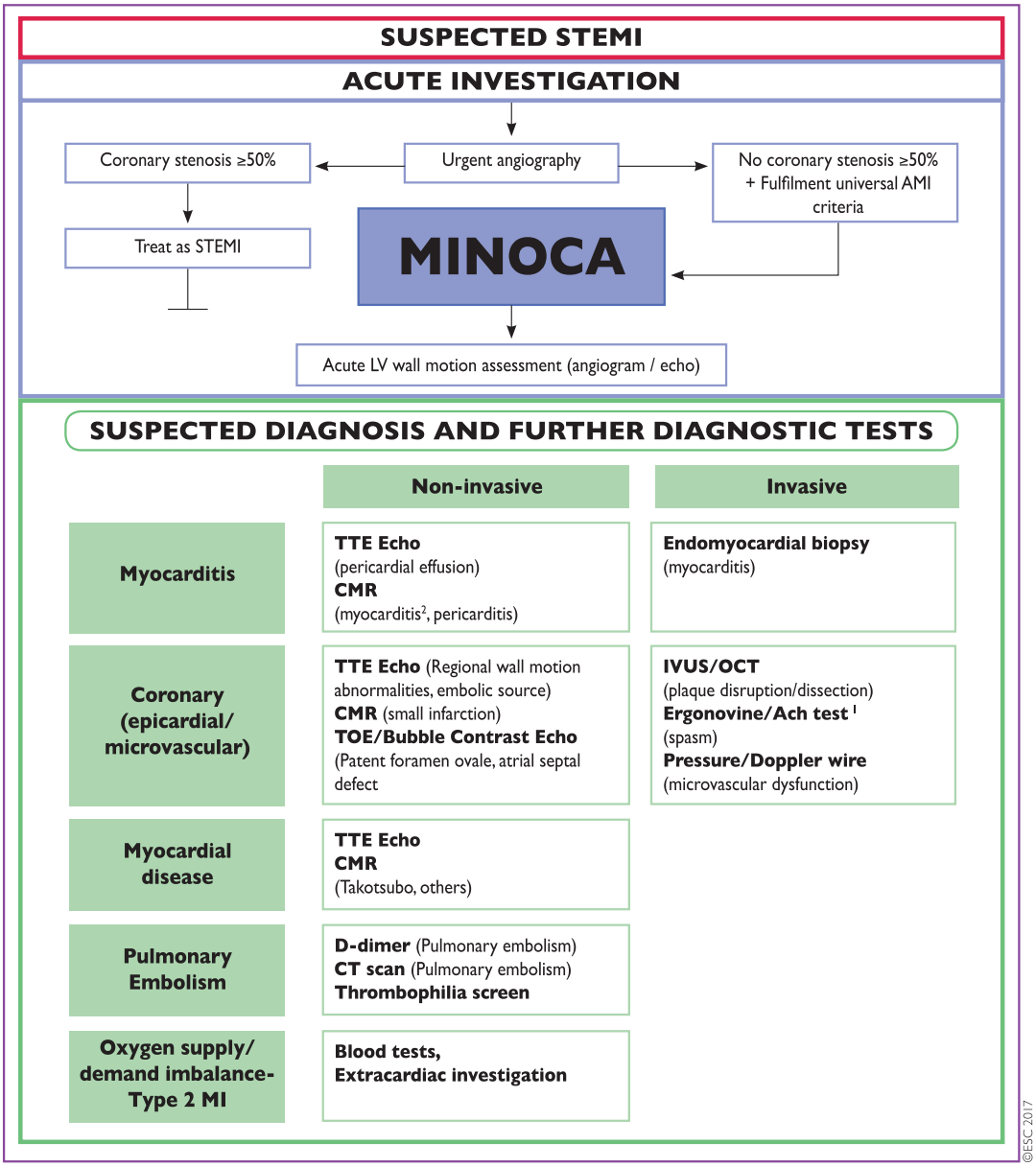

Figure 7 Diagnostic test flow chart in MINOCA. CMR = Cardiac Magnetic Resonance; IVUS = IntraVascular UltraSound; LV = Left Ventricle; MINOCA = Myocardial Infarction with Non-Obstructed Coronary Arteries; OCT = Optical Coherence Tomography; STEMI = ST segment Elevation Myocardial Infarction; TOE = Trans-Oesofageal Echocardiography; TTE = Trans-Thoracic Echocardiography. Takotsubo syndrome cannot be diagnosed with certainty in the acute phase as the definition requires follow up imaging to document recovery of left ventricular function. IVUS and OCT frequently show more atherosclerotic plaque than may be appreciated on angiography. They also increase sensitivity for dissection. If intracoronary imaging is to be performed, it is appropriate to carry out this imaging at the time of the acute cardiac catheterization, after diagnostic angiography. Patients should be made aware of the additional information the test can provide and the small increase in risk associated with intracoronary imaging.

1 • Provocative testing for coronary artery spasm might be considered in selected patients with a recent AMI with suspected vasospastic angina. Provocative manoeuvres have to be always performed by operators with experience and not necessarily in the acute phase of STEMI.

2 • Clinically suspected myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus non ischemic pattern on CMR. Definite myocarditis by ESC Task Force criteria = No angiographic stenosis ≥50% plus endomyocardial biopsy confirmation (histology, immunohistology, polymerase-chain reaction based techniques to search for genome of infectious agents, mainly viruses).

Table 11 Quality indicators

Type of indicator and process	Quality indicator
Structural measures (organization)	1) The centre should be part of a network specifically developed for the rapid and efficient management of STEMI patients with written protocols covering the following points: • *Single emergency telephone number* for patients to contact the emergency services • *Prehospital interpretation of the ECG* for diagnosis and decision for immediate transfer to a PCI centre • *Prehospital activation* of the catheterization laboratory • *Transportation* (ambulance-helicopter) equipped with ECG defibrillators 2) Key times to reperfusion are systematically recorded and periodically reviewed for quality assessments by the centre or network participants
Performance measures for reperfusion therapy	1) Proportion of STEMI patients arriving in the first 12 h receiving reperfusion therapy 2) Proportion of patients with timely reperfusion therapy, defined as: • For patients attended to in the pre-hospital setting: ♦ <90 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI ♦ <10 min from STEMI diagnosis to lytic bolus for reperfusion with fibrinolysis • For patients admitted to PCI centres: ♦ <60 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI • For transferred patients: ♦ <120 min from STEMI diagnosis to IRA wire crossing for reperfusion with PCI ♦ <30 min door-in-door-out for patients presenting in a non-PCI centre (en route to a PCI centre)
Performance measures for risk assessment in hospital	1) Proportion of patients having LVEF assessed before discharge
Performance measures for antithrombotic treatment in hospital	1) Proportion of patients without a clear and documented contra-indication for aspirin and/or a $P2Y_{12}$ inhibitor, discharged on DAPT
Performance measures for discharge medication and counselling	1) Proportion of patients without contra-indications with a statin (high-intensity) prescribed at discharge 2) Proportion of patients with LVEF ≤40% or clinical evidence of heart failure and without contra-indications with a beta-blocker prescribed at discharge 3) Proportion of patients with LVEF ≤40% or clinical evidence of heart failure without contra-indications with an ACE inhibitor (or ARB if not tolerated) prescribed at discharge 4) Proportion of patients with smoking cessation advice/counselling at discharge 5) Proportion of patients without contra-indications enrolled in a secondary prevention/cardiac rehabilitation programme at discharge
Patient-reported outcomes	• Availability of a programme to obtain feedback regarding the patient's experience and quality of information received, including the following points: ♦ Angina control. ♦ Explanations provided by doctors and nurses (about the disease, benefit/risk of discharge treatments, and medical follow-up) ♦ Discharge information regarding what to do in case of recurrence of symptoms and recommendation to attend a rehabilitation programme (including smoking cession and diet counselling)
Outcome measures	1) 30-day adjusted mortality (e.g. GRACE risk score-adjusted) 2) 30-day adjusted readmission rates
Opportunity-based composite quality indicators	• Proportion of patients with LVEF >40% and no evidence of heart failure receiving at discharge low-dose aspirin and a $P2Y_{12}$ inhibitor and high-intensity statins • Proportion of patients with LVEF ≤40% and/or heart failure receiving at discharge low-dose aspirin, a $P2Y_{12}$ inhibitor, high-intensity statins, an ACE inhibitor (or ARB), and a beta-blocker

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ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; DAPT = dual antiplatelet therapy; ECG = electrocardiogram; GRACE = Global Registry of Acute Coronary Events; IRA = Infarct-related artery; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

(see Web Addenda). Quality indicators are intended to measure and compare the quality of health service provision and serve as a foundation for quality improvement initiatives.[476] Proposed quality indicators to assess the quality of the care for patients are presented in *Table 11*.

Expanded text about quality indicators can be found in the Web Addenda.

11. Gaps in the evidence and areas for future research

Despite the great advances in STEMI management over recent decades, important areas of uncertainty persist that should be explored in the future. Here, we identify some, but not all, specific areas that should be addressed within the next few years.

Public awareness and emergency care

The very early stages of STEMI are the most vulnerable time, when most sudden cardiac deaths occur. Public campaigns aiming to increase early alerting of patients with ischaemic symptoms should clearly state that the safest way to alert is to call the EMS. While selected centres and geographic areas have made great progress in ensuring high-quality rapid care for STEMI patients with routine pre-alert of the interventional team, there remains a need for streamlining of (pre-)hospital management in a homogeneous fashion worldwide, including rural areas. Educational programmes and cross-country exchange of experiences should help in this matter.

The selection of a 120 min from STEMI diagnosis to PCI-mediated reperfusion as the cut-off to choose PCI or fibrinolysis is based on relatively old registries and trials with different treatment strategies from those presented in this document. The identification of the best cut-off timing to choose a strategy is of extreme importance.

Reduction of ischaemia/reperfusion injury

Final infarct size is one of the best predictors of long-term adverse events in STEMI survivors. The introduction of a specific infarct-limiting therapy in clinical practice might have a massive clinical and socioeconomic impact. Several strategies, including pharmacological and mechanical therapies, have shown a reduction of infarct size by reducing ischaemia/reperfusion injury (including MVO) in experimental and small-scale clinical trials, but to date no large trial has demonstrated a clinical benefit. One potential reason for this poor translation is the difficulty of securing funds to conduct proper large-scale clinical trials in this context.

Refinement of (acute and long-term) antithrombotic regimes

Antithrombotic therapy is the cornerstone of the pharmacological approach in STEMI. Despite major recent advances, important questions remain unaddressed. What is the best acute and maintenance antithrombotic regimen in patients who have an indication for oral anticoagulants? What is the best timing for the loading dose of oral $P2Y_{12}$ inhibitors and what are the best strategies for i.v. antithrombotic therapies? What is the role of potent $P2Y_{12}$ inhibitors in patients undergoing fibrinolysis? What is the real role of aspirin in this new era of potent antiplatelet agents and low dose anticoagulation? What is the best duration of maintenance therapy with $P2Y_{12}$ inhibitors as single or multiple antithrombotic regimens?

Beta-blockers and ACE inhibitors

Although research regarding these classes of drugs was intense several decades ago, more recently, there has been a lack of properly powered clinical trials. The best timing for initiation (and route of administration) of beta-blockers is still not well established. The role of maintenance beta-blocker therapy is well established for patients with heart failure and/or low LVEF, but its clinical value for the rest of STEMI has not been prospectively tested in dedicated clinical trials of reperfused patients. Similar limitations apply to the use of maintenance ACE inhibitors.

Post-STEMI risk stratification

The optimal therapeutic strategy to minimize the risk of sudden death in patients who develop VT or VF during or early after STEMI is not entirely clear. Despite the clinical benefit of ICDs in patients with low LVEF and reduced functional class weeks after STEMI being well established, there is a need for better sudden death risk stratification algorithms.

The best management of non-IRA lesions should be addressed. Unresolved issues are the best criteria to guide PCI (angiography, FFR, or assessment of plaque vulnerability) and the best timing for complete revascularization if indicated (during index PCI or staged, including staged during hospitalization vs. after discharge).

Shock and left ventricular assist devices

Severe heart failure and shock are among the most important negative prognostic predictors in patients with STEMI. In addition to urgent revascularization of IRA and standard medical therapies for pre- and afterload reduction, there is limited evidence for the systematic use of inotropic and vasopressor agents as well as mechanical support. Similarly, the benefit of routine complete revascularization during the index PCI procedure has not been formally demonstrated. The use of IABP has not met prior expectations of benefit, while LV assist devices and ECMO are increasingly popular but have not been sufficiently evaluated in clinical trials. Systematic evaluation of pharmacological and interventional strategies and LV assist devices for patients with shock are urgently needed.

Myocardial repair/rescue

The effectiveness and safety of novel therapies able to replace dead myocardium or prevent poor remodelling (e.g. cell therapy or gene therapy) is an unfulfilled promise. There is a strong need for basic research studies to better understand the biological processes involved in cardiac development and repair, in order for there to be strong grounds to translate studies into clinically relevant animal models and finally into humans.

Need for observational data and real-world evidence

In order to understand shortcomings and challenges in clinical practice, for quality assessment and for benchmarking, unselected and validated registries and clinical databases are needed. In this document, we have specified quality indicators intended to measure and compare the quality of health service provision and serve as a foundation for quality improvement initiatives. Their effects on procedural and clinical outcomes need to be evaluated.

Need for pragmatic real-life clinical trials

One major limitation of highly selective controlled clinical trials is their applicability in the real world. Strict inclusion criteria, tailored management, and very close follow-up results in a bias that precludes universal implementation. An opportunity is the implementation of pragmatic clinical trials including registry-based randomized clinical trials.[477] These trials are less selective and less expensive alternatives to classical ones, especially for therapies used in clinical practice.

12. Key messages

(1) Epidemiology of STEMI: Although the rate of mortality associated with ischaemic heart disease have reduced in Europe over the last few decades, this is still the single most common cause of death worldwide. The relative incidences of STEMI and NSTEMI are decreasing and increasing, respectively. Despite the decline in acute and long-term death associated with STEMI, in parallel with the widespread use of reperfusion, mortality remains substantial. The in-hospital mortality rates of unselected patients with STEMI in national European registries vary between 4–12%.

(2) Gender aspects: Women tend to receive reperfusion therapy and other evidence-based treatments less frequently and/or in a delayed way than men. It is important to highlight that women and men receive equal benefit from a reperfusion and other STEMI-related therapies, and so both genders must be managed equally.

(3) ECG and STEMI diagnosis: In some cases, patients may have coronary artery occlusion/global ischaemia in the absence of characteristic ST elevation (e.g. bundle branch block, ventricular pacing, hyperacute T-waves, isolated ST-depression in anterior leads, and/or universal ST depression with ST-elevation in aVR). In patients with the mentioned ECG changes and clinical presentation compatible with ongoing myocardial ischaemia, a primary PCI strategy (i.e. urgent angiography and PCI if indicated) should be followed.

(4) Reperfusion strategy selection: STEMI diagnosis (defined as the time at which the ECG of a patient with ischaemic symptoms is interpreted as presenting ST-segment elevation or equivalent) is the time zero in the reperfusion strategy clock. STEMI patients should undergo a primary PCI strategy unless the anticipated absolute time from STEMI diagnosis to PCI-mediated reperfusion is > 120 min, when fibrinolysis should be initiated immediately (i.e. within 10 min of STEMI diagnosis).

(5) STEMI management networks: Coordination between EMS and hospitals with common written protocols is at the centre of STEMI management. EMS should transfer patients to 24/7 high-volume PCI centres irrespective of whether the primary treatment strategy is PCI or pre-hospital fibrinolysis. EMS should always alert the PCI centre immediately after selection of the reperfusion strategy. Patient transfer to the PCI centre should bypass the emergency department.

(6) Cardiac arrest and reperfusion strategy: Patients with ST-elevation on post-resuscitation ECG should undergo a primary PCI strategy. In cases without ST-segment elevation on post-resuscitation ECG but with a high suspicion of ongoing myocardial ischaemia, urgent angiography should be done within 2 h after a quick evaluation to exclude non-coronary causes. In all cases, the decision to perform urgent coronary angiography should take into account factors associated with poor neurological outcome.

(7) Technical aspects during primary PCI: Routine radial access and routine DES implant is the standard of care during primary PCI. Routine thrombus aspiration or deferred stenting are contraindicated.

(8) Management of non-IRA lesions: Treatment of severe stenosis (evaluated either by angiography or FFR) should be considered before hospital discharge (either immediately during the index PCI or staged at a later time). In cardiogenic shock, non-IRA PCI should be considered during the index procedure.

(9) Antithrombotic therapy: Anticoagulants and DAPT are the cornerstone of the pharmacological approach in the acute phase of STEMI. Primary PCI: unfractionated heparin (enoxaparin and bivalirudin may be alternative), and loading dose of aspirin and prasugrel/ticagrelor. Fibrinolysis: enoxaparin (unfractionated heparin may be alternative), and loading dose of aspirin and clopidogrel. Maintenance therapy in the majority of patients is based on one year DAPT in the form of aspirin plus prasugrel/ticagrelor.

(10) Early care: After reperfusion therapy, patients should be monitored for at least 24 h. Early ambulation and early discharge are the best option in uncomplicated patients. Consequently, time for implementing secondary prevention is limited highlighting the importance of close collaboration between all stakeholders.

(11) Special patient subsets: Patients taking oral anticoagulants with renal insufficiency and/or the elderly represent a challenge in terms of optimal antithrombotic therapy. Special attention should be paid to dose adjustment of some pharmacological strategies in these subsets. Patients with diabetes and those not undergoing reperfusion represent another subset of patients that require additional attention.

(12) Imaging in STEMI: Non-invasive imaging is very important for the acute and long-term management of STEMI patients.

(13) MINOCA: A sizeable proportion of STEMI patients do not present significant coronary artery stenosis on urgent angiography. It is important to perform additional diagnostic tests in these patients to identify the aetiology and tailor appropriate therapy, which may be different from typical STEMI.

(14) Quality indicators: In some cases, there is a gap between optimal guideline-based treatment and actual care of STEMI patients. In order to reduce this gap, it is important to measure established quality indicators to audit practice and improve outcomes in real-life. The use of well-defined and validated quality indicators to measure and improve STEMI care is recommended.

13. Evidenced-based 'to do and not to do' messages from the Guidelines

Recommendations

Recommendations for initial diagnosis	Class[a]	Level[b]
Twelve-lead ECG recording and interpretation is indicated as soon as possible at the point of FMC, with a maximum target delay of 10 min.	I	B
ECG monitoring with defibrillator capacity is indicated as soon as possible in all patients with suspected STEMI.	I	B
Recommendations for relief of hypoxaemia and symptoms		
Routine oxygen is not recommended in patients with $SaO_2 \geq 90\%$.	III	B
Recommendations for cardiac arrest		
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.	I	B
Targeted temperature management is indicated early after resuscitation of cardiac arrest patients who remain unresponsive.	I	B
Pre-hospital cooling using a rapid infusion of large volumes of cold i.v. fluid immediately after return of spontaneous circulation is not recommended.	III	B
Recommendations for logistics of pre-hospital care		
It is recommended that the pre-hospital management of STEMI patients is based on regional networks designed to deliver reperfusion therapy expeditiously and effectively, with efforts made to make primary PCI available to as many patients as possible.	I	B
It is recommended that primary PCI-capable centres deliver a 24/7 service and are able to perform primary PCI without delay.	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory.	I	B
Recommendations for reperfusion therapy		
Reperfusion therapy is indicated in all patients with symptoms of ischaemia of ≤ 12 h duration and persistent ST-segment elevation.	I	A
If primary PCI cannot be performed in a timely way after STEMI diagnosis, fibrinolytic therapy is recommended within 12 h of symptom onset in patients without contraindications.	I	A
In asymptomatic patients, routine PCI of an occluded IRA >48 h after onset of STEMI is not indicated.	III	A
Recommendations for procedural aspects of the primary PCI strategy		
Primary PCI of the IRA is indicated.	I	A
Stenting is recommended (over balloon angioplasty) for primary PCI.	I	A
Stenting with new-generation DES is recommended over BMS for primary PCI.	I	A
Radial access is recommended over femoral access if performed by an experienced radial operator.	I	A
Routine use of thrombus aspiration is not recommended.	III	A
Routine use of deferred stenting is not recommended.	III	B
Recommendations for periprocedural and post-procedural antithrombotic therapy in patients undergoing primary PCI		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contraindications such as excessive risk of bleeding.	I	A

Continued

Aspirin oral or i.v. (if unable to swallow) is recommended as soon as possible for all patients without contraindications.	I	B
Fondaparinux is not recommended for primary PCI.	III	B
Recommendations for Fibrinolytic therapy		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after STEMI diagnosis, preferably in the pre-hospital setting.	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.	I	B
Oral or i.v. aspirin is indicated.	I	B
Clopidogrel is indicated in addition to aspirin.	I	A
Anticoagulation is recommended in patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v. followed by s.c. (preferred over UFH).	I	A
• UFH given as a weight-adjusted i.v. bolus followed by infusion.	I	B
Transfer to a PCI-capable centre following fibrinolysis is indicated in all patients immediately after fibrinolysis.	I	A
Emergency angiography and PCI if indicated is recommended in patients with heart failure/shock.	I	A
Rescue PCI is indicated immediately when fibrinolysis has failed (<50% ST-segment resolution at 60–90 min) or at any time in the presence of haemodynamic or electrical instability, or worsening ischaemia.	I	A
Angiography and PCI of the IRA, if indicated, is recommended between 2–24 h after successful fibrinolysis.	I	A
Emergency angiography and PCI if needed is indicated in the case of recurrent ischaemia or evidence of reocclusion after initial successful fibrinolysis.	I	B
Recommendations for imaging and stress testing in STEMI patients		
Routine echocardiography during hospital stay to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients.	I	B
Recommendations for behavioural aspects after STEMI		
It is recommended to identify smokers and provide repeated advice on stopping, with offers to help with the use of follow-up support, nicotine replacement therapies, varenicline, and bupropion individually or in combination.	I	A
Participation in a cardiac rehabilitation programme is recommended.	I	A
Recommendations for maintenance antithrombotic strategy after STEMI		
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel are not available or are contra-indicated) is recommended for 12 months after PCI, unless there are contraindications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.	I	B
Recommendations for routine therapies in the acute, subacute, and long-term phases		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF ≤40% unless contraindicated.	I	A
Intravenous beta-blockers must be avoided in patients with hypotension, acute heart failure, or AV block or severe bradycardia.	III	B
It is recommended to start high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term.	I	A
An LDL-C goal of < 1.8 mmol/L (70 mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 1.8–3.5 mmol/L (70–135 mg/dL) is recommended.	I	B
ACE inhibitors are recommended, starting within the first 24 h of STEMI in patients with evidence of heart failure, LV systolic dysfunction, diabetes, or an anterior infarct.	I	A

Continued

An ARB, preferably valsartan, is an alternative to ACE inhibitors in patients with heart failure and/or LV systolic dysfunction, particularly those who are intolerant of ACE inhibitors.	I	B
MRAs are recommended in patients with an ejection fraction ≤40% and heart failure or diabetes, who are already receiving an ACE inhibitor and a beta-blocker, provided there is no renal failure or hyperkalaemia.	I	B
Recommendations for the management of LV dysfunction and acute heart failure in STEMI		
ACE inhibitor (or if not tolerated, ARB) therapy is indicated as soon as haemodynamically stable for all patients with evidence of LVEF ≤40% and/or heart failure to reduce the risk of hospitalization and death.	I	A
Beta-blocker therapy is recommended in patients with LVEF ≤40% and/or heart failure after stabilization, to reduce the risk of death, recurrent MI, and hospitalization for heart failure.	I	A
An MRA is recommended in patients with heart failure and LVEF ≤40% with no severe renal failure or hyperkalaemia to reduce the risk of cardiovascular hospitalization and death.	I	B
Recommendations for the management of cardiogenic shock in STEMI		
Immediate PCI is indicated for patients with cardiogenic shock if coronary anatomy is suitable. If coronary anatomy is not suitable for PCI, or PCI has failed, emergency CABG is recommended.	I	B
Routine intra-aortic balloon pumping is not indicated.	III	B
Recommendations for management of atrial fibrillation		
Digoxin is ineffective in converting recent onset AF to sinus rhythm and is not indicated for rhythm control.	III	A
Calcium channel blockers and beta-blockers including sotalol are ineffective in converting recent onset AF to sinus rhythm.	III	B
Prophylactic treatment with antiarrhythmic drugs to prevent AF is not indicated.	III	B
Recommendations for management of ventricular arrhythmias and conduction disturbances in the acute phase		
Intravenous beta-blocker treatment is indicated for patients with polymorphic VT and/or VF unless contraindicated.	I	B
Prophylactic treatment with antiarrhythmic drugs is not indicated and may be harmful.	III	B
Recommendations for long-term management of ventricular arrhythmias and risk evaluation for sudden death		
ICD therapy is recommended to reduce sudden cardiac death in patients with symptomatic heart failure (New York Heart Association class II–III) and LVEF ≤35%, despite optimal medical therapy for >3 months and at least 6 weeks after MI, who are expected to survive for at least 1 year with good functional status.	I	A

Recommendations with a class I or III and a level of evidence A or B. See 'Abbreviations and acronyms' list for explanation of abbreviations.
[a]Class of recommendation.
[b]Level of evidence.

14. Web addenda

All Web figures and Web tables are available in the online Web Addenda at: European Heart Journal online and also via the ESC Website at: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Myocardial-Infarction-in-patients-presenting-with-ST-segment-elevation-Ma

15. Appendix

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Learning Objectives

1. Manage cardiac arrest from the initiation of basic life support to the use of post–cardiac arrest care.
2. List the indications and contraindications for medication administration during cardiac arrest.
3. Recognize the utility of therapeutic hypothermia and the patient groups to whom it should be applied.
4. State the common complications of therapeutic hypothermia and explain how to ameliorate them.
5. Define the different presentations of hypertensive crisis.
6. Outline the therapeutic goals and clinical indications for the medications used in hypertensive emergency.

Abbreviations in This Chapter

ACLS	Advanced cardiac life support
AED	Automated external defibrillator
BLS	Basic life support
CPR	Cardiopulmonary resuscitation
ED	Emergency department
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
MICU	Medical intensive care unit
PEA	Pulseless electrical activity
ROSC	Return of spontaneous circulation
SCA	Sudden cardiac arrest
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–5 pertain to the following case.

T.B. is a 72-year-old man with a history of atrial fibrillation, coronary artery disease after drug-eluting stent placement in 2009, heart failure with reduced ejection fraction (although his most recent ejection fraction was 45% on echocardiogram in 2013), and gastroesophogeal reflux disease. T.B. is sent to the catheterization laboratory for suspected acute myocardial infarction. Laboratory values for T.B. are as follows: international normalized ratio (INR) 1, platelet count 200,000/mm^3, hemoglobin 12 g/dL, serum creatinine (SCr) 1.7 mg/dL (baseline 1.5 mg/dL), white blood cell count (WBC) 17 x 10^3 cells/mm^3, and aspartate aminotransferase (AST) 100 IU/L. He is admitted to the coronary care unit for observation after catheterization when he suddenly loses consciousness and becomes pulseless. The coronary care unit team of which you are part is called to the bedside. Of note, T.B. has peripheral intravenous access and was on room air by nasal cannula before this event.

1. Which is most accurate regarding the appropriate first steps in T.B.'s resuscitation?
   A. T.B. needs to be emergently intubated first because this is likely a hypoxic pulmonary arrest.
   B. T.B. should first have a central line placed because he will need vasopressors, and they are preferred to be administered centrally.
   C. T.B. should have pads placed when starting cardiopulmonary resuscitation (CPR), beginning with chest compressions.
   D. T.B. should have pads placed when CPR is initated, beginning with 2 breaths by bag-mask ventilator first.

2. The monitor reveals that T.B. is in ventricular fibrillation (VF). Which is the most appropriate management of T.B.'s VF arrest?
   A. T.B. should receive a shock as soon as possible with your biphasic defibrillator (manufacturer recommendation 200 J).
   B. T.B. should receive intravenous amiodarone at a dose of 300 mg x 1 as soon as possible.
   C. T.B. should receive intravenous atropine at a dose of 0.4 mg x 1 as soon as possible.
   D. T.B. should receive emergent pacing for his VF arrest because it is superior to other interventions.

3. T.B.'s rhythm changes from VF to pulseless electrical activity (PEA) on the monitor. Which is the most appropriate management of T.B.'s PEA arrest?
   A. T.B. should receive a shock as soon as possible with your biphasic defibrillator (manufacturer recommendation 200 J)
   B. T.B. should receive high-quality chest compressions and consideration of the treatable causes of cardiac arrest.

C. T.B. should receive intravenous lidocaine 1 mg/kg x 1, followed by 0.5 mg/kg every 5 minutes until a maximum total dose of 3 mg/kg because this is of substantial benefit in PEA arrest.
D. T.B. should receive intravenous atropine 0.4 mg x 1 as soon as possible because this is of substantial benefit in PEA arrest.

4. T.B. has return of spontaneous circulation (ROSC) after 15 minutes of total resuscitation. Your team is deciding whether targeted temperature management (therapeutic hypothermia) would be appropriate for T.B. Which is most accurate regarding targeted temperature management for T.B.?
   A. T.B. should not be considered for targeted temperature management because he had a VF arrest first, and most data come from PEA arrest.
   B. T.B. should not be considered for targeted temperature management because he has transaminitis, which is a contraindication for therapeutic hypothermia.
   C. T.B. should be considered for targeted temperateure management, but his renal function should be vigilantly monitored because of his baseline SCr and the worsening of glomerular filtration that occurs during cooling with therapeutic hypothermia.
   D. T.B. should be considered for targeted temperature management, but empiric thrombolysis should be initiated concurrently because hypothermia places patients at a significant risk of clotting.

5. Your team wants further information about the literature regarding therapeutic hypothermia. Which is the most appropriate information regarding the data to support therapeutic hypothermia?
   A. Therapeutic hypothermia improves survival in VF cardiac arrests and therefore should be reserved for these patients.
   B. Therapeutic hypothermia is the only intervention shown to improve neurologic outcomes and therefore has been applied to most cardiac arrests, independent of cause.
   C. Therapeutic hypothermia is superior when targeting a core temperature of 36°C compared with 33°C in recent studies.
   D. Therapeutic hypothermia has been most studied in patients with asystole; therefore, some institutions do not apply the results to patients with other presenting rhythms (ventricular tachycardia [VT], VF, and PEA).

Questions 6–8 pertain to the following case.

J.H. is a 48-year-old woman with no known medical history who presents to the emergency department (ED) for acute onset of shortness of breath, side pain, and some blurry vision. She denies any illicit drug use or cigarette use, but she confirms social alcohol intake (about 3 drinks per week). Urine toxicology is negative. Initial vital signs are as follows: blood pressure (BP) 202/140 mm Hg, heart rate (HR) 88 beats/minute, respiratory rate (RR) 22 breaths/minute, and pain 4/10 (chest and side pain). Initial laboratory values are as follows: SCr 0.8 mg/dL, AST 60 U/L, ALT 45 U/L, lipase 20 U/L, total bilirubin (Tbil) 1 mg/dL, direct bilirubin (Dbil) 0.4 mg/dL, WBC 6 x 10^3 cells/mm^3, hemoglobin 11 mg/dL, troponin T less than 0.01 ng/mL, and D-dimer less than 0.5 mcg/mL. Chest radiography shows moderate bilateral pleural effusions and no focal consolidations. Chest computed tomography (CT) is negative for pulmonary embolism. Of note, J.H. is taking no prescription or over-the-counter medications.

6. Which is most accurate regarding the classification of J.H.'s BP?
   A. J.H. is having a hypertensive urgency because she has no signs of target organ damage with severe acute BP elevations.
   B. J.H. is having a hypertensive urgency because she has signs of target organ damage with severe acute BP elevations.
   C. J.H. is having a hypertensive emergency because she has no signs of target organ damage with severe acute BP elevations.
   D. J.H. is having a hypertensive emergency because she has signs of target organ damage with severe acute BP elevations.

7. Which is most appropriate regarding the management of J.H.'s BP?

   A. J.H. should be initiated on phentolamine 1 mg intravenously every 30 minutes as needed because she has a unique indication for phentolamine.
   B. J.H. should be initiated on metoprolol 25 mg orally every 12 hours because rapid BP reduction is not indicated.
   C. J.H. should be initiated on nitroprusside 0.25 mcg/kg/minute by continuous intravenous infusion because it can be used safely in the first 24 hours.
   D. J.H. should be initiated on enalaprilat 10 mg intravenously every 6 hours because it can be used safely in the first 24 hours.

8. Which is the most appropriate goal for J.H.'s BP reduction?

   A. Goal mean arterial pressure (MAP) reduction of 25% over the first 60 minutes.
   B. Goal MAP reduction of 50% over the first 60 minutes.
   C. Goal MAP reduction of 25% over the first 24 hours.
   D. Goal MAP reduction of 50% over the first 24 hours.

I. ADVANCED CARDIAC LIFE SUPPORT

A. Background
1. Foundation of advanced cardiac life support (ACLS) is effective and timely basic life support (BLS).
2. Sudden cardiac arrest (SCA) continues to be a leading cause of death in many parts of world.
3. SCA can vary in etiology (noncardiac vs. cardiac), circumstances (unwitnessed vs. witnessed), and setting (in vs. out of hospital).
4. Because of heterogeneity, action links that are denoted the "Chain of Survival" were developed for guidance and include (Circulation 2010;121:948-54; Circulation 2010;122:S685-705):
    a. Immediate recognition of SCA and activation of the emergency response system
    b. Early CPR that emphasizes chest compressions
    c. Rapid defibrillation, if indicated
    d. Effective ACLS
        i. Airway management and ventilation support
        ii. Treatment of bradyarrhythmias and tachyarrhythmias
        iii. Integrated post–cardiac arrest care
5. When following the Chain of Survival effectively, can affect survival (e.g., with out-of-hospital, witnessed VF arrest survival rates that can approach 50%) (Circulation 2006;114:2760-5)
6. Because BLS and ACLS are often experienced as a team approach in the hospital setting, it is imperative to be familiar with all aspects of BLS and ACLS in order to fulfill any role during the arrest situation.

B. BLS – Chain of Survival
1. Immediate recognition of SCA and activation of emergency response system:
    a. Unresponsive patient or witnessed sudden collapse with absent or gasping abnormal breathing (Circulation 2010;122:S68-705; Acad Emerg Med 2007;14:877-83)
        i. Ensure that scene is safe.
        ii. Check for response by tapping on shoulder and shouting at victim; simultaneously check for normal breathing.
        iii. Activate emergency response system (e.g., facility emergency response team), and follow instructions from trained dispatchers/responders (Ann Emerg Med 1993;22:354-65).
2. Begin CPR. Follow the sequence of C-A-B (compressions-airway-breathing).
    a. Chest compressions an essential component of CPR
        i. Often not provided by laypeople until professional emergency responders arrive (Circ Cardiovasc Qual Outcomes 2010;3:63-81)
        ii. Both an increase in intrathoracic pressure and a direct compression of the heart lead to perfusion and oxygen delivery to the brain and myocardium.
        iii. All patients with SCA should receive chest compressions (Acta Anaesthesiol Scand 2008;52:914-9).
        iv. Place patient on a hard surface, use backboard (unless it will cause interruptions in chest compressions, delay in initiation of CPR, or dislodgment of lines/tubing), and/or deflate air-filled mattresses (J Intensive Care Med 2009;24:195-9; Acta Anaestheiol Scand 2007;51:747-50; Resuscitation 2004;61:55-61).
        v. Compress at a rate of at least 100 compressions/minute at a depth of at least 2 inches, and allow chest recoil after each compression to avoid decreases in coronary perfusion, cardiac index, myocardial blood flow, and cerebral perfusion (Crit Care Med 2010;38:1141-6; Resuscitation 2006;71:137-45; Resuscitation 2006;71:341-51; Resuscitation 2005;64:363-72).
        vi. Actual number of chest compressions given per minute is a function of the compression rate and proportion of time without interruption. Goal is to minimize interruptions to chest compressions.

(a) Increasing the number of compressions given per minute can affect survival from cardiac arrest (JAMA 2008;299:1158-64) and is a determinant of ROSC and neurologically intact survival (Circulation 2009;120:1241-7; Circulation 2005;111:428-34).
(b) Rescuer fatigue is common and may lead to inadequate compression quality (Resuscitation 2009;80:918-4). Recommended to change compressors every 2 minutes (or after five cycles of compressions at a rate of 30:2 compressions/ventilation) with no more than 5 seconds between changes (Resuscitation 2009;80:1015-8).
(c) Providers have difficulty and take too long to check for a pulse (Resuscitation 2000;44:195-201). Pulse checks (including initial) should last no more than 10 seconds.
(d) Compression-first (or "compression only") CPR decreases time until first compression (Resuscitation 2004;62:283-9) and may increase layperson participation but needs to be validated to replace traditional compression-ventilation CPR

Patient Case

1. A.C., a 50-year-old man with a history of gastroesophageal reflux disorder and chronic obstructive lung disease, was admitted for shortness of breath, palpitations, and presumed exacerbation of his lung disease. On hospital admission day 4, A.C. has witnessed cardiac arrest on the medicine unit. The emergency response team of which you are part is called, and when you arrive, the bedside nurse has already begun chest compressions. Which insight would be best shared regarding chest compressions for A.C.?

   A. Because the nurse has already begun chest compressions, she should remain the one doing compressions throughout BLS and ACLS.
   B. Compressions increase intrathoracic pressure and directly compress the heart, which can generate cardiac output and deliver oxygen.
   C. Because increasing the intrathoracic pressure is vital to oxygen delivery, chest recoil is unnecessary and should be avoided.
   D. Number of chest compressions given per minute has no impact on any outcomes, so pulse checks, line placements, and airways can be placed as needed without regard to interrupting chest compressions.

b. Airway
   i. For patients without an advanced airway, use the head-tilt, chin-lift technique if patients have no evidence of head or neck trauma and the jaw thrust alone if cervical spine injury is suspected (JAMA 1960;172:812-5; JACEP 1976;5:588-90) (see "Rescue Breaths" following).
   ii. Cricoid pressure is the technique of applying pressure to the victim's cricoid cartilage to push the trachea posteriorly and compress the esophagus with the goal of preventing aspiration
      (a) Recommend against use for adult cardiac arrest because of possible delay or prevention of advanced airway, lack of protection from aspiration, and lack of mastery from expert and non-expert rescuers (Emerg Med Australas 2005;17:376-81; Br J Anaesth 1994;72:47-51).
      (b) May help in visualizing vocal cords during tracheal intubation
   iii. If a foreign body airway obstruction (FBAO) occurs:
      (a) Do not act if the patient is coughing forcefully because this is a mild FBAO.
      (b) Signs of severe FBAO include a silent cough, stridor, or increasing respiratory difficulty. If these occur, ask the patient, "Are you choking?" If patients clutch their neck (universal sign of choking) or nod without answering verbally, consider severe FBAO:
         (1) Activate the emergency response system.
         (2) Administer abdominal thrusts to non-obese adults.
         (3) In obese adults or women in the late stage of pregnancy, administer chest thrusts.

(c) If the patient becomes unresponsive:
(1) Place on ground and begin CPR because chest compressions have been shown to generate higher airway pressure than abdominal thrusts (Resuscitation 2000;44:105-8).
(2) Each time the airway is opened during CPR to provide a rescue breath, look for an object in the victim's mouth and, if found, remove it. If not found, continue giving the rescue breaths, followed by 30 chest compressions.
(3) No studies have evaluated the routine use of the finger sweep to clear an airway in the absence of visible airway obstruction. Case reports have shown some efficacy, but harm has also been done in patients and rescuers. A finger sweep should not be used in the absence of visible airway obstruction.

iv. Advanced airways
(a) Supraglottic airway devices such as the laryngeal mask airway, the esophageal-tracheal Combitube, and the King airway device are considered within the scope of BLS in some districts.
(b) Will be discussed further in ACLS (following)

c. Rescue breaths
i. Primary purpose is to assist in maintaining oxygenation, with secondary purpose of eliminating carbon dioxide (CO_2).
ii. Compressions should always be initiated first because the arterial oxygen content of blood remains unchanged until CPR is initiated.
iii. Optimal compression/ventilation ratio, inspired oxygen concentration, tidal volume, and RR yet to be determined
iv. Recommended compression/ventilation ratio of 30:2 until advanced airway is placed; then ventilations at a rate of 8–10 per minute (every 6–8 seconds) after advanced airway is in place
(a) Low minute ventilation (low tidal volume and low RR) can maintain oxygenation and ventilation because of a reduced cardiac output by around 25%–33% even during chest compressions, resulting in a low oxygen uptake and CO_2 delivery (Circulation 1997;95:1635-41).
(b) Excessive ventilation can increase intrathoracic pressure and decrease venous return as well as cause gastric inflation, which can lead to aspiration and regurgitation and decrease survival (Circulation 2004;109:1960-5; Resuscitation 1998;36:71-3; JAMA 1987;257:512-5).
v. Deliver each rescue breath over 1 second. Mouth-to-mouth, mouth-to-barrier, mouth-to-stoma, and mouth-to-nose variations in initial rescue breathing are all acceptable and can produce oxygenation and ventilation (Chest 1994;106:1806-10; Br J Anaesth 1964;36:542-9).
vi. Give sufficient tidal volume to produce visible chest rise (Resuscitation 1996;31:231-4).
vii. Positive-pressure ventilation
(a) Bag-mask ventilation
(1) Components include a nonjam inlet valve, either no pressure relief valve or a pressure relief valve that can be bypassed, standard 15-mm/22-mm fittings, an oxygen reservoir to allow for high oxygen delivery, and a non-rebreathing outlet valve (Respir Care 1992;37:673-90; discussion 690-4).
(2) Should not be used by a single rescuer
(3) Should use an adult bag (1 or 2 L) and deliver (two-thirds or one-third of bag volume, respectively) about 600 mL of tidal volume, which can produce chest rise, oxygenation, and normocarbia (Resuscitation 2005;64:321-5; Resuscitation 2000;43:195-9)
(b) Supraglottic airway devices (e.g., King airway device) are considered an acceptable alternative to bag-mask ventilation during cardiac arrest (assuming proper training is supplied to rescuer) (Circ J 2009;73:490-6; Prehosp Emerg Care 1997;1:1-10).

Patient Case

2. L.S. is a 66-year-old woman visiting her husband at the hospital on the hospice unit. She is buying lunch in the cafeteria, and while in line to check out, she collapses. The emergency response team of which you are part is summoned. L.S. does not respond to voice or tapping of the shoulder, and a brief look at her chest shows no chest movement. Chest compressions are initiated while the crash cart and defibrillator are retrieved. Of note, a bag-mask ventilator is available at the scene because it is carried with the emergency response team. Which is most accurate about L.S.'s airway and breathing management?

   A. A compression/ventilation ratio of 60:1 should be used because cardiac arrest patients have minimal blood flow; therefore, oxygenation/ventilation requirements are lower.
   B. Because it is a multiple-rescuer scene, bag-mask ventilation should not be used because it is recommended only in single-rescuer resuscitations.
   C. A compression/ventilation ratio of 30:2 should be used with strict avoidance of excessive ventilation, which can decrease venous blood return to the heart.
   D. Bag-mask ventilation should not be used in any patient because advanced airways are the only way to supply oxygen and eliminate CO_2.

3. Rapid defibrillation with a manual or automated external defibrillator (AED) (Chain of Survival)
   a. Successful defibrillation is defined as 5 seconds or greater of termination of arrhythmia after a shock is delivered.
   b. Early defibrillation of VF is crucial because the most frequently witnessed out-of-hospital SCA is caused by VF, survival diminishes rapidly over time, and VF often progresses to asystole over time (Resuscitation 2000;44:7-17; (Electrical therapies; 2008;) Circulation 1997;96:3308-13).
   c. Three key actions must occur within moments of VF SCA to increase the likelihood of survival: activation of the emergency medical services system (e.g., emergency response team), provision of CPR, and shock delivery (Ann Emerg Med 1993;22:1652-8).
   d. Performing chest compressions while a defibrillator is obtained significantly improves the probability of survival (Circulation 2009;120:1241-7). When VF is present for more than a few minutes, the myocardium becomes deplete of oxygen and energy substrates.
      i. CPR can provide the oxygen and energy needed until the shock is delivered.
      ii. Increased likelihood of termination of VF from shock delivery and ROSC if CPR given first (Circulation 2004;110:10-5)
      iii. If CPR is initiated immediately, survival can double or triple at most time intervals until defibrillation occurs (Resuscitation 2000;44:7-17; Ann Emerg Med 1995;25:780-4; Ann Emerg Med 1993;22:1652-8).
   e. Early defibrillation is a powerful predicator of ROSC after VF.
      i. Survival rates are highest for VF when CPR and defibrillation occur within 3–5 minutes of the event (Circ Cardiovasc Qual Outcomes 2010;3:63-81; Resuscitation 2009;80:1253-8).
         (a) For every minute that passes after collapse, survival from VF decreases 7%–10% (Ann Emerg Med 1993;22:1652-8).
         (b) CPR prolongs VF and delays the progression to asystole (Resuscitation 2000;47:59-70; Am J Emerg Med 1985;3:114-9).
      ii. There is conflicting evidence to recommend delaying shock delivery in order to provide CPR first in VF and pulseless VT; subsequently, CPR should be initiated immediately, with shock delivery as soon as possible.

iii. One-shock biphasic (bidirectional) shock protocols are better than or equivalent to three-shock monophasic (one-directional) stacked protocols in terminating VF.
  (a) Almost all AEDs manufactured currently are biphasic.
  (b) Polyphasic waveform defibrillators are currently under investigation.
iv. With any shock delivery, chest compressions should resume immediately, and pulse check should be delayed until the end of the next cycle of CPR because this can improve defibrillation and ROSC (Circulation 2004;110:10-5; Circulation 2002;105:2270-3).
v. The optimal shock energy for biphasic first shock has yet to be determined.
  (a) Low-energy dosages (200 J or less) are safe and have equivalent or higher efficacy of termination of VF compared with monophasic waveform shocks at the same or higher energy (Circulation 2007;115:1511-7; Prehosp Emerg Care 2000;4:305-13).
  (b) The energy dosage used should be according to the manufacturer's recommendation (e.g., 120 or 200 J).
vi. If additional shocks are needed, it is recommended that at least equivalent and potentially higher energy be used.
vii. Electrode placement
  (a) Pad positioning is equally effective in terminating ventricular arrhythmias in four positions: anterolateral, anteroposterior, anterior-left infrascapular, and anterior-right infrascapular (Medicina (Kaunas) 2006;42:994-8; Physiol Meas 2006;27:1009-22).
  (b) Lateral pads should be placed under breast tissue, and hirsute men should be shaved before the placement of pads.
  (c) In patients with an implantable cardioverter-defibrillator or a pacemaker, it may be beneficial to avoid placing the pads or paddles over the device.
  (d) Do not place the pads on top of a medication patch because this can cause impedance or burning (Am J Emerg Med 1992;10:128-9).
viii. In-hospital AED use should be considered in ambulatory and unmonitored areas.

f. Pulseless VT is treated like VF.
g. Pacing is not recommended for unstable VF or pulseless VT (Circulation 2010;122:S685-705).

Patient Case

3. T.V. is a 72-year-old man with a history of chronic liver disease, hypoglycemia, and atrial fibrillation. He was admitted to your medical intensive care unit (MICU) 2 days ago for severe sepsis requiring aggressive fluid resuscitation and intravenous antibiotics. T.V. did not require vasopressors to treat his severe sepsis. On ICU day 3, T.V. develops VF on telemetry, loses consciousness, and becomes pulseless; the MICU team of which you are part is summoned for a presumed VF cardiac arrest. Pads are placed on T.V. by the time your team arrives, and the rhythm is confirmed to be VF. Which is most accurate regarding defibrillation for T.V.?

A. Three vital actions with VF can lead to increased survival if they occur rapidly: activate emergency response system, provide CPR, and deliver shock.
B. T.V. should not be defibrillated but should be paced out of the VF, if possible, because pacing is more effective for pulseless VF.
C. T.V. should not have CPR until the defibrillator is charged—especially chest compressions because they decrease the likelihood of successful defibrillation.
D. Alternative treatments such as antiarrhythmics, vasopressors, and magnesium should be tried first because there is no time-sensitive nature of VF to predict the success of defibrillation.

C. ACLS – Chain of Survival
   1. Airway control and ventilation
      a. Background
         i. During CPR, oxygen delivery to the heart and brain becomes more flow-dependent than arterial oxygen saturation–dependent (Ann Emerg Med 1990;19:1104-6).
         ii. Placement of an advanced airway in cardiac arrest should not delay CPR or defibrillation.
         iii. No studies address the optimal timing of advanced airway placement. The guiding general concept is to place the advanced airway while minimizing interruptions to chest compressions.
         iv. Conflicting evidence exists for the urgent placement of an advanced airway.
            (a) An in-hospital cardiac arrest study has shown an increased 24-hour survival in patients with an advanced airway placed within 5 minutes but no difference in ROSC (Resuscitation 2010;81:182-6); however, another study has shown a worse overall survival rate in cardiac arrest patients who required intubation (Arch Intern Med 2001;161:1751-8).
            (b) Out-of-hospital cardiac arrest studies have shown that intubation in the rural and urban setting and, more specifically intubation within 13 minutes, is associated with better survival (Med J Aust 2006;185:135-9; Prehosp Emerg Care 2004;8:394-9).
      b. Oxygen during CPR
         i. Unclear what the optimal concentration of inspired oxygen content should be during CPR
         ii. 100% inspired oxygen carries the risk of toxicity, but this toxicity has not been shown in the short-term setting of adult CPR (Resuscitation 1999;42:221-9).
         iii. Use of 100% inspired oxygen is recommended as soon as it is available to optimize arterial oxyhemoglobin content and, subsequently, delivery.
         iv. During chest compressions, air is forcefully expelled from the chest, and oxygen is drawn into the chest by passive recoil. Because the ventilation requirements are lower than normal, passive oxygen delivery is theorized to be sufficient for several minutes of initial CPR (Circulation 1994;90:3070-5), but recommendations to remove ventilation cannot be made.
      c. Bag-mask ventilation: Viable option for oxygenation and ventilation during CPR but should be provided only by multiple rescuers and trained personnel (for more details, see earlier discussion) (Circulation 2010;122:S729-767)
      d. Airway adjuncts
         i. *Cricoid pressure* should be used only in special circumstances to help visualize the vocal cords and should be relaxed, released, or adjusted if it impedes ventilation or advanced airway placement.
         ii. *Oropharyngeal airways* can be considered to help facilitate bag-mask ventilation in the unresponsive patient with no cough or gag reflex.
         iii. *Nasopharyngeal airways* can be considered in patients with airway obstruction and clenched jaw but should be used cautiously in craniofacial injury and avoided in known coagulopathy because of an increased risk of bleeding (J Trauma 2000;49:967-8; Anaesthesia 1993;48:575-80).
      e. Advanced airways
         i. Endotracheal intubation
            (a) Attempted placement by unskilled providers leads to unacceptably large periods of chest compression interruption and hypoxemia.
            (b) Benefits include keeping the airway patent, allowing for suctioning of airway, high oxygen concentration delivery, medications administration, allowing for specific tidal volume delivery, and protection from aspiration.

ii. Supraglottic airways
   (a) Do not require visualization of glottis, which allow for continuous chest compressions
   (b) Types studied during cardiac arrest include laryngeal mask airway, esophageal-tracheal tube (Combitube), and laryngeal tube (Laryngeal Tube or King LT).
      (1) Laryngeal mask airway: Compared with bag-mask ventilation, is more secure and reliable and has a lower incidence of aspiration. Easier to place than endotracheal tubes, which would allow placement when access to the patient is limited or positioning constraints are in place
      (2) Combitube: Compared with bag-mask ventilation, allows isolation of airway, more reliable ventilation, and protection from aspiration. Compared with endotracheal tubes, may be easier to train personnel, and all levels of experience can use (Prehosp Emerg Care 1997;1:1-10)
      (3) Laryngeal Tube or King LT: Potentially easier to insert compared with the Combitube but not as vigorously evaluated in the cardiac arrest population
   (c) When used by trained providers, they allow as effective oxygenation and ventilation as bag-mask ventilation and endotracheal intubation.

iii. After advanced airways are secured, proper placement should be confirmed with clinical assessment and objective measures without interruptions to chest compressions.
   (a) Physical assessments include visually inspecting chest rise bilaterally and listening to the epigastrium (breath sounds should be absent) and lung fields (should be equal and adequate).
   (b) Exhaled CO_2 or esophageal detector devices are a reasonable and objective means of confirmation if continuous waveform capnography is not readily available.
   (c) Continuous waveform capnography is the most reliable and objective way to ensure, confirm, and monitor correct endotracheal tube placement. Although not specifically studied with supraglottic airways, readings should be similar to endotracheal readings.
   (d) False-positive CO_2 detection (CO_2 detected not from ventilation) is rare, whereas false-negative CO_2 detection (no CO_2 detection when ventilation is occurring) is more common. Most common cause of false-negative CO_2 detection is a reduction in blood flow or CO_2 delivery to lungs (e.g., lack of quality chest compressions, pulmonary embolism, severe airway obstruction).

iv. Post–intubation airway management
   (a) Airway should be marked (from front of teeth/gums) and secured (with tape or commercial device), avoiding compression around the neck, which could impair venous return from brain.
   (b) Chest radiography is suggested for confirmation of location of end of endotracheal tube in relation to the carina.
   (c) Slower ventilator rates (6–12 breaths/minute) have been shown to improve hemodynamic values and short-term survival in animal models (Crit Care Med 2006;34:1444-9; Circulation 2004;109:1960-5; Resuscitation 2004;61:75-82) of cardiac arrest.

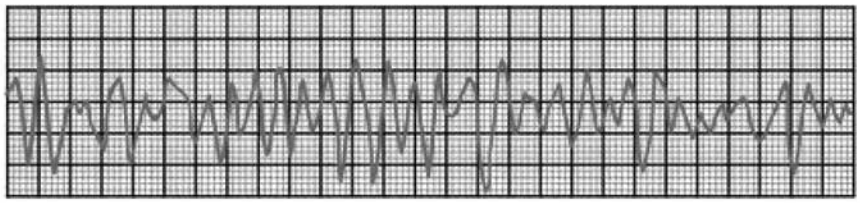
v. After placement, continuous chest compressions should be given at a rate of least 100 compressions/minute. A breath should be delivered every 6–8 seconds, making sure to avoid over-ventilation, which could decrease venous return and cardiac output.

Patient Case

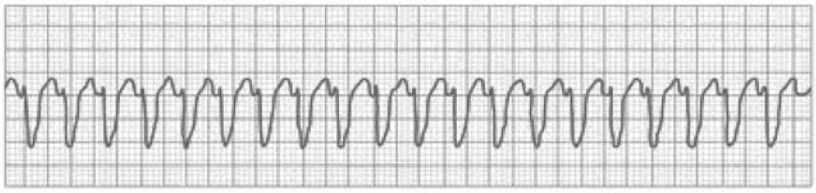
4. F.V. is a 63-year-old woman with a history of diabetes, heart failure with preserved ejection fraction, hypertension, and obstructive sleep apnea who presents to the ED with chest tightness and "feeling funny." In the ED, F.V. loses consciousness and develops pulseless VT. Chest compressions are initiated immediately, pads are placed, and bag-mask ventilation is given at a compression/ventilation ratio of 30:2. The monitor confirms the rhythm of pulseless VT. The defibrillator is charged, the patient is cleared, and the first shock is delivered. Chest compressions resume, and during the next pulse check, the patient is intubated. F.V. still does not have a pulse, and chest compressions are continued. Which is most accurate about F.V.'s resuscitation after an advanced airway is in place?

   A. After the advanced airway is in place, the compression/ventilation ratio should remain 30:2 to avoid excessive ventilation.
   B. This case was mismanaged because the advanced airway should have been placed before defibrillation and CPR for pulseless VT.
   C. The patient should be placed on room air (21% F_{IO_2} [fraction of inspired oxygen]) to avoid the proven toxicity that occurs with 100% oxygen in the cardiac arrest situation.
   D. After the advanced airway is secured, proper placement should be confirmed with clinical assessment and objective measures.

2. Management of cardiac arrest
   a. Background
      i. Cardiac arrest can be caused by four primary rhythms: VF, pulseless VT, PEA, and asystole.
      ii. These rhythms can also be classified as shockable (VF and pulseless VT) and non-shockable (PEA and asystole).
         (a) Ventricular fibrillation
            (1) Wide complex
            (2) Polymorphic
            (3) Disorganized
            (4) Coarse or fine
            (5) No/minimal forward flow

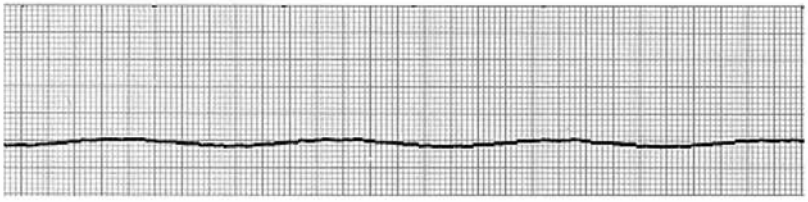


         (b) Pulseless VT
            (1) Wide complex
            (2) Monomorphic or polymorphic
            (3) Generally organized
            (4) No/minimal forward flow



(c) Pulseless electrical activity
   (1) Not a rhythm itself, but defined as an organized rhythm that would be expected to produce mechanical activity but does not
   (2) Absence or insufficient mechanical ventricular activity

(d) Asystole (ventricular asystole)
   (1) Absence of detectable ventricular electrical activity
   (2) Accompanied by absence of ventricular mechanical activity



iii. Survival requires both BLS and ACLS. Foundation of ACLS is high-quality BLS. In addition to CPR, the only proven rhythm-specific therapy that increases survival at hospital discharge is defibrillation of VF/pulseless VT.
iv. Medications and advanced airways have not been shown to increase survival of cardiac arrest but have been shown to increase the ROSC (exception: amiodarone in out-of-hospital arrest [see text that follows]) (Resuscitation 2010;81:182-6; Med J Aust 2006;185:135-9; Resuscitation 2000; 45:161-6; N Engl J Med 1999;341:871-8).
   (a) Vascular access and medication delivery should never interrupt CPR and/or defibrillation. All other therapies are "considerations" and should never compromise chest compressions.
   (b) Interruptions in chest compressions should occur only for brief rhythm assessment, shocking of VF/VT, pulse check when an organized rhythm is detected, and advanced airway placement.
v. During cardiac arrest treatment, it is imperative to evaluate, treat, and/or reverse any treatable causes of cardiac arrest (Table 1).
vi. Post–cardiac care should begin immediately after ROSC is obtained to avoid re-arrest.

Table 1. Treatable Causes of Cardiac Arrest

H's	T's
Hypoxia	Toxins
Hypovolemia	Tamponade (cardiac)
Hydrogen ion (acidosis)	Thrombosis • Pulmonary embolism • Coronary thrombosis
Hypoglycemia	
Hypo/hyperkalemia	Tension pneumothorax
Hypothermia	

Patient Case

5. V.B., a 62-year-old man with an unknown medical history, comes to your ED altered and incoherent. He is admitted to the ED for observation, where he suddenly becomes unconscious and pulseless. The ED staff, of which you are part, immediately initiates CPR for V.B. Which statement is best regarding V.B.'s cardiac arrest?
   A. Survival from V.B.'s cardiac arrest is solely dependent on medications and advanced airways. Therefore, V.B. should have CPR discontinued so that lines can be placed immediately for medication administration, and V.B. should be intubated before resuming CPR.
   B. The treatable causes of V.B.'s cardiac arrest should be reviewed and addressed. Laboratory tests should be done as able during/after, or if known, they should be reviewed during CPR to address these causes.
   C. If V.B. is in a shockable rhythm (e.g., PEA or asystole), pads should be placed, the patient cleared, and shock delivered immediately.
   D. No strategies are in place for care after V.B.'s arrest to avoid re-arrest or improve outcomes from the cardiac arrest.

b. Medication background (rhythm-independent)
   i. Goal: Increase myocardial blood flow during CPR and help achieve ROSC
   ii. Drug delivery
      (a) Central intravenous administration is recommended, if available. Central line placement should not interrupt CPR. The advantage of central administration is higher peak and shorter drug circulation times compared with peripheral routes (Crit Care Med 1988;16:1138-41; Ann Emerg Med 1981;10:73-8; Ann Emerg Med 1981;10:417-9).
      (b) If peripheral administration of medications is necessitated, the bolus injection should be followed by a 20-mL bolus of an intravenous fluid (e.g., 0.9% sodium chloride) to facilitate drug flow from the extremity to the central circulation (Am J Emerg Med 1990;8:190-3).
      (c) If proximal humerus intraossesous access is used, administration and drug delivery are similar to central venous access. If proximal or distal tibial intraosseous access in used, administration and drug delivery are similar to peripheral venous access.
      (d) Endotracheal (ET) delivery
         (1) NAVEL acronym summarizes medications that have been studied and shown to have tracheal absorption by ET tube delivery. N – naloxone, A – atropine, V – vasopressin, E – epinephrine, L – lidocaine
         (2) Serum concentrations of medications are less when given by ET delivery.

(3) Optimal ET dose unknown; typically, it is 2–2.5 times the intravenous dose but may be higher (e.g., up to 3–10 higher for epinephrine) (Crit Care Med 1987;15:1037-9)
(4) Should be diluted with either 5–10 mL of 0.9% sodium chloride or sterile water and injected directly into the ET tube (Crit Care Med 1994;22:1174-80)

(e) Peak effect of intravenous or intraosseous medication delayed 1–2 minutes during CPR
(f) Theoretical concern that giving high-dose bolus vasopressors after ROSC following defibrillation may precipitate cardiac instability and re-arrest. May be avoided by using physiologic monitoring such as quantitative waveform capnography, intra-arterial pressure monitoring, or continuous central venous oxygen saturation monitoring and avoiding administration if ROSC occurs (J Emerg Med 2009;38:614-21; Ann Emerg Med 1992;21:1094-101; Ann Emerg Med 1990;19:1104-6)

Patient Case

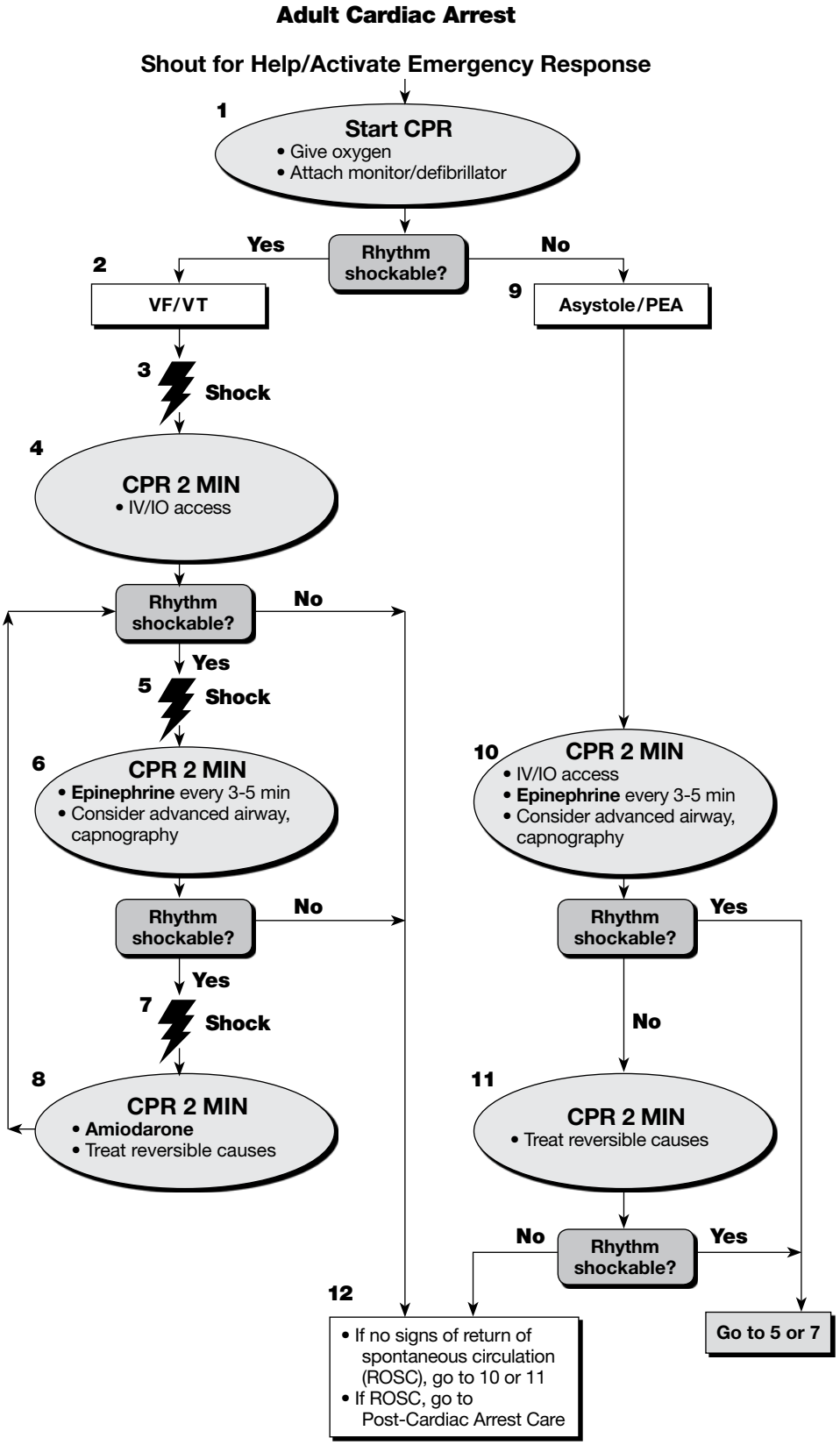
6. M.G., a 58-year-old woman with a history of chronic osteoarthritis and peptic ulcer disease, is admitted to the MICU with hypovolemic shock caused by a suspected bleeding gastric ulcer. Endoscopy is performed, confirming the gastric ulceration. The ulcer is cauterized, and M.G. is stabilized. On ICU day 2, M.G. becomes lethargic, hypoxic, and subsequently pulseless. The MICU team is summoned, and the monitor reveals VF. Which general principles are most accurate regarding the medication management of M.G.'s VF arrest?

A. Endotracheal delivery is preferred because all cardiac arrest medications can be delivered by the endotracheal route.
B. Peripheral administration is preferred because the peak concentrations are higher and the circulation time is shorter compared with other routes.
C. Intraosseous administration is preferred because administration and dosing are similar to that for the endotracheal route.
D. Central administration is preferred because dosing is easier and circulation time of cardiac arrest medications is shorter.

c. Management of VF/pulseless VT (Figure 1): Defibrillation (summary, details available above in the Chain of Survival: defibrillation section)
   i. When VF/pulseless VT detected, CPR should continue until defibrillator (either manual or automatic) charging period is over
   ii. It is strongly recommended that CPR be performed while the defibrillator is readied because chest compressions can delivery oxygen and potentially unload the ventricles, increasing the likelihood that a perfusing rhythm will return after shock is delivered.
   iii. Because intentionally delaying defibrillation for CPR has mixed results, it cannot currently be recommended.
   iv. Once defibrillator is charged, patient is "cleared."
   v. Shock is delivered, and CPR is immediately resumed, beginning with chest compressions.
      (a) Pulse check is delayed until 2 minutes of CPR is given.
      (b) Pause for rhythm and pulse check; continue CPR, if necessary.
   vi. If biphasic defibrillator is available:
      (a) Provider should use manufacturer's recommended energy dose (e.g., 120–200 J).
      (b) If information unavailable, the maximum dosing can be considered
      (c) Second and subsequent defibrillator energy dosages should be equivalent, and consideration should be made for escalating energy doses, if possible.

vii. If monophasic defibrillator is available:
  (a) Initial energy dose should be 360 J.
  (b) Second and subsequent defibrillator energy dosages should be 360 J.
viii. If VF/pulseless VT is terminated by defibrillation and reoccurs, resulting in an arrest, the successful energy dosage used previously should be employed.
ix. Change of multimodal defibrillator from automatic to manual mode may result in fewer interruptions of CPR but also an increased frequency of inappropriate shocks (Resuscitation 2007;73:131-6; Resuscitation 2007;73:212-20).

d. Medication therapy for VF/pulseless VT
  i. Consider medication therapy after one shock and 2 minutes of CPR (one cycle). The optimal timing of medication administration is unclear.
  ii. Vasopressors:
    (a) First-line medications include epinephrine or vasopressin (Figure 1; Table 2).
    (b) No other vasopressors (e.g., phenylephrine or norepinephrine) have shown any benefit compared with epinephrine (JAMA 1992;268:2667-72; Acta Anaesthesiol Scand 1985;29:610-3).
    (c) Adding methylprednisolone and vasopressin to epinephrine during ACLS plus stress dose hydrocortisone for post-ROSC shock compared with placebo may aid in the ROSC during cardiac arrest and improve discharge neurologic function in patients who survive. Role of steroids may be debated, given the addition of vasopressin in the study arm (JAMA 2013;310:270-9).
  iii. Antiarrhythmics:
    (a) No evidence that, in cardiac arrest, any antiarrhythmics increase survival to discharge
    (b) Amiodarone (Table 2) increases survival to hospital admission in out-of-hospital arrest compared with placebo and lidocaine (N Engl J Med 2002;346:884-90; N Engl J Med 1999;341:871-8).
      (1) Should be considered for refractory (unresponsive to shock, CPR, and a vasopressor) VF/pulseless VT
      (2) Administered as intravenous/intraosseous push if pulseless. If pulse is obtained, must be given as slow intravenous piggyback
      (3) Hemodynamic effects of bradycardia and hypotension may be partly related to vasoactive solvents (polysorbate 80 and benzyl alcohol) (Am J Cardiol 2002;90:853-9).
    (c) Lidocaine has no proven short- or long-term efficacy in cardiac arrest, but it can be considered if amiodarone is unavailable (Table 2).
    (d) Magnesium sulfate (Table 2) is effective for cardiac arrest caused by torsades de pointes (i.e., caused by early afterdepolarizations during phase 2 of the action potential).
      (1) Not effective when VF/pulseless VT is not associated with torsades de pointes
      (2) May consider for emergency magnesium replacement in patients who sustain cardiac arrest and are hypomagnesemic
      (3) Optimal dosing has not been established.



CPR Quality
- Push hard (≥2 inches [5 cm]) and fast (≥100/min) and allow complete chest recoil
- Minimize interruptions in compressions
- Avoid excessive ventilation
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio
- Quantitative waveform capnography
  - If $PETCO_2$ <10 mm Hg, attempt to improve CPR quality
- Intra-arterial pressure
  - If relaxation phase (diastolic) pressure <20 mm Hg, attempt to improve CPR quality

Return of Spontaneous Circulation (ROSC)
- Pulse and blood pressure
- Aburpt sustained increase in $PETCO_2$ (typically ≥40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock Energy
- **Biphasic:** Manufacturer recommendation (eg, initial dose of 120-200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug Therapy
- **Epinephrine IV/IO Dose:** 1 mg every 3-5 minutes
- **Vasopressin IV/IO Dose:** 40 units can replace first or second dose of epinephrine
- **Amiodarone IV/IO Dose:** First dose: 300 mg bolus. Second dose: 150 mg.

Advanced Airway
- Supraglottic advanced airway or endotracheal intubation
- Waveform capnography to confirm and monitor ET tube placement
- 8-10 breaths per minute with continuous chest compressions

Reversible Causes
- —**H**ypovolemia
- —**H**ypoxia
- —**H**ydrogen ion (acidosis)
- —**H**ypo-/hyperkalemia
- —**H**ypothermia
- —**T**ension pneumothorax
- —**T**amponade, cardiac
- —**T**oxins
- —**T**hrombosis, pulmonary
- —**T**hrombosis, coronary

Figure 1. Adult cardiac arrest algorithm.

Table 2. Medications Used During Sudden Cardiac Arrest

Medication	Primary Mechanism of Action in Cardiac Arrest	Dosage, Route, Frequency	Clinical Benefits
Epinephrine (N Engl J Med 1992;327:1045-50; Circulation 1984;69:822-35; Crit Care Med 1979;7:293-6)	α-Adrenergic agonist effects leading to vasoconstriction	1 mg IV/IO q3–5 min 2–2.5 mg ET q3–5 min	Increases coronary and cerebral perfusion pressure during CPR Increases ROSC
Vasopressin (Arch Intern Med 2005;165:17-24; N Engl J Med 2004;350:105-13; Lancet 2001;358:105-9)	Nonadrenergic vasoconstrictor (vasopressin-1 receptor mediated)	40 units IV/IO x 1 (can replace epinephrine as either the first or second dose)	No difference in ROSC, neurologic recovery, or survival to discharge compared with epinephrine
Amiodarone (N Engl J Med 2002;346:884-90; N Engl J Med 1999;341:871-8)	$Na^+/K^+/Ca^{2+}$ channel and β-receptor antagonist	First dose: 300 mg or 5 mg/kg IV/IO x 1 Second dose: 150 mg IV/IO x 1 Max: 2.2 g/day	Increases survival to hospital admission compared with lidocaine or placebo for VF/pulseless VT arrest
Lidocaine (Resuscitation 1997;33:199-205)	Na^+ channel antagonist	First dose: 1–1.5 mg/kg IV/IO x 1 Subsequent dosing: 0.5–0.75 mg/kg q5–10 min Max 3-mg/kg cumulative dose	Increases ROSC and possibly survival to admission for out-of-hospital VF cardiac arrest. No improvement in overall or discharge survival Insufficient evidence to recommend for refractory VF/pulseless VT unless amiodarone unavailable
Magnesium (Clin Cardiol 1993;16:768-74; New Trends Arrhythmias 1991;7:437-42; Circulation 1988;77:392-7)	Stops EAD in torsades de pointes by inhibiting Ca^{2+} channel influx	1–2 g diluted in 10 mL of 5% dextrose or sterile water IV/IO x 1	Can aid in stopping torsades de pointes in patients with prolonged QT interval

EAD = early afterdepolarization; ET = endotracheal; IO = intraosseously; IV = intravenously; min = minute; q = every.

e. Management of PEA/asystole
   i. CPR and treatment of reversible causes are vital to treatment of PEA/asystole.
   ii. Medication therapy
      (a) Vasopressors (e.g., epinephrine and vasopressin) can be given as soon as feasible (Table 2).
      (b) Atropine has been removed from the algorithm because of its lack of therapeutic benefit.

f. Role in treating reversible causes
   i. Echocardiography may be helpful, if available, in the management of PEA to help differentiate the following (Am J Cardiol 1992;70:1056-60):
      (a) Intravascular volume status (ventricular volume)
      (b) Cardiac tamponade
      (c) Massive pulmonary embolism (right ventricular size, function)
      (d) Mass lesions (tumor, clot)
      (e) Coronary thrombosis (right and left ventricular function, regional wall motion abnormalities)
   ii. Because hypoxia often causes of PEA arrest, more focused attention may be given to placement of airway and oxygen delivery.
   iii. Please see the specific chapters for pulmonary disorders (massive pulmonary embolism and tension pneumothorax), cardiology (acute myocardial infarction and cardiac tamponade), shock (hypovolemic shock and oxygen delivery), acid-base disorders (acidemia), endocrinologic disorders (hypoglycemia), and electrolytes (hypo/hyperkalemia).

g. Interventions to avoid in cardiac arrest
   i. Sodium bicarbonate
      (a) Tissue acidosis and acidemia result during cardiac arrest for several reasons, including inadequate or absent blood flow, arterial hypoxia, or underlying pathophysiology.
      (b) Mainstays of restoring acid-base status include high-quality chest compressions and appropriate ventilation/oxygenation.
      (c) Conflicting evidence exists for the use of sodium bicarbonate, with most data showing no benefit or poor outcome with use (Ann Emerg Med 1998;32:544-53; Resuscitation 1995;29:89-95; Am J Emerg Med 1992;10:4-7; Chest 1990;97:413-9; Resuscitation 1989;17(suppl):S161-172; discussion S199-206).
      (d) Detrimental effects may be associated with sodium bicarbonate in cardiac arrest, including:
         (1) Compromised coronary perfusion pressure by reducing systemic vascular resistance (JAMA 1991;266:2121-6)
         (2) Shifting the oxyhemoglobin dissociation curve to the left by creating an extracellular alkalosis and decreased release of oxygen
         (3) Causing hypernatremia and subsequent hyperosmolarity
         (4) Producing excess CO_2 through rapid dissociation, which can freely diffuse intracellularly (e.g., myocardial and cerebral cells) and cause intracellular acidosis (Science 1985;227:754-6)
         (5) Inactivation of concurrently administered catecholamines (e.g., epinephrine) (Hosp Pharm 1969;4:14-22)
      (e) Certain circumstances may warrant sodium bicarbonate use such as tricyclic antidepressant overdose, bicarbonate-wasting causes of metabolic acidosis, and hyperkalemia. Initial dosage should usually be 1 mg/kg intravenous push with monitoring of clinical status, bicarbonate concentration, laboratory values, and blood gas analysis.
   ii. Calcium
      (a) No trial has established any impact on survival in either in- or out-of-hospital cardiac arrest (Ann Emerg Med 1985;14:626-9; Ann Emerg Med 1985;14:630-2).
      (b) Consider in patients with preexisting hypocalcemia and signs and symptoms of acute hypocalcemia (e.g., severe tetany or seizures).

iii. Atropine
(a) No prospective studies have evaluated atropine for bradycardic PEA or asystolic cardiac arrest.
(b) Conflicting results exist from retrospective analyses and case reports (Acta Anaesthesiol Scand 2000;44:48-52; Ann Emerg Med 1984;13:815-7; Ann Emerg Med 1981;10:462-7).
(c) Atropine has not been associated with harm in treating bradycardic PEA or asystolic cardiac arrest, but because of the lack of convincing evidence of benefit, it is no longer recommended for cardiac arrest.
iv. Intravenous fluids
(a) Normothermic, hypertonic, and chilled fluids have been evaluated in animal models and small human studies, with no survival benefit.
(b) If hypovolemic shock is the suspected cause of the cardiac arrest, fluid resuscitation should be initiated immediately.
v. For indications of fibrinolysis for cardiac arrest, please see the pulmonary chapter for treatment of pulmonary embolism and the cardiology chapter for treatment of acute myocardial infarction.
vi. Pacing
(a) Transcutaneous, transvenous, and transmyocardial pacing not beneficial in cardiac arrest and does not improve ROSC or survival
(b) Not recommended for routine use in cardiac arrest

h. For information on acute symptomatic arrhythmias (bradycardias and tachycardias), see the cardiology chapter.

D. Post–Cardiac Arrest Care – Chain of Survival: Objectives of post–cardiac arrest care can be divided into initial and subsequent (Circulation 2010;122:S768-786; Circulation 2008;118:2452-83).
1. Initial
a. Optimize hemodynamics: Target MAP 65–100 mm Hg or greater, central venous pressure 8–12 mm Hg, central venous oxygen saturation greater than 70%, urine output greater than 1 mL/kg/hour, and normal serum lactate
i. Consider the patient's normal BP, cause of arrest, and severity of myocardial dysfunction for all values above.
ii. Use intravenous crystalloids and colloids, continuous vasopressors and inotropes, transfusions, and renal replacement as needed to meet target goals.
b. Transfer patient (out-of-hospital arrest) to a system or unit (in-hospital arrest) that can provide advanced post–cardiac arrest care, including continuous electrocardiographic (ECG) monitoring with immediate 12-lead ECG, central intravenous access if possible, coronary reperfusion, and/or therapeutic hypothermia.
c. Try to identify and treat the reversible causes of cardiac arrest (Table 1). Laboratory and diagnostic tests should be performed to aid in identifying a potential underlying cause.
2. Subsequent
a. Consider therapeutic hypothermia and body temperature regulation. Should be considered for any patient with ROSC who does not follow commands (i.e., comatose) after cardiac arrest. Best evidence exists for out-of-hospital VF/pulseless VT cardiac arrest, but it should be considered for all types and locations of cardiac arrest (Circulation 2010;122:S768-786)
i. Only intervention that has been shown to improve neurologic recovery after SCA
ii. Optimal targets, timing, duration, and other variables still unclear:
(a) Goal target body temperature 32°C–34°C (N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63), though targeting 36°C instead of 33°C may be equivocal (N Engl J Med 2013;369:2197-206)

(b) Duration of at least 12 hours; optimally, a minimum of 24 hours
(c) Initiation of therapeutic hypothermia as soon as possible, within 2 hours, if possible, with goal temperature attainment within 6–8 hours; however, several retrospective studies have
not confirmed the timing of initiation or the timing of temperature attainment as predictors
of neurologic outcome (Acta Anaesthesiol Scand 2009;53:962-34; Int J Cardiol 2009;133:223-8)
(d) Modality for cooling includes feedback-controlled endovascular systems, surface-cooling devices, ice packs/bags, cooling blankets, and/or iced isotonic fluids.
(e) Axillary or oral temperature monitoring is inadequate for therapeutic hypothermia (Acta Anaesthesiol Scand 1998;42:1222-6; J Cardiothorac Vasc Anesth 1996;10:336-41) and requires esophageal, bladder (avoid in anuric patients), or pulmonary artery temperature monitoring. Ideally, the monitoring modality chosen will be used for other indications as well.

iii. Major complications of therapeutic hypothermia (Table 3)

Table 3. Major Organ-Specific Complications of Therapeutic Hypothermia

Musculoskeletal (N Engl J Med 2013;369:2197-206; Anesthesiology 2009;111:110-5; Br J Anaesth 2005;94:756-62; N Engl J Med 2002;346:549-56; N Engl J Med 2002;346:557-63; JAMA 1997;277:1127-34; Am J Physiol 1960;198:481-6)	**Shivering:** A. Body's natural response to hypothermia, preceded by arteriovenous vasoconstriction. Can increase metabolic heat production by 600%, thereby slowing the induction of hypothermia 1. Typically slows or stops at core temperatures < 34°C 2. Continuous or as-needed paralytics can be used for prevention and treatment of shivering (see the chapter on management of paralytics for appropriate selection and dosing of agent[s]) i. Hypothermia decreases clearance and prolongs the duration of neuromuscular-blockade (see Table 4 for examples) ii. Train-of-four is not a reliable method of monitoring during hypothermia; clinical monitoring or continuous EEG (electroencephalography) may be warranted 3. Agents that decrease the shivering threshold: i. Scheduled acetaminophen 650 mg q4–6 hr or buspirone 30 mg q12 hr as alternatives to paralysis may reduce the shivering threshold ii. Magnesium sulfate also reduces the shivering threshold, and administration during the induction phase of hypothermia can be considered iii. Meperidine decreases the shivering threshold but should be avoided because of decreased effective glomerular filtration rate (GFR) during hypothermia and subsequent increased risk of seizures when meperidine is used in patients with decreased GFR iv. Dexmedetomidine and clonidine also decrease the shivering threshold, but extreme caution should be used because of the hypotensive and bradycardic effects of both agents

Table 3. Major Organ-Specific Complications of Therapeutic Hypothermia *(continued)*

Neurologic (Circulation 2010;122:S729-767; Circulation 2008;118:2452-83; Pharmacotherapy 2008;28:102-11)]	**Sedation and Analgesia:** A. Adequate pain control and sedation must be employed B. Target Richmond Agitation and Sedation Scale score of -3 to -5 (see chapter on sedation for agent selection and dosing) during hypothermia C. Accumulation of parent and active metabolites can be expected for each analgesic and sedative, which lead to prolonged sedation and potentially untoward adverse effects (see Table 4 for examples) **Seizures:** A. Possible complications of cardiac arrest and therapeutic hypothermia B. Consider benzodiazepines as first line to break seizures C. Phenytoin, barbiturates, valproic acid, and propofol can all be used, with vigilant monitoring of adverse effects because of decreased clearance (see Table 4 for examples; for dosing and monitoring values, see the Status Epilepticus chapter)
Cardiac (Heart Lung 2001;30:161-3; Int Anesthesiol Clin 1964;2:803-27)	**Arrhythmias:** A. Include VT, VF, and atrial fibrillation B. If life threatening, should consider discontinuing therapeutic hypothermia and active rewarming C. Sinus bradycardia is common and, in isolation, should not be treated unless it leads to hemodynamic instability (hypotension or organ dysfunction) **Electrocardiography observations:** A. Prolonged PR, QRS, and QT intervals B. Caution should be exercised when using medications that prolong the QT interval **Hemodynamics:** A. Decreased cardiac output
Hepatobiliary (Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;23:192-7; Anesthesiology 2000;92:84-93; Clin Pharmacol Ther 1979;25:1-7)	A. Elevated transaminases B. Reduced activity of non-cytochrome and cytochrome P450–mediated metabolism C. See Table 4 for examples of metabolic changes in selected medications during hypothermia
Endocrinologic (N Engl J Med 2002;346:557-63; Endocrinology 1970;87:750-5)	A. Hyperglycemia caused by a decreased insulin production and effect in periphery, increased gluconeogenesis, and glycogenolysis B. Continuous insulin infusions may be necessary for glucose control. Goal should be < 180 mg/dL without inducing hypoglycemia
Renal (Resuscitation 2004;60:253-61; J Neurosurg 2001;94:697-705)	A. Decreased effective glomerular filtration (urine output may increase because of cold diuresis, but not effective) B. Electrolyte loss (K^+, PO_4^{3-}, Na^+, Ca^{2+}) during cooling phase; caution when replacing during rewarming phase
Hematologic (Pharmacotherapy 2008;28:102-11; Bri J Haematol 1999;104:64-8; Crit Care med 1992;20:1402-5)	A. Coagulopathy caused by thrombocytopenia, impaired activation and activity of clotting factors, impaired platelet function B. Actively bleeding patients should not be cooled

hr = hour(s).

Table 4. Pharmacokinetic and Pharmacodynamic Changes of Selected Medications During Hypothermia

Fentanyl	Plasma concentration increases by 25% with a 3.7-fold decrease in clearance
Morphine	Receptor affinity (μ) decreased as temperature decreases
Propofol	Plasma concentration increases by 28%; decreased clearance
Midazolam	Clearance decreases by about 11% per degree Celsius below 36.5°C
Rocuronium	Decreased clearance by 50%, increased duration of action 2-fold
Vecuronium	Decreased clearance by 11% per degree Celsius; increased duration of action 2-fold
Cisatracurium	Eliminated by Hofmann elimination, which is a temperature-dependent enzymatic process; anticipate prolonged activity
Phenytoin	AUC (area under the concentration-time curve) increased by 180%; clearance and elimination rate constant decrease by 50%

nformation from: Pharmacotherapy 2008;28:102-11; Ther Drug Monit 2001;233: 192-7; Anesthesiology 2000;92:84-93; Br J Haematol 1999;104:68-8; Eur J Anaesthesiol Suppl 1995;1:95-106; Cllin Pharmacol Ther 1979;25:1-7).

iv. Rewarming should be a passive process over 8 hours (around .33°C–0.5°C per hour) (Acta Anaesthesiol Scand 2009;53:926-34; N Engl J Med 2002;346:557-63; N Engl J Med 2002;346:549-56).

b. Identify and treat acute coronary syndromes.
   i. Cardiovascular disease and acute coronary ischemia are the most common causes of cardiac arrest (Am Heart J 2009;157:312-8; N Engl J Med 1997;336:1629-33).
   ii. Consideration of treatment of acute coronary syndromes should not be deferred in patients who are comatose or when therapeutic hypothermia is used.
   iii. See the Cardiology chapter for the workup and treatment of acute coronary syndromes.

c. Optimize mechanical ventilation.
   i. Goal arterial oxygen saturation is 94% or greater.
   ii. Avoid hyperventilation or over-bagging to avoid increase in intrathoracic pressure and decrease in cardiac output.
   iii. Goal $Paco_2$ is 40–45 mm Hg or $PETCO_2$ 35–40 mm Hg.

d. Support organ systems
   i. Vasopressor/inotropes to support end-organ perfusion (see Table 5)
      (a) Adrenergic medications should not be administered with alkaline solutions or sodium bicarbonate because they are inactivated (Hosp Pharm 1969;4:14-22).
      (b) Central line is recommended because any agent with α-agonist properties can lead to extravasation and tissue necrosis.

Table 5. Common Vasoactive Agents Used After Cardiac Arrest[a]

Medication	Typical Dosing Range (mcg/kg/minute)	Clinical Pearls
Epinephrine	0.03–0.3	• Mixed α and β activity • Used to treat severe hypotension (e.g., SBP < 70 mm Hg) • Used for symptomatic bradycardia • Used for hemodynamically unstable anaphylactic reactions
Norepinephrine	0.03–0.3	• α- > β-receptor activity • Used to treat severe hypotension (e.g., SBP < 70 mm Hg) • Should be used in volume-resuscitated patients • Currently first line for septic shock

Table 5. Common Vasoactive Agents Used After Cardiac Arrest[a] *(continued)*

Medication	Typical Dosing Range (mcg/kg/minute)	Clinical Pearls
Phenylephrine	0.3–3	• Pure α agonist • Used to treat severe hypotension (e.g., SBP < 70 mm Hg) • Should be used in volume-resuscitated patients
Dopamine	2–20	• Dose-related receptor activity: 2–5 mcg/kg/minute dopamine receptor, 5–10 mcg/kg/minute β_1-receptor, > 10 α_1-receptor • Does not provide exclusive receptor activity across dosing ranges • Use cautiously in patients with a history of heart disease or arrhythmias • Useful for patients with bradycardia and hypotension
Dobutamine	2–20	• Predominance of inotropic properties but with activity on β_1-, β_2-, and α_1-receptor • Used to treat low cardiac output • α_1-agonist and β_2-agonist counterbalance, leading to little change in systemic vascular resistance • Can lead to vasodilation at higher doses or in select patients • Less systemic or pulmonary vasodilation than milrinone • More tachycardia than milrinone • Use cautiously in patients with a history of heart disease or arrhythmias
Milrinone	0.25–0.5	• Phosphodiesterase type 3 inhibitor • Used to treat low cardiac output • Longer onset of activity, which may warrant loading dose. Caution should be used with loading dose because of significant systemic hypotension • Longer duration of activity than dobutamine • Accumulates in renal dysfunction • More systemic and pulmonary vasodilation than dobutamine • Less tachycardia than dobutamine

[a]See chapter on shock for a detailed discussion regarding selection of agent, dosing, pharmacology, and clinical considerations.

ii. Glucose management (Circulation 2010;122:S768-786; Circulation 2008;118:2452-83)
   (a) Avoidance of severe hypoglycemia (40 mg/dL or less)
   (b) Target moderate glucose control: 144–180 mg/dL
   (c) May require continuous insulin infusion to maintain above goals
   (d) Seizure control/prevention (Neurology 1988;38:401-5; JAMA 1985;253:1420-6): Seizures, myoclonus, or both occur in 5%–15% of adult patients who achieve ROSC and is more frequent in those who remain comatose.
   (e) Seizures, myoclonus, or both occur in 5%–15% of adult patients who achieve ROSC and is more frequent in those who remain comatose.
      (1) Clonazepam, valproic acid, and levetiracetam are all effective for myoclonus, but clonazepam should be considered first line.
      (2) Benzodiazepines, phenytoin, valproic acid, propofol, and barbiturates are all effective for post–cardiac arrest seizures.
      (3) For dosing and monitoring parameters, see the Status Epilepticus chapter.

iii. Renal dysfunction: The indications for initiating renal replacement therapy in cardiac arrest survivors are the same as in critically ill patients in general (Lancet 2005;365:417-30).

e. Assess prognosis.
   i. Brain injury and cardiovascular instability are the major determinants of survival after cardiac arrest (Intensive Care Med 2004;30:2126-8).
   ii. If therapeutic hypothermia is considered, a delay of 72 hours after rewarming should be implemented for withdrawal of care.
   iii. If therapeutic hypothermia is not considered, several different variables have predicted outcomes at 24 hours and for up to 72 hours. No clinical neurologic signs have reliably predicted poor neurologic outcomes less than 24 hours after cardiac arrest (Neurology 2006;66:62-8; Crit Care Med 1987;15:820-5).
   iv. Prudent to perform any prognostication after removal of opioids, sedatives, paralytics, and so forth
f. Assist survivors with rehabilitation needs.

Patient Case

7. K.G., a 71-year-old woman with a history of atrial fibrillation, coronary artery disease after three-vessel coronary bypass artery grafting 6 years ago, diabetes, and osteoarthritis, is being admitted to your MICU for therapeutic hypothermia after PEA arrest and subsequent ROSC. K.G., who remained comatose after the ROSC, was intubated; she is hemodynamically stable (BP 94/72 mm Hg and HR 86 beats/minute). Which is most accurate regarding targeted temperature management (therapeutic hypothermia) for K.G.?
   A. K.G. may experience hypoglycemia because this is a common complication and may require continuous dextrose 10% in water or dextrose 20% in water infusions.
   B. Dose modifications or medication avoidance for cytochrome P450–metabolized medications should occur for K.G. during therapeutic hypothermia, given reduced enzymatic activity.
   C. The optimal duration of K.G.'s therapeutic hypothermia should be at least 72 hours to affect survival.
   D. Temperature targets should be 28°C–30°C to improve the neurologic recovery.

II. HYPERTENSIVE CRISIS

A. Definitions (Cardiol Clin 2012;30:533-43; Chest 2007;131:1949-62; Cardiol Clin 2006;24:135-46):
   1. Hypertensive urgency: A systolic blood pressure (SBP) of 180 mm Hg or greater and/or a diastolic blood pressure (DBP) of 110 mm Hg or greater without evidence of target organ damage
   2. Hypertensive emergency: Presence of an abrupt significantly elevated BP (often defined as SBP greater than 200 mm Hg and/or DBP greater than 120 mm Hg) with concurrent target organ dysfunction (e.g., acute kidney injury/failure, heart failure exacerbation, obtundation). Table 6 lists example conditions that, when accompanied by high BP, define hypertensive emergency.
   3. MAP: Average pressure in the arteries experienced over one cardiac cycle. Calculated by MAP = 1/3 SBP + 2/3 DBP

Table 6. Examples of Acute Target Organ Damage and Clinical Presentations

Eclampsia, preeclampsia	Hypertensive encephalopathy
Acute kidney injury/failure	Acute shortness of breath, flash pulmonary edema, or acute left ventricular dysfunction
Acute aortic dissection (type A or B)	Acute intracranial bleeding (nontraumatic)
Seizures	Acute myocardial ischemia/infarction
Retinopathy	Cerebral infarction

B. Less than 1% of patients with hypertension will experience a hypertensive crisis (Acta Med Scand Suppl 1981;650:1-62).

C. 10-year survival approaches 70% (Int J Med 1993;96:485-93), with 1-year survival greater than 90%.

D. Common Causes (Cardiol Clin 2012;30:533-43; Cardiol Clin 2006;24:135-46):
   1. Intoxications – Cocaine, amphetamines, phencyclidine hydrochloride, stimulant diet pills
   2. Nonadherence to antihypertensive regimen
   3. Withdrawal syndromes – Clonidine or β-antagonists
   4. Drug-drug/drug-food interactions (e.g., monoamine oxidase inhibitors and tricyclic antidepressants, antihistamines, or tyramine)
   5. Spinal cord disorders
   6. Pheochromocytoma
   7. Pregnancy

E. Management:
   1. Hypertensive urgency: Lower BP slowly over 24–48 hours using oral medications (often, home regimen reinitiation). Does not require an ICU admission for treatment
   2. Hypertensive emergency: Requires ICU monitoring and intravenous medications. See goals listed in Table 7.

Table 7. Timeframe for BP Lowering with Hypertensive Emergency[a]

Goal time	BP target
< 60 min	↓ DBP by 10%–15% or MAP by 25% with goal DBP ≥ 100 mm Hg
2–6 hr	SBP 160 mm Hg and/or DBP 100–110 mm Hg
6–24 hr	Keep above BP goals (hours 2–6) during first 24 hours
24–48 hr	Outpatient BP targets

[a]See exceptions to these goals in the text that follows.

   a. A 25% reduction in MAP over the first hour is targeted in order to maintain cerebral perfusion (blood flow autoregulation) and not to precipitate ischemia, which has been found with 50% reductions (Stroke 1984;15:413-6).
   b. If neurologic function deterioriates during the initial 25% decrease (or during subsequent lowering), therapy should be discontinued (N Engl J Med 1990;323:1177-83).
   c. Exceptions exist regarding the timing and BP goals listed earlier:
      i. Acute aortic dissection
         (a) Propogation of acute aortic dissection is dependent on arterial BP and shear stress (force of left ventricular contraction as a function of time).
         (b) HR and contractility control can minimize shear stress and, together with BP, become a target of management.
         (c) Goal HR less than 60 beats/minute and SBP less than 100 mm Hg as soon as possible (within 5–10 minutes)
      ii. Acute ischemic stroke
         (a) Hypertension with ischemic stroke is an adaptive response to maintain cerebral perfusion pressure to the brain.
         (b) Cerebral perfusion pressure equals mean arterial pressure minus intracraial pressure: CPP = MAP – ICP.

(c) Treatment should occur only if thrombolytic therapy is required (goal SBP less than 185 mm Hg and DBP less than 100 mm Hg to decrease risk of bleeding), other target organ damage occurs, or SBP is greater than 220 mm Hg and/or DBP is greater than 120 mm Hg.

(d) Goal 15%–20% MAP reduction over 24 hours (Cardiol Clin 2012;30:533-43)

iii. Intracranial hemorrhage

(a) BP reduction goals will be based on individual factors, including medical history; ICP, if known; demographics such as age; presumed cause of hemorrhage (e.g., arteriovenous malformation); and interval since onset.

(b) Theoretical risk of worsening bleeding with uncontrolled BP must be balanced with risk of decreased cerebral perfusion pressure with overly aggressive treatment.

(c) Patients can tolerate a BP reduction in SBP of 180 mm Hg or less and/or a MAP less than 130 mm Hg over 24 hours (Crit Care Med 2006;34:1975-80).

(d) Retrospective data showed an increased rate of death with a more rapid BP reduction in the acute hospital setting (Crit Care Med 1999;27:480-5).

3. Agents for BP management of hypertensive emergency

a. The drug of choice for hypertensive emergency is intravenous nitroprusside.

i. Intravenous nitroprusside works rapidly and is safe in the presence of renal and/or hepatic impairment for short-term use (24 hours or less).

ii. Continuous BP monitoring (e.g., arterial line) is recommended with use because rapid changes can occur.

iii. Nitroprusside can increase ICP and may result in coronary steal; caution or avoidance should be considered in patients with elevated ICP and acute mycocardial ischemia/infarction.

b. Table 8 summarizes available agents, dosing, onset, duration, and hemodynamic considerations. Table 9 summarizes possible indications and special considerations.

Table 8. Medications Used in Hypertensive Emergencies

Medication	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
Nitroprusside	IV 0.25–10 mcg/kg/min Titrate by 0.1–0.2 mcg/kg/min q5 min	Seconds	1–2 min	↓	↓↓	↑
Hydralazine	IV bolus: 10–20 mg IM: 10–40 mg q30 min prn	IV: 10 min IM: 20 min	IV: 1–4 hr IM: 2–6 hr	↔	↓	↑
Nicardipine	IV 5–15 mg/hr Titrate by 2.5 mg/hr q5–10 min	5–10 min	2–6 hr	↔	↓	↑
Clevidipine	IV 1–6 mg/hr Titrate by 1–2 mg/hr q90s. Max 32 mg/hr	1–4 min	5–15 min	↔	↓	↑
Nitroglycerin	IV 5–200 mcg/min Titrate by 5–25 mcg/min q5–10 min	2–5 min	5–10 min	↓↓	↓↔	↔↑

Table 8. Medications Used in Hypertensive Emergencies *(continued)*

Medication	Usual Dosing Range	Onset	Duration	Preload	Afterload	Cardiac Output
Esmolol	IV 25–300 mcg/kg/min (bolus of 0.5 mg/kg, not often required given short onset) Titrate by 25 mcg/kg/min q3–5 min	1–2 min	10–20 min	↔	↔	↓
Metoprolol	IV bolus: 5–15 mg q5–15 min prn	5–20 min	2–6 hr	↔	↔	↓
Labetolol	IV bolus: 20 mg, may repeat escalating doses of 20–80 mg q5–10 min prn IV 1–2 mg/min Titrate by 1–2 mg/min q2 hr given longer half-life	2–5 min, peak 5–15 min	2–6 hr	↔	↓	↓
Enalaprilat	IV bolus: 1.25 mg q6 hr Titrate no more than q12–24 hr; max dose 5 mg q6 hr	15–30 min	12–24 hr	↓	↓	↑
Phentolamine	IV bolus: 1–5 mg prn; max 15 mg	Seconds	15 min	↔	↓	↑
Fenoldopam	IV 0.03–1.6 mcg/kg/min Titrate by 0.05–1 mcg/kg/min q15 min	10–15 min	10–15 min	↔ ↓	↓	↑

IM = intramuscular; IV = intravenous.

Table 9. Indications and Special Considerations for Medications Used for Hypertensive Emergencies

Medication	Indication	Special Consideration
Nitroprusside	Most indications (excluding conditions with ICP elevation and coronary infarction/ischemia caused by coronary steal)	• Liver failure – cyanide accumulation • Renal failure – thiocyanate accumulation • Can draw serum cyanide and thiocynate concentrations to monitor • Toxicity associated with prolonged infusions (> 72 hr) or high doses (> 3 mcg/kg/min) • May result in coronary steal • Increases ICP
Hydralazine	Pregnancy	• Can result in prolonged hypotension (less predictable dose response) • Risk of reflex tachycardia • Headaches, lupus-like syndrome (with long-term use)
Nicardipine	Acute ischemic or hemorrhagic stroke	• Risk of reflex tachycardia • Infusion can lead to large fluid volumes administered

Table 9. Indications and Special Considerations for Medications Used for Hypertensive Emergencies *(continued)*

Medication	Indication	Special Consideration
Clevidipine	Acute ischemic or hemorrhagic stroke	• Formulated in oil-in-water formulation providing 2 kcal/mL of lipid calories • Caution for patients allergic to soy or eggs
Nitroglycerin	Coronary ishemia/ infarction Acute left ventricular failure Pulmonary edema	• Tachyphylaxis occurs rapidly, requiring dose titrations • Adverse effects: Flushing, headache, erythema; often dose-limiting adverse effects • Veno > arterial vasodilator
Esmolol	Aortic dissection Coronary ischemia/ infarction	• Contraindicated in acute decompensated heart failure • Should be used in conjunction with an arterial vasodilator for BP management in aortic dissection (initiate esmolol first because of the delayed onset relative to vasodilators such as nitroprusside) • Metabolism is organ-independent (hydrolyzed by esterases in blood) • Useful in tachyarrhythmias
Metoprolol	Aortic dissection Coronary ischemia/ infarction	• Contraindicated in acute decompensated heart failure • Should be used in conjunction with an arterial vasolidator for BP management in aortic dissection (initiate metoprolol first because of the delayed onset relative to vasodilators such as nitroprusside) • Useful in tachyarrhythmias
Labetalol	Acute ishemic or hemorrhagic stroke Aortic dissection Coronary ischemia/ infarction Pregnancy	• May be used as monotherapy in acute aortic dissection • Contraindicated in acute decompensated heart failure • Prolonged hypotension may be experienced with over-treatment; dose cautiously
Enalaprilat	Acute left ventricular failure	• Contraindicated in pregnancy • Caution in dose adjustments given prolonged duration of action
Phentolamine	Catecholamine excess (e.g., pheochromocytoma)	• Use in cathecholamine-induced hypertensive emergency
Fenoldopam	Most indications	• Risk of reflex tachycardia • Caution with glaucoma • Can cause hypokalemia, flushing • May increase ICP

ICH = intracranial hemorrhage; ICP = intracranial pressure.

c. Certain populations require specific medication therapy approaches:
   i. Pregnancy
      (a) Severe preeclampsia can only be managed by delivery of the baby.
      (b) Magnesium can be considered as an adjunctive therapy to decrease seizure risk or if seizures develop.
      (c) Intravenous medications should only be considered for persistently elevated BPs (SBP greater than 160 mm Hg and/or DBP greater than 110 mm Hg).

(d) Hydralazine and labetalol are feasible first-line options, and labetalol may have fewer adverse effects (Am J Health Syst Pharm 2009;66:337-44).

ii. Catecholamine-induced hypertensive emergency

(a) Phentolamine is the drug of choice because it competively inhibits α-adrenergic receptors.

(b) β-Antagonists are contraindicated unless the patient is fully α-blocked.

(c) Cocaine-induced hypertensive emergency (Ann Emerg Med 2008;52:S18-20; Chest 2007;131:1949-62)

(1) Benzodiazepines are used to target the central effects of cocaine as first-line therapy and often will result in control of tachycardia and hypertension. Diazepam 5–10 mg intravenously or lorazepam 2–4 mg intravenously titrated to effect

(2) If central control of cocaine-induced hypertension fails, consider direct α-antagonism with phentolamine. Phentolamine 1 mg intravenously; repeat every 5 minutes as needed

(3) If direct α-antagonism does not gain control, consider additional antihypertensives:

(A) Nitroglycerin, nicardipine, nitroprusside, or fenoldopam titrated to effect are viable options (see Table 7 for dosing and consideration).

(B) Verapamil and diltiazem decrease coronary vasospasm associated with acute cocaine intoxiciation (Am J Cardiol 1994;73:510-3).

(C) Controvery exists regarding the use of β-blockers.

- Labetaolol has shown conflicting results regarding ability to control MAP but not alleviate cocaine-induced coronary vasoconstriction.
- Consensus opinion recommends β-blockers only if full α-antagonism is employed first.

d. All intravenous medications should be transitioned to oral medications as soon as possible.

i. Oral antihypertensives should be initiated within 24 hours.

ii. Medication history and reconciliation can assist in resuming home regimens.

iii. Additional or new agents should be selected according to disease-specific indications.

Patient Case

8. B.B. is a 44-year-man with no medical history who presents to the ED with a ripping sensation in his chest. His social history includes cigarette smoking, 1.5 packs/day for the past 20 years. Chest radiography in the ED reveals mediastinal widening. Cardiac enzymes are within normal limits. Laboratory values include sodium (Na^+) 135 mEq/L, potassium (K+) 4.3 mEq/L, bicarbonate (HCO3-) 24 mEq/L, SCr 0.55 mg/dL, glucose 110 mg/dL, DBil 0.2 mg/dL, and AST 39 U/L. B.B. is rushed for a chest CT and angiography, which reveal an acute type A and B aortic dissection. His vital signs include BP 208/140 mm Hg and HR 120 beats/minute. Which is most appropriate regarding B.B.'s BP management?

A. B.B.'s BP reduction goal is a 25% reduction in MAP over the first 60 minutes, which can be accomplished with esmolol as first line.

B. B.B.'s BP reduction goal is a reduction to 160/100 mm Hg over the first 24 hours, which can be accomplished with initation of hydrochlorothiazide and lisinopril.

C. B.B.'s goals include BP and HR, which would be a 25% reduction in MAP and HR less than 60 beats/minute in the first 60 minutes, and can be accomplished with labetalol as first line.

D. B.B.'s goals include BP and HR, which would be an SBP less than 100 mm Hg and an HR less than 60 beats/minute as soon as possible with esmolol with or without nitroprusside as first line.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Because rescuer fatigue is common and may lead to inadequate compression quality, it is recommended to change rescuers every 2 minutes, with no more than 5 seconds between changes. Compressions are vital because they increase intrathoracic pressure and directly compress the heart, leading to oxygen delivery to the vital organs. Specific aspects of chest compression quality are necessary. These include a rate of at least 100 compressions/minute at a depth of 2 inches in adults, allowing for recoil after each compression; placement of the patient on a hard surface (e.g., backboard); and minimization of interruptions. Outcomes, including neurologically intact survival, ROSC, and possibly overall survival, are linked to minimizing interruptions in chest compressions. Because of this, it is recommended that interruptions (e.g., pulse checks and intubation) be less than 10 seconds and that chest compressions be resumed immediately.

2. Answer: C

Cardiac arrest patients have minimal blood flow, and oxygenation/ventilation requirements are lower; the current compression/ventilation ratio recommended is 30:2. Although the optimal ratio is unclear and chest compressions appear to be more vital to resuscitation, other ratios cannot currently be recommended. It is clear, however, that excessive ventilation can lead to decreased venous return and gastric inflation, which can lead to aspiration, regurgitation, and impacts on outcomes. In this case, a bag-mask ventilator is available, and multiple rescuers are involved, so the bag-mask ventilator should be used. In single-rescuer situations, the bag-mask ventilator should never be used, and mouth-to-mouth or mouth-to-barrier resuscitation is recommended. Advanced airways can be considered but should be placed only by experienced and trained personnel. Bag-mask ventilation can provide adequate oxygenation/ventilation until an airway can be secured.

3. Answer: A

Three vital actions with VF aid in survival: call emergency response team (already accomplished in case), begin CPR (needs to be initiated in case), and deliver shock (needs to occur in case). Pacing can be effective in overriding stable VT but should not be used in the cardiac arrest or hemodynamically unstable patient. It is currently unclear whether postponing defibrillation for the provision of chest compressions first is of benefit, but it is clear that chest compressions should be initiated until the defibrillator is ready, charged, and set to deliver the shock because this increases the likelihood of success with defibrillation. Because time in VF predicts survival and the longer patients are in VF, the more difficult it is to terminate the arrhythmia, alternative treatments such as medications should not impede the provision of defibrillation.

4. Answer: D

After the advanced airway is in place, it is crucial to confirm placement in order to provide the intended oxygenation/ventilation. The confirmation should occur with both clinical and objective measurements. These include a physical assessment of the chest and epigastrium, end-tidal CO_2 monitoring, and/or continuous waveform capnography. In most cardiac arrests (particularly in this patient's pulseless VT), airway management should not impede the provision of CPR and/or defibrillation (when defibrillation is indicated). After the advanced airway is in place, 100% oxygen should be delivered to optimize the arterial oxygen saturation. In the cardiac arrest population, this has not been shown to carry the same toxicity as in other populations. Furthermore, after advanced airway is placed, compressions should be administered at a rate of at least 100 compressions/minute continuously, with breaths given 6–8 times per minute.

5. Answer: B

In all cardiac arrests, the treatable causes (i.e., H's and T's) should be reviewed and addressed, if possible. In patients for whom the laboratory and diagnostic data are known, the information should be reviewed while CPR is being provided. In patients for whom the information is unknown, clinical evaluation and attainment of information should occur, when possible. This retrieval of information, together with the administration of medications and advanced airway placement, should never impede on the provision of CPR or defibrillation, if indicated, because defibrillation (for VF and pulseless VT) and CPR are the only strategies that have been shown to affect survival from cardiac arrest. Pulseless electrical

activity and asystole are not wide complex rhythms, and defibrillation would not be indicated if either were detected. Post–cardiac arrest care is crucial in the prevention of re-arrest and, in therapeutic hypothermia, can significantly affect neurologic outcomes.

6. Answer: D

In general, it is important to remember that medication administration benefits only myocardial blood flow and ROSC in cardiac arrest. Medication administration should never impede the provision of CPR and/or defibrillation. Central administration is preferred for several reasons. These include higher peak concentrations, shorter circulation time, more standard dosing, and the lack of additional administration techniques needed. Endotracheal administration is an option, but only NAVEL (naloxone, atropine, vasopressin, epinephrine, and lidocaine) medications can be administered, the optimal doses are unknown, and medications must be diluted before administered. Given that this patient is in VF arrest, amiodarone, for example, could not be administered by endotracheal administration if it were indicated. Peripheral administration can be used, but it requires an additional bolus of fluid afterward and has a longer circulating time than does central administration. Intraosseous can also be used, with the caveat that intraosseous administration is similar to peripheral administration.

7. Answer: B

Targeted temperature management (therapeutic hypothermia) improves neurologic recovery when initiated, optimally within 2 hours but in up to 6–8 hours for VF cardiac arrest (application to all forms), and employed for 12–24 hours. The goal temperature is 32°C–34°C. Newer data suggest there is no benefit of 33°C versus 36°C in improvement of survival or neurologic outcomes. If targeted temperature management will be used, close monitoring of complications should occur. These complications include hyperglycemia caused by decreased insulin production and peripheral activity, bradycardias, enzymatic slowing (including cytochrome P450 system), increased incidence of sepsis and infections, coagulopathies, decreased glomerular filtration, and shivering.

8. Answer: D

This patient is experiencing a hypertensive emergency with his target organ damage being an acute aortic dissection. Aortic dissection is one of the unique hypertensive emergencies that has a unique mechanism of worsening (propogation) from BP and shear stress, which require both rapid BP and HR control. Given the gravity of propogation, goals for aortic dissection are HR less than 60 beats/minute and SBP less than 100 mm Hg within minutes, if possible. This can be accomplished with either a single agent like labetalol, which will control HR with its β-antagonist properties and decrease BP (afterload) with its α-antagonist properties. Esmolol can also be used as first line but will likely require an additional afterload-reducing agent such as nitroprusside.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The largest portion of adult cardiac arrests are caused by cardiovascular, not respiratory, events. In addition, this patient was on room air and nasal cannula immediately before the event, which could suggest his respiratory status was stable and unlikely to lead to cardiac arrest. Advanced airways and medications have only been shown to facilitate ROSC in cardiac arrest in contrast to chest compressions and defibrillation (if indicated), which can improve survival. Because of this, CPR should begin immediately for this patient, starting with chest compressions in accordance with the BLS guidelines with pads placed simultaneously to facilitate rapid defibrillation if the patient's rhythm reveals a shockable rhythm.

2. Answer: A

The cornerstone of therapy for VF cardiac arrest is rapid defibrillation. The recommended dosage of voltage for biphasic defibrillators is 200 J or the manufacturer's recommendation (often the same dosage). Although amiodarone is in the treatment algorithm for VF cardiac arrest, it is reserved and recommended for refractory VF cardiac arrest, which is defined as defibrillation refractory. Therefore, defibrillation should occur first. Atropine has been removed from the cardiac arrest algorithms for PEA and asystole because of a lack of benefit on outcomes and should be not be considered for VF cardiac arrest. Pacing has not shown benefit in the cardiac arrest situation and should not be used.

3. Answer: B

Because the rhythm detected is PEA and no longer VF, the cornerstone of therapy changes from giving defibrillation to giving high-quality chest compressions and addressing the treatable causes of cardiac arrest (H's and T's). Lidocaine is reserved for refractory VF/pulseless VT (defined as defibrillator refractory) when amiodarone is unavailable. Atropine was previously recommended for PEA/asystole, but in the 2010 ACLS guidelines, it was removed because of a lack of data supporting any beneficial outcomes. Therefore, the correct answer for this patient would be targeting high-quality chest compressions and reversing any treatable causes.

4. Answer: C

Targeted temperature management is a consideration according to the international guidelines for all patients with ROSC who remain comatose after a cardiac arrest. Although most well-designed and executed studies primary enrolled patients with VF cardiac arrest, application is recommended for all patients with a cardiac arrest independent of rhythm. Although worsening trasaminitis and hepatic enzymatic function slowing is likely to occur during hypothermia, neither of these principles would be considered a contraindication for hypothermia. Furthermore, renal function in terms of glomerular filtration worsens which requires viginlant monitoring of renal function and close attention paid to renal dose modifications and serum concentration monitoring of medications when applicable. An additional complication of therapeutic hypothermia is an induced coagulopathy which leads patients to be at risk of bleeding. Thrombolytics may carry specific indications for cardiac arrest (e.g., pulmonary embolism or acute coronary syndromes), but they would not be recommended empirically.

5. Answer: B

Therapeutic hypothermia improves neurologic recovery in patients after a cardiac arrest. Most patients included in randomized clinical trials are patients who have VF as their causative rhythm. Because of its impact on neurologic recovery, guideline recommendations have applied this literature to cardiac arrests of all rhythms and many instutitions have adopted this same recommendation. Recent studies targeting mild hypothermia (36°C vs. 33°C) have shown no difference regarding outcomes between the two modalities, and because of this, some question of the utility of hyptohermia at all in an era of potentially more advanced cardiac arrest care.

6. Answer: D

By definition, this patient is having a hypertensive emergency because she has an abrupt, severe increase in BP with target organ damage—in this case, potentially shock liver and vision changes. Hypertensive urgency would be defined by a systolic blood pressure (SBP) greater than 180 mm Hg and/or a diastolic blood pressure (DBP) greater than 110 mm Hg without evidence of target organ damage. But given the patient's presentation, she would be classified as having a hypertensive emergency.

7. Answer: C

The patient should be initiated on nitroprusside for BP management. Although she has transaminitis, nitroprusside can be used safely in the first 24 hours in these patients. Phentolamine would be reserved for hypertenisve crisis that presents from a catecholamine crisis. Oral metoprolol might be an appropriate option to transition to after the emergency is resolved, but because of the target organ damage, more rapid reduction is needed using an intravenous agent such as nitroprusside. Enalaprilat is an option, but 10 mg every 6 hours would not be an appropriate starting dose because it would put the patient at risk of overshooting and, given the long duration of activity, could lead to unwanted consequences.

8. Answer: A

The initial goal reduction for J.H.'s BP, given that he is experiencing a hypertensive emergency, is a 25% reduction in MAP within the first 60 minutes. More rapid BP reductions may result in a lack of cerebral perfusion; therefore, they are not recommended. J.H. is not experiencing any of the unique hypertensive emergencies (e.g., aortic dissection) that would call for a more rapid BP reduction. In addition, J.H. is not experiencing a hypertensive emergency that would require a slower BP reduction (e.g., stroke).

New evidence has emerged since the 2013 ESH/ESC Arterial Hypertension Guidelines and this has resulted in changes to some of the recommendations in the 2018 ESC/ESH Hypertension Guidelines which are highlighted in Table 3. In addition, the new guidelines contain a number of new sections, recommendations and concepts, as shown in Table 4.

Table 4 New sections, recommendations and concepts

New sections/recommendations

- When to suspect and how to screen for the causes of secondary hypertension
- Management of hypertension emergencies
- Updated recommendations on the management of BP in acute stroke
- Updated recommendations on the management of hypertension in women and pregnancy
- Hypertension in different ethnic groups
- The effects of altitude on BP
- Hypertension and chronic obstructive pulmonary disease
- Hypertension and AF and other arrhythmias
- Oral anticoagulant use in hypertension
- Hypertension and sexual dysfunction
- Hypertension and cancer therapies
- Perioperative management of hypertension
- Glucose-lowering drugs and BP
- Updated recommendations on CV risk assessment and management: (i) using the SCORE system to assess risk in patients without CVD; (ii) the importance of HMOD in modifying CV risk; and (iii) the use of statins and aspirin for CVD prevention

New concepts

New concepts

BP measurement

- **Wider use of out-of-office BP measurement with ABPM and/or HBPM, especially HBPM,** as an option to confirm the diagnosis of hypertension, detect white-coat and masked hypertension, and monitor BP control.

Less conservative treatment of BP in older and very old patients

- **Lower BP thresholds and treatment targets for older patients,** with emphasis on considerations of biological rather than chronological age (i.e. the importance of frailty, independence, and the tolerability of treatment).
- Recommendation that **treatment should never be denied or withdrawn on the basis of age,** provided that treatment is tolerated.

A SPC treatment strategy to improve BP control

- **Preferred use of two-drug combination** therapy for the initial treatment of most people with hypertension.
- **A single-pill treatment strategy for hypertension,** with the preferred use SPC therapy for most patients.
- **Simplified drug-treatment algorithms** with the preferred use of an ACE-inhibitor or ARB, combined with a CCB or/and a thiazide/thiazide-like diuretic, as the core treatment strategy for most patients, with beta-blockers used for specific indications.

New target ranges for BP in treated patients

- **Target BP ranges for treated patients** to better identify the recommended BP target and **lower safety boundaries for treated BP,** according to a patient's age and specific comorbidities.

Detecting poor adherence to drug therapy

- A strong emphasis on the **importance of evaluating treatment adherence** as a major cause of poor BP control.

A key role for nurses, pharmacists in the longer-term management of hypertension

- **The important role of nurses and pharmacists** in the education, support, and follow-up of treated hypertensive patients is emphasized as part of the overall strategy to improve BP control.

The relationship between BP and CV and renal events and mortality is continuous, making the distinction between normotension and hypertension somewhat arbitrary. In practice, threshold BP values are used for pragmatic reasons, to simplify the diagnosis and decisions about treatment. Hypertension is defined as the level of BP at which the benefits of, unequivocally outweigh the risks of treatment, as documented by clinical trials.

The classification of BP and definition of hypertension based on seated office BP measurement is unchanged from the previous guideline (**Table 5**). Hypertension is defined as office systolic BP (SBP) values ≥140 mmHg and/or diastolic BP (DBP) values ≥90 mmHg.

Table 5 Classification of Blood Pressure and definitions of hypertension grade[b]

Category[a]	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

[a]BP category is defined according to seated clinic BP and by the highest level of BP, whether systolic or diastolic.
[b]Isolated systolic hypertension is graded 1, 2, or 3 according to SBP values in the ranges indicated.
The same classification is used for all ages from 16 years.

Classification of blood pressure		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that BP be classified as optimal, normal, high-normal, or grades 1–3 hypertension, according to office BP.	I	C

[a]Class of recommendation - [b]Level of evidence.

Hypertension often clusters with other CV risk factors such and dyslipidaemia and glucose intolerance, which have a multiplicative effect on CV risk. Quantification of total CV risk is important for the risk stratification of patients with hypertension, to determine whether additional treatments such as statins and anti-platelet therapies may be indicated to further reduce CV risk (see section here). Classification of CV risk according to the SCORE system is recommended (**Table 6**).

Hypertension and cardiovascular risk assessment

Recommendations	Class[a]	Level[b]
CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very high risk due to established CVD, renal disease, or diabetes, a markedly elevated single risk factor (e.g. cholesterol), or hypertensive LVH.	I	B

CVD = cardiovascular disease; LVH = left ventricular hypertrophy; SCORE = Systematic COronary Risk Evaluation. [a]Class of recommendation - [b]Level of evidence.

Table 6 Ten year cardiovascular risk categories (Systematic COronary Risk Evaluation system)

Very high-risk	People with any of the following: **Documented CVD, either clinical or unequivocal on imaging.** • **Clinical CVD** includes; acute myocardial infarction, acute coronary syndrome, coronary or other arterial revascularization, stroke, TIA, aortic aneurysm, and PAD. • **Unequivocal documented CVD on imaging** includes: significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound. It does not include increase in carotid intima-media thickness. • **Diabetes mellitus with target organ damage,** e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR <30 mL/min/1.73 m^2) • **A calculated 10-year SCORE of ≥10%**
High-risk	People with any of the following: • **Marked elevation of a single risk factor,** particularly cholesterol >8 mmol/L (>310 mg/dL) e.g. familial hypercholesterolaemia, grade 3 hypertension (BP ≥180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, that may be moderate risk)
	Hypertensive LVH
	Moderate CKD eGFR 30–59 mL/min/1.73 m^2)
	A calculated 10-year SCORE of 5–10%
Moderate-risk	People with: • **A calculated 10-year SCORE of ≥1% to <5%** • **Grade 2 hypertension** • **Many middle-aged people belong to this category**
Low-risk	People with: • **A calculated 10-year SCORE of <1%**

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; PAD = peripheral artery disease; SCORE = Systematic COronary Risk Estimation.

Patients with hypertension may also present with features of hypertension-mediated organ damage (HMOD) (see **Tables 13-16**) as well as diabetes mellitus or chronic kidney disease, which may shift the estimated risk according to SCORE to a higher category as illustrated in **Figure 1**.

Very high-risk	tion, stroke, TIA, aortic aneurysm, and PAD. • **Unequivocal documented CVD on imaging** includes: significant plaque (i.e. ≥50% stenosis) on angiography or ultrasound. It does not include increase in carotid intima-media thickness. • **Diabetes mellitus with target organ damage,** e.g. proteinuria or a with a major risk factor such as grade 3 hypertension or hypercholesterolaemia • **Severe CKD** (eGFR <30 mL/min/1.73 m^2) • **A calculated 10-year SCORE of ≥10%**
High-risk	People with any of the following: • **Marked elevation of a single risk factor,** particularly cholesterol >8 mmol/L (>310 mg/dL) e.g. familial hypercholesterolaemia, grade 3 hypertension (BP ≥180/110 mmHg) • **Most other people with diabetes mellitus** (except some young people with type 1 diabetes mellitus and without major risk factors, that may be moderate risk)
	Hypertensive LVH
	Moderate CKD eGFR 30–59 mL/min/1.73 m^2)
	A calculated 10-year SCORE of 5–10%
Moderate-risk	People with: • **A calculated 10-year SCORE of ≥1% to <5%** • **Grade 2 hypertension** • **Many middle-aged people belong to this category**
Low-risk	People with: • **A calculated 10-year SCORE of <1%**

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; LVH = left ventricular hypertrophy; TIA = transient ischaemic attack; PAD = peripheral artery disease; SCORE = Systematic COronary Risk Estimation.

Patients with hypertension may also present with features of hypertension-mediated organ damage (HMOD) (see **Tables 13-16**) as well as diabetes mellitus or chronic kidney disease, which may shift the estimated risk according to SCORE to a higher category as illustrated in **Figure 1**.

Figure 1 Classification of hypertension stages according to blood pressure levels, presence of cardiovascular risk factors, hypertension-mediated organ damage, or comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥180 or DBP ≥110
Stage 1 (uncomplicated)	No other risk factors	Low-risk	Low-risk	Moderate risk	High-risk
	1 or 2 risk factors	Low-risk	Moderate risk	Moderate to high-risk	High-risk
	≥3 risk factors	Low to Moderate risk	Moderate to high-risk	High-Risk	High-risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high-risk	High-risk	High-risk	High to very high-risk
Stage 3 (established disease)	Established CVD, CKD grade ≥4, or diabetes mellitus with organ damage	Very high-risk	Very high-risk	Very high-risk	Very high-risk

BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic Coronary Risk Evaluation.
[a]CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions.

BP may be measured in the doctor's office, at home or by ambulatory BP monitoring (ABPM). In all cases, it is important that BP is measured carefully using a validated device (**Table 7**).

Table 7 Office blood pressure measurement

Patients should be seated comfortably in a quiet environment for 5 min before beginning BP measurements.
Three BP measurements should be recorded, 1–2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings.
Additional measurements may have to be performed in patients with unstable BP values due to arrhythmias, such as in patents with AF, in whom manual auscultatory methods should be used as most automated devices have not been validated for BP measurement in patients with AF.[a]
Use a standard bladder cuff (12–13 cm wide and 35 cm long) for most patients, but have larger and smaller cuffs available for larger (arm circumference >32 cm) and thinner arms, respectively.
The cuff should be positioned at the level of the heart, with the back and arm supported to avoid muscle contraction and isometric exercise-dependant increases in BP.
When using auscultatory methods, use phase I and V (sudden reduction/disappearance) Korotkoff sounds to identify SBP and DBP, respectively.
Measure BP in both arms at the first visit to detect possible between-arm differences. Use the arm with the higher value as the reference.
Measure BP 1 minute and 3 min after standing from seated position in all patients at the first measurement to exclude orthostatic hypotension. Lying and standing BP measurements should also be considered in subsequent visits in older people, people with diabetes, and people with other conditions in which orthostatic hypotension may frequently occur.
Record heart rate and use pulse palpation to exclude arrhythmia.

AF = atrial fibrillation; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.

[a]Most automatic devices are not validated for BP measurement in patients with AF, and will record the highest individual systolic pressure wave form rather than an average of several cardiac cycles. This will lead to overestimation of BP.

Home BP is measured as the average of all BP readings performed with a semiautomatic, validated BP monitor, for at least 3 days and preferably fo 6–7 consecutive days before each clinic visit, with readings in the morning and the evening, taken in a quiet room, after 5 min of rest, with the patient seated with their back and arm supported. Two measurements should be taken at each measurement session, performed 1–2 min apart.

ABPM provides the average of BP readings over a defined period, usually 24 hrs. The device is typically programmed to record BP at 15–30 min intervals, and average BP values are usually provided for daytime, night-time, and 24 hrs. A minimum of 70% usable BP recordings are required for a valid ABPM measurement session. Home and ABPM values are on average lower than office BP values, and the corresponding diagnostic thresholds for hypertension are shown in **Table 8**.

Table 8 Definitions of hypertension according to office, ambulatory, and home blood pressure levels

Category	SBP (mmHg)		DBP (mmHg)
Office BP[a]	≥140	and/or	≥90
Ambulatory BP			
Daytime (or awake) mean	≥135	and/or	≥85
Night-time (or asleep) mean	≥120	and/or	≥70
24-h mean	≥130	and/or	≥80
Home BP mean	≥135	and/or	≥85

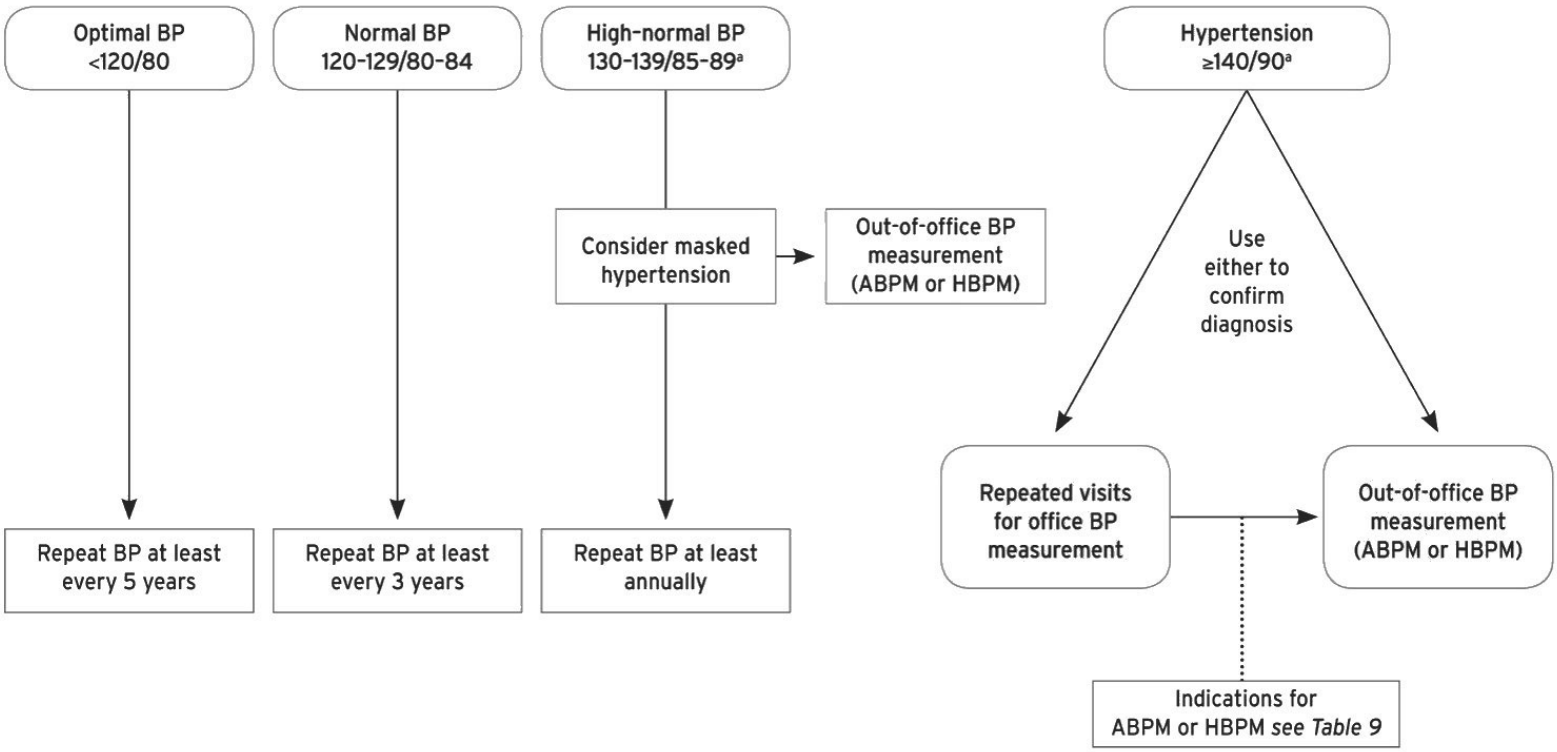
BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Refers to conventional office BP rather than unattended office BP.

Hypertension is predominantly an asymptomatic condition that is best detected by population screening programmes or opportunistic BP measurement (see **Figure 2**).All adults should have their BP recorded in their medical record and be aware of their BP, and further screening should be undertaken at regular intervals with the frequency dependent on the BP level.

For healthy people with an optimal office BP (<120/80 mmHg), BP should be re-measured at least every 5 years and more frequently when opportunities arise. In patients with a normal BP (120–129/80–84), BP should be re-measured at least every 3 years.

Patients with high-normal BP (130–139/85–89 mmHg) should have their BP recorded annually because of the high rates of progression of high-normal BP to hypertension.

Figure 2 Screening and diagnosis of hypertension



ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HBPM = home blood pressure monitoring.

[a]After detecting a specific BP category on screening, either confirm BP elevation with repeated office BP measurements on repeat visits, or arrange use of out-of-office BP to confirm the diagnosis of hypertension.

The diagnosis of hypertension should not be based on a single set of BP readings at a single office visit, unless the BP is substantially increased (e.g. grade 3 hypertension) and there is clear evidence of HMOD (e.g. hypertensive retinopathy with exudates and haemorrhages, or LVH, or vascular or renal damage). For all others (i.e. almost all patients), the diagnosis of hypertension should be based on BP measurements at repeat office visits, or home BP or ABPM, when these measurements are feasible (Figure 2). ABPM is also indicated for specific indications see **Table 9**.

Table 9 Clinical indications for home blood pressure monitoring or ambulatory blood pressure monitoring

Conditions in which white-coat hypertension is more common, e.g. • Grade I hypertension on office BP measurement • Marked office BP elevation without HMOD
Conditions in which masked hypertension is more common, e.g. • High-normal office BP • Normal office BP in individuals with HMOD or at high total CV risk
Postural and post-prandial hypotension in untreated and treated patients
Evaluation of resistant hypertension
Evaluation of BP control, especially in treated higher-risk patients Exaggerated BP response to exercise
When there is considerable variability in the office BP
Evaluating symptoms consistent with hypotension during treatment
Specific indications for ABPM rather than HBPM: • Assessment of nocturnal BP values and dipping status (e.g. suspicion of nocturnal hypertension, such as in sleep apnoea, CKD, diabetes, endocrine hypertension, or autonomic dysfunction)

ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; HBPM = home blood pressure monitoring.

Blood pressure measurement

Recommendations	Class[a]	Level[b]
Screening programmes for hypertension are recommended. All adults (18 years or older) should have their office BP measured and recorded in their medical file and be aware of their BP.	I	B
• Further BP recording is indicated, at least every 5 years if BP remains optimal.	I	C
• Further BP recording is indicated, at least every 3 years if BP remains normal.	I	C
• If BP remains high-normal, further BP recording, at least annually, is recommended.	I	C
• In older patients (>50 years), more frequent screening of office BP should be considered for each BP category because of the steeper rise in SBP with ageing.	IIa	C
It is recommended that office BP should be measured in both arms at least at the first visit because a between-arm SBP difference of >15 mmHg is suggestive of atheromatous disease and is associated with an increased CV risk.	I	A

rise in SBP with ageing.		
It is recommended that office BP should be measured in both arms at least at the first visit because a between-arm SBP difference of >15 mmHg is suggestive of atheromatous disease and is associated with an increased CV risk.	I	A
If a between-arm difference in BP is recorded, then it is recommended that all subsequent BP readings use the arm with the higher BP reading.	I	C
It is recommended to base the diagnosis of hypertension on: • Repeated office BP measurements on more than one visit, except when hypertension is severe (e.g. grade 3 and especially in high-risk patients). At each visit, three BP measurements should be recorded, 1–2 min apart, and additional measurements should be performed if the first two readings differ by >10 mmHg. The patient's BP is the average of the last two BP readings. Or • Out-of-office BP measurement with ABPM and/or HBPM, provided that these measurements are logistically and economically feasible.	I	C
Out-of-office BP (i.e. ABPM or HBPM) is specifically recommended for a number of clinical indications, such as identifying white-coat and masked hypertension, quantifying the effects of treatment, and identifying possible causes of side-effects (e.g. symptomatic hypotension).	I	A
It is recommended that all hypertensive patients undergo pulse palpation at rest to determine heart rate and search for arrhythmias such as AF.	I	C
Other BP measures and indices (pulse pressure, BP variability, exercise BP, and central BP) may be considered but are not often used for routine clinical use at present. They may provide useful additional information in some circumstances and are valuable tools for research.	IIb	C

ABPM = ambulatory blood pressure monitoring; AF = atrial fibrillation; BP = blood pressure; CV = cardiovascular; HBPM = home blood pressure monitoring; SBP = systolic blood pressure.
[a]Class of recommendation.
[b]Level of evidence.

Key info to be collected

The purpose of the clinical evaluation is to:

1. Establish the diagnosis and grade of hypertension.
2. Screen for potential secondary causes of hypertension.
3. Identify factors potentially contributing to the development of hypertension (lifestyle, concomitant medications, or family history).
4. Identify concomitant CV risk factors (including lifestyle and family history).
5. Identify concomitant diseases.
6. Establish whether there is evidence of HMOD or existing CV, cerebrovascular, or renal disease.

Table 10 Key information to be collected in personal and family medical history

Risk factors
Family and personal history of hypertension, CVD, stroke, or renal disease
Family and personal history of associated risk factors (e.g. familial hypercholesterolaemia)
Smoking history
Dietary history and salt intake
Alcohol consumption
Lack of physical exercise/sedentary lifestyle
History of erectile dysfunction
Sleep history, snoring, sleep apnoea (information also from partner)
Previous hypertension in pregnancy/pre-eclampsia
History and symptoms of HMOD, CVD, stroke, and renal disease
Brain and eyes: headache, vertigo, syncope, impaired vision, TIA, sensory or motor deficit, stroke, carotid revascularization, cognitive impairment, or dementia (in the elderly)
Heart: chest pain, shortness of breath, oedema, myocardial infarction, coronary revascularization, syncope, history of palpitations, arrhythmias (especially AF), heart failure
Kidney: thirst, polyuria, nocturia, haematuria, urinary tract infections
Peripheral arteries: cold extremities, intermittent claudication, pain-free walking distance, pain at rest, peripheral revascularization
Patient or family history of CKD (e.g. polycystic kidney disease)
History of possible secondary hypertension
Young onset of grade 2 or 3 hypertension (<40 years), or sudden development of hypertension or rapidly worsening BP in older patients
History of renal/urinary tract disease
Recreational drug/substance abuse/concurrent therapies: corticosteroids, nasal vasoconstrictor, chemotherapy, yohimbine, liquorice
Repetitive episodes of sweating, headache, anxiety, or palpitations, suggestive of Phaeochromocytoma
History of spontaneous or diuretic-provoked hypokalaemia, episodes of muscle weakness, and tetany (hyperaldosteronism)
Symptoms suggestive of thyroid disease or hyperparathyroidism
History of or current pregnancy and oral contraceptive use
History of sleep apnoea
Antihypertensive drug treatment
Current/past antihypertensive medication including effectiveness and intolerance to previous medications
Adherence to therapy

AF = atrial fibrillation; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; HMOD =hypertension-mediated organ damage; TIA = transient ischaemic attack.

Table 11 Key steps in physical examination

Body habitus
Weight and height measured on a calibrated scale, with calculation of BMI
Waist circumference
Signs of hypertension-mediated organ damage
Neurological examination and cognitive status
Fundoscopic examination for hypertensive retinopathy
Palpation and auscultation of heart and carotid arteries
Palpation of peripheral arteries
Comparison of BP in both arms (at least once)
Secondary hypertension
Skin inspection – café-au-lait patches of neurofibromatosis (phaeochromocytoma)
Kidney palpation for signs of renal enlargement in polycystic kidney disease
Auscultation of heart and renal arteries for murmurs or bruits indicative of aortic coarctation or renovascular hypertension
Comparison of radial with femoral pulse – to detect radio-femoral delay in aortic coarctation
Signs of Cushing's disease or acromegaly
Signs of thyroid disease

BMI = body mass index; BP = blood pressure; HMOD = hypertension-mediated organ damage.

Table 12 Routine work-up for evaluation of hypertensive patients

Routine laboratory tests
Haemoglobin and/or haematocrit
Fasting blood glucose and glycated HbA1c
Blood lipids: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol
Blood triglycerides
Blood potassium and sodium
Blood uric acid
Blood creatinine and eGFR
Blood liver function tests
Urine analysis: microscopic examination; urinary protein by dipstick test or, ideally, albumin:creatinine ratio
12-lead ECG

eGFR = estimated glomerular filtration rate; ECG = electrocardiogram; HbA1c = haemoglobin A1c.

Table 13 Assessment of Hypertension-mediated organ damage

Basic screening tests for HMOD	Indication and interpretation
12-lead ECG	Screen for LVH and other possible cardiac abnormalities and to document heart rate and cardiac rhythm
Urine albumin:creatinine ratio	To detect elevations in albumin excretion indicative of possible renal disease
Blood creatinine and eGFR	To detect possible renal disease
Fundoscopy	To detect hypertensive retinopathy, especially in patients with grade 2 or 3 hypertension
More detailed screening for HMOD	**Indication and interpretation**
Echocardiography	To evaluate cardiac structure and function, when this information will influence treatment decisions
Carotid ultrasound	To determine the presence of carotid plaque or stenosis, particularly in patients with cerebrovascular disease or vascular disease elsewhere
Abdominal ultrasound and Doppler studies	• To evaluate renal size and structure (e.g. scarring) and exclude renal tract obstruction as possible underlying causes of CKD and hypertension • Evaluate abdominal aorta for evidence of aneurysmal dilatation and vascular disease • Examine adrenal glands for evidence of adenoma or phaeochromocytoma (CT or MRI preferred for detailed examination) – see section here regarding screening for secondary hypertension. • Renal artery Doppler studies to screen for the presence of renovascular disease, especially in the presence of asymmetric renal size
PWV	An index of aortic stiffness and underlying arteriosclerosis
ABI	Screen for evidence of LEAD
Cognitive function testing	To evaluate cognition in patients with symptoms suggestive of cognitive impairment
Brain imaging	To evaluate the presence of ischaemic or haemorrhagic brain injury, especially in patients with a history of cerebrovascular disease or cognitive decline

ABI = ankle–brachial index; ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CKD = chronic kidney disease; CT = computed tomography; ECG = electrocardiogram; HBPM = home blood pressure monitoring; HMOD = hypertension-mediated organ damage; LEAD = lower extremity artery disease; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; PAD = peripheral artery disease; PWV = pulse wave velocity.

Table 14 The most commonly used simple criteria and recognised cut-off points for definitions of electrocardiogram left ventricular hypertrophy

ECG voltage criteria	Criteria for LVH
$S_{V1}+R_{V5}$ (Sokolow-Lyon criterion)	>35 mm
R wave in aVL	≥11 mm
$S_{V3}+Ra_{VL}$ (Cornell voltage)[a]	>28 mm (men)
	>20 mm (women)
Cornell duration product[b]	>2440 mm.ms

ECG = electrocardiogram; LVH = left ventricular hypertrophy.
[a]Sum of limb and precordial lead voltage - [b]Product of Cornell voltage x QRS duration (mm.ms).

Table 15 Echocardiographic definitions of left ventricular hypertrophy, concentric geometry, left ventricular chamber size, and left atrial dilatation

Parameter	Measure	Abnormality threshold
LVH	LV mass/height$^{2.7}$ (g/m$^{2.7}$)	>50 (men) >47 (women)
LVH[a]	LV mass/BSA (g/m^2)	>115 (men) >95 (women)
LV concentric geometry	RWT	≥0.43
LV chamber size	LV end-diastolic diameter/height (cm/m)	>3.4 (men) >3.3 (women)
Left atrial size (elliptical)	Left atrial volume/height^2 (mL/m^2)	>18.5 (men) >16.5 (women)

BSA = body surface area; LV = left ventricular; LVH = left ventricular hypertrophy; RWT = relative wall thickness.
[a]BSA normalization may be used in normal weight patients.

Table 16 Sensitivity to detect treatment-induced changes, reproducibility and operator independence, time to changes, and prognostic value of changes provided by markers of hypertension-mediated organ damage

Marker of HMOD	Sensitivity to changes	Reproducibility and operator independence	Time to changes	Prognostic value of the change
LVH by ECG	Low	High	Moderate (>6 months)	Yes
LVH by echocardiogram	Moderate	Moderate	Moderate (>6 months)	Yes
LVH by CMR	High	High	Moderate (>6 months)	No data
eGFR	Moderate	High	Very slow (years)	Yes
Urinary protein excretion	High	Moderate	Fast (weeks to months)	Moderate
Carotid IMT	Very low	Low	Slow (>12 months)	No
PWV	High	Low	Fast (weeks to months)	Limited data
Ankle-brachial index	Low	Moderate	Slow (>12 months)	Moderate

CMR = cardiac magnetic resonance; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; IMT = intima-media thickness; LVH = left ventricular hypertrophy; PWV = pulse wave velocity.

Clinical evaluation and hypertension-mediated organ damage assessment		
Recommendations	**Class[a]**	**Level[b]**
Heart		
12-lead ECG is recommended for all hypertensive patients.	I	B
Echocardiography: • Is recommended in hypertensive patients when there are ECG abnormalities or signs or symptoms of LV dysfunction.	I	B
• May be considered when the detection of LVH may influence treatment decisions.	IIb	B
Blood vessels		
• Ultrasound examination of the carotid arteries:	I	B
• May be considered for the detection of asymptomatic atherosclerotic plaques or carotid stenosis, in patients with documented vascular disease elsewhere.	IIb	B
Measurement of PWV may be considered for measuring arterial stiffness.	IIb	B
Measurement of ABI may be considered for the detection of advanced LEAD.	IIb	B
Kidney		
Measurement of serum creatinine and eGFR is recommended in all hypertensive patients.	I	B
Measurement of urine albumin:creatinine ratio is recommended in all hypertensive patients.	I	B
Renal ultrasound and Doppler examination should be considered in patients with impaired renal function, albuminuria, or for suspected secondary hypertension.	IIa	C
Fundoscopy		
Is recommended in patients with grades 2 or 3 hypertension and all hypertensive patients with diabetes.	I	C
May be considered in other hypertensive patients.	IIb	C
Brain		
In hypertensive patients with neurological symptoms and/or cognitive decline, brain MRI or CT should be considered for detecting brain infarctions, microbleeds, and white matter lesions.	IIa	B

ABI = ankle–brachial index; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HMOD = hypertension-mediated organ damage; LEAD = lower extremity arterial disease; LV = left ventricular; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; PWV = pulse wave velocity; TIA = transient ischaemic attack.
[a]Class of recommendation - [b]Level of evidence.

Most patients with hypertension will be managed in the primary care setting. There are, however, circumstances in which a referral for hospital-based evaluation and treatment may be required:

- Patients in whom secondary hypertension is suspected.
- Younger patients (<40 years) with grade 2 or more severe hypertension in whom secondary hypertension should be excluded.
- Patients with treatment-resistant hypertension.
- Patients in whom more detailed assessment of HMOD would influence treatment decisions.
- Patients with sudden onset of hypertension when BP has previously been normal.
- Other clinical circumstances in which the referring doctor feels more specialist evaluation is required.

There are also rarer circumstances in which a patient with hypertension should referred to hospital for emergency care, which will often require in-patient care (see section here).

The routine treatment of hypertension involves lifestyle interventions for all patients (including those with high normal BP) and drug therapy for most patients.

Key considerations are:

- At what BP threshold BP is drug treatment indicated or should be considered?
- How low BP should be lowered?
- What lifestyle and drug treatment strategies should be used to lower BP?

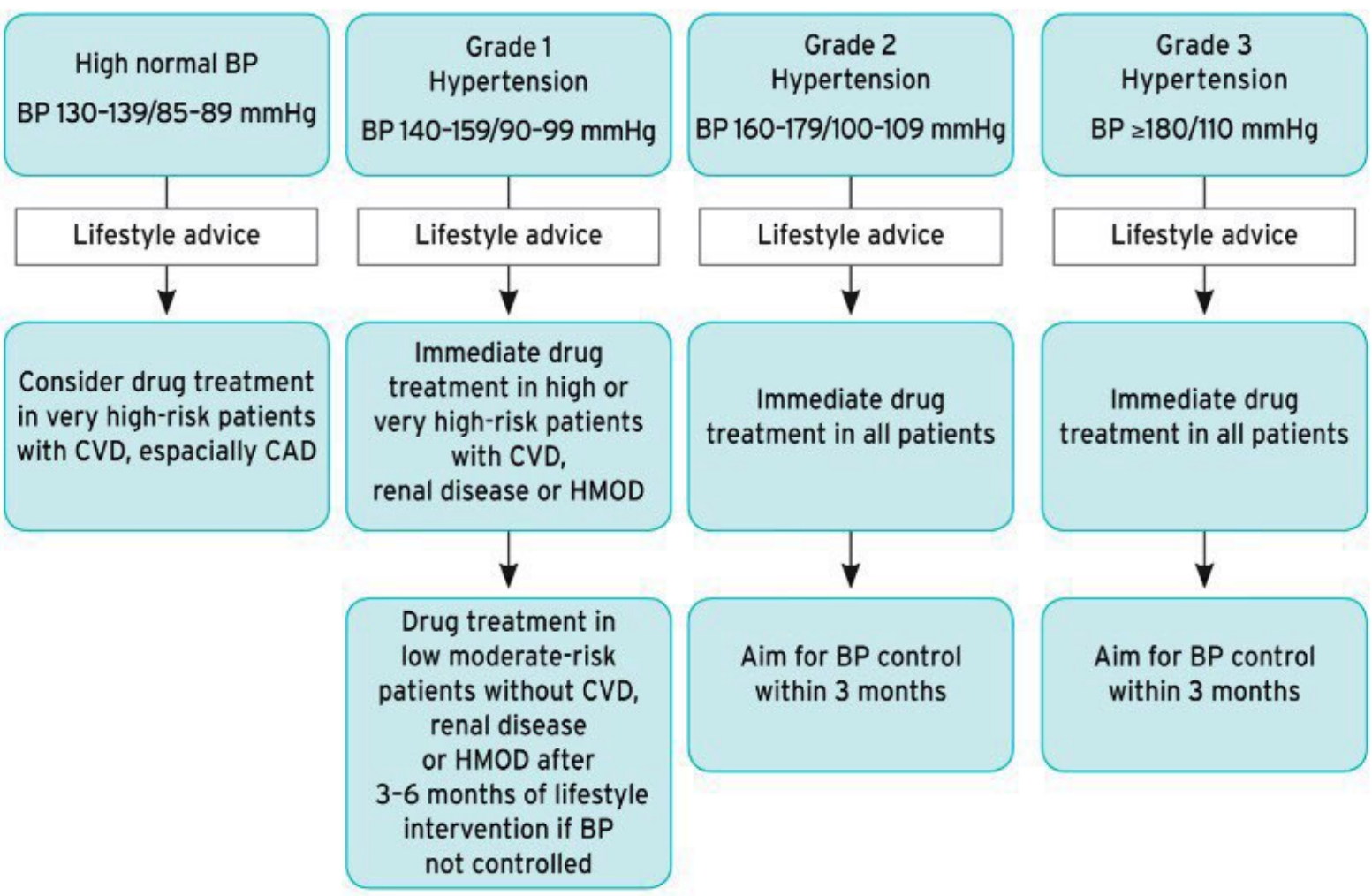
Lifestyle interventions (see section here) are recommended for all patients with high-normal BP or hypertension. The BP threshold for drug treatment and timing of initiation of drug treatment depends on the patient's age and risk (Figure 3 and Table 17).

Table 17 Summary of office blood pressure thresholds for treatment

Age group	Office SBP treatment threshold (mmHg)					Office DBP treatment threshold (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke/TIA	
18-65 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
65-79 years	≥140	≥140	≥140	≥140[a]	≥140[a]	≥90
≥80 years	≥160	≥160	≥160	≥160	≥160	≥90
Office DBP treatment threshold (mmHg)	≥90	≥90	≥90	≥90	≥90	

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.
[a]Treatment may be considered in these very high-risk patients with high-normal SBP (i.e. SBP 130–140 mmHg).

Figure 3 Initiation of BP-lowering treatment (lifestyle changes and medication) at different initial office BP levels



BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.

Initiation of hypertension treatment according to office blood pressure

Recommendations	Class[a]	Level[b]
Prompt initiation of BP-lowering drug treatment is recommended in patients with grade 2 or 3 hypertension at any level of CV risk, simultaneous with the initiation of lifestyle changes.	I	A
In patients with grade 1 hypertension: • Lifestyle interventions are recommended to determine if this will normalize BP.	IIa	B
• In patients with grade 1 hypertension at low-moderate risk and without evidence of HMOD, BP-lowering drug treatment is recommended if the patient remains hypertensive after a period of lifestyle intervention.[c]	I	A
• In patients with grade 1 hypertension and at high-risk or with evidence of HMOD, prompt initiation of drug treatment is recommended simultaneously with lifestyle interventions.	I	A
In fit older patients with hypertension (even if age >80 years), BP-lowering drug treatment and lifestyle intervention are recommended when SBP is ≥160 mmHg.	I	A
BP-lowering drug treatment and lifestyle intervention are recommended for fit older patients (>65 years but not >80 years) when SBP is in the grade 1 range (140–159 mmHg), provided that treatment is well tolerated.	I	A

Antihypertensive treatment may also be considered in frail older patients if tolerated.	IIb	B
Withdrawal of BP-lowering drug treatment on the basis of age, even when patients attain an age of ≥80 years, is not recommended, provided that treatment is well tolerated.	III	A
In patients with high-normal BP (130–139/85–89 mmHg): • Lifestyle changes are recommended	I	A
• Drug treatment may be considered when their CV is very high due to established CVD, especially CAD.	IIb	A

BP = blood pressure; CAD = coronary artery disease; CV = cardiovascular; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure.
[a]Class of recommendation - [b]Level of evidence - [c]In patients with grade 1 hypertension and at lowto- moderate risk, drug treatment may be preceded by a prolonged period of lifestyle intervention to determine if this approach will normalize BP. The duration of the lifestyle intervention alone will depend on the level of BP within the grade 1 range, i.e. the likelihood of achieving BP control with lifestyle intervention alone, and the opportunities for significant lifestyle change in individual patients.

BP treatment targets

The level to which BP should be lowered with drug treatment will depend on the patients' age, comorbidities and tolerability of treatment. A target range is recommended to indicate a lower safety boundary beyond which BP should not usually be lowered. Office BP target ranges are summarised below and in Table 18. Corresponding BP targets for home or ambulatory BP are less well validated but an office systolic BP <130mmHg probably corresponds to a 24hr ABPM systolic BP of <125mmHg and a home average systolic BP of <130mmHg.

Office blood pressure treatment targets in hypertensive patients

Recommendations	Class[a]	Level[b]
It is recommended that the first objective of treatment should be to lower BP to <140/90 mmHg in all patients, and provided that the treatment is well tolerated, treated BP values should be targeted to 130/80 mmHg or lower, in most patients.	I	A
In patients <65 years receiving BP-lowering drugs, it is recommended that SBP should be lowered to a BP range of 120–129 mmHg in most patients.[c]	I	A
In older patients (aged ≥65 years) receiving BP-lowering drugs: • It is recommended that SBP should be targeted to a BP range of 130–139 mmHg.	I	A
• Close monitoring of adverse effects is recommended.	I	C
• These BP targets are recommended for patients at any level of CV risk and in patients with and without established CVD.	I	A
A DBP target of <80 mmHg should be considered for all hypertensive patients, independent of the level of risk and comorbidities.	IIa	B

BP = blood pressure; CV = cardiovascular; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Class of recommendation - [b]Level of evidence
[c]Less evidence is available for this target in low–moderate-risk patients.

Table 18 Office blood pressure treatment target range

Age group	Office SBP treatment target ranges (mmHg)					Office DBP treatment target range (mmHg)
	Hypertension	+ Diabetes	+ CKD	+ CAD	+ Stroke[a]/TIA	
18-65 years	**Target to 130** or lower if tolerated Not <120	**Target to 130** or lower if tolerated Not <120	**Target to <140 to 130** if tolerated	**Target to 130** or lower if tolerated Not <120	**Target to 130** or lower if tolerated Not <120	70-79
65-79 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70-79
≥80 years[b]	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	**Target to 130-139** *if tolerated*	70-79
Office DBP treatment threshold (mmHg)	70-79	70-79	70-79	70-79	70-79	

BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease (includes diabetic and non-diabetic CKD); DBP = diastolic blood pressure; SBP = systolic blood pressure; TIA = transient ischaemic attack.
[a]Refers to patients with previous stroke and does not refer to BP targets immediately after acute stroke.
[b]Treatment decisions and BP targets may need to be modified in older patients who are frail and independent.

Heathy lifestyle choices can prevent or delay the onset of hypertension and can reduce CV risk. Effective lifestyle changes may be sufficient to delay or prevent the need for drug therapy in patients with grade 1 hypertension and can also augment the effects of BP-lowering therapy in treated patients. However, lifestyle intervention should never delay the initiation of drug therapy in patients with HMOD or at a high level of CV risk. Recommended lifestyle measures that have been shown to reduce BP are shown below.

Adoption of lifestyle changes in patients with hypertension

Recommendations	Class[a]	Level[b]
Salt restriction to <5 g per day is recommended.	I	A
It is recommended to restrict alcohol consumption to: • Less than 14 units per week for men. • Less than 8 units per week for women.	I	A
Increased consumption of vegetables, fresh fruits, fish, nuts, unsaturated fatty acids (olive oil), low consumption of red meat, and consumption of low-fat dairy products are recommended.	I	A
Body-weight control is indicated to avoid obesity (BMI >30 kg/m^2 or waist circumference >102 cm in men and >88 cm in women) and aim at a healthy BMI (about 20–25 kg/m^2) and waist circumference values (<94 cm in men and <80 cm in women) to reduce BP and CV risk.	I	A
Regular aerobic exercise (e.g. at least 30 min of moderate dynamic exercise on 5–7 days per week) is recommended.	I	A
Smoking cessation and supportive care and referral to smoking cessation programs are recommended.	I	B
It is recommended to avoid binge drinking.	III	C

BMI = body mass index; BP = blood pressure; CV = cardiovascular.
[a]Class of recommendation - [b]Level of evidence mostly based on the effect on BP and/or CV risk profile.

Most hypertensive patients will require drug therapy in addition to lifestyle measures to achieve optimal BP control. Five major drug classes are recommended for the routine treatment of hypertension: ACE-inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like diuretics such as chlorthalidone and indapamide), based on: (i) proven ability to reduce BP; (ii) evidence from placebo-controlled studies that they reduce CV events; and (iii) evidence of broad equivalence at reducing CV morbidity and mortality. Each of these drug classes has compelling or possible contraindications to their use (Table 19).

Table 19 Compelling and possible contraindications to the use of specific antihypertensive drugs

Drugs	Contraindications	
	Compelling	Possible
Diuretics (thiazides/ thiazide-like, e.g. chlortalidone and indapamide)	Gout	• Metabolic syndrome • Glucose intolerance • Pregnancy • Hypercalcemia • Hypokalemia
Beta-blockers	• Asthma • Any high-grade sino-atrial or atrioventricular block • Bradycardia (heart rate <60 beats per min)	• Metabolic syndrome • Glucose intolerance • Athletes and physically active patients
Calcium antagonists (dihydropyridines)		• Tachyarrhythmia • Heart failure (HFrEF, Class III or IV) • Pre-existing severe leg oedema
Calcium antagonists (verapamil, diltiazem)	• Any high-grade sino-atrial or atrioventricular block • Severe LV dysfunction (LV ejection fraction <40%) • Bradycardia (heart rate <60 beats per min)	• Constipation
ACE-inhibitors	• Pregnancy • Previous angioneurotic oedema • Hyperkalaemia (potassium >5.5 mmol/L) • Bilateral renal artery stenosis	• Women of child-bearing potential without reliable contraception
ARBs	• Pregnancy • Hyperkalaemia (potassium >5.5 mmol/L) • Bilateral renal artery stenosis	• Women of child-bearing potential without reliable contraception

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular.

Overview

Despite the availability of proven and effective drug therapies for hypertension, the global rates of BP control remain poor. Thus, there is an urgent need to address the factors contributing to the poor control of BP in treated hypertensive patients, especially treatment inertia (clinician failure to up-titrate treatment) and poor patient adherence to multiple medications. The drug treatment algorithm has been developed to provide a simple and pragmatic treatment recommendation for the treatment of hypertension, based on a few key principles and recommendations:

1. The initiation of treatment in most patients should be with a single pill combination (SPC) of two drugs, to improve the speed, efficiency, and predictability of BP control. This normalises the concept that effective initial treatment of hypertension requires at least 2 drugs for most patients.
2. The preferred two-drug combinations are a RAS blocker (ACE-inhibitor or ARB) with a CCB or a diuretic. A beta-blocker in combination with a diuretic or any drug from the other major classes is an alternative, when there is a specific indication for a beta-blocker, e.g. angina, post-myocardial infarction, heart failure, or heartrate control.
3. Monotherapy should usually only be used as initial therapy for; (i) low-risk patients with stage 1 hypertension whose SBP is <150 mmHg, (ii) when it is decided to treat very high-risk patients with high-normal BP, or (iii) frail older patients.
4. A three-drug SPC comprising an RAS blocker + CCB + diuretic, should be used if BP is not controlled by a two-drug SPC.
5. Spironolactone is the preferred initial treatment for resistant hypertension, unless contraindicated (see section here).
6. Other classes of antihypertensive drugs may be used in the rare circumstances in which BP is not controlled by the above treatment strategy.

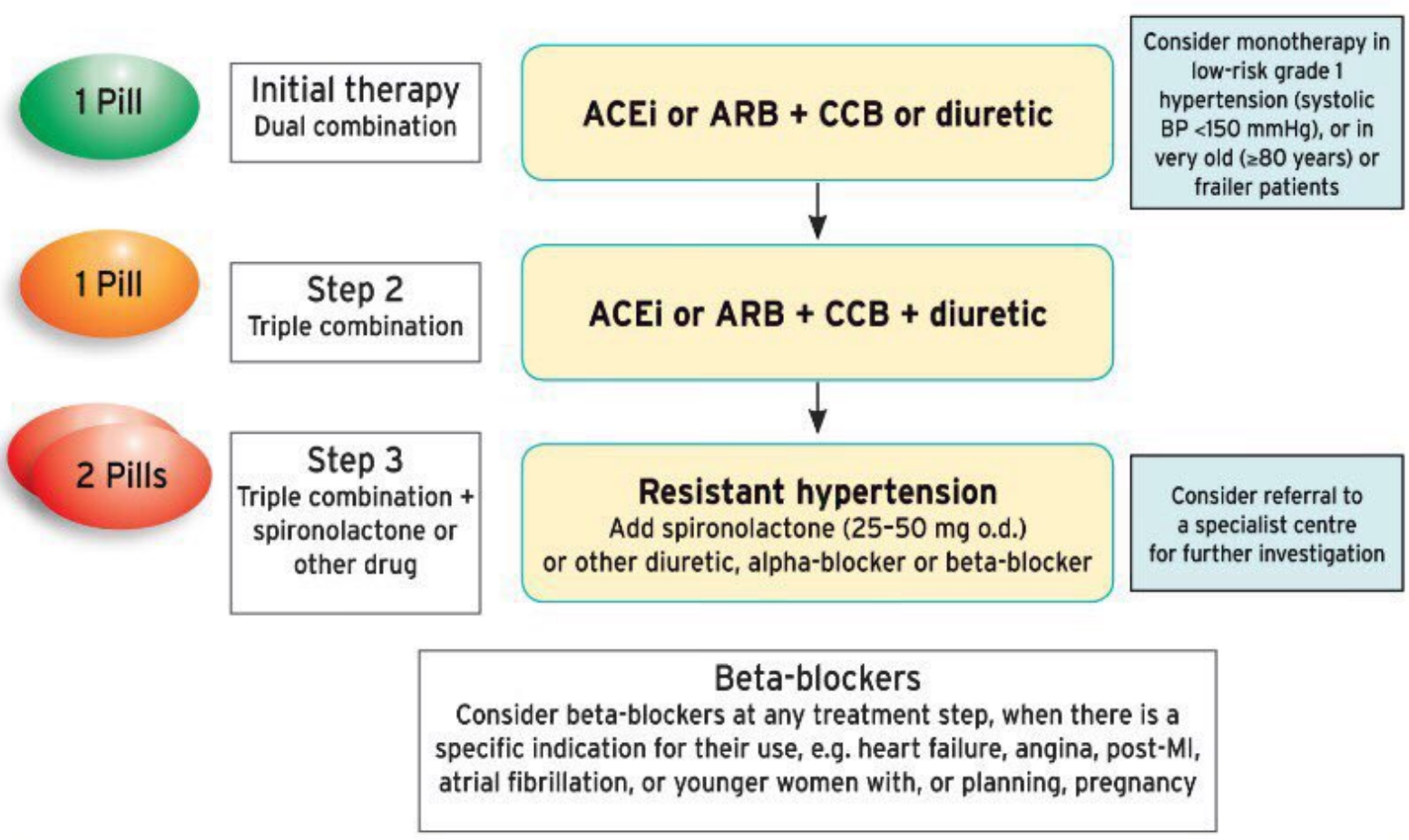
The core drug treatment algorithm is shown in Figure 4, and variations in the algorithm for patients

Drug treatment strategy for hypertension		
Recommendations	**Class[a]**	**Level[b]**
Among all antihypertensive drugs, ACE-inhibitors, ARBs, beta-blockers, CCBs, and diuretics (thiazides and thiazide-like such as chlortalidone and indapamide) have demonstrated effective reduction of BP and CV events in RCTs, and thus are indicated as the basis of antihypertensive treatment strategies.	I	A
Combination treatment is recommended for most hypertensive patients as initial therapy. Preferred combinations should comprise a RAS blocker (either an ACE inhibitor or an ARB) with a CCB or diuretic. Other combinations of the five major classes can be used	I	A
It is recommended that beta-blockers are combined with any of the other major drug classes when there are specific clinical situations, e.g. angina, post-myocardial infarction, heart failure, or heart rate control.	I	A
It is recommended to initiate an antihypertensive treatment with a two-drug combination, preferably in a SPC. Exceptions are frail older patients and those at low risk and with grade 1 hypertension (particularly if SBP is <150 mmHg).	I	B
It is recommended that if BP is not controlledc with a two-drug combination, treatment should be increased to a three-drug combination, usually an RAS blocker + CCB + thiazide/thiazide-like diuretic, preferably as an SPC.	I	A

as an SPC.		
It is recommended that if BP is not controlled[c] with a three-drug combination, treatment should be increased by the addition of spironolactone or, if not tolerated, other diuretics such as amiloride or higher doses of other diuretics, a beta-blocker, or an alphablocker.	I	B
The combination of two RAS blockers is not recommended.	III	A

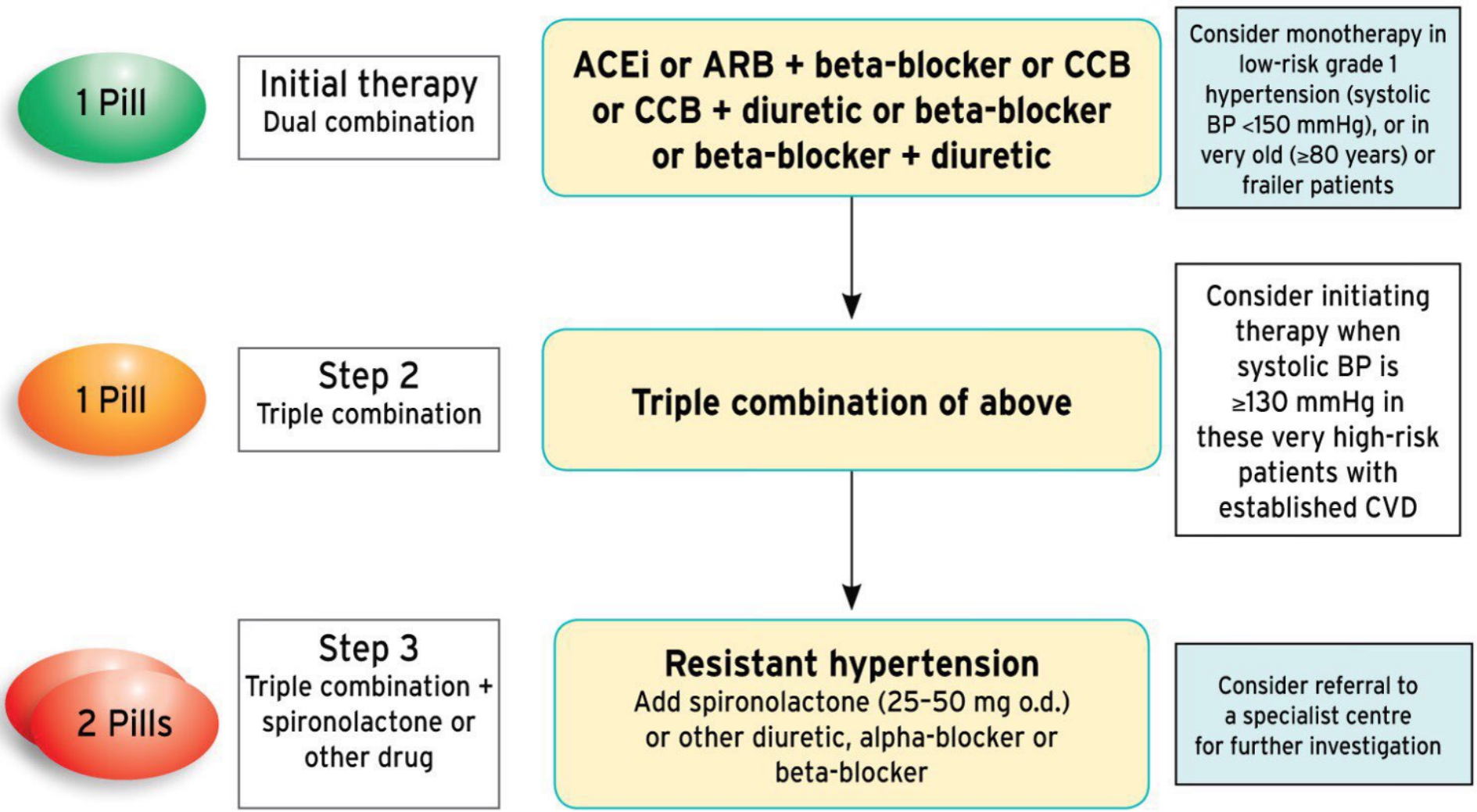
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; CV = cardiovascular; RAS = renin–angiotensin system; RCT = randomized controlled trial; SBP = systolic blood pressure; SPC = single-pill combination.
[a]Class of recommendation.
[b]Level of evidence.
[c]Adherence should be checked.

Figure 4 Core drug-treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with hypertension-mediated organ damage (HMOD), cerebrovascular disease, diabetes, or peripheral artery disease (PAD)



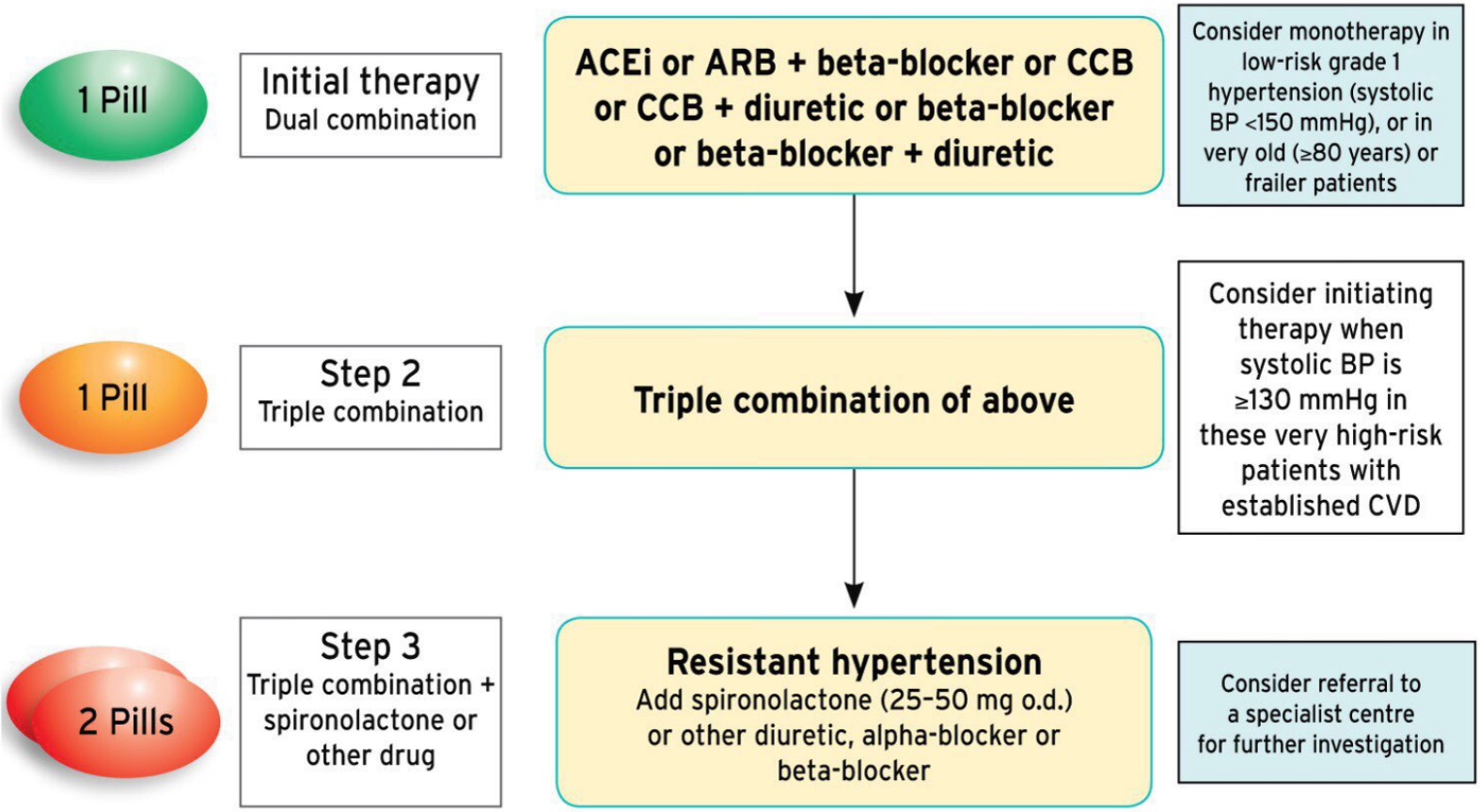
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; HMOD = hypertension-mediated organ damage; o.d. = omni die (every day); PAD = peripheral artery disease.

Figure 5 Drug-treatment strategy for hypertension and coronary artery disease (CAD)



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCB = calcium-channel blocker; CVD = cardiovascular disease; o.d. = omni die (every day).

Figure 6 Drug-treatment strategy for hypertension and chronic kidney diseasea (CKD)



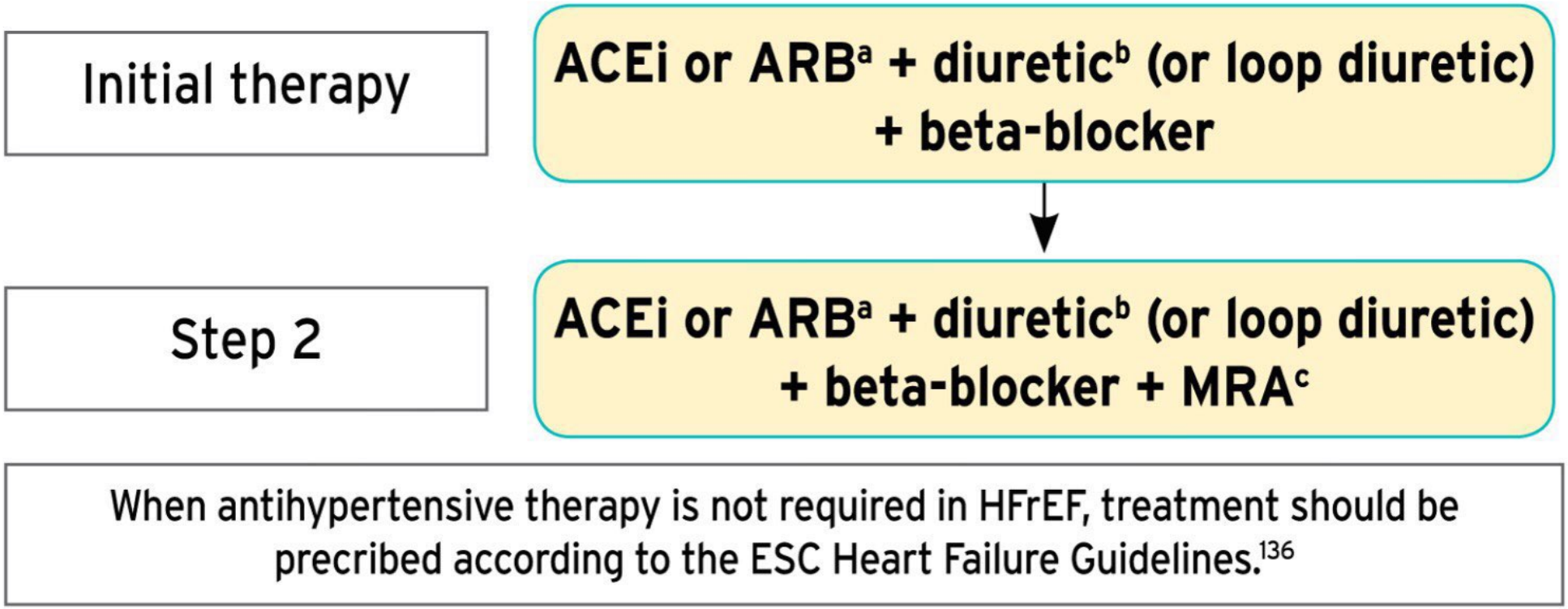
ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; o.d. = omni die (every day).

[a]CKD is defined as an eGFR <60 mL/min/1.72 m^2 with or without proteinuria.

[b]Use loop diuretics when eGFR is <30 mL/min/1.72 m^2 because thiazide/thiazide-like diuretics are much less effective/ineffective when eGFR is reduced to this level.

[c]Caution: risk of hyperkalaemia with spironolactone, especially when eGFR is <45 mL/min/1.72 m^2 or baseline K+ ≥4.5 mmol/L.

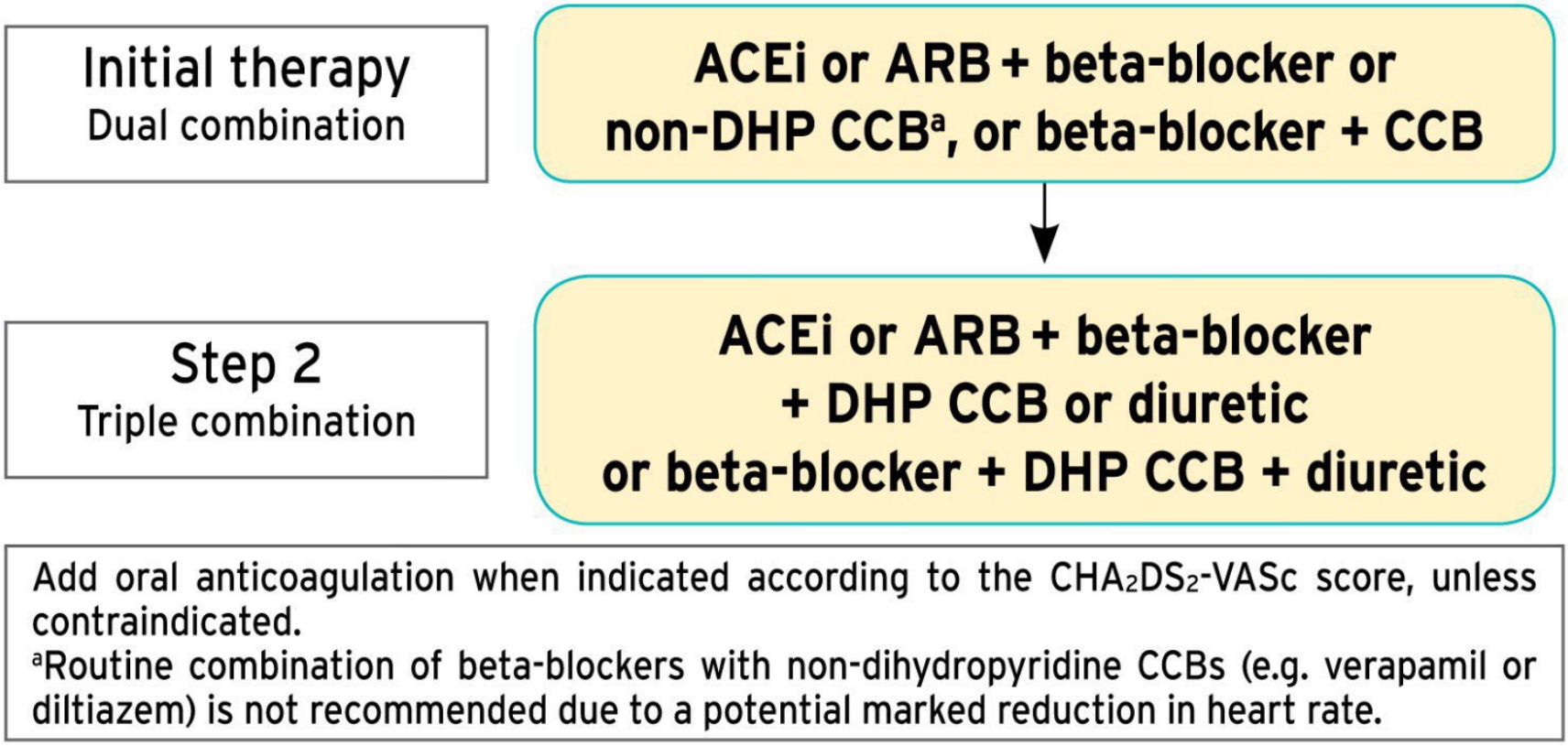
Figure 7 Drug-treatment strategy for hypertension and heart failure with reduced ejection fraction (HFrEF). Do not use non-dihydropyridine CCBs (e.g. verapamil or diltiazem).



ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

[a]Consider an angiotensin receptor/neprilysin inhibitor instead of ACEi or ARB per ESC Heart Failure Guidelines. [b]Diuretic refers to thiazide/thiazide-like diuretic. Consider a loop diuretic as an alternative in patients with oedema. cMRA (spironolactone or eplerenone).

Figure 8 Drug-treatment strategy for hypertension and atrial fibrillation (AF)



Add oral anticoagulation when indicated according to the CHA_2DS_2-VASc score, unless contraindicated.
[a]Routine combination of beta-blockers with non-dihydropyridine CCBs (e.g. verapamil or diltiazem) is not recommended due to a potential marked reduction in heart rate.

ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; CHA_2DS_2-VASc = Cardiac failure, Hypertension, Age ≥75 [Doubled], Diabetes, Stroke [Doubled] – Vascular disease, Age 65–74 and Sex category [Female]; DHP = dihydropyridine.
[a]Non-dihydropyridine CCB (non-DHP CCB, e.g. verapamil or diltiazem).

Device-based therapy for hypertension is a fast-moving field. Although some positive data has emerged from recent small sham-controlled studies, especially with renal denervation, further sham-controlled studies are needed before devicebase therapies can be recommended for the routine treatment of hypertension outside of the framework of clinical trials.

Device-based therapies for hypertension

Recommendations	Class[a]	Level[b]
Use of device-based therapies is not recommended for the routine treatment of hypertension, unless in the context of clinical studies and RCTs, until further evidence regarding their safety and efficacy becomes available.	III	B

[a]Class of recommendation - [b]Level of evidence.

Definition of resistant hypertension

Hypertension is defined as resistant to treatment when the recommended treatment strategy (see above) fails to lower office BP to below 140/90 mmHg, and inadequate BP control is confirmed by ABPM or HBPM, in patients whose adherence to therapy has been confirmed.

The recommended treatment strategy should include appropriate lifestyle measures and treatment with optimal or best-tolerated doses of three or more drugs that should include a diuretic and typically an ACE-inhibitor or ARB, and a CCB. Pseudoresistant hypertension (see below) and secondary causes of hypertension should also have been excluded (see section 6). Patient characteristics, causes and factors contributing to resistant hypertension are shown in Table 20.

Table 20 Resistant hypertension: Patient characteristics, secondary causes, and contributing factors

Characteristics of patients with resistant hypertension	Causes of secondary resistant hypertension	Drugs and substances that may cause raised BP
Demographics • Older age (especially >75 years) • Obesity • More common in black people • Excess dietary sodium intake • High baseline BP and chronicity of uncontrolled hypertension	**More common causes** • Primary hyperaldosteronism • Atherosclerotic renovascular disease • Sleep apnoea • CKD	**Prescribed drugs** • Oral contraceptives • Sympathomimetic agents (e.g. decongestants in proprietary cold remedies) • Non-steroidal antiinflammatory drugs • Cyclosporin • Erythropoietin • Steroids (e.g. prednisolone, hydrocortisone) • Some cancer therapies
Concomitant disease • HMOD: LVH and/or CKD • Diabetes • Atherosclerotic vascular disease • Aortic stiffening and isolated systolic hypertension	**Uncommon causes** • Phaeochromocytoma • Fibromuscular dysplasia • Aortic coarctation • Cushing's disease • Hyperparathyroidism	**Non-prescription drugs** • Recreational drugs (e.g. cocaine, amphetamines, anabolic steroids) • Excess liquorice ingestion • Herbal remedies (e.g. ephedra, ma huang)

BP = blood pressure; CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage; LVH = left ventricular hypertrophy.

1. **Poor adherence to prescribed medicines**
2. **White-coat phenomenon:** Office BP is elevated but BP is controlled with ABPM or HBPM.
3. **Poor office-BP measurement technique:** Cuffs that are too small relative to the arm circumference, can result in a spurious elevation of BP
4. **Marked brachial artery calcification:** Usually in older patients with heavily calcified arteries.
5. **Clinician inertia:** Resulting in inadequate doses or irrational combinations of BP-lowering drugs

Effective treatment combines lifestyle changes (especially reducing sodium intake), discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy (usually an ACE-inhibitor or ARB + CCB + diuretic).

Low dose spironolactone (25-50mg per day) is an effective treatment for resistant hypertension, however, its efficacy and safety has not been established in patients with significant renal impairment. Consequently, the use of spironolactone for resistant hypertension should usually be restricted to patients with an eGFR ≥45 mL/min and a plasma potassium concentration of ≤4.5 mmol/L. Electrolytes and eGFR should be monitored soon after initiation. Amiloride (10–20 mg/day) has recently been shown to be as effective as spironolactone 25–50 mg daily) but has the same limitations with regard to renal function and potassium. A loop diuretic should replace thiazides/thiazide-like diuretics if the eGFR is <30 mL/min.

Resistant hypertension

Recommendations	Class[a]	Level[b]
It is recommended that hypertension be defined as resistant to treatment (i.e. resistant hypertension) when: • Optimal doses (or best-tolerated doses) of an appropriate therapeutic strategy, which should include a diuretic (typically an ACE-inhibitor or ARB + CCB + thiazide/thiazide-like diuretic), fails to lower clinic SBP and DBP values to <140 mmHg and/or <90 mmHg, respectively; and • The inadequate control of BP has been confirmed by ABPM or HBPM; and • After exclusion of various causes of pseudo-resistant hypertension (especially poor medication adherence) and secondary hypertension.	I	C

hypertension (especially poor medication adherence) and secondary hypertension.		
Recommended treatment of resistant hypertension is: • Reinforcement of lifestyle measures, especially sodium restriction. • Addition of low-dose spironolactone[c] to existing treatment. • Or the addition of further diuretic therapy if intolerant to spironolactone, with either eplerenone,[c] amiloride,[c] higher dose thiazide/thiazide-like diuretic, or a loop diuretic.[d] • Or the addition of bisoprolol or doxazosin.	I	B

ABPM = ambulatory blood pressure monitoring; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HBPM = home blood pressure monitoring.

[a]Class of recommendation - [b]Level of evidence.

[c]When spironolactone is not tolerated, replace with amiloride or eplerenone. The use of these drugs should be restricted to patients with an estimated glomerular filtration rate ≥45 mL/min and a plasma potassium concentration of ≤4.5 mmol/L, because of the risk of hyperkalaemia.

[d]A loop diuretic should replace thiazides/thiazide-like diuretics if the estimated glomerular filtration rate is <30 mL/min.

Secondary hypertension is hypertension due to an identifiable cause, which may be treatable with an intervention specific to the cause. A high index of suspicion (see Table 21) and early detection of secondary causes of hypertension is important because interventions may be curative, especially in younger patients. Common causes of secondary hypertension and screening investigations are shown in Tables 22 and 23. Some medications may also increase BP and these are listed in Table 24.

Table 21 Patient characteristics that should raise the suspicion of secondary hypertension

Characteristic
Younger patients (<40 years) with grade 2 hypertension or onset of any grade of hypertension in childhood
Acute worsening hypertension in patients with previously documented chronically stable normotension
Resistant hypertension
Severe (grade 3) hypertension or a hypertension emergency
Presence of extensive hypertension-mediated organ damage
Clinical or biochemical features suggestive of endocrine causes of hypertension or CKD
Clinical features suggestive of obstructive sleep apnoea
Symptoms suggestive of phaeochromocytoma or family history of phaeochromocytoma

CKD = chronic kidney disease; HMOD = hypertension-mediated organ damage.

Secondary HTN - characteristics

Table 22 Common causes of secondary hypertension

Cause	Prevalence in hypertensive patients	Suggestive symptoms and signs	Screening Investigations
Obstructive sleep apnoea	5-10%	Snoring; obesity (can be present in non-obese); morning headache; daytime somnolence	Epworth score + ambulatory polygraphy
Renal parenchymal disease	2-10%	Mostly asymptomatic; diabetes; haematuria, proteinuria, nocturia; anaemia, renal mass in adult polycystic CKD	Plasma creatinine and electrolytes, eGFR; urine dipstick for blood and protein, urinary albumin:creatinine ratio; renal ultrasound
Renovascular disease			
Atherosclerotic renovascular disease	1-10%	Older; widespread atherosclerosis (especially PAD); diabetes; smoking; recurrent flash pulmonary oedema; abdominal bruit	Duplex renal artery Doppler or CT angiography or MR angiography
Fibromuscular dysplasia		Younger; more common in women; abdominal bruit	
Primary Aldosteronism	5-15%	Mostly asymptomatic; muscle weakness (rare)	Plasma aldosterone and renin, and aldosterone: renin ratio; hypokalaemia (in a minority): note hypokalaemia can depress aldosterone levels
Phaeochromocytoma	<1%	Episodic symptoms (the 5 'Ps'): paroxysmal hypertension, pounding headache, perspiration, palpitations, and pallor; labile BP; BP surges precipitated by drugs (e.g. betablockers, metoclopramide, sympathomimetics, opioids, and tricyclic antidepressants)	Plasma or 24 h urinary fractionated metanephrines
Cushing's syndrome	<1%	Moon face, central obesity, skin atrophy, striae and bruising; diabetes; chronic steroid use	24-h urinary free cortisol
Thyroid disease (hyper- or hypothyroidism)	1-2%	Signs and symptom of hyper- or hypothyroidism	Thyroid function tests
Hyperparathyroidism	<1%	Hypercalcaemia, hypophosphatemia	Parathyroid hormone, Ca^{2+}
Coarctation of the aorta			
Coarctation of the aorta	<1%	Usually detected in children or adolescence; different BP (≥20/10 mmHg) between upper–lower extremities and/or between right–left arm and delayed radial-femoral femoral pulsation; low ABI interscapular ejection murmur; rib notching on chest X-ray	Echocardiogram

ABI = ankle–brachial index; BP = blood pressure; CKD = chronic kidney disease; CT = computed tomography; eGFR = estimated glomerular filtration rate; PAD = peripheral artery disease.

Table 23 Incidence and typical causes of secondary hypertension according to age

Age group	Per cent with underlying cause	Typical causes
Young children (<12 years)	70–85	Renal parenchymal disease Coarctation of the aorta Monogenic disorders
Adolescents (12–18 years)	10–15	Renal parenchymal disease Coarctation of the aorta Monogenic disorders
Young adults (19–40 years)	5–10	Renal parenchymal disease Fibromuscular dysplasia (especially in women) Undiagnosed monogenic disorders
Middle-aged adults (41–65 years)	5–15	Primary aldosteronism Obstructive sleep apnoea Cushing's syndrome Phaeochromocytoma Renal parenchymal disease Atherosclerotic renovascular disease
Older adults (<65 years)	5–10	Atherosclerotic renovascular disease Renal parenchymal disease Thyroid disease

Table 24 Medications and other substances that may increase blood pressure

Medication/substance	
Oral contraceptive pill	Especially oestrogen containing – cause hypertension in ~5% of women, usually mild but can be severe
Diet pills	For example, phenylpropanolamine and sibutramine
Nasal decongestants	For example, phenylephrine hydrochloride and naphazoline hydrochloride
Stimulant drugs	Amphetamine, cocaine, and ecstasy – these substances usually cause acute rather than chronic hypertension
Liquorice	Chronic excessive liquorice use mimics hyperaldosteronism by stimulating the mineralocorticoid receptor and inhibiting cortisol metabolism
Immunosuppressive medications	For example, cyclosporin A (tacrolimus has less effect on BP and rapamycin has almost no effect on BP), and steroids (e.g. corticosteroids, hydrocortisone)
Antiangiogenic cancer therapies	Antiangiogenic drugs, such as VEGF inhibitors (e.g. bevacizumab), tyrosine kinase inhibitors (e.g. sunitinib), and sorafenib, have been reported to increase BP
Other drugs and substances that may raise BP	Anabolic steroids, erythropoietin, non-steroidal antiinflammatory drugs, herbal remedies (e.g. ephedra, ma huang)

BP = blood pressure; VEGF = vascular endothelial growth factor.

Hypertension emergencies are situations in which severe hypertension (usually grade 3) is associated with acute organ damage, which is often life-threatening and requires immediate but careful intervention to lower BP, in hospital, usually with intravenous (i.v.) therapy. Typical presentations of a hypertension emergency are:

- Patients with malignant hypertension, characterised by severe hypertension (usually grade 3) associated with characteristic funduscopic changes (flame haemorrhages and/or papilloedema), microangiopathy, and disseminated intravascular coagulation, encephalopathy (in about 15% of cases), acute heart failure, and acute deterioration in renal function. The term "malignant" reflects the very poor prognosis for this condition if untreated.
- Patients with severe hypertension associated with other clinical conditions likely to require an urgent reduction of BP, e.g. acute aortic dissection, acute myocardial ischaemia, or acute heart failure.
- Patients with sudden severe hypertension due to phaeochromocytoma
- Pregnant women with severe hypertension or pre-eclampsia

The term ***"hypertension urgency"*** has also been used to describe severe hypertension presenting to the emergency department in patients in whom there is no clinical evidence of acute HMOD. Whilst these patients require BP reduction, they rarely require admission to hospital, and BP reduction is best achieved with oral medication according to the drug treatment algorithm shown in Figures 4-8. These patients will require urgent outpatient review to ensure their BP is coming under control.

Table 25 Diagnostic work-up for patients with a suspected hypertension emergency

Common tests for all potential causes
Fundoscopy is a critical part of the diagnostic work-up
12-lead ECG
Haemoglobin, platelet count, fibrinogen
Creatinine, eGFR, electrolytes, LDH, haptoglobin
Urine albumin:creatinine ratio, urine microscopy for red cells, leucocytes, and casts
Pregnancy test in women of child-bearing age
Specific tests by indication
Troponin, CK-MB (in suspected cardiac involvement, e.g. acute chest pain or acute heart failure) and NT-proBNP
Chest X-ray (fluid overload)
Echocardiography (aortic dissection, heart failure, or ischaemia)
CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
CT or MRI brain (nervous system involvement)
Renal ultrasound (renal impairment or suspected renal artery stenosis)
Urine drug screen (suspected methamphetamine or cocaine use)

CK-MD = creatine kinase-muscle/brain; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B natriuretic peptide.

CT angiography of thorax and/or abdomen in suspected acute aortic disease (e.g. aortic dissection)
CT or MRI brain (nervous system involvement)
Renal ultrasound (renal impairment or suspected renal artery stenosis)
Urine drug screen (suspected methamphetamine or cocaine use)

CK-MD = creatine kinase-muscle/brain; CT = computed tomography; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-B natriuretic peptide.

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Table 26 Hypertensive emergencies requiring immediate BP lowering with i.v. drug therapy

Clinical presentation	Timeline and target for BP reduction	First-line treatment	Alternative
Malignant hypertension with or without acute renal failure	Several hours Reduce MAP by 20–25%	Labetalol Nicardipine	Nitroprusside Urapidil
Hypertensive encephalopathy	Immediately reduce MAP by 20–25%	Labetalol Nicardipine	Nitroprusside
Acute coronary event	Immediate reduce SBP to <140 mmHg	Nitroglycerine Labetalol	Urapidil
Acute cardiogenic pulmonary oedema	Immediately reduce SBP to <140 mmHg	Nitroprusside OR nitroglycerine (with loop diuretic)	Urapidil (with loop diuretic)
Acute aortic dissection	Immediately reduce SBP to <120 mmHg AND heart rate to <60 bpm	Esmolol AND nitroprusside OR nitroglycerine OR nicardipine	Labetalol OR metoprolol
Eclampsia and severe pre-eclampsia/HELLP	Immediately reduce SBP to <160 mmHg AND DBP to <105 mmHg	Labetalol OR nicardipine AND magnesium sulphate	Consider delivery

BP = blood pressure; BPM = beats per minute; DBP = diastolic blood pressure; HELLP = haemolysis, elevated liver enzymes, low platelets; i.v. = intravenous; MAP = mean arterial pressure; SBP = systolic blood pressure.

Hypertensive disorders in pregnancy remain a major cause of maternal, foetal, and neonatal morbidity and mortality.

The definition of hypertension in pregnancy is based on office BP values, SBP ≥140 mmHg and/or DBP ≥90 mmHg. Hypertension in pregnancy is classified as mild (140–159/90–109 mmHg) or severe (≥160/110 mmHg), in contrast to the conventional hypertension grading.

Hypertension in pregnancy is not a single entity but comprises:

- Pre-existing hypertension: precedes pregnancy or develops before 20 weeks of gestation and usually persists for more than 6 weeks post-partum and may be associated with proteinuria.
- Gestational hypertension: develops after 20 weeks of gestation and usually resolves within 6 weeks post-partum.
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- Pre-eclampsia: gestational hypertension with significant proteinuria (>0.3 g/24 h or ≥30 mg/mmol albumin: creatinine ratio). It is more frequent in the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease, or diabetes. The only cure for pre-eclampsia is delivery. Pre-eclampsia should be suspected when hypertension is accompanied by headache, visual disturbances, abdominal pain, or abnormal laboratory tests, specifically low platelets and/or abnormal liver function - proteinuria may be a late manifestation of pre-eclampsia.

Management of hypertension in pregnancy

Recommendations	Class[a]	Level[b]
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension, or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended when SBP is ≥140 or DBP ≥90 mmHg.	I	C
In all other cases, initiation of drug treatment is recommended when SBP is ≥150 mmHg or DBP is ≥95 mmHg.	I	C
Methyldopa, labetalol, and CCBs are recommended as the drugs of choice for the treatment of hypertension in pregnancy	I	B (Methyldopa)
	I	C (Labetalol or CCBs)
ACE-inhibitors, ARBs, or direct renin inhibitors are not recommended during pregnancy.	III	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and admission to hospital is recommended.	I	C
In severe hypertension, drug treatment with i.v. labetalol or oral methyldopa or nifedipine is recommended.	I	C
The recommended treatment for hypertensive crisis is i.v. labetalol or nicardipine and magnesium.	I	C
In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an i.v. infusion is recommended.	I	C
In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks.	I	B
It is recommended to expedite delivery in pre-eclampsia with adverse conditions such as visual disturbances or haemostatic disorders.	I	C

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; DBP = diastolic blood pressure; i.v. = intravenous; SBP = systolic blood pressure.
[a]Class of recommendation - [b]Level of evidence.

Patients with white coat hypertension have an elevated office BP but their BP is normal on home BP monitoring and/or 24hr ABPM. It is most common in patients with grade 1 hypertension on office BP measurement and it is unlikely that home BP or ABPM will be normal in patients with grade 2 hypertension on office BP. White coat hypertension is not benign with the risk intermediate between normotension and sustained hypertension. Routine drug treatment is not indicated for white coat hypertension but lifestyle interventions are recommended. Long term periodic review of these patients is important because many will develop an elevated BP on home BP monitoring or ABPM, which will require drug treatment.

Patients with masked hypertension have an office which appears normal i.e. BP <140/90mmHg but their BP is elevated BP on home BP monitoring or 24hr ABPM. Masked hypertension is more common in patients with a high normal BP on office BP measurement and should be suspected when HMOD is present. These patients are at increased CV risk, equivalent to that in patients with sustained hypertension. These patients should be advised to implement lifestyle changes and drug treatment should be considered because of their increased CV risk, with the aim of normalising their out of office BP levels.

Management of white-coat hypertension

Recommendations	Class[a]	Level[b]
In white-coat hypertensive patients, it is recommended to implement lifestyle changes aimed at reducing CV risk as well as a regular follow-up with periodic out-of-office BP monitoring.	I	C
In patients with white-coat hypertension: • Drug treatment may be considered in people with evidence of HMOD or in whom CV risk is high or very high.	IIb	C
• Routine drug treatment is not indicated.	III	C

BP = blood pressure; CV = cardiovascular; HMOD = hypertension-mediated organ damage.
[a]Class of recommendation - [b]Level of evidence.

Management of masked hypertension

Recommendations	Class[a]	Level[b]
In masked hypertension, lifestyle changes are recommended to reduce CV risk, with regular follow-up, including periodic out-of-office BP monitoring.	I	C
Antihypertensive drug treatment should be considered in masked hypertension to normalize the out-of-office BP based on the prognostic importance of out-of-office BP elevation.	IIa	C
Antihypertensive drug uptitration should be considered in treated patients whose out-of-office BP is not controlled (i.e. masked uncontrolled hypertension), because of the high CV risk of these patients.	IIa	C

BP = blood pressure; CV = cardiovascular.
[a]Class of recommendation - [b]Level of evidence.

The management of hypertension can be influenced by the presence of co-morbidities. The drug treatment algorithms for hypertension associated with various comorbidities are shown in figures 4-8 and the recommended therapeutic strategies for specific comorbidities are listed in next chapters.

Treatment strategies in people with diabetes

Recommendations	Class[a]	Level[b]
Antihypertensive drug treatment is recommended for people with diabetes when office BP is ≥140/90 mmHg.	I	A
In people with diabetes receiving BP-lowering drugs it is recommended: • To target SBP to 130 mmHg and <130 mmHg, if tolerated, but not <120 mmHg.	I	A
• In older people (aged ≥65 years), to target to a SBP range of 130–139 mmHg.	I	A
• To target the DBP to <80 mmHg, but not <70 mmHg.	I	C
It is recommended to initiate treatment with a combination of an RAS blocker with a CCB or thiazide/thiazide-like diuretic.[c]	I	A
Simultaneous administration of two RAS blockers, e.g. and ACE-inhibitor and ARB, is not indicated.	III	A

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; RAS = renin–angiotensin system; SBP = systolic blood pressure. [a]Class of recommendation - [b]Level of evidence - [c]When eGFR <30 mL/min/1.73 m^2, avoid thiazide/thiazide-like diuretics and consider using a loop diuretic when a diuretic is required.

Therapeutic strategies for treatment of hypertension in Chronic Kidney Disease

Recommendations	Class[a]	Level[b]
In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.	I	A
In patients with diabetic or non-diabetic CKD: • It is recommended to lower SBP to a range of 130–139 mmHg.	I	A
• Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.	IIa	C
RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.	I	A
A combination of a RAS blocker with a CCB or a diuretic[c] is recommended as initial therapy.	I	A
A combination of two RAS blockers is not recommended.	III	A

BP = blood pressure; CCB = calcium-channel blocker; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; RAS = renin–angiotensin system; SBP = systolic blood pressure.
[a]Class of recommendation - [b]Level of evidence - [c]In case of eGFR <30 mL/min/1.73 m^2, avoid thiazide/ thiazide like diuretic and consider using a loop diuretic if

Therapeutic strategies in hypertensive patients with coronary artery disease

Recommendations	Class[a]	Level[b]
In patients with CAD receiving BP-lowering drugs, it is recommended: • To target SBP ≤130 mmHg and lower, if tolerated, but not <120 mmHg.	I	A
• In older patients (aged ≥65 years), to target to a SBP range of 130–140 mmHg.	I	A
• To target DBP to <80 mmHg, but not <70 mmHg.	I	C
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment.	I	A
In patients with symptomatic angina, beta-blockers ad/or CCBs are recommended.	I	A

BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; DBP = diastolic
blood pressure; RAS = renin–angiotensin system; SBP = systolic blood pressure
[a]Class of recommendation - [b]Level of evidence.

Therapeutic strategies in hypertensive patients with coronary artery disease

Recommendations	Class[a]	Level[b]
In patients with CAD receiving BP-lowering drugs, it is recommended: • To target SBP ≤130 mmHg and lower, if tolerated, but not <120 mmHg.	I	A
• In older patients (aged ≥65 years), to target to a SBP range of 130–140 mmHg.	I	A
• To target DBP to <80 mmHg, but not <70 mmHg.	I	C
In hypertensive patients with a history of myocardial infarction, beta-blockers and RAS blockers are recommended as part of treatment.	I	A
In patients with symptomatic angina, beta-blockers ad/or CCBs are recommended.	I	A

BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; DBP = diastolic
blood pressure; RAS = renin–angiotensin system; SBP = systolic blood pressure
[a]Class of recommendation - [b]Level of evidence.

Therapeutic strategies in hypertensive patients with heart failure or Left Ventricular Hypertrophy

Recommendations	Class[a]	Level[b]
In hypertensive patients with heart failure (with reduced or preserved ejection fraction), BP-lowering treatment should be considered if BP is ≥140/90 mmHg.	IIa	B
In patients with HFrEF, it is recommended that BP-lowering treatment comprises an ACE-inhibitor or ARB and a beta-blocker and diuretic and/or mineralocorticoid receptor antagonist if required.	I	A
Dihydropyridine CCBs may be added if BP control is not achieved.	IIb	C
In patients with HFpEF, BP-treatment threshold and target values should be the same as for HFrEF.	IIa	B
Because no specific drug has proven its superiority, all major agents can be used.	I	C
In all patients with LVH: • It is recommended to treat with an RAS blocker in combination with a CCB or diuretic.	I	A
• SBP should be lowered to a range of 120–130 mmHg.	IIa	B

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CCB = calcium-channel blocker; HFrEF = heart failure with reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; LVH = left ventricular hypertrophy; RAS = renin–angiotensin system; SBP = systolic blood pressure. [a]Class of recommendation - [b]Level of evidence.

Therapeutic strategies in hypertensive patients with acute stroke and cerebrovascular disease

Recommendations	Class[a]	Level[b]
In patients with acute intracerebral haemorrhage: • Immediate BP lowering is not recommended for patients with SBP <220 mmHg.	III	A
• In patients with SBP ≥220 mmHg, careful acute BP lowering with i.v. therapy, to <180 mmHg should be considered.	IIa	B
In acute ischaemic stroke, routine BP lowering with antihypertensive therapy is not recommended, with the exceptions:	III	A
• In patients with acute ischaemic stroke who are eligible for i.v. thrombolysis, BP should be carefully lowered and maintained to <180/105 mmHg for at least the first 24 h after thrombolysis.	IIa	B
• In patients with markedly elevated BP who do not receive fibrinolysis, drug therapy may be considered, based on clinical judgement, to reduce BP by 15% during the first 24 h after the stroke onset.	IIb	C
In hypertensive patients with an acute cerebrovascular event, antihypertensive treatment is recommended: • Immediately for TIA.	I	A
• After several days in ischaemic stroke.	I	A
In all hypertensive patients with ischaemic stroke or TIA, a SBP target range of 120–130 mmHg should be considered.	IIa	B
The recommended antihypertensive drug treatment strategy for stroke prevention is a RAS blocker plus a CCB or a thiazide-like diuretic.	I	A

BP = blood pressure; CCB = calcium-channel blocker; i.v. = intravenous; RAS = renin–angiotensin system; SBP = systolic blood pressure; TIA = transient ischaemic attack.
[a]Class of recommendation - [b]Level of evidence.

Therapeutic strategies in hypertensive patients with Atrial Fibrillation

Recommendations	Class[a]	Level[b]
In patients with AF, screening for hypertension is recommended.	I	C
A beta-blocker or non-dihydropyridine CCB should be considered as part of the treatment of hypertension if rate control is needed.	IIa	B
Stroke prevention with oral anticoagulation is recommended in patients with AF and hypertension and a CHA2DS2-VASc score of ≥2 in men and ≥3 in women.	I	A
Stroke prevention with oral anticoagulants should be considered in AF patients with hypertension, even when hypertension is the single additional risk factor (CHA2DS2-VASc score of 1).	IIa	B
Oral anticoagulants should be used with caution in patients with marked BP elevation (SBP ≥180 mmHg and/or DBP ≥100 mmHg) and the aim should be to lower SBP to at least <140 mmHg and SBP lowering to <130 should be considered. If this is not possible, then patients should make an informed decision that they accept that the stroke protection provided by the anticoagulant will be associated with higher bleeding risk.	IIa	B

AF = atrial fibrillation; BP = blood pressure; CCB = calcium-channel blocker; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65–74 years, Sex category (female); DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a]Class of recommendation - [b]Level of evidence.

Therapeutic strategies in hypertensive patients with Lower Extremity Arterial Disease

Recommendations	Class[a]	Level[b]
BP-lowering treatment is recommended to reduce CV risk.	I	A
A combination of an RAS blocker, CCB, or diuretic should be considered as initial therapy.	IIa	B
Beta-blockers may also be considered.	IIb	C

BP = blood pressure; CCB = calcium-channel blocker; CV = cardiovascular; LEAD = lower extremity arterial disease; RAS = renin–angiotensin system. [a]Class of recommendation - [b] Level of evidence.

Many patients with hypertension will be at sufficiently increased CV risk to be considered for additional treatment strategies to reduce their CV risk, especially statins and anti-platelet therapy.

Treatment of CV risk factors associated with hypertension

Recommendations	Class[a]	Level[b]
CV risk assessment with the SCORE system is recommended for hypertensive patients who are not already at high or very risk due to established CVD, renal disease, or diabetes.	I	B
For patients at very high CV risk, statins are recommended to achieve LDL-C levels of <1.8 mmol/L (70 mg/dL), or a reduction of ≥50% if the baseline LDL-C is 1.8–3.5 mmol/L (70–135 mg/dL).	I	B
For patients at high CV risk, statins are recommended to achieve an LDL-C goal of <2.6 mmol/L (100 mg/dL) or a reduction of ≥50% if the baseline LDL-C is 2.6–5.2 mmol/L (100–200 mg/dL).	I	B
For patients at low-moderate CV risk, statins should be considered, to achieve an LDL-C value of <3.0 mmol/L (115 mg/dL).	IIa	C
Antiplatelet therapy, in particular low-dose aspirin, is recommended for secondary prevention in hypertensive patients.	I	A
Aspirin is not recommended for primary prevention in hypertensive patients without CVD.	III	A

CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SCORE = Systematic COronary Risk Evaluation.
[a]Class of recommendation - b Level of evidence.

After the initiation of antihypertensive drug therapy, the patient should be reviewed to evaluate the BP control and assess possible adverse effects of treatment. SPC therapy should reduce BP within 1–2 weeks and may continue to reduce BP over the next 2 months. The initial review should be within the first 2 months and the frequency of review will depend on the severity of hypertension, the urgency to achieve BP control, and the patient's comorbidities. Once the BP target is reached, the review visit interval will depend on the need to monitor comorbidities or renal function and will range from 3 to 12 months. Strategies that may help increase adherence to treatment are shown in table 27. These are especially important in patients whose BP is not controlled.

According to local policies and the availability of local health resources, many of the later visits may be performed by nurses or other non-physician health workers. For stable patients, HBPM and electronic communication with the physician may provide an alternative to reduce the frequency of visits. It is advisable to assess risk factors and asymptomatic organ damage at least every 2 years.

Table 27 Interventions that may improve drug adherence in hypertension

Physician level
Provide information on the risks of hypertension and the benefits of treatment, as well as agreeing a treatment strategy to achieve and maintain BP control using lifestyle measures and a single-pill–based treatment strategy when possible (information material, programmed learning, computer-aided counselling)
Empowerment of the patient
Feedback on behavioural and clinical improvements
Assessment and resolution of individual barriers to adherence

Collaboration with other healthcare providers, especially nurses and pharmacists
Patient level
Self-monitoring of BP (including telemonitoring)
Group sessions
Instruction combined with motivational strategies
Self-management with simple patient-guided systems
Use of reminders
Obtain family, social, or nurse support
Provision of drugs at worksite
Drug-treatment level
Simplification of the drug regimen favouring the use of SPC therapy
Reminder packaging
Health-system level
Support the development of monitoring systems (telephone follow-up, home visits, telemonitoring of home BP)
Support financially the collaboration between healthcare providers (pharmacists, nurses)
Reimbursement of SPC pills
Development of national databases, including prescription data, available for physicians and pharmacists
Accessibility to drugs

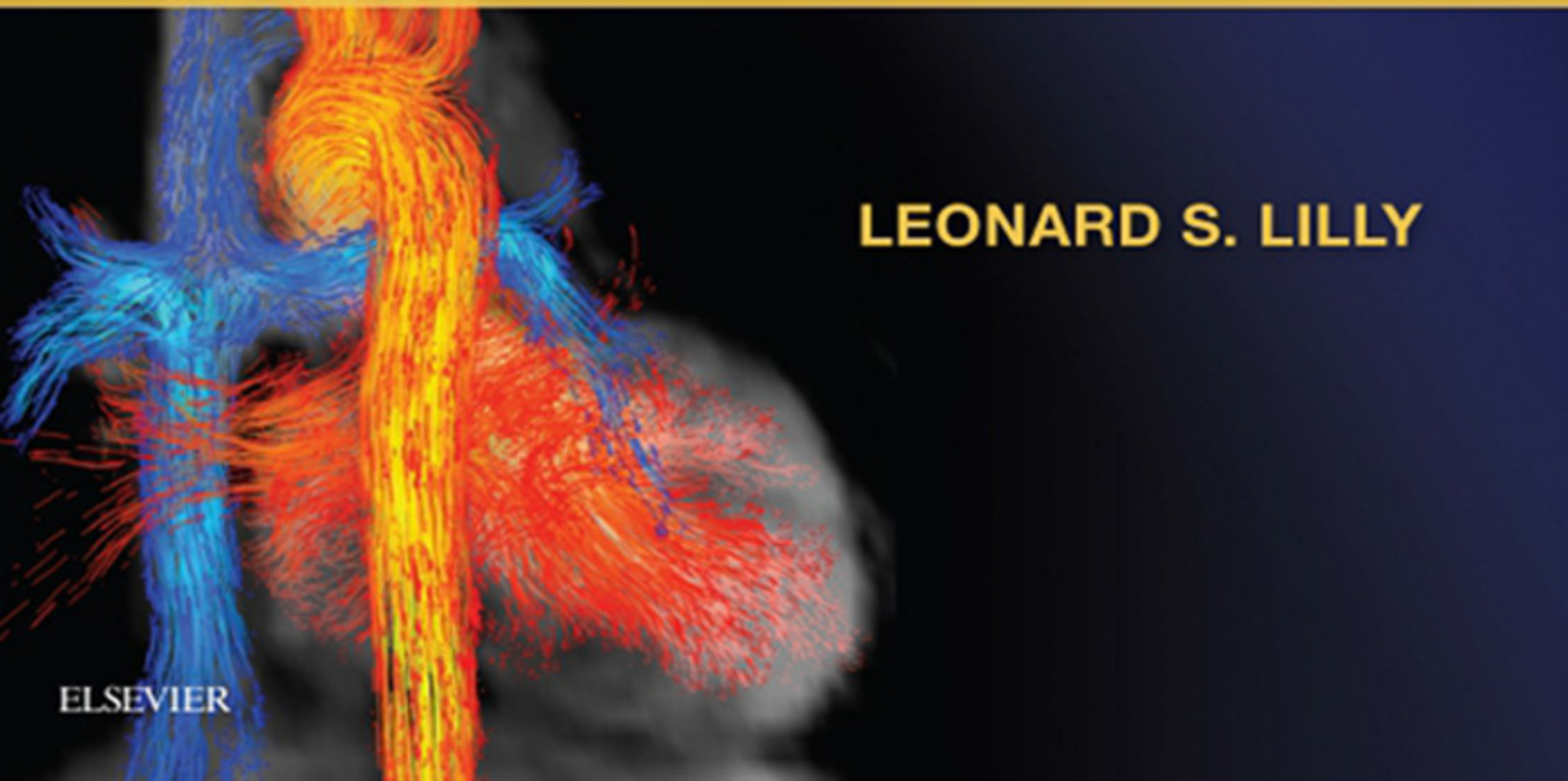
BP = blood pressure; SPC = single-pill combination.

BRAUNWALD'S HEART DISEASE

Z.F

REVIEW AND ASSESSMENT

ELEVENTH EDITION



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BRAUNWALD'S HEART DISEASE

REVIEW AND ASSESSMENT

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BRAUNWALD'S HEART DISEASE

REVIEW AND ASSESSMENT

ELEVENTH EDITION

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BRAUNWALD'S HEART DISEASE REVIEW AND ASSESSMENT, ELEVENTH EDITION

ISBN: 978-0-323-54634-8

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Library of Congress Control Number: 2018951883

Content Strategist: Dolores Meloni
Content Development Specialist: Jennifer S. Ehlers
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Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Preface

Review and Assessment is a comprehensive study guide designed to accompany the 11th edition of *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, edited by Dr. Douglas Zipes, Dr. Peter Libby, Dr. Robert Bonow, Dr. Douglas Mann, and Dr. Gordon Tomaselli. It consists of 706 questions that cover key topics in the broad field of cardiovascular medicine. A detailed answer is provided for each question, often comprising a "mini-review" of the subject matter. Each answer refers to specific pages, tables, and figures in *Braunwald's Heart Disease* and to additional pertinent citations. Topics of greatest clinical relevance are emphasized, and subjects of particular importance are intentionally reiterated in subsequent questions for reinforcement.

Review and Assessment is intended primarily for cardiology fellows, practicing cardiologists, internists, advanced medical residents, and other professionals wishing to review contemporary cardiovascular medicine in detail. The subject matter is suitable to help prepare for the Subspecialty Examination in Cardiovascular Disease offered by the American Board of Internal Medicine.

All questions and answers in this book were designed specifically for this edition of *Review and Assessment.* I am grateful for the contributions by my colleagues at Brigham and Women's Hospital who expertly authored new questions and updated material carried forward from the previous edition: Dr. David Berg, Dr. Brian Bergmark, Dr. Akshay Desai, Dr. Sanjay Divakaran, Dr. Bradley Maron, Dr. Fidencio Saldaña, and Dr. Garrick Stewart. I also acknowledge with appreciation the following colleagues who provided additional material or support to this edition: Dr. Ron Blankstein, Dr. Sharmila Dorbala, Dr. Raymond Kwong, and the Brigham and Women's Hospital team of cardiac ultrasonographers, led by Jose Rivero, who expertly obtained several of the images that appear in this book.

It has been a pleasure to work with the editorial and production departments of our publisher, Elsevier, Inc. Specifically, I thank Ms. Jennifer Ehlers, Ms. Dolores Meloni, Ms. Beula Christopher, and their associates for their expertise and professionalism in the preparation of this edition of *Review and Assessment*. Finally, I am very thankful to my family for their support and patience during the long hours required to prepare this text.

On behalf of the contributors, I hope that you find this book a helpful guide in your review of cardiovascular medicine.

Leonard S. Lilly, MD
Boston, Massachusetts

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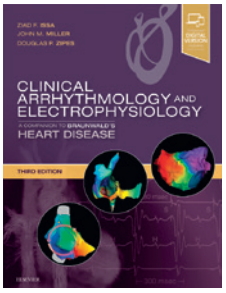
BRAUNWALD'S HEART DISEASE FAMILY OF BOOKS

BRAUNWALD'S HEART DISEASE COMPANIONS



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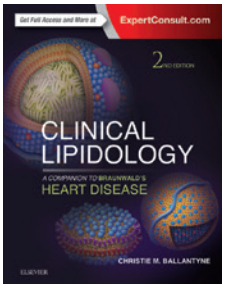

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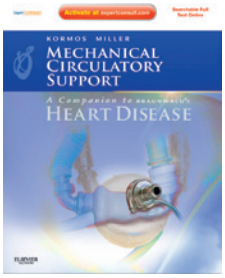

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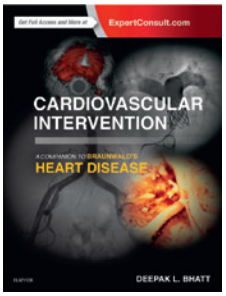

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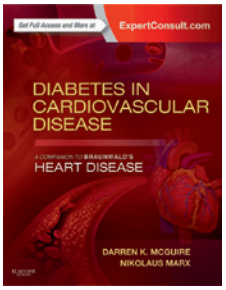

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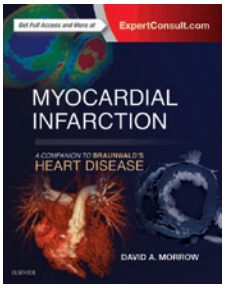

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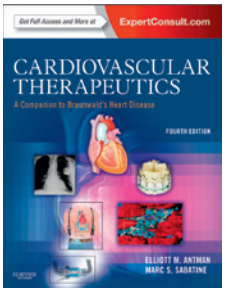

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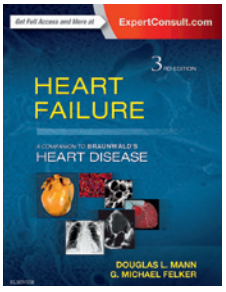

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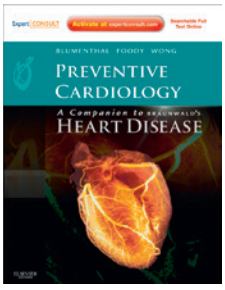

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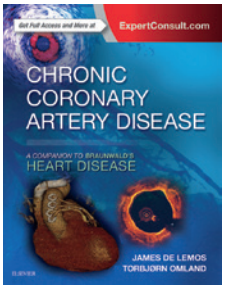

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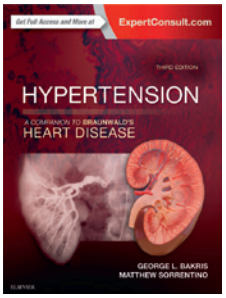

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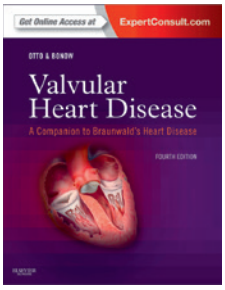

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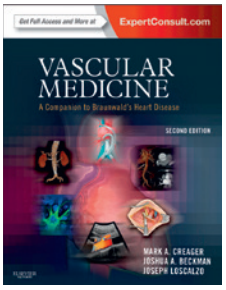

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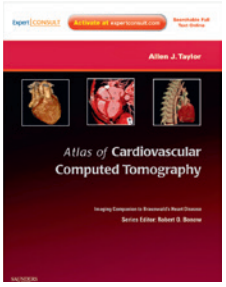

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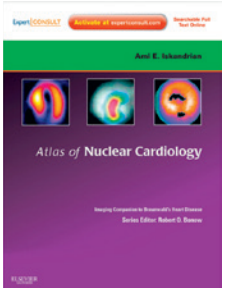

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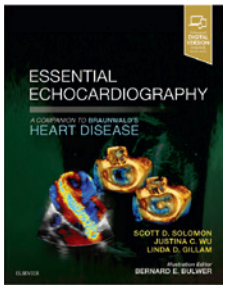

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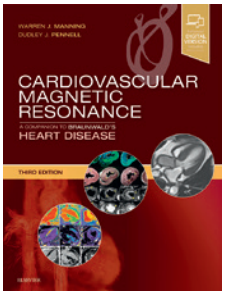

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SECTION I QUESTIONS

(CHAPTERS 1 TO 20)

Fundamentals of Cardiovascular Disease; Genetics and Personalized Medicine; Evaluation of the Patient

Sanjay Divakaran and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 1

A 54-year-old African-American man with a history of hypertension and hypercholesterolemia undergoes a treadmill exercise test using the standard Bruce protocol. He stops at 11 minutes 14 seconds because of fatigue, at a peak heart rate of 152 beats/min and peak systolic blood pressure of 200 mm Hg. The diastolic blood pressure declines by 5 mm Hg during exercise. During recovery, the systolic blood pressure decreases to 15 mm Hg below his preexercise pressure. There are no ischemic changes on the ECG during or after exercise. Which of the following is correct?

A. His peak systolic blood pressure during exercise exceeds that normally observed
B. The change in diastolic blood pressure during exercise is indicative of significant coronary artery disease
C. This test is nondiagnostic owing to an inadequate peak heart rate
D. These results are consistent with a low prognostic risk of a coronary event
E. The postexercise reduction in systolic blood pressure is suggestive of severe coronary artery disease

QUESTION 2

Which of the following statements regarding the second heart sound (S_2) is TRUE?

A. Earlier closure of the pulmonic valve with inspiration results in physiologic splitting of S_2
B. Right bundle branch block results in widened splitting of S_2
C. Paradoxical splitting of S_2 is the auscultatory hallmark of an ostium secundum atrial septal defect
D. Fixed splitting of S_2 is expected in patients with a right ventricular electronically paced rhythm
E. Severe pulmonic valvular stenosis is associated with a loud P_2

QUESTION 3

A state-of-the-art blood test has been developed for the rapid, noninvasive diagnosis of coronary artery disease. The assay has a sensitivity of 90% and a specificity of 90% for the detection of at least one coronary stenosis of >70%. In which of the following scenarios is the blood test likely to be of most value to the clinician?

A. A 29-year-old man with exertional chest pain who has no cardiac risk factors
B. A 41-year-old asymptomatic premenopausal woman
C. A 78-year-old diabetic woman with exertional chest pain who underwent two-vessel coronary stenting 6 weeks ago
D. A 62-year-old man with exertional chest pain who has hypertension, dyslipidemia, and a 2-pack-per-day smoking history
E. A 68-year-old man with chest discomfort at rest accompanied by 2 mm of ST-segment depression in the inferior leads on the ECG

QUESTION 4

A murmur is auscultated during routine examination of an 18-year-old asymptomatic college student, at the second left intercostal space, close to the sternum. The murmur is crescendo-decrescendo, is present throughout systole and diastole, and peaks simultaneously with S_2. It does not change with position or rotation of the head. Which of the following best describes this murmur?

A. This is a continuous murmur, most likely a venous hum commonly heard in adolescents
B. This is a continuous murmur resulting from mixed aortic valve disease
C. This is a continuous murmur due to a congenital shunt, likely a patent ductus arteriosus
D. Continuous murmurs of this type can only be congenital; murmurs due to acquired arteriovenous connections are purely systolic
E. This murmur, the result of left subclavian artery stenosis, is not considered continuous, because a continuous murmur can result only from an arteriovenous communication

QUESTION 5

Unequal upper extremity arterial pulsations are often found in each of the following disorders EXCEPT
A. Aortic dissection
B. Takayasu disease
C. Supravalvular aortic stenosis
D. Subclavian artery atherosclerosis
E. Subvalvular aortic stenosis

QUESTION 6

A 58-year-old woman with metastatic breast cancer presents with exertional dyspnea and is found to have a large circumferential pericardial effusion, jugular venous distention, and hypotension. Which of the following echocardiographic signs is likely present?
A. Collapse of the right ventricle throughout systole
B. Exaggerated decrease in tricuspid inflow velocity during inspiration
C. Exaggerated decrease in mitral inflow velocity during inspiration
D. Exaggerated increase in left ventricular outflow tract velocity during inspiration
E. Markedly increased E/A ratio of the transmitral Doppler velocity profile

QUESTION 7

Which of the following statements about pulsus paradoxus is correct?
A. Inspiration in normal individuals results in a decline of systolic arterial pressure of up to 18 mm Hg
B. Accurate determination of pulsus paradoxus requires intra-arterial pressure measurement
C. Pulsus paradoxus in tamponade is typically accompanied by the Kussmaul sign
D. Pulsus paradoxus is unlikely to be present in patients with significant aortic regurgitation, even in the presence of tamponade
E. Pulsus paradoxus is common in patients with hypertrophic cardiomyopathy

QUESTION 8

A 57-year-old man with a history of hypertension and elevated LDL cholesterol presents to the emergency room with the acute onset of substernal chest pressure, dyspnea, and diaphoresis. His blood pressure is 158/96 mm Hg and the heart rate is 92 beats/min. Physical examination reveals clear lung fields and no cardiac gallop or murmurs. The ECG shows sinus rhythm with a prominent R wave in lead V_2, 0.5 mm of ST elevation in lead III, and 2 mm of horizontal ST depression in leads V_1–V_3. Which of the following would be diagnostically useful to plan a course of action?
A. Repeat the ECG with right-sided precordial leads
B. Repeat the ECG with V_7–V_9 leads
C. Await results of serum cardiac biomarkers
D. Obtain a chest computed tomography (CT) to assess for pulmonary embolism

QUESTION 9

Which of the following combinations does NOT have the potential for significant pharmacologic interaction?
A. Simvastatin and erythromycin
B. Sildenafil and nitroglycerin
C. Pravastatin and ketoconazole
D. Cyclosporine and St. John's wort
E. Digoxin and verapamil

QUESTION 10

It would be reasonable and safe to order an exercise stress test for a patient with which of the following conditions?
A. Symptomatic hypertrophic obstructive cardiomyopathy
B. Advanced aortic stenosis
C. Acute myocarditis
D. Abdominal aortic aneurysm with transverse diameter of 5.5 cm
E. Unstable angina

QUESTION 11

A 42-year-old woman with hypertension and dyslipidemia underwent a 1-day rest-stress exercise myocardial perfusion single-photon emission computed tomography (SPECT) study with technetium-99m imaging to evaluate symptoms of "atypical" chest pain. Her resting ECG showed left ventricular hypertrophy. She exercised for 12 minutes 30 seconds on the standard Bruce protocol and attained a peak heart rate of 155 beats/min. She developed a brief sharp parasternal chest pain during the test that resolved quickly during recovery. Based on the images in Fig. 1.1, which of the following statements is correct?
A. The SPECT myocardial perfusion images are diagnostic of transmural myocardial scar in the distribution of the mid–left anterior descending coronary artery
B. The anterior wall defect on the SPECT images is likely an artifact due to breast tissue attenuation
C. Thallium-201 would have been a better choice of radiotracer to image this patient
D. Gated SPECT imaging cannot differentiate attenuation artifacts from a true perfusion defect
E. A transmural scar is associated with reduced wall motion but normal wall thickening on gated SPECT imaging

QUESTION 12

A 62-year-old man is noted to have an extra heart sound shortly after S_2. Which of the following is NOT a possible cause of that sound?
A. Opening snap
B. Third heart sound
C. Ejection click
D. Tumor plop
E. Pericardial knock

QUESTION 13

A 56-year-old asymptomatic man with a history of hypertension and cigarette smoking is referred for an exercise treadmill test. After 7 minutes on the standard Bruce protocol, he is noted to have 1 mm of flat ST-segment depression in leads II, III, and aVF. He stops exercising at 9 minutes because of leg fatigue and breathlessness. The peak heart rate is 85% of the maximum predicted for his age. The ST segments return to baseline by 1 minute into recovery. Which of the following statements is correct?

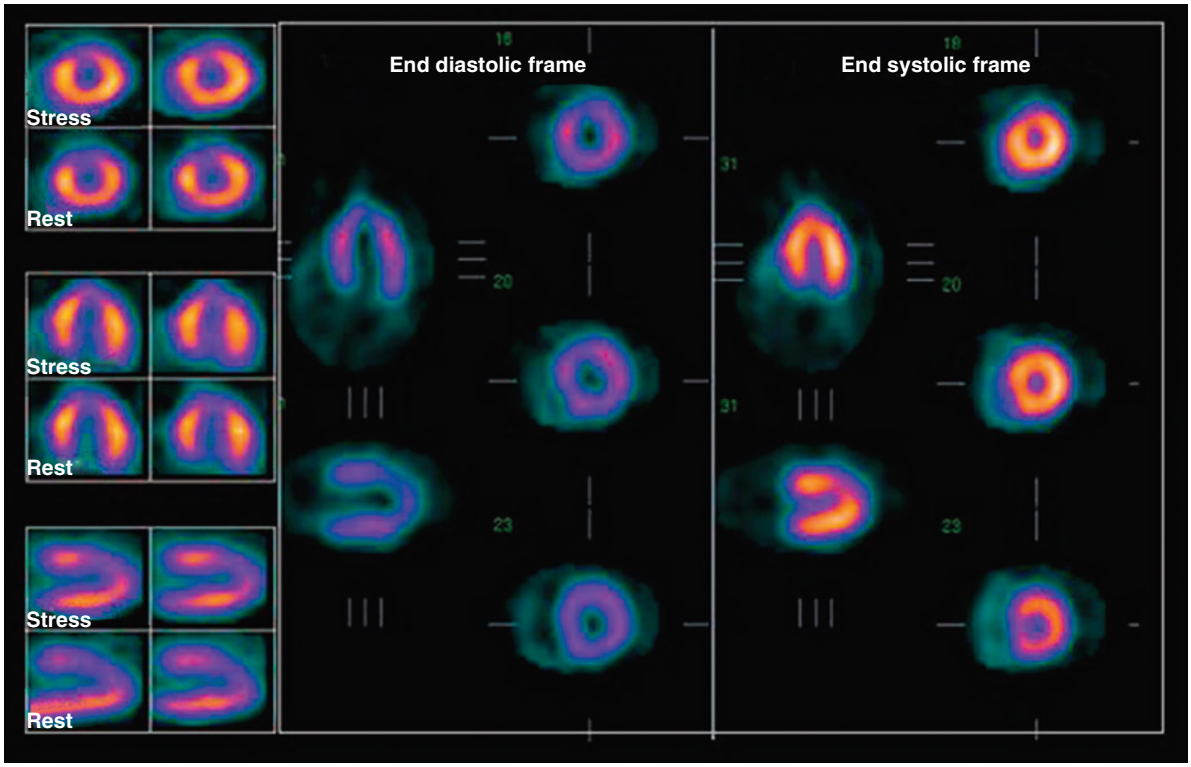


FIG. 1.1

A. This test is conclusive for severe stenosis of the proximal right coronary artery
B. His risk of death due to an acute myocardial infarction during the next year is >50%
C. He should proceed directly to coronary angiography
D. The test predicts a 25% risk of cardiac events over the next 5 years, most likely the development of angina
E. This is likely a false-positive test

QUESTION 14

In which of the following clinical scenarios do ST-segment depressions during standard exercise testing increase the diagnostic probability of significant coronary artery disease?
A. A 56-year-old man with left bundle branch block and a family history of premature coronary disease
B. A 45-year-old woman with diabetes and hypertension, with left ventricular hypertrophy on her baseline ECG
C. A 76-year-old woman with new exertional dyspnea, a history of cigarette smoking, and a normal baseline ECG
D. A 28-year-old woman with pleuritic left-sided chest pain after a gymnastics class
E. A 63-year-old man with exertional dyspnea on beta blocker, digoxin, and nitrate therapies

QUESTION 15

Which of the following statements regarding cardiac catheterization is TRUE?
A. The risk of a major complication from cardiac catheterization is 2.0% to 2.5%
B. The incidence of contrast-induced nephrotoxicity in patients with renal dysfunction is decreased with intravenous administration of mannitol before and after the procedure
C. High osmolar nonionic contrast agents demonstrate a reduced incidence of adverse hemodynamic reactions compared with low osmolar ionic contrast agents
D. One French unit (F), a measurement of catheter diameter, is equivalent to 0.33 mm
E. Retrograde left-sided heart catheterization is generally a safe procedure in patients with tilting-disc prosthetic aortic valves

QUESTION 16

A 75-year-old woman was brought urgently to the cardiac catheterization laboratory in the setting of an acute ST-elevation myocardial infarction. She had presented with chest pain, epigastric discomfort, and nausea. Physical examination was pertinent for diaphoresis, heart rate 52 beats/min, blood pressure 85/50 mm Hg, jugular venous distention, and slight bilateral pulmonary rales. Coronary angiography demonstrated ostial occlusion of a dominant right coronary artery, without significant left-sided coronary artery disease. Which of the following statements is correct?
A. Isolated infarction of the right ventricle, without left ventricular involvement, is likely
B. ST-segment elevation in leads V_1 and V_2 would be expected to accompany inferior ST elevation
C. The abnormal heart rate and blood pressure are likely a consequence of vagal stimulation
D. ST-segment depression is expected in lead V_4R

QUESTION 17

Using Doppler echocardiography, the following values are obtained in a patient with a restrictive ventricular septal defect (VSD) and mitral regurgitation: systolic transmitral

flow velocity = 5.8 m/s and systolic flow velocity at the site of the VSD = 5.1 m/s. The patient's blood pressure is 144/78 mm Hg. The estimated right ventricular systolic pressure is (choose the single best answer)

A. 20 mm Hg
B. 30 mm Hg
C. 40 mm Hg
D. 50 mm Hg
E. Not able to be determined from the provided information

QUESTION 18

A 68-year-old woman with a history of diabetes and cigarette smoking and previously normal cardiac examination is admitted to the hospital with the new onset of shortness of breath with exertion and orthopnea. She describes having experienced a "muscle ache" in her anterior chest 10 days earlier that lasted several hours and has not recurred. Her blood pressure is 109/88 mm Hg, the heart rate is 102 beats/min, and she is afebrile. Her examination reveals an elevated jugular venous pressure (JVP), bibasilar crackles, and 1+ pitting edema of both ankles. On auscultation, there is a II/VI early systolic murmur between the left sternal border and apex. The ECG reveals sinus tachycardia with inferior Q waves that were not present on a tracing 6 months earlier. The chest x-ray is consistent with pulmonary edema. She is admitted to the hospital and a transthoracic echocardiogram is obtained that is technically limited due to her body habitus. It reveals a left ventricular ejection fraction of 60% with inferior wall hypokinesis. The mitral valve is not well visualized but appears thickened and there is an anteriorly directed jet of mitral regurgitation that is difficult to quantitate. A diuretic is administered.

Which of the following is the next most reasonable approach in her management?

A. Urgent coronary angiography with planned percutaneous coronary intervention
B. Nuclear stress testing to evaluate for ongoing ischemia
C. Transesophageal echocardiography and surgical consultation
D. Initiate long-term management with aspirin, angiotensin-converting enzyme (ACE) inhibitor, and beta blocker therapies
E. Urgent right heart catheterization to evaluate for a left-to-right shunt

QUESTION 19

Which of the following statements regarding altered electrolytes and electrocardiographic abnormalities is TRUE?

A. Hypokalemia causes peaked T waves
B. Hyperkalemia causes QRS narrowing and increased P wave amplitude
C. Hypomagnesemia is associated with monomorphic ventricular tachycardia
D. Hypocalcemia causes prolongation of the QT interval
E. Severe hypocalcemia has been associated with the presence of a J wave (Osborn wave)

QUESTION 20

A 46-year-old woman with progressive exertional dyspnea was recently found to have bilateral hilar adenopathy on chest x-ray and first-degree atrioventricular (AV) block on her ECG. A transbronchial biopsy demonstrated noncaseating granulomas consistent with sarcoidosis and she is referred to you for assessment of cardiac involvement. Which of the following statements is TRUE regarding the diagnostic evaluation of cardiac sarcoidosis?

A. Left ventricular regional wall motion abnormalities in sarcoidosis are typically present in coronary distributions
B. An elevated serum angiotensin-converting enzyme level has low sensitivity, but high specificity, for the diagnosis of sarcoidosis
C. Sarcoid-associated late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging is usually localized to the endocardial border
D. CMR is not useful in the assessment of clinically silent cardiac sarcoidosis
E. ^{18}F-fluorodeoxyglucose (FDG) uptake on cardiac positron emission tomography (PET) differentiates active cardiac sarcoidosis from inactive scar tissue

QUESTION 21

Which of the following statements about the ECG depicted in Fig. 1.2 is correct?

A. The basic rhythm is wandering atrial pacemaker
B. The fifth QRS complex on the tracing is likely a premature ventricular beat
C. The Ashman phenomenon is present and it occurs because the refractory period is directly related to the length of the preceding RR interval
D. The bundle of His is the likely anatomic location of conduction delay in the fifth beat because it has the longest refractory period of conduction tissue

QUESTION 22

The timing of an "innocent" murmur is usually

A. Early systolic
B. Presystolic
C. Midsystolic
D. Holosystolic
E. Early diastolic

FIG. 1.2 *From Marriott HJL.* Rhythm Quizlets: Self Assessment. *Philadelphia: Lea & Febiger; 1987:14.*

QUESTION 23

Which of the following statements about the jugular venous wave form is correct?

A. The Kussmaul sign is pathognomonic for constrictive pericarditis
B. The *c* wave is a reflection of ventricular diastole and becomes visible in patients with diastolic dysfunction
C. The *x* descent is less prominent than the *y* descent in cardiac tamponade
D. Phasic declines in venous pressure (the *x* and *y* descents) are typically more prominent to the eye than the positive pressure waves (the *a*, *c*, and *v* waves)
E. Cannon *a* waves indicate intraventricular conduction delay

QUESTION 24

Which of the following statements regarding the measurement of cardiac output is correct?

A. In the thermodilution method, cardiac output is directly related to the area under the thermodilution curve
B. The thermodilution method tends to underestimate cardiac output in low-output states
C. In the presence of tricuspid regurgitation, the thermodilution method is preferred over the Fick technique for measuring cardiac output
D. A limitation of the Fick method is the necessity of measuring oxygen consumption in a steady state
E. Cardiac output is directly proportional to systemic vascular resistance

QUESTION 25

Which of the following conditions is associated with the Doppler transmitral inflow pattern shown in Fig. 1.3?

A. Gastrointestinal hemorrhage
B. Constrictive pericarditis
C. Normal aging
D. Restrictive cardiomyopathy
E. Hyperthyroidism

QUESTION 26

A 32-year-old woman, a native of India, is referred by her primary care physician for further evaluation of dyspnea on exertion. On examination, both an opening snap and mid-diastolic rumble are appreciated at the apex. An echocardiogram is obtained. Which of the following CANNOT be assessed from the transmitral Doppler tracing shown in Fig. 1.4?

A. The presence and severity of mitral stenosis
B. The presence of mitral regurgitation
C. The transmitral diastolic pressure gradient
D. The etiology of the valvular lesion
E. The mitral valve area

QUESTION 27

A 37-year-old woman with no significant past medical history presents to the emergency department with acute shortness of breath and pleuritic chest pain. Her only medication is an oral contraceptive. Her examination is notable for sinus tachycardia. A chest computed tomography (CT) shows subsegmental pulmonary emboli, and she is started on anticoagulation therapy. An echocardiogram is performed, which demonstrates the McConnell sign as well as mild tricuspid regurgitation with the following values:

Peak systolic velocity across the tricuspid valve = 3 m/s
Inferior vena cava (IVC) diameter = 1.9 cm with <50% collapse with inspiration

Which of the following statements is correct?

A. The McConnell sign refers to localized dyskinesis of the right ventricular apex in patients with acute pulmonary embolism
B. The Kussmaul sign may result from acute pulmonary embolism
C. This patient's estimated pulmonary artery systolic pressure is 64 mm Hg
D. This patient's right atrial pressure should be estimated as ~15 mm Hg

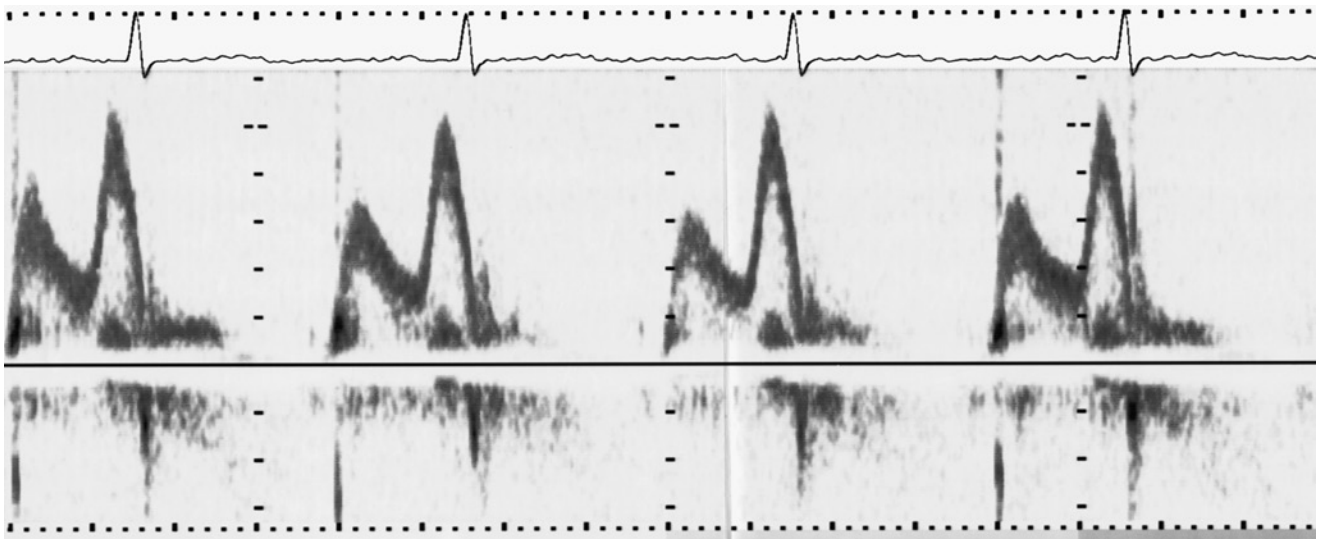


FIG. 1.3

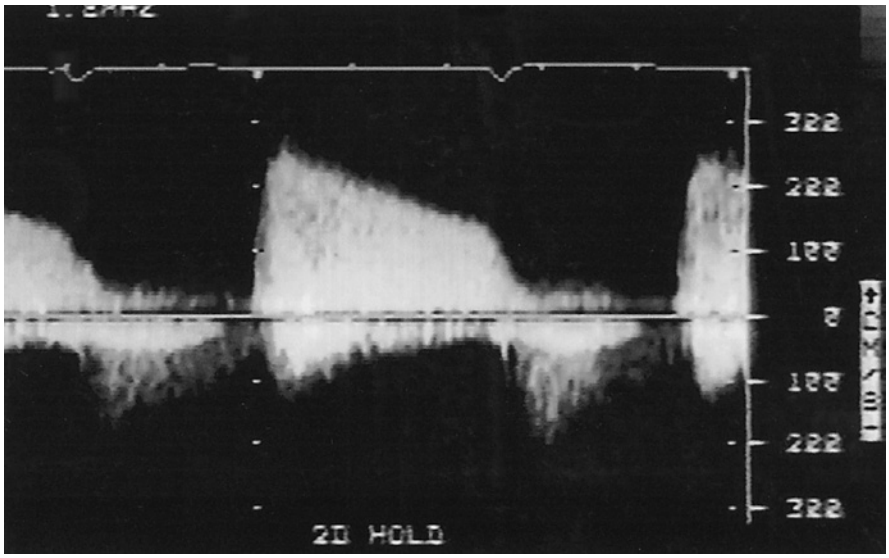


FIG. 1.4

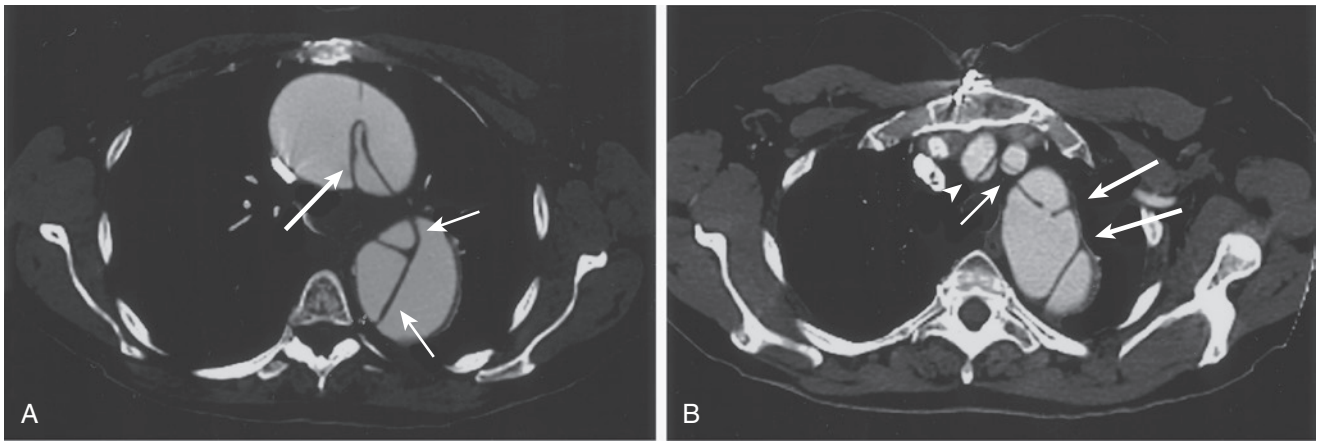


FIG. 1.5 *Courtesy of RC Gilkeson, MD, Case Western Reserve University, Cleveland, OH.*

QUESTION 28

Which of the following statements is TRUE regarding the response of healthy older adults to aerobic exercise?

A. Ventricular stroke volume decreases with age such that there is an age-related fall in cardiac output during exercise
B. Systolic and diastolic blood pressures each rise significantly during aerobic exercise
C. A decline in beta-adrenergic responsiveness contributes to a fall in the maximum heart rate in older individuals
D. A normal adult's cardiac output doubles during maximum aerobic exercise
E. Maximum aerobic capacity does not change significantly with age in sedentary individuals

QUESTION 29

Physiologic states and dynamic maneuvers alter the characteristics of heart murmurs. Which of the following statements is correct?

A. In acute mitral regurgitation, the left atrial pressure rises dramatically so that the murmur is heard only during late systole
B. Rising from a squatting to a standing position causes the murmur of mitral valve prolapse to begin later in systole
C. The diastolic rumble of mitral stenosis becomes more prominent during the strain phase of a Valsalva maneuver
D. The murmur of aortic stenosis, but not mitral regurgitation, becomes louder during the beat after a premature ventricular contraction
E. The murmur of acute aortic regurgitation can usually be heard throughout diastole

QUESTION 30

Which of the following statements regarding the computed tomograms of the chest shown in Fig. 1.5 is TRUE?

A. The patient's disorder should be managed medically, with surgical intervention considered only if there is evidence of secondary organ involvement
B. The left common carotid artery is spared by this process
C. The sensitivity of computed tomography for the diagnosis of this condition is >95%
D. Fewer than 50% of patients with this condition will report chest pain
E. Transesophageal echocardiography is necessary to confirm the diagnosis

QUESTION 31

Which of the following statements regarding ST-segment changes during exercise testing is TRUE?

A. The electrocardiographic localization of ST-segment depression predicts the anatomic territory of coronary obstructive disease
B. The J point is the proper isoelectric reference point on the ECG
C. J point depression during exercise is diagnostic for significant cardiac ischemia
D. Persistence of ST-segment depression for 60 to 80 milliseconds after the J point is necessary to interpret the electrocardiographic response as abnormal
E. ST-segment depression must be present both during exercise and in recovery to be interpreted as abnormal

QUESTION 32

An ECG is obtained as part of the routine preoperative evaluation of an asymptomatic 45-year-old man scheduled to undergo wrist surgery. The tracing is shown in Fig. 1.6 and is consistent with

A. Right ventricular hypertrophy
B. Left posterior fascicular block
C. Reversal of limb lead placement
D. Left anterior fascicular block and counterclockwise rotation
E. Dextrocardia with situs inversus

QUESTION 33

Which of the following statements is correct regarding exercise test protocols?

A. Regardless of the exercise protocol, the heart rate and systolic and diastolic blood pressures all must increase substantially to achieve a valid test
B. Bicycle, treadmill, and arm ergometry protocols all produce approximately equal heart rate and blood pressure responses
C. The standard Bruce protocol is characterized by only small increases in oxygen consumption between stages
D. A fall in systolic blood pressure during exercise is associated with severe coronary artery disease
E. An optimal graded treadmill exercise test rarely requires more than 5 minutes of exercise on the Bruce protocol

QUESTION 34

Which of the following patients is LEAST likely to have a cardiac cause of his/her recent onset of dyspnea?

A. An active 54-year-old man with a congenitally bicuspid aortic valve who has recently noticed shortness of breath walking his usual 18 holes of golf
B. A 70-year-old woman who sustained an anterior myocardial infarction 1 year ago with a left ventricular ejection fraction of 50% at that time. She has not had recurrent angina but has noted dyspnea during her usual housework over the past 2 months
C. A 46-year-old woman with a history of asymptomatic rheumatic mitral stenosis who recently noticed irregular palpitations and shortness of breath while climbing stairs
D. A 38-year-old woman with a previously asymptomatic ostium secundum atrial septal defect, now 8 months pregnant, who has noted shortness of breath during her usual weekly low-impact aerobics class
E. A 22-year-old man with trisomy 21 and a heart murmur who has described shortness of breath carrying grocery bundles over the past 3 months

QUESTION 35

A 68-year-old man with a history of diabetes, hypertension, and hyperlipidemia is transported to the hospital via ambulance, complaining of crushing substernal chest pain. Emergency medical services personnel report that ST segments are >2 mm elevated in multiple anterior leads. Which of the following electrocardiographic findings is LEAST likely in this patient?

A. Hyperacute T waves in the precordial leads
B. ST-segment depression in leads III and aVF
C. Shortened QT interval
D. New right bundle branch block

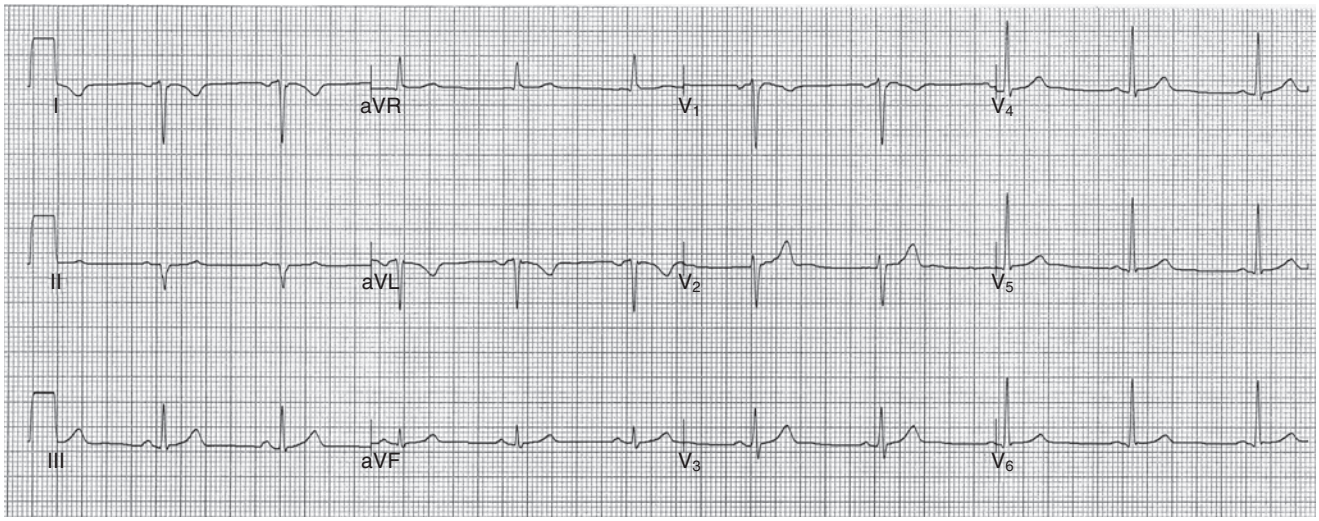


FIG. 1.6

QUESTION 36

Which of the following statements regarding nuclear imaging and acute myocardial infarction (MI) is TRUE?

A. The size of the resting myocardial perfusion defect after acute MI does not correlate with the patient's prognosis
B. Increased lung uptake of radioisotope at rest correlates with a favorable prognosis
C. Submaximal exercise imaging soon after MI is a better predictor of late complications than adenosine myocardial perfusion imaging
D. Technetium-99m sestamibi imaging is inaccurate in assessing the effectiveness of reperfusion therapy
E. Measuring infarct size by technetium-99m sestamibi imaging before discharge from the hospital is a reliable way to predict subsequent ventricular remodeling

QUESTION 37

A 61-year-old man presents for a treadmill exercise test because of intermittent chest pain. He believes he had a "small heart attack" in the past. He has a history of prior tobacco use and his father died of a myocardial infarction at age 68. His baseline ECG shows normal sinus rhythm with Q waves in the inferior leads. At 6 minutes into the Bruce protocol he develops mild anterior chest heaviness and the ECG demonstrates ST elevation in leads I, aVL, V_5, and V_6. Which of the following statements regarding ST-segment elevation during exercise testing is correct?

A. ST-segment elevation during exercise testing is a common finding in patients with coronary artery disease
B. ST-segment elevation in a lead that contains a pathologic Q wave at baseline indicates severe myocardial ischemia
C. The electrocardiographic leads that manifest ST-segment elevation during exercise localize the anatomic regions of ischemia
D. ST-segment elevation that develops during exercise is usually a manifestation of benign early repolarization
E. ST-segment elevation during exercise is commonly associated with the development of complete heart block

QUESTION 38

Which of the following statements regarding coronary calcium assessment by electron beam tomography (EBT) is TRUE?

A. The amount of calcium on EBT strongly correlates with the severity of coronary disease detected by angiography
B. Patients who benefit most from screening with EBT are those at a high risk for coronary events based on traditional risk factors
C. The absence of coronary calcium completely excludes the presence of severe obstructive coronary artery stenosis
D. Interpretation of the calcium score is independent of the patient's age and gender
E. A coronary calcium score higher than the median confers an increased risk of myocardial infarction and death

QUESTION 39

Which of the following statements is TRUE regarding prognosis as determined by myocardial perfusion imaging?

A. Patients with normal perfusion in the presence of angiographically documented coronary artery disease have very low rates of cardiac events (<1% per year)
B. Thallium imaging results in less breast attenuation artifact compared with technetium-99m sestamibi
C. Transient ischemic dilatation of the left ventricle and lung uptake of the nuclear tracer are common findings in normal individuals
D. The combination of clinical and cardiac catheterization data is more predictive of subsequent cardiac events than the combination of clinical and myocardial perfusion data
E. The risk of future cardiac events is unrelated to the number or extent of myocardial perfusion defects

QUESTION 40

A previously healthy 28-year-old man presented to the hospital because of 1 month of progressive exertional dyspnea, weakness, and weight loss. One day before hospitalization he was unable to climb one flight of stairs because of shortness of breath. On examination, he appeared fatigued with mild respiratory distress. His blood pressure was 110/70 mm Hg without pulsus paradoxus. His heart rate was 110 beats/min and regular. The jugular veins were distended without the Kussmaul sign. Pulmonary auscultation revealed scant bibasilar rales. The heart sounds were distant. There was mild bilateral ankle edema. As part of the evaluation during hospitalization, he underwent cardiac magnetic resonance imaging. A short-axis view at the midventricular level is shown in Fig. 1.7. Which of the following is the most likely diagnosis?

A. Pericardial malignancy
B. Chronic organized pericardial hematoma
C. Constrictive pericarditis
D. Extracardiac tumor compression of the heart
E. Congenital partial absence of the pericardium with cardiac herniation

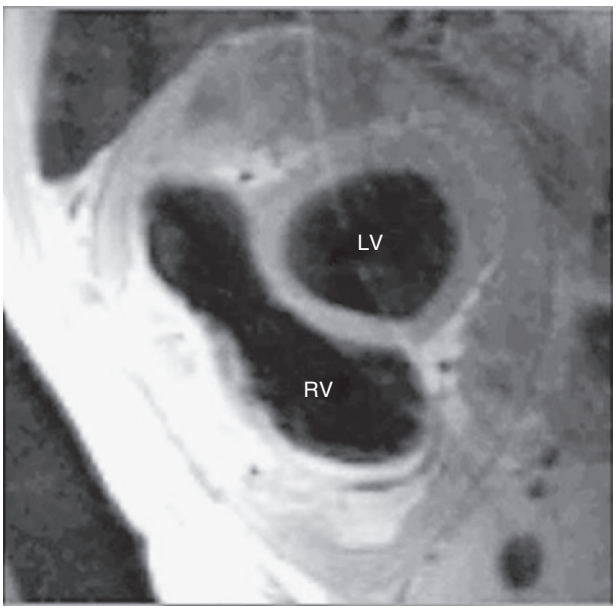


FIG. 1.7

QUESTION 41

Which of the following statements regarding intracardiac shunts is correct?

A. A left-to-right shunt should be suspected if the difference in oxygen saturation between the superior vena cava (SVC) and the pulmonary artery is 3% or more
B. Oxygen saturation in the SVC is normally higher than that in the inferior vena cava (IVC)
C. In a suspected atrial septal defect with left-to-right flow, mixed venous O_2 content should be measured at the level of the pulmonary artery
D. A pulmonic-to-systemic blood flow ratio (Q_p/Q_s) >1 indicates a net right-to-left shunt
E. Pulmonary artery oxygen saturation exceeding 80% should raise the suspicion of a left-to-right shunt

QUESTION 42

A 46-year-old man with dyspnea on exertion is noted to have a systolic ejection murmur along the left sternal border. An echocardiogram is obtained. Fig. 1.8 shows Doppler pulsed-wave interrogation of the left ventricular outflow tract, recorded from the apex. Which of the following recommendations would be most appropriate?

A. Strict fluid restriction
B. Avoid volume depletion
C. Aortic valve replacement
D. Bed rest

QUESTION 43

Which of the following statements regarding echocardiography in pericardial disease is correct?

A. Small pericardial effusions tend to accumulate anterior to the heart
B. Up to 100 mL of pericardial fluid is present in normal individuals
C. In cardiac tamponade, right ventricular diastolic collapse occurs less frequently if pulmonary hypertension is present
D. In the presence of a pericardial effusion, right atrial diastolic indentation is a more specific sign of cardiac tamponade than early diastolic collapse of the right ventricle
E. Transthoracic echocardiography is superior to chest computed tomography as a means to accurately measure pericardial thickness

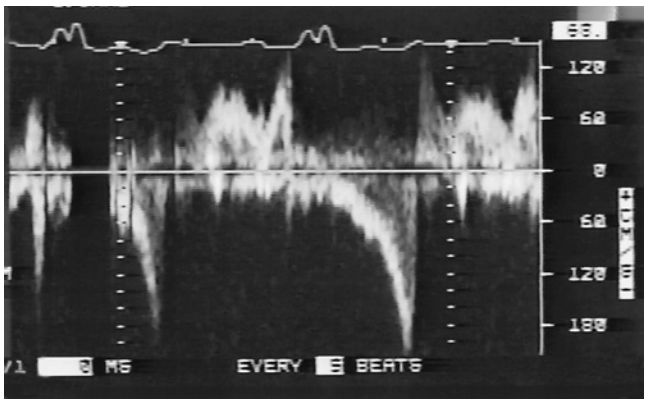


FIG. 1.8

QUESTION 44

Which of the following statements regarding nuclear imaging in cardiac disease is TRUE?

A. The use of single-photon emission computed tomography (SPECT) with electrocardiographic gating has no impact on the specificity of nuclear testing in women with attenuation artifacts
B. Exercise nuclear stress imaging, rather than pharmacologic stress testing, is the preferred diagnostic modality for patients with left bundle branch block
C. The presence of reversible defects on pharmacologic stress perfusion imaging before noncardiac surgery predicts an increased risk of perioperative cardiac events, but the magnitude of risk is not related to the extent of ischemia
D. Cardiovascular event rates are similar in diabetics compared with nondiabetics for any given myocardial perfusion abnormality
E. Viability of noncontracting myocardium can be accurately evaluated by thallium-201 imaging

QUESTION 45

A 45-year-old woman was referred for exercise echocardiography because of a history of intermittent chest pain. She has a strong family history of premature coronary artery disease but no other atherosclerotic risk factors. The exercise echocardiogram achieved the desired heart rate goal and demonstrated a focal wall motion abnormality of the left ventricular anterior wall at rest, which was unchanged at maximum exercise. A subsequent cardiac magnetic resonance study was performed to characterize the myocardial tissue in that region. A delayed image taken after intravenous administration of gadolinium is shown in Fig. 1.9. What is the most likely cause of the anterior wall motion abnormality?

A. Transient myocardial ischemia due to a significant coronary artery stenosis
B. Prior myocardial infarction
C. Myocarditis
D. Infiltrative cardiomyopathy
E. Breast attenuation artifact

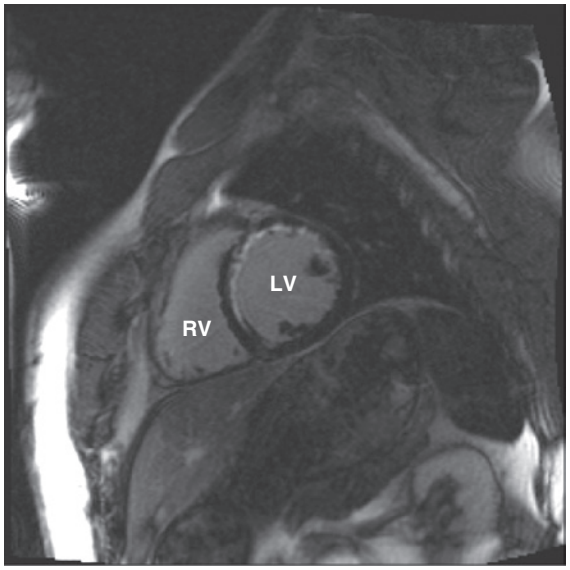


FIG. 1.9

QUESTION 46

Which of the following statements concerning the echocardiographic evaluation of aortic stenosis is TRUE?

A. The peak-to-peak gradient measured at cardiac catheterization routinely exceeds the peak instantaneous aortic valve pressure gradient assessed by Doppler echocardiography
B. Patients with impaired left ventricular function may have severe aortic stenosis, as determined by the continuity equation, despite a peak outflow velocity of only 2 to 3 m/s
C. Among Doppler techniques, the most accurate transaortic valve flow velocity in aortic stenosis is measured by pulsed-wave Doppler imaging
D. The greatest degree of error in the calculation of aortic valve area using the continuity equation resides in inaccurate measurement of the transaortic valve flow velocity
E. The mean aortic valve gradient measured by Doppler echocardiography is typically higher than the mean gradient measured by cardiac catheterization

QUESTION 47

Which of the following statements regarding the assessment for intracardiac shunts during cardiac catheterization is correct?

A. In normal subjects, there should be no difference in O_2 content in different portions of the right atrium
B. Atrial septal defect, anomalous pulmonary venous drainage, and ruptured sinus of Valsalva aneurysm all are associated with a significant step-up in O_2 saturation between the right atrium and the right ventricle
C. Because of the normal variability in O_2 saturation, shunts with pulmonary-to-systemic flow ratios (Q_p/Q_s) ≤1.3 at the level of the pulmonary artery or right ventricle may escape detection by oximetry run analyses
D. When a shunt is bidirectional, its magnitude can be calculated as the difference between the pulmonary and systemic blood flows ($Q_p - Q_s$) as determined using the Fick equation
E. In patients with a pure right-to-left shunt, the Q_p/Q_s ratio should be >1.0

QUESTION 48

Which of the following findings during an exercise test is NOT associated with multivessel (or left main) coronary artery disease?

A. Early onset of ST-segment depression
B. Persistence of ST-segment changes late into the recovery phase
C. ST-segment elevation in lead aVR
D. Sustained ventricular tachycardia
E. Failure to increase systolic blood pressure by at least 10 mm Hg

QUESTION 49

Which of the following statements regarding the auscultatory findings in aortic stenosis is TRUE?

A. Initial squatting decreases the intensity of the murmur
B. The murmur is increased in intensity during the strain phase of the Valsalva maneuver
C. In patients with premature ventricular contractions, aortic stenosis can be differentiated from mitral regurgitation because there is beat-to-beat variation in the intensity of the aortic stenosis murmur while the intensity of the mitral regurgitation remains constant
D. Respiration typically has a prominent effect on the intensity of the murmur

QUESTION 50

A 59-year-old business executive presents because of episodes of retrosternal chest discomfort that does not radiate. It is an aching, burning sensation, occurring most frequently at night, occasionally awakening the patient shortly after he has fallen asleep. It does not occur while walking or climbing stairs. His internist prescribed nitroglycerin, which he has taken infrequently. However, it does relieve his pain, usually within 10 to 20 minutes. The previous day during a luncheon meeting he had a severe episode while presenting a new financial plan; the discomfort seemed to lessen when he sat down and finished lunch. The most likely explanation for his chest discomfort is

A. Prinzmetal angina
B. Esophageal reflux and spasm
C. Pericarditis
D. Unstable angina pectoris
E. Biliary colic

QUESTION 51

A 44-year-old man with diabetes and a strong family history of premature coronary artery disease underwent cardiac evaluation because of episodes of exertional substernal chest pressure. His resting ECG demonstrated normal sinus rhythm and borderline left ventricular hypertrophy. During exercise myocardial perfusion imaging, he developed his typical chest discomfort and stopped at 03:20 minutes of the standard Bruce protocol, at a peak heart rate of 105 beats/min (60% of his age-predicted maximal heart rate). The systolic blood pressure decreased by 20 mm Hg at peak exercise. Based on the myocardial perfusion images in Fig. 1.10, which of the following statements is TRUE?

A. There is no evidence of reversible ischemia
B. Transient dilatation of the left ventricle after exercise stress is absent
C. The increased lung uptake of the radiotracer evident on stress imaging is a normal physiologic response
D. There is increased right ventricular tracer uptake on the post-stress images, which is a specific marker of multivessel or left main coronary disease
E. The test results are inconclusive owing to failure to achieve the target heart rate

QUESTION 52

Which of the following statements about the transaortic valve Doppler flow tracing shown in Fig. 1.11 is TRUE?

A. The probability of critical aortic stenosis in this patient is low
B. The estimated peak transaortic valvular gradient is 90 to 100 mm Hg
C. Aortic insufficiency is severe
D. Based on the Doppler findings, premature closure of the mitral valve is likely
E. The echocardiogram likely reveals normal left ventricular wall thickness

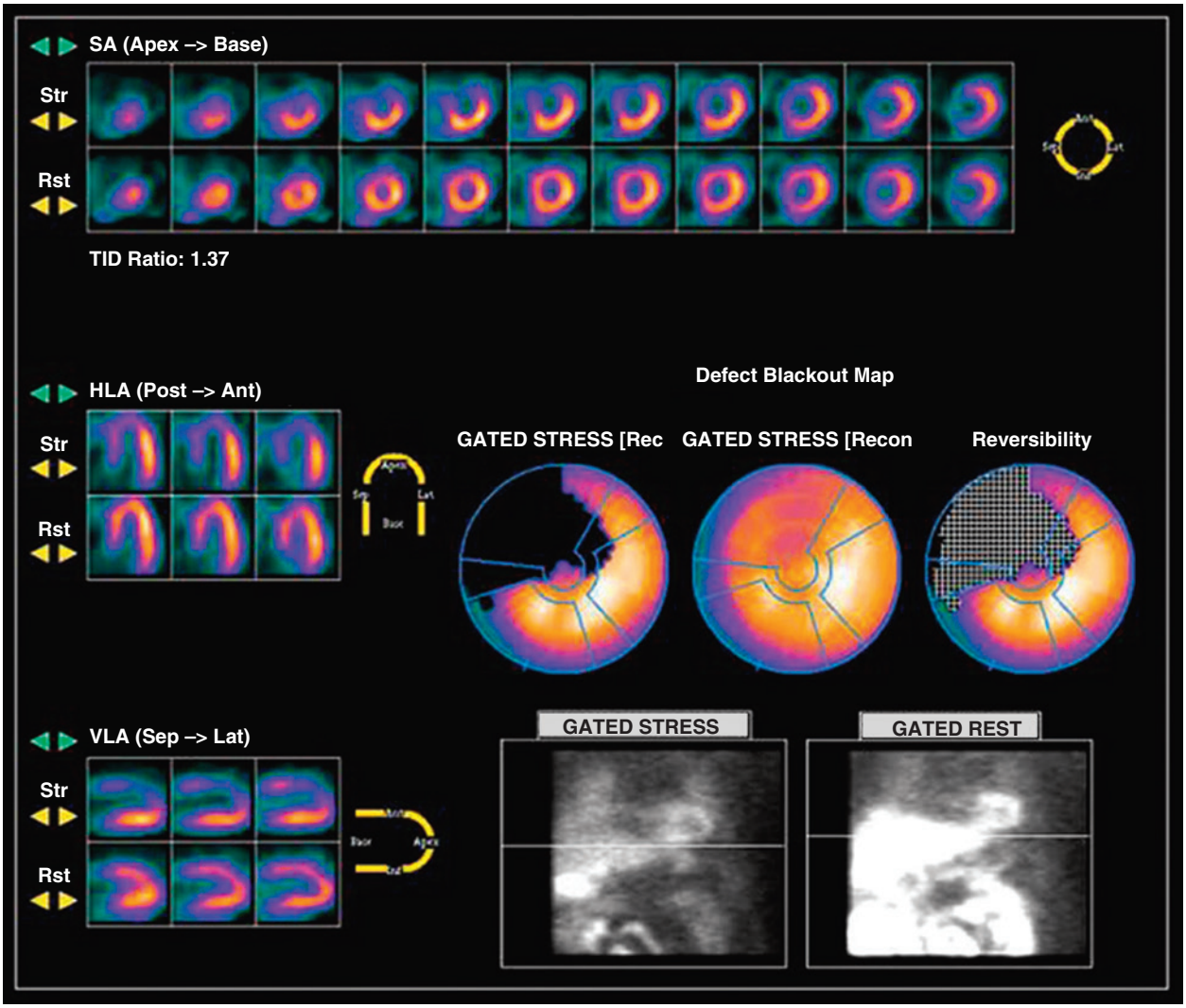


FIG. 1.10

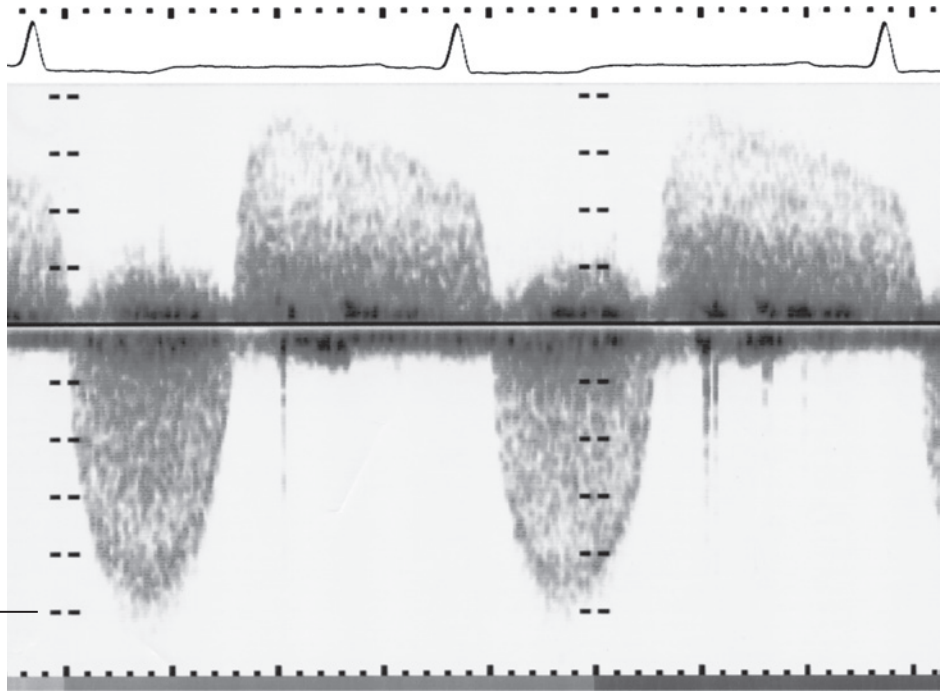


FIG. 1.11

QUESTION 53

Which of the following statements regarding abnormalities of the extremities in cardiac conditions is FALSE?
A. Arachnodactyly is associated with Marfan syndrome
B. A thumb with an extra phalanx commonly occurs in Turner syndrome
C. Quincke sign is typical of chronic aortic regurgitation
D. Osler nodes are tender, erythematous lesions of the fingers and toes in patients with infective endocarditis
E. Differential cyanosis is typical of patent ductus arteriosus with a reversed shunt

QUESTION 54

Which of the following is NOT commonly associated with the disorder illustrated in Fig. 1.12?
A. Tricuspid regurgitation
B. Patent foramen ovale
C. Wolff-Parkinson-White syndrome
D. Systemic hypertension
E. Atrial fibrillation

QUESTION 55

Which of the following statements is TRUE regarding the echocardiographic evaluation of suspected infective endocarditis?
A. Vegetations of the mitral valve typically appear on the ventricular aspect of the leaflets
B. The sensitivity of transthoracic echocardiography (TTE) for detection of vegetations is <70%
C. After successful antibiotic therapy, previously detected vegetations should not be visible by echocardiography
D. Functional and structural consequences of valvular infection are rarely observed by transthoracic echocardiographic evaluation, such that a transesophageal study (TEE) is always mandatory
E. TTE and TEE have similar sensitivities for detection of myocardial abscess formation

QUESTION 56

Which of the following statements is TRUE regarding examination of the arterial pulse?
A. A reduced-volume brachial pulse with a late systolic peak is the most characteristic arterial finding on physical examination in patients with severe aortic stenosis
B. A bisferious pulse is characterized by a systolic and then a diastolic peak and is typical of mixed mitral valve disease
C. The carotid artery is the blood vessel used to best appreciate the contour, volume, and consistency of the peripheral vessels
D. In coarctation of the aorta, the femoral pulse demonstrates a later peak than the brachial pulse.
E. The normal abdominal aorta is palpable both above and below the umbilicus

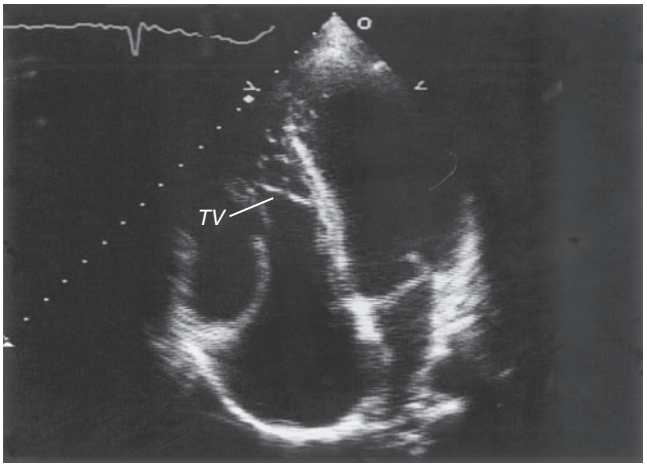


FIG. 1.12

QUESTION 57

Which of the following statements regarding cardiac catheterization is TRUE?
A. When catheterization is performed from the groin, the risk of retroperitoneal hemorrhage is decreased when the femoral artery puncture is made above the inguinal ligament
B. An international normalized ratio (INR) <2.2 is acceptable for radial artery catheterization
C. Patients with shellfish allergy are at greater risk of intravenous contrast reactions than patients with other food allergies
D. Pseudoaneurysm formation is more likely to occur if the femoral artery puncture is made above the bifurcation of the common femoral artery

QUESTION 58

Which of the following statements regarding the use of cardiopulmonary exercise testing in patients with congestive heart failure is TRUE?
A. A peak oxygen consumption <14 mL/kg/min identifies patients who would benefit from cardiac transplantation
B. Patients with ejection fractions <20% consistently have peak oxygen consumptions <10 mL/kg/min, and exercise testing is of little utility in this population
C. The exercise limitation in severe heart failure is due primarily to an inability to raise the heart rate
D. Exercise training in congestive heart failure patients improves functional capacity but has no effect on abnormalities of autonomic and ventilatory responsiveness or increased lactate production
E. Results of exercise testing are rarely useful when making clinical decisions about heart failure patients, such as timing of cardiac transplantation

QUESTION 59

In which of the following clinical scenarios is magnetic resonance imaging NOT a superior imaging modality for assessment?
A. Diagnosis of iron overload cardiomyopathy in a pediatric patient with beta-thalassemia major and congestive heart failure
B. Diagnosis of arrhythmogenic right ventricular cardiomyopathy in a 24-year-old man who recently survived a cardiac arrest
C. Diagnosis of aortic coarctation in a 17-year-old girl with hypertension and radial-femoral artery delay on physical examination

D. Serial evaluation of left ventricular function in a 54-year-old woman with metastatic breast cancer receiving doxorubicin chemotherapy
E. Diagnosis of renal artery stenosis in a 78-year-old man with refractory hypertension

QUESTION 60

Fig. 1.13 shows the post-test probability of coronary artery disease (CAD) as a function of the pretest probability of CAD and results of exercise electrocardiography—either a positive [(+) ST, red bars] or negative [(–) ST, blue bars] response. Four different patient examples are plotted. Which of the following statements is correct?

A. Stress testing should be pursued in the 45-year-old man with atypical chest pain because, if positive, the test will have the best positive predictive value of the cases shown
B. Stress testing should be pursued in the 55-year-old man with typical chest pain because, if negative, the test will have the best negative predictive value of the cases shown
C. The positive and negative predictive values cannot be determined for these patients from the given information
D. A 45-year-old asymptomatic man with a positive stress test is less likely to have CAD than is a man of the same age with atypical chest pain and a negative stress test
E. The pretest probability of coronary artery disease in a 45-year-old man depends solely on the presence of symptoms

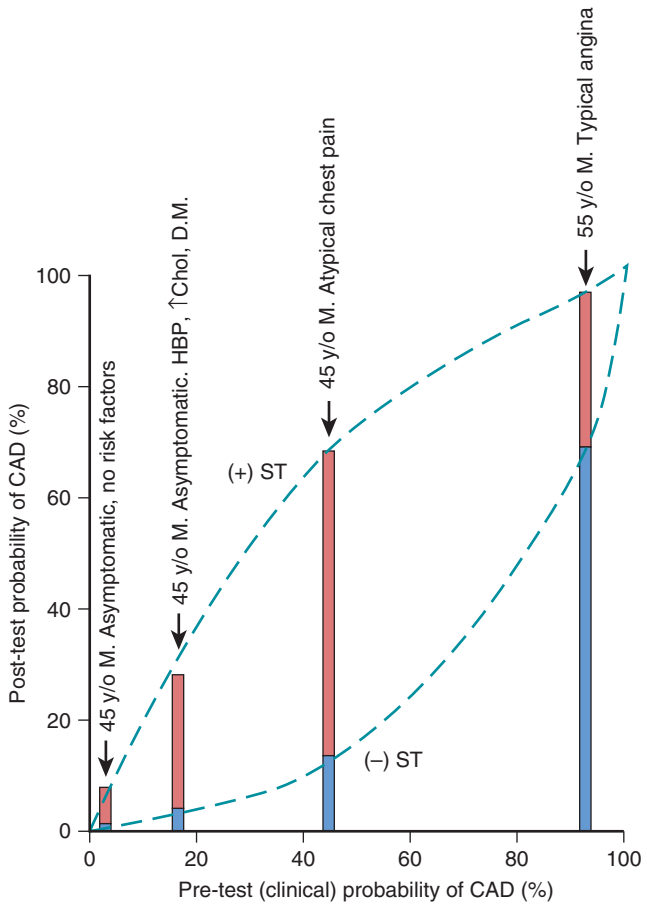


FIG. 1.13

QUESTION 61

Which of the following statements concerning imaging findings in hypertrophic cardiomyopathy (HCM) is TRUE?

A. The presence of systolic anterior motion of the mitral valve is consistent with dynamic outflow tract obstruction
B. Diastolic notching of the aortic valve on M-mode examination is typical in patients with outflow tract obstruction
C. Septal thickness is always abnormal in patients with HCM
D. Myocardial relaxation velocities measured by tissue Doppler imaging are typically normal

QUESTION 62

Each of the following statements regarding cardiac hemodynamics is true EXCEPT:

A. The *x* descent of the right atrial pressure wave form represents relaxation of the atrium and downward tugging of the tricuspid annulus by right ventricular contraction
B. In the left atrium, in contrast to the right atrium, the *v* wave is more prominent than the *a* wave
C. The *y* descent is blunted in cardiac tamponade
D. Tricuspid stenosis results in prominence of the *y* descent

QUESTION 63

Which of the following statements regarding the effects of maneuvers on the auscultation of cardiac murmurs is TRUE?

A. In patent ductus arteriosus, the diastolic phase of the murmur is softened by isometric handgrip
B. The murmur of hypertrophic obstructive cardiomyopathy becomes softer with standing or during a Valsalva strain maneuver
C. The murmur of a ventricular septal defect decreases with isometric handgrip
D. Isometric handgrip decreases the diastolic murmur of aortic regurgitation
E. The diastolic murmur of mitral stenosis becomes louder with exercise

QUESTION 64

A 62-year-old previously healthy man is brought to the emergency department because of severe headache and dizziness. He has no chest pain or dyspnea. He takes no medications. His blood pressure is 186/98 mm Hg; his heart rate is 56 beats/min and regular. The presenting ECG is shown in Fig. 1.14. Which of the following actions is appropriate?

A. Initiate antiplatelet therapy with aspirin and clopidogrel
B. Initiate antithrombotic therapy with heparin
C. Initiate anti-ischemic therapy with intravenous nitroglycerin and a beta blocker
D. Obtain a head computed tomographic scan
E. Proceed directly to cardiac catheterization if ST-segment/T wave abnormalities fail to quickly normalize with anti-ischemic therapy

QUESTION 65

Which of the following statements about diastolic murmurs is FALSE?

FIG. 1.14

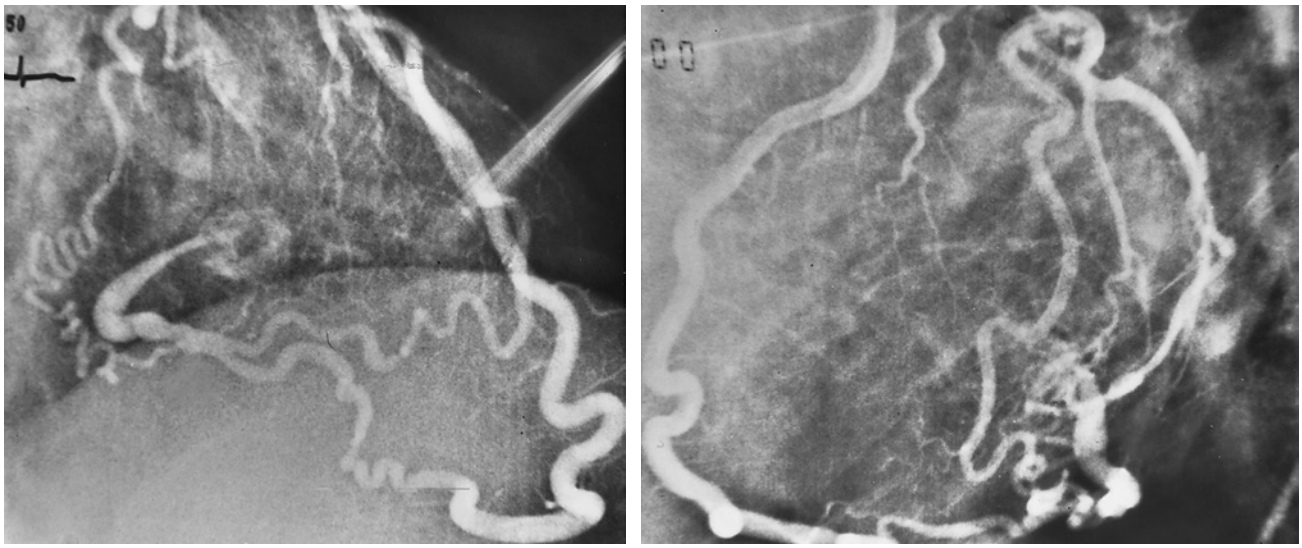


FIG. 1.15

A. Diastolic murmurs are classified according to their time of onset as early diastolic, mid-diastolic, or late diastolic
B. In aortic regurgitation due to aortic root dilatation, the murmur typically radiates to the right sternal border
C. It is possible to differentiate the murmur of acute severe aortic regurgitation from that of chronic aortic regurgitation at the bedside
D. Late diastolic (presystolic) accentuation of the murmur indicates that the patient is in atrial fibrillation.
E. The Graham Steell murmur begins in early diastole after a loud P_2

QUESTION 66

Which of the following statements regarding coronary artery anatomy is NOT correct?
A. At cardiac catheterization, the left main coronary artery is best visualized in the anteroposterior projection with slight caudal angulation
B. A ramus intermedius branch is present in more than 25% of people
C. The left circumflex artery is the dominant vessel in 45% of people
D. The most densely vascularized area of the heart is the interventricular septum
E. The abnormality shown in Fig. 1.15 is the most common type of coronary congenital abnormality that is hemodynamically significant

QUESTION 67

A 25-year-old asymptomatic man presents for routine physical examination with his new primary care physician. The physician notes that the patient is tall with unusually long limbs and pectus excavatum. There is no family history of Marfan syndrome. Which of the following is among the "major criteria" for the diagnosis of Marfan syndrome?
A. Mitral valve prolapse
B. Mild pectus excavatum
C. Joint hypermobility
D. Descending aortic aneurysm
E. Ectopia lentis

QUESTION 68

Which one of the following echocardiographic findings suggests that aortic regurgitation is severe?

A. Diastolic flow reversal in the descending thoracic aorta
B. Premature closure of the aortic valve
C. Pressure half-time of the aortic regurgitation Doppler spectrum of 500 milliseconds
D. A color Doppler regurgitant jet that extends to the tips of the papillary muscles
E. A left ventricular outflow tract systolic gradient of 64 mm Hg

QUESTION 69

Which of the following statements regarding pharmacologic agents used in myocardial perfusion stress testing is FALSE?

A. Patients who cannot perform exercise can be adequately evaluated for coronary artery disease (CAD) using vasodilating medications and nuclear scintigraphy
B. Dipyridamole blocks the cellular uptake of adenosine, an endogenous vasodilator
C. During perfusion stress testing, administration of adenosine or dipyridamole commonly provokes myocardial ischemia in patients with CAD
D. Radiopharmaceutical agents should be injected 1 to 2 minutes before the end of exercise
E. Dobutamine pharmacologic scintigraphy increases coronary blood flow less than adenosine

QUESTION 70

Which of the following statements regarding the auscultatory findings of mitral stenosis is correct?

A. The opening snap (OS) is a late diastolic sound
B. A long A_2-OS interval implies severe mitral stenosis
C. In atrial fibrillation, the A_2-OS interval does not vary with cycle length
D. The "snap" is generated by rapid reversal of the position of the posterior mitral leaflet
E. The presence of an opening snap implies a mobile body of the anterior mitral leaflet

QUESTION 71

Which of the following statements about digitalis-induced arrhythmias is FALSE?

A. Ventricular bigeminy with varying morphology and regular coupling is a sign of digitalis toxicity
B. Nonparoxysmal junctional tachycardia is a common digitalis-induced arrhythmia
C. Atrial tachycardia with block is diagnostic of digitalis toxicity
D. The development of atrioventricular dissociation in a patient taking digitalis is a likely indication of digitalis toxicity
E. Ventricular premature beats are common but are not highly specific for the presence of digitalis toxicity

QUESTION 72

An 82-year-old man presents after a recent non–ST-elevation myocardial infarction. Coronary angiography revealed severe three-vessel disease with 100% occlusion of the proximal left anterior descending (LAD) coronary artery, 100% mid–right coronary artery occlusion, and a 70% stenosis of the proximal left circumflex coronary artery. Echocardiography demonstrated akinesis of the entire anterior wall, septum, and mid- and apical anterolateral wall, with an estimated left ventricular ejection fraction of 20%. Myocardial viability was evaluated using cardiac positron emission tomography (PET) with rest rubidium-82 (^{82}Rb flow tracer) and ^{18}F-labeled fluorodeoxyglucose (^{18}F-FDG metabolism tracer) as shown in Fig. 1.16. The images show a large region of PET perfusion metabolism mismatch in the mid-LAD distribution. Which of the following statements about myocardial viability is FALSE?

A. This finding is consistent with the presence of hibernating (viable) myocardium
B. Radionuclide techniques are more sensitive than measurement of inotropic contractile reserve by dobutamine echocardiography for the detection of viable myocardium
C. Inotropic contractile reserve measured by dobutamine echocardiography is more specific than radionuclide techniques for predicting functional recovery after revascularization
D. Survival benefit associated with revascularization of hibernating myocardium has been demonstrated in randomized clinical trials
E. The transmural extent of myocardial scar can be assessed accurately using gadolinium-enhanced cardiac magnetic resonance imaging

QUESTION 73

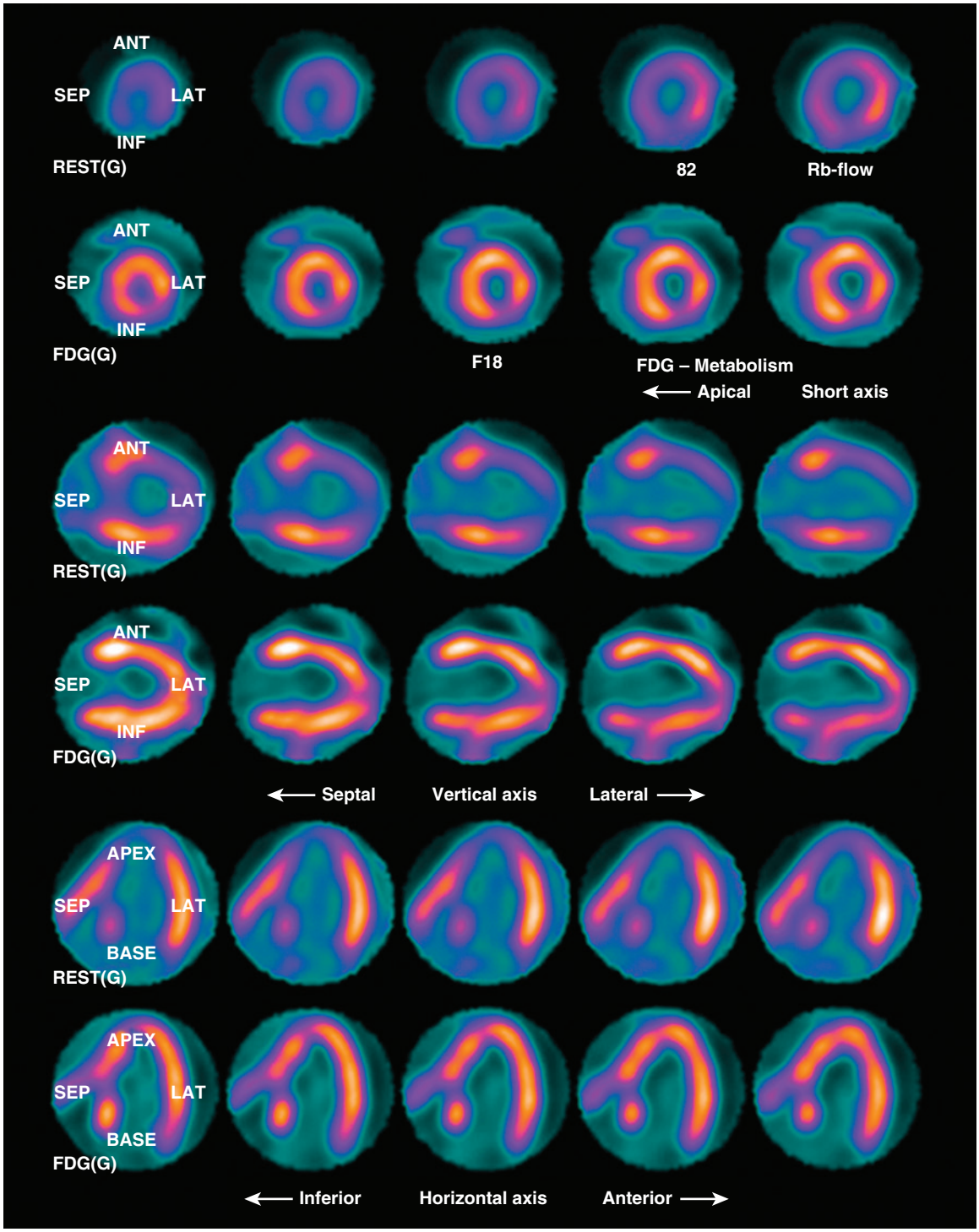
Which of the following statements regarding physical findings that distinguish the murmur of aortic stenosis (AS) from the murmur of hypertrophic cardiomyopathy (HCM) is TRUE?

A. The strain phase of the Valsalva maneuver decreases the intensity of the murmurs of both AS and HCM
B. The carotid upstroke in HCM is more brisk than in AS
C. The murmurs of AS and HCM both radiate to the carotid arteries
D. If a systolic thrill is present, it is most often located in the second right intercostal space in HCM and at the apex in AS
E. Squatting increases the intensity of the murmur of HCM

QUESTION 74

Which of the following statements is correct regarding the oral anticoagulants dabigatran, rivaroxaban, and apixaban in the treatment of patients with atrial fibrillation?

A. These agents are as effective as warfarin for prevention of thromboemboli in patients with atrial fibrillation and mechanical heart valves
B. Each of these drugs can be used safely in patients with advanced renal disease
C. Intravenous idarucizumab rapidly reverses the anticoagulant effect of dabigatran
D. For patients whose INR levels on warfarin have varied due to noncompliance, rivaroxaban is an excellent alternative given its once-daily dosing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SEP
LAT
INF
REST(G)
82
Rb-flow
ANT
SEP
LAT
INF
FDG(G)
F18
FDG – Metabolism
Apical
Short axis
ANT
SEP
LAT
INF
REST(G)
ANT
SEP
LAT
INF
FDG(G)
Septal
Vertical axis
Lateral
APEX
SEP
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REST(G)
APEX
SEP
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BASE
FDG(G)
Inferior
Horizontal axis
Anterior

FIG. 1.16

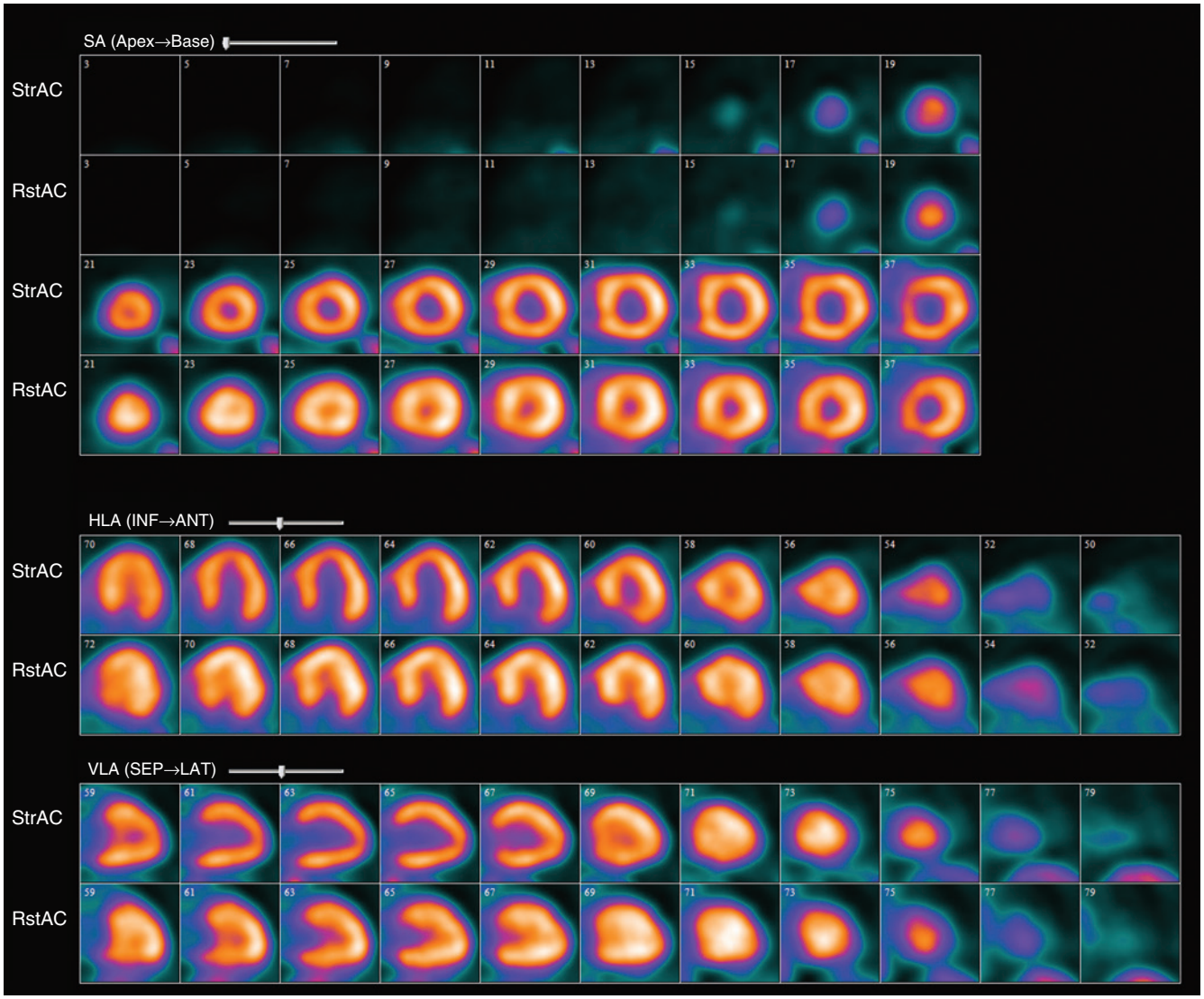


FIG. 1.17

QUESTION 75

A 73-year-old woman with exertional angina is referred for a standard Bruce protocol exercise tolerance test with thallium-201 single-photon emission computed tomography. Her nuclear images are shown in Fig. 1.17. What is the likely diagnosis?

A. Dilated cardiomyopathy
B. Single-vessel coronary artery disease involving the left circumflex artery
C. Prior inferior myocardial infarction with high-grade stenosis of the right coronary artery
D. Left main or severe multivessel coronary artery disease
E. Normal coronary arteries; the images demonstrate breast attenuation artifact

QUESTION 76

Which of the following statements regarding pulsus alternans in patients with marked LV dysfunction is true?

A. It is usually associated with electrical alternans of the QRS complex
B. It is less readily detected in the femoral as compared with radial arteries
C. It cannot be detected by noninvasive sphygmomanometry
D. It can be enhanced by the assumption of erect posture
E. It is uncommon for patients with pulsus alternans also to have an S_3 gallop

QUESTION 77

Which of the following statements regarding exercise testing is TRUE?

A. Frequent ventricular ectopy in the early postexercise phase predicts a worse long-term prognosis than ectopy that occurs only during exercise
B. Patients who develop QT interval prolongation during exercise testing are good candidates for class IA antiarrhythmic drugs

C. The appearance of sustained supraventricular tachycardia during exercise testing is diagnostic of underlying myocardial ischemia
D. Exercise-induced left bundle branch block is not predictive of subsequent cardiac morbidity and mortality
E. Tachyarrhythmias are commonly precipitated during exercise testing in patients with Wolff-Parkinson-White syndrome

QUESTION 78

Which of the following statements regarding extra systolic sounds is FALSE?
A. Ejection sounds are high-frequency "clicks" that occur early in systole
B. Ejection sounds due to a dilated aortic root have a similar timing as those associated with aortic valvular disease
C. The ejection sound associated with pulmonic stenosis decreases in intensity during inspiration
D. Aortic ejection sounds vary with respiration, occurring later in systole during inspiration
E. The bedside maneuver of standing from a squatting position causes the click of mitral valve prolapse to occur earlier in systole

QUESTION 79

Which of the following statements regarding the ECG in chronic obstructive lung disease with secondary right ventricular hypertrophy is correct?
A. The mean QRS axis is typically <15 degrees
B. The amplitude of the QRS complex is abnormally high in the precordial leads
C. Even mild right ventricular hypertrophy produces diagnostic electrocardiographic abnormalities
D. A deep S wave in V_6 is typical
E. Precordial lead transition is typically rotated in a counterclockwise fashion (early transition)

QUESTION 80

Which of the following statements regarding shunt detection is TRUE?
A. When an "anatomic" shunt is present, arterial oxygen saturation normalizes with administration of 100% oxygen
B. Methods of shunt detection include oximetry, echocardiography, and magnetic resonance imaging, but not radionuclide imaging
C. Among the sources of right atrial venous blood, the inferior vena cava (IVC) has the lowest oxygen saturation
D. Due to the low sensitivity of oximetry for shunt detection, most clinically relevant left-to-right shunts cannot be detected using this method
E. The Flamm formula is used to estimate mixed venous oxygen content proximal to a left-to-right shunt at the right atrial level

QUESTION 81

Which of the following conditions is NOT often associated with a prominent R wave in electrocardiographic lead V_1?
A. Right ventricular hypertrophy
B. Wolff-Parkinson-White syndrome
C. Duchenne muscular dystrophy
D. Left anterior fascicular block
E. Misplacement of the chest leads

QUESTION 82

The hemodynamic tracing illustrated in Fig. 1.18 is associated with which of the following features?
A. Advanced valvular aortic stenosis
B. A bifid aortic pulse contour
C. Normal left ventricular end-diastolic pressure
D. A delayed rise in the carotid artery pulsation
E. Expected clinical improvement with transcatheter aortic valve replacement

QUESTION 83

Which of the following statements regarding axis positions of the heart and findings on the ECG is FALSE?
A. A "horizontal" heart results in a tall R wave in lead aVL
B. "Clockwise rotation" refers to a delayed transition zone in the precordial leads
C. In patients with a "vertical" heart, the QRS complex is isoelectric in lead I
D. "Counterclockwise rotation" mimics left ventricular hypertrophy
E. When all six limb leads show isoelectric complexes, it is not possible to calculate the axis in the frontal plane

QUESTION 84

Which of the following statements concerning the cardiac catheterization evaluation of valve orifice areas is TRUE?
A. Valve area as calculated by the Gorlin formula is inversely proportional to the flow across the valve
B. Accompanying valvular regurgitation will result in a falsely high calculated valve area because actual flow across the valve is less than the flow calculated from the systemic cardiac output

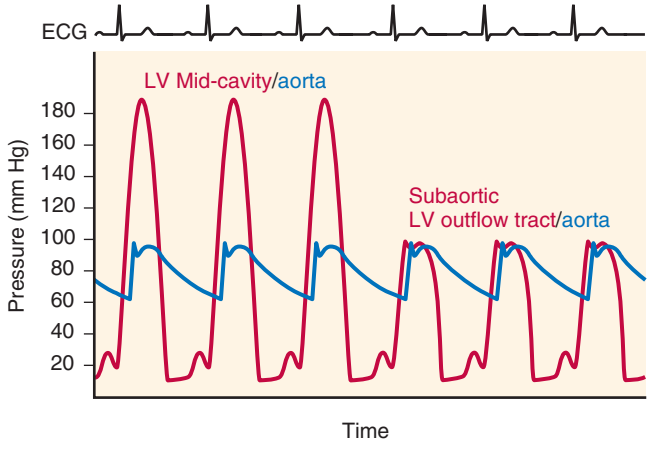


FIG. 1.18

C. Calculation of mitral valve area typically relies on substitution of a confirmed pulmonary capillary wedge pressure for left atrial pressure
D. Valve area calculation is more strongly influenced by errors in the pressure gradient measurement than by errors in cardiac output measurement

QUESTION 85

A 56-year-old man who underwent coronary artery bypass graft surgery 6 years ago has experienced exertional chest discomfort in recent months. He is not able to perform an exercise test because of chronic hip pain. He undergoes an adenosine positron emission tomography (PET) vasodilator stress test, images from which are shown in Fig. 1.19. What is the correct interpretation of this study?

A. No perfusion defects
B. A partially reversible defect of the entire inferior wall
C. A severe predominantly reversible defect of the anterior wall
D. A fixed defect of the anterior wall without reversibility
E. Fixed defects of the apex and lateral walls

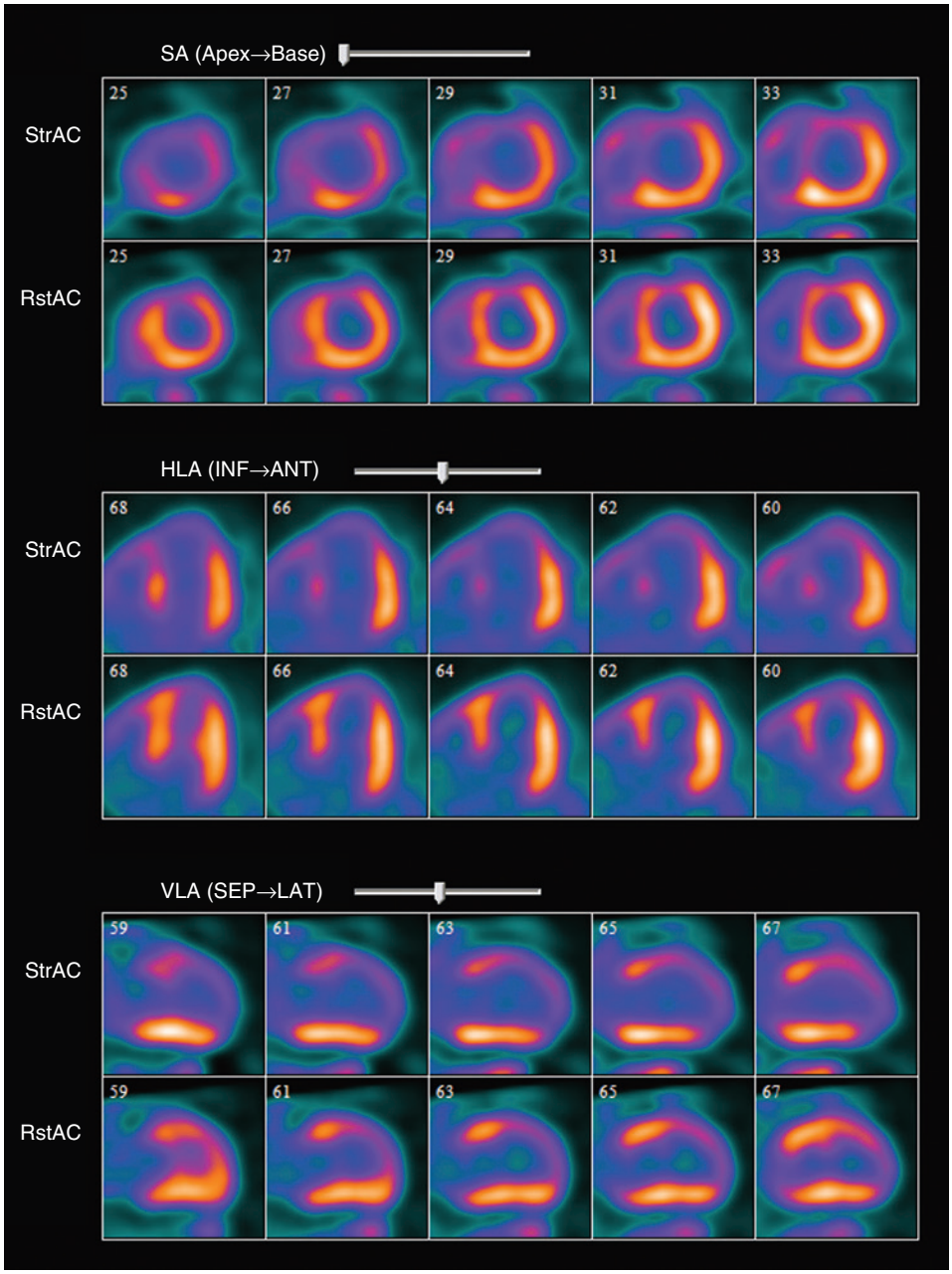


FIG. 1.19

QUESTION 86

A 40-year-old man presents to his physician with shortness of breath on exertion, peripheral edema, and arthritis of his hands. On examination, his vital signs are normal. His sclerae are icteric and his skin has a bronzed hue. Lung examination demonstrates rales at the bases; the carotids are of normal upstroke. The cardiac impulse is displaced laterally and there is an audible S_3. His abdomen is distended, with evidence of hepatosplenomegaly and ascites. There is peripheral pitting edema. Laboratory studies reveal a serum glucose level of 225 mg/dL and a transferrin saturation of 70%. Which of the following statements about this condition is TRUE?

A. It is inherited as an autosomal dominant condition
B. Cardiac involvement results in a mixed dilated and restrictive cardiomyopathy
C. Early cardiac death is common, due primarily to accelerated atherosclerosis
D. Ventricular hypertrophy with increased QRS voltages is the most common electrocardiographic finding
E. Echocardiography often shows a thickened ventricle with a "granular sparkling" appearance

QUESTION 87

A 56-year-old woman presents for routine evaluation. On examination, a systolic murmur is noted. Which of the following responses to maneuvers would be suggestive of mitral valve prolapse as the cause of the murmur?

A. With isometric handgrip, the murmur starts earlier in systole and becomes louder
B. With standing from a supine position, the murmur begins later in systole
C. Carotid sinus massage increases the intensity of the murmur
D. Valsalva maneuver causes the murmur to arise earlier in systole
E. Squatting from a standing position moves the onset of the murmur earlier in systole

QUESTION 88

Which of the following statements regarding the effect of the potassium concentration on the ECG is TRUE?

A. The earliest electrocardiographic sign of hyperkalemia is a reduction in P wave amplitude
B. Deep symmetric T wave inversions are characteristic of early hyperkalemia
C. Hyperkalemia predisposes to digitalis-induced tachyarrhythmias
D. Prominent U waves are a characteristic feature of hyperkalemia
E. QRS complex widening is common in severe hyperkalemia

QUESTION 89

Which of the following conditions does NOT result in significant electrocardiographic Q waves in the absence of infarction?

A. Left bundle branch block
B. Left ventricular dilatation with posterior rotation of the heart
C. Electrocardiographic lead misplacement
D. Acidosis
E. Wolff-Parkinson-White syndrome

QUESTION 90

Which of the following statements regarding the interpretation of exercise electrocardiography is TRUE?

A. The presence of right bundle branch block does not alter the sensitivity of exercise electrocardiography for the diagnosis of myocardial ischemia
B. ST-segment depressions in the inferior leads during exercise testing are specific for significant right coronary artery disease
C. The location of ST-segment elevations during exercise testing predicts the anatomic site of clinically advanced coronary stenosis
D. Digoxin therapy is not associated with false-positive findings on exercise electrocardiography if the baseline ST segments are normal

QUESTION 91

A patient underwent echocardiography as part of the evaluation of exertional dyspnea. Fig. 1.20 displays an image from the continuous-wave Doppler interrogation across the mitral valve, obtained from the apical long-axis view. Each of the statements below is true EXCEPT

A. The early diastolic peak velocity of 2.7 m/s is within the normal range
B. There is an abnormally delayed decline of the transmitral velocity signal during diastole
C. Significant mitral stenosis is present
D. Abnormal transmitral systolic blood flow is demonstrated
E. With color Doppler imaging, the extent of mitral regurgitation can be underestimated if the regurgitant jet is directed along the left atrial wall

QUESTION 92

Which of the following statements regarding commonly used quality improvement strategies is correct?

A. Iterative PDSA (Plan-Do-Study-Act) cycles are most successful when goals are subjective, allowing the quality improvement team to think creatively without being constrained by a discrete goal

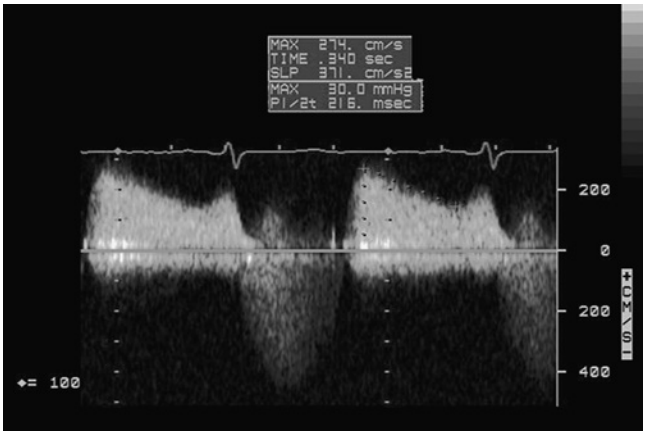


FIG. 1.20

B. The Lean approach focuses on high level concepts, avoiding getting bogged down in the details of a process
C. The Lean approach focuses on reducing unnecessary variation in a process
D. Six Sigma is an iterative process of Define, Measure, Analyze, Improve, and Control

QUESTION 93

A 25-year-old man died suddenly while jogging, and a postmortem examination was performed. A histologic section of left ventricular myocardium is shown in Fig. 1.21. Which of the following statements is TRUE?
A. The histologic findings are of normal myocardium subjected to chronic vigorous exercise
B. This condition is inherited as an autosomal dominant trait
C. This is a disease of plasma membrane protein synthesis
D. The greatest risk to affected patients is the development of complete heart block
E. One specific mutation has been identified that accurately predicts sudden cardiac death in the majority of patients with this disorder

QUESTION 94

A 28-year-old woman presents for evaluation after a syncopal episode. Her family history is notable for sudden death in an older sibling. Physical examination reveals woolly hair and palmar keratosis. Electrocardiography demonstrates T wave inversions in leads V_1–V_3. An ambulatory (Holter) electrocardiographic monitor captures runs of ventricular tachycardia with a left bundle morphology and superior axis. A signal-averaged ECG demonstrates late potentials. Echocardiography demonstrates a mildly dilated right ventricle with reduced systolic function; the left ventricle appears structurally normal. Which of the following statements is TRUE about this condition?
A. The majority of patients with this disorder have an abnormality of the ryanodine receptor
B. Endomyocardial biopsy establishes the diagnosis with high sensitivity
C. This patient likely has a mutation in the plakoglobin gene
D. This condition is transmitted in an autosomal dominant fashion
E. Noncaseating granulomas are likely present in the right ventricular myocardium

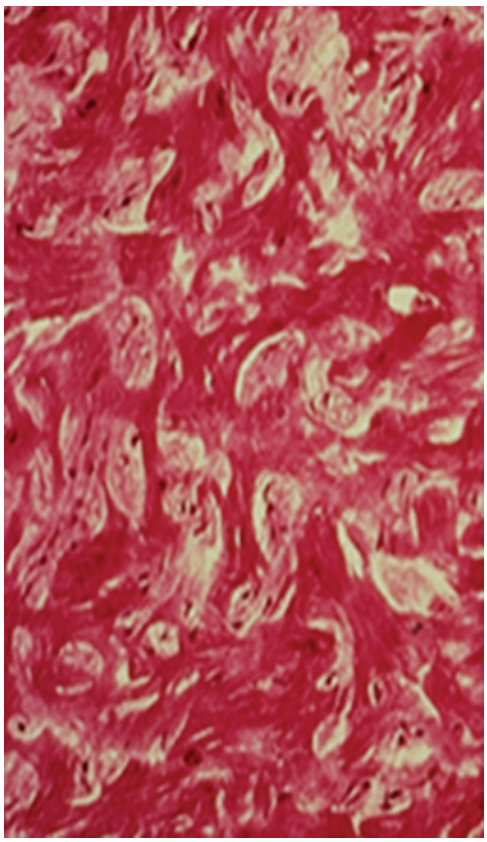


FIG. 1.21

QUESTION 95

A 72-year-old man with multiple myeloma presents with progressive exertional dyspnea, orthopnea, and peripheral edema. On examination the blood pressure is 118/62 mm Hg without pulsus paradoxus, but there is a 25 mm Hg systolic pressure postural decline. The jugular venous pressure is 12 cm, and there is periorbital purpura, macroglossia, hepatomegaly, and prominent symmetric pitting edema to the level of the mid-thighs. His electrocardiogram is remarkable for very low limb lead voltage. Which of the following echocardiographic findings is expected?
A. Increased right ventricular wall thickness with normal left ventricular thickness
B. Abnormal regional longitudinal strain on speckle tracking that spares the apex
C. Reversal of normal tissue Doppler mitral annular E′ velocity ratio (medial > lateral)
D. Very large pericardial effusion

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 96 TO 100

Match each of the following clinical scenarios to the most likely cause of syncope:
A. Ventricular tachycardia
B. High-degree atrioventricular block
C. Epilepsy
D. Neurocardiogenic syncope
E. Hysterical fainting

96. A 73-year-old man with a remote history of myocardial infarction feels the onset of palpitations while driving, then awakens having driven his car into a ditch, unaware of what has transpired
97. A 25-year-old woman on chronic antiseizure medication becomes warm, diaphoretic, and very pale after donating blood, then suffers frank syncope while seated upright in a chair. After being helped to the floor, she awakens embarrassed and alert

98. A 73-year-old woman with recent episodes of dizziness begins to feel lightheaded while seated at church, then within seconds turns pale and slumps to the floor with a few clonic jerks. She regains consciousness 1 minute later, completely aware of where she is and asks what has happened. When an ambulance arrives, her blood pressure is 108/70 mm Hg and the heart rate is 60 beats/min
99. A 32-year-old man with a history of prior syncope notices an odd odor, after which he falls to the ground. He awakens 3 minutes later, confused and disoriented, and is found to be incontinent of urine
100. An 18-year-old Army recruit falls to the ground while standing at attention for 20 minutes during his first week of basic training. He immediately awakens, feels a bit groggy, but quickly is able to rejoin his squad

QUESTIONS 101 TO 104

For each clinical scenario, select the most likely ECG from the four tracings shown in Fig. 1.22:

101. A 19-year-old male college student with exertional lightheadedness and a harsh systolic murmur that intensifies after standing from a squatting position
102. A 56-year-old woman with sudden onset of pleuritic chest discomfort and dyspnea
103. A 36-year-old man with sharp inspiratory precordial chest discomfort that radiates to the left shoulder
104. A 71-year-old alcoholic man with epigastric discomfort after 18 hours of intermittent vomiting

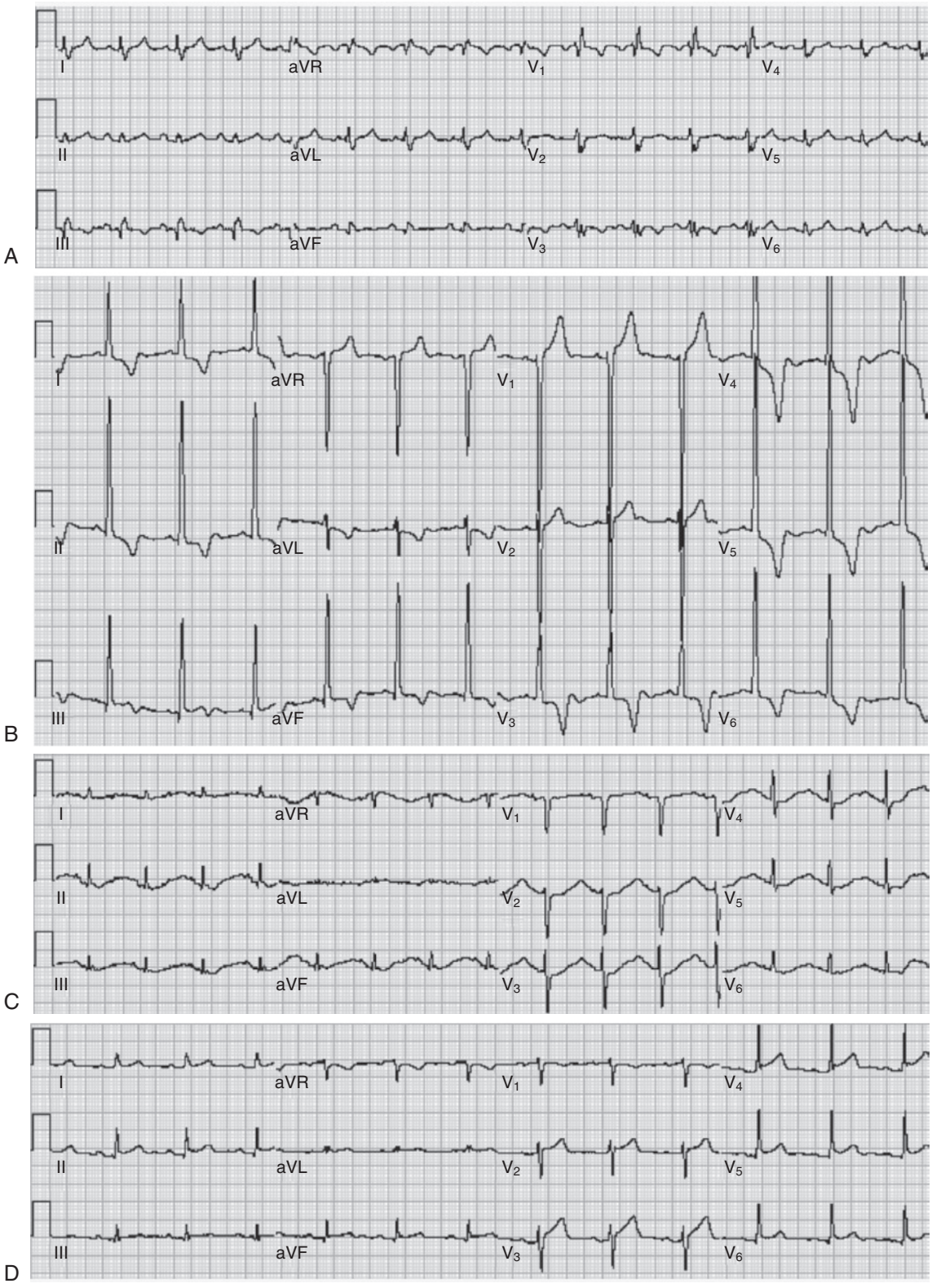

A
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
B
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
C
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
D
I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6

FIG. 1.22

QUESTIONS 105 TO 109

Match the most appropriate descriptive phrase to each angiogram shown in Fig. 1.23:

105. Right anterior oblique (RAO) projection: left anterior descending (LAD) artery, demonstrating myocardial bridging with narrowing in systole and near-normal caliber in diastole
106. Left anterior oblique (LAO) projection: right coronary arteriogram demonstrating anomalous origin of the left circumflex artery from the right coronary sinus
107. Collateral vessels arising from the distal right coronary artery (RCA) and supplying an occluded LAD artery
108. Right coronary arteriogram demonstrating diffuse coronary spasm and restoration of normal caliber with introduction of nitroglycerin
109. A dilated left circumflex artery and subsequent coronary sinus opacification due to a congenital coronary fistula

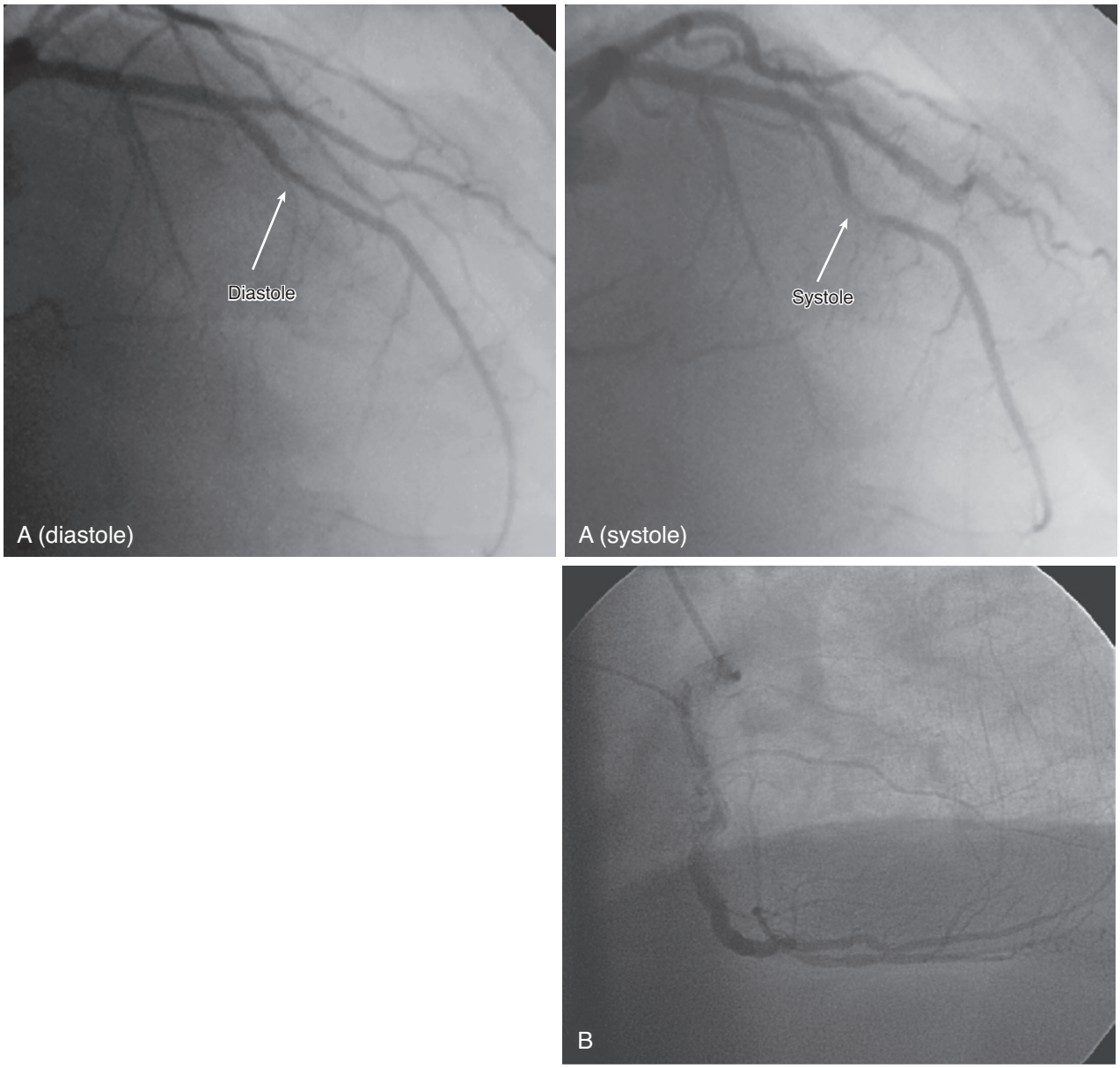


FIG. 1.23

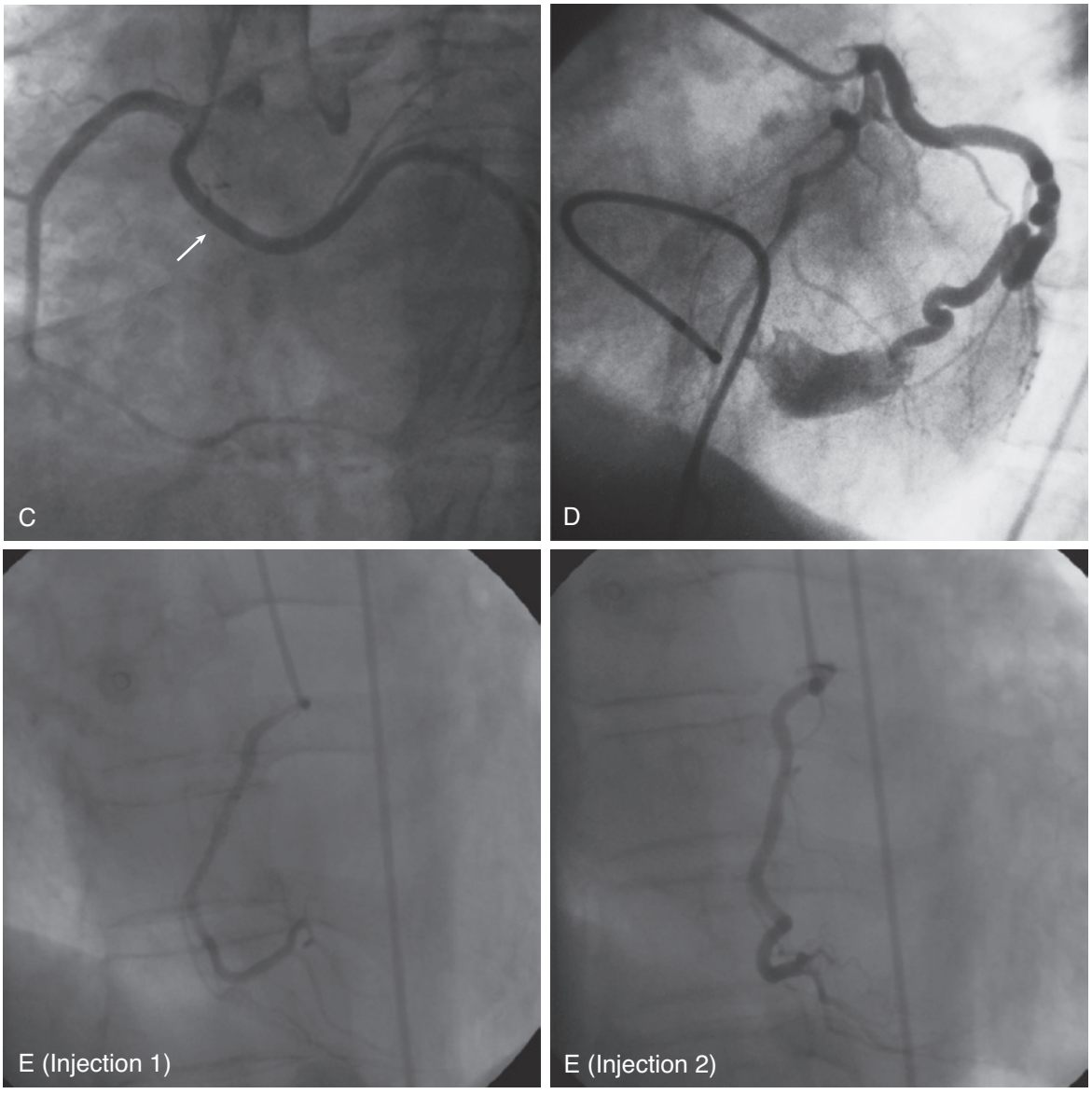


FIG. 1.23, cont'd

QUESTIONS 110 TO 113

For each clinical scenario, match the most likely computed tomogram in Fig. 1.24:

110. A 53-year-old woman with exertional dyspnea, recurrent transient ischemic attacks, lightheadedness with sudden changes in position, and a 15-pound weight loss over the past 6 months
111. A 21-year-old man with recurrent syncope
112. A 69-year-old woman with recent myocardial infarction and subsequent stroke
113. A 71-year-old man with jugular venous distention, ascites, and marked peripheral edema

QUESTIONS 114 TO 117

For each condition, match the appropriate pattern of left ventricular (LV) filling as recorded by Doppler of diastolic mitral flow velocities (E wave = early diastolic filling; A wave = period of atrial contraction; normal LV deceleration time in early diastole is >190 milliseconds):

A. E wave > A wave, LV deceleration time >190 milliseconds
B. E wave > A wave, LV deceleration time <190 milliseconds
C. E wave < A wave, LV deceleration time >200 milliseconds
D. E wave ≫ A wave, LV deceleration time <150 milliseconds

114. Restrictive cardiomyopathy
115. Normal pattern
116. Pseudonormalized pattern
117. Impaired LV diastolic relaxation

QUESTIONS 118 TO 121

For each of the chest radiographs shown in Fig. 1.25, match the most appropriate cardiac diagnosis:

118. Mitral stenosis
119. Aortic regurgitation
120. Atrial septal defect
121. Pericardial effusion

QUESTIONS 122 TO 125

Match each description below to the most appropriate cardiac rhythm:

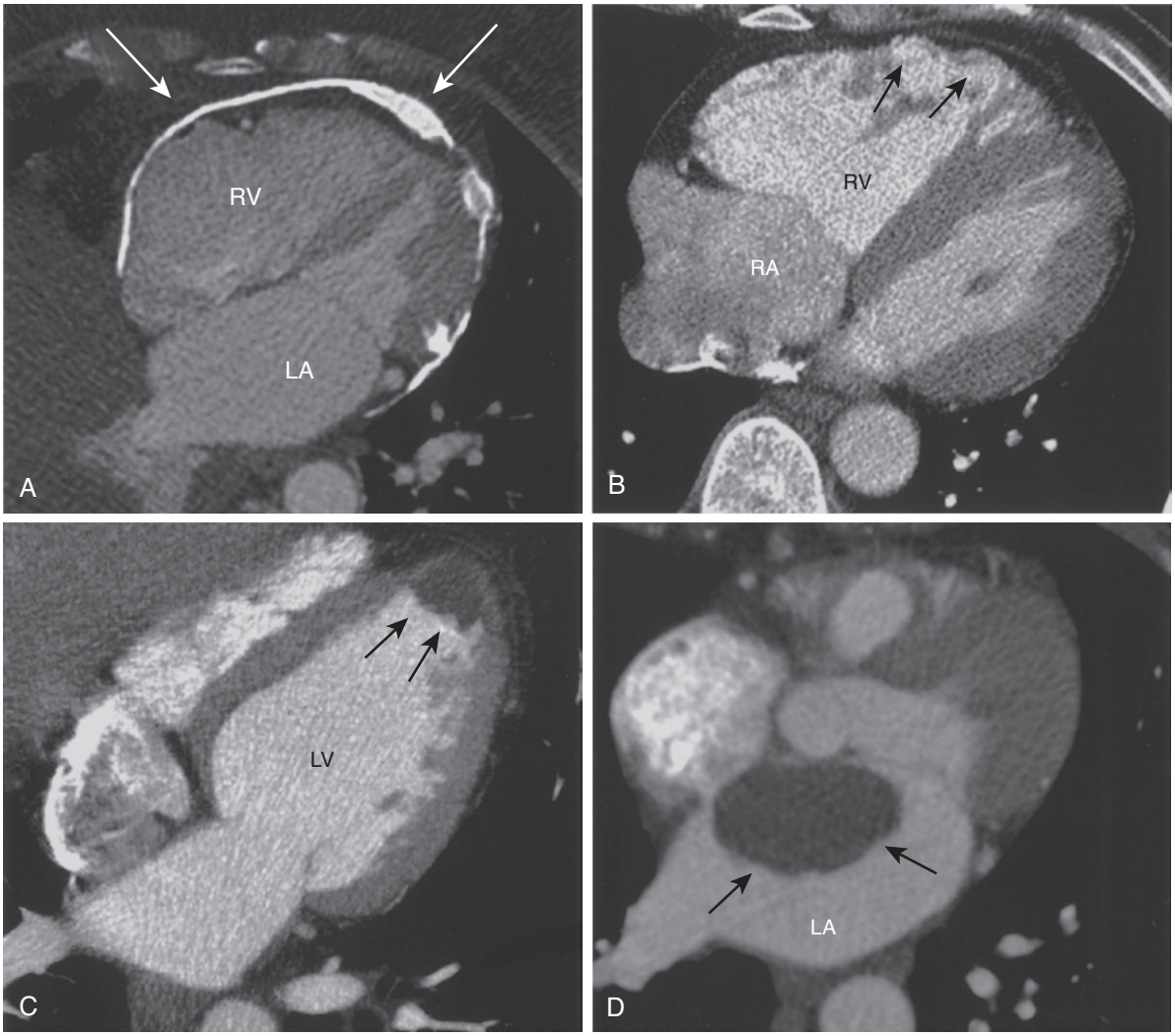


FIG. 1.24

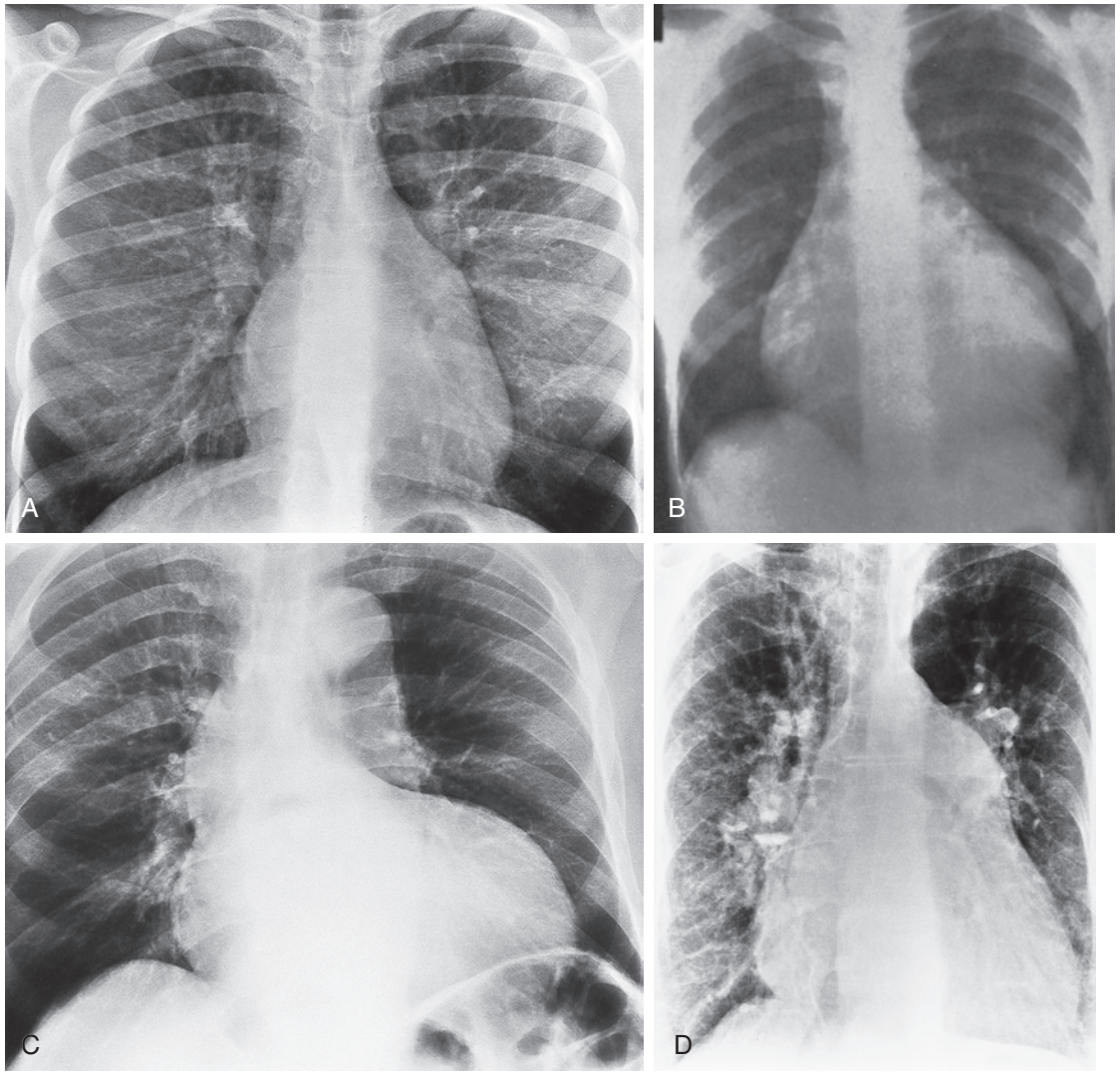


FIG. 1.25 *A, C, and D from Miller SW.* Cardiac Imaging: The Requisites. *2nd ed. Philadelphia: Elsevier; 2005. B, From Daves ML.* Cardiac Roentgenology. *Chicago: Year Book Publishers; 1981:470.*

A. Atrial tachycardia
B. Atrial flutter
C. Sinus rhythm
D. Atrioventricular nodal reentrant tachycardia
E. Atrial fibrillation

122. P waves are negative in lead aVR and upright in leads I, II, and aVF
123. Rhythm can be due to automaticity, reentry, or triggered mechanisms
124. Macroreentrant mechanism in the right atrium
125. The initial P wave of the tachycardia is usually different from the subsequent P waves

QUESTIONS 126 TO 129

For the receiver-operating curve (ROC) for two diagnostic tests shown in Fig. 1.26, match the following:

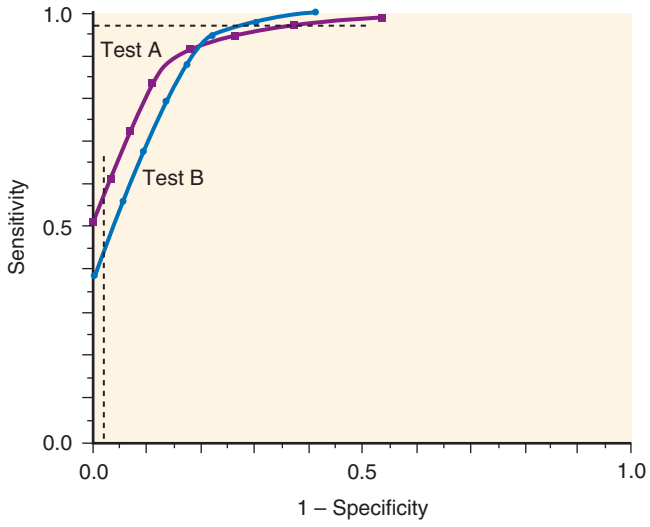


FIG. 1.26

A. 11%
B. 40%
C. 59%
D. 47%
E. Test A
F. Test B

126. The false-positive rate of Test A at a sensitivity of 98%
127. The sensitivity of Test A at a specificity of 98%
128. The positive predictive value of Test A with a sensitivity of 98%, for a population with disease prevalence of 50/1000
129. The superior screening test

QUESTIONS 130 TO 133

For each clinical scenario, select the appropriate ECG from those provided in Fig. 1.27:

130. A 49-year-old man with chronic renal failure and progressive fatigue
131. A 37-year-old man with a recent viral syndrome and sharp anterior chest pain that worsens when he changes position
132. A 59-year-old man with severe lightheadedness
133. A 38-year-old woman with perioral and peripheral cyanosis, digital clubbing, and a history of cardiac surgery as a child

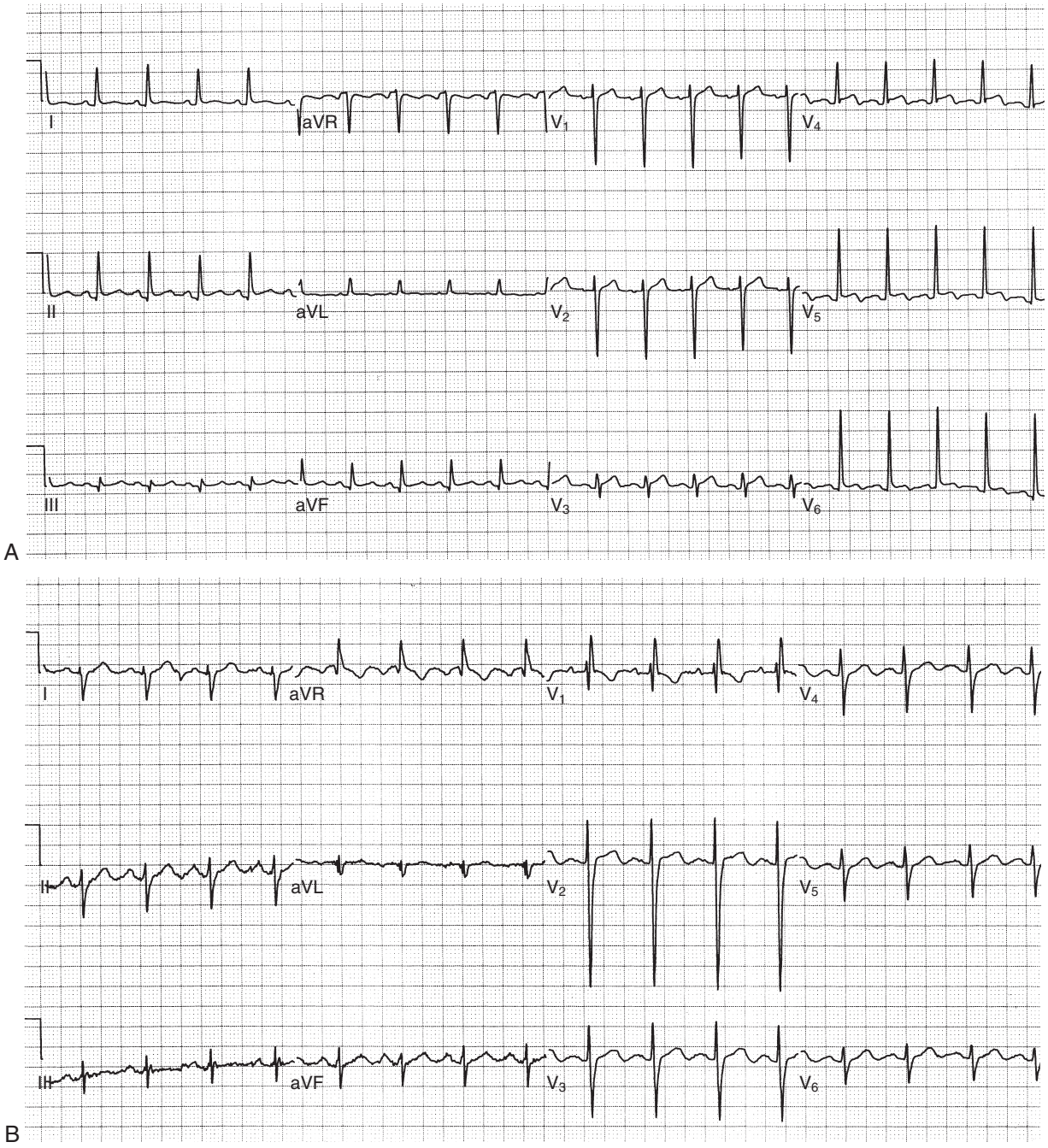
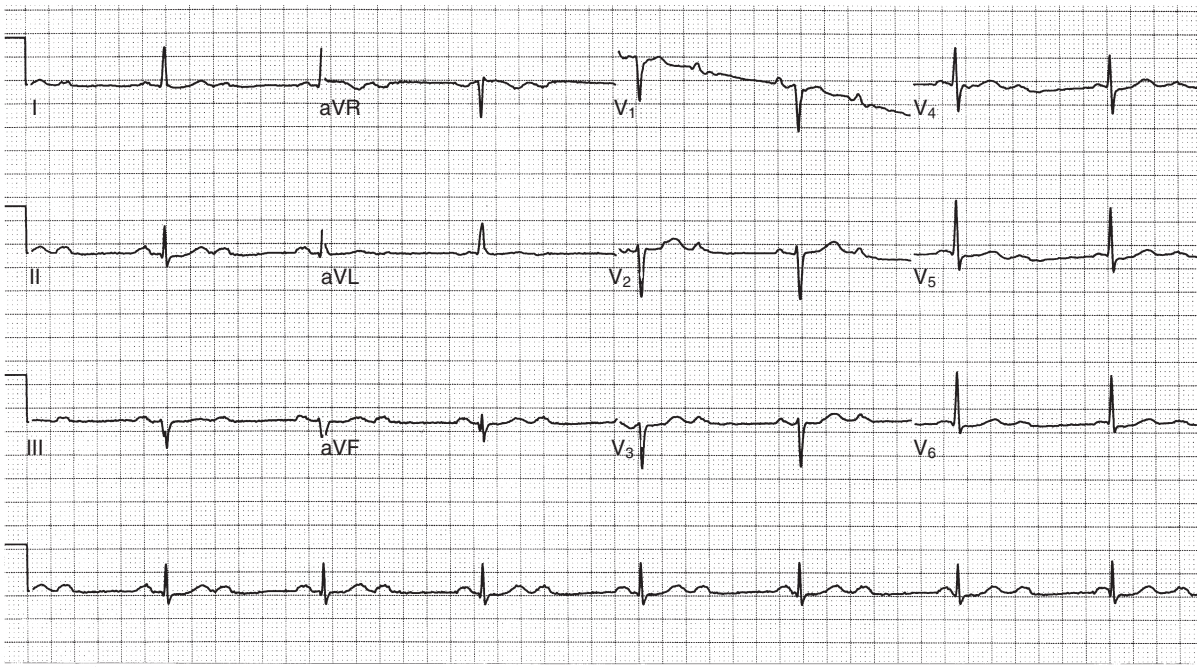
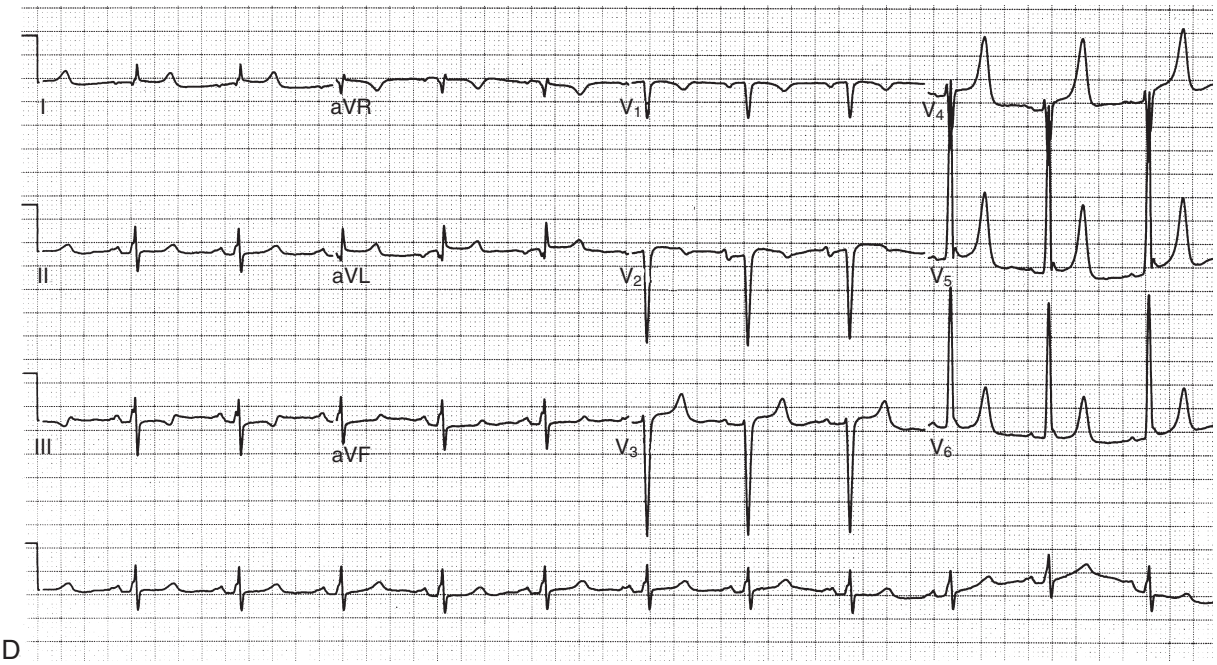


FIG. 1.27



C



D

FIG. 1.27, cont'd

ECHOCARDIOGRAMS (QUESTIONS 134–142)

Directions:

Each of the still-frame echocardiographic images below is introduced by a brief clinical scenario. For each image, comment on the major abnormal findings:

134. A 62-year-old man who sustained a myocardial infarction 1 month ago (Fig. 1.28)

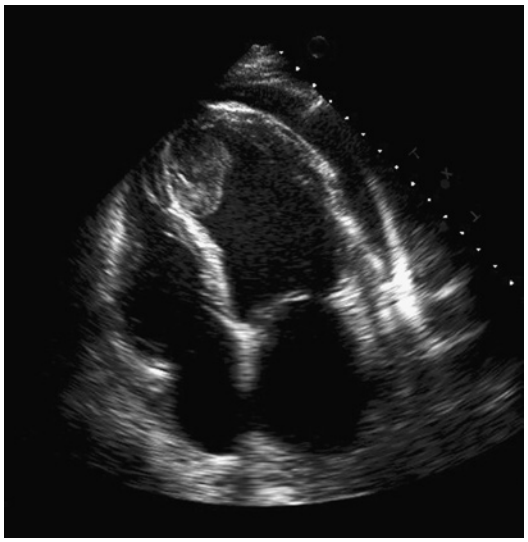


FIG. 1.28

135. A 33-year-old woman with an early systolic click (Fig. 1.29)

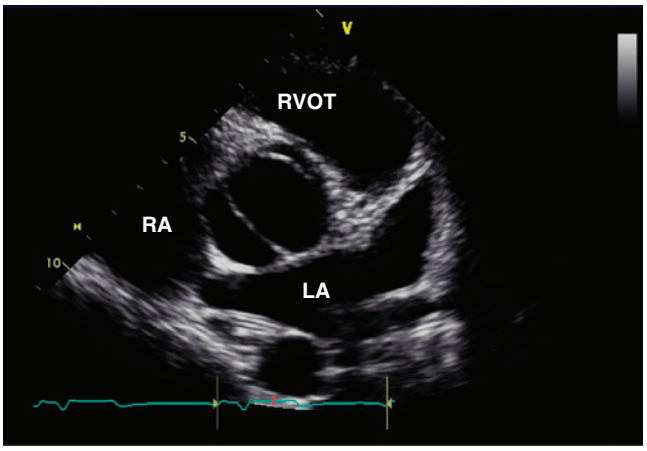


FIG. 1.29

136. A 26-year-old man with a loud asymptomatic systolic murmur (Fig. 1.30)

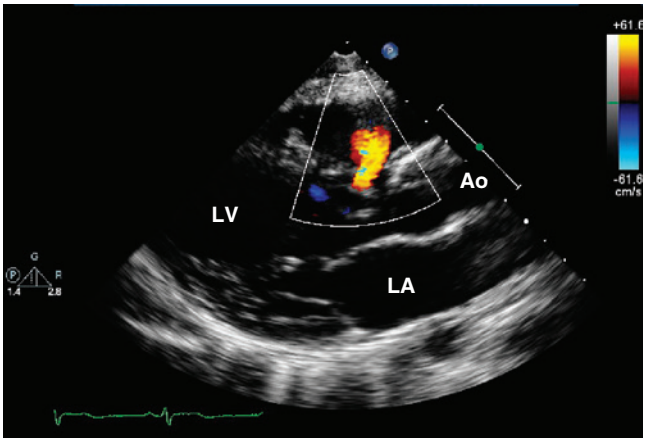


FIG. 1.30

137. A tall, thin 31-year-old woman with a diastolic murmur (Fig. 1.31)

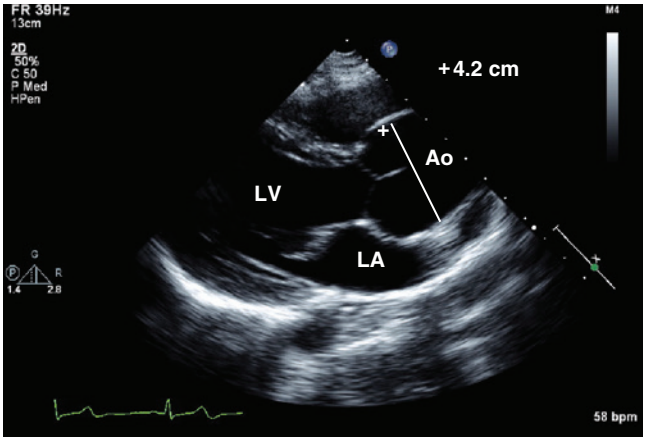


FIG. 1.31

138. A 59-year-old woman with a systolic murmur (Fig. 1.32)

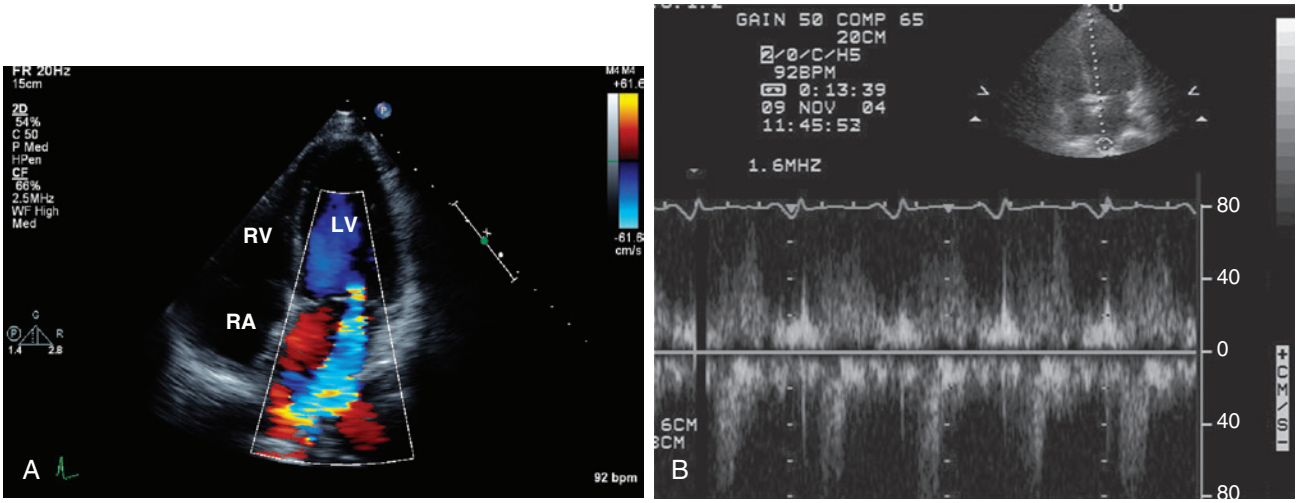


FIG. 1.32

139. Doppler tissue imaging in a 54-year-old man with multiple myeloma, exertional dyspnea, and peripheral edema (Fig. 1.33)

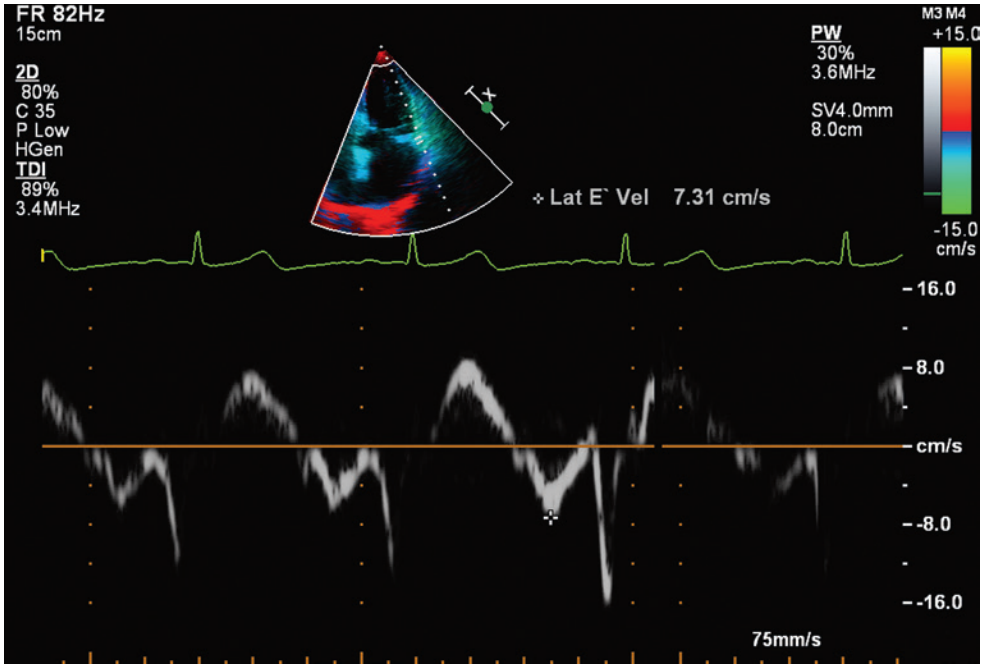


FIG. 1.33

140. A 44-year-old woman with an acute stroke (Fig. 1.34)

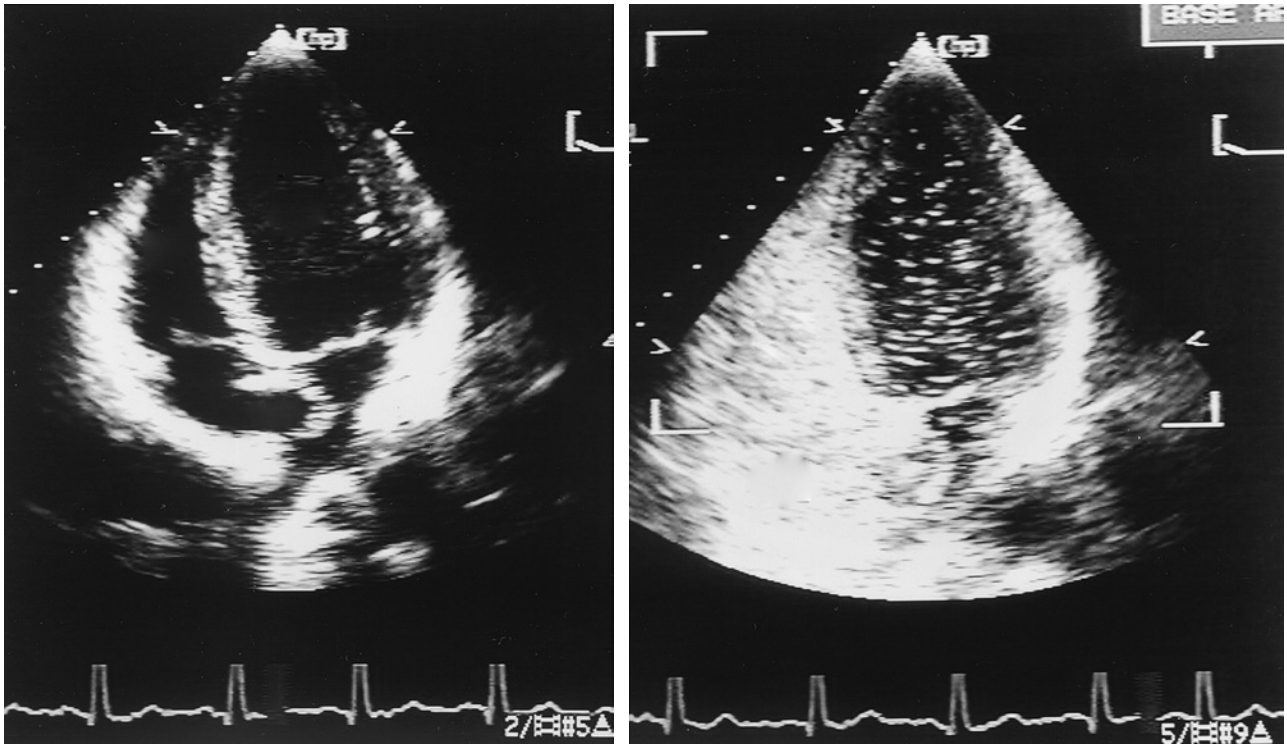


FIG. 1.34

141. A 78-year-old woman with atrial fibrillation (Fig. 1.35)

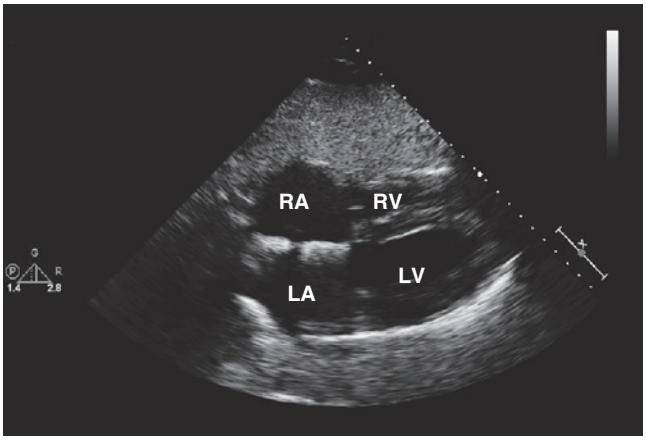


FIG. 1.35

142. A 66-year-old man with dyspnea (Fig. 1.36)

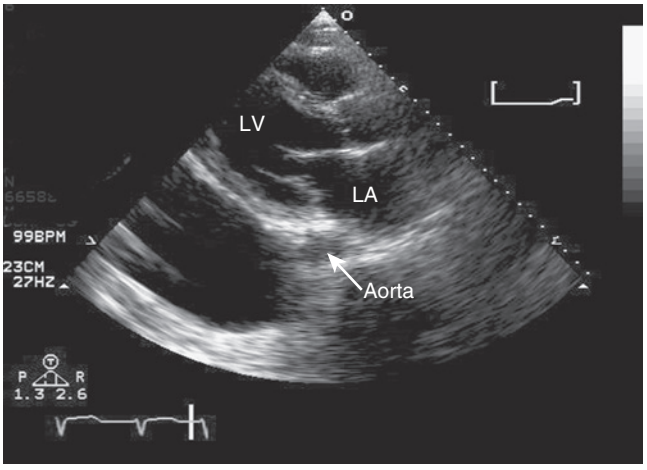


FIG. 1.36

ELECTROCARDIOGRAMS

Electrocardiogram Response Form (For Use With Questions 143–167)

General Features
- ☐ 1. Normal ECG
- ☐ 2. Normal variant
- ☐ 3. Incorrect electrode placement
- ☐ 4. Artifact

P Wave Abnormalities
- ☐ 5. Right atrial abnormality/enlargement
- ☐ 6. Left atrial abnormality/enlargement

Atrial Rhythms
- ☐ 7. Sinus rhythm
- ☐ 8. Sinus arrhythmia
- ☐ 9. Sinus bradycardia (<60)
- ☐ 10. Sinus tachycardia (>100)
- ☐ 11. Sinus pause or arrest
- ☐ 12. Sinoatrial exit block
- ☐ 13. Atrial premature complexes
- ☐ 14. Atrial parasystole
- ☐ 15. Atrial tachycardia
- ☐ 16. Atrial tachycardia, multifocal
- ☐ 17. Supraventricular tachycardia
- ☐ 18. Atrial flutter
- ☐ 19. Atrial fibrillation

AV Junctional Rhythms
- ☐ 20. AV junctional premature complexes
- ☐ 21. AV junctional escape complexes
- ☐ 22. AV junctional rhythm/tachycardia

Ventricular Rhythms
- ☐ 23. Ventricular premature complex(es)
- ☐ 24. Ventricular parasystole
- ☐ 25. Ventricular tachycardia (3 or more consecutive complexes)
- ☐ 26. Accelerated idioventricular rhythm
- ☐ 27. Ventricular escape complexes or rhythm
- ☐ 28. Ventricular fibrillation

AV Conduction
- ☐ 29. AV block, 1°
- ☐ 30. AV block, 2°—Mobitz type I (Wenckebach)
- ☐ 31. AV block, 2°—Mobitz type II
- ☐ 32. AV block, 2:1
- ☐ 33. AV block, 3°
- ☐ 34. Wolff-Parkinson-White pattern
- ☐ 35. AV dissociation

Abnormalities of QRS Voltage or Axis
- ☐ 36. Low voltage
- ☐ 37. Left axis deviation (>–30 degrees)
- ☐ 38. Right axis deviation (>+100 degrees)
- ☐ 39. Electrical alternans

Ventricular Hypertrophy
- ☐ 40. Left ventricular hypertrophy
- ☐ 41. Right ventricular hypertrophy
- ☐ 42. Combined ventricular hypertrophy

Intraventricular Conduction
- ☐ 43. right bundle branch block (RBBB), complete
- ☐ 44. RBBB, incomplete
- ☐ 45. Left anterior fascicular block
- ☐ 46. Left posterior fascicular block
- ☐ 47. left bundle branch block (LBBB), complete
- ☐ 48. LBBB, incomplete
- ☐ 49. Intraventricular conduction disturbance, nonspecific type
- ☐ 50. Functional (rate-related) aberrancy

Q Wave Myocardial Infarction

	AGE RECENT, OR PROBABLY ACUTE	AGE INDETERMINATE, OR PROBABLY OLD
Anterolateral	☐ 51	☐ 52
Anterior or anteroseptal	☐ 53	☐ 54
Lateral	☐ 55	☐ 56
Inferior	☐ 57	☐ 58
Posterior	☐ 59	☐ 60

ST, T, U Wave Abnormalities
- ☐ 61. Normal variant, early repolarization
- ☐ 62. Normal variant, juvenile T waves
- ☐ 63. Nonspecific ST and/or T wave abnormalities
- ☐ 64. ST and/or T wave abnormalities suggesting myocardial ischemia
- ☐ 65. ST and/or T wave abnormalities suggesting myocardial injury
- ☐ 66. ST and/or T wave abnormalities suggesting electrolyte disturbances
- ☐ 67. ST and/or T wave abnormalities secondary to hypertrophy
- ☐ 68. Prolonged QT interval
- ☐ 69. Prominent U waves

Clinical Disorders
- ☐ 70. Brugada syndrome
- ☐ 71. Digitalis toxicity
- ☐ 72. Torsades de pointes
- ☐ 73. Hyperkalemia
- ☐ 74. Hypokalemia
- ☐ 75. Hypercalcemia
- ☐ 76. Hypocalcemia
- ☐ 77. Dextrocardia, mirror image
- ☐ 78. Chronic lung disease
- ☐ 79. Acute cor pulmonale including pulmonary embolus
- ☐ 80. Pericardial effusion
- ☐ 81. Acute pericarditis
- ☐ 82. Hypertrophic cardiomyopathy
- ☐ 83. Central nervous system disorder
- ☐ 84. Hypothermia

Pacemaker Function
- ☐ 85. Atrial or coronary sinus pacing
- ☐ 86. Ventricular demand pacemaker (VVI), normally functioning
- ☐ 87. Dual-chamber pacemaker (DDD), normally functioning
- ☐ 88. Pacemaker malfunction, not constantly capturing (atrium or ventricle)
- ☐ 89. Pacemaker malfunction, not constantly sensing (atrium or ventricle)
- ☐ 90. Biventricular pacing or cardiac resynchronization therapy

Directions:

Each of the 12-lead ECGs below is introduced by a brief clinical description of the patient. For each ECG, perform a systematic reading. Consider the rhythm, rate, axis, and intervals and whether atrioventricular conduction disturbances are present. Then determine if criteria are met for atrial or ventricular hypertrophy, intraventricular conduction disturbances, or prior myocardial infarction. Continue by noting abnormalities of the ST segment and T waves. Conclude by suggesting a clinical diagnosis compatible with each tracing. You may use the electrocardiographic response form (p. 33) and its numerical codes, representative of that used by the American Board of Internal Medicine Cardiovascular Disease Certification Examination, as a framework.

143. A 70-year-old woman presents to the emergency department with severe chest pain and dyspnea (Fig. 1.37)

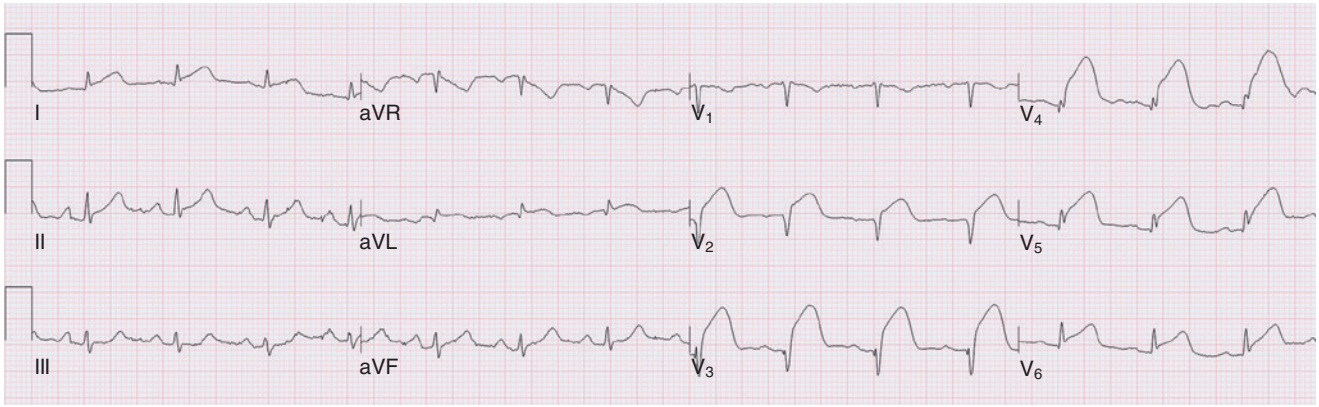


FIG. 1.37

144. A 66-year-old man with a history of cigarette smoking, who has not received medical care for many years, presents to his new primary care physician for a routine examination (Fig. 1.38)

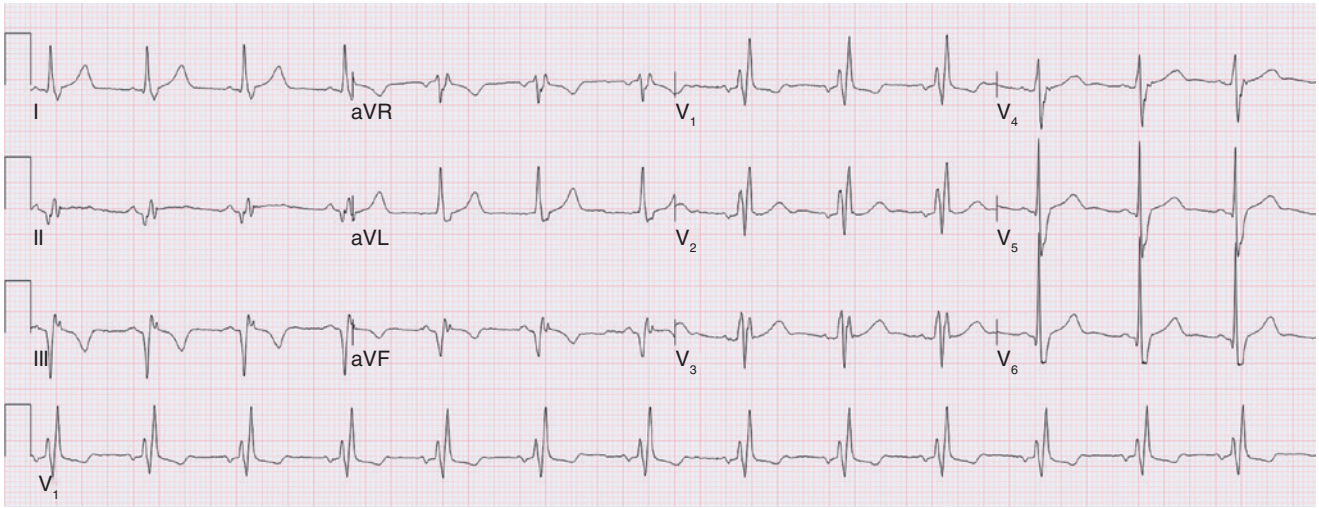


FIG. 1.38

145. A 28-year-old man with a lifelong heart murmur (Fig. 1.39)

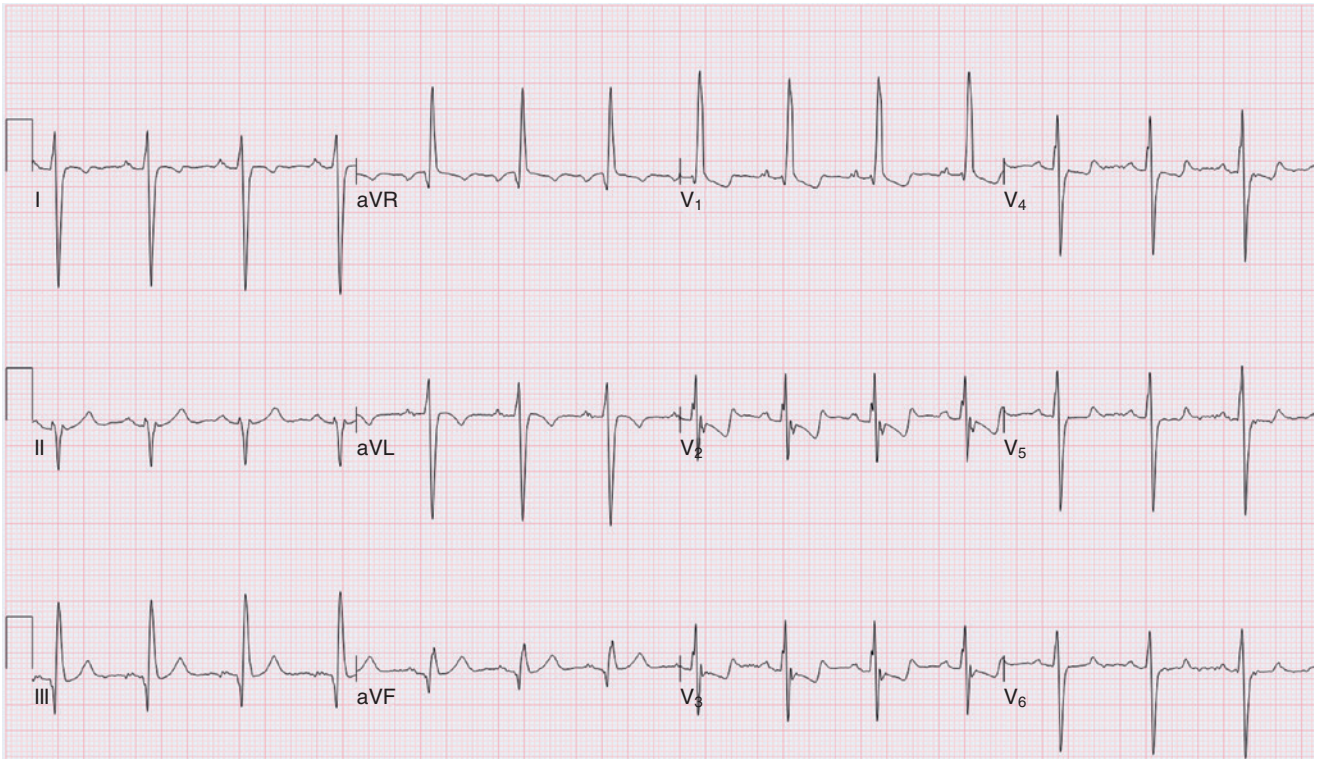


FIG. 1.39

146. An 85-year-old woman who comes for a routine appointment with her cardiologist (Fig. 1.40)

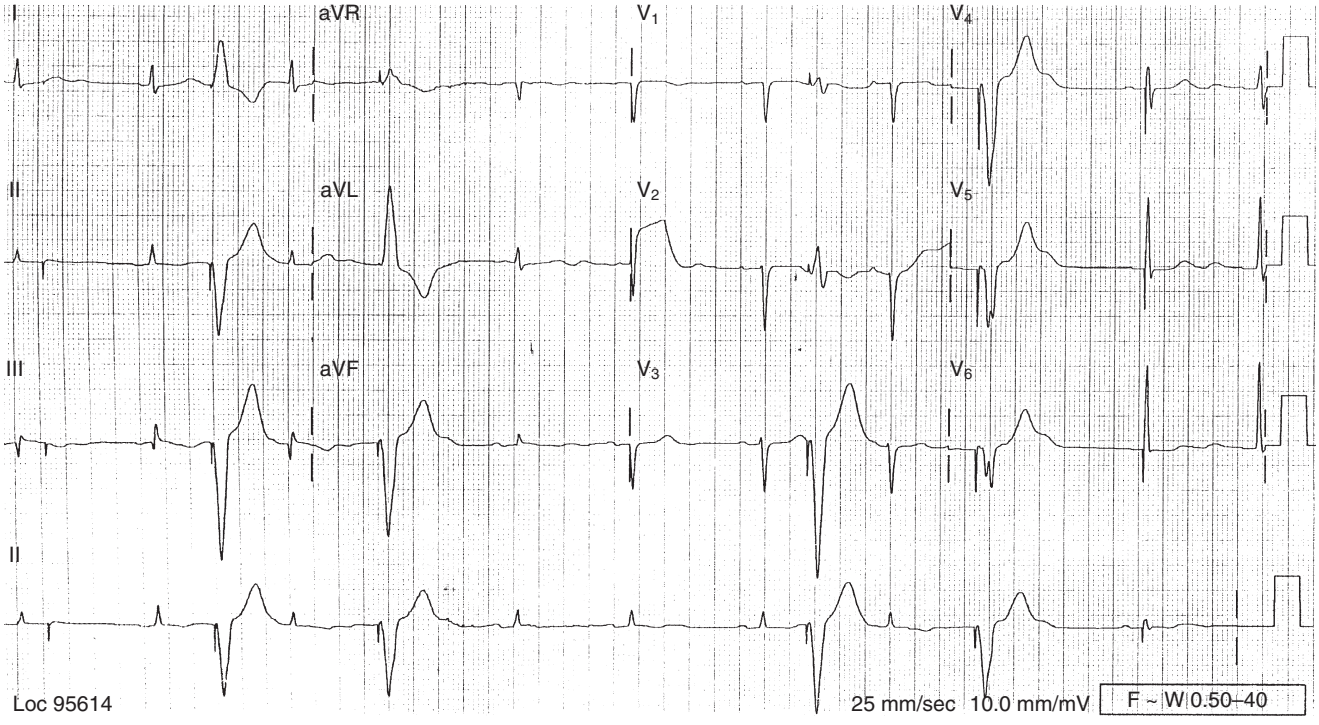


FIG. 1.40

147. A 47-year-old man with episodes of syncope (Fig. 1.41)

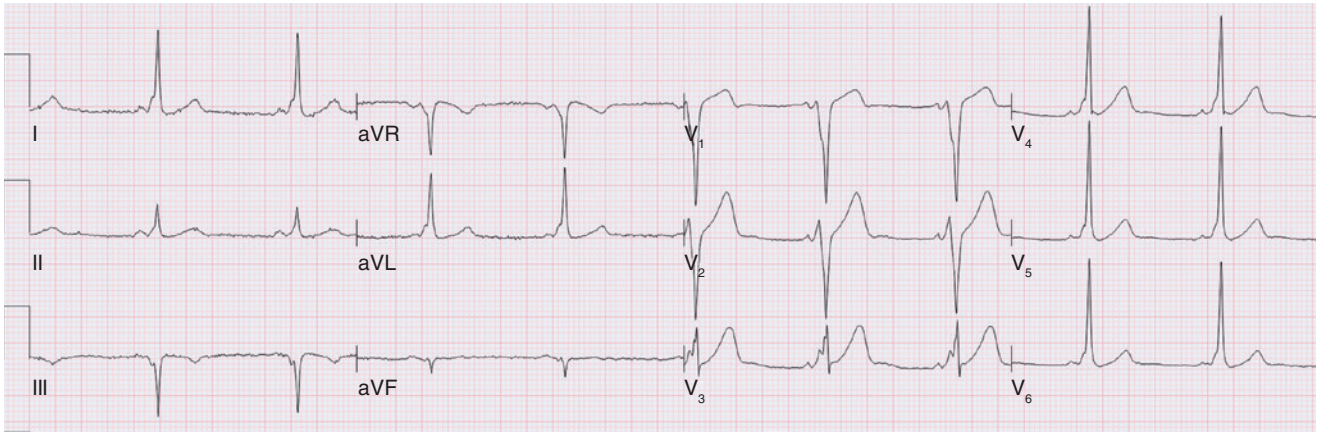


FIG. 1.41

148. A 63-year-old man with a rapid heart rate (Fig. 1.42)

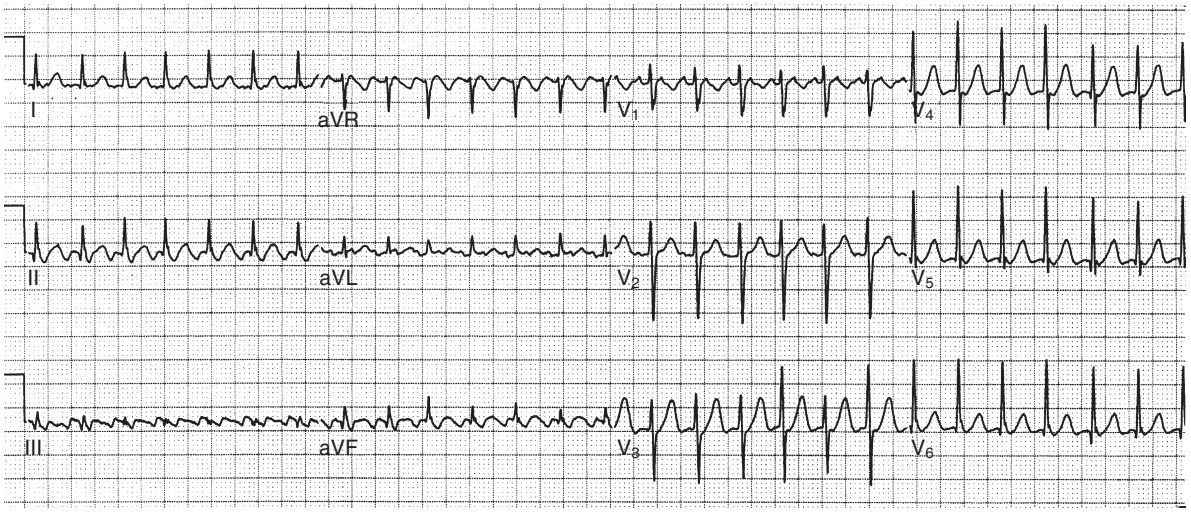


FIG. 1.42

149. A 78-year-old woman with a history of a heart murmur presents with intermittent dyspnea and lightheadedness (Fig. 1.43)

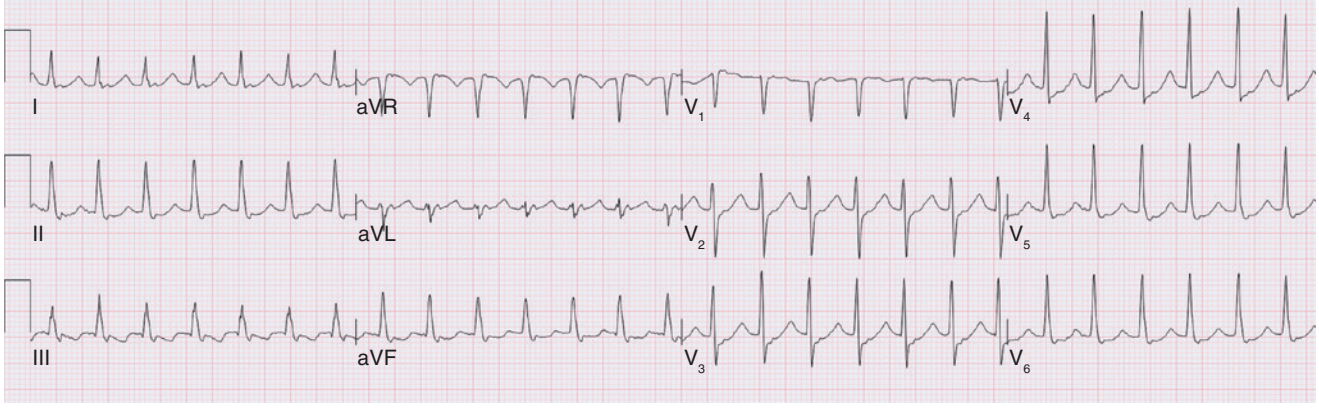


FIG. 1.43

150. A 21-year-old woman with palpitations and presyncope (Fig. 1.44)

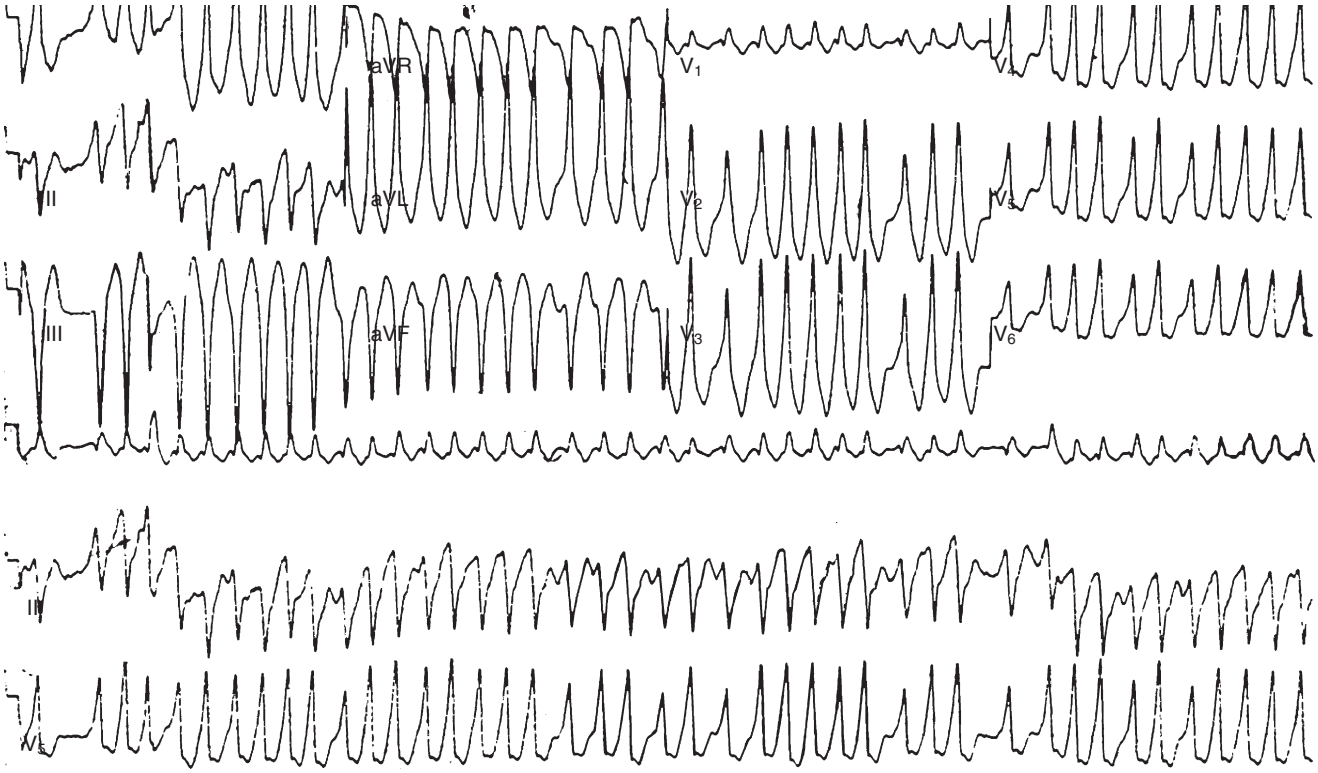


FIG. 1.44

151. A 48-year-old woman with nausea (Fig. 1.45)

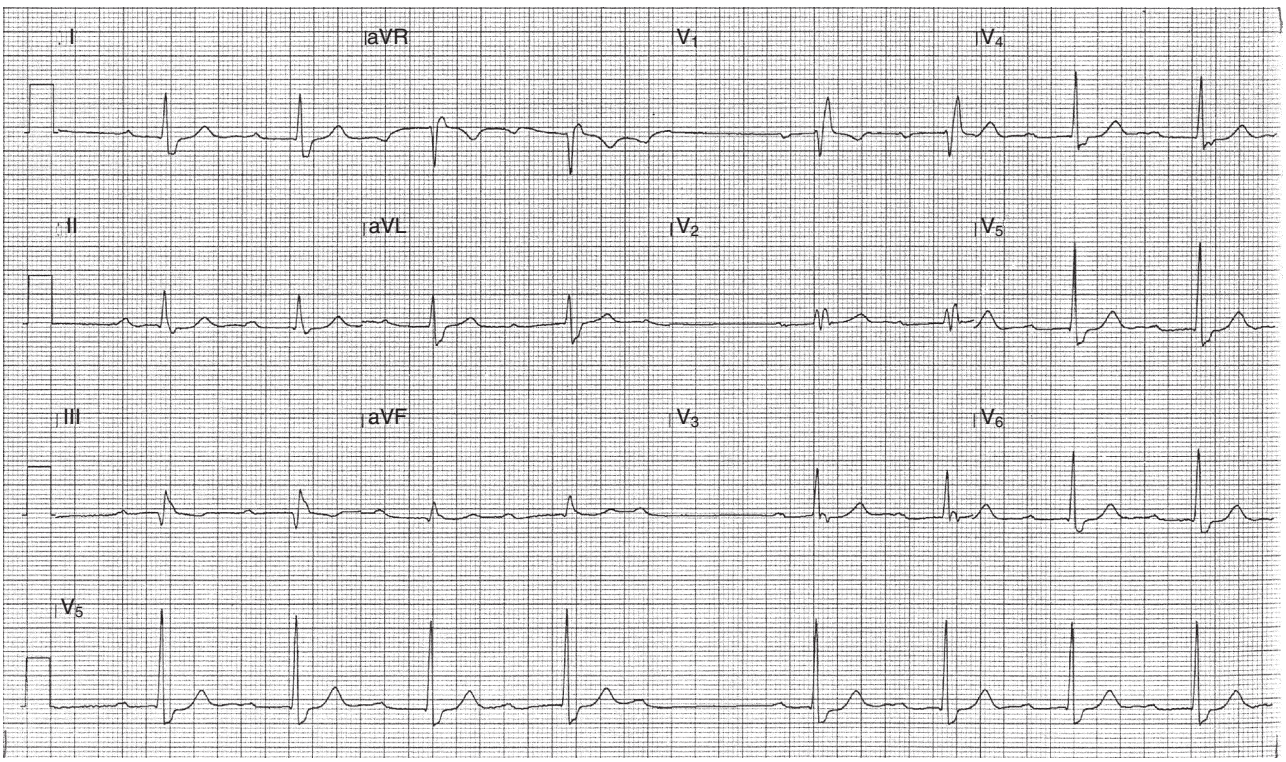


FIG. 1.45

152. A 61-year-old man admitted with frequent dizziness (Fig. 1.46)

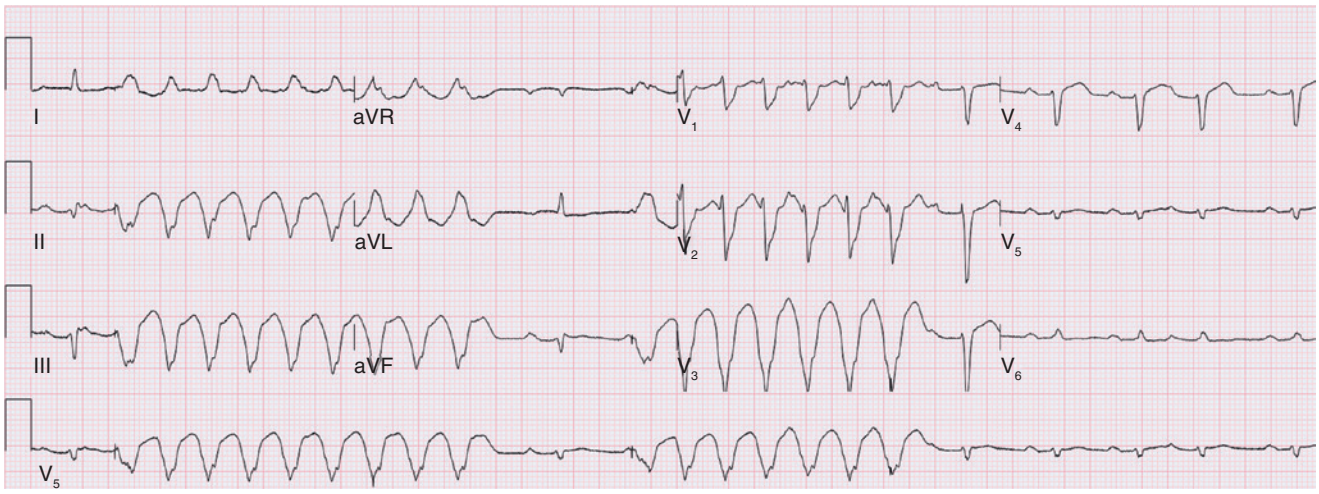


FIG. 1.46

153. A 65-year-old man who underwent coronary artery bypass graft surgery 24 hours ago (Fig. 1.47)

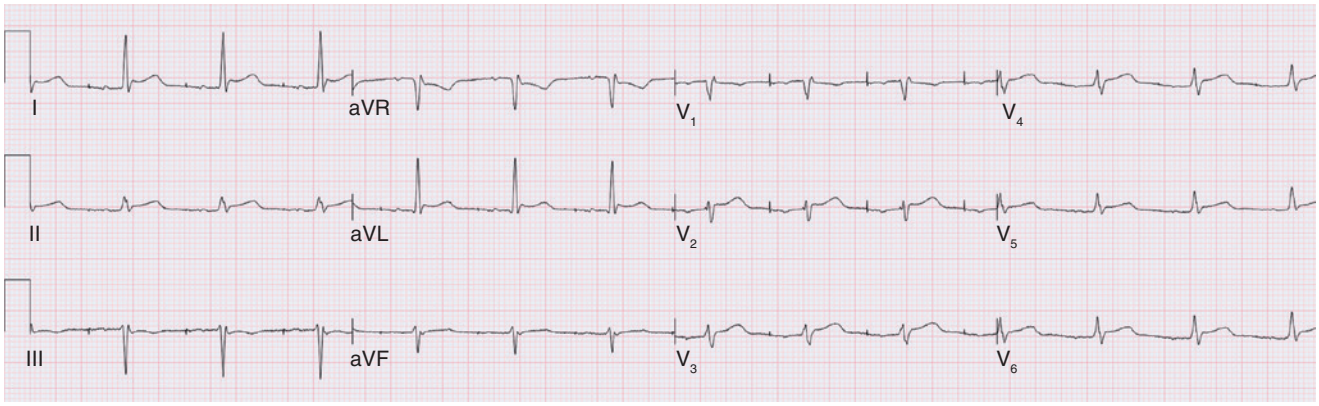


FIG. 1.47

154. A 74-year-old man with an irregular pulse (Fig. 1.48)

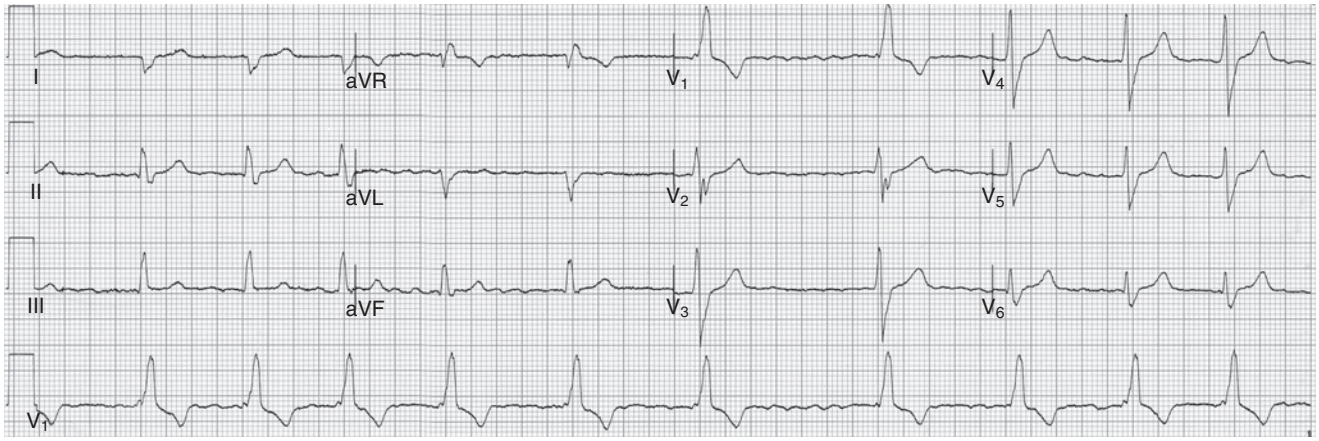


FIG. 1.48

155. A 28-year-old man presents for a pre-employment physical examination (Fig. 1.49)

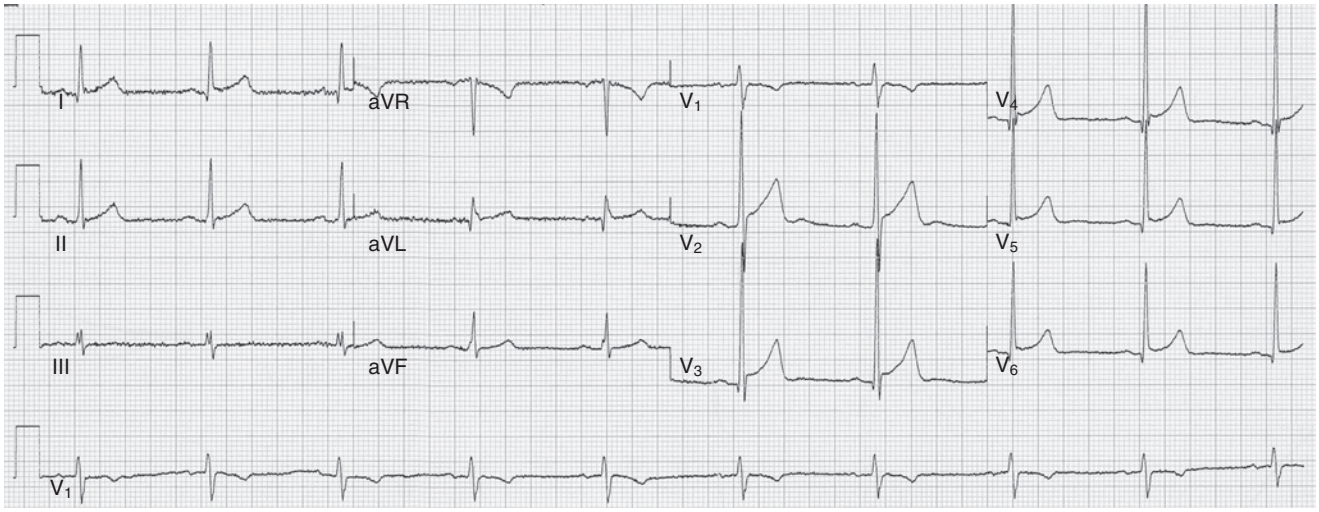


FIG. 1.49

156. A 66-year-old woman with renal failure, palpitations, and lightheadedness (Fig. 1.50)

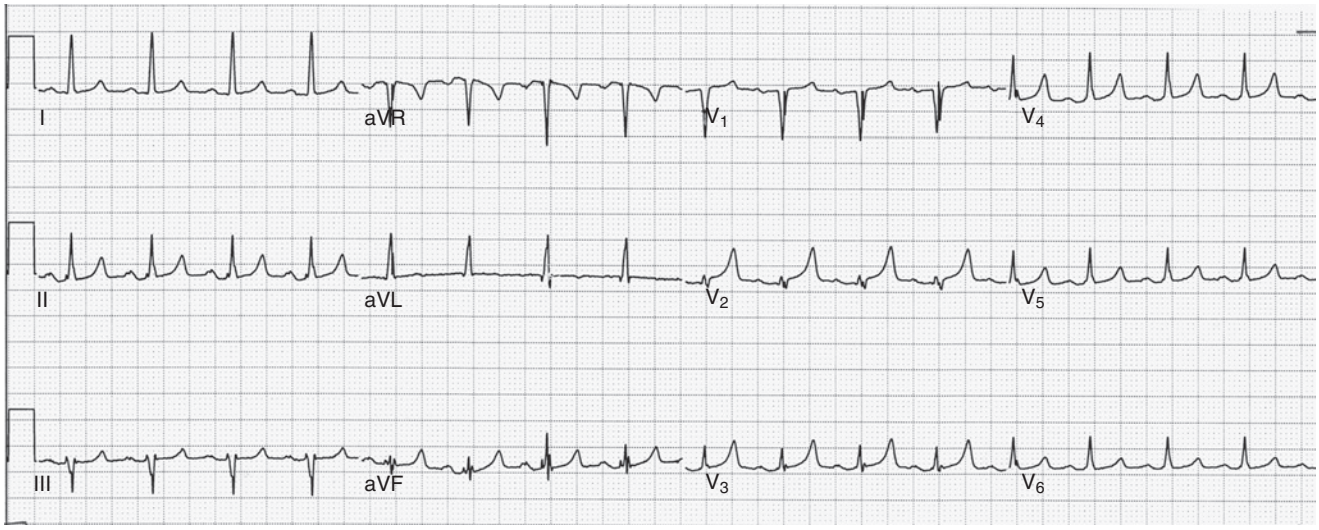


FIG. 1.50

157. A 63-year-old man admitted for elective orthopedic surgery (Fig. 1.51)

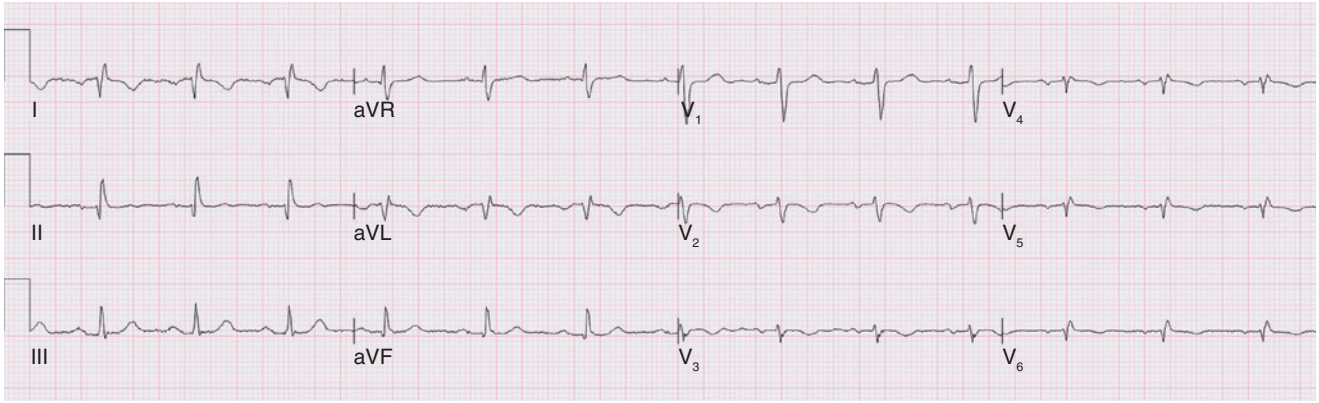


FIG. 1.51

158. A 54-year-old man with sudden lightheadedness (Fig. 1.52)

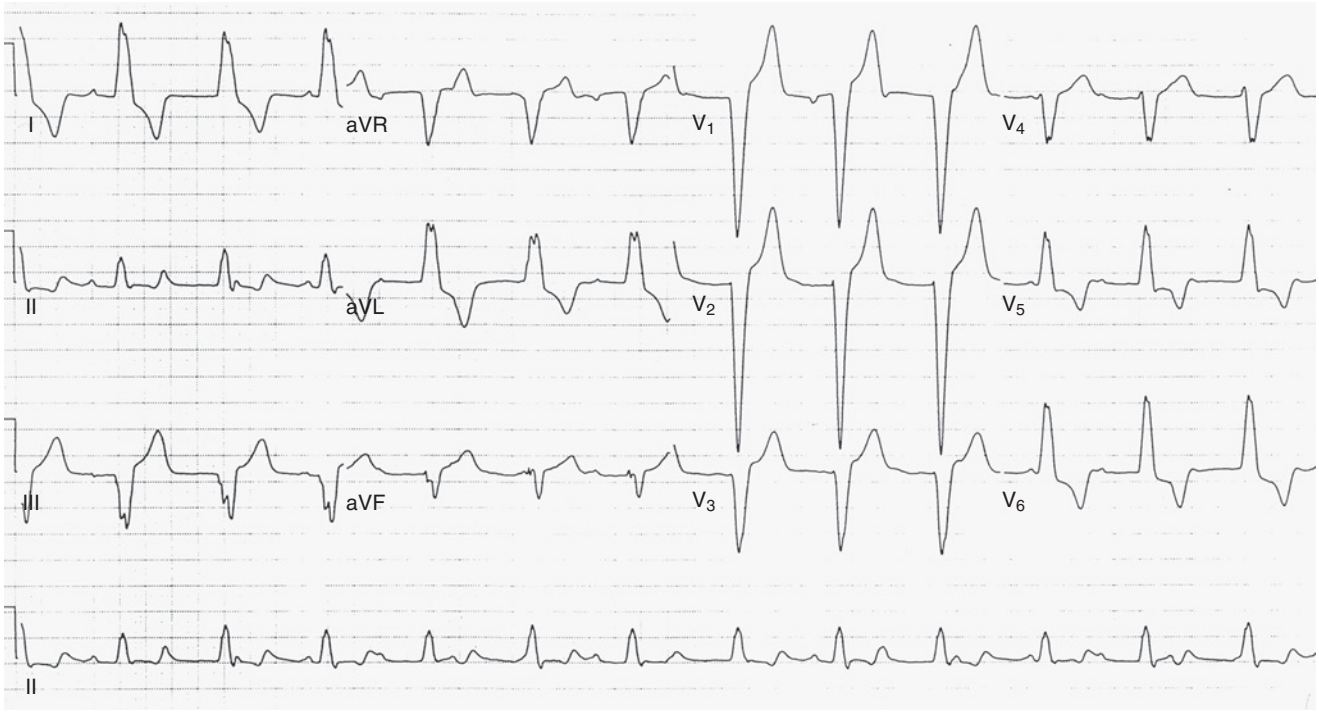


FIG. 1.52

159. A 64-year-old woman with profound nausea and diaphoresis (Fig. 1.53)

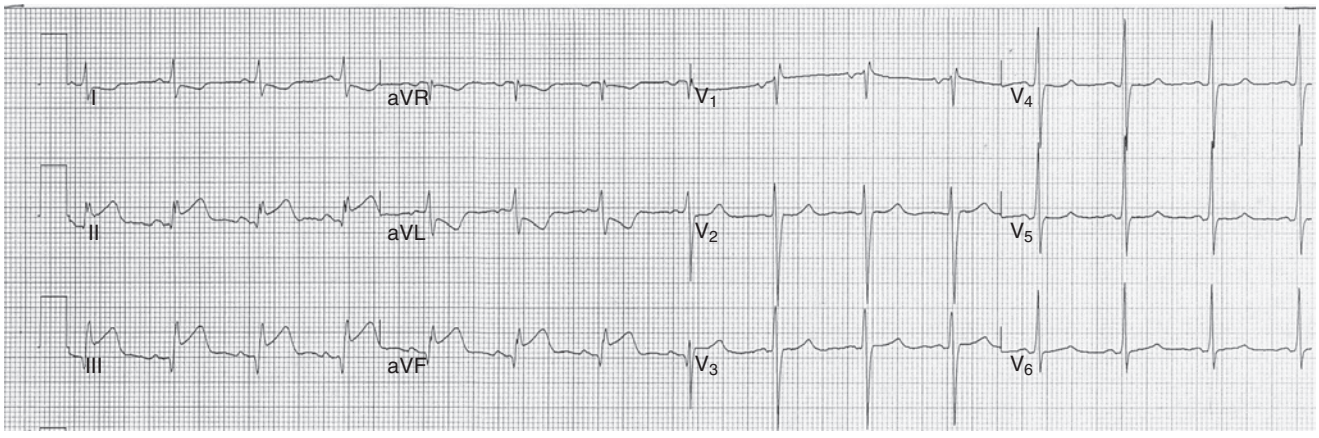


FIG. 1.53

160. A 55-year-old man with long-standing hypertension (Fig. 1.54)

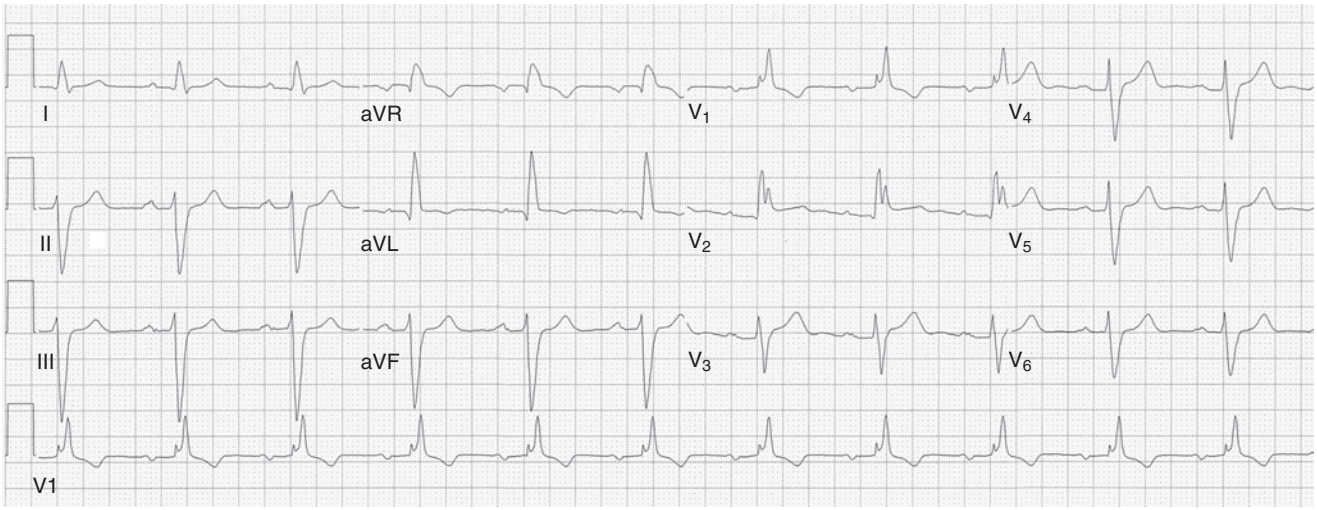


FIG. 1.54

161. An asymptomatic 36-year-old man presents for an insurance physical examination (Fig. 1.55)

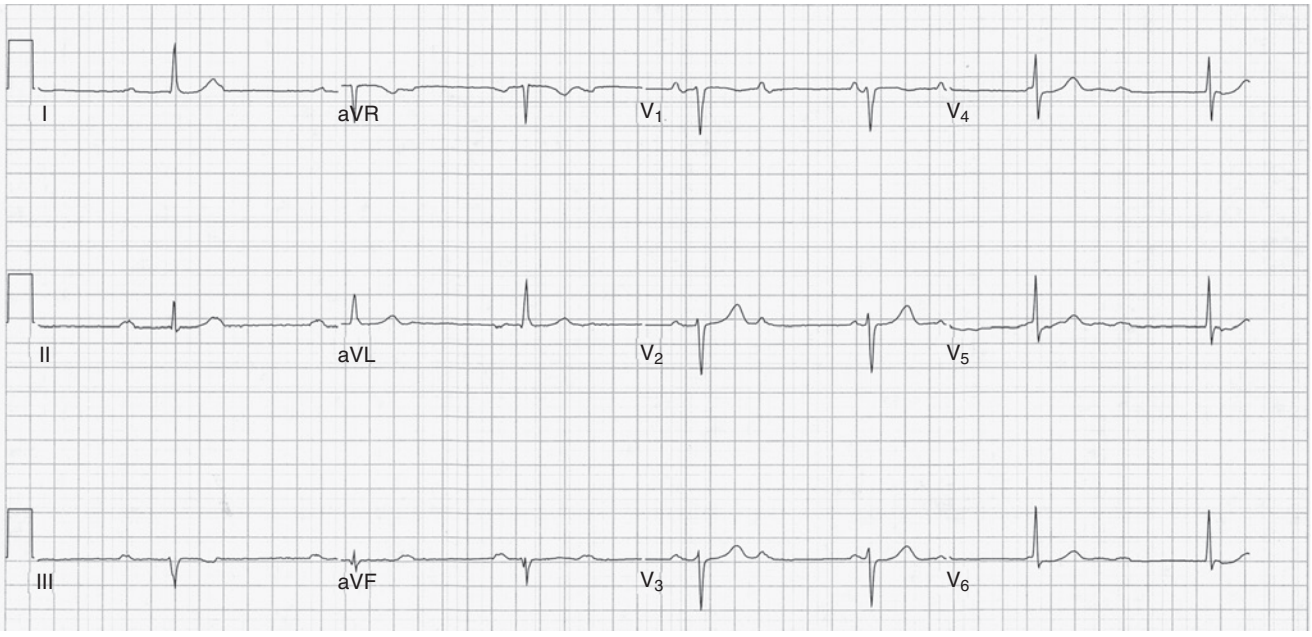


FIG. 1.55

162. A 23-year-old woman referred to the cardiology clinic because of a murmur and abnormal ECG (Fig. 1.56)

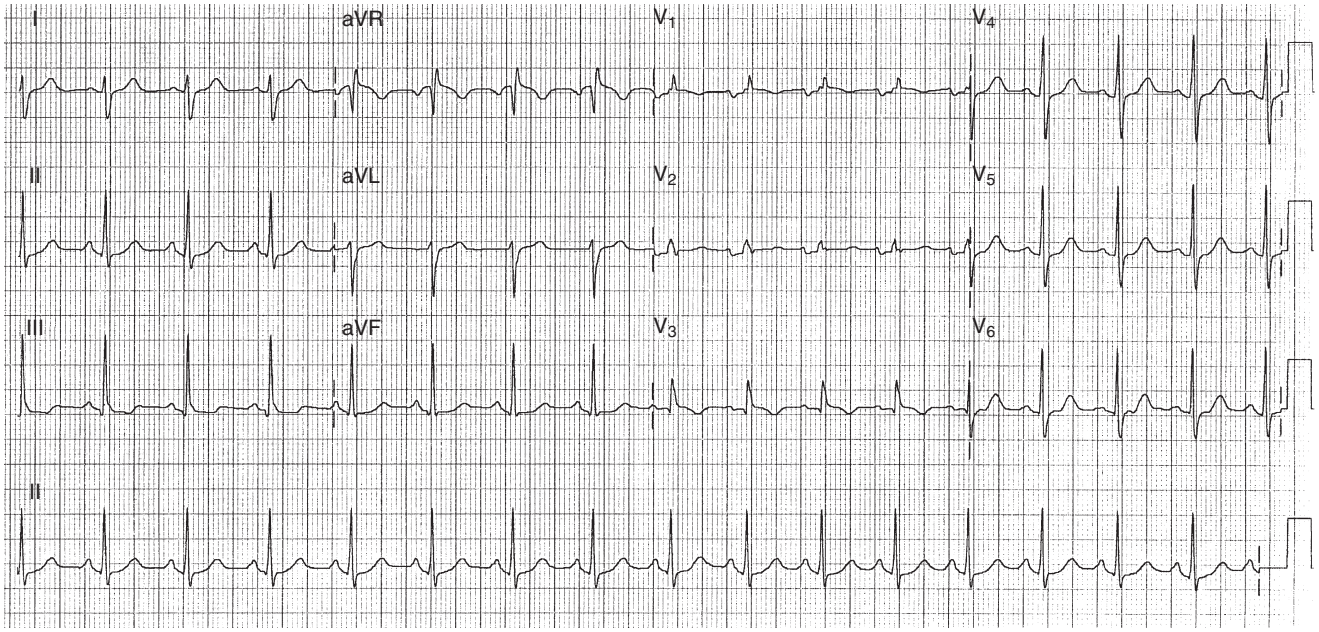


FIG. 1.56

163. A 51-year-old woman with discrete episodes of presyncope (Fig. 1.57)

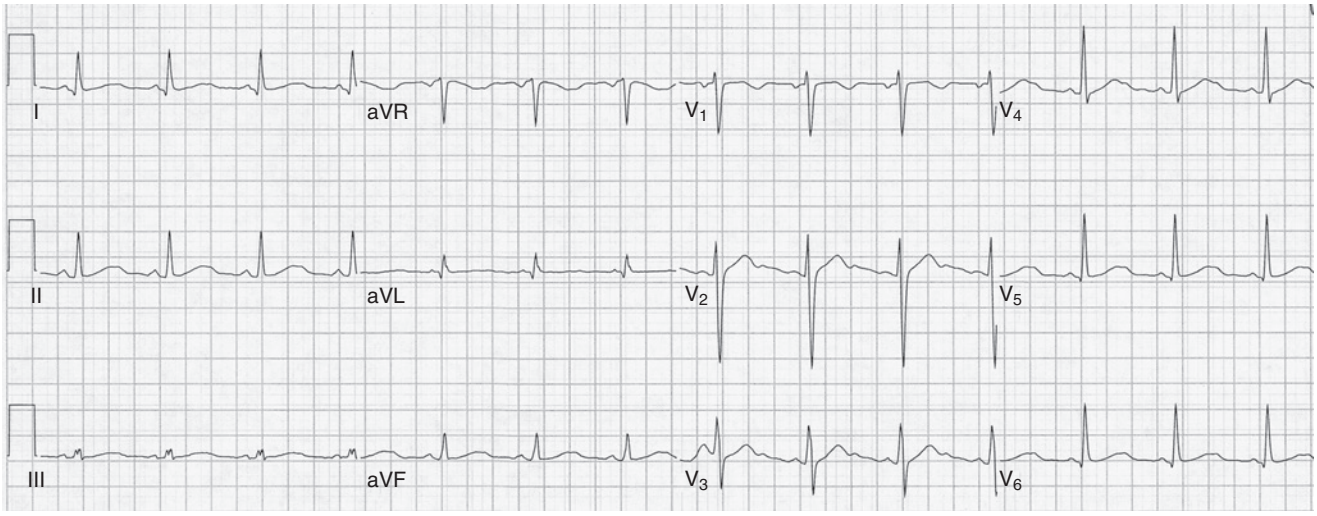


FIG. 1.57

164. A 72-year-old man with palpitations after coronary artery bypass surgery (Fig. 1.58)

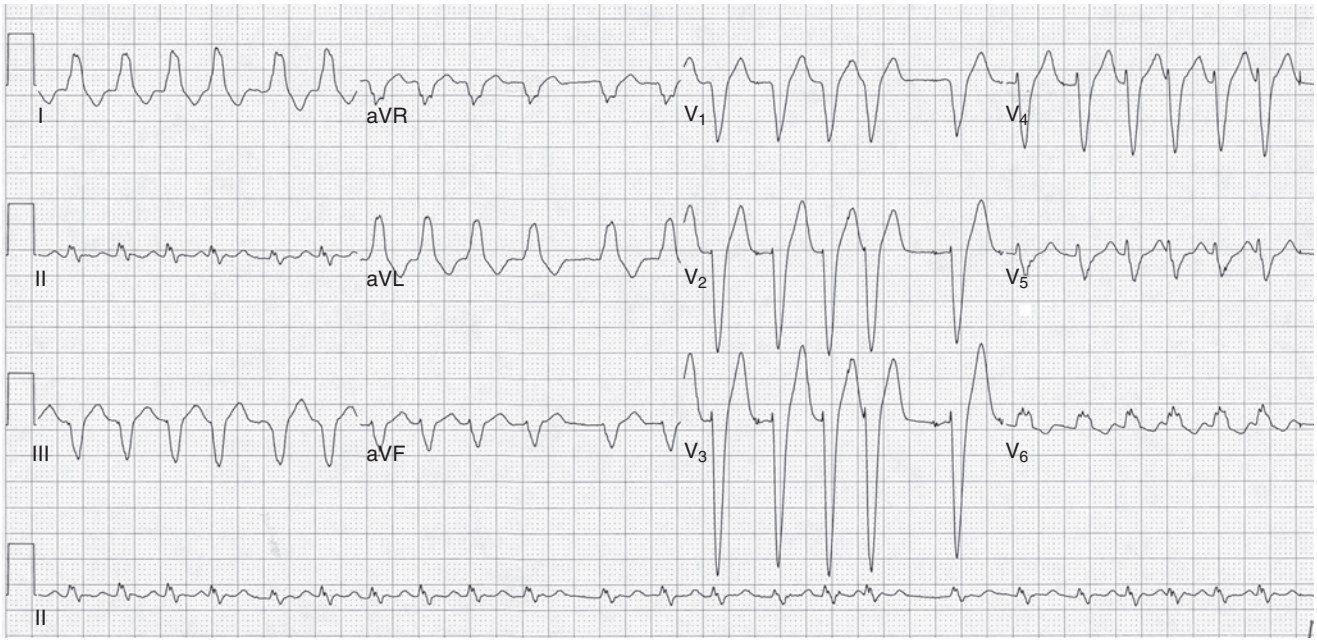


FIG. 1.58

165. A 78-year-old man with a long history of cigarette smoking and paroxysmal atrial fibrillation (Fig. 1.59)

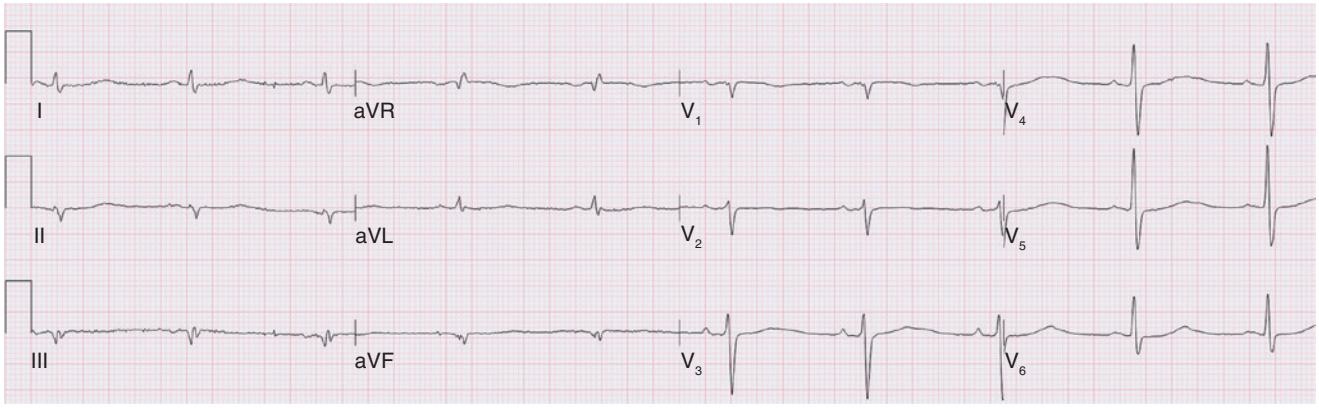


FIG. 1.59

166. A 69-year-old man with a history of dilated cardiomyopathy (Fig. 1.60)

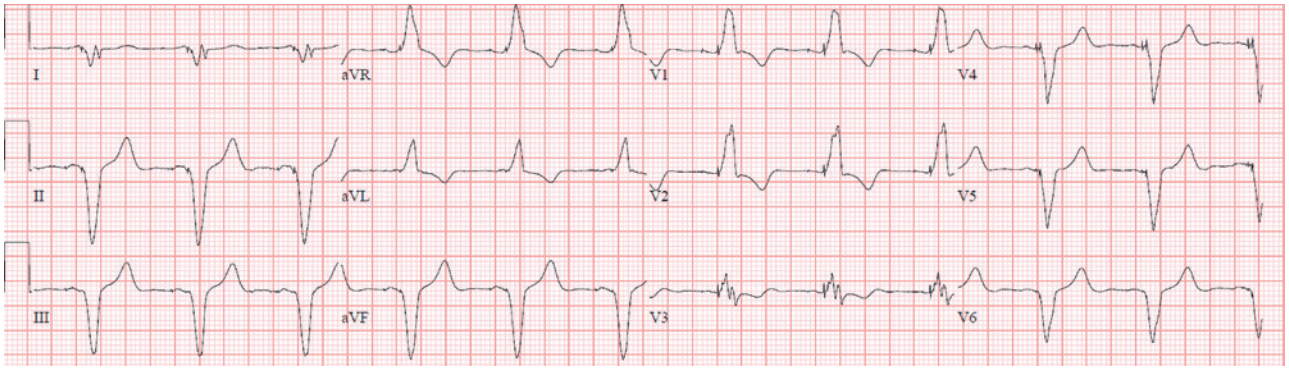


FIG. 1.60

167. An elderly nursing home resident with fatigue (Fig. 1.61)

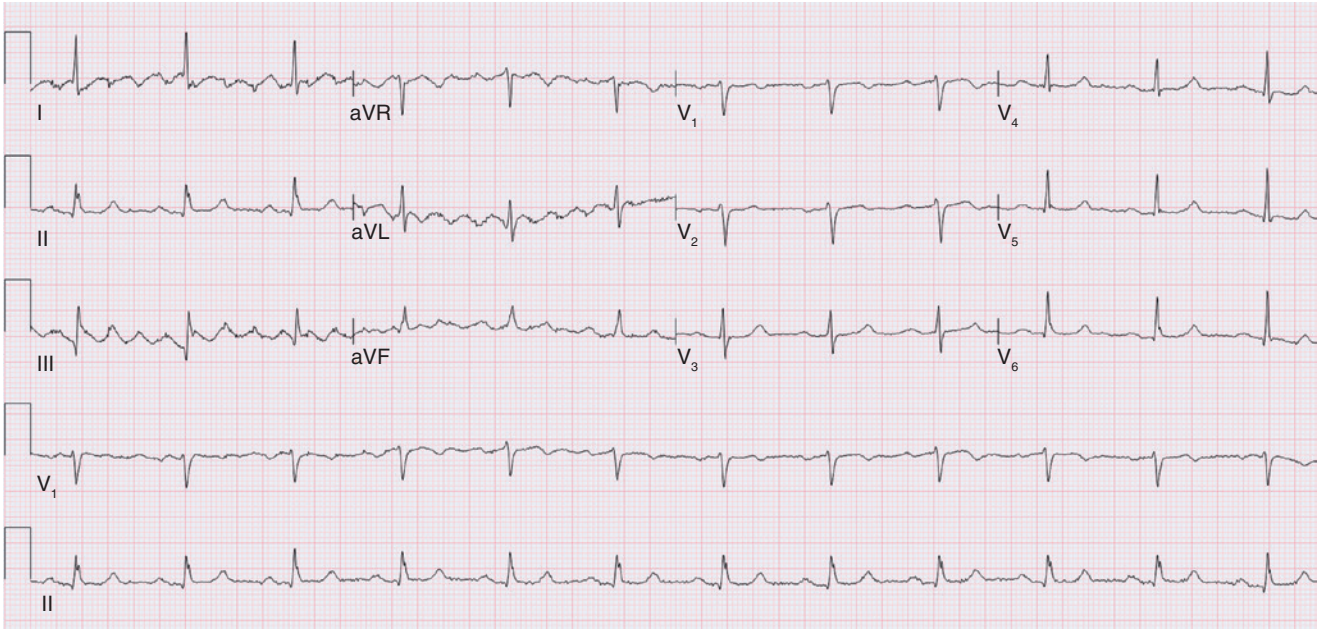


FIG. 1.61

SECTION I ANSWERS

(CHAPTERS 1 TO 20)

Fundamentals of Cardiovascular Disease; Genetics and Personalized Medicine; Evaluation of the Patient

ANSWER TO QUESTION 1

D (Braunwald, pp. 160–161)

The normal systolic blood pressure response during exercise is a progressive increase to a peak value between 160 and 200 mm Hg. The higher end of this range is more commonly observed in older patients; in general, black patients tend to have a higher systolic blood pressure response to exercise than white patients. A failure to increase systolic blood pressure to at least 120 mm Hg, or a decline in systolic blood pressure during exercise, is abnormal. Such exertional hypotension occurs in 3% to 9% of patients and is suggestive of underlying multivessel or left main coronary artery disease (CAD). Other causes of a decline in systolic blood pressure, or a failure to increase systolic blood pressure with exercise, include cardiomyopathy, vasovagal reactions, ventricular outflow obstruction, hypovolemia, arrhythmias, and prolonged vigorous exercise. Subjects who demonstrate hypotension in the *postexercise* period are much less likely to have advanced underlying CAD; about 3% of normal subjects younger than 55 years of age demonstrate such a response.

In normal subjects, diastolic blood pressure does not change significantly during exercise. A large change in diastolic blood pressure is uncommon and has not been shown to correlate with underlying CAD.

The age-related maximum predicted heart rate (MPHR) is estimated from the following formula:

$$\text{MPHR} = 220 - \text{age (in years)}$$

which in this patient would be 166 beats/min. The peak heart rate he achieved during the test was 152 beats/min, or 92% of the MPHR (i.e., 152/166 beats/min). An achieved heart rate of ≥85% MPHR is indicative of an adequate diagnostic workload.

Predictors of low prognostic coronary risk in his case include his very good functional capacity (having achieved stage IV of the Bruce protocol) and lack of cardiopulmonary symptoms or ST-segment changes during the test.

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ANSWER TO QUESTION 2

B (Braunwald, p. 91)

The normal second heart sound (S_2) consists of two parts, an earlier aortic component and a later pulmonic component. During inspiration, the increased filling of the right ventricle prolongs the ejection phase of the right side of the heart leading to *delayed* closure of the pulmonic valve. This is the predominant factor in normal inspiratory splitting of the S_2. Right bundle branch block delays right ventricular (RV) activation and ejection and is therefore associated with *widened* splitting of S_2. Conditions in which left ventricular activation is late, such as left bundle branch block or RV pacing, cause closure of the aortic valve to be delayed. In that setting, the pulmonic valve closure sound actually precedes that of the aortic valve. Then, during inspiration (and prolongation of RV ejection), the delayed closure of the pulmonic valve narrows the timing between the two sounds, a situation known as *paradoxical* splitting.

Fixed splitting of the S_2 is typical of an uncomplicated ostium secundum atrial septal defect. In this condition, closure of the pulmonic valve is delayed because of the increased flow through the right-sided cardiac chambers and an increase in pulmonary vascular capacitance, contributing to a widened split of S_2. On inspiration, augmentation of the systemic venous return is counterbalanced by a reciprocal decrease in the volume of the left-to-right shunt, such that RV filling and the timing of P_2 relative to A_2 do not change, resulting in the fixed splitting.

When valvular stenosis restricts opening of a cardiac valve, the decreased excursion of the leaflets *reduces* the intensity of the closure sound. Thus, in pulmonic stenosis, the pulmonic component of S_2 becomes softer.

ANSWER TO QUESTION 3

D (Braunwald, p. 26; Figs. 3.3–3.5)

In addition to accuracy and reliability, the performance of a diagnostic test depends on its ability to distinguish between the presence and absence of disease. Test performance depends on its sensitivity and specificity, as well as the

prevalence of disease in the population of patients to be studied or the pretest probability of disease in a particular patient. Sensitivity and specificity are characteristics of the diagnostic test that are not altered by disease prevalence or pretest probability. Sensitivity is the percentage of patients with disease who will be correctly identified by the test. Specificity is the percentage of patients without disease who will be correctly identified as disease free by the test. Positive predictive value is the probability that a positive test correctly identifies the presence of disease. Negative predictive value is the probability that a negative test correctly identifies the absence of disease. A perfect diagnostic test has a positive predictive value of 100% (no false-negative results) and a negative predictive value of 100% (no false-positive results).

For a diagnostic test with moderately high sensitivity and specificity, the test will perform best in a population of patients with an intermediate pretest probability of disease (patient D). In patients with a low pretest probability of disease (patients A and B), the positive predictive value of the test is low and there will be a large number of false-positive tests that may prompt unnecessary testing and procedures. In patients with an extremely high pretest probability of disease (patients C and E), the negative predictive value of the test is low and the possibility that a negative result represents a false negative is unacceptably high.

ANSWER TO QUESTION 4

C (Braunwald, pp. 92–93; Table 10.6; Fig. 10.8)

The term *continuous* applies to murmurs that begin in systole and continue without interruption into part or all of diastole. The murmur described here, that of a patent ductus arteriosus, is the classic continuous murmur, peaking in intensity just before or after S_2, then decreasing in intensity during diastole, sometimes disappearing before the subsequent first heart sound. Continuous murmurs may be congenital or acquired and can be caused by (1) an aortopulmonary shunt, such as patent ductus arteriosus; (2) an arteriovenous shunt, including arteriovenous fistulas, coronary artery fistulas, or rupture of an aortic sinus of Valsalva aneurysm into a right heart chamber; (3) constricted arterial vessels (e.g., a femoral arterial atherosclerotic stenosis); (4) turbulence in nonconstricted arteries (e.g., the "mammary souffle," an innocent flow murmur heard during late pregnancy and the puerperium over the lactating breast and augmented by light pressure with the stethoscope); or (5) venous murmurs, such as a cervical venous hum, an often "rough" sounding murmur present in healthy children and young adults. The cervical hum may be accentuated by deforming the internal jugular vein with rotation of the head. It is augmented during pregnancy and in disease states in which there is increased venous flow, such as thyrotoxicosis.

The combined murmurs of aortic stenosis and regurgitation have distinct systolic and diastolic components and do not constitute a continuous murmur.

ANSWER TO QUESTION 5

E (Braunwald, pp. 89–91; Fig. 10.5)

Reduced or unequal arterial pulsations may occur in the arms of patients with atherosclerosis affecting the subclavian arteries, aortic dissection, and uncommon arteritides such as Takayasu disease. In supravalvular aortic stenosis (AS), there may be selective streaming of the arterial jet toward the innominate artery and right arm, leading to higher pressures in that extremity. This is not the case, however, with subvalvular or valvular AS. Valvular AS leads to pulsus parvus et tardus, a slowly rising and weak pulse best appreciated by palpation of the carotid arteries. Coarctation of the aorta in adults usually involves the aorta distal to the origin of the left subclavian artery and leads to higher blood pressure in the upper extremities compared with the legs; the arm pulses and pressures are typically equal.

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ANSWER TO QUESTION 6

C (Braunwald, p. 219; Figs. 14.64 and 14.65)

This patient with metastatic breast cancer and a large pericardial effusion has clinical findings consistent with cardiac tamponade.[1] Tamponade physiology results when an accumulation of pericardial effusion causes equilibration of intrapericardial and intracardiac pressures.[2,3] In addition to the presence of an echo-free space surrounding the heart, characteristic echocardiographic and Doppler findings reflect the aberrant physiology of this disorder. Collapse of the right ventricle during early *diastole* occurs because the abnormally elevated pericardial pressure transiently exceeds right ventricular (RV) pressure at that phase of the cardiac cycle. Indentation of the right atrial wall during diastole is a more sensitive marker of increased pericardial pressure, but is less specific for tamponade physiology than RV collapse and tends to occur earlier in the course of hemodynamically significant pericardial effusion. Cardiac tamponade is associated with exaggerated ventricular interdependence, a phenomenon manifested at the bedside by pulsus paradoxus. The Doppler correlate of pulsus paradoxus is amplified respirophasic variation of flow across the right- and left-sided cardiac valves. This includes a prominent inspiratory decrease in flow velocity across the mitral and aortic valves (see the transmitral tracing in Fig. 1.62), whereas inspiration causes

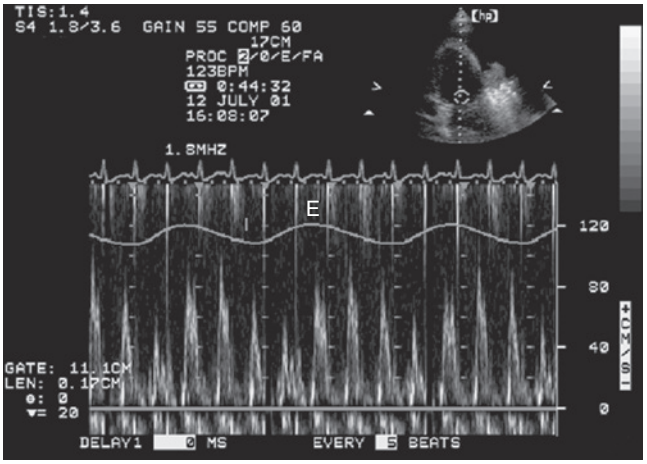

FIG. 1.62

a prominent reciprocal *increase* in flow velocity across the tricuspid and pulmonic valves.

A marked increase of the E/A ratio of the mitral valve inflow velocity is a finding typical of constrictive pericarditis, not cardiac tamponade.

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ANSWER TO QUESTION 7

D (Braunwald, pp. 88, 90)

Pulsus paradoxus is an exaggeration of the normal tendency for arterial pulse strength to fall with inspiration and can be measured easily and accurately at the bedside with a sphygmomanometer. A decline of more than 8 to 10 mm Hg with inspiration is considered abnormal and can be observed in a variety of conditions. Pulsus paradoxus is characteristic of patients with cardiac tamponade, is seen in approximately one-third of patients with chronic constrictive pericarditis, and is noted as well in patients with wide intrapleural pressure swings (e.g., bronchial asthma and emphysema), pulmonary embolism, pregnancy, extreme obesity, and hypovolemic shock.

Notably, aortic regurgitation augments left ventricular diastolic pressure and tends to prevent pulsus paradoxus even in the presence of tamponade.

The Kussmaul sign manifests as inappropriate augmentation of the jugular venous pressure during inspiration and implies the presence of constrictive pericarditis, not isolated cardiac tamponade.

ANSWER TO QUESTION 8

B (Braunwald, pp. 118, 136–138; Tables 12.1 and 12.9)

The clinical presentation is concerning for an acute coronary syndrome and rapid evaluation of the ECG is critical to detect whether an acute ST-segment elevation myocardial infarction (STEMI) is present, which would warrant prompt coronary revascularization. The ECG in this patient is not diagnostic for STEMI, with <1 mm of ST elevation in only one lead (III). However, the presence of ST depressions and a prominent R wave in the anterior precordial leads should raise suspicion for an acute ST elevation myocardial infarction in the *posterior* territory. Since standard leads are not placed on the patient's back, myocardial injury of the posterior wall is typically identified as mirror-image ECG findings in the opposite anatomic position, namely leads V_1–V_3. In this circumstance, posteriorly placed ECG leads (V_7–V_9) placed from the posterior axillary line to the left border of the spine would be helpful to evaluate for true posterior ST elevations.

Right-sided precordial leads are useful to detect right ventricular involvement in the setting of an inferior STEMI. Awaiting the results of cardiac biomarkers would delay care. Diagnostic tests should focus first on an acute coronary syndrome rather than pulmonary embolism, based on the presenting clinical symptoms.

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ANSWER TO QUESTION 9

C (Braunwald, Tables 8.1–8.3)

All drugs prescribed to achieve a particular clinical benefit also have the potential for toxicity. Many factors determine the likelihood of drug toxicity, including the pharmacokinetic and pharmacodynamic properties of the drug and its target, genetic variability in the patient's response to the drug, and drug-drug interactions.

Many medications are metabolized by isoforms of the cytochrome P-450 (CYP) enzyme system, which are expressed in the liver and other tissues. Ketoconazole, erythromycin, and clarithromycin (but not azithromycin) are examples of drugs that inhibit CYP3A4 and CYP3A5. Because these P-450 isoforms are responsible for metabolism of simvastatin, atorvastatin, and lovastatin, combined therapy with such inhibitors may increase the likelihood of myopathy due to these statins.[1,2] Pravastatin is not metabolized by the CYP3A system, and thus the risk of myopathy is not increased in the presence of CYP3A inhibitors.

St. John's wort induces activity of CYP3A and results in decreased cyclosporine levels.[3]

Sildenafil, a selective inhibitor of phosphodiesterase type 5 prescribed to treat erectile dysfunction, potentiates the vasodilatory effect of nitrates. Administration of nitrates within 24 hours of sildenafil use has been associated with profound hypotension.

Verapamil inhibits the P-glycoprotein-mediated efflux of digoxin into bile and urine and may contribute to digoxin toxicity.

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ANSWER TO QUESTION 10

D (Braunwald, p. 156; Table 13.1)

Treadmill exercise testing is a safe procedure with an associated mortality of <0.01% and risk of myocardial infarction of 0.04%.[1] The risk of a procedure-related complication is determined by the clinical characteristics of the patient to be studied. Patients with high-grade obstruction of the left ventricular outflow tract, such as those with hypertrophic obstructive cardiomyopathy or critical aortic stenosis, are at an increased risk of a procedural complication owing to the inability of cardiac output to compensate for peripheral vasodilatation during exercise. Patients with unstable angina should not be subjected to the high myocardial oxygen demands of exercise and should be referred

for coronary angiography instead. Acute myocarditis is associated with an increased risk of exercise-associated sudden death.

Despite the theoretical risk of aortic rupture due to increased wall stress, treadmill exercise testing may be safely performed in patients with an abdominal aortic aneurysm.[2] In contrast, aortic dissection is a contraindication to the stress of exercise testing.[3]

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ANSWER TO QUESTION 11

B (Braunwald, pp. 262–263, 266, 268; Table 16.1; Figs. 16.11 and 16.12)

The images show a fixed defect in the mid- and apical anterior wall segments with preserved wall motion and thickening as evident from the end-diastolic and end-systolic frames. These findings are most consistent with imaging artifact due to breast tissue attenuation.

Attenuation artifacts are a common source of error in single-photon emission computed tomography (SPECT). Regional wall motion and wall thickening should be assessed on the electrocardiographic-gated SPECT data in any region that shows a fixed perfusion defect. Although a transmural myocardial scar would be associated with reduced wall motion and wall thickening, attenuation artifact is more likely where there is a fixed perfusion defect with normal regional wall motion and wall thickening.

Thallium-201 is a lower-energy radiotracer that results in more attenuation artifacts than technetium-99m imaging, and hence would be an inferior choice in this case.

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ANSWER TO QUESTION 12

C (Braunwald, pp. 91–92; Figs. 10.4 and 10.8)

S_2 coincides with closure of the aortic and pulmonic valves and marks the onset of diastole at the bedside. Several abnormal heart sounds may follow S_2. The opening snap of mitral stenosis (MS) is a high-frequency sound that occurs shortly after S_2. It is generated when the superior bowing of the anterior mitral leaflet during systole rapidly reverses direction toward the left ventricle in early diastole, owing to the high left atrial (LA) pressure. The delay between the aortic component of S_2 and the opening snap corresponds to the left ventricular (LV) isovolumic relaxation time. As MS becomes more severe, this phase shortens because of the greater LA pressure, and the interval between S_2 and the opening snap decreases. Other sounds that occur shortly after S_2 are associated with the rapid filling phase of diastole. These include the third heart sound (S_3), which is a low-frequency sound thought to be caused by sudden limitation of LV expansion during brisk early diastolic filling. An S_3 is normal in children and young adults, but the presence of this sound beyond age 40 is abnormal and reflects flow into a dilated ventricle or an increased volume of flow in early diastole, as may occur in mitral regurgitation. A tumor "plop" may be auscultated when an atrial myxoma, attached to the interatrial septum by a long stalk, moves into and obstructs the mitral or tricuspid valve orifice during early diastole. In constrictive pericarditis, a pericardial "knock" may be heard during the rapid filling phase of early diastole as the high-pressure atria rapidly decompress into relatively noncompliant ventricles.

An ejection click is an early *systolic* sound that represents opening of an abnormal semilunar valve, characteristically a bicuspid aortic valve.

ANSWER TO QUESTION 13

D (Braunwald, pp. 161–163, 165–166)

Electrocardiographic changes during exertion in an asymptomatic patient must be interpreted in light of the pretest likelihood of coronary disease. An exercise-induced ST-segment abnormality is an independent predictor of future cardiac events in men with and without conventional risk factors for coronary disease, although the risk is greatest among the former. However, in over 5 years of follow-up, only one in four such patients will actually develop symptoms of cardiac disease, most commonly angina. Because the patient described in this question is asymptomatic and demonstrates good exercise capacity, there is no need for immediate aggressive intervention such as cardiac catheterization. Appropriate recommendations for this patient with asymptomatic coronary artery disease would include aggressive risk factor modification: smoking cessation, control of hypertension, the addition of aspirin, and statin therapy.

The distribution of ST-segment depressions during exercise testing correlates poorly with the location of coronary stenoses. Conversely, the location of ST-segment *elevations*, when present, does correlate well with the anatomic lesion causing ischemia.

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ANSWER TO QUESTION 14

C (Braunwald, pp. 126, 145; Fig. 12.44; pp. 164–165, 168, 172, 285)

Several clinical situations affect the ST segment and impair the diagnostic utility of the standard exercise ECG. These

include the presence of left bundle branch block (LBBB), left ventricular hypertrophy, ventricular preexcitation (Wolff-Parkinson-White syndrome), and digitalis therapy. In these situations, other aspects of the exercise test, such as exercise duration, presence or absence of symptoms, and abnormal blood pressure or heart rate responses, may still provide useful diagnostic information. However, in the presence of these baseline electrocardiographic abnormalities, concurrent imaging (e.g., nuclear scintigraphy or echocardiography) is frequently required when more specific diagnostic information is needed. In the case of LBBB, a vasodilator pharmacologic (e.g., adenosine or regadenoson) stress test with myocardial perfusion imaging helps to avoid artifactual septal perfusion defects compared with exercise protocols.

In patients with a low prior probability of significant coronary artery disease (CAD), such as a young woman without significant cardiac risk factors, the development of ST-segment depression on exercise testing is more often a nonspecific false-positive result than an indicator of previously undetected CAD.

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ANSWER TO QUESTION 15

D (Braunwald, pp. 350, 356; Table 19.1)

Diagnostic cardiac catheterization is a relatively safe procedure, with an overall risk of a major complication of 1%. Mortality rates related to the procedure depend on the population studied and range from 0.08% to 0.75%. The risk of myocardial infarction is approximately 0.05%, and neurologic complications occur in 0.03% to 0.2% of patients. The incidence of acute renal dysfunction in patients with baseline renal insufficiency can be most effectively decreased with intravenous saline administration before and after the procedure. The addition of mannitol or furosemide to saline infusion has been shown to *worsen* renal outcomes in patients receiving an intravenous contrast agent.

Nonionic low osmolar contrast agents reduce the likelihood of adverse hemodynamic and electrophysiologic reactions during angiography. They also reduce the incidence of contrast-induced nephropathy in patients with baseline renal insufficiency, with or without diabetes. Of note, in patients with normal renal function, there is no advantage of low osmolar agents over ionic agents in the prevention of nephrotoxicity.

Cardiac catheters are available in many sizes, shapes, and lengths. The outer diameter of the catheter is specified using French units (F), where 1 F is equal to 0.33 mm.

Patients with tilting-disc prosthetic aortic valves should not undergo retrograde left-sided heart catheterization because of the risk of catheter entrapment, occlusion of the valve, or possible dislodgement of the disc with embolization.

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ANSWER TO QUESTION 16

C (Braunwald, pp. 140–141; Fig. 12.37)

Proximal occlusion of a dominant right coronary artery (RCA) leads to infarction of the left ventricular (LV) inferior wall, but often also involves the posterior wall, the right ventricle, and portions of the conduction system, which are all supplied by branches of the RCA. ST-segment elevation in leads II, III, and aVF is the sine qua non of transmural infarction of the inferior wall. If the posterior wall is involved, ST-segment depression is usually evident in V_1 and V_2, reflecting a current of injury on the side of the heart opposite those leads (if unipolar leads were placed on the patient's back overlying the posterior wall, ST-segment elevation would be observed instead). Very proximal occlusion of the RCA is often accompanied by right ventricular (RV) infarction because the RV arterial branch arises near the origin of that vessel. If RV infarction is present, right-sided precordial electrocardiographic leads, particularly V_4R, often demonstrate ST-segment elevation as well (Fig. 1.63). Sinus bradycardia may occur, especially in inferior or posterior infarction. This arrhythmia, particularly when accompanied by hypotension, may arise from stimulation of cardiac vagal afferent fibers, which are prominent in the inferoposterior left ventricle. Sinus bradycardia may also be a vasovagal response to the severe chest pain in acute myocardial infarction or reflect ischemia of the sinoatrial artery, which arises from the RCA in 60% of the population. Another potential cause of bradycardia in this patient is the development of atrioventricular (AV) block because of either vagal stimulation or ischemia of the AV node. The AV node is supplied by the AV nodal artery, which arises from the RCA 85% of the time.

ANSWER TO QUESTION 17

C (Braunwald, pp. 178, 196; eFig. 14.2)

One of the most clinically important applications of Doppler technology is the estimation of pressure gradients across stenotic orifices or septal defects in the cardiovascular system. The Bernoulli equation relates the pressure difference across a narrowed area to the convective acceleration, flow acceleration, and viscous friction. By modifying the Bernoulli equation, a more clinically useful simplified formula is derived. The simplified Bernoulli equation states that the pressure difference across a flow-limiting orifice = $4V^2$, where V is the peak velocity distal to the obstruction. In this question, the patient's systolic blood pressure is 144 mm Hg, which,

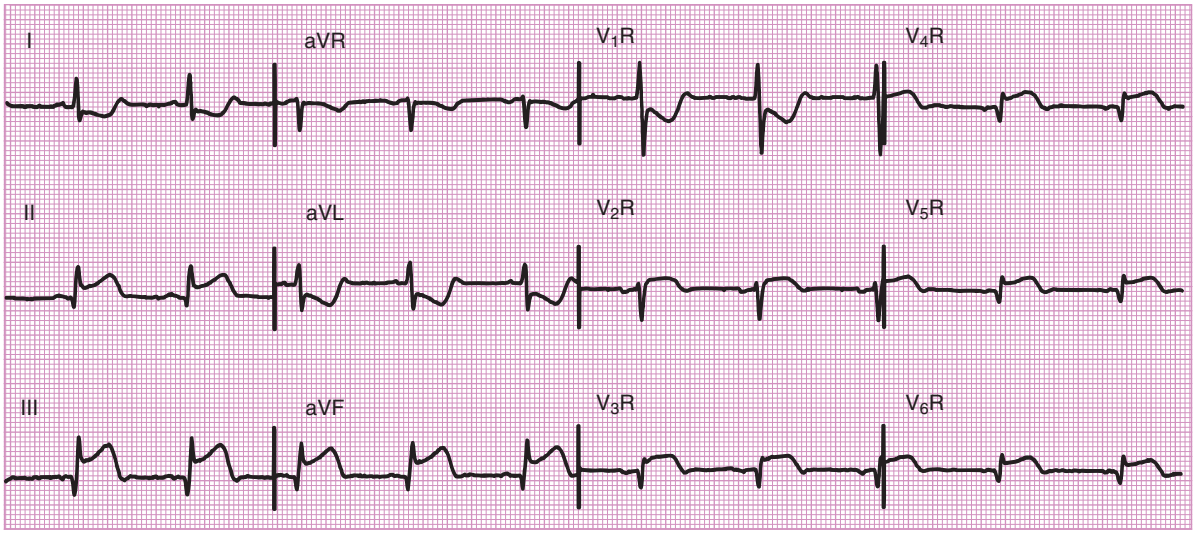

FIG. 1.63

in the absence of left ventricular (LV) outflow obstruction, is also the LV systolic pressure. If the ventricular septal defect (VSD) flow is 5.1 m/s, then using the modified Bernoulli equation, the pressure gradient across the VSD is $4 \times (5.1)^2 = 104$ mm Hg. The right ventricular systolic pressure can then be calculated by subtracting that gradient from the LV systolic pressure: 144 to 104, or 40 mm Hg. The transmitral flow velocity is not needed for this calculation.

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ANSWER TO QUESTION 18

C (Braunwald, pp. 92–93, 98–99; Table 10.6; p. 195; Fig. 14.30)

This patient's history is concerning for an undetected acute myocardial infarction (MI) 10 days earlier, including the prolonged chest "muscle ache," new Q waves in the inferior leads, and inferior wall motion abnormalities on echocardiography. The lack of acute intervention places the patient at risk for post-MI mechanical complications, including acute mitral regurgitation (MR) due to dysfunction or rupture of a papillary muscle, ventricular septal defect (VSD), and free wall rupture. The brief systolic murmur on examination in the setting of new-onset heart failure should raise suspicion for acute MR. Although chronic MR typically produces a holosystolic murmur at the apex, in acute MR there may only be a soft, early systolic murmur due to the rapid systolic increase in pressure in the unprepared and noncompliant left atrium (LA) that attenuates the pressure gradient between the left ventricle and LA responsible for the murmur.

The presumed recent right coronary artery occlusion in this patient would impair the blood supply to the posteromedial papillary muscle. Dysfunction or rupture of this papillary muscle often produces MR in an eccentric direction, which may be underestimated by transthoracic echocardiography, especially in this patient with poor acoustic windows. Given the high suspicion for papillary muscle involvement resulting in acute MR, a transesophageal echocardiogram would be appropriate, with cardiac surgical consultation for consideration of urgent valve repair. In most cases, coronary revascularization would be addressed with bypass grafting at the time of valve surgery rather than with percutaneous intervention.

A nuclear stress test would not address the urgent mechanical process in this patient's situation. The location of the murmur and echocardiographic findings are not consistent with a VSD such that urgent right heart catheterization alone would not be the best immediate approach.

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ANSWER TO QUESTION 19

D (Braunwald, pp. 146–147; Figs. 12.45 and 12.46)

Many electrolyte disturbances result in characteristic electrocardiographic manifestations. Decreased extracellular calcium in hypocalcemia prolongs phase 2 of the action potential (AP), thereby lengthening the AP duration and the QT interval. The long QT interval in hypocalcemia is characteristically flat (i.e., isoelectric), without the concave configuration of many drug-induced prolonged QT states. *Increased* extracellular calcium shortens the ventricular AP and the duration of the QT interval. The appearance of a J wave (also known as an Osborn wave—see arrow in Fig. 1.64), an extra deflection at the junction of the QRS complex and the ST segment that is typically observed in severe hypothermia, has been reported with severe *hyper*calcemia.[1]

Hyperkalemia causes a specific sequence of electrocardiographic changes depending on its severity. The earliest manifestation is narrow, peaked T waves. The QT interval is usually decreased at that time because of shortened AP duration. Progressive hyperkalemia reduces the resting membrane potentials in both the atria and ventricles, thus

FIG. 1.64

inactivating sodium channels. The net result is to slow depolarization and reduce AP conduction velocity. The ECG shows widening of the QRS complex with a decrease in P wave amplitude. PR-segment prolongation may also occur. Very marked hyperkalemia leads to slow, undulating ventricular flutter (a "sine wave" appearance) followed by eventual asystole. Hypokalemia, in contrast, manifests primarily as ST-segment depressions with flattened T waves and U wave prominence. Because of prolongation of the QT interval, there is a propensity for polymorphic ventricular tachycardia (torsades de pointes).

The effects of magnesium on the surface ECG are not as well characterized. Magnesium deficiency may predispose to prolongation of the QT interval, primarily as a result of a prolonged U wave (QU interval), and *polymorphic* ventricular tachycardia.

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ANSWER TO QUESTION 20

E (Braunwald, pp. 199, 229; eFig. 14.27; pp. 293, 313, 1594–1595; Fig. 77.11)

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The lungs are affected in >90% of patients. Autopsy studies demonstrate cardiac involvement in at least 25% of patients who have pulmonary sarcoid. The three principal manifestations of cardiac sarcoidosis are conduction abnormalities, ventricular arrhythmias, and/or ventricular dysfunction. Several imaging modalities are useful in the diagnosis of cardiac sarcoidosis. Although echocardiography may show no abnormalities in clinically silent disease, systolic and/or diastolic ventricular dysfunction can be visualized in patients with active sarcoidosis. Discrete regional wall motion abnormalities typically appear in *non-coronary* distributions.

Cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is sensitive for identifying abnormalities in sarcoidosis. LGE is usually patchy and nontransmural, with *sparing* of the endocardial border. LGE most commonly occurs in the basal septum and lateral wall and/or mid-myocardium. CMR is helpful in the assessment of clinically silent disease, as it can identify small regions of LGE, even in patients with normal systolic function. Of note, CMR cannot distinguish regions of active inflammation from permanent scar.

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) which reveals regions of inflammation in active disease, is complementary to CMR in the diagnosis of cardiac sarcoidosis and in the monitoring of response to therapy. Focal FDG PET uptake identifies areas of active inflammation typical of active cardiac sarcoidosis; in distinction, areas of scarring without active inflammation do not show uptake by this technique.

Although angiotensin-converting enzyme levels are elevated in 60% of patients with sarcoidosis, the test has both low sensitivity and specificity for identifying the condition.

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ANSWER TO QUESTION 21

C (Braunwald, p. 135; Table 12.8)

The underlying rhythm is atrial fibrillation. The Ashman phenomenon (as exemplified by the fifth QRS complex in the tracing) represents conduction aberrancy caused by changes in the preceding cycle length. Because the duration of the refractory period is a function of the immediate preceding cycle length, the longer the preceding cycle, the longer the ensuing refractory period and the more likely that the next impulse will be conducted with delay. Normally the length of the refractory periods of the conduction system components are as follows: right bundle branch > left bundle branch = atrioventricular node ≫ His bundle. Therefore, it would be unusual for the bundle of His to be the site of conduction delay and, as is commonly the case, the aberrant beat on this tracing demonstrates right bundle branch block morphology in lead V_1.

ANSWER TO QUESTION 22

C (Braunwald, pp. 92–93; Table 10.6)

Innocent (normal) systolic murmurs are related to intracardiac flow rates and are usually loudest in midsystole. They may be caused by normal vibrations of the pulmonary leaflets, by exaggeration of normal ejection vibrations within the pulmonary artery, or may be associated with sclerosis at the base of the aortic valve leaflets in the absence of significant valvular stenosis. The mammary souffle, heard over the breasts of normal women in late pregnancy or during lactation, may also be midsystolic in timing or continuous. Careful auscultation usually reveals a time delay between S_1 and onset of this murmur.

ANSWER TO QUESTION 23

D (Braunwald, pp. 87–88; Figs. 10.3 and 10.4)

A great deal of information about right-sided heart hemodynamics can be ascertained from the jugular venous pressure waveforms. The *a* wave results from venous distention due to right atrial contraction; the *x* descent reflects atrial relaxation and downward descent of the base of the right atrium (RA) during right ventricular (RV) systole. The *c* wave is an inconstant positive deflection in the jugular venous pulse that interrupts the *x* descent and corresponds to ventricular contraction. The *v* wave results from right

atrial filling during ventricular systole when the tricuspid valve is closed, and the *y* descent occurs after the tricuspid valve opens and right atrial pressure declines. It is easier for an observer to see the *x* and *y* descents than the positive pressure waves (*a, c,* and *v* waves) in the neck because the former produce larger excursions. An elevated jugular venous pressure reflects increased right atrial pressure. During inspiration, the jugular venous pressure normally declines as intrathoracic pressure becomes more negative. The Kussmaul sign is a paradoxical rise in the height of the venous pressure during inspiration. It reflects an inability of the right-sided chambers to accept additional volume, typical of constrictive pericarditis, but may also be observed in patients with right-sided heart failure, severe cor pulmonale, or tricuspid stenosis.

The *a* wave becomes more prominent in conditions that increase the resistance to right atrial contraction, such as RV hypertrophy, pulmonary hypertension, or tricuspid stenosis. Amplified "cannon" *a* waves are evident during any situation that causes atrioventricular dissociation, because the RA intermittently contracts against a closed tricuspid valve.

In constrictive pericarditis, the *y* descent is rapid and deep because the very earliest phase of diastolic RV filling is unimpeded. In contrast, in cardiac tamponade, the *y* descent is blunted and it is the *x* descent that is more prominent.

ANSWER TO QUESTION 24

D (Braunwald, p. 360; Fig. 19.9; eFig. 19.11)

There is no completely accurate method for measuring cardiac output in the cardiac catheterization laboratory. Two commonly used methods are the thermodilution and the Fick techniques. The former involves injection of a bolus of fluid (i.e., saline or dextrose) into the proximal port of a right-sided balloon flotation (e.g., Swan-Ganz) catheter, after which alterations in temperature are measured at the distal end of the catheter. The change in the temperature over time is then plotted to derive the cardiac output, which is *inversely* related to the area under the thermodilution curve (Fig. 1.65). In low cardiac output states, there is a larger area under the curve owing to the longer time required for the temperature curve to return to its baseline. However, this technique tends to *overestimate* cardiac output in the setting of low output states, because the dissipation of the cooler temperature to the surrounding cardiac structures results in a reduction in the total area under the curve. In patients with severe tricuspid regurgitation, the back-and-forth flow across the tricuspid valve also creates significant error in measurement, producing a falsely low cardiac output by this technique.

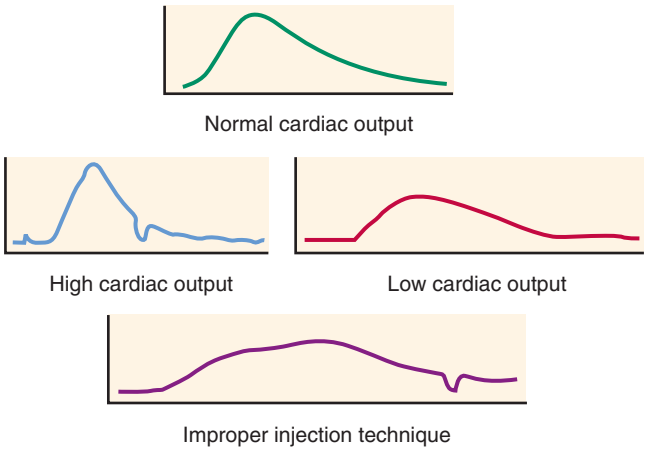

FIG. 1.65

The Fick technique is based on the principle that cardiac output is equal to the oxygen consumption divided by the difference in oxygen content between arterial and mixed venous blood. That is,

$$\text{Cardiac output} = \frac{\text{O}_2\ \text{Consumption}}{\text{A} - \text{VO}_2\ \text{Difference}}$$

The Fick technique is more accurate than thermodilution in patients with low cardiac outputs; however, its main limitation is in measuring true oxygen consumption in a steady state. Many laboratories use an "assumed" oxygen consumption by considering the patient's age, gender, and body surface area. Inaccuracy in the oxygen consumption measurement can result in substantial variability in reported cardiac outputs.

Systemic vascular resistance (SVR) is derived by dividing the difference between the mean aortic and right atrial (RA) pressures by the systemic cardiac output (and then multiplying by a constant to convert to the commonly used units of dynes·sec·cm^{-5}):

$$\text{SVR} = 80 \times \frac{\text{Mean Aortic Pressure} - \text{Mean RA Pressure}}{\text{Systemic cardiac output}}$$

The pulmonary vascular resistance (PVR) is obtained by dividing the difference between the mean pulmonary artery (PA) and left atrial (LA) pressures by the pulmonic cardiac output (then multiplying by the same constant). The pulmonary capillary wedge (PCW) pressure is commonly used as a surrogate for LA pressure:

$$\text{PVR} = 80 \times \frac{\text{Mean PA Pressure} - \text{Mean LA (or PCW) Pressure}}{\text{Pulmonic cardiac output}}$$

In the absence of intracardiac shunts, the systemic and pulmonic cardiac outputs should be the same.

ANSWER TO QUESTION 25

C (Braunwald, pp. 186–188; Fig. 14.18; eTable 14.1; Table 14.4)

Pulsed Doppler interrogation of mitral valve inflow is useful in identifying disorders of left ventricular (LV) diastolic function. In normal adults, the early (E wave) velocity exceeds the late (A wave) velocity such that the normal E/A ratio is >1.2. The figure accompanying this question illustrates an abnormal pattern of mitral inflow, with an E/A ratio <1.0. Although this pattern may be present in patients who have documented abnormalities of LV relaxation, it can also occur as a result of normal aging.[1] In fact, most people older than age 70 have an E/A ratio <1.0. In addition, the pattern of diastolic mitral inflow is load dependent. If a patient with the illustrated pattern of impaired relaxation were administered intravenous volume, the mitral inflow pattern could change to the "pseudonormalized" form, with an E/A ratio >1.0, without any alteration in the intrinsic relaxation properties of the

ventricle. Caution should thus be used when inferring a diastolic or relaxation abnormality from the mitral inflow pattern. Although none of the available echocardiographic indices of diastolic function is infallible, and even stepwise approaches using the mitral inflow pattern, Doppler tissue imaging, and assessment of pulmonary venous inflow can result in internally inconsistent results,[2] echocardiographic measures of diastolic function nonetheless provide clinically important diagnostic and prognostic information.[3]

Constrictive pericarditis and restrictive cardiomyopathy are clinical situations in which the bulk of ventricular filling occurs in early diastole. In these conditions there is a high E/A ratio, often >2.0. Hyperthyroidism and hemorrhage each result in hyperdynamic states in which diastolic relaxation is enhanced, such that reversal of the E/A ratio would be unusual.

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ANSWER TO QUESTION 26

D (Braunwald, pp. 206–207; Figs. 14.36–14.38)

The figure accompanying this question displays continuous Doppler interrogation of transmitral valvular flow obtained from the apical four-chamber transducer position. During diastole, the deceleration of transmitral inflow is prolonged, consistent with a persistent pressure gradient between the left atrium and left ventricle (i.e., mitral stenosis [MS]). In systole, a faint signal of mitral regurgitation (MR) is seen as a downward velocity spectrum. To determine the extent of MR noninvasively, simultaneous two-dimensional echocardiography and color Doppler interrogation would be required. However, the presented Doppler spectrum of mitral inflow is sufficient to determine the severity of MS, including the transmitral pressure gradient and the valve area, as described below.

The mitral valve area can be calculated noninvasively by three distinct noninvasive echo-Doppler methods. First, if an adequate two-dimensional short-axis image can be obtained in diastole, the valve orifice can be traced and the valve area measured directly using planimetry. The second method (which can be applied to the provided figure) utilizes the Doppler pressure half-time (PHT), which calculates the time in milliseconds required for the diastolic transmitral pressure gradient to decline to one-half of its peak value. Because of the relationship between velocity and pressure, this requires determining the time it takes for the peak diastolic velocity to fall to the peak velocity divided by the square root of 2. Most modern echocardiographic machines calculate the PHT automatically once the Doppler profile is traced on the screen, using the following equation:

$$\text{Mitral valve area} = 220 \div \text{PHT}$$

This relationship becomes less accurate when there is marked MR or aortic regurgitation, which interferes with the measured pressure gradient across the mitral valve. The third method to calculate the mitral valve area utilizes the continuity equation, which is based on the principle that the volume rate of flow through the heart is constant.

The cause of mitral stenosis (MS) in the vast majority of adults is rheumatic heart disease. Occasionally, other etiologies can be identified, such as congenital abnormalities of the valve or heavy calcification that restricts transvalvular flow. The transvalvular Doppler pattern cannot distinguish the etiology of MS, but two-dimensional echocardiographic imaging is usually diagnostic in this regard.

ANSWER TO QUESTION 27

B (Braunwald, pp. 88, 178, 206; eFig. 14.2; Fig. 14.76)

The McConnell sign is a distinct regional wall motion abnormality associated with acute pulmonary embolism in which the right ventricular (RV) *midwall* is dyskinetic, with sparing of the apex. The Kussmaul sign refers to a rise in jugular venous pressure (or its failure to decrease) with inspiration, which occurs in states of reduced RV compliance and right-sided volume overload. It is typically associated with constrictive pericarditis, but is also seen in pulmonary embolism, RV infarction, and restrictive cardiomyopathy.

The general calculation of a pressure gradient across a cardiac valve is determined by the simplified Bernoulli equation:

$$\Delta \text{ Pressure} = 4 \times \text{velocity}^2$$

In this patient, the pressure gradient between the RV and right atrium (RA) is 36 mm Hg (4×3^2). The RV pressure can then be calculated as this pressure gradient plus the RA pressure. The right atrial pressure can be estimated from the echocardiographic diameter of the inferior vena cava (IVC) and its respiratory variation (see Braunwald, Table 14.7). In this case, the IVC diameter is normal (<2.1 cm), but there is <50% inspiratory collapse, consistent with a right atrial pressure of 5 to 10 mm Hg. With a right atrial pressure of 5 to 10 mm Hg and a pressure gradient of 36 mm Hg between the RA and RV, the RV systolic pressure can then be estimated at 41 to 46 mm Hg. In the absence of pulmonic stenosis, the pulmonary artery (PA) systolic pressure is equal to the RV systolic pressure, such that the estimated PA systolic pressure in this patient is also 41 to 46 mm Hg.

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ANSWER TO QUESTION 28

C (Braunwald, pp. 154–155, 160; Figs. 13.1 and 13.2)

With normal aerobic exercise, the heart rate and systolic blood pressure both rise. Diastolic blood pressure, however, typically does not change significantly. During *isometric* exercise, both systolic and diastolic blood pressures may increase. In normal individuals, the cardiac output rises fourfold to sixfold above basal levels during maximum exercise. The physiologic response to physical activity often becomes attenuated as an individual ages. The heart rate response to exercise is blunted in the elderly, and the predicted maximum heart rate decreases with age (estimated by 220 minus age in years). This is due in part to decreased beta-adrenergic responsiveness in older individuals. The average stroke volume is preserved in normal older adults, and the observed decline in maximum cardiac output is due primarily to the blunted heart rate response. Maximal aerobic capacity ($\dot{V}O_2max$) declines 8% to 10% per decade in sedentary individuals, such that there is a 50% fall between ages 30 and 80. Thus, the exercise protocol chosen to test elderly individuals should take into account predicted limitations in exertional capacity.

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ANSWER TO QUESTION 29

D (Braunwald, pp. 91–93; Figs. 10.7 and 10.9; Tables 10.6 and 10.7)

The intensity of a heart murmur is related to the pressure gradient and rate of flow across the responsible orifice. Physiologic changes or bedside maneuvers that alter the driving pressure gradient or the rate of flow lead to audible changes in murmur intensity. In acute mitral regurgitation (MR), flow is directed backward from the left ventricle into a relatively noncompliant left atrium (LA), leading to a rapid increase in left atrial pressure during systole. Because this abolishes the pressure gradient between the left ventricle and LA in late systole, the murmur of acute MR is often present only in *early* systole. Similarly, in acute aortic regurgitation, the left ventricular (LV) diastolic pressure rises rapidly, leading to cessation of the diastolic murmur in mid- to late diastole, as LV and aortic pressures equalize. In patients with mitral valve prolapse, the auscultatory findings vary prominently with physiologic alterations. The valve physically prolapses into the LA, and the associated click/murmur commences when the reduction of LV volume during contraction reaches the point at which the mitral leaflets fail to coapt. Maneuvers that decrease LV volume, such as standing from a squatting position, cause the valve prolapse, the click, and the murmur to all occur earlier in systole. In mitral stenosis, the diastolic rumbling murmur increases with any maneuver that augments transvalvular flow and decreases in situations that reduce transmitral flow, such as the strain phase of the Valsalva maneuver.

The systolic murmurs of aortic valvular stenosis and MR are sometimes difficult to distinguish. However, the intensity of aortic stenosis varies from beat to beat when the duration of diastole is not constant, as in atrial fibrillation or after a premature contraction. The murmur of MR is not affected in this manner, because the changes in driving pressure between the left ventricle and the LA are smaller.

ANSWER TO QUESTION 30

C (Braunwald, pp. 222–225; Figs. 14.70 and 14.81; p. 357)

This computed tomogram demonstrates a type A aortic dissection involving the ascending (large arrow, A) and descending (small arrows, A) thoracic aorta. In addition, the dissection extends into the aortic arch vessels (large arrows, B), the left common carotid artery (small arrow, B), and the innominate artery (arrowhead, B). Dissection membranes are clearly visualized in the involved segments. Acute aortic dissection is often lethal; survival depends on prompt clinical recognition and definitive imaging of the aorta. Type A aortic dissections involve the ascending aorta. Type B aortic dissections do not involve the ascending aorta. The most common symptom of acute aortic dissection is chest or back pain, reported in up to 96% of patients. The pain is typically sudden in onset and severe, often with a "ripping" or "tearing" quality. The patient discussed in this question may have also presented with pulse deficits or neurologic symptoms, given the branch artery involvement demonstrated on the computed tomogram. Computed tomography (CT) and magnetic resonance imaging (MRI) have outstanding sensitivity for the diagnosis of aortic dissection, on the order of 96% to 100%. Transesophageal echocardiography is unnecessary in this case, but it is also an excellent imaging modality for the diagnosis of aortic dissection (sensitivity of ~98% and specificity of 94% to 97%), with the caveat that visualization of the distal ascending aorta and proximal aortic arch may be limited by interference by the trachea and bronchus. Conversely, the sensitivity of standard transthoracic echocardiography for aortic dissection is relatively poor (59% to 85%). Aortography is rarely necessary and has inferior diagnostic capabilities for aortic dissection compared with CT and MRI. Because of its rapid availability in most emergency departments, CT is the initial diagnostic test of choice for suspected aortic dissection in many centers.

All patients with acute aortic dissection should receive immediate parenteral therapy for hypertension, typically an intravenous beta blocker to additionally provide rate control and reduce aortic wall stress, after which vasodilators can be added as needed to further control blood pressure. Patients with acute type A aortic dissection should be referred for emergent surgery. Surgery is also the treatment of choice for patients with acute type B aortic dissection complicated by vital organ compromise, rupture or impending aortic rupture, retrograde extension into the ascending aorta, or Marfan syndrome. Patients with uncomplicated acute type B aortic dissections can typically be safely managed initially with parenteral agents for blood pressure control, in-hospital monitoring, and serial imaging of the aorta to assess for retrograde extension or other indications for surgery, and then conversion to oral antihypertensive therapy.

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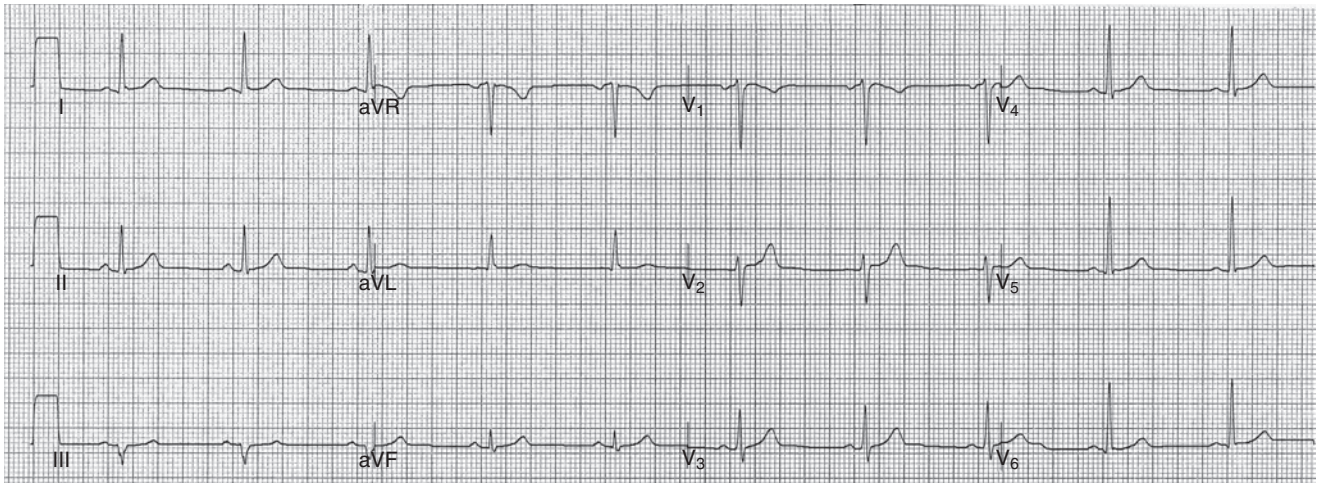

FIG. 1.66

ANSWER TO QUESTION 31

D (Braunwald, pp. 161–163; Fig. 13.14)

ST-segment displacement is the primary means by which ischemia is detected during standard exercise testing. ST-segment depression is the most common form of abnormal response, whereas ST-segment elevation in a lead without pathologic Q waves is found only in about 1% of patients with obstructive coronary disease. J point depressions with upsloping ST segments are a normal finding during exercise. Patients with ischemic heart disease usually display true ST-segment depression with a horizontal or downsloping configuration. The correct isoelectric reference point for the ST segment is the TP segment. However, because this segment is shortened during exercise, the PQ junction is typically chosen as the reference point instead. In normal individuals who have an early repolarization pattern on the resting ECG, the chronically elevated J point usually returns to baseline during exercise. In this setting, any ST-segment deviations during exercise should be referenced to the PQ junction, not to the original J point position. Ischemic ST-segment depressions may develop only during exercise or may occur during exercise and persist into recovery. In 10% of patients, ischemic changes are observed only during the recovery phase. The onset of ST-segment changes during recovery occurs more commonly in asymptomatic individuals compared with those with symptomatic coronary artery disease. An abnormal ST-segment response is considered to be 0.10 mV (1 mm) or greater of J point depression, with a flat or downsloping ST segment that remains depressed to 0.10 mV or greater at 80 milliseconds after the J point.

Although ST-segment *elevation* is helpful to localize ischemia to particular coronary territories, the location of ST-segment *depression* during exercise does not accurately predict the responsible coronary anatomy.

ANSWER TO QUESTION 32

C (Braunwald, pp. 118–121; Figs. 12.1–12.4; Table 12.1)

This ECG demonstrates extreme right-axis deviation of the QRS complex and an abnormally rightward P wave axis (the P waves are inverted in leads I and aVL). Although this pattern might suggest dextrocardia with situs inversus, the normal progression of the R waves in the precordial leads is not consistent with that diagnosis (in dextrocardia, R wave progression would be reversed). Rather, the tracing is most consistent with right and left arm lead reversal, a common error of lead placement. In this situation, the recordings from leads aVL and aVR are interchanged and the complexes in lead I are the mirror image of what would be expected in that lead had the limb leads been placed correctly. Fig. 1.66 shows the ECG from the same patient with the leads placed correctly.

ANSWER TO QUESTION 33

D (Braunwald, pp. 154–155, 157–159; Figs. 13.1 and 13.2; Tables 13.3, 13.6, 13.7)

An understanding of the differences between stress testing protocols is required to choose the appropriate study for a specific patient. Six to 12 minutes of progressive exercise, leading to a level of maximal oxygen consumption, provides the greatest diagnostic and prognostic information. An optimal exercise study is characterized by an appropriate rise in both heart rate and systolic blood pressure. The diastolic blood pressure may fall, rise, or stay the same, depending on the protocol used and the workload achieved. When systolic blood pressure falls during exercise, it is often indicative of severe underlying coronary artery disease (typically three-vessel or left main disease) or severe left ventricular (LV) contractile dysfunction. Other potential causes include LV outflow obstruction (e.g., advanced aortic stenosis or hypertrophic obstructive cardiomyopathy) and hypovolemia.

Treadmill protocols are the most commonly used form of stress testing and are characterized by achievement of high maximum heart rates and oxygen consumption. Bicycle protocols are sometimes better tolerated by deconditioned patients because of the ramped nature of the test and achieve maximum heart rates similar to, but maximal oxygen consumption less than, treadmill tests. Arm crank ergometry can be useful for patients who cannot perform leg exercise, such as patients with severe peripheral arterial disease. Arm

protocols typically produce a higher heart rate and blood pressure response for a given workload than leg exercise protocols; however, the maximum heart rate achieved during arm ergometry testing is typically only about 70% of that achieved during treadmill or bicycle tests. Maximal oxygen consumption and minute ventilation are also lower for arm cycling than for leg exercise. The standard treadmill Bruce protocol is the most commonly used, and a large diagnostic and prognostic database has been accumulated with this regimen. The primary limitation of the Bruce protocol is the large increase in oxygen consumption from one stage to the next, which limits the utility of this protocol in elderly, deconditioned, or ill individuals. In such patients a more gradual regimen, such as the Naughton or Weber protocol, using 1- to 2-minute stages with 1 metabolic equivalent (MET) increases per stage, or a ramped bicycle protocol with small increases in workload each minute, is typically better tolerated.

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ANSWER TO QUESTION 34

D (Braunwald, pp. 83–85, 95–97)

The development of new exertional dyspnea in a patient with cardiac disease may herald progression or a change in the clinical syndrome. Each of the patients in this question has a known, previously asymptomatic cardiac lesion and has recently developed shortness of breath with physical activities. A congenitally bicuspid aortic valve often becomes progressively stenotic with age, and symptoms associated with aortic stenosis (angina, syncope, heart failure) frequently develop in mid- to late adulthood. A patient with a history of myocardial infarction who presents with new dyspnea without recurrent angina is likely to have developed left ventricular (LV) dysfunction due to ventricular remodeling. Other potential contributing factors include dyspnea as an anginal equivalent or a superimposed arrhythmia. New irregular palpitations in a patient with a history of rheumatic heart disease may indicate superimposed atrial fibrillation. This is a poorly tolerated complication in patients with mitral stenosis because of the abbreviated LV diastolic filling period during rapid heart rates.

Most young adults with an uncomplicated ostium secundum atrial septal defect (ASD) have normal exercise tolerance. Previously asymptomatic ostium secundum ASDs, in the absence of pulmonary hypertension, are typically well tolerated during pregnancy. Although problems may arise because of paradoxical embolism in the setting of lower extremity venous thrombosis, symptoms of ventricular dysfunction or reversed shunting across the ASD are rare. Exertional dyspnea in the third trimester of pregnancy in such patients is more likely the result of impaired diaphragmatic excursion from the increasing size of the uterus.

The most common causes of morbidity and mortality in trisomy 21 (Down syndrome) are congenital heart defects, which are present in 40% to 50% of patients. The most characteristic abnormalities are endocardial cushion defects, such as ostium primum ASD and "cleft" mitral valve with mitral regurgitation. Approximately one-third of the congenital heart lesions are complex defects that are detected early, but simpler cardiac anomalies may remain unnoticed into adulthood. The onset of exertional dyspnea in a patient with trisomy 21 warrants evaluation for such lesions.

ANSWER TO QUESTION 35

C (Braunwald, pp. 136–143; Figs. 12.31, 12.32, 12.38–12.40)

Early recognition of myocardial infarction (MI) is critical to take full advantage of emergent percutaneous revascularization or fibrinolytic therapy. The earliest electrocardiographic finding in acute ST-elevation MI is ST-segment elevation and hyperacute (tall, positive) T waves overlying the affected region of myocardium. Reciprocal ST-segment depressions are often noted in leads overlying the opposite cardiac territories. In the absence of reperfusion therapy, T wave inversions become evident in the leads overlying the region of infarction over a matter of hours, accompanied by Q wave development. In the case of an anterior Q wave MI, the early ST-segment deflections become apparent in the anterior precordial leads, whereas ST-segment depressions are often present in the inferior leads. Acute infarction affecting portions of the conduction system may produce a new bundle branch block. The presence of a new right bundle branch block (RBBB) does not obscure the diagnosis of an acute MI, because the ST-segment elevations in the precordium should remain interpretable. However, the ST-segment and T wave changes that accompany a new left bundle branch block (LBBB) typically mask the ST-segment and T wave changes of acute infarction, making the diagnosis more difficult. In a patient with a convincing history of prolonged ischemic chest discomfort, a new LBBB is an acceptable criterion of acute infarction.

A shortened QT interval is typical of hypercalcemia, not acute MI.

ANSWER TO QUESTION 36

E (Braunwald, pp. 268–270, 290–292; Fig. 16.13; eFig. 16.15)

Myocardial perfusion imaging with either thallium-201- or technetium-99m-labeled compounds (e.g., technetium-99m sestamibi) is useful for the detection of myocardial ischemia and infarction (MI), to characterize infarct size (which predicts future ventricular remodeling), and to determine the effectiveness of acute revascularization. Nuclear imaging is also useful for early risk stratification after an acute MI. The size of the resting myocardial perfusion defect correlates with prognosis: the larger the defect, the worse the outcome. Certain resting image patterns seen after acute MI, such as increased lung uptake of radioisotope, have been associated with an unfavorable prognosis because they are indicative of impaired left ventricular (LV) function.

Pharmacologic stress testing with nuclear imaging after an acute MI has been shown to be safe and to predict in-hospital and late cardiac complications better than submaximal exercise stress imaging. Gated single-photon emission computed tomography myocardial perfusion imaging allows

for determination of LV function, which adds additional prognostic information in the management of the postinfarction patient.

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ANSWER TO QUESTION 37

C (Braunwald, pp. 161–163; Fig. 13.4; see also Answer to Question 31)

The development of ST-segment elevation during exercise testing is predictive of the presence of transmural ischemia owing to vasospasm or a high-grade coronary narrowing. It is very uncommon, occurring in only about 1% of patients with obstructive coronary artery disease. In contrast to ST-segment depression, the development of ST-segment elevation is useful in localizing the anatomic site of ischemia and typically correlates with a perfusion defect on imaging studies. In patients with early repolarization, the normal response is for elevated J points to return to baseline during exercise.

ST-segment elevation during exercise testing does not have predictive significance when it occurs in leads that contain pathologic Q waves. In that situation, it may represent a region of myocardial scar with a resting wall motion abnormality. There is no direct association between exercise-induced ST-segment elevation and the development of conduction system abnormalities.

ANSWER TO QUESTION 38

E (Braunwald, pp. 324–326; Figs. 18.4 and 18.5)

Assessment of coronary artery calcification by electron beam tomography (EBT) using electrocardiographic gating is a technique to screen for coronary artery disease (CAD). Although coronary artery calcification is a surrogate marker for coronary atherosclerotic plaque, the correlation between the amount of coronary calcium and the actual angiographic severity of the CAD is weak. The complete absence of coronary calcification on EBT has a strong negative predictive value for high-grade coronary stenosis, but does not completely rule out the presence of significant CAD. The Agatston score is the most frequently used system for reporting the severity of coronary artery calcifications, and reference data sets for interpretation are stratified by age and gender. Annual rates of myocardial infarction or cardiovascular death rise with increasing Agatston scores, even in patients with similar Framingham risk scores. Coronary EBT is of most clinical value for patients who are at *intermediate* risk for coronary events based on traditional cardiovascular risk factors and for whom an abnormal scan will have an impact on clinical management.

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ANSWER TO QUESTION 39

A (Braunwald, pp. 266–267, 283–289; Fig. 16.29; eFig. 16.11)

Myocardial perfusion imaging provides an important source of prognostic information in patients with coronary artery disease (CAD). Stress myocardial perfusion imaging has been shown to be a powerful predictor of subsequent cardiac events. The combination of clinical and myocardial perfusion data is more predictive than the combination of clinical and cardiac catheterization data. Indeed, even when angiographic CAD is present, a normal myocardial perfusion study confers a very low risk of a subsequent cardiovascular event (<1% per year).

Stress perfusion defects in multiple locations corresponding to multiple vascular territories are suggestive of left main or three-vessel CAD. Other indicators of high-risk CAD include large defects, transient pulmonary uptake of tracer, and left ventricular cavity dilatation with exercise. The severity of a myocardial perfusion defect can be assessed in terms of both its size and the extent of its reversibility. The severity of defects as well as their number and size are important indicators of prognosis. The predictive value of myocardial perfusion imaging is independent of the imaging technique (planar or single-photon emission computed tomography [SPECT]) and the imaging agent used (e.g., thallium-201- or technetium-99m-based compounds), with one important exception. There is a decreased likelihood of significant breast attenuation artifact with the use of technetium-99m-based agents with ECG-gated SPECT imaging.

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ANSWER TO QUESTION 40

A (Braunwald, p. 315)

Cardiac magnetic resonance (CMR) imaging is an excellent technique to define pericardial anatomy and abnormalities. It is highly sensitive for the detection of pericardial fluid, masses, and pericardial thickening. The T1-weighted spin-echo CMR image in this case demonstrates diffuse encasement of the heart by a structure within the pericardium that has intermediate signal intensity resembling myocardial tissue (labeled with asterisks in Fig. 1.67). The features are most consistent with pericardial malignancy.

Biopsy of the affected region demonstrated pericardial angiosarcoma. This is a rare primary pericardial malignancy that arises from the pericardial vasculature and typically does not metastasize. However, it usually proliferates widely throughout the pericardial cavity and may invade the myocardium. This case was considered inoperable at surgery and the patient died 4 days after presentation.

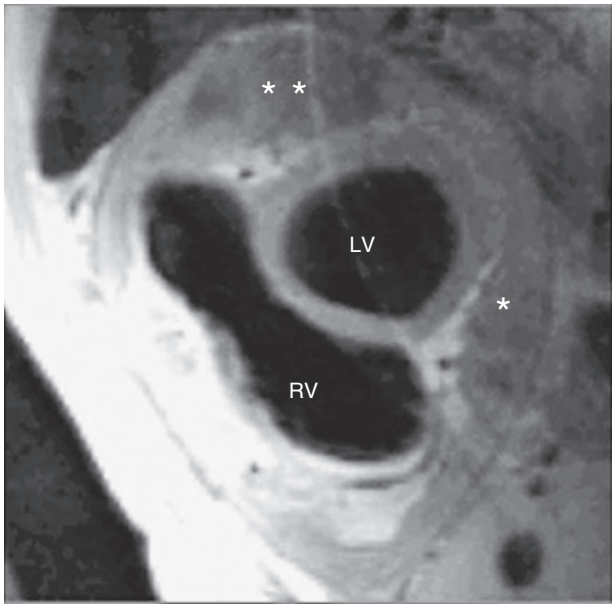

FIG. 1.67

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ANSWER TO QUESTION 41

E (Braunwald, pp. 364–366)

In a normal individual, systemic and pulmonary cardiac outputs are approximately equal. In the presence of an intracardiac shunt, blood flows abnormally between the pulmonary and systemic circulations. Although many shunts are detected by noninvasive means, certain findings during right and left heart catheterization may point to unexpected intracardiac communications. For example, suspicion for a left-to-right shunt should be raised if the pulmonary artery (PA) oxygen saturation exceeds 80% or if the difference in oxygen saturation between the superior vena cava (SVC) and the PA is 8% or more. A right-to-left shunt should be considered if the systemic arterial saturation is <93% without any other reason.

Normally, the oxygen saturation in the inferior vena cava (IVC) is higher than that in the SVC. Mixed venous saturation is most accurately determined in the PA, because complete mixing of venous return has occurred at that level. However, when assessing a transatrial shunt, the mixed venous saturation must be determined proximal to the shunt and can be estimated by the Flamm formula, measuring oxygen content in the SVC and IVC:

$$\text{Mixed venous oxygen content} = \frac{3(\text{SVC } O_2 \text{ content}) + 1(\text{IVC } O_2 \text{ content})}{4}$$

The ratio of pulmonic to systemic blood flow (Q_p/Q_s) is used to determine the significance of an intracardiac shunt. A Q_p/Q_s <1 indicates net right-to-left shunting. A Q_p/Q_s of 2.0 or more indicates a large left-to-right shunt that generally requires repair. A Q_p/Q_s of 1.0 to 1.5 indicates a small left-to-right shunt.

ANSWER TO QUESTION 42

B (Braunwald, p. 201; Fig. 14.32; p. 1606; Fig. 78.6)

The pulsed-wave Doppler spectrum in the illustration demonstrates late systolic acceleration of flow characteristic of left ventricular outflow tract (LVOT) obstruction, typically seen in patients with hypertrophic cardiomyopathy (HCM). This abnormal Doppler signal ("dagger" pattern) is detected in the LVOT and peaks significantly later than that of valvular aortic stenosis, owing to the dynamic nature of the obstruction. Because the disorder is at the subvalvular level, there is no therapeutic role for aortic valve surgery.

The LVOT obstruction may be worsened by any action that decreases left ventricular volume and narrows the distance between the interventricular septum and the anterior mitral leaflet, including volume depletion. Bed rest has no specific role in the management of HCM.

ANSWER TO QUESTION 43

C (Braunwald, pp. 218–221; Figs. 14.62, 14.64–14.66; p. 315)

Echocardiography is an excellent technique to detect and grossly quantify the volume of pericardial effusions. The normal pericardial space contains 35 to 50 mL of serous fluid between the visceral and parietal pericardial layers. Small pathologic effusions tend to accumulate posteriorly, external to the left ventricular free wall, because of the effects of gravity. Larger effusions tend to circumscribe the heart. Certain echocardiographic features are good indicators of the presence of cardiac tamponade physiology in patients with pericardial effusion. These include early diastolic collapse of the right ventricle, which indicates the presence of elevated intrapericardial pressure (see Braunwald, Fig. 14.64). However, right ventricular (RV) diastolic collapse may be absent in clinical tamponade if pulmonary hypertension or RV hypertrophy is present, because these forces oppose RV indentation. Diastolic invagination of the right atrium (see Braunwald, Fig. 14.64) is a more sensitive, but less specific, marker of tamponade physiology. Doppler interrogation can also provide clues to the presence of tamponade, including exaggerated respiratory variation of transvalvular velocities (see Answer to Question 6).

Transthoracic echocardiographic imaging is often inadequate in direct assessment of the thickness of the pericardium; transesophageal echocardiography, computed tomography, and magnetic resonance imaging are more accurate techniques for this purpose.

ANSWER TO QUESTION 44

E (Braunwald, pp. 266–270, 280, 285, 295; Fig. 16.13)

Although nuclear stress testing is commonly used in the evaluation of women with suspected coronary artery

disease (CAD), there is the possibility of breast attenuation artifact in female patients. The use of technetium-99m-based agents with single-photon emission computer tomography imaging and electrocardiographic gating reduce the likelihood of a false-positive study due to such artifact, thereby increasing the specificity of nuclear testing in women. Breast attenuation artifact typically appears as a fixed defect of the anterior or anterolateral wall. If this defect is due to artifact rather than prior infarction, the involved segment(s) will demonstrate normal wall motion on the gated images (see Answer to Question 11).

Patients with left bundle branch block (LBBB) may demonstrate artifactual exercise-induced perfusion defects, especially in the septal and anteroapical regions. Pharmacologic stress testing with adenosine, regadenoson, or dipyridamole minimizes the incidence of such artifacts. Thus, it is recommended that patients with complete LBBB on the ECG be evaluated by vasodilatory agents, rather than an exercise protocol, to avoid false-positive results.

Nuclear imaging is a useful modality for preoperative risk stratification before noncardiac surgery, especially for patients at intermediate clinical risk.[1] For example, dipyridamole stress testing with perfusion imaging is predictive of perioperative cardiac events and the magnitude of risk correlates with the extent of ischemia. Patients with diabetes are at increased risk for CAD and its complications, and perfusion defects during testing predict *higher* event rates in diabetics compared with nondiabetics.[2]

In patients with CAD, assessment of myocardial viability may be of importance in defining revascularization options. Modalities for the determination of myocardial viability include thallium-201 imaging, magnetic resonance imaging, dobutamine echocardiography, and positron emission tomography.[3]

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ANSWER TO QUESTION 45

B (Braunwald, pp. 302, 308–312)

In this delayed cardiac magnetic resonance (CMR) image, the midseptum and midanterior segments of the left ventricle demonstrate subendocardial late enhancement (the bright area indicated by the white arrows in Fig. 1.68) that involves approximately half of the transmural thickness of the myocardium. This finding, as well as the matching wall motion abnormality by echocardiography, is most consistent with a prior nontransmural myocardial infarction (MI). The presence of MI (acute or old) can be determined accurately using the protocol of late gadolinium enhancement (LGE). Gadolinium is an extracellular contrast agent that only minimally enters normal myocardial cells. However, disrupted myocardium after an MI allows expansion of the volume of distribution and delayed entry of the contrast agent into the affected region. A subendocardial distribution is indicative of MI. Both conventional CMR and LGE are useful in assessing myocardial viability, to help determine whether a segment of poorly contracting myocardium would benefit from mechanical revascularization. For example, improved wall thickening with low-dose dobutamine CMR correlates well with the presence of viable myocardium. Using LGE, a transmural extent of MI (i.e., region of late enhancement) of <50% is also predictive of functional recovery after revascularization.

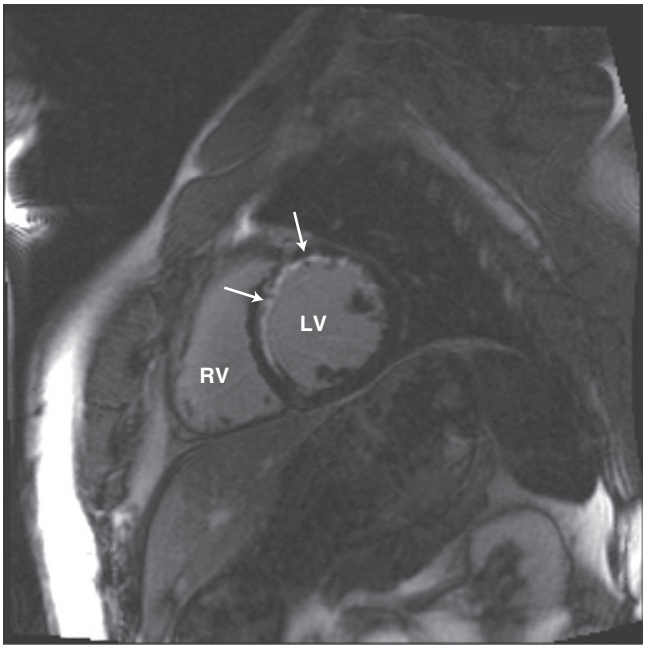

FIG. 1.68

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ANSWER TO QUESTION 46

B (Braunwald, pp. 210–212; Figs. 14.47 and 14.48; pp. 361–364; Figs. 19.10 and 19.11)

As with most stenotic valvular lesions, echocardiographic evaluation of aortic stenosis (AS) is accurate and clinically useful. The morphology of the valve can be examined by two-dimensional imaging to assess for congenital or rheumatic abnormalities or age-related changes of valvular architecture. The peak outflow velocity is then measured using continuous-wave Doppler imaging. Important AS usually results in outflow velocities of 3.5 m/s or greater, which is out of the range for accurate quantification by pulsed-wave Doppler imaging. From the continuous-wave Doppler measurement, both the peak and mean gradients can be determined. The peak instantaneous gradient measured by Doppler imaging reflects the true maximum pressure difference between the left ventricle and aorta. The peak-to-peak gradient measured

in the catheterization laboratory has no actual physiologic basis and does not directly correspond to the echocardiographically measured values—the peak instantaneous gradient routinely exceeds the peak-to-peak valve gradient. Conversely, the mean gradients determined noninvasively and in the catheterization laboratory show excellent agreement, because they both measure the difference in pressure between the left ventricular (LV) and aorta averaged throughout systole.

The aortic valve area can be calculated using the continuity equation (see Braunwald, Fig. 14.48), comparing the volume rate of flow across the left ventricular outflow tract (LVOT) with that through the aortic valve. The greatest potential error introduced into this calculation resides in inaccurate measurement of the *LVOT diameter*. In practice, a peak transaortic valvular gradient >50 mm Hg correlates with clinically significant AS. Similarly, a patient with normal LV contractile function and a low gradient is unlikely to have significant stenosis. However, in the presence of impaired LV function, a more modest gradient (corresponding to transvalvular velocities of 2 to 3 m/s) may be clinically important, and calculation of the aortic valve area by the continuity equation can be helpful in this case.

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ANSWER TO QUESTION 47

C (Braunwald, pp. 364–366)

Detection and localization of intracardiac shunts is possible at catheterization by a traditional oximetry run, in which samples are drawn at numerous sites in the right side of the heart and adjacent vessels. The technique involves measurement of O_2 saturations to identify a significant step-up between consecutive chambers. Using averaged samples, an O_2 saturation step-up of ≥8% is typically necessary to diagnose a left-to-right shunt at the atrial level, whereas one ≥5% suffices at the level of the right ventricle or pulmonary artery (PA; O_2 content in different portions of the right atrium may vary by as much as 2%, reflecting the streaming of blood that enters from the superior vena cava, the inferior vena cava, and the coronary sinus).

The data obtained in the course of an oximetry run may be used to quantify shunt size. Pulmonary and systemic blood flows can be calculated using the standard Fick equation. The ratio of pulmonary to systemic blood flow (Q_p/Q_s) is used to determine the significance of a shunt. A Q_p/Q_s of <1.5 indicates a small left-to-right shunt. A Q_p/Q_s of 2.0 or more indicates a large left-to-right shunt that generally warrants percutaneous or surgical closure. Because of normal variability in O_2 saturation, left-to-right shunts with Q_p/Q_s ≤1.3 at the PA or right ventricular levels and those with Q_p/Q_s <1.5 at the atrial level may not be detected. A Q_p/Q_s of <1 indicates a net right-to-left shunt. For *unidirectional* shunts, the magnitude of the shunt can also be expressed by the difference $Q_p - Q_s$. From this calculation, it can be deduced that a negative value will occur with pure right-to-left shunts.

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ANSWER TO QUESTION 48

C (Braunwald, pp. 159–164)

The exercise ECG is very likely to be abnormal in patients with severe coronary artery disease (CAD). There are several abnormalities that are suggestive of multivessel CAD and an adverse prognosis. These include the early onset of ischemic ST-segment depression, such as during the first stage of a standard Bruce protocol. In addition, ST-segment depression of ≥2 mm (0.20 mV) involving five or more leads, or persisting ≥5 minutes into recovery, is suggestive of more severe underlying coronary atherosclerosis. Exercise-induced ST-segment elevation is also consistent with multivessel CAD, except in lead aVR, which may demonstrate ST-segment elevation in a variety of circumstances, including less severe coronary disease. A failure to increase systolic blood pressure by 10 mm Hg, or a sustained decrease in systolic blood pressure of 10 mm Hg or more, is suggestive of multivessel (or left main) CAD and an adverse prognosis. Multifocal premature ventricular contractions occurring during exercise are not correlated with extensive disease, but reproducible, sustained, or symptomatic ventricular tachycardia is highly suggestive of multivessel CAD.

ANSWER TO QUESTION 49

C (Braunwald, pp. 91–92; Fig. 10.7; Tables 10.6 and 10.7)

Squatting increases venous return to the heart and ventricular stroke volume. The resultant augmented flow and turbulence across the stenotic aortic valve increase the intensity of the murmur. In distinction, during the early phase of the Valsalva maneuver, venous return (and therefore stroke volume) is decreased so that the intensity of the murmur of aortic stenosis (AS) lessens.

The systolic murmur of AS can be confused with mitral regurgitation (MR). However, if the patient has an irregular rhythm or premature ventricular contractions, beat-to-beat variations in diastolic filling of the left ventricle result in changes of the intensity of the AS murmur, whereas the murmur of MR does not demonstrate such variability. Respiration has little effect on the intensity of left-sided heart murmurs, including AS, but can accentuate most right-sided murmurs, including tricuspid regurgitation.

ANSWER TO QUESTION 50

B (Braunwald, pp. 83–85)

This man has classic findings of chest discomfort caused by esophageal reflux and spasm. Differentiation of esophageal disorders from ischemic heart disease can be difficult, because the sensations are often located in similar areas and both can be associated with emotional stress. However, although each condition may produce substernal burning, features in this case are more suggestive of an esophageal rather than cardiac origin. These include a prolonged

continuous ache, a discomfort that is primarily retrosternal but does not radiate toward the arms, and the fact the symptom is not precipitated by exercise but occurs while recumbent. Classically, esophageal disease associated with regurgitation causes "water brash," a taste in the mouth consistent with regurgitation of gastric contents. Frequently, patients with esophageal spasm experience some relief with nitroglycerin. Unlike angina due to myocardial ischemia, however, esophageal pain is often relieved by milk, antacids, or food. Biliary colic also may be confused with angina pectoris. It is usually caused by a rapid rise in biliary pressure due to obstruction of the cystic or bile ducts. Thus, the pain is usually abrupt in onset and steady in nature and lasts from minutes to hours. In many cases, the discomfort is described as colicky. It should be suspected when a history of dyspepsia, fatty food intolerance, and indigestion is present.

The chest discomfort of pericarditis is typically described as sharp, stabbing, or knife-like. Pain due to pericarditis is often localized in the substernal or apical areas and can radiate to the neck or left shoulder. The pain is often worsened by deep breathing or lying in a supine position. Patients may find relief from the chest discomfort of pericarditis by sitting up and leaning forward.

ANSWER TO QUESTION 51

D (Braunwald, pp. 161, 265–267; Fig. 16.9)

The perfusion images display a large region of reversible ischemia in the anteroseptal territory, in the distribution of the left anterior descending coronary artery. In addition, compared with the rest images, there are additional postexercise abnormalities, including dilatation of the left ventricular (LV) cavity (best seen on the short-axis images), increased right ventricular (RV) tracer uptake (most evident in the horizontal long-axis images), and increased lung uptake. Transient dilatation of the LV cavity after stress is associated with extensive and severe coronary artery disease (CAD). It is thought to represent diffuse subendocardial ischemia resulting in an apparent LV dilatation, rather than true cavity enlargement. Increased pulmonary radiotracer uptake after stress is a marker of elevated LV end-diastolic pressure and is predictive of a poor prognosis. It is usually associated with multivessel CAD, depressed LV function, and extensive ischemia. Increased RV tracer uptake on the post-stress images, compared with the rest images, is a specific marker of severe multivessel or left main disease. Finally, a fall in systolic blood pressure of 10 mm Hg or more during exercise is also predictive of left main or three-vessel CAD. In this case, all of these findings are present, along with a large and severe reversible perfusion defect, indicative of severe CAD despite failure to achieve the target heart rate.

ANSWER TO QUESTION 52

B (Braunwald, pp. 178, 210–213; Figs. 14.47–14.50)

The Doppler tracing was obtained across the left ventricular outflow tract of a patient with combined aortic stenosis (AS) and aortic insufficiency. The tracing shows a characteristic delayed onset of peak velocity, consistent with significant AS. The pressure gradient across the aortic valve can be calculated using the modified Bernoulli equation (pressure gradient = $4 \times V^2$). The peak velocity across the aortic valve of approximately 4.8 m/s in the figure corresponds to an instantaneous peak systolic gradient of 92 mm Hg. In general, when the aortic flow velocity is >4 m/s, the probability of critical AS is high. In contrast, an aortic flow velocity <3 m/s is usually associated with only mild AS. For aortic flow velocities that are intermediate, echocardiographic calculation of the aortic valve area or additional hemodynamic data are often needed.

The diastolic flow on this tracing represents aortic insufficiency. Severe aortic insufficiency is associated with a rapidly declining flow velocity, whereas mild aortic insufficiency demonstrates a gradually declining velocity. In this case, the decline in diastolic velocity is gradual and the degree of aortic insufficiency is likely mild. Premature diastolic closure of the mitral valve may be observed in patients with severe, acute aortic insufficiency owing to the greatly elevated diastolic left ventricular (LV) pressure; it would not be expected in this patient given the mild degree of aortic insufficiency present.

Additional findings on the echocardiogram that may help assess the severity of aortic valve disease include measurements of LV size and thickness. In this patient with severe AS, one would expect to find concentric LV hypertrophy.

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ANSWER TO QUESTION 53

B (Braunwald, pp. 85, 86, 99)

Many congenital and acquired cardiac diseases are associated with abnormalities of the extremities. Arachnodactyly—abnormally long and slender digits—is a manifestation of Marfan syndrome. A common finding in arachnodactyly is that when a clenched fist is made around the thumb, the latter extends beyond the ulnar side of the hand (the "thumb sign"). Characteristic extremity abnormalities associated with Turner syndrome include short stature and bowed arms. It is the Holt-Oram syndrome that consists of an atrial septal defect (ASD) and skeletal abnormalities, including deformities of the radius and ulna, and a "fingerized" thumb (i.e., the thumb has an extra phalanx).

Quincke sign, systolic flushing of the nail beds, is common in chronic aortic regurgitation and other conditions with a widened pulse pressure.

Osler nodes are small, tender erythematous skin lesions observed primarily on the pads of the fingers and toes but also on the palms of the hands and soles of the feet. They result from infective microemboli in patients with endocarditis. In contrast, Janeway lesions are slightly raised, nontender, hemorrhagic lesions on the palms of the hands and soles of the feet that may also appear in patients with infective endocarditis. Both types of lesions were more common in the pre-antibiotic era.

Differential cyanosis is the condition in which the hands and fingers are pink but the feet and toes are cyanotic. It is

typical of patent ductus arteriosus with pulmonary hypertension and a reversed shunt, in which case desaturated blood is directed to the lower body.

ANSWER TO QUESTION 54

D (Braunwald, Fig. 14.96; pp. 1565–1566; Fig. 75.42)

The echocardiographic image is an apical four-chamber view of a patient with Ebstein anomaly. Ebstein anomaly is a congenital malformation of the tricuspid valve characterized by elongation and tethering of the anterior leaflet ("sail-like" appearance) and apical displacement of a diminutive septal leaflet. This anomaly results in conversion of a portion of the right ventricle into an "atrialized" right ventricle. There is typically severe right atrial enlargement. Because of the structural deformity of the tricuspid valve, varying degrees of tricuspid regurgitation, and occasionally tricuspid stenosis, are present. The symptomatic presentation of patients with Ebstein anomaly depends on the severity of the valvular regurgitation and the presence of additional congenital heart lesions.

Ebstein anomaly is associated with a number of other congenital heart defects, including patent foramen ovale or ASD in approximately 50% of patients. Up to 25% of patients with Ebstein anomaly have an accessory conduction pathway (Wolff-Parkinson-White pattern on the ECG), which is typically right-sided. Atrial arrhythmias, particularly atrial fibrillation and atrial flutter, are common.

Although coarctation of the aorta can rarely be associated with Ebstein anomaly, systemic hypertension is not a common finding among patients with this disorder.

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ANSWER TO QUESTION 55

B (Braunwald, pp. 226–228; Fig. 14.77)

Echocardiography plays a key role in the diagnosis and evaluation of infective endocarditis. The echocardiographic hallmark is the presence of a valvular vegetation, which is a collection of thrombus, necrotic valvular debris, inflammatory material, and bacteria. Typically, vegetations are located on the atrial aspect of atrioventricular (mitral, tricuspid) valves and the ventricular aspect of the semilunar (aortic, pulmonic) valves; however, large and aggressive lesions may involve both surfaces of the involved valve. The sensitivity of transthoracic echocardiography for detection of vegetations is only ~63%. Transesophageal echocardiography (TEE) is more sensitive for detection of small vegetations (94% to 100% sensitive). However, there is little additional diagnostic yield of TEE when a high-quality transthoracic study is completely normal, without evidence of valve thickening or pathologic regurgitation. Echocardiography also plays a critical role in the identification of structural and functional impairments that result from endocarditis. The degree of valvular destruction and regurgitation can be assessed, particularly with TEE, but TEE is not mandatory if a high-quality transthoracic study provides all relevant information. TEE is more sensitive than transthoracic echocardiography for identification of myocardial abscess formation, valvular perforation, chordal rupture, and endocarditis of prosthetic valves.

Echocardiography can assist in determining whether corrective surgical intervention is appropriate in endocarditis, but the decision to operate should be made primarily on clinical grounds. Factors that predict poor outcome and favor earlier surgical intervention include a perivalvular abscess, intractable heart failure due to valve dysfunction, very large (>1 cm) and hypermobile vegetations, recurrent embolic events despite antibiotic therapy, infection by aggressive organisms, or persistent bacteremia.

It is not necessary to routinely repeat echocardiography in the presence of clinical improvement. Residual vegetation often is evident despite bacteriologic cure, and the patient's clinical status, as well as repeat blood cultures after completion of an appropriate antibiotic course, should dictate further clinical decision making.

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ANSWER TO QUESTION 56

D (Braunwald, p. 90; Figs. 10.5 and 10.6)

The volume and contour of the arterial pulse depend in part on the left ventricular stroke volume, the ejection velocity, and the compliance and capacity of the arterial system. Pulsus parvus et tardus—a small pulse with a delayed systolic peak—is characteristically seen in severe aortic stenosis (AS) and is best appreciated by palpating the carotid artery rather than a peripheral vessel such as the brachial artery. In patients with severe AS and congestive heart failure, the delayed upstroke is not usually evident, leaving only pulsus parvus.

Pulsus bisferiens, characterized by two systolic peaks, occurs when a large stroke volume is ejected rapidly from the ventricle. It is typical of pure aortic regurgitation (AR) and of AR combined with AS. It is also seen in hypertrophic cardiomyopathy with dynamic outflow obstruction.

The *peripheral* pulse rate of rise, contour, and volume is best appreciated by palpation of the brachial artery. The carotid pulse provides the most accurate representation of the *central* aortic pulse.

In coarctation of the aorta, the carotid and brachial pulses are usually bounding and rapidly rising and have large volumes. Conversely, the lower extremity pulses, such as at the femoral artery, have reduced systolic and pulse pressures with a slow rate of rise and a late peak. The femoral artery delay can be appreciated by palpating the brachial and femoral arteries simultaneously.

The normal aorta is often palpable only above the umbilicus. If the aorta is palpable below the umbilicus, an abdominal aortic aneurysm should be suspected.

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ANSWER TO QUESTION 57

B (Braunwald, pp. 350–351, 352–354; Fig. 19.2)

Over 1 million diagnostic cardiac catheterizations are performed annually in the United States.[1] Common vascular entry sites are the femoral, brachial, and radial artery approaches. To decrease the risk of retroperitoneal hemorrhage when using the femoral artery approach, the puncture of the common femoral artery should be made below the inguinal ligament but proximal to the bifurcation of the superficial femoral and profunda arterial branches. If the puncture site is proximal to the inguinal ligament, it may be difficult to establish hemostasis with manual compression. If the puncture site is distal to the bifurcation, there is an increased risk for the formation of a pseudoaneurysm after sheath removal.

For patients on anticoagulation, warfarin should generally be held for 3 days prior to catheterization and the international normalized ratio (INR) should be <1.8 at the time of the procedure to minimize bleeding when the femoral artery approach is used. An INR <2.2 is acceptable for radial artery access. Dabigatran should be held for 24 hours prior to the procedure in patients with normal renal function, and at least 48 hours before when the estimated glomerular filtration rate (GFR) is <50 mL/min. Rivaroxaban and apixaban should also be held the day prior to the procedure.

Contrary to common belief, patients with a history of shellfish allergy are not at higher risk of contrast media reactions than patients with other types of food allergies. The allergens in shellfish are non-iodine-containing proteins (e.g., tropomyosin).[2]

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ANSWER TO QUESTION 58

A (Braunwald, pp. 154–155)

Exercise testing and exercise training play a critical role in the care of patients with advanced congestive heart failure. It has been demonstrated that peak oxygen consumption and anaerobic threshold, measured during cardiopulmonary exercise testing, provide independent prognostic information in this population and are superior to measures such as ejection fraction or functional class in predicting outcome. Patients with severely depressed ejection fractions exhibit a wide range of exercise capacities, with some being near normal, and exercise testing can be critical to quantifying the true functional limitation. A peak oxygen consumption of <14 mL/kg/min has been shown to predict poor survival and to identify a population in whom mortality is improved by cardiac transplantation. Patients at this level of impairment demonstrate a profound exercise limitation, with maximal exercise capacity being required for activities such as walking, golf, or raking leaves. Such a patient would be unable to complete stage I on a standard Bruce protocol. Conversely, patients who achieve a peak oxygen consumption of >14 mL/kg/min have a mortality rate similar to patients who have undergone transplantation and would be less likely to benefit from that intervention.

The exercise limitation in patients with congestive heart failure is correlated most strongly with alterations in skeletal muscle metabolism. Abnormalities in autonomic and ventilatory responsiveness, increased lactate production, and inability to augment cardiac output are also contributing factors. All of these limitations improve with exercise training, and long-term moderate exercise has been shown to benefit functional capacity, reduce symptoms, and enhance quality of life.

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ANSWER TO QUESTION 59

D (Braunwald, pp. 308–317)

Cardiac magnetic resonance (CMR) imaging is a powerful noninvasive tool for the diagnosis of several heart and vascular disorders. There has been significant growth in the use of CMR for clinical and research applications due to a number of factors, including outstanding image quality, reproducibility, and attractive safety features (i.e., no need for ionizing radiation exposure or iodinated contrast). CMR is well suited for identification of congenital heart lesions and cardiac tumors, assessment of myocardial infarction and viability, and characterization of cardiomyopathies. CMR has been used to identify the presence of iron overload in patients with beta-thalassemia and to guide chelation therapy. CMR can define the structure and function of the right ventricle and is useful in the diagnosis of arrhythmogenic right ventricular cardiomyopathy. CMR can also be useful in the evaluation of stenotic and regurgitant valves when echocardiographic windows are inadequate. The use of CMR for pharmacologic myocardial perfusion imaging and dobutamine stress testing is another important clinical application. Compared with nuclear (single-photon emission computed tomography) imaging, CMR myocardial perfusion imaging is not limited by attenuation artifacts, does not require ionizing radiation, and has higher spatial resolution.

Although CMR can accurately measure global left ventricular function with excellent reproducibility, echocardiography (or radionuclide ventriculography) remains the superior option for the patient described in answer D, in light of cost and patient comfort issues (e.g., breath holding, confined space, and relatively lengthy scan times for CMR).

Magnetic resonance angiography (MRA) is an excellent imaging technique for assessment of the aorta and peripheral arteries, and coarctation of the aorta can be readily characterized by this technique. MRA has also been validated for the noninvasive diagnosis of renal artery stenosis and is the screening test of choice for this condition at many medical centers.

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ANSWER TO QUESTION 60

D (Braunwald, pp. 26–29, 164; eFig. 16.4)

The figure demonstrates the impact of pretest probability on prognostic information that can be determined from a positive or negative stress test. The test provides the greatest impact on patients whose pretest probability is in an intermediate range—in such patients, a negative test results in a much lower post-test probability than pretest probability, whereas a positive test results in a much higher post-test probability, relative to the pretest probability. For patients who have a high pretest probability, the post-test probability that disease is present remains high even if the test is negative (i.e., there is a high likelihood that the result is a false negative). In such patients, the negative predictive value of the test is low. Similarly, for patients who have a low pretest probability, the positive predictive value of the test is low.

ANSWER TO QUESTION 61

A (Braunwald, pp. 186–188, 201; Fig. 14.32)

In hypertrophic cardiomyopathy (HCM) with outflow tract obstruction, the anterior leaflet of the mitral valve is abnormally drawn toward the hypertrophied interventricular septum during systole. This systolic anterior motion of the valve can be readily identified by echocardiography (see Braunwald, Fig. 14.32) and plays an integral role in the development of outflow tract obstruction in this condition. In addition, characteristic systolic, not diastolic, notching of the aortic valve is often evident, particularly by M-mode recordings, owing to the dynamic nature of the obstruction. Asymmetric hypertrophy of the interventricular septum is common in HCM and is readily identifiable by echocardiography. However, pathologic localized hypertrophy in this condition can instead be confined to the apex, lateral, or inferior segments, typically without dynamic outflow obstruction. Cardiac magnetic resonance imaging is complementary to echocardiography by visualizing regions that are difficult to assess by echocardiography.

The Doppler spectral mitral inflow pattern in HCM can be variable, but usually reflects the abnormal diastolic filling of the hypertrophied ventricle. Usually there is evidence of a diminished E wave and prominent A wave. Abnormalities of diastolic function can also be identified by Doppler tissue imaging, which typically demonstrates reduced early diastolic mitral annular velocities (E′) as a measure of impaired myocardial relaxation.

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ANSWER TO QUESTION 62

D (Braunwald, pp. 359–360; eTable 19.2; Table 19.3; Fig. 19.8)

As summarized in the Answer to Question 23, the right atrial pressure waveform contains three positive deflections termed the *a, c,* and *v* waves. The *a* wave represents atrial systole and occurs after the P wave on the ECG. The *x* descent represents the relaxation of the atrium and downward tugging of the tricuspid annulus by right ventricular contraction. The *c* wave interrupts the *x* descent and represents the protrusion of the closed tricuspid valve into the right atrium (RA). The *v* wave represents the passive venous filling of the atrium, which occurs during ventricular systole. The height of the *v* wave reflects atrial compliance. In the left atrium, as opposed to the RA, the *v* wave is generally more prominent than the *a* wave. The *y* descent follows the *v* wave, and it represents right atrial emptying after the tricuspid valve opens.

Conditions that blunt the right atrial *y* descent include cardiac tamponade, ventricular ischemia, and tricuspid stenosis. Conversely, constrictive pericarditis is associated with prominence of the *y* descent, because the very earliest phase of diastolic ventricular filling is unimpeded in this condition.

Blunting of the *x* descent can be observed in the presence of atrial fibrillation or atrial ischemia.

ANSWER TO QUESTION 63

E (Braunwald, pp. 91–93; Figs. 10.7 and 10.8; Tables 10.6 and 10.7)

Dynamic auscultation is the technique of altering circulatory dynamics with physiologic maneuvers and then determining the effect on cardiac murmurs. Typical maneuvers include changes in respiration, the Valsalva maneuver, squatting or standing, and isometric exercise.

Patent ductus arteriosus causes a continuous murmur that is loudest at the second left intercostal space. The diastolic phase of this murmur is increased by isometric handgrip as a result of augmented systemic vascular resistance (SVR).

Hypertrophic obstructive cardiomyopathy is associated with a harsh, crescendo-decrescendo systolic murmur best heard between the apex and left sternal border. Actions that reduce left ventricular (LV) size, such as standing or the strain phase of a Valsalva maneuver, bring the anterior mitral leaflet and the interventricular septum into closer proximity, thus *intensifying* the murmur. These maneuvers are useful in differentiating hypertrophic obstructive cardiomyopathy from a fixed orifice obstruction (i.e., aortic stenosis), in which the murmur softens with standing or the Valsalva maneuver.

The murmur of an uncomplicated ventricular septal defect is holosystolic because LV systolic pressure and systemic resistance exceed right ventricular systolic pressure and pulmonary resistance from the beginning to the end of systole. Isometric handgrip increases SVR and may further intensify the murmur.

Aortic regurgitation is a diastolic murmur best heard with the patient sitting forward and holding a deep expiration. The murmur may be accentuated by maneuvers that increase the arterial pressure, such as isometric handgrip.

The diastolic murmur of mitral stenosis is a low-pitched, rumbling murmur best heard at the apex. Maneuvers that increase the rate of transmitral flow, including exercise, accentuate the murmur.

ANSWER TO QUESTION 64

D (Braunwald, p. 145; Fig. 14.43)

Although the ST-segment and T wave abnormalities on this ECG may suggest myocardial ischemia, the deeply inverted T waves are typical of acute cerebrovascular conditions, including subarachnoid hemorrhage. Given the presenting symptoms of headache, nausea, and dizziness, a cranial imaging study such as computed tomography should be obtained rapidly. In this scenario, antiplatelet agents and antithrombotic therapy should be withheld until intracranial bleeding has been excluded. In the absence of findings to suggest unstable myocardial ischemia, anti-ischemic therapies and cardiac catheterization are not initially appropriate. Electrocardiographic abnormalities are present in a large percentage of patients with acute cerebral events. These abnormalities may include tachyarrhythmias or bradyarrhythmias, conduction disturbances, repolarization abnormalities that resemble myocardial ischemia, prolongation of the QT interval, and prominent U waves. The mechanisms responsible for such electrocardiographic changes are unknown, but appear to be related to abnormal autonomic nervous system function. Myocardial damage with release of serum markers (cardiac-specific troponins, CK-MB) and subendocardial hemorrhage can actually occur in the setting of acute severe cerebrovascular disease, believed to be related to the release of excessive local myocardial catecholamines.

In the appropriate clinical situation, diffuse deep T wave inversions are also found in some patients with hypertrophic cardiomyopathy (HCM). Giant inverted T waves in the midprecordial leads are particularly characteristic of the apical form of HCM.

ANSWER TO QUESTION 65

D (Braunwald, p. 92; Fig. 10.8; Table 10.6)

Diastolic murmurs are classified according to their time of onset as early diastolic, mid-diastolic, or late diastolic. Early diastolic murmurs include aortic regurgitation (AR) and pulmonic regurgitation (PR). AR begins with the aortic component of the second heart sound (S_2) and PR starts with the pulmonic component of S_2. Mid- and late diastolic murmurs begin at a clear interval after S_2. When the murmur of AR radiates selectively to the right sternal border (and not the left sternal border), it implies that aortic root dilatation, rather than aortic valve disease, is the cause.

The murmur of acute severe AR differs importantly from the murmur of chronic severe AR. The high-pitched murmur of chronic AR begins with the aortic component of S_2 and has an early peak and a dominant decrescendo pattern throughout diastole. In contrast, in acute severe AR (e.g., caused by infective endocarditis or aortic dissection), the diastolic murmur is of short duration and tends to be soft, because the aortic diastolic pressure rapidly equilibrates with the steep rise in diastolic left ventricular pressure.

Presystolic accentuation of diastolic murmurs, owing to atrial activation and a transient increase in driving pressure, is typical of patients with mitral or tricuspid stenosis who are in sinus rhythm. Such accentuation is absent in atrial fibrillation because of the lack of organized atrial contraction.

When PR develops in the setting of pulmonary hypertension, the murmur begins with a loud P_2 and may last throughout diastole (the Graham Steell murmur).

ANSWER TO QUESTION 66

C (Braunwald, pp. 383–386; Fig. 20.1; Table 20.8)

The left main coronary artery arises from the superior portion of the left aortic sinus. It ranges from 3 to 6 mm in diameter and is up to 10 mm in length. This vessel is best visualized in the anteroposterior projection with slight caudal angulation. The left main coronary artery bifurcates into the left anterior descending (LAD) artery and the left circumflex (LCx) artery. In up to 37% of patients, however, the left main trifurcates into a third vessel known as the ramus intermedius, which lies between the LAD and the LCx. The right coronary artery is the dominant vessel in 85% of patients, supplying the posterior descending artery. The LCx artery is the dominant vessel 15% of the time. The interventricular septum is the most densely vascularized area of the heart. It is supplied by septal branches of the LAD that interconnect with septal branches from the posterior descending artery, producing a network of potential collateral channels. There are a number of congenital anomalies that can cause myocardial ischemia. Coronary artery fistulas (abnormal communications between a coronary artery and a cardiac chamber or major vessel) comprise the most common congenital coronary abnormality that is of hemodynamic significance. About half of the patients with such an anomaly are asymptomatic, but the remainder develop complications including heart failure, infective endocarditis, ischemia, or rupture of an aneurysm. The figure in this question demonstrates a congenital coronary fistula, arising from branches of the LAD and circumflex coronary arteries, that drains into the left ventricle (see right anterior oblique view in *A* and left anterior oblique view in *B*). Other congenital anomalies that may result in myocardial ischemia include anomalous origin of the left coronary artery from the pulmonary artery, congenital coronary stenosis, and anomalous origin of either coronary artery from the contralateral sinus of Valsalva.

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ANSWER TO QUESTION 67

E (Braunwald, pp. 85, 86, 90)

The clinical diagnosis of Marfan syndrome has historically depended on characteristic abnormalities of the skeletal, cardiovascular, and ocular systems. Genetic testing for mutations in the *FBN1* gene has not been required for routine assessment. Since 1996, the Ghent criteria have been the standard for diagnosis and rely on "major" and "minor" manifestations. Major criteria include the following:

Skeletal findings: at least four of the following: pectus carinatum, pectus excavatum requiring surgery, arm span/height ratio >1.05, positive thumb sign (distal phalanx

protrudes beyond clenched fist) and wrist sign (thumb and fifth finger overlap while encircling the wrist), scoliosis >20 degrees or spondylolisthesis, reduced elbow extension <170 degrees, pes planus (flat feet), and protrusio acetabulae

Cardiovascular findings: Dilation of sinuses of Valsalva and ascending aorta, or ascending aortic dissection

Ocular finding: Ectopia lentis (lens dislocation identified by slit lamp examination)

Central nervous system finding: Lumbosacral dural ectasia (identified by computed tomography or magnetic resonance imaging)

Family or genetic history: First-degree relative who meets diagnostic criteria or who has known Marfan mutation

Minor criteria include lesser skeletal abnormalities (joint hypermobility, nonsurgical pectus excavatum, high arched palate, and facial features such as malar hypoplasia), mitral valve prolapse, and dilation/dissection of the descending thoracic/abdominal aorta before age 50.

In the absence of a family history, the diagnosis of Marfan syndrome requires one major manifestation in two of the above organ systems, with involvement (major or minor criterion) in a third organ system, or if a mutation known to cause Marfan syndrome is found, the diagnosis is based on one major criterion plus involvement (major or minor criterion) in a second organ system.

In this patient's case, ectopia lentis is a major criterion, the other choices are minor criteria.

In 2010, an international expert committee proposed revised diagnostic nosology for Marfan syndrome that emphasizes the importance of the cardiovascular manifestations of this condition. By the new criteria, in the absence of a family history of Marfan syndrome, the combination of aortic root dilatation and ectopic lentis is sufficient to establish the diagnosis. In the absence of either of these findings, the identification of a known *FBN1* mutation or a combination of systemic findings is required for confirmation.

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ANSWER TO QUESTION 68

A (Braunwald, pp. 212–213; eFigs. 14.21–14.23; Fig. 14.50)

Assessment of the severity of regurgitant valvular lesions by Doppler echocardiography is less straightforward than assessment of stenotic conditions. Often a combination of findings must be visually integrated, because no one criterion has sufficient accuracy for quantification. In aortic regurgitation (AR), findings that suggest marked elevation of left ventricular (LV) end-diastolic pressure are among the more predictive indicators of lesion severity. Unlike mitral regurgitation, in which the overall jet size correlates with the degree of regurgitation, the size and depth of penetration of the AR color Doppler signal are less strongly correlated with the magnitude of the lesion. This is in part due to merging of the color jet signals of AR with normal mitral inflow into the left ventricle. Measurements of the jet width may also be misleading, because it may rapidly widen after passing through the more restricted valvular orifice, giving a falsely severe appearance. Careful imaging of the regurgitant signal in the parasternal short-axis view often gives the best sense of true jet width.

In the presence of severe AR, there is rapid elevation of LV diastolic pressure such that the velocity of retrograde flow into the left ventricle quickly decays, resulting in a shortened pressure half-time (PHT). A PHT < 250 milliseconds correlates with severe AR. In addition, the rapid rise of diastolic LV pressure can force the *mitral* valve to close prematurely. Such premature closure is often best visualized by M-mode imaging, in which the mitral leaflets coapt before the subsequent QRS complex appears.

Although the depth of the Doppler signal in the left ventricle correlates poorly with the severity of AR, in advanced AR such flow typically extends past the tips of the papillary muscles and into the apex. Finally, detection of diastolic flow reversal in the descending thoracic aorta, imaged from the suprasternal notch, is a sign of moderate-to-severe regurgitation.

Elevated LV outflow tract systolic gradients are a sign of systolic obstruction and do not provide direct information about the severity of AR.

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ANSWER TO QUESTION 69

C (Braunwald, pp. 277–279; Table 16.3)

Several pharmacologic stress-testing agents are available for patients who cannot exercise because of orthopedic limitations, neurologic conditions, or peripheral arterial disease. Dipyridamole acts by inhibiting the cellular uptake and intracellular breakdown of adenosine, increasing the concentration of the latter in the circulation. The subsequent increased activation of adenosine A_{2a} receptors results in vasodilatation and increased coronary blood flow in healthy coronary arteries. However, atherosclerotic vessels tend to be maximally dilated distal to the site of significant stenosis at baseline, such that adenosine does not cause further dilatation in those territories. Therefore, perfusion imaging with dipyridamole, adenosine, or the selective A_{2a} agonist regadenoson in a patient with clinically significant coronary artery disease (CAD) reveals regions of relatively hypoperfused myocardium adjacent to normal zones of increased myocardial blood flow, with little change in myocardial oxygen demand. As a result, in a "positive" test, the infusion of the pharmacologic agent results in heterogeneity of myocardial perfusion, but does not actually provoke myocardial ischemia in the majority of patients with CAD, unlike standard exercise stress testing. Ischemic ST-segment depression may occur in 10% to 15% of patients receiving these vasodilators and tends to correlate with the presence of multiple perfusion defects and extensive CAD. In contrast, chest pain without electrocardiographic changes is a common symptom after infusion of these agents, is likely due to stimulation of adenosine A_1 receptors, and is of no prognostic significance. Of note, xanthine derivatives (e.g., theophylline and caffeine) compete for adenosine receptors and consumption of substances that contain these agents (e.g., coffee) before the test can result in a false-negative study.

Dobutamine is an alternative pharmacologic agent when adenosine or dipyridamole should not be used, as in patients with bronchospastic pulmonary disease (because stimulation of the adenosine A_{2b} receptor can produce bronchospasm). Dobutamine increases myocardial oxygen demand by augmenting myocardial contractility, heart rate, and blood pressure. The increase in coronary blood flow is similar to that in physical exercise, but less than that caused by dipyridamole or adenosine.

In myocardial perfusion imaging, radiotracer agents such as technetium-99m sestamibi or thallium-201 should be injected 1 to 2 minutes before the end of exercise. It is important to maintain the elevated heart rate and blood pressure to allow accumulation of the radiotracer at a "steady" ischemic state.

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ANSWER TO QUESTION 70

E (Braunwald, pp. 90, 92–93, 98; Fig. 10.8)

In mitral stenosis (MS), the opening snap is an *early* diastolic sound generated when superior systolic bowing of the *anterior* mitral valve leaflet is rapidly reversed toward the left ventricle in early diastole, as a result of the high left atrial (LA) pressure. The presence of an opening snap implies a mobile body of the anterior mitral leaflet. The first heart sound tends to be quite loud in MS for a similar reason: it relates to the abrupt systolic movement of the body of the anterior mitral leaflet, which was recessed into the left ventricle throughout diastole because of the elevated LA pressure.

The timing of the A_2-OS interval relates to the severity of MS. When MS is advanced and LA pressure is therefore high, LA and left ventricular pressures equilibrate earlier in diastole, resulting in a *shorter* A_2-OS interval. This interval does vary in atrial fibrillation according to the previous cycle length. During relatively short cycles, LA pressure is higher (because less atrial emptying can occur) and the A_2-OS interval lessens.

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ANSWER TO QUESTION 71

C (Braunwald, p. 145; Fig. 12.44; p. 687)

A large number of arrhythmias may result from digitalis excess. These include bradyarrhythmias related to enhanced vagal tone (e.g., sinus bradycardia or arrest, or atrioventricular [AV] nodal blocks) and tachyarrhythmias attributed to delayed afterdepolarization-triggered activity (e.g., atrial, junctional, and ventricular tachycardias). One of the most common manifestations of excess digitalis is the appearance of ventricular premature beats (VPBs). However, because these are morphologically similar to VPBs of other causes, they are not highly specific for digitalis toxicity. When ventricular bigeminy occurs, varying morphology of the VPBs is suggestive of digitalis excess. Some forms of ventricular tachycardia are also more indicative of digitalis toxicity as the cause, including ventricular tachycardia with exit block and bidirectional ventricular tachycardia. Atrial tachycardia with block may be caused by excess digitalis but can also occur in the setting of structural heart disease without digitalis toxicity. The rhythm must be distinguished from atrial flutter, and because the amplitude of the atrial depolarization may be low, this rhythm is sometimes difficult to recognize. Nonparoxysmal junctional tachycardia is highly suggestive of digitalis excess, although other causes of this rhythm must be excluded, including myocardial ischemia, recent cardiac surgery, and myocarditis. The term *nonparoxysmal* refers to the gradual appearance and disappearance of the rhythm. The majority of patients with this arrhythmia demonstrate AV dissociation due to acceleration of the AV junctional pacemaker. AV dissociation that appears in the course of digitalis therapy should be considered a sign of digitalis intoxication until proven otherwise.

ANSWER TO QUESTION 72

D (Braunwald, pp. 262–263, 275, 277, 280–281, 291–292; Figs. 16.26, 16.28, 16.37, 16.38)

Myocardial perfusion and integrity of cell membranes can be assessed using thallium-201 or technetium-99m radiotracers. However, flow and metabolism can be simultaneously assessed with positron emission tomography using rubidium-82- or nitrogen-13-labeled ammonia as a flow tracer, and ^{18}F-fluorodeoxyglucose as a metabolic tracer. A mismatch pattern (preserved metabolic activity despite reduced flow), as in this case, is indicative of the presence of viable myocardium. Conversely, a true myocardial scar would demonstrate reduced flow and a matched reduction in metabolism (a perfusion-metabolism match). Additional modalities used to assess for viability include dobutamine echocardiography (which is more specific but less sensitive than radionuclide techniques) and delayed hyperenhancement assessed by gadolinium-enhanced magnetic resonance imaging, which has excellent resolution and can accurately estimate the transmural extent of myocardial scar.[1]

Observational studies have suggested that patients with ischemic cardiomyopathy and large areas of viable myocardium identified by noninvasive cardiac imaging have superior rates of survival, more substantial improvements in left ventricular function, a greater reduction in symptoms of heart failure, and better exercise tolerance after revascularization than patients with large areas of nonviable myocardium. However, the prospective, randomized STICH trial failed to show a difference in outcome with revascularization in patients with or without viable myocardium.[2]

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ANSWER TO QUESTION 73

B (Braunwald, pp. 90–93; Fig. 10.5; Tables 10.6 and 10.7)

Both aortic stenosis (AS) and hypertrophic cardiomyopathy (HCM) cause harsh systolic murmurs, but these conditions

frequently can be differentiated by careful physical examination. For example, the carotid upstroke quality is different (see Braunwald, Fig. 10.5). In AS, there is fixed outflow obstruction and the carotid upstrokes are diminished in amplitude and delayed (pulsus parvus et tardus). In contrast, the carotid upstroke in HCM is initially brisk, then diminishes in midsystole as the left ventricular (LV) outflow gradient becomes more pronounced. Another differentiating feature is the pattern of radiation of the murmur. In AS, the systolic murmur radiates to the carotid arteries, which is not the rule in HCM. If a systolic thrill is present, it is usually located in the second right intercostal space in AS, whereas it is more likely to be felt at the fourth left intercostal space in HCM. Dynamic bedside maneuvers are helpful to distinguish AS from HCM. Physiologic maneuvers that enhance contractility increase the intensity of both murmurs. Maneuvers that reduce LV filling (e.g., strain phase of Valsalva maneuver or standing from a squatting position) decrease the intensity of the AS murmur, but in HCM the decreased intraventricular volume causes LV dynamic outflow obstruction to intensify and the murmur of HCM becomes louder. The murmur of HCM diminishes in intensity with maneuvers that augment LV filling, such as sudden squatting from the standing position.

ANSWER TO QUESTION 74

C (Braunwald, pp. 1841–1843)

The direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban and apixaban, are non-vitamin K antagonist oral anticoagulants approved by the US Food and Drug Administration for the prevention of stroke in patients with nonvalvular atrial fibrillation. Each of these agents has been shown to be noninferior, or superior, to warfarin in efficacy and produce less serious bleeding than warfarin.[1] Additional advantages of these agents over warfarin include a fixed dosing regimen (no need to monitor laboratory tests to assess degree of anticoagulation), rapid onset of action such that bridging therapy with parenteral agents is not necessary, fewer drug interactions, and no important food interactions. Disadvantages compared to warfarin include higher cost and lack of a laboratory test to accurately monitor compliance.

The new oral anticoagulants are *not* approved for patients with prosthetic heart valves. Indeed, dabigatran resulted in more thromboembolic complications and greater bleeding risk compared to warfarin in the RE-ALIGN trial of patients with mechanical valves.[2]

The dose of each of these agents must be adjusted in patients with renal dysfunction, and should not be used in severe renal disease. Despite its once-daily dosing in patients with atrial fibrillation, rivaroxaban actually has a shorter half-life (5 to 9 hours) than do apixaban or dabigatran (10 to 16 hours), which are administered twice daily. All of these agents lose most of their anticoagulant effect after 24 hours of discontinuation, so they do not offer an advantage in patients with drug noncompliance.

The antibody fragment idarucizumab binds dabigatran with high affinity, forming an essentially irreversible complex that is cleared through the kidneys. It rapid reverses the anticoagulant effect of dabigatran.

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ANSWER TO QUESTION 75

D (Braunwald, pp. 265–267; Fig. 16.9; see also Answer to Question 51)

These single-photon emission computed tomographic images demonstrate transient ischemic dilatation of the left ventricle during stress. The size of the left ventricular (LV) cavity appears larger in the exercise images than in the rest images. This phenomenon is typically due to extensive exercise-induced ischemia with transient LV dysfunction and dilatation. In some patients, the appearance of LV chamber dilatation is actually due to the development of global subendocardial ischemia with reduced tracer uptake along the internal border of the left ventricle. As a result, there is the appearance of a larger chamber without true chamber dilatation. Regardless of the precise underlying mechanism, transient LV dilatation is a high-risk marker of severe ischemia and correlates with extensive coronary artery disease (CAD; i.e., multivessel or left main coronary artery) on angiography.[1] Similarly, increased lung uptake is another marker of extensive CAD and indicates increased risk for an adverse cardiac event.[1]

LV dilatation that is present both at rest and with exertion would be typical for dilated cardiomyopathy. Nuclear images of a patient with chest pain due to single-vessel disease of the left circumflex artery would likely demonstrate a reversible isolated perfusion defect at the lateral or posterior wall. For the patient with prior inferior myocardial infarction, a fixed inferior wall defect, with or without partial reversibility, would be expected. Breast attenuation artifact typically appears as a fixed defect of the anterior or anterolateral wall. A number of techniques have been developed to reduce the likelihood of a false-positive test due to breast attenuation artifact, including the use of technetium-99m-based agents and electrocardiographic gating.

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ANSWER TO QUESTION 76

D (Braunwald, pp. 90, 92; Fig. 10.6)

Pulsus alternans (Fig. 1.69) is a sign of marked left ventricular dysfunction characterized by alternating strong and weak ventricular contractions, which results in alternating intensity of the peripheral pulses. It is thought to reflect cyclic changes in intracellular calcium levels and action potential duration. It is more easily detectable in the femoral than in the brachial, radial, or carotid artery and can be observed with sphygmomanometry by slowly deflating the blood pressure cuff below the systolic level. When present, this sign can be enhanced with maneuvers that decrease venous return, such as assumption of erect posture. Because patients with pulsus alternans generally have markedly reduced ventricular contractile function, an S_3 gallop sound is common. Pulsus alternans would only rarely be accompanied by electrical

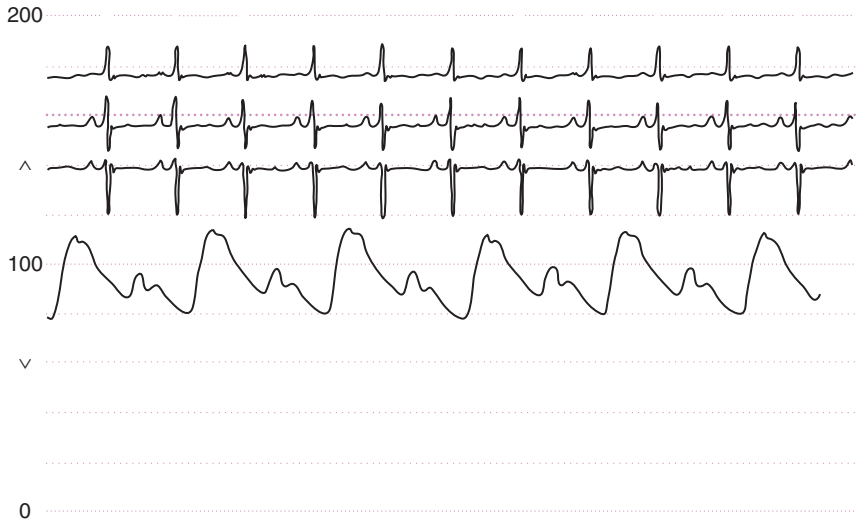

FIG. 1.69 *Pulsus alternans in a patient with severe left ventricular systolic dysfunction. The systolic pressure varies from beat to beat independently of the respiratory cycle. The rhythm is sinus throughout.*

alternans of the QRS complex on the ECG. The latter is more likely to be found in patients with large pericardial effusions.

ANSWER TO QUESTION 77

A (Braunwald, pp. 163, 168–169; Table 13.13)

Exercise testing is often helpful in the assessment of patients with known or suspected arrhythmias. In select patients, particularly those with exercise-induced palpitations, exercise testing is a crucial component of the evaluation. In others, exercise testing can be an important adjunct to ambulatory monitoring and invasive electrophysiologic testing. In association with exercise testing, ventricular arrhythmias may occur during the recovery period, in part because circulating catecholamines continue to increase for several minutes after exertion. In fact, frequent ventricular ectopy in the early postexercise phase predicts a worse long-term cardiac prognosis than ectopy that occurs only during exercise. Supraventricular tachycardia during exercise testing occurs in 4% to 10% of normal individuals and in up to 40% of patients with underlying heart disease. Sustained supraventricular tachycardia develops in only 1% to 2% of patients and is not diagnostic for underlying ischemic heart disease. Patients with known preexcitation, such as Wolff-Parkinson-White (WPW) syndrome, only rarely experience tachyarrhythmias during exercise testing, because antegrade conduction through the atrioventricular node is favored by the catecholamine response to exercise. As such, the delta wave disappears during exercise in 20% to 50% of patients with WPW syndrome.

Exercise testing is also useful to assess the response and risks of antiarrhythmic drug therapy. This is particularly important for patients on class IC antiarrhythmic agents, such as propafenone and flecainide, because QRS widening during exercise on such drugs is predictive of a proarrhythmic effect and reentrant ventricular tachycardia. In addition, prolongation of the QT interval of >10 milliseconds during exercise identifies patients at particularly high risk of a proarrhythmic effect on class IA antiarrhythmic agents.

The development of left bundle branch block (LBBB) during exercise is predictive of subsequent progression to permanent LBBB. Patients with exercise-induced LBBB also have a threefold increase in the risk of death or major cardiac events compared with patients without this abnormality.

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ANSWER TO QUESTION 78

D (Braunwald, pp. 91, 93; Figs. 10.7 and 10.8; Tables 10.6 and 10.7)

Ejection sounds are high-frequency "clicks" that occur in early systole. They may be either aortic or pulmonic in origin, require a mobile valve for their generation, and begin at the exact time of maximal opening of the semilunar valve in question. If the valve is structurally abnormal, the ejection sound is believed to be caused by the abrupt halting of valve opening at its maximum level of ascent in early systole. If the sound is associated with a structurally normal valve, it is called a "vascular" ejection sound (e.g., associated with a dilated aortic root), in which case the origin of the sound is not clearly defined. In valvular pulmonic stenosis, the ejection sound is loudest during expiration. With inspiration, increased venous return augments atrial systole and results in partial opening of the pulmonic valve before ventricular systole commences. In contrast, with expiration, the pulmonic valve is forced to open from a fully closed position, thus generating a louder ejection sound as the valve's systolic movement is suddenly halted. Aortic ejection sounds do not vary with respiration.

The click of mitral valve prolapse occurs in mid- or late systole and coincides with maximal systolic excursion of the prolapsed leaflet(s) into the left atrium. The generation of the click has been attributed to sudden tensing of the redundant leaflets and elongated chordae tendineae.

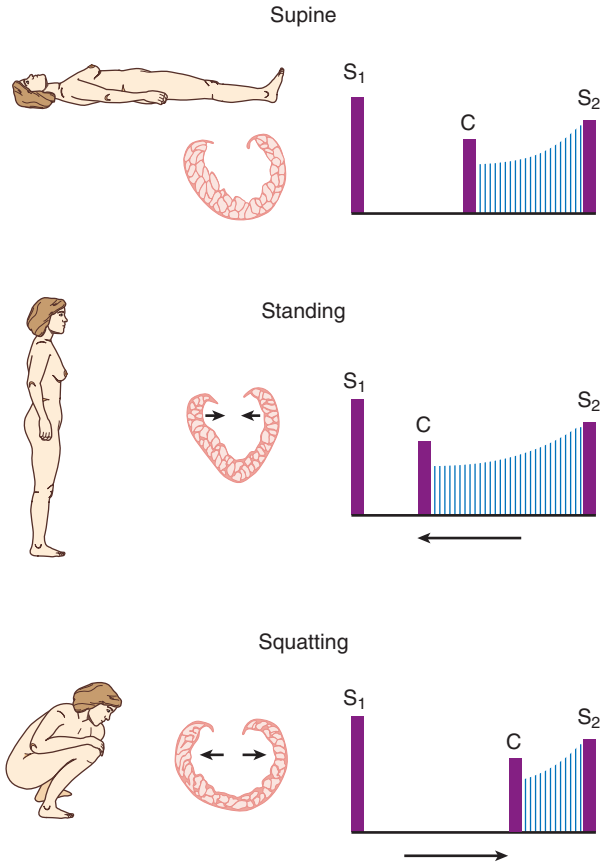

FIG. 1.70 *From Shaver JA, Leonard JJ, Leon DF.* Examination of the Heart: IV Auscultation of the Heart. *Dallas: American Heart Association; 1990:13.*

Maneuvers that decrease left ventricular volume, such as the strain phase of the Valsalva maneuver or standing from a squatting position, move the click earlier in systole (Fig. 1.70).

ANSWER TO QUESTION 79

D (Braunwald, pp. 124, 128, 132, 143, 147; Fig. 12.18; Table 12.10)

Chronic obstructive pulmonary disease (COPD) causes several electrocardiographic abnormalities related to changes of the position of the heart in the chest and hyperinflation of the lungs. These include reduced amplitude of the QRS complex, right-axis deviation, and *delayed* transition in the precordial leads, which may be sufficiently prominent to simulate anterior myocardial infarction (see Braunwald, Fig. 12.18).

For right ventricular hypertrophy (RVH) to be evident on the ECG, it must be severe enough to overcome the opposing effects of the larger left ventricular forces. In patients with COPD, additional electrocardiographic abnormalities that support the presence of true RVH include (1) marked right-axis deviation (>110 degrees); (2) deep S waves in the lateral precordial leads; and (3) an $S_1Q_3T_3$ pattern (S wave in lead I, prominent Q in lead III, inverted T waves in the inferior leads).

ANSWER TO QUESTION 80

E (Braunwald, p. 234; Fig. 14.83; pp. 315, 354–366; see also Answer to Question 41)

Detection and quantification of shunts within the cardiac chambers or great vessels can be accomplished by cardiac catheterization, echocardiography, magnetic resonance imaging, and radionuclide scintigraphy. Shunt evaluation by cardiac catheterization involves utilizing oximetry in multiple locations and calculation of pulmonary and systemic blood flow. Comparison of pulmonary and systemic blood flows helps to establish the presence and magnitude of the shunt, whereas oximetry in multiple locations helps to localize the site of abnormal flow. "Physiologic" shunting, such as occurs in hypoventilation, pulmonary edema, and cardiogenic shock, should be correctable with the administration of 100% oxygen. Failure to correct with 100% oxygen suggests an "anatomic" shunt.

A shortcoming of oximetric shunt detection is its lack of sensitivity, although most clinically relevant shunts *can* be detected using this method. When performing an oximetry run, multiple sites in the inferior vena cava (IVC), superior vena cava (SVC), and right atrium must be sampled because the oxygen saturation from these sites may vary widely. The IVC, because of the relatively low renal oxygen consumption, usually has the *highest* oxygen saturation. Conversely, the coronary sinus delivers venous blood with a very low oxygen saturation. The Flamm formula is used to estimate the mixed venous oxygen content (Mvo_2) proximal to a left-to-right shunt at the right atrial level:

$$Mvo_2 = \frac{3(\text{SVC } O_2 \text{ content}) + 1(\text{IVC } O_2 \text{ content})}{4}$$

ANSWER TO QUESTION 81

D (Braunwald, pp. 124, 130–132; Figs. 12.17 and 12.21; Tables 12.5, 12.6, 12.9)

The normal QRS complex in lead V_1 consists of a small R wave, representing initial septal depolarization, followed by an S wave, which is inscribed as the bulk of electrical forces swing in the direction of the left ventricle.

In right ventricular hypertrophy, the increased right-sided forces cause abnormally tall R waves in leads V_1 and V_2, deep S waves in the lateral precordial leads, and right-axis deviation. The Wolff-Parkinson-White (WPW) syndrome, a form of preexcitation, is characterized by a short PR interval and an initial slur (delta wave) with prolongation of the QRS complex. When WPW is caused by a posterior or lateral left ventricular (LV) accessory pathway, the delta wave is positive in lead V_1, associated with prominence of the R wave. A tall R wave in the right precordial leads is also typical of Duchenne muscular dystrophy. In that disorder, myocardial dystrophy of the posterobasal and contiguous lateral LV wall results in deep Q waves in leads I, aVL, and V_5 and V_6, with reciprocal changes (tall R waves) in leads V_1 and V_2. Accidental placement of the right precordial leads too low on the chest wall is a common technical error that results in prominent R waves in leads V_1 and V_2.

In left anterior fascicular block, the amplitude of the R waves in the right precordial leads is often *diminished* and deep S waves are present in leads V_5 and V_6 because of the anterosuperiorly directed late QRS forces.

ANSWER TO QUESTION 82

B (Braunwald, p. 90; Fig. 10.5; pp. 201, 364; Fig. 19.14)

The hemodynamic pressure tracing is consistent with hypertrophic obstructive cardiomyopathy (HCM). In the tracing, a large gradient exists between the midcavity of the left ventricle and the aorta as shown during the first three full beats. As the catheter is withdrawn into the subaortic left ventricular (LV) outflow tract, the gradient is no longer observed (last three beats). In patients with valvular aortic stenosis (AS), the pressure gradient would persist in the latter location.

A bifid aortic pulse contour is demonstrated in the tracing, with a notch on the upstroke ("spike-and-dome" configuration) characteristic of HCM. This is in contrast to delayed rise of the aortic pressure tracing (and therefore carotid artery pulsation) expected in patients with valvular AS. In addition, LV diastolic dysfunction is common in HCM, owing to impaired LV compliance, which leads to a prominent LV *a* wave and elevation of end-diastolic pressure, as shown on the tracing (~20 mm Hg in this example).

There is no role for aortic valve replacement in the treatment of HCM. In selected patients with HCM and severe symptomatic obstruction due to septal hypertrophy, surgical myomectomy or alcohol septal ablation may be beneficial.

ANSWER TO QUESTION 83

D (Braunwald, pp. 119–121, 123–124; Figs. 12.4 and 12.9)

The normal mean QRS complex in the frontal plane ranges from –30 degrees to +90 degrees. A mean axis more positive than +90 is referred to as *right-axis deviation*, whereas an axis more negative than –30 degrees is *left-axis deviation*. The axis is *indeterminate* (i.e., cannot be calculated in the frontal plane) if all six limb leads record isoelectric QRS complexes (i.e., equal positive and negative deflections).

The designation "vertical" heart is applied when the mean QRS complex is near +90 degrees, in which case the QRS recording in lead I would be isoelectric. A "horizontal" heart refers to a mean axis near 0 degrees, in which case there is a tall R wave in leads I and aVL and an isoelectric QRS complex in aVF.

The normal QRS complex in precordial leads V_1 and V_2 shows small R waves with more prominent S waves, reflecting early septal depolarization followed by activation of the posteriorly located left ventricle. Proceeding from V_1 to V_6, the R wave becomes gradually taller and the S wave less deep. The transition zone represents the lead in which the R wave height surpasses the depth of the S wave and is usually localized to lead V_3 or V_4. An early transition (termed *counterclockwise rotation* as viewed from under the diaphragm) is present when the height of the R wave is greater than the depth of the S wave prior to lead V_3 and would not be expected in left ventrocular hypertrophy. Conversely, a delayed transition *(clockwise rotation)* is present when the S wave depth exceeds the height of the R wave beyond lead V_4.

ANSWER TO QUESTION 84

C (Braunwald, pp. 362–363)

The pioneering work of Gorlin and Gorlin provided equations to calculate cardiac valve areas based on the measured transvalvular pressure gradient and blood flow. The valve area is proportional to

$$\frac{F}{K \times \sqrt{\Delta P}}$$

in which F represents flow across the valve, ΔP is the mean pressure gradient across the orifice, and K is an empiric constant for the valve in question. In the calculation of mitral valve area, a confirmed pulmonary capillary wedge pressure is typically substituted for the left atrial pressure.

There are assumptions and potential pitfalls in the determination of valve area by catheterization techniques. Because flow in the Gorlin equation is assumed to be systemic (forward) cardiac output, the presence of regurgitation across the valve in question results in a falsely *low* value for F in the Gorlin equation, and therefore the calculated valve area may be underestimated. In such cases, the calculated valve area actually represents the lower limit of the true valve area.

Accurate and simultaneous determinations of cardiac output and mean pressure gradient are essential in the determination of a stenotic orifice area. Both of these measurements are subject to error. Because it is the square root of the mean pressure gradient that is used in the Gorlin formula, errors in measurement of the cardiac output have a proportionately greater influence on the calculated valve area.

ANSWER TO QUESTION 85

C (Braunwald, pp. 275–279; Fig. 16.25; Table 16.3; see also Answer to Question 69)

Exercise testing is the preferred stress modality to evaluate for coronary artery disease because it allows a correlation between exertional symptoms and objective findings of ischemia and provides substantial prognostic information. However, many patients are not capable of attaining a sufficient level of exercise (because of physical limitations or poor conditioning) and undergo pharmacologic stress testing instead. The most widely used agents for pharmacologic stress testing are (1) coronary arteriolar vasodilators (adenosine, dipyridamole, and regadenoson) and (2) adrenergic agents such as dobutamine. During pharmacologic perfusion positron emission tomographic scintigraphy of a normal individual, there is homogeneous uptake of the radiotracer (e.g., rubidium-82) throughout the myocardium in both the exercise and resting states. The images in the case of this patient demonstrate severe vasodilator-induced ischemia (hypoperfusion) of the anterior and anteroseptal walls. That is, there is a large region of hypoperfusion on the stress images that is predominantly *reversible:* it almost completely fills in on the resting images. A *fixed* defect is one that is present and unchanged on both exercise and rest images and corresponds to a region of prior myocardial infarction or scar. This patient subsequently underwent cardiac catheterization. A 90% stenosis at the anastomosis of the left internal mammary artery to the left anterior descending artery was found, and successful percutaneous intervention was performed.

ANSWER TO QUESTION 86

B (Braunwald, pp. 85, 201)

This patient has an advanced form of hemochromatosis, a disease that leads to abnormal deposition of iron in tissues.

The most common form of hemochromatosis is *inherited* as an autosomal recessive disorder due to a mutation in the *HFE* gene that codes for a transmembrane protein responsible for regulating iron uptake in the intestine and liver. *Acquired* hemochromatosis is the result of excess iron load due to an underlying disease process (e.g., thalassemia) or increased ingestion of iron.

Normal body content of iron is maintained by the regulated absorption of iron in the intestines. In inherited hemochromatosis, mucosal absorption is inappropriately high, which leads to elevated plasma iron levels and increased transferrin saturation. The extra iron load is deposited in multiple organs, including the heart, pancreas, and liver. A classic presentation therefore is that of "bronze diabetes" due to excess iron deposition in the dermis and pancreas. Other findings include hypogonadism (impaired hypothalamic-pituitary function), arthropathy (often the small joints of the hands), and cirrhosis. The severity of cardiac involvement in hemochromatosis varies widely and may culminate in heart failure due to a mixed dilated and restrictive cardiomyopathy. Electrocardiographic findings may include supraventricular arrhythmias, varying degrees of atrioventricular block, and *low* QRS voltage. Diagnosis is based on the history, an elevated plasma iron level, normal or low total iron-binding capacity (TIBC), and markedly increased transferrin saturation (iron:TIBC ratio) and serum ferritin levels. Treatment options include phlebotomy and chelating agents (e.g., desferrioxamine).

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ANSWER TO QUESTION 87

D (Braunwald, pp. 91–93, 99; Fig. 10.7; Tables 10.6 and 10.7; see also Answer to Question 78)

Physiologic maneuvers that alter left ventricular (LV) filling can aid in the bedside diagnosis of mitral valve prolapse (MVP). Any maneuver that reduces LV volume, such as the Valsalva maneuver or standing from a supine position, causes the valve to prolapse into the left atrium sooner, such that the click and onset of the murmur occur earlier in systole and the murmur may become louder. Conversely, actions that augment impedance to LV emptying, such as isometric handgrip, increase the LV volume and thus delay the click and murmur. Squatting from a standing position will also delay the click and murmur due to the increased venous return and augmented LV volume.

Carotid sinus massage is not generally helpful in differentiating the murmur of MVP from other valvular abnormalities. This maneuver can be useful to slow the heart rate in a tachycardic patient to help characterize extra heart sounds.

ANSWER TO QUESTION 88

E (Braunwald, pp. 135, 143, 144, 146–147; Fig. 12.46; Tables 12.8, 12.10, 12.11; see also Answer to Question 19)

Hyperkalemia is associated with a distinctive sequence of electrocardiographic abnormalities, beginning with narrowing and peaking (tenting) of the T wave, with a shortened QT interval. Progressive hyperkalemia reduces atrial and ventricular resting membrane potentials, which inactivates sodium channels and decreases conduction velocity. At that stage, the QRS complex begins to widen and the P wave amplitude decreases. Complete loss of observed P waves may occur. In that situation, sinus rhythm typically persists but the P wave amplitude is so small that it is not recorded on the surface ECG. Very marked hyperkalemia leads to asystole, sometimes preceded by a slow undulatory (sinusoidal wave) pattern on the ECG caused by marked QRS widening.

Hypokalemia, in contrast, is associated with hyperpolarization of the resting membrane potential and increased action potential duration. This results in resting ST-segment depression and QT interval prolongation. The T waves often become flat, whereas U waves become prominent. The QT prolongation predisposes to torsades de pointes. Hypokalemia, not hyperkalemia, predisposes to digitalis-associated tachyarrhythmias.

ANSWER TO QUESTION 89

D (Braunwald, p. 143; Table 12.10)

Noninfarction Q waves can be produced by any condition that results in (1) abnormal heart position, (2) altered ventricular conduction, (3) ventricular enlargement, or (4) myocardial damage or replacement. Wolff-Parkinson-White syndrome is an example of altered ventricular conduction, in which early activation of the inferoposterior wall by a bypass tract results in inferior Q waves and a pseudoinfarction pattern. Similarly, left bundle branch block is frequently associated with noninfarction Q waves due to altered ventricular activation. Any condition that displaces the mass of the left ventricle posteriorly, such as cardiomyopathy with ventricular dilatation, or chronic obstructive pulmonary disease, is associated with Q waves in the right-sided chest leads and poor R wave progression across the precordium. Incorrect superior placement of the right precordial chest leads can also result in the appearance of Q waves in those leads.

Acidosis leads to hyperkalemia with the characteristic changes of that condition (see Answer to Question 88), but not to the development of Q waves.

ANSWER TO QUESTION 90

C (Braunwald, pp. 134, 145, 161–164; Fig. 13.4)

Several abnormalities on the baseline ECG limit the interpretation of standard exercise electrocardiography. These patterns include preexcitation syndromes, paced ventricular rhythms, left ventricular hypertrophy, and left bundle branch block. Digoxin can accentuate ischemic exercise-induced ST-segment changes, even if the resting ECG is without evidence of ST-segment depression.

Right bundle branch block (RBBB) is associated with T wave and ST-segment changes in the anterior precordial leads. Exercise-induced ST-segment depression in these leads (V_1 to V_4) is a common finding in patients with RBBB and is nondiagnostic for ischemia. Thus, RBBB decreases the sensitivity of the test; however, the ST segments in leads V_5 and V_6, and in leads II and aVF, remain interpretable in patients with this conduction disorder.

ST-segment *depressions* typically are not predictive of the anatomic site of ischemia. In contrast, ST-segment *elevations* in leads that do not contain pathologic Q waves *are* specific for exercise-induced ischemia and are predictive of the anatomic location of ischemia.

Certain findings on exercise electrocardiography are indicative of severe (left main or multivessel) coronary artery disease and should be considered "high risk" markers. These include ≥2-mm ST-segment depressions (particularly at low levels of exercise), ST-segment depressions in more than five leads, ST-segment depressions that persist more than 5 minutes during the recovery phase, ST-segment elevations, and hypotension during exercise (see Answer to Question 48).

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ANSWER TO QUESTION 91

A (Braunwald, pp. 205–209; Figs. 14.38, 14.39, 14.42, 14.43; eFig. 14.20)

The continuous-wave Doppler profile demonstrates combined mitral stenosis (MS) and mitral regurgitation (MR). In the figure, diastolic flow toward the transducer (into the left ventricle) is represented by velocities above the baseline while flow away from the transducer (into the left atrium [LA]) is indicated by velocities below the baseline. In a normal individual, there would be no flow across the valve during systole and the peak diastolic velocity would be <1.3 m/s. The presence of MS results in a high diastolic velocity (usually >1.5 m/s). In addition, the persistent diastolic pressure gradient between the LA and left ventricle in patients with MS results in an abnormally delayed decline of the transmitral velocity signal, as shown in this case. The severity of MS can be determined from Doppler measurements by calculating the pressure decline half-time (see Answer to Question 26).

Two-dimensional echocardiography and Doppler interrogation are also very useful techniques for assessing MR and determining its cause. The continuous-wave Doppler examination shown here demonstrates abnormal systolic flow directed retrograde into the LA. Doppler color flow imaging (not shown in this example) estimates the magnitude of MR, which can be estimated by the area of the visualized regurgitant jet. When MR is severe, Doppler interrogation demonstrates reversal of systolic flow in the pulmonary veins. MR jets that are peripherally directed along the left atrial wall, rather than centrally located, may underestimate the severity of MR as determined by Doppler techniques (Coanda effect).

ANSWER TO QUESTION 92

D (Braunwald, p. 37; Fig. 4.2)

Quality improvement initiatives are increasingly used in healthcare settings, employing several approaches. A commonly used model is PDSA (Plan-Do-Study-Act) in which goals, metrics, and changes to implement are set, and then tested in an iterative PDSA cycle (see Braunwald, Fig. 4.2). This model works best with goals that are measurable, allowing quantification of the effects of a given iteration. The Lean approach was developed at Toyota as a means to improve the efficiency of automobile production. Lean is focused on reducing wasteful processes (including overproduction, unnecessary motion, and uneven production). In healthcare, this approach relies on mapping the essential components of complex processes and empowering all team members to identify targets and areas of potential waste. Whereas Lean focuses on eliminating waste, Six Sigma focuses on reducing unnecessary variation in care delivery, and reducing error rates to less than six standard deviations below average. Six Sigma's iterative process (Define, Measure, Analyze, Improve, and Control) is a variation on the PDSA theme, adding the "control" element to underscore the need for continued monitoring of care processes after successfully reducing variability.

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ANSWER TO QUESTION 93

B (Braunwald, p. 1604; Fig. 78.1)

The microscopic specimen demonstrates marked myocyte disarray typical of hypertrophic cardiomyopathy (HCM). HCM is a genetic disorder caused by more than 900 mutations in genes that encode sarcomeric proteins. It is transmitted in an autosomal-dominant fashion, and specific mutations are often unique to affected families. More than 50% of all HCM mutations occur in genes that encode β-myosin heavy chain or cardiac myosin-binding protein C.

The risk of most concern for patients with HCM is sudden cardiac death. It results from ventricular tachycardia/fibrillation and may occur at any age, but is most often a complication in adolescents and young adults with HCM. The risk is greatest in those with specific clinical markers, for whom primary prevention with an implantable cardioverter-defibrillator is often appropriate, particularly in younger patients: (1) a family history of HCM-related death, especially if sudden; (2) unexplained syncope; (3) hypotensive or attenuated blood pressure response on exercise testing; (4) multiple, prolonged nonsustained bursts of ventricular tachycardia on ambulatory electrocardiographic monitoring; and (5) marked left ventricular hypertrophy (wall thickness ≥30 mm).

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ANSWER TO QUESTION 94

C (Braunwald, pp. 1586–1588)

This patient has a form of arrhythmogenic right ventricular cardiomyopathy (ARVC), a condition in which fibrofatty replacement of myocardium, most commonly of the right ventricle, leads to ventricular arrhythmias and sudden cardiac death. ARVC results from mutations in genes that encode

components of cardiac desmosomes, cell membrane structures that maintain structural and functional contacts between neighboring myocytes. ARVC can occur as an isolated cardiomyopathy or as a syndromic disorder. In *Naxos syndrome*, ARVC is accompanied by woolly, kinky hair and palmar-plantar keratosis. It arises from autosomal *recessive* mutations (in distinction to isolated ARVC, which is transmitted in an autosomal-dominant fashion) in the gene that encodes plakoglobin, a cytoplasmic desmosomal protein. Patients with *Carvajal syndrome* display similar hair and skin findings, but the cardiomyopathic findings predominantly affect the left ventricle. The patient in this question has predominantly right ventricular involvement and therefore has Naxos syndrome.

Major diagnostic criteria for ARVC include (1) RV enlargement and dysfunction visualized by echocardiography, cardiac magnetic resonance imaging, or angiography; (2) fibrofatty replacement of myocardium on endomyocardial biopsy (however, there is a high false-negative rate of diagnosis because of sampling error and because the RV septum [the region sampled by the bioptome] may not display characteristic changes); (3) electrocardiographic abnormalities including inverted T waves in V_1 to V_3, an epsilon wave between the QRS complex and the T wave in leads V_1 to V_3, late potentials on signal averaged electrocardiography, nonsustained or sustained ventricular tachycardia with a left bundle branch morphology, and superior axis; and (4) a confirmed family history of ARVC in a first-degree relative.

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ANSWER TO QUESTION 95

B (Braunwald, pp. 201, 1591–1594; Fig. 77.9)

The presented clinical scenario is most consistent with cardiac amyloidosis, an infiltrative cardiomyopathy in which amyloid fibrils (in this case, abnormal amyloid light-chains [AL] associated with multiple myeloma) expand the extracellular space of cardiac tissues. Clinical manifestations include progressive heart failure (often right-sided > left-sided), postural hypotension due to autonomic dysfunction, macroglossia, and periorbital purpura (in AL amyloidosis). This patient's electrocardiogram shows reduced limb lead voltage due to myocardial infiltration of amyloid fibrils.

The echocardiogram in cardiac amyloidosis typically demonstrates increased thickness of both ventricles with an echobright appearance of the myocardium, diffusely thickened valves, and biatrial enlargement. Diastolic dysfunction is common, as manifest by tissue Doppler imaging, with reduced early diastolic E′ velocities at both the lateral and medial mitral annular levels (note that medial > lateral mitral annular E′ ["annulus reversus"] in answer choice C is characteristic of constrictive pericarditis, not amyloidosis) (see Braunwald, p. 1673).

Although the LV ejection fraction may appear normal in patients with symptomatic cardiac amyloidosis, systolic dysfunction is often present by strain imaging (speckle-tracking), which characteristically reveals severely reduced longitudinal strain at the LV base, but preserved apical strain (Fig. 1.71).

While pericardial effusion is a common finding in cardiac amyloidosis, it is rarely large.

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ANSWERS TO QUESTIONS 96 TO 100

96–A, 97–D, 98–B, 99–C, 100–D (Braunwald, pp. 83–84)

Cardiac syncope is usually of rapid onset and is not preceded by an aura. Patients typically regain consciousness promptly with a clear sensorium. In any patient with a history of coronary artery disease (CAD), cardiac causes of syncope should be carefully investigated, even when the presenting history is somewhat atypical. Neurologic syncope is sometimes preceded by an aura, is more characteristically associated with incontinence and tongue biting, and is notable for a clouded sensorium with slow clearing after return of consciousness. Seizure-like activity may occur at any time cerebral perfusion is impaired and is not particularly helpful in distinguishing different types of syncope.

Distinguishing cardiac syncope due to tachyarrhythmias (usually ventricular tachycardia) from that due to bradyarrhythmias can be difficult on clinical grounds alone. Patients with a history of CAD are at increased risk for ventricular tachyarrhythmias. Bradyarrhythmias are more common in patients with a history of conduction abnormalities.

A neurocardiogenic (vasovagal) cause accounts for approximately 50% of syncopal episodes. It may be precipitated by emotional distress, fear, pain, or extreme fatigue or may occur in the setting of diminished venous return with a reduced stroke volume. Each of these situations results in high catecholamine activity with sympathetic stimulation of the heart. In susceptible individuals, the resultant hypercontractility excessively stimulates cardiac mechanoreceptors (vagal afferent C fibers), which then leads to sympathetic withdrawal, vasodilatation, and bradycardia. When extreme, this activation leads to frank syncope.

Hysterical fainting is typically not accompanied by a change in pulse, blood pressure, or skin color. It is often associated with paresthesias of the hands or face, hyperventilation, dyspnea, and other manifestations of acute anxiety.

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ANSWERS TO QUESTIONS 101 TO 104

101–B, 102–A, 103–D, 104–C (Braunwald, pp. 83–85, 92, 93, 100; Table 10.7; pp. 123, 128–130, 131, 134, 143, 144, 146–147; Figs. 12.14, 12.15, 12.19, 12.42, 12.46; Table 12.11)

The ECG of the young man with exertional chest discomfort and a systolic murmur demonstrates marked left ventricular (LV) hypertrophy with a "strain" pattern. In this case, the

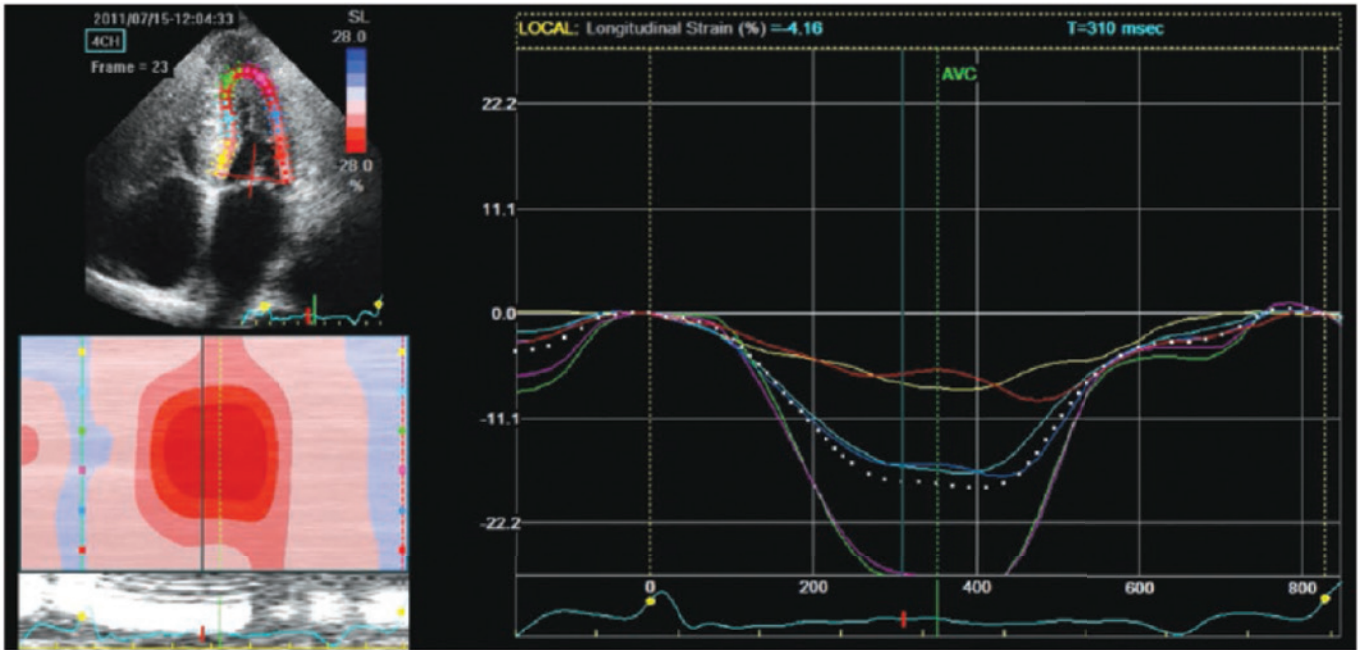

FIG. 1.71 *Echocardiographic strain imaging in amyloid cardiomyopathy. The "bulls-eye" appearance of the longitudinal strain pattern from an echocardiographic apical four-chamber view is shown in a patient with familial amyloid cardiomyopathy and a normal ejection fraction. The appearance represents a gradient of longitudinal strain from the apex to the base with relatively well-preserved apical strain and severely impaired basal strain. In contrast, normal subjects have no significant strain gradient from the apex to the base. This appearance, a useful diagnostic finding, is seen in more than 80% of patients with cardiac amyloidosis, regardless of the precursor amyloid protein.*

systolic murmur is due to dynamic LV outflow obstruction because of hypertrophic cardiomyopathy. Such a murmur becomes louder with maneuvers that decrease LV preload, such as standing from a squatting position or during the strain phase of the Valsalva maneuver. The 56-year-old woman with pleuritic chest discomfort and dyspnea has suffered a pulmonary embolism. Her ECG demonstrates borderline sinus tachycardia, an incomplete right bundle branch block, and an $S_1Q_3T_3$ pattern in the limb leads. The latter reflects a deep S wave in lead I, and a prominent Q wave with T wave inversion in lead III, a pattern that can be observed in individuals with hemodynamically significant pulmonary embolism. However, the sensitivity of this finding is low and it is observed in only a minority of such patients. The most common electrocardiographic findings of hemodynamically important pulmonary embolism are sinus tachycardia and T wave inversions in the anteroseptal leads that may mimic anterior myocardial ischemia. The 36-year-old man with sharp inspiratory chest discomfort has acute pericarditis. His ECG demonstrates diffuse ST-segment elevations. There is also subtle PR-segment depression in the limb leads (especially lead II) and slight PR-segment elevation in lead aVR. All are common findings in patients with acute pericarditis. The elderly alcoholic man with vomiting and epigastric discomfort has developed hypokalemia and hypomagnesemia. His ECG is consistent with these electrolyte derangements, including a prolonged QT (actually QU) interval and low-voltage T waves.

ANSWERS TO QUESTIONS 105 TO 109

105–A, 106–C, 107–B, 108–E, 109–D (Braunwald, pp. 384–386, 390; Figs. 20.15–20.19, 20.22, 20.23, 20.25, 20.26; Tables 20.7 and 20.8)

Coronary arteriography remains the benchmark to assess coronary anatomy. Coronary artery spasm (in the figure see *E*, Injections 1 & 2) may be due to organic vascular disease or may be induced by the mechanical stimulation of the artery by the catheter tip. In 1% to 3% of patients who do not receive vasodilators (e.g., nitroglycerin) before arteriography, spasm may be observed. Whereas the major coronary arteries usually pass along the epicardial surface of the heart, occasional short segments tunnel into the myocardium, leading to myocardial bridging, as demonstrated in the figure in *A* (diastole and systole). Such bridging has been identified in about 5% of human hearts at autopsy. Angiographic identification of a myocardial bridge usually is most common in the left anterior descending (LAD) artery.

Intercoronary collateral vessels in the interventricular septum are normally <1 mm in diameter, are characterized by moderate tortuosity, and tend to serve as connections between numerous septal branches of the LAD and smaller posterior septal branches that arise from the posterior descending artery. Recruitment and development of such collateral vessels due to occlusion of the LAD artery are shown in part *B* of the figure.

The most prevalent hemodynamically significant congenital coronary artery anomaly is the coronary arteriovenous fistula (see *D*). When the fistula drains into any of several areas—the coronary sinus, superior vena cava, pulmonary artery, or a right-sided cardiac chamber—a left-to-right shunt is created. When present in infancy and childhood, approximately half of such patients develop symptoms of congestive heart failure, but the majority of these patients come to attention because of the presence of a loud continuous murmur.

Anomalous coronary origins are present in 1% to 5% of patients undergoing coronary angiography. Ectopic origin of the right coronary artery is present in approximately 2% of patients. Ectopic origin of the left circumflex from the right coronary cusp (see *C*) occurs in <1% of patients. Other abnormal coronary origins occur even less frequently.

ANSWERS TO QUESTIONS 110 TO 113

110–D, 111–B, 112–C, 113–A (Braunwald, pp. 198, 201, 220–221, 231–234; Figs. 14.25, 14.26, 14.31, 14.65–14.67, 14.79; Table 14.11; pp. 312, 315, 317; Fig. 17.17; Tables 17.1 and 17.2; p. 337)

Computed tomography (CT) provides high-resolution morphologic imaging of the heart and is very useful in the diagnosis of a number of cardiovascular disorders. The 53-year-old woman with dyspnea, embolic events, positional lightheadedness, and weight loss has a left atrial (LA) myxoma, the most common primary cardiac tumor. In this case, the myxoma is identified as a large LA mass attached to the interatrial septum (arrows in *D* of the figure). CT and magnetic resonance imaging (MRI) can supplement echocardiography in the assessment of cardiac tumors because of excellent spatial resolution.[1] The young man with recurrent syncope has arrhythmogenic right ventricular (RV) cardiomyopathy. The computed tomogram in *B* demonstrates a dilated right ventricle and aneurysmal bulging of the RV free wall with a scalloped appearance (arrows). Fatty infiltration, fibrosis, and wall motion abnormalities may also be visualized on imaging studies.[2] The 69-year-old woman with prior myocardial infarction has suffered a cerebral thromboembolism due to the left ventricular apical thrombus demonstrated in *C*. The x-ray attenuation of the thrombus is markedly different from that of the surrounding myocardium.

The computed tomogram in *A* demonstrates a thickened pericardium with prominent calcification, typical of constrictive pericarditis, manifest by findings of right-sided heart failure in the clinical scenario presented. Diffuse or localized pericardial thickness >4 mm on cardiac CT is found in the majority of patients with pericardial constriction. Either CT or MRI may be used to image thickened pericardium in suspected constrictive disease; however, pericardial calcification cannot be directly visualized by MRI.[3]

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ANSWERS TO QUESTIONS 114 TO 117

114–D, 115–A, 116–B, 117–C (Braunwald, pp. 186–188; Figs. 14.17 and 14.18; eFig. 14.11; eTable 14.1; Table 14.4)

Normal left ventricular (LV) filling, as recorded by Doppler imaging of diastolic mitral flow velocities, is characterized by a rapid early diastolic phase (the E wave), followed by late additional filling during atrial contraction (the A wave). The relative contribution of early versus late filling is expressed as the E/A ratio. Normally this ratio is >1 and the time required for LV deceleration in early diastole is >190 milliseconds. These relationships are altered in states of abnormal LV filling.

When impaired LV diastolic relaxation is present, there is a reduced diastolic gradient between the left atrium and left ventricle, resulting in a decreased early LV filling (E wave) with a reversed E/A ratio of <1, and the early deceleration time may be prolonged.

The pseudonormalized pattern is observed in patients with more severe diastolic impairment. In this situation there is restoration of the normal early diastolic LV pressure gradient due to elevated left atrial (LA) pressure. Thus, the E wave is taller than the A wave, but the LV deceleration time is more rapid compared with normal (see Braunwald, Figs. 14.17 and 14.18).

The restrictive pattern of LV filling is seen in patients with infiltrative disease and other forms of restrictive cardiomyopathy. Because of the markedly elevated LA pressure, there is enhanced early filling of the left ventricle such that early mitral inflow (E wave) is much greater than the atrial (A wave) contribution to filling and the LV deceleration time is shortened. In this situation, atrial contraction often contributes little to LV filling and the A wave may be barely detected.

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ANSWERS TO QUESTIONS 118 TO 121

118–A, 119–C, 120–D, 121–B (Braunwald, pp. 253–258; Figs. 15.3, 15.5, 15.6; eFigs. 15.18 and 15.19; Table 15.2)

The chest radiograph in patients with abnormalities of the mitral valve commonly displays left atrial (LA) enlargement, whether the lesion is mitral stenosis (MS) or mitral regurgitation. The characteristic chest film in MS (see *A*) displays a heart that is often normal in size, except for the enlargement of the left atrium, which is even more prominent in patients with atrial fibrillation. Calcification of the mitral valve may also be visible. Severe MS is commonly accompanied by pulmonary hypertension, which may be associated with right ventricular dilatation on the chest radiograph. With advanced MS there may be pulmonary vascular redistribution or frank interstitial edema.

A number of findings may be present on the chest radiograph in patients with aortic regurgitation (see *C*). Enlargement of the left ventricle results in displacement of

the cardiac apex downward, to the left, and posteriorly. In addition, the ascending aorta may be dilated. In contrast, aortic stenosis (AS) tends to be more difficult to recognize on plain chest films. Abnormalities in the shape of the heart, although sometimes present, tend to be subtle. Significant left ventricular dilatation occurs only with myocardial failure in end-stage AS. Although calcification of the aortic valve is common in AS, it may not be appreciated on routine chest films. Similarly, routine views may not visualize the post-stenotic dilatation of the ascending aorta that often occurs in this condition.

The ostium secundum type of atrial septal defect (ASD; see *D*) is a congenital cardiac lesion that may be first identified in adulthood. Findings on the chest radiograph include dilatation of the main pulmonary artery, enlargement of the right ventricle, and a generalized increase in the pulmonary vascularity. Right atrial enlargement may be present. Although the chest film in a patient with a secundum ASD may be similar to that of the patient with MS, in the latter condition there is usually LA enlargement (as noted in image *A*) and redistribution of pulmonary blood flow with dilatation of upper lobe vessels and constriction of the vessels at the lung bases. In contrast, when significant left-to-right shunting is present in an ASD, all the pulmonary vessels—including those at the bases—are dilated.

The presence of pericardial effusion (see *B*) leads to a characteristic set of changes in the chest x-ray. With increasing volumes of pericardial fluid, enlargement of the cardiac silhouette with smoothing out and loss of the normal cardiac contours occurs, leading to a symmetrically distended, flask-shaped cardiac shadow. Although such a pattern may be seen with the generalized dilatation that occurs in heart failure, the appearance of the pulmonary hila distinguishes between these two conditions. In pericardial effusion, the pericardial sac tends to cover the shadows of the hilar vessels as it is further distended. In contrast, the failing heart is usually associated with abnormally prominent hilar vessels and pulmonary vascular congestion.

ANSWERS TO QUESTIONS 122 TO 125

122–C, 123–A, 124–B, 125–D (Braunwald, pp. 122–123, 126, 127)

Sinus rhythm is initiated by impulses from the sinus node at rates between 60 and 100 beats/min. Because the wave of depolarization spreads downward from the right atrium (RA) toward the left atrium and ventricles, the P wave is upright in leads I, II, and aVF and is negative in lead aVR. The rate of atrial tachycardia is generally 150 to 200 beats/min, with a P wave contour that is different from that of the normal sinus P wave. This rhythm occurs most commonly in patients with structural heart disease (coronary artery disease, cor pulmonale, digitalis intoxication), but can also occur in normal hearts. Potential mechanisms of atrial tachycardia include automaticity, triggered activity, and reentry. Focal atrial tachycardia due to automaticity generally accelerates after its initiation, but the initiating P wave has the same contour as subsequent ones. In contrast, in reentrant rhythms such as atrioventricular nodal reentrant tachycardia, the first P wave is usually different in shape compared with subsequent P waves because the tachycardia is initiated by a premature atrial complex, whereas subsequent P waves derive from retrograde atrial activation.

Atrial flutter is a macroreentrant atrial rhythm. In the typical form, the reentrant pathway circulates in a counterclockwise direction in the RA, constrained anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and eustachian ridge. The atrial rate during typical atrial flutter is 250 to 350 beats/min. The ECG shows recurring regular sawtooth flutter waves often best visualized in leads II, III, and aVF. In typical counterclockwise flutter, the flutter waves are inverted (negative) in these leads.

ANSWERS TO QUESTIONS 126 TO 129

126–B, 127–C, 128–A, 129–F (Braunwald, pp. 26–29; Figs. 3.3–3.5; pp. 163–164; Table 13.10; pp. 264–265; eFig. 16.4)

Test selection depends in part on the goal of the test (i.e., is the test intended to select a subpopulation with increased probability of disease for further testing [a screening test], or is the purpose to definitively rule out the presence of disease [a confirmatory test])? Sensitivity quantifies a test's ability to detect disease when present, whereas specificity quantifies a test's ability to rule out disease. As demonstrated in the receiver operating curve, sensitivity and specificity are inversely related—as sensitivity increases, the specificity of the test decreases, and vice versa. Sensitivity and specificity can be derived from the graph: the dashed vertical line denotes 98% specificity, at which point Test A has a sensitivity of ~59%, but Test B has a sensitivity of only ~47%. Test A is thus a better test to confirm the presence of disease (i.e., better sensitivity at the high level of specificity required for a confirmatory test). In contrast, an ideal screening test has high sensitivity while minimizing false positives (i.e., maximizing specificity). In the high-sensitivity range, Test B has a higher specificity (specificity ~70% at a sensitivity of 98%, denoted by the dashed line) than does Test A (specificity ~60% at the same sensitivity of 98%), making Test B the better screening test.

$$\text{Sensitivity} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Negatives}}$$

$$\text{Specificity} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Positives}}$$

Sensitivity and specificity are specific to a test, whereas positive predictive value and negative predictive value reflect the characteristics not only of the test but also of the population in which the test is being used.

$$\text{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}} \times 100$$

$$\text{Negative Predictive Value} = \frac{\text{True Negatives}}{\text{True Negatives} + \text{False Negatives}} \times 100$$

For the population in question with a disease prevalence of 50/1000,

True Positives = Number of people affected × Sensitivity = $50 \times 0.98 = 49$

False Negatives = Number affected − True Positives = $50 - 49 = 1$

True Negatives = Number unaffected × Specificity = 950 × 0.6 = 570

False Positives = Number unaffected − True Negatives = 950 − 570 = 380

$$\text{Positive Predictive Value} = \frac{\text{True Positives}}{\text{True Positives} + \text{False Positives}} \times 100 = \frac{49}{49+380} \times 100 = 11\%$$

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ANSWERS TO QUESTIONS 130 TO 133

130–D, 131–A, 132–C, 133–B (Braunwald, pp. 123, 130–131, 134–135, 144, 146–147; Figs. 12.17, 12.42, 12.46; Tables 12.5, 12.7, 12.11)

The patient with renal failure has developed hyperkalemia. The ECG was obtained when the serum potassium level was 7.2 and shows the characteristic narrow, peaked T waves of hyperkalemia (see *D* in the figure). The QT interval is shortened relative to the baseline, and there is mild QRS widening. The P wave amplitude is normal at this time, but would decrease with progressive, untreated hyperkalemia. The patient with positional, sharp chest discomfort has acute viral pericarditis, manifest on the ECG by diffuse ST-segment elevation, PR-segment depression, and a resting tachycardia (see *A*). The ECG of the man with lightheadedness demonstrates complete heart block. Although the initial portion of the rhythm may suggest 2:1 second-degree atrioventricular block (see *C*), there is actually no relationship between the P waves and QRS complexes (note that the PR interval varies). The 38-year-old woman has congenital heart disease with partially corrective surgery as a child and has subsequently developed pulmonary hypertension with a right-to-left shunt through an atrial septal defect, resulting in systemic oxygen desaturation. The ECG shows findings of right ventricular (RV) hypertrophy, including right-axis deviation in the frontal plane, deep S waves, and abnormally small R waves in the left-sided leads, with reversal of normal R wave progression across the precordium (see *B*). The rSR′ pattern in lead V_1 is consistent with RV conduction delay.

ANSWERS TO QUESTIONS 134 TO 142

(Braunwald, Chapter 14)

134. Transthoracic echocardiogram, apical four-chamber view in systole. There is left ventricular (LV) enlargement with a thinned region of the distal septum and apex, which bulges outward and contains a large thrombus. There is a pericardial effusion external to the left ventricle. *Diagnosis:* LV aneurysm with thrombus and pericardial effusion.
135. Transthoracic echocardiogram, parasternal short-axis view at the aortic valve level. A bicuspid aortic valve is present (10-o'clock to 4-o'clock orientation). *Diagnosis:* Congenital bicuspid aortic valve.
136. Transthoracic echocardiogram, parasternal long-axis view. Turbulent color flow across the interventricular septum is consistent with a left-to-right shunt through a perimembranous ventricular septal defect. *Diagnosis:* Congenital ventricular septal defect.
137. Transthoracic echocardiogram, parasternal long-axis view. There is dilatation of the aortic root. *Diagnosis:* Patient has aortic root dilatation because of Marfan syndrome.
138. Transthoracic echocardiogram, apical four-chamber view, with color Doppler interrogation (*A*). The blue (retrograde flow) color Doppler signal extends to the level of the pulmonary veins, consistent with severe mitral regurgitation. In *B*, pulsed Doppler interrogation of a pulmonary vein confirms reversed systolic flow at that level (the systolic Doppler signal below the baseline indicates flow from the left atrium into the pulmonary vein). *Diagnosis:* Severe mitral regurgitation.
139. Doppler tissue imaging (DTI) at the lateral mitral annulus. The early diastolic relaxation velocity (the deflection below the baseline after the electrocardiographic T wave) is recorded at 7.3 cm/s. Values <10 cm/s are consistent with impaired diastolic relaxation. An example of a normal DTI is shown in Fig. 1.72 (The arrow indicates the early diastolic relaxation velocity.). *Diagnosis:* Diastolic dysfunction, due in this case to cardiac amyloidosis.
140. Transthoracic echocardiogram, apical four-chamber view. Images are before (*left*) and after (*right*) injection of agitated saline into an antecubital vein (a "bubble study"). A redundant and mobile interatrial septum bulges into the left atrium. Passage of "bubbles" into the left side of the heart is consistent with a right-to-left shunt. *Diagnosis:* Atrial septal aneurysm with likely patent foramen ovale and right-to-left shunt (possible paradoxical embolism as the cause of the stroke).
141. Transthoracic echocardiogram, subcostal view. There is a thickened interatrial septum that spares the fossa ovalis. *Diagnosis:* Lipomatous hypertrophy of the atrial septum.
142. Transthoracic echocardiogram, parasternal long-axis view. There is a large left-sided pleural effusion posterior to the left ventricle (note that the effusion extends posterior to the descending aorta; pericardial effusions accumulate *anterior* to the descending aorta). *Diagnosis:* Dyspnea due to large pleural effusion.

ANSWERS TO QUESTIONS 143 TO 167

The numbers in brackets refer to features on the Electrocardiogram Response Form on page 32.

143. [7] Normal sinus rhythm (rate 89)
[36] Low voltage (borderline)
[53] Acute anterior Q wave myocardial infarction
[65] Anterior ST-segment elevation consistent with myocardial injury
(Patient presented with an acute anterior STEMI)
144. [7] Normal sinus rhythm (rate 74)
[6] Left atrial abnormality
[43] Right bundle branch block
[58] Inferior Q waves consistent with old MI
(The ECG suggests patient has had prior inferior MI, and right bundle branch block)
145. [7] Normal sinus rhythm (rate 83)
[38] Right-axis deviation

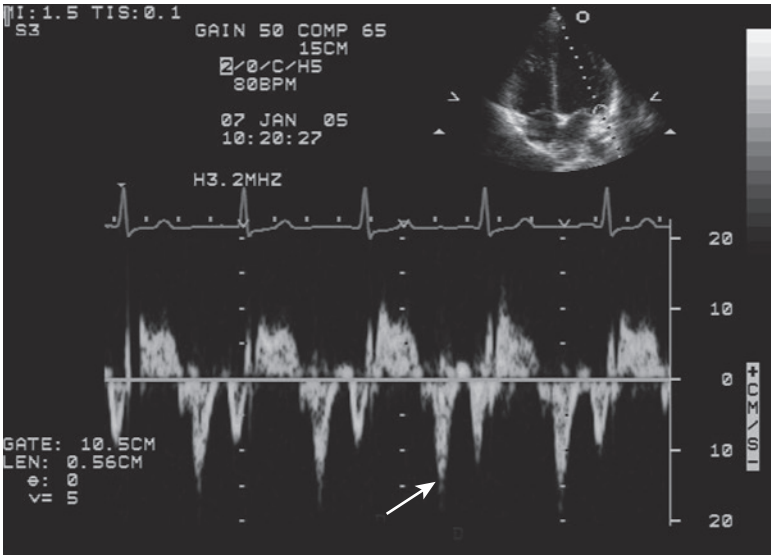

FIG. 1.72

[41] Right ventricular hypertrophy
[43] Right bundle branch block
(The patient has pulmonic stenosis with right ventricular hypertrophy)

146. [9] Sinus bradycardia (rate 55)
[89] Inappropriate ventricular paced beats (failure to sense [complex 11])
[63] Nonspecific inferior T wave abnormality
[69] Prominent U waves
(Pacemaker malfunction)

147. [7] Normal sinus rhythm (rate 67)
[34] Wolff-Parkinson-White syndrome (type B)

148. [18] Atrial flutter with 2:1 atrioventricular conduction, ventricular rate 160 (the flutter waves are seen best in the inferior leads)

149. [17] Supraventricular tachycardia
(Note retrograde P waves between QRS and T wave, best seen in leads V_3–V_6)

150. [19] Rapid atrial fibrillation (ventricular rate ~220)
[37] Left-axis deviation
[34] Wolff-Parkinson-White syndrome
(Patient has Wolff-Parkinson-White syndrome with atrial fibrillation and rapid conduction through the accessory pathway, which is probably located in the left posteroseptal region)

151. [8] Sinus arrhythmia
[30] Type I second-degree atrioventricular block (Wenckebach)
[43] Right bundle branch block
(Patient experienced a vagal reaction during an uncomfortable medical procedure)

152. [8] Sinus arrhythmia
[36] Low voltage of native beats
[37] Left-axis deviation (borderline)
[25] Nonsustained ventricular tachycardia
(He has bursts of nonsustained ventricular tachycardia triggered by paced beats)

153. [85] Atrial paced rhythm
[81] Diffuse ST elevation consistent with acute pericarditis
(Patient has findings of postoperative pericarditis)

154. [19] Atrial fibrillation (ventricular rate ~60)
[43] Right bundle branch block
[38] Right-axis deviation
[46] Left posterior fascicular block

155. [9] Sinus bradycardia (rate 58)
Counterclockwise rotation
[61] Early repolarization
(Diffuse ST-segment elevation is <25% height of the T wave and there is no PR-segment depression, which helps distinguish early repolarization from pericarditis)

156. [10] Borderline sinus tachycardia (rate 100)
[49] Intraventricular conduction delay
[66, 73] Peaked T waves consistent with hyperkalemia
(This patient with chronic renal failure presented with a serum potassium level of 7.5 mmol/L)

157. [7] Sinus rhythm (rate 78)
[77] Dextrocardia
(Patient has total situs inversus and is asymptomatic [note inverted P in I, aVL and reverse R wave progression across the chest leads])

158. [10] Sinus tachycardia (atrial rate 106)
[33, 27] Third-degree atrioventricular block with ventricular escape rhythm (or possibly AV junctional rhythm with left bundle branch block [22])

159. [7] Normal sinus rhythm (rate 84)
[44] Incomplete right bundle branch block
[57] Acute ST-elevation inferior myocardial infarction

160. [7] Normal sinus rhythm (rate 66)
[29] First-degree atrioventricular block
[43] Right bundle branch block
[45] Left anterior fascicular block
[40] Left ventricular hypertrophy

161. [7] Normal sinus rhythm (atrial rate ~84)
[33, 22] Third-degree atrioventricular block with junctional escape rhythm
(Patient has congenital complete heart block related to maternal systemic lupus erythematosus)

162. [7] Normal sinus rhythm (rate 90)
[38] Right-axis deviation
[6] Left atrial abnormality

[49] Right ventricular conduction delay
[41] Right ventricular hypertrophy
[63] Nonspecific ST-segment/T wave abnormality in anterior leads
(A 23-year-old woman with a secundum atrial septal defect)

163. [7] Normal sinus rhythm (rate 82)
[68] Prolonged QT interval
(Patient with congenital prolongation of the QT interval whose subsequent ambulatory monitor showed periods of polymorphic ventricular tachycardia as the cause of her presyncopal episodes)

164. [19] Atrial fibrillation with rapid ventricular response (ventricular rate ~140)
[37] Borderline left-axis deviation
[47] Left bundle branch block

165. [9] Sinus bradycardia (rate 58)
[36] Low voltage
[37] Left-axis deviation
[58] Inferior Q waves—old inferior MI
[68] Prolonged QT interval
(Patient has COPD, and QT interval is prolonged because of amiodarone therapy)

166. [90] Biventricular pacing (cardiac resynchronization therapy)

167. [4] Baseline artifact due to resting tremor
[7] Sinus rhythm (rate 70)
Otherwise normal tracing
(Patient has Parkinson disease.)

SECTION II QUESTIONS

(CHAPTERS 21 TO 43)

Heart Failure; Arrhythmias, Sudden Death, and Syncope

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Directions:

For each question below, select the ONE BEST response.

QUESTION 168

Based on current heart failure guidelines, switching from an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker to the angiotensin receptor neprilysin inhibitor sacubitril/valsartan would be appropriate for which of the following patients?

A. A 60-year-old woman with anthracycline-induced cardiomyopathy, left ventricular ejection fraction (LVEF) of 35%, New York Heart Association (NYHA) class IV symptoms, permanent atrial fibrillation (AF), heart rate 75 beats/min, and blood pressure 90/70 mm Hg, who currently takes lisinopril 5 mg daily, metoprolol succinate 25 mg daily, and spironolactone 25 mg daily
B. A 40-year-old man with ischemic cardiomyopathy, LVEF 40%, NYHA class II symptoms, heart rate 70 beats/min in sinus rhythm, blood pressure 105/70 mm Hg, and prior intolerance of ACE inhibitors due to angioedema, currently treated with carvedilol 25 mg twice daily, losartan 100 mg daily, furosemide 80 mg twice daily, and eplerenone 50 mg daily
C. A 75-year-old woman with heart failure and preserved ejection fraction, LVEF 50%, NYHA class III symptoms, heart rate 75 beats/min in sinus rhythm, blood pressure 120/80 mm Hg, treated with metoprolol succinate 100 mg daily and hydrochlorothiazide 25 mg daily, valsartan 160 mg twice daily, and spironolactone 25 mg daily
D. A 64-year-old man with nonischemic dilated cardiomyopathy, LVEF 35%, NYHA class III symptoms, permanent AF, heart rate 65 beats/min, blood pressure 104/70 mm Hg who is currently treated with bisoprolol 10 mg twice daily, candesartan 16 mg daily, spironolactone 25 mg daily, and torsemide 40 mg daily

QUESTION 169

Which of the following statements about natriuretic peptides is NOT correct?

A. Circulating levels of both atrial natriuretic peptide and brain natriuretic peptide (BNP) are elevated in patients with heart failure
B. Plasma BNP level is useful in distinguishing cardiac from noncardiac causes of dyspnea in the emergency department setting
C. Elevated plasma BNP levels predict adverse outcomes in patients with acute coronary syndromes
D. Prohormone BNP is cleaved into the biologically inactive N-terminal (NT) proBNP and biologically active BNP
E. Circulating levels of NT-proBNP levels decrease with age

QUESTION 170

Which of the following conditions is likely to precipitate symptomatic heart failure in patients with previously compensated left ventricular contractile dysfunction?

A. Atrial fibrillation
B. Marked sinus bradycardia
C. Atrioventricular dissociation
D. Right ventricular apical pacing
E. All of the above

QUESTION 171

An 80-year-old woman with a history of hypertension and type 2 diabetes is hospitalized because of progressive exertional dyspnea and orthopnea. Her examination is notable for an elevated jugular venous pressure (JVP) to the angle of the jaw, pitting peripheral edema with warm extremities, normal blood pressure, and clear mental status. The admission chest radiograph is shown in Fig. 2.1, demonstrating cardiomegaly, small bilateral pleural effusions, and vascular engorgement. After 4 days of treatment with a loop diuretic, she appears clinically euvolemic with a JVP of 7 cm H_2O. However, the serum creatinine value has risen from 1.6 mg/dL at the time of admission to 2.3 mg/dL. Which of the following statements about this patient's condition is NOT correct?

A. Diabetes and hypertension predispose to the development of cardiorenal syndrome
B. Worsening renal function during hospitalization for acute heart failure is an important predictor of early hospital readmission and mortality
C. Decreased renal venous pressure contributes to the cardiorenal syndrome

FIG. 2.1

D. High-dose loop diuretic therapy activates neurohormones that contribute to the cardiorenal syndrome
E. A disproportionate rise in blood urea nitrogen compared with serum creatinine is a sign of renal hypoperfusion

QUESTION 172

Which of the following statements regarding therapy for heart failure with reduced ejection fraction is NOT correct?
A. Angiotensin-converting enzyme (ACE) inhibitors improve survival in heart failure more than the combination of hydralazine plus isosorbide dinitrate
B. Digoxin therapy decreases hospitalizations and mortality in patients with chronic heart failure
C. Angiotensin II receptor blockers provide morbidity and mortality benefits comparable with ACE inhibitors in patients with heart failure
D. Spironolactone reduces mortality in patients with class III to IV heart failure symptoms
E. The aldosterone antagonist eplerenone reduces mortality in patients with class II to III heart failure

QUESTION 173

Which of the following statements about cardiac transplantation is NOT true?
A. Use of the immunosuppressant agent cyclosporine improves long-term outcomes after cardiac transplantation
B. Younger patients have better survival rates than older patients after cardiac transplantation
C. Cardiac transplant patients lack the chronotropic response necessary to support the hemodynamic demands of exercise
D. Endomyocardial biopsy is the most reliable current technique to assess allograft rejection
E. Risk of death from malignancy rises with time after transplantation, whereas mortality from infection declines

QUESTION 174

Which of the following statements about diuretics in heart failure is TRUE?
A. Mannitol is an effective diuretic in cardiac surgical patients with decompensated heart failure
B. Aldosterone receptor antagonists lessen the tendency of angiotensin-converting enzyme inhibitors to cause hyperkalemia
C. Loop diuretics often result in hypokalemia and metabolic acidosis
D. The effectiveness of loop diuretic agents is reduced by nonsteroidal anti-inflammatory drugs

QUESTION 175

Which of the following statements about laboratory findings in heart failure is NOT correct?
A. Serum electrolyte values are usually normal in patients with untreated heart failure of short duration
B. Contributors to hyponatremia in heart failure include dietary sodium restriction, diuretic therapy, and an elevated circulating vasopressin level
C. Elevated serum aspartate aminotransferase levels may accompany congestive hepatomegaly due to heart failure
D. Acute hepatic venous congestion due to heart failure may produce a syndrome that closely resembles viral hepatitis
E. Pulmonary capillary wedge pressures of 13 to 17 mm Hg are commonly responsible for pulmonary vascular redistribution and interstitial edema on the chest radiograph

QUESTION 176

Each of the following statements about myocardial contraction is true EXCEPT
A. $Beta_1$-adrenergic stimulation increases the concentration of intracellular calcium
B. $Beta_1$-adrenergic stimulation promotes production of intracellular cyclic guanosine monophosphate
C. Interaction of calcium with troponin C is essential for myocyte contraction
D. Myosin molecules are tethered to the Z line by the protein titin
E. The sarcoplasmic reticulum plays a key role in the release and uptake of calcium

QUESTION 177

A 45-year-old woman who underwent orthotopic cardiac transplantation because of a familial dilated cardiomyopathy presents 2 months later for routine post-transplant surveillance. An endomyocardial biopsy is obtained (Fig. 2.2). Which of the following statements is NOT correct?
A. Endomyocardial biopsy is the most reliable technique to assess for this complication
B. This disorder is caused by preexisting recipient antibodies to allogeneic antigens on the vascular endothelium of the donor organ
C. Lymphocyte infiltration and myocyte necrosis are the most important biopsy features in the diagnosis of this disorder

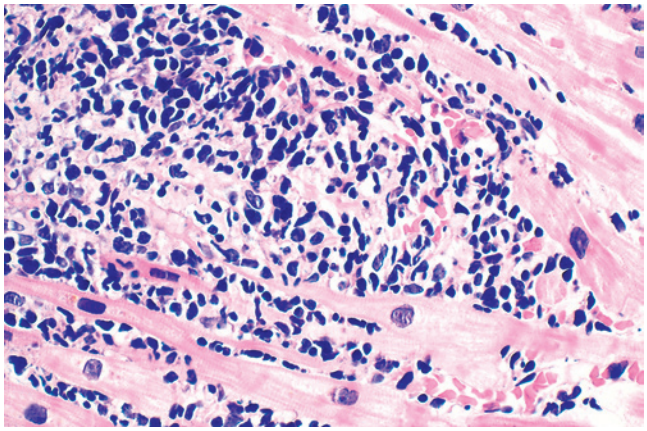

FIG. 2.2 *From Kumar V, Abbas AK, Fausto N, eds.* Robbins and Cotran Pathologic Basis of Disease. *7th ed. Philadelphia: Elsevier; 2005:615.*

D. Most episodes of this complication arise <6 months after transplantation
E. Pulsed corticosteroid therapy is the treatment of choice for this finding

QUESTION 178

Which of the following statements is NOT correct?
A. Major determinants of cardiac output are heart rate and ventricular stroke volume
B. The myocardium extracts oxygen from blood nearly maximally at rest such that the coronary sinus oxygen saturation is <40%
C. During strenuous exercise, O_2 consumption can increase up to 18-fold
D. The peak O_2 consumption and the anaerobic threshold as measured by cardiopulmonary exercise testing are highly reproducible when measured days or weeks apart
E. A measured peak O_2 consumption of 20 mL/min/kg at exercise testing indicates severe functional impairment

QUESTION 179

Which of the following statements regarding structural and hemodynamic left ventricular (LV) parameters in chronic pressure- and volume-overload states is correct?
A. LV systolic stress is proportional to intracavitary pressure and chamber radius
B. Eccentric hypertrophy is characteristic of pressure overload
C. Concentric hypertrophy is characteristic of volume overload
D. LV wall thickness is greater in volume-overload states than in pressure-overload states

QUESTION 180

Which of the following statements concerning therapy of patients with left ventricular (LV) dysfunction is NOT correct?
A. Amiodarone reduces mortality in patients with class II or III heart failure who have a left ventricular ejection fraction <35%
B. Implantation of a cardioverter-defibrillator is indicated in patients with the combination of LV dysfunction and unexplained syncope or resuscitated cardiac arrest
C. Patients with LV dysfunction and a transient or correctable cause of ventricular tachycardia remain at high risk for sudden death
D. Prophylactic implantation of a cardioverter-defibrillator is effective in reducing mortality in patients with coronary artery disease and severe LV dysfunction
E. Use of dronedarone in patients with moderate or severe heart failure is associated with increased mortality

QUESTION 181

A 56-year-old man with ischemic cardiomyopathy and a left ventricular ejection fraction of 25% comes for an outpatient clinic visit complaining of dyspnea and fatigue with minimal exertion (New York Heart Association class III). His medical regimen includes lisinopril, carvedilol, eplerenone, and furosemide, as well as aspirin and atorvastatin. Resting electrocardiography reveals sinus rhythm with a QRS complex duration of 160 milliseconds and left bundle branch morphology. He is being considered for implantation of a biventricular pacemaker. Which of the following statements about cardiac resynchronization therapy (CRT) is correct?
A. CRT reduces mortality in patients with class III or IV heart failure only when combined with an implantable cardioverter-defibrillator
B. A patient with right bundle branch block is as likely to respond to CRT as a patient with left bundle branch block and similar QRS duration
C. CRT improves myocardial performance without increasing myocardial oxygen consumption
D. Echocardiographic measures of dyssynchrony are part of the standard selection criteria for CRT

QUESTION 182

A 35-year-old woman with peripartum cardiomyopathy, left ventricular ejection fraction 25%, and a dual chamber implantable cardioverter-defibrillator (ICD) comes to see you for a routine clinic evaluation. She is able to perform most of her daily activities without limitation, but becomes short of breath walking one flight of stairs. She is currently treated with metoprolol succinate 50 mg daily, candesartan 32 mg daily, furosemide 40 mg daily, and spironolactone 25 mg daily. On examination the heart rate is 84 beats/min, blood pressure 110/70 mm Hg, jugular venous pressure 7 cm, the lungs are clear to auscultation, and there is no peripheral edema. The electrocardiogram shows sinus rhythm with right bundle branch block and QRS duration of 120 ms. Which of the following is the most appropriate next step in her heart failure management?
A. Increase metoprolol succinate to 100 mg once daily
B. Add ivabradine 5 mg twice daily
C. Substitute candesartan with sacubitril/valsartan 24/26 mg twice daily
D. Upgrade her ICD to a device that also provides cardiac resynchronization therapy (biventricular pacing)
E. Her symptoms are stable; make no changes to the regimen

QUESTION 183

A 52-year-old businessman presents to the office complaining of increasing fatigue and shortness of breath. He has also recently noticed that he is more comfortable sleeping on three pillows. He denies chest discomfort or pleuritic pain. His only

medications are hydrochlorothiazide 25 mg daily and atenolol 50 mg daily for hypertension of 10 years' duration with good control. His past medical history includes an appendectomy. He smokes ½ pack of cigarettes per day. He drinks whiskey socially and admits to two martinis at lunchtime each day. There is no family history of heart disease.

On examination, his heart rate is 104 beats/min, respirations are 20 breaths/min, and blood pressure is 134/84 mm Hg. There are no hypertensive changes in the fundi. There are bibasilar rales over the lower third of the lung fields; the carotid upstrokes are normal. The apical impulse is laterally displaced and sustained. S_1 and S_2 are normal. There is both a loud S_4 and S_3. There is a grade 2/6 holosystolic murmur that radiates to the axilla. The remainder of the examination findings are normal except for a trace of pedal edema. The chest radiograph shows left ventricular (LV) enlargement. The ECG is consistent with LV hypertrophy. The most likely cause for this man's heart failure is

A. Hypertension
B. Alcoholic cardiomyopathy
C. Coronary atherosclerosis
D. Hypertrophic cardiomyopathy
E. Excessive beta blocker dosage

QUESTION 184

A 68-year-old woman with long-standing hypertension presents to the emergency department because of progressive exertional dyspnea and fatigue over the past several months. She notes that it is increasingly difficult to put on her shoes because of ankle edema and is uncomfortable sleeping on one pillow due to a cough while recumbent. She denies chest discomfort or palpitations. Her medications include atenolol and hydrochlorothiazide.

On examination, she is an overweight woman with heart rate of 70 beats/min, respirations of 20 breaths/min, and blood pressure of 170/90 mm Hg. The jugular venous pressure is 14 cm H_2O. Examination of the chest is notable for bibasilar rales. The cardiovascular examination reveals a normal S_1, physiologically split S_2, and S_4 gallop. There is no audible murmur. The extremities demonstrate pitting edema to the midcalf bilaterally.

The ECG reveals sinus rhythm with voltage criteria for left ventricular (LV) hypertrophy. The chest radiograph shows a normal cardiac silhouette with bilateral pleural effusions with mild interstitial pulmonary edema. Echocardiography demonstrates concentric LV hypertrophy. The estimated ejection fraction is 70%.

Which of the following pharmacologic agents has been shown to consistently improve survival in this condition?

A. Digoxin
B. Perindopril
C. Spironolactone
D. Candesartan
E. None of the above

QUESTION 185

A 40-year-old man is admitted to the hospital with progressive exertional dyspnea, fatigue, and palpitations. He has no significant past medical history and was well until 4 weeks ago, when he developed flu-like symptoms with low-grade fever, myalgias, pharyngitis, and cough. Clinical examination is consistent with decompensated heart failure. The electrocardiogram shows first-degree atrioventricular block and T wave inversions in the anterior precordial leads. Echocardiography at the time of admission reveals normal left ventricular (LV) size, global hypokinesis with an ejection fraction (EF) of 40%, and no valve abnormalities.

Viral myocarditis is suspected and lisinopril, metoprolol, and furosemide are administered. However, the patient's symptoms rapidly progress, accompanied by frequent episodes of nonsustained ventricular tachycardia (VT). IV amiodarone is initiated, but VT episodes continue. His blood pressure is 88/40 mm Hg, the heart rate is 115 beats/min. Echocardiogram is repeated on the third hospital day: LV contractile function is now severely decreased, with an estimated EF of 15%.

Which of the following management strategies would be most appropriate?

A. Place an implantable cardioverter-defibrillator
B. Treat with high-dose methylprednisolone
C. Add intravenous milrinone
D. Administer intravenous immune globulin
E. Perform an endomyocardial biopsy and consult cardiac surgery regarding mechanical circulatory support

QUESTION 186

A 72-year-old diabetic man with long-standing dilated cardiomyopathy presents for evaluation of dyspnea at rest. He has been hospitalized three times within the past year for decompensated heart failure and recently underwent a cardiopulmonary exercise test showing a peak oxygen consumption of 10 mL/kg/min during maximal effort. His past medical history is notable for prior placement of an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death, and prostatectomy 1 year earlier for adenocarcinoma. For the past 6 months he has been intolerant of beta-adrenergic blockers because of hypotension. He has a supportive family, adheres to therapeutic recommendations, and does not use tobacco.

Physical examination reveals a blood pressure of 92/78 mm Hg, resting heart rate of 106 beats/min, body mass index of 26 kg/m^2, jugular venous pressure of 10 cm H_2O, clear lungs, an S_3 apical gallop, and cool extremities but no evidence of hepatomegaly or ascites. Laboratory studies are notable for the following: sodium 126 mEq/L; potassium 4.6 mEq/L; blood urea nitrogen 34 mg/dL; and creatinine 2.5 mg/dL. Liver function tests and the complete blood cell count are normal. Electrocardiography shows sinus tachycardia and a QRS complex duration of 96 milliseconds. Echocardiography demonstrates a dilated left ventricle with an ejection fraction of 20%, mild mitral regurgitation, and normal right ventricular size and function.

Which of the following is the most appropriate consideration for this patient?

A. Cardiac resynchronization therapy
B. Urgent listing for cardiac transplantation
C. Listing for combined heart-kidney transplantation
D. Implantation of a left ventricular assist device
E. Implantation of a biventricular assist device

QUESTION 187

Which of the following statements regarding the cardiac cycle is NOT correct?

A. The third heart sound (S_3) corresponds to rapid early diastolic filling of the ventricles

B. The absence of an *a* wave on the right atrial pressure tracing is typical of atrial fibrillation
C. Isovolumic ventricular contraction corresponds to the period between mitral valve closure and aortic valve opening
D. The *v* wave on the right or left atrial pressure tracing occurs before the T wave on the electrocardiogram
E. The mitral valve opens in diastole when the left ventricular pressure falls below the left atrial pressure

QUESTION 188

Which of the following statements about physical findings in heart failure is TRUE?
A. Hydrothorax in heart failure is most often bilateral, but when unilateral it is usually confined to the right side of the chest
B. The absence of pulmonary rales on examination excludes the presence of an elevated pulmonary capillary pressure
C. Hepatomegaly typically follows the development of overt peripheral edema
D. The absence of peripheral edema indicates the lack of volume overload and systemic venous congestion
E. In left ventricular failure, P_2 is often reduced in intensity

QUESTION 189

A 66-year-old man with a history of diabetes and hypertension presents for evaluation of exertional dyspnea. He denies associated chest discomfort, but frequently awakens from sleep with shortness of breath. On examination, he has prominent jugular venous distention, a regular heart rhythm with an apical S_4 gallop, bibasilar rales, hepatomegaly, and mild bilateral pedal edema. Electrocardiography reveals sinus rhythm at a rate of 94 beats/min without ST-segment deviations or pathologic Q waves. Echocardiography is notable for a left ventricular ejection fraction of 25% and akinesis of the anterior wall. Subsequent coronary angiography reveals severe three-vessel coronary artery disease with distal targets suitable for surgical revascularization. Which of the following statements about this patient's ischemic cardiomyopathy is correct?
A. Coronary artery bypass grafting (CABG) is superior to medical therapy only if angina is present
B. In this patient's case, dobutamine echocardiography could be used to differentiate anterior wall infarction from hibernating myocardium
C. CABG improves quality of life and survival more than medical therapy only if >50% of the myocardium is shown to be viable
D. Stunned myocardium refers to persistent contractile dysfunction caused by chronically reduced coronary blood flow
E. Surgical ventricular reconstruction should be performed along with CABG because the anterior wall is akinetic

QUESTION 190

Which of the following statements about digitalis toxicity is NOT correct?
A. Lidocaine is a useful agent for treating arrhythmias due to digitalis excess
B. Second- and third-degree atrioventricular blocks in this setting often respond to atropine
C. Recurrence of digitalis toxicity may occur 24 to 48 hours after the administration of antidigoxin immunotherapy
D. Direct-current cardioversion may precipitate ventricular arrhythmias in patients with digitalis intoxication and should be avoided
E. Dialysis is effective in cases of massive overdose

QUESTION 191

A 57-year-old man is admitted to the hospital with 2 hours of severe chest pain. His initial electrocardiogram shows 3-mm ST-segment elevations and small Q waves in leads V_1–V_4. Emergency coronary angiography reveals occlusion of the proximal left anterior descending artery (LAD) without collateral vessel flow. The left circumflex and right coronary arteries are patent without significant obstruction. Primary percutaneous coronary intervention of the LAD restores Thrombolysis in Myocardial Infarction grade 3 flow.

Following coronary intervention, his physical examination reveals a blood pressure of 120/70 mm Hg and heart rate of 70 beats/min. The jugular venous pressure is not elevated. On lung auscultation, bibasilar crackles are audible without wheezes. Cardiac examination reveals a normal apical impulse, a prominent fourth heart sound, and a grade II/VI apical holosystolic murmur. His extremities are warm and peripheral pulses are symmetric and full. The chest radiograph shows a normal cardiac silhouette with interstitial pulmonary edema.

Echocardiography reveals a reduced left ventricular ejection fraction of 34% with anteroapical akinesis. No apical thrombus is visualized. Moderate mitral regurgitation is present. Brief runs of nonsustained ventricular tachycardia are noted on the first hospital day.

His current regimen includes aspirin 81 mg daily, clopidogrel 75 mg daily, atorvastatin 80 mg daily, metoprolol succinate 50 mg daily, and lisinopril 10 mg daily.

Which of the following interventions prior to discharge would further reduce his mortality risk?
A. Implantation of a defibrillator
B. Valsartan 80 mg daily
C. Eplerenone 25 mg daily
D. Amiodarone 200 mg daily
E. Warfarin adjusted to an international normalized ratio of 2.0 to 3.0

QUESTION 192

The circulatory support device seen in the radiograph in Fig. 2.3 has been shown to significantly improve survival and quality of life in select patients with advanced heart failure. Common adverse events associated with this therapy include all of the following EXCEPT
A. Stroke
B. Driveline infection
C. Pump rotor failure
D. Gastrointestinal bleeding
E. Right ventricular failure

QUESTION 193

A 56-year-old woman with atrial fibrillation and nonischemic dilated cardiomyopathy is admitted to the hospital with acute decompensated heart failure. Her past medical history is notable for type 2 diabetes, chronic renal insufficiency, and

gout. Her admission blood pressure is 90/76 mm Hg with an irregular heart rate of 94 beats/min and her examination is notable for pulmonary and systemic congestion. Treatment is initiated with a continuous IV furosemide infusion at 10 mg/h after an intravenous bolus. However, her urine output remains <70 mL/h and her serum creatinine increases from 1.4 mg/dL to 2.1 mg/dL over the first 48 hours of hospitalization. Short runs of nonsustained ventricular tachycardia are noted on telemetry.

Which of the following would be most appropriate in the management of this patient?

A. Addition of dopamine 2 mcg/kg/min by continuous IV infusion
B. Addition of milrinone 0.25 mcg/kg/min by continuous IV infusion
C. Addition of sodium nitroprusside 20 mcg/min by continuous IV infusion
D. Insertion of a pulmonary artery catheter for assessment of central hemodynamics
E. Initiation of bedside ultrafiltration

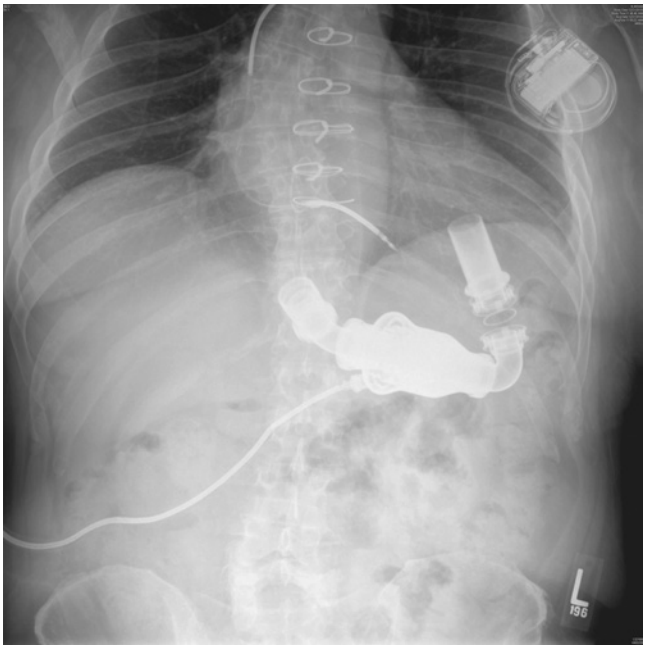

FIG. 2.3

QUESTION 194

Fig. 2.4 displays posteroanterior and lateral chest radiographs of a patient with an idiopathic cardiomyopathy, symptomatic heart failure, left ventricular ejection fraction <0.35, and left bundle branch block on the ECG. Which of the following statements about the pictured device is NOT correct?

A. Implantation of this device reduces left ventricular dimensions and mitral regurgitation
B. Placement of this type of device is associated with improved survival
C. A complication of device implantation is phrenic nerve stimulation with diaphragmatic pacing
D. Minimization of this form of ventricular pacing is important to prevent progressive heart failure
E. QRS duration on the surface ECG is an important predictor of clinical benefit

QUESTION 195

Which of the following conditions is NOT associated with the development of pulmonary edema?

A. Increased pulmonary venous pressure
B. High altitude
C. Increased plasma oncotic pressure
D. Eclampsia
E. Heroin overdose

QUESTION 196

True statements about cardiac physical findings in patients with heart failure include all of the following EXCEPT

A. Cardiomegaly is usually absent in primary restrictive cardiomyopathy
B. Elevated jugular venous pressure and an S_4 gallop in patients with heart failure are each associated with a poor prognosis
C. Pulsus alternans results from variation of the stroke volume, likely owing to incomplete recovery of contracting myocardial cells

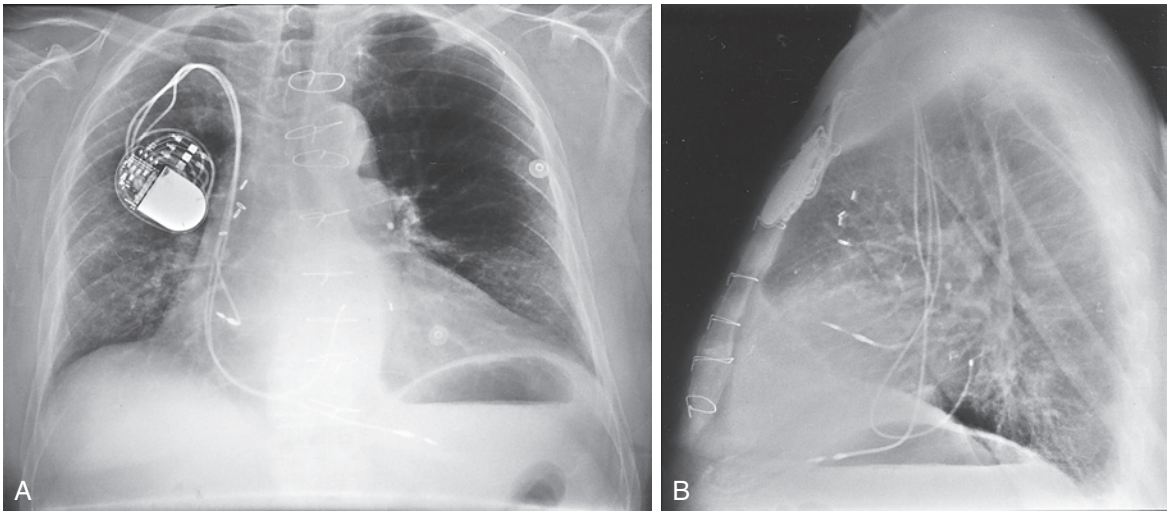

FIG. 2.4

D. Low-grade fever may occur in advanced heart failure in the absence of underlying infection
E. Sleep-disordered breathing is common in patients with heart failure

QUESTION 197

Which of these statements regarding the relationship between perfusion pressure and airway pressure in the upright lung is NOT correct?
A. Pulmonary artery pressure is greater than alveolar pressure at the lung apices
B. Pulmonary venous pressure exceeds alveolar pressure at the lung bases
C. Measurement of pulmonary capillary wedge pressure is most meaningful in lung zones in which pulmonary venous and arterial pressures exceed alveolar pressure
D. Pulmonary vascular redistribution on the chest radiograph occurs when there is a relative reduction in perfusion of the bases with a relative increase in apical perfusion

QUESTION 198

Which of the following is NOT likely to be a complication of cyclosporine therapy in the cardiac transplant recipient?
A. Gingival hyperplasia
B. Myelosuppression
C. Hypertension
D. Tremor
E. Hirsutism

QUESTION 199

Which of the following statements about acute heart failure is NOT correct?
A. Most patients with acute heart failure present with normal or elevated blood pressure
B. Milrinone does not improve in-hospital mortality
C. Serum vasopressin levels are elevated in acute heart failure and contribute to hyponatremia, a marker of poor prognosis
D. Tolvaptan, a vasopressin receptor antagonist, reduces the risk of death and heart failure re-hospitalization
E. Noninvasive ventilation in patients with acute pulmonary edema does not reduce short-term mortality compared with oxygen alone

QUESTION 200

Which of the following statements about patients with symptomatic heart failure is NOT correct?
A. Plasma norepinephrine level is usually elevated
B. Serum B-type natriuretic peptide is elevated
C. Cardiac beta-adrenergic receptor density is increased
D. Serum aldosterone level is elevated
E. The circulating level of tumor necrosis factor-alpha is increased

QUESTION 201

Which of the following statements regarding post-cardiac transplantation complications is NOT true?
A. Infectious complications are responsible for approximately 20% of deaths during the year after transplantation
B. Allograft coronary artery disease is the most significant factor limiting long-term survival
C. The propensity for allograft rejection decreases with time
D. Cytomegalovirus infection is associated with development of post-transplantation lymphoproliferative disorder
E. Transplant recipients have an increased incidence of cancer compared with age-matched controls

QUESTION 202

Which of the following statements regarding intra-aortic balloon (IAB) counterpulsation is NOT correct?
A. The tip of the IAB should be positioned just distal to the left subclavian artery
B. The IAB should be timed to deflate during the isovolumetric phase of left ventricular contraction
C. Inflation of the IAB should be timed with aortic valve closure on the arterial pressure waveform
D. Aortic valve stenosis is a strict contraindication to the use of an IAB
E. In the SHOCK II trial, IAB therapy did not reduce 30-day mortality in comparison to medical therapy among patients with acute myocardial infarction complicated by cardiogenic shock for whom early revascularization was planned

QUESTION 203

Which of the following statements regarding therapy for patients with heart failure is NOT correct?
A. Angiotensin receptor blocking drugs are less effective than angiotensin-converting enzyme (ACE) inhibitors in the reduction of mortality in patients with heart failure
B. ACE inhibitors are indicated in patients with heart failure and left ventricular dysfunction, irrespective of the functional New York Heart Association classification
C. Digoxin has been shown to decrease heart failure hospitalizations
D. Spironolactone has been shown to decrease mortality in patients with class III to IV symptoms
E. Regular physical exercise does not reduce mortality in patients with chronic heart failure

QUESTION 204

Which of the following statements about the use of adenosine in the management of cardiac arrhythmias is NOT correct?
A. Adenosine administration aids in the diagnosis of wide QRS complex tachycardias
B. Slow, peripheral intravenous administration of 6 to 12 mg of adenosine terminates supraventricular tachycardias involving the atrioventricular node
C. Patients with heart transplants demonstrate an exaggerated response to adenosine
D. Adenosine may be ineffective in patients who have recently consumed caffeine
E. Flushing, dyspnea, and chest pressure are common side effects of adenosine

QUESTION 205

Which of the following statements regarding dysrhythmias is NOT correct?
A. The prevalence of premature ventricular complexes increases with age

B. In the absence of structural heart disease, detection of premature ventricular complexes has no impact on survival
C. Class IC antiarrhythmic agents are the drugs of choice for suppression of premature ventricular complexes after myocardial infarction
D. Most concealed accessory pathways are located between the left ventricle and the left atrium
E. A concealed accessory pathway should be suspected in narrow-complex tachycardias when the retrograde P wave occurs after completion of the QRS complex

QUESTION 206

A 56-year-old man with a history of hypercholesterolemia and smoking is referred to the cardiology clinic for preoperative risk assessment before an orthopedic procedure. He denies any cardiovascular symptoms and exercises regularly. His ECG is shown in Fig. 2.5. Which of the following statements is NOT correct?

A. This syndrome is thought to account for 40% to 60% of all cases of idiopathic ventricular fibrillation
B. Genetic mutations in the sodium channel have been identified in some families with this syndrome
C. An implantable cardioverter-defibrillator is appropriate therapy for some patients with this syndrome to prevent sudden death
D. Antiarrhythmic therapy with procainamide reliably prevents ventricular arrhythmias in this syndrome
E. Screening of family members for this condition is recommended

QUESTION 207

True statements regarding the prevention of sudden cardiac death (SCD) include all of the following EXCEPT

A. The therapy of choice for survivors of SCD is implantation of a cardioverter-defibrillator
B. Defibrillators reduce the risk of sudden death from arrhythmia in patients with nonischemic cardiomyopathy and left ventricular ejection fraction (LVEF) ≤35%
C. For survivors of out-of-hospital cardiac arrest not associated with a myocardial infarction, the risk of recurrent cardiac arrest at 1 year is about 30%
D. Prophylactic defibrillator implantation is appropriate for prevention of sudden death in patients with left ventricular dysfunction (LVEF ≤ 30%) and prior myocardial infarction
E. Amiodarone is the most appropriate long-term prophylactic strategy for patients with hypertrophic cardiomyopathy and a prior history of syncope

QUESTION 208

Which of the following statements regarding atrioventricular (AV) block is NOT correct?

A. In first-degree AV block, the intensity of the first heart sound is increased
B. The conduction abnormality in Mobitz type I second-degree heart block with normal QRS complex duration is almost always at the level of the AV node, proximal to the His bundle
C. In typical Mobitz type I second-degree heart block, the RR interval progressively shortens over consecutive beats until a beat is dropped
D. In Mobitz type II second-degree heart block, the PR intervals are constant prior to the nonconducted P wave
E. The ventricular escape rate in acquired complete heart block is usually <40 beats/min

QUESTION 209

Which of the following statements about the use of ambulatory electrocardiographic monitoring for the detection of cardiac arrhythmias is NOT correct?

A. A long-term loop recorder is frequently useful for diagnosis in patients with frequent symptoms and an unrevealing Holter recording
B. Type I second-degree atrioventricular block is commonly present in normal subjects

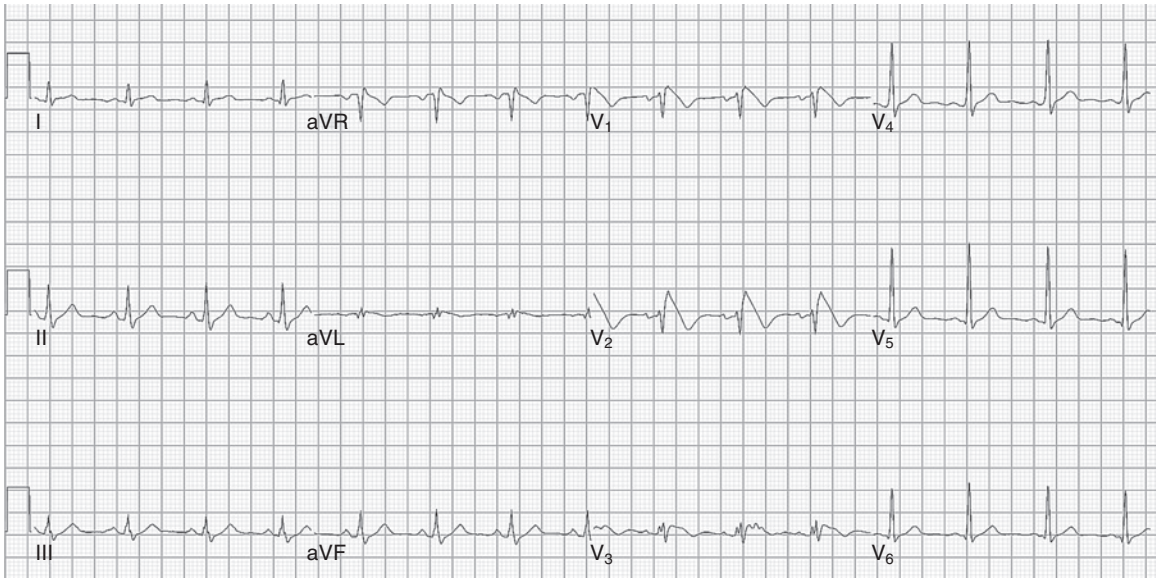

FIG. 2.5

C. Sinus bradycardia with rates as low as 35 beats/min and sinoatrial exit block may be found in persons without cardiac disease
D. Long-term monitoring of patients with a history of atrial fibrillation (AF) indicates that symptomatic AF episodes occur more commonly than asymptomatic episodes
E. The frequency of ventricular premature beats after myocardial infarction increases over the first several weeks

QUESTION 210

Which of the following statements regarding syncope is NOT correct?
A. Cardiac causes account for 10% to 20% of syncopal episodes
B. Syncope of cardiac origin is associated with a 30% 1-year mortality
C. The most common causes of syncope are vascular in origin, including reflex-mediated syncope and orthostatic hypotension
D. Supraventricular tachycardia has been identified as a common cause of syncope
E. The cause of syncope can be identified in a large percentage of patients based on history and physical examination alone

QUESTION 211

Which of the following statements about permanent pacemakers is NOT correct?
A. AAIR pacing is appropriate for patients with sinus node dysfunction and intact atrioventricular (AV) conduction
B. Symptomatic Wenckebach AV block is an indication for permanent pacing
C. Pacemaker syndrome can be manifest in any pacing mode in which there is AV dissociation
D. Medically refractory hypertrophic cardiomyopathy is a class I indication for the placement of a permanent dual-chamber pacemaker
E. A pacemaker mode-switching option is beneficial for patients with paroxysmal supraventricular rhythm disturbances

QUESTION 212

Which of the following statements regarding pacemaker-mediated tachycardia (PMT) is NOT correct?
A. A dual-chamber system must be present to cause PMT
B. Intact atrial sensing is required for PMT
C. Premature ventricular contractions frequently initiate PMT
D. Shortening the postventricular atrial refractory period will prevent PMT
E. Retrograde P waves are typically present

QUESTION 213

A 76-year-old man with diabetes mellitus and exertional angina is found to have three-vessel coronary artery disease and a left ventricular ejection fraction of 40%. He undergoes successful coronary artery bypass grafting surgery. A rhythm strip obtained on the second postoperative day is shown in Fig. 2.6. Preoperative administration of each of the following therapies has been shown to prevent this dysrhythmia after cardiac surgery EXCEPT
A. Amiodarone
B. Atorvastatin
C. Sotalol
D. Digoxin
E. Metoprolol

QUESTION 214

Which of the following statements about procainamide is NOT correct?
A. At therapeutic concentrations, procainamide prolongs the QRS complex duration on the surface ECG
B. Procainamide may accelerate the ventricular rate in patients with atrial flutter
C. Procainamide suppresses conduction in the accessory pathway of patients with Wolff-Parkinson-White syndrome
D. A positive antinuclear antibody in procainamide-treated patients signals a drug-induced lupus syndrome
E. Rapid intravenous administration of procainamide may precipitate hypotension

QUESTION 215

Each of the following statements about invasive cardiac electrophysiologic study is true EXCEPT
A. Of the common arrhythmic causes of syncope, tachyarrhythmias are most reliably initiated in the electrophysiology laboratory, followed by sinus node abnormalities and His-Purkinje block
B. Supraventricular tachycardias are characterized by a His-ventricular interval that is shorter than that recorded during normal sinus rhythm

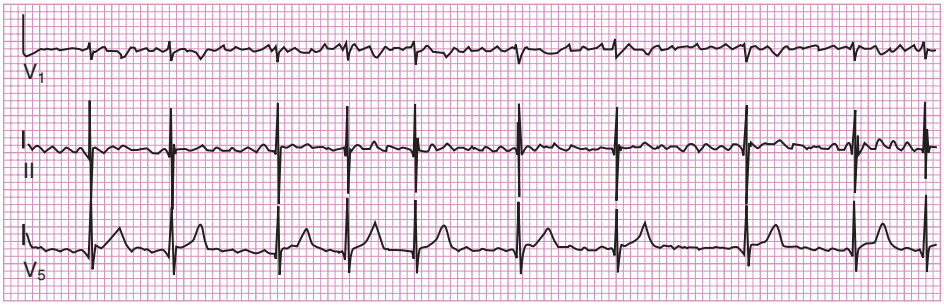

FIG. 2.6

C. Patients with sinus node dysfunction often have atrioventricular nodal conduction abnormalities
D. Sinus node recovery time is defined as the difference between the spontaneous sinus node cycle length prior to pacing and the duration to the first spontaneous sinus response after termination of pacing
E. Accessory pathways are most commonly left lateral in location

QUESTION 216

Which of the following statements regarding the antiarrhythmic drug dronedarone is NOT correct?
A. Its electrophysiologic properties are similar to amiodarone
B. It is safe for use in patients with heart failure symptoms
C. The prevalence of thyroid toxicity is low
D. QT prolongation is typical during use, but only rarely results in proarrhythmia
E. Mortality is increased when it is prescribed to patients with permanent atrial fibrillation

QUESTION 217

A 34-year-old teacher is referred for consultation because of intermittent palpitations and is found to have paroxysmal atrial fibrillation (AF) on ambulatory electrocardiography. His pertinent co-morbid conditions include mild obesity, controlled hypertension, and untreated obstructive sleep apnea. Ethanol and caffeine consumptions are minimal. Echocardiography demonstrates normal left ventricular size and contractile function and mild left atrial enlargement. Exercise treadmill testing reveals no evidence of ischemia. Despite initiation of metoprolol and flecainide, symptomatic paroxysmal AF continues and the patient is referred for catheter ablation. Which of the following statements about ablation for AF is correct?
A. A trial of suppressive antiarrhythmic drug therapy is mandatory before proceeding to AF ablation
B. The efficacy of catheter ablation for paroxysmal AF is higher than for persistent AF
C. A successful procedure requires focal ablation of premature atrial beats originating deep within the pulmonary veins
D. Radiofrequency ablation in the posterior left atrium is associated with a risk of atrial-tracheal fistula
E. Catheter ablation eliminates the need for chronic anticoagulation in subsequently asymptomatic individuals

QUESTION 218

A 76-year-old woman is evaluated by her cardiologist because of recently recognized paroxysmal atrial fibrillation. She has a history of hypertension, diabetes, obesity (current weight is 80 kg), and chronic kidney disease with a serum creatinine of 1.3 mg/dL. She does not have a contraindication to antithrombotic therapy. Which of the following would be the most appropriate antithrombotic regimen for this patient?
A. Aspirin 325 mg daily
B. Aspirin 162 mg plus clopidogrel 75 mg daily
C. Warfarin, dose adjusted to achieve international normalized ratio 2.5 to 3.5
D. Apixaban 5 mg twice daily
E. Apixaban 2.5 mg twice daily

QUESTION 219

Which of the following statements concerning atrial fibrillation (AF) is correct?
A. AF develops in 10% to 20% of patients after cardiac surgery
B. Patients who have been in AF for less than 72 hours can be safely cardioverted without the need for prolonged anticoagulation
C. Restoration of sinus rhythm results in superior clinical outcomes compared with chronic rate control and anticoagulation in patients with asymptomatic AF
D. A chronically rapid ventricular response rate in AF results in impaired left ventricular systolic function
E. The incidence of AF declines after age 60

QUESTION 220

Which of the following statements regarding the cardiac conduction system is NOT correct?
A. The sinus node is innervated with postganglionic adrenergic and cholinergic nerve terminals
B. In 60% of people, the arterial supply to the atrioventricular node is derived from a branch of the left circumflex artery
C. The conduction system in the upper muscular interventricular septum receives its blood supply from branches of the anterior and posterior descending arteries
D. Inhibition of the delayed rectifier K^+ current (I_{kr}) has been implicated in the acquired form of the long QT syndrome
E. The resting transmembrane potential of the cardiac myocyte is close to the equilibrium potential of potassium

QUESTION 221

Which of the following statements regarding amiodarone for the treatment of cardiac arrhythmias is correct?
A. The mean terminal half-life of amiodarone is 6 months
B. Among patients with systolic heart failure, amiodarone is of comparable efficacy as implantable cardioverter-defibrillator therapy in the prevention of sudden cardiac death
C. Corneal deposits develop in <10% of patients who are treated with amiodarone for more than 6 months
D. Hyperparathyroidism is a known complication of long-term amiodarone therapy
E. Amiodarone-induced pulmonary toxicity may develop within the first week of therapy

QUESTION 222

Which of the following statements regarding the mechanisms of cardiac arrhythmias is correct?
A. In the common form of atrioventricular (AV) nodal reentrant tachycardia, anterograde conduction occurs down the "fast" pathway
B. In orthodromic AV reentrant tachycardia, the activation wave travels via the accessory pathway to the ventricles, then retrograde via the AV node to the atria
C. In most patients with Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than the normal AV node but takes longer to recover excitability
D. Abnormal automaticity is the most common mechanism of atrial flutter
E. All forms of ventricular tachycardia arise from abnormal automaticity

QUESTION 223

A 14-year-old boy suffers two episodes of sudden syncope during gym class while jogging and is referred for further evaluation. His paternal uncle had died suddenly during physical exercise at age 20. Laboratory evaluation includes an ECG that shows normal sinus rhythm with a normal QTc interval. Cardiac magnetic resonance imaging reveals a structurally normal heart. Computed tomography angiography demonstrates normal coronary anatomy. He undergoes treadmill exercise testing, and the rhythm displayed in Fig. 2.7 is noted after 3 minutes of exercise. What is the first-line treatment for this condition?

A. Magnesium
B. Dual-chamber pacemaker
C. Beta blocker and an implantable cardioverter-defibrillator
D. Exercise training with adequate hydration
E. Cardiac sympathectomy

QUESTION 224

A 72-year-old man with nonischemic dilated cardiomyopathy, left ventricular ejection fraction 38%, New York Heart Association class III symptoms, and chronic kidney disease (creatinine = 2.8 mg/dL) presents with symptomatic paroxysmal atrial fibrillation. Electrocardiography (ECG) when in sinus rhythm shows a corrected QT interval of 442 milliseconds. Which of the following is the most appropriate initial oral antiarrhythmic regimen to maintain sinus rhythm in this patient?

A. Outpatient initiation of dofetilide 250 mcg twice daily
B. Outpatient initiation of sotalol 120 mg twice daily
C. Inpatient initiation of disopyramide extended release 200 mg every 12 hours
D. Inpatient initiation of dronedarone 400 mg twice daily with close ECG monitoring
E. Outpatient oral amiodarone 200 mg three times daily for 2 weeks followed by 200 mg daily

QUESTION 225

A sample tracing from an electrophysiologic study in a patient with a narrow-complex tachycardia is displayed in Fig. 2.8. What is the diagnosis?

A. Sinus tachycardia
B. Atrial flutter
C. Typical (slow-fast) atrioventricular (AV) nodal reentrant tachycardia
D. Orthodromic AV reentrant tachycardia using an accessory pathway
E. Atrial tachycardia

QUESTION 226

A 75-year-old woman presents following an episode of syncope. She was watching television with her husband when she suddenly lost consciousness and was unresponsive for approximately 20 seconds. She awoke slightly confused, but otherwise felt well. Her past medical history is unremarkable. The baseline ECG demonstrates right bundle branch block and left anterior fascicular block. An electrophysiologic study was performed, and a panel from that procedure is shown in Fig. 2.9. Which of the following is the most appropriate recommendation?

A. Catheter ablation for atrioventricular nodal reentrant tachycardia
B. Beta blocker therapy
C. Neurologic consultation
D. Permanent pacemaker implantation
E. Coronary angiography with anticipated percutaneous revascularization

QUESTION 227

All of the following statements about distinguishing ventricular tachycardia (VT) from a supraventricular tachycardia (SVT) with aberrant conduction in a patient with a wide-complex rapid rhythm are true EXCEPT

A. The presence of fusion beats supports the diagnosis of VT
B. Termination of the tachycardia by vagal maneuvers is consistent with an SVT
C. The presence of atrioventricular dissociation implies VT
D. Concordance of the QRS complexes in the precordial leads is more suggestive of SVT than VT
E. A past history of myocardial infarction makes the diagnosis of VT significantly more likely

QUESTION 228

A 53-year-old man with symptomatic atrial fibrillation (AF) presents for elective outpatient cardioversion. For the past 3 months he has been taking appropriately dosed rivaroxaban as an anticoagulant, and diltiazem for rate control. Which of the following statements about external electrical cardioversion is correct?

A. Administration of intravenous ibutilide before electrical cardioversion facilitates successful conversion of AF to normal sinus rhythm
B. Electrical cardioversion is most effective at terminating tachycardias that arise from enhanced automaticity
C. Repeated shocks at the same energy level increase chest wall impedance
D. Rivaroxaban can be safely discontinued 7 days after successful cardioversion if sinus rhythm is achieved

QUESTION 229

Each of the following predisposes to the arrhythmia shown in Fig. 2.10 EXCEPT

A. Congenital severe bradycardia
B. Hypokalemia
C. Loss of function mutation in the *SCN5A* gene
D. Tricyclic antidepressant overdose
E. Disopyramide

QUESTION 230

A 60-year-old man presents with presyncope and is found to have a wide-complex tachycardia at 140 beats/min. An electrophysiologic study is performed and tachycardia is induced, as shown in Fig. 2.11. The mechanism of this tachycardia is

A. Atrioventricular reciprocating tachycardia utilizing an accessory pathway
B. Atrioventricular nodal reentrant tachycardia with aberrant ventricular conduction
C. Ventricular tachycardia
D. Atrial flutter with aberrant ventricular conduction
E. Sinus tachycardia

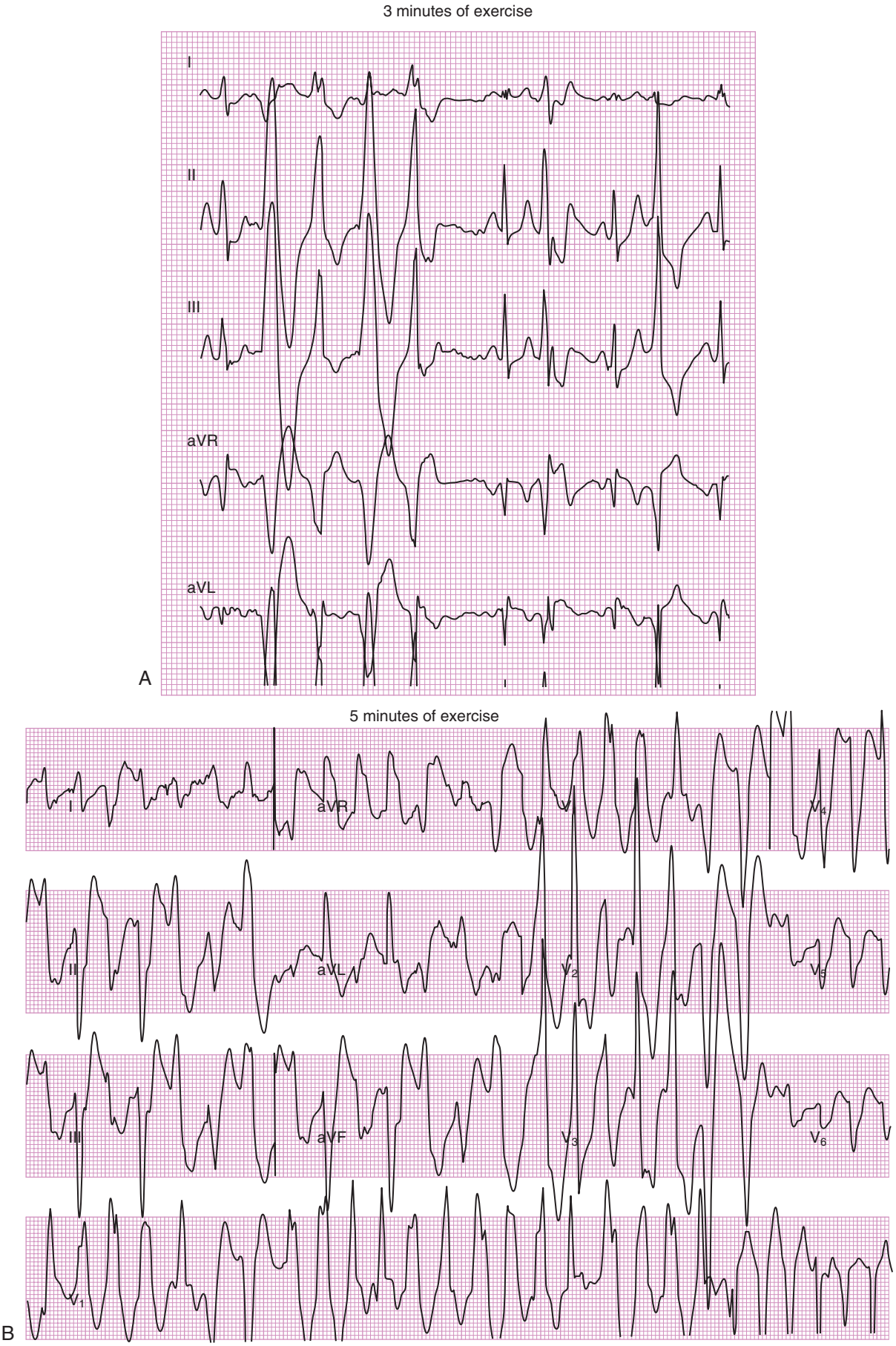
3 minutes of exercise
I
II
III
aVR
aVL
A
5 minutes of exercise
I
aVR
V1
II
aVL
V2
V5
III
aVF
V3
V6
V1
B

FIG. 2.7

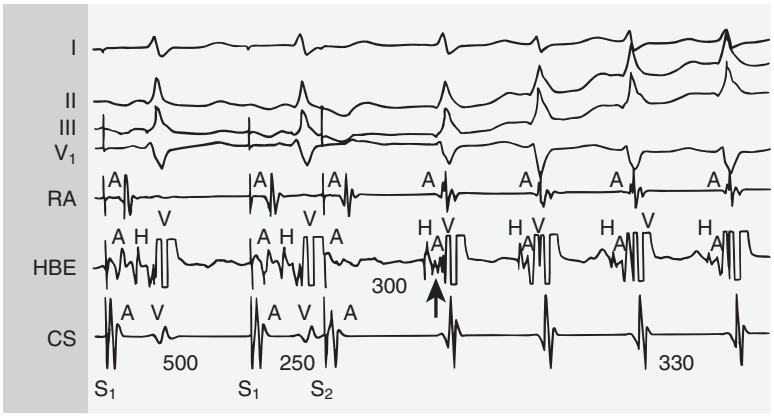

FIG. 2.8

FIG. 2.9

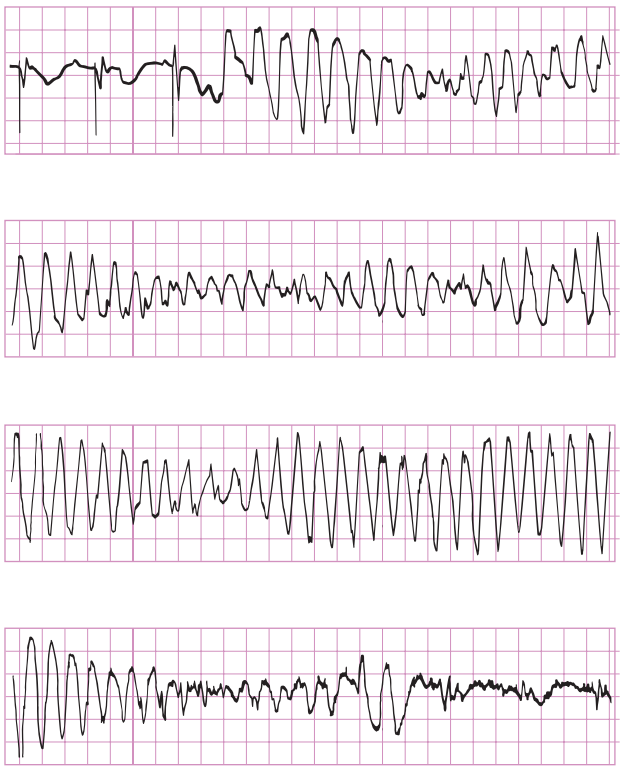

FIG. 2.10

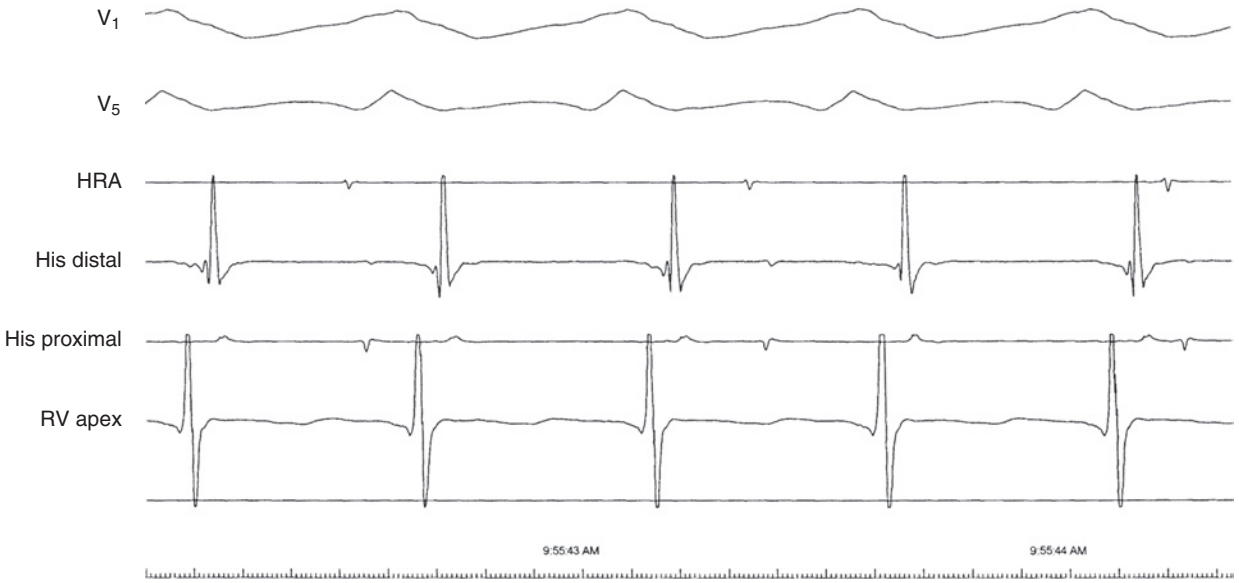

FIG. 2.11

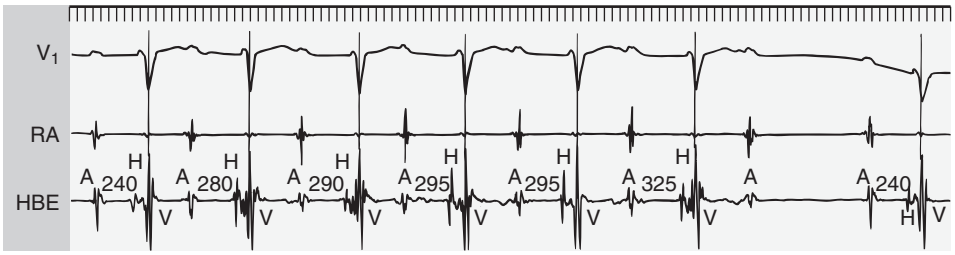

FIG. 2.12

QUESTION 231

Which of the following statements is correct regarding the electrophysiologic abnormality depicted in Fig. 2.12?

A. It is associated with syncope and sudden death
B. When present with an inferior myocardial infarction, it is an indication for temporary pacing
C. It typically reflects block at the level of the atrioventricular node, proximal to the His bundle
D. Carotid sinus massage typically abolishes this abnormality

QUESTION 232

For which of the following patients is permanent cardiac pacing NOT reasonable therapy?

A. A 35-year-old man with asymptomatic type II second-degree atrioventricular (AV) block and sinus bradycardia at 38 beats/min
B. A 70-year-old man with left ventricular hypertrophy, persistent fatigue, and lightheadedness, with marked first-degree AV block (PR interval = 0.36 second)
C. A 57-year-old man with acquired asymptomatic third-degree AV block
D. A 40-year-old woman with asymptomatic congenital complete AV block
E. A 56-year-old marathon runner with calf cramps and 3.4-second pauses during sleep

QUESTION 233

A 62-year-old man underwent pacemaker insertion 4 years ago because of marked bradycardia. As part of his exercise program, he has been using a rowing machine. Recently, he has had several episodes of near-syncope that have occurred only during such exercise. An ambulatory ECG (Holter monitor) demonstrated the rhythm strip shown in Fig. 2.13 during one near-syncopal episode while rowing. Which of the following is correct?

A. There is evidence of a single-chamber pacing system
B. There is inappropriate inhibition of ventricular pacing
C. There is undersensing of atrial activity
D. There is lack of capture of the ventricles
E. There is lack of capture of the atria

QUESTION 234

The ECG in Fig. 2.14 is compatible with all of the following diagnoses EXCEPT

A. Lead insulation breach
B. Hyperkalemia
C. Lead dislodgment
D. Loose set screw
E. Impending battery depletion

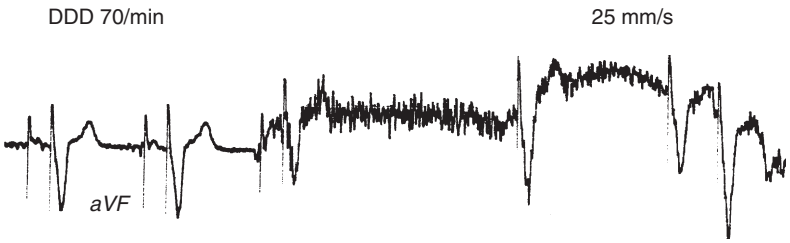

FIG. 2.13

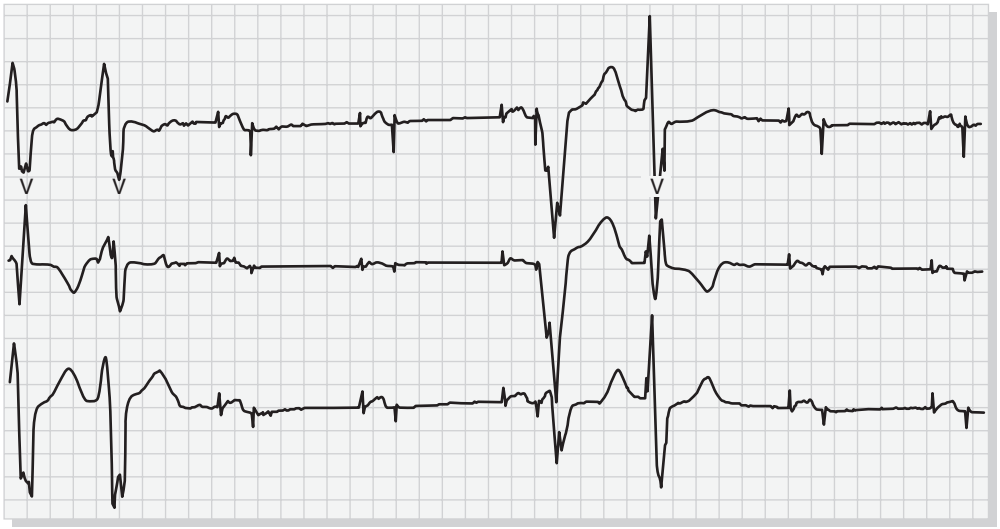

FIG. 2.14

QUESTION 235

Which of the following statements regarding sinus node function is correct?

A. Atropine enhances cardioinhibitory input to the sinus node
B. Sinus arrest is defined as a pause that is an exact multiple of the PP interval of the underlying rhythm
C. Vasodepressor carotid sinus hypersensitivity is defined as asystole exceeding 2 seconds during carotid sinus massage
D. In the respiratory form of sinus arrhythmia, the PP interval cyclically shortens during inspiration

QUESTION 236

Which of the following statements regarding arrhythmogenic right ventricular cardiomyopathy (ARVC) is correct?

A. Ventricular tachycardia (VT) in patients with ARVC typically has a right bundle branch block morphology
B. ARVC is more common in women
C. Fatty or fibrofatty infiltration of the right ventricle is the pathologic hallmark
D. Pathologic changes do not occur in the left ventricle
E. Radiofrequency ablation is successful at preventing VT

QUESTION 237

A 62-year-old man with ischemic cardiomyopathy underwent routine generator change of his implanted cardioverter-defibrillator 2 weeks ago. He now presents with mildly tender erythema and scant purulent drainage at the defibrillator pocket. He is afebrile, otherwise feels well, and blood cultures grow no organisms. The defibrillator leads were implanted 11 years prior. Which of the following would be the best approach to management?

A. The generator should be explanted. A new generator should be implanted, using the old leads, after a period of antibiotic therapy
B. The generator should be explanted. After a period of antibiotic therapy, a new system should be implanted on the contralateral side, leaving the abandoned leads in place
C. The entire generator and lead system should be removed, and a new system implanted on the contralateral side after a period of antibiotic therapy
D. Since the infection appears localized, a course of intravenous antibiotic therapy alone should be attempted; if evidence of infection recurs after antibiotics, then device extraction should be considered
E. Needle aspiration of the pocket should be performed to isolate the organism responsible for the apparent infection prior to treatment decisions

QUESTION 238

An 80-year-old man with permanent rate-controlled atrial fibrillation, hypertension, diabetes, chronic kidney disease (serum creatinine 2.5 mg/dL), and spinal stenosis has sustained three mechanical falls over the past year, without serious injury. He has a history of occasional lower gastrointestinal bleeding without a source of blood loss identified

by upper, lower, and capsule endoscopy. Of the following, which is the most appropriate method for stroke prevention in this patient?
A. Aspirin 325 mg daily
B. Enoxaparin 80 mg twice daily
C. Apixaban 5 mg twice daily
D. Ablation of the atrioventricular node
E. Implantation of a left atrial appendage closure device

QUESTION 239

A 30-year-old woman presents because of recurrent episodes of paroxysmal tachycardia with dyspnea and presyncope. A maternal uncle died suddenly at age 27. An electrophysiologic study is performed. The intracardiac electrograms at baseline (*A*) and during tachycardia (*B*) are shown in Fig. 2.15. Of the following choices, the most appropriate therapy is
A. Ablation of the atrioventricular nodal slow pathway
B. Ablation of an accessory pathway
C. Implantation of an automatic cardioverter-defibrillator
D. Direct-current cardioversion followed by long-term anticoagulation with warfarin
E. No further therapy is required

QUESTION 240

Which of the following statements about congenital long QT syndromes (LQTS) is TRUE?
A. Most forms of LQTS result from mutations in genes that code for proteins in cardiac calcium channels

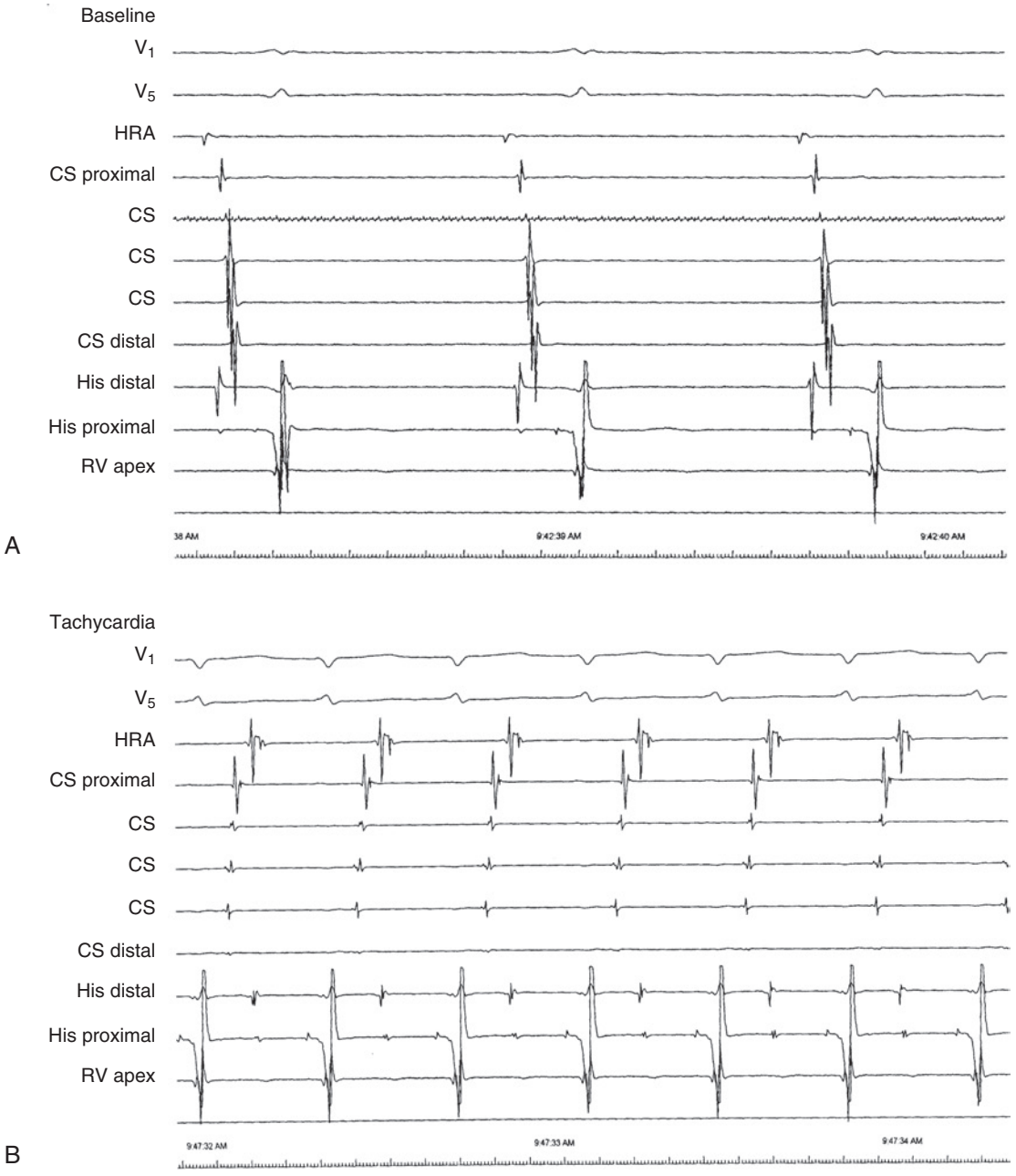

FIG. 2.15

B. LQT1 patients experience a high frequency of cardiac events during swimming
C. Sudden loud acoustic events are a common trigger of syncope in LQT3 patients
D. Cardiac events during sleep are common in patients with LQT2

QUESTION 241

All of the following statements regarding sudden cardiac death (SCD) are true EXCEPT
A. There are over 350,000 SCDs annually in the United States
B. The peak incidence of SCD among adults is between the ages of 45 and 75 years
C. Hereditary causes of SCD include hypertrophic cardiomyopathy, long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and the Brugada syndrome
D. SCD is more common in women than in men
E. An intraventricular conduction abnormality on the ECG is a stronger predictor of SCD than findings of left ventricular hypertrophy

QUESTION 242

All of the following are likely in a patient with the ECG shown in Fig. 2.16 EXCEPT
A. A gradual increase in atrial rate with the administration of digoxin
B. An irregular atrial rate
C. Precipitation of the arrhythmia by hypokalemia
D. Absence of underlying cardiac disease
E. Frequent ventricular premature beats

QUESTION 243

Which of the following statements regarding sudden cardiac death (SCD) in patients with coronary artery disease is correct?
A. SCD accounts for 10% of all coronary artery disease-related deaths
B. Compared with Caucasians, African Americans have a higher age-adjusted incidence of SCD
C. The most common mechanism of cardiac arrest is asystole
D. The outcome of patients with bradycardic/asystolic out-of-hospital cardiac arrest is better than if ventricular tachycardia is the initial arrhythmia
E. Successfully resuscitated ventricular fibrillation during the first 48 hours of an acute MI identifies individuals at increased risk of future SCD and warrants implantable cardioverter-defibrillator therapy

QUESTION 244

A 62-year-old woman with permanent atrial fibrillation takes dabigatran 150 mg twice daily for stroke prevention. Thirty minutes ago she sustained trauma in a motor vehicle collision on her way to work, was stabilized at the scene, then rapidly transported to the nearby emergency department. Upon arrival, she is unresponsive, intubated, and hypotensive. Computed tomography imaging demonstrates a small intracranial subdural hematoma and a retroperitoneal hemorrhage that requires urgent exploratory laparotomy. Which of the following is the most appropriate method to reverse anticoagulation in this patient with life-threatening bleeding in need of emergency surgery?
A. Vitamin K 10 mg intravenously
B. Oral activated charcoal
C. Idarucizumab 5 g intravenously
D. 4-factor prothrombin complex concentrate 25 U/kg intravenously
E. Hemodialysis

QUESTION 245

Which of the following patients is the most appropriate candidate for placement of an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death?
A. 45-year-old man 1 week after acute anterior myocardial infarction with left ventricular ejection fraction (LVEF) 35% and New York Heart Association (NYHA) class III symptoms
B. 66-year-old woman with a history of nonischemic dilated cardiomyopathy and LVEF 30% despite medical therapy with an angiotensin-converting enzyme-inhibitor and beta blocker for the past 6 months
C. 22-year-old man who presents with chest pain and reduced LVEF of 50% who has a normal surface ECG but evidence of myocarditis on cardiac MR imaging
D. 78-year-old man with history of ischemic cardiomyopathy, LVEF 30%, end-stage renal disease on dialysis, and recently diagnosed metastatic non-small cell lung cancer
E. 52-year-old man with history of alcoholism with newly recognized LVEF of 20% and NYHA class II symptoms

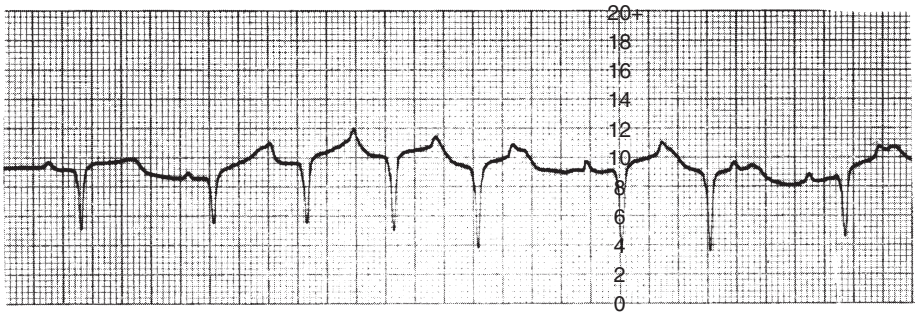

FIG. 2.16

QUESTION 246

Which of the following statements regarding cardiac pacing modes is correct?

A. Ventricular inhibited pacing (VVI) restores and maintains atrioventricular (AV) synchrony
B. VVI pacing provides rate responsiveness in the chronotropically incompetent patient
C. Single-chamber triggered pacing (AAT or VVT) increases the drain on the pacemaker battery
D. Atrial inhibited pacing is an appropriate mode of pacing for patients with AV nodal dysfunction
E. Dual-chamber pacing and sensing with inhibition and tracking (DDD) is the preferred mode of pacing for patients in atrial fibrillation

QUESTION 247

Which of the following statements regarding cardiac pacemakers is NOT correct?

A. Hyperkalemia results in pacing and sensing threshold abnormalities
B. Lead dislodgement or inadequate initial lead placement should be suspected if true undersensing is present
C. Cellular telephones do not cause clinically important pacemaker interference during normal use
D. Right bundle branch block is the expected electrocardiographic pattern during right ventricular pacing
E. Pseudofusion on the surface ECG is identified by an appropriately timed pacing stimulus that does not alter the morphology of a superimposed intrinsic QRS

QUESTION 248

The finding on the chest radiograph shown in Fig. 2.17 would be associated with which of the following measurements on device interrogation?

A. High-voltage threshold, high lead impedance
B. Low-voltage threshold, high lead impedance
C. High-voltage threshold, low lead impedance
D. Low-voltage threshold, low lead impedance
E. High-voltage threshold, normal lead impedance

QUESTION 249

The electrocardiographic abnormality displayed in Fig. 2.18 is associated with all of the following EXCEPT

A. An absence of underlying structural heart disease in most adults
B. Beneficial response to treatment with verapamil
C. An association with Ebstein anomaly
D. A higher prevalence in men
E. A right posteroseptal pathway

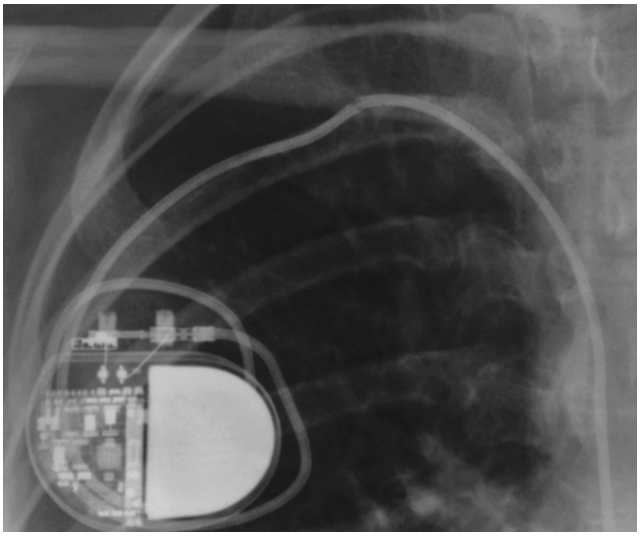

FIG. 2.17

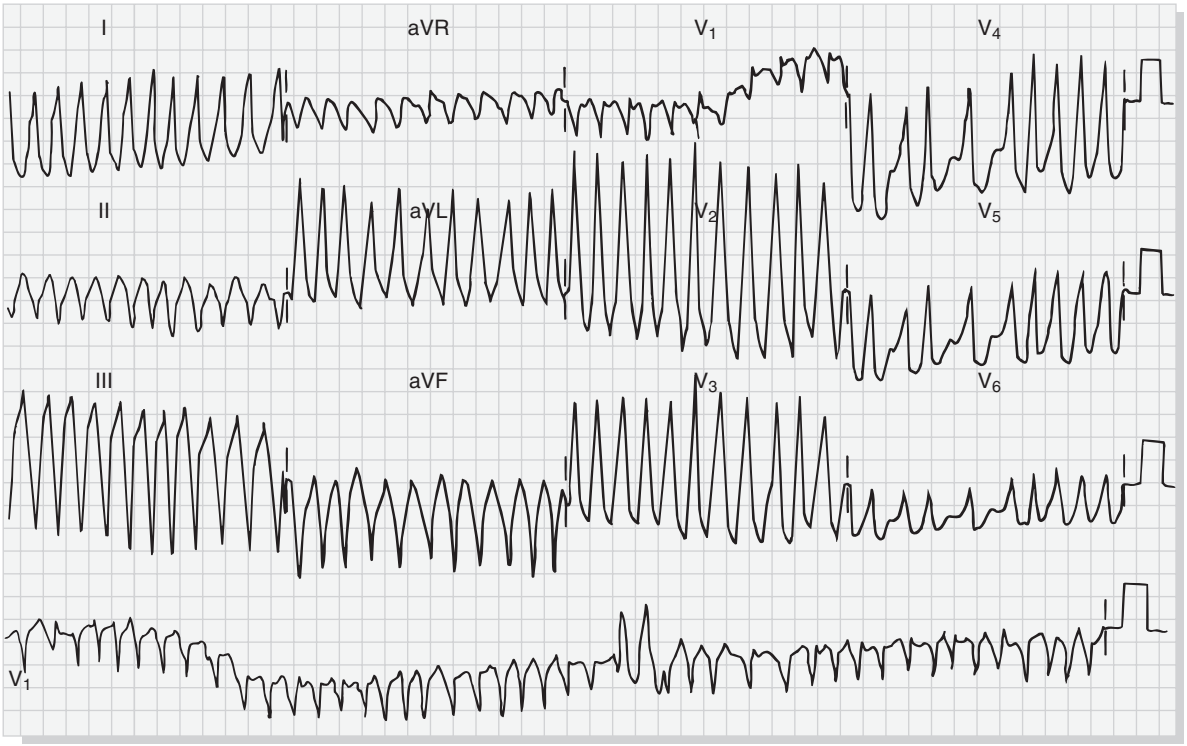

FIG. 2.18

FIG. 2.19

QUESTION 250

A 65-year-old diabetic man with a history of myocardial infarction presents to your office for evaluation. He is known to have a left ventricular ejection fraction of 30% with anterior wall hypokinesis. He is comfortable at rest, but reports dyspnea with simple household activities and cannot ascend a flight of stairs without stopping to catch his breath. He does not describe chest discomfort and there is no evidence of reversible ischemia by exercise scintigraphy. His current medical regimen includes carvedilol 25 mg twice daily; lisinopril 20 mg daily; furosemide 40 mg daily; and spironolactone 25 mg daily. His physical examination reveals blood pressure of 90/50 mm Hg, heart rate of 70 beats/min, normal jugular venous pressure, and clear lungs to auscultation. The apical cardiac impulse is laterally displaced toward the anterior axillary line. On auscultation there is a normal S_1, paradoxically split S_2, an apical S_3 gallop, and a grade 3/6 holosystolic murmur at the apex that radiates to the axilla. There is no peripheral edema. His ECG is shown in Fig. 2.19. Which of the following is the most appropriate approach to device therapy in this patient?

A. No device implantation is indicated
B. Implantation of a cardioverter-defibrillator is warranted
C. Implantation of a combined cardiac resynchronization-defibrillator system is appropriate
D. Refer the patient for echocardiography to assess dyssynchrony and, if present, implant a cardiac resynchronization-defibrillator
E. Implantation of a cardiac-resynchronization pacemaker without defibrillation capability is most appropriate

QUESTION 251

The electrophysiologic study tracing in Fig. 2.20 is obtained from a 28-year-old man with palpitations, recurrent syncope, and a structurally normal heart. Which of the following is the most appropriate therapy?

A. Atenolol
B. Verapamil

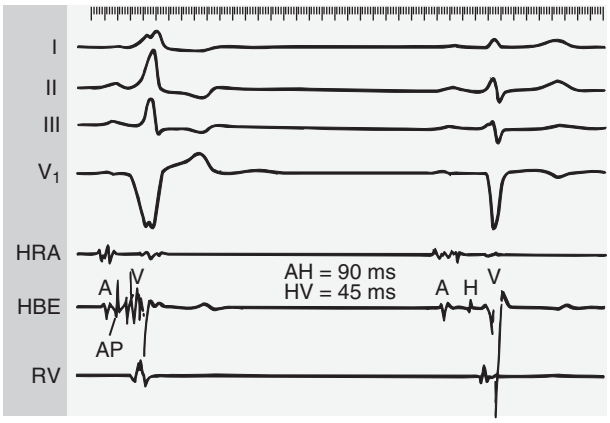

FIG. 2.20 *From Prystowsky EN, Browne KF, Zipes DP. Intracardiac recording by catheter electrode of accessory pathway depolarization.* J Am Coll Cardiol. *1983;1:468.*

C. Pacemaker implantation
D. Radiofrequency catheter ablation
E. Defibrillator implantation

QUESTION 252

Which of the following statements about the antiarrhythmic drug dofetilide is NOT correct?

A. It has significant renal excretion
B. It prolongs the QT interval in a dose-dependent fashion
C. It is unsafe in patients with prior myocardial infarction
D. Patients must be admitted to hospital for drug initiation
E. It should not be used in patients taking verapamil

QUESTION 253

A 26-year-old construction worker comes to the emergency department on the morning of January 2 in atrial fibrillation. He states that for the past few months he has had occasional episodes of palpitations, almost always on Mondays. His vital signs include heart rate of 140 beats/min, respirations of 16 breaths/min, and blood pressure of 160/95 mm Hg.

His physical examination is unremarkable. While being observed in the hospital, he spontaneously reverts to normal sinus rhythm. The most likely precipitating cause is
A. Caffeine
B. Cocaine
C. Alcohol
D. Hypertension
E. Mitral valve prolapse

QUESTIONS 254 TO 257

For each of the following descriptions, match the appropriate disorders:
A. Jervell and Lange-Nielsen syndrome
B. Romano-Ward syndrome
C. Right ventricular outflow tract ventricular tachycardia
D. Brugada syndrome

254. Autosomal recessive disorder associated with sensorineural deafness
255. ECG shows right bundle branch block morphology with ST-segment elevation in the anterior precordial leads
256. Autosomal dominant long QT syndrome with normal hearing
257. Left bundle branch block with an inferior axis

QUESTIONS 258 TO 261

Match the following antiarrhythmic drug actions with the appropriate Vaughan-Williams drug classification:
A. Predominantly block potassium channels and prolong repolarization
B. Predominantly block beta-adrenergic receptors
C. Predominantly block slow calcium channels ($I_{Ca.L}$)
D. Reduce the rate of rise of the action potential upstroke (V_{max}) and prolong the action potential duration
E. Block sodium channels, but shorten the action potential duration and do not reduce V_{max}

258. Class IA drugs
259. Class II drugs
260. Class III drugs
261. Class IV drugs

QUESTIONS 262 TO 265

Assume that you have decided to prescribe antiarrhythmic drug therapy to prevent recurrent episodes of atrial fibrillation for each of the patients described below. Match each patient with the most appropriate antiarrhythmic from the provided list:
A. Flecainide
B. Sotalol
C. Amiodarone
D. Mexiletine

262. A 64-year-old man with remote history of anterior myocardial infarction and left ventricular ejection fraction of 50%
263. A 74-year-old woman with long-standing hypertension and left ventricular hypertrophy (wall thickness = 1.6 cm)
264. A 58-year-old man with nonischemic cardiomyopathy and class III congestive heart failure
265. A 46-year-old otherwise healthy man with no structural heart disease

QUESTIONS 266 TO 269

For each of the following diuretic agents, match the appropriate adverse effect:
A. Ototoxicity
B. Gynecomastia
C. Metabolic acidosis
D. Hypercalcemia
E. Hyperkalemia

266. Acetazolamide
267. Metolazone
268. Torsemide
269. Eplerenone

QUESTIONS 270 TO 273

For each clinical condition, match the most appropriate pacemaker mode:
A. VAT
B. VVIR
C. DDD
D. DDDR
E. AAIR

270. A 58-year-old man with tachycardia-bradycardia syndrome who develops symptomatic sinus bradycardia with beta-blocker therapy
271. A 70-year-old woman with long-standing atrial fibrillation who complains of dizziness and is found on examination to have a ventricular rate of 30 beats/min
272. A 62-year-old man with complete heart block after aortic valve surgery
273. A 45-year-old man with symptomatic sinoatrial exit block and an appropriate junctional escape rhythm

QUESTIONS 274 TO 277

For each clinical description, match the corresponding etiology of dilated cardiomyopathy with electric instability:
A. Cardiac sarcoidosis
B. Giant cell myocarditis
C. Chagas disease
D. Arrhythmogenic right ventricular cardiomyopathy
E. Cardiolaminopathy

274. A 30-year-old man with a history of syncope who is found to have low-amplitude deflections on the ST segment in the right precordial leads and abnormal desmosomes on cardiac immunohistochemistry
275. A 38-year-old man with gastrointestinal dysmotility, complete heart block, and an apical aneurysm
276. A 50-year-old woman with a history of restrictive lung disease who presents with syncope in the setting of first-degree atrioventricular block and right bundle branch block
277. A 42-year-old woman with rapidly deteriorating cardiac function, frequent bursts of ventricular tachycardia, and widespread myocyte necrosis on endomyocardial biopsy

QUESTIONS 278 TO 282

For each of the following conditions, match the corresponding clinical presentations of syncope:
A. A 20-year-old woman "blacked out" during phlebotomy for a routine blood test

B. A 65-year-old woman lost consciousness after arm exercises
C. A 35-year-old man sustained syncope during exercise and has a systolic murmur that intensifies on standing upright
D. A 74-year-old man experiences sudden syncope while shaving
E. A 28-year-old woman with recurrent episodes of breathlessness, lightheadedness, and syncope after changes in body position

278. Hypertrophic cardiomyopathy
279. Subclavian steal syndrome
280. Vasovagal syncope
281. Carotid sinus hypersensitivity
282. Left atrial myxoma

QUESTIONS 283 TO 286

For each condition capable of precipitating high-output cardiac failure, match the appropriate physical findings:

A. Hyperthyroidism
B. Beriberi
C. Arteriovenous fistula
D. Carcinoid syndrome
E. Osler-Weber-Rendu syndrome

283. Nicoladoni-Branham sign
284. Hepatomegaly and abdominal bruits
285. Means-Lerman scratch
286. Paresthesias and painful glossitis

QUESTIONS 287 TO 290

For each of the following descriptions, match the appropriate medication:

A. One of the least lipid-soluble beta blockers
B. Cardioselective beta blocker with intrinsic sympathomimetic activity
C. Beta blocker with alpha-blocking activity
D. Noncardioselective beta blocker with intrinsic sympathomimetic activity

287. Atenolol
288. Carvedilol
289. Acebutolol
290. Pindolol

QUESTIONS 291 TO 294

	END-DIASTOLIC VOLUME (mL/m^2)	STROKE VOLUME (mL/m^2)	LV MASS (g/m^2)
Normal =	70	45	92
A.	84	44	172
B.	193	92	200
C.	199	37	145
D.	70	40	80

For each disease state, match the appropriate left ventricular volume and mass data:

291. Aortic valve stenosis with peak systolic gradient >30 mm Hg
292. Myocardial disease (primary dilated cardiomyopathy)
293. Aortic regurgitation with regurgitant flow >30 mL per beat
294. Mitral valve regurgitation with regurgitant flow >20 mL per beat

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Section II Answers

(CHAPTERS 21 TO 43)

Heart Failure; Arrhythmias, Sudden Death, and Syncope

ANSWER TO QUESTION 168

D (Braunwald, pp. 560–507; Fig. 25.13)

Sacubitril/valsartan is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI) that combines the effects of the angiotensin receptor blocker (ARB) valsartan with those of the neprilysin inhibitor sacubitril. Neprilysin inhibition augments the circulating levels of several vasoactive peptides, including the natriuretic peptides, bradykinin, and adrenomedullin resulting in vasodilatory, natriuretic, antifibrotic, and antihypertrophic effects in patients with heart failure. The incremental benefits of ARNI over angiotensin-converting enzyme (ACE) inhibition were studied in the PARADIGM-HF trial, in which 8399 subjects with heart failure with reduced ejection fraction (left ventricular ejection fraction ≤40%), New York Heart Association (NYHA) II to IV symptoms, and elevated natriuretic peptides were randomized to treatment with sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily after a run-in period designed to ensure tolerability of both drugs at target doses.[1] In this trial, which enrolled predominantly NYHA II and III subjects, treatment with sacubitril/valsartan resulted in a 20% reduction in the composite outcome of cardiovascular death or heart failure hospitalization and a 16% reduction in overall mortality compared with enalapril.

Heart failure guidelines have accordingly been updated to recommend that for patients with heart failure and reduced ejection fraction and NYHA II to III functional capacity, substitution of an ARNI for ACE inhibitor or ARB therapy should be considered to reduce morbidity and mortality.[2] ARNIs are not currently indicated for patients with heart failure and preserved ejection fraction or those with acute decompensated heart failure. In addition, like ACE inhibitors, there is a risk of angioedema with this agent. Thus, ARNIs should not be administered to patients with a history of angioedema or to those who have received an ACE inhibitor dose within the prior 36 hours.

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ANSWER TO QUESTION 169

E (Braunwald, pp. 446–447; Fig. 23.6)

Natriuretic peptides are of importance in the diagnosis, and assessment of prognosis, in patients with heart failure. The natriuretic peptide system consists of five structurally similar peptide hormones: atrial natriuretic peptide (ANP), urodilatin (an isoform of ANP), brain-type natriuretic peptide (BNP), C-type natriuretic peptide (CNP), and dendroaspis natriuretic peptide (DNP). ANP is released by atrial myocytes in response to acute increases in atrial pressure. Prohormone BNP is released in response to hemodynamic stress from ventricular dilatation, hypertrophy, or increased wall tension. Prohormone BNP is cleaved by a circulating endoprotease into two polypeptides: the inactive N-terminal proBNP (NT-proBNP), 76 amino acids in length, and the biologically active peptide BNP, 32 amino acids in length.

Circulating levels of ANP and BNP are elevated in patients with heart failure. Both ANP and BNP promote vasodilatation and natriuresis, thereby counteracting the salt- and water-retaining effects of the adrenergic, renin-angiotensin-aldosterone, and vasopressin systems. BNP and NT-proBNP levels *rise* with increasing age and worsening renal function. In contrast, BNP levels have an inverse relationship with body mass index.

CNP is derived predominantly from endothelial cells in the peripheral vasculature. The precise roles of CNP, urodilatin, and DNP in cardiovascular physiology are unclear.

A large, multicenter study of patients in the emergency department undergoing evaluation for acute dyspnea showed that a BNP level of >100 pg/mL is 90% sensitive and 76% specific in identifying a cardiac etiology. A BNP level >400 pg/mL rendered the diagnosis of heart failure likely. Analogous results were found for NT-proBNP—patients in acute heart failure had mean levels >4000 pg/mL compared with 130 pg/mL in those without heart failure.

A substudy of the TACTICS-TIMI 18 trial demonstrated that an elevated BNP level in patients presenting with acute

coronary syndromes is associated with a higher risk of subsequent congestive heart failure and death.

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ANSWER TO QUESTION 170

E (Braunwald, p. 469; Fig. 24.5; p. 543)

Cardiac arrhythmias are common in patients with structural heart disease, can contribute to worsening intracardiac hemodynamics, and may precipitate acute decompensated heart failure.[1] Cardiac output (CO) is dependent on maintenance of adequate stroke volume (SV) and heart rate. Tachyarrhythmias increase myocardial oxygen demand and reduce the time available for ventricular filling in diastole, compromising ventricular SV and CO.

Since SV is compromised in patients with left ventricular (LV) dysfunction, maintenance of CO is largely dependent on an adequate heart rate. Thus, excessive heart rate slowing (i.e., bradyarrhythmias) may also depress CO.

Dissociation between atrial and ventricular contraction (as in high-grade atrioventricular block) reduces the atrial contribution to ventricular filling, impairing subsequent SV and CO in patients with systolic or diastolic dysfunction. Abnormal intraventricular conduction, as in ventricular tachycardia or right ventricular apical pacing, may impair myocardial performance because of the loss of synchronized ventricular contraction.[2] Optimization of atrioventricular and ventriculoventricular synchrony is the primary mechanism of benefit from cardiac resynchronization therapy (biventricular pacing) in patients with LV dysfunction and heart failure.[3]

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ANSWER TO QUESTION 171

C (Braunwald, pp. 472, 1922–1923; Figs. 98.12 and 98.13)

The cardiorenal syndrome is characterized by worsening renal function during a heart failure hospitalization, or soon after discharge, despite symptomatic improvement with diuretic therapy and maintenance of adequate intravascular volume. Underlying chronic kidney disease (e.g., associated with diabetes or hypertension) increases the risk of cardiorenal syndrome, as does neurohormonal activation resulting from impaired cardiac output (CO) and excessive loop diuretic therapy.

Renal function is an important prognostic indicator in patients with acute heart failure syndromes. Impaired baseline renal function and worsening renal function, during hospitalization or early after discharge, are potent predictors of adverse outcomes, including early readmission rates and mortality. *Elevated*, not reduced, systemic venous pressure appears to be an important contributing factor to the development of cardiorenal syndrome, because venous congestion contributes to elevated intra-abdominal pressure that can impair glomerular filtration.

An increase in blood urea nitrogen (BUN) out of proportion to serum creatinine is a sign of renal hypoperfusion, resulting from low forward CO or intravascular volume depletion because of high doses of intravenous diuretics. The neurohormonal activation accompanying renal hypoperfusion increases proximal sodium and urea reabsorption, while creatinine handling is unaffected, leading to an elevated BUN/creatinine ratio.

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ANSWER TO QUESTION 172

B (Braunwald, pp. 504–509; Table 25.8)

The effectiveness of digoxin was studied in the Digitalis Investigators Group trial, which enrolled 6800 patients with class I to III heart failure, with a mean left ventricular ejection fraction (LVEF) of 28%.[1] Over 37 months of follow-up, there was a significant decrease in heart failure hospitalizations but no significant improvement in total mortality with digoxin therapy compared with placebo.

Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of therapy for patients with chronic heart failure with reduced ejection fraction or asymptomatic left ventricular (LV) dysfunction because of their favorable hemodynamic effects and unsurpassed benefit on long-term mortality. The Vasodilator Heart Failure Trial II (V-HEFT II) compared the ACE inhibitor enalapril with the combination of hydralazine plus isosorbide dinitrate in the treatment of chronic moderate congestive heart failure. Survival in the enalapril-treated group proved superior.[2]

Aggregate clinical data indicate that angiotensin receptor blockers (ARBs) are as effective as ACE inhibitors in reducing HF-related morbidity and mortality. Candesartan significantly reduced the primary composite of cardiovascular death or hospital admission for heart failure among ACE-inhibitor intolerant patients enrolled in the CHARM-Alternative Trial.[3] The VALIANT trial randomized patients with LV dysfunction after myocardial infarction to valsartan, captopril, or both and found similar benefit with the ACE inhibitor or ARB in reducing mortality.[4] Thus, ARBs are currently accepted as appropriate substitutes for patients with LV dysfunction who are intolerant of ACE inhibitors.[5] The incremental benefit of ARBs in patients already treated with ACE inhibitors is less clear.

In the RALES trial, the aldosterone antagonist spironolactone was shown to reduce mortality when added to standard heart failure therapy in patients with class III to IV heart failure with an ejection fraction <35%.[6] In the EMPHASIS trial, eplerenone, a selective aldosterone antagonist, significantly reduced mortality compared with placebo when added to standard heart failure therapy in patients with class II or III systolic heart failure.[7]

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ANSWER TO QUESTION 173

C (Braunwald, pp. 560–566; Fig. 28.9)

Long-term outcomes after transplantation improved dramatically with the introduction of the calcineurin inhibitor cyclosporine as the cornerstone of immunosuppression. The median survival of all cardiac transplant patients is now >10 years, with a median survival of 13 years among those patients who are alive 1 year after transplant.[1] By the first year after transplantation, 90% of surviving patients report no functional limitations.[2]

The selection of candidates for transplantation is a complex process that integrates assessment of hemodynamics, comorbidities that might limit post-transplantation survival, and psychosocial factors that may impair compliance. Optimal candidates for heart transplantation are younger patients with advanced heart failure, minimal comorbid illness or end-organ damage, a history of adherence to prescribed medical therapy, and a strong family and social network.

The transplanted heart is denervated and relies on atypical adaptive mechanisms to meet varying demands for cardiac output (CO). As a result of increased venous return at the onset of exercise, the transplanted heart responds with the intrinsic Frank-Starling mechanism to augment CO. Circulating catecholamine levels rise as exercise ensues, providing a delayed chronotropic response. This mechanism allows near-normal hemodynamic function at rest, and the capacity to support at least moderate exercise in a large majority of long-term survivors. Of note, beta blockers may impair the heart rate response and should be used cautiously after heart transplantation.

As no reliable serologic markers for allograft rejection have been identified, right ventricular endomyocardial biopsy remains the gold standard for this diagnosis. Biopsies are typically performed through a transjugular vein approach and are carried out on a routine schedule during the post-transplantation period and over the life of the transplant. High-grade rejection may be signaled by the development of clinical heart failure, atrial arrhythmias, low QRS voltage on the ECG, or echocardiographic evidence of left ventricular dysfunction; however, definitive diagnosis or identification of early or subtle lower-grade rejection requires histologic examination of the myocardium.

Allograft rejection and infection are the most common causes of death early after transplant. The risk of infection diminishes with time as the intensity of immunosuppression therapy is reduced. In contrast, the risk of fatal malignancy increases progressively in the years thereafter. The most common fatal early malignancies are post-transplant lymphoproliferative disorders and lung cancer.

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ANSWER TO QUESTION 174

D (Braunwald, pp. 496–498, 501; Fig. 25.7; Table 25.6)

Mannitol is an inert osmotic agent that expands the extracellular fluid volume; its use is *contraindicated* in patients with decompensated heart failure.

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) act at the renal distal convoluted tubule and cortical collecting tubule to reduce sodium reabsorption and inhibit K^+ and H^+ excretion. Although only weak diuretics, they have been shown to reduce morbidity and mortality in systolic heart failure.[1] However, aldosterone receptor antagonists may contribute to clinically significant hyperkalemia, particularly when used in combination with angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers.[2]

Loop diuretics, such as furosemide, torsemide, and bumetanide, are inhibitors of the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb of the loop of Henle. Inhibition of this cotransporter markedly increases the fractional excretion of sodium and chloride. However, the delivery of large amounts of sodium and fluid to the distal nephron increases K^+ and H^+ secretion, leading to hypokalemia and metabolic *alkalosis*.

Nonsteroidal anti-inflammatory agents (NSAIDs) may impair renal function and diminish the action of diuretics by inhibiting the production of vasodilating prostaglandins. All NSAIDs, including aspirin, have this potential effect, which can contribute to diuretic resistance in individuals with an initially favorable diuretic response.[3]

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ANSWER TO QUESTION 175

E (Braunwald, pp. 407–408)

A variety of laboratory abnormalities may be noted in patients with congestive heart failure. Alterations in serum electrolyte values usually occur only after patients have begun treatment or in more long-standing, severe cases of heart failure. Hyponatremia is seen in up to 25% of patients with acute heart failure decompensation and is an important negative prognostic indicator.[1] It may be present for a variety of reasons, including sodium restriction, intensive diuretic therapy, a decrease in the ability to excrete water related to reductions in renal blood flow and glomerular filtration rate (GFR), and elevations in the concentration of circulating vasopressin.[2] Hypokalemia may result from aggressive diuretic therapy. Conversely, hyperkalemia may occasionally occur in patients with severe heart failure who have marked reductions in GFR or who are receiving aldosterone receptor antagonists (spironolactone or eplerenone).

Congestive hepatomegaly due to "backward" failure and cardiac cirrhosis from long-standing heart failure is often accompanied by impaired hepatic function, reflected by abnormal circulating liver enzymes. In acute hepatic venous congestion, jaundice may result, with bilirubin levels as high as 15 to 20 mg/dL, dramatic elevations of serum aspartate aminotransferase levels, and prolongation of the prothrombin time. Although the clinical and laboratory profiles of such an event may resemble viral hepatitis, the diagnosis of hepatic congestion is confirmed by rapid normalization of these values with successful treatment of heart failure. In patients with long-standing heart failure and secondary severe hepatic damage, albumin synthesis may become impaired. Rarely, more severe sequelae may occur, including hepatic hypoglycemia, fulminant hepatic failure, and hepatic coma.

Elevations in pulmonary capillary pressure are reflected by the appearance of the vasculature on the chest radiograph. With minimal elevations (i.e., ~13 to 17 mm Hg), early equalization in the size of the vessels in the apices and bases is first discernible. It is not until greater pressure elevations occur (~18 to 20 mm Hg) that actual pulmonary vascular redistribution occurs. When pressure exceeds 20 to 25 mm Hg, frank interstitial pulmonary edema is usually observed. Importantly, however, in patients with *chronic* left ventricular failure, higher pulmonary pressures can be accommodated with few clinical and radiologic signs of congestion due to enhanced lymphatic drainage.

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ANSWER TO QUESTION 176

B (Braunwald, pp. 421–422, 430–431, 432–433; Figs. 22.12 and 22.13)

The binding of a beta-adrenergic agonist to its myocyte receptor initiates a complex system of messengers within the sarcolemma and cytosol of the cell. The $beta_1$ receptor is coupled, via G-proteins, to activation of adenylate cyclase and formation of cyclic *adenosine* monophosphate (cAMP). This molecule acts via protein kinases to phosphorylate proteins and enzymes within the cell. Such action stimulates enhanced entry of calcium ions through voltage-dependent L-type calcium channels, followed by additional calcium-induced calcium release from the sarcoplasmic reticulum. The rise in cytosolic calcium increases calcium-troponin C interaction, a necessary step for subsequent contraction. The activated troponin C binds tightly to the inhibitory molecule troponin I, thus removing inhibition of actin-myosin cross-bridge formation, and contraction ensues.

Whereas cAMP is a second messenger for the beta-adrenergic system, another cyclic nucleotide, cyclic guanosine monophosphate (cGMP), acts as a second messenger during cholinergic stimulation. In vascular smooth muscle, cGMP acts as an intracellular messenger after nitric oxide stimulation.

Titin is a large protein that provides elasticity and supports the myosin molecule by tethering it to the myocyte Z line.

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ANSWER TO QUESTION 177

B (Braunwald, p. 563; Table 28.4)

Rejection is a ubiquitous concern after solid organ transplantation. It results from cell- or antibody-mediated allograft injury owing to recognition of the allograft as non-self tissue. Three major types of rejection have been identified: hyperacute, acute, and chronic. *Hyperacute* rejection occurs within minutes to hours after heart transplantation and is mediated by preexisting antibodies to allogeneic antigens on the vascular endothelium that fix complement. This results in occlusion of graft vasculature and overwhelming graft failure. In contrast, the biopsy specimen in this question shows a dense lymphocytic infiltrate and myocyte damage typical of *acute* cellular allograft rejection. Acute cellular rejection is a T-cell-mediated process that develops in the first weeks to 6 months after transplantation. *Chronic* rejection, or late graft failure, is an irreversible deterioration of graft function years after transplant mediated by antibodies or progressive graft loss from ischemia.

Risk factors for rejection include female gender, black recipient race, recipient-positive cytomegalovirus serology, prior infections, and the number of human leukocyte antigen (HLA) mismatches.[1] Patients who do not experience acute rejection within the first 6 months after transplantation have a lower incidence of late rejection.

Although progress has been made in novel noninvasive serologic approaches, such as gene expression profiling, to identify acute rejection,[2] endomyocardial biopsy remains the diagnostic gold standard. The procedure is performed under fluoroscopic or echocardiographic guidance using a bioptome inserted percutaneously via the right internal jugular vein. Potential complications include pneumothorax, transient rhythm disturbances, myocardial perforation, and tricuspid regurgitation.

The most important feature of the post-transplant biopsy specimen is the detection of lymphocyte infiltration and the presence of myocyte necrosis. A revised continuum scale

has been established for grading cardiac biopsies from no rejection (grade OR) to diffuse damaging inflammatory cell infiltrates with encroachment of myocytes and disruption of normal cell architecture (grade 3R).[3] Appropriate therapy for acute cellular rejection depends on the timing and severity of the rejection episode. Episodes that occur within the first 3 months, or episodes that are moderate to severe, are initially treated with pulsed-dose methylprednisolone. If steroid therapy is ineffective, then more aggressive therapy with OKT3 monoclonal antibody or ATGAM (horse antithymocyte globulin) may be necessary.[4]

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ANSWER TO QUESTION 178

E (Braunwald, pp. 435, 438–439, 411)

The four primary determinants of cardiac output (CO) are (1) heart rate; (2) preload, which is closely related to left ventricular (LV) end-diastolic volume; (3) afterload, which is closely related to aortic impedance (i.e., the sum of the external factors that oppose ventricular ejection); and (4) contractility, a fundamental property of cardiac muscle that reflects the level of activation of cross-bridge formation. Preload, afterload, and contractility determine the ventricular stroke volume (SV), and CO = Heart rate × SV.

Unlike other organs, the myocardium extracts oxygen from blood nearly maximally. Thus, even at rest, the oxygen saturation in coronary venous blood (measured at the coronary sinus) is quite low, usually <40%.

The body's oxygen consumption at peak exercise is an indirect measure of the CO. The peak oxygen uptake ($\dot{V}O_2$ max) is defined as the value achieved when $\dot{V}O_2$ plateaus despite a continued increase in the intensity of exercise. The anaerobic threshold is indicated by the $\dot{V}O_2$ at which carbon dioxide production starts to rise, resulting in an increase in the $\dot{V}CO_2/\dot{V}O_2$ ratio. Both the peak oxygen consumption and the anaerobic threshold are reproducible when measured days or weeks apart. During exercise, the CO of a normal heart increases up to sixfold and the body's oxygen consumption can increase up to 18-fold.

In patients with LV dysfunction, cardiopulmonary exercise tests are often performed to determine functional capacity. A peak oxygen consumption of >20 mL/kg/min reflects mild or no functional impairment. Conversely, a peak oxygen consumption of <12 mL/kg/min indicates severe impairment and a poor prognosis. Serial tests can be performed over time to assess the response to pharmacologic therapies in patients with heart failure and can help guide the need for aggressive interventions such as cardiac transplantation or placement of a ventricular assist device.

ANSWER TO QUESTION 179

A (Braunwald, pp. 436–437; Fig. 22.18)

By the law of Laplace, left ventricular (LV) wall stress (σ) is directly proportional to intracavitary pressure and chamber radius and inversely proportional to wall thickness. Ventricular hypertrophy is therefore an adaptive mechanism that serves to reduce ventricular wall stress. Myocardial hypertrophy and remodeling proceed in different patterns based on the timing and nature of the provocative stimulus. When the primary stimulus is pressure overload (as in aortic stenosis or hypertension), an increase in wall stress during ventricular systole triggers the addition of new myofibrils in parallel, leading to wall thickening at the expense of chamber size, in a pattern of *concentric* hypertrophy. When the primary stimulus is volume overload (as in chronic mitral regurgitation), increased wall stress during ventricular diastole triggers the replication of sarcomeres in series, elongation of myocytes, and ventricular cavity dilatation, in a pattern of *eccentric* hypertrophy. Therefore, although both chronic pressure and volume overload are associated with a compensatory increase in LV mass, the pattern of hypertrophy is distinct in each case.

With the use of echocardiography, concentric hypertrophy can be distinguished from eccentric hypertrophy visually, or on the basis of the ratio between wall thickness and the LV internal diameter during diastole (i.e., the relative wall thickness = [2 × posterior wall thickness]/LV internal dimension). A relative wall thickness <0.45 suggests eccentric hypertrophy, whereas a higher ratio is more consistent with concentric hypertrophy.

ANSWER TO QUESTION 180

A (Braunwald, pp. 547–548, 551; Table 27G.2; pp. 681–683)

Amiodarone has been studied extensively in patients with left ventricular (LV) dysfunction. It effectively suppresses ventricular and supraventricular arrhythmias and appears to be safe for use in this subset of patients. However, convincing evidence of mortality reduction has not been shown. In the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) study of patients with class II to III heart failure and a left ventricular ejection fraction (LVEF) of 35% or less, amiodarone did not improve survival compared with placebo.[1]

Dronedarone is a derivative of amiodarone that shares its electrophysiologic properties, but does not contain iodine and is associated with lower rates of lung and thyroid toxicity. Dronedarone is approved to facilitate maintenance of sinus rhythm in patients with atrial fibrillation or atrial flutter. It should not be prescribed in class III to IV heart failure because its use was associated with increased mortality in such patients in the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Heart Failure Evaluating Morbidity Decrease trial.[2]

The results of several randomized, controlled clinical trials support the benefit of implantable cardioverter-defibrillator (ICD) therapy in reducing mortality among patients with LV dysfunction. The Antiarrhythmics Versus Implantable Defibrillators study randomized patients with reduced LVEF and prior resuscitated cardiac arrest, or symptomatic sustained ventricular tachycardia (VT), to therapy with amiodarone or an ICD. ICD therapy was associated with a 29% reduction

in all-cause mortality compared with amiodarone. A concurrent registry of patients with transient or correctable causes of VT or ventricular fibrillation not enrolled in the primary trial revealed that the risk of mortality in these patients remains comparable with those with primary VT or ventricular fibrillation.[3] ICD therapy is therefore recommended as the standard of care for secondary prevention of sudden cardiac death or symptomatic ventricular tachyarrhythmias in patients with LV dysfunction.

The data for ICD efficacy in primary prevention of sudden cardiac death are also compelling. The results of the Multicenter Automatic Defibrillator Implantation II Trial confirm that, in patients with coronary artery disease, prior myocardial infarction, and LVEF ≤30%, prophylactic implantation of a defibrillator reduces mortality by 31% relative to conventional medical therapy.[4] The results of the SCD-HeFT extended the benefits of ICD therapy to patients with nonischemic cardiomyopathy.[1] Thus, current American College of Cardiology/American Heart Association guidelines recommend that patients with mild to moderate heart failure and an LV ejection function ≤35% on optimal medical therapy are potential candidates for ICD implantation.[5]

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ANSWER TO QUESTION 181

C (Braunwald, pp. 543–547)

Ventricular dyssynchrony is defined as a QRS duration >120 milliseconds on the surface ECG regardless of the QRS morphology. Ventricular conduction delay alters the timing of ventricular activation and places an already failing ventricle under further mechanical disadvantage by reducing contractility and ventricular filling and prolonging the duration of mitral regurgitation.[1] Cardiac resynchronization therapy (CRT), also known as biventricular pacing, serves to better coordinate left ventricular (LV) contraction, leading to improved ventricular performance and reduced LV filling pressures.

CRT improves ventricular function without increasing myocardial energy consumption, in contrast to the effects of inotropic agents such as dobutamine. CRT may also reverse LV remodeling over time, reducing LV mass and end-diastolic dimension while increasing the ejection fraction.

The CARE-HF trial demonstrated that CRT alone, without a defibrillator, reduces mortality in patients with classes III and IV heart failure, left ventricular ejection fraction ≤35%, and ventricular dyssynchrony.[2] CRT combined with an implantable cardioverter-defibrillator (CRT-D) has been shown to reduce death and hospitalization rates in patients with classes II and III heart failure and LV systolic dysfunction.[3] The benefit of CRT has more recently been extended to patients with less severe (class I to II) heart failure, left ventricular dysfunction, and QRS widening based on the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy trial.[4]

Approximately 25% of patients receiving CRT under current indications are nonresponders. Contributing factors to nonresponse include coronary venous anatomy that precludes optimal LV lead placement, the presence of ventricular scar, or suboptimal atrioventricular or ventriculo-ventricular activation timing. The greatest benefit of CRT appears to accrue to patients with QRS widening >150 milliseconds and left bundle branch block morphology, compared with those with lesser QRS widening or with right bundle branch block or nonspecific intraventricular conduction delay.[5]

Echocardiography can identify mechanical dyssynchrony, but has not proved useful in selecting patients for successful CRT.[6]

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ANSWER TO QUESTION 182

A (Braunwald, pp. 507–609, 510; Fig. 25.15; pp. 545–546)

This patient has heart failure with reduced ejection fraction and New York Heart Association (NYHA) II symptomatology on a pharmacologic regimen that includes a beta blocker, angiotensin receptor blocker, and mineralocorticoid receptor antagonist. Although she has only mild heart failure symptoms, treatment guidelines recommend further medical optimization for additional clinical benefit.[1] Notably, her heart rate is 84 beats/min in sinus rhythm, and the beta blocker dosage is below guideline-recommended targets (i.e., up to 200 mg daily for metoprolol succinate). The appropriate next step is therefore to upwardly titrate the beta blocker. If she does not tolerate augmentation of the beta blocker, then consideration of the I_f channel inhibitor, ivabradine, would be appropriate for heart rate reduction. In the SHIFT trial, patients with symptomatic heart failure, left ventricular ejection fraction (LVEF) ≤35%, and heart rate ≥70 beats/min in sinus rhythm, who were receiving standard heart failure therapy (including beta blockers)

were randomized to treatment with ivabradine or placebo. Patients assigned to ivabradine experienced an 18% reduction in the composite of cardiovascular death or heart failure hospitalization, driven principally by a reduction in the latter.[2] This result led to a class IIa indication for the addition of ivabradine in patients meeting the SHIFT inclusion criteria.

Although replacement of candesartan with the angiotensin receptor neprilysin inhibitor sacubitril/valsartan would also be a reasonable consideration for this patient, this step should follow optimization of the beta blocker dosage, and for a patient tolerating candesartan 32 mg daily, the appropriate starting dose of sacubitril would be 49/51 mg twice daily, not the 24/26 mg twice daily listed in the question.

By current heart failure guidelines, cardiac resynchronization therapy is indicated in NYHA II to IV heart failure patients with LVEF ≤35% who are in sinus rhythm with *left* bundle branch block and QRS duration ≥120 milliseconds (a class IIa indication; QRS ≥150 milliseconds would be a class I indication), and would be less beneficial for this patient with right bundle branch block and QRS duration of 120 milliseconds.

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ANSWER TO QUESTION 183

B (Braunwald, pp. 1631–1632)

This 52-year-old man has symptoms and signs of heart failure. There are several possible contributors to his left ventricular (LV) dysfunction based on the clinical history. The history of smoking and hypertension put him at high risk for coronary artery disease, but there is no evidence of angina or prior myocardial infarction by history or ECG. Long-standing, severe, uncontrolled hypertension may ultimately lead to heart failure owing to progressive LV hypertrophy and diastolic dysfunction; however, this patient's hypertension has been well controlled in recent years. The evidence by chest radiograph and physical examination for an enlarged heart with decompensated heart failure is most consistent with a dilated cardiomyopathy. His confessed alcohol use is moderate; however, patients with excessive alcohol intake may underreport their true consumption. Of the choices presented, the best unifying diagnosis is alcoholic cardiomyopathy.

Heavy alcohol consumption is the leading cause of nonischemic dilated cardiomyopathy in the United States for both men and women. In general, alcoholic cardiomyopathy is associated with heavy alcohol consumption, although the precise amount of alcohol that is "safe" for any given individual is variable. Excessive alcohol consumption causes abnormalities of both systolic and diastolic function as well as progressive LV cavity enlargement. Frequently, individuals with alcoholic cardiomyopathy develop atrial fibrillation or ventricular arrhythmias.

There is no definitive diagnostic test for alcoholic cardiomyopathy. As a result, it is often recommended that patients with dilated cardiomyopathy abstain completely from alcohol consumption. Total cessation in the early stages of the disease frequently leads to resolution of the manifestations of congestive heart failure and the return of the heart size to normal. Continued alcohol consumption leads to further myocardial damage and fibrosis, with the development of refractory heart failure. Patients with alcoholic cardiomyopathy benefit from treatment with standard medical therapies for heart failure with reduced ejection fraction. Because nutritional deficiencies are common in alcoholics and may contribute to myocardial dysfunction, vitamin supplementation (in particular, thiamine) should be considered.

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ANSWER TO QUESTION 184

E (Braunwald, pp. 536–538; Fig. 26.10)

This patient's presentation is most consistent with the syndrome of heart failure with preserved ejection fraction (HFpEF). She exhibits many of the typical demographic features including advanced age, a history of hypertension, and elevated body mass index, as well as clinical signs and symptoms of decompensated heart failure.

In contrast to heart failure with reduced ejection fraction, there are only limited data from prospective, randomized clinical trials to guide appropriate management of this large population of patients. Although aggressive management of hypertension in this disorder is beneficial,[1] no specific therapy has been clearly associated with a survival benefit. In the subgroup of HFpEF patients enrolled in the Digitalis Investigators Group trial, digoxin did not improve the composite primary endpoint of heart failure hospitalization or cardiovascular mortality.[2]

The Perindopril in Elderly People with Chronic Heart Failure[3] trial randomized a population of patients with heart failure, normal or near-normal EF, and age >70 years to treatment with the angiotensin-converting enzyme inhibitor perindopril or placebo and failed to demonstrate a benefit in the primary endpoint of all-cause mortality or unplanned heart failure hospitalizations.

The Candesartan Heart Failure: Assessment of Reduction in Mortality and Morbidity-Preserved trial randomized patients with chronic heart failure and ejection fraction >40% to treatment with the angiotensin receptor blocker candesartan or placebo.[4] Fewer hospitalizations for heart failure occurred in the candesartan group, but cardiovascular survival was not improved. The I-PRESERVE trial studied patients >60 years old with symptomatic heart failure and ejection fraction ≥45%. After randomization to irbesartan or placebo, there was no significant effect on mortality or hospitalizations from a cardiovascular cause.[5]

The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist trial examined the role of spironolactone in patients with HFpEF and found no impact on the composite of cardiovascular death, heart failure hospitalization, or aborted cardiac arrest relative to placebo; there was a statistically significant reduction in heart failure

hospitalizations, however, with spironolactone treatment.[6] In addition, post hoc analysis suggested geographic differences in results in that patients from the Americas with HFpEF benefited from spironolactone, but those from the countries of Russia and Georgia did not, possibly reflecting variation in clinical characteristics of the patients or in technical performance of the study.[7] Accordingly, in the absence of other evidence-based therapy, current guidelines suggest consideration of spironolactone for selected patients with HFpEF to decrease hospitalizations.[8]

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ANSWER TO QUESTION 185

E (Braunwald, p. 1626)

The clinical presentation of new-onset heart failure in the context of a viral prodrome suggests myocarditis. While most cases of myocarditis with antecedent viral infection are related to lymphocytic myocarditis, the rapid and fulminant progression of disease with worsening ventricular function, hypotension, ventricular arrhythmias, and hypoperfusion in this case suggest giant cell myocarditis (GCM). In patients with suspected GCM, endomyocardial biopsy is indicated to clarify the pathologic diagnosis.

Fulminant lymphocytic myocarditis generally carries a favorable prognosis if the patient can be supported through the period of acute illness. Immune suppression has generally not been effective in facilitating myocardial recovery. GCM, by contrast, carries a very poor prognosis with a mean transplant-free survival of only 5.5 months. Combination immunosuppressive therapy including cyclosporine, azathioprine, and corticosteroids has been demonstrated to prolong the time to transplantation or death once the diagnosis is confirmed. However, due to the rapid progression and poor survival, urgent mechanical circulatory support as a bridge to cardiac transplantation is the treatment of choice.

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ANSWER TO QUESTION 186

D (Braunwald, pp. 515, 568, 570–573)

The patient in this vignette has New York Heart Association (NYHA) class IV and American College of Cardiology/American Heart Association stage D congestive heart failure. He is not a candidate for cardiac resynchronization therapy because the QRS complex duration is normal (see Answer to Question 181). Repeated hospitalizations for heart failure, hyponatremia, intolerance to beta-adrenergic blockade, and a markedly reduced peak oxygen uptake of 10 mL/kg/min are all markers of poor prognosis and, taken together, predict mortality >50% in the next year. Such a patient should be considered for advanced therapies, including heart transplantation and mechanical circulatory support. Given the limitations of donor supply, cardiac transplantation is generally reserved for younger patients with few comorbid conditions. In addition, because of renal insufficiency and the recent diagnosis of cancer, this patient is unlikely to be eligible for transplantation (either heart alone or combined heart-kidney). Furthermore, the typically long waiting time for a donor heart renders transplantation an impractical immediate solution for this patient with a very limited predicted short-term survival.

Durable mechanical circulatory devices (i.e., ventricular assist devices) can extend survival and enhance the quality of life in patients with advanced heart failure. Mechanical support can be used as a "bridge to transplantation" and also as permanent "destination therapy" in patients for whom cardiac transplantation is not feasible. Such devices may also be used as a "bridge to recovery" in rare cases of an identifiable, potentially reversible cause of cardiac decompensation, such as acute myocarditis, postcardiotomy syndrome, or peripartum cardiomyopathy. Because this patient is ineligible for transplantation, destination therapy would be the most appropriate mechanical support strategy.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial evaluated patients with NYHA class IV symptoms and left ventricular ejection fraction <25%, most of whom were on continuous intravenous inotropes.[1] REMATCH demonstrated the superiority of an early-generation pulsatile left ventricular assist device (LVAD) compared with medical therapy, but by 2 years of follow-up only 23% of the patients with the assist devices were still alive.

The HeartMate II, an axial flow LVAD providing continuous blood flow, is approved by the US Food and Drug Administration both as a bridge to transplantation and as destination therapy. Continuous-flow pumps are relatively low profile devices that allow implantation in smaller patients and offer mechanical durability but do expose patients to the risk of stroke, infection, and bleeding. The HeartMate II LVAD confers an actuarial survival of 68% at 1 year and 58% at 2 years, while dramatically improving the quality of life in the majority of patients.[2,3]

The Heartware ventricular assist device is a smaller, intrapericardial, continuous-flow pump that is an alternative to the HeartMate II for use as a bridge to cardiac transplant, but is currently not approved for destination therapy.[4] More recently, data from the MOMENTUM 3 trial suggested improved clinical outcomes with implantation of a fully magnetically levitated centrifugal flow pump (HeartMate 3) compared with an axial flow pump (HeartMate II), driven largely by the lesser need for reoperation for pump malfunction.[5] Of note, patients being considered for destination LVAD therapy must have adequate native right ventricular (RV) function, because postoperative RV failure is associated with high mortality.

Although mechanical biventricular support is also available as a bridge to transplantation, it is not currently approved as destination therapy. Because this patient has adequate right ventricular function by echocardiography, he should be well supported by an isolated LVAD.

Finally, palliative and hospice level care play important roles in the care of stage D heart failure patients for whom these advanced options are not practical and there are no reasonable prospects for improvement in quality or length of life.

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ANSWER TO QUESTION 187

D (Braunwald, pp. 433–435; Fig. 22.16)

The Wiggers diagram of the cardiac cycle graphically demonstrates the important temporal relationships between the electrical and mechanical events of cardiac contraction and relaxation (Fig. 2.21). Nearly simultaneous events occur in the right and left sides of the heart during the cardiac cycle; here we concentrate on the left-sided events. Filling of the left ventricle begins in early diastole when the left ventricular (LV) pressure falls below left atrial pressure and the mitral valve opens. The subsequent early phase of rapid ventricular filling corresponds to the timing of the third heart sound (S_3), which may be audible when filling pressures are increased (as in patients with heart failure).

As the pressures in the left atrium and ventricle equalize, ventricular filling slows. Filling is then augmented at the end of diastole owing to atrial contraction, which generates the *a* wave on the left atrial pressure tracing. Temporally, the *a* wave occurs just after the P wave on the surface ECG and coincides with the fourth heart sound (S_4). In atrial fibrillation, organized atrial contraction is absent and a discrete *a* wave is usually not evident.

With the onset of the QRS complex on the surface ECG, ventricular systole begins and the LV pressure begins to rise. When LV pressure exceeds that in the left atrium, the mitral valve closes, producing the first heart sound (S_1). Ventricular pressure continues to rise at constant ventricular volume (isovolumic contraction) until it exceeds aortic pressure. At this point, the aortic valve opens and rapid ejection begins. After contraction, as the pressure in the left ventricle falls below the aortic pressure, ejection ceases and the aortic valve closes, generating the second heart sound (S_2). Isovolumic relaxation then occurs, beginning ventricular diastole again.

The *v* waves on the right and left atrial pressure tracings correspond to venous return to the atria when the tricuspid and mitral valves are closed. The peak of the *v* wave is usually inscribed after electrical repolarization of the ventricles, so that it *follows* the T wave on the ECG.

ANSWER TO QUESTION 188

A (Braunwald, pp. 406–407; Table 21.4)

Because the pleural veins drain into both the systemic and pulmonary venous beds, hydrothorax (pleural effusion) may develop when there is marked elevation of pressure in either venous system. Heart failure-related pleural effusions are usually bilateral, but when they are unilateral they are usually present on the right side. When hydrothorax develops, dyspnea becomes more marked because of a further reduction in vital capacity. The absence of pulmonary rales does not exclude considerable elevation of the pulmonary capillary pressure, especially in patients with chronic heart failure who may have well-developed lymphatic drainage.

Hepatomegaly is often present in patients with heart failure *before* the development of overt peripheral edema. When it develops rapidly with acute congestion, the liver may be tender as a result of rapid capsular distention.

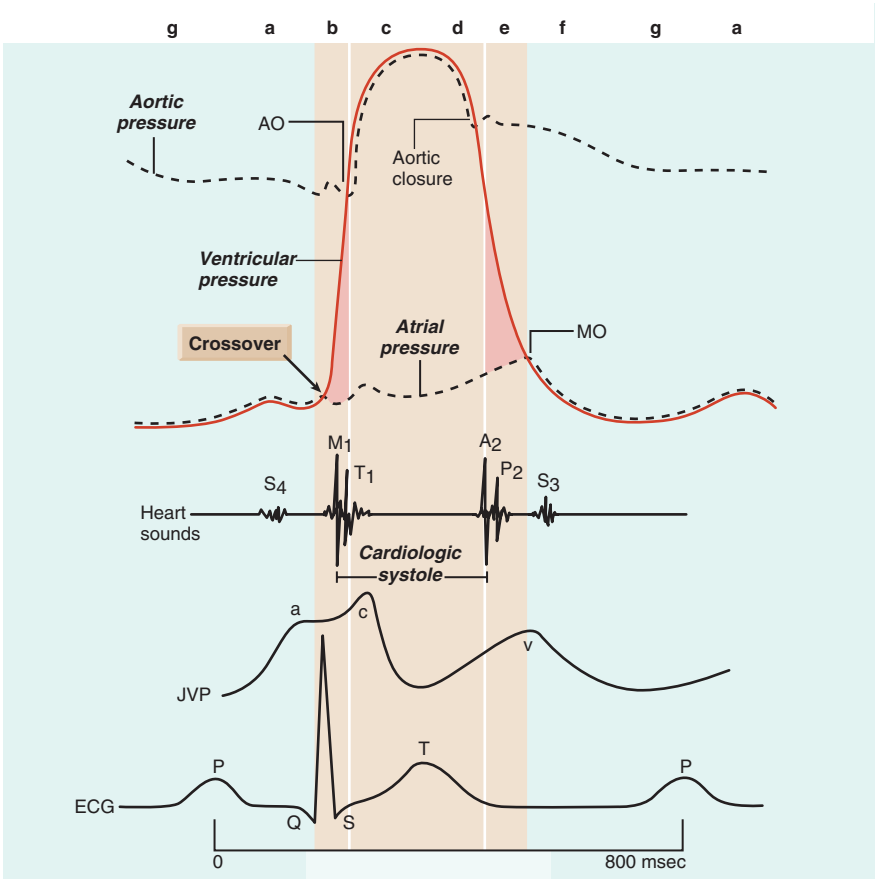
Peripheral edema often does not correlate well with the degree of systemic venous congestion. Usually, a substantial gain of extracellular fluid volume (>4 L in adults) must occur before peripheral edema develops.

With the development of left ventricular failure, pulmonary artery pressures rise and the pulmonic component of the second heart sound is *accentuated*. A systolic murmur of mitral regurgitation may also be audible owing to ventricular cavity dilatation.

ANSWER TO QUESTION 189

B (Braunwald, pp. 553–555; Figs. 28.1 and 28.2; Table 28.1)

This patient has ischemic cardiomyopathy due to multivessel obstructive coronary artery disease (CAD). Patients with left ventricular (LV) dysfunction and heart failure due to CAD may benefit from coronary artery bypass grafting (CABG) regardless of whether angina is present. Although the primary results of the STICH trial did not demonstrate a difference in the primary endpoint of all-cause mortality between medical therapy and surgical revascularization of patients with LV dysfunction and CAD amenable to CABG, secondary outcomes were improved in the revascularization group.[1] The recently published 10-year follow up of the STICH cohort



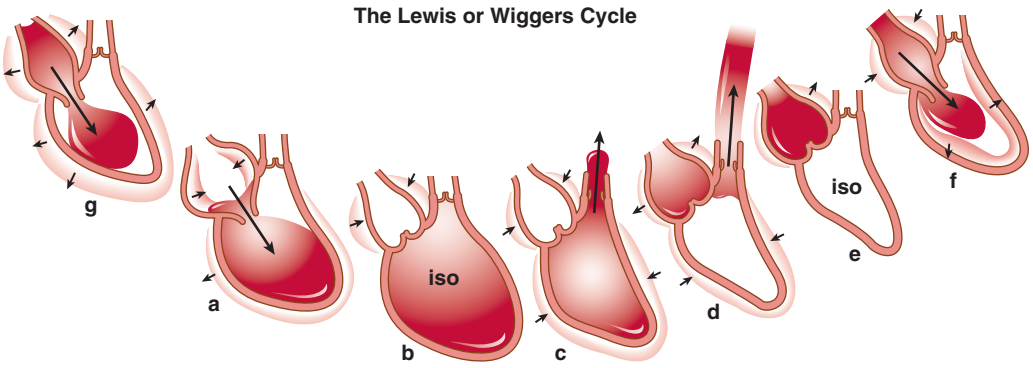


FIG. 2.21 *From Opie LH.* Heart Physiology: From Cell to Circulation. *Philadelphia: Lippincott Williams & Wilkins; 2004; copyright L.H. Opie, 2004.*

confirms the benefits of CABG over medical therapy, with improved median survival observed in subjects allocated to revascularization.[2] Many factors should be considered before referring such a patient for CABG, including the coronary anatomy, the degree of LV dysfunction, the severity of heart failure symptoms, and the magnitude of comorbid medical conditions. Because the benefits of revascularization are thought to result in part from improvement in blood flow to previously underperfused but still viable myocardium, testing to assess cellular viability has been utilized to identify patients likely to derive greatest benefit from CABG.[3] In patients with ischemic cardiomyopathy, the weight of evidence has suggested that significant myocardial viability (≥25%) predicts improvement in survival and quality of life with CABG over medical therapy alone. The myocardial viability substudy of the STICH trial called this conclusion into question, as assessment of viability did not identify patients with a survival benefit with CABG compared with medical therapy alone (i.e., the presence of viable myocardium in patients with CAD and LV dysfunction was associated with greater survival regardless of the treatment approach). Thus, the role of testing for viability is still evolving.[4]

Segments of markedly hypokinetic or akinetic myocardium identified by resting echocardiography may contain substantially viable myocardium if those areas are simply hibernating or stunned. Myocardial *hibernation* refers to persistent contractile dysfunction caused by a chronically reduced blood supply, usually a result of multivessel CAD. In such regions, irreversible damage has not occurred and ventricular function can improve with restoration of adequate blood flow through revascularization.[5] Myocardial *stunning* refers to reversible postischemic contractile dysfunction that

persists for a prolonged period after reperfusion. It is thought to be caused by the generation of oxygen-derived free radicals or the transient loss of contractile filament sensitivity to calcium. This patient's anterior wall akinesis may have resulted from cell death due to prior infarction, or it may represent hibernating myocardium. Viability testing with thallium perfusion imaging, positron emission tomography, or dobutamine echocardiography can confirm whether the anterior wall is viable or permanently scarred.

Surgical ventricular reconstruction (SVR) involves the resection of an aneurysmal or akinetic segment after transmural myocardial infarction and reconstruction with a patch. The exclusion of thinned, scarred myocardium restores an elliptical shape to the left ventricle with the goal of diminishing wall stress, mitral regurgitation, and residual ischemia. However, the results of the SVR portion of the STICH trial indicate that routine performance of SVR at the time of coronary artery bypass surgery is not associated with improved clinical outcomes.[6]

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ANSWER TO QUESTION 190

E (Braunwald, pp. 510–511)

Disturbances of cardiac rhythm are important and potentially life-threatening complications of cardiac glycoside administration. Side effects can be minimized by maintaining therapeutic levels of digoxin between 0.5 and 1.0 ng/mL. Although overt digitalis toxicity is usually manifest at serum levels >2.0 ng/mL, adverse drug effects may occur at lower levels, particularly if hypokalemia or hypomagnesemia is present. Digitalis toxicity may be manifest by neurologic symptoms (visual abnormalities, confusion), gastrointestinal disturbance (nausea, vomiting) or ventricular or supraventricular tachycardias and bradyarrhythmias. Common rhythm disturbances include junctional or ventricular ectopic beats, varying grades of atrioventricular (AV) block, accelerated AV junctional rhythm, paroxysmal atrial tachycardia with block, excessively slow ventricular response to atrial fibrillation, or bidirectional ventricular tachycardia. The class IB antiarrhythmic lidocaine may be helpful in managing ventricular arrhythmias due to digoxin toxicity, and vagally mediated AV block in this setting often responds to atropine. Conversely, direct-current cardioversion can precipitate serious ventricular arrhythmias in patients with overt digitalis toxicity.

Owing to its significant binding to plasma proteins and its large volume of distribution, digoxin is not efficiently removed by dialysis. Conversely, in cases of life-threatening overdose, antidigoxin immunotherapy can prove lifesaving. Doses of purified antidigoxin antigen-binding fragments (Fab) are administered on the basis of estimated dose of digoxin ingested, or total body burden. Although rare, recurrence of toxicity can occur, usually 24 to 48 hours after administration of antidigoxin immunotherapy.

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ANSWER TO QUESTION 191

C (Braunwald, pp. 1142–1143, 1166, 1167–1168; Fig. 59.19)

Current American College of Cardiology/American Heart Association guidelines for the management of ST elevation myocardial infarction (MI) recommend a number of predischarge pharmacologic interventions to reduce mortality risk, including antiplatelet agents (aspirin plus a platelet $P2Y_{12}$ receptor antagonist), a beta blocker, a high-dose HMG-CoA reductase inhibitor, and an angiotensin-converting enzyme (ACE) inhibitor, especially when left ventricular dysfunction is present.[1] For acute MI patients with left ventricular ejection fraction ≤40% and clinical heart failure or diabetes, the addition of a mineralocorticoid receptor antagonist is recommended based on the results of the EPHESUS trial.[2] This study showed that compared with placebo, the mineralocorticoid antagonist eplerenone resulted in a 15% decrease in death from any cause and reduced hospitalizations for cardiovascular events.

Implantation of a defibrillator prophylactically for a low ejection fraction should be deferred until 40 days after a MI based on the results of the DINAMIT trial.[3] The other answer choices (amiodarone, warfarin, or supplementing an ACE inhibitor with the angiotensin receptor antagonist valsartan) have not demonstrated mortality benefits in the post-MI setting.

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ANSWER TO QUESTION 192

C (Braunwald, pp. 575–577; eTable 29.1)

This radiograph displays a continuous-flow left ventricular assist device (LVAD) in the center of the figure. This rotary, axial-flow pump is implanted below the diaphragm, with an inflow cannula inserted in the left ventricular apex and

an outflow cannula connected to the ascending aorta. Continuous-flow LVADs have a smaller profile, lower weight, and greater durability than earlier-generation pulsatile LVADs and very low mechanical failure rates. The HeartMate II continuous-flow LVAD is approved by the US Food and Drug Administration for use both as a bridge to cardiac transplantation and as permanent destination therapy in patients not eligible for transplantation. In a pivotal destination therapy trial, patients with a HeartMate II had an actuarial survival of 68% at 1 year and 58% at 2 years, a significant improvement over the earlier-generation pulsatile device.[1] As indicated in the Answer to Question 186, data from the recent MOMENTUM 3 trial indicates even better clinical outcomes with implantation of a fully magnetically levitated centrifugal flow pump (HeartMate 3) compared with an axial flow pump (HeartMate II), driven largely by the lesser need for reoperation for pump malfunction.

Despite improved pump design and survival, disabling strokes remain a common complication of continuous-flow LVAD therapy, with rates approaching 10% per year. Device-related infections are the second leading cause of death after cardiac failure. Bacterial pathogens dominate and are found most commonly in the blood or the percutaneous driveline. Device endocarditis requires systemic antibiotics and device explantation. Gastrointestinal bleeding is more common with continuous-flow LVADs compared with earlier-generation pulsatile pumps and may be related to either an acquired von Willebrand factor defect (secondary to shear-related damage of high-molecular-weight von Willebrand factor multimers) or to enhanced development of gastrointestinal arteriovenous malformations (possibly as a consequence of low pulse pressure). Bleeding complications may be further exacerbated by the requirement for both antiplatelet and anticoagulant therapy to prevent pump thrombosis and device-related thromboembolism.[2] Rates of pump thrombosis appear to be lower with the newest generation centrifugal flow pump (HeartMate 3).[3]

LVAD therapy is associated with a high rate of right-sided heart failure, which may prolong hospitalization and reduce survival. Right-sided heart failure may be the consequence of underlying right-sided heart disease and LVAD-related hemodynamic alterations. A continuous-flow LVAD generates increased right-sided venous return and can produce interventricular septal shifts that can further impair right ventricular performance.[4] Therefore, patients with preoperative right ventricular dysfunction may not be candidates for isolated left-sided mechanical support.

The device in the upper left chest in the radiograph is an implantable cardioverter-defibrillator.

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ANSWER TO QUESTION 193

D (Braunwald, pp. 1922–1923; see also Answer to Question 171)

Cardiorenal syndrome, or coexistent cardiac and renal dysfunction, is common in patients with heart failure.[1] Furthermore, 15% to 30% of patients develop worsening renal insufficiency during a heart failure hospitalization. This patient has several risk factors for deterioration of renal function with heart failure treatment including older age, diabetes, and baseline renal dysfunction. Management of her apparent diuretic resistance would be aided by delineation of her intravascular hemodynamics with a pulmonary artery (PA) catheter. While there is no role for routine PA catheterization in the management of acute decompensated heart failure (ADHF), current guidelines recommend consideration of hemodynamic assessment in patients who are refractory to initial therapy, including high-dose or combination diuretics.[2]

Adding a low-dose inotrope has not been shown to improve short-term outcomes in heart failure and may exacerbate this patient's ventricular arrhythmia. Empiric administration of nitroprusside without arterial monitoring is inadvisable given the patient's hypotension. Ultrafiltration as a rescue strategy in this context would not be a preferred option based on the results of the CARESS study.[3] This randomized trial of patients with ADHF, worsened renal function, and congestion compared a strategy of ultrafiltration with stepped pharmacologic therapy. Compared with patients treated pharmacologically, those randomized to ultrafiltration showed higher creatinine levels, no significant change in weight, and more adverse effects (e.g., renal failure, bleeding, and IV catheter complications).

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ANSWER TO QUESTION 194

D (Braunwald, pp. 543–546)

The chest radiographs illustrate a biventricular pacing system, implanted for the purpose of cardiac resynchronization therapy (CRT). Three pacing leads are present, including standard leads in the right atrium and right ventricle and a third lead placed via the coronary sinus (CS) into a lateral marginal vein for left ventricular (LV) pacing. For patients with left ventricular ejection fraction (LVEF) ≤0.35, prolonged QRS duration on the surface ECG, and symptomatic heart failure (class II to IV) despite optimal medical therapy, there is compelling evidence that CRT, either alone or with defibrillator capability, is associated with improvements in functional capacity, quality of life, and mortality. For example, the RAFT trial of CRT in patients with class II to III heart failure, ejection fraction ≤0.30, and prolonged QRS complex demonstrated a 25% reduction in all-cause mortality and a 32% reduction in heart failure hospitalizations, confirming the results previously shown in Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy.[1]

Improvements in ventricular mechanical delay with CRT are associated with reductions in the end-systolic volume index and mitral regurgitation and an augmented LVEF. These data support a potential "reverse remodeling" benefit of CRT in patients with heart failure and reduced ejection fraction.

To date, the QRS complex duration (a marker of delayed electrical activation) is the most extensively validated criterion in selection of patients for CRT. Although it is an imperfect surrogate for mechanical ventricular dyssynchrony, QRS complex duration predicts acute hemodynamic improvement after CRT, especially among patients with left bundle branch block in sinus rhythm.

Because the LV lead is typically placed over the surface of the left ventricle via a CS branch, inadvertent phrenic nerve stimulation and diaphragmatic pacing may complicate device implantation.

To achieve the clinical and hemodynamic benefits of CRT, biventricular pacing must be continuous. This is in distinction to isolated right ventricular apical pacing, a mode that can *contribute* to dyssynchrony and a higher risk of heart failure symptoms.[2]

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ANSWER TO QUESTION 195

C (Braunwald, pp. 464–465, 467–468)

Pulmonary edema is initiated by an imbalance of Starling forces. Such an imbalance results from (1) increased pulmonary capillary pressure, (2) *decreased* plasma oncotic pressure, (3) increased negativity of interstitial pressure, or (4) increased interstitial oncotic pressure. An increased pulmonary venous pressure (e.g., due to mitral stenosis or left ventricular failure) raises the pulmonary capillary pressure and can result in pulmonary edema.

High-altitude pulmonary edema may occur in individuals who rapidly ascend to altitudes >2500 meters and then perform strenuous physical exercise before they have become acclimated.[1] The pathogenesis appears to involve hypoxic pulmonary vasoconstriction leading to increased capillary pressure. Symptoms respond quickly to descent to a lower altitude or to administration of a high inspiratory concentration of oxygen.

Acute pulmonary edema may develop in women with preeclampsia or eclampsia, most commonly in the postpartum period.[2] Multiple factors likely contribute, including the increased afterload of acute systemic hypertension, hypervolemia, hypoalbuminemia, and increased vascular permeability.

Heroin overdose is a recognized cause of pulmonary edema. The mechanism is not known, but may relate to an alveolar-capillary membrane leak induced by the drug.

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ANSWER TO QUESTION 196

B (Braunwald, pp. 406–407; Table 21.4; pp. 468–469, 1731–1732)

Systolic dysfunction sets into motion a cascade of neurohormonal events that promote ventricular remodeling and progressive left ventricular cavity enlargement. As a consequence, cardiomegaly is common in patients with heart failure and reduced systolic function. However, many patients develop heart failure without systolic dysfunction. This group of patients with heart failure and preserved ejection fraction comprises a diverse group of patients with primary diastolic heart failure, pericardial disease, valvular heart disease, hypertrophic heart disease, or primary restrictive cardiomyopathy. These syndromes present with signs and symptoms of heart failure typically in the absence of cardiomegaly.

Analysis of the Studies of Left Ventricular Dysfunction treatment trial has demonstrated that the physical examination carries important prognostic information in patients with heart failure. In particular, elevated jugular venous pressure and a *third* heart sound are each independently associated with adverse outcomes, including progression of heart failure.[1]

Pulsus alternans is characterized by a regular rhythm with an alternating strong and weak peripheral pulse. It signifies advanced myocardial disease and is likely the result of cyclic alteration in left ventricular stroke volume due to incomplete myocardial recovery after contraction. It often disappears with successful treatment of heart failure.

The presence of fever in heart failure should always raise the possibility of underlying infection, pulmonary infarction, or infective endocarditis. In severe heart failure, low-grade fever may be seen as a consequence of cutaneous vasoconstriction and impairment of heat loss from sustained adrenergic nervous system activation. Sleep-disordered breathing is common in heart failure and is an independent risk factor for death and need for cardiac transplantation. *Central* sleep apnea, commonly manifested by Cheyne-Stokes breathing, is present in approximately 40% of patients with a reduced left ventricular ejection fraction, whereas *obstructive* sleep apnea is present in another 10%. Sleep-disordered breathing causes recurrent apnea-related hypoxemia and sleep arousal, contributing to chronic neurohormonal activation, peripheral vasoconstriction, and reduced cardiac performance.[2]

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ANSWER TO QUESTION 197

A (Braunwald, pp. 357–358)

The lung can be divided into three zones on the basis of the relationship between pulmonary arterial, alveolar, and pulmonary venous pressures. In zone 1 (at the apex), the alveolar pressure exceeds both pulmonary arterial and pulmonary venous pressures, so that there is ventilation without perfusion (dead space). In zone 2, alveolar pressure

exceeds the venous but not the arterial pressure at some stage of the respiratory cycle. In zone 3, the alveolar pressure does not exceed either arterial or venous pressures. Zone 3 alveoli are therefore the best perfused and in the upright patient are situated in the dependent areas of the lung.

Measurement of the pulmonary capillary wedge pressure using a balloon-tipped catheter will be misleading if the catheter tip is wedged in a zone 1 or zone 2 arterial branch. In these zones, the wedge pressure measures alveolar pressure rather than the true left atrial pressure. In most spontaneously breathing patients, a flow-directed balloon-tipped catheter is naturally directed to zone 3 (because these areas are best perfused) and the pulmonary artery occlusion pressure is a truer estimate of the left atrial pressure.

Pulmonary vascular redistribution on the chest radiograph reflects a relative reduction of perfusion of the bases and a relative increase in apical perfusion. This phenomenon is likely due to compression of vessels at the lung bases owing to dependent edema in that zone.

ANSWER TO QUESTION 198

B (Braunwald, p. 562)

The calcineurin inhibitors (cyclosporine and tacrolimus) interfere with T-cell activation and have become the cornerstone of immunosuppression in solid organ transplantation. Despite reducing episodes of rejection and prolonging survival after transplantation, cyclosporine use is associated with a number of potential complications. Hypertension and nephrotoxicity are common, and cyclosporine levels must be monitored carefully to limit progressive renal failure. Adverse gastrointestinal tract side effects include hepatotoxicity and cholelithiasis, leading to dose-dependent abnormalities in liver function tests. Fine tremors, paresthesias, and occasionally seizures are potential neurologic side effects of cyclosporine therapy. Many patients who receive cyclosporine develop hypertrichosis (hirsutism) or gingival hyperplasia. The latter complication is reported to occur more frequently in those treated simultaneously with nifedipine. Myelosuppression in transplant patients is most commonly associated with azathioprine, not cyclosporine.

Tacrolimus has a different side-effect profile. Hirsutism and gingival hyperplasia do not occur with tacrolimus, and this drug is associated with a lower incidence of hypertension and dyslipidemia than cyclosporine. However, hyperglycemia and neurologic toxicity may be more common with tacrolimus.

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ANSWER TO QUESTION 199

D (Braunwald, pp. 470–472, 479–481; Fig. 24.6)

Acute heart failure syndromes (AHFS) are responsible for >1 million hospitalizations annually in the United States. Systolic blood pressure is usually normal or high (≥180 mm Hg) in patients with AHFS regardless of ejection fraction, likely related to enhanced sympathetic tone. Fewer than 10% of patients are hypotensive (<90 mm Hg), usually in association with advanced left ventricular (LV) systolic dysfunction and reduced cardiac output (CO). Patients with low CO may benefit hemodynamically from infusion of intravenous inotropes with vasodilating properties, such as the phosphodiesterase-3 inhibitor milrinone for short-term support. However, milrinone use has not been shown to improve hospital mortality rates and can be associated with hypotension, arrhythmias, and myocardial ischemia. It should be used only for patients who do not respond to diuretics and noninotropic vasodilators.[1]

Vasopressin (antidiuretic hormone) mediates (1) vasoconstriction via binding to the V_{1a} receptor on vascular smooth muscle, and (2) free water retention via the V_2 receptor at the renal collecting duct. Vasopressin levels are elevated in both acute and chronic heart failure and are thought to be a major contributor to hyponatremia, an adverse prognostic marker. Tolvaptan, an orally available V_2 receptor antagonist, has been shown to improve the pulmonary capillary wedge pressure and to normalize serum sodium concentrations. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial failed to demonstrate a reduction in mortality or re-hospitalizations for heart failure with use of this agent.[2]

Initial management of AHFS with noninvasive ventilation reduces respiratory distress and improves LV function by lowering afterload. Noninvasive mask ventilation may be administered by continuous positive airway pressure or noninvasive intermittent positive-pressure ventilation. The Three Interventions in Cardiogenic Pulmonary Oedema trial demonstrated that noninvasive ventilation improves dyspnea, hypercapnia, and acidosis compared with standard therapy, but does not reduce mortality or the need for intubation in patients with pulmonary edema.[3]

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ANSWER TO QUESTION 200

C (Braunwald, pp. 442–444; Fig. 23.1)

Neurohormonal activation is an important aspect of heart failure syndromes.[1] Although initially a beneficial compensatory response to falling cardiac output (CO), sustained neurohormonal activation ultimately contributes to ventricular remodeling and heart failure progression. Neurohormonal modulation is consequently a cornerstone of heart failure treatment.

Reduced CO in patients with heart failure triggers adrenergic nervous system stimulation and increased norepinephrine (NE) release. The degree of elevation in the plasma NE concentration correlates with the severity of left ventricular dysfunction, and plasma NE levels are a potent predictor of mortality in heart failure patients. Low forward CO also activates the renin-angiotensin system,

increasing circulating levels of angiotensin II and aldosterone and promoting salt and water retention. Increased preload and afterload in the failing heart contribute to mechanical atrial and ventricular stretch, which triggers the release of natriuretic peptides. These peptides, in particular atrial natriuretic peptide and B-type natriuretic peptide, promote compensatory vasodilatation and natriuresis. Circulating levels of inflammatory cytokines, including tumor necrosis factor-alpha, are also increased in heart failure and may contribute to the cachexia seen in patients with end-stage disease.[2]

In typical patients with heart failure, there is progressive *downregulation* of cardiac beta-adrenergic receptors, proportional to disease severity, likely mediated by increased circulating NE levels.

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ANSWER TO QUESTION 201

D (Braunwald, pp. 563–566)

Mortality from infection accounts for approximately 20% of deaths over the first year after transplantation.[1] Infections in the first postoperative month tend to involve nosocomial bacterial and fungal pathogens. Later post-transplantation infections are more diverse and involve opportunistic infections such as cytomegalovirus (CMV), herpes simplex, *Candida, Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), *Nocardia*, and *Toxoplasma gondii*.

CMV infection is one of the most frequent post-transplantation infections. CMV-negative recipients who receive a CMV-positive allograft are at highest risk, but prior seropositivity does not fully protect against this complication. Prophylactic therapy with trimethoprim-sulfamethoxazole (TMP-SMZ) is prescribed to prevent infections by *Pneumocystis* and *T. gondii*. For patients allergic to TMP-SMZ, oral atovaquone prophylaxis against *Pneumocystis* pneumonia is commonly prescribed.

Allograft rejection is a very important potential complication of heart transplantation, but the likelihood is substantially reduced with effective immunosuppression. Immunologic tolerance to the donor organ develops in the recipient over time, making rejection less likely, which permits a gradual decrease in the intensity of immunosuppressive drugs.

More than 1 year from heart transplantation, the leading cause of death is the development of coronary artery disease in the allograft. It is pathologically distinct from typical atherosclerosis and is associated with intimal hyperplasia and smooth muscle cell proliferation that lead to progressive obliteration of the vessel lumen and loss of tertiary branching.[2] Patients with CMV infection appear to be at higher risk. The diagnosis of this complication is established by surveillance angiography, which is typically performed on an annual basis in patients after transplantation.

Transplant recipients have a markedly increased incidence of various cancers compared with age-matched controls. This increased risk is related to the intensity and chronicity of immunosuppression therapy. Skin cancers are the most common malignancy after transplantation, followed by lymphoproliferative disorders (which are associated with Epstein-Barr virus infection, not CMV). Other common malignancies after transplantation include adenocarcinomas of the prostate, lung, bladder, and kidney.

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ANSWER TO QUESTION 202

D (Braunwald, pp. 573–574; Fig. 29.1)

The intra-aortic balloon (IAB) is a catheter-mounted counterpulsation device that is most commonly inserted percutaneously through the common femoral artery and positioned in the descending aorta just distal to the left subclavian artery. The balloon timing should be adjusted such that inflation occurs at the dicrotic notch of the arterial pressure waveform, which coincides with the timing of aortic valve closure. The resultant diastolic rise in aortic pressure increases coronary blood flow. The IAB is timed to deflate during the isovolumic phase of left ventricular (LV) contraction. That relative reduction of afterload decreases peak LV pressure and myocardial oxygen consumption.

IAB counterpulsation improves aberrant hemodynamics in cardiogenic shock after cardiac surgery, acute myocardial infarction (MI), or during high-risk coronary interventions.[1] IAB therapy is indicated for stabilization of patients compromised by mechanical complications of acute MI such as mitral regurgitation or ventricular septal defect. IAB may also be useful as a treatment of refractory angina or ventricular arrhythmias and as a means to stabilize critically ill patients awaiting cardiac transplantation before insertion of a ventricular assist device. Of note, the SHOCK II trial showed that IAB therapy did not reduce 30-day mortality in comparison to medical therapy among patients with acute MI complicated by cardiogenic shock for whom early revascularization was planned.[2] Whether IAB therapy reduces mortality of cardiogenic shock in conditions other than acute MI remains unanswered. Absolute contraindications to the use of an IAB include aortic valve *insufficiency* and aortic dissection. An IAB should not be inserted via the femoral artery in patients with an abdominal aortic aneurysm or severe calcific aortoiliac or femoral arterial disease.

Major complications of IAB therapy include limb ischemia, aortic dissection, aortoiliac laceration or perforation, and deep wound infection.

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ANSWER TO QUESTION 203

A (Braunwald, pp. 504–511)

The annual mortality rate of patients with ventricular dysfunction and heart failure ranges from 2% to 5% in asymptomatic patients (class I) to greater than 25% in those who are severely symptomatic (class IV).

Many clinical trials have confirmed that angiotensin-converting enzyme (ACE) inhibitors should be the mainstay of treatment for patients with left ventricular (LV) dysfunction. In patients with asymptomatic LV dysfunction (class I), ACE inhibitors slow progression to symptomatic heart failure. In patients who have established symptomatic heart failure (class II to IV), ACE inhibitors significantly reduce mortality. For individuals who are intolerant of ACE inhibitors, an angiotensin receptor blocker (ARB) or the combination of hydralazine plus long-acting nitrates should be considered, because both of these strategies have shown outcome benefits in patients with symptomatic heart failure. The CHARM trial demonstrated that ARB therapy results in comparable outcomes as ACE inhibition in patients with chronic heart failure.[1] The use of a combined ARB and neprilysin inhibitor, sacubitril/valsartan, has been shown to reduce mortality more than enalapril in patients with heart failure and reduced ejection fraction, and this combination is now recommended to replace ACE inhibitors or ARBs in selected patients with heart failure and reduced ejection fraction.[2] In heart failure patients of African American descent, data from the A-HeFT trial show that addition of hydralazine plus isosorbide dinitrate to standard therapy results in improved clinical endpoints.[3] Beta blockers (in particular, carvedilol or metoprolol succinate) should also be prescribed to heart failure patients in stable condition (those without substantial fluid retention or recent episodes of acute decompensation requiring inotropic therapy).

The Digitalis Investigation Group trial demonstrated that digoxin decreases hospitalizations for heart failure in patients with class II to IV symptoms, but has no effect on overall mortality. The RALES trial showed that the addition of spironolactone to standard heart failure therapy decreases mortality in patients with advanced (class III to IV) symptoms.[4]

Historically, patients with chronic heart failure were instructed to avoid physical exercise and to rest in bed. This practice is no longer recommended because regular exercise has been shown to improve functional capacity. In addition, exercise may improve excessive neurohormonal activation and quality of life. However, moderate levels of exercise have not been demonstrated to improve the natural history of heart failure.[5]

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ANSWER TO QUESTION 204

B (Braunwald, pp. 686–687; Tables 36.1, 36.3, 36.4)

Intravenous administration of adenosine slows the sinus rate and conduction through the atrioventricular (AV) node, causing transient AV block. Its AV nodal effects, in combination with its extremely short half-life (1.5 seconds), make adenosine a safe and effective drug for the diagnosis and treatment of reentrant supraventricular tachycardias (SVTs) involving the AV node. Atrioventricular nodal reentrant tachycardia and atrioventricular reentrant tachycardia nearly always terminate after adenosine administration. In addition, the transient AV block induced by adenosine may help to unmask other underlying supraventricular arrhythmias such as atrial tachycardia or atrial flutter. Because of its short half-life, adenosine must be administered as a *rapid* intravenous bolus to achieve adequate blood and tissue levels. Short duration of action also implies a brief period of side effects, which differentiates adenosine from other drugs (e.g., beta blockers, calcium channel blockers) that are used to treat SVTs.

Adenosine may also be helpful in the differentiation of wide-QRS complex tachycardias. Ventricular tachycardia (VT) is usually unaffected by adenosine (except rare forms of RV outflow VT), whereas SVT with aberrant conduction will either terminate or be exposed by transient AV block after adenosine. However, a theoretical risk of adenosine use in these patients is acceleration of conduction through an accessory pathway, if one is present, as in patients with Wolff-Parkinson-White syndrome. Transient side effects are common with adenosine, occurring in up to 40% of patients. The most common are dyspnea, chest pressure, and flushing, all of which are fleeting and generally resolve within 1 minute. Adenosine may provoke bronchospasm in patients with severe asthma or obstructive lung disease. Patients after heart transplantation are particularly sensitive to the effects of adenosine, and appropriate caution should be exercised in this population. Since caffeine and theophylline antagonize the adenosine receptor, adenosine is less likely to be effective in patients with recent exposure to these substances.

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ANSWER TO QUESTION 205

C (Braunwald, pp. 719–721, 753–754)

Premature ventricular complexes (PVCs) are common and their prevalence increases with age. Their frequency may be exacerbated by a variety of factors, including electrolyte imbalances (especially hypokalemia and hypomagnesemia), infection, hypoxia, and excessive use of tobacco, caffeine, or alcohol. In the absence of structural heart disease, isolated

PVCs have no impact on survival. Conversely, after myocardial infarction (MI), PVCs identify patients who are at increased risk for ventricular tachycardia or sudden death. In the Cardiac Arrhythmia Suppression trial, the use of class IC antiarrhythmic drugs (encainide and flecainide) to suppress asymptomatic ventricular arrhythmias after acute MI was associated with an *increased* rate of death, and such agents should not be used in the setting of coronary artery disease.

Approximately 30% of patients with paroxysmal supraventricular tachycardias referred for electrophysiologic study are found to have a concealed accessory pathway, most commonly between the left ventricle and the left atrium. These concealed pathways conduct unidirectionally from the ventricles to the atria, but not in the opposite direction. Thus, the ventricle is not preexcited and the ECG does not demonstrate a delta wave during normal sinus rhythm. Nonetheless, concealed pathways may participate in reentrant AV tachycardias. This mechanism should be suspected during tachycardias when the QRS complex is of normal width (due to anterograde conduction down the atrioventricular node) and the retrograde P wave occurs after completion of the QRS complex, in the ST segment or T wave.

ANSWER TO QUESTION 206

D (Braunwald, pp. 767–768; Fig. 39.11; eFig. 39.1; pp. 820–821)

The ECG demonstrates right bundle branch block with prominent ST-segment elevation in the anterior precordial leads, typical of Brugada syndrome. This condition can lead to sudden cardiac death due to ventricular fibrillation despite the fact that the heart is structurally normal.[1] The clinical presentation is distinguished by male predominance and appearance of arrhythmic events at an average age of 40 years. It is believed that this syndrome accounts for 40% to 60% of cases of idiopathic ventricular fibrillation. In many families the syndrome segregates in an autosomal dominant fashion and is associated with loss of function mutations in the sodium channel *SCN5A*.[2] Screening of family members, including an ECG, is therefore important. Pharmacologic therapies are not effective in treating ventricular arrhythmias associated with Brugada syndrome. Administration of procainamide may be useful in bringing out the typical electrocardiographic phenotype in patients with a history of aborted sudden cardiac death (SCD) and an equivocal ECG. Implantation of a defibrillator is the therapy of choice for patients with Brugada syndrome with a history of aborted SCD or spontaneous ventricular tachycardia/ventricular fibrillation (VT/VF) (class I indication) or history of syncope (class IIa indication). ICD implantation can also be considered for patients with a Brugada pattern on the ECG and inducible VT/VF with ≤2 extra stimuli at electrophysiologic testing.[3]

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ANSWER TO QUESTION 207

E (Braunwald, pp. 787, 803–805; see also Answer to Question 180)

The preferred therapy for survivors of cardiac arrest at risk for recurrence is an implantable cardioverter-defibrillator (ICD), rather than antiarrhythmic drug therapy.[1] Among survivors of out-of-hospital cardiac arrest not associated with a myocardial infarction (MI), the risk of recurrent cardiac arrest after 1 year is 30% and after 2 years it is about 45%. In the Antiarrhythmics Versus Implantable Defibrillators trial, ICD implantation resulted in a 27% relative risk reduction in total mortality over 2 years of follow-up.

A number of studies directed at the primary prevention of sudden cardiac death (SCD) in high-risk patients have been reported. In patients with left ventricular (LV) dysfunction (ejection fraction ≤30%) and prior history of MI, prophylactic ICD implantation is associated with a reduction in all-cause mortality.[2] Defibrillator implantation also reduces death rates in patients with symptomatic systolic heart failure from nonischemic causes. In the Sudden Cardiac Death in Heart Failure Trial of patients with class II to III heart failure and left ventricular ejection fraction ≤35%, ICD implantation reduced overall mortality by 23% and was superior to amiodarone therapy.[2]

ICDs are also an appropriate consideration in primary and secondary prevention of SCD in high-risk individuals with hypertrophic cardiomyopathy. High-risk features include a history of syncope, a family history of SCD, the presence of marked LV hypertrophy (wall thickness >30 mm), and the finding of nonsustained ventricular tachycardia on noninvasive monitoring.[3]

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ANSWER TO QUESTION 208

A (Braunwald, pp. 775–779)

Atrioventricular (AV) block is present when atrial impulses are conducted to the ventricles with abnormal delay or are not conducted at all. There are three categories. *First-degree AV block* is present when the PR interval is prolonged (>0.20 second) in a constant fashion and every atrial impulse conducts to the ventricle. In *second-degree heart block*, some impulses fail to conduct from the atria to the ventricles. Second-degree block is divided into two groups: *Mobitz type I* and *Mobitz type II*. In the former type (also termed *Wenckebach block*), the PR interval progressively increases (and the RR interval usually progressively shortens) until an atrial impulse fails to conduct to the ventricles. In Mobitz type II block, the PR intervals are constant and without warning there is intermittent failure of an atrial impulse to conduct to the ventricles. *Third-degree heart block* is present when

all atrial impulses fail to conduct to the ventricles such that the atrial and the ventricular rhythms are independent of one another.

In first-degree heart block, the delay between atrial and ventricular contraction allows the leaflets of the mitral and tricuspid valves to drift toward a partially closed position prior to ventricular systole. Therefore, the intensity of the first heart sound is *diminished*. First-degree heart block and Mobitz type I second-degree heart block often arise in normal healthy adults and well-trained athletes, owing to increased vagal tone.

Mobitz type I second-degree heart block with a normal QRS duration almost always occurs at the level of the AV node, proximal to the His bundle. Conversely, type II second-degree heart block, especially when accompanied by a bundle branch block QRS morphology, usually reflects a more serious abnormality in the His-Purkinje system.

In third-degree heart block there is complete AV dissociation. As a result, the ventricular rate is governed not by the atrial rate but by an independent ventricular escape pacemaker. In acquired forms of third-degree heart block, the ventricular rate is usually <40 beats/min. The ventricular rate tends to be faster in patients with congenital complete heart block, about 50 beats/min.

ANSWER TO QUESTION 209

D (Braunwald, pp. 652–654)

Prolonged ambulatory electrocardiographic (Holter) monitoring of patients engaged in normal daily activity is useful to document the nature and frequency of underlying cardiac arrhythmias and to correlate a patient's symptoms with rhythm disturbances. Although significant rhythm disturbances are uncommon in healthy persons, a variety of arrhythmias, including sinus bradycardia (with rates as low as 35 beats/min), sinus arrhythmia, sinoatrial exit block, type I second-degree atrioventricular block (especially during sleep), and junctional escape complexes may be seen in normal persons. In addition, the prevalence of arrhythmias in normal subjects increases with older age. Persons with ischemic heart disease, especially those recovering from acute myocardial infarction (MI), exhibit ventricular premature beats (VPBs) when long-term recordings of the heart rhythm are obtained. The frequency of VPBs increases over the first several weeks after infarction and decreases about 6 months after infarction. Frequent and complex ventricular ectopy is associated with a twofold to fivefold increased risk of sudden cardiac death after MI.

Long-term electrocardiographic recordings are useful for the detection of underlying rhythm disturbances in patients with hypertrophic cardiomyopathy and mitral valve prolapse, as well as in patients who have unexplained syncope or transient cerebrovascular symptoms. In normal subjects and in patients with underlying rhythm disturbances, the cardiac rhythm may vary dramatically from one long-term recording period to the next.

On many occasions, the relatively brief period of recording provided by standard Holter monitoring (24 to 48 hours) may be inadequate to identify an abnormal rhythm responsible for a patient's symptoms. Longer-term monitoring in such patients, using an external event recorder, may help to establish a diagnosis. For patients with very infrequent symptoms, implantable loop recorders may be appropriate as they can remain in place for months or years. These devices have proven useful in establishing a diagnosis in patients with recurrent syncope and prior unrevealing evaluations.

Long-term monitoring has demonstrated a high frequency of asymptomatic recurrences of atrial fibrillation in patients treated for that condition. The frequency of asymptomatic episodes exceeds that of symptomatic episodes, which has important implications for the risk of discontinuing anticoagulant medications.

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ANSWER TO QUESTION 210

D (Braunwald, pp. 848–851)

Syncope may result from vascular, cardiac, neurologic, and metabolic causes. Vascular causes of syncope are the most common, accounting for about one-third of all episodes. Vascular causes include orthostatic hypotension and reflex-mediated syncope, such as carotid sinus hypersensitivity and neurocardiogenic (vasovagal) syncope.

Cardiac abnormalities, especially tachyarrhythmias and bradyarrhythmias, represent the second most common causes of syncope, accounting for 10% to 20% of episodes. Ventricular tachycardia is the rhythm disorder that most frequently causes loss of consciousness. Bradyarrhythmias such as sick sinus syndrome and advanced atrioventricular blocks can also result in syncope, but less commonly. Supraventricular tachycardias are much more likely to present as less severe symptoms such as palpitations or light-headedness rather than loss of consciousness. Although the prognosis of patients with noncardiac causes of syncope tends to be benign, those who have syncope of cardiac origin have a 30% mortality rate over the next year.

The history and physical examination are the most important part of the evaluation of patients presenting with syncope. Studies estimate that, in up to one-fourth of cases, an accurate diagnosis can be made on the basis of history and physical examination alone. The ECG is the most useful initial diagnostic test; any abnormality of the baseline ECG in patients with syncope is an independent predictor of mortality and indicates the need to pursue a cardiac etiology.

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ANSWER TO QUESTION 211

D (Braunwald, pp. 783–784; Table 41.1)

The most common nomenclature for pacemaker coding uses a four-letter code. The first position reflects the chamber

that is being paced (O = none, A = atrium, V = ventricle, D = dual [both atrium and ventricle are paced]); the second position reflects the chamber being sensed (O, A, V, and D as above); the third position corresponds to the response to sensing (O = none, T = triggered, I = inhibited, D = dual); and the fourth position reflects programmability and rate modulation (e.g., O = none, R = rate modulation). As an example, a patient with a dual-chamber, rate-adaptive pacemaker would have a DDDR code.

Rate-adaptive pacemakers incorporate a sensor that can modulate the pacing rate independently of intrinsic cardiac activity by monitoring physiologic processes such as physical activity or minute ventilation. Mode switching is a useful feature in which the pacemaker mode automatically changes (e.g., from DDDR to DDIR) in response to inappropriate rapid atrial rhythms. This is particularly beneficial for patients with paroxysmal supraventricular tachyarrhythmias, such as atrial fibrillation or flutter, to avoid rapid ventricular pacing during those episodes.

"Pacemaker syndrome" refers to the deterioration of hemodynamics with associated patient symptoms, or a limitation of optimal functional status, despite a normally functioning pacing system. This is observed most commonly with ventricular inhibited pacing, but may occur in any pacing mode in which atrioventricular (AV) synchrony is lost. Patients may experience a sensation of fullness in the head and neck, syncope or presyncope, hypotension, cough, dyspnea, congestive heart failure, or weakness. Physical findings include cannon *a* waves in the jugular venous pulsations and a fall in blood pressure during pacing compared with normal sinus rhythm (Fig. 2.22). Symptomatic AV block of any kind (including Wenckebach) is an indication for permanent pacing. In patients with hypertrophic cardiomyopathy, dual-chamber pacing has been shown to reduce the left ventricular outflow tract gradient and lead to symptomatic improvement in some trials. There is, however, a significant placebo effect from pacing, and other studies have not confirmed clinical benefit. Thus, the American College of Cardiology/American Heart Association guidelines consider pacemaker placement a class IIb indication in patients with medically refractory hypertrophic cardiomyopathy and significant outflow tract obstruction.

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ANSWER TO QUESTION 212

D (Braunwald, p. 787; eFig. 41.9)

Pacemaker-mediated tachycardia (PMT), or endless loop tachycardia, is a syndrome of upper rate behavior that occurs when there is intact ventriculoatrial conduction resulting in retrograde P waves. If these retrograde P waves are sensed by the atrial sensing circuit, the pacemaker atrioventricular interval is initiated and a paced ventricular contraction follows, which generates another retrograde P, and so on, generating a perpetual "loop." The diagnosis should be suspected in patients with a dual-chamber device who present with a paced tachycardia near the maximum tracking limit of the device. It is managed by *increasing* the postventricular atrial refractory period, which prevents atrial sensing of the retrograde P wave. Because episodes of PMT are often triggered by a premature ventricular complex (PVC), some commercially available devices offer automatic extension of the postventricular refractory period after a PVC.

ANSWER TO QUESTION 213

D (Braunwald, pp. 742–743)

Postoperative atrial fibrillation (AF) occurs in up to 40% of patients undergoing coronary artery bypass grafting or valvular surgery. This dysrhythmia is associated with an increased stroke risk in this setting and is the most common cause of prolonged hospitalization after cardiac surgery.[1] Risk factors for postoperative AF include advanced age (>70 years), male gender, diabetes, obesity, chronic lung disease, and left ventricular dysfunction. Several antiarrhythmic drugs have been shown to reduce the risk of developing AF after cardiac surgery. Oral beta blockers such as metoprolol lower the risk by 31%.[2] Other effective prophylactic antiarrhythmic agents are the class III agents amiodarone and sotalol. Digoxin may have a role in rate control of AF when it occurs, but has not been shown to prevent postoperative AF. Atrial pacing using temporary electrodes attached to either the right atrium or both atria reduces the probability of postoperative AF.

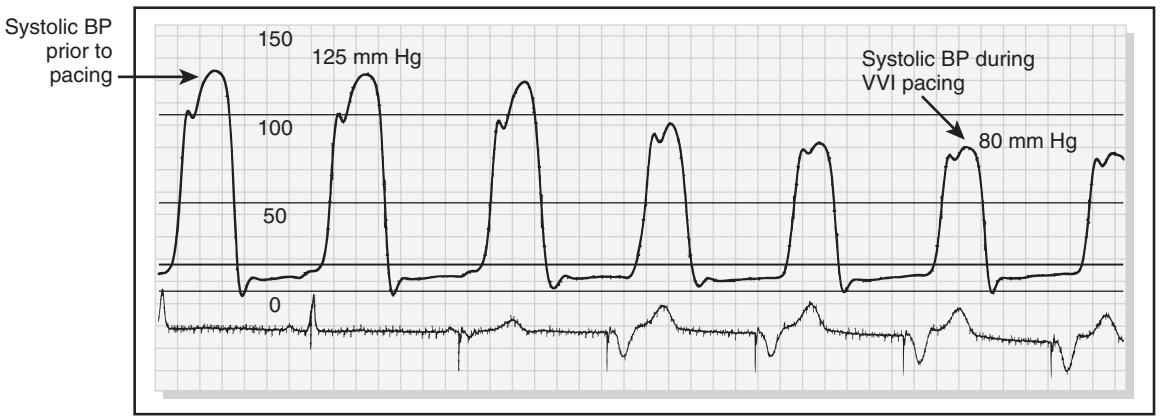

FIG. 2.22

Atorvastatin, an HMG-CoA reductase inhibitor, has been shown to reduce postoperative AF by 62%, an effect that is likely independent of its lipid-lowering properties.[3] Other agents that have also been shown in randomized trials to reduce the incidence of postoperative AF are hydrocortisone and colchicine (in patients who tolerate and continue the drug), presumably through their anti-inflammatory effects.[4,5]

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ANSWER TO QUESTION 214

D (Braunwald, pp. 676–677)

Procainamide, a class IA antiarrhythmic agent, is effective in the management of both supraventricular and ventricular arrhythmias. As a sodium channel-blocking agent, it acts to depress phase 0 depolarization, thereby slowing conduction. In addition, it has moderate potassium channel-blocking activity (largely owing to the action of its metabolite *N*-acetyl-procainamide), which leads to slowing of repolarization and prolongation of the action potential duration. A widened QRS complex duration is seen at therapeutic concentrations owing to slowing of conduction in the Purkinje system and ventricular muscle. QT interval prolongation occurs with rising serum concentrations and may precipitate ventricular arrhythmias.

In patients with atrial fibrillation (AF) or flutter, procainamide may lead to chemical cardioversion to normal sinus rhythm. Otherwise, since procainamide slows the atrial rate, it may facilitate rapid 1:1 conduction through the atrioventricular node and increase the ventricular response rate in atrial flutter or fibrillation unless a nodal blocking agent (e.g., a beta blocker) is co-administered. In patients with AF and Wolff-Parkinson-White syndrome, procainamide is effective at prolonging the effective refractory period of the bypass tract and suppresses extranodal atrioventricular conduction.

Multiple noncardiac side effects of procainamide have been reported, including rashes, myalgias, digital vasculitis, Raynaud phenomenon, gastrointestinal side effects, and central nervous system toxicity. Higher doses of the drug may depress myocardial contractility and diminish myocardial performance; rapid intravenous administration has been associated with hypotension due to a reduction in systemic vascular resistance. Chronic administration of procainamide is associated with a positive antinuclear antibody in almost all patients, particularly slow acetylators. However, symptoms of drug-induced lupus (arthritis, arthralgias, pleuritis) occur only in 15% to 20% of patients. Many of these patients exhibit positive antihistone antibodies, and the syndrome resolves after drug discontinuation.

ANSWER TO QUESTION 215

B (Braunwald, pp. 656–659)

Invasive electrophysiologic study (EPS) is employed for the evaluation of patients with disturbances of cardiac rhythm and conduction. It provides information about the type of rhythm abnormality and its electrophysiologic mechanism. Therapeutically, it is possible during EPS to terminate tachycardias by electrical stimulation, to evaluate the effects of antiarrhythmic therapies, and to ablate myocardium responsible for tachycardias.

EPS is the gold standard for evaluation of arrhythmic causes of syncope, including the three most common: sinus node dysfunction, His-Purkinje block, and tachyarrhythmias. Of the three, tachyarrhythmias are most reliably initiated in the electrophysiology laboratory, followed by sinus node abnormalities and His-Purkinje block.

EPS allows the measurement of intracardiac conduction times and the sequence of myocardial activation using catheter electrodes capable of sensing and pacing. In patients with acquired atrioventricular (AV) block and related symptoms, EPS evaluates the length of the His-ventricular (HV) interval, in order to assess infranodal conduction abnormalities that might prompt pacemaker implantation. HV intervals >55 milliseconds are associated with organic heart disease, a greater likelihood of developing trifascicular block, and higher mortality.

EPS is helpful in the management of patients with suspected sinus node dysfunction. The sinus node recovery time (SNRT) is used to assess the effects of overdrive suppression on sinus node automaticity. The SNRT is measured by subtracting the spontaneous sinus node cycle length before pacing from the time delay to the first spontaneous sinus response after termination of pacing. Normal values are generally <525 milliseconds, and prolongation of the SNRT suggests abnormal sinus node function. Because many patients with impaired sinus node function also exhibit abnormal AV conduction, it is important also to evaluate AV nodal and His-Purkinje function in this population.

In patients with wide-QRS complex tachycardias, EPS may be used to differentiate supraventricular tachycardia (SVT) with aberrancy from ventricular tachycardia, because the sequence of, and relation between, atrial and ventricular activation can be determined. SVTs are characterized in part by the presence of an HV interval during tachycardia equal to or greater than that recorded during normal sinus rhythm. Shortening of the HV interval during tachycardia suggests either VT or the presence of an accessory pathway. EPS is also used to locate and ablate accessory pathways in preexcitation syndromes. Left lateral accessory pathways are most common (~50%), followed by posteroseptal, right anteroseptal, and right lateral locations.

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ANSWER TO QUESTION 216

B (Braunwald, p. 683)

Dronedarone is an antiarrhythmic drug derived from amiodarone and the two agents share electrophysiologic properties, including blockade of the delayed rectifier potassium current (class III effect), inhibition of the rapid sodium and L-type calcium currents, and antiadrenergic effects. However, unlike amiodarone, dronedarone does not contain iodine molecules, a property that likely accounts for its much lower rate of thyroid and pulmonary toxicity.

Dronedarone is indicated for maintenance of sinus rhythm in patients with a history of atrial fibrillation (AF) or flutter.[1] It is orally absorbed, is hepatically metabolized, and has a much shorter elimination half-life than amiodarone (only 13 to 19 hours). Like amiodarone, the QT interval may become prolonged, but the risk of proarrhythmia is small.

In the Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Heart Failure Evaluating Morbidity Decrease, patients on dronedarone had *increased* mortality compared with those taking a placebo (8.1% vs. 3.8%); thus, the drug should *not* be used in patients with recent or current heart failure.[2] In addition, in distinction to patients who maintain sinus rhythm on the drug, dronedarone is associated with increased mortality when prescribed to patients who have permanent atrial fibrillation (e.g., for rate control).[3]

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ANSWER TO QUESTION 217

B (Braunwald, pp. 738–741)

Early techniques of AF ablation were aimed at eliminating sites of initiating premature atrial contractions at their origin deep within the pulmonary veins, the site of origin of AF in many patients. However, only a small number of patients have sufficient atrial premature beats to serve as such a target, and ablation deep within these veins can result in pulmonary vein stenosis. Subsequently, techniques shifted to electrical isolation of the pulmonary veins by creating a circumferential line of block encircling the venous ostia, so as to prevent spread of impulses from the site of initiation to the remainder of the atria. At high-volume centers, single-procedure success rates (freedom from recurrences after 1 year) are 70% to 75% in patients with paroxysmal AF and 50% to 60% in patients with persistent AF. These success rates improve with additional follow-up ablation procedures. Success rates appear to be similar independent of the ablation technique used (radiofrequency catheter or cryoballoon).

Candidates for AF ablation are those without significant structural heart disease in whom AF interferes with quality of life. Catheter ablation is usually not appropriate for patients with AF who are asymptomatic. For symptomatic patients, it is usually appropriate to attempt AF control with at least one antiarrhythmic agent before proceeding to ablation. However, ablation may be appropriate first-line therapy for young individuals with symptomatic AF, those with sinus node dysfunction for whom antiarrhythmic drugs may cause significant bradycardia, and for patients who decline to take pharmacologic therapy. Since AF can recur after a successful ablation procedure, the need for ongoing anticoagulation is determined by the risk of stroke as estimated by the CHA_2DS_2-VASc score (summarized in the answer to question 218), rather than the presence or absence of symptoms.

Major complications occur in 5% to 6% of patients after catheter ablation for AF. The most common are cardiac tamponade, pulmonary vein stenosis, and cerebral thromboembolism, each of which occurs in approximately 1% of patients. Left atrial-esophageal fistula (not atrial-tracheal fistula) has been reported as a rare, but potentially lethal, complication of ablation in the posterior left atrium.

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ANSWER TO QUESTION 218

D (Braunwald, pp. 734–735; Fig. 38.6)

Stroke prevention is a major goal of therapy in patients with atrial fibrillation (AF). Because of the risk of hemorrhage, anticoagulants are reserved for patients with a risk of thromboembolism greater than that of bleeding. Thus, risk estimators have been developed for nonvalvular AF on the basis of clinical history, including the CHA_2DS_2-VASc score, which accurately discriminates between low-risk and intermediate-risk patients.[1,2] In this scoring system, the presence of congestive heart failure, hypertension, diabetes, female gender, vascular disease, and age ≥65 years are each assigned 1 point, while age ≥75 years and prior stroke (or transient ischemic attack) are assigned 2 points each. The higher the number of total points, the greater the stroke risk, and in general a score >1 warrants anticoagulation therapy.[1] The patient in this case vignette has a CHA_2DS_2-VASc score of 5 (hypertension, age ≥75 years, diabetes, and female gender), which corresponds to an annual stroke rate of ~4% (Fig. 2.23) such that prescription of therapeutic anticoagulation is appropriate.

If warfarin were chosen as the anticoagulant, the target INR for this patient would be 2.0 to 3.0. A higher target range of 2.5 to 3.5 for a patient in AF would be recommended in the presence of a mechanical mitral or aortic valve prosthesis. Antithrombotic therapy with either single- or dual -antiplatelet therapy is insufficient to prevent stroke in this high-risk patient.

The non-vitamin K antagonist oral anticoagulants (the direct thrombin inhibitor dabigatran and factor Xa inhibitors, including apixaban, rivaroxaban, and edoxaban) have several advantages over vitamin K antagonists, including fixed dosing regimens that eliminate the need for frequent laboratory testing. Novel oral anticoagulants have been shown to be

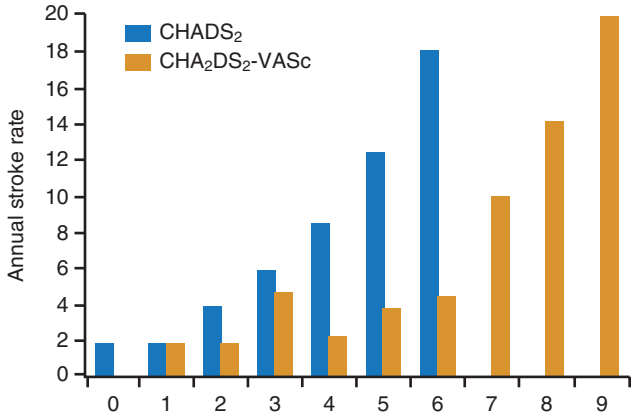

FIG. 2.23 *The annual risk of stroke (percent risk/year) based on the $CHADS_2$ and CHA_2DS_2-VASc scores. Based on data from Lip GY. Implications of the CHA(2) DS(2)-VASc and HAS-BLED Scores for thromboprophylaxis in atrial fibrillation.* Am J Med. *2011;124:111–114.*

noninferior or superior to warfarin in efficacy for stroke prevention and have a lower rate on intracranial hemorrhage. Risk factors for bleeding while on oral factor Xa inhibitors include small body size, renal dysfunction, and advanced age. For the direct factor Xa inhibitor apixaban, the appropriate dose for prevention stroke in nonvalvular AF is 5 mg twice daily. Apixaban 2.5 mg twice daily is recommended for patients with at least two of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

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ANSWER TO QUESTION 219

D (Braunwald, pp. 731, 736–737, 742)

Atrial fibrillation (AF) commonly occurs in patients with hypertensive heart disease, hyperthyroidism, rheumatic heart disease, cardiomyopathy, coronary artery disease, or after cardiac surgery (in up to 40% of patients). The incidence of AF approximately doubles with each decade of adult life. It is an independent risk factor for mortality, after adjustment for other risk factors, including age, diabetes, hypertension, congestive heart failure, rheumatic and non-rheumatic valvular disease, and myocardial infarction. The presence of AF increases the risk of stroke by threefold to fivefold.

Treatment of AF varies depending on the clinical presentation, but includes three components: (1) assessment of the need for, proper timing of, and appropriate method for the restoration of sinus rhythm; (2) anticoagulation to prevent embolic stroke; and (3) medication to control the ventricular rate (to reduce symptoms and prevent the development of tachycardia-related cardiomyopathy).[1] Several randomized studies have demonstrated that a strategy of sinus rhythm maintenance with antiarrhythmic drugs offers no survival advantage over a strategy of long-term rate control in patients with AF and that long-term anticoagulation is imperative in all high-risk patients to prevent thromboembolic complications.[2]

In patients presenting with AF of <48 hours' duration, electrical or chemical cardioversion for restoration of sinus rhythm can be performed without the need for prolonged anticoagulation. In those presenting with AF of longer duration, anticoagulation for at least 3 weeks is advised before cardioversion, given the potential for dislodging formed thrombus within the left atrial appendage. If intra-atrial thrombus is first excluded by transesophageal echocardiography, more expeditious cardioversion may be safely performed in these patients.

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ANSWER TO QUESTION 220

B (Braunwald, pp. 619–621, 624–625, 631–632; Table 34.1; Fig. 34.2)

The sinus node is composed of nodal cells, transitional cells, and atrial muscle cells and is richly innervated by both postganglionic adrenergic and cholinergic nerve terminals. Vagal stimulation releases acetylcholine and slows the discharge rate of the sinus node, whereas adrenergic stimulation releases norepinephrine and speeds the discharge rate.

The arterial supply to the atrioventricular node arises from a branch of the right coronary artery in 85% to 90% of human hearts and from a branch of the circumflex in 10% to 15%. The upper muscular interventricular septum is supplied by both the anterior and posterior descending arteries.

Phase 3 (final rapid depolarization) of the cardiac action potential results from activation of repolarizing K^+ currents and inactivation of the inward calcium current. Interference with potassium currents by genetic mutation or drugs can result in prolongation of the QT interval. For example, a number of medications, including erythromycin, terfenadine, and ketoconazole, can inhibit the delayed rectifier K^+ current (I_{Kr}), resulting in an acquired form of the long QT syndrome, thereby predisposing to the ventricular arrhythmia torsades de pointes.

Phase 4 of the action potential represents the resting membrane potential in cardiac myocytes. During this phase, a set of potassium membrane channels are open, while other ionic channels are essentially impermeable to flow, such that the resting transmembrane potential of a ventricular myocyte is primarily determined by the equilibrium potential of potassium, at approximately –91 mV.

ANSWER TO QUESTION 221

E (Braunwald, pp. 681–683; Tables 36.1, 36.3, 36.4)

Amiodarone is a class III antiarrhythmic agent that is used to treat and suppress a wide spectrum of supraventricular

and ventricular arrhythmias. The onset of action of the intravenous form is within 1 to 2 hours. After oral administration, the onset of action is delayed by days or weeks but is shortened by large loading doses. Elimination is primarily by hepatic excretion into bile with some enterohepatic recirculation. Renal elimination of amiodarone is negligible and the dose does not need to be adjusted in the presence of renal insufficiency. Amiodarone's elimination half-life is multiphasic, with an initial 50% reduction in plasma concentration 3 to 10 days after drug cessation, followed by a terminal half-life ranging from 26 to 107 days, with a mean of ~53 days.

Unlike many other antiarrhythmic drugs, amiodarone is tolerated by patients with left ventricular dysfunction and it is not associated with increased mortality in patients with heart failure. However, all prospective, randomized comparisons have shown that implanted defibrillators are superior for the prevention of sudden cardiac death in this population.

Amiodarone is associated with a number of significant extracardiac toxicities. Of great significance is the development of pulmonary toxicity, which may reflect a hypersensitivity reaction. This complication can occur as early as 6 days after amiodarone's initiation or may appear after long-term use.

Additional adverse effects of amiodarone include hepatic toxicity, neurologic dysfunction, photosensitivity, and bluish skin discoloration. Both hypothyroidism (2% to 4%) and hyperthyroidism (1% to 2%) have been reported with the use of this drug. Amiodarone is not associated with hyperparathyroidism or disturbances of calcium homeostasis. Corneal deposits, visualized by slit lamp examination, occur in almost all patients who are treated with amiodarone for more than 6 months, but resultant visual impairment is unusual. Optic neuritis is a more serious potential adverse ophthalmic effect, but is very rare.

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ANSWER TO QUESTION 222

C (Braunwald, pp. 636–641, 643–646; Table 34.3; Fig. 34.14)

Mechanisms of cardiac arrhythmias can be classified into those of disordered impulse formation (e.g., abnormal automaticity, triggered activity) and those of disordered impulse conduction (e.g., conduction blocks, reentry). Common examples of reentry include atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial flutter.

AVNRT arises from reentry involving dual AV nodal pathways. In the *common* form of AVNRT, the anterograde conduction occurs down the "slow" pathway and retrograde conduction occurs up the "fast" pathway. As a result, retrograde P waves on the ECG are typically superimposed on the terminal portion of the QRS complex. In the *uncommon* form of AVNRT, anterograde conduction occurs down the "fast" pathway and retrograde conduction is delayed as it proceeds up the "slow" pathway. Thus, in this form, retrograde P waves occur later, after the QRS complex.

In most cases of AVRT due to preexcitation, such as those in Wolff-Parkinson-White syndrome, the accessory pathway conducts more rapidly than the normal AV node, but takes a longer time to recover excitability (i.e., the accessory pathway has a longer anterograde refractory period than the AV node). The consequence is that a premature atrial complex may be blocked in the accessory pathway, continue to the ventricle over the normal AV node and His bundle, and return to the atrium retrograde via the accessory pathway. This creates a continuous conduction loop for generation of a narrow-complex, *orthodromic* AVRT. In *antidromic* AVRT, anterograde conduction to the ventricles occurs down the accessory pathway with retrograde conduction up the AV node, resulting in a wide-QRS complex tachycardia.

The typical form of atrial flutter ("counterclockwise" flutter) is due to *reentry* within the right atrium. Radiofrequency ablation of the cavotricuspid isthmus often interrupts the reentrant pathway and eliminates recurrences of the arrhythmia.

Ventricular tachycardias can be caused by numerous mechanisms, including reentry (e.g., bundle branch reentry), triggered activity (e.g., right ventricular outflow tachycardias), or abnormal automaticity.

ANSWER TO QUESTION 223

C (Braunwald, pp. 612–613; Fig. 33.5; pp. 762–763; Fig. 39.9)

In the absence of structural heart disease or coronary artery anomalies, a history of recurrent, exertionally related syncope in a young person is of concern for a predisposition to ventricular dysrhythmias. His ECG during exercise confirms the likely cause of syncope with the onset of polymorphic ventricular tachycardia. This constellation of findings, the family history of sudden cardiac death during exertion, and the normal corrected QTc interval at rest suggests the diagnosis of *catecholaminergic polymorphic ventricular tachycardia (CPVT)*, an inherited form of ventricular tachycardia. CPVT is triggered by stress, which first induces sinus tachycardia, followed by ventricular premature beats, then by polymorphic or bidirectional VT, as shown in the figure. Approximately 30% of CPVT patients have a family history of sudden death or stress-induced syncope. Mutations in the ryanodine receptor gene have been linked to an autosomal dominant form of CPVT that accounts for half of all cases.[1]

The treatment of choice for CPVT is beta blocker therapy (to blunt the impact of catecholamine surges) along with an implantable cardioverter-defibrillator for prevention of sudden death. Patients with CPVT should be counseled to avoid vigorous exercise. Cardiac sympathectomy has been reported to be effective in some cases, but is not considered first-line therapy. Magnesium has not been shown to be effective in patients with CPVT.[2]

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ANSWER TO QUESTION 224

E (Braunwald, pp. 681–684; Tables 36.1, 36.3, 36.4; p. 737)

Before initiating antiarrhythmic drug therapy to maintain sinus rhythm, precipitating or reversible causes of atrial fibrillation should be considered and addressed. The selection of an antiarrhythmic drug must take into account the underlying heart condition and comorbidities that may increase specific drug toxicities.

Dofetilide, an oral class III agent approved for the treatment of atrial flutter and fibrillation, acts by blocking the rapid component of the delayed rectifier potassium current (I_{Kr}), thereby prolonging repolarization. The most important adverse effect is torsades de pointes, which occurs in 2% to 4% of patients. The greatest risk of torsades is at the time of drug initiation, so drug loading must occur in a hospitalized setting with continuous electrocardiographic monitoring. The risk of torsades can be reduced by calculating the drug's appropriate dose based on the patient's creatinine clearance and by carefully monitoring the QT interval.

Sotalol is a nonspecific beta blocker that also prolongs repolarization. It should be used cautiously in patients with reduced contractile function because its negative inotropic effect may cause a further decline in cardiac index and precipitate heart failure. The most common and serious cardiac side effect of sotalol use is proarrhythmia; new or worsened ventricular tachyarrhythmias occur in about 4% of cases, and this complication is due to torsades de pointes in ~2.5%. Sotalol is primarily eliminated via the kidney and should be avoided in patients with chronic renal insufficiency.

Disopyramide, a class IA drug, is a negative inotrope that can exacerbate heart failure symptoms and is *contraindicated* in patients with systolic left ventricular dysfunction.

Dronedarone is a class III agent similar to amiodarone but with fewer extracardiac side effects. However, dronedarone should not be prescribed to patients with symptomatic systolic heart failure, as it has been associated with increased mortality in this population.

Despite the many potential extracardiac side effects of amiodarone (as described in the Answer to Question 221), it is generally well tolerated in patients with systolic dysfunction, does not require dose adjustment in patients with renal insufficiency, and unlike other class III antiarrhythmic drugs can typically be initiated in an outpatient setting, since torsades de pointes rarely occurs with this agent. Monitoring of thyroid function, liver function tests, and pulmonary symptoms is required during long-term amiodarone administration. The lowest effective maintenance dose of amiodarone should be used to minimize adverse effects.

ANSWER TO QUESTION 225

C (Braunwald, pp. 715–719; Figs. 37.8 and 37.10)

The figure depicts the initiation of a narrow-complex tachycardia during electrophysiologic study by rapid atrial pacing from the coronary sinus (CS). A train of stimuli is delivered at a cycle length of 500 milliseconds (S_1), followed by a premature stimulus (S_2) at an S_1–S_2 interval of 250 milliseconds. The effects of this premature stimulus on intracardiac conduction are seen in the His bundle recording (HBE). The AH interval, reflecting the conduction time from the atrium to the His bundle, is markedly prolonged after the premature stimulus, increasing to 300 milliseconds. This occurs because, in this patient with dual atrioventricular (AV) nodal pathways, the premature atrial stimulus encounters a refractory *fast* pathway and conducts anterograde through the *slow* pathway instead. In a patient without such dual AV nodal pathways, the premature stimulus would merely extinguish in the AV node. In this case, the slowed conduction through the AV node initiates a narrow-complex tachycardia. Such a "jump" in the AH interval during rapid atrial pacing is the electrophysiologic signature of dual AV nodal physiology. Examination of the sequence of atrial activation in the subsequent tachycardia reveals that the earliest atrial activation is in the His bundle recording (low right atrium, HBE lead), later progressing to the high right atrium and CS, (reflecting left atrial activation). These features identify this rhythm as an AV nodal reentrant tachycardia.

ANSWER TO QUESTION 226

D (Braunwald, pp. 775–777; p. 801; Table 41G.2)

The electrogram depicted demonstrates spontaneous infrahisian block, consistent with infrahisian conduction disease. Four QRS complexes are shown, with two surface electrocardiographic leads (V_1 and V_5), three His catheter electrograms (proximal, mid-, and distal pole), and a right ventricular electrogram. The surface ECG shows right bundle branch block and sinus rhythm with a single dropped beat after the second QRS complex. After the second QRS complex, deflections are present on the three His catheter channels, representing atrial depolarization. This event is followed by a small, sharp deflection evident only on the distal His channel, representing the His electrogram. That His bundle deflection fails to conduct to the ventricles because there is no QRS complex immediately following it. Together with bifascicular block evident on the surface ECG, this is a class I indication for permanent pacing.

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ANSWER TO QUESTION 227

D (Braunwald, pp. 757–759; Table 39.2; Fig. 39.6)

The differential diagnosis of wide-QRS complex tachycardia includes ventricular tachycardia (VT) and supraventricular tachycardia (SVT) with aberrancy. Several features of the clinical history and surface ECG may assist in this differentiation, although none is absolute. The clinical scenario is important, because a history of myocardial infarction makes the diagnosis of VT more likely. On the ECG, the presence of fusion beats (which indicate activation of the ventricle from two different foci, one of ventricular origin), capture

beats (intermittent narrow-complex QRS at an interval shorter than the rate of tachycardia), or atrioventricular dissociation all support the diagnosis of VT. Concordance of the QRS complex in the precordial leads (all complexes are positively directed or all are negatively directed) favors VT over SVT. Slowing or termination of the tachycardia by vagal maneuvers is consistent with SVT. Hemodynamic stability is not a useful criterion for differentiating SVT from VT.

Specific QRS contours are also helpful. For example, a triphasic QRS complex (rSR′) in lead V_1 supports the presence of SVT. Conversely, monophasic or biphasic QRS complexes in lead V_1 are more consistent with VT. VT with a left bundle branch block configuration typically demonstrates a small Q-large R (qR) or QS pattern in lead V_6 and a broad, prolonged (>40 milliseconds) R wave in lead V_1. VT with a right bundle branch pattern demonstrates a monophasic or biphasic QRS in lead V_1 and small R-large S waves or QS complexes in lead V_6.

ANSWER TO QUESTION 228

A (Braunwald, pp. 688–690; Fig. 36.1)

Electrical cardioversion is very effective for termination of supraventricular and ventricular tachyarrhythmias, particularly those due to reentry. The cardioversion of tachycardias caused by disorders of enhanced automaticity is less successful. For example, ectopic atrial tachycardia and other arrhythmias caused by disorders of impulse formation typically recur within seconds after the electrical discharge.

Except in patients with ventricular fibrillation or rapid ventricular flutter, a synchronized shock (delivered during the QRS complex) should be used to minimize the risk of firing on the ST segment or T wave, which might precipitate ventricular fibrillation. The minimal effective energy should be employed initially to reduce the risk of myocardial damage, with upward titration as required. If the "maximum" energy level of the electrical cardioverter fails to terminate the abnormal rhythm, repeated shocks at the same energy level can *decrease* the chest wall impedance and may succeed. Treatment with the class III intravenous agent ibutilide may convert atrial fibrillation to sinus rhythm, and when used as pretreatment also enhances the success of subsequent electrical cardioversion. Direct-current cardioversion is contraindicated in suspected digitalis-induced tachyarrhythmias because of the potential of inducing ventricular proarrhythmia.

After successful cardioversion, anticoagulation should be continued for an additional 3 to 4 weeks because full recovery of atrial mechanical activity often lags behind the return of normal electrical function and persistent blood stasis could permit thrombus formation.

ANSWER TO QUESTION 229

C (Braunwald, pp. 763–765; Fig. 39.10)

The arrhythmia in the figure is *torsades de pointes*, a form of polymorphic ventricular tachycardia that may develop in patients with delayed ventricular repolarization, manifest by a prolonged QT interval on the ECG. Torsades de pointes is thought to be triggered by early afterdepolarizations during the vulnerable period of ventricular repolarization, producing QRS complexes of changing amplitude twisting around the isoelectric line at a rate of 200 to 250 beats/min.

A prolonged corrected QT interval on the surface ECG is defined as >0.46 millisecond in men or >0.47 millisecond in women. A long QT interval, the electrocardiographic substrate for torsades de pointes, can be either congenital or acquired. Congenital forms include those associated with congenital severe bradycardia or loss of function mutations in the *KCNQ1* (LQT1) and *KCNQ2* (LQT2) potassium channel genes or a *gain* of function mutation in the *SCN5A* sodium channel gene, which is responsible for LTQ3. Loss of function mutations in the *SNC5A* gene (which result in accelerated sodium channel recovery or inactivated sodium channels) are associated with Brugada syndrome (and ventricular fibrillation) rather than prolongation of the QT interval and torsades de pointes.

Multiple drugs, both in toxic and therapeutic doses, can result in prolongation of the QT interval and an increased risk of torsades de pointes, including commonly used agents such as tricyclic antidepressants, phenothiazines, and erythromycin. Antiarrhythmic drugs that prolong the QT interval and predispose to torsades de pointes include quinidine, procainamide, disopyramide, sotalol, and dofetilide. Electrolyte disturbances, including hypokalemia or hypomagnesemia, may also contribute to a long QT interval and torsades de pointes.

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ANSWER TO QUESTION 230

C (Braunwald, pp. 756–759)

Intracardiac electrograms are shown depicting electrical activity in the high right atrium (HRA), in the bundle of His (His proximal and His distal), and at the right ventricular apex. The surface electrocardiographic leads V_1 and V_5 also are shown. The surface ECG demonstrates a wide-complex tachycardia at approximately 140 beats/min with a right bundle branch block morphology. The His distal and RV apical electrograms show deflections corresponding to each QRS complex, which represent ventricular depolarization. Smaller, periodic deflections at a slower rate are evident on the HRA and His proximal electrograms that represent atrial depolarizations. The lack of relationship between the atrial and ventricular depolarizations confirms the presence of atrioventricular dissociation. Thus, this rhythm represents ventricular tachycardia.

ANSWER TO QUESTION 231

C (Braunwald, pp. 775–777; Fig. 40.7)

The electrophysiologic tracing in the figure depicts Mobitz type I (Wenckebach) second-degree atrioventricular (AV) block. This is evident both in the surface electrocardiographic channel, which demonstrates progressive PR interval prolongation followed by a nonconducted P wave, and in the His bundle tracing (HBE), which shows progressive AH interval prolongation followed by block within the AV node. In contrast, in patients with Mobitz type II second-degree

heart block, there would be sudden block of impulse conduction (a P wave not followed by a QRS complex) without prior lengthening of the PR interval.

Type I second-degree AV block with normal QRS duration almost always reflects block at the level of the AV node proximal to the His bundle, typically portends a benign clinical course, and no specific intervention is indicated in the absence of symptoms. When type I AV block occurs in acute myocardial infarction (MI), it is usually in the setting of an inferior wall infarction. Such occurrences are usually transient and do not typically require therapy. The presence of higher degrees of AV block, including type II second-degree block, in acute MI indicates greater myocardial damage and predicts higher mortality.

Vagal maneuvers, such as carotid sinus massage, may *enhance* type I AV block by further prolonging AV nodal conduction and may therefore be useful in differentiating type I from type II AV block.

ANSWER TO QUESTION 232

E (Braunwald, p. 800; Tables 41G.1 and 41G.2)

Acquired atrioventricular (AV) blocks are most commonly idiopathic and related to aging. However, many defined conditions can impair AV conduction, including coronary artery disease, infections (e.g., Lyme disease, Chagas disease, endocarditis), collagen vascular diseases (e.g., rheumatoid arthritis, scleroderma, dermatomyositis), infiltrative diseases (e.g., sarcoid, amyloid), neuromuscular disorders, and drug effects.

Indications for permanent pacing in AV conduction disorders include (1) permanent or intermittent complete (third-degree) heart block, (2) permanent or intermittent type II second-degree AV block, and (3) type I second-degree AV block if accompanied by symptoms or evidence of block at, or inferior to, the bundle of His.

Pacing is not indicated in asymptomatic first-degree AV block or type I second-degree AV block proximal to the bundle of His. Occasionally, patients with first-degree AV block with marked prolongation of the PR interval (>300 milliseconds) are hemodynamically symptomatic because of the loss of effective AV synchrony. In that case, consideration of a pacemaker is appropriate if reversible contributors to the AV block are not identified. Because of vagal influences, many normal persons (particularly those with high resting vagal tone, such as conditioned athletes) may exhibit pauses significantly longer than 3 seconds during sleep; in and of itself, therefore, this finding is not sufficient to warrant permanent pacemaker implantation.

Controversy exists about the appropriateness of permanent pacing in adults with asymptomatic congenital complete heart block. Because of the high incidence of unpredictable syncope, the tendency is to implant permanent pacemakers in adults with this condition (class IIb indication).

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ANSWER TO QUESTION 233

B (Braunwald, p. 786; Fig. 41.13; Table 41.2)

Some dual-chamber pacemakers operate with unipolar leads, as in this case. The metal capsule of the generator serves as the indifferent electrode. This can result in oversensing, in which skeletal muscle potentials result in inappropriate inhibition or triggering of pacing.

The first two beats in the tracing show appropriate dual-chamber atrial and ventricular sensing and pacing at a rate of 70 beats/min. There is no evidence of lack of capture (all pacing stimuli cause myocardial depolarizations) or undersensing (because there are no native atrial or ventricular complexes).

After the third complex there is a long pause during which no pacemaker activity is observed. There is significant baseline artifact (due to muscle contractions) during this period. The lack of pacemaker activity during the pause indicates that the ventricular lead has sensed the electrical activity generated by the arm and chest muscles and has inappropriately inhibited pacemaker output.

In cases of suspected oversensing, placing the pacemaker in an asynchronous mode (with application of a magnet) will abolish the symptoms caused by pacemaker malfunction and aid in the diagnosis. Conversion of the lead system to a bipolar configuration frequently eliminates oversensing of myopotentials.

ANSWER TO QUESTION 234

D (Braunwald, p. 786; Fig. 41.12; Table 41.2)

The figure is an electrocardiographic tracing from a patient with a dual-chamber pacemaker. Atrial pacing artifacts with effective atrial depolarization are seen throughout the tracing. However, all but one ventricular pacing artifact (complex 5) fail to result in ventricular depolarization. Because the pacemaker generates appropriate output but not consistent, effective ventricular depolarization, this is an example of intermittent failure to capture of the ventricular lead.

Failure to capture most commonly occurs due to dislodgment of the pacemaker lead from the endocardial surface, a complication that usually occurs within the first few weeks after implantation. Modern designs for active and passive fixation of pacemaker leads are associated with a low frequency of lead dislodgement. Failure to capture may also occur due to a lead insulation break, which allows some of the electrode current to dissipate into the surrounding tissues. Even if the lead system is intact and in contact with the myocardium, failure to capture may occur if the pacing threshold required to depolarize the myocardium exceeds the programmed voltage amplitude and pulse duration. This can occur in the setting of exit block, in which an inflammatory reaction or fibrosis at the electrode-myocardium interface raises the depolarization threshold; the risk of this complication is greatly reduced through the use of a steroid-eluting lead. Pacing thresholds (and the likelihood of failure to capture) may also be increased in the setting of marked metabolic abnormalities (e.g., hyperkalemia) or therapy with antiarrhythmic drugs (e.g., flecainide).

Impending total battery depletion may also result in a subthreshold pacing stimulus and failure to capture. Total battery depletion usually results in complete failure to output, which is not the case here, because consistent atrial and

ventricular pacing and atrial capture are seen. In patients with a unipolar pacemaker, air in the pacemaker pocket may act as an insulator and reduce the effective pacemaker output, resulting in noncapture.

A loose set screw (which helps secure the lead to the generator) is a cause of failure to output, but not failure to capture. That diagnosis is inconsistent with this tracing, because consistent ventricular pacing artifacts are seen.

ANSWER TO QUESTION 235

D (Braunwald, pp. 772–774; eFigs. 40.1 and 40.2; Fig. 40.2)

There are several forms of bradycardia related to sinus node function. *Sinus bradycardia* is defined as a sinus node discharge <60 beats/min. It is generally a benign arrhythmia and well tolerated in most patients. It can result from excessive vagal stimulation or decreased sympathetic discharge and is common in well-trained athletes. During sleep, the heart rate in normal individuals can decrease to 35 to 40 beats/min and pauses of 2 to 3 seconds or even longer are not uncommon. Asymptomatic sinus bradycardia does not require specific therapy. Symptomatic patients can be treated acutely with intravenous atropine (which increases the sinus node discharge rate) or sympathetic stimulants. For chronic, symptomatic sinus bradycardia, electronic pacing may be required.

Carotid sinus hypersensitivity can be cardioinhibitory (ventricular asystole >3 seconds during carotid sinus stimulation) or vasodepressor (defined as a decrease in systolic blood pressure more than 50 mm Hg). Atropine is a competitive muscarinic acetylcholine receptor antagonist that *blocks* cardioinhibitory input to the sinus node. Atropine transiently abolishes cardioinhibitory carotid sinus hypersensitivity, but most symptomatic patients require permanent pacemaker placement.

Sick sinus syndrome encompasses a number of sinus node abnormalities including persistent spontaneous sinus bradycardia, sinus arrest or exit block, combinations of SA and AV conduction disturbances, and alternations of paroxysmal rapid atrial tachyarrhythmias with periods of slow atrial rates. *Sinus arrest* (which is distinct from sinus exit block) is identified by a pause in the sinus rhythm and a PP interval surrounding the pause that *is not* a multiple of the underlying PP rate. Sinus arrest can be due to sinus node ischemia during an acute myocardial infarction, degenerative fibrotic changes, digitalis toxicity, or excessive vagal tone. A large proportion of patients with sleep apnea have periods of sinus arrest as well as atrioventricular block.

Sinus arrhythmia is defined as phasic variations in the sinus cycle length, and it can appear in two forms: respiratory and nonrespiratory. In the respiratory form, the PP interval shortens in a cyclical fashion during inspiration owing to inhibition of vagal tone. In the nonrespiratory form, as seen in digitalis toxicity, the phasic variation is unrelated to the respiratory cycle. Symptoms are uncommon, and therapy is generally not necessary.

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ANSWER TO QUESTION 236

C (Braunwald, p. 762; Fig. 39.8; Table 39.4)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is depicted by fatty or fibrofatty infiltration of the right ventricular (RV) wall. Clinically, the disease is characterized by life-threatening ventricular arrhythmias in otherwise healthy-appearing young people, afflicting males most commonly. The prevalence is estimated at 1 in 5000 individuals, although the difficulty of diagnosis makes the true prevalence difficult to estimate. In its familial form, mutations have been identified in genes that encode desmosomal proteins (e.g., plakoglobin, desmoplakin, and others). Immunohistochemistry of desmosomal proteins in endomyocardial biopsy samples has been shown to be a sensitive and specific diagnostic test for ARVC. Most patients with ARVC demonstrate RV abnormalities by echocardiography, computed tomography, RV angiography, or magnetic resonance imaging. In advanced forms, the left ventricle may be involved.

The ECG in patients with ARVC in sinus rhythm may demonstrate a complete or incomplete right bundle branch block, with a terminal notch in the QRS complex, known as an *epsilon wave* (see arrowheads in Fig. 2.24). Ventricular tachycardia (VT) occurs commonly in patients with ARVC, usually with a *left* bundle branch block morphology due to its RV origin.

Because of the progressive nature of this disease and the multiple morphologies of the VT it produces, radiofrequency catheter ablation is not often successful. Use of an implantable cardioverter-defibrillator is usually the treatment of choice, even in asymptomatic patients.

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ANSWER TO QUESTION 237

C (Braunwald, p. 798)

Cardiac implanted electronic device (CIED) infections are increasing in incidence and are more common after a generator change than at the time of initial implantation. The organisms responsible for early infections are typically gram-positive cocci derived from the skin, predominantly staphylococcal species. Pocket infections can present with pain, erythema, purulent discharge, and/or generator or lead erosion. Septic pulmonary emboli may be the first manifestation. Patients with evidence of an infection of a CIED, including localized pocket infections without evidence of systemic involvement, should undergo complete removal of the system hardware (generator and leads). The risk of transvenous lead extraction increases the longer the lead has been in place. However, when performed by an experienced operator, this procedure can be performed with low morbidity rates.

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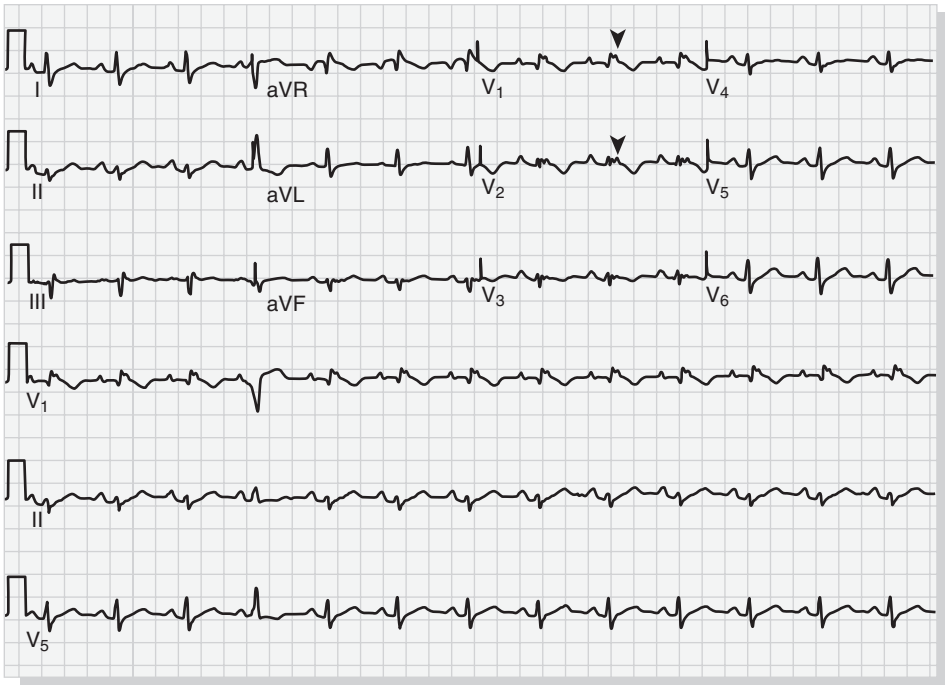

FIG. 2.24

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ANSWER TO QUESTION 238

E (Braunwald, p. 753)

Nearly all left atrial thrombi form in the left atrial appendage (LAA). Surgical or percutaneous device exclusion of the LAA may reduce thromboembolic complications in patients with atrial fibrillation (AF), especially in those who are not candidates for long-term anticoagulation. A US Food and Drug Administration-approved LAA percutaneous occlusion device (WATCHMAN, a fenestrated fabric-covered nitinol plug implanted via the femoral vein with transseptal catheterization) was demonstrated to be noninferior to warfarin for stroke prevention, with a lower risk of hemorrhagic stroke, in long-term follow-up.[1] At present, implantation of this device requires short-term anticoagulation for 45 days, followed by transesophageal echocardiographic-confirmation that there is no residual peri-device flow. Approximately 95% of patients are able to discontinue anticoagulation at that time.

This patient is at high risk for stroke (CHA_2DS_2-VASc score is 4, with 1 point for hypertension, 1 point for diabetes, and 2 points for age ≥75 years) such that aspirin alone would be insufficient to reduce stroke risk. The patient has also had recurrent falls and repetitive gastrointestinal bleeding that increase the risk for bleeding events on anticoagulation, such that implantation of an LAA closure device is a reasonable option.[2]

Enoxaparin is typically used as a temporary bridge for some patients during warfarin interruption. In chronic kidney disease, the elimination of enoxaparin is prolonged, the bleeding risk is increased, and it would not be an appropriate choice for this patient's chronic anticoagulation. Like other novel oral anticoagulants, the factor Xa inhibitor apixaban is noninferior or superior to warfarin for prevention of thromboemboli in patients with nonvalvular AF, while causing less major bleeding. It would be a safer option than warfarin for this patient, but the appropriate dose would be 2.5 mg twice daily (age ≥80 years, creatinine ≥1.5 mg/dL). AV nodal ablation is useful for symptomatic patients with AF and persistently rapid ventricular rates, but the procedure does not reduce the risk of stroke.

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ANSWER TO QUESTION 239

B (Braunwald, pp. 721–726; Figs. 37.13–37.15, 37.18; Table 37.5)

The two intracardiac electrograms include surface electrocardiographic leads V_1 and V_5, a recording from a catheter in the high right atrium, a series of five recordings from a multiple-pole catheter placed in the coronary sinus (CS; displayed from the proximal to distal CS), recordings from a bundle of His position catheter (His proximal and His distal), and a recording from a catheter at the right ventricular (RV) apex.

The baseline electrogram demonstrates preexcitation: the surface ECG shows that the QRS complex occurs nearly simultaneously with the small, sharp His potential deflection on the His distal electrogram. This implies that ventricular activation occurs well before depolarization of the His-Purkinje system.

In the electrogram recorded during tachycardia, the surface ECG leads show a narrow-complex rhythm at approximately 160 beats/min. The intracardiac electrograms demonstrate ventricular depolarizations at the His and RV apical catheters corresponding to the QRS complex on each surface ECG. Each ventricular depolarization is preceded by a His depolarization. Atrial depolarization is apparent in the His catheter positions and throughout the CS electrograms. The sequence of atrial activation begins at the distal CS electrogram and proceeds to the proximal and His catheters. These observations are consistent with orthodromic AV reentrant tachycardia via an accessory pathway. Specifically, the location of the accessory pathway is likely to be left lateral based on the sequence of atrial activation.

ANSWER TO QUESTION 240

B (Braunwald, pp. 604–609; Figs. 33.2 and 33.3; Table 33.1)

Congenital long QT syndromes (LQTS) are inherited disorders characterized by delayed repolarization of the myocardium (QTc >480 milliseconds) and susceptibility to life-threatening ventricular arrhythmias (torsades de pointes). Hundreds of causal mutations have been identified in at least 12 LQTS susceptibility genes.

Approximately 75% of disease-causing mutations occur in three genes, comprising the most common forms of this condition: LQT1 (mutations in the *KCNQ1* gene, which encodes the alpha subunit of the I_{Ks} potassium channel, causing loss of function), LQT2 (mutations in *KCNH2*, the gene that encodes the alpha subunit of the I_{Kr} potassium channel, causing loss of function), and LQT3 (mutations in the *SCN5A* gene, which encodes the cardiac sodium channel, causing gain of function).

Clinical symptomatology in LQTS is highly variable and is related in part to the genetic locus that is affected. LQT1 patients experience the majority of cardiac events during physical (especially swimming) or emotional stress, suggesting a connection with sympathetic nervous system activation. In contrast, LQT2 patients are at highest risk for lethal events by auditory triggers or during the postpartum period. Cardiac events during sleep or at rest are most common in LQT3.

For patients who have congenital LQTS but no history of syncope, ventricular arrhythmias, or family history of sudden cardiac death, generally no therapy or treatment with a beta blocker (to reduce triggered activity) is appropriate. Permanent pacing is indicated in select patients with atrioventricular block or pause-dependent torsades de pointes. In patients deemed at high risk for sudden death (e.g., those with a history of syncope or resuscitated cardiac arrest), an implantable cardioverter-defibrillator is the therapy of choice.

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ANSWER TO QUESTION 241

D (Braunwald, pp. 807–815; Figs. 42.1–42.3; Tables 42.1 and 42.3)

Sudden cardiac death (SCD) is defined as a natural death due to cardiac causes, in which abrupt loss of consciousness occurs within 1 hour of the onset of acute symptoms. An estimated 390,000 out-of-hospital cases occur in the United States annually. There are two peak age distributions of sudden death: (1) from birth to 6 months of age (i.e., sudden infant death syndrome) and (2) between 45 and 75 years of age. Coronary artery disease is the structural basis for ~80% of SCDs.

SCD is more common in men than woman, with a fourfold to sevenfold excess of SCD in men compared with women before age 65. At older ages, the difference decreases to 2:1 or less. A number of hereditary conditions can result in SCD, including hypertrophic cardiomyopathy, the long QT syndrome, arrhythmogenic right ventricular cardiomyopathy, and Brugada syndrome. This observation allows potential screening and preventive therapy for individuals at high risk.

Hypertension and cigarette smoking, but not hypercholesterolemia, have been established as risk factors for SCD. Interestingly, in the Framingham study, intraventricular conduction abnormalities on the ECG (but not left ventricular hypertrophy or nonspecific ST-segment T wave abnormalities) were associated with an increased risk of SCD. Psychosocial factors such as social isolation and a high level of life stress were also found to increase the risk of sudden death.

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ANSWER TO QUESTION 242

D (Braunwald, pp. 687, 715; Fig. 37.6)

The ECG illustrated shows atrial tachycardia with block. In this condition, an atrial rate of 130 to 200 beats/min, with a ventricular response less than or equal to the atrial rate, is present. Digitalis toxicity accounts for this rhythm in 50% to 75% of cases, and in such instances the atrial rate may show a gradual increase if digoxin is continued. Other signs of digitalis excess are often present, including frequent premature ventricular complexes.

In nearly one-half of all patients with atrial tachycardia with block, the atrial rate is irregular and demonstrates a characteristic isoelectric interval between each P wave, in contrast to the morphology of atrial flutter waves. Most instances of this rhythm occur in patients with significant organic heart disease. Causes other than digitalis toxicity include ischemic heart disease, myocardial infarction, and cor pulmonale. In patients taking digitalis, potassium depletion may precipitate the arrhythmia, and the oral administration of potassium and the withholding of digoxin often will allow reversal to sinus rhythm. Because atrial tachycardia with block is seen primarily in patients with serious underlying heart disease, its onset may lead to significant clinical deterioration.

ANSWER TO QUESTION 243

B (Braunwald, pp. 808–809, 815; Fig. 42.7)

Approximately 50% of deaths caused by coronary artery disease (CAD) are sudden and unexpected, and ~80% of all sudden cardiac deaths in Western countries are related to CAD. Such events may complicate either an acute coronary syndrome or previously stable coronary disease, and in the

latter case, often relate to myocardial scar from prior infarction. The extent of left ventricular dysfunction and the presence of premature ventricular complexes in convalescence after myocardial infarction (MI) are both powerful predictors of sudden cardiac death (SCD). However, the occurrence of ventricular fibrillation in the earliest stages of acute MI (within the first 48 hours) does not identify long-term risk and is not an indication for implantable cardioverter-defibrillator therapy.

The arrhythmias that most commonly cause cardiac arrest, in decreasing order of frequency, are ventricular fibrillation, bradyarrhythmias/asystole or pulseless electrical activity, and sustained ventricular tachycardia (VT). Survival after an out-of-hospital cardiac arrest is best for those patients in whom sustained VT was the initial recorded rhythm. Patients with bradycardic/asystolic cardiac arrest have the worst prognosis.

There are racial differences in the incidence of SCD throughout adulthood: compared with Caucasians, African Americans display a higher incidence of sudden cardiac death (Fig. 2.25).

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ANSWER TO QUESTION 244

C (Braunwald, pp. 734–735, 1842)

Non-vitamin K-dependent oral anticoagulants (NOACs) include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, rivaroxaban, edoxaban, and betrixaban. Compared with warfarin, these agents produce predictable anticoagulation, are more convenient to administer, and do not require routine blood test monitoring of coagulation. They are at least as effective as warfarin and cause fewer serious bleeding complications, especially less intracranial hemorrhage.[1]

NOACs have short half-lives so that minor bleeding complications can usually be managed by simply withholding the drug. More extensive measures are necessary for serious hemorrhage, but unlike for bleeding caused by warfarin, vitamin K administration is ineffective. Idarucizumab is a humanized monoclonal antibody fragment indicated for reversal of dabigatran in the case of life-threatening bleeding and/or when emergency surgery is necessary, and would be the most appropriate choice for this patient. The RE-VERSE AD trial confirmed the effectiveness of idarucizumab for rapid and safe reversal of dabigatran in 503 patients with uncontrolled bleeding or who were about to undergo an urgent invasive procedure.[2] Hemodialysis may also be used to remove active dabigatran from the circulation in patients with renal failure, but is better suited for less severe bleeding because of its delayed effect compared with idarucizumab.[3]

In 2018, andexanet alfa was approved for use in the United States to rapidly reverse the anticoagulant effect of the factor Xa inhibitors apixaban and rivaroxaban. An alternative approach to reverse the anticoagulant effect of current NOACs is 4-factor prothrombin complex concentrate.[4]

Oral activated charcoal may help prevent absorption of NOACs ingested within the prior 4 hours and can be useful in the case of drug overdose.

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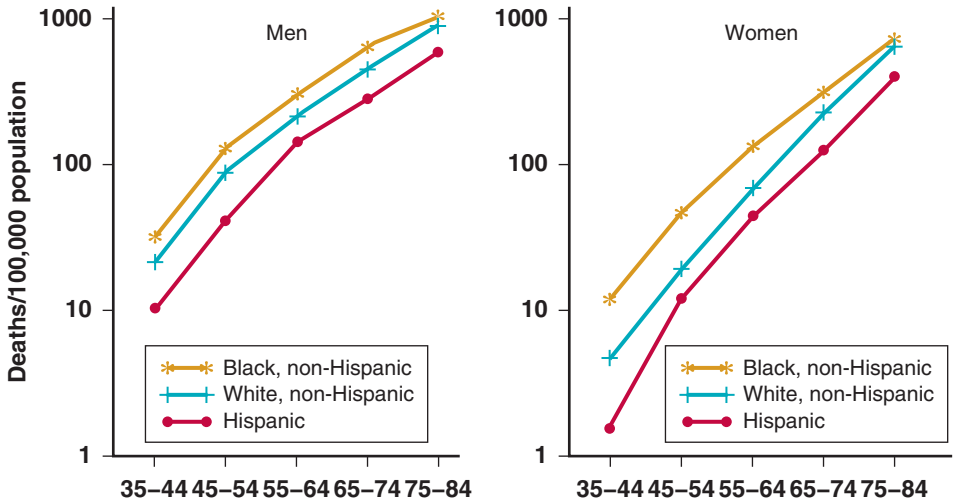

FIG. 2.25 *Age-, sex-, and race-specific risks for sudden cardiac death (SCD). Data modified from Gillum RF. Sudden cardiac death in Hispanic Americans and African Americans.* Am J Public Health. *1997;87:1461.*

ANSWER TO QUESTION 245

B (Braunwald, pp. 787–791; Table 41G.11; Answer to Question 207)

Implantable cardioverter-defibrillators (ICDs) are indicated to prevent sudden death due to ventricular tachyarrhythmias. The strongest evidence for their use is for secondary prevention in patients with reduced left ventricular (LV) function and resuscitated cardiac arrest or unstable sustained ventricular tachyarrhythmias. There is also strong evidence for ICDs as beneficial in primary prevention of sudden death, a therapy that has changed the approach to chronic heart failure care in patients with systolic dysfunction and left ventricular ejection fraction (LVEF) from chronically <30% to 40%.

Patients with ischemic cardiomyopathy who have been shown to derive benefit from ICD therapy are those at least 40 days after acute myocardial infarction. In patients with nonischemic cardiomyopathy and LVEF ≤35%, a trial of optimal heart failure therapy, with reassessment of the LVEF, is appropriate prior to ICD placement since systolic dysfunction may improve in the interim. Patients with identifiable reversible causes of cardiomyopathy (e.g., tachycardia-mediated, alcoholic) should not receive an ICD until reassessment of ventricular function after correction of those contributors.

Patients with significant comorbid conditions that would limit survival with acceptable functional status (e.g., metastatic cancer and end-stage renal disease) to <1 year are generally not appropriate candidates for an ICD.

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ANSWER TO QUESTION 246

C (Braunwald, pp. 783–785; Fig. 41.9; Table 41.1; see also Answer to Question 211)

Selection of the appropriate mode of cardiac pacing depends on many factors, including the underlying rhythm disturbance, the patient's exercise capacity, and the chronotropic response to exercise. Ventricular inhibited pacing (VVI) inhibits ventricular pacemaker output if a ventricular event is sensed, but it does not sense or pace the atrium. This mode protects against bradycardias, but does not restore or maintain atrioventricular (AV) synchrony, so that AV dissociation is common. In addition, in chronotropically incompetent patients in whom the sinus heart rate does not increase with exercise, this mode does not provide rate responsiveness. These deficiencies may result in the "pacemaker syndrome" of reduced functional capacity, shortness of breath, dizziness, and fatigue, which can occur in up to 20% of patients with normally functioning VVI pacing.

Single-chamber triggered pacing (AAT or VVT) generates an output pulse every time a native event is sensed. As a result, it accelerates the rate of battery depletion. This mode of pacing is not frequently used.

Atrial inhibited pacing inhibits atrial pacemaker output if an atrial event is sensed. It does not sense or pace the ventricle. It is an appropriate mode for patients with sinus node dysfunction who have normal AV conduction, but should not be used in individuals with AV nodal disease. Dual-chamber pacing and sensing with inhibition and tracking (DDD) is typically the preferred mode of pacing for patients with combined sinus and AV node dysfunction, because physiologic pacing reduces the frequency of the pacemaker syndrome and may reduce the incidence of atrial fibrillation (AF). However, no randomized trial has demonstrated any effect of pacing mode choice (DDD vs. VVI) on mortality in patients with sinus node dysfunction.

In patients with AF, standard DDD or DDDR is not desirable because P-synchronous pacing is not possible and sensing of the chaotic atrial rhythm could trigger an accelerated ventricular pacing response. To compensate for this deficiency, DDD and DDDR devices commonly have an automatic mode switching feature that, when AF develops, inhibits atrial-sensed ventricular pacing.

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ANSWER TO QUESTION 247

D (Braunwald, pp. 785–787; eTable 41.2)

Pacemaker malfunction may be manifested by impaired pacemaker output or failure to capture or sense the appropriate cardiac chamber. On the ECG, failure to capture is identified when a pacing "spike" is present without evidence of subsequent myocardial depolarization (a P wave or QRS complex). This condition can result from an abnormally elevated electrical threshold, lead dislodgement or perforation, impending battery depletion, or circuit failure. Threshold alterations may be due to medications (e.g., class IC antiarrhythmic agents) or electrolyte and metabolic abnormalities, including hyperkalemia, severe acidosis and alkalosis, hypercapnia, hypoxemia, and myxedema. Failure to sense can result from lead dislodgement or inadequate initial lead placement, lead insulation or circuit failure, electromagnetic radiation, or battery depletion.

Patients with pacemakers should be cautioned about electromagnetic interference that could result in malfunction. An example is industrial-strength welding equipment; close contact should be avoided. Patients with pacemakers should be warned not to lean on or linger near electronic antitheft devices (situated at the exits of many stores) because pacemaker malfunction has been reported in that setting; simply walking past or through such devices is not problematic. Cellular telephones rarely interfere with the function of cardiac pacemakers; when they are placed in the normal position over the ear, rather than over the device,

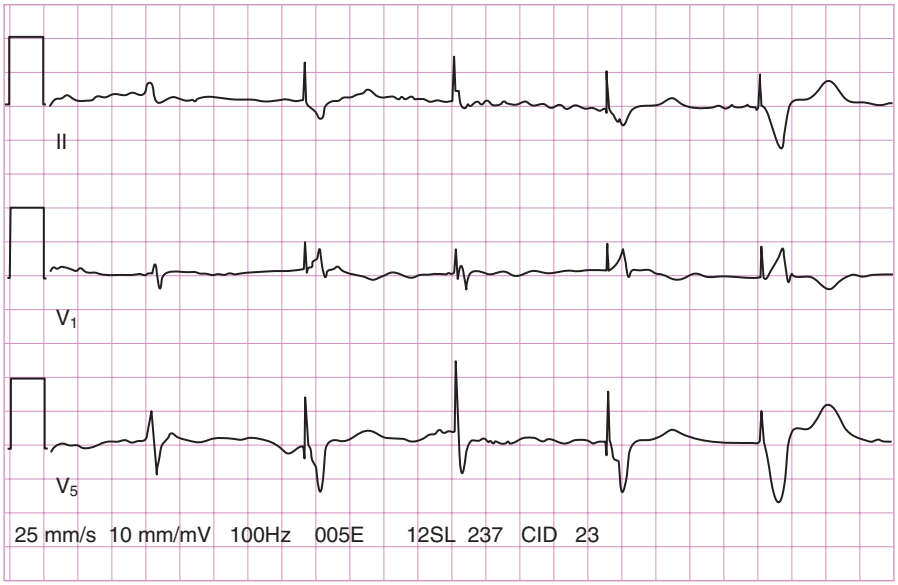

FIG. 2.26 *Three-channel tracing from an ambulatory monitor. The first QRS is intrinsic. The second and fourth beats represent fusion; the third beat is pseudofusion, that is, the underlying morphology is nearly identical to the intrinsic QRS; and the final QRS represents paced depolarization.*

they do not pose a significant risk. As a general rule, they should not be carried in the breast pocket ipsilateral to the pacemaker.

Left bundle branch block morphology is the expected electrocardiographic pattern during standard right ventricular pacing owing to the delay in depolarization of left ventricular myocardium. The presence of right bundle branch block after right ventricular pacemaker implantation is suggestive of accidental lead placement or migration into the left ventricle.

Pseudofusion is present on the surface ECG when a pacing spike does not alter the normal morphology of a superimposed intrinsic QRS complex (Fig. 2.26). This results when a pacing impulse is delivered at the appropriate escape interval into myocardium whose action potentials are in the absolute refractory period owing to slightly earlier intrinsic activation. Pseudofusion can be distinguished from a *fusion beat*, in which the QRS complex represents the combination of intrinsic ventricular activation and *effective* pacemaker depolarization, producing a morphology intermediate between intrinsic and paced beats.

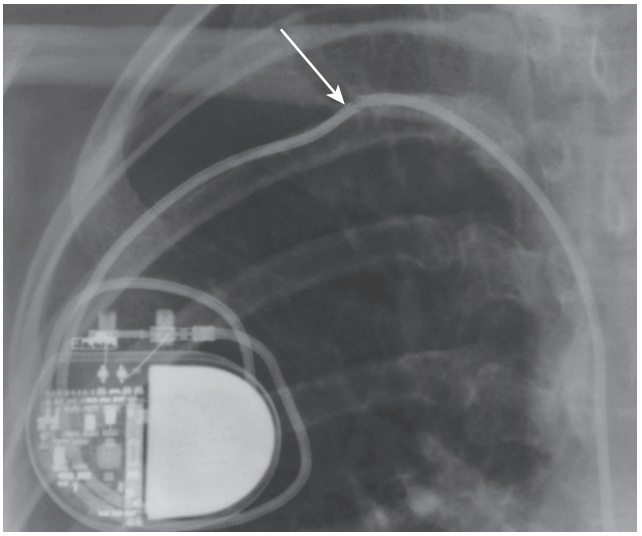

FIG. 2.27

ANSWER TO QUESTION 248

A (Braunwald, pp. 795–798; Fig. 41.25; eFig. 41.18)

The figure depicts a close-up view of a chest radiograph in a patient with a single-chamber pacemaker. The finding of note is a fracture at the point where the lead dives below the clavicle (*arrow* in Fig. 2.27). The patient presented with intermittent failure to capture and intermittent failure to output on the ventricular lead. Lead impedance was greatly elevated.

The telemetric measurement of voltage and current thresholds, lead impedance, and electrograms is very helpful in differentiating the causes of pacemaker malfunction. When a pacemaker wire has fractured, both the voltage threshold and the lead impedance are high. In the case of an insulation break, the voltage threshold and the lead impedance are low. In the setting of a dislodged lead, the voltage threshold is high but the lead impedance is normal. Exit block may occur as the result of an inflammatory reaction at the point of contact between the pacemaker lead and the myocardium. When this occurs, the measured voltage and current thresholds are high but lead impedance is normal.

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ANSWER TO QUESTION 249

B (Braunwald, pp. 721–722; Figs. 37.13–37.15; Table 37.5)

The ECG in the figure depicts atrial fibrillation (AF) with rapid ventricular rate and aberrant conduction in a patient

with Wolff-Parkinson-White (WPW) syndrome and a right posteroseptal accessory pathway. The latter localization is possible because of the negative initial deflections in leads II, III, aVF, and V_1, with upright initial forces in leads I and aVL. Acute treatment of this dysrhythmia should include agents that prolong refractoriness in the accessory pathway, such as intravenous procainamide or amiodarone. In hemodynamically unstable patients, direct-current cardioversion is the treatment of choice. Intravenous verapamil prolongs conduction time in the atrioventricular node without affecting conduction through the accessory pathway. Thus the administration of verapamil to a patient with WPW in AF may *accelerate* conduction through the bypass tract and precipitate ventricular fibrillation, such that it should not be used in this setting.

Electrocardiographic evidence of WPW syndrome is present in approximately 0.25% of healthy individuals. Three basic features characterize the electrocardiographic abnormalities of the syndrome: the presence of a PR interval <120 milliseconds during sinus rhythm; a QRS duration >120 milliseconds with a slurred, slowly rising onset of the QRS in some leads (the delta wave); and secondary ST-segment/T wave changes generally directed opposite to the major QRS vector. The axis of the delta waves on the surface ECG can be used to localize the position of the accessory pathway in the heart. Left free wall accessory pathways are the most common, followed by posteroseptal, right free wall, and anteroseptal locations.

The prevalence of WPW is higher in men and decreases with age. Most associated dysrhythmias are reciprocating (reentrant) tachycardias (80%), with 15% to 30% presenting as AF and 5% as atrial flutter. Although most adults with WPW syndrome have normal hearts, a number of cardiac defects are occasionally associated with this syndrome, including Ebstein anomaly. In patients with Ebstein anomaly, multiple accessory pathways are often present and are located on the right side of the heart, with preexcitation localized to the atrialized ventricle.

ANSWER TO QUESTION 250

C (Braunwald, pp. 543–547; Table 27G.1)

This patient has ischemic cardiomyopathy with a reduced left ventricular ejection fraction of 30% and left bundle branch block with a QRS complex duration of ~190 milliseconds. He is on optimal medical therapy with apparently normal filling pressures by physical examination and has persistent class III symptoms. Accordingly, he meets the guideline-based criteria for cardiac resynchronization therapy (CRT).[1] In addition, based on the reduced ejection fraction and persistent symptoms, he qualifies for implantation of a cardioverter-defibrillator for primary prevention of sudden cardiac death. The results of the COMPANION trial suggest incremental mortality benefit from a device capable of combined cardiac resynchronization and defibrillation over cardiac resynchronization alone in this population. The PROSPECT study did not support the use of echocardiographic measures of dyssynchrony as selection criteria for CRT in patients with a QRS duration ≥120 milliseconds. Patients with systolic heart failure who are most likely to respond to CRT are those in sinus rhythm, with typical left bundle branch block, QRS duration ≥150 milliseconds, and NYHA class II to IV symptoms despite optimal guideline-based medical therapy.

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ANSWER TO QUESTION 251

D (Braunwald, pp. 691–692; Figs. 36.4 and 36.5)

The electrophysiologic tracing depicts a recording of ventricular depolarization over an accessory pathway. The first QRS complex is preexcited, with a short PR interval and delta wave on the surface ECG. The His bundle activation is buried within the ventricular complex (see lead His bundle recording). During the second beat, the accessory pathway is refractory and normal conduction over the atrioventricular (AV) node ensues, generating a normal QRS complex. In this normal complex, His bundle activation clearly precedes ventricular activation, with a measurable His-ventricular interval of 45 milliseconds. Ventricular preexcitation in association with a delta wave is consistent with a diagnosis of Wolff-Parkinson-White (WPW) syndrome.

Patients with ventricular preexcitation and symptomatic tachyarrhythmia require therapy. Options for management include pharmacologic therapy with class IA or IC antiarrhythmic drugs (which prolong the refractory period in the accessory pathway) and invasive treatment with radiofrequency catheter ablation. Both atenolol and verapamil prolong AV nodal conduction time, but do not directly affect conduction through the accessory pathway. As a result, in patients with WPW syndrome and atrial fibrillation, these drugs may actually *enhance* ventricular response and precipitate ventricular fibrillation, and therefore they should be avoided. Radiofrequency catheter ablation in patients with WPW syndrome has a high success rate, a low frequency of complications, and is cost effective. It is the therapy of choice in this symptomatic young patient.

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ANSWER TO QUESTION 252

C (Braunwald, p. 684; Tables 36.1 and 36.4)

Dofetilide is a class III antiarrhythmic drug whose sole electrophysiologic effect appears to be blockade of the rapid component of the delayed rectifier potassium current (I_{Kr}). Its effect is most pronounced in the atria, and the drug is approved for the acute conversion of atrial fibrillation (AF) to sinus rhythm as well as chronic suppression of recurrent AF. Its role in therapy for ventricular arrhythmias is not well established. Dofetilide has a neutral effect on mortality (i.e., it does not increase it) in patients after myocardial infarction.

Dofetilide is well absorbed orally, with over 90% bioavailability. Fifty percent to 60% of the drug is excreted in the urine, whereas the remainder undergoes hepatic metabolism to inert compounds. The drug's dosage must be carefully adjusted based on the creatinine clearance (Ccr), and it should not be administered to patients with a Ccr <20 mL/min. The most important adverse effect of dofetilide is QT interval prolongation with development of torsades de pointes, occurring in 2% to 4% of patients receiving the drug. The risk is highest in patients with hypokalemia, those taking other drugs that prolong repolarization, and when there is baseline QT interval prolongation. For this reason, dofetilide is approved only for inpatient initiation so that the QT interval can be closely monitored. Patients with a corrected baseline QT interval >440 milliseconds are not candidates for dofetilide therapy. Verapamil, ketoconazole, and trimethoprim all increase the serum dofetilide concentration and should not be used concurrently with this drug.

ANSWER TO QUESTION 253

C (Braunwald, pp. 731–732)

This 26-year-old man presents with atrial fibrillation (AF) after the New Year holiday, and most of his prior episodes of AF have occurred following weekends. These facts should prompt consideration of the "holiday heart syndrome," which is the occurrence of palpitations, chest discomfort, and syncope after a binge of alcohol consumption.

The most common arrhythmia associated with this syndrome is AF, followed by atrial flutter and frequent ventricular premature beats. Electrophysiologic testing in subjects without heart disease suggests that alcohol enhances the vulnerability of the heart to induction of atrial arrhythmias. AF in this situation usually occurs several hours after the last drink and may also be related to the onset of early withdrawal symptoms, especially sympathetic hyperactivity. Treatment is typically focused on abstinence from alcohol.

Regular excess alcohol consumption is also an important cause of hypertension and left ventricular (LV) systolic dysfunction. In fact, ethanol abuse is a leading cause of nonischemic dilated cardiomyopathy in industrialized nations. The likelihood of developing cardiomyopathy appears to correlate with the amount and duration of daily alcohol consumption, but there are wide variations in the susceptibility of individual patients to myocardial toxicity. With abstinence from alcohol, LV systolic and diastolic dysfunctions often improve.

Cocaine is associated with multiple cardiovascular complications, most commonly myocardial ischemia and infarction due to coronary artery vasoconstriction and cocaine-enhanced platelet aggregation. Long-term cocaine use is also associated with left ventricular hypertrophy and systolic dysfunction, perhaps the sequelae of repeated, profound sympathetic stimulation. The direct arrhythmogenic potential of cocaine is not well established.

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ANSWERS TO QUESTIONS 254 TO 257

254–A, 255–D, 256–B, 257–C (Braunwald, pp. 604–609, 613; Figs. 33.1 and 33.3; Table 33.1; see also Answers to Questions 206, 229, and 240)

Many specific syndromes associated with ventricular tachycardia (VT) have been identified. The *long QT syndromes*, either familial or acquired, can result in ventricular arrhythmias (torsades de pointes) and sudden death. The *familial* phenotypes include (1) the autosomal recessive Jervell and Lange-Nielsen syndrome and (2) the autosomal dominant Romano-Ward syndrome. The former is associated with sensorineural deafness, whereas patients with the latter condition have normal hearing. Genetic abnormalities in potassium and sodium channels cause the familial long QT syndromes, and specific mutations carry varying degrees of risk for the development of ventricular arrhythmias. The *acquired* form of long QT syndrome can result from many medications, including quinidine, procainamide, sotalol, tricyclic antidepressants, erythromycin, and ketoconazole. Electrolyte abnormalities, including hypokalemia, hypomagnesemia, and hypocalcemia, can also result in significant prolongation of the QT interval and predispose to ventricular arrhythmias.

Right ventricular outflow tract VT is a type of idiopathic VT with a characteristic left bundle branch block morphology and inferior axis. Vagal maneuvers and adenosine administration may terminate this type of VT, whereas exercise or isoproterenol infusion can initiate it. Beta blockers and verapamil may suppress VT in this disorder, and catheter ablation can be curative. The prognosis is generally good.

Brugada syndrome is a form of idiopathic ventricular fibrillation (VF) associated with characteristic abnormalities on the surface ECG and a high risk of sudden cardiac death. The ECG in sinus rhythm typically demonstrates a right bundle branch block morphology with unusual ST-segment elevation in the anterior precordial leads. Loss of function mutations in the gene that encodes the cardiac sodium channel *(SCN5A)* have been identified in some families with this syndrome. Implantable cardioverter-defibrillator implantation is warranted in patients with Brugada syndrome with spontaneous VT/VF or history of aborted sudden cardiac death (class I indication) or history of syncope (class IIa).

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ANSWERS TO QUESTIONS 258 TO 261

258–D, 259–B, 260–A, 261–C (Braunwald, pp. 670–673; Table 36.1)

The Vaughan-Williams classification is a commonly used system for grouping similarly acting antiarrhythmic agents. Not all drugs within a class have identical effects, and drug actions are more complex than those depicted by this classification scheme.

Class I drugs predominantly block the fast sodium channels and are divided into three subgroups. Class IA drugs (e.g., quinidine, procainamide, disopyramide) reduce the rate of rise of the action potential upstroke (V_{max}) and prolong the

action potential duration. Class IB drugs (e.g., lidocaine, mexiletine, phenytoin) reduce V_{max} to only a minimal degree and *shorten* the action potential duration. Class IC drugs (e.g., flecainide, propafenone) reduce V_{max}, slow conduction, and minimally prolong refractoriness.

Class II drugs are beta-adrenergic receptor blockers (e.g., metoprolol, timolol, propranolol). Class III drugs (e.g., sotalol, amiodarone, dronedarone, ibutilide, dofetilide) primarily block potassium channels and prolong repolarization. Class IV drugs are slow calcium channel ($I_{Ca.L}$) blockers (e.g., verapamil, diltiazem).

ANSWERS TO QUESTIONS 262 TO 265

262–B, 263–C, 264–C, 265–A (Braunwald, p. 737)

Many antiarrhythmic drugs are available to maintain sinus rhythm in patients with a history of atrial fibrillation (AF). Standard beta blockers are sometimes useful for this purpose and are generally well tolerated. Conversely, when more potent antiarrhythmic agents are required, the benefit of the drug must be weighed against the risk of potentially dangerous adverse effects. Such risk can be minimized by choosing a drug that is appropriate for the patient's underlying cardiac disease (Table 2.1). For example, Vaughan-Williams class IC drugs (e.g., flecainide or propafenone) are well tolerated and are reasonably safe drugs for patients without ischemic or structural heart disease, but are associated with increased morbidity and mortality in patients with these conditions. Similarly, class IA agents (e.g., quinidine) and the class III drug sotalol should not be used in patients with a prolonged QT interval or left ventricular hypertrophy (e.g., wall thickness >1.3 cm) because of the risk of precipitating torsades de pointes. The class III drug amiodarone is the most potent agent available to prevent recurrent AF. It is only rarely proarrhythmic, even in patients with underlying structural heart disease. It is, however, associated with significant noncardiac toxicities (especially affecting the lungs, liver, and thyroid), and therefore therapy with this drug must be monitored carefully.

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TABLE 2.1

CARDIAC CONDITION	FIRST-LINE DRUG	SECOND-LINE DRUG
Structurally normal heart without coronary disease	Class IC agent (e.g., flecainide, propafenone), sotalol, dronedarone	Amiodarone
Hypertension with LV wall thickness >1.3 cm	Amiodarone	
Coronary artery disease with preserved LV function	Sotalol, dofetilide, dronedarone	Amiodarone
Heart failure	Amiodarone, dofetilide	

LV, Left ventricular.

ANSWERS TO QUESTIONS 266 TO 269

266–C, 267–D, 268–A, 269–E (Braunwald, pp. 496–498; Fig. 25.7)

Diuretics are frequently used in the management of heart failure and hypertension. Collectively, they act to lower plasma volume by increasing excretion of sodium and water. Diuretics can be classified into four categories based on mechanism and site of action in the nephron: (1) carbonic anhydrase inhibitors (e.g., acetazolamide), which act at the proximal tubule; (2) loop diuretics, which inhibit the $Na^+/K^+/Cl^-$ transporter in the thick ascending limb of the loop of Henle (e.g., furosemide, torsemide, bumetanide, and ethacrynic acid); (3) thiazide-like diuretics, which inhibit the Na^+/Cl^- cotransporter in the distal convoluted tubule (e.g., chlorothiazide, hydrochlorothiazide, metolazone, indapamide, and chlorthalidone); and (4) potassium-sparing diuretics, which block sodium reabsorption in the collecting duct. Potassium-sparing diuretics are available in two classes: (1) those that directly inhibit epithelial sodium channels (e.g., triamterene, amiloride) and (2) those that antagonize the mineralocorticoid type I receptor, inhibiting the effects of aldosterone (spironolactone and eplerenone).

Each type of diuretic is associated with potential adverse effects. For example, acetazolamide, a carbonic anhydrase inhibitor, may result in increased urinary excretion of sodium, potassium, and bicarbonate, leading to metabolic acidosis. As a result of this "adverse effect," it can be useful in treating alkalemia caused by other diuretics.

Metolazone is a thiazide-like diuretic that can elevate the serum calcium and uric acid levels. It can also result in hypokalemia and hypomagnesemia, particularly when utilized in combination with loop diuretics. Hydrochlorothiazide, which is in the same family as metolazone, can cause elevations in serum low-density lipoproteins and triglyceride levels.

Torsemide, like other loop diuretics, may cause ototoxicity. High doses of loop diuretics should be used cautiously in combination with aminoglycoside antibiotics due to an additive ototoxic effect.

The aldosterone antagonists may be associated with hyperkalemia, particularly in patients with renal insufficiency, owing to their inhibition of potassium excretion in the collecting duct. This side effect can be favorably exploited to help limit potassium wasting caused by loop diuretics. Spironolactone, in contrast to eplerenone, has potent antiandrogenic side effects and may be associated with gynecomastia in male patients.

ANSWERS TO QUESTIONS 270 TO 273

270–D, 271–B, 272–C, 273–E (Braunwald, pp. 783–785; Fig. 41.9; Table 41.1; see also Answer to Question 246)

The listed examples are all class I indications for pacing, as recommended by the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines. In general, dual-chamber pacemakers should be used in patients who require sensing or pacing of both the atria and the ventricles. Rate-modulating pacemakers should be used in patients with chronotropic incompetence due to abnormal or absent sinus node function.

In the 58-year-old man with tachycardia-bradycardia syndrome who developed symptomatic sinus bradycardia with beta blocker therapy, the most appropriate pacemaker mode would be DDDR. Ventricular pacing is necessary here because there is a risk of atrioventricular block due to beta blockers, and the rate-modulating function is important because of the abnormal sinus node function. Use of a non–rate-responsive (DDD) pacemaker in this patient would most likely result in lower rate pacing most of the time, with inappropriate response to physical activity.

In the 70-year-old woman with atrial fibrillation (AF) who complains of dizziness and is found on examination to have a ventricular rate of 30 beats/min, VVIR pacing is most appropriate. Atrial sensing or pacing is not possible because of chronic AF, and the rate-modulating function is necessary because of the evident chronotropic dysfunction.

In the 62-year-old man with complete heart block after aortic valve surgery, there is no indication of sinus node disease and DDD pacing should be sufficient.

In the 45-year-old man with symptomatic sinoatrial exit block and junctional escape rhythm, loss of sinus mechanism requires atrial pacing and rate modulation. There is no evidence of AV block and ventricular pacing support is therefore not necessary, so the AAIR pacing mode is appropriate.

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ANSWERS TO QUESTIONS 274 TO 277

274–D, 275–C, 276–A, 277–B (Braunwald, pp. 1586–1588, 1594–1595; eTable 77.2; pp. 1621–1622)

Multiple disease processes produce a clinical phenotype of dilated cardiomyopathy (DCM) with electrical instability. Sarcoidosis is a systemic inflammatory disease of unknown etiology that most often causes thoracic lymphadenopathy and interstitial lung disease; cardiac involvement can be identified by imaging studies in at least 25% of patients with pulmonary sarcoidosis. Clinical cardiac sarcoid findings include cardiomyopathy of variable severity accompanied by heart block and/or ventricular tachycardia (VT). Although the identification of noncaseating granulomas by endomyocardial biopsy is consistent with cardiac sarcoid, the false-negative rate is high because of the patchy nature of the disease. Cardiac magnetic resonance imaging with gadolinium enhancement is sensitive for detecting abnormalities in cardiac sarcoid; ^{18}F-fluorodeoxyglucose positron emission tomography is complementary to magnetic resonance imaging, and serial studies are helpful in monitoring the response to therapy.

Giant cell myocarditis is notable for its rapidly progressive clinical course, widespread necrosis with giant cells on histology, and association with autoimmune disease and thymoma. Prompt diagnosis via endomyocardial biopsy along with early institution of mechanical circulatory support and immunosuppression is critical, because the prognosis is generally poor, with many cases progressing to cardiac transplant or death.

Chagas disease is caused by the protozoan parasite *Trypanosoma cruzi* endemic to Central and South America. A common noncardiac manifestation of Chagas disease is gastrointestinal dysmotility. Cardiac involvement is notable for conduction disease, apical aneurysm formation often with mural thrombus, and VT. Chagas disease is a common cause of heart failure leading to transplantation in South America.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable disorder of cardiac desmosomes characterized by fibrofatty infiltration of the right ventricular myocardium (see Answer to Question 236). The hallmark of ARVC on the surface ECG (apparent in ~50% of cases) is a low-amplitude "notch" in the ST segment near the terminal portion of the QRS complex in the right precordial leads V_1 to V_3 (termed an *epsilon wave*). Additional electrocardiographic findings include right-sided T wave inversions and ventricular tachycardia with a left bundle branch block morphology indicating its origin in the right ventricle. The cardinal pathologic feature of ARVC, typically apparent on immunohistochemistry, is evidence of disruption in the desmosomes connecting cardiomyocytes, leading to abnormal cell-to-cell signaling and loss of structural integrity.

Cardiolaminopathy is a cause of autosomal dominant familial DCM resulting from a mutation in the *LMNA* gene, encoding the nuclear envelope protein lamin A/C. The clinical course is highly variable, with typically subtle initial manifestations of conduction system disease (e.g., first-degree atrioventricular block) frequently delaying recognition until adulthood when more significant heart block, arrhythmias, or ventricular dysfunction become apparent.

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ANSWERS TO QUESTIONS 278 TO 282

278–C, 279–B, 280–A, 281–D, 282–E (Braunwald, pp. 848–851; Tables 43.1 and 43.2)

The approach to the patient with syncope begins with a careful clinical history and physical examination, which can often suggest a specific cause. For example, syncope in patients with hypertrophic cardiomyopathy typically occurs with exertion, and examination may demonstrate the typical murmur associated with dynamic left ventricular outflow tract obstruction. Syncope with exertion is also typical of patients with the long QT syndrome (LQT1 in particular), aortic stenosis, pulmonary hypertension, mitral stenosis, coronary artery disease, and idiopathic ventricular tachycardia.

Patients with the subclavian steal syndrome may present with syncope after arm exercises. In this condition, atherosclerotic stenosis of a subclavian artery is present proximal to the origin of the vertebral artery. Retrograde blood flow through the ipsilateral vertebral artery, enhanced by exercise

involving the affected arm, can induce cerebral ischemia. Auscultation over the supraclavicular fossa may demonstrate a bruit caused by the subclavian stenosis, and the blood pressure is usually diminished in the affected arm.

Vasovagal (neurocardiogenic) syncope occurs after a sudden unexpected pain; an unpleasant sight, sound, or smell; prolonged standing; or a stressful situation. This common form of syncope is characterized by the abrupt onset of hypotension with or without bradycardia.

Carotid sinus hypersensitivity is manifest during stimulation of the carotid sinus baroreceptors and syncopal events in patients with this disorder may be associated with head rotation or application of pressure to the carotid sinus with shaving or wearing tight shirt collars. The physiologic response to carotid hypersensitivity syndrome can be cardioinhibitory (e.g., marked bradycardia), vasodepressor (e.g., decrease in blood pressure in the absence of bradycardia), or mixed.

Left atrial myxoma is a rare cause of syncope. Symptoms may be positional as the tumor shifts and transiently obstructs the mitral orifice.

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ANSWERS TO QUESTIONS 283 TO 286

283–C, 284–E, 285–A, 286–B (Braunwald, p. 1598; pp. 1815–1817)

Each of the conditions listed is associated with sustained increases in cardiac output (CO) that may ultimately precipitate heart failure symptoms. Clinical findings in hyperthyroidism include constitutional changes such as nervousness, diaphoresis, heat intolerance, and fatigue, as well as cardiovascular manifestations such as palpitations, atrial fibrillation, and sinus tachycardia with a hyperkinetic heart action. Cardiovascular examination may reveal tachycardia, widened pulse pressure, brisk arterial pulsations, and a variety of findings associated with the hyperkinetic state. These may include a prominent S_1, the presence of an S_3 or S_4 or both, and a midsystolic murmur along the left sternal border secondary to increased flow. When a particularly hyperdynamic cardiac effect is seen, this murmur may have a scratching component known as the *Means-Lerman scratch.* This is thought to be caused by the rubbing together of normal pleural and pericardial surfaces.

Systemic arteriovenous (AV) fistulas may be acquired as a result of trauma, or they may be congenital. The increase in CO that such lesions create is related to the size of the communication and the resultant reduction in the systemic vascular resistance that it promotes. In general, systemic AV fistulas lead to a widened pulse pressure, brisk arterial pulsations, and mild tachycardia. The *Nicoladoni-Branham sign,* defined as the slowing of heart rate after manual compression of the fistula, is commonly present. The maneuver may also raise arterial and lower venous pressure.

Osler-Weber-Rendu disease, or hereditary hemorrhagic telangiectasia, is an inherited condition that may include AV fistulas, especially in the liver and the lungs. The disease may produce a hyperkinetic circulation with abdominal bruits and hepatomegaly due to intrahepatic AV connections.

Beriberi heart disease is a rare condition caused by severe thiamine deficiency that leads to impaired oxidative metabolism. It occurs most frequently in the Far East; in Western society, alcoholic cardiomyopathy may contribute to, or overlap with, this syndrome because of the tendency for alcoholics to become vitamin deficient. Patients with beriberi may present with a high-output state due to vasodilation and increased blood volume, followed by eventual impairment of contractile function. Typical findings include peripheral neuropathy with paresthesias of the extremities, decreased or absent knee and ankle jerks, hyperkeratinized skin lesions, and painful glossitis. The presence of edema characterizes "wet beriberi" and differentiates this condition from the "dry" form.

Carcinoid syndrome is an uncommon disease that results from the release of serotonin and other vasoactive substances by carcinoid tumors. Physical findings may include cutaneous flushing, telangiectasia, diarrhea, and bronchial constriction due to release of humoral mediators.

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ANSWERS TO QUESTIONS 287 TO 290

287–A, 288–C, 289–B, 290–D (Braunwald, pp. 680–681)

Beta blockers can be classified by their degree of cardioselectivity, that is, their ability to block the $beta_1$-adrenergic receptors in the heart compared with the $beta_2$-adrenergic receptors in the bronchi, peripheral blood vessels, and other sites. Beta blockers can be further classified into those that possess intrinsic sympathomimetic activity (ISA) versus those that do not. Beta blockers with ISA induce an agonist response, but at the same time block the greater agonist effects of endogenous catecholamines. The result is to lower blood pressure similar to other beta blockers but to cause less bradycardia.

Acebutolol is a selective beta blocker with ISA. Atenolol, metoprolol, and esmolol are examples of selective beta blockers without ISA. Atenolol and nadolol are less lipid soluble than other beta blockers; as a result, they may cause fewer central nervous system side effects.

Pindolol, carteolol, and penbutolol are nonselective beta blockers with ISA. Nadolol, propranolol and timolol are examples of nonselective beta blockers without ISA.

Carvedilol is a minimally $beta_1$-receptor selective agent that also expresses high affinity for $alpha_1$-adrenergic receptors and is used primarily in patients with heart failure. Because of its vasodilating property, orthostatic symptoms can occur and upward dose titration must be undertaken carefully.

ANSWERS TO QUESTIONS 291 TO 294

291–A, 292–C, 293–B, 294–B (Braunwald, Fig. 23.7; eFig. 23.9; Fig. 68.14)

Left ventricular mass increases in response to chronic pressure or volume overload or secondary to primary myocardial

disease. With predominant pressure overload, as in aortic stenosis, there is an increase in mass with little change in chamber volume (concentric hypertrophy, as exemplified by patient A). In contrast, chronic volume overload (as in aortic or mitral regurgitation), or primary dilated cardiomyopathy, results in ventricular dilatation with only a small increase in wall thickness (eccentric hypertrophy). In chronic regurgitant disease (patient B), there is usually an increased stroke volume in the compensated state, whereas in cardiomyopathy there is impaired systolic function and a reduced stroke volume (patient C).

SECTION III QUESTIONS

(CHAPTERS 44 TO 66)

Preventive Cardiology; Atherosclerotic Cardiovascular Disease

Brian A. Bergmark and Leonard S. Lilly

Directions:

For each below, select the ONE BEST response.

QUESTION 295

A 48-year-old man with elevated low-density lipoprotein (LDL) cholesterol, hypertension, and a family history of premature coronary disease presents to his physician's office for routine evaluation. He does not have diabetes. He smokes one pack of cigarettes per day and is exploring means to quit. His 10-year risk of atherosclerotic cardiovascular disease using the ACC/AHA Pooled Cohort Equations was recently calculated to be 18.8%, compared with a 1.7% risk in a similarly aged man with optimal risk factors. He also has a history of supraventricular tachycardia that has been successfully suppressed by verapamil, after not tolerating a beta blocker. He is currently taking simvastatin 20 mg daily, verapamil sustained-release 180 mg daily, and aspirin 81 mg daily. His blood pressure is 138/70 mm Hg. Laboratory studies include total cholesterol 250 mg/dL; high-density lipoprotein cholesterol 42 mg/dL; LDL cholesterol 166 mg dL; and triglycerides 210 mg/dL. The hepatic transaminase levels are normal. Which of the following is the most appropriate recommendation regarding lipid-altering therapy?

A. He does not have active coronary artery disease—no further adjustment in medication is required
B. Simvastatin should be increased to 40 mg daily
C. Simvastatin should be increased to 80 mg daily
D. Replace simvastatin with atorvastatin 20 mg daily or rosuvastatin 10 mg daily
E. Gemfibrozil 150 mg twice daily should be added

QUESTION 296

Which one of the following interventions does not have a blood pressure–lowering effect?

A. A diet that reduces caloric intake by 1000 calories per day
B. Reduction of dietary sodium
C. Daily magnesium and calcium supplements
D. Reduction of ethanol consumption to less than 1 oz (30 mL)/day

QUESTION 297

With respect to renovascular hypertension, which of the following statements is correct?

A. Worsening renal function with angiotensin-converting enzyme inhibitor therapy suggests unilateral renovascular disease
B. Atherosclerotic disease most commonly involves the proximal third of the main renal artery
C. Fibromuscular renovascular disease arises primarily in women aged >60 years
D. When atherosclerotic renal artery stenosis is found, mechanical revascularization is the treatment of choice
E. Patients with severe, accelerated hypertension are unlikely to have renovascular disease as the cause

QUESTION 298

Which of the following statements regarding hypertension is TRUE?

A. Pure "white coat" hypertension is found in 5% of patients
B. Renal parenchymal disease is the most common cause of secondary hypertension
C. Inaccurately low blood pressure is typically recorded in patients with sclerotic brachial arteries
D. When measuring the blood pressure, an inappropriately small cuff size results in a spuriously low systolic measurement
E. Coarctation of the aorta, Cushing disease, and pheochromocytoma together account for ~10% of hypertensive patients

QUESTION 299

A 76-year-old man with type 2 diabetes and hypertension sustained an inferior non-ST-elevation myocardial infarction 3 years ago. A right coronary artery drug-eluting stent was placed and he has been free of angina since. His left ventricular ejection fraction is 45% with inferior wall hypokinesis. He experiences intermittent peripheral edema, particularly after salty meals, relieved by furosemide. He has stable claudication of the right calf that develops after walking two blocks. Review of systems is notable for obstructive sleep apnea and

recurrent urinary tract infections. His current medications are aspirin 81 mg daily, atorvastatin 80 mg daily, metoprolol succinate 25 mg daily, lisinopril 20 mg daily, furosemide 20 mg daily, and metformin 500 mg twice daily. The serum creatinine is 1.14 mg/dL and hemoglobin A1c is 9.4%.

Which of the following would be most appropriate to prescribe to improve this patient's glycemic control and reduce his risk of future cardiac events?

A. Pioglitazone (a thiazolidinedione)
B. Liraglutide (a glucagon-like peptide [GLP]-1 receptor agonist)
C. Empagliflozin (a sodium/glucose co-transporter [SGLT]-2 inhibitor)
D. Linagliptin (a dipeptidyl peptidase [DPP]-4 inhibitor)

QUESTION 300

Which of the following statements regarding the association of oral contraceptives (OCs) and hypertension is NOT correct?

A. Among OC users, the likelihood of developing hypertension is increased by alcohol consumption
B. The likelihood of developing hypertension is independent of the age of the user
C. Elevated blood pressure normalizes within 6 months of initiating OC therapy in 50% of patients
D. The mechanism for contraceptive-induced hypertension likely involves renin-aldosterone-mediated volume expansion

QUESTION 301

A 57-year-old black businessman visits his primary physician for follow-up of dyslipidemia, for which he takes atorvastatin 10 mg daily. His blood pressure is 138/84 mm Hg, similar to measurements at other recent office visits and on a home sphygmomanometer (range: 134 to 138/78 to 86 mm Hg). He does not smoke. He consumes three to four alcoholic beverages per week. His body mass index is 28. His predicted 10-year risk for a first atherosclerotic cardiovascular event is 12% using the ACC/AHA pooled cohort risk assessment equations. Which of the following statements is consistent with current ACC/AHA hypertension guidelines?

A. His blood pressure is not in a range that requires intervention; only serial monitoring of blood pressure is needed
B. He should follow lifestyle modifications, including cessation of alcohol intake and weight loss, but drug therapy should not be initiated at this point
C. He should follow lifestyle modifications and begin antihypertensive drug therapy using a beta blocker or angiotensin-converting enzyme inhibitor
D. His target on-therapy blood pressure is <130/80 mm Hg

QUESTION 302

Which of the following statements regarding adverse effects of antihypertensive agents is correct?

A. Cough resulting from angiotensin-converting enzyme (ACE) inhibitors arises more commonly in Caucasians than in Asians
B. ACE inhibitor–induced cough reliably resolves within 5 days after discontinuation of the drug
C. Gingival hyperplasia is a recognized adverse effect of calcium channel blockers
D. Bradycardia is a common side effect of hydralazine
E. Volume depletion and alopecia are established side effects of minoxidil therapy

QUESTION 303

Which of the following abnormalities is NOT associated with the use of thiazide-type diuretics?

A. Hypomagnesemia
B. Hypouricemia
C. Hypercalcemia
D. Hypertriglyceridemia
E. Hyponatremia

QUESTION 304

Which of the following statements regarding the effects of HMG-CoA reductase inhibitors ("statins") is correct?

A. Expression of hepatic low-density lipoprotein receptors is decreased
B. Hepatic production of very-low-density lipoprotein is increased
C. Myonecrosis with muscle symptoms and elevated serum creatine kinase (CK) >10 times normal occurs in 5% of patients
D. Concurrent administration of erythromycin increases the risk of myositis

QUESTION 305

Which statement regarding the effect of medications on the serum lipid profile is correct?

A. Nonselective beta blockers increase high-density lipoprotein (HDL) levels
B. Thiazide diuretics decrease triglyceride levels
C. Estrogen replacement therapy decreases HDL and triglyceride levels
D. Protease inhibitors raise total cholesterol and triglyceride levels
E. Corticosteroids reduce triglyceride levels

QUESTION 306

Which of the following statements regarding genetic lipoprotein disorders is correct?

A. Familial hypercholesterolemia (FH) results from mutations in the gene that encodes the enzyme HMG-CoA reductase
B. Mutations in the apo B gene results in a form of hypercholesterolemia that is indistinguishable from FH
C. Patients with familial hypertriglyceridemia typically develop xanthomas or xanthelasmas
D. Gain-of-function mutations in the *PCSK9* gene result in decreased low-density lipoprotein (LDL) cholesterol levels and a reduction in coronary events
E. Patients with familial combined hyperlipidemia have elevations of both LDL and high-density lipoprotein cholesterol levels and a rate of coronary events similar to populations with normal lipid levels

QUESTION 307

Which of the following statements regarding niacin is correct?

A. It acts primarily via upregulation of the hepatic low-density lipoprotein (LDL) receptor
B. It raises plasma high-density lipoprotein cholesterol levels, but has no effect on LDL levels
C. It reduces the circulating level of lipoprotein (a)
D. Niacin added to statin therapy reduces coronary event rates

QUESTION 308

Which of the following statements about apolipoproteins is correct?

A. Apo AI is a major component of low-density lipoprotein cholesterol
B. Apo B48, synthesized by the small intestine, and apo B100, secreted by the liver, are synthesized by two distinct genes
C. Apo B48 is the major apoprotein in high-density lipoprotein cholesterol
D. Type III hyperlipoproteinemia (also termed dysbetalipoproteinemia) is a disorder of apoprotein E

QUESTION 309

Which of the following statements regarding hypertriglyceridemia is NOT correct?

A. Hypertriglyceridemia is associated with diabetes mellitus, chronic renal failure, and obesity
B. Cigarette smoking and excessive alcohol consumption are associated with secondary hypertriglyceridemia
C. In epidemiologic studies, adjustment for high-density lipoprotein levels and other factors diminishes the role of hypertriglyceridemia as an independent predictor of coronary artery disease
D. There is a stronger relationship between hypertriglyceridemia and cardiovascular risk in women than in men
E. The addition of fenofibrate to simvastatin lowers triglyceride levels and has been shown to reduce coronary events in type 2 diabetic patients, compared with simvastatin alone

QUESTION 310

Which of the following statements regarding lipoprotein (a) [Lp(a)] is NOT correct?

A. One component of Lp(a) is structurally identical to low-density lipoprotein and another is similar to plasminogen
B. Lp(a) levels do not vary significantly between racial groups
C. Lp(a) levels vary little with changes in dietary fat intake
D. Observational studies have associated elevated Lp(a) levels with cardiovascular events

QUESTION 311

Which statement regarding lipid-lowering medications is NOT correct?

A. Fibric acid derivatives lower triglycerides, raise high-density lipoprotein levels, and may increase low-density lipoprotein cholesterol levels
B. Fish oil therapy raises triglyceride levels
C. Other medications should not be taken within 1 hour before or within 3 hours after taking a bile acid–binding resin
D. Ezetimibe added to statin therapy in patients with a recent acute coronary syndrome reduces subsequent coronary event rates more than statin therapy alone

QUESTION 312

A 70-year-old businessman presented to the emergency department (ED) of a university medical center with multiple episodes of anterior substernal chest discomfort over the prior 2 days, each lasting 5 to 10 minutes in duration. He has a history of hypertension, elevated low-density lipoprotein-cholesterol, and had been a regular cigarette smoker until stopping 4 months ago. He experienced a single transient ischemic attack 1 year ago. His home medications included aspirin 81 mg daily, atorvastatin 10 mg daily, and lisinopril 10 mg daily. The initial ECG was unremarkable, but while being evaluated in the ED he experienced another 5-minute episode of chest discomfort, during which the ECG demonstrated transient 1-mm ST depression in leads II, III, aVF, V_5, and V_6. The initial cardiac troponin T was 0.06 ng/mL (reference range <0.01). He received aspirin, IV unfractionated heparin, beta blocker, and high-dose (80 mg) atorvastatin therapies and suffered no further episodes of chest discomfort.

On examination, the blood pressure is 116/82, heart rate 72 beats/min, jugular venous pressure 6 cm water, the chest is clear, cardiac examination shows an apical S_4 and no murmur, the abdomen is benign, and there is no peripheral edema. No arrhythmias are observed on telemetry. Three hours after presentation, the cardiac troponin T is 0.08 ng/mL. The serum creatinine is 1.11 mg/dL.

Of the following approaches, which would be most appropriate?

A. Add prasugrel and pursue an ischemia-guided (i.e., "conservative") strategy
B. Add clopidogrel and pursue an ischemia-guided strategy
C. Add either ticagrelor or clopidogrel and pursue an early invasive strategy
D. Add prasugrel and pursue an early invasive strategy
E. Do not add additional antiplatelet therapy at this time and pursue an ischemia-guided strategy

QUESTION 313

Which of the following statements regarding the secondary prevention of atherothrombotic stroke is correct?

A. Clopidogrel monotherapy is superior to aspirin plus dipyridamole for secondary prevention of noncardioembolic stroke
B. Hypertension should not be a target of secondary prevention after an ischemic stroke because elevated blood pressure is necessary to maintain adequate cerebral perfusion
C. Treatment with HMG-CoA reductase inhibitors reduces the risk of recurrent stroke
D. The combination of aspirin plus clopidogrel is superior to aspirin alone for prevention of recurrent stroke
E. Compared with aspirin, chronic warfarin therapy reduces the risk of recurrent stroke

QUESTION 314

Which of the following statements regarding the relationship between alcohol and coronary artery disease is NOT correct?

A. Moderate alcohol intake (1 or 2 drinks daily) is associated with a lower incidence of coronary heart disease than is no alcohol intake
B. Alcohol consumption reduces platelet aggregation
C. Heavy alcohol intake is associated with increased cardiovascular mortality
D. Alcohol lowers low-density lipoprotein levels
E. Alcohol raises high-density lipoprotein levels

QUESTION 315

Which of the following statements regarding smoking cessation is NOT correct?
A. Smoking cessation reduces the risk of a coronary event by 50% within 2 years
B. Patients who continue to smoke after a myocardial infarction have twice the mortality rate of those who stop smoking
C. Patients who successfully quit usually do so after five or more unsuccessful attempts
D. Physician counseling is as effective as pharmacologic aids in achieving smoking cessation

QUESTION 316

Which of the following statements regarding exercise training and rehabilitation of patients with coronary artery disease is TRUE?
A. Home programs should emphasize bursts of exercise to the onset of marked dyspnea
B. Augmented cardiac output during exercise is due more to an increase in stroke volume than in heart rate
C. During exercise, increased myocardial oxygen consumption is provided more by a rise in augmented oxygen extraction than by coronary blood flow
D. Exercise-based cardiac rehabilitation participation is associated with lower mortality rates
E. Approximately 80% of the improvement in exercise performance with physical training is due to increased cardiac output and 20% to peripheral adaptations that improve tissue oxygen extraction

QUESTION 317

Which of the following statements regarding homocysteine is NOT correct?
A. Inherited defects of methionine metabolism may cause extremely high serum levels of homocysteine and premature atherothrombosis
B. Polymorphisms in the methylene tetrahydrofolate reductase gene are associated with elevated homocysteine levels
C. Epidemiologic studies have linked mild hyperhomocysteinemia with an increased risk of coronary events
D. Folic acid and other vitamin B supplements reduce serum homocysteine levels
E. Dietary supplementation with a combination of B vitamins (folic acid, B_6, and B_{12}) reduces the risk of atherothrombotic events

QUESTION 318

Which of the following is NOT a component of the atherogenic "metabolic syndrome"?
A. Hyperglycemia
B. Elevated serum triglycerides
C. Abdominal obesity
D. Serum low-density lipoprotein >140 mg/dL
E. Hypertension

QUESTION 319

A 52-year-old woman presents for routine outpatient management. She is interested in nonpharmacologic approaches to blood pressure reduction. Which of the following statements is TRUE?
A. Acupuncture is an effective modality to achieve long-term blood pressure reduction
B. Biofeedback methods that teach individuals to breathe more rapidly are effective for lowering blood pressure
C. Garlic supplementation stimulates angiotensin II production and raises blood pressure
D. The DASH diet can lead to a sustained 10 mm Hg decline in systolic blood pressure

QUESTION 320

Clinical trials of which of the following dietary interventions have NOT shown significant improvements in coronary artery disease endpoints?
A. Mediterranean-style diet supplemented with alpha-linolenic acid
B. Mediterranean-style diet supplemented with extra-virgin olive oil or nuts
C. Low-carbohydrate, high-protein, high-fat diet (e.g., Atkins-style diet)
D. Regular fatty fish or fish oil consumption

QUESTION 321

Which of the following statements about pharmacologic therapy for secondary prevention of coronary artery disease is NOT correct?
A. Long-term aspirin use after myocardial infarction (MI) reduces cardiovascular mortality, re-infarction, and stroke rates
B. After MI, beta blocker therapy significantly reduces mortality over the next 2 to 3 years
C. Angiotensin-converting enzyme inhibitors administered after MI confer an early mortality reduction only in patients with left ventricular dysfunction
D. Administration of HMG-CoA reductase inhibitors reduces cardiovascular deaths after MI in patients with average cholesterol levels
E. After an acute MI, intensive lipid lowering with a high-dose statin confers better clinical outcomes compared with only moderate lipid lowering

QUESTION 322

Which of the following statements regarding heterozygous familial hypercholesterolemia is correct?
A. It is a relatively common disorder with a gene frequency of at least 1 in 500 persons in the population
B. Tendon xanthomas are rare
C. It is inherited as a recessive trait
D. Cutaneous planar xanthomas are common
E. The fundamental defect is the presence of only one-quarter of the normal number of low-density lipoprotein surface receptors

QUESTION 323

Which of the following is characteristic of familial hypertriglyceridemia?
A. Plasma low-density lipoprotein is usually high
B. Plasma triglyceride levels can rise as high as 1000 mg/dL after a meal

C. Plasma high-density lipoprotein cholesterol is usually increased
D. It is accompanied by a threefold increased incidence of atherosclerosis
E. Hypertriglyceridemia is usually manifest in childhood

QUESTION 324

Which of the following statements about coronary stent thrombosis is NOT correct?
A. The strongest predictor of late stent thrombosis is premature discontinuation of dual antiplatelet therapy
B. The risk of bare metal stent thrombosis is greatest 2 to 6 months following implantation
C. Stent thrombosis has been reported to occur more than a year after the placement of drug-eluting stents
D. Late-stent thrombosis is more likely to occur in individuals with diabetes or renal failure than in patients without these conditions

QUESTION 325

A 60-year-old man was admitted to the hospital with an acute anterior myocardial infarction (MI). He underwent urgent cardiac catheterization and successful reperfusion was achieved after a complex coronary angioplasty with stent placement. His hospital course was complicated by rising serum creatinine and urea nitrogen levels. In addition, a purple, net-like discoloration developed on his lower extremities (Fig. 3.1). Which of the following statements is correct?
A. These findings likely resulted from the presenting MI rather than from the catheterization procedure
B. The urinalysis likely reveals an active sediment with cells and casts
C. A high serum complement level is likely
D. Transient eosinophilia is often part of this syndrome
E. Recovery of renal function within a few days is expected

QUESTION 326

Which of the following statements about low-density lipoprotein (LDL) is correct?
A. Apo AI comprises 25% of LDL mass
B. LDL is derived from metabolism of high-density lipoprotein
C. The predominant lipid components of LDL are esterified cholesterol and triglyceride

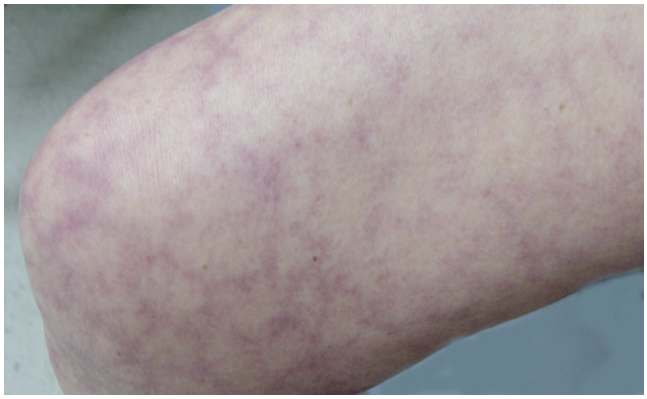

FIG. 3.1 *From Firestein.* Kelley's Textbook of Rheumatology. *8th ed. Philadelphia: Elsevier; 2008.*

D. The majority of patients with plasma LDL >190 mg/dL carry a familial hypercholesterolemia mutation

QUESTION 327

Which of the following statements regarding high-sensitivity C-reactive protein (hsCRP) is NOT correct?
A. Statins reduce hsCRP in a manner directly related to their low-density lipoprotein-lowering effect
B. An hsCRP level >3 mg/L in a patient with unstable angina is associated with an increased risk of recurrent coronary events
C. An elevated level of hsCRP is predictive of the onset of type 2 diabetes mellitus
D. Statin therapy has been shown to reduce cardiovascular events in apparently healthy individuals with elevated hsCRP even if the baseline LDL-C is <130 mg/dL
E. The cardiovascular benefit of aspirin therapy appears to be greatest in patients with elevated hsCRP levels

QUESTION 328

Which of the following is a feature of renovascular hypertension due to atherosclerosis as opposed to fibromuscular hyperplasia?
A. Age <60 years
B. Female gender
C. No family history of hypertension
D. Progression more likely to complete renal artery occlusion
E. Absence of carotid bruits

QUESTION 329

A newly diagnosed diabetic patient presents with multiple blood pressure (BP) readings that are 150/90 mm Hg or higher. Which of following statements about treatment of this patient's hypertension is NOT correct?
A. Current guidelines recommend a BP target of <130/80 mm Hg in diabetics
B. Control of BP reduces cardiovascular event rates more in diabetics than in nondiabetics
C. Pharmacologic blockade of the renin-angiotensin system reduces the risk of both microvascular and macrovascular events
D. Antihypertensive therapy with dihydropyridine calcium channel blockers reduces cardiovascular event rates
E. Aggressive BP control (target systolic BP <120 mm Hg) in diabetics has been shown to reduce cardiovascular event rates more than a target systolic BP <140 mm Hg

QUESTION 330

Which of the following statements regarding the use of percutaneous coronary intervention (PCI) as primary therapy in acute ST-segment elevation myocardial infarction (STEMI) is NOT correct?
A. PCI is associated with lower rates of intracranial hemorrhage than fibrinolysis
B. The primary success rate for PCI during acute STEMI is approximately 90%
C. In trials comparing primary PCI with fibrinolysis, patients randomized to primary PCI had a lower incidence of death or re-infarction by hospital discharge and at 6-month follow-up

D. Primary PCI does not improve survival in patients with acute STEMI who present with cardiogenic shock
E. When performed in experienced centers, hospital length of stay and follow-up costs are significantly less than for patients treated with fibrinolysis

QUESTION 331

A 67-year-old man with hypertension, elevated low-density lipoprotein cholesterol, chronic obstructive lung disease, and gastroesophageal reflux presents to the emergency department (ED) with 1 hour of 8/10 substernal chest pressure that radiates to the left arm. He had previously been healthy with no known history of coronary disease, though he led a sedentary lifestyle with little physical activity. His medications are aspirin 81 mg daily, lisinopril 40 mg daily, atorvastatin 40 mg daily, albuterol inhaler as needed, and omeprazole 20 mg daily.

Vital signs in the ED include a temperature of 37.2°C, heart rate 92 beats/min, blood pressure 160/93 mm Hg, respirations 20 breaths/min, and oxygen saturation 98% on room air. Physical examination reveals a well-developed man in moderate distress with jugular venous pulsation at 8 cm H_2O, clear lungs to auscultation, regular heart rhythm with no murmurs or gallops, and warm extremities with no peripheral edema.

The electrocardiogram shows normal sinus rhythm with normal intervals and axis and 3 mm ST elevations in leads V_1–V_4.

Aspirin 325 mg and ticagrelor 180 mg orally are administered and he is taken emergently to the cardiac catheterization laboratory. Two angiographic views are shown in Fig. 3.2. Which of the following interventions would be most appropriate?

A. Percutaneous coronary intervention (PCI) of left anterior descending (LAD) coronary artery now, and consideration of PCI of the left circumflex (LCX) and/or right coronary artery (RCA) at the same time, or as a staged procedure later
B. PCI of LAD now. Additional PCI of LCX and/or RCA should be avoided now
C. PCI of LCX first now. Additional PCI of LAD and/or RCA to follow at same setting or as staged procedure later
D. PCI of LCX only. Additional PCI of LAD and/or RCA should be avoided
E. Proceed to coronary artery bypass surgery now

QUESTION 332

Which statement about atrial infarction is FALSE?

A. Atrial infarction is found in <20% of autopsy-proven cases of myocardial infarction
B. Atrial infarction typically occurs in conjunction with left ventricular infarction
C. Rupture of the atrial wall is a recognized complication
D. Atrial infarction commonly leads to supraventricular arrhythmias
E. Infarction of the left atrium occurs more commonly than infarction of the right atrium

QUESTION 333

Which statement regarding ventricular free wall rupture complicating myocardial infarction (MI) is NOT correct?

A. It is more likely to occur in patients with a history of prior MI
B. It occurs most commonly within the first 48 hours after infarction
C. It occurs in 1% to 2% of patients after MI
D. It is more common in elderly patients and in women
E. A history of hypertension is a risk factor for free wall rupture

QUESTION 334

Which statement about right ventricular infarction (RVI) is FALSE?

A. RVI is a cause of the Kussmaul sign
B. ST-segment elevation in lead V_4 is commonly present
C. Echocardiography typically demonstrates right ventricular enlargement and hypokinesis

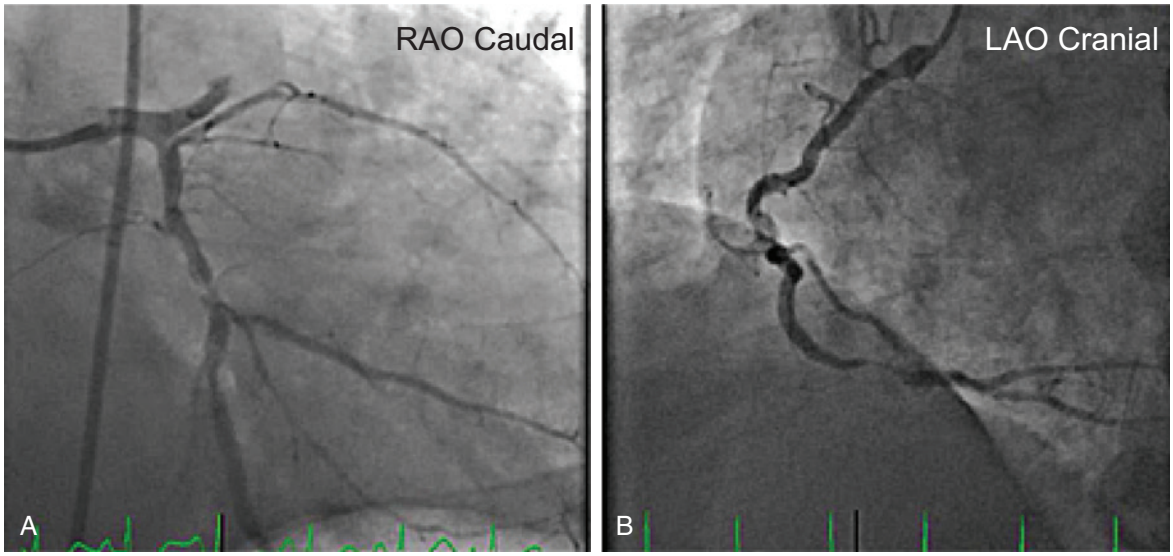

FIG. 3.2

D. A marked hypotensive response to nitroglycerin administration is consistent with this diagnosis
E. Atrioventricular sequential pacing offers greater hemodynamic benefit than single-chamber ventricular pacing in patients with RVI

QUESTION 335

A 60-year-old man is admitted to the coronary care unit after 14 hours of chest pain that had resolved by the time of hospital presentation. The initial ECG reveals 0.5-mm ST-segment elevations with T wave inversions and pathologic Q waves in leads II, III, and aVF. The initial cardiac examination is unremarkable. On the second day, a faint late systolic murmur is heard at the apex, and by the third day this murmur has increased to grade III/VI. The patient has mild dyspnea, and a chest radiogram shows pulmonary vascular redistribution. The most likely explanation for the murmur is
A. Ruptured posterior papillary muscle
B. Ruptured anterior papillary muscle
C. Infarcted posterior papillary muscle
D. Infarcted anterior papillary muscle
E. Ruptured chordae tendineae

QUESTION 336

Which statement about pericarditis and pericardial effusion in the setting of acute myocardial infarction (MI) is FALSE?
A. Post-MI pericardial effusions are found most often in patients with larger infarcts, in those with congestive heart failure, and in the setting of an anterior wall MI
B. Early post-MI pericarditis should be treated with nonsteroidal anti-inflammatory therapy (e.g., ibuprofen) plus colchicine
C. When present, Dressler syndrome manifests 1 to 8 weeks after infarction
D. Tamponade due to pericarditis in the setting of acute MI is rare

QUESTION 337

Which statement about conduction disturbances in acute myocardial infarction (MI) is FALSE?
A. Most patients with acute MI and first-degree atrioventricular (AV) block have an intranodal conduction disturbance
B. Sinus bradycardia in acute MI often results from increased vagal tone
C. Of patients with acute MI and second-degree AV block, the majority have Mobitz type I (Wenckebach) block
D. Mobitz type II second-degree AV block occurs more commonly in anterior infarction than in inferior infarction
E. In patients with anterior infarction who develop third-degree AV block, the conduction disturbance almost always appears without prior intraventricular conduction abnormalities

QUESTION 338

Which statement regarding the use of fibrinolytic therapy in acute myocardial infarction (MI) is TRUE?
A. Fibrinolytic therapy reduces the mortality of ST-segment elevation MI by 70% at 35 days after the event
B. Compared with patients with anterior ST-segment elevation, those who present with left bundle branch block have a similar risk reduction with fibrinolytic therapy
C. Compared with patients with anterior ST-segment elevation, patients with inferior ST-segment elevation demonstrate a greater risk reduction with fibrinolytic therapy
D. Clinical trial data demonstrate no mortality benefit of fibrinolysis administered more than 6 hours after the onset of symptoms
E. Patients older than age 75 years experience a greater relative reduction in mortality than patients younger than 55 years

QUESTION 339

Which statement regarding acute coronary syndromes is FALSE?
A. Occlusive coronary thrombosis is typically responsible for ST-segment elevations
B. Q waves develop in approximately 75% of patients with ST-segment elevation myocardial infarction who do not undergo acute reperfusion interventions
C. The presence of pathologic Q waves reliably indicates the transmural involvement of myocardial infarction
D. Nonocclusive coronary thrombosis typically results in ST-segment depressions and/or T wave inversions

QUESTION 340

Which statement regarding primary percutaneous coronary intervention (PCI) performed by experienced operators in acute ST-segment elevation myocardial infarction is FALSE?
A. PCI results in higher coronary artery patency rates than fibrinolysis
B. PCI results in lower mortality than fibrinolysis
C. PCI results in lower stroke rates than fibrinolysis
D. Radial artery access and femoral artery access in primary PCI result in similar rates of mortality and bleeding complications

QUESTION 341

Each of the following statements about left ventricular (LV) aneurysm after myocardial infarction is correct EXCEPT
A. Aneurysms typically range from 1 to 8 cm in diameter
B. Inferoposterior aneurysms are more common than apical aneurysms
C. The presence of an aneurysm increases the mortality rate compared with patients with similar ejection fractions without an aneurysm
D. Persistent ST-segment elevation on the ECG does not necessarily indicate aneurysm formation
E. True LV aneurysms rarely rupture

QUESTION 342

The rhythm shown in Fig. 3.3 developed in a 72-year-old man on the second day of hospitalization for an acute ST-segment elevation myocardial infarction (STEMI). Which statement is NOT correct?
A. The presence of this rhythm in STEMI is associated with increased mortality
B. This rhythm tends to be persistent, rather than transient, in the setting of acute STEMI
C. This rhythm may result from left ventricular failure, pericarditis, or left atrial ischemia in the setting of STEMI
D. If associated with hemodynamic compromise, it should be treated by immediate electrical conversion

FIG. 3.3

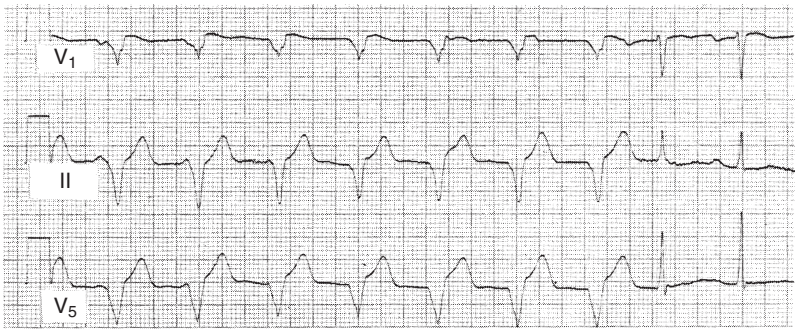

FIG. 3.4

QUESTION 343

Which of the following statements about the arrhythmia illustrated in Fig. 3.4, observed in the setting of an acute myocardial infarction (MI), is NOT correct?

A. This rhythm is associated with increased mortality
B. This rhythm is observed in up to 20% of patients with acute MI
C. It often occurs as a result of slowing of the sinus rhythm
D. Approximately 50% of such episodes are initiated by a premature beat
E. This is the most common arrhythmia after reperfusion with fibrinolytic therapy

QUESTION 344

Which of the following statements concerning the utility of cardiac biomarkers in patients with acute coronary syndromes is FALSE?

A. Levels of C-reactive protein (CRP) are greatly elevated in patients with an acute coronary syndrome (ACS) compared with patients with stable coronary disease
B. CRP and cardiac-specific troponin levels offer complementary information in the prognosis of patients with ACS
C. In patients with unstable angina, an elevated myeloperoxidase level is associated with increased risk of death
D. Patients with elevated levels of B-type natriuretic peptide have a twofold to threefold increased risk of adverse events
E. Patients with non–ST-elevation MI and elevated white blood cell (WBC) counts have similar mortality rates as those with normal WBC counts

QUESTION 345

A 76-year-old woman with permanent nonvalvular atrial fibrillation, hypertension, and peripheral artery disease presents to the emergency department with anterior chest pressure of two hours' duration. Her medications include apixaban 5 mg BID, metoprolol succinate 100 mg daily, indapamide 2.5 mg daily, and atorvastatin 80 mg daily. Initial vital signs are heart rate 84 beats/min, blood pressure 149/86 mm Hg, respiratory rate 18 breaths/min, and oxygen saturation 97% on ambient air. The ECG shows atrial fibrillation with a ventricular rate of 84 beats/min. There are 2 mm ST-segment depressions in leads II, III, and aVF, which are new when compared with a tracing 6 months earlier. Serum cardiac troponin-T is elevated at 1.3 ng/mL. At coronary angiography there is a 95% stenosis of the mid-right coronary artery, which is treated with a drug-eluting stent. In consideration of subsequent medications, which of the following statements about combined anticoagulant and antiplatelet therapy is correct?

A. Oral anticoagulation therapy plus clopidogrel, without aspirin ("double therapy") significantly reduces bleeding rates compared to "triple therapy" (anticoagulation plus aspirin and clopidogrel) in patients with a need for long-term anticoagulation who undergo percutaneous coronary intervention (PCI)
B. Rivaroxaban 15 mg daily plus a $P2Y_{12}$ receptor inhibitor has been shown to be as beneficial as the combination of warfarin plus dual antiplatelet therapy (aspirin + $P2Y_{12}$ inhibitor) for prevention of ischemic events in patients undergoing PCI
C. After an acute coronary syndrome (ACS), the addition of very low-dose rivaroxaban (2.5 or 5 mg twice daily) to aspirin plus a $P2Y_{12}$ inhibitor reduces the risk of cardiovascular death, nonfatal myocardial infarction, or stroke, without increasing the bleeding risk
D. Substituting rivaroxaban 2.5 mg BID for low-dose aspirin following a recent ACS reduces the rate of cardiovascular death, but increases the bleeding risk

QUESTION 346

Which statement about the progression of atherosclerosis after coronary artery bypass graft (CABG) surgery is FALSE?

A. Between 15% and 30% of vein grafts occlude by the end of the first year after CABG
B. The annual rate of saphenous vein graft occlusion between years 2 through 5 after CABG is about 2%
C. At 10 years, the overall occlusion rate for a saphenous vein graft approaches 50%
D. The atherosclerotic process that occurs in venous grafts is histologically distinct from that which occurs in native arterial vessels

QUESTION 347

Which of the following statements regarding myocardial stunning is NOT correct?
A. Stunning is a state of depressed myocardial function due to chronic hypoperfusion
B. Stunning can be global or regional
C. Stunning can follow cardiac surgery with cardiopulmonary bypass
D. Oxygen free radicals and excess intracellular calcium likely contribute to stunning
E. Stunning affects both systolic and diastolic function

QUESTION 348

Which of the following statements regarding antithrombotic therapies in the treatment of unstable angina or non–ST-segment elevation MI is FALSE?
A. The early beneficial cardiac outcome effects of clopidogrel in acute coronary syndromes persist for 12 months after hospital discharge
B. The combination of aspirin and an anticoagulant is superior to aspirin alone in prevention of death and nonfatal MI
C. Anticoagulation with the low-molecular-weight heparin enoxaparin is superior to unfractionated heparin in reducing the rate of death, nonfatal MI, and recurrent ischemia
D. Compared with enoxaparin, treatment of acute coronary syndromes with the factor Xa inhibitor fondaparinux results in excess major bleeding
E. Bivalirudin therapy alone is noninferior to the combination of low-molecular-weight heparin plus a glycoprotein IIb/IIIa inhibitor for prevention of ischemic endpoints in patients for whom an invasive strategy is planned, but results in less bleeding

QUESTION 349

Which statement regarding coronary collateral circulation is FALSE?
A. Preexisting collateral vessels open immediately after coronary occlusion
B. Increased flow through preexisting collateral vessels triggers a maturation process that produces a vessel nearly indistinguishable structurally from a normal coronary artery
C. Exercise does not increase coronary collateral circulation formation
D. Collateral vessels can provide nearly as much blood flow as the native coronary circulation
E. In the setting of an acute myocardial infarction, the presence of preexisting collateral vessels decreases infarct size and improves survival

QUESTION 350

Which of the following statements regarding medical therapy versus percutaneous coronary intervention (PCI) for chronic stable angina is correct?
A. PCI reduces the risk of future myocardial infarction compared with optimal medical therapy
B. In patients with stable coronary disease, fractional flow reserve-guided PCI plus optimal medical therapy reduces anginal episodes, but not the need for future urgent revascularization, compared with optimal medical therapy alone
C. PCI is superior to medical therapy alone in reducing cardiovascular mortality in patients with chronic stable angina
D. In the COURAGE trial, patients treated with PCI experienced less angina after 1 year, but not after 5 years of follow-up, compared with optimal medical therapy alone

QUESTION 351

Which of the following statements regarding the surgical management of abdominal aortic aneurysms (AAA) is correct?
A. Small aneurysms enlarge faster than larger ones
B. Aortic aneurysms grow and rupture at greater rates in men than in women
C. It is generally safe to wait until an AAA is ≥6.0 cm in diameter before proceeding with surgical repair
D. With aneurysm rupture, 60% of patients die before reaching the hospital
E. In men, surgical repair of aneurysms with diameters of 4.0 to 5.5 cm offers a mortality benefit over continued surveillance

QUESTION 352

Which of the following statements regarding the abnormality in Fig. 3.5 is correct?
A. Without treatment, expected mortality is approximately 5% in the first 24 hours
B. Outcomes with pharmacologic therapy are equivalent to surgical repair in the management of this condition when it occurs proximally

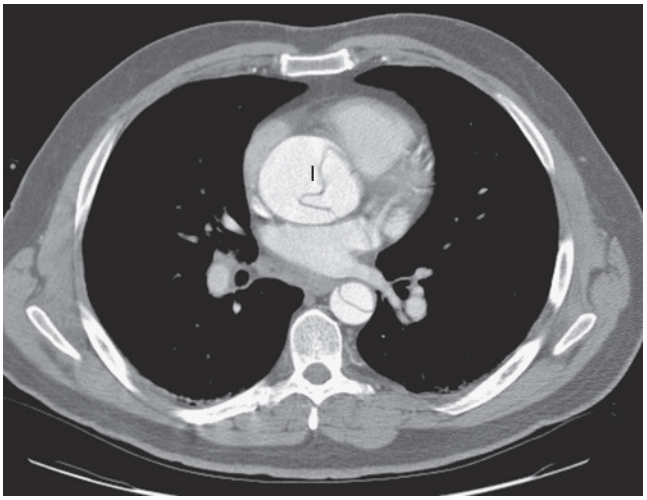

FIG. 3.5 *From Isselbacher EM. Aortic dissection. In: Creager MA, ed.* Atlas of Vascular Disease. *2nd ed. Philadelphia: Current Medicine; 2003.*

C. Initial pharmacologic therapy without surgery is recommended when this condition is distal in location and uncomplicated
D. Aortic valve replacement is universally required when there is accompanying aortic regurgitation
E. Labetalol should be avoided in patients with this condition

QUESTION 353

A 65-year-old man with cirrhosis and chronic stable angina presents to the cardiovascular clinic for evaluation. He describes his typical angina climbing one flight of stairs, despite beta blocker and long-acting nitrate therapies. Stress testing with nuclear perfusion imaging confirms exercise-induced reversible ischemia of the anterior left ventricular wall; the left ventricular ejection fraction is 50%. Coronary angiography reveals a long occlusion of the left anterior descending artery in its mid-segment with collateral perfusion to the distal vessel from the right coronary artery. The lesion is not amenable to percutaneous intervention. You are hesitant to increase the beta blocker and nitrate dosages because his resting heart rate is 50 beats/min and the blood pressure is 102/78 mm Hg. Which of the following statements is correct?

A. Ranolazine would decrease the blood pressure and heart rate further and should be avoided
B. Ranolazine does not offer incremental antianginal benefit to patients already taking beta blocker, long-acting nitrate, or calcium channel blocker therapies
C. Compared with placebo, ranolazine increases the risk of torsades de pointes
D. Ranolazine is metabolized in the liver and it should be avoided in this patient
E. The most common side effect of ranolazine is diarrhea

QUESTION 354

Which statement regarding the abnormality labeled "A" in Fig. 3.6 is correct?

A. The majority are symptomatic
B. Physical examination tends to underestimate the size
C. Imaging by ultrasonography is usually not sufficient to plan surgical repair
D. Although magnetic resonance angiography can define the size, it cannot accurately determine the proximal extent of disease

QUESTION 355

Which of the following statements regarding the use of platelet glycoprotein (GP) IIb/IIIa inhibitors in percutaneous coronary intervention procedures is NOT correct?

A. They decrease the need for urgent revascularization over the next 30 days
B. They decrease the rate of subsequent myocardial infarction
C. The major reduction of clinical events with GP IIb/IIIa inhibitors occurs within the first 48 hours
D. For patients with acute non–ST-segment elevation myocardial infarction, routine early administration of a GP IIb/IIIa inhibitor at initial encounter improves 30-day mortality rates without a significant increase in bleeding

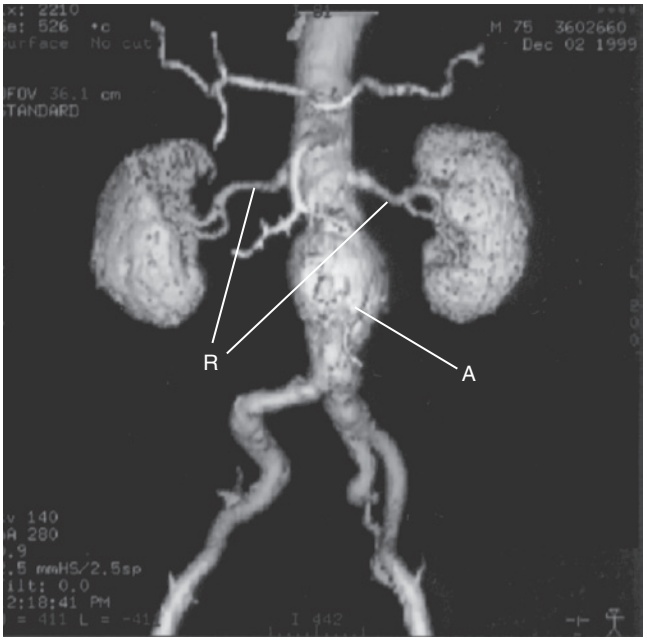

FIG. 3.6 *Courtesy of John A. Kaufman, MD, Division of vascular radiology, Massachusetts General Hospital, Boston.*

QUESTION 356

Which of the following statements regarding Prinzmetal (variant) angina is FALSE?

A. The majority of coronary sites that manifest focal vasospasm have evidence of underlying atherosclerosis
B. It can be precipitated by administration of 5-fluorouracil
C. Calcium channel blockers and nitrates are useful in treating and preventing attacks of Prinzmetal angina
D. Provocative testing is indicated in patients with nonobstructive lesions on coronary angiography, a clinical picture consistent with vasospasm, and documented transient ST-segment elevations on electrocardiography
E. Patients with isolated Prinzmetal angina have a low rate of sudden cardiac death

QUESTION 357

Which statement about the condition shown in Fig. 3.7 is NOT correct?

A. The most common cause is surgical manipulation of an atherosclerotic aorta
B. Cardiac catheterization may lead to this condition
C. Angiography is the definitive test to diagnose this condition
D. Stigmata of this disorder may be visible on direct inspection of the retinal arteries
E. Livedo reticularis is a recognized manifestation

QUESTION 358

Which statement regarding nitric oxide (NO) is FALSE?

A. NO production by endothelial cells is augmented by hypoxia, thrombin, and adenosine diphosphate
B. In atherosclerotic vessels, acetylcholine causes unopposed smooth muscle constriction
C. NO is formed in endothelial cells by the actions of NO synthase on the substrate L-arginine

FIG. 3.7 *Modified from Beckman JA, Creager MA. In: Creager MA, Dzau VJ, Loscalzo J, eds.* Vascular Medicine: A Companion to Braunwald' s Heart Disease. *Philadelphia: Elsevier; 2006:259.*

D. NO stimulates increased cyclic adenosine monophosphate formation in vascular smooth muscle cells
E. The vasodilatory effects of nitroglycerin and prostacyclin are independent of endothelial NO production

QUESTION 359

Which of the following statements regarding aortic intramural hematoma is TRUE?
A. Symptoms are indistinguishable from those of classic aortic dissection
B. This condition results from an intimal tear in the aorta
C. A history of hypertension or aortic atherosclerosis is unusual
D. Computed tomography is less sensitive than aortography for diagnosis

QUESTION 360

Which of the following statements regarding low-molecular-weight heparins is correct?
A. They possess greater anti–factor IIa activity than anti–factor Xa activity
B. They are contraindicated in patients with type II heparin-induced thrombocytopenia
C. They cause significant elevations in the activated partial thromboplastin time, which is useful for monitoring the anticoagulant effect
D. Their clearance is minimally affected by renal impairment

QUESTION 361

All of the following are independent adverse risk predictors in patients who present with unstable angina or non–ST-segment elevation myocardial infarction EXCEPT:
A. Increased cardiac troponin level
B. ST-segment deviation ≥0.05 mV
C. Diabetes mellitus
D. Lack of prior aspirin use
E. Increased C-reactive protein level

QUESTION 362

Which of the following statements regarding peripheral arterial disease (PAD) is correct?
A. The prevalence of PAD is 5% in patients older than 75 years
B. Hypercholesterolemia is a more powerful risk factor than cigarette smoking
C. Claudication symptoms are present in only 10% to 30% of patients with PAD
D. The earliest aortic site of fatty streak and atheroma development is in the ascending thoracic aorta

QUESTION 363

Which of the following statements about the clinical manifestations of aortic dissection is FALSE?
A. Men are more frequently affected than women
B. Severe pain is the most common presenting symptom
C. Patients with aortic dissection usually present with hypotension
D. Pulse deficits are more common in proximal than in distal aortic dissection

QUESTION 364

Which of the following statements about patients with peripheral arterial disease (PAD) is NOT correct?
A. Intermittent claudication is characterized by pain precipitated by walking as well as by standing upright for several minutes
B. On examination, arterial bruits and hair loss of the affected extremity are common
C. Segmental pressure measurements demonstrate gradients of >20 mm Hg in the lower extremities or >10 mm Hg in the upper extremities
D. The ankle/brachial index is typically <1.0
E. Magnetic resonance angiography is >90% sensitive and specific for the diagnosis of PAD in the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries

QUESTION 365

Which of the following statements regarding anticoagulation therapy in percutaneous coronary intervention (PCI) procedures is FALSE?
A. Clinical outcomes are similar for patients treated with fixed-dose unfractionated heparin (UFH) or weight-adjusted UFH during PCI
B. In patients pretreated with clopidogrel, bivalirudin is associated with a lower rate of major bleeding complications than UFH
C. Routine administration of intravenous UFH after PCI procedures results in a reduced number of ischemic complications
D. In conjunction with platelet glycoprotein IIb/IIIa inhibitor therapy, standard-dose UFH results in a similar rate of ischemic complications, but a higher rate of hemorrhagic complications when compared with low-dose weight-adjusted UFH
E. No additional anticoagulation is required during PCI if a patient has received a dose of the low-molecular-weight heparin enoxaparin within the previous 8 hours

QUESTION 366

Which of the following statements regarding nitrates in ischemic heart disease is FALSE?
A. Nitrates directly relax vascular smooth muscle
B. The vasodilator effects of nitrates predominate in the venous circulation
C. Coronary arteries containing significant atherosclerotic plaque often dilate in response to nitrates
D. An intact endothelium is required for nitrate-induced vasodilatation
E. Nitrates reduce left ventricular wall tension

QUESTION 367

Which of the following statements regarding glycoprotein (GP) IIb/IIIa inhibitors is NOT correct?
A. Abciximab administration before transport to the cardiac catheterization laboratory reduces ischemic complications in patients with ST-segment elevation myocardial infarction pretreated with clopidogrel who undergo percutaneous intervention
B. Administration of eptifibatide immediately before percutaneous coronary intervention (PCI) is as efficacious as early upstream therapy prior to PCI in patients presenting with acute coronary syndrome
C. Tirofiban has a half-life of approximately 2 hours
D. Long-term benefits of GP IIb/IIIa inhibitors are greater when administered with heparin
E. Human antichimeric antibodies develop in approximately 5% of patients treated with abciximab

QUESTION 368

Which of the following statements about atherosclerotic renal artery stenosis (RAS) and percutaneous renal artery intervention is correct?
A. Renal percutaneous transluminal angioplasty has a technical success rate of 60% for nonostial lesions
B. Compared with surgical revascularization, percutaneous renal artery interventions result in similar blood pressure control and stabilization of renal function
C. Stenting of hemodynamically significant RAS allows discontinuation of antihypertensive medications in the majority of patients
D. Compared to medical therapy alone, percutaneous treatment of atherosclerotic RAS results in fewer subsequent cardiovascular events

QUESTION 369

Which of the following statements regarding patients with the syndrome of recurrent angina-like chest pain and normal coronary angiograms is correct?
A. During stress testing, such patients do not develop chest pain or scintigraphic evidence of ischemia
B. During periods of increased myocardial oxygen demand, patients with this syndrome consistently produce elevated myocardial lactate
C. The prognosis is similar to patients with obstructive coronary artery disease
D. Endothelial and microvascular coronary dysfunction and enhanced pain sensitivity have been associated with this syndrome
E. The incidence of coronary calcification by multislice computed tomography is the same as normal subjects

QUESTION 370

Which of the following statements regarding endovascular repair of abdominal aortic aneurysms is FALSE?
A. Anatomic constraints limit the use of endografts
B. Primary success rates for aneurysm exclusion are >75%
C. Endoleaks are a serious complication after implantation
D. Thirty-day mortality rates are lower with endovascular repair compared with open surgical repair
E. Long-term outcomes are better with endografts than with open surgical repair

QUESTION 371

Which of the following statements regarding treatment of peripheral arterial disease is NOT correct?
A. Pentoxifylline's actions are mediated through its hemorheologic properties
B. Cilostazol's benefits arise via calcium channel blockade
C. Supervised exercise training programs improve maximum walking distances by 50% to 200%
D. Percutaneous transluminal angioplasty of the iliac artery results in 4-year patency rates of 60% to 80%
E. Aortobifemoral bypass results in 10-year patency rates of nearly 90%

QUESTION 372

Which of the following steps is NOT appropriate in the management of patients with acute aortic dissection?
A. Intravenous sodium nitroprusside
B. Intravenous beta blocker therapy
C. Emergent surgical repair for uncomplicated type B dissection
D. Use of narcotics for pain relief

QUESTION 373

Which of the following statements regarding diabetes mellitus as a cardiovascular risk factor is correct?
A. The prevalence of diabetes is decreasing in the developed world
B. A glycosylated hemoglobin (hemoglobin A1c) level >7.0% is required to make a diagnosis of diabetes
C. Statin therapy reduces coronary events only in diabetics with abnormal cholesterol levels
D. Fibric acid therapy, added to a statin, improves cardiovascular outcomes in type 2 diabetics
E. Lifestyle modifications significantly reduce the rate of diabetes development in at-risk individuals

QUESTION 374

Which of the following statements regarding blood flow in the subendocardium as compared with the subepicardium is correct?
A. Systolic flow is greater in the subendocardium
B. Under normal conditions, total subepicardial flow is equal to or greater than subendocardial flow

C. An elevation of ventricular end-diastolic pressure will reduce subendocardial flow to a greater extent than subepicardial flow
D. The reserve for vasodilatation in the subendocardium is greater than in the subepicardium

QUESTION 375

Which of the following statements regarding myocardial stunning and hibernation is NOT correct?
A. Stunning refers to myocardial dysfunction that persists after periods of severe ischemia
B. Molecular contributors to stunning include oxygen-derived free radicals, calcium overload, and reduced sensitivity of myofilaments to calcium
C. Stunned myocardium does not respond to inotropic agents
D. Hibernating myocardium reflects decreased myocardial function due to chronically decreased coronary blood flow that can be reversed with revascularization
E. Histopathologic studies of hibernating myocardium reveal dedifferentiation and apoptosis

QUESTION 376

Which of the following statements regarding atherosclerotic plaque in unstable angina is FALSE?
A. Approximately 15% of patients presenting with unstable angina have no significant coronary artery disease on angiography
B. The culprit lesion in unstable angina typically exhibits an eccentric stenosis
C. Patients with unstable angina due to coronary microvascular dysfunction have a poor short-term prognosis
D. Intravascular ultrasonography often reveals vulnerable plaques in unstable angina to be echolucent, consistent with a lipid-rich core with a thin fibrous cap

QUESTION 377

In patients with stable coronary artery disease, each of the following statements about the role of percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery is correct EXCEPT
A. In the majority of patients there is no mortality advantage of one treatment strategy compared with the other
B. CABG is consistently associated with a lower rate of subsequent myocardial infarction
C. PCI is associated with a higher rate of recurrent angina
D. Patients with diabetes and severe multivessel disease demonstrate a greater reduction in mortality with CABG
E. In patients with single-vessel disease (>70% stenosis) of the left anterior descending coronary artery, there is no difference between PCI and CABG in the rates of subsequent myocardial infarction or cardiovascular death

QUESTION 378

Which of the following statements regarding high-dose statin therapy (e.g., 80 mg/day) is NOT correct?
A. High-dose simvastatin results in a greater degree of skeletal myopathy compared with low-dose (20 mg/day) therapy
B. High-dose atorvastatin results in measurable regression of atherosclerotic coronary stenosis
C. High-dose simvastatin has been shown to reduce coronary events after an acute coronary syndrome compared with less intensive therapy
D. Compared with less intensive statin therapy, high-dose atorvastatin reduces subsequent mortality in patients after an acute coronary syndrome

QUESTION 379

Which of the following statements regarding oral antiplatelet agents is correct?
A. Aspirin's principal antiplatelet action is via inhibition of the PAR-1 thrombin receptor
B. Clopidogrel and prasugrel are irreversible inhibitors of the platelet $P2Y_{12}$ adenosine diphosphate receptor
C. Prasugrel displays a slower onset of action than clopidogrel
D. Nonsteroidal anti-inflammatory drugs such as ibuprofen enhance the antiplatelet effect of aspirin
E. Cilostazol's mechanism of action is via activation of nitric oxide synthesis

QUESTION 380

Which of the following statements regarding pharmacologic inhibition of the renin-angiotensin system in patients with ST-segment elevation myocardial infarction (STEMI) is FALSE?
A. Oral angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with STEMI
B. In patients with STEMI and left ventricular dysfunction, an angiotensin receptor blocker in combination with an ACE inhibitor results in better cardiovascular outcomes than an ACE inhibitor alone
C. In short-term trials, one-third of the mortality benefit of ACE inhibitors in STEMI occurs within the first 2 days of therapy
D. Oral administration of the selective aldosterone inhibitor eplerenone is associated with reduced mortality in patients with STEMI and left ventricular dysfunction

QUESTION 381

A 42-year-old man with a long smoking history presents with claudication and rest pain of his right calf and foot. An angiogram of his posterior tibial artery is shown in Fig. 3.8. Which of the following statements about this condition is correct?
A. It affects primarily the large vessels of the arms and legs
B. High-dose statin therapy improves symptoms
C. Smoking cessation improves clinical outcomes
D. Vascular surgery is usually required emergently
E. More than 75% of patients with this condition are women

QUESTION 382

Which of the following characteristics is typical of a hypertensive crisis?
A. Central retinal artery occlusion
B. Constriction of cerebral arterioles with decreased vascular permeability
C. Renal insufficiency without proteinuria
D. Microangiopathic hemolytic anemia

QUESTION 383

Which of the following conditions has NOT been associated with the abnormality demonstrated in the transesophageal echocardiogram image in Fig. 3.9?
A. Heroin use
B. Hypertension
C. Marfan syndrome
D. Bicuspid aortic valve
E. Pregnancy

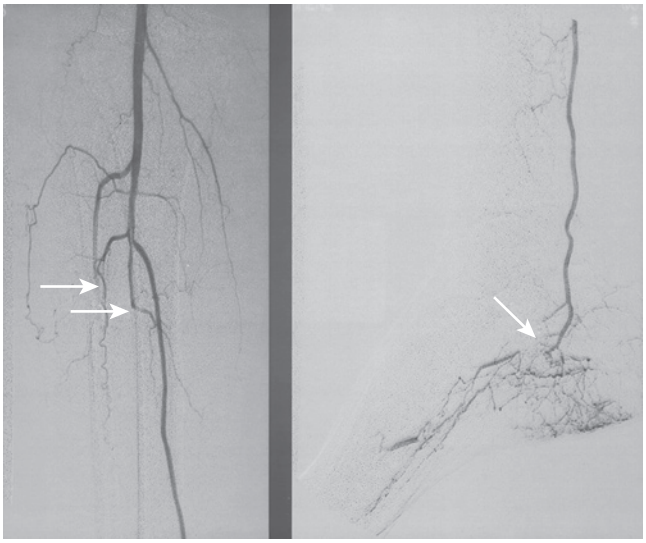

FIG. 3.8

QUESTION 384

Which of the following would NOT be an appropriate intervention for a patient with acute ST-segment elevation myocardial infarction and cardiogenic shock?
A. Percutaneous left ventricular assist device
B. Fibrinolytic therapy
C. Urgent percutaneous coronary intervention
D. Vasopressor drugs
E. Coronary artery bypass surgery

QUESTION 385

Which statement about the diagnosis and treatment of right ventricular infarction (RVI) is NOT correct?
A. Hypotension in response to small doses of nitroglycerin in patients with inferior infarction suggests RVI
B. Unexplained systemic hypoxemia in RVI raises the possibility of a patent foramen ovale
C. Hemodynamic parameters in RVI often resemble those of patients with pericardial disease
D. Loop diuretics are usually the preferred initial therapy for patients with RVI and intact left ventricular contractile function
E. ST-segment elevation in lead V_4R is a sensitive and specific sign of RVI

QUESTION 386

A 65-year-old man presents with several months of right lower extremity discomfort and fatigue while walking. Segmental pressure measurements were obtained as shown in Fig. 3.10. Which of the following statements is TRUE?

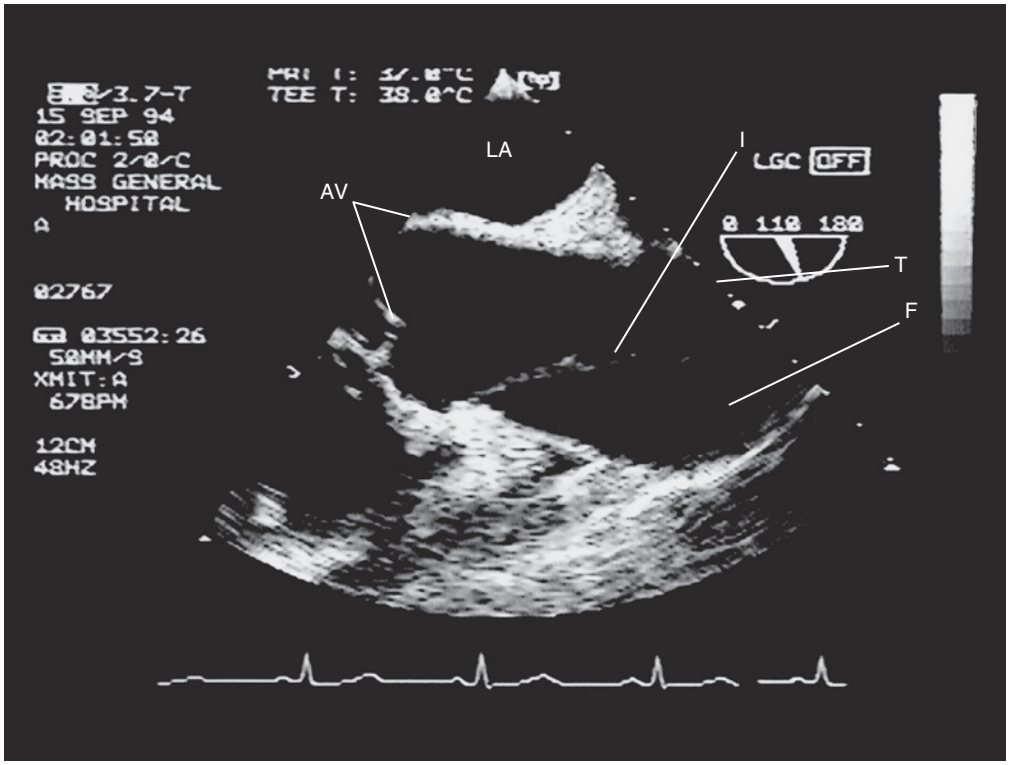

FIG. 3.9

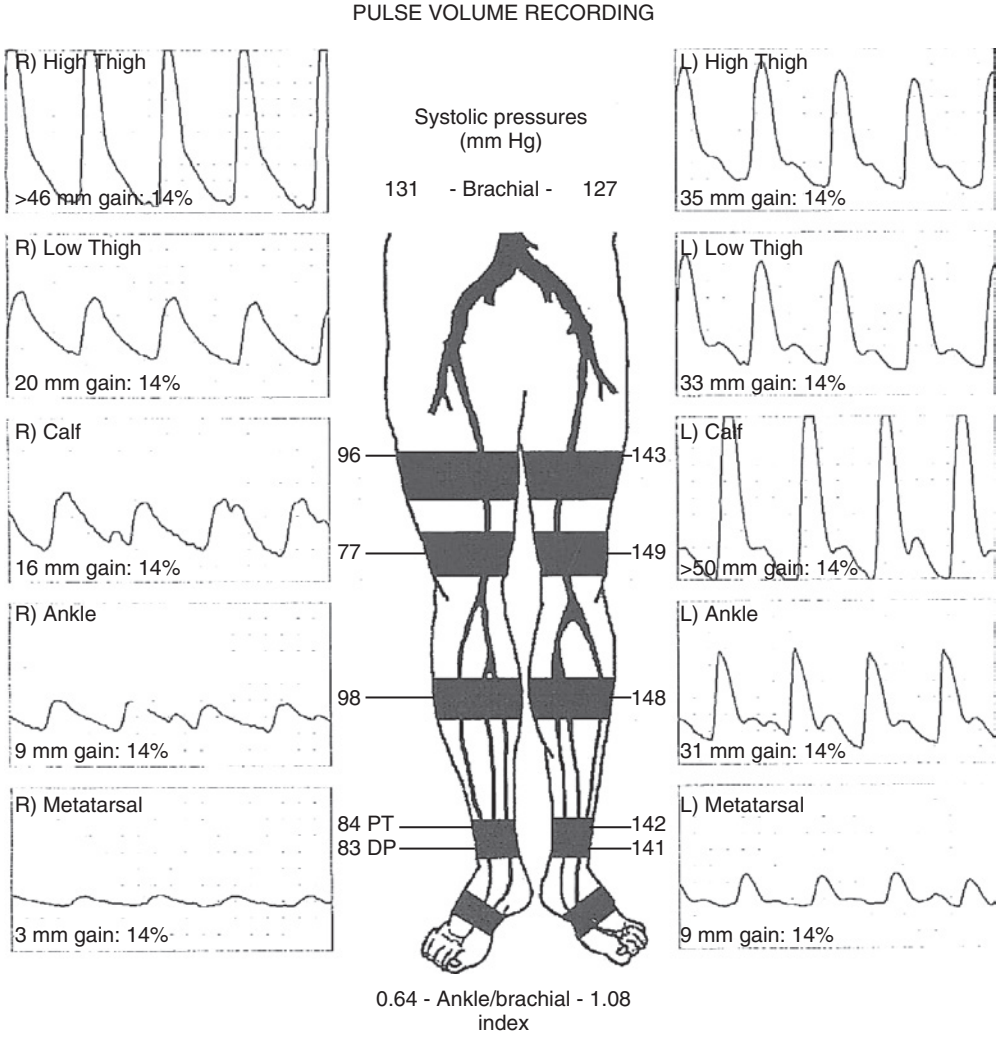

FIG. 3.10

A. An ankle/brachial index >0.85 is considered normal
B. A pressure difference >20 mm Hg between successive cuffs is evidence of significant arterial stenosis
C. Critical limb ischemia is associated with an ankle/brachial index of 0.8 or less
D. The sensitivity of the ankle/brachial index for the diagnosis of peripheral arterial disease is increased in severely calcified arteries
E. This patient's main abnormality is right tibial artery stenosis

QUESTION 387

Which of the following statements regarding bare metal stents (BMSs) is correct?
A. BMSs have a 5% to 10% rate of angiographic in-stent restenosis
B. BMS in-stent restenosis is more likely to occur in diabetics
C. Direct coronary atherectomy and rotational atherectomy are the preferred therapies for in-stent restenosis
D. Brachytherapy is more effective than placement of a drug-eluting stent for BMS in-stent restenosis

QUESTION 388

Which of the following statements regarding drug-eluting stents (DES) is correct?
A. DES stimulate local neointimal proliferation
B. The rate of angiographic restenosis after DES implantation is 10% to 15%
C. Paclitaxel stabilizes microtubules and prevents cell division
D. DES that incorporate everolimus are less effective at preventing target lesion failure compared with stents that incorporate paclitaxel
E. Zotarolimus-eluting stents significantly reduce the frequency of late-stent thrombosis compared with sirolimus DES

QUESTION 389

Which of the following is an effect of regular exercise?
A. Favorable changes in the fibrinolytic system
B. Decreased heart rate variability
C. Decreased expression of nitric oxide synthase
D. Decreased HDL levels
E. Increased systolic and diastolic blood pressures

QUESTION 390

Each of the following is a major determinant of myocardial oxygen demand (MVO_2) EXCEPT
A. Ventricular wall tension
B. Plasma hemoglobin level
C. Myocardial contractile state
D. Heart rate
E. Left ventricular volume

QUESTION 391

A 63-year-old man with long-standing insulin-requiring diabetes presented to his physician's office 2 weeks ago for management of hypertension. His blood pressure was 160/94 mm Hg. The serum creatinine was 1.6 mg/dL and blood urea nitrogen (BUN) was 30 mg/dL, with otherwise normal serum chemistries. A potassium-sparing diuretic (triamterene plus hydrochlorothiazide) was prescribed. When he returns 2 weeks later, the serum potassium level is 6.8 mmol/L with no significant change in BUN or creatinine level. The most likely contributing mechanism is
A. Excessive consumption of bananas and tomatoes
B. A recent urinary tract infection
C. Primary hyperaldosteronism
D. Hyporeninemic hypoaldosteronism
E. Cushing syndrome

QUESTION 392

Which of the following statements about the use of prasugrel is NOT correct?
A. Compared with clopidogrel, platelet aggregation is more effectively inhibited by prasugrel
B. Compared with clopidogrel, prasugrel reduces the risk of stent thrombosis
C. Compared with clopidogrel, bleeding complications associated with prasugrel are lower
D. Prasugrel is contraindicated in patients with a history of stroke
E. The risk of bleeding with prasugrel is higher in patients >75 years of age

Directions:

For each below, select the ONE BEST response.

QUESTIONS 393 TO 396

Match the following cell types potentially involved in atherogenesis with the appropriate descriptive phrase:
A. Endothelial cell
B. Smooth muscle cells
C. Macrophage
D. Platelet

393. Demonstrate(s) proliferation in the intima in atherosclerosis
394. Is (are) the principal cell(s) of the fatty streak
395. Secrete(s) prostacyclin
396. Is (are) capable of little or no protein synthesis

QUESTIONS 397 TO 400

For each statement, match the corresponding beta blocker:
A. Atenolol
B. Carvedilol
C. Propranolol
D. Acebutolol

397. Has alpha- and beta-receptor blocking activity
398. Is most hydrophilic
399. Has inherent sympathomimetic activity
400. Has shortest half-life

QUESTIONS 401 TO 405

For each statement, match the most appropriate complication following myocardial infarction:
A. Aneurysm
B. Pseudoaneurysm
C. Both
D. Neither

401. Low risk of rupture
402. Narrow base
403. Due to true myocardial rupture
404. Associated thrombus is common
405. Surgical repair is usually required

QUESTIONS 406 TO 409

For each statement, match the corresponding anticoagulant(s):
A. Unfractionated heparin (UFH)
B. Low-molecular-weight heparin (LMWH)
C. Bivalirudin
D. UFH and bivalirudin
E. LMWH and bivalirudin

406. Binds directly to thrombin, independent of antithrombin
407. Dose(s) should be adjusted if creatinine clearance is <30 mL/min
408. Degree of anticoagulation can be monitored using the activated partial thromboplastin time
409. Least likely to trigger type II heparin-induced thrombocytopenia

QUESTIONS 410 TO 414

Match the descriptions with the appropriate cell type:
A. Monocytes
B. Smooth muscle cells
C. Both
D. Neither

410. Migrate into the arterial intima from the media in response to chemoattractants
411. Primary constituent(s) of fibrous plaques
412. Require low-density lipoprotein receptor to become foam cells
413. Rely on chemoattractants to enter into developing atherosclerotic intimal lesions
414. Adhesion molecules, including vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, regulate adherence to endothelial cells

QUESTIONS 415 TO 418

For each statement, match the most appropriate fibrinolytic agent:

A. Streptokinase
B. Alteplase
C. Reteplase
D. Tenecteplase

415. Shortest half-life
416. Most fibrin-specific
417. Administered as a single bolus
418. Lowest intracranial hemorrhagic risk

QUESTIONS 419 TO 422

For each statement, match the most likely complication following acute myocardial infarction:

A. Acute ventricular septal rupture
B. Acute mitral regurgitation
C. Both
D. Neither

419. The murmur may decrease in intensity as arterial pressure falls
420. Pulmonary artery wedge pressure tracing demonstrates large *v* waves
421. Associated with the pathologic process shown in Fig. 3.11
422. Occurs primarily with large infarctions

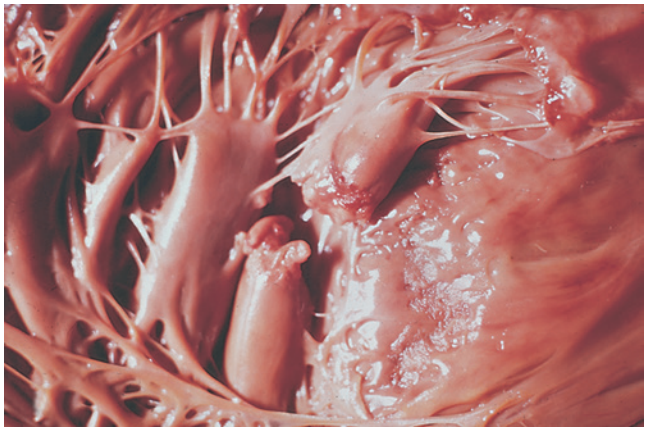

FIG. 3.11 *From Schoen FJ. The heart. In: Kumar V, Abbas AK, Fausto N, eds.* Robbins & Cotran Pathologic Basis of Disease. *8th ed. Philadelphia: Elsevier; 2010:529–587.*

QUESTIONS 423 TO 427

For each of the following prospective lipid-lowering trials, match the most appropriate statement.

A. Statistically significant reduction in nonfatal myocardial infarction
B. Statistically significant reduction in overall mortality
C. Both
D. Neither

423. Scandinavian Simvastatin Survival Study (4S)
424. The Heart Protection Study (HPS)
425. Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA)
426. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (JUPITER)
427. Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER)

QUESTIONS 428 TO 431

For each pharmacologic agent, match the associated lipoprotein effect:

A. Elevate(s) high-density lipoprotein (HDL) cholesterol
B. Elevate(s) low-density lipoprotein (LDL) cholesterol
C. Have (has) no significant effect on lipoproteins
D. Lower(s) HDL cholesterol
E. Lower(s) very-LDL cholesterol

428. Corticosteroids
429. Propranolol
430. Second-generation antipsychotic medications (e.g., olanzapine)
431. Calcium channel antagonists

QUESTIONS 432 TO 435

For each clinical feature in Fig. 3.12, match the appropriate condition:

A. Familial hypercholesterolemia
B. Type III hyperlipoproteinemia (familial dysbetalipoproteinemia)
C. Both
D. Neither

432. See part A
433. See part B
434. See part C
435. See part D

FIG. 3.12 *(A and B) From Gotto A.* Cholesterol Education Program: Clinician's Manual. *Dallas: American Heart Association; 1991:34–36. By permission of the American Heart Association, Inc; (C and D) From* Habif: Clinical Dermatology. *5th ed. St. Louis: Elsevier; 2009.*

Section III Answers

(CHAPTERS 44 TO 66)

Preventive Cardiology; Atherosclerotic Cardiovascular Disease

ANSWER TO QUESTION 295

D (Braunwald, pp. 971–974; Tables 48.8 and 48.9; Fig. 48.7)

This patient has multiple coronary risk factors and his 10-year risk of cardiovascular (CV) disease is significantly elevated. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines recommend moderate- or high-intensity statin therapy for primary prevention of CV disease for individuals with an estimated 10-year risk ≥7.5%.[1]

Because each doubling of statin dosage results in only another approximately 6% decline in low-density lipoprotein (LDL) cholesterol, this patient would require a substantial increase in the dose of simvastatin to achieve further desired LDL reduction. However, the US Food and Drug Administration (FDA) has issued an advisory against augmenting simvastatin to 80 mg daily because of an increased risk of muscle injury compared with patients taking lower doses.[2] Furthermore, simvastatin is metabolized primarily by cytochrome P-450 CYP3A4, which if inhibited by other medications leads to an augmented serum simvastatin level and the potential for increased toxicity, including myositis and rhabdomyolysis. Among commonly used CV medications, such impaired simvastatin metabolism can result from verapamil (which this patient takes), diltiazem, gemfibrozil, and amiodarone.[3] The FDA advises that gemfibrozil not be prescribed concurrently with simvastatin, and that the dosage of simvastatin should not exceed 10 mg daily for patients who also take verapamil, diltiazem, or amiodarone.[2]

As a reasonable next step, this patient could be switched to an alternate, higher-potency statin. For primary prevention for this patient at ≥7.5% 10-year atherosclerotic risk, moderate intensity regimens recommended by the 2013 ACC/AHA guidelines include atorvastatin 10 to 20 mg daily or rosuvastatin 5 to 10 mg daily. Optional high-intensity regimens include atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

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3. Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol*. 2014;8:S30.

ANSWER TO QUESTION 296

C (Braunwald, p. 897; Figs. 45.20 and 45.21)

Lifestyle modifications benefit most individuals with hypertension.[1] Obesity contributes to elevated blood pressure (BP) and even small degrees of weight loss can lower it, no matter what type of diet is employed.[2]

Modest sodium restriction can also improve hypertension. Reduction of dietary sodium intake to <100 mmol/day (2.4 g of sodium or 6 g sodium chloride) decreases systolic BP approximately 2 to 8 mm Hg. Not all hypertensive individuals respond to lower salt intake, and some patients (African Americans and the elderly) may be particularly sensitive to sodium reduction.[3] Adoption of the DASH (Dietary Approaches to Stop Hypertension) eating plan—rich in fruits, vegetables, and low-fat dairy products and low in total and saturated fat—has been shown to reduce BP by 11.4/5.5 mm Hg. Even greater reductions are manifest by combining the DASH diet with reduced sodium intake.[3] Magnesium and calcium supplements have not been demonstrated to significantly reduce BP.

Ethanol consumption of no more than 1 oz/day (24 oz beer, 10 oz wine, 3 oz 80-proof liquor for a normal-size man and less for a woman) is associated with decreased cardiac mortality, but excessive alcohol intake exerts a pressor effect, so that alcohol abuse is actually a cause of reversible hypertension.

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ANSWER TO QUESTION 297

B (Braunwald, pp. 922–923; Fig. 46.16; Table 46.65)

Renovascular disease is one of the most common causes of secondary hypertension and has two main etiologies. The most common cause (80% to 90% of cases) is atherosclerotic disease affecting the proximal third of the main renal artery, typically seen in older men. The prevalence of atherosclerotic renovascular disease is higher with advanced age, diabetes, and evidence of atherosclerosis in other arterial beds.

The second, and less common, form of renal artery stenosis is fibromuscular dysplasia, which primarily afflicts women aged 20 to 60 years. It involves mainly the distal two-thirds of the main renal artery, and, although all layers of the vessel may be affected, involvement of the media is most common. A renovascular etiology of hypertension should be suspected in patients who develop high blood pressure before age 30, or after age 50 with the abrupt onset of severe and resistant hypertension and signs of atherosclerosis elsewhere, or in patients with recurrent sudden unexplained pulmonary edema. *Bilateral* renal artery stenosis should be suspected if renal insufficiency is present, especially if renal function worsens following initiation of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy.[1]

The treatment of choice for renal fibromuscular dysplasia is balloon angioplasty of the affected segment. However, the cornerstone of therapy for patients with atherosclerotic renovascular disease is pharmacologic control of blood pressure and other atherosclerotic risk factors such as dyslipidemia. Mechanical intervention should be reserved for patients with refractory hypertension or progressive renal insufficiency.[2]

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ANSWER TO QUESTION 298

B (Braunwald, pp. 910–926; Fig. 46.2 and eFig. 46.5; Tables 46.1 and 46.2)

Essential hypertension accounts for approximately 90% of patients with elevated blood pressure.[1] Renal parenchymal disease is the second most common cause, responsible for approximately 5%. Grouped together, coarctation of the aorta, Cushing disease, and pheochromocytoma contribute to <1%. Primary aldosteronism accounts for ~1% of hypertension in the general population, but a higher percentage (~11%) in patients with resistant hypertension.[2]

Pure "white coat" hypertension, in which blood pressures taken in the office are persistently elevated but out-of-office readings are not, is found in 20% to 30% of patients. Most patients with white coat hypertension are found to be free of target organ damage and have an excellent 10-year prognosis with respect to cardiovascular disease.

When measuring the blood pressure, the correct cuff size should be used. The cuff bladder should encircle and cover two-thirds of the length of the arm. If the cuff bladder is too small, blood pressure readings may be spuriously *high*.[3]

In elderly patients, the brachial arteries are often sclerotic and may not become occluded until the blood pressure cuff is inflated to a very high pressure. As a result, the recorded cuff pressure may be much higher than that measured intra-arterially, resulting in "pseudohypertension."

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ANSWER TO QUESTION 299

B (Braunwald, pp. 1012–1018; Tables 51.3 and 51.4)

The goal of glucose-lowering therapy for most type 2 diabetic patients is to achieve a hemoglobin A1c level <7.0%, which reduces microvascular complications including diabetic neuropathy, nephropathy, and retinopathy. More recent attention has focused on the cardiovascular safety of these agents, including their effects on macrovascular events (i.e., myocardial infarction [MI], stroke). Notably, recent clinical trials have demonstrated significant cardiovascular outcomes benefits with specific glucagon-like peptide (GLP)-1 receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors.[1]

The LEADER trial randomized 9340 patients with type 2 diabetes at high risk of cardiovascular disease to the GLP-1 receptor agonist liraglutide or placebo, in addition to standard therapy.[2] After a median follow-up of 3.8 years, the composite endpoint of cardiovascular death, nonfatal MI, and stroke was significantly reduced in the liraglutide group (hazard ratio 0.87; 95% confidence interval [CI], 0.78 to 0.97, $P = .01$ for superiority). In the SUSTAIN-6 trial, the GLP-1 receptor antagonist semaglutide (not yet approved for use in the United States) was randomized versus placebo in 3297 patients with type 2 diabetes and high cardiovascular risk.[3] After 104 weeks, the composite of cardiovascular death, nonfatal MI, and stroke was significantly reduced in those receiving the GLP-1 receptor antagonist (hazard ratio 0.74; 95% CI, 0.58 to 0.95, $P = .02$ for superiority).

In the EMPA-REG OUTCOME trial, the SGLT2 inhibitor empagliflozin was randomly assigned versus placebo to 7020 patients with type 2 diabetes and known cardiovascular disease.[4] After a median of 3.1 years, there were fewer events (cardiovascular death, nonfatal MI, or stroke) in those

randomized to empagliflozin (hazard ratio 0.86; 95% CI, 0.74 to 0.99, $P = .04$ for superiority). In the CANVAS trials, patients randomized to the SGLT2 inhibitor canagliflozin also demonstrated a reduced composite outcome of cardiovascular death, nonfatal MI, and stroke compared with placebo, but patients treated with this drug experienced a higher incidence of lower extremity amputations.[5] The patient presented in this question has a history of claudication and presumed peripheral vascular disease, so canagliflozin should be avoided in his case. Other potential side effects of SGLT2 inhibitors include volume depletion and recurrent urinary tract infections.

The thiazolidinedione pioglitazone was studied in a placebo-controlled randomized trial of 5238 patients with type 2 diabetes and cardiovascular disease in the PROactive trial.[6] There was a lower incidence of a secondary endpoint (death, nonfatal MI, stroke) with pioglitazone. However, like other thiazolidinediones, it is associated with a higher incidence of heart failure in diabetics and should be avoided in this patient with a history of heart failure symptoms.

An analysis of 19 trials of patients with type 2 diabetes concluded that the dipeptidyl peptidase 4 inhibitor linagliptan does not increase the composite outcome of cardiovascular death, MI, or stroke, but unlike other agents described above, it is not associated with a reduction of these adverse cardiovascular events.

As of this writing (mid 2018), the American Diabetes Association recommends that empagliflozin or liraglutide be considered as preferred agents to add to standard therapy (e.g., metformin) to reduce mortality and major cardiovascular events in suboptimally controlled type 2 diabetics with established cardiovascular disease.[1] For the patient presented in this question, liraglutide is the preferred answer. His history of urinary tract infections makes empagliflozin an inferior choice.

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ANSWER TO QUESTION 300

B (Braunwald, pp. 915–916; Fig. 46.9; eFig. 46.4)

The use of oral contraceptives (OCs) is a cause of secondary hypertension in young women. The risk of such patients developing hypertension is increased by alcohol consumption, age >35 years, and obesity and is likely related to the estrogen content of the agent. Because estrogen increases the hepatic production of angiotensinogen, a probable mechanism for hypertension induced by OCs is activation of the renin-angiotensin system with subsequent sodium retention and volume expansion. Nonetheless, angiotensin-converting enzyme inhibitors do not influence blood pressure to a greater degree in women with contraceptive-induced hypertension than in those with primary essential hypertension. Of note, blood pressure normalizes within 6 months of initiating OC therapy in approximately 50% of patients.

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ANSWER TO QUESTION 301

D (Braunwald, pp. 952–953)

Per the 2017 American College of Cardiology/American Heart Association Hypertension Guidelines, this patient has stage 1 hypertension (Table 3.1) with a consistent systolic pressure 130 to 139 mm Hg.[1] The Guideline recommends that his target blood pressure should be <130/80 mm Hg. This endorsement is based in part on the Systolic Blood Pressure Intervention Trial (SPRINT) trial, which randomized 9361 hypertensives with high cardiovascular risk to a systolic pressure target of either <120 mm Hg or <140 mm Hg.[2] The trial was stopped early at 3.3 years when the lower blood pressure target group demonstrated superior outcomes, namely lower rates of acute coronary syndromes, stroke, heart failure, or cardiovascular death. Since blood pressure measurements taken in practice are generally higher than in the careful experimental setting of the SPRINT trial, the Hypertension Guideline relaxed the target systolic pressure to <130 mm Hg.

All patients with elevated blood pressure or stage 1 or stage 2 hypertension (defined in Table 3.1) should follow lifestyle modifications that can improve blood pressure (e.g., a Dietary Approach to Stop Hypertension [DASH] diet, reduced sodium intake, weight loss if overweight, increased exercise, and moderation of ethanol intake [≤2 drinks day for men, ≤1 drink day for women]). Furthermore, the Guideline recommends that antihypertensive drug therapy be initiated for patients with stage 2 hypertension, and for those with stage 1 hypertension who have a 10-year predicted cardiovascular risk >10% using the ACC/AHA pooled cohort risk assessment equations (http://tools.acc.org/ASCVD-Risk-Estimator).

Recommended initial drugs are those that have been shown to reduce cardiovascular risk in hypertensive patients, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and thiazide-type diuretics.[1] Beta blockers are not recommended for initial therapy, as clinical trials have not shown a mortality

TABLE 3.1 Blood Pressure Categories

CATEGORY	SYSTOLIC PRESSURE (MM HG)		DIASTOLIC PRESSURE (MM HG)
Normal	<120	and	<80
Elevated	120–129	and	<80
Stage 1 Hypertension	130–139	or	80–89
Stage 2 Hypertension	≥140	or	≥90

benefit when used for hypertension (possibly in part because the key trials used inadequately dosed atenolol). In addition, for black patients, thiazide-type diuretics and calcium channel blockers are more effective at lowering blood pressure then are beta blockers or drugs that interfere with the renin-angiotensin system.

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ANSWER TO QUESTION 302

C (Braunwald, pp. 932–937; Tables 47.5–47.7)

All antihypertensive medications have potential side effects that may limit their use. Angiotensin-converting enzyme (ACE) inhibitors lower blood pressure by blocking the formation of angiotensin II and by increasing the circulating concentration of the vasodilator bradykinin. The most common side effect is an annoying dry cough that occurs in in 5% to 20% of patients taking ACE inhibitors, likely related to increased bradykinin.[1] Its incidence is higher in African American and Asian patients compared with Caucasians. The cough may persist for more than 3 weeks after discontinuation of the medication. Substitution with an angiotensin receptor blocker results in a similar antihypertensive effect, without producing cough in the majority of affected patients.

Calcium channel blockers vasodilate and lower blood pressure by interacting with plasma membrane L-type calcium channels in vascular smooth muscle and cardiac myocytes. A common side effect is ankle edema (which arises because of arterial > venous vasodilation). Less common adverse effects include headache, flushing, and gingival hyperplasia. Verapamil and diltiazem can also impair cardiac conduction and cause bradycardia.

Hydralazine is a direct vasodilator with potential adverse effects that include *tachycardia*, flushing, and headaches. These side effects can be prevented, and the antihypertensive effect increased, by co-administration of a beta blocker.

Minoxidil is a direct vasodilator that is occasionally used in patients with renal failure and severe hypertension. Its side effects include a reflex increase in cardiac output, fluid *retention*, and *hirsutism*. Approximately 3% of patients who take minoxidil develop a pericardial effusion, even in the absence of renal or cardiac dysfunction.

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ANSWER TO QUESTION 303

B (Braunwald, p. 935; Table 47.6)

Thiazide diuretics are among the most frequently prescribed first-line agents for the treatment of hypertension. They have a number of important side effects. The most common metabolic disturbance is hypokalemia; the hazard ratio for moderate or severe hypokalemia (≤3.0 mmol/L) with any thiazide exposure is 2.41 (95% confidence interval [CI] 1.28 to 4.53) after adjustment for age, sex, renal function, and use of RAS inhibitors.[1] The serum potassium level falls an average 0.7 mmol/L after institution of 50 mg/day of hydrochlorothiazide, and 0.4 mmol/L with 25 mg/day, but there is almost no decline with 12.5 mg/day.[2] Hypomagnesemia is usually mild but may prevent the restoration of an intracellular deficit of potassium and it should be corrected.

*Hyper*uricemia is present in one-third of untreated hypertensive persons, and it develops in another third during therapy with thiazide diuretics. This is likely a result of increased proximal tubular reabsorption of urate.[2] There may also be a rise in serum calcium (usually <0.5 mg/dL) on thiazide therapy, which is probably secondary to increased proximal tubular reabsorption. Hyponatremia may occur with thiazide therapy, especially in the elderly. Thiazides in higher dosages (≥50 mg daily) may increase the total blood cholesterol, low-density lipoprotein, and triglyceride levels in a dose-related fashion.[3]

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ANSWER TO QUESTION 304

D (Braunwald, pp. 971–974; Tables 48.8 and 48.9; Fig. 48.7)

The HMG-CoA reductase inhibitors (statins) are competitive inhibitors of the rate-limiting enzyme in cholesterol synthesis, primarily in the liver. By reducing the intracellular cholesterol concentration, the expression of cell-surface low-density lipoprotein (LDL) receptors is *increased* (resulting in enhanced removal of LDL particles from the circulation) and the hepatic production of very-low-density lipoprotein (VLDL), the precursor of LDL cholesterol, is *reduced*. As a result of these actions, total and LDL cholesterol levels fall, as do triglycerides, the major component of VLDL particles. Statins are very well tolerated. Reversible elevations of hepatic transaminases (alanine transaminase [ALT], aspartate transaminase [AST]) are almost always asymptomatic and rarely require stopping the drug. Myonecrosis, consisting of muscle aching or weakness in association with a serum creatine kinase level >10 times normal, occurs in <0.5% of patients. This adverse effect mandates immediate discontinuation of the statin. The risk of myopathy is increased when there is concurrent therapy with other drugs that interfere with cytochrome P-450 metabolism of many of the statins. Examples of such drugs include erythromycin, cyclosporine, and antifungal agents.

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ANSWER TO QUESTION 305

D (Braunwald, p. 971; Table 48.7; p. 1651)

Many medications have the potential to alter a patient's lipid profile. Beta blockers, particularly non–beta$_1$-selective agents, increase triglyceride levels and *lower* high-density lipoprotein (HDL) levels. Thiazides tend to *increase* triglyceride levels.

Hormonal replacement therapy with estrogen increases both HDL and triglyceride levels. Despite the augmented HDL effect, the use of estrogen to improve the lipid profile is not recommended because of an associated increase in cardiovascular events.[1] Immunosuppressive drugs and corticosteroids tend to raise triglyceride levels.

Protease inhibitors, for patients with human immunodeficiency virus infection, can induce a dyslipidemic syndrome characterized by elevated triglyceride and total cholesterol levels with decreased HDL levels. Chronic use of protease inhibitors has been associated with an increased risk of myocardial infarction compared with antiretroviral regimens that do not include a protease inhibitor.[2,3]

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ANSWER TO QUESTION 306

B (Braunwald, pp. 965–971; Tables 48.4 and 48.5)

Most clinically encountered lipoprotein disorders arise from an interaction between diet, lack of exercise, excessive weight, and an individual's genetic composition. Genetic lipoprotein disorders may affect low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, lipoprotein (a), and remnant lipoprotein molecules.

Familial hypercholesterolemia (FH) is an autosomal co-dominant disorder that results from defects in the LDL receptor gene.[1] More than 1000 different mutations of the LDL receptor gene have been described. Patients with FH have LDL levels > the 95th percentile for age and gender. Corneal arcus, tendinous xanthomas, and xanthelasmas are common. Men with heterozygous FH usually develop coronary artery disease (CAD) by the third or fourth decade. Affected women present 8 to 10 years later. Familial defective apolipoprotein B, which results from mutations in the apo B gene, is clinically indistinguishable from FH. It results in a reduced affinity of affected LDL particles for the LDL receptor.

Familial combined hyperlipidemia (FCH) is one of the most common familial lipoprotein disorders. It is a polygenic condition with abnormalities that include elevations of LDL and/or triglycerides, a *reduction* in HDL, and elevated apo B levels.[2] Patients with FCH have an *increased* risk of CAD, and there can be considerable clinical overlap between FCH and the insulin-resistance metabolic syndrome. Physical findings such as corneal arcus or xanthomas are rare.

Familial hypertriglyceridemia (type IV hyperlipoproteinemia) is also a polygenic disorder and is characterized by elevated triglycerides with normal or low LDL levels and reduced HDL. Patients do not develop xanthomas or xanthelasmas, and the relationship with CAD is not as strong or consistent as with FCH.

The proprotein convertase subtilisin/kexin type 9 gene (*PCSK9*) encodes a protease that binds to the LDL receptor and targets it for lysosomal degradation. Gain-of-function mutations in this gene decrease the availability of the LDL receptor, which causes *higher* plasma LDL cholesterol levels and an *increased* risk of ischemic heart disease.[3] Loss-of-function mutations in this gene result in lower LDL-cholesterol and coronary event rates.

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ANSWER TO QUESTION 307

C (Braunwald, p. 975; Table 48.8)

Niacin (nicotinic acid) is a B vitamin with lipid-lowering effects when taken at pharmacologic doses. Its primary action is to reduce very-low-density lipoprotein secretion from the liver, which causes a subsequent reduction in intermediate-density lipoprotein and low-density lipoprotein (LDL) levels. In addition, niacin decreases the release of free fatty acids from adipocytes (which are used by the liver for triglyceride synthesis), thus reducing triglyceride levels. In therapeutic doses, niacin reduces LDL cholesterol by 10% to 25% and triglycerides by 20% to 50%, and increases high-density lipoprotein (HDL) cholesterol by 15% to 35%. The increase in HDL cholesterol is caused by decreased catabolism of HDL and apo AI.[1] Niacin also reduces circulating levels of lipoprotein (a). Despite these effects on the lipid profile, its widespread use has been limited historically because of side effects, including flushing, hepatotoxicity, hyperuricemia, hyperglycemia, and gastritis.

In the Coronary Drug Project, a trial of patients with prior MI performed before the statin era, 15-year mortality was reduced in patients randomized to niacin therapy. However, in more recent trials of patients treated aggressively with statin therapy (AIM-HIGH,[2] HPS2-THRIVE[3]), the addition of niacin did not further lower cardiovascular risk compared with the statin alone.

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ANSWER TO QUESTION 308

D (Braunwald, pp. 960–966; Tables 48.1–48.3; Figs. 48.2–48.6)

The apoprotein components of lipoproteins serve several functions, including structural support, receptor recognition, and, in some cases, enzymatic activity. Apo AI is the major protein in high-density lipoprotein (HDL) and its concentration is inversely correlated with angiographic evidence of coronary disease.[1] Circulating apo AI interacts with the ABCA1 transporter on peripheral cell membranes, initiating lipidation of HDL particles. Apo AI also activates the plasma enzyme lecithin-cholesterol acyltransferase, which esterifies free cholesterol, an important step in the reverse cholesterol transport pathway.

The two forms of apoprotein B (apo B48 and apo B100) arise from a *single* gene that displays a unique editing mechanism that allows for synthesis of both proteins.[2] Apo B100 is the primary apoprotein of low-density lipoprotein (LDL), allowing recognition of the particle by the LDL receptor on cell surfaces.

Apoprotein E is found in very-low-density lipoproteins (VLDL) particles as well as in chylomicrons, in intermediate-density lipoprotein (IDL) particles, and, to a small extent, in HDL. Most patients with type III hyperlipoproteinemia (also termed *dysbetalipoproteinemia* or *broad beta disease*) are homozygous for the apoprotein E2/2 genotype. This disorder is characterized by premature atherosclerosis and is notable for both hypercholesterolemia and hypertriglyceridemia owing to an increase in IDL and/or VLDL particle populations.

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ANSWER TO QUESTION 309

E (Braunwald, pp. 968–969 and 974–975)

The relation between triglyceride levels and coronary artery disease (CAD) remains controversial.[1] Although hypertriglyceridemia has been shown to be a risk factor for CAD in univariate analyses, its significance has typically been weakened in multivariable analyses. This is likely due to the association of elevated triglyceride levels with other degenerative conditions, such as diabetes mellitus, chronic renal failure, obesity, cigarette smoking, and excessive alcohol consumption. In addition, it would be difficult to design a trial to isolate the benefits of triglyceride reduction because most antilipidemic agents have multiple effects on the lipid profile. The association between hypertriglyceridemia and cardiovascular risk appears to be stronger in women than in men.[2]

In the ACCORD trial, type 2 diabetic patients already treated with simvastatin achieved a marked reduction in triglycerides with the addition of fenofibrate. However, compared with placebo, clinical outcomes (fatal cardiovascular events, nonfatal myocardial infarction, or stroke) were not reduced by the addition of fenofibrate.[3]

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ANSWER TO QUESTION 310

B (Braunwald, p. 968)

Lipoprotein (a) [Lp(a)] consists of a low-density lipoprotein particle with its apo B100 component linked by a disulfide bridge to apolipoprotein (a) [apo(a)]. Apo(a) is a complex molecule that has sequence homology with plasminogen. The latter structural feature has raised the possibility that Lp(a) may inhibit endogenous fibrinolysis by competing with plasminogen for binding at the endothelial surface.

The primary determinant of Lp(a) levels is genetic; changes in diet and physical activity have no significant impact. In addition, Lp(a) levels vary widely across racial groups and are higher in African Americans compared with whites. In several studies, Lp(a) has been shown to be an independent risk factor for vascular risk. A meta-analysis of 36 prospective studies including more than 12,000 patients found that the adjusted risk ratio of cardiovascular events is 1.13 for each standard deviation increase in Lp(a). Niacin is one of the few interventions that can significantly reduce Lp(a); statin drugs do not. However, no study yet has shown that targeted pharmacologic reduction of Lp(a) improves cardiovascular outcomes.

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ANSWER TO QUESTION 311

B (Braunwald, pp. 974–975)

Fibric acid derivatives (e.g., gemfibrozil, fenofibrate) are used primarily to reduce elevated triglyceride levels. These agents interact with a nuclear transcription factor (PPAR-alpha) that regulates the transcription of the lipoprotein lipase, apo CII, and apo AI genes. The resultant increase in lipoprotein lipase augments hydrolysis of triglycerides from very-low-density lipoproteins (VLDL) at peripheral tissues, which decreases VLDL and plasma triglyceride levels. However, this action may cause low-density lipoprotein (LDL) levels to rise. A meta-analysis of fibrate trials has shown a modest reduction in rates of myocardial infarction but no reduction in mortality.[1]

Fish oils are rich in omega-3 polyunsaturated fatty acids. They *decrease* plasma triglyceride levels by reducing VLDL synthesis and have antithrombotic effects. Such therapy is recommended in cases of hypertriglyceridemia refractory to other conventional therapies. Robust clinical trials to evaluate the efficacy of fish oil in reducing myocardial infarction and stroke are lacking.[2]

Bile acid–binding resins prevent the reabsorption of bile acids from the small intestine, thereby reducing the return of cholesterol to the liver through the enterohepatic circulation, with subsequent upregulation of hepatic LDL receptors.

The latter action enhances removal of LDL from the circulation. Resins are used occasionally as an adjunct to statins in patients with severe elevations of LDL cholesterol. Side effects include constipation, abdominal fullness, and hypertriglyceridemia. In addition, resins can interfere with the absorption of other medications, which therefore should be ingested at least 1 hour before or 3 hours after the resin.

Ezetimibe selectively inhibits cholesterol uptake by intestinal epithelial cells and reduces LDL cholesterol when used alone or in combination with statins. The IMPROVE-IT trial compared the effect of ezetimibe plus simvastatin to simvastatin alone in 18,144 patients with a recent acute coronary syndrome. Patients assigned to combined therapy achieved a median LDL cholesterol of 53.7 mg/dL compared to 69.5 mg/dL in those who received simvastatin alone. The primary outcome (cardiovascular death, acute coronary syndrome, stroke, or need for coronary revascularization) was significantly lower in the ezetimibe plus simvastatin group (32.7% vs. 34.7%, hazard ratio 0.94, $P = .016$).[3]

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ANSWER TO QUESTION 312

C (Braunwald, pp. 1189–1192, 1195; Table 60.5; Figs. 60.8 and 60.9)

This patient's clinical presentation, ECG abnormalities, and troponin elevation are consistent with a non–ST-segment elevation myocardial infarction (NSTEMI). Acute therapy of NSTEMI is directed at clinical symptoms and stabilization of the culprit lesion. Antiplatelet therapy should include aspirin and a $P2Y_{12}$ platelet receptor inhibitor, whether an early invasive or ischemia-guided strategy is pursued.[1] $P2Y_{12}$ inhibitor options for all NSTEMI patients include clopidogrel and ticagrelor. Compared with clopidogrel, ticagrelor has a more rapid onset of action and a faster recovery of platelet function once the drug is stopped. In the PLATO trial, ticagrelor reduced the risk of vascular death, myocardial infarction (MI), or stroke compared with clopidogrel, without an increase in major bleeding.[2] As a result, a class IIa recommendation of the 2016 American College of Cardiology/American Heart Association (AHA/ACC) dual antiplatelet therapy guidelines is that it is reasonable to prescribe ticagrelor in preference to clopidogrel for NSTEMI patients.[3] A potential disadvantage of ticagrelor compared with clopidogrel is a shorter half-life, necessitating twice daily dosage. Of note, ticagrelor's advantage over clopidogrel in the PLATO trial was found only in patients taking ≤100 mg aspirin daily, such that ticagrelor-treated patients should not take higher doses of aspirin. For patients directed to an early invasive strategy, a third $P2Y_{12}$ inhibitor option is prasugrel, which, like clopidogrel, is a thienopyridine drug and an irreversible antagonist of the platelet $P2Y_{12}$ receptor. Prasugrel's onset of action is more rapid than that of clopidogrel, and in the TRITON-TIMI 38 trial of acute coronary syndrome patients for whom percutaneous coronary intervention was planned, prasugrel reduced the incidence of cardiovascular death, MI, or stroke by 19%, but at a cost of significantly increased bleeding.[4] The bleeding risk was greatest in patients ≥age 75 and in those with reduced body weight (≤60 kg), such that those populations derived no net benefit from prasugrel, and patients with a history of stroke or transient ischemic attack (TIA) actually experienced net harm. The patient in this vignette has a history of TIA and he should not receive prasugrel.

The two general treatment pathways of patients with NSTEMI are (1) an early invasive strategy (coronary angiography with revascularization as appropriate) and (2) a more conservative ischemia-guided strategy in which patients proceed to invasive evaluation only if they develop recurrent ischemic symptoms despite medical therapy, either spontaneously or on noninvasive stress testing. AHA/ACC guidelines recommend an early invasive strategy for initially stabilized patients who are at high risk for clinical events, using risk stratification models such as the TIMI (Table 3.2) or GRACE risk scores.[1] The patient presented in this vignette has high TIMI and GRACE scores (calculated at 6 and 176, respectively), such that proceeding to an early invasive strategy would be appropriate.

TABLE 3.2 TIMI Risk Factors and Risk of Cardiovascular Endpoint

TIMI Risk Factors
Age 65 years or older ≥3 CAD risk factors Known CAD (>50% stenosis) Previous aspirin use ≥2 anginal episodes in previous 24 h ST deviation ≥0.5 mm on initial ECG Elevated cardiac biomarkers

NUMBER OF TIMI RISK FACTORS	RISK OF CARDIOVASCULAR ENDPOINT[a] AT 14 DAYS (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

[a]Cardiovascular endpoints are death, myocardial infarction, or urgent revascularization.

CAD, Coronary artery disease.

Data from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. *2000;284:835.*

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ANSWER TO QUESTION 313

C (Braunwald, pp. 1352–1357; eFigs. 65.1–65.6, 65.8; Figs. 65.1–65.3, 65.6, 65.7)

In the United States, stroke is the third leading cause of death; only heart disease and cancer are more common. Each year, more than 795,000 strokes occur, and of these, ~185,000 are recurrent events in patients with a history of stroke. Treatable risk factors for ischemic stroke include hypertension, diabetes, and cigarette smoking.[1]

Blood pressure lowering is safe and beneficial in the period after an ischemic stroke, and the American Stroke Association recommends such therapy. For example, in the PROGRESS trial,[2] 6105 stable patients with a recent stroke were randomized to placebo or antihypertensive therapy with an angiotensin-converting enzyme inhibitor and diuretic. After 4 years, the relative risk of a new stroke declined by 28% in the patients randomized to the medical regimen compared with placebo.

Although data relating hypercholesterolemia to stroke risk have been equivocal, statins have been shown to reduce the incidence of stroke in patients at increased risk of vascular disease. A meta-analysis of 90,000 patients in cholesterol-lowering trials showed that each 10% reduction in low-density lipoprotein (LDL) level reduced the risk of stroke by 15.6%. In the Heart Protection Study (see Answer to Question 424), treatment with simvastatin was associated with a highly significant reduction in stroke rates. In the SPARCL study, 4731 patients with a history of cerebrovascular disease (recent stroke or transient ischemic attack [TIA]) and baseline LDL 100 to 190 mg/dL, but no known coronary disease, were randomized to atorvastatin 80 mg daily or placebo. After a mean follow-up of 4.9 years, there was a 16% reduction in subsequent stroke rates.[3]

Aspirin, or the combination of aspirin plus dipyridamole, has been shown to be effective for secondary prevention of ischemic stroke. In the MATCH trial, the combination of aspirin plus clopidogrel was compared with aspirin alone in 7599 patients who had sustained an ischemic stroke or TIA.[4] After 18 months, there was a nonsignificant reduction in the primary outcome (a composite of ischemic stroke, TIA, myocardial infarction, or vascular death) without a difference in all-cause mortality; life-threatening bleeding was higher in the combination group. Thus, dual antiplatelet therapy with aspirin and clopidogrel is not routinely recommended for secondary prevention after ischemic stroke.

In the PRoFESS study, aspirin plus dipyridamole was comparable with clopidogrel monotherapy for secondary stroke prevention in patients with noncardioembolic stroke; however, there were more major hemorrhages in the aspirin plus dipyridamole group.[5]

In three large trials of aspirin versus vitamin K antagonists (VKAs), VKAs did not reduce ischemic events but they increased the risk of intracranial hemorrhage.[2]

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ANSWER TO QUESTION 314

D (Braunwald, pp. 901–903)

Alcohol's interaction with the cardiovascular system is complex. Heavy alcohol intake is associated with increased cardiovascular and total mortality rates. However, several primary and secondary prevention studies have found that the relation between alcohol intake and cardiovascular disease is J-shaped, in that moderate (1 to 2 drinks) daily intake of alcohol is associated with lower risk compared with individuals who do not drink any alcoholic beverages.[1] Alcohol's beneficial effects may be a result of its ability to raise high-density lipoprotein levels, improve fibrinolysis, and reduce platelet aggregation. Alcohol intake is not associated with decreased low-density lipoprotein levels.

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ANSWER TO QUESTION 315

D (Braunwald, pp. 878–880; Fig. 45.4)

Cigarette smoking is one of the strongest risk factors for coronary artery disease but is also one of the hardest to modify.[1] Among its deleterious effects, smoking increases platelet aggregation, serum fibrinogen, and oxidation of low-density lipoprotein cholesterol. Patients who continue to smoke after a myocardial infarction have twice the mortality rate of those who stop.

Observational studies show that smoking cessation reduces the risk of a coronary event by 50% within 2 years, compared with patients who continue to smoke. The cardiovascular risk approaches a person who never smoked after 3 to 5 years of smoking cessation.

Addiction to nicotine can be intense. Patients who successfully quit smoking usually do so after five or more unsuccessful attempts. Physician counseling alone carries a poor success rate, with only 6% of patients achieving 1 year of abstinence. Greater success is achieved when pharmacologic aids are included in the treatment program, along with counseling. Agents approved by the US Food and Drug Administration for smoking cessation include (1) nicotine replacement therapy (available as patches, gums, lozenges, nasal spray, and an inhaler), (2) the psychoactive drug bupropion, and (3) varenicline, a partial nicotinic acetylcholine receptor agonist.

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ANSWER TO QUESTION 316

D (Braunwald, pp. 897–899, 1046–1049; Fig. 54.2)

Comprehensive rehabilitation for patients with coronary disease includes physical exercise training, which benefits the cardiovascular system and skeletal muscle in ways that improve work performance. Different formats for outpatient physical activity include supervised and unsupervised programs. In supervised programs, the aerobic training goal is typically exercising to 70% to 80% of the maximum predicted heart rate; some patients may require lower intensities. In unsupervised home programs, patients are encouraged to exercise to the onset of mild dyspnea, which eliminates the need for monitoring the pulse rate.

Several meta-analyses have studied the relation between exercise-based cardiac rehabilitation and clinical outcomes and have come to similar conclusions: mortality rates are lower among exercise-program participants compared with patients who did not participate.[1] Most of the studies included in these meta-analyses were performed before the current era of aggressive revascularization and may overestimate the expected mortality results in current practice.

During exercise, an increase in heart rate accounts for a greater percentage of the augmented cardiac output than does the rise in stroke volume. In addition, at rest, the heart extracts about 75% of oxygen in the coronary flow. Because of the limited reserve, any increase in myocardial oxygen demand must be met by augmentation of coronary blood flow. With physical training, half the improvement in exercise performance is due to increased cardiac output and half to peripheral adaptations that actually improve oxygen extraction.

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ANSWER TO QUESTION 317

E (Braunwald, p. 902)

Homocysteine is an amino acid derived from the demethylation of dietary methionine. Inherited disorders of methionine metabolism cause extremely high levels of homocysteine as well as homocystinuria. The most common cause of severe hyperhomocystinemia is cystathionine beta-synthase deficiency. Patients with this genetic defect present with atherothrombosis as early as the first decade of life. In contrast, mild to moderate elevations in homocysteine (>15 µmol/L) are common in the general population. Such elevations are often due to insufficient dietary intake of folate, use of folate antagonists such as methotrexate, polymorphisms in the methylene tetrahydrofolate reductase gene, hypothyroidism, or renal insufficiency.

A large number of epidemiologic studies have shown a link between mildly elevated homocysteine levels and atherosclerosis.[1] Folic acid supplementation can decrease homocysteine levels by approximately 25%. Additional vitamin B_{12} supplementation typically reduces levels by another 7%. Nevertheless, clinical studies that have included over 37,000 subjects have shown that reduction in plasma homocysteine concentration with B-vitamin supplements does not reduce the risk of atherothrombotic events.[2]

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ANSWER TO QUESTION 318

D (Braunwald, pp. 998–1002)

Metabolic syndrome is a common constellation of risk factors that greatly increases the risk of cardiovascular disease. Insulin resistance, the underlying abnormality in metabolic syndrome, may in part explain the association between hyperglycemia and atherosclerosis. Because it precedes overt diabetes mellitus, insulin resistance may also explain why many patients with newly diagnosed type 2 diabetes already have extensive vascular disease. The severity of insulin resistance correlates with the rates of myocardial infarction, stroke, and peripheral arterial disease, whereas decreasing insulin resistance pharmacologically may reduce vascular events.[1]

Early study of metabolic syndrome was hampered by the absence of a universal definition of this process. In 2009, a joint definition of metabolic syndrome was published by the International Diabetes Federation, the U.S. National Heart, Lung and Blood Institute, and the American Heart Association. According to this definition, metabolic syndrome exists when three or more of the following are present: fasting serum glucose ≥110 mg/dL, abdominal obesity (waist circumference above a region/ethnicity-specific threshold, generally >85 to 102 cm in men or >80 to 90 cm in women), serum triglycerides ≥150 mg/dL, low serum high-density lipoprotein cholesterol (<40 mg/dL in men or <50 mg/dL in women), and hypertension (systolic BP ≥130 and/or diastolic BP ≥85 mm Hg).[2]

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ANSWER TO QUESTION 319

D (Braunwald, pp. 928–930; Fig. 47.1; Tables 47.1–47.4)

Many nonpharmacologic approaches have been proposed for treatment of hypertension. In addition to dietary approaches, commonly used complementary and alternative medicine practices are hypnotherapy, relaxation, meditation, music therapy, acupuncture, yoga, and biofeedback. The Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes consumption of fruit, vegetables, and low-fat dairy products, with low intake of saturated fat, reduced systolic blood pressure by ~10 mm Hg and diastolic blood pressure by 5 mm Hg among hypertensives.[1] Garlic contains a compound (allicin) that *inhibits* angiotensin II, thus inducing

vasodilation and blood pressure reduction. A meta-analysis of garlic ingestion in hypertensives showed a blood pressure reduction of 9.1 mm Hg systolic and 3.8 mm Hg diastolic at a daily dose of approximately 600 to 900 mg.[2] There was a high degree of heterogeneity and overall low quality of evidence in this meta-analysis.

Slow breathing has been shown to increase parasympathetic activity and reduce sympathetic activation. Use of a device-guided biofeedback program of slow breathing has been shown to be associated with a significant blood pressure reduction in a meta-analysis of eight studies, though there was significant variation in the study results.[3] Although a small number of studies have suggested a possible acute, nonsustained improvement in blood pressure with acupuncture, the overall data quality is poor and two meta-analyses concluded that the current evidence is inconclusive.[4]

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ANSWER TO QUESTION 320

C (Braunwald, p. 991; Tables 49.1 and 49.2)

Several clinical trials have examined the effects of diet on reducing cardiovascular events. The Lyon Diet Heart study randomized patients with coronary artery disease to either a Mediterranean-style diet (rich in fruits, legumes, vegetables, and fiber and reduced meat, butter, and cream), supplemented with alpha-linolenic acid–enriched margarine, or a control diet. Despite a similar percentage of total fat in each diet and similar lipid profiles, there was a significant reduction in all-cause mortality and nonfatal myocardial infarction in the Mediterranean-style diet group compared with the control group.[1] In the primary prevention PREDIMED study, individuals without known cardiovascular disease, but who were at increased risk, were randomized to a Mediterranean-style diet (supplemented with extra-virgin olive oil or mixed nuts) or a control diet with advice to reduce dietary fat intake. After a median follow-up of 4.8 years, there were fewer cardiac events in the patients randomized to the Mediterranean diets (hazard ratio [HR] ~0.7).[2]

A pooled estimate of two randomized controlled trials of either regular fatty fish consumption (200 to 400 g/week) or fish oil supplementation (~900 EPA and DHA per day) in coronary artery disease patients showed a reduction in mortality (HR 0.77; 95% confidence interval [CI] 0.66 to 0.89).[3]

A diet of reduced-carbohydrate, high-protein, and high-fat content was shown to result in greater weight loss at 12 months, increased high-density lipoprotein, and reduced triglycerides when compared with a low-calorie, high-carbohydrate, low-fat diet, but has not been shown in controlled trials to reduce cardiovascular events.[4]

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ANSWER TO QUESTION 321

C (Braunwald, pp. 1123–1168; Fig. 59.34, eFig. 59.10)

Aspirin has proven efficacy in acute treatment and secondary prevention of myocardial infarction (MI).[1] Clinical trials support the administration of 325 mg in the acute setting and 81 to 162 mg/day in chronic usage.[1] Studies prior to the acute reperfusion era showed that beta blocker therapy initiated during the convalescent phase of ST-elevation MI (STEMI) reduced long-term mortality by 23%. Observational studies in patients who have undergone primary percutaneous coronary intervention for STEMI also generally support the use of beta blocker therapy for secondary prevention.[2] In the absence of contraindications, AHA/ACC guidelines recommend oral beta blocker therapy for at least 2 to 3 years post-MI.[1]

Angiotensin-converting enzyme (ACE) inhibition is another important therapy during and after hospitalization for MI. In large clinical trials, more than 120,000 patients have been randomized to an ACE inhibitor or placebo in the setting of acute MI (regardless of left ventricular [LV] function), and the results are consistent: ACE inhibitors reduce morbidity and mortality during and after the acute event. The greatest benefit accrues during the first week post-MI, especially in the highest-risk patients. Putative beneficial effects include vasodilatation, increased production of nitric oxide, decreased aldosterone secretion, lowered sympathetic tone, and reduced adverse LV remodeling. In addition, in patients with documented LV dysfunction after MI, ACE inhibitor use has been associated with a 20% to 30% relative risk reduction in mortality over approximately 3 years of follow-up.[3]

Many studies support the benefit of statin therapy for secondary prevention after MI.[4] The 4S and CARE trials examined the effects of statins after MI among patients with elevated and average cholesterol levels, respectively. Each demonstrated a marked reduction in cardiovascular death and MI in patients randomized to the cholesterol-lowering regimen. The PROVE IT—TIMI 22 trial of patients with an acute coronary syndrome showed superior long-term outcomes with a high-intensity statin (atorvastatin 80 mg daily) compared with less intense therapy (pravastatin 40 mg daily), such that higher-dose regimens are the standard of care.[5,6]

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ANSWER TO QUESTION 322

A (Braunwald, pp. 967–968; Tables 48.5 and 48.6)

Inherited mutations in familial hypercholesterolemia (FH) occur in the gene that codes for the low-density lipoprotein (LDL) receptor. Heterozygotes inherit one mutant gene and one normal gene and therefore produce only half the normal number of receptors. Heterozygote FH affects about 1 in 500 persons, with an even higher frequency in populations with a founder effect. Homozygotes inherit two mutant alleles and so have virtually no LDL receptors. Physicians rarely see homozygotes, whose frequency in the population is 1 in 1 million.

FH heterozygotes commonly present with tendon xanthomas, which are nodules that may involve the Achilles tendon and various extensor tendons of the forearm and leg. They consist of deposits of cholesterol derived from LDL particles. Cutaneous planar xanthomas occur only in homozygotes and usually manifest within the first 6 years of life. These xanthomas are yellow to bright orange and occur over areas of trauma. Both the heterozygous and homozygous forms of FH are associated with an increased incidence of coronary artery disease, the homozygous form far more severely than the heterozygous form. The presence of FH may be verified by assaying the density of functional LDL receptors on circulating lymphocytes or by genetic testing, although this is rarely clinically necessary.

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ANSWER TO QUESTION 323

B (Braunwald, pp. 968–969)

Familial hypertriglyceridemia is a relatively common disorder in which the concentration of very-low-density lipoprotein is elevated in the plasma.[1] The prevalence is between 1 in 100 and 1 in 50. Affected patients do not usually exhibit hypertriglyceridemia until puberty or early adulthood, at which time plasma triglyceride levels are moderately elevated, in the range of 200 to 500 mg/dL. Both low-density lipoprotein and high-density lipoprotein (HDL) cholesterol levels are usually reduced. These individuals exhibit only a slightly increased incidence of atherosclerosis, and it is unclear whether this is caused by the hypertriglyceridemia, by accompanying decreases in HDL cholesterol, or by associated illnesses. Patients with hypertriglyceridemia can experience severe exacerbations, with plasma triglyceride levels as high as 1000 mg/dL, when exposed to a variety of precipitating factors (e.g., excessive alcohol ingestion, poorly controlled diabetes, use of birth control pills containing estrogen, or hypothyroidism), or even after a meal. Such high triglyceride levels may lead to pancreatitis and eruptive xanthomas.

The disorder appears to be genetically heterogeneous in that patients from different families may have different mutations. No consistent abnormalities of lipoprotein structure or receptor function have been described. Lipoprotein electrophoresis shows an increase in the prebeta fraction (type IV lipoprotein pattern). Affected individuals can often be treated by controlling the exacerbating conditions, such as obesity, and restricting the intake of fats and alcohol.[2]

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ANSWER TO QUESTION 324

B (Braunwald, pp. 1283–1284; Table 62.2; see also Answer to Question 388)

Stent thrombosis is an uncommon, but potentially devastating complication of coronary stenting. Stent thrombosis that occurs immediately after stent implantation is referred to as *acute thrombosis*, an occurrence within the first month is termed *subacute thrombosis*, and *late thrombosis* denotes cases that occur thereafter. Stent thrombosis is effectively prevented by the combination of aspirin and an inhibitor of the platelet $P2Y_{12}$ receptor (e.g., clopidogrel, prasugrel, or ticagrelor). In the case of bare metal stents, the risk of thrombosis becomes negligible after 1 month of such therapy. However, drug-eluting stents (DES) retard the development of neointima such that there is a more prolonged exposure of the thrombogenic surface to circulating blood elements, necessitating a longer duration of dual antiplatelet medications. While newer-generation DES appear to manifest lower rates of stent thrombosis than first-generation devices, the current recommendation is that at least 12 months of dual antiplatelet therapy be administered following DES placement.[1] Clinical decision tools are currently under study to clarify which patients would be expected to benefit from

even longer duration of $P2Y_{12}$ inhibitor therapy,[2] versus shorter duration for those at high bleeding risk.

The strongest predictor for stent thrombosis is premature cessation of antiplatelet therapies. Other factors that increase this risk include stent placement in small vessels, long stents, overlapping stents, multiple lesions, ostial or bifurcation lesions, prior brachytherapy, a suboptimal stent result (e.g., under-expansion or residual dissection), low ejection fraction, diabetes mellitus, and renal failure.

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ANSWER TO QUESTION 325

D (Braunwald, pp. 1344–1346)

The patient described in this question has likely experienced renal atheroembolism, triggered by the catheterization procedure. Atheroemboli can be produced by mechanical manipulation of the aorta via catheters or surgery, and the kidneys are common targets for such embolism. This complication can result in acute renal failure with a stepwise decline in function. Some patients may progress to end-stage renal disease, whereas others recover full kidney function. The emboli may lodge in terminal arteries of the kidney, causing localized glomerular ischemia, or may compromise the large arteries and result in the loss of entire renal function.[1,2]

The urinalysis is often unremarkable, with only mild proteinuria and a bland sediment. Rarely, lipid droplets in the urine can be observed. Peripheral eosinophilia and low serum complement levels may be present. Livedo reticularis, the purple discoloration described in this patient and shown in the figure, occurs in 50% of patients and is due to areas of impaired perfusion, most often in the lower extremities. Other cutaneous manifestations of atheroembolic disease include purple toes, purpura, and gangrene. Often, the diagnosis of renal embolization can be made on clinical grounds alone. If there is cutaneous involvement, biopsy of the skin and muscle may be helpful. Renal biopsy may provide useful information, but carries a significant complication rate. The management of atheroemboli centers on supportive care, which may include hemodialysis. Large emboli may be amenable to surgical or catheter removal.

Contrast nephropathy after angiographic procedures can also result in renal insufficiency. Findings that point to atheroemboli rather than a contrast effect as the cause of renal dysfunction include: (1) evidence of peripheral emboli to other sites (e.g., the cutaneous manifestations described in the previous paragraph), (2) the presence of eosinophilia and reduced complement levels, and (3) prolonged renal dysfunction (e.g., >1 week).

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ANSWER TO QUESTION 326

C (Braunwald, pp. 961–967; Figs. 48.4–48.6)

Low-density lipoprotein (LDL) is the major cholesterol-carrying component of the plasma. It is formed mainly from metabolism of hepatic-derived very-low-density lipoprotein (VLDL) in the circulation: VLDL undergoes hydrolysis by lipoprotein lipase to form intermediate-density lipoprotein, which is then further delipidated by hepatic lipase to form LDL. The major lipid components of LDL are esterified cholesterol and triglyceride. Apo *B100* is the predominant protein present in LDL and comprises approximately 25% of LDL mass. Cells internalize LDL after it binds to cell surface LDL receptors.

Familial hypercholesterolemia is an autosomal dominant disorder caused predominantly by mutations in one of three genes (the LDL receptor gene, the apolipoprotein B gene, and the *PCSK9* gene) resulting in plasma LDL cholesterol levels >190 mg/dL and often premature coronary artery disease. Approximately 7% of American adults have a plasma LDL ≥190 mg/dL, but fewer than 2% of such individuals actually have a familial hypercholesterolemia mutation.[1]

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ANSWER TO QUESTION 327

A (Braunwald, pp. 872, 890–893; Figs. 45.13–45.15)

C-reactive protein (CRP), a circulating member of the pentraxin family, plays an important role in innate immunity. It is formed primarily in the liver, but is also elaborated from coronary arteries, especially atherosclerotic intima. Levels of CRP are elevated in inflammatory states and multiple epidemiologic studies have demonstrated that CRP measured by high-sensitivity assays (hsCRP) is strongly associated with myocardial infarction, stroke, peripheral arterial disease, and sudden death.[1] hsCRP levels can be classified as low (<1 mg/L), intermediate (1 to 3 mg/L), or high (>3 mg/L). In patients with acute coronary events, high hsCRP levels are associated with worse outcomes, including increased mortality.[2]

An elevated level of hsCRP also predicts the onset of type 2 diabetes, perhaps because it correlates with insulin sensitivity, endothelial dysfunction, and hypofibrinolysis. Many medications lower hsCRP levels, in particular statins, fibrates, and niacin. Statin therapy reduces hsCRP levels largely unrelated to the low-density lipoprotein-lowering effect.[3] Furthermore, statin therapy has been shown to benefit patients with relatively normal LDL, if the hsCRP is elevated. In the JUPITER trial, rosuvastatin resulted in a 44% reduction in vascular events in apparently healthy individuals with baseline LDL <130 mg/dL and hsCRP >2 mg/L.[4,5]

Aspirin does not directly lower hsCRP levels, but appears to have the greatest cardiovascular benefit in patients with elevated baseline hsCRP.

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ANSWER TO QUESTION 328

D (Braunwald, pp. 922–923; Fig. 46.6; Table 46.6)

As reviewed in the Answer to Question 297, there are two major forms of renovascular disease—atherosclerosis and fibromuscular dysplasia. Atherosclerotic patients are older and have higher systolic blood pressure, greater target organ damage, and evidence of atherosclerotic disease elsewhere. Patients with fibromuscular hyperplasia are younger, are more often female, have no family history of hypertension, and have less evidence of target organ damage. Patients with fibromuscular dysplasia are less likely to progress to complete renal artery occlusion or develop ischemic nephropathy compared with patients with atherosclerotic renal artery stenosis.

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ANSWER TO QUESTION 329

E (Braunwald, pp. 930–931; Table 47.11)

Hypertension frequently accompanies diabetes and greatly augments the risk of cardiovascular events in this population. Control of hypertension reduces future cardiovascular events in diabetics even more than in nondiabetics, and all diabetics with a persistent blood pressure (BP) >130/80 mm Hg should be on antihypertensive therapy.[1] Many BP lowering agents, including diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta blockers, have been shown to improve blood pressure control in diabetics, and there has been much controversy about whether one group is superior to others in reducing cardiovascular morbidity and mortality. Early small studies suggested that ACE inhibitors were superior to dihydropyridine calcium channel blockers in this regard. However, the United Kingdom Prospective Diabetes Study (UKPDS), Systolic Hypertension in Europe (Sys-Eur), and HOT trials found that the degree of blood pressure control is more important than the agents used to achieve it; the antihypertensives captopril, atenolol, and the dihydropyridine calcium channel blockers felodipine and nitrendipine all led to beneficial reductions in cardiovascular events.

Drugs that interfere with the renin-angiotensin system do appear to have a special place in the treatment of diabetic patients, especially with renal disease.[2] In patients with type 1 diabetes, ACE inhibitors slow the progression of diabetic nephropathy and end-stage renal disease, and several studies have demonstrated that ARBs provide similar benefit in patients with type 2 diabetes. Furthermore, in the Heart Outcomes and Prevention Evaluation study, the ACE inhibitor ramipril reduced cardiac events, stroke risk, and death in diabetic patients.[3] The Losartan Intervention For Endpoint study randomized 1195 diabetic patients with hypertension and left ventricular hypertrophy to the ARB losartan or atenolol therapy.[4] Although blood pressure control was similar in both groups, those who received the ARB had reduced all-cause mortality.

In the ACCORD trial, very aggressive reduction of BP, targeting systolic BP <120 mm Hg, was compared with "standard" therapy at the time (target systolic BP <140 mm Hg) in 4733 type 2 diabetics without advanced renal dysfunction.[5] The more aggressive blood pressure lowering *failed* to reduce the composite primary outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes over a mean follow-up of 4.7 years. While intensive therapy led to a reduction of the prespecified secondary outcome endpoint of stroke, it also caused significantly more serious adverse effects, including hypotension, bradycardia, hyperkalemia, syncope, and renal failure.

Based on results from major trials, the 2017 American hypertension practice guideline recommends a treatment BP goal of <130/80 mm Hg in diabetics.

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ANSWER TO QUESTION 330

D (Braunwald, pp. 1128–1134; Tables 59.4 and 59.5; Figs. 59.5, 59.9, 59.11; eFigs. 59.3 and 59.5)

Primary percutaneous coronary intervention (PCI) for acute ST-segment elevation myocardial infarction has several important differences and advantages when compared with pharmacologic fibrinolysis. The safety and success rate in establishing reperfusion (>90%) is superior to that of fibrinolytic agents, and there is less likelihood of developing complications such as reocclusion, re-infarction, and stroke with primary PCI. Multiple studies have demonstrated that primary PCI, when performed at experienced centers, results in a significant reduction in the rates of death (7% vs. 9%), reinfarction (3% vs. 9%), stroke (1% vs. 2%), and hemorrhagic

stroke (0.05% vs. 1%) compared with fibrinolysis.[1–3] In addition, primary angioplasty has been associated with shorter hospital stays and lower follow-up costs. Patients presenting with an acute myocardial infarction and cardiogenic shock are at the highest risk of death and cardiovascular complications. The SHOCK trial randomized 302 patients with cardiogenic shock to early revascularization or medical management. Early revascularization with primary PCI or urgent bypass surgery was associated with improved survival at 6 months (49.7% vs. 36.9%, P = .027) and 1 year (46.7 vs. 33.6%, P = .025).[4]

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ANSWER TO QUESTION 331

A (Braunwald, pp. 1151–1162; Fig. 59.24)

Part *A* of the image is a right anterior oblique caudal view of the left coronary artery showing total proximal occlusion of the left anterior descending (LAD), the presumed culprit lesion. Within the mid-left circumflex (LCx) there is an 80% stenosis. Part *B* is a left anterior oblique view of the right coronary artery (RCA) showing a 60% stenosis of the mid-vessel and 90% stenosis of the distal vessel.

Approximately half of patients who undergo coronary angiography for ST-segment elevation myocardial infarction (STEMI) have multivessel disease.[1] Historically, percutaneous coronary intervention (PCI) of a non-infarct related artery at the time of primary PCI for STEMI in hemodynamically stable patients was a class III (considered harmful) recommendation of American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[2] This caution was based on the combination of observational data and safety concerns, including increased contrast exposure and longer procedure times, as well as concern for a possibly increased risk of stent thrombosis during the heightened inflammatory state of the acute STEMI.

Subsequent to the 2013 ACC/AHA STEMI guidelines, four randomized controlled trials of multivessel PCI at the time of primary PCI, or as a planned, staged procedure, have been reported and have led to reconsideration of this recomendation.[1] These trials were PRAMI,[3] CvLPRIT,[4] DANAMI-3-PRIMULTI,[5] and PRAGUE-13.[6] In three of these trials, a strategy of multivessel PCI (at the time of primary PCI or a later planned, staged procedure) was shown to be safe and to benefit composite cardiovascular outcomes (PRAMI: hazard ratio [HR] 0.35 [95% confidence interval (CI) 0.21 to 0.58], P < .001; CvLPRIT: HR 0.49 [95% CI 0.24 to 0.84], P = .009; DANAMI-3-PRIMULT: HR 0.56 [95% CI 0.38 to 0.83], P = .004). However, in the PRAGUE-13 trial, randomization to revascularization of all ≥70% diameter non-infarct stenoses did not result in improved cardiovascular outcomes (death, nonfatal MI, stroke) compared with culprit-only PCI.

As a result of these newer trials, the 2016 focused update STEMI guidelines upgraded the recommendation of multivessel PCI at the time of primary culprit vessel PCI, or as a subsequent staged procedure, in hemodynamically stable patients, to class IIb ("may be reasonable").[1]

The patient in this question presents with an acute anterior STEMI with proximal occlusion of the LAD, the culprit vessel, as well as high-grade lesions within the LCx and RCA. The LAD should be reperfused expeditiously. Consideration may be given to PCI of the LCx and/or RCA at the time of the LAD PCI or as a staged procedure in this hemodynamically stable patient.

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ANSWER TO QUESTION 332

E (Braunwald, p. 1083)

Studies have revealed that atrial infarction occurs in 7% to 17% of autopsy-proven cases of myocardial infarction. Atrial infarction is often seen in conjunction with left ventricular infarction and more commonly involves the right atrium than the left. This difference may reflect the presence of well-oxygenated blood in the left atrium, which could help nourish an ischemic atrial wall. Atrial infarction is frequently accompanied by supraventricular arrhythmias, including atrial fibrillation, sinus arrhythmia, and wandering atrial pacemaker. In addition, atrial infarction may be complicated by rupture of the atrial wall.

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ANSWER TO QUESTION 333

A (Braunwald, pp. 1155–1159; Table 59.11; Figs. 59.27–59.30; eFig. 59.8)

Free wall rupture is one of the most lethal complications of acute myocardial infarction (MI) because it usually leads to hemopericardium and cardiac tamponade. Rupture typically arises after a large MI in the left anterior descending artery territory at the junction of infarcted and normal muscle. Whereas older series have quoted an incidence of free wall rupture of approximately 5%, occurring within 3 to 6 days after MI, more recent observations implicate an incidence of 1% to 2%, occurring primarily within the first 48 hours.[1] Patients with free wall rupture tend to have had greater delays to hospitalization and are more likely to have been physically active after the onset of MI. Additional risk factors include advanced age, female gender, a history of hypertension, and the *absence* of previous infarction. It is thought that patients with prior MI are "protected" against rupture, because previous scars may reduce the magnitude of the shear forces between the fresh infarct and the healthy myocardium.[1] The rate of free wall rupture is lower after primary percutaneous coronary intervention than after fibrinolytic therapy.[2]

The frequency of free wall rupture has decreased over the past 30 years, and survival has improved but remains poor.[2]

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ANSWER TO QUESTION 334

B (Braunwald, pp. 1153–1154; Fig. 59.26)

Patients with right ventricular infarction (RVI) may have a hemodynamic profile that resembles that of patients with pericardial disease. For example, elevations in right atrial (RA) and right ventricle (RV) filling pressures, as well as a rapid RA *y* descent and an early diastolic dip-and-plateau ("square root sign") may occur. In addition, the Kussmaul sign may be present in patients with RVI and is highly predictive for RV involvement in the setting of inferior wall infarction.[1,2] Patients who present with inferior wall infarction who are suspected of having RV involvement should have an ECG obtained with precordial leads placed on the right side of the chest: most patients with RVI demonstrate ST-segment elevation of 1 mm or more in lead V_4R (not standard lead V_4).[3] Echocardiography can confirm the presence of RV dilatation and depression of systolic function and is able to distinguish RVI from other hemodynamically similar conditions, including pericardial tamponade and constrictive pericarditis.

From a hemodynamic standpoint, treatment is typically aimed at increasing RA and RV filling pressures through administration of intravenous fluids, so as to maintain normal left-sided preload. A marked hypotensive response to nitroglycerin may be a clinical clue to the presence of RVI, reflecting the impact of RV filling pressure in this condition. Similarly, the contribution of atrial contraction to RV filling is important in patients with RVI. Thus, patients who require pacemaker therapy benefit from atrioventricular sequential pacing, which has been shown to improve hemodynamic parameters in this condition.

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ANSWER TO QUESTION 335

C (Braunwald, pp. 1156–1158; Fig. 59.31)

The progressive development of mitral regurgitation (MR) in this 60-year-old patient after an inferior myocardial infarction (MI) is most consistent with infarction of the posterior papillary muscle. Because papillary muscles are perfused via terminal portions of the coronary vascular bed, they are particularly vulnerable to ischemia. The posterior papillary muscle, supplied usually by only the posterior descending branch of the right coronary artery, is more susceptible to ischemia and infarction than the anterolateral papillary muscle, which has a dual blood supply from the diagonal branches of the left anterior descending artery and the marginal branches from the left circumflex artery. Although necrosis of a papillary muscle is a potential complication of MI, particularly of inferior infarction, frank rupture is far less common. Total papillary muscle rupture is usually fatal because of the extremely severe and rapid-onset MR that it produces. MR may also develop later after MI, in which case it usually results from left ventricular dilatation. In that case, dyskinesis of the left ventricle results in an abnormal spatial relationship between the papillary muscles and the chordae tendineae, hence promoting MR.

Rupture of chordae tendineae is also an important cause of MR, although such an event bears no special relation to MI. Common causes of chordal rupture include congenitally abnormal chordae, infective endocarditis, trauma, rheumatic fever, and myxomatous degeneration. Posterior chordae rupture spontaneously more frequently than do anterior chordae.

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ANSWER TO QUESTION 336

B (Braunwald, p. 1163)

Post-myocardial infarction (MI) pericarditis has become uncommon in the era of acute coronary reperfusion therapies, likely because current pharmacologic and mechanical interventions limit infarct size. In a modern series, the incidence of early post-MI pericarditis in 743 patients with acute ST-segment elevation myocardial infarctions treated with primary percutaneous coronary intervention was 4.2%, with an increasing prevalence in patients with longer delays to hospital presentation.[1] Post-MI pericarditis can develop as early as the first day after the infarction. The diagnosis is often based on the presence of pleuritic, positional chest pain that may radiate to the trapezius ridge and/or a pericardial friction rub; typical ECG changes of pericarditis are

less common. Post-MI pericardial effusions are found most often in patients with larger infarcts, when congestive heart failure is present, and in the setting of an anterior MI; progression to tamponade is rare. Early post-MI pericarditis is best treated with high-dose aspirin (e.g., 650 mg 4 to 6 times daily); other nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids should be avoided, as they may interfere with healing of the infarct.[2,3] Colchicine therapy has not been formally studied for this type of pericarditis. Anticoagulation should be avoided if possible in the setting of post-MI pericarditis to avoid the uncommon complication of hemorrhagic tamponade.

Dressler syndrome is a form of pericarditis that may occur 1 to 8 weeks after infarction. Patients present with malaise, fever, pericardial pain, leukocytosis, elevated inflammatory markers, and pericardial effusion. Like early post-MI pericarditis, Dressler syndrome has become infrequent, likely related to limitation of infarct size by current reperfusion therapies. When it develops within the first month after MI, aspirin therapy is advised, rather than other NSAIDs, to prevent interference with scar formation, as indicated in the previous paragraph.

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ANSWER TO QUESTION 337

E (Braunwald, pp. 1160–1162; Table 59.13)

A variety of conduction disturbances can occur in acute myocardial infarction (MI). In almost all patients with first-degree atrioventricular (AV) block, the disturbance is intranodal (above the bundle of His) and generally does not require specific treatment. First-degree AV block may also be a manifestation of increased vagal tone in the setting of acute MI. Other manifestations of increased vagal tone include sinus bradycardia and hypotension that are generally responsive to atropine.

Approximately 90% of patients with second-degree AV block admitted to coronary care units have Mobitz type I (Wenckebach) block. Mobitz type I block occurs most commonly in patients with inferior MI, is usually transient, and rarely progresses to complete AV block. It usually resolves within 72 hours after infarction and does not require specific therapy. In contrast, Mobitz type II block typically reflects conduction disease below the bundle of His, is associated with a widened QRS complex, and almost always occurs in the setting of anterior infarction. Mobitz type II block may progress to complete heart block and therefore generally justifies pacemaker placement.

Complete AV block (third-degree AV block) may occur in either anterior or inferior infarction. Its prognosis relates to the location of the infarction. In inferior infarction, complete heart block usually evolves from first-degree and type I second-degree AV block, typically has a stable escape rhythm, and is most often transient, with spontaneous resolution. Patients with anterior infarction may develop third-degree AV block without warning; however, it is usually preceded by less advanced conduction abnormalities such as Mobitz type II block. In general, patients in this setting have unstable escape rhythms, wide QRS complexes, and a high mortality rate.

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ANSWER TO QUESTION 338

B (Braunwald, pp. 1130–1134; Table 59.4; eFig. 59.3)

Overall, fibrinolytic therapy in ST-segment elevation myocardial infarction is associated with a 15% to 20% reduction in mortality at 35 days. The Fibrinolytic Therapy Trialists' Collaborative Group performed an overview of nine major fibrinolytic trials that each randomized more than 1000 patients. Among patients stratified by presenting ECG, patients with left bundle branch block (LBBB) had the highest overall mortality, followed by patients with anterior ST-segment elevations, and then patients with inferior ST-segment elevations.[1] The relative risk reductions with fibrinolytic therapy in patients with LBBB and anterior ST-segment elevation were both approximately 21%. Compared with patients with anterior ST-segment elevation, patients with inferior ST-segment elevation had less of a risk reduction.

The benefits of fibrinolysis are time dependent, and there is a stepwise decrease in improvement with later therapy over the first 24 hours. Two trials (LATE and EMERAS) showed a mortality reduction in patients treated with fibrinolytic therapy 6 to 12 hours after the onset of ischemic symptoms. However, there was no benefit for individuals treated beyond that time. Patients treated within 1 to 2 hours after onset of symptoms gained the most benefit.

Fibrinolytic trials have demonstrated that patients older than 75 years have a more modest relative risk reduction compared with individuals younger than 55 years. However, because the risk of adverse outcomes is so high for older patients, the absolute risk reductions are comparable between the age groups.[2]

The STREAM trial compared fibrinolysis followed by timely coronary angiography with primary percutaneous coronary intervention (PCI) in patients early in STEMI who were not able to undergo PCI within 1 hour of first medical contact. The fibrinolytic strategy resulted in effective reperfusion and comparable 30-day outcomes as the primary PCI group, but was associated with a slightly increased risk of intracranial bleeding.[3]

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ANSWER TO QUESTION 339

C (Braunwald, pp. 1097–1105; Figs. 58.1 and 58.4; eFig. 58.2)

Plaque rupture and plaque erosion are mechanisms that lead to coronary thrombosis and acute coronary syndromes.[1] When the resulting intracoronary thrombus is only partially occlusive, ST-segment depressions or T wave inversions (or both) commonly develop. When the thrombus is completely occlusive, ST-segment elevations typically occur. In the latter setting, Q waves subsequently form in approximately 75% of patients who are not treated with fibrinolysis or acute mechanical coronary revascularization.[2] In the remaining 25%, other ECG manifestations may develop, including reduction of the R wave height or notching of the QRS complex.

In the pre-fibrinolytic era, it was common to divide patients with myocardial infarction (MI) into those experiencing either a "Q wave MI" (now called "ST-segment elevation MI") or a "non–Q wave" MI (now called "non–ST-segment elevation MI") based on the evolution of the ECG over several days. Q wave infarction was considered to be synonymous with the pathology of a transmural infarction, whereas non–Q wave infarctions were considered to involve only the subendocardial layer. However, contemporary studies using cardiac magnetic resonance imaging indicate that the development of a Q wave on the ECG is determined more by the size of the infarct than the depth of mural involvement.[3]

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ANSWER TO QUESTION 340

D (Braunwald, pp. 1128–1134; Table 59.5; Figs. 59.10 and 59.11; eFig. 59.5)

Percutaneous coronary intervention (PCI) in acute ST-segment elevation myocardial infarction has been shown in large registries and randomized trials to result in higher patency rates (93% to 98% vs. 54%) and lower 30-day mortality rates (5% vs. 7%) than fibrinolytic therapy.[1] An additional advantage of PCI over fibrinolysis is a significant reduction in bleeding complications and strokes.

When performing primary PCI, radial artery access now tends to be preferred over femoral artery access based on the European Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX trial, which showed a reduction in bleeding and all-cause mortality when radial access was used.[2]

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ANSWER TO QUESTION 341

B (Braunwald, pp. 1163–1164; eFig. 59.8)

Left ventricular (LV) aneurysms arise in <5% of patients who survive acute ST-segment elevation myocardial infarction (MI). Formation of the aneurysm is presumed to occur when intraventricular tension leads to expansion of the noncontracting, infarcted myocardial tissue. An anterior MI complicated by LV aneurysm occurs due to total occlusion of a poorly collateralized left anterior descending artery. The presence of multivessel disease, extensive collateral vessels, or a nonoccluded left anterior descending artery makes the development of an aneurysm much less likely. Aneurysms occur approximately four times more often at the apex and in the anterior wall than in the inferoposterior wall and, in general, range from 1 to 8 cm in diameter.

True LV aneurysms, in contrast to pseudoaneurysms, rarely rupture. However, even when compared with mortality in patients having comparable LV ejection fractions, the presence of an LV aneurysm leads to a mortality that is up to six times higher than that of patients without aneurysm. Death in such patients is often sudden and presumed to be secondary to a high incidence of associated ventricular tachyarrhythmias. The diagnosis of an aneurysm is best made by echocardiography, magnetic resonance imaging, computed tomography, or left ventriculography. The "classic" evidence of aneurysm on the ECG—persistent ST-segment elevation in the area of the infarction—actually indicates a large infarct, but does not necessarily imply an aneurysmal segment.[1]

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ANSWER TO QUESTION 342

B (Braunwald, pp. 1158–1159, 1162; Table 59.12)

The ECG demonstrates atrial fibrillation with a rapid ventricular rate. Atrial fibrillation in acute myocardial infarction is usually transient and occurs more commonly in patients with left ventricular failure, infarct-associated pericarditis, or ischemic injury to the atria. Atrial fibrillation is more common during the first 24 hours after infarction than later. It is associated with increased mortality, in part because it occurs more frequently with extensive anterior wall infarctions.[1–3] The rapid ventricular response and loss of atrial contribution to ventricular filling may lead to an important reduction in cardiac output.

In patients who are hemodynamically stable, the use of a negative chronotropic drug (usually a beta blocker) is appropriate to slow the ventricular rate. However, cardioversion is the treatment of choice in patients with evidence of hemodynamic decompensation. Patients with recurrent episodes of atrial fibrillation should be anticoagulated.

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ANSWER TO QUESTION 343

A (Braunwald, p. 1159; Table 59.12)

The rhythm displayed is accelerated idioventricular rhythm (AIVR), which is defined as a ventricular escape rhythm with a rate between 60 and 100 beats/min. This rhythm is frequently referred to as "slow ventricular tachycardia" and appears in up to 20% of patients with acute myocardial infarction (MI), most commonly in the first 2 days after presentation. In addition, AIVR is the most common arrhythmia noted after reperfusion of an occluded coronary artery by fibrinolytic therapy. Approximately 50% of all episodes of AIVR are initiated by a premature beat; the rest emerge during periods of sinus slowing. In general, episodes of AIVR are of short duration and may show variation in rate. Unlike more rapid forms of ventricular tachycardia, episodes of AIVR have not been found to affect prognosis in acute MI and usually do not require intervention. If AIVR is accompanied by hemodynamic compromise, treatment with atropine or atrial pacing will often suppress the rhythm.

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ANSWER TO QUESTION 344

E (Braunwald, pp. 1115–1118; eFig. 58.4; Figs. 58.17 and 58.18)

Several cardiac biomarkers have been found to have prognostic value in patients with acute coronary syndrome (ACS), independent of more established markers of cardiac necrosis such as cardiac-specific troponins. The level of C-reactive protein (CRP), an acute-phase reactant, is approximately five times higher in patients with an ACS compared with those with stable coronary disease, and patients with the highest levels of CRP have an increased risk of death, even if cardiac troponin levels are not elevated.[1] The white blood cell count is a simpler but nonspecific marker of inflammation. Patients with unstable angina/non-ST-segment elevation myocardial infarction (MI) and elevated white blood cell counts have higher mortality and recurrent MI rates. This association is independent of CRP levels.[2]

Myeloperoxidase, a hemoprotein expressed by neutrophils, is a potent pro-oxidant that is associated with the presence of angiographic coronary artery disease. In patients with an ACS, myeloperoxidase levels have been associated with increased rates of death or recurrent MI, independent of other cardiac markers.[3]

Elevated levels of B-type natriuretic peptide, a neurohormone released in response to ventricular wall stress, are associated with a twofold to threefold higher risk of death by 10 months.[4]

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ANSWER TO QUESTION 345

A (Braunwald, pp. 1194–1195; Fig. 60.10)

This patient has an indication for long-term oral anticoagulation (OAC) because of atrial fibrillation with an elevated stroke risk (CHA_2DS_2-VASc score is at least 5—see Answer to Question 218). Additionally, she has a new indication for dual antiplatelet therapy (DAPT), having just undergone drug-eluting stent placement following an non-ST-segment elevation myocardial infarction. Managing patients with indications for "triple" antithrombotic therapy presents a dilemma because of the elevated bleeding risk and uncertainty about the ischemic consequences of reducing the OAC dose, or eliminating one of the antiplatelet agents. In addition, recent studies have evaluated the role of low-dose OAC in reducing future ischemic events in patients with recent myocardial infarction (MI) who do not have a separate indication for anticoagulation. How antiplatelet therapy should be modified in such patients remains an open question.

The WOEST trial randomized 573 patients undergoing percutaneous coronary intervention (PCI), who also required long-term OAC therapy, to OAC plus clopidogrel alone ("double" therapy), or OAC plus DAPT with clopidogrel and aspirin ("triple" therapy).[1] At 1 year, there was a significant reduction in bleeding events with "double" therapy (hazard ratio [HR] 0.36; 95% confidence interval [CI] 0.26 to 0.50); $P < .0001$). There was no increased risk of ischemic events in the "double" therapy group, though this small trial was not powered for ischemic outcomes.

The PIONEER AF trial randomized 2124 patients with atrial fibrillation undergoing PCI to one of three regimens: (1) "triple" therapy with warfarin (target international normalized ratio [INR] 2.0 to 3.0) plus DAPT; (2) low-dose rivaroxaban (15 mg daily) plus a $P2Y_{12}$ inhibitor without aspirin; or (3) very low-dose rivaroxaban (2.5 mg twice daily) plus a $P2Y_{12}$ inhibitor without aspirin.[2] Patients who received reduced doses of rivaroxaban and only one antiplatelet agent had less bleeding at 12 months compared with patients receiving

"triple" therapy. Importantly, the trial participants had preexisting atrial fibrillation and were not treated with approved doses of rivaroxaban for stroke prevention. The trial was not powered for ischemic events, but there were numerically more strokes in the two rivaroxaban arms than the warfarin arm. Thus, as in WOEST, the data from this trial showed reduced bleeding with "double" therapy, but do not clarify whether "double" and "triple" therapies are equally effective for reduction of ischemic events.

Two recent trials have assessed the role of anticoagulation in the post-acute coronary syndrome (ACS) setting in patients without a separate indication for long-term OAC therapy. ATLAS ACS 2-TIMI 513 randomized 15,526 patients with a recent ACS to very low-dose rivaroxaban (2.5 or 5 mg twice daily) or placebo in addition to standard post-ACS dual antiplatelet therapy. This well-powered trial found that the addition of rivaroxaban significantly reduced the risk of cardiovascular death, MI, or stroke, but at a cost of increased bleeding.[3] In 2017, GEMINI-ACS-14 reported the results of a phase 2 trial that randomized 3037 patients with recent ACS to rivaroxaban 2.5 mg twice daily plus single antiplatelet therapy (ticagrelor or clopidogrel) versus DAPT (aspirin plus ticagrelor or clopidogrel).[4] The trial was powered only for bleeding events and the rivaroxaban arm was found to be non-inferior to DAPT in this regard.

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ANSWER TO QUESTION 346

D (Braunwald, pp. 1241–1242; Fig. 61.14)

Venous graft occlusion occurs in 8% to 12% of patients before they leave the hospital, and by 1 year post-coronary artery bypass grafting 15% to 30% of vein grafts had become occluded.[1] Graft occlusion within the first year usually involves vessel thrombosis, with or without intimal hyperplasia. After the first year, atherosclerotic changes begin to accumulate in saphenous grafts. The histologic appearance of atherosclerosis in venous bypass grafts is indistinguishable from that seen in arterial vessels. The annual occlusion rate for vessels after the first year is 2%, although in grafts that are between 6 and 10 years old, an increased annual attrition rate of 4% is observed. The overall occlusion rate by 10 years is 40% to 50%. Internal mammary artery grafts have much longer durability than vein grafts, with patency rates of 95%, 88%, and 83% at 1, 5, and 10 years, respectively.[2] Aspirin (80 to 325 mg daily, started preoperatively and continued indefinitely) and lipid-lowering therapy have favorable impacts on the development of graft disease.

Historically, atherosclerotic progression in nongrafted arteries has occurred at a rate of 18% to 38% over the first decade, although this may potentially be lessened by aggressive lipid-lowering regimens. The risk of disease progression in the native circulation is three to six times higher in vessels to which a graft is placed, compared with ungrafted native arteries. This is the basis for the recommendation that arteries with minimal disease not receive a bypass graft.

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ANSWER TO QUESTION 347

A (Braunwald, pp. 1088–1092; Table 57.1; Figs. 57.25–57.28; eFigs. 57.7 and 57.8)

Myocardial stunning represents prolonged myocardial dysfunction that follows a brief episode of severe ischemia, with gradual return of contractile activity. Conversely, *Myocardial hibernation* is the term applied to myocardial dysfunction resulting from chronic hypoperfusion.[1]

Myocardial stunning affects both systolic and diastolic function and may occur in globally as well as regionally ischemic myocardium. Clinically, stunning is most frequently seen in patients recovering from ischemic arrest during cardiopulmonary bypass. It is also observed in ischemic regions adjacent to infarcted zones and in territories that are severely ischemic in patients with unstable angina. There are three likely mechanisms of myocardial stunning: (1) generation of oxygen-derived free radicals, (2) calcium overload, and (3) reduced sensitivity of myofilaments to calcium.[2,3]

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ANSWER TO QUESTION 348

D (Braunwald, pp. 1181–1182, 1189–1193; Table 60.5; Figs. 60.7–60.9)

Unstable angina/non-ST-segment elevation MI (UA/NSTEMI) is typically caused by atherosclerotic plaque rupture with formation of a platelet-rich intracoronary nonocclusive thrombus. Aspirin significantly reduces the risk of cardiovascular death and nonfatal myocardial infarction (MI) in this setting.[1] Clopidogrel is an irreversible inhibitor of the platelet $P2Y_{12}$ ADP receptor. The CURE trial demonstrated that the addition of clopidogrel to standard acute coronary syndrome (ACS) therapy resulted in a 20% reduction in death, MI, or stroke. Further analysis of this trial showed that the beneficial effects became apparent within 24 hours of treatment initiation and persisted for 12 months.[2]

The addition of an anticoagulant improves clinical outcomes of patients with UA/NSTEMI more than antiplatelet therapy alone.[1] Studies of patients with unstable angina in the era before the use of dual antiplatelet regimens showed that the addition of unfractionated heparin (UFH) to aspirin reduced adverse event rates.[1] Low-molecular-weight heparins (LMWHs) have been compared with UFH in the setting of UA/NSTEMI. In a large meta-analysis, new or recurrent MI occurred less often with the LMWH enoxaparin, with similar rates of bleeding.[3] Enoxaparin is the preferred LMWH for ACS on the basis of several clinical trials that demonstrate its efficacy, whereas the experience with other LMWHs has not been as convincing.

The factor Xa inhibitor fondaparinux was studied in patients with UA/NSTEMI in the OASIS-5 trial and was associated with a *lower* risk of major bleeding and of mortality at 30 days when compared with enoxaparin.[4]

Another anticoagulant option, bivalirudin, is a direct thrombin inhibitor. In the ACUITY trial of patients with non-ST-segment elevation MI (most of whom received aspirin plus clopidogrel) for whom an invasive strategy was planned, bivalirudin was compared with two other antithrombotic regimens: (1) bivalirudin plus a glycoprotein (GP) IIb/IIIa inhibitor, or (2) UFH or LMWH with a GP IIb/IIIa inhibitor. There were no differences in ischemic events between the treatment arms, but bivalirudin alone caused less bleeding than either regimen that included a GP IIb/IIIa inhibitor.[5] Thus, bivalirudin (with aspirin plus a $P2Y_{12}$ inhibitor, but without a GP IIb/IIIa inhibitor) is an alternative for an early invasive strategy in NSTEMI patients, particularly if there is an increased bleeding risk.

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ANSWER TO QUESTION 349

D (Braunwald, pp. 1087, 1106–1107)

Preexisting collateral vessels are small (20 to 200 μm) vascular channels that interconnect epicardial coronary arteries. They are normally closed and nonfunctional, because there is no pressure gradient between the arteries they connect. However, with an acute coronary occlusion, the distal pressure drops suddenly and any preexisting collateral vessels open quickly. The increased flow through these rudimentary collateral vessels triggers a maturation process that includes three stages. In the first 24 hours there is passive widening due to the increased flow. Over the next several weeks, increased flow and shear stress trigger endothelial cell activation, with subsequent inflammation and cellular proliferation with fragmentation of the basement membrane, dissolution of the extracellular matrix, and recruitment of leukocytes. Over several months, the collateral vessel wall thickens as a result of deposition of extracellular matrix. The resultant blood vessel is a three-layer structure that is nearly indistinguishable from a normal coronary artery, with a luminal diameter as large as 1 mm.[1]

Growth of the collateral circulation is triggered primarily by the severity of coronary obstruction. There is no clear evidence that exercise by itself triggers collateral formation. The reduction of myocardial ischemia in the setting of exercise training is more likely to be related to improved conditioning. Conditions that reduce endothelial production of nitric oxide, such as diabetes mellitus, may reduce the ability of collateral vessels to develop.

In angioplasty studies, collateral vessels typically provide <50% of normal coronary blood flow. Nonetheless, in the setting of an acute MI, they have been shown to decrease infarct size and contribute to improved survival. In patients with stable coronary disease, those with well-developed collateral circulations have a significantly lower rate of ischemic events.[2]

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ANSWER TO QUESTION 350

D (Braunwald, pp. 1237–1240; Figs. 61.11–61.13)

Several trials have compared pharmacologic therapy to percutaneous coronary intervention (PCI) for patients with chronic stable angina. In most of these, PCI has resulted in greater symptomatic relief as measured by severity of angina, the need for antianginal medications, and improved quality of life. However, with respect to major cardiac events (e.g., myocardial infarction [MI] or cardiac death), the two strategies appear equivalent. In the largest of the trials, COURAGE, 2287 patients with moderately severe chronic angina were randomized to PCI and optimal medical therapy (including aspirin, lipid lowering to a low-density lipoprotein goal of 60 to 85 mg/dL, antianginal drugs and angiotensin-converting enzyme inhibitors) or optimal medical therapy alone. Bare metal stents were used for PCI in the majority of patients in the PCI group. After 4.6 years of follow-up, there was no reduction in death and/or myocardial infarction in patients randomized to PCI compared with medical therapy.[1] Patients initially treated with PCI experienced less angina at 1 and 3 years, but by 5 years there was no difference compared with patients treated initially with optimal medical therapy alone.

The FAME 2 trial compared optimal medical therapy alone, to optimal medical therapy plus PCI, in patients with angina and at least one stenosis with a fractional flow reserve (FFR) ≤0.80 (rather than performing PCI simply for angiographic findings). The trial was terminated early after FFR-guided PCI was found to reduce the combined primary outcome of death, MI, or urgent revascularization. This benefit was entirely based on a highly significant reduction in the need for urgent revascularization in patients treated with PCI

plus medical therapy (1.6%) versus medical therapy alone (11.1%; hazard ratio 0.13, 95% confidence interval 0.06 to 0.30, $P < .001$). PCI did not confer a reduction in death or MI in this trial.[2]

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ANSWER TO QUESTION 351

D (Braunwald, pp. 1296–1299; eFig. 63.1; Figs. 63.3 and 63.4)

Although the average rate of expansion of abdominal aortic aneurysms (AAAs) is 0.4 cm per year, larger aneurysms tend to expand faster than smaller ones, as a consequence of Laplace's law (wall tension is proportional to the radius of the aneurysm). Once aneurysm rupture has occurred, mortality is extremely high: 60% of patients die before they reach the hospital, and 50% of those who are successfully hospitalized die perioperatively. Surveillance of asymptomatic aneurysms until the size is >5.5 cm is associated with a low rate of rupture (~1% per year). However, the 5-year risk of rupture is 30% to 40% for AAAs that are 5.5 to 6.0 cm in diameter. Thus for asymptomatic patients, current guidelines recommend repair of AAAs ≥5.0 to 5.5 cm.[1]

For AAAs >4.5 cm, computed tomography is preferred over ultrasound for imaging surveillance because of greater accuracy of measurement. The Society of Vascular Surgery recommends the following frequency of imaging: for AAAs 3.0 to 3.4 cm, every 3 years; 3.5 to 4.4 cm, every 12 months; and 4.5 to 5.4 cm, every 6 months.[2] Of note, women have a higher rate of rupture of AAAs than men and at a smaller aneurysm diameter. Rupture is also more common among current smokers and those with hypertension.

Clinical trials have examined the value of immediate repair of aneurysms 4.0 to 5.5 cm in diameter versus serial surveillance with ultrasound or computed tomographic scanning. These studies have found no mortality difference between the two strategies.[3] Important limitations of these trials were that they enrolled almost exclusively men and follow-up was much more intense than in general practice.

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ANSWER TO QUESTION 352

C (Braunwald, pp. 1307–1321; Tables 63.3 and 63.4; eTable 63.2; Figs. 63.11, 63.12, 63.18, 63.19, 63.21; eFigs. 63.20, 63.21, 63.24)

The figure displays a contrast-enhanced chest computed tomogram showing an intimal flap ("I") due to aortic dissection. Acute aortic dissection is a medical and surgical emergency. Mortality in untreated cases exceeds 25% in the first 24 hours and 50% in the first week after presentation. Immediate medical management should focus on reduction of blood pressure, reduction of arterial dP/dt (the force of left ventricular ejection), fluid resuscitation if necessary, and preparation of the patient for operative intervention if indicated. Beta blockers are the agents of choice for lowering blood pressure; labetalol is an appropriate initial choice of beta blocker because it combines blood pressure–lowering effects (alpha- and beta-blockade) with reduction of dP/dt (beta-blockade). IV sodium nitroprusside can be added for additional blood pressure control if needed.

Surgical therapy for type A (proximal) acute dissection improves survival compared with medical therapy alone.[1] This is because progression of proximal dissection can (1) compromise flow to major vessels, including the coronary arteries, (2) rupture into the pericardium, resulting in tamponade and death, or (3) lead to severe aortic valve regurgitation.[1] Uncomplicated type B (distal) dissections, however, can be managed with initial pharmacologic therapy alone, with a 30-day survival rate of 92%. For patients with complicated type B dissections (e.g., intractable pain or visceral ischemia), invasive intervention is necessary. Open surgical repair in such patients is associated with high mortality rates; endovascular repair is often appropriate instead.[2]

A small percentage of patients present with chronic aortic dissections. By surviving the acute stage, these patients represent a select subset of lower-risk patients who can be managed conservatively with medical therapy regardless of the location of the dissection, unless the dissection is complicated by aneurysm, rupture, vascular compromise, or aortic regurgitation.

When aortic regurgitation complicates acute dissection, decompression of the false lumen may be all that is required to correct the geometry of the aortic valve and restore valve competence. If abnormalities of the aortic valve leaflets prevent such repair, then aortic valve and root replacement are usually necessary.

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ANSWER TO QUESTION 353

D (Braunwald, pp. 1233–1234)

Ranolazine is an antianginal agent that may be used in combination with beta blockers, nitrates, and calcium channel blockers. Unlike beta blockers, nitrates, and calcium channel blockers, ranolazine exerts its anti-ischemic effect without significant effect on heart rate or blood pressure. Ranolazine inhibits the slowly inactivating component of the cardiac sodium current (late I_{NA}^{+}) and is therefore believed to reduce the deleterious effects of intracellular sodium and calcium

overload that accompany, and may promote, myocardial ischemia.[1]

Clinical trials have shown that ranolazine is effective as monotherapy, or in combination with traditional antianginal agents. In studies of patients with moderate angina, ranolazine decreased the frequency of angina and need for sublingual nitroglycerin.[2]

Ranolazine is generally well tolerated; its most common side effects are dizziness, headache, and constipation. Because ranolazine produces a concentration-dependent prolongation of repolarization and the QT interval, there has been concern that it may precipitate arrhythmias such as torsades de pointes. However, in the MERLIN-TIMI 36 study of 6560 patients with acute coronary syndromes, there was no difference in the rates of documented dysrhythmias or sudden cardiac death in patients receiving ranolazine compared with placebo.[1]

Ranolazine is metabolized in the liver (primarily by CYP3A), and its use is contraindicated in patients with significant hepatic impairment.

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ANSWER TO QUESTION 354

C (Braunwald, pp. 1296–1298; eFig. 63.1; Fig. 63.3)

The figure is an axial contrast-enhanced computed tomographic (CT) scan demonstrating a large abdominal aortic aneurysm (AAA). The majority of AAAs are asymptomatic. On physical examination, such an aneurysm may be appreciated as a pulsatile mass extending variably from the xiphoid process to the umbilicus. The size of an aneurysm tends to be overestimated by physical examination, owing to the difficulty in distinguishing the aorta from adjacent structures. AAAs may be sensitive to palpation, especially if they are rapidly expanding.[1]

Ultrasonography and CT are both helpful means to diagnose and quantitate the size of AAAs. However, ultrasonography is not sufficient for planning operative repair because it cannot define associated mesenteric and renal artery anatomy. Spiral CT with three-dimensional reconstruction provides a more comprehensive evaluation of the aortic tree. It also tends to measure aneurysms as slightly larger than by ultrasonography. Aortography, historically the gold standard for preoperative aneurysm evaluation, may actually underestimate the size of an AAA if nonopacified mural thrombus lines the wall. Magnetic resonance angiography is an alternative to angiography that is highly accurate in determining aneurysm size and, with three-dimensional reconstruction, can define the proximal extent of disease and iliofemoral involvement in more than 80% of cases.

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ANSWER TO QUESTION 355

D (Braunwald, p. 1192; Fig. 60.7)

The use of platelet glycoprotein (GP) IIb/IIIa inhibitors in the setting of percutaneous coronary intervention has been tested in multiple randomized trials, involving the full spectrum of coronary disease, from stable angina to ST-segment elevation myocardial infarction (MI). Excluding studies that used inadequate doses, the trials are consistent in demonstrating significant reductions in the composite endpoint of death, MI, and need for urgent revascularization over 30 days of follow-up.[1] Most of this benefit is realized by patients experiencing an acute coronary syndrome and relates to reductions in peri-procedural MI and the need for urgent revascularization. Several studies have concluded that patients who sustain a peri-procedural MI have a worse long-term prognosis. The disadvantage of GP IIb/IIIa inhibitors is an increased risk of bleeding complications.

The reduction in clinical events with GP IIb/IIIa inhibition is typically achieved in the first 48 hours, with little separation of the event rate curves after that time. They do not appear to have any long-term effects on rates of restenosis.[2]

For patients with acute non-ST-segment elevation MI who have received aspirin plus clopidogrel there is only a modest benefit of early "upstream" GP IIb/IIIa inhibitor administration, compared to provisional administration of the drug in the cardiac catheterization laboratory. In a meta-analysis of 12 studies involving more than 46,000 patients, there was a small reduction in the endpoint of death or MI at 30 days, but there was no reduction in mortality alone, and there was a 23% relative increase in major bleeding.[3] Thus, *routine* early administration of a GP IIb/IIIa inhibitor prior to transport to the cardiac catheterization laboratory is not recommended. For select high-risk patients on aspirin and a $P2Y_{12}$ inhibitor for whom an early invasive strategy is planned, and who have a low bleeding risk, early use of a GP IIb/IIIa inhibitor (specifically eptifibatide or tirofiban) can be considered (class IIb recommendation).[4]

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ANSWER TO QUESTION 356

D (Braunwald, pp. 962–966; Fig. 48.8)

Prinzmetal angina is caused by transient coronary artery vasospasm. Although the site of vasospasm may not appear to contain a significant plaque on angiography, intravascular ultrasound studies have shown that nearly all such sites have underlying atherosclerosis. Both nitrates and calcium channel blockers have been shown to be efficacious in treating and preventing attacks of Prinzmetal angina.[1] Provocative testing with ergonovine or acetylcholine is indicated only when Prinzmetal angina is suspected and ECG evidence of transient ST-segment elevation is lacking, because these agents can cause severe prolonged coronary spasm, resulting in myocardial infarction or arrhythmias. Coronary spasm has been observed after administration of ergot derivatives, 5-fluorouracil, cyclophosphamide, and serotonin reuptake inhibitors.[2] Patients with isolated Prinzmetal angina generally have an excellent prognosis, with very low rates of sudden cardiac death or myocardial infarction.

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ANSWER TO QUESTION 357

C (Braunwald, pp. 1344–1346; see also Answer to Question 325)

The figure shows atheroemboli to the left foot resulting in "blue toe syndrome." Showers of microemboli that arise from atherosclerotic plaques in the aortic or major arterial trunks lead to clinical and pathologic changes as the particulate material lodges in small arterial branches. Atheromatous embolism (also called "cholesterol embolism") occurs most often after surgery involving manipulation of an atherosclerotic aorta, such as major abdominal vascular procedures, especially resection of abdominal aortic aneurysms. Showers of atherosclerotic emboli may also be provoked by cardiac catheterization, cardiopulmonary bypass, and intra-arterial cannulations of any type and may occasionally occur spontaneously as well. Clinical findings in this disorder may include bilateral lower extremity and/or abdominal pain, livedo reticularis, purpuric and ecchymotic lesions in the lower extremities, and possibly visualization of cholesterol particles in the retinal arteries, when the proximal aorta is involved. Laboratory analysis may reveal eosinophilia, anemia, thrombocytopenia, and azotemia. While imaging studies (e.g., computed tomography, magnetic resonance angiogram, or transesophageal echocardiography) may document shaggy atheromatous sources of substrate, definitive diagnosis of atheroembolism rests upon identification of cholesterol crystals on skin or muscle biopsy specimens.

Two important recognized complications of cholesterol emboli after abdominal aortic surgery are pancreatitis and renal failure due to diffuse microinfarction of the affected organ. The resulting renal failure may be severe and irreversible. There is no specific therapy for cholesterol emboli; treatment of the resulting complications of the disorder is the cornerstone of management. The use of anticoagulants to prevent further episodes of embolization remains controversial. Antiplatelet and antilipid agents should be considered in affected patients because these therapies may prevent other cardiovascular events in this high-risk population.

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ANSWER TO QUESTION 358

D (Braunwald, pp. 1070–1075; eTable 57.1; Figs. 57.7 and 57.9)

Nitric oxide (NO) is formed in endothelial cells by the action of NO synthase on L-arginine. In this reaction, the terminal nitrogen from the guanidino group of L-arginine forms NO, and L-citrulline is produced as a by-product, which is recycled back to L-arginine. NO diffuses to neighboring smooth muscle cells, where it activates guanylate cyclase, causing an increase in cyclic *guanosine* monophosphate and smooth muscle relaxation.

Hypoxia, thrombin, and adenosine diphosphate all stimulate endothelial NO production. Acetylcholine (ACh) induces both endothelium-dependent (i.e., NO-mediated) vasodilatation and direct smooth muscle constriction. As a result, ACh induces vasodilatation in healthy vessels, but vasoconstriction predominates in atherosclerotic vessels in which there is dysfunctional endothelium. Some vasodilators (e.g., nitroglycerin, nitroprusside, and prostacyclin) act independently of endothelial NO production and continue to produce vascular smooth muscle relaxation even in the setting of a dysfunctional endothelium.

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ANSWER TO QUESTION 359

A (Braunwald, pp. 1321–1322; Fig. 63.24)

Intramural hematoma (IMH) is a condition closely related to aortic dissection. It consists of a hematoma contained within the medial layer of the aortic wall with no intimal flap or false lumen. Although the pathogenesis remains uncertain, rupture of the vasa vasorum has been postulated to be the initiating event. The hemorrhage occurs in the outer media and may extend into the adventitia. IMH is responsible for 10% to 20% of acute aortic syndromes. It localizes to the ascending aorta in 30%, to the aortic arch in 10%, and to the descending aorta in ~60% of affected patients.

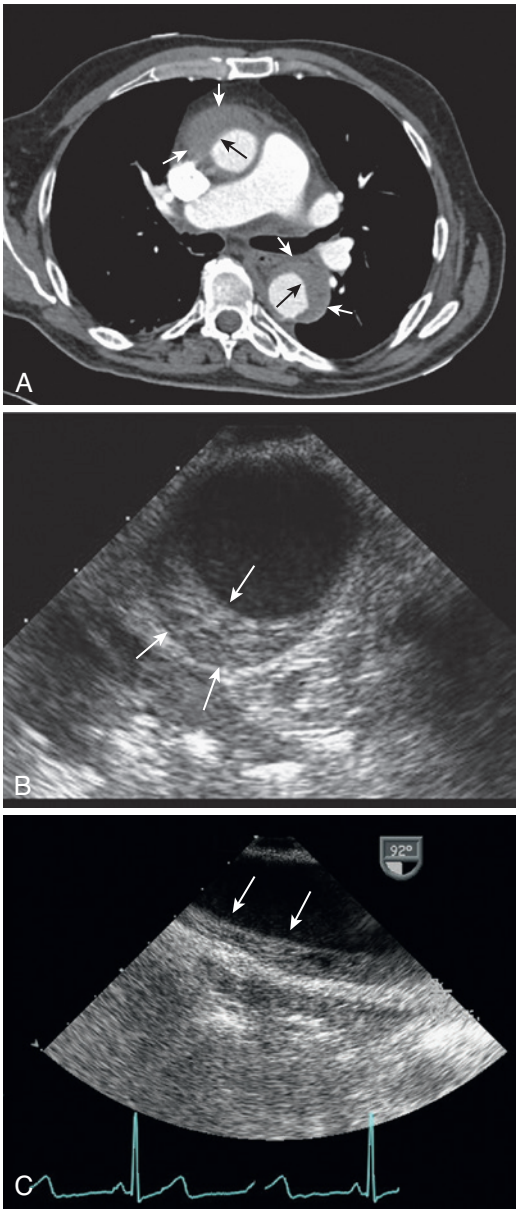

FIG. 3.13 *Intramural hematoma (IMH) of the aorta. (A) Contrast-enhanced computed tomography scan demonstrating type A IMH of the aorta. Note the circumferential hematoma involving the ascending aorta* (upper arrows) *and the crescentic hematoma involving the descending aorta* (lower arrows). *(B) Transesophageal echocardiogram short-axis view of the descending aorta demonstrating typical crescentic thickening of the aortic wall* (arrows) *in acute type B IMH. (C) Transesophageal echocardiogram longitudinal view of the aorta demonstrating IMH* (arrows).

Intramural hematoma can be identified by computed tomography (CT), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI). Non-contrast-enhanced CT demonstrates a crescentic, high-attenuation area along the aortic wall without an intimal tear. Contrast CT demonstrates failure of the intramural hematoma to enhance (Fig. 3.13A). TEE shows crescentic or circumferential aortic wall thickening, an eccentric aortic lumen, and echolucency within the aortic wall, with no intimal flap (see Fig. 3.13B and C). On MRI, an intramural hematoma is identified as a crescent-shaped area of high intensity along the aortic wall. Because there is lack of communication with the aorta, aortography actually has a low sensitivity for this diagnosis.

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ANSWER TO QUESTION 360

B (Braunwald, pp. 1135–1136)

Low-molecular-weight heparins (LMWHs) are derived from unfractionated heparin (UFH) through chemical or enzymatic depolymerization. The shorter molecules still contain the critical pentasaccharide sequence necessary for binding to and activating antithrombin (resulting in its anti-factor IIa effect), but the anti-Xa activity is much greater.[1] They do not cause a significant rise in the activated partial thromboplastin time, and that test is not useful for clinical monitoring. Although the anticoagulation effect of LMWHs can be determined by measuring anti-Xa activity, the stable pharmacokinetics of these drugs usually renders such measurement unnecessary.

Clearance of LMWH is reduced in patients with renal impairment, and dosage reduction is appropriate if used in such patients. Compared with UFH, treatment with LMWHs is less likely to result in type II heparin-induced thrombocytopenia (HIT). However, HIT antibodies can cross-react with LMWHs, and the latter should not be used when type II HIT has occurred.[1]

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ANSWER TO QUESTION 361

D (Braunwald, pp. 1182–1186; Figs. 60.4–60.6)

Unstable angina and non–ST-segment elevation myocardial infarction (MI) are heterogeneous conditions with a range of possible outcomes. Clinical trials have identified subgroups of patients who are at greatest risk and who are more likely to accrue benefit from therapeutic interventions.[1] High-risk individuals include those with acute rest pain or post-MI unstable angina, and those who are of advanced age or who have diabetes, cerebrovascular disease, or peripheral vascular disease.[2,3] In addition, patients who present with unstable angina despite having been on prior chronic aspirin therapy appear to be at particularly high risk.

The presence of ST-segment deviations of as little as 0.05 mV is associated with an adverse prognosis in unstable angina, and the greater the ST-segment deviation, the worse the outcome. Similarly, an elevated cardiac troponin level confers a higher risk of death.[4] Increased levels of C-reactive protein (CRP) have also been related to an augmented risk of MI and death. Although CRP, as a marker of inflammation, is often elevated in acute coronary syndromes, those patients with the highest levels have worse short- and long-term outcomes.[4]

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ANSWER TO QUESTION 362

C (Braunwald, pp. 1328–1329; Table 64.1; eFig. 64.1)

The prevalence of peripheral artery disease (PAD) varies depending on the population studied and the diagnostic methods used, but ranges from 6% in people 40 years and older to 20% in those 65 and older. The same risk factors that contribute to coronary artery disease are also associated with PAD, including cigarette smoking, diabetes mellitus,[1,2] hypercholesterolemia, hypertension, and hyperhomocystinemia. Of these, however, hypercholesterolemia is not one of the strongest predictors, conveying only a 1.7-fold increased risk. Rather, cigarette smoking and diabetes mellitus are more significantly associated, with relative risks of 4.5 and 2.7, respectively.

Evidence of PAD has been observed even in young individuals. Data from the Pathobiological Determinants of Atherosclerosis in Youth Study indicated that, in patients younger than 35 years, fatty streaks and atheroma form first in the dorsal portion of the abdominal aorta, later followed by similar lesions in the descending thoracic aorta.

The lack of symptoms is not a reliable way to exclude the presence of PAD, because only 10% to 30% of patients ≥50 years with PAD experience classic claudication.

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ANSWER TO QUESTION 363

C (Braunwald, pp. 1307–1311; Table 63.6)

Aortic dissection affects twice as many men as women and occurs most commonly in the sixth and seventh decades. Over 90% of patients presenting with aortic dissection complain of severe pain. The pain is usually sudden in onset, most intense at its inception, and may be described as "tearing" or "ripping" in quality. The discomfort tends to migrate in association with propagation along the aortic wall. On physical examination, patients may appear to be in shock, but the measured blood pressure is typically *elevated*, especially in patients with distal dissection. Characteristic physical findings associated with aortic dissection, such as pulse defects, are more common in proximal dissection. New aortic regurgitation may appear with proximal dissection that extends into the aortic valve apparatus.

Several conditions may mimic the pain of aortic dissection, including myocardial infarction, thoracic nondissecting aneurysm, mediastinal tumors, and pericarditis.

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ANSWER TO QUESTION 364

A (Braunwald, pp. 1331–1335; Fig. 64.4)

Intermittent claudication due to peripheral artery disease (PAD) is characterized by pain or a sense of fatigue during exercise that resolves with rest. In contrast, neurogenic pseudoclaudication (e.g., due to spinal stenosis) is associated with pain with both walking and standing. Classic physical findings in PAD include diminished or absent distal pulses, bruits over regions of stenosis, and coolness and signs of chronic low-grade ischemia such as hair loss, smooth shiny skin, and brittle nails of the affected extremity.

Among the simpler noninvasive diagnostic tests for PAD are systolic blood pressure measurements along select segments of each extremity. A pressure gradient of >20 mm Hg between successive segments in the lower extremities or >10 mm Hg in the upper extremities is evidence of significant stenosis. A sensitive office-based screening method for the diagnosis of PAD is the ankle/brachial index (ABI), the ratio between the ankle and brachial systolic blood pressures. An ABI value <1 is consistent with arterial insufficiency of the measured lower extremity and is 95% sensitive for that diagnosis. The ABI of patients with symptoms of leg claudication is typically 0.5 to 0.8, and in those with critical limb ischemia it is usually <0.5. Contrast angiography is the invasive gold standard for the identification of arterial stenoses. However, the resolution of gadolinium-enhanced magnetic resonance angiography (MRA) approaches that of conventional contrast-enhanced digital subtraction angiography. MRA is 95% sensitive and 96% specific for anatomic resolution of the aorta, iliac, femoral-popliteal, and tibial-peroneal arteries.

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ANSWER TO QUESTION 365

C (Braunwald, p. 1282)

Intravenous unfractionated heparin (UFH) has been the standard anticoagulant administered during percutaneous coronary interventions (PCIs) to prevent arterial thrombus formation on the percutaneous guidewires and catheters. Use of lower, weight-adjusted heparin dosing of 50 to 70 IU/kg has been shown to result in similar clinical outcomes. The routine use of intravenous heparin *after* the procedure is not recommended because that approach does not

reduce ischemic complications but does increase the risk of bleeding.[1]

In the ISAR-REACT 3 trial, which compared the intravenous direct thrombin inhibitor bivalirudin to UFH in patients pretreated with clopidogrel (600 mg), there were no differences in the rates of ischemic complications in patients undergoing PCI.[2] However, the incidence of major bleeding was lower in patients who received bivalirudin. The 2011 ACCF/AHA/SCAI guideline for PCI recommends bivalirudin as a useful anticoagulant in place of UFH for patients undergoing PCI, including patients with heparin-induced thrombocytopenia (class I recommendation, level of evidence: B). Of note, a later 2014 meta-analysis of 16 trials involving >33,000 patients with planned PCI confirmed a decreased rate of bleeding with bivalirudin compared with UFH, but an increased risk of myocardial infarction and stent thrombosis.[3]

In the EPILOG trial, in which glycoprotein (GP) IIb/IIIa inhibition was used, standard-dose UFH (10,000 unit bolus, with activated clotting time [ACT] goal >300 seconds) resulted in similar rates of ischemic events, but a greater number of hemorrhagic complications compared with weight-adjusted UFH (70 units/kg bolus, ACT goal >200 seconds). Therefore, when used in combination with a GP IIb/IIIa inhibitor, lower-dose weight-adjusted UFH is preferred.

The low-molecular-weight heparin enoxaparin is efficacious as an anticoagulant during PCI but cannot be monitored by the ACT test. However, the pharmacokinetics of this agent are so predictable that patients who received their last dose within 8 hours of the procedure do not require further anticoagulation. An intravenous bolus of 0.3 mg/kg is appropriate if the last dose was 8 to 12 hours before the procedure.[4] If the last dose was more than 12 hours earlier, then standard heparin anticoagulation during PCI is appropriate.

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ANSWER TO QUESTION 366

D (Braunwald, pp. 1231–1233; eFig. 61.3)

Nitrates are important agents in the treatment of ischemic heart disease. They directly relax vascular smooth muscle by activating intracellular guanylate cyclase, thus causing an increase in cyclic guanosine monophosphate, which triggers smooth muscle relaxation. Since nitrates act directly on smooth muscle, they do not require an intact endothelium to secrete nitric oxide (NO) as a secondary messenger. The vasodilating effect of nitrates is manifest in both arteries and veins but predominates in the venous circulation. The decrease in venous tone lessens venous return to the heart and thereby reduces preload and ventricular dimensions, which in turn diminishes wall tension. As well as decreasing wall tension and myocardial oxygen demand, nitrates may also increase oxygen supply by dilating coronary arteries. Such dilatation can be effected in vessels containing atherosclerosis, presumably because the pathologic atherosclerotic changes are eccentric and normal vascular smooth muscle, which can respond to nitrates, is present in a portion of the plaque.

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ANSWER TO QUESTION 367

A (Braunwald, pp. 1281–1282)

The glycoprotein (GP) IIb/IIIa inhibitors are a powerful class of antiplatelet agents. By impairing the final common pathway of platelet aggregation, they greatly limit thrombus formation. There are significant differences between the three agents of this class currently approved for use. Abciximab is a monoclonal antibody that has high affinity but relatively low specificity for the GP IIb/IIIa receptor. Although the original murine monoclonal antibody was chimerized with human immunoglobulin to minimize antibody formation, antichimeric antibodies develop in 5% to 6% of patients treated with abciximab. Although there has been no evidence of severe allergic reactions after the re-administration of abciximab to previously exposed patients, thrombocytopenia has been reported.

Eptifibatide and tirofiban are small-molecule GP IIb/IIIa inhibitors that have lower affinity but higher specificity for the GP IIb/IIIa receptor. Eptifibatide is a cyclic heptapeptide related to pygmy rattlesnake venom, whereas tirofiban is a nonpeptide molecule based on the structure of fibrinogen. Both have half-lives of about 2 hours. Current evidence suggests that the long-term benefits of GP IIb/IIIa inhibitors are greater when they are administered in conjunction with heparin.

The upstream administration of a GP IIb/IIIa inhibitor *before* transport to the catheterization laboratory in acute ST-segment elevation myocardial infarction has not been shown to benefit patients pretreated with dual antiplatelet therapy (aspirin plus clopidogrel 600 mg).[1,2] In a placebo-controlled trial of 9492 patients presenting with acute coronary syndrome without ST-segment elevation, early initiation of eptifibatide, at least 12 hours prior to angiography, did not lead to decreased ischemic events compared with eptifibatide started at the time of percutaneous coronary intervention (PCI).[3]

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ANSWER TO QUESTION 368

B (Braunwald, pp. 922–923; Fig. 46.6; Table 46.6)

Renovascular disease is common and can contribute to hypertension and progressive deterioration of kidney function. Renal artery stenosis (RAS) can be managed with percutaneous renal artery angioplasty and stenting, and the technical success rate of these procedures exceeds 95%. The use of stents has greatly improved the procedural outcome even for ostial lesions and reduces restenosis rates.[1] Clinical trial data of patients with unilateral RAS have demonstrated that surgical revascularization and percutaneous angioplasty lead to similar degrees of blood pressure improvement and stabilization of renal function.

Although successful percutaneous treatment of atherosclerotic RAS commonly improves blood pressure, at least modestly, complete resolution of hypertension is unusual because many affected patients have accompanying essential hypertension or intrinsic renal disease. As a result, only about two-thirds of patients who undergo successful intervention have a reduced requirement of antihypertensive medications.

Furthermore, recent data have not demonstrated superior benefit of percutaneous intervention compared with medical antihypertensive therapy alone. The ASTRAL trial prospectively randomized 806 patients with atherosclerotic renal artery disease to either percutaneous revascularization or medical therapy and the revascularization group did not experience superior clinical effect as measured by progression of renal dysfunction, blood pressure levels, or cardiovascular events. Among the patients assigned to percutaneous revascularization there were serious periprocedural complications, including cholesterol embolism leading to gangrene and toe or limb amputation.[2] In the CORAL trial,[3] 947 patients with atherosclerotic RAS and hypertension or chronic kidney disease were randomized to renal artery stenting or medical therapy. There was no benefit in terms of clinical outcomes with renal artery stenting. An important criticism of the ASTRAL and CORAL trials is that the patients enrolled had only modest RAS severity. Thus, the effectiveness of renal artery stenting in patients with severe RAS remains incompletely investigated.

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ANSWER TO QUESTION 369

D (Braunwald, p. 1199)

The syndrome of angina-like chest pain in the presence of a normal coronary arteriogram encompasses a heterogeneous population that includes patients with true heart disease as well as those with noncardiac chest pain. Although most studies have failed to reveal consistent biochemical evidence of ischemia, such as an elevation of myocardial lactate with exercise, evidence of decreased perfusion may be found in many of these patients by exercise testing or scintigraphy using single-photon emission computed tomography or positron emission tomography. The incidence of coronary calcification on multislice computed tomography is higher than that of normal subjects but lower than that of patients with obstructive coronary artery disease (CAD). Some patients with this syndrome have evidence of endothelial and microvascular dysfunction with inadequate vasodilator reserve and an exaggerated response to vasoconstrictor stimuli.[1] Increased sensitivity to pain has also been associated with this condition.

Largely because of the heterogeneous population, studies of potential treatments have given varying and often contradictory results.[2] Nitrates have been shown to both improve and reduce exercise tolerance. Calcium channel blockers and estrogen therapy in women are sometimes effective, perhaps by enhancing endothelial-dependent vasodilatation. In addition, some patients appear to benefit from antidepressant drugs. Overall, the cardiac prognosis of patients with this syndrome is very good and better than that of patients with obstructive CAD. Notably, however, in the Women's Ischemic Syndrome Evaluation study, women with angina and nonobstructive CAD who had persistent symptoms demonstrated more than a twofold increase in future cardiovascular events.[3]

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ANSWER TO QUESTION 370

E (Braunwald, p. 1299)

For patients with an abdominal aortic aneurysm (AAA) and suitable anatomy, endovascular aortic aneurysm repair (EVAR) is a less invasive approach than standard open surgery. The endograft is introduced percutaneously or via arterial cutdown into the femoral artery and maneuvered to the involved aortic segment. Anatomic constraints limit the use of EVAR, but reported primary success rates for aneurysm exclusion in carefully chosen patients have ranged from 78% to 99%. An endoleak (persistent flow into the aneurysmal sac external to the endograft after it has been deployed) is a serious complication of EVAR and leaves the patient at risk for aneurysm rupture.

Randomized trials have shown a lower 30-day mortality for endovascular repair of abdominal aortic aneurysm compared with an open surgical procedure.[1] Additional trials have begun to define the long-term outcomes of EVAR. In the United Kingdom Endovascular Aneurysm Repair 1 trial,[2] 1252 patients with a large AAA (≥5.5 cm) were randomized to endovascular or open operative repair. The 30-day mortality rate favored

endovascular repair, but there was no difference in mortality over the long-term (median follow-up of 6 years), and the endovascular procedure was associated with higher rates of complications (including fatal endograft rupture), need for re-intervention, and increased cost. Similarly, an analysis of 79,932 Medicare patients with abdominal aortic aneurysm showed that EVAR resulted in lower perioperative mortality and complications than open surgical repair, but at 8-year follow-up mortality rates were the same and EVAR-treated patients required more aneurysm-related reinterventions.[3]

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ANSWER TO QUESTION 371

B (Braunwald, pp. 1338–1340; Figs. 64.11 and 64.12; eFig. 64.5; Table 64.5)

Treatment of symptomatic peripheral arterial disease (PAD) is multidisciplinary. Currently available drug therapy is not as effective as agents used to treat chronic coronary artery disease (CAD). Pentoxifylline is a xanthine derivative, and its beneficial effects in PAD are believed to be mediated by its hemorheologic properties, including an increase in red blood cell flexibility, as well as by its anti-inflammatory and antiproliferative effects. Several studies have shown that pentoxifylline increases both the walking distance to initial claudication symptoms and the absolute distance able to be traveled. Cilostazol acts by inhibiting phosphodiesterase 3, thereby augmenting cyclic adenosine monophosphate (cAMP) levels, and it has been shown to enhance vasodilatation and inhibit platelet aggregation. Clinical trials have demonstrated that cilostazol improves walking distances and quality of life. It should not be prescribed to patients with heart failure, since other drugs with similar mechanisms of action decrease survival in that population.[1]

Supervised exercise rehabilitation significantly improves symptoms of claudication. Meta-analyses have found that walking programs increase maximum walking distances in patients with PAD by 50% to 200%.[2]

Revascularization options in patients with PAD include percutaneous transluminal angioplasty (PTA) and bypass surgery. PTA of the iliac artery results in patency rates of 60% to 80% at 4 years. This figure improves further with the use of stenting.[3] Aortobifemoral bypass surgery results in 10-year patency rates of nearly 90%.

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ANSWER TO QUESTION 372

C (Braunwald, pp. 1314–1318; Figs. 63.18 and 63.19; see also Answer to Question 352)

The immediate therapeutic goals in the management of aortic dissection are reduction of blood pressure and vascular wall stress and controlling pain. The 2010 thoracic aortic disease guideline recommends initiating an intravenous beta blocker (to reduce the rise in force of left ventricular contraction, dP/dt) such as labetalol. If systolic blood pressure remains >120 mm Hg, the addition of an intravenous vasodilator (e.g., sodium nitroprusside) is recommended to further lower arterial pressure. Such an approach allows for temporary stabilization in appropriate surgical candidates and is the treatment of choice for those patients in whom surgery is not indicated. The appearance of a life-threatening complication such as aortic rupture, acute aortic regurgitation, cardiac tamponade, or compromise of a vital organ mandates immediate surgical intervention.

As indicated in the Answer to Question 352, surgical repair is the standard of therapy for type A (proximal) acute dissection because it has been shown to improve survival. Conversely, patients with uncomplicated type B (distal) aortic dissection can typically be safely managed with initial pharmacologic therapy alone.

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ANSWER TO QUESTION 373

E (Braunwald, pp. 1007–1025; Table 51.1; Figs. 51.1–51.3, 51.7)

Diabetes is a major risk factor for atherosclerosis of the coronary, cerebral, and peripheral arteries, and the prevalence of this condition is increasing in both developed and developing countries.[1] According to the American Diabetes Association, diagnostic criteria for the presence of diabetes include a fasting plasma glucose concentration >126 mg/dL or a hemoglobin A1c level ≥6.5%.[2]

Aggressive and comprehensive risk factor modification reduces adverse cardiovascular outcomes in diabetic patients. In addition to glycemic control, key targets for intervention include hypertension, cigarette smoking, and modification of abnormal lipid levels. A strategy of antilipidemic therapy in diabetic patients without markedly increased cholesterol levels has been tested in several trials. In the CARDS study,[3] diabetic subjects without established coronary disease or high cholesterol levels were randomized to atorvastatin 10 mg daily or placebo. After 4 years, atorvastatin reduced major cardiovascular events by 37% and total mortality by 27%. Baseline lipid levels did not predict benefit from statin therapy: patients with lower than median LDL at entry received the

same advantage from statin therapy as did patients with higher cholesterol levels.

Patients with type 2 diabetes often display reduced serum high-density lipoprotein (HDL), increased triglycerides, and near-normal low-density lipoprotein cholesterol levels. Fibrate therapy (e.g., gemfibrozil or fenofibrate) is effective at reducing triglycerides and raising HDL cholesterol, but the impact of such therapy has not been shown to be beneficial on cardiovascular outcomes in diabetics. In the FIELD study, 9795 middle-aged type 2 diabetics were randomized to placebo or fenofibrate.[4] Over 5 years, fenofibrate did not significantly reduce the risk of the primary outcome of coronary events and there was a trend toward higher total mortality. Similarly, in the ACCORD trial, the addition of fenofibrate to statin therapy did not improve cardiovascular outcomes in type 2 diabetics over 4.7 years of follow-up.[5]

The rate of diabetes development can be reduced by interventions that target undesired lifestyles. In the Diabetes Prevention Program, 3234 nondiabetic persons with impaired glucose tolerance were randomized to an intense lifestyle-modification program (with goals of ≥7% weight loss and at least 150 minutes of physical activity per week), to standard lifestyles, or to metformin. After an average follow-up of 2.8 years, the incidence of diabetes was significantly reduced in both the intense lifestyle group and those taking metformin, but more so in the intense lifestyle group (reductions of 58% and 31%, respectively).[6]

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ANSWER TO QUESTION 374

C (Braunwald, pp. 1069–1082; Figs. 57.1–57.5)

Blood flow to the myocardium is determined by the perfusion pressure gradient and the vascular resistance of the myocardial bed. The latter is influenced by extrinsic forces (e.g., compression by the myocardium) and by intrinsic metabolic, neural, and humoral factors. Intramyocardial pressure is determined primarily by the ventricular pressure throughout the cardiac cycle. Because the ventricular pressure is so much higher in systole than it is in diastole, myocardial compressive forces acting on intramyocardial vessels are greater during this phase. Therefore, the subendocardium, which is subject to higher systolic pressures, receives less systolic flow than the subepicardium. However, *total* flow is greater in the subendocardium than the subepicardium because there is enhanced basal vasodilatation in the former as a result of higher metabolic demands.

Actions that reduce the perfusion pressure gradient during diastole, when the majority of subendocardial flow occurs, lower the ratio of subendocardial to subepicardial flow and may cause the subendocardium to become ischemic. Thus, an increase in ventricular end-diastolic pressure or a decrease in diastolic filling time (e.g., during tachycardia) can reduce subendocardial flow disproportionately. Because the subendocardium has lower basal vascular tone, the reserve for vasodilatation is less than in the subepicardium. Therefore, as perfusion is reduced, the deeper layers of the myocardium become ischemic sooner than the more superficial ones.

ANSWER TO QUESTION 375

C (Braunwald, pp. 1088–1092; Table 57.1; Figs. 57.24, 57.26–57.28; eFigs. 57.7 and 57.8)

As described in the Answer to Question 347, *myocardial stunning* is defined as myocardial dysfunction that persists after a period of severe ischemia, with gradual return of contractile activity. Molecular mechanisms include the generation of oxygen-derived free radicals, calcium overload, and reduced sensitivity of myofilaments to calcium.[1] Stunned myocardium does respond to inotropic therapy, hence the appropriateness of transient inotropic support in some patients after myocardial infarction until the adjacent stunned myocardium recovers contractile function.

In contrast, *hibernating* myocardium refers to myocardial dysfunction that results from chronically decreased coronary blood flow, a condition that can be reversed with revascularization.[2] Histopathologic studies reveal both myocyte dedifferentiation and apoptosis, suggesting that irreversible changes may occur if revascularization is not undertaken.

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ANSWER TO QUESTION 376

C (Braunwald, pp. 1181–1182; Fig. 60.1)

About 15% of patients who present with symptoms consistent with unstable angina are found to have no significant coronary artery disease on angiography. Approximately one-third of such patients present with impaired coronary flow, suggesting the presence of microvascular dysfunction. The short-term prognosis is excellent in this situation.

For patients with a clear culprit lesion, the responsible plaque is typically eccentric, with overhanging edges consistent with a disrupted atherosclerotic locus. Intravascular ultrasonography in patients with unstable angina often demonstrates more soft echolucent lesions (thin fibrous cap and lipid-rich core) and fewer calcified lesions compared with patients with chronic stable angina.

ANSWER TO QUESTION 377

B (Braunwald, pp. 1236–1249; Table 61.14; Fig. 61.16; eFigs. 61.6–61.8)

Comparison of outcomes of coronary artery bypass grafting (CABG) with those of percutaneous coronary intervention (PCI) is a "moving target" because new technologies for both strategies continue to improve outcomes and reduce complications. Nonetheless, randomized trials comparing the two approaches have yielded consistent results.[1] For the majority of patients, there is no difference in the rates of subsequent death or myocardial infarction. Such similar outcomes have been observed in patients with single-vessel coronary artery disease (including left anterior descending coronary artery disease) as well as in patients with multivessel disease. There is, however, consistent evidence that patients who undergo PCI are more likely to have recurrent angina or require additional subsequent interventional procedures.

The SYNTAX (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery) trial, performed between 2005 and 2007, was a major randomized clinical study with long-term follow-up comparing CABG to drug-eluting stent (DES) implantation. It confirmed that CABG and PCI survival rates are similar in patients with relatively uncomplicated coronary disease, but for those with the most complex and widespread CAD, CABG appears to offer a survival advantage. In this trial, 1800 patients with multivessel disease were randomized to CABG or DES implantation. At 12 months, the rates of death or myocardial infarction were similar between the two groups, but the stroke rate was higher in the CABG patients. At 5 years of follow-up, all-cause mortality and stroke rates did not differ, but the occurrence of myocardial infarction or need for repeat revascularization was higher among the PCI patients.[2] Post hoc analysis revealed that at 3 and 5 years of follow-up, patients with the most severe and complex CAD had more adverse cardiac outcomes, including worsened survival, with PCI compared to CABG.

Among diabetic patients with multivessel disease, bypass surgery has also been shown to offer improved survival compared with PCI. For example, the Bypass Angioplasty Revascularization Investigation trial was a large comparison of the two treatment strategies among symptomatic patients with angina whose coronary anatomy was deemed suitable for revascularization by either technique (i.e., two- or three-vessel disease, but not left main stenosis). In this study, patients with diabetes and multivessel disease showed significantly improved survival with CABG compared with coronary angioplasty. These findings were confirmed in the Future REvascularization Evaluation in patients wtih Diabetes Mellitus study. This trial compared CABG and PCI with drug-eluting stents in 1900 diabetic patients with multivessel disease and found CABG reduced all-cause mortality and the incidence of myocardial infarction.[3]

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ANSWER TO QUESTION 378

C (Braunwald, pp. 971–974; Table 48.7)

Multiple studies have demonstrated the benefits of statin therapy in primary and secondary prevention of coronary disease. Most of the early studies compared a moderate dose of statin with placebo therapy. Subsequent trials examined the role of high-dose statins and more aggressive lipid lowering in patients with established coronary artery disease. For example, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering trial found that treatment with high-dose atorvastatin (80 mg/day) over 4 months reduced cardiac events by 16% compared with placebo.[1]

The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial compared high-dose atorvastatin (80 mg/day) versus moderate-dose pravastatin (40 mg/day) begun within 10 days of an acute coronary syndrome (ACS) and found that the risk of death, nonfatal myocardial infarction, or revascularization was reduced by 25% by the more intense regimen, with a significant difference seen within 30 days of randomization.[2] The Reversal of Atherosclerosis with Aggressive Lipid Lowering study compared similar doses of pravastatin and high-dose atorvastatin and, using intravascular ultrasound, demonstrated reduction in atheroma size in the patients randomized to the high-dose atorvastatin over 18 months of therapy.[3]

Not all studies have demonstrated an advantage of high-dose statin therapy over less intense regimens. In the Aggrastat to Zocor (A to Z—TIMI 21) trial, patients with ACS were randomized to an initial therapy of moderate-dose simvastatin (40 mg/day) for 1 month followed by high-dose (80 mg/day) therapy versus placebo for 4 months, followed by low-dose simvastatin (20 mg/day). After 2 years of follow-up, there was no difference in the composite endpoint of cardiovascular events. However, myopathy (creatine kinase >10 times the upper limit of normal) occurred in nine patients receiving high-dose simvastatin versus one patient receiving the less intensive regimen (P = .02). Three patients developed rhabdomyolysis while taking the high-dose simvastatin regimen.[4] Furthermore, the SEARCH trial showed that the incidence of major vascular events was no lower in those randomized to simvastatin 80 mg daily compared with patients receiving 20 mg daily.[5]

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ANSWER TO QUESTION 379

B (Braunwald, p. 1281)

Antiplatelet agents act at a variety of sites to block platelet aggregation. Aspirin is an irreversible inhibitor of cyclooxygenase (COX) that impairs the formation of thromboxane A_2, a potent mediator of platelet aggregation and vasoconstriction. Because platelets are incapable of new COX synthesis, the effect is permanent for the 7- to 10-day lifetime of the affected platelet.[1] Other nonsteroidal anti-inflammatory drugs (NSAIDs) may prevent acetylation of COX by aspirin. For example, there is evidence that concomitant administration of some nonselective NSAIDs, such as ibuprofen, may inhibit the effects of aspirin on COX and *reduce* aspirin's antiplatelet efficacy.[2]

Clopidogrel and prasugrel are thienopyridine derivatives that block the adenosine diphosphate-dependent pathway of platelet activation. Both result in irreversible blockade of the $P2Y_{12}$ ADP receptor and therefore have long effective half-lives.[1] Prasugrel is a more potent inhibitor of the $P2Y_{12}$ receptor and has favorable pharmacokinetics with a more rapid onset of action than clopidogrel. In the TRITON-TIMI 38 trial of patients with moderate-to-high risk acute coronary syndromes with planned percutaneous coronary intervention, those who received prasugrel had a lower composite rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke compared with those who received clopidogrel, but at an increased risk of major bleeding.[3]

Cilostazol is a potent inhibitor of platelet phosphodiesterase-3 that has vasodilator properties. It has been shown to benefit individuals with intermittent claudication due to peripheral arterial disease (see Answer to Question 371).

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ANSWER TO QUESTION 380

B (Braunwald, pp. 1142–1143; see also Answer to Question 321)

The SAVE study was the first trial to demonstrate that angiotensin-converting enzyme (ACE) inhibitor therapy reduces mortality in patients with ST-segment elevation myocardial infarction. Many subsequent studies have demonstrated a similar and consistent benefit of these agents at reducing cardiovascular endpoints after myocardial infarction (MI). This has been shown with short-term use in all patients with MI and in long-term treatment of patients with depressed left ventricular systolic function after MI. Analysis of short-term trials indicates that one-third of the mortality benefit occurs within the first 2 days of ACE inhibitor therapy.[1]

Two studies, OPTIMAAL and VALIANT, evaluated the efficacy of the angiotensin receptor blockers (ARBs) losartan and valsartan, respectively, versus the ACE inhibitor captopril in MI patients. In OPTIMAAL, losartan was better tolerated but there was a nonsignificant trend toward improved survival with captopril. In the VALIANT trial, captopril and valsartan resulted in similar clinical outcomes. The combination of valsartan plus captopril did not offer any advantage of either drug used alone.[2] Thus, in patients intolerant of ACE inhibitors, an ARB is an adequate substitute, but there does not appear to be an advantage of combining the two together in post-MI patients.

The EPHESUS trial examined the role of the selective aldosterone inhibitor eplerenone in patients with MI complicated by left ventricular dysfunction. During 16 months of follow-up, this agent resulted in a 15% relative risk reduction in mortality compared with standard treatment. Such therapy must be prescribed with care, because significant hyperkalemia was more common among the patients treated with eplerenone.[3]

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ANSWER TO QUESTION 381

C (Braunwald, pp. 1341–1342; Fig. 64.14)

This history and angiogram are consistent with thromboangiitis obliterans (TAO), also known as Buerger disease. This disease of *small and medium* arteries of the arms and legs predominantly affects young individuals (onset usually <45 years) and is almost always associated with tobacco use.[1,2] TAO is more prevalent in Asia than in North America and Europe, and >75% of affected patients are men. The most common presentation includes resting pain of the feet, calves, hands, or forearms, and digital ulcerations are frequently observed. Raynaud phenomenon and superficial thrombophlebitis are common.

Angiography of affected limbs in patients with TAO demonstrates segmental occlusion of small and medium vessels, the absence of atherosclerosis, and corkscrew collateral vessels bypassing the occlusions.

Smoking cessation is the most important therapy for this condition. Patients who continue to smoke face a 40% to 45% risk of future amputation. There is no evidence that statin therapy is beneficial and there is usually no role for vascular surgery because of the diffuse nature of the disease and the generally poor distal vasculature.

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ANSWER TO QUESTION 382

D (Braunwald, pp. 950–952; Tables 47.14 and 47.15; Fig. 47.10)

The incidence of hypertensive emergencies is falling as a result of widespread treatment of chronic hypertension. In addition to a marked rise in blood pressure, a hypertensive crisis is associated with end-organ damage. Acute retinal effects include hemorrhages, exudates, or papilledema (termed *accelerated-malignant hypertension*). *Hypertensive encephalopathy* is manifest by headache, irritability, confusion, somnolence, stupor, focal neurologic deficits, seizures, and eventually coma. In previously normotensive individuals, encephalopathy may occur at a lower blood pressure than in those with a history of chronic hypertension. The pathogenesis of hypertensive encephalopathy is thought to involve failure of cerebral autoregulation, with *dilatation* of cerebral arterioles leading to excessive cerebral blood flow and damage to the arteriolar wall with *increased* vascular permeability.

Other clinical features of hypertensive crises include renal insufficiency *with* proteinuria, microangiopathic hemolytic anemia, congestive heart failure, and nausea and vomiting. Patients who have elevated blood pressure and any end-organ manifestations of hypertensive emergency require rapid therapeutic intervention, usually with parenteral drug therapy.

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ANSWER TO QUESTION 383

A (Braunwald, pp. 1307–1313; Table 63.5)

The transesophageal echocardiogram shows the proximal ascending aorta in long-axis view in a patient with proximal aortic dissection. The aortic valve, and true (T) and false (F) lumina are identified. The linear shadow (labeled "I") is an intimal flap. The major predisposing factor for aortic dissection is cystic medial degeneration. Of the conditions that promote cystic medial degeneration, age and hypertension are the two most common. Hereditary abnormalities of connective tissue—Marfan syndrome, Loeys-Dietz syndrome, and Ehlers-Danlos syndrome—are all associated with cystic medial degeneration, as is bicuspid aortic valve.

Approximately half of all dissections in women younger than 40 years occur in association with pregnancy, most commonly in the third trimester or early postpartum period.[1] Cocaine, but not heroin use, has also been associated with aortic dissection.[2]

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ANSWER TO QUESTION 384

B (Braunwald, pp. 1148–1158)

Cardiogenic shock is defined as persistent hypotension with systolic arterial pressure <90 mm Hg and a reduction of the cardiac index (<2.2 L/min/m^2) with an elevated left ventricular (LV) filling pressure (pulmonary capillary wedge pressure >18 mm Hg). Mechanical complications of myocardial infarction, such as acute mitral regurgitation or ventricular septal rupture, should be excluded in order to attribute cardiogenic shock to LV dysfunction. The SHOCK trial randomized patients with cardiogenic shock due to LV failure to either medical therapy or urgent revascularization by percutaneous coronary intervention or bypass surgery. At 30 days there was no significant difference in cardiovascular outcomes between the medical and revascularization groups. However, after 1 year, survival rates were higher in the patients who had undergone revascularization therapies.[1]

From this evidence, urgent mechanical revascularization is recommended for patients with cardiogenic shock. Vasopressors, intra-aortic balloon counterpulsation, and percutaneous left ventricular assist devices all improve hemodynamics in cardiogenic shock and are often useful as temporizing measures. However, these interventions have not been shown to improve long-term survival in randomized trials.[2,3]

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ANSWER TO QUESTION 385

D (Braunwald, pp. 1153–1154; see also Answer to Question 334)

Right ventricular infarction (RVI) frequently accompanies inferior left ventricular infarction and may be recognized by a characteristic clinical and hemodynamic pattern. Hypotension or a marked hypotensive response to nitroglycerin or diuretics in patients with inferior infarction suggests the diagnosis of RVI. The hemodynamic picture of this condition is similar to that of pericardial disease and may include an elevated right ventricle (RV) filling pressure, a steep right atrial *y* descent, and a "square root sign" in the RV pressure tracing. The Kussmaul sign may also be present. The presence of unexplained systemic hypoxemia in the setting of RVI suggests the possibility of right-to-left shunting through a patent foramen ovale because of the elevated right-sided pressures. The placement of right-sided precordial ECG leads is helpful in establishing the diagnosis of RVI. ST-segment elevation in lead V_4R is specific and sensitive for this diagnosis.

Because left-sided filling pressures are dependent on the transport of blood from the right heart, RVI may reduce left ventricular preload and result in a marked reduction in LV stroke volume and systemic hypotension. Thus, initial therapy for hypotension in RVI should usually include volume expansion, and diuretics should generally be avoided.

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ANSWER TO QUESTION 386

B (Braunwald, p. 1333; Fig. 64.4)

Segmental pressure measurements and determination of the ankle/brachial index (ABI) are simple and very useful noninvasive methods to evaluate symptoms of peripheral arterial disease. To measure segmental pressures, pneumatic cuffs are placed over the upper and lower thigh, calf, and ankle and above the metatarsal area of the foot, then systolic pressures are measured using a Doppler probe. In the iliac and femoral arteries, a 70% to 90% decrease in the cross-sectional area of the artery must be present to create a pressure gradient. A gradient >20 mm Hg between successive levels of the cuffs is evidence of a significant stenosis.

Measurement of the ABI is an even simpler screening tool that represents the ratio of the systolic pressure at the ankle to that of the brachial artery, typically measured using a Doppler flow probe. A normal ABI is >1.0. An ABI of <0.9 is very sensitive for angiographic evidence of an arterial stenosis. Patients with critical limb ischemia typically have an ABI of <0.5. The sensitivity of the ABI is *decreased* in severely calcified arteries because such vessels do not compress and therefore have spuriously high systolic pressure readings.

The patient in this case has segmental pressure measurements consistent primarily with significant stenoses in the right iliac and common femoral arteries.

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ANSWER TO QUESTION 387

B (Braunwald, p. 1283)

Restenosis after percutaneous coronary intervention is due to the local proliferation of neointimal tissue. Factors that increase rates of restenosis include small vessels, long lesions, and the presence of diabetes. Original plain balloon angioplasty was associated with a high (30% to 40%) rate of restenosis. The introduction of bare metal stents reduced the rate of angiographic restenosis to 20% to 30%. The initial placement of a drug-eluting stent in appropriate lesions is the most effective means to suppress local neointimal proliferation and restenosis rates, as discussed in the answer to a subsequent question.

There is no evidence that treatment of in-stent restenosis with either direct coronary atherectomy or rotational atherectomy improves recurrences of in-stent restenosis compared with balloon angioplasty using a cutting balloon. Brachytherapy, using gamma radiation, prevents neointimal proliferation and reduces the rate of this complication; however, implantation of a drug-eluting stent is more effective for treating bare metal stent (BMS) restenosis.[1]

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ANSWER TO QUESTION 388

C (Braunwald, pp. 1278–1280; see also Answer to Question 324)

Drug-eluting stents (DES) release pharmaceutical agents that suppress neointimal proliferation, and are very effective at preventing restenosis after percutaneous coronary interventions. Currently available systems include those that slowly release sirolimus, paclitaxel, zotarolimus, or everolimus. *Sirolimus* is a cytostatic inhibitor of neointimal growth. In the RAVEL study, the first large study comparing a DES with a bare metal stent, there was no angiographic restenosis in the patients randomized to the sirolimus-eluting group.[1] The larger SIRIUS trial demonstrated a 4.1% restenosis rate compared with 16.6% in the bare-metal stent group.[2] *Paclitaxel* stabilizes microtubules and prevents cell division. The TAXUS-IV trial, a large randomized study of bare metal versus paclitaxel-eluting stents, found that the latter exhibited a marked reduction of subsequent in-stent stenosis. The target vessel revascularization at 9 months was reduced from 11.3% to 3%.[3] *Everolimus* and *zotarolimus* are rapamycin analogs with immunosuppressive and antiproliferative properties. Everolimus was compared with paclitaxel in the SPIRIT IV trial of patients with coronary artery disease undergoing percutaneous coronary intervention. Those who received the everolimus-eluting stent had *reduced* target lesion failure over 2 years of follow-up.[4] Zotarolimus-eluting stents were not shown to reduce target lesion revascularization (TLR) or late stent thrombosis more than sirolimus[5]; rates of TLR were similar when zotarolimus was compared to paclitaxel-eluting stents.[6]

Because a DES impairs endothelial regrowth after balloon expansion, extended use of aspirin plus an oral $P2Y_{12}$ platelet receptor antagonist (clopidogrel, prasugrel, or ticagrelor) is required after implantation to prevent thrombosis. Rare cases of life-threatening late stent thrombosis have been reported many months or years after DES implantation, particularly when dual antiplatelet therapy has been discontinued prematurely. A large randomized trial compared stent thrombosis at 3 years between zotarolimus and sirolimus DES and found no difference in the occurrence of late thrombosis.[7] Current guidelines recommend at least 12 months of dual antiplatelet therapy after DES implantation.[8]

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ANSWER TO QUESTION 389

A (Braunwald, pp. 897–899)

A program of regular exercise is associated with reduced cardiovascular risk presumably because of its beneficial effects on traditional risk factors such as hypertension, dyslipidemia, and diabetes. Regular exercise also appears to contribute to a less prothrombotic state by altering the activity of the fibrinolytic system: exercise reduces plasma fibrinogen and plasminogen activator inhibitor-1 levels and increases tissue plasminogen activator levels. In addition, although sudden exercise in chronically sedentary individuals may increase platelet activation, a program of regular exercise has the beneficial opposite effect.

Heart rate variability is a measure of autonomic function that is dependent on the relation between parasympathetic and sympathetic tone. Reduced heart rate variability is associated with an elevated risk of coronary artery disease and mortality. Regular exercise reduces parasympathetic tone and *increases* (i.e., improves) heart rate variability.

Exercise has been shown to improve the impaired endothelial-dependent vasodilatation typical of patients with coronary artery disease or coronary risk factors, likely because of increased expression of nitric oxide (NO) synthase and NO production. Exercise also tends to produce beneficial changes in the lipid profile, including higher levels of high-density lipoprotein and lower levels of low-density lipoprotein and triglycerides.

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ANSWER TO QUESTION 390

B (Braunwald, pp. 1069–1070; Figs. 57.1, 57.2)

The three major components of myocardial oxygen demand (MVO_2) are heart rate, the myocardial contractile state, and wall tension. In turn, wall tension during systole is proportional to the aortic pressure and intraventricular volume. An increase in any of these parameters results in augmented myocardial oxygen consumption.

Heart rate is generally the most important determinant of MVO_2 and the balance between myocardial oxygen supply and demand. For example, during tachycardia MVO_2 increases and, at the same time, coronary oxygen supply may suffer because the shortened diastolic filling period tends to reduce subendocardial coronary blood flow.

The circulating content of hemoglobin is an important determinant of myocardial oxygen supply, not MVO_2.

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ANSWER TO QUESTION 391

D (Braunwald, pp. 1012, 1023–1024)

Diabetes and hypertension frequently coexist and augment the risk of coronary events. Diabetics with even mild chronic renal disease are prone to hyperkalemia because of the associated syndrome of hyporeninemic hypoaldosteronism, combined with impaired insulin secretion, both of which increase the serum potassium concentration. Thus, supplemental potassium and potassium-sparing diuretics must be used with caution in such patients.

Although tomatoes and bananas are rich sources of potassium, it would be unusual for a normal diet to cause such a marked rise in potassium. Urinary tract infections may increase potassium in the setting of worsened renal function (which was not observed in this patient). Primary hyperaldosteronism and Cushing syndrome are more likely to cause hypokalemia than hyperkalemia.

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ANSWER TO QUESTION 392

C (Braunwald, p. 1281)

Prasugrel, like clopidogrel, is a thienopyridine derivative that impairs platelet aggregation through irreversible inhibition of the $P2Y_{12}$ receptor.[1] Active metabolites of prasugrel render it 10 times more potent an antiplatelet agent than clopidogrel. In the TRITON-TIMI 38 trial, 13 608 patients with acute coronary syndromes for whom PCI was planned were randomized to either prasugrel (60 mg loading dose, followed by 10 mg daily) or clopidogrel (300 mg loading dose, followed by 75 mg daily).[2] Over 15 months of follow-up, prasugrel reduced the outcomes of cardiovascular death, myocardial infarction, or stroke by 19%. In patients who received stents, prasugrel also reduced the risk of stent thrombosis by half. However, prasugrel was associated with an increased rate of fatal bleeding compared with clopidogrel (0.4 vs. 0.1%, $P = .002$). Bleeding complications were greatest in the elderly (≥75 years), patients with prior stroke or transient ischemic attack, and those who weigh <60 kg, so that prasugrel should be avoided in such patients.[3]

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ANSWERS TO QUESTIONS 393 TO 396

393–B, 394–C, 395–A, 396–D (Braunwald, pp. 859–869; Figs. 44.4, 44.5, 44.7)

Each of the cell types listed is involved in atherogenesis. *Endothelial cells*, which represent a large and extensive lining of the entire vascular tree, form a highly selective, permeable barrier to the bloodstream and maintain a non-thrombogenic surface. They also actively manufacture and secrete several important vasoactive substances. Endothelial cells have a surface coat of heparan sulfate, which reduces thrombogenicity, and produce prostaglandin derivatives, in particular prostacyclin. The latter is a vasodilator that inhibits platelet aggregation. In addition, endothelial cells secrete tissue plasminogen activator, which contributes to lysis of fibrin clots, and nitric oxide, which causes vasodilatation and inhibits platelet aggregation. Thus, endothelial cells regulate or provide protection against the development of inappropriate thrombus formation through several mechanisms.

Smooth muscle cells are primarily derived from the media of the vessel wall. Their principal physiologic role in the media is to maintain arterial wall tone via the capacity to alter contractile state in response to many substances. For example, prostacyclin induces relaxation and vasodilatation, whereas epinephrine and angiotensin cause smooth muscle contraction. During atheroma formation, smooth muscle cells migrate into the intima, likely attracted by platelet-derived growth factor and other chemoattractants. Extensive proliferation of smooth muscle cells in the intima contributes significantly to the development of mature atherosclerotic plaque.

Macrophages, derived from circulating blood monocytes, are capable of secreting a large number of biologically active substances that participate in inflammatory and immune responses. Macrophages become foam cells by extensive, non-low-density lipoprotein receptor-mediated, accumulation of cholesteryl ester and as such form the principal cells in the fatty streak. The macrophage foam cells provide a major source of proinflammatory mediators, which are thought to play a critical role in atherogenesis.

Platelets interact in an important manner with both the endothelium and developing atherosclerotic plaque. Although platelets are capable of little or no protein synthesis, they contain numerous substances in their granules that are released on platelet activation. These include contributors to the coagulation cascade as well as several potent growth factors or mitogens. Growth factors may play an important role in stimulating both vasoconstriction and subsequent proliferation in the injured vessel wall.

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ANSWERS TO QUESTIONS 397 TO 400

397–B, 398–A, 399–D, 400–C (Braunwald, p. 952)

Beta blockers inhibit the beta-adrenergic receptor, which is part of the adenylate cyclase system.[1] Inhibition results in lower levels of cyclic adenosine monophosphate and cytosolic calcium. Beta blockers can be divided into three general groups. First-generation agents are nonselective, inhibiting both $beta_1$- and $beta_2$-adrenergic receptors (e.g., propranolol); second-generation agents are relatively $beta_1$ selective, although this selectivity diminishes with higher doses (e.g., metoprolol or atenolol); and third-generation agents have additional vasodilatation properties (e.g., carvedilol, which has alpha- and beta-receptor blocking activities).

In addition to these pharmacodynamic properties, there are also important pharmacokinetic differences among beta blockers. For example, propranolol is very lipophilic, is readily absorbed from the gastrointestinal tract, is metabolized by the liver, and has a short half-life. In contrast, atenolol is very hydrophilic, is not as readily absorbed from the gastrointestinal tract, is metabolized by the kidney, and has a longer half-life so that it can be administered less frequently.

Some beta blockers (e.g., pindolol, acebutolol) have partial beta-agonist activity. These agents produce low-grade beta stimulation when sympathetic tone is low (e.g., at rest), but behave like more conventional beta blockers when sympathetic activity is high, such as during exercise.

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ANSWERS TO QUESTIONS 401 TO 405

401–A, 402–B, 403–B, 404–C, 405–B (Braunwald, pp. 1163–1164, 1155–1156; eFig. 59.8)

Both aneurysms and pseudoaneurysms can complicate acute myocardial infarction. A true aneurysm is a discrete dyskinetic region of the ventricular wall that results from expansion and dilatation of a segment of scarred, thinned myocardium. The wall always contains some myocardial elements. The base of a true aneurysm is wide and the risk of free wall rupture is low. Mural thrombus may form along the wall of the aneurysmal segment, and anticoagulation is usually appropriate, at least temporarily. Surgical repair is sometimes indicated, for example, if the aneurysm results in intractable heart failure or uncontrolled ventricular arrhythmias.

In contrast, pseudoaneurysms represent an incomplete rupture of the ventricular free wall that is sealed by organizing thrombus and pericardium. Pseudoaneurysms can become very large and communicate with the left ventricle through a narrow neck. Although the base is narrow, the risk of progressive rupture is high and surgical repair is indicated. The distinction between true aneurysms and pseudoaneurysms can usually be readily discerned by echocardiography.

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ANSWERS TO QUESTIONS 406 TO 409

406–C, 407–E, 408–D, 409–C (Braunwald, p. 1282)

Unfractionated heparin (UFH) is a glycosaminoglycan with a high binding affinity for antithrombin. When bound to heparin, antithrombin undergoes a conformational change that results in greater inactivation of factor IIa (thrombin) and factor Xa, thus interfering with clot formation.

Low-molecular-weight heparins (LMWHs) are derived from UFH via chemical or enzymatic depolymerization. The shorter molecules still activate antithrombin but have greater anti-factor Xa than anti-factor IIa activity. This feature causes LMWHs to inhibit thrombin generation more effectively, and the high bioavailability permits subcutaneous, rather than intravenous, administration. The reduced binding of LMWHs to plasma proteins allows a predictable drug effect such that routine monitoring of anticoagulant activity is not usually necessary. If the anticoagulant effect does need to be assessed (e.g., in obese individuals or patients with renal impairment), anti-Xa activity, not the activated partial thromboplastin time (aPTT), should be measured. LMWHs are less likely to trigger type II heparin-induced thrombocytopenia (HIT), but are still contraindicated in patients with this syndrome, because HIT antibodies can cross-react with LMWH.

Bivalirudin is a synthetic peptide that is an intravenous direct thrombin inhibitor—it binds directly to thrombin without requiring antithrombin. Because it is cleaved once bound to thrombin, bivalirudin has a very short half-life. It appears to be safe in patients with a history of HIT. Its anticoagulant effect can be followed by measuring the aPTT. The doses of both bivalirudin and LMWH require adjustment in the setting of advanced renal insufficiency.

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ANSWERS TO QUESTIONS 410 TO 414

410–B, 411–C, 412–D, 413–C, 414–A (Braunwald, pp. 859–869; Figs. 44.4, 44.5, 44.7; see also Answers to Questions 393–396)

The initial stages of atherogenesis include extracellular lipid accumulation and leukocyte recruitment.[1] The latter process is mediated by several groups of adhesion molecules. One group includes members of the immunoglobulin superfamily, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. Another group includes selectins such as P-selectin and E-selectin. Expression of these adhesion molecules on the surface of endothelial cells regulates the adherence of monocytes and T cells to the arterial wall. Entry of leukocytes into the intima is then mediated by chemoattractant cytokines such as monocyte chemoattractant protein-1.

Once recruited into the arterial intima, monocytes imbibe lipid particles to become lipid-laden macrophages, termed foam cells. Although other cells in the body express surface low-density lipoprotein (LDL) receptors that regulate LDL uptake, this is not true of foam cells. In these cells, scavenger uptake receptors allow unregulated lipid accumulation. The precursor atherosclerotic lesion composed of foam cells is known as the fatty streak.

A subsequent step in formation of an atherosclerotic lesion involves smooth muscle cell migration and proliferation in the intima. Many of the smooth muscle cells in atherosclerotic lesions derive from the arterial medial layer.[2] The chemoattractants responsible for migration into the intima include platelet-derived growth factor, which is secreted by activated macrophages. With the addition of extracellular matrix consisting of collagen and proteoglycans secreted by the smooth muscle cells, the fibrous plaque is formed.

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ANSWERS TO QUESTIONS 415 TO 418

415–B, 416–D, 417–D, 418–A (Braunwald, pp. 1129–1132; Table 59.4; eFigs. 59.3 and 59.4)

Each of the available fibrinolytic drugs for use in acute ST-segment elevation myocardial infarction (MI) possesses unique characteristics. The first-generation fibrinolytic agent was *streptokinase* (SK), which is an indirect plasminogen activator and therefore relatively nonspecific for fibrin. In comparative trials, it had the lowest rate of intracranial hemorrhage. Produced by beta-hemolytic streptococci, SK is antigenic and allergic reactions occur in 5% to 6% of patients. *Alteplase* (tissue plasminogen activator [tPA]) is a second-generation, more fibrin-specific fibrinolytic. It has the shortest half-life (4 to 8 minutes) of all current fibrinolytics and therefore is administered as a bolus followed by continuous infusion over 90 minutes or longer.

Modifications to the basic structure of tPA have yielded a series of third-generation fibrinolytics with more prolonged plasma clearance rates, including *reteplase* (RPA) and *tenecteplase* (TNK-tPA). RPA is a deletion mutant of tPA with a longer half-life (15 minutes) but reduced fibrin specificity. It is administered as a double intravenous bolus, 30 minutes apart. TNK-tPA is a triple mutant with resultant increased fibrin specificity, a longer half-life, and reduced sensitivity to plasminogen activation inhibitor-1. It is administered as a single intravenous bolus.

The third-generation fibrinolytics result in 30-day post-MI mortality rates similar to tPA. However, they offer the convenience of bolus administration.

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ANSWERS TO QUESTIONS 419 TO 422

419–C, 420–C, 421–B, 422–A (Braunwald, pp. 1155–1158; Table 59.11; Figs. 59.27–59.30)

Rupture of the interventricular septum after acute myocardial infarction (MI) usually occurs in the setting of anterior wall infarction and in patients with poor collateral circulation.

In fibrinolytic trials, it developed in only 0.8% of patients, with an associated 30-day mortality of 74%. Septal defects in patients with anterior infarction tend to be apical in location, whereas inferior infarctions are associated with perforation of the basal septum (a more difficult area to surgically repair). Partial or total rupture of a papillary muscle (as shown in the figure) in the setting of acute MI is usually due to ischemic damage to the posteromedial papillary muscle in inferior wall infarction. Papillary muscle rupture occurs with relatively small infarctions in approximately half of the cases, in contrast to rupture of the ventricular septum, which almost always results from large infarcts.

Clinically, patients with both lesions develop a new holosystolic murmur. The murmur of interventricular septal rupture is often louder and accompanied by a systolic thrill. In both lesions, the murmur may decrease or disappear as arterial blood pressure (and therefore systemic afterload) falls. The distinction between acute ventricular septal rupture and mitral regurgitation can be made readily by echocardiography.

At heart catheterization, patients with either lesion may demonstrate tall *v* waves in the pulmonary capillary wedge tracing. Measurement of oxygen saturation via a pulmonary artery catheter can distinguish between the two: in ventricular septal rupture there is a "step-up" in oxygen saturation in the right ventricle (compared with the right atrium) as a result of oxygenated blood entering the right ventricle from the left ventricle.

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ANSWERS TO QUESTIONS 423 TO 427

423–C, 424–C, 425–A, 426–C, 427–A (Braunwald, pp. 971–977; Tables 8.8 and 48.9; Figs. 48.7 and 48.9)

The Scandinavian Simvastatin Survival Study (4S) was a secondary prevention trial that examined the effect of simvastatin over 5.4 years in 4444 individuals with known coronary disease and very high serum cholesterol. Treatment with simvastatin was associated with highly significant reductions in nonfatal myocardial infarction (MI) and cardiovascular death (34%) and overall mortality (30%).[1]

The HPS study compared the benefit of simvastatin (40 mg/day) with placebo in over 20,000 patients at risk for vascular events who would not have met criteria for lipid lowering at the time of enrollment. The study included patients with established atherosclerotic disease and those with multiple risk factors. Randomization to simvastatin was associated with a 24% reduction in major vascular events and 13% reduction in all-cause mortality. Subgroup analysis showed there was equal benefit for women, the elderly, and diabetic patients.[2]

The ASCOT-LLA investigators randomized 10,305 hypertensive patients with total cholesterol <250 mg/dL to either atorvastatin 10 mg daily or placebo. Patients with a history of myocardial infarction, cerebrovascular disease, or current angina were excluded. After 3.3 years, atorvastatin was associated with a 27% reduction in stroke and a 21% reduction in total cardiovascular events, but overall mortality was not significantly impacted.[3]

The JUPITER trial examined the effects of rosuvastatin 20 mg daily versus placebo over 1.9 years in 17,802 apparently healthy men and women who had low-density lipoprotein (LDL) cholesterol <130 mg/dL but high-sensitivity C-reactive protein >2.0 mg/L. Treatment with rosuvastatin was associated with a significant 44% reduction of the composite outcome of MI, stroke, revascularization, unstable angina, or cardiovascular death. The individual components of the primary outcome were also significantly reduced, as was overall mortality. There was a higher incidence of physician-reported diabetes in the rosuvastatin-treated group.[4]

The FOURIER trial randomized over 27,000 patients with atherosclerotic cardiovascular (CV) disease and LDL concentrations of ≥70 mg/dL on statin therapy to the PCSK9 inhibitor evolocumab or placebo.[5] Among these patients with LDL cholesterol levels not previously considered elevated, the addition of evolocumab resulted in a mean 59% further reduction in LDL concentration over a mean follow-up of 2.2 years. In the evolocumab group, there was a significant reduction in the primary composite endpoint of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, as well as the key secondary endpoint of CV death, MI, or stroke. MI and stroke were each individually reduced with evolocumab, though the reduction seen for CV death was not statistically significant.

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ANSWERS TO QUESTIONS 428 TO 431

428–D, 429–D, 430–B, 431–C (Braunwald, p. 971; Table 48.7)

Many medications affect serum lipid levels. Beta blockers (excluding those with intrinsic sympathomimetic activity and those with concurrent alpha-blocking properties) can lower serum high-density lipoprotein (HDL) cholesterol. Second-generation antipsychotic medications (e.g., clozapine, olanzapine) can contribute to weight gain, insulin resistance, and increased triglyceride and low-density lipoprotein cholesterol levels.[1] Corticosteroids raise triglyceride levels and lower serum HDL levels.

Examples of cardiovascular drugs that have no significant effect on plasma lipoproteins include calcium channel antagonists, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

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ANSWERS TO QUESTIONS 432 TO 435

432–A, 433–A, 434–C, 435–B (Braunwald, pp. 966–970; Tables 48.5 and 48.6)

Familial hypercholesterolemia (FH) is associated with specific dermatologic lesions. Heterozygotes may develop nodular swellings of the tendons around the knee, elbow, dorsum of the hand, and ankle, known as *tendon xanthomas*, as shown in part *B* of the figure. Microscopically, these consist of large deposits of cholesterol, both extracellularly and within scavenger macrophage cells.

Although deposition of cholesterol in the tissues of the eyelid and within the cornea, known respectively as *xanthelasma* (part *C* in the figure) and *arcus corneae*, may be observed in FH, they can also occur in adults with other lipid disorders and even in those with normal plasma lipid levels.

Patients with *homozygous* FH have dramatic elevations in plasma low-density lipoprotein from birth, with levels typically sixfold to eightfold higher than normal. In addition, they demonstrate a unique cutaneous finding, the *planar xanthoma*. The latter may be present at birth but always develops within the first 6 years of life. Planar xanthomas are yellow and occur at points of trauma over the knees, elbows, and buttocks. In addition, they may be found in the interdigital webs of the hands, especially between the thumb and index finger (part *A* in the figure). Tendon xanthomas, xanthelasma, and arcus corneae also occur in homozygotes.

Type III hyperlipoproteinemia, or familial dysbetalipoproteinemia, is a single-gene disorder that requires both the presence of a mutation in the gene for apolipoprotein E and contributory environmental or genetic factors. In this disorder, the plasma concentrations of both cholesterol and triglycerides are elevated because of the accumulation of remnant-like particles derived from the partial metabolism of both very-low-density lipoprotein and chylomicrons. Two specific dermatologic lesions are characteristic of type III hyperlipoproteinemia. Xanthoma striatum palmare appears as orange or yellow discolorations of the palmar and digital creases, as illustrated in part *D* in the figure. In addition, tuberoeruptive xanthomas are characteristically located over the elbows and knees in this disorder (not shown).

SECTION IV QUESTIONS

(CHAPTERS 67 TO 87)

Diseases of Heart Valves, Myocardium, Pericardium, and Pulmonary Vascular Bed

Fidencio Saldaña, Bradley A. Maron, David D. Berg, and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 436

A 62-year-old woman, previously healthy except for hypertension, presents to the hospital with severe substernal chest heaviness and dyspnea for the past 2 hours. The discomfort began minutes after being told that her son was seriously injured in an automobile accident. On examination she appears diaphoretic, the blood pressure is 152/84 mm Hg, heart rate 88 beats/min, O_2 saturation 96%, jugular venous pressure 8 cm, the chest is clear, cardiac examination shows no gallop or murmur, and there is no peripheral edema. The ECG shows new diffuse T-wave inversions, and the cardiac troponin T is 1.07 ng/mL (reference <0.01 ng/mL). She receives aspirin, clopidogrel, intravenous unfractionated heparin, metoprolol, and atorvastatin. The chest discomfort persists despite IV nitroglycerin, and coronary angiography is undertaken. No coronary stenoses are found. Left ventriculography is performed (Fig. 4.1). Which of the following statements is correct?

A. She should receive anticoagulation with warfarin for the next 4 months
B. An echocardiogram 2 months later will likely show apical akinesis
C. A recanalized coronary thrombus is the likely etiology
D. This syndrome occurs predominantly in postmenopausal women
E. Her expected in-hospital mortality is ~15%

QUESTION 437

A 55-year-old previously healthy man is brought to the emergency department because of left-sided chest pain over the past 3 hours. He denies shortness of breath or cough. The discomfort is less intense when he sits forward. The chest radiograph is unremarkable; the ECG is shown in Fig. 4.2. Which of the following statements regarding this patient's condition is TRUE?

A. Fibrinolytic therapy is indicated if cardiac catheterization is not immediately available
B. Nitrates will substantially relieve the chest pain
C. Nonsteroidal anti-inflammatory therapy is indicated
D. Glucocorticoid therapy should be initiated immediately
E. Measurement of serum cardiac troponin I would clearly differentiate the cause of his chest pain

QUESTION 438

Which of the following statements about coarctation of the aorta is TRUE?

A. After successful repair, systemic hypertension frequently persists
B. Coarctation is more common in females
C. Chest pain and palpitations are common symptoms in older children and adults
D. Atrial septal defect is the most common associated cardiac finding
E. A midsystolic murmur over the mid-anterior abdomen is common

QUESTION 439

An 80-year-old man presents with syncope. During evaluation a systolic murmur is auscultated and an echocardiogram is obtained. A continuous-wave Doppler recording through the aortic valve is shown in Fig. 4.3. Which of the following statements about this disorder is NOT correct?

A. A gradual decrease in exercise tolerance or dyspnea on exertion is the earliest manifestation
B. Up to 50% of patients with this condition who describe typical angina do not have significant coronary arterial obstruction
C. Syncope commonly occurs without significant change in systemic vascular tone
D. Orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema are late manifestations
E. Gastrointestinal bleeding has been associated with this disorder

QUESTION 440

A 28-year-old man presents to the emergency department because of severe chest pain and dyspnea after cocaine

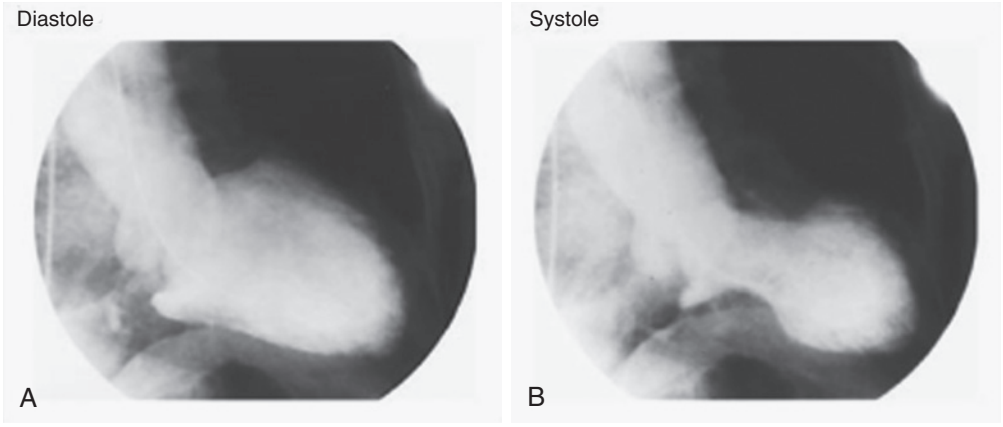

FIG. 4.1 *(A) Diastole; (B) systole.*

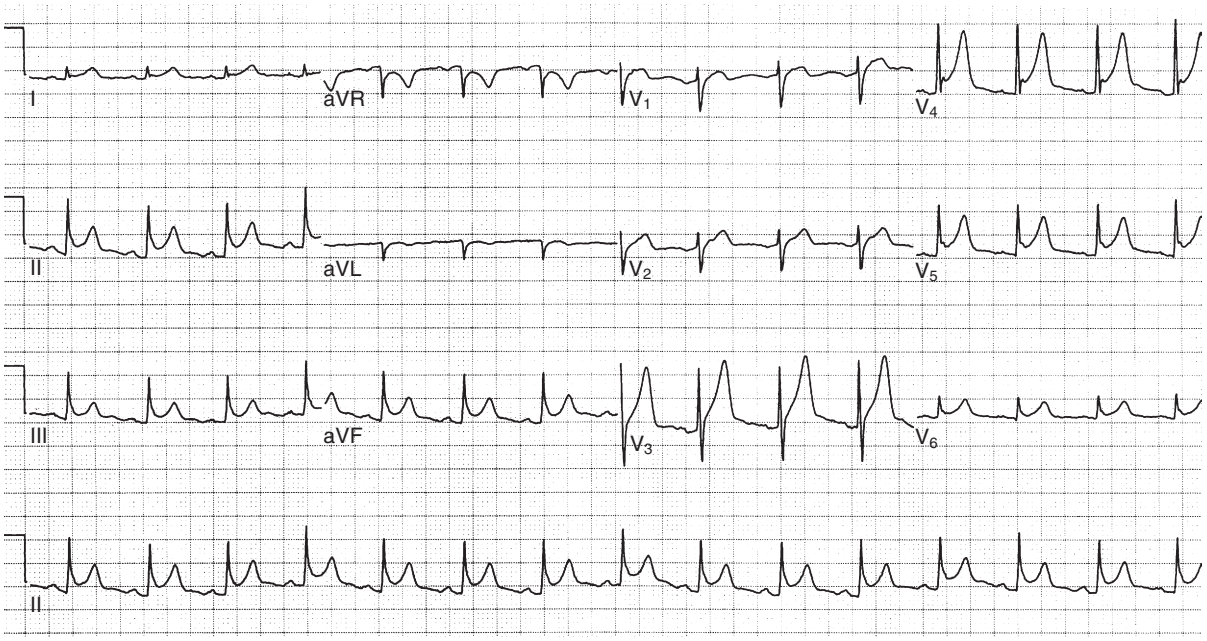

FIG. 4.2

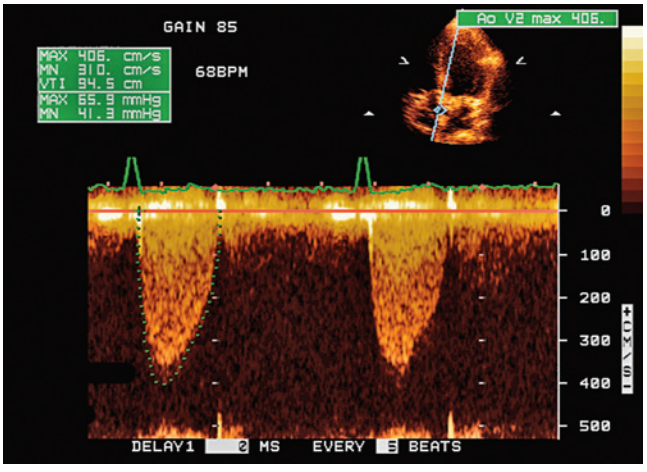

FIG. 4.3

use. His medical history is notable for several years of intermittent cocaine use, alcohol abuse, and cigarette smoking. He has no other known cardiac risk factors. Which of the following statements about cocaine use and the cardiovascular system is NOT true?

A. Cocaine use increases the risk of myocardial infarction (MI) 24-fold in individuals otherwise at low risk for MI
B. The risk of MI after cocaine is related to the amount ingested and the frequency of its use
C. Left ventricular systolic dysfunction can occur both acutely and after long-term cocaine use
D. Mechanisms of cocaine-related myocardial ischemia and infarction include coronary arterial vasoconstriction and enhanced platelet aggregation

QUESTION 441

Which of the following statements about atrial septal abnormalities is NOT correct?

A. The sinus venosus-type atrial septal defect (ASD) is almost always accompanied by anomalous pulmonary venous connections

B. A patent foramen ovale can be found in approximately 25% of healthy adults
C. The most common presenting symptoms of ASDs in adults are exercise intolerance and palpitations
D. Children with ASDs typically experience easy fatigability and exertional dyspnea
E. Atrial arrhythmias are uncommon in children with ASDs

QUESTION 442

True statements about the ECG in congenital heart disease include all of the following EXCEPT
A. First-degree atrioventricular (AV) block is often present in patients with AV septal defects, congenitally corrected transposition of the great arteries, or Ebstein anomaly
B. Atrial fibrillation is more common than atrial flutter in young patients with congenital heart disease
C. The presence of right ventricular hypertrophy suggests pulmonary hypertension or right ventricular outflow tract obstruction
D. In infants, the electrocardiographic pattern of myocardial infarction is associated with anomalous origin of a coronary artery
E. Deep Q waves in the left chest leads can be caused by left ventricular volume overload in a young person with aortic or mitral regurgitation

QUESTION 443

Which of the following statements regarding ventricular septal defects (VSDs) is NOT correct?
A. Muscular VSDs are bordered entirely by myocardium
B. Small VSDs pose a high risk of endocarditis
C. A restrictive VSD does not cause significant hemodynamic derangement and may close spontaneously during childhood
D. Infants with large, nonrestrictive VSDs come to medical attention at an earlier age than those with restrictive defects
E. The ECG after VSD repair usually demonstrates right bundle branch block

QUESTION 444

Which of the following statements regarding atrial septal defects (ASDs) is TRUE?
A. Percutaneous device closure of ASDs improves functional status in symptomatic patients and exercise capacity in both asymptomatic and symptomatic patients
B. Children who have undergone repair of an isolated secundum defect should receive lifelong endocarditis prophylaxis
C. Murmurs are not typically present in patients with uncomplicated ASDs
D. Left-axis deviation of the QRS complex on the ECG suggests the presence of a sinus venosus ASD
E. Surgical or device closure is not indicated in a patient with a pulmonary to systemic shunt ratio (Q_p/Q_s) <2.5

QUESTION 445

A 34-year-old woman presents with recurrent syncope. In recent months she has noted a 10-lb unintentional weight loss, malaise, and diffuse arthralgias. She denies dyspnea, palpitations, or chest pain. A two-dimensional echocardiogram (subcostal view) is shown in Fig. 4.4. Which of the following statements is TRUE about this patient's condition?

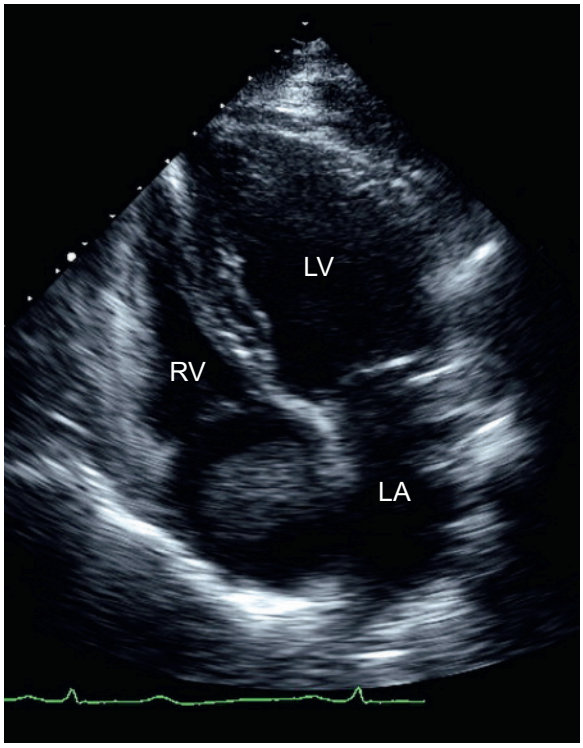

FIG. 4.4

A. The abnormality in the right atrium is most likely a thrombus
B. This lesion is more likely to develop in the right atrium than the left atrium
C. Embolism from this lesion is rare
D. The presence of fever would be indicative of active infection
E. Surgical resection is warranted

QUESTION 446

A 42-year-old woman underwent mitral valve replacement with a St. Jude mechanical prosthesis. She was maintained on warfarin therapy and was documented to have adequate anticoagulation. Two years after the operation she had recurrent transient ischemic attacks. Transthoracic echocardiography proved unrevealing. A transesophageal echocardiogram was performed (Fig. 4.5). Which of the following statements is NOT correct?
A. Large vegetations are seen on the left atrial surface of the St. Jude valve
B. *Streptococcus viridans* is the most likely organism to be cultured in this setting
C. The prosthetic mitral valve is seated in a normal position
D. Transesophageal echocardiography is consistently more sensitive than transthoracic studies for establishing this diagnosis

QUESTION 447

An 84-year-old woman comes for an office visit because of progressive exertional dyspnea. Evaluation, including

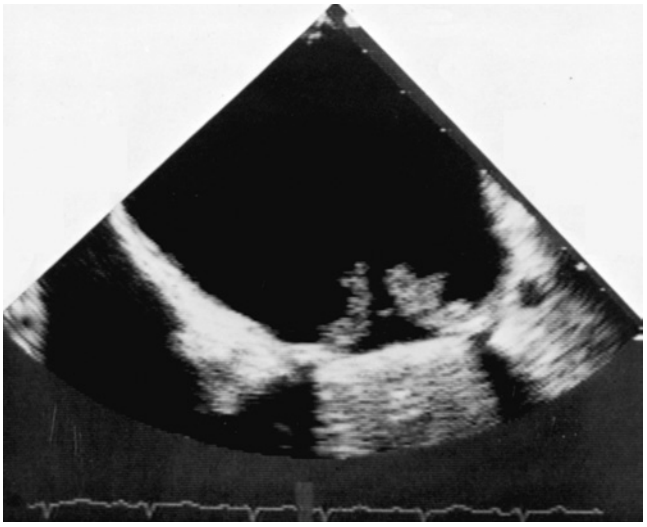

FIG. 4.5

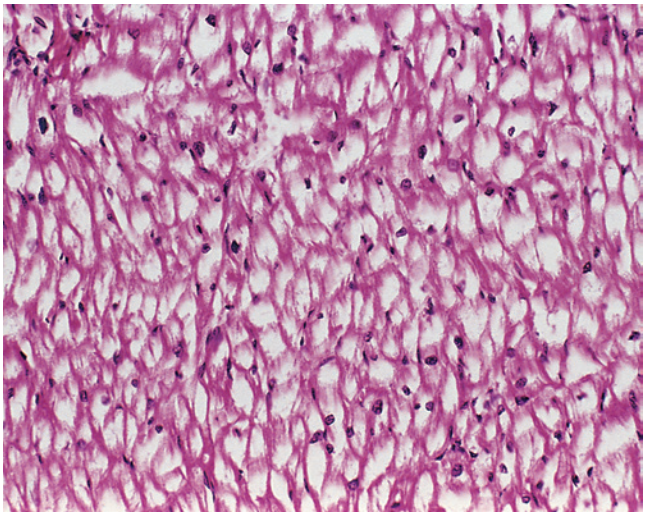

FIG. 4.6 *From Cotran RS, Kumar V, Collins T.* Robbins Pathologic Basis of Disease. *6th ed. Philadelphia: WB Saunders; 1999.*

echocardiography, reveals severe calcific aortic stenosis (peak transvalvular gradient 92 mm Hg, mean transvalvular gradient 45 mm Hg, calculated aortic valve area 0.6 cm^2), with normal left ventricular (LV) contractile function, moderate LV hypertrophy, and no significant mitral valve disease. Coronary angiography 2 years ago showed no coronary artery disease. Her review of systems is notable for chronic obstructive lung disease, hypertension, insulin-dependent diabetes, and moderate renal insufficiency. Her predicted cardiac surgical mortality determined by the Society of Thoracic Surgeons (STS) risk calculator is 18%. She is evaluated by a multidisciplinary heart team and is considered to be at high risk for surgical aortic valve replacement (AVR), but is not inoperable. Which of the following statements is correct?

A. Her predicted 2-year mortality is greater with surgical AVR than with transcatheter aortic valve replacement (TAVR)
B. The 30-day stroke risk is the same after surgical AVR compared to TAVR
C. The presence of more than trivial aortic insufficiency after TAVR is predictive of reduced late survival
D. Complete heart block requiring a permanent pacemaker occurs in <5% of patients who undergo TAVR

QUESTION 448

A 9-month-old infant is found to have a well-circumscribed mass in the left ventricle. There is a family history of tuberous sclerosis. Which of the following cardiac tumors is most likely?

A. Lipoma
B. Papillary fibroelastoma
C. Angiosarcoma
D. Atrial myxoma
E. Rhabdomyoma

QUESTION 449

A 3-month-old infant is referred for evaluation because of failure to thrive and cardiomegaly. Gestation and delivery were normal. The physical examination shows evidence of congestive heart failure and poor skeletal muscle tone. Chest radiography shows cardiomegaly and mild pulmonary edema. The ECG reveals tall, broad QRS complexes consistent with left ventricular hypertrophy and a PR interval of 0.08 second. An endomyocardial biopsy was obtained and the histopathology is shown in Fig. 4.6. The most likely diagnosis is

A. Endocardial fibroelastosis
B. Coarctation of the aorta
C. Shone syndrome
D. Type II glycogen storage disease (Pompe disease)
E. Friedreich ataxia

QUESTION 450

A 53-year-old woman with ischemic cardiomyopathy presents for percutaneous ablation of ventricular tachycardia. She tolerates the procedure well; however, a few hours after the procedure she develops hypotension and sinus tachycardia. An emergent echocardiogram reveals a large circumferential pericardial effusion with findings consistent with tamponade physiology. Each of the following statements about the pathophysiology of cardiac tamponade is correct EXCEPT

A. Cardiac tamponade occurs when the intrapericardial pressure rises to, or above, the mean right atrial and right ventricular diastolic pressures
B. In the presence of pulmonary hypertension, echocardiographic findings of right-sided chamber compression in cardiac tamponade are less notable
C. Equalization of intrapericardial and ventricular filling pressures leads to an inspiratory increase in left ventricular stroke volume
D. Sinus bradycardia may be a manifestation of severe cardiac tamponade

QUESTION 451

A 57-year-old woman comes to your office because of 6 months of fatigue, weight loss, and periods of tachycardia, flushing, and diarrhea. She also describes vague fullness in her neck. Examination discloses clear lungs, an irregular pulse, distended jugular veins with a prominent *v* wave, a holosystolic murmur at the lower left sternal border that intensifies with inspiration, and peripheral edema. She is afebrile. The likely cause of her illness is

A. Bacterial endocarditis
B. Carcinoid syndrome
C. Ebstein anomaly
D. Chronic pulmonary emboli
E. Pheochromocytoma

QUESTION 452

A 32-year-old woman with a history of IV drug abuse presents to the emergency department with fatigue and night sweats. Physical examination reveals a temperature of 38.4°C (101.1°F), scattered rhonchi and wheezes in the lung fields, tachycardia without heart murmurs, and needle tracks on her arms. The chest radiograph reveals several small infiltrates in the left lung field. A transthoracic echocardiogram is obtained and an apical four-chamber view highlighting the right-sided chambers is displayed in Fig. 4.7. Which of the following statements about this case is NOT true?

A. The vegetation displayed occupies the most common endocardial site of infection in IV drug abusers
B. The site of involvement displayed is associated with a higher mortality than other endocardial sites
C. The most likely associated organism is *Staphylococcus aureus*
D. Gram-negative bacilli are a prominent cause of such lesions
E. The majority of patients with this presentation are found to have pneumonia or multiple septic emboli on a chest radiograph

QUESTION 453

A 63-year-old man has a history of unrepaired patent ductus arteriosus and ventricular septal defect with long-standing cyanosis. He is admitted to the hospital because of urinary sepsis and intravenous ciprofloxacin is initiated. A urinary catheter is placed and oral tamsulosin is begun for prostatic obstruction. His fever resolves, but over the next day he develops hypotension and worsening cyanosis. Which of the following interventions would be most appropriate?

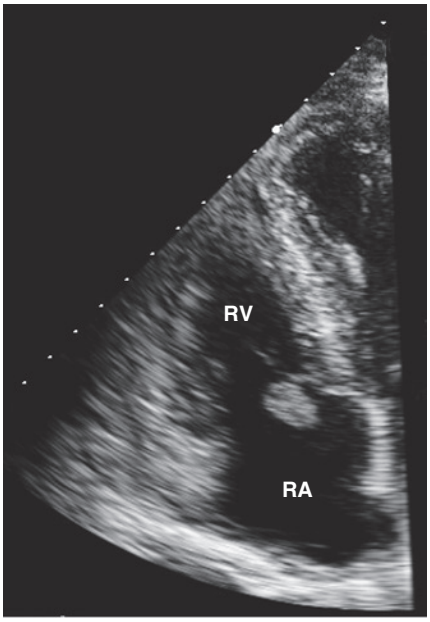

FIG. 4.7

A. Intravenous methylprednisolone and cefepime
B. Intravenous dobutamine and oral sildenafil
C. Intravenous phenylephrine and cessation of tamsulosin
D. Intravenous saline and magnesium

QUESTION 454

A 54-year-old man with a history of hypertension and previously unknown and untreated human immunodeficiency virus (HIV) infection presents with worsening shortness of breath. The chest radiograph shows diffuse bilateral infiltrates that is found to represent *Pneumocystis jiroveci* pneumonia. An echocardiogram is performed to assess left ventricular function, and the study is notable for a small posterior pericardial effusion without cardiac chamber compression. Which one of the following statements regarding pericardial effusion in patients with HIV infection is TRUE?

A. Progression to a symptomatic effusion and/or cardiac tamponade is likely
B. Direct HIV infection of the pericardium is almost exclusively the cause of such effusions
C. The presence of a pericardial effusion in HIV patients has no impact on prognosis
D. Most effusions of this type require glucocorticoid therapy for resolution
E. Pericardial effusion has become an extremely rare cardiac manifestation of HIV infection in patients treated with highly active antiretroviral therapy

QUESTION 455

Which of the following statements about the clinical findings in patients with atrial septal defect (ASD) is NOT correct?

A. A midsystolic ejection murmur and a diastolic rumbling murmur at the lower left sternal border are common features on cardiac examination
B. Patients with ostium primum defects usually show right ventricular hypertrophy, a small rSR′ pattern in the right precordial levels, and rightward axis on the ECG
C. Tall R or R′ waves in V_1 may signal the development of pulmonary hypertension
D. Echocardiographic features of ASD include right ventricular and pulmonary arterial dilatation and paradoxical intraventricular septal motion
E. Radiographic features include cardiomegaly, dilated central pulmonary arteries, and pulmonary plethora

QUESTION 456

A 54-year-old man presents with dyspnea on exertion. He had been routinely exercising four or five times a week, but over the past few months he has noted a decline in exertional capacity. His blood pressure has been consistently <130/85 mm Hg at his physician's office. An apical four-chamber view image from his echocardiogram is shown in Fig. 4.8. Which of the following statements regarding this condition is TRUE?

A. This variant represents <10% of hypertrophic cardiomyopathy in Japan
B. Tall peaked precordial T waves are typically present on the ECG
C. A subaortic dynamic pressure gradient is typically present
D. Magnetic resonance imaging would show a spade-like deformity of the ventricle

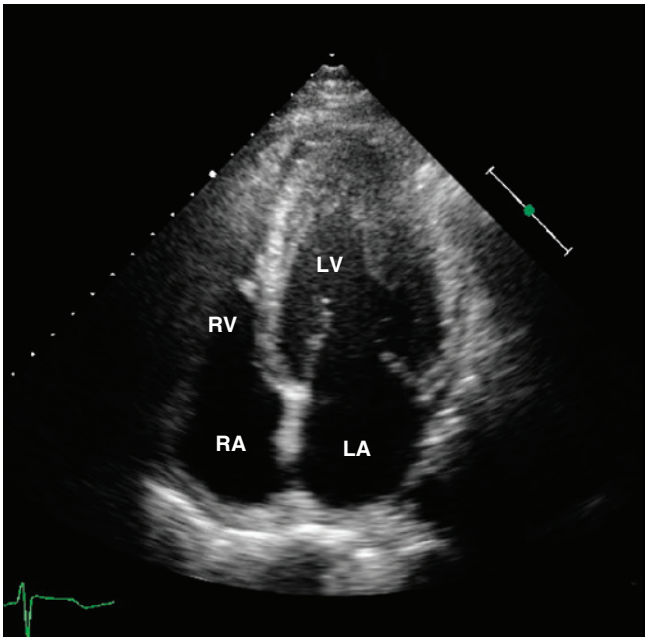

FIG. 4.8

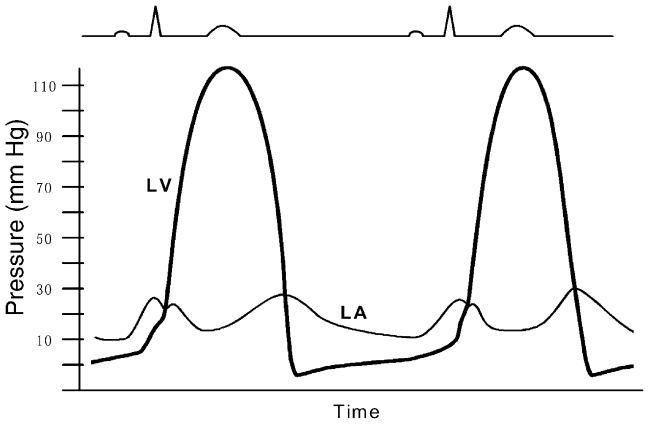

FIG. 4.9

QUESTION 457

A 36-year-old man from the Dominican Republic presents to the emergency department with shortness of breath. A grade III/VI systolic murmur is auscultated at the apex. The chest radiograph demonstrates pulmonary vascular congestion. Echocardiography in the emergency department confirms the presence of mitral regurgitation and vigorous left ventricular contractile function. Which of the following findings would suggest the *acute* onset of mitral regurgitation?

A. Presence of cardiomegaly on the chest radiograph
B. Left atrial and ventricular hypertrophy on the ECG
C. The systolic murmur is short and ends prior to S_2
D. Normal jugular venous pressure

QUESTION 458

The hemodynamic tracing in Fig. 4.9 is most consistent with

A. Constrictive pericarditis
B. Mitral stenosis
C. Mitral regurgitation
D. Restrictive cardiomyopathy
E. None of the above

QUESTION 459

A 45-year-old woman is evaluated by her physician because of the new onset of pleuritic, positional left anterior chest pain that radiates to the left trapezius ridge. Three weeks earlier she had been evaluated for a viral respiratory tract infection. Cardiac auscultation reveals evanescent coarse scratching sounds at the lower left sternal border with components in both systole and diastole. Which of the following statements about expected findings on this patient's electrocardiogram is correct?

A. ST-segment elevations with a convex upward configuration are likely
B. PR-segment depressions may be the only electrocardiographic manifestation
C. Reciprocal ST-segment depressions are typically present
D. Sinus bradycardia is common
E. T-wave inversions develop concurrently with ST-segment elevations

QUESTION 460

Which of the following statements regarding post-myocardial infarction (post-MI) pericarditis is correct?

A. Fibrinolytic therapy increases the incidence of early post-MI pericarditis
B. Post-MI pericarditis is more common after non–ST-segment elevation MI compared with ST-segment elevation MI
C. When present, clinical pericarditis does not arise until >48 hours after infarction
D. The use of heparin is associated with an increased risk of pericarditis
E. The incidence of early post-MI pericarditis is related to infarct size

QUESTION 461

The hemodynamic tracing in Fig. 4.10 is characteristic of which of the following disorders?

A. Aortic stenosis
B. Mitral regurgitation
C. Dilated cardiomyopathy
D. Hypertrophic cardiomyopathy
E. Infiltrative cardiomyopathy

QUESTION 462

A 24-year-old man presents for the evaluation of chest discomfort on exertion. A systolic murmur is auscultated and images from his echocardiogram (color Doppler and spectral Doppler images from parasternal short-axis views) are shown in Fig. 4.11. Which of the following statements is correct?

A. A likely physical finding is a midsystolic click at the second left intercostal space that increases with inspiration
B. Long-term survival of patients with this condition is reduced even if a corrective procedure is performed
C. Valve replacement with a mechanical prosthesis is indicated
D. Balloon valvotomy is typically a successful long-term strategy for this condition

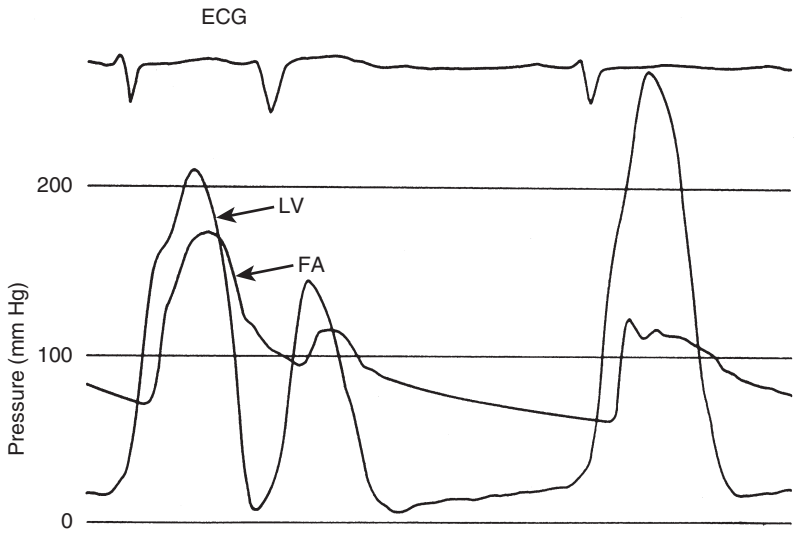

FIG. 4.10 LV, *Left ventricle;* FA, *femoral artery. From Baim D, Grossman W, eds.* Cardiac Catheterization, Angiography and Intervention. *Baltimore: Williams & Wilkins; 1996:794.*

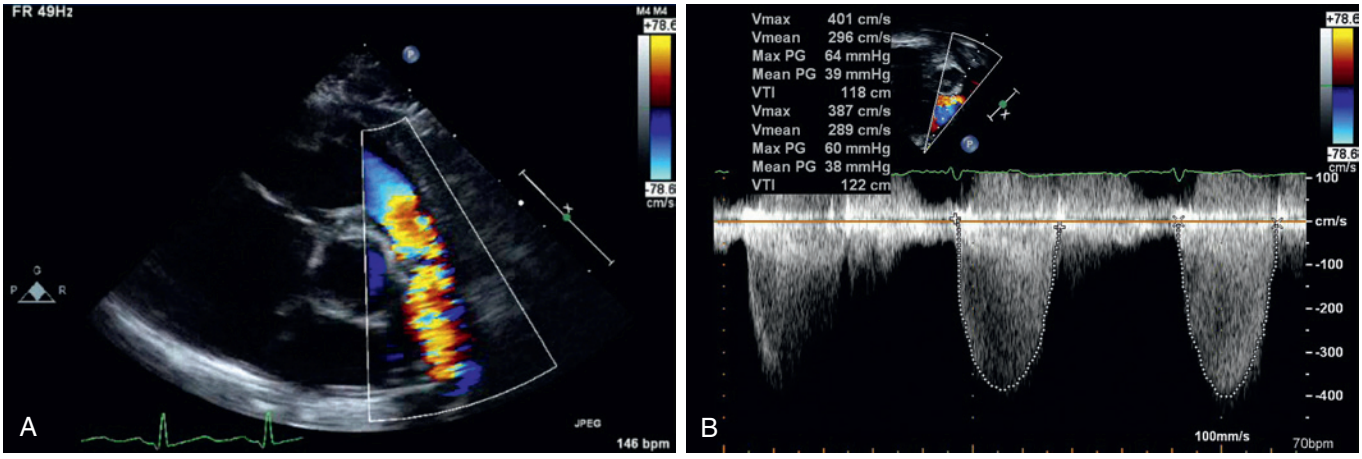

FIG. 4.11

QUESTION 463

Which statement about congenital heart disease in infancy and childhood is TRUE?

A. Extracardiac anomalies occur in ~75% of infants with significant congenital heart disease
B. Patent ductus arteriosus is found more commonly in males
C. Two-thirds of infants with both cardiac and extracardiac congenital anomalies have an established syndrome
D. Features of the rubella syndrome include patent ductus arteriosus or pulmonic valvular stenosis
E. Maternal systemic lupus erythematosus is associated with congenital cardiac malformations, including ventricular septal defect and pulmonic stenosis

QUESTION 464

According to the American Heart Association guidelines for the prevention of infective endocarditis, antibiotic prophylaxis is appropriate for each of the following cardiac conditions before invasive dental procedures EXCEPT

A. Presence of a prosthetic cardiac valve
B. Unrepaired cyanotic congenital heart disease
C. Cardiac transplantation recipients with cardiac valvulopathy
D. Mitral valve prolapse with audible murmur and severe mitral regurgitation
E. Previous episode of infective endocarditis

QUESTION 465

In patients with pulmonary arterial hypertension, which of the following is the most reliable predictor of mortality?

A. Elevated right atrial pressure
B. Elevated mean pulmonary artery pressure
C. Diastolic septal flattening on transthoracic echocardiography
D. Transpulmonary gradient ≤10 mm Hg

QUESTION 466

A 45-year-old man presents with fevers, chills, and shortness of breath. His chest radiograph shows pulmonary edema. Echocardiography reveals vigorous left ventricular contractile function. Vegetations are identified on the aortic valve and there is nonhomogeneous thickening within the aortic root concerning for abscess formation. Cardiac surgery is undertaken and an aortic valve homograft is selected as a means of

replacing the diseased structures. Which one of the following statements is TRUE regarding the use of aortic valve homografts in the surgical management of aortic valve disease?

A. Homografts have high thrombogenicity and require chronic anticoagulation therapy
B. The rate of structural degeneration of cryopreserved homografts is significantly less than that of porcine xenograft valves
C. Homografts are advantageous for patients with endocarditis of the aortic valve who require valve replacement and aortic reconstruction
D. Homografts offer a less favorable hemodynamic profile than mechanical valves
E. The operative mortality of aortic homograft placement is higher than that of mechanical valve replacement surgery

QUESTION 467

Which of the following statements concerning the auscultatory findings of the valvular abnormality depicted in Fig. 4.12 is correct?

A. In patients with leaflets that are flexible, S_1 is softened
B. In patients with heavily calcified leaflets, the intensity of S_1 is accentuated
C. As the severity of this condition increases, the A_2-opening sound (OS) interval (the interval between A_2 and the mitral opening sound) shortens
D. The intensity of the diastolic murmur is closely related to the severity of this condition
E. P_2 (the pulmonic valve closure sound) is commonly diminished

QUESTION 468

Which of the following statements regarding the physical examination in aortic regurgitation is TRUE?

A. The typical murmur is of low frequency and heard best with the bell of the stethoscope placed along the left sternal border
B. The severity of regurgitation correlates better with the intensity rather than the duration of the murmur
C. Dilatation of the ascending aorta should be suspected if the murmur is loudest at the right side of the sternum
D. The intensity of the murmur is decreased by isometric exercise (e.g., strenuous handgrip)

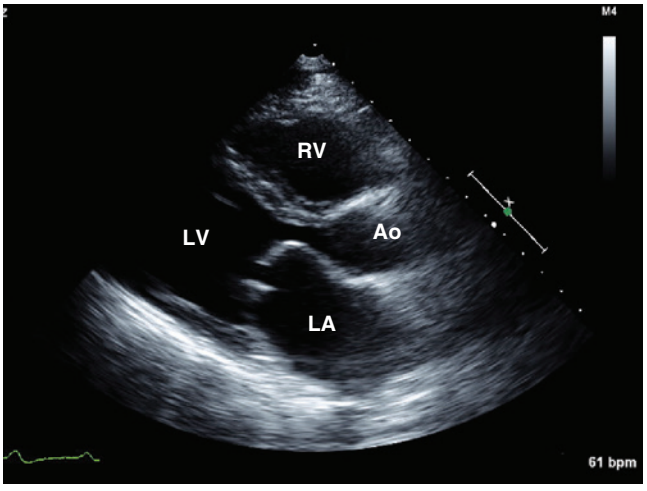

FIG. 4.12

QUESTION 469

A 75-year-old woman with chronic obstructive pulmonary disease and chronic renal insufficiency presents with fever, rigors, productive cough, and worsening shortness of breath. On physical examination she is overtly dyspneic, the temperature is 38.9°C (102.1°F), heart rate 120 beats/min, and blood pressure 82/50 mm Hg. The chest radiograph shows a dense left lower lobe infiltrate and symmetric enlargement of the cardiac silhouette. Echocardiography demonstrates a large circumferential pericardial effusion. She is admitted to the intensive care unit for suspected bacterial pericarditis. Which of the following statements is true?

A. Uremic pericarditis with a preexisting pericardial effusion predisposes to bacterial pericarditis
B. Direct extension into the pericardium of bacterial pneumonia accounts for only a minority of cases of purulent pericarditis
C. Bacterial pericarditis is most often a subacute illness
D. The modern survival rate of this condition is excellent
E. Antibiotics administered intravenously do not achieve high concentrations in the pericardial space

QUESTION 470

A 16-year-old asymptomatic teenager undergoes physical examination before competing in high school athletics. His mother states that a first cousin died suddenly while playing basketball and she recalls that there was something wrong with his heart. His vital signs are heart rate 64 beats/min, respirations 12 breaths/min, and blood pressure 120/75 mm Hg. His cardiac examination is remarkable for a grade 2/6 systolic ejection murmur along the left sternal border, which decreases with squatting and increases with sudden standing. The ECG shows left ventricular hypertrophy (LVH) with prominent septal forces and echocardiography confirms marked LVH. Your recommendations regarding participation in athletics are:

A. No competitive sports
B. Noncontact competitive sports are acceptable
C. Noncontact competitive sports with beta blocker therapy are acceptable
D. High-intensity competitive sports are acceptable with beta blocker therapy

QUESTION 471

Abnormalities of left ventricular (LV) function and hemodynamics in asymptomatic aortic stenosis typically include all of the following EXCEPT

A. Normal cardiac output at rest
B. Elevated LV end-diastolic pressure
C. Elevated LV end-diastolic volume
D. Increased *a* wave in the left atrial pressure curve
E. Normal LV stroke volume

QUESTION 472

A 76-year-old man presents to the emergency department with aphasia and dense right hemiplegia. His wife reports that he had experienced intermittent fevers and chills over the previous 2 weeks. Cardiac examination is notable for a

grade 2/6 systolic ejection murmur at the upper right sternal border and grade 1/4 early diastolic murmur at the upper left sternal border. Four sets of blood cultures grow *Staphylococcus aureus*. A transthoracic echocardiogram demonstrates normal left ventricular contractile function and mild aortic stenosis. No vegetations are seen. Computed tomography of the head shows an acute nonhemorrhagic stroke in the territory of the left middle cerebral artery. Which of the following statements is TRUE?

A. The presenting stroke is an indication for urgent valve replacement
B. Endocarditis caused by *S. aureus* is an absolute indication for surgery
C. Despite the aggressiveness of *S. aureus* native valve endocarditis, antibiotic therapy alone without surgical intervention is often curative
D. The presence of a vegetation >1.0 cm in diameter would be a class I indication for valve replacement
E. Even if intractable heart failure develops, corrective valve surgery should be postponed until after blood cultures have become sterile

QUESTION 473

Which of the following statements about tuberculous pericarditis is NOT correct?

A. Tuberculous pericarditis usually arises via retrograde spread from adjacent lymph nodes or by early hematogenous spread from the primary infection
B. Tuberculous pericardial effusions usually accumulate slowly
C. Measurement of adenosine deaminase in pericardial fluid is a highly sensitive and specific test for the diagnosis of tuberculous pericarditis
D. It is often difficult to isolate the organism from pericardial fluid
E. The addition of corticosteroids to a three-drug antibacterial regimen reduces mortality in patients with tuberculous pericarditis

QUESTION 474

A 42-year-old previously healthy salesman presents to his physician with a complaint of lower extremity edema. On further questioning, he says he has also experienced "flushing" episodes over the past several months, intermittent wheezing, and episodic diarrhea. On physical examination, there is jugular venous distention, a prominent holosystolic murmur at the lower left sternal border, a pulsatile liver, and peripheral edema. The urinary 5-hydroxyindoleacetic acid level is markedly elevated. Which of the following statements is TRUE?

A. The underlying disorder involves the liver
B. Echocardiography typically demonstrates thickened mitral and/or aortic valve leaflets with left ventricular dilatation
C. The symptoms are associated with low levels of circulating serotonin
D. The primary disease usually invades the myocardium

QUESTION 475

A 65-year-old woman, who is originally from Puerto Rico, presents for evaluation of known mitral stenosis. Over the past few months she has developed worsening exertional dyspnea, atrial fibrillation, and is found to have moderate pulmonary hypertension. Which of the following statements regarding percutaneous balloon mitral valvuloplasty for this condition is TRUE?

A. The risk of stroke during the procedure is 10%
B. Transthoracic echocardiography is the appropriate imaging study before the procedure to exclude the presence of left atrial thrombus
C. Balloon mitral valvuloplasty is the treatment of choice for patients with hemodynamically significant mitral stenosis, without left atrial thrombus and an echo score of ≤8
D. A small atrial septal defect is detected in 25% of patients after the procedure
E. Approximately 10% of patients develop severe mitral regurgitation as a result of the procedure

QUESTION 476

A 25-year-old man is an unrestrained driver in a head-on motor vehicle accident. He is brought into the emergency department trauma bay where he is unconscious and is noted to have multiple head lacerations, a large contusion on his anterior chest, and abdominal enlargement. Each of the following statements regarding the acute evaluation of a patient with blunt cardiac trauma is true EXCEPT

A. Chest radiography should be obtained urgently
B. Serum cardiac-specific troponin measurements correlate with the presence and prognosis of blunt myocardial injury
C. Common consequences of blunt cardiac trauma can be correctly identified by transesophageal echocardiography
D. Arrhythmias and conduction blocks frequently occur after blunt cardiac trauma
E. Traumatic ventricular septal defect formation is a recognized complication

QUESTION 477

Which of the following statements regarding patients with sarcoid heart disease is TRUE?

A. Fewer than 5% of patients with pulmonary sarcoidosis have cardiac sarcoid involvement
B. Granulomatous infiltration of the cardiac valves is found in most patients with sarcoid heart disease
C. Percutaneous endomyocardial biopsy (EMB) is a highly sensitive means to establish the diagnosis
D. Magnetic resonance imaging and positron emission tomography (PET) scanning are more sensitive than EMB in establishing the diagnosis of cardiac sarcoid

QUESTION 478

Which of the following statements about the natural history of untreated ventricular septal defect (VSD) in adults is NOT correct?

A. The natural history of VSD differs depending on the size of the defect and the magnitude of pulmonary vascular resistance
B. Regardless of size, the presence of a VSD confers an increased risk for endocarditis
C. Progressive pulmonary vascular disease with reversal of shunting (Eisenmenger complex) most often becomes manifest in the fifth or sixth decade
D. Women with VSDs and ratios of pulmonary to systemic flow <2:1 generally tolerate pregnancy well

QUESTION 479

Each of the following statements regarding endomyocardial fibrosis (EMF) is correct EXCEPT
A. This condition is characteristically found in tropical and subtropical Africa
B. It is predominantly a disease of children and young adults
C. Involvement of the mitral valve apparatus typically results in mitral stenosis
D. EMF involves the left ventricle, alone or in combination with the right ventricle, in 90% of patients
E. Echocardiographic features include increased endocardial reflectivity, fibrotic obliteration of the apex, atrial enlargement, and pericardial effusion

QUESTION 480

Which of the following is NOT an independent indication for placement of an implantable cardioverter-defibrillator in a patient with hypertrophic cardiomyopathy?
A. Recent unexplained syncope
B. Hypotensive blood pressure response to exercise
C. Left ventricular outflow tract gradient ≥30 mm Hg
D. Left ventricular wall thickness ≥30 mm
E. Family history of premature sudden death in a first-degree relative

QUESTION 481

An 8-month-old boy is evaluated because of cyanosis that was first noted at 2 months of age, which worsens with physical activity or crying. A systolic thrill is present at the left sternal border and there is a loud systolic murmur across the precordium. Echocardiography is diagnostic for tetralogy of Fallot. Which of the following statements about tetralogy of Fallot is correct?
A. Classic tetralogy of Fallot is composed of a large ventricular septal defect, infundibular or valvular pulmonic stenosis, right ventricular (RV) hypertrophy, and a cleft mitral valve
B. Downward displacement of the septal leaflet of the tricuspid valve commonly accompanies tetralogy of Fallot
C. A right aortic arch is present in ~25% of patients
D. Survival of patients with uncorrected tetralogy of Fallot into adult life is common regardless of the degree of RV outflow obstruction

QUESTION 482

A 54-year-old man with a bicuspid aortic valve presents with a 1-week history of fevers and chills. Initial blood cultures are negative, but echocardiography reveals a large vegetation on the aortic valve. On the fifth hospital day, blood cultures become positive for gram-negative bacteria. Which of the following is NOT a member of the fastidious, slow-growing group of HACEK organisms that may be the cause of this patient's endocarditis?
A. *Haemophilus parainfluenzae*
B. *Aggregatibacter actinomycetemcomitans*
C. *Cardiobacterium hominis*
D. *Escherichia coli*
E. *Kingella kingae*

QUESTION 483

Which of the following statements regarding endocardial fibroelastosis (EFE) is TRUE?
A. Symptoms of EFE first manifest in early adolescence
B. Myocardial involvement is characteristic
C. The clinical course is usually benign
D. Hypereosinophilia is typically present
E. There is an association with maternal mumps during pregnancy

QUESTION 484

Which of the following statements is TRUE regarding the Fontan procedure?
A. It involves creation of a transatrial shunt
B. It is a curative operation for the underlying congenital defect
C. Coronary-aorta fistula formation is a common complication
D. The most common cause of postoperative death is infection
E. Protein-losing enteropathy is a recognized complication

QUESTION 485

A 27-year-old woman presents with 2 days of shortness of breath. The plasma D-dimer level is elevated. A high-resolution chest computed tomographic scan reveals a segmental pulmonary embolism, and deep vein thrombosis is found in the right femoral vein. She denies any recent travel, immobility, or surgery. Which of the following primary hypercoagulable states is most frequent among patients who present with deep vein thrombosis?
A. Protein C deficiency
B. Activated protein C resistance
C. Antithrombin deficiency
D. Prothrombin gene 20210 mutation
E. Protein S deficiency

QUESTION 486

A 48-year-old man comes to the office because of episodic palpitations. His other symptoms include paroxysmal nocturnal dyspnea, nocturnal enuresis, and mild angina. His wife adds that he snores loudly. He has a history of several recent automobile accidents. On examination, his blood pressure is elevated at 190/100 mm Hg and he is moderately overweight. Laboratory evaluation reveals a hematocrit of 58%. The most likely cardiac finding would be
A. Mitral valve stenosis
B. Aortic valve stenosis
C. Right ventricular hypertrophy
D. Pulmonary valve stenosis
E. Atrial septal defect

QUESTION 487

A 78-year-old man describes exertional dyspnea 3 days after a 12-hour intercontinental flight. His blood pressure is 128/76 mm Hg, heart rate 92 beats/min and regular. His oxygen saturation is 96%. He weighs 78 kg. There is no jugular venous distension, the chest is clear to auscultation, and there is no peripheral edema or calf tenderness. The serum D-dimer is elevated and subsequent imaging demonstrates a segmental pulmonary embolism and thrombus within the

left femoral vein. There are no echocardiographic signs of right ventricular strain. Serum electrolyte measurements are normal, the serum creatinine is 1.0 mg/dL, and the estimated creatinine clearance is 62 mL/min. His current medications are atorvastatin 20 mg daily and lisinopril 10 mg daily. Of the following choices, which would be the best initial anticoagulation strategy?

A. Enoxaparin 1 mg/kg subcutaneous injection once, followed by oral warfarin daily to achieve an INR of 2.0-3.0
B. Dabigatran 150 mg orally twice daily
C. Rivaroxaban 20 mg orally once daily, with the evening meal
D. Apixaban 10 mg orally twice daily for 7 days, then 5 mg twice daily
E. Enoxaparin 1 mg/kg subcutaneously twice daily for 3 days, then oral edoxaban 30 mg once daily

QUESTION 488

A 20-year-old previously healthy woman is brought to the hospital because of fatigue and exertional dyspnea over the past month. Past medical history is unremarkable except for an upper respiratory tract infection 4 weeks earlier. She is not pregnant. There is no family history of cardiac illness. She does not consume alcoholic beverages or use illicit drugs. On examination in the emergency department, the patient's blood pressure is 90/60 mm Hg and the heart rate is 110 beats/min. The jugular veins are distended to 10 cm H_2O, the chest examination reveals bilateral rales, and on cardiac examination there is a prominent apical S_3 gallop. An echocardiogram demonstrates dilatation of both ventricles with diffuse hypokinesia; the left ventricular ejection fraction is 15%. Which one of the following statements regarding this patient's disorder is NOT correct?

A. The most likely etiology of this patient's disorder is viral
B. Myocardial biopsy would not likely reveal a specific etiology
C. Corticosteroids will likely slow progression of the illness
D. Cardiac magnetic resonance imaging would be a useful diagnostic modality
E. Serum cardiac troponin elevation may occur in the absence of coronary artery disease

QUESTION 489

A 28-year-old man is referred for evaluation after his brother was diagnosed with a cardiac condition that caused recurrent syncope. As part of his evaluation, he underwent echocardiography and cardiac magnetic resonance imaging. Representative images are shown in Figs. 4.13 and 4.14. Which of the following is correct in the management of this patient's condition?

A. Endocarditis prophylaxis is mandatory before dental procedures
B. Beta blockers are contraindicated
C. He should refrain from highly competitive sports
D. Digitalis glycosides are beneficial
E. Anemia is associated with a decrease in murmur intensity

QUESTION 490

A 32-year-old woman presents with progressive exertional dyspnea over the past year. Physical examination is notable for a blood pressure of 123/81 mm Hg, heart rate 91 beats/min, resting oxygen saturation 91%, clear lungs, a loud pulmonic component of S_2, and symmetric lower extremity edema. As part of her treatment, her physician prescribed a diuretic and warfarin. After 3 months there was no clinical improvement. Right heart catheterization is undertaken and demonstrates the following: right atrial pressure 14 mm Hg; pulmonary artery pressure (mean) 38 mm Hg; pulmonary vascular resistance 6.8 Wood units (544 dyn·sec·cm^{-5}); pulmonary capillary wedge pressure 8 mm Hg. A pulmonary angiogram is performed (Fig. 4.15). Which

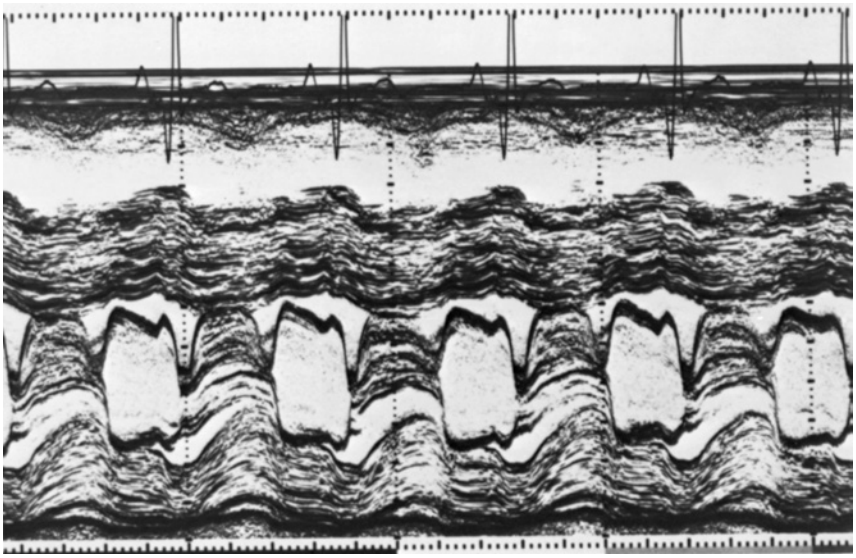

FIG. 4.13

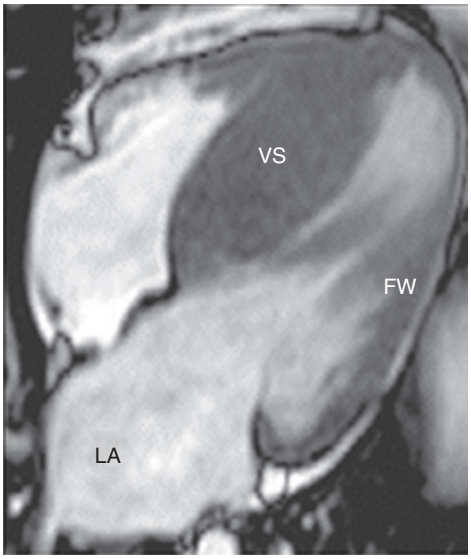

FIG. 4.14 *From Maron BJ, Maron MS.* Lancet. *2013;381:242.*

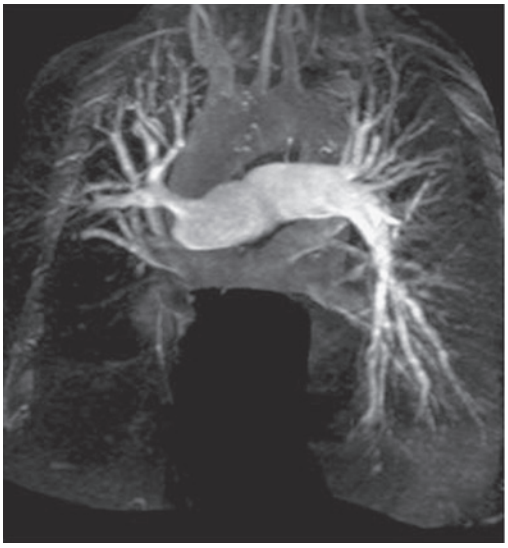

FIG. 4.15

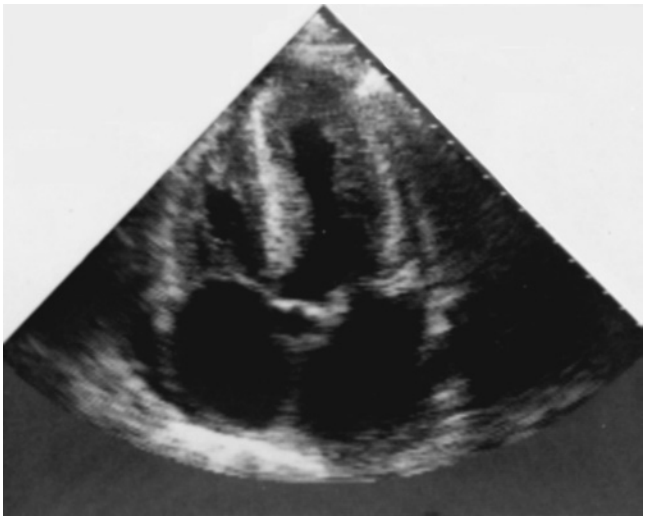

FIG. 4.16

of the following would be most appropriate in managing this patient?

A. Intravenous prostacyclin titrated to maximum tolerated dose
B. Oral sildenafil three times daily
C. Initiation of a nonselective endothelin receptor antagonist
D. Refer for cardiac surgical intervention

QUESTION 491

A 70-year-old man with multiple myeloma presents with new biventricular heart failure. An apical four-chamber view from a transthoracic echocardiographic study is shown in Fig. 4.16. Which of the following statements about this case is TRUE?

A. This disease is caused by sarcomeric gene mutation encoding for beta-myosin heavy chain
B. The ECG likely demonstrates criteria for left ventricular hypertrophy
C. The most common cardiac presentation of this disorder is restrictive cardiomyopathy
D. Recurrent blood transfusion is a risk factor for this disorder

QUESTION 492

The 2D and M-mode echocardiogram images in Fig. 4.17 were recorded from an asymptomatic 24-year-old woman. Valvular regurgitation is absent by Doppler interrogation. Which of the following statements is TRUE?

A. The patient should undergo repeat echocardiography every 6 months to follow this disorder
B. She should receive antibiotic prophylaxis to prevent infective endocarditis prior to invasive dental procedures
C. She is at increased risk of sudden cardiac death
D. She is at increased risk of thromboembolism and requires chronic oral anticoagulation therapy
E. Advanced age and male gender are risk factors for progression of this disorder and ultimate need for surgical intervention

QUESTION 493

A 75-year-old woman presented to her physician with severe fatigue and intermittent cyanosis. Initial evaluation revealed that cyanosis had been present for approximately 1 year and occurred chiefly during mild to moderate exertion. Transthoracic echocardiography (TTE) yielded images that were suboptimal; therefore, TEE was peformed. Part *A* in Fig. 4.18 shows a basal image from the TEE, and part *B* shows an image obtained after injection of agitated saline into the right antecubital vein. Which of the statements about this patient and the echocardiographic images displayed is NOT correct?

A. The saline contrast image demonstrates right-to-left interatrial flow
B. The images verify a secundum-type atrial septal defect
C. An anomalous pulmonary vein is demonstrated
D. In TTE, the subcostal position is most useful for studying the lesion displayed
E. When left atrial pressure exceeds right atrial pressure in this condition, echocardiography with IV saline contrast injection may demonstrate a negative contrast effect within the right atrium

QUESTION 494

A 29-year-old man is referred by his family practitioner for evaluation of a heart murmur that was first heard during childhood. He is asymptomatic. Part of his evaluation included an echocardiogram. An M-mode panel from that study is displayed in Fig. 4.19. Which of the statements about this case is NOT correct?

A. A vegetation is present on the anterior leaflet of the mitral valve
B. A bicuspid aortic valve is a cause of this finding
C. This disorder can be associated with ankylosing spondylitis
D. The M-mode finding may be present even in mild forms of this condition

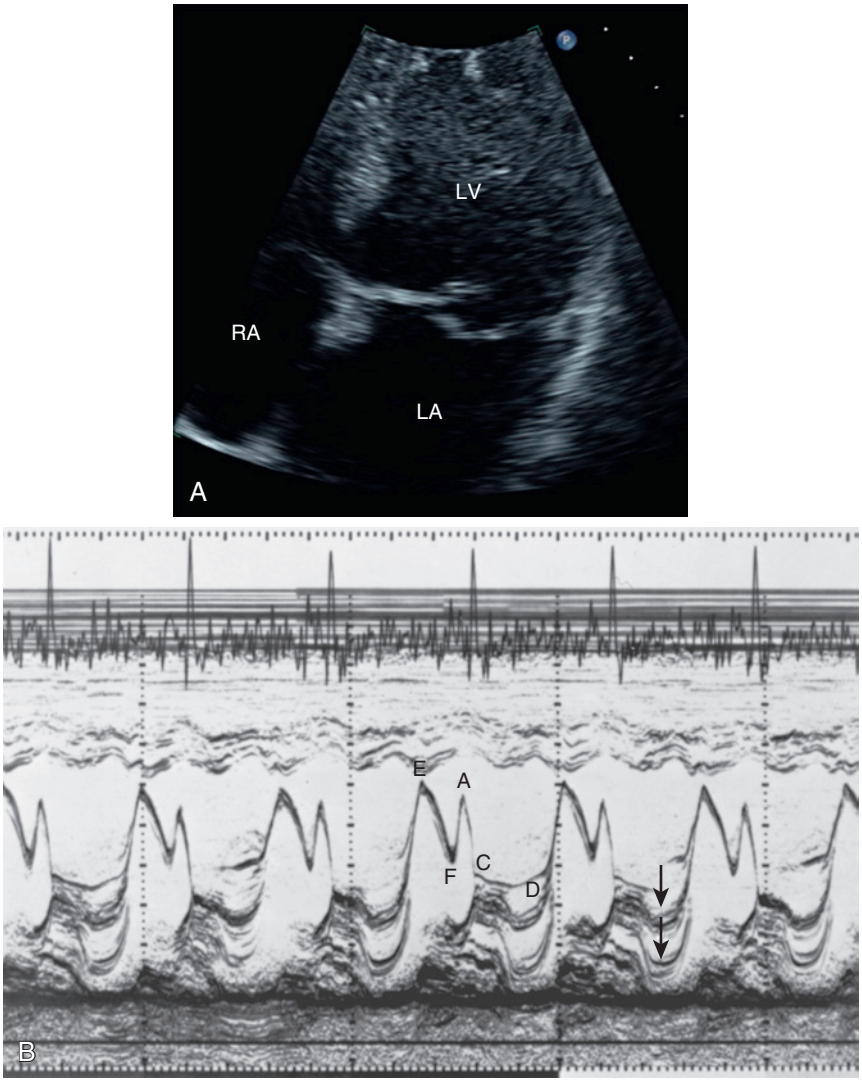

FIG. 4.17

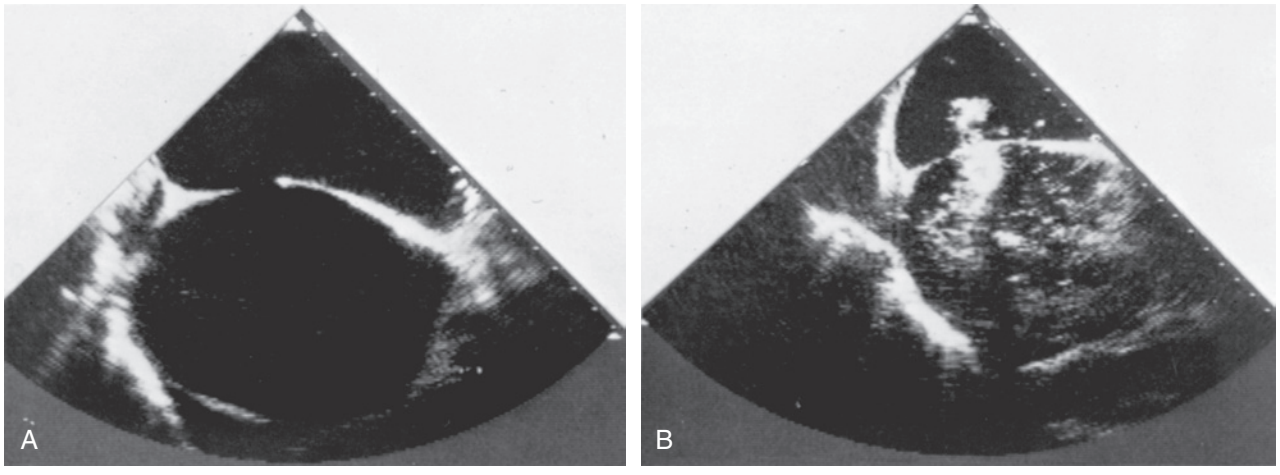

FIG. 4.18

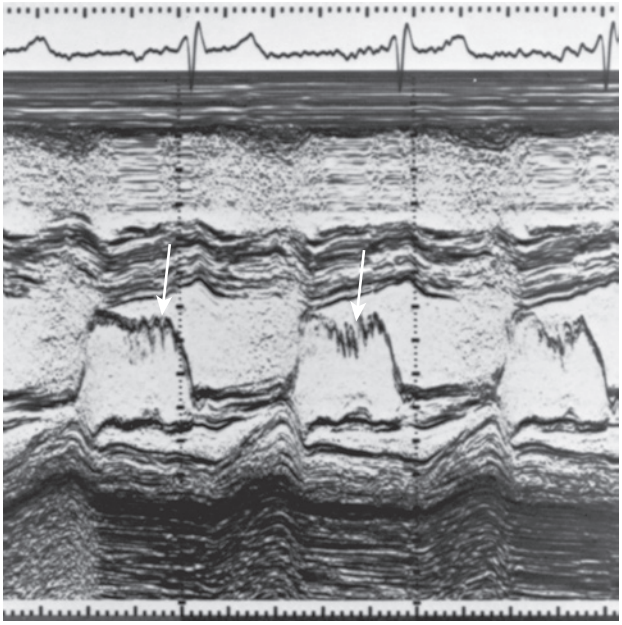

FIG. 4.19

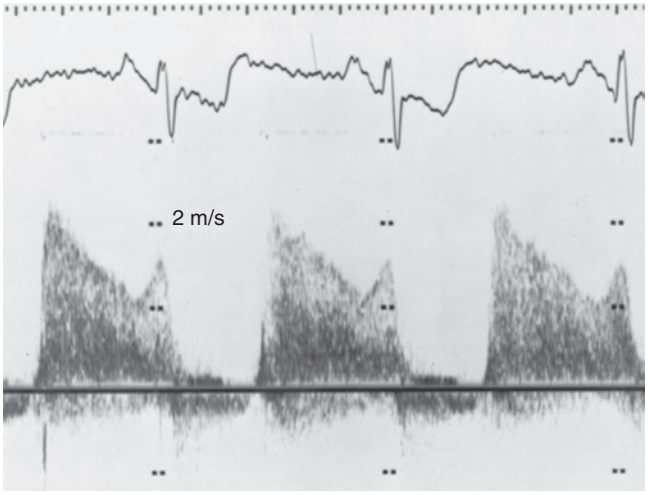

FIG. 4.20

QUESTION 495

A 34-year-old woman presents with dyspnea and is found to be in atrial fibrillation. Following conversion to normal sinus rhythm, an echocardiographic study is obtained. Fig. 4.20 displays a continuous-wave Doppler recording through the mitral valve. Which of the statements about this condition is NOT correct?

A. Two-dimensional echocardiography would demonstrate thickening of the valve leaflets and chordal apparatus
B. The peak velocity of transmitral flow in this case is decreased
C. In early diastole, the posterior leaflet of the mitral valve commonly moves in an anterior direction in patients with this condition
D. Mitral orifice size can be accurately determined by Doppler pressure half-time measurement
E. Elevation of the pulmonary artery systolic pressure, as estimated by the tricuspid regurgitant jet, would likely be present in this patient

QUESTION 496

A 34-year-old man with human immunodeficiency virus (HIV) infection presented with the recent onset of fever and dyspnea. Physical examination revealed fever, tachycardia, jugular venous distention, a pericardial friction rub, and hepatomegaly. The chest radiograph shown in part *A* of Fig. 4.21 was obtained. A diagnosis was ascertained by obtaining pericardial fluid and a pericardial biopsy specimen. The pericardial fluid was notable for an elevated level of adenosine deaminase. The chest radiograph in part *B* was obtained 3 weeks after the initiation of appropriate therapy. Which of these statements about this case is NOT correct?

A. In industrialized nations, the incidence of this disorder has decreased markedly in recent decades
B. This condition is the most common cause of pericardial disease in African HIV-infected patients
C. Clinical detection of this disorder usually occurs either in the effusive stage or after the development of constrictive pericarditis
D. The acute onset of characteristic severe pericardial pain is common
E. This disorder is most likely to be diagnosed if both pericardial fluid and a pericardial biopsy specimen are obtained

QUESTION 497

Which of the following statements about ostium primum atrial septal defects (ASDs) is NOT correct?

A. Ostium primum ASDs often displace and cause a "cleft" appearance of both the anterior and posterior leaflets of the mitral valve
B. The clinical features of ostium primum ASDs are similar to those of the ostium secundum type
C. Imaging usually reveals both right atrial and right ventricular enlargement
D. The presence of an ostium primum ASD accompanied by a ventricular septal defect comprises a complete atrioventricular canal malformation
E. Left ventriculography may demonstrate a "gooseneck" deformity

QUESTION 498

Which of the following warrants an implantable cardioverter-defibrillator for primary prevention of sudden cardiac death in a patient with hypertrophic cardiomyopathy?

A. Sustained atrial fibrillation
B. Late gadolinium enhancement on contrast-enhanced cardiac MRI that comprises >15% of left ventricular mass.
C. Interventricular septal wall thickness of 25 mm
D. Loss of function mutation in the fibrillin-1 (*FBN1*) gene

QUESTION 499

A 53-year-old man has a grade III/VI apical holosystolic murmur. His echocardiographic apical three-chamber view with color Doppler imaging is shown in Fig. 4.22. Measurements included a left ventricular (LV) end-diastolic chamber diameter of 56 mm, end-systolic dimension of 38 mm, and LV ejection fraction of 60%. He is asymptomatic and has not experienced inordinate dyspnea on exertion, orthopnea, or lower extremity edema. For this patient, which of the

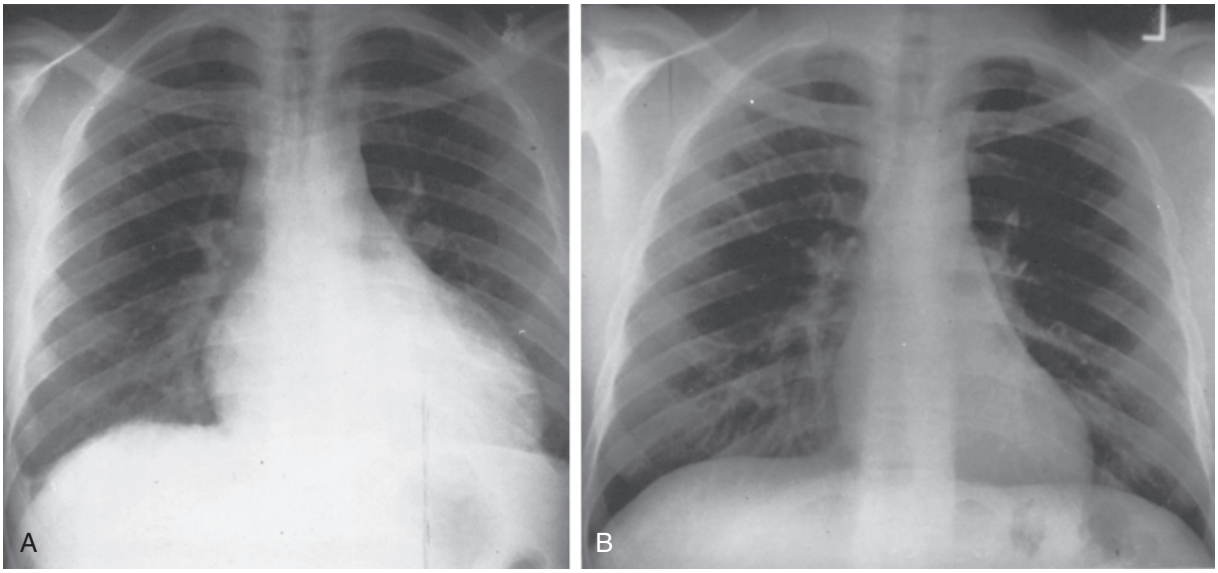

FIG. 4.21 *From Jay M.* Plain Film in Heart Disease. *Boston: Blackwell Scientific Publishing; 1992.*

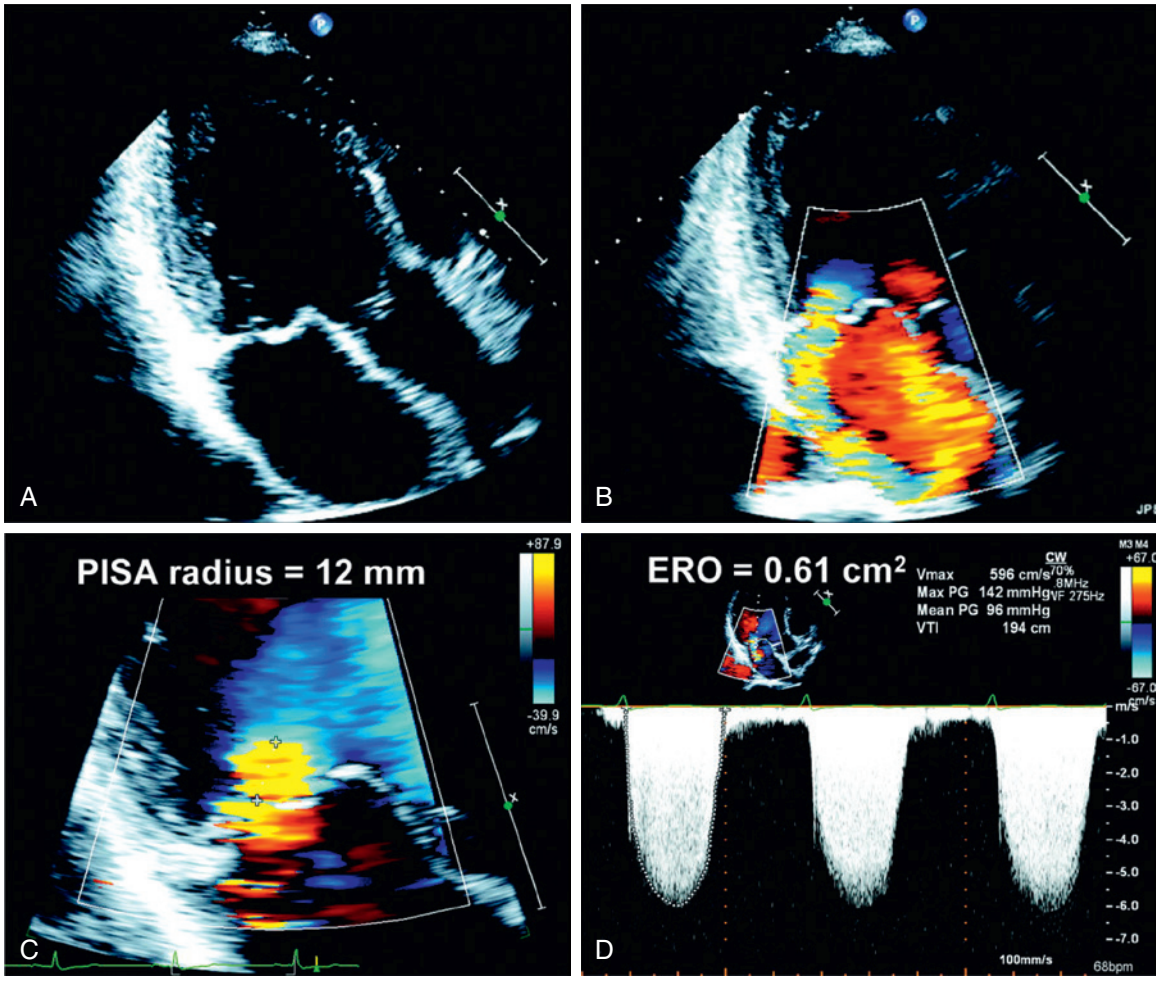

FIG. 4.22 *From Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation.* Circulation. *2009;119:797.*

following statements is correct regarding the timing of mitral valve surgery?

A. Surgical correction should be undertaken as soon as possible
B. The risk of postoperative heart failure is low as long as the preoperative ejection fraction is >50%
C. His postoperative prognosis will not suffer if he undergoes valve surgery before the LV end-systolic diameter exceeds 55 mm
D. Chronic administration of an angiotensin-converting enzyme inhibitor would delay the need for surgery
E. A resting pulmonary artery systolic pressure of 55 mm Hg is a class IIa indication for mitral valve surgery

QUESTION 500

A 23-year-old women delivers a baby boy at 36 weeks' gestation. Soon after delivery, the neonate is noted to be cyanotic with a physical examination notable for a right ventricular impulse and a systolic thrill along the left sternal border. An echocardiogram reveals obstruction to right ventricular outflow, an outlet ventricular septal defect, overriding of the aorta, and right ventricular hypertrophy. With regard to the management of this condition, which one of the following statements is NOT correct?

A. Early definitive repair is indicated
B. Postoperative increases in pulmonary venous return often lead to right ventricular decompensation
C. The size of the pulmonary arteries is the single most important determinant in assessing candidacy for primary repair
D. If early corrective operation is not possible, a palliative procedure that leads to increased pulmonary blood flow is recommended
E. Bleeding complications are common in the postoperative period after repair

QUESTION 501

A 62-year-old man presents with the acute onset of shortness of breath 2 weeks after prostate surgery. A high-resolution contrast chest computed tomographic scan is shown in Fig. 4.23. Which of the following statements is correct?

A. Echocardiography would be useful for further risk stratification of this patient
B. Pulmonary angiography is required to make a definitive diagnosis
C. This technique is insensitive for detecting thrombi in subsegmental pulmonary arteries
D. The majority of patients with this disorder have evidence of deep vein thrombosis in the systemic venous system

QUESTION 502

Which one of the following conditions is NOT associated with elevated right ventricular diastolic pressures with the pattern shown in Fig. 4.24?

A. Cardiac tamponade
B. Acute right ventricular infarction
C. Massive pulmonary embolism
D. Constrictive pericarditis
E. Restrictive cardiomyopathy

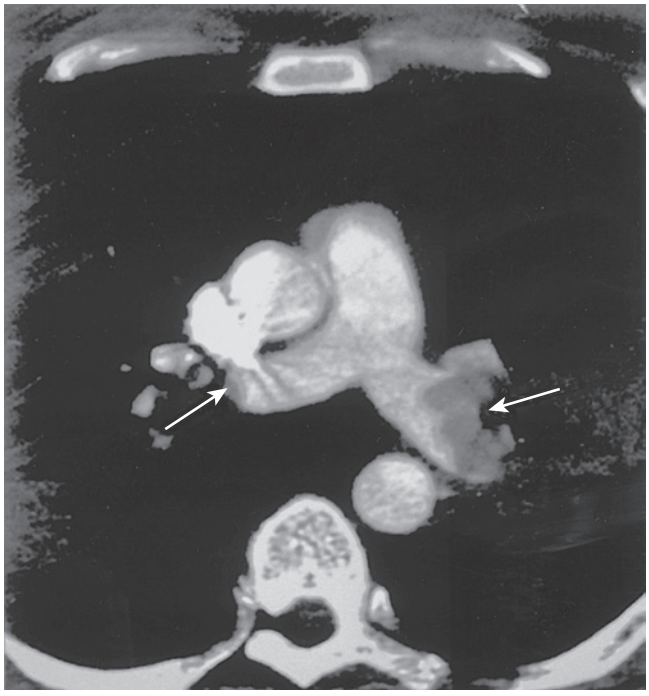

FIG. 4.23

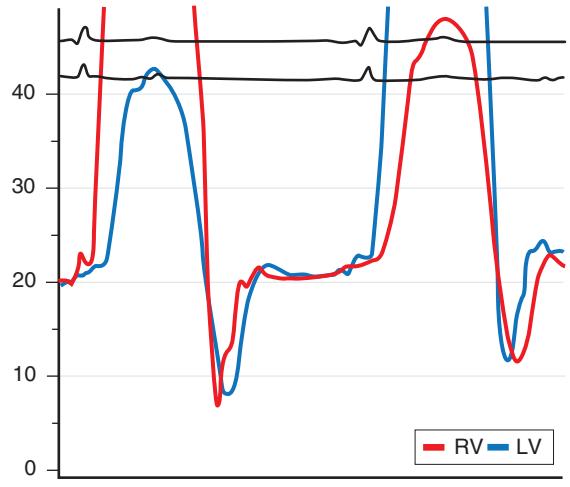

FIG. 4.24 *From Vaitkus PT, Cooper KA, Shuman WP, Hardin NJ. Images in cardiovascular medicine: constrictive pericarditis.* Circulation. *1996;93:834.*

QUESTION 503

A 54-year-old man presented with increasing dyspnea on exertion. He was initially treated for an upper respiratory tract infection; however, his symptoms persisted. A subsequent echocardiogram revealed an intracardiac mass suggestive of a malignant tumor. Regarding primary malignancies of the heart, which of the following statements is TRUE?

A. The right atrium is the most common site of involvement
B. The vast majority of patients already have metastases at the time of diagnosis
C. Malignant tumors account for half of primary cardiac tumors
D. Lymphomas are the most common primary malignancies of the heart

QUESTION 504

A 63-year-old man without known cardiac history presented with a 4-month history of dyspnea on exertion and lower extremity edema. Echocardiography revealed a normal LV ejection fraction with no significant valvular disease. A chest computed tomographic scan showed a dense rim of calcium around the heart. Coronary angiography showed no significant coronary disease. Hemodynamic evaluation demonstrated elevation and equalization of right and left ventricular diastolic pressures with a "dip and plateau" configuration. Which of the following statements about this condition is correct?

A. Evaluation for tuberculosis is appropriate
B. The mortality rate associated with pericardiectomy in the contemporary era is <1.0%
C. Nearly all patients develop a high-output syndrome immediately after pericardiectomy due to rapid expansion of the heart
D. Symptomatic improvement is reported in only 50% of surgical survivors
E. Pericardiectomy should be reserved only for patients with New York Heart Association functional class III or IV symptoms

QUESTION 505

A 25-year-old woman presents to her primary care doctor with fatigue and a rash. She recently returned from a New England vacation during which she hiked at least 6 miles daily. On physical examination she has a well-demarcated erythematous rash with central clearing on her chest. Lyme disease is suspected. Which of the following statements regarding cardiac involvement in Lyme disease is TRUE?

A. Cardiac manifestations of Lyme disease typically occur within days of the development of erythema chronicum migrans
B. Less than 10% of patients with Lyme disease develop cardiac manifestations in the current era
C. Supraventricular and ventricular tachyarrhythmias are the most common cardiac manifestations of Lyme disease
D. Cardiomegaly and congestive heart failure are common among patients who develop Lyme carditis

QUESTION 506

Which of the following statements regarding the natural history of idiopathic pulmonary arterial hypertension is TRUE?

A. The prevalence is equal in males and females
B. Chest pain related to right ventricular ischemia is the most common manifesting symptom
C. Sudden cardiac death is a potential complication, but only in patients with class IV symptoms
D. Increased intensity of S_1 is the most common physical finding
E. Electrocardiographic evidence of right ventricular hypertrophy is present in a minority of patients

QUESTION 507

Which of the following statements is TRUE about the heart valve abnormality shown in Fig. 4.25?

A. The abnormality is most likely congenital
B. Cardiac auscultation is almost certainly normal

FIG. 4.25 *From Salem DN, Isner JM. Percutaneous aortic valvuloplasty.* Chest. *1987;92:326.*

C. Endocarditis frequently leads to this abnormality
D. Diabetes mellitus and hypercholesterolemia are risk factors for its development
E. A loud diastolic blowing murmur is likely

QUESTION 508

Which of the following statements about hemodynamic findings in constrictive pericarditis and restrictive cardiomyopathy is correct?

A. A diastolic "dip-and-plateau" pattern is present in the right ventricular (RV) waveform in constrictive pericarditis, but not restrictive cardiomyopathy
B. Concordance of left ventricular and RV systolic pressures during respiration is typical of constrictive pericarditis
C. In constrictive pericarditis, the ratio of RV systolic pressure to RV end-diastolic pressure is usually >3
D. An RV systolic pressure >50 mm Hg is more consistent with restrictive cardiomyopathy than with constrictive pericarditis

QUESTION 509

Riociguat is a recently approved medication that results in improved exercise tolerance in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. The mechanism of action of riociguat is

A. Nitric oxide donor
B. Soluble guanylyl cyclase stimulator
C. Heme oxygenase-1 inhibitor
D. Kv1.5 channel stabilizer

QUESTION 510

A 54-year-old man presents to his physician with a 1-week history of dyspnea on exertion, cough, and pleuritic chest pain. His examination is notable for an elevated jugular venous pressure, distant heart sounds, and mild bilateral lower extremity edema. The chest radiograph reveals an enlarged cardiac silhouette. Echocardiography demonstrates a large circumferential pericardial effusion. An echocardiographic-guided pericardiocentesis is performed, removing most of the fluid; cytologic evaluation reveals adenocarcinoma. Which one of the following statements is NOT correct?

A. The most likely primary malignancy in this patient is in the lung
B. The prognosis is poor despite aggressive surgery or chemotherapy
C. Pericardial sclerotherapy would not significantly improve the long-term prognosis
D. Total surgical pericardiectomy should be performed urgently
E. Echocardiography should be repeated within 72 hours

QUESTION 511

A 34-year-old man presents to the emergency department with pleuritic chest pain after a recent upper respiratory tract infection. The pain is positional, relieved by sitting up. Cardiac examination is notable for a three-component friction rub. The ECG demonstrates diffuse ST-segment elevation with PR-segment depression in several leads. Which of the following statements about the evolution of the ECG in this condition is correct?
A. PR-segment deviation occurs in fewer than 25% of patients with this condition
B. Initial ST-segment elevation is usually most prominent in lead aVR
C. The ratio of the height of ST-segment elevation to the height of the T wave in this condition is typically <0.25 in lead V_6
D. T-wave inversion is expected to occur within days, while the ST segment is still elevated
E. T-wave inversion may persist for months after the acute presentation

QUESTION 512

Which of the following statements regarding the natural history of untreated aortic stenosis (AS) is correct?
A. Average survival from the onset of syncopal symptoms is approximately 6 months
B. Average survival from the onset of congestive heart failure is approximately 2 years
C. Syncope due to AS usually occurs at rest
D. Sudden death in patients with AS usually occurs in previously asymptomatic individuals
E. Atrial fibrillation is typically well tolerated in patients with advanced AS

QUESTION 513

A 46-year-old postmenopausal woman with a history of systemic sclerosis is admitted to the coronary care unit because of progressive dyspnea and chest pain. Initial data include blood pressure 88/55 mm Hg, heart rate 104 beats/min, and oxygen saturation 95%. General examination is notable for cool extremities and symmetric edema of the lower extremities. The electrocardiogram demonstrates right ventricular hypertrophy with a strain pattern. The serum troponin T is 1.10 ng/mL (reference range <0.01 ng/mL), and contrast enhanced thoracic computed tomography demonstrates RV cavitary enlargement without pulmonary embolism. Coronary arteriography shows minimal coronary artery disease without coronary vasospasm. Right heart catheterization reveals the following: mean pulmonary artery pressure 61 mm Hg; mean pulmonary capillary wedge pressure 10 mm Hg; pulmonary vascular resistance 16.2 Wood units (1296 dyn·sec·cm^{-5}). Her body surface area is 1.6 m^2. Which of the following is the most appropriate initial treatment for this patient?
A. Oral macitentan 10 mg daily
B. Intravenous epoprostenol initiated at 2 ng/kg/min
C. Tissue plasminogen activator 100 mg, administered as a continuous IV infusion over 2 hours
D. Digoxin 0.125 mg daily

QUESTION 514

A 45-year-old man is transported to the emergency department, a victim of a stab wound to the chest that occurred during a robbery attempt at his convenience store. Which of the following statements about penetrating cardiac trauma is correct?
A. The left ventricle is the cardiac chamber most commonly injured by penetrating trauma
B. Penetrating injuries to the atria are associated with better survival than wounds to the ventricles
C. Rupture of the interventricular septum is a potential late complication
D. In penetrating cardiac injury with suspected tamponade, urgent pericardiocentesis is mandatory

QUESTION 515

Which of the following statements regarding persistent patent ductus arteriosus (PDA) in adults is NOT correct ?
A. Patients with small shunts and no audible murmur are at negligible risk of endovascular infection
B. Patients with moderate-sized PDA typically present with dyspnea or palpitations
C. Patients with moderate-sized PDA typically have a loud continuous “machinery” murmur and a narrow pulse pressure
D. Patients with large PDA may develop enlarged central pulmonary arteries with peripheral pruning on chest radiograph
E. Transcatheter devices result in successful closure rates of >95%

QUESTION 516

A 46-year-old man is admitted to the hospital because of worsening shortness of breath. His history is notable for hypertension, treated with an angiotensin-converting enzyme inhibitor. Social history reveals that he has consumed one-half pint of liquor daily for the past 10 years. Physical examination shows an elevated jugular venous pressure (14 cm), bibasilar rales on pulmonary examination, a laterally displaced cardiac apical impulse, a grade II/VI holosystolic murmur, an S_3 gallop at the apex, and pitting edema of both lower extremities. Echocardiography demonstrates a dilated left ventricle with an ejection fraction of 25% and moderate mitral regurgitation. Which of the following statements regarding the cardiac effects of alcohol is correct?
A. Chronic heavy alcohol consumption is associated with low systemic blood pressure
B. The likelihood of developing dilated cardiomyopathy correlates with the amount of alcohol consumed over a lifetime
C. Women are less susceptible than men to alcohol-associated cardiomyopathy

D. Moderate alcohol consumption is associated with an increased rate of sudden death
E. Dilated cardiomyopathy due to alcohol consumption is irreversible

QUESTION 517

Expected clinical manifestations of amyloidosis of the cardiovascular system include which of the following?
A. Constrictive pericarditis
B. High-output heart failure
C. Orthostatic hypotension
D. ECG voltage criteria for left ventricular hypertrophy
E. Electrical alternans

QUESTION 518

Which of the following statements regarding endocarditis caused by *Staphylococcus aureus* is correct?
A. Central nervous system complications are rare, occurring in fewer than 5% of patients
B. *Staphylococcus aureus* native valve endocarditis is an absolute indication for surgical debridement
C. The prognosis of right-sided *S. aureus* native valve endocarditis is similar to that of left-sided involvement
D. Empirical initial therapy with oxacillin or cefazolin is appropriate for suspected *S. aureus* endocarditis
E. Prosthetic valve endocarditis with *S. aureus* is associated with a 50% mortality rate in patients treated medically

QUESTION 519

Which of the following is NOT associated with Ebstein anomaly of the tricuspid valve?
A. Atrial septal defect
B. Paradoxical splitting of S_2
C. Ventricular preexcitation
D. A widely split S_1
E. Atrial flutter

QUESTION 520

A 42-year-old man from Uganda is diagnosed with Löffler endocarditis. Which of the following is NOT an expected finding?
A. Eosinophilia
B. Signs and symptoms of heart failure
C. Asthma and nasal polyposis
D. Right ventricular pressure tracing showing a "dip-and-plateau" pattern
E. Normal left ventricular ejection fraction

QUESTION 521

A 57-year-old man is referred for transthoracic echocardiography to investigate unexplained exertional dyspnea. The right ventricular outflow tract Doppler profile is shown in Fig. 4.26 and demonstrates midsystolic notching. This finding is most strongly associated with which of the following?
A. Decreased pulmonary artery pressure
B. Increased pulmonary vascular resistance
C. Pneumothorax
D. Left-sided heart failure

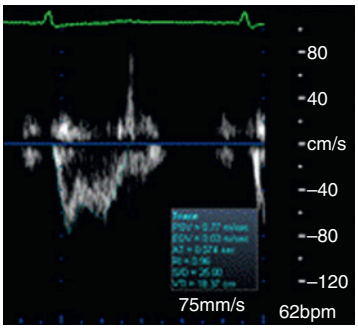

FIG. 4.26 *From Opotowsky AR, Clair M, Afilalo J, et al. A simple echocardiographic method to estimate pulmonary vascular resistance.* Am J Cardiol. *2013;112:873–882.*

QUESTION 522

A 55-year-old woman seeks medical attention because of progressive exertional dyspnea and rapid heart action. At age 12 she suffered from rheumatic fever, and a heart murmur has been subsequently noted. She has had intermittent episodes of atrial fibrillation over the past 2 years with good rate control on metoprolol succinate. Her vital signs include a heart rate of 80 beats/min, blood pressure 130/80 mm Hg, and respirations 16 breaths/min. She has inspiratory rales at the lung bases. Her cardiac impulse is displaced laterally. There is a loud S_1, a single S_2, an apical opening snap, a holodiastolic rumbling murmur at the apex, and a soft diastolic blowing murmur along the left sternal border. Isometric handgrip augments the diastolic murmurs. She has mild peripheral edema. Her ECG is shown in Fig. 4.27. The most likely valve lesions are
A. Mitral regurgitation and tricuspid stenosis
B. Mitral stenosis and mitral regurgitation
C. Mitral stenosis and aortic regurgitation
D. Mitral stenosis and pulmonic regurgitation
E. Tricuspid stenosis and pulmonic regurgitation

QUESTION 523

Which of the following statements regarding the medical management of mitral stenosis (MS) is NOT correct?
A. Antibiotic prophylaxis is not recommended for patients with MS undergoing dental surgery
B. Diuretic therapy is an appropriate measure for relieving symptoms of dyspnea
C. In pure MS with normal left ventricular function, digoxin is of benefit only if atrial fibrillation is present
D. The benefits of beta blocker therapy in MS include heart rate reduction and improved exercise tolerance
E. Anticoagulation is indicated to prevent thromboembolism in patients with MS regardless of the heart rhythm or history of previous thromboembolic events

QUESTION 524

Which of the following statements regarding infectious causes of pericarditis is correct?
A. Tuberculosis is the leading cause of constrictive pericarditis in developed nations
B. *Haemophilus influenzae* is the most common organism responsible for bacterial pericarditis
C. In the contemporary era, the prognosis of patients with bacterial pericarditis is comparable to that of viral pericarditis

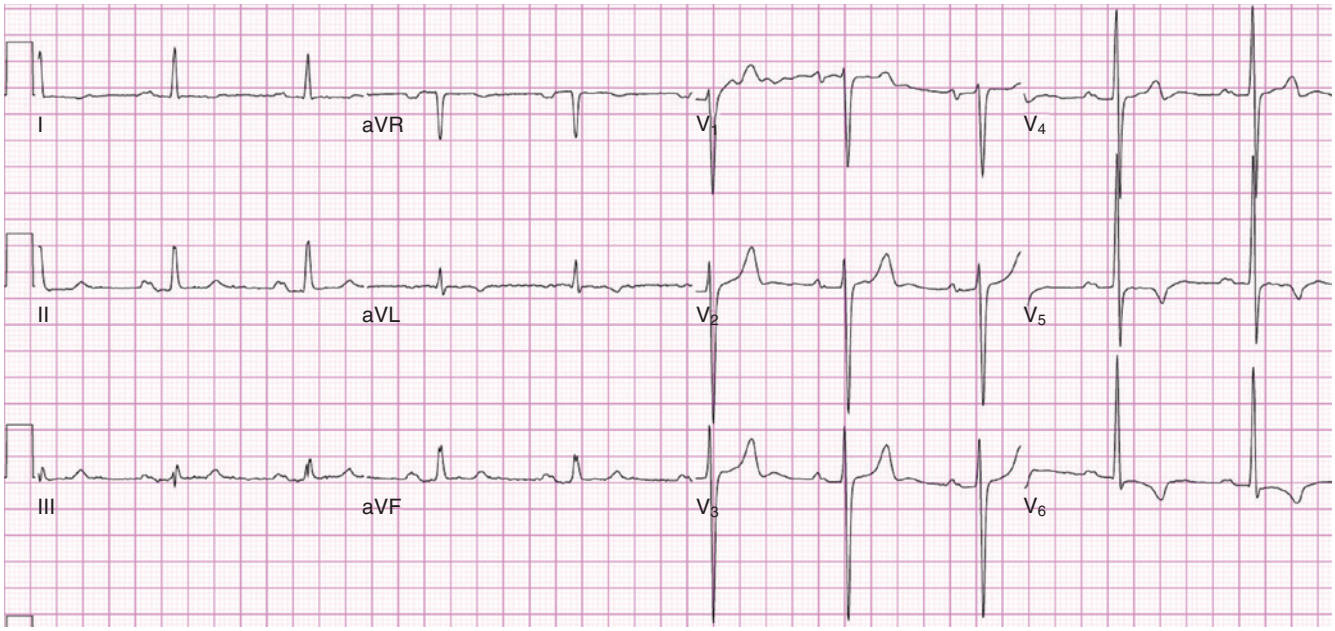

FIG. 4.27

D. Enteroviruses are among the most frequent causes of viral pericarditis
E. Prolonged antifungal therapy is required to manage isolated pericardial disease caused by *Histoplasma*

QUESTION 525

A 25-year-old graduate student presents to your office for physical examination. Several years ago, while growing up in Ecuador, he was diagnosed with Chagas disease when he had presented with fever, malaise, myalgias, and unilateral eyelid edema. Which of the following statements regarding Chagas disease is NOT correct?

A. The level of parasitemia does not correspond to the severity of chronic Chagas disease
B. The disease is transmitted to humans by the reduviid bug
C. An asymptomatic phase typically lasts for many years between initial infection and chronic manifestations of the disease
D. The most common ECG abnormality in chronic Chagas disease is left bundle branch block
E. The classic echocardiographic findings of chronic cardiac Chagas disease are those of a dilated cardiomyopathy with apical aneurysm formation

QUESTION 526

A 29-year-old woman was diagnosed with a congenital heart defect 6 years ago. At a routine office visit she describes occasional single palpitations during periods of emotional stress. An echocardiogram is obtained; the apical four-chamber view is shown in Fig. 4.28. Which of the following is demonstrated?

A. Bilateral atrial myxomas
B. Lipomatous hypertrophy of the interatrial septum
C. Normal position of an atrial septal closure device
D. Infiltrative disease, most likely amyloidosis
E. Normal echocardiogram

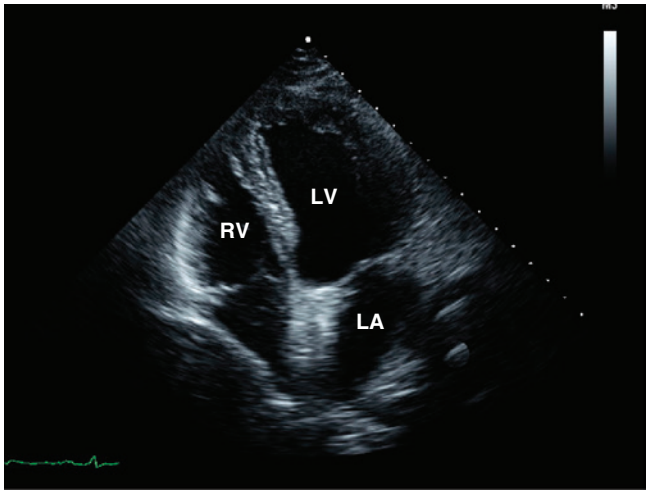

FIG. 4.28

QUESTION 527

A 42-year-old woman, originally from Thailand, presents for evaluation because of exertional dyspnea. As part of her evaluation, an echocardiographic study is performed; a parasternal long-axis view and a Doppler recording from the apical four-chamber view are displayed in Fig. 4.29. Which of the following statements is correct?

A. This abnormality results from myxomatous valvular degeneration
B. The Doppler profile in part *B* in the figure is essentially normal
C. The severity of this abnormality correlates with the likelihood of developing endocarditis
D. The risk of systemic embolism in this condition correlates with age
E. Chest pain accompanies this condition in the majority of patients

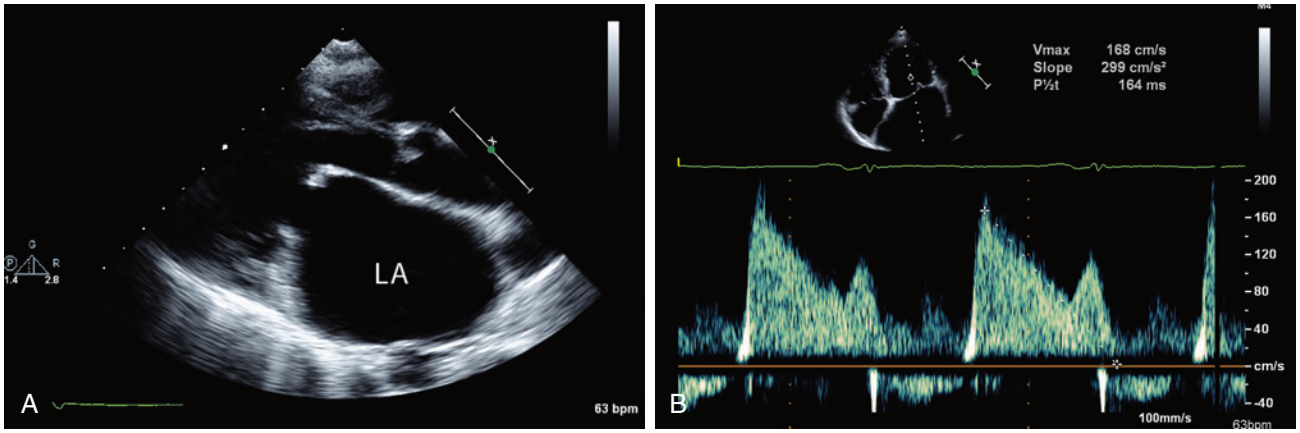

FIG. 4.29

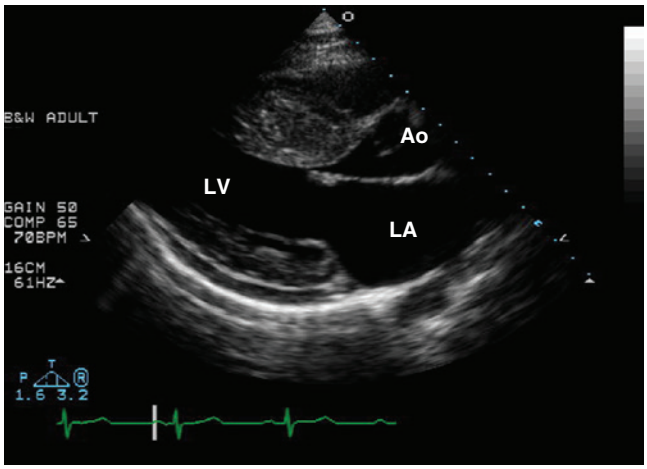

FIG. 4.30

QUESTION 528

A premature infant is found to have bounding peripheral pulses, a continuous murmur in the infraclavicular and interscapular regions, and precordial hyperactivity. An echocardiogram demonstrates a left-to-right shunt between the proximal descending aorta and the pulmonary artery. Which of the following statements about this condition is TRUE?

A. Most preterm infants with a birth weight <1500 g have this condition
B. Cardiopulmonary deterioration occurs in nearly all such infants
C. Chest radiography likely shows a decreased size of the cardiac silhouette
D. Surgical ligation is the only effective treatment
E. Noninvasive imaging typically shows right ventricular enlargement with normal left ventricular size

QUESTION 529

A 17-year-old boy has a syncopal event while playing soccer. He is noted to have a systolic ejection murmur on examination. An echocardiogram is obtained and a parasternal long-axis view is shown in Fig. 4.30. Which of the following statements about hemodynamic findings in patients with this condition is correct?

A. Diastolic function is usually impaired to a greater extent than systolic function
B. The majority of ventricular emptying is less rapid than usual
C. Left ventricular end-systolic volume is usually increased
D. Left ventricular ejection fraction is typically reduced

QUESTION 530

A 46-year-old man is admitted with fever, dyspnea, hypotension, and a new murmur of aortic regurgitation. Which of the following is typical of acute aortic regurgitation?

A. A widened systemic pulse pressure
B. A long, decrescendo diastolic murmur
C. Delayed closure of the mitral valve on echocardiography
D. Diastolic mitral regurgitation on echocardiography
E. An enlarged left ventricle

QUESTION 531

A 36-year-old woman with tetralogy of Fallot presents for routine outpatient evaluation. She had undergone surgical heart repair at age 5 months, including ventricular septal defect closure with a Dacron patch and relief of right ventricular outflow tract obstruction with a transannular patch. She denies shortness of breath or presyncope. Her electrocardiogram demonstrates normal sinus rhythm with intraventricular conducton delay (QRS duration = 190 msec). Cardiac magnetic resonance imaging reveals a low-normal left ventricular ejection fraction, severe pulmonary regurgitation, right ventricular dilatation with moderate right ventricular systolic dysfunction, and moderate tricuspid regurgitation. Cardiopulmonary exercise testing shows that her maximal oxygen consumption is 56% of the predicted value for her age and body surface area. Which of the following statements is correct?

A. She should be referred for pulmonary valve replacement
B. Her risk of sudden cardiac death is low
C. The presence of tricuspid regurgitation in this case does not influence the risk of developing atrial arrhythmias
D. She does not require antibiotic prophylaxis prior to dental procedures

QUESTION 532

A 68-year-old man presents for evaluation of progressive dyspnea. He has an extensive smoking history. Pulmonary

function testing is consistent with severe airway obstruction. An echocardiogram shows normal left ventricular systolic function, right ventricular hypertrophy and dilation, and an elevated calculated pulmonary artery systolic pressure. Which of the following therapies improves survival in patients with chronic obstructive lung disease with pulmonary hypertension?
A. Digoxin
B. Oxygen
C. Beta-adrenergic agonists
D. Theophylline
E. Bosentan

QUESTION 533

Which of the following statements regarding coarctation of the aorta is correct?
A. It is more common in females than males
B. Most infants and children with coarctation are asymptomatic
C. Ten percent of adults with coarctation also have a bicuspid aortic valve
D. Mean survival time in the presence of uncorrected coarctation is 60 years

QUESTION 534

A 30-year-old woman presented to the hospital after a recent transient neurologic event consistent with a small cerebral embolism. During her evaluation, a transthoracic echocardiogram was performed. An apical four-chamber view from the study is displayed in Fig. 4.31, with panels from both systole and diastole. Which of the following statements is TRUE?
A. The echocardiographic appearance is most consistent with an intracardiac thrombus
B. Systemic symptoms associated with this condition include fever, malaise, and an elevated erythrocyte sedimentation rate
C. Surgery is indicated only if there is hemodynamic compromise
D. The majority of such lesions are familial
E. Unlike this patient, this condition most commonly arises in the right atrium

QUESTION 535

A 54-year-old woman with chronic kidney disease presents to the emergency department because of sudden shortness of breath and right-sided pleuritic chest pain. She recently returned from vacation on a 12-hour flight. Physical examination demonstrates a tachypneic, normotensive, and tachycardic woman. The serum creatinine is chronically elevated, and precludes performing a chest computed tomographic angiogram. Which of the following results would be most useful in EXCLUDING the diagnosis of pulmonary embolism?
A. Normal PaO_2 by arterial blood gas determination
B. Normal cardiopulmonary examination
C. Intermediate probability (ventilation/perfusion) lung scan
D. Normal plasma level of D-dimer
E. Absence of right-sided heart strain or $S_1Q_3T_3$ pattern on ECG

QUESTION 536

Which of the following statements regarding primary tumors of the heart is NOT correct?
A. Benign tumors are more common than malignant tumors
B. The most common malignant cardiac tumors are angiosarcomas and rhabdomyosarcomas
C. The presence of a hemorrhagic pericardial effusion is more consistent with a malignant tumor
D. Malignant tumors are more likely to occur on the left side of the heart

QUESTION 537

A 67-year-old man with adenocarcinoma of the lung presents with dyspnea and weakness. Physical examination is notable for hypotension with pulsus paradoxus and jugular venous distention. An echocardiogram is ordered. Which of the following statements regarding echocardiography in cardiac tamponade is TRUE?
A. On inspiration, there is augmentation of transmitral flow velocities and reduction in transtricuspid flow velocities
B. The absence of right ventricular diastolic collapse ensures that the pericardial pressure is not elevated

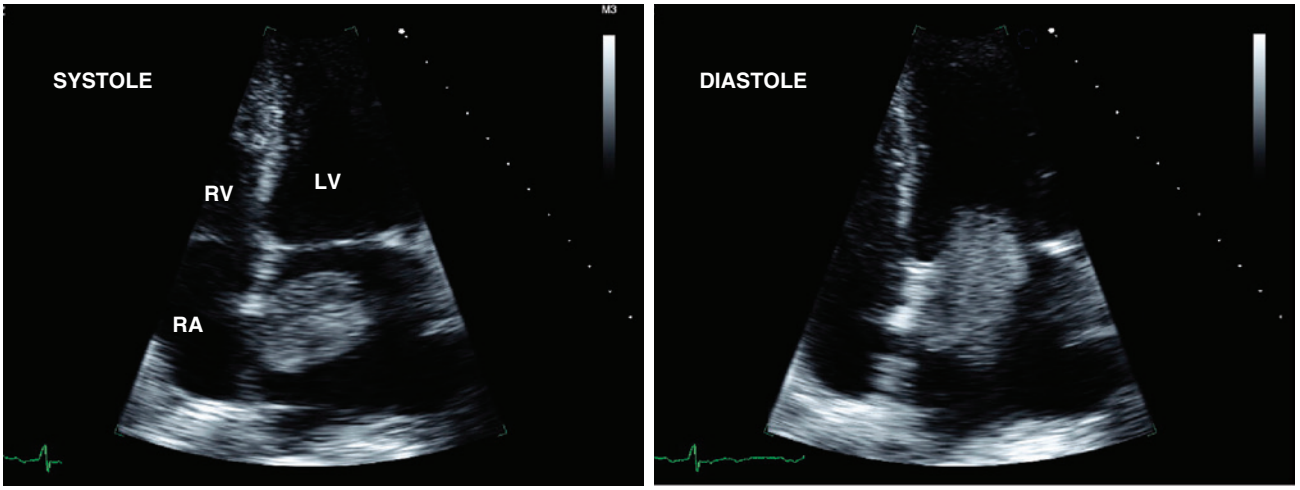

FIG. 4.31

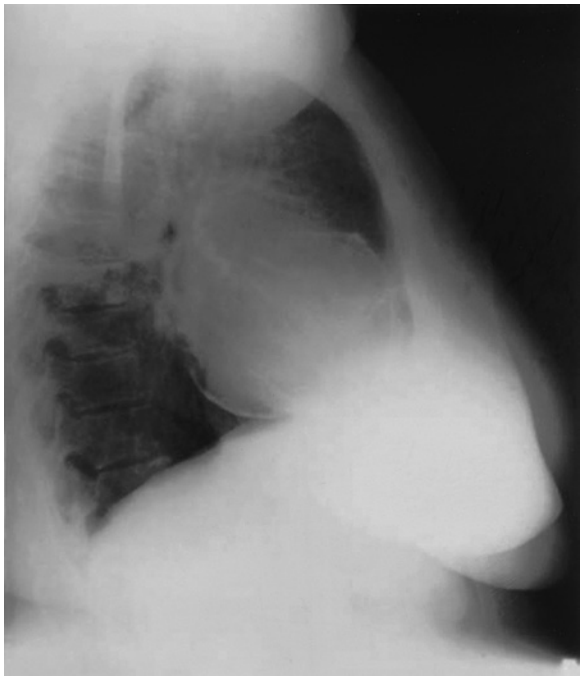

FIG. 4.32

C. Right ventricular diastolic collapse is more specific than right atrial collapse in the diagnosis of tamponade
D. Cardiac tamponade is associated with normal inferior vena cava collapse with inspiration
E. A small-volume pericardial effusion observed on echocardiography excludes the presence of tamponade

QUESTION 538

A 64-year-old woman with a remote history of chest irradiation presents with gradually progressive symptoms of fatigue, abdominal bloating, and lower extremity edema over the past 4 months. Her lateral chest radiograph is shown in Fig. 4.32. Which of the following findings would be inconsistent with the likely diagnosis?
A. Kussmaul sign
B. Hepatomegaly
C. Early diastolic pericardial knock
D. Right and left ventricular systolic pressure concordance during inspiration
E. Elevation and equalization of intracardiac diastolic pressures

QUESTION 539

Which of the following statements regarding the causes of aortic stenosis (AS) is TRUE?
A. A congenitally bicuspid valve accounts for 20% of patients requiring surgical treatment for AS in the United States
B. In patients younger than 70 years, rheumatic deformity is the most common cause of AS that leads to surgical valve replacement
C. There are no established risk factors for the development of calcific AS of a trileaflet valve other than age
D. Age-related calcification of a congenitally bicuspid, or normal trileaflet valve, is the most common cause of AS in adults in the United States
E. Isolated rheumatic deformity of the aortic valve, without mitral valve involvement, is more common than rheumatic involvement of both valves

QUESTION 540

A 68-year-old man with chronic aortic regurgitation presents for office evaluation. He describes reduced stamina, progressive symptoms of exertional dyspnea, and occasional orthopnea. His echocardiogram shows severe aortic regurgitation, a left ventricular (LV) end-systolic diameter of 48 mm, and an LV ejection fraction of 45%. Which of the following statements regarding valve replacement for chronic aortic regurgitation (AR) is NOT correct?
A. Asymptomatic patients with advanced AR who have normal LV function and end-systolic diameter <50 mm have an excellent prognosis such that surgery can be safely postponed
B. An LV end-systolic diameter >55 mm before surgical intervention portends a worse postoperative prognosis than does a smaller ventricular diameter
C. Angiotensin-converting enzyme inhibitors delay the need for aortic valve replacement in chronic AR
D. Patients with chronic AR who have symptoms of congestive heart failure accompanied by reduced LV ejection fraction should be referred for aortic valve replacement
E. A preoperative ejection fraction <50% increases the risk of postoperative death from LV dysfunction

QUESTION 541

A 44-year-old man with human immunodeficiency virus (HIV) infection and a history of non-adherence to prescribed antiretroviral therapy presents to your office for evaluation of shortness of breath. He reports 2 months of progressive fatigue and dyspnea on exertion. His CD4 count is 15 cells/mm^3 (normal = 500 to 1500 cells/mm^3). Transthoracic echocardiography reveals a dilated heart with a left ventricular (LV) ejection fraction of 15% and a small pericardial effusion. Which of the following statements is TRUE?
A. Fifty percent of HIV-infected individuals will ultimately develop symptomatic LV dysfunction
B. Large asymptomatic pericardial effusions are the most common cardiac manifestation of HIV infection, but the presence of effusion is not associated with increased mortality
C. In HIV-infected individuals, LV dysfunction has little bearing on 1-year mortality rates
D. Protease inhibitor therapy is associated with an increased risk of myocardial infarction

QUESTION 542

Which of the following statements regarding the cardiovascular consequences of Turner syndrome is NOT correct?
A. Cardiovascular defects are seen in fewer than 5% of patients
B. Coarctation of the aorta is the most commonly associated congenital cardiovascular abnormality
C. There is an increased risk of aortic dissection

D. Bicuspid aortic valve occurs at a higher frequency than in the general population
E. Partial anomalous venous drainage occurs more frequently than in the general population

QUESTION 543

A 20-year-old man with Duchenne muscular dystrophy presents for evaluation. Regarding cardiac involvement in this condition, which of the following statements is TRUE?
A. Fewer than 25% of patients with Duchenne muscular dystrophy >18 years develop a dilated cardiomyopathy
B. The ECG typically shows tall R waves with increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads
C. There is a direct association between the presence of dilated cardiomyopathy and electrocardiographic abnormalities
D. The most common rhythm disturbance is ventricular tachycardia

QUESTION 544

A 34-year-old man is receiving doxorubicin chemotherapy for lymphoma. Which of the following statements regarding the risk of doxorubicin-induced cardiotoxicity is NOT correct?
A. Previous or concurrent mediastinal irradiation increases the risk of cardiotoxicity
B. The age groups most at risk are the very young and the very old
C. Cardiomyopathy does not develop unless the total cumulative dose exceeds 700 mg/m^2
D. Concurrent use of cyclophosphamide increases the risk of cardiotoxicity
E. A baseline left ventricular ejection fraction of 45% increases the risk of cardiotoxicity

QUESTION 545

A 63-year-old man with metastatic colon cancer is prescribed therapy targeting vascular endothelial growth factor (VEGF). Which of the following statements is correct about the use of the monoclonal antibody/VEGF antagonist bevacizumab?
A. The left ventricular ejection fraction tends to increase with use of this drug
B. Hypotension is a common side effect
C. The risk of arterial, but not venous, thromboembolic events is increased
D. Hemorrhagic pericardial effusion is associated with continuous use of this agent

QUESTION 546

A 2-year-old boy with Down syndrome and a heart murmur is brought to the pediatrician's office because of poor weight gain. The most likely finding on cardiac auscultation is
A. An early diastolic opening sound at the apex followed by a diastolic rumbling murmur
B. A midsystolic murmur at the upper left sternal border and wide, fixed splitting of S_2
C. A midsystolic click followed by a late systolic murmur at the apex
D. A blowing diastolic murmur at the right upper sternal border
E. A late-peaking systolic ejection murmur heard best at the upper right sternal border with a diminished S_2

QUESTION 547

A 35-year-old man presents with complaints of exertional dyspnea. His medical history is significant for chest radiation therapy as a teenager for treatment for a hematologic malignancy. Regarding cardiovascular effects of radiation therapy, which of the following statements is correct?
A. Most complications develop within 5 years of radiation exposure
B. Constrictive pericarditis is typically an acute reaction to radiation therapy
C. The conduction system is typically spared from adverse effects of radiation
D. Dilated cardiomyopathy is the most common manifestation of mediastinal radiation therapy
E. Cancer survivors who received head and neck radiation are at a heightened risk of stroke

QUESTION 548

Which of the following statements is correct regarding familial forms of dilated cardiomyopathy (DCM)?
A. Familial forms account for less than 3% of cases of DCM
B. Most inherited forms of dilated cardiomyopathy fit an autosomal recessive pattern
C. Familial DCM most commonly results from mutations in genes that encode sarcolemmal surface receptors
D. In symptomatic patients, histologic examination of the heart typically demonstrates extensive areas of interstitial and perivascular fibrosis
E. Familial cardiomyopathy can be readily identified as the cause of DCM by specific immunologic markers

QUESTION 549

A 65-year-old man with a history of chest radiation therapy for lymphoma presents with worsening exertional dyspnea. On physical examination the heart rate is 120 beats/min, blood pressure 90/55 mm Hg, with pulsus paradoxus of 15 mm Hg. The jugular venous pressure is 10 cm H_2O with a prominent *x* descent. He is found by echocardiography to have a large pericardial effusion, which is drained by pericardiocentesis in the cardiac catheterization laboratory. After the procedure, the intrapericardial pressure normalizes but the initially elevated right atrial pressure fails to decline and displays a prominent *y* descent. This scenario is most consistent with
A. Persistence of pericardial tamponade
B. Cor pulmonale
C. Effusive-constrictive pericarditis
D. Restrictive cardiomyopathy
E. Uremic pericarditis

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely

associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 550 TO 553

For each statement below, match the appropriate lesion:
A. Osler nodes
B. Janeway lesions
C. Roth spots
D. Subungual hemorrhages
E. Bracht-Wächter bodies

550. Small (1- to 4-mm diameter), irregular, erythematous, nontender macules present on the thenar and hypothenar eminences of the hands
551. Small, raised red (or purple) tender lesions present in the pulp spaces of the terminal phalanges of the fingers
552. Collections of lymphocytes in the nerve layer of the retina
553. Linear or flame-shaped streaks

QUESTIONS 554 TO 558

For each cardiac condition, match the electrocardiographic finding that is most closely associated with it:
A. Low QRS voltage
B. Atrioventricular nodal block
C. Right bundle branch block
D. Global ST-segment elevation
E. Deeply inverted precordial T waves

554. Chronic Chagas disease
555. Sarcoidosis
556. Apical hypertrophic cardiomyopathy
557. Amyloidosis
558. Lyme carditis

QUESTIONS 559 TO 562

For each statement, match the appropriate prosthetic valve type:
A. Starr-Edwards caged-ball valve
B. Carpentier-Edwards Magna valve
C. St. Jude bileaflet valve
D. Medtronic-Hall valve

559. Single tilting disc valve
560. Lowest profile mechanical valve
561. Least thrombogenic mechanical prosthesis for the mitral position
562. Bovine pericardial valve

QUESTIONS 563 TO 566

For each description, match the related cardiac condition(s):
A. Constrictive pericarditis
B. Restrictive cardiomyopathy
C. Both
D. Neither

563. Atrial fibrillation, low QRS voltage
564. Right and left ventricular systolic pressure discordance with respiration during cardiac catheterization
565. Physical cause of abnormality often visualized by chest computed tomography
566. Reduced medial mitral annular E′ velocity by Doppler tissue imaging

QUESTIONS 567 TO 571

For each statement listed below, match the most appropriate condition:
A. Cardiac myxoma
B. Large papillary fibroelastoma
C. Both
D. Neither

567. Familial predilection
568. Risk of distal embolism
569. Surgical excision is management of choice
570. May undergo malignant transformation
571. Typically attaches to valves and subvalvular structures

QUESTIONS 572 TO 575

Match the description with the associated form of therapy for pulmonary embolism:
A. Unfractionated heparin or low-molecular-weight heparin
B. Fibrinolytic therapy
C. Both
D. Neither

572. May be effective in pulmonary embolism even 1 to 2 weeks after the onset of symptoms
573. Dissolution of recently formed thrombus is a major action
574. Should be administered along with an antiplatelet agent
575. May suppress aldosterone secretion

QUESTIONS 576 TO 580

Match each description with the associated condition:
A. Hemochromatosis
B. Amyloidosis
C. Both
D. Neither

576. May result in restrictive cardiomyopathy
577. Early-stage disease is reversible with chelating agents
578. Ventricular tachyarrhythmia is the most common initial presentation
579. Autosomal recessive inheritance may be responsible
580. Low-voltage QRS on ECG is typical

QUESTIONS 581 TO 585

Match each description with the associated condition:
A. Tricuspid stenosis
B. Pulmonic stenosis
C. Both
D. Neither

581. Usually rheumatic in origin
582. Typical of carcinoid heart disease
583. Most adults are asymptomatic
584. Ascites is common on physical examination
585. Balloon valvuloplasty is the treatment of choice

QUESTIONS 586 TO 589

Match each description with the associated drug therapy in patients with idiopathic (group 1) pulmonary arterial hypertension (PAH):
A. Calcium channel blockers
B. Epoprostenol (prostacyclin)

C. Both
D. Neither
586. Studies have shown a survival benefit in patients with PAH
587. Should be started empirically in all patients with group 1 PAH
588. Not approved for oral administration
589. Exert(s) an antithrombotic effect

QUESTIONS 590 TO 593

Match each hemodynamic scenario with the associated condition:
A. Chronic constrictive pericarditis
B. Cardiac amyloidosis
C. Both
D. Neither
590. Right ventricular (RV) pressure tracing shows a deep and rapid early decline at the onset of diastole, with a rapid rise to a plateau in early diastole ("dip and plateau" configuration)
591. Left ventricular end-diastolic pressure exceeds right ventricular end-diastolic pressure (RVEDP) by 10 mm Hg
592. Peak RV systolic pressure = 35 mm Hg, RVEDP = 18 mm Hg
593. Pulmonary artery systolic pressure = 68 mm Hg, RVEDP = 15 mm Hg

QUESTIONS 594 TO 597

Match the following descriptions with the appropriate symptom in aortic stenosis:
A. Palpitations
B. Angina
C. Syncope
D. Exertional dyspnea as a manifestation of heart failure
594. Most significant clinical marker for adverse outcome in aortic stenosis, predictive of a 1- to 2-year survival if the valve lesion is not surgically corrected
595. Associated with reduced survival in untreated aortic stenosis of 3 to 5 years
596. Associated with reduced survival in untreated aortic stenosis of 2 to 3 years
597. Not a marker of reduced survival in patients with aortic stenosis

QUESTIONS 598 TO 601

For each type of procedure below, match the appropriate prophylactic antibiotic regimen:
A. No antibiotic prophylaxis required
B. Amoxicillin, 2 g orally, taken 30 to 60 minutes before the procedure
C. Clindamycin 600 mg orally, taken 30 to 60 minutes before the procedure
D. Ampicillin, 2 g intramuscular (IM) or IV 30 to 60 minutes before the procedure
598. Elective colonoscopy in a patient with a mechanical mitral valve
599. Dental extraction in a patient with a bioprosthetic aortic valve
600. Dental extraction in penicillin-allergic patient with a mechanical aortic valve
601. Elective cholecystectomy in a patient with mitral stenosis

QUESTIONS 602 TO 606

Match the following descriptions with the appropriate condition:
A. Complete atrioventricular septal defect
B. Complete transposition (d-transposition) of the great arteries
C. Both
D. Neither
602. Presents with cyanosis
603. Right-axis deviation on the ECG
604. An interatrial communication is almost always present
605. On echocardiography, the AV valves appear abnormally aligned at the same level
606. A high-pitched, blowing, decrescendo diastolic murmur is common at the left sternal border

QUESTIONS 607 TO 611

Match the following descriptions with the appropriate condition:
A. Kartagener syndrome
B. Holt-Oram syndrome
C. LEOPARD syndrome
D. Noonan syndrome
607. Webbed neck, pulmonic stenosis, left anterior fascicular block
608. Deafness, pulmonic stenosis, complete heart block
609. Lentigines, pulmonic stenosis, PR prolongation
610. Sinusitis, dextrocardia, bronchiectasis
611. Abnormal scaphoid bone, atrial septal defect, right bundle branch block

QUESTIONS 612 TO 615

Match each photograph in Fig. 4.33 with the condition it represents:
A. Part A
B. Part B
C. Part C
D. Part D
612. Fabry disease
613. Infective endocarditis
614. Amyloidosis
615. Systemic sclerosis

QUESTIONS 616 TO 619

Match the following descriptions with the appropriate association:
A. Turner syndrome
B. Noonan syndrome
C. Both
D. Neither
616. Coarctation of the aorta
617. Normal karyotype

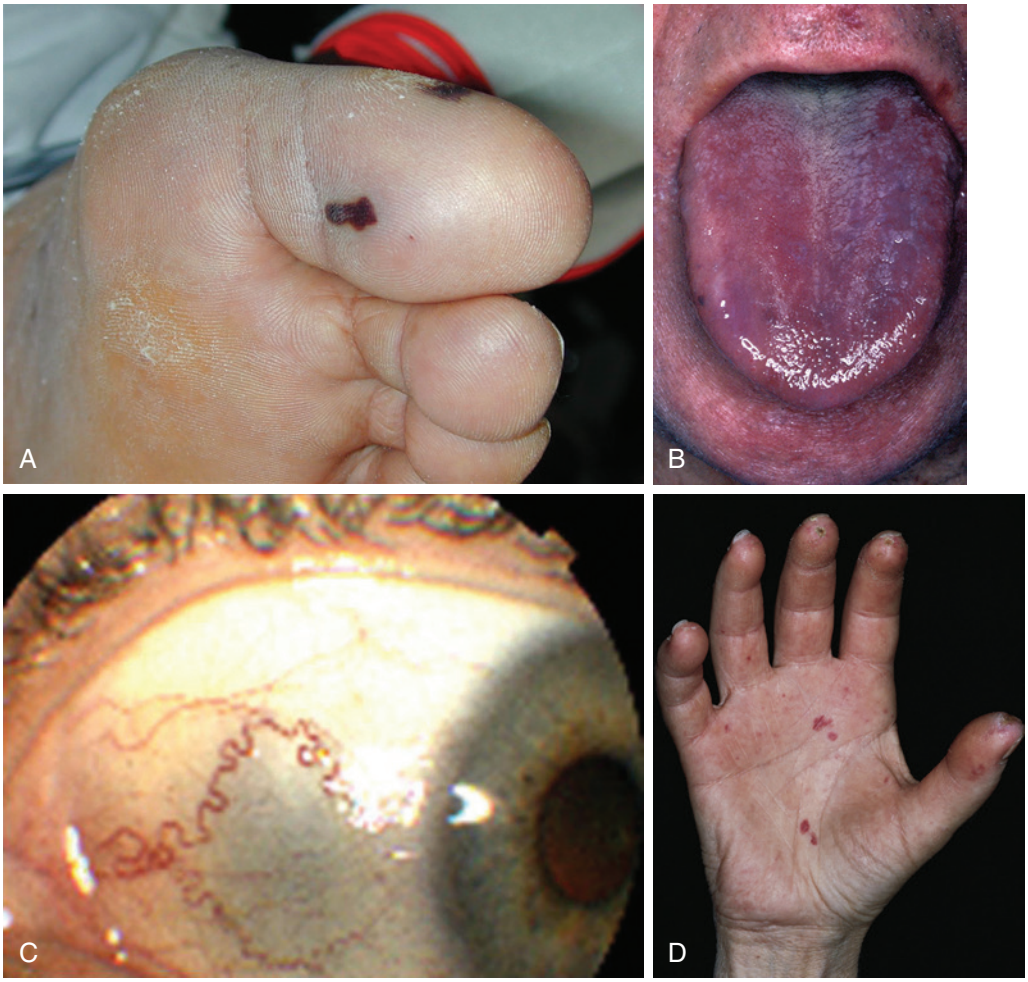

FIG. 4.33 *(A) Courtesy Alan J. Lesse, MD; (B) From duVivier A.* Atlas of Clinical Dermatology. *3rd ed. Philadelphia: Elsevier; 2002; (C) From Samiy N. Ocular features of Fabry disease: diagnosis of a treatable life-threatening disorder.* Surv Ophthalmol. *2008;53:416–423; (D) From Habif TP.* Clinical Dermatology. *5th ed. Philadelphia: Mosby Elsevier; 2009.*

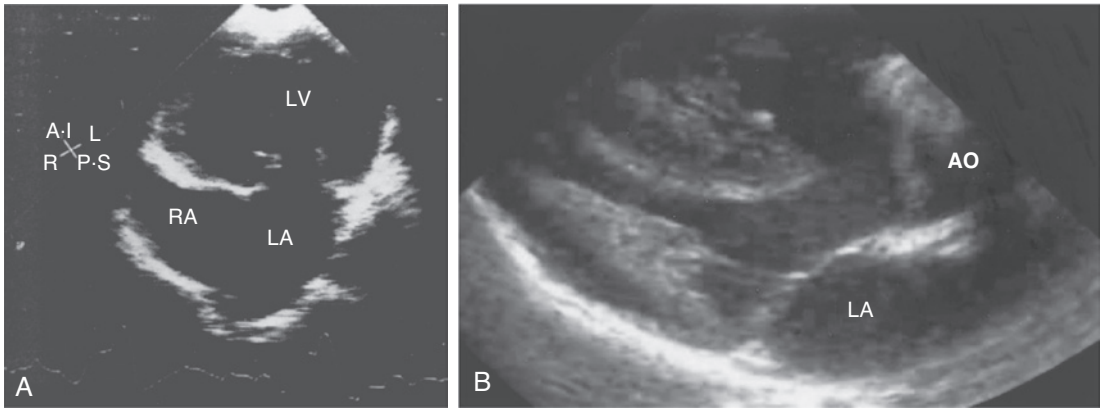

FIG. 4.34

618. Pulmonic stenosis
619. Short stature, webbing of the neck, skeletal anomalies, and renal anomalies

QUESTIONS 620 TO 624

Match the following descriptions with the appropriate part of Fig. 4.34:
A. Part A
B. Part B
C. Both
D. Neither

620. A ventricular septal defect typically accompanies this anomaly
621. d-Transposition of the great arteries is known to accompany this anomaly
622. Coronary variations in this disorder include abnormal origin of the anterior descending artery from the right coronary artery
623. Cyanosis and an electrocardiographic finding of left ventricular hypertrophy are typical
624. The Fontan procedure may be a useful intervention for this condition

QUESTIONS 625 TO 629

Match the following descriptions with the associated antineoplastic therapy:
A. Thoracic radiation therapy
B. Anthracycline therapy
C. Both
D. Neither

625. Pericarditis is the most common cardiac complication
626. Premature coronary atherosclerosis
627. Left ventricular systolic dysfunction
628. Ventricular arrhythmias
629. Aortic dissection

Section IV Answers

(CHAPTERS 67 TO 87)

Diseases of Heart Valves, Myocardium, Pericardium, and Pulmonary Vascular Bed

ANSWER TO QUESTION 436

D (Braunwald, p. 1590; Table 77.2; eFig. 77.6)

This woman presents with features of an acute coronary syndrome, but coronary angiography demonstrates no significant coronary disease. Rather, left ventricular (LV) angiography demonstrates a large region of apical akinesis and preserved contraction at the base. These features are consistent with takotsubo cardiomyopathy (also termed stress-induced cardiomyopathy or apical ballooning syndrome). This is a reversible condition that mimics acute myocardial infarction and occurs primarily in postmenopausal women, usually precipitated by a profound emotional or physical event. Regional contractile abnormalities are typical, usually causing apical akinesis with compensatory hypercontractility at the base. However, in some affected patients the akinetic or dyskinetic segment is located at the midventricle or base instead.

This syndrome is usually transient with rapid contractile recovery within days to weeks. However, early complications occur rarely, including malignant arrhythmias, thromboembolism, LV rupture, and cardiogenic shock, such that acute in-hospital mortality is 1.2%. The mechanism by which takotsubo cardiomyopathy arises is speculative; it may be a response to a catecholamine surge resulting in regional microvascular dysfunction in susceptible patients. Recurrences occur in <5% of patients. Anticoagulation is not routinely recommended, despite the frequently present apical wall motion abnormality (unless thrombus is visualized) because of the usually rapid resolution of the disorder.

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Pelliccia F, Kaski JC, Crea F, et al. Pathophysiology of takotsubo syndrome. *Circulation.* 2017;135:2426–2441.

ANSWER TO QUESTION 437

C (Braunwald, pp. 1663–1667)

The ECG demonstrates diffuse ST-segment elevations and PR-segment depressions that are most consistent with acute pericarditis.[1] ST-segment elevations in all leads except aVR develop in the majority of patients with acute pericarditis, and PR-segment depression is found in up to 80%.

Although chest pain is the most common symptom in acute pericarditis, its location and quality are variable. The pain is often positional in that it improves by sitting upright or leaning forward and is aggravated with coughing, deep inspiration, or lying supine. Fever is common, but the cardinal physical finding is a pericardial friction rub. The three components of the complete pericardial rub correspond to atrial systole, ventricular systole, and the early filling phase of ventricular diastole.

Cardiac serum biomarkers can be elevated in acute pericarditis because of inflammation of the adjacent myocardium. As a result, an initial determination of markers such as cardiac troponin I cannot reliably differentiate between acute pericarditis and myocardial infarction.[2]

Fibrinolytic therapy is of potential harm if administered to a patient with acute pericarditis, because hemorrhagic tamponade could follow. Initial therapy for patients with acute viral or idiopathic pericarditis should include aspirin or other nonsteroidal anti-inflammatory drugs. Randomized prospective clinical trials show that colchicine reduces the duration of acute symptomatology and recurrences of pericarditis.[3] For truly refractory symptoms, glucocorticoids may be beneficial, but should not be prescribed as initial therapy, as such use is associated with increased recurrence rates of pericarditis. Nitrates have no role in the management of pericardial symptoms.

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2. Imazio M, Demichelis B, Cecchi E, et al. Cardiac troponin I in acute pericarditis. *J Am Coll Cardiol.* 2003;42:2144.
3. Lilly LS. Treatment of acute and recurrent idiopathic pericarditis. *Circulation.* 2013;127:1723–1726.

ANSWER TO QUESTION 438

A (Braunwald, pp. 1559–1561)

Localized coarctation of the aorta consists of a shelf in the posterolateral aortic wall opposite the ductus arteriosus. It is more common in males and there is a high degree of association with bicuspid aortic valve and Turner

syndrome. Other associated congenital cardiac malformations include patent ductus arteriosus, ventricular septal defect, and mitral valve abnormalities. Young patients with coarctation are usually asymptomatic. In older children or adults, symptoms may include headache, leg fatigue, and intermittent claudication. Patients may also come to medical attention because of symptoms associated with left ventricular failure, infective endarteritis, or aortic rupture or dissection.

Simultaneous palpation of the upper and lower extremities in patients with coarctation often reveals diminished and delayed femoral pulses compared with the radial pulse. Exercise typically accentuates this finding. A midsystolic murmur over the chest and back is often present. In addition, auscultation may demonstrate the ejection click and systolic murmur of a coexistent bicuspid aortic valve.

Persistent systemic hypertension after repair of the coarctation occurs in up to one-third of patients, even in the absence of recoarctation. Risk factors include older age at repair and higher blood pressure at the time of repair.[1,2]

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2. Vohra HA, Adamson L, Haw MP. Does surgical correction of coarctation of the aorta in adults reduce established hypertension. *Interact Cardiovasc Thorac Surg.* 2009;8:127.

ANSWER TO QUESTION 439

C (Braunwald, pp. 1389–1399)

The Doppler recording displays a symmetric systolic profile with an elevated transaortic valve systolic velocity of 4 m/s, which corresponds to a peak instantaneous systolic gradient of 64 mm Hg (from the simplified Bernoulli equation: Pressure gradient = 4 × velocity^2). This patient thus presents with symptomatic aortic stenosis (AS). Angina pectoris, syncope, and heart failure are the cardinal symptoms of this condition.[1] The onset of symptoms in patients with AS is an ominous sign: natural history survival trends show that the time of death following symptom occurrence is approximately 5 years for patients with angina, 3 years for those with syncope, and 2 years for patients with heart failure. Angina is present in approximately two-thirds of patients with critical AS. It arises in the absence of significant coronary artery obstruction in up to half of patients, owing to both increased oxygen demand and impaired coronary vasodilatory reserve with microcirculatory dysfunction.[2] Whereas the most common early symptom in patients with AS is a decrease in exercise tolerance or dyspnea on exertion (due to left ventricular diastolic dysfunction or the limited ability to increase cardiac output with exercise), symptoms of advanced heart failure (orthopnea, paroxysmal nocturnal dyspnea, and pulmonary edema) occur late in the course.

Syncope in AS typically occurs with exertion and is due to systemic vasodilatation with reduced vascular tone in the setting of a fixed cardiac output.

An association between calcific aortic stenosis and gastrointestinal hemorrhage, particularly due to angiodysplasia, has been observed (termed the Heyde syndrome).[3] Associated bleeding is thought to arise because of shear stress-induced platelet aggregation by the stenotic valve with reduction of high-molecular-weight multimers of von Willebrand factor and an increased number of proteolytic fragments. This abnormality is correctable by aortic valve replacement.

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2. Rajappan K, Rimoldi OE, Dutka DP, et al. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation.* 2002;105:470.
3. Loscalzo J. From clinical observation to mechanism: Heyde's syndrome. *N Engl J Med.* 2012;367:1954.

ANSWER TO QUESTION 440

B (Braunwald, pp. 1634–1636)

Cocaine is the most commonly used illicit drug among patients presenting to emergency departments, and associated cardiovascular consequences include ischemia and infarction, myocardial diastolic and/or systolic dysfunction, and arrhythmias.[1,2] The mechanisms of myocardial ischemia and infarction include (1) increased myocardial oxygen demand in the setting of limited oxygen supply, (2) intense coronary arterial vasoconstriction,[3] and/or (3) enhanced platelet aggregation and thrombogenicity. In addition, the vascular injury caused by cocaine may lead to increased endothelial permeability and accelerated atherogenesis. Cocaine use increases the risk of myocardial infarction (MI) 24-fold over the following 60 minutes in individuals otherwise at low risk for MI. Notably, the occurrence of myocardial infarction after cocaine is not associated with the amount ingested, route of administration, or frequency of use.

Mechanisms of myocardial dysfunction after long-term cocaine use include (1) myocardial ischemia or infarction, (2) cardiomyopathy due to repeated sympathetic stimulation, and (3) altered myocardial and endothelial cytokine production. Myocardial dysfunction can also occur acutely after cocaine use, likely reflecting drug-associated metabolic disturbances or direct toxic effects of the drug.

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3. Gurudevan SV, Nelson MD, Rader F, et al. Cocaine-induced vasoconstriction in the human coronary microcirculation: new evidence from myocardial contrast echocardiography. *Circulation.* 2013;12:598.

ANSWER TO QUESTION 441

D (Braunwald, pp. 1535–1537)

The common anatomic types of atrial septal defect (ASD) include the sinus venosus or "high" ASD, the ostium secundum ASD, and the ostium primum ASD. The sinus venosus defect is often accompanied by anomalous pulmonary venous return. The ostium secundum type of ASD, which appears in the mid-interatrial septum, should be distinguished from patent foramen ovale, which occurs in up to 25% of adults.

Ostium primum ASDs are a type of atrioventricular septal defect, discussed in a subsequent question.

Patients with ASDs are usually asymptomatic in early life, and only rare children with this disorder experience exertional dyspnea and easy fatigability. Atrial arrhythmias are uncommon. Children with ASDs do tend to be underdeveloped physically and prone to respiratory tract infections. The diagnosis of ASD in the young is most often prompted by detection of a heart murmur on routine physical examination. In adults, the most common manifesting symptoms are exercise intolerance and palpitations.

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ANSWER TO QUESTION 442

B (Braunwald, p. 1528)

The ECG is helpful in the assessment of congenital heart disease. In particular, evaluation for right-axis deviation and right ventricular hypertrophy, and rhythm and conduction disturbances, is important. For example, right ventricular hypertrophy may be a sign of pulmonary hypertension or right ventricular outflow tract obstruction or other disorders causing right-sided pressure or volume overload, including septal defects.

Atrial arrhythmias commonly accompany congenital heart disease. Atrial flutter is much more frequent in young patients than atrial fibrillation. It often arises in patients with a history of surgical repair and can be challenging to treat. Pharmacologic agents are generally ineffective, and catheter ablation is usually necessary; recurrence is common. Conduction disturbances, such as first-degree atrioventricular (AV) block, are often evident in patients with AV septal defects, congenitally corrected transposition of the great arteries, and Ebstein anomaly.

The electrocardiographic findings of myocardial infarction in an infant suggest the presence of an anomalous origin of a coronary artery. Left ventricular volume overload due to aortic or mitral regurgitation can result in deep Q waves in the left precordial leads.

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Mondésert B, Abadir S, Khairy P. Arrhythmias in adult congenital heart disease: the year in review. *Curr Opin Cardiol*. 2014;28:8354.

ANSWER TO QUESTION 443

D (Braunwald, pp. 1541–1542)

Ventricular septal defects (VSDs) may be classified by their locations and margins. Muscular VSDs are bordered entirely by myocardium and may be found in the trabecular septum, inlet septum, or outlet septum. Membranous VSDs are bordered in part by fibrous continuity between an atrioventricular valve and an arterial valve. Doubly committed subarterial VSDs, which are more common in Asian and South American patients, are situated in the outlet septum and bordered by fibrous continuity of the aortic and pulmonary valves.

The size of a VSD relates to the consequent pathophysiology and potential complications. A restrictive VSD is small (Q_p/Q_s <1.4) and thus produces a significant pressure gradient between the left and right ventricles. It typically does not cause hemodynamic impairment and may eventually spontaneously close, but the turbulence of the high-pressure jet across the defect presents a high risk of endocarditis. Because of the high gradient, infants with a restrictive VSD demonstrate a loud murmur and often present at an early age. Conversely, infants with large nonrestrictive defects present at a later age because the equalization of pressures across the defect attenuates the systolic murmur. A large, nonrestrictive VSD (Q_p/Q_s >2.2) is accompanied by a substantial left-to-right shunt, with subsequent development of an elevated pulmonary artery systolic pressure. Such patients may eventually develop left ventricular volume overload, heart failure, and Eisenmenger syndrome (related to the progressive rise in pulmonary artery pressure). Closure of the defect, either surgically or by transcatheter device placement, is the treatment of choice for those with a significant VSD in the absence of contraindications (e.g., irreversible pulmonary hypertension). After repair, the ECG is usually notable for right bundle branch block.

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ANSWER TO QUESTION 444

A (Braunwald, pp. 1535–1537)

Although atrial septal defects (ASDs) are frequently asymptomatic, children may experience exertional dyspnea or frequent chest infections. Physical examination usually demonstrates wide fixed splitting of the second heart sound. Other common findings include a systolic murmur of increased flow across the pulmonic valve or a mid-diastolic rumble due to increased flow through the tricuspid valve. The ECG may be helpful in determining the type of ASD. Secundum ASD patients often exhibit right-axis deviation on the ECG, whereas those with primum ASD characteristically exhibit left-axis deviation. Patients with sinus venosus ASD exhibit left-axis deviation of the P wave.

ASD repair is advised for patients with a Q_p/Q_s ≥1.5, particularly if the anatomy is suitable for percutaneous transcatheter device closure. Repair improves New York Heart Association functional class in symptomatic patients. For adults who are asymptomatic or mildly symptomatic, device closure improves exercise capacity.[1–3] In patients who undergo successful repair of an isolated secundum defect (by surgery or by transcatheter device), lifelong endocarditis prophylaxis is not required. Prophylaxis *is* appropriate for the first 6 months after device closure, while the device endothelializes.

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ANSWER TO QUESTION 445

E (Braunwald, p. 1869)

The echocardiogram demonstrates a pedunculated mass in the right atrium that is most suggestive of an atrial myxoma. Features that suggest myxoma include (1) attachment of the mass to the interatrial septum (the most common site of attachment is in the region of the fossa ovalis) and (2) a mass that is pedunculated and heterogeneous in appearance. Other cardiac tumors, including lipomas and rhabdomyomas, would be within the differential diagnosis. However, these other tumors are rarely pedunculated and more often infiltrate into the myocardium itself. The echocardiographic appearance would also prompt consideration of an intracardiac thrombus. However, atrial thrombi tend to be located in the posterior portion of the atrium and have more of a layered appearance than the heterogeneous mottling apparent in this example.

Atrial myxoma is the most common primary tumor of the heart, and >80% of such tumors arise in the left atrium. The clinical presentation of a myxoma is related to intracardiac obstruction, embolization, and/or constitutional symptoms. Nearly 70% of patients with left atrial myxomas have cardiac symptoms, typically related to obstructive heart failure and syncope. Embolic events occur in approximately 30% of patients, with left atrial myxomas causing strokes and transient ischemic attacks and right atrial myxomas leading to pulmonary emboli. Myxomas may secrete interleukin-6, an inflammatory cytokine associated with systemic symptoms such as fever, malaise, and weight loss. Surgical resection of myxomas is warranted to relieve systemic or intracardiac obstructive symptoms and to prevent embolic complications.

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ANSWER TO QUESTION 446

B (Braunwald, pp. 1483–1502)

Prosthetic valve endocarditis (PVE) may occur "early," within the first 60 days after placement of the valve, or "late," in subsequent months or years. While this distinction is somewhat arbitrary, differences in both the clinical features and microbial patterns have been documented. Cases of early PVE usually are due to contamination in the immediate operative or perioperative setting. *Staphylococcus aureus* is the most common organism isolated in this group, occurring in ~35% of cases, of which one-quarter are methicillin resistant. Coagulase negative staphylococci account for ~28% of early PVE cases.

In late cases, as in this question, the source of infection is often difficult to identify but is presumed to be seeding of the valve by transient bacteremia. Staphylococci are also the most common organisms responsible for late PVE, but less so than for early PVE (~20% of late PVE results from coagulase negative staphylococci, and ~19% from *S. aureus*). Enterococci (~13%) and *Streptococcus viridans* (~11%) are less frequent causes of late PVE.

The transesophageal echocardiographic image displayed demonstrates that the mitral valve prosthesis is well seated in the appropriate position. The prominent vegetations seen on the atrial side of the valve are well delineated and provide an example of the increased sensitivity of this form of echocardiography compared with transthoracic studies (as described in a subsequent answer).

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ANSWER TO QUESTION 447

C (Braunwald, pp. 1398–1399, 1464–1466)

This patient with severe symptomatic aortic stenosis (AS) requires aortic valve replacement (AVR), but is at high risk for an open surgical procedure. Per American Heart Association/American College of Cardiology Valvular Guidelines, transcatheter aortic valve replacement (TAVR) is a class I indication for patients who warrant AVR, but who have a prohibitive risk for surgery and who otherwise have a predicted survival >12 months. TAVR also has a class I indication as an alternative to surgical AVR (sAVR) for patients at high surgical risk (e.g., Society of Thoracic Surgeons [STS] predicted risk of mortality ≥8%), as is this patient's circumstance.[1] Most recently, TAVR has been shown to be a reasonable alternative to sAVR (class IIa indication) for patients with symptomatic severe AS and an intermediate surgical risk (STS score 4% to 8%).[1] Approved transcatheter valves in the United States include balloon-expandable (e.g., Edwards SAPIEN) and self-expanding devices (e.g., Medtronic CoreValve).

The PARTNER randomized, prospective trial evaluated TAVR in patients with severe aortic stenosis who were either inoperable (Cohort B) or were at high risk for surgical AVR (Cohort A), using the first-generation transcatheter Edwards SAPIEN valve. In the patients who were considered inoperable, the outcome of TAVR was greatly superior to continued medical therapy, with absolute reductions in mortality of 20% at 1 year, 24% at 2 years, and 21.8% at 5 years.[2] Complications of TAVR in this cohort included an increased stroke rate at 30 days, and iliofemoral vascular complications associated with sheath placement and instrumentation. In patients who were candidates for surgical AVR but at high risk (Cohort A of the trial), TAVR was noninferior to surgical valve replacement, with similar mortality rates at 1, 2, and 5 years of follow-up.[3] Stroke and vascular complications were again more frequent with TAVR, but bleeding occurred more often with surgical AVR. As a result of the stroke risk with TAVR, cerebral protection devices have been devised to capture emboli during the procedure and continue to undergo study.[4]

Two randomized trials have compared TAVR (one trial with balloon-expandable valves, the other with self-expanding valves) with sAVR in patients at intermediate surgical risk.[5,6] Both trials showed noninferiority of TAVR compared to sAVR for the combined endpoint of death or stroke at 2 years.

Conduction abnormalities, including complete heart block requiring permanent pacemaker placement, may complicate TAVR because of device impingement on the LV outflow tract and underlying conduction tissue. The risk ranges from

10% to 30%, with recent studies showing a trend toward the lower end of this range.[7]

Paravalvular leaks may occur following TAVR because of poor sealing or alignment of the prosthesis. Even mild-to-moderate leaks are associated with reduced late survival.[8] Incremental design improvements in newer transcatheter valves have reduced this complication.

Since the long-term durability of TAVR prosthetic valves remains unknown, surgical AVR remains the procedure of choice for younger patients at low or intermediate risk for surgery.

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ANSWER TO QUESTION 448

E (Braunwald, pp. 1867–1874)

Primary tumors of the heart are rare—autopsy series indicate a prevalence of 0.001% to 0.03%. Metastatic tumors to the heart are far more common. Approximately three-fourths of primary cardiac tumors are benign. The most common benign primary cardiac tumor in children is rhabdomyoma, and 80% of such tumors appear before the age of 1 year. Rhabdomyomas typically arise in the left ventricle. The majority of such patients have a history (or family history) or tuberous sclerosis.

The most common malignant cardiac tumor in children is rhabdomyosarcoma. In adults, the most common benign primary cardiac tumor is the atrial myxoma. Lipomas and papillary fibroelastomas are the next most common benign primary tumors. The most frequent malignant primary tumor of the heart in adults is angiosarcoma, accounting for 30% to 37% of cases.

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ANSWER TO QUESTION 449

D (Braunwald, p. 1597)

The patient described has the clinical signs and findings of type II glycogen storage disease.[1] This disease is a consequence of the deficiency of alpha-1,4-glucosidase (acid maltase), a lysosomal enzyme that hydrolyzes glycogen into glucose. The condition commonly manifests in the neonatal period. Characteristic symptoms include failure to thrive, progressive hypotonia, lethargy, and a weak cry. Of all the glycogen storage diseases, type II (Pompe disease) is the most likely to cause cardiac symptoms. The ECG shows tall, broad QRS complexes with a short PR interval (commonly <0.09 second). The chest radiograph frequently shows cardiomegaly with pulmonary vascular redistribution. The diagnosis is confirmed by demonstrating the enzymatic deficiency in lymphocytes, skeletal muscle, or liver. The myocardial biopsy (Fig. 4.35B) shows prominent vacuoles within the myocardial

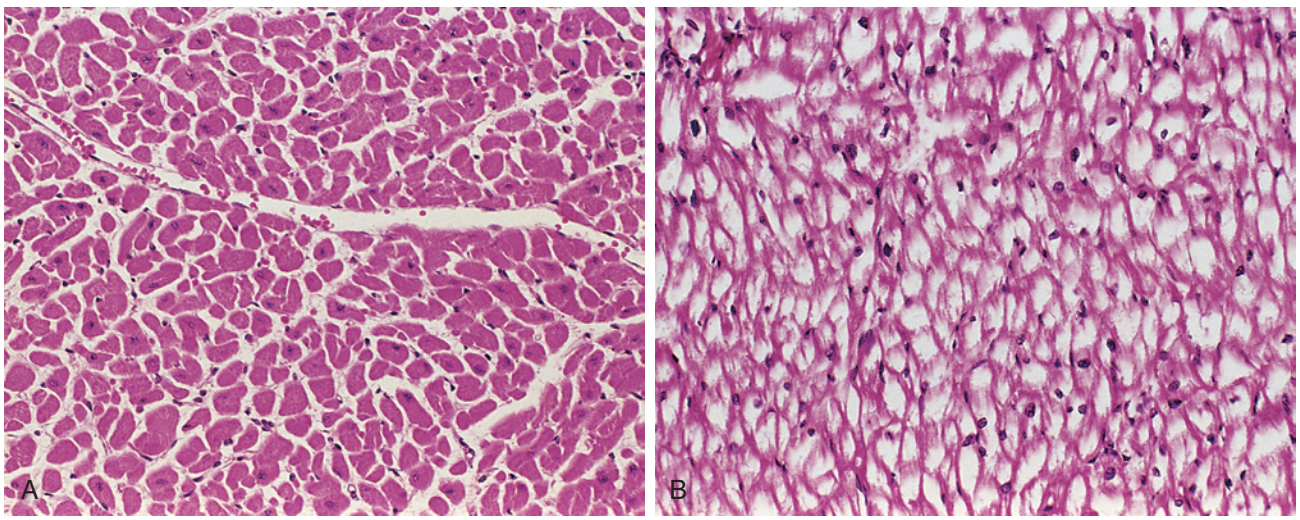

FIG. 4.35 *From Cotran RS, Kumar V, Collins T.* Robbins Pathologic Basis of Disease. *5th ed. Philadelphia: WB Saunders; 1999.*

fibers, which contain glycogen. Normal myocardial histology is shown in Fig. 4.35A for comparison.

Cardiac glycogenosis may be confused with other entities that cause cardiac failure, particularly in association with cardiomegaly in the early months of life. Endocardial fibroelastosis, a disease of unknown etiology, differs from Pompe disease in lacking the short PR interval and the fact that symptoms are limited to the cardiac system, whereas in Pompe disease skeletal muscle hypotonia is prominent. Furthermore, in endocardial fibroelastosis, mitral regurgitation and abnormalities of the cardiac valves, especially mitral and aortic, are frequent. Coarctation of the aorta, another cause of congestive heart failure in infants, can readily be distinguished by the presence of pulse and blood pressure discrepancies between the upper and lower extremities. Myocarditis, yet another cause of congestive heart failure, is usually of abrupt onset and is not associated with hypotonia. Anomalous pulmonary origin of the left coronary artery can cause cardiomegaly but usually has a distinctive electrocardiographic pattern of anterolateral myocardial infarction.

Shone syndrome is a developmental complex that consists of four obstructive anomalies: (1) a supravalvular ring of the left atrium; (2) a parachute mitral valve; (3) subaortic stenosis; and (4) coarctation of the aorta. It typically manifests with findings of mitral stenosis, because flow from the left atrium must pass through the abnormal intrachordal spaces of the mitral valve, which poses functional obstruction. Pulmonary venous hypertension is a common finding in this condition because of left ventricular inflow and outflow obstruction. Shone syndrome manifests more often in early childhood than in infancy and lacks the skeletal muscle changes of Pompe disease.

Friedreich ataxia is a hereditary autosomal recessive disease that manifests during late childhood with progressive ataxia. The limbs, in addition to being ataxic, generally show considerable weakness. About 50% of patients with Friedreich ataxia have cardiac involvement, typically hypertrophic cardiomyopathy.

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ANSWER TO QUESTION 450

C (Braunwald, pp. 1667–1672)

Cardiac tamponade occurs when the accumulation of pericardial fluid causes significant cardiac chamber compression. It is characterized by an increase in intrapericardial pressure and impedance to diastolic filling of the ventricles, with a consequent fall in cardiac output. Normal intrapericardial pressure is several millimeters of mercury lower than right ventricular (RV) and left ventricular (LV) diastolic pressures. As fluid accumulates in the pericardial space, intrapericardial pressure rises to, or exceeds, the level of right atrial (RA) and RV diastolic pressures and tamponade physiology ensues.

As intrapericardial and RV diastolic pressures rise toward the level of LV diastolic pressure, all three pressures equalize, leading to a marked decrease in transmural distending pressures, decreased filling, and to a fall in stroke volume. Cardiac output and blood pressure in this setting may initially be maintained by reflex tachycardia and increased vascular tone. However, as pericardial fluid further accumulates, compensatory mechanisms cannot maintain cardiac output and blood pressure falls. Whereas tachycardia is the usual response to falling stroke volume, bradycardia can be seen in severe tamponade. Both the cardiac depressor branches of the vagus nerve and sinoatrial node ischemia are believed to contribute to this phenomenon.

Normal inspiration causes increased right-sided cardiac filling and shifting of the interventricular septum toward the left, accompanied by reduced LV filling as a manifestation of ventricular interdependence. This effect is enhanced in tamponade since the ventricles are compressed and share a reduced total volume. Such proportionally greater *reductions* in LV filling and stroke volume with inspiration contribute to pulsus paradoxus.

Echocardiographic features of tamponade include RA inversion and RV diastolic collapse. In the presence of concurrent pulmonary hypertension, the elevated right-sided pressures blunt the effect of right-sided chamber compression.

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ANSWER TO QUESTION 451

B (Braunwald, pp. 1447–1450)

This woman presents with physical findings and symptoms of tricuspid regurgitation (TR). By history, the course of her illness is relatively rapid and includes systemic symptoms of fatigue, weight loss, and episodes of rapid heartbeat, flushing, and diarrhea. The most likely diagnosis is carcinoid syndrome. Carcinoid is a slowly growing neuroendocrine malignancy that leads to focal or diffuse deposits of fibrous tissue in the endocardium of the valvular cusps and cardiac chambers. The white fibrous carcinoid plaques are most extensive on the right side of the heart because vasoactive substances are released from hepatic metastases and drain through the inferior vena cava into the right atrium. This results in endocardial damage and fibrosis and causes the cusps of the tricuspid valve to adhere to the underlying right ventricle, producing TR (often accompanied by pulmonic valve disease on a similar basis, as described in a later question). Carcinoid syndrome is suggested by the coexistence of TR with flushing and diarrhea, which result from the release of vasoactive amines by the tumor cells.

Other causes of isolated TR may be divided into those involving an anatomically abnormal valve (*primary* TR) and those with an anatomically normal valve (*functional* TR). The latter, in which TR is due to dilatation of the right ventricle and tricuspid annulus, is more common. The most frequent cause of functional TR is right ventricular (RV) hypertension, especially as a result of mitral valve disease, congenital heart disease, pulmonary hypertension, or cor pulmonale. RV infarction may also cause functional TR.

Certain disease processes may affect the tricuspid valve directly, leading to primary TR. Among these are (1) congenital abnormalities of the tricuspid valve (e.g., Ebstein anomaly or an atrioventricular canal defect); (2) rheumatic tricuspid valve disease (which is much less common than rheumatic mitral or aortic disease); (3) connective tissue

disorders, including myxomatous redundancy of the leaflets; and (4) infective endocarditis. Other even less common causes include endomyocardial fibroelastosis, trauma, cardiac tumors (particularly right atrial myxomas), transvenous pacemaker leads, repeated endomyocardial biopsies in a transplanted heart, or exposure to certain drugs, such as methysergide or the appetite suppressant dexfenfluramine.

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ANSWER TO QUESTION 452

B (Braunwald, pp. 1483–1502)

This patient has right-sided endocarditis in the setting of illicit IV drug use. The echocardiographic image shows a large vegetation on the atrial surface of the septal leaflet of the tricuspid valve (*arrow* in Fig. 4.36). Injection drug users with endocarditis most frequently demonstrate right-sided valvular involvement (the tricuspid valve in 46% to 78%), with less common involvement of the left-sided valves (mitral valve involvement in 24% to 32% and aortic valve involvement in 8% to 19%); however, the latter group displays greater mortality. *Staphylococcus aureus* infections account for more than 50% of IV drug user endocarditis (and 60% to 70% of those with tricuspid valve involvement), with the remainder caused by streptococcal species, gram-negative bacilli, and fungi. Pulmonary findings are frequent in those with right-sided endocarditis, with 65% to 75% displaying evidence of septic pulmonary emboli on chest radiograph. Other pulmonary complications include pulmonary infarction, abscess formation, and empyema. Serious cardiac complications include destruction of the tricuspid valve apparatus, with consequent severe regurgitation and right-sided heart failure.

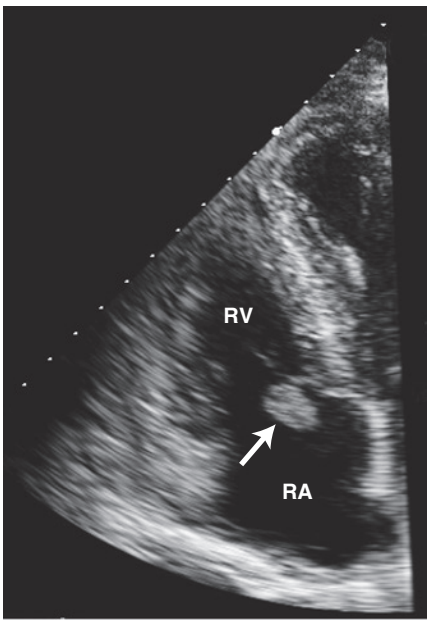

FIG. 4.36

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ANSWER TO QUESTION 453

C (Braunwald, pp. 1524–1526)

The patient has Eisenmenger syndrome, with currently exacerbated right-to-left shunting due to decreased systemic vascular resistance (SVR) after starting alpha-blocker (tamsulosin) therapy. Thus, initial treatment should include augmenting the SVR (e.g., using the alpha agonist phenylephrine) and discontinuing the alpha blocker.

Eisenmenger syndrome is characterized by irreversibly increased pulmonary vascular resistance with reversal of chronic left-to-right shunting to a bidirectional, or right-to-left, shunt direction, resulting in cyanosis. Shunts that may progress to Eisenmenger physiology include atrial septal defects, ventricular septal defects, patent ductus arteriosus, atrioventricular canal defects, and univentricular hearts. Such patients may survive into adulthood when the most common causes of mortality are sudden cardiac death, congestive heart failure, and pulmonary hemorrhage. The degree of right-to-left shunting in patients with Eisenmenger physiology is highly dependent on the SVR. For example, a decline in SVR (as a result of sepsis, hypovolemia, adrenal insufficiency, anesthesia, or vasodilators), as in this case, augments the right-to-left shunt and further reduces systemic oxygen saturation.

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ANSWER TO QUESTION 454

E (Braunwald, p. 1677)

The introduction of highly active antiretroviral therapy (HAART) greatly reduced the incidence of cardiac manifestations in patients with human immunodeficiency virus (HIV) infection. In a recent cohort trial of HIV patients, most of whom received HAART, pericardial effusion was present in <1%. Conversely, in the setting of untreated HIV infection, pericardial effusions are common. Such effusions tend to be small, rarely cause symptoms, and may spontaneously resolve without specific intervention. While cardiac tamponade rarely results, such effusions tend to occur in patients with lower CD4 counts and more advanced HIV disease and have been shown to be a marker for increased mortality.

The causes of pericardial effusions in HIV infection include opportunistic infections and malignancy (e.g., Kaposi sarcoma or lymphoma); however, a definite etiology is often not found. In some cases, the development of effusions (pericardial and pleural) may occur as a result of a capillary leak phenomenon induced by elevated cytokine levels in patients with advanced HIV disease. Tuberculosis

is the most common cause of pericardial effusion in African HIV patients.

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ANSWER TO QUESTION 455

B (Braunwald, pp. 1535–1537; see also Answer to Question 444)

Common findings on physical examination of patients with an atrial septal defect (ASD) include a prominent right ventricular (RV) impulse, palpable pulmonary artery pulsations, accentuation of the tricuspid valve closure sound, and a midsystolic ejection murmur due to increased flow across the pulmonic valve. If the shunt is large, a mid-diastolic rumbling murmur may be audible at the lower left sternal border. This murmur results from increased blood flow across the tricuspid valve.

The ECG may be helpful in the diagnostic evaluation of a patient with suspected ASD. In the common ostium secundum ASD, the tracing may show right-axis deviation and an rSR′ or rsR′ pattern in the right precordial leads with a normal QRS complex duration. The presence of negative P waves in the inferior leads (indicating a low atrial pacemaker) suggests the presence of a sinus venosus-type ASD. *Left*-axis deviation and superior orientation of the QRS complex in the frontal plane is consistent with an ostium primum defect. Tall R or R′ waves in V_1 may indicate the presence of pulmonary hypertension and concomitant RV hypertrophy.

The chest radiograph may reveal enlargement of the right atrium and right ventricle, pulmonary arterial dilatation, and increased pulmonary vascular markings. Echocardiographic evaluation of ASD may show pulmonary arterial and RV dilatation and paradoxical intraventricular septal motion if RV volume overload is present. The defect itself may be visualized by two-dimensional echocardiography, particularly on the subcostal view. Doppler interrogation reveals the presence and direction of the transatrial shunt and allows calculation of the Q_p/Q_s ratio.

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ANSWER TO QUESTION 456

D (Braunwald, p. 1603)

This patient displays the apical variant of hypertrophic cardiomyopathy (HCM), evidenced on this echocardiographic apical long-axis (four-chamber) view. This variant is marked by predominant hypertrophy of the left ventricular apex, which causes the chamber to display a "spade-like" deformity on cardiac imaging. This is even more clearly demonstrated on this patient's subsequent cardiac magnetic resonance imaging study (*arrows* in Fig. 4.37). Apical HCM is rare in other parts of the world, but in Japan it accounts for 25% of patients with HCM. The ECG in this condition is frequently striking for deep, *inverted* T waves in the apical precordial leads. Intraventricular pressure gradients are usually *absent*. Symptoms associated with the apical variant tend to be more mild and the risk of sudden death is lower than in the traditional septal form of HCM.

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ANSWER TO QUESTION 457

C (Braunwald, pp. 1429–1430, 1433, 1440)

Physical findings in mitral regurgitation (MR) are influenced by the compliance of the left atrium. In patients with severe, *acute* mitral regurgitation (e.g., due to rupture of chordae

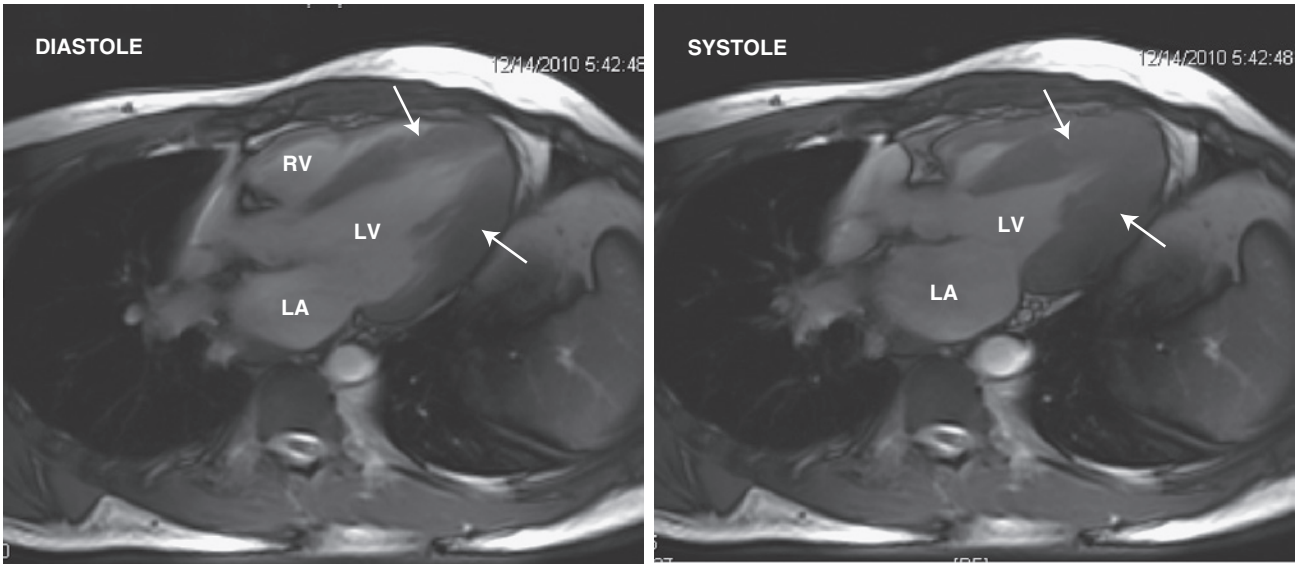

FIG. 4.37

tendineae), the regurgitant volume encounters an unprepared, relatively noncompliant left atrium. As a result, the left atrial pressure quickly rises, which serves to limit the pressure gradient between the left ventricle and left atrium late in systole, causing the systolic murmur to shorten and end before the second heart sound. However, the acutely elevated left atrial pressure also augments the pulmonary venous pressure and commonly results in acute pulmonary edema as well as findings of right-sided heart failure (e.g., jugular venous distention).

In contrast, the more gradual development of *chronic* MR allows the left atrium to gradually dilate and increase its compliance, such that the chamber is able to accommodate larger volumes without a substantial increase in pressure. As a result, in compensated chronic MR, substantial elevation in pulmonary venous and capillary pressures is avoided. However, the mitral regurgitant volume returns to the left ventricle during diastole, resulting in gradual left ventricular enlargement. Thus, in distinction to acute MR, patients with chronic MR commonly demonstrate left ventricular and left atrial enlargement on cardiac imaging.

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ANSWER TO QUESTION 458

B (Braunwald, pp. 1415–1417; Figs. 19.13 and 69.3)

The tracing shows the simultaneous recording of left atrial (LA) and left ventricular (LV) pressures and depicts the hemodynamic profile of mitral stenosis. The LA pressure is elevated (mean ~20 mm Hg) with a prominent atrial contraction *(a)* wave and an abnormally gradual pressure decline in diastole after mitral valve opening (*y* descent). There is a persistent gradient between LA and LV pressure throughout diastole, in contrast to the normal situation, in which there is rapid equilibration of LA and LV pressures in diastole.

Mitral regurgitation would be associated with prominent *v* waves on the LA pressure tracing, but not a persistent diastolic atrioventricular pressure gradient.

In constrictive pericarditis and restrictive cardiomyopathy, the atrial pressure decline in the earliest part of diastole is typically brisk (prominent *y* descent), the converse of this example.

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ANSWER TO QUESTION 459

B (Braunwald, p. 1664)

This patient has typical symptoms and signs of acute pericarditis. The majority of patients with pericarditis manifest electrocardiographic abnormalities. The most common early finding is global ST-segment elevation, particularly in the inferior, lateral, and apical leads. The ST-segment elevations are believed to represent a current of injury caused by superficial inflammation of the adjacent myocardium. In contrast to the acute ST-segment abnormalities of ST-elevation myocardial infarction (STEMI), the elevations in pericarditis tend to be oriented in a *concave* upward direction and reciprocal ST-segment depressions in the opposite leads are not present. In later stages of pericarditis (days or weeks after presentation), the ST segment returns to baseline, and thereafter the T waves may deeply invert.

The PR segment is found to be depressed (or elevated in lead aVR) in 75% to 80% of patients with acute pericarditis. This finding may be the result of abnormal atrial repolarization due to atrial inflammation and is not typical of other conditions such as acute STEMI. PR-segment depression may occur even in the absence of ST-segment elevation and can be the initial, or only, electrocardiographic manifestation of acute pericarditis. Sinus *tachycardia* is also a common finding in acute pericarditis, related to pericardial inflammation, pain, or fever.

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ANSWER TO QUESTION 460

E (Braunwald, p. 1677)

Two forms of pericarditis can follow acute myocardial infarction (MI): early and delayed. When present, early acute fibrinous pericarditis develops within the first few days after MI. The incidence and degree of such pericardial inflammation is associated with the size of the infarct. Acute percutaneous coronary intervention or fibrinolytic therapy for ST-elevation MI (STEMI), which limits infarct size, *reduces* the incidence of pericarditis. In addition, pericarditis is less common after non-ST-segment elevation infarction compared with STEMI. The use of heparin has not been associated with increased risk of pericarditis or tamponade. Clinical evidence of pericarditis can be found as early as 12 hours after MI, and the earliest sign may be a pericardial friction rub. In about 70% of patients, the rub may be accompanied by pleuritic chest pain.

The appearance of symptoms and signs of pericarditis more than 10 days after MI is consistent with the second type of post-MI pericarditis, termed *Dressler syndrome*. This delayed phenomenon is believed to be autoimmune in origin and has become rare in the era of acute reperfusion therapies.

Typical diagnostic electrocardiographic changes of pericarditis are uncommon in post-MI pericarditis or Dressler syndrome. Instead, atypical T-wave changes have been described, consisting of persistently upright T waves or premature reversal of initially inverted T waves after infarction.

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ANSWER TO QUESTION 461

D (Braunwald, pp. 1604–1606)

The tracing demonstrates simultaneous recordings of left ventricular (LV) and systemic pressure in a patient in

normal sinus rhythm. The second electrocardiographic complex is a ventricular premature beat (VPB). The beat following the VPB demonstrates a rise in LV pressure due to post-extrasystolic potentiation. However, the aortic systolic pressure and the pulse pressure decline in the post-VPB beat. This is an example of the Brockenbrough-Braunwald phenomenon that is typical of hypertrophic cardiomyopathy (HCM) and is a reliable sign of dynamic LV outflow tract obstruction.

In normal subjects, and even in those with valvular abnormalities such as aortic stenosis or mitral regurgitation, a post-VPB contraction is associated with *increased* systolic aortic pressure and pulse pressure. Conversely, in HCM, the premature contraction increases the force of contraction and the degree of outflow obstruction of the subsequent beat, causing a decline in the pulse pressure. While increased ventricular filling during the post-VPB compensatory pause would be expected to reduce the outflow gradient in HCM, that effect is outweighed by the increased contractility associated with post-extrasystolic potentiation. In addition to the narrowed pulse pressure, the peripheral arterial waveform may show a "spike-and-dome" configuration, reflecting the attenuation of LV output due to dynamic outflow obstruction (see Section I, Fig. 1.18).

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ANSWER TO QUESTION 462

D (Braunwald, pp. 1450, 1567–1569)

The color Doppler profile in part *A* of the figure demonstrates systolic turbulence due to valvular pulmonic stenosis. As quantitated by the continuous Doppler profile in part *B*, the peak velocity across the valve is ~4.0 m/s, corresponding to a peak transpulmonic valve systolic gradient of 64 mm Hg (calculated from the simplified Bernoulli equation, $P = 4v^2$). Thus, in light of his chest discomfort, this patient likely has symptomatic pulmonic stenosis (PS).

PS is most commonly due to congenital deformity of the valve; much less common causes are carcinoid plaques or rheumatic inflammation. Congenital PS is characterized by fused leaflets and doming of the valve in systole with a narrowed opening. Typical features on physical examination include a prominent jugular venous *a* wave (due to secondary right ventricular hypertrophy), a systolic ejection click, a crescendo-decrescendo ejection murmur at the upper left sternal border, and a widely split S_2. Unlike other right-sided valvular lesions, the systolic click *decreases* in intensity with inspiration (with inspiration, the augmented right-sided filling elevates the leaflets into the pulmonary artery prior to RV contraction, preempting the rapid tensing in early systole that is thought to produce the sound).

Mechanical treatment of PS is indicated for symptomatic patients with a mean transvalvular gradient ≥30 mm Hg or a peak systolic gradient ≥50 mm Hg. In asymptomatic patients, intervention is usually recommended for a mean gradient >50 mm Hg. The intervention of choice is transcatheter balloon valvuloplasty, which has shown excellent short- and medium-term results. For patients with prominently dysplastic valves, balloon valvotomy may not offer sufficient gradient relief, such that pulmonary valve replacement becomes necessary.

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ANSWER TO QUESTION 463

D (Braunwald, pp. 1519–1521)

Whereas the true incidence of congenital cardiovascular malformations is difficult to determine, it has been estimated that approximately 0.8% of live births are complicated by such a disorder. The most common significant malformation is ventricular septal defect, followed in frequency by atrial septal defect (ASD) and patent ductus arteriosus. These data do not include the common anomalies of a congenital, functionally normal bicuspid aortic valve and mitral valve prolapse.

Specific defects show a sex predilection. For example, patent ductus arteriosus and ASDs are more common in females, whereas valvular aortic stenosis, congenital aneurysms of the sinus of Valsalva, coarctation of the aorta, tetralogy of Fallot, and transposition of the great arteries are seen more frequently in males. Extracardiac anomalies occur in approximately 25% of infants born with significant cardiac disease and often are multiple.

Approximately one-third of infants with both cardiac and extracardiac anomalies have an established syndrome. For example, maternal rubella during pregnancy is associated with the rubella syndrome, which consists of cataracts, deafness, microcephaly, and some combination of patent ductus arteriosus, pulmonic valvular or arterial stenosis or both, and ASD. Maternal systemic lupus erythematosus during pregnancy has been linked to congenital complete heart block, but not to any specific anatomic abnormality.

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ANSWER TO QUESTION 464

D (Braunwald, pp. 1505–1508; Table 73G-1)

The American Heart Association guidelines for the prevention of infective endocarditis (IE) enumerate the type of patients for whom antibiotic prophylaxis is recommended. The statement recognizes that (1) IE is more likely to occur after random bacteremias (e.g., after daily tooth brushing) than from dental and/or genitourinary or gastrointestinal procedures; and (2) because prophylaxis may prevent only a small number of cases of IE, the risk of antibiotic use in many cases may outweigh the benefit.

According to current guidelines, prophylaxis is only recommended for those patients with cardiac conditions associated with the highest risk of complications from endocarditis, including the presence of (1) prosthetic cardiac valves or other prosthetic material for valve repair, (2) previous IE, (3) cardiac transplantation recipients with valvular lesions, and (4) specific types of congenital heart disease (unrepaired cyanotic lesions, repaired congenital lesions with residual

defects, or during the first 6 months after repair with prosthetic material or devices). Prophylaxis is not recommended for other valvular abnormalities such as mitral valve prolapse with murmur.

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ANSWER TO QUESTION 465

A (Braunwald, p. 1706; Table 85.4)

The prognostic importance of elevated right atrial pressure on mortality in pulmonary arterial hypertension has been demonstrated in large patient registries. Although increased mean pulmonary artery pressure (mPAP) is also associated with increased mortality, mPAP may decrease as right ventricular failure progresses. Therefore, a normal or low mPAP may be present despite the presence of end-stage pulmonary vascular disease. Diastolic flattening on echocardiography indicates right heart volume overload, but is not specific for pulmonary arterial hypertension. A low transpulmonary gradient (calculated as the difference between mean pulmonary capillary wedge pressure and mean pulmonary artery pressure) is indicative of an elevated left ventricular end-diastolic pressure relative to pulmonary artery pressure and excludes the diagnosis of pulmonary arterial hypertension.

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ANSWER TO QUESTION 466

C (Braunwald, p. 1456)

Homograft (also known as allograft) aortic valves are harvested from human cadavers usually within 24 hours of death, sterilized, cryopreserved, and then placed directly into the recipient's heart without the use of a prosthetic stent. Often the valve is implanted with a portion of attached donor aorta as a root replacement, with reimplantation of the coronaries into the graft. Aortic homografts provide potential advantages. The rate of thromboembolism is low, similar to that of animal-derived bioprosthetic valves, and therefore lifelong anticoagulation is not necessary. They provide a more physiologic hemodynamic profile than mechanical valves, and, because a prosthetic support stent is not used, they are also hemodynamically superior to stented porcine tissue valves. In addition, homografts have been considered to be more resistant to infection than other prostheses, so they are often chosen for patients with infective endocarditis of the aortic valve, particularly when complex root anatomy is present.

In experienced hands, the surgical mortality related to homograft placement is 1% to 2%, similar to that of other valve replacements. The rate of structural degeneration of cryopreserved homografts has been similar to that of porcine xenografts. In one recent retrospective review of 840 cryopreserved aortic allografts, durability exceeded 15 years in middle-aged and older patients. The estimated median time until structural deterioration in this study was 20 years.[1]

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ANSWER TO QUESTION 467

C (Braunwald, p. 1418; Fig. 69.3)

The echocardiographic image demonstrates diastolic doming of the mitral valve leaflets, typical of rheumatic mitral stenosis (MS). Patients with preserved flexibility of the leaflets in MS (i.e., fusion confined to the valve commissures) demonstrate an accentuated S_1. This is thought to occur because the persistent pressure gradient between the left atrium and left ventricle at the end of diastole keeps the flexible portion of the leaflets in a maximally separated position prior to ventricular contraction. Contraction then forces the leaflets together from a relatively wide position, causing the intensity of S_1 to be loud. If, however, the valve is markedly calcified, there is little movement of the leaflets during the cardiac cycle, such that S_1 becomes abnormally soft.

The opening snap occurs when the left ventricular diastolic pressure falls below that of the left atrium and the stenotic mitral leaflets open. The more severe the mitral stenosis, the higher the left atrial pressure becomes, such that mitral opening occurs earlier and therefore the interval between A_2 and the opening snap shortens. In patients with long-standing MS, pulmonary hypertension develops, in part because of the chronically elevated left atrial pressure. As a result, P_2 becomes accentuated. The intensity of the diastolic murmur is not a good guide to the severity of mitral stenosis. A more reliable sign is the duration of the murmur: increasing severity of stenosis causes greater persistence of the gradient between the left atrium and left ventricle, and therefore the murmur lasts longer in diastole.

ANSWER TO QUESTION 468

C (Braunwald, pp. 1403–1404)

The murmur of aortic regurgitation (AR) is of *high* frequency and begins immediately after A_2. It is best heard with the *diaphragm* of the stethoscope applied firmly while the patient is sitting up and leaning forward, with the breath held in expiration. The severity of regurgitation correlates better with the duration rather than severity of the murmur, and in cases of severe AR, a holodiastolic murmur with a "rough" quality may be heard. However, with the development of heart failure, equilibration of aortic and left ventricular diastolic pressures abolishes the late diastolic component and the murmur becomes shorter. When the murmur is musical ("cooing dove" murmur), it usually signifies eversion or perforation of a cusp. Regurgitation due to primary aortic valve disease is usually loudest at the left sternal border at the third and fourth intercostal spaces. When the murmur is loudest at the right side of the sternum, it usually indicates the presence of a dilated ascending aorta as the cause of valvular insufficiency. In general, maneuvers that increase afterload, such

as a strenuous handgrip, augment aortic regurgitation and the associated murmur.

ANSWER TO QUESTION 469

A (Braunwald, p. 1676)

Bacterial (purulent) pericarditis arises from one of several mechanisms, including hematogenous seeding during bacteremia, contiguous spread of infection after thoracic surgery, or via rupture of a perivalvular abscess in endocarditis. The majority of occurrences, however, are attributable to direct extension from an adjacent pulmonary infection. Several factors predispose to the development of purulent pericarditis, including a preexisting pericardial effusion in uremic pericarditis, or in immunosuppressed states such as hematologic malignancies or following severe burns. Bacterial pericarditis is usually an acute fulminant illness of rapid onset that is characterized by high spiking fevers, rigors, night sweats, and dyspnea. Typical symptoms of pericarditis may be absent, and the process may be heralded by new jugular venous distention and pulsus paradoxus as a result of cardiac tamponade.

Despite the lower incidence of purulent pericarditis in the antibiotic era, overall survival is poor, with a mortality of approximately 30% in most series. The poor prognosis is in large part due to delayed diagnosis, as well as disease severity and comorbidities. Early complete drainage (via pericardiocentesis and usually surgical drainage) and parenteral antibiotic therapy are critical. High concentrations of antibiotics are achieved in pericardial fluid with parenteral therapy; therefore, instillation of antibiotics directly into the pericardial space is not warranted.

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ANSWER TO QUESTION 470

A (Braunwald, pp. 1607–1609)

This 16-year-old youth has an examination and ECG consistent with hypertrophic cardiomyopathy, which should be confirmed by echocardiography. Current recommendations are that competitive sports not be allowed in this condition if high-risk clinical features are present, including marked ventricular hypertrophy, evidence of significant outflow gradient, supraventricular or ventricular arrhythmias, history of exertional syncope or hypotension, or history of sudden death in close relatives. Low-intensity sports may be allowed if none of these conditions is present. This teen has evidence of substantial left ventricular hypertrophy and a history of sudden death in a first cousin. Thus, competitive sports should be avoided.

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ANSWER TO QUESTION 471

C (Braunwald, pp. 1390–1391)

The left ventricle responds to *sudden* obstruction to outflow by dilatation and reduction of stroke volume. However, in most adults with aortic stenosis the obstruction develops slowly over a long period of time, resulting in significant compensatory measures. Fundamentally, left ventricular (LV) output is maintained by development of LV hypertrophy with generation of increased contractile force. This enables the LV to sustain a large pressure gradient across the aortic valve without reduction in cardiac output, chamber dilatation, or symptoms. The compensation is contributed to by coexisting left atrial (LA) hypertrophy; the more forceful atrial contraction helps to maintain LV filling, but also contributes to a large *a* wave in the LA pressure curve and an elevated LV end-diastolic pressure. The latter is also augmented by reduced LV diastolic compliance due to ventricular hypertrophy. However, it is only the patient with LV contractile dysfunction in whom dilatation and an increase in LV end-diastolic volume occur.

ANSWER TO QUESTION 472

C (Braunwald, pp. 1501–1502)

Although helpful, the observation of vegetations by echocardiography is not mandatory to establish the diagnosis of endocarditis. In addition, although the sensitivity of transesophageal echocardiography to detect vegetations in suspected endocarditis is 85% to 95%, the sensitivity of transthoracic echocardiography is substantially less. *Staphylococcus aureus* is an aggressive organism that results in rapid destruction of valves and perivalvular tissue. Nonetheless, antibiotic therapy alone is often curative for native valve endocarditis caused by this organism.

Vegetations >10 mm in diameter have a greater risk of thromboembolism than smaller vegetations, but it has not been definitively proved that early surgical intervention in patients with larger vegetations improves long-term outcome; early surgical intervention is an American Heart Association/American College of Cardiology class IIb indication for such patients. Although cerebral embolism can be a devastating complication of endocarditis, the rate of recurrence declines during the course of appropriate antibiotic treatment. Patients with endocarditis and intractable heart failure due to valve dysfunction have a 55% to 85% mortality rate when treated medically; the mortality falls to 10% to 30% with early surgical intervention.

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ANSWER TO QUESTION 473

E (Braunwald, p. 1676)

Although tuberculous pericarditis is now uncommon in industrialized countries, the disease continues to be an important problem in developing nations and in immunosuppressed patients, and is the most common cause of pericardial disease in

human immunodeficiency virus patients in Africa. Tuberculous pericarditis usually develops by retrograde spread from peritracheal, peribronchial, or mediastinal lymph nodes or by early hematogenous spread from the primary tuberculous infection. The process is usually chronic, with the gradual development of pericardial effusion. Symptoms may be systemic and nonspecific, and clinical detection of tuberculous pericarditis often does not occur until the effusive or late constrictive pericarditic stages are reached. The typical pericardial chest pain of acute viral or idiopathic pericarditis is uncommon in tuberculous pericarditis. In addition, typical signs and symptoms of cavitary pulmonary tuberculosis are usually absent.

Examination of patients with tuberculous pericarditis may reveal evidence of chronic cardiac compression, which can mimic heart failure. Common symptoms include cough, dyspnea, orthopnea, weight loss, and peripheral edema. Definitive diagnosis of tuberculous pericarditis is usually difficult because of the low yield of the bacillus in pericardial fluid, frequent failure to culture the organism, and/or the need to observe cultures for a minimum of 8 weeks. The probability of a definitive diagnosis is greatest if both pericardial fluid and a pericardial biopsy are obtained in the effusive stage of the disease. Polymerase chain reaction amplification of pericardial specimens offers the potential to obtain results more rapidly than standard cultures, but its sensitivity is low. Measurement of pericardial fluid adenosine deaminase *is* diagnostically useful, with reported sensitivity and specificity for tuberculous pericarditis of 88% and 83%, respectively.

Initial therapy for tuberculous pericarditis includes a three-drug regimen ordinarily consisting of isoniazid, rifampin, and streptomycin or ethambutol. The role of corticosteroids remains unclear. Studies have failed to show that the early use of corticosteroids affects mortality or progression to constriction, although such therapy may shorten the duration of symptoms.

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ANSWER TO QUESTION 474

A (Braunwald, p. 1598; see also Answer to Question 451)

This patient has findings of carcinoid syndrome, characterized by episodic flushing, diarrhea, and bronchoconstriction. The vast majority of carcinoid tumors originate in the appendix and other areas of the gastrointestinal tract, with the remainder arising in the respiratory tract. Carcinoid tumors secrete large amounts of vasoactive substances, including serotonin and bradykinin, which are usually inactivated by the liver, lungs, and brain. However, in the presence of large hepatic metastases, these vasoactive substances reach the systemic circulation and heart. Cardiovascular involvement occurs in up to two-thirds of patients with carcinoid syndrome and includes the formation of fibrous plaques in the right heart endocardium, which can lead to fixation and retraction of the tricuspid and pulmonic valves. This results in tricuspid and/or pulmonic valve dysfunction and eventual right-sided heart failure. Higher circulating serotonin levels are associated with greater severity and progression of cardiac disease. Left-sided heart involvement is not common (occurring in <10% of patients), presumably because of pulmonary inactivation of the vasoactive hormones.[1] Patients who do develop left-sided disease may have a right-to-left intracardiac shunt or a primary pulmonary carcinoid tumor. It is rare for a carcinoid tumor to actually metastasize to the heart.

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ANSWER TO QUESTION 475

C (Braunwald, pp. 1421, 1467–1468)

Percutaneous balloon mitral valvuloplasty (BMV) is the treatment of choice for patients with mitral stenosis who require mechanical intervention. Surgical valve repair or replacement is reserved for patients who are not candidates for the percutaneous procedure. In the most commonly practiced form of BMV, a catheter is maneuvered across the interatrial septum through a small septal puncture and a balloon device is advanced across the mitral valve. Balloon inflation separates and fractures the calcified valve commissures, improving the transmitral gradient, valve area, and cardiac output. Selection of patients for this approach is usually determined by echocardiographic features including (1) mitral valve rigidity, (2) leaflet thickening, (3) valve calcification, and (4) subvalvular apparatus thickening and calcification. In a commonly used scoring system, each of these factors is assigned a score from 0 to 4, with 0 representing the absence of each abnormality and 4 representing the most severe form. A total score ≤8 is associated with excellent results after balloon valvuloplasty. Transesophageal echocardiography is usually performed before the procedure to exclude the presence of left atrial thrombus, a potential source of embolism during catheter manipulation.

The major complications of BMV include death (1% to 2%), thromboembolism (1% to 2%), cardiac perforation (1%), and severe mitral regurgitation requiring surgical repair (approximately 2%). A small residual iatrogenic atrial septal defect persists in approximately 5% of patients and is rarely hemodynamically significant.

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ANSWER TO QUESTION 476

B (Braunwald, p. 1667)

The incidence of cardiac injury after blunt chest trauma varies by mode of injury and criteria for diagnosis, but ranges between 10% and 50%. Potential cardiac complications include septal rupture, free wall rupture, coronary artery thrombosis, rupture of chordae tendineae or papillary muscles, and dysrhythmias. Immediate evaluation should include assessment for cardiac tamponade (e.g., hypotension, pulsus paradoxus, distended jugular veins, and muffled heart sounds). Chest radiography is an important part of the evaluation that can identify pneumothorax, bony fractures, or an enlarged cardiac silhouette suggesting pericardial effusion. Echocardiography can confirm the presence of traumatic blood in the pericardial space, but a transthoracic study

has limited value in identifying other consequences of blunt trauma, as accompanying chest wall injuries typically render the study technically limited. Conversely, transesophageal echocardiography is sensitive in identifying the effects of blunt injury, including traumatic ventricular septal defects, rupture of chordae tendineae or portions of papillary muscle with valvular insufficiency, and wall motion abnormalities.

The most common electrocardiographic abnormalities in blunt cardiac trauma are sinus tachycardia and ventricular premature beats. Other ECG findings can include ST-segment abnormalities, atrioventricular blocks, right bundle branch block (with or without left anterior fascicular block), atrial fibrillation, and ventricular tachycardia. Although debate exists over the role of cardiac-specific biomarker elevations after chest trauma, studies have not shown a consistent correlation between cardiac troponin levels and the presence and prognosis of blunt cardiac injury.

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ANSWER TO QUESTION 477

D (Braunwald, pp. 1594–1595)

Cardiac sarcoidosis was previously thought to occur in ~5% of patients with pulmonary sarcoidosis based on clinical findings, but recent imaging studies have demonstrated cardiac involvement in >25% of patients with pulmonary sarcoid. The pathologic feature of cardiac sarcoidosis is the presence of noncaseating granulomas in the myocardium that result in ventricular dysfunction and eventually become fibrotic scars. The granulomas may involve any region of the heart, but the left ventricular (LV) free wall and interventricular septum are the most common sites. Infiltration of the conduction system may lead to atrioventricular (AV) block, and atrial and ventricular arrhythmias are also common. Sudden death is the most common cause of mortality in sarcoid heart disease, potentially resulting from paroxysmal ventricular arrhythmias or high-grade AV block. Involvement of cardiac valves is unusual. While the murmur of mitral regurgitation is often present, it typically results from LV dilatation or papillary muscle involvement rather than from sarcoid infiltration of the valve.

Percutaneous myocardial biopsy may be useful in establishing the diagnosis of sarcoid heart disease. However, cardiac involvement tends to be patchy such that biopsy is often low-yield and a negative biopsy does not exclude the diagnosis. Magnetic resonance imaging has emerged as a more sensitive modality for the diagnosis. Delayed gadolinium enhancement in this condition is usually nontransmural, typically appearing at the basal and/or midventricular septum. ^{18}Fluorodeoxyglucose (FDG) positron emission tomography (PET) is another useful imaging modality that reveals regions of inflammation in active sarcoid and can be used to monitor the response to anti-inflammatory therapies.

It is common to administer glucocorticoid therapy to patients with evidence of sarcoid heart disease, though the benefit of this approach has not been confirmed in randomized trials. In patients who do not respond, methotrexate is commonly used, based on experienced opinion. Management of arrhythmias may require permanent pacing and/or implantation of a cardiac defibrillator (ICD), including ICD implantation for primary prevention of sudden death in patients with markedly reduced LV ejection fraction, similar to other heart failure patients. Cardiac transplantation has been undertaken in patients with severe cardiac sarcoid after evaluating for noncardiac sarcoid involvement.

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ANSWER TO QUESTION 478

C (Braunwald, pp. 1541–1542)

The size of ventricular septal defects (VSDs) and the degree to which pulmonary vascular resistance is altered determine the clinical presentation. In general, adults with small defects are asymptomatic and are not at risk for the development of pulmonary vascular obstructive disease. However, all individuals with ventricular septal defects are at increased risk for infective endocarditis, which arises in up to 4% of patients with VSDs. The infection usually develops in the right ventricle at the site where shunted blood impacts the ventricular wall.

In an asymptomatic individual, a VSD with a normal pulmonary artery pressure and a pulmonary:systemic flow ratio <1.5:1 generally does not require surgical closure. Women with VSDs and pulmonary:systemic flow ratios <2:1 with only modest pulmonary hypertension generally tolerate pregnancy well. In women with larger left-to-right shunts, however, left ventricular failure may occur during pregnancy. In those who have Eisenmenger complex, pregnancy is poorly tolerated, with a maternal mortality between 40% and 45%.

The development of Eisenmenger complex due to progressive pulmonary vascular disease is one of the most serious complications of VSDs. This usually develops in early adulthood, in the second or third decade of life, and may be complicated by heart failure, hemoptysis, chest pain, cerebral abscess, thromboembolism, and sudden death.

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ANSWER TO QUESTION 479

C (Braunwald, p. 1599)

Endomyocardial fibrosis (EMF), a cause of restrictive cardiomyopathy, is found primarily in tropical and subtropical Africa, but has been increasingly recognized in tropical regions of South America, Asia, and the Middle East. It arises most commonly in children and young adults and only occasionally manifests in older individuals. It results in fibrous obliteration of the apex of the affected ventricle(s) and typically involves the papillary muscles and chordae tendineae. EMF affects both ventricles in approximately 50% of patients, purely the left ventricle in 40%, and solely the right ventricle in 10%. Its cause remains unknown.

Echocardiographic features include increased endocardial reflectivity, fibrotic obliteration of the affected ventricular apex, atrial enlargement, and pericardial effusion. Fibrotic lesions of the papillary muscles and chordae tendineae distort the valve apparatus and, in the case of the left ventricle, lead to mitral *regurgitation*.

Clinical features of EMF depend on which of the ventricles is involved: left-sided disease manifests as pulmonary congestion, and right-sided involvement may manifest as symptoms and signs similar to other restrictive cardiomyopathies or constrictive pericarditis. The clinical course of EMF tends to be progressive and complications include heart failure and thromboemboli, because the fibrotic tissue provides a site for thrombus formation. Up to 50% of patients with advanced disease die within 2 years.

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ANSWER TO QUESTION 480

C (Braunwald, pp. 1609–1611)

Among patients with hypertrophic cardiomyopathy (HCM), ICD implantation is appropriate for those at greatest risk of sudden death (SD). Those with prior cardiac arrest or sustained ventricular tachycardia warrant an ICD, while an ICD should be considered for primary prevention in HCM patients with any of the following high-risk predictors of SD: recent unexplained syncope (especially in a young patient), a family history of HCM-related sudden death, a hypotensive response to exercise testing, multiple nonsustained bursts of VT on ambulatory monitoring, or those with marked LV hypertrophy (wall thickness ≥30 mm). Patients with extensive late gadolinium enhancement on contrast-enhanced cardiac magnetic resonance imaging (involving ≥ 15% of the LV mass) are also at high risk of SD and prophylactic ICD implantation might be considered in such individuals.

Most studies have failed to establish an association between the left ventricular outflow tract (LVOT) gradient in HCM and risk of sudden death. Thus, an elevated LVOT gradient is not considered an indication for ICD placement in the absence of other risk factors.

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ANSWER TO QUESTION 481

C (Braunwald, pp. 1544–1545; Fig. 75.23)

Classic tetralogy of Fallot is marked by a large ventricular septal defect (VSD) in association with infundibular or valvular pulmonic stenosis or both, right ventricular (RV) hypertrophy, and an overriding aorta. In all cases, the VSD is located proximal to the level of the RV outflow tract obstruction and is therefore associated with elevated RV systolic pressure and right-to-left shunting. This is in contrast to the situation in patients who have a double-chambered right ventricle and a membranous VSD, in whom the septal defect communicates with the low-pressure distal portion of the right ventricle and leads to simple VSD physiology rather than the right-to-left shunting and cyanosis that mark tetralogy of Fallot.

Symptoms and clinical findings of tetralogy of Fallot depend on the severity of RV outflow tract obstruction. With only mild obstruction, a left-to-right shunt through the VSD is predominant and the patient may remain acyanotic. The condition in patients with RV obstruction severe enough to cause cyanosis usually is recognized during infancy or early childhood; such patients may then undergo palliative or total surgical repair. Patients with uncorrected tetralogy of Fallot who survive into adult life usually have at most moderate obstruction to RV outflow, in association with relatively well-preserved pulmonary blood flow.

Because the large VSD allows for decompression of the right ventricle in tetralogy of Fallot, the RV systolic pressure does not exceed that in the aorta, even in the presence of severe obstruction to RV outflow. Congestive heart failure is unusual in patients with tetralogy of Fallot. Instead, a decrease in cardiac reserve in adults with this condition is more typical, with symptoms of dyspnea and limited exercise tolerance.

Associated anomalies in patients with tetralogy of Fallot include a right aortic arch in ~25%, and coronary anomalies in ~5%.

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ANSWER TO QUESTION 482

D (Braunwald, p. 1485)

The HACEK group of organisms refers to a number of fastidious gram-negative bacilli that colonize the oropharynx and upper respiratory tract and are a cause of community-acquired subacute endocarditis. The E in HACEK stands for *Eikenella corrodens*, not *Escherichia coli*. Although they are fastidious and slow growing, HACEK organisms can usually be detected in blood cultures within 5 days. Native valve endocarditis with HACEK organisms have been associated with large vegetations and a high frequency of systemic emboli. All of these organisms share common antibiotic sensitivities.

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ANSWER TO QUESTION 483

E (Braunwald, p. 1598)

Endocardial fibroelastosis (EFE) is a rare disorder of infants in which there is thickening of the endocardium due to deposition of collagen and elastin. This entity is distinct from endomyocardial fibrosis (see Answer to Question 479), a tropical and subtropical condition in which there is prominent myocardial involvement and, commonly, eosinophilia. EFE does not appear to be a specific disease but rather a reaction in the first 1 to 2 years of life to stressors that include viral infections (including mumps exposure during fetal life), metabolic disorders, and congenital left-sided obstructive lesions. Recent reports also implicate mitochondrial disorders and placental insufficiency as causative. EFE predominantly involves the left ventricle and usually progresses to severe congestive heart failure and death.

The echocardiographic finding of a highly reflective endocardial surface of the ventricle suggests the presence of endocardial fibroelastosis.

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ANSWER TO QUESTION 484

E (Braunwald, pp. 1547, 1550)

The Fontan procedure, developed originally for tricuspid atresia, involves surgical diversion of systemic venous return directly to the pulmonary arteries without passing through a subpulmonary ventricle. It is a palliative, not curative, operation. The majority of patients (~90%) are in functional class I or II 5 years after the operation, but progressive deterioration over time is typical. The most common causes of death are congestive heart failure and arrhythmias.

Physical findings after the Fontan procedure include an elevated nonpulsatile jugular venous pulse and a single S_2 (the pulmonary artery is typically tied off).

Supraventricular arrhythmias are common (especially atrial fibrillation and flutter), observed in 15% to 20% of patients by 5 years after the operation, and the development of such arrhythmias can lead to hemodynamic deterioration and heart failure. Thromboemboli occur in 6% to 25% of patients, sources of which include atrial arrhythmias, right atrial dilatation with blood stasis, and the potentially thrombogenic material used to construct the circuit.

Protein-losing enteropathy (PLE) develops in 4% to 13% of patients, and 5-year survival in this subgroup is approximately 50%. This complication is diagnosed by the finding of low plasma $alpha_1$-antitrypsin levels and high $alpha_1$-antitrypsin stool clearance. Chronically elevated systemic venous pressure with resultant intestinal lymphangiectasia and protein leakage has been implicated in the pathogenesis of PLE.

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ANSWER TO QUESTION 485

B (Braunwald, p. 1686)

A primary hypercoagulable state (inherited thrombophilia) should be suspected when a patient presents with deep vein thrombosis (DVT) in the absence of a predisposing condition such as trauma, prolonged bed rest, or malignancy. Activated protein C (aPC) resistance is a form of thrombophilia in which aPC cannot appropriately cleave and inactivate coagulation factor V. This is caused by a single point mutation in the factor V gene, known as the factor V Leiden mutation, that abolishes a protein C cleavage site. Because factor V is critical in the conversion of prothrombin to thrombin and subsequent clot formation, the inability to inactivate it leads to a hypercoagulable state and triples the risk of DVT. This mutation has been found in nearly 20% of unselected patients with DVT.

The prothrombin gene 20210 mutation (a single G-to-A substitution at nucleotide position 20210) results in increased levels of prothrombin and doubles the risk of DVT. It has been identified in 5% to 8% of patients with venous thrombosis, whereas protein C deficiency has been found in 2% to 4%, protein S deficiency in 2% to 5%, and antithrombin deficiency in 1% to 3%.

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ANSWER TO QUESTION 486

C (Braunwald, p. 1726; Table 87.1)

This man has classic findings of sleep apnea, with daytime sleepiness, nighttime snoring with apnea, nocturnal awakenings, and automobile accidents due to falling asleep at the wheel. Specific findings include paroxysmal nocturnal dyspnea, morning headaches, cardiac arrhythmias, truncal obesity, pulmonary hypertension, nocturnal enuresis, peripheral edema, hypertension, and an elevated hematocrit on laboratory examination.

Three patterns of sleep apnea have been described: central apnea, obstructive apnea, and mixed apnea. In *central apnea*, there is impaired central nervous system control of respiratory effort. Conversely, in *obstructive apnea*, the upper airway becomes transiently obstructed, causing airflow to stop despite continuing efforts of the respiratory muscles. Affected patients experience apneic periods, which can occur between 40 and 100 times per hour. During prolonged periods of apnea, the Po_2 can fall to values as low as 20 to 25 mm Hg with oxygen saturation <50%. Sustained hypoxemia of this type leads to arrhythmias, including sinus bradycardia, sinus arrest, long asystoles, frequent atrial premature beats, and ventricular arrhythmias. Pulmonary hypertension may develop with secondary right ventricular hypertrophy.

An effective therapy for many patients with sleep apnea is continuous positive airway pressure (CPAP), applied during sleep via mask or nasal prongs. Patients treated with CPAP demonstrate improved neuropsychiatric function and reduced daytime somnolence. Nocturnal desaturation, pulmonary hypertension, and right-sided heart failure findings can all improve with this technique.

More severe forms of sleep apnea may require palatal corrective surgery or, in the most difficult cases, tracheostomy.

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ANSWER TO QUESTION 487

D (Braunwald, pp. 1691, 1823)

This patient with acute venous thromboembolism (VTE) after a prolonged airplane flight is hemodynamically stable without signs of right heart strain. Initial management should focus on anticoagulation therapy. In the absence of pregnancy, active cancer, or severely reduced renal function, effective anticoagulant approaches include: (1) subcutaneous

low-molecular-weight heparin (LMWH) followed by oral warfarin (which requires ~5 days of overlap to prevent the procoagulant effect of unopposed warfarin monotherapy) or (2) use of non-vitamin K antagonist oral anticoagulants (NOACs). The American College of Chest Physicians Guidelines recommend NOACs over the warfarin-based strategy, as NOACs are noninferior to warfarin in treatment of VTE and cause less serious bleeding. For patients with cancer-associated thrombosis, a continuous course of low-molecular-weight heparin is currently recommended over either warfarin or NOACs.

NOACs that are approved for treatment of VTE include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. Dabigatran and edoxaban require at least 5 days of pretreatment with a parenteral anticoagulant such as LMWH. Rivaroxaban and apixaban do not require preceding parenteral anticoagulation. Approved standard regimens for these agents are:

- Rivaroxaban 15 mg twice daily for 21 days, then 20 mg daily
- Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
- Dabigatran 150 mg twice daily, after ≥5 days of a parenteral anticoagulant
- Edoxaban 60 mg daily (if creatinine clearance [Ccr] is 50 to 95 mL/min; 30 mg daily if Ccr ≤15 to 50 mL/min, or if weight ≤60 kg, or patient takes a potent P-glycoprotein inhibitor such as verapamil), after ≥5 days of a parenteral anticoagulant

Of the provided choices in the question, selection D would therefore be the most appropriate drug and dosage for this patient with normal renal function.

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ANSWER TO QUESTION 488

C (Braunwald, p. 1580; Table 77.1; Fig. 77.4)

This patient presents with symptoms of a dilated cardiomyopathy (DCM) of recent onset. In North America, the majority of new DCMs are not found to have a specific cause and the cause is often presumed to be related to viral myocarditis, which is relevant in this patient's case given her antecedent respiratory tract infection. The most common viruses that have been implicated are the enteroviruses (including coxsackie viruses) and adenovirus. There is also the possibility of a genetic form of cardiomyopathy, as familial forms are believed to be responsible for 20% to 30% of what were once classified as idiopathic DCM.

Endomyocardial biopsy (EMB) is rarely helpful in identifying the etiology of DCM because the findings are often nonspecific. Furthermore, a negative biopsy does not rule out active viral myocarditis, because the myocardial damage may be focal and not included in the biopsy specimen. EMB is more helpful in patients with fulminant new-onset heart failure, for example when giant cell myocarditis is suspected, to establish the diagnosis and direct therapy. In contrast to EMB, cardiac magnetic resonance imaging has high diagnostic accuracy for the presence of global or focal myocarditis and further can identify infiltrative or ischemic contributions to DCM.

When viral myocarditis is suspected, acute and convalescent serologic testing can be obtained to confirm a viral cause, but the findings are not available sufficiently rapidly to affect management. Myocardial damage in viral myocarditis is believed to be due to cell-mediated immunologic recognition of new antigens expressed on myocardial cells by the infecting virus, although direct invasion of the myocardium and production of a myocardial toxin may play a role. As a result of myocardial cell destruction, serum myocardial markers, including the cardiac troponins, can be elevated in active myocarditis even in the absence of coronary artery disease. Because of the immunologic nature of cell death, it stands to reason that corticosteroid therapy would be beneficial in the treatment of acute myocarditis. However, randomized trial data to date indicate that immunosuppressive therapy for acute viral myocarditis does not significantly affect left ventricular function or survival.

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ANSWER TO QUESTION 489

C (Braunwald, p. 1603; Fig. 78.2)

The M-mode and cardiac magnetic resonance images demonstrate marked asymmetric septal hypertrophy in this patient with hypertrophic cardiomyopathy. Furthermore, on the M-mode tracing, the motion of the mitral valve is abnormal: the anterior leaflet moves anteriorly during systole, toward the interventricular septum, consistent with dynamic outflow tract obstruction. The patient should be advised to refrain from competitive sports, because such activity may increase the likelihood of syncope and sudden death. Initial medical therapy for this disorder includes beta blocker therapy, to reduce myocardial oxygen consumption and lower the outflow gradient in patients with dynamic obstruction.

Diuretics should generally be avoided, or administered carefully, in patients with HCM to prevent intravascular volume depletion and intensification of the outflow gradient. Digoxin should be avoided in HCM in the absence of systolic dysfunction; the increased inotropic effect could exacerbate the LV outflow gradient. HCM is not an indication for routine antibiotic prophylaxis before dental procedures.

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ANSWER TO QUESTION 490

D (Braunwald, p. 1715)

This patient's clinical history and hemodynamic data are consistent with pulmonary vascular disease, with increased mean pulmonary artery pressure (normal <25 mm Hg) and pulmonary vascular resistance (normal <2.5 Wood units) but a normal pulmonary capillary wedge pressure. The pulmonary angiogram in the figure demonstrates abrupt

tapering and cutoff of vessels with decreased opacification of the medium and small pulmonary arterioles, consistent with chronic thromboembolic pulmonary hypertension (CTEPH). Unlike other forms of pulmonary hypertension, surgical pulmonary endarterectomy is the definitive treatment for CTEPH, typically resulting in improved symptoms and hemodynamics.

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ANSWER TO QUESTION 491

C (Braunwald, p. 1591; Figs. 77.9 and 77.10)

The provided apical four-chamber view demonstrates biventricular increased wall thickness, enlarged atria, and a small pericardial effusion, which are typical findings of cardiac amyloidosis. Systemic amyloidosis represents a collection of pathologic disorders that result in the extracellular deposition of insoluble fibrillar proteins in organs and tissues. The most common form is primary (AL) amyloidosis, which is associated with plasma cell dyscrasias such as multiple myeloma. Cardiac involvement occurs in approximately 50% of patients with AL amyloidosis, and the most common presentation is that of restrictive cardiomyopathy. In such cases, right-sided heart failure findings predominate on physical examination.

Another presentation of cardiac amyloidosis is congestive heart failure due to systolic dysfunction, generally a later finding. In approximately 10% of patients with amyloidosis, orthostatic hypotension occurs and is presumed to be a result of amyloid infiltration of the autonomic nervous system. A fourth, rare presentation of cardiac amyloidosis infiltration is impaired cardiac impulse formation and conduction. Such patients present with arrhythmias and conduction disturbances and sudden death may occur.

Although not obvious in this example, the echocardiographic findings in cardiac amyloidosis may include a distinctive granular, sparkling appearance of the thickened cardiac walls, representative of the infiltrative process. Despite the thickened ventricular walls, the ECG in cardiac amyloidosis typically demonstrates low limb lead voltage, often accompanied by ventricular conduction delay and pseudoinfarction patterns.

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ANSWER TO QUESTION 492

E (Braunwald, p. 1424)

The figure shows two-dimensional (apical four-chamber) and M-mode (mid-ventricular level) echocardiographic views demonstrating prominent late-systolic mitral valve prolapse (MVP). In part *B* of the figure, point C represents coaptation of the anterior and posterior mitral valve leaflets at the onset of systole. The posterior displacement (the U-shaped deformity) of the C-D segment represents prolapse of the leaflets into the left atrium in late systole.

By using standardized echocardiographic criteria, the prevalence of MVP in the population is 2.4%. MVP is twice as common in women as in men, and there appears to be a strong hereditary component. The majority of affected people are asymptomatic, and moderate or severe mitral regurgitation (MR) is found in only 10%. For asymptomatic patients who do not have significant MR, reassurance is appropriate, with follow-up every few years, including repeat echocardiographic evaluation if there is a clinical change. For patients with advanced MR, more frequent (e.g., yearly) clinical and echocardiographic evaluations are recommended. Patients with MVP do not routinely require predental antibiotic prophylaxis to prevent endocarditis (see Answer to Question 464).

The risk of sudden death in patients with MVP in the absence of significant MR is very low. Evaluation for arrhythmias is not warranted for asymptomatic patients, but should be pursued in those with a history of sustained palpitations, lightheadedness, or syncope. Cerebral embolic events have been reported to be more common in patients with MVP. However, a large case-controlled study showed no association between this disorder and ischemic neurologic events in patients <45 years. The most common serious complication of MVP is progressive MR. Those at the highest risk are men and individuals >50 years.

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ANSWER TO QUESTION 493

C (Braunwald, pp. 1591, 1533; Fig. 75.14)

These images reveal an ostium secundum atrial septal defect (ASD). Two-dimensional echocardiography, especially from the subcostal position, allows direct examination of the interatrial septum. Some types of ASDs, such as the sinus venosus defect, may be difficult to identify by transthoracic esophagography and can be more easily resolved by a transesophageal study. Both color flow Doppler and saline contrast echocardiography (part *B*) may be used to evaluate the direction of flow across an ASD. In the uncomplicated situation, in which flow is directed predominantly from the left to the right atrium, left atrial (noncontrast) blood passes through the ASD and produces a negative contrast effect within the right atrium. Conversely, when Eisenmenger syndrome has developed, as in the case described, the shunt reverses (i.e., right-to-left direction) and contrast medium passes from the right atrium into the left-sided chambers after a peripheral vein saline injection. Anomalous pulmonary venous return (not demonstrated in this case) is most commonly associated with the sinus venosus type of ASD and is best visualized by transesophageal esophagography.

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ANSWER TO QUESTION 494

A (Braunwald, pp. 1404, 1405, 1409)

This M-mode panel displays high-frequency vibration of the anterior leaflet of the mitral valve in diastole, which is characteristic of aortic regurgitation (AR). This sign is an echocardiographic correlate of the Austin Flint murmur, although, unlike the auscultatory finding, it may occur even in cases of mild AR.

AR develops due to abnormalities of the aortic valve itself and/or because of dilatation of the aortic root. In recent decades, primary aortic root pathology has become the most common cause of pure AR in the United States, reflecting the decline of rheumatic heart disease. AR due to dilatation of the ascending aorta is typically degenerative in origin (annuloaortic ectasia), and it may also be associated with specific disorders, including systemic hypertension, cystic medial necrosis of the aorta (isolated or in association with Marfan syndrome), giant cell arteritis, ankylosing spondylitis, rheumatoid arthritis, and syphilis. Causes of *valvular* AR include a bicuspid aortic valve, endocarditis, traumatic injury, and rheumatic aortic valve disease.

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ANSWER TO QUESTION 495

B (Braunwald, p. 1415; Figs. 69.1 and 69.2)

The transmitral Doppler pattern is typical of mitral stenosis (MS). Echocardiographic study in a patient with MS provides a wealth of information about the presence and severity of the lesion. Typical findings include leaflet thickening, decreased leaflet separation in diastole, and anterior movement of the posterior mitral valve leaflet during early diastole. The chordae are variably thickened, fused, and shortened.

Accurate determination of mitral orifice size can be obtained from two-dimensional and Doppler echocardiography (see Answer to Question 26). Planimetry of the mitral orifice in the parasternal short-axis view permits an accurate determination of the valve area. Doppler echocardiography is especially useful in quantifying the severity of MS. The peak velocity of transmitral flow is *increased* in MS, as in this case, and the rate of decline is reduced during early diastole. In the continuous-wave Doppler flow velocity signal illustrated, the peak velocity exceeds 2 m/s, yielding a peak transmitral gradient of >16 mm Hg (per the modified Bernoulli equation, $P = 4v^2$), consistent with advanced MS. In addition, the valve area may be estimated using the pressure half-time, which is based on the correlation between the size of the mitral orifice and the time required for peak pressure to reach half its initial level. Finally, Doppler interrogation of the tricuspid regurgitant jet can estimate the degree of elevated pulmonary artery pressure.

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ANSWER TO QUESTION 496

D (Braunwald, pp. 1663–1672; Table 83.1)

This case illustrates a patient infected with human immunodeficiency virus (HIV) presenting with tuberculous pericarditis during the effusive stage of the illness. Whereas the incidence of tuberculous pericarditis has decreased in industrialized nations in recent decades, the disorder remains an important problem in immunosuppressed patients, including those with HIV disease. It is also a major cause of pericarditis among populations in developing regions, especially in sub-Saharan Africa. Among Africans with HIV infection, tuberculosis is the most common cause of pericardial disease.

Tuberculous pericarditis usually manifests in the effusive stage, as in this case, or late in its course, following the development of constrictive pericarditis. The disease usually arises slowly and is marked by nonspecific systemic findings, including fever, night sweats, dyspnea, and fatigue. The acute onset of severe pericardial pain, which is seen frequently in viral or idiopathic pericarditis, is *uncommon* in tuberculous pericarditis. Abnormalities on physical examination may include fever, tachycardia, and a pericardial friction rub, as well as jugular venous distention, ascites, and hepatomegaly.

The chest radiograph in this case displays common features of effusive tuberculous pericarditis. These include an enlarged cardiac silhouette with accompanying mediastinal widening suggestive of a pericardial effusion, normal lung hila and apices, and a small pleural effusion. Patients may also present with chronic constrictive pericarditis with symptoms and signs consistent with severe systemic venous congestion. The diagnosis of tuberculous pericarditis requires a high index of suspicion and is best confirmed by obtaining both pericardial fluid and a pericardial biopsy specimen during the early effusive stage. The measurement of a high level of adenosine deaminase activity (>40 U/L) is also supportive of the diagnosis, with a sensitivity of 88% and a specificity of 83%. In addition, polymerase chain reaction to detect *Mycobacterium tuberculosis* from small amounts of fluid or pericardial tissue can sometimes accelerate the diagnosis. Without antituberculous therapy, the disease is fatal, with an early mortality >80%. The effectiveness of corticosteroids in tuberculous pericarditis remains unclear, but some trials suggest that the addition of steroid therapy to standard antituberculous agents may shorten the time to resolution of symptoms.

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ANSWER TO QUESTION 497

A (Braunwald, p. 1535; Fig. 75.18)

Atrioventricular (AV) septal defects include malformations characterized by varying degrees of incomplete

development of the atrial septum, the inflow portion of the ventricular septum, and the AV valves. These anomalies are also known as endocardial cushion defects or AV canal defects.

An ostium primum atrial septal defect (ASD), a type of AV septal defect, occurs immediately adjacent to the AV valves, either of which may be deformed or incompetent. Most commonly it is only the anterior leaflet of the mitral valve that is displaced and "cleft"; the posterior leaflet of the mitral valve and the tricuspid valve are generally not involved. Ostium primum ASDs lead to prominent left-to-right transatrial shunting and have clinical features that resemble those of ostium secundum defects. In addition to similar findings on physical examination, imaging typically reveals right atrial and right ventricular prominence and increased pulmonary vascular markings. Transthoracic echocardiography successfully displays the features of this condition. If cardiac catheterization is undertaken, left ventriculography may show a pathognomonic "gooseneck" deformity that results from a narrowed and elongated left ventricular outflow tract.

When a ventricular septal defect accompanies an ostium primum septal defect (and a common AV orifice is therefore present), the malformation is known as a *complete AV canal defect*. Approximately 35% of patients with common AV canal have accompanying cardiovascular abnormalities, including tetralogy of Fallot, double-outlet right ventricle, transposition of the great arteries, total anomalous pulmonary venous connections, left ventricular outflow tract obstruction, pulmonic stenosis, and persistent left superior vena cava. In addition, common AV canal is often present in patients with trisomy 21 (Down syndrome).

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ANSWER TO QUESTION 498

B (Braunwald, p. 1611; Fig. 78.12; Table 78.2)

As described in the Answer to Question 480, primary prevention risk markers in patients with hypertrophic cardiomyopathy (HCM) include family history of sudden death due to HCM, unexplained recent syncope, repetitive nonsustained VT on ambulatory monitoring, hypotensive or attenuated blood pressure response to exercise, left ventricular (LV) wall thickness ≥30 mm, and extensive or diffuse gadolinium enhancement on cardiac magnetic resonance imaging, defined as >15% of LV mass.

Mutations in the fibrillin-1 gene cause Marfan syndrome, not hypertrophic cardiomyopathy.

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ANSWER TO QUESTION 499

E (Braunwald, p. 1438; Fig. 69.22)

The figure demonstrates mitral valve prolapse with posteriorly directed severe mitral regurgitation by color Doppler (the blue/yellow jet, representing a high-velocity aliasing signal, extends to the posterior left atrium and pulmonary veins). The optimal timing of mitral valve repair or replacement in patients with chronic asymptomatic severe primary mitral regurgitation (MR) is often a difficult clinical decision. The goal is to operate, even in asymptomatic individuals, before irreversible left ventricular (LV) dilatation and dysfunction have developed. If congestive heart failure or ventricular dysfunction supervenes, surgery should be performed as soon as possible to prevent further dysfunction. Thus, serial evaluation of the LV ejection fraction can be helpful in deciding when to intervene. The ejection fraction should be supranormal in patients with advanced MR. Once it falls below 60%, early systolic dysfunction is likely and the risk of postoperative LV dysfunction increases. The LV end-systolic diameter (LVESD) is also helpful in timing surgical intervention. Patients should be referred for surgery before the LVESD exceeds 40 mm, to minimize the risk of postoperative LV dysfunction. Early pulmonary hypertension is considered a relative indication for mitral valve surgery, because patients with this complication, especially if it is accompanied by right ventricular dysfunction, have a worse prognosis. Although they may reduce the regurgitant fraction and improve forward cardiac output, neither angiotensin-converting enzyme inhibitors nor other vasodilators have been shown to delay the need for surgery or improve long-term outcomes in patients with chronic MR.

Per the updated 2017 AHA/ACC guidelines, class I indications for mitral valve surgery in chronic severe MR include symptomatic patients with left ventricular ejection fraction (LVEF) >30%, and asymptomatic patients with evidence of LV dysfunction (LVEF 30% to 60% and/or LV end-systolic diameter [LVESD] ≥40 mm). Class IIa indications include asymptomatic patients with preserved LV function in whom there is >95% likelihood of successful repair, patients with a high likelihood of repair and the development of either atrial fibrillation or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg), and patients with preserved LV function who demonstrate a progressive increase in LVESD or decrease in LVEF.

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ANSWER TO QUESTION 500

B (Braunwald, p. 1544; Fig. 75.23; see also Answer to Question 481)

This patient has tetralogy of Fallot, the components of which are (1) an outlet ventricular septal defect, (2) obstruction to right ventricular (RV) outflow, (3) overriding of the aorta, and (4) RV hypertrophy. In general, total correction of tetralogy of Fallot is advised for almost all patients, even in infancy.[1] Successful early correction appears to prevent the consequences of progressive infundibular obstruction and acquired pulmonary atresia, delayed growth and development, and the complications secondary to hypoxemia and polycythemia. The size of the pulmonary arteries is most important in determining candidacy for primary repair of tetralogy of Fallot, as opposed to the age or size of the infant or child. Marked hypoplasia of the pulmonary arteries is a relative contraindication to a total corrective operation. If this is present, a palliative procedure designed to increase pulmonary blood flow is generally recommended, such as balloon valvuloplasty of the right ventricular outflow tract and pulmonary arteries. Total correction of the tetralogy may then be carried out later in childhood or adolescence at lower risk.

The postoperative period after palliative or corrective surgery is susceptible to several common complications. A sudden increase in pulmonary venous return may lead to left ventricular decompensation, whereas varying degrees of pulmonic valvular regurgitation may increase right ventricular cavity size. In addition, bleeding difficulties may be seen, especially in older polycythemic patients. Complete right bundle branch block or left anterior hemiblock is often observed postoperatively.[2] The greatest cause of early and late mortality and poor surgical results is restriction of pulmonary arterial flow owing to persistent right-sided outflow tract obstruction.[3] Most often, surgical repair leads to relief of symptoms of hypoxemia and severe exercise intolerance that mark the preoperative period.

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ANSWER TO QUESTION 501

A (Braunwald, p. 1688; Figs. 84.8 and 84.9)

The high-resolution contrast-enhanced chest computed tomography (CT) shows large thromboemboli in the right and left main pulmonary arteries (*arrows* in figure). High-resolution chest CT is the primary imaging test in patients with suspected pulmonary embolism (PE), as it offers a number of advantages over other modalities, including direct visualization of thrombus within the pulmonary arteries, the ability to concurrently identify thrombi in the proximal veins in the legs, and imaging of the lung parenchyma to identify alternative diagnoses. Whereas early CT scanners could image the proximal pulmonary arteries, current generation multidetector devices allow high-resolution imaging of even subsegmental pulmonary arteries.[1] Although invasive pulmonary angiography was historically the gold standard for the diagnosis of PE, contrast CT has assumed that role.

Echocardiography is very helpful in risk stratification in patients with large PE. The presence of right ventricular dysfunction portends a higher risk of complications and may warrant consideration of more aggressive treatment such as fibrinolysis or catheter embolectomy.[2]

In patients with suspected PE, the identification of deep vein thrombosis (DVT) of the lower extremities by venous ultrasonography can provide circumstantial evidence of PE disease. The absence of DVT in such patients, however, does not exclude pulmonary embolism because the majority of patients with PE do not have imaging evidence of DVT elsewhere.[3]

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ANSWER TO QUESTION 502

A (Braunwald, p. 1673)

Each of the listed conditions results in elevated right-sided heart pressures. The diastolic "dip-and-plateau" pattern shown in the figure, also known as a "square root sign," is produced when early rapid diastolic inflow into the ventricle commences but is then abruptly halted by an opposing force. In the case of constrictive pericarditis, early diastolic inflow is terminated as ventricular filling reaches the volume limit imposed by the surrounding rigid pericardium. In restrictive cardiomyopathy, the myocardium is abnormally "stiff" and impaired relaxation accounts for a ventricular filling pattern that mimics pericardial constriction. Other conditions with similar right-sided hemodynamics as pericardial constriction include acute right ventricular infarction and massive pulmonary embolism. In these entities, filling of the acutely strained and dilated right ventricle is limited by an unprepared and relatively noncompliant pericardium.

In cardiac tamponade, the surrounding elevated pericardial pressure equalizes the diastolic pressures of the cardiac chambers. Because even early diastolic ventricular filling is impaired (manifest by blunting of the *y* descent on right atrial tracing), there is no dip-and-plateau configuration.

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ANSWER TO QUESTION 503

A (Braunwald, p. 1866)

Primary cardiac tumors are much less common than metastatic cardiac lesions. Approximately 25% of primary cardiac tumors display malignant characteristics, and up to 75% of these are sarcomas. Primary cardiac lymphomas are the next most common group. The sites of cardiac malignancies, in decreasing order of frequency, are the right atrium, the left atrium, the right ventricle, and the left ventricle.

Tumors limited to the myocardium without intracavitary involvement may be asymptomatic or cause arrhythmias or conduction disturbances. Other typical presentations of cardiac malignancies include precordial pain, heart failure, pericardial effusion, tamponade, conduction system disorders, and/or vena caval obstruction. Tumors that involve the right-sided heart chambers may predominantly cause right-sided heart failure. The prognosis of cardiac malignancies is poor, with common survival times of a few weeks to 2 years after diagnosis. Historically, 75% of patients with cardiac sarcoma had evidence of distant metastases at the time of death, but more recent series have shown that only 25% to 50% of patients have metastatic disease at the time of diagnosis, likely owing to earlier detection with improvements in noninvasive diagnostic capabilities.

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ANSWER TO QUESTION 504

A (Braunwald, p. 1675)

This patient has constrictive pericarditis, etiologies of which include prior idiopathic or post-cardiac surgical pericarditis, previous mediastinal radiation therapy, and tuberculosis. Because of the progressive nature of this condition, the majority of patients become symptomatic and come to medical attention because of weakness, peripheral edema, or ascites. The treatment of constrictive pericarditis is complete resection of the pericardium, including excision from the anterior and inferior surfaces of the right ventricle and the diaphragmatic and anterolateral surfaces of the left ventricle. This procedure has been performed more successfully via median sternotomy than by left thoracotomy because the former allows greater mobility of the heart. In recent series, the average operative mortality has ranged between 2.2% and 15%, with a correlation between the degree of the functional disability before the operation and survival after repair. Thus, it is generally recommended that patients undergo pericardiectomy soon after the development of symptoms. Between 14% and 28% of patients display a *low-output* syndrome in the immediate postoperative period, possibly related to rapid dilatation of the heart after release of the restraining pericardium.

Predictors of late survival include preoperative New York Heart Association class, age, renal function, pulmonary artery pressure, and history of radiotherapy exposure to the heart. Symptomatic improvement occurs in approximately 80% of survivors of pericardiectomy, although the time course for such recovery varies. Some patients experience an immediate decrease in symptoms, whereas others may have a delayed or partial response that requires weeks or months for resolution of elevated jugular venous pressure and abnormal filling pressures. The 5-year postoperative survival is approximately 75%. Outcomes are worst in patients with radiation-induced constriction.

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ANSWER TO QUESTION 505

B (Braunwald, p. 1621)

Lyme disease is a tickborne illness caused by the spirochete *Borrelia burgdorferi*. Patients who contract this condition typically develop a rash (erythema chronicum migrans) at the site of the tick bite. Weeks to months later, if the condition is untreated, patients may develop complications involving the joints, central nervous system, and cardiovascular system.[1] In early studies, up to 10% of untreated patients reportedly developed cardiac complications, but in the modern era with early use of antibiotics, Lyme carditis is rare (only 1.1% of patients with Lyme disease reported to the Centers for Disease Control and Prevention [CDC]).[2] The most frequent cardiac manifestation is transient atrioventricular (AV) nodal block, including complete heart block. Although some patients require temporary pacing, AV block usually improves spontaneously and a permanent pacemaker is rarely needed. Lyme disease can also result in myocarditis, which is usually mild and self-limited. Manifestations include nonspecific ST-segment and T-wave abnormalities on the ECG; only rarely do such patients develop symptoms of heart failure. The efficacy of antibiotics for Lyme carditis has not been established, although they are routinely prescribed.

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ANSWER TO QUESTION 506

C (Braunwald, p. 1701)

The natural history of idiopathic pulmonary artery hypertension was defined by a National Institutes of Health (NIH) Registry of patients studied in the 1980s. In this registry, 63% of the patients were female with a mean age of 36 years at the time of diagnosis. The most common initial symptoms were dyspnea (80%), fatigue (19%), syncope (13%), and Raynaud

phenomenon (10%). Patients may describe chest pain, but it is not a very common symptom. In the NIH Registry the most common physical finding was a loud pulmonic component of the second heart sound (P_2). Tricuspid regurgitation was found in 40% and peripheral edema in 32%. Eighty-seven percent of patients had electrocardiographic evidence of right ventricular hypertrophy.

The most common cause of death of patients in the NIH Registry was progressive right-sided heart failure (47%). Sudden cardiac death occurred in 26% and was limited to patients with severe (class IV) symptoms.

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ANSWER TO QUESTION 507

D (Braunwald, p. 1389)

The valve depicted is a calcified, stenotic aortic valve with three cusps. This is an acquired type of aortic stenosis (AS), and the thickened leaflets and nodular calcification are typical of the degenerative form seen in elderly patients. If the valve were bicuspid, it would reflect congenital AS. Historically, degenerative calcific AS was assumed to be due to long-standing mechanical stress on the valve, but more recent studies suggest that chronic inflammation with lipid accumulation is evident, a process that may be similar to the pathogenesis of coronary atherosclerosis. It is therefore salient that diabetes mellitus, hypercholesterolemia (elevated low-density lipoprotein), smoking, and hypertension increase the risk of aortic valve calcification.

The most likely murmur in this case would be crescendo-decrescendo during systole, loudest at the upper right sternal border and radiating toward the neck. Because apposition of the valve leaflets otherwise appears intact, it is unlikely that this individual has significant aortic regurgitation.

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ANSWER TO QUESTION 508

D (Braunwald, pp. 1673–1674; Table 83.7)

It is clinically important to differentiate constrictive pericarditis from restrictive cardiomyopathies, because the former is typically a treatable condition, whereas therapeutic options for the latter are very limited. Both conditions have similar hemodynamic findings during heart catheterization: all of the intracardiac diastolic pressures are elevated and the left and right ventricular pressure tracings usually demonstrate a "dip-and-plateau" configuration. There are, however, several hemodynamic features that can help differentiate these two entities. Because restrictive cardiomyopathy tends to cause some left ventricular (LV) systolic dysfunction as well as the diastolic abnormality, pulmonary hypertension and elevated right ventricular (RV) systolic pressure are frequently also present. Therefore, the ratio of RV systolic pressure to RV end-diastolic pressure (RVEDP) is usually >3 mm Hg, whereas in constrictive pericarditis it is typically <3 mm Hg. Similarly, an RV systolic pressure >50 mm Hg is more consistent with restrictive cardiomyopathy than with pericardial constriction.

Close inspection of simultaneous RV and LV pressure tracings can also help discern which of these conditions is present. The pathophysiology of ventricular interdependence imposed by constrictive pericarditis leads to a *discordance* of LV and RV systolic pressures during respiration. That is, in contrast to the normal situation or in patients with restrictive cardiomyopathy, simultaneous LV and RV pressure measurements during inspiration in constriction show that RV systolic pressure rises as LV pressure falls. Furthermore, in constriction, the LV end-diastolic pressure (LVEDP) and RVEDP are equal, whereas in restriction, disproportionate LV involvement often causes the LVEDP to be more than 5 mm Hg greater than the RVEDP. In restriction (but not constriction), an intravenous volume challenge in the cardiac catheterization laboratory can help accentuate this difference.

Other techniques are also used to distinguish constriction from restrictive cardiomyopathy. For example, chest computed tomography or magnetic resonance imaging most often (>80% of patients) demonstrate a thickened pericardium in constriction, but not in restrictive disease. Also, if performed, a transvenous endomyocardial biopsy is usually normal in constriction but abnormal in myocardial restrictive disease.

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ANSWER TO QUESTION 509

B (Braunwald, pp. 1709, 1715)

Riociguat is a first-in-class therapy approved to improve exercise capacity and functional class in patients with chronic thromboembolic pulmonary hypertension (CTEPH; World Health Organization [WHO] Group 4) who are inoperable, or who have persistent or recurrent symptoms after surgical treatment. It is also approved for use in patients with WHO Group 1 pulmonary arterial hypertension. Riociguat stimulates soluble guanylyl cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). The latter is a potent second messenger that results in vasorelaxation. Although nitric oxide is also a critical biological stimulator of soluble guanylyl cyclase, riociguat does not influence nitric oxide bioactivity.

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ANSWER TO QUESTION 510

D (Braunwald, p. 1678)

This patient has a malignant pericardial effusion. The most common tumors that invade the pericardium are, in order of decreasing frequency, lung, breast, and lymphoma.[1] Malignant pericardial effusions may result from direct extension of tumor into the pericardium or from hematogenous or lymphatic spread. In patients who develop malignant

pericardial effusions, the prognosis is poor; in a study of such patients, the mean survival was 15.1 weeks.[2] After initial drainage of a large malignant pericardial effusion, a repeat echocardiographic study should be obtained within 72 hours to assess the rate of reaccumulation and to ensure the absence of tamponade physiology. If the fluid reaccumulates at a rapid rate, repeat pericardiocentesis followed by more aggressive therapy is warranted. Intrapericardial instillation of a sclerosing agent, such as tetracycline, during catheter drainage has been advocated as a means of controlling recurrences, although complications such as fever, chest pain, and constriction may be troublesome and prognosis of the underlying condition is not significantly improved by this technique.[3] Surgical pericardiectomy is not usually advocated in this situation because of the high operative mortality and the poor prognosis related to the underlying condition. Rather, more limited subxiphoid pericardiostomy ("pericardial window") or video-assisted thoracoscopic pericardiectomy is appropriate for symptomatic palliation.

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ANSWER TO QUESTION 511

E (Braunwald, p. 1664; Fig. 83.2)

This patient has acute pericarditis, a condition with electrocardiographic alterations that are diagnostically useful. Four stages of abnormalities of the ST segments and T waves may be distinguished. *Stage I* includes ST-segment elevation, in which the segment is concave upward; this elevation typically occurs in all leads *except* aVR and V_1. The T waves during this stage are usually upright. PR-segment depression (or PR elevation in aVR) occurs in this stage in approximately 80% of patients. The return of ST segments to baseline, accompanied by T wave flattening, comprises *stage II* of this process. *Stage III*, which occurs in some but not all patients, is characterized by inversion of the T waves, such that the T wave vector is directed opposite to that of the ST segment. This should be contrasted to early inversion of the T wave in acute ST-segment elevation myocardial infarction (in the absence of successful early reperfusion), which occurs *before* the return of ST segments to baseline. In those who develop T wave inversions, *stage IV* represents reversion of the T wave to normal and may not occur for weeks to months after the acute event.

Whereas all four stages are detected in approximately half of patients with acute pericarditis, about 90% of patients will demonstrate *some* of these electrocardiographic abnormalities that allow characterization of an acute chest pain episode as pericarditis.

Stage I changes of pericarditis can be differentiated from the electrocardiographic presentation of early repolarization. An ST-segment/T wave ratio >0.25 in lead V_6 is more consistent with acute pericarditis, whereas a ratio <0.25 is more suggestive of early repolarization.

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ANSWER TO QUESTION 512

B (Braunwald, pp. 1393–1394)

The most serious symptoms of aortic stenosis (AS) in adults are angina pectoris, syncope, and heart failure. When symptoms become manifest, the prognosis for untreated AS is poor. Natural history survival studies show that the interval from the onset of symptoms to the time of death is approximately 5 years in patients with angina, 3 years in those with syncope, and 2 years in patients with heart failure (Fig. 4.38). Angina is present in approximately two-thirds of patients with critical AS, even in the absence of coronary artery disease, resulting from the combination of increased oxygen demand and the reduction of oxygen delivery.

Syncope in AS occurs most commonly *during or after exertion*. It is related to reduced cerebral perfusion caused by systemic vasodilatation during exercise in the presence of a fixed cardiac output. Sudden death occurs with increased frequency in patients with critical AS, but almost invariably in those who have had previous symptoms.

Symptoms of AS may become exacerbated by the development of atrial fibrillation. Because of the decreased diastolic compliance of the hypertrophied ventricle, patients with AS are highly dependent on atrial contraction to deliver preload and maintain cardiac output. Thus, when atrial fibrillation develops, significant hemodynamic deterioration may follow.

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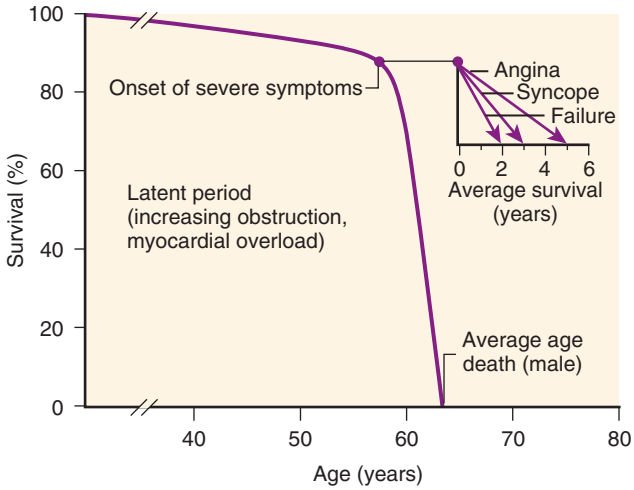

FIG. 4.38 *From Ross Jr J, Braunwald E. Aortic stenosis.* Circulation. *1968;38(suppl V):61.*

ANSWER TO QUESTION 513

B (Braunwald, p. 1708)

This patient has severe pulmonary hypertension with systemic hypotension. Using the provided data, the patient's cardiac output ([mean pulmonary artery pressure – mean pulmonary capillary wedge pressure] / pulmonary vascular resistance) is 3.1 L/min and the cardiac index (= cardiac output / body surface area) is reduced at 2.0 L/min/m^2, consistent with cardiogenic shock (see Answer to Question 384). Current guidelines recommend initiation of intravenous prostacyclin in patients with severe pulmonary hypertension and cardiogenic shock. Although macitentan, a nonselective endothelin receptor antagonist, is approved for the treatment of pulmonary arterial hypertension, no data are currently available for use of this therapy in patients with cardiogenic shock. The other two options (tPA and digoxin) would not be appropriate for this clinical scenario.

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ANSWER TO QUESTION 514

C (Braunwald, pp. 1667, 1671, 1677)

Penetrating cardiac trauma is most commonly due to stab wounds and gunshot injuries. The consequences of such injury depend on the nature of the penetrating object, the size of the wound, the entering location, and the structures that are impacted. The site of cardiac injury can be predicted by the location of entry on the chest wall. Because of its anterior location, the *right* ventricle is at greatest risk of penetrating chest trauma. Of note, survival is higher in patients who suffer penetrating injuries to the ventricles than the atria, because the former are thicker walled structures more likely to seal the laceration site.

Patients who suffer penetrating injuries to the chest wall are at high risk of cardiac tamponade because of bleeding into the pericardial sac. If this complication develops, patients usually have muffled heart sounds, jugular venous distention, and hypotension with a narrowed pulse pressure; pulsus paradoxus is often present. Many trauma surgeons discourage pericardiocentesis for suspected tamponade after acute trauma because clots form quickly and often cannot be drained successfully through a needle and a negative pericardiocentesis does not rule out tamponade. Furthermore, if there is continued bleeding from cardiac perforation, any beneficial effect of pericardiocentesis would be short-lived. Therefore, patients with penetrating chest injuries, significant bleeding, and a clinical picture that raises concern of tamponade should proceed directly to thoracotomy. Rupture of the interventricular septum has been described as a potential late complication in patients who have experienced penetrating chest trauma.

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ANSWER TO QUESTION 515

C (Braunwald, p. 1543)

The presentation of persistent PDA in adults depends on the degree of left-to-right shunting. Small *silent* shunts (i.e., those without murmurs) are almost always asymptomatic and are incidental findings during echocardiography. The risk of endarteritis is negligible in such patients. However, small *audible* shunts may occasionally present because of a superimposed endovascular infection.

Moderate shunts impose a volume load on the left ventricle and left atrium, resulting in left ventricular dysfunction and atrial fibrillation. Such patients typically present with either dyspnea or palpitations. On physical examination, a loud continuous "machinery" murmur is best appreciated in the first or second left intercostal space. The pulse pressure is usually *wide* owing to aortic diastolic runoff into the pulmonary trunk.

Large shunts initially cause left-sided volume overload, but subsequently lead to irreversible pulmonary hypertension and Eisenmenger physiology. Chest radiology at that stage reveals enlarged central pulmonary arteries with peripheral pruning. Closure of a clinically detectable PDA is recommended except when it is accompanied by irreversible pulmonary hypertension. A multicenter trial of the Amplatzer occluder device indicates that transcatheter closure can achieve a success rate of 99% for complete ductal closure at 1 year.

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ANSWER TO QUESTION 516

B (Braunwald, p. 1586)

Chronic heavy consumption of alcohol is associated with systolic and diastolic ventricular dysfunction, systemic hypertension, arrhythmias, and sudden death. Alcohol abuse is a leading cause of nonischemic dilated cardiomyopathy. The likelihood of developing alcohol-induced dilated cardiomyopathy correlates with the amount of alcohol consumed over a lifetime. Most men with this condition have consumed more than 90 g of ethanol daily for over 5 years. Women appear to be *more* susceptible to the development of dilated cardiomyopathy at the same level of alcohol consumption as men. With abstinence from alcohol, left ventricular systolic and diastolic function typically improve, often dramatically. Most of the improvement occurs in the first 6 months of abstinence, but systolic function may continue to normalize over a more prolonged time. The prognosis of patients who continue to drink heavily is poor.

Alcohol consumption at *moderate* levels in those without known coronary artery disease is associated with a reduction in cardiovascular mortality, including a *lower* incidence of sudden death.

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ANSWER TO QUESTION 517

C (Braunwald, pp. 1591–1592)

Amyloidosis can afflict the cardiovascular system in several ways. Restrictive cardiomyopathy with diastolic dysfunction is the most common presentation and is due to myocardial infiltration by amyloid protein. In this situation, right-sided heart failure symptoms often predominate, with peripheral edema, hepatic congestion, and elevated jugular venous pressure. A second common presentation is biventricular heart failure due to systolic dysfunction. In some patients, congestive symptoms may be exacerbated by amyloid deposition in the atria with loss of effective atrial transport, despite the presence of sinus rhythm. Orthostatic hypotension occurs in 10% of patients with amyloidosis and results from infiltration of the autonomic nervous system. Other cardiovascular presentations include rhythm disturbances (especially atrial fibrillation) and conduction system disease. The ECG typically demonstrates *low* limb lead voltage. Small pericardial effusions are often observed by echocardiography in cardiac amyloidosis; however, significant pericardial disease is rare and cardiac tamponade and pericardial constriction are not typical complications.

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ANSWER TO QUESTION 518

E (Braunwald, pp. 1484, 1498)

Staphylococcus aureus is one of the most aggressive organisms responsible for infective endocarditis, and infection with this bacterium results in rapid destruction of heart valves and surrounding tissues. *S. aureus* has a propensity to cause metastatic infections, including in the central nervous system, which is affected in 30% to 50% of patients.[1] Central nervous complications include cerebral embolism, meningitis, and cerebral and subarachnoid hemorrhage due to rupture of mycotic aneurysms. Patients with right-sided endocarditis (i.e., tricuspid valve involvement) due to *S. aureus* have a better prognosis than those with left-sided infections.

Because *S. aureus* endocarditis is so destructive, it requires prompt and aggressive therapy. Although some experts have advocated early surgical intervention for native valve endocarditis due to this organism, there is a risk of infecting the new prosthetic valve if surgery is performed before adequate sterilization of the blood. Therefore, initial aggressive antibiotic therapy should be undertaken, with surgery reserved for those who fail to respond or for those who develop complications such as intractable heart failure. In contrast, prosthetic valve endocarditis caused by *S. aureus* carries an extremely high mortality rate, approaching 50% in patients treated medically,[2] and early surgical therapy is generally recommended.

Methicillin-resistant *S. aureus* (MRSA) is a common cause of both nosocomial and community-acquired infections, such that empiric therapy for suspected *S. aureus* endocarditis should begin with an agent that is effective against MRSA, such as vancomycin.

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ANSWER TO QUESTION 519

B (Braunwald, p. 1565; Fig. 75.42)

In Ebstein abnormality, there is apical displacement of the septal leaflet of the tricuspid valve. Associated anomalies include atrial septal defects (or patent foramen ovale) in 50% of patients, accessory conduction pathways (usually right-sided) in 25%, and less commonly pulmonic stenosis or atresia, ventricular septal defects, aortic coarctation, and patent ductus arteriosus.

The usual clinical manifestations of Ebstein anomaly with severe tricuspid deformity in infancy are cyanosis, failure to thrive, and congestive heart failure. However, patients with less advanced disease may be asymptomatic until early adulthood, when symptoms include exertional dyspnea and fatigue, palpitations, and cyanosis due to right-to-left shunting. Cardiac examination typically shows wide splitting of S_1, a *widely* split S_2 (due to accompanying right bundle branch block [RBBB]), a right-sided S_3, and the murmur of tricuspid regurgitation.

The ECG may be normal, but common findings include right atrial enlargement, a prolonged PR interval, and RBBB. When an accessory conduction pathway is present, the ECG may show preexcitation with a shortened PR interval and delta wave.

The diagnosis of Ebstein anomaly can be confirmed by echocardiography, with the finding of apical displacement of the septal leaflet of the tricuspid valve, combined with an elongated anterior leaflet.

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ANSWER TO QUESTION 520

C (Braunwald, p. 1598)

Löffler endocarditis is a syndrome associated with eosinophilia that occurs in temperate climates. The typical patient with this condition is a male in his fourth decade with a persistent eosinophilia count >1500/mm^3 for at least 6 months, and evidence of organ involvement.[1] Cardiac manifestations are present in approximately 75% of patients. The eosinophilia may be reactive (e.g., associated with an allergic or parasitic disorder), associated with leukemia, or there may be no apparent cause. The combination of hypereosinophilia and cardiac involvement is also part of the Churg-Strauss syndrome, which can be differentiated from Löffler endocarditis by the coexisting presence of asthma, nasal polyposis, and necrotizing vasculitis.[2]

The pathology of Löffler endocarditis involves mural endocardial thickening of the inflow and apical portions

of both ventricles. Histologic findings include (1) an acute inflammatory eosinophilic myocarditis, (2) thrombosis and inflammation of intramural coronary vessels, (3) mural thrombosis, and (4) fibrotic thickening of the ventricular wall.

Clinically, patients present with weight loss, fever, cough, rash, and heart failure. Cardiomegaly is present early in the course and the murmur of mitral regurgitation is common. Systemic embolism occurs frequently and may lead to neurologic and renal dysfunction.

Laboratory findings include an elevated erythrocyte sedimentation rate and an increased eosinophil count. Imaging frequently demonstrates localized thickening of the posterobasal left ventricular wall with absent or reduced motion of the mitral posterior leaflet by echocardiography. The apex may contain thrombus. Systolic ventricular function is usually normal. The hemodynamic consequences of the dense endocardial scarring are those of a restrictive cardiomyopathy (RCM) with abnormal diastolic filling. Findings at cardiac catheterization are consistent with RCM, including elevated ventricular filling pressures with an early diastolic "dip-and-plateau" configuration.

Medical treatment of Löffler endocarditis is moderately effective. Administration of steroids and hydroxyurea can improve survival.

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ANSWER TO QUESTION 521

B (Braunwald, p. 1699)

The figure demonstrates a midsystolic notch in the right ventricular outflow tract Doppler velocity profile, which is indicative of elevated pulmonary vascular resistance. Notching occurs due to a reflective fluid wave from the pulmonary vascular bed toward the right ventricle and is a consequence of decreased pulmonary vascular compliance. It occurs more commonly in patients with pulmonary hypertension due to pulmonary vascular disease (e.g., group I pulmonary hypertension) than in patients with pulmonary hypertension on the basis of left heart failure.

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ANSWER TO QUESTION 522

C (Braunwald, p. 1418)

This woman has rheumatic heart disease. She has mitral stenosis (MS) based on the loud S_1 and apical opening snap. Many patients with advanced MS have an early blowing diastolic murmur along the left sternal border and a normal systemic pulse pressure. In the majority of such patients, the murmur is due to mild aortic regurgitation (AR) and it is usually of little clinical importance. However, approximately 10% of patients with MS have severe rheumatic AR. This can usually be recognized by peripheral signs of AR, such as a widened pulse pressure and signs of left ventricular (LV) enlargement by ECG and chest radiograph, with confirmation by echocardiography.

In patients with multivalvular disease, a proximal valve lesion may mask the presence of a more distal abnormality. Thus, significant AR may not be easily auscultated in patients with severe MS. The widened pulse pressure, in particular, may be absent in the presence of severe MS. Furthermore, the apical diastolic Austin Flint murmur associated with AR may be mistaken for the rumbling murmur of MS. These two murmurs may be distinguished during auscultation by means of bedside maneuvers. Isometric handgrip and squatting augment the diastolic murmur of AR (and the associated Austin Flint murmur), but have little effect on the murmur of MS. In this patient, the response to handgrip is consistent with the presence of an Austin Flint murmur.

The fact that the ECG of this patient shows LV hypertrophy in addition to left atrial enlargement is inconsistent with simple MS and suggests that the degree of superimposed AR is significant. There is no evidence on examination of tricuspid stenosis or mitral regurgitation. Pulmonic regurgitation due to pulmonary hypertension in patients with MS can also cause an early diastolic murmur along the left sternal border. However, such a murmur would be associated with a loud pulmonic component of S_2 and would not intensify with handgrip.

ANSWER TO QUESTION 523

E (Braunwald, pp. 1420–1421)

Diuretic therapy and negative chronotropic agents are the mainstays of medical therapy for patients with symptomatic mitral stenosis (MS). The high left atrial pressure in this condition elevates pulmonary venous pressure, resulting in dyspnea due to transudation of fluid into the alveolar spaces and stimulation of pulmonary J fibers. Diuretics reduce intravascular volume and left atrial pressure and therefore improve dyspnea. Maintaining a controlled, relatively slow heart rate prolongs diastole, maximizes the time for left atrial emptying, and reduces left atrial pressure. Thus, negative chronotropic agents such as beta blockers improve exercise capacity in MS patients, even in individuals in sinus rhythm.

Since left ventricular contractile function is normal in pure MS, digitalis glycosides have no beneficial hemodynamic effect and are useful only as agents for ventricular rate control if atrial fibrillation supervenes, though beta blockers are preferred for this purpose. There is insufficient evidence to support the routine use of anticoagulants to reduce the risk of thromboembolic events in patients with MS in the absence of atrial fibrillation, a history of thromboembolism, or extreme left atrial enlargement.

As reviewed in the Answer to Question 464, endocarditis prophylaxis before dental procedures is not recommended for native valve abnormalities such as MS.

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Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2489.

ANSWER TO QUESTION 524

D (Braunwald, pp. 1676–1677)

Most cases of infectious acute pericarditis are caused by a virus. The most commonly implicated viruses are the enteroviruses and adenovirus. In contrast, the incidence of nontuberculous bacterial pericarditis is low, approximately 5% of cases, and it develops most often as a complication of pneumonia, mediastinitis, or infective endocarditis. The most frequently involved bacterial organisms are streptococcal and staphylococcal species. The overall survival in bacterial pericarditis is poor, averaging 30%.

Tuberculosis was once the leading cause of constrictive pericarditis worldwide. However, with effective screening and treatment programs, the incidence of this condition is now rare in developed nations, and it is encountered mostly in immunocompromised hosts and in developing societies.

Pericarditis associated with fungal disease is most often caused by *Histoplasma*. It occurs in otherwise healthy young individuals and is thought to be a noninfectious inflammatory effusion secondary to fungal infection in nearby mediastinal lymph nodes. This process should be considered in patients with suspected pericarditis who live where the fungus is endemic—the Ohio and Mississippi rivers' valleys. It is generally a self-limited disease, and treatment typically consists of nonsteroidal anti-inflammatory agents without antifungal therapy. The latter is necessary only when there is evidence of disseminated histoplasmosis.

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ANSWER TO QUESTION 525

D (Braunwald, pp. 1621–1622)

Chagas disease is caused by the protozoan *Trypanosoma cruzi*. It is prevalent in Central and South America, where 8 to 10 million people are infected. The disease is characterized by three phases: acute, latent, and chronic. During the acute phase, the disease is transmitted to humans by the bite of a reduviid bug, commonly called the kissing bug. After inoculation, protozoa multiply and migrate widely through the body. Clinical manifestations during the acute phase may include fever, muscle pains, hepatosplenomegaly, myocarditis, and meningoencephalitis. The disease then enters an asymptomatic latent phase for many years. Typically, chronic cardiac manifestations become evident 5 to 15 years after the initial infection. Interestingly, only 30% of infected individuals develop symptoms of chronic Chagas disease, and many individuals with high parasite burdens do not. There is poor correlation between the level of parasitemia and the severity of disease later.

The major cardiovascular findings of the chronic phase of Chagas disease include myocardial fibrosis, conduction system abnormalities, ventricular dilation (dilated cardiomyopathy), and apical aneurysm formation. Associated clinical manifestations include progressive heart failure (predominantly right-sided), arrhythmias, conduction disturbances, and possible thromboembolism. There is usually severe cardiomegaly, with the most common electrocardiographic abnormalities being *right* bundle branch block and left anterior fascicular block; atrioventricular block occurs less frequently. Ventricular arrhythmias are common.

The diagnosis of Chagas disease is confirmed using a complement-fixation test (Machado-Guerreiro test). Antitrypanosomal therapy should be administered to patients with acute disease, those with positive serologies without symptoms of chronic disease, and those with early cardiac involvement. Such therapy is not effective in reversing pathologic changes and complications in those with advanced chronic Chagas cardiac disease; standard heart failure and antiarrhythmic treatments should be undertaken instead.

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ANSWER TO QUESTION 526

C (Braunwald, p. 1537)

The echocardiogram demonstrates prominent echogenicity along both surfaces of the interatrial septum (*arrow* in Fig. 4.39), consistent with normal deployment of a transcatheter atrial septal defect (ASD) closure device. Indications for this method are the same as for surgical closure of an ASD, but strict structural criteria must be met. Successful closure can be accomplished in the majority of patients, and complications, such as device embolization or atrial perforation, are rare.

Atrial myxomas are the most common primary heart tumor. When attached to the interatrial septum, echocardiography most commonly demonstrates a mobile mass attached to the limbus of the fossa ovalis by a stalk. Lipomatous hypertrophy of the interatrial septum occurs most

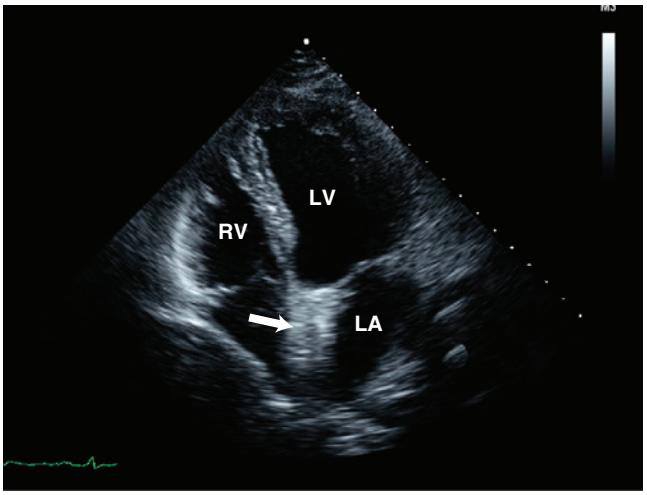

FIG. 4.39

often in obese, elderly female patients. It represents a prominent fatty deposition at the interatrial septum that spares the fossa ovalis, creating a thick "dumbbell" appearance on echocardiography. This condition is associated with a high incidence of atrial arrhythmias. In cardiac amyloidosis, infiltration causes increased thickness of all cardiac chamber walls, not just the interatrial septum.

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ANSWER TO QUESTION 527

D (Braunwald, pp. 1415–1420; Fig. 69.1; see also Answer to Question 467)

The parasternal long-axis view displays typical rheumatic deformity of the mitral valve with diastolic doming of the leaflets, with a "hockey-stick" appearance of the anterior leaflet (*arrow* in Fig. 4.40). There is accompanying left atrial enlargement. The transmitral spectral Doppler in part *B* in Fig. 4.29 shows an increased early diastolic velocity with a slowed diastolic descent, indicative of a diastolic pressure gradient across the valve due to mitral stenosis (MS).

Atrial fibrillation (AF) is common in patients with MS, and the prevalence increases with age. It tends to be poorly tolerated because of the lack of effective atrial contribution to left ventricular filling and the shortened diastolic filling time in patients with rapid ventricular rates. AF also predisposes to atrial thrombus formation and embolization. The risk of systemic embolism in MS correlates directly with patient age and left atrial size and inversely with cardiac output.

Infective endocarditis in MS tends to be more common in patients with milder forms of the disease, occurring less frequently on very thickened and calcified mitral valves.

Only about 15% of patients with isolated MS experience anginal-type chest discomfort. This symptom may arise from right ventricular hypertension, concomitant atherosclerosis, or coronary obstruction due to embolization of left atrial thrombus.

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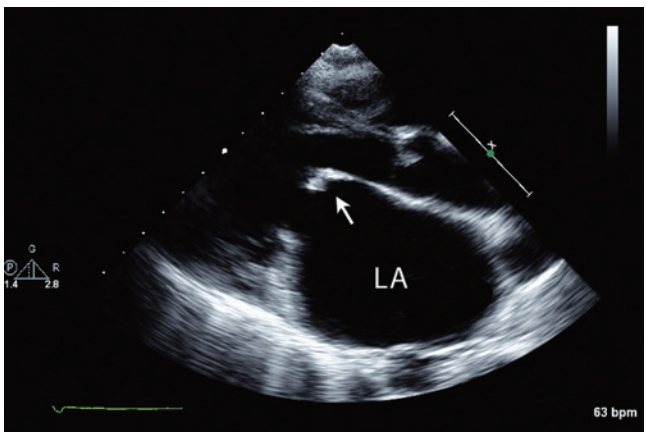

FIG. 4.40

Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:e57–e185.

ANSWER TO QUESTION 528

A (Braunwald, pp. 1542–1543)

These findings are consistent with patent ductus arteriosus (PDA). In the majority of preterm infants weighing <1500 g, a PDA persists for a prolonged period, and in approximately one-third of those infants, a large shunt leads to significant cardiopulmonary deterioration. Noninvasive evaluation may reveal evidence of significant shunting before the appearance of physical findings of ductal patency. Physical examination may reveal bounding peripheral pulses, an infraclavicular and interscapular systolic murmur (sometimes heard as a continuous murmur), a hyperactive precordium, hepatomegaly, and recurrent episodes of apnea and bradycardia. An increase in the cardiothoracic ratio is seen on sequential chest radiographs and may be accompanied by increased pulmonary arterial markings, perihilar edema, and ultimately generalized pulmonary edema. Echocardiography may demonstrate increased left ventricular end-diastolic and left atrial dimensions, and color Doppler confirms the presence of left-to-right shunting.

Management of the premature infant with a PDA depends on the clinical presentation of the disorder. In an asymptomatic infant, intervention is usually unnecessary, because the PDA will almost always undergo spontaneous closure and will not require surgical ligation and division. Infants with respiratory distress syndrome and signs of a significant ductal shunt usually are unresponsive to medical measures to control congestive heart failure and require closure of the PDA for survival. This is usually accomplished pharmacologically with indomethacin to inhibit prostaglandin synthesis and achieve constriction and closure. Approximately 10% of infants are unresponsive to indomethacin and require ligation.

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ANSWER TO QUESTION 529

A (Braunwald, pp. 1603–1609)

The echocardiogram demonstrates hypertrophic cardiomyopathy (HCM) with asymmetric septal hypertrophy. The most common physiologic abnormality in HCM is not systolic, but rather diastolic dysfunction. HCM is characterized by abnormal stiffness of the left ventricle, which results in impaired diastolic filling. The abnormal diastolic relaxation increases the left ventricular (LV) end-diastolic pressure with subsequent elevations of left atrial, pulmonary venous, and pulmonary capillary pressures.

Although the generation of a pressure gradient due to associated subaortic obstruction would imply that LV ejection

is slowed or impeded during systole, there is actually *rapid* ventricular emptying and a normal, or even augmented, ejection fraction in such patients. Hemodynamic studies have confirmed that the majority of LV output is unusually rapid in patients with HCM and is completed earlier in systole than normal, regardless of whether an outflow gradient is present. Thus, the common symptom of dyspnea in this condition is largely due to impaired diastolic relaxation rather than compromised systolic ejection. Although there is a strong temporal and quantitative relationship between mitral valve systolic anterior motion and the development of subaortic obstruction, symptoms do not necessarily correlate with the magnitude of the generated gradient. Furthermore, there can be significant variations on a daily basis in both the extent of the obstruction (and associated murmur) and symptomatology.

Exertional syncope and angina occur in some patients with HCM, and these symptoms are likely related, at least in part, to systolic obstruction.

The echolucent space posterior to the left ventricle in the echocardiogram represents a tiny pericardial effusion.

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ANSWER TO QUESTION 530

D (Braunwald, pp. 1409–1410)

Acute aortic regurgitation (AR) is most often caused by infective endocarditis, aortic dissection, or trauma. Many of the physical findings typical of chronic AR are not present in patients with acute AR. In acute AR, the left ventricle has not yet dilated and is relatively noncompliant, such that its early diastolic pressure rises rapidly. If the resulting left ventricular (LV) diastolic pressure exceeds the left atrial pressure, the mitral valve may close *prematurely* and can produce diastolic mitral regurgitation. Because the elevated LV diastolic pressure blunts runoff of blood from the aorta into the left ventricle, the aortic diastolic pressure does not decline as substantially as in chronic AR. Therefore, the pulse pressure does not widen significantly, and physical findings typical of an increased pulse pressure, such as Corrigan pulse (abrupt upstroke, then quick collapse of the arterial pulse), are absent. Similarly, the duration of the diastolic murmur is shorter than in chronic AR.

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ANSWER TO QUESTION 531

A (Braunwald, pp. 1544–1547, 1574–1575; see also Answer to Question 481)

Tetralogy of Fallot is the most common cyanotic congenital cardiac defect that presents after the newborn period. Most experts advocate surgical repair in the first 6 months of life to avoid chronic cyanosis and its complications. Although initial operative outcomes are excellent, provided that the ventricular septal defect is adequately closed and right ventricular outflow tract obstruction is relieved, many patients develop progressive pulmonary regurgitation, especially when a transannular patch is used to enlarge the right ventricular outflow tract. The optimal timing to correct this complication with pulmonary valve replacement (PVR) remains uncertain, but it is appreciated that PVR should be performed when there is severe pulmonary regurgitation with substantial right ventricular dilation or dysfunction, even in the absence of subjective dyspnea. In fact, adults with congenital heart disease tend to underestimate their exercise intolerance, underscoring the importance of objective measures of exercise capacity, such as cardiopulmonary exercise testing.

Patients with repaired tetralogy of Fallot are at increased risk of sudden death (SD). Although criteria for an implantable cardioverter-defibrillator for primary prevention remain controversial, a QRS width >180 ms and left ventricular dysfunction have been identified as risk factors for SD. Atrial arrhythmias are also common in patients with repaired tetralogy of Fallot; risk factors include left atrial dilation and tricuspid regurgitation.

The American Heart Association guideline for the prevention of endocarditis recommends predental antibiotic prophylaxis for patients with repaired congenital heart disease with residual defects at the site of, or adjacent to, prosthetic material (e.g., Dacron patch).

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ANSWER TO QUESTION 532

B (Braunwald, pp. 1713–1715)

The development of pulmonary hypertension in patients with chronic obstructive lung disease (COPD) arises from several factors including pulmonary vasoconstriction induced by alveolar hypoxemia, acidemia, the mechanical effects of high lung volumes on the pulmonary vessels, and small-vessel loss in regions of emphysema.[1] Right ventricular (RV) hypertrophy and dilatation may develop over time (Fig. 4.41).

The only effective treatment for patients with COPD and pulmonary hypertension is supplemental oxygen, with several studies showing an improvement in morbidity and mortality.[2] In a series of trials in the 1980s, continuous oxygen supplementation was more effective than nocturnal therapy alone. Thus, long-term oxygen therapy is recommended if the resting PaO_2 is <60 mm Hg.

Although digoxin may improve the RV ejection fraction in some patients with RV dilation and dysfunction, it can also contribute to adverse pulmonary vasoconstriction and has not been shown to have a beneficial effect on survival.

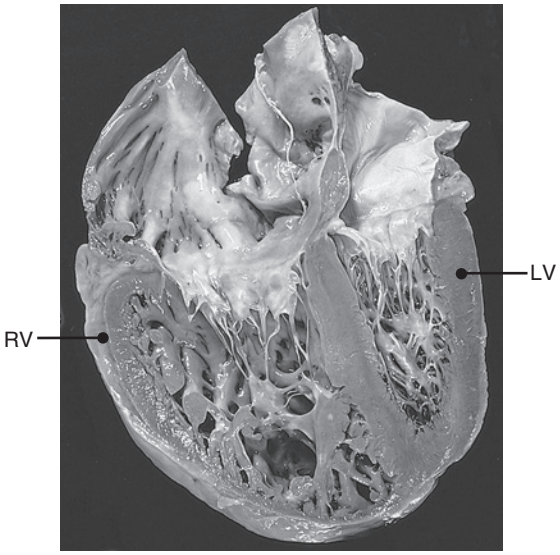

FIG. 4.41 *From Kumar V, Abbas AK, Fausto N, eds.* Robbins and Cotran Pathologic Basis of Disease. *7th ed. Philadelphia: Elsevier; 2005:588.*

Furthermore, digitalis toxicity may be precipitated by the hypoxemia and acidemia often associated with COPD. Theophylline, beta-agonists, hydralazine, and other pulmonary vasodilators (e.g., phosphodiesterase inhibitors, endothelin receptor antagonists such as bosentan) have not been shown to improve survival of patients with pulmonary hypertension due to COPD.[3–5]

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ANSWER TO QUESTION 533

B (Braunwald, pp. 1559–1561)

Coarctation of the aorta (Fig. 4.42) occurs two to five times more commonly in males.[1] Most infants and children with coarctation are asymptomatic. In contrast, neonates with severe coarctation often develop overt heart failure due to the sudden rise in left ventricular (LV) afterload when the ductus arteriosus closes at birth. Coarctations discovered in the adult are frequently associated with additional abnormalities, including bicuspid aortic valve (50% to 85%) and intracranial aneurysms.

Pathophysiologically, significant coarctation places a pressure load on the left ventricle, which leads to LV hypertrophy and ultimately heart failure. On physical examination, findings include a differential systolic blood pressure (brachial artery pressure greater than popliteal artery pressure by >10 mm Hg) and radial-femoral pulse delay. The mean survival time of patients with uncorrected coarctation is 35 years. Heart failure is the most common cause of death in adults, followed by bacterial endocarditis, intracranial hemorrhage, and aortic dissection. Surgical repair is associated with low mortality. Outcomes are most influenced by the presence of other congenital anomalies or more complex variants of aortic coarctation involving the aortic arch, rather than the type of surgery performed.

Recoarctation and true aneurysm formation at the site of repair can occur.[2] The reported incidence of these complications varies widely in the surgical literature, ranging from 6% to 60%. Prior hypertension resolves in up to 50% of patients but it may recur later in life.[2,3]

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ANSWER TO QUESTION 534

B (Braunwald, p. 1869)

The apical four-chamber views demonstrate a large mass attached to the interatrial septum, which in diastole prolapses across the orifice of the mitral valve and is most consistent with a left atrial myxoma. Echocardiography is helpful in differentiating between left atrial thrombus and myxoma. Thrombus usually produces a layered appearance and tends to localize to the more posterior segments of the atrium. In contrast, left atrial myxoma is often mottled in appearance and typically attaches along the limbus of the fossa ovalis of the interatrial septum. In some atrial myxomas, including the one demonstrated here, echolucent areas are seen within the tumor mass that correspond pathologically to regions of hemorrhage.

Eighty-three percent of cardiac myxomas appear in the left atrium and 12.7% in the right atrium; the remainder are biatrial or located in one of the ventricles. Signs and symptoms of left atrial myxoma may be similar to those of mitral valve disease owing to interference of the mass with normal mitral valvular function. Physical examination may demonstrate pulmonary congestion and an intensified S_1. It is believed that the loud S_1 occurs when there is late onset of mitral valve closure as a consequence of tumor prolapse through the valvular orifice. An early diastolic sound (tumor "plop") may be present, although this is often positional and may be confused with an S_3. Cardiac myxomas may also produce a variety of constitutional symptoms and extracardiac findings, including fever, weight loss, and arthralgias. These symptoms have been attributed to the tumor's production of interleukin-6. Several abnormal laboratory findings may be present, including an elevated erythrocyte sedimentation rate, polycythemia, leukocytosis, and anemia.

Approximately 10% of cardiac myxomas are familial. In such cases, patients typically present at a younger age

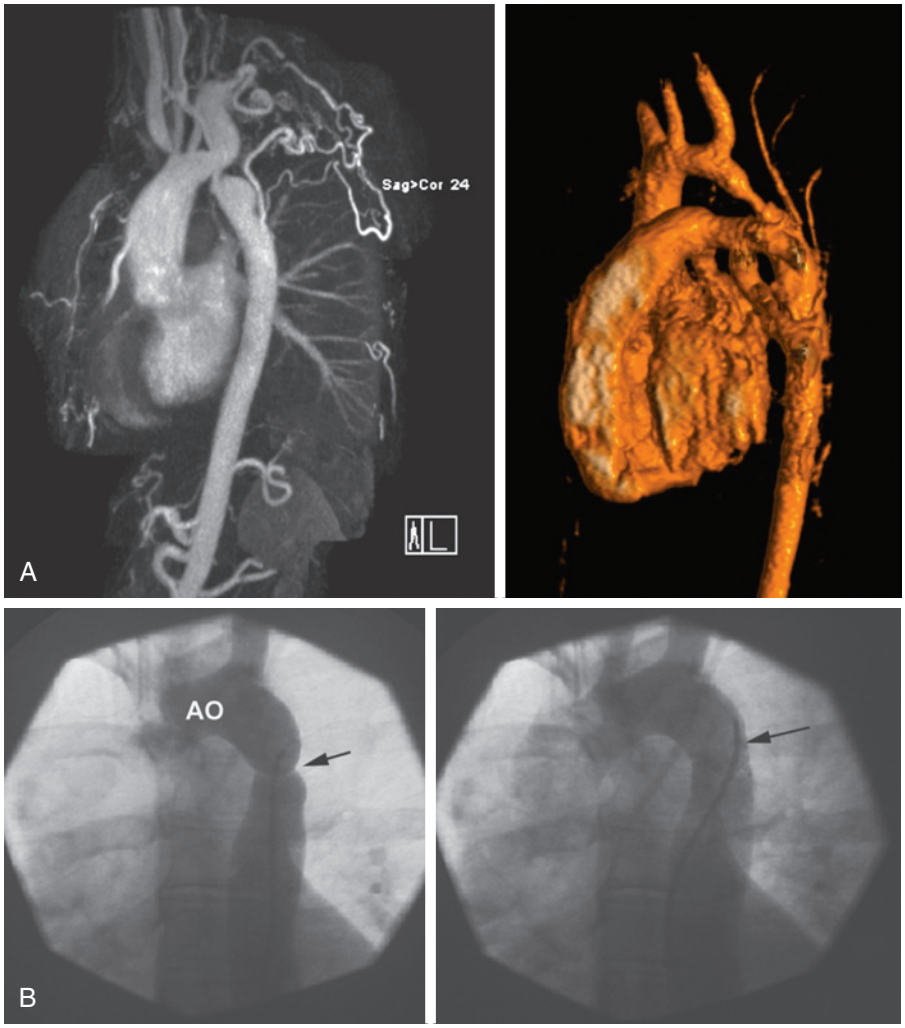

FIG. 4.42 *(A) Montage of coarctation of the aorta. The left image is a specimen that shows the site of the posterior shelf. The right image is from magnetic resonance imaging and shows the posterior shelf and some associated transverse arch hypoplasia. (B) Angiogram of coarctation of the aorta before and after stenting* (arrows). AO, *Aorta.*

and are more likely to have multiple additional myxomas in noncardiac locations. *Carney complex* is inherited as an autosomal dominant syndrome consisting of cardiac myxomas, along with dermatologic (hyperpigmented skin lesions) and endocrine abnormalities (adrenal, pituitary, testicular).

The treatment of symptomatic cardiac myxoma is prompt surgical resection of the tumor. Recurrences appear in approximately 3% of patients, with a higher incidence in those with familial myxomas.

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ANSWER TO QUESTION 535

D (Braunwald, pp. 1686–1689; Fig. 84.11)

The diagnostic approach for possible pulmonary embolism (PE) involves careful clinical assessment in conjunction with judicious diagnostic testing (Fig. 4.43). The most common symptoms of PE are dyspnea and pleuritic chest pain. Physical examination may be unremarkable, or findings may include tachycardia, tachypnea, and increased intensity of the pulmonic component of S_2.

Arterial blood gas determinations are generally not helpful in the diagnosis of PE. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, the PaO_2 did not differentiate between individuals with and without PE. Thus, normal values of the alveolar-arterial oxygen gradient do not exclude PE.

When PE is highly suspected, chest computed tomographic (CT) angiography is the superior imaging test.[1,2] This technique has the capability to visualize even subsegmental pulmonary emboli. When the clinical probability of PE is not high, a normal plasma D-dimer assay usually suffices to rule out this condition.[3,4] The D-dimer assay is highly sensitive for the presence of PE, but has low specificity because elevations also occur in sepsis, recent surgery or trauma, malignancies, and other systemic illnesses. A normal D-dimer assay therefore has excellent negative predictive value.

In patients with large PE, electrocardiographic signs of right-sided heart strain may be present (including ST-segment and T wave abnormalities in the right precordial leads (V1–V4), right-axis deviation, new right bundle branch block,

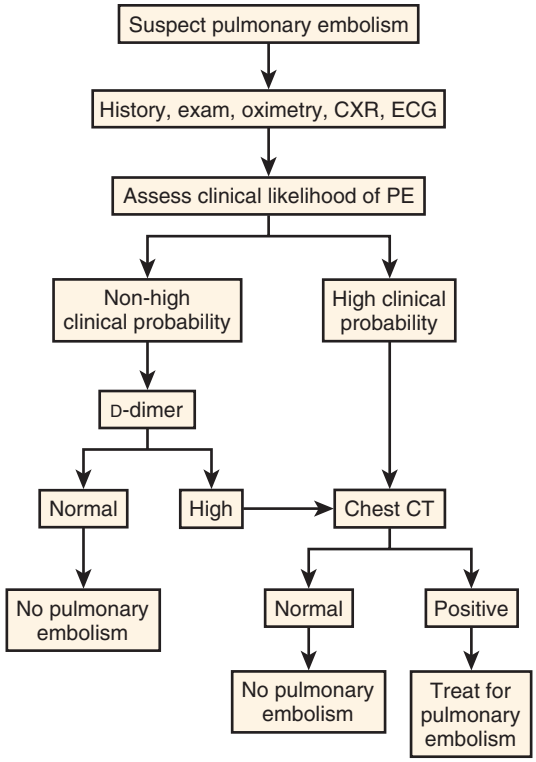

FIG. 4.43

and an $S_1Q_3T_3$ pattern), but such findings are generally absent when small PEs are present. The most common electrocardiographic abnormality in PE is simply sinus tachycardia, and a normal tracing does not exclude PE.

Ventilation-perfusion lung scanning results are often ambiguous. Although PE is very unlikely to be present with a completely normal scan, and very likely when the test is "high probability," scans frequently fall between these two extremes ("intermediate probability") and do not provide definitive results. This test is now useful for diagnosis of acute PE only in occasional circumstances (e.g., renal insufficiency, a history of anaphylaxis to IV contrast agents precluding a CT angiogram, or pregnancy).

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ANSWER TO QUESTION 536

D (Braunwald, pp. 1866–1973)

Primary tumors of the heart are rare (autopsy incidence 0.001% to 0.03%), with benign tumors representing >80%. The majority of benign cardiac tumors are myxomas, followed in frequency by lipomas, papillary fibroelastomas, rhabdomyomas, and fibromas. Among the malignant tumors, the most common are sarcomas, and of these, angiosarcoma and rhabdomyosarcoma are the most frequent forms.[1]

Although it can be difficult to differentiate benign from malignant tumors clinically, certain findings may be helpful. The presence of distant metastases, local mediastinal invasion, evidence of rapid growth in tumor size, hemorrhagic pericardial effusion, precordial pain, location of the tumor on the *right* as opposed to the left side of the heart, and extension into the pulmonary veins are all suggestive of a malignant rather than a benign tumor. Furthermore, infiltration of the myocardium is more indicative of a malignant process.[2] Benign tumors are more likely to occur on the left side of the interatrial septum and to grow slowly.

Cardiac symptoms caused by tumors are primarily determined by mechanical interferences. Myxomas that are located on the left side may produce mitral valve symptoms, whereas right-sided malignant tumors may produce signs of right-sided failure.[3]

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ANSWER TO QUESTION 537

C (Braunwald, pp. 1702–1704)

Echocardiography is the most useful noninvasive test to evaluate for cardiac tamponade.[1] Findings most suggestive of tamponade physiology include (1) a large pericardial effusion, (2) right atrial (RA) and right ventricular (RV) diastolic compression, (3) an exaggerated inspiratory *increase* in transtricuspid flow velocities with concurrent *decrease* in transmitral flow velocities, and (4) inferior vena caval dilatation with absence of normal inspiratory collapse.

RV diastolic collapse is the most predictive sign of tamponade. It is more specific than RA compression and more sensitive and specific than pulsus paradoxus in detecting increased pericardial pressure. However, diastolic RV collapse may not be evident in patients with elevated intrapericardial pressure who also have pulmonary hypertension, because RV pressures are higher than normal in that case.

A small pericardial effusion makes tamponade less likely, but does not exclude the diagnosis, especially if the pericardial fluid has accumulated rapidly. In addition, small pericardial effusions can be associated with "low-pressure" tamponade in patients with intravascular volume depletion. Small loculated effusions (e.g., after cardiac surgery) can also result in tamponade physiology because of localized chamber compression.

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ANSWER TO QUESTION 538

D (Braunwald, pp. 1672–1674)

The lateral chest radiograph shows calcification of the pericardium, suggestive of constrictive pericarditis. In this patient's case, prior radiation therapy is the likely cause of constriction.

The clinical presentation of patients with chronic constrictive pericarditis (CP) is predominantly that of right-sided heart failure. In early stages, signs include jugular venous distention (with a rapid *y* descent) and Kussmaul sign (inspiratory augmentation of the jugular venous pressure, instead of the normal decline), peripheral edema, and vague abdominal discomfort due to passive hepatic congestion. As the disease progresses, ascites, jaundice, and anasarca may ensue.

The most notable auscultatory finding observed in some patients with advanced CP is the pericardial knock, an early diastolic sound heard best at the left sternal border or apex that corresponds to the sudden cessation of ventricular filling imposed by the rigid, constricting pericardium. The pericardial knock occurs earlier and is of higher frequency than an S_3 gallop sound and may be confused with the opening snap of mitral stenosis (MS), but is not followed by the diastolic rumbling murmur of MS.

Heart catheterization in patients with CP is notable for elevation and equalization of the intracardiac diastolic pressures and a diastolic "dip-and-plateau" configuration of the ventricular pressure tracings. Intravascular volume depletion can mask these typical hemodynamic findings, but they can be uncovered with an intravenous fluid challenge. One important way to distinguish CP from restrictive cardiomyopathy (CMP) during catheterization is to observe the variation in simultaneously recorded right and left ventricular systolic pressures. In contrast to normal individuals or those with restrictive CMP, there is usually a striking *discordance* between these pressures during respiration in CP: with inspiration, the left ventricular systolic pressure falls while that of the right ventricle increases. This finding reflects the exaggerated ventricular interdependence that results from pericardial constraint.

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ANSWER TO QUESTION 539

D (Braunwald, pp. 1389–1390)

The three primary causes of valvular aortic stenosis (AS) are (1) a congenitally bicuspid valve that becomes calcified, (2) calcification of a structurally normal trileaflet valve, and (3) rheumatic disease (Fig. 4.44). Calcification of a congenitally bicuspid or of a normal trileaflet valve is the most common etiology of AS in adults.

Although calcific aortic valve disease was once considered to result from years of mechanical stress on the valve, it actually appears to represent proliferative and inflammatory changes, with lipid accumulation and infiltration of macrophages and T lymphocytes, in a manner similar to vascular calcification. As in atherosclerosis, cigarette smoking, hyperlipidemia, and diabetes are risk factors for the development of this valvular process.

Rheumatic valvular disease has declined in frequency in industrialized countries, but remains an important condition in developing nations. Rheumatic AS results from postinflammatory fusion and adhesion of the valve commissures and rarely develops in the absence of rheumatic mitral involvement.

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ANSWER TO QUESTION 540

C (Braunwald, pp. 1407–1409; Fig. 68.19)

Appropriate timing for surgical intervention in chronic aortic regurgitation (AR) depends on the patient's symptoms and state of left ventricular (LV) contractile function. Regardless of the severity of AR, patients who are symptomatic and have reduced LV systolic function should be referred for surgery, unless an absolute contraindication exists.[1] Asymptomatic patients with advanced AR who have normal LV systolic function without prominent ventricular dilatation (i.e., an end-systolic diameter <50 mm) have an excellent prognosis and typically can be observed clinically and by echocardiography to assess for changes in LV size and function.

In patients who do undergo aortic valve surgery, the end-systolic diameter is valuable in predicting the postoperative outcome. An end-systolic diameter <40 mm predicts a low likelihood of postoperative instability or heart failure. However, an end-systolic diameter >55 mm, or a preoperative ejection fraction <50%, increases the risk of postoperative death from LV dysfunction.[1]

Several vasodilators, including angiotensin-converting enzyme inhibitors, have been shown to provide beneficial hemodynamic effects in chronic AR. However, a randomized trial comparing nifedipine, enalapril, and placebo in patients with chronic AR did not demonstrate a benefit of either vasodilator regimen in reducing symptoms or LV dysfunction warranting valve replacement.[2]

Fig. 4.45 summarizes the current American Heart Association/American College of Cardiology Foundation management strategy for patients with chronic severe AR.[1]

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ANSWER TO QUESTION 541

D (Braunwald, pp. 1651, 1652, 1659)

Non-AIDS conditions (including cardiovascular disease) now account for the majority of deaths among human

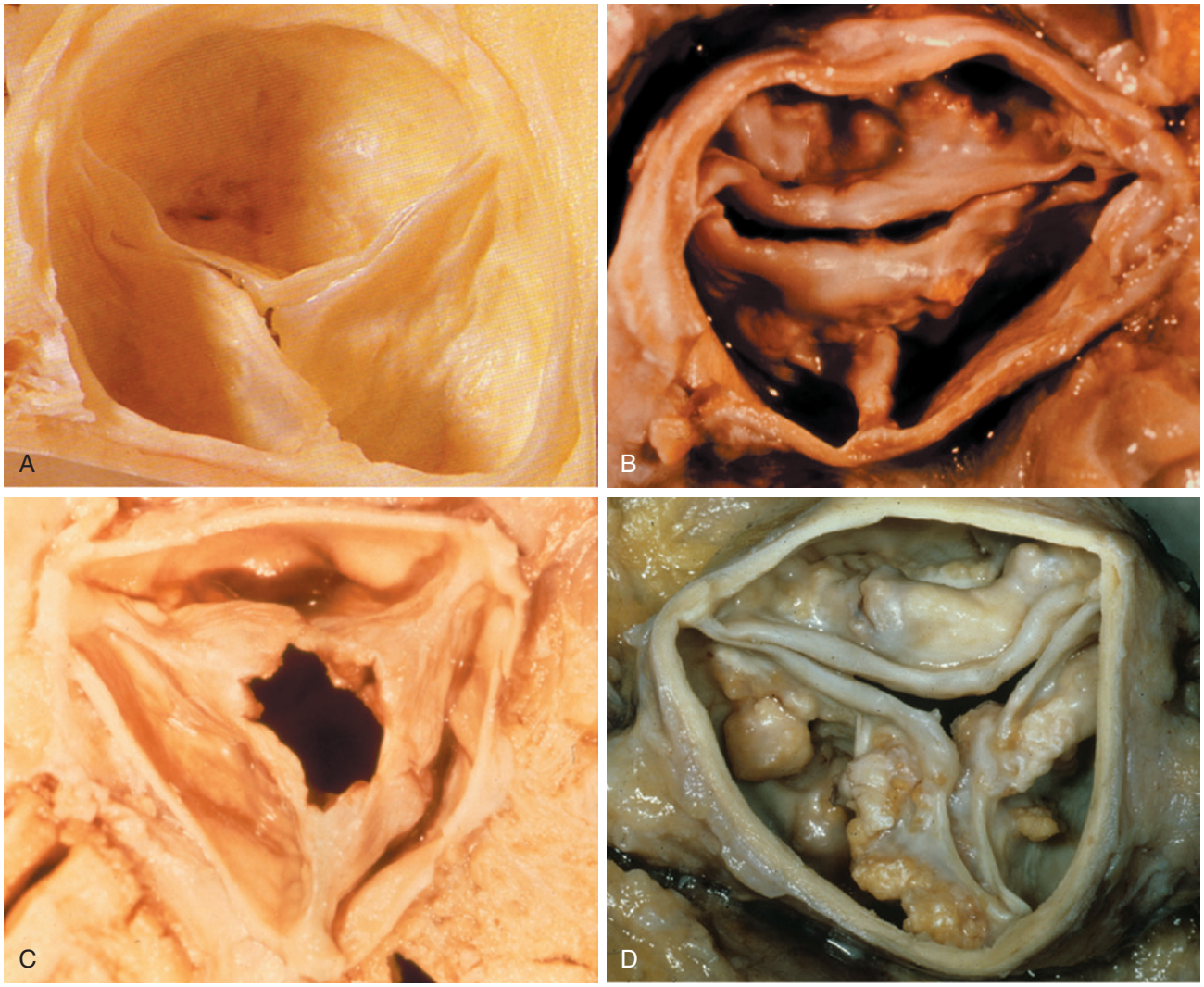

FIG. 4.44 *Major types of aortic valve stenosis. (A) Normal aortic valve. (B) Congenital bicuspid aortic stenosis. A false raphe is present at the 6 o'clock position. (C) Rheumatic aortic stenosis. The commissures are fused with a fixed central orifice. (D) Calcific degenerative aortic stenosis. (A) From Manabe H, Yutani C, eds.* Atlas of Valvular Heart Disease. *Singapore: Churchill Livingstone; 1998:6, 131; (B–D) Courtesy Dr. William C. Roberts, Baylor University Medical Center, Dallas, TX.*

immunodeficiency virus (HIV)-infected individuals taking antiretroviral therapy (ART).[1] Although most HIV-associated CV disease is related to atherosclerosis, HIV and ART can affect the myocardium and pericardium as well.[2] In the pre-ART era, HIV-associated cardiomyopathy was commonly seen in patients with advanced HIV disease and was associated with a poor prognosis. While the incidence of dilated cardiomyopathy has decreased dramatically in the current era, HIV patients who are not adherent to ART remain at risk.[3,4] In addition, more subtle LV dysfunction (both systolic and diastolic) may be detected on echocardiography in asymptomatic HIV patients taking ART.[5] Putative mechanisms for LV dysfunction include direct viral infection of cardiomyocytes, immune-mediated myocarditis, nutritional deficiencies, and direct toxicities of antiretroviral therapies.

Pericardial effusion was also common among HIV patients in the pre-ART era, but the incidence has declined significantly with current therapies.[6] Typically, such effusions are small and a large number resolve spontaneously. Most are of "idiopathic" origin, but can also be related to opportunistic infections, drug toxicities, uremia, or malignancy. The presence of a pericardial effusion increases the mortality risk in HIV-infected patients.

In the contemporary era, most cardiovascular complications in HIV-infected patients are the result of accelerated atherosclerotic disease. Potential contributory mechanisms may include direct HIV vasculopathy with endothelial dysfunction, chronic inflammation, or co-infection with other viruses. Moreover, ART drugs, especially earlier generation protease inhibitors, can contribute to dyslipidemia and insulin resistance, predisposing to increased risk of myocardial infarction.[7]

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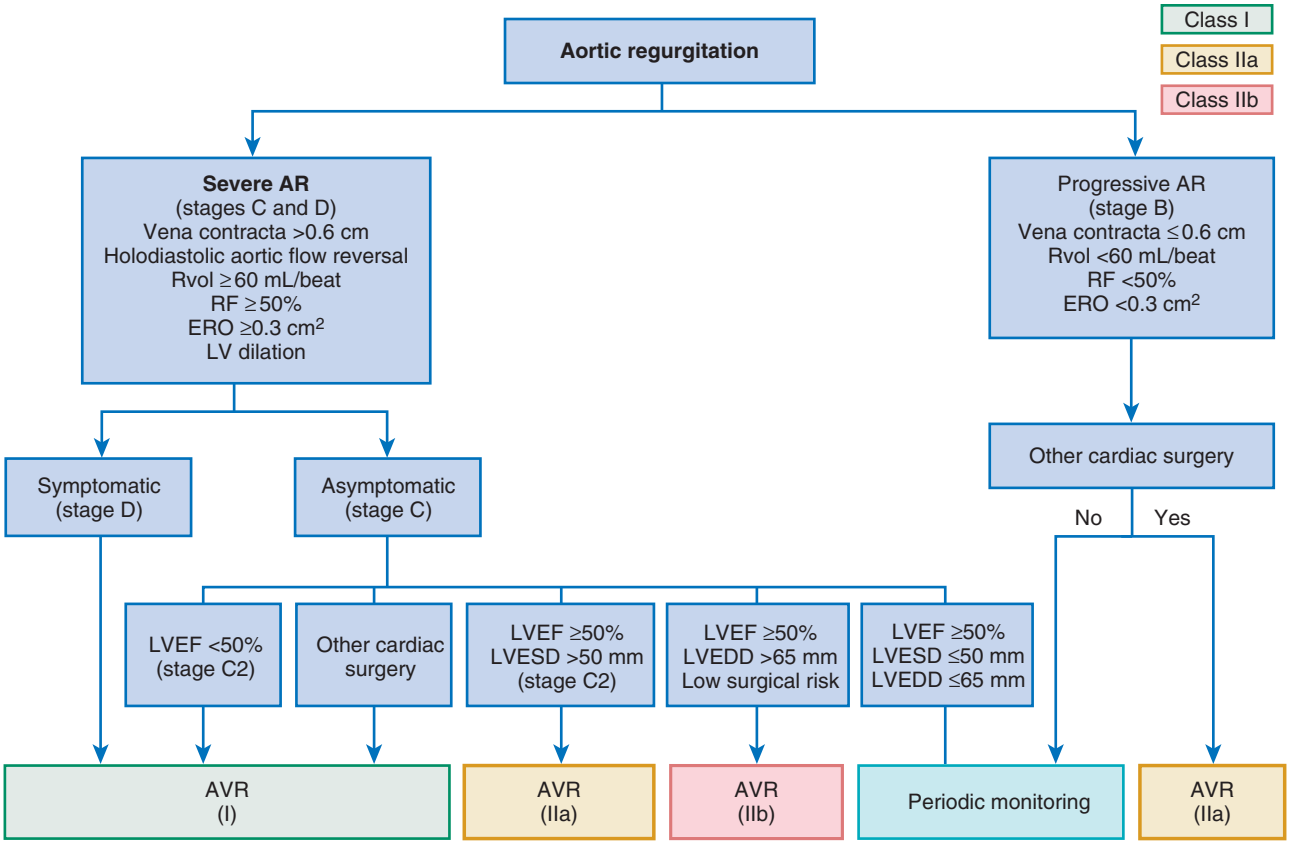

FIG. 4.45 AR, *Aortic regurgitation;* AVR, *aortic valve replacement;* ERO, *effective regurgitant orifice;* LVEDD, *LV end-diastolic diameter;* LVEF, *left ventricular (LV) ejection fraction;* LVESD, *LV end-systolic diameter;* RF, *regurgitant fraction;* Rvol, *regurgitant volume. From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACCF guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.* J Am Coll Cardiol. *2014;63:e57.*

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ANSWER TO QUESTION 542

A (Braunwald, pp. 1527, 1560)

Turner syndrome, also termed *gonadal dysgenesis*, occurs in 1 of every 2500 females. Clinical features include primary amenorrhea, short stature, and immature genital and breast development. The condition arises from defects of the X chromosome, including the 45,XO karyotype in about 50% of cases. Cardiovascular abnormalities are common, occurring in 20% to 50% of patients.[1] The most frequent manifestation is coarctation of the aorta, found in 50% to 70% of patients with Turner syndrome who have cardiovascular defects. Coarctation can occur alone or in combination with other aortic abnormalities, including bicuspid aortic valve and a dilated aortic root.

Patients with Turner syndrome are also at increased risk for aortic dissection independent of other aortic abnormalities. Histopathologic studies have shown abnormalities of the elastic media similar to those in patients with diseases of collagen formation. Partial anomalous pulmonary venous drainage is also found frequently in patients with this condition.

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ANSWER TO QUESTION 543

B (Braunwald, pp. 1890–1893)

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that arises from mutations in the gene that encodes dystrophin.[1] Most patients with DMD develop dilated cardiomyopathy, and specific mutations in the dystrophin gene predict ventricular dysfunction.[2] Preclinical cardiac involvement is present in 25% of DMD patients by age 6. Up to 90% of patients with DMD who are 18 years of age or older will have developed echocardiographic evidence of dilated cardiomyopathy. There is a predilection for involvement of the inferobasal and lateral left ventricle, which likely accounts for the classic electrocardiographic abnormalities: tall R waves with increased R/S amplitude in V_1 and deep narrow Q waves in the left precordial leads (Fig. 4.46). There does not appear to be an association between the presence of dilated cardiomyopathy and electrocardiographic abnormalities.[3]

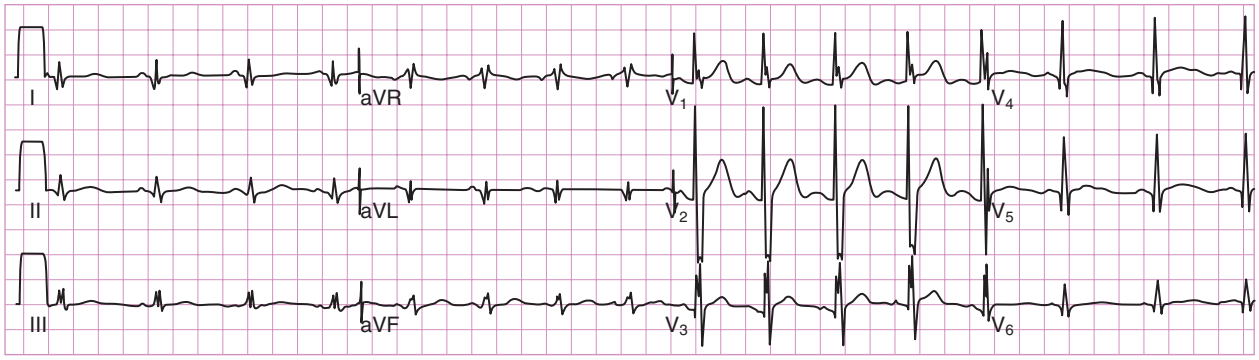

FIG. 4.46 *Dilated cardiomyopathy in a 19-year-old man with Duchenne muscular dystrophy. ECG shows a QRS complex that is typical of a Duchenne muscular dystrophy, with tall R waves in V1 and deep narrow Q waves in leads I and aVL.*

Persistent or labile sinus tachycardia is the most common arrhythmia in DMD. In advanced DMD cardiomyopathy, both atrial arrhythmias (including atrial fibrillation and atrial flutter) and ventricular arrhythmias occur, similar to other cardiomyopathies.[4]

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ANSWER TO QUESTION 544

C (Braunwald, pp. 1641–1643)

The anthracycline antineoplastic agents (doxorubicin, daunorubicin, and idarubicin) are widely recognized for their potential cardiac toxicity. Rarely, a single high dose of an anthracycline causes an acute cardiotoxic reaction manifested by atrial and ventricular arrhythmias and conduction disturbances. The more common complication is chronic cardiomyopathy after long-term exposure.[1] The major risk factor for this complication is the cumulative dose. Retrospective analyses have indicated that the incidence of heart failure is 1.7% at a cumulative dose of 300 mg/m^2, 4.7% at 400 mg/m^2, 15.7% at 500 mg/m^2, and 48% at 650 mg/m^2.[2] Thus, oncologists typically limit the total dose to no more than 400 to 450 mg/m^2. Age at the time of exposure is another important risk factor, because the very young and the very old are particularly susceptible.[1]

Additional risk factors for anthracycline cardiotoxicity include prior mediastinal radiation, the concurrent administration of other cardiotoxic agents (e.g., cyclophosphamide or trastuzumab), and a history of cardiac disease. For example, cardiotoxicity is more likely to arise when the baseline left ventricular ejection fraction is <50%.[3]

In randomized trials, the iron chelator dexrazoxane has demonstrated a protective effect against anthracycline cardiotoxicity. Because there has been concern that dexrazoxane may reduce anthracycline anti-neoplastic efficacy, its use is generally limited to patients who have received >300 mg/m^2 of doxorubicin or its equivalent.

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ANSWER TO QUESTION 545

C (Braunwald, p. 1645)

Vascular endothelial growth factor (VEGF) antagonists interfere with the vascular supply of tumors. The monoclonal antibody bevacizumab targets VEGF-A, and when combined with chemotherapy, improves survival in patients with metastatic colorectal cancer and metastatic nonsquamous non-small cell lung cancer. Several adverse reactions may occur with this agent. Hypertension (not hypotension) is a common side effect and can be severe in 8% to 20% of patients. Bevacizumab is also associated with heart failure, and although the risk of precipitating left ventricular dysfunction is low, it is more likely to develop in patients who have also received anthracyclines or irradiation. There is an approximately twofold increase in arterial (but not venous) thromboembolic events with bevacizumab.[1,2]

Hemorrhagic pericardial effusion is not a common side effect of bevacizumab therapy.

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ANSWER TO QUESTION 546

B (Braunwald, pp. 1527, 1538–1541)

Congenital heart lesions are the most common cause of morbidity and mortality in individuals with Down syndrome. The most frequent abnormalities are endocardial cushion defects, including partial or complete atrioventricular septal defects. The typical presentation includes a history of poor weight gain and frequent respiratory infections in the first year of life. Cardiac auscultation findings depend on the degree of atrial and ventricular septal communications and whether there is atrioventricular valve involvement. In patients with the more common partial endocardial cushion defect, the examination findings are similar to those of an ostium primum atrial septal defect. There is a prominent midsystolic flow murmur (because of increased flow across the pulmonic valve) followed by wide, fixed splitting of S_2. A middiastolic murmur is also common owing to increased flow through the tricuspid valve. When a cleft mitral valve is part of the partial endocardial cushion defect, a holosystolic murmur at the apex is present that frequently radiates toward the sternum, because the right atrium receives regurgitant flow in this condition. When interventricular communication exists as part of the defect, a holosystolic murmur is usually present at the mid- to lower left sternal border.

A midsystolic click followed by a late systolic murmur at the apex describes the auscultatory findings of mitral valve prolapse. Mitral valve prolapse occurs more frequently in patients with Down syndrome than in typical individuals, but it generally does not become evident until later in life. Choice A describes rheumatic mitral stenosis, choice D is the murmur of aortic regurgitation, and choice E represents aortic stenosis. These entities do not occur at an increased frequency in patients with Down syndrome.

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ANSWER TO QUESTION 547

E (Braunwald, pp. 1646–1647)

Radiation therapy is used to treat several types of malignancies. Historically, the heart and vasculature were subjected to high doses of radiation in patients with lymphoma and in those with cancers of the breast, lung, or esophagus. As a consequence, cardiovascular complications are leading causes of mortality among long-term cancer survivors treated with older radiation techniques. Modern approaches since the 1980s have limited and focused radiation delivery to minimize heart exposure, which has led to a decline in cardiovascular complications.

Radiation therapy may cause myocardial damage and fibrosis, endothelial dysfunction, and arterial intimal hyperplasia. The resulting clinical effects on the cardiovascular system usually do not manifest themselves until long after the irradiation has occurred, often arising 10 to 20 years (or longer) after exposure. Late cardiovascular complications include constrictive pericarditis, proximal coronary artery disease, conduction system disease, valvular disease (especially of the aortic valve), and heart failure due to myocardial fibrosis and restrictive cardiomyopathy. In addition, long-term cancer survivors who have received head and neck irradiation have a two- to threefold increased risk of stroke and transient ischemic attacks.

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ANSWER TO QUESTION 548

D (Braunwald, pp. 1580–1585)

Approximately 30% of patients with dilated cardiomyopathy (DCM) have an inherited form of the disease. Most familial examples of DCM fit an autosomal *dominant* pattern of inheritance, although some autosomal recessive and X-linked examples have been identified. Familial DCM appears to result primarily from mutations in genes that code for cytoskeletal, nuclear membrane, or contractile proteins; mitochondrial DNA mutations have also been reported.

Like other forms of DCM, cardiac histologic examination typically demonstrates extensive areas of interstitial and perivascular fibrosis, particularly in the left ventricular subendocardium. There are currently no specific immunologic, histochemical, or ultrastructural markers that can differentiate a genetic cause from other common forms of DCM.

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ANSWER TO QUESTION 549

C (Braunwald, p. 1676)

The clinical scenario is most consistent with effusive-constrictive pericarditis, which indicates the simultaneous presence of a hemodynamically significant pericardial effusion and visceral pericardial constriction. This pathophysiology leads to the hemodynamic hallmark of the condition, which is continued elevation of the right atrial pressure following aspiration of the pericardial fluid despite the return of intrapericardial pressure to normal. The causes of this entity are the same as those for chronic constrictive pericarditis. The most common include idiopathic or postviral pericarditis, neoplastic infiltration of the pericardium, mediastinal radiation therapy, and tuberculosis. The physical findings on initial presentation are most consistent with cardiac tamponade, including pulsus paradoxus and jugular venous distention with a prominent *x* descent.

The diagnosis of effusive-constrictive pericarditis is made at cardiac catheterization, with careful hemodynamic monitoring of intrapericardial and right atrial pressures before and after pericardiocentesis. Although intrapericardial pressure returns to baseline (i.e., ~0 mm Hg) after pericardiocentesis, intracardiac pressures do not normalize. Rather, hemodynamic findings convert to a form more consistent with constrictive pericarditis, with a prominent *y* descent in the right atrial pressure tracing and a "dip-and-plateau" pattern in the right ventricular pressure tracing. As might be expected from the pathophysiology, pericardiocentesis provides only partial and transient symptomatic relief; definitive therapy for this condition requires total pericardiectomy.

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ANSWERS TO QUESTIONS 550 TO 553

550–B, 551–A, 552–C, 553–D (Braunwald, pp. 1483–1487)

The classic peripheral manifestations of infective endocarditis (IE) are encountered only occasionally in the modern era. Janeway lesions are small, painless, nontender macular lesions on the thenar and hypothenar eminences of the palms and soles. They appear less often on the tips of the fingers or plantar surfaces of the toes. Lesions on the hands and feet blanch with pressure and with elevation of the extremities. In cases of acute valvular infections, the lesions tend to be purple and hemorrhagic.

In contrast, Osler nodes are small, raised, nodular, and tender lesions present most often in the pulp spaces of the terminal phalanges of the fingers. They may also be present on the backs of the toes, the soles, and the thenar and hypothenar eminences. The most characteristic feature of these lesions is their tenderness. Lesions may be fleeting in some cases, disappearing within a few hours after they have developed; however, they usually persist for 4 to 5 days. Although almost completely restricted to the subacute form of endocarditis, Osler nodes are occasionally present in acute valvular infection.

Subungual or splinter hemorrhages in IE are linear (or sometimes flame-shaped) dark red streaks in the proximal nailbed. Distal splinter hemorrhages at the nail tip are nondiagnostic and are frequently caused simply by trauma.

The ocular signs of endocarditis include retinal petechiae and Roth spots. The latter are located in the nerve layer of the retina and appear as hemorrhagic exudates. Histologically, they consist of aggregations of cytoid bodies (perivascular accumulation of lymphocytes with or without surrounding hemorrhage).

Bracht-Wächter bodies represent embolic events to the myocardium in IE that cause a localized inflammatory reaction consisting of collections of lymphocytes and mononuclear cells.

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ANSWERS TO QUESTIONS 554 TO 558

554–C, 555–B, 556–E, 557–A, 558–B (Braunwald, pp. 1593–1594, 1621)

The ECG is often nonspecific in cardiomyopathic disorders, but certain features are common in each of the listed conditions. In chronic Chagas disease, the most common electrocardiographic findings are right bundle branch block, left anterior fascicular block, atrial fibrillation, and premature ventricular complexes. Sarcoidosis has a propensity to infiltrate the atrioventricular (AV) node and bundle of His, producing heart block. Ventricular tachyarrhythmias are also common in this disorder. Apical hypertrophic cardiomyopathy is associated with deeply inverted T waves in the precordial leads. Amyloidosis results in low QRS voltage due to myocardial infiltration by amyloid proteins. Other electrocardiographic features in amyloidosis include rightward axis, first-degree AV block, and a pseudoinfarct pattern in II, III, aVF, and V1–V3. Lyme carditis results in variable degrees of AV block, often with transient diffuse ST-segment and T-wave abnormalities.

ANSWERS TO QUESTIONS 559 TO 562

559–D, 560–C, 561–C, 562–B (Braunwald, pp. 1455–1457)

Artificial cardiac valves consist of mechanical prostheses and bioprosthetic (tissue) valves (Fig. 4.47). Mechanical prostheses are divided into three structural groups: caged-ball, bileaflet, and tilting-disc valves. The Starr-Edwards caged-ball valve was one of the earliest prostheses used and has a long record of predictable performance. However, it has a bulky design, which makes it unsuitable for patients with a small left ventricular cavity or a narrow aortic annulus. Furthermore, the flow characteristics and action of the ball in the cage can generate low-level hemolysis. Tilting-disc valves have largely replaced the caged-ball prostheses, primarily because they are less bulky and have a lower profile. The Medtronic-Hall valve is a type of pivoting disc prosthesis. The bileaflet St. Jude valve has two semicircular discs that pivot between open and closed positions without need for supporting struts. It has a lower transvalvular gradient than either the caged-ball or tilting-disc types and has particularly favorable hemodynamic characteristics in the smaller sizes. Thrombogenicity of the bileaflet St. Jude prosthesis is the lowest of the mechanical valves listed, which makes it an excellent candidate for use in mitral valve replacement in adults.

All of the mechanical prosthetic valves are durable, but they are associated with a risk of thromboembolism, which is greatest in the first postoperative year. Without anticoagulation, the incidence of thromboembolism is three- to sixfold higher than in properly anticoagulated patients. Despite treatment with anticoagulants, the incidence of thromboembolic complications is still 1 to 2 nonfatal events per 100 patient-years. The incidence is significantly higher for prostheses in the mitral as compared to the aortic position. The thrombosis rate of mechanical prostheses in the tricuspid position is extremely high, and for this reason bioprostheses are preferred. Administration of warfarin also carries its own morbidity and mortality, estimated at 2.2 and 0.2 per 100 patient-years, respectively.

The high risk of thromboembolism inherent with the use of mechanical valves was the impetus for the development

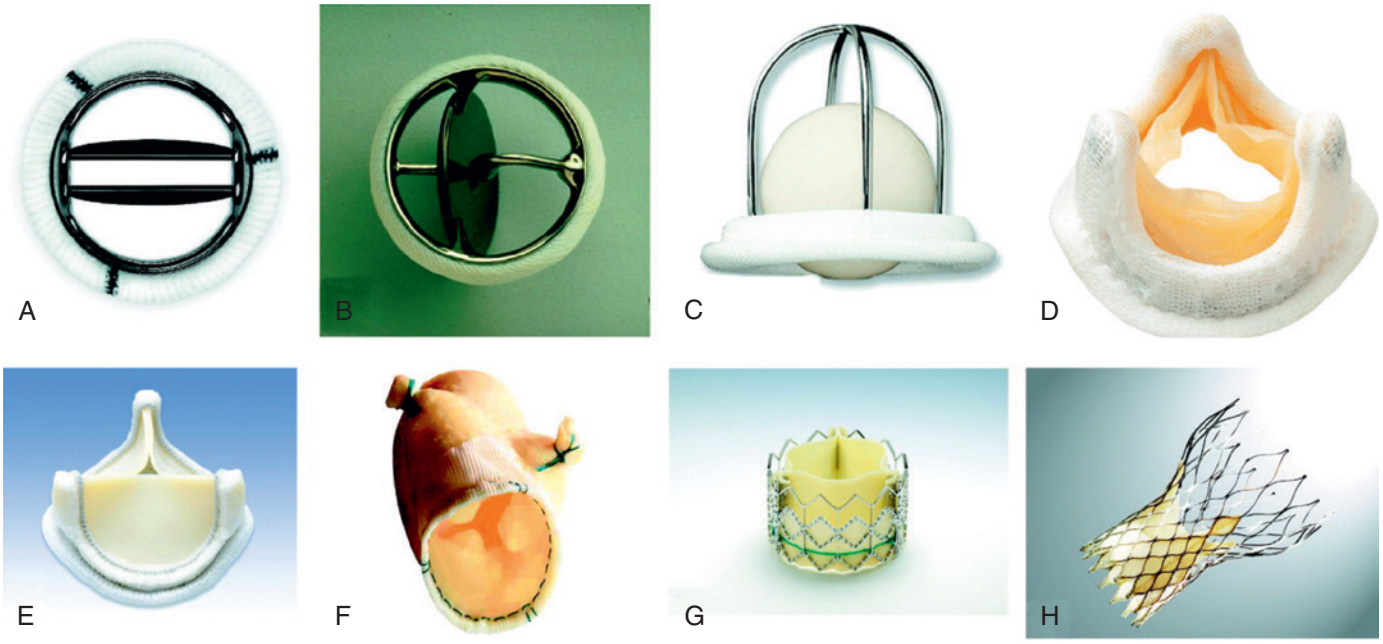

FIG. 4.47 *Types of prosthetic valves. (A) Bileaflet mechanical valve (St. Jude); (B) monoleaflet mechanical valve (Medtronic Hall); (C) caged ball valve (Starr-Edwards); (D) stented porcine bioprosthesis (Medtronic Mosaic); (E) stented pericardial bioprosthesis (Carpentier-Edwards Magna); (F) stentless porcine bioprosthesis (Medtronic Freestyle); (G) percutaneous bioprosthesis expanded over a balloon (Edwards Sapien); (H) self-expandable percutaneous bioprosthesis (CoreValve). From Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management.* Circulation. *2009;119:1034.*

of bioprosthetic prostheses. Among the tissue valves are the Hancock and Medtronic Mosaic porcine heterografts and Carpentier-Edwards Magna bovine pericardial valves. Anticoagulation for such valves is generally desirable for the first 3 months postoperatively (especially in the mitral position) while the sewing ring endothelializes. Thereafter, anticoagulants are generally not required. The main limitation of bioprosthetic valves is limited durability over time, and such deterioration occurs more frequently in the mitral than in the aortic position, and more rapidly in younger patients than in the elderly.

Selection of an artificial valve requires consideration of durability, hemodynamic properties, and thromboembolism risk. In general, tissue valves are preferred over mechanical prostheses for patients in whom anticoagulation is difficult or hazardous. Per the 2017 American Heart Association/American College of Cardiology valvular heart disease guideline update, an aortic or mitral mechanical prosthesis is reasonable for patients <50 years old without a contraindication to anticoagulation. A bioprosthesis is recommended for patients >70 years. For patients aged 50 to 70, either a mechanical valve or bioprosthesis is suitable, balancing the risk of bleeding (with a mechanical prosthesis on anticoagulation therapy) versus potential need for repeat intervention for valve deterioration (bioprosthetic valves).

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ANSWERS TO QUESTIONS 563 TO 566

563–C, 564–A, 565–A, 566–B (Braunwald, pp. 1674–1675; Table 83.7)

The clinical distinction between constrictive pericarditis (CP) and restrictive cardiomyopathy (RCM) may be difficult. Both RCM and CP may show electrocardiographic changes of left atrial abnormality, diffuse low voltage, and T wave flattening. The presence of atrioventricular block and conduction disturbances favors the diagnosis of RCM, especially infiltrative diseases such as amyloidosis.

In both conditions, right ventricular (RV) and left ventricular (LV) diastolic pressures are elevated, stroke volume and cardiac output are decreased, and LV end-diastolic volume is normal or decreased, with impaired diastolic filling. A diagnosis of RCM is more likely when marked RV systolic hypertension is present (pressure >60 mm Hg) and when LV and RV diastolic pressures at rest, or during exercise, differ by more than 5 mm Hg. Some patients with RCM may display hemodynamics that are indistinguishable from those seen with CP, including sustained and complete equilibration of RV and LV diastolic pressures, as well as the presence of a "dip-and-plateau" pattern in the ventricular waveform. However, simultaneous RV and LV systolic pressure measurements can aid in the differentiation of these conditions. Unlike normal individuals and those with RCM, patients with CP often demonstrate marked discordance of RV and LV systolic pressure during inspiration.[1,2] Specifically, with the onset of inspiration, LV systolic pressure declines with a reciprocal increase in RV systolic pressure (Fig. 4.48).

Echocardiography in restrictive cardiomyopathy may reveal abnormally thickened ventricular myocardium, often with a "sparkling" appearance if amyloidosis is present. Other useful differentiating features on echocardiography include

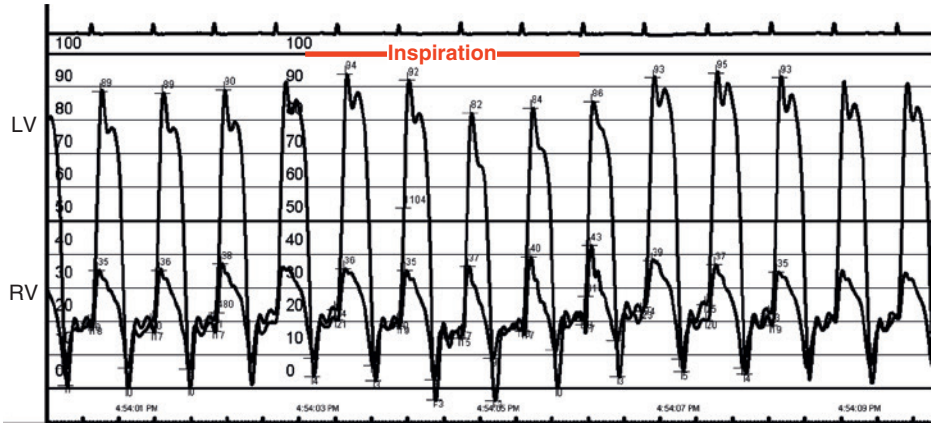

FIG. 4.48

a diastolic septal "bounce" and a normal or increased tissue Doppler medial mitral annular E′ velocity in constriction, in distinction to a blunted E′ value (<8 cm/s) in RCM.[3] Chest computed tomography and magnetic resonance imaging are also helpful in distinguishing these entities, demonstrating a thickened pericardium in >80% of patients with constrictive pericarditis, but not in patients with restrictive cardiomyopathy.[4]

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ANSWERS TO QUESTIONS 567 TO 571

567–A, 568–C, 569–C, 570–D, 571–B (Braunwald, pp. 1867–1869, 1871)

Cardiac myxomas and papillary fibroelastomas are two of the most common primary tumors of the heart. They are benign and do not undergo malignant transformation. Papillary fibroelastomas are the most common primary tumors found on cardiac valves. These lesions are usually small, frond-like structures that consist of a collagen core surrounded by elastic fibers and loose connective tissue. They are most often detected as an incidental finding on echocardiography or at postmortem examination. Papillary fibroelastomas are often clinically insignificant, but there is the potential for embolization or valve orifice obstruction if the tumor is large. Anticoagulation does not appear to protect against embolic risk. Surgical resection of these tumors is generally recommended, especially those in left-sided locations, to prevent thromboemboli. Resection can usually be performed with valve-sparing techniques. There is no known familial syndrome associated with papillary fibroelastomas.

Approximately 10% of myxomas are familial, transmitted in an autosomal dominant pattern. Sporadic myxomas most commonly attach to the interatrial septum; valvular origins for myxoma are rare. Myxomas have a high risk of distal embolization due to the friable nature of the tumor. Surgical resection is recommended to avoid new or recurrent complications, including progressive constitutional symptoms, embolism, and valvular obstruction.

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ANSWERS TO QUESTIONS 572 TO 575

572–C, 573–B, 574–D, 575–A (Braunwald, pp. 1835–1838, 1843–1845)

Unfractionated heparin (UFH) has been the historic acute therapy for pulmonary embolism. UFH is a porcine- or bovine-derived glycosaminoglycan that acts by binding to antithrombin with subsequent inhibition of the procoagulant factors thrombin (IIa), Xa, IXa, XIa, and XIIa. Heparin prevents additional thrombus formation and promotes endogenous fibrinolysis; however, it does not directly dissolve formed clots. For patients at average bleeding risk, a weight-based intravenous bolus of 80 units/kg is begun, followed by 18 units/kg/h by continuous infusion. The activated partial thromboplastin time should be maintained between 1.5 and 2.5 times the control value (typical therapeutic range is 60 to 80 seconds) for effective treatment. The major risk of heparin use is hemorrhage. Thrombocytopenia, osteopenia, and elevated liver enzymes can all complicate heparin therapy. Protamine may be used to reverse the anticoagulant effects of unfractionated heparin.

Low-molecular-weight heparin (LMWH) formulations are now the preferred parenteral therapy for acute management of PE in hemodynamically stable patients. LMWH has greater bioavailability than unfractionated heparin, has a more predictable dose response, and does not require serial measurements of the aPTT. Compared with UFH, LMWH results in reduced mortality, less bleeding, and fewer recurrent thromboemboli. If needed, the effectiveness of LMWH can be monitored by measuring the plasma heparin (anti-factor Xa) level. Both unfractionated heparin and LMWHs can inhibit the secretion of aldosterone, particularly with prolonged administration. This effect can result in hyperkalemia, especially in patients

with renal failure or diabetes. Alternatives to LMWH include subcutaneous fondaparinux, a factor Xa inhibitor with similar benefits and risks, and the oral factor Xa inhibitors rivaroxaban and apixaban. Dabigatan (an oral direct thrombin inhibitor) and edoxaban (another oral factor Xa inhibitor) are approved to treat acute venous thromboembolism following initial treatment with a parenteral anticoagulant.

Fibrinolytic therapy (alteplase) physically dissolves anatomically obstructing pulmonary arterial thrombus and improves pulmonary capillary blood flow, but is associated with a substantial risk of bleeding complications. High-risk subgroups who may benefit from fibrinolytic therapy include patients with massive pulmonary embolism who have moderate-to-severe right ventricular dysfunction and elevation of cardiac biomarkers. Unlike in acute ST-segment elevation myocardial infarction, fibrinolytic therapy for PE may be efficacious when used up to 2 weeks after the onset of symptoms.

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ANSWERS TO QUESTIONS 576 TO 580

576–C, 577–A, 578–D, 579–A, 580–B (Braunwald, pp. 1591–1594, 1597–1598)

Hemochromatosis and amyloidosis are both infiltrative diseases. Hemochromatosis results in deposition of excessive iron within the myocardium and other organs, including the liver, pancreas, and gonads. It most commonly arises on a hereditary basis (mutations in *HFE* gene, autosomal recessive transmission), from other causes of increased iron absorption (e.g., states of ineffective erythropoiesis), or as a result of multiple blood transfusions.

Cardiac amyloidosis refers to the deposition of misfolded products of various protein precursors in the heart. Light-chain (AL) amyloidosis results from production of a protein derived from immunoglobulin light chains by plasma cells, frequently in the setting of plasma cell dyscrasias such as multiple myeloma. A familial form of amyloidosis is inherited in an autosomal dominant fashion in which a mutant version of the hepatically expressed protein transthyretin represents the amyloid precursor protein. The previously termed "senile" form of amyloidosis is due to deposition of amyloid protein derived from normal (wild-type) transthyretin in older individuals. Secondary (AA) amyloidosis may arise in systemic inflammatory conditions, resulting in organ amyloid deposits derived from the inflammatory protein serum amyloid A, but this condition rarely involves the heart.

Because of the infiltrative nature of these conditions, each initially leads to a "stiffened" myocardium and usually presents as a restrictive cardiomyopathy. In later stages, however, dilatation of the ventricles may ensue. Although arrhythmias are common in both conditions, rhythm disorders are not usually prominent initial symptoms. The ECG in hemochromatosis usually shows diffuse ST-segment and T wave abnormalities as well as supraventricular arrhythmias. Abnormal rhythms, especially atrial fibrillation, are also common in amyloidosis, in addition to electrocardiographic findings of low-voltage QRS complexes and pseudoinfarction patterns.

If diagnosed early, the cardiomyopathy of hemochromatosis may be reversed with phlebotomy and chelating agents. Both computed tomography and cardiovascular magnetic resonance imaging have been used to detect early subclinical myocardial involvement at a time when therapy is most effective.[1] Cardiac amyloidosis generally carries a grim prognosis, but progress has been made at improving longer-term survival. For example, in AL amyloidosis, the proteasome inhibitor bortezomib has been successful at controlling the underlying plasma cell dyscrasia, with normalization of serum light chains and improvement in heart failure symptoms.[2] Cardiac transplantation has been performed for AL amyloidosis, however, outcomes tend to be poor due to progression of amyloidosis in other organs or recurrence in the transplanted heart. Some patients with mutant transthyretin amyloidosis may benefit from liver or combined liver-heart transplantation.

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ANSWERS TO QUESTIONS 581 TO 585

581–A, 582–B, 583–B, 584–A, 585–B (Braunwald, pp. 1445–1446, 1450)

Tricuspid stenosis (TS) is most commonly rheumatic in origin. It almost never occurs as an isolated lesion, but rather accompanies rheumatic mitral valve disease. Typical findings include fatigue, right-sided heart failure with hepatomegaly, abdominal swelling due to ascites, and anasarca. Auscultation usually reveals signs of mitral stenosis (MS), and these often overshadow those of TS. The diastolic murmur of TS is heard best along the lower left sternal border at the fourth intercostal space and is usually softer, higher pitched, and shorter in duration than the murmur of MS. The management of severe TS is surgical and requires valvulotomy or valve replacement when the orifice is less than ~2 cm^2. In general, tissue valves are used preferentially in the tricuspid position because of the high risk of thrombosis with mechanical prostheses.

The most common form of pulmonic stenosis (PS) is congenital. A rarer form results from carcinoid plaques. The latter cause constriction of the pulmonic valve ring, retraction and fusion of the cusps, and PS with or without pulmonic regurgitation. Carcinoid heart disease can also involve the tricuspid valve, but most commonly leads to tricuspid regurgitation.

Most adults with mild to moderate PS are asymptomatic, and it is only the more severe forms that result in dyspnea and fatigue. Patients with advanced PS may develop secondary tricuspid regurgitation and right ventricular failure.

In the majority of patients, valvular PS is a stable or slowly progressive disease. Physical examination is notable for a systolic thrill along the left upper sternal border, a prominent systolic ejection murmur heard at the location of the thrill, and often an associated ejection click. In contrast to the inspiratory increase in most right-sided cardiac sounds, the

intensity of the pulmonic click in PS decreases with inspiration. Echocardiography can define the lesion, and Doppler imaging allows accurate estimation of the gradient across the valve. In adults, percutaneous balloon valvuloplasty for advanced valvular PS is safe and effective and is the treatment of choice.

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ANSWERS TO QUESTIONS 586 TO 589

586–C, 587–D, 588–B, 589–B (Braunwald, pp. 1112–1114; Fig. 58.4)

Calcium channel blockers and prostacyclin are two forms of vasodilator therapy used in the chronic management of patients with idiopathic (group 1) pulmonary arterial hypertension (PAH). They are prescribed to carefully selected patients with hemodynamic guidance. Up to 20% of patients with idiopathic PAH show a vasoreactive response and demonstrate a dramatic drop in pulmonary artery pressure and resistance with high-dose calcium channel blockers.[1] Such patients have improved quality of life and survival compared with control subjects and with those who do not demonstrate a dramatic hemodynamic response. Potential adverse effects of calcium channel blockers in patients with PAH include a right ventricular negative inotropic effect and reflex sympathetic stimulation with tachycardia.

Chronic intravenous epoprostenol (prostacyclin) administration has been shown to improve symptoms, quality of life, and survival in patients with idiopathic PAH.[2] It also demonstrates antithrombotic effects that may be of benefit in the management of the thrombo-occlusive component of PAH and may help to restore the integrity of the pulmonary vascular endothelium. Epoprostenol therapy is, however, cumbersome because it requires a surgically implanted central venous catheter and an infusion pump system. The prostacyclin analogs iloprost (by inhalation) and treprostinil (subcutaneously or by inhalation) improve symptoms and are more easily administered, but evidence of survival benefit is lacking.[3]

Additional agents are available that improve the quality of life in patients with group 1 PAH. The phosphodiesterase type 5 inhibitors sildenafil, tadalafil, and vardenafil reduce pulmonary arterial pressure, improve exertional capacity, and are well tolerated. Additionally, a group of endothelin receptor blockers (bosentan, ambrisentan, macitentan) improve hemodynamics, symptoms, and stamina in this condition.[4] Side effects of this group include peripheral edema and hepatic toxicity. More recently, riociguat, a soluble guanylate cyclase stimulator, has been shown to improve exercise capacity and functional class in patients with PAH.[5]

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ANSWERS TO QUESTIONS 590 TO 593

590–C, 591–B, 592–A, 593–B (Braunwald, pp. 1674–1675; Table 83.7; see also Answers to Questions 563 to 566)

The clinical and hemodynamic features of restrictive heart disease such as those caused by cardiac amyloidosis may be very similar to those of chronic constrictive pericarditis. Endomyocardial biopsy, computed tomography, and magnetic resonance imaging may be useful in differentiating the two diseases. The typical hemodynamic feature present in both conditions is the deep and rapid early decline in ventricular pressure at the onset of diastole, followed by a rapid rise to a plateau in early diastole. Patients with restrictive cardiomyopathy may have left ventricular filling pressures that exceed RV filling pressures by >5 mm Hg (whereas there is <5 mm Hg difference between them in pericardial constriction), and this difference can be accentuated by exercise. Furthermore, the pulmonary artery systolic pressure may be >60 mm Hg in patients with restrictive cardiomyopathy, but is usually lower in constrictive pericarditis. As a result, the plateau of the RV diastolic pressure is usually greater than one-third of the peak RV systolic pressure in patients with constrictive pericarditis, while it is more commonly less than one-third in patients with restrictive cardiomyopathy.

In the atrial tracings, the dip-and-plateau sign manifests as a prominent *y* descent followed by a rapid rise in pressure. The *x* descent may also be prominent, and the combination results in the characteristic M-shaped waveform in the atrial pressure tracing.

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ANSWERS TO QUESTIONS 594 TO 597

594–D, 595–B, 596–C, 597–A (Braunwald, pp. 1393–1394)

The natural history of aortic stenosis (AS) has been described in a cohort of patients who did not undergo aortic valve surgery. Patients whose only symptom of AS was angina had an average survival of 3 to 5 years. Those with syncope had a shorter average survival of 2 to 3 years. Those with signs and symptoms of congestive heart failure had the worst prognosis—an average survival of only 1.5 to 2 years. Because of such reduced longevity, patients with AS and any of these symptoms should be referred for surgical correction,

especially if symptoms of heart failure are present. Palpitations are not a marker for adverse survival in patients with AS.

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ANSWERS TO QUESTIONS 598 TO 601

598–A, 599–B, 600–C, 601–A (Braunwald, p. 1507; Table 73G-1)

The American Heart Association (AHA) has published a set of consensus recommendations for antibiotic prophylaxis for the prevention of infective endocarditis (IE).[1] This statement simplified older guidelines and focused on prophylaxis for patients at the highest risk of complications from IE. High-risk patients are considered to be those with (1) prosthetic heart valves, (2) prior endocarditis, (3) specific types of congenital heart disease (unrepaired cyanotic lesions, repaired congenital lesions with residual defects, or during the first 6 months after repair with prosthetic material or device), and (4) cardiac transplant recipients with valvulopathy. Routine gastrointestinal or genitourinary tract procedures are not indications for antibiotic prophylaxis unless there is an active gastrointestinal or genitourinary tract infection in a patient with one of these high-risk cardiac conditions. These recommendations were incorporated in the 2014 American College of Cardiology/AHA valvular heart disease guidelines.[2]

The first patient in this question is at high risk owing to the prosthetic mitral valve, but prophylaxis is not recommended for routine gastrointestinal procedures such as colonoscopy. The second and third patients are at high risk owing to the prosthetic valves, and prophylaxis is recommended. The third patient is penicillin-allergic, so an alternative regimen such as clindamycin should be administered instead. The fourth patient is not at high risk, and prophylaxis for gastrointestinal procedures is not recommended unless there is active infection.

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ANSWERS TO QUESTIONS 602 TO 606

602–B, 603–B, 604–C, 605–A, 606–D (Braunwald, pp. 1538–1541, 1553–1555)

Complete atrioventricular canal defects (also known as endocardial cushion defects) comprise a group of abnormalities in which the common features are (1) absence of the membranous and muscular atrioventricular septum (causing the atrioventricular [AV] valves to appear at the same level on echocardiography), (2) inlet/outlet disproportion resulting in an elongated left ventricular outflow tract (producing a "gooseneck" deformity on angiography), (3) lateral rotation of the posteromedial papillary muscle, and (4) abnormal configuration of the AV valves (e.g., the left AV valve is trileaflet with a "cleft" appearance). Infants usually present in the first year of life with a history of poor weight gain and frequent respiratory infections, and heart failure is common. On physical examination, several murmurs may be present, including a holosystolic murmur along the lower left sternal border due to the VSD, a holosystolic murmur at the apex due to mitral regurgitation, and a right ventricular (RV) outflow tract systolic murmur. Because the direction of intracardiac shunting is left to right, cyanosis is not typical. Typical electrocardiographic findings include left-axis deviation due to left anterior fascicular block and incomplete right bundle branch block. Echocardiography is usually diagnostic for this condition.

In complete transposition (d-transposition) of the great arteries (d-TGA), the aorta arises from the morphologic right ventricle and the pulmonary artery arises from the morphologic left ventricle. This anatomic arrangement results in two separate and parallel circulations. Some communication between the pulmonary and systemic circulations must exist after birth to sustain life. Almost all patients have an interatrial communication, two-thirds have a patent ductus arteriosus (PDA), and one-third have an associated VSD. The typical clinical manifestations are dyspnea and cyanosis, progressive hypoxemia, and congestive heart failure. Cardiac murmurs are absent or insignificant in 30% to 50% of patients with d-TGA and an intact ventricular septum. In infants with d-TGA and a large PDA, fewer than half have the typical continuous murmur of the aortopulmonary connection. Electrocardiographic findings include right-axis deviation, right atrial enlargement, and RV hypertrophy. Echocardiography is usually diagnostic for identifying the abnormal great-vessel relationship and accompanying abnormalities. An arterial switch operation is the treatment of choice.

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ANSWERS TO QUESTIONS 607 TO 611

607–D, 608–C, 609–C, 610–A, 611–B (Braunwald, pp. 1521, 1527)

Noonan syndrome is a relatively common (1 per 1000) genetic disorder with autosomal dominant inheritance. About one-half of patients have mutations in the *PTPN11* gene on chromosome 12. This syndrome is characterized phenotypically by short stature, a unique facial appearance, mild mental retardation, webbing of the neck, cryptorchidism, and renal anomalies. Approximately half of all patients with Noonan syndrome have congenital heart disease, the most common lesion of which is valvular pulmonic stenosis. The ECG commonly displays left anterior fascicular block. Approximately 20% of patients with Noonan syndrome

have an accompanying atrial septal defect or hypertrophic cardiomyopathy.

The *LEOPARD* syndrome is a rare, single-gene complex of congenital malformations. The acronym LEOPARD symbolizes the main components of the syndrome: L, lentigines; E, electrocardiographic conduction defects; O, ocular hypertelorism; P, pulmonic valve stenosis; A, abnormalities of the genitals; R, retardation of growth; and D, deafness. Eighty percent of patients display lentigines, whereas deafness and abnormalities of the genitals occur in about 20%. The most common structural cardiac feature is pulmonic stenosis, which may exist as an isolated anomaly or in combination with aortic stenosis. The most common electrocardiographic conduction defects are PR-segment prolongation, QRS complex widening, left anterior fascicular block, and complete heart block. The most striking physical feature of the syndrome is the presence of small, dark lentigines, which are concentrated over the neck and upper extremities. LEOPARD syndrome is transmitted in an autosomal dominant fashion, with cardiovascular abnormalities in at least 95% of affected patients.

Kartagener syndrome is an autosomal recessive disorder, the primary defect of which has been elucidated by electron microscopic investigation of cilia from affected individuals' bronchial mucosa or sperm. Dynein arms, which are protein structures that normally form cross-bridges between adjacent microtubules in cilia and sperm tails, are abnormal in this disorder. Several mutations capable of producing the syndrome are recognized, and in each case, the mutant gene disrupts the synthesis either of the dynein protein itself or of a protein that binds dynein to the microtubules. Clinically, the syndrome consists of the triad of sinusitis, bronchiectasis, and situs inversus with dextrocardia. Cases of Kartagener syndrome usually come to attention in infancy due to recurrent upper respiratory infections or pneumonia, and development of classic sinusitis and chronic bronchiectasis occurs as childhood progresses. The majority of individuals with Kartagener syndrome have dextrocardia as the only cardiac manifestation, which leads to an abnormal 12-lead ECG, but no other clinical consequences. On rare occasions, associated cardiac anomalies may be present, including transposition of the great vessels.

Holt-Oram syndrome is a rare autosomal dominant disorder. The classic clinical manifestation is the simultaneous occurrence of congenital heart disease and an upper limb deformity. The most common cardiovascular abnormality is an atrial septal defect of the secundum type, with ventricular septal defect being the next most common. Electrocardiographic abnormalities are frequently present as well and may include first-degree atrioventricular block, right bundle branch block, and bradycardia. Deformities of the forearm and hand are the most apparent features of Holt-Oram syndrome (e.g., hypoplasia or triphalangeal abnormalities of the thumbs). The most specific upper extremity finding, an abnormal scaphoid bone or accessory carpal bones or both, may be detected by wrist radiography. One form of Holt-Oram syndrome has been linked to mutations in the *TBX5* gene located on chromosome 12. *TBX5* is a member of the T-box family of transcription factors that critically regulate morphogenesis in the developing embryo.

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ANSWERS TO QUESTIONS 612 TO 615

612–C, 613–A, 614–B, 615–D (Braunwald, pp. 1487, 1593, 1595–1596, 1856)

Extracardiac manifestations of systemic disorders that also have major cardiac involvement may provide important clues to the underlying diagnosis. One example is infective endocarditis, in which specific lesions may appear in the skin and the eyes. In the skin, these include petechiae, Osler nodes, Janeway lesions, Roth spots, subungual ("splinter") hemorrhages, and embolic infarcts of the digits, as may occur with *Staphylococcus aureus* infection of the left-sided valves; the last are illustrated in part *A* in the figure. Osler nodes are small, raised, nodular, and painful red to purple lesions that appear in the pulp spaces of the terminal phalanges of the fingers. Janeway lesions are small, irregular, flat, and nontender macules occurring most often on the thenar and hypothenar eminences of the hands and soles. Roth spots on the retina have the appearance on funduscopic examination of a "cotton wool" exudate and consist of aggregations of cytoid bodies. All of these peripheral stigmata of infective endocarditis have become uncommon in the modern era.[1]

Amyloidosis is a systemic illness in which unique protein-derived fibrils are deposited in a variety of organs. Cardiac involvement is common in primary (AL) amyloidosis (often a consequence of multiple myeloma) and in familial amyloidosis (an autosomal dominant condition that typically results from a mutated form of the protein transthyretin).[2] Cardiac sequelae include restrictive cardiomyopathy with diastolic dysfunction, conduction abnormalities, systolic dysfunction, and orthostatic hypotension. Dermatologic findings include small papules on the face, scalp, neck fold, or intertriginous folds. In addition, small, smooth, and yellowish papules may be seen in the area around the eyes and be mistaken for xanthomas. Amyloid infiltration can result in macroglossia, as shown in part *B*.

Fabry disease is a sex-linked disorder that is due to a deficiency of the enzyme alpha-galactosidase A. The disorder is characterized by the accumulation of glycosphingolipid within the myocardium, skin, and kidneys. Systemic hypertension, mitral valve prolapse, renovascular hypotension, and congestive heart failure are all common clinical manifestations. Fabry disease may also cause restrictive cardiomyopathy. Ocular signs in the disorder are common. Approximately 90% of patients have corneal opacities, whereas two-thirds of patients have conjunctival vessel tortuosity as illustrated in part *C* of the figure.[3] Hypertensive cardiovascular disease, renal failure, and cerebrovascular disease are the major causes of death in this disorder. Purified human alpha-galactosidase A is available as an intravenous therapeutic option, which reduces tissue storage of the offending glycosphingolipid.

Progressive systemic sclerosis, or scleroderma, presents as tightening and thickening of the skin, with Raynaud phenomenon occurring in almost all patients.[4] Cardiac involvement is common and is a frequent cause of death, second only to involvement of the kidneys as a factor shortening survival. Scleroderma heart disease is primarily a myocardial process, leading to vascular insufficiency and fibrosis in the small vessels of the heart, which produces cardiomyopathy with congestive heart failure, conduction system abnormalities, and/or ventricular dysrhythmias. Pericardial involvement with fibrinous pericarditis is common,

as is the development of pulmonary hypertension due to intrinsic pulmonary vascular disease or interstitial fibrosis. The CREST variant of this syndrome describes patients with calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Recurrent painful ulcerations of the fingertips, which may become infected, are a common problem in this disorder and are illustrated in part *D*.

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ANSWERS TO QUESTIONS 616 TO 619

616–A, 617–B, 618–B, 619–C (Braunwald, p. 1527; see also Answers to Questions 607 to 611)

The Turner and Noonan syndromes share several superficial features, including short stature, webbing of the neck, skeletal anomalies, renal abnormalities, and congenital heart disease. Because of these clinical similarities, Noonan syndrome is frequently referred to as male Turner syndrome or as Turner phenotype with normal chromosomes. However, there are several striking genetic and clinical differences that can readily distinguish these two disorders. Turner syndrome occurs exclusively in females. In about 50% of patients, the karyotype is 45,XO. The remaining patients are mosaics with various other X chromosome abnormalities. Most fetuses with the 45,XO form of Turner syndrome die in utero. Of those who survive, cardiovascular abnormalities occur in 35% to 50%. Coarctation of the aorta is the most common cardiovascular lesion. Other abnormalities include bicuspid aortic valve, hypertrophic cardiomyopathy, atrial septal defect, mitral valve prolapse, and dextrocardia. Stenosis of the pulmonic valve is rarely seen in Turner syndrome, in contrast to Noonan syndrome.

Noonan syndrome appears physically similar to Turner syndrome; however, as indicated in Answers to Questions 607 to 611, affected patients have a unique facial appearance, with hypertelorism, strabismus, small chin, and low-set ears. It is inherited as an autosomal dominant trait and, in contrast to Turner syndrome, both males and females are susceptible to this condition; the karyotype in both sexes is normal. In many families, the genetic abnormality maps to chromosome 12q24; about half have a mutation in the *PTPN11* gene in that region. Approximately 50% of patients with Noonan syndrome have congenital heart disease; the most common lesion is valvular pulmonary stenosis, occurring in about 60% of patients. Characteristically, the annulus of the pulmonary valve is normal, but the leaflets are thickened and immobile. Other findings include atrial septal defect and hypertrophic cardiomyopathy.

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ANSWERS TO QUESTIONS 620 TO 624

620–C, 621–A, 622–B, 623–A, 624–A (Braunwald, pp. 1544–1548)

The two-dimensional echocardiogram in part *A* of the figure displays an apical, four-chamber view of tricuspid atresia, demonstrating a dense band in the tricuspid annulus and an enlarged left ventricle. This anomaly is marked by the absence of the tricuspid orifice with an atrial septal defect, usually with hypoplasia of the right ventricle, and communication between the ventricles, typically via a ventricular septal defect. In 60% to 70% of patients with this condition, the great arteries have normal relationships; the remainder have d-transposition of these vessels. In addition, pulmonic stenosis or atresia may be present. Clinically, the marked diminution in pulmonary blood flow usually leads to severe cyanosis. In those infants in whom transposition coexists with a ventricular septal defect and an unobstructed pulmonary outflow tract, torrential pulmonary blood flow will occur, leading to heart failure rather than cyanosis as the predominant problem. The majority of infants with tricuspid atresia have pulmonary hypoperfusion and the clinical picture of cyanosis, with electrocardiographic findings of left ventricular hypertrophy, left-axis deviation, and right atrial enlargement.

Echocardiographic examination in this disorder is usually diagnostic. At cardiac catheterization, the right ventricle cannot be entered from the right atrium. When the great arteries are normally related, pulmonary blood flow is maintained via a ventricular septal defect or patent ductus arteriosus. However, in complete transposition, the pulmonary artery blood flow is derived directly from the left ventricle. Functional correction of tricuspid atresia has been accomplished by the Fontan procedure, which consists of construction of a prosthetic conduit between the right atrium and pulmonary artery and closure of the intra-atrial communication.

The two-dimensional echocardiogram in part *B* is a parasternal long-axis view of tetralogy of Fallot, which demonstrates (1) the aorta overriding the interventricular septum and (2) a ventricular septal defect. The two other components that comprise this malformation are (1) right ventricular (RV) outflow obstruction and (2) RV hypertrophy. The clinical presentation in tetralogy of Fallot is determined principally by the degree of obstruction to pulmonary blood flow. Infants with tetralogy of Fallot become symptomatic and cyanotic before the age of 1 year. There is a direct correlation between the time of onset of symptoms and the severity of pulmonary outflow tract obstruction. Intense cyanotic spells related to sudden increases in venoarterial shunting and simultaneous decreases in pulmonary blood flow occur between 2 and 9 months of age and may be life threatening.

Physical examination of infants with tetralogy of Fallot usually reveals varying degrees of underdevelopment and cyanosis, commonly with clubbing of the terminal digits within the first year of life. An RV impulse and systolic thrill

may often be appreciated along the left sternal border. A systolic flow murmur across the pulmonic valve is often present, and the intensity and duration of this murmur vary inversely with the severity of the pulmonic outflow tract obstruction. The ECG usually shows RV hypertrophy. On chest radiography, a normal-sized boot-shaped heart with prominence of the right ventricle and a concavity in the region of the underdeveloped RV outflow tract is typical. Echocardiographic findings are diagnostic. Cardiac catheterization is used to delineate the course of the pulmonary arteries and collateral channels when patients have pulmonary atresia as part of the syndrome and to document the coronary artery anatomy before surgical repair. Coronary variations in this disorder include the abnormal origin of the anterior descending artery from the right coronary artery or a single right or left coronary artery giving rise to the remaining coronary vessels.

The management of tetralogy of Fallot consists of total correction of the anomaly, with early definitive repair being advocated in most centers, often during the first 6 months. Pulmonary arterial size is the single most important determinant in evaluating a patient for primary repair. For those in whom marked hypoplasia of the pulmonary arteries is present, balloon dilatation may be used in a palliative manner to allow the infant to survive until an older age, at which time total correction may be carried out at lower risk.

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ANSWERS TO QUESTIONS 625 TO 629

625–A, 626–A, 627–B, 628–B, 629–D (Braunwald, pp. 1641–1643, 1646–1647)

Radiation therapy and chemotherapeutic agents both have potentially serious cardiac adverse effects. Cardiac exposure may occur as a result of therapeutic irradiation of lung, breast, or esophageal cancers or mediastinal radiation for lymphomas. All cardiac structures are susceptible to radiation damage, especially the pericardium, but also the myocardium, coronary arteries, conduction system, and valves. The effects of radiation on the pericardium may be acute (e.g., hemorrhagic effusions) or delayed for several years (fibrosis with constrictive pericarditis). Radiation therapy is also a cause of premature coronary artery disease (CAD). Retrospective studies have demonstrated that children treated with radiation therapy for Hodgkin disease have a significantly increased risk of developing symptomatic CAD at an early age. Radiation-induced myocardial fibrosis is common and may lead to restrictive cardiomyopathy. Radiation effects on the conduction system may cause sinus node disease and atrioventricular block. Radiation exposure of the aortic valve and papillary muscles has been implicated as a cause of regurgitation of the aortic and mitral valves.

As described in the Answer to Question 544, anthracycline chemotherapeutic agents can have an acute direct toxic effect on the myocardium, resulting in ventricular and supraventricular dysrhythmias as well as conduction system blocks. More commonly, cumulative exposure to anthracyclines results in a chronic cardiomyopathy, especially at a total cumulative dose >400 mg/m^2. Rare cases of acute myocarditis-pericarditis within 2 weeks of anthracycline therapy have been described.

Aortic dissection is not associated with these antineoplastic therapies.

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SECTION V QUESTIONS

(CHAPTERS 88 TO 99)

Cardiovascular Disease in Special Populations; Cardiovascular Disease and Disorders of Other Organs

David D. Berg and Leonard S. Lilly

Directions:

For each question below, select the ONE BEST response.

QUESTION 630

A 24-year-old man who is training for the Olympic decathlon team experiences a presyncopal event and is referred for evaluation. He has been training aggressively for the past 2 years and, aside from occasional single palpitations, has not noticed any prior lightheadedness, other cardiac symptoms, or physical limitations. He has no history of hypertension and his family history is free of premature coronary disease or sudden cardiac death (SCD). On physical examination his blood pressure and heart rate are normal. A grade II/VI rough crescendo-decrescendo systolic murmur is auscultated along the left sternal border, which becomes louder when the patient stands. The patient is anxious to return to his training regimen. Which of the following statements is TRUE?

A. Voltage criteria for left ventricular hypertrophy on this patient's electrocardiogram is sufficient to establish the diagnosis of hypertrophic cardiomyopathy (HCM) and should prohibit him from resuming competitive athletics
B. An echocardiographic end-diastolic septal wall thickness of 14 mm would be diagnostic of HCM
C. Persistent left ventricular hypertrophy by echocardiography 6 months after cessation of exercise is consistent with genetic HCM
D. A maximum oxygen uptake of 50 mL/kg/min on cardiopulmonary exercise testing is more consistent with HCM than "Athlete's Heart"
E. Anomalous origin of the left coronary artery is a more common cause of SCD in young athletes than HCM

QUESTION 631

A 66-year-old man with chronic kidney disease (CKD) is referred for office evaluation after a recent admission for an acute coronary syndrome (ACS). Which of the following statements is correct concerning CKD and cardiovascular disease?

A. Patients with CKD are at increased risk of bleeding but decreased risk of thrombotic events when compared with normal individuals
B. The outcomes of patients with CKD who present with ACSs are similar to those of patients with normal renal function
C. Patients with CKD who present to the hospital with chest pain comprise a relatively low-risk group of ACSs, with a cardiac event rate of <5% at 30 days
D. Renal dysfunction is the most significant independent predictor of mortality of patients in coronary care units
E. Uremia is associated with enhanced platelet aggregation

QUESTION 632

A 20-year-old female student presents to the emergency department with recent malaise, myalgias, fevers, sweats, and claudication of the right lower extremity and left arm. On physical examination the blood pressure is 160/90 mm Hg in the right arm and 120/85 mm Hg in the left arm. The left radial and right femoral pulses are diminished and a left-sided subclavian bruit is auscultated. The erythrocyte sedimentation rate is markedly elevated. Which of the following statements about this condition is TRUE?

A. Arterial biopsy would reveal a polymorphonuclear infiltrate
B. Aortic aneurysm formation is more common than arterial stenoses
C. This condition is 10 times more common in women than men
D. Claudication occurs more commonly in the lower extremities than the upper extremities
E. Coronary vasculitis is not typical in this syndrome

QUESTION 633

A 58-year-old woman complains of a new-onset severe headache, jaw pain with chewing, and temporal artery

tenderness. Laboratory examination shows an erythrocyte sedimentation rate (ESR) of 80 mm/h. Which of the following is TRUE regarding treatment of this condition?

A. Corticosteroids should not be administered until biopsy evidence confirms the diagnosis
B. Clinical improvement with appropriate treatment generally occurs over several weeks
C. Anti-tumor necrosis factor (TNF) therapies have been shown to be beneficial in this condition
D. In the absence of contraindications, low-dose aspirin should be prescribed
E. Normalization of the ESR is a reliable indicator of treatment response

QUESTION 634

A 35-year-old woman with hypertension is considering pregnancy. She is currently taking lisinopril 10 mg daily. Which of the following statements is correct?

A. She should remain on her current antihypertensive regimen before and during pregnancy
B. An angiotensin receptor blocker should be substituted
C. Labetalol should be avoided during pregnancy
D. Women with preexisting hypertension have a higher incidence of preeclampsia compared with those with new-onset hypertension during pregnancy
E. Antihypertensive therapy is effective in preventing preeclampsia during pregnancy

QUESTION 635

A 58-year-old woman in good health presents for evaluation. She is concerned about cardiovascular risk because her father sustained a myocardial infarction at age 70. Which of the following statements about heart disease in women is NOT correct?

A. Cardiovascular disease is the leading cause of death in women
B. In recent decades, age-adjusted cardiovascular mortality in the United States has increased in women while it has declined in men
C. Coronary heart disease presents approximately 10 years later in women than in men
D. Cardiovascular disease is twice as common in women with diabetes compared with nondiabetics
E. Hormone replacement therapy with estrogen does not reduce the risk of cardiac events in postmenopausal women

QUESTION 636

A 36-year-old woman with no prior history of cardiac disease develops exertional dyspnea and orthopnea 1 month after delivering a healthy full-term infant. Echocardiography demonstrates a dilated left ventricle with globally reduced contractile function. Which of the following statements regarding peripartum cardiomyopathy (PPCM) is TRUE?

A. Symptoms of PPCM always arise during the last month of pregnancy or within 1 week after delivery
B. Clinical and hemodynamic findings in PPCM are indistinguishable from those of other forms of dilated cardiomyopathy
C. The incidence of PPCM is greatest in first pregnancies
D. Approximately 10% of PPCM patients show recovery within the first 6 months after delivery
E. Younger maternal age is a risk factor for PPCM

QUESTION 637

A 67-year-old man with multivessel coronary disease is scheduled for coronary artery bypass graft surgery (CABG). Which of the following statements regarding CABG and perioperative complications is correct?

A. In-hospital mortality after isolated CABG has increased over the past 2 decades because of the increased complexity of patients who undergo the procedure
B. Early postoperative cognitive decline occurs in <10% of patients after CABG surgery
C. Atrial fibrillation appears in approximately 40% of patients after CABG surgery
D. Of patients who develop postoperative atrial fibrillation, only 20% will spontaneously revert to sinus rhythm within 24 hours
E. *N*-Acetylcysteine prevents renal dysfunction after CABG

QUESTION 638

The patient in Question 637 undergoes coronary artery bypass graft (CABG) surgery without complication. At his first postoperative office visit he reports resolution of his anginal symptoms and asks how long the benefit will last. Which of the following statements regarding CABG surgery is TRUE?

A. Fewer than 2% of saphenous vein grafts become occluded in the early perioperative period
B. Internal mammary artery grafts typically develop intimal hyperplasia over time
C. Saphenous vein grafts have a 10-year patency rate of >75%
D. Radial artery grafts are less likely to develop vasospasm than internal mammary grafts
E. Patients who receive internal mammary artery grafts suffer fewer late deaths and myocardial infarctions than those who receive only saphenous vein grafts

QUESTION 639

A previously healthy 17-year-old high school athlete collapses during a basketball game. He is noted to have brief seizure-like activity and has no initial pulse but is immediately resuscitated by a brisk precordial thump. Assuming that this event represents sudden cardiac death (SCD), which of the following statements is NOT correct?

A. Arrhythmogenic right ventricular cardiomyopathy is responsible for approximately 30% of SCD in young athletes
B. Anomalous origin of the left main coronary artery from the right coronary cusp is the most common of the congenital coronary abnormalities that result in SCD in young athletes
C. His normal pretraining history and physical examination do not exclude the possibility of hypertrophic cardiomyopathy (HCM)
D. Patients who experience SCD due to HCM often have no history of prior cardiac symptoms
E. Congenital aortic stenosis is a cause of SCD in young athletes

QUESTION 640

A 68-year-old woman with a history of hypertension presents to the emergency department with the new onset of dyspnea and nausea. The electrocardiogram shows anterolateral ST-segment depressions, and the initial serum measurement of cardiac troponin T is elevated. Which of the following statements is TRUE regarding women who present with acute coronary syndromes (ACS)?

A. Most women presenting with an acute myocardial infarction do not describe chest pain
B. Women presenting with myocardial infarction are less likely than men to have accompanying cardiovascular comorbidities
C. Women with ACS are more likely to present earlier in the course of symptoms than men
D. Women who present with chest discomfort are more likely than men to have nonatherosclerotic causes of ischemia, such as coronary vasospasm
E. Women are admitted to the hospital for the evaluation of chest pain less often than men

QUESTION 641

A 65-year-old man with end-stage renal disease, on stable hemodialysis, is diagnosed with atrial fibrillation. It is determined that he warrants anticoagulation for stroke prevention. Which of the following agents is labeled for use in patients on hemodialysis?

A. Rivaroxaban
B. Apixaban
C. Dabigatran
D. Edoxaban
E. None of the above

QUESTION 642

A 58-year-old postmenopausal woman presents for a routine office visit. She inquires about oral hormone replacement therapy recommended by her gynecologist. Which of the following statements is TRUE regarding the use of hormone replacement therapy and cardiovascular risk?

A. Current guidelines recommend hormone replacement therapy for postmenopausal women who do not have a history of coronary artery disease
B. The prospective Women's Health Initiative trial showed a reduced rate of coronary events in postmenopausal women randomized to estrogen-only treatment
C. The Women's Health Initiative showed no difference in the rate of stroke or pulmonary embolism in patients randomized to estrogen therapy
D. The American Heart Association guidelines assign a class III recommendation to starting or continuing estrogen plus progestin therapy for primary or secondary prevention of cardiovascular disease

QUESTION 643

A 55-year-old overweight man (body mass index = 31.0) with type 2 diabetes mellitus and atrial fibrillation is found to have three-vessel coronary disease at angiography and is scheduled for coronary artery bypass graft surgery in 1 week. Which of the following conditions is associated with increased perioperative mortality in this specific patient?

A. His age
B. Timing of surgery
C. Atrial fibrillation
D. Obesity

QUESTION 644

A 38-year-old woman presents at the 37th week of pregnancy because of severe substernal chest pain over the past 30 minutes. An electrocardiogram demonstrates 4-mm ST-segment elevations in leads V_1 to V_4. Which of the following statements is correct?

A. Coronary artery spasm is the most common cause of this finding during pregnancy
B. Coronary artery dissection is the most likely cause in the peripartum period
C. Pregnancy does not alter the risk of sustaining a myocardial infarction
D. Inferior wall myocardial infarction is more common than anterior wall myocardial infarction during pregnancy
E. Pregnancy is an absolute contraindication to angiography

QUESTION 645

An 83-year-old man with hypertension and diabetes underwent coronary artery bypass graft (CABG) surgery 14 hours ago on an emergency basis. Preoperative angiography revealed severe stenoses of the left main and right coronary arteries. During the operation, the left internal mammary artery was grafted to the native left anterior descending artery and saphenous vein grafts were anastomosed to the first obtuse marginal branch of the circumflex coronary artery and to the posterior descending artery. The surgeon consults you because he is concerned that the patient may have suffered a perioperative myocardial infarction (MI). Which of the following statements is NOT correct?

A. His age, the emergency nature of his procedure, and the presence of left main coronary artery disease put this patient at increased risk for perioperative MI
B. Chest pain is not a reliable sign of MI in the post-CABG patient
C. An elevation of cardiac-specific troponin T more than three times the 99% upper reference limit is diagnostic of MI in this setting
D. The finding of new Q waves on the electrocardiogram is a reliable sign of perioperative MI
E. Paradoxical motion of the interventricular septum on echocardiography is a common finding after cardiac surgical procedures and does not necessarily indicate MI

QUESTION 646

A 78-year-old man presents with chest pain and acute 2-mm ST-segment elevations in leads V_1 to V_3. Which of the following statements is true regarding the management of acute myocardial infarction (MI) in elderly patients?

A. Fibrin-specific fibrinolytic agents are not associated with heightened intracerebral bleeding rates in patients >75 years
B. Antiplatelet therapy with prasugrel leads to superior outcomes compared with clopidogrel in patients >75 years of age who undergo percutaneous intervention

C. Angiotensin-converting enzyme inhibitors have been shown to reduce fatal and nonfatal events after MI in elderly patients
D. Elderly patients are less likely than younger patients to benefit from beta blockade for secondary prevention

QUESTION 647

Which of the following preoperative clinical characteristics most strongly predicts an increased risk of perioperative cardiovascular complications in patients >40 years of age undergoing major noncardiac surgery?
A. Presence of an S_3 gallop
B. Active cigarette smoking
C. Serum creatinine = 1.5 mg/dL
D. Mitral stenosis with calculated valve area of 2.0 cm^2
E. Hypertension controlled on drug therapy

QUESTION 648

A 69-year-old woman presents for a routine office visit. She has a history of hypertension and her blood pressure today is 165/90 mm Hg. The only medication is metoprolol succinate 25 mg daily. Which of the following statements regarding hypertension in the elderly is TRUE?
A. Therapy for isolated systolic hypertension in the elderly does not reduce the incidence of future cardiac events
B. Clinical trials have shown that beta blockers offer less cardiovascular protection than diuretic therapy
C. The presence of left ventricular hypertrophy in hypertensive patients >65 years is not an independent risk factor for adverse cardiovascular outcomes
D. Hypertensive hypertrophic cardiomyopathy of the elderly is more common in men

QUESTION 649

Which of the following statements regarding hemodynamic changes during normal pregnancy is NOT correct?
A. Total blood volume increases
B. Cardiac output increases
C. Stroke volume increases
D. Systemic vascular resistance increases
E. Heart rate increases

QUESTION 650

Which of the following cancer therapies is NOT associated with the listed cardiotoxic side effect?
A. Trastuzumab: Systolic heart failure
B. Bevacizumab: Hypertension
C. Ipilimumab: Myocarditis
D. Anastrozole: Venous thromboembolism

QUESTION 651

A 60-year-old woman with a history of hypertension and diabetes mellitus is admitted to the hospital because of an acute severe headache, nausea, and vomiting. Physical examination demonstrates a blood pressure of 180/90 mm Hg, normal jugular venous pressure, bibasilar rales, no cardiac gallops or murmurs, and no focal neurologic signs. The troponin I is elevated at 0.62 ng/dL (normal: <0.10 ng/dL). Computed tomography of the brain demonstrates an acute subarachnoid hemorrhage. The patient's electrocardiogram is shown in Fig. 5.1. Which of the following statements is TRUE?
A. A ruptured coronary plaque with partially occlusive thrombus is likely present
B. QT interval prolongation is uncommon in this setting
C. All of the cardiac abnormalities can be attributed to autonomic dysfunction in the setting of acute brain injury
D. Beta blockers are not effective at controlling ventricular tachycardia and fibrillation in this situation
E. The magnitude of electrocardiographic abnormalities in such a patient correlates with a poor cardiovascular outcome

QUESTION 652

A 68-year-old man with a history of myocardial infarction is scheduled for elective hernia repair. Which of the following statements regarding perioperative medication use in coronary disease patients undergoing noncardiac surgery is TRUE?
A. Cardiac adverse event rates are reduced when high-dose beta blocker therapy is initiated immediately before surgery
B. Nitrates decrease intraoperative myocardial ischemia and reduce rates of adverse cardiac outcomes

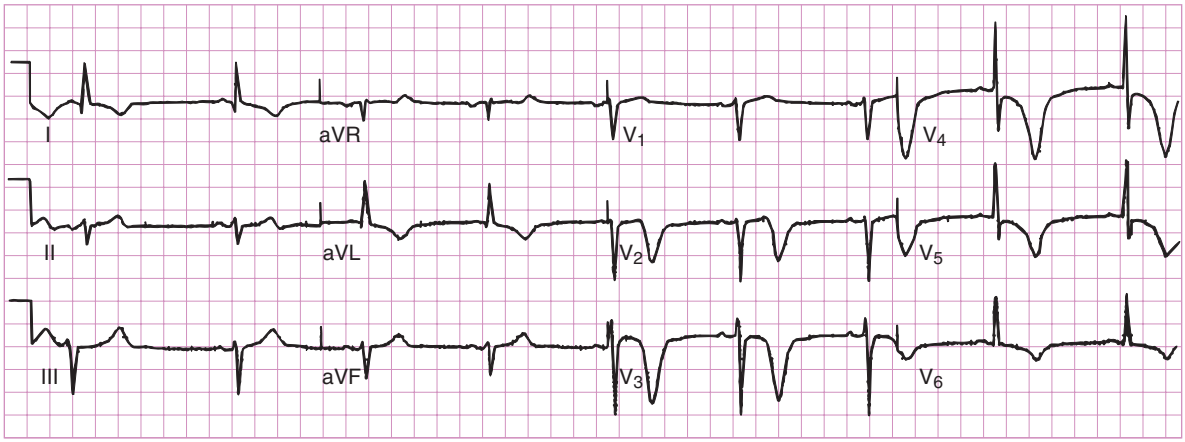

FIG. 5.1 *Courtesy Dr. Charles Fisch, Indiana University of Medicine, Indianapolis.*

C. Most cardiac medications should be discontinued 2 to 3 days before surgery and resumed as soon as the patient can tolerate oral intake
D. Statin therapy has been associated with reduced perioperative cardiovascular event rates in high-risk patients

QUESTION 653

Which of the following statements regarding alterations in cardiovascular function with aging is NOT correct?
A. Endothelial production of nitric oxide decreases with age
B. Left ventricular myocardial cells typically develop moderate hypertrophy
C. There is a fall in stroke volume due to a decrease in peak contractile force
D. Heart rate during exercise increases less in older, compared with younger, individuals
E. The resting ejection fraction tends to remain constant with age in the absence of cardiac disease

QUESTION 654

A 58-year-old diabetic man develops fever and tenderness at the sternal wound site 12 days after coronary artery bypass graft surgery. Which of the following has NOT been associated with the development of deep sternal wound infection after cardiac surgery?
A. Prolonged cardiopulmonary bypass time
B. Use of both internal mammary arteries as bypass vessels
C. Diabetes
D. History of cigarette smoking prior to surgery
E. Preoperative atrial fibrillation

QUESTION 655

A 27-year-old woman undergoes right-sided heart catheterization for the assessment of suspected pulmonary arterial hypertension. The mean pulmonary artery pressure (PAP) is 44 mm Hg, and the pulmonary capillary wedge pressure (PCWP) is 11 mm Hg. Infusion of epoprostenol reduces the mean PAP to 31 mm Hg with no significant change in systemic blood pressure or PCWP. Which of the following statements is NOT correct?
A. Both intravenous adenosine and inhaled nitric oxide are alternative useful agents to assess vasoreactivity
B. The observed drop in mean PAP is predictive of a favorable response to oral calcium channel blockers
C. The failure of the systemic blood pressure to decline suggests that the vasodilator challenge was ineffective
D. Very high doses of chronic calcium channel blocker therapy would likely be necessary to realize full clinical benefit
E. A rise in PCWP in response to vasodilator therapy would be of concern for impending left ventricular failure

QUESTION 656

Which of the following interventions has been shown to reduce the incidence of contrast-induced acute kidney injury after coronary angiography in patients with chronic renal insufficiency?
A. Infusion of 20% mannitol before angiography
B. Administration of atrial natriuretic peptide
C. Normal saline administration before and after angiography
D. Intravenous furosemide administration before angiography
E. Low-dose dopamine infusion

QUESTION 657

A 42-year-old woman presents to her primary care physician with recent fatigue and weight gain. Laboratory evaluation reveals a markedly elevated thyroid-stimulating hormone level. Which of the following is NOT a common cardiac finding in patients with hypothyroidism?
A. Hypotension
B. Decreased heart rate
C. Pericardial effusion
D. Decreased cardiac output
E. Prolonged QT interval on the electrocardiography

QUESTION 658

A 28-year-old woman with Marfan syndrome presents for an office visit. Her echocardiogram shows mitral valve prolapse, an aortic root diameter of 4.5 cm, and mild aortic regurgitation. Which of the following statements regarding cardiovascular disease in patients with Marfan syndrome is NOT correct?
A. Sixty percent to 80 percent of patients with Marfan syndrome have mitral valve prolapse on echocardiography
B. The development of aortic regurgitation correlates with the aortic root diameter
C. Patients with Marfan syndrome should be considered for elective aortic root replacement once the aortic root diameter exceeds 5.5 cm
D. Beta blockers should be administered to all patients with Marfan syndrome unless a contraindication exists
E. The risk of aortic dissection during pregnancy in patients with Marfan syndrome is increased if the diameter of the aortic root exceeds 4 cm

QUESTION 659

A 54-year-old man was admitted to the hospital because of acute pulmonary embolism. Intravenous administration of heparin was begun. On admission, the platelet count was 223,000/μL. Four days later it fell to 16,000/μL, although the patient remained asymptomatic, without overt bleeding. Which of the following statements regarding this patient's condition is TRUE?
A. Low-molecular-weight heparin can be safely substituted for intravenous unfractionated heparin
B. A direct thrombin inhibitor, such as lepirudin, should be substituted for heparin
C. Intravenous heparin should be continued, because the low platelet count represents a laboratory artifact without clinical significance
D. Antibodies directed against the platelet glycoprotein IIb/IIIa receptor participate in this disorder
E. This is a transient reaction to heparin and does not preclude future heparin treatment for this patient

QUESTION 660

A 51-year-old woman presents to discuss anticoagulation options for atrial fibrillation. Her history is notable for rheumatic mitral stenosis, which led to mitral valve replacement with a St. Jude mechanical prosthesis 6 years ago. She had

atrial fibrillation prior to cardiac surgery and it has persisted thereafter. She has been maintained successfully on warfarin anticoagulation, but she wishes to free herself of the required frequent testing of the prothrombin time and dose adjustments. She asks if one of the newer anticoagulants would be an option for her. She has normal renal function. Which of the agents below would be appropriate for this patient?
A. Rivaroxaban
B. Apixaban
C. Dabigatran
D. None of the above

QUESTION 661

Which of the following statements regarding metastatic disease involving the heart is TRUE?
A. Tumor metastases frequently involve the cardiac valves
B. A chylous pericardial effusion is characteristic of metastatic breast carcinoma
C. The most common cause of cardiac metastasis in men and women is lung cancer
D. A solitary cardiac mass is more likely to be malignant than benign

QUESTION 662

While volunteering at a medical clinic in rural India, you are asked to examine a 12-year-old girl who presents with fever, migratory polyarthritis, and an erythematous rash on her trunk that forms a snakelike ring with central clearing. Her cardiac examination is notable for a soft, high-pitched pansystolic murmur at the apex. She recalls a prolonged painful pharyngitis a few weeks ago. Two older family members are known to have mitral stenosis. In addition to the "major criteria" used for diagnosing this patient's likely condition, each of the following would offer supporting evidence EXCEPT
A. Prolonged QT interval
B. Fever
C. Elevated C-reactive protein
D. Arthralgia

QUESTION 663

A 42-year-old woman with rheumatoid arthritis (RA) presents with exertional dyspnea. Echocardiography demonstrates a small circumferential pericardial effusion without hemodynamic compromise. Which of the following statements regarding cardiovascular involvement in RA is TRUE?
A. Acute pericarditis related to RA occurs in 10% to 15% of patients
B. Patients with RA have a reduced incidence of clinical CAD compared to the general population
C. Conduction system disease in RA is most commonly due to inflammation of the conduction system.
D. Women with RA are twice as likely as age-matched controls to suffer myocardial infarction
E. At autopsy, epicardial coronary arteritis is found in >50% of patients with RA

QUESTION 664

A 76-year-old man with hypertension and diabetes is found to have atrial fibrillation for the first time at a routine office visit. He has no history of cardiac symptoms, and an echocardiogram shows normal left ventricular contractile function and no valvular disease or pericardial effusion. His physician initiates dabigatran etexilate for long-term anticoagulation. Which of the following statements is TRUE?
A. Anticoagulation for this patient is not warranted because his risk of thromboembolism is low
B. Dabigatran etexilate is an oral factor Xa inhibitor
C. The risk of stroke or systemic embolism with dabigatran 150 mg twice daily is lower than that with warfarin anticoagulation and a target international normalized ratio of 2.0 to 3.0
D. Dabigatran 150 mg twice daily is associated with a higher rate of hemorrhagic stroke than warfarin anticoagulation
E. Hepatotoxicity is the major gastrointestinal side effect of dabigatran

QUESTION 665

A 66-year-old man with a history of atrial fibrillation successfully suppressed by amiodarone presents with tremors and recent weight loss. His physician suspects amiodarone-induced thyroid dysfunction. Which of the following statements about amiodarone and thyroid function is NOT correct?
A. Amiodarone inhibits the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3)
B. During initial therapy, amiodarone decreases thyroid-stimulating hormone levels
C. Amiodarone contains 30% iodine by weight
D. Amiodarone's iodine content inhibits synthesis and release of T_4 from the thyroid gland
E. Glucocorticoid therapy is beneficial for patients with amiodarone-induced hyperthyroidism who have elevated circulating levels of interleukin-6

QUESTION 666

A 54-year-old man presents for evaluation of excessive daytime sleepiness. His wife has observed his prominent snoring and gasping at night. Which of the following statements regarding sleep-related breathing disorders and cardiovascular disease is NOT correct?
A. Individuals with obstructive sleep apnea exhibit persistently increased sympathetic activity, even during daytime wakefulness
B. Obstructive sleep apnea is associated with drug-resistant hypertension, automatic tachycardias, and nocturnal bradycardias
C. Positive airway pressure therapy in obstructive sleep apnea is associated with improved health-related quality-of-life, mood, and blood pressure
D. Unlike obstructive sleep apnea, central sleep apnea is not associated with cardiovascular disease
E. Positive airway pressure benefits both obstructive sleep apnea and central sleep apnea

QUESTION 667

A 38-year-old man with a recent history of unprovoked deep vein thrombosis presents to discuss long-term therapy for recurrent venous thromboembolism (VTE) prevention. He has just completed 6 months of warfarin anticoagulation without complication. Which of the following is NOT an evidenced-based regimen to reduce the risk of recurrent VTE?

A. Aspirin 100 mg daily
B. Warfarin 2 mg every other day
C. Apixaban 2.5 mg twice daily
D. Rivaroxaban 10 mg daily

QUESTION 668

Which of the following statements regarding perioperative cardiac risk assessment in patients undergoing noncardiac surgery is TRUE?
A. Preoperative serum creatinine concentration >1.5 mg/dL is an independent predictor of cardiac complications
B. Controlled insulin-dependent diabetes mellitus is a predictor of postoperative adverse cardiac outcomes
C. Transurethral prostate surgery is considered a high-risk procedure with respect to cardiac complications
D. In the current era, there is a 20% risk of reinfarction if surgery is performed 3 to 6 months after an acute MI
E. A history of exertional angina indicates high perioperative risk, even if the patient can carry a bag of groceries up one flight of stairs without stopping

QUESTION 669

A previously healthy 36-year-old woman presents to her primary care physician 3 weeks after the delivery of her second child because of new dyspnea, orthopnea, and peripheral edema. On examination, she appears fatigued. The blood pressure is 100/70 mm Hg and the heart rate is 120 beats/min. The jugular venous pressure is 12 cm H_2O. There are basilar rales, a prominent apical S_3 gallop, hepatomegaly, and bilateral lower extremity edema. An echocardiogram shows four-chamber cardiac enlargement and severe, global reduction of biventricular systolic function, compared with a normal study before pregnancy. Which of the following statements regarding this patient's condition is NOT correct?
A. The incidence of this disorder is greater with twin pregnancies
B. Approximately half of the patients with this disorder will completely recover normal cardiac function
C. Subsequent pregnancies are usually well tolerated
D. This condition becomes symptomatic in most patients during the last trimester of gestation or in the early postpartum period
E. The incidence of this disorder is higher among African American women than among whites

Directions:

Each group of questions below consists of lettered headings followed by a set of numbered questions. For each question, select the ONE lettered heading with which it is most closely associated. Each lettered heading may be used once, more than once, or not at all.

QUESTIONS 670 TO 674

For each description listed below, match the appropriate diagnosis:
A. Behçet syndrome
B. Systemic sclerosis
C. Ankylosing spondylitis
D. Reactive arthritis
E. Giant cell arteritis

670. Granuloma formation in the coronary arteries
671. Aortitis, uveitis, and urethritis
672. Myocardial fibrosis and contraction band necrosis
673. Histologically similar to syphilitic aortitis
674. Occlusion of the subclavian artery and aneurysms of the common carotid artery

QUESTIONS 675 TO 678

Match the cardiac medication with the potential adverse effect:
A. Heparin
B. Alpha-methyldopa
C. Procainamide
D. Ticagrelor

675. Erythematous rash, leukopenia
676. Coombs-positive hemolysis
677. Dyspnea
678. Thrombocytopenia

QUESTIONS 679 TO 683

Match the description with the associated disease:
A. Takayasu arteritis
B. Giant cell arteritis
C. Both
D. Neither

679. Occurrence is predominantly in women
680. Onset is typically during teenage years
681. Jaw muscle claudication suggests the diagnosis
682. Fever is almost always present
683. Steroid therapy is a cornerstone of management

QUESTIONS 684 TO 688

Match the chemotherapeutic agent with the likely cardiac complication:
A. Myocardial infarction
B. Acute myopericarditis
C. Capillary leak syndrome
D. Arrhythmias (acutely) and dilated cardiomyopathy (chronically)
E. Hypertension

684. Interleukin-2
685. 5-Fluorouracil
686. Cyclophosphamide
687. Doxorubicin
688. Sunitinib

QUESTIONS 689 TO 693

Match the cardiac finding with the most likely endocrine abnormality:
A. Hyperparathyroidism
B. Hypothyroidism
C. Hyperaldosteronism
D. Cushing syndrome
E. Hyperthyroidism

689. U waves on the electrocardiogram
690. Cardiac myxoma
691. Means-Lerman scratch
692. Shortened QT interval
693. Pericardial effusion

QUESTIONS 694 TO 697

Match the description to the associated fibrinolytic agent:
A. Streptokinase
B. Tissue-type plasminogen activator
C. Urokinase
D. Tenecteplase

694. Both single- and two-chain forms demonstrate proteolytic activity
695. Synthesized in renal tubular epithelial cells and endothelial cells
696. Prolonged half-life allows administration as a single bolus
697. Must form complex with plasminogen to exhibit enzymatic activity

QUESTIONS 698 TO 702

Match the finding to the associated anticoagulant:
A. Unfractionated heparin
B. Low-molecular-weight heparin
C. Both
D. Neither

698. Hyperkalemia
699. Bioavailability after subcutaneous injection is >90%
700. Inactivates clot-bound thrombin
701. Thrombocytopenia
702. Increases vascular permeability

QUESTIONS 703 TO 706

Match the following complications with the associated rheumatologic disorder:
A. Aortitis and headaches
B. Libman-Sacks endocarditis
C. Pulmonary hypertension
D. Aneurysmal dilatation of the subclavian and carotid arteries

703. Behçet syndrome
704. Systemic lupus erythematosus
705. Giant cell arteritis
706. Systemic sclerosis

Section V Answers

(CHAPTERS 88 TO 99)

Cardiovascular Disease in Special Populations; Cardiovascular Disease and Disorders of Other Organs

ANSWER TO QUESTION 630

C (Braunwald, pp. 1039–1040, 1042; Fig. 78.12; eTable 78.1)

In the United States, standard screening of young athletes typically consists only of history-taking and physical examination. This approach has a limited capability of detecting serious forms of cardiac disease that could lead to sudden cardiac death (SCD) during training, such as hypertrophic cardiomyopathy (HCM), anomalous origin of the coronary arteries, arrhythmogenic right ventricular cardiomyopathy, and inherited arrhythmia syndromes (e.g., long QT syndromes or Brugada syndrome). Patients with a family history of SCD or premature heart disease, and those with cardiac symptoms (including inordinate exertional dyspnea, chest pain, syncope, or near-syncope) or a heart murmur that augments with standing or Valsalva maneuver, warrant a more complete evaluation, usually including electrocardiography and echocardiography. This issue is particularly relevant since implantation of automatic defibrillators can prevent SCD in patients with predisposing conditions.

The most common cause of SCD in athletes in the United States is HCM. This diagnosis can be difficult to distinguish from the physiologic hypertrophy observed in individuals who participate in chronic endurance or isometric activities ("athlete's heart"), in whom left ventricular (LV) wall thicknesses of 13 to 15 mm can be observed (Fig. 5.2). Thus, voltage criteria for LV hypertrophy do not establish the diagnosis of hypertrophic or hypertensive cardiomyopathy in trained athletes. Echocardiographic findings more suggestive of *pathologic* hypertrophy include (1) LV wall thicknesses >15 mm, (2) prominent asymmetric LV hypertrophy, (3) LV end-diastolic cavity diameter <45 mm, (4) marked left atrial enlargement, (5) abnormal LV Doppler filling patterns, and (6) lack of regression of hypertrophy after a period of deconditioning. A distinguishing feature during cardiopulmonary exercise testing is that conditioned athletes with physiologic hypertrophy can achieve maximum oxygen uptakes >45 mL/kg/min (>110% predicted), whereas those with HCM typically cannot. Patients in whom cardiac assessment reveals HCM should be restricted from competitive athletics.

Anomalous origin of the coronary arteries is the second most common cause of SCD in athletes in the United States. Evaluation for this diagnosis includes coronary angiography or computed tomography angiography.

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ANSWER TO QUESTION 631

D (Braunwald, pp. 1910, 1917–1918)

Chronic kidney disease (CKD) identifies a patient population at high risk for cardiovascular events. Up to 40% of patients with CKD who present to the hospital with chest pain have a cardiac event within 30 days. Moreover, patients with end-stage renal disease have the highest mortality after acute myocardial infarction of any large population with chronic disease. Contributors to poor outcomes after acute coronary syndromes in patients with CKD include (1) high prevalence of comorbidities such as diabetes mellitus and heart failure, (2) reduced use of effective therapeutics due to fear of worsening renal dysfunction, (3) therapeutic toxicities, and (4) vascular dysfunction that is exacerbated by renal failure, including a procoagulable and proinflammatory state. Whereas the latter contributes to increased rates of coronary thrombosis, uremia is also associated with impaired platelet aggregation, so patients with CKD can display increased bleeding risk at the same time.

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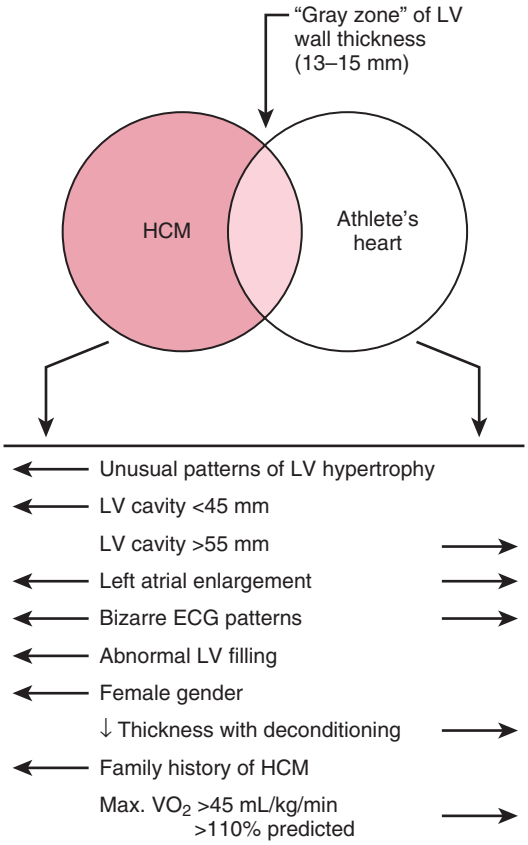

FIG. 5.2 *Modified from Maron BJ, Pelliccia A: The heart trained athletes: cardiac remodeling and the risks of sports including sudden death.* Circulation. *2006;114:1633.*

TABLE 5.1 "Red Flags" for Takayasu Arteritis

In patients younger than 40 years, the following may be indicative of TA:
Unexplained acute-phase response (raised ESR and/or CRP)
Carotidynia
Hypertension
Discrepant blood pressure between the arms (>10 mm Hg)
Absent/weak peripheral pulse or pulses
Limb claudication
Arterial bruit
Angina

CRP, C-reactive protein; *ESR,* erythrocyte sedimentation rate; *TA,* Takayasu arteritis.

TABLE 5.2 Clinical Profile of Giant Cell Arteritis

ABNORMALITY	FREQUENCY (%)
Atypical headache	60–90
Tender temporal artery	40–70
Systemic symptoms not attributable to other diseases	20–50
Fever	20–50
Polymyalgia rheumatica	30–50
Acute visual abnormalities	12–40
Transient ischemic attack or stroke	5–10
Claudication	
Jaw	30–70
Extremity	5–15
Aortic aneurysm	15–20
Dramatic response to corticosteroid therapy	~100
Positive temporal artery biopsy	~50–80

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ANSWER TO QUESTION 632

C (Braunwald, pp. 1850–1854, 1861; Table 94.3)

This patient has signs and symptoms of Takayasu arteritis (TA), an idiopathic large-vessel vasculitis that usually affects the aorta and its branches. TA is 10 times more likely to affect women than men, and the median age of onset is 25 years old. This disease occurs worldwide with a prevalence of 2.6 per million in the United States and 1.26 per million in northern Europe. Features that should prompt consideration of TA are listed in Table 5.1.

Clinically, arterial stenoses occur three to four times more often than aneurysms. Thus, claudication (more common in the upper than lower extremities) is the major symptom; on physical examination, bruits and asymmetric pulses are the most frequent findings. When aneurysms occur, the aortic root is the most common location, which can lead to aortic regurgitation. Hypertension is common and is often caused by renal artery stenosis. Coronary arterial vasculitis most often affects the ostia of the vessels, leading to myocardial ischemia. In addition, myocarditis occurs in about 18% of patients.

Treatment involves high-dose corticosteroids, but relapses are common. Patients with resistant or relapsing symptoms may respond to azathioprine, mycophenolate mofetil, methotrexate, leflunomide, or intravenous cyclophosphamide. More recently, anti-interleukin-6 therapy (i.e., tocilizumab) has been used successfully in some patients with TA that is refractory to conventional therapies. Anatomic bypass of clinically significant stenosis may be necessary. Involvement of the aortic root may necessitate aortic repair, with or without valve replacement.

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ANSWER TO QUESTION 633

D (Braunwald, pp. 1850, 1853–1854)

This patient has characteristic features of giant cell arteritis (GCA), which typically includes the new onset of headache, scalp and temporal artery tenderness, polymyalgia rheumatica, acute visual abnormalities, and claudication of the jaw (Table 5.2).[1] Such symptoms, in the presence of an

increased erythrocyte sedimentation rate (ESR), support the diagnosis of GCA and mandate treatment, even without proof of diagnosis from a temporal artery biopsy. Corticosteroid treatment is the most effective therapy for GCA, and dramatic clinical improvement typically follows within 24 to 72 hours. The ESR itself does not always normalize with effective therapy, and it should not be relied on as the main measure of disease activity.

Most cytotoxic and other immunosuppressive agents, including anti-TNF agents, have not proved effective in GCA in controlled trials. However, a recent trial of tocilizumab (anti-interleukin-6 therapy) used in combination with corticosteroids resulted in a higher rate of sustained remission from GCA at 1 year as compared to corticosteroids alone.[2] Two retrospective studies have demonstrated that the use of low-dose aspirin reduces cerebral ischemic events three- to fourfold compared with patients who had not received such therapy. Therefore, most patients with GCA should receive low-dose daily aspirin.[3]

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ANSWER TO QUESTION 634

D (Braunwald, p. 1791; Table 90.4)

Hypertension during pregnancy is associated with increased maternal mortality and morbidity and consists of four forms (Table 5.3): (1) chronic hypertension (hypertension that precedes pregnancy), (2) gestational hypertension (hypertension that develops after 20 weeks of gestation and resolves by the 12th postpartum week), (3) preeclampsia (de novo or superimposed on chronic hypertension), and (4) white coat hypertension. *Preeclampsia* is identified by the new onset of hypertension after the 20th week of gestation with proteinuria, maternal organ dysfunction, and/or uteroplacental insufficiency. It is more likely to occur in primigravid patients, in twin pregnancies, and in those with preexisting hypertension. Preeclampsia is an emergency and requires hospitalization for close maternal-fetal monitoring, control of hypertension, magnesium sulfate to prevent eclamptic seizures, and consideration of urgent delivery of the fetus, especially after 37 weeks' gestation, after which blood pressure usually normalizes rapidly. *Eclampsia* is present when findings of preeclampsia are accompanied by neurologic complications, including seizures.

Pharmacologic therapies that have been used successfully to lower blood pressure during pregnancy include methyldopa, beta blockers (particularly labetalol), calcium channel blockers, and hydralazine. Although these medications are effective in treating chronic hypertension that has worsened during pregnancy, they are not effective in preventing preeclampsia.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increase the risk of congenital malformations and neonatal renal failure and should *not* be used in pregnancy.

TABLE 5.3 Classification of Hypertension in Pregnancy

HYPERTENSION TYPE	DEFINITION/DESCRIPTION
Chronic hypertension	Hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) present before pregnancy or that is diagnosed before the 20th week of gestation
Gestational hypertension	• New hypertension with a blood pressure of 140/90 mm Hg on two separate occasions, without proteinuria, arising de novo after the 20th week of pregnancy • Blood pressure normalizes by 12 weeks postpartum
Preeclampsia superimposed on chronic hypertension	Increased blood pressure above the patient's baseline, a change in proteinuria, or evidence of end-organ dysfunction
Preeclampsia-eclampsia	• Proteinuria (protein excretion >0.3 g during 24 hours or grade ++ in two urine samples) in addition to new hypertension • Edema no longer included as diagnostic criterion because of poor specificity • In the absence of proteinuria, the disease should nevertheless be suspected when increased blood pressure is associated with headache, blurred vision, abdominal pain, low platelets, or abnormal liver enzymes

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ANSWER TO QUESTION 635

B (Braunwald, pp. 1767, 1770)

Cardiovascular disease is the number one cause of mortality for women in the United States, accounting for 1 in 4 deaths. Fortunately, age-adjusted heart disease mortality has *declined* in both men and women in recent decades, attributed to beneficial risk factor modifications and the influence of evidence-based therapies in the treatment of coronary artery disease, acute coronary syndromes, and heart failure.[1]

Coronary heart disease first presents approximately 10 years later in women than in men, most commonly after menopause. The INTERHEART study demonstrated that this pattern is widely consistent across the world. The age difference is likely contributed to by a protective effect of circulating estrogen before menopause. Nonetheless, pharmacologic replacement of estrogen after menopause does not prevent clinical cardiovascular events.[2,3]

As in men, hyperlipidemia, hypertension, tobacco use, diabetes mellitus, obesity, and a sedentary lifestyle are all important modifiable risk factors for the development of heart disease in women. In the United States, nearly 36% of women have a low-density lipoprotein cholesterol level ≥130 mg/dL and more than 45 million women are hypertensive, a prevalence that exceeds that of men after age 60. There are >15 million women with diabetes mellitus, a population in which the rate of fatal coronary heart disease is higher than that of diabetic men.

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ANSWER TO QUESTION 636

B (Braunwald, pp. 1589, 1790)

Peripartum cardiomyopathy (PPCM) is a form of dilated cardiomyopathy that occurs for the first time in the antepartum or postpartum period and is clinically indistinguishable from other types of dilated cardiomyopathy. PPCM is not a precisely defined entity, but general features include: (1) the development of heart failure (HF) in the last month of pregnancy or within 5 months of delivery, (2) reduced left ventricular ejection fraction (generally <45%), and (3) absence of previously known structural heart disease.[1,2] Recent studies have suggested significant overlap in the genetic predisposition to PPCM and other forms of idiopathic dilated cardiomyopathy.[3]

The incidence of PPCM varies by geographic region but is estimated to be between 1 in 1000 and 1 in 3200 live births. Risk factors for its occurrence include multiparity, African American race, older maternal age, and preeclampsia.

Approximately 50% of patients with PPCM show complete or near-complete left ventricular recovery on standard medical therapy. The other 50% demonstrate either continued deterioration or persistent left ventricular dysfunction and chronic HF symptomatology. Subsequent pregnancies in patients with PPCM with persistent cardiac dysfunction should be discouraged because of the high likelihood of relapse. Even patients who have recovered from an episode of PPCM have a 30% risk of experiencing relapse during subsequent pregnancies.[2]

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ANSWER TO QUESTION 637

C (Braunwald, pp. 1242–1243)

The frequency of perioperative complications in coronary artery bypass graft surgery (CABG) has increased because of the greater percentage of high-risk patients who undergo the operation.[1,2] However, the in-hospital *mortality* after isolated CABG has actually declined, from ~3% in 1997–1999 to ~2% in 2015. The reported incidence of perioperative myocardial infarction varies widely, with a median of 2.9%.

Cerebrovascular complications can occur after cardiac surgery by mechanisms that include atherosclerotic cerebral emboli from the aorta, emboli related to the cardiopulmonary bypass machine, and intraoperative hypotension. Prospective studies reveal a post-cardiac surgical incidence of stroke ranging from 1.5% to 5.0%.[3] Short-term cognitive decline has been identified in >50% of patients at the time of hospital discharge.

Atrial fibrillation (AF) is one of the most frequent complications of bypass surgery, developing in approximately 40% of patients within 3 days after surgery. It is associated with a two- to threefold increase in postoperative stroke. Up to 80% of patients spontaneously revert to sinus rhythm within 24 hours without treatment other than rate control agents. Prophylactic use of beta blockers or amiodarone reduces the occurrence of postoperative AF.[4]

The incidence of renal failure requiring dialysis after CABG is low (0.5% to 1.0%) but is associated with greater morbidity and mortality when it occurs. Predictors of postoperative renal dysfunction include advanced age, diabetes, preexisting renal dysfunction, and heart failure. In a randomized trial, *N*-acetylcysteine did not prevent renal dysfunction after CABG.[5]

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ANSWER TO QUESTION 638

E (Braunwald, pp. 1240–1241)

A variety of conduit options are available for coronary artery bypass graft surgery. Saphenous vein grafts are relatively easy to harvest, but they have several drawbacks. Approximately 8% to 12% of saphenous vein grafts become occluded during the early perioperative period. By 1 year, 15% to 30% of vein grafts occlude. Some of these occlusions may be due to endothelial denuding during surgical preparation, thereby predisposing the graft to early thrombosis. Intimal hyperplasia and accelerated atherosclerosis in vein grafts are common, and by 10 years after surgery, the patency rate of saphenous vein conduits is <50%.

In contrast, internal mammary artery (IMA) grafts, although more difficult to harvest, do not develop intimal hyperplasia and have 10-year patency rates of >80%. Several potential explanations for the superiority of IMA grafts have been suggested: (1) the medial layer of arterial grafts may derive additional nourishment from the vasa vasorum, (2) the endothelium of the IMA produces high levels of endogenous

vasodilators, and (3) the diameter of the IMA is closer to that of the recipient coronary artery than is the diameter of the saphenous vein. Compared to patients with saphenous vein grafts, patients who receive IMA conduits have a decreased risk of death, myocardial infarction, and reoperation. Other arterial conduits, such as the radial artery, are used less often. Although more likely to develop vasospasm than IMA grafts, radial artery grafts are also effective conduits with high long-term patency rates.

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ANSWER TO QUESTION 639

A (Braunwald, pp. 822, 1039–1040; see also Answer to Question 630)

Sudden cardiac death (SCD) in young athletes is a rare, tragic event. The most common cause of SCD in the United States is hypertrophic cardiomyopathy (HCM). It is common for SCD victims with HCM to have been asymptomatic throughout their lives, and even routine history and physical examination before undertaking competitive sports will miss many cases.

The second most common etiology of SCD in young athletes is anomalous origin of a coronary artery. The most frequent form is anomalous origin of the left main coronary artery from the right coronary cusp. The opposite configuration, anomalous origin of the right coronary artery from the left aortic sinus, has also been identified as a cause of SCD. Myocardial ischemia in individuals with anomalous coronaries may relate to a kinked takeoff of the artery or compression of the vessel between the aorta and pulmonary trunk during exercise. Like HCM, coronary anomalies are very difficult to identify by routine screening.

Much less common causes of SCD in young athletes include atherosclerotic coronary disease, myocarditis, aortic dissection, congenital valvular aortic stenosis, and arrhythmogenic right ventricular cardiomyopathy.

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ANSWER TO QUESTION 640

D (Braunwald, pp. 1770–1773)

Compared with men, women experiencing an acute coronary syndrome more frequently describe milder symptoms and are more likely to have "atypical" and often nonspecific symptoms, including dyspnea, pain or discomfort in other body locations, fatigue, indigestion, nausea, or generalized weakness. Despite sex differences in symptom perception of myocardial ischemia, however, the majority of women with acute myocardial infarctions report chest pain.[1] In addition, women presenting with myocardial infarctions typically have more comorbidities (e.g., hypertension) than men, and often present later in the course of symptoms and more frequently with high-risk clinical findings such as heart failure.[2]

Women are hospitalized more frequently than men each year for the evaluation of chest pain, but women who present with chest discomfort are more likely than men to have a nonatherosclerotic cause of ischemia, including coronary vasospasm, stress "takotsubo" cardiomyopathy, and spontaneous coronary artery dissection.

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ANSWER TO QUESTION 641

B (Braunwald, pp. 1841–1843; Table 93.10; see also Answer to Question 74)

The direct thrombin inhibitor dabigatran, and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban, are non–vitamin K antagonist oral anticoagulants (NOACs) approved by the US Food and Drug Administration (FDA) for the prevention of stroke in patients with nonvalvular atrial fibrillation (AF), and the treatment of deep venous thrombosis and pulmonary embolism. Each of these agents is in part cleared through renal excretion, and the doses of all four agents must be lowered in patients with reduced creatinine clearance (CCr). Additionally, rivaroxaban, edoxaban, and dabigatran should not be prescribed at all for patients with CCr <15 mL/min.[1]

Apixaban has the lowest proportion of renal excretion (25%) among the available NOACs. Its FDA-approved labeling recommends reduced dosage (2.5 mg twice daily, instead of 5 mg twice daily) for patients with AF and serum creatinine >1.5 mg/dL, *if* the patient also weighs ≤60 kg, or if age is ≥80 years. Apixaban is also approved for use in hemodialysis (5 mg twice daily, or 2.5 mg twice daily for age ≥80 years or body weight ≤60 kg) based on a small pharmacokinetic study.[2] In a retrospective review that compared apixaban with warfarin in patients with severe renal impairment, these anticoagulants resulted in similar bleeding and thrombotic complications.[3] Nonetheless, for patients with end-stage renal disease, and for those on dialysis, there is a long track record of acceptable safety with warfarin, which currently remains the anticoagulant of choice in these conditions.

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ANSWER TO QUESTION 642

D (Braunwald, p. 1770)

Past observational studies had suggested a benefit of postmenopausal hormone replacement therapy in primary and secondary prevention of coronary artery disease events. However, more recent large randomized prospective trials have shown that hormone replacement therapy fails to reduce coronary events. In the Women's Health Initiative estrogen-only trial, 10,739 postmenopausal women were randomized to placebo or 0.625 mg of oral conjugated equine estrogens daily. The trial was stopped early because there was no significant benefit of estrogen on the primary composite endpoint of death or nonfatal myocardial infarction, but the risk of stroke and pulmonary embolism *increased* in the estrogen arm of the study. Current American Heart Association guidelines assign a class III recommendation to the use of estrogen plus progestin for primary and secondary prevention (i.e., risk is greater than benefit and should not be used).

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ANSWER TO QUESTION 643

C (Braunwald, pp. 1242–1243)

Factors that significantly increase mortality with coronary artery bypass graft surgery (CABG) include increasing age, urgent or emergent surgery, prior cardiac surgery, serum creatinine >2 mg/dL, female gender, left ventricular dysfunction, peripheral arterial disease, severe neurologic disease, and chronic obstructive lung disease. Scoring systems including the Society of Thoracic Surgeons risk estimator and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) can be used to assess the risk of adverse outcomes in individual patients.[1,2] Obesity has not been shown to be an independent predictor of mortality or cerebrovascular accidents after CABG; however, it does predict risk of developing of postoperative mediastinitis. Although not included in the EuroSCORE, preoperative atrial fibrillation is also associated with increased perioperative mortality and morbidity in patients undergoing cardiac surgery.[3]

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ANSWER TO QUESTION 644

B (Braunwald, p. 1790)

Acute myocardial infarction (AMI) is rare in women of childbearing age, but pregnancy increases the risk three- to fourfold. AMI can occur during any stage of pregnancy and is more frequent in multigravida women. Most events occur in women >30 years and the majority of the time the location is the anterior wall. Although atherosclerotic disease is typically uncommon in young women, there is a relatively high incidence of traditional risk factors among those who experience AMI during pregnancy, including cigarette smoking, hyperlipidemia, hypertension, and diabetes. The most common findings at coronary angiography in pregnant women with AMI are atherosclerotic disease (with or without intracoronary thrombus) or coronary artery dissection, the latter being the most common cause of AMI in the peripartum period. Coronary spasm or embolism is much rarer. Even during pregnancy, acute management of ST-segment elevation AMI warrants urgent coronary angiography, with percutaneous coronary intervention and stenting if appropriate. The safety of drug-eluting stents and their required prolonged dual antiplatelet therapy is unknown in pregnancy, and most experience to date has been with bare metal stents.

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ANSWER TO QUESTION 645

C (Braunwald, p. 1243)

Perioperative myocardial infarction (MI) has a major adverse effect on early and late prognosis following coronary artery bypass grafting (CABG).[1] The reported incidence of this complication is variable (0% to >10%) because of heterogeneous diagnostic criteria, with a median of 2.9%. The diagnosis of MI immediately after CABG can be difficult because usual criteria are not often applicable. For example, symptoms are not reliable because most patients are sedated and may not sense ischemic pain. Conversely, any chest discomfort described by the patient may be difficult to distinguish from sternal or pericardial sensations. The electrocardiogram may not be diagnostic because ST-segment abnormalities are very common after CABG. If new ST-segment *elevations* are observed, however, there should be concern for acute graft failure or spasm, which must be differentiated from the common diffuse ST-segment elevations representative of postoperative pericardial inflammation. The most reliable electrocardiographic findings of a post-CABG MI are new and persistent Q waves. Echocardiography may aid in the diagnosis of postoperative MI, as new wall motion abnormalities support the diagnosis of myocardial injury. However, abnormal septal motion is not specific because most patients who undergo cardiac surgery have paradoxical septal movement for at least several months after cardiac surgery. Serum markers of myocardial necrosis are also difficult to interpret in the post-CABG setting. Total creatine kinase elevations are almost universally observed because of damage to skeletal muscle in the chest wall. Myocardial-specific creatine kinase-MB isoenzymes and cardiac troponins are frequently detected in the serum as a result of myocardial incisions made for cardiopulmonary bypass. As a result, the third Universal Definition of Myocardial Infarction defines MI after CABG as an elevation of cardiac biomarker values to more than 10 times the 99th percentile upper reference limit (in patients with normal baseline troponin values) in the presence of

other clinical findings supportive of myocardial infarction, including (1) new pathologic Q waves or new left bundle branch block, (2) angiographic evidence of new coronary or bypass graft occlusion, and/or (3) imaging evidence of new infarcted territory.[2]

Clinical risk factors for peri-CABG MI include older age, longer pump time, elevated left ventricular end-diastolic pressure, preoperative unstable angina, and significant left main coronary artery disease.

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ANSWER TO QUESTION 646

C (Braunwald, pp. 1745–1746)

Older patients (>65 years of age) comprise 60% of hospital admissions for acute myocardial infarction (MI). According to a review of Medicare beneficiaries, elderly patients who present with an acute MI are more likely to have comorbid illnesses and exhibit higher rates of congestive heart failure, ventricular rupture, and mortality compared with younger individuals. Like younger age groups, there is a significant survival benefit from reperfusion therapies (percutaneous coronary intervention [PCI] or fibrinolysis) in acute ST-segment elevation MI in older patients, although few individuals >75 years have been included in pertinent clinical trials. For individuals up to the age of 75 years, most trials show that fibrinolytic, antiplatelet, and anticoagulant therapies are associated with a survival advantage; however, bleeding and transfusion rates are higher in older patients. Even fibrin-specific fibrinolytic agents are associated with increased stroke risk due to intracerebral hemorrhage in those >75 years. In patients >75 years who undergo PCI, antiplatelet therapy with prasugrel is associated with an increased risk of fatal bleeding events compared with clopidogrel and should be avoided in that population.

Ventricular remodeling after infarction may differ in the elderly because of alterations in the inflammatory response, decreased ability of the myocardium to hypertrophy, and increased collagen content of cardiac tissue. However, elderly patients benefit as much as younger individuals from beta blocker therapy for secondary prevention. In addition, in patients >65 years of age who have sustained an MI with residual left ventricular ejection fraction <40%, angiotensin-converting enzyme inhibitors reduce fatal and nonfatal events just as they do for younger individuals.

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ANSWER TO QUESTION 647

A (Braunwald, pp. 102–103, 108)

Many patients >40 years old are likely to have coronary artery disease or other cardiac conditions that may influence the safety of noncardiac surgery. The Revised Cardiac Risk Index (RCRI) is one tool used to estimate the risk of perioperative cardiovascular complications. The RCRI includes the following six independent predictors of increased risk: high-risk type of surgery, history of ischemic heart disease, history of congestive heart failure (e.g., the S_3 gallop described in the vignette), history of cerebrovascular disease, preoperative treatment with insulin, and a preoperative serum creatinine >2 mg/dL. The more variables present, the greater the risk of a perioperative cardiovascular complication.

Notably, statistically nonsignificant risk factors include smoking, hyperlipidemia, and mild to moderate hypertension. And while preoperative unstable symptoms of angina portend a complicated postoperative course, such is not the case for patients with stable class I to II angina or remote MI without active angina. A history of supraventricular arrhythmias such as atrial fibrillation should alert the clinician to the possible development of similar rhythm disturbances postoperatively. Nonsustained ventricular tachycardia has not been associated with poor postoperative outcomes.

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ANSWER TO QUESTION 648

B (Braunwald, pp. 1757–1758)

Data from several major randomized placebo-controlled trials indicate that therapy for systolic and/or diastolic hypertension in elderly patients reduces cardiovascular events. For example, in the landmark Hypertension in the Very Elderly trial, treatment of systolic hypertension reduced the incidence of both stroke and all-cause mortality. The 8th Joint National Committee on Prevention, Evaluation, and Treatment of Hypertension (JNC 8) had recommended a goal blood pressure of <150/90 in adults age 60 years or more.[1] More recently, however, the 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults revised the target to a blood pressure <130/80 for all adults, with the caveat that clinical judgment, patient preference, and a team-based approach to assess risks and benefits be applied for older adults (≥65 years old).[2]

Several studies, including the ALLHAT trial, have demonstrated that thiazide diuretics are efficacious and

a preferred first-line antihypertensive agent in the elderly. In large clinical trials, beta blockers have resulted in less cardiovascular protection than diuretics as first-line therapy. Other first-line agents include calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

Data from the Framingham Study have confirmed the importance of left ventricular hypertrophy as an independent risk factor for adverse cardiac outcomes in older, hypertensive subjects. Hypertensive hypertrophic cardiomyopathy in the elderly tends to be more common in women, and the presenting symptom is usually dyspnea.

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ANSWER TO QUESTION 649

D (Braunwald, p. 1780; Fig. 90.2)

Several hemodynamic alterations occur during normal pregnancy (Fig. 5.3). Blood volume increases substantially, beginning during the second month, then rising to an average volume expansion of 50% by late pregnancy. The increase in blood volume occurs more quickly than an increase in hemoglobin, so anemia is common. The increased blood volume augments ventricular preload and stroke volume. The heart rate also rises steadily, usually by 10 to 20 beats/min by the third trimester. The augmented heart rate and stroke volume lead to a rise in cardiac output throughout pregnancy. Systemic vascular resistance begins to fall during the first trimester, reaches its lowest level in mid-pregnancy, then returns to the pre-pregnancy level before delivery. The drop in systemic vascular resistance likely reflects a combination of circulating gestational hormones, vasodilating prostaglandins, atrial natriuretic peptides, and nitric oxide, as well as the low-resistance circulation of the gravid uterus.

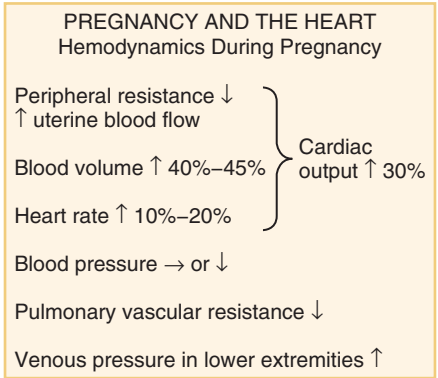

FIG. 5.3

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ANSWER TO QUESTION 650

D (Braunwald, pp. 1644–1646; Table 81.1)

Trastuzumab is a humanized monoclonal antibody that targets a subdomain of the human epidermal growth factor receptor 2 (HER2), termed ErbB2. It is predominantly used to treat HER2-positive metastatic breast cancer, but may also be effective in non-small cell lung cancer, gastric cancer, and esophageal cancer. The main potential cardiotoxicity of trastuzumab is cardiomyopathy, which may lead to severe clinical heart failure (HF). The risk of cardiomyopathy and HF is greatest in the setting of prior or concomitant anthracycline exposure. In many cases, the cardiomyopathy is partially or completely reversible with avoidance of trastuzumab and initiation of neurohormonal blockade.

Bevacizumab is a humanized recombinant monoclonal antibody that targets the vascular endothelial growth factor (VEGF) signaling pathway and has activity against a broad range of solid tumors. VEGF inhibitors may cause substantial systemic arterial hypertension through mechanisms that are incompletely understood. Less common cardiovascular complications of VEGF inhibitors include heart failure and arterial thromboembolic events.

Ipilimumab is an immune checkpoint inhibitor that targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Checkpoint proteins like CTLA-4 are important negative regulators of T-cell activation, and inhibiting their function results in antineoplastic activity by preventing tumors from evading the immune system. Because checkpoint inhibitors do not selectively enhance the anti-tumor immune response, they can also cause widespread adverse inflammatory reactions. Although the risk is low, these agents have been associated with clinically significant and in some cases lethal myocarditis.

Anastrozole is an aromatase inhibitor, which blocks the conversion of androgens to estrogen and is a highly effective therapy in the treatment of hormone-receptor positive breast cancer. In contrast to the selective estrogen receptor modulator tamoxifen, aromatase inhibitors are *not* associated with an increased risk of venous thromboembolism. They are, however, associated with increased total cholesterol and hypertension.

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ANSWER TO QUESTION 651

C (Braunwald, pp. 1906–1907)

This patient presents with an acute subarachnoid hemorrhage and a markedly abnormal electrocardiogram.

Electrocardiographic abnormalities are present in approximately 70% of patients with subarachnoid hemorrhage and can include ST-segment elevation or depression, deep symmetric T wave inversions as in this patient, and a prolonged QT interval that can lead to torsades de pointes. The mechanism of cardiac and electrocardiographic abnormalities in acute brain injury likely relates to autonomic nervous system dysfunction and excessive myocardial catecholamine release. In this setting, myocardial damage can occur with release of cardiac biomarkers, without primary acute coronary plaque rupture or thrombus formation. The magnitude of peak troponin elevation, but not the degree of electrocardiographic abnormality, is predictive of an adverse cardiac outcome. Beta blockers appear useful in minimizing myocardial damage and controlling arrhythmias in patients with subarachnoid hemorrhage.

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ANSWER TO QUESTION 652

D (Braunwald, p. 114)

It is generally safe and appropriate to continue most chronically administered cardiac medications up to the day of surgery and to resume them as soon as possible after the operation. This is true of beta blockers in patients with underlying coronary artery disease (or other indications for chronic beta blocker use) and continuing such therapy perioperatively is a class I American College of Cardiology/American Heart Association guideline recommendation.[1] However, there has been controversy about the role of *initiating* preoperative beta blocker therapy for the purpose of risk reduction.[2] Conclusions from randomized clinical trials have varied, in part related to methodologic differences in the studies. The evidence to date suggests that beta blockers reduce the perioperative risk of cardiovascular events (ischemia, atrial fibrillation, need for coronary interventions), but can be associated with bradycardia, hypotension, and stroke, particularly if high doses or long-acting preparations are initiated shortly before surgery.[3] If initiation of preoperative beta blocker therapy is planned, it should be started at least 2 to 7 days before surgery to assess tolerability and safety and to allow titration of the dosage if appropriate. Thus, current guidelines recommend against initiation of a beta blocker without dose titration immediately before surgery (especially high-dose or long-acting forms).[1]

Although nitrates reduce intraoperative ischemia, cardiac outcomes are not affected.

Statins have anti-inflammatory and plaque-stabilizing properties, and studies in patients undergoing vascular surgery have demonstrated reduced cardiac event rates in patients on statin therapy perioperatively.[4]

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ANSWER TO QUESTION 653

C (Braunwald, pp. 1735–1739)

Assessment of the heart's normal aging process is difficult because of the high prevalence of cardiovascular disease in older individuals. Studies in which coronary artery disease and other common cardiovascular conditions have been carefully excluded have revealed several pertinent findings. First, there is moderate hypertrophy of left ventricular myocardial cells, probably in response to increased arterial stiffness and loss of cardiac myocyte number with age. Although myocardial cells are unable to proliferate, they can increase in size as an adaptive response. Despite alterations in contractile proteins leading to reductions in the velocity of contraction and lengthening of contraction and relaxation times, peak contractile force production is maintained at normal levels, and there appear to be no changes in cardiac output, stroke volume, or ejection fraction at rest with normal aging. However, there are changes in beta-adrenoceptor-mediated inotropic and chronotropic cardiovascular responses with aging that result from generalized desensitization. Thus, the maximal heart rate during exercise and other cardiovascular responses to exercises are blunted.

Among the cellular and molecular changes that occur with aging, endothelial production of nitric oxide (NO) decreases, likely reflecting a combination of decreased endothelial cell mass (due to cell senescence and apoptosis) and increased NO utilization because of elevated vascular superoxide anion production in older subjects.

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ANSWER TO QUESTION 654

D (Braunwald, pp. 1242–1243)

Deep sternal wound infection is among the most serious complications of cardiac surgery. Patients with deep sternal wound infections present approximately 2 weeks after surgery with fever, leukocytosis, bacteremia, discharge, and erythema at the wound site. Risk factors for the development of

mediastinal infection include a prolonged cardiopulmonary bypass time, excessive bleeding necessitating reexploration for hemostatic control, the use of both internal mammary arteries, and older age. Atrial fibrillation is also a predictor of mediastinitis in patients undergoing coronary artery bypass grafting. Obesity is the most important risk factor for sternal dehiscence, whether or not infection is present.[1]

The incidence of postoperative deep sternal wound infection appears to be decreasing.[2] A significant contribution to this reduction is that the rate among diabetics has fallen from about 3.2% to about 1.0% over the past decade, possibly related to the introduction of perioperative intravenous insulin.

About half of deep sternal wound infections are caused by *Staphylococcus* species, and gram-negative organisms account for about 40%. Confirmation of a sternal wound infection often requires surgical exploration and removal of material for Gram stain and culture. Imaging techniques, including computed tomography or magnetic resonance imaging, are helpful. Intravenous antibiotics, with possible debridement and irrigation, may be required for prolonged periods. Early diagnosis and initiation of treatment enhance the prognosis. Mediastinal infections have not been shown to change patency rates of bypass grafts.

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ANSWER TO QUESTION 655

C (Braunwald, p. 1706)

Cardiac catheterization plays an important role in patients with suspected pulmonary arterial hypertension (PAH) to confirm the diagnosis, establish the severity of disease, and determine prognosis. Patients with PAH demonstrate a normal or low pulmonary capillary wedge pressure (PCWP), distinguishing PAH from pulmonary venous hypertension. A vasodilator challenge during catheterization allows assessment of pulmonary vasoreactivity and helps to guide therapy. Such a challenge can be accomplished with intravenous adenosine, intravenous epoprostenol, or inhaled nitric oxide. A favorable acute effect of these vasodilators (i.e., >10 mm Hg decrease in mean pulmonary artery pressure [PAP] to an absolute mean PAP lower than 40 mm Hg) without adverse effects (e.g., a decline in cardiac output or systemic blood pressure, or a rise in PCWP) is predictive of a favorable response to oral calcium channel blockers. An increase in PCWP during vasodilator testing would be consistent with pulmonary veno-occlusive disease or impending left ventricular failure.

When oral calcium channel blockers are used to treat PAH, high doses are required to achieve full clinical benefit.

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ANSWER TO QUESTION 656

C (Braunwald, pp. 1913–1914; Fig. 98.5)

Risk factors for contrast-induced acute kidney injury (CI-AKI) include chronic renal insufficiency, diabetic nephropathy, intravascular volume depletion, renal artery stenosis, and concurrent use of agents that alter renal hemodynamics (e.g., angiotensin-converting enzyme inhibitors). The smallest possible volume of contrast agent should be used in patients with renal insufficiency, because the risk of nephrotoxicity is related to the amount injected.

At present, the intervention that has been demonstrated to consistently reduce the incidence of this complication in patients at risk is intravenous (IV) normal saline hydration before and after the procedure. A randomized trial of IV isotonic sodium bicarbonate in elective coronary procedures showed no difference in post-procedure CI-AKI compared with IV saline, such that either could be used for hydration. Several other agents have been evaluated for prevention of CI-AKI, including mannitol, calcium channel antagonists, dopamine, and atrial natriuretic peptide; however, none has been shown to reduce the risk of renal complications.[1]

It has been hypothesized that lower ionic strength contrast agents should reduce the incidence of contrast nephropathy. Although that has not been demonstrated in patients with normal baseline renal function, the risk of contrast-induced nephropathy *is* reduced in patients with baseline renal insufficiency (with or without diabetes) if nonionic low-osmolar contrast medium is used.

Small studies had suggested that oral administration of *N*-acetylcysteine, an antioxidant, could reduce the risk of CI-AKI; however, several large randomized trials did not confirm this benefit.[2,3]

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ANSWER TO QUESTION 657

A (Braunwald, pp. 1817–1818)

The major cardiovascular changes that occur in hypothyroidism include a reduction in cardiac contractility, an increase in systemic vascular resistance, and a slowing of the heart rate. The decreased cardiac contractility and relative bradycardia result in a lower cardiac output. Thyroid hormone normally reduces smooth muscle tone, resulting in a decrease in peripheral vascular resistance. In the

relative absence of thyroid hormone, peripheral vascular tone increases and contributes to *hypertension*, which is common in hypothyroid patients. Thyroid hormone deficiency results in alterations in myocardial depolarization that can prolong the QT interval. Hypothyroidism is also associated with increased vascular permeability. Thus, pericardial effusions are common, developing in approximately one-third of patients, although progression to cardiac tamponade is rare.

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ANSWER TO QUESTION 658

C (Braunwald, pp. 1300, 1307; see also Answer to Question 67)

Marfan syndrome, caused by mutations in the fibrillin gene (*FBN1*), is associated with significant morbidity and mortality from cardiovascular causes. The most life-threatening complication is aortic dissection, to which patients with Marfan syndrome are predisposed because of aortic cystic medial degeneration. Such dissections usually commence just above the coronary ostia and may extend into the entire length of the aorta. Beta blockers limit aortic shear stress and are an important component of prevention. Prospective studies have confirmed a slowing of aortic dilatation and reduced risk of dissection in patients treated with beta-blockers. Limited data suggest that therapy with an angiotensin receptor blocker may also slow progression of aortic enlargement, presumably through effects on transforming growth factor beta signaling.

The dimension of the proximal aorta can be followed serially by transthoracic echocardiography, computed tomography, or magnetic resonance imaging. Prophylactic aortic root replacement is recommended in Marfan syndrome patients once the diameter approaches 5 cm to prevent dissection and progressive aortic regurgitation.[1,2] Some groups recommend replacement even earlier, when the diameter is in the 4.5- to 5.0-cm range.

Aortic dissection is an unfortunate potential complication of pregnancy in Marfan syndrome, occurring most commonly between the third trimester and the first month postpartum. The risk of dissection in this setting is related to the size of the aortic root and appears to be low in patients with root diameters of ≤4 cm.[3]

Progressive valvular impairments are also common in patients with Marfan syndrome. The risk of severe aortic regurgitation increases as the diameter of the aortic root enlarges. Mitral valve prolapse, associated with elongated and redundant leaflets, is detected in 60% to 80% of patients by echocardiography.[4] Progression to severe mitral regurgitation occurs in up to 25% of patients.

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ANSWER TO QUESTION 659

B (Braunwald, p. 1837; Tables 93.5 and 93.6)

This patient has heparin-induced thrombocytopenia (HIT), of which there are two forms. Type I HIT is the common, milder form that likely results from non–immune-mediated heparin-induced aggregation of platelets. Platelet counts usually drop within 2 days of therapy but rarely fall below 100,000/μL, and patients do not often develop bleeding complications. In the majority of such cases, heparin can be continued and the platelet count will improve.

Type II HIT, which has developed in the patient presented in this question, is the more dangerous form. It produces more severe thrombocytopenia, with levels often <50,000/μL. It develops when antibodies form against the heparin-platelet factor 4 (PF4) complex. These antibodies bind simultaneously to the heparin-PF4 complex and to platelet Fc receptors, an action that stimulates platelet activation and thrombosis. The diagnosis can be confirmed by the measurement of anti-heparin/PF4 antibodies.

Type II HIT usually becomes manifest for the first time within 4 to 14 days of the initiation of heparin therapy. However, on subsequent exposure, it can present quickly after even small doses of heparin. Therefore, patients with a history of type II HIT should never receive any form of heparin.[1]

When type II HIT develops, heparin should be stopped immediately (Table 5.4). If further anticoagulation is needed, a parenteral direct thrombin inhibitor, such as lepirudin, argatroban, or bivalirudin, can be substituted.[2] Fondaparinux, a synthetic pentasaccharide with anti-factor Xa activity, is another anticoagulant that can be used safely in patients with HIT.[3]

TABLE 5.4 Management of Heparin-Induced Thrombocytopenia

Stop all heparin.
Give an alternative anticoagulant, such as lepirudin, argatroban, bivalirudin, or fondaparinux.
Do not give platelet transfusions.
Do not give warfarin until the platelet count returns to baseline levels; if warfarin was administered, give vitamin K to restore the international normalized ratio to normal.
Evaluate for thrombosis, particularly deep vein thrombosis.

Low-molecular-weight heparins (LMWHs) are associated with a lower incidence of HIT than is intravenous unfractionated heparin (UFH). However, antibodies to UFH cross-react with LMWHs, so once a diagnosis of type II HIT is made, both types of heparin should be avoided.

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ANSWER TO QUESTION 660

D (Braunwald, pp. 1458, 1839–1843)

The non–vitamin K antagonist oral anticoagulants are approved for use in nonvalvular atrial fibrillation, among other indications. However, none of these agents is approved for use in patients with mechanical heart valves. Dabigatran was compared to warfarin in the randomized, prospective RE-ALIGN trial of patients with bileaflet mechanical heart valves. The trial was terminated early because dabigatran was associated with increased rates of thromboembolic and bleeding complications compared with warfarin.

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ANSWER TO QUESTION 661

C (Braunwald, pp. 1873–1874)

Metastatic tumors to the heart or pericardium are much more common than are primary cardiac malignancies. Metastases within cardiac structures are present at autopsy in approximately 9.1% of patients with malignant disease, whereas primary cardiac tumors are found in fewer than 0.1% of individuals postmortem. The most common malignancy that metastasizes to the heart is carcinoma of the lung (36% to 39% of metastases), followed in frequency by carcinoma of the breast and hematologic malignancies. Single metastases to the heart are rare, such that the finding of a solitary cardiac tumor is more likely indicative of a benign process.

Cardiac metastases typically involve the pericardium and myocardium, while the valves and endocardium are only rarely affected. Many cardiac metastases are clinically silent. For example, in malignant melanoma, 28% to 56% of patients have metastases to the myocardium or pericardium, yet cardiac symptoms are rare. The most common clinical manifestations of metastatic disease are due to pericardial effusion (i.e., tamponade), tachyarrhythmias, conduction blocks, and congestive heart failure.

A chylous pericardial effusion is characteristic of lymphoma.

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ANSWER TO QUESTION 662

A (Braunwald, pp. 1514–1515; Table 74.2)

This patient presents with acute rheumatic fever (ARF) after probable streptococcal pharyngitis. ARF typically manifests as a subset of five major manifestations (the "Jones criteria"): carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum. In addition, several other symptoms and laboratory findings are usually present in this condition and constitute minor criteria. These include nonspecific arthralgias, especially of large joints, fever, elevated acute-phase reactants (i.e., erythrocyte sedimentation rate and C-reactive protein), and electrocardiographic findings that include prolongation of the PR interval (not the QT interval). The diagnosis of ARF is made in the presence of preceding group A beta-hemolytic streptococcal infection when two major criteria, or one major and two minor criteria are present.

In 2015, the Jones criteria were revised to recognize that their clinical utility is determined by the background disease prevalence of acute rheumatic fever in a given population (i.e., the pretest probability). As such, different thresholds are required for meeting the major and minor criteria in low-risk versus moderate- and high-risk populations (Table 5.5).[1]

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TABLE 5.5 2015 Jones Criteria for the Diagnosis of Rheumatic Fever[a]

LOW-RISK POPULATIONS	MODERATE- AND HIGH-RISK POPULATIONS
Major Criteria	
Carditis (clinical or subclinical[b]) Arthritis (polyarthritis only) Chorea Erythema marginatum Subcutaneous nodules	Carditis (clinical or subclinical) Arthritis (including polyarthritis, monoarthritis, or polyarthralgia[c]) Chorea Erythema marginatum Subcutaneous nodules
Minor Criteria	
Polyarthralgia Fever (≥38.5°C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	Monoarthralgia Fever (≥38°C) ESR ≥30 mm in the first hour and/or CRP ≥3.0 mg/dL[d] Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

Joint manifestations are only considered in either the major or minor categories, but not both in the same patient.

[a]Annual ARF incidence of ≤2 per 100,000 school-aged children or all age RHD prevalence of ≤1 per 1000 people per year.

[b]Defined as echocardiographic.

[c]Polyarthralgia should only be considered as a major manifestation in moderate- and high-risk populations after exclusion of other causes.

[d]CRP value must be greater than the normal laboratory upper limit. In addition, as the ESR might evolve during the course of ARF, peak ESR values should be used.

ARF, Acute rheumatic fever; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *RHD,* rheumatic heart disease.

ANSWER TO QUESTION 663

D (Braunwald, pp. 1848, 1856, 1859; Table 94.1)

Rheumatoid arthritis (RA) is the most common systemic rheumatic disorder. Potential cardiac complications include pericardial, myocardial, coronary, or conduction system disease. The incidence of symptomatic pericarditis has declined (<2% of patients) with current aggressive management and increasing use of biologic therapies in RA, and asymptomatic pericardial effusions are more common than acute pericarditis. Very rarely, pericardial constriction develops.

Arrhythmias or conduction abnormalities (first-degree atrioventricular [AV] block, most commonly) are not unusual in RA, occurring in up to 50% of patients, but are rarely symptomatic. Conduction disease may result from impingement on the conduction fibers by rheumatoid nodules, or in the case of AV block, by rare rheumatic myocarditis or amyloid deposition.

Patients with RA have an increased incidence of atherosclerotic coronary artery disease (CAD), likely related to both traditional risk factors and disease-related inflammation. Symptoms of CAD may be masked in RA patients with limited physical mobility, but the risk for myocardial infarction is similar to that of diabetics. Women with RA are twice as likely as age-matched controls to suffer myocardial infarction. In the past, coronary arteritis had been reported in up to 20% of patients in autopsy series; however, in the current anti-inflammatory era, it is only rarely of clinical significance. The epicardial arteries are generally spared, because arteritis is usually confined to smaller intramyocardial vessels.

Autopsy studies have demonstrated rheumatoid involvement of the cardiac valves, but such lesions are only occasionally identified clinically. Valvular thickening may be evident echocardiographically, more commonly in patients with seropositive RA and prominent extra-articular nodular disease.

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ANSWER TO QUESTION 664

C (Braunwald, pp. 1841–1843)

A major goal of therapy in patients with atrial fibrillation (AF) is to prevent thromboembolic complications such as stroke. This patient is at increased risk for thromboembolism in the setting of AF because of his age, hypertension, and diabetes (CHA_2DS_2-VASc score = 4) and therefore warrants chronic anticoagulation therapy.

Dabigatran etexilate is an oral direct thrombin inhibitor that reduces the risk of stroke and systemic embolism in patients with nonvalvular AF. In the RE-LY trial, dabigatran (at doses of 110 and 150 mg twice daily) was compared prospectively with warfarin (dose adjusted to achieve an international normalized ratio between 2.0 and 3.0) for stroke and systemic embolism prevention in 18,113 patients with nonvalvular AF, followed for a median of 2 years. The annual rate of stroke or systemic embolism was 1.7% with warfarin, 1.5% with the lower-dose dabigatran regimen ($P < .001$), and 1.1% with the higher-dose regimen ($P < .001$). The lower-dose dabigatran regimen was noninferior to warfarin, whereas the higher dose regimen was actually superior for stroke and embolism prevention. The annual rates of major bleeding were 3.4% with warfarin compared with 2.7% and 3.1% with the lower-dose and higher-dose dabigatran regimens, respectively. That is, the lower-dose dabigatran regimen was associated with less major bleeding than warfarin, whereas the rates were similar in the higher-dose dabigatran and warfarin cohorts. Episodes of hemorrhagic stroke were significantly fewer with either dose of dabigatran compared with warfarin.

The most common gastrointestinal side effects of dabigatran are dyspepsia and gastritis; hepatotoxicity was not observed with dabigatran in the RE-LY trial.

The labeling for dabigatran recommends a dose adjustment to 75 mg twice daily for patients with a reduced creatinine clearance between 15 and 30 mL/min. There is insufficient experience to recommend a dose for a creatinine clearance <15 mL/min.

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ANSWER TO QUESTION 665

B (Braunwald, p. 1819; Fig. 92.7)

Amiodarone, a potent class III antiarrhythmic agent, has two primary effects on thyroid function. First, it inhibits the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3), causing a reduction of serum T_3 and a transient rise in thyroid-stimulating hormone (TSH). Within a short time, however, a compensatory increase in serum T_4 levels occurs and TSH returns to normal. Clinically, such patients are euthyroid, even though T_4 levels are elevated. Amiodarone's second effect relates to its large content of iodine (30% by weight), which inhibits synthesis and release of T_4 from the thyroid gland, causing a more sustained rise in TSH. In some patients, especially those with underlying thyroid disease, clinical hypothyroidism and a marked rise in TSH result.

Amiodarone-induced hyperthyroidism is less common and may arise from two distinct mechanisms. Type I develops primarily in individuals with underlying thyroid disease, typically in iodine-deficient environments. Such patients display evidence of thyroid autoimmunity, including antithyroid antibodies. In contrast, type II is a form of thyroiditis that develops in a previously normal gland, presumably mediated by proinflammatory cytokines, marked by an elevation of circulating interleukin-6. This condition is a thyroid-destructive process, and hyperthyroidism results from release of preformed thyroid hormone, a situation that can persist for months. Unlike type I, this form of hyperthyroidism tends to respond to glucocorticoid therapy.

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ANSWER TO QUESTION 666

D (Braunwald, pp. 1726–1727, 1729–1730, 1732; see also Answer to Question 486)

The two principal sleep disorders associated with cardiovascular disease are obstructive sleep apnea (OSA) and

central sleep apnea (CSA). OSA is characterized by transient upper airway occlusion that results in partial or complete cessation in airflow leading to hypoxia, sympathetic activation, repeated arousal and wakefulness, and sleep fragmentation. Individuals with OSA demonstrate persistently heightened sympathetic activity, even during daytime wakefulness. This in turn leads to peripheral vasoconstriction and hypertension, as well as automatic tachycardias driven by the augmented sympathetic tone. In addition, reflex parasympathetic activity can lead to profound nocturnal bradycardias.

Continuous positive airway pressure (CPAP) is the cornerstone of OSA management. This therapy effectively splints open the airway, thus preventing airway collapse, improving nocturnal hypoxia, and reducing sympathetic activity. Randomized controlled trials of CPAP in OSA have demonstrated decreased daytime sleepiness, improved health-related quality-of-life and mood, and lower blood pressure.[1] While observational trials have suggested decreased mortality with CPAP usage, randomized trials to date have not confirmed that.[2,3] Importantly, such trials have been limited by either inadequate power or modest CPAP adherence.

In contrast to OSA, CSA represents an instability of ventilatory control, resulting in oscillations in ventilation with periodic hyperpnea and apnea.[4] When manifest as Cheyne-Stokes respirations, it is associated with advanced heart failure. CPAP is effective in the management of CSA, is associated with decreased sympathetic drive, reduced ventricular afterload, and improvement in left ventricular ejection fraction. CPAP has been shown to improve nocturnal oxygen saturation and 6-minute walk distance in patients with class II to IV heart failure and CSA.

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ANSWER TO QUESTION 667

B (Braunwald, pp. 1692–1693; Table 84.7)

Approximately 20% of patients with unprovoked deep venous thrombosis experience a recurrence within 2 years of stopping anticoagulation therapy. Therefore, after the initial treatment period of at least 3 months, many experts recommend extended-duration anticoagulation. In a randomized trial of patients who had completed 6 to 12 months of anticoagulation for acute venous thromboembolism (VTE), both standard-dose apixaban (5 mg twice daily) and low-dose apixaban (2.5 mg twice daily) were shown to reduce the rate of recurrent VTE compared to placebo without increasing major bleeding.[1] Similarly, extended-duration treatment with rivaroxaban (20 mg daily) in patients who had completed 6 to 12 months of anticoagulation for VTE reduced the rate of recurrent VTE compared to placebo in the EINSTEIN DVT Continued Treatment trial.[2] More recently, in the EINSTEIN CHOICE trial, extended-duration treatment with either standard-dose rivaroxaban (20 mg daily) or low-dose rivaroxaban (10 mg daily) reduced the rate of recurrent VTE compared to aspirin.[3] Extended-duration anticoagulation with both standard-intensity warfarin (international normalized ratio [INR] target 2.0 to 3.0) or low-intensity warfarin (INR target 1.5 to 2.0) are also valid evidence-based options for extended-duration anticoagulation.[4] However, in contrast to the non-vitamin K antagonist oral anticoagulants, dosing of vitamin K antagonists requires close monitoring and dose adjustment rather than fixed dosing.

Two studies have tested low-dose aspirin (100 mg daily) versus placebo in patients with unprovoked VTE who had completed at least 6 months of standard anticoagulation.[5,6] In a meta-analysis, there was a 32% reduction in the rate of recurrence of VTE with aspirin during a median follow-up of >2 years, without an increase in major bleeding. Thus, while patients with unprovoked VTE derive the lowest recurrence rates with extended-duration standard anticoagulants, aspirin offers an evidence-based benefit for patients who do not wish to restrict their lifestyle or be subject to the bleeding risk of indefinite-duration standard anticoagulation.

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ANSWER TO QUESTION 668

B (Braunwald, pp. 102–103, 108)

When surgery is elective, it is appropriate to estimate cardiovascular risk using multifactorial indices. Independent predictors of complications with noncardiac surgery include (1) high-risk type of operation, (2) history of ischemic heart disease, (3) history of heart failure, (4) history of stroke, (5) diabetes with preoperative insulin use, and (6) preoperative serum creatinine >2 mg/dL. An example of a high-risk operation is abdominal aortic aneurysm surgery, whereas low-risk procedures include endoscopy, cataract surgery, superficial procedures and biopsies, and transurethral prostate surgery. Carotid endarterectomy poses an intermediate risk.

Ischemic heart disease is a major determinant of perioperative morbidity and mortality. However, if a patient is clinically stable, and can carry a grocery bag up one flight of stairs (the equivalent of >4 METS of activity) without stopping or experiencing anginal symptoms, most surgical procedures will be well tolerated and no additional preoperative cardiac testing is typically necessary. Conversely, a patient who develops shortness of breath or chest discomfort with only minor exertion is at high risk for postoperative cardiac events

and warrants additional cardiac testing, especially if more than a minor surgical procedure is planned.

Historically, the cardiac risk of noncardiac surgery in patients with prior myocardial infarction (MI) has related inversely to the length of time that has passed since the acute coronary event. Studies from the 1970s concluded that purely elective surgery should be delayed for 6 months after an MI to ensure that cardiovascular risk had returned to baseline. In those studies, the risk of reinfarction or death was approximately 30% when patients were operated on within 3 months of an MI, but only 5% when 6 months had elapsed before the operation. Later studies, in the era of careful perioperative monitoring, demonstrated much lower cardiac complication rates: approximately 6% risk of reinfarction for operations performed within 3 months of an MI and 2% risk for operations performed within 3 to 6 months. These historic risks are less relevant today in the era of early revascularization (mechanical or fibrinolytic) and aggressive postevent pharmacologic therapy for acute coronary syndromes (ACS). Current guidelines suggest that the highest risk of elective surgery for such patients is limited to the first 30 days after an ACS while the disrupted coronary plaque and myocardium are healing.

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ANSWER TO QUESTION 669

C (Braunwald, pp. 1589, 1790; see also Answer to Question 636)

The presentation of this patient is most consistent with peripartum cardiomyopathy (PPCM). This disorder is a form of dilated cardiomyopathy that manifests in the last trimester of pregnancy or in the early postpartum period. The incidence is higher in women >30 years of age, women with twin pregnancies, multiparous women, and African American women. Recent studies have suggested significant overlap in the genetic predisposition to PPCM and other forms of idiopathic dilated cardiomyopathy.

The prognosis of this disorder is favorable compared with other forms of dilated cardiomyopathy, with approximately 50% of patients showing marked improvement or complete recovery within 6 months postpartum. The remainder either stabilizes with reduced cardiac function or declines progressively, eventually requiring cardiac transplantation. The predictors for a poor outcome include older age, higher parity, severe left ventricular dilatation, and onset of symptoms later after delivery. There is a high risk of relapse of PPCM in subsequent pregnancies, and that risk appears to be greatest in women who have persistently impaired cardiac function.

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ANSWERS TO QUESTIONS 670 TO 674

670–E, 671–D, 672–B, 673–C, 674–A (Braunwald, pp. 1850, 1857–1859, 1862)

The spondyloarthropathies, including ankylosing spondylitis, reactive arthritis, and psoriatic arthritis, have a predilection for arthritis of the sacroiliac and lumbosacral joints. These diseases are associated with the histocompatibility antigen HLA-B27 and occur predominantly in men. *Ankylosing spondylitis* is the most common of these syndromes to involve the heart and classically causes dilatation of the aortic valve ring with fibrous thickening and inflammation.[1] The aorta in ankylosing spondylitis is histologically similar to that in syphilitic aortitis, including adventitial scarring, intimal proliferation, and narrowing of the vasa vasorum. Aortic regurgitation results from thickening of the valvular cusps and dilatation of the aortic root. Conduction system disorders, due to fibrous infiltration in the atrioventricular node and the bundle of His, may be seen in ankylosing spondylitis as well.

Reactive arthritis is a form of nonpurulent arthritis that may follow enteric or urogenital infections. It may be accompanied by uveitis/conjunctivitis and nongonococcal urethritis (formerly termed Reiter syndrome). The cardiac complications of reactive arthritis are similar to those of ankylosing spondylitis.[2]

Cardiac abnormalities in patients with *systemic sclerosis/scleroderma* often relate to systemic or pulmonary hypertension, but may also include myocardial fibrosis and contraction band necrosis, causing diastolic and/or systolic ventricular dysfunction. Symptomatic pericarditis occurs in 7% to 20% of patients. Conduction defects and thickening of the mitral and aortic valves may also occur.[3]

Giant cell arteritis predominantly causes inflammation of the aorta, its major branches, and coronary arteries. Weakening of the vessels may lead to dilatation, aneurysm formation, and valvular insufficiency. The vascular pathology often reveals granuloma formation.[4]

Behçet syndrome is a multisystem disorder characterized by recurrent oral and genital ulcers and uveitis. The ulcers are often painful and necrotic, and eye involvement occasionally progresses to blindness. The etiology of the disease is unclear, but appears to involve endothelial activation as a mediator of vascular inflammation. Venous and arterial thrombosis may occur, as well as aneurysm formation of the large vessels. Diffuse aortitis in Behçet syndrome can lead to aortic root dilatation and valvular insufficiency.[5]

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ANSWERS TO QUESTIONS 675 TO 678

675–C, 676–B, 677–D, 678–A (Braunwald, pp. 677, 1831, 1833, 1837)

Numerous cardiac medications can cause adverse effects. For example, heparin can result in thrombocytopenia by two main mechanisms as described in the Answer to Question 659.

A positive direct Coombs test is seen in up to 10% of patients who receive alpha-methyldopa, an antihypertensive that is sometimes used in pregnancy. In these patients, IgG antibody is directed against the Rh complex of red cells. Hemolysis may be severe but improves within several weeks after cessation of the medication.

The most common side effects of ticagrelor, a platelet $P2Y_{12}$ receptor inhibitor, are bleeding, dyspnea (~15% of patients in the PLATO trial),[1] and ventricular pauses, which are typically asymptomatic. Dyspnea, when present, usually occurs soon after initiating therapy and is self-limited. The mechanism is unknown.

Procainamide may cause a syndrome resembling systemic lupus erythematosus (SLE). Symptoms consist of polyarthralgias, pleuritis, and photosensitive rashes. Unlike conventional SLE, nephritis and central nervous system complications are very rare. Patients with drug-induced lupus are antinuclear antibody (ANA) positive with antibodies to histones but rarely display hypocomplementemia or antibodies to DNA. Discontinuation of procainamide typically results in improvement of symptoms within a few days to weeks. However, ANA levels may remain elevated for years.

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ANSWERS TO QUESTIONS 679 TO 683

679–C, 680–A, 681–B, 682–B, 683–C (Braunwald, pp. 1850–1852; see also Answers to Question 632 and Question 633)

Takayasu arteritis (TA), also termed *pulseless disease*, is of unknown etiology and is characterized by marked fibrous and degenerative scarring of the elastic fibers of the vascular media.[1] It most commonly involves the aorta and carotid arteries. The disease is 10 times more common in women than in men, and in most patients onset occurs during the teen years. Patients typically present initially with malaise, weight loss, night sweats, arthralgias, pleuritic pain, anorexia, and fatigue. Regardless of whether a patient goes through this initial phase, symptoms and signs referable to the obliterative and inflammatory changes in affected blood vessels begin to appear following a latent period. These include diminished or absent pulses with claudication (upper extremities > lower extremities), hypertension (related to renal artery stenosis or increased vessel rigidity), and aortic root aneurysms with aortic regurgitation. Common laboratory abnormalities include elevated sedimentation rate, low-grade leukocytosis, and normocytic anemia. Treatment includes glucocorticoid therapy. Patients with refractory symptoms may respond to azathioprine, mycophenolate mofetil, methotrexate, leflunomide, intravenous cyclophosphamide, tumor necrosis factor antagonists, or tocilizumab (an interleukin-6 receptor antagonist).

Giant cell arteritis (GCA; also termed temporal arteritis) is a disease of unknown etiology characterized by granulomatous inflammation of large- to medium-caliber arteries with a special predilection for the vessels of the head and neck.[2] It arises primarily in elderly people with a female predominance. Clinically, the triad of severe headache, fever, and marked malaise characterizes the illness. The headaches are often severe and are typically localized over involved temporal arteries. Claudication of the jaw muscles during chewing is present in up to two-thirds of patients. Involvement of the ophthalmic artery leads to visual symptoms and may result in irreversible blindness. The syndrome of polymyalgia rheumatica, consisting of diffuse muscular aching and stiffness, occurs in about 40% of patients with GCA. In a minority of cases, involvement of the aorta or its major branches may lead to symptoms and signs similar to those of TA, although renal artery involvement is rare in GCA.

Patients with GCA appear ill and are almost always febrile. Affected vessels feel abnormal to palpation and are tender, allowing experienced examiners to make the diagnosis of temporal arteritis at the bedside by identifying an indurated, beaded, tender temporal artery. Laboratory tests often reveal a very high erythrocyte sedimentation rate, normochromic, normocytic anemia, and elevated acute-phase reactants. Biopsy of an involved temporal artery confirms the diagnosis.

Management of GCA includes early intervention with high-dose steroid therapy followed by a gradual taper to a maintenance dose, which is typically continued for 1 to 2 years. Early administration of steroid therapy is crucial to prevent involvement of the ophthalmic arteries and possible blindness. Recent evidence suggests that combining tocilizumab with steroid therapy may lead to higher rates of sustained remission in GCA.[3]

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ANSWERS TO QUESTIONS 684 TO 688

684–C, 685–A, 686–B, 687–D, 688–E (Braunwald, pp. 1641–1645; Table 81.1)

Many chemotherapeutic agents have potential cardiovascular toxicities. The anthracyclines (e.g., doxorubicin, daunorubicin, and idarubicin) may cause acute cardiac effects (including atrial and ventricular arrhythmias and pericardial effusion) or more chronic impairment (dilated cardiomyopathy with heart failure). As described in the Answer to Question 544, heart failure due to anthracycline therapy is dose related and develops more frequently when concurrent risk factors are present, including prior heart disease, radiation therapy exposure to the heart, and use of other cardiotoxic chemotherapeutic agents (e.g., trastuzumab, paclitaxel).

Patients receiving 5-fluorouracil may experience acute chest pain and myocardial infarction during or immediately after infusion. The mechanism of this adverse effect is

unknown. Cyclophosphamide and ifosfamide are alkylating agents that can cause an acute hemorrhagic myopericarditis. Interleukins, which are potent modulators of the immune system, are associated with capillary leak syndrome, hypotension, noncardiogenic pulmonary edema, and nephrotoxicity.

Sunitinib is a tyrosine kinase inhibitor that targets vascular endothelial cell growth factor receptors and is used to inhibit progression of renal cell carcinoma and gastrointestinal stromal tumors. Hypertension is a common side effect, with marked elevation in blood pressure in 8% to 20% of patients.

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ANSWERS TO QUESTIONS 689 TO 693

689–C, 690–D, 691–E, 692–A, 693–B (Braunwald, pp. 1809–1810, 1812, 1815–1818)

Endocrine disorders often exhibit cardiovascular manifestations. Excess thyroid hormone levels result in tachycardia, palpitations, and hypertension, often with a widened pulse pressure.[1] Cardiac examination reveals a hyperdynamic impulse with an accentuated S_1. Systolic murmurs are common, and a *Means-Lerman scratch,* a grating systolic sound at the upper left sternal border, may be auscultated during expiration.

The cardiovascular manifestations of hypothyroidism include bradycardia, diastolic hypertension with a narrowed pulse pressure, cardiomegaly with a reduced ejection fraction, and pericardial effusion, which only rarely results in tamponade physiology.[1]

Cushing syndrome, a state of augmented glucocorticoid exposure, is associated with accelerated atherosclerosis, likely related to hypertension and hyperglycemia in this condition. *Carney complex* is a genetic syndrome that includes cardiac myxomas, pigmented dermal lesions, and endocrine overactivity that can include Cushing syndrome. This autosomal-dominant condition arises from mutations in the *PRKAR1A* gene, which encodes a regulatory subunit of protein kinase A.[2]

Hyperaldosteronism is associated with excess aldosterone production from an adrenal or extra-adrenal source. Hypertension, hypokalemia, and metabolic alkalosis are common findings.[3] Many of the cardiac findings are nonspecific and are a consequence of the metabolic and electrolyte abnormalities. For example, U waves and ventricular arrhythmias result from associated hypokalemia.

Parathyroid hormone has direct inotropic and chronotropic effects on the heart, likely due to increased myocyte calcium entry. Hypercalcemia associated with hyperparathyroidism may result in excess calcium deposition in the heart, hypertension, and shortening of the QT interval.[4]

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ANSWERS TO QUESTIONS 694 TO 697

694–B, 695–C, 696–D, 697–A (Braunwald, pp. 1843–1844)

Tissue-type plasminogen activator (tPA), the major physiologic activator of plasminogen, is both synthesized naturally by endothelial cells and produced commercially by recombinant DNA technology for the purpose of therapeutic fibrinolysis. The protein is synthesized in a single-chain form, which is subsequently converted to a two-chain form by proteolytic cleavage of a single plasmin-sensitive site. Both the single-chain and the two-chain forms have endogenous proteolytic activity. The alpha chain of tPA is derived from the amino-terminal portion of single-chain tPA and contains a pair of finger-like structures referred to as "kringle" domains. Lysine binding sites located on these domains confer binding specifically for fibrin. As a result, tPA is a relatively fibrin-specific activator that converts plasminogen to plasmin two or three times more efficiently in the presence of fibrin. The protease domain of tPA contains a proteolytic site responsible for this conversion. This portion is homologous with other serine proteases, such as urokinase and trypsin.

Urokinase is a two-chain serine protease that is synthesized in both renal tubular epithelial cells and endothelial cells. While urokinase converts plasminogen to plasmin by hydrolyzing the same bond as that acted on by tPA, the proteolytic activity of urokinase is not enhanced by the presence of fibrin. Therefore, urokinase may activate circulating plasminogen as effectively as plasminogen absorbed onto fibrin thrombi.

Streptokinase is a single polypeptide chain of 414 amino acids that is produced by a strain of hemolytic streptococci. Streptokinase does not cause thrombolysis by intrinsic enzymatic activity. Instead, it activates the fibrinolytic system by combining with plasminogen to form a plasminogen activator complex that is then capable of converting plasminogen to plasmin. Plasmin then degrades fibrin and other procoagulant proteins. Many individuals have circulating antibodies to streptokinase as a result of previous streptococcal infections. Therefore, a large dose of streptokinase is administered to neutralize these antibodies. Antistreptococcal antibodies may remain high for up to 6 months after administration.

Tenecteplase is a genetically engineered mutant form of tPA that displays a prolonged half-life and increased fibrin specificity. Unlike tPA, which requires a continuous infusion, tenecteplase is injected as a single intravenous bolus, which facilitates administration.

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TABLE 5.6 Advantages of Low-Molecular-Weight Heparin Over Unfractionated Heparin

ADVANTAGE	CONSEQUENCE
Better bioavailability and longer half-life after subcutaneous injection	Can be given subcutaneously once or twice daily for both prophylaxis and treatment
Dose-independent clearance	Simplified dosing
Predictable anticoagulant response	Monitoring of coagulation is unnecessary in most patients
Lower risk for HIT	Safer than heparin for short- or long-term administration
Lower risk for osteoporosis	Safer than heparin for long-term administration

HIT, Heparin-induced thrombocytopenia.

ANSWERS TO QUESTIONS 698 TO 702

698–A, 699–B, 700–D, 701–C, 702–A (Braunwald, pp. 1835–1838)

Unfractionated heparin (UFH) is a naturally occurring compound that acts in vivo by combining with antithrombin (an inhibitor of thrombin and factors X, IX, and XI). The conformational change that occurs in antithrombin allows for an accelerated interaction with the activated clotting factors, limiting thrombin generation and fibrin formation. Commercial heparin is extracted from porcine intestinal mucosa and bovine lung and does not inactivate clot-bound thrombin or factor VII. Heparin is not absorbed by the gastrointestinal tract and is therefore administered in intravenous or subcutaneous forms. The bioavailability of subcutaneous injections of UFH is only 30%.

The activated partial thromboplastin time (aPTT) test is used to determine the inhibitory effect of UFH. For acute thrombosis or embolism, intravenous heparin is administered with a goal aPTT of 1.5 to 2 times the control value. Subcutaneous UFH is often used for patients who require a lower level of anticoagulation. Heparin therapy's major complication is bleeding. There is up to a 30% incidence of heparin-induced thrombocytopenia (HIT) that may be associated with thromboembolic events and often resolves with discontinuation of the drug (see Answer to Question 659). In addition, heparin may cause osteoporosis, elevated liver enzymes, increased vascular permeability, alopecia, and hypoaldosteronism (and associated hyperkalemia).

Low-molecular-weight heparin (LMWH) also produces an anticoagulant effect by binding to antithrombin. However, in distinction to UFH, LMWH preferentially inhibits factor Xa more than thrombin. LMWH formulations bind less with platelet factor 4, plasma proteins, and endothelial cells, and therefore have >90% bioavailability when administered by subcutaneous injection. Other advantages of LMWH include a prolonged half-life and predictable anticoagulant responses (Table 5.6).

Patients receiving LMWH do not require serial laboratory monitoring of the anticoagulant effect, except in the presence of renal failure, extreme obesity, or pregnancy. HIT can occur with LMWH but is less common than with UFH.

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ANSWERS TO QUESTIONS 703 TO 706

703–D, 704–B, 705–A, 706–C (Braunwald, pp. 1850, 1858–1860, 1862; see also Answers to Question 670 to Question 674)

Rheumatologic disorders often involve the cardiovascular system and can result in pericardial, myocardial, valvular, or arterial abnormalities. Aortic involvement is estimated to occur in 15% of patients with giant cell arteritis. Inflammation often involves the proximal aorta and aortic valve cusps, resulting in dilatation of the vessel and aortic regurgitation.[1] Other rheumatologic diseases that prominently involve the aorta include ankylosing spondylitis and psoriatic arthritis.

Valvular abnormalities are found by transesophageal echocardiography in 50% of patients with systemic lupus erythematosus. The most common involvement, termed *Libman-Sacks endocarditis,* represents noninfectious valve thickening, usually on the atrial side of the mitral valve and the arterial side of the aortic valve. Over time, fibrosis may result in valvular insufficiency. Much less commonly, the vegetations may occlude the valve orifice, causing stenosis. Clinical manifestations of Libman-Sacks lesions, such as infective endocarditis or peripheral embolism, are rare.[2]

Although pulmonary hypertension can develop in many rheumatologic disorders, it is a particularly prominent feature of systemic sclerosis and is one of the leading causes of morbidity and mortality in that condition.[3] Behçet disease typically results in inflammation of the thoracic aorta and branch vessels, leading to stenoses and aneurysmal dilatation of the subclavian and carotid arteries.[4] Thoracic and abdominal aortic aneurysms may also result.

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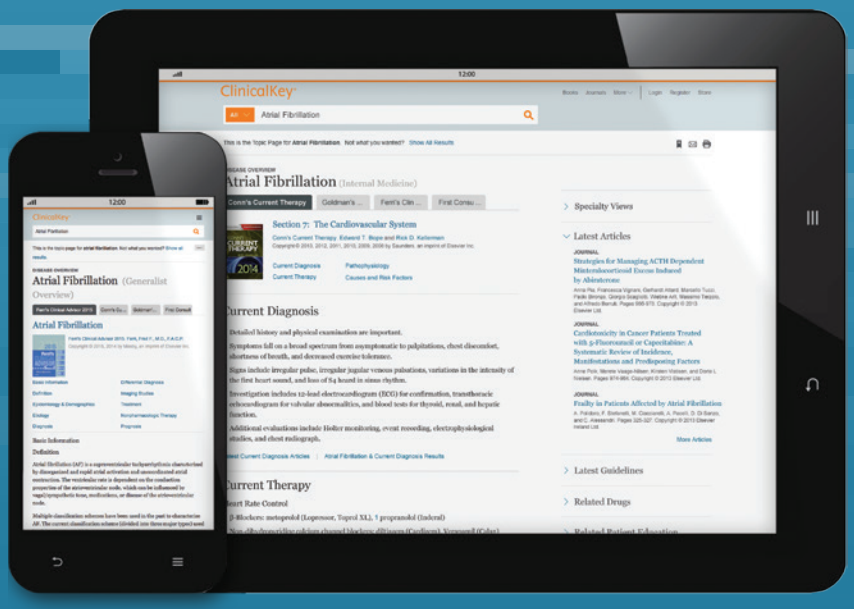

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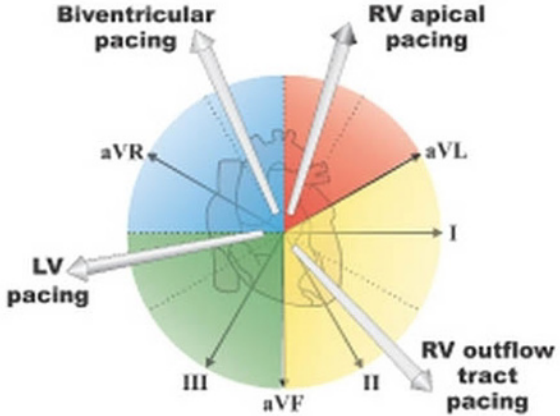

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© 2004 S. Serge Barold, Roland X. Stroobandt and Alfons F. Sinnaeve
Published by Futura, an imprint of Blackwell Publishing

Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148-5020, USA
Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK
Blackwell Science Asia Pty Ltd, 550 Swanston Street, Carlton, Victoria 3053, Australia

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First published 2004
Reprinted 2004

ISBN: 1-4051-1647-1

Library of Congress Cataloging-in-Publication Data

Barold, S. Serge.
Cardiac pacemakers step by step : an illustrated guide/S. Serge Barold, Roland X. Stroobandt, Alfons F. Sinnaeve.—1st ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-4051-1647-1
1. Cardiac pacemakers—Pictorial works.
[DNLM: 1. Cardiac Pacing, Artificial—methods. 2. Pacemaker, Artificial.
3. Electrocardiography—methods. WG 168 B264c 2004] I. Stroobandt, R. (Roland) II. Sinnaeve, Alfons F. III. Title.
RC684.P3B365 2004
617.4'120645—dc22

2003020390

A catalogue record for this title is available from the British Library

Acquisitions: Jacques Strauss
Production: Tom Fryer
Typesetter: Sparks Computer Solutions Ltd, in Great Britain
Printed and bound in Denmark by Narayana Press, Odder

For further information on Blackwell Publishing, visit our website:
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Preface

The impetus for writing this book came from our observations that many health care professionals and young physicians working in emergency rooms, intensive and coronary care units were unable to interpret simple pacemaker electrocardiograms correctly. Over the years we also heard many complaints from beginners in the field of cardiac pacing that virtually all, if not all, the available books are too complicated and almost impossible to understand. Indeed, the ever-changing progress in electrical stimulation makes cardiac pacing a moving target. Therefore we decided to take up the challenge and write a book for beginners equipped with only a rudimentary knowledge of electrocardiography and no knowledge of cardiac pacing whatsoever. Because many individuals first see the pacemaker patient after implantation, the book contains little about indications for pacing and implantation techniques. The book starts with basic concepts and progressively covers more advanced aspects of cardiac pacing including troubleshooting and follow-up.

As one picture is worth a thousand words, this book tries to avoid unnecessary text and focuses on visual learning. We undertook this project with the premise that learning cardiac pacing should be enjoyable. Cardiac pacing is a logical discipline and should be fun and easy to learn with the carefully crafted illustrations in this book. The artwork is simple for easy comprehension. Many of the plates are self-explanatory and the text in the appendix only intends to provide further details and a comprehensive overview.

Many of the images used to create the illustrations in this book are taken from CorelDraw and Corel Mega Gallery clipart collections.

We are grateful to Charlie Hamlyn of Blackwell Publishing and Tom Fryer of Sparks for their superb work in the production of this book.

S. Serge Barold
Roland X. Stroobandt
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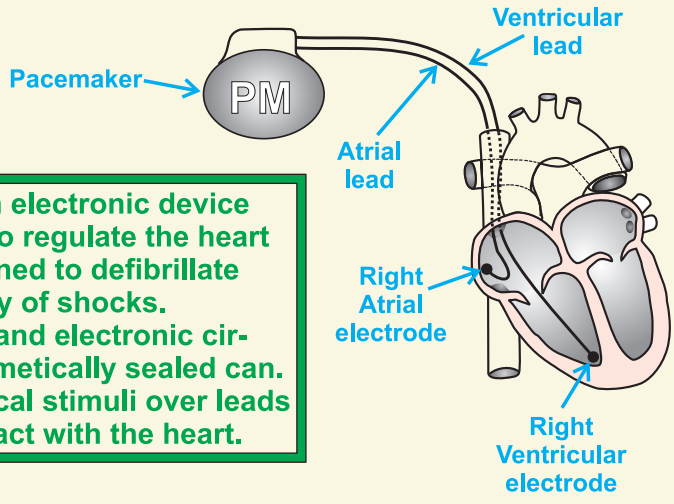
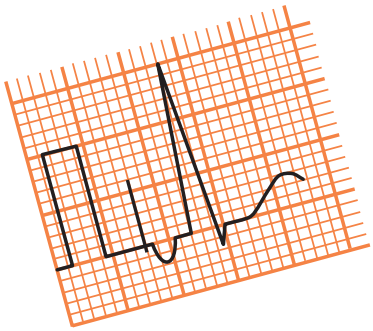
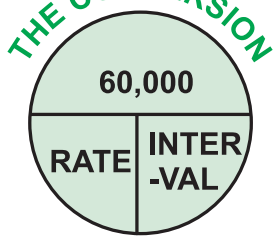
WHAT IS A PACEMAKER ???



A pacemaker (PM) is an electronic device implanted in the body to regulate the heart beat. A PM is not designed to defibrillate the heart by the delivery of shocks.
It consists of a battery and electronic circuits enclosed in a hermetically sealed can. The PM delivers electrical stimuli over leads with electrodes in contact with the heart.

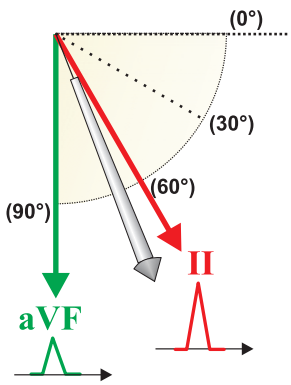
A. F. Sinnaeve

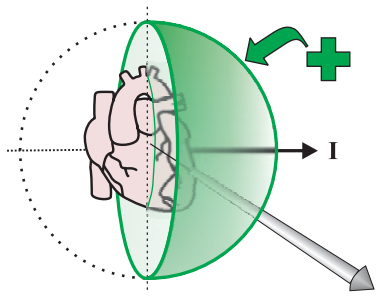




RECORDING PACEMAKER ACTIVITY

* 12-lead ECG during transvenous pacing
* Standard chest electrode positions
* Grid for measuring intervals
* The electrical axis in the frontal plane
* Determination of the mean frontal plane axis 1
* Determination of the mean frontal plane axis 2
* A rule of thumb for the mean frontal plane axis





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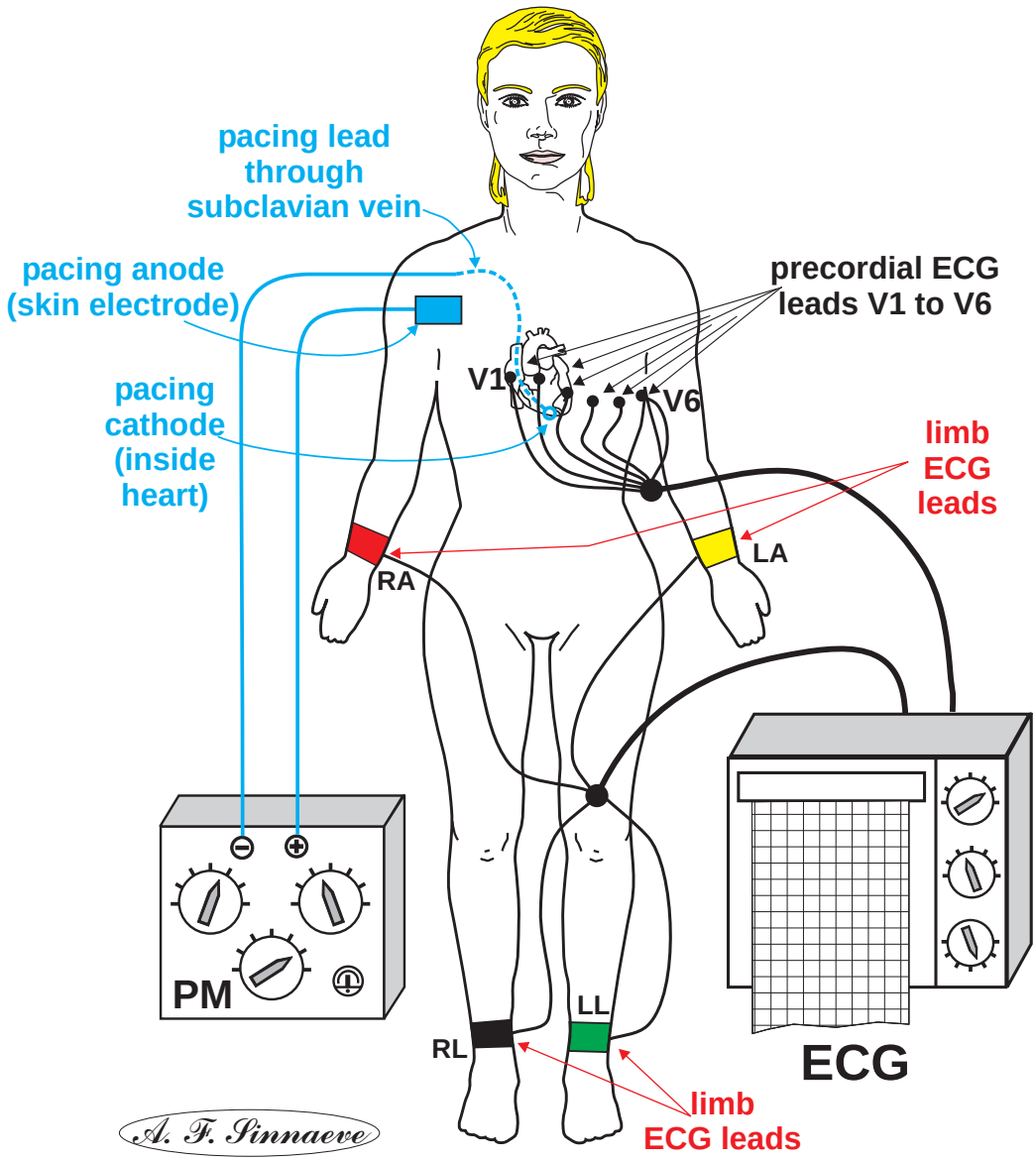
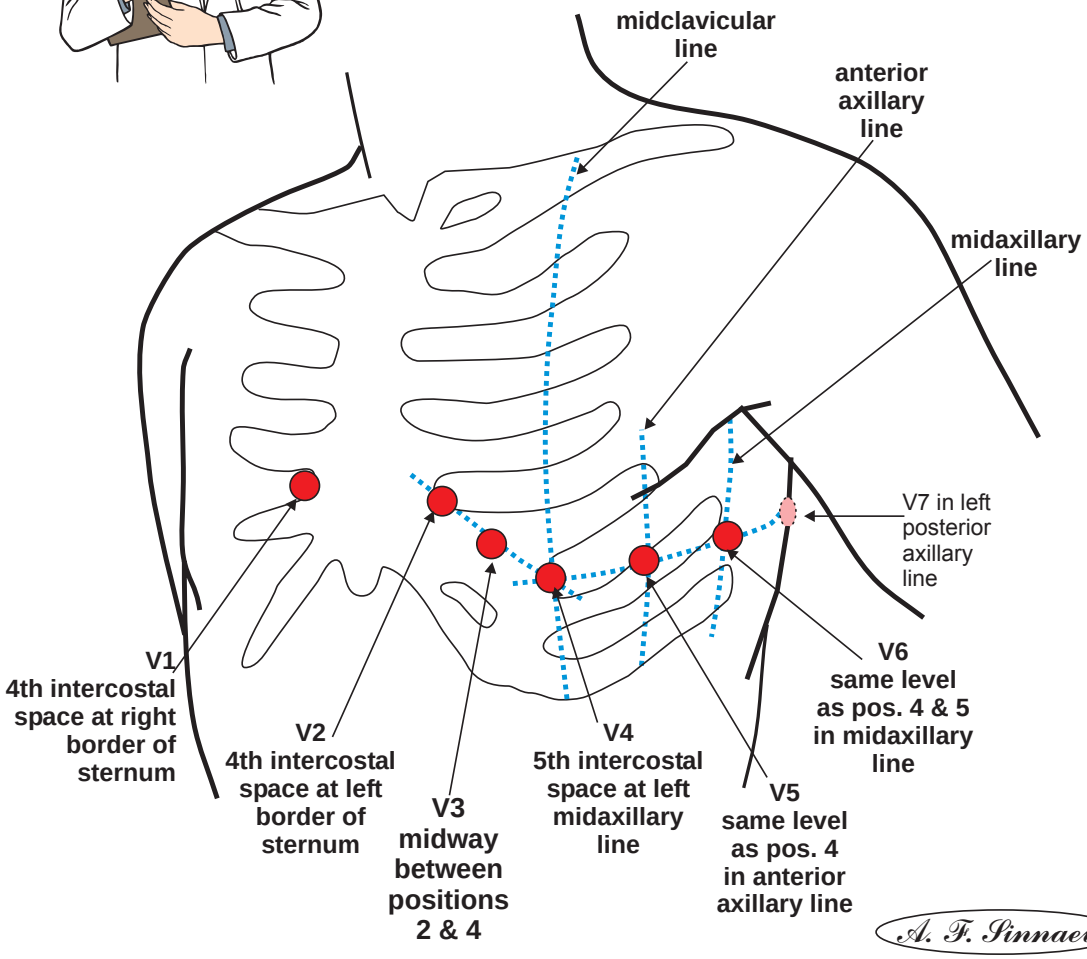
CONFIGURATION OF 12-LEAD ECG DURING TRANSVENOUS PACING



STANDARD CHEST ELECTRODE POSITIONS

The right position of all the electrodes is extremely important !!!



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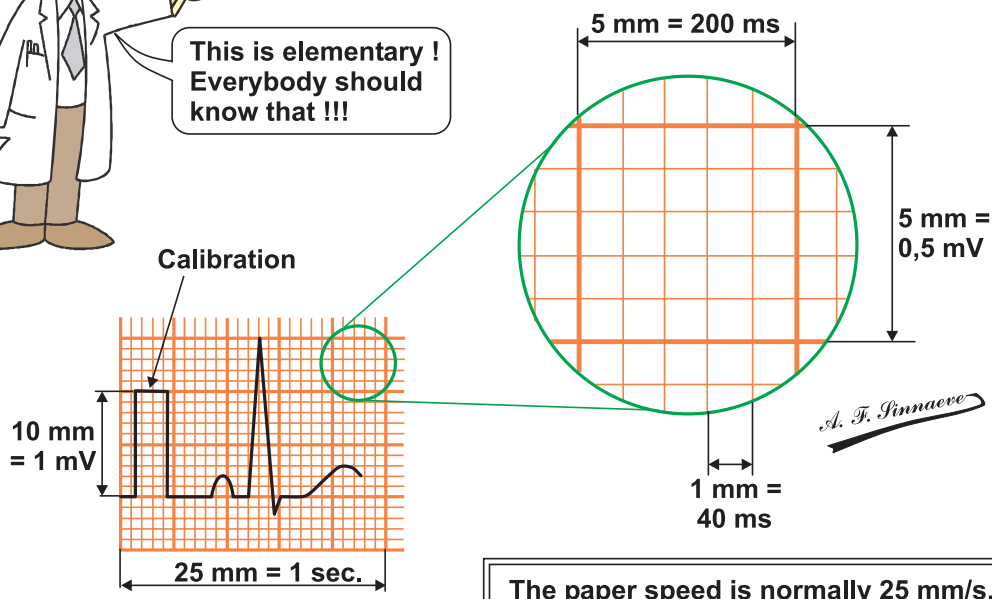
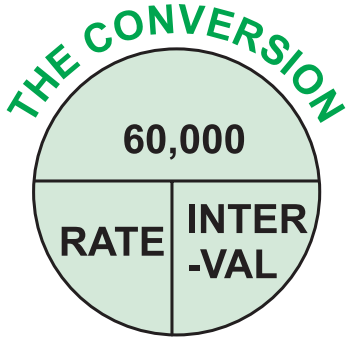
TIMING INTERVALS VERSUS RATE



The paper speed is normally 25 mm/s, thus 1 mm on the paper corresponds with 1/25 s = 0.04 s = 40 ms



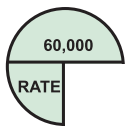
UNITS OF TIME

1 minute = 60 seconds
or 1 min = 60 s
1 second = 1,000 milliseconds
or 1 s = 1,000 ms
1 minute = 60,000 milliseconds
or 1 min = 60,000 ms

RATE is expressed in beats per minute or bpm

$$\text{RATE (in bpm)} = \frac{60{,}000}{\text{INTERVAL (in ms)}}$$

The pacemaker rate is the average of several intervals calculated for 1 minute of time

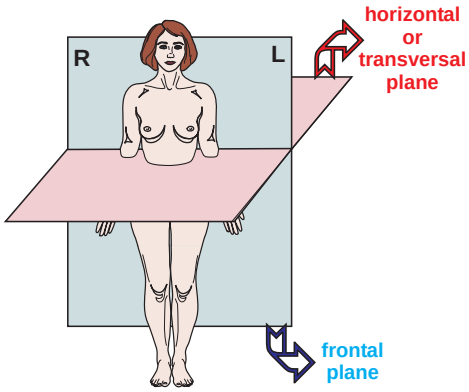


$$\text{INTERVAL (in ms)} = \frac{60{,}000}{\text{RATE (in bpm)}}$$

An interval is the time between two consecutive events, e.g. Vp-Vp or Vs-Vs

Abbreviations : min = minute ; mm = millimeter ; ms = millisecond ; mV = millivolt ; s = second ; Vp = ventricular paced event ; Vs = ventricular sensed event

THE ELECTRICAL AXIS IN THE FRONTAL PLANE



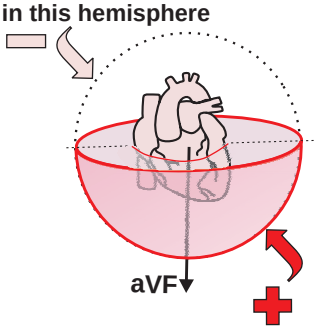
At any time during depolarization, there is a resultant instantaneous vector which represents the electrical activity of the depolarization process of all the ventricular myocardium. As depolarization proceeds, the magnitude and direction of this instantaneous vector varies continuously.
The mean frontal plane vector or axis represents the summation of all the instantaneous vectors recorded in the frontal plane that occur during depolarization, and is depicted as a single mean vector.

Why is the frontal plane axis important during pacing ?

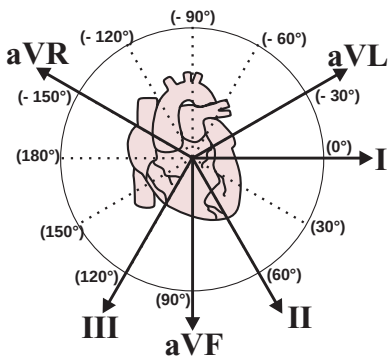
Because it can help locate the 4 important sites of stimulation which are the RV apex, RV outflow tract, LV and biventricular (i.e. simultaneous RV and LV) pacing.

To determine the mean frontal plane axis, you have to understand the frontal plane diagram and arrangement of the frontal plane ECG leads. You also have to understand the hemisphere concept of the various frontal plane ECG leads. If the mean QRS vector or axis is situated in the positive (+) hemisphere of a particular lead, this ECG lead will show a positive (+) deflection

Lead aVF will be negative if the mean QRS vector is in this hemisphere



Lead aVF will be positive if the mean QRS vector is situated in this hemisphere



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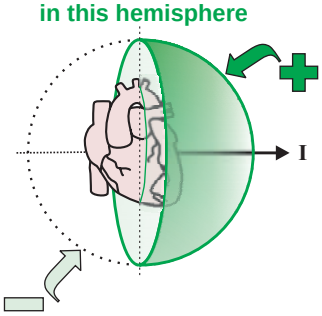
Lead I will be positive if the mean QRS vector is situated in this hemisphere

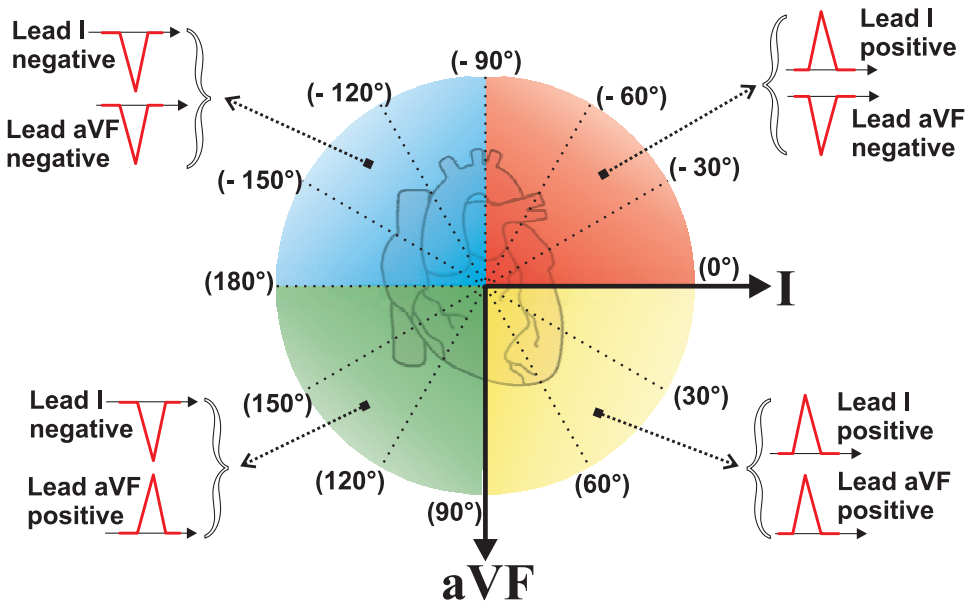


Lead I will be negative if the mean QRS vector is in this hemisphere

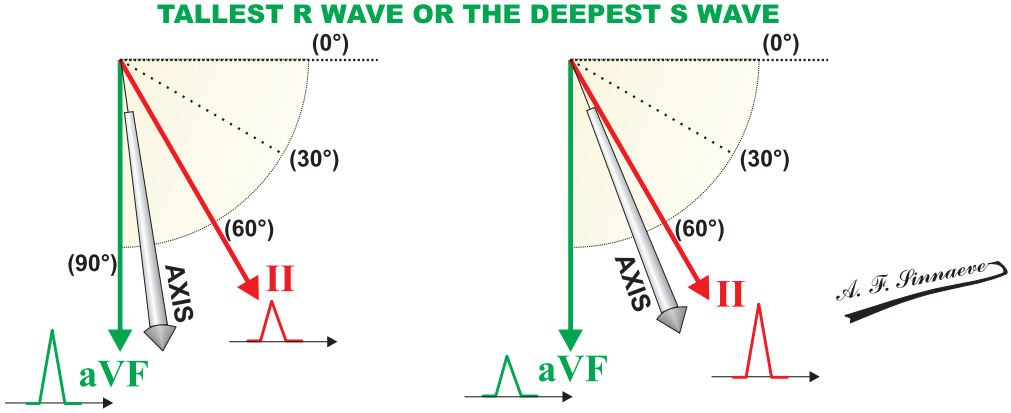
DETERMINATION OF THE MEAN FRONTAL PLANE AXIS

JUST REMEMBER 3 IMPORTANT QUESTIONS :
* In which quadrant is the QRS vector situated ?
* Which of the adjacent leads has the tallest R wave or the deepest S wave ?
* Which is the most equiphasic lead (or zero lead)?

STEP 1 : LOOK AT LEADS I & aVF TO DETERMINE IN WHICH QUADRANT THE FRONTAL PLANE AXIS IS SITUATED



STEP 2 : LOOK IN THE APPROPRIATE QUADRANT FOR THE TALLEST R WAVE OR THE DEEPEST S WAVE



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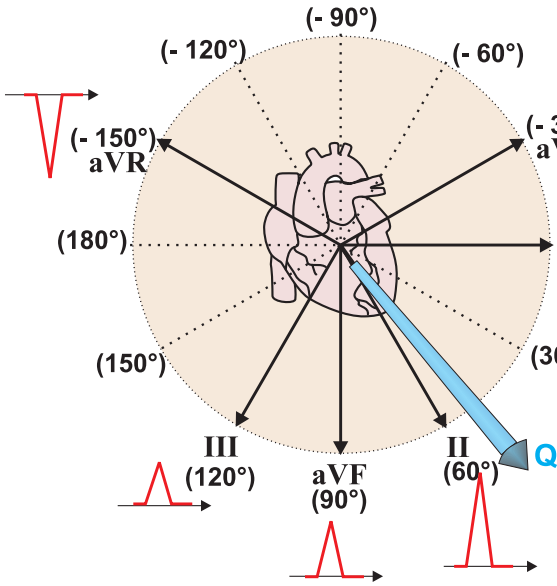
The lead nearest to (or parallel along) the QRS axis has the largest positive deflection. If two leads have equal positive deflections, the axis is exactly in the middle between these two leads.

DETERMINATION OF THE MEAN FRONTAL PLANE AXIS CONT'D

STEP 3 : LOOK FOR THE MOST EQUIPHASIC LEAD (where the positive minus the negative defection is closest to zero)
THIS LEAD IS PERPENDICULAR TO THE QRS AXIS



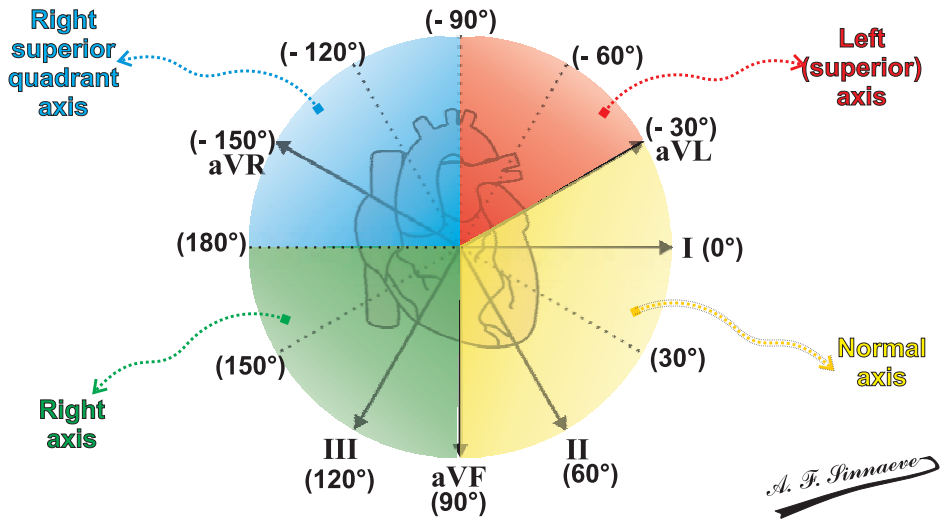
aVL is equiphasic
Lead aVL is perpendicular to the QRS axis

Lead I is positive, thus the QRS axis is on the left

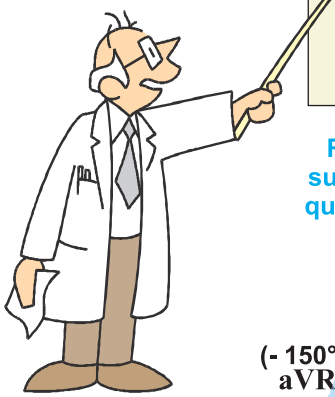
QRS axis in the frontal plane

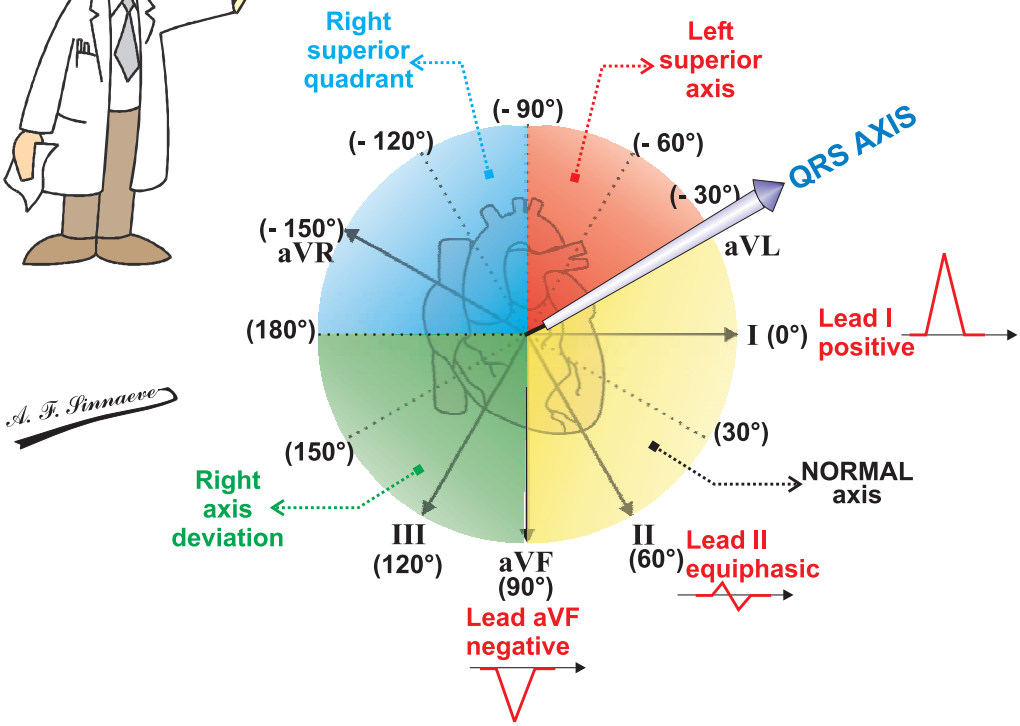
QRS axis is along lead II. Note that lead II has the largest positive deflection, confirming the direction of the axis.

SUMMARY : the QRS axes of the heart (not paced)



RULE OF THUMB FOR DETERMINING THE FRONTAL PLANE AXIS
LOOK AT LEADS I AND aVF





1/ If both leads I and aVF are positive (dominant R wave), the axis is normal (yellow area)

2/ If lead I is positive and lead aVF is negative, you must look at lead II

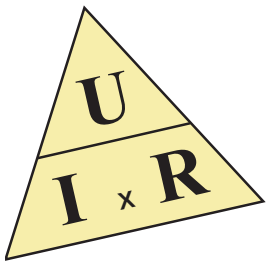
a. If lead II is equiphasic (positivity is equal to negativity so that the algebraic sum is zero), the axis is directed along lead aVL. This because an equiphasic lead (lead II in this case) is perpendicular to the axis (along lead aVL)

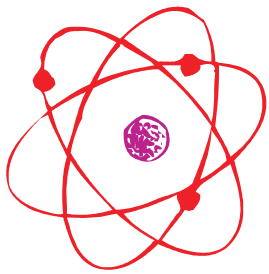
b. If lead II is more positive than negative, the axis is below -30° and normal (yellow area)

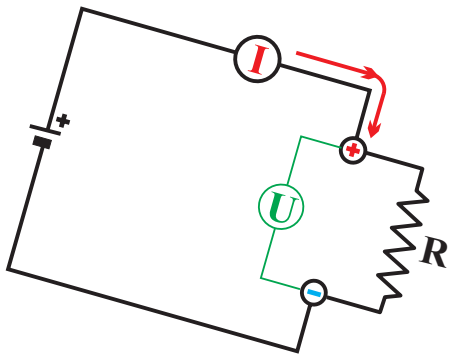
c. If lead II is more negative than positive, the axis is more negative than -30° and is in the left superior quadrant (red area)

3/ If lead I is negative (down) and aVF is positive (up) the axis is in the right inferior quadrant (green area - right axis deviation)

4/ If leads I and aVF are negative (down), the axis is in the right superior quadrant (blue area). The axis is simply described as being in the right superior quadrant. It is called neither extreme right nor extreme left axis deviation.

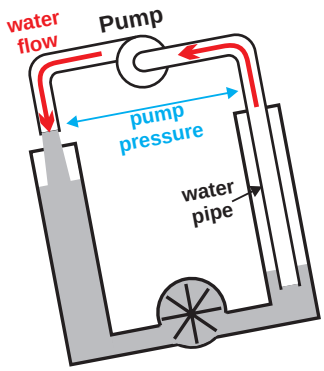


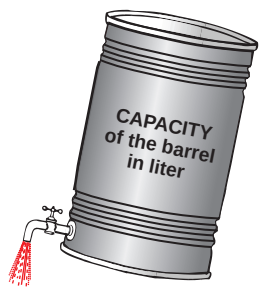




FUNDAMENTALS of ELECTRICITY

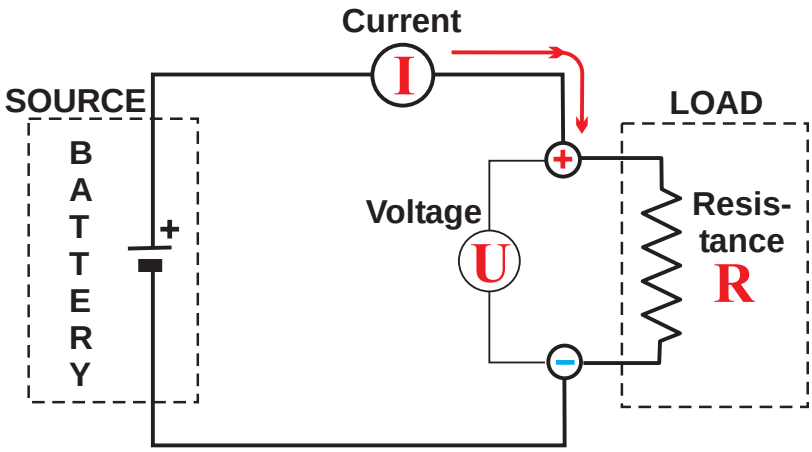
* Ohm's law
* Water equivalent
* Impedance
* Common units for pacemaker variables
* Battery 1
* Battery 2
* Battery impedance and battery voltage
* Battery capacity





OHM's LAW

This is the most important law of electricity !!!
Everybody should be familiar with these three variables, their relation and their units !



U = voltage (in volt V)

I = current (in ampere A)

R = resistance (in ohm Ω)

Voltage

Current

Resistance

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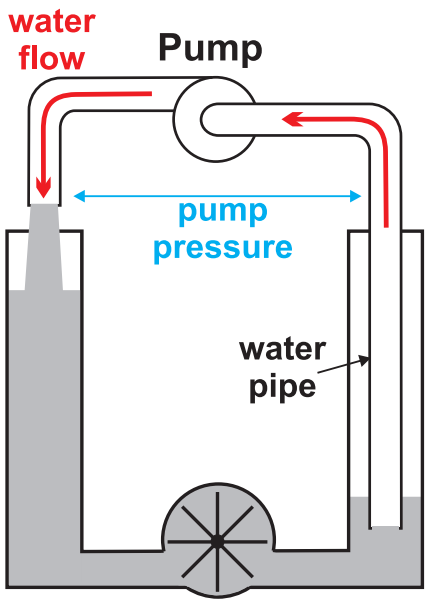
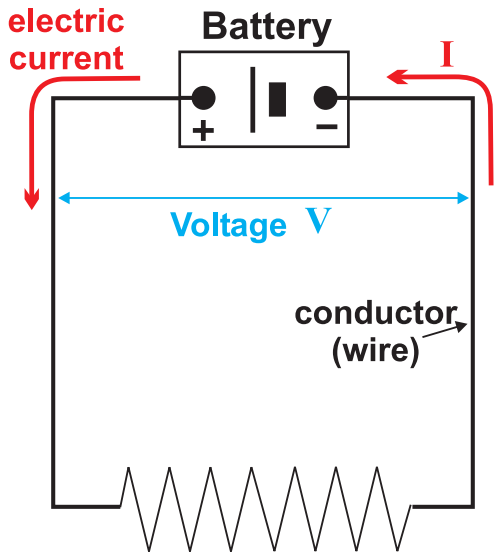
THE WATER EQUIVALENT

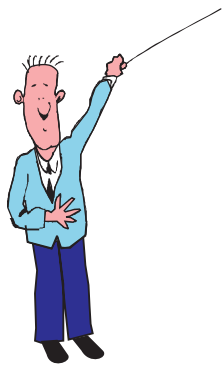


water mill
resisting the water flow



RESISTANCE to
the flow of electrons

WATER	ELECTRICITY
* waterpump	* battery
* pump pressure	* voltage
* quantity of water	* electric charge
* liter	* ampere.second
* **flow of water**	* **electric current**
* liter per sec	* ampere
* water pipe	* wire
* resistance	* resistance



Note for the electricians :
ampere.second (As) = coulomb (C)

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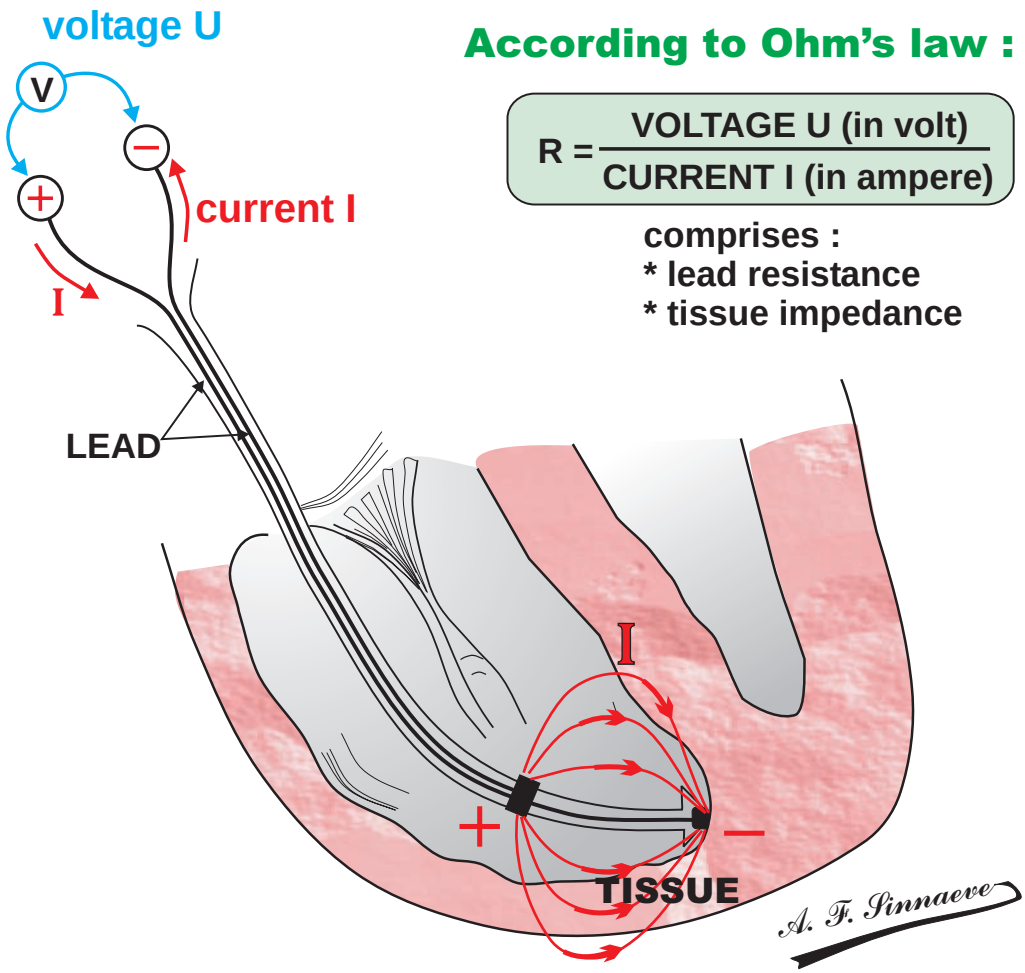
PACING IMPEDANCE



According to Ohm's law :

$$R = \frac{\text{VOLTAGE U (in volt)}}{\text{CURRENT I (in ampere)}}$$

comprises :
* **lead resistance**
* **tissue impedance**

INSULATION DEFECT < 250Ω	NORMAL PACING IMPEDANCE ca. 500Ω	LEAD FRACTURE > 1000Ω

Note for electricians :
The pacing impedance is not purely resistive (the tissue impedance is capacitive) and should be indicated by a Z. In the clinical practice only the absolute value or magnitude of the pacing impedance is considered and since it is expressed in "OHM" according to Ohm's law, most people simply call it "resistance"

COMMON UNITS FOR PACEMAKERS

VOLTAGE

Basic unit : volt - symbol V

Sometimes used : millivolt - symbol mV

1 V = 1,000 mV or 1 mV = $\frac{1}{1{,}000}$ V = 10^{-3} V

CURRENT

Basic unit : ampere - symbol A

Used stimulus amplitude : milliampere - symbol mA

1 A = 1,000 mA or 1 mA = $\frac{1}{1{,}000}$ A = 10^{-3} A

Used for battery current drain : microampere - symbol μA

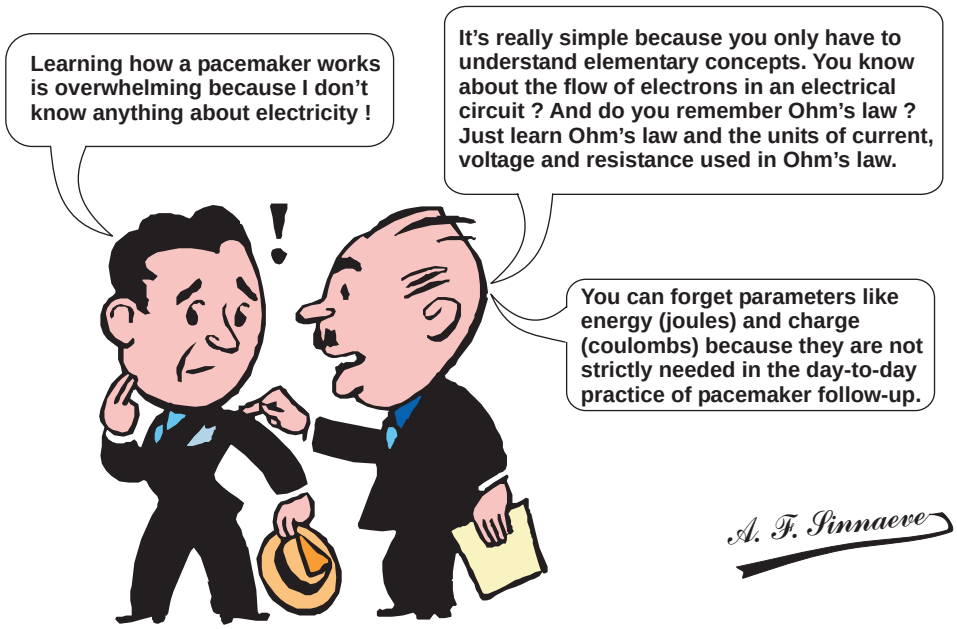
1 A = 1,000,000 μA or 1 μA = $\frac{1}{1{,}000{,}000}$ A = 10^{-6} A

RESISTANCE

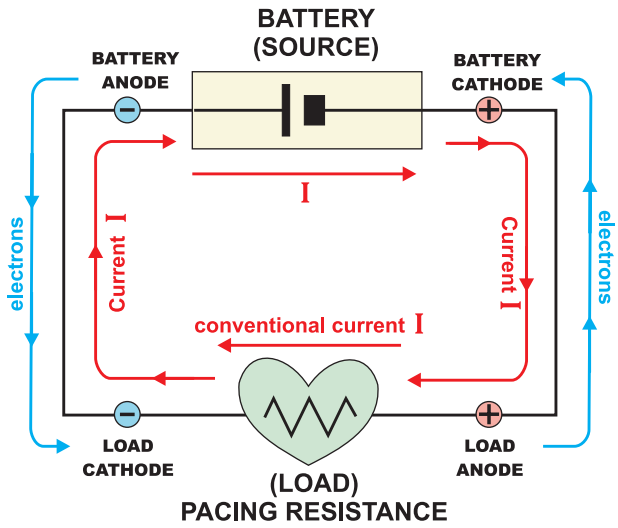
Basic unit : ohm - symbol Ω

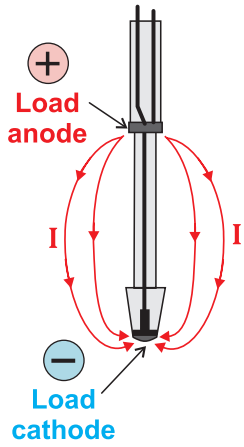
Sometimes used : kilo-ohm - symbol kΩ

1 Ω = $\frac{1}{1{,}000}$ kΩ or 1 kΩ = 1,000 Ω = 10^{3} Ω



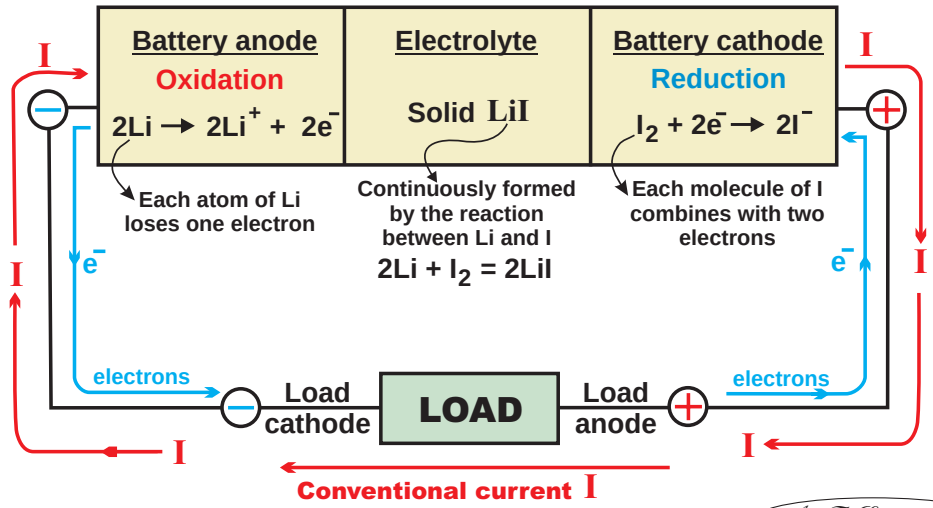
ANODE - CATHODE & ELECTRIC CURRENT





* First, you have to know that electric current only flows if the circuit is closed and that the external resistance or load limits the current.
* Second, you have to understand that in a closed circuit the **electrons** flow from the negative pole of the battery, through the load and back to the positive pole of the battery. However, **conventional electric current** flows in the opposite direction from the + pole of the battery via the load to its - pole. That's a historical convention dating from the time electrons weren't yet discovered.
* Third, just remember that the battery is the source delivering electricity while the load consumes electricity. If you follow the circuit, you will see that the anode is always the electrode by which the electrons leave (A for anode in "Away"). The cathode on the contrary, is always the electrode into which the electrons enter or come (C for cathode in "Come"). That's easy isn't it ? This terminology applies to both the battery and the load !

The Lithium - Iodine battery

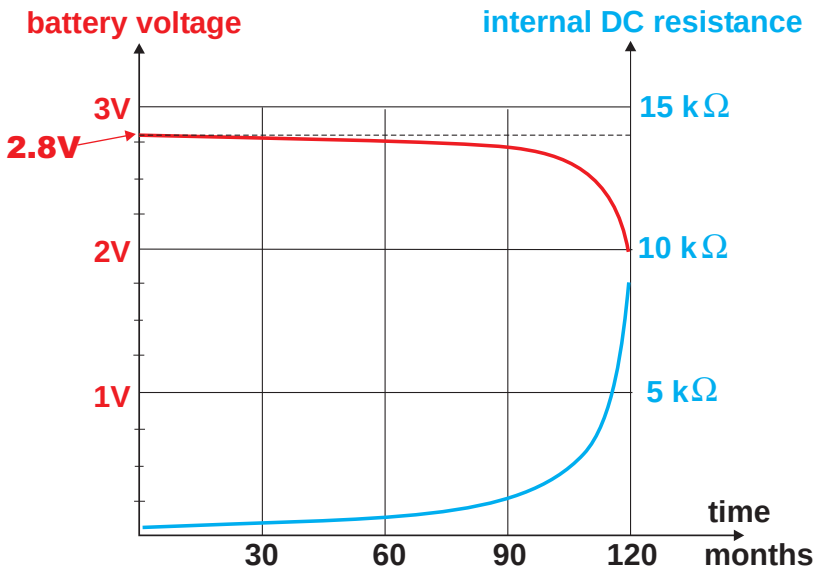


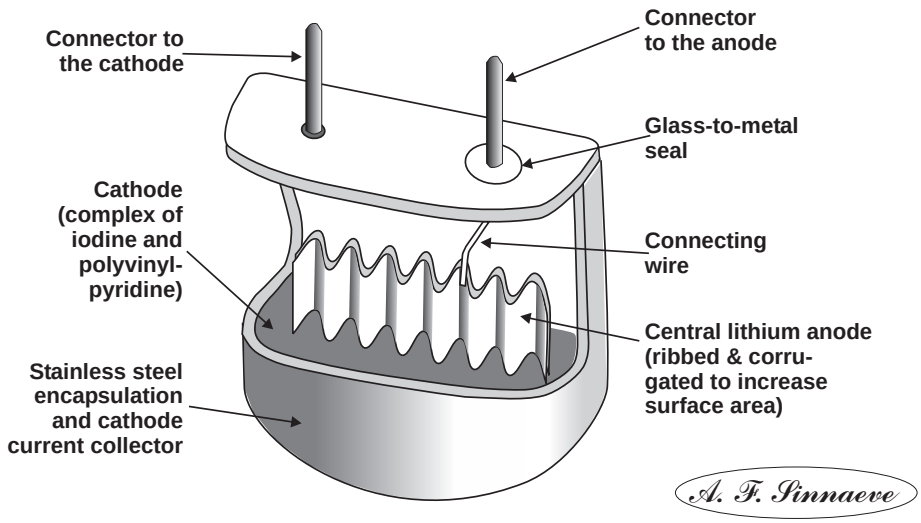
A. F Sinnaeve

How about the lithium-iodine battery ? Someone told me that no electrons can flow through that battery ?

Yes, that's true, but it isn't difficult to understand. The anode of a lithium-iodine battery is the place where electrons free themselves from lithium atoms to form Li^+ ions. With the electrolyte of the battery serving as an electron barrier and all electrons being negative and repelling each other, the electrons are pushed outside the battery to start their journey through the electrical circuit.
Following the electrical conductors, the electrons enter the load via its cathode. Just as a liquid, electricity cannot be compressed. So, an equal amount of electrons is leaving the load via its anode, being attracted by the positive pole of the battery. The electrons enter the battery cathode where they combine with iodine I_2 to form $2I^-$ ions.
Inside the battery, the electrical circuit is closed by the flow of the Li^+ and I^- ions. These ions attract each other and diffuse through the electrolyte. When the two kinds of ions meet each other, they combine to form lithium-iodide LiI.
However, the lithium-iodide is not a good electrical conductor and so the buildup of this LiI increases the internal resistance of the battery.

The Lithium - Iodine battery





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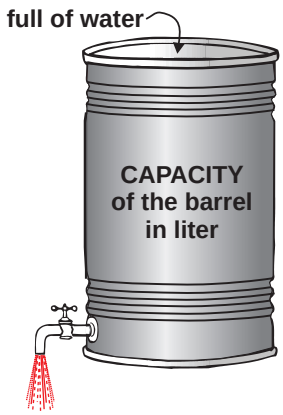
The anode of the battery produces lithium ions, while the cathode is producing iodine ions. These ions are moving to the other pole of the battery and are recombining to lithium iodide (LiI). This discharge product forms a barrier for the further movement of ions and thus an internal battery resistance is built up.
At the BOL the electrolyte barrier is thin with a low normal impedance. However, at the EOL the layer becomes thick and when the cathode material is almost depleted, the internal resistance is very high.

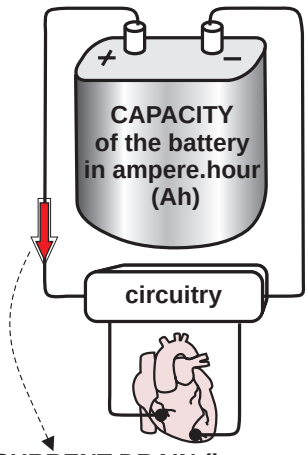
BOL = beginning-of-life ; **EOL =** end-of-life

BATTERY CAPACITY & LONGEVITY

LIFE EXPECTANCY = $\frac{\text{capacity}}{\text{drain}}$



OUTFLOW = DRAIN $\left(\frac{\text{liter}}{\text{minute}}\right)$



CURRENT DRAIN (in ampere A)
(1 ampere = 1,000,000 μA)
(1A = 10^6 μA)

e.g. **CAPACITY : 60 liters**
DRAIN : 0.5 liters/minute
EXPECTED TIME to empty the barrel:

$\frac{60}{0.5}$ **= 120 minutes**

= 2 hours

e.g. **CAPACITY : 2 ampere.hours = 2 Ah**
DRAIN : 25 μA = 25 *MICROAMPERE*
= 0.000025 A
EXPECTED LIFE TIME of the battery :

$\frac{2\ \text{Ah}}{0.000025\ \text{A}}$ **= 80,000 hours**

= about 9 years

Battery life expectancy increases if the current drain decreases by using :
*** pulses with a smaller voltage amplitude**
*** pulses with a shorter duration**
Hence the importance of determining the chronic pacing threshold so as to program the output voltage and pulse duration to provide an adequate safety margin and also conserve battery capacity to extend battery life

The output current of the pulses to the heart is expressed in mA (1 mA = 1/1,000 A)
The current drain of the battery is expressed in μA (1 μA = 1/1,000.000 A)
1 milliampere (mA) = 1,000 microampere (μA)

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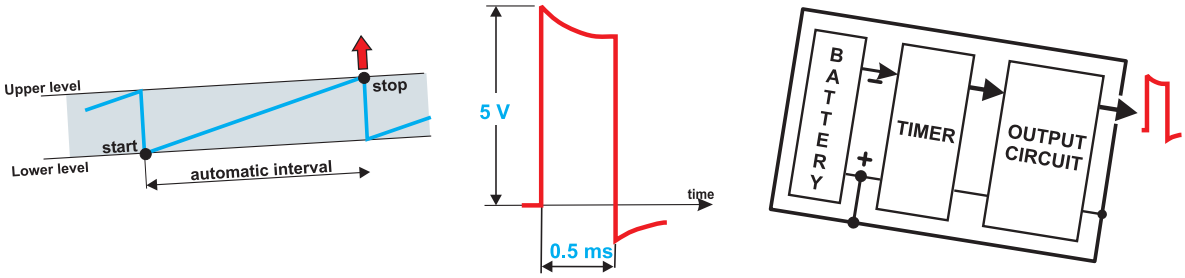
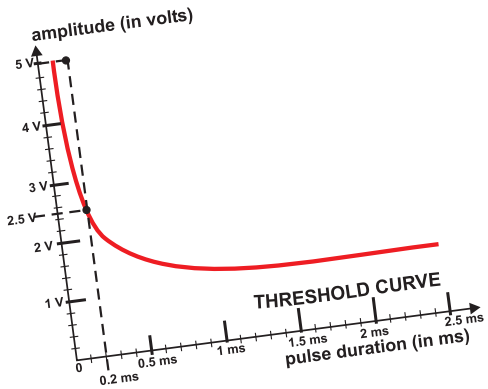
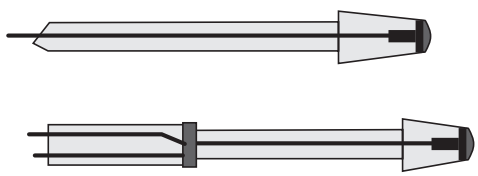


VENTRICULAR STIMULATION

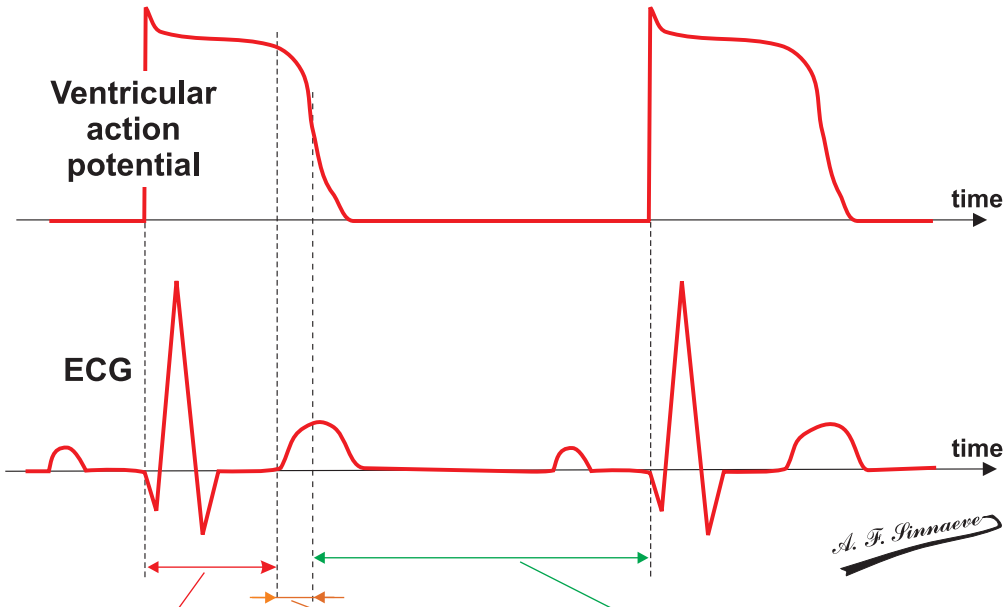
* Myocardial refractory period
* Asynchronous ventricular pacing (VOO)
* Ventricular depolarization by pacing
* The output pulse of the pacemaker
* The programmer and telemetry
* Panic button
* Programming amplitude and pulse width
* Determination of pacing threshold with constant pulse width
* Determination of pacing threshold with constant voltage
* Strength-duration curve
* Safety margin for capture
* Autocapture
* Bipolar vs unipolar pacing -
  - stimulus on analog recorder
* Variable stimulus appearance on digital recorder





Always keep in mind ! The myocardial refractory period refers to stimulation. In contrast the pace-maker refractory period refers to the sensing function of the device.

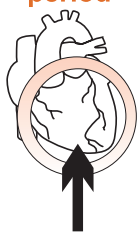
VENTRICULAR MYOCARDIAL REFRACTORY PERIOD



Absolute refractory period

No stimulus can activate the ventricle

Relative refractory period



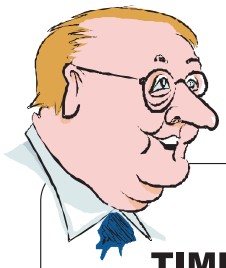
Only a stronger than normal stimulus can activate the ventricle

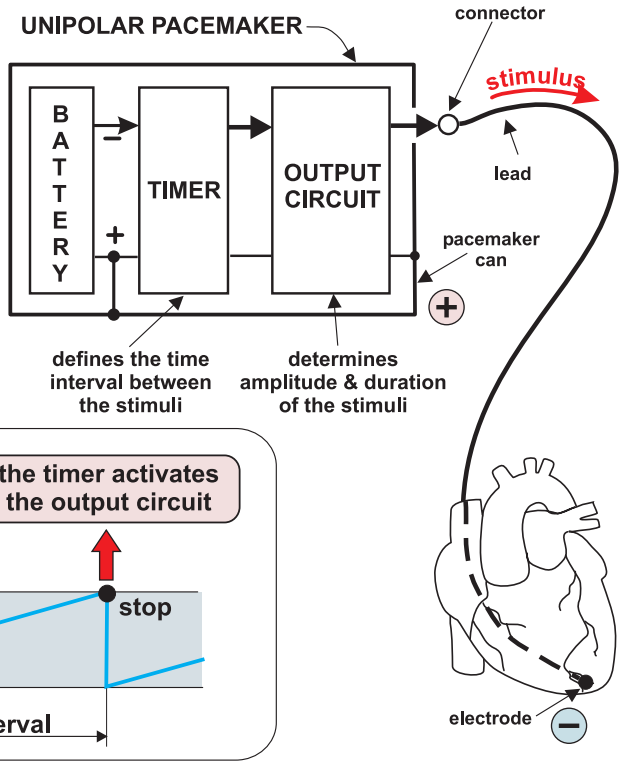
NORMAL

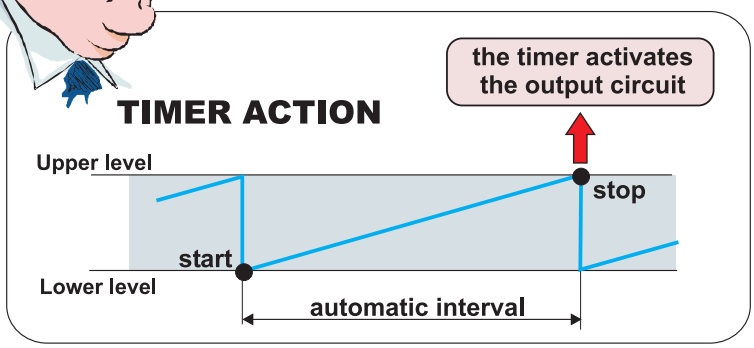
A normal stimulus activates the ventricular myocardium

ASYNCHRONOUS VENTRICULAR PACING (VOO)

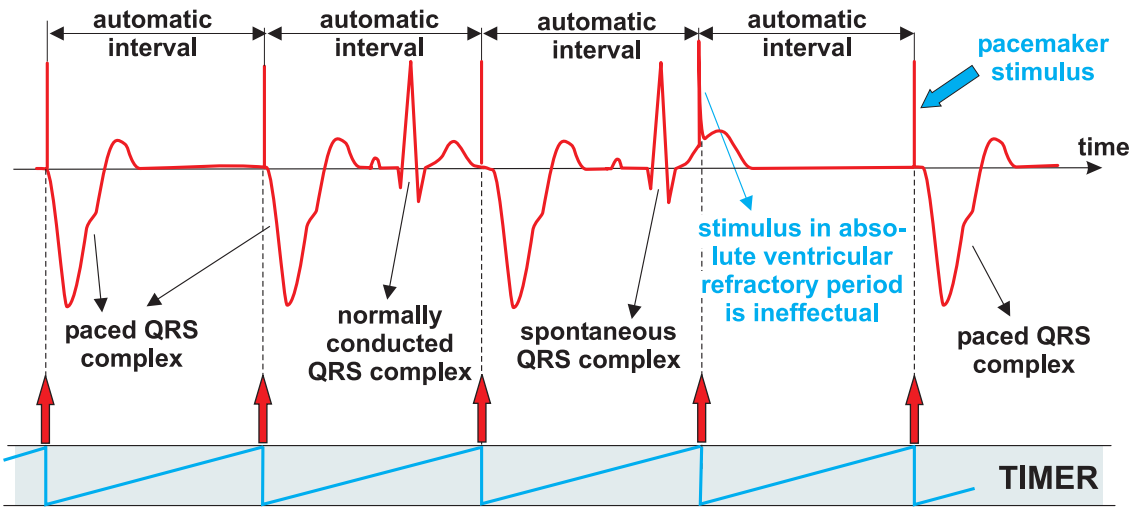
Note that the VOO mode causes a competitive rhythm because there is no sensing of spontaneous ventricular activity. Only stimuli beyond the ventricular myocardial refractory period cause successful capture !







ASYNCHRONOUS PACING with COMPETITIVE RHYTHM !!!



CAUTION

Modern pacemakers are non-competitive but assume asynchronous function only as long as a special magnet is placed over the pacemaker

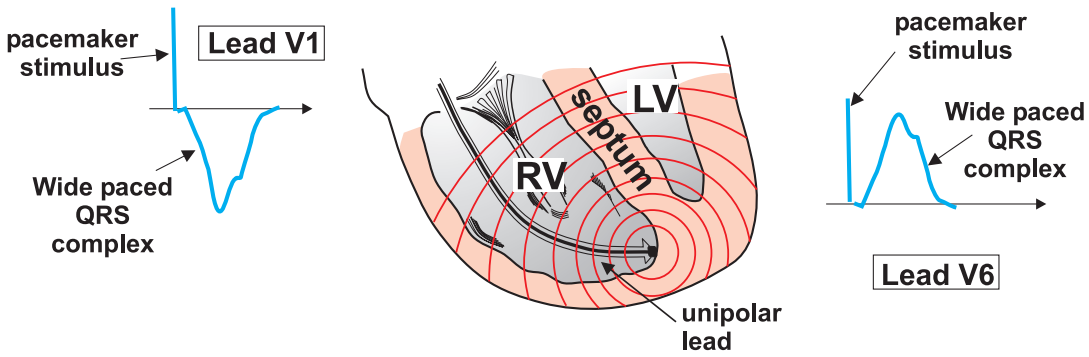
A. F. Sinnaeve

VENTRICULAR DEPOLARIZATION BY PACING

* The depolarization caused by the pacemaker does not occur via the specialized His-Purkinje network and propagates slower through ordinary myocardium
* The QRS complex is therefore wide like a ventricular extrasystole (premature ventricular contraction)

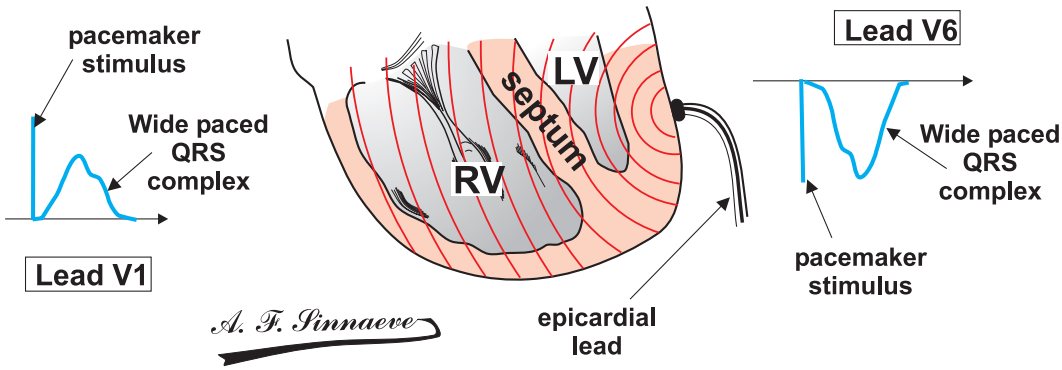
ENDOCARDIAL STIMULATION FROM RIGHT VENTRICLE

ECG resembles LBBB (LBBB = left bundle branch block)



EPICARDIAL STIMULATION FROM LEFT VENTRICLE

ECG resembles RBBB (RBBB = right bundle branch block)



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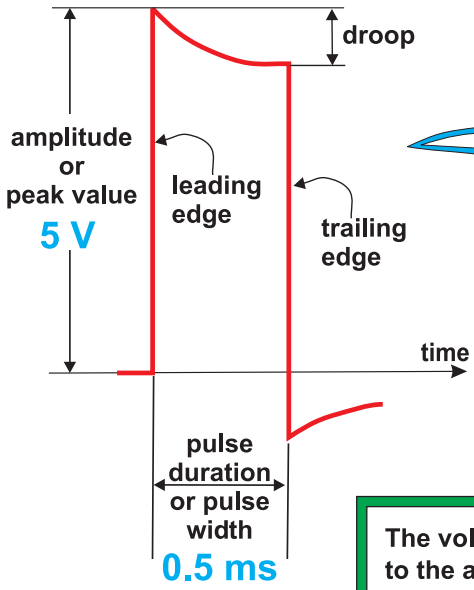
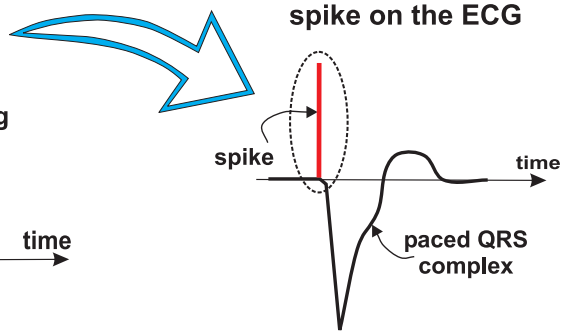
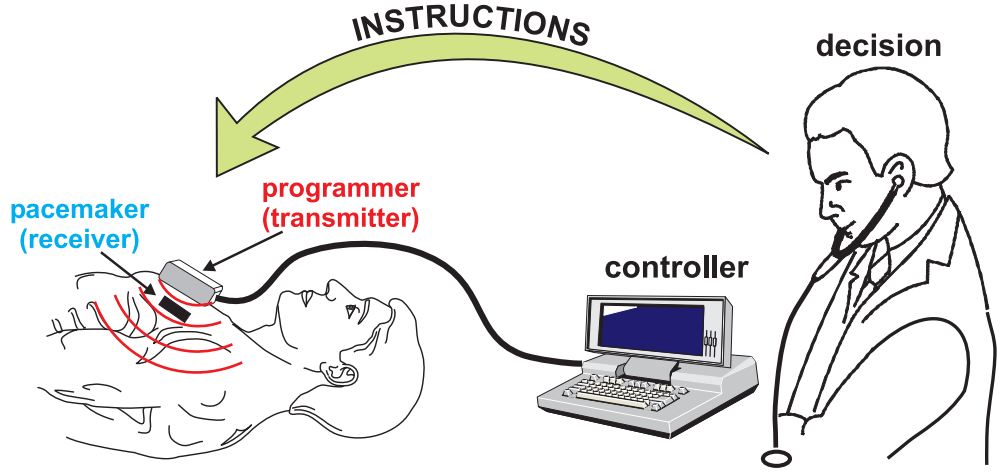
THE OUTPUT PULSE OF THE PACEMAKER





The voltage of a permanent pacemaker refers to the amplitude of the leading edge, which is always constant. It is actually closer to 5.4 V because the lithium iodine cell generates a voltage of 2.8 V which is then doubled electronically.
The droop is influenced by a variety of factors but visualization of the droop and trailing edge are not required for the management of patients.
The process does not terminate with the trailing edge. The pacemaker stimulus charges the electrode-tissue interface to a large voltage (polarization voltage) which is subsequently dissipated over a much longer period than the brief pacemaker stimulus. One must understand the existence of this “afterpotential” because it can play a role in problems associated with oversensing, i.e. unintended sensing of certain events.

PROGRAMMING : from controller to pacemaker

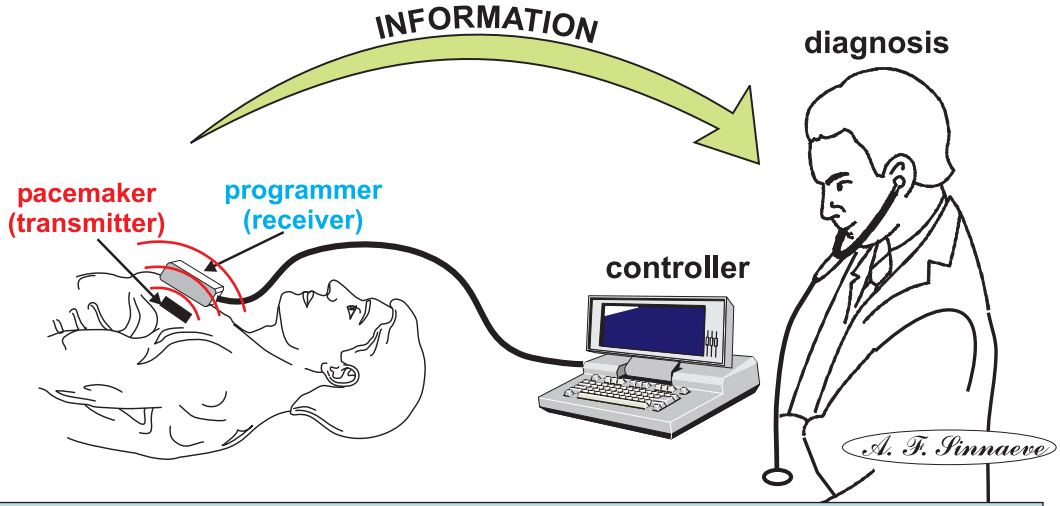


Pacemakers have many programmable functions that can be altered noninvasively with a special programmer. Unfortunately there is no universal programmer and each manufacturer provides programmers that will work only with their pacemakers

WARNING

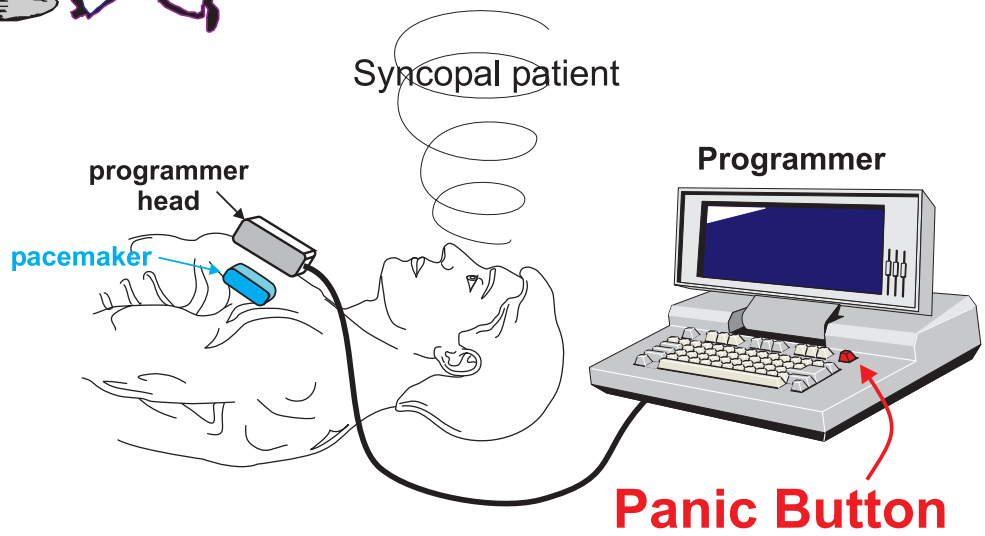
* Asystole can occur when programming the output. In an emergency use the panic button to restore pacing with a preset combination of parameters.
* Always have 2 programmers in case one malfunctions or breaks down

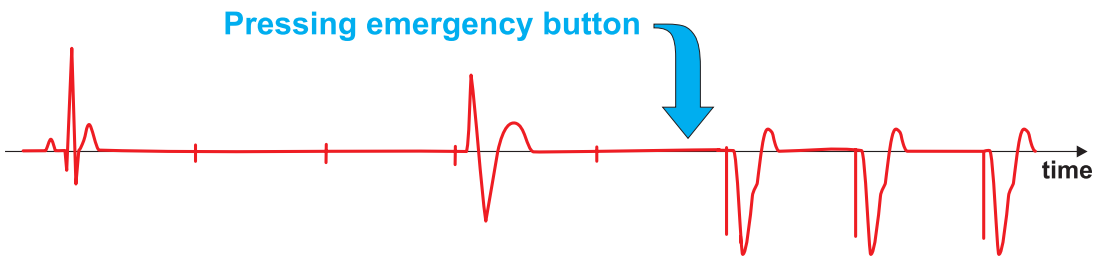
TELEMETRY : from pacemaker to controller



The stored parameters or instructions to the pacemaker can be retrieved by interrogation with a special programming head placed over the pacemaker. The data is then sent to the programmer which automatically delivers a printout. Parameters include rate, output (amplitude in volts and pulse duration in ms) and sensitivity.

THE EMERGENCY BUTTON





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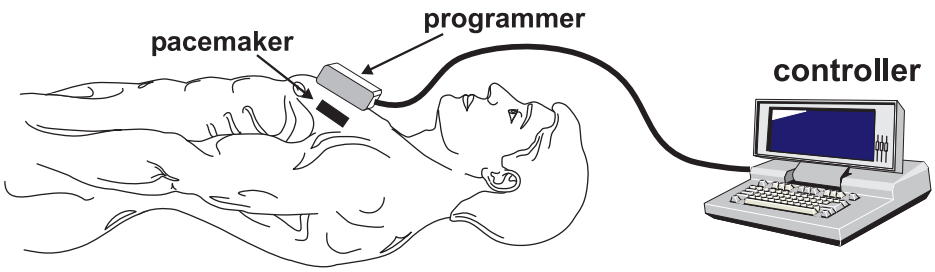
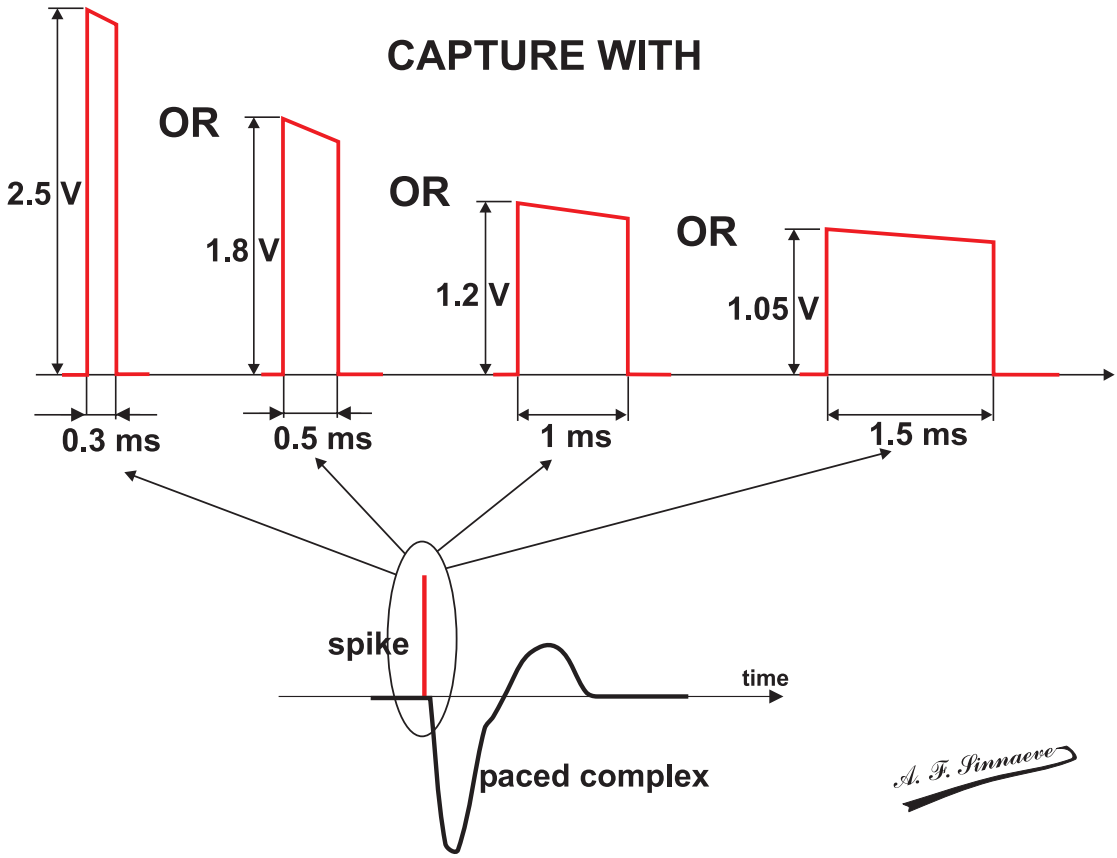
VOLTAGE AND PULSE DURATION MAY BE CHANGED BY AN EXTERNAL PROGRAMMER





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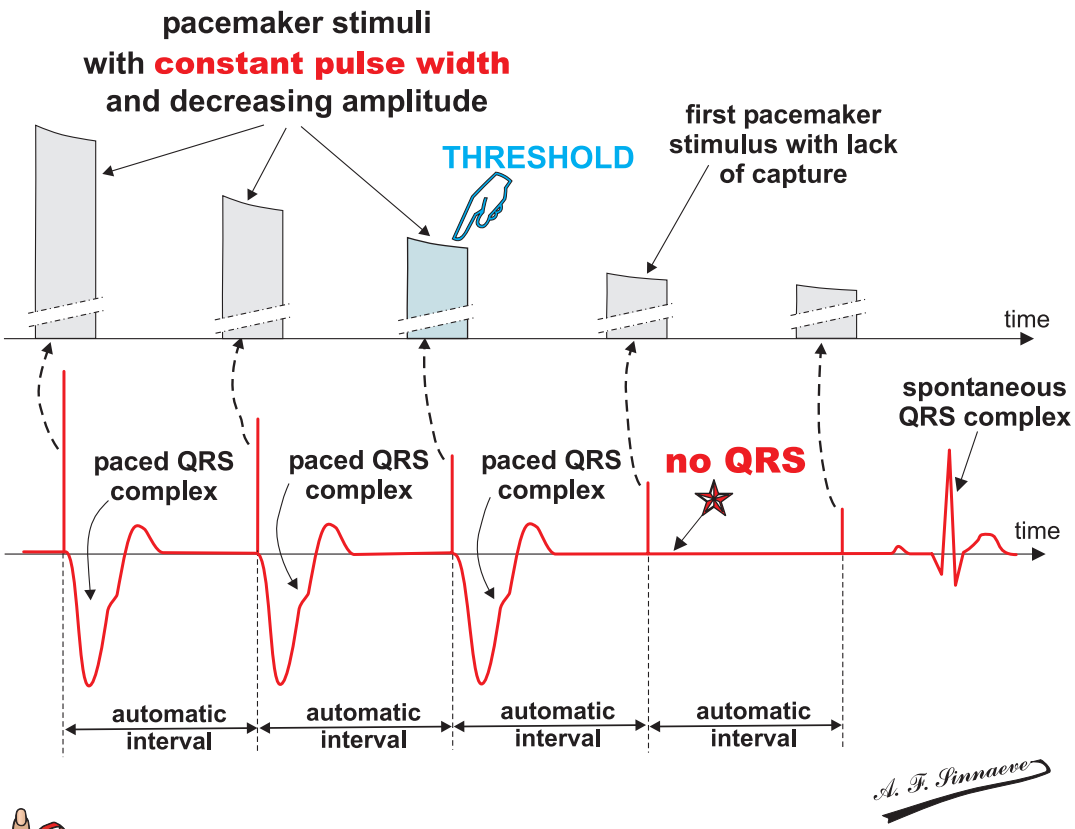
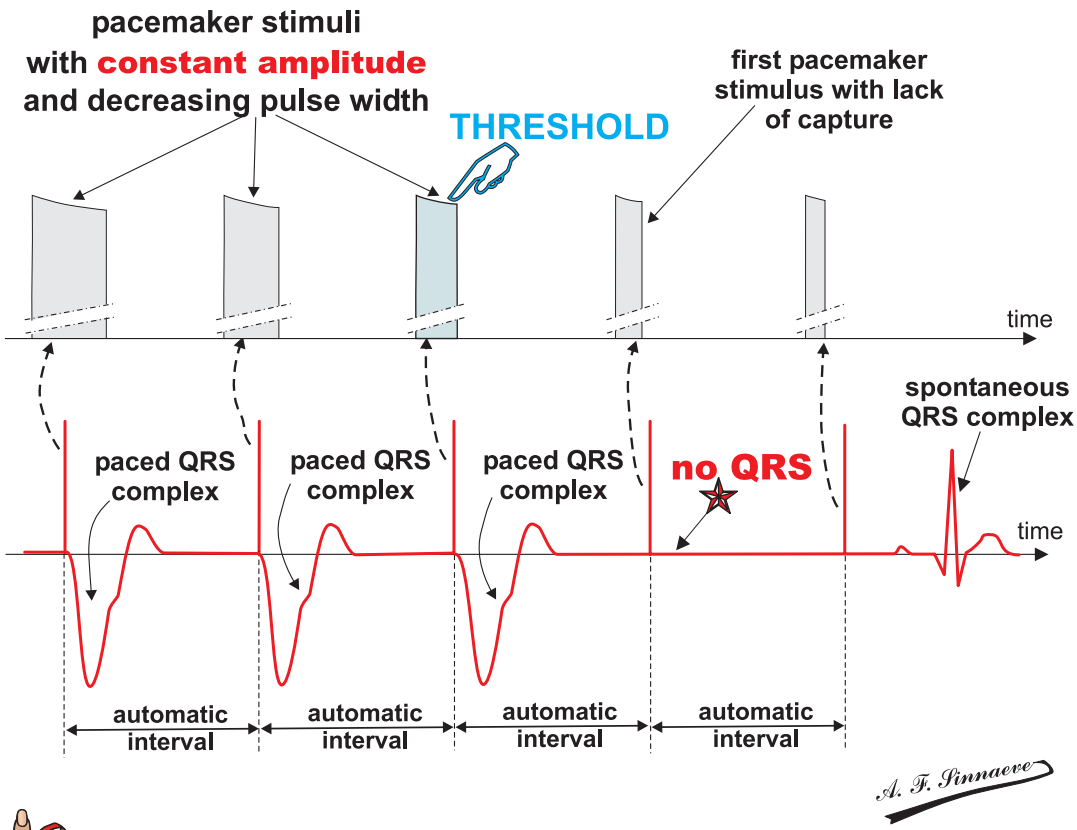
DETERMINATION OF PACING THRESHOLD



REMINDER

The pacing threshold is always expressed in terms of both voltage and pulse duration. The pacing threshold can be determined in terms of the smallest output voltage that captures the heart while keeping the pulse duration constant.

DETERMINATION OF PACING THRESHOLD



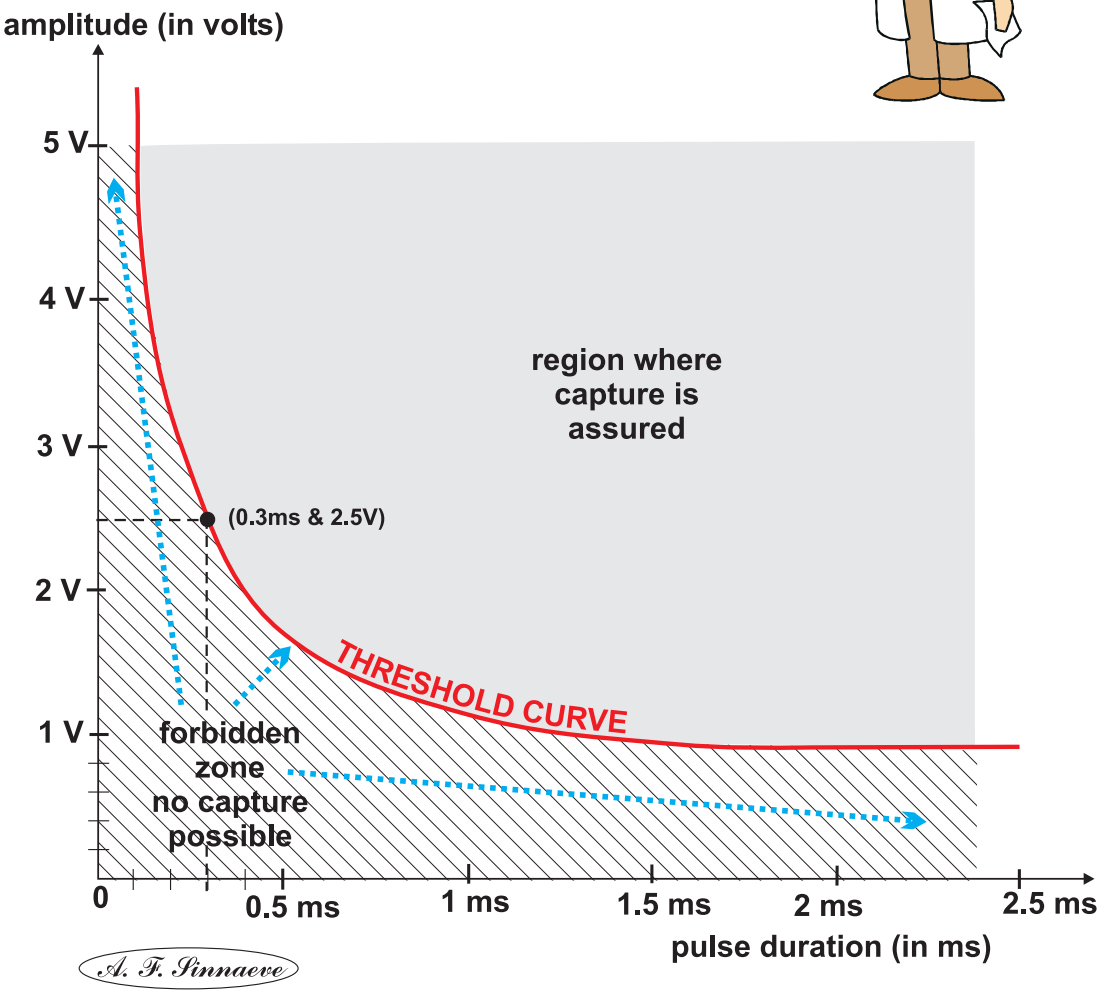
A. F. Sinnaeve

REMINDER

The pacing threshold is always expressed in terms of both voltage and pulse duration. The pacing threshold can be determined in terms of the shortest pulse duration that captures the heart while keeping the output voltage constant.

STRENGTH - DURATION CURVE

This is the most important law governing the whole field of electrostimulation !!!



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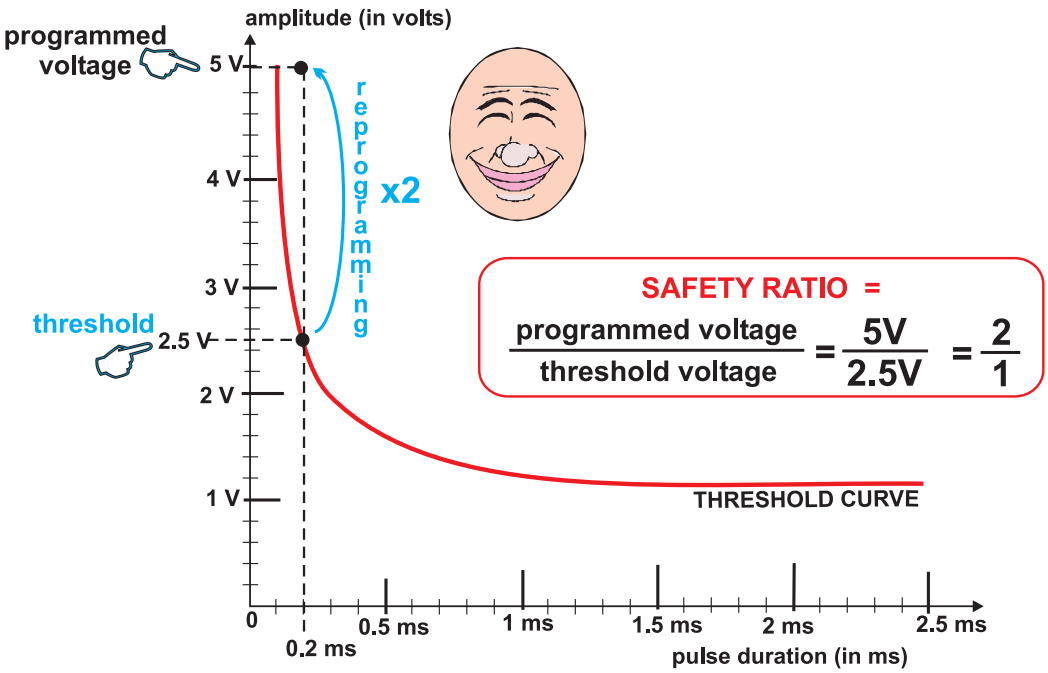
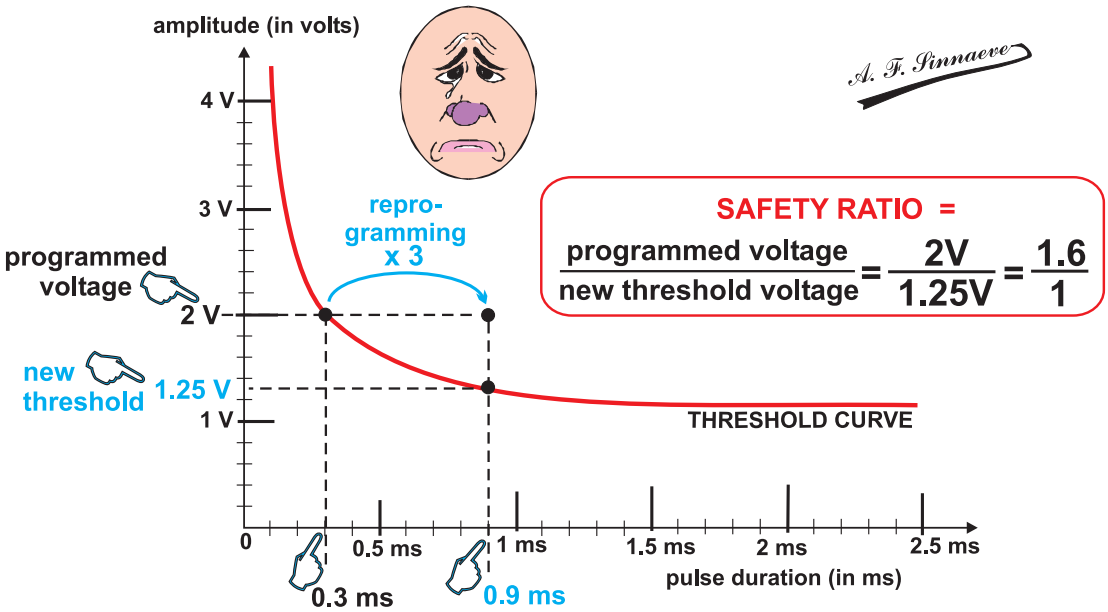
SAFETY RATIO CONCEPT FOR CAPTURE

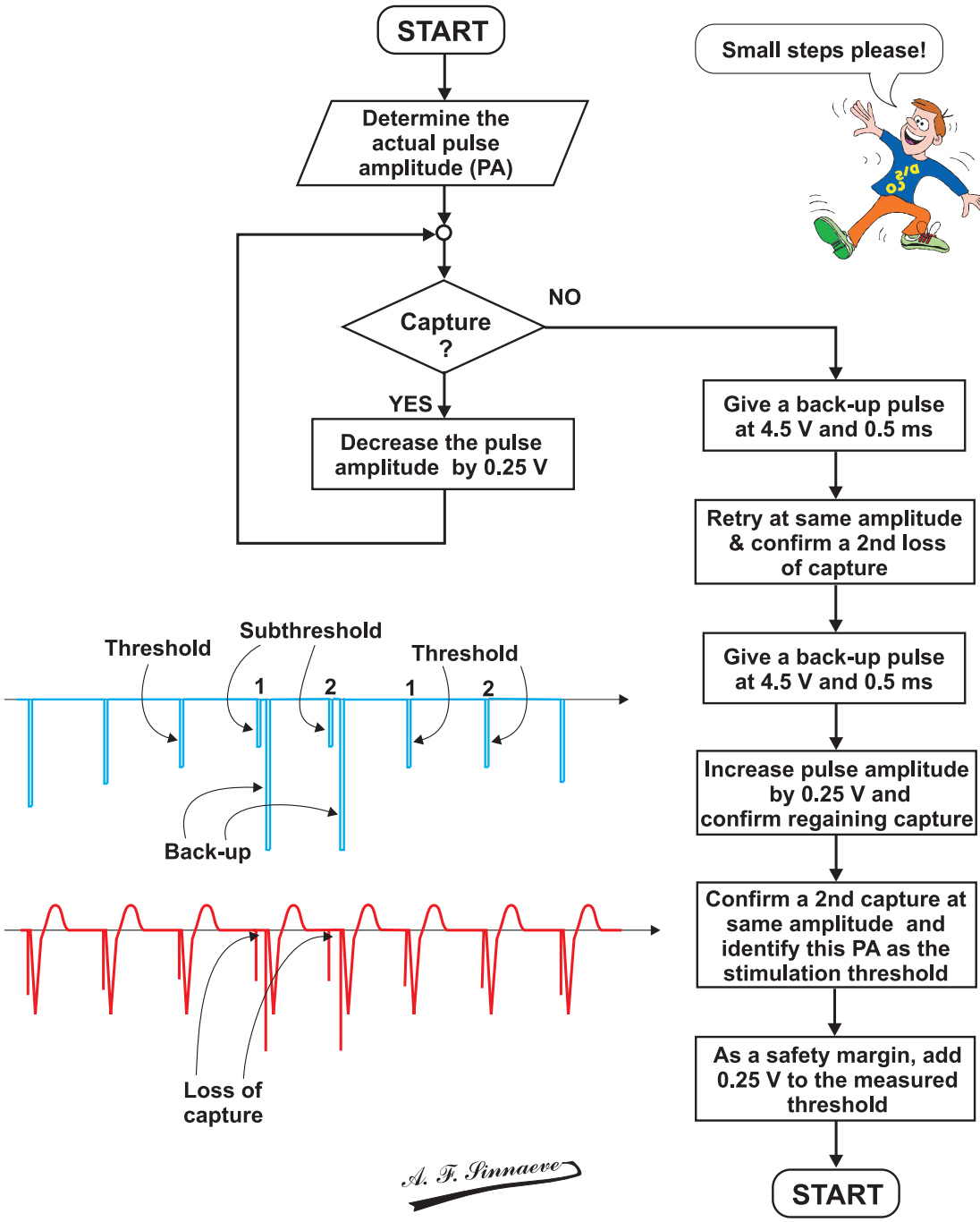


$$\text{SAFETY RATIO} = \frac{\text{programmed voltage}}{\text{threshold voltage}} = \frac{5V}{2.5V} = \frac{2}{1}$$

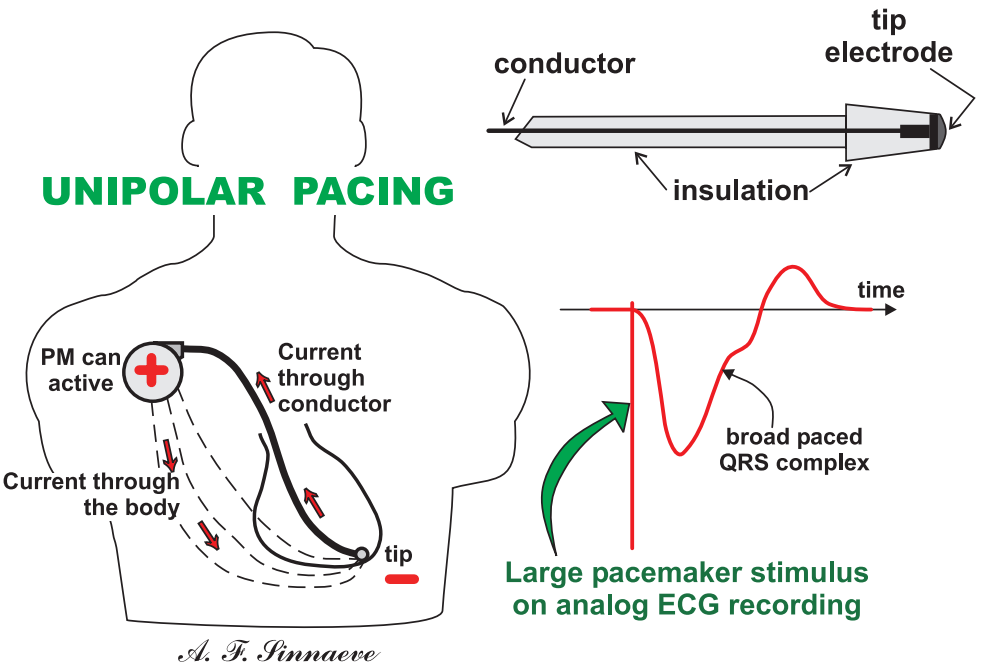


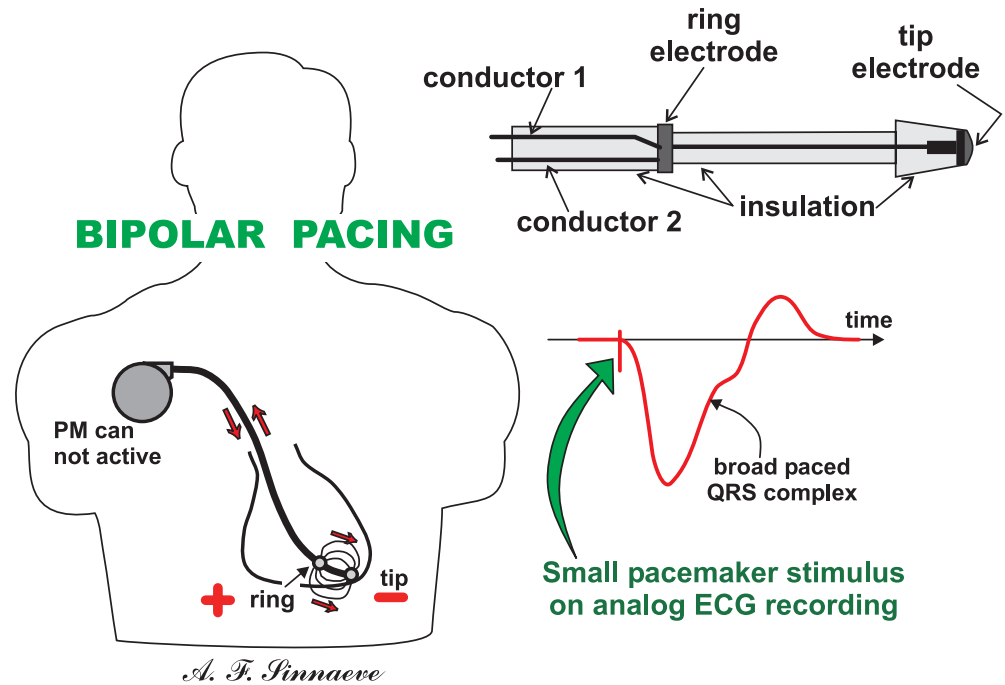
$$\text{SAFETY RATIO} = \frac{\text{programmed voltage}}{\text{new threshold voltage}} = \frac{2V}{1.25V} = \frac{1.6}{1}$$

AUTOMATIC STIMULATION THRESHOLD SEARCH



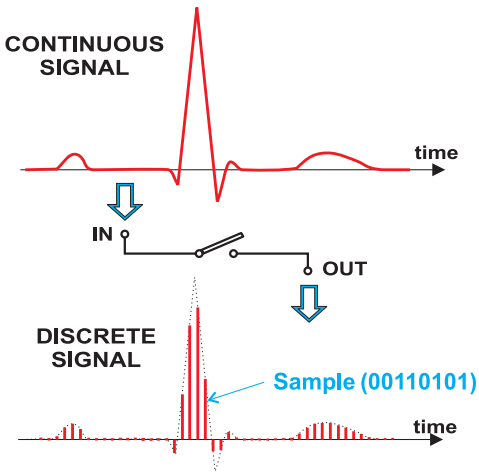
BIPOLAR vs UNIPOLAR PACING
SIZE OF THE STIMULUS ON ECG





VARIABILITY OF THE STIMULUS ARTIFACT ON A DIGITAL ELECTROCARDIOGRAPH

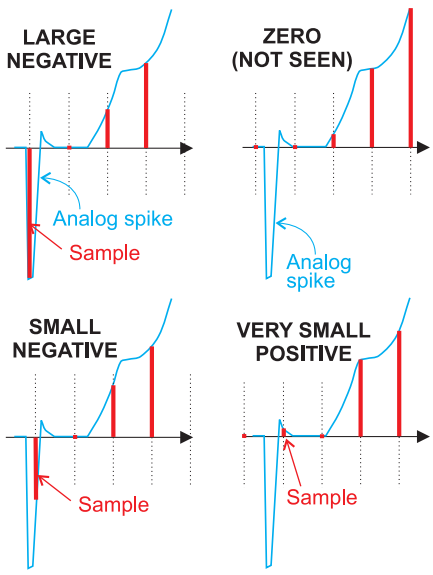
An analog recording system attempts to recreate the information as it actually happens. A digital ECG machine is not able to deal directly with continuously changing voltages, so the signals have to be prepared. A digital system takes the information and transforms it into a series of "samples". Consequently each sample is translated or "coded" in a binary number i.e. a series of zeros and ones called "bits".



SAMPLING A SIGNAL

Digital sampling is like sending the signal through a system with a very fast switch. The signal is measured repeatedly during a very brief instant by closing the switch.

Since the signal is only sampled at discrete points in time, some information may be missed when the sampling frequency is too low. In particular, sharp peaks and transitions in the slope of a signal are likely to be lost. The stimulus artifact or part of it can be easily missed by the sampling system with resultant varying amplitudes and direction of the pacemaker spike as it is recorded on the ECG.



The marked variation of the stimulus in amplitude and direction provided by a digital recorder may be confusing to the beginner who might wrongly assume there is pacemaker malfunction. What do you think ?

The diagnostic value of the pacemaker stimulus recorded by a digital recorder is zero ! Older analog recorders were more useful for that purpose

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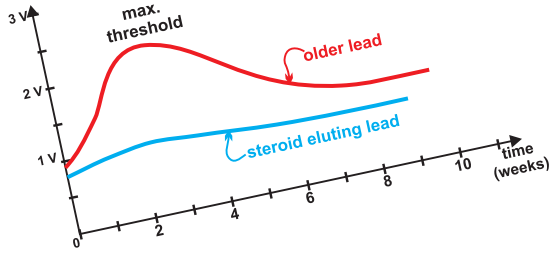
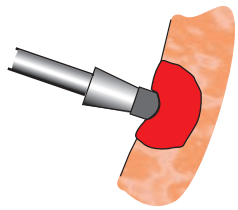
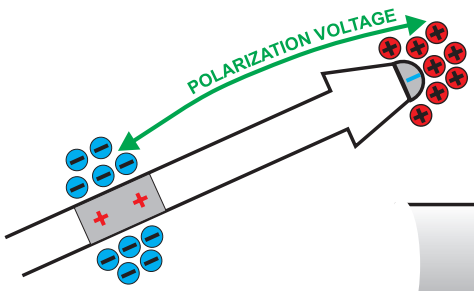
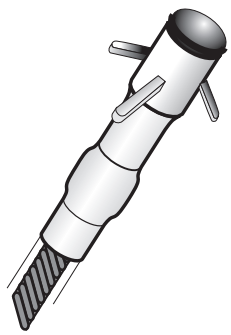




PACING LEADS

* The polarization phenomenon
* Fixation and conductors
* Evolution of the pacing threshold
* The porous electrode
* Low impedance vs high impedance electrode
* Lead displacement





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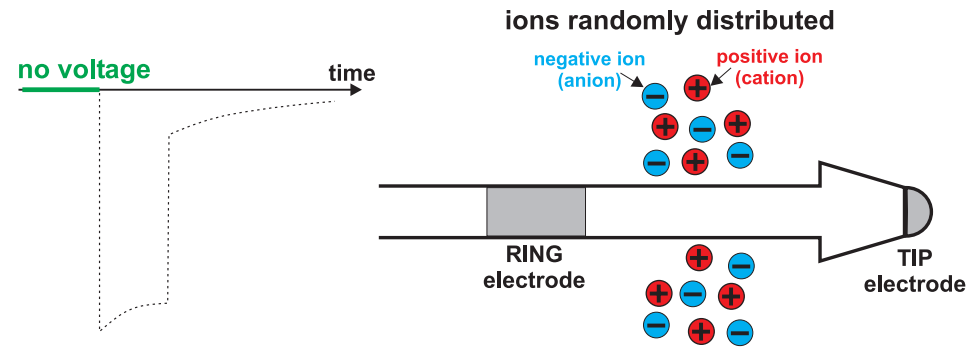
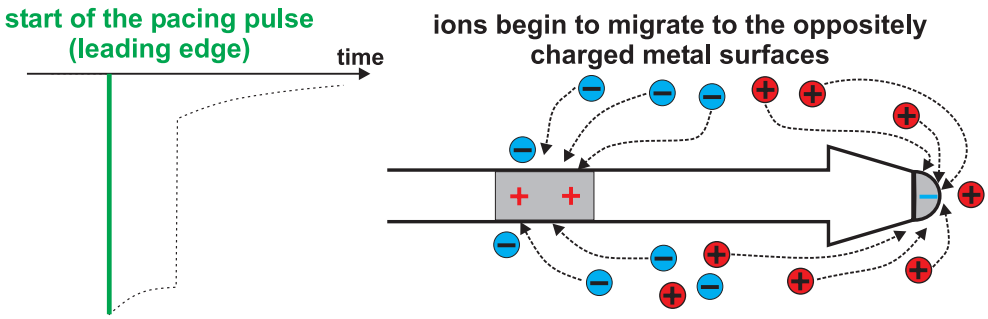
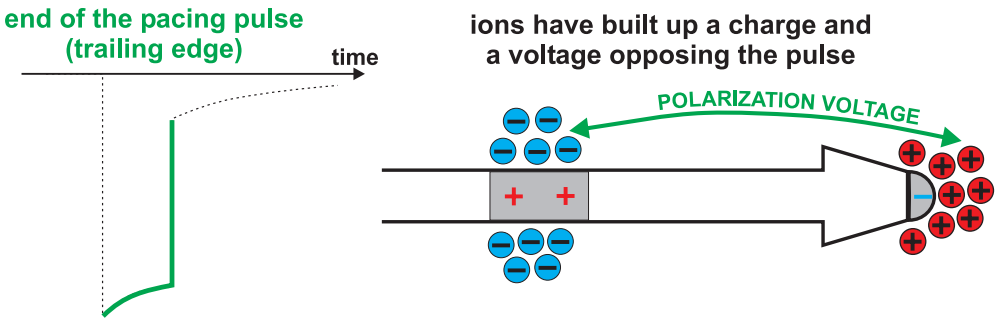
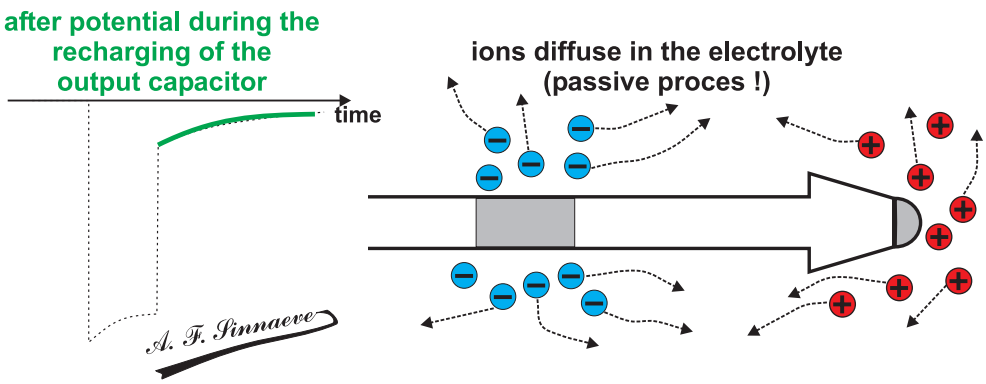
THE POLARIZATION PHENOMENON

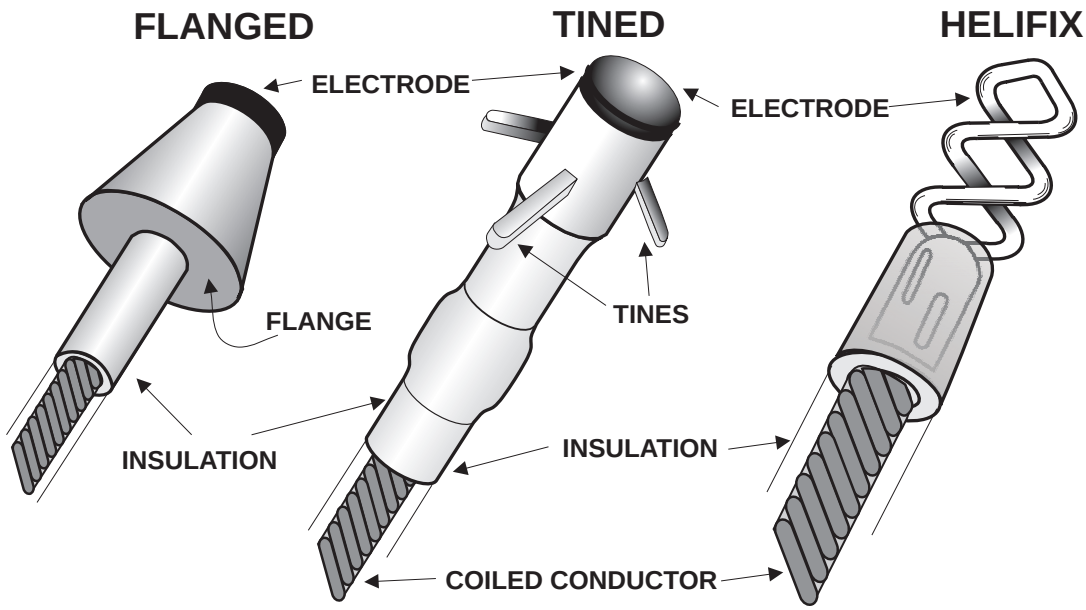




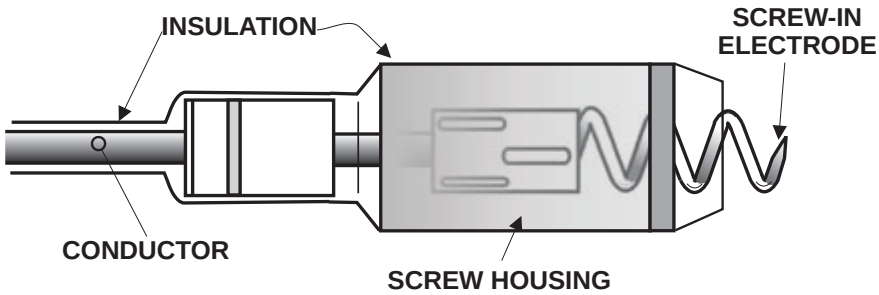




PASSIVE LEAD FIXATION



ACTIVE LEAD FIXATION



A TRI-FILAR CONDUCTOR COIL

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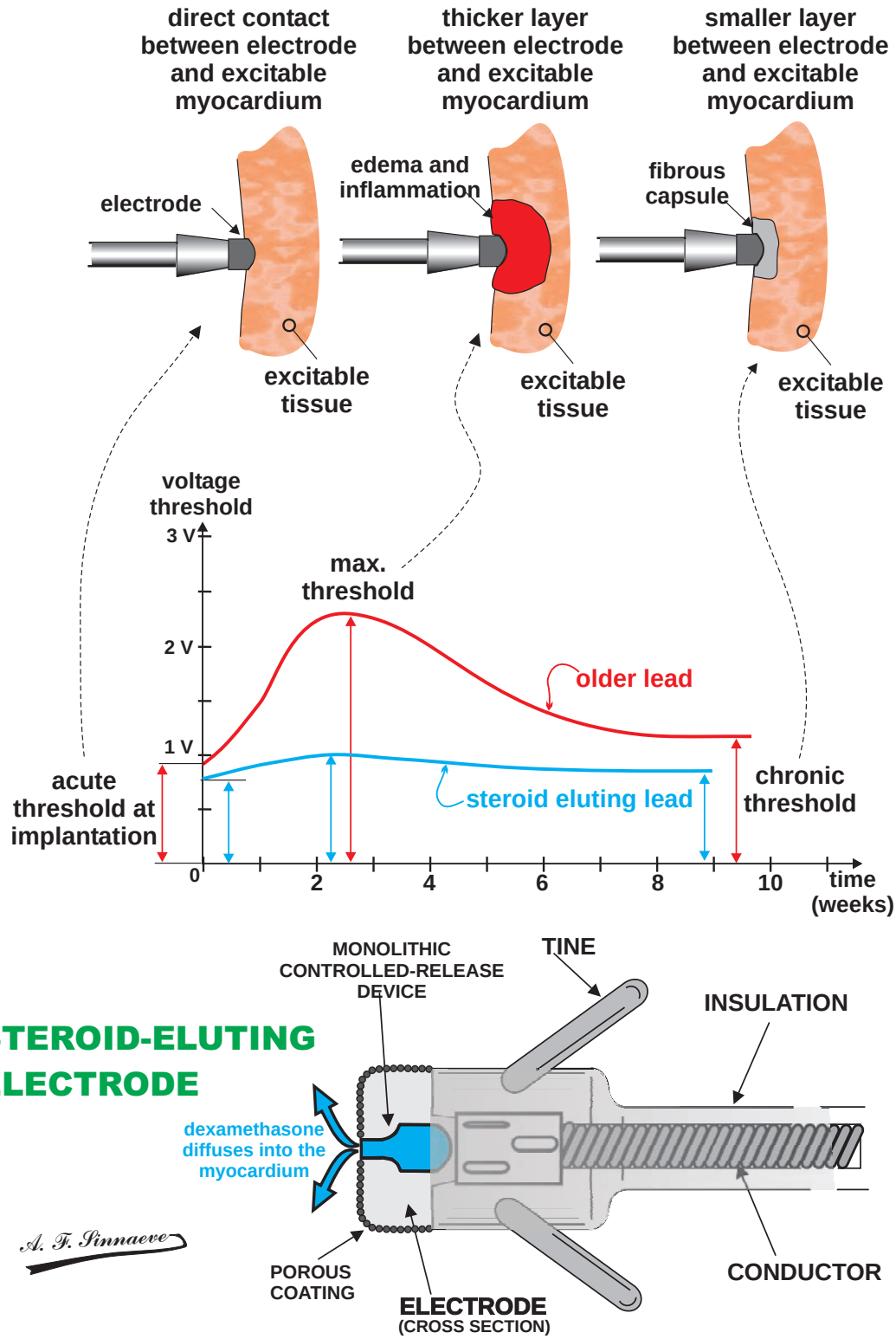
EVOLUTION OF PACING THRESHOLD



STEROID-ELUTING ELECTRODE

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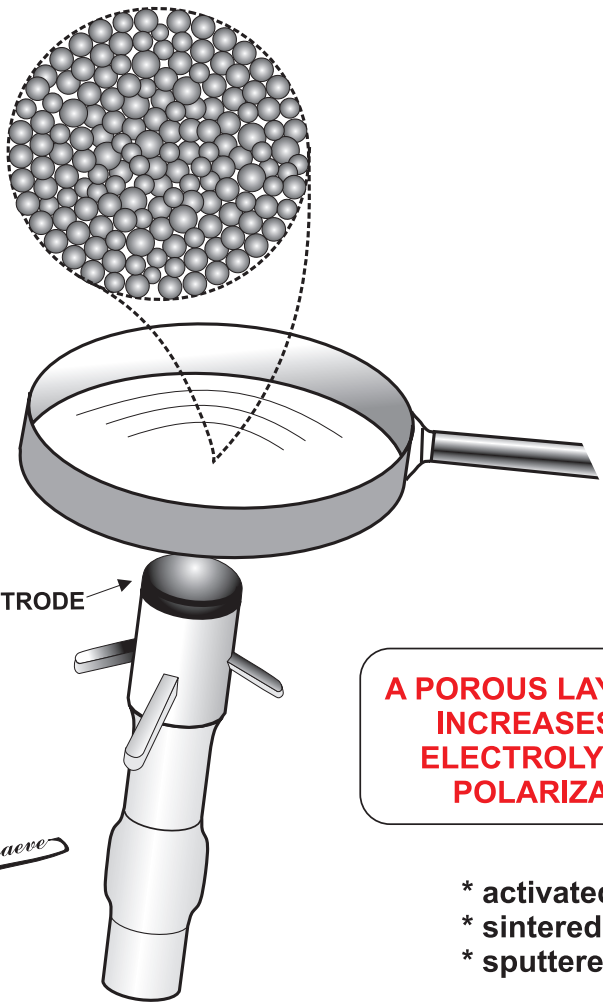
THE POROUS ELECTRODE

For good sensing,
the polarization voltage and the
afterpotential should be very low !
So, we use porous electrodes !



A POROUS LAYER ON THE ELECTRODE INCREASES CONTACT WITH THE ELECTROLYTE AND REDUCES THE POLARIZATION PHENOMENON

* activated carbon
* sintered platinum-iridium
* sputtered titanium-nitride

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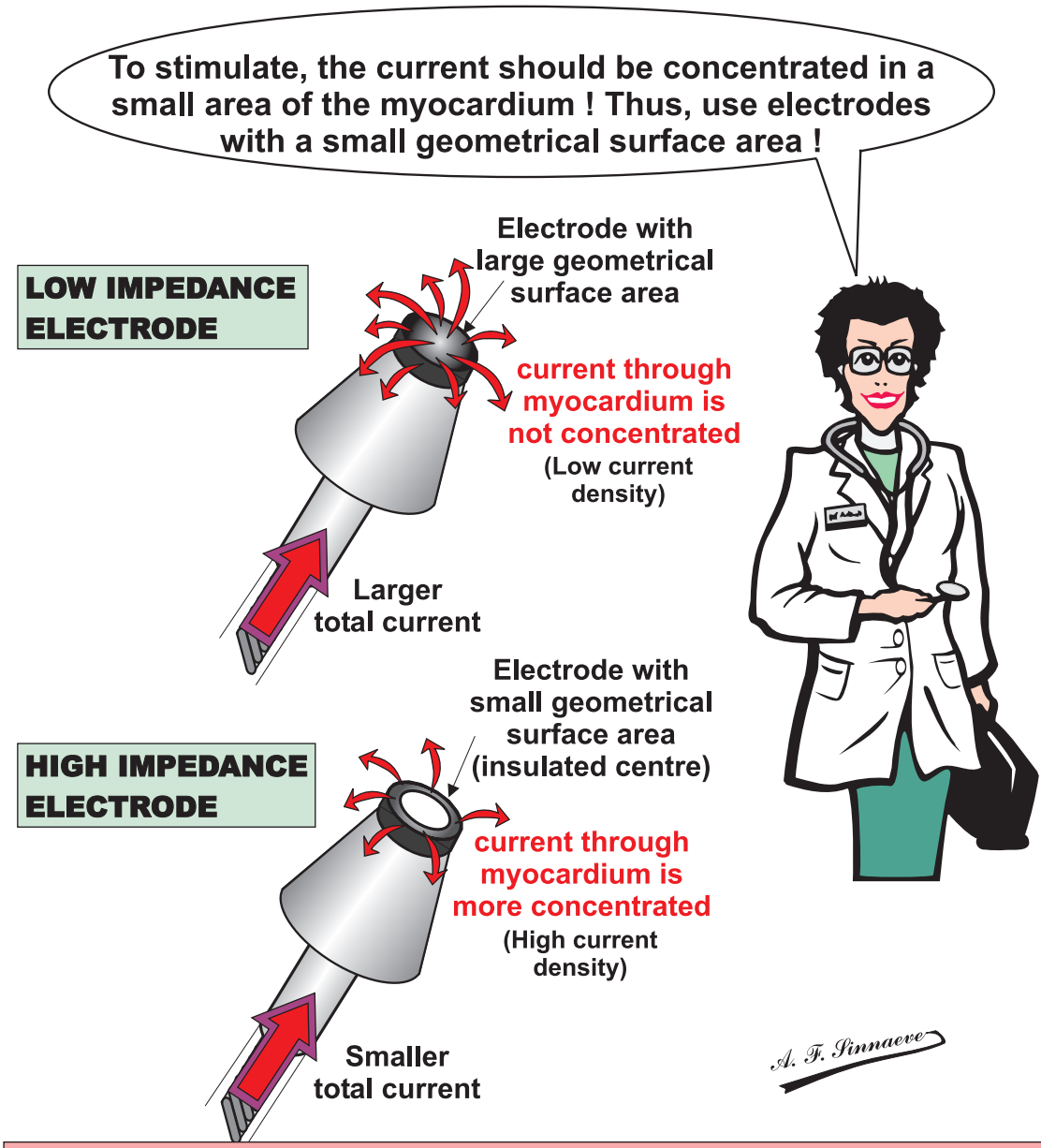
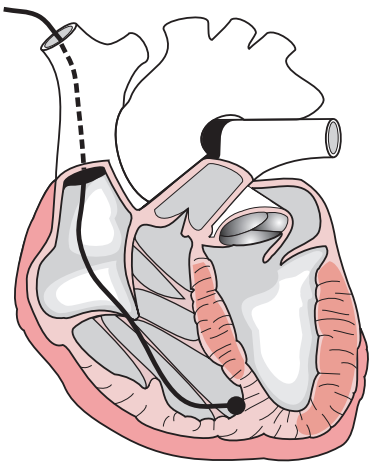
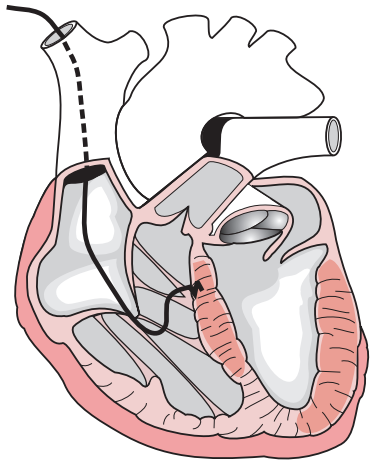


Reducing the geometric surface area of pacing electrodes increases the pacing impedance. Small area high impedance electrodes (>1000Ω) have become popular because their pacing thresholds are comparable or even better than those of conventional electrodes. A high impedance causes a decreased current drain from the battery as predicted by Ohm's law (I = U/R). The sensing characteristics of high impedance leads are similar to conventional ones. Thus, with the same performance as conventional leads, high impedance (better called high efficiency) leads significantly reduce current drain from the battery for stimulation and thereby increase battery longevity.

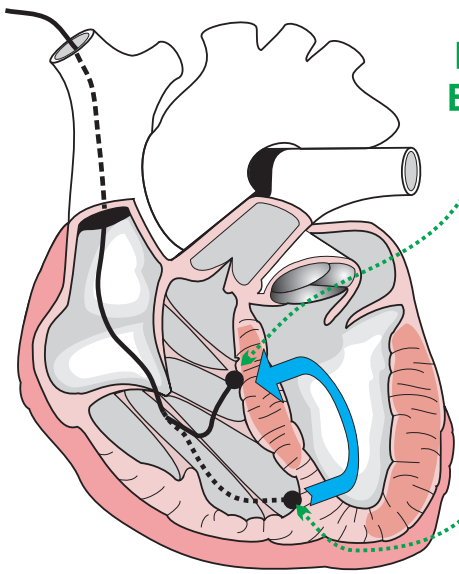
LEAD DISPLACEMENT



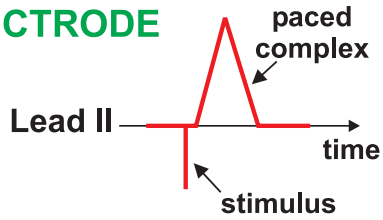
Normally positioned lead at right ventricular apex



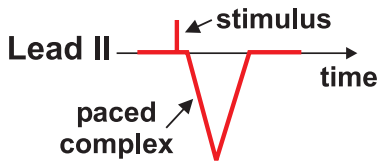
Normally positioned screw-in lead at RV outflow tract



DISPLACED ELECTRODE



NORMALLY PLACED RV ELECTRODE



Abbreviations : RV = right ventricle (right ventricular)

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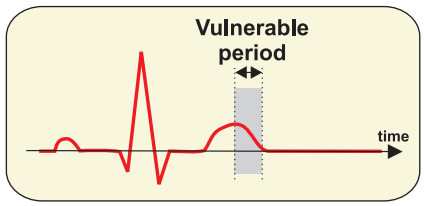
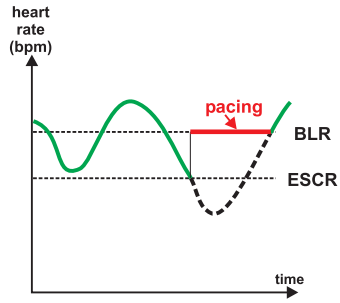
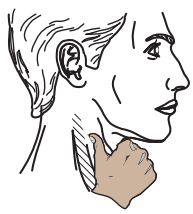
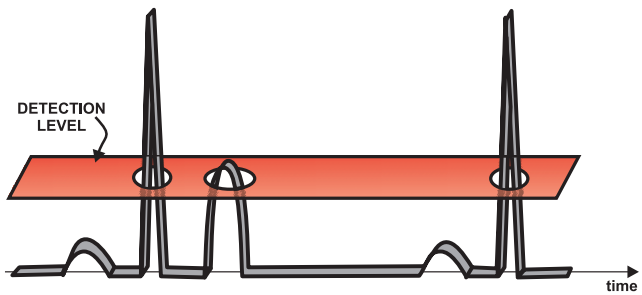




SENSING - BASIC CONCEPTS

* Firing on the T wave - Ventricular fibrillation
* VVI or demand ventricular pacing
* What does the pacemaker sense ?
* Markers and symbols
* Three-letter code for single chamber pacemakers
* The intracardiac electrogram - Sensing 1
* The intracardiac electrogram - Sensing 2
* Undersensing by the demand pacemaker
* What exactly is over- and undersensing ?
* No ventricular capture with normal ventricular sensing
* Carotid sinus massage and asystole
* Magnet application on a pacemaker
* Does the pacemaker function ? Apply magnet !
* The magnetic reed switch
* Hysteresis 1
* Hysteresis 2
* Programmability of a VVI pacemaker
* Telemetry - Printout from the programmer





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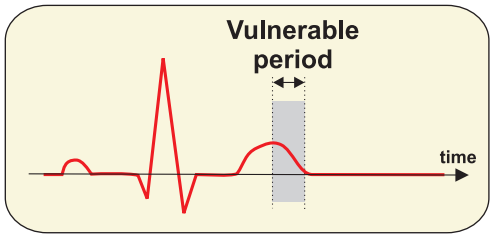
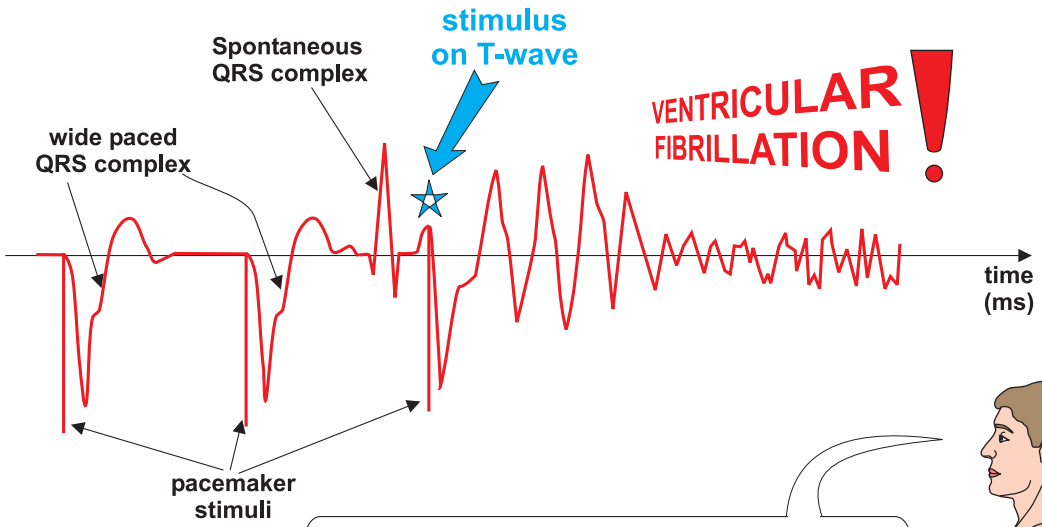
ASYNCHRONOUS PACING & STIMULUS ON T-WAVE

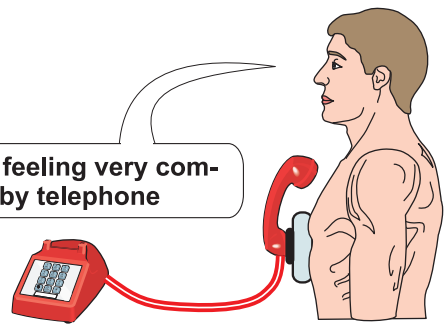
There must be a risk of firing a pacemaker stimulus into the ventricular vulnerable period !?



The risk is very small in the usual clinical situations. Countless patients transmit their ECG safely over the phone during follow-up when the magnet is placed over the pacemaker with the creation of a competitive ventricular rhythm and firing of the pacemaker on the T wave. The risk is confined to patients with serious metabolic (electrolyte) abnormalities or acute myocardial infarction or ischemia.



I'm not scared and I'm still feeling very comfortable with the follow-up by telephone



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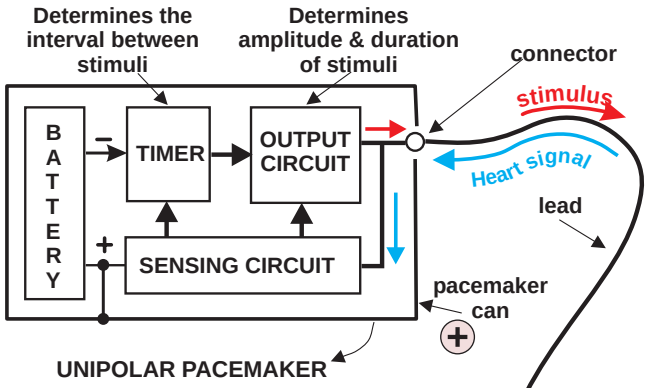
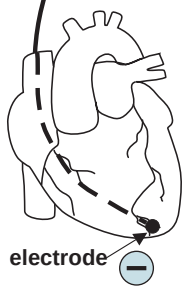
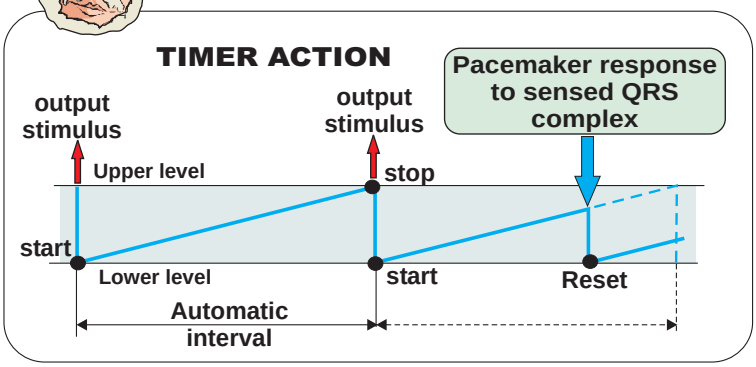
VENTRICULAR DEMAND PACING (VVI)

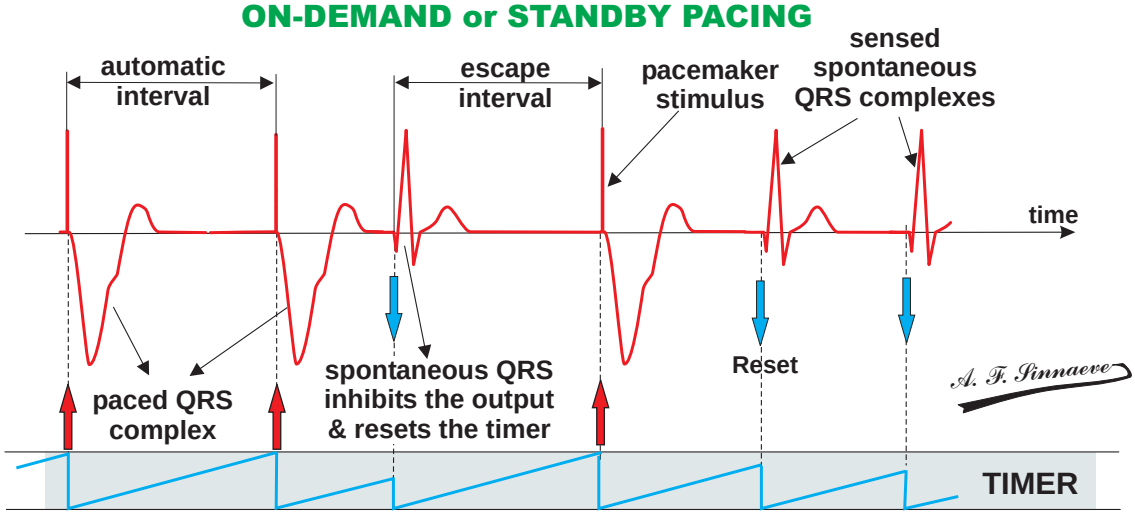
Note that in the VVI mode, a competitive rhythm is not possible. Moreover the lifetime of the battery is extended because the pacemaker is not pacing during long periods of time when it is on standby.







ON-DEMAND or STANDBY PACING

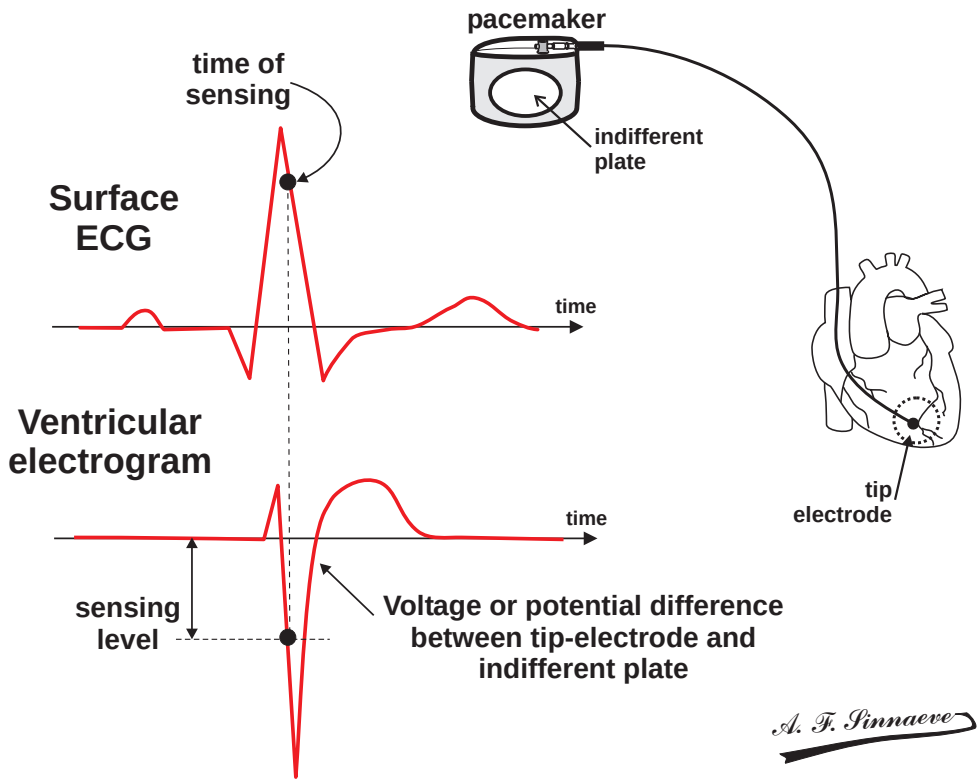


The electronic escape interval (starting at the time of intracardiac sensing) is equal to the automatic interval. The escape interval is measured on the surface ECG from the onset of the QRS complex because the time of intracardiac sensing cannot be determined accurately. Therefore the escape interval so measured will be slightly longer than the automatic interval because intracardiac sensing occurs later than the beginning of the surface QRS complex.

WHAT DOES THE PACEMAKER SENSE ?

How does a demand pacemaker know when to deliver a stimulus ? Does it recognize the ECG ?

The pacemaker does not sense the surface ECG nor the ECG near the pacemaker can. It detects what is going on inside the heart itself by measuring the potential difference (voltage) between the two electrodes used for pacing. The voltage of intracardiac depolarization is larger than that of the surface ECG and is called an electrogram rather than electrocardiogram.
Therefore, the time of electronic sensing the intracardiac electrogram does not correspond with the onset of the surface ECG because it takes a finite time for the activation to reach the electrodes (for example in the right ventricle) and generate the electrogram



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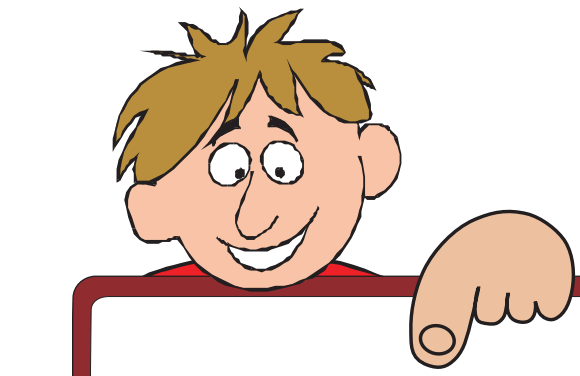
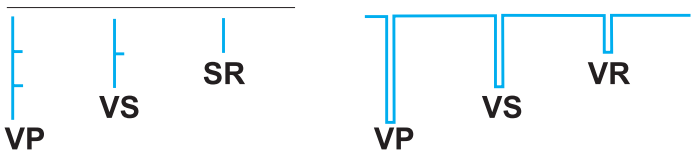


MARKERS & SYMBOLS
ACCORDING TO MANUFACTURERS

SYSTEM 1



VP = ventricular pace
VS = ventricular sense
SR or VR = ventricular sense in refractory period

SYSTEM 2

V = ventricular pace
R = ventricular sense (R wave)
R = ventricular sense in refractory period

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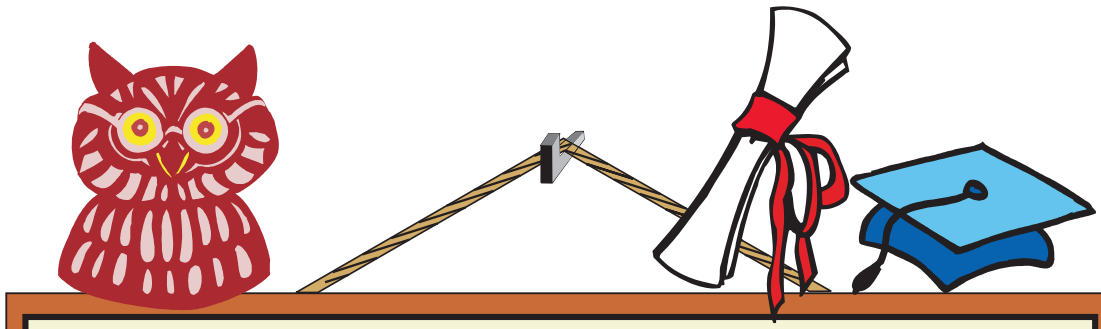

THREE-LETTER PACEMAKER CODE (ICHD)

POSITION	1st	2nd	3rd
CATEGORY	CHAMBER(S) PACED	CHAMBER(S) SENSED	MODE OF RESPONSE
LETTERS	V = VENTRICLE A = ATRIUM S = SINGLE	V = VENTRICLE A = ATRIUM S = SINGLE O = NONE	T = TRIGGERED I = INHIBITED O = NONE

EXAMPLES :

AAI = a pacemaker pacing and sensing in the atrium, being inhibited by spontaneous electrical activation of the atrium

VVT = a pacemaker pacing and sensing in the ventricle and working in the triggered mode (each sensed ventricular event elicits a pacemaker stimulus)

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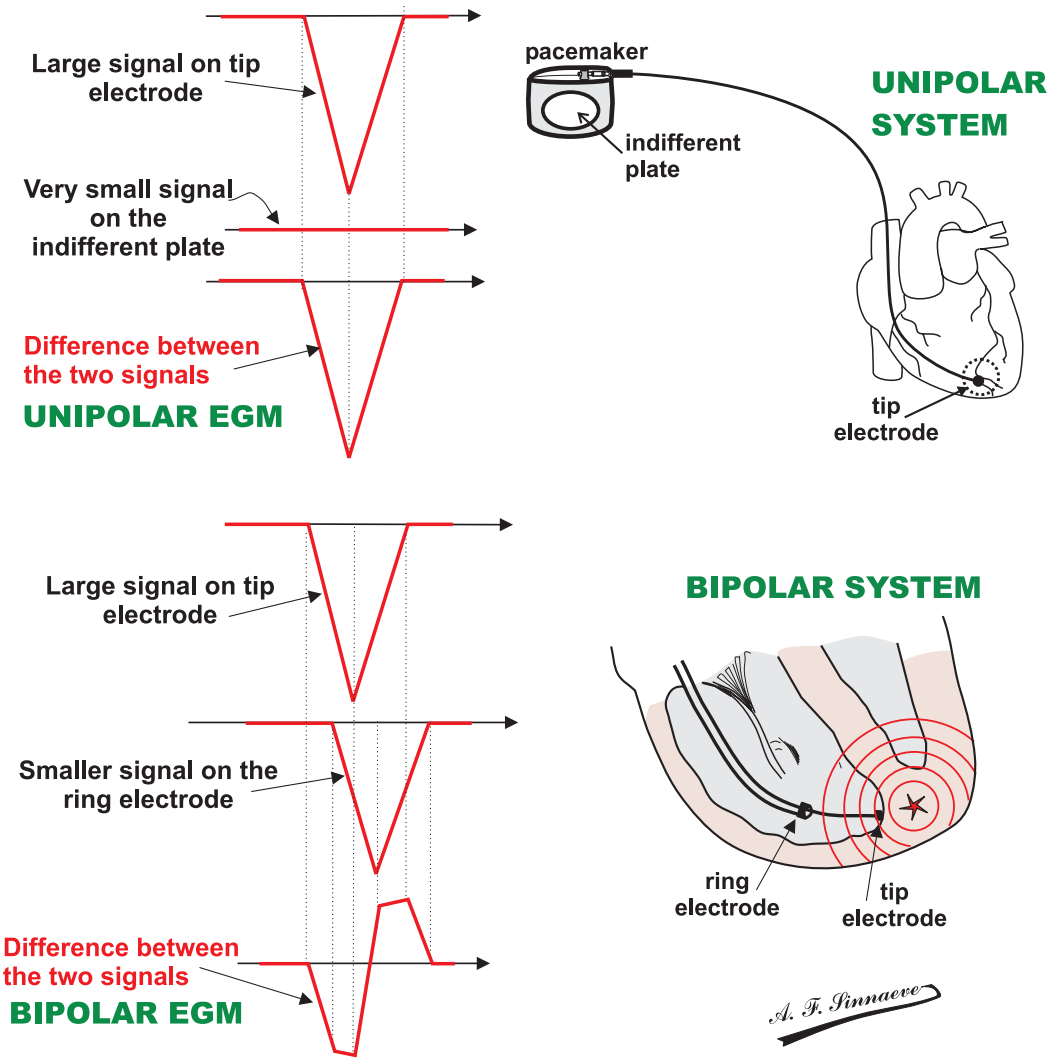
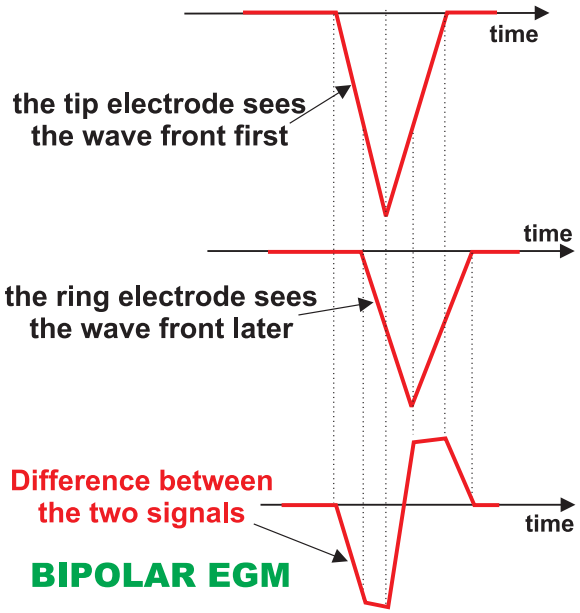
THE SENSING AMPLIFIER MEASURES THE DIFFERENCE BETWEEN TWO SIGNALS AT THE PACING ELECTRODES



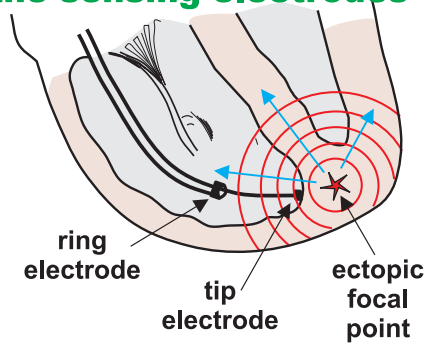
Note that on each instant of time, the bipolar electrogram (EGM) is the difference between the EGMs recorded at the tip and ring electrodes. The EGMs arrive at different times and this timing or phase difference generates the bipolar EGM.

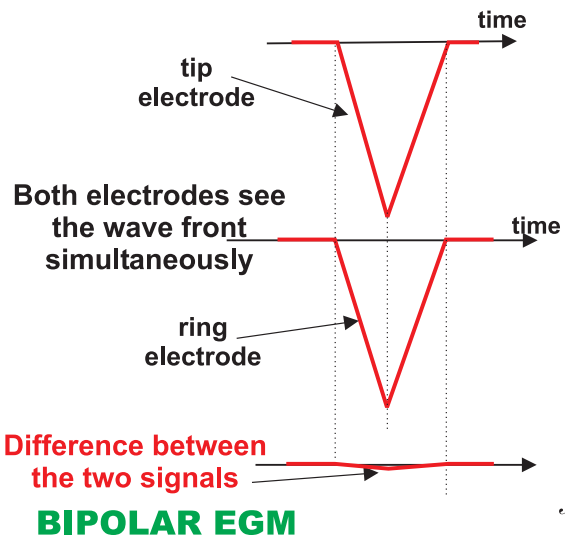
VARIABILITY OF BIPOLAR SENSING

* The sensed signal to the pacemaker is the voltage or potential difference between the two intracardiac electrodes
* The bipolar EGM depends on both the amplitude and timing (phase difference) of the electrograms registered at each of the two intracardiac electrodes

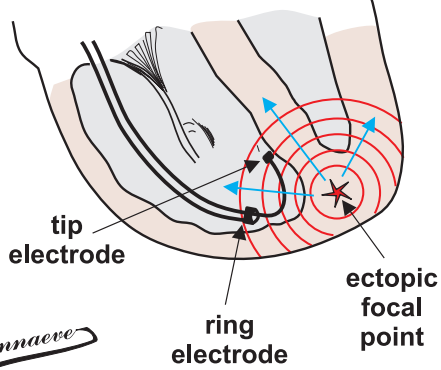


Wave front advancing parallel to the axis of the sensing electrodes





Wave front advancing perpendicular to the axis of the sensing electrodes



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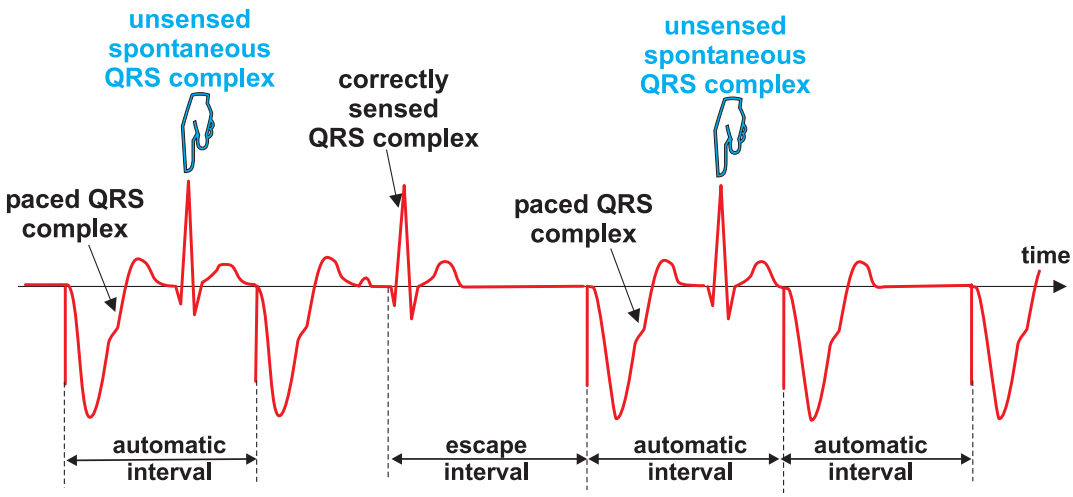
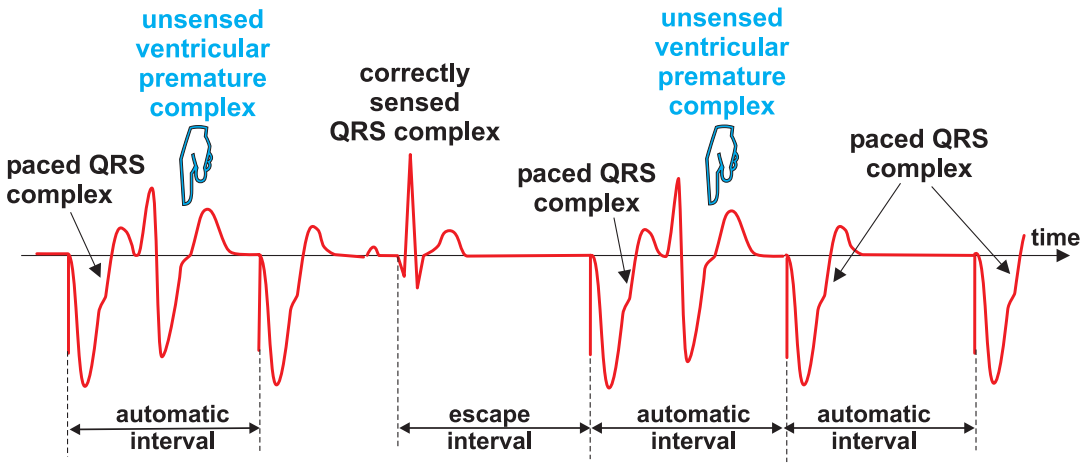
Identical signals arriving exactly at the same time at the two electrodes will yield a zero bipolar electrogram (EGM). Although this is theoretical, it is possible for two large unipolar EGMs to generate a relatively small bipolar EGM. In this situation, if there is undersensing, the bipolar sensing mode can be reprogrammed to the unipolar sensing mode.

1 INTERMITTENT UNDERSENSING OF A DEMAND PACEMAKER



2 UNDERSENSING OF VPC BY DEMAND PACEMAKER



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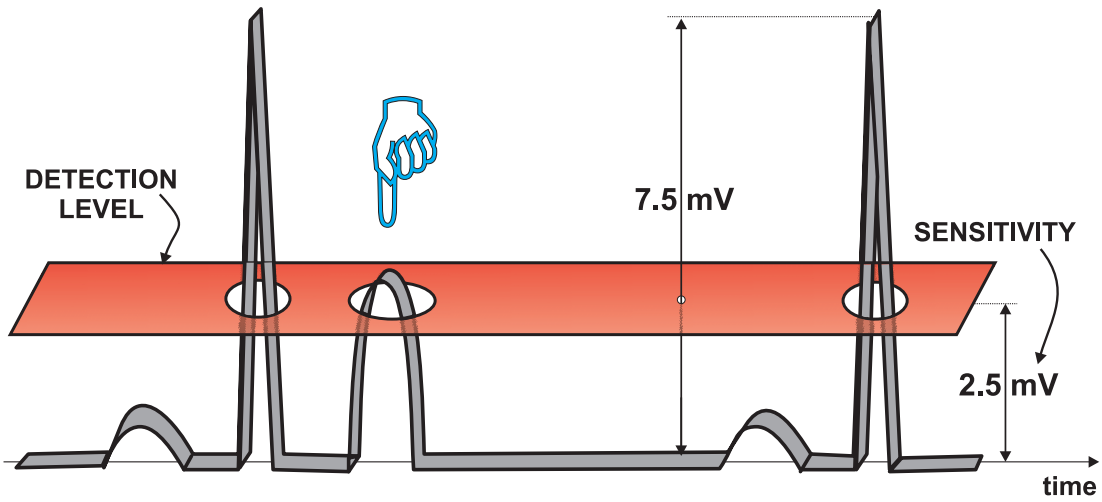
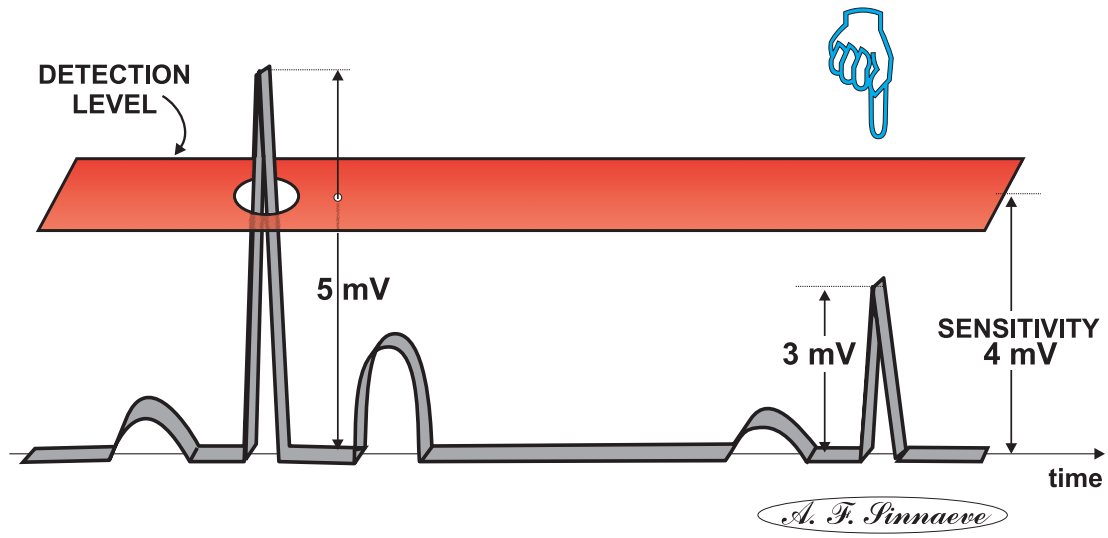
OVERSENSING



UNDERSENSING



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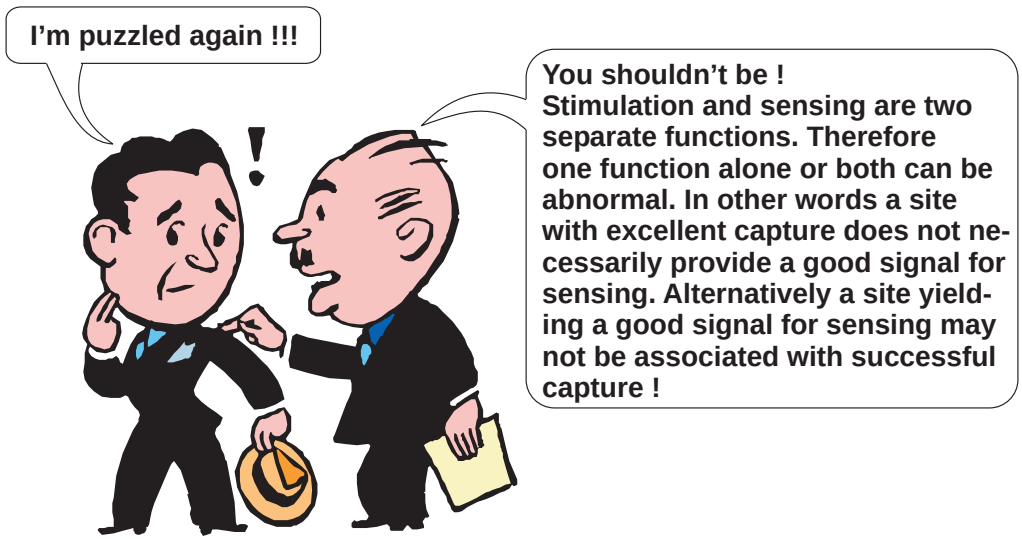
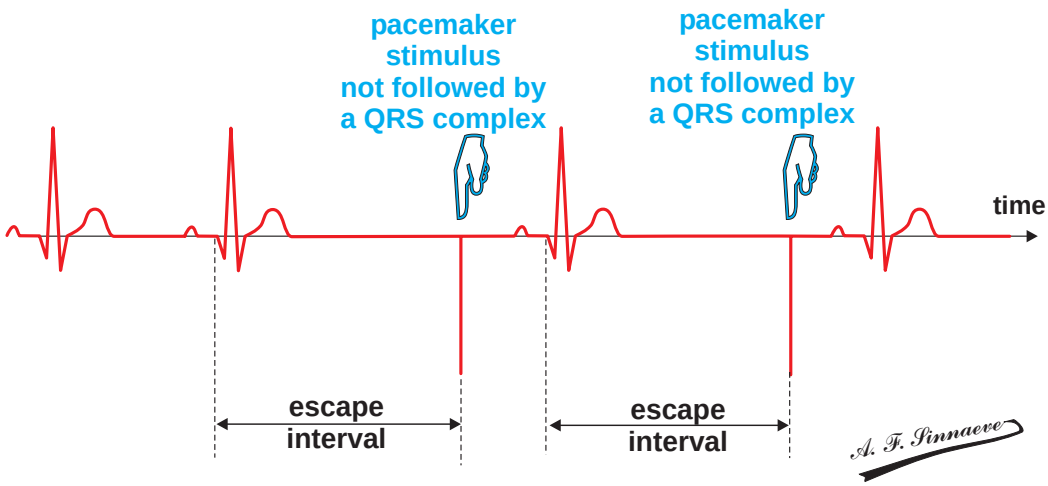
The voltage refers to the intracardiac electrogram and not the surface QRS complex. Sensitivity refers to a programmable parameter of the pacemaker. A sensitivity of 4 mV means that the pacemaker can only sense a signal equal to or greater than 4 mV. It will sense a signal of 5 mV but not a signal of 3 mV.

LACK OF VENTRICULAR CAPTURE OF A DEMAND PACEMAKER WITH NORMAL SENSING

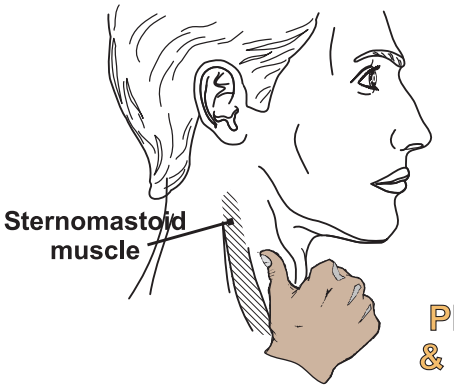




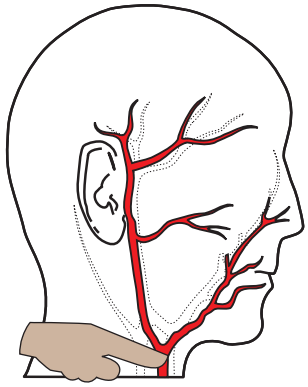
WARNING

Capture and sensing must be tested separately

CAROTID SINUS MASSAGE



PRESSURE
& MASSAGE



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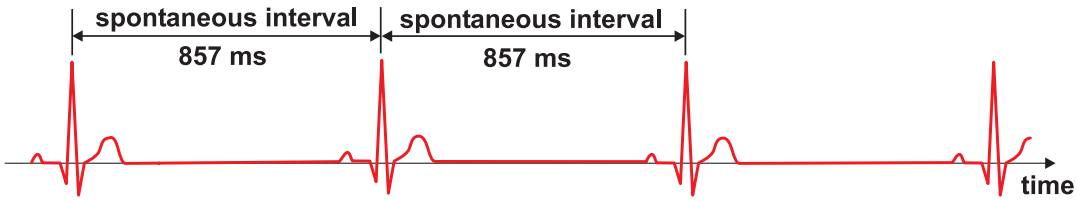
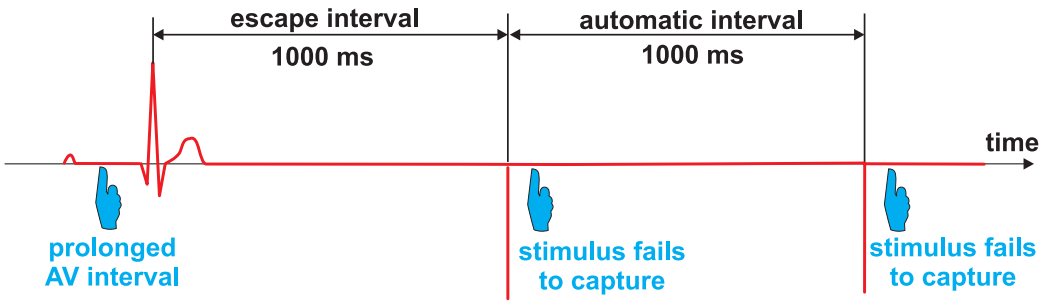
Without massage



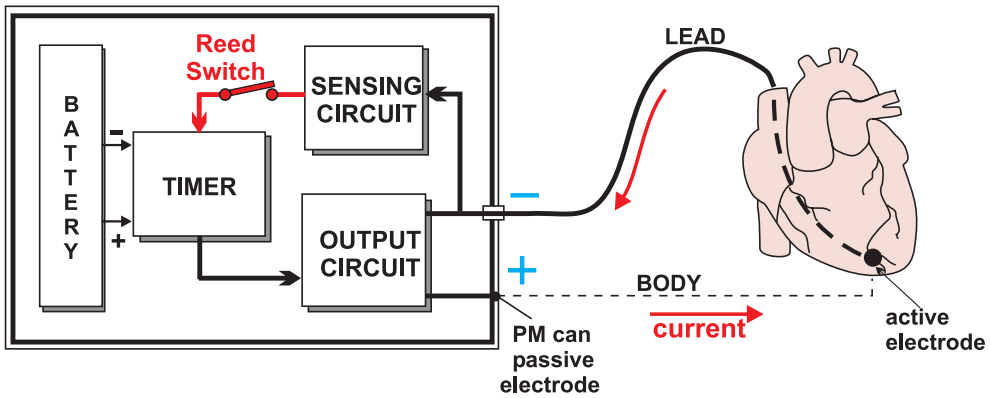
During massage (CSP =carotid sinus pressure)

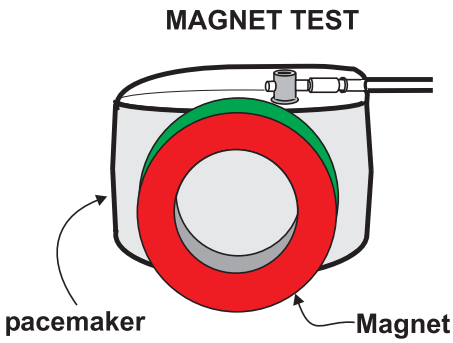


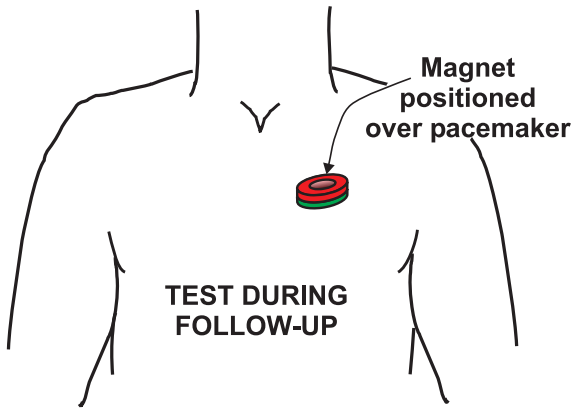
WARNING !!!

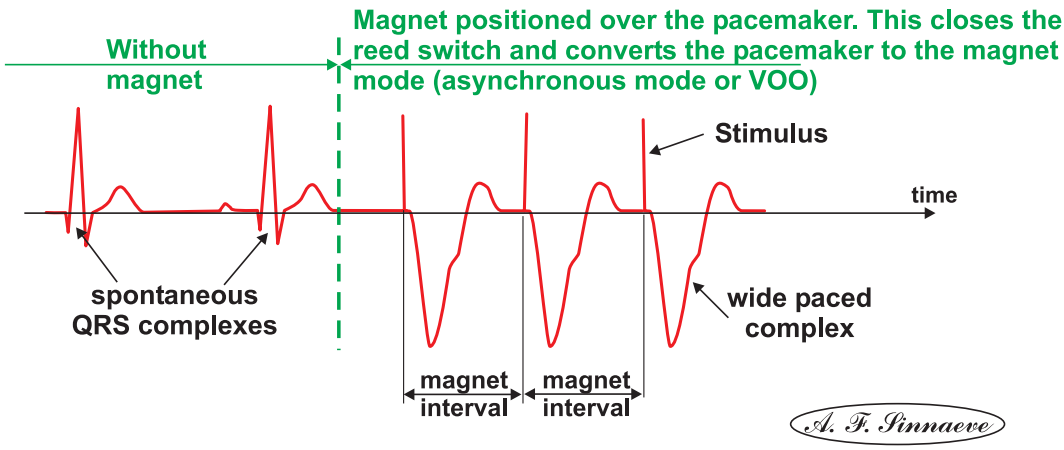
When a patient presents with an ECG showing no pacemaker stimuli, do not perform carotid sinus massage to test the pacemaker because it may cause prolonged bradycardia. The pacemaker will then deliver its stimuli that may or may not capture the heart. The pacing function should be tested first by the application of a pacemaker magnet, which converts any pacemaker to the fixed-rate or asynchronous mode (VVI to VOO).

MAGNET APPLICATION ON A DEMAND PACEMAKER









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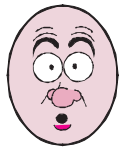
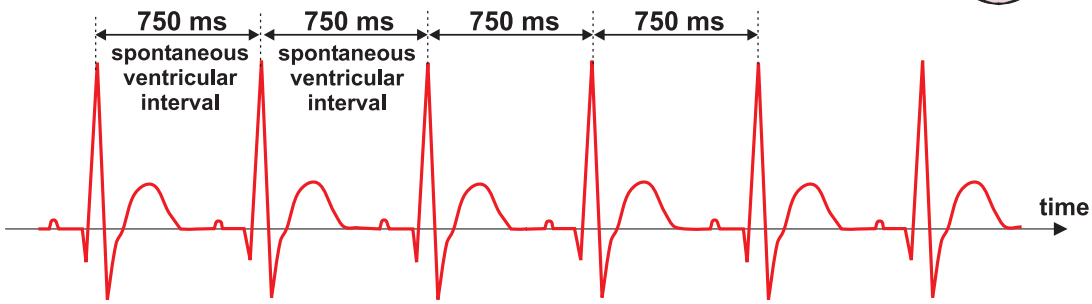
DOES THE PACEMAKER FUNCTION ?

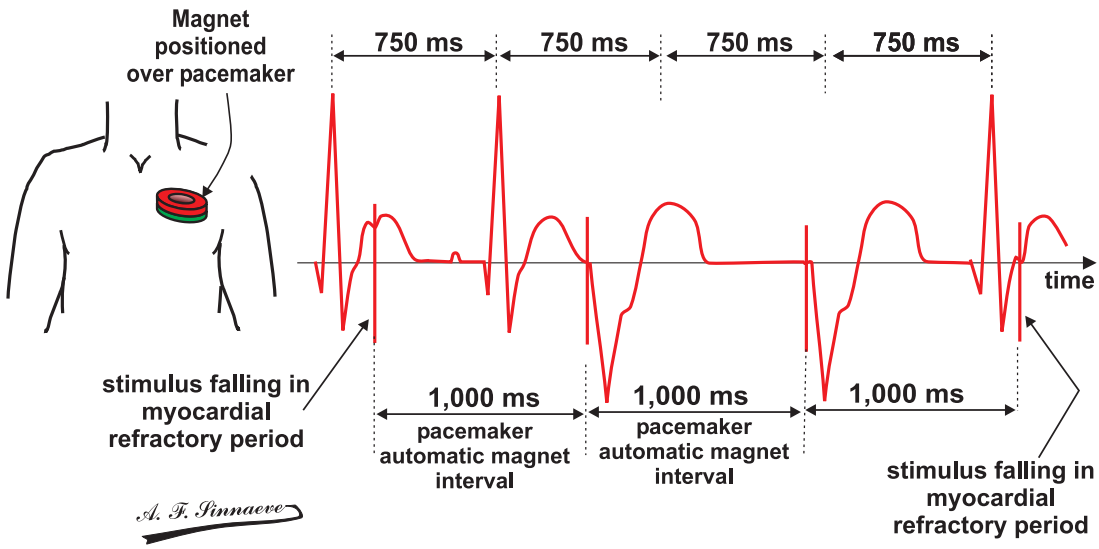
Spontaneous rhythm of the patient 80 bpm (beats per minute)

(or spontaneous R-R interval = $\frac{60{,}000}{80}$ = 750 ms)



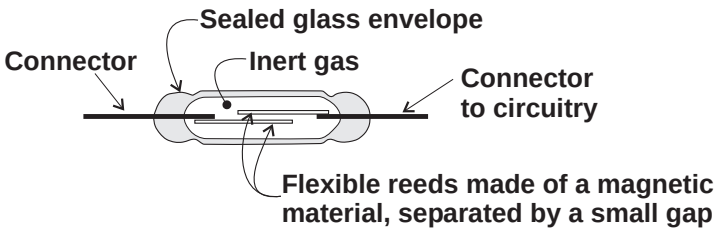


After magnet application, showing the pacemaker programmed at 60 bpm (or an automatic interval = $\frac{60{,}000}{100}$ = 1,000 ms also equal to the magnet interval of this pacemaker)

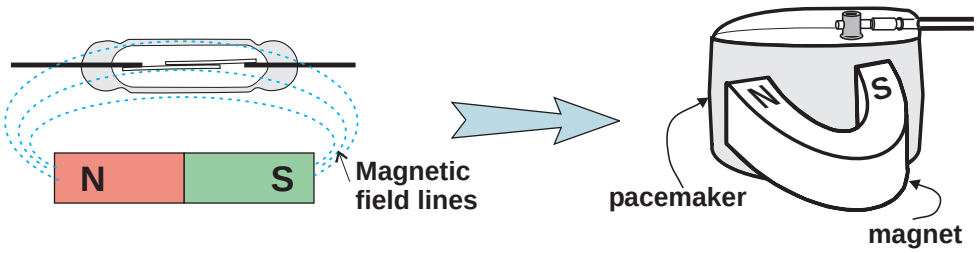


THE MAGNETIC REED SWITCH

NORMAL REED SWITCH
OPEN CONTACT WITHOUT MAGNETIC FIELD



NORMAL REED SWITCH
CLOSED CONTACT WITH MAGNETIC FIELD



A MAGNET AND A REED SWITCH ARE NEEDED FOR TESTING

* Magnet mode forces the pacemaker's programmed operation to an asynchronous mode (DOO in dual chamber devices and VOO/AOO in single chamber devices)
* The programming system of many pacemakers requires preliminary closure of the reed switch before the command is transmitted from the programmer to the pacemaker; in such a case the programming head contains an appropriate magnet for this purpose.

THE MAGNET IS UNABLE TO CLOSE THE REED SWITCH IF

° the magnet is not properly positioned (wrong site)
° the distance between magnet and reed switch may be too large in obese patients
° the magnet is too weak (try 2 or 3 toroid magnets on top of each other)
° the magnet function is programmed OFF

TRUE MALFUNCTION OF THE REED SWITCH IS VERY RARE

* Failure to close : the pacemaker cannot be converted to the magnet mode
* The "sticky" reed switch stays permanently closed with persistent asynchronous pacing

Caution : as a rule, application of a magnet on an ICD, deactivates tachycardia therapy but not its pacing and sensing function for bradycardia therapy.

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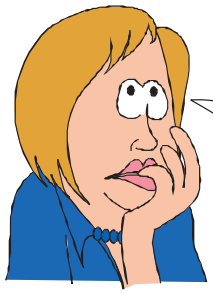
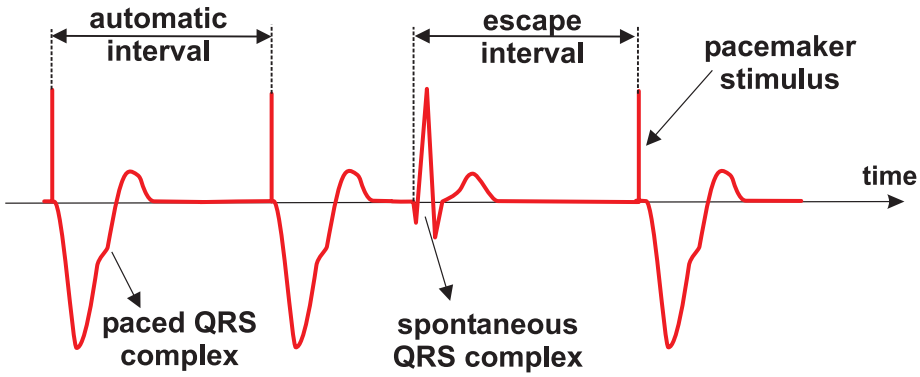
HYSTERESIS 1

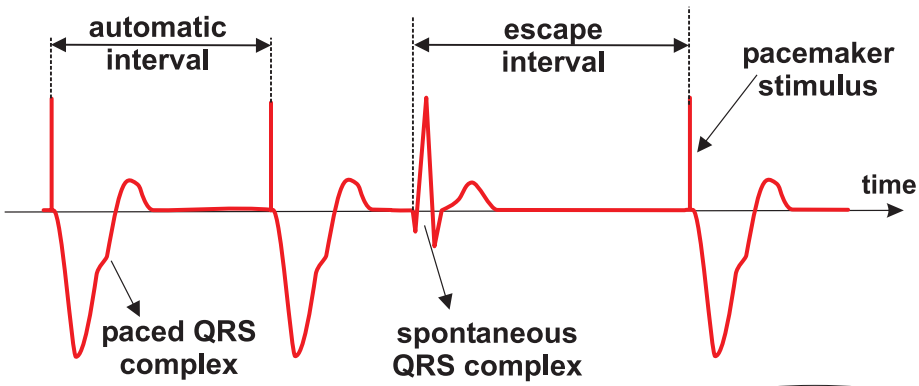


This isn't looking very easy to me !
And the interval between two ventricular events can be longer than the basic or automatic interval ?

WITHOUT HYSTERESIS
the automatic interval equals the escape interval



WITH HYSTERESIS
the escape interval is longer than the automatic interval



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HYSTERESIS 2

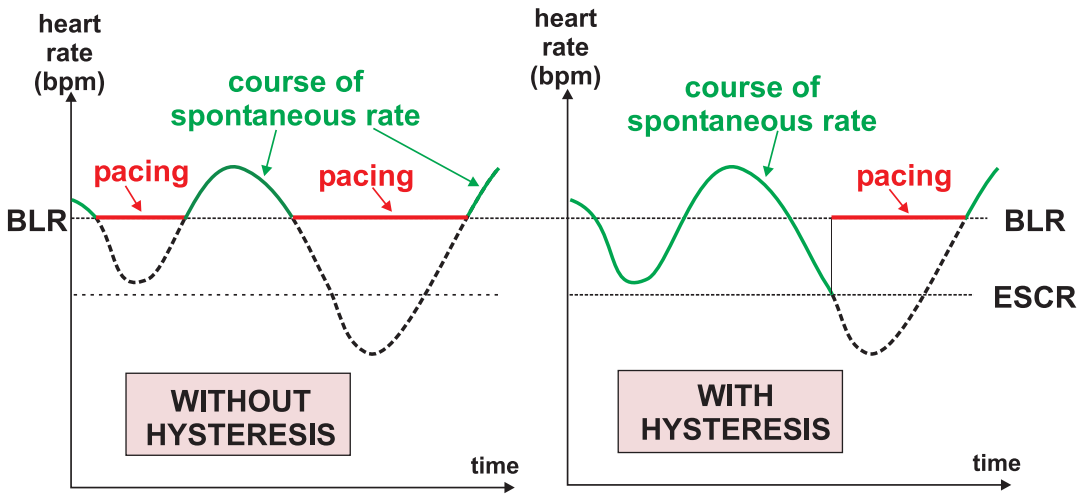
Hysteresis has some fine advantages :
* the spontaneous AV synchrony can be maintained as long as possible
* it prevents symptomatic retrograde VA conduction
* allowing a lower rate increases the longevity of the battery

LRI = basic lower rate interval = automatic interval (in ms)

ESCI = escape interval (in ms)

BLR = basic lower rate = $\frac{60\ 000}{LRI}$ (in bpm)

ESCR = escape rate = $\frac{60\ 000}{ESCI}$ (in bpm)



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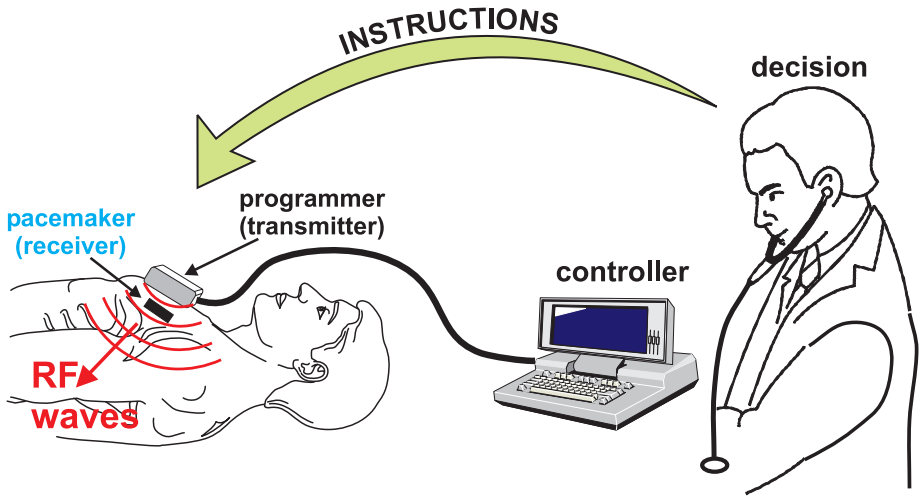
PROGRAMMABILITY



PROGRAMMABLE PARAMETERS IN VVI PACEMAKERS

* Rate
* Pulse width
* Voltage amplitude
* Sensitivity of the sensing circuit
* Refractory period
* Hysteresis
* Mode of pacing

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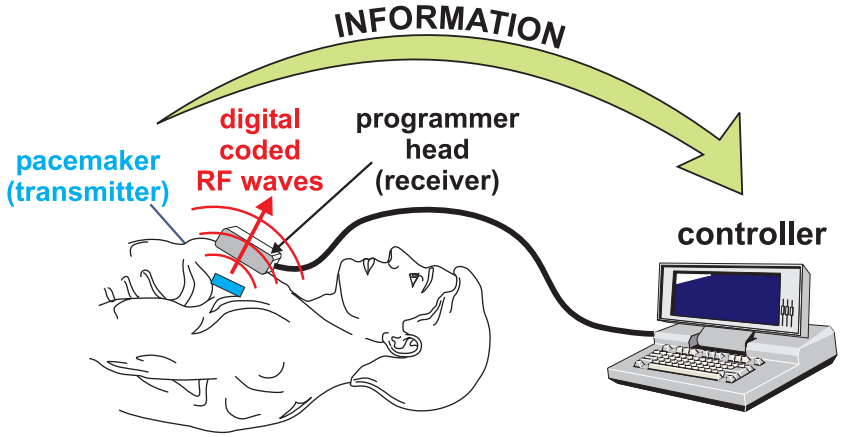
THE CONCEPT OF TELEMETRY



DATA OBTAINABLE BY TELEMETRY

* **ADMINISTRATIVE DATA** (model, serial number, patient's name, date of implantation, indication for implantation)

* **PROGRAMMED DATA** (mode, rate, refractory period, hysteresis on/off, pulse amplitude & width, sensitivity)

* **MEASURED DATA** (rate, pulse amplitude, pulse current, pulse energy, pulse charge, lead impedance, battery impedance, battery voltage, battery current drain)

* **STORED DATA** (Holter function, rhythm histogram, ...)

* **MARKER SIGNALS** for ECG interpretation

* **INTRACARDIAC ELECTROGRAM**

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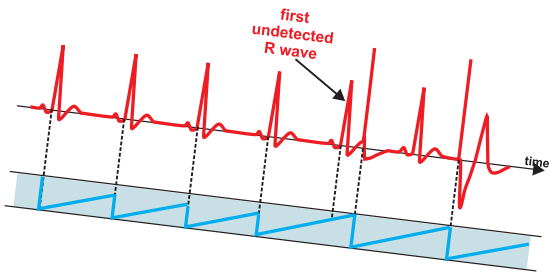
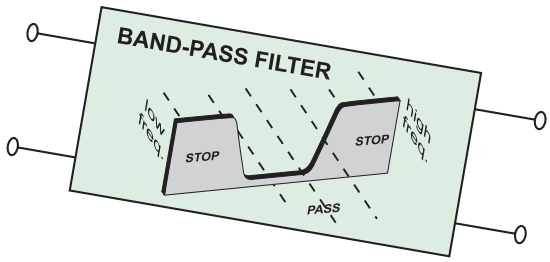
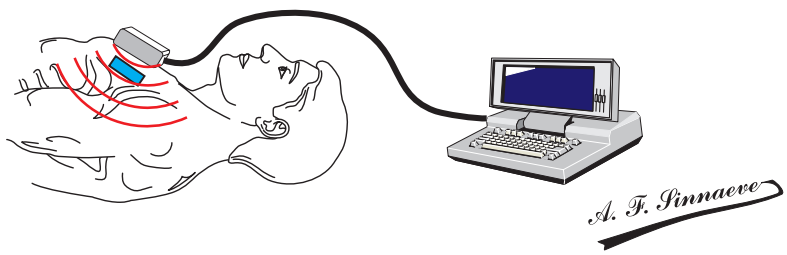


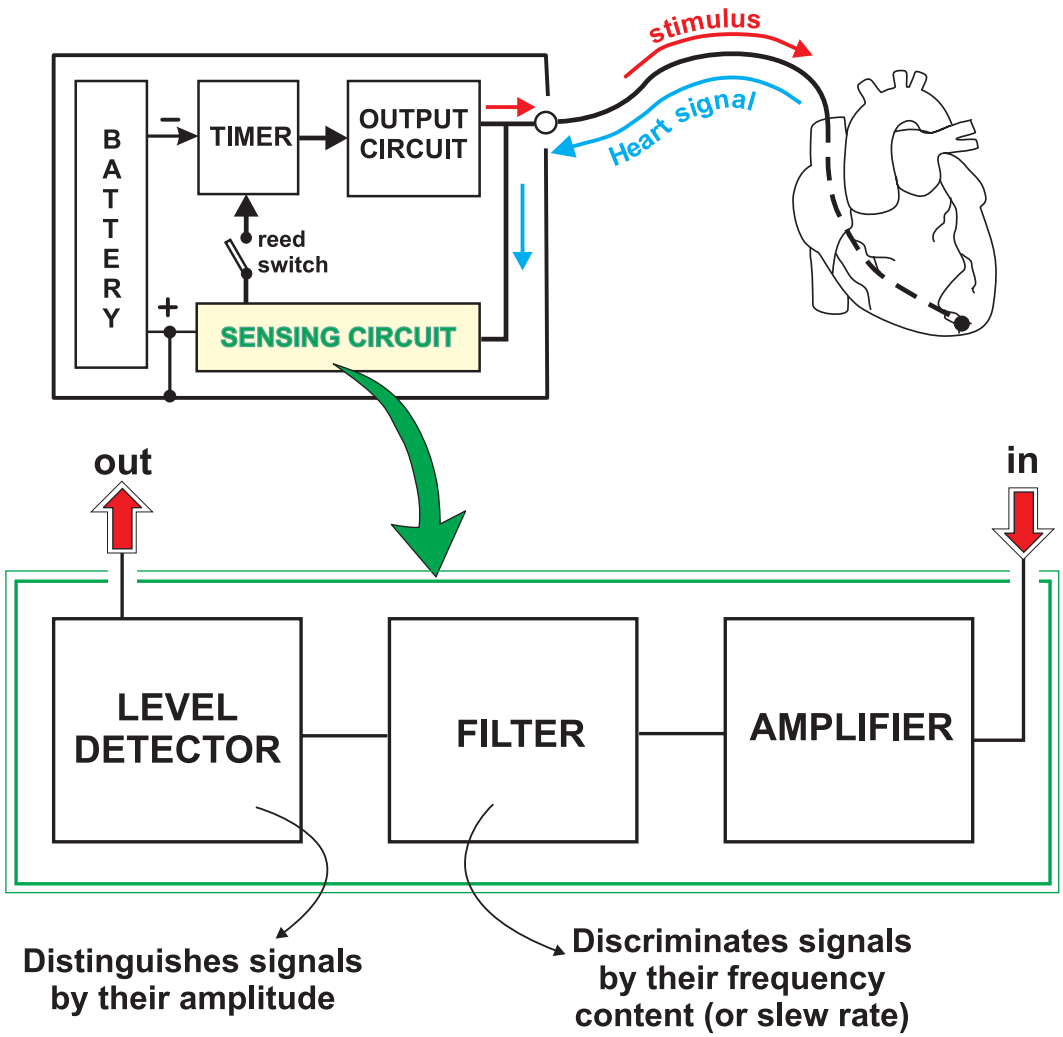


SENSING - ADVANCED CONCEPTS

* Sensing circuit - Basic block diagram
* Intrinsic deflection and slew rate
* Filtering the endocardial signal 1
* Filtering the endocardial signal 2
* Traditional ventricular refractory period (VRP)
* Functions of VRP
* The pacemaker VRP
* The blanking period
* Programming lower sensitivity
* Programming higher sensitivity
* Sensing threshold - nonautomatic determination
* Electrographic (EGM) signal recording with ECG machine



THE SENSING FUNCTION



"Amplifier" and "Level Detector" determine the SENSITIVITY expressed in millivolts

* high sensitivity is characterized by a small number of mV (i.e. the sensing circuit already reacts on small signals)
* low sensitivity is expressed by a large number of mV (i.e. the sensing circuit only reacts upon large signals)

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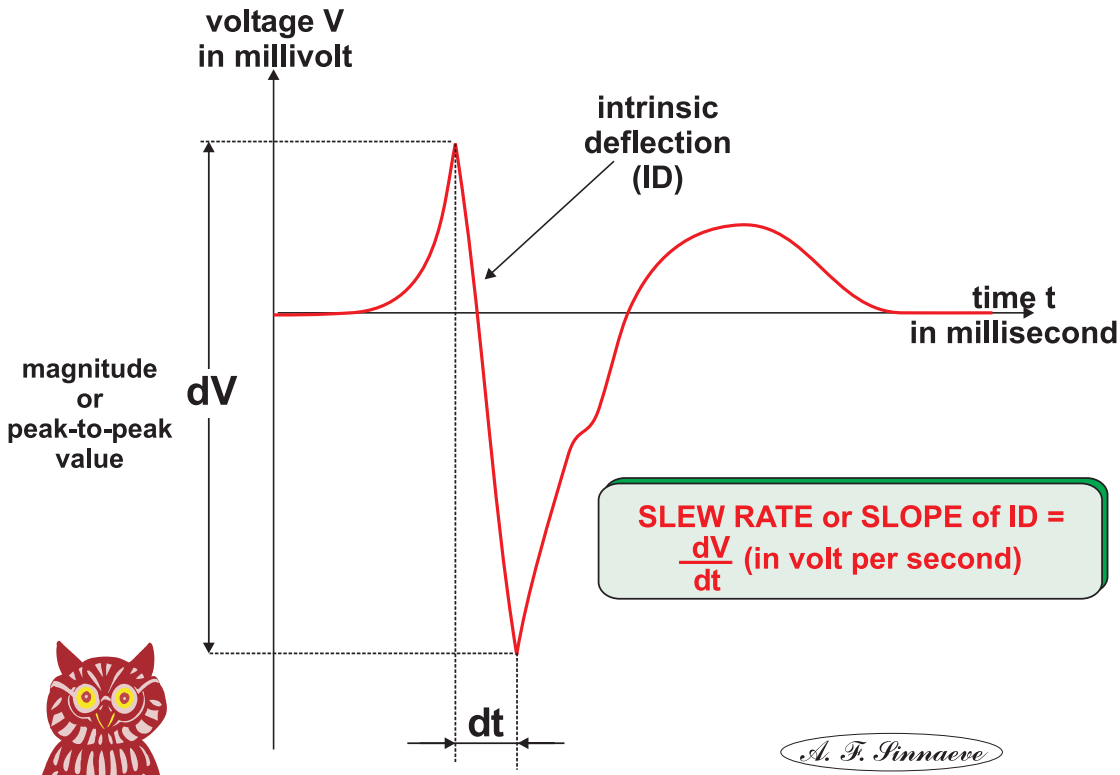
VENTRICULAR ELECTROGRAM
INTRINSIC DEFLECTION & SLEW RATE

INTRINSIC DEFLECTION :

The rapid biphasic portion of the endocardial electrogram which occurs as the myocardium underlying the electrode depolarizes

SLEW RATE :

The rate of change in signal amplitude per unit of time



SLEW RATE or SLOPE of ID = $\frac{dV}{dt}$ (in volt per second)

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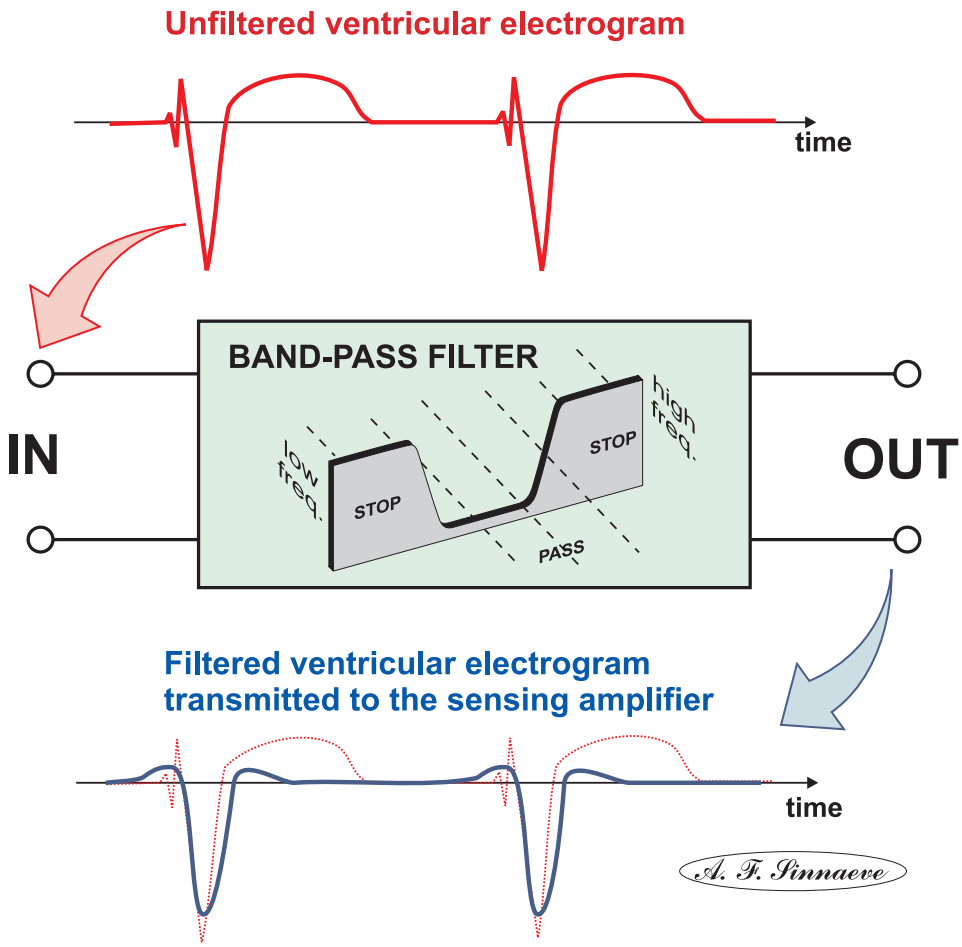
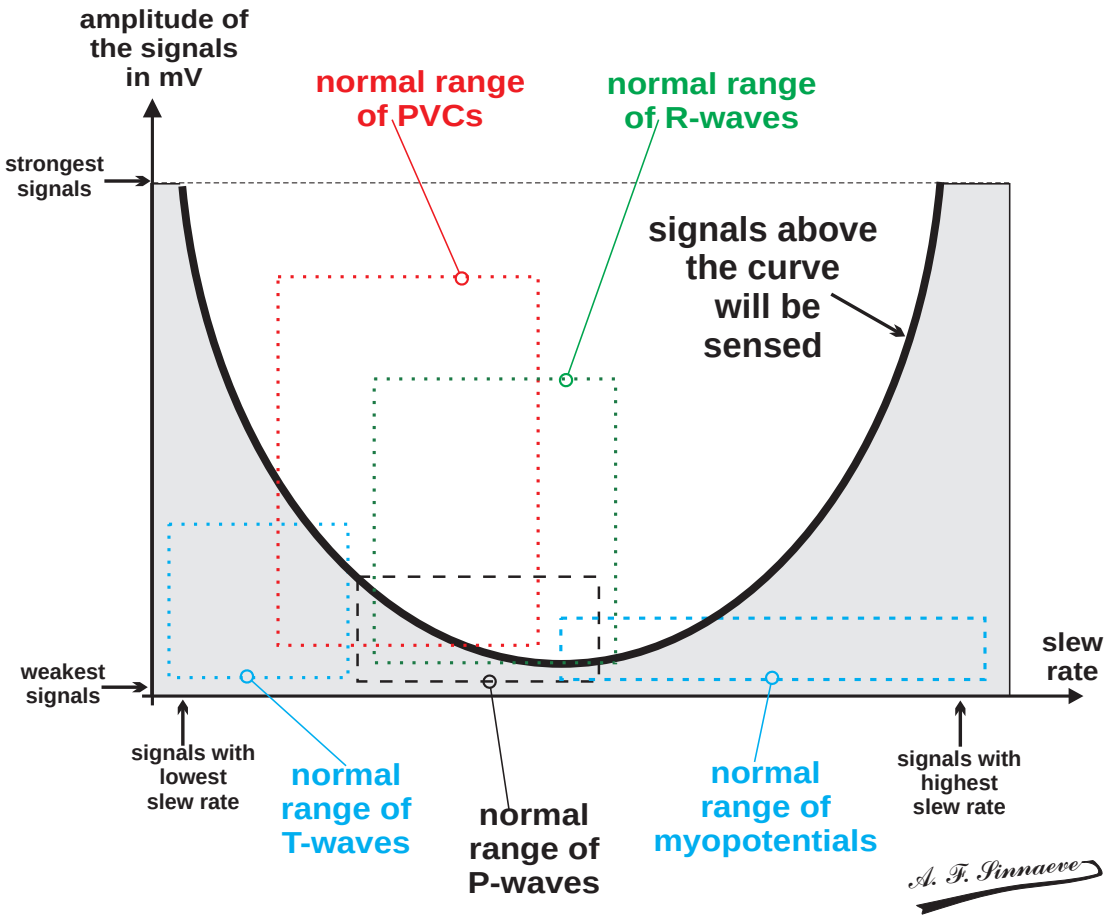
A large intracardiac signal (electrogram or EGM) almost always has a good (i.e. sharp rising) slew rate for sensing. The slew rate becomes important in relatively small signals : in this situation a pacemaker may not be able to sense an EGM with a slow-rising slope. The slew rate can be determined at the time of implantation. Although the EGM can be visualized noninvasively after implantation, the slew rate cannot !

FILTERING OF THE ENDOCARDIAL SIGNAL



Heart signals with the right slew rate easily pass through the filter without attenuation and can affect the timer of the pacemaker.
Signals with a very high slew rate (i.e. changing very rapidly) probably originate from an external source (myopotentials from skeletal muscles, electromagnetic interference, etc.). They are strongly attenuated so that they no longer can affect the timer. Signals with a very low slew rate corresponding with T waves are also strongly attenuated and unable to affect the timer of the pacemaker.
Only signals with the right slew rate i.e. with the right frequency content, will pass through the filter without attenuation, hence the name “band-pass filter”.

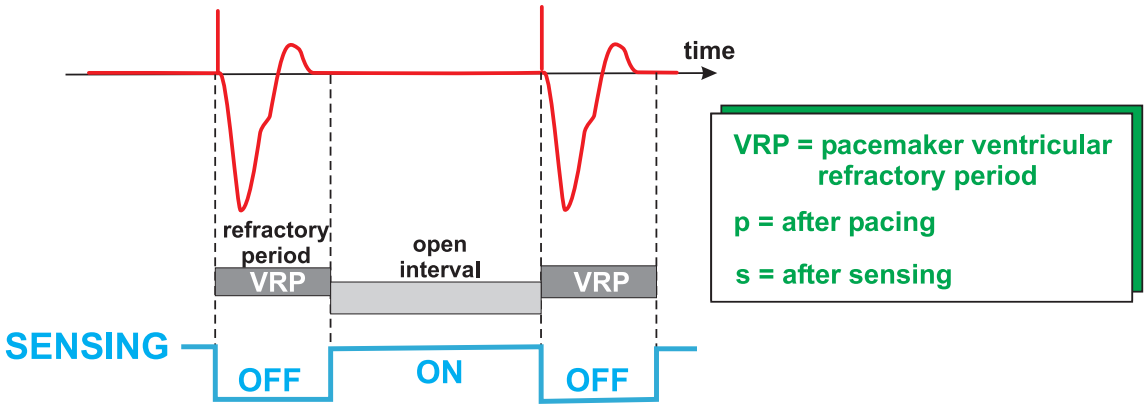
THE FILTERING OF SENSED SIGNALS



Signals are characterized by their amplitude and their slew rate. Each rectangle is the idealized representation of the set of all possible amplitude & slew rate combinations that are typical for a specific heart signal. Obviously these sets of values overlap each other and discrimination by slew rate only is not possible; a level detector will be necessary.
The shape of the filter characteristic above which detection is guaranteed, is always a technical compromise. Apparently some amplitude & slew rate combinations for T-waves and myopotentials may be above the detection level and can be sensed (over-sensing). Some combinations for PVCs and R- waves are beneath the detection level and cannot be detected (undersensing).

Abbreviations : PVC = premature ventricular complex

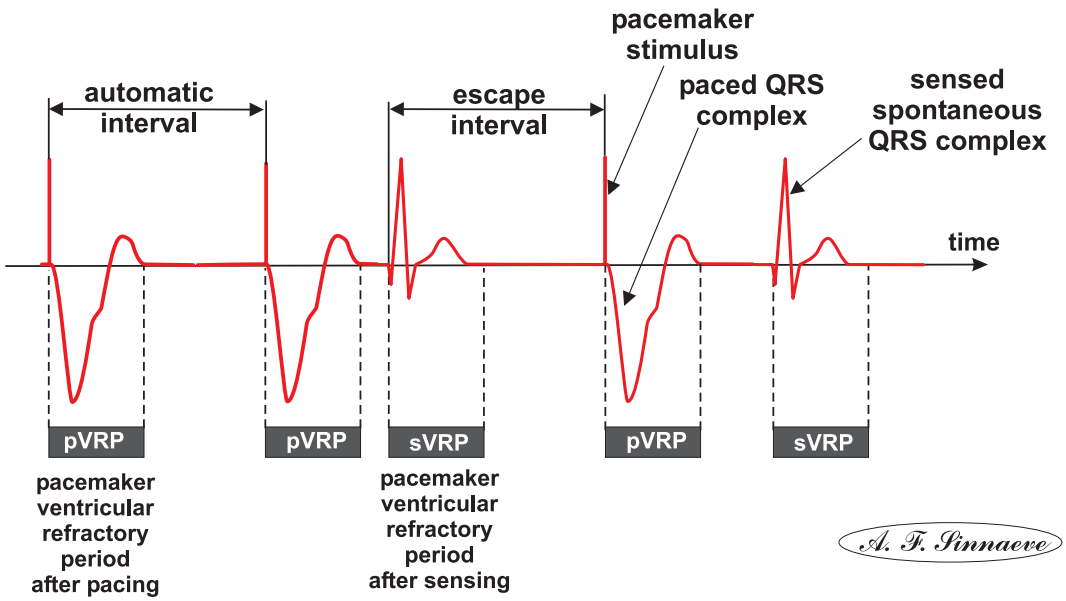
THE PACEMAKER REFRACTORY PERIOD TRADITIONAL CONCEPT



VRP = pacemaker ventricular refractory period

p = after pacing

s = after sensing



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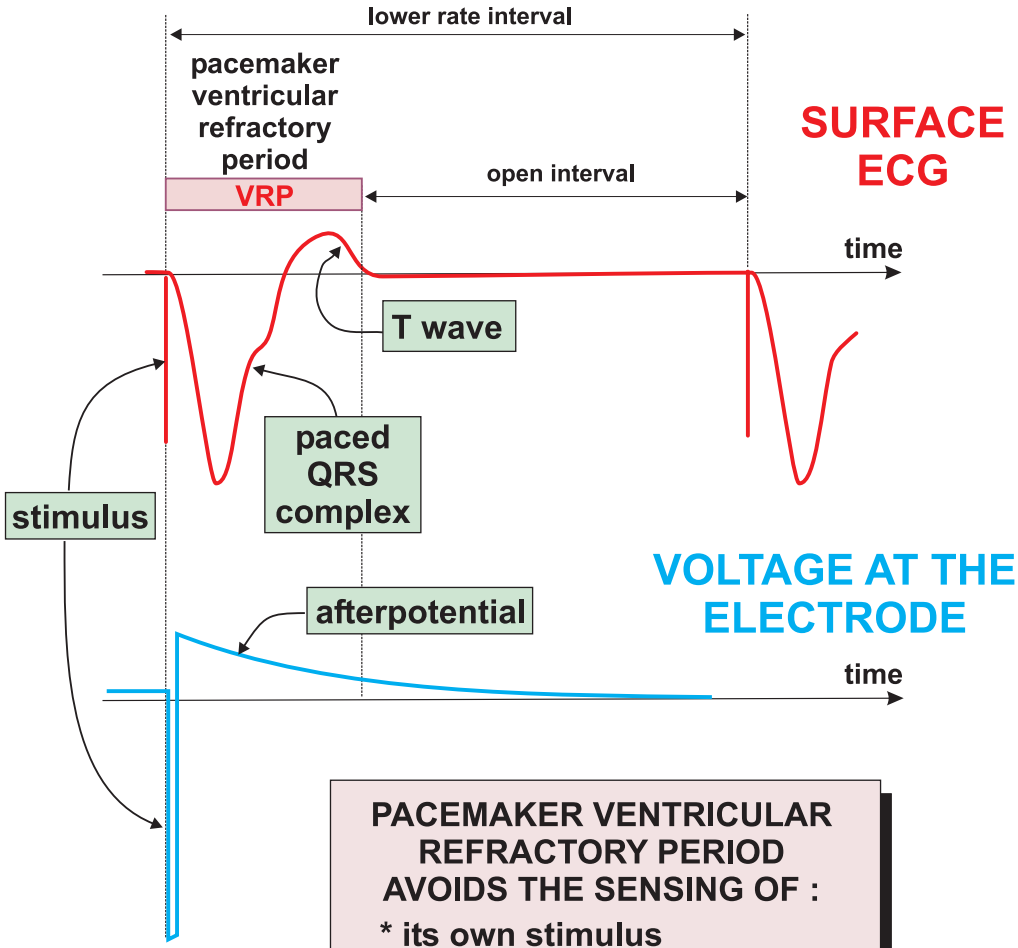
pVRP is often equal to sVRP

FUNCTIONS OF THE PACEMAKER
VENTRICULAR REFRACTORY PERIOD



PACEMAKER VENTRICULAR REFRACTORY PERIOD AVOIDS THE SENSING OF :

* its own stimulus
* the paced QRS complex
* the T wave
* (excessive) afterpotential
* the combination of T wave and afterpotential

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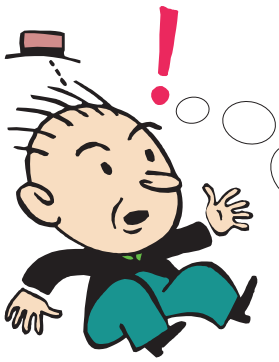
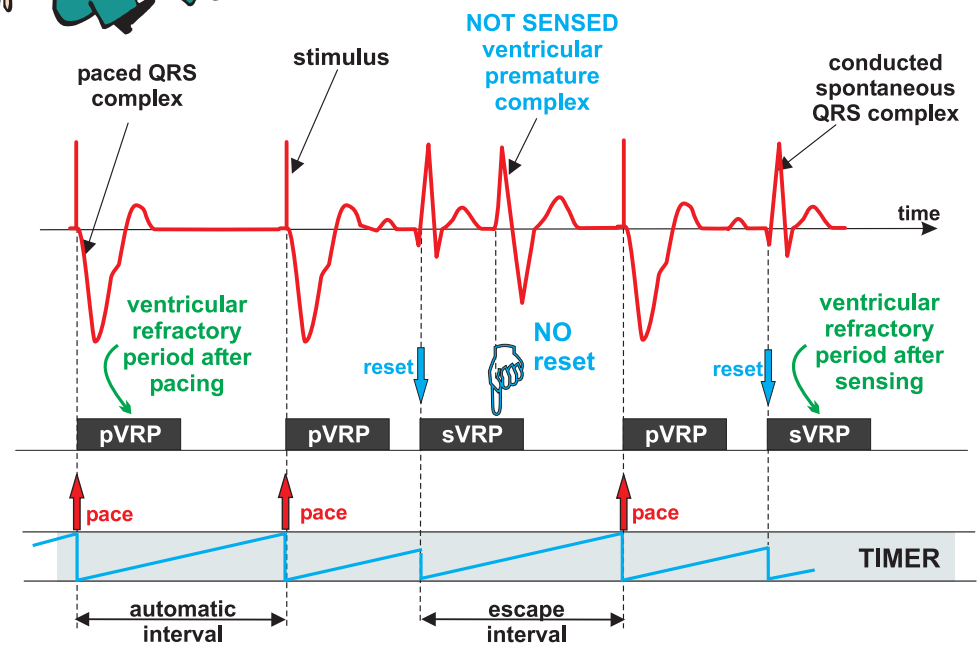
The duration of the pacemaker ventricular refractory period (VRP) is usually 200 - 300 ms

THE PACEMAKER VENTRICULAR REFRACTORY PERIOD



Don’t panic ! It is not a malfunction !



A signal generated during the pacemaker ventricular refractory period can never restart another lower rate interval (corresponding to the lower rate)

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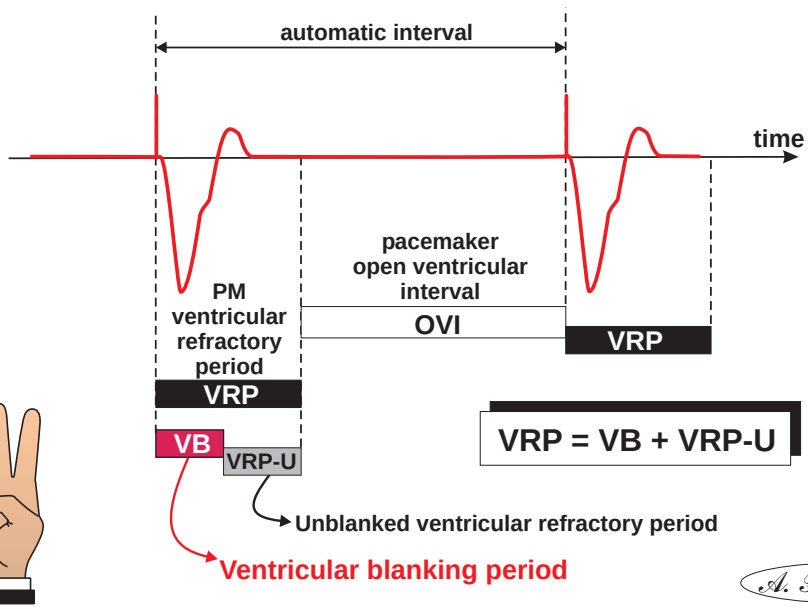
Let me tell you some basic facts about timing !

THE BLANKING PERIOD



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VRP = pacemaker ventricular refractory period, during which no basic lower rate interval can be started by a detected signal

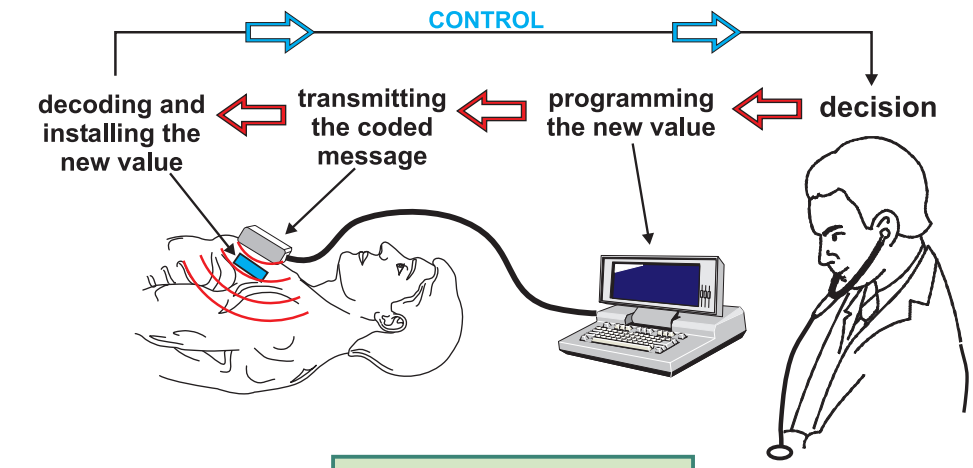
VB = ventricular blanking period during which the detection of all signals is blocked

VRP-U = unblanked ventricular refractory period during which signals can be detected but the lower rate interval cannot be reinitiated. The detected signals in the VRP-U can be used by the pacemaker to control some timing cycles for a variety of functions while the LRI remains unaffected.

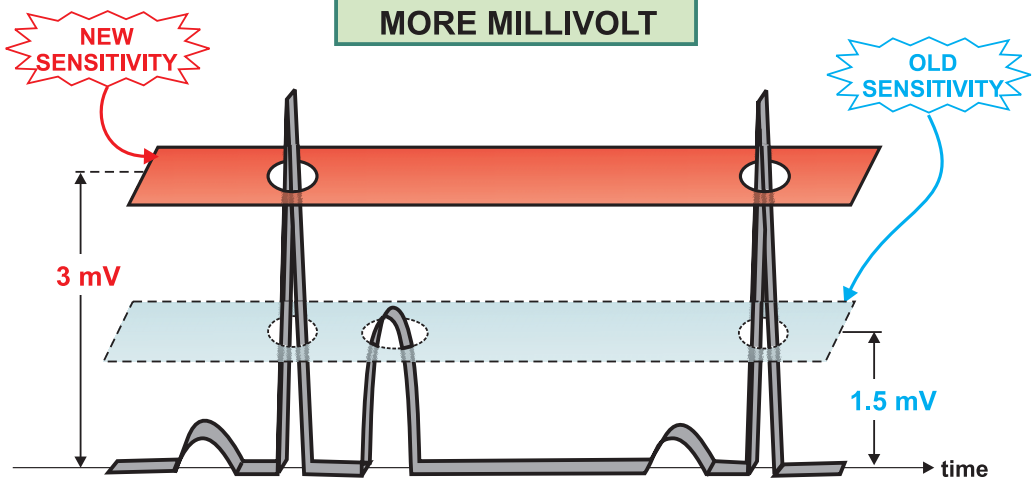
RULE

All refractory periods begin with a blanking period. Blanking periods can be free-standing and need not necessarily be followed by an unblanked refractory period such as VRP-U

PROGRAMMING LOWER SENSITIVITY



LOWER SENSITIVITY means MORE MILLIVOLT



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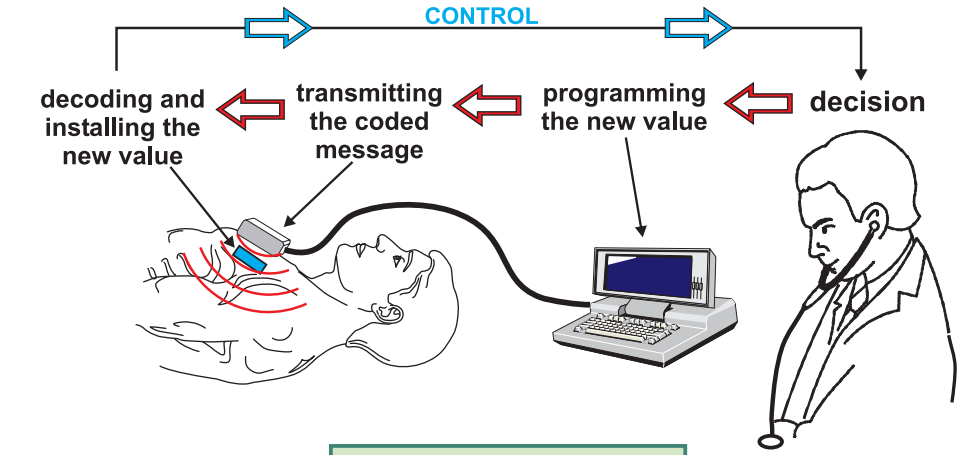
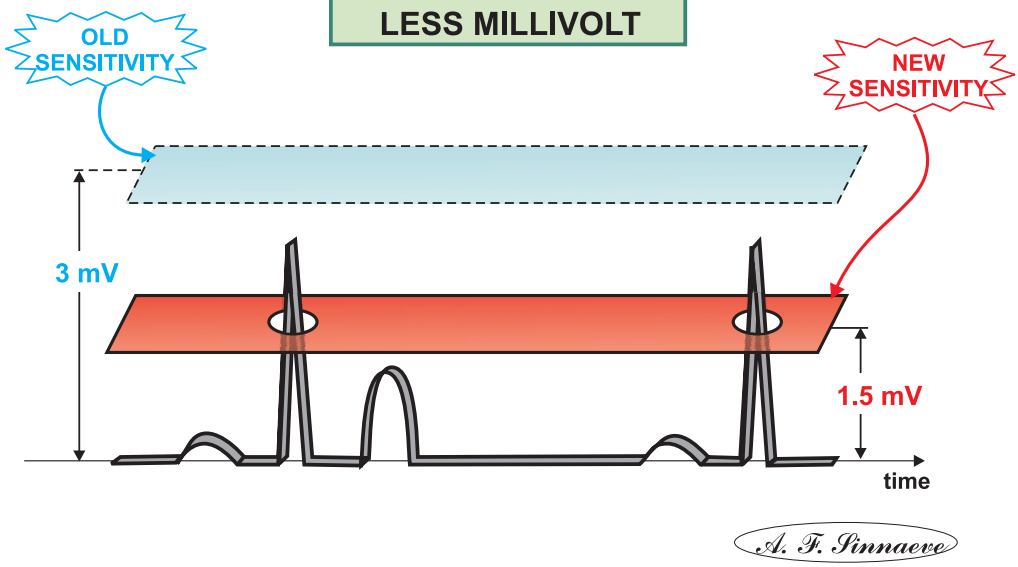
PROGRAMMING HIGHER SENSITIVITY



HIGHER SENSITIVITY means LESS MILLIVOLT



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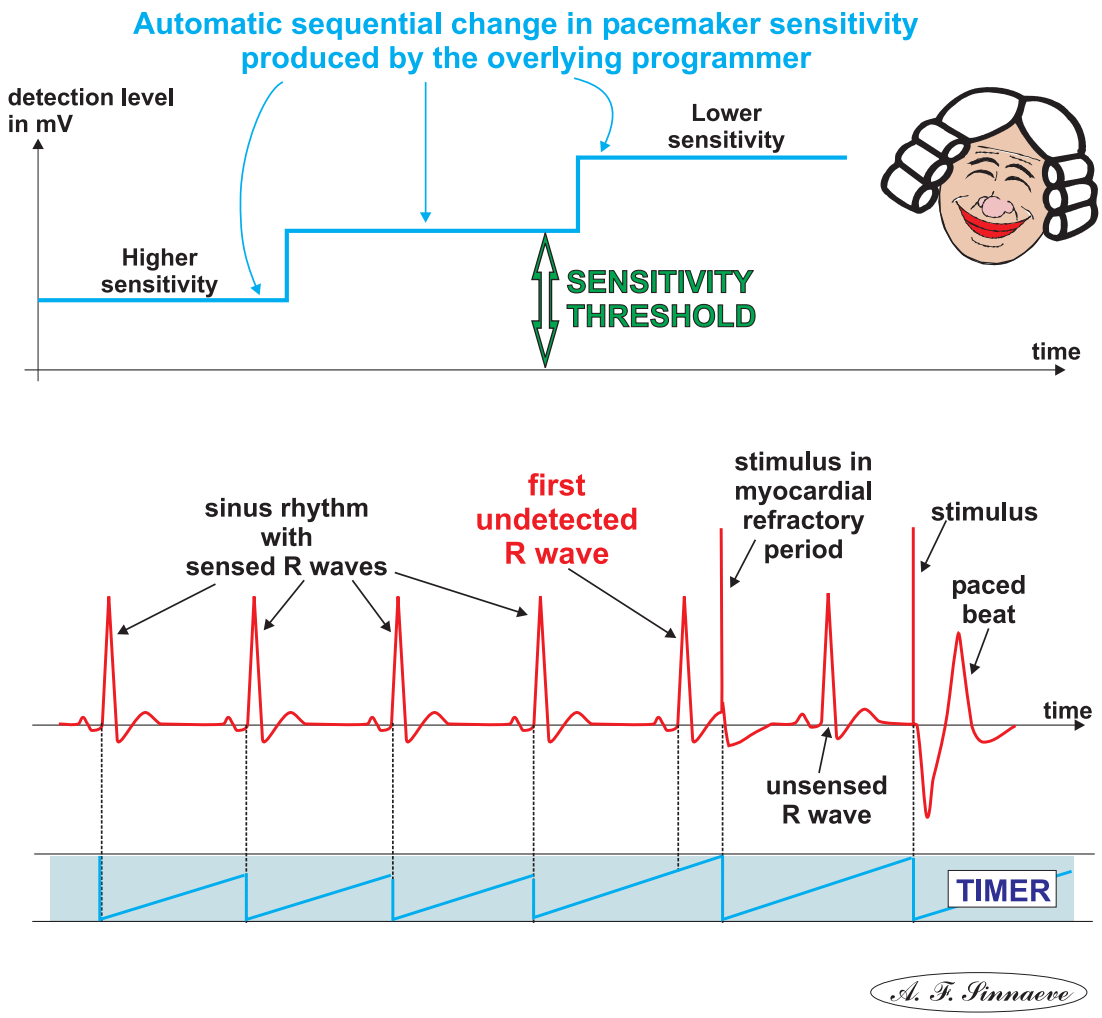
DETERMINATION OF SENSING THRESHOLD



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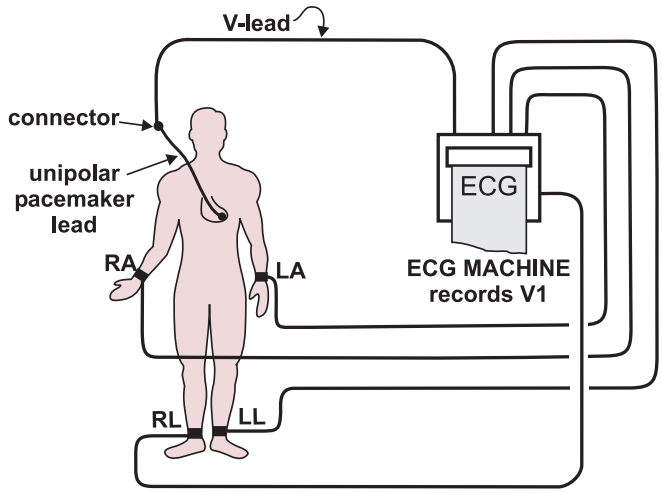
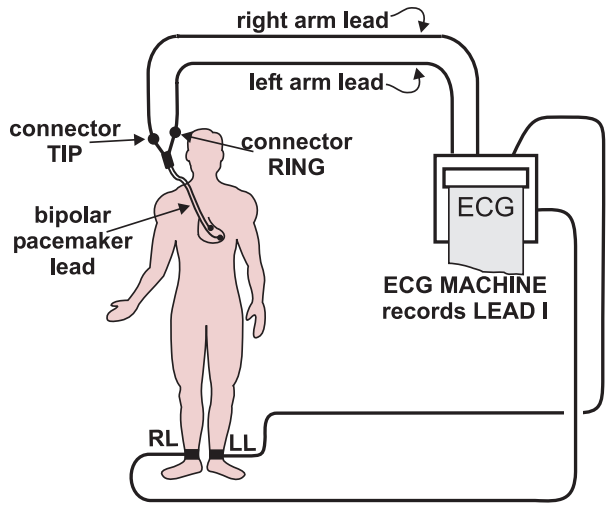
MEASUREMENT OF INTRACARDIAC SIGNALS WITH AN ECG MACHINE AT THE TIME OF IMPLANTATION

UNIPOLAR VENTRICULAR ELECTROGRAM



V-lead of ECG machine connected to the unipolar pacemaker lead

BIPOLAR VENTRICULAR ELECTROGRAM



LEAD 1 records the difference between the left arm and the right arm electrodes which is therefore the difference between the two intracardiac electrodes

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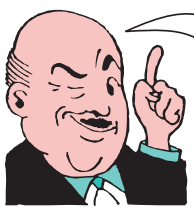
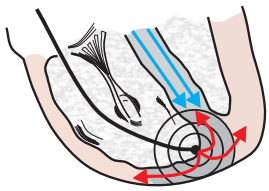
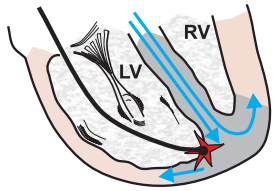


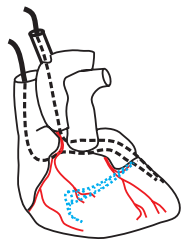
It is important to know that the signal (electrogram) available for sensing by a pacemaker can be easily measured with an ECG machine at the time of implantation. This procedure is sometimes neglected. After implantation, the electrogram can be transmitted noninvasively by telemetry to an appropriate programmer.

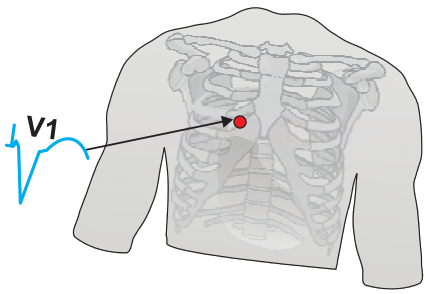


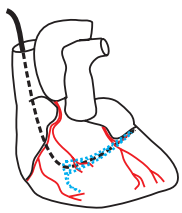


BASIC PACEMAKER ELECTROCARDIOGRAPHY

* ECG of right ventricular pacing : right ventricular apex (RVA) and right ventricular outflow tract (RVOT)
* Axis in the frontal plane with RVA & RVOT pacing
* Myocardial infarct and RV pacing
* Pacing and memory effect
* Patterns of atrial activity with ventricular pacing
* Ventricular fusion
* Ventricular pseudofusion
* Isoelectric ventricular fusion
* Tall R waves in lead V1
* Left ventricular pacing
* Influence of the ECG machine







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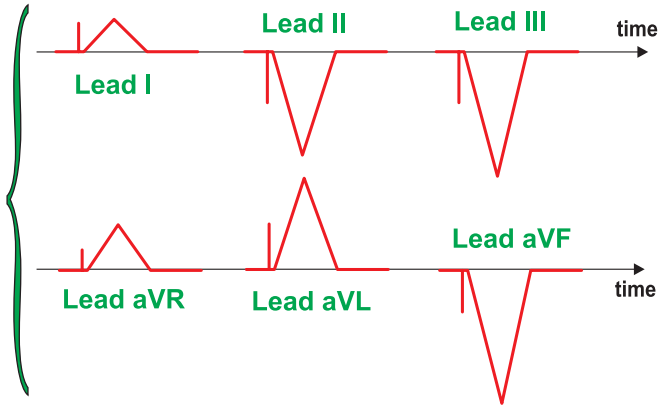
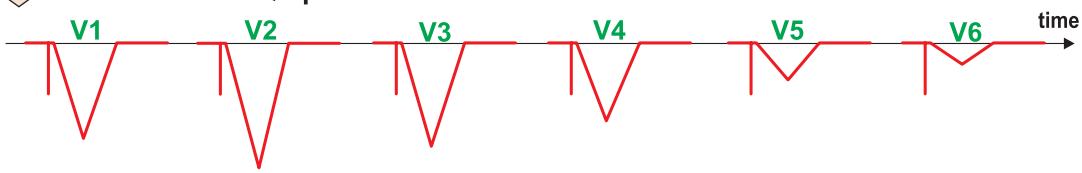
ECG OF RIGHT VENTRICULAR PACING

RV APICAL PACING

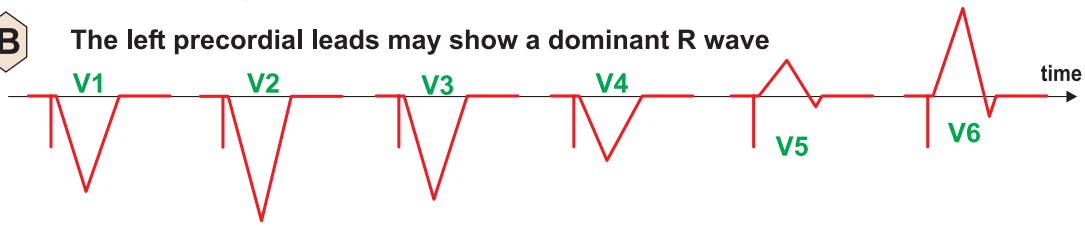
The frontal plane axis is usually left superior . It may also be in the right superior quadrant, where it causes leads I, II & III to be negative and lead aVR to show the largest positive deflection.



A A typical LBBB pattern in the left precordial leads may not be present and all leads show a QS pattern

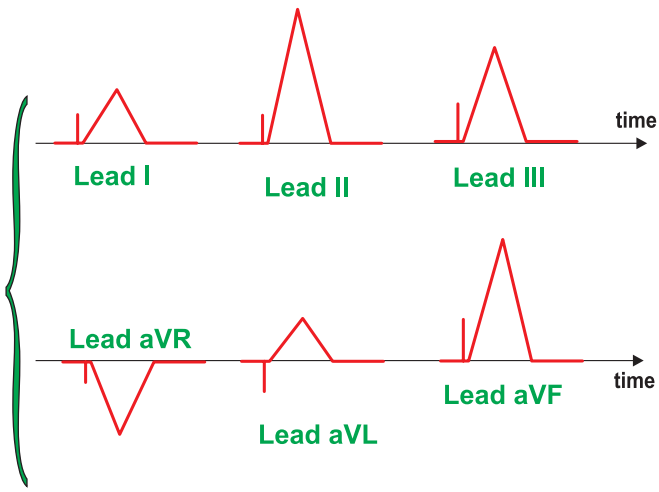


B The left precordial leads may show a dominant R wave



RV OUTFLOW TRACT PACING

The frontal plane axis is normal i.e. as for normally conducted beats. But as the lead moves towards the pulmonary valve, the axis becomes deviated to the right. A qR pattern can occur only in leads I & aVL



The precordial V leads are similar to those with RV apical pacing !

Abbreviation : LBBB = left bundle branch block

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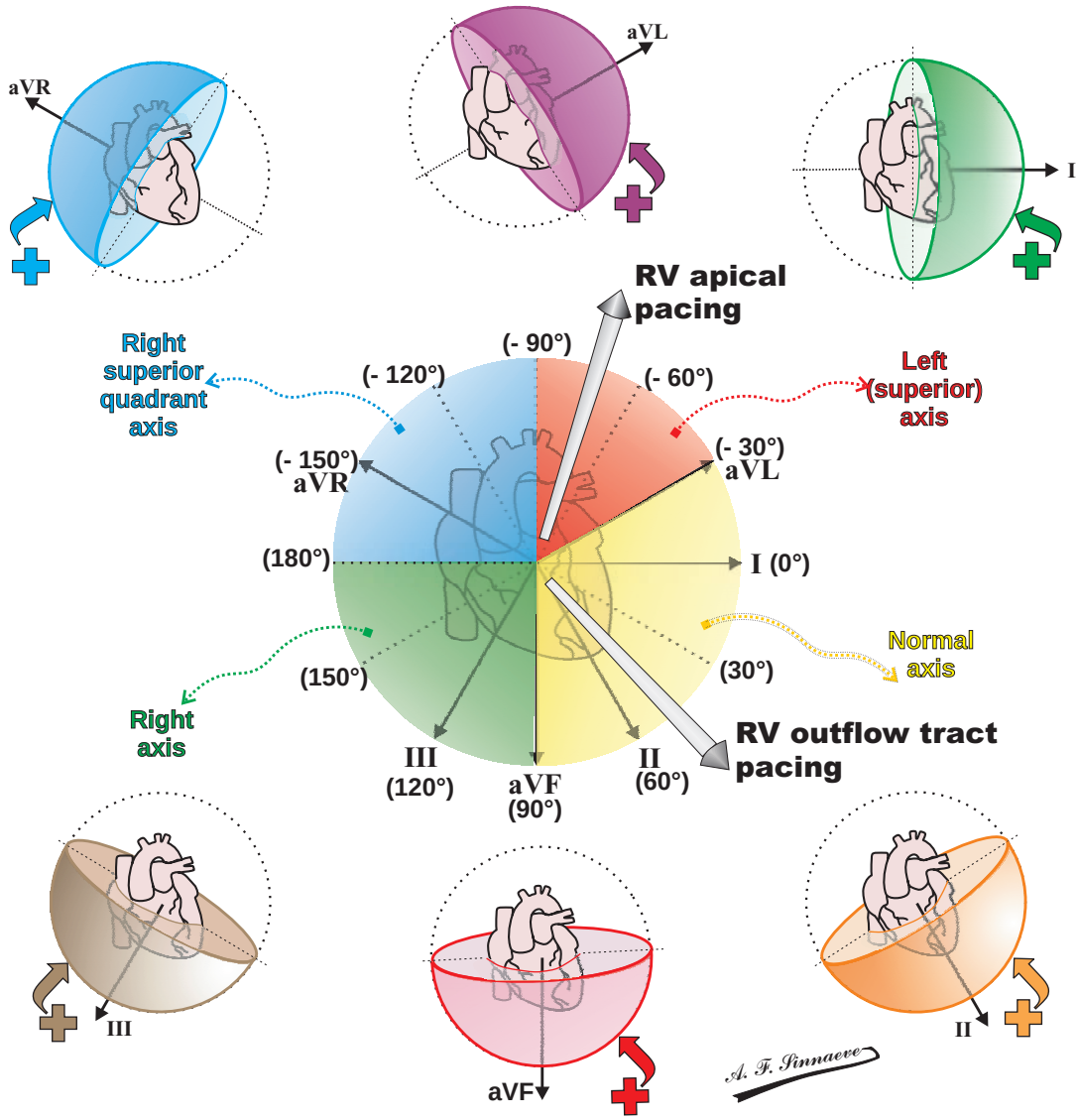
THE MEAN QRS AXIS IN THE FRONTAL PLANE DURING RIGHT VENTRICULAR PACING

During pacing the mean frontal plane QRS axis reflects the site of the pacing !

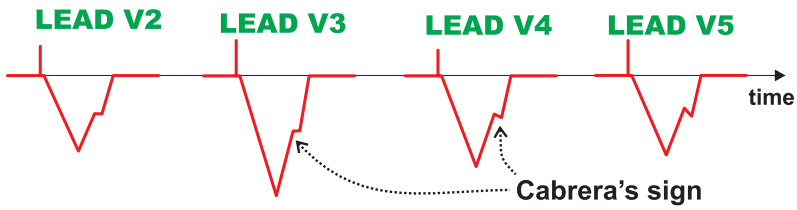


Right ventricular apical pacing activates the inferior part of the heart first. The activation then moves superiorly away from the inferior ECG leads (II, III and aVF) towards the superior leads. The mean frontal plane axis of the paced QRS complex lies superiorly in the left upper quadrant but sometimes in the right superior quadrant. In the latter case, leads I, II and aVF will be negative.
Right ventricular outflow tract pacing, produces a mean frontal plane axis of the paced beat in a direction seen with spontaneous activation of a normal heart: left lower quadrant or “normal” axis. Pacing more superiorly near the pulmonary valve produces right axis deviation: right lower quadrant.

You cannot imagine what little details these cardiologists are looking at ...!

RIGHT VENTRICULAR PACING & OLD ANTERIOR MYOCARDIAL INFARCT

A qR or Qr pattern in leads V5 and V6 often indicates an old anterior myocardial infarct (MI). This pattern may also occur in leads I and aVL.



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A shelf like notch (0.04sec) on the ascending limb of the S wave, called Cabrera's sign, in leads V2 - V5 often indicates an old anterior myocardial infarct.

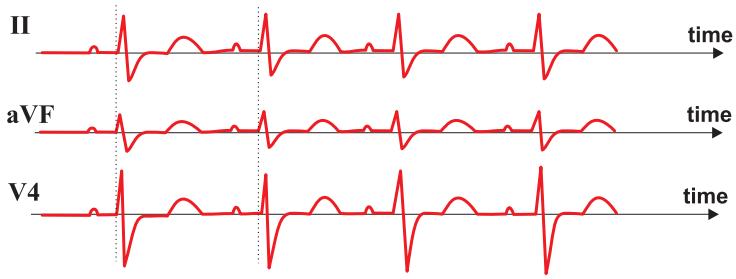
In the case of Cabrera's sign, rule out ventricular fusion beats and retrograde P waves

Wow ! The heart has a memory and therefore a brain. I'm flabbergasted !!!

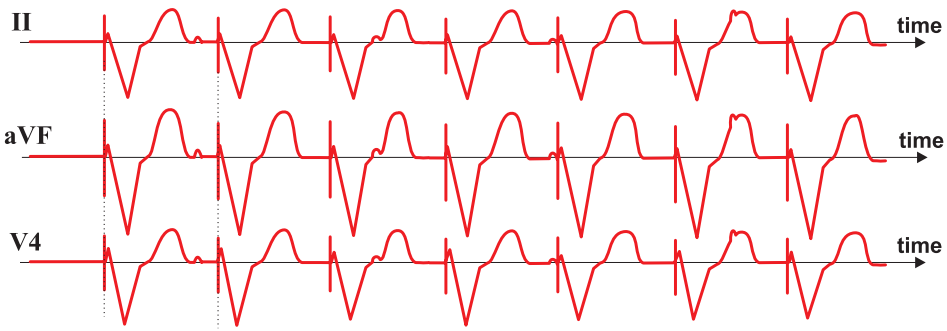
VENTRICULAR PACING & THE MEMORY EFFECT

The underlying ECG cannot be used for the diagnosis of cardiac ischemia because inverted T waves may be due to the memory effect !!!

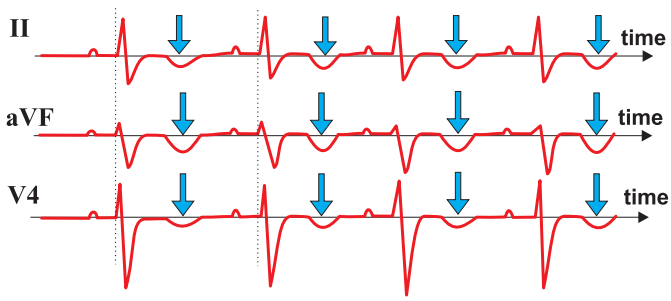
BEFORE PACING



DURING PACING



AFTER PACING



For some time after pacing, the heart seems to remember the abnormal depolarizations.
The duration of the memory effect (negative T waves) depends upon the duration of pacing

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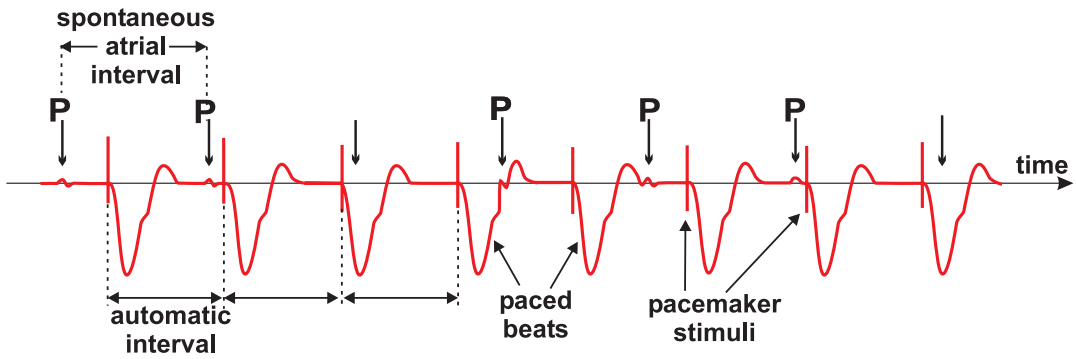
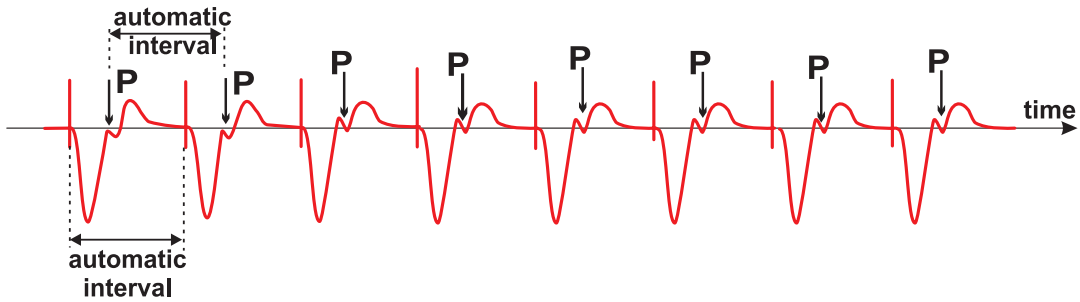
PATTERNS OF ATRIAL ACTIVITY DURING VENTRICULAR PACING

AV dissociation during pacing

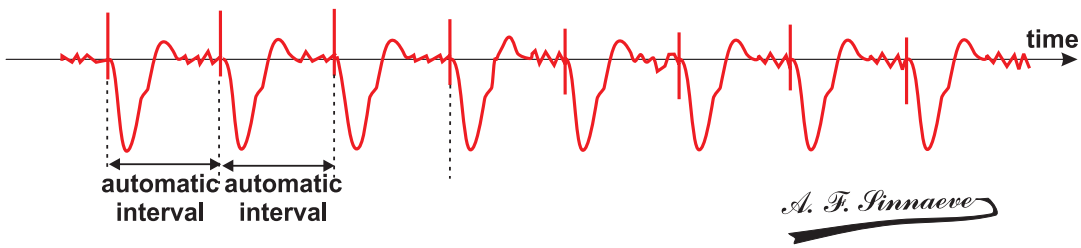
P waves march through the paced QRS complexes



Retrograde ventriculoatrial conduction during pacing



Atrial fibrillation during pacing



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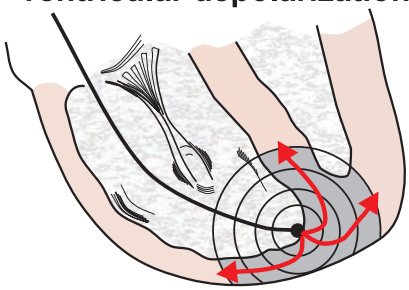
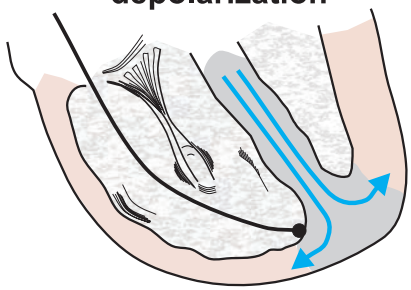
Attention please ! Peculiar QRS complexes may be seen !!!

VENTRICULAR FUSION BEAT

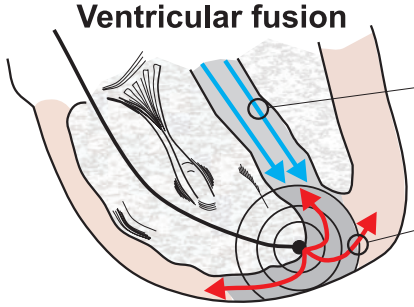
Pacemaker-induced ventricular depolarization



Spontaneous ventricular depolarization

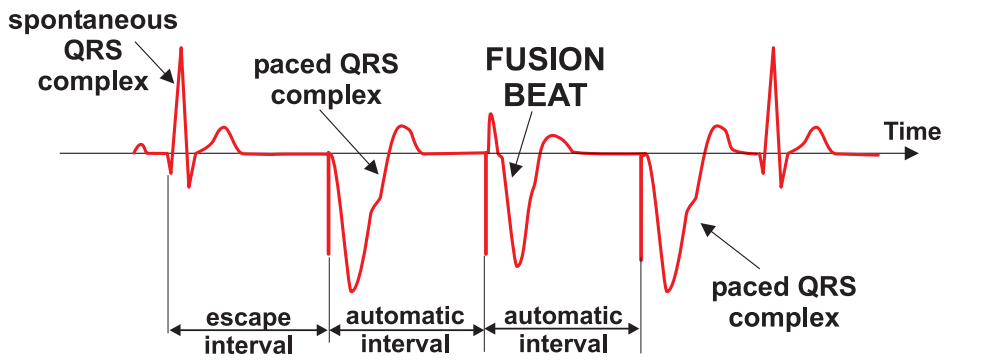


Ventricular fusion



rapid conduction via Purkinje fibers

slower conduction via ordinary myocardial cells



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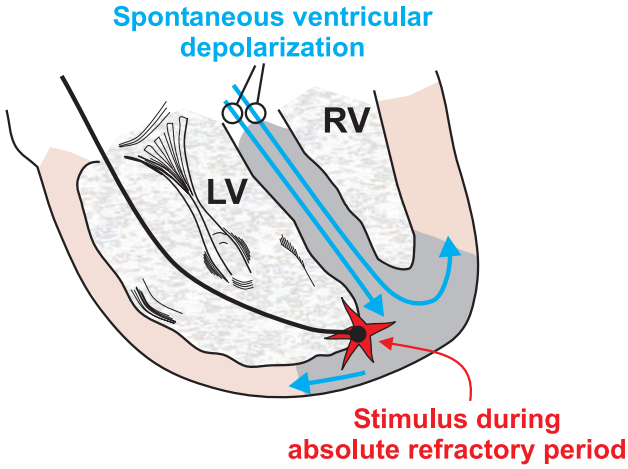
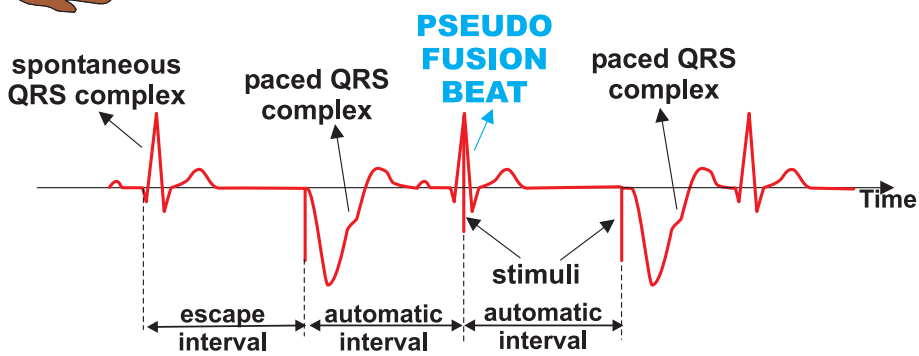
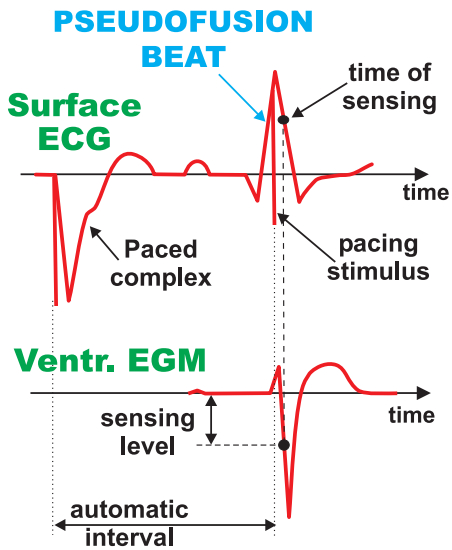
VENTRICULAR PSEUDOFUSION BEAT





The pacemaker senses the intracardiac ventricular electrogram registered between the 2 pacing electrodes. A substantial portion of the surface QRS complex can be inscribed before the intracardiac electrogram generates the required voltage (according to the programmed sensitivity) to inhibit the ventricular channel of a VVI pacemaker. Consequently a VVI pacemaker can deliver a ventricular stimulus within the spontaneous QRS complex (recorded in the surface ECG) before the device has the opportunity to sense the "delayed" electrogram generated in the right ventricle as the depolarization reaches the electrode(s). The PM stimulus can therefore fall in the absolute refractory period of the ventricular myocardium when it cannot depolarize any portion of the ventricles. True ventricular fusion does not occur. In other words depolarization originates from only one focus !



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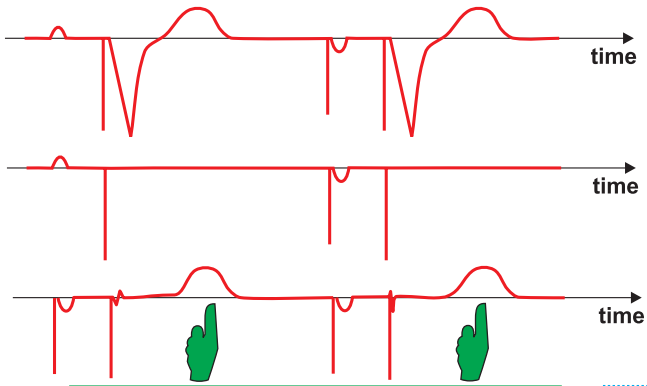
ISOELECTRIC VENTRICULAR FUSION BEATS

Pay attention !!!
The pacemaker may function normally while no QRS complexes are seen on the surface ECG



Normal paced ventricular complexes : a depolarization is followed by a repolarization.

There is loss of capture here !
No depolarization is seen.

ISOELECTRIC FUSION BEATS !
The QRS complex may be so narrow as to resemble a stimulus or even zero !!!

Look at the T wave !!! If there is a repolarization, a depolarization has occurred before !

Note that this appearance is seen in only one ECG lead. To confirm the diagnosis, look at different ECG leads where the QRS complex of the ventricular fusion beat will be visible.

What about the atrium ?
I often see no atrial activity on the monitoring lead.

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You have to realize that the P wave is much smaller than the QRS complex and evaluation of atrial activity in the ECG can sometimes be tricky ! Isoelectric atrial fusion beats may occur but are rare. An isoelectric or flat segment between an atrial and ventricular stimulus can be due to successful atrial capture which is not visible in a particular ECG lead. Again, one must examine other ECG leads to determine the presence of a paced P wave and sometimes take an ECG at double standardization to bring out the P wave

SIGNIFICANCE OF A DOMINANT R WAVE OF PACED VENTRICULAR BEATS IN LEAD V1 DURING TRANSVENOUS PACING

A lead in the LV via a foramen ovale !!!

This would not have happened if a 12 lead ECG had been taken at the time of pacemaker implantation to exclude a dominant R wave of the paced beats in the right-sided chest leads !

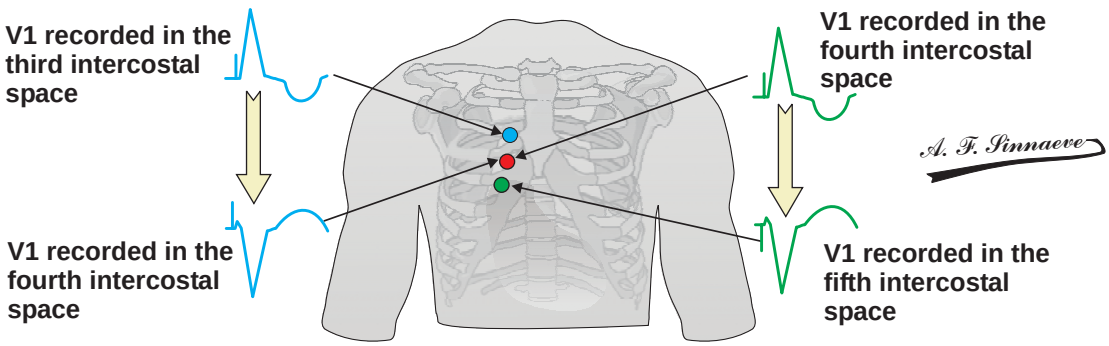
CAUSES OF A DOMINANT R WAVE IN V1

1. Ventricular fusion with spontaneous beats conducted with an RBBB pattern
2. A paced beat in the relative refractory period of the heart resulting in aberrant conduction with RBBB morphology
3. Left ventricular (LV) endocardial stimulation
4. A catheter in the coronary sinus or middle cardiac vein activating the LV epicardial surface
5. A change of electrically induced ventricular depolarization from LBBB to RBBB strongly suggesting catheter perforation of the free wall of RV or the ventricular septum with LV stimulation
6. Uncomplicated RV pacing as shown below

CAUTION

CHECK THE POSITION OF THE LEADS VERY CAREFULLY

* The positivity of V1 depends upon the correct position of the chest (V) electrode
* A dominant R wave may be seen during uncomplicated RV apical pacing



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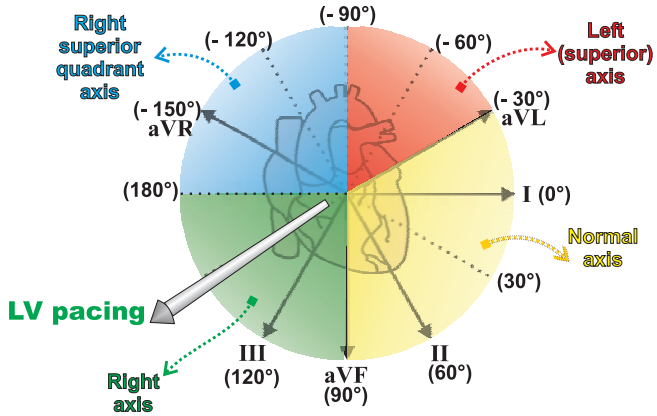
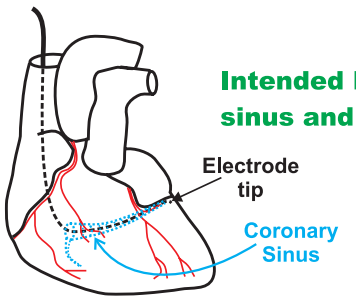
Abbreviations : LBBB = left bundle branch block ; LV = left ventricle ; RBBB = right bundle branch block ; RV = right ventricle ; **Foramen ovale** is a potential communication from the right atrium to the left atrium that may allow passage of a pacemaker lead from the right atrium to the left one and then to the left ventricle. The lead in the left ventricle may appear to be in the right ventricle on standard fluoroscopy.

LEFT VENTRICULAR PACING



The mean frontal plane axis of the paced beat is directed to the right lower quadrant (right axis deviation). There is a characteristic tall R wave in lead V1 to at least V3 and often further into the left precordial leads.



Intended LV pacing via coronary sinus and coronary vein

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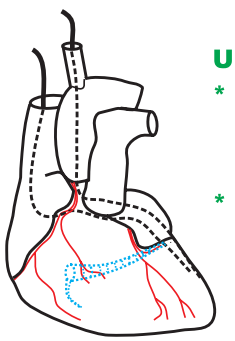
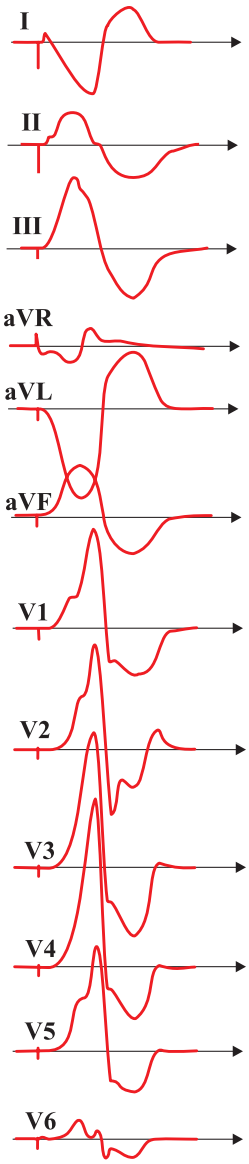


Unintended LV pacing :

* **Passage of lead into LV via patent foramen ovale (from right atrium to left atrium and LV)**
* **Via subclavian artery (across the aortic valve) mistaken for the subclavian vein**



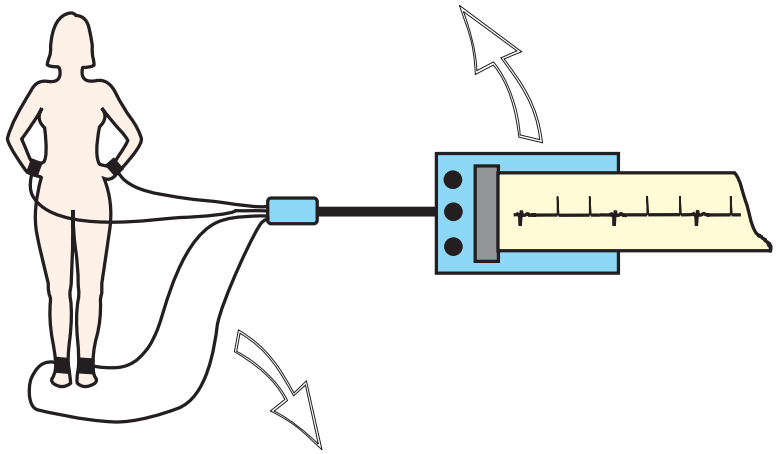
DANGER

A lead within the LV cavity (endocardial site) may cause thrombus formation, cerebral emboli and stroke.
The diagnosis of LV endocardial lead misplacement should be suspected if there is a tall R wave at least in leads V1 to V3 and sometimes further in the left-sided precordial leads. The definitive diagnosis requires echocardiography especially by the transesophageal method.

INFLUENCE OF THE ECG-MACHINE

I think there is no capture here !
All I see are some ventricular escape beats...

Surface ECG shown on saturated ECG machine



Same ECG with properly adjusted ECG machine

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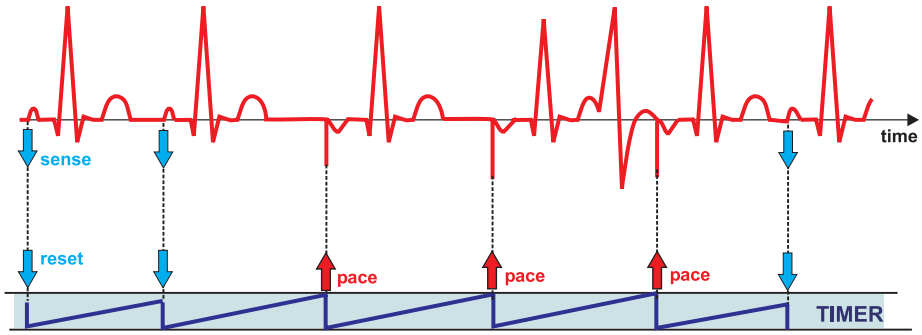
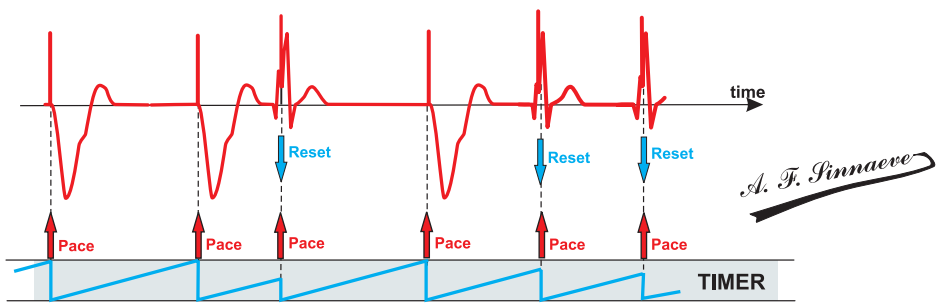
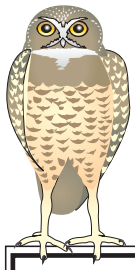
In some ECG machines, when the automatic gain control (AGC) is not activated, the input circuit may be saturated by large unipolar stimuli. During this saturation the machine is unable to detect any small signals and it is impossible to see if the stimuli capture the heart or not.



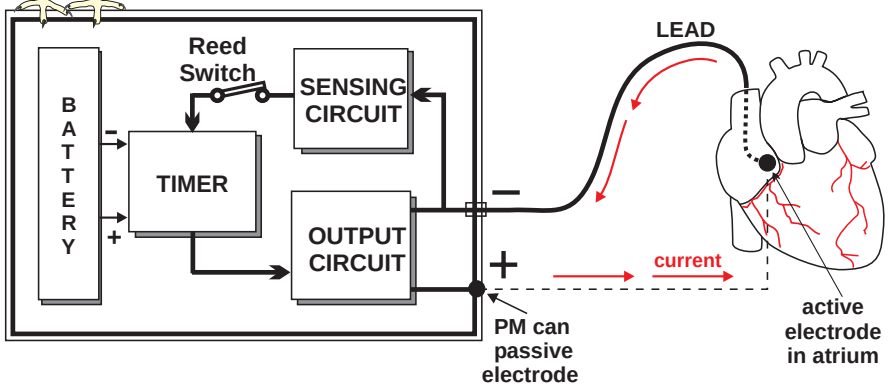
OTHER SINGLE CHAMBER PACEMAKERS

* The AAI pacing mode
* The VVT pacing mode

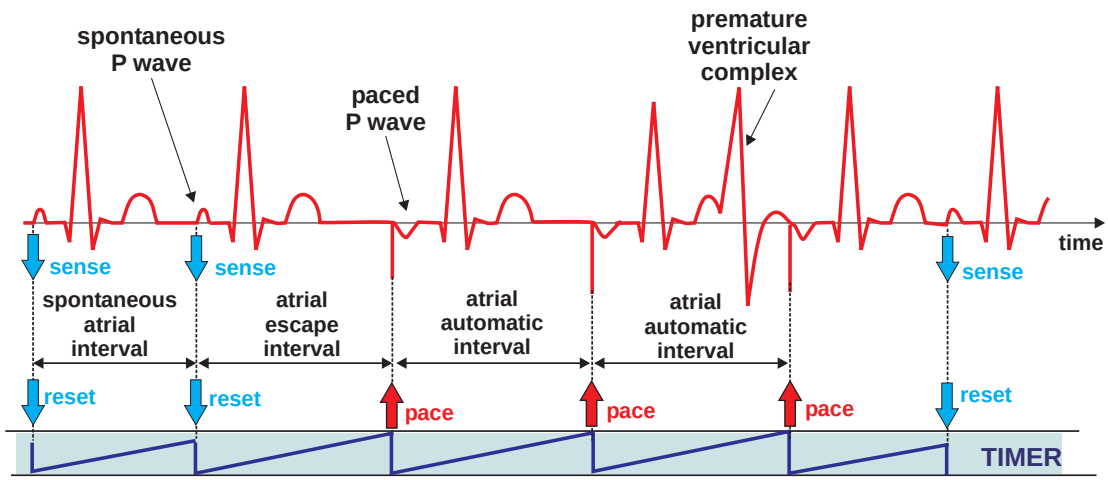




THE AAI PACEMAKER



Compared to the VVI pacemaker the SENSITIVITY should be higher (i.e. a lower number in mV) because P waves have lower amplitudes than R waves



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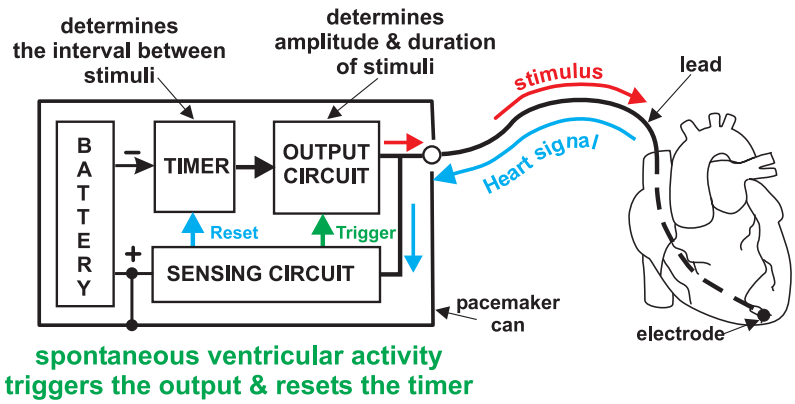
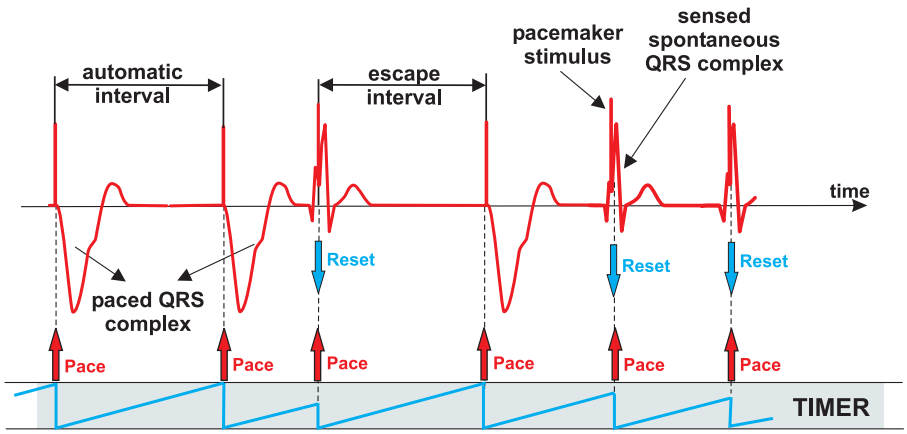
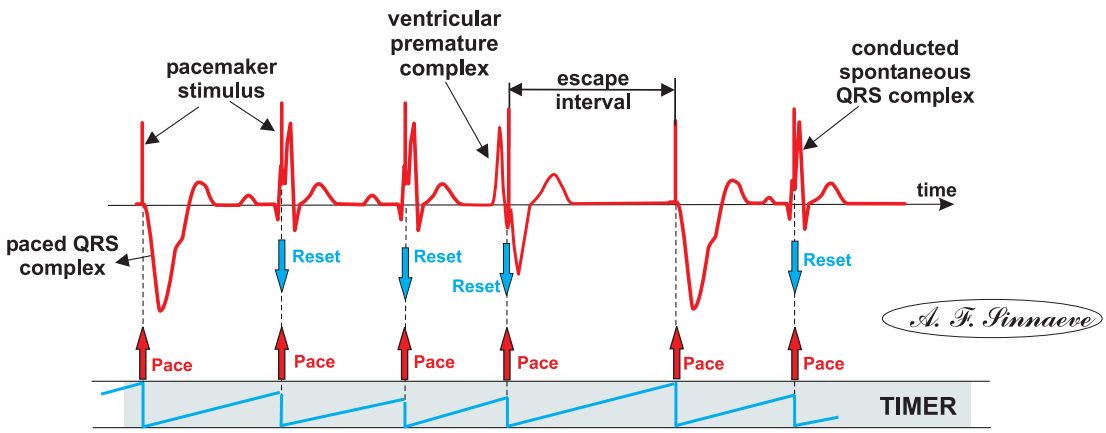
THE VVT MODE



spontaneous ventricular activity
triggers the output & resets the timer





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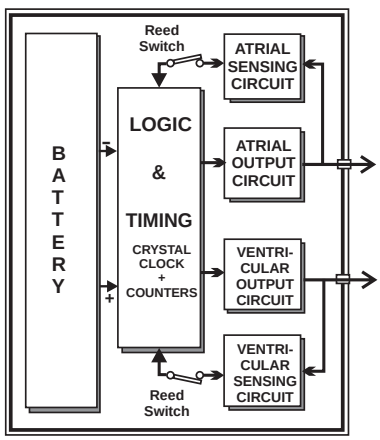
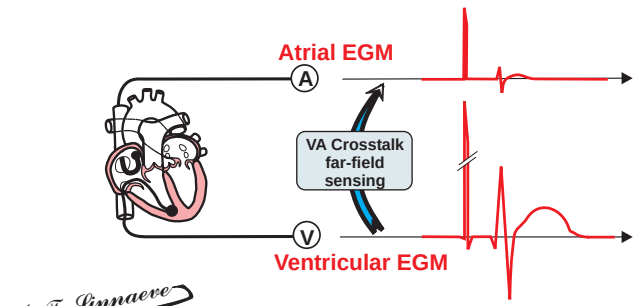
DDD PACEMAKERS - BASIC FUNCTIONS

* Block diagram of dual chamber pacemakers
* 4 fundamental timing cycles - part 1
* 4 fundamental timing cycles - part 2
* Functions of the postventricular atrial blanking period
* Pacemaker with 4 timing cycles at work
* Three-letter-code for dual chamber pacemakers
* Manifestations of crosstalk
* Fifth timing cycle : postatrial ventricular blanking
* Postatrial ventricular blanking
* Addition of a 6thcycle. Diagram
* Ventricular safety pacing (VSP)
* VSP and crosstalk
* ECG with VSP
* VSP with VPCs
* Testing for crosstalk
* Prevention of crosstalk
* Sensing the terminal part of QRS





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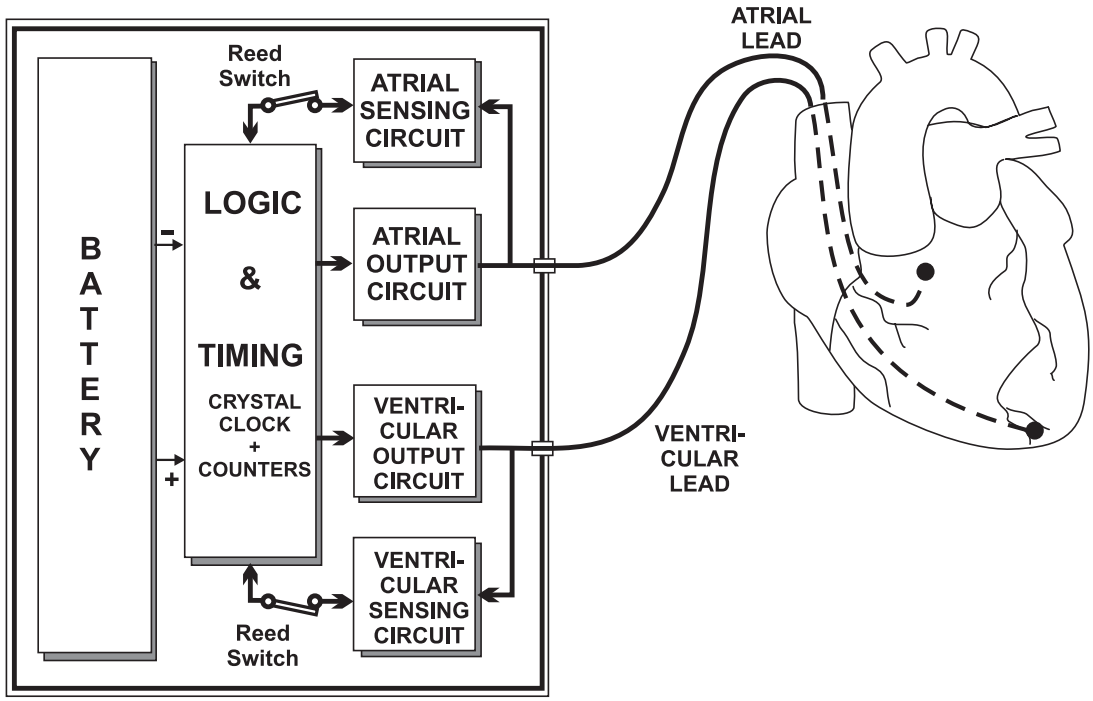
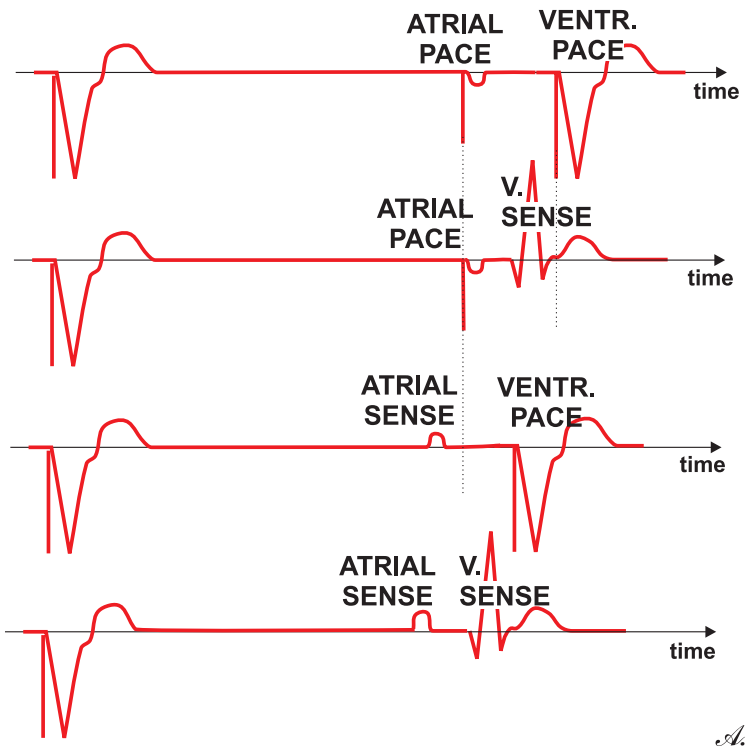
DUAL CHAMBER PACING





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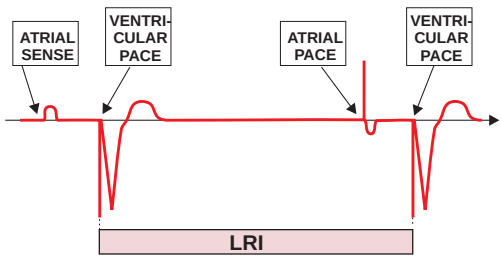
THE 4 FUNDAMENTAL TIMING CYCLES OF A DDD PACEMAKER

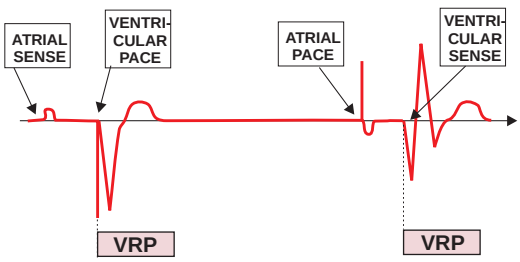
PART 1 : THE VENTRICULAR CHANNEL

FUNDAMENTAL TIMING CYCLE 1
LRI = LOWER RATE INTERVAL



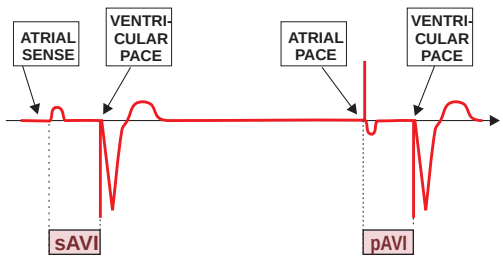
Longest interval between a paced or sensed ventricular event and the succeeding ventricular paced event without intervening sensed events

FUNDAMENTAL TIMING CYCLE 2
VRP = VENTRICULAR REFRACTORY PERIOD



Interval initiated by a ventricular event during which a new lower rate interval (LRI) cannot be initiated

FUNDAMENTAL TIMING CYCLE 3
AVI = ATRIOVENTRICULAR INTERVAL



Interval between an atrial event and the scheduled delivery of a ventricular stimulus

sAVI = after a sensed atrial event
pAVI = after a paced atrial event

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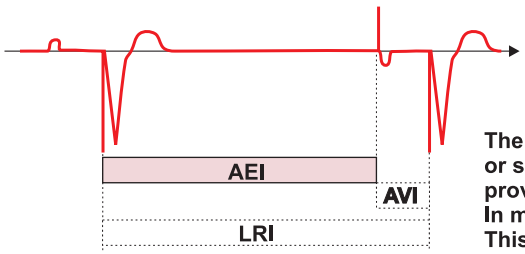
*** the electronic analog of the P-R interval**
*** the atrial channel is refractory during the AV interval (a new AV delay cannot be initiated when one is already in progress)**

THE 4 FUNDAMENTAL TIMING CYCLES OF A DDD PACEMAKER

PART 2 : THE ATRIAL CHANNEL

DERIVED : AEI = ATRIAL ESCAPE INTERVAL

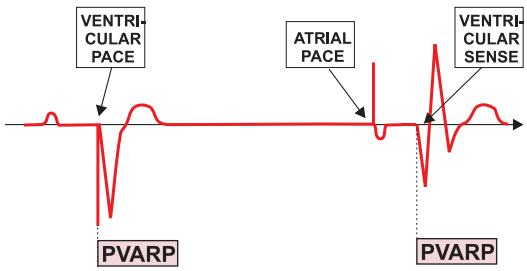


AEI = LRI - AVI

With AVI = AV interval
and LRI = lower rate interval

The atrial escape interval is the interval between a paced or sensed ventricular event to the succeeding atrial stimulus provided there are no intervening sensed events.
In most pacemakers lower rate timing is ventricular-based. This means that the LRI starts with a ventricular event. In such a system the atrial escape interval is always constant.

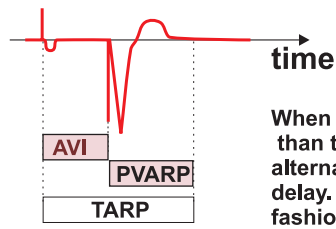
FUNDAMENTAL TIMING CYCLE 4
PVARP = POSTVENTRICULAR REFRACTORY PERIOD



Interval after a ventricular paced or sensed event during which an atrial event cannot initiate a new AVI

* avoids inappropriate atrial sensing of ventricular events
* eliminates sensing of retrograde P waves from ventriculoatrial conduction

DERIVED : TARP = TOTAL ATRIAL REFRACTORY PERIOD



TARP = AVI + PVARP

When the interval between 2 consecutive P waves becomes shorter than the TARP, tracking of every P wave becomes impossible. Every alternate P wave will fall in the PVARP where it cannot initiate an AV delay. The pacemaker will thus respond to the P waves in a 2 : 1 fashion. This form of upper rate response is called 2 : 1 block and the TARP effectively becomes the upper rate interval.

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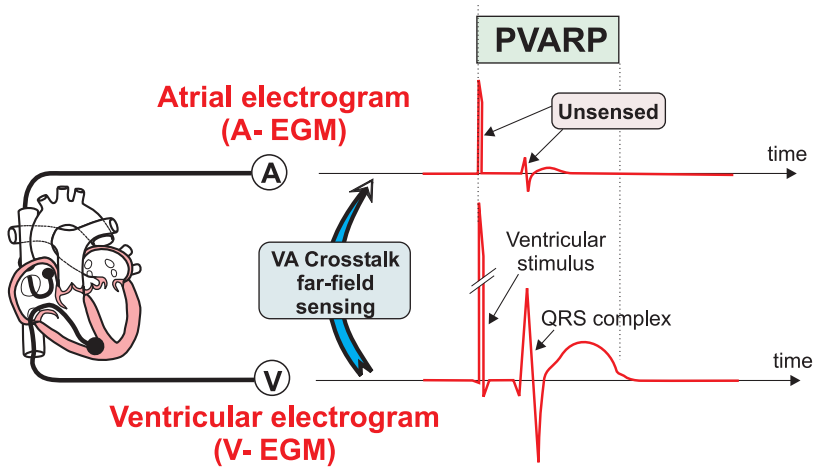
All examples of pacemaker timing in this book involve ventricular-based lower rate timing, unless otherwise specified.

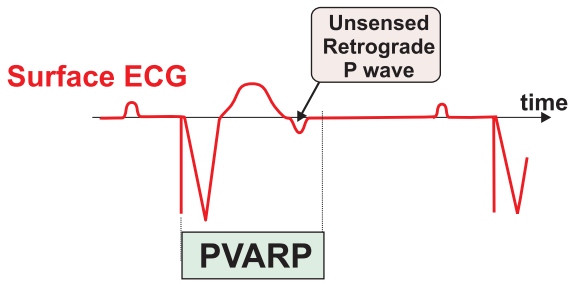
FUNCTIONS OF THE POSTVENTRICULAR ATRIAL REFRACTORY PERIOD (PVARP)

PVARP Interval after a ventricular paced or sensed event during which the atrial channel is refractory !!!

1. Avoids the inappropriate atrial sensing of ventricular events (ventricular stimuli, QRS complexes, aberrant T waves)



2. Avoids sensing of retrogradely conducted P waves



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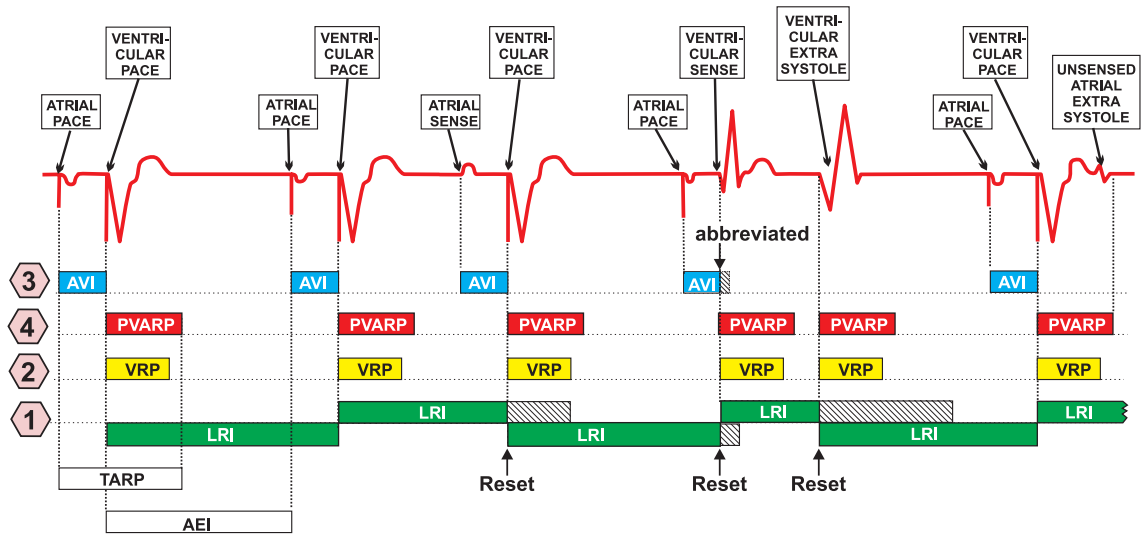
DDD PACEMAKER WITH 4 TIMING CYCLES AT WORK



FUNDAMENTAL INTERVALS

1. LRI = Lower Rate Interval
2. VRP = Ventricular Refractory Period
3. AVI = Atrioventricular Interval
4. PVARP = Postventricular Atrial Refractory Period

DERIVED INTERVALS

TARP = Total Atrial Refractory Period
= AVI + PVARP
= Upper Rate Interval
= URI

AEI = Atrial Escape Interval
= LRI - AVI

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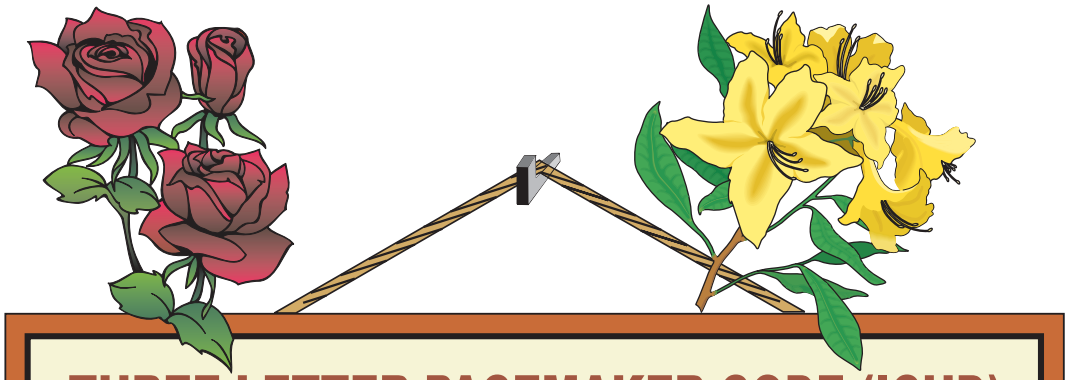

THREE-LETTER PACEMAKER CODE (ICHD)

POSITION	1st	2nd	3rd
CATEGORY	CHAMBER(S) PACED	CHAMBER(S) SENSED	MODE OF RESPONSE
LETTERS	V = VENTRICLE A = ATRIUM S = SINGLE D = DOUBLE (V & A)	V = VENTRICLE A = ATRIUM S = SINGLE O = NONE D = DOUBLE (V & A)	T = TRIGGERED I = INHIBITED O = NONE D = DOUBLE inhibited & triggered

EXAMPLE :

DDD = a pacemaker pacing and sensing in both the atrium and the ventricle; pacing is inhibited in the atrial channel by sensed ventricular or atrial activity and is inhibited in the ventricular channel by ventricular activity but triggered by sensing atrial activity.

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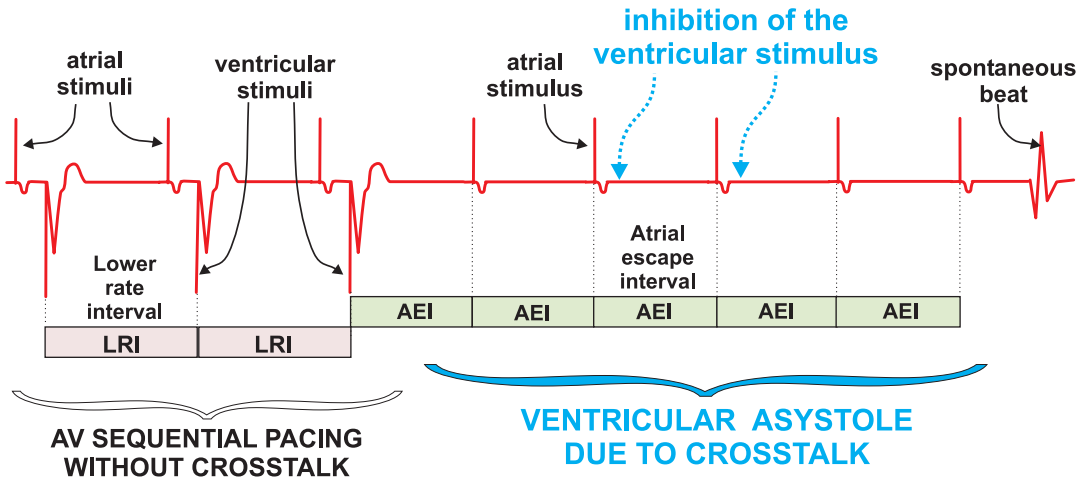
MANIFESTATIONS of AV CROSSTALK

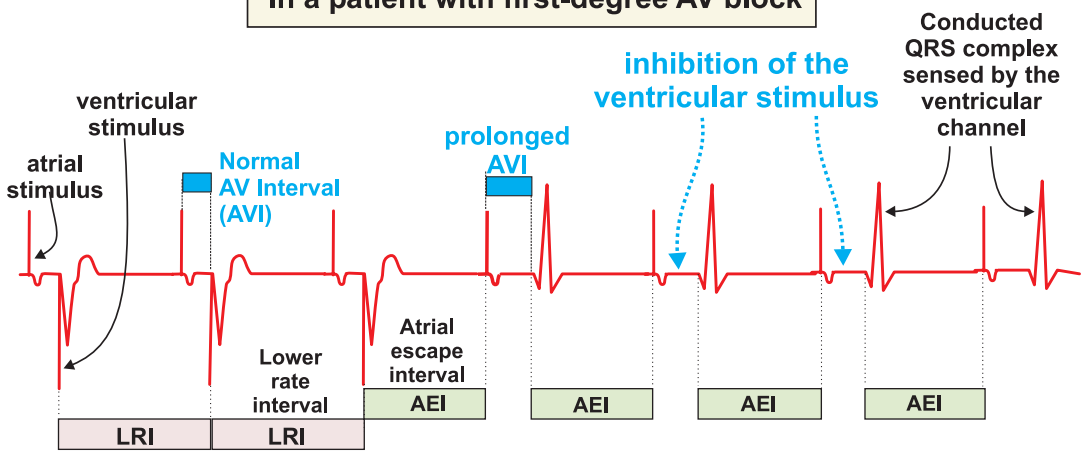
SENSING OF THE ATRIAL STIMULUS BY THE VENTRICULAR CHANNEL

During crosstalk, the atrial pacing rate increases if the ventricular channel does not sense any QRS complexes either because they are absent or they fall in the ventricular refractory period

In a patient without underlying spontaneous rhythm



In a patient with first-degree AV block



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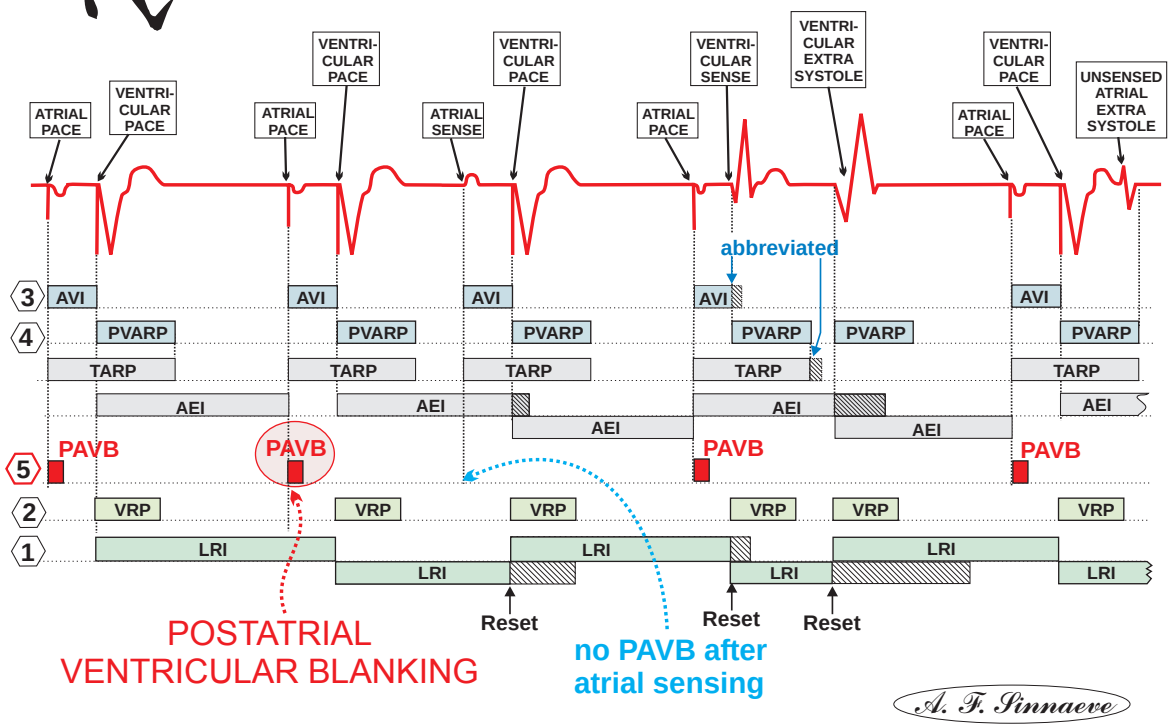
ADDITION OF A FIFTH TIMING CYCLE TO A SIMPLE DDD PACEMAKER TO PREVENT AV CROSSTALK

Stop the influence of the atrial stimulus upon the ventricular channel !!



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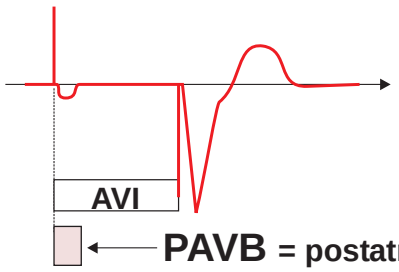
PAVB = a brief interval (10 to 60 ms) initiated by an atrial output pulse when the ventricular channel is switched off and cannot sense.
PAVB is often programmable

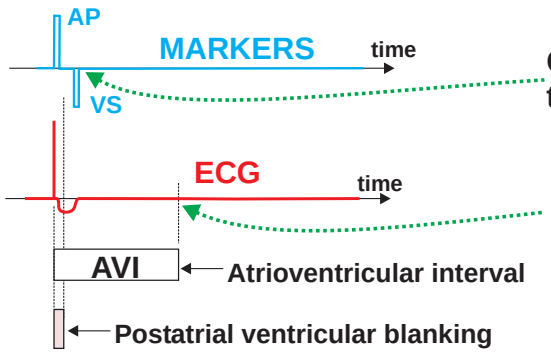
Abbreviations : AEI = atrial escape interval ; AVI = atrioventricular interval ; LRI = lower rate interval ; PAVB = post-atrial ventricular blanking ; PVARP = postventricular atrial refractory period ; TARP = total atrial refractory period ; VRP = ventricular refractory period

THE POSTATRIAL VENTRICULAR BLANKING PERIOD



A brief ventricular interval initiated by an atrial output pulse when the ventricular sensing amplifier is switched off. It prevents AV crosstalk or sensing of the atrial stimulus by the ventricular channel

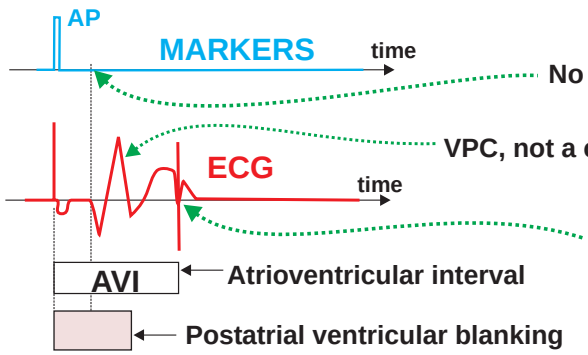
WHEN PAVB IS TOO SHORT : OVERSENSING



Crosstalk : ventricular oversensing of the voltage generated by the atrial pulse

Inhibition of the ventricular pulse "self-inhibition"

WHEN PAVB IS TOO LONG : UNDERSENSING



No ventricular sensing during PAVB

VPC, not a conducted beat from the paced P wave

DANGEROUS : stimulus on T wave

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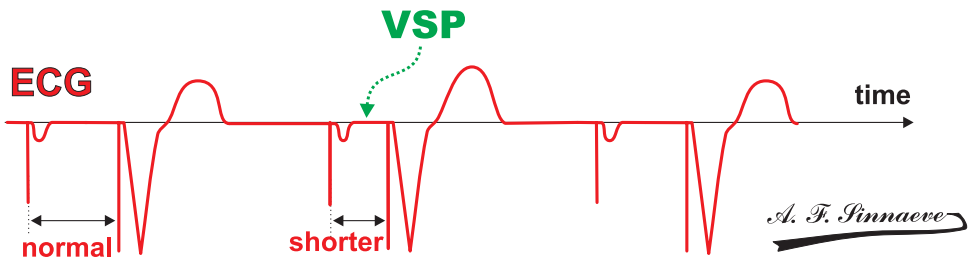
Abbreviations : AVI = atrioventricular interval ; AP = atrial pace ; VS = ventricular sense

THE ADDITION OF THE 6th CYCLE : VSP or VENTRICULAR SAFETY PACING

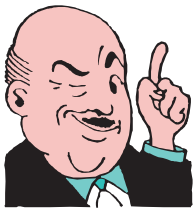
If this happens, the consequences of crosstalk can be prevented by adding a 6th timing cycle often called the VSP period in the first part of the AV delay. A signal sensed in the VSP will trigger a premature stimulus at the end of the VSP. In this way ventricular inhibition by crosstalk cannot occur....

The postatrial ventricular blanking period does not always prevent crosstalk !?

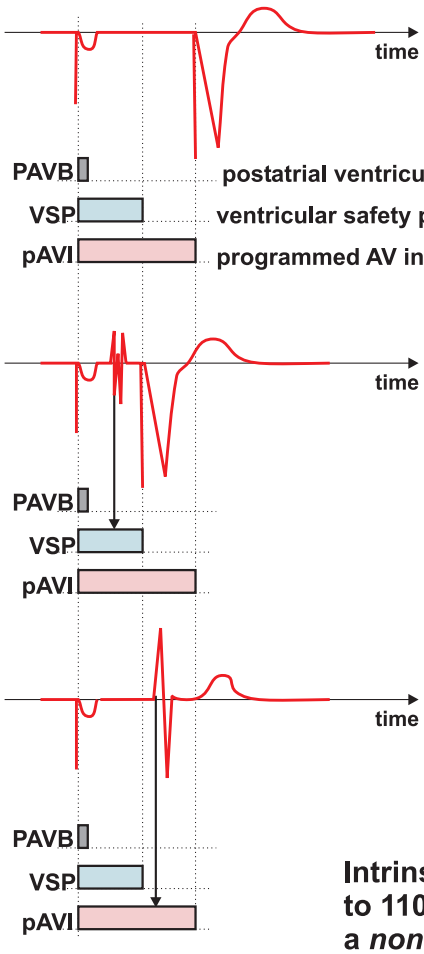
Let me show you !



VSP does not prevent crosstalk.
It simply prevents its consequences !



VENTRICULAR SAFETY PACING



No spontaneous conduction, no crosstalk, no interference : stimulation at the end of the programmed AV interval

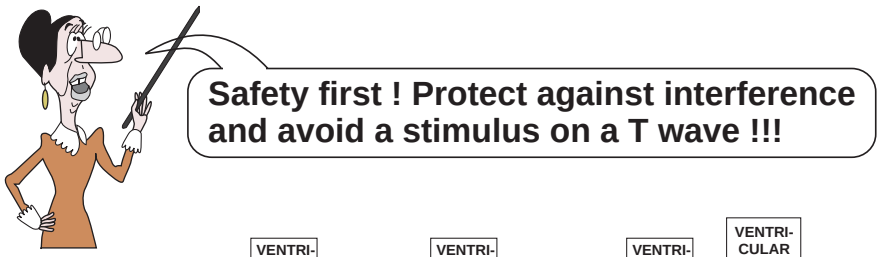
Interference (or early QRS) during the VSP window (beyond the PAVB) results in a committed ventricular stimulus at the end of that window and a characteristic shortening of the AV interval

Normal inhibition of the ventricular channel by a conducted QRS

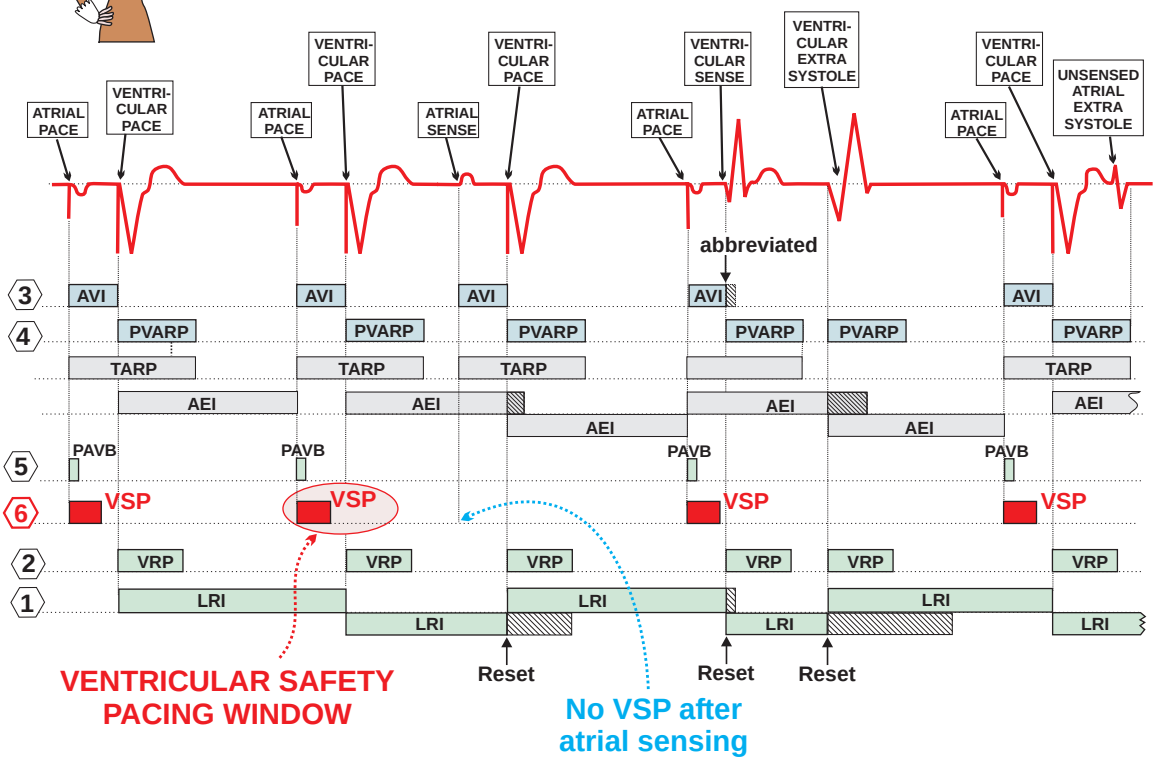
Intrinsic P-R intervals are usually longer than 100 to 110 ms, therefore the VSP window is often called a *non-physiologic AV delay*

A. F. Sinnaeve

ADDITION OF A SIXTH TIMING CYCLE TO A SIMPLE DDD PACEMAKER TO PREVENT THE CONSEQUENCES OF AV CROSSTALK



Safety first ! Protect against interference and avoid a stimulus on a T wave !!!



Ventricular Safety Pacing Window : by convention the VSP starts at the time of the atrial stimulus and its duration is usually 100 to 110 ms. The PAVB period, also activated by the atrial stimulus, occupies the initial portion of the VSP. Ventricular sensing cannot occur during this blanking period. Therefore ventricular sensing can occur in the VSP only after completion of the relatively short PAVB period.

ABBREVIATIONS : AVI = AV interval; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; AEI = atrial escape interval; PAVB = postatrial ventricular blanking; VSP = ventricular safety pacing window; VRP = ventricular refractory period; LRI = lower rate interval

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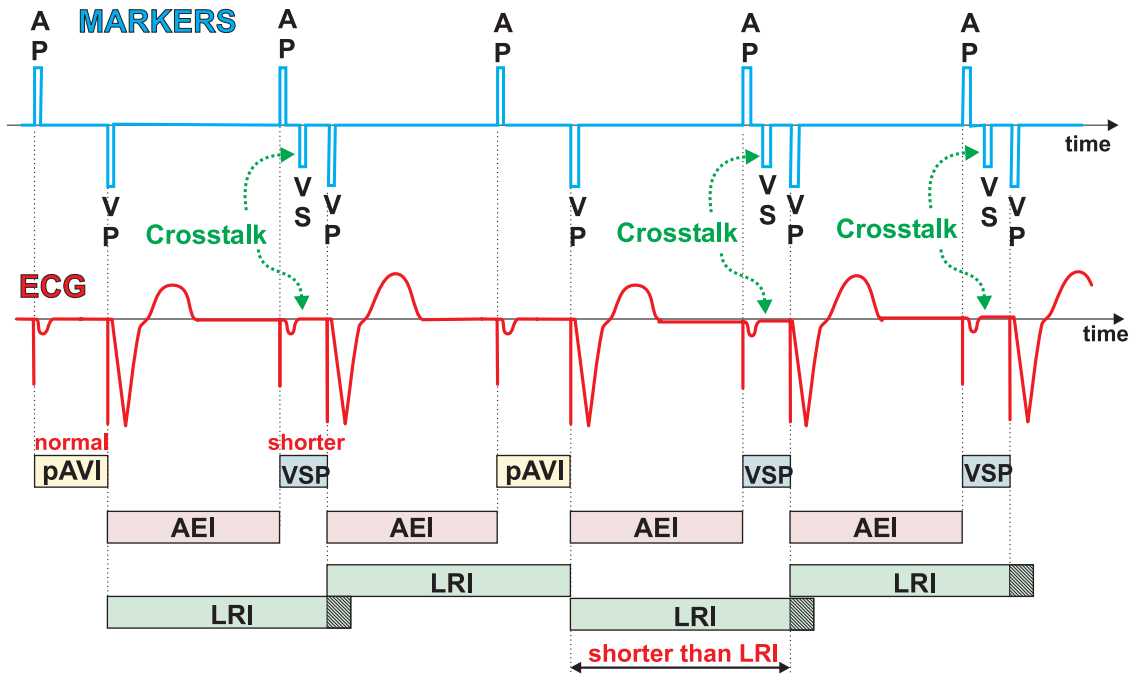
ECG PATTERNS of VENTRICULAR SAFETY PACING
Intermittent crosstalk during DDD pacing



CONSEQUENCES OF CROSSTALK* :
> the paced AV delay (Ap-Vp) shorter than expected
> interval between consecutive ventricular stimuli shorter than expected
(* In a system with ventricular-based lower rate timing)

ABBREVIATIONS : Ap = atrial paced event; Vp = ventricular paced event; Vs = ventricular sensed event; pAVI = paced atrioventricular interval; VSP = ventricular safety pacing window; AEI = atrial escape interval; LRI = lower rate interval

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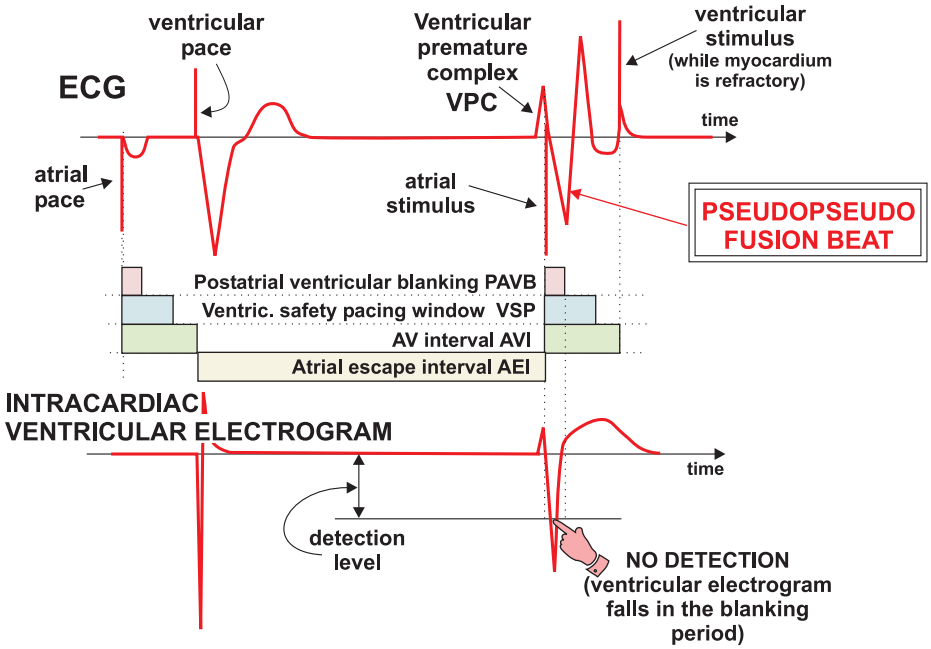
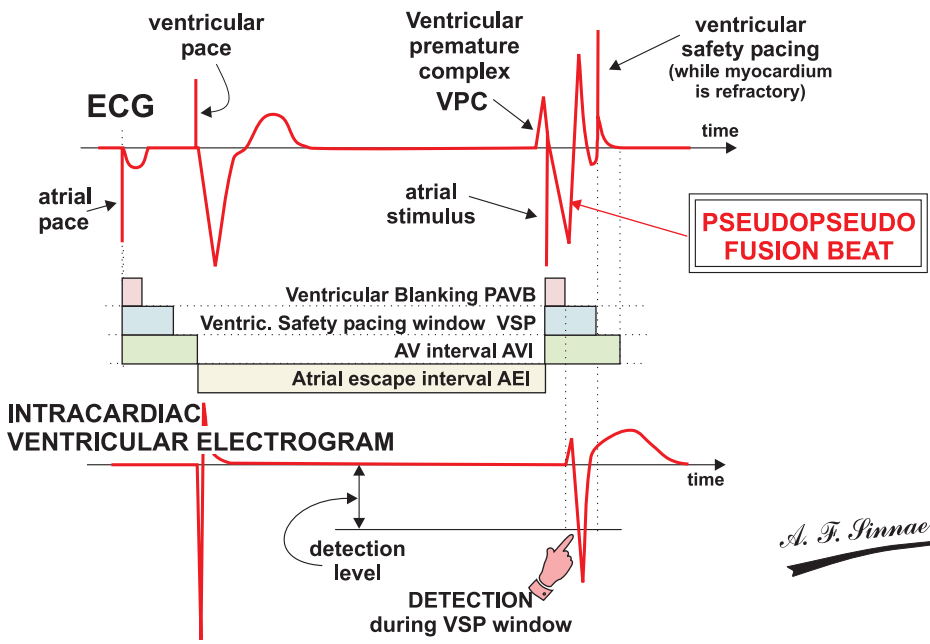
MANIFESTATIONS of VENTRICULAR SAFETY PACING with VENTRICULAR PREMATURE COMPLEXES

UNSENSED QRS COMPLEX



SENSED QRS COMPLEX



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TESTING FOR AV CROSSTALK

ESTABLISH CONTINUAL ATRIAL AND VENTRICULAR PACING : AVOID COMPETITION

♣ Set the lower rate above the patient's own spontaneous rate

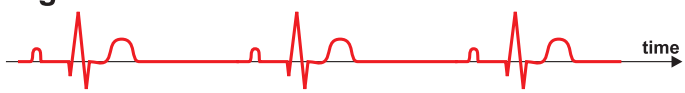
♠ Shorten the AV delay to less than the spontaneous PR interval

UNVEIL POTENTIAL PROBLEMS :

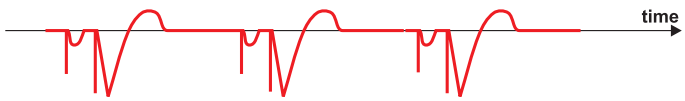
♦ Reprogram the atrial output to its maximal value (voltage and/or pulse duration)

♥ Reprogram the ventricular sensitivity to its most sensitive setting

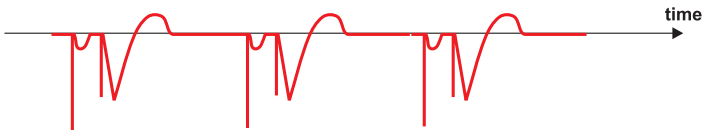
Patient's original ECG



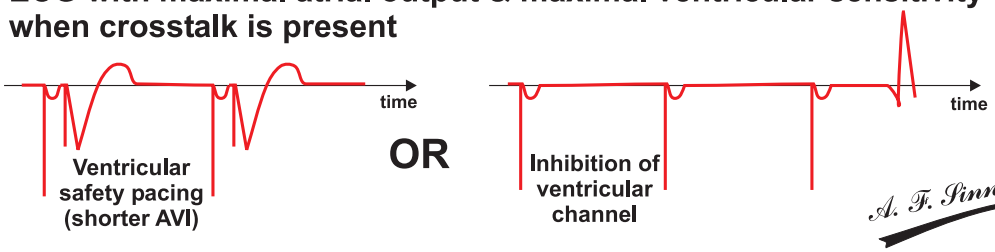
ECG after programming a faster rate & shorter AV interval



ECG with maximal atrial output & maximal ventricular sensitivity in the absence of crosstalk



ECG with maximal atrial output & maximal ventricular sensitivity when crosstalk is present



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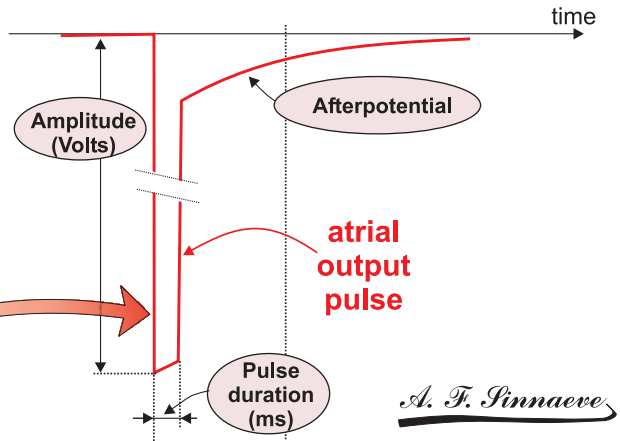
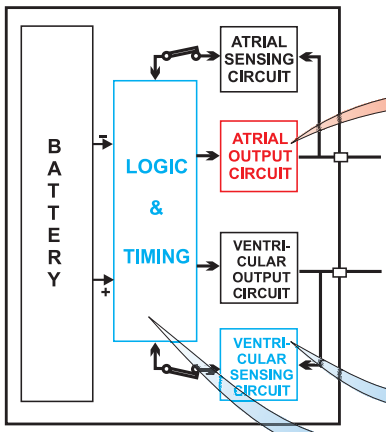
PREVENTION of AV CROSSTALK
(or SELF- INHIBITION)

Reduction of atrial output





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Alteration of sensing

- Reduce ventricular sensitivity
- Blind the ventricular channel for an appropriate duration after the emission of the atrial stimulus (PAVB)

MANAGEMENT OF CROSSTALK

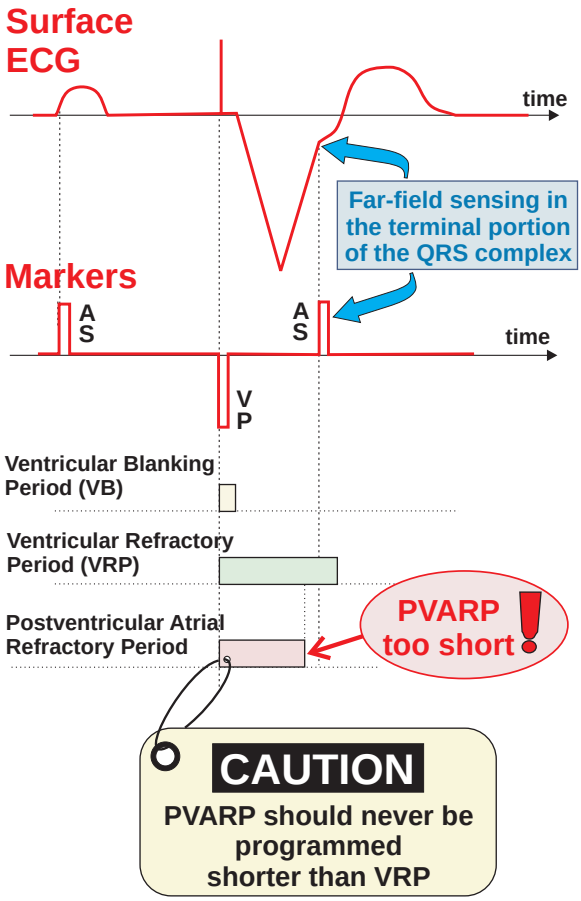
1. Crosstalk is best prevented by using bipolar dual-chamber devices.
2. If crosstalk is observed, decrease the atrial output (voltage and/or pulse duration).
3. Decrease the sensitivity of the ventricular channel (the numerical value - mV - of the sensitivity on the programmer will therefore increase).
4. Prolong the postatrial ventricular blanking period (PAVB). The PAVB lasts 10 to 60 ms and is programmable in most pacemakers !
5. Program ventricular safety pacing ON (if VSP is available).

SENSING OF THE TERMINAL PORTION OF THE QRS COMPLEX

If sufficient large, the far-field QRS complex may be picked up by the atrial channel if :

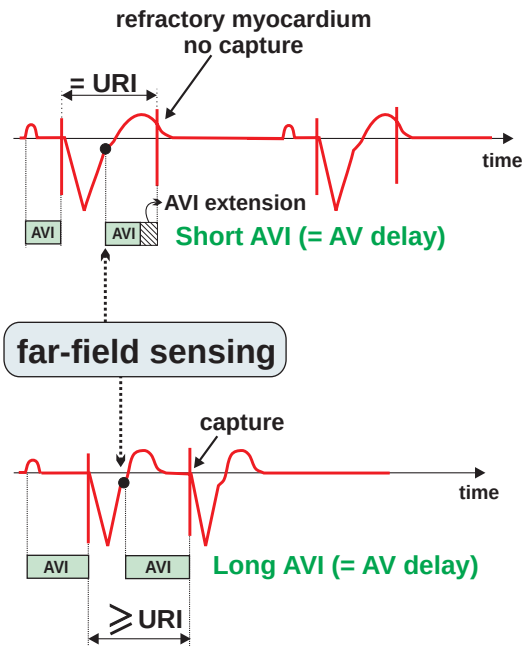
* the PVARP is relatively short

* the atrial sensitivity is high allowing sensing of the far-field signal



CAUTION

PVARP should never be programmed shorter than VRP



If the far-field QRS is sensed by the atrial channel, the pacemaker interprets it as a P wave, initiates an AV delay and triggers a ventricular stimulus at the completion of this AV delay (AVI).
The ventricular stimulus may or may not capture the ventricle according to its timing relative to the ventricular myocardial refractory period.

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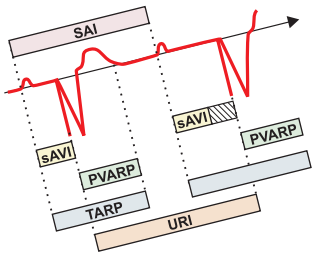
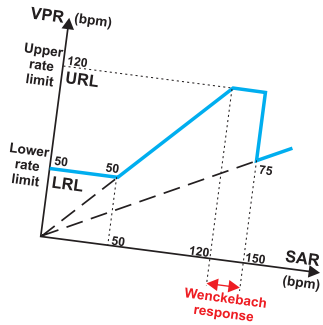
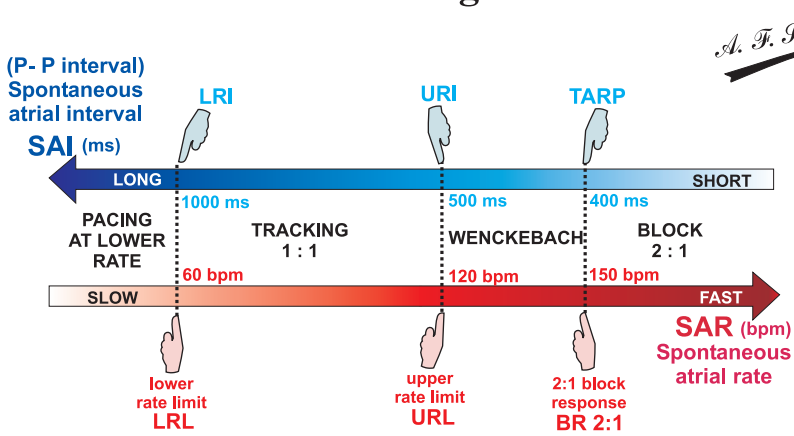
Abbreviations : AS = atrial sense ; VP = ventricular pace ; URI = upper rate interval ; PVARP = postventricular atrial refractory period ; VRP = ventricular rafractory period ; VB = ventricular blanking ; AVI = AV delay



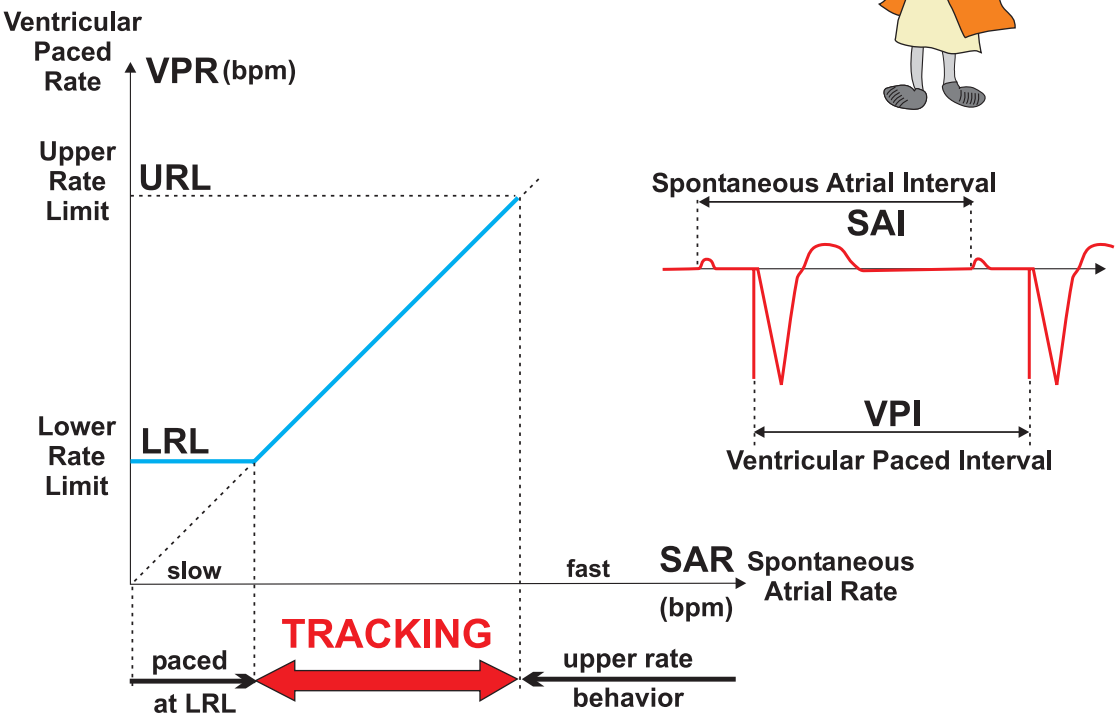


DDD PACEMAKERS - UPPER RATE RESPONSE

* Tracking
* Fixed-ratio block 2 : 1
* Fixed-ratio block - Stress test
* Addition of 7th timing cycle to obtain upper rate response with Wenckebach block
* Wenckebach upper rate limitation
* How to ensure Wenckebach block
* Wenckebach upper rate response - part 1
* Wenckebach upper rate response - part 2
* Management of upper rate
* Rate smoothing
* Atrial premature complexes (APCs)
* APCs - More difficult
* Premature ventricular events - Definitions
* Functional atrial undersensing
* Apparent lack of atrial tracking



TRACKING is present when the ventricular paced rate follows the spontaneous atrial rate in a 1 : 1 way



Spontaneous Atrial Rate (SAR in bpm)	=	$\frac{60{,}000}{\text{Spontaneous Atrial Interval (SAI in ms)}}$
Ventricular paced Rate (VPR in bpm)	=	$\frac{60{,}000}{\text{Ventricular Paced Interval (VPI in ms)}}$

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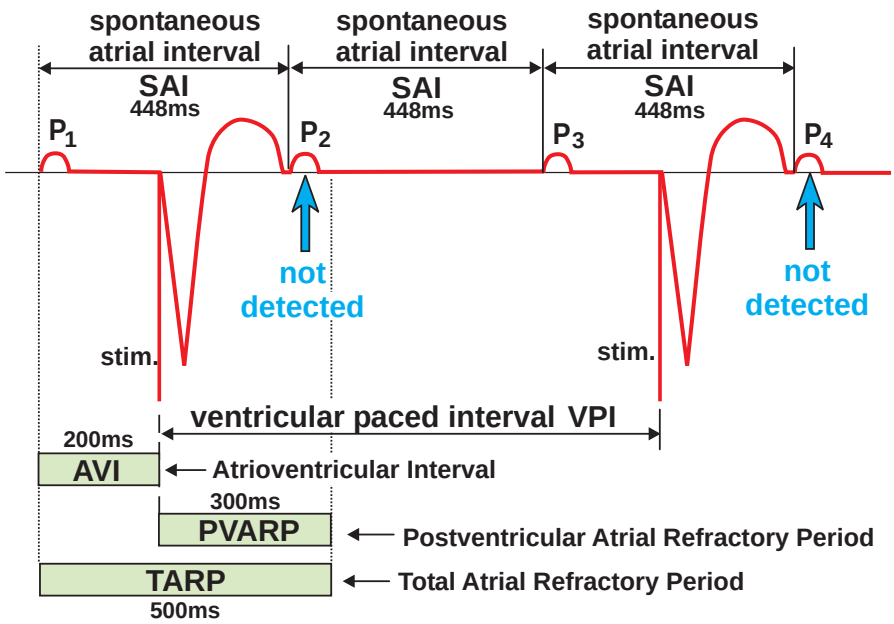
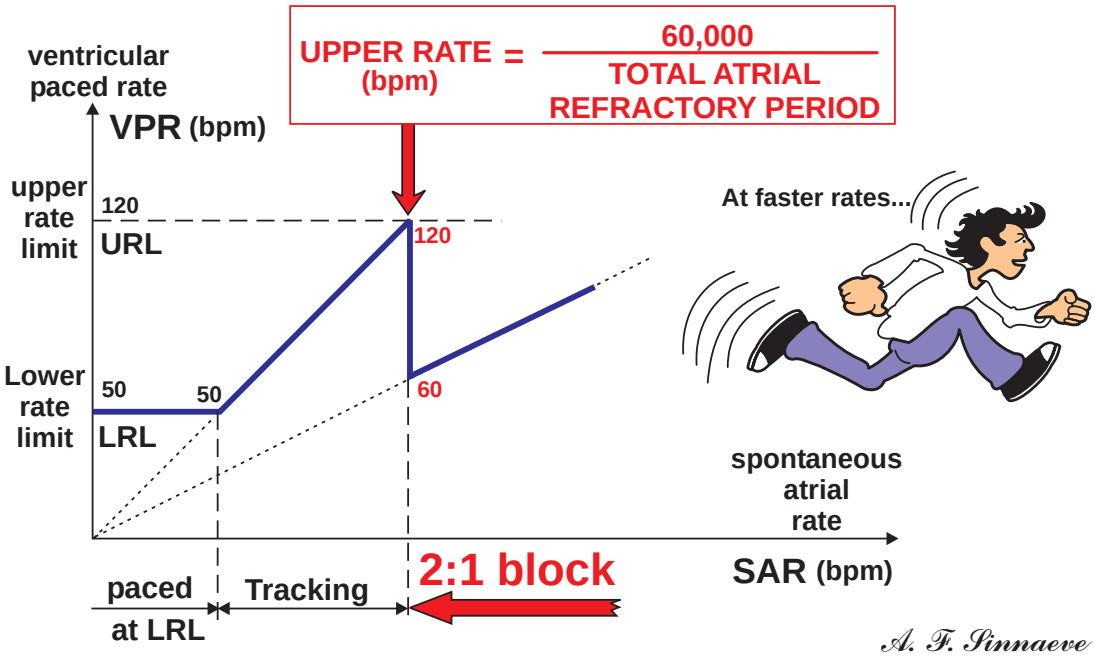
FIXED RATIO BLOCK 2 :1





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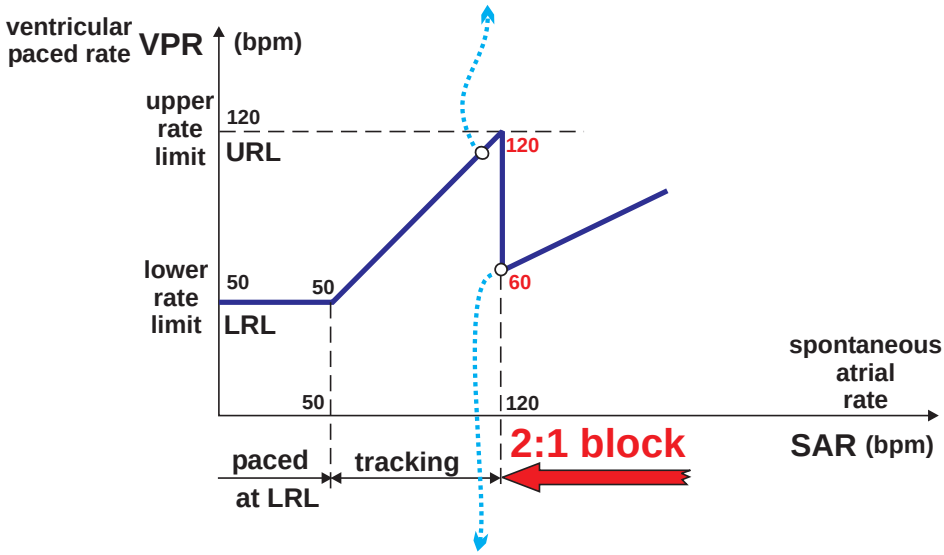
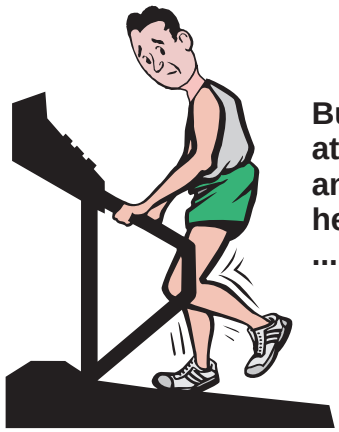
THE TREADMILL STRESS TEST

At an atrial rate of 115 bpm
and the same paced rate, he
still loved his physician....





But...
at an atrial rate of 120 bpm
and a paced rate of 60 bpm
he felt himself very unhappy
.....

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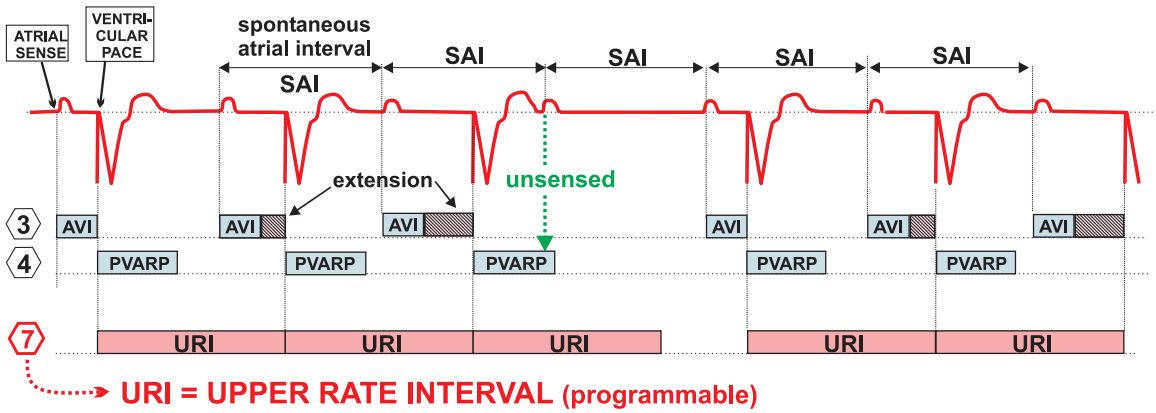
UPPER RATE LIMITATION

ADDITION OF A SEVENTH TIMING CYCLE TO A DDD PACEMAKER

Upper rate limitation by the abrupt development of 2:1 block should be prevented !



URI = UPPER RATE INTERVAL (programmable)

A Wenckebach upper rate response can only occur when the upper rate interval (URI) is programmed longer than the total atrial refractory period (TARP). The latter is the sum of the atrioventricular interval (AVI) and the postventricular atrial refractory period (PVARP) i.e. TARP = AVI + PVARP
If the upper rate interval (URI) equals the total atrial refractory period (TARP), no Wenckebach upper rate behavior is possible and the upper rate response will consist of 2:1 block.

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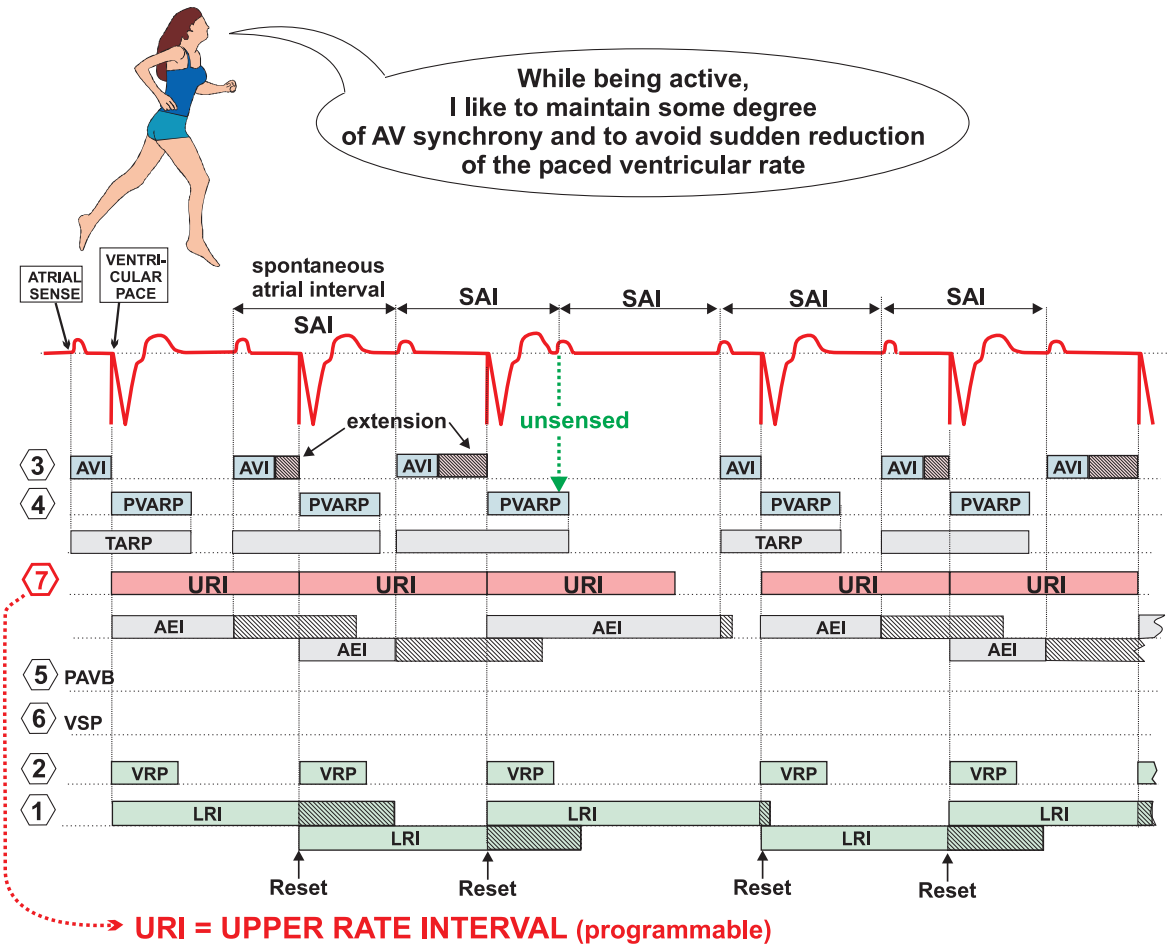
ADDITION OF A SEVENTH TIMING CYCLE TO A DDD PACEMAKER TO AVOID ABRUPT 2:1 BLOCK



A pacemaker Wenckebach upper rate response can only occur if the pacemaker permits an upper rate interval (URI) longer than the pacemaker total atrial refractory period (TARP)

ABBREVIATIONS : AVI = AV interval; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; AEI = atrial escape interval; PAVB = postatrial ventricular blanking; VSP = ventricular safety pacing window; VRP = ventricular refractory period; LRI = lower rate interval

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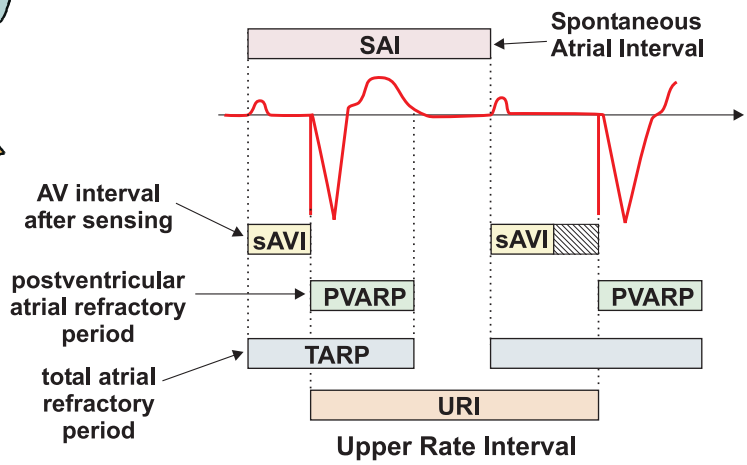
HOW TO ENSURE A WENCKEBACH UPPER RATE BEHAVIOR OF A PACEMAKER

A pacemaker Wenckebach upper rate response can only occur if the pacemaker permits an upper rate interval longer than the pacemaker total atrial refractory period



A shorter Total Atrial Refractory Period (TARP) pushes the 2 : 1 block rate to a higher level, thereby allowing the programming of a faster rate at which the Wenckebach response begins.
Manipulation of the sAVI and/or the PVARP allows the establishment of a faster upper rate by :

- **Programming a shorter basic AV Interval after sensing (sAVI)**
- **Shortening the sAVI with an increase in atrial rate**
- **Programming a shorter Postventricular Atrial Refractory Interval (PVARP)**
- **An adaptive PVARP shortening on exercise**

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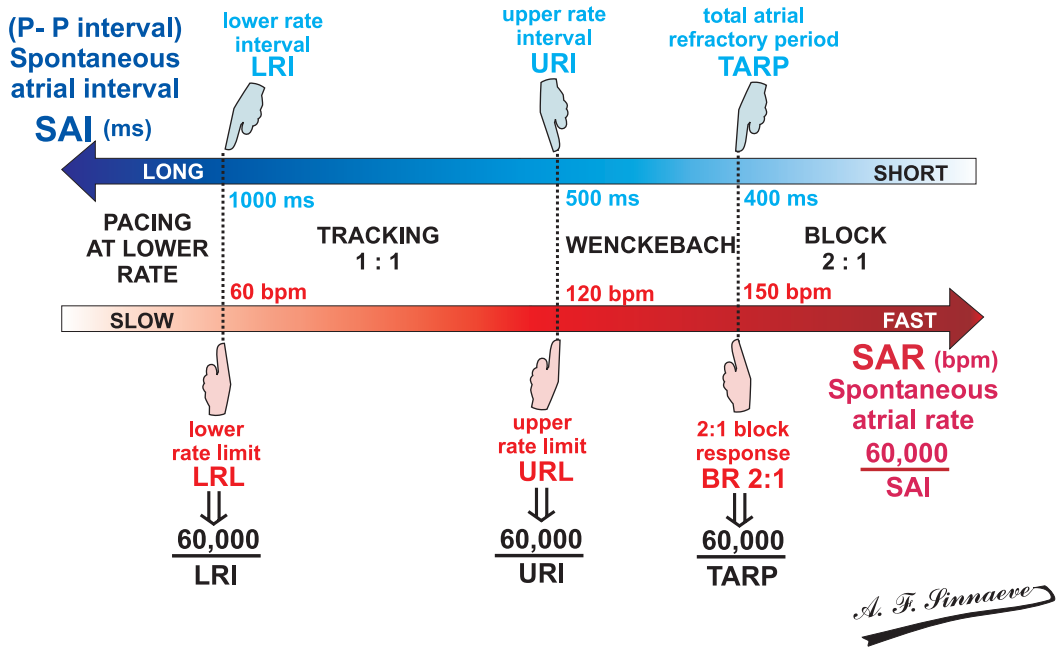
WENCKEBACH UPPER RATE RESPONSE

$$\text{RATE (bpm)} = \frac{60{,}000}{\text{INTERVAL (ms)}}$$

WENCKEBACH BEHAVIOR OCCURS IF :

1. The upper rate interval (URI) is longer than the total atrial refractory period (TARP)
2. The spontaneous atrial interval (SAI) is longer than the total atrial refractory interval (TARP) but shorter than the upper rate interval (URI)



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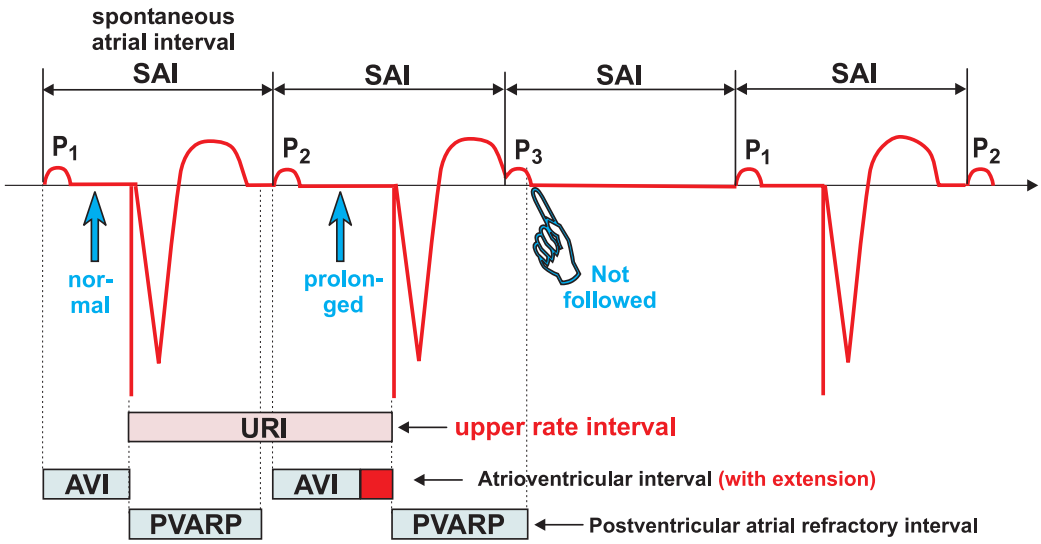
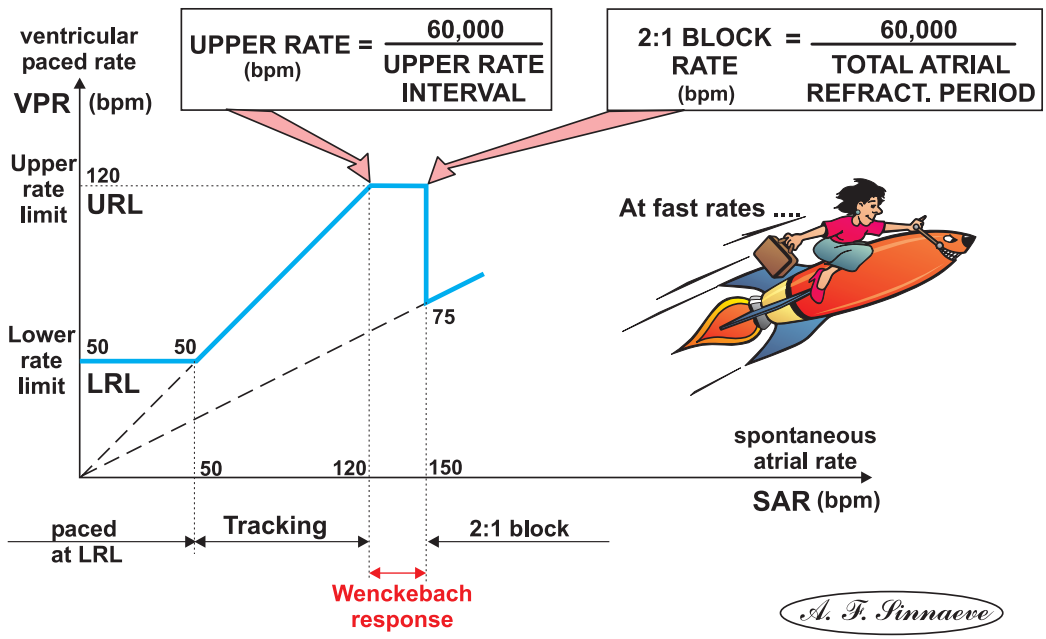
WENCKEBACH UPPER RATE RESPONSE





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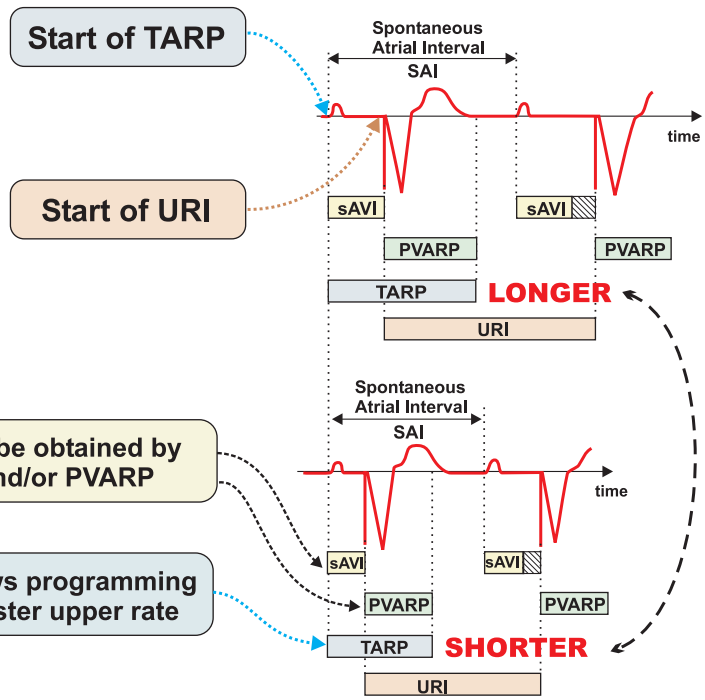
MANAGEMENT OF UPPER RATE ?

TARP DETERMINES THE RATE AT WHICH 2:1 BLOCK STARTS

WENCKEBACH UPPER RATE RESPONSE ONLY IF URI > TARP

WENCKEBACH UPPER RATE RESPONSE IMPOSSIBLE IF URI = TARP



* sAVI can be programmed shorter than pAVI at rest

* sAVI and therefore TARP can shorten further if the pacemaker contains an algorithm to shorten the sAVI as the sensed atrial rate increases

* in some pacemakers the PVARP can also shorten on exercise

Abbreviations : sAVI = AV interval after sensing; SAI = spontaneous atrial interval; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; URI = upper rate interval;

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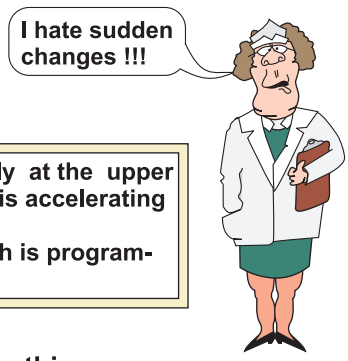
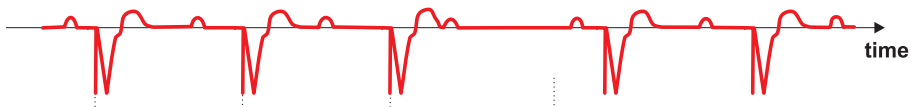
RATE SMOOTHING

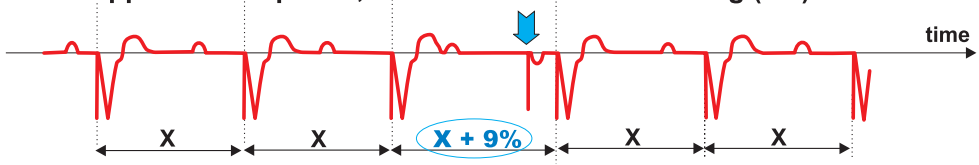


* Rate smoothing limits the changes in cycle length not only at the upper rate of DDD pacemakers, but also any time the sinus rate is accelerating or decelerating.
* The permitted maximum change in the pacing cycle length is programmable (3%,6%, 9%, 12%)

Wenckebach upper rate response without rate smoothing

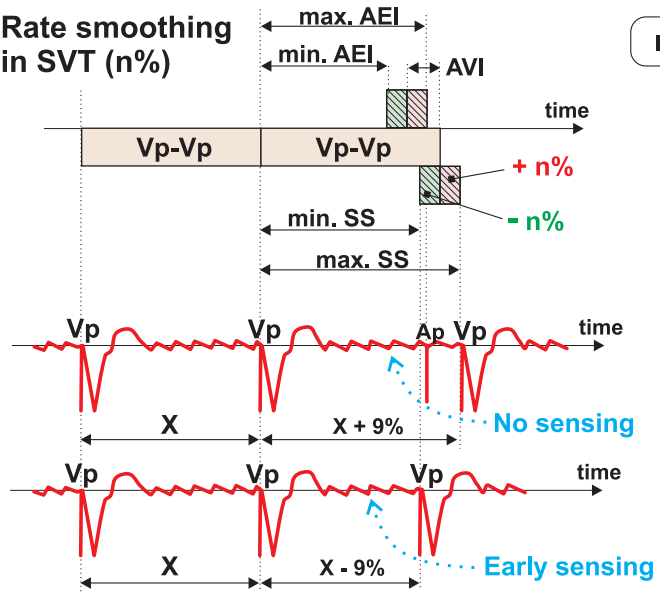


Same upper rate response, but with true rate smoothing (9%)



Note : A response similar to rate smoothing can also occur during rate-responsive DDDR pacing. With increased sensor input generated by exercise or activity, the pause at the end of a Wenckebach upper rate response can be attenuated or eliminated according to the prevailing sensor-driven interval. This response is potentially important in patients who do not tolerate the pauses in the Wenckebach upper rate response of DDD pacemakers

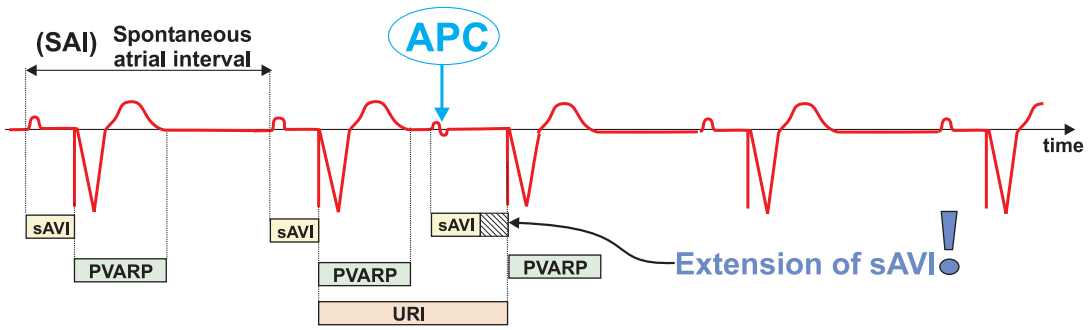
Rate smoothing in SVT (n%)



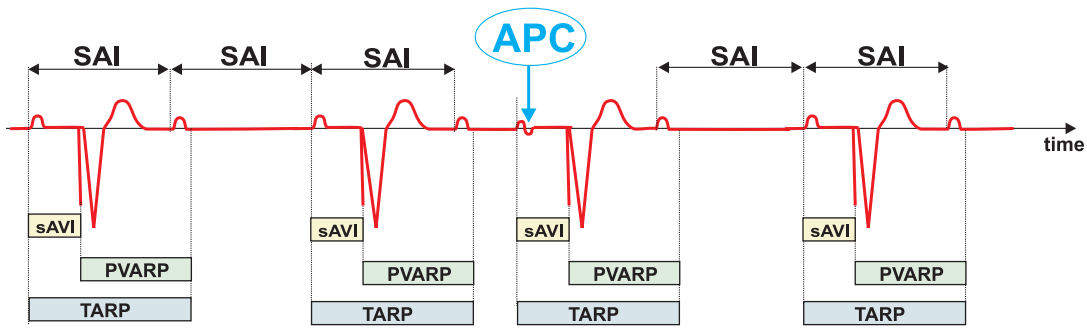
Abbreviations :
AEI = atrial escape interval ; AVI = AV delay
Ap = atrial pace ; Vp = ventricular pace ;
SS = interstimulus interval ; SVT = supra-ventriclar tachycardia

ATRIAL PREMATURE COMPLEXES AND UPPER RATE LIMITATION
* SOME EXAMPLES *

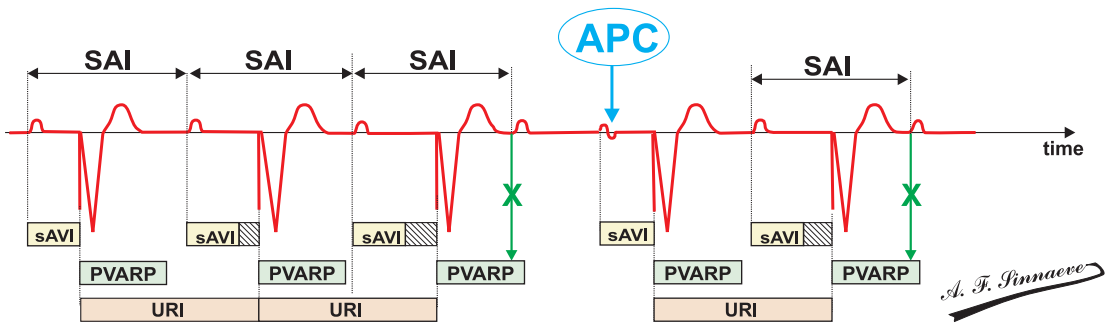
1. While tracking (LRI > SAI > URI)



2. During upper rate response with 2 : 1 block



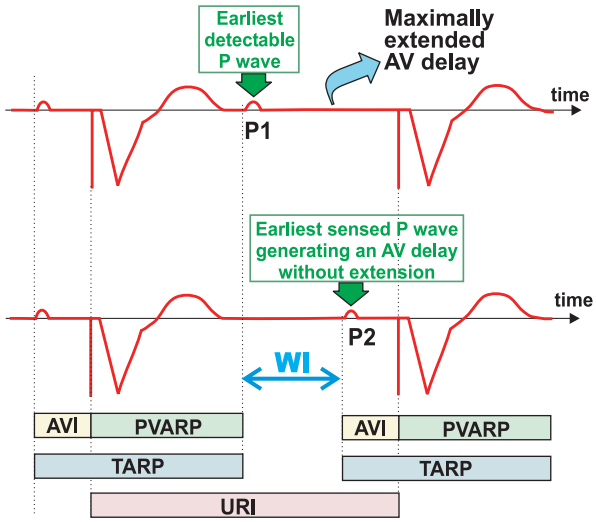
3. During upper rate response with Wenckebach behavior



Abbreviations : APC = atrial premature complex ; LRI = lower rate interval ; PVARP = postventricular atrial refractory period ; SAI = spontaneous atrial interval ; sAVI = AV delay after sensing ; TARP = total atrial refractory period ; URI = upper rate interval

ATRIAL PREMATURE COMPLEXES AND UPPER RATE LIMITATION
DDD pacemaker with URI > TARP

The AV delay initiated by an APC depends on its timing in the pacemaker cycle ! Unexplained upper rate limitation is often due to an APC !!!



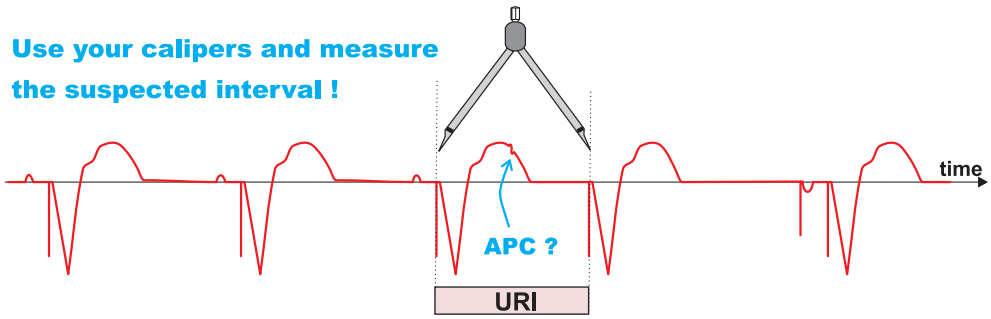
The Wenckebach interval (WI) is equal to the longest prolongation of the AV delay. It is therefore equal to :

$$WI = URI - (AVI + PVARP)$$

$$WI = URI - TARP$$

A P wave (P1) immediately after PVARP termination will exhibit the longest interval (AVI +WI) to conform to the constancy of the URI. A P wave (P2) just beyond the WI will initiate an AV interval equal to the programmed value. P waves in the WI will exhibit varying degrees of AV prolongation to conform to the URI.

Use your calipers and measure the suspected interval !



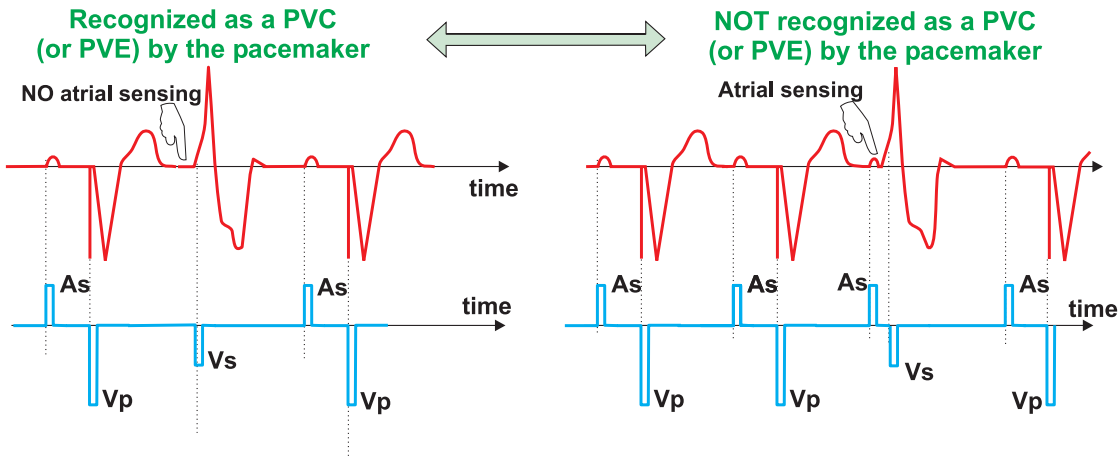
The URI can be identified on the ECG by moving calipers from the early ventricular stimulus back to the previous ventricular event. If this measured interval equals URI, it provides proof that an atrial sensed event occurred between the two ventricular events bracketing the URI. By far the most likely cause is an APC or less commonly a retrograde P wave as an isolated event. Far-field T wave sensing by the atrial channel is very rare, even at very high atrial sensitivity.

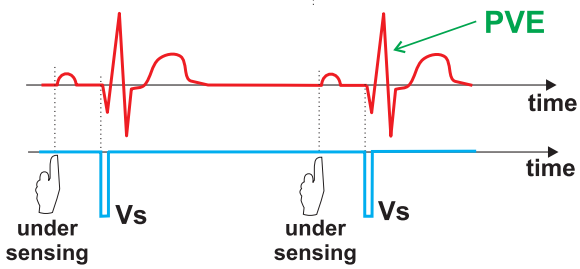
Abbreviations : APC = atrial premature complex; AVI = AV interval or AV delay; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; URI = upper rate interval; WI = Wenckebach interval

A. F. Sinnaeve

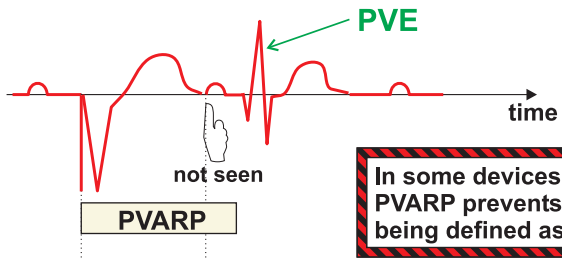
ABOUT PREMATURE VENTRICULAR EVENTS (PVE)

DEFINITION : a PVE is a sensed R wave that is not preceded by an atrial event, paced or sensed, according to the pacemaker.
Thus a pacemaker-defined PVE terminates an interventricular interval without an intervening atrial event.
A pacemaker's PVE is not necessarily the same event as a clinician's PVC !





Atrial undersensing with spontaneous AV conduction.
Since the P wave is not seen by the pacemaker, the R wave is stored as a PVC.



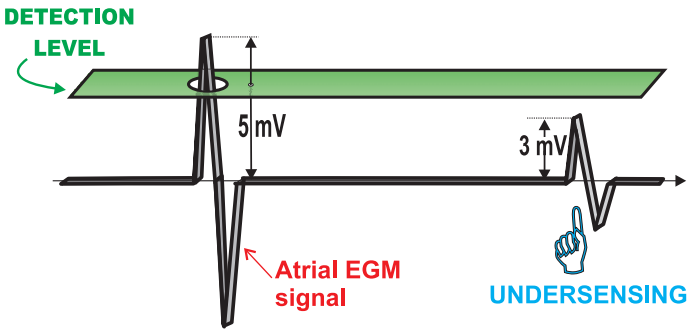
Functional atrial undersensing.
The P wave is not seen because it falls within the refractory period. The subsequent R wave is stored as a PVC

In some devices, an atrial refractory sensed event in the PVARP prevents a succeeding ventricular event from being defined as a pacemaker-PVE

Abbreviations : PVARP = postventricular atrial refractory period; PVE = premature ventricular event; PVC = premature ventricular complex ; As = atrial sensed event; Ap = atrial paced event; Vp = ventricular paced event; Vs = ventricular sensed event

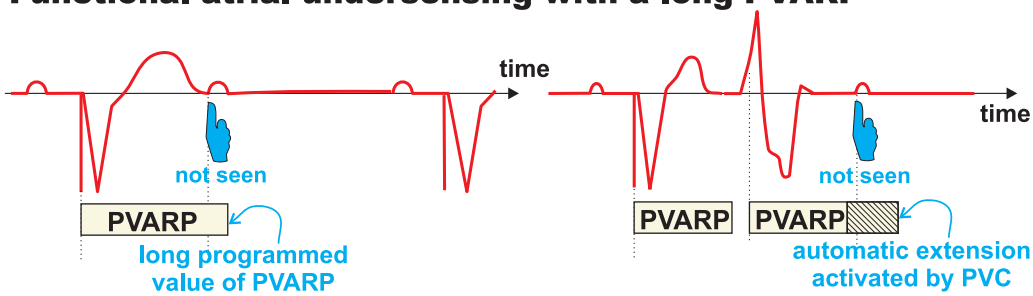
A. F. Sinnaeve

FUNCTIONAL ATRIAL UNDERSENSING

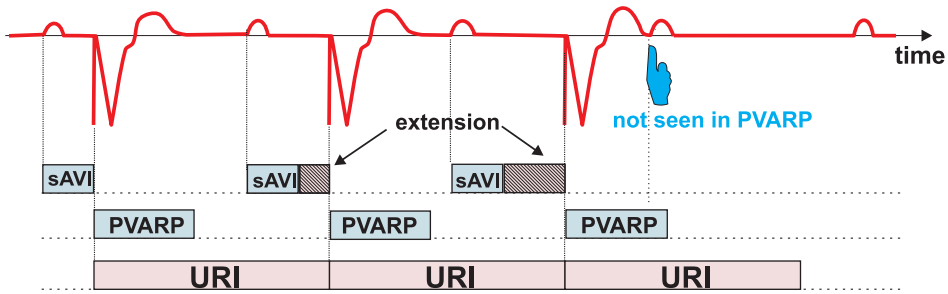


REMEMBER :
true atrial undersensing occurs when the amplitude is too small

Functional atrial undersensing with a long PVARP



Apparent or functional atrial undersensing due to upper rate limitation (displacement of the P wave in the PVARP as a function of the atrial rate).



CAUTION

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Remember that automatic PVARP extension after a pacemaker-defined PVC may cause functional atrial undersensing even when the basic PVARP is relatively short.

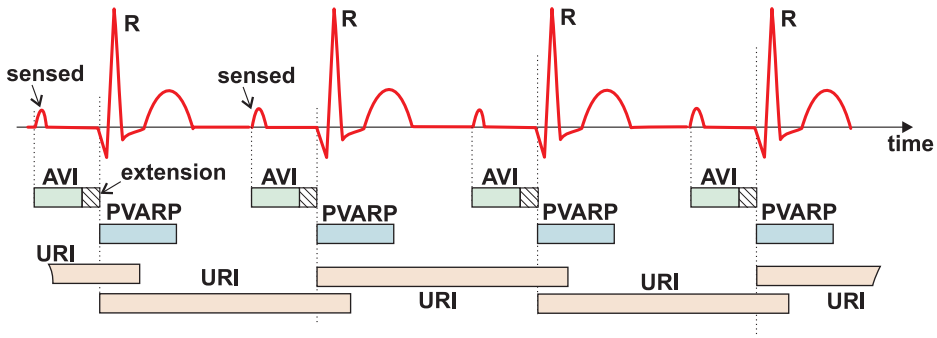
Abbreviations : EGM = electrogram; mV = millivolt; PVC = premature ventricular complex; PVARP = postventricular atrial refractory period; sAVI = AV delay after a sensed atrial event; URI = upper rate interval

Sometimes we see a prolongation of the interval between atrial-sensed and ventricular-sensed events beyond the programmed AV interval, while there is no true atrial undersensing because the amplitude of the atrial electrogram is adequate for atrial sensing !!!

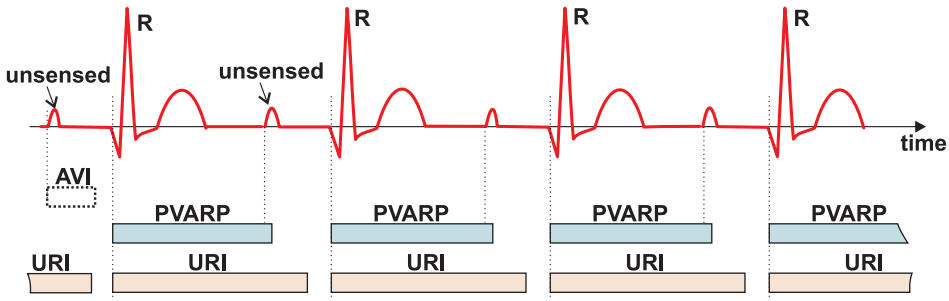
APPARENT LACK OF ATRIAL TRACKING

1 Spontaneous R-R interval shorter than ventricular upper rate interval (URI)

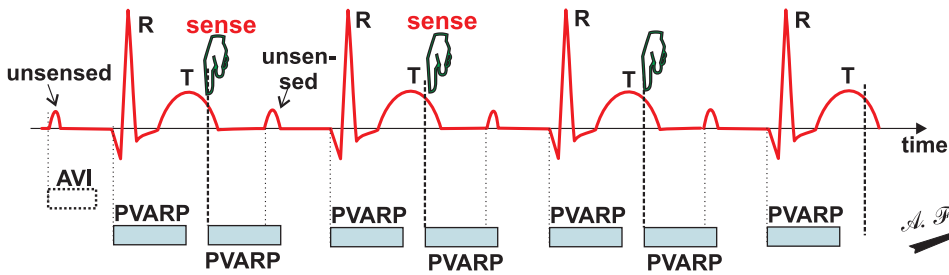
(Repetitive pre-empted Wenckebach upper rate response)



2 Excessively long PVARP prevents the detection of P waves (at relatively fast spontaneous atrial rate)



3 Ventricular oversensing (T wave sensing) starts a new PVARP thus preventing normal P wave sensing



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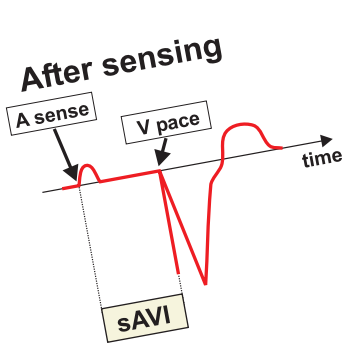
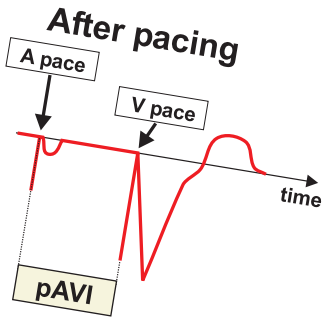
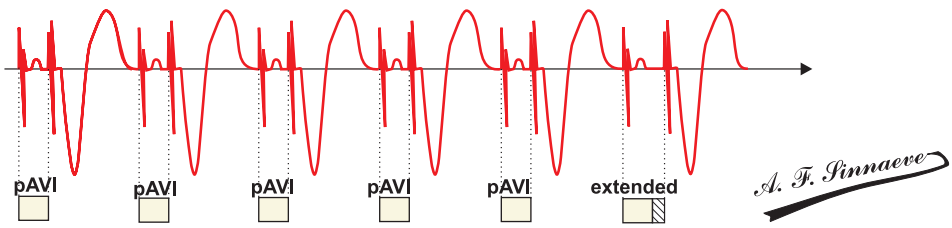
Abbreviations : AVI = programmed AV delay; PVARP = postventricular atrial refractory period; URI = upper rate interval





ATRIOVENTRICULAR INTERVAL (AVI)

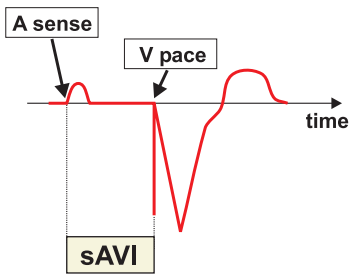
* AV delay - paced and sensed
* Rate-adaptive AV delay
* How to program the AV delay ?
* AV search hysteresis



The AV DELAY or ATRIOVENTRICULAR INTERVAL (AVI)

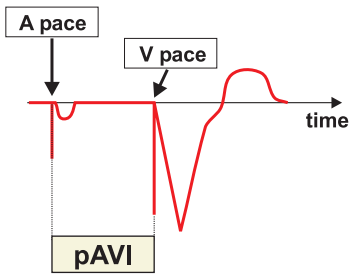
AVI is the interval between an atrial event (either sensed or paced) and the scheduled delivery of a ventricular stimulus

After sensing



sAVI starts with an atrial sensed event

After pacing



pAVI starts with an atrial stimulus

- Separate AV intervals for paced and sensed atrial events are available
- **Usually sAVI < pAVI**
  typically sAVI is 30-50 ms shorter than pAVI
- The AV intervals may be programmed to fixed values or (optionally) rate-adaptive i.e. shortening with increasing atrial rates

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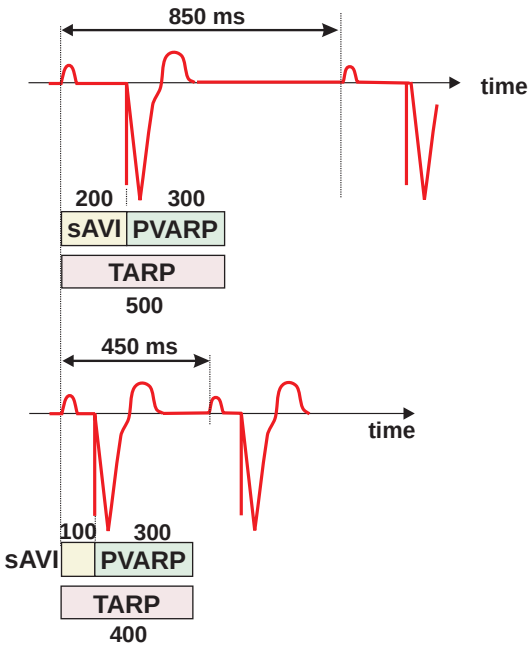
THE RATE-ADAPTIVE AV INTERVAL

My AV delay is normal or physiologic.
It shortens whenever I exercise !

The rate-adaptive AV interval mimics the physiologic response of the heart



RELATIVELY SLOW ATRIAL RATE
→ LONGER AV DELAY

Spontaneous atrial interval SAI = 850 ms

Spontaneous atrial rate SAR = 71 bpm

Sensed atrioventricular interval sAVI = 200 ms

FASTER ATRIAL RATE
→ SHORTER AV DELAY

Spontaneous atrial interval SAI = 450 ms

Spontaneous atrial rate SAR = 133 bpm

Sensed atrioventricular interval sAVI = 100 ms

THE PROGRAMMER MAY CHANGE

- *** the maximum value of sAVI**
- *** the minimum value of sAVI**
- *** the value of the gradual decrement of sAVI between these 2 rates**
- *** the range of rates where the change in the sAVI occurs**

pAVI can also shorten according to the input of a nonatrial sensor that reflects increased activity

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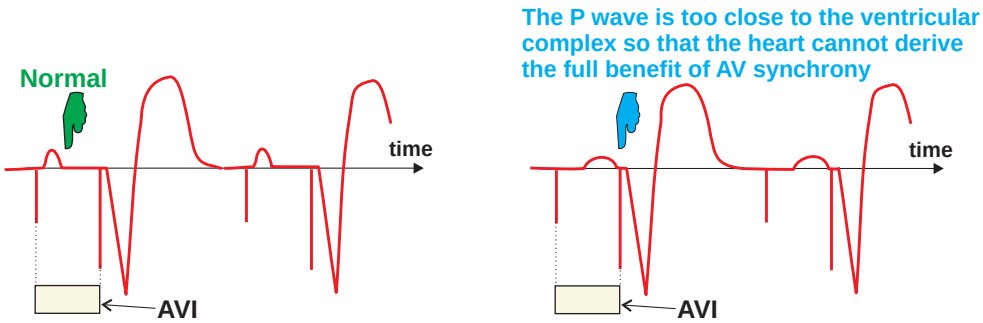
HOW TO OBTAIN AN OPTIMAL AV DELAY ?

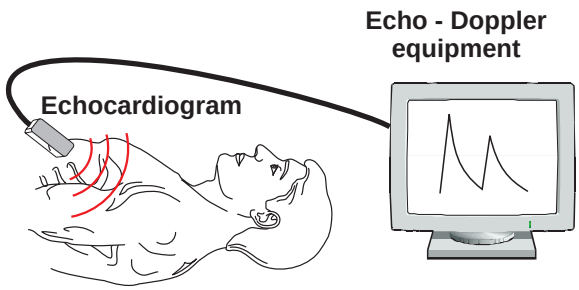
* In healthy individuals at rest, the optimal basic PR or AV interval normally lies between 120 and 210 ms
* The optimal value varies greatly from one patient to another as a function of several physiologic and pathologic factors including age (shorter in young people)
* Optimization of the AV delay (AVI) is needed at rest and exercise

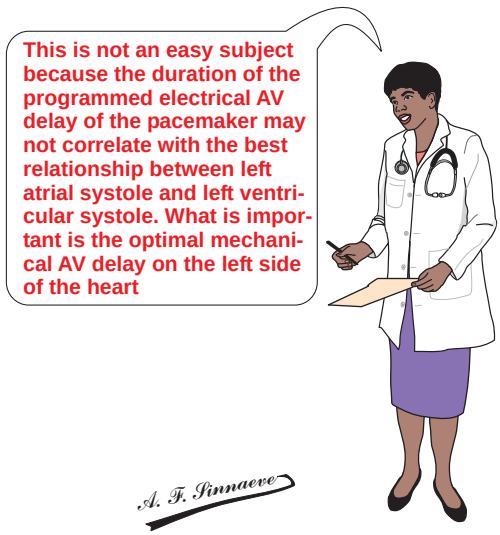


The electrical AV delay on the right side of the heart controlled by programming the pacemaker must produce an appropriate mechanical AV delay on the left side of the heart to preserve the atrial contribution to the cardiac output and optimize left ventricular function !!!

The optimal AV delay cannot be determined from the surface ECG !!!

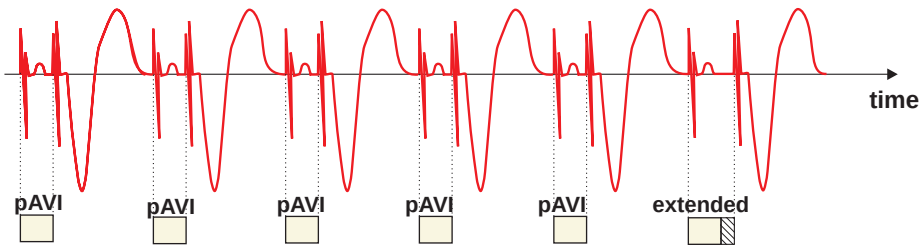
Doppler echocardiography is required to determine the optimal AV delay that produces the best stroke volume and cardiac output for each individual





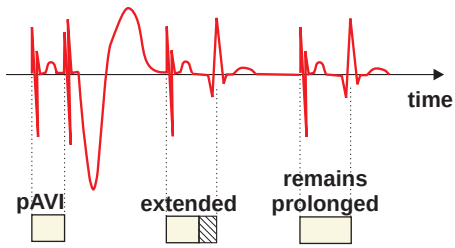
AV DELAY HYSTERESIS

Facilitation of normal AV conduction to promote normal ventricular depolarization

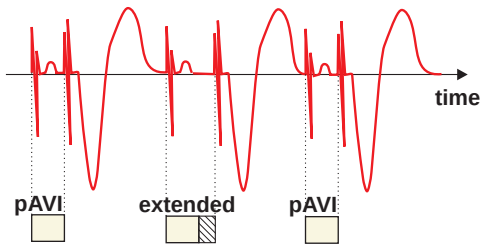


After "n" consecutive ventricular paced complexes, the AV delay is prolonged for "1" cycle

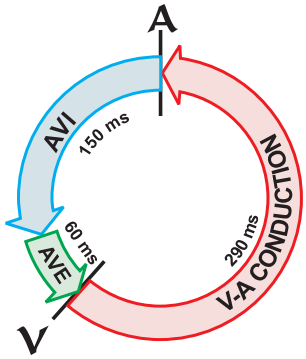
1 **If an intrinsic ventricular event is sensed, the AV delay remains prolonged**



2 **If no intrinsic ventricular event is sensed, the AV delay returns to the programmed value**

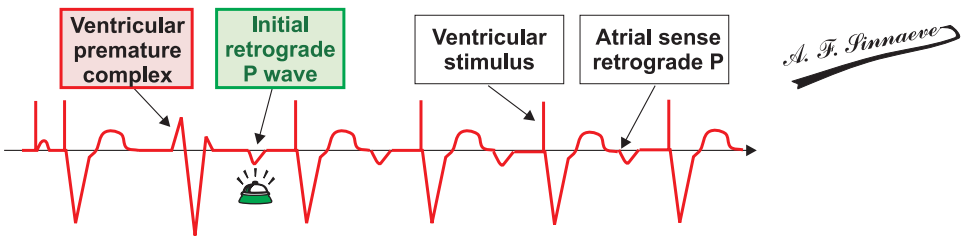


Abbreviations : AV = atrio-ventricular ; pAVI = paced atrioventricular interval

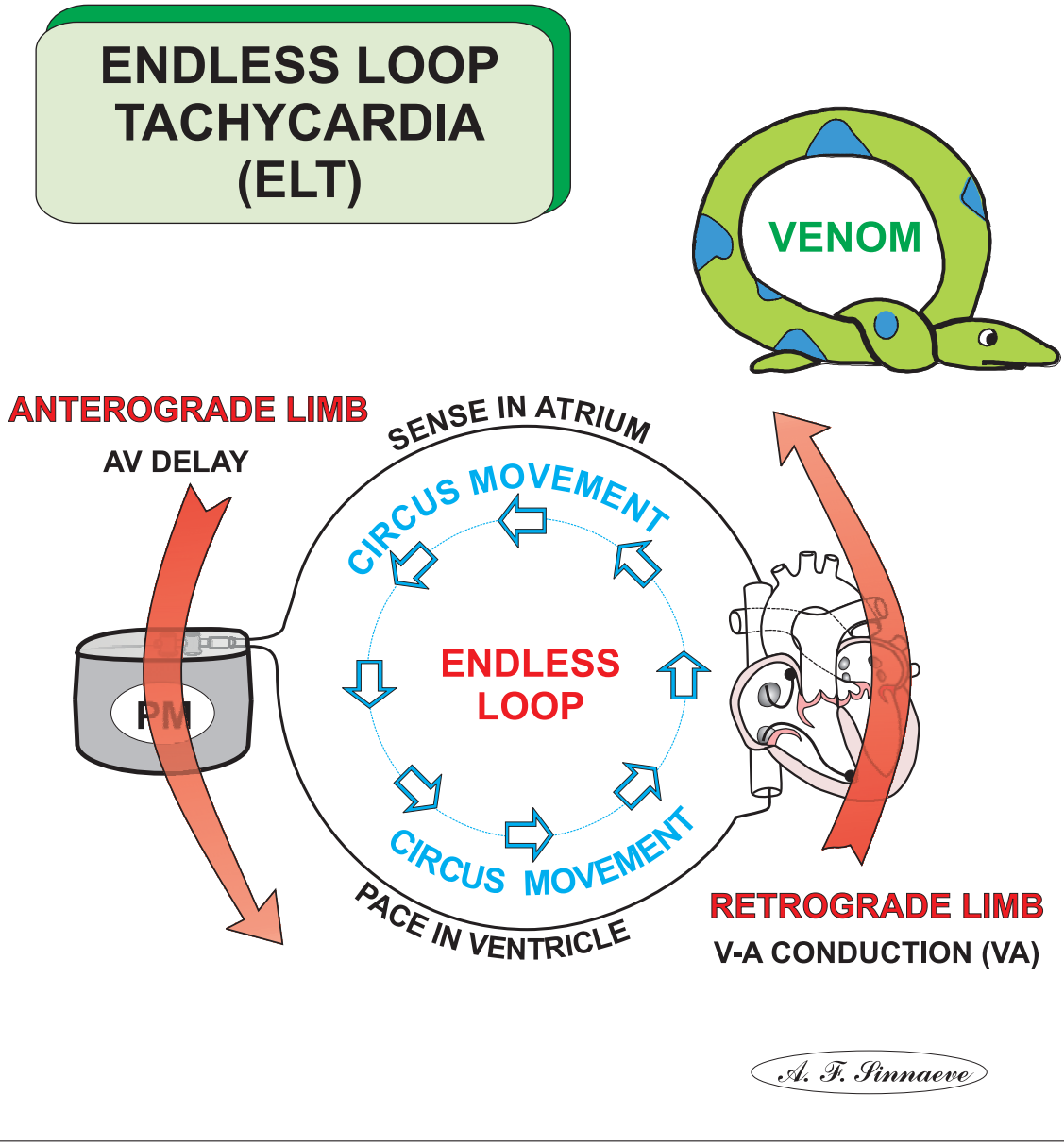


RETROGRADE VENTRICULOATRIAL SYNCHRONY IN DUAL CHAMBER PACEMAKERS

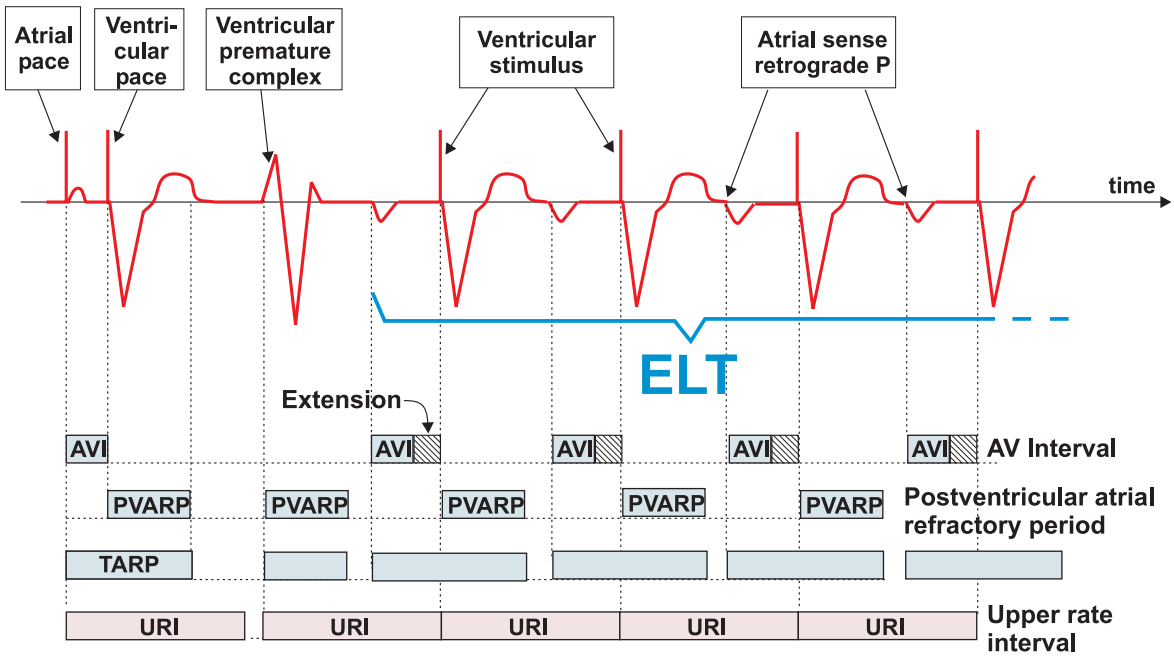
* Mechanism of endless loop tachycardia (ELT)
* ECG of ELT
* ELT : precipitating factors
* Rate of ELTs
* Testing for retrograde ventriculoatrial (VA) conduction
* Far-field ELT
* ECG of repetitive nonreentrant VA synchrony (RNRVAS)
* RNRVAS : prevention & treatment
* The cousins : ELT and RNRVAS
* Algorithms for ELT prevention - part 1
* Algorithms for ELT prevention - part 2
* Algorithms for ELT prevention - part 3



ENDLESS LOOP TACHYCARDIA (ELT)



DDD PACEMAKER & ENDLESS LOOP TACHYCARDIA



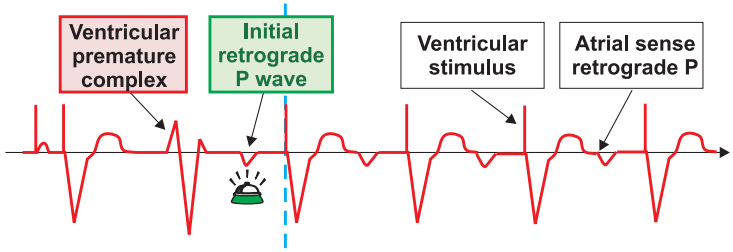
Endless loop tachycardia often occurs at the upper rate. In such a case as the programmed upper rate interval (URI) is longer than the total atrial refractory interval (TARP), the AV delay is extended to conform to the upper rate interval (URI)

Abbreviations : AVI = atrioventricular interval ; AVE = extension of AVI ; ELT = endless loop tachycardia ; PVARP = postventricular atrial refractory period ; TARP = total atrial refractory period ; URI = upper rate interval

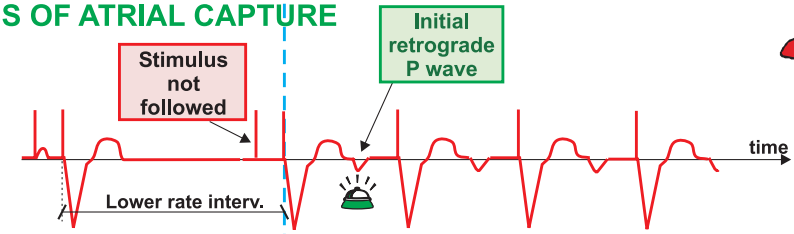
A. F. Sinnaeve

ENDLESS LOOP TACHYCARDIA PRECIPITATING FACTORS

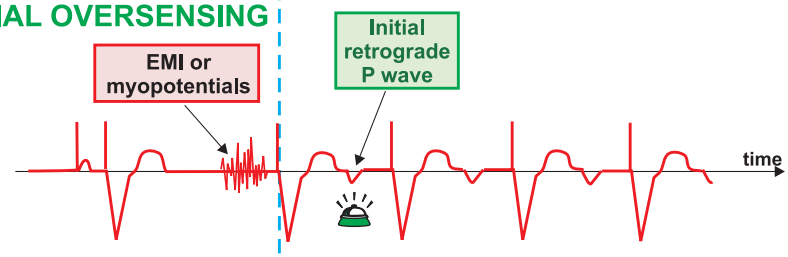
1 VENTRICULAR EXTRASYSTOLES



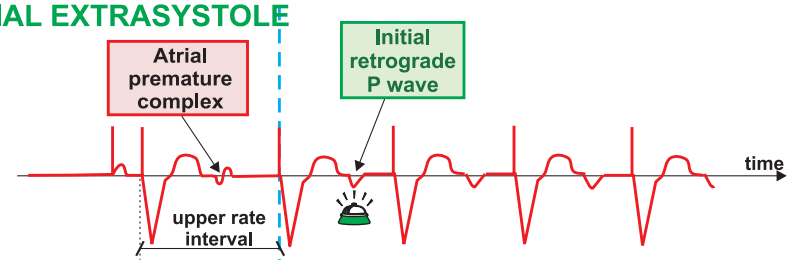
2 LOSS OF ATRIAL CAPTURE



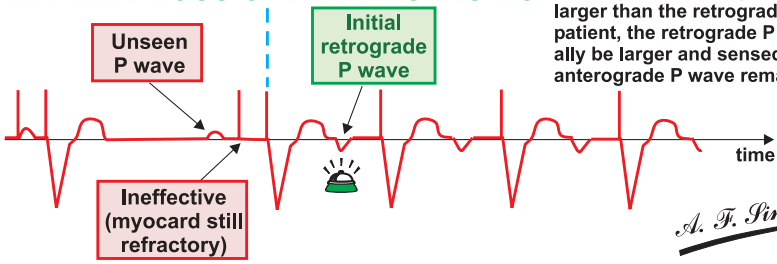
3 ATRIAL OVERSENSING



4 ATRIAL EXTRASYSTOLE



5 INTERMITTENT LOSS OF ATRIAL SENSING



Although the anterograde P wave is usually larger than the retrograde P wave in a given patient, the retrograde P wave may occasionally be larger and sensed when the smaller anterograde P wave remains unsensed.

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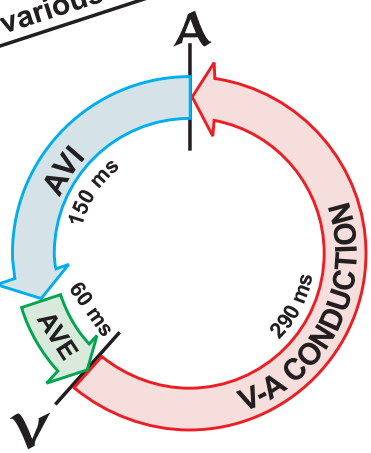
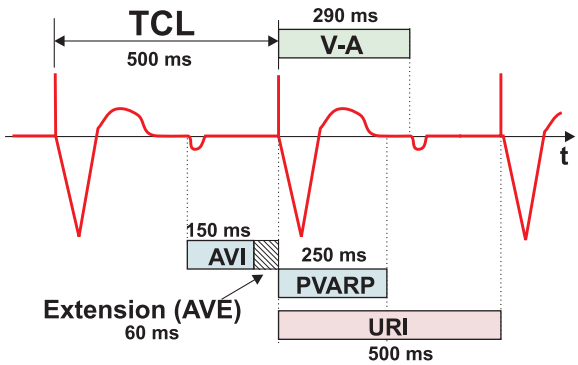
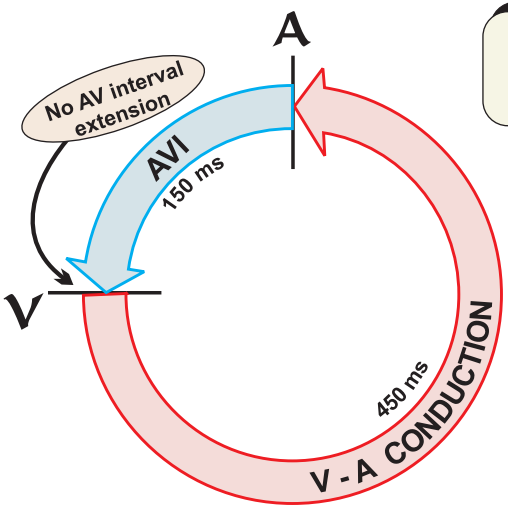
Abbreviations : EMI = electromagnetic interference ; Myopotentials = random signals (noise) caused by the action of some muscles ; myocard = myocardium or cardiac muscle

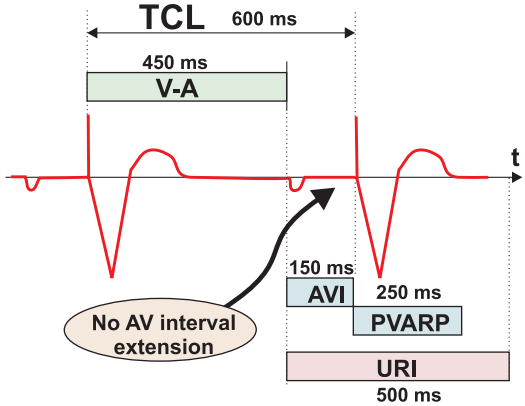
ENDLESS LOOP TACHYCARDIA AT UPPER RATE





ENDLESS LOOP TACHYCARDIA SLOWER THAN UPPER RATE



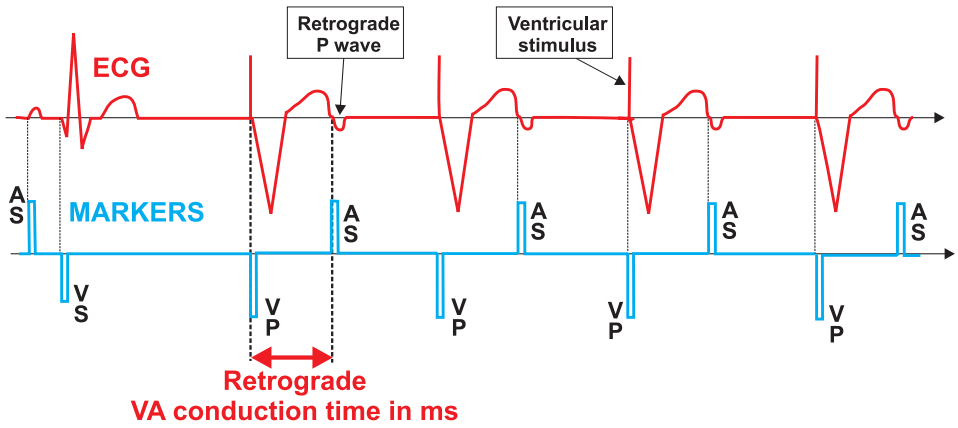


Abbreviations : AVI = atrioventricular interval ; AVE = extension of AVI ; ELT = endless loop tachycardia ; PVARP = postventricular atrial refractory period ; TARP = total atrial refractory period ; URI = upper rate interval; V-A = retrograde V-A conduction time; TCL = tachycardia cycle length

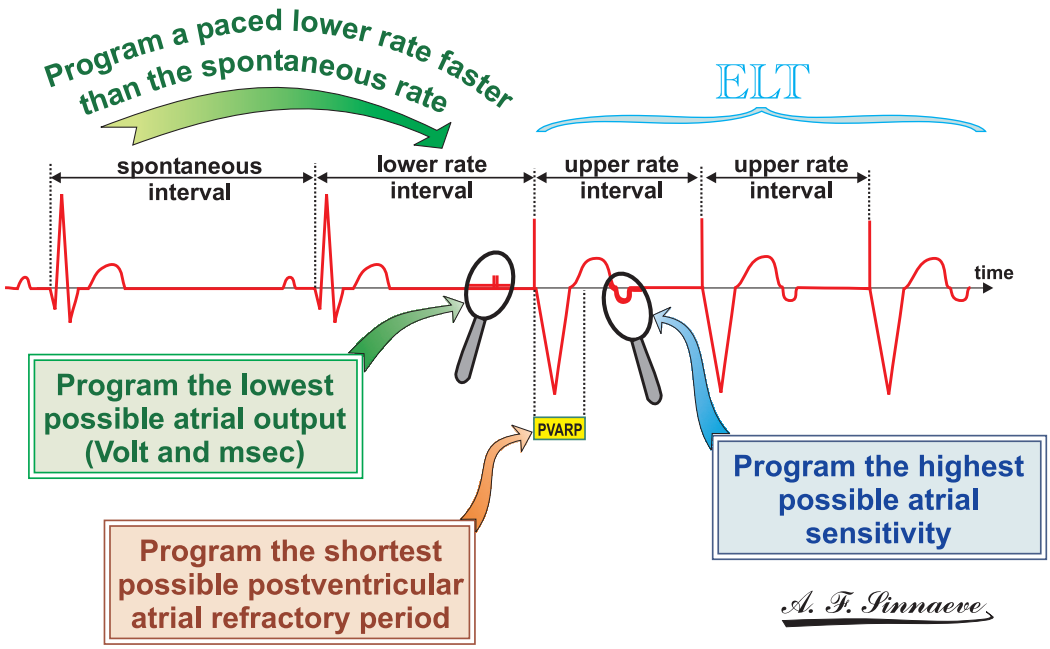
A. F. Sinnaeve

EVALUATION OF RETROGRADE VA CONDUCTION

Reprogram the pacemaker to the VVI mode at a rate faster than the spontaneous rhythm

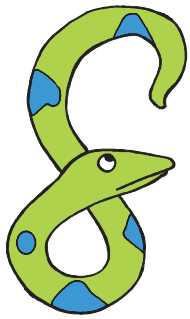


TEST FOR PROPENSITY TO ENDLESS LOOP TACHYCARDIA

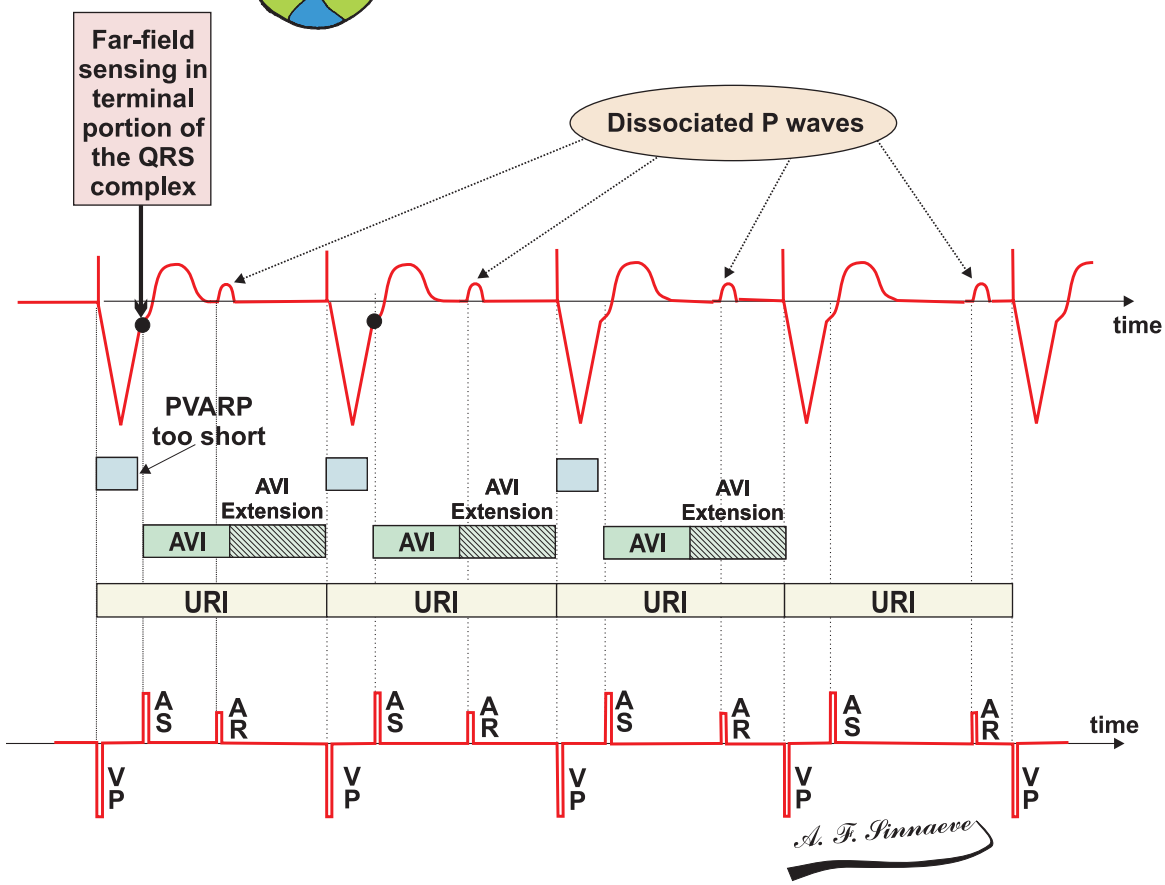


Abbreviations : AS = atrial sense ; ELT = endless loop tachycardia ; ms = millisecond ; PVARP = postventricular atrial refractory period ; VA = ventriculoatrial ; VP = ventricular pace ; VS = ventricular sense

FAR-FIELD ENDLESS LOOP TACHYCARDIA

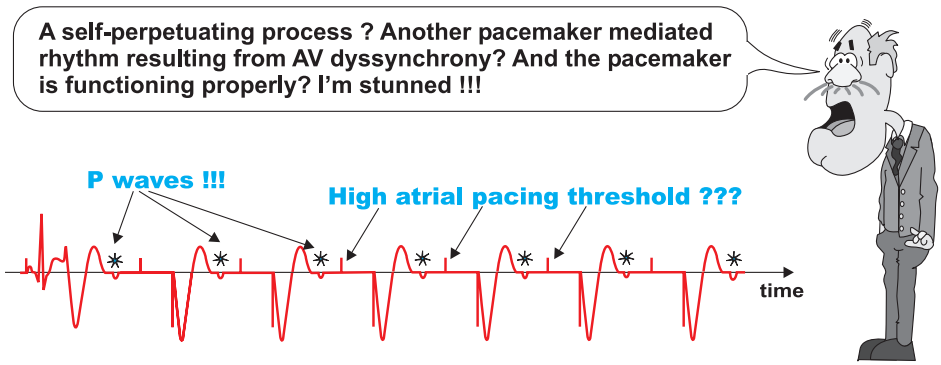


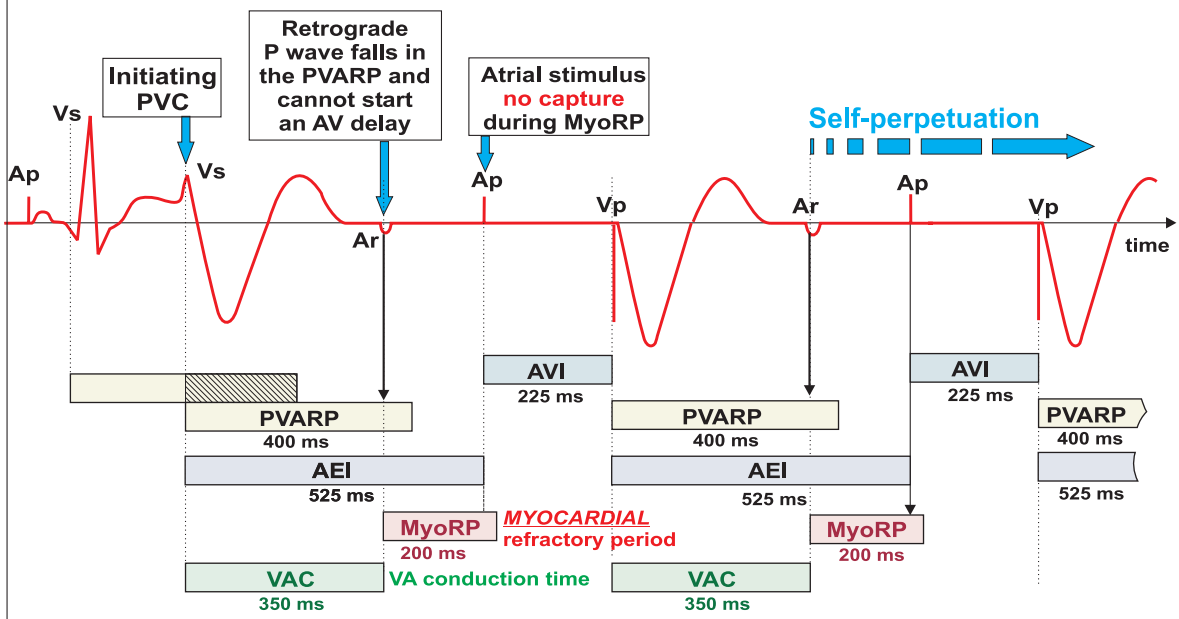
IN CAUDA VENENUM !!!



Abbreviations : AS = atrial sense ; AR =atrial sense in refractory period ; VP = ventricular pace ; AVI = atrioventricular interval ; URI = upper rate interval ; PVARP = postventricular atrial refractory period ;
In cauda venenum = (latin) the venom is in the tail !

REPETITIVE NONREENTRANT VA SYNCHRONY (RNRVAS)





PREDISPOSING FACTORS
- * Long VA conduction time
- * Long PVARP
- * Short LRI (lower rate interval)
- * Long AVI

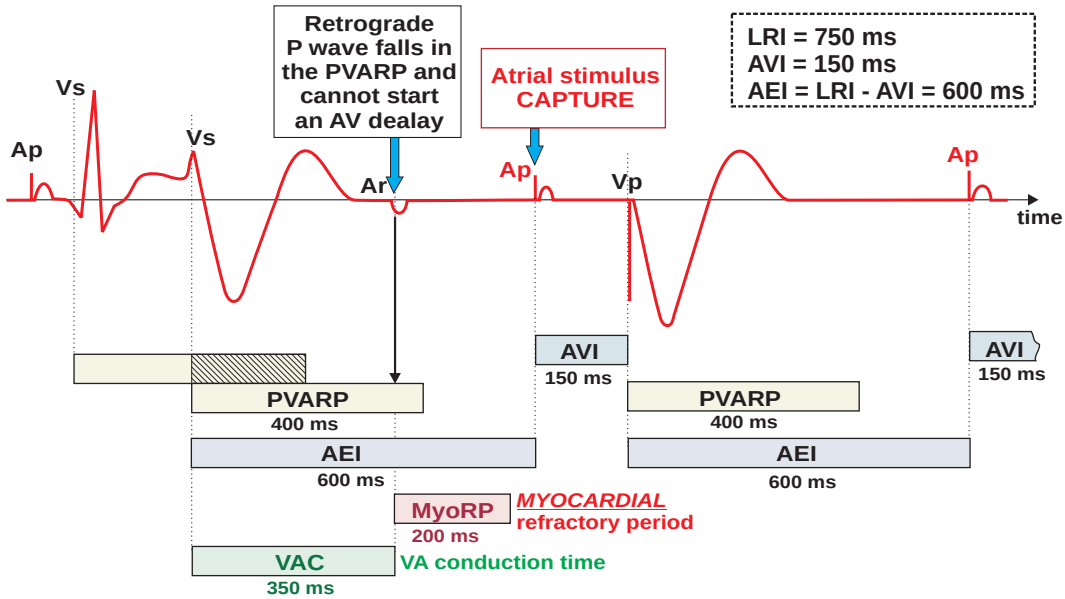
Abbreviations : Ap = atrial pace ; Ar = atrial sense during refractory period ; Vp = ventricular pace ; Vs = ventricular sense ; AVI = pacemaker AV delay ; PVARP = postventricular atrial refractory period ; PVC = ventricular premature complex ; AEI = atrial escape interval

A. F. Sinnaeve

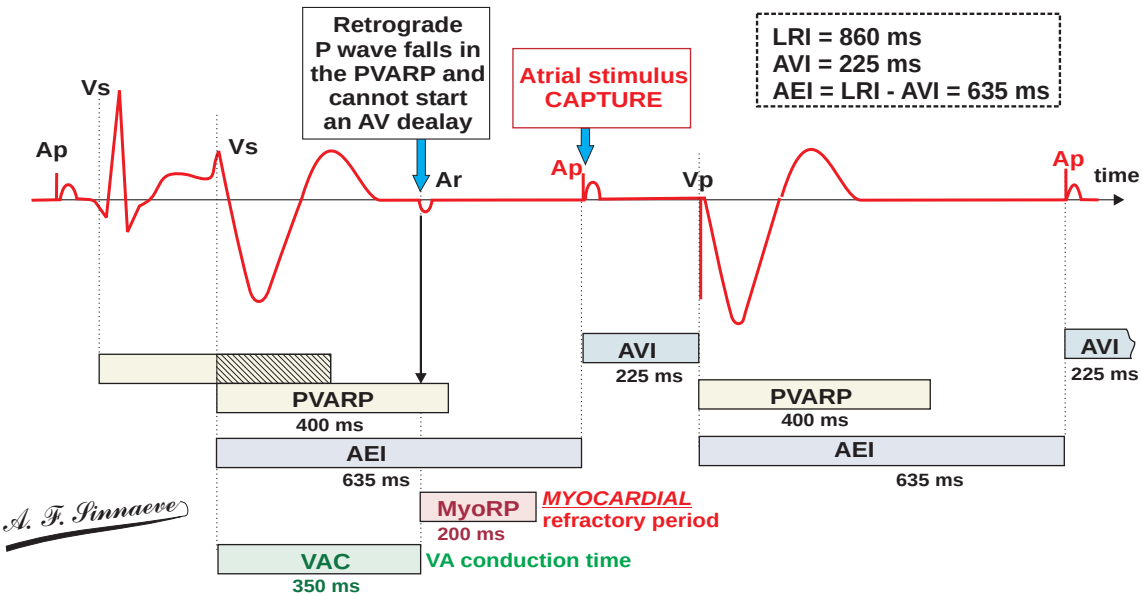
RNRVAS - PREVENTION AND TREATMENT

PROLONGATION OF THE ATRIAL ESCAPE INTERVAL TO DISPLACE THE ATRIAL STIMULUS FROM THE RETROGRADE P WAVE

CORRECTION 1 : SHORTER AVI



CORRECTION 2 : LONGER LRI



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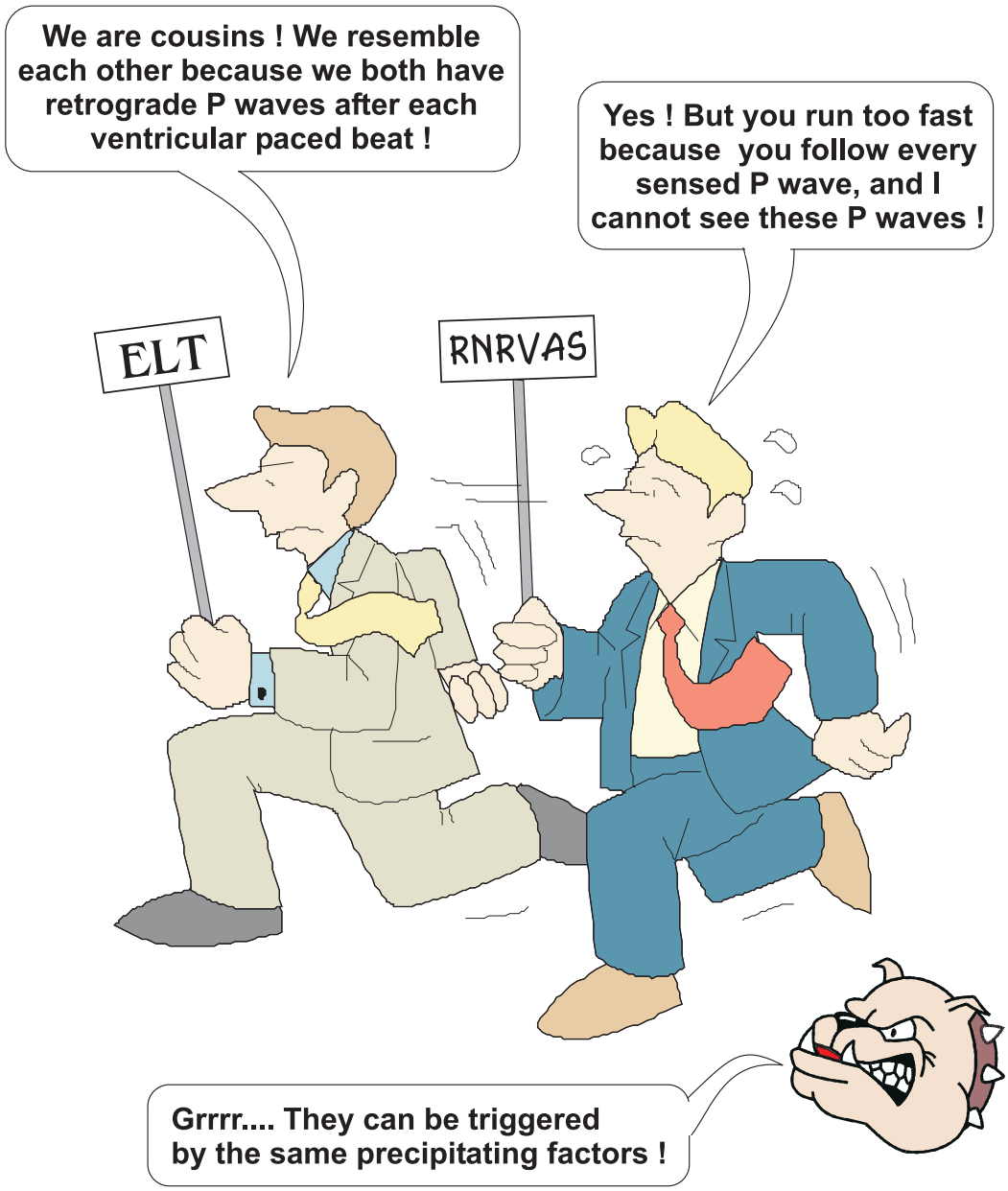
Abbreviations : AEI = atrial escape interval ; Ap = atrial pace ; Ar = atrial sense during refractory period ; Vp = ventricular pace ; Vs = ventricular sense ; AVI = pacemaker AV delay ; PVARP = postventricular atrial refractory period ; PVC = ventricular premature complex ; LRI = lower rate interval ; RNRVAS = repetitive nonreentrant VA synchrony

SUSTAINED PACEMAKER MEDIATED RHYTHMS RELATED TO VENTRICULOATRIAL (VA) SYNCHRONY



Abbreviations : ELT = endless loop tachycardia
RNRVAS = repetitive non-reentrant VA synchrony

ALGORITHMS FOR AUTOMATIC TERMINATION OF ENDLESS LOOP TACHYCARDIA

DETECTION OF THE TACHYCARDIA

* number of consecutive paced cycles at upper rate
* number of consecutive paced cycles above a programmed rhythm
* stability of the Vp-As (VP) interval

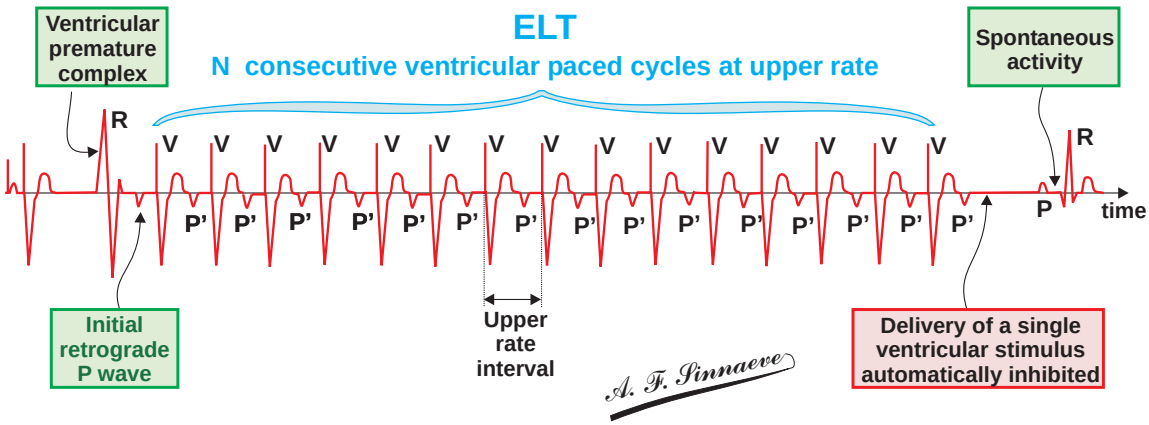
TERMINATION OF THE TACHYCARDIA by uncoupling atrial and ventricular events

* Inhibition of one (1) ventricular stimulus
* extension of one (1) PVARP to contain the following P wave

AFTER THE INTERVENTION

* spontaneous atrial activity at normal rate
* atrial pacing at an appropriate rate
* restart of detection if there is still a tachycardia

System 1 : number of ventricular paced cycles at upper rate

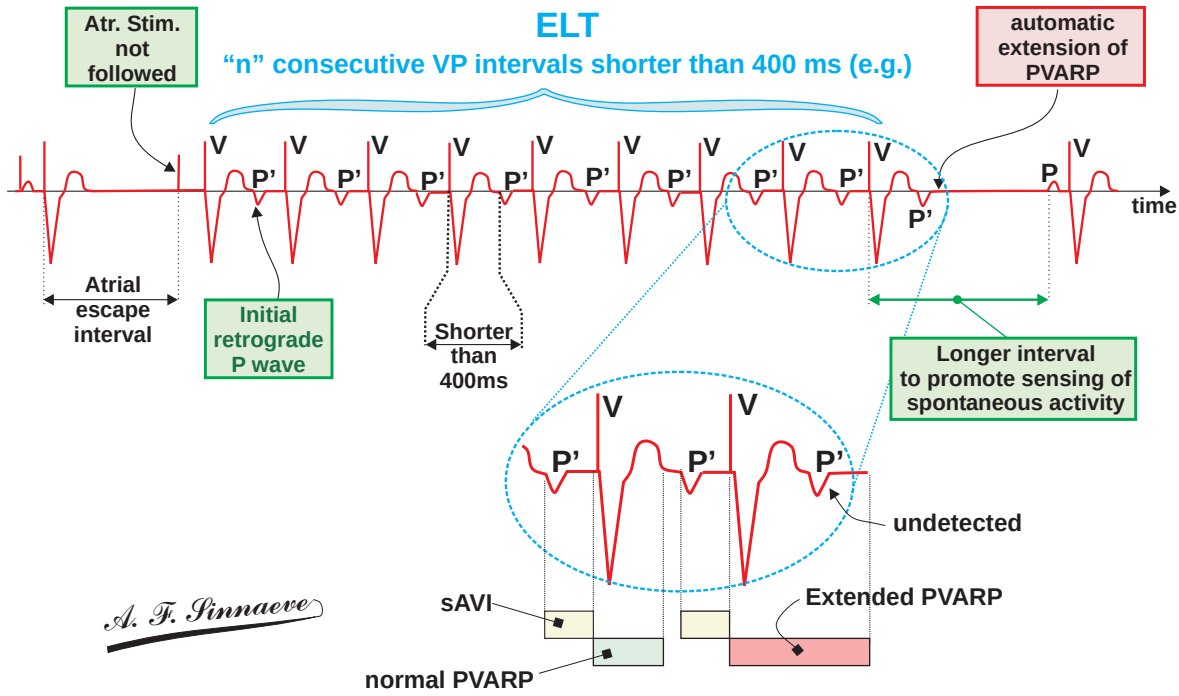


In some pacemakers, the number N of consecutive ventricular paced cycles may be programmable.

Abbreviations : ELT = endless loop tachycardia = PMT = pacemaker-mediated tachycardia ; P = anterograde P wave ; P' = retrograde P wave ; PVARP = postventricular atrial refractory period ; R = spontaneous ventricular event ; sAVI = sensed AV delay ; V = ventricular stimulus ; VP = Vp-As = interval between a ventricular stimulus and the consequent atrial event

ALGORITHMS FOR AUTOMATIC TERMINATION OF ENDLESS LOOP TACHYCARDIA

System 2 : “n” consecutive Vp-As or VP intervals shorter than a given value



A PMT (= ELT) may be present if the following criteria are fulfilled :
*** “n” consecutive VP intervals shorter than a specified duration**
*** all intervals start with a ventricular paced event**
*** all intervals end with an atrial sensed event**

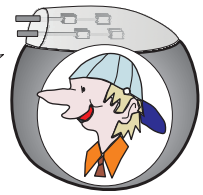
Some models have sensor corroboration before intervening i.e. they only assume a PMT if the sensor indicated interval is longer (or sensor indicated rate is slower) than a certain value to prevent misdiagnosis of sinus tachycardia for PMT

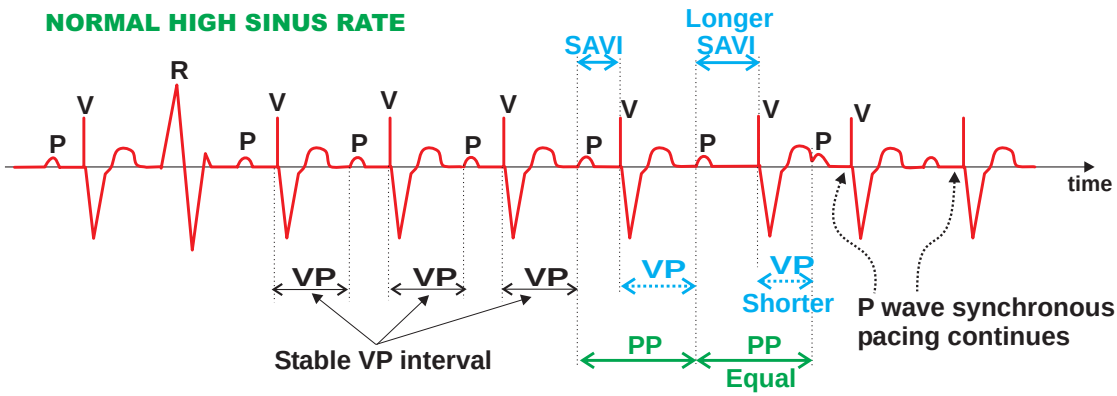
Abbreviations : ELT = endless loop tachycardia = PMT = pacemaker-mediated tachycardia ; P = anterograde P wave ; P’ = retrograde P wave ; PVARP = postventricular atrial refractory period ; R = spontaneous ventricular event ; sAVI = sensed AV delay ; V = ventricular stimulus ; VP = Vp-As = interval between a ventricular stimulus and the consequent atrial event

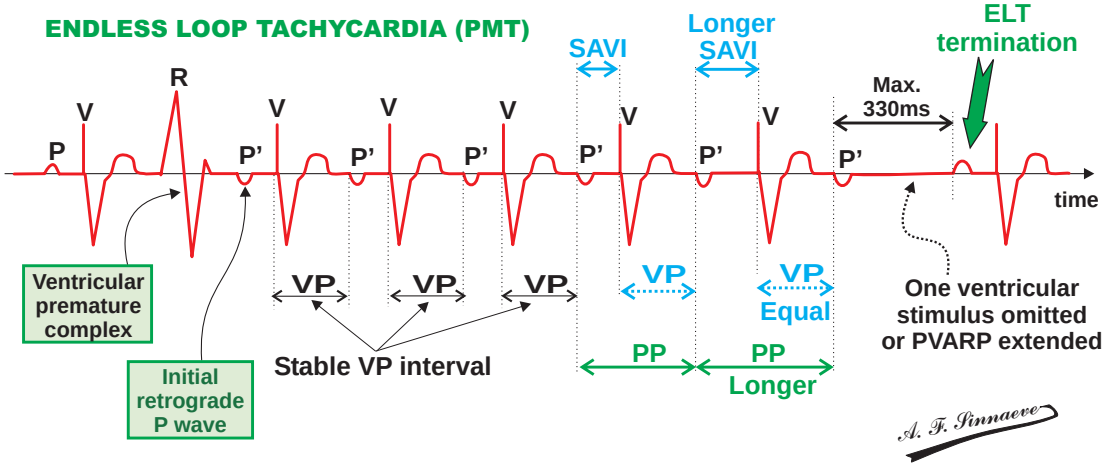
ALGORITHMS FOR AUTOMATIC TERMINATION OF ENDLESS LOOP TACHYCARDIA

System 3 : monitoring the VP interval

VP is the interval from the ventricular stimulus to the point of sensing atrial depolarization. I know that a stable VP interval might indicate a possible ELT or PMT. My microprocessor is instructed to monitor such stable intervals and to change the sAVI upon detection of it ! If the VP interval remains constant, the P in the VP interval is a retrograde P wave (P').







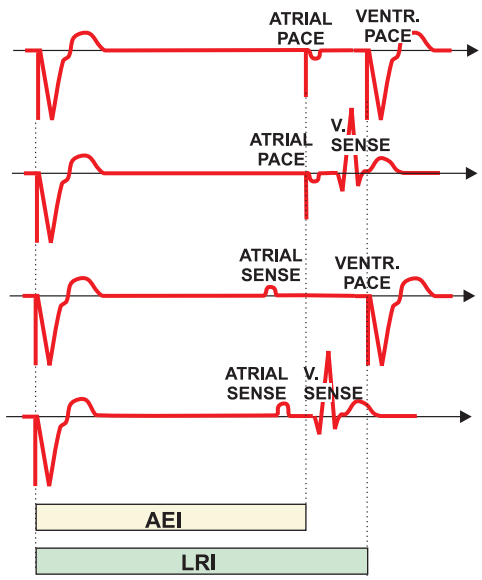
Abbreviations : ELT = endless loop tachycardia = PMT = pacemaker-mediated tachycardia ; P = anterograde P wave ; P' = retrograde P wave ; R = spontaneous ventricular event ; sAVI = sensed AV delay ; V = ventricular stimulus ; VP = interval between a ventricular stimulus and the consequent atrial event

DDD

DVI ? VDD ? DOO ? DDI ?

ALL DUAL CHAMBER PACEMAKERS FUNCTION IN THE DDD MODE

* The garden of dual chamber pacemakers
* The DVI mode
* The DDI mode
* The VDD mode
* Two types of VDD timing cycles
* Single lead VDD pacing
* Selection of pacing mode - 1
* Selection of pacing mode - 2



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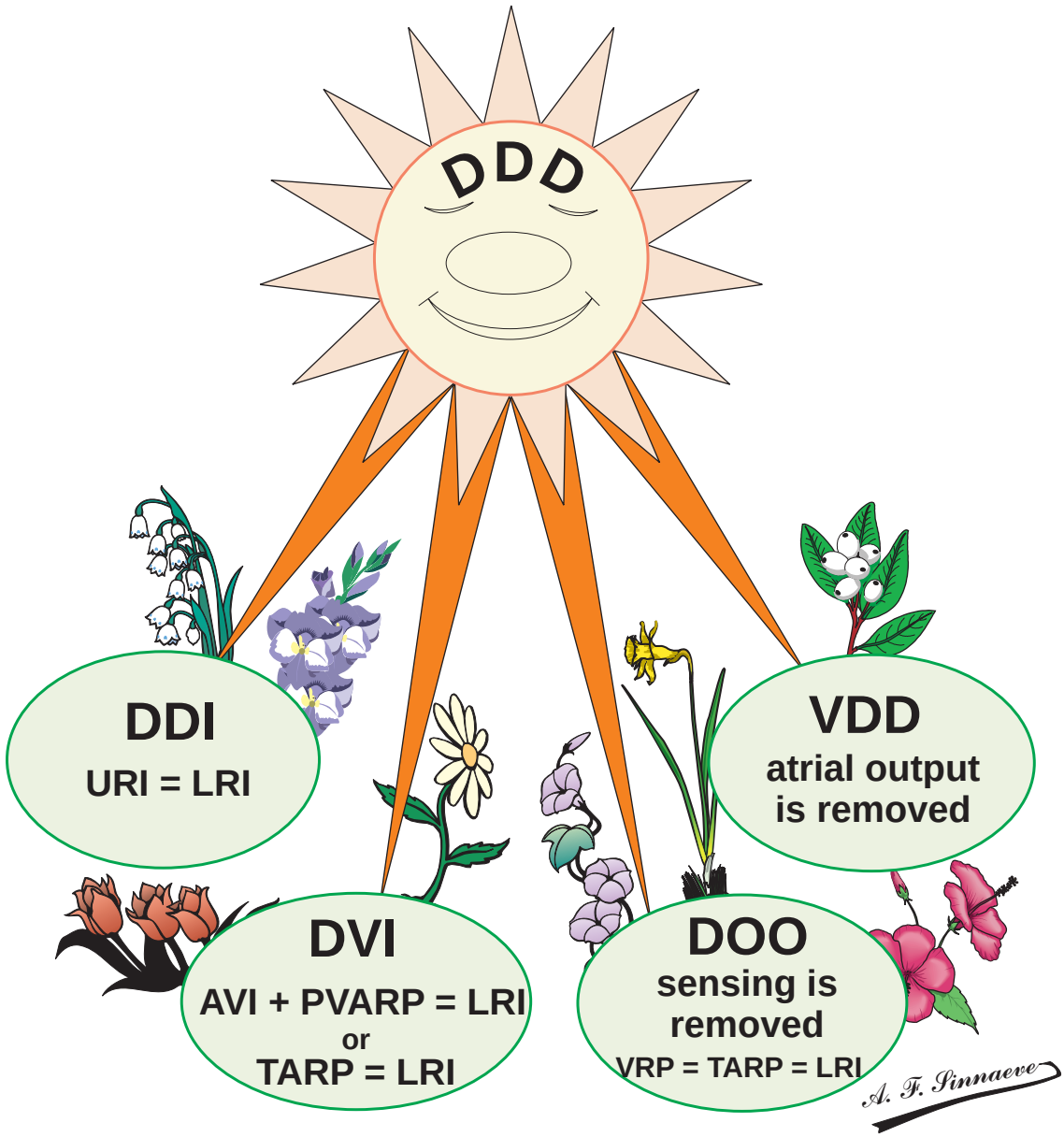
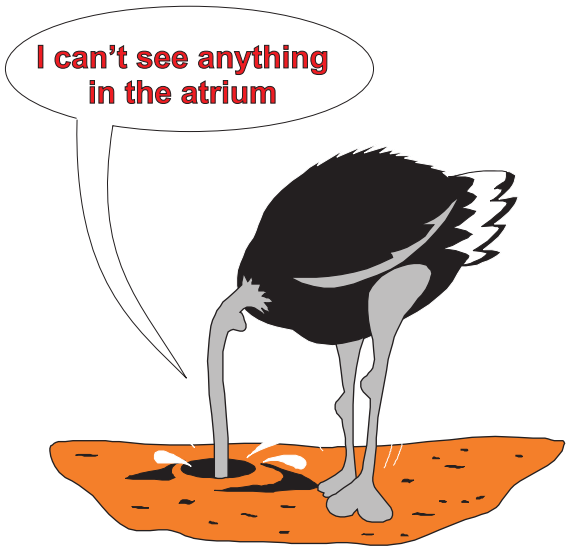
DDD GOVERNS THE GARDEN OF DUAL CHAMBER PACING

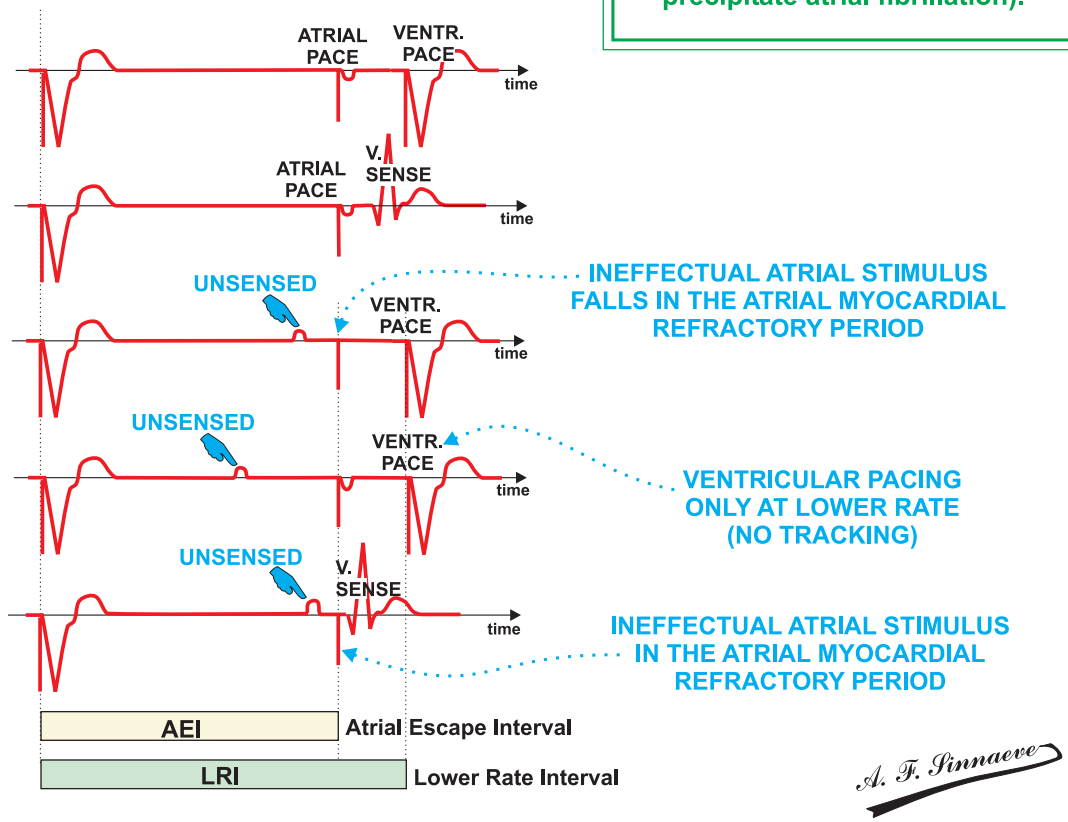


Abbreviations : URI = upper rate interval; LRI = lower rate interval; AVI = atrioventricular interval or AV delay; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; VRP = ventricular refractory period



DUAL CHAMBER PACING in DVI MODE

Pacing occurs in both the atrium and ventricle (D) but there is only sensing in the ventricle (V). The mode of response is inhibition (I). No sensing of the atrial electrogram and lack of tracking results in asynchronous atrial pacing (competitive atrial pacing may precipitate atrial fibrillation).



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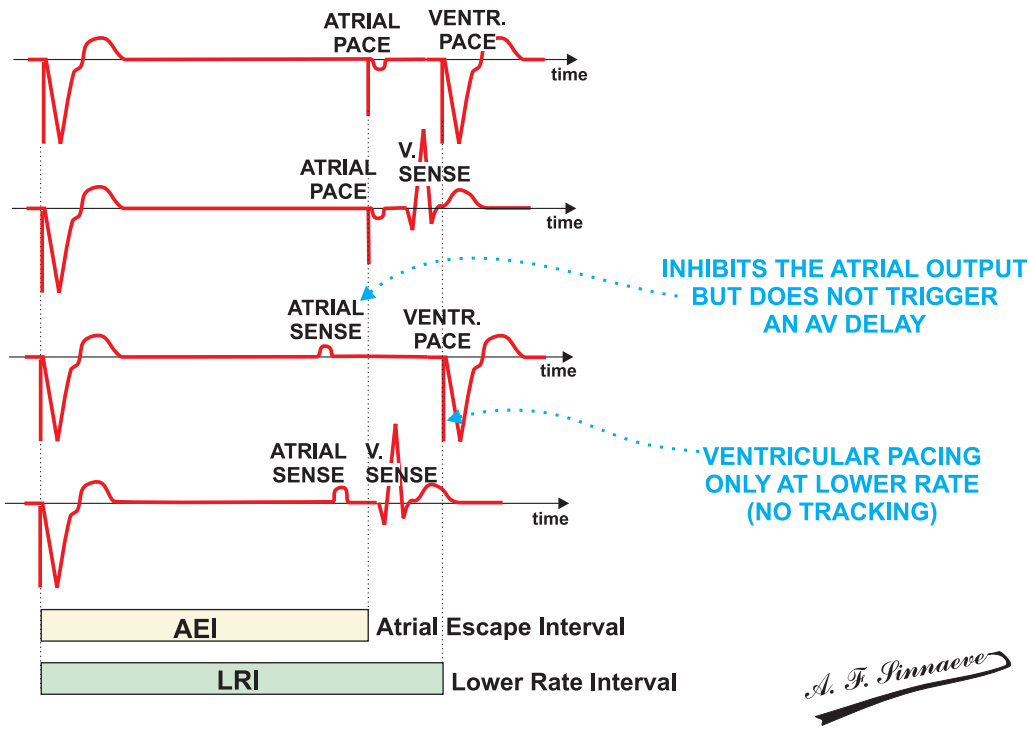
DUAL CHAMBER PACING in DDI MODE

Pacing and sensing occur in both the atrium and ventricle (DD) and the mode of response is inhibited (I).
Sensed atrial activity inhibits the atrial output impulse, but does not trigger a ventricular output impulse. In other words an atrial sensed event cannot produce a physiologic AV delay equal or shorter to the AV delay initiated by an atrial paced event .



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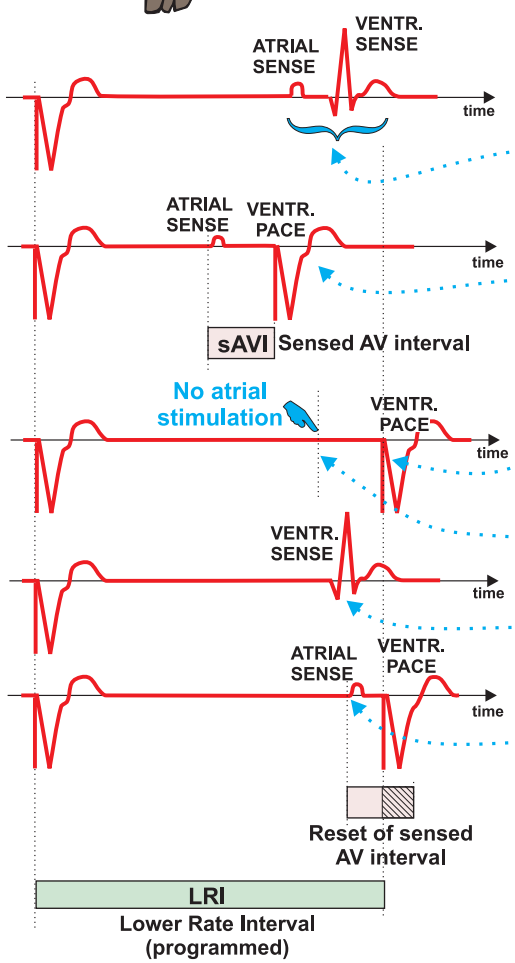
DUAL CHAMBER PACING in VDD MODE

In the VDD mode there is no atrial stimulus and therefore no AV crosstalk. There are no crosstalk timing cycles : postatrial ventricular blanking period and ventricular safety pacing function.

But, this is not for me... This is for young people and they can have fast upper rates!!!

Pacing occurs in the ventricle only (V) but there is sensing in both the atrium and ventricle (D). The mode of response is inhibition and triggering (D).
A sensed atrial event triggers (T) a ventricular stimulus after completion of the AVI. A sensed ventricular event inhibits the ventricular output (I). Hence the response is T + I = D.



Atrial sensing. Conducted QRS occurs before completion of the AV delay and therefore inhibits the ventricular stimulus

Atrial tracking : atrial sensing followed by ventricular pacing after the programmed AV delay

VVI pacing at the lower rate during sinus bradycardia slower than the programmed pacemaker lower rate

As there is no atrial stimulation, there is no need for an atrial escape interval

Resets the lower rate interval

The P wave is sensed but not tracked, i.e. it does not trigger a ventricular stimulus after the programmed AV delay. The P wave is not tracked because it falls in the implied AV delay which terminates with the emission of a ventricular stimulus at the completion of the lower rate interval.

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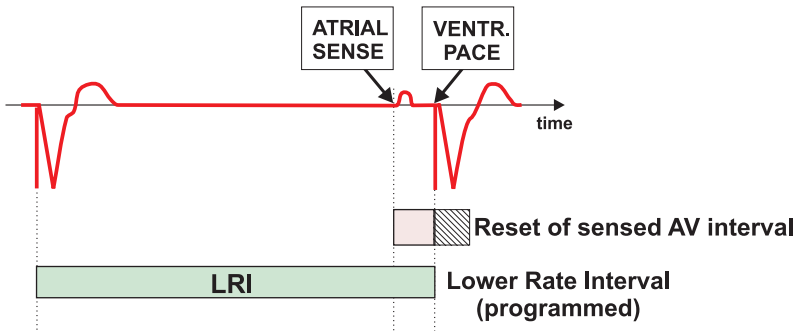
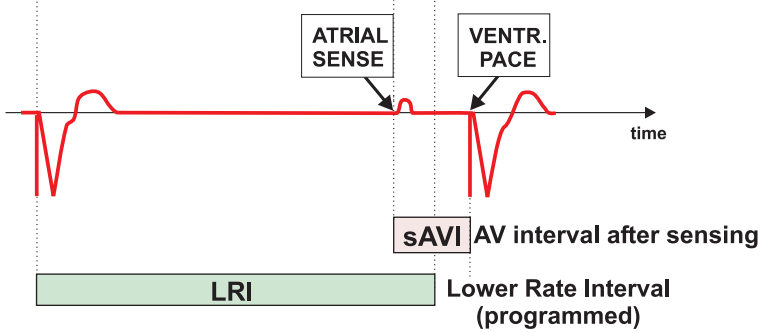
2 TYPES OF VDD TIMING CYCLES

TYPE 1 : The lower rate interval dominates



TYPE 2 : The AV delay (sAVI) dominates



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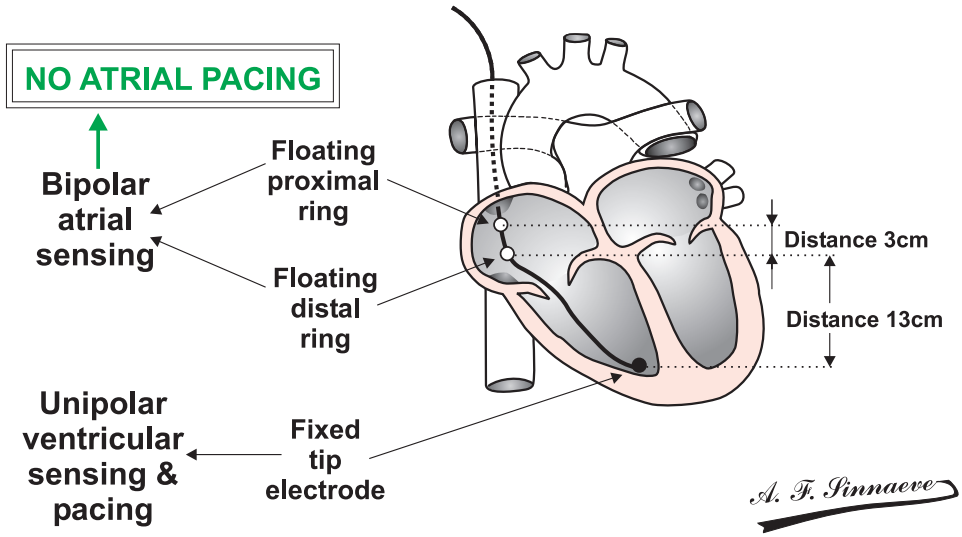
SINGLE LEAD VDD PACING



Atrial signals from floating (non-contact) electrodes tend to be small and therefore high atrial sensitivity is required for sensing

This system should not be used in patients with sick sinus syndrome (sinus bradycardia) or atrial chronotropic incompetence (abnormal response of atrial rate on exercise)

WHICH PACING MODE SHOULD BE CHOSEN? A DECISION TREE

START

Check carefully the ATRIAL RHYTHM

Any persistent or predominant atrial tachyarrhythmias present ?

Yes

No

Is the response to exercise chronotropic adequate ?

Yes

No

VVI ventricular demand pacing

VVIR rate-adaptive ventr. demand pacing

Is the present or anticipated AV conduction normal?

Yes

No

Is the response to exercise chronotropic adequate ?

Yes

No

AAI atrial demand pacing

AAIR rate-adaptive atrial demand pacing

Is the response to exercise chronotropic adequate ?

Yes

No

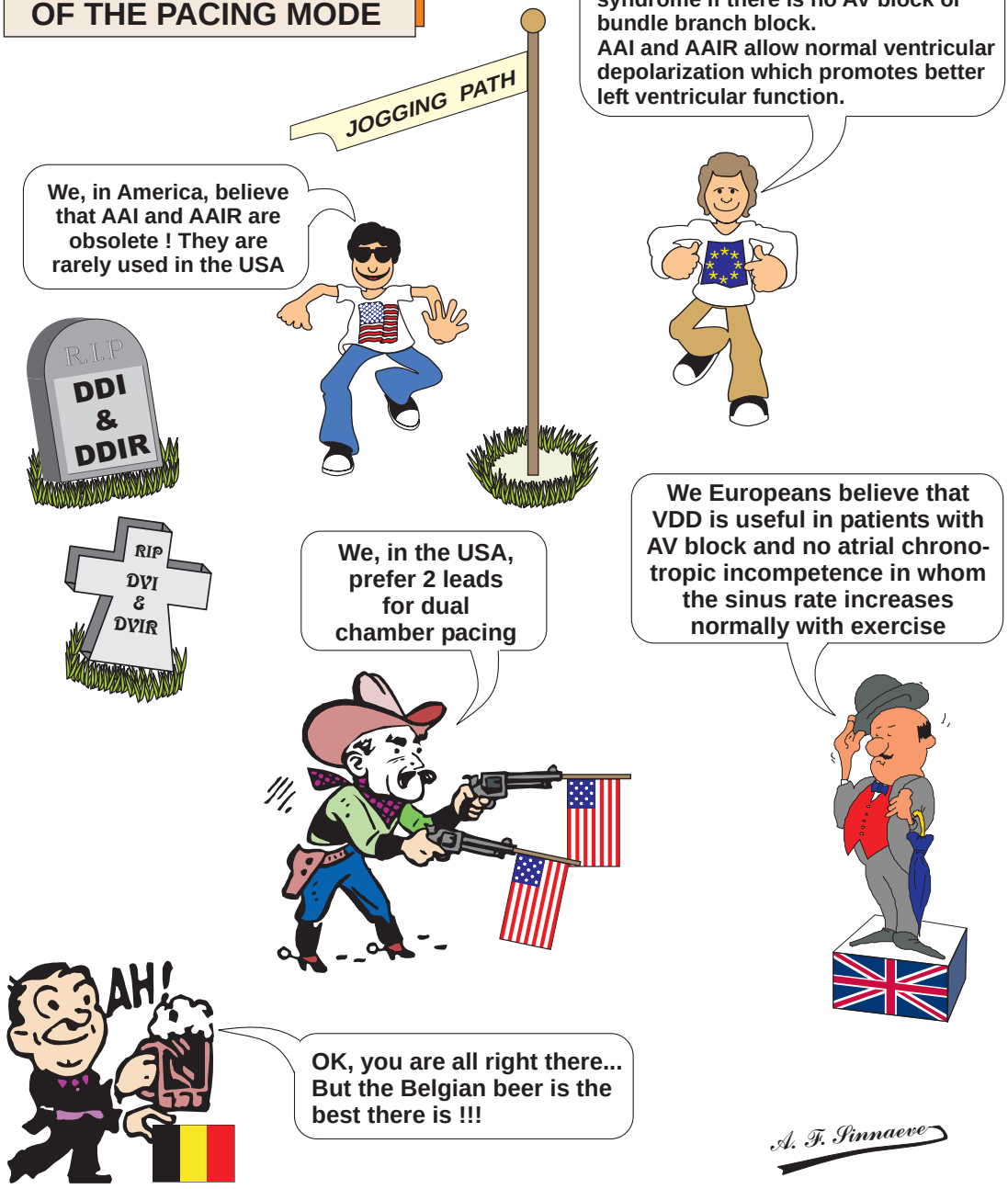
DDD dual chamber AV synchron. pacing

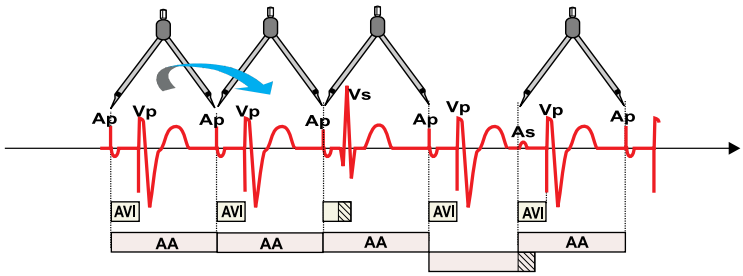
DDDR rate-adaptive dual chamber pacing

A. F. Simaeve

Note : VVIR, DDDR and AAIR are equal to VVI, DDD and AAI modes respectively with additional rate-adaptive function provided by an artificial sensor for rate increase on activity.

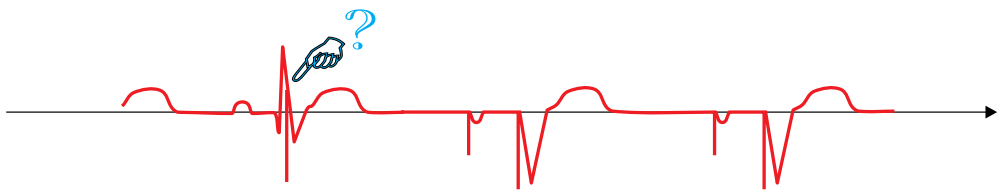
CONTROVERSIES IN THE SELECTION OF THE PACING MODE





TYPES OF LOWER RATE TIMING

* Atrial-based lower rate timing - part 1.
* Atrial-based lower rate timing - part 2.
* Atrial-based lower rate timing - part 3 (AV delay).
* Faster atrial pacing rate with ventricular-based lower rate timing.
* What is the pacing mode during inhibition ?
* Spike in QRS complex.



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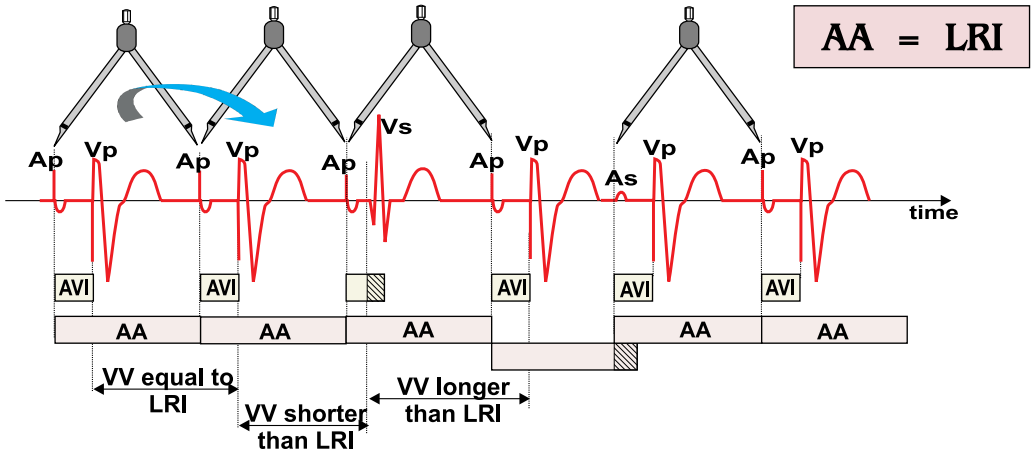
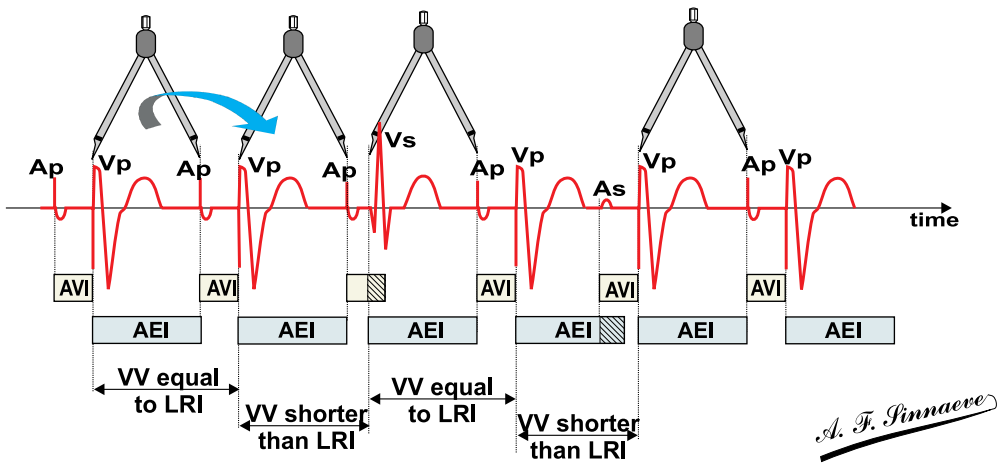
ATRIAL-BASED LOWER RATE TIMING - PART 1

With atrial-based lower rate timing, the AA interval (Ap-Ap or As-Ap) is constant and equal to the programmed LRI. The atrial escape interval (Vp-Ap or Vs-Ap) varies to maintain a constant AA interval as shown in this example where Vs-Ap > Vp-Ap .

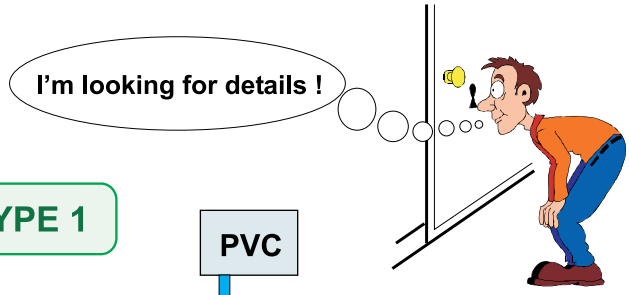


With ventricular-based lower rate timing the AEI or atrial escape interval (Vp-Ap or Vs-Ap) is constant

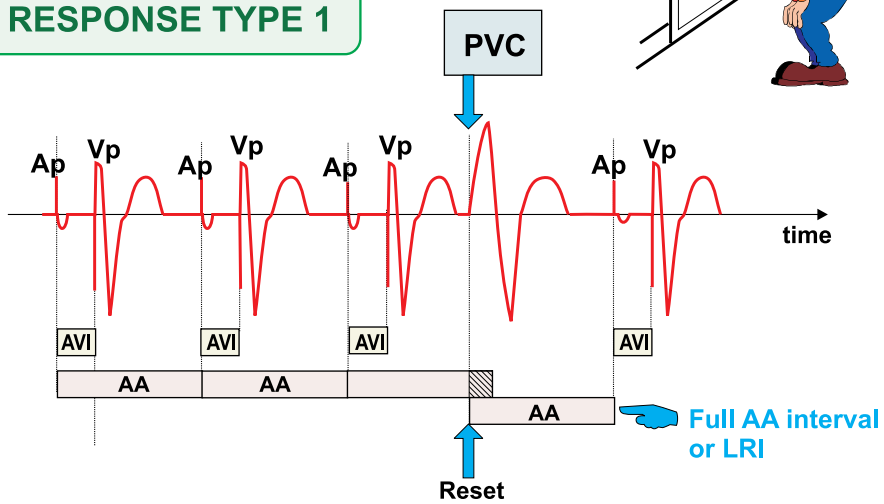


Abbreviations : Ap = atrial pace ; As = atrial sense ; AEI = atrial escape interval ; AVI = AV delay ; AA = programmed atrial lower rate interval = Ap-Ap or As-Ap ; LRI = lower rate interval ; VV = interval between two consecutive ventricular events

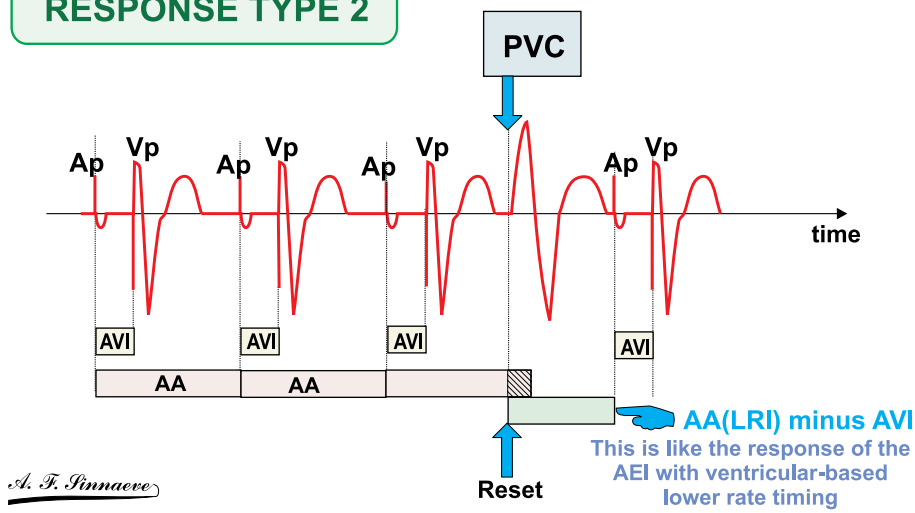
ATRIAL-BASED LOWER RATE TIMING - PART 2
Response after a premature ventricular complex (PVC)



RESPONSE TYPE 1



RESPONSE TYPE 2



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Abbreviations : Ap = atrial pace ; As = atrial sense ; AEI = atrial escape interval ; AVI = AV delay ;
AA = programmed atria-based lower rate interval = Ap-Ap or As-Ap interval ;
LRI = lower rate interval ; PVC = premature ventricular complex

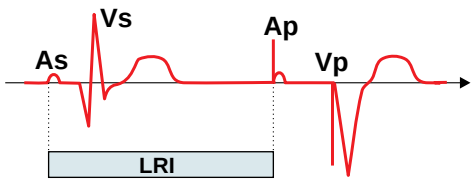
ATRIAL-BASED LOWER RATE TIMING - PART 3

This is a difficult subject !!!
Which circumstances involving the AV delay will activate atrial-based lower rate timing ??

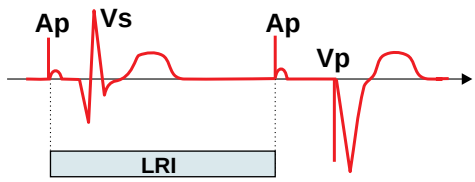
We know that circumstances causing an *AV delay longer than the programmed value* are always associated with ventricular-based lower rate timing

When the *AV delay is shorter than the programmed value* of Ap-Vp any number of the following combinations of AV delay can initiate atrial-based lower rate timing

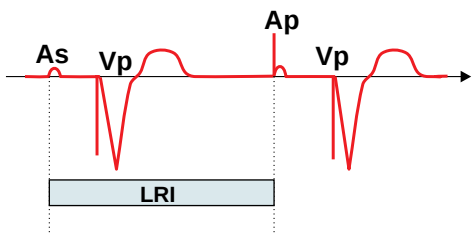
As-Vs
normal conduction



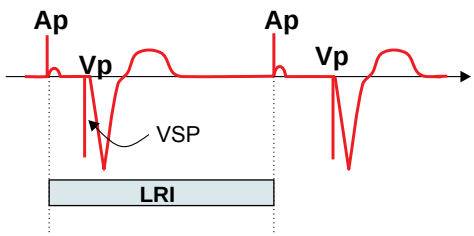
Ap-Vs
normal conduction



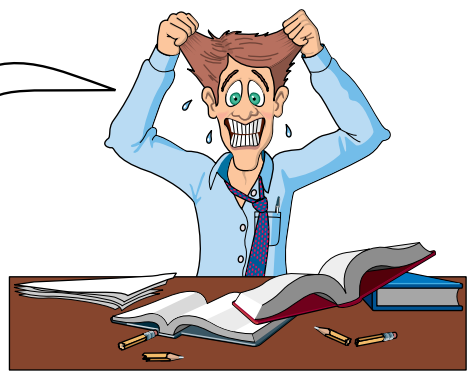
As-Vp < Ap-Vp
programmed shorter than Ap-Vp



Abbreviated Ap-Vp
(ventricular safety pacing due to crosstalk)



Any one of the combinations of AV delay (As-Vp, As-Vs, Ap-Vs, abbreviated Ap-Vp) can initiate atrial-based lower rate timing. Without knowledge of the type of lower rate timing according to circumstances, one cannot interpret the ECG !!!!



Abbreviations : AVI = AV delay ; AEI = atrial escape interval ; AVE = extension of AVI ; LRI = lower rate interval ; Ap = atrial pacing ; As = atrial sensing ; Vp = ventricular pacing ; Vs = ventricular sensing ; VSP = ventricular safety pacing

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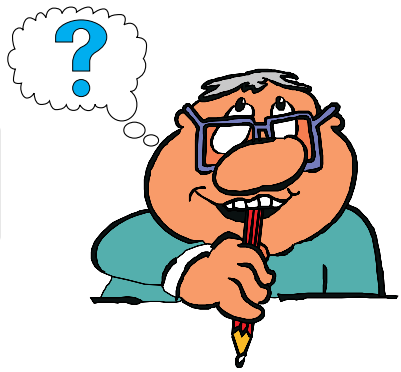
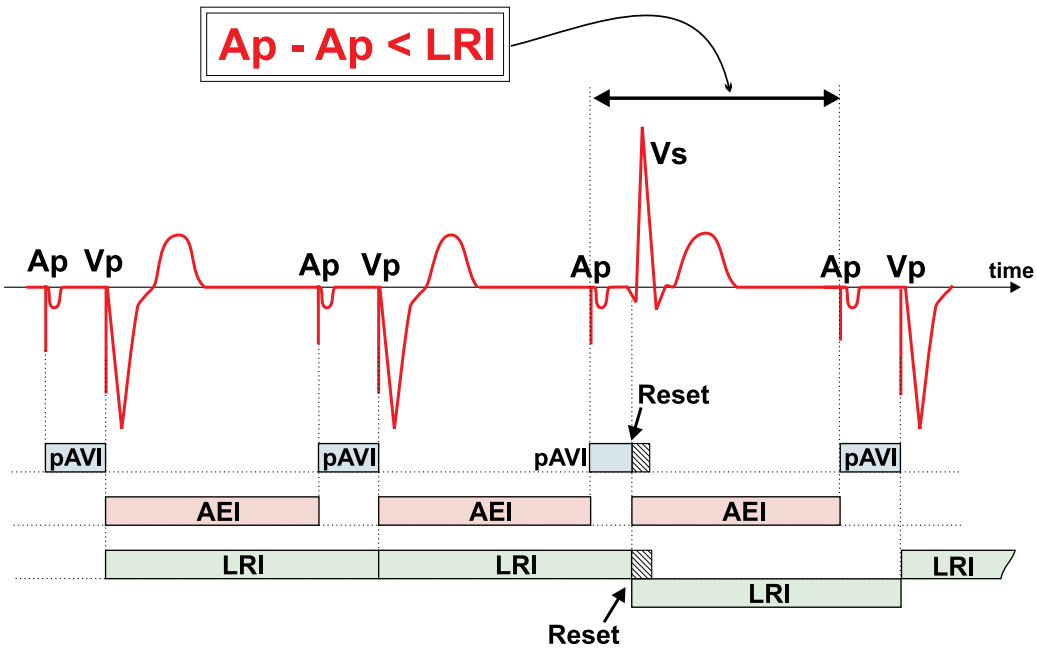
THE ATRIAL PACING RATE MAY BE FASTER THAN THE PROGRAMMED LOWER RATE





With ventricular-based lower rate timing, the atrial escape interval (AEI) and the lower rate interval (LRI) start from a sensed or paced ventricular event. The hallmark of ventricular-based lower rate timing is constancy of the AEI

Abbreviations : Ap = atrial pace ; Vp = ventricular pace ; Vs = ventricular sense ;
pAVI = AV delay after pacing ; AEI = atrial escape interval ;
LRI = lower rate interval

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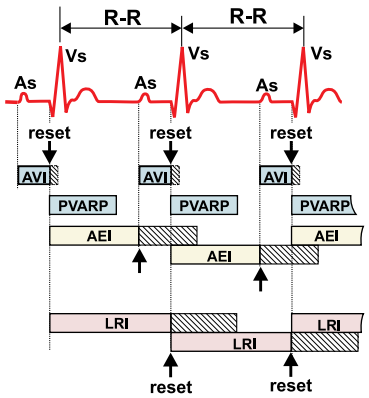
YOU MAY HAVE A QUESTION ABOUT THE PACING MODE IF THE R-R INTERVAL IS SHORTER THAN THE ATRIAL ESCAPE INTERVAL

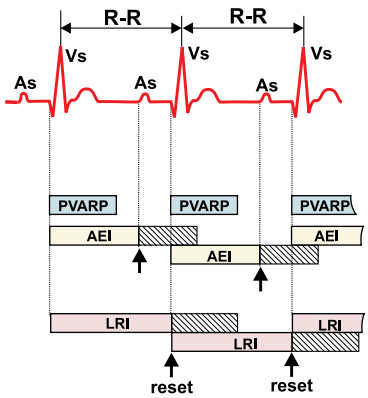
At relatively fast spontaneous rates and normal AV conduction, nobody can tell whether the mode is DDD or DDI or DVI by only looking at the ECG !!!

DDD, DDI or DVI modes with R-R or Vs-Vs interval < AEI

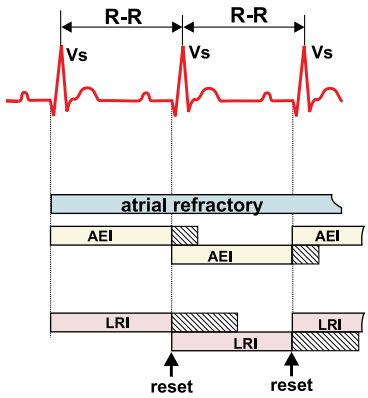
DDD MODE



DDI MODE



DVI MODE



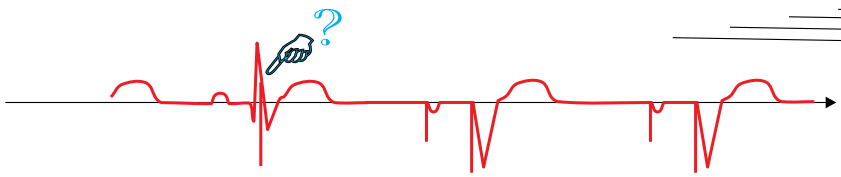
The same ECG may also represent the VDD mode if As-Vs < programmed As-Vp and the spontaneous atrial rate is faster than the programmed lower rate

A. F. Sinnaeve

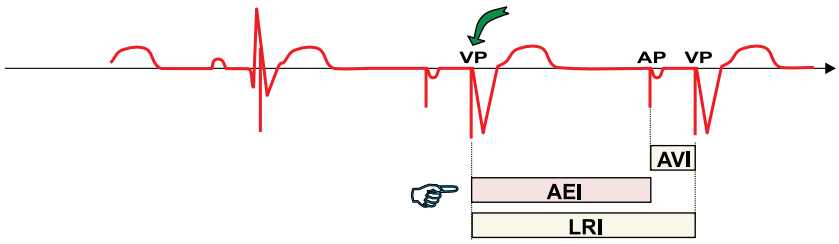
Abbreviations : As = atrial sense ; Vs = ventricular sense ; AVI = AV delay ; AEI = atrial escape interval ; LRI = lower rate interval ; PVARP = postventricular atrial refractory period

It took some time and a lot of exercise to become an expert in marching backwards, but at the end it isn't difficult at all.....

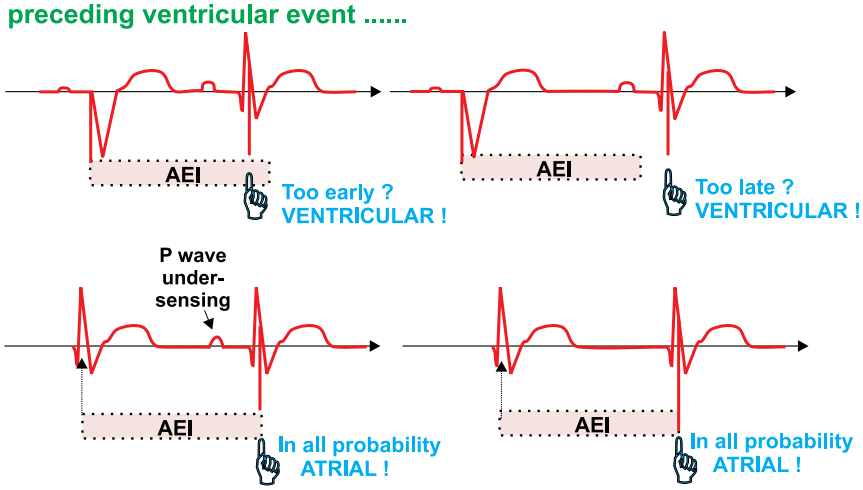
A SPIKE WITHIN A QRS COMPLEX ! IS IT AN ATRIAL OR A VENTRICULAR STIMULUS ?



① **Establish the duration of the AEI, starting with any VP**
(alternatively the duration of AEI can be determined from the onset of a sensed QRS complex to the succeeding atrial stimulus)



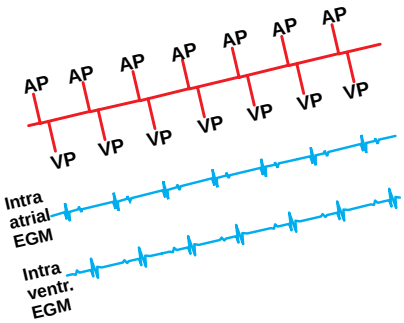
② **Measure the interval from the stimulus in question back to the preceding ventricular event .....**

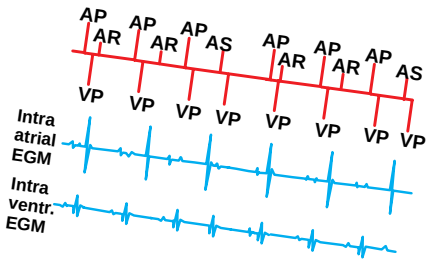


This rule is only valid for DDD pacemakers with ventricular-based lower rate timing

A. F. Sinnaeve

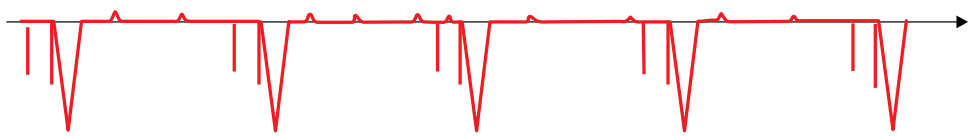
Abbreviations : Ap = atrial pace; Vp = ventricular pace; AEI = atrial escape interval; AVI = AV delay; LRI = lower rate interval





ATRIAL CAPTURE

* Testing for atrial capture - part 1
* Testing for atrial capture - part 2
* Testing for atrial capture - part 3
* Pitfalls in the evaluation of atrial capture
* Dislodgment of the atrial lead - part 1
* Dislodgment of the atrial lead - part 2
* Dislodgment of the atrial lead - part 3
* Dislodgment of the atrial lead - part 4
* Reversed atrial and ventricular leads



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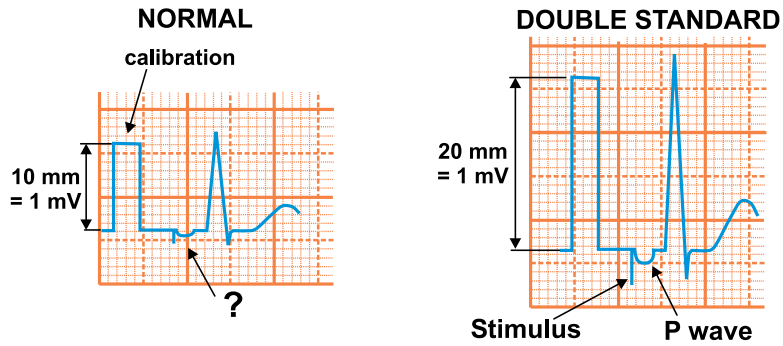
HOW TO TEST FOR ATRIAL CAPTURE - PART1

ONE

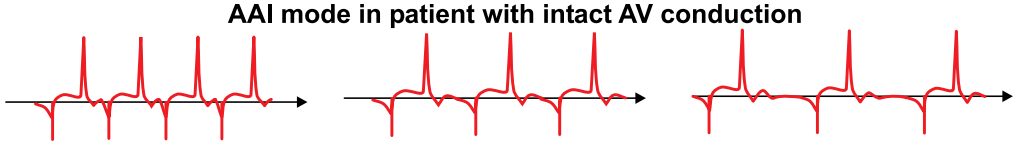
Take a 12-lead ECG recorded at double standardization to bring out paced P waves and/or tiny bipolar stimuli



TWO

Reprogram to the AAI or AOO mode (at several pacing rates)

AAI mode in patient with intact AV conduction



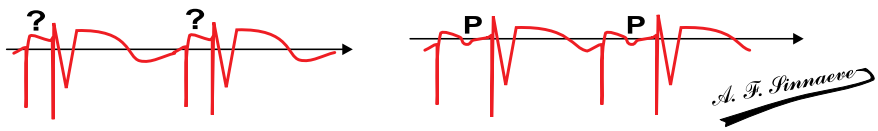
Atrial capture is present when the rate of the conducted QRS complexes (ventricular rate) always remains equal to the changing atrial pacing rates used during testing

AAI mode in patient with complete AV block and idioventricular rhythm

This maneuver can only be performed if there is an underlying ventricular rhythm during AAI pacing. A spontaneous ventricular rhythm is often present when the pacing rate in the VVI mode is slowly decreased to allow the emergence of a slow spontaneous idioventricular rhythm. If this rate is satisfactory, testing is done in the AAI mode.

THREE

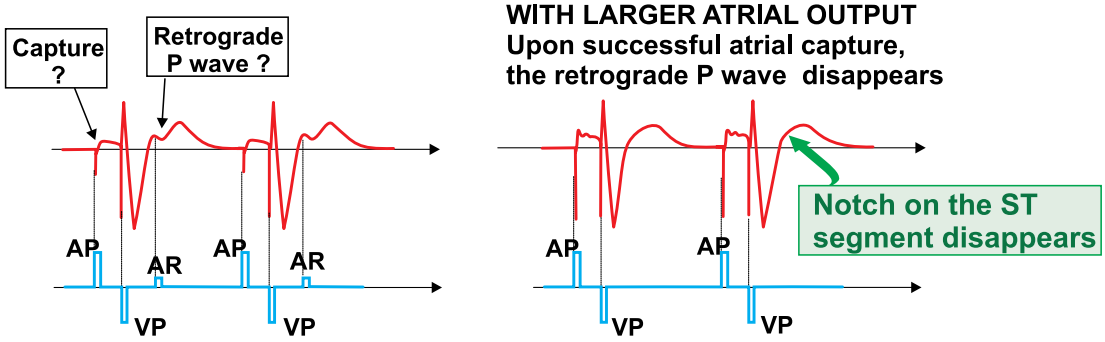
Unmask P waves by programming a long AV delay (250-300 ms) e.g. with latency or considerable delay in interatrial conduction



HOW TO TEST FOR ATRIAL CAPTURE - PART2

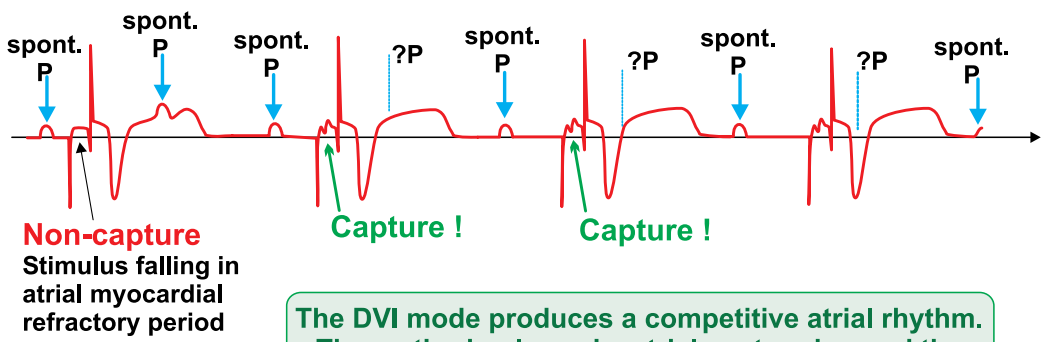
FOUR

Retrograde VA conduction suggests lack of capture by the preceding atrial stimulus. Verify retrograde conduction by event markers and eventually increase the atrial output to capture the atrium



FIVE

Program the DVI mode for patients with relatively fast sinus rhythm



The DVI mode produces a competitive atrial rhythm. The method only seeks atrial capture beyond the atrial myocardial refractory period

A. F. Sinnaeve

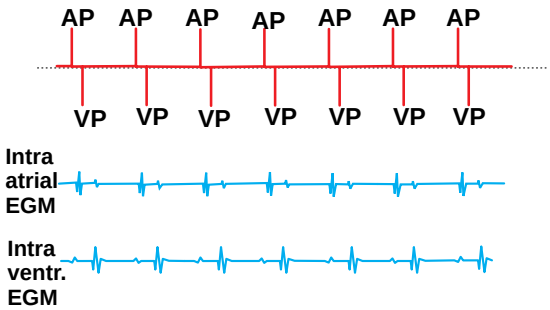
Abbreviations : AP = paced atrial event ; AR = atrial sensing in atrial refractory period ; VP = ventricular paced event ; VA = ventriculoatrial (from ventricle to atrium)

HOW TO TEST FOR ATRIAL CAPTURE - PART 3

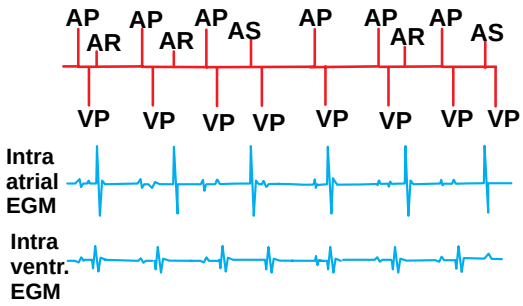
SIX

Using only the programmer, program the DDD mode and increase the atrial pacing rate above the spontaneous rate, then increase or decrease the atrial output and look at the markers

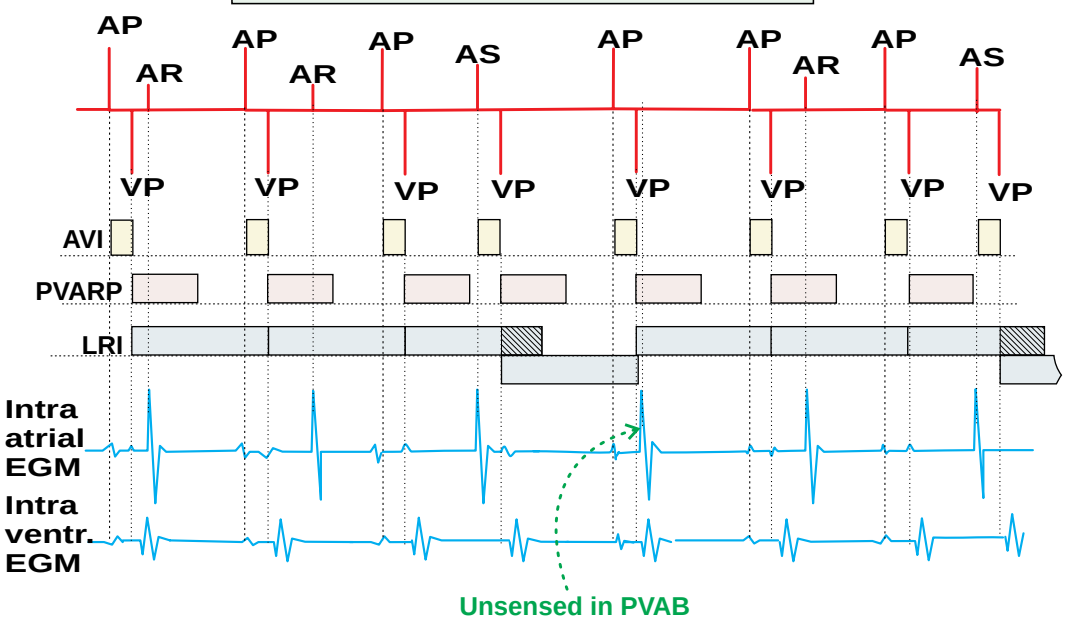
Atrial stimulus 1 V / 0.4 ms
CAPTURE !!!



Atrial stimulus O.5 V / 0.4 ms
NO CAPTURE !!!



CLARIFICATION OF THE MARKERS



Abbreviations : AVI = AV delay ; PVARP = postventricular atrial refractory period ; LRI = lower rate interval ; AP = atrial pacing ; AS = atrial sensing ; AR = atrial sensing during refractory period ; VP = ventricular pacing ; EGM = electrogram ; PVAB = postventricular atrial blanking period

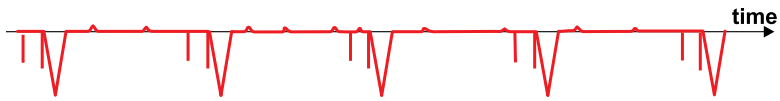
A. F. Pinnaeve

PITFALLS IN THE EVALUATION OF ATRIAL CAPTURE

1. **High threshold situation**
   Suspect hyperkalemia if the QRS is unduly wide. Hyperkalemia causes loss of atrial capture before ventricular capture.

2. **Isoelectric P waves : look at the 12 lead ECG at double standardization.**

3. **Atrial fibrillation**

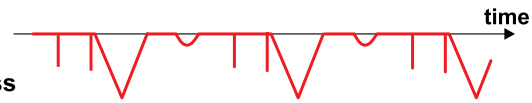


WARNING

The presence of underlying atrial fibrillation is often missed and the patient is denied anticoagulant therapy. The diagnosis is easily made on the ECG by programming the pacemaker to the VVI mode at a slow rate. Look at the telemetered atrial electrogram.

4. **Latency or delayed interatrial conduction.**
   The P wave moves towards and into the QRS. Program the maximum AV delay to bring out the P wave for diagnosis

5. **Repetitive nonreentrant VA synchrony.**
   The atrial output is supra-threshold and loss of atrial capture occurs because the atrial stimulus falls in the atrial myocardial refractory period of the preceding retrograde P wave



6. **Invisible unsensed atrial premature complex that precede the atrial stimulus which then falls in the atrial myocardial refractory period.**

THINK

The telemetered atrial electrogram helps in the diagnosis. However successful atrial capture cannot be determined from the atrial electrogram.

A. F. Sinnaeve

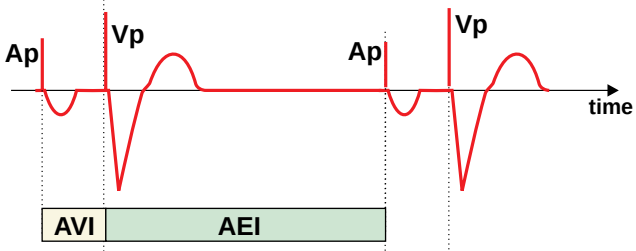
DISLODGMENT OF THE ATRIAL LEAD INTO THE RIGHT VENTRICLE

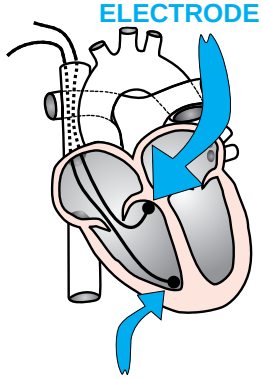
Forewarned is forearmed !!!

PART 1

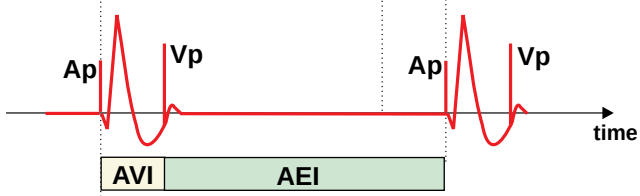
POSSIBLE PATTERNS ON ECG - LEAD II

1 **REFERENCE. Normal AV sequential pacing with programmed AVI and AEI**

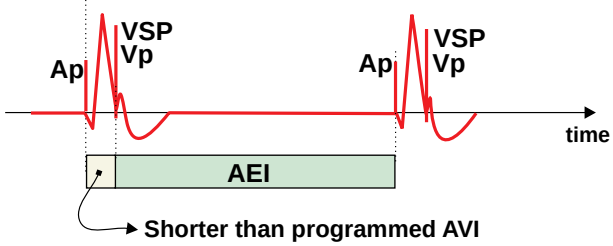




2 **When neither the atrial stimulus nor the paced QRS complex (generated by the atrial channel) is seen by the undisplaced ventricular electrode. Ap paces the RV**



3 **Crosstalk : if the atrial stimulus or the paced QRS complex generated by the displaced atrial electrode is sensed by the undisplaced ventricular electrode, ventricular safety pacing is activated whereupon the Ap-Vp interval shortens**



A. F. Sinnaeve

Abbreviations : Ap = atrial paced event; Vp = ventricular paced event;
AVI = programmed AV delay; AEI = atrial escape interval; VSP = ventricular safety pacing

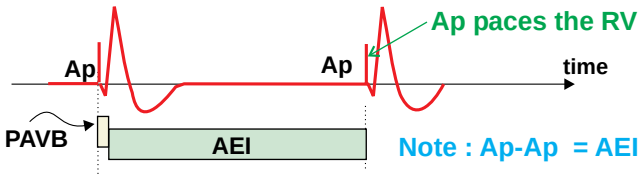
DISLODGMENT OF THE ATRIAL LEAD INTO THE RIGHT VENTRICLE

Forewarned, yes....
But still very tricky!!!

PART 2

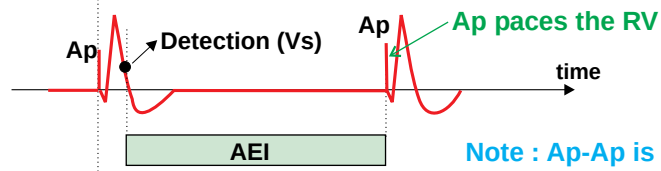
POSSIBLE PATTERNS ON ECG - LEAD II

4 **Crosstalk : if the stimulus from the displaced atrial electrode is sensed by the undisplaced ventricular electrode and the pacemaker has no VSP**



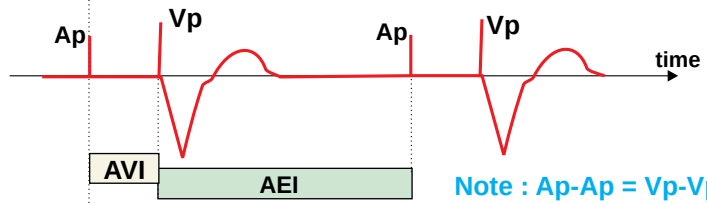
Note : Ap-Ap = AEI + PAVB = shorter than LRI

5 **The correctly positioned ventricular electrode senses a signal of the paced QRS complex induced by the dislodged atrial electrode.**
The pacemaker has no VSP or the detection (Vs) occurs after the VSP interval.



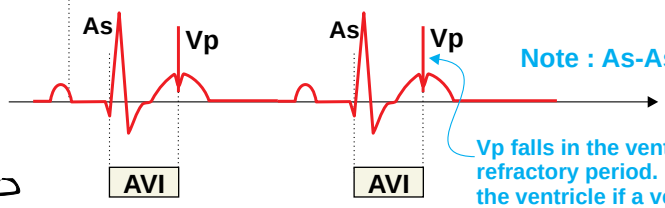
Note : Ap-Ap is still shorter than LRI

6 **Lack of capture of the displaced atrial lead (however programming the maximal atrial output may cause ventricular pacing by the atrial electrode)**



Note : Ap-Ap = Vp-Vp = AVI + AEI = LRI

7 **The atrial electrode senses the spontaneous QRS complex and delivers a ventricular stimulus after an AV delay**



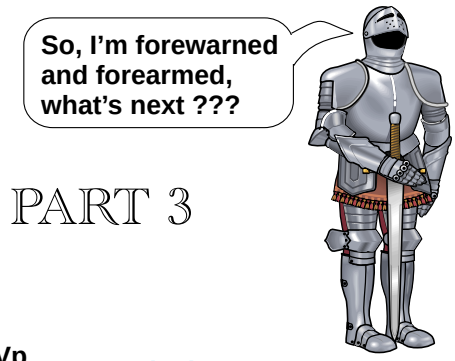
Note : As-As shorter than LRI

Vp falls in the ventricular myocardial refractory period. It may however capture the ventricle if a very long AVI is programmed

A. F. Sinnaeve

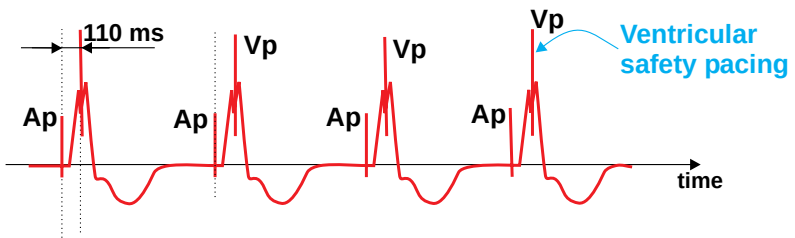
Abbreviations : Ap = atrial paced event; AEI = atrial escape interval; AVI = atrioventricular interval or AV delay; PAVB = postatrial ventricular blanking; Vp = ventricular paced event; Vs = ventricular sensed event; VSP = ventricular safety pacing; LRI = lower rate interval

DISLODGMENT OF THE ATRIAL LEAD INTO THE RIGHT VENTRICLE

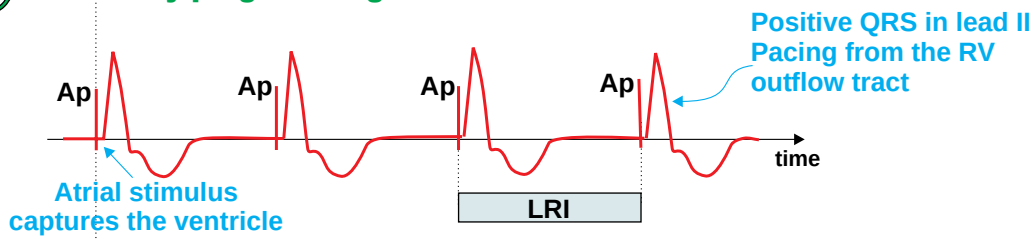


PART 3

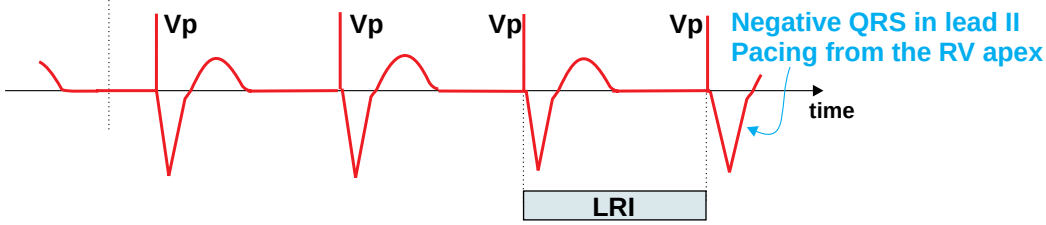
Representative ECG



① Confirm by programming to AAI mode



② and by programming to the VVI mode

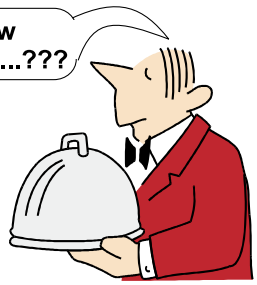


TAKE A CHEST X RAY FOR A DEFINITIVE CONFIRMATION

Abbreviations : Ap = atrial paced event; Vp = ventricular paced event; LRI = lower rate interval

A. F. Sinnaeve

DISLODGMENT OF THE ATRIAL LEAD INTO THE RIGHT VENTRICLE



PART 4

SOME IMPORTANT QUESTIONS :

1/ Does Ap capture the ventricle ?

2/ Does the ventricular-paced QRS configuration in the 12-lead ECG match the one recorded during VVI pacing ?

3/ What is being sensed by the displaced atrial electrode ?

4/ Does the pacemaker have a ventricular safety pacing (VSP) function ?

5/ Is the VSP function activated ?

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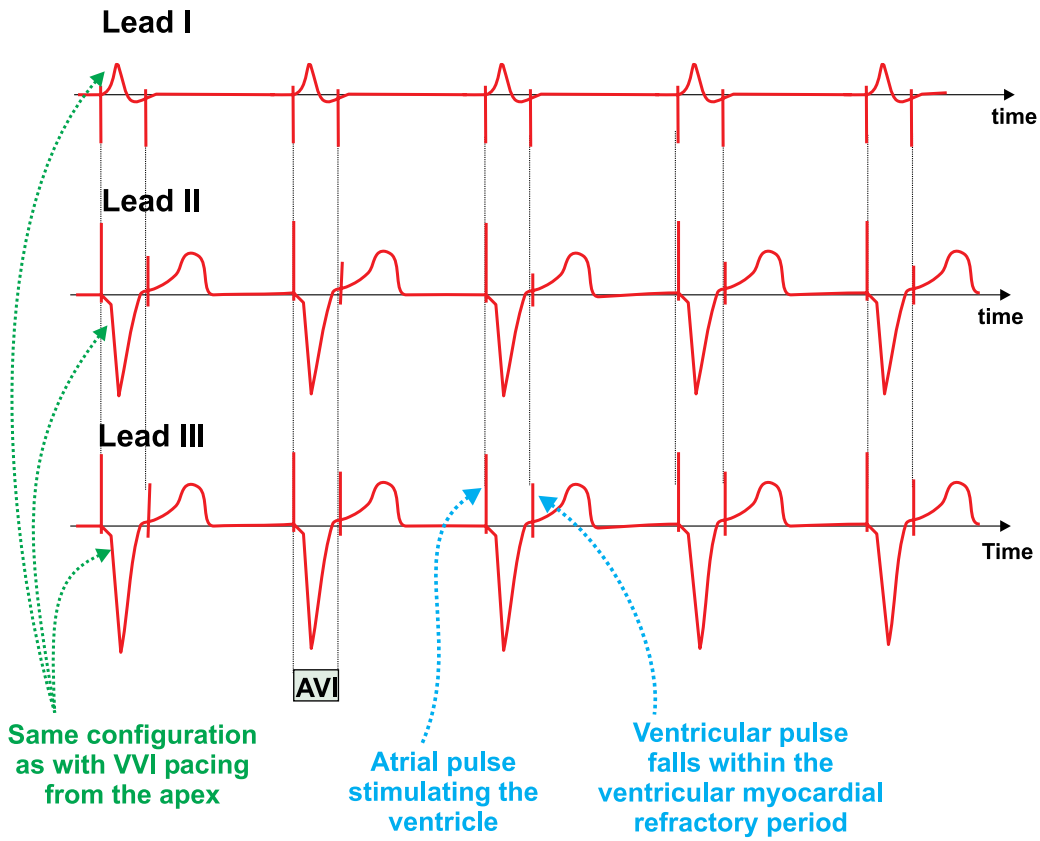
They say I'm a real dummy, just because I've interchanged a couple of wires

REVERSED CONNECTION OF ATRIAL AND VENTRICULAR LEADS



NOTE : * programming to the AAI mode will cause VVI pacing
*** programming to the VVI mode will cause AAI pacing**

Abbreviations : AVI = programmed AV delay

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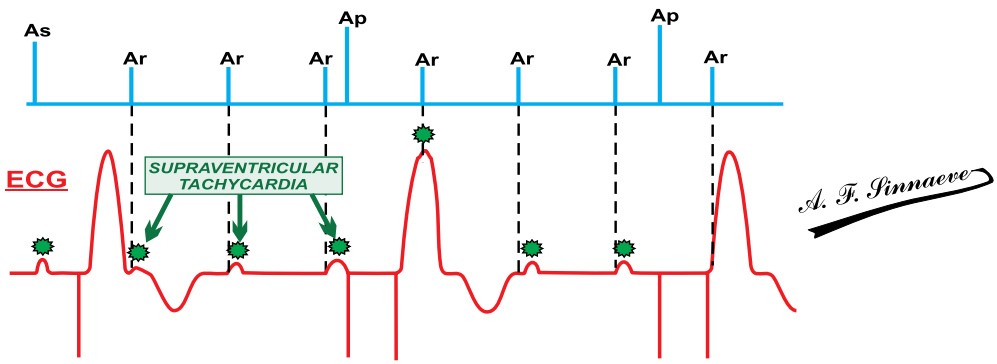
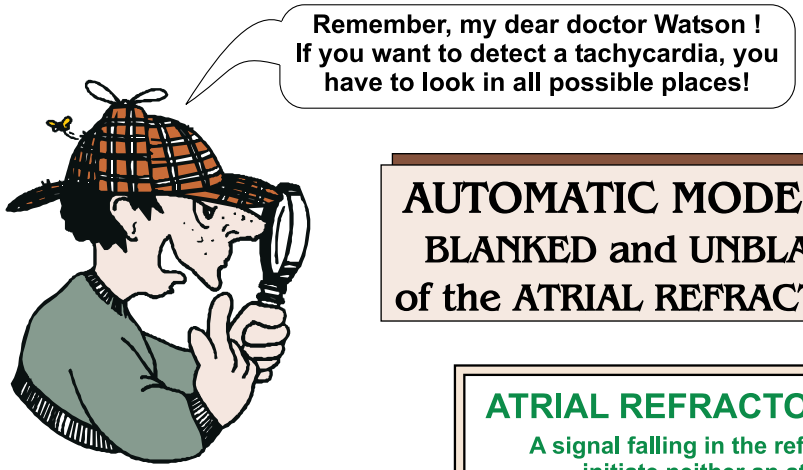
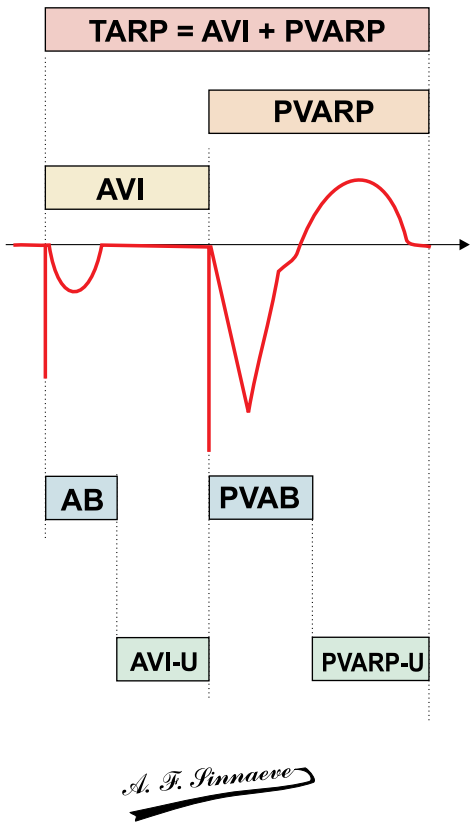
AUTOMATIC MODE SWITCHING

* Blanked and unblanked parts of the atrial refractory periods
* Timing cycles of a dual chamber pacemaker
* Failure of automatic mode switching
* Influence of the AV interval and blanking periods during atrial tachycardia
* Blanked atrial flutter search algorithm
* Mechanism of far-field sensing during the AV interval
* Retriggerable atrial refractory periods





AUTOMATIC MODE SWITCHING
BLANKED and UNBLANKED PARTS of the ATRIAL REFRACTORY PERIODS



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ATRIAL REFRACTORY INTERVALS

A signal falling in the refractory period can initiate neither an atrioventricular interval (AVI) nor a lower rate interval (LRI)

AVI = atrioventricular interval

PVARP = postventricular atrial refractory interval

TARP = total atrial refractory period

ATRIAL BLANKING INTERVALS

During these intervals the atrial channel is insensitive or blind to all signals.
By a special circuit, the electrogram can still be detected and displayed, but cannot influence the function of the pacemaker itself.

AB = atrial blanking period

PVAB = postventricular atrial blanking

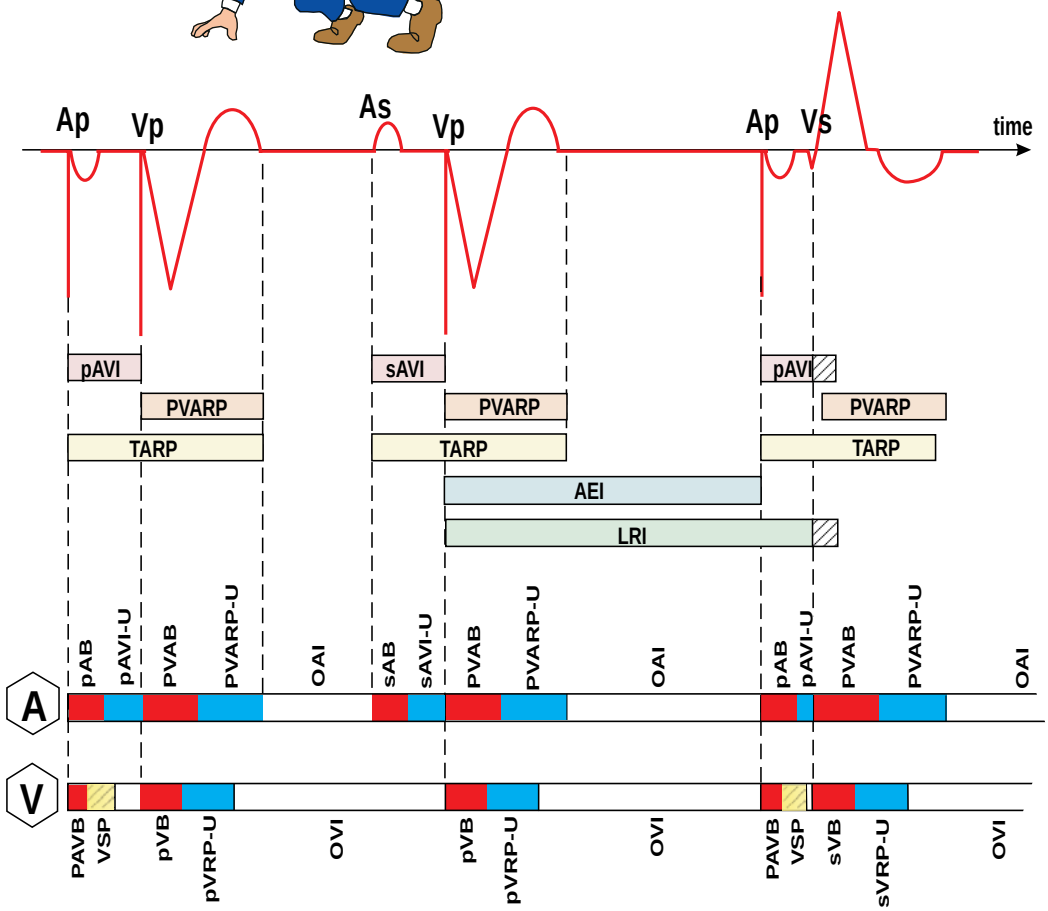
UNBLANKED ATRIAL REFRACTORY PERIODS

During these intervals signals can be sensed by the atrial channel and used to alter certain pacing timing cycles including the automatic mode switching (AMS), although they are unable to start an AVI or LRI.
Refractory sensed signals are depicted differently by the marker channel (Ar or AR).

AVI-U = unblanked atrioventricular interval

PVARP-U = unblanked postventricular atrial refractory interval

DIAGRAMMATIC REPRESENTATION OF TIMING CYCLES OF A DUAL CHAMBER PACEMAKER WITH AUTOMATIC MODE SWITCHING CAPABILITY



Abbreviations : Ap = atrial paced event; As = atrial sensed event; pAVI = paced atrioventricular interval; sAVI = sensed atrioventricular interval; AB = blanked first part of AVI; AVI-U = unblanked last part of AVI; PVAB = postventricular atrial blanking; PVARP = postventricular atrial refractory period; PVARP-U = unblanked second part of PVARP; TARP = total atrial refractory interval; AEI = atrial escape interval; OAI = open atrial interval;
Vp = ventricular paced event; Vs = ventricular sensed event; PAVB = postatrial ventricular blanking interval; VSP = ventricular safety pacing window ; VB = ventricular blanking period (p: after pacing - s: after sensing); VRP-U = unblanked ventricular refractory period; LRI = lower rate interval (ventricular timing); OVI = open ventricular interval

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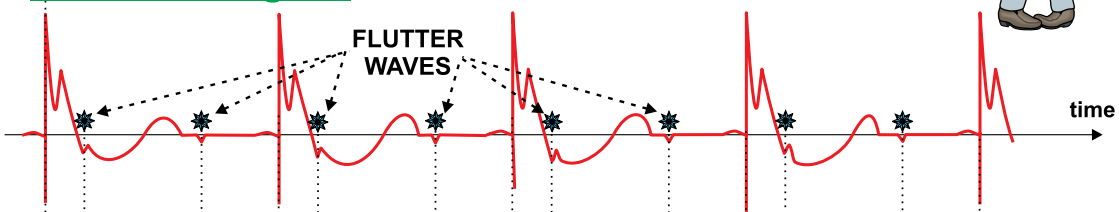
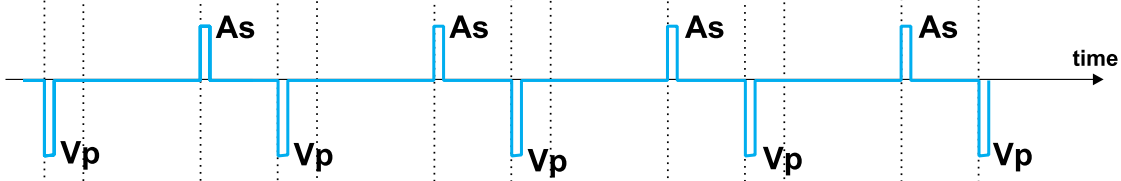
FAILURE OF AUTOMATIC MODE SWITCHING DUE TO THE 2 : 1 LOCK-IN RESPONSE IN ATRIAL FLUTTER

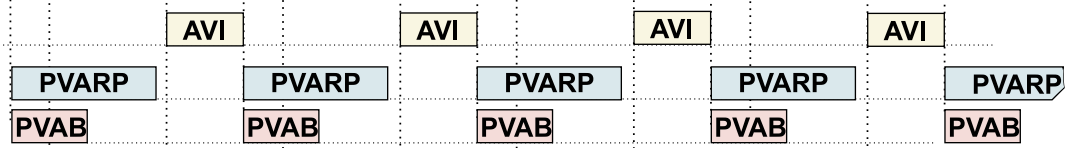
Electrocardiogram



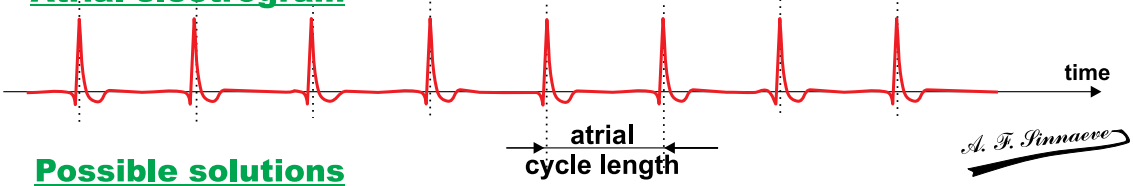
Marker channel



Programmed timing cycles



Atrial electrogram



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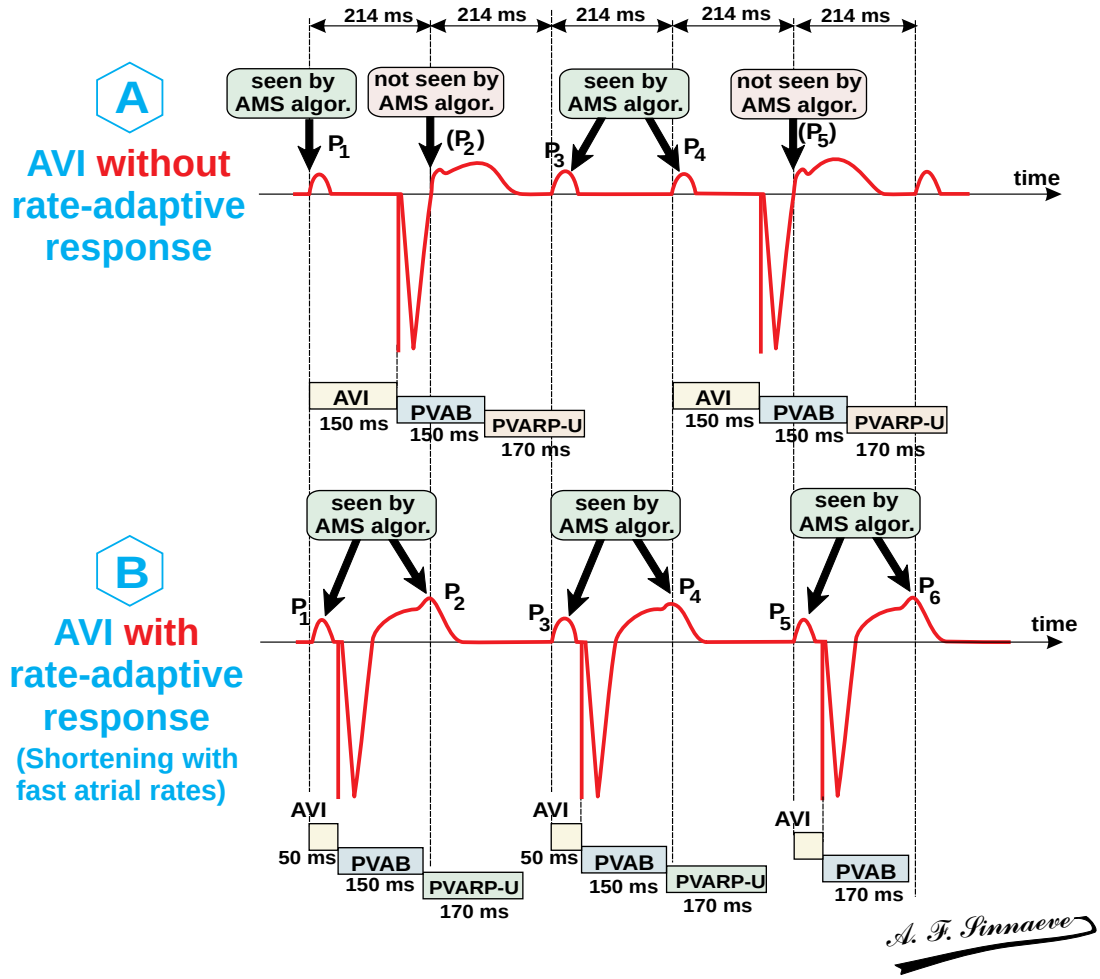
Possible solutions

- Reprogram the pacemaker such that AVI + PVAB becomes shorter than the atrial cycle length
- Use a special atrial flutter search program

Abbreviations : As = atrial sensed event; Vp = ventricular paced event; AVI = programmed AV delay; PVARP = postventricular atrial refractory period; PVAB = postventricular atrial blanking

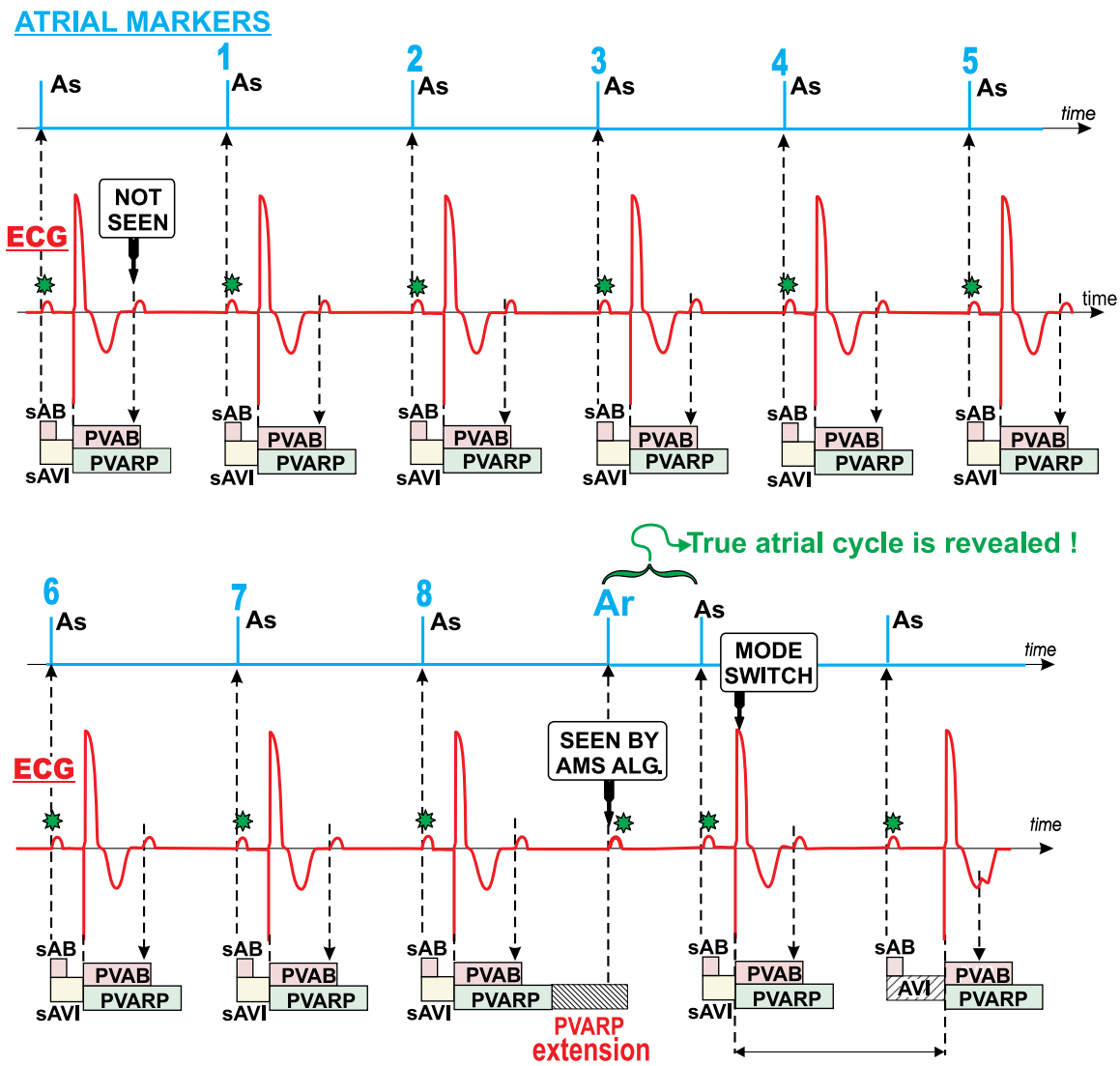
AUTOMATIC MODE SWITCHING AND THE INFLUENCE OF AVI AND BLANKING PERIODS DURING ATRIAL TACHYCARDIA



ABBREVIATIONS : AMS = automatic mode switching; AVI = atrioventricular interval; PVAB = postventricular atrial blanking; PVARP-U = unblanked second part of PVARP; PVARP = postventricular atrial refractory period; Algor. = algorithm

BLANKED FLUTTER SEARCH ALGORITHM

When 8 consecutive atrial intervals measure less than 2 times the (AVI + PVAB) interval and less than 2 times the tachycardia detection interval, the device extends the PVARP for 1 beat to search of atrial flutter signals.



Abbreviations : As = atrial sensed event; Ar =atrial refractory sensed event; sAVI = sensed atrioventricular interval; sAB = blanked first part of sAVI; PVARP = postventricular atrial refractory period; PVAB = postventricular atrial blanking

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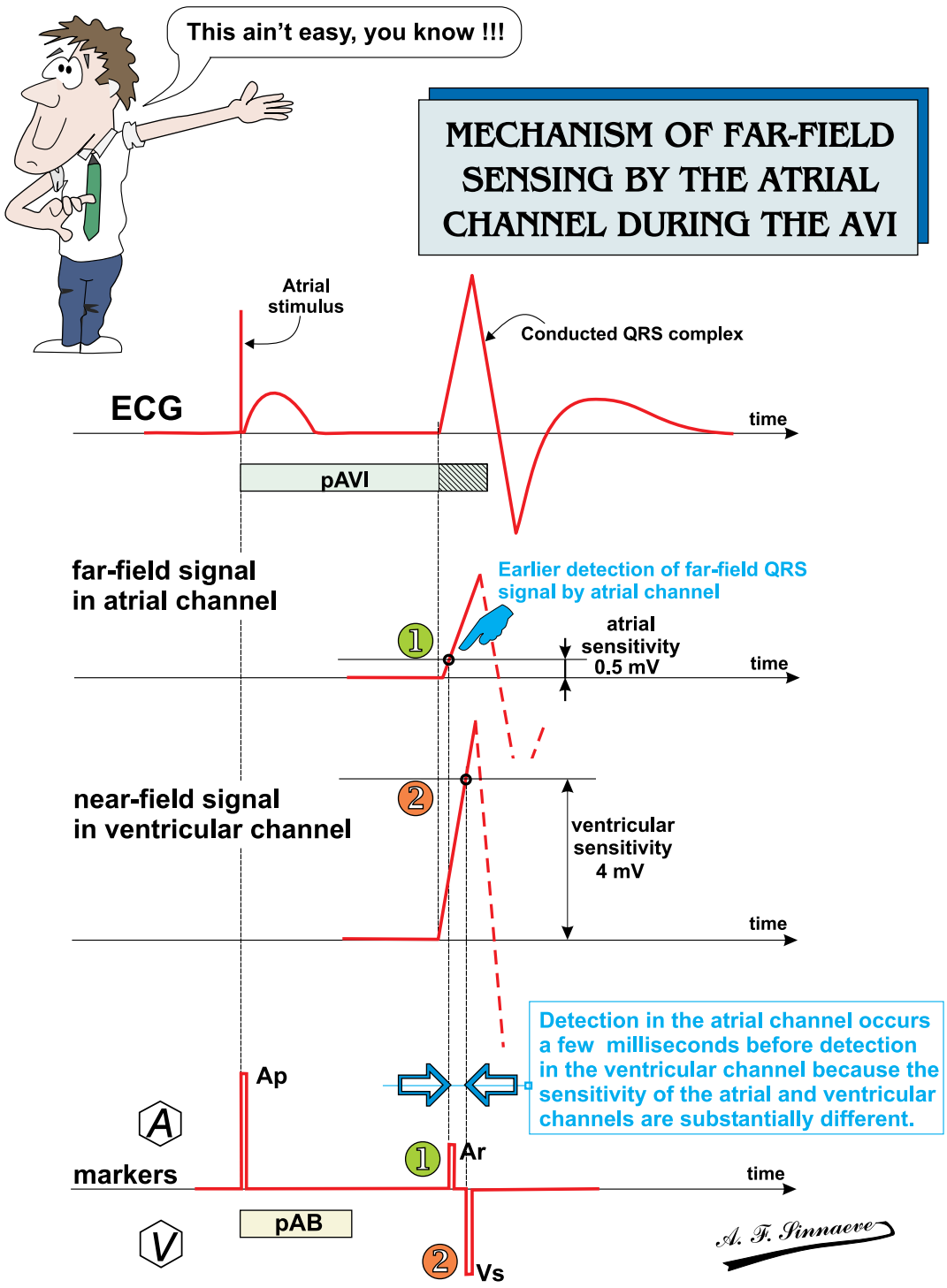
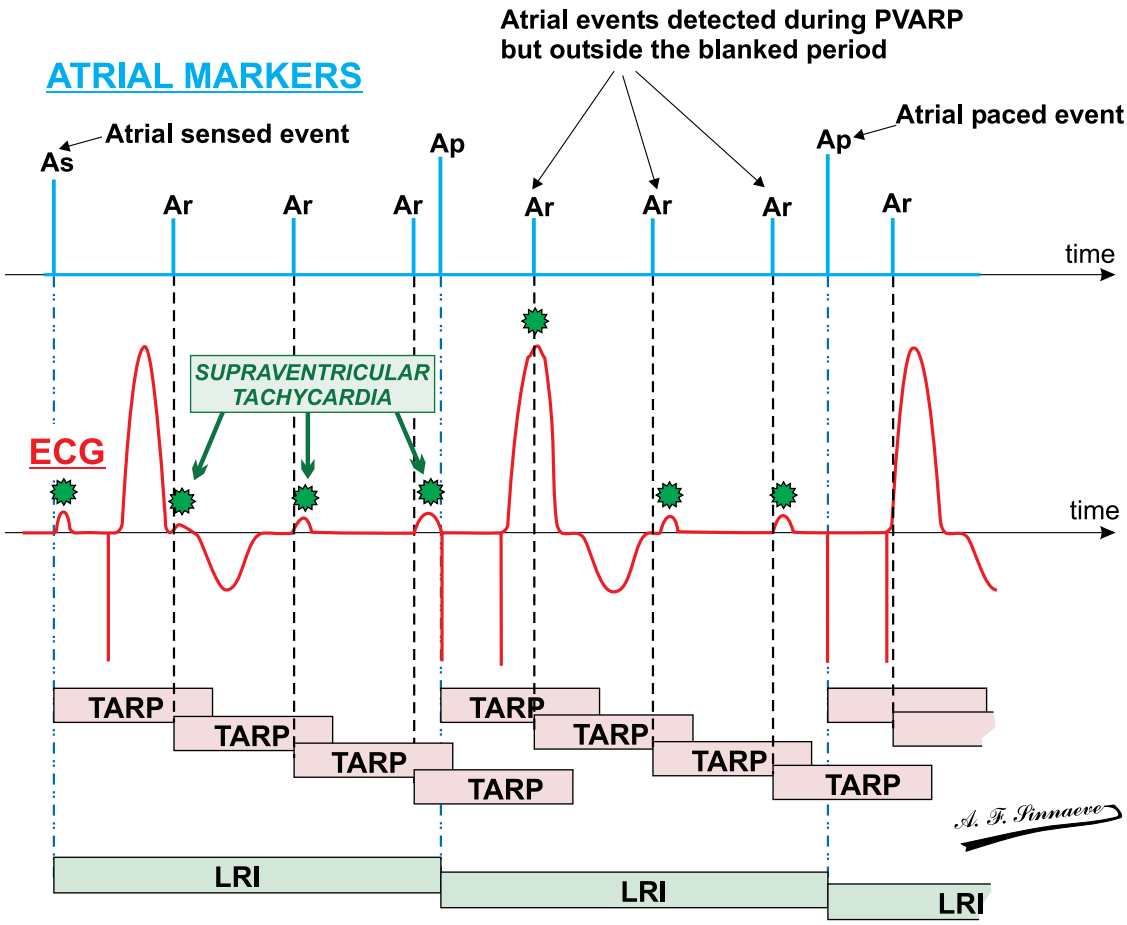
Blanked Flutter Search Algorithm is from Medtronic Inc.



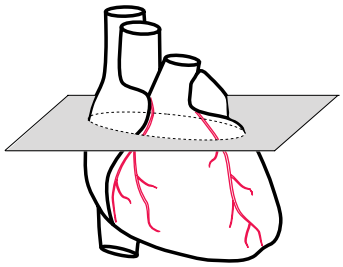
Abbreviations : Ap = atrial paced event; Ar = atrial refractory sensed event; Vs = ventricular sensed event; pAVI = paced atrioventricular interval; pAB = blanked first part of pAVI; AVI = programmed AV delay

DIAGRAMMATIC REPRESENTATION OF RETRIGGERABLE ATRIAL REFRACTORY PERIODS



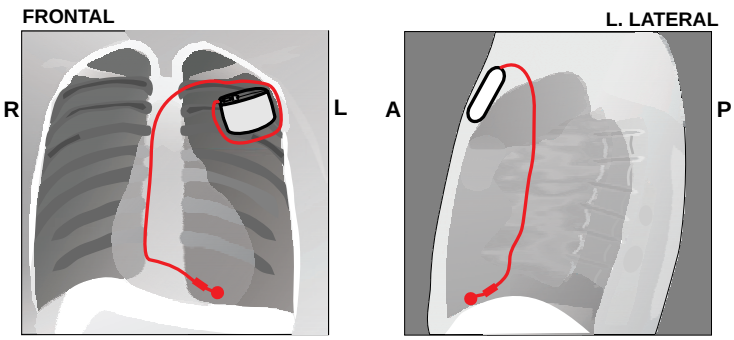
NOTE : The pacemaker is working in the DVI mode asynchronously in the atrial channel. The process provides a form of automatic mode switching.

Abbreviations : As = atrial sensed event; Ar = atrial refractory sensed event; Ap = atrial paced event; PVARP = postventricular atrial refractory period; TARP = total atrial refractory period; LRI = lower rate interval



PACEMAKER RADIOGRAPHY

* Topographic anatomy of the heart
* Lead position for VVI pacing
* Lead position for dual chamber pacing - part 1
* Lead position for dual chamber pacing - part 2



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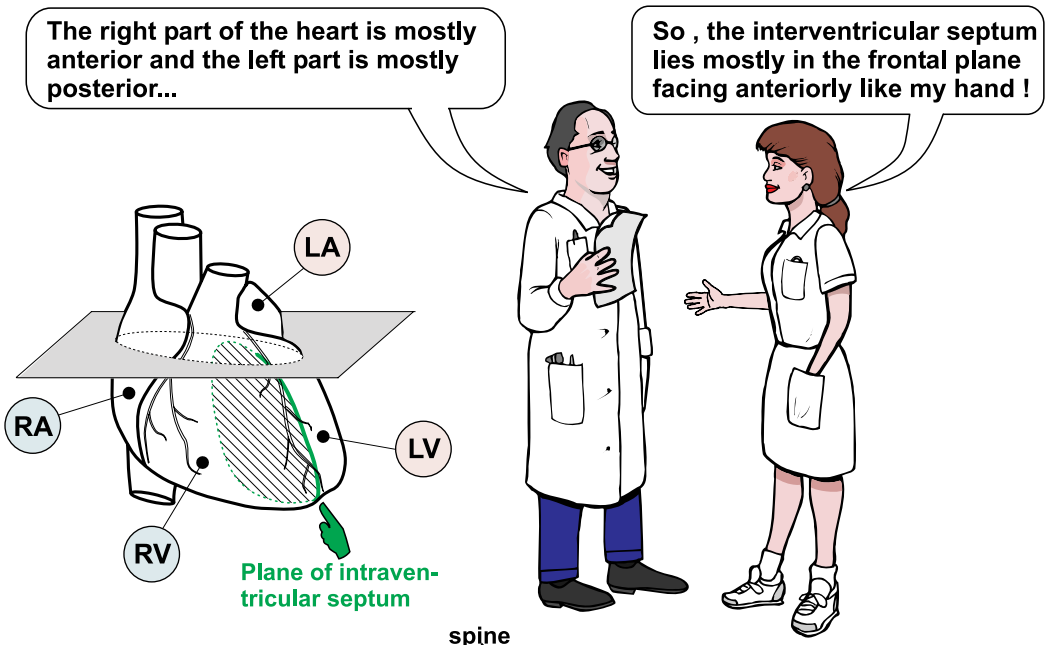
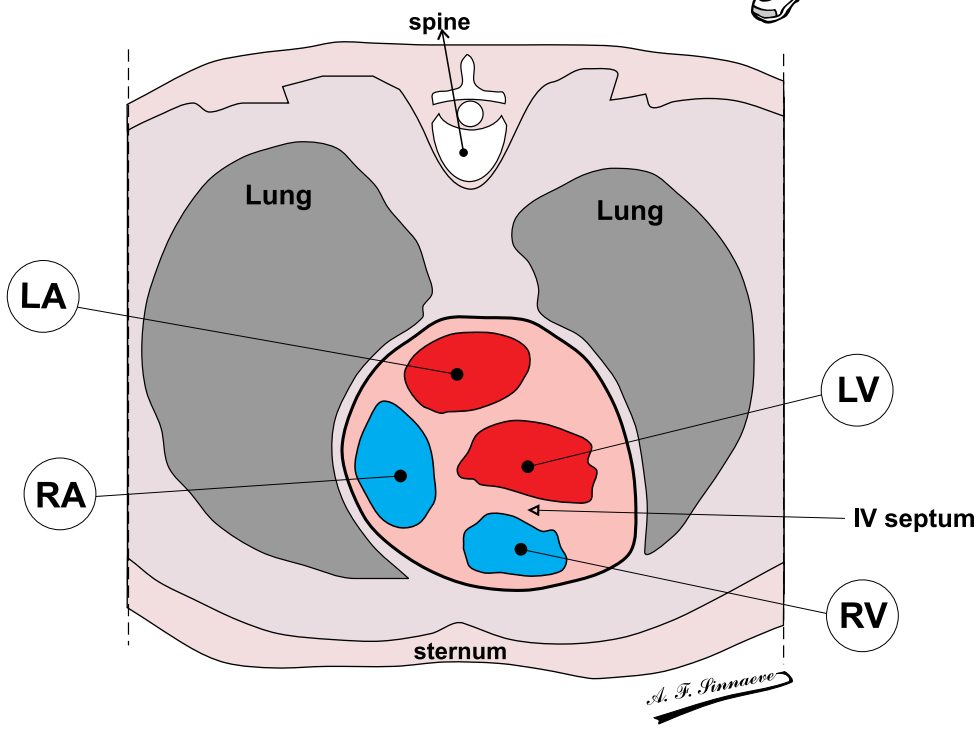
TOPOGRAPHIC ANATOMY OF THE HEART

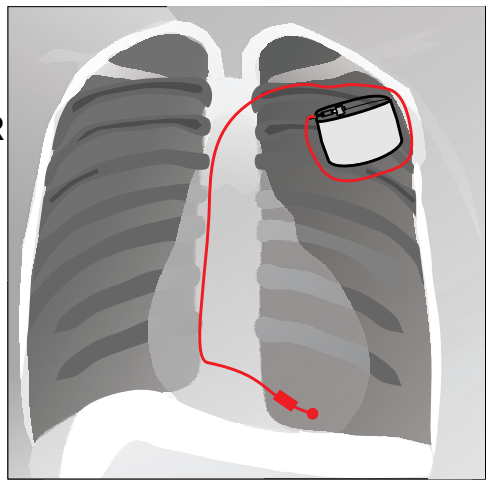




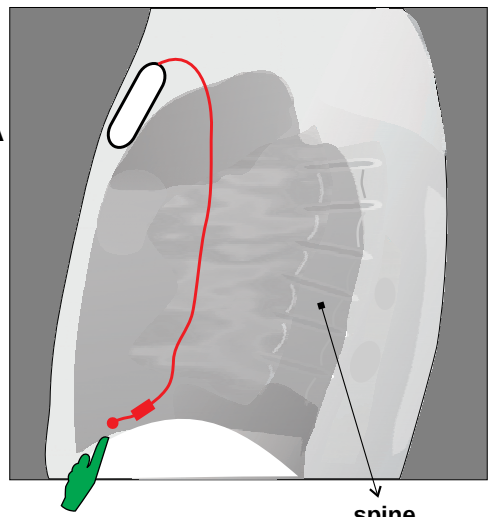
SCHEMATIC REPRESENTATION OF LEAD POSITION FOR VVI PACING

Ventricular lead in right ventricular apex

FRONTAL

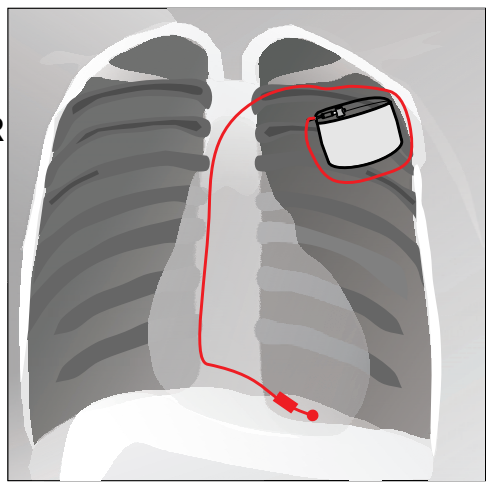


L. LATERAL



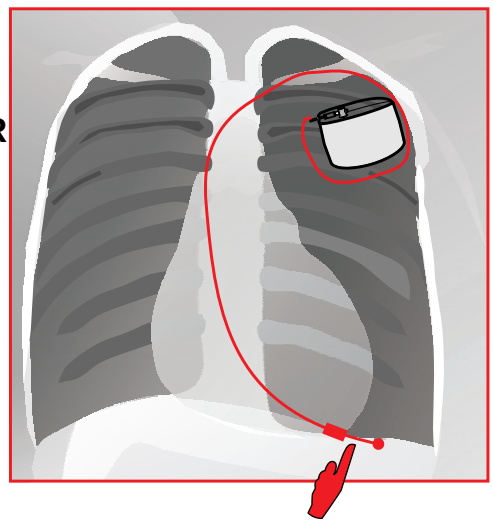
The RV lead is anterior because the right ventricle is anterior

FRONTAL



The RV lead may plunge below the diaphragmatic shadow. This is normal and may not be interpreted as perforation without other findings !!!

FRONTAL



PERFORATION !

The lead is clearly beyond the cardiac shadow !

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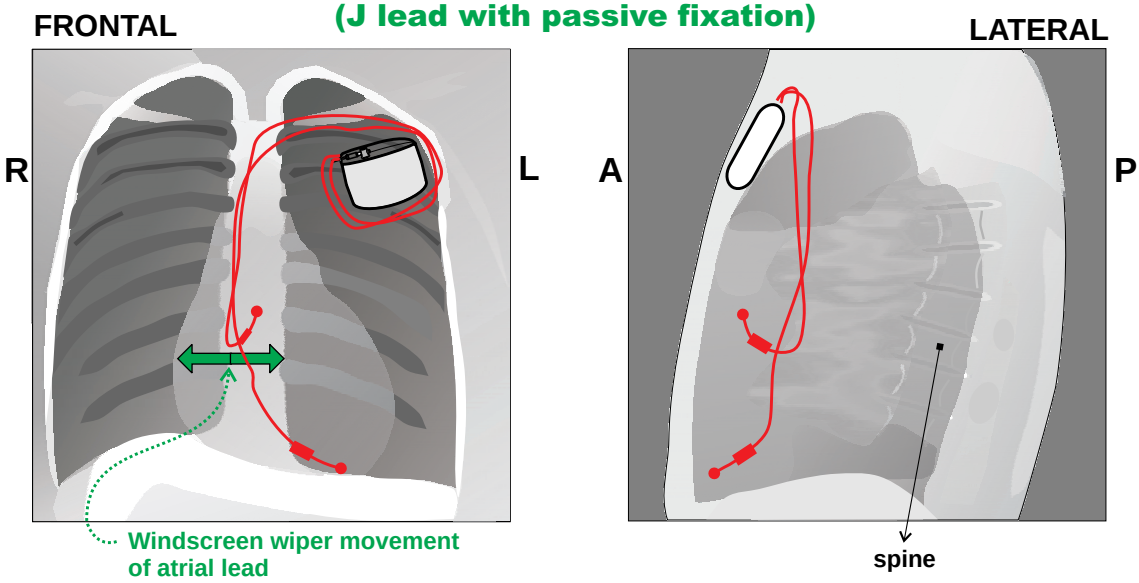
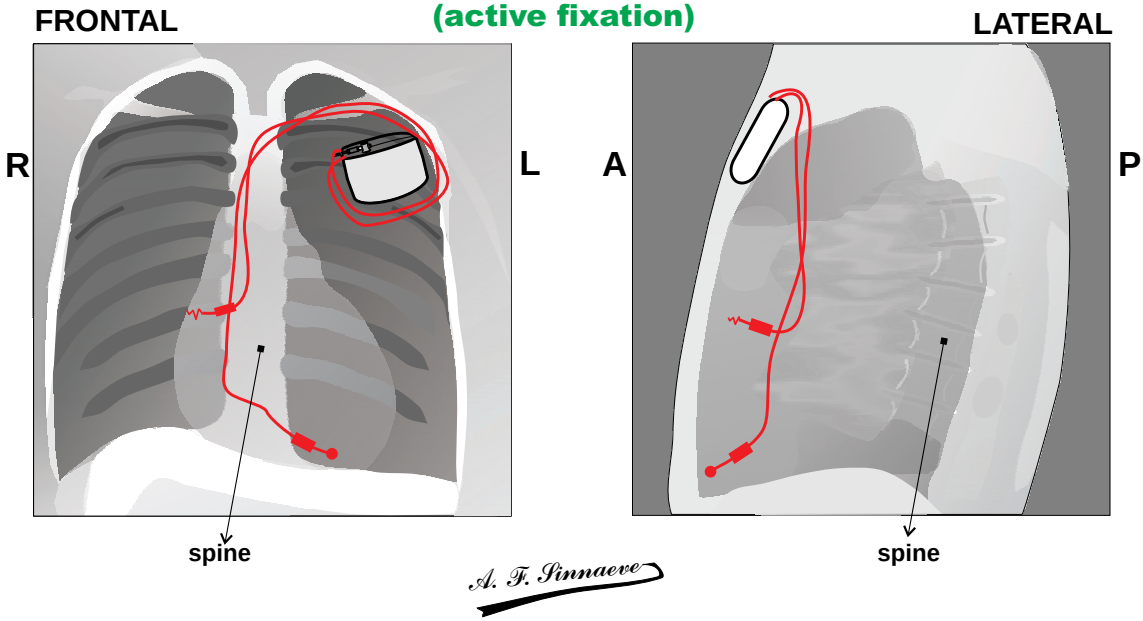
SCHEMATIC REPRESENTATION OF LEAD POSITIONS FOR DUAL CHAMBER PACING

Atrial lead in right atrial appendage (J lead with passive fixation)



Atrial screw-in lead in the mid-lateral wall (active fixation)



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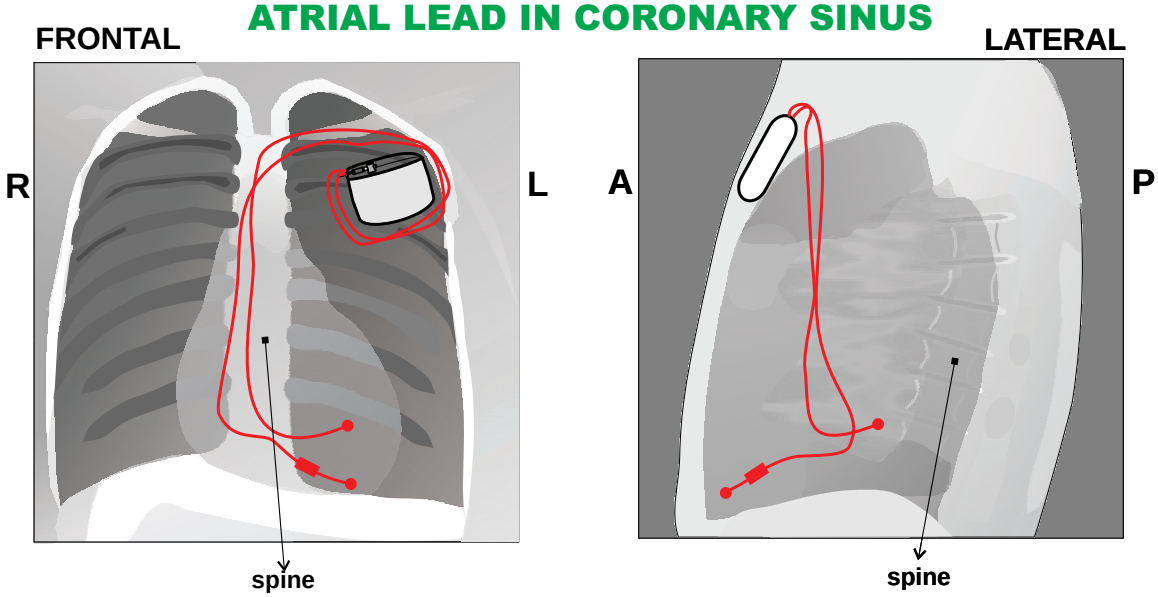
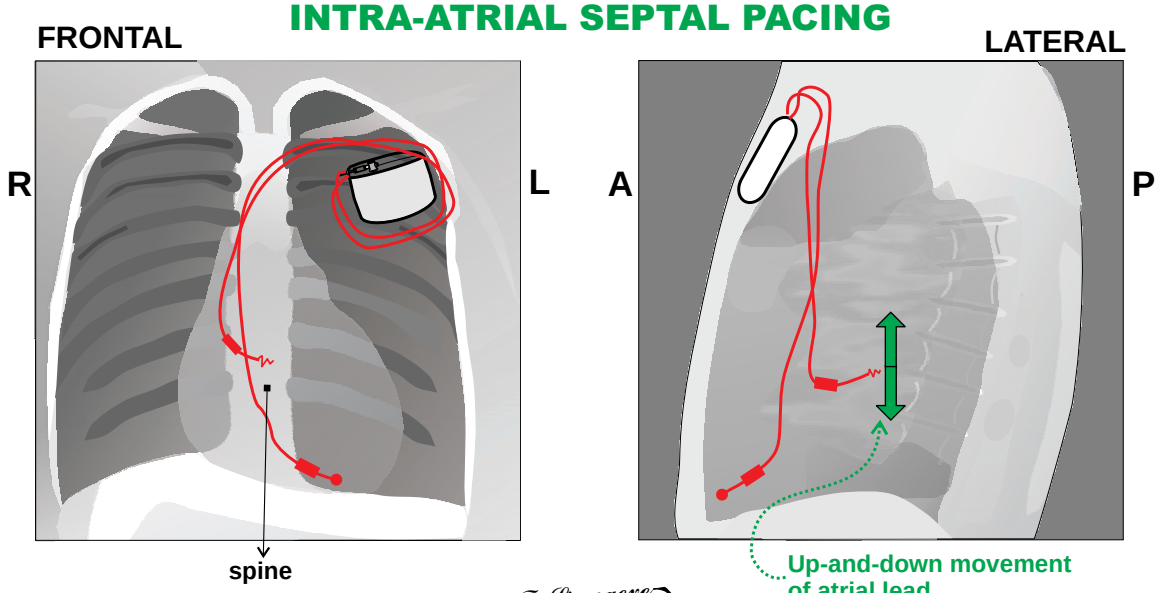
SCHEMATIC REPRESENTATION OF LEAD POSITIONS FOR DUAL CHAMBER PACING

ATRIAL LEAD IN CORONARY SINUS



INTRA-ATRIAL SEPTAL PACING



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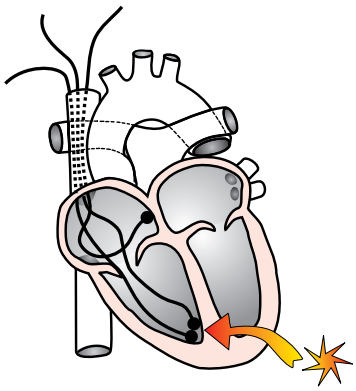
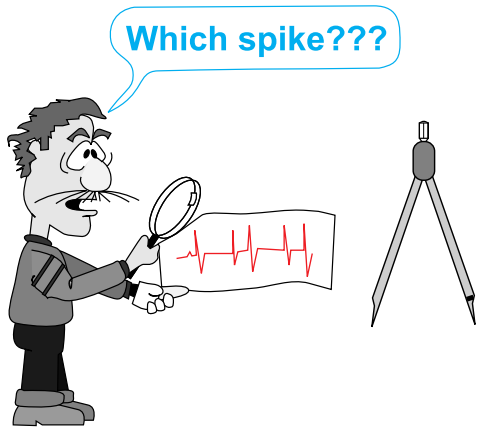
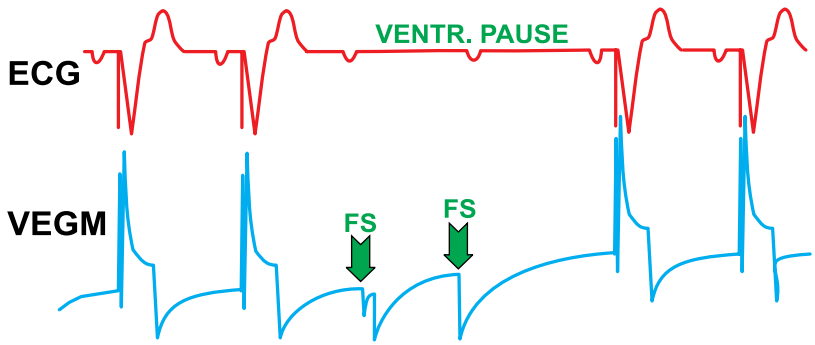




OVERSENSING

* What does the pacemaker sense ?
* False signals
* Mechanism of false signals
* Interaction of two leads with false signals



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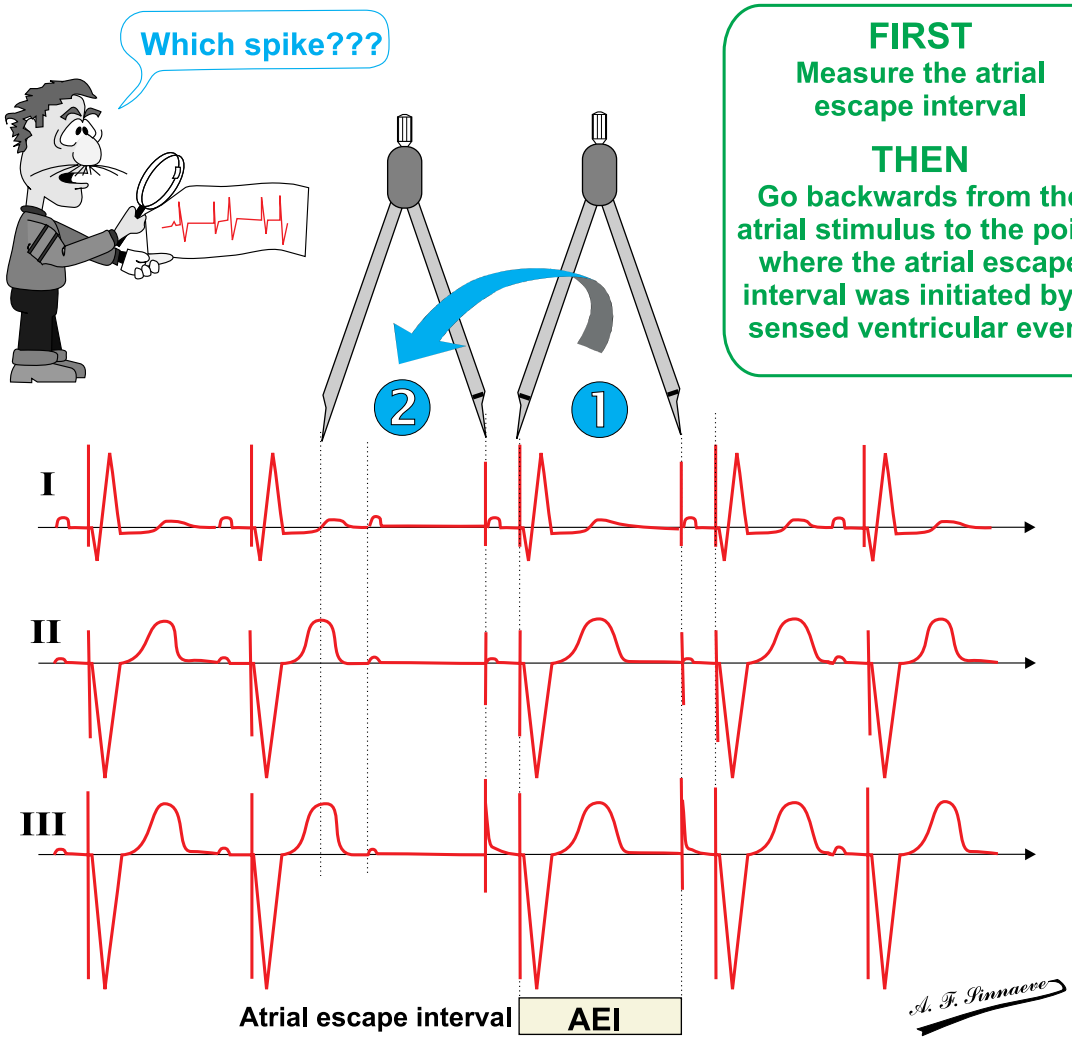
WHAT DOES THE VENTRICULAR CHANNEL OF THE PACEMAKER SENSE ?
T wave, afterpotential, false signal, … ?



FIRST
Measure the atrial escape interval

THEN
Go backwards from the atrial stimulus to the point where the atrial escape interval was initiated by a sensed ventricular event

* In ventricular-based sensing, the atrial escape interval (AEI) always remains constant.
* Measure backwards from an atrial stimulus to the preceding point of sensing because a ventricular event (paced or sensed) always initiates an AEI

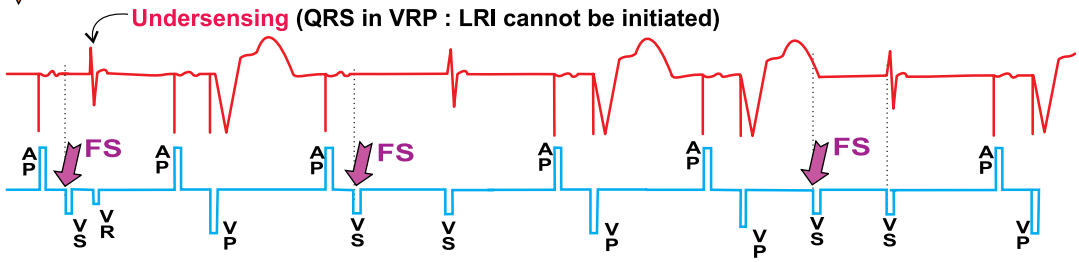
This method cannot be used in pacemakers with atrial-based lower rate timing

FALSE SIGNALS
FROM INTERMITTENT DERANGEMENT OF LEAD FUNCTION

Abrupt and large changes in resistance within a pacing system can cause corresponding voltage changes between the electrodes. These signals are called “false signals” or transients.

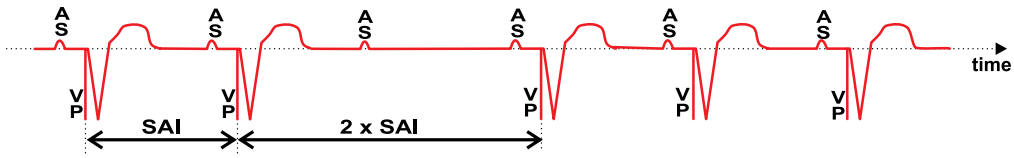
* These signals may be quite large but are almost always not seen on the surface ECG
* The usual causes are lead fractures and insulation defects
* False signals usually occur at random. Long rhythm strips will show the irregularirty of the abnormality with pauses of varying duration
* Oversensing of false signals is the great imitator of pacing

1 OVERSENSING OF FALSE SIGNALS CAN CAUSE UNDERSENSING



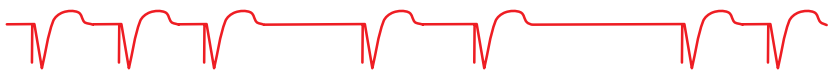
Erratic pacemaker behavior with pauses of varying duration and occasional undersensing strongly suggests a defective lead system creating false signals

2 THE PAUSES MAY BE EXACT MULTIPLES OF THE SINUS INTERVAL DURING SENSED SINUS RHYTHM



3 APPLICATION OF THE MAGNET CONVERTS IRREGULAR PAUSES TO A SITUATION WITH PAUSES OF REGULAR DURATION THAT ARE AN EXACT MULTIPLE OF THE MAGNET INTERVAL (DIAGNOSTIC OF LEAD FRACTURE)

VVI pacemaker without a magnet



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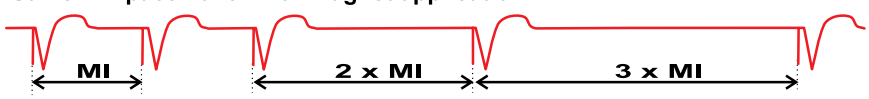
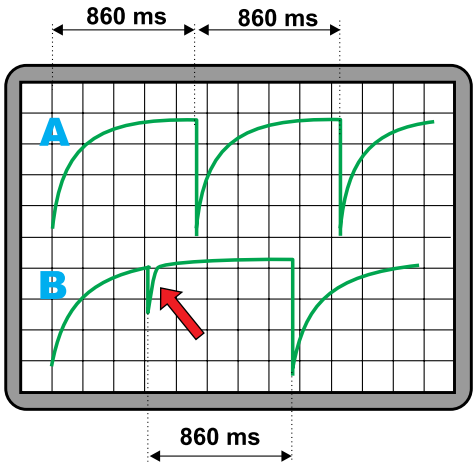
Same VVI pacemaker with magnet application



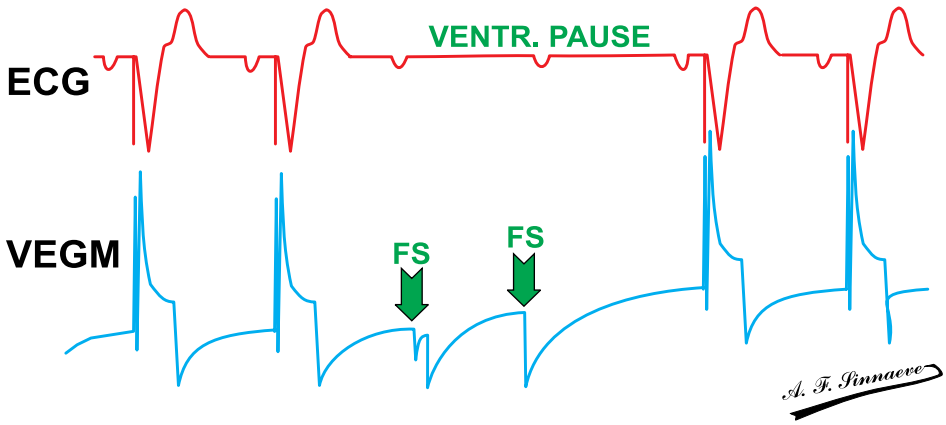
A lead problem can resemble T wave oversensing if mechanical systole creates false signals (making and breaking the circuit) only at a specific part of the cardiac cycle. Such an abnormality can be identical to T wave sensing even after application of the magnet. The diagnosis can be made by the configuration of the false signal in the telemetered EGM

Abbreviatons : AP = atrial pace; AS = atrial sense; FS = false signal; MI = magnet interval; SAI = spontaneous atrial interval; VP = ventricular pace; VS = ventricular sense; VR = ventricular sense in refractory period; LRI = lower rate interval

MECHANISM OF FALSE SIGNALS FROM INTERMITTENT CIRCUIT DISRUPTION



Voltage waveforms on an oscilloscope of a VVI pacemaker connected to a pacing lead in normal saline solution. The recording shows the mechanism of production of "false signals" from intermittent derangement of the pacemaker circuit. A shows an automatic interval of 860ms. In B, a false signal is deliberately created by manually breaking the connection between pacemaker and electrode for an instant. The disturbance causes a rapidly rising voltage of almost 200mV, well outside the refractory period of the pacemaker, which therefore senses it and recycles with an escape interval of 860ms. The reciprocal signal, caused by the return of voltage to the "baseline", because it occurs about 100ms after the initial signal, falls inside the refractory period of the pacemaker. Consequently it is not sensed.



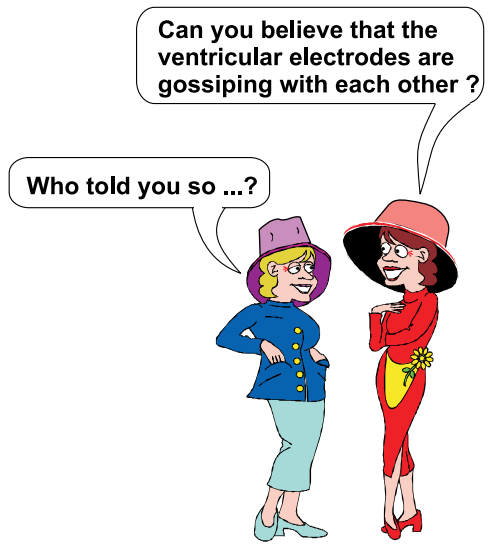
LEAD PROBLEMS CREATE FALSE SIGNALS

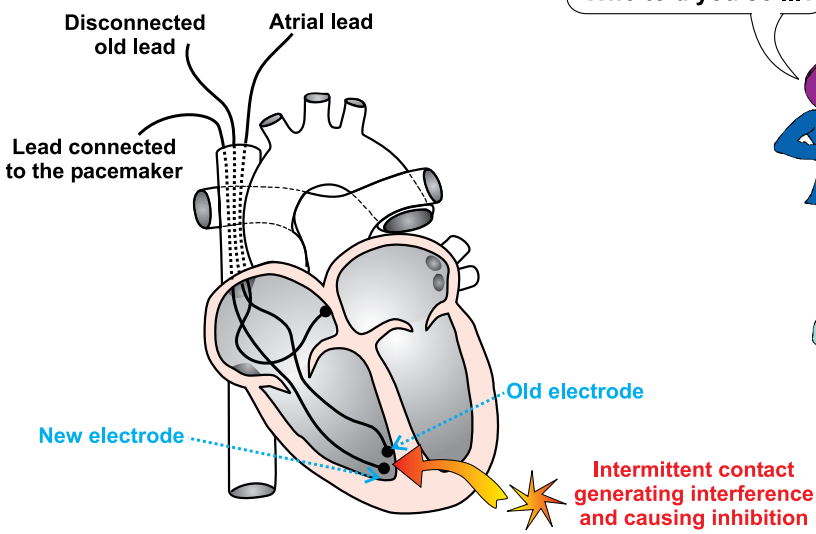
LEAD FRACTURE

INSULATION DEFECT

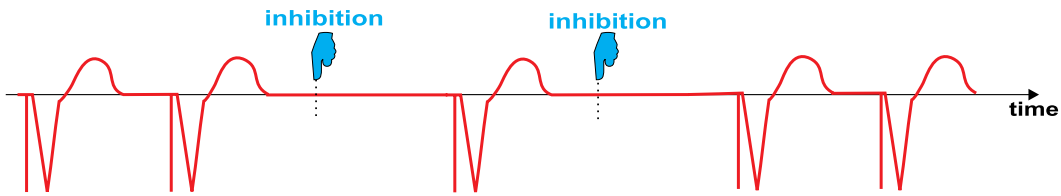
Abbreviations : ECG = surface electrocardiogram ; VEGM = ventricular electrogram ; FS = false signal

INTERACTION OF ACTIVE AND INACTIVE ELECTRODES LYING SIDE-BY-SIDE

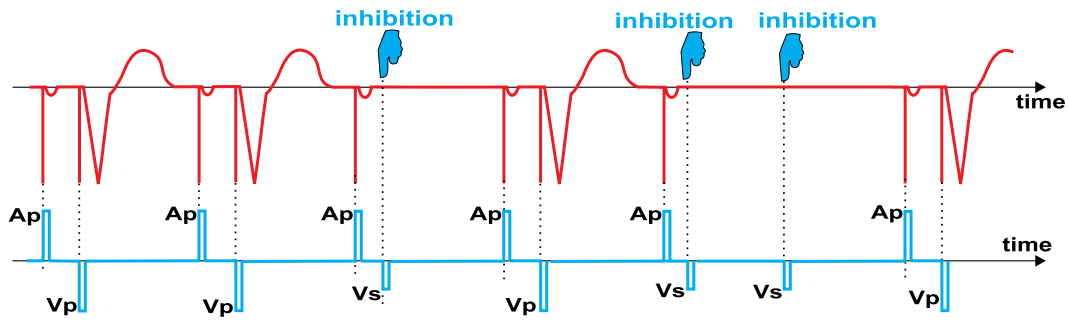




IN A VVI PACEMAKER



IN A DDD PACEMAKER



* Application of the magnet over the pacemaker eliminates the pauses related to oversensing and restores regular pacing at magnet rate.
* The false signals created by intermittent contact of the electrodes are invisible on the surface ECG. However, they can be seen in the intracardiac electrogram transmitted by telemetry.

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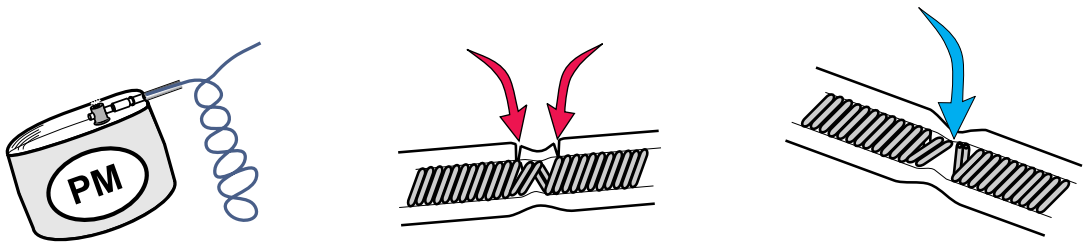
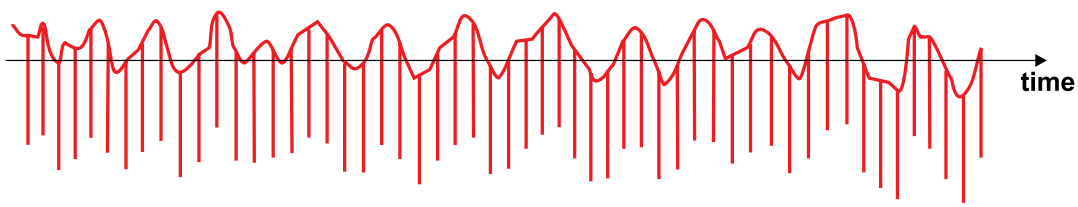


TROUBLESHOOTING

* High threshold - Exit block
* Loss of ventricular capture by visible pacemaker stimuli
* Missing stimuli during VVI pacing
* Lead insulation defect
* Lead fracture
* Analysis of lead problems
* Lead fracture - Conversion from bipolar to unipolar
* Subclavian crush syndrome
* Twiddler's syndrome
* Diaphragmatic stimulation
* Muscle stimulation
* Runaway pacemaker



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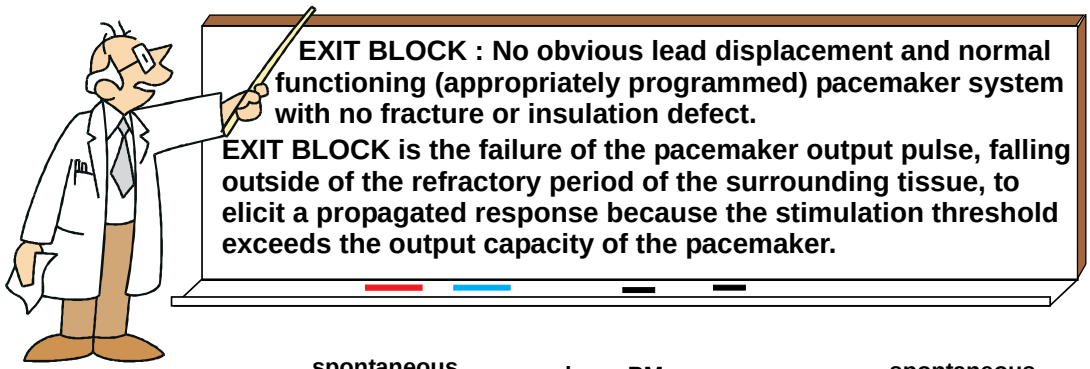
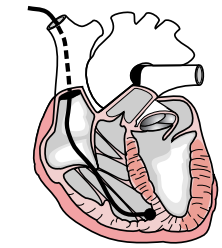
HIGH THRESHOLD - EXIT BLOCK

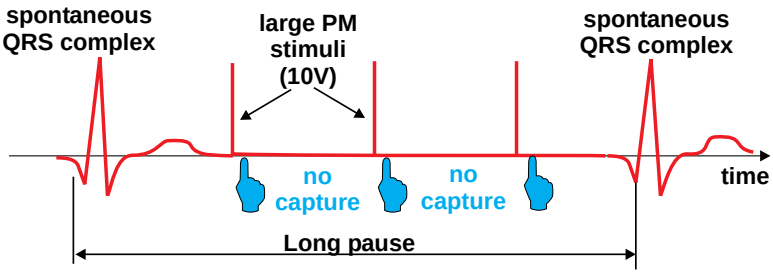


EXIT BLOCK : No obvious lead displacement and normal functioning (appropriately programmed) pacemaker system with no fracture or insulation defect.

EXIT BLOCK is the failure of the pacemaker output pulse, falling outside of the refractory period of the surrounding tissue, to elicit a propagated response because the stimulation threshold exceeds the output capacity of the pacemaker.



properly positioned electrode



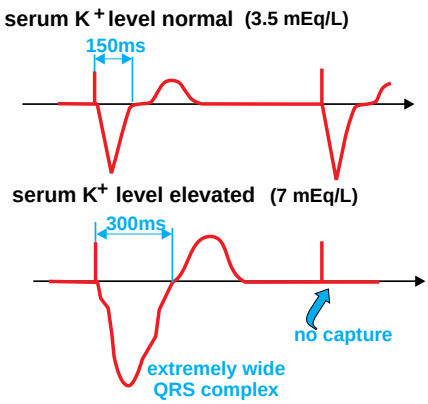
CAUSES :

* excessive tissue reaction around the lead tip
* various antiarrhythmic drugs (e.g. flecainide)
* electrolyte abnormality (e.g. hyperkalemia, acidosis and hypothyroidism)
* myocardial infarction & tissue damage from defibrillation, electrocautery and radiotherapy

HYPERKALEMIA

AN ELEVATED POTASSIUM LEVEL CAUSES :

* disappearance of P waves due to atrial asystole
* very wide QRS complexes (up to 3OOms)
* pacemaker exit block



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LOSS OF VENTRICULAR CAPTURE BY VISIBLE PACEMAKER STIMULI

1 FUNCTIONAL

- ✓ Normal situation : stimuli in myocardial refractory period.

2 ELECTRODE-TISSUE INTERFACE

☞ LEAD DISPLACEMENT

- ✓ Early displacement or unstable position of pacing leads (commonest cause).
- ✓ Malposition into the coronary venous system.
- ✓ Twiddler's syndrome causing late displacement.
- ✓ Perforation of right ventricle by ventricular lead.

☞ NO APPARENT LEAD DISPLACEMENT

- ✓ Microdislodgment (a diagnosis of exclusion) causes a marked rise in capture threshold but displacement is not apparent on a chest x-ray.
- ✓ Elevated pacing threshold without obvious lead displacement (exit block) : Acute or chronic reaction at the electrode-tissue interface.
- ✓ Subcutaneous emphysema.
- ✓ Myocardial infarction or ischemia, hypoxia.
- ✓ Hypothyroidism.
- ✓ Elevation of pacing threshold after defibrillation or cardioversion. This is usually transient for a few minutes or less.
- ✓ Electrolyte abnormalities usually hyperkalemia, severe acidosis.
- ✓ Drug effect : Flecainide and propafenone can elevate the pacing threshold with therapeutic doses.

3 ELECTRODE

- ✓ Fracture, short circuit or insulation break.

4 PULSE GENERATOR

- ✓ Normal pacemaker with incorrect programming of parameters.
- ✓ Pacemaker failure from exhaustion or component failure.
- ✓ Iatrogenic causes : Component failure after defibrillation, electrocautery and therapeutic radiation.

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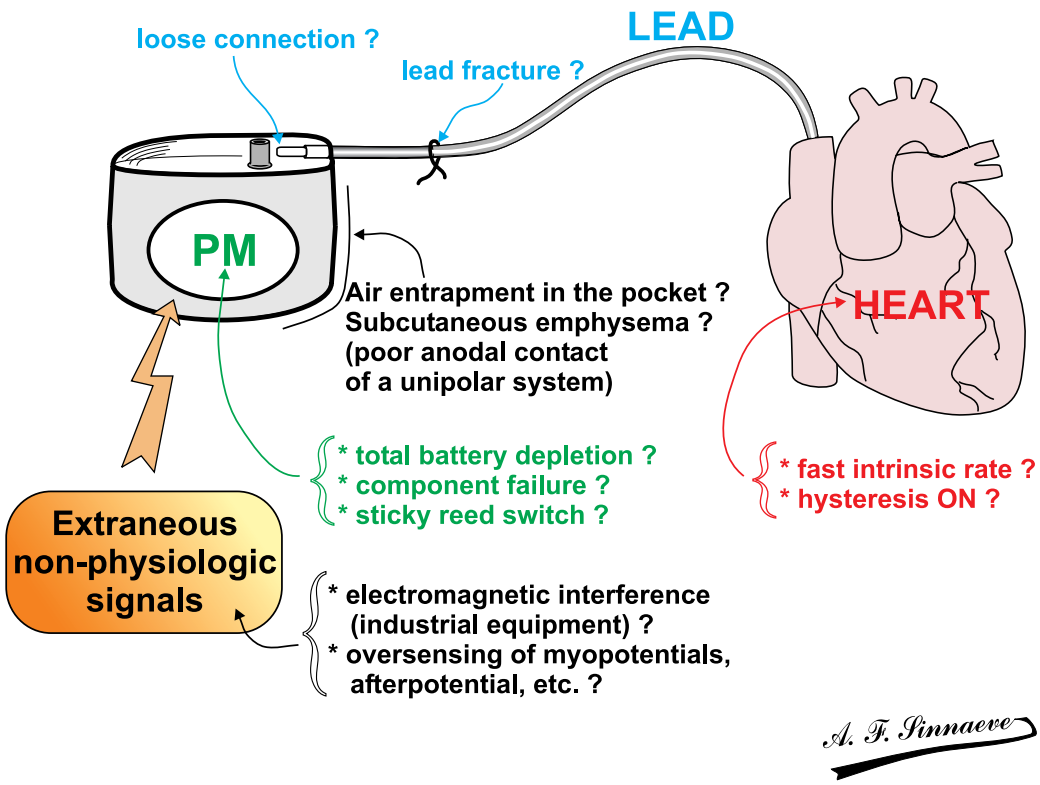
CAUSES OF MISSING STIMULI DURING VVI PACING



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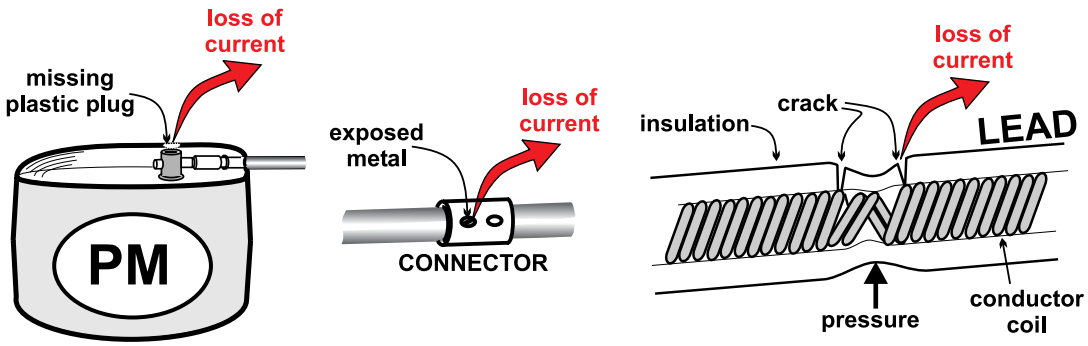
!!!

Pseudomalfunction : when overlooking the tiny bipolar pacemaker stimuli on the surface ECG

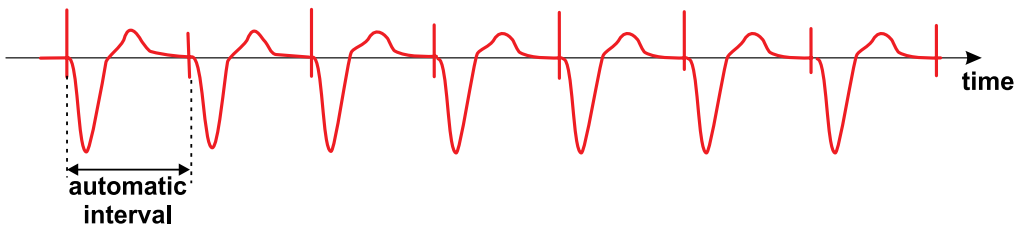
LEAD INSULATION DEFECTS



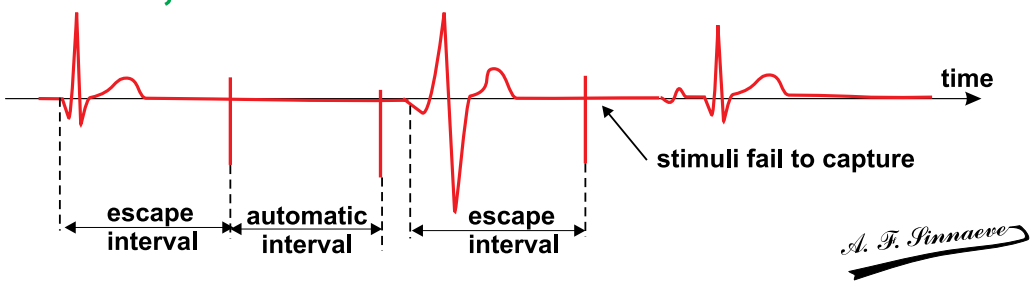
POSSIBLE CONSEQUENCES

* pacing may or may not be preserved
* stimuli are always present
* the pacing impedance is decreased
* excessive current loss leads to premature battery depletion

PACING IS PRESERVED



STIMULI, BUT FAIL TO CAPTURE



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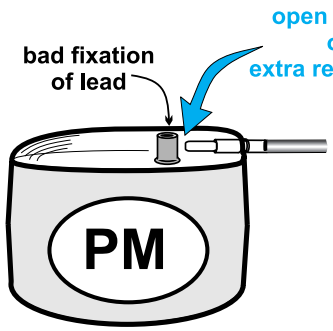
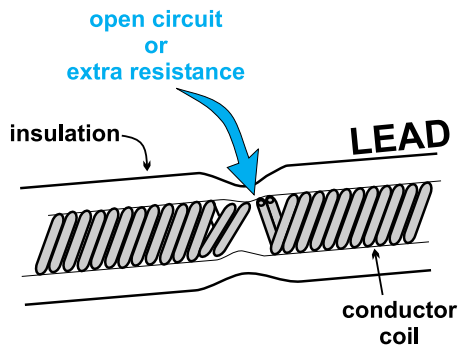
LEAD FRACTURE

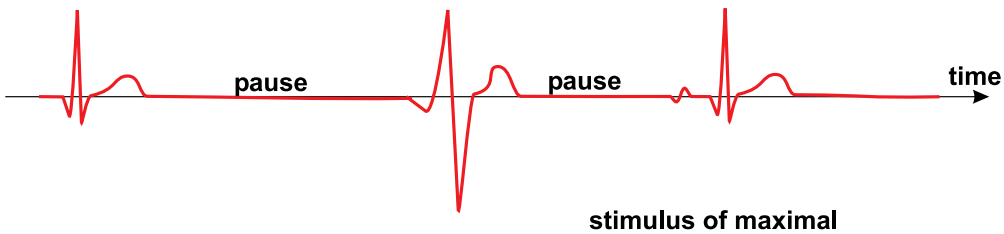




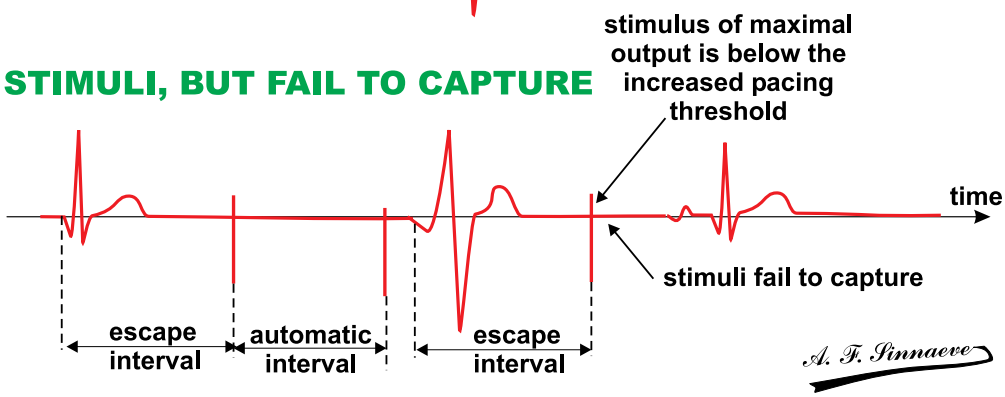
POSSIBLE CONSEQUENCES

* Stimuli may and may not be absent
* The voltage threshold is high
* The pacing impedance is increased

ALL STIMULI ABSENT



STIMULI, BUT FAIL TO CAPTURE



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ANALYSIS OF LEAD PROBLEMS

Be cunning as a fox ! You can get a lot of information about the leads, just by looking at the pacing impedance and the voltage threshold. The secret is to look at both !

	IMPEDANCE	VOLTAGE THRESHOLD
NORMAL LEAD PLACEMENT	NORMAL	NORMAL
LEAD DISPLACEMENT OR EXIT BLOCK	NORMAL	HIGH
LEAD FRACTURE	HIGH	HIGH
LEAD INSULATION DEFECT	LOW	MAY BE MODERATELY INCREASED

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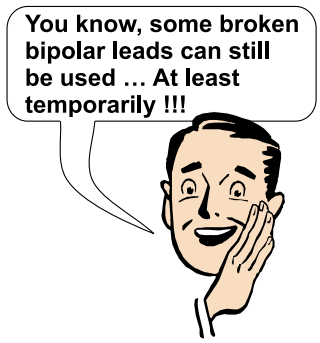
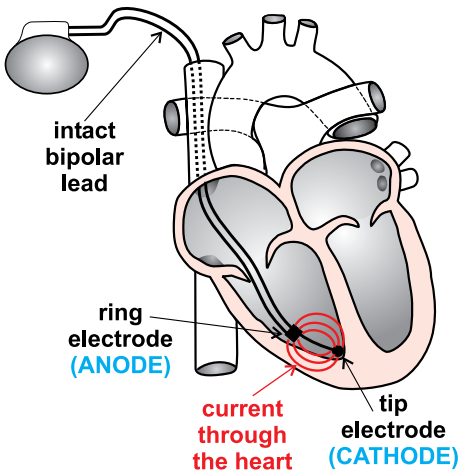
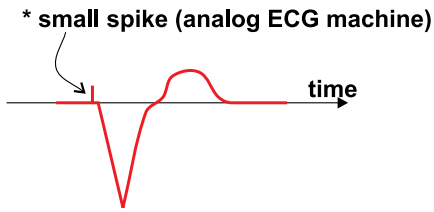
LEAD FRACTURE WITH CONVERSION FROM BIPOLAR TO UNIPOLAR MODE

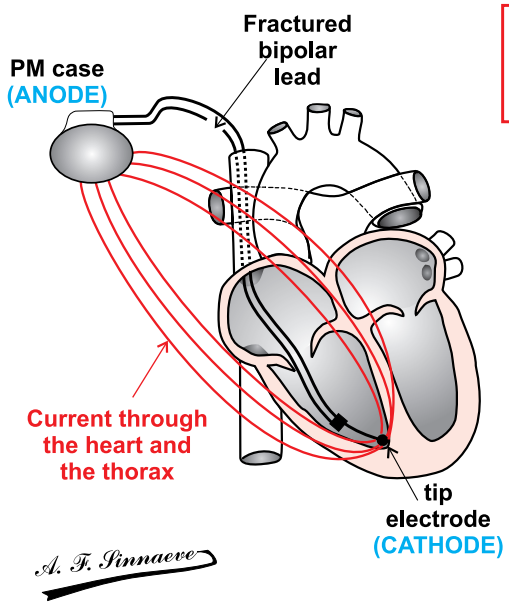




NORMAL BIPOLAR STIMULATION



* normal pacing impedance
(Z = about 500 ohm)



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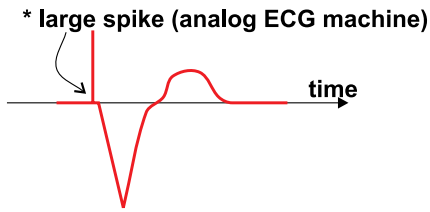
If one of the conductors in the bipolar lead is fractured, the pacing impedance becomes high !!!

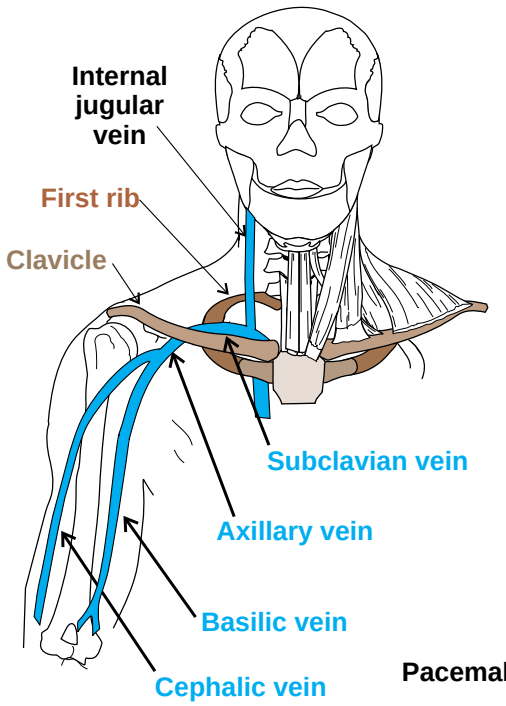
UNIPOLAR STIMULATION (via the distal tip electrode of a bipolar lead)

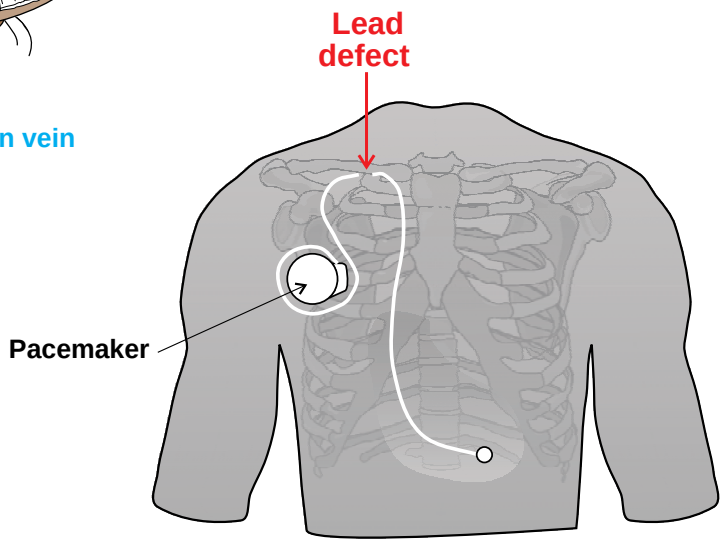


* normal pacing impedance
(Z = about 500 ohm)

Some contemporary pacemakers can measure lead impedance periodically and store the data which can be eventually retrieved by telemetry.
Some pacemakers are designed to detect the high impedance of an electrode fracture whereupon the device automatically converts its function from the bipolar to the unipolar mode of pacing and sensing (using the intact electrode as the cathode).
During follow-up, application of a magnet will temporarily restore bipolar function with resultant loss of capture.

SUBCLAVIAN CRUSH SYNDROME





DEFINITION :

The subclavian crush syndrome is described with pacemaker leads implanted via subclavian puncture. This may occur when conductor fractures and insulation breaches develop by compression of a lead between the first rib and the clavicle.

PREVENTION :

The subclavian crush syndrome occurs when the puncture is too medial and may be avoided by a more lateral subclavian puncture or by using the axillary vein or even the cephalic vein.

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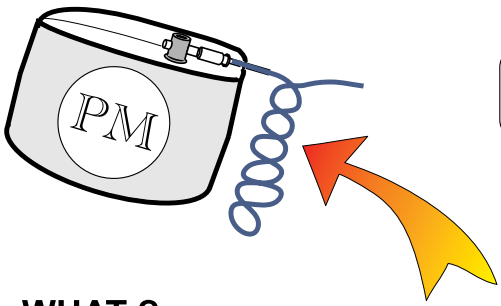
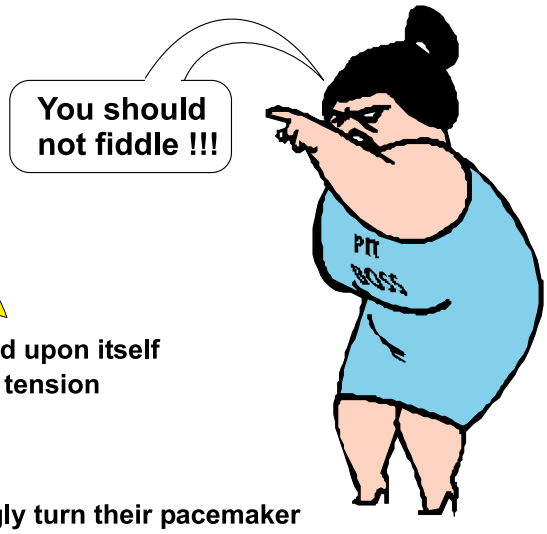
TWIDDLER'S SYNDROME





WHAT ? The lead is tightly twisted upon itself with the development of tension

CAUSES ?

* Elderly patients who unwittingly turn their pacemaker
* Obese patients with a loose pacemaker pocket
* Excessively large pacemaker pocket

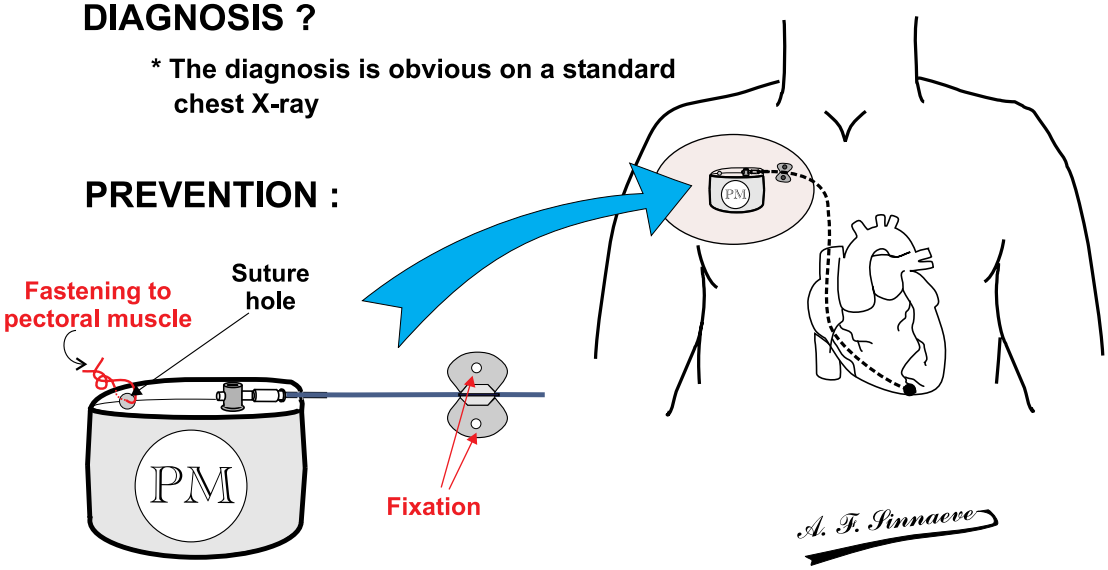
CONSEQUENCES ?

* Dislocation of the lead with failure to pace
* Lead fracture
* Insulation defect

DIAGNOSIS ?

* The diagnosis is obvious on a standard chest X-ray

PREVENTION :



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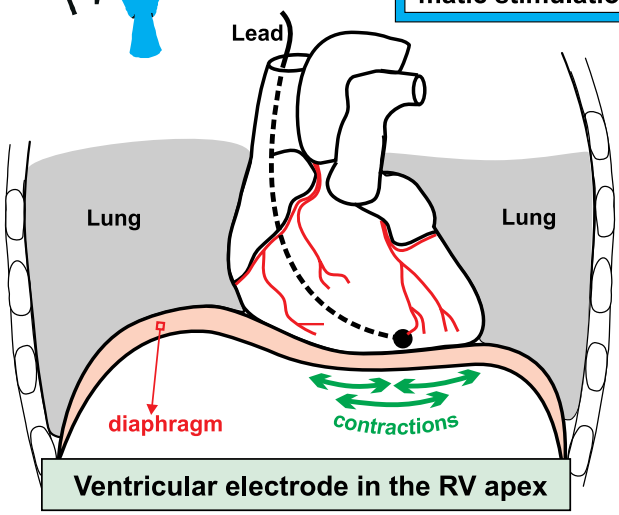
DIAPHRAGMATIC STIMULATION

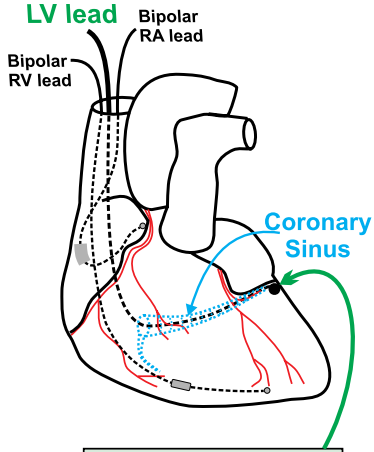
WARNING

Always consider the possibility of RV lead perforation when left diaphragmatic stimulation is observed !

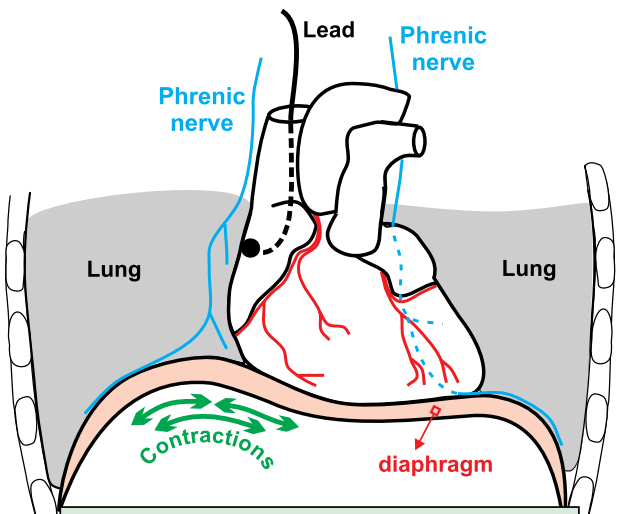


Ventricular electrode in the RV apex

BIVENTRICULAR PACING WITH TRANSVENOUS LEFT VENTRICULAR LEAD



Tip electrode in CS pacing the LV and stimulating the phrenic nerve



Lead at the lateral border of the right atrium stimulating the phrenic nerve

Diaphragmatic pacing is an important complication of left ventricular pacing from a coronary vein .

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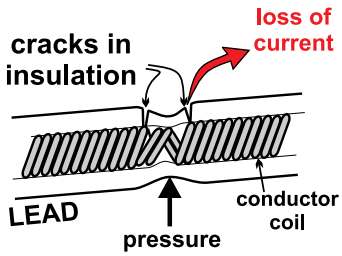
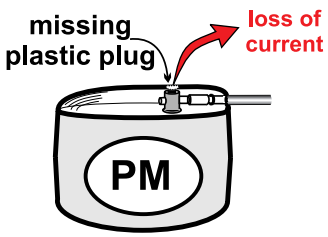
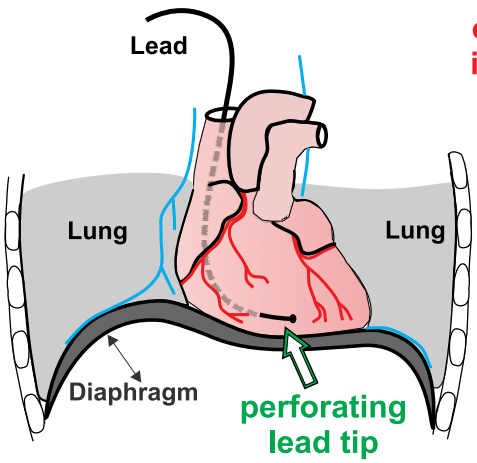
Abbreviations : RV = right ventricle ; LV = left ventricle

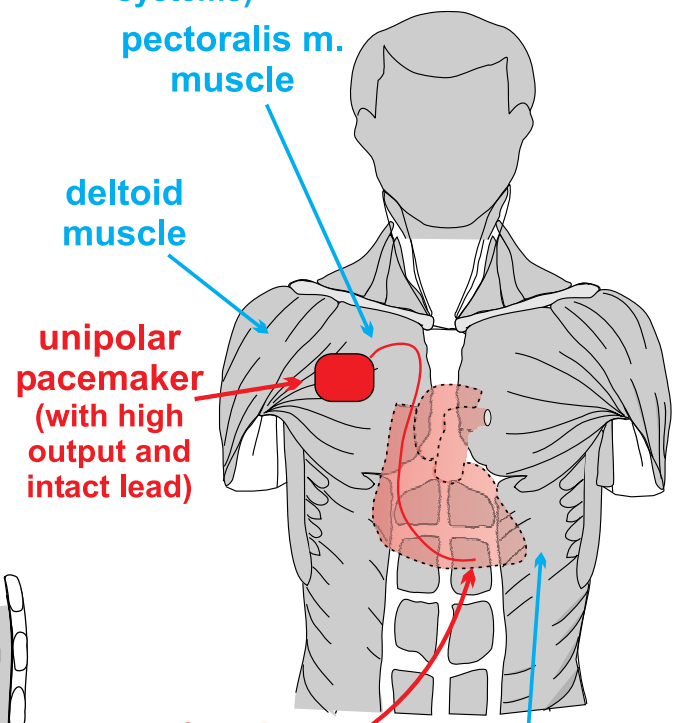
MUSCLE STIMULATION







(Extravascular lead insulation defect in unipolar or bipolar systems)



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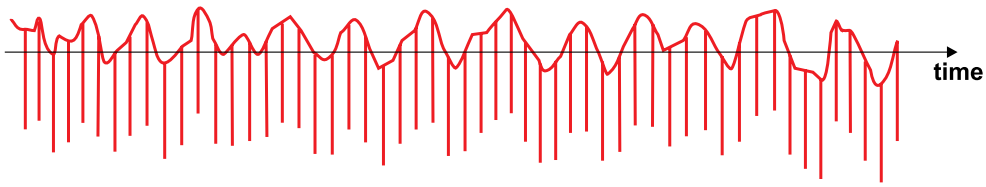
PACEMAKER RUNAWAY

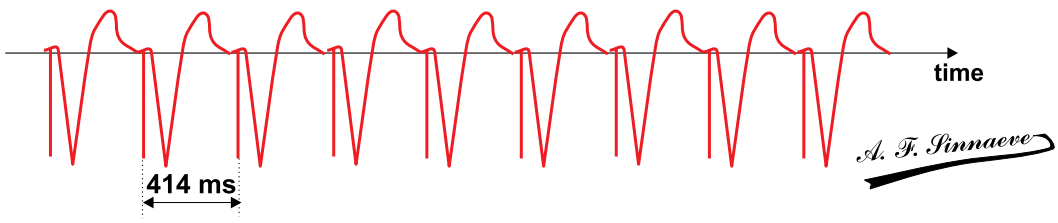
RUNAWAY OF AN OLD PACEMAKER AT 475 ppm

The VVI pacemaker emits stimuli at a rate of 475 ppm, too fast to cause 1:1 capture because of the ventricular myocardial refractory period. Such a situation may induce ventricular fibrillation. Emergency treatment consists of cutting the pacing lead.



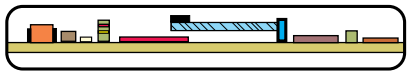
RUNAWAY OF A RECENT VVI PACEMAKER

The pacemaker was programmed at 70 ppm and paced at 145 ppm.
(The patient presented with palpitations and dyspnea until the unit was removed)

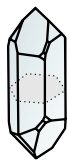


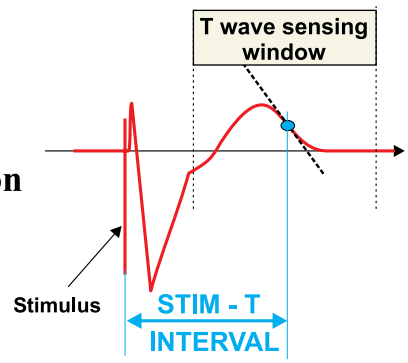
Runaway is a serious component malfunction of pacemakers. It is now rare because of improved technology. All contemporary pacemakers are equipped with a "runaway protection circuit", usually limiting the maximum pacing rate to 150 - 180 bpm.

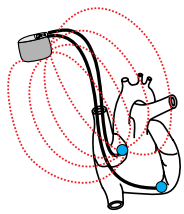
PACEMAKER HEMODYNAMICS & RATE-ADAPTIVE PACING



* Stroke volume and heart rate
* Benefit of AV synchrony and rate on exercise
* Atrial chronotropic incompetence
* Pacemaker syndrome with ventricular pacing
* Pacemaker syndrome with dual chamber pacing
* Maintenance of normal depolarization
* Indicators for rate-adaptive pacing
* Open loop rate-adaptive pacing
* Sensors of body motion
* Pressure on activity sensors
* Thoracic impedance and minute ventilation
* The minute ventilation sensor - part 1
* The minute ventilation sensor - part 2
* The QT sensor
* Rate-adaptive pacing - Definitions
* Algorithms for rate-adaptive pacing - part 1
* Algorithms for rate-adaptive pacing - part 2
* Sensor-driven and atrial-driven upper rates
* Unwanted responses of sensors - part 1
* Unwanted responses of sensors - part 2
* Dual sensors & sensor blending - part 1
* Dual sensors & sensor blending - part 2
* Dual sensors & sensor cross-checking - part 3
* Wenckebach upper rate response with rate-adaptive pacing
* Fixed-ratio block with rate-adaptive pacing
* The rate-adaptive postventricular atrial refractory period (PVARP)
* Non-competitive atrial pacing (NCAP)







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This is basic ! Everybody must know that !!!

HEMODYNAMICS OF THE NORMAL HEART

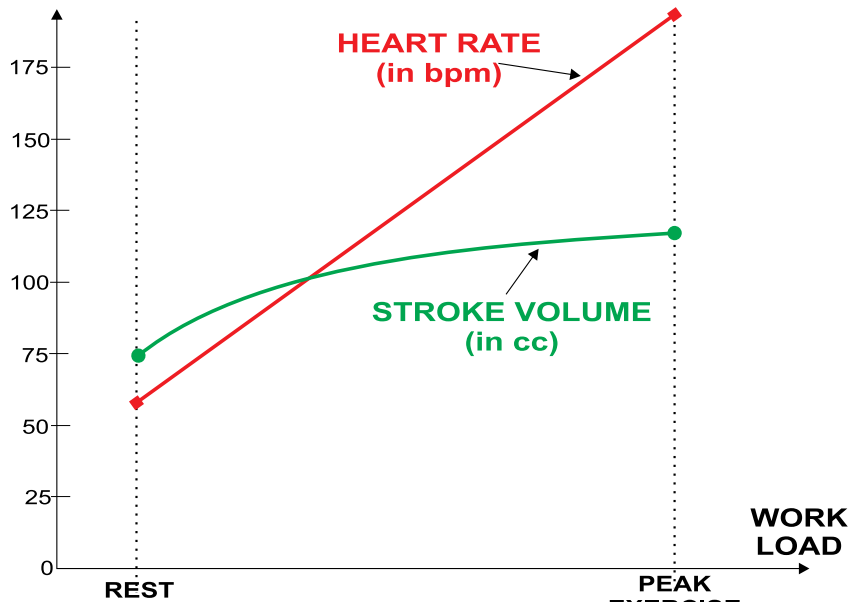
Heart Rate (HR) in bpm

Stroke Volume (SV) in liter per beat

Cardiac output (C.O.) in liter per minute

C.O. = HR x SV

$$\frac{\text{Liter}}{\text{Minute}} = \frac{\text{Beats}}{\text{Minute}} \times \frac{\text{Liter}}{\text{Beat}}$$



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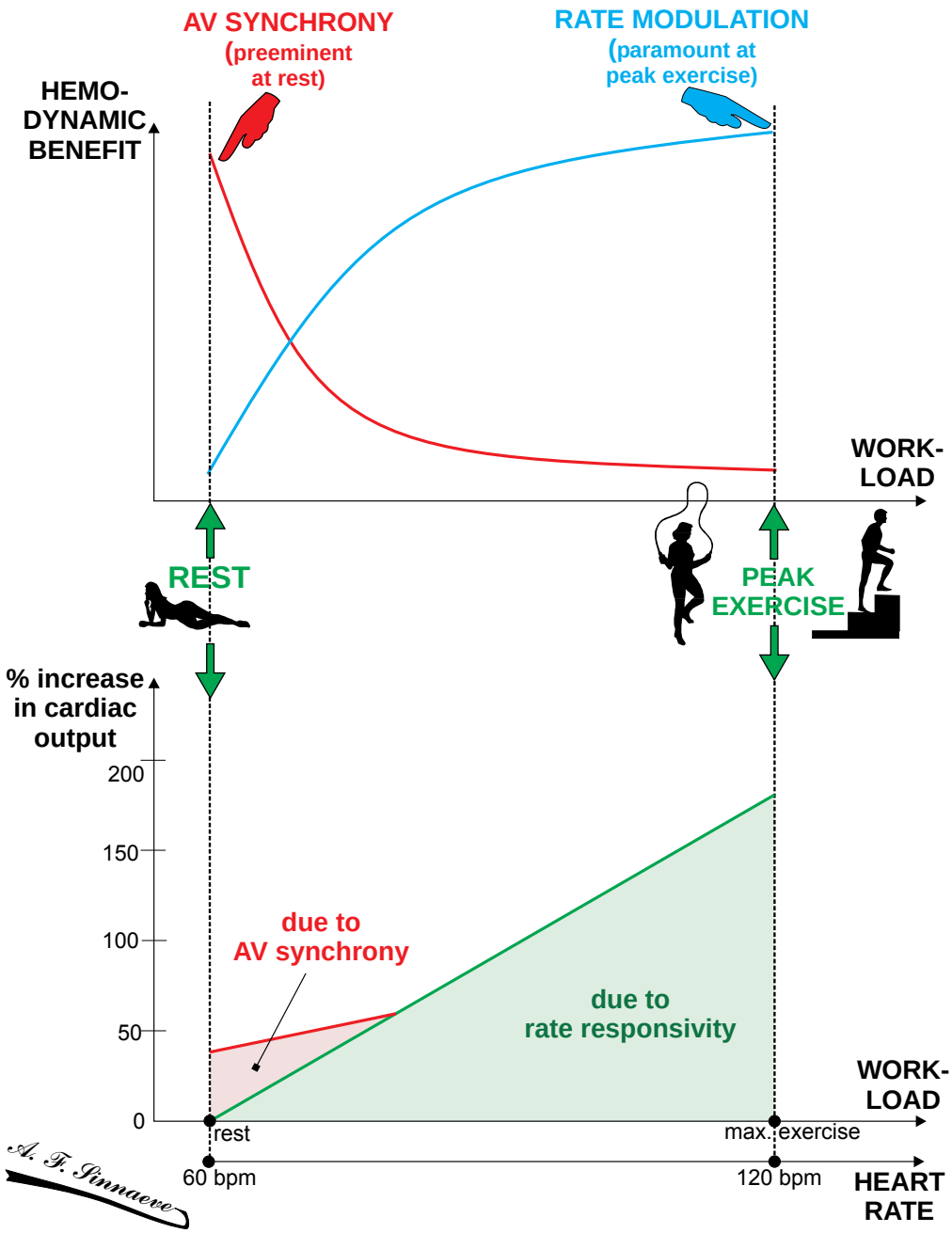
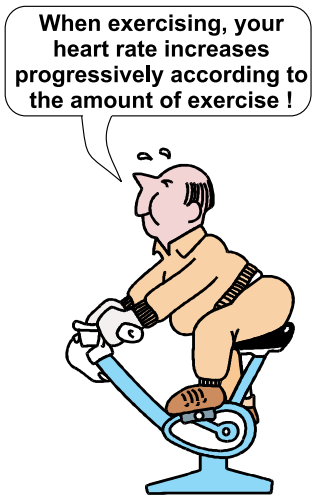
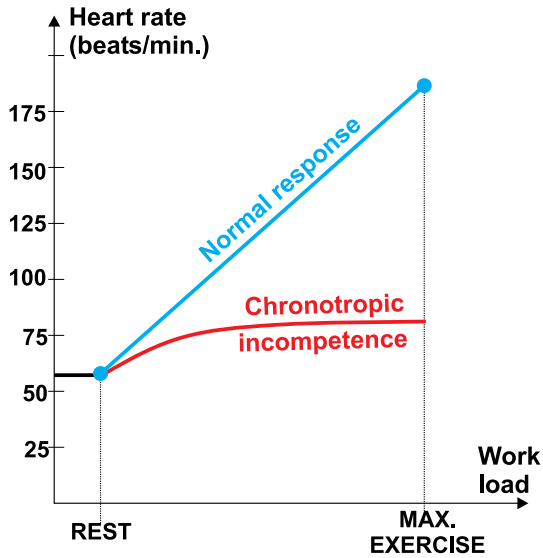
THE HEMODYNAMIC BENEFIT
AV SYNCHRONY VERSUS RATE MODULATION

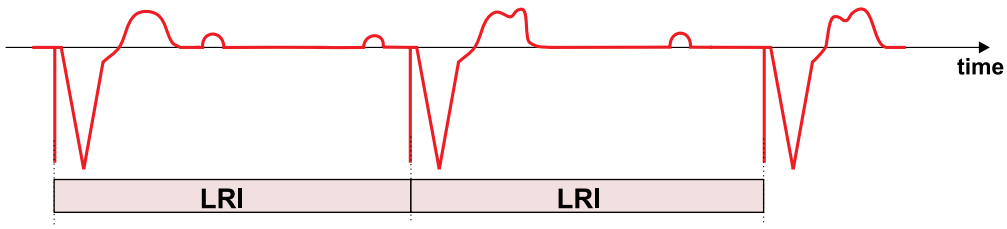


RATE - ADAPTIVE PACING AND CHRONOTROPIC INCOMPETENCE

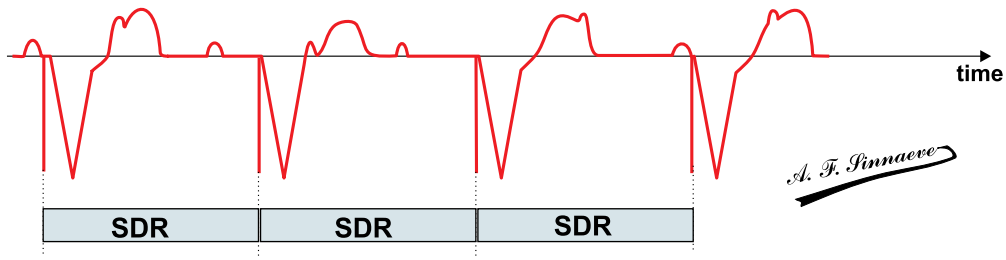




With a VVI pacemaker the ventricular pacing rate remains constant



With a VVIR pacemaker the ventricular pacing rate increases when the workload increases



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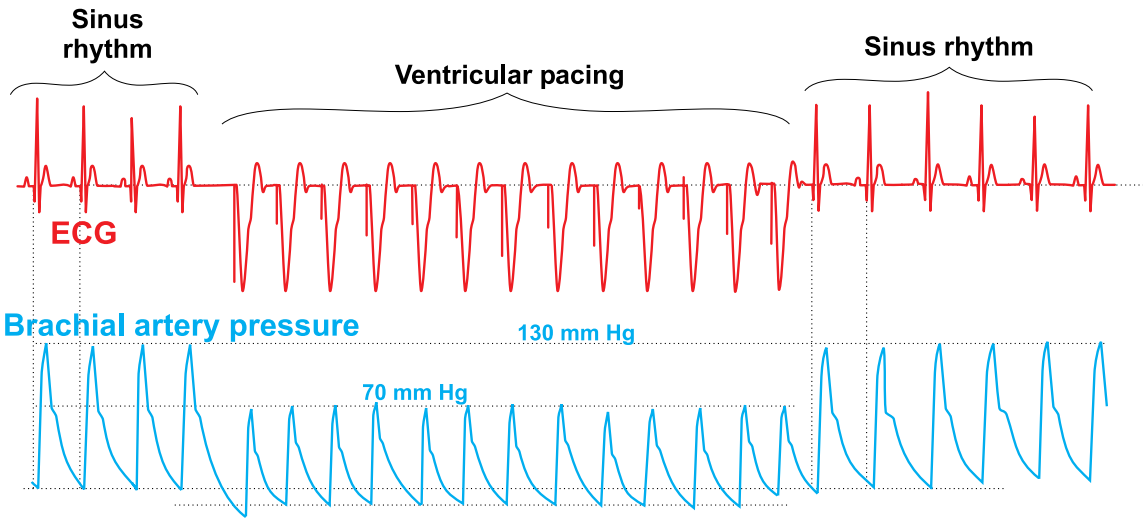
Abbreviations : LRI = lower rate interval ; SDR = sensor-driven interval

VVI PACING AND THE PACEMAKER SYNDROME



Blood pressure	=	Cardiac output	X	Peripheral resistance

or

BP = CO x PR

Normal : if CO↓↓↓ then PR↑↑↑ and BP ≅ constant

With pacemaker syndrome :
If CO↓↓↓ then PR↑↑ and BP↓

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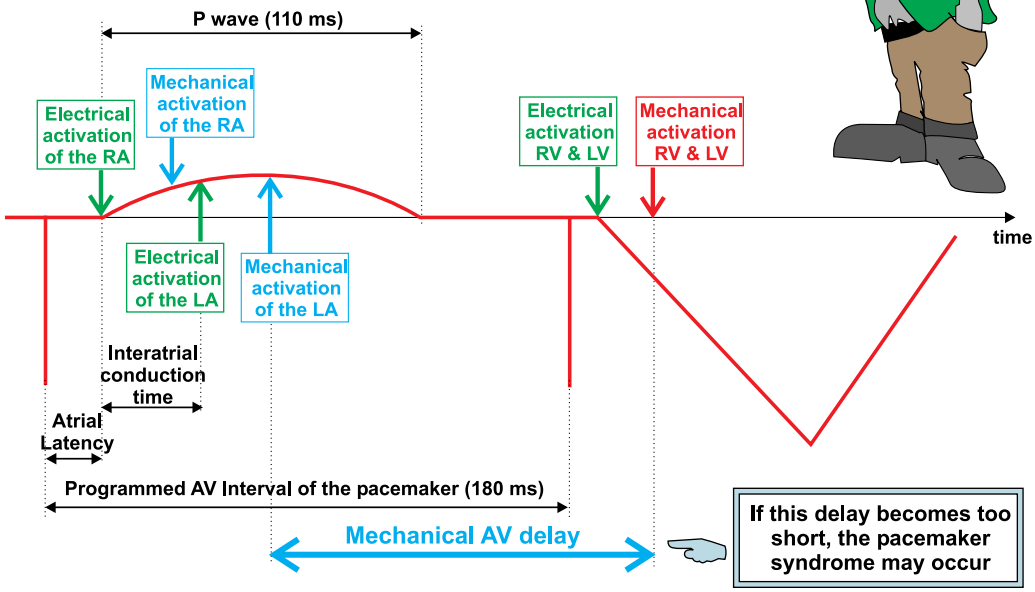
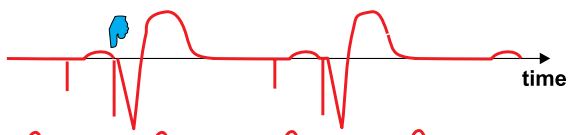
PACEMAKER SYNDROME WITH DUAL CHAMBER PACEMAKERS

The pacemaker syndrome refers to symptoms and signs present in the pacemaker patient which are caused by inadequate timing of atrial and ventricular contractions.

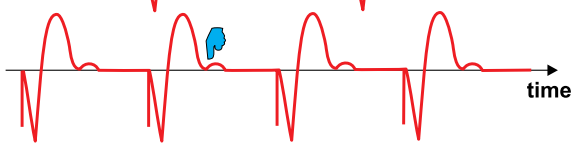


PM syndrome in atrial tracking pacemakers

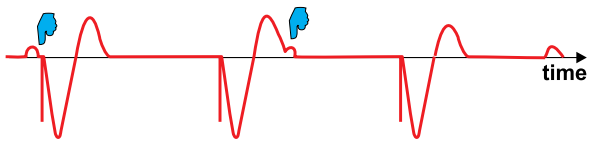
Marked delay of left atrial activation at rest and/or exercise



Sinus tachycardia with long programmed AV delay which does not shorten on exercise



VDD mode : sinus bradycardia at rest at a rate slower than the programmed lower rate



Repetitive nonreentrant VA synchrony

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MAINTENANCE OF NORMAL VENTRICULAR DEPOLARIZATION

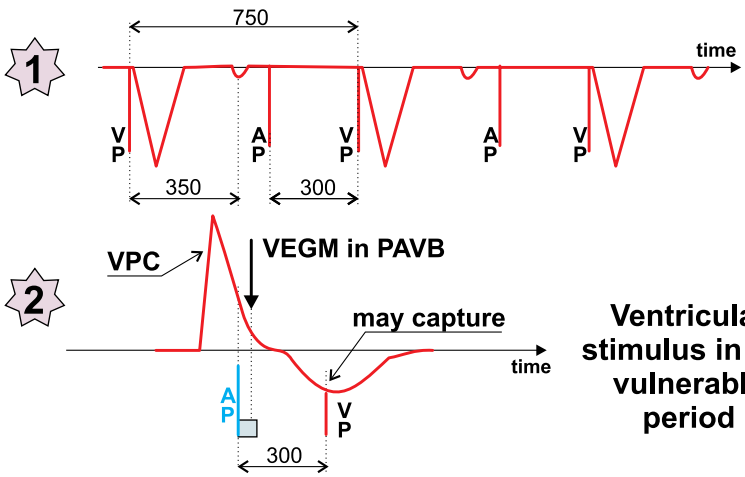
Ventricular depolarization via the normal pathway is hemodynamically superior to pacemaker induced depolarization on a short-term as well as on a long-term basis

Attempt to promote normal ventricular depolarization
if possible in specific circumstances, provided the PR interval remains shorter than 260 - 280 ms.

* AAI(R) mode . Risk of AV block !
* DDI(R) mode with long AV delay.
* DDD(R) mode with long AV delay.
* DDD(R) mode with AV search hysteresis or device with automatic switching to AAI(R) mode as required.

A long AV delay cannot always prevent pacemaker-induced ventricular depolarization in patients with normal AV conduction because of fusion and pseudo-fusion beats and other circumstances.

Risks of a long AV delay !!!



Repetitive nonreentrant VA synchrony (RNRVAS)

Ventricular stimulus in the vulnerable period

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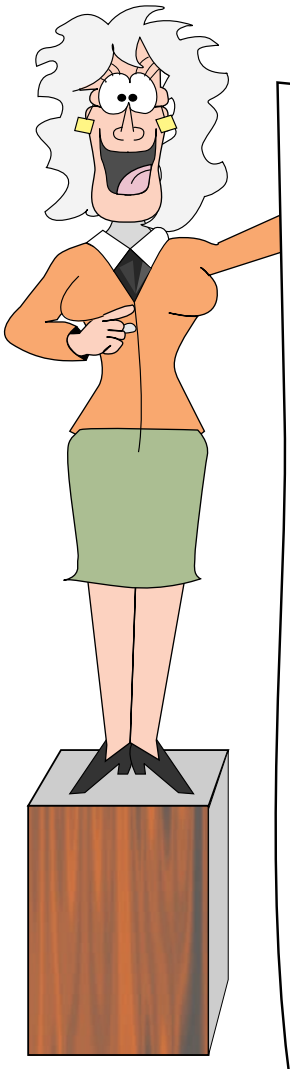
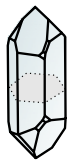
Abbreviations : AP = atrial pace; VP = ventricular pace; VPC = ventricular premature complex; VEGM = ventricular electrogram ; PAVB = postatrial ventricular blanking



INDICATORS FOR RATE-ADAPTIVE PACING

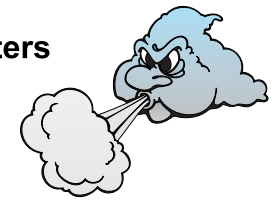
1. NON - PHYSIOLOGIC



* Vibration (Activity)
* Acceleration

2. PHYSIOLOGIC

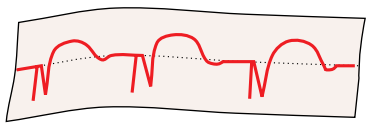
A/ Non-cardiac parameters
Indirect metabolic



* Minute ventilation

B/ Cardiac parameters

* QT interval



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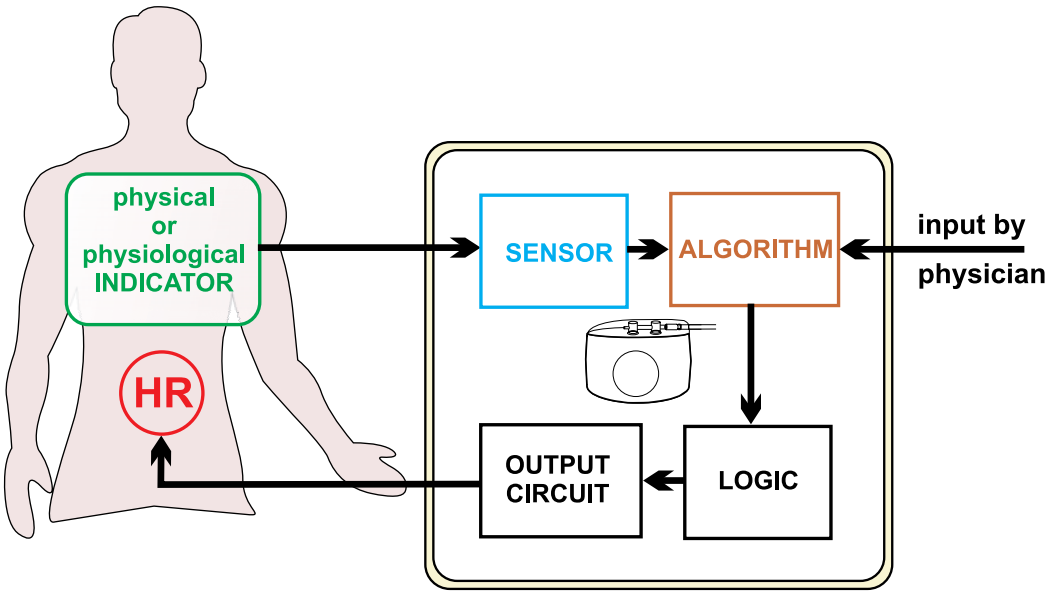
OPEN LOOP RATE - ADAPTIVE PM SYSTEM



HEART RATE (HR) :
The heart rate should be adapted to the need of the body

INDICATOR :
An indicator is a physical or physiological parameter, changing according to the metabolic needs of the body

SENSOR :
A sensor is a device that converts non-electrical data (i.e. an indicator) into electrical signals. The response of the indicator to the body function determines the magnitude and frequency of the electrical signals

ALGORITHM :
The algorithm is the software function of the pacemaker that converts the electrical signals from the sensor into an appropriate pacing response by the device

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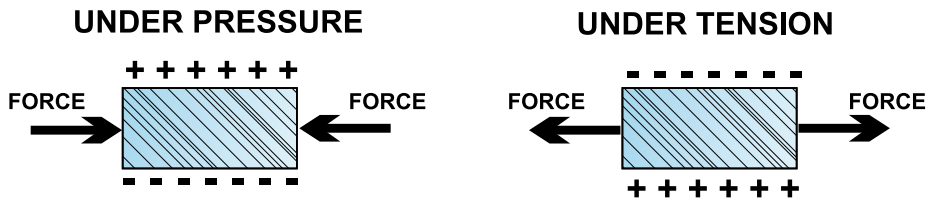
SENSORS OF BODY MOTION

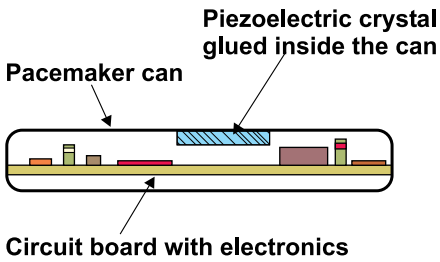
① THE PIEZOELECTRIC EFFECT

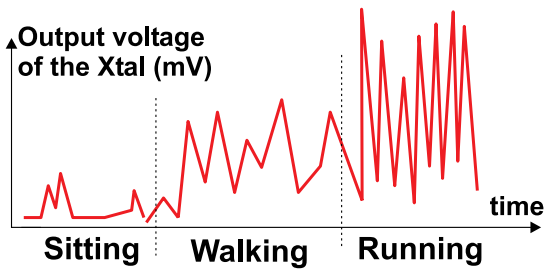
Some crystals (e.g. quartz) generate an electric voltage when they are subjected to mechanical stress.



② THE ACTIVITY SENSOR

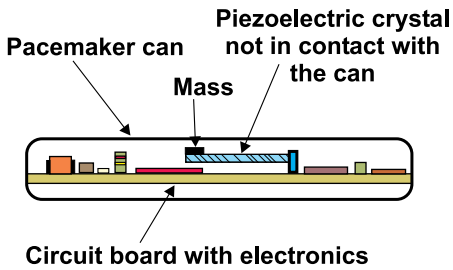
Responds to body vibrations.
Reacts to external stimuli that should not increase the pacing rate e.g. pressure on the device.





③ THE ACCELEROMETER

A very small mass in the pacemaker reacts upon acceleration and deforms the crystal which generates a voltage. This system has greater specificity than the activity sensor above, i.e. less false positive responses.



Both the activity sensor and the accelerometer react very fast upon the onset of any movement. The capability of early exercise detection makes the activity sensor a good component of dual sensor systems : e.g. activity + minute ventilation or activity + QT sensing

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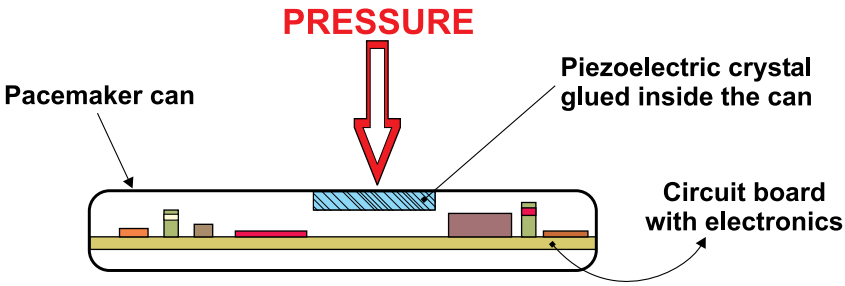
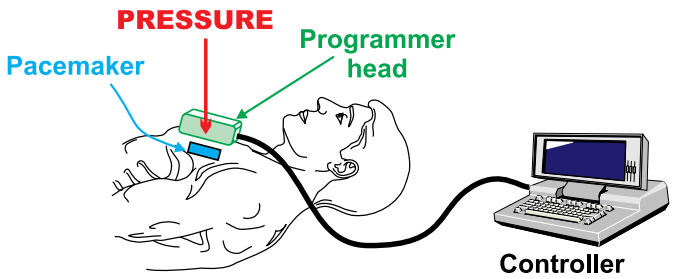
Abbreviations : mV = millivolt ; Xtal = crystal

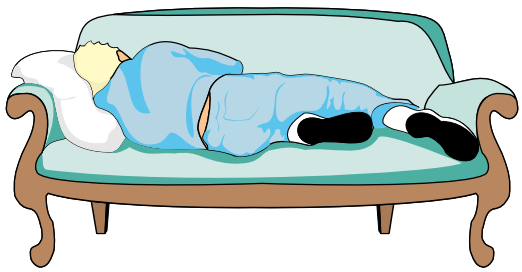
PRESSURE ON DEVICES EQUIPPED WITH AN ACTIVITY SENSOR



Since the crystal is in contact with the pacemaker can, pressure on the device may increase the heart rate without any exercise of the patient !!!



To avoid an increased rate, devices with an activity sensor should be reprogrammed temporarily to the DDD mode before testing the function of the pacemaker other than its rate-adaptive function.



Sleeping on one's abdomen may create pressure upon the pacemaker and increase the heart rate.
Even when the patient moves in bed, the pacing rate may go up.

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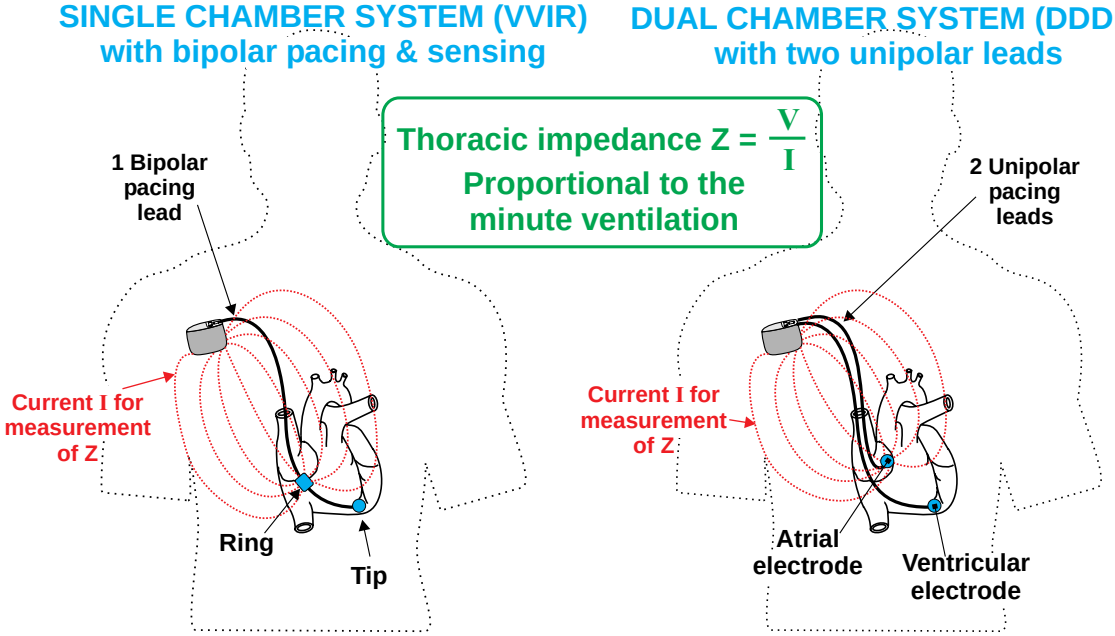
ARRANGEMENT OF MINUTE VENTILATION SENSORS

SINGLE CHAMBER SYSTEM (VVIR) with bipolar pacing & sensing

DUAL CHAMBER SYSTEM (DDDR) with two unipolar leads

Thoracic impedance Z = $\frac{V}{I}$
Proportional to the minute ventilation

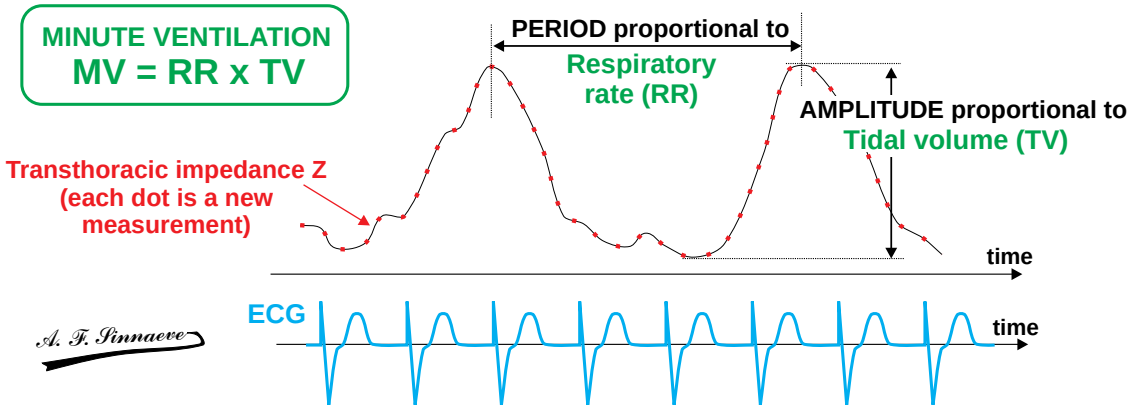


Current injection(I) between PM can and ring electrode
Voltage measurement (V) between PM can and tip electrode

Current injection(I) between PM can and atrial electrode
Voltage measurement (V) between PM can and ventricular electrode

* the current pulses I for impedance measurement are subthreshold, they have a low amplitude and are very short (pulse duration 5 to 15 μs)
* the measurement is frequently repeated (480 to 1200 times per minute)

MINUTE VENTILATION
MV = RR x TV



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MINUTE VENTILATION SENSOR

Minute ventilation (liter/minute) = **Tidal volume (liter)** X **Respiratory rate (breaths/minute)**

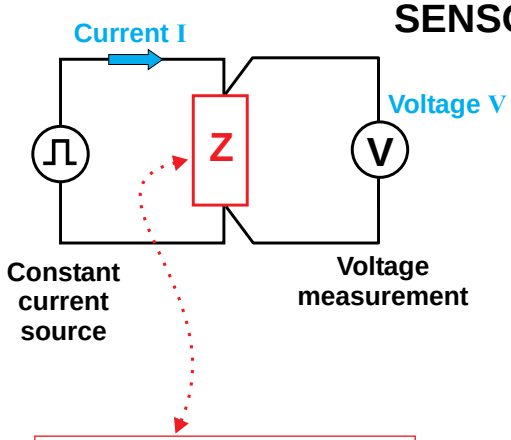
Tidal volume (liter) → **Amplitude of transthoracic impedance Z signal**

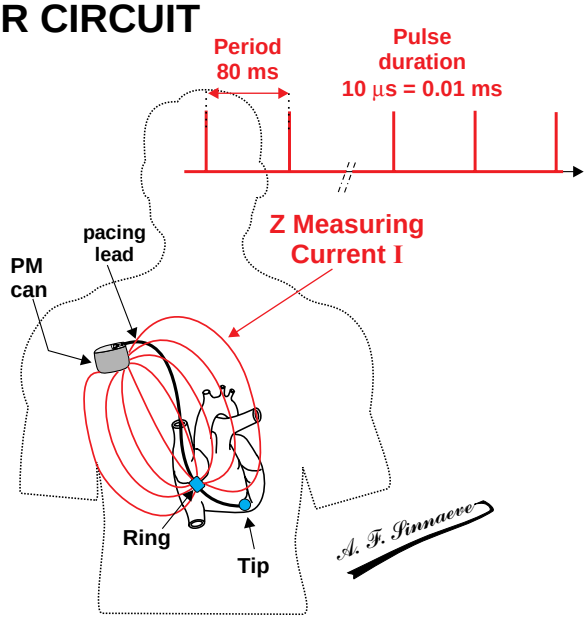
Respiratory rate (breaths/minute) → **Frequency of transthoracic impedance Z signal**

Amplitude of transthoracic impedance Z signal X **Frequency of transthoracic impedance Z signal** → **ALGORITHM (ampl. x freq.)**

A special circuit inside the pacemaker sends very short subthreshold current pulses I of known amplitude through the thorax. The device measures the voltage V between 2 thoracic sites as shown in the diagram below. This voltage is proporional to the transthoracic impedance Z

SENSOR CIRCUIT





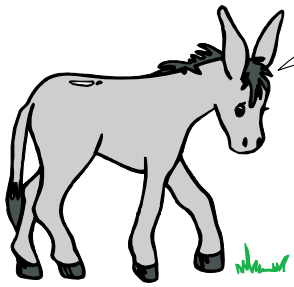
Thoracic impedance = $\frac{V}{I}$ = Z

FOR SENSOR FUNCTION

* Current I between can and ring electrode
* Voltage V between can and tip electrode

Movement of the arm may cause impedance changes and a faster pacing rate

MINUTE VENTILATION SENSOR - PART 2

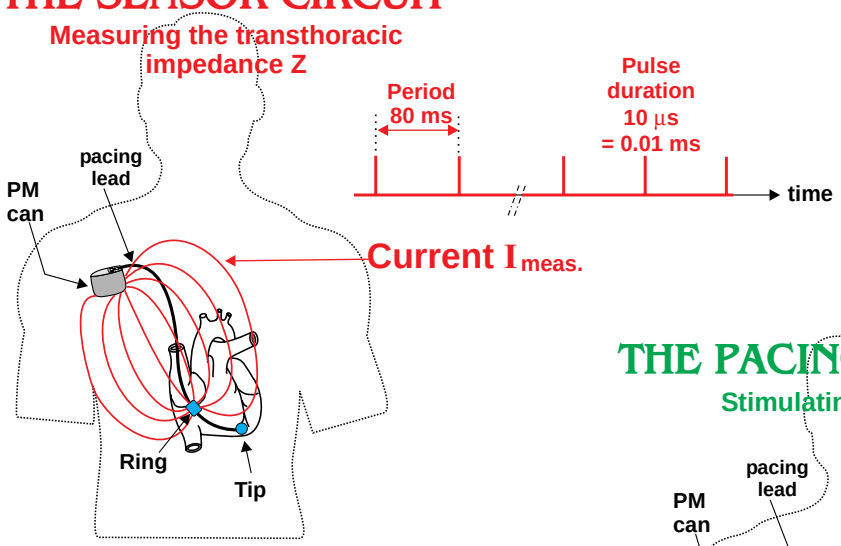


According to the engineers it's a piece of cake... and I don't even understand what they are talking about !!!
But I am only a little donkey...

NOTE THE DIFFERENCE !!!
THERE ARE 2 SEPARATE ELECTRIC CIRCUITS INVOLVED

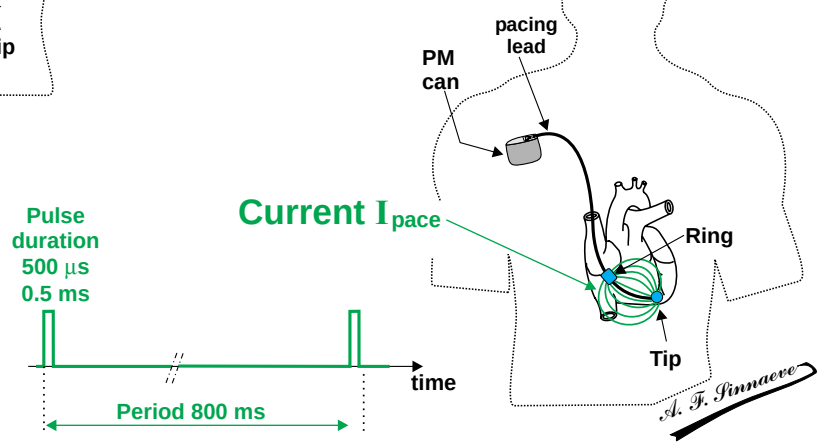
THE SENSOR CIRCUIT

Measuring the transthoracic impedance Z



THE PACING CIRCUIT

Stimulating the heart



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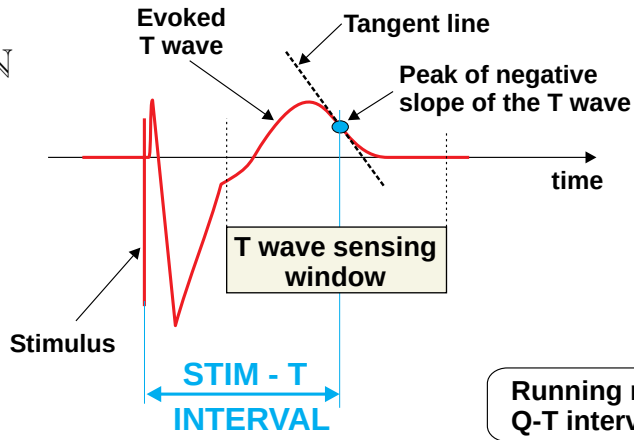
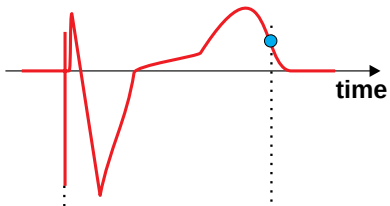
SENSING the QT or STIMULUS - T INTERVAL

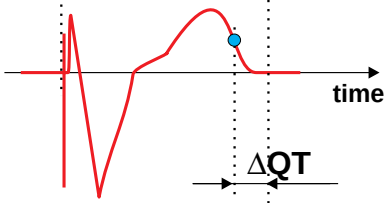
DEFINITION
of
STIMULUS - T INTERVAL
or
EVOKED Q-T INTERVAL

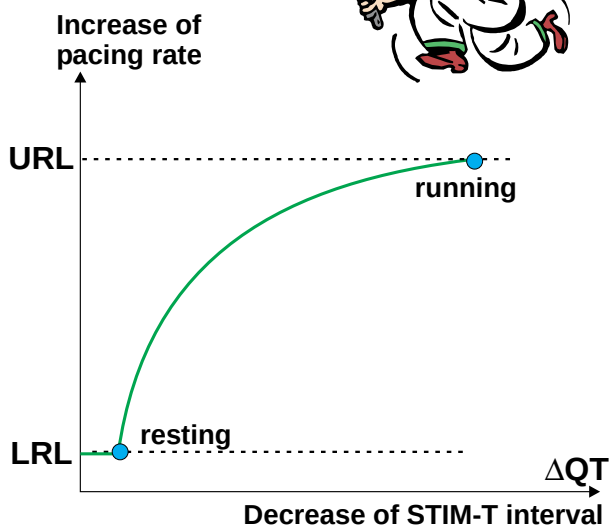


RESTING : LARGER
STIM-T INTERVAL



RUNNING : SHORTER
STIM-T INTERVAL





Abbreviations : URL = upper rate limit ; LRL = lower rate limit

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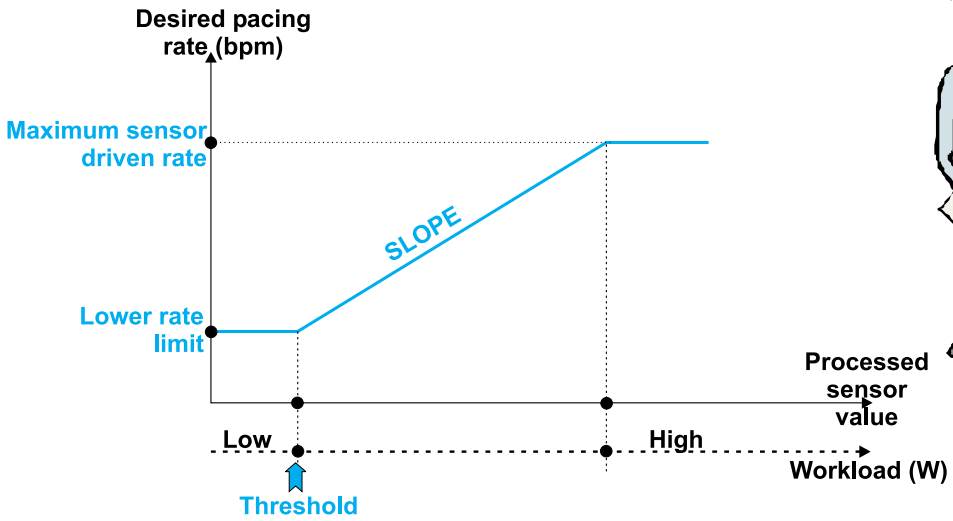
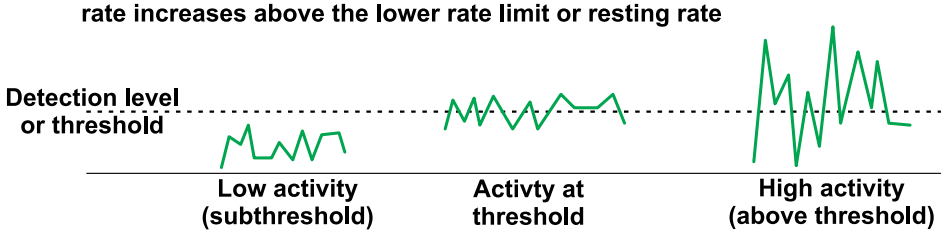
RATE-ADAPTIVE PACING DEFINITIONS

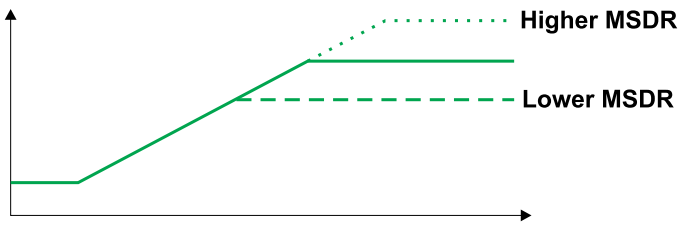


LOWER RATE LIMIT : the minimum desired resting heart rate of the patient (average 65 bpm)

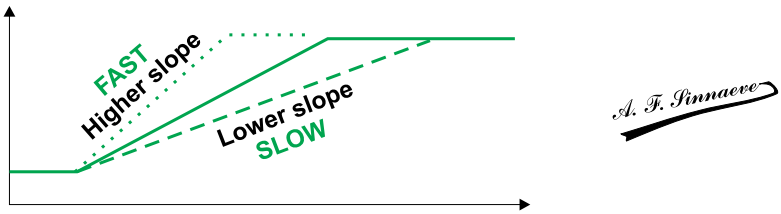
THRESHOLD : minimum workload (or minimum activity) at which the sensor driven pacing rate increases above the lower rate limit or resting rate



MAXIMUM SENSOR DRIVEN RATE : maximum pacing rate induced by the sensor



SLOPE : how fast the sensor driven pacing rate increases in response to the increasing workload (or increasing sensor output signal)



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ALGORITHMS FOR RATE-ADAPTIVE PACING

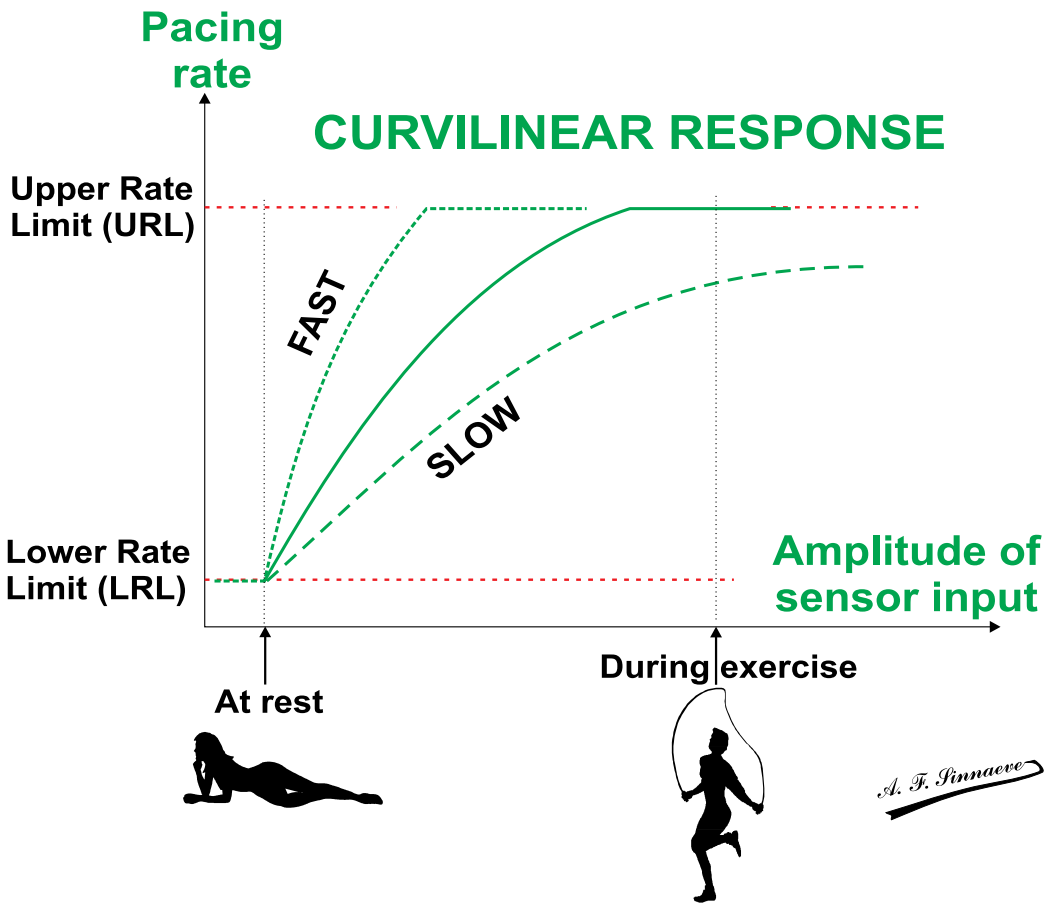
PARAMETERS PROGRAMMED BY THE OPERATOR

THE RANGE OF POSSIBLE PACING RATES

The lower rate limit (LRL) and the upper rate limit (URL) or maximal sensor-driven rate (MSDR) must be programmed

THE RATE RESPONSE SLOPE

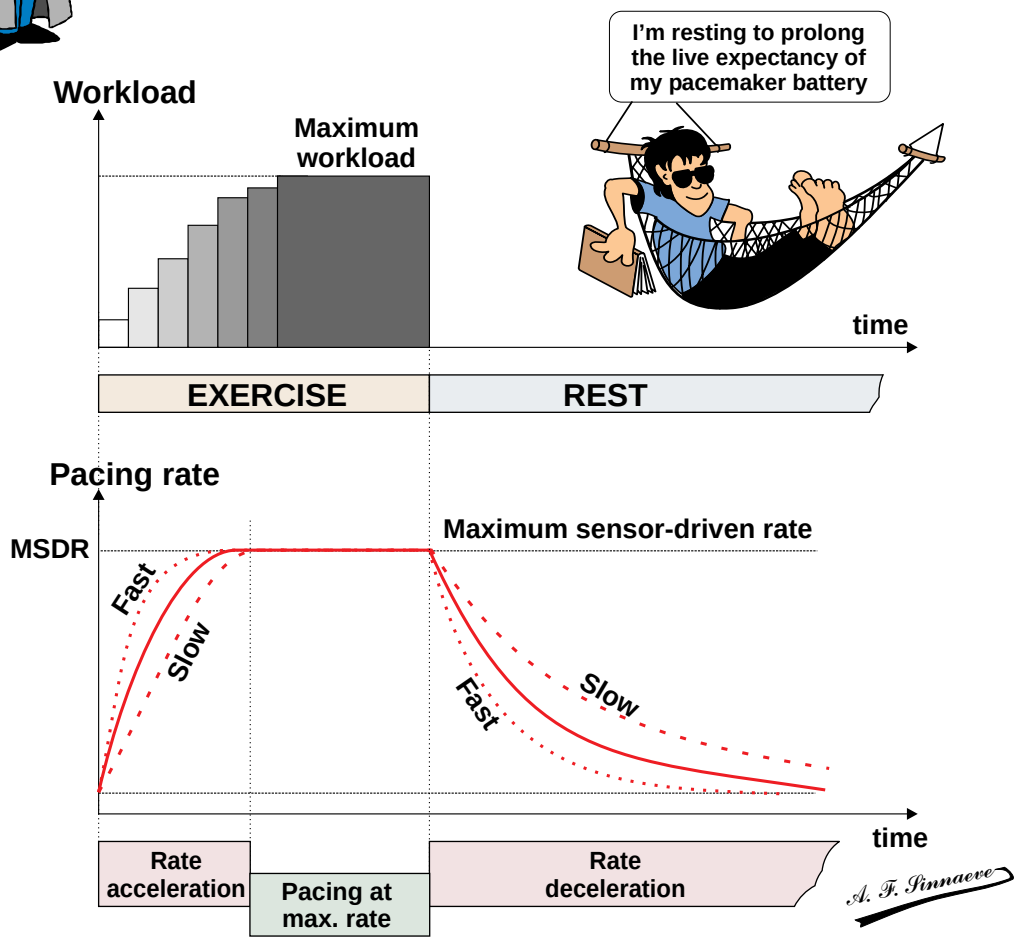
The response of the pacing rate to the signal of the sensor (detected activity, minute ventilation or Q-T time) may be programmed from fast (F) to slow (S) with many different settings



ALGORITHMS FOR RATE-ADAPTIVE PACING

PARAMETERS PROGRAMMED BY THE OPERATOR - PART 2

Many rate adaptive pacemakers use different sets of curves for the post-exercise recovery. The slope of these deceleration curves may be programmed by the operator.

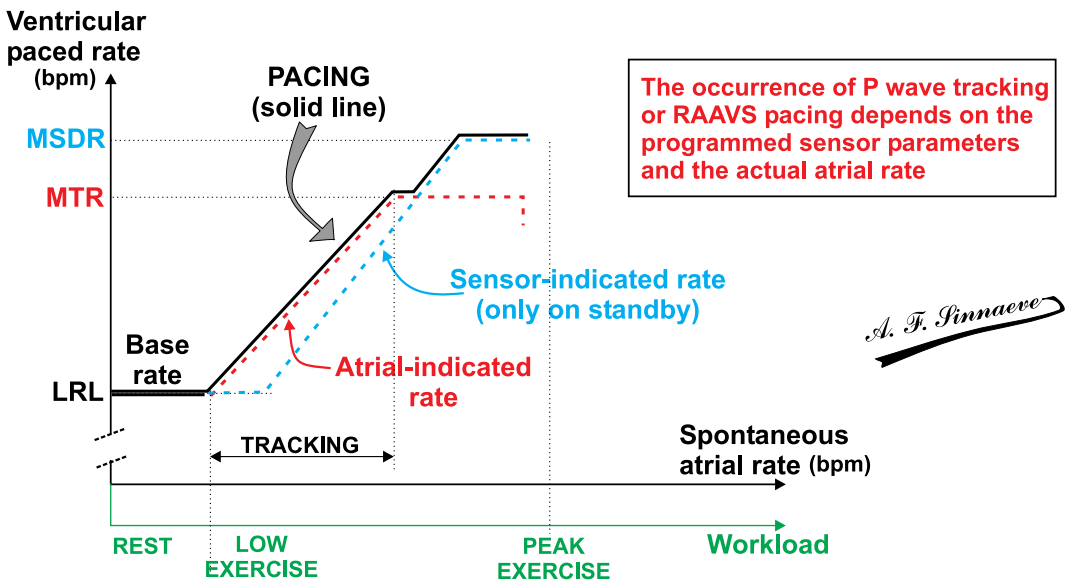


PAY ATTENTION !!! NOTE THE DIFFERENCE BETWEEN ATRIAL-DRIVEN RATE AND SENSOR-DRIVEN RATE

DUE TO INTRINSIC ATRIAL ACTIVITY (e.g. Sinus Node)	DUE TO THE SIGNAL OF THE SENSOR (e.g. Minute Ventilation)
Spontaneous Atrial Interval (SAI)	Sensor-driven Interval (SDI)
Spontaneous Atrial Rate (SAR)	Sensor-driven Rate (SDR)
$\text{SAR (bpm)} = \frac{60\,000}{\text{SAI (ms)}}$	$\text{SDR (bpm)} = \frac{60\,000}{\text{SDI (ms)}}$
Atrial-Driven Upper Rate = Maximum Tracking Rate (MTR)	Sensor-Driven Upper Rate = Maximum Sensor-Driven Rate (MSDR)

Theoretically, there are three possible settings :

* *MSDR > MTR* generally used in patients with atrial chronotropic incompetence
* *MSDR = MTR* useful for rate smoothing to prevent sudden pauses at high atrial rates
* *MSDR < MTR* limited usefulness e. g. when the sinus rate may suddenly drop during exercise (sick sinus syndrome) and in certain patients with activity sensors who are obligatorily exposed to vibrations (Parkinson's disease, truck drivers, etc.)



The occurrence of P wave tracking or RAAVS pacing depends on the programmed sensor parameters and the actual atrial rate

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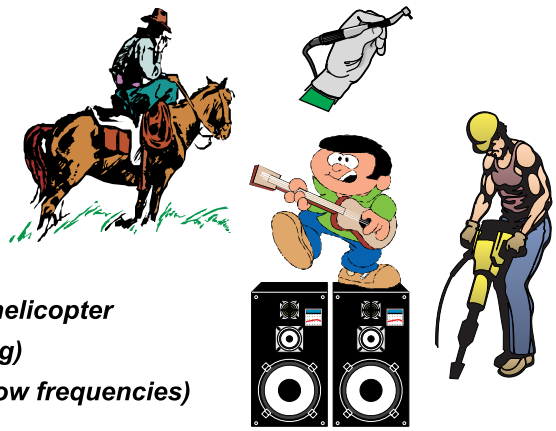
Abbreviations : LRL = lower rate limit; MSDR = maximum sensor-driven rate; MTR = maximum tracking rate; RAAVS = rate-adaptive AV sequential pacing; SAI = spontaneous atrial interval; SAR = spontaneous atrial rate; SDI = sensor-driven interval; SDR = sensor-driven rate.

UNWANTED RESPONSES OF SENSORS - PART 1

1 SENSORS OF BODY MOTION

The pacing rate of devices with an activity sensor or an accelerometer depends on the type of activity and does not correlate well with the level of exertion or the amount of work, i.e. body vibration is not proportional to the level of energy expenditure

1/ Environmental interference may cause an unwanted increase in pacing rate (less pronounced for devices equipped with an accelerometer) :

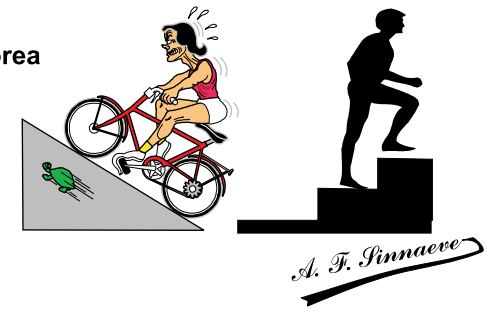


- ***riding on horseback***
- ***driving in a car on rough terrain***
- ***riding on a motorcycle on a bad road***
- ***flying in a small-engine aircraft or in a helicopter***
- ***the use of drills (including dental drilling)***
- ***very loud rock music (especially ultra-low frequencies)***

2/ Postoperative shivering and anxiety-provoked shivering may cause a persistent pacemaker tachycardia

3/ Epileptic seizures and myotonic jerking with chorea can increase the pacing rate

4/ When bicycling the condition of the road influences the rate response excessively, while walking downstairs may cause a larger rate increase than walking upstairs



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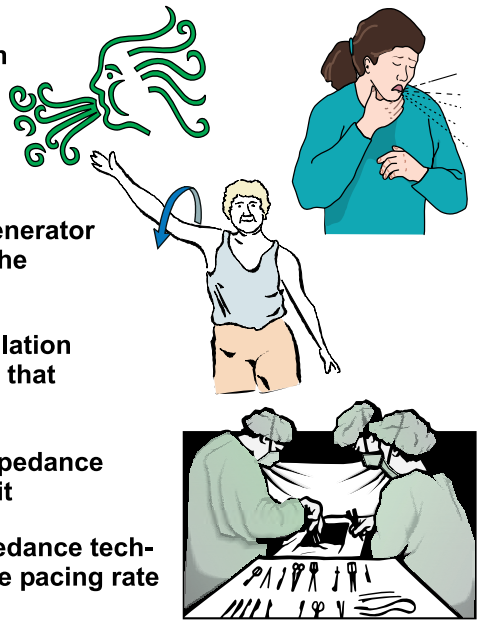
UNWANTED RESPONSES OF SENSORS - PART 2

2 SENSORS OF MINUTE VENTILATION

Systems with a minute ventilation sensor are highly physiologic and therefore highly specific. Occasionally the reaction to the onset of exercise may be delayed and the rate may be too fast after the end of exercise



1/ Hyperventilation, coughing and tachypnea from chest infection or congestive heart failure can increase the pacing rate
(contraindicated in patients with chronic obstructive pulmonary disease)

2/ Swinging of the arm on the side of the pulse generator and rotating shoulder movements may increase the pacing rate

3/ During general anesthesia, an increase in ventilation can produce a substantial increase in pacing rate that may cause hypotension

4/ Electrocautery may provoke changes of the impedance and thus increase the pacing rate to its upper limit

5/ Some systems in the CCU that use similar impedance technology to monitor respiration, can also disturb the pacing rate

3 Q-T SENSOR

The Stim-T interval not only responds to exercise, but also to emotion. However, the QT interval reacts rather slowly.

1/ T wave detection may be hampered by frequent ventricular ectopy, by ventricular fusion beats and by substantial lead polarization

2/ The Q-T interval may be affected by electrolyte disturbances, some medications and coronary artery disease with myocardial ischemia or infarction

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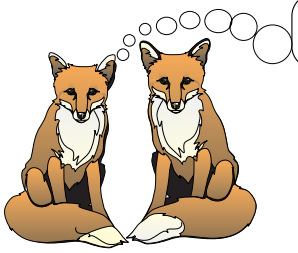
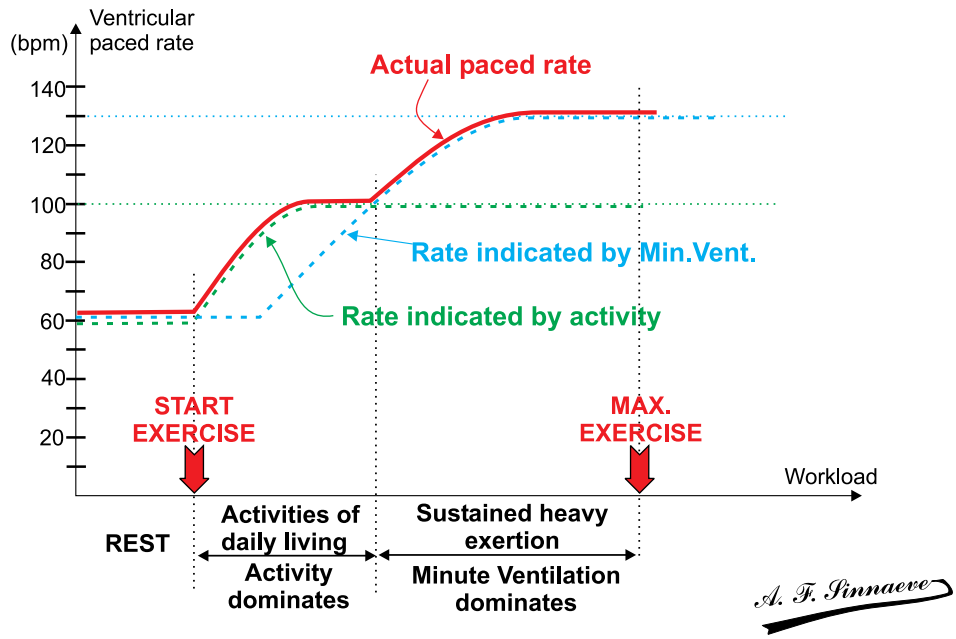


DUAL SENSORS & SENSOR BLENDING PART 1

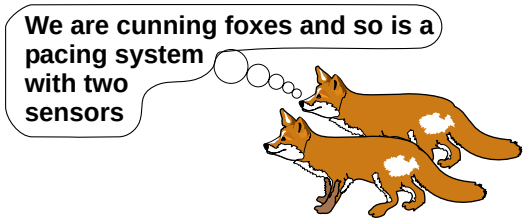
A combination of two sensors is used to improve the correlation to workload for various forms of exercise and to minimize paradoxical responses

NON-PHYSIOLOGIC OR MECHANICAL INDICATORS	PHYSIOLOGIC OR METABOLIC INDICATORS
SENSORS : Activity sensors Accelerometers	*SENSORS* : Minute Ventilation QT- interval
PRO : fast responding	*CONTRA* : slow responding
CONTRA : low specificity i.e. Increased incidence of false positive responses unrelated to actual exercise	*PRO* : high specificity i.e. Lesser incidence of false positive responses unrelated to actual exercise

The combination of a physiologic and a non-physiologic sensor results in a rate response that mimics normal sinus node response closely and that to a great extent ignores false positive sensor information

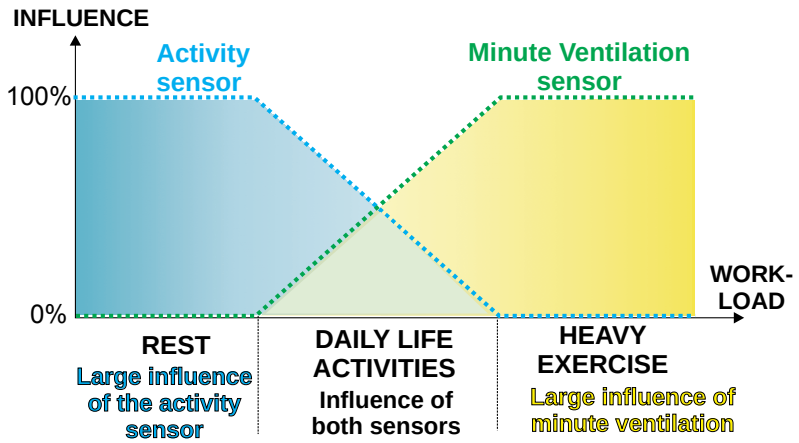


DUAL SENSOR PACING PART 2



SENSOR BLENDING determines the relative influence of each sensor upon the pacing rate.

Depending upon the sophistication of the algorithm, the blending may be programmed in fixed steps (0/100 - 30/70 - 50/50 - 70/30 - 100/0) or the relative contribution of each sensor may vary automatically across the rate response range



SENSOR CROSS-CHECKING reduces false responses

ONE — The activity sensor indicates a higher rate, while the minute ventilation sensor indicates a constant low rate (e.g. nonphysiologic vibrations) : only a limited increase of stimulation rate will occur during a short period of time

TWO — The activity sensor denotes a constant low rate while the minute ventilation sensor is asking for a higher rate (e.g. due to fever or to hyperventilation) : the simulation rate will only slightly increase

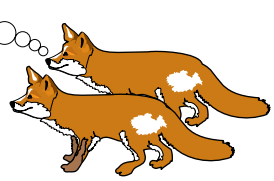
THREE — Both the activity sensor and the minute ventilation sensor are indicating a higher rate : the stimulation rate will augment in the correct way

FOUR — Both the activity sensor and the minute ventilation sensor are pointing towards a lower rate : the stimulation rate will decrease appropriately

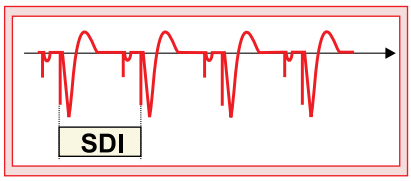
A. F. Sinnaeve

DUAL SENSOR PACING
PART 3 : SENSOR CROSS-CHECKING

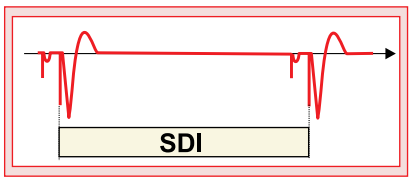
We are cunning foxes and so is a pacing system with two sensors



I had a pacemaker with an activity sensor. Every time I drove on this bumpy road, my heart rate went up a lot … !!!



Now I have a pacemaker with two sensors, activity and QT.
Even driving faster on the same bumpy road, my heart rate goes up only slightly!!!

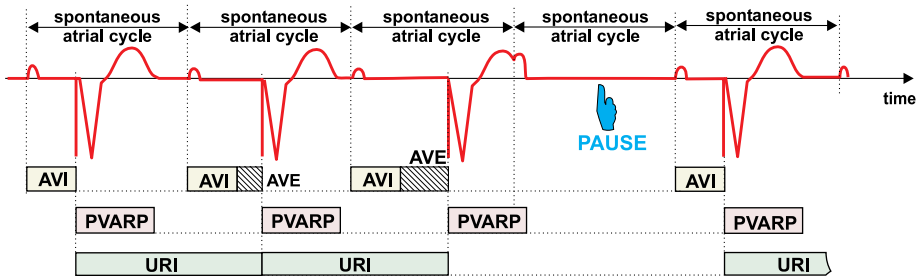


A. F. Sinnaeve

Abbreviations : SDI = sensor driven interval

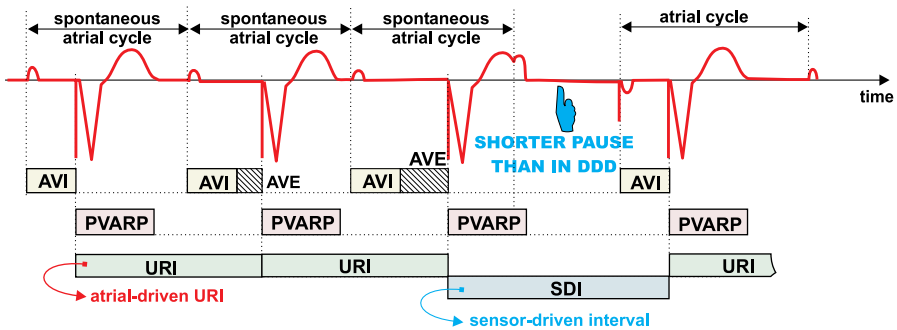
WENCKEBACH UPPER RATE BEHAVIOR DURING RATE - ADAPTIVE PACING

1. DDD pacing (ventricular-based timing)

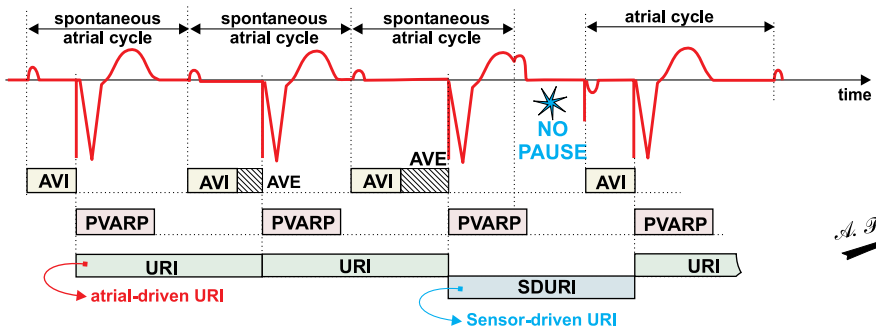


2. Sensor-driven rate smoothing (DDDR ventricular-based timing)

When the sensor-driven interval is longer than the atrial-driven upper rate interval



When the sensor-driven interval (equal to the sensor-driven upper rate interval SDURI) is equal to the atrial-driven upper rate interval

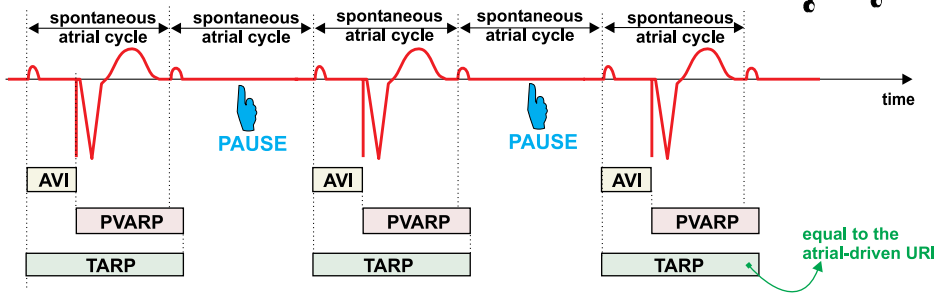


A. F. Pinnaeve

Abbreviations : AVI = programmed AV delay ; AVE = AV extension ; PVARP = postventricular atrial refractory period ; URI = atrial-driven upper rate interval ; SDI = sensor driven interval ; SDURI = sensor-driven upper rate interval

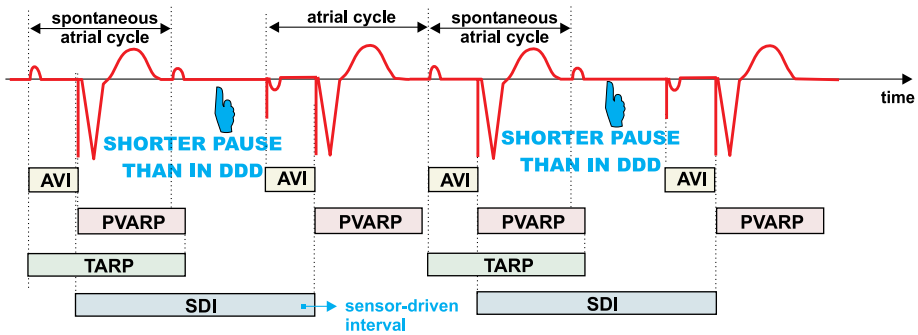
2 :1 BLOCK UPPER RATE BEHAVIOR DURING RATE - ADAPTIVE PACING

1. DDD pacing (ventricular-based timing)

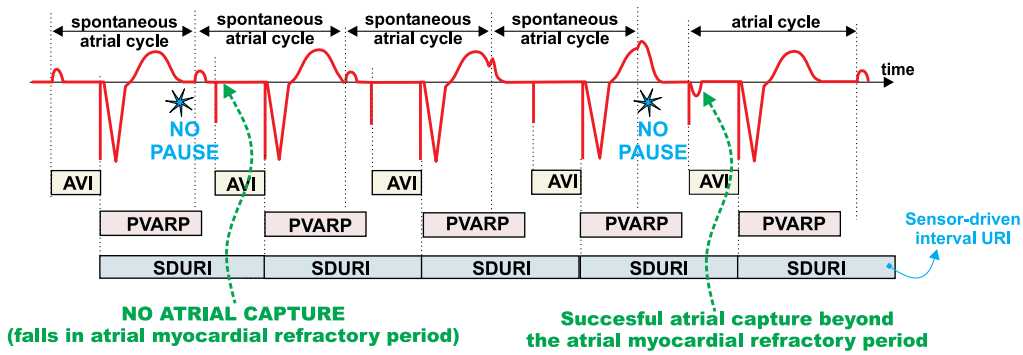


2. Sensor-driven rate-smoothing (DDDR ventricular-based timing)

When the sensor-driven interval is longer than the atrial-driven upper rate interval



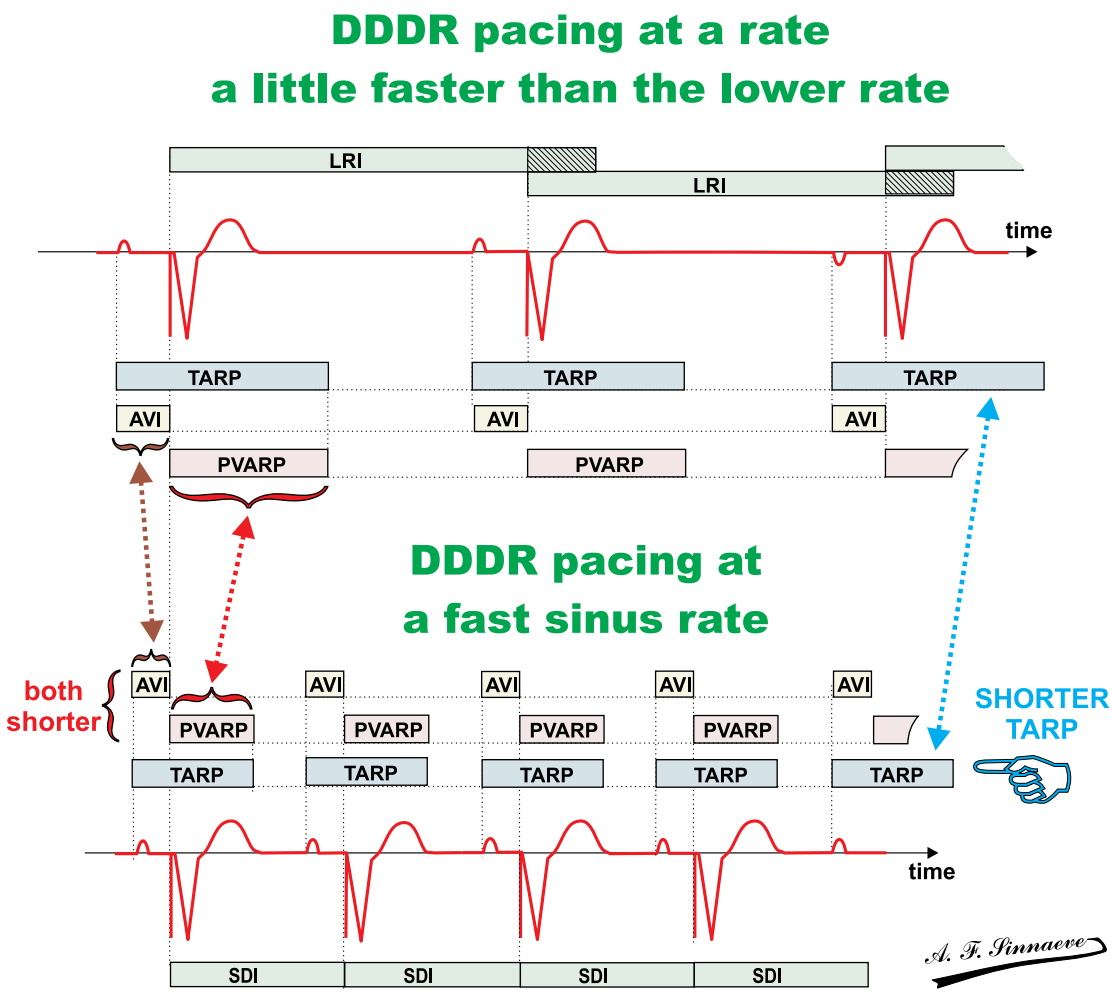
When the sensor-driven interval (equal to the sensor-driven upper rate interval SDURI) is equal to the atrial-driven upper rate interval



Abbreviations : AVI = programmed AV delay ; AVE = AV extension ; PVARP = postventricular atrial refractory period ; URI = atrial-driven upper rate interval ; SDI = sensor driven interval ; SDURI = sensor-driven upper rate interval ; TARP = total atrial refractory interval

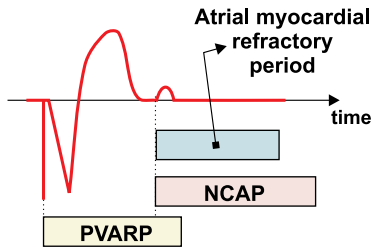
RATE-ADAPTIVE PVARP

- At low rates, the PVARP is longer. A long PVARP enhances protection against sensing of retrograde P waves and induction of endless loop tachycardia.
- At high sensor-indicated rates, PVARP shortening (in conjunction with a shorter rate adaptive sAVI) shortens the TARP thus providing for a higher 2:1 block rate and tracking faster atrial rates on a 1:1 basis than otherwise possible

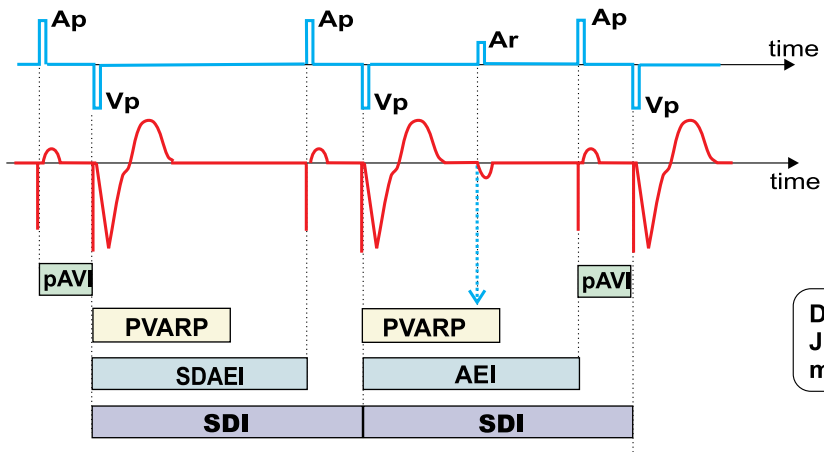


Abbreviations : AVI = programmed AV delay; PVARP = postventricular atrial refractory period; SDI = sensor-driven interval; LRI = lower rate interval; TARP = total atrial refractory period

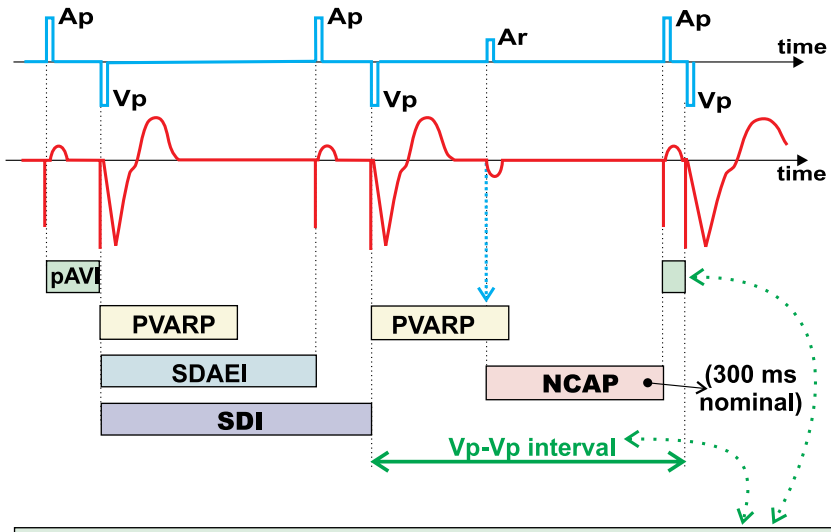
NON-COMPETITIVE ATRIAL PACING (NCAP)



The NCAP interval is a period of time when the pacemaker is prevented from delivering an atrial stimulus. This function was designed to prevent the induction of atrial tachyarrhythmias by an atrial pacing stimulus falling into the atrial relative refractory period and the vulnerable period of the atrium.



WITHOUT NCAP

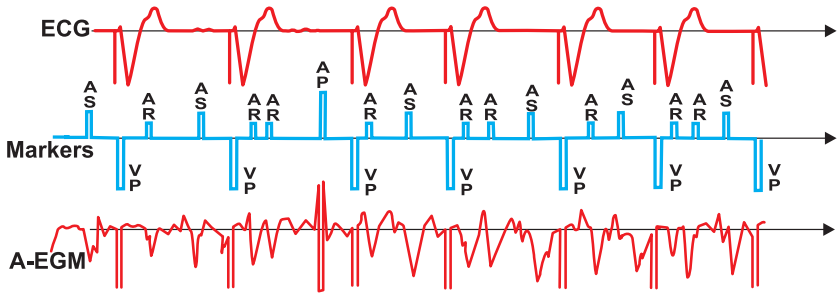


WITH NCAP

The pacemaker tries to maintain the sensor-driven ventricular cycle at the expense of the AV delay which may shorten for this adaption

A. F. Sinnaeve

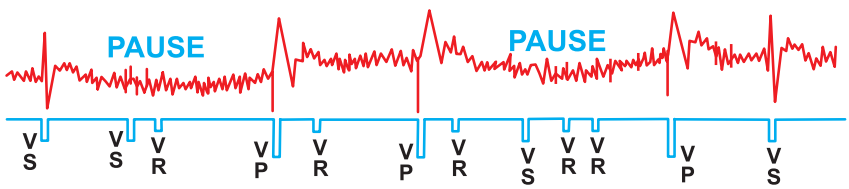
Abbreviations : Ap = atrial paced event; Ar = atrial refractory sensed event; Vp = ventricular paced event; pAVI = paced atrioventricular interval; PVARP = postventricular atrial refractory period; SDAEI = sensor driven atrial escape interval; SDI = sensor driven interval; NCAP = non-competitive atrial pacing period.



PACEMAKER TACHYCARDIAS - PART 1

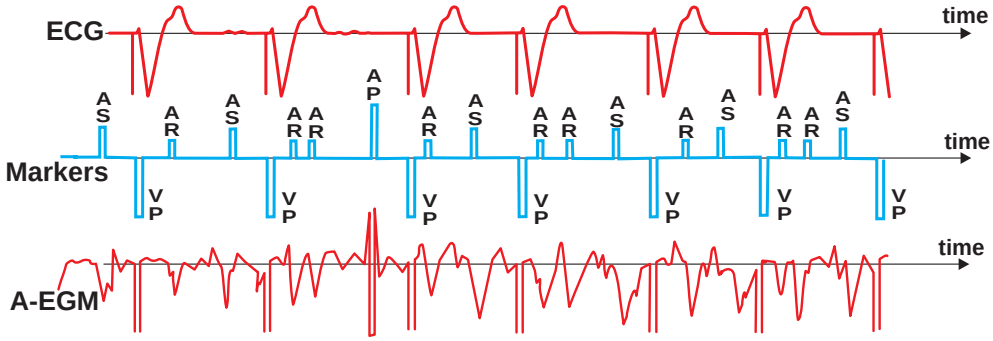
* Atrial fibrillation - part 1
* Atrial fibrillation - part 2
* Myopotential oversensing - part 1
* Myopotential oversensing - part 2
* Maneuvers to demonstrate myopotentials

A. F. Sinnaeve



DDD PACEMAKERS AND ATRIAL FIBRILLATION - Part 1

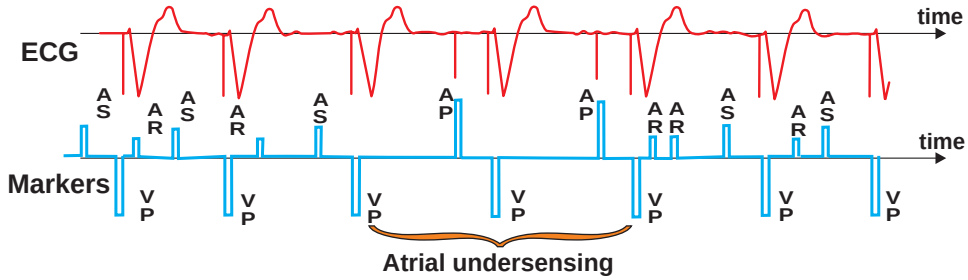
1 A FIB may provoke a fast ventricular response (regular or irregular)



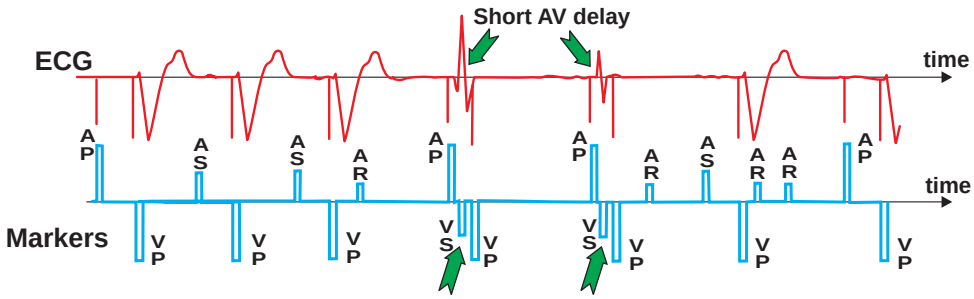
CAUTION
ELIMINATE DOUBT...LOCK IT OUT

A fast and irregular pacemaker tachycardia is almost always due to atrial fibrillation !!!

2 Intermittent sensing of f waves ; mixed response



3 Ventricular safety pacing when f waves are unsensed (VSP occurs with a spontaneous QRS complex or an EMI signal that comes after AP but before the expected VP)



Abbreviations : AS = sensed atrial event; AR = atrial sense in refractory period; AP = atrial pace; VP = ventricular pace; VS = ventricular sense; SDI = sensor-driven interval; A FIB = atrial fibrillation; AMS = automatic mode switching; PAVB = postatrial ventricular blanking; VSP = ventricular safety pacing; EMI = electromagnetic interference

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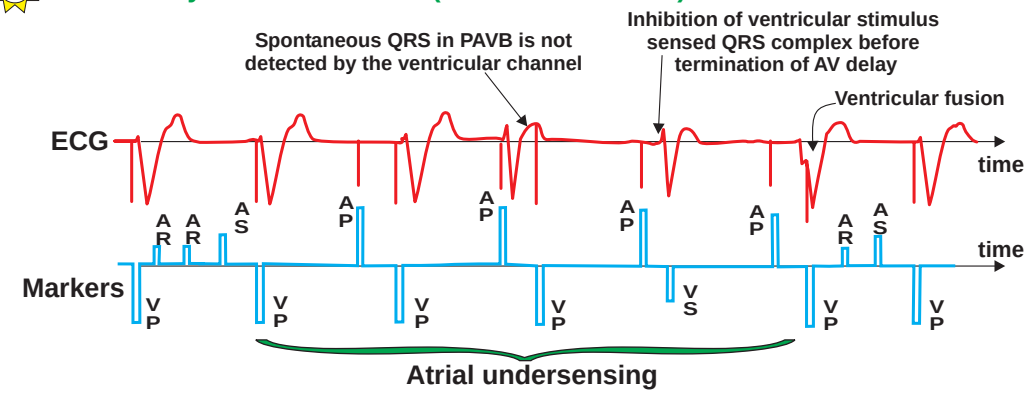
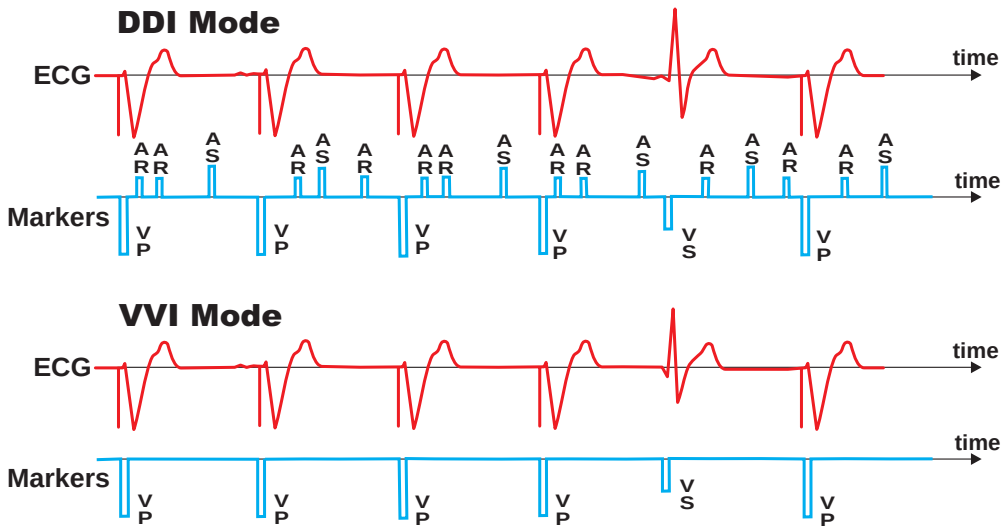
DDD PACEMAKERS AND ATRIAL FIBRILLATION - Part 2

4 A FIB may create confusion (VSP switched OFF)



5 A FIB and Automatic Mode Switching (AMS)

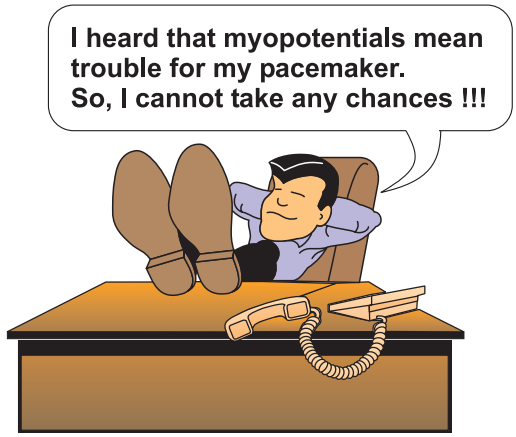


* **AMS protects the patient from tracking rapid atrial rates by switching to a non-atrial tracking mode**
* **According to programmability, AMS can switch from DDD or DDD(R) to VVI, VVI(R), DDI or DDI(R)**
* **The DDI mode is functionally identical to the VVI mode**

Abbreviations : AS = sensed atrial event; AR = atrial sense in refractory period; AP = atrial pace; VP = ventricular pace; VS = ventricular sense; SDI = sensor-driven interval; A FIB = atrial fibrillation; AMS = automatic mode switching; PAVB = postatrial ventricular blanking; VSP = ventricular safety pacing

A. F. Sinnaeve

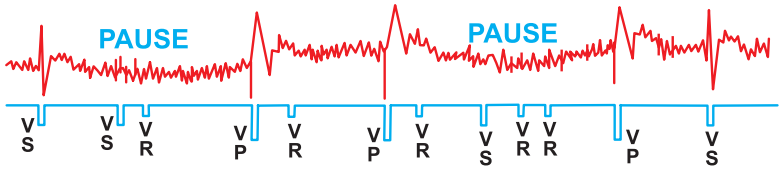
MYOPOTENTIAL SENSING DURING UNIPOLAR DDD PACING - Part 1



Baseline interference of the surface ECG is characteristic of myopotential oversensing

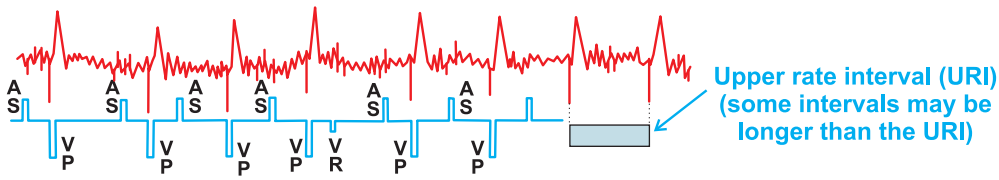
1 INHIBITION OF THE VENTRICULAR CHANNEL

(VVI Mode)

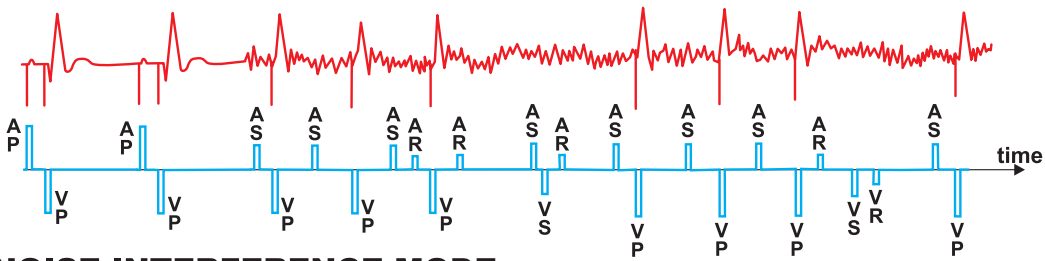


2 TRIGGERING OF RAPID VENTRICULAR RATES

Sensing by the atrial channel with resultant triggering of ventricular pacing and increase in the paced ventricular rate : tachycardia which can cause symptoms of uncomfortable palpitations, angina, dyspnea, etc.

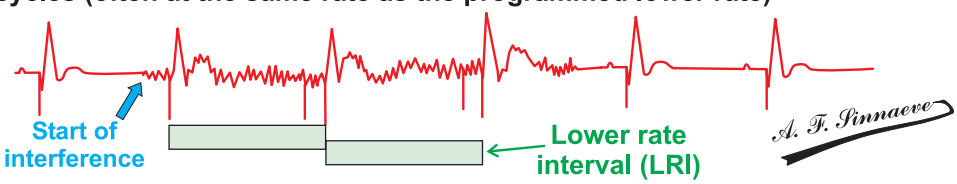


3 MIXED RESPONSE WITH INHIBITION & TRIGGERING



4 NOISE INTERFERENCE MODE

Reversion to the asynchronous noise interference mode is possible for 1 or more cycles (often at the same rate as the programmed lower rate)

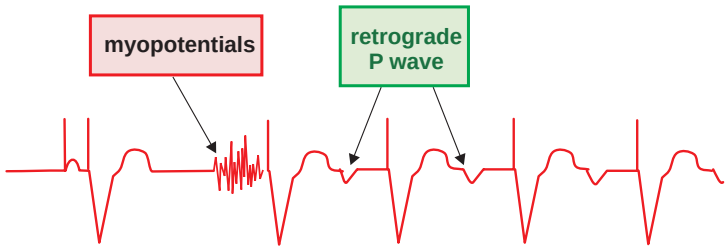


Abbreviations : AP = atrial pace; AS = atrial sense; AR = atrial sense in refractory period; VP = ventricular pace; VS = ventricular sense; VR = ventricular sense in refractory period; URI = upper rate interval

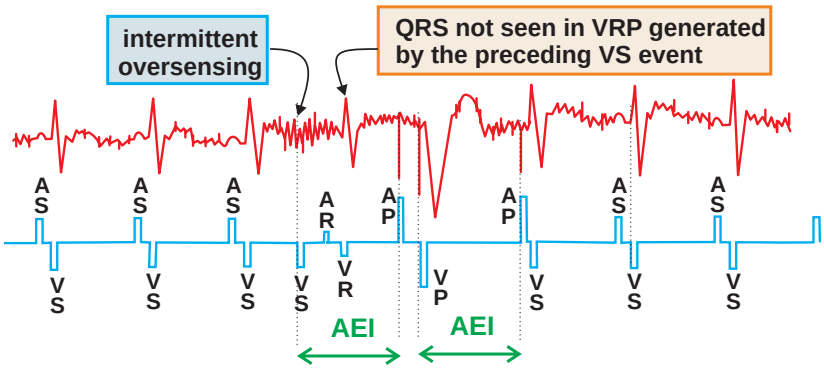
MYOPOTENTIAL SENSING DURING DDD PACING
Part 2

5 PRECIPITATION OF ELT

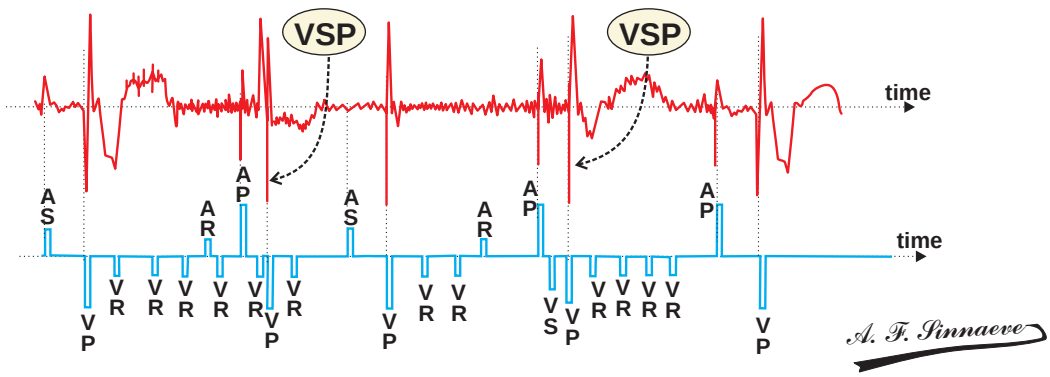
Myopotential sensing by the atrial channel can precipitate an endless loop tachycardia



6 UNDERSENSING SECONDARY TO OVERSENSING



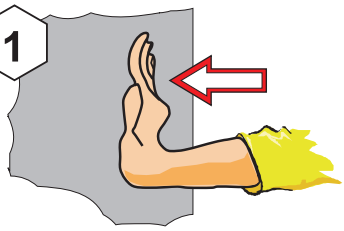
7 MIXED RESPONSE WITH VENTRICULAR SAFETY PACING



Abbreviations : AP = atrial pace; AS = atrial sense; AR = atrial sense in refractory period; VP = ventricular pace; VS = ventricular sense; VR = ventricular sense in refractory period; URI = upper rate interval; VSP = ventricular safety pacing; AEI = atrial escape interval; VRP = ventricular refractory period; ELT = endless loop tachycardia

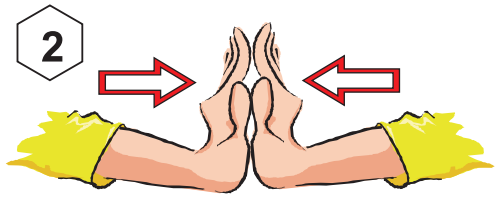
COMMONLY USED MANEUVERS TO DEMONSTRATE MYOPOTENTIALS

1



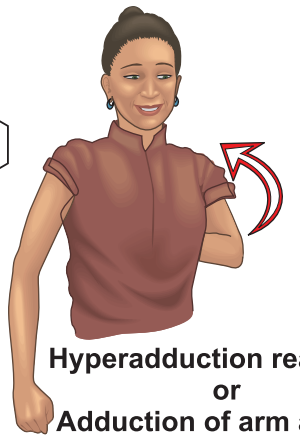
Pressing against a wall

2



Pressing hands against each other

3

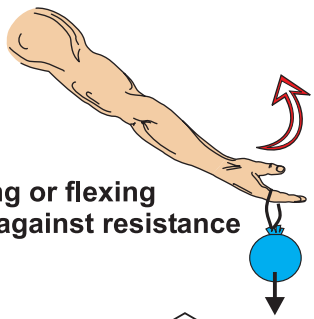


Hyperadduction reach test
or
Adduction of arm against resistance

4

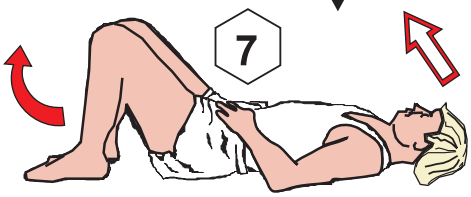
Cup the hand over the shoulder and exert firm and sustained downward pressure

5



Lifting or flexing arm against resistance

7



Trunk lifting or
Lifting & holding legs

6

Treadmill stress test

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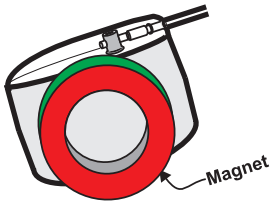
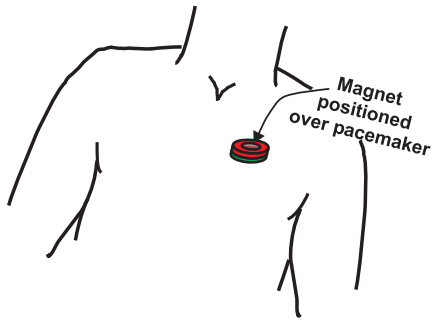
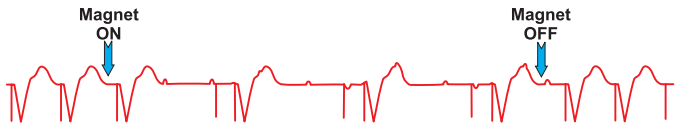
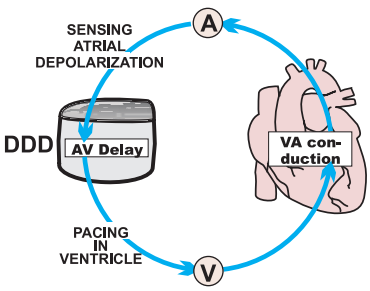


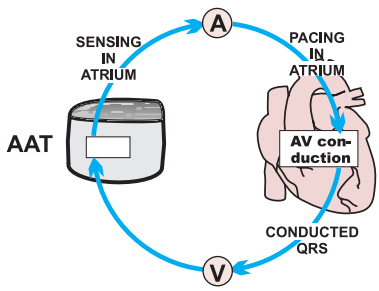




PACEMAKER TACHYCARDIAS - PART 2

* Differential diagnosis of tachycardia - part 1
* Differential diagnosis of tachycardia - part 2
* Orthodromic tachycardia



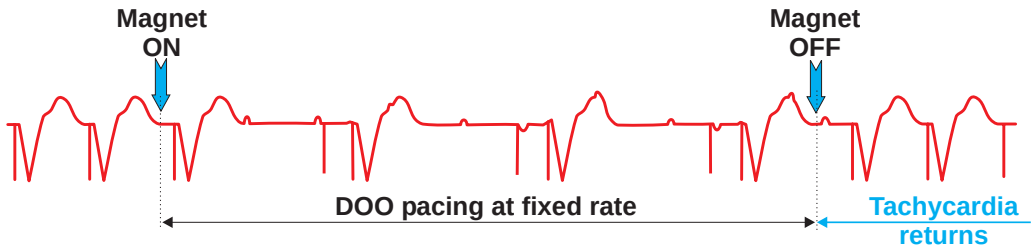


A. F. Sinnaeve

DIFFERENTIAL DIAGNOSIS OF TACHYCARDIA DURING DDD(R) PACING part 1

1 SINUS TACHYCARDIA

* Application of the magnet (slower DOO mode) may reveal P waves. The tachycardia returns upon withdrawal of the magnet.



* Atrial electrogram and markers will also reveal a regular atrial rate
* Pacemaker Wenckebach upper rate response suggests a regular rate faster than the programmed upper rate. In this case it could also be an atrial tachycardia ! A Wenckebach upper rate response effectively rules out endless loop tachycardia.

2 ATRIAL FLUTTER & FIBRILLATION

* The paced ventricular rate is fast and may be regular or irregular
* Diagnosis is suggested when the ventricular pacing rate is fast and irregular and may be confirmed by recording the telemetered atrial electrogram

3 MYOPOTENTIAL TRIGGERING

* A pacemaker tachycardia can be triggered by myopotentials sensed by the atrial channel of pacemakers with unipolar sensing
* The tachycardia may be regular or irregular, with pacing cycles often at the upper rate interval. The tachycardia is mostly short-lived and pacing quickly returns to baseline
* Diagnosis : the tachycardia is reproducible by standard maneuvers to bring out myopotentials. A decrease in atrial sensitivity followed by a repeat of the maneuvers often shows elimination of the tachycardia.

A. F. Sinnaeve

Abbreviations : EMI = electromagnetic interference; DOO = asynchronous dual chamber pacemaker

DIFFERENTIAL DIAGNOSIS OF TACHYCARDIA DURING DDD(R) PACING - part 2

4 ENDLESS LOOP TACHYCARDIA

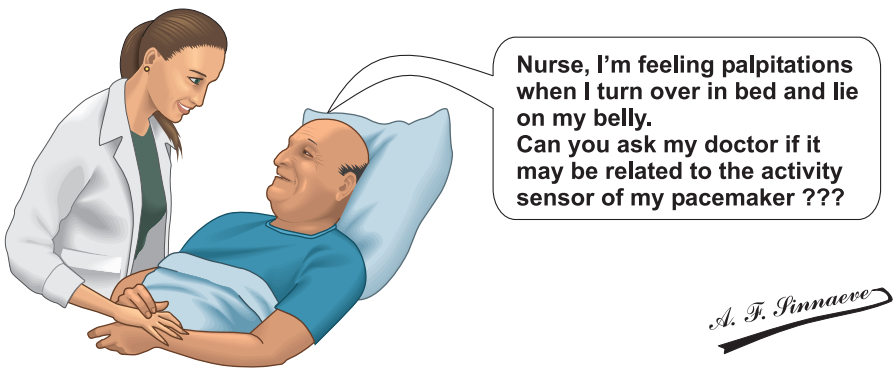
* The telemetered markers show a constant VA (Vs-As) interval
* Disappears upon application of the magnet and with programming a longer PVARP
* There are two types : near-field and far-field (rare)

5 ORTHODROMIC PACEMAKER TACHYCARDIA

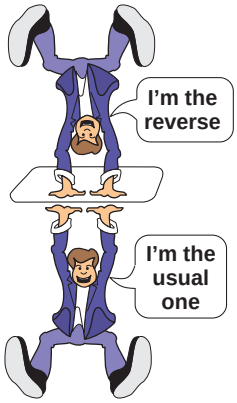
* The opposite of ELT in that there is atrial pacing associated with conducted QRS complexes (rare)

6 SENSOR RELATED TACHYCARDIAS

* Inappropriate overprogramming of the sensor response with exessive response to effort
* Minute ventilation sensor in patients with CHF and in patients undergoing electro-cautery during a surgical intervention
* ECG monitors, etc. using the same high frequency low amplitude signals as the minute ventilation sensor of the pacemaker, may cause pacing at upper rate
* Excessive shivering or post-epileptic state of patients with activity sensors
* Firm pressure over an activity-driven pacemaker



Abbreviations : ELT = endless-loop tachycardia; CHF = congestive heart faillure; DOO = asynchrone dual chamber pacemaker.



ORTHODROMIC MACRO-REENTRANT PACEMAKER TACHYCARDIA

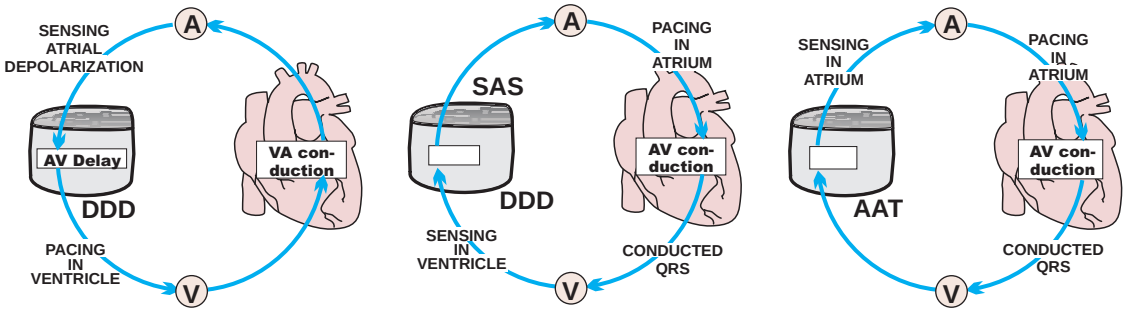
Orthodromic pacemaker tachycardia has been called "reverse endless loop tachycardia". There is anterograde conduction across the AV junction and the QRS is conducted and not paced. This is the opposite of ELT where there is ventricular pacing. The return pathway is via the pacemaker by producing atrial pacing in contrast to ELT where there is atrial sensing !

Endless loop tachycardia or ELT

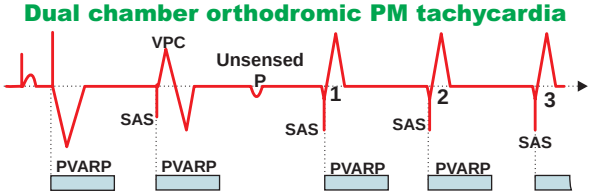
Orthodromic macro-reentrant pacemaker tachycardia

Near-field dual chamber

Far-field single chamber

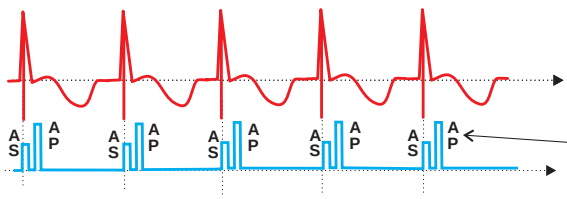


Dual chamber orthodromic PM tachycardia



Mechanism of orthodromic pacemaker tachycardia during DDD pacing with synchronous atrial stimulation (SAS) algorithm to prevent ELT. SAS delivers an atrial stimulus on detection of a VPC. In this way, retrograde VA conduction engendered by a VPC cannot cause atrial depolarization because it is pre-empted by SAS that renders the atrium refractory. A VPC is sensed by the ventricular electrode, thereby triggering SAS. This is followed by an unsensed P wave outside the PVARP. The unsensed P wave is conducted and gives rise to the first conducted QRS complex that is sensed beyond the ventricular refractory period of the PM. The pulse generator interprets this conducted QRS complex as a VPC and delivers SAS. This again leads to a conducted QRS complex (2) with a very long PR interval. The second QRS complex causes SAS 2, and SAS 2 causes QRS 3, etc...

AAT single chamber orthodromic PM tachycardia



Far-field sensing of the R wave triggers an atrial stimulus which captures the atrium. The P wave is conducted to the ventricle. The conducted QRS is again sensed by the atrial lead as a far-field signal and the process perpetuates itself.

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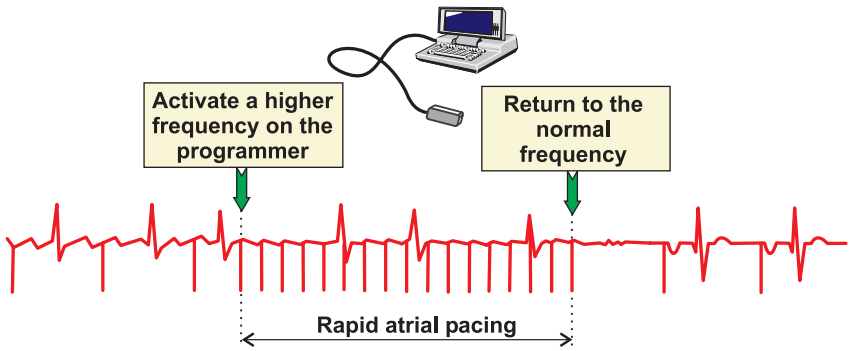
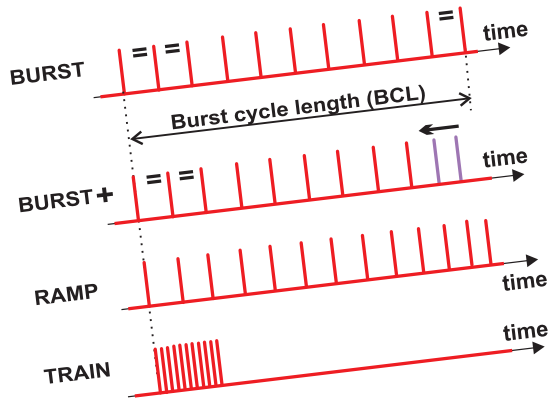
Abbreviations : AAT = an atrial stimulus is promptly delivered upon sensing in the atrium; ELT = endless-loop tachycardia; SAS = synchronous atrial stimulation; PVARP = postventricular atrial refractory period; VPC = ventricular premature coplex; AS = atrial sensed event; AP = atrial pacing; PM = pacemaker



TREATMENT OF TACHYCARDIA

* Antitachycardia pacing (ATP) - part 1
* Antitachycardia pacing (ATP) - part 2
* Prevention of atrial fibrillation



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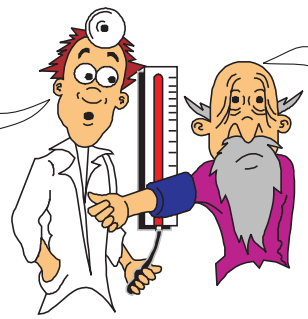
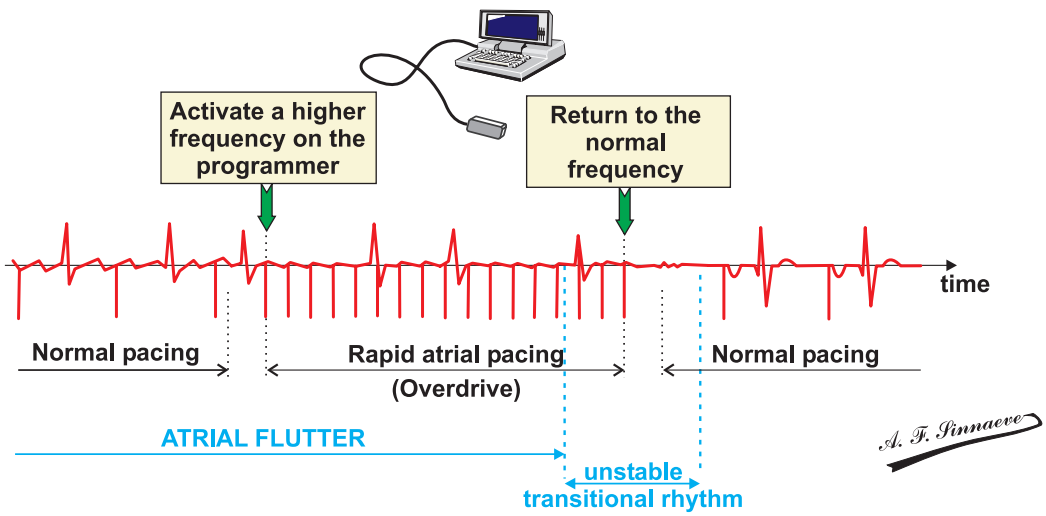
TREATMENT OF TACHYCARDIA WITH PACING PART 1

Manual procedure with the programmer : Overdrive pacing

Overdrive pacing at a fast rate is easy to perform.
Put the head of the programmer over the pacemaker and temporarily program a pacing rate faster than the heart rate. Upon termination of the tachycardia, return to the normal pacing rate.



I don't trust those machines !
My physician has to do it himself !!!



CAUTION

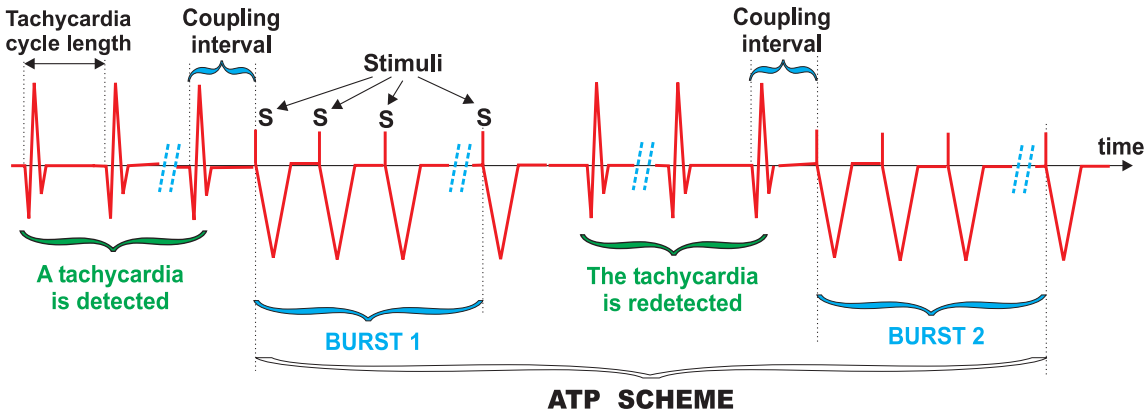
The procedure requires a standby defibrillator in the rare case of a complication

Rapid overdrive pacing is important for the treatment of reentrant supraventricular tachyarhythmias such as atrial flutter and other organized atrial tachycardias. It is ineffectual for atrial fibrillation.

TREATMENT OF TACHYCARDIA WITH PACING PART 2

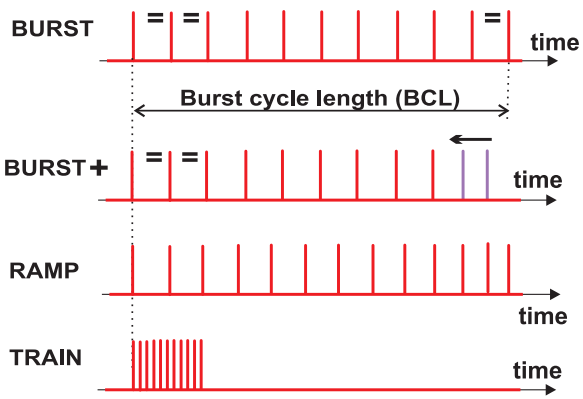
Automatic : Antitachycardia Pacing (ATP)

This function is available in pacemakers for atrial pacing in the treatment of supraventricular tachyarrhythmias. Only defibrillators (ICDs) can deliver rapid ventricular pacing for ventricular tachycardia because the procedure may occasionally accelerate the tachycardia or precipitate ventricular fibrillation, arrhythmias that require immediate defibrillation !!!



ATP SCHEME

Some basic stimulation patterns



All pacing intervals within the burst are the same

A burst followed by 2 stimuli with a decremental coupling interval

The pacing intervals within the burst are continuously decreased (or increased in some pacemakers)

A high frequency burst pacing at 50Hz (3000bpm) during 0.5 - 3 seconds

WHAT CAN BE PROGRAMMED ?

* The number of bursts delivered
* The number of pulses within each burst
* The coupling interval as a % of the tachycardia cycle length
* The burst cycle length
* A minimum pacing interval

Many combinations are possible and different terminology is used by different manufacturers !

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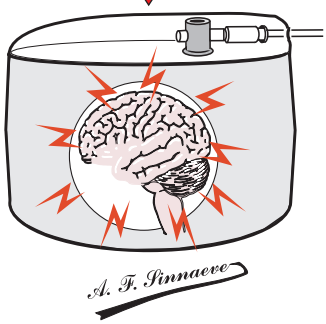
THE PREVENTION OF ATRIAL FIBRILLATION

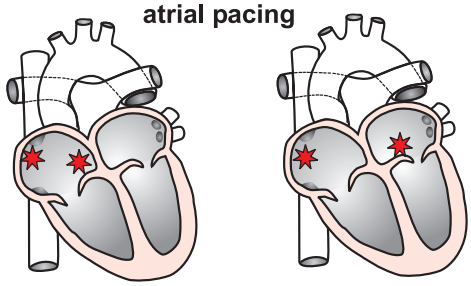
- **Continuous overdrive of sinus rate at a dynamic rate**. This ensures atrial pacing without an excessive increase in the rate.
- **Prevention of post-extrasystolic pauses**. This prevents short-long sequences.
- **Overdrive pacing at an increased rate after atrial premature beats**.
- **Overdrive pacing at an increased rate after the termination of atrial fibrillation**. This attempts to reduce the immediate reinitiation of the arrhythmia which is a common clinical problem.

Special algorithms

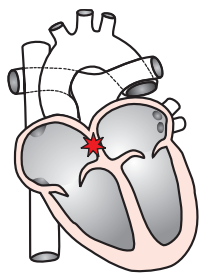


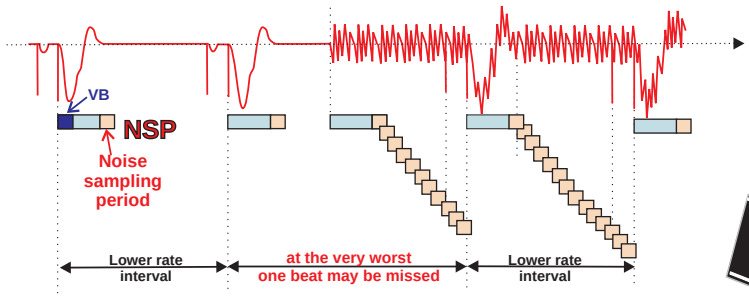
Alternative sites of stimulation

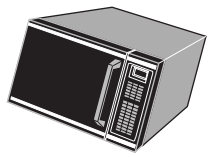
Dual site atrial pacing



Atrial septal pacing

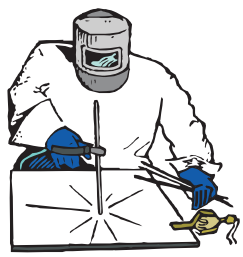


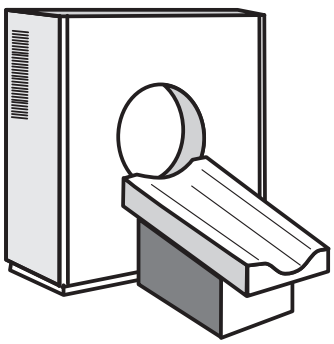




PACEMAKER INTERFERENCE

* Timing cycles - Noise sampling period
* General surgery
* External cardioversion & defibrillation
* Electromagnetic Interference (EMI) inside the hospital
* EMI outside the hospital
* Pacemaker reset





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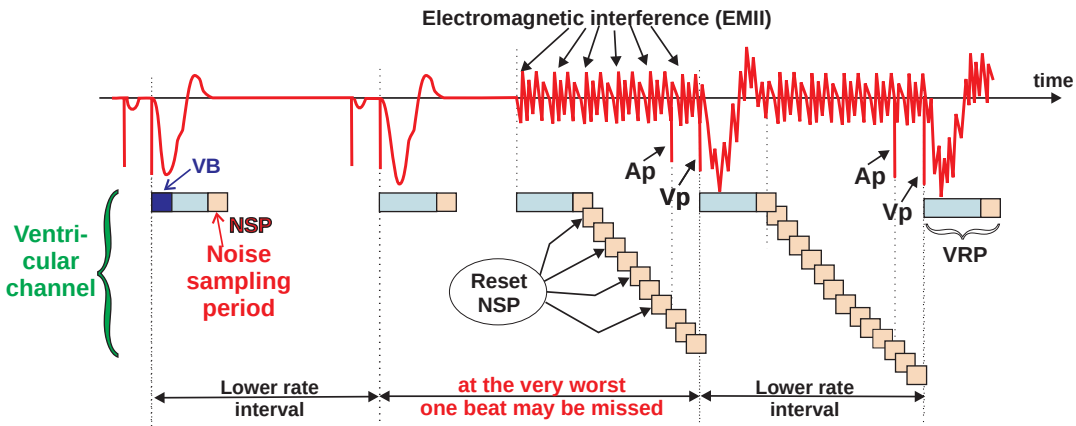
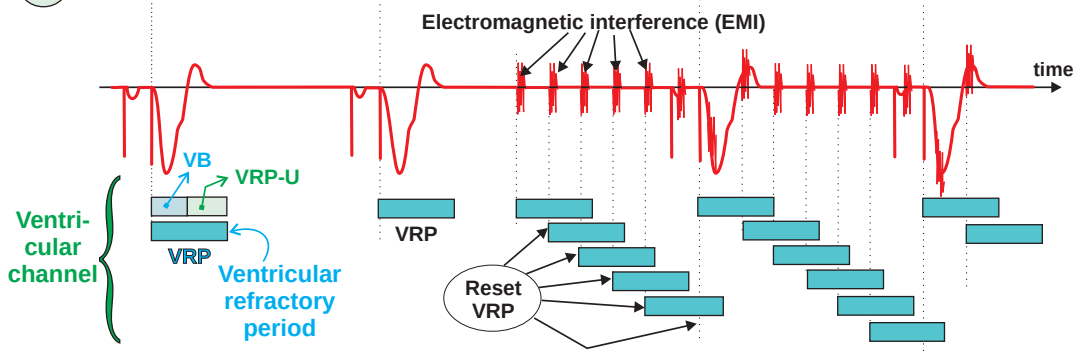
ELECTROMAGNETIC INTERFERENCE & NOISE SAMPLING

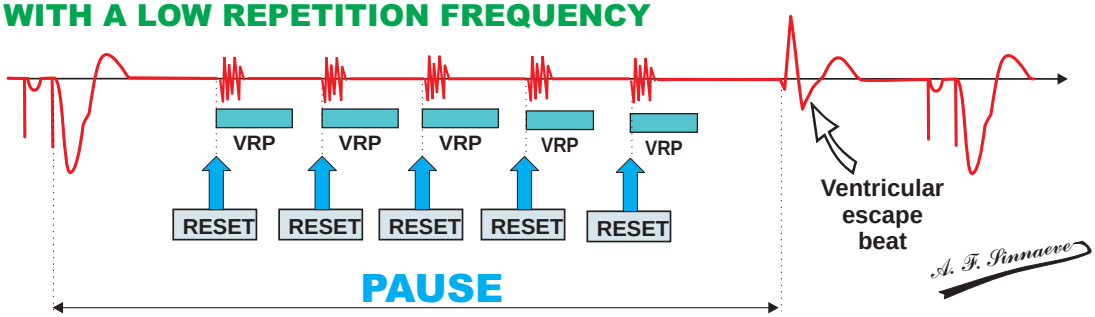
1 RE-INITIATION OF THE NOISE SAMPLING PERIOD



2 RE-INITIATION OF THE TOTAL REFRACTORY PERIOD



NOTE :
THE HAZARD OF PULSED ELECTROMAGNETIC INTERFERENCE WITH A LOW REPETITION FREQUENCY



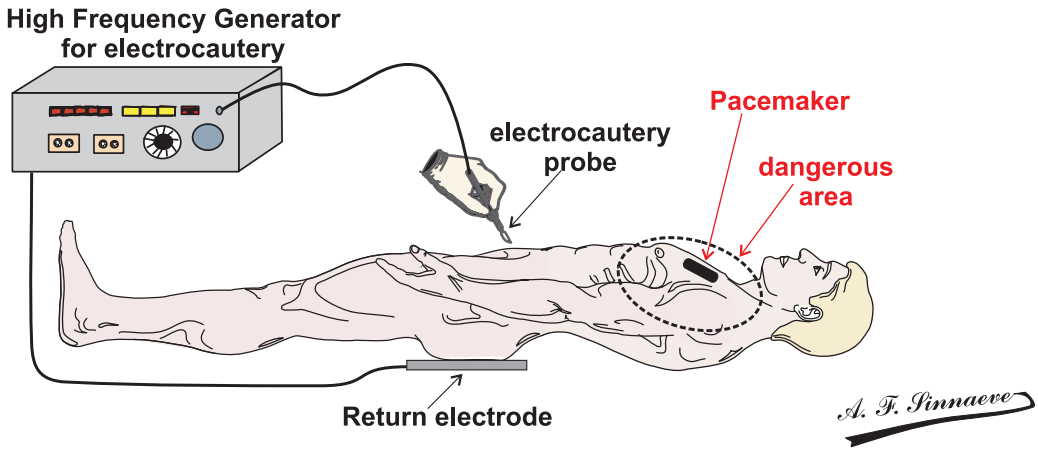
Abbreviations : VB = ventricular blanking period; VRP = ventricular refractory period; VRP-U= unblanked part of VRP; NSP = noise sampling period ; EMI = electromagnetic interference

We have to take some extra precautions.
The guy has a pacemaker !
And don't cut in the insulation of the lead!!!

THE PACEMAKER PATIENT AND GENERAL SURGERY

PRECAUTIONS :

* Avoid electrocautery if possible
* Electrocautery is not to be used within a few inches of the pacemaker and the pacemaker lead !!!
* The return electrode has to be positioned under the buttock away from the pacemaker
* Program the pacemaker to DOO or VOO mode or apply a magnet over the pacemaker
* The pacemaker should be carefully tested after the surgery !!!



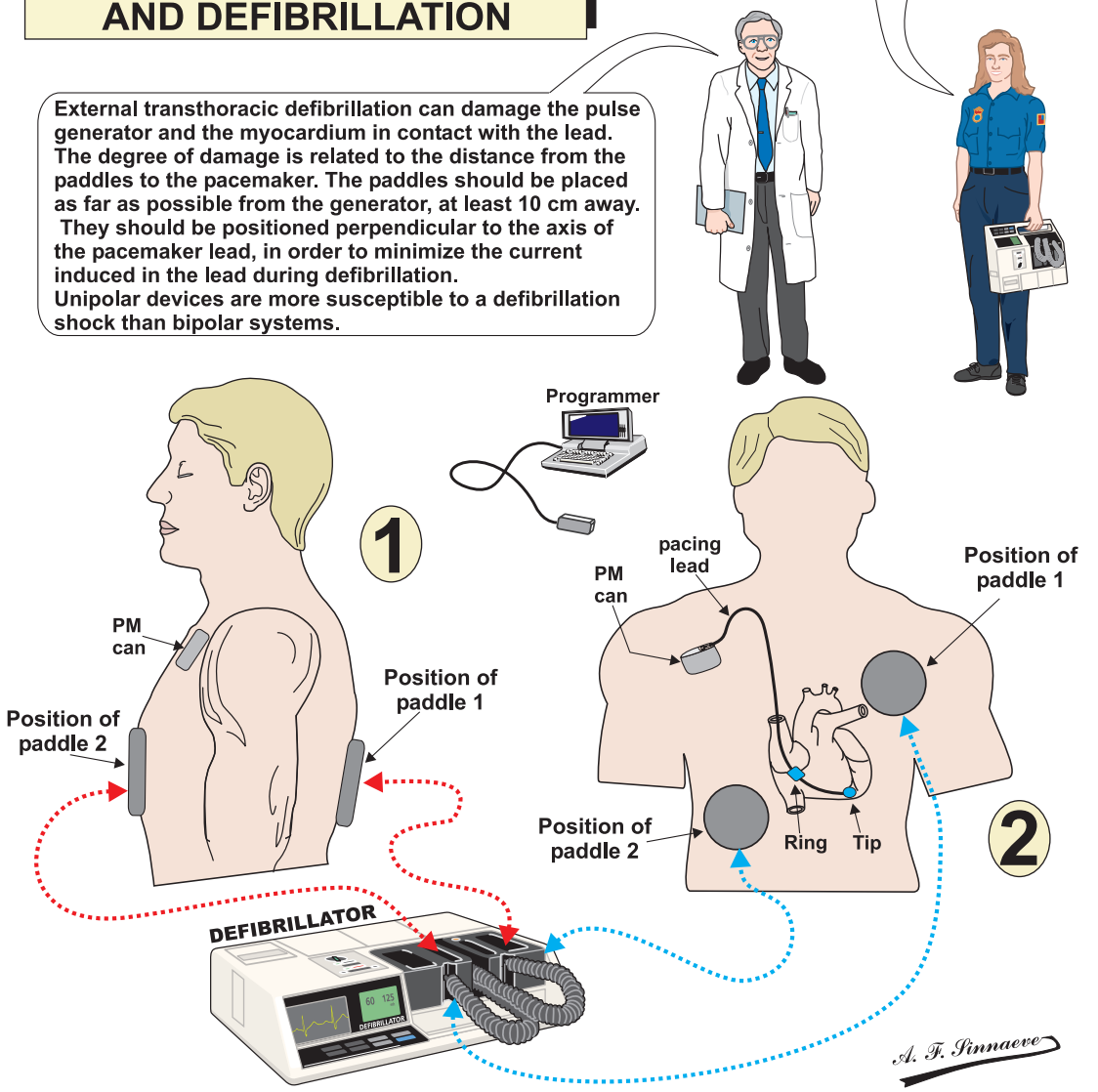
POSSIBLE CONSEQUENCES OF ELECTROCAUTERY IN THE VICINITY OF THE PACEMAKER OR THE LEAD :

* inhibition of the pacemaker
* resetting or reprogramming of the pacemaker
* damage of the pacemaker electronics (eventually causing pacemaker runaway)
* upper rate pacing (especially in rate-adaptive pacemakers based upon impedance measurement such as the minute ventilation sensing)
* current induced in the lead may cause internal burns and scarring, creating a higher pacing threshold or even exit block

EXTERNAL CARDIOVERSION AND DEFIBRILLATION

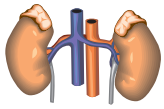
Doctor, how should I position the paddles if my patient has a pacemaker ?

External transthoracic defibrillation can damage the pulse generator and the myocardium in contact with the lead. The degree of damage is related to the distance from the paddles to the pacemaker. The paddles should be placed as far as possible from the generator, at least 10 cm away. They should be positioned perpendicular to the axis of the pacemaker lead, in order to minimize the current induced in the lead during defibrillation.
Unipolar devices are more susceptible to a defibrillation shock than bipolar systems.

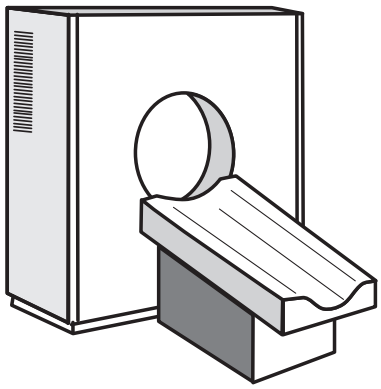


* IMPORTANT : After defibrillation, the device should be interrogated and the programmed parameters compared with those before defibrillation-cardioversion.
* Although all pacemakers have a defibrillation protection circuit, it can be overwhelmed by the extremely high energy of a defibrillation shock. Therefore, it is wise to have a transcutaneous pacemaker nearby.
* A transient rise in threshold can be treated by increasing the output (voltage and pulse duration) of the pacemaker. A prolonged severe increase in ventricular threshold is rare. Transient undersensing is not a serious problem.
* The defibrillation shock can also erase the programmed settings in the memory of the pulse generator. Contemporary devices have a built in protection called “Power On Reset” which automatically reprograms the pacemaker to a safe set of values (normally in VVI mode). The pacemaker is not damaged and can be reprogrammed from the reset mode to its usual parameters.

ELECTROMAGNETIC INTERFERENCE (EMI) INSIDE THE HOSPITAL



MRI
SCANNER
LITHOTRIPSY
RADIOTHERAPY



Extracorporeal Shock Wave Lithotripsy (ESWL) can produce VPCs and it is synchronized to the R wave. The PM should be programmed to VVI, VOO or DOO. The piezoelectric crystal of activity-driven PMs can be shattered if the PM is placed in the focal point of ESWL. Therefore avoid ESWL with abdominal PMs.

Magnetic Resonance Imaging (MRI) is normally catastrophic for pacemakers and deadly for PM-dependent patients. A pacemaker is still considered as a contraindication for MRI.

Radiotherapy can result in inhibition, tracking and noise reversion when the machine is switched on or off. The ionizing radiation may cause permanent damage to the electronic circuitry of the generator (CMOS structures). Minimize the total dose upon the PM ; maximize shielding and distance of the PM to the radiation beam. Check device function after each therapy session and regularly for several weeks thereafter. Any PM dysfunction after the acute phase may be due to a potentially serious component failure and requires device replacement.

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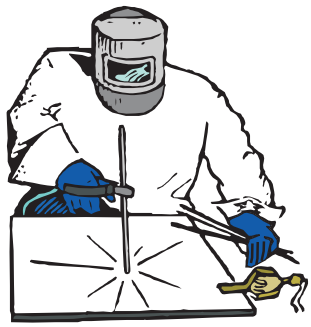
ELECTROMAGNETIC INTERFERENCE (EMI) OUTSIDE THE HOSPITAL

If a PM-dependent patient works in an industrial environment with strong EMI, on-site evaluation may be required. The device manufacturer should be contacted. Holter recordings and pacemaker diagnostics may suffice in non-pacemaker-dependent patients

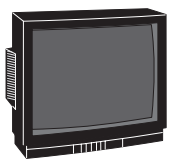


ELECTRIC ARC WELDING

Most common EMI situations are essentially benign for pacemakers !

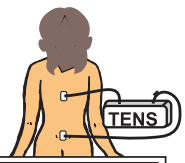
Cellular phones :
The highest risk of interference is when the phone is placed directly over the PM. Minimal interference occurs at the ear position and most interference is eliminated if the phone is kept 8 to 10cm (3 to 4 inches) from the device

Metal detector gates :
Asynchronous pacing or inhibition for 1-2 beats without any ill effects

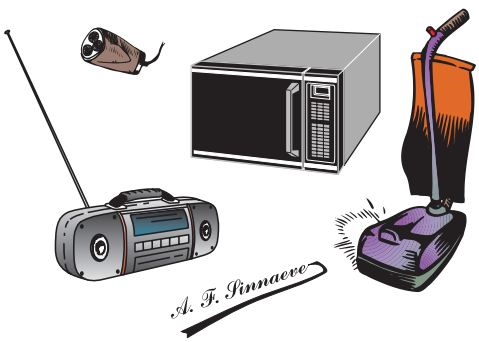


Appliances and Electronics at home (microwave oven, TV remote control, etc.) have normally no effect on contemporary pacemakers

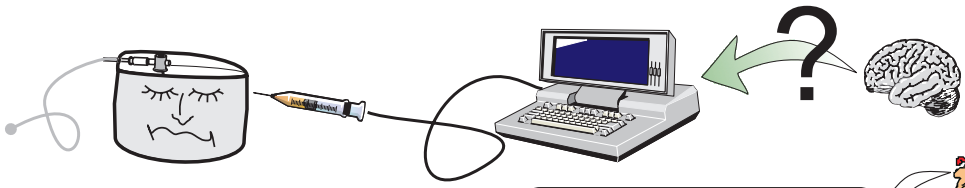
Electronic Article Surveillance (antitheft) : Asynchronous pacing and inhibition for 1-2 beats without any ill effects in most situations. Possible pacemaker reset on rare occasions.



Transcutaneous electrical nerve stimulation may inhibit the pacemaker and require reprogramming of the sensitivity



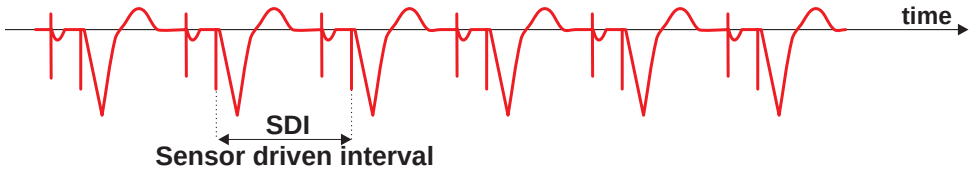
A. F. Simmaco



PACEMAKER RESET

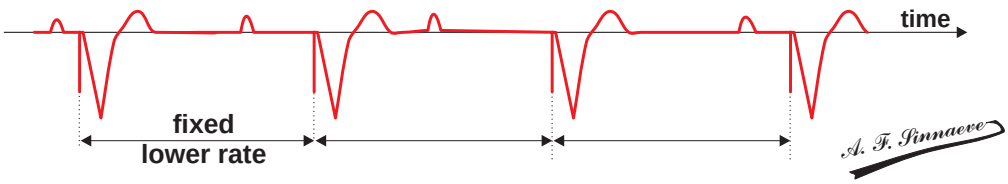
BEFORE RESET

DDDR pacing at a higher sensor driven rate (SDR) with a programmed amplitude and pulse width.



AFTER RESET

VVI pacing at a special fixed lower rate defined by the manufacturer and at nominal amplitude and pulse width.

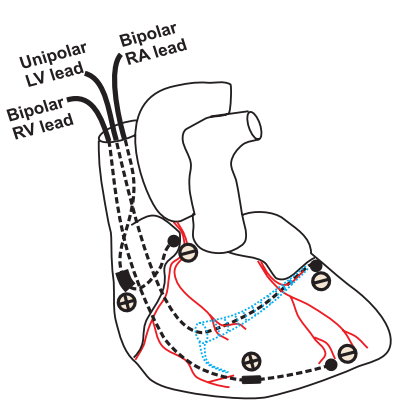


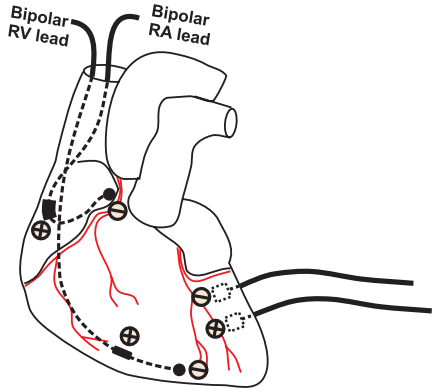
CAUTION

Reset may be poorly tolerated in patients hemodynamically dependent on AV synchrony !!!

*** Reset is reversible by programming ! No permanent damage is done to the pacemaker.**
*** Pacemaker reset may be due to therapeutic radiation, electrocautery, heavy electro-magnetic interference and defibrillation shock.**
*** High level interference may erase the pacemaker programs that are stored in RAM, but do not affect the safety programs stored in ROM.**
*** Reset must be differentiated from ERT (check the battery voltage and impedance !)**

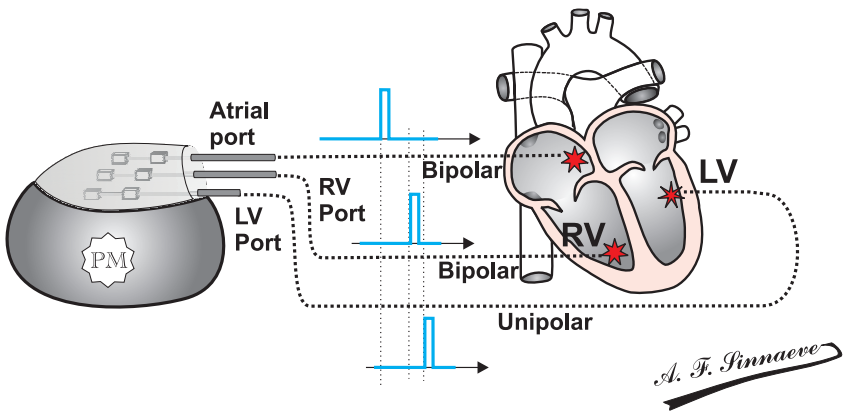
Abbreviations : ERT = elective replacement time (just before battery depletion) ; RAM = random access memory (can be changed by the programmer) ; ROM = read only memory (a fixed content that can only be read by the microprocessor inside the pacemaker)





BIVENTRICULAR PACING (BiV)

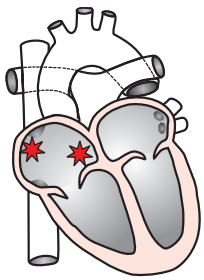
* Cardiac resynchronization - General concepts
* Leads for BiV pacing
* Types of BiV pacemakers
* Mean QRS axis in the frontal plane
* BiV pacing - ECG patterns
* ECG evaluation - Diagnosis of capture
* Pacing impedance of BiV pacing systems
* Pre-empted or aborted Wenckebach response



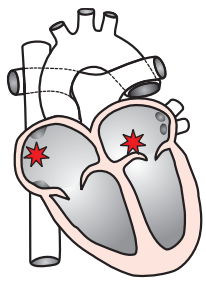
CARDIAC RESYNCHRONIZATION or MULTISITE PACING

Cardiac resynchronization refers to stimulation techniques that change the degree of atrial and ventricular electromechanical asynchrony in patients with major intra-atrial or interatrial and ventricular conduction disorders. Atrial and ventricular resynchronzation is usually accomplished by pacing from more than one site in an electrical chamber either simultaneously or one site before the other (pre-excitation).

ATRIAL RESYNCHRONIZATION

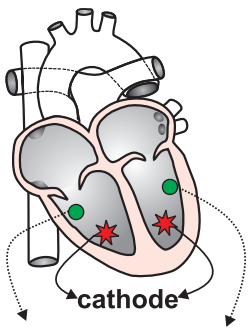


BIFOCAL ATRIAL PACING



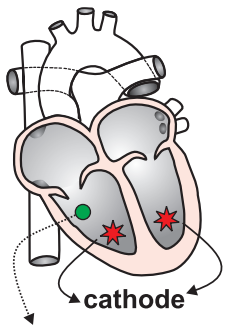
BIATRIAL PACING

VENTRICULAR RESYNCHRONIZATION or BIVENTRICULAR PACING



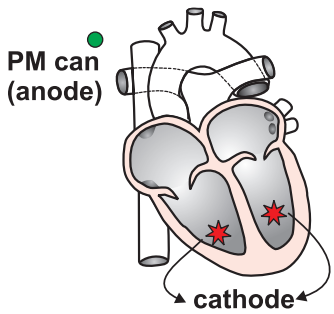
non-stimulating anode

DUAL BIPOLAR



shared or common ring
(non-stimulating anode)

BIPOLAR/UNIPOLAR



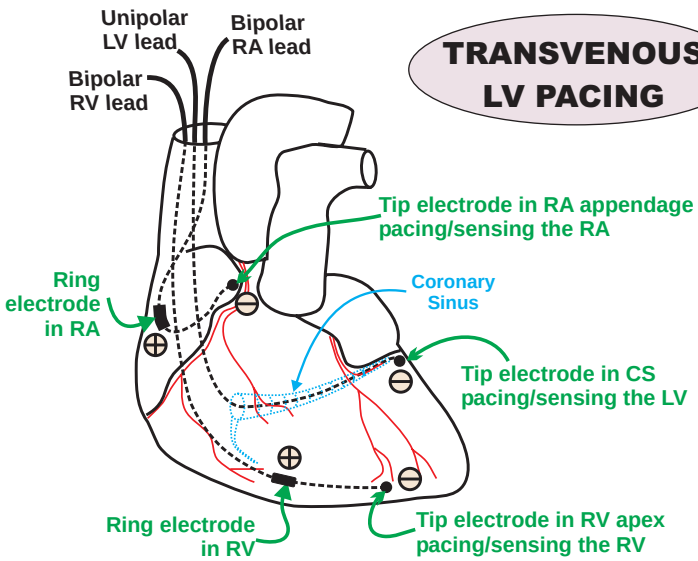
DUAL UNIPOLAR

A. F. Sinnaeve

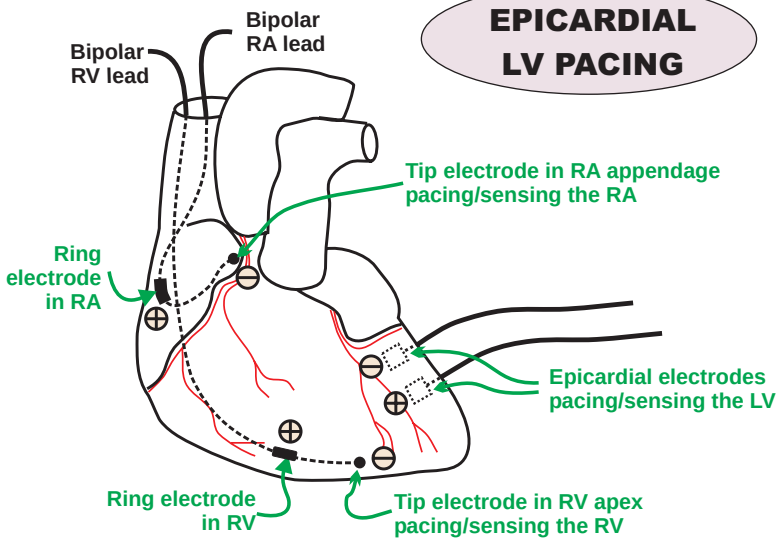
LEADS AND ELECTRODES FOR BIVENTRICULAR PACING

A 3 chamber pacemaker for congestive heart failure ! What will they think of next ?

TRANSVENOUS LV PACING



EPICARDIAL LV PACING



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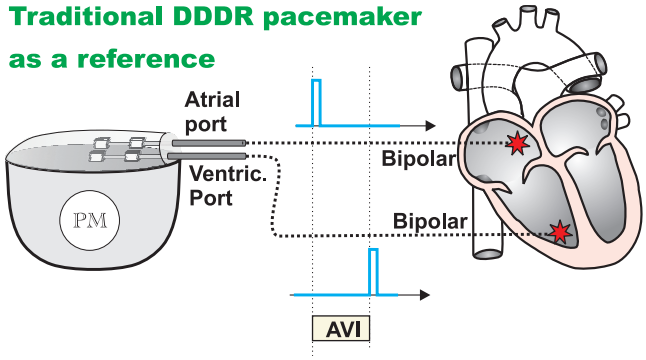
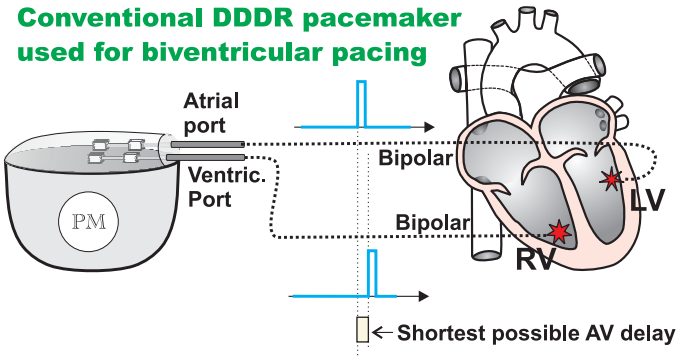
Abbreviations : CS =coronary sinus; LV = left ventricle; RA = right atrium; RV = right ventricle

BIVENTRICULAR PACING SYSTEMS

Traditional DDDR pacemaker as a reference



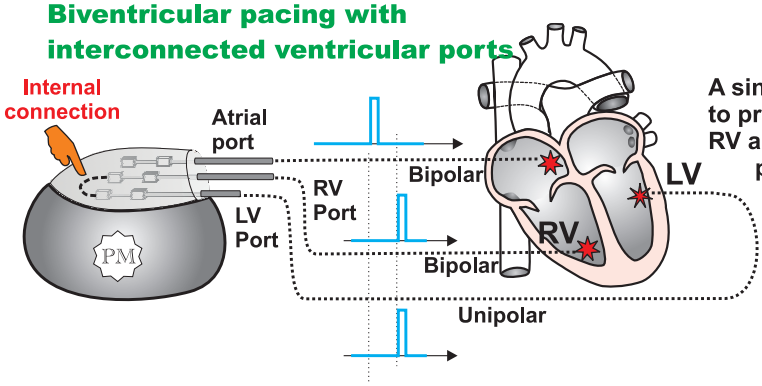
Conventional DDDR pacemaker used for biventricular pacing



This can only be used in patients with permanent atrial fibrillation.

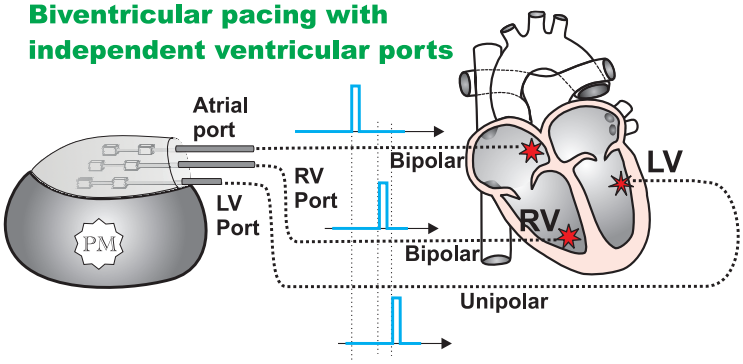
The shortest AV interval (0 - 30 ms) should be programmed.

Biventricular pacing with interconnected ventricular ports



A single ventricular output is divided to provide simultaneous pacing of RV and LV (dual cathodal system with parallel outputs). The pacemaker senses RV and LV activity simultaneously.

Biventricular pacing with independent ventricular ports



The time delay between the LV and RV stimuli may be programmed and optimized for each patient.
Each ventricle has its own sensing and output circuits.

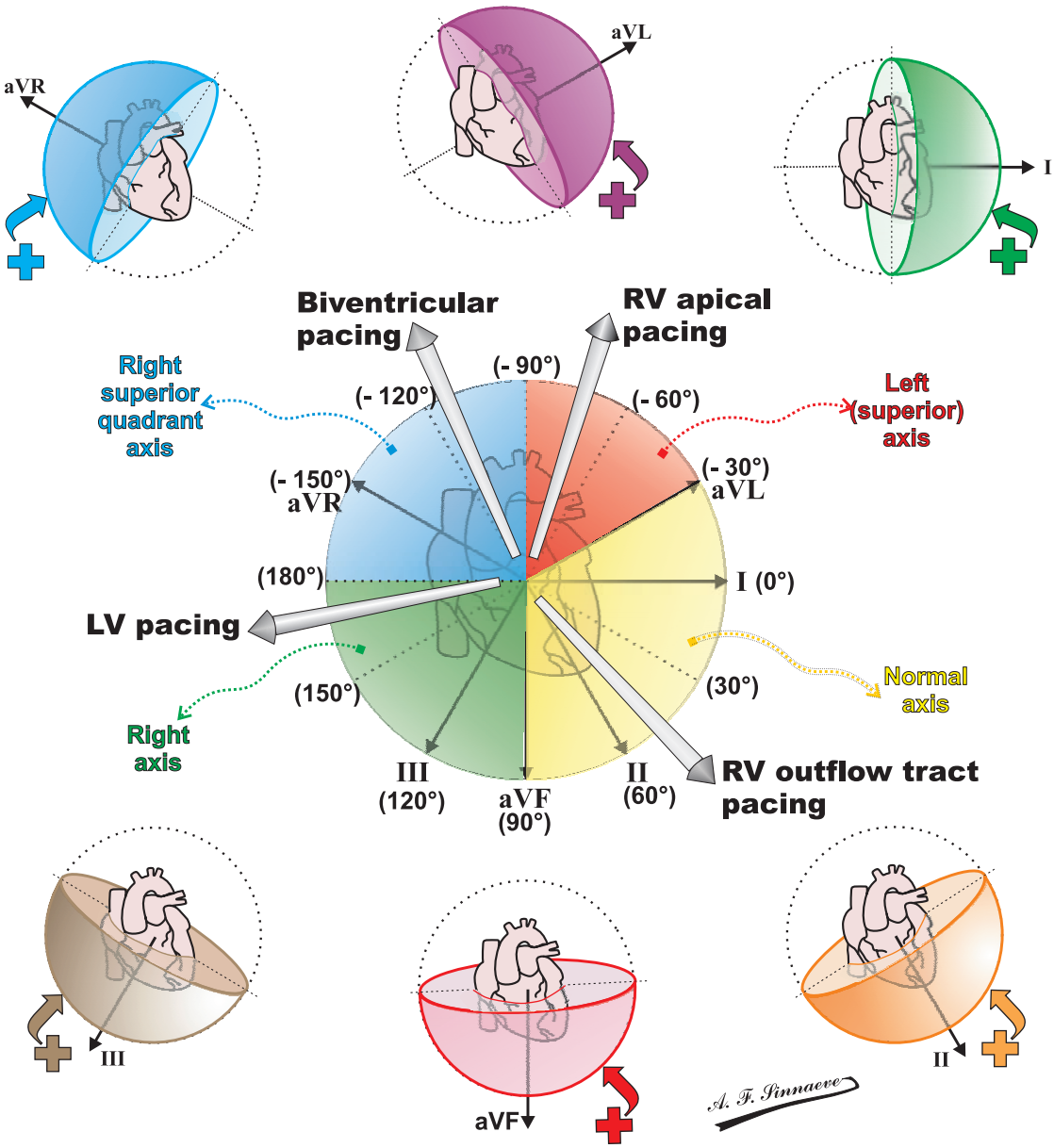
Abbreviations :
LV = left ventricle ; RV = right ventricle

THE MEAN QRS AXIS IN THE FRONTAL PLANE DURING CARDIAC PACING

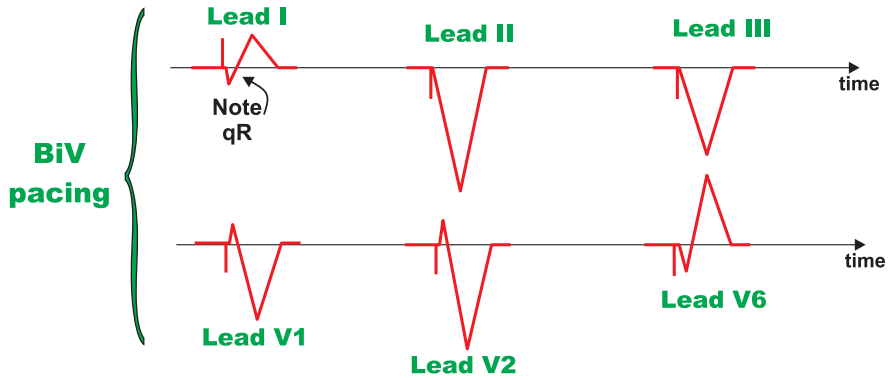
During pacing the mean frontal plane QRS axis reflects the site of the pacing :

*** for RV pacing : apex vs outflow tract**

*** for biventricular pacing : RV only, LV only or biventricular**



BIVENTRICULAR (BiV) PACING



To show ventricular capture in pacemakers with a common output, lower the voltage and/or the pulse width. The left ventricle (LV) will lose capture first in almost all cases because pacing threshold is higher than that of the right ventricle (RV).
Loss of capture in one ventricle will cause a change in the morphology of the beats in the 12-lead ECG. Examination of a single lead may be misleading.

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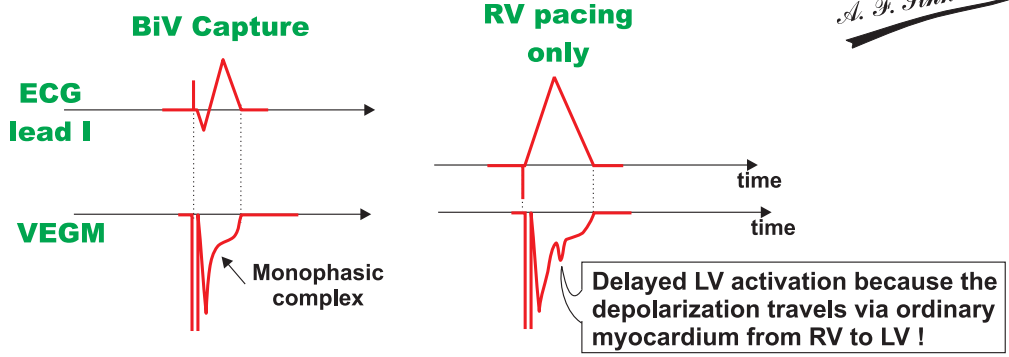
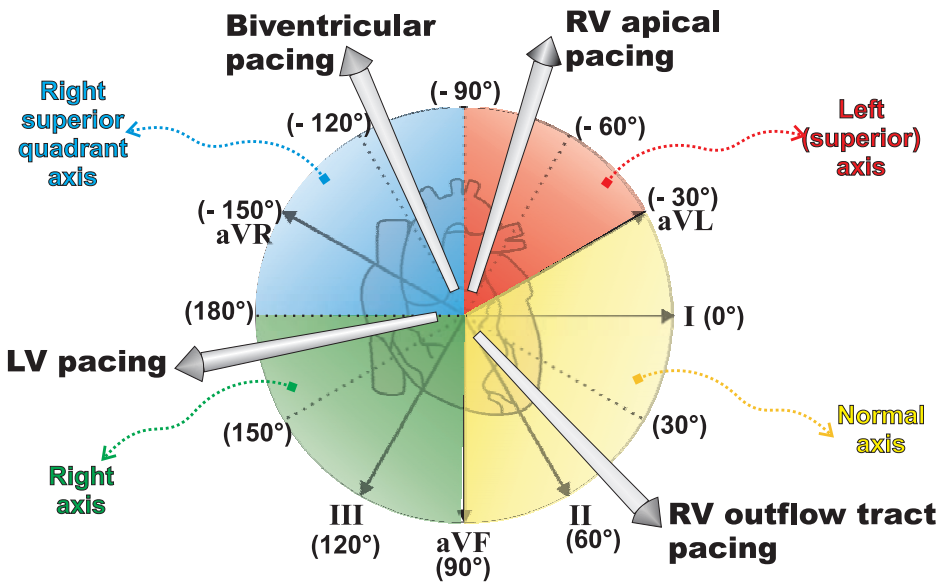
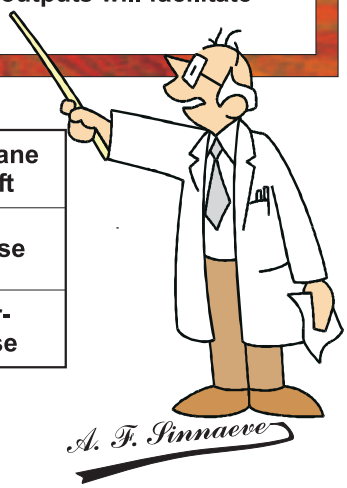


* A change in frontal plane axis may corroborate loss of capture in one ventricle
* Simultaneous recording of ECG, markers and ventricular electrogram (VEGM) is very helpful
* Beware of ventricular fusion beats with the conducted spontaneous QRS complex. The absence of fusion is verified by shortening the AV delay whereupon no change in QRS morphology should take place

ECG EVALUATION OF BIVENTRICULAR PACING



1. Establish a template for the best ECG lead showing morphological differences in RV, LV and BiV pacing. Store the pattern and use it for follow-up.
2. More than one lead is needed to confirm capture. Leads I and III are often enough. Make sure the leads are properly connected. Consider a 12-lead ECG in all cases.
3. Do the threshold test in the DDD mode with a short AV delay or in the VVI mode (if tolerated) at a rate higher than the intrinsic rate.
4. When in doubt, start at the maximum output (voltage and pulse duration) to ensure pacing of RV and LV.
5. Newer devices with separately programmable RV and LV outputs will facilitate ECG interpretation.



Pacing site	QRS in Lead I	QRS in Lead III	Frontal plane axis shift
BiV → RV	Greater positivity	Greater * negativity	Clockwise
BiV → LV	Greater negativity	Greater positivity	Counter-clockwise

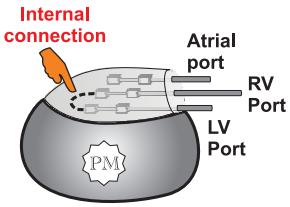
* QRS in lead III is more negative than in lead II

Abbreviations : BiV = biventricular ; LV = left ventricle ; RV = right ventricle

THE PACING IMPEDANCE OF BIVENTRICULAR PACING SYSTEMS

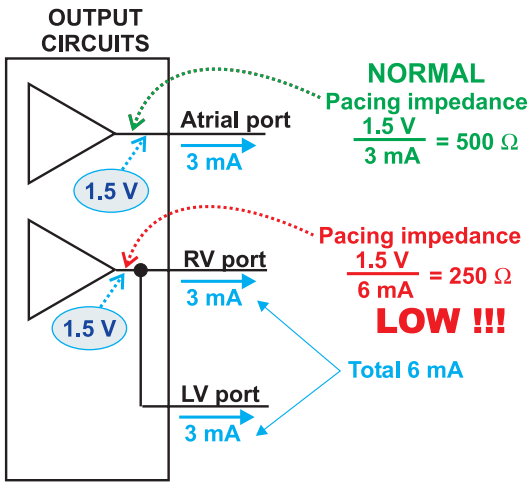
The values for voltage (1.5 V), current (3 mA) and lead impedance (500 Ω) are arbitrarily choosen as an example

Biventricular pacing with interconnected ventricular ports

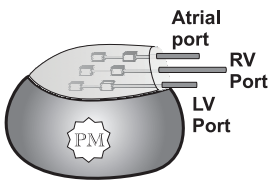


The two ventricular leads are in parallel

$$\frac{1}{R_{tot}} = \frac{1}{R_1} + \frac{1}{R_2}$$



Biventricular pacing with independent ventricular ports



Most PM workers favor high impedance leads !!!

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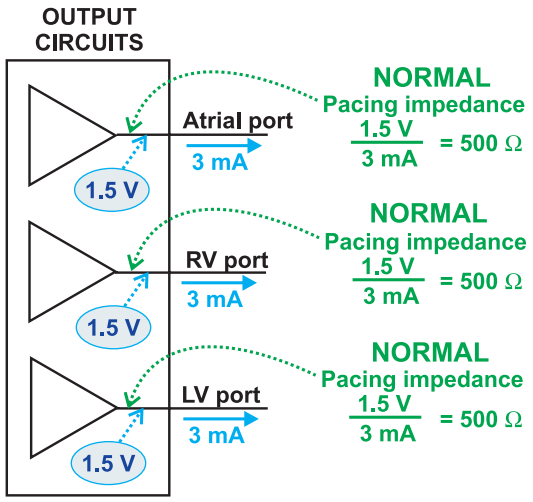
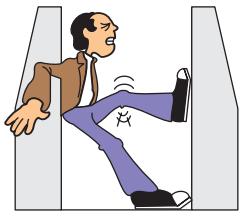


BEWARE : DIAGNOSIS OF LEAD PROBLEMS IN BIVENTRICULAR SYSTEMS

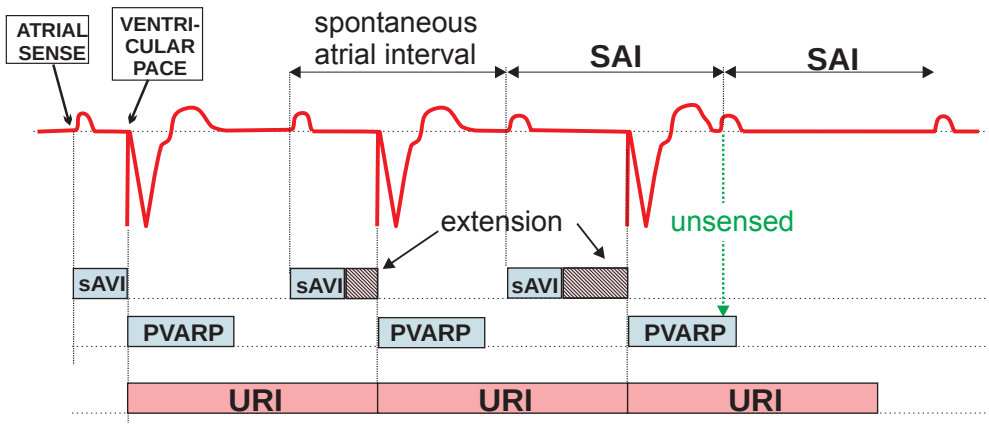
The total lead impedance may be low (in the range of 250 to 400 Ω) in a normally functioning biventricular system. A mechanical problem in one of the ventricular leads but not in the other, may not be readily detectable using standard impedance criteria. A conductor fracture involving one lead will not result in the very high impedance seen with single chamber pacing. Rather, that lead will effectively be taken out of the system and the measured impedance will reflect that of the intact ventricular lead. Hence, with a lead fracture in one of the two ventricular leads, the impedance may rise to the normal range for a univentricular lead.

The low telemetered impedance seen with an insulation failure in a single chamber lead may be the "normal" range during intact biventricular pacing. The normally low impedance in a dual cathodal system may thus complicate the diagnosis of an insulation failure in one of the leads.

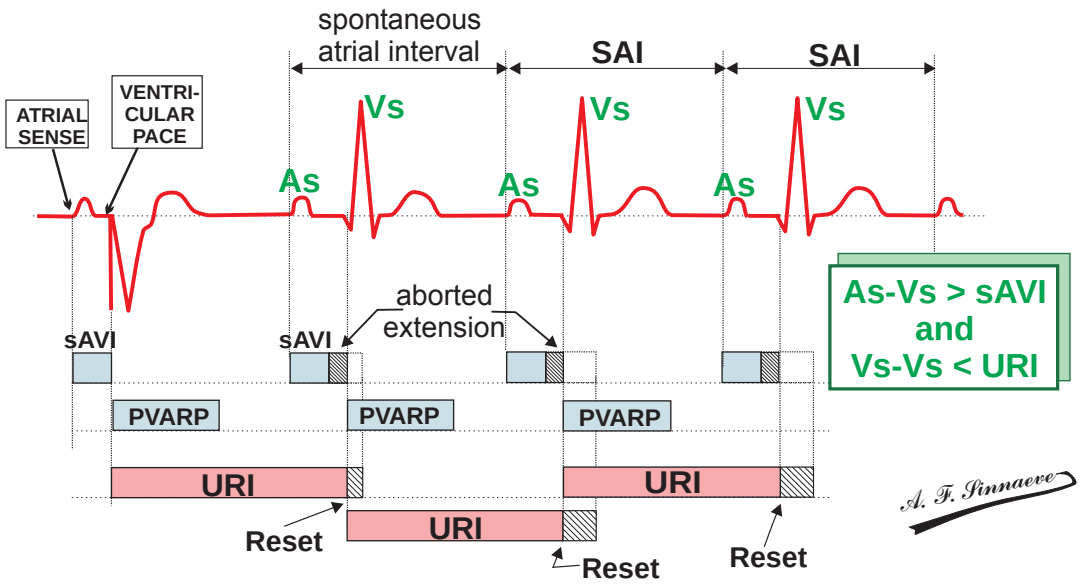


THE PRE-EMPTED or ABORTED WENCKEBACH BEHAVIOR

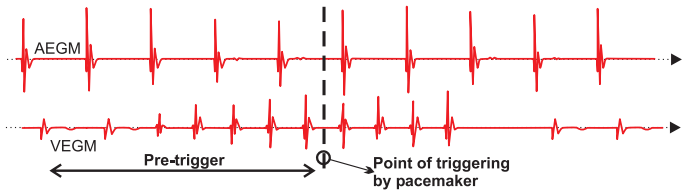
Normal upper rate response of the Wenckebach type



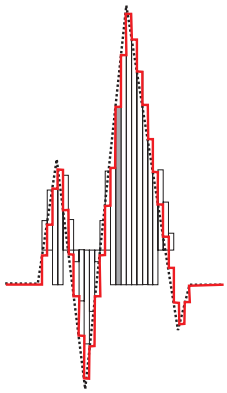
The pre-empted Wenckebach behavior with short sAVI

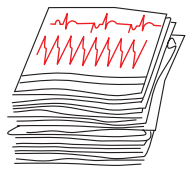


Abbreviations : As = atrial sense; Vs = ventricular sense; sAVI = AV delay after sensing; PVARP = postventricular atrial refractory period; URI = upper rate interval; SAI = spontaneous atrial interval

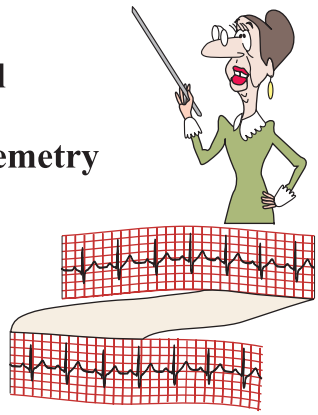


PACEMAKER FOLLOW-UP





* Pacemaker implantation
* Requirements for follow-up
* Central role of ventriculoatrial (VA) conduction
* Central role of postventricular atrial refractory period (PVARP)
* Transtelephonic follow-up
* General approach - part 1
* General approach - part 2
* Systematic follow-up - Various steps
* Automatic threshold determination - Initial steps
* Automatic threshold determination - End active phase
* Follow-up of AAI pacemakers
* Application of the triggered mode
* End-of-life (EOL) and elective replacement indicator (ERI)
* Pacemaker as a Holter recorder
* Memory of a VVI pacemaker
* The concept of telemetry - General
* Telemetry - Interrogation
* Measurement of impedance by telemetry
* Telemetry - Memorized data
* Telemetry - Measured data
* Unidentified pacemaker
* The memory train
* Storage of pacing states
* Stored histograms
* P wave amplitude histogram
* Heart rate histogram
* Beware of stored data
* Telemetered ventricular electrogram
* Example of real-time readout
* Stored electrograms - part 1
* Stored electrograms - part 2



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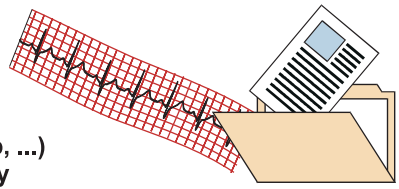
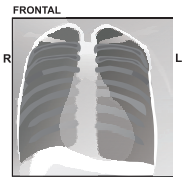
PACEMAKER IMPLANTATION

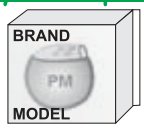
Have the patient's chart :

* Indication for pacemaker
* Medications
* Allergies
* Laboratory tests (INR, blood group, ...)
* Latest 12-lead ECG and chest X ray



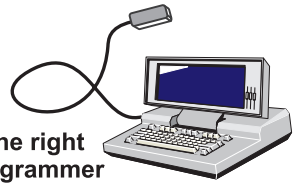


Make sure that the right pacemaker, leads, manual, and programmer are at your disposal

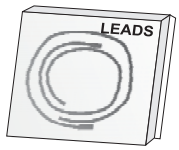


Sterile pacemaker

Technical manual provided by the pacemaker manufacturer



The right programmer



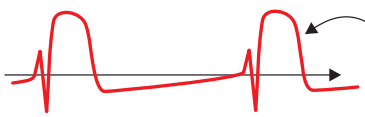
Sterile leads

Measure, verify and adjust

Use a PSA or Pacemaker System Analyzer permitting measurements of the output and the sensitivity of the pacemaker to be implanted and the thresholds and R- and P-wave characteristics of the implanted leads. The PSA also measures impedance

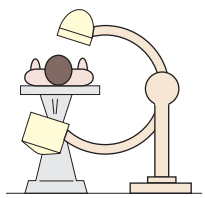
ACCEPTABLE VALUES AT IMPLANTATION	Atrial	Ventricular
Voltage threshold (at 0.5ms pulse width)	<1.5V	<0.5V
Sensitivity (signal amplitude)	>1.5mV	>5mV
Pacing impedance (at 5V and 0.5ms)°	<750Ω	<750Ω
Slew rate (only measured if the amplitude is small)	>0.5V/s	0.5V/s

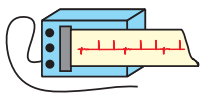
° Special high impedance leads will register a higher impedance (consult manufacturers notes)

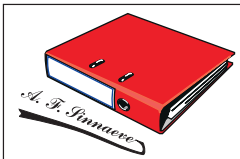


ST-segment shift due to current of injury indicates good endocardial contact of RV. This ensures a low pacing threshold.
(Unipolar electrogram from tip electrode)

* Try pacing near threshold with deep respiration and coughing and look for eventual unstable position of the leads
* Look at lateral or near lateral fluoroscopy to document the anterior position of the right ventricular lead and/or atrial lead if positioned in the right atrial appendage
* If there is sensing when the pacemaker is placed in the subcutaneous tissue, apply the magnet to make sure that both channels are capable of pacing
* Pace both A and V at 10V to rule out diaphragmatic stimulation
* Take a 12-lead ECG to make sure that the ventricular lead does not pace the left ventricle
* Look for retrograde VA conduction at the time of implantation or later before hospital discharge.





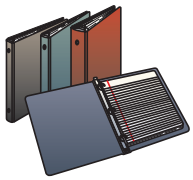


* Take a permanent chest x-ray soon after implantation for lead position and to rule out pneumothorax
* Interrogate the PM and reprogram if necessary; make a print-out for the patient's file
* Document all implantation data in the patient's chart

SYSTEMATIC PACEMAKER FOLLOW-UP

Requirements

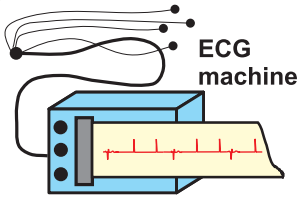
Technical manuals provided by pacemaker manufacturers



Planner

Magnets

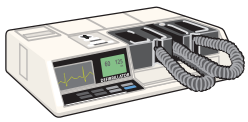
Official guidelines for pacemaker follow-up (e.g. NASPE)

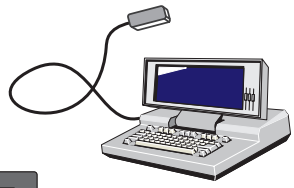


ECG machine

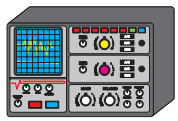
Programmers

External defibrillator

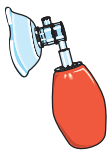




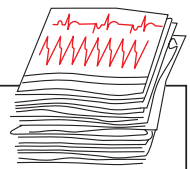
Scope & electronic counter to measure spontaneous and magnet automatic intervals



Crash cart for emergencies



HISTORY & PHYSICAL EXAMINATION
are part of pacemaker follow-up



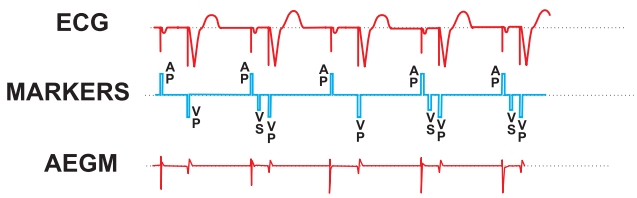
Thou shalt take long rhythm strips and thou shalt be rewarded to the fullness of thy days !

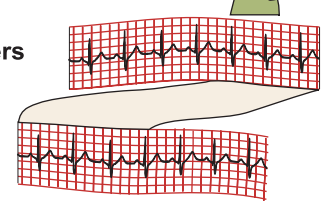
12-LEAD ECG WITH AND WITHOUT MAGNET

1. Verify automatic interval with and without magnet application
2. Estimate degree of pacemaker dependence
3. Verify appropriate depolarization sequence, capture, sensing, fusion and pseudofusion beats

MARKERS & INTRACARDIAC ELECTROGRAMS

Make a simultaneous recording of ECG annotated markers and intracardiac electrograms





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IMPACT OF RETROGRADE CONDUCTION IN CARDIAC PACING

PACEMAKER SYNDROME

HEMODYNAMIC DISADVANTAGE

ENDLESS LOOP TACHYCARDIA (ELT)

REPETITIVE NONREENTRANT VA SYNCHRONY (RNRVAS)

VA CONDUCTION
100-400 ms
rarely longer

INFLUENCED BY AUTONOMIC FACTORS, DRUGS, etc.

MAY PROLONG WITH INCREASE IN HEART RATE

RARELY OCCURS ONLY ON EXERCISE

OCCURS IN :
70-80 % of SSS pts
35 % of AV block pts

MANIFESTATIONS OF SUSTAINED VA CONDUCTION

* Regular 1 : 1 VA conduction
* Regular or irregular 2 : 1, 3 : 1 VA conduction
* Regular Wenckebach phenomenon of VA conduction

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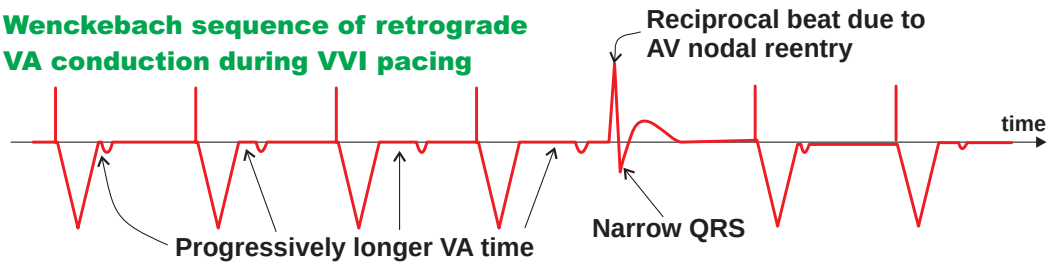
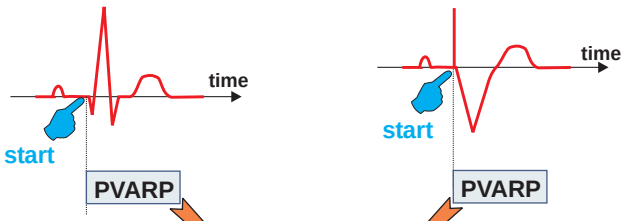
Wenckebach sequence of retrograde VA conduction during VVI pacing



Abbreviations : AV = atrioventricular (anterograde or orthograde); VA = ventriculoatrial (retrograde); SSS = sick sinus syndrome; pts = patients

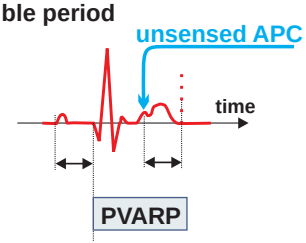
THE CENTRAL ROLE OF THE POSTVENTRICULAR ATRIAL REFRACTORY PERIOD (PVARP) IN DUAL CHAMBER PACING



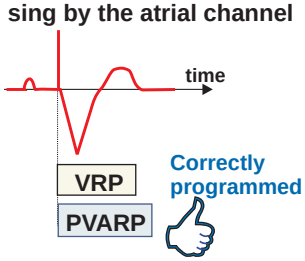
PVARP

OPTIMAL ATRIAL SENSING

Prevents sensing of early atrial events thereby avoiding delivery of a ventricular stimulus on the T wave and ventricular vulnerable period

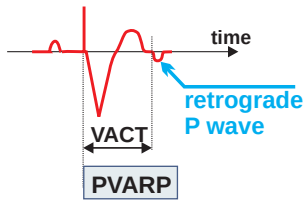


PVARP should not be shorter than the ventricular refractory period (VRP) so as to avoid far-field sensing by the atrial channel

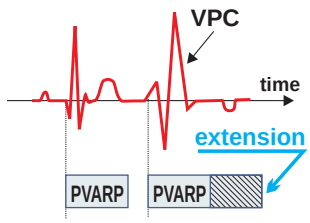


PREVENTION OF ENDLESS LOOP TACHYCARDIA

Program PVARP to = VACT + 50 ms (VACT = VA conduction time) (does not prevent retrograde VA conduction)



Automatic PVARP extension with recognition of ventricular premature complex (VPC)



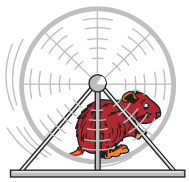
CONTROL OF UPPER RATE

TARP = AVI + PVARP

If there is no separately programmable upper rate

$$\text{Upper rate (bpm)} = \frac{60{,}000}{\text{TARP (ms)}}$$

Or 2:1 blocking rate if there is a separately programmable upper rate



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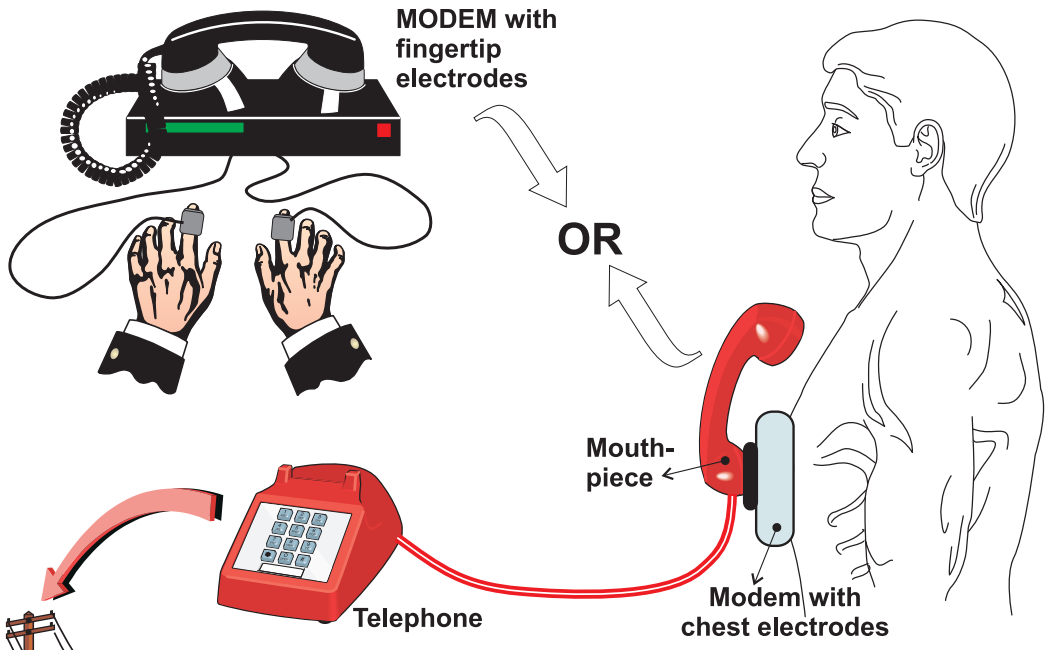
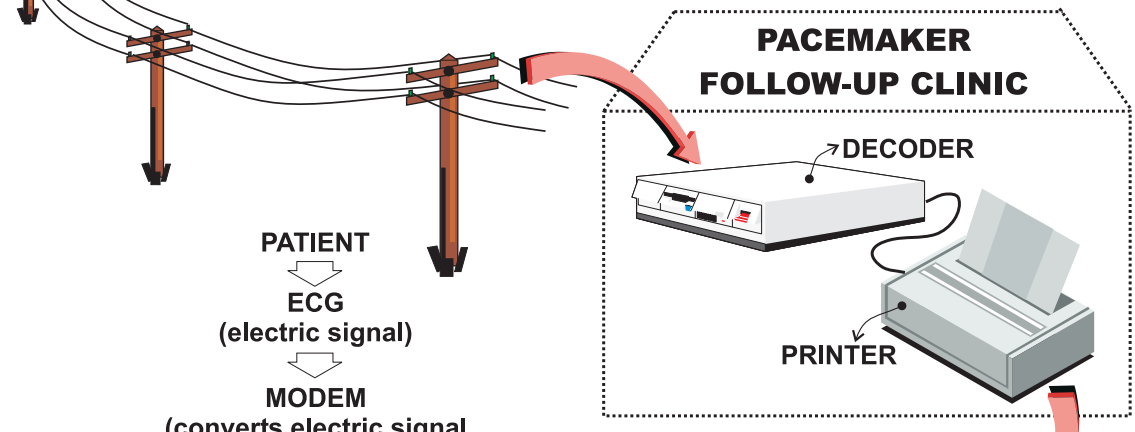
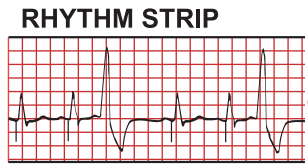
Abbreviations : VA = ventriculoatrial; APC = atrial premature complex; TARP = total atrial refractory period; VRP = ventricular refractory period

TRANSTELEPHONIC FOLLOW-UP





PATIENT
⇩
ECG
(electric signal)
⇩
MODEM
(converts electric signal
into sound waves)
⇩
TELEPHONE
⇩
DECODER
(translates the analog
telephone signal into a
digital signal for the printer)



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GENERAL APPROACH TO FOLLOW-UP PART 1

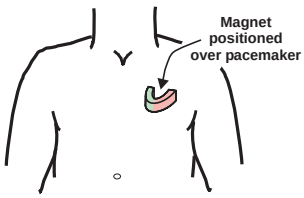
1 EXAMINATION & PATIENT HISTORY

A clinical approach is very important !!!

2 BLOOD PRESSURE

The pacemaker syndrome causes a fall in blood pressure during pacing !!!

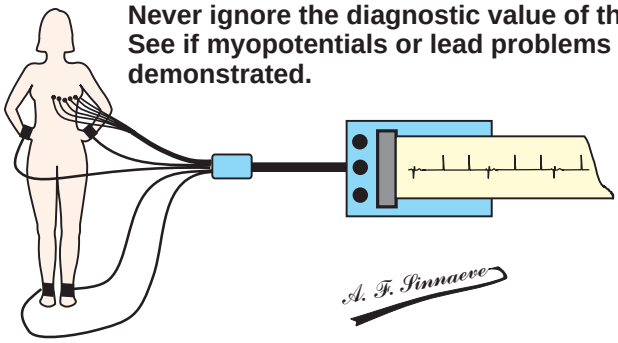
3 APPLICATION OF THE MAGNET

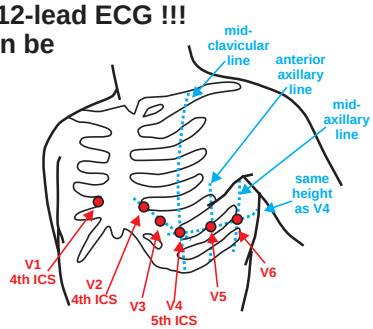


1. **Asynchronous pacing at the magnet rate. The rate and mode (DOO or VOO for dual chamber pacemakers) are device specific.**
2. **AV interval usually shortens**
3. **The magnet rate (which may differ from the programmed rate according to design) reflects the status of the battery and indicates an intensified follow-up period, ERT and EOL**
4. **Some devices allow the magnet response to be programmed on or off**

4 VERIFY THE ECG THOROUGHLY

Never ignore the diagnostic value of the 12-lead ECG !!!
See if myopotentials or lead problems can be demonstrated.

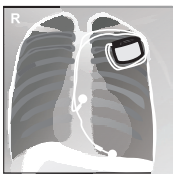




Abbreviations : DOO= Dual chamber AV sequential asynchronous mode; VOO = Ventricular asynchronous pacing mode; ECG = Electrocardiogram; EOL = End-of -Life; ERT = Elective Replacement Time; ICS = intercostal space

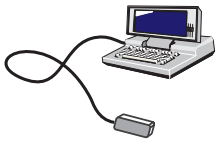
GENERAL APPROACH TO FOLLOW-UP PART 2

5 EXAMINE THE CHEST X- RAY



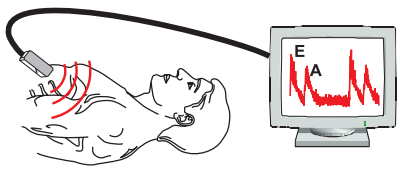
1. Identification of manufacturer and model if unknown
2. Check for lead position
3. Check for lead fracture
4. Check for LV failure

6 USE THE PROGRAMMER



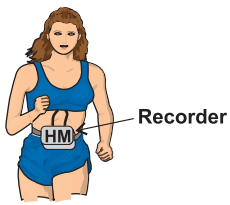
Match the programmer with the pacemaker !!!

7 ECHOCARDIOGRAPHY



1. Anatomic
   a. Diagnosis of unusual lead position such as LV site best documented by TEE
   b. Ventricular lead perforation (with possible pericardial effusion)
2. Hemodynamic
   a. Optimization of AV delay
   b. Evaluation of biventricular pacing

8 HOLTER MONITORING



To complement data in pacemaker memory in patients who remain symptomatic

9 TREADMILL or WALKING TEST

* Evaluation of atrial chronotropic incompetence
* Optimize sensor programming
* Evaluation of special functions on exercise : biventricular pacing, pacing for hypertrophic cardio-myopathy, etc.

A. F. Sinnaeve

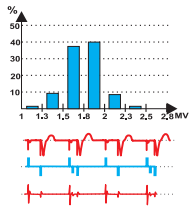
Abbreviations : AV = atrioventricular; LV = left ventricular; TEE = transesophageal echocardiography

SYSTEMATIC PACEMAKER FOLLOW-UP

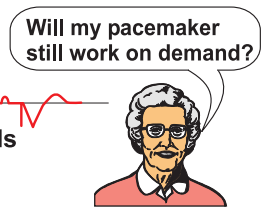
Make sure that the programming head is positioned carefully over the pacemaker

PACEMAKER INTERROGATION

1. Verify the administrative data
2. Check on the programmed data
3. Examine the measured or real-time data { Output ? Battery ? Leads ?
4. Inspect the memorized data



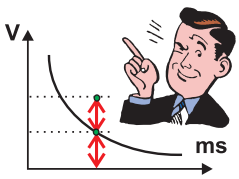
A higher sensitivity means a lower number in mV !



DETERMINATION OF SENSING THRESHOLDS

1. Automated and/or manual determination of sensing thresholds is needed if patient has periods of spontaneous rhythm
2. Reprogram sensitivity as necessary

Make sure that the safety margin is adequate !



DETERMINATION OF PACING THRESHOLDS

1. Automated and/or manual determination of pacing thresholds
2. Reprogram voltage and/or pulse duration as necessary

CHECK THE SPECIFIC FUNCTIONS

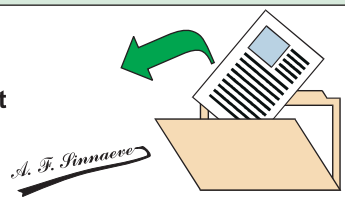
1. Check for crosstalk
2. Evaluate retrograde VA conduction and propensity to endless loop tachycardia
3. Look for eventual myopotential interference interference in unipolar PMs
4. Examine rate-adaptive function, sleep rate, hysteresis, automatic mode switching, histogram settings, etc.

IF NECESSARY ORDER SPECIAL TESTS : Chest X ray, Holter, etc.

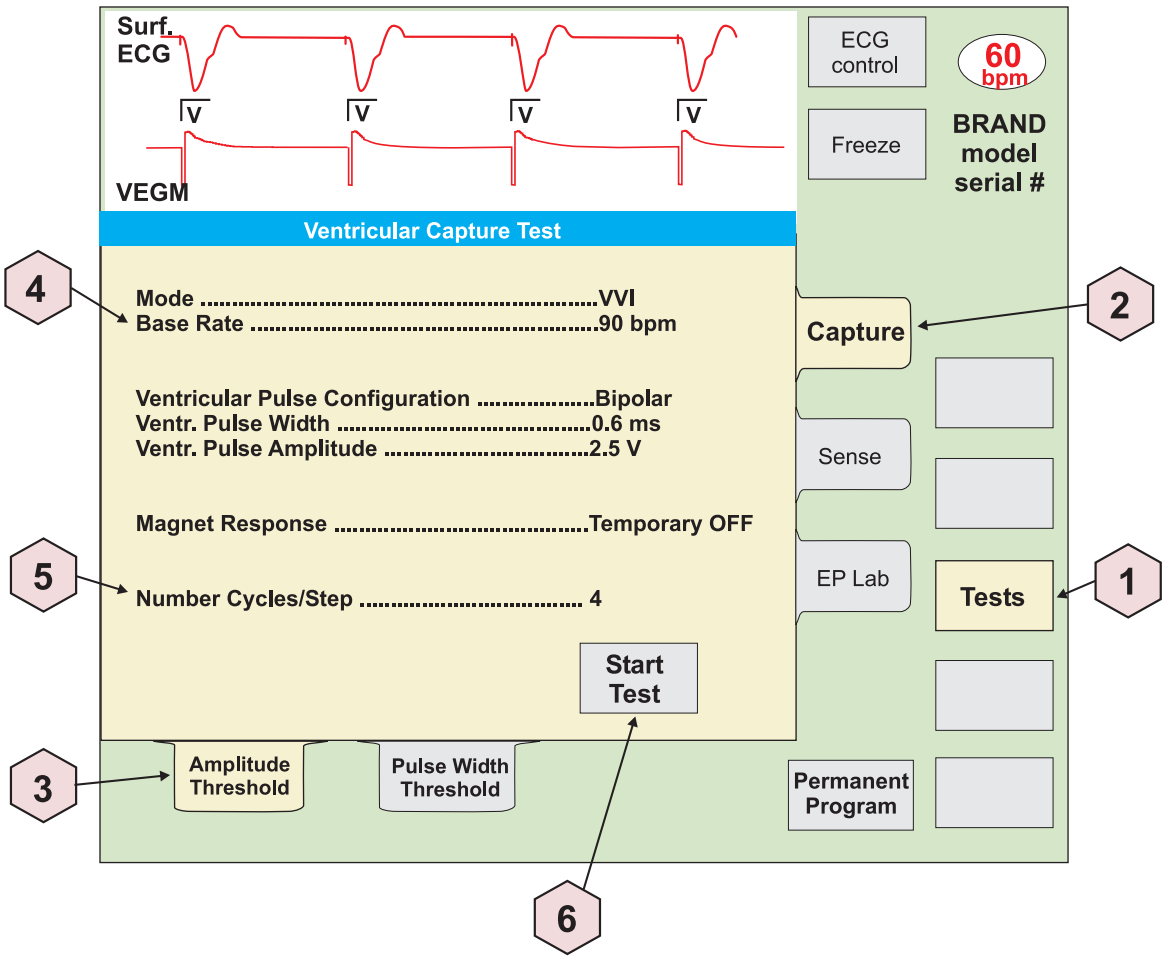
PREPARE YOUR REPORT

Meticulous record-keeping is necessary

1. Clear the appropriate memorized data
2. Make the final print-outs
3. Compare final parameters with those at presentation
4. Give the patient a copy of the print-out



AUTOMATIC DETERMINATION OF THRESHOLD
INITIAL STEPS



* Initial Step 4 : The actual "Base Rate" (60) indicated in red in the upper right corner is programmed to a higher temporary value (90) above the patient's intrinsic rate to ensure pacing

*Initial Step 6 : When {Start Test} is touched, a "Test in Progress" message will appear with two option buttons {End Test} and {Stop Test}. The {Stop Test} is the emergency button, immediately restoring the settings to the previously programmed values

* When capture is lost, touching {End Test} terminates the test and restores the previously programmed value (amplitude or pulse width). The system then displays the "Confirm Capture Test" screen and stores the test in the memory of the programmer.

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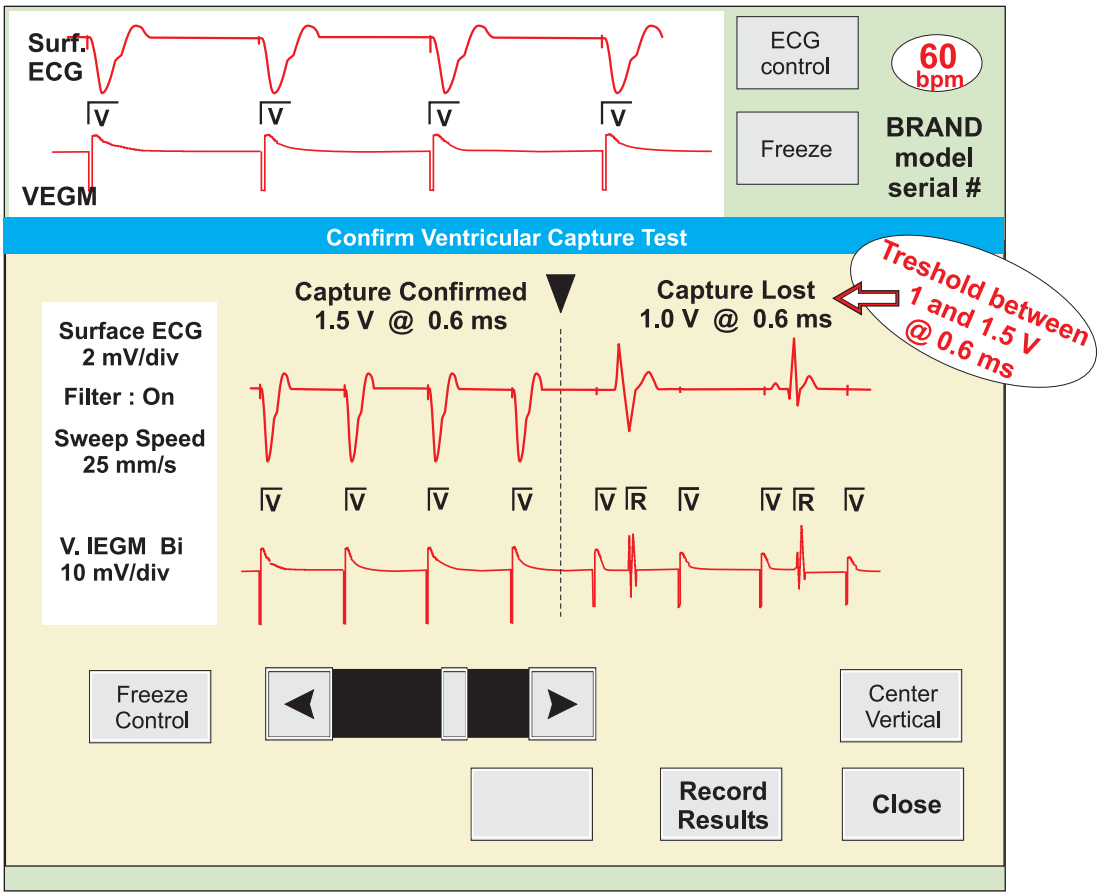
AUTOMATIC DETERMINATION OF THRESHOLD END OF ACTIVE PHASE



* During the test the temporary actual rate (90) is indicated in red in the upper right corner. At the end of the test, the programmed "Base Rate" (60) is restored.

* The test will start at a value (amplitude or pulse width depending upon choice) one step lower then the prevailing value. After every programmed "Number Cycles/Step", the value of the test parameter will decrease by one step. Each step is indicated by the appearance of a vertical line on the ECG display.

* Pressing {End Test} not only terminates the test, but restores the previously programmed values, i.e. 2.5 V - 0.6 ms - 60 bpm. These settings may be checked in the upper part of the display

* After touching {Close} the pacemaker should be programmed to yield a suitable safety margin for reliable long-term pacing (confirm with {Permanent program})

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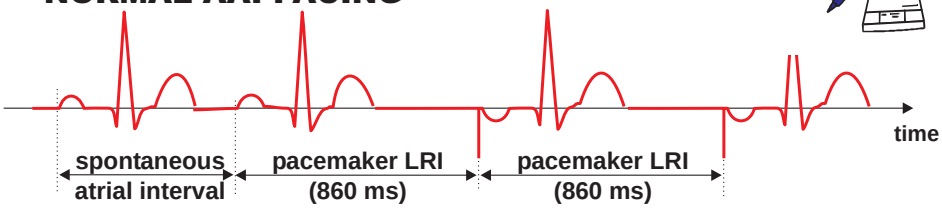
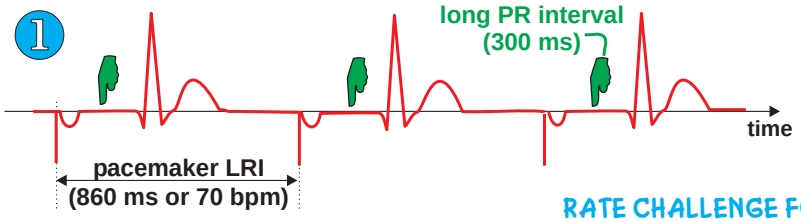
You know, even in carefully selected patients for AAI and AAIR pacemakers, there is always a small but definite risk of second- and third-degree AV block with the passage of time. The status of AV conduction must be carefully evaluated during follow-up to detect the earliest manifestations of potentially serious AV block that may require upgrading to a dual chamber pacemaker.

AAI PACEMAKERS AND THEIR FOLLOW-UP

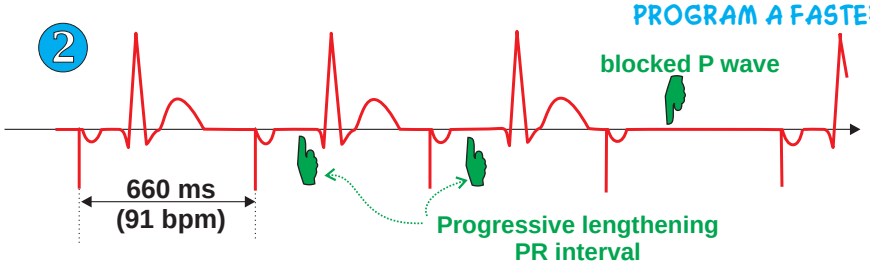
NORMAL AAI PACING



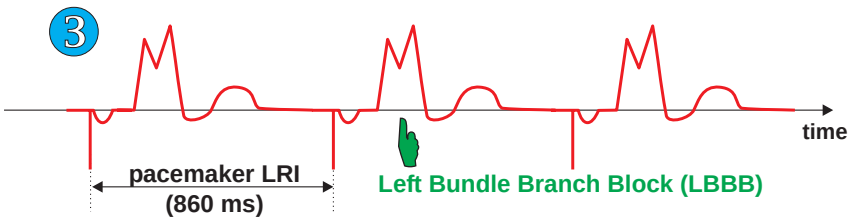


Marked 1st degree AV block

RATE CHALLENGE FOR AV CONDUCTION !!!
PROGRAM A FASTER LOWER RATE.



Wenckebach type I second-degree AV block



Beware of new bundle branch block

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Abbreviations : LRI = lower rate interval ; LBBB = left bundle branch block ; AAI = atrial demand pacemaker mode ; AAIR = atrial demand rate-adaptive pacemaker mode

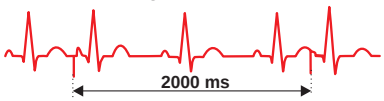
APPLICATION OF THE TRIGGERED PACING MODE

Remember that a DDD pacemaker functions in the triggered mode in the atrium because atrial sensing triggers a ventricular output after a delay equivalent to the programmed AV interval. In the AAT or VVT modes triggering occurs immediately after sensing without delay so that the pacemaker stimulus falls within the sensed event, P wave or QRS complex.

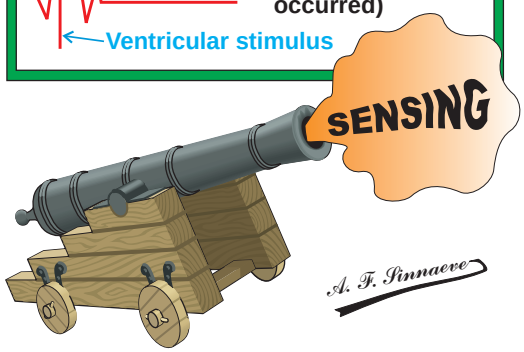
DDD pacemaker (basic or lower rate 60 bpm)
Is the atrial channel correctly sensing ?

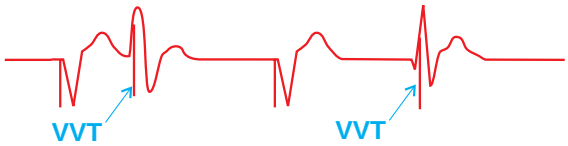
Temporary pacing at the AAT mode (30 bpm) when atrial sensing is properly adjusted

Temporary pacing at the AAT mode (30 bpm) with undersensing of the atrial channel



This could be asynchronous pacing, a pseudofusion beat (sensing has not yet occurred) or a triggered response (sensing has already occurred)

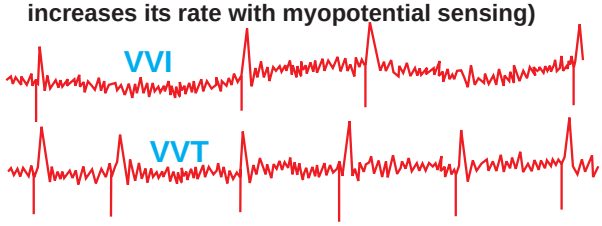




Triggered pacemaker modes are intended mostly for pacemaker diagnostic purposes :

1/ to facilitate identification of sensed events with pacing artifacts e.g. in high noise environment

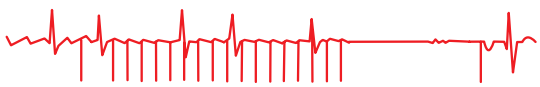
2/ to correct myopotential oversensing unresponsive to lowering sensitivity (the pacemaker then increases its rate with myopotential sensing)



3/ to correct oversensing from noisy leads, until lead replacement can be performed

4/ to show retrograde P waves and to measure the sensed signal in DDT mode

5/ to perform electrophysiologic studies and termination of tachycardias by chest wall stimulation (CWS) in pacemakers without these functions



The triggered modes can be used in Holter recordings in patients with suspected oversensing that cannot be demonstrated in the pacemaker clinic with telemetered markers. The triggered impulse represents a marker for the diagnosis and the timing of sensed signals.

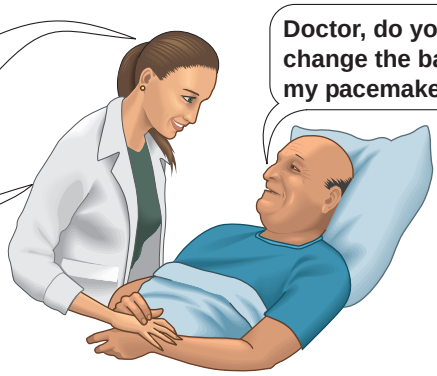
Abbreviations : CWS = chest wall stimulation: delivery of pacemaker stiumuli to the chest wall with an external pacemaker (painless procedure unable to capture the heart) to be sensed by an implanted pacemaker ; **LRI** = lower rate interval ; **VRP** = ventricular refractory period ; **DDT** mode = a triggered response occurs in the atrium upon atrial sensing and a triggered response also occurs in the ventricle upon ventricular sensing

BATTERY DEPLETION & END OF LIFE

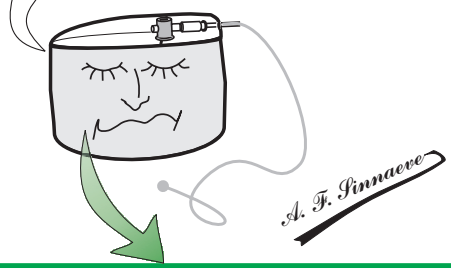
The battery of your pacemaker is almost depleted. The mode of the device is changed and its pacing rate remains low.

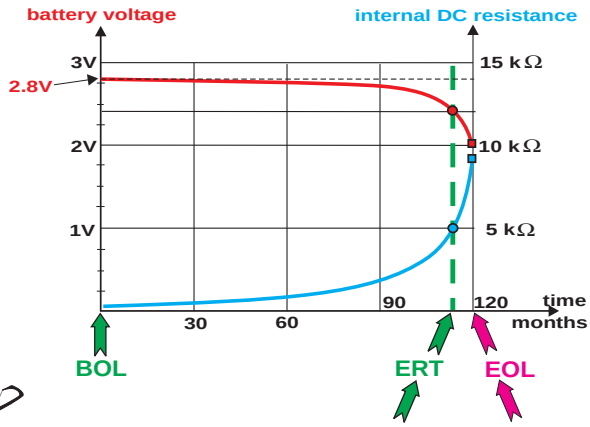
Doctor, do you have to change the batteries of my pacemaker ?

No, we have to replace the device, not just the battery ! We are taking you to the operating room.



I can predict the end of my life and I report it to the doctor by a diagnostic elective replacement indicator !
I do not want to reach the end-of-life point when my function will be erratic and may cause complications.





DIAGNOSTIC ELECTIVE REPLACEMENT INDICATORS

1. Percent or fixed decrease in the magnet rate; the free-running rate may also decrease according to design
2. Increase in pulse width duration in some pacemakers to compensate for a lower voltage output delivered to the heart.
3. Change to simpler pacing mode : DDDR to VVI, VVIR to VVI or VOO to reduce battery current drain and delay the time to end of life.

BOL = Beginning-Of-Life : when the pacemaker is new - battery voltage approx. 2.8V and battery impedance less than 1kΩ

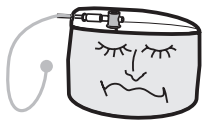
EOL = End-Of-Life : when the battery is depleted and the basic pacer functions not longer supported - battery voltage lower than approx. 2.1 - 2.4V and battery impedance higher than 5 - 10kΩ

ERT = Elective Replacement Time : generator replacement should be considered well in advance of end of life - battery voltage is reduced but still able to support basic or all pacer functions

ERI = Elective Replacement Indicator : battery voltage approx. 2.1 - 2.4V and battery impedance approx. 5 - 10kΩ

SPECIFIC VALUES OF EOL & ERI WILL VARY FROM MANUFACTURER TO MANUFACTURER

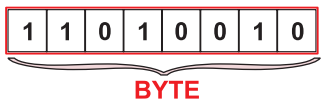
THE PACEMAKER AS A HOLTER RECORDER



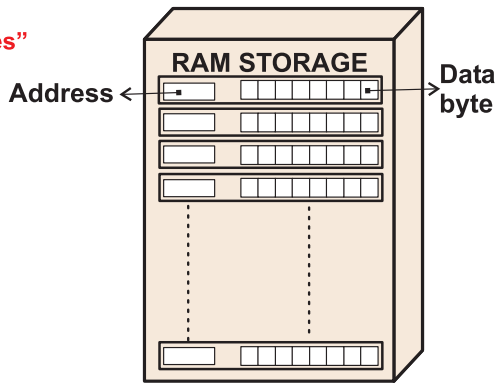
DECIMAL COUNTING FOR HUMANS	BINARY COUNTING FOR MACHINES
Ten digits : 0, 1, 2, 3, 4, 5, 6, 7, 8, 9	Only two digits : 0 and 1 called "bits"
$14 = 1.10^1 + 4.10^0$	$1110 = 1.2^3 + 1.2^2 + 1.2^1 + 0.2^0$
$= 10 + 4$	$= 8 + 4 + 2 + 0$

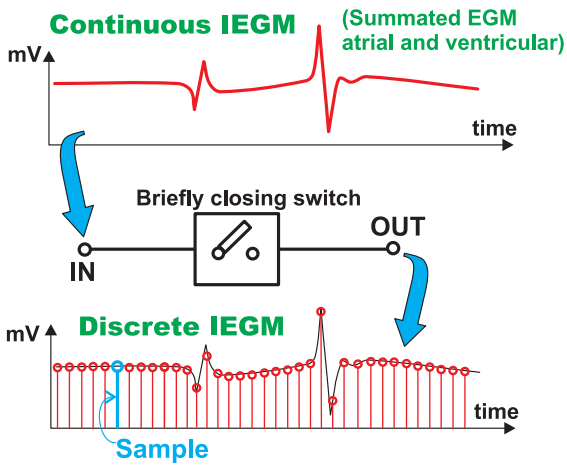
EQUIVALENT

A sequence of eight adjacent bits forms a "byte".



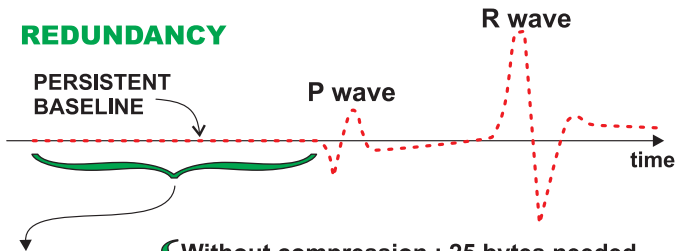
When information is read by the pacemaker and stored in its electronic memory, it is done byte-by-byte. Memory is usually measured in "kilobytes" (kB). One kilobyte = 1024 bytes.





The microprocessor cannot handle continuous signals. Hence, "sampling" is used to measure the signal repeatedly during a very brief instant, creating a set of discrete values or "samples". Sampling is usually performed at 128 or 256 samples per second.

The intracardiac electrogram (IEGM) is immediately stored in the RAM of the pacemaker. Each sample corresponds with one byte of data storage. Each byte is stored at a specific memory address for retrieval at a later time. A 128kB RAM includes 128 x 1024 = 131 072 bytes. When sampling at 256 samples/s, this RAM is sufficient for 131,072 / 256 = 512 s = 8.5 minutes of IEGM.



Compression algorithms reduce the number of bytes and increase the amount of IEGM that can be stored in the RAM of the pacemaker

REQUIREMENTS FOR 24-h RECORDING OF IEGM :
24 h/day x 60 min/h x 60 s/min = 86,400 s/day
128 samples/s x 1 byte/sample x 86,400 s/day = 11million bytes/day
Sampling at 128 samples/s requires a RAM of 11,000 kB

THE FUTURE : within 3 - 5 years ??

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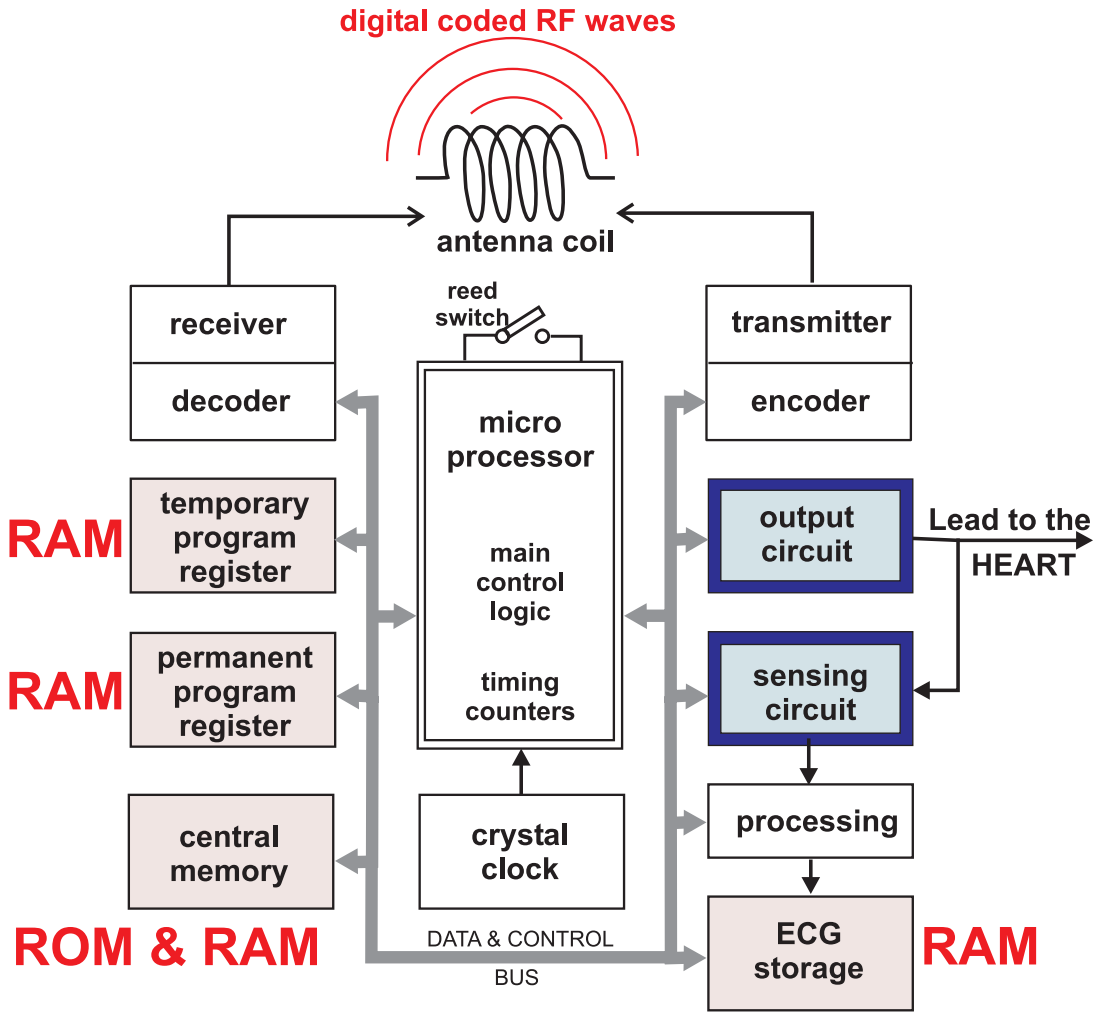
THE MEMORY OF A VVI PACEMAKER



ROM = read only memory
(is installed by the manufacturer; cannot be modified by the physician via the programmer)

RAM = random access memory (read & write)
(content can be changed by measurements of the pace-maker or by the physician via the programmer)

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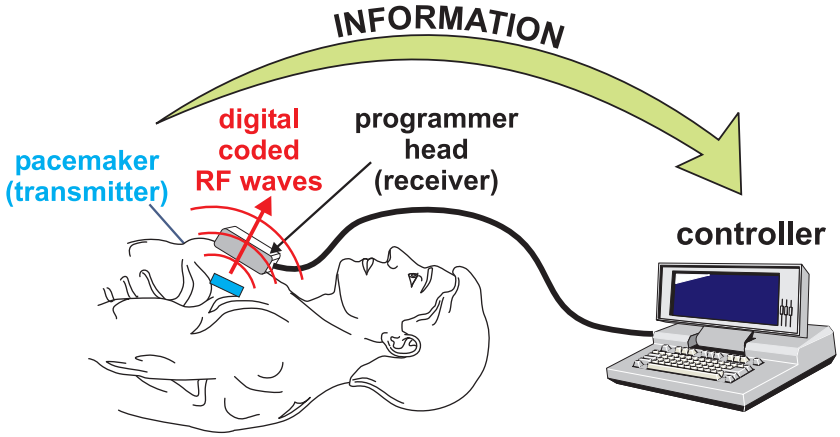
THE CONCEPT OF TELEMETRY



DATA OBTAINABLE BY TELEMETRY

* **ADMINISTRATIVE DATA** (model, serial number, patient's name, date of implantation, indication for implantation)

* **PROGRAMMED DATA** (mode, rate, refractory period, hysteresis on/off, pulse amplitude & width, sensitivity)

* **MEASURED DATA** (rate, pulse amplitude, pulse current, pulse energy, pulse charge, lead impedance, battery impedance, battery voltage, battery current drain)

* **STORED DATA** (Holter function, rhythm histogram, ...)

* **MARKER SIGNALS** for ECG interpretation

* **INTRACARDIAC ELECTROGRAM**

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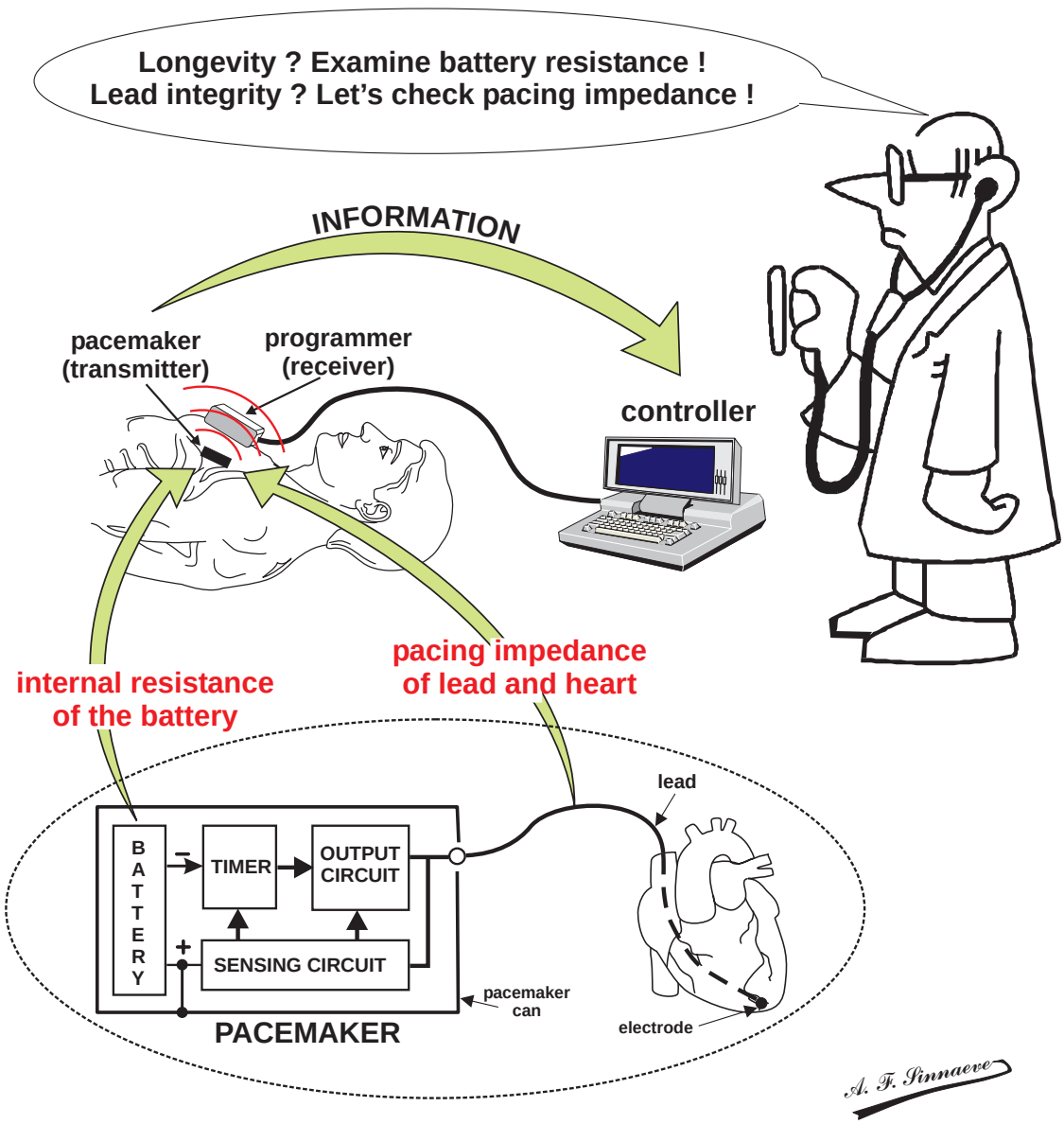
THE INTERROGATION

The guy has a pacemaker ! Let's interrogate him and his device. Make sure you use the correct programmer for his device and apply the programming head carefully over the pacemaker for telemetry. Press "Interrogate" and obtain the basic information.
You should get 4 lots of data. 1. Administrative data. 2. Programmed data. 3. Measured or real-time data. 4. Memorized data.
These print-outs will provide preliminary evidence that the pacemaker is working properly ! OK ?

Sir, I'll look at the administrative data first, so that we know the model, serial number and implantation data if nobody forgot to program that data into the pacemaker.
Then, I'll look at the programmed data to determine the basic parameters of the device.

MEASUREMENT OF RESISTANCE & IMPEDANCE BY TELEMETRY



THE MEMORIZED DATA

Advances in pacemaker technology have improved the memory function of pacemakers. The quantity of memorized data can be intimidating. Important memory functions include :

1. **% paced and sensed events in each chamber.**
2. **% of pacemaker events : As-Vs, As-Vp, Ap-Vs, Ap-Vp, VPC.**
3. **Histograms of various functions including heart rate with and without sensor activation, time and duration of automatic mode switching (and detected atrial rate).**
4. **Trends : display of periodic automatic recordings of lead impedance and intracardiac P and QRS amplitude.**
5. **Diagnosis of arrhythmias with marker chains and/or stored atrial and ventricular electrograms. This function can be automatic or patient-activated by placing a magnet or activator over the pacemaker.**

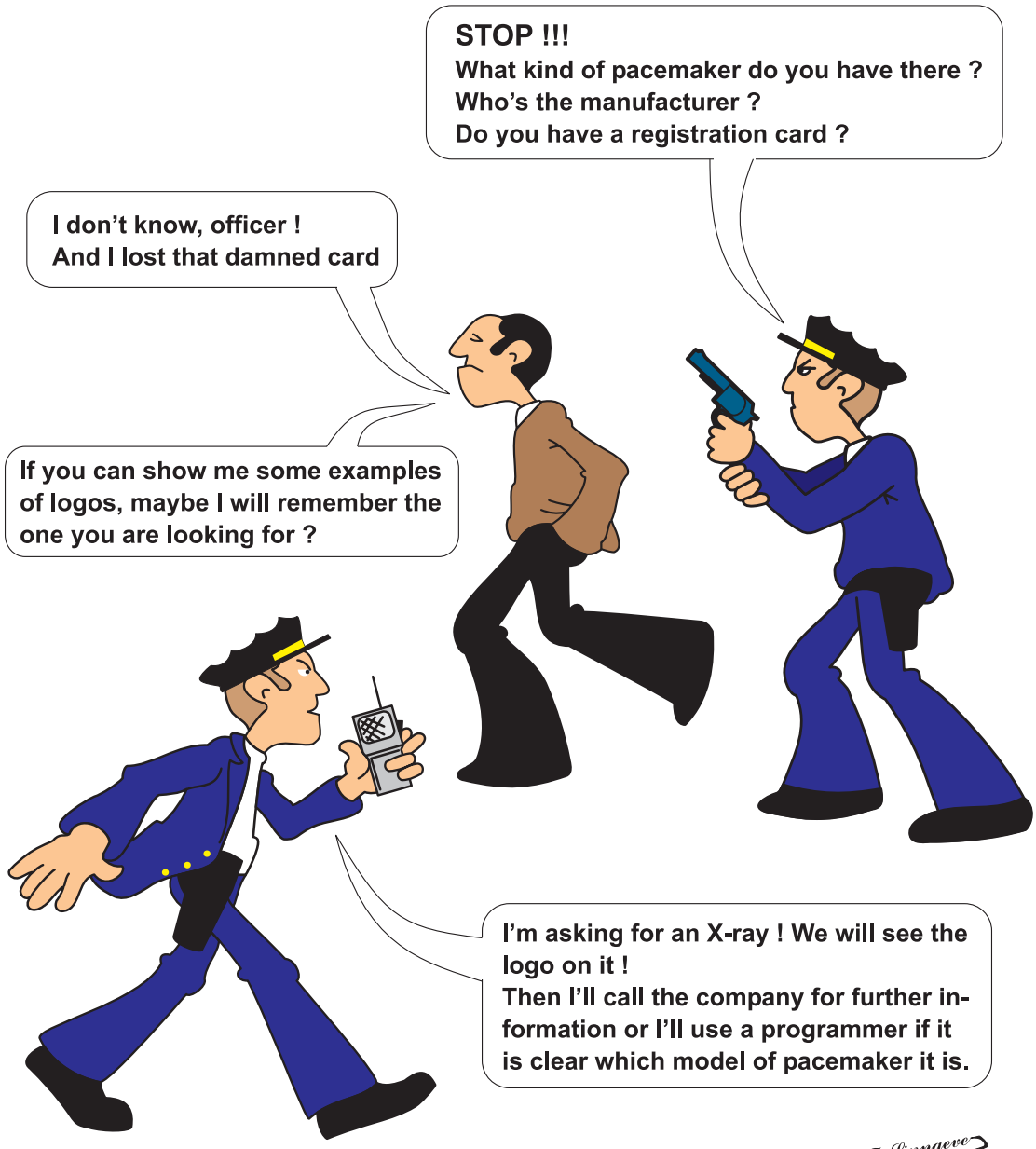
Abbreviatons : Ap = atrial paced event; As = atrial sensed event; Vp = ventricular paced event; Vs = ventricular sensed event; VPC = ventricular premature complex

THE MEASURED DATA

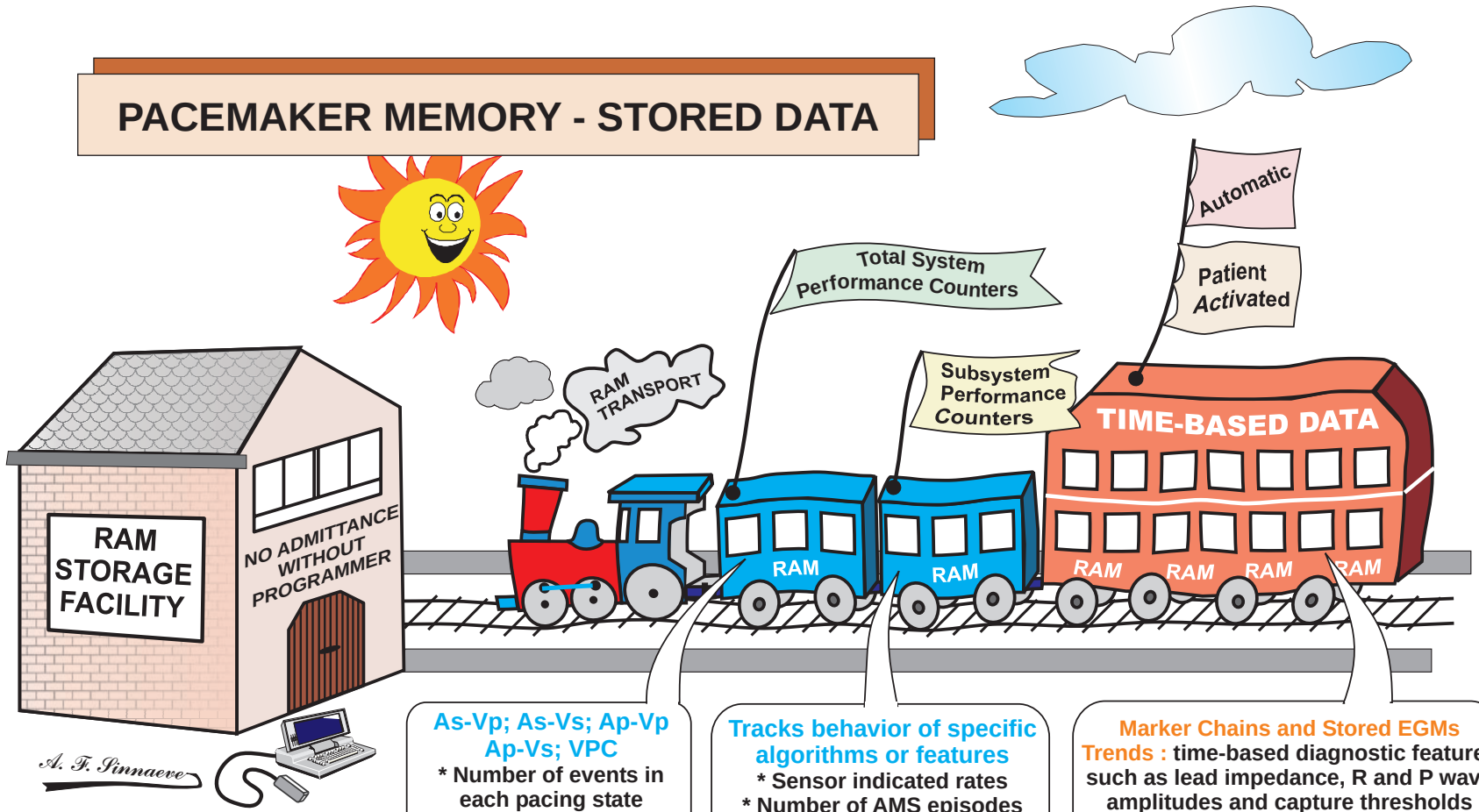
The measured data is real-time ! And the data of 2 channels (A and V) is displayed simultaneously. We have here information about :

1. The output - pacing rate in beats per minute (bpm)
   - pulse voltage amplitude in volts (V)
   - pulse duration in milliseconds (ms)
2. The battery - battery voltage in volts (V)
   - battery current drain in microamperes (μA)
   - battery impedance in ohms (Ω)
3. The leads - lead impedance in ohms (Ω)
   - lead configuration (bipolar/unipolar)

THE UNIDENTIFIED PACEMAKER



PACEMAKER MEMORY - STORED DATA



As-Vp; As-Vs; Ap-Vp Ap-Vs; VPC
* Number of events in each pacing state
* Rate distribution within each pacing state
* % paced in atrium and ventricle

Tracks behavior of specific algorithms or features
* Sensor indicated rates
* Number of AMS episodes (duration and atrial rate)
* Amount of time spent at maximum rate
* etc.

Marker Chains and Stored EGMs
Trends : time-based diagnostic features such as lead impedance, R and P wave amplitudes and capture thresholds often presented as graphs

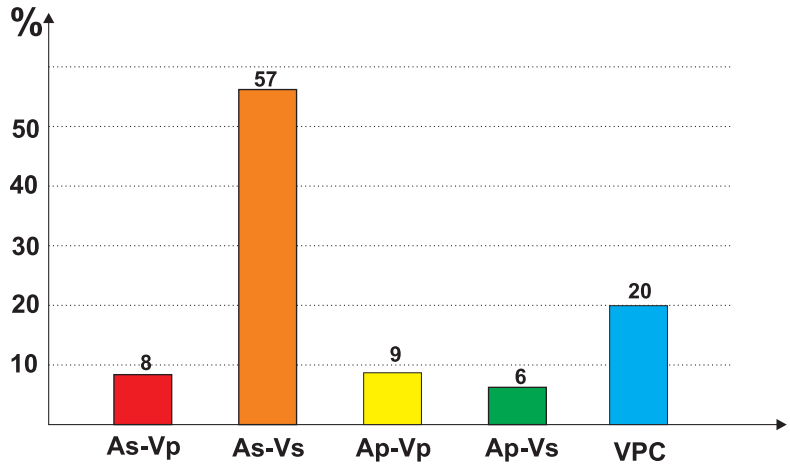
In system performance counters, time-based individual events are placed in the sequence of their occurrence !!!

Vocabulary :

As-Vp (= PV) = atrial sense-ventricular pace; As-Vs (= PR) = atrial sense - ventricular sense; Ap-Vp (= AV) = atrial pace-ventricular pace; Ap-Vs (= AR) = atrial pace-ventricular sense; VPC = ventricular premature complex; EGM = electrogram; RAM = random access memory; AMS = automatic mode switching

STORAGE OF PACING STATES

I can make a "short term histogram" for the last three-to-six days or a "long term histogram" containing data since the last programming session



(Ap-Vp) + (Ap-Vs) : total % of atrial paced events ;
- *** if this total is large, there is a lot of pacing at the basic rate**
- *** if this total is large, it suggests sick sinus syndrome and atrial incompetence**

(As-Vp) + (As-Vs) : total % of atrial sensed events ;
- *** if As-Vp is very large there is an AV block or the AV delay (AVI) is programmed too short**
- *** if As-Vs is large, the pacemaker functions on stand-by basis most of the time**

(As-Vs) + (Ap-Vs) : total % of sensed ventricular events
- *** if this total is large, there is a good spontaneous AV conduction**

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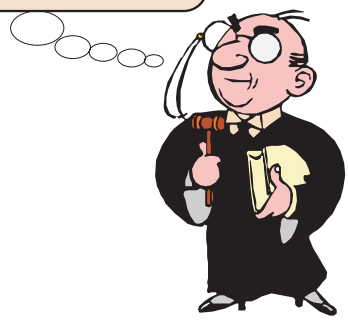
(As-Vp) + (Ap-Vp) : total % of paced ventricular events

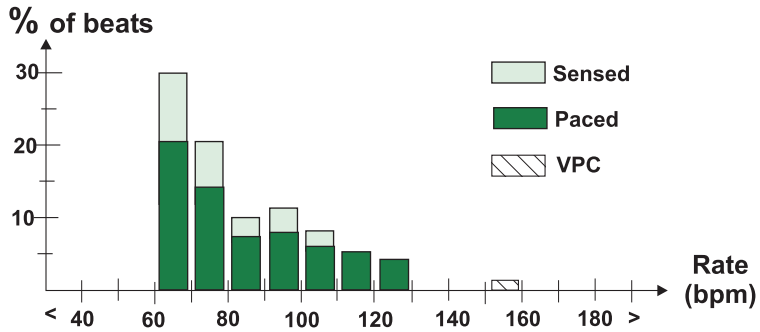
VPC : note that a VPC according to the pacemaker is not necessarily equal to a clinical PVC

Abbreviations :
As-Vp (= PV) = atrial sense-ventricular pace; As-Vs (= PR) = atrial sense-ventricular sense; Ap-Vp (= AV) = atrial pace-ventricular pace; Ap-Vs (= AR) = atrial pace-ventricular sense; VPC = ventricular premature complex; PVC = premature ventricular complex

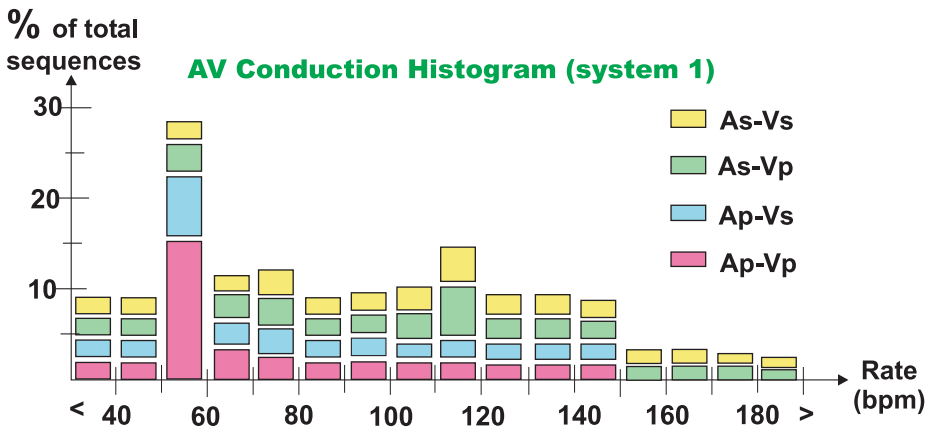
DO NOT RELY ON JUST ONE HISTOGRAM !
INTERPRET IT IN CONNECTION WITH OTHER DATA.



Ventricular Heart Rate Histogram



AV Conduction Histogram (system 1)



AV Conduction Table (system 2)

Rate (bpm)	As-Vp	As-Vs	Ap-Vp	Ap-Vs	VPC
30 - 54	45	0	9 546	0	0
55 - 69	308 978	79	2 974 366	1 322	0
70 - 89	298 459	1 504	621 788	1 908	6 968
90 - 109	11 693	989	608	398	84 241
110 - 129	100	315	0	0	7 173
130 - 149	0	152	0	0	447
150 - 179	0	409	0	0	2 235
180 - 224	0	205	0	0	625
225 - 249	0	0	0	0	1
> 250	0	0	0	0	0
Total :	619 275	3 653	3 606 308	3 628	101 690

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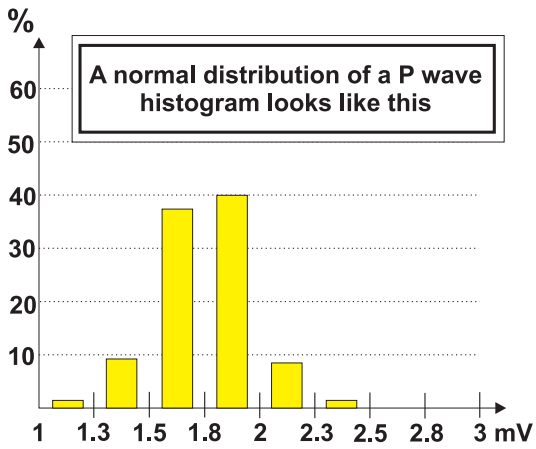
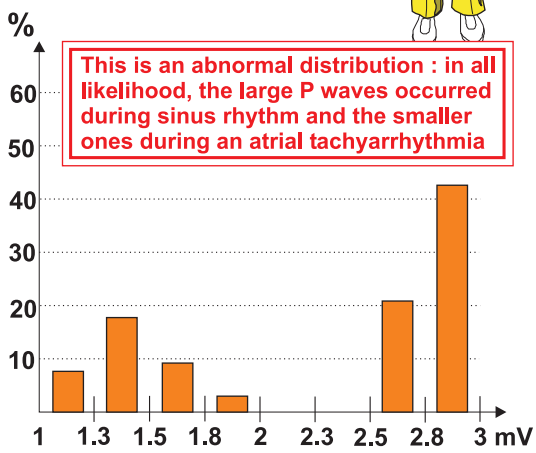
Abbreviations :
As-Vs (= PR) = atrial sense - ventricular sense; As-Vp (=PV)= atrial sense - ventricular pace; Ap-Vs (=AR) = atrial pace - ventricular sense; Ap-Vp (=AV) = atrial pace - ventricular pace; bpm = beats per minute; VPC = ventricular premature complex

P WAVE AMPLITUDE HISTOGRAM

The P wave histogram can be helpful for :
* Evaluation of the safety margin for atrial sensing
* Detection of lead displacement
* Detection of atrial arrhythmias
* Detection of interference
* Detection of near-field & far-field sensing



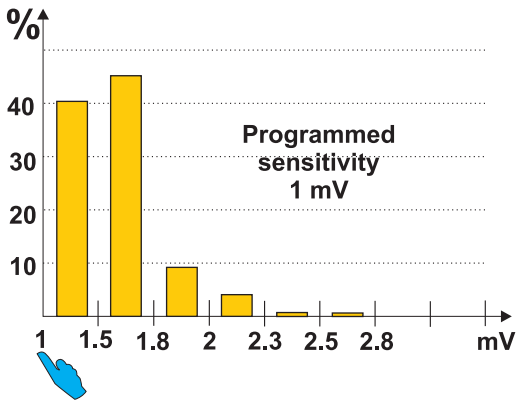
A normal distribution of a P wave histogram looks like this

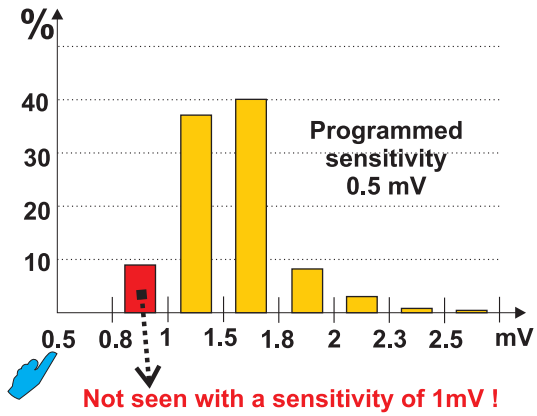


This is an abnormal distribution : in all likelihood, the large P waves occurred during sinus rhythm and the smaller ones during an atrial tachyarrhythmia

Evaluation of the safety margin for atrial sensing. Signal vs. programmed sensitivity.

The histogram is limited on its lower side by the programmed sensitivity !!!
Programming different sensitivities may unmask undersensing





Not seen with a sensitivity of 1mV !

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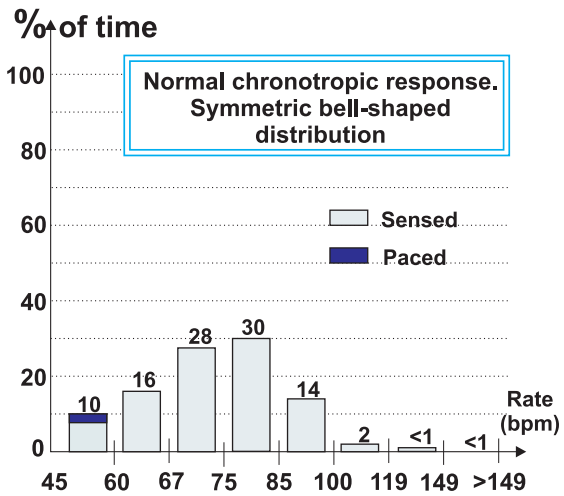
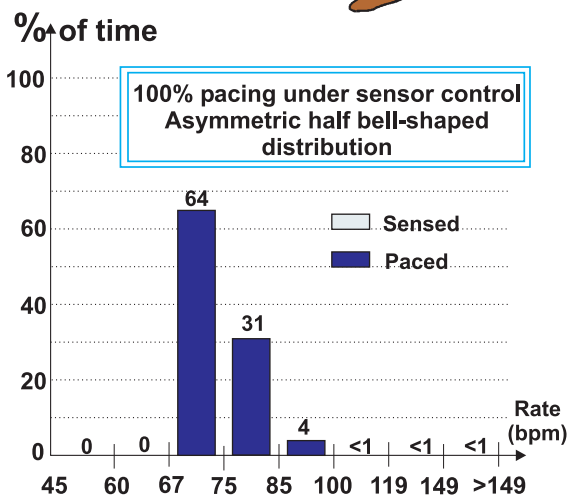
The pacemaker automatically collects the data !
These histograms are very useful for the evaluation of the condition of the patient, the performance of the total system and the adjustment of the sensor characteristics.

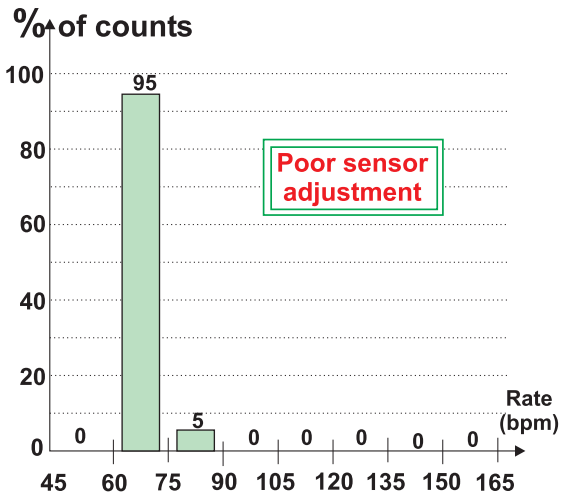
HEART RATE HISTOGRAM

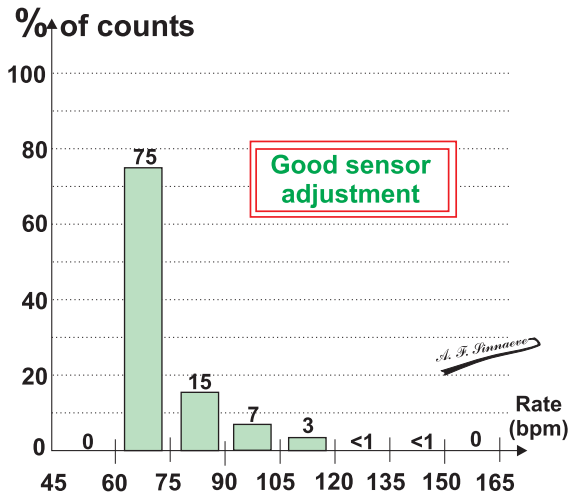




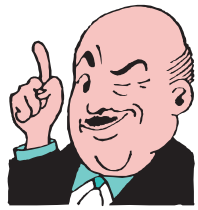
SENSOR INDICATED RATE HISTOGRAM

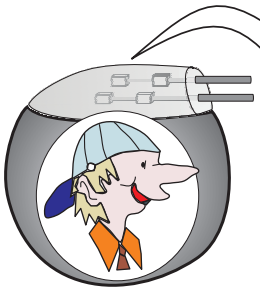
Such histograms are useful to determine whether the sensor is adjusted properly !
The histogram indicates the rate the pacemaker would be pacing if the patient were 100% paced.
If the spontaneous rate is faster than the sensor indicated rate and inhibits the pacemaker, this histogram is an underestimation of the actual heart rate.





BEWARE OF STORED DATA IN THE PACEMAKER MEMORY

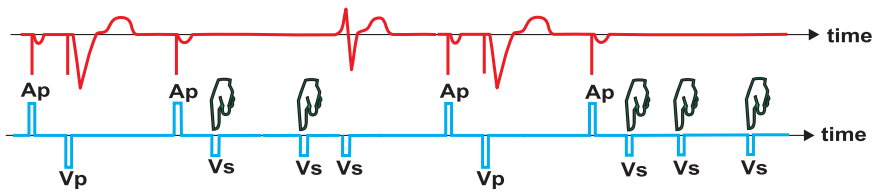




I am a very smart pacemaker because I can tell precisely when stimuli are delivered to the atrial and ventricular channels. I also know exactly when I sense activity from the atrial and ventricular channels. I relay this information faithfully to the marker channel for visual proof.
Sorry, but I am not smart enough to know whether a stimulus actually captures the heart and I have no idea whatsoever whether a sensed event is physiologic or some undesirable potential.

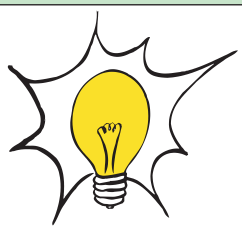
The pacemaker is right ! It's really up to us to determine the presence of capture and the precise nature of the sensed events.
You know that the simultaneous display of markers and real-time electrograms by telemetry can pinpoint the exact nature of a sensed event which is impossible with markers alone.
However, the electrogram has limitations because it cannot tell us whether capture has occurred.

A simultaneously recorded electrogram might reveal the true nature of the oversensed signals : false signals from a defective lead? myopotentials? electromagnetic interference? etc.



LIMITATIONS OF STORED DATA :

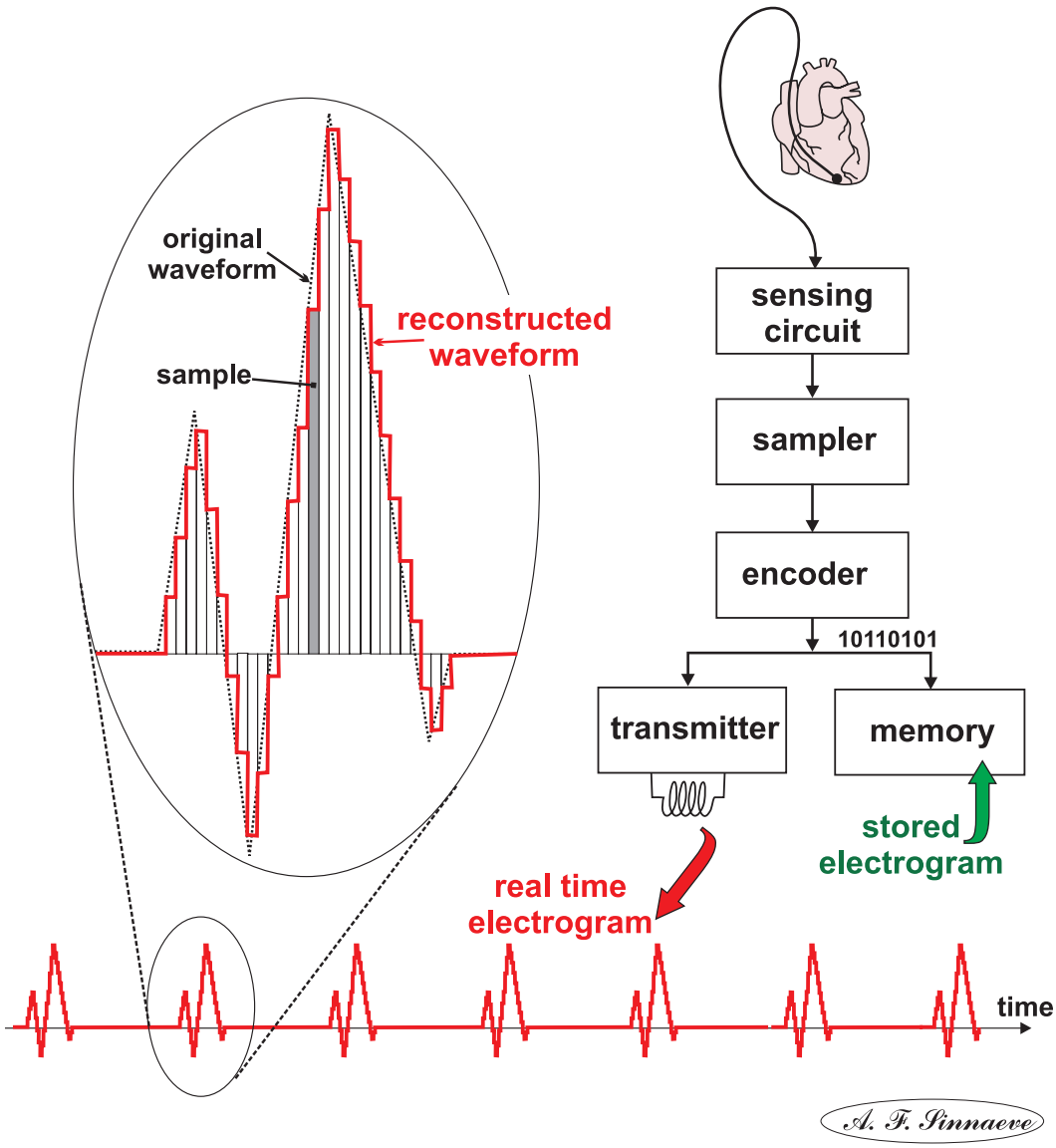
* Many VPCs at a low rate may indicate atrial undersensing with intact AV conduction
* A large percentage of As-Vp complexes may indicate AV block or an AV interval programmed too short
* A majority of Ap-Vp or Ap-Vs complexes do not allow the diagnosis of atrial chronotropic incompetence without knowing the actual rates achieved in each pacing state



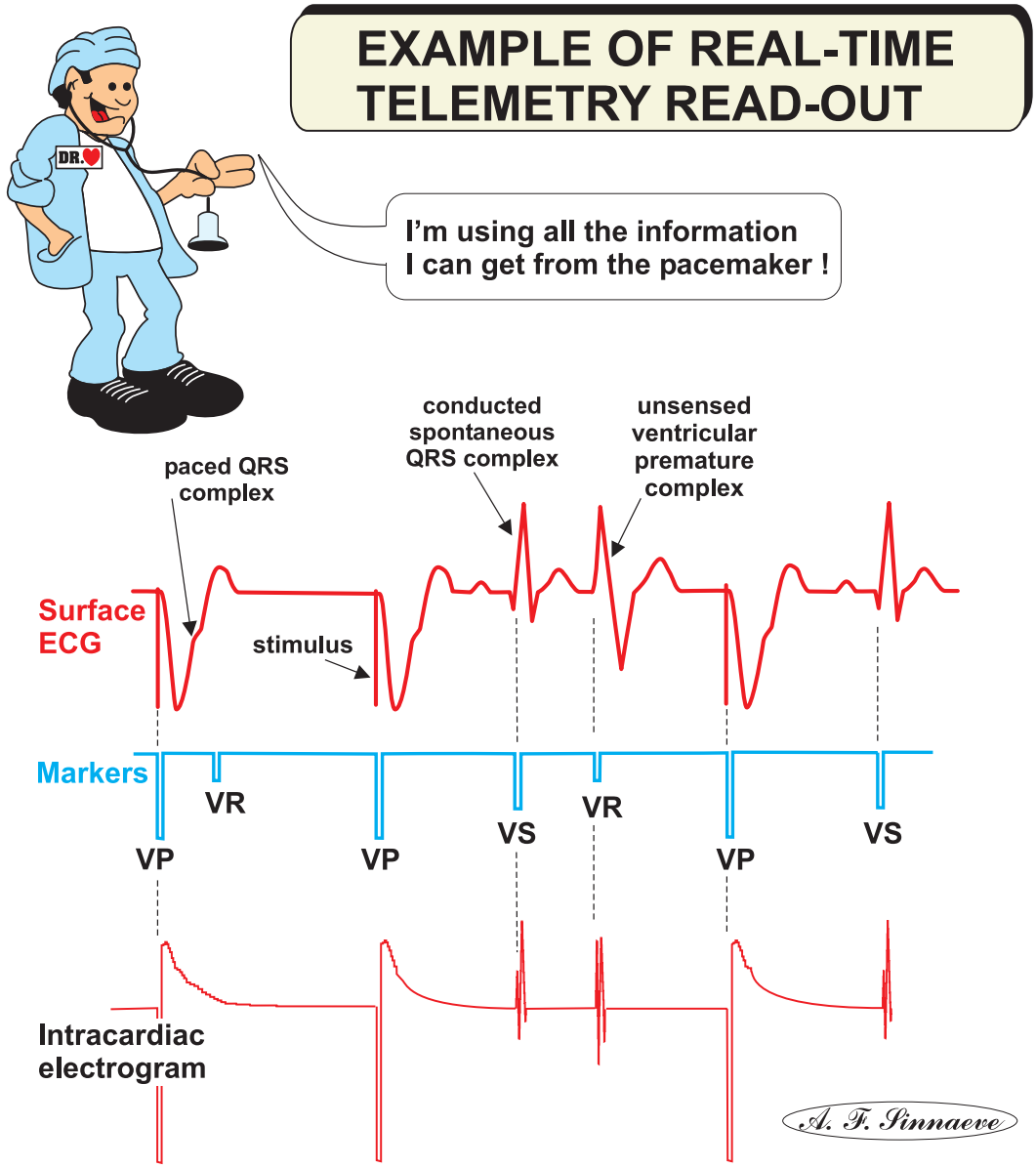
A true pacemaker problem could be missed if one relies only on the counters. However, counter data is useful when one is absolutely certain that the pacemaker system is functioning normally.

A. F. Sinnaeve

TELEMETERED VENTRICULAR ELECTROGRAM



EXAMPLE OF REAL-TIME TELEMETRY READ-OUT



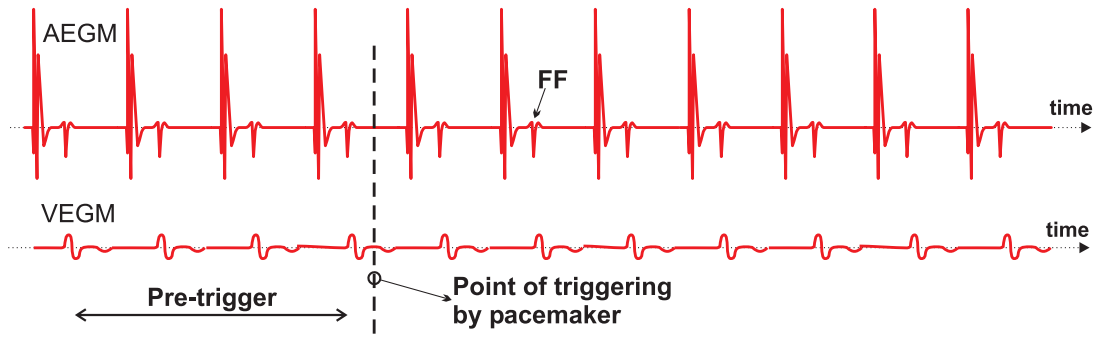
Abbreviations : VP = ventricular pace ; VS = ventricular sense ; VR = ventricular sense in the refractory period

STORED ELECTROGRAMS AN ASSISTANCE FOR DIAGNOSIS PART 1

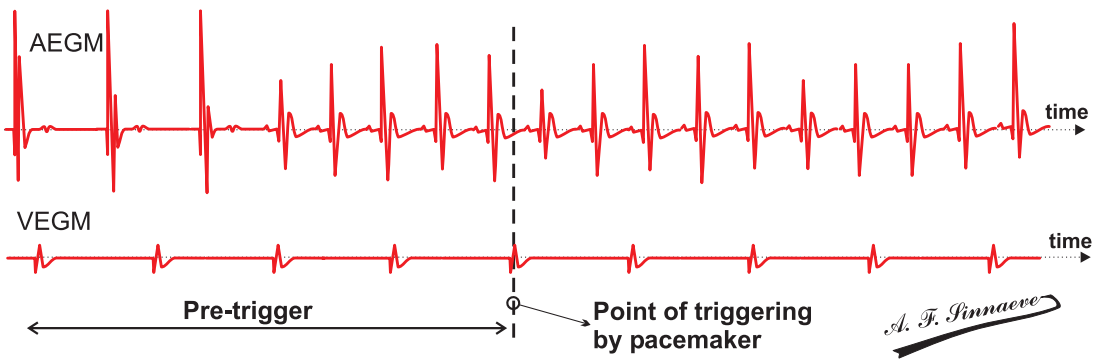
THE GOLD STANDARD

1. Separate channels for atrial and ventricular EGMs of sufficient resolution and duration.
2. An EGM scale to quantify signal amplitude and thus discriminate between small far-field signals, intrinsic beats, and giant false signals generated by lead disruption.
3. Onset and termination data : a programmable number of cardiac cycles before arrhythmia onset (pre-trigger EGM) and some cycles after arrhythmia termination to distinguish between correct detection of the onset of a new episode such as immediate or early recurrence of AT and intermittent signal dropout.
4. Marker annotations and intervals to facilitate understanding why and how the pacemaker detected and classified an event. An additional marker (e.g. arrow, line) should indicate the exact moment when arrhythmia detection criteria were fulfilled.

VA CROSSTALK - Sinus rhythm labeled SVT by the pacemaker. Note the far-field R wave in the atrial electrogram sensed by the atrial channel



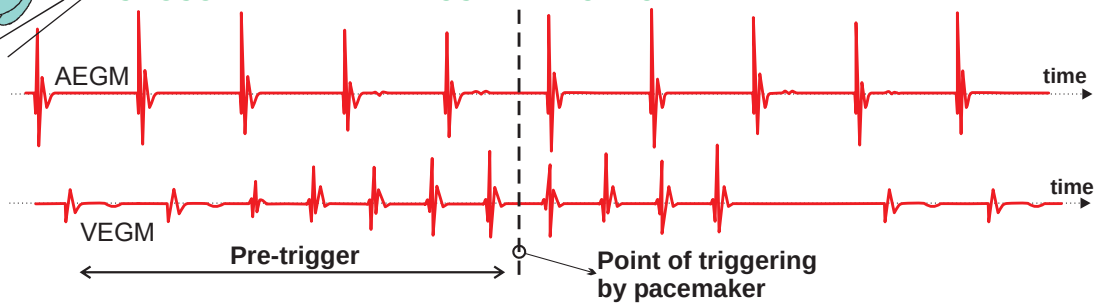
INITIATION OF ATRIAL FLUTTER



Abbreviations : AEGM = atrial electrogram ; AT = atrial tachycardia ; EGM = electrogram ; FF = far-field R wave ; SVT = supraventricular tachycardia ; VEGM = ventricular electrogram

STORED ELECTROGRAMS AN ASSISTANCE FOR DIAGNOSIS PART 2

UNSUSTAINED VENTRICULAR TACHYCARDIA



ATRIAL FIBRILLATION RECORDED BY MAGNET ACTIVATION OVER THE PM WHEN THE PATIENT WAS SYMPTOMATIC

ADVANTAGES OF STORED EGMs

1. Markers without simultaneous EGM recordings are of limited value in diagnosis
2. The many pitfalls must be recognized. The PM diagnosis may be incorrect. However, visual inspection of EGMs and markers guarantees the right diagnosis in almost 100% of cases.
3. Explanation of symptoms by patient's triggered recordings.
4. EGM recordings permit fine-tune programming of the device.
5. Identify AT and VT onset mechanisms which may have therapeutic implications

LIMITATIONS OF DEVICES IN AT DIAGNOSIS

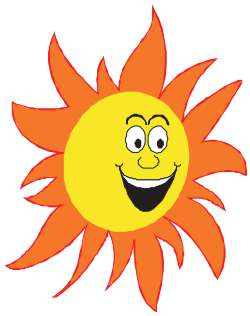
1. Intermittent atrial sensing : a single AT episode will be stored as multiple short episodes
2. Atrial undersensing : may cause the PM to make the false diagnosis of VT
3. Long blanking period will cause 2 : 1 undersensing of atrial flutter
4. Far-field R wave oversensing causes false diagnosis of AT by PM

FACTORS INFLUENCING AT DETECTION

1. The detection algorithm of the PM
2. The signal quality and the programmed sensitivity
3. Timing cycles : blanking periods

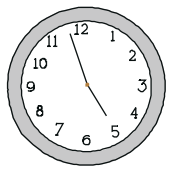
A. F. Simmaeve

Abbreviations : AEGM = atrial electrogram ; AT = atrial tachycardia ; EGM = electrogram ; PM = pacemaker ; SVT = supraventricular tachycardia ; VEGM = ventricular electrogram ; VT = ventricular tachycardia



CONCLUSION

* Professional success
* Ten commandments of pacemaker care



Timing !!!!

A. F. Sinnaeve

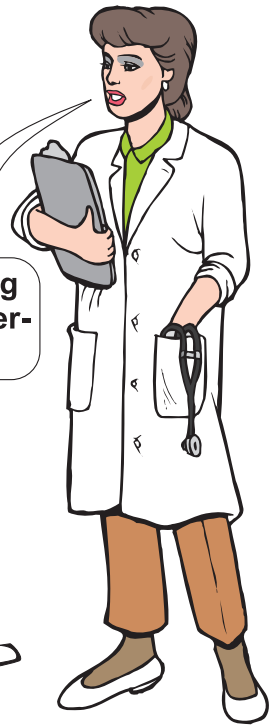
PROFESSIONAL SUCCESS

The secret of my success ?

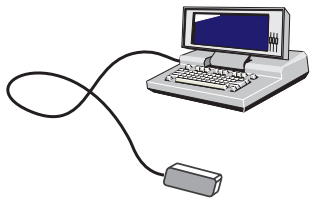
LOCATION ! LOCATION ! LOCATION !

The secret of my success ?

Pacemaker timing cycles !
Pacemaker timing cycles !
Pacemaker timing cycles !



I agree ! Knowing the timing cycles is the secret to understanding pacemakers

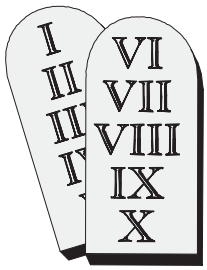


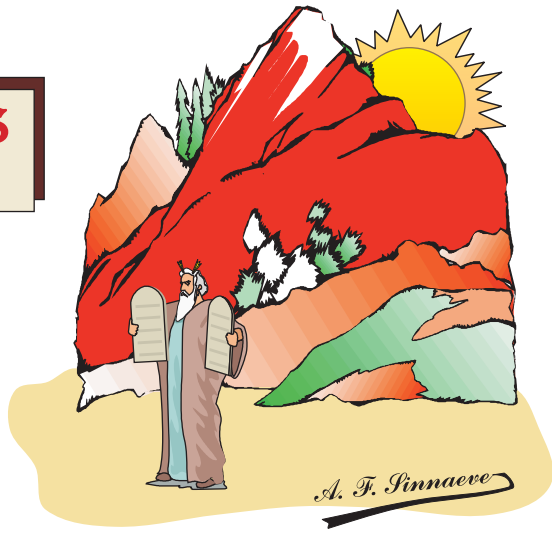
A. F. Sinnaeve

"All comprehension of pacemaker electrocardiography depends on the interpretation of pacemaker timing cycles"

SEYMOUR FURMAN MD, pioneer in cardiac pacing

THE 10 COMMANDMENTS OF PACEMAKER CARE





1. Thou shalt take long rhythm strips with markers and electrograms and thou shalt be rewarded with correct diagnosis.
2. Ignore the value of the 12-lead paced ECG at your own peril.
3. Know the timing cycles and you will know the pacemaker.
4. The purpose of antibradycardia pacing is not simply to treat bradycardia but to restore the quality-of-life.
5. Do not attribute a patient's symptoms to old age before you exclude a reversible cause such as pacemaker syndrome.
6. Leaving a pacemaker at factory settings (out-of-the-box parameters) without programming is a sin ! Like drug therapy, there is a pacemaker prescription for the individual patient and it should be changed according to circumstances.
7. Make every effort to conserve battery life and provide an appropriate safety margin by carefully programming voltage output and pulse duration.
8. The optimal AV delay cannot be predicted in the individual patient
9. You shall live in eternal damnation if you fail to test for retrograde ventriculoatrial conduction and program the pacemaker accordingly.
10. You will be banished into the wilderness for ever, if you fail to keep meticulous records of pacemaker follow-up.

Text: overview of cardiac pacemakers

Implantation

A pacemaker (also known as a pulse generator) is a device that delivers electrical stimuli over leads with electrodes in contact with the heart. The lithium–iodine battery is sealed in a titanium can and provides electricity through a chemical reaction. The pacemaker is like a little computer. The epoxy connector block on top of the pacemaker makes the connection from lead to pacemaker. The lead is an insulated wire. There are two types of leads: bipolar with the two electrodes embedded inside the heart; and unipolar with one electrode inside the heart and the other electrode being the pacemaker can. Both types are widely used. In both types, the tip electrode is virtually always the negative pole or cathode. Virtually all pacemakers are implanted intravenously under local anesthesia using either the cephalic vein exposed by surgery or percutaneous puncture of the subclavian vein. The leads are passed to the right side of the heart under X-ray vision (fluoroscopy). More recently for the treatment of heart failure, the left ventricle may be paced by insertion of a lead into a tributary of the coronary sinus, a venous structure on the epicardial surface of the left ventricle. The pacemaker pocket is fashioned over the pectoralis major muscle below the collar bone. True epicardial leads require thoracic surgery and are used only when there is no venous access.

Basic function

The pacing lead functions as a "two-way street" for the transmission of electricity to the heart for pacing as well as for the sensing of spontaneous cardiac electric activity from the heart to the pacemaker. The operative techniques and intraoperative measurements are straightforward compared to the technical knowledge required to understand the electrophysiology of pacing and follow-up of patients for the best use of the important programmable functions. The function of an implanted pacemaker can be altered by means of a programmer, which is a type of dedicated desktop computer. A modern pacemaker lasts 7–10 years. When the battery is depleted, the entire pacemaker (excluding the leads) is replaced.

Power source

The lithium–iodine battery is the gold standard of pacemaker power sources and the only one presently used in pacemakers. The battery has a long shelf life and can be hermetically sealed to protect the electronic components of the pacemaker. In lithium–iodine batteries, lithium is the anode and iodine the cathode. When delivering electric current, this battery progressively develops a slow rise in internal resistance that can be measured by telemetry. The rising battery impedance causes a fairly linear drop in cell voltage translated by design into a gradual decline in the pacing rate reflecting the status of the battery. The battery retains a satisfactory voltage for 90% of its life. Battery capacity expressed in ampere-hours is the quantity that expresses the longevity of a lithium–iodine battery. A pacemaker generally holds a capacity between 0.8 and 2.5 Ah (ampere-hours).

The current drain from the battery (expressed in microamperes, μA) is used to produce the stimulus and to feed the various sensing, detection and "housekeeping" electronic circuits. The output voltage of a fresh cell is 2.8 V (volt). The cell voltage at the elective replacement point is 2.2–2.4 V. The pacemaker replacement time can be determined by measuring the pacemaker rate upon application of a magnet or the battery voltage and/or impedance by telemetry with the programmer.

Reminder: The pacemaker (or pacing) stimulus is also known as a spike, an artifact or an output pulse.

Caveat: Do not confuse cathode with anode! The terminology of the battery terminals appears different from that of the load. For the battery, the anode is the negative electrode where electrons are freed from lithium atoms and *positive* lithium ions are produced. In the battery the cathode is the positive terminal where free electrons rebind with iodine to form *negative* iodide ions. At the load, the cathode is the negative terminal and the anode is the positive

one. The connection of battery to circuit is simple: positive to positive and negative to negative. Remember that the anode of the battery or load is where the electrons leave. The cathode of both the battery and load is where the electrons enter. It is as simple as that! These are the universal definitions found in all good books about electricity and/or electronics. It is not true that the anode and cathode of the battery are reversed by convention. The only convention is that the electric current flows from positive to negative.

Rate or interval?

The pacemaker, design engineers, and medical staff all "think" in terms of intervals rather than rate. The term rate should not be used when defining timing cycles. Rate is a relatively simple designation during continuous pacing or continuous inhibition, but it is of little value and confusing if pacing and sensing alternate. Yet for ease of programming, manufacturers have expressed parameters in terms of rate rather than interval. Programmed rates may also be useful when communicating with the patient or anyone with little knowledge of pacing. The abbreviation b.p.m. refers to beats per minute of the intrinsic heart rate and p.p.m. refers to the paced rate. These abbreviations, however, are often used interchangeably.

Caveat: Peculiar rhythms are created by electrocardiograph (ECG) machines and Holter recorders functioning at an incorrect speed. In a Holter recording, intermittent slowing of the recording will cause a pseudotachycardia. The diagnosis is evident when the duration of the QRS and T waves are too narrow when compared to those recorded at normal speed. Conversely, a faster speed will cause pseudobradycardia, with excessively long atrioventricular (AV) delays or PR intervals as well as QRS complexes.

Single chamber pacemakers

A ventricular asynchronous (VOO) pacemaker generates stimuli with no relationship to the spontaneous rhythm. The VOO mode is labeled "fixed-rate" or asynchronous. The competitive stimuli will capture the ventricle only when they fall outside the absolute refractory period of the ventricle that follows spontaneous beats. The VOO mode is now obsolete and used only for testing purposes by applying a magnet over the pacemaker. Ventricular fibrillation induced by a competitive pacemaker stimulus falling in the ventricular vulnerable period (the R-on-T phenomenon) is very rare outside of circumstances such as myocardial ischemia or infarction, electrolyte abnormalities or autonomic imbalance. Indeed transtelephonic transmission of the electrocardiogram with a magnet over a pacemaker is quite safe.

A ventricular inhibited (VVI) pacemaker senses the intracardiac ventricular depolarization or electrogram which is recorded by measuring the potential (voltage) difference between the two electrodes (anode and cathode) used for pacing. A VVI pacemaker has an internal clock or lower rate timing cycle that begins with a paced (VP) or sensed ventricular event (VS). The initial portion of the cycle (after VP or VS) consists of the ventricular refractory period (*VRP*, usually 200–350 ms) during which the pacemaker cannot sense any signals. More specifically, any signal during the refractory period cannot initiate a new lower rate interval (*LRI*). Beyond the *VRP*, a sensed ventricular event inhibits the pacemaker and resets the *LRI* so that the timing clock returns to baseline. A new pacing cycle is reinitiated and if no event is sensed, the timing cycle ends with the release of a ventricular stimulus according to the *LRI*. The sensing function prevents the competition between pacemaker and intrinsic rhythm that is seen with VOO pacing. Hence, the old term "demand pacemaker" for a VVI pacemaker to describe the delivery of a stimulus when the spontaneous rate is less than the lower rate of the pacemaker.

Caveats:

1. When a patient presents with an ECG showing no pacemaker stimuli, the pacing function should be tested by the application of a pacemaker magnet, which converts any pacemaker to the fixed-rate or asynchronous mode (VVI to VOO). One should refrain from performing carotid sinus massage (a vagal reflex producing sinus node slowing and AV block) in this situation because it may cause prolonged bradycardia resulting in the delivery of pacemaker stimuli that may or may not be capable of capture. It is safer first to establish effective pacing with magnet application.
2. The stimulus-to-stimulus interval (automatic interval) is usually equal to the escape interval, which is measured electronically from the time of intracardiac sensing to the succeeding stimulus. In practice, the escape interval is measured from the onset of the sensed QRS complex in the surface ECG. The escape interval measured in this way must necessarily be longer than the electronic escape interval because intracardiac sensing takes place a finite time after the onset of the surface ECG. Thus, if the QRS complex is wide and intracardiac sensing occurs 90 ms from the beginning of the surface ECG, the measured escape interval (with calipers) will be 90 ms longer than the programmed automatic interval.

Hysteresis

In hysteresis the electronic escape interval is longer than the automatic interval. Its purpose is to maintain sinus rhythm and AV synchrony for as long as possible at a spontaneous rate lower (e.g. 50 b.p.m.) than the automatic rate of the pacemaker (e.g. 70 p.p.m.). Thus when the spontaneous rate drops below 50 b.p.m., the pacemaker will take over at 70 p.p.m. It will continue to pace at 70 p.p.m. until the spontaneous rate exceeds the automatic rate, i.e. when the spontaneous QRS complex occurs within the 857 ms automatic interval.

Caveat: Do not misinterpret hysteresis for oversensing with pauses.

Symbolic representation of pacemaker events and basic measurements

Symbols are as follows: AS (P), atrial sensed event; AP (A), atrial paced event; VS (R), ventricular sensed event; VP (V), ventricular paced event; AR, atrial event sensed in the pacemaker refractory period; VR, ventricular event sensed in the ventricular refractory period. The second letter may be a capital or lower case. Note that in the designation using a single capital letter for an event (P, A, V, R), AR represents an AV interval (atrial pacing, ventricular sensing) and should not be confused with an atrial sensed event in the refractory period in the other designation (AR or Ar). Some devices depict a ventricular premature complex as a VPC or PVC. The refractory period is defined below. The intervals between events are measured by electronic calipers.

Timing cycles are expressed in milliseconds (ms): 1 s =1000 ms.

The 60 000 rule is useful in converting rate to intervals:

60 000/heart rate = interval in milliseconds;

60 000/interval in milliseconds = heart rate.

A pacemaker rate of 70 p.p.m. gives an interval of 857 ms.

Other single chamber pacemakers

A ventricular triggered (VVT) pacemaker releases a ventricular stimulus immediately upon sensing, which is the opposite of inhibition with the VVI mode. The VVT mode requires three timing intervals: *LRI* and *VRP* similarly to the VVI mode, but additionally it needs an upper rate interval to limit the maximum paced ventricular rate in response to ventricular sensing of rapidly occurring potentials. Upon sensing a QRS complex the pacemaker immediately discharges a stimulus (within it) in the absolute refractory period of the ventricular myocardium. The VVT mode ensures stimulation rather than inhibition whenever the pacemaker senses signals other than the QRS complex. The triggered mode is now rarely used as a primary pacing mode, but it was useful in the early days when VVI pacemakers were highly susceptible to external interference and the VVT mode was used to prevent inhibition.

An atrial inhibited (AAI) pacemaker is identical to the VVI mode except that it paces and senses in the atrium. It requires a higher sensitivity because the atrial electrogram is smaller than the ventricular one. The pacemaker refractory period (during which the *LRI* cannot be initiated) should be > 400 ms to prevent sensing of the conducted QRS complex as a far-field event in the atrial electrogram. Sensing of the far-field QRS complex by an AAI pacemaker (especially a more sensitive unipolar system) will cause slowing of the pacing rate because the sensed event (though not originating from the atrium itself) resets the *LRI*. An AAI pacemaker may be considered in patients with sick sinus syndrome with normal AV conduction. The subsequent development of AV block in carefully selected patients is < 2% per year. The advantages of AAI pacing are related to the preservation of normal ventricular depolarization and cost effectiveness. This is in contrast to modes with pacing-induced ventricular depolarization that tend to produce long-term left ventricle (LV) dysfunction related to the cumulative duration of right ventricular (RV) pacing.

Reminder: An appropriately programmed AAI pacemaker senses the normal P wave, and occasionally retrograde P waves and ventricular premature beats. The latter may be sensed despite the absence of a ventricular lead because ventricular depolarization can generate a far-field QRS signal on the atrial electrogram, which may be detected by an AAI pacemaker and interpreted as an atrial signal. Sensed signals other than sinus P waves may create puzzling pauses.

The atrial asynchronous (AOO) and atrial triggered (AAT) modes work in the atrium and are functionally similar to their ventricular counterparts.

Basic electricity

Electrons flow from the negative terminal to the positive terminal of an electric circuit. In the early days, the concept of electron flow was not fully understood so scientists randomly decided that current in a conductor flowed from the positive terminal and into the negative terminal. It is still convention (and confusing to some) today to show current flowing in this direction (i.e. opposite to electron flow). Current is the amount of charge (electrons or other charged

particles) that flows through an electric circuit within a unit of time. Its unit is the ampere (A). The flow of water is a good analogy of electricity. Water flows through a pipe because of water pressure. Voltage is the potential difference that controls the flow of electrons through an electric circuit. Current flows from a site of high potential to a low one. The basic unit of electric potential and voltage is the volt (V). The electrons in a pacemaker circuit come from the battery. Thus, voltage is the force behind the electrons and current is a measure of how many electrons are flowing per unit of time. Resistance or impedance is a measure of the opposition to the flow of electrons. Resistance limits the current that flows through a circuit for a particular applied voltage. The unit of resistance is the ohm (Ω).

Current (I), voltage (V) and resistance (R) are related by Ohm's law: $V = I \times R$. According to Ohm's law an increase in the pressure (voltage) must cause an increase in the flow (current) if the resistance remains the same. Increasing the resistance while keeping the voltage the same, decreases the current (flow).

The battery supplies the voltage that creates the flow (current) in a circuit with a given load or resistance. The battery capacity expresses "how long the battery will last while providing a current of 1 A." It is measured in ampere-hour (Ah). So a battery with a capacity of 1000 mAh would last for 1 h in a 1 A circuit. (1000 mAh is 1 A for 1 h). A lithium–iodine battery with a capacity of 2 Ah in a pacemaker circuit with a current drain of 25 μA (= 0.000 025 A) will last for 2 Ah ÷ 0.000 025 A = 80 000 h or approximately 3333 days = approximately 9 years.

Chronic pacing threshold and safety margin

The pacing threshold is the minimum "electrical activity" that causes consistent pacing outside the myocardial refractory period of the heart. In practice the pacing threshold is determined in terms of volts (V) and pulse duration. Every effort should be made at the time of implantation to obtain a pacing threshold as low as possible because its initial value may ultimately determine the threshold at maturity and hence the voltage and pulse duration required for safe long-term pacing. Local steroid elution attenuates the increase of pacing threshold during lead maturation and maintains low pacing thresholds during follow-up. Steroid elution has made the implantation of high-efficiency pacing leads with a small surface of 1.2 mm^2 feasible. Steroid-eluting leads are associated with remarkably low pacing threshold by virtue of their effect on the electrode–myocardial interface and tissue reaction. About 8 weeks after implantation the pacing threshold has usually stabilized and attained its chronic value. The output voltage and pulse duration of the pacemaker should then be programmed to maintain consistent long-term capture with an adequate margin of safety and maximal conservation of battery capacity. The capture threshold can vary during the course of a normal day and according to metabolic and pharmacological factors. Consequently it is important to provide protection for threshold fluctuations by a safety margin in terms of the pacemaker output.

In practice, the safety margin is determined in terms of volts and not pulse duration. The general recommendation is a voltage safety margin of 2 (or 100%). The output voltage of the pacemaker should be double the chronic voltage threshold at the same pulse duration. Voltage safety margin = output voltage/threshold voltage = 2:1 at an identical pulse duration. This value is acceptable in pacemakers without automatic adjustment of the output. However, the concept of a 2:1 safety margin has been challenged in view of data gathered by systems capable of automatic determination of the pacing threshold and adjustment of the output pulse. This experience has shown that for a few patients a safety margin of 2:1 may not be sufficient. Indeed, some physicians program a larger safety margin in pacemaker-dependent patients.

The relationship of voltage and pulse duration at threshold and at any time afterwards is not linear and is represented by the *strength–duration curve*. A shorter pulse duration requires a higher voltage to attain the pacing threshold. The strength–duration curve is steep with a short pulse duration and becomes essentially flat at a pulse duration of > 2 ms, a point which is called the rheobase. The curve shifts to the right as the chronic pacing threshold becomes established. Although the terms rheobase and chronaxie are used to describe the strength–duration curve, they are rarely used in the routine follow-up of pacemaker patients.

Important reminders:

1. At a fixed voltage, increasing the pulse duration from 0.1 to 0.2 ms may not necessarily yield a voltage safety margin of 2 or 100% despite the steepness of the strength–duration curve (on the left) for short pulse durations.
2. At a fixed voltage, tripling the pulse duration (not starting beyond 0.2 ms) will provide an adequate voltage safety margin based on the configuration of the strength–duration curve. Thus, a threshold of 2.5 V at 0.2 ms permits a programmed "chronic" output of 2.5 V at 0.6 ms for a voltage safety margin of 2.
3. When the pulse duration is ≥ 0.3 ms, tripling the pulse duration when keeping the voltage con-

stant may not provide a voltage safety margin of 2 because of the less steep and eventually straight configuration of the strength–duration curve (on the right) at longer pulse durations.

4. The relatively flat configuration of the strength–duration curve from 0.5 to 1.5 ms indicates that an increase in pulse duration in this range (keeping the voltage constant) will certainly not provide a voltage safety margin of 2.
5. Try to pace at a voltage lower than the traditional output of 5 V for greater efficiency and less wasted battery output.

Supernormal phase

The pacing threshold is lowest during a short period corresponding with the second half of the T wave. Consistent ventricular capture during this period and failure at other times, suggests that the pacemaker output is near threshold.

Considerations in pacing threshold

Let us consider some examples:

(a) threshold 2.5 v at 0.1 ms: program 2.5 v at 0.3 ms;
(b) threshold 2.5 v at 0.2 ms: program 2.5 v at 0.6 ms;
(c) threshold 2.5 v at 0.3 ms: program 5v at 0.3 ms;
(d) threshold 0.5 v at 0.2 ms: this is a very low pacing threshold; the pacemaker can be programmed at 0.5 V 0.6 ms but many would prefer going to 1 V at 0.4 or 0.5 ms, a setting that would still provide substantial battery conservation;
(e) threshold 5 V at 0.3 ms; increasing the pulse duration when the voltage is fixed at 5 V may not provide an adequate voltage margin. Increase the voltage output above 5 V if available in the pacemaker. If not, watch the patient carefully for bradycardia and asystole and decide whether to reposition the lead or implant a high output pulse generator providing a 10 V output.

Reminder: The chronic pacing thresholds are < 2.5 V at 0.5 ms pulse duration in > 95% patients with steroid-eluting leads. Patients with such leads rarely have a significant pacing threshold increase compared to those with nonsteroid leads. Consequently it does not make sense to leave the output (voltage and pulse duration) at nominal values. Appropriate programming of the pacemaker output can increase battery longevity. Furthermore, as the voltage of the lithium–iodine battery is 2.8 V, pacing is more efficient when performed close to that voltage (i.e. 2.5 V).

Caveats:

1. Always test the pacing threshold on deep respiration and coughing to detect an unstable electrode.
2. In the presence of left bundle branch block with a QRS complex resembling a paced ventricular beat, pseudocapture will be seen when the rate of the pacemaker stimulus is very close to that of the spontaneous rhythm and the stimulus falls just before the spontaneous QRS complex. This may resemble capture with latency (delayed interval from stimulus to ventricular activation). Long rhythm strips are needed for the diagnosis which will be obvious when the ventricular stimulus moves away from the QRS complex.
3. Beware of isoelectric paced QRS complexes that can mimic lack of capture. Look for the T wave because the presence of repolarization means that depolarization must have occurred.

Automatic determination of the pacing threshold

Some pacemakers have algorithms that periodically and automatically measure the ventricular capture threshold. The pacemaker recognizes the presence of capture, provides a stronger backup pulse if there is loss of capture and then adjusts the output automatically at a given value over the pacing threshold. Such periodic threshold measurements are memorized by the device and the threshold graph during the preceding follow-up period can be retrieved by interrogation of the pacemaker. Autocapture has increased patient safety but it is still unclear whether it increases battery longevity.

Some programmers are also designed to perform a pacing threshold test automatically at the time of follow-up and a printout of the procedure can be filed in the pacemaker chart.

Sensing

A pacemaker senses the potential difference between the two electrodes (anode and cathode) used for pacing. A bipolar system senses the potential difference between the two electrodes in the heart and requires recording of the bipolar electrogram to determine the characteristics of the signal available for sensing. The final bipolar electrogram depends on the electrograms registered at the two sites and the travel time of depolarization between the two electrodes. The bipolar electrogram can be easily recorded at the time of implantation with an ECG machine (leads applied to the two legs) by connecting the tip and proximal electrodes of the pacing lead to the free or loose right arm and left arm electrodes. Then, by using lead I on the ECG machine the bipolar electrogram can be recorded. This is because lead I provides the potential difference between the two arms and therefore the potential difference between the two intracardiac electrodes.

For a unipolar system (one electrode in the heart and the other on the pacemaker can), the unipolar

electrogram from the tip electrode closely resembles the available voltage for sensing. The contribution from the unipolar plate is usually so small that it can be neglected. The unipolar electrogram can be easily recorded by connecting the unipolar V lead of the ECG to the tip electrode while the other ECG electrodes are on the limbs in the usual way. The amplitude and slew rate of the electrogram must exceed the sensitivity of the pacemaker for reliable sensing. The ventricular signal often measures 6–15 mV, a range that exceeds the commonly programmed ventricular sensitivity of 2–3 mV. Occasionally a pacemaker senses the conducted QRS complex normally, but does not detect some ventricular extrasystoles because their electrogram (originating from a different site) is smaller, a situation not always correctable by reprogramming ventricular sensitivity. This is an accepted limitation of the sensing function of pacemakers. The atrial signal is smaller and should ideally exceed 2 mV. A signal with a gradual slope is more difficult to sense than one with a sharp upstroke. If the signal amplitude is large enough, the slew rate will always be sufficient and need not be measured. Determination of the slew rate is most useful when a signal is low or borderline (3–5 mV in the ventricle). On a long-term basis, the amplitude of the signal diminishes slightly but the slew rate may diminish further. These changes are usually of no clinical importance for sensing, except in the case of smaller signals.

The sensing circuit contains a bandpass filter that transmits some electrical frequencies more freely than others. A pacemaker filter is designed to pass all the signals of interest with negligible loss of amplitude and attenuate unwanted signals such as T waves or external interference. A typical bandpass filter favors the passage of signals with a frequency of 20–80 Hz in order to sense the wide range of QRS complexes and attenuates signals outside this range such as the T wave.

Caveat: The escape interval in a VVI pacemaker is measured from the onset of the surface QRS complex. In pacemakers with identical automatic and electronic escape intervals, the measured escape interval must of necessity be longer than the automatic interval by a value ranging from a few milliseconds to almost the entire duration of the QRS complex (with "late" sensing) depending on the temporal relationship of the intracardiac electrogram and the surface ECG. Do not confuse this with hysteresis.

Sensitivity

Programmability of sensitivity is important because the ideal electrode for sensing does not exist. Sensitivity is a measure of the minimal potential difference required between the terminals of a pacemaker to suppress its output. Looking above a wall is a good analogy of the numeral representation of sensitivity. The higher the wall, the less one will see above it. The lower the wall, the more one will see above it. The higher the numerical value of sensitivity, the less sensitive the pacemaker becomes. Thus, a setting of 6 mV can only sense a signal of 6 mV or greater and cannot sense signals smaller than 6 mV. On the other hand, a "higher" sensitivity of 1 mV will allow sensing of all signals of 1 mV or larger. The sensing threshold is determined by programming the pacing rate lower than the intrinsic rate while the sensitivity is gradually reduced (larger numerical value in mV) until failure to sense is observed. The sensing threshold is the largest possible numeric sensitivity value associated with regular sensing. As a rule, sensitivity should be programmed at a numerical value at least half the threshold value, e.g. from a sensing threshold of 8 mV one can program a sensitivity of 4 mV. Oversensing requires a decrease in sensitivity (increase in the numerical value). Most programmers now permit a fully automatic assessment of the signal amplitude at the time of follow-up. These measurements are taken from the sense amplifier and represent the signal amplitude after it has been processed.

Caveats:

1. Always test appropriate sensing, especially atrial sensing, with deep respiration to unmask significant fluctuations of the signal with respiration.
2. The absolute amplitude of the signal measured from the electrogram is only a rough approximation of the signal used for sensing. This is because the sensing circuit filters and processes the signal for sensing.

Polarity: unipolar vs. bipolar pacing and sensing

New lead technology and design have eliminated the previous advantage of unipolar leads. In practice, the long-term performance of unipolar and bipolar systems is similar. Bipolar leads by virtue of their greater signal-to-noise ratio (promoting greater protection against extraneous interference) allow the use of higher sensitivities. A high sensitivity is especially useful for atrial sensing, an important requirement of contemporary dual chamber pacemakers with the capability of diagnosing supraventricular tachyarrhythmias. This diagnosis permits a change in the pacing mode automatically to avoid rapid ventricular pacing. Bipolar leads are also associated

with less crosstalk in dual chamber pacemakers (ventricular sensing of the atrial stimulus). Bipolar leads are less sensitive than unipolar systems to external interference (myopotentials, etc.). The configuration of many pacemakers is programmable to either the unipolar or bipolar mode (provided they have bipolar leads) to correct certain pacemaker problems. In some devices when the circuit detects a high impedance (resistance) from a fracture in one of the electrodes, the pacemaker can automatically change from the bipolar to the unipolar mode of pacing using the intact electrode.

Reminders:

1. The tip electrode is almost always the cathode because the cathodal pacing threshold is lower. In a bipolar system the proximal (ring) electrode is the anode, and in a unipolar system a plate on the pacemaker can becomes the anode.
2. Contemporary pacemakers allow programming of unipolar or bipolar function in a variety of ways in individual channels: pacing only, sensing only, or both. A bipolar lead can be unipolarized by using either the tip or the ring electrode as the only intracardiac electrode for sensing and/or pacing.

Ventricular fusion and pseudofusion beats

Ventricular fusion beats occur when the ventricles are depolarized simultaneously by spontaneous and pacemaker-induced activity. A ventricular fusion beat can exhibit various configurations depending on the relative contributions of the two foci involved in ventricular activation. A ventricular fusion beat is often more narrow than a pure ventricular paced beat. Fusion therefore occurs in the heart itself.

Ventricular pseudofusion beats consist of the superimposition of an ineffectual ventricular stimulus on a surface QRS complex originating from a single focus and represent a normal manifestation of VVI pacing. A VVI pacemaker obviously does not sense the surface QRS complex. Rather, it senses the intracardiac ventricular electrogram registered between the two pacing electrodes. A substantial portion of the *surface* QRS complex can be inscribed before the *intracardiac* electrogram generates the required voltage (according to the programmed sensitivity) to inhibit the ventricular channel of a VVI pacemaker. Thus a VVI pacemaker can deliver a ventricular stimulus within the spontaneous QRS complex before the device has the opportunity to sense the "delayed" electrogram generated in the right ventricle as the depolarization reaches the recording site(s). The stimulus thus falls in the absolute refractory period of the ventricular myocardium. The stimulus does not depolarize any portion of the ventricles and true fusion does not occur. The "fusion" occurs on the ECG recording and not in the heart itself as in ventricular fusion. True sensing failure must always be excluded with long ECG recordings. Pacemaker stimuli falling beyond the surface ECG always indicate undersensing. A pseudopseudofusion beat (discussed later) is a variant of a pseudofusion beat seen in patients with dual chamber pacemakers.

Operational characteristics of a simple DDD pacemaker

1. *Ventricular channel*. As in a standard VVI pacemaker, the ventricular channel of an AV universal (DDD) pacemaker requires two basic timing cycles: the lower rate interval (corresponding to the programmed lower rate) and the ventricular refractory period. *The lower rate interval* (*LRI*) of a DDD pacemaker is the longest interval between consecutive ventricular stimuli without an intervening sensed P wave or from a sensed ventricular event to the succeeding ventricular stimulus without an intervening sensed P wave. The *ventricular refractory period* (*VRP*) is traditionally defined as the period during which the pacemaker is insensitive to incoming signals. The function of the ventricular refractory period in a DDD pacemaker is similar to that in a VVI pacemaker. Yet, many pacemakers can now actually sense within part of the refractory period to perform pacemaker functions (and influence certain timing cycles) other than resetting the lower rate interval. The pacemaker ventricular refractory period now focuses only on the lower rate interval which cannot be reset or reinitiated by a ventricular signal falling within the refractory interval. The ventricular refractory period starts with either a sensed or paced ventricular event and is usually equal after pacing or sensing. The lower rate (interval) of many DDD pacemakers is ventricular-based in that it is initiated by a paced or sensed ventricular event. Atrial-based lower rate timing is more complex and is discussed later.
2. *DDD pacing or VVI pacing with an atrial channel*. Now the pacemaker acquires an atrioventricular interval (*AVI*) and an upper rate interval. The *AVI* is the electronic analog of the PR interval and is designed to maintain AV synchrony between the atria and the ventricles. The AV interval starts from the atrial stimulus and extends to the following ventricular stimulus or it starts from the point when the P wave is sensed and also termi-

nates with the release of the ventricular stimulus. "Atrial tracking" is a term used to describe the response of a dual chamber pacemaker to a sensed atrial event which leads to the emission of a ventricular output pulse. Let us assume for now that the AV delay in our simple DDD pacemaker after atrial sensing is equal to that after atrial pacing though they may be different in more complex pacemakers. *The upper rate interval* is the speed limit to control the response of the ventricular channel to sensed atrial activity. For example, if the upper rate interval is 500 ms (upper rate = 120 p.p.m.), a P wave occurring earlier than 500 ms from the previous atrial event (atrial rate faster than 120 p.p.m.) will not be followed by a ventricular stimulus. Such an arrangement allows atrial sensing with 1:1 AV synchrony between the lower rate and the upper rate. The upper rate interval of any DDD pacemaker is a ventricular interval and is defined as the shortest interval between two consecutive ventricular stimuli or from a sensed ventricular event to the succeeding ventricular stimulus while maintaining 1:1 AV synchrony with sensed atrial events. In a simple DDD pacemaker the upper rate interval is intimately related to the electronic refractory period of the atrial channel as discussed later.

3. *Derived timing cycles*. The four basic timing cycles of a simple DDD pacemaker as already explained consist of: lower rate interval (*LRI*), ventricular refractory period (*VRP*), AV interval (*AVI*) and upper rate interval (*URI*). Additional timing intervals can be derived from these 4 basic intervals. Let us assume that the lower rate of our simple DDD pacemaker is ventricular-based. The atrial escape interval is the lower rate interval minus the AV delay. This is sometimes called the VA interval. The atrial escape interval starts with either a ventricular paced or sensed event and terminates with the release of the atrial stimulus. Although derived from two other intervals, the atrial escape interval is crucial in the analysis of DDD pacemaker function because it represents the interval the pacemaker uses to determine when the next atrial stimulus should occur after a sensed or paced ventricular event. In our DDD pacemaker with ventricular-based lower rate timing, the atrial escape interval always remains constant after programming the lower rate interval and AV delay. At this point our simple DDD pacemaker has four basic intervals and one derived interval. As the DDD pacemaker grows in complexity, we shall see how the upper rate interval is best thought of in terms of the total atrial refractory period rather than a truly fundamental interval as considered up to this point for the sake of simplicity in the construction of a simple DDD pacemaker.

4. *Influence of events in one chamber upon the other*. The operation of the two channels of a DDD pacemaker are intimately linked and an event detected by one channel generally influences the function of the other.
   (a) Atrial channel. As in the normal heart, an atrial event must always be followed by a ventricular event after some delay. A sensed atrial event alters pacemaker function in two ways:
      (i) it *triggers* a ventricular stimulus (after a delay equal to the AV interval) provided the ventricular channel senses no signal during the AV interval;
      (ii) it *inhibits* the release of the atrial stimulus that would have occurred at the completion of the atrial escape interval. In other words, it aborts the atrial escape interval which therefore does not time out in its entirety. This is self-evident because the atrial cycle starts with a sensed P wave and there is no need for atrial stimulation immediately after a spontaneous atrial event.

   Therefore the atrial channel functions simultaneously in the triggered mode (to deliver the ventricular stimulus for AV synchrony) and in the inhibited mode to prevent competitive release of an atrial stimulus after sensing a P wave. The function of the atrial channel can thus be depicted in terms of "TI" in the third position of the standard pacemaker code. Because the ventricular channel functions only in the inhibited mode, a DDD pacemaker can be coded as a DDTI/I device which would be more awkward but more correct than the traditional DDD designation.
   (b) Ventricular channel. A sensed ventricular event *outside the AV delay* such as a ventricular extrasystole (or premature ventricular complex) will inhibit the atrial and ventricular channels. The atrial escape interval in progress is immediately terminated and release of the atrial stimulus inhibited. The sensed ventricular event also inhibits the ventricular channel and initiates a new atrial escape interval. Thus both the atrial and ventricular channels are inhibited simultaneously. When a ventricular event is sensed *within the AV delay* there is no need for the pacemaker to release a ventricular stimulus at the completion of the AV delay because spontaneous ventricular activity is already in progress. Therefore the pacemaker aborts the AV delay

by virtue of the sensed ventricular event. The AV delay is thus abbreviated. The sensed ventricular event immediately starts a new atrial escape interval.

5. *Atrial refractory period*. It is axiomatic that the atrial channel of a DDD pacemaker must be refractory during the *AV delay* to prevent initiation of a new AV delay before completion of an AV delay already in progress.
   (a) The postventricular atrial refractory period (*PVARP*) begins immediately after the emission of a ventricular event and is the same after a ventricular stimulus or a sensed ventricular signal. An atrial signal falling within the *PVARP* cannot initiate a programmed AV interval. The *PVARP* is designed to prevent the atrial channel from sensing the ventricular stimulus, the far-field QRS complex (a voltage that can be seen by the atrial channel), very premature atrial ectopic beats and retrograde P waves. In the normal heart, an isolated ventricular event may occasionally be followed by a retrograde P wave because of retrograde ventriculoatrial (VA) conduction (the AV junction being a two-way street). Although this is a physiological phenomenon, it may be hemodynamically unfavorable if it becomes sustained. The *PVARP* should be programmed to a duration longer than the retrograde VA conduction time to prevent the atrial channel from sensing retrograde P waves.
   (b) The total atrial refractory period (*TARP*) is the sum of the AV delay and the *PVARP*. The duration of the *TARP* always defines the shortest upper rate interval or the fastest paced ventricular rate. The AV delay, *PVARP* and the upper rate interval are interrelated in a simple DDD pacemaker without a separately programmable upper rate interval. In such a system, the upper rate interval is controlled solely by the duration of the *TARP* according to the formula: upper rate (p.p.m.) = 60 000/*TARP* (ms). So far, the *TARP* is the upper rate interval in the simple DDD pacemaker being constructed by means of a few timing cycles.
   (c) Sensing in the refractory period. *True or false?* The first part of any refractory period consists of a blanking period during which the pacemaker cannot sense at all. The second part of the refractory period permits sensing and each detected event is often represented symbolically by a "refractory sense marker." In the atrium refractory sensed events cannot initiate an AV delay and in the ventricle they cannot start an atrial escape interval or lower rate interval. In one designation AR and VR depict an atrial refractory sensed event and ventricular refractory sensed event respectively. The rapid and irregular atrial rates in atrial fibrillation if sensed by the atrial channel will inscribe many AR events within the AV delay beyond the initial blanking period (initiated by atrial sensing or pacing) and multiple AR events in the *PVARP* beyond the initial postventricular atrial blanking period initiated by ventricular pacing or sensing.
6. *Upper rate interval vs.* PVARP *as a basic interval.* Now that the function of the *PVARP* is clear, it makes sense to consider the *PVARP* itself as a basic interval controlling the upper rate. In this way the upper rate interval can be demoted to a derived interval. This manipulation converts the upper rate interval of our evolving DDD pacemaker or the *TARP* (*AVI* + *PVARP*) to a derived function.
7. *The six intervals of a simple DDD pacemaker.* According to the above concepts, we now have a DDD pacemaker working with four basic intervals (lower rate interval, ventricular refractory period, AV delay and *PVARP*) and two derived intervals (atrial escape interval, and the *TARP* = upper rate interval). Such a pacemaker can function quite well provided the atrial stimulus does not interfere with the function of the ventricular channel. If it does, the disturbance is called AV *crosstalk* because the atrial stimulus, if sensed by the ventricular channel, can cause ventricular inhibition.
8. *The fifth fundamental timing cycle*. Prevention of crosstalk is mandatory and requires the addition of a brief ventricular blanking period beginning coincidentally with the release of the atrial stimulus. This is known as the *postatrial ventricular blanking* (*PAVB*) period. No signal can be detected during this blanking period. The ventricular channel then "opens" after this short blanking period so that ventricular sensing (with reset of the atrial escape interval and lower rate interval) can occur during the remainder of the AV delay. Obviously a long postatrial ventricular blanking period will predispose to ventricular undersensing. The addition of this important blanking interval yields a DDD pacemaker with five basic cycles and two derived cycles. This format was the basis of first generation DDD pacemakers that were clinically used and accepted. Even a sophisticated contemporary DDD pacemaker reduced to having only these seven intervals would function satisfactorily if appropriately programmed. Further addition of timing cycles represents re-

finements rather than essential elements of DDD pacing.

9. *Do we need more than seven intervals in our evolving DDD pacemaker?* Further refinements of DDD pacemaker function have introduced two other timing intervals:
   (a) ventricular safety pacing (*VSP*) to complement the blanking period in dealing with crosstalk – this function does not prevent crosstalk but merely offsets its consequences;
   (b) upper rate interval programmable independently of the *TARP* for a smoother upper rate response than the rather abrupt slowing provided by the *TARP* when it is the only interval controlling the upper rate (interval).
10. *Refractory periods.* In a DDD pacemaker how does an event in one channel affect the refractory period of the other? Four possible events may be considered: AP, AS, VS, VP.
   (a) VS and VP both initiate the *VRP* and *PVARP* starting simultaneously.
   (b) AP initiates the AV delay and an atrial refractory period extending through the entire duration of the AV delay. The AV delay is therefore the first part of the *TARP*, the second part being the *PVARP*. Release of AP initiates an important interval (postatrial ventricular blanking period) to prevent crosstalk which is a pacemaker disturbance where the ventricular channel senses the atrial stimulus (discussed later).
   (c) AS generates an atrial refractory period in the AV delay like AP but it is not associated with a postatrial ventricular blanking period because AS cannot induce crosstalk (discussed later).
11. *The faces of DDD pacing.* A DDD pacemaker with ventricular-based lower rate timing capable of dealing with four events (AS, AP, VS, VP) can behave in one of four ways judged by the examination of a single cycle starting with VS and the way the cycle terminates:
   (a) DVI: VS–AP–VP;
   (b) AAI: QRS–AP–QRS;
   (c) VDD: VS–AS–VP;
   (d) totally inhibited "mode" without stimuli.

   In the inhibited situation the RR interval (VS–VS) is shorter than the lower rate interval and the PR interval is shorter than the programmed AV delay. Inhibition does not always mean that the pacemaker senses both the atrial and ventricular signals. Indeed, in the presence of atrial undersensing, the ECG may show inhibition if the pacemaker (actually working in the DVI mode) emits no stimuli because the RR interval is shorter than the atrial escape interval.
12. *Ventricular pseudopseudofusion beats.* Remember that in a DDD pacemaker, a sensed ventricular event inhibits both the atrial and ventricular channels. A ventricular pseudofusion beat occurs when a ventricular stimulus falls within the spontaneous QRS before the intracardiac ventricular electrogram has developed sufficient amplitude to be sensed. In the same way an atrial stimulus can fall within the surface QRS complex before the intracardiac ventricular electrogram has developed sufficient amplitude to be sensed. In this situation when an atrial stimulus deforms the QRS complex, the arrangement is called a pseudopseudofusion ventricular beat to underscore that the process involves two chambers instead of one as is the case of pseudofusion beats.

Caveat: In the presence of normal atrial and ventricular sensing, a pacemaker stimulus falling within the QRS complex may be atrial (pseudopseudofusion) or ventricular (pseudofusion). In a device with a ventricular-based lower rate, the stimulus is atrial if it terminates the atrial escape interval, which is always constant. In a device with an atrial-based lower rate system (where atrial events control the lower rate), the stimulus is atrial if it terminates an interatrial interval equal to the lower rate interval.

Crosstalk and crosstalk intervals

In patients without an underlying cardiac rhythm, inhibition of the ventricular channel by crosstalk can be catastrophic. The postatrial ventricular blanking period (*PAVB*) starts with the atrial stimulus and is usually programmable from about 10 to 60 ms. Note again that no blanking period is in effect after atrial sensing. Some pacemakers are designed with an additional safety mechanism to counteract the inhibitory effect of crosstalk should the postatrial ventricular blanking period be unsuccessful. This special "safety period" is really a crosstalk detection window and is often described in pacemaker specifications as starting from the atrial stimulus. In fact, it cannot be functional until the brief postatrial ventricular blanking period has timed out. Nevertheless, the AV delay is often described as having two parts. The first part is the *ventricular safety pacing* (*VSP*) window which extends from the onset of the AV delay for a duration of 100–110 ms. During the *VSP* interval, a sensed ventricular signal does not inhibit the DDD pacemaker. Rather, it immediately *triggers* a ventricular stimulus delivered prematurely only at the completion of the *VSP* interval, producing a characteristic abbreviation of the paced *AVI* (AP–VP). If a QRS complex is sensed within the

VSP window, it will also trigger an early ventricular stimulus. However this triggered ventricular stimulus falls harmlessly within the QRS complex in the absolute period of the ventricular myocardium. In the second part of the AV delay beyond the *VSP* interval, a sensed ventricular signal inhibits the pacemaker in the usual fashion.

Manifestations of crosstalk

1. In pacemakers with a *VSP* interval, crosstalk will cause shortening of the paced AV delay (AP–VP). In a device with ventricular-based lower rate timing, the pacing rate will increase because the sum of the constant atrial escape interval and the abbreviated AV delay becomes less than the lower rate interval.
2. In pacemakers without a *VSP* interval, the ECG will show: (a) prolongation of the interval between the atrial stimulus and the succeeding conducted QRS complex to a value greater than the programmed AV delay; (b) if there is no AV conduction ventricular asystole will occur. The atrial pacing rate interval (there are no ventricular stimuli) will be shorter than the lower rate interval (atrial pacing rate faster than the lower rate) because the interval between two consecutive atrial stimuli becomes equal to the sum of the atrial escape interval (*AEI*) and the short *PAVB* because sensing of the atrial stimulus can only occur after the blanking period has timed out.
3. Crosstalk tachycardia. In pacemakers with *VSP* and ventricular-lower rate timing, a lower rate of 80 p.p.m. (*LRI* = 750 ms) yields an atrial escape interval of 450 ms if the AV delay = 300 ms. During continual crosstalk with an abbreviated paced AV delay (AP–VP) of 100 ms, the pacing interval becomes 450 + 100 = 550 ms corresponding to a rate of 109 p.p.m.

Caveat: VSP can be puzzling in the ECG without markers. When the atrial stimulus falls within a QRS complex and is invisible on the surface ECG, a single visible ventricular stimulus will fall beyond the QRS complex. This must not be interpreted as ventricular undersensing. To make the diagnosis, go back to the previous ventricular event and with calipers move to the end of the atrial escape interval when the atrial stimulus should have occurred. Then, add the *VSP* interval and its end should coincide with the late stimulus in question thereby proving it is ventricular and establishing normal pacemaker function. If *VSP* has not occurred and the QRS complex fell in the postatrial ventricular blanking period, add the AV delay to the atrial escape interval (measured as indicated) rather than the *VSP* interval.

Reminders:

1. The frequent occurrence of *VSP* involving spontaneous QRS complexes should immediately raise the possibility of atrial undersensing.
2. The opposite of AV crosstalk is ventriculoatrial (VA) crosstalk where the atrial channel senses ventricular activity. VA crosstalk is important in pacemakers with automatic mode switching (discussed later).

Increasing complexity: our simple DDD pacemaker grows to nine intervals

Many pacemakers have nine timing cycles, five related to the ventricular channel and four to the atrial channel. A ventricular paced or sensed event initiates: lower rate interval (*LRI*), upper rate interval or *URI* (independent of the *TARP*), *PVARP*, ventricular refractory period (*VRP*) and atrial escape interval (*AEI*). An atrial paced or sensed event initiates: *AVI*, *TARP* (derived as the sum of *AVI* and *PVARP*); an atrial paced event initiates the postatrial ventricular blanking period (*PAVB*) and the *VSP* interval.

A pacemaker with the capability of programming a longer upper rate interval independently of the *TARP* provides two levels of upper rate response. The first level defines the onset of the Wenckebach upper rate response and occurs when the P–P interval is shorter than the upper rate interval but longer than the *TARP*. The second level uses the *TARP* itself to define the onset of block when the P–P interval becomes shorter than the *TARP*.

Upper rate response of DDD pacemakers

The maximum paced ventricular rate of a DDD pacemaker can be defined either by the duration of the *TARP* or by a separate timing circuit controlling the ventricular channel. In general, upper rate limitation by only the *TARP* (as in our early DDD pacemaker) is less suitable because it produces a sudden fixed-ratio block such as 2:1 or 3:1 block. In contrast a smoother response occurs with a Wenckebach upper rate response, which requires a separate *URI* timing interval that must be longer than the *TARP*.

Fixed-ratio block

In this system the upper rate becomes a function of only the *TARP* (*AVI* + *PVARP*). As the atrial rate increases, any P wave falling within the *PVARP* is

unsensed and, in effect, blocked. The AV delay always remains constant. If the programmed upper rate is 120 p.p.m. (*TARP* = 500 ms) and the lower rate is 60 p.p.m., a 2:1 response will occur when the atrial rate reaches 120 p.p.m.,. One P wave is blocked (or unsensed) and the other initiates an AV delay and triggers a ventricular response. The situation is not as simple mathematically when the lower rate is 70 p.p.m. because the ventricular rate cannot fall below the lower rate. An upper rate response using fixed-ratio block may be inappropriate in young or physically active individuals because the sudden reduction in the ventricular rate with activity may be poorly tolerated.

Wenckebach upper rate response

The Wenckebach upper rate response requires a separately programmable upper rate interval. The purpose of the Wenckebach response is to avoid a sudden reduction of the paced ventricular rate (as occurs in fixed-ratio block) and to maintain some degree of AV synchrony at faster rates. The upper rate interval (*URI*) must be longer than the *TARP*. During the Wenckebach upper rate response, the pacemaker will synchronize its ventricular stimulus to sensed atrial activity. The pacemaker cannot violate its *URI*. Therefore upon atrial sensing, the pacemaker has to wait until the *URI* has timed out before it can release a ventricular stimulus. For this reason the AV delay (initiated by atrial sensing) must be extended to deliver the ventricular stimulus at the completion of the *URI*. The sensed AV delay gradually lengthens throughout the Wenckebach sequence but the ventricular rate remains constant at the programmed upper rate. Mathematically the AV delay must progressively lengthen in the Wenckebach progression simply because the *URI* cannot be violated and the atrial rate interval or P–P interval is shorter than the *URI* but longer than the *TARP*. Eventually a P wave will fall in the *PVARP* where it will not be followed by a ventricular stimulus and a pause will occur. In other words, the Wenckebach response maintains the constant *URI* at the expense of extension of the AV delay (AS–VP).

1. The maximum prolongation of the *AVI* represents the difference between the *URI* and the *TARP*.
2. With progressive shortening of the P–P interval, the Wenckebach upper rate response eventually switches to 2:1 fixed ratio block when the P–P interval becomes shorter than the *TARP*.
3. There are only two ventricular paced intervals during a Wenckebach upper rate sequence:
   (a) repeated ventricular pacing at the upper rate interval;
   (b) a longer interval (pause) between 2 successive ventricular beats following the undetected P wave in the *PVARP*; the pause may terminate with AS or AP and the ventricular event may be VP or VS according to circumstances.

   Some patients feel the pause at the end of a Wenckebach sequence as an uncomfortable sensation. The pause may be abbreviated or even eliminated with appropriate programming of the sensor function of a DDDR pacemaker. This process has been called sensor-driven rate-smoothing.
4. Let us consider two clinical examples.
   (a) a DDD pacemaker is programmed as follows: upper rate = 100 p.p.m. (upper rate interval = 600 ms); AV delay = 150 ms; *PVARP* = 250 ms. The *TARP* will be 250 + 150 = 400 ms. The pacemaker will therefore respond to an atrial rate faster than 100 b.p.m. by exhibiting Wenckebach sequences with the longest prolongation of the *AVI* being (*URI* minus *TARP*) or 200 ms. Thus the AV delay will vary from its programmed value of 150 ms to a maximum of 350 ms. Fixed-ratio block will occur when the P–P interval is shorter than the *TARP* (400 ms) or at an atrial rate of 150 b.p.m.
   (b) When the same DDD pacemaker is programmed with AV delay = 200 ms, *PVARP* = 250 ms, upper rate = 125 p.p.m. (upper rate interval = 480 ms), it would be difficult to produce an actual Wenckebach upper rate response. The maximum prolongation of the *AVI* would be (*URI* minus *TARP*) = 30 ms and its maximum duration = 230 ms. In this case, the pacemaker will respond with a Wenckebach sequence at an atrial rate of 125 b.p.m., but < 133 p.p.m. When the atrial rate exceeds 133 b.p.m., fixed-ratio block will occur (P–P shorter than *TARP* of 450 ms).

Remember the three important variables: *URI*, *TARP* and the P P interval (atrial rate)

1. *URI* shorter or equal to *TARP*. No Wenckebach response is possible.
2. *URI* > *TARP*:
   (a) P–P interval > *URI*, the pacemaker maintains 1:1 AV synchrony;
   (b) P–P interval < *URI*: when the P–P interval becomes shorter than the *URI* but longer than the *TARP*, that is, *URI* > P–P > *TARP*, the pacemaker responds with a Wenckebach upper rate response;
   (c) P–P < *TARP*: when the P–P interval is shorter than the *TARP*, the pacemaker can only re-

spond with a fixed-ratio form of upper rate limitation.

Duration of the AV interval and programmability of the upper rate

The sensed *AVI* (*sAVI*) initiated by AS (AS–VP) and not the one initiated by AP (*pAVI*), determines the point where fixed-ratio block occurs, i.e. when P–P interval < *TARP* or (AS–VP) + *PVARP*. In many pacemakers the *sAVI* (AS–VP) can be programmed to a shorter value than the *pAVI* (AP–VP) interval thereby shortening the *TARP* during sensing. Furthermore the *sAVI* (AS–VP) can decrease further with exercise according to the sensed atrial rate and/or sensor activity. This shortening on exercise mimics the physiological response of the PR interval and provides hemodynamic benefit and a more advantageous shorter *TARP*. (In some pacemakers the *TARP* can also shorten further on exercise because of an adaptive *PVARP*). Therefore a shorter *TARP* allows programming of a shorter (separately programmable) *URI* to permit a Wenckebach upper rate response to occur at faster atrial rate.

Lower rate timing of dual chamber pacemakers

Traditional DDD pacemakers are designed with ventricular-based lower rate timing. In this system a ventricular paced (VP) or ventricular sensed (VS) event initiates the lower rate interval (*LRI*) and the atrial escape interval. The atrial escape interval always remains constant. The *LRI* is the longest VP–VP or VS–VP interval without intervening atrial and ventricular sensed events. In atrial-based lower rate timing, the *LRI* is initiated and therefore controlled by atrial sensed or paced (AS or AP) events rather than ventricular events. The *LRI* becomes the longest AP–AP or AS–AS interval. The atrial escape interval becomes variable and adapts its duration to maintain a constant AP–AP or AS–AP interval equal to the *LRI*. The duration of the atrial escape interval can be calculated as the *LRI* minus the *AVI* immediately preceding the atrial escape interval in question. In an atrial-based lower rate system, ventricular premature complexes initiate either the basic atrial escape interval (as if it were ventricular-based) or a complete *LRI* according to design.

Table 1. Basic multiprogrammability.

Rate	Increase	(a) To optimize cardiac output; (b) to overdrive or terminate tachyarrhythmias; (c) to adapt to pediatric needs; (d) to test AV conduction in AAI pacemakers; (e) to confirm atrial capture using the AAI mode by observing a concomitant increase in the ventricular rate; (f) rate drop response for the treatment of vasovagal syncope. An abrupt fall in the spontaneous rate causes pacing at a higher rate (than the low basic pacing rate) for a given duration
	Decrease	(a) To assess underlying rhythm and dependency status; (b) to adjust the rate below the angina threshold; (c) to allow the emergence of sinus rhythm and preservation of atrial transport; (d) to test sensing function; (e) sleep mode to provide a lower rate during the expected sleep time. Some devices use an activity sensor to drop the rate automatically with inactivity
Output	Increase	To adapt to pacing threshold
	Decrease	(a) To test pacing threshold; (b) to program pacemaker according to chronic threshold to enhance battery longevity; (c) to reduce extracardiac stimulation (voltage rather than pulse duration)of pectoral muscles or diaphragm; (d) to assess underlying rhythm and dependency status.

continued

Table 1. Basic multiprogrammability (*continued*).

Sensitivity	Increase	To sense low amplitude P or QRS electrograms.
	Decrease	(a) To test sensing threshold; (b) to prevent T wave or afterpotential sensing by ventricular channel; (c) to avoid sensing extracardiac signals such as myopotentials.
Refractory period	Increase	(a) Atrial: to minimize sensing of the far-field QRS during AAI pacing
		(b) Ventricular: to minimize T wave or afterpotential sensing by the ventricular channel
	Decrease	(a) To maximize QRS sensing; (b) to detect early ventricular premature beats
Hysteresis		In the VVI mode to delay onset of ventricular pacing to preserve atrial transport function
Polarity	Conversion to unipolar mode	(a) To amplify the signal for sensing when the bipolar electrogram is too small; (b) to compensate temporarily for a defect in the other electrode
	Conversion to bipolar mode	(a) To decrease electromagnetic or myopotential interference; (b) to evaluate oversensing; (c) to eliminate extracardiac anodal stimulation
AVI	Increase or decrease to optimize LV function	(a) Differential: to permit a longer interval after an atrial paced event than a sensed atrial event
		(b) Rate-adaptive: to shorten the AV delay with an increase in heart rate
PVARP	Increase	To prevent sensing of retrograde P waves
PVARP extension after a VPC	On/off	To prevent sensing of retrograde P wave after a VPC
Postatrial ventricular blanking period	Increase	To prevent crosstalk
Ventricular safety pacing	On/off	To guarantee ventricular stimulation in the presence of crosstalk
Separately programmable upper rate	*URI* > *TARP*	To provide a smoother (Wenckebach) upper rate response and avoid abrupt slowing of the ventricular rate when *URI* = *TARP*

Phantom programming

This is unintended, inadvertent or mysterious reprogramming of a pacemaker. It may be the result of intentional reprogramming by an operator who made no record of it in the patient's chart. It may also be caused by electromagnetic interference unbeknown to the patient.

Programmability of lower rate

Patients with coronary artery disease and angina pectoris tend to have their pacemaker programmed to a low rate to avoid the precipitation of angina (chest pain). This may be true for VVI pacing but not for VDD, DDD, rate-adaptive DDD (DDDR) and rate-adaptive VVI (VVIR) pacing, which such patients tolerate well because their heart responds more efficiently on exercise. The upper rate, however, should be programmed cautiously. Patients with sick sinus syndrome and atrial tachyarrhythmias may benefit from overdrive suppression by increasing the pacing rate to 80 b.p.m., which may eliminate or reduce atrial tachyarrhythmias.

Endless loop tachycardia

Endless loop tachycardia (ELT), sometimes called pacemaker-mediated tachycardia, is a well-known complication of DDD, DDDR and VDD pacing. It represents a form of ventriculoatrial (VA) synchrony or the reverse of AV synchrony. Any circumstance that causes AV dissociation (separation of the P wave from the paced or spontaneous QRS complex) can initiate ELT only in patients who have the capability of retrograde VA conduction. The most common initiating mechanism is a ventricular premature complex (VPC) with retrograde VA conduction. (Table 2).

Reminder: ELT should be considered a complication of the past because it is almost always prevented by programming the PVARP to contain the retrograde P waves. Problems arise when the VA conduction time is very long and a long PVARP restricts programmability of the upper rate. In such cases, pacemakers use special automatic tachycardia-terminating algorithms.

When the atrial channel senses a retrograde P wave, a ventricular stimulus is issued at the completion of the AV delay which may have to be extended to conform to the *URI*. The pacemaker provides the antegrade loop of a process similar to the reentrant mechanism of many spontaneous tachyarrhythmias. VA conduction following ventricular pacing provides the retrograde limb of the reentrant loop. The atrial channel of the pacemaker again senses the retrograde P wave and the process perpetuates itself. The cycle length of ELT is often equal to the *URI* but it can be longer than the *URI* if retrograde VA conduction is delayed. The tachycardia is called a balanced ELT when its rate is slower than the programmed upper rate. The true programmed AV delay will be seen in ELT when the rate is slower than the programmed upper rate because the *AVI* is not extended. When the ELT is at the upper rate, the AV delay is extended to conform to the upper rate interval.

Reminder: Application of the magnet over the pacemaker immediately terminates ELT in virtually 100% of cases.

Caveat: The rate of ELT is not always at the programmed upper rate. In the DDI mode an endless loop with repetitive retrograde VA conduction will occur at the lower rate (no tachycardia is possible).

Table 2. Initiating mechanism of endless loop tachycardia.

1. Ventricular extrasystoles (commonest cause)
2. Subthreshold atrial stimulation (commonly used for testing)
3. Atrial extrasystole with prolongation of AV delay to conform to the programmed upper rate interval > total atrial refractory period
4. Application and withdrawal of the magnet
5. Decrease in atrial sensitivity; undersensing of anterograde P waves with preserved sensing of retrograde P waves
6. Myopotential sensing usually by the atrial channel
7. Programmer electromagnetic interference sensed by the atrial channel only
8. Excessively long AV delay
9. Programming the VDD mode when the sinus rate is slower than the programmed lower rate.
10. Treadmill exercise (rarely) and increase in sinus rate with Wenckebach upper rate response and AV delay extension
11. Sensing of a far-field signal by the atrial lead, usually the far-field R wave

Diagnosis and prevention of endless loop tachycardia

The presence of retrograde VA conduction and its duration must always be determined (Table 3). Rarely, retrograde VA conduction is intermittent.

The maneuvers to initiate ELT are repeated until appropriate programming of the pacemaker prevents induction of tachycardia. In general the *PVARP* should be programmed at least 50 ms longer than the VA conduction time. A *PVARP* of 300 ms offers protection against ELT in most patients with retrograde conduction (Table 4).

The best way to initiate ELT is to program subthreshold atrial stimulation, the shortest *PVARP* and a lower rate faster than the spontaneous sinus rate.

Caveat: Programming a long PVARP will limit the upper rate. This may be important in vigorous or young patients.

Table 3. Situations permitting evaluation of retrograde VA conduction.

1. Programming to VVI mode
2. Programming the atrial output to subthreshold level in the DDD mode
3. Application and withdrawal of the magnet
4. Holter monitoring
5. Treadmill exercise (rarely)

Table 4. Programmability for the prevention of endless loop tachycardia.

1. Program *PVARP*
2. Automatic *PVARP* after VPC (defined by a pacemaker as a ventricular event not preceded by a P wave; thus, a true VPC will not be labeled a VPC if preceded by a P wave)
3. Adaptive *PVARP*
4. Programmable sensitivity: 60–75% of anterograde P waves are at least 0.5 mV larger than retrograde P waves
5. Shortening of the AV delay
6. Programming to a nontracking mode such as DDI is no longer acceptable

Repetitive nonreentrant VA synchrony: the cousin of endless loop tachycardia

Endless loop tachycardia (ELT) is a form of repetitive VA synchrony and as mentioned it is a reentrant or circus movement tachycardia. Repetitive VA synchrony can occur in the VVI or VVIR with continual retrograde VA conduction where it may cause hemodynamic impairment and pacemaker syndrome. Repetitive VA synchrony can also occur in the DDD or DDDR mode when a paced ventricular beat causes retrograde VA conduction but the retrograde P wave is unsensed (unlike ELT) because it falls within the *PVARP*. Under certain circumstances, this form of VA synchrony can become self-perpetuating when the pacemaker continually delivers an ineffectual atrial stimulus (despite being well above the pacing threshold under normal circumstances) in the atrial myocardial refractory period generated by the preceding retrograde P wave. The potential reentrant circuit does not close as in ELT and this arrhythmia is often labeled as being nonreentrant. Both ELT and repetitive nonreentrant VA synchrony depend on VA conduction and are physiologically similar. Both share similar initiating and terminating mechanisms. Repetitive nonreentrant VA synchrony depends on a short atrial escape interval (relatively fast lower rate and/or a long AV delay) and a relatively long VA conduction time. Thus, it is more likely to occur during sensor-driven faster pacing rates. The process may therefore occur when programming a very long AV delay to promote AV conduction and normal ventricular activation. Occasionally during ELT, magnet application over the pacemaker can cause a locked arrangement similar to repetitive nonreentrant VA synchrony (with preservation of VA conduction) so that removal of the magnet reinitiates ELT.

Types of dual chamber pacemakers

Simpler pacing modes can be easily derived from the DDD mode by the removal of certain intervals and equalizing others. All retain a fundamental *LRI*, ventricular refractory period, AV delay initiated by atrial pacing except for the DOO mode which has only an AV delay and *LRI*.

DVI mode

The AV sequential (DVI) mode may be considered as the DDD mode with the *PVARP* lasting through the entire duration of the atrial escape interval. As the

AV delay is always refractory in a DDD pacemaker, the *TARP*, in effect, lasts through the entire *LRI*. No *URI* can exist because atrial sensing is impossible. Therefore, the *LRI*, *TARP* and *URI* are all equal. Crosstalk intervals are retained. The DVI mode is rarely used and is obsolete as a primary pacing mode. The terms "committed" or variants thereof are therefore obsolete descriptions of the DVI mode.

DDI mode

The DDI mode may be considered as the DDD mode with equal *URI* and *LRI*. This concept facilitates understanding of complex rhythms generated by this mode although this conceptualization is not recommended by some experts. Nevertheless, it is easy to remember and apply. Remember the DDTI/I designation for the DDD mode. The DDI mode is simply created by removing the "T" from the atrial channel. Thus atrial sensing occurs but no "T" function is possible. In other words, a sensed P wave cannot trigger a ventricular stimulus and a programmed *AVI* cannot occur after atrial sensing. The programmed AV delay can only exist as the AP–VP interval. This means that atrial tracking cannot occur. The DDI mode will therefore always exhibit a constant ventricular paced rate equal to the *LRI*. There is no *URI* (or a *URI* equal to the *LRI*). A *PVARP* is retained because atrial sensing occurs. Crosstalk intervals are retained. In the early days of DDD pacing, the DDI mode was useful in patients with AV block and paroxysmal atrial tachyarrhythmias because it prevented rapid ventricular pacing during tachycardia. The use of the primary continuous DDI mode for this problem has been superseded by automatic mode switching of a DDD pacemaker to the DDI mode upon the detection of an atrial tachyarrhythmia and reversion to the DDD mode automatically upon termination of tachycardia.

During DDI pacing with atrial fibrillation and AV block, many AR markers (atrial refractory sense events) will be seen in the atrial refractory period (in the AV delay and the *PVARP*) and AS markers outside the atrial refractory period. AS cannot start an AV delay. The AR markers provide diagnostic representation of the underlying arrhythmia and insight as to how the pacemaker activates the automatic mode switching function.

VDD mode

The original atrial synchronous pacemaker was the VAT system without ventricular sensing. Then, ventricular sensing was added (VAT + VVI = VDD). The VDD mode functions like the DDD mode except that the atrial output is turned off. The required timing cycles include *LRI*, *URI*, *AVI* and *PVARP*. The omitted atrial stimulus begins an implied AV delay during which, according to traditional design, the atrial channel is refractory. In the absence of atrial activity, the VDD mode will continue to pace effectively in the VVI mode (at the *LRI* of its DDD parent) because the VDD keeps all the basic cycles of the DDD mode despite the missing atrial output. This is an important disadvantage of the VDD mode because VVI pacing during sinus bradycardia may be poorly tolerated and cause pacemaker syndrome. No crosstalk intervals are required because there is no atrial stimulation in the VDD mode.

Reminder: One can easily derive the function and timing cycles of all dual chamber pacemakers starting with a thorough knowledge of the timing cycles of a DDD pacemaker.

Caveats:
There are two types of response to the sensed P wave in the VDD mode according to design.

1. A P wave falling in the implied AV delay is not sensed. The *LRI* always remains constant.
2. In some pacemakers a P wave in the implied *AVI* can be sensed and actually reinitiates an entirely new AV delay so that the VS–VP or VP–VP interval becomes longer than the programmed (ventricular-based) *LRI*. This produces a form of hysteresis with the maximum extension of the *LRI* being equal to the AS–VP interval.

Overdrive suppression and the underlying rhythm

Continuous pacing may suppress the underlying spontaneous rhythm, a phenomenon called overdrive suppression. Thus, the sudden interruption of pacing may cause prolonged asystole because it takes time for a dormant rhythm to "wake up." The underlying rhythm is determined by programming to the VVI and *gradually* reducing the rate, sometimes to as low as 30 p.p.m. Often a slow rhythm "warms-up" and will emerge. Most patients tolerate such a slow rate of pacing. A patient that has a poor underlying rhythm is often labeled as being "pacemaker dependent." This is a vague term which has never been clearly defined. It may be defined as the occurrence of severe or life-threatening symptoms with failure to pace as may occur with lead dysfunction, battery failure or electromagnetic interference. Pacemaker dependency may be tested by totally and abruptly inhibiting the pacemaker, but this may dangerous. The emergence of a slow rhythm during gradual reduction of the pacemaker rate to 30 p.p.m. does not

mean that the patient is not pacemaker-dependent. The presence of pacemaker dependency should be displayed prominently on the cover of the pacemaker chart.

Caveat: Always have two programmers on hand in case one malfunctions during induced severe bradycardia or asystole.

Pacemaker hemodynamics

The early pacemakers had little in the way of electronics and no hemodynamic refinement. VVI pacing was basically nonphysiologic and ignored the atrium. Pacemaker syndrome was relatively common. The advent of DDD pacing was hailed as the universal pacing mode. Patients with sick sinus syndrome and poor atrial chronotropic function, however, complained of fatigue and the inability to perform exercise to a level that they thought reasonable because the heart rate did not increase during exercise. The subsequent development of rate-adaptive pacemakers (with artificial sensors in addition to the natural P wave sensor) permitted a pacemaker to respond by increasing its rate similarly to the normal heart on effort. These pacemakers improved effort tolerance in patients with bradycardia at rest or with activity. Many older patients have little ability to increase their cardiac output by increasing left ventricular contractility and therefore stroke volume (volume of blood ejected per heart beat), so that an increase in heart rate is their only way to increase cardiac output on effort. The cardiac output may increase by as much as 300% on exercise by rate increase alone. Unfortunately the settings on rate-adaptive pacemakers are often left on factory settings unless the patient becomes symptomatic or the physician has a particular interest in the technology.

AV synchrony

The atrial contribution provides about 15–30% of the cardiac output (volume of blood in liters ejected by the heart per minute) at rest in individuals with normal LV systolic function. Although the atrial contribution plays little or no role on exercise when heart rate is basically the only determinant of cardiac output, AV synchrony at rest is vital to prevent pacemaker syndrome and atrial tachyarrhythmias. The loss of AV synchrony can be especially detrimental in patients with LV diastolic dysfunction where the systolic function can be normal but the ventricle is stiff and noncompliant, as in hypertrophy from hypertension. Furthermore, patients with heart failure often do not tolerate loss of AV synchrony.

Reminder: Loss or inappropriate AV synchrony is the cause of pacemaker syndrome. The optimal AV delay for the individual patient cannot be predicted but can be evaluated by echocardiography.

Ventricular activation sequence

While the AV delay and rate responsiveness are essential components of pacemakers, the role of the ventricular activation sequence is presently becoming recognized. In patients with sick sinus syndrome and normal AV conduction, AAI or AAIR pacing (associated with a small risk of AV block even in highly selected patients) provides the best hemodynamics because it preserves normal ventricular activation. Long-term RV pacing, which by necessity causes abnormal LV activation (similar to left bundle branch block), may cause long-term deterioration of LV function or precipitate congestive heart failure in patients with poor LV function. This disturbance seems to be based on the cumulative duration of right ventricular pacing. For this reason, the AV delay should be programmed to promote AV conduction if possible so that the advantage of normal ventricular depolarization offsets the depressant effect of pacing on the LV. Patients with relatively normal AV conduction who require minimal or backup pacing could be paced with a slow lower rate such as 40–50 p.p.m. to allow a spontaneous rhythm most of the time with the hope of preventing long-term deterioration of LV function. Patients with a long PR interval ≥ 0.28 s require ventricular pacing for optimal hemodynamic benefit because the shorter AV delay offsets the negative impact of abnormal pacing-induced LV depolarization.

Biventricular pacemakers are used to treat congestive heart failure in patients with poor LV function and left bundle branch block. The latter produces an inefficient left ventricular contraction because of abnormal ventricular depolarization and contraction. Biventricular pacing produces "resynchronization" by promoting a more physiologic pattern of depolarization and a more efficient LV contraction.

Caveat: Programming a long AV delay to promote normal AV conduction may increase the risk of endless loop tachycardia and repetitive nonreentrant VA synchrony by promoting retrograde VA conduction. A long AV delay may also favor the delivery of ventricular stimulation on the T wave (vulnerable period).

Rate-adaptive pacemakers

A sensor monitors the need for a faster pacing rate according to activity and works independently of intrinsic atrial activity. A VVI pacemaker with a rate-adaptive function is coded as a VVIR pacemaker. A DDDR pacemaker is thus a DDD device with rate-adaptive function or rate modulation. However the VDDR mode is a misnomer because such a mode operates in the VDD mode except when it is sensor-driven, when the pacing mode becomes VVIR.

Five basic parameters can be programmed in sensor-driven pacemakers: sensor threshold, lower rate, upper sensor rate, upper tracking (or atrial-driven) rate, and sensor slope. Unfortunately many pacemakers are left at their nominal settings (out of the box) which may not be optimal for some patients.

The sensor threshold is the minimum degree of sensor activation required to initiate an increase in heart rate. In other words, it sets the lowest level of sensor activation that will be counted and used for rate control. Threshold settings may be numeric or descriptive. Sedentary patients may require a more sensitive setting. The sensor slope determines the rate of change of the heart rate in response to sensor activation. Increasing the slope will result in an increased pacing rate for the same amount of activity. The normal sinus node produces a linear increase in the heart rate during exercise. The slope can be variable, however, and depends on the degree of conditioning. Some manufacturers have designed pacemakers with an autoresponsive slope and threshold. The pacemaker learns the appropriate settings based on the patient's activity. These automatic system are not perfect but are better than empiric systems or not programming the rate-adaptive response.

The pause in the Wenckebach upper rate response can be attenuated or even eliminated by appropriate programming of a DDDR pacemaker. This process is called sensor-driven rate smoothing.

The sensor in DDDR pacemakers can also influence intervals other than the *LRI*. These include:

1. the AV delay that shortens on exercise to mimic physiologic shortening of the *PR* interval;
2. the *PVARP*.

Shortening of the *PVARP* on exercise coupled with adaptive shortening of the *AVI* produce substantial shortening of the total atrial refractory period. This allows programming of a faster upper rate. An adaptive *PVARP* allows programming of a relatively long *PVARP* at rest when endless loop tachycardia is likely to occur. Initiation of endless loop tachycardia is quite unusual on exercise with fast atrial-driven ventricular pacing when a shorter *PVARP* is safe.

Programming the pacemaker

An easy way to program the sensor-driven response, is to have the patient walk up and down and adjust the parameters accordingly. Avoid overprogramming the threshold response, which will produce an excessively fast pacing rate poorly tolerated by patients.

Table 5. Characteristics of commonly used pacing modes.

Characteristics	VVI	VVIR	AAI	AAIR	DDD	DDI	DDDR	DDIR
Simplicity	+++	+++	++	++	+	+	–	–
AV synchrony	–	–	+	+	+	+[a]	+	+[a]
Potential for pacemaker syndrome	+	+	–	–	–	–	–	–
Normal LV activation	–	–	+	+	–[b]	–[b]	–[b]	–[b]
Propensity to endless loop tachycardia	–	–	–	–	+	+[c]	+	+[c]
Tracking of supraventricular tachycardia	–	–	–	–	+	–	+	–
Contraindicated in AV block	–	–	+	+	–	–	–	–
Increase of pacing rate in atrial chronotropic incompetence	–	+	–	+	–[d]	–	+	+
Cost	–	+	–	+	++	++	+++	+++

[a] In the DDI mode, if normal sinus rhythm is faster than the programmed rate, and in the DDIR mode if normal sinus rhythm is faster than the sensor-driven rate, AV dissociation with hemodynamic disadvantage is frequent in patients with AV block.
[b] Unless AV delay is prolonged to allow for normal antegrade conduction.
[c] Endless loop without tachycardia at the lower rate or at the sensor-driven rate.
[d] Ventricular pacing rate does not increase if the sinus rate does not increase on exercise.

Caveat: After the implantation of a pacemaker, fluid in the pacemaker pocket may dampen vibrations and the response of activity rate-adaptive pacemakers. If these devices are programmed too early, there may be an excessive rate response several weeks later after the absorption of fluid. It seems wise to leave the rate-adaptive function of activity-driven devices turned off soon after implantation to prevent constantly changing pacing rates when the patient turns in bed, etc. Such fluctuations may cause confusion for the personnel monitoring the patient.

The pacemaker stimulus

Contemporary digital ECG recorders distort the pacemaker stimulus, so it may become larger and show striking changes in amplitude and polarity. Digital recorders can also miss some of the pacemaker stimuli because of sampling characteristics. Diagnostic evaluation of the pacemaker stimulus is only possible with analog machines. Many inkjet recorders and ECG machines with a stylet writer are analog recorders. With such recorders, the direction and amplitude of the pacemaker stimulus may yield valuable information about lead displacement or defects. A bipolar lead with an insulation defect may exhibit a very large stimulus artifact on the electrocardiogram (unipolar–bipolar phenomenon) and pace normally in contrast to the tiny deflections with an intact bipolar lead.

Caveats:

1. Static interference may generate deflections mimicking pacemaker stimuli. Careful scrutiny of the deflections often suggests they are not pacemaker stimuli. When in doubt, measure the timing cycles to and from the deflection in question and establish the lack of relationship to pacemaker function.
2. The interval from the stimulus to the onset of cardiac depolarization is called latency. The normal value is 40 ms or less. If there is a relatively long isoelectric (zero) interval from stimulus to the QRS or P wave, the commonest cause is isoelectric depolarization in the ECG lead in question. Confirmation requires the recording of several ECG leads simultaneously to demonstrate the true onset of cardiac depolarization. Hyperkalemia is a common cause of increased latency. Other causes of latency include serious metabolic disorders, right ventricular infarction and terminal situations.

Magnet mode

The magnet mode refers to the response of a pacemaker when a magnet is applied over it. The magnet closes the special reed-switch within the pulse generator causing the device to pace at the asynchronous mode at the magnet rate. The behavior of the magnet mode varies according to the manufacturer and so does the magnet rate. The magnet mode is used to assess pacemaker function and battery depletion. The magnet mode can be programmed "off" in some pacemakers.

QRS patterns during ventricular pacing

Pacing from the RV apex produces negative paced QRS complexes in the inferior leads (lead II, lead III and lead aVF) simply because the activation starts in the inferior part of the heart and travels superiorly away from the inferior leads. The mean QRS frontal plane axis is superior either in the left or the right superior quadrant. Displacement of the electrode towards the RV outflow tract should be suspected whenever the frontal plane QRS axis shifts to where it is considered "normal" (at least for spontaneous QRS complexes) so that the inferior leads QRS complexes become positive. As stated pacing from RV outflow tract produces a dominant R wave in the inferior leads and may generate qR, QR, or Qr complexes in leads I and aVL. The axis of the paced ventricular beats moves in a clockwise fashion to the so-called "normal" sites (for spontaneous beats) and then to the (inferior) right quadrant as the pacing lead approaches the pulmonary valve. Occasionally with slight displacement of the pacing lead from RV apex to the RV outflow tract, leads I and aVL may register a qR complex in conjunction with the typical negative complexes of RV apical stimulation in the inferior leads. This qR pattern must not be interpreted as a sign of myocardial infarction. RV pacing from any site does not produce qR complexes in V5 and V6. A qR (Qr) complex in the precordial or inferior leads is always abnormal in the absence of ventricular fusion. Right ventricular outflow tract pacing produces a left bundle branch block pattern in the precordial leads similar to that from right ventricular apical pacing.

Dominant R wave in lead V1

A dominant R wave in V1 during ventricular pacing has been called a right bundle branch block (RBBB) pattern of depolarization, but this terminology is

misleading because this pattern is often not related to RV activation delay. A dominant R wave of the paced beat in the right precordial leads occurs in approximately 8–10% of patients with uncomplicated RV apical pacing. The position of V1 and V2 should be checked because a dominant R wave can sometimes be recorded at the level of the third intercostal space during uncomplicated RV pacing. The pacing lead is almost certainly in the RV (apex or distal septal site) if V1 and V2 are negative when recorded one space lower (fifth intercostal space). Furthermore the "RBBB" pattern from pacing at the RV sites results in a precordial vector change from positive to negative by V3. Therefore a tall R wave in V3 and V4 signifies that the lead is not in the RV provided ventricular fusion from spontaneous AV conduction is excluded.

Unintended endocardial left ventricular pacing

Unintended and unsuspected passage of a pacing lead into the LV cavity occurs via the subclavian artery or an atrial septal defect (patent foramen ovale). An LV lead is a potential source of cerebral emboli and stroke. The access sites to the LV can be easily identified by the RBBB pattern during pacing, standard chest radiographs and transesophageal echocardiography.

Reminder: Always look at lead V1 for the absence of a dominant R wave during ventricular pacing.

Complications of pacemakers

Two major groups of complications are associated with pacemaker implantation: (a) nonelectrical complications including acute complications at the time of implantation such as pneumothorax and complications of lead placement and pocket formation; (b) electrical complications.

Nonelectrical complications

Infection

Transesophageal echocardiography is superior to transthoracic imaging for the detection of pacing lead vegetations in patients with intravascular infected pacemakers (endocarditis). Vegetations may occur in the right atrium, right ventricle and the tricuspid valve. Vegetations are best visualized by transesophageal echocardiography.

Perforation

Perforation of a cardiac chamber is now an uncommon complication. It may occur at the time

Table 6. Dif culties in the diagnosis of myocardial infarction during ventricular pacing.

1. Large unipolar stimuli may obscure initial forces, cause a pseudo Q wave and false ST segment current of injury
2. Fusion beats may cause a pseudoinfarction pattern (qR/Qr complex or notching of the upstroke of the S wave)
3. QRS abnormalities have low sensitivity (many false negatives) but high specificity (few false positives). These include qR or Qr patterns and Cabrera's sign in the appropriate leads.
4. Retrograde P waves may simulate Cabrera's sign
5. Diagnosis of acute MI:
   - signs in QRS complex are not useful for the diagnosis of acute MI
   - looking at the underlying rhythm: cardiac memory. Repolarization ST–T wave abnormalities (mostly T wave inversion) in the spontaneous rhythm may be secondary to RV pacing per se and not related to ischemia or non Q wave MI
   - differentiation of MI vs. ischemia may be impossible
   - differentiation of acute MI vs. old or indeterminate age MI may be impossible if old MI is associated with prominent chronic T wave changes usually indicative of an acute process
   - ST segment abnormalities may help the diagnosis of acute myocardial infarction during ventricular pacing. ST elevation ≥ 5 mm in predominantly negative paced QRS complexes is the best marker. ST depression ≥ 1 mm in V1, V2, and V3 and ST elevation ≥ 1 mm in leads with a concordant (same direction) QRS deflection. So-called primary T wave abnormalities where the T wave is in the same direction as the QRS complex are not diagnostically useful during RV pacing

Table 7. Nonelectrical or arrhythmic complications.

Venous access	Pneumothorax Hemothorax Air embolism Brachial plexus injury Thoracic duct injury Trauma to the subclavian artery Hematoma
Pacemaker pocket	Infection, septicemia, etc. Conservative therapy is often unsuccessful and removal of the entire system may be required Hematoma/seroma Erosion Pacemaker migration Twiddler's syndrome Muscle stimulation from either a flipped but normally functioning unipolar or extravascular insulation defect Chronic pain including subcuticular malposition of the pulse generator
Intravascular	Subclavian or inominate vein thrombosis Thrombosis of superior vena cava Coronary sinus dissection or perforation during implantation of a left ventricular lead Large right atrial thrombus Endocarditis with vegetations Manifest pulmonary embolism (rare) Cardiac perforation Cardiac tamponade Entanglement of lead in the tricuspid valve and ruptured chordae Tricuspid insufficiency Pericardial rub
Lead problems	Displacement Malposition in the coronary venous system Endocardial left ventricular malposition across a patent foramen ovale or via subclavian arterial puncture (or via atrial or ventricular septum defect) Right ventricular perforation or lead perforation of the interventricular septum Diaphragmatic pacing. Left side with or without right ventricular perforation and right side by phrenic nerve stimulation by atrial pacing Intercostal muscle stimulation due to right ventricular perforation Post pericardiotomy syndrome (pericarditis etc.) with or without lead perforation Intracardiac rupture of lead during attempt to remove old or broken lead

of implantation or days afterwards. Perforation may be catastrophic when it occurs acutely at the time of implantation, but it is less dramatic when recognized after initial implantation. Perforation of an atrial lead is quite rare. In ventricular perforation, the lead lies more commonly in the pericardial space and less commonly across the ventricular septum. Perforation may be asymptomatic or cause chest pain from pericarditis. It causes intermittent or complete failure to pace and/or diaphragmatic pacing. Diaphragmatic stimulation can also occur in the absence of perforation. Obvious intercostal muscle stimulation may also occur with perforation. The ECG may show a right bundle branch pattern

(dominant R wave) in lead V1 during pacing if the lead stimulates the left ventricle. The chest radiograph may show the lead beyond the cardiac shadow. Transesophageal echocardiography is superior to transthoracic echocardiography in delineating the entire course of a pacing lead. A two-dimensional echocardiogram may be diagnostic in localizing the tip of the lead outside the heart and may show a pericardial effusion. Multiple views are required to follow the lead and localize the tip beyond the epicardium. Echocardiography is superior to radiography, conventional and spiral computed tomography (CT) scan for the diagnosis.

Accessory muscle stimulation

Accessory muscle stimulation may occur at several sites.

1. Contraction of the diaphragm. Left diaphragmatic stimulation by pacemaker stimuli may occur during traditional pacing with and without lead perforation of the RV. Perforation must always be excluded when diaphragmatic pacing is observed. Late appearance of diaphragmatic pacing suggests an insulation defect of the pacing lead. Left ventricular pacing from a coronary vein (in the absence of perforation) is an important and troublesome cause of left diaphragmatic pacing during biventricular pacing for the treatment of heart failure. Contraction of the right diaphragm is related to a malpositioned right atrial electrode.
2. Left intercostal muscle stimulation is invariably the result of ventricular lead perforation.
3. Deltopectoral muscle stimulation (twitching) owing to:
   (a) an extravascular lead insulation leak. In the case of a bipolar pacemaker, it always indicates an insulation problem;
   (b) a unipolar pacemaker that has flipped over in a large pocket so that the anodal plate faces the skeletal muscle;
   (c) a normally functioning unipolar pacemaker without any other problems. This is now rare with better pacemaker design but can occur at high voltage outputs.

Decreasing the output voltage with preservation of an adequate safety margin often minimizes or eliminates accessory muscle stimulation. Decreasing the pulse duration alone is usually ineffective.

Pacemaker syndrome

Pacemaker syndrome refers to a clinical situation in the pacemaker patient caused by inadequate timing of atrial and ventricular contractions. The main problems are reduced cardiac output and hypotension. The symptoms may be obvious in about 10–20% of patients with VVI pacemakers, but may be more common with less severe manifestations. The clinical manifestations can be subtle and easily missed. Obvious symptoms include dizziness, syncope, dyspnea (precipitation of pulmonary venous congestion), fatigue, pulsations in the neck, and cough. Pacemaker syndrome occurs typically in patients with intermittent VVI pacing, mostly with retrograde VA conduction. The diagnosis is supported by comparing the blood pressure during AV synchrony and during ventricular pacing. During ventricular pacing the systolic pressure should drop 20 mmHg or more for the diagnosis. The pacemaker syndrome is most commonly associated with retrograde ventriculoatrial (VA) conduction but it may also be caused by complete AV dissociation without retrograde VA conduction. Patients with a VVIR pacemaker may develop pacemaker syndrome only during exercise when the spontaneous rate is adequate at rest but not on exercise when pacing supervenes. The treatment of the pacemaker syndrome is restoration of AV synchrony. The implantation of a dual chamber pacemaker does not necessarily prevent pacemaker syndrome if the mode or programming fails to provide appropriate AV synchrony. It is therefore important to optimize the AV delay of DDD pacemakers for maximum hemodynamic benefit.

Caveat: Do not attribute symptoms to "old age" because pacemaker syndrome is basically an iatrogenic condition which is easily reversible.

Electrical complications

The various complications and methods of troubleshooting are presented in Tables 8–17. Loss of capture by visible stimuli is presented in the illustrated section.

Never neglect determination of atrial capture in dual chamber pacemakers

The presence of atrial stimuli does not mean atrial capture. Unsuspected atrial fibrillation is a common cause of lack of atrial capture. Telemetered AP markers simply reflect release of AP and cannot indicate successful atrial capture.

Table 8. Absence of pacemaker stimuli.

1. Normal situation: total inhibition of pacemaker when the intrinsic rate is faster than the preset pacemaker rate
2. Hysteresis with normal pacemaker function: escape interval after ventricular sensing is longer than the automatic interval during pacing
3. Pseudomalfunction: overlooking tiny bipolar stimuli in the ECG
4. Normal pulse generator with poor anodal contact:
   (a) subcutaneous emphysema with air preventing contact of anode of unipolar pacemaker with the tissues. This occurs soon after subclavian vein puncture
   (b) air entrapment in the pacemaker pocket preventing contact of anode of unipolar pacemaker with the tissues; this may occur after battery replacement when a smaller (new) pacemaker is inserted in a large pacemaker pocket
5. Lead problems: fracture, loose connection or set screw problem on the pacemaker itself
6. Abnormal pulse generator:
   (a) total battery depletion
   (b) component failure
   (c) sticky reed switch (magnet application produces no effect)
7. Extreme electromagnetic interference
8. Oversensing of signals originating from outside or inside the pulse generator
9. Filter settings of ECG recorder masking pacing stimuli
10. Saturation of ECG amplifier

Table 9. How to test for atrial capture.

1. If the paced P wave is not discernible in the 12-lead ECG, record the ECG at double standardization to bring out P waves and tiny bipolar stimuli; faster paper speed may help
2. In the presence of relatively normal AV conduction, program the AAI or AOO mode; use several pacing rates to demonstrate the consistent relationship of the atrial stimulus to the succeeding spontaneous conducted QRS complex
3. In patients with AV block, reduce the pacing gradually to 30 p.p.m.; this is often well tolerated. Then use the AAI or AOO at various fast rates to determine atrial capture by looking at the P wave configuration and rate which must correspond to the pacing rate
4. A paced P wave may be difficult to see if the AV delay is too short. A relatively late P wave can be unmasked by prolonging the AV delay. A "late" P wave from the atrial stimulus usually indicates interatrial conduction delay and the risk of delivering the P wave too late to provide appropriate AV synchrony. In other words the atrial transport function provided by atrial pacing may be largely wasted if the P wave is too close to the paced QRS complex. In severe cases the paced P wave occurs inside the paced QRS complex. Such a patient requires careful programming of the AV delay under echocardiographic control and evaluation for pacemaker syndrome
5. Shorten the AV delay; if the paced QRS morphology changes, it means that there was ventricular fusion with the spontaneous QRS complex at the longer AV delay and therefore atrial capture giving rise to AV conduction
6. In patients with relatively fast sinus rhythm, program the DVI mode which provides competitive atrial pacing beyond the atrial myocardial refractory period
7. In patients with retrograde VA conduction, subthreshold atrial stimulation causes retrograde P waves identifiable in the ST segment. Such P waves reflect lack of atrial capture and may be documented with event markers. Their disappearance constitutes presumptive evidence of successful atrial capture
8. Atrial capture can also be evaluated with only the programmer using its ECG recorder and markers. Increase the pacing rate above the intrinsic rate and decrease the atrial output. Lack of capture will cause AS, AR and AP markers to march through in a seemingly haphazard way. Increase the atrial output gradually until the AS and AR markers disappear. At that point atrial capture has occurred. This provides an easy way to determine the pacing threshold without a regular ECG machine

Table 10. Causes of undersensing.

Normal situations	Ventricular premature complexes with a small electrogram different from that of sensed conducted beats Beats falling inside blanking or refractory periods. Oversensing can cause undersensing because an oversensed signal generates a refractory period into which a succeeding physiologic signal cannot be sensed*
Abnormal situations	Poor lead position with low amplitude electrogram Lead dislodgment: low amplitude electrogram Lead malfunction: insulation defect or partial fracture Hyperkalemia, severe metabolic disturbance and toxic effects of antiarrhythmic drugs Transient undersensing after cardioversion or defibrillation Chronic fibrosis and scarring around the electrode Signal attenuation with the passage of time Development of new bundle branch block Myocardial infarction near the electrode Electronic component failure (rare) Jammed magnetic reed switch (rare) Interference with reversion to the noise-reversion asynchronous rate Attenuation of adequate cardiac signal upon entry in the pacing system: mismatch between input and source impedance (e.g. combination of large surface area electrode with low input impedance pulse generator (rare with contemporary pacemakers)

*Ventricular pseudofusion beats should not be mistaken for undersensing.

Reminder: Occasionally undersensing with a small bipolar signal can be corrected by programming to unipolar sensing. Do not expect an appropriately programmed pacemaker to sense all kinds of VPCs because they are associated with a variety of electrograms some of which may not be sensed because of a low amplitude and/or slow slew rate. Attempting to increase sensitivity to sense all VPCs may cause oversensing.

Apparent atrial undersensing in dual chamber pacing (functional atrial undersensing)

True atrial undersensing is an important cause of prolongation of the interval from AS to VS beyond the programmed AV delay. Barring true atrial undersensing from a low voltage atrial electrogram, the causes of lack of atrial tracking include the following.

1. Ventricular oversensing during the AV delay.
2. Long or extended *PVARP*. In the presence of a large atrial electrogram, a P wave may be forced into an excessively long *PVARP* sometimes due to automatic extension initiated by a pacemaker-defined VPC. If the patient's PR interval is quite long and the spontaneous rate is relatively fast, there is a greater likelihood that a P wave will fall closer to the preceding QRS complex and therefore in the *PVARP*, which need not be unduly long to cause "functional" atrial undersensing.
3. Upper rate response (preempted Wenckebach upper rate response). Prolongation of the AS-VS interval may result from failure of delivery of the ventricular stimulus if the *URI* has not timed out by the time the *AVI* has terminated. In this situation the interval between 2 consecutive QRS complexes must be shorter than the *URI* of the pulse generator.
4. Short but reinitiated *PVARP*. If the ventricular channel senses a signal other than the QRS (e.g. T wave), the *PVARP* is reinitiated by the oversensed signal and the P wave may fall in this new *PVARP*. In this situation, P wave sensing may be restored by decreasing the sensitivity of the ventricular channel.

Reminder: What looks like atrial undersensing may be functional atrial undersensing when associated with a large atrial signal.

Table 11. Causes of oversensing intracorporeal voltages.

Ventricular oversensing	T wave Afterpotential P wave (rare) Crosstalk: sensing of atrial stimulus Myopotentials False signals Triboelectric signals (static) in unipolar devices
Atrial oversensing	Far-field R wave (VA crosstalk) Myopotentials False signals Ventricular T wave (rare) Triboelectric signals (static) in unipolar devices

Afterpotential

The cathodal pacemaker stimulus charges the electrode–tissue interface to a large voltage (polarization voltage) that is subsequently dissipated over a relatively long time to electrical neutrality. The decay of the afterpotential (of lower amplitude, opposite polarity but longer duration than the output stimulus) creates a voltage that changes with time and thus it can be sensed (similarly to a changing spontaneous intracardiac signal) by a pacemaker coming out of its refractory period, when it will reset the lower rate interval. Sensing of the afterpotential should be suspected when the interval between two consecutive pacemaker stimuli lengthens to a value approximately equal to the sum of the lower rate interval and the pacemaker refractory period. This form of oversensing is now rare and is easily controlled by prolonging the refractory period or decreasing the output or the sensitivity.

False signals (voltage transients)

Abrupt changes in the resistance within a pacing system can produce large voltage changes between the poles used for pacing. Such signals are called false signals. False signals are almost always invisible on the surface ECG so that their presence must be assumed until they are revealed by a telemetered ventricular electrogram. Such "make-break" signals may occur with intermittent derangement of a pacemaker circuit from loose connections, wire fracture with otherwise well-apposed ends, insulation defect, short circuits, poorly designed active fixation leads or the interaction of two leads in the heart (one active, the other inactive) lying side by side and touching each other intermittently. Oversensing of false signals from a defective lead can cause erratic pacemaker behavior with pauses of varying duration. False signals often occur at random and can be demonstrated in the telemetered ventricular electrogram, often as large and irregular voltage deflections.

Remember that oversensing can be associated with undersensing, because the ventricular refractory period generated by a sensed false signal may contain a spontaneous QRS complex. This mixture of disturbances and the constantly changing pauses often create a chaotic pattern of pacing that is characteristic of a lead problem and must not be misinterpreted as pacemaker component failure. The characteristic pattern of false signals usually permits the exclusion of P wave oversensing (rare), T wave oversensing and/or afterpotential oversensing, which can be identified by more regular manifestations. The telemetered ventricular electrogram can be diagnostic when oversensing of false signals (potentially serious) mimics T wave sensing (less serious as it causes only bradycardia).

Reminder: If false signals causing oversensing are suspected, move the pacemaker around in its pocket and evaluate the effect of deep respiration, arm movement and changes in position to unmask an extravascular lead problem such an intermittent fracture. The lead impedance can be normal if the fracture is intermittent.

Myopotentials

Myopotentials represent electrical activity originating from skeletal muscles. A unipolar ventricular pacemaker may sense such myopotentials and cause ventricular inhibition. In a DDD pacemaker myopotentials sensed only by the atrial channel can be tracked and cause an increase in the ventricular pacing rate. Various maneuvers can bring out this interference during follow-up evaluation. This disturbance can often be controlled by a reduction in sensitivity or by programming to the bipolar mode if this is feasible.

Caveat: Lack of ventricular pacing during provocative maneuvers for myopotential oversensing may be the result of myopotential inhibition (oversensing), but may sometimes be caused by an intermittent lead fracture that has become manifest during the testing procedure.

Pacemaker response to oversensing interference

Pacemakers can be inhibited by low frequency interference which is uncommon. Pacemakers are designed to respond to rapidly occurring (high frequency) extraneous signals by reverting temporarily to the protective asynchronous mode (interference mode) functioning usually at the programmed lower rate. A signal sensed in the unblanked portion of the ventricular refractory period (*VRP*) or in a part thereof (specifically called the noise sampling period) reinitiates a new *VRP* or noise sampling period respectively. This process repeats itself with each detected signal so that the "overlapping" effect of these special timing cycles prevents the initiation of a lower rate interval because the entire pacemaker cycle consists of *VRP* or noise sampling periods. This repeated reinitiation or overlapping effect assures the delivery of a pacemaker stimulus at the interference rate. The pacemaker returns to its normal operating mode when noise is no longer detected.

Follow-up of lead impedance

The lead is the weakest link in the pacing system. Lead impedance tends to fall in the first 2 weeks after implantation but then reaches a plateau and remains relatively stable at approximately 15% higher than the implantation value. Some pacemakers automatically track the impedance over time by making periodic measurements. The trend data can be retrieved by standard pacemaker interrogation. Fluctuations of impedance by as much as 300 Ω are often considered normal. Such a change in an asymptomatic patient, however, warrants closer follow-up.

Reminder: A magnet over an ICD eliminates its antitachycardia function but does not convert it to asynchronous pacing.

Table 12. Causes of changes in pacing rate.

Normal function	Application of the magnet Inaccurate speed of ECG machine Apparent malfunction in special situations such as hysteresis, sleep rate Reversion to interference rate in response to electromagnetic interference if the noise reversion rate differs from the programmed lower rate
Abnormal function	Battery depletion with slowing of the rate Runaway pacemaker Component failure Permanent or temporary change in mode after electrocautery, therapeutic radiation, or defibrillation Phantom reprogramming (done without documentation) or misprogramming Oversensing (e.g. T wave sensing) Crosstalk resulting with ventricular safety pacing causing an increase in the pacing rate

Table 13. Manifestations of lead fracture.

- No stimuli because of an open circuit (markers may show normal emission of stimulus)
- Stimuli without capture
- Oversensing of false signals; the false signals are invisible on the ECG but can be demonstrated by telemetry of event markers and electrograms
- Oversensing can cause undersensing; occasionally the sensed signal itself can be attenuated
- Telemetry showing an abnormally high lead impedance, but the value can be normal if the fracture is intermittent or there is a concomitant insulation break
- Maneuvers: if suspected, one should apply pressure along the course of the subcutaneous portion of the lead, extend the arm on the side of the pacemaker, place the arm behind the back, and rotate the shoulder backward to unmask a crush injury due to clavicle–first rib compression
- A fracture may or may not be detectable on a radiograph

Table 14. Manifestations of insulation defect.

- Extracardiac muscle stimulation if the defect is extravascular (twitching)
- Pacing may be preserved but loss of capture can occur when a large current is shunted from the electrodes; an insulation defect accelerates battery depletion
- Undersensing from signal attenuation
- Oversensing of false signals; oversensing can cause undersensing
- False signals are invisible on the ECG but telemetry with annotated markers can demonstrate false signals on the electrogram (also programming in the AAT or VVT mode may be of help)
- Telemetry shows an abnormally low lead impedance, but the value can be normal if the insulation defect is intermittent
- The insulation is radiolucent and abnormalities cannot be detected on a radiograph

Table 15. Presence of an atrial stimulus but no ventricular stimulus during DDD or DDDR pacing.

1. Atrial pacing followed by a conducted QRS complex before completion of the AV delay; apply the magnet for diagnosis
2. Isoelectric or tiny ventricular stimuli; use double standardization of the ECG machine
3. Concealed ventricular stimuli within the QRS complex (pseudofusion); marker channel confirms diagnosis
4. Disconnection of the ventricular circuit as in a lead fracture; this causes apparent AAI pacing; reprogram to the VVI mode whereupon no stimuli will be seen in the VVI and VOO (magnet) modes
5. Crosstalk in devices *without* ventricular safety pacing; application of the magnet confirms diagnosis
6. Oversensing during the AV delay; apply magnet; use telemetry to demonstrate the electrogram and annotated markers

Table 16. Presence of ventricular stimulus but no atrial stimulus during DDD or DDDR pacing.

1. In some devices, magnet application causes VOO pacing
2. Disconnection of the atrial circuit: VVI pacing in the DDD mode and no stimulation the AAI and AOO modes
3. Isoelectric or tiny atrial stimuli; use double standardization of the ECG machine
4. Concealed atrial stimuli within the QRS complex (pseudopseudofusion); use marker channel for diagnosis
5. DDI mode when the atrial channel is continually inhibited; apply magnet for diagnosis
6. Apparent VVI pacing: the atrial stimulus (occasionally because of atrial undersensing) is coincident with the onset of the spontaneous QRS complex with a left bundle branch block configuration

Table 17. Pacemaker magnet application.

1. Conversion to the asynchronous mode; VOO or DOO according to programmed mode
2. Assess capture during asynchronous pacing
3. Elective replacement indicator
4. Provides reed switch activation as required for some programmers to function
5. Eliminates sensing; useful during electrocautery; provides diagnosis of oversensing
6. Patient can trigger electrogram storage during symptomatic episode
7. Termination of endless loop tachycardia
8. Competitive underdrive pacing for the termination of some reentrant tachycardias
9. May help identification of device as some have typical magnet response

Table 18. Data required in pacemaker chart.

Patient data	Name, age, address, phone number, etc.
Pacemaker data	Date of implantation
	Model and serial number of leads
	Model and serial number of pulse generator
Data form implantation	Pacing threshold(s)
	Sensing threshold(s)
	Intracardiac electrograms
	Lead impedance(s)
	Status of retrograde VA conduction
	Presence of diaphragmatic or accessory muscle stimulation with 5 and 10 V output
Technical specifications	Pacemaker behavior in the magnet mode
	Record of elective replacement indicator: magnet and/or free running rate, mode change, telemetered battery data (impedance and voltage)
Data from pacemaker clinic	Programmed parameters from time of implantation and most recent changes
	12-lead ECG and long rhythm strips showing pacing and inhibition of pacing to evaluate underlying rhythm
	12-lead ECG upon application of the magnet
	Electronic rate intervals and pulse duration measured with a special monitor
	Interrogation and printout of telemetric data
	Always print a copy of the initial interrogation and measured data.
Systematic evaluation of pacing system	Atrial and ventricular pacing and sensing thresholds
	Retrograde VA conduction and propensity to endless loop tachycardia
	Evaluation of crosstalk
	Myopotential interference (record best way of reproducing abnormality)
	Special features: automatic mode switching parameters, ventricular safety pacing, noncompetitive atrial pacing, etc.
	Evaluation of sensor function with exercise protocols, histograms and other data to demonstrate heart rate response in the rate-adaptive mode
	Final telemetry printout at end of evaluation and date. Check that any changes in parameters are intentional by comparing the final parameters with those obtained at the time of initial pacemaker interrogation. Any discrepancy must be justified in the record.
Ancillary data	Symptoms and potential pacemaker problems
	ECG with event markers and electrograms mounted in the chart
	Intolerance of VOO pacing upon application of the magnet

Table 19. Causes of increased battery current drain affecting battery longevity. This is the most important determinant of battery longevity (expressed in A). Pacing requires more current than sensing.

1. The greater the % pacing, the shorter the longevity
2. Increase in the pacing rate (cycle length).
3. Increase in output voltage
4. Increase in pulse duration
5. Change from single chamber to dual chamber mode
6. Use of rate-adaptive function with nonatrial sensor
7. Decrease in lead impedance
8. Programming, telemetering, storage of diagnostics

Impedance while not programmable, can be controlled by selecting a high impedance lead at the time of implantation.

Pacemaker longevity can be enhanced by careful programming and selecting steroid-eluting leads with a small radius tip electrode (small surface area for stimulation) that provide low thresholds and efficient high impedance (over 1000 Ω). The high impedance is at the electrode–tissue level where the maximum voltage is available at the electrode tip for stimulation. The high impedance reduces current drain from the battery by Ohm's law. Thus, ideally one should implant small surface area, steroid eluting and porous electrodes. The porosity creates a complex surface structure which increases the effective surface area for sensing and improves the efficiency of sensing.

Caveat: Do not confuse battery current drain with current output (mA) at the electrode–myocardial interface with delivery of the pacemaker pulse. When trying to conserve battery life, monitor the battery current drain as you program various parameters.

Caveat: From the elective replacement indicator (ERI) point, a pacemaker will reach end-of-life (EOL) or end-of-service (EOS) in about 3 months. At EOL pacing becomes erratic and unreliable with the possibility of total system failure.

Table 20. Elective replacement indicator (ERI) vs. reset situation. Differential diagnosis when the mode of operation is identical.

The reset mode, usually VVI or VOO, represents a normal protective response to high intensity electromagnetic interference. A reset pacemaker does not represent malfunction and it can easily be reprogrammed to its previous mode.

The backup pacing circuit of certain DDD pacemakers can produce a similar situation when activated by low battery voltage as a mechanism to reduce the current requirement from the battery

1. In ERI (or recommended replacement time – RRT), the battery voltage is low and the battery impedance is high. The ERI point is manufacturer-defined. Note that when the battery voltage of a dual chamber pacemaker reaches ERI, switching to the VVI mode automatically increases the battery voltage to a higher level than the specified ERI point. In reset, the battery voltage is high and the battery impedance has not yet reached the ERI point
2. Battery stress test: program the pacemaker to dual chamber mode at a relatively fast rate and high output and watch for a while. If the pacemaker continues to function normally, the diagnosis was reset. If it switches back to VVI the diagnosis was ERI

Automatic mode switching

In the past, paroxysmal atrial arrhythmias constituted a contraindication to dual chamber pacing. Advances in pacemaker technology have now made it possible to use dual chamber pacemakers safely in this patient population. Dual chamber pacemakers equipped with automatic mode switching (AMS) can now protect the patient from rapid ventricular pacing by automatically functioning in a nonatrial tracking mode (VVI, VVIR, DDI, DDIR) during supraventricular tachycardia. AMS requires fundamental changes in the operation of pacemaker timing cycles to maximize

supraventricular tachycardia detection above the programmed upper rate. Although many of the AMS algorithms from a variety of manufacturers are device-specific, the timing cycles required for supraventricular tachycardia detection are basically independent of AMS algorithm design. For appropriate supraventricular tachycardia detection the atrial signal should be of sufficient amplitude and the obligatory blanking periods (when the sensing amplifier is temporarily disabled), should be restricted to a small fraction of the pacing cycle. Blanking periods cannot be eliminated because they prevent oversensing of undesirable signals inherent to all pacing systems.

VA crosstalk

The atrial channel cannot sense a signal associated with the ventricular stimulus because the atrial channel of all pacemakers is blinded or blanked by the relatively long postventricular atrial blanking that starts coincidentally with emission of the ventricular stimulus. Ventriculoatrial (VA) or reverse crosstalk refers to far-field sensing that occurs when ventricular signals in the atrial electrogram are sensed by the atrial channel in the *PVARP* beyond the postventricular atrial blanking period (sensing the paced QRS complex) or in the unblanked terminal portion of the AV delay (sensing the spontaneous QRS complex). VA crosstalk occurs because the smaller atrial electrograms during supraventricular tachycardia require programming a higher atrial sensitivity for sensing than those needed to sense the normal rhythm. VA crosstalk can often be eliminated by reducing atrial sensitivity but this carries the risk of atrial undersensing during supraventricular tachycardia when atrial signals become smaller. Far-field atrial sensing may be reduced by the use of bipolar sensing and improved pulse generator and lead technology.

Caveat: Detection of smaller signals during atrial tachyarrhythmias requires a high atrial sensitivity, which predisposes to VA crosstalk.

Timing cycles related to automatic mode switching

The unblanked portion of the *AVI* (initiated by a paced or sensed atrial event) was designed to enhance sensing of atrial fibrillation during the *AVI* to facilitate AMS. A ventricular paced or sensed event initiates the postventricular atrial refractory period (*PVARP*), the first portion of which is the postventricular atrial blanking period (*PVAB*). The second part of the *PVARP* is unblanked (*PVARP*-U) but sensing within it cannot initiate an AV delay. The *PVARP* initiated by ventricular pacing is almost always equal to the *PVARP* initiated by ventricular sensing. Far-field sensing within the *PVARP* can be corrected by programming lower atrial sensitivity or the *PAVB* to a longer value. Programmability of the *PVAB* is a relatively new feature of pacemakers. A long *PVAB* predisposes to atrial undersensing of supraventricular tachycardia crucial for AMS activation. Sensing of supraventricular tachycardia for AMS function is therefore possible during the unblanked refractory periods (*AVI-U* and *PVARP-U*) as well as during the cycle without atrial refractory periods where atrial sensing initiates an AV delay.

Retriggerable atrial refractory period

Some pacemakers work with an atrial refractory period that can be retriggered or reset by reverting to the DVI or DVIR mode upon sensing a fast atrial rate. In such a system, an atrial signal detected in the *PVARP* beyond the initial *PVAB* does not start an *AVI* but reinitiates a new total atrial refractory period (*TARP*) or the sum of *AVI* and *PVARP*. This process repeats itself so that supraventricular tachycardia faster than the programmed upper rate (i.e. P–P interval <*TARP*) automatically converts the atrial channel to the asynchronous mode and the pacemaker to the DVI mode at the lower rate or the DVIR mode according to design and programmability.

Reminder: The concept of overlapping refractory periods is also important in the ventricular channel of pacemakers to prevent continuous inhibition from rapidly recurring extraneous signals from interference.

Testing for VA crosstalk

The propensity for VA crosstalk during the *PVARP* should be tested during ventricular pacing. The AS–VP interval is shortened to permit continual ventricular capture. The pacemaker is then programmed to the highest atrial sensitivity and the largest ventricular output (voltage and pulse duration). These settings should be evaluated at several pacing rates to at least 110–120 p.p.m. because faster ventricular pacing rates impair dissipation of the afterpotential or polarization voltage at the electrode–myocardial interface. Such parameters enhance the afterpotential and therefore generate a voltage superimposed on the tail end of the paced QRS complex. The combined voltage from these two sources may be sensed as a far-field signal by the atrial channel. VA crosstalk can be eliminated by decreasing atrial sensitivity provided one knows that the atrial signals

during supraventricular tachycardia can be sensed at the lower sensitivity. In devices with a programmable *PAVB*, the testing procedure if positive for VA crosstalk can be performed at various durations of the *PVAB* until VA crosstalk is eliminated. VA crosstalk within the *AVI* is evaluated by programming a low lower rate and long *AVI* to promote spontaneous sinus rhythm and AV conduction.

Detection of atrial flutter by dual chamber pacemakers

In some designs, the duration of the blanking periods prevents the pacemaker from detecting atrial flutter, if the atrial cycle does not match the sensing window of the atrial channel. In other words, the duration of the *PVAB* imposes mathematical limits on the detection of atrial flutter. If *AVI* + *PVAB* > atrial cycle length (P–P or f–f interval), the pacemaker will exhibit 2:1 atrial sensing of atrial flutter (2:1 lockout). Sensing of alternate atrial signals will occur if *AVI* + *PVARP* < 2 atrial cycles. Abbreviation of the *PVAB* may solve the problem if far-field R wave sensing does not occur. If *PVAB* is nonprogrammable, restoration of 1:1 atrial sensing would require programming of the *AVI* to very short durations such as 50 ms. Restoration of AMS function by shortening of the *AVI* to circumvent a fixed *PVAB*, produces unfavorable hemodynamics for long-term pacing if the *AVI* remains permanently short in the absence of supraventricular tachycardia.

The detection of atrial signals can be ameliorated by reducing the blanked *AVI*. Thus, a design that allows substantial shortening of the AS–VP interval only with increasing sensed atrial rates, optimizes sensing of atrial flutter, and yet preserves a physiologic *AVI* at rest and low levels of exercise. During supraventricular tachycardia when (AS–VP interval) + *PVAB* = 30 + 150 = 180 ms this combination allows sensing of atrial flutter with a cycle length up to 180 ms (rate = 333/min). Another algorithm specifically designed for atrial flutter, automatically extends the *PVARP* for one cycle whenever the pacemaker detects an atrial cycle length less than twice (*AVI* + *PVAB*) and the atrial rate is greater than half the tachycardia detection rate (or the atrial interval is less than twice the tachycardia detection interval). AMS occurs if an atrial event is sensed within the extended *PVARP* thereby revealing the true atrial cycle.

Caveat: Troubleshooting automatic mode switching requires knowledge of the algorithm, blanking periods and atrial signal in sinus rhythm and atrial sensitivity.

Pacemaker follow-up

The frequency and type of follow-up depend on the projected battery life, type, mode, and programming of pacemakers, the stability of pacing and sensing, the need for programming change, the underlying rhythm (pacemaker dependency), travel logistics, type of third party insurance and alternative methods of follow-up such as the telephone. Most centers follow the Medicare guidelines for pacemaker follow-up (i.e. for single chamber pacemakers: twice during the first 6 months after implant and then once every 12 months; for dual chamber pacemakers: twice during the first 6 months after implant and then once every 6 months). Transtelephonic monitoring is recommended as part of a comprehensive and cost-effective pacemaker patient management program. Telephone follow-up is designed to supplement periodic visits to the pacemaker center and should not replace comprehensive follow-up. It provides early detection of device-related complications. As a rule, transtelephonic follow-up from the convenience of the patient's home does not allow programming and transmission of telemetry data though the latter may soon become possible via the Internet. Medicare guidelines have also been published for telephone follow-up. A typical transtelephonic test takes approximately 15 min. Patients use a simple device that transmits useful information regarding the basic functional capabilities of the pacemaker.

Holter recordings in pacemaker follow-up

Holter monitoring is useful in the investigation of unexplained symptoms such as syncope, dizziness and palpitations. In *routine* Holter recordings the commonest abnormalities consist of atrial undersensing and myopotential interference in unipolar systems. The interpretation of recordings from DDD pacemakers may be difficult or impossible because of various pauses, apparent shortening of intervals, or missing or concealed stimuli. A system that enhances the pacemaker stimulus (and displays it in a separate channel) may be very useful. However, such a system may generate electrostatic discharges that produce deflections from loose electrodes, etc., resembling pacemaker stimuli. Spurious pacemaker stimuli should not be misinterpreted as pacemaker malfunction.

The pacemaker as an implantable Holter system

Histograms cannot separate events or determine when they occur. However, histograms are useful to evaluate the programmed sensor response provided there is a breakdown of the heart rates into ranges. Histograms may also enhance programmability of the *AVI*. Intermittent atrial fibrillation should be suspected if an atrial histogram shows a high rate event. It is questionable whether marker annotations alone stored in pacemaker memory are useful in assessing the number and duration of arrhythmic episodes. The recent development of electrogram storage and retrieval by pacemakers (available for some time in ICDs) has added a new dimension to the diagnosis of spontaneous arrhythmias and device malfunction in patients with pacemakers. Pacemakers store the data either automatically according to a detection algorithm or by a patient-activated system whenever a symptomatic patient applies a magnet or a special activator over the device. Annotated high-quality electrograms allow reliable assessment of stored episodes by visual inspection in practically 100% of cases. The final diagnosis of the retrieved data scrutinized by the physician may, of course, differ from the automatic interpretation by detection algorithm of the device. Detection algorithms for the detection of supraventricular tachyarrhythmias are further developed than those for ventricular tachyarrhythmias which are still rudimentary.

The electrogram must be sampled at twice the minimal frequency component to register all the information contained in it. Sampling at 256 samples/s allows good reproduction and a minimum rate of 128 samples/s is necessary to achieve a sufficiently diagnostic EGM quality. One byte of memory is generally required for each sample. Assuming a pacemaker with 8 K of memory dedicated to EGM recording, and a sampling rate of 128 samples/s, the duration of (uncompressed) single channel EGM recording is 8 K × 1024 bytes/K ÷ 128 bytes/s which is equal to 64 s. Compression algorithms can increase this duration further because repeated sequences such as the baseline can be stored using far less memory. Thus the 64 s in the previous example can be expanded to 320 s with 5:1 average compression yielding 320 s of EGM storage.

Pacemaker technology can now store electrograms with the following features:

1. separate channels for atrial and ventricular EGMs of sufficient resolution and duration;
2. onset and termination data: a programmable number of cardiac cycles before arrhythmia onset ("pre-trigger EGM") and some cycles after arrhythmia termination;
3. simultaneous annotated markers (essential); marker annotations and intervals to facilitate understanding why and how the pacemaker detected and classified an event. An additional marker annotation (e.g. arrow, line) should indicate the exact moment when arrhythmia detection criteria are fulfilled.

The memory capability of modern pacemakers promises to improve our understanding of a variety of electrophysiologic mechanisms that will enhance the diagnosis and treatment of atrial and ventricular tachyarrhythmias. The memory function will be especially useful to optimize programming of increasingly complex devices.

What is cardiac resynchronization?

Cardiac resynchronization refers to stimulation techniques that improve the degree of atrial and/or ventricular electrical dyssynchrony in patients with major (intra- or inter-) atrial and/or ventricular conduction disorders. The latter includes left bundle branch block and the interventricular conduction delay induced by conventional RV pacemakers. Resynchronization produces beneficial hemodynamic effects because of a more physiologic or effective pattern of depolarization. For example, in the treatment of congestive heart failure with dilated cardiomyopathy and left bundle branch block, the change in electrical activation from resynchronization (with biventricular pacing), which has no positive inotropic effect as such, is translated into mechanical improvement with a more coordinated ventricular contraction.

Atrial resynchronization

Multisite atrial resynchronization was introduced for the treatment of severe interatrial conduction delay in patients with sick sinus syndrome and/or paroxysmal atrial fibrillation. Interatrial conduction delay can usually be diagnosed from the ECG in the presence of P waves > 120 ms. Hemodynamically, the delay of electrical activation from a single pacing site in the right atrium to the left atrium may not produce an optimal mechanical AV delay on the left side of the heart. Thus, conventional right atrial pacing may generate left atrial systole too close to or during ventricular systole with the resultant loss of effective atrial contribution. Additionally atrial resynchronization may prevent paroxysmal atrial fibrillation in selected patients. Atrial resynchronization can be achieved with simultaneous (biatrial)

pacing from the right atrial appendage and the left atrium (via the coronary sinus), or a bifocal system involving simultaneous atrial pacing from the right atrial appendage and the atrial septum very close to the coronary sinus os.

Dilated cardiomyopathy and congestive heart failure: ventricular resynchronization

Dual site or biventricular (RV and LV) pacing has emerged as an effective therapy for patients with dilated cardiomyopathy (severe systolic LV dysfunction) and congestive heart failure associated with major left-sided intraventricular conduction delay such as left bundle branch block. This intraventricular conduction disorder causes an inefficient dyssynchronous or uncoordinated pattern of LV activation with segments contracting at different times with a characteristic wobble of the interventricular septum. The erratic LV contraction causes a shorter diastole and/or overlapping systole/diastole with aggravation of functional mitral regurgitation. Biventricular pacing works by reducing the degree of electromechanical disparity. Thus, the improved sequence of electrical activation (a process known as resynchronization) translates into beneficial acute and long-term hemodynamic effects by virtue of a more coordinated and efficient LV contraction associated with a reduction of functional mitral regurgitation. The hemodynamic benefit occurs virtually with an on/off effect (with possible long-term reverse remodeling of the LV) and stems primarily from ventricular recoordination rather than optimization of the AV delay. A recent study suggests that this therapy may also reduce mortality. An optimized AV delay is important but it is not the major factor for improvement in most patients. The proper site of LV stimulation (best in the lateral or posterolateral area) is the most important determinant of a successful hemodynamic response. Some hemodynamic benefit may be obtained by programming the V–V interval (interval between RV and LV stimulation) available in second-generation biventricular pacemakers under echocardiographic control. The LV usually has to be programmed ahead of the RV.

The clinical value of resynchronization with biventricular stimulation has now been established for ≥ 2 years in clinical trials. The functional benefit of resynchronization is sustained over time. However about 20–30% of patients are nonresponders. Patients with idiopathic cardiomyopathy respond better than those with coronary artery disease. In general, long-term resynchronization improves the systolic blood pressure, cardiac output, LV ejection fraction (3–5%) and reduces mitral regurgitation (about 50%). Patients with permanent atrial fibrillation benefit from resynchronization to a lesser degree than those in sinus rhythm. With atrial fibrillation, RF ablation of the AV junction is necessary to ensure continual ventricular depolarization by the biventricular system.

Indications for biventricular pacing (cardiac resynchronization)

Patients with a QRS duration > 150 ms are more likely to improve than those with a QRS between 120 and 150 ms. In a given patient, however, the precise QRS duration is not always predictive of benefit. Biventricular pacing should be considered in medically refractory symptomatic New York Heart Association class III or IV patients with idiopathic dilated or ischemic cardiomyopathy, prolonged QRS (≥ 130 ms), LV end-diastolic diameter ≥ 55 mm (on the echocardiogram), and LV ejection fraction ≤ 35%. Patients with systolic congestive heart failure and a previously implanted RV pacemaker (with a very wide paced QRS complex) are also candidates for biventricular pacing.

Complications

Complications of biventricular pacing include lead dislodgment (5–10%), high pacing threshold (of LV pacing), acute cardiac tamponade from coronary sinus dissection (though dissection is often benign) and phrenic nerve stimulation (causing disturbing diaphragmatic contractions), which can be a major problem. The long duration of the implantation procedure is associated with a higher rate of pocket infection. First generation devices with simultaneous sensing from both ventricles may exhibit special problems, such as double sensing of the QRS complex and oversensing of the P wave by the LV lead (usually because of displacement towards the left atrium) as discussed later.

Electrocardiography

A baseline 12-lead ECG should be recorded at the time of implantation during assessment of the independent capture thresholds of the RV and LV to identify the specific morphology of the paced QRS complexes in a multiplicity of leads. This requires having the patient connected to a multichannel 12-lead ECG during the implantation procedure. A total of four 12-lead ECGs are required:

1. intrinsic rhythm and QRS complex before any pacing;
2. paced QRS associated with RV pacing;

3. paced QRS associated with LV pacing;
4. paced QRS associated with biventricular pacing.

The four tracings should be examined to identify the lead configuration that best demonstrates a discernible and obvious difference between the four pacing states (inhibited, RV only, LV only, and biventricular). This ECG lead should then be used as the surface monitoring lead for subsequent evaluations. Loss of capture in one ventricle will cause a change in the morphology of ventricular paced beats in the 12-lead ECG to that of either single chamber RV pacing or single chamber LV pacing. When there is intact capture in both the RV and LV, the evoked response on the ventricular electrogram will show a monophasic complex in contrast to two distinct deflections (RV and LV electrograms) during spontaneous conduction if the native QRS is wide (left intraventricular conduction delay). With loss of capture in one of the ventricles, the ventricular lead which is still effective will cause a depolarization of that ventricle. The impulse will then have to be conducted via the native pathways to the other ventricle in an manner identical to single ventricular systems with standard pacing. If RV pacing is preserved and there is failure of LV capture associated with a significant left intraventricular conduction delay, the ventricular electrogram will change from a monophasic complex to one showing one relatively late and discrete deflection (electrogram) representing late activation of the LV. A shift in the frontal plane axis may be useful to corroborate the loss of capture.

Reminder: A qR or Qr complex in lead I is rare in uncomplicated RV apical pacing. It is present in 90% of cases of biventricular pacing. In biventricular pacing, loss of the q or Q wave in lead I is 100% predictive of loss of LV capture.

The preempted Wenckebach upper rate response

In a traditional Wenckebach upper rate response, a dual chamber pacemaker (where upper rate interval > total atrial refractory period) delivers its ventricular stimulus only at the completion of the (atria-driven) upper rate interval. The AV delay initiated by a sensed P wave increases progressively because the ventricular channel waits to deliver its output at the end of the upper rate interval. Eventually a P wave falls in the *PVARP*, a pause occurs and the ventricular *paced* sequence repeats itself. In patients with pacemakers implanted for congestive heart failure, the Wenckebach upper rate response (or more precisely the manifestation of upper rate > total atrial refractory period) assumes a form that is not immediately recognizable because no paced beats are evident.

In patients with normal or near normal sinus node function and AV conduction, a pacemaker Wenckebach upper rate response takes the form of a repetitive preempted process which consists of an attempted Wenckebach upper rate response with each cycle, associated with continual *partial* or *incomplete* extension of the programmed *AVI*. The conducted spontaneous QRS complex continually occurs before completion of the upper rate interval. It is therefore sensed by the pacemaker, and ventricular pacing is preempted. In other words, the pacemaker cannot time out the upper rate interval and thus cannot emit a ventricular stimulus at its completion. This form of upper rate response tends to occur in patients with relatively normal AV conduction, a short programmed AV delay, a relatively slow programmed (atrial-driven) upper rate, and a sinus rate faster than the programmed (atrial-driven) upper rate. It is therefore more likely to emerge on exercise or during times of distress when adrenergic tone is high. Consequently the preempted Wenckebach upper rate response has become important recently because pacemakers are now implanted in patients with congestive heart failure (or hypertrophic cardiomyopathy) where there is usually relatively normal sinus node function and AV conduction. The occurrence of a preempted Wenckebach response in such patients defeats the very purpose of this type of cardiac stimulation. Hence, in patients with congestive heart failure susceptible to sinus tachycardia (despite beta-blocker therapy and especially during decompensation), it is important to program a relatively fast upper rate during biventricular pacing to avoid a preempted Wenckebach upper rate response with resultant loss of cardiac resynchronization manifested by the emergence of the patient's own QRS in the electrocardiogram.

In summary, a preempted Wenckebach upper rate response has *no paced events* and is characterized by four features:

1. VS–VS interval < atrial-driven upper rate interval (VS = ventricular sensed event);
2. PR interval (AS–VS) > programmed AS–VP. The spontaneous PR interval remains relatively constant (AP, atrial paced event; AS, atrial sensed event);
3. There are no unsensed (or refractory sensed) P waves as in a typical Wenckebach upper rate response in the presence of AV block;
4. P wave tracking will not be restored until the atrial cycle length exceeds the duration of the intrinsic total atrial refractory period (intrinsic *PR* + *PVARP*).

Caveats:

1. Patients with congestive heart failure and no bradycardia may develop sinus tachycardia under certain circumstances. Therefore the upper rate of biventricular pacemakers should be relatively fast to avoid a preempted Wenckebach response that desynchronizes the heart and withholds beneficial biventricular pacing.
2. If the upper rate is programmed too low in a patient with angina pectoris, loss of ventricular resynchronization on exercise may actually precipitate angina. Such patients usually do better with a higher upper rate to permit ventricular resynchronization and improved cardiac efficiency during activity.

Double counting of the ventricular electrogram

In first generation biventricular systems, the pacemaker paces and senses from the two ventricles simultaneously. Double counting of the ventricular complex involves the spontaneous conducted wide QRS complex of left bundle branch block (as most patients do not have AV block). This situation produces temporal separation of right ventricular (RV) and left ventricular (LV) electrograms. The degree of separation depends on the severity of the interventricular conduction delay (left bundle branch block) and the location of the electrodes. The LV electrogram may therefore be sensed some time after detection of the RV electrogram if the LV signal extends beyond the relatively short ventricular blanking period initiated by RV sensing. With ventricular rhythms, the LV electrogram may precede that from the RV. Double counting in first generation biventricular cardioverter-defibrillators (sensing both RV and LV simultaneously) may cause inappropriate shocks. Second generation devices allow programming of the sensing function of the ventricular channels individually to prevent double counting (RV and LV electrograms).

The circumstances leading to the emergence of the spontaneous QRS complex and the perpetuation of double QRS counting must be understood because it prevents the delivery of therapeutic biventricular stimulation and the problem can often be corrected by appropriate programming of the pacemaker. The main causes are a long *PVARP* (that may be extended after a VPC) which pushes the sinus P in the *PVARP* (refractory sensed) where it cannot initiate an AV delay and sinus tachycardia above the programmed upper rate. When the sinus rate increases beyond the programmed upper rate, spontaneous AV conduction occurs in the form of a preempted Wenckebach upper rate response and therapeutic biventricular pacing is inhibited. Hence the importance of programming a relatively fast upper rate to prevent this process. Supraventricular and ventricular tachycardias also cause double counting, but their impact is more important in biventricular cardioverter-defibrillators when double counting may cause the delivery of an inappropriate shock.

Table 21. How to ensure biventricular pacing in a rst generation dual chamber system with a dual cathodal system (simultaneous pacing and sensing in both ventricles).

1. Low ventricular sensitivity to prevent oversensing of far-field left atrial activity
2. High output (at least initially) to ensure LV pacing
3. Program a high upper rate to prevent a preempted Wenckebach upper rate response. Programming a relatively slow rate to control angina may be counterproductive
4. Program appropriate rate-adaptive AV delay
5. Program a relatively short *PVARP*:
   (a) this may require using the "PMT" intervention function on in case the patient is prone to endless loop tachycardia
   (b) program off the *PVARP* extension response to a VPC
   (c) turn off automatic mode switching in pacemakers requiring a relatively long *PVARP* for the algorithm
6. Treat atrial fibrillation aggressively to prevent the emergence of spontaneously conducted QRS complexes
7. Use pacemaker diagnostics for % ventricular sensing to assess efficacy of biventricular pacing
8. Consider AV junction ablation in patients with atrial fibrillation and fast ventricular rate unresponsive to beta blockers

PMT = pacemaker mediated tachycardia

Caveats:

1. Ensure the absence of ventricular fusion beats with the spontaneous QRS complex to provide the patient the full benefit of biventricular pacing. The absence of fusion is determined by observing the QRS configuration in the 12-lead ECG during gradual shortening of the AV delay.

2. During follow-up, check the memory data of the pacemaker to confirm the absence of spontaneous AV conduction.
3. Remember that the site of LV stimulation is the most important determinant of successful therapy. (The wrong site may actually aggravate heart failure.) Optimization of the AV delay provides only modest benefit but may be more important in patients with a long PR interval. New devices permit optimization of the LV–RV interval but this also provides modest benefit.

Anodal stimulation

This phenomenon may be confusing but it has no clinical importance. During bipolar ventricular pacing, cathodal and anodal capture can occur at high outputs but such anodal stimulation is not seen on the electrocardiogram. In first-generation biventricular systems, the RV lead is bipolar and the LV lead unipolar. The ring of the RV lead provides a common anode for both RV and LV pacing. The increased current density at the common anode (pacing two ventricles) may cause anodal capture in the RV when the common output is high. This causes a change in the paced ECG which disappears when biventricular pacing is performed at a lower output or as true unipolar pacing of the RV and LV using the pacemaker can as the anode. Anodal stimulation can also occur when a second-generation biventricular pacemaker is programmed to pace only the LV, whereupon anodal capture will mimic biventricular pacing.

Signi cance of the paced QRS duration

Evaluation of the paced QRS duration as an index of efficacy is simplistic and potentially misleading. It is possible to have a wide biventricular paced QRS (longer than the spontaneous QRS) with clinical improvement if the LV walls contract more homogeneously. In other words, lack of QRS shortening with biventricular pacing is not a marker for a poor clinical response. The best example of this concept is provided by unichamber LV pacing (mostly documented in acute studies), which produces significant hemodynamic improvement in the setting of a very large paced QRS complex. In other words, the electrical manifestations are of limited value in the clinical assessment. Proper evaluation of the consequences of biventricular pacing requires the use of mechanical indices by echocardiographic techniques

Far- eld sensing of atrial depolarization

An LV lead located in one of the coronary veins may sense the far-field P wave because of electrode proximity to the left atrium especially if anatomical constraints prevent placement of the lead in a desirable distal site away from the AV groove. Moreover, the higher dislocation rates of LV leads towards the AV groove increases the likelihood of sensing relatively large atrial signals from the coronary sinus. Far-field P wave sensing by a displaced lead in the coronary sinus can be devastating in pacemaker-dependent patients who have undergone ablation of the AV junction for atrial fibrillation. Far-field atrial sensing by the ventricular channel can inhibit biventricular pacing and withhold therapy for congestive heart failure.

Table 22. Indicators for far- eld P wave sensing in biventricular pacemakers.

1. Recurrence or development of symptoms of congestive heart failure
2. Inappropriately short AS–VP delay on surface ECG
3. Unexpected inhibition of ventricular output (DDD mode) with a PR interval > programmed AS–VP delay (at rates *below* the maximum tracking rate)
4. Event markers recorded with simultaneously telemetered ventricular electrogram and surface ECG

Table 23. Management of atrial far- eld P wave oversensing in biventricular pacemakers.

1. Prophylaxis: some cases of far-field P sensing may be prevented by repositioning the LV lead at the time of implantation if the LV or biventricular electrogram registers a large atrial deflection
2. Reduce ventricular sensitivity while monitoring the rhythm using the programmer, and marker channel
3. Use the DOO mode in selected cases
4. Obtain 24-h Holter monitor looking for undersensing of ventricular premature beats and competition to determine whether the reduced sensitivity should be maintained
5. If far-field sensing of the P wave cannot be eliminated by programming or reducing the sensitivity, the LV lead needs to be repositioned or the device replaced by one that senses only from the RV

Impedance measurements in first-generation biventricular pacemakers

Before totally independent programmability became available for each lead, a divided pacemaker output or common dual cathodal system (simultaneous dual site cathodal stimulation with the leads connected in parallel) was widely used. The parallel arrangement and the larger combined surface area of the right and left ventricular leads (compared to a single lead) result in a reduced stimulation impedance. Thus, the total lead impedance is likely to be low (in the range of 250–400 Ω) in a normally functioning biventricular system. A mechanical problem in one of the ventricular leads but not the other may not be readily detectable using standard impedance criteria. An open circuit (conductor fracture) involving one lead will not result in the very high impedances that are present with single chamber pacing. Rather, that lead will effectively be taken out of the system and the measured impedance will reflect the expected impedance for the intact ventricular lead. Hence, with an open circuit on one of the two ventricular leads, the measured impedance may rise to the normal range for a univentricular lead. The normally low impedance in a dual cathodal system may also complicate the diagnosis of an insulation failure in one of the leads. The low telemetered impedance that is associated with an insulation failure in a single chamber lead may be in the "normal" range during intact biventricular pacing.

Caveat: In most cases the RV pacing threshold will be lower than the LV threshold. The monochamber LV pacing threshold is not the same as the biventricular threshold.

Biventricular pacing with conventional pacemakers

Although conventional dual chamber pacemakers are not designed for biventricular pacing and generally do not allow programming of an AV delay of zero or near zero, they are being increasingly used with their shortest "AV delay" (0–30 ms) for ventricular resynchronization in congestive heart failure patients with permanent atrial fibrillation. Their advantages include programming flexibility, avoidance of a cumbersome Y adapter (required for conventional VVIR devices), protection against far-field sensing of atrial activity (an inherent risk of dual cathodal devices with simultaneous sensing from both ventricles), and cost considerations. When a conventional dual chamber pacemaker is used for biventricular pacing, the "atrial" channel is generally connected to the LV and the "ventricular" channel to the RV. This arrangement provides:

1. LV stimulation before RV activation (LV preexcitation);
2. protection against ventricular asystole related to oversensing far-field atrial activity by dual cathodal devices in case of displacement of the LV lead towards the AV groove.

The DVI(R) mode behaves like the VVI(R) mode except that there are always two closely coupled stimuli (or electrocardiographically fused stimuli if the "AV delay" is very short) thereby facilitating evaluation of pacemaker function. Furthermore the DVI(R) mode provides absolute protection against far-field sensing of atrial activity in case of LV lead displacement. The short delay between LV and RV stimulation imposed by the shortest "AV delay" may not be a significant limitation in many patients because it is LV pacing that generally provides the salutary effect of biventricular pacing.

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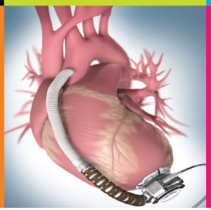

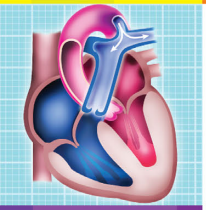

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A Practical Handbook

David Laflamme
Foreword by Dr Paul Dorian

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CRC Press
Taylor & Francis Group

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CRC Press
Taylor & Francis Group

From the same publisher

Prescription guidelines in cardiology, R. Haïat, G. Leroy, 5th edition, 2015
www.cardio-log.com

Cover illustrations

HeartWare HVAD, ventricular assist device, HeartWare International, Framingham, MA, USA (with permission)

EnSite NavX Navigation & Visualization Technology, St. Jude Medical, St. Paul, MN, USA (with permission)

Edwards SAPIEN XT transcatheter heart valve, Edwards Lifesciences LLC, Irvine, CA, USA (with permission)

Artistic direction and graphic design

Julie Laflamme

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frison-roche 19 rue des Lyanes, 75020 Paris, 2016
infos@editions-frison-roche.com / www.editions-frison-roche.com

ISBN 978-2-87671-585-1

CRC Press
Taylor & Francis Group
an informa business

6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
711 Third Avenue
New York, NY 10017
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

ISBN 978-1-4987-7981-4

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Foreword

There has been a near exponential increase in the amount of information available on the pathophysiology and management of heart diseases over the past decades. Meanwhile, our understanding of the underlying pathology and physiology has deepened and broadened with new methodologies to monitor cardiac structure and function. These developments have led to an overwhelming amount of information available to students, trainees, and physicians on all aspects of cardiac disease. What is in short supply is a comprehensive yet concise and clear description of the important cardiac conditions and disorders, an approach to their management, and an easily consulted and well indexed summary to be used at the bedside or in the clinic.

The Cardiology Handbook fills an extremely important, not well occupied niche in providing junior and senior practitioners alike with a brief yet detailed summary of "what you need to know" about virtually all important cardiovascular conditions.

This handbook does not aim to be a comprehensive review of all of the evidence pertaining to pathophysiology, investigation, and treatment of cardiovascular disorders. It does however wonderfully clearly get "straight to the point" and I think will be a frequently used and extremely effective resource for a brief "look up" in the clinic, in the emergency room, and on the wards.

I anticipate this handbook will be a treasured resource for senior medical students, trainees in internal medicine, emergency medicine, anesthesia, and other specialties where cardiovascular disorders are commonly seen. The effective use of figures and tables makes this appealing both visually and cognitively, and for those unfamiliar with the complex and varied terrain of cardiovascular medicine, will prove an outstanding trail map to allow successful navigation of unfamiliar terrain. In an era where there is often "too much information", this handbook provides just the right amount.

Sincerely,

Paul Dorian, MD, FRCPC, FHRS
Dexter H.C. Man Chair in Cardiology
Director Division of Cardiology, University of Toronto
Past President, Canadian Heart Rhythm Society

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To my parents, Diane and Marcel,
for their constant support,
and to Anne-Sophie, for
her extraordinary patience.

Preface

Cardiology is a fascinating medical specialty. This vast discipline combines various fields of expertise, including research, prevention, clinical evaluation, diagnostic examinations, therapeutic management, invasive interventions and rehabilitation.

As a result of the spectacular progress over the last two decades, cardiology now comprises sophisticated and advanced diagnostic and therapeutic tools (validated by evidence-based medicine) allowing cardiologists to more effectively manage their patients, who have greatly benefited in terms of survival and/or quality of life.

In relation to such an effervescent and increasingly complex discipline, physicians who have the privilege to practice cardiology must have access to resources that enable them to acquire, update, refine and organize their knowledge.

The purpose of this book is to provide a concise overview of modern cardiology. More than 10,000 pages of references have been condensed and organized into less than 350 pages. This pocket book provides practising clinicians with specific and accurate information on a particular subject. It is also designed to allow students, interns and all other personnel working in the field of cardiology to acquire and organize their valuable knowledge.

The design of this cardiology handbook was a captivating but colossal task. The information presented in this book is derived from numerous valid and up-to-date sources and has been verified by various reviewers, experts in their respective fields. The various recommendations are also derived from American, European or Canadian learned society evidence-based guidelines.

I sincerely hope that this book will inspire or maintain your passion for cardiology and I wish you an enjoyable read.

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February 2016

The author has no conflicts of interest to declare concerning this book.

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Legal statement

Every physician is responsible for his or her acts. Although the recommendations and management presented in this book are based on valid, reliable and up-to-date references at the time of writing, the author and publisher decline all responsibility and remind the reader that every physician must practice medicine according to current medical and scientific guidelines, taking into account his or her own capacities and limitations, and, if necessary, seeking advice from more experienced specialists.

Cardiac diagnostic assessment

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1.1/ CARDIAC PHYSICAL EXAMINATION

EXAMINATION OF THE PATIENT

GENERAL INSPECTION: Diaphoresis; Signs of hypoperfusion; Cachexia; Mitral facies; Cheyne-Stokes breathing

CUTANEOUS INSPECTION: Cyanosis (central vs peripheral); Pallor; Telangiectasias (Osler-Weber-Rendu; scleroderma); Tanned skin (hemochromatosis); Jaundice (liver disease); Ecchymoses (coagulopathy); Petechiae (thrombocytopenia); Purpura (vasculitis; endocarditis); characteristic axillary skin fold (pseudoxanthoma elasticum); Lentiginosis (LEOPARD; Carney); Lupus pernio - erythema nodosum (sarcoidosis); blue sclera (osteogenesis imperfecta); nicotine stains (smoking)

- **Familial hypercholesterolemia:** Arcus senilis; pathognomonic tendinous xanthomas (extensor tendons; MCP; Achilles tendon); Xanthelasma
- **Familial hypertriglyceridemia (LPL deficiency)**: Eruptive xanthomas; Lipemia retinalis
- **Dysbetalipoproteinemia:** Tuberous xanthomas (elbows; knees); Palmar xanthomas

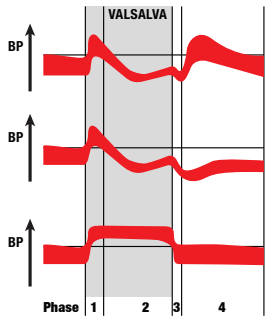
SIGNS OF ENDOCARDITIS: Roth's spots; Janeway lesions; Osler's nodes; splinter hemorrhages; mucosal petechiae

FUNDOSCOPY: hypertensive retinopathy (arteriovenous nicking; exudates; hemorrhages; cotton-wool spots; papilledema); diabetic retinopathy; endocarditis (Roth's spot); Hollenhorst plaque (cholesterol embolism); Lipemia retinalis

VITAL SIGNS

BLOOD PRESSURE: in both arms (± legs)

- **Large pulse pressure (> 50% of SBP)**: Age - HTN; AR; Patent ductus arteriosus; Ruptured aneurysm of the sinus of Valsalva; Fever; Anemia; Hyperthyroidism; Pregnancy; AV fistula; Paget's disease
- **Narrow pulse pressure (< 25% of SBP)**: Cardiac tamponade; Heart failure; Cardiogenic shock; Aortic stenosis
- **BP difference between the two arms > 10 mmHg**: Normal variant; PAD; Inflammatory vascular disease (Takayasu; giant cell arteritis); Supravalvular aortic stenosis; CoA; Aortic dissection
- **BP difference between the arms and legs > 20 mmHg**: Hill's sign (significant AR); CoA; severe PAD
- **Pulsus paradoxus:** ↘ SBP > 10 mmHg on inspiration
- **Orthostatic hypotension**: ↘ SBP > 20 mmHg or ↘ DBP > 10 mmHg during the first 3 minutes after standing up
- **Valsalva response**



NORMAL RESPONSE (SINUSOIDAL)
1. ↑ BP (↑ intrathoracic pressure)
2. ↓ venous return; ↓ BP; ↑ SVR; Reflex tachycardia
3. Release: ↓ BP (brief)
4. Overshoot: ↑ venous return; ↑ BP; ↓ SVR; Reflex bradycardia

NO OVERSHOOT (PHASE 4)
Systolic dysfunction

SQUARE WAVE
↑ filling pressure (little impact of ↓ venous return)

OTHER VITAL SIGNS: Pulse; heart rate regularity; Respiratory rate; Oxygen saturation; Temperature; Weight; Height; Waist

› **Body surface area (m^2)** = **0.007184 x weight (kg) x height (cm)** +

NECK

CAROTID PULSE

› **Shape**: ▸▸| Hemodynamic assessment (arterial recording)

› **Carotid sinus massage:** abnormal response if **asystole > 3 seconds (sinus arrest or AV block) and/or significant and symptomatic fall in SBP** +

JUGULAR VEINS

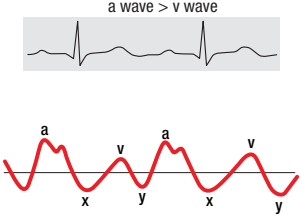
› **Jugular vein vs carotid artery**: Biphasic; Height modified by inspiration and position and hepatojugular reflux (HJR); Impalpable; Compressible +

› **Height**: distance between the sternal angle and the summit of venous pulsation; **normal < 3 cmH_2O** +

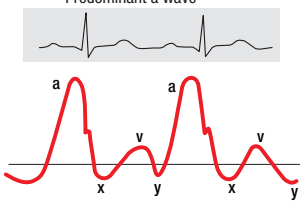
- **CVP (cmH_2O):** height above the sternal angle + 5 cmH_2O
- **Normal CVP**: **< 8 cmH_2O (< 6 mmHg)** +
- **Conversion**: **1.36 cmH_2O = 1 mmHg** +

› **Waves**: ▸▸| Hemodynamic assessment (atrial recording)

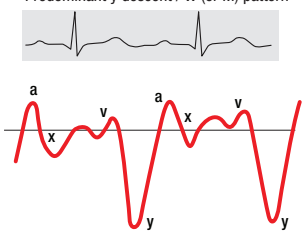
Normal pattern
a wave > v wave



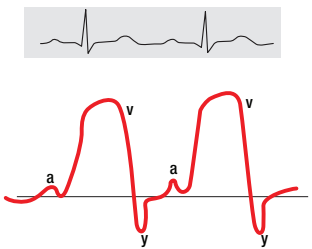
Tricuspid stenosis (or RVH)
Predominant a wave



Constrictive pericarditis
Predominant y descent / W (or M) pattern



Tricuspid regurgitation
Predominant v wave



› **Kussmaul's sign**: inspiratory increase (or absence of decrease) of CVP (constriction; RCM; RV infarction; pulmonary embolism; TS; RA tumor; right heart failure)

› **Hepatojugular reflux (HJR)**: Right upper quadrant (RUQ) compression (25 mmHg) x 15 seconds

- **Abnormal response**: **sustained ↗ of CVP > 3 cm throughout compression** (patient breathing normally)**; reflects right heart failure and/or wedge pressure > 15 mmHg** +

PRECORDIUM

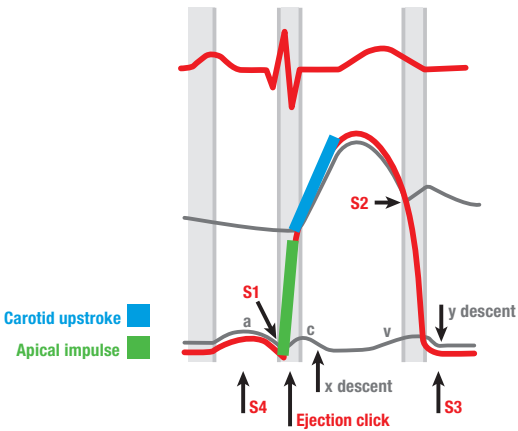
INSPECTION OF THE RIB CAGE: pectus excavatum; pectus carinatum; kyphoscoliosis; barrel chest; surgical scars; breathing; PPM / ICD

INSPECTION OF THE PRECORDIUM: position and dimensions of the apical impulse

PALPATION: patient in 30° supine position

- **Apical impulse**: with the fingertips; left lateral supine position as required; **medial to the midclavicular line; 4th or 5th intercostal space; diameter < 2 cm** +
  - **Apical pulsation: corresponds to isovolumic contraction of the LV**
  - **Hyperdynamic apex:** increased amplitude of apical impulse but of normal duration; AR; patent ductus arteriosus; MR; VSD; hyperthyroidism; anemia; pregnancy
  - **Sustained apical impulse**: **the impulse persists during or after the carotid upstroke; associated with pressure overload** (AS; HCM; HTN) +
  - **Enlarged apical impulse**: dilatation > 2 cm and/or shift downwards and to the left; associated with **LV volume overload** +
  - **Palpable S3**: LV volume overload
  - **Palpable S4**: noncompliant LV / ↗ end-diastolic pressure
  - **Triple apical impulse**: HCM (early-systole; end-systole due to dynamic LVOT obstruction; S4)
- **Ectopic pulsation**: LV aneurysm (mid-precordial or anterior axillary)
- **Left parasternal heave**: associated with RVH
- **Thrill:** palpate the 4 areas (palm of the hand at the level of the MCP joints)
- **Pulsation in the 2nd right intercostal space:** ascending aortic aneurysm
- **Pulsation in the 2nd left intercostal space**: PA dilatation

AUSCULTATION - SYSTOLIC HEART SOUNDS



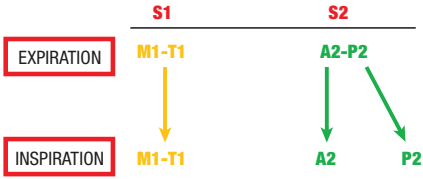
LOOK FOR: S1; Ejection click; Mid-systolic click; S2

S1: M_1-T_1 (interval: 20-30 ms); maximum at the apex; T1 mainly in the 5th left intercostal space; **precedes the carotid upstroke**

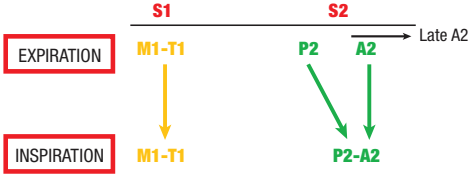
- **↗ Intensity of S1 (S1 ≥ S2 in the 2nd left intercostal space)**: Rheumatic MS (early stage); Hyperdynamic state (↗ dP/dt); PR < 120 ms; ↗ flow through mitral valve (VSD; patent ductus arteriosus)
- **↘ Intensity of S1**: Calcified MS (↘ mobility); Systolic dysfunction; PR > 200 ms; acute AR
- **Variable intensity of S1:** AF; AV dissociation; Tamponade
- **Split S1 (split sound in the 5th left intercostal space)**: RBBB; ASD (delayed T1); ST (delayed T1); Ebstein's anomaly

S2: A2-P2; maximum in the 2nd left intercostal space

- **Normal physiological splitting:** on inspiration; 2nd left intercostal space; interval: 20-60 ms



- **Normal but narrow inspiratory splitting**: PHT (associated with ↗ P2)
- **Increased splitting**: RBBB; severe MR (early A2); VSD (early A2); RVOT obstruction (late P2)
- **Fixed splitting (A2-P2 variation < 20 msec):** ASD; right heart failure (absence of variation of ejection volume according to RV preload)
- **Paradoxical splitting:** LBBB; RV PPM; AS; HCM; LV systolic dysfunction; AR (prolonged ejection)



- **↗ intensity of A2:** HTN; CoA; Ascending aortic aneurysm; Transposition of the great arteries; supravalvular AS
- **↘ intensity of A2:** Valvular AS; AR
- **↗ intensity of P2**: **P2 > A2 in the 2nd left intercostal space or P2 heard at the apex or palpable P2**; PHT; Supravalvular RVOT obstruction
- **↘ intensity of P2**: Valvular PS; pulmonary regurgitation (except if secondary to PHT); Transposition of the great arteries
- **Single S2**: ↘ A2 (AS) or ↘ P2 (PS); Transposition of the great arteries

VALVULAR EJECTION CLICK: coincides with carotid upstroke (120-140 ms after QRS); high-pitched sound; diffuse radiation; best heard in lower left parasternal region; associated with bicuspid aortic valve (valve still pliable) or **congenital PS** **(↘ click on inspiration; valve still pliable)**

- **Vascular ejection click**: **Aortic root dilatation**; PA dilatation (idiopathic; post-stenotic; PHT)

MID-SYSTOLIC CLICK OF MVP: non-ejection click (after the carotid pulsation); high-pitched sound; earlier if the patient stands up; ± MR murmur

AUSCULTATION - DIASTOLIC HEART SOUNDS

LOOK FOR: S2; Opening snap; Pericardial knock; S3; Tumor plop; S4; Friction rub

MITRAL OPENING SNAP: High-pitched sound; stethoscope diaphragm at the apex; **A2-opening snap interval inversely proportional to the severity of MS** (40-120 ms after S2); interval decreases with tachycardia; ↘ intensity of opening snap when the valve is calcified

PERICARDIAL KNOCK: Constrictive pericarditis; early diastolic sound (at the end of the y descent); 100-120 ms after S2

S3: left lateral supine position; stethoscope bell at the apex; 140-160 ms after S2; during rapid ventricular filling (at the end of the y descent); associated with **ventricular volume overload** +

- **Etiologies:** Dilated cardiomyopathy; heart failure; MR; AR; VSD; patent ductus arteriosus; diastolic dysfunction; young subjects in good health; normal pregnancy
- **Right S3:** lower left parasternal region; ↗ on inspiration; TR; right heart failure; PHT

S4: left lateral supine position; stethoscope bell at the apex; occurs during atrial kick (after the P wave); associated with a **poorly compliant ventricle** and **↗ filling pressure** +

- **Etiologies**: HTN; AS; HCM; LVH; Ischemia; Acute AR; Acute MR; Age
- **Right S4**: lower left parasternal region; ↗ on inspiration; RVOT obstruction; PHT

SUMMATION GALLOP: fusion of S3 and S4 during tachycardia

TUMOR PLOP: prolapse of the tumor through the AV valve; sound varies with position

PERICARDIAL FRICTION RUB: **1 or 2 or 3 components** (rapid ventricular filling; atrial kick; ventricular systole); forced expiration while leaning forward; stethoscope diaphragm in left parasternal region

AUSCULTATION - MURMURS

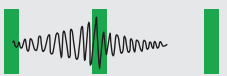
IDENTIFY: Moment of the cycle; Configuration (crescendo; decrescendo; crescendo-decrescendo; plateau); Site; Radiation; Tone; Intensity; Modifiers (breathing; special maneuvers)

- **1/6**: Very faint murmur (barely perceptible)
- **2/6**: Faint murmur but heard immediately
- **3/6:** Moderate murmur
- **4/6**: Palpable thrill
- **5/6:** Very loud; heard even when only part of the stethoscope is in contact with the chest
- **6/6**: Heard even when the stethoscope is not in contact with the chest

BENIGN MURMUR: 1-2/6 in left parasternal region; Ejection murmur; S2 of normal intensity with normal physiological splitting; No other heart sounds or murmurs; No LVH (on examination or ECG); Murmur not increased by Valsalva maneuver or standing

INDICATIONS FOR TTE: Diastolic or continuous or holosystolic or end-systolic or early systolic murmur or associated with ejection click or ≥ 3/6 with mid-systolic peak or radiating to the neck or back or signs or suspicion of MR, MVP, HCM or VSD on dynamic auscultation

SYSTOLIC MURMUR	
Mid-systolic (often diamond-shaped)	• Benign • Ejection murmur: High output state (pregnancy; hyperthyroidism; anemia; AV fistula; AR; PR; ASD) • Aortic stenosis (supravalvular; valvular; subvalvular) • Aortic sclerosis • HCM • PS (supravalvular; valvular; subvalvular) • CoA • Functional / ischemic MR

Holosystolic 	• MR • TR • VSD (restrictive)
Early systolic 	• Acute MR • Primary TR (without PHT) • VSD: small muscular VSD or large VSD with significant PHT
End-systolic 	• MVP • Functional / ischemic MR (↗ on exercise) • Tricuspid valve prolapse
DIASTOLIC MURMUR (ALWAYS INVESTIGATE)	
Early diastolic 	• AR • Graham-Steell: PR secondary to PHT (decrescendo; high-pitched; signs of associated PHT) • PR without PHT (faint murmur)
Mid-diastolic 	• MS • TS • Austin-Flint (absence of opening snap) • Myxoma • ↗ diastolic flow through AV valve (MR; TR; VSD; patent ductus arteriosus; ASD; abnormal pulmonary venous return) • Carey Coombs murmur (mitral valvulitis during acute rheumatic fever)
End-diastolic 	• MS (presystolic accentuation) • TS • Austin-Flint • Myxoma • Rytand's murmur: diastolic mitral regurgitation in a context of complete AV block
CONTINUOUS MURMUR (OFTEN PATHOLOGICAL)	
Starts at systole and continues uninterrupted during diastole  	• Patent ductus arteriosus (Gibson's murmur; machinery murmur) • Aortopulmonary window • Coronary arteriovenous fistula • Ruptured aneurysm of the sinus of Valsalva • Neck venous hum • Mammary murmur of pregnancy • Stenosis of peripheral branch of pulmonary artery • Lutembacher's syndrome: MS + ASD • CoA / Intercostal collateral vessels • Pulmonary or systemic AV fistula • Bronchial collateral vessels

DYNAMIC AUSCULTATION

MANEUVERS	AS	HCM	MVP	MR	OTHER
Valsalva (↘ preload)	↘	↗	↗ duration of murmur	↘	↘ AR
Standing up (↘ preload)	↘	↗	↗ duration of murmur	↘	
Squatting or leg raising (↗ preload)	unchanged or ↗	↘	↘ duration of murmur	↗	↗ AR - ↗ VSD
Hand grip (↗ afterload)	unchanged or ↘	↘	↘ duration of murmur	↗	↗ AR - ↗ VSD ↗ MS (↗ HR)
Amyl nitrate (↘ afterload)	↗	↗	↗ duration of murmur	↘	↗ MS (↗ HR) ↘ AR - ↘ VSD ↘ Austin Flint
Post-PVC (↗ contractility)	↗	↗	↘ duration of murmur (↗ LV volume)	un-changed	

INSPIRATION: louder right heart sounds/murmurs (except for pulmonary valve ejection click); ↗ splitting of S2

PHYSICAL EXAMINATION - OTHER EXAMINATIONS

LUNGS: crackles; effusion; wheezing; pleural friction rub

ABDOMEN: Liver (pulsation); Ascites; Splenomegaly; Aorta; Murmurs

LOOK FOR PRESACRAL EDEMA

UPPER LIMBS: clubbing; arachnodactyly; signs of endocarditis; nicotine stains; sclerodactyly; pulse in both arms

LOWER LIMBS: murmurs; lower limb edema; pulse in both legs; capillary refill; discoloration; ulcer; coldness; atrophic changes; hair loss

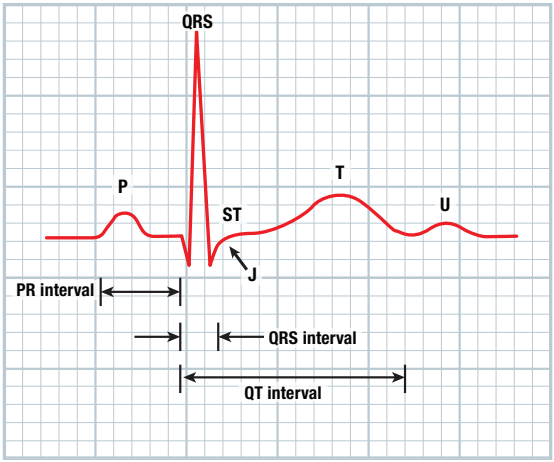
- **Radiofemoral delay:** CoA
- **Pulse**: 0 = absent; 1 = decreased; 2 = normal; 3 = bounding

BRIEF NEUROLOGICAL EXAMINATION

1.2/ ELECTROCARDIOGRAM (ECG)

SYSTEMATIC APPROACH

a) **HEART RATE**: 1500 / number of small squares between 2 QRS or 300-150-100-75-60-50-43-38
b) **RHYTHM** (⏭ Chapter 6 - Arrhythmias)
c) **P WAVE:** morphology
d) **AV CONDUCTION**
e) **QRS**: frontal axis; intraventricular conduction; precordial QRS transition; voltage / chamber hypertrophy
f) **REPOLARIZATION**: ST segment - T wave - QT interval - U wave
g) **MYOCARDIAL INFARCTION / Q WAVE**



NORMAL VALUES	
Calibration	• **Vertical: 10 mm = 1 mV** • **Horizontal: 1 mm = 40 msec**
P wave duration and amplitude	< 120 ms and < 2.5 mm in amplitude
P wave axis	60° (positive I-II-aVL-aVF; negative aVR) Normal axis: 0-90°
PR interval	120-200 ms
QRS duration	≤ 110 ms
QRS axis	-30° to +90°
Precordial QRS transition	R = S in V3 or V4
QRS amplitude	• **Limbs:** > 5 mm • **Precordial**: > 10 mm
J Point / ST segment	**Elevation** • **V2-V3**: < 2 mm (men > 40 years); < 2.5 mm (men < 40 years); < 1.5 mm (women) • **Other leads**: < 1 mm **Depression**: < 0.5 mm
T wave	• **Positive:** I-II-V3-V4-V5-V6 › **V5-V6**: T wave inversion < 1 mm in 2% • **Negative:** aVR • **Variable:** aVL-III-V1-V2 • **Maximum amplitude V2**: < 14 mm (men) and 10 mm (women)
QTc	• **Men:** < 450 ms • **Women:** < 460 ms

TECHNICAL CONSIDERATIONS

ARM LEAD REVERSAL: P and QRS and T wave inverted in I and aVL but not in V6

PRECORDIAL LEAD MALPOSITION: abnormal precordial QRS transition

RIGHT HEART OR POSTERIOR LEADS: V3R-V4R or V7-V8-V9

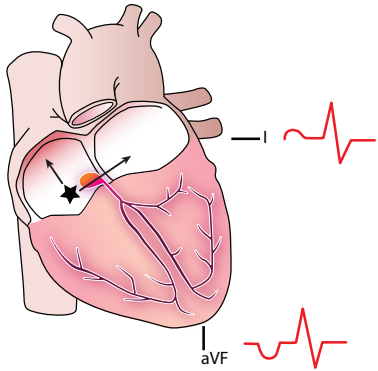
ARTIFACTS: tremor; Parkinson's disease (pseudo-flutter)

SINUS RHYTHM

▸▸| Chapter 6 - Arrhythmias

SINUS RHYTHM (SR): origin of sinoatrial node; HR 60 -100 bpm

- **Sinus tachycardia**: HR > 100 bpm
- **Sinus bradycardia**: HR < 60 bpm
- **Normal atrial activation**: RA to AV node and to LA; P axis 0° to +90° (positive P wave I-II-aVL-aVF); biphasic P wave in V1-V2; duration < 120 ms
- **Retrograde atrial activation**: retrograde AV conduction or ectopic atrial pacemaker close to AV node; negative P wave in II and aVF



SINUS ARRHYTHMIA: phasic respiratory variation of the duration of the PP interval; variation ≥ 120 ms or PPmax - PPmin / PPmin > 10%

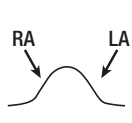
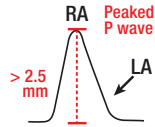
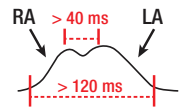
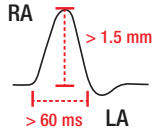
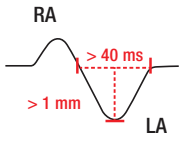
SUPRAVENTRICULAR ARRHYTHMIAS

▸▸| Chapter 6 - Arrhythmias

VENTRICULAR ARRHYTHMIAS

▸▸| Chapter 6 - Arrhythmias

P WAVE

	NORMAL	RA ABNORMALITY	LA ABNORMALITY
II			
V1			
	• Axis 60° • Duration < 120 ms	• Axis > 75°	• Axis terminal portion -30° to -90° (negative in III)

INTRA-ATRIAL CONDUCTION BLOCK: Duration of P wave > 120 ms; biphasic P wave in inferior leads; does not satisfy the criteria for RA or LA anomaly

› **Abnormal activation:** RA activation → Bachmann's bundle block → LA activation from coronary sinus (from inferior to superior)

AV CONDUCTION

▸▸| Chapter 6 - Arrhythmias

NORMAL PR INTERVAL: 120-200 ms

LONG PR INTERVAL: PR > 200 ms; 1st degree AV block

SHORT PR INTERVAL: PR < 120 ms in sinus rhythm; rule out accessory pathway

› **Lown-Ganong-Levine syndrome**: atrio-His accessory pathway (James fibers) short-circuiting the AV node; narrow QRS

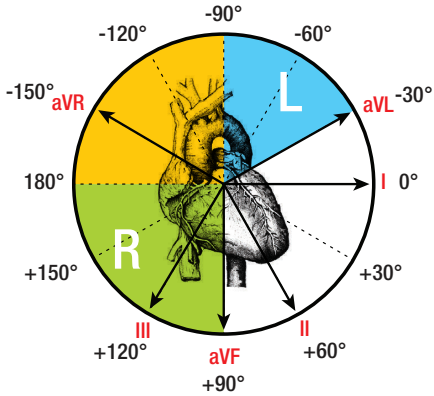
X:Y AV CONDUCTION: failure of AV node to conduct certain atrial impulses to the ventricle; **the refractory period of the AV node is longer when it is stimulated more rapidly (decremental conduction)**

› **AV block with variable conduction**: 2:1 3:1...; frequent in atrial flutter

AV DISSOCIATION: independent atrial and ventricular rhythms; 3 situations:

1) 3rd degree AV block; RR interval > PP interval
2) Accelerated junctional rhythm or junctional tachycardia or VT (without retrograde VA conduction); RR < PP; ± fusion or capture beats
3) Sinus bradycardia with junctional or ventricular escape (without retrograde VA conduction); RR < PP; ± isorhythmic dissociation

FRONTAL QRS AXIS

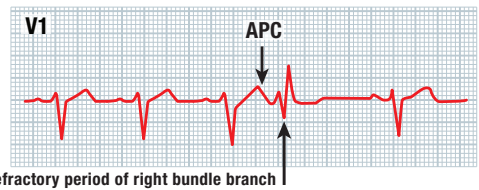


Normal axis	-30° to + 90°	I + aVF + (if aVF - → II +)	
Right axis deviation	+90° to +180°	I - aVF +	**DDx:** RVH; LPHB; dextrocardia; lateral infarction; secundum ASD; vertical heart (COPD); pulmonary embolism
Left axis deviation	-30° to -90°	I + aVF - and II -	**DDx**: LVH; LAHB; primum ASD; complete AV canal defect; Tricuspid atresia (under-developed RV); pregnancy; ascites; inferior infarction
Extreme "North-West" axis deviation	- 90° to 180°	I - aVF -	

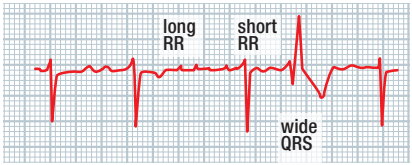
INDETERMINATE AXIS: Equiphasic QRS in all frontal leads (with no dominant QRS); axis perpendicular to the frontal plane

QRS: INTRAVENTRICULAR CONDUCTION

ABERRANT CONDUCTION OF SUPRAVENTRICULAR BEATS: arrival of a supraventricular beat during the relative refractory period of intraventricular conduction tissue; conduction with wide QRS (RBBB > LBBB morphology)



ASHMAN PHENOMENON: **Long RR then short RR** → wide QRS (frequent RBBB morphology); **long RR associated with ↗ refractory period of His-Purkinje tissue**

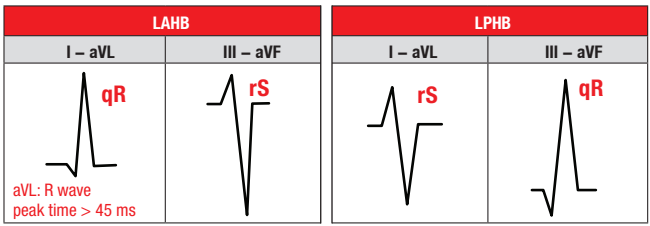


LAHB (LEFT ANTERIOR HEMIBLOCK)

1) Left axis deviation -45° to -90°
2) qR in I and aVL
3) rS in III and aVF
4) QRS duration < 120 ms
5) R wave peak time in aVL > 45 ms
   - Late precordial QRS transition
   - **Rule out differential diagnoses**: LVH; COPD; inferior infarction

LPHB (LEFT POSTERIOR HEMIBLOCK)

1) Right axis deviation +90° to +180°
2) rS in I and aVL
3) qR in III and aVF
4) QRS duration < 120 ms
   - **Rule out differential diagnoses**: RVH; COPD; lateral infarction; dextrocardia; arm lead reversal



LBBB (LEFT BUNDLE BRANCH BLOCK)

1) QRS ≥ 120 ms
2) Wide monophasic R wave in I-aVL-V5-V6
3) Absence of septal q wave in I-V5-V6
4) R wave peak time > 60 ms in V5-V6
5) ST and T in opposite direction to QRS (appropriate discordance)

Acute myocardial infarction with a LBBB (Sgarbossa criteria)	**1) ST elevation ≥ 1 mm in leads with positive QRS (inappropriate concordance)** **2)** ST depression ≥ 1 mm V1-V2-V3 (inappropriate concordance) **3)** ST elevation ≥ 5 mm in leads with negative QRS (extreme discordance)
Old myocardial infarction in LBBB	**1) Cabrera's sign:** Notch of the upslope of the S wave in V2-V3-V4 **2) Chapman's sign:** Notch of the upslope of the R wave in V5-V6-I-aVL

INCOMPLETE LEFT BUNDLE BRANCH BLOCK

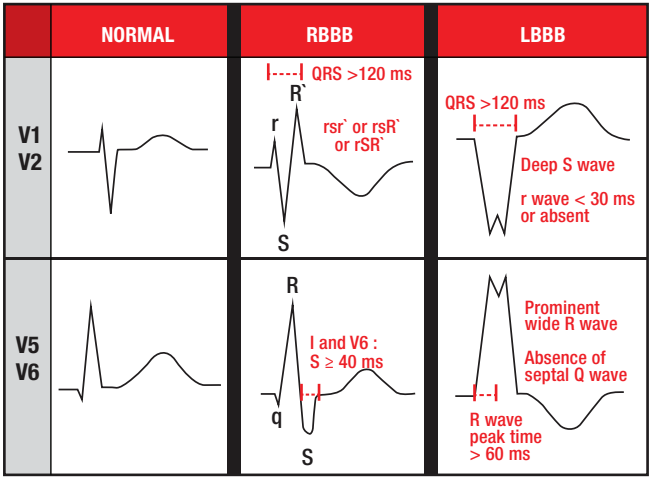
1) QRS 110-119 ms
2) LVH pattern
3) R wave peak time > 60 ms in V5-V6
4) Absence of septal q wave in I-V5-V6

RBBB (RIGHT BUNDLE BRANCH BLOCK)

1) QRS ≥ 120 ms
3) rsr', rsR', or rSR' in V1 or V2 (width of R' or r' > width of r)
4) S > 40 ms in I and V6 (S larger than R in V6)
   - In a minority of patients, wide monophasic R wave in V1 and/or V2 (with R wave peak time > 50 ms in V1)
   - **If axis deviation:** consider bifascicular block (RBBB with LAHB or RBBB with LPHB)
   - **If bifascicular block with ↗ PR**: consider lesion of 3 branches with prolonged HV interval

INCOMPLETE RIGHT BUNDLE BRANCH BLOCK

1) QRS 110-119 ms
2) Other criteria similar to RBBB

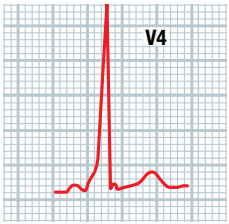


NONSPECIFIC INTRAVENTRICULAR CONDUCTION DISORDER

1) QRS > 110 ms
2) Absence of criteria of RBBB or LBBB

VENTRICULAR PRE-EXCITATION

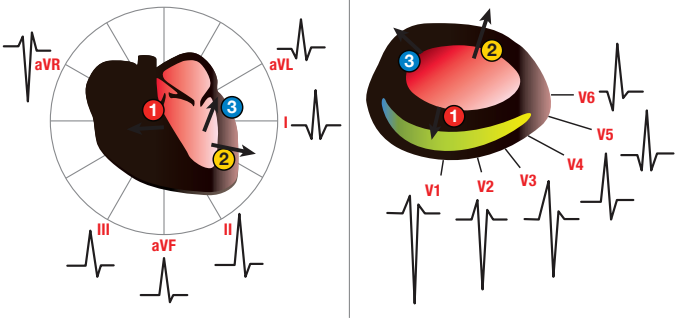
1) PR interval < 120 ms (in sinus rhythm)
2) **Delta Wave:** slow rise of the initial portion of the QRS
3) QRS ≥ 120 ms
4) Secondary ST and T anomalies
   - Possible pseudo-infarction (Q waves)
   - **Concertina effect**: the degree of pre-excitation can vary according to conduction and the refractory period of the accessory pathway and AV node



SITE OF ACCESSORY PATHWAY	V1	aVF	aVL
Left lateral	+	+	-
Posterior or left septal	+	-	+
Posterior or right septal	-	-	+
Anterior or right lateral	-	+	+

QRS: PRECORDIAL R WAVE TRANSITION

NORMAL VENTRICULAR ACTIVATION: **1)** Left-to-right septal activation (septal q wave in I-aVL-V5-V6; septal r wave in aVR and V1; **2)** Anterior LV then lateral LV activation; **3)** Posterobasal LV activation



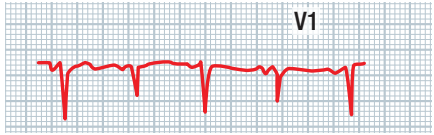
NORMAL PRECORDIAL TRANSITION: rS V1 → qR V6; R = S in V3 or V4

› **DDx of abnormal precordial transition**: lead malposition; dextrocardia; anterior or anteroseptal or posterior myocardial infarction; LVH; RVH; LAHB; LBBB; RBBB; dilated or infiltrative cardiomyopathy; pre-excitation (right or anteroseptal accessory pathway); COPD; pneumothorax; chest wall anomaly...

LOW VOLTAGES: QRS amplitude **< 5 mm on frontal leads and < 10 mm on precordial leads**

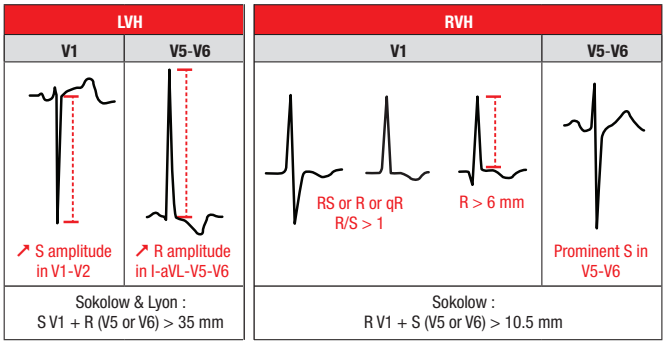
› **DDx**: COPD; obesity; cardiomyopathy; infiltrative disease - amyloidosis - tumor; myocarditis; extensive MI; pericardial effusion; constrictive pericarditis; pleural effusion; myxedema; anasarca; calibration; left pneumothorax

ELECTRICAL ALTERNANS: QRS amplitude varies between beats



- **DDx**: pericardial effusion; severe cardiomyopathy; severe AR; supraventricular tachycardia
- **P wave alternans**: pathognomonic of pericardial effusion
- **T wave alternans**: long QT syndrome

QRS: CHAMBER HYPERTROPHY



LEFT VENTRICULAR HYPERTROPHY (LVH): multiple criteria

- **Sokolow & Lyon:** S V1 + R (V5 or V6) ≥ 35 mm
- **Cornell voltage**: S V3 + R aVL ≥ 28 mm (men) and ≥ 20 mm (women)
- **R aVL**: > 11 mm (> 18 mm if left axis deviation)

ROMHILT-ESTES SCORE		
Frontal leads: R or S max ≥ 20 mm or SV1 or SV2 ≥ 30 mm or RV5 or RV6 ≥ 30 mm	3 points	≥ 5 points: definite LVH 4 points: probable LVH
ST-T abnormality (without Digoxin) **ST-T abnormality (with Digoxin)**	3 points 1 point	
LA abnormality	3 points	
Left axis deviation (-30° to -90°)	2 points	
QRS duration ≥ 90 ms	1 point	
R wave peak time V5 or V6 ≥ 50 ms	1 point	

- **Other**: secondary repolarization abnormalities; left axis deviation; LA abnormality; Prolonged R wave peak time in V5-V6

- **LVH associated with LBBB**: consider concomitant LVH if: **A)** LA abnormality; **B)** QRS > 155 ms; **C)** Precordial voltage criteria
- **LVH associated with RBBB**: consider concomitant LVH if: **A)** LA abnormality; **B)** Left axis deviation; **C)** S V1 > 2 mm; **D)** R V5 or V6 > 15 mm; **E)** Left axis deviation and precordial SR max > 29 mm; **F)** R in I > 1 mm

RIGHT VENTRICULAR HYPERTROPHY (RVH): multiple criteria

- **Sokolow**: R V1 + S (V5 or V6) > 10.5 mm
- **R/S V1**: > 1
  - **DDx of prominent R wave in V1-V2**: **Lead malposition; Dextrocardia; posterior myocardial infarction; Duchenne muscular dystrophy; RVH (right axis deviation); septal HCM; RBBB; Preexcitation (left posterior or lateral pathway); pediatric ECG** +
- **R V1:** > 6 mm
- **R wave peak time V1**: > 35 ms
- **R/S V5 or V6**: < 0.75 (V5) or < 0.4 (V6)
- **S V5 or V6**: > 10 mm (V5) or > 3 mm (V6)
- **Other:** Right axis deviation; T wave inversion V1-V2-V3; RA abnormality; S1S2S3; S1Q3
- **RVH associated with RBBB**: consider concomitant RVH if **R in V1 > 15 mm** and right axis deviation +

BIVENTRICULAR HYPERTROPHY: look for criteria of both RVH and LVH

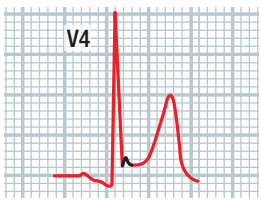
- **LVH:** consider concomitant RVH if → prominent S in V5 or V6; right axis deviation; unusual biphasic R/S complexes on several precordial leads (late precordial transition); RA hypertrophy
- **RVH**: consider concomitant LVH if → combined R/S amplitude in V2 to V4 > 60 mm; LA hypertrophy; prominent R wave in right and left precordial leads

REPOLARIZATION: ST - T - QT - U

ST ELEVATION (AT J POINT IN ≥ 2 CONTIGUOUS LEADS	
V2 – V3	• Men ≥ 40 years: ≥ 2 mm • Men < 40 years: ≥ 2.5 mm • Women: ≥ 1.5 mm
All other leads	≥ 1 mm
V3R – V4R – V7 – V8 – V9	≥ 0.5 mm

DDX OF ST ELEVATION: Myocardial ischemia / STEMI; normal variant (early repolarization); LV aneurysm; pericarditis; myocarditis; cardiomyopathy; Prinzmetal angina / Vasospasm; Takotsubo; LVH; LBBB; pre-excitation; PPM; Brugada syndrome; pulmonary embolism; hyperkalemia; intracranial haemorrhage / SAH; hypothermia (Osborn); post-ECV; lead malposition; hypercalcemia; Rx (class IC AAD)…

- **Early repolarization:** 2-5% of the population; concave ST segment elevation (V2-V3-V4-V5) from J point; notch at J point; prominent T wave



ST DEPRESSION (AT J POINT ON ≥ 2 CONTIGUOUS LEADS)
≥ 0.5 mm (horizontal or descending)

DDX OF ST DEPRESSION: ischemia; LVH; RVH; LBBB; RBBB; pre-excitation; myocarditis; pericarditis; cardiomyopathy; amyloidosis; hypokalemia; Digoxin; pulmonary embolism; intracranial hemorrhage; stroke; acute systemic disease; sepsis; fever; acidosis; anemia; postoperative period after cardiac surgery; hyperventilation...

T WAVE INVERSION (ON ≥ 2 CONTIGUOUS LEADS)
≥ 1 mm; leads with R/S > 1

DDX OF T WAVE INVERSION: persistent juvenile pattern; RBBB; LBBB; pre-excitation; LVH; RVH; apical HCM; ARVD; Brugada; acute CNS lesion; PVC; ventricular pacing ("*memory T wave*")

› **Persistent juvenile pattern:** T wave inversion in V1-V2-V3 persisting since childhood

GIANT T WAVE INVERSION (>10 MM): Apical HCM; ischemia; Wellens' syndrome; post-STEMI; CNS lesion

› **Wellens' syndrome**: deep T wave inversion in V2-V3-V4 with ↗ QT interval associated with proximal LAD lesion

SYMMETRICALLY PEAKED T WAVES
≥ 5 mm (frontal leads); ≥ 10 mm (precordial leads)

DDX OF SYMMETRICALLY PEAKED T WAVES: hyperkalemia; acute ischemia (early STEMI); CNS lesion; LVH or LBBB (asymmetrical T waves)

PROLONGED QT INTERVAL
QTc ≥ 450 ms (men) or ≥ 460 ms (women)

DDX OF PROLONGED QT INTERVAL: medication - **www.qtdrugs.org** (interrupt agent when **QTc > 500 ms or increases by > 60 ms**); long QT syndrome; hypocalcemia; hypokalemia; hypomagnesemia; hypothermia; CNS lesion; ischemia; severe bradycardia... +

› **Normal QT**: **< 1/2 RR interval**
- **Bazett's equation**: **QTc = QT (msec) / √R-R (s)** (HR < 100 bpm) +
- **Linear model**: **QTc = QT + 1.75 x (HR - 60)**
- **Significant change on medication: > 60 ms**

› **Measurement of QT:** longest interval (often V2-V3); draw a tangent from the most pronounced descent of the T wave to intersect the TP segment

› **QT associated with prolonged QRS**: **JTc interval** (QT duration - QRS duration) (normal < 370 ms)

SHORT QT INTERVAL: **QTc ≤ 390 msec** (HR < 100 bpm) +

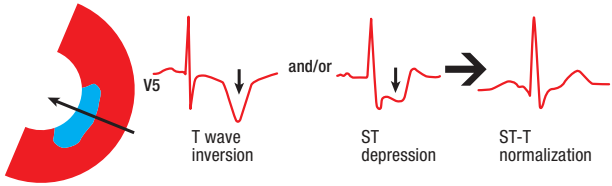
› **Etiologies**: hypercalcemia; hyperkalemia; Digoxin; congenital short QT syndrome

PROMINENT U WAVE (> 2 MM): hypokalemia; hypercalcemia; Digoxin; class IA and IC AAD; thyrotoxicosis; intracranial hemorrhage; congenital long QT syndrome

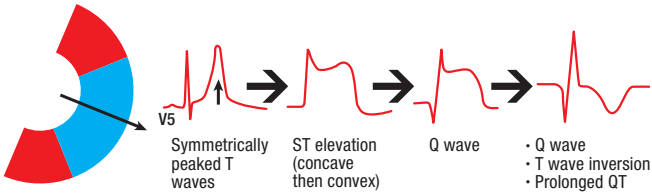
› **U wave inversion**: leads on which the T wave is positive; sign of ischemia

MYOCARDIAL INFARCTION (▶▶| Chapter 2 - Myocardial infarction)

SUBENDOCARDIAL ISCHEMIA



TRANSMURAL ISCHEMIA



ST ELEVATION OR SYMMETRICALLY PEAKED T WAVES	
V1-V2	Anteroseptal infarction
V3-V4	Anteroapical infarction
V5-V6 (± aVL - I)	Anterolateral infarction
V1-V2-V3-V4-V5-V6	Extensive anterior infarction
aVL-I	Lateral infarction
II-III-aVF	Inferior infarction
V3R-V4R (± V1) (+ II-III-aVF)	RV infarction
V7–V8–V9 (mirror changes in V1–V2)	Posterior infarction

ABNORMAL Q WAVE (IN ≥ 2 CONTIGUOUS LEADS)	
V2-V3	QS or Q duration ≥ 20 ms
I-II-aVL-aVF V4-V5-V6 V7-V8-V9	QS or Q ≥ 30 ms and > 1 mm
V1-V2	Consider old posterior infarction if R > 40 ms with R/S ≥ 1 in absence of conduction disorder

DDX OF Q WAVES (PSEUDO-INFARCTION): septal Q waves (V4-V5-V6; I; aVL; aVF); normal variant in V1 or III; LVH; RVH; LBBB; LAHB; pre-excitation; myocarditis; RCM - Infiltration (amyloidosis; sarcoidosis; tumor); HCM; DCM; dextrocardia; hyperkalemia; chest deformity; pneumothorax; COPD; pulmonary embolism...

CLINICAL ENTITIES

ACUTE PERICARDITIS: 4 phases

1) Diffuse ST elevation (concave); PR segment depression; mirror image in aVR
2) Normalisation of ST segment with depression of J point
3) T wave inversion
4) Normalisation of T waves

PERICARDIAL EFFUSION: low voltage; electrical alternans

PULMONARY EMBOLISM: sinus tachycardia; QR or qR in III-aVF / V1-V2-V3 (pseudo-infarction); S1Q3T3 (12% of patients); ST depression (sometimes elevation) and T wave inversion in V1-V2-V3; complete or incomplete RBBB; delayed precordial QRS transition; right axis deviation

HYPERTROPHIC CARDIOMYOPATHY (HCM): LVH; LAH; left axis deviation; pseudo-infarction (Q waves - inferior - lateral - precordial leads); giant T wave inversion in precordial leads (apical HCM)

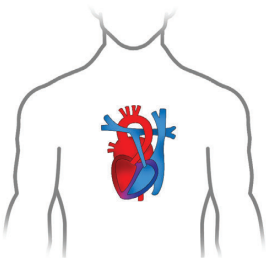
PRIMUM ASD: RBBB; left axis deviation; RAH

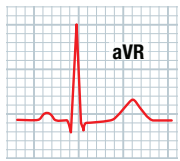
SECUNDUM ASD: Incomplete RBBB; right axis deviation; RAH; notch in the upslope of the R wave in inferior leads

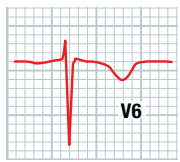
MITRAL STENOSIS: RVH; right axis deviation; LAH ± RAH

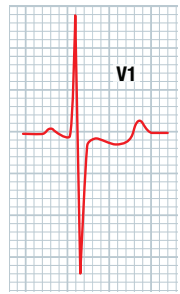
LEFT VENTRICULAR ANEURYSM: persistent convex ST elevation (3 weeks post-MI) in the presence of a Q wave

DEXTROCARDIA: inverted P and QRS and T waves in I and aVL; positive QRS in aVR; inverted precordial QRS transition





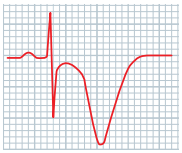




COPD: RVH; RAH; right axis deviation; ↘ QRS amplitude on frontal leads (electrical isolation due to hyperinflation); delayed precordial transition (cardiac position modified by hyperinflation and lowering of the diaphragm); persistent S wave in all precordial leads; low amplitude R wave in V6; pseudoinfarction (Q waves); MAT - APCs - AF - Flutter

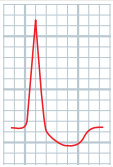
ACUTE CNS LESION: giant T wave inversions on precordial leads (sometimes positive and prominent); ↗ QT interval; U waves; transient ST elevation; ± Torsade de pointes

V2



DIGOXIN IMPREGNATION: **scooped ST**; flattened T wave; ↘ QT interval; ↗ PR interval; U wave

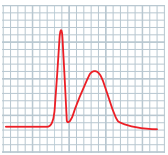
V5



DIGOXIN TOXICITY: sinus bradycardia; sinus arrest; ectopic atrial tachycardia; "regularized" AF (junctional escape rhythm); junctional tachycardia; AV block; PVCs; VT; bidirectional VT; VF

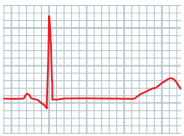
HYPERCALCEMIA: ↘ QT interval; sharp T wave upstroke; ↗ PR interval

V5



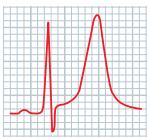
HYPOCALCEMIA: **↗ QT interval** (due to ↗ ST interval; T wave unchanged)

V5



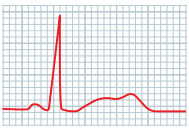
HYPERKALEMIA: **symmetrically peaked T waves**; ↘ QT interval → **↗ QRS duration** and ↗ PR interval; conduction disorders (RBBB; LBBB; bifascicular block; AV block) → **flattened P wave** (or even loss of P wave with sinoventricular rhythm; unexcitable atrial muscle); ST elevation → ventricular flutter / sinusoidal rhythm → asystole

V5



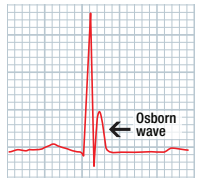
HYPOKALEMIA: **prominent U wave**; ST depression; flat T wave; ↗ QT interval; blocks; atrial - ventricular - junctional tachyarrhythmias / Torsade de pointes

V5



HYPOTHERMIA (< 34°C): Osborn wave; bradycardia; ↗ QT interval; ↗ QRS duration; ↗ PR interval; artefacts secondary to rigors; junctional bradycardia; ventricular arrhythmia; asystole

› **Osborn wave**: notch and elevation of J point (maximal in V5-V6)



HYPOTHYROIDISM: low voltage; sinus bradycardia; flat T wave; ↗ PR interval; conduction disorders; ↗ QT interval

1.3/ STRESS TEST

INDICATION

INDICATION FOR STRESS TEST

DIAGNOSTIC
Intermediate pretest probability of CAD
(stop anti-ischemic medication 5 half-lives before the test)

and/or

PROGNOSTIC
Known CAD or intermediate or high probability of CAD

	SENSITIVITY	SPECIFICITY
General population	68 %	77 %
LMCA or 3–vessel disease	86 %	53 %

CONTRAINDICATIONS

ABSOLUTE	RELATIVE
• Acute infarction ≤ 48 h • High-risk unstable angina • Decompensated heart failure • Uncontrolled arrhythmia with symptoms or hemodynamic instability • Myocarditis or acute pericarditis • Severe symptomatic aortic stenosis • Acute pulmonary embolism • Acute aortic dissection	• Left main coronary artery stenosis • Moderate stenotic valvular heart disease • Electrolyte disorders • Severe HTN: > 200/110 mmHg • Tachyarrhythmia or bradyarrhythmia • HCM • Advanced AV block • Mentally unable to perform the exercise **ANOMALIES ON BASELINE ECG** • Pre-excitation • LBBB • Ventricular pacing • ST depression > 1 mm • Digoxin and LVH with repolarization abnormalities (false-positive)

COMPLICATIONS: 3.5 infarctions - 4.8 arrhythmias - 0.5 deaths per 10,000 examinations performed

PROTOCOLS

STAGE	% SLOPE	SPEED (mph)	TIME (min)	VO_2 (mL/kg/min)	METs
BRUCE PROTOCOL					
0	0	1.7	-6 to -3		
0.5	5	1.7	-3 to 0	11	3
1	10	1.7	3	17	4.5
2	12	2.5	6	25	7
3	14	3.4	9	35	10
4	16	4.2	12	47	13
CORNELL PROTOCOL					
1	0	1.7	2	7	2
2	5	1.7	4	11	3
3	10	1.7	6	17	4.5
4	11	2.1	8	19	5.5
5	12	2.5	10	25	7
6	13	3	12	30	8.5
7	14	3.4	14	35	10
8	15	3.8	16	40	11.5
9	16	4.2	18	47	13
NAUGHTON PROTOCOL					
1	0	2	2	7	2
2	3.5	2	4	10.5	3
3	7	2	6	14	4
4	10.5	2	8	17.5	5
5	14	2	10	21	6
6	17.5	2	12	24.5	7
7	12.5	3	14	28	8

1 MET: = **3.5 mL O_2/kg/min** (O_2 consumption in a resting subject)

ESTIMATED VO_2: = [(2.68 x mph) x (0.1 + (% slope x 1.8))] + 3.5

MONITORING: **ECG - HR - BP - Rating of perceived exertion (Borg scale)** at the end of each stage; at the end of exercise; every 2-3 min during recovery (for 6-10 min or normalization of ECG)

BRUCE PROTOCOL: change of speed and slope at each 3-min stage; modified Bruce with the addition of 2 initial stages if necessary

CORNELL PROTOCOL: more gradual increase of exertion (each Bruce stage is subdivided into 2 substages)

NAUGHTON PROTOCOL: 2-min stages; increase of 1 MET per stage; used during evaluation of VO_2 max

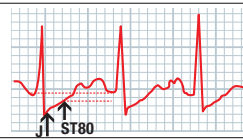
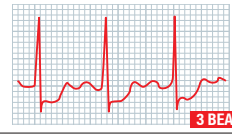
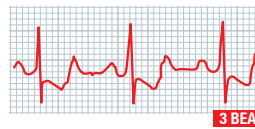
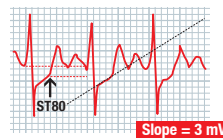
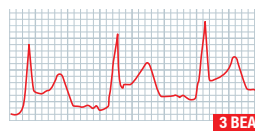
RAMP PROTOCOL: the slope and speed increase progressively according to the patient's previously estimated functional class (according to an activity scale expressed in METs) to achieve exercise lasting about 8 to 12 minutes

POST-INFARCTION: **A)** Prescription of physical activity; **B)** Effects of treatment; **C)** Prognostic value (unknown coronary anatomy)

- **Submaximal stress test (3-4 days):** Modified Bruce or Naughton; stop if HR ≥ 120 bpm or ≥ 70% of predicted HRmax or 5 METs or Angina or Dyspnea or ↘ ST 2 mm or ↘ BP or ≥ 3 consecutive PVCs
- **Stress test limited by symptoms (3 weeks):** standard test

ELECTROCARDIOGRAPHIC EVALUATION

ST SEGMENT: depression compared to PQ segment, **80 ms from point J (ST80)** or 60 ms from point J if HR > 130 bpm (ST60)

Normal response: ascending ST depression	• ST80 depression < 1.0 mm • Ascending slope ≥ 1 mV/s (1 mV = 10 mm)	
Abnormal response: horizontal ST depression	• J and ST80* depression ≥ 1 mm • Horizontal slope (< 0.7 to 1 mV/s)	
Abnormal response: descending ST depression	• J and ST80* depression ≥ 1 mm • Descending slope (< -1 mV/s)	
Gray zone: ST depression with slow rise	• ST80 depression ≥ 1.0 mm • Ascending slope ≥ 1 mV/s • Evaluate according to the patient's pretest probability of CAD	
Transmural ischemia: ST elevation	• J and ST60 elevation ≥ 1 mm • Absence of Q wave • Localize ischemia	

* ST60 if HR > 130 bpm

MORE SPECIFIC LEADS: **V4-V5-V6**; isolated ST abnormalities in II and aVF often associated with false-positive results

ST DEPRESSION: does not localize the ischemia

ST ELEVATION IN AVR: associated with left main coronary / ostial LAD stenosis

U WAVE INVERSION: associated with significant CAD

BASELINE RBBB: ignore leads V1-V2-V3-V4 during the stress test

FALSE-POSITIVE: baseline ST abnormality; anemia; cardiomyopathy; Digoxin; hyperventilation; hypokalemia; intraventricular conduction disorders; LVH; pre-excitation; severe AS; severe HTN; severe hypoxia; severe volume overload; supraventricular tachycardia; MVP

INDICATIONS TO TERMINATE THE TEST

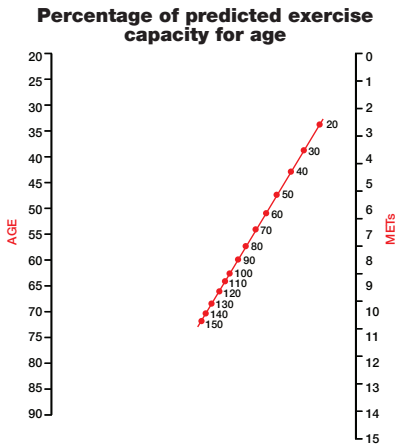
ABSOLUTE	RELATIVE
• ↘ BP ≥ 10 mmHg with ischemia • Severe and intolerable angina (CCS 3 to 4/4 on tolerance scale) • Ataxia; Faintness • Hypoperfusion (cyanosis; pallor) • Technical difficulty • Patient wants to stop • Sustained VT • ST elevation: ≥ 1 mm (in absence of Q wave and elsewhere than in aVR or V1)	• ↘ BP ≥ 10 mmHg • ST depression: > 2 mm • Marked change of QRS axis • Arrhythmia: polymorphic PVCs; triplet PVCs; supraventricular tachycardia; block; bradyarrhythmia • Fatigue - Dyspnea - Wheezing - Leg cramps - Claudication • Intraventricular conduction disorder unable to be distinguished from VT • Worsening retrosternal chest pain • Exaggerated hypertensive response: BP > 250/115

OTHER ELEMENTS TO BE EVALUATED

NON-DIAGNOSTIC TEST: **insufficient exercise (< 85% of predicted HRmax for age)**

› **Predicted HRmax for age**: **= 220 - age**

MAXIMUM FUNCTIONAL CAPACITY: # METs; powerful prognostic marker



Source: *Morris CK, Myers J, Froelicher VF, et al. JACC 1993; 22; 175-182.*

DOUBLE PRODUCT: HR x SBP / 1000 (normal: 20-35 mmHg x bpm x 10^{-3})

ANGINA: generally occurs after ST abnormalities

SYSTOLIC BLOOD PRESSURE: peak generally observed between 160 and 200 mmHg

- **Abnormal response**: failure to reach 120 mmHg or ↘ > 10 mmHg or ↘ below baseline SBP; associated with significant ischemia or cardiomyopathy or LVOT obstruction or antihypertensive medication or significant dehydration
- **Exaggerated hypertensive response**: SBP > 210 mmHg in men or > 190 mmHg in women; risk of developing HTN in the future in a currently normotensive patient; indicates an insufficient reduction of systemic vascular resistance by arteries and arterioles during exercise; ABPM may be indicated

CHRONOTROPIC INCOMPETENCE: failure to achieve > 80-85% of predicted HRmax for age (with significant exercise); associated with poor prognosis

- **Chronotropic index**: observed HR reserve (maximum HR on stress test - HR at rest) / (predicted HRmax for age - HR at rest); chronotropic incompetence if **< 80 %**

DE NOVO LBBB ON EXERTION: associated with ↗ risk of mortality and significant CAD

RECOVERY OF HR AT 1 MIN: = peak HR - HR after 1 minute of rest

- **Abnormal HR recovery:** < 12 bpm (standing) or 18 bpm (supine); associated with poor prognosis

PVCS DURING RECOVERY: associated with ↗ risk of mortality (compared to patients with PVCs on exertion only)

DUKE TREADMILL SCORE (DTS)

DTS = EXERCISE TIME (MIN) - (5 X MAXIMUM ST DEPRESSION IN MM) -4 X (ANGINA SCORE)	
ANGINA SCORE • Angina requiring termination = 2 • Angina not requiring termination = 1 • No angina = 0	**ONE-YEAR MORTALITY** • DTS -11 and less: 5.0% • DTS between +4 and -10: 1.25% • DTS ≥ +5: 0.25 %

Mark DB, Hlatky MA, Harrell FE Jr et al. Ann Intern Med. 1987; 106:793.

FACTORS OF POOR PROGNOSIS

DUKE TREADMILL SCORE: -11 and less +

LOW FUNCTIONAL CAPACITY: < 5 METs +

LOW THRESHOLD ANGINA OR ISCHEMIA: < 70% predicted HRmax or HR < 120 bpm or ≤ 4 METs +

SEVERE ST DEPRESSION: ≥ 2 mm +

MULTIPLE LEADS: ischemia on ≥ 5 leads +

PERSISTENCE: ischemia ≥ 3 min during recovery +

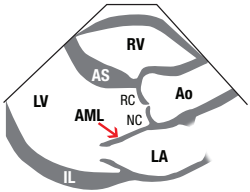
ST ELEVATION: ≥ 1 mm (except for aVR) +

ABNORMAL BP RESPONSE: failure to achieve 120 mmHg or ↘ > 10 mmHg or ↘ below baseline SBP

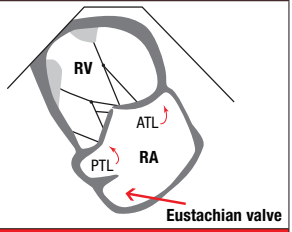
SUSTAINED OR SYMPTOMATIC VT

1.4/ TRANSTHORACIC ECHOCARDIOGRAPHY (TTE)

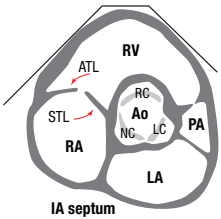
PARASTERNAL – LONG AXIS (PLAX)



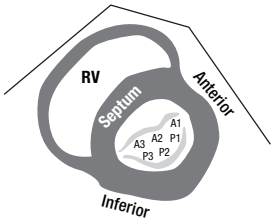
PARASTERNAL – RV INFLOW TRACT



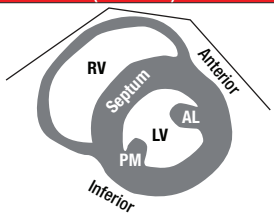
SHORT AXIS – AORTIC VALVE LEVEL



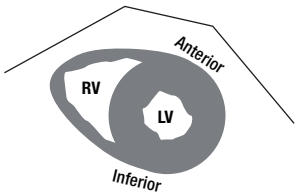
SHORT AXIS – MITRAL VALVE LEVEL



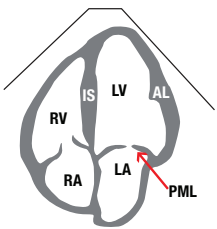
SHORT AXIS – MITRAL PAPILLARY MUSCLES (MID 1/3 LV)



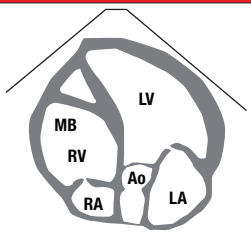
SHORT AXIS – APICAL

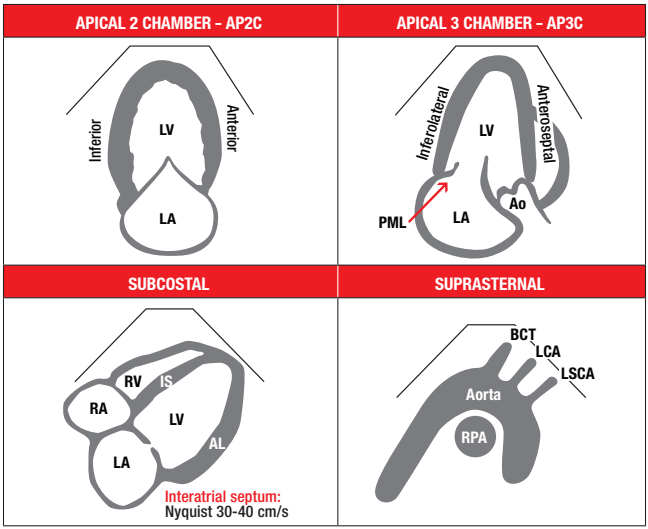


APICAL 4 CHAMBER – AP4C



APICAL 5 CHAMBER – AP5C

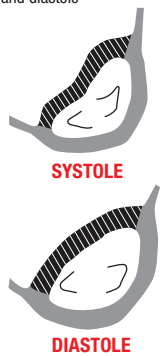
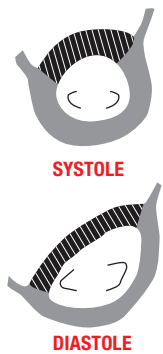


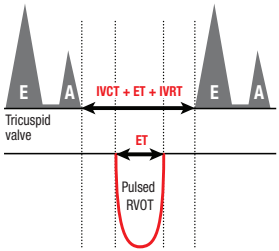


LV - RV - LA - RA - PA EVALUATION

	LEFT VENTRICLE			
	NORMAL	SLIGHTLY ABNORMAL	MODERATELY ABNORMAL	SEVERELY ABNORMAL
LVDD: Diastolic diameter (mm)	F: 38-52 M: 42-58	F: 53-56 M: 59-63	F: 57-61 M: 64-68	F: ≥ 62 M: ≥ 69
LVSD: Systolic diameter (mm)	F: 22-35 M: 25-24	F: 36-38 M: 41-43	F: 39-41 M: 44-45	F: ≥ 42 M: ≥ 46
Indexed diastolic volume (mL/m²)	F: 29-61 M: 34-74	F: 62-70 M: 75-89	F: 71-80 M: 90-100	F: ≥ 81 M: ≥ 101
Index systolic volume (mL/m²)	F: 8-24 M: 6-10	F: 25-32 M: 32-38	F: 33-40 M: 39-45	F: ≥ 41 M: ≥ 46
Interventricular septum (mm)	F: 6-9 M: 6-10	F: 10-12 M: 11-13	F: 13-15 M: 14-16	F: ≥ 16 M: ≥ 17
Posterior wall (mm)	F: 6-9 M: 6-10	F: 10-12 M: 11-13	F: 13-15 M: 14-16	F: ≥ 16 M: ≥ 17
Indexed LV mass (g/m²) by linear method	**LV mass = 0.6 g + 0.8 x (1.04 x [(LVDD + PW + Septum)³ - LVDD³])**			
	F: 43-95 M: 49-115	F: 96-108 M: 116-131	F: 109-121 M: 132-148	F: ≥ 122 M: ≥ 149

<table>
<tr><td rowspan="4">Relative wall thickness (RWT)</td><td colspan="4">RWT = 2 x PW / LVDD</td></tr>
<tr><td>F: 0.22-0.42
M: 0.24-0.42</td><td>F: 0.43-0.47
M: 0.43-0.46</td><td>F: 0.48-0.52
M: 0.47-0.51</td><td>F: ≥ 0.53
M: ≥ 0.52</td></tr>
<tr><td colspan="2"><u>CONCENTRIC REMODELING</u>
Indexed mass: ≤ 95 g/m² (F) and ≤ 115 g/m² (M)
RWT > 0.42</td><td colspan="2"><u>CONCENTRIC LVH</u>
Indexed mass: > 95 g/m² (F) and > 115 g/m² (M)
RWT > 0.42</td></tr>
<tr><td colspan="2"><u>NORMAL GEOMETRY</u>
Indexed mass: ≤ 95 g/m² (F) and ≤ 115 g/m² (M)
RWT ≤ 0.42</td><td colspan="2"><u>ECCENTRIC LVH</u>
Indexed mass: > 95 g/m² (F) and > 115 g/m² (M)
RWT ≤ 0.42</td></tr>
<tr><td rowspan="2">LVEF (%) (Simpson biplane)</td><td colspan="4">LVEF = ED volume - ES volume / ED volume</td></tr>
<tr><td>F: 54-74
M: 52-72</td><td>F: 41-53
M: 41-51</td><td>30-40</td><td>< 30</td></tr>
<tr><td>LVEF (%) (Dumesnil)</td><td colspan="4">LVEF = stroke volume / ED volume
• Stroke volume = 0.785 x LVOT diameter ² x LVOT VTI
• ED volume = 7 x LVDD³ / (2.4 + LVDD)</td></tr>
<tr><td rowspan="2">Endocardial shortening fraction (%)</td><td colspan="4">% shortening = LVDD - LVSD / LVDD</td></tr>
<tr><td>F: 27-45
M: 25-43</td><td>F: 22-26
M: 20-24</td><td>F: 17-21
M: 15-19</td><td>F: ≤ 16
M: ≤ 14</td></tr>
<tr><td rowspan="2">Cardiac output (L/min)</td><td colspan="4">• CO = HR x (0.785 x LVOT diameter ² x LVOT VTI)
• CO = HR x (ED volume - ES volume)</td></tr>
<tr><td colspan="4">Normal cardiac output : 4 - 6 L/min</td></tr>
<tr><td rowspan="2">dP/dt (isovolumic contraction)</td><td colspan="4">dP/dt = 32 / time for velocity of MR jet to increase from 1 m/s to 3 m/s</td></tr>
<tr><td colspan="4">Normal dP/dt: > 1200 mmHg/sec</td></tr>
<tr><td rowspan="2">LIMP (Left MPI)</td><td colspan="4">LIMP = IVCT + IVRT / ET ejection time</td></tr>
<tr><td colspan="4">• Global myocardial performance index
• ▶▶| RV MPI (right ventricle)
• Normal LV MPI : < 0.39 ± 0.05</td></tr>
<tr><td colspan="5">RIGHT VENTRICLE</td></tr>
<tr><td>RV dilatation (qualitative; AP4C)</td><td>Size of RV < size of LV; apex belongs to LV</td><td>Size of RV similar to size of LV; apex belongs to LV</td><td>Size of RV similar to size of LV; apex shared between the two</td><td>RV > LV; apex belongs to RV</td></tr>
</table>

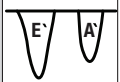
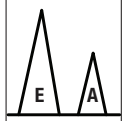
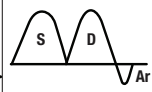
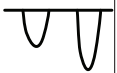
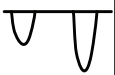
Basal RV diameter AP4C (mm)	Dilatation: > 41 mm	RV-focused apical 4-chamber view; LV apex centered and not truncated, while displaying the largest basal RV diameter
Mid–cavity RV diameter AP4C (mm)	Dilatation: > 35 mm	
Longitudinal RV diameter AP4C (mm)	Dilatation: > 83 mm	
RVOT diameter (mm)	• **Proximal**: PLAX (dilatation if > 30 mm) or PSAX above the Ao valve (dilatation if > 35 mm) • **Distal**: PSAX above the P valve (dilatation if > 27 mm)	
RV wall thickness (mm)	RVH: > 5 mm Subcostal; end-diastole; at the extremity of T valve leaflets	
Septal curvature	**Pressure overload** D-shaped septum in systole and diastole  SYSTOLE DIASTOLE	**Volume overload** D-shaped septum in diastole  SYSTOLE DIASTOLE
FAC: RV fractional area change (%)	RV systolic dysfunction: < 35%	**FAC = (end-diastolic area - endsystolic area) / end-diastolic area x 100%** AP4C; include the trabeculae in the cavity
RV S' (Tissue Doppler)	RV systolic dysfunction: < 9.5 cm/s	AP4C; Velocity of longitudinal systolic excursion of basal segment of the free wall of the RV; angle dependant
TAPSE (tricuspid annular plane systolic excursion)	RV systolic dysfunction: < 17 mm	AP4C; RV longitudinal function; Tricuspid lateral annular longitudinal excursion by M-mode (mm)

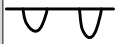
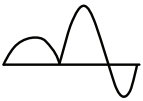
RIMP (Right MPI): Global myocardial performance index	**Tissue Doppler:** RV dysfunction if > 0.54 **Pulsed Doppler:** RV dysfunction if > 0.43	**RIMP = IVCT + IVRT / ET ejection time** • **Tissue Doppler**: tricuspid annulus: ET = duration S`; IVCT + IVRT + ET = interval between the end of A` and the start of E` • **Pulsed Doppler**: 

LEFT AND RIGHT ATRIA				
LA diameter PLAX (mm)	F: 27-38 M: 30-40	F: 39-42 M: 41-46	F: 43-46 M: 47-52	F: ≥ 47 M: ≥ 52
Indexed LA volume (mL/m²)	**LA volume = (0.85 x A1 x A2) / L** Area and long axis on biplane views (AP4C and AP2C)			
	16-34	35-41	42-48	≥ 48
Indexed RA volume (mL/m²)	**RA volume = RA area ² / L** (AP4C, single-plane) Normal: F: 21 ± 6 M: 25 ± 7			
Indexed RA length AP4C (cm/m²)	**Long axis** (parallel to the interatrial septum) Normal: F: 2.5 ± 0.3 M: 2.4 ± 0.3			
Indexed RA diameter AP4C (cm/m²)	**Short axis** (lateral wall of RA to interatrial septum) Normal: 1.9 ± 0.3			
RA pressure (CVP) estimated by subcostal view of inferior vena cava (mmHg)	• **IVC ≤ 21 mm and collapse > 50%**: RA pressure = 3 mmHg (0-5 mmHg) • **IVC > 21 mm and collapse < 50%**: RA pressure = 15 mmHg (10-20 mmHg) • **Intermediate**: RA pressure = 8 mmHg (5-10 mmHg) • **Ventilated patient**: IVC ≤ 12 mm associated with RA pressure < 10 mmHg			
PULMONARY ARTERY				
Systolic PAP (mmHg)	**sPAP = 4 x TR pressure gradient ² + RA pressure** In the absence of RVOT obstruction			
	< 35	35 - 50	50 - 80	> 80
Diastolic PAP (mmHg)	**dPAP = 4 x PR end–diastolic velocity ² + RA pressure**			

Mean PAP (mmHg)	• **mPAP = 1/3 sPAP + 2/3 dPAP** • **mPAP = 4 x early diastolic PR velocity² + RA pressure** • **Mahan: mPAP = 79 – (0.45 x PA acceleration time)** › If PA acceleration time < 120 ms: mPAP = 90 - (0.62 x PA acceleration time) › **PA acceleration time**: start of QRS to peak pulmonary flow velocity; pulsed Doppler			
Pulmonary artery diameter (mm)	15-21	22-25	26-29	≥ 30

DIASTOLIC FUNCTION

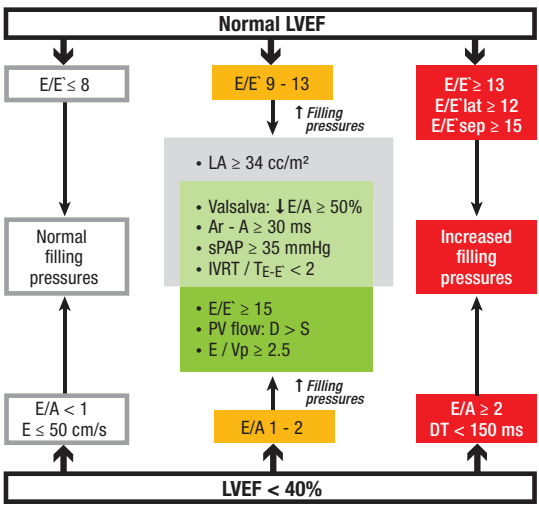
	DIASTOLIC FUNCTION - GRADING				
	E` (cm/s) E/E`	**LA (mL/m²)**	**E/A DT (ms) IVRT (ms)**	**PV FLOW AR - A (ms)**	**VALSALVA**
NORMAL PATTERN	E`sep ≥ 8 E`lat ≥ 10 E/E`≤ 8 	< 34	E/A 0.8 - 1.5 DT 160-200 	PV S > D Ar - A < 0 	Reduction of E/A ratio < 0.5
GRADE I: ABNORMAL RELAXATION PATTERN	E`sep < 8 E`lat < 10 E/E`≤ 8 	≥ 34	E/A < 0.8 DT > 200 IVRT ≥ 100 	PV S > D Ar - A < 0 	Reduction of E/A ratio < 0.5
	Normal filling pressures (generally)				
	> 60 years: E/A < 1 and DT > 200 ms in the absence of LVH or heart disease → normal for age				
GRADE II: PSEUDO-NORMAL PATTERN	E`sep < 8 E`lat < 10 E/E` 9-12 	≥ 34	E/A 0.8 - 1.5 DT 160-200 	VP D > S Ar - A ≥ 30 	Reduction of E/A ratio ≥ 0.5
	↗ Filling pressures				

GRADE III: RESTRICTIVE PATTERN	E`sep < 8 E`lat < 10 E/E`> 13 E/E`sep ≥ 15 E/E`lat > 12 	≥ 34	E/A ≥ 2 DT < 160 IVRT ≤ 60	PV D > S Ar - A ≥ 30 	Variable
	↗↗↗ Filling pressures **DDx**: Severe decompensated heart failure; advanced RCM; severe CAD; severe acute AR; Constrictive pericarditis				
	IIIa: filling pattern improves in response to treatment **IIIb**: absence of improvement of the filling pattern in response to treatment				

IVRT: Continuous Doppler LVOT; interval between end of Ao ejection and start of mitral filling (E wave)

FUSION OF E AND A: E wave > 20 cm/s at the beginning of the A wave

FILLING PRESSURES



- **Increased filling pressures**: Wedge pressure > 12 mmHg or LVEDP > 16 mmHg
- **TE-E`**= (interval between QRS and onset of E) - (interval between QRS and onset of E`)
- **Vp**: velocity of propagation of diastolic flow on color M-mode
- **AF**: ↗ filling pressures if **IVRT ≤ 65 ms or DT of pulmonary vein diastolic flow ≤ 220 ms or septal E/E' ≥ 11**

SEGMENTAL WALL MOTION

LEFT VENTRICLE: **divided into 16 segments** (+ apical cap)

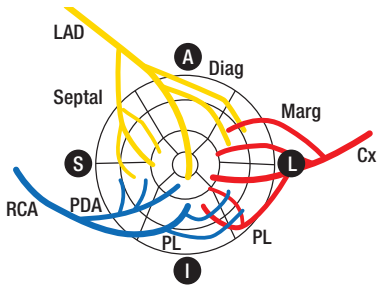
› **Interventricular septum**: between the attachments of the RV to the LV

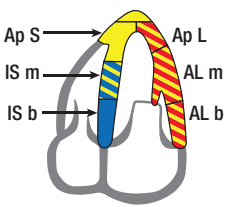
LEFT VENTRICULAR CHAMBER: **3 levels → A) Base - B) Mid 1/3 (papillary muscles) - C) Apex**

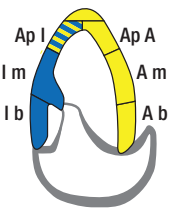
SEGMENTAL WALL MOTION: **evaluate endocardial excursion and segmental thickening** +

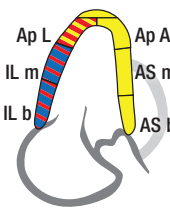
– 1 – NORMAL (or hyperdynamic)	– 2 – HYPOKINESIA	– 3 – AKINESIA	– 4 – DYSKINESIA	– 5 – ANEURYSM
Thickening > 40% in systole	Thickening 10-40%	Thickening < 10% (negligible)	Paradoxical systolic movement	Diastolic deformity

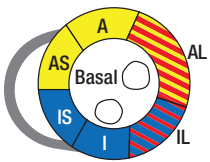
WMSI = Sum of each segment / Number of segments evaluated
Normal = 1; WMSI > 1.7 associated with perfusion defect > 20% (MIBI)

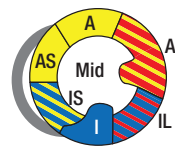


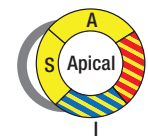












AORTIC STENOSIS		SEVERE
Maximum jet velocity	Look for parallel alignment between continuous Doppler and the jet	**> 4 m/s**
Mean gradient	Mean of instantaneous mean gradients during ejection	**> 40 mmHg**
Valve area by continuity equation	**Aortic valve area = 0.785 x LVOT diameter² x LVOT VTI / Aortic valve VTI**	**< 1 cm²**
	• LVOT VTI and LVOT diameter obtained at the same distance from the valve • **Proximal velocity (LVOT) > 1.5 m/s**: use peak velocity and maximum gradient to grade severity **› Maximum gradient = 4 (maximum v² – proximal v²)**	
LVOT VTI / Ao valve VTI ratio	Independent of measurement of LVOT	**< 0.25**
Velocity > 4 m/s and Area > 1 cm²: high output; significant AR; tall patient **Velocity < 4 m/s and Area < 1cm²:** low output; small patient; significant MR		

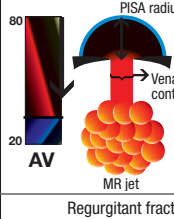
MITRAL STENOSIS		SEVERE
Mean gradient	Mean of instantaneous mean gradients during filling	**> 10 mmHg**
Valve area by planimetry	• Method of choice in rheumatic MS • At the extremity of the leaflets (PSAX)	**< 1 cm²**
Valve area by pressure half-time	**Mitral valve area = 220 / PHT**	**< 1 cm²**
	• Use the slope of the E wave at mid-diastole • Method of choice in rheumatic MS • **Caveats**: immediately after balloon valvuloplasty; severe AR (short PHT); abnormal LV relaxation (long PHT); ↗ LVEDP (short PHT); prosthetic valve (do not calculate prosthetic area but report PHT)	
Valve area by continuity equation	**Mitral valve area = 0.785 x LVOT diameter² x LVOT VTI / mitral valve VTI**	**< 1 cm²**
Valve area by PISA	**Mitral valve area = [6.28 x PISA radius x Aliasing velocity / Peak MS velocity] x alpha/180°**	**< 1 cm²**

INDICATE HR AT THE TIME OF MEASUREMENTS; EVALUATE PAP

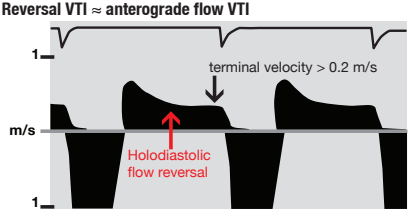
BVR SCORE – BALLOON VALVULOPLASTY REGISTRY (WILKINS SCORE)				
	– 1 – Mobility of leaflets	**– 2 – Thickening of leaflets**	**– 3 – Calcification of leaflets**	**– 4 – Thickening of subvalvular apparatus**
1 point	Very mobile valve; restriction of the extremity of the leaflets	Leaflets measure 4-5 mm	A single hyperechodense zone	Minimal thickening under the leaflets

2 points	Normal mobility of the base and middle parts of the leaflets	Localized thickening (5-8 mm)	Several localized hyperechodense zones on the leaflets	Thickening of the chordae (1/3 of their length)
3 points	Mobility of the base of the valve	Thickening of all of the leaflet (5-8 mm)	Hyperechodensities as far as the middle portion of the leaflets	Thickening of the chordae as far as their distal third
4 points	Minimal or absent movement of the leaflets	Considerable thickening of the entire leaflet (8-10 mm)	Extensive hyperechodensities on the majority of the leaflets	Severe thickening as far as the papillary muscles

Score ≤ 8 associated with a favorable result of balloon valvuloplasty

MITRAL REGURGITATION		SEVERE
Vena contracta	Narrowest portion of the jet distal to the regurgitating orifice; avoid AP2C; Nyquist 50-60 cm/s	**≥ 7 mm**
Regurgitant volume	**VOLUMETRIC METHOD** Regurgitant volume = (0.785 x Mitral annulus diameter ² x anterograde mitral VTI) - (0.785 x LVOT diameter ² x LVOT VTI) • **Mitral annulus diameter**: mean of PLAX and AP4C • **Significant AR**: use pulmonic valve flow **PISA**: Regurgitant volume = EROA x MR VTI	**≥ 60 cc**
EROA (Effective Regurgitation Orifice Area)	**VOLUMETRIC METHOD** EROA = Regurgitant volume / MR VTI **PISA** EROA = 6.28 x PISA radius ² x "aliasing" velocity / peak MR velocity  • PISA corresponds to the time of peak MR velocity • "Aliasing" velocity adjusted to the direction of regurgitation to obtain hemispheric convergence flow (Nyquist 20-40 cm/s)	**≥ 0.40 cm²** **(≥ 0.20 cm² if functional MR)**
Regurgitant fraction	Regurgitant fraction = Regurgitant volume / (0.785 x Mitral annulus diameter ² x anterograde mitral VTI)	**≥ 50 %**
PISA radius	Nyquist 40 cm/s	**≥ 9 mm**
MR jet	• Nyquist 50-60 cm/s • **Severe MR:** Large central jet > 10 cm² (or > 40% LA area) or eccentric jet adhering to the wall of the LA (Coanda effect)	

E wave	Dominant E wave	**> 1.2 m/s**
Envelope of the jet on continuous Doppler	• **Severe MR**: dense envelope; early peak and triangular shape • **MVP:** mid- or end-systolic envelope	
Pulmonary venous flow	**Severe MR**: systolic reversal	
LA dilatation and LV dilatation; Carpentier's mechanism		

AORTIC REGURGITATION		**SEVERE**
Vena contracta	Narrowest portion of the jet distal to the regurgitating orifice; PLAX; Nyquist 50-60 cm/s	**≥ 6 mm**
Regurgitant volume	**VOLUMETRIC METHOD** Regurgitant volume = (0.785 x LVOT diameter ² x LVOT VTI) - (0.785 x Mitral annulus diameter ² + anterograde mitral VTI) • **Mitral annulus diameter**: mean of PLAX and AP4C • **Significant MR**: use pulmonic valve flow **PISA**: Regurgitant volume = EROA x AR VTI	**≥ 60 cc**
EROA (effective regurgitation orifice area)	**VOLUMETRIC METHOD** EROA = Regurgitant volume / AR VTI **PISA** EROA = 6.28 x PISA radius ² x "aliasing" velocity / peak AR velocity	**≥ 0.3 cm²**
Regurgitant fraction	**Regurgitant fraction = Regurgitant volume / (0.785 x LVOT diameter ² x LVOT VTI)**	**≥ 50 %**
Jet width / LVOT diameter	PLAX; 1 cm inside the Ao valve; Nyquist 50-60 cm/s	**≥ 65 %**
Jet area / LVOT area	PSAX	**≥ 60 %**
Pressure half-time	• Continuous Doppler • End-diastolic speed > 4 m/s • ↘ **PHT**: HTN; ↘ LV compliance; ↗ LVEDP	**< 200 ms**
Envelope of the jet on continuous Doppler	**Severe AR**: dense envelope (compare with density of the anterograde flow); rapid deceleration	
Holodiastolic flow reversal in descending aorta	• Pulsed Doppler (after the origin of the L subclavian) • Also look for reversed flow in abdominal aorta • **Reversal VTI ≈ anterograde flow VTI** 	
LV dilatation; Ao dilatation; look for eversion or malcoaptation of leaflets; severe acute AR → restrictive mitral filling pattern		

PROSTHETIC VALVE

LOOK FOR: normal 60° opening of leaflets (normal movement of acoustic shadows); dehiscence / rocking movement; vegetation; thrombus; pannus; structural degeneration; abscess; intracardiac mass; pseudoaneurysm; fistula; periprosthetic regurgitation

- **Thrombus**: large mass; similar density to that of myocardium; recent symptoms; recent subtherapeutic INR; more frequent on mechanical mitral valve prosthesis
- **Pannus**: small, dense mass; not visualized in 30% of cases; more frequent in aortic valve prostheses

PROSTHETIC VALVE HEMODYNAMIC MEASUREMENTS: vary according to the model and dimensions of the prosthesis (compare with manufacturer's data); vary according to cardiac output

RECOVERY PRESSURE PHENOMENON: Ao transprosthetic gradient overestimated on TTE compared to catheterization (especially if proximal aortic diameter < 30 mm and small prosthesis)

PROSTHETIC REGURGITATION: distinguish physiological regurgitation specific to the prosthesis from pathological regurgitation; metallic mitral valve can hide MR due to shadowing

- **Central pathological regurgitation**: immobility of a mechanical leaflet; prolapse or perforation of a biological leaflet; mass - vegetation - thrombus
- **Periprosthetic pathological regurgitation:** dehiscence; rocking movement

PATIENT-PROSTHESIS MISMATCH: area of the effective prosthetic orifice too small for the patient's body surface area; **valve functions normally but with ↗ transvalvular gradients; normal prosthetic area (non-indexed) for the type of prosthesis**

- **Mild**: Indexed EOA > 0.85 cm²/m²
- **Moderate**: Indexed EOA: 0.65-0.85 cm²/m²
- **Severe**: Indexed EOA < 0.65 cm²/m²; associated with ↗ mortality (especially if LV dysfunction)
- **Mitral prosthesis:** aim for indexed EOA > 1.2 cm²/m²

	PROSTHETIC AORTIC VALVE DYSFUNCTION		
	PEAK VELOCITY	**VTI 1/2 RATIO**	**ACCELERATION TIME (AORTIC SYSTOLIC FLOW)**
Obstruction (degeneration; thrombus; pannus)	> 3 m/s	< 0.25	> 100 ms Delayed and parabolic peak
Regurgitation or ↗ cardiac output	> 3 m/s	Normal (≥ 0.25)	AT < 80 ms Early triangular peak
Patient-prosthesis mismatch	**Indexed EOA < 0.85 cm²/m²**		
	> 3 m/s	≥ 0.25	AT < 80 ms

	PROSTHETIC MITRAL VALVE DYSFUNCTION			
	PEAK VELOCITY	**GRADIENT**	**PHT**	**PROSTHETIC MITRAL VALVE VTI / LVOT VTI RATIO**
Obstruction (degeneration; thrombus; pannus)	≥ 1.9 m/s	> 5 mmHg	> 130 ms	> 2.2
Regurgitation	≥ 1.9 m/s	> 5 mmHg	< 130 ms	> 2.2
Hyperdynamic state / High output state	≥ 1.9 m/s	> 5 mmHg	< 130 ms	< 2.2 (normal)

ECHOCARDIOGRAPHIC MASS

MASSES / STRUCTURES: Eustachian valve / crista terminalis bridge / Chiari network (RA); vegetation; thrombus; degenerative valve disease; calcification; pacemaker lead; central catheter; lipomatous interatrial septum; pericardial cyst; hydatid cyst; hiatal hernia; tuberculoma; Lambl's excrescences / valvular strands (filiform structures; lenght 3-10 mm; atrial aspect of AV valves and ventricular aspect of semilunar valves; on the line of leaflet closure); benign or malignant cardiac tumor (or metastasis)

THROMBUS: absence of opacification with contrast; adherent to a hypokinetic or akinetic region

CONTRAST ECHOCARDIOGRAPHY

AGITATED SALINE: 10 mL of saline solution; 0.25 mL of air emulsified with 2 syringes; right heart imaging

- **Intracardiac shunt**: **opacification of L chambers within 3 beats** (± Valsalva) +
- **Intrapulmonary shunt (AVMs)**: **opacification of L chambers after 5 beats** +
- **Persistent left SVC:** injection into left arm → opacification of coronary sinus

MICROBUBBLES: lipid microspheres containing gas and able to cross the pulmonary circulation allowing visualization of left cardiac structures; useful for LVEF - segmental wall motion - stress echocardiography - L chamber mass / thrombus (no enhancement in the presence of thrombus) - aneurysm / pseudoaneurysm - HCM - LV noncompaction

- **Complications**: 0.01 %
- **Contraindications**: perflutren allergy; significant PHT; R → L shunt
- **Microbubbles mode**: reduction of mechanical index (0.4-0.5)

TISSUE AND STRAIN DOPPLER

TISSUE DOPPLER IMAGING (TDI): evaluates the velocity of longitudinal movement of a cardiac structure (low velocities); angle dependant

STRAIN (%): longitudinal deformation evaluation; percentage change in length of the muscle during contraction (negative value by convention) or relaxation (positive value by convention)

STRAIN RATE: instantaneous measurement of the deformation (contraction or relaxation)

TISSUE TRACKING: distance covered (displacement) by a structure over a given time interval

TISSUE DOPPLER (S WAVE) (CM/S)	SYSTOLIC STRAIN (%)	STRAIN RATE (S^{-1})	TISSUE TRACKING (cm)
Normal basal septum: 5.97 ± 1.14	Normal basal septum: -17.5 ± 5.32	Normal basal septum: 0.99 ± 0.49	Normal basal septum: 1.2 ± 0.19

SPECKLE TRACKING: evaluation of the deformation of a structure; angle-independent, which allows measurement of longitudinal, radial or circumferential deformation (counterclockwise systolic movement of the apex and clockwise systolic movement of the base)

- **Global longitudinal strain (%)**: relative length change of the LV myocardium between end-diastole and end-systole **(normal peak GLS in the range of -20%)** +

1.5/ TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE)

EVALUATION: mitral valve; aortic valve; prosthetic valve; endocarditis; LA; LAA - thrombus (pre-ECV); intracardiac mass; ASD; acute aortic syndrome; pulmonary venous return; perioperative; cardioembolic source; guidance of percutaneous procedures

COMPLICATIONS: < 1%; dental trauma; esophageal trauma; bronchospasm; laryngospasm; aspiration; respiratory depression; arrhythmias; methemoglobinemia (benzocaine)

PREPARATION

- **Contraindications**: dysphagia; esophageal disease; recent esophageal symptoms; esophageal varices; history of radiotherapy to the neck
- **NPO:** minimum 6 hours before the examination (H_2O allowed until 2 hours before the examination)
- Continuous ECG; IV route; O2; saturation and BP monitor; suction
  - Resuscitation trolley at hand
  - Flumazenil 0.2 mg IV PRN (benzodiazepine antagonist); Naloxone 0.1 to 0.4 mg IV PRN
- **Anesthesia:** topical (lidocaine); IV sedation (midazolam 0.075 mg/kg, i.e. 2-4 mg; fentanyl PRN); Meperidine PRN (anti-gag; 25-50 mg IV)

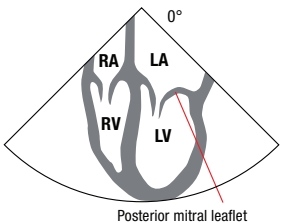
POST-EXAMINATION: NPO 2 hours post-examination; no driving for 12 hours

5 POSSIBLE MOVEMENTS

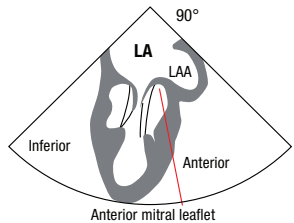
1) Advance - withdraw the probe
2) Rotation of the plane of section (0 degree = horizontal; 90 degrees = vertical)
3) Rotation of the hand piece: clockwise (R heart) or counterclockwise (L heart)
4) Anteflexion (bending of the tip of the probe toward the sternum) or retroflexion
5) Lateral flexion to the right or left (rarely used)

INFERIOR TRANSESOPHAGEAL (30–35 CM)

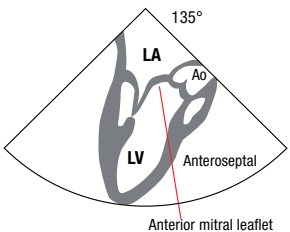
4 CHAMBERS - 0°



2 CHAMBERS - 90°



LONG AXIS - 135°

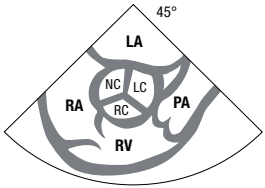


LEFT ATRIAL APPENDAGE

- **45° on mitral valve**: LAA to the right on the screen
  - Progressive rotation of the plane to evaluate the LAA (± slight withdrawal of the probe)
- **Rule out intra-LAA thrombus** (circumscribed mass; bright; uniform texture and different from that of the LA wall)
- **Intra–appendicular velocities (Pulsed Doppler):** < 20 cm/s **associated with a risk of thromboembolic events**
- **Look for spontaneous echo contrast** (prothrombotic state)

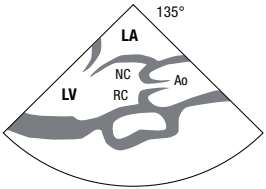
SUPERIOR TRANSESOPHAGEAL

SHORT AXIS (AORTIC VALVE) – 45°



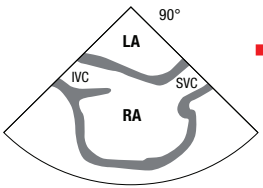
- **Coronary ostia:** 2 o'clock (left) and 6 o'clock (right)
- **Pulmonary valve and PA:** 100-130° ± counterclockwise rotation

LONG AXIS – 135°



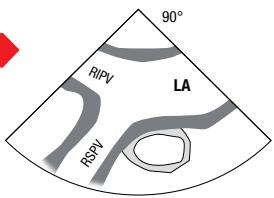
- NC = Non-coronary aortic leaflet
- RC = Right coronary aortic leaflet

BICAVAL VIEW – 90°



- Clockwise rotation of the hand piece
- Longitudinal interatrial septum
- **Rule out shunt**: Color Doprler (Nyquist 30-40 cm/s); agitated saline (± Valsalva)
- Pacemaker lead; central catheter

PULMONARY VEINS – 90°



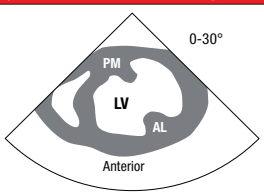
- On the bicaval view → clockwise rotation of the hand piece
- Counterclockwise rotation of the hand piece: left pulmonary veins (adjacent to the LAA)

LEFT PULMONARY VEINS

- **LSPV**: position the probe over the LAA (next to LSPV); slight withdrawal of the probe + anteflexion + counterclockwise rotation of the hand piece (± rotation of the plane)
- **LIPV:** after having localized the LSPV, look for the LIPV by counterclockwise rotation of the hand piece and/or progressive rotation of the plane

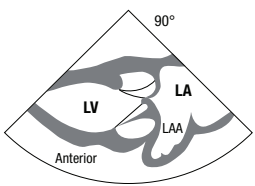
TRANSGASTRIC

SHORT-AXIS LV (MITRAL PAPILLARY MUSCLES) 0–30°



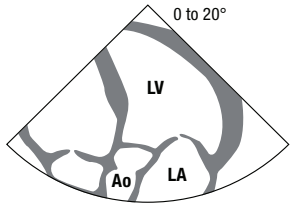
Mitral valve, short axis: slightly withdraw the probe + slight anteflexion + 10-20°

2 CHAMBERS – 90°



110–135°: long axis (LVOT - Ao valve)

5 CHAMBERS (DEEP TRANSGASTRIC) – 0 to 20°



- Maximum anteflexion
- Evaluation of LVOT

DESCENDING THORACIC AORTA

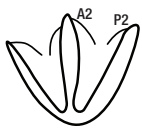
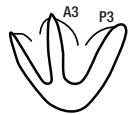
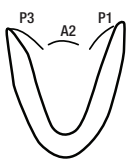
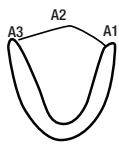
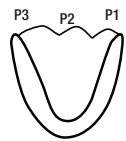
- Counterclockwise rotation of the hand piece
- 0°: short axis; 90°: long axis
- **Complex atherosclerosis**: plaque thickness ≥ 4 mm or mobile / pedunculated debris (= thrombus) or ulceration

MITRAL REGURGITATION - NATIVE VALVE

MECHANISM: Carpentier classification (▶▶| Chapter 4 - Valvular heart disease); prolapse; eversion; restriction; annular dilatation; perforation

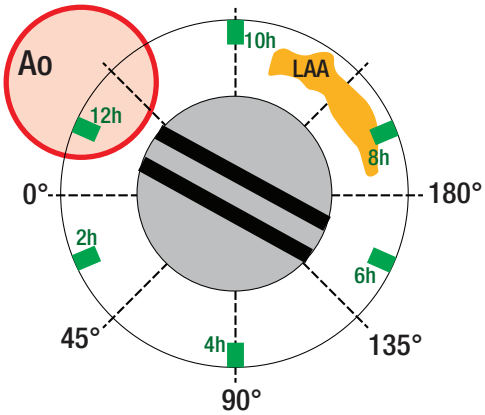
IDENTIFICATION OF THE SEGMENTS INVOLVED

- **A1-P1**: anterolateral
- **A3-P3:** posteromedial

STEP 1 **Transesophageal inferior 4 chambers (0°)**	 Baseline image	 Anteflexion or withdrawal of the probe	 Probe advanced or retroflexion
STEP 2 **Transesophageal inferior 70° (parallel to long axis of mitral valve)**	 Baseline image	 Clockwise rotation of hand piece	 Counterclockwise rotation of hand piece

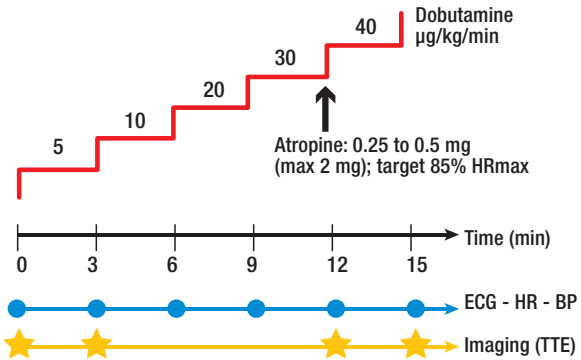
MITRAL REGURGITATION - PROSTHETIC VALVE

IDENTIFICATION OF THE SURGICAL QUADRANT: transesophageal 4 chambers (0); rotation of the plane of section every 10° for 180°



1.6/ STRESS ECHOCARDIOGRAPHY

STRESS: exercise (Bruce protocol) or Dobutamine



INDICATIONS TO STOP DOBUTAMINE STRESS ECHOCARDIOGRAPHY: > 85 % HRmax predicted for age; moderate *de novo* (or progressive) RWMA; significant arrhythmia; hypotension; severe HTN; intolerable symptoms

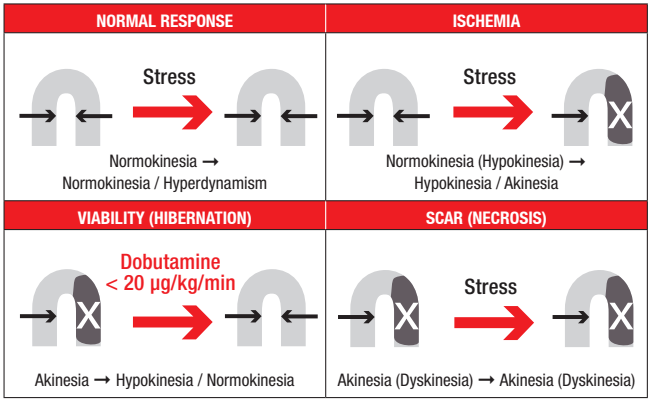
› **Antidote to dobutamine:** beta-blocker

COMPLICATIONS (DOBUTAMINE): angina; hypotension; VT (4%); supraventricular tachyarrhythmia / AF; VF or myocardial infarction (1 / 2,000 studies)

CONTRAST AGENT: ≥ 2 segments poorly visualized on baseline TTE

STRESS-INDUCED ISCHEMIA

a) **RWMA (regional wall motion abnormality):** deterioration ≥ 1 grade of segmental wall motion (normokinetic or hypokinetic segment at rest); deterioration of endocardial excursion and/or segmental thickening
b) **Tardikinesia**: delayed and slow segmental contraction
c) **Chamber dilatation:** ↗ end-systolic LV volume
d) **↘ LVEF:** deterioration of global systolic function



SCAR: regional wall motion abnormality unchanged by stress test (fixed deficit); thin < 6 mm and echodense (fibrotic) segment

DECREASED PREDICTIVE VALUE: target HR not achieved; LVH / concentric remodeling; imaging > 60 s post-stress; 1-vessel disease (particularly circumflex); LBBB; ventricular pacing

FINDINGS IN REPORT: type of stress protocol; result of stress test or dose of dobutamine used; maximum HR reached; test validity (> 85% HRmax); BP; reason for interruption; symptoms on stress test; ECG abnormalities; arrhythmias; ischemic threshold; segmental wall motion at rest and on stress test; LVEF and end-systolic LV volume at rest and on stress test

FACTORS OF POOR PROGNOSIS

- **Resting LVEF:** < 35 %
- **Low ischemic threshold:** dobutamine ≤ 10 µg/kg/min or < 70% HRmax predicted or HR < 120 bpm
- **WMSI on effort:** > 1.4 to 1.7
- **Extensive ischemia:** ≥ 3 segments
- **Ischemia in several coronary territories (≥ 2 vessels)**
- **Deterioration of LVEF (< 45% or ↘ LVEF ≥ 10%) or LV dilatation on stress test**

NEGATIVE STRESS ECHOCARDIOGRAPHY: annual risk of cardiac event < 1% (exercise) or < 2% (dobutamine)

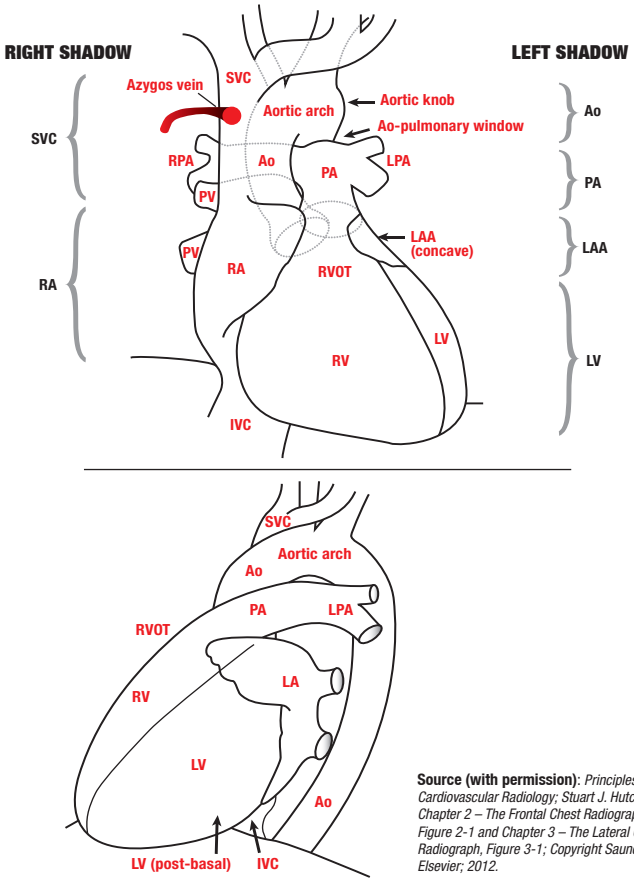
VIABILITY: improvement of the segmental wall motion (≥ 1 grade x ≥ 2 segments) with low-dose dobutamine (2.5 - 5 - 7.5 - 10 - 20 µg/kg/min)

- **Biphasic response**: improvement of wall motion at low-dose then deterioration at higher dose (up to 40 µg/kg/min); specific for improvement of wall motion post-revascularization
- **Sustained improvement**: viable but non-ischemic segment

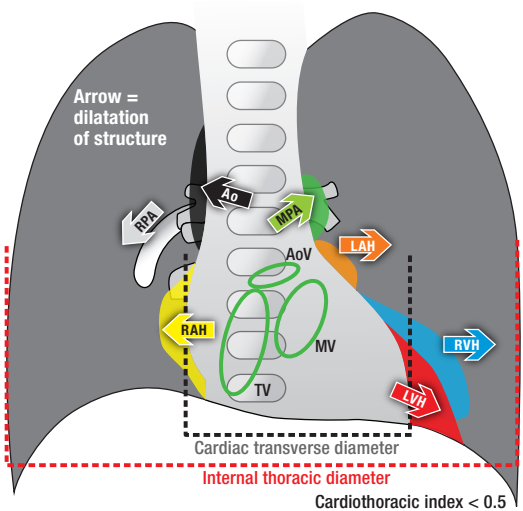
1.7/ CHEST X-RAY

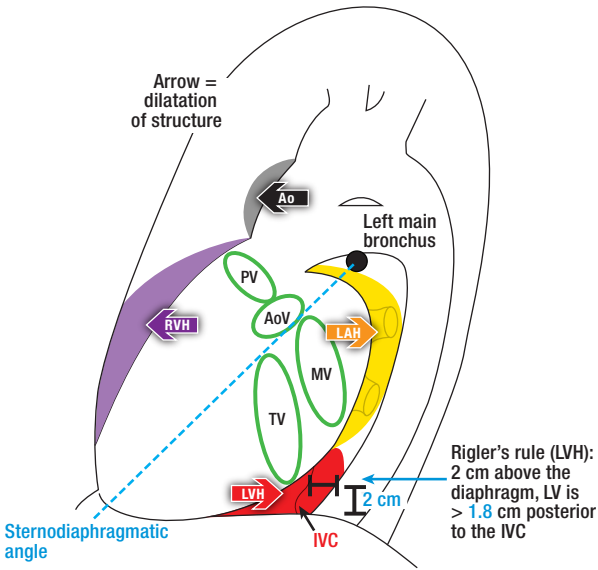
QUALITY CONTROL: **A)** Patient - Date; **B)** Adequate inspiration (right hemidiaphragm below the 6th rib anteriorly and below the 10th rib posteriorly); **C)** Patient centered - Absence of rotation (tracheal air column in the center of the vertebral bodies; spinous processes of vertebral bodies centered between clavicles); **D)** Adequate penetration (spinous processes of thoracic vertebral bodies visible); **E)** Compare with previous films

SYSTEMATIC APPROACH: Situs (gastric bubble and apex); Cardiothoracic index; Heart shadow and cardiac structures (RA; LA; RV; LV; Ao; PA); Calcifications; Pulmonary venous and arterial blood supply; Hila; Lung parenchyma; Pleura; Bone structures; Prosthetic material



Source (with permission): *Principles of Cardiovascular Radiology; Stuart J. Hutchison; Chapter 2 – The Frontal Chest Radiograph, Figure 2-1 and Chapter 3 – The Lateral Chest Radiograph, Figure 3-1; Copyright Saunders Elsevier; 2012.*

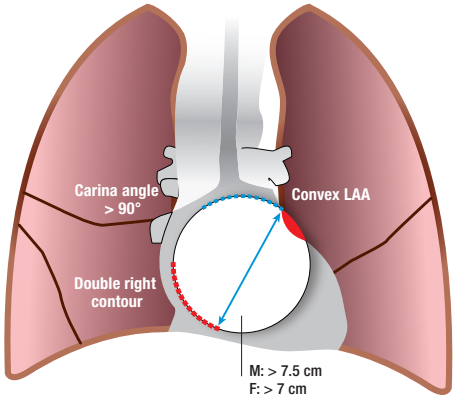

Arrow =
dilatation
of structure
RPA
Ao
MPA
LAH
AoV
RAH
MV
RVH
TV
LVH
Cardiac transverse diameter
Internal thoracic diameter
Cardiothoracic index < 0.5


Arrow =
dilatation
of structure
Ao
Left main
bronchus
PV
RVH
AoV
LAH
MV
TV
LVH
2 cm
IVC
Sternodiaphragmatic
angle
Rigler's rule (LVH):
2 cm above the
diaphragm, LV is
> 1.8 cm posterior
to the IVC

CARDIOTHORACIC INDEX (PA): < 0.5

› **False-positive**: AP film; Obesity; Pregnancy; Pectus excavatum; Ascites; Scoliosis; Under-inspiration

LA DILATATION: convexity of the LAA (between LPA and LV); quadruple contour (Ao; PA; LAA; LV); elevation of left main bronchus (carina angle > 90°); right double contour; posterior dilatation on lateral film



RA DILATATION: right shadow shifted towards the right; ± dilatation of SVC - IVC - azygos vein secondary to ↗ CVP

RV DILATATION: **transverse displacement of the left shadow**; **RV > 1/3 of the distance between the cardiophrenic angle and the sternal angle (lateral film)**; ± PA dilatation

› **DDx of filling of retrosternal space**: post-sternotomy; lymphadenopathy; mediastinal mass (lymphoma; thymoma; thyroid); pulmonary trunk dilatation; aortic root dilatation; small antero-posterior diameter (pectus excavatum; scoliosis; kyphosis)

LV DILATATION: prominent apex displaced downwards; downward displacement of gastric bubble and posterior displacement of LV (> 1.8 cm with respect to IVC) on the lateral film

PA DILATATION: L⟶R shunt; post-stenotic dilatation (main PA and LPA); Pulmonary hypertension (venous or arterial); PR; idiopathic

› **RPA dilatation**: > **17 mm**
› **Main PA dilatation**: prominence between the aortic knob and the LAA

ASCENDING AORTA DILATATION: prominent right contour of mediastinum; prominent anterior contour of mediastinum on lateral film; distance between left lateral edge of tracheal air column and aortic knob > 35 mm

NORMAL PULMONARY BLOOD SUPPLY: peripheral attenuation (distal 1/3 not visible); vessels at base > vessels at lung apex

› **Venous congestion (venous PHT)**: redistribution to apices (cephalization); blurred peripheral vessels; Kerley B lines (1-3 cm long; 1 mm thick; horizontal; arising from pleura); interstitial edema; peribronchial edema; prominent and blurred hila; edema of fissure; pleural effusions; alveolar edema; PA dilatation
  • **Dilatation of azygos vein (>1 cm)**: Right heart failure (↗ CVP); SVC obstruction; Constrictive pericarditis; IVC interruption (venous return via azygos system); anomalous PV connection

- **Peripheral hypervascularization** (vessels visible below the diaphragm)
  a) **L→R shunt**: Dilated PA; branches of PA > associated bronchi; dilatation of heart chambers
  b) **High output state**: pregnancy; hyperthyroidism; anemia
- **Peripheral hypovascularization**
  a) **PHT**: RVH; PA - LPA - RPA dilatation; **early and marked attenuation of peripheral vessels**
  b) **RVOT obstruction**: post-stenotic LPA dilatation in the presence of PS; RVH

1.8/ CORONARY ANGIOGRAPHY

PREPARATION

BASIC WORK-UP: CBC; ECG; electrolytes; creatinine-BUN; Clotting tests; target INR < 2.0

DIABETES: Discontinue metformin in the event of post-coronary angiography ARF

PREVENTION OF CONTRAST NEPHROPATHY: particularly if GFR < 60 mL/min or DM

a) **Hydration with normal saline**: **1 mL/kg/h x 3-12 h before and 6-24 h after angiography** (0.5 mL/kg/h if LVEF < 35% or NYHA III-IV)
b) **Minimize the volume of contrast: < 300 mL or < 4 mL/kg; avoid a contrast volume (mL) / GFR ratio > 3.7**; avoid multiple procedures < 48-72 h
c) **No benefit of N-acetyl-L-cysteine** (★ACT)
d) **Avoid nephrotoxic medications** (NSAIDs; ACE inhibitors; ARB)
e) **Preferred contrast agents: nonionic** (iso-osmolar or low osmolar)

IODINE ALLERGY: Prednisone 50 mg 12 h and 1 h before coronary angiography; Diphenhydramine 50 mg PO and Ranitidine 150 mg PO 1 h before coronary angiography

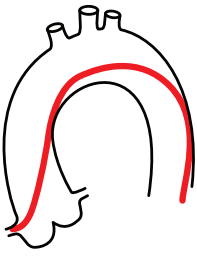
- **Urgent coronary angiography**: Methylprednisolone 125 mg IV + Diphenhydramine 50 mg

VASCULAR ACCESS

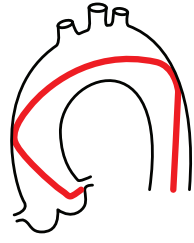
FEMORAL ACCESS: use the common femoral artery; puncture site 3 cm below the inguinal ligament (anterior superior iliac crest to superior pubic ramus) but proximal to the femoral bifurcation (bifurcation distal to the middle third of the femoral head); risk of retroperitoneal bleeding if the artery is punctured too high; risk of pseudoaneurysm if the artery is punctured too low

- **Withdrawal of the introducer**: ACT < 180 s

RADIAL ACCESS: Allen's test before (color returns to normal < 10 seconds); intraarterial Verapamil; Heparin IV (bolus of 2000 to 5000 units); 4-6 F catheters (1 F = 0.3 mm)

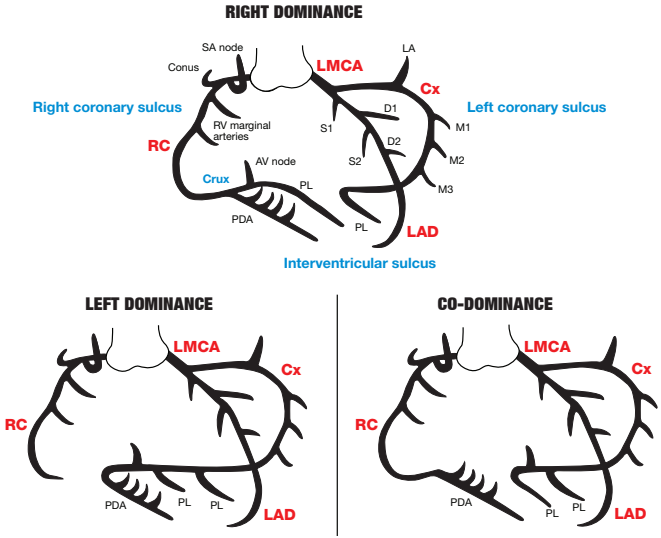


Right Judkins Catheter in the RCA



Left Judkins Catheter in the LCA

CORONARY ANATOMY



Source (with permission): *CathSource iPad application; Rocky Bilhartz, MD; http://ecgsource.com*

RIGHT DOMINANCE: 85% of patients; **PDA + ≥ 1 PL arise from the RCA**

- **Left dominance**: 7%; PDA and ≥ 1 PL arise from the circumflex; small RCA that does not perfuse the LV wall (ends before the crux cordis)
- **Co-dominance**: 7%; PDA arises from the RCA; all PL arise from the circumflex

VEIN GRAFT: adjacent to surgical clip

a) **Bypass graft of the RCA**: 5 cm above the sinotubular junction; right anterolateral aspect of the Ao
b) **Bypass graft of the LAD**: 7 cm above the sinotubular junction; anterior aspect of the Ao
c) **Bypass graft of the circumflex**: 9 cm above the sinotubular junction; left anterolateral aspect of the Ao

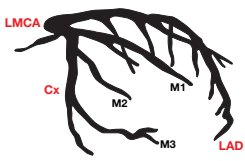
ANGIOGRAPHIC VIEWS

OBTAIN AT LEAST 2 PERPENDICULAR VIEWS for each vessel (to exclude eccentric lesions)

1) **RAO versus LAO versus PA versus lateral**
2) **Cephalic versus Caudal** (depending on the direction towards which the image intensifier above the patient is inclined); cephalic view → circumflex superior on the image; caudal view → LAD superior on the image

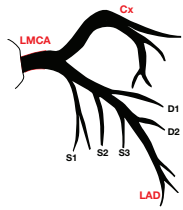
LEFT CORONARY

RAO 30° - CAUDAL 25°



Cx - Marginals - Distal LAD

RAO 10° - CEPHALIC 40°

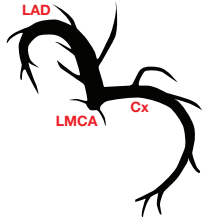


LAD - Septal - Diagonals

LAO 45° - CEPHALIC 25°

Mid and distal LAD - Diagonals - Distal dominant Cx

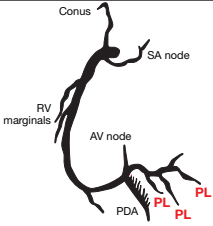
SPIDER: LAO 45° - CAUDAL 45°



LMCA - Proximal LAD - Proximal Cx

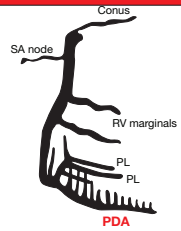
RIGHT CORONARY

LAO 30° - 0°



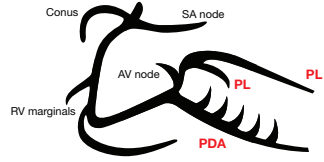
Proximal and mid RCA; PLs

RAO 30°- 0°



Mid RCA / Mid PDA

PA - 20° CEPHALIC



Distal RCA: PDA and PLs

Redrawn and expanded from (with permission): *Uptodate 2015; Zimetbaum PJ, Josephson ME. Conduction abnormalities after myocardial infarction; www.uptodate.com; Post TW (Ed), UpToDate, Waltham, MA, March 2015.*

CORONARY ARTERY STENOSIS

ANGIOGRAPHIC	HEMODYNAMIC	IVUS (INTRAVASCULAR ULTRASOUND)
≥ 70 % (LMCA: ≥ 50%)	FFR ≤ 0.80	• LMCA: Area < 6 mm² (6 to 7.5 mm² → determine FFR) • Other vessels: Area < 4 mm²

CHARACTERISTICS OF THE CORONARY LESION		
TYPE A: PCI WITH HIGH SUCCESS RATE (> 85%) AND LOW RISK	**TYPE B: PCI WITH MODERATE SUCCESS RATE (60-85%) AND MODERATE RISK**	**TYPE C: PCI WITH LOW SUCCESS RATE (< 60%) AND HIGH RISK**
• Short (10 mm) • Concentric • Only slightly calcified • Not totally occluded • Not ostial • Easily accessible • Not angulated (< 45°) • Regular contours • No branch lesion • Absence of thrombus	• Tubular (10-20 mm) • Eccentric • Moderately calcified • Total occlusion < 3 months • Ostial • Moderate tortuosities of proximal segment • Moderate angulation (45-90°) • Irregular contours • Bifurcation • Presence of thrombus	• Diffuse (> 20 mm) • Severe tortuosities of proximal segment • Extreme angulation (> 90°) • Bifurcation with impossibility to protect a major branch • Vein graft with friable lesions

a) **Length**: short (< 10 mm) - tubular (10-20 mm) - diffuse (> 20 mm)
b) **Ostial**: < 3 mm from the ostium; aorto-ostial stenosis often fibrocalcified
c) **Bifurcation**: Medina's X, Y, Z classification
   - **X**: 0 if absence of stenosis or 1 if stenosis in the main proximal segment
   - **Y:** 0 if absence of stenosis or 1 if stenosis in the main distal segment
   - **Z:** 0 if absence of stenosis or 1 if stenosis in the daughter branch
d) **Calcification**: confers rigidity and non-compliance to the dilatation
e) **Angulation**: > 45° moderate; > 90° severe; makes stent placement more difficult and associated with a risk of late stent fracture
f) **Thrombus**: risk of distal microembolism
g) **Eccentricity**: variable stenosis according to angiographic view
h) **Irregularities**: ulcer; intimal flap; aneurysm; saw tooth irregularities (multiple successive irregular stenoses)
i) **Tortuosity of the proximal segment**: moderate (2 proximal curves > 75°) or severe (3 proximal curves > 75°)
j) **Presence of collaterals**: Rentrop classification
k) **TIMI flow**

TIMI 0	Total occlusion
TIMI 1	Presence of a very faint anterograde flow beyond the stenosis; no opacification of the distal coronary bed
TIMI 2	Opacification of the entire distal coronary bed, but sluggish flow (compared to vessels with normal flow)
TIMI 3	Anterograde perfusion of all of the distal coronary bed; normal filling velocity

MICROVASCULAR EVALUATION: myocardial "blush" score

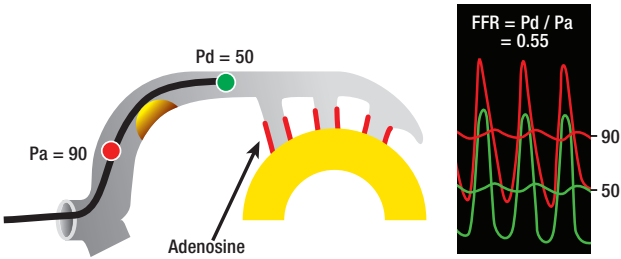
FRACTIONAL FLOW RESERVE (FFR)

INDICATION: **estimate the hemodynamic impact of an intermediate angiographic stenosis (50-70%)**

CALCULATION: Pressure distal to lesion (Pd) / Pressure proximal to lesion (Pa) ratio during maximum hyperemia (IV or intracoronary adenosine)

CORONARY BLOOD FLOW DEPENDS ON: **A)** DBP; **B)** Arteriolar resistance; **C)** Left intraventricular pressure; **D)** Degree of coronary stenosis

› **Abnormal FFR:** ≤ 0.80 (★FAME; ★FAME-2)

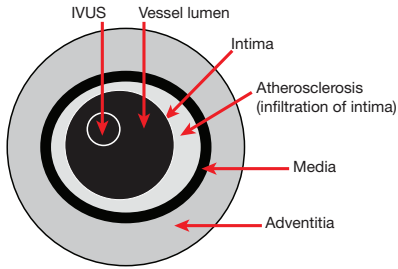


INTRAVASCULAR ULTRASOUND (IVUS)

Transverse ultrasound section of the lumen and arterial wall

EVALUATION: real dimensions of the lumen; abnormality of the arterial wall; degree of atherosclerotic infiltration; positive vascular remodeling (Glagov phenomenon)

INDICATION: A) Specify the severity of LMCA stenosis; **B)** Complex lesion (ostial; bifurcation; aneurysm; dissection); **C)** Bypass graft disease; **D)** Restenosis or intra-stent thrombosis; **E)** Guidance during PCI / evaluation of stent deployment



COMPLICATIONS

COMPLICATIONS: **Major complications < 1%;** Death; MI; Contrast nephropathy; Stroke; Local vascular complication (thrombosis; distal embolism; dissection; hematoma; pseudoaneurysm; AV fistula); Arrhythmia; Allergy; Air embolism; Coronary artery dissection; Atheroembolism

ANAPHYLAXIS: epinephrine 1:10,000 - **1 mL IV every minute (0.1 mg every minute)**

HEPARIN ANTIDOTE: Protamine (1 mg for every 100 units of heparin; if IV infusion of heparine → 25-50 mg of protamine IV slowly); risk of allergy if the patient is treated with NPH insulin

› www.medicines.org.uk/emc/medicine/10807/spc

RETROPERITONEAL HEMATOMA: secondary to puncture above the inguinal ligament; hypotension / abdominal pain / back pain; CBC - clotting tests; CT scan; reverse anticoagulation; transfusion PRN; medical treatment in the majority of cases (or covered stent)

PSEUDOANEURYSM: pulsatile mass with systolic murmur; ultrasound diagnosis; good prognosis if diameter < 2 cm

› **Noninvasive percutaneous treatment**: ultrasound-guided compression or local injection of thrombin; follow-up US at 1 month
› **Surgery:** large or rapidly progressive pseudoaneurysm or infected or failure of noninvasive treatment

AV FISTULA: secondary to puncture below the femoral bifurcation; thrill or continuous murmur; surgical treatment in the majority of cases (risk of progression)

RADIAL ACCESS COMPLICATIONS: Hematoma; Arterial dissection or occlusion; Loss of radial pulse; Compartment syndrome; Spasm

POST-CORONARY ANGIOGRAPHY ARF

› **Contrast nephropathy**: **Early and reversible ARF; Improvement by day 3 to 5**

RISK OF CONTRAST NEPHROTOXICITY POST–PCI		
Hypotension	5 points	**≤ 5 POINTS** • Contrast nephropathy: 7.5% • Dialysis: 0.04% **6-10 POINTS** • Contrast nephropathy: 14% • Dialysis: 0.1% **11-16 POINTS** • Contrast nephropathy: 26% • Dialysis: 1% **> 16 POINTS** • Contrast nephropathy: 57% • Dialysis: 13%
IABP	5 points	
Heart failure	5 points	
> 75 years	4 points	
Anemia	3 points	
Diabetes	3 points	
Each 100 mL of contrast	1 point	
Creatinine > 130 mmol/L or GFR 40-60 mL/m² GFR 20-40 mL/m² GFR < 20 mL/m²	4 points or 2 points 4 points 6 points	

Mehran R, Aymong ED, Nikolsky E et al. JACC 2004; 44; 1393-1399.

› **Atheroembolism: subacute ARF** (several days to several weeks); **eosinophilia / eosinophiluria; slightly active urinary sediment; hypocomplementemia; other micro atheroembolic lesions** (toes; livedo reticularis; petechiae; splinter hemorrhage; mesenteric or pancreatic ischemia; retinal Hollenhorst plaques); slight improvement of renal function

1.9/ HEMODYNAMIC ASSESSMENT

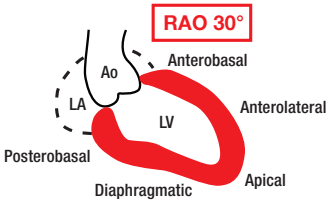
INDICATIONS: More refined assessment of heart disease when noninvasive evaluation is insufficient (heart failure; valvular heart disease; PHT; complicated myocardial infarction; congenital heart disease; intracardiac shunt; pericardial disease; cardiomyopathy; biopsy)

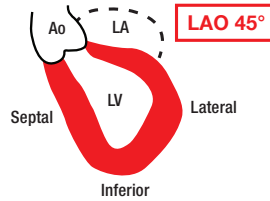
COMPLICATIONS: < 1%; death; MI; stroke; arrhythmia; access site complication; allergy to contrast agent; cardiac tamponade / perforation; RBBB during catheterization of RV and LBBB during catheterization of LV; pulmonary infarction; PA perforation

RIGHT CARDIAC CATHETERIZATION: RA - RV - PA - pulmonary capillary wedge pressures; cardiac output; search for a shunt; calculation of pulmonary vascular resistance

LEFT CARDIAC CATHETERIZATION: LA pressure (transseptal or estimated by wedge pressure) - LV - Ao pressures; coronary angiography; left ventriculography and aortography; calculation of systemic vascular resistance; evaluation of valvular heart disease

- **Transseptal**: verification of the correct position (LA) by atrial pressure curve - oxygen saturation - contrast injection
- **Left ventriculography**: RAO 30° ± LAO 45° (30-40 mL of contrast)





HEMODYNAMIC DATA

MEASUREMENTS: **at the end of expiration**

	MEAN	NORMAL
Cardiac output (L/min)	5	4 - 6
Cardiac Index (L/min/m²)	3.5	2.5 - 4.5
Aorta pressure (mmHg)		
Systole	130	90-140
End-diastole	70	60-90
Mean	85	70-105
Mean BP = 1/3 x SBP + 2/3 X DBP		
LV PRESSURE (mmHg)		
Systole	130	90-140
End-diastole	8	5-12
LA pressure (v > a) (mmHg)		
Max	12	6-21
Mean	8	2-12
PCWP (mmHg)		
Mean	9	4-12
PAP (mmHg)		
Systole	25	15-30
End-diastole	9	4-12
Mean	15	9-19
Mean PAP = 1/3 x sPAP + 2/3 x dPAP		

	MEAN	NORMAL
RV pressure (mmHg)		
Systole	25	15-30
End-diastole	4	1-7
RA (a > v) (mmHg)		
Max	6	2-7
Mean	3	1-5
Resistance (dyn x s / cm^5)		
Systemic vascular resistance	1100	700-1600
Pulmonary vascular resistance	70	20-130

- **Δ P = Q x R**
- **Systemic vascular resistance (WU)** = Mean arterial pressure - Mean RA pressure / Systemic output
- **Pulmonary vascular resistance (WU)** = Mean PAP - Mean wedge pressure / Pulmonary output
- **Conversion**: 1 WU = 80 dyn x s / cm^5

CARDIAC OUTPUT

FICK: gold standard method

- **Systemic cardiac output (L/min)** = O_2 consumption (mL/min) / 1.36 x Hb (g/L) x (Aortic SaO_2 - Mixed venous SaO_2)
- **Pulmonary cardiac output (L/min)** = O_2 consumption (mL/min) / 1.36 x Hb (g/L) x (PV SaO_2 - PA SaO_2)

- **Estimation of O_2 consumption**: 125 ml/m² in young subjects; 110 mL/m² in elderly subjects
- **SaO_2:** expressed as a decimal (70% = 0.70)
- **Mixed venous SaO_2**: = 3/4 x SVC SaO_2 + 1/4 x IVC SaO_2

› **Caveats**: **A)** Estimation of VO_2 (instead of measurement of VO_2 by face tent); **B)** High output (attenuated arteriovenous O_2 difference)

THERMODILUTION: injection of a bolus of NaCl into the vena cava; detection of a change of temperature as a function of time in a distal port (pulmonary artery); **cardiac output is inversely proportional to the area under the curve**

› **Caveats**: **A)** Significant TR (underestimates cardiac output); **B)** Low output (< 2.5 L/m) in which case cardiac output is overestimated; **C)** Intracardiac shunt (cardiac output overestimated if L⟶R shunt)

ANGIOGRAPHIC METHOD

- **Cardiac output** = (LV end-diastolic volume - LV end-systolic volume) x HR

› **Caveats**: **A)** Evaluation of cardiac output in a single cardiac axis; **B)** Less reliable in the presence of MR, AR or AF

HEMODYNAMIC CURVES

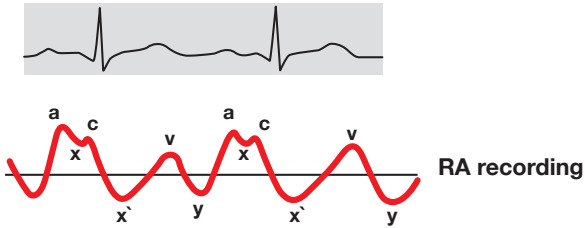
Use the ECG to identify waves on the curves

A) Polyphasic curves: atrial recording; pulmonary capillary wedge pressure recording

B) Monophasic curve

- **Ventricular recording**: End-diastolic pressure > Early diastolic pressure
- **Arterial recording**: Early diastolic pressure > End-diastolic pressure

ATRIAL RECORDING



A WAVE: atrial kick; **follows the P wave on the ECG**

- **Normally**: a > v in RA; v > a in LA
- ↗ **a wave**: MS (or TS); ↘ ventricular compliance (LVH or RVH; LVOT or RVOT obstruction)
- **Canon a wave**: AV dissociation (AV block; ventricular pacemaker; VT; PVC; PAC)
- **Absent a wave**: AF or atrial flutter; severe atrial disease (Ebstein; rheumatic MS; cardiac amyloidosis)

X DESCENT: atrial relaxation; **after S1**

- ↗ **x descent**: Tamponade; Constriction (W-M pattern)

C WAVE: protrusion of the AV valve into the atrium during isovolumic contraction of the ventricle

X' DESCENT: atrial relaxation + descent of AV valve during systolic ejection

V WAVE: passive atrial filling during ventricular systole in the presence of a closed AV valve; **at the end of the T wave on the ECG**

- ↗ **v wave**: MR (or TR); VSD (or ASD on RA recording); rheumatic MS (↘ LA compliance); Heart failure

Y DESCENT: emptying of the atrium following opening of the AV valve (rapid ventricular filling); **after S2**

- ↗ **y descent**: Constriction; RCM; MR (or TR)
- ↘ **y descent**: Tamponade; MS (or TS)

PCWP: pulmonary capillary wedge pressure; similar curve to LA but delayed by 40-120 ms (pressure transmission delay) and slightly attenuated

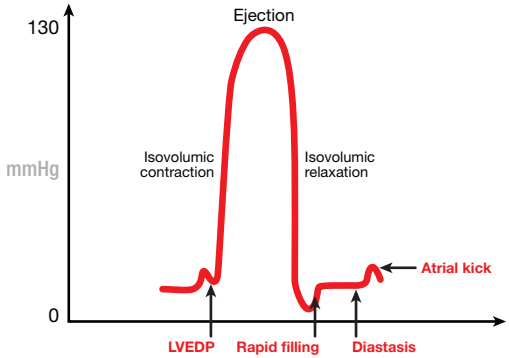
- **Adequate wedge pressure**: oximetric confirmation (SaO_2 > 95 %); injection of contrast; respiratory variation of the curve
- **Inequality between wedge pressure and LA pressure**: PV obstruction; ↗ Pleural pressure; Catheter in non-dependent pulmonary zone (target West zone 3)
- **dPAP > Wedge**: Pulmonary disease; Pulmonary embolism; significant PHT

VENTRICULAR RECORDING

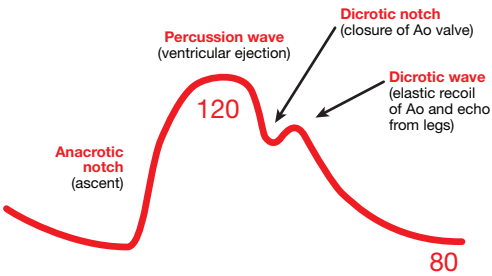
SYSTOLE: **A)** Isovolumic contraction; **B)** Ejection; **C)** Reduced ejection then start of relaxation

DIASTOLE: A) Isovolumic relaxation; **B)** Rapid filling; **C)** Slow filling (diastasis); **D)** Atrial kick

- **End-diastolic pressure**: after atrial kick at point c (simultaneous with QRS)



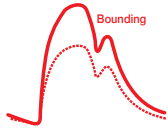
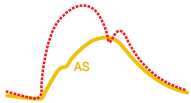
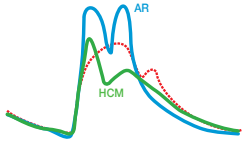
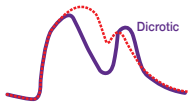
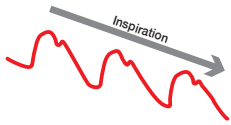
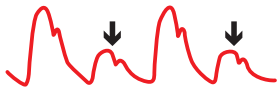
ARTERIAL RECORDING



PULSE PRESSURE: reflects the stroke volume and compliance of the arterial system

- ↗ **pulse pressure: > 50 % of SBP** (or > 40 mmHg); HTN; Age; AR; patent ductus arteriosus; Ruptured aneurysm of the sinus of Valsalva; Fever; Anemia; Hyperthyroidism; Pregnancy; AV fistula; Paget's disease +
- ↘ **pulse pressure**: **< 25% of SBP**; Tamponade; Heart failure; Cardiogenic shock; Aortic stenosis +

CAROTID PULSE: similar to central aortic pulsation

CORRIGAN'S PULSE (BOUNDING)	 Abrupt systolic ascent, followed by rapid collapse; increased pulse pressure	**DDx**: AR; patent ductus arteriosus; truncus arteriosus; fever; anemia; hyperthyroidism; pregnancy; exercise; AV fistula; Paget's disease; Beriberi; bradycardia in an elderly patient with non-compliant aorta
PULSUS PARVUS ET TARDUS (ANACROTIC)		• **AS** • **Tardus**: slow ascent • **Parvus:** decreased amplitude • ± Thrill
PULSUS BISFERIENS (BIFID)	 2 peaks during systole (percussion wave then tidal wave)	• **DDx**: AR; HCM; patent ductus arteriosus • **Tidal wave:** echo from leg vessels • **HCM: spike and dome** (rapid initial ascent then dynamic LVOT obstruction)
DICROTIC PULSE	 1 peak in systole and 1 peak in diastole	**DDx**: IABP; severe heart failure; tamponade; hypovolemia; sepsis
PULSUS PARADOXUS	 **> 10 mmHg reduction** of systolic blood pressure on inspiration	**DDx**: Tamponade; constriction - effusion; RCM; COPD; Asthma; Pulmonary embolism; Pneumothorax; Hypovolemia; Obesity; Pregnancy • **Reversed pulsus paradoxus:** HCM
PULSUS ALTERNANS		**DDx**: Severe heart failure; bigeminy; tamponade; severe AR; tachypnea

AORTIC STENOSIS

TRANSVALVULAR GRADIENT: measurement of blood pressures in proximal Ao and LV

- **Mean gradient**: integral of the transvalvular gradient during systole
- **Peak-to-peak gradient**: not physiological as peaks not simultaneous
- **Pressure in femoral artery**: **underestimation** of transvalvular gradient (due to peripheral amplification of SBP)

FIXED OBSTRUCTION: **pulsus parvus et tardus** on aortic recording

CARABELLO'S SIGN: **> 10 mmHg** increase in SBP following withdrawal of the catheter from the LV towards the aorta (obstructive catheter in critical aortic stenosis)

HAKKI FORMULA: Aortic valve area = CO (L/min) / √ mean gradient (or peak-to-peak gradient)

GORLIN FORMULA: Aortic valve area = Stroke volume (mL/beat) / (44.3 x Systolic ejection period (s / beat) x √ Mean gradient mmHg)

CAVEATS: A) Concomitant AR: calculate cardiac output (or stroke volume) by the angiographic method; **B)** Aortic stenosis in the presence of low cardiac output (dobutamine challenge)

MITRAL STENOSIS

TRANSVALVULAR GRADIENT: transseptal measurement of LA and LV pressures

- **LA pressure estimated by PCWP**: **overestimates the transvalvular gradient** (delayed transmission of pressure waves and attenuation of y descent)

GORLIN FORMULA: Mitral valve area = Stroke volume (mL/beat) / (37.7 x Diastolic filling period (s / beat) x √ mean gradient mmHg)

CAVEAT: Concomitant MR: calculate stroke volume by angiographic method

VALVULAR REGURGITATION

REGURGITANT VOLUME = Angiographic stroke volume (end-diastolic volume - end-systolic volume) - Net anterograde stroke volume (Fick or Thermodilution)

REGURGITANT FRACTION = Regurgitant volume / Angiographic stroke volume

SEMIQUANTITATIVE ANGIOGRAPHIC EVALUATION (ventriculography or aortography)

GRADE	Regurgitant fraction	Opacification of the proximal chamber
1	< 20 %	• Slight opacification • Rapid elimination of contrast at each beat
2	21-40 %	• Moderate opacification • Density less than that of the proximal chamber • Rapid elimination of contrast with subsequent beats
3	41-60 %	• Intense opacification • Similar density to that of the proximal chamber in 4-5 beats
4	> 60 %	• Intense and rapid opacification • Density greater than that of the proximal chamber in ≤ 3 beats • ± PV reflux in the presence of MR

INTRACARDIAC SHUNT

Level of L→R shunt	Increased SaO_2 (step-up)	Example
Screening	PA SaO_2 - SVC SaO_2 ≥ 8%	Shunt at any level between the SVC and the PA
Atrial	RA SaO_2 - mixed venous SaO_2 ≥ 7%	ASD; Partial anomalous pulmonary venous connection; Ruptured aneurysm of the sinus of Valsalva; VSD + TR; Coronary fistula to RA
Ventricular	RV SaO_2 - RA SaO_2 ≥ 5%	VSD; Patent ductus arteriosus + PR; Primum ASD; Coronary fistula to RV
Pulmonary artery	PA SaO_2 - RV SaO_2 ≥ 5%	Patent ductus arteriosus; Aortopulmonary window; Palliative shunt (Pots; Waterston)

QP / QS: Pulmonary blood flow / Total systemic blood flow

QP / QS = Ao SaO_2 - mixed venous SaO_2 / PV SaO_2 - PA SaO_2

MIXED VENOUS SaO_2 = 3/4 x SVC SaO_2 + 1/4 x IVC SaO_2

PV SaO_2: ≈ Ao saturation in the absence of R→L shunt

Qp / Qs < 1.5	Qp / Qs 1.5 - 2	Qp / Qs > 2
Small L→R shunt	Moderate L→R shunt	Large L→R shunt

OXIMETRIC RUN: SVC (2 x); IVC (2 x); RA (3 x); RV (3 x); main PA; RPA; LPA; LV; Ao; ± PV and ± LA

SCREENING OF R→L SHUNT: Ao SaO_2 < 95% despite FiO2 = 100%

1.10/ NUCLEAR MEDICINE

SPECT MYOCARDIAL PERFUSION IMAGING

SPECT: Single-Photon Emission Computed Tomography

PRINCIPLE: Injection of a radioisotope (at rest then on exercise) → extraction by viable perfused myocytes → **emission of photons proportional to myocyte perfusion**

THREE STANDARD PERPENDICULAR PLANES: **A)** Short axis (apex to base); **B)** Vertical long axis (septum to lateral wall); **C)** Horizontal long axis (inferior wall to anterior wall)

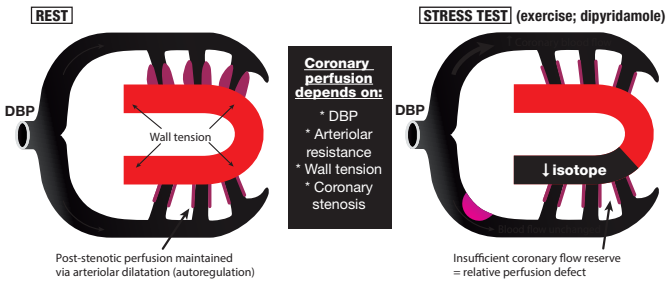
ARTIFACTS / FALSE-POSITIVES: **A)** Movement during acquisition; **B)** Extraction of radioisotope by visceral organs; **C)** LBBB (use pharmacological stress); **D)** Septal HCM (relative perfusion deficit in lateral wall compared to hypertrophied septum); **E)** Dilated cardiomyopathy or HCM (zones of fibrosis; endothelial dysfunction); **F)** Attenuation

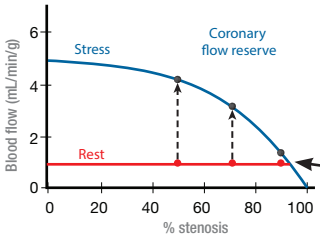
- **Attenuation by interposed structure**: **A)** Breasts → anterior / anterolateral attenuation; **B)** Diaphragm → inferobasal attenuation (improvement when patient upright)
  - **Rule out attenuation: A)** Raw cine mode (look for interposed structure); **B)** Ventricular function (real perfusion deficit unlikely if normal wall motion on stress test)
- **Normal variants**: Membranous basal septum (less perfused); Apical thinning; Lateral wall appears to be better perfused than the septum (closer to the camera)

	201–Thallium	99m Technetium
Molecule	Cation; similar properties to K+	• Fat-soluble cationic compound • Sestamibi and Tetrofosmin
Photon energy	80 keV	140 keV
Half-life	73 h	6 h
First-pass myocardial extraction	• 85 % • Perfusion-dependent • Via Na-K-ATPase pump	• 60 % • Perfusion-dependent • Passive myocardial extraction (radioisotope trapped in mitochondria)
Myocardial redistribution	• Imaging 3-4 h or 24 h post-injection • Clearance of radioisotope is slower in ischemic myocardium ("differential washout")	Minimal (2 injections are therefore necessary: stress test and at rest)
Protocol	1. **Detection of ischemia**: Injection on stress test with imaging #1; imaging #2 post-redistribution 2. **Viability study**: Injection at rest with imaging #1; imaging #2 post redistribution (re-injection at this time to improve sensitivity)	1. **Same day**: injection at rest (8-10 mCi) with imaging #1; injection on stress test with imaging #2 (22-30 mCi) 2. **2 days**: injection at rest (20-30 mCi) with imaging #1; injection on stress test (20-30 mCi) with imaging #2 3. **Combined with Thallium**: Injection of Thallium at rest with imaging #1; imaging #2 4h pre-Technetium (redistribution; viability study); injection of Technetium on stress test with imaging #3 (to detect ischemia)

DIPYRIDAMOLE PHARMACOLOGICAL STRESS TEST: ↗ intracellular adenosine → stimulation of smooth muscle cell adenosine A2a receptors → ↗ cAMP → coronary arteriolar vasodilatation → ↗ coronary blood flow

- **Dose**: 142 µg/kg/min x 4 min (then inject isotope 3 min later)
- **Adverse effects**: ↘ SBP and ↘ DBP (8-10 mmHg); reflex tachycardia **(↗ 10-20 bpm); minimal increase of double product (i.e. slightly ↗ 0_2 demand)**; flushing; retrosternal chest pain; asthma; blocks; real ischemia (in 10% of cases; coronary steal in ischemic collateral vessels)
- **Antidote**: aminophylline 1-2 mg/kg





HIGH RISK CRITERIA

- **Negative test:** 1-year risk of death or myocardial infarction < 1% (exercise) or < 2% (dipyridamole)
- **Resting LVEF**: < 35 %
- **Extensive perfusion abnormality during stress**: ≥ 10% of the myocardium or involving ≥ 2 vascular territories
- **Pulmonary uptake of ^{201}Tl (during stress)**: marker of severe CAD (↗ wedge pressure and ↘ LVEF during stress)
- **Transient LV dilatation (during stress)**: ↗ ventricular chamber size; marker of severe CAD (↘ LVEF during stress and/or diffuse subendocardial ischemia)

VENTRICULAR FUNCTION: ECG-gated imaging → mean of hundreds of beats to obtain one cardiac cycle

RADIONUCLIDE VENTRICULOGRAPHY (RVG)

Evaluation of LVEF and RVEF

EQUILIBRIUM (MUGA): ECG gating; 99m Technetium-labeled RBC; mean of 1000 cycles; 3 standard views (anterior; LAO with optimal separation of RV and LV; lateral); evaluation of chamber dimension - regional wall motion - systolic function

- **Systolic function:** estimated on biplane mode by counting photon emissions in the ventricle (diastole - systole / diastole)
  - **Systolic volume**: the count is proportional to ventricular volume (which can be estimated from a blood sample of a given volume and a given photon emission); measurement not influenced by ventricular geometry
- **Diastolic function**: curve of ventricular volume as a function of time

FIRST-PASS: rapid bolus of Technetium 99m-DTPA → RA - RV → Lungs → LA - LV; can distinguish the activity of right and left (**better evaluation of the RV and shunt**); RAO view

POSITRON EMISSION TOMOGRAPHY

Quantitative evaluation of myocardial perfusion

ADVANTAGES VERSUS SPECT: better spatial resolution; better correction of attenuation; evaluates **absolute quantitative regional perfusion (mL/g/min) (unlike SPECT which evaluates relative regional perfusion);** better evaluation of balanced ischemia or microvascular disease

- **Disadvantages**: requires a cyclotron; short half-life (pharmacological stress test only)
- **^{82}Rubidium**: cation with similar properties to those of the potassium and thallium; transport via Na-KATPase pump; half-life 75 s; perfusion-dependent myocardial extraction
- **[^{13}N]ammonia**: passive diffusion or transport via Na-K-ATPase pump; half-life 10 min; perfusion-dependent myocardial extraction

VIABILITY STUDY: quantitative evaluation of myocardial metabolism (2-[^{18}F]FDG); **glucose extraction maintained in ischemic myocardium** (anaerobic glycolysis); **"mismatch" between myocardial perfusion and glucose metabolism in ischemic but viable (hibernating) myocardium** +

MULTIMODAL EVALUATION OF VIABILITY			
DOBUTAMINE ECHOCARDIOGRAPHY	**THALLIUM**	**CARDIAC PET**	**GADOLINIUM ENHANCED CARDIAC MRI**
Hibernating myocardium: Biphasic response	**Hibernating myocardium:** Redistribution	**Hibernating myocardium:** Perfusion-metabolism discordance	**Late gadolinium enhancement** = scar (absence of viability)
Resting Baseline RWMA **Dobutamine 5 µg/kg/min** Improvement **Dobutamine 20 µg/kg/min** Deterioration	**Resting** Relative perfusion deficit **Redistribution** Differential washout	**Resting** Relative perfusion deficit **FDG metabolism** Glucose extraction maintained	**Resting** Late gadolinium enhancement = scar

1.11/ CARDIAC MAGNETIC RESONANCE IMAGING (CARDIAC MRI)

PHYSICAL PRINCIPLE: detects electromagnetic signals of nuclei of hydrogen atoms following application of a specific sequence of magnetic fields

PRECAUTIONS

CONTRAINDICATIONS: **ferromagnetic material** (stents and valve prosthese safe); **www.mrisafety.com**

- **Pacemaker and defibrillator (before new compatible generation)**: contraindication to MRI; risk of arrhythmia; displacement of the device; inhibition; inappropriate shock; lead injury; battery depletion...

GADOLINIUM: risk of nephrogenic systemic fibrosis if **CrCl < 30 mL/min/1.73 m²**

TISSUE CHARACTERIZATION

T1	**Fat content:** ARVD; myocardial mass	
T2	**Myocardial water content:** acute myocarditis; acute myocardial infarction (high-risk zone); graft rejection	
T2*	**T2* < 20 msec:** (associated with LV dysfunction) compatible with iron overloard cardiomyopathy (repeated transfusions; hemochromatosis)	
T1 Gadolinium-enhanced	Visualization of intravascular (blood) and extravascular water (myocardium) • **First pass**: myocardial perfusion • **Early gadolinium enhancement (EGE):** sign of inflammation (myocarditis; acute myocardial infarction) • **Late gadolinium enhancement (LGE):** 15 minutes post-redistribution; sign of fibrosis / myocardial necrosis	
Ischemic heart disease	**LGE**: **subendocardial or transmural scar**	
Nonischemic cardiomyopathy	**LGE: non-subendocardial scar**	
HCM	**LGE:** scars in hypertrophied regions or in IV septum or close to the insertion of the RV	
Amyloidosis	• Rapid accumulation of contrast in the myocardium (rapid first-pass washout from blood) • **LGE**: circumferential subendo-cardial enhancement; transmural patchy enhancement • Late atrial enhancement	
Sarcoidosis Myocarditis	• **LGE**: intramural or subepicardial or epicardial scar, sparing the endocardium • **Sarcoidosis**: anteroseptal and inferolateral walls often affected	

INDICATIONS

CARDIOMYOPATHY / HEART FAILURE / MYOCARDITIS: dimensions; systolic and diastolic functions; segmental wall motion; measurement of deformation (strain); tissue characterization (sarcoidosis; myocarditis; amyloidosis; hemochromatosis); viability - scars (LGE); HCM; ARVD; LV noncompaction; Chagas…

CORONARY DISEASE: scar - viability (LGE); congenital anomaly of coronary arteries; coronary fistula; segmental wall motion (at rest and with dobutamine); first-pass gadolinium perfusion study (at rest and with dipyridamole); acute myocardial infarction (T2)

VALVULAR HEART DISEASE: stenosis (phase contrast is used to measure transvalvular velocities); regurgitation (volumetric method comparing RV and LV stroke volumes; phase contrast is used to measure anterograde and retrograde transvalvular velocities to calculate the regurgitant volume); perivalvular mass (fibroelastoma; vegetation; thrombus); complication of endocarditis; prosthetic valve dysfunction

CARDIAC MASSES: intracardiac thrombus (**non-vascularized**; absence of gadolinium enhancement); primary and secondary tumors (metastases)

PERICARDIAL DISEASE: constriction (paradoxical movement of the interventricular septum; ventricular interdependence; IVC distension); congenital absence of pericardium

CONGENITAL HEART DISEASE: anatomical assessment; structure - dimensions - function of chambers; conduits; shunts; Ao and PA

THORACIC AORTA: aneurysm; ulcer; dissection; CoA; aortitis; post-surgery; intramural thrombus

1.12/ CARDIAC CT

UNENHANCED CORONARY CALCIUM SCAN

This technique estimates the global coronary atherosclerotic burden; **very high sensitivity but low specificity for significant coronary stenosis**; independent predictor of coronary events (score of 0 associated with excellent prognosis)

INDICATIONS: **asymptomatic patient with intermediate risk of cardiac events (10-20% at 10 years)** +

- **Agatston score**: score > 300 confers a 10-year risk of myocardial infarction or cardiovascular mortality of 28% (score of 100-399 increases the risk x 4 versus score < 100; score > 400 increases the risk x 6)

CARDIAC CT ANGIOGRAPHY (CCTA)

STRUCTURES EVALUATED: heart chambers; ventricular function (R and L); coronary arteries; bypass grafts; aortic and pulmonary arteries; pericardium; other adjacent structures; congenital heart disease; congenital coronary artery anomalies; endocarditis; ARVD; prosthetic valve; cardiac mass / thrombus; pulmonary veins

CORONARY CT ANGIOGRAPHY: good spatial resolution (vessels > 1.5 mm); **excellent sensitivity for significant coronary stenosis (very high negative predictive value for CAD); stenosis identified is not necessarily hemodynamically significant** and is not necessarily associated with ischemia (FFR-CT under development); decreased specificity in the presence of significant calcifications (Agatston score > 400) or obesity or HR > 65 bpm or AF or stent; independent predictor of coronary events (negative CCTA associated with excellent prognosis); can be used to evaluate patency of coronary bypass grafts; no difference on clinical outcome between CCTA vs. Functional testing in patients with suspected CAD (★ PROMISE) +

› **Indication: A)** Patient with no history of CAD presenting with retrosternal chest pain and intermediate pretest probability (especially when other noninvasive tests are inconclusive); **B)** Patient with low to moderate risk ACS (★ROMICAT-II); **C)** Rule out congenital anomaly of coronary arteries; **D)** Potential value for pre-op assessment before cardiac surgery when bypass graft is not planned (rule out significant CAD)

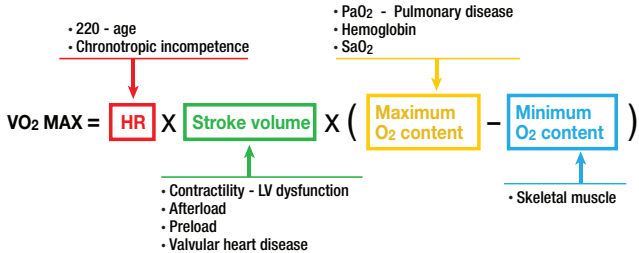
1.13/ CARDIOPULMONARY EXERCISE TESTING

Global evaluation of the oxygen transport system

INDICATIONS: **A)** Pre-transplantation assessment; **B)** Distinguish cardiac dyspnea from pulmonary dyspnea

PROTOCOL: Naughton; ↗ 1 MET every 2 min

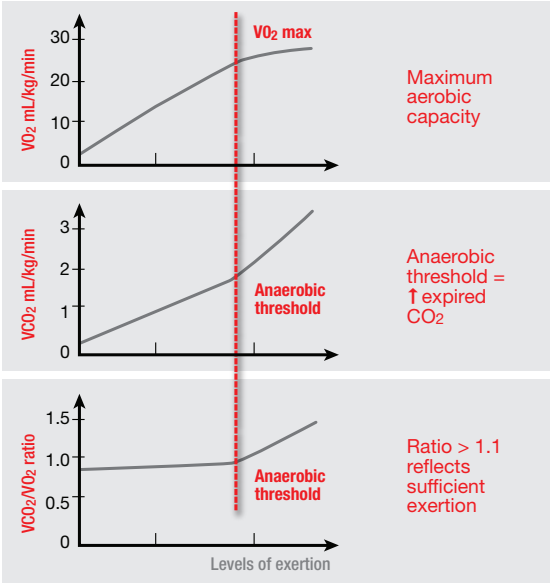
FICK EQUATION



PARAMETERS MEASURED: VO_2 (O_2 consumption); VCO_2 (CO_2 production); VE (minute ventilation); HR; BP; RR; SaO_2; PFTs; exercise ECG

- › **Ventilatory anaerobic threshold (VAT):** value of VO_2 when the slope of VE (or the slope of VCO_2) increases disproportionately to the slope of VO_2 (↗ CO_2 to be expired secondary to anaerobic glycolysis with formation of lactate); often at 50-60% of VO_2max (point at which dyspnea is experienced); activities of daily living situated below the VAT
- › **Respiratory exchange ratio (VCO_2/VO_2)**: **ratio > 1.05 means that the patient has achieved adequate exertion** +
- › **VE/VCO_2 slope**: **slope > 35 associated with poor prognosis**; reflects hyperventilation secondary to V/Q abnormalities with ↗ dead space +
- › **Borg scale**: quantification of the exertion perceived by the patient; > 18 / 20 = maximum exertion; > 15-16 / 20 = anaerobic threshold reached

	VO_2 MAX	ANAEROBIC THRESHOLD	MAXIMUM CARDIAC INDEX
Heart failure with good prognosis	> 18 mL O_2/kg/min	> 14 mL O_2/kg/min	> 8 L/min/m²
High-risk heart failure (consider transplantation)	< 10 mL O_2/kg/min (anaerobic threshold reached)	< 8 mL O_2 /kg/min	< 4 L/min/m²
Gray zone	VE/VCO_2 slope > 35 associated with poor prognosis		



1.14/ EXPOSURE TO RADIATION DURING CARDIAC EXAMINATIONS

CXR (PA - lateral)	0.1 mSv
Diagnostic coronary angiography	7 mSv
PCI (or RF ablation)	15 mSv
Coronary CT angiography	5 mSv
Coronary calcium scan	3 mSv
MibiP	9.4 mSv
Thallium (stress - redistribution)	41 mSv
FDG PET	8 mSv
V/Q scintigraphy	2.2 mSv
CT pulmonary angiography	15 mSv
Radionuclide ventriculography (equilibrium)	7.8 mSv

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Coronary artery disease (CAD) & Myocardial infarction

02

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2.1/ STABLE ANGINA

O_2 DEMAND
- HR
- Wall stress (preload; afterload)
- Contractility

O_2 SUPPLY
- Coronary perfusion pressure (DBP – LVEDP)
- Patent coronary arteries
- Blood O_2 content

ANGINA: Clinical diagnosis +

Constrictive retrosternal chest pain	On exertion (or emotions)	Relieved by rest (5–10 min) or nitrates
Typical chest pain = 3	Atypical chest pain = 2	Nonanginal chest pain = 1

CLINICAL HISTORY: Nature; Site; Radiation; Tempo; Duration; Modifiers; Associated symptoms (cardiovascular; respiratory; gastrointestinal)

SEVERITY OF ANGINA

CCS 1/4	Ordinary activity does not cause angina	**≥ 7 METs** • Angina occurs with strenuous or rapid or prolonged exertion only
CCS 2/4	Slight limitation of ordinary activity	**5–7 METs** • ≥ 2 flights of stairs • Walking ≥ 3 blocks on the level (or walking uphill) • Exertion after meals or in cold weather
CCS 3/4	Marked limitation of ordinary activity	**2–5 METs** • ≤ 1 flight of stairs • Walking one or two blocks on the level
CCS 4/4	Inability to carry out any physical activity without discomfort or angina at rest	**< 2 METs** • Any activity • Walking several steps

ANGINA EQUIVALENT: Dyspnea; Tiredness

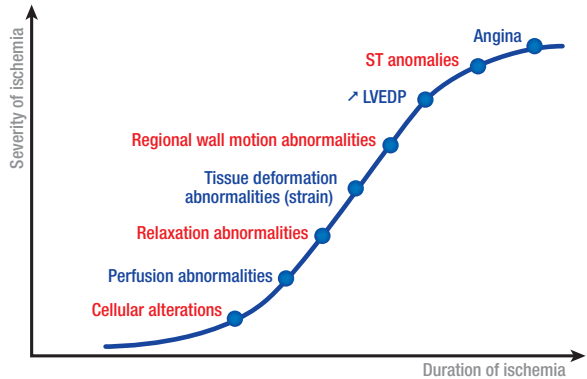
CHARACTERISTICS NOT IN FAVOR OF CARDIAC CHEST PAIN: Pleuritic; Abdominal; Localized; Reproduced on palpation; Reproduced on movement; Duration < several seconds or > several hours

DDX: Aortic dissection; Aortic stenosis; HCM; Secondary ischemia (anemia; hyperthyroidism; arrhythmia); Cocaine; Pericarditis; Myocarditis; Takotsubo; Cardiac syndrome X (Microvascular); Pulmonary embolism; Pneumothorax; Pneumonia; PHT (RV ischemia); Pleurisy; Ruptured esophagus (Boerhaave); Pancreatitis; Cholecystitis; Cholelithiasis; Peptic ulcer (perforated); GERD; Esophageal spasm; Musculoskeletal; Costochondritis; Neck pain; Shoulder tendinitis; Shingles; Psychiatric

TWO OBJECTIVES

a) Confirm the diagnosis of CAD
b) Establish the prognosis of the patient's CAD

ISCHEMIC CASCADE



PRETEST PROBABILITY OF SIGNIFICANT CAD on coronary angiography in a patient with retrosternal chest pain

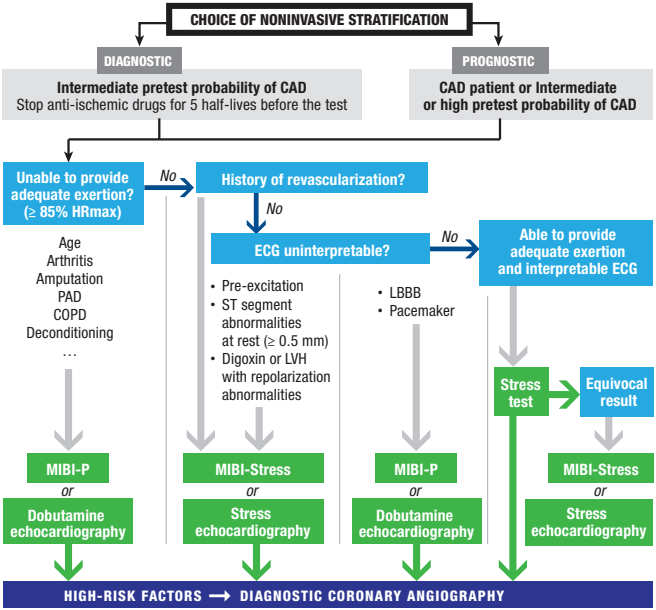
AGE	NONANGINAL CHEST PAIN (≤ 1 CHARACTERISTIC)		ATYPICAL CHEST PAIN (2 CHARACTERISTICS)		TYPICAL CHEST PAIN (3 CHARACTERISTICS)	
	M	F	M	F	M	F
30–39	4 %	2 %	34 %	12 %	76 %	26 %
40–49	13 %	3 %	51 %	22 %	87 %	55 %
50–59	20 %	7 %	65 %	31 %	93 %	73 %
60–69	27 %	14 %	72 %	51 %	94 %	86 %

Diamond GA, Forrester JS. N Engl J Med 1979; 300:1350

BAYES' THEOREM: the predictive value of a test depends on its sensitivity, specificity, and the pretest probability of the disease

› The diagnostic value of the test (when it is used to confirm the diagnosis of CAD) is maximal in patients with an **intermediate pretest probability of CAD (10-90%)**

CHOICE OF NONINVASIVE STRATIFICATION MODALITY

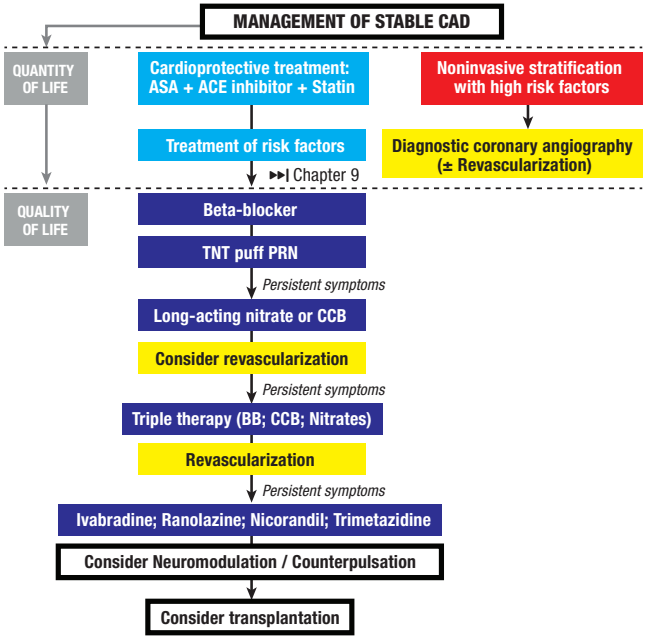


SENSITIVITY AND SPECIFICITY OF DIAGNOSTIC TESTS TO PREDICT SIGNIFICANT CORONARY ARTERY STENOSIS ON CORONARY ANGIOGRAPHY

	SENSITIVITY	SPECIFICITY
Stress test	68 %	77 %
MIBI–Stress	88 %	72 %
MIBI–Dipyridamole	90 %	75 %
Stress echocardiography	85 %	81 %
Dobutamine echocardiography	81 %	79 %
Coronary CT angiography	95 %	83 %

RISK ASSESSMENT DURING NONINVASIVE STRATIFICATION	
HIGH RISK (ANNUAL MORTALITY OR MYOCARDIAL INFARCTION > 3%)	• **LVEF**: < 35% at rest (coronary cause) • **LVEF**: LV dysfunction during stress with LVEF at peak stress < 45% or ↘ LVEF ≥ 10% • **LV dilatation during stress** • **Stress test:** Duke score ≤ -11 • **Stress test:** ST depression ≥ 2 mm (at low workload or persisting during recovery) or ST elevation or VT/VF on exercise • **Echocardiography**: regional wall motion abnormality during stress involving ≥ 3 segments and/or ≥ 2 vascular territories • **Echocardiography**: regional wall motion abnormality occurring at a low dose of Dobutamine (10 µg/kg/min) or at low HR (< 120 bpm) • **MIBI**: perfusion abnormality at rest involving ≥ 10% of the myocardium (in the absence of a history of MI) • **MIBI:** perfusion abnormality on stress involving ≥ 10% of the myocardium (or involving ≥ 2 vascular territories) • **Agaston score (non-contrast CT):** > 400 • **Coronary CT angiography**: multiple vessel disease (stenosis ≥ 70%) or LMCA involvement (stenosis ≥ 50%)
INTERMEDIATE RISK (ANNUAL MORTALITY OR MI: 1-3%)	• **LVEF**: 35-49% at rest (coronary cause) • **Stress test**: Duke score: -10 to +4 • **Stress test**: ST depression ≥ 1 mm + symptoms on exertion • **Echocardiography**: regional wall motion abnormality during stress on 1-2 segments (involving 1 vascular territory) • **MIBI**: perfusion abnormality at rest involving 5 to 9.9% of the myocardium (in the absence of a history of MI) • **MIBI**: perfusion abnormality on stress involving 5 to 9.9% of the myocardium (involving 1 vascular territory) • **Agaston score (non-contrast CT)**: 100-399 • **Coronary CT angiography**: 1 vessel with stenosis ≥ 70% (or ≥ 2 vessels with 50-69% stenosis)
LOW RISK (ANNUAL MORTALITY FROM MI < 1%)	• **Stress test:** Duke score ≥ +5 (or absence of ST abnormalities and symptoms with exercise achieving 85% of predicted HRmax) • **Echocardiography**: normal or limited regional wall motion abnormality at rest and unchanged during stress • **MIBI**: normal or small perfusion defect at rest or on stress involving < 5% of the myocardium • **Agaston score (non-contrast CT)**: < 100 • **Coronary CT angiography**: absence of stenosis > 50%

MANAGEMENT



CARDIOPROTECTIVE TREATMENT

TREATMENT IMPROVING SURVIVAL: **A) ACE inhibitors; B) ASA; C) Statin**

ASA (★ Antithrombotic Trialists' Collaboration); Plavix if allergy (★ CAPRIE)

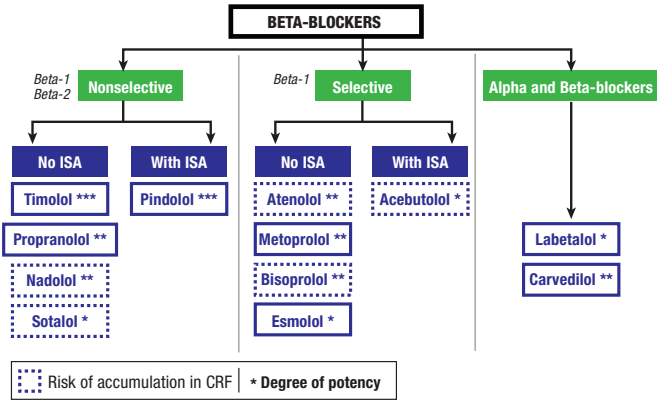
ACE INHIBITORS: ★ HOPE; ★ EUROPA; cardioprotective effect; particularly beneficial if LV dysfunction / DM / HTN / CRF

TREATMENT OF RISK FACTORS: **▸▸| Chapter 9**; HTN; Dyslipidemia (statins); DM; Smoking; Exercise program; Target healthy weight; Balanced diet

ANTI-ANGINAL TREATMENT

BB: **first-line**; antagonist of catecholamine adrenergic receptors; **negative inotropic and negative chronotropic agent** (↗ duration of diastole → ↗ coronary perfusion); anti-anginal; antihypertensive; antiarrhythmic +

› **Intrinsic sympathetic activity (ISA):** partially beta-agonist at rest



NITRATES: converted into NO in the cell → ↗ intracellular cGMP → smooth muscle relaxation (by decreasing intracellular Ca^{2+}); **veinodilatation** (↘ preload); **coronary vasodilatation** (↗ perfusion); **systemic arterial vasodilatation** (↘ afterload)

CALCIUM CHANNEL BLOCKERS

- **Dihydropyridines**: Nifedipine (★ ACTION); Amlodipine (★ CAMELOT); **systemic arterial vasodilatation** (↘ afterload); **coronary vasodilatation** (↗ perfusion)
- **Nondihydropyridines**: Verapamil; Diltiazem; **negative inotropic and negative chronotropic agent; systemic and coronary arterial vasodilatation**

IVABRADINE (PROCORALAN): sinus node I_f channel inhibitor; ↘ **HR** (↗ duration of diastole → ↗ coronary perfusion); ★ INITIATIVE; ★ ASSOCIATE; ★ SIGNIFY: no effect on CV death or MI (but ↗ primary end point among patients with angina of CCS class ≥ 2/4)

RANOLAZINE (RANEXA): ↘ myocyte calcium overload by I_{Na} inhibition; anti-anginal (★ CARISA; ★ ERICA; ★ MERLIN-TIMI 36)

NICORANDIL: 3 mechanisms: **A)** Opening of potassium channels of ischemic cells **(mimics ischemic preconditioning)**; **B)** Opening of potassium channels allowing **systemic and coronary arterial vasodilatation**; **C) Similar properties to Nitrates**

- ★ **IONA:** Stable CAD; ↘ primary outcome with Nicorandil (cardiovascular mortality - MI - hospitalization)

TRIMETAZIDINE (VASTAREL): **fatty acid oxidation inhibitor**; ★TRIMPOL II

EXTERNAL COUNTERPULSATION: 35 one-hour treatments for 7 weeks; cuffs on lower limbs that inflate in early diastole and deflate in pre-systole; ↗ **collateral circulation and/or angiogenesis and/or improvement of endothelial function**

- **Contraindications:** active DVT; PAD; Aortic aneurysm; Aortic stenosis; Aortic regurgitation; Uncontrolled HTN; Decompensated heart failure

NEUROMODULATION: Spinal cord stimulation (T1-T2); ↘ **nociceptive transmission to CNS**

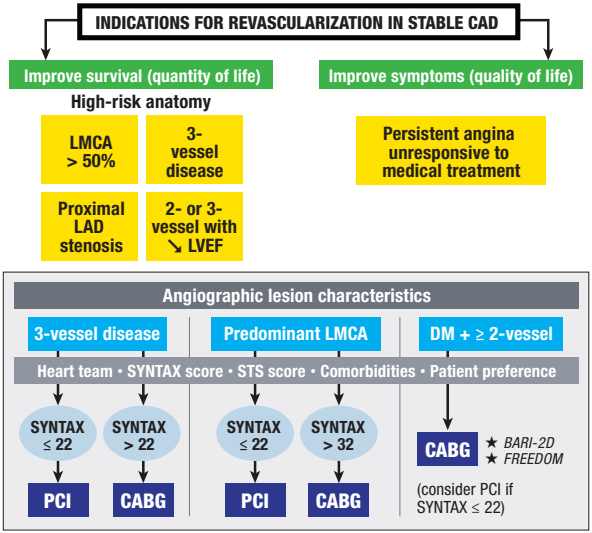
LASER MYOCARDIAL REVASCULARIZATION DURING CARDIAC SURGERY (THERAPEUTIC ANGIOGENESIS): **create subendocardial channels** by left intraventricular laser; consider during refractory angina in the presence of a nonrevascularizable ischemic territory; used exceptionally

ANTI–ANGINAL	DOSES	ADVERSE EFFECTS
BETA-BLOCKERS	**Target resting HR 50-60 bpm** **Maintenance dose** • Metoprolol: 50 - 100 mg bid • Bisoprolol: 2.5 - 10 mg qd • Carvedilol: 3.125 - 50 mg bid • Atenolol: 50 - 100 mg qd • Propranolol LA: 80 - 320 mg qd • Nadolol: 40 - 240 mg qd • Esmolol: Bolus IV 500 µg/kg; infusion 50 - 200 µg/kg/min	Bradycardia - Blocks; Negative inotropic agent (heart failure); Bronchospasm; Depression / Tiredness; Nightmares; Erectile dysfunction; masked symptoms of hypoglycemia (prefer Bisoprolol or Metoprolol); rebound ischemia after sudden discontinuation; Possible exacerbation of PAD or Raynaud or Prinzmetal (unopposed alpha stimulation); ↗ TG and ↘ HDL (nonselective BBs)
NITRATES	• Sublingual: 0.4 mg/puff every 5 min x 3 • Patch: 0.2 - 0.8 mg/h; 8:00 a.m. to 8:00 p.m. • Isosorbide 5-mononitrate (Imdur): 30 to 240 mg qd • Isosorbide dinitrate: 10 - 40 mg tid • IV: 5 - 200 µg/min	Headache; Flushing; Hypotension; Tolerance (prevention by 12-hour period without TNT each day); Methemoglobinemia; Interaction with PDE5 inhibitors; Avoid in the presence of aortic stenosis or HCM
DIHYDROPYRIDINE CCBS	• Nifedipine SR (long-acting): 30 - 60 - 90 mg qd • Amlodipine: 2.5 - 10 mg qd	Headache; Faintness; Hypotension; Flushing; Leg edema
NONDIHYDRO-PYRIDINE CCBS	**Diltiazem** • PO: 30 - 90 mg tid-qid • CD: 120 - 360 mg qd • Bolus: 0.25 mg/kg IV • Infusion: 5 - 15 mg/h **Verapamil** • PO: 80 - 120 mg tid-qid • SR: 120 - 480 mg qd • Bolus: 0.075 - 0.15 mg/kg	Block; Bradycardia; Heart failure (negative inotropic agent); Hypotension; Flushing; Headache; Leg edema; Drug interactions
IVABRADINE	• 5 to 7.5 mg bid	Bradycardia; Phosphenes
NICORANDIL	• 10-20 mg bid	Ulcers; Nausea; Hypotension; Headache; Weakness; Flushing
TRIMETAZIDINE	• 20 mg tid or 30 mg bid	Nausea; Vomiting; Parkinsonism
RANOLAZINE	• 500 to 1000 mg bid	Drug interactions; Nausea; Weakness; ↗ QT (but ↘ delayed after-depolarizations)

REVASCULARIZATION

2 OBJECTIVES

a) Improve quantity of life (prognosis)
b) Improve quality of life (symptoms)



FACTORS AFFECTING THE PATIENT'S PROGNOSIS

a) **Markers of high risk on noninvasive stratification**
b) **Significant ischemia (> 10% of LV)**
c) **LV dysfunction**
d) **Anatomical extent of CAD / Number of vessels involved**

BENEFITS OF CABG VERSUS MEDICAL TREATMENT ON SURVIVAL: **A) LMCA; B) 3 vessels; C) 2 vessels with proximal LAD** (★ Yusuf; ★ VA Cooperative; ★ CASS; ★ ECSS)

PCI VERSUS MEDICAL TREATMENT: ★ **COURAGE** → Stable CAD (30% with proximal LAD) → PCI vs medical treatment; similar survival and infarction rates; ↘ **angina with PCI**

CABG VERSUS PCI: **similar mortality and infarction rates (in patients eligible for both procedures)**; ↗ reintervention with PCI; ↗ Procedural stroke with CABG (★ EAST; ★ BARI; ★ ARTS; ★ SOS; ★ BEST)

★ **SYNTAX**: 3-vessel CAD or LMCA (eligible for both procedures) → CABG vs PCI; **similar mortality**; ↗ MI and ↗ reintervention with PCI

SYNTAX score ≤ 22	SYNTAX score 23–32	SYNTAX score ≥ 33
Similar primary outcome with CABG and PCI	↗ adverse events with PCI	↗ adverse events with PCI

CABG VERSUS PCI FOR LMCA: ★ SYNTAX subgroup **(patients eligible for both procedures)**: ↗ reintervention with PCI; ↗ Procedural stroke with CABG

2.2/ BIOMARKERS

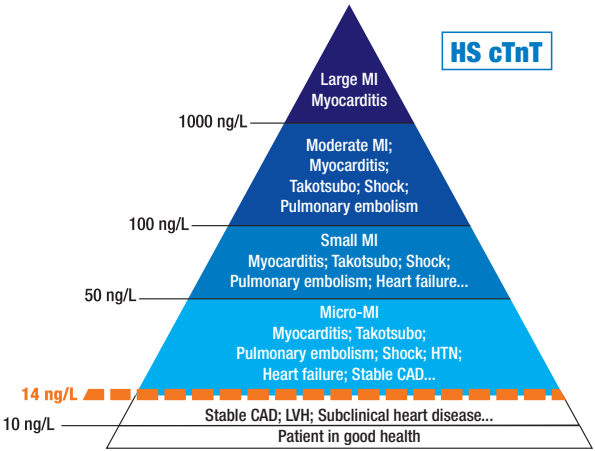
Released following myocyte necrosis (myocyte injury)

TROPONINS T AND I (CTNT AND CTNI): very sensitive and specific for myocyte necrosis **but not very specific for myocardial infarction (ischemic myocyte necrosis)**

MYOCYTE NECROSIS = LABORATORY DIAGNOSIS
MYOCARDIAL INFARCTION = CLINICAL DIAGNOSIS

DIFFERENTIAL DIAGNOSIS OF ELEVATED TROPONIN

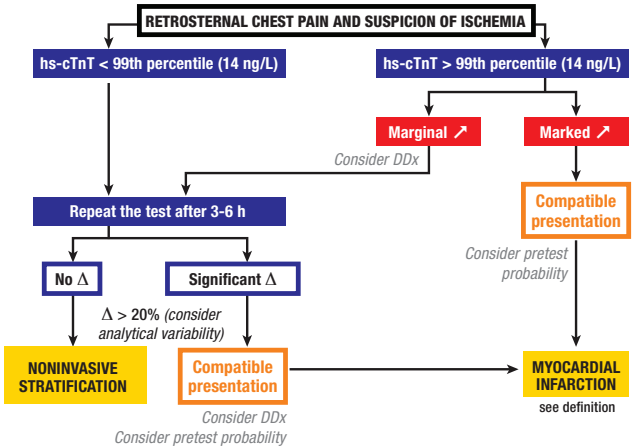
- Infarction
- Heart failure
- Bradyarrhythmia or Tachyarrhythmia
- Myocarditis
- Pulmonary embolism
- Aortic valve disease
- Myocardial contusion
- Takotsubo
- Infiltrative cardiomyopathy
- HCM
- Hypertensive crisis
- Aortic dissection
- Coronary vasospasm
- Endothelial dysfunction without CAD
- PCI
- Cardiac surgery
- Balloon valvuloplasty
- ECV / Defibrillation
- Electrophysiological ablation
- Graft rejection
- Sepsis
- Renal failure
- Significant PHT
- Severe anemia
- Respiratory failure
- Intense physical exercise
- Cardiotoxic chemotherapy
- Cardiotoxins
- Subarachnoid hemorrhage
- Acute brain syndrome
- Rhabdomyolysis
- Body burn (> 30% BSA)
- Scorpion venom



STANDARD TROPONIN: obtain a baseline value on arrival in the emergency room (0 h) and ≥ 1 value **> 6-9 h** after onset of chest pain

HIGH-SENSITIVITY TROPONIN: First troponin assay on arrival → sensitivity and specificity of 90% and NPV of 97%

› **If hs-cTn negative on arrival (0 h) and 3-6 h after arrival with no significant difference between the two tests (< 20%) → NPV of 99%** +



REINFARCTION: assay Troponin at 0h - 3h - 6h; **diagnosis of reinfarction if ↗ ≥ 20%** + (when cTn > 99th percentile pre-reinfarction but with stable or ↘ level)

	INITIAL ELEVATION	PEAK	RETURN TO NORMAL
CK-MB	3-12 h	24 h	48-72 h
Troponin I	3-12 h	24 h	5-10 d
Troponin T	3-12 h	12 h-48 h	5-14 d
Myoglobin	1-4 h	6-7 h	24 h

2.3/ MYOCARDIAL INFARCTION: DEFINITION

NECROSIS OF THE MYOCARDIUM IN THE PRESENCE OF MYOCARDIAL ISCHEMIA

DIAGNOSTIC CRITERIA

Detection of ↗ and/or ↘ of a cardiac biomarker (preferably cTn) with ≥ 1 value > 99th percentile (coefficient of variation of the test ≤ 10%) in the presence of myocardial ischemia **+** **≥ 1 of the following elements**	• **Symptoms** compatible with **ischemia** • Δ **ECG changes** compatible with **ischemia** (Δ ST-T abnormalities) or *de novo* LBBB • *De novo* pathological **Q waves** • **Imaging:** loss of viable myocardium or *de novo* RWMA • Intracoronary **thrombus** (on coronary angiography or at autopsy) +

CLASSIFICATION

TYPE 1	**Acute coronary syndrome: primary coronary event** • Plaque rupture / erosion / ulceration; Coronary dissection
TYPE 2	**Infarction secondary to O_2 supply and demand imbalance** • Anemia; Hypoxemia; Arrhythmia; HTN; Hypotension; Cocaine; Coronary spasm; Endothelial dysfunction; Coronary embolism
TYPE 3	**Cardiac arrest / Sudden death** • Symptoms suggestive of ischemia + • Δ ECG changes compatible with ischemia or *de novo* LBBB + • No biomarker assays
TYPE 4a	**Infarction secondary to PCI** • Symptoms suggestive of ischemia or ischemic ECG changes or angiographic findings compatible with procedural complication or imaging compatible with loss of viable myocardium or *de novo* RWMA + • Positive biomarkers a) ↗ cTn **≥ 5 x upper limit of normal** (> 99th percentile) when baseline cTn normal (< 99th percentile) or b) ↗ cTn **> 20 %** when baseline value elevated (> 99th percentile) but stable
TYPE 4b	**Infarction secondary to stent thrombosis**
TYPE 5	**Infarction secondary to CABG** • ↗ cTn **≥ 10 x upper limit of normal** (> 99th percentile) when baseline cTn normal (< 99th percentile) + • *De novo* Q waves or de novo LBBB or new coronary (or CABG) occlusion on coronary angiography or imaging compatible with loss of viable myocardium or *de novo* RWMA

CAUSES OF INFARCTION IN THE ABSENCE OF ATHEROSCLEROSIS

O_2 SUPPLY/DEMAND IMBALANCE: AS; AR; CO poisoning; Hyperthyroidism; Prolonged hypotension; Hypertensive crisis; Sepsis - Fever; Anemia; Respiratory failure; AV fistula; HCM; Tachyarrhythmia; Cocaine; Endothelial dysfunction

CORONARY EMBOLISM: Endocarditis (infective or non-infective); MVP; Intracardiac thrombus; Prosthetic valve; Myxoma; Iatrogenic; Paradoxical embolism; Fibroelastoma; Valvular calcification

ARTERITIS: Syphilis; SLE; Takayasu (coronary ostium); PAN; Kawasaki; RA; Ankylosing spondylitis; Giant cell arteritis; Scleroderma

› **SLE:** Arteritis; endothelial dysfunction; thrombosis (antiphospholipid syndrome); accelerated atherosclerosis; coronary aneurysm

TRAUMA: Laceration; Iatrogenic; Radiotherapy; Contusion

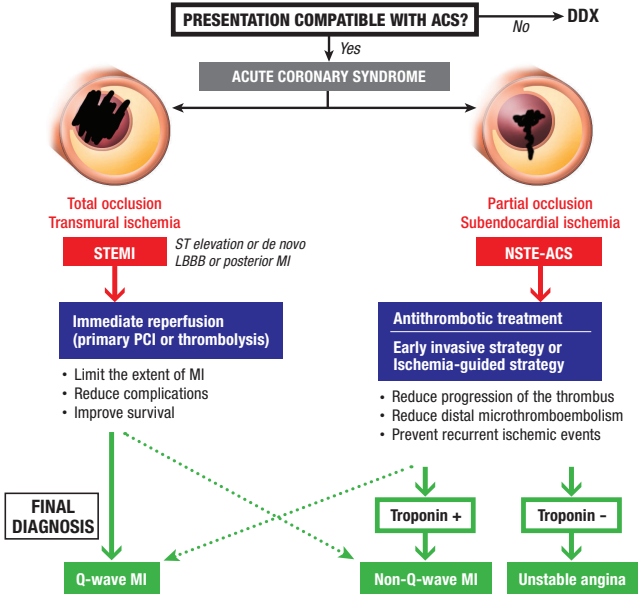
INFILTRATIVE / PROLIFERATIVE: Hurler's; Homocysteinuria; Fabry; Amyloidosis; Pseudoxanthoma elasticum

CONGENITAL: ALCAPA; Anomalous coronary origin; Coronary fistula; Coronary aneurysm

HEMATOLOGICAL (*IN SITU* THROMBOSIS): Hyperviscosity; Polycythemia; Thrombocytosis; Hypercoagulable state - Antiphospholipid syndrome; TTP; DIC

OTHER: Prinzmetal; Aortic dissection; Coronary dissection (pregnancy; Marfan; Ehlers-Danlos; Cocaine); Takotsubo; Thrombosis then spontaneous thrombolysis; Medications; Myocardial bridge

2.4/ UNSTABLE ANGINA & NSTEMI



IN-HOSPITAL MORTALITY of STEMI is 50% higher than that of NSTEMI

› **Similar one-year mortality for STEMI and NSTEMI** (high risk of recurrent events after NSTEMI)

PATHOPHYSIOLOGY: Rupture / Erosion of an unstable and friable atherosclerotic plaque with exposure of the subendothelial matrix then activation of primary and secondary hemostasis and thrombus formation

ASSESSMENT

SYMPTOMS OF ACS	UNSTABLE NATURE
Retrosternal chest pain* • **Nature:** Constrictive - Tightness • **Radiation**: Neck - Jaw - Upper limb • **Associated symptoms**: Dyspnea; Nausea; Vomiting; Diaphoresis * Atypical presentation / Anginal equivalent in elderly - DM - women	**Any one of the following**: • ***De novo* angina** < 2 months after presentation with CCS ≥ 3/4 • **Crescendo angina**: more frequent or longer or on less exertion (with CCS ≥ 3/4) • **Angina at rest** (often lasting > 20 min) < 1 week after presentation

CLINICAL FEATURES: Diaphoresis; Cold skin; Sinus tachycardia; PVCs; ± Hypotension; S3 or S4; Ischemic MR murmur; Crackles

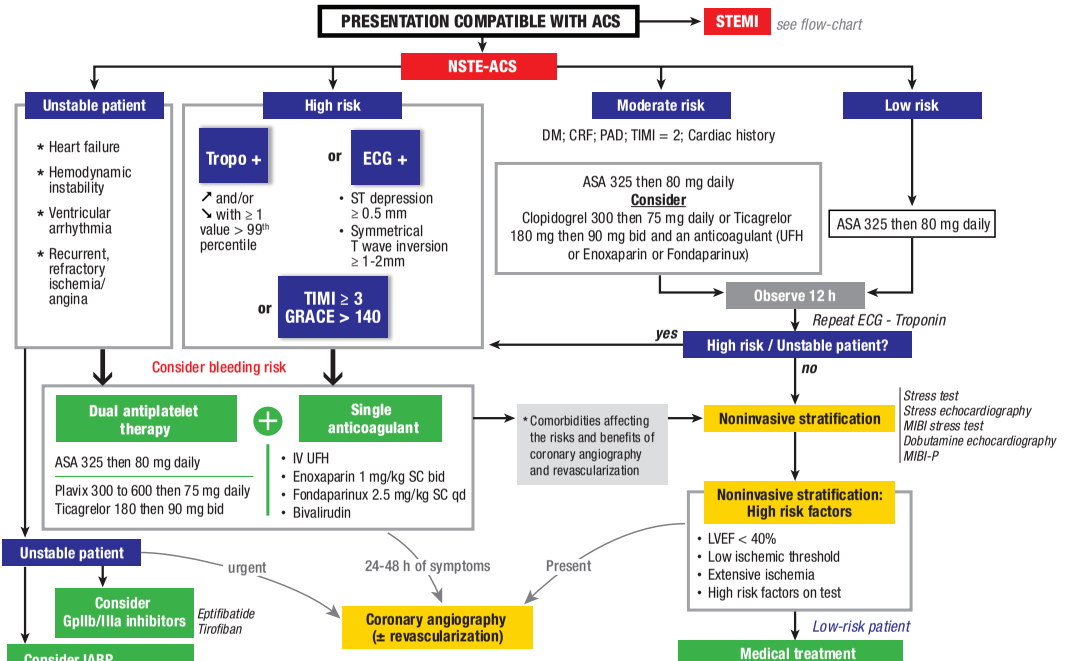
ECG

ST depression	• Horizontal or descending • **≥ 0.5 mm** (≥ 2 contiguous leads)
T–wave inversion	• **≥ 1-2 mm** (≥ 2 contiguous leads) › Leads with R/S > 1

NSTE–ACS AND UNSTABLE ANGINA

HIGH RISK (≥ 1 CRITERION)	INTERMEDIATE RISK (≥ 1 CRITERION)	LOW RISK
Unstable atherosclerotic plaque; Urgent evaluation		**Outpatient stratification possible**
• Accelerated angina < 48 h • Prolonged and persistent retrosternal chest pain at rest (> 20 min) • Ischemic pulmonary overload • *De novo* MR murmur • S3 or Crackles • Hypotension or Bradycardia or Tachycardia • Age > 75 years • Angina at rest with transient ST changes > 0.5 mm • *De novo* bundle branch block • Sustained VT • Significant elevation of troponins	• History: myocardial infarction or PAD or cerebrovascular disease or history of CABG • Treatment with ASA • Prolonged retrosternal chest pain at rest (> 20 min) but resolved • Prolonged retrosternal chest pain (> 20 min), but resolved with rest or TNT • Nocturnal angina • CCS III or IV angina (*de novo* or progressive) < 2 weeks without prolonged retrosternal chest pain at rest (> 20 min) • Age > 70 years • T wave abnormalities • Pathological Q waves or ST depression at rest < 1 mm on multiple leads • Marginal elevation of troponins	• More frequent or more severe or more persistent angina • Angina induced by a lower workload • *De novo* angina: between 2 weeks to 2 months before presentation • Normal ECG • Normal troponin

TIMI SCORE	GRACE SCORE
1) Age > 65 years 2) ≥ 3 risk factors for CAD 3) Known stenosis > 50% 4) ASA < 7 days 5) ≥ 2 episodes of retrosternal chest pain x 24 h 6) ST depression ≥ 0.5 mm 7) Biomarkers **Death / MI / Urgent revascularization within 14 days** 0-1 point.....4.7 % 2 points .....8.3 % 3 points .....13.2 % 4 points .....19.9 % 5 points .....26.2 % 6-7 points.....40.9 %	www.gracescore.org 1) Age 2) SBP 3) HR 4) Killip Class 5) Heart failure 6) Cardiac arrest at presentation 7) ST segment depression 8) Biomarkers 9) Creatinine **In–hospital mortality** GRACE ≤ 108 points.....< 1 % GRACE 109-140 points .....1-3 % GRACE > 140 points .....> 3 %


PRESENTATION COMPATIBLE WITH ACS
STEMI
see flow-chart
NSTE-ACS
Unstable patient
* Heart failure
* Hemodynamic instability
* Ventricular arrhythmia
* Recurrent, refractory ischemia/ angina
High risk
Tropo +
or
ECG +
↗ and/or ↘ with ≥ 1 value > 99th percentile
• ST depression ≥ 0.5 mm
• Symmetrical T wave inversion ≥ 1-2mm
or
TIMI ≥ 3
GRACE > 140
Moderate risk
DM; CRF; PAD; TIMI = 2; Cardiac history
Low risk
ASA 325 then 80 mg daily
Consider
Clopidogrel 300 then 75 mg daily or Ticagrelor 180 mg then 90 mg bid and an anticoagulant (UFH or Enoxaparin or Fondaparinux)
ASA 325 then 80 mg daily
Observe 12 h
Repeat ECG - Troponin
yes
High risk / Unstable patient?
no
Consider bleeding risk
Dual antiplatelet therapy
ASA 325 then 80 mg daily
Plavix 300 to 600 then 75 mg daily
Ticagrelor 180 then 90 mg bid
Single anticoagulant
• IV UFH
• Enoxaparin 1 mg/kg SC bid
• Fondaparinux 2.5 mg/kg SC qd
• Bivalirudin
* Comorbidities affecting the risks and benefits of coronary angiography and revascularization
Noninvasive stratification
Stress test
Stress echocardiography
MIBI stress test
Dobutamine echocardiography
MIBI-P
Noninvasive stratification: High risk factors
• LVEF < 40%
• Low ischemic threshold
• Extensive ischemia
• High risk factors on test
Low-risk patient
Medical treatment
Unstable patient
urgent
24-48 h of symptoms
Present
Consider GpIIb/IIIa inhibitors
Eptifibatide
Tirofiban
Consider IABP
Coronary angiography (± revascularization)

INITIAL MANAGEMENT

ARRIVAL IN THE EMERGENCY ROOM: ECG within 10 min; IV lines; Monitor; ASA 325 mg; Sublingual TNT (except when contraindicated); O_2 (for SaO2 > 90%); ± Morphine 2.5 mg IV if persistent chest pain

CHOICE OF STRATEGY

EARLY INVASIVE STRATEGY	ISCHEMIA–GUIDED STRATEGY
↘ Mortality; ↘ MI; ↘ Hospitalization (★ FRISC-II; ★ RITA-3; ★ TACTICS-TIMI 18)	**According to non–invasive stress test (★ ICTUS)**
• **Unstable patient** (urgent coronary angiography) › Acute heart failure › Hemodynamic instability › Ventricular arrhythmia › Recurrent and refractory angina/ischemia • **Troponin +** • **Positive ECG** (*De novo* ST depression) • Patient at high risk of recurrent events › **TIMI ≥ 3** › **GRACE > 140** • **PCI < 6 months** (rule out restenosis) • **History of CABG** (multiple anatomical possibilities)	• **TIMI score 0-1** • **GRACE < 109** • **Risk of complications** associated with coronary angiography and/or revascularization • **Comorbidities; Frailty** • Patient's **preference**

DUAL ANTIPLATELET THERAPY

ASA: Irreversible inhibitor of COX-1 (and TXA synthesis)
› ★ **Antithrombotic Trialists**: ↘ all-cause mortality; ↘ recurrent ischemic events
› **Dose:** 325 mg then 80 mg qd (★ CURRENT-OASIS 7)

CLOPIDOGREL: Second-generation thienopyridine; irreversible ADP $P2Y_{12}$ receptor antagonist
› ★ **CURE**: ↘ recurrent ischemic events (**at 12 months**); ↗ major bleeding
› ★ **CURRENT-OASIS 7**: High-dose clopidogrel (600 mg then 150 mg qd for 6 days then 75 mg qd) versus standard doses (300 mg then 75 mg qd) → potential benefit in **the subgroup of patients undergoing PCI** (but ↗ bleeding risk)
› **Disadvantage**: **A)** Slow onset of action (requires 2 metabolism and activation steps); **B)** Genetic polymorphisms of the cytochrome P450 enzyme responsible for metabolism (and activation) of clopidogrel (some patients metabolize and activate the medication less effectively); **C)** Inhibits 50-60% of platelets

TICAGRELOR: Reversible direct $P2Y_{12}$ receptor antagonist; rapid onset of action
› ★ **PLATO**: Ticagrelor versus clopidogrel (**47% of patients had received clopidogrel prior to randomization**); Revascularization or medical treatment → ↘ **all-cause mortality**; ↘ recurrent ischemic events; ↗ major bleeding not related to CABG
› **Adverse effects**: Dyspnea; ↗ ventricular pauses; ↗ creatinine (reversible)
› **Contraindication**: History of intracranial bleeding; active bleeding; severe liver disease; potent CYP3A4 inhibitor
› ★ **PEGASUS**: Ticagrelor (60 or 90 mg bid) versus Placebo in patients with a myocardial infarction 1-3 years earlier; ↘ **CV death - MI - Stroke but ↗ major bleeding**

PRASUGREL: **no benefit** in ★ ACCOAST (upfront therapy) and ★ TRILOGY ACS (ischemia-guided strategy)

GPIIB/IIIA INHIBITORS : Block the formation of bridges between platelets (cross-links between GPIIb/IIIa receptors and fibrinogen)

- ★ **EARLY-ACS**: **no benefit** of eptifibatide initiated routinely > 12 h before coronary angiography versus eptifibatide initiated on demand during PCI
- **Consider the use of GPIIb/IIIa inhibitors** in patients treated with Ticagrelor (or Prasugrel): **during PCI for bailout situations / thrombotic complications**
  - **Eptifibatide**: **A)** Bolus: 180 µg/kg IV then 2nd bolus of 180 µg/kg within 10 min; **B)** Infusion: 2 µg/kg/min (initiated after 1st bolus); decrease the dose by 50% if GFR < 50 mL/min
  - **Tirofiban**: **A)** Bolus: 25 µg/kg IV; **B)** Infusion: 0.15 µg/kg/min; decrease the dose by 50% if GFR < 30 mL/min
  - **Abciximab**: **A)** Bolus: 0.25 mg/kg IV; **B)** Infusion: 0.125 µg/kg/min (max 10 µg/min)
- **Adverse effects**: thrombocytopenia; bleeding

ANTICOAGULATION

Avoid crossover between antithrombins; stop anticoagulation after PCI (unless otherwise indicated)

UNFRACTIONATED HEPARIN

- ★ **Eikelboom meta-analysis**: ↘ mortality (before the age of dual antiplatelet therapy and early revascularization)
- **Doses:** 60 IU/kg bolus then 12 IU/kg/h; PTT every 6 h; target PTT 50-70 s (1.5 to 2 x control)
  - **During coronary angiography:** additional UFH as needed (2000-5000 U); **A)** Absence of GPIIb/IIIa inhibitors→ target ACT 250-300 s (HemoTec) or 300-350 s (Hemochron); **B)** Presence of GPIIb/IIIa inhibitors → target ACT 200-250 s
- **Complications:** bleeding; HIT (consider Bivalirudin)

ENOXAPARIN (LMWH): Xa inhibitor and weak thrombin inhibitor (factor IIa inhibitor)

- ★ **SYNERGY**: Enoxaparin vs Unfractionated heparin →↗ **bleeding** during early invasive strategy with enoxaparin
- **Doses:** 1 mg/kg SC bid (reduce to once daily if GFR < 30 mL/min)
- **PCI:** Last dose > 8 h → 0.3 mg/kg IV bolus

FONDAPARINUX: indirect Xa inhibitor

- ★ **OASIS-5**: Fondaparinux vs enoxaparin →↘ bleeding;↘ all-cause mortality; ↗ **catheter thrombosis during PCI** (as it does not act on already formed thrombin)
- **Doses:** 2.5 mg SC once daily (avoid if GFR < 20 mL/min)
- **PCI:** Add a bolus of unfractionated heparin (70-85 IU/kg; 50-60 IU/kg with concomitant GPIIb/IIIa inhibitors)

BIVALIRUDIN: thrombin inhibitor (factor IIa inhibitor)

- ★ **ACUITY:** Bivalirudin vs unfractionated heparin + GPIIb/IIIa inhibitors → non-inferiority for primary outcome; ↘ major bleeding
- ★ **MATRIX**: ACS with PCI anticipated; Bivalirudin vs unfractionated heparin → no benefit
- **Dose**: **A)** Bolus: 0.1 mg/kg; **B)** Infusion: 0.25 mg/kg/h
  - **During PCI: A)** Bolus: 0.5 mg/kg; **B)** Infusion: 1.75 mg/kg/h

RIVAROXABAN: oral Xa inhibitor

- ★ **ATLAS ACS-TIMI 51:** Recent ACS on dual antiplatelet therapy; Rivaroxaban (2.5 or 5 mg bid; initiated an average of 4.5 days post-ACS) vs placebo; ↘ recurrent ischemic events; ↘ **all-cause mortality (2.5 mg bid)**; ↗ major bleeding
- **Consider:** in combination with ASA and Clopidogrel (if Ticagrelor or Prasugrel are not available) in patients with high ischemic and low bleeding risks

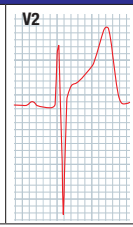
URGENT CORONARY ANGIOGRAPHY	EARLY INVASIVE STRATEGY (< 48 H)	ISCHEMIA–GUIDED STRATEGY
1) ASA 325 mg **2)** Ticagrelor 180 mg **or** Clopidogrel 600 mg **3)** ± GpIIb/IIIa inhibitors (during PCI for bailout situations) **4)** Unfractionated heparin	**1)** ASA 325 mg **2)** Ticagrelor 180 mg then 90 mg bid **or** Clopidogrel 300 mg then 75 mg qd (consider an additional 300 mg if PCI then 150 mg qd for 6 days then 75 mg) **3)** Unfractionated heparin or Enoxaparin or Fondaparinux or Bivalirudin › Stop after PCI in the absence of complications	**1)** ASA 325 mg **2)** Ticagrelor 180 mg then 90 mg bid **or** Clopidogrel 300 mg then 75 mg qd (consider an additional 300 mg if PCI then 150 mg qd for 6 days then 75 mg) **3)** Unfractionated heparin (48 h or until PCI is performed) or Enoxaparin or Fondaparinux if bleeding risk (for the duration of hospitalization or until PCI is performed)

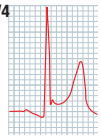
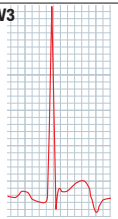
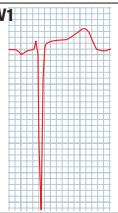
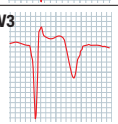
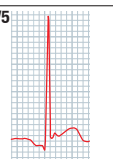
- **Patient already on Clopidogrel:** another loading dose of 300 to 600 mg if PCI planned
- **Patient on Warfarin**: wait for INR < 2.0-2.5 before starting anticoagulant

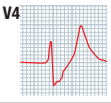
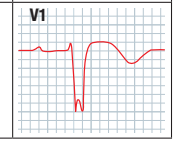
2.5/ ST SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)

ECG CRITERIA

ST ELEVATION (FROM POINT J IN ≥ 2 CONTIGUOUS LEADS)	
V2 – V3	• Male ≥ 40 years: ≥ 2 mm • Male < 40 years: ≥ 2.5 mm • Female: ≥ 1.5 mm
All other leads	≥ 1 mm
V3R – V4R – V7 – V8 – V9	≥ 0.5 mm

DDX OF ST ELEVATION		
Male ST pattern	• 90% of men < 35 years • Concave ST elevation > 1 mm in V1 to V3 (especially V2)	

Early repolarization	• Large T waves (especially in V4) • ST elevation in V2-V3-V4 (concave) • Notch at point J • PR segment depression	
Juvenile T wave pattern and early repolarization	• T wave inversion (juvenile T wave pattern) combined with early repolarization • Short QT	
LVH	• Concave ST elevation in V1 to V3 • Positive voltage criteria	
Post–MI with aneurysm	• Persistent ST elevation (> 3 weeks post-MI) in the presence of Q waves	
LBBB (or paced rhythm)	• Concave ST elevation; the ST deviation is discordant with the QRS axis **Sgarbossa criteria** (infarction in the presence of LBBB) 1) **ST elevation ≥ 1 mm in leads with positive QRS (inappropriate concordance)** - Criterion with the best predictive value 2) ST depression ≥ 1 mm V1-V2-V3 (inappropriate concordance) 3) ST elevation ≥ 5 mm in leads with negative QRS (extreme discordance)	
Acute pericarditis	• Diffuse concave ST elevation (multiple anatomical territories) • PR segment depression • Reciprocal changes in aVR	

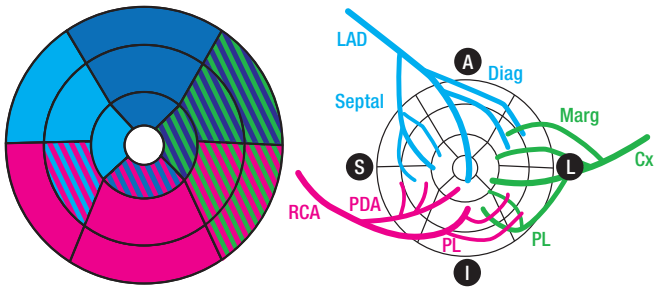
Brugada syndrome	• rSR' and ST elevation in V1 and V2 with descending slope and T wave inversion	
Hyperkalemia	• Peaked and symmetrical T waves • ST elevation • Other signs: Wide QRS; decreased amplitude of P waves; blocks; asystole	
Pulmonary embolism	• T wave inversion and ST elevation in right precordial and inferior leads • S1 Q3 T3 • RBBB • Sinus tachycardia	

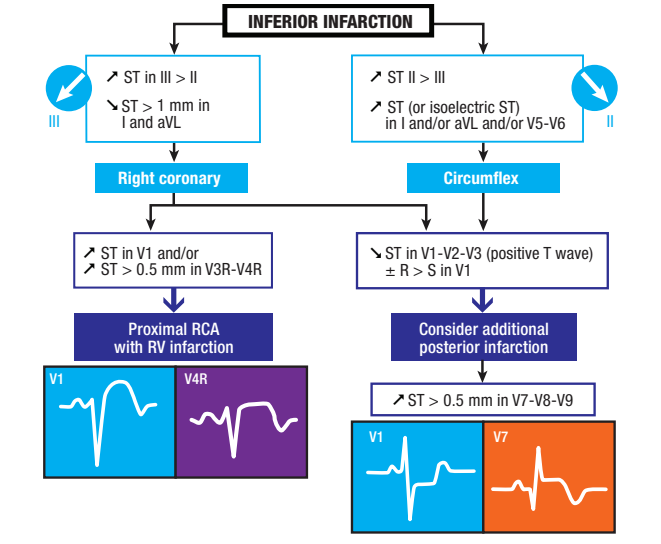
SITE OF INFARCTION ON ECG

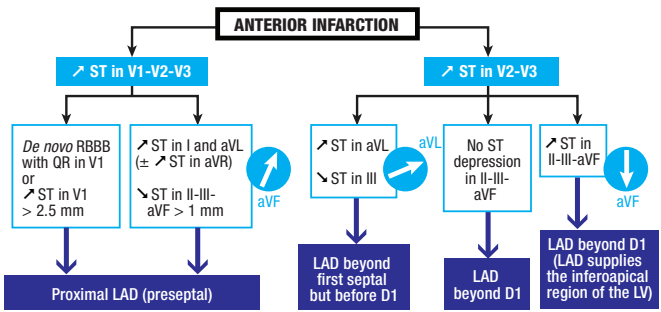
I Lateral	aVR	V1 Antero-septal	V4 Anterior
II Inferior	aVL Lateral	V2 Antero-septal	V5 Antero-lateral
III Inferior	aVF Inferior	V3 Anterior	V6 Antero-lateral

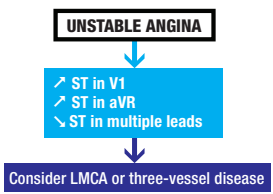
V3R-V4R Right heart

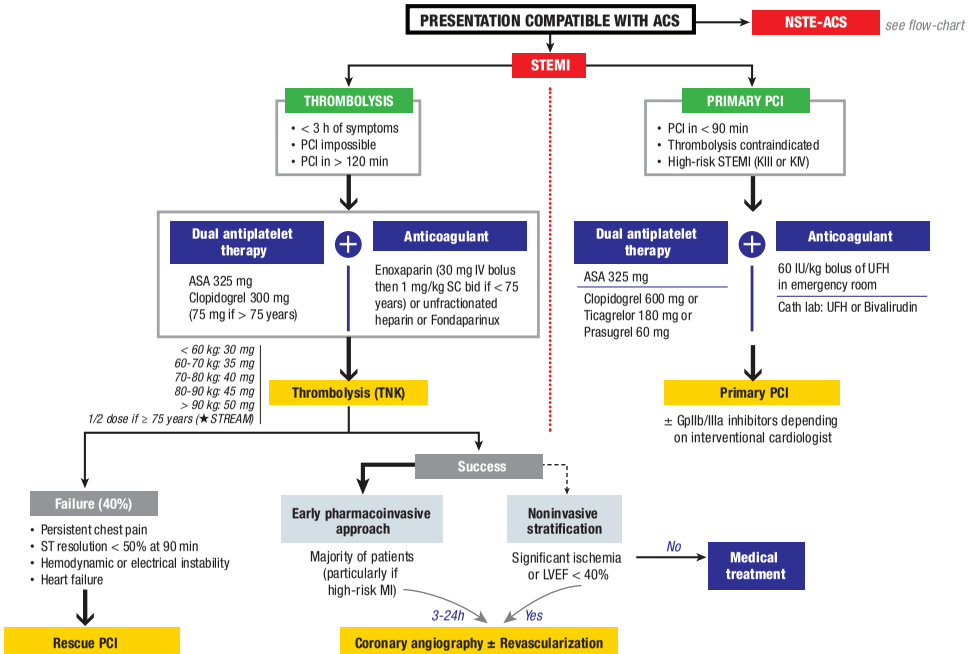
V7-V8-V9 Posterior




INFERIOR INFARCTION
↗ ST in III > II
↘ ST > 1 mm in I and aVL
III
↗ ST II > III
↗ ST (or isoelectric ST) in I and/or aVL and/or V5-V6
II
Right coronary
Circumflex
↗ ST in V1 and/or ↗ ST > 0.5 mm in V3R-V4R
↘ ST in V1-V2-V3 (positive T wave) ± R > S in V1
Proximal RCA with RV infarction
Consider additional posterior infarction
V1
V4R
↗ ST > 0.5 mm in V7-V8-V9
V1
V7


ANTERIOR INFARCTION
↗ ST in V1-V2-V3
↗ ST in V2-V3
De novo RBBB with QR in V1 or ↗ ST in V1 > 2.5 mm
↗ ST in I and aVL (± ↗ ST in aVR)
↘ ST in II-III-aVF > 1 mm
aVF
↗ ST in aVL
↘ ST in III
aVL
No ST depression in II-III-aVF
↗ ST in II-III-aVF
aVF
Proximal LAD (preseptal)
LAD beyond first septal but before D1
LAD beyond D1
LAD beyond D1 (LAD supplies the inferoapical region of the LV)


UNSTABLE ANGINA
↗ ST in V1
↗ ST in aVR
↘ ST in multiple leads
Consider LMCA or three-vessel disease


PRESENTATION COMPATIBLE WITH ACS
NSTE-ACS
see flow-chart
STEMI
THROMBOLYSIS
• < 3 h of symptoms
• PCI impossible
• PCI in > 120 min
PRIMARY PCI
• PCI in < 90 min
• Thrombolysis contraindicated
• High-risk STEMI (KIII or KIV)
Dual antiplatelet therapy
ASA 325 mg
Clopidogrel 300 mg
(75 mg if > 75 years)
Anticoagulant
Enoxaparin (30 mg IV bolus then 1 mg/kg SC bid if < 75 years) or unfractionated heparin or Fondaparinux
Dual antiplatelet therapy
ASA 325 mg
Clopidogrel 600 mg or
Ticagrelor 180 mg or
Prasugrel 60 mg
Anticoagulant
60 IU/kg bolus of UFH in emergency room
Cath lab: UFH or Bivalirudin
< 60 kg: 30 mg
60-70 kg: 35 mg
70-80 kg: 40 mg
80-90 kg: 45 mg
> 90 kg: 50 mg
1/2 dose if ≥ 75 years (★ STREAM)
Thrombolysis (TNK)
Primary PCI
± GpIIb/IIIa inhibitors depending on interventional cardiologist
Success
Failure (40%)
• Persistent chest pain
• ST resolution < 50% at 90 min
• Hemodynamic or electrical instability
• Heart failure
Early pharmacoinvasive approach
Majority of patients (particularly if high-risk MI)
Noninvasive stratification
Significant ischemia or LVEF < 40%
No
Medical treatment
3-24h
Yes
Rescue PCI
Coronary angiography ± Revascularization

INITIAL MANAGEMENT

EMERGENCY ROOM: ECG within 10 min; IV lines; Monitor; ASA 325 mg; Sublingual TNT (except when contraindicated); O_2 (for $SaO_2 > 90\%$); ± Morphine 2.5 mg IV if persistent chest pain

KILLIP CLASSIFICATION

Killip I	No crackles; No S3
Killip II	Crackles (< 50% of lung fields) ± S3
Killip III	Crackles > 50% of lung fields
Killip IV	Cardiogenic shock

TIMI SCORE IN STEMI

CRITERIA	# POINTS	30-DAY MORTALITY
Age 65-74 years or ≥ 75 years	2 or 3 points	**0 : 0.8 %**
SBP < 100	3 points	**1 : 1.6 %**
HR > 100 bpm	2 points	**2 : 2.2 %**
Killip II-III-IV	2 points	**3 : 4.4 %**
History: DM or HTN or Angina	1 point	**4 : 7.3 %**
< 67 kg	1 point	**5 : 12.4 %**
Time to treatment > 4 h	1 point	**6 : 16.1 %**
Anterior STEMI or LBBB	1 point	**7 : 23.4 %**
		8 : 26.8 %
		> 8 : 35.9 %

IMMEDIATE REPERFUSION

THROMBOLYSIS	PRIMARY PCI
< 30 min after 1st medical contact*	**< 90 min after 1st medical contact***
↘ Mortality (vs Placebo) **(★ GISSI; ★ ISIS-2; ★ ASSET)**	**↘ Mortality (vs Thrombolysis)** **↘ Recurrent infarction** **↘ Risk of intracranial hemorrhage**
Fibrinolysis less effective > 6 h after symptom onset • Early presentation: < 3 h of symptoms • Significantly delayed PCI (1st medical contact until PCI **> 120 min**) • PCI impossible (cath lab not available; vascular access impossible)	• PCI available in < 90 min after 1st medical contact • > 3 h of symptoms • Contraindication to thrombolysis - Bleeding risk / Intracranial bleeding • High-risk STEMI • Doubtful diagnosis

*** Including paramedics**

THROMBOLYSIS

TENECTEPLASE (TNK): < 60 kg → 30 mg; 60-70 kg → 35 mg; 70-80 kg → 40 mg; 80-90 kg → 45 mg; ≥ 90 kg → 50 mg; **if ≥ 75 years → half dose** (★STREAM)

› ★ **ASSENT-2:** Tenecteplase vs tPA → ↘ major bleeding with TNK

TIME TO ADMINISTRATION: **maximum benefit on mortality < 2-3 h of symptoms**

- ↘ **Response of thrombus** to thrombolysis **after > 3 h of symptoms**
- It is reasonable to perform thrombolysis up to 12-24 h after onset of symptoms in the presence of persistent ischemia (angina and ↗ ST on ECG) and significant infarction
  - ★ LATE - ★ EMERAS: ↘ **mortality between 6-12 h of symptoms**

ABSOLUTE CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
• History of intracranial hemorrhage • Structural CNS vascular disease • Intracranial neoplasm • Stroke < 3 months • Suspicion of aortic dissection • Active bleeding (excluding menstruation) or bleeding diathesis • Significant facial / head trauma < 3 months • Intracranial or spinal cord surgery < 2 months • Severe refractory HTN	• SBP > 180 mmHg and/or DBP > 110 mmHg • Stroke > 3 months or dementia or intracranial disease • CPR > 10 min or traumatic • Major surgery < 3 weeks • Internal bleeding < 2-4 weeks • Noncompressible vascular puncture • Pregnancy • Active peptic ulcer • Oral anticoagulant
• Risk of intracranial bleeding → **Prefer PCI if ≥ 2 criteria present** **1)** > 65 years; **2)** BP > 160-170/95; **3)** M < 70 kg and F < 65 kg	

PRIMARY PCI: ADJUVANT TREATMENT

ASA: 325 mg then 80 mg qd

CLOPIDOGREL: 600 mg then 75 mg qd

PRASUGREL: Third-generation thienopyridine; irreversible inhibition of the $P2Y_{12}$ receptor; one-step activation (versus 2 steps for clopidogrel); metabolism not affected by genetic polymorphisms of cytochrome P450 enzymes

- ★ **TRITON-TIMI 38: thienopyridine-naive patients; known coronary anatomy** (except if primary PCI) → ↘ ischemic events; ↘ stent thrombosis; ↗ major bleeding
- **Avoid in patients**: **> 75 years; < 60 kg; History of stroke - TIA**

TICAGRELOR

- ★ **PLATO**: Clopidogrel-naive or non-naive patients; ↘ all-cause mortality; ↘ recurrent ischemic events; ↘ stent thrombosis; ↗ major bleeding not related to CABG

GPIIB/IIIA INHIBITORS: in the cath lab at **the interventional cardiologist's discretion** (significant thrombus; insufficient prior antiplatelet treatment; slow- or no-reflow; thrombotic complication)

- **Abciximab**: **A)** Bolus: 0.25 mg/kg IV; **B)** Infusion: 0.125 µg/kg/min

UNFRACTIONATED HEPARIN: 60 IU/kg bolus (max 4000 IU) then IV infusion with target aPTT of 50-70 s (12 IU/kg/h; max 1000 IU/h)

- **During coronary angiography**: **A)** Absence of GPIIb/IIIa inhibitors → target ACT 250-300 s (HemoTec) or 300-350 s (Hemochron); **B)** Presence of GPIIb/IIIa inhibitors → target ACT 200-250 s

BIVALIRUDIN: Thrombin inhibitor; used in cath lab

- ★ **HORIZONS-AMI**: Bivalirudin vs UFH + GPIIb/IIIa inhibitors; ↘ **all-cause mortality**; ↘ major bleeding
- ★ **MATRIX**: ACS (55% STEMI) with PCI anticipated; Bivalirudin vs UFH → no benefit with Bivalirudin
- **Dose**: **A)** Bolus: 0.75 mg/kg; **B)** Infusion: 1.75 mg/kg/h (decrease to 1 mg/kg/h if CrCl < 30 mL/min)

THROMBOLYSIS: ADJUVANT TREATMENT

ASA: 325 mg then 80 mg qd (long-term); ★ ISIS-2

CLOPIDOGREL: 300 mg (75 mg if > 75 years) then 75 mg qd (14 days to 1 year);
★ CLARITY-TIMI 28 and ★ COMMIT

ENOXAPARIN: ★ EXTRACT-TIMI 25 → **Enoxaparin superior to Unfractionated heparin** but ↗ major bleeding

- **Bolus**: 30 mg IV (< 75 years)
- **Maintenance**: 1 mg/kg SC bid (max 100 mg for first 2 doses) (if > 75 years: 0.75 mg/kg SC bid; max 75 mg for first 2 doses)
- **GFR < 30 mL/min**: 1 mg/kg SC once daily
- **Duration**: until discharge from hospital (or for one week or until revascularization)

FONDAPARINUX: 2.5 mg IV bolus then 2.5 mg SC once daily until discharge from hospital (or for one week or until revascularization); avoid if CrCl < 30 mL/min

- ★ **OASIS-6:** Fondaparinux vs Heparin; ↘ mortality; ↘ MI recurrence rate

UNFRACTIONATED HEPARIN: 60 IU/kg (max 4000 IU) then IV infusion for 48 h (or until revascularization) with target aPTT of 50-70 s (12 IU/kg/h; max 1000 IU/h)

EARLY PHARMACOINVASIVE STRATEGY: **immediate transfer post-thrombolysis** for coronary angiography ± revascularization within 3 to 24 h

- ★ **TRANSFER-AMI and ★ CARESS-in-AMI**: ↘ **recurrent ischemic events** +

RESCUE PCI: ★ REACT → ↘ recurrent MI; ↘ heart failure

- **Particularly beneficial if significant ischemic territory** (anterior MI; inferior infarction with RV involvement or with ST depression in V1-V3)

INTRACRANIAL HEMORRHAGE

a) Stop all agents potentially responsible
b) Brain imaging + Neurology / Neurosurgery consultation
c) 10 units of cryoprecipitate (fibrinogen and fVIII) + 2 units of FFP (fV and fVIII) + Protamine (1 mg for every 100 units of heparin over the last 4 hours) + Platelet transfusion (6-8 units)
d) ↘ Intracranial pressure (hyperventilation; Mannitol; head of bed to 30°; surgery)

2.6/ ACUTE CORONARY SYNDROME: ADJUVANT TREATMENTS

NITRATES: **venodilator** (↘ preload); **coronary vasodilator** (↗ perfusion); **arterial vasodilator** (↘ afterload)

- **Indications**: **A)** Ischemia / Recurrent angina; **B)** Significant HTN; **C)** Heart failure
- **Doses**: 0.4 mg sublingual every 5 min x 3 then IV infusion PRN (5-10 µg/min IV; increase by 10 µg/min every 5 min PRN up to a dose of 200 µg/min)
- **Contraindications**: SBP < 90 mmHg; HR < 50 bpm; HR > 100 bpm in the absence of heart failure; RV infarction; PDE-5 inhibitor (24 h for Sildenafil; 48 h for Tadalafil)

BETA-BLOCKERS: negative inotropic / negative chronotropic agent; ↘ O_2 demand

- ★ **MIAMI - ★ ISIS-1 - ★ COMMIT** → ↘ mortality; ↘ recurrent ischemic events; ↘ VF
- **Start orally within 24 h of presentation**
- **Contraindications**: Signs of heart failure; Low output state; Risk of cardiogenic shock (> 70 years; SBP < 120 mmHg; Sinus tachycardia > 110 bpm; HR < 60 bpm; Late presentation); PR > 0.24 s; 2nd or 3rd degree AV block; Active asthma
  - **Avoid BB with ISA**
  - **Short-acting BB:** IV Esmolol
  - **Verapamil or Diltiazem** as an alternative in the absence of contraindications and LV dysfunction

AGENT	INDICATION	DURATION	CAUTION
ASA	• All patients with ACS (★ Antithrombotic Trialists' Collaboration)	**Long term**	ASA allergy Peptic ulcer
Clopidogrel (75 mg qd)	• Post-ACS (without Ticagrelor or Prasugrel) (★CURE)	• 1 year if DES • Up to 1 year if BMS or medical treatment • BMS: minimum 2-4 weeks	Clopidogrel allergy
Ticagrelor (90 mg bid)	• Post-ACS (without Clopidogrel or Prasugrel) (★PLATO) • Consider > 1 year post MI in high-risk patients (★PEGASUS)	• 1 year if DES • Up to 1 year if BMS or medical treatment	Dyspnea Ventricular pauses
Prasugrel (10 mg qd)	• Post-ACS (without Clopidogrel or Ticagrelor) (★TRITON-TIMI 38)	• 1 year if DES • Up to 1 year if BMS	Avoid if weight < 60 kg or > 75 years or history of stroke - TIA
ACE inhibitor	• All patients with CAD (± HTN or DM or CRF) (★HOPE; ★EUROPA) • Post-ACS with LVEF < 40% or heart failure (★TRACE; ★SAVE; ★AIRE)	**Start within 24 h of presentation** **Long term**	ARF; Hyperkalemia; Cough; Angioedema Contraindicated if SBP < 100 mmHg
ARB (Valsartan or Candesartan)	• Intolerance of ACE inhibitors with LVEF < 40% or heart failure (★VALIANT; ★CHARM-Alternative)	Long term	ARF; Hyperkalemia; Hypotension
Beta-blockers	• All patients post-myocardial infarction (★ Freemantle meta-analysis) • Post-ACS with LVEF < 40% (★ CAPRICORN) • Residual coronary stenosis (anti-anginal)	• **Long term** if LV dysfunction or as antianginal • **Otherwise**: ≥ 3 years • **Target HR 50-60 bpm; use BB without ISA**	Active heart failure AV block Asthma
Statines	• All patients with ACS (★PROVE IT-TIMI 22)	• **Long term** • **High–dose statin**	Myopathy Myositis Transaminase
Eplerenone (25 mg then 50 mg qd)	• ACS with LVEF < 40% (with heart failure or DM) (★EPHESUS)	Long term	Hyperkalemia > 5 mmol/L GFR < 30 mL/min
TNT (Nitropuff)	• All patients with coronary disease	Long term	Avoid if hypotension or PDE-5 inhibitor
Warfarin	• LV thrombus • Significant LV dysfunction with extensive regional wall motion abnormalities or LV aneurysm (class IIb recommendation)	**3 months then reevaluate** Long term if mobile / pedunculated thrombus	**Target INR 2-2.5** in the presence of dual antiplatelet therapy Add PPI

GLYCEMIC CONTROL: target blood glucose **< 10 mmol/L (180 mg/dL)** (★DIGAMI); avoid hypoglycemia (★NICE-SUGAR) +

PPI (PREFER PANTOPRAZOLE): patient on dual antiplatelet therapy with ≥ 1 risk factor:
A) History of upper GI bleeding / ulcer; **B)** > 60 years; **C)** Anticoagulant or Corticosteroids or NSAID; **D)** *H. pylori* - positive

ANEMIA: target hemoglobin > 70-80 g/L +

AVOID NSAID

› **If unavoidable** (despite Acetaminophen; ASA; Narcotics) → **prefer nonselective NSAID** (Naproxen; Ibuprofen) +

AVOID HORMONE THERAPY

STRESS TEST BEFORE DISCHARGE FROM HOSPITAL

› No angina / Heart failure / Arrhythmia for 48-72 h
› **Submaximal stress test (3-5 days)**: stop if HR ≥ 120 bpm or ≥ 70% of predicted HRmax or ≥ 5 METs or Angina or Dyspnea or ↘ ST 2 mm or Hypotension or ≥ 3 consecutive PVCs
› **Stress test limited by symptoms (3 weeks):** not guided by HR or METs

MANAGEMENT ON DISCHARGE FROM HOSPITAL

MANAGEMENT OF RISK FACTORS: ▸▸| Chapter 9

ADMISSION TO CARDIAC REHABILITATION CENTER

SMOKING CESSATION

CONTROL OF LIPIDS

› **Lipid profile** on day 1 of ACS (↘ TC and ↘ HDL within 24-48 h of ACS)
› **Target**: High-dose statin; **target ↘ > 50% LDL** +

BP CONTROL: < 140/90 mmHg (< 140/85 mmHg in the presence of DM) +

DM CONTROL: **HbA1c < 7 %** +

WEIGHT: **BMI: 18.5-24.9 kg/m2; waist < 102 cm (M) and < 88 cm (F)** +

BALANCED DIET

PHYSICAL ACTIVITY: **30 minutes of moderate exercise (rapid walking) 5 times a week** +

› Pre-training stress test if necessary depending on risk factors

INFLUENZA VACCINE annually

TREAT DEPRESSION post-IM

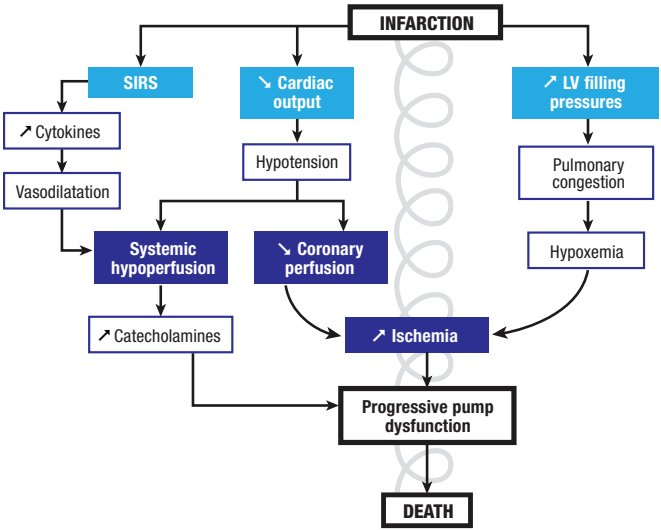
SICK LEAVE: determined case by case; 2 weeks to 10 weeks

SEXUAL ACTIVITY: resume after 7-10 days (equivalent to one flight of stairs)

PLANE TRAVEL: ▸▸| Chapter 9

2.7/ COMPLICATIONS OF MYOCARDIAL INFARCTION

CARDIOGENIC SHOCK



↘ Cardiac output with inadequate tissue perfusion (despite sufficient filling pressures)

HEMODYNAMIC PARAMETERS

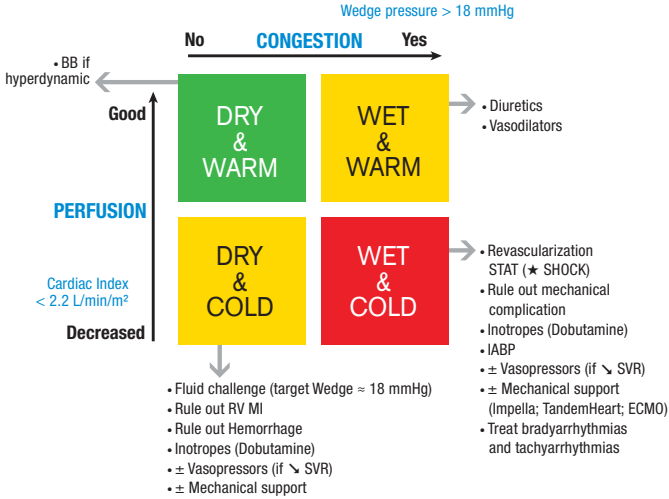
- Hypotension (SBP < 90 mmHg)
- Systemic hypoperfusion (cold extremities; altered level of consciousness; ↘ urinary output; SVO_2 < 70 %)
- ↘ Cardiac Index (< 2.2 L/min/m²)
- ↗ Filling pressures (Wedge pressure > 18 mmHg)

ETIOLOGIES: **Extensive infarction; Mechanical complication; RV infarction**

- **DDx:** Hemorrhage; Pulmonary embolism; Tamponade; Sepsis; Myocarditis; Takotsubo; HCM; Endocarditis; Aortic dissection

MANAGEMENT

- ★ **SHOCK:** **↘ mortality with early revascularization (< 75 years)**

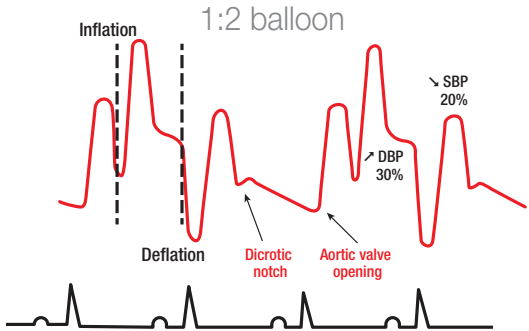


INTRA-AORTIC BALLOON PUMP

INDICATIONS: A) Cardiogenic shock; **B)** Refractory ischemia; **C)** Mechanical complication of MI; **D)** Support during a procedure at high risk of hemodynamic instability

MECHANISM: Inflation in diastole immediately after closure of the aortic valve (↗ **coronary perfusion);** deflation at systole just before opening of the aortic valve **(suction effect; ↘ afterload)**

- Increases cardiac output ≈ **10-15 %**
- Monitored by ECG and BP monitor
- ★ IABP-SHOCK II study: no benefit



CXR POSITION: tip of the catheter **at the level of the carina** (> 4 cm below the aortic knob) +

CONTRAINDICATIONS: Moderate to severe AR; Aortic dissection; Significant abdominal aortic aneurysm; severe PAD; Uncontrolled sepsis

COMPLICATIONS: Aortic lesion / perforation; Bleeding at site of introduction; Ischemia distal to introducer (target the common femoral artery during introduction); Thrombocytopenia; Hemolysis; Atheroembolism; Renal ischemia; Cerebral ischemia in the case of proximal migration of the balloon; Infection

RIGHT VENTRICULAR INFARCTION

RV very resistant to ischemia (thin myocardium)

› **Excellent recovery of RV function post-MI**

CLINICAL FEATURES: Shock; ↗ CVP (↗ Y descent; mimics constrictive pericarditis); Kussmaul sign; Pulsus paradoxus; Clear lungs

HEMODYNAMIC PARAMETERS: Hypotension; ↗ RA pressure / ↗ RVEDP; ↘ RV systolic pressure; ↘ Wedge pressure; ↘ Cardiac index

ECG: **ST elevation > 0.5-1 mm V3R and/or V4R** (in the context of infarction of the inferior wall of the LV); ± ST elevation in V1-V2 +

DDX: Pulmonary embolism **(absence of RWMA in inferior wall of LV)** +

COMPLICATIONS: R → L shunt (via PFO); Shock; Pulmonary embolism; Arrhythmia; AV block; Death

MANAGEMENT: **1)** Avoid TNT; **2)** Reperfusion; **3)** Bolus of normal saline to maintain adequate RV preload (attention to interdependence with LV; **avoid RVEDP > 15 mmHg)**; **4)** Target Wedge pressure 15-18 mmHg; **5)** Inotropes (Dobutamine); **6)** Decrease RV afterload (avoid hypoxia; minimize PEEP; NO); **7)** Maintain AV synchrony (to ensure good filling of the ischemic RV and to increase RV output); **8)** IABP; RVAD; Impella; Creation of an ASD when necessary +

LEFT VENTRICULAR FREE WALL RUPTURE

One to 14 days post-transmural infarction

› **Secondary to extension of the infarction**: thinning and dilatation of the necrotic zone
› Often anterior or lateral LV wall

PRESENTATION: Pleuritic pain; Hypotension; Shock; Sudden death (pulseless electrical activity)

CLINICAL FEATURES: JVD; Pulsus paradoxus; Shock

TTE: signs of tamponade; look for the site of rupture

LEFT VENTRICULAR PSEUDOANEURYSM

Ventricular rupture contained by the pericardium and by thrombus / organized hematoma

Narrow neck (<< diameter of the pseudoaneurysm)

High risk of rupture and hemopericardium

LEFT VENTRICULAR ANEURYSM

Thinning of myocardium (but no rupture, in contrast with pseudoaneurysm)

Dyskinesia with paradoxical systolic expansion (alters the geometry and efficacy of contraction; ↗ wall stress)

Large neck (≥ 0.5 x diameter of the aneurysm)

Low risk of rupture

ECG: persistent ST elevation

COMPLICATIONS: Embolism; Arrhythmia; Heart failure; Angina

INTRAVENTRICULAR THROMBUS

↗ RISK OF EMBOLIZATION: Mobile; Protrusion into the ventricle; Visualized on several sections; Contiguous zones of akinesia and hyperkinesia

MANAGEMENT: Anticoagulant therapy for 3-6 months then re-evaluate

VENTRICULAR SEPTAL RUPTURE

SITE

- **Anterior infarction** → apical interventricular septum
- **Inferior infarction** → inferobasal interventricular septum (less favorable prognosis)

PRESENTATION: Hypotension - Shock; Acute pulmonary edema; R and L heart failure; Blocks

CLINICAL FEATURES: Shock; **Prominent holosystolic murmur ± thrill; S3;** Pulmonary edema; Signs of right heart failure

TTE: L→R shunt; RV insufficiency

CARDIAC CATHETERIZATION: O_2 step-up between RA and RV; Prominent V wave +

TREATMENT: Nitroprusside; IABP; Inotropes; Surgery vs percutaneous closure

PAPILLARY MUSCLE RUPTURE

Posteromedial papillary muscle (inferior infarction; supplied by PDA) >> anterolateral papillary muscle (double blood supply by LAD and circumflex) +

PRESENTATION: Hypotension; Shock; Acute pulmonary edema; **Systolic murmur, often minor** (early systolic equalization of transvalvular pressures) +

TTE (± TEE): Rupture of a papillary muscle or chorda tendineae; Leaflet eversion; Severe MR on Doppler; Hyperdynamic LV; PHT

CARDIAC CATHETERIZATION: Prominent V wave; ↗ PAP (± contaminated by V wave) +

TREATMENT: Nitroprusside; IABP; Inotropes; Mechanical ventilation; Urgent surgery

PERICARDITIS

EARLY: pericardial extension of transmural MI

- **Presentation:** Pleuritic pain radiating to the trapezius; **Pericardial friction rub**; **Localized ECG changes** +
- **Management:** Caution with anticoagulants (risk of hemorrhagic pericarditis; monitor by TTE); ASA 650 mg PO every 4-6 h; Colchicine

LATE (> 7 DAYS): Dressler's syndrome; Immune phenomenon

ARRHYTHMIAS AND BLOCKS

PVC: BB; Correct electrolyte disorders; No benefit of AAD (★ CAST; ★ SWORD)

MONOMORPHIC VT: Correct electrolyte disorders; BB; AAD; ECV; **ICD if > 48 h (probable permanent arrhythmogenic substrate)**

POLYMORPHIC VT: **Rule out ischemia**; Rule out ↗ QT; BB; Correct electrolyte disorders

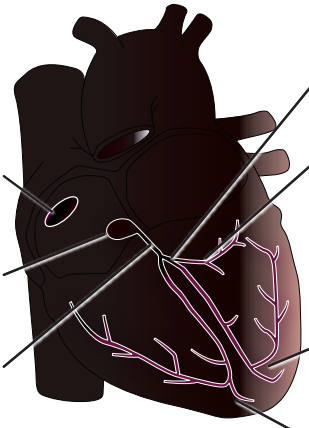
VF: Rule out ischemia; BB; AAD (Lidocaine; Amiodarone); ICD if > 48 h

AIVR: Ventricular rhythm 60-100 bpm; **Specific marker of reperfusion; Observation**; ↗ Sinus rhythm PRN (Atropine; Atrial pacing)

SINUS BRADYCARDIA: often associated with inferior STEMI (**Bezold-Jarish reflex**); Atropine; Atrial pacing

AV BLOCK AND INTRAVENTRICULAR BLOCKS

INFERIOR INFARCTION	ANTEROSEPTAL INFARCTION
RCA 90%; Circumflex 10%	**Proximal LAD (± septal branches)**
• Mechanism: ↗ **Vagal tone** (< 6h; Bezold-Jarish) and/or **AV node ischemia**	• Mechanism: **Extensive necrosis of the septum and conduction tissue** (His-Purkinje system)
Bradyarrhythmias • Sinus bradycardia • **Intranodal** AV block 1st degree AV block or 2nd degree Mobitz I AV block or sometimes 3rd degree intranodal AV block	**Bradyarrhythmias** • **Infranodal** AV block 2nd degree Mobitz II AV block or 3rd degree infranodal AV block • ↗ PR secondary to slowing of His-Purkinje conduction
• Progressive onset of AV block	• Sudden onset of AV block (< 24 h); often preceded by RBBB ± LAHB
• **Jonctional escape rhythm** (His); narrow QRS; 40-60 bpm	• **Escape rhythm distal to His bundle** • Wide QRS; unstable; risk of asystole
• **Often benign and transient (5-7 days)**	• **Often associated with extensive infarction**
• Atropine within the first 24 h (vagal hypertonia) • Permanent pacemaker rarely indicated (reversible conduction disorder)	**Temporary pacemaker** • 2nd degree Mobitz II or 3rd degree AV block • Alternating RBBB with LBBB • Acute bifascicular block or *de novo* LBBB • RBBB with ↗ PR **Permanent pacemaker** • 2nd degree intra- or infrahisian AV block with alternating branch block • 3rd degree intra- or infrahisian AV block • Persistent 2nd or 3rd degree AV block with symptoms • High-grade transient infranodal 2nd degree or 3rd degree AV block with associated branch block (except for isolated left anterior hemiblock)



2.8/ REVASCULARIZATION - PCI

SIGNIFICANT STENOSIS

ANGIOGRAPHIC	HEMODYNAMIC	IVUS (INTRAVASCULAR ULTRASOUND)
≥ 70% (LMCA: ≥ 50%)	FFR ≤ 0.80	• LMCA: Area < 6 mm² (6 to 7.5 mm² → determine FFR) • Other vessels: Area < 4 mm²

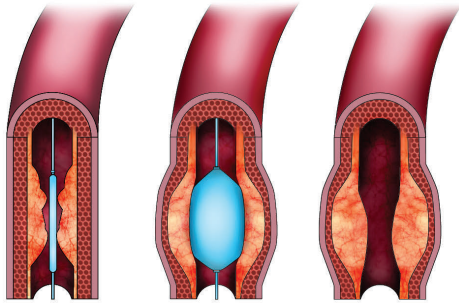
TECHNIQUES

BALLOON ANGIOPLASTY (PTCA): **stretches / tears / redistributes the atherosclerotic plaque in order to enlarge the coronary lumen;** risk of dissection or abrupt closure; risk of restenosis

STENT: treats the dissection associated with PTCA and ↘ the risk of abrupt closure; ↘ risk urgent CABG; ↘ restenosis

- **One-year clinical restenosis rate**: **PTCA 30%; BMS 10-15%; DES 3-5%**
  - **Clinical restenosis**: during the **first 6-9 months** post-PCI
- **DES**: ↘ restenosis and ↘ reintervention; ↗ very late stent thrombosis (> 1 year) (risk markedly decreased with new generation DES)
  - **New generation DES:** thin-strut platform; limus-based antiprolferative drug; polymer with improved biocompatibility; improved safety compared to early-generation DES; should be considered by default in all clinical conditions and lesion subsets

BALLOON ANGIOPLASTY



PREFER DES	CONSIDER BMS
• LMCA • Small vessels (< 2.5 mm diameter) • Long lesion (> 20 mm) • DM • In-stent restenosis • Bifurcation • Vein graft • Chronic total occlusion	• Dual antiplatelet therapy for 3-6 months impossible • Probable surgery < 6 months • Bleeding risk • Anticoagulation (Warfarin or DOAC) required

FFR (Fractional flow reserve): **to determine whether an intermediate stenosis (50-70%) is hemodynamically significant**

› **Quantify the trans-stenotic pressure gradient**

› ★ **FAME**: angioplasty guided by fractional flow reserve (FFR) determination **associated with improvement of primary outcome** (death; MI; reintervention)

IVUS (Intravascular ultrasound): **A)** Determines the severity of a stenosis on the LMCA; **B)** Determines the mechanism of stent restenosis or thrombosis; **C)** Guidance during complex PCI; **D)** Follow-up of cardiac allograft vasculopathy

MANUAL ASPIRATION THROMBECTOMY: aspiration of intra-coronary thrombus; ↘ distal embolism (no benefit in ★ TASTE and ★ TOTAL)

ROTATIONAL ATHERECTOMY: Grinding of calcified atherosclerotic plaque; facilitates passage and deployment of the balloon and stent; risk of coronary perforation

SPECIFIC LESIONS

IN-STENT RESTENOSIS: DES implantation or drug-coated balloons; intracoronary imaging

CHRONIC TOTAL OCCLUSION (CTO): revascularization in the presence of significant viability and a significant ischemic territory

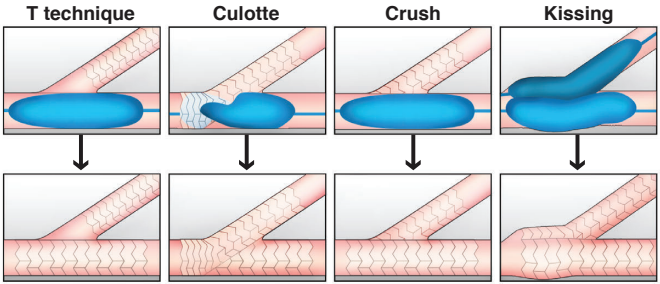
› **Percutaneous revascularization**: complex technique via an anterograde approach (± subintimal dissection and re-entry) and/or retrograde approach (via collateral pathways)

PCI ON VEIN GRAFT: ↗ risk of periprocedural MI and no-reflow (atheroembolism); use an embolic protection device

BIFURCATION: 2 strategies

a) PCI with stent in the main vessel only (angioplasty and/or stent in the branch if necessary) (★ Nordic-Baltic Study IV and ★ TRYTON)

b) PCI with stenting of both vessels (especially if complex bifurcation with large branch and significant risk of occlusion); terminate the operation with simultaneous inflation of a balloon in each vessel ("kissing")



LEFT MAIN CORONARY ARTERY: percutaneous revascularization possible if low risk of procedural complications (proximal LMCA; SYNTAX ≤ 32) or high surgical risk

COMPLICATIONS OF PCI

RISK OF COMPLICATIONS DURING PCI ACCORDING TO THE TYPE OF LESION

TYPE I: Low risk	1. Patent Lesion 2. Does not meet the criteria for a type C lesion
TYPE II	1. Patent Lesion 2. Meets one of the criteria of a type C lesion › Diffuse lesion (> 20 mm long) › Severe proximal tortuosities › Extreme angle (> 90°) › Impossible to protect a major branch › Vein graft with friable lesions
TYPE III	• Occluded lesion • Does not meet the criteria for a type C lesion
TYPE IV: High risk	• Occluded lesion • Meets one of the criteria of a type C lesion

COMPLICATIONS: Death (0.7% elective PCI); MI; Stroke (0.2%); TIA; Vascular access site complication; Coronary perforation (± tamponade); Coronary dissection (abrupt closure); No-reflow (↘ anterograde flow in the absence of epicardial stenosis secondary to distal microembolism / vasospasm / endothelial dysfunction; management with Adenosine or intracoronary Verapamil or GPIIb/IIIa inhibitors); Branch occlusion; Urgent CABG (0.4%); ARF; Hemorrhage

› **Femoral or radial access complications**: ▶▶| Chapter 1 - Coronary angiography

› **Post-coronary angiography ARF**: ▶▶| Chapter 1 - Coronary angiography

EARLY CHEST PAIN POST-PCI: Stent thrombosis; Residual dissection / Abrupt closure; No reflow; Distal embolism; Branch occlusion

STENT THROMBOSIS: 1% at 1 year; Mortality 20-45%

- **BMS**: **during first 30 days** (rare after 30 days due to complete neo-endothelialization)
- **DES**: **can occur after 1 year** (very late thrombosis due to incomplete neo-endothelialization); decreased risk with new generation DES
- **Risk factors:** acute myocardial infarction; Nonadherence with P2Y12 inhibitor; Resistance to Clopidogrel; DM; Long segment; Small vessels (diameter < 2.5 mm); Bifurcation; Incomplete stent apposition; Dissection at the stent margin; Overlapping stents
- **Treatment:** emergency PCI; Prasugrel or Ticagrelor; IVUS or OCT to detect mechanical problems

ADJUVANT TREATMENT - ELECTIVE PCI

▶▶| Chapter 1 - Coronary angiography

ASA: 325 mg then 80 mg qd (long term)

CLOPIDOGREL: 600 mg loading dose for elective stenting (★ ARMYDA-2) **then 75 mg qd**

- **BMS with bleeding risk**: Clopidogrel for a **minimum of 2-4 weeks**
- **DES**: dual antiplatelet therapy for a minimum of **6 months** (★ ISAR-SAFE)
  - Strict minimum of 3-6 months with new generation DES
  - ★ **DAPT**: 30 months of DAPT (vs 12 months) associated with ↘ stent thrombosis and MACCE but ↗ moderate or severe bleeding
  - **Prolonged dual antiplatelet therapy**: consider in the presence of a high risk of stent thrombosis (according to anatomy / procedure) or if late stent thrombosis would have major consequences (LMCA; bifurcation; ostium...)

GPIIB/IIIA INHIBITORS: at the interventional cardiologist's discretion

UNFRACTIONATED HEPARIN: **A)** Procedure without GPIIb/IIIa inhibitors: 70-100 U/kg targeting ACT 250-300 s (HemoTec) or 300-350 s (Hemochron); **B)** Procedure with GPIIb/IIIa inhibitors: 50-70 IU/kg targeting ACT 200-250 s

STATIN PRE-PCI ↘ risk of periprocedural MI (★ ARMYDA; ★ NAPLES II)

2.9/ REVASCULARIZATION - SURGERY

ASSESSMENT OF PERIOPERATIVE RISK

STS SCORE: in-hospital or 30-day mortality, and in-hospital morbidity / http://riskcalc.sts.org

EUROSCORE II: in-hospital mortality / www.euroscore.org

ADJUVANT TREATMENT

ASA: for all patients (to protect graft patency)

P2Y12 INHIBITORS: Stop Clopidogrel and Ticagrelor > 5 days pre-op; Stop Prasugrel > 7 days preop

GPIIB/IIIA INHIBITORS: Stop Eptifibatide / Tirofiban 2-4 h pre-op; Stop Abciximab > 12 h pre-op

STATIN: for all patients

ACE INHIBITORS: for all patients (start postoperatively when hemodynamic stability is achieved)

BB: **> 24h pre-op** (in the absence of contraindication) to prevent perioperative AF (continue post-op)

GLYCEMIC CONTROL: target perioperative blood glucose **< 10 mmol/L**

ASSESSMENT OF CAROTID ARTERIES

CAROTID DOPPLER IN HIGH-RISK PATIENTS: > 65 years; LMCA; PAD; History of TIA - stroke; HTN; Smoking; DM

INDICATIONS FOR PRE-CABG REVASCULARIZATION (angioplasty / stent or endarterectomy)

a) History of TIA or stroke with 50-99% stenosis (class IIa recommendation)
b) Severe bilateral stenoses (70-99%) or severe unilateral stenosis (70-99%) with contralateral occlusion (class IIb recommendation)
- › Note: diverging indications according to the various guidelines
- › Assessment on an individual basis by a multidisciplinary team including a neurologist

COMPLICATIONS

COMPLICATIONS: Death; Stroke (micro- or macroembolism; hypoperfusion); Cardiogenic shock; Tamponade (often localized over the RA); post-CPB cognitive deficits; ARF; post-CPB SIRS; Hemorrhage; Re-exploration; Prolonged mechanical ventilation; Sternal osteomyelitis / Mediastinitis; Perioperative myocardial infarction; AF; Pulmonary complications (ARDS; Pneumonia; Atelectasis; Phrenic nerve palsy); Intestinal ischemia

MEDIASTINITIS / STERNAL INFECTION

- › **Risk factors**: DM; Obesity; COPD; Prolonged CPB; REDO; Prolonged intubation; Repeat surgical exploration
- › **Management:** Antibiotics; Surgical debridement; Reconstruction (pectoralis muscle flap); VAC; Sternal plate

VEIN GRAFT: Early occlusion rate (before discharge from hospital): 10%; 1-year occlusion rate: 25%; **10-year occlusion rate: 50%** +

- › **Arterial bypass graft**: **10-year patency rate > 90%** +

POSTOPERATIVE ATRIAL FIBRILLATION

0-5 days post-op; Frequently resolves spontaneously in 6-12 weeks

PROPHYLAXIS: BB (1st choice); Amiodarone if BB contraindicated (400 mg PO bid x 6 days preop and 6 days post-op) +

- › **Other options**: Sotalol; IV magnesium (1.5 g IV daily for 4 days post-op); Atrial overdrive; Colchicine (★ COPPS-POAF)

MANAGEMENT: rate control or rhythm control according to symptoms; anticoagulation if **AF > 48 h**; review treatment at 12 weeks +

MINIMALLY INVASIVE SURGERY

BEATING HEART (OFF-PUMP): requires sternotomy with cardiac stabilization device; theoretically avoids the disadvantages of CPB and clamping of the ascending aorta

- › **No demonstrated benefit** to date (★ ROOBY, ★ GOPCABE, ★ CORONARY)

MIDCAB: left anterior mini-thoracotomy; beating heart internal mammary artery bypass graft to LAD; ventilation of only one lung

- › **Hybrid procedure:** LIMA to LAD; PCI of other vessels; avoids sternotomy and clamping of the aorta

ROBOTIC TOTAL ENDOSCOPIC BYPASS GRAFT: with femoro-femoral CPB

2.10/ PRINZMETAL ANGINA (VASOSPASTIC ANGINA)

Severe angina at rest with transient ST elevation

- Worse between midnight and 8:00 am
- **Risk factors**: Smoking; Migraine; Raynaud; 5-fluorouracil; Cyclophosphamide; Hyperventilation; Cold

COMPLICATIONS: MI; VT; VF; AV block; Asystole; Sudden death

STRESS TEST: 1/3 negative; 1/3 with ST elevation; 1/3 with ST depression

CORONARY ANGIOGRAPHY: Coronary spasm; RCA > LAD; Multiple spontaneous spasms on multiples vessels possible

- **Provocation test rarely performed**
  - **Ergonovine provocation test**: 0.05 to 0.2 mg IV
  - **Acetylcholine provocation test**: 10-25-50-100 µg intracoronary; focal spasm during Prinzmetal angina

MANAGEMENT: Smoking cessation; CCB (combination of dihydropyridine and nondihydropyridine PRN); Nitrates; Prazosin (alpha-blocking agent) and Nicorandil if necessary; Avoid nonselective BB (risk of unopposed alpha stimulation); Avoid ASA (inhibits prostacyclin synthesis); PCI if associated stenosis; Mg^{2+} supplement; Statins may be beneficial; Defibrillator for secondary prevention (especially if ischemia persists despite treatment)

2.11/ CARDIAC SYNDROME X

More or less typical retrosternal chest pain with ischemia documented on noninvasive test (ST depression and/or perfusion abnormality) in the absence of any significant epicardial CAD

Associated with increased CARDIOVASCULAR RISK

MECHANISM: **probable microvascular endothelial dysfunction with decreased vasodilatation reserve;** ± hypersensitivity to pain

- **40-50% of the resistance to coronary flow is derived from the microvasculature**; an insufficient vasodilatation reserve decreases coronary perfusion on exertion

MANAGEMENT: ACE inhibitors and Statins (improve endothelial dysfunction); Nitrates; BB; CCB; Treatment of risk factors; Regular exercise

- **Persistent retrosternal chest pain**: Nicorandil; Imipramine or Amitriptyline; Aminophylline; Neurostimulation (spinal cord); External counterpulsation; Psycho-intervention...

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Heart failure 03

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3.1/ HEART FAILURE: ASSESSMENT

DEFINITION: Complex clinical syndrome secondary to a functional or structural abnormality of the heart which impairs the capacity of the ventricle to eject blood (and perfuse tissues) or to be adequately filled

› **This clinical syndrome leads to typical symptoms and signs**

SYSTOLIC HEART FAILURE	HEART FAILURE WITH PRESERVED LVEF
1. Typical symptoms **2. Typical signs** **3. ↘ LVEF**	1. Typical symptoms 2. Typical signs 3. Normal or slightly decreased LVEF; non-dilated LV 4. Structural heart disease (LVH; LAH) and/or diastolic dysfunction

LVEF = stroke volume (end-diastolic volume – end-systolic volume) / end-diastolic volume

› **When LVEF is decreased: stroke volume is maintained by increasing end-diastolic volume** (eccentric LVH)

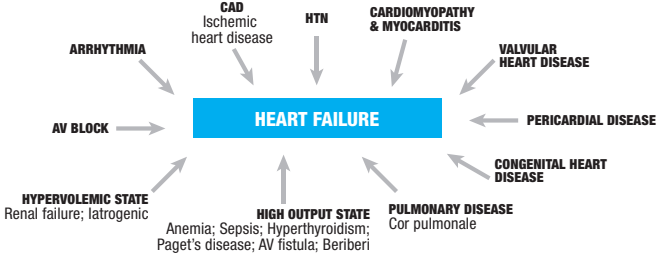
SYMPTOMS	SIGNS
• Dyspnea • **Orthopnea** • **PND** (1-2 h after going to bed; resolution in 15-30 min) • **↘ Exercise tolerance** • Tiredness • Lower limb edema • **Peripheral edema** • **Nocturnal cough** • Wheezing • Weight gain • Loss of appetite • RUQ pain • Nocturia	• Cachexia • Hypotension; OH; Narrow pulse pressure • Pulsus alternans; ↘ Pulse amplitude • **Tachycardia** • Tachypnea • Cheyne-Stokes breathing • **JVD** ; HJ reflux • Lateralized and widened apex • Left parasternal heave / Signs of PHT • Decreased S1 • **S3** - S4 (± palpable) • AV valve regurgitation • **Crackles** • Wheezing • **Signs of pleural effusion** • **Hepatomegaly (± pulsatile)** • **Peripheral edema** (leg edema; scrotum; presacral; ascites) • Cold extremities • Confusion / Decreased level of consciousness

NYHA FUNCTIONAL CLASS

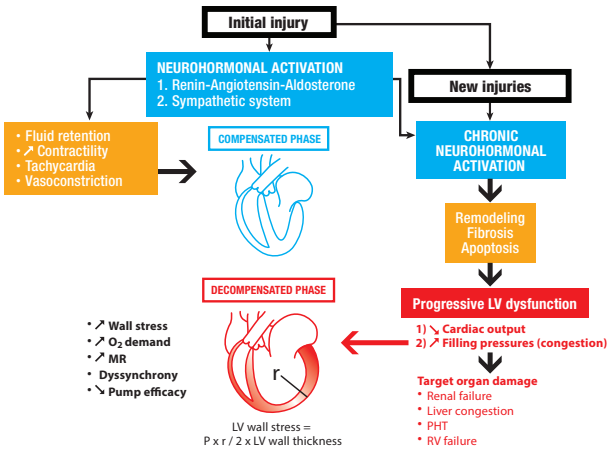
NYHA I	No limitation in ordinary physical activity (no tiredness, dyspnea or palpitations)	**≥ 7 METs** • Climbing one flight of stairs with a bag of groceries • Shoveling snow • Bicycling; Skiing; Jogging/walking (8 kph)

NYHA II	Slight limitation during physical activity; ordinary physical activity causes symptoms (tiredness, dyspnea, palpitations)	**5-7 METs** • Climbing one flight of stairs without stopping • Walking briskly on level ground (6.5 kph) • Gardening; Dancing
NYHA III	Marked limitation during physical activity; comfortable at rest; less than ordinary activity causes symptoms (tiredness, dyspnea, palpitations)	**2-5 METs** • Showering without a break • Getting dressed without a break • Walking briskly on level ground (4 kph) • Making a bed • Bowling; Golf
NYHA IV	Inability to carry on any physical activity without discomfort ± symptoms at rest	**< 2 METs** • Unable to perform the activities of NYHA III

ETIOLOGIES



PATHOPHYSIOLOGY



ASSESSMENT

WORK-UP: CBC; Electrolytes (including Ca^{2+}/Mg^{2+}); Creatinine - BUN; LFTs; Blood glucose; HbA1c; TSH; Urinalysis; Lipids

› **If necessary**: CK; Iron assessment; HIV; ANA; RF; Urine metanephrines; SPEP - UPEP; Uric acid; CRP; Troponin; Polysomnography

ECG: Sinus tachycardia; arrhythmia (AF; PVCs; NSVT); Conduction disorder / LBBB; LVH; LAH; Q waves; ischemia; low voltage QRS

› **AV block**: Drug-induced; myocardial infarction; myocarditis; sarcoidosis; familial cardiomyopathy (LMNA; SCN5A); Lyme disease

CXR: prominent hila; Kerley B lines (fine horizontal linear opacities extending to the pleura); peribronchial edema; interstitial / alveolar edema; redistribution to apices; pleural effusion; fluid in the fissure; cardiomegaly; other cause of dyspnea

TTE (± CONTRAST): chamber dimensions; LVH; systolic and diastolic function; LVEF (Simpson); valves; PAP; thrombus; cardiac output (LVOT VTI)

RADIONUCLIDE VENTRICULOGRAPHY: LVEF; RVEF

CARDIAC MRI: cardiac structure and function; LVEF; tissue characterization; evaluation of cardiomyopathy / myocarditis

CORONARY ANGIOGRAPHY (± FFR): rule out significant CAD

› **Noninvasive evaluation** (MIBI-P; stress echocardiography; coronary CT angiography) possible if few risk factors / low pre-test probability / low impact of the result on management

STRESS TEST / 6MWT / VO_2MAX: **A)** Objective evaluation of functional class; **B)** Rule out ischemia; **C)** Pre-transplant (VO_2max); **D)** Prescription of exercise; **E)** Prognosis; **F)** Distinguish cardiac from pulmonary cause

› **VO_2max < 12 mL O_2/kg/min** associated with poorer survival than in patients with a heart transplant +

› **6MWT**: normal > 600 m; < 350 m roughly equivalent to NYHA III

BIOPSY: ▸▸| Chapter 5

BNP: released by the failing heart or in response to hemodynamic stress; reflects wall stress and filling pressures

› Increases with age; decreases with obesity

› **DDx ↗**: CRF; arrhythmia; ACS; pulmonary embolism; severe COPD / PHT; sepsis; cirrhosis

› **Indications**: **A)** Identify the cause of dyspnea (cardiac versus non-cardiac); **B)** Prognosis

- BNP-guided management of heart failure remains controversial; studies report divergent results

ACUTE HEART FAILURE UNLIKELY	NT-proBNP < 300 pg/mL (NPV 98 %)	BNP < 100 pg/mL
PROBABLE ACUTE HEART FAILURE	NT-proBNP > 450 pg/mL (< 50 years) > 900 pg/mL (50-75 years) > 1800 pg/mL (> 75 years)	BNP > 500 pg/mL

› **Variation**: a change of > 30% in BNP level should call for more intesive follow-up / treatment

PROGNOSIS

SEATTLE HEART FAILURE MODEL: http://depts.washington.edu/shfm

HEART FAILURE SURVIVAL SCORE

PROGNOSTIC FACTORS: Demographics; Etiology; Comorbidities; NYHA; Hemodynamics (LVEF; PAP; Wedge; Cardiac index; Transpulmonary gradient); Exercise stress test (BP; 6MWT; VO_2max; Anaerobic threshold; Ve/VCO_2 slope > 35); Anemia; Hyponatremia; QRS duration; BNP; Troponin...

3.2/ SYSTOLIC HEART FAILURE: MANAGEMENT

OBJECTIVES

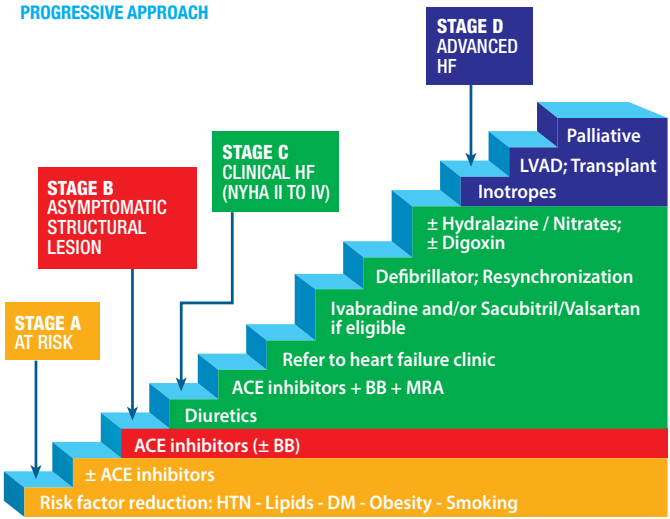
QUALITY OF LIFE

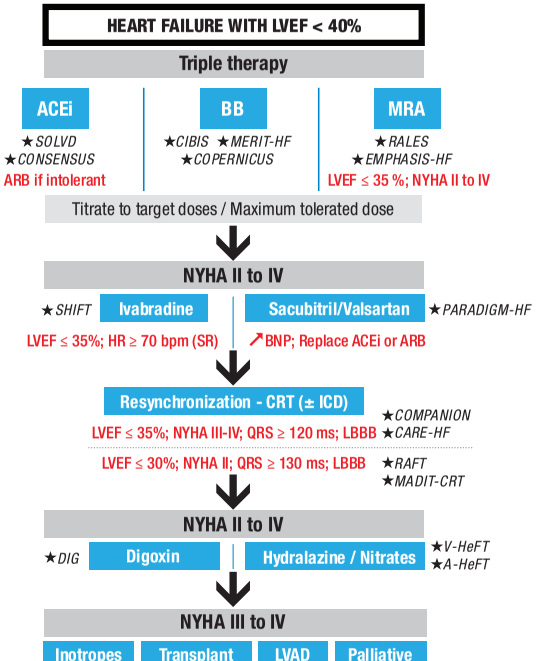
- ↓ Symptoms
- ↓ Hospitalizations
- Improve functional class
- Prevent disease progression

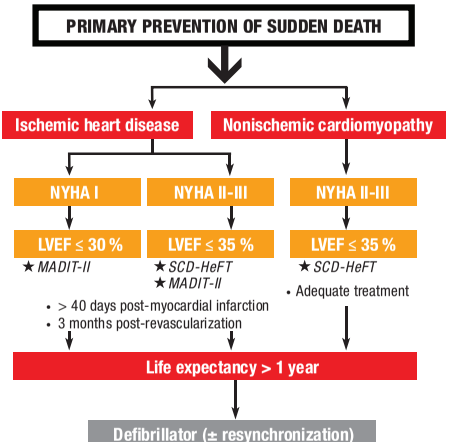
QUANTITY OF LIFE

- ↑ Survival

PROGRESSIVE APPROACH




HEART FAILURE WITH LVEF < 40%
Triple therapy
ACEi
★SOLVD
★CONSENSUS
ARB if intolerant
BB
★CIBIS ★MERIT-HF
★COPERNICUS
MRA
★RALES
★EMPHASIS-HF
LVEF ≤ 35 %; NYHA II to IV
Titrate to target doses / Maximum tolerated dose
NYHA II to IV
★SHIFT
Ivabradine
LVEF ≤ 35%; HR ≥ 70 bpm (SR)
Sacubitril/Valsartan
★PARADIGM-HF
↗BNP; Replace ACEi or ARB
Resynchronization - CRT (± ICD)
★COMPANION
LVEF ≤ 35%; NYHA III-IV; QRS ≥ 120 ms; LBBB ★CARE-HF
LVEF ≤ 30%; NYHA II; QRS ≥ 130 ms; LBBB ★RAFT
★MADIT-CRT
NYHA II to IV
★DIG
Digoxin
Hydralazine / Nitrates
★V-HeFT
★A-HeFT
NYHA III to IV
Inotropes
Transplant
LVAD
Palliative


PRIMARY PREVENTION OF SUDDEN DEATH
Ischemic heart disease
Nonischemic cardiomyopathy
NYHA I
NYHA II-III
NYHA II-III
LVEF ≤ 30 %
LVEF ≤ 35 %
LVEF ≤ 35 %
★MADIT-II
★SCD-HeFT
★MADIT-II
★SCD-HeFT
• > 40 days post-myocardial infarction
• 3 months post-revascularization
• Adequate treatment
Life expectancy > 1 year
Defibrillator (± resynchronization)

	INITIAL DOSE (mg)	TARGET DOSE (mg) (to be reached whenever possible)
ACE INHIBITORS - ANGIOTENSIN-CONVERTING ENZYME INHIBITORS		
Captopril	6.25 tid	50 tid
Enalapril	1.25 bid	10-20 bid
Lisinopril	2.5 qd	20-40 qd
Ramipril	1.25 bid	5 bid
Perindopril	2.5 qd (2 qd in Canada)	10 qd (8 qd in Canada)
Trandolapril	0.5 qd	4 qd
BB - BETA-BLOCKERS		
Bisoprolol	1.25 qd	10 qd
Carvedilol	3.125 bid	25-50 bid
Metoprolol succinate XL	12.5-25 qd	200 qd
ARB - ANGIOTENSIN RECEPTOR BLOCKERS		
Candesartan	4 qd	32 qd
Valsartan	20-40 bid	160 bid
NEPRILYSIN INHIBITOR		
Sacubitril / Valsartan	50 (24/26) - 100 (49/51) mg bid	200 (97/103) mg bid
I_F CHANNEL INHIBITOR		
Ivabradine	5 bid	7.5 bid
LOOP DIURETICS		
Furosemide	20-40 qd or bid (adjusted to renal function)	max 600 /24h
Bumetanide	0.5-1 qd or bid	max 10 /24h
MRA - MINERALOCORTICOID RECEPTOR ANTAGONISTS		
Spironolactone or Eplerenone	**Eplerenone** CrCl > **50 mL/min**: 25 mg qd; CrCl **30-49 mL/min**: 25 mg every 2 days **Spironolactone** CrCl > **50 mL/min**: 12.5 to 25 mg qd; CrCl **30-49 mL/min**: 12.5 mg qd or every 2 days	**Eplerenone** CrCl > **50 mL/min**: 50 mg qd; CrCl **30-49 mL/min**: 25 mg qd **Spironolactone** CrCl > 50 mL/min: 25 mg qd or bid; CrCl 30-49 mL/min: 12.5 to 25 mg qd
THIAZIDE DIURETICS		
Hydrochlorothiazide	25 qd ou bid	max 200 /24h
Metolazone	2.5-5 qd	max 20 /24h
Indapamide	2.5 qd	max 5 /24h
DIGOXIN		
Digoxin	0.125 **Adjusted to renal function** Total loading dose of 1 mg PO per 24 h in 4 doses divided on the 1st day when rapid effect is required; adjusted to renal function	Plasma target: **0.5 to 0.9 ng/mL** (1 week after titration)
HYDRALAZINE / NITRATES		
Hydralazine / Nitrates	Hydralazine: 10-25 tid Isosorbide dinitrate: 10 tid	Hydralazine: 75 tid Isosorbide dinitrate: 40 tid

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS

↘ Mortality; ↘ Hospitalization; Stabilizes remodeling; ↘ Symptoms

STUDIES: ★ CONSENSUS - ★ SOLVD; ★ SOLVD-Prevention (asymptomatic ↘ LVEF - NYHA I); ★ SAVE - ★ AIRE - ★ TRACE (myocardial infarction with heart failure and/or ↘ LVEF); ★ ATLAS (low-dose vs high-dose Lisinopril)

ADVERSE EFFECTS: ARF; hyperkalemia; hypotension; cough (secondary to ↗ bradykinins); angioedema

CONTRAINDICATIONS: angioedema; bilateral renal artery stenosis; pregnancy

› **Caution**: creatinine > 221 µmol/L (> 2.5 mg/dL) or GFR < 30 mL/min/1.73m^2; hyperkalemia > 5.5 mmol/L; SBP < 90 mmHg
  • **< 30% rise in creatinine** or elevation of **K+ up to 5.5 mmol/L** is acceptable +
› **Follow-up**: assessment 1 week after titration (creatinine; BUN; electrolytes)

BETA-BLOCKERS (BB)

↘ Mortality; ↘ Hospitalization; ↘ Remodeling; ↘ Symptoms

STUDIES: ★ CIBIS (Bisoprolol) - ★ COPERNICUS (Carvedilol) - ★ MERIT-HF (Metoprolol succinate XL); ★ SENIORS (Nebivolol; > 70 years); ★ COMET (Carvedilol vs Metoprolol tartrate); ★ B-CONVINCED (BB continued in the presence of decompensation); ★ CAPRICORN - ★ BEAT (post-myocardial infarction)

ADVERSE EFFECTS: decompensated heart failure; bronchospasm; bradycardia / block; hypotension; tiredness; depression; nightmares; erectile dysfunction; glucose intolerance

CONTRAINDICATIONS: **active decompensated heart failure** (continue BB if already used predecompensation); shock - hypoperfusion; asthma; 2nd or 3rd degree AV block; severe PAD (ischemia at rest) +

› **Treat congestion before initiating a BB; target euvolemia** +
› **Titrate the dose every 2 weeks**
› **Caution**: HR < 60 bpm; recent decompensation; NYHA IV; SBP < 90 mmHg
› **COPD**: favor beta-1 selective BB (Bisoprolol; Metoprolol)

MINERALOCORTICOID RECEPTOR ANTAGONISTS (MRA)

↘ Mortality; ↘ Hospitalization; ↘ Symptoms

STUDIES: ★ RALES (NYHA III-IV; LVEF < 35 %); ★ EMPHASIS-HF (NYHA II; LVEF < 30 % or < 35 % with QRS > 130 ms; Recent hospitalization or ↗ BNP); ★ EPHESUS (myocardial infarction; LVEF < 40%; heart failure or DM)

ADVERSE EFFECTS: hyperkalemia; ARF; gynecomastia - impotence - ↘ libido - menstrual irregularities (Spironolactone)

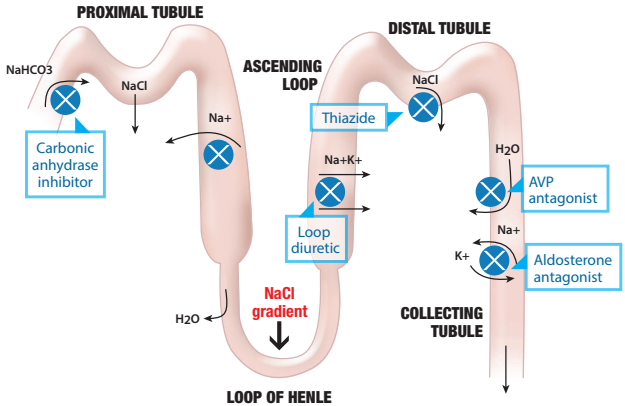
CONTRAINDICATIONS: CRF **(creatinine > 221 µmol/L in males or > 177 µmol/L in females or GFR < 30 mL/min); hyperkalemia > 5 mmol/L** +

› Titration every 4-8 weeks
› **Follow-up**: assessment 1 week and 4 weeks after titration; at 8 weeks - 12 weeks; at 6 - 9 - 12 months; then every 4 months

DIURETICS

↘ Symptoms

Target dry weight; target lowest possible dose



ADVERSE EFFECTS: ARF; hypovolemia; hypokalemia; hyponatremia (thiazides); hypomagnesemia; metabolic alkalosis; hyperuricemia; ototoxicity

CAUTION: CRF; hypokalemia; hypotension

› **Follow-up:** assessment 1 week after titration (creatinine; BUN; electrolytes; Mg^{2+})

› **Target K+ 4-5 mmol/L**

	SODIUM EXCRETION	DURATION OF ACTION	COMMENTS
Loop diuretics	25 %	4-8 h (furosemide)	• Inhibition of the ascending loop Na-K-2Cl pump • **Secreted into the proximal tubule** (this secretion depends on renal perfusion and the bioavailability of the drug) • **Dose–effect response** (a tubular concentration threshold must be reached to obtain an effect) • Venodilator effect
Thiazides	5-10 %	6-12 h (HCTZ) 12-24 h (Metolazone)	• Inhibition of the distal tubule Na-Cl pump • Less effective when GFR < 30 mL/min • ↘ **clearance of free water** (risk of hyponatremia); ↗ Ca^{2+} reabsorption
Mineralo–corticoid receptor antagonists	1-2 %	2-3 h	• Inhibition of the collecting tubule Na-K pump at the site of action of aldosterone • **Antagonism of the harmful effects of aldosterone on the heart**
Vasopressin antagonist	0 %	24 h	• Free water diuresis (aquaretic) • Action on collecting tubule (V2 receptors) • Useful in the presence of hyponatremia; no benefit in ★EVEREST

DIURETIC RESISTANCE

- **Mechanisms**: **A)** Post-sodium excretion stimulation of RAA / sympathetic systems (rebound sodium absorption); **B)** ↘ Drug absorption (edema of intestinal wall); **C)** ↘ Cardiac output (↘ renal perfusion therefore ↘ tubular secretion of the diuretic); **D)** Hypertrophy of distal tubule; **E)** ARF or cardiorenal syndrome
- **Management**
  - **a)** Strict water / NaCl restriction
  - **b)** Increase the dose of the loop diuretic or increase the frequency of administration
  - **c)** Addition of an mineralocorticoid receptor antagonist
  - **d)** Combination of loop diuretic and metolazone (temporary measure; daily assessments)
  - **e)** Continuous Lasix infusion (sustained sodium excretion):
    - 20-40 mg IV bolus then infusion 5-40 mg/h (400 mg/100 mL NS)
  - **f)** Inotropes: Dopamine (renal effect) or Dobutamine or Milrinone
  - **g)** Ultrafiltration: refractory patient (★UNLOAD: ↘ Hospitalization; no benefit in ★CARESS-HF); slow continuous veno-venous method

ANGIOTENSIN RECEPTOR BLOCKERS (ARB)

INDICATIONS: A) Intolerance to ACE inhibitors (cough; angioedema); **B)** In combination with ACE inhibitors if intolerant to mineralocorticoid receptor antagonists and persistent symptoms

STUDIES

- **Intolerance to ACE inhibitors**: ★ CHARM-Alternative (Candesartan); ↘ Cardiovascular mortality; ↘ Hospitalization
- **ARB combined with ACE inhibitors**: ★ Val-HeFT (Valsartan) - ★ CHARM-ADDED (Candesartan); ↘ Cardiovascular mortality (Candesartan); ↘ Hospitalization; ↘ Symptoms
- **Post-myocardial infarction** (with heart failure and/or ↘ LVEF): ★ VALIANT (Valsartan vs Captopril vs Combinaison) → Valsartan non-inferior to Captopril

NEPRILYSIN INHIBITOR

↗ Active natriuretic peptides

★ **PARADIGM-HF**: LVEF ≤ 35-40 %; NYHA II-IV; NTproBNP ≥ 600 pg/ml (or ≥ 400 pg/ml if hospitalized < 12 months); Sacubitril + Valsartan vs Enalapril → ↘ Mortality; ↘ Hospitalization; ↘ Symptoms; ↗ Hypotension; ↗ Angioedema

DOSING (SACUBITRIL/VALSARTAN): stop ACEi 36 h before; start with 50 (24/26) or 100 (49/51) mg bid; double the dose after 2-4 weeks; target dose of 200 (97/103) mg bid if tolerated

IVABRADINE

Inhibits the sinoatrial node I_f current channel

STUDIES: ★ SHIFT (LVEF ≤ 35 %; NYHA II-IV; HR ≥ 70 bpm; recent hospitalization); ↘ Hospitalization; ↘ Symptoms; ↘ Remodeling

ADVERSE EFFECTS: bradycardia; phosphenes

DIGOXIN

Inhibits the Na-K-ATPase pump: ↗ intramyocyte Ca^{2+} (positive inotropic agent); ↗ vagal tone

INDICATIONS: **A)** Persistent symptoms despite standard treatment; **B)** AF (rate control)

STUDIES: ★ DIG (NYHA II-IV; LVEF < 45 %) → ↘ Hospitalization; ↘ Symptoms

Adjustment according to renal function and serum digoxin levels

› **Target serum Digoxin level 0.5 to 0.9 ng/mL** +

ADVERSE EFFECTS: atrial / junctional / ventricular arrhythmias (especially in the presence of hypokalemia) combined with blocks; visual disorders; confusion; GI symptoms

CONTRAINDICATIONS: CRF; bradycardia - blocks

MULTIPLE DRUG INTERACTIONS

› ↗ **Serum Digoxin levels**: Amiodarone; Verapamil; Nifedipine; Diltiazem; Quinidine; Propafenone; Captopril; Carvedilol; Spironolactone; Cyclosporine; Macrolides

HYDRALAZINE - ISOSORBIDE DINITRATE

↘ **Mortality in Afro-Americans;** ↘ Hospitalization; ↘ Symptoms

INDICATIONS: A) Intolerance to ACE inhibitors and ARB; **B)** Persistent symptoms despite BB - ACE inhibitors - MRA **(particularly in Afro-Americans)**

STUDIES: ★ V-HeFT-1 and 2; ★ A-HeFT (Afro-Americans)

ADVERSE EFFECTS: headache; hypotension; nausea; arthralgia; asymptomatic ↗ ANA; drug-induced lupus

NON-PHARMACOLOGICAL TREATMENT

SELF-SURVEILLANCE OF WEIGHT

› Daily weight; on waking; before getting dressed; post-voiding → increase the dose of diuretics or notify if weight ↗ > 1.5-2 kg or 3-4 lbs (x 2-3 days)

SODIUM: < 2-3 g per day

FLUIDS: < 2 liters per day (especially if hyponatremia or refractory congestion)

VACCINATION: influenza (annually); pneumococcus (every 5 years)

TREATMENTS TO BE AVOIDED: **A)** Thiazolidinediones; **B)** Non-dihydropyridine CCBs; **C)** NSAIDs; **D)** Certain AAD: Dronedarone (★ ANDROMEDA); Class I AAD (★ CAST); **E)** Alpha-blockers

EXERCISE

★ **HF-ACTION** → improves symptoms and functional capacity

Regular isotonic exercise (walking; stationary bike) after stress test (rule out ischemia - arrhythmia)

› **Prescription**: 3-5 times a week; 30-45 min; **60-70% of peak heart rate** (or peak VO_2) **or 4-5-6/10 on Borg's scale** (▶▶| Chapter 9)

IMPLANTABLE CARDIAC DEFIBRILLATOR (ICD)

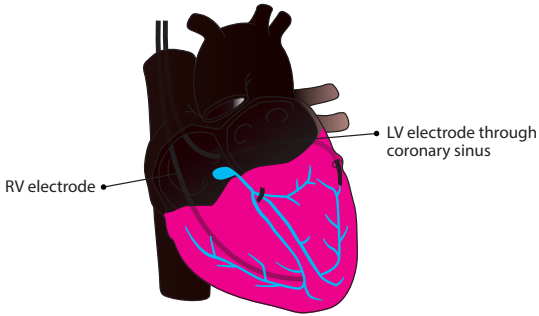
SECONDARY PREVENTION: defibrillator indicated

PRIMARY PREVENTION

› **Studies**: ★ SCD-HeFT (nonischemic cardiomyopathy or ischemic heart disease; NYHA II-III; LVEF ≤ 35% [mean = 25%]) and ★ MADIT-II (ischemic heart disease; LVEF ≤ 30%; NYHA I-III) → ↘ mortality

› **Avoid in NYHA IV (except when the patient is a candidate for transplant or mechanical support) due to poor prognosis and death predominantly secondary to progressive heart failure** +

CARDIAC RESYNCHRONIZATION THERAPY (CRT)



INDICATIONS

✓ **AMBULANT, NYHA III OR IV** ✓ **LVEF ≤ 35 %** ✓ **LBBB – QRS ≥ 120 MS** ✓ **SINUS RHYTHM** ✓ **LIFE EXPECTANCY > 1 YEAR**	✓ **NYHA II** ✓ **LVEF ≤ 30 %** ✓ **LBBB – QRS ≥ 120–130 MS** ✓ **SINUS RHYTHM** ✓ **LIFE EXPECTANCY > 1 YEAR**
STUDIES: ★ CARE-HF - COMPANION ↘ Mortality; ↘ Hospitalization; ↘ Symptoms; Reverse remodeling	**STUDIES: ★ RAFT - MADIT-CRT** ↘ Mortality (★ RAFT); ↘ Hospitalization; ↘ Symptoms; Reverse remodeling

UNCERTAIN BENEFICIAL EFFECTS OF RESYNCHRONIZATION

a) **Permanent AF with above indications** (consider AV node blocking agents or AV node ablation to force resynchronization)
b) **Patient with systolic dysfunction and frequent RV pacing** (consider resynchronization **if significant RV pacing > 40%)** +

PROCEDURAL SUCCESS: 90 %

› Minithoracotomy approach with epicardial lead PRN
› **Complications (14% in ★ RAFT)**: pneumothorax; pocket hematoma; pocket infection; lead migration; coronary sinus perforation / dissection (1%)

PARAMETERS INFLUENCING THE RESPONSE TO RESYNCHRONIZATION: % biventricular pacing; baseline degree of asynchrony (QRS ≥ 150 ms); lead position (target = basal lateral branch of CS); lead pacing scar tissue; ischemic heart disease << nonischemic cardiomyopathy; CRT programming (AV delay; VV delay)

› **Non-responders**: 30 %

ATRIAL FIBRILLATION

RATE CONTROL: **non-inferior to rhythm control (★ AF-CHF)** +

› **A)** BB; **B)** Digoxin; **C)** Amiodarone to control HR as necessary (patient should be anticoagulated for 1 month because of the risk of CCV); **D)** AV node ablation + PPM; consider resynchronization

RHYTHM CONTROL: patients with severe symptoms or reversible cause / precipitating factor

› **A)** ECV; **B)** Amiodarone or Dofetilide; **C)** ± PV isolation (benefit in ★ PABA-CHF and ★ AATAC-AF)

WARFARIN - ANTICOAGULATION

INDICATIONS: **A)** AF; **B)** Thrombus; **C)** History of thromboembolic disease

No benefit in ★ WARCEF study (LVEF < 35% in SR; for thromboembolic primary prevention)

SLEEP-DISORDERED BREATHING

CENTRAL SLEEP APNEA - CHEYNE-STOKES (40%): hyperventilation followed by apnea (≥ 10 s with no ventilatory effort); **associated with pulmonary congestion**; independent risk factor of mortality

- **Diagnosis**: Polysomnography
- **Treatment**: Optimize management of heart failure; CPAP (no benefit in ★ CANPAP study); Adaptive servo-ventilation associated with ↗ mortality in ★ SERVE-HF

OBSTRUCTIVE SLEEP APNEA (10%): Leads to hypoxemia / hypercapnia / intermittent sympathetic stimulation

- Look for obesity / ↗ neck circumference; snoring; daytime sleepiness; apneas
- **Complications**: refractory HTN; nocturnal HTN; PHT; arrhythmias
- **Diagnosis**: Polysomnography (screening with nocturnal saturometry)
- **Treatment**: Weight loss; CPAP

ANEMIA

Multifactorial

TREATMENT: Transfusions; IV iron (★ FAIR-HF; ★ CONFIRM HF); no benefit for EPO (★ RED-HF)

ISCHEMIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

REVASCULARIZATION: possible benefit in the presence of significant viability; highly controversial topic (mixed results of ★ STICH study; ★ ISCHEMIA study ongoing)

FUNCTIONAL MITRAL REGURGITATION

Carpentier I and IIIb mechanisms; maintains systolic dysfunction (which maintains MR)

MVR OR MITRAL ANNULOPLASTY: possible improvement in functional class; associated with reverse remodeling; no convincing data on survival; MVR possibly superior (★ CTSN)

- Consider in severe secondary MR with: CABG or concomitant AVR (class IIa recommendation) or refractory NYHA III - IV (class IIb recommendation)

MITRACLIP: consider in the presence of significant MR with refractory symptoms in a patient who is not a candidate for surgery

3.3/ DIASTOLIC HEART FAILURE (preserved LVEF)

Secondary to abnormal active relaxation and/or ↗ passive rigidity

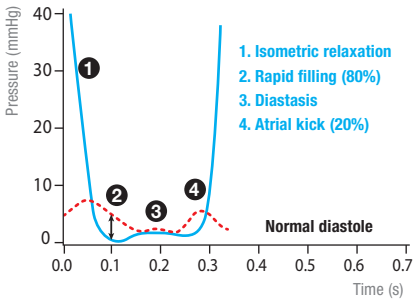
50% of patients with heart failure

ALL-CAUSE MORTALITY similar to that of heart failure with ↘ LVEF

- Mortality is mostly due to non-cardiovascular causes

RISK FACTORS: Age; Female; HTN; LVH; Ischemia; DM; Obesity; RCM; HCM

FACTORS ASSOCIATED WITH DECOMPENSATION: uncontrolled / labile HTN; AF; Ischemia; Volume overload; Extracardiac cause



DIASTOLIC DYSFUNCTION
Abnormal relaxation
and/or ↑ passive rigidity
↓
↑ Filling pressures
↓
↑ LA pressure

ETIOLOGIES OF ↓ RELAXATION VELOCITY
- ↑ LV afterload
- Ischemia
- Age
- Systolic dysfunction (↓ recoil)
- LVH

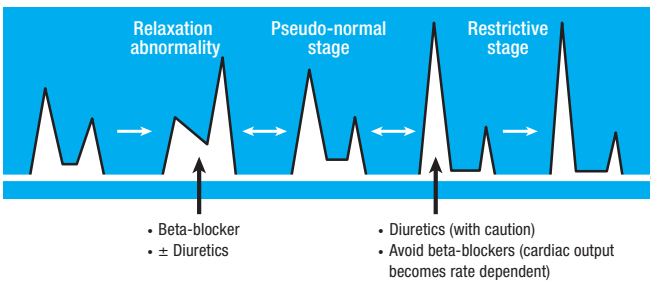
TTE: LVH - concentric remodeling; diastolic pattern; filling pressures; LA dilatation; PAP; RV function; Rule out pericardial disease

› ↗ **Filling pressures**: E/e' > 15; E/A inversion with Valsalva; diastolic dominance (PV outflow); prolonged reversal of flow in PV during atrial kick; LA dilatation; PHT

STRESS TEST: Rule out exaggerated hypertensive response (which exacerbates diastolic dysfunction); Rule out chronotropic incompetence

BNP: less sensitive than in systolic heart failure

MANAGEMENT



No treatment proven to decrease morbidity or mortality

› **No benefit in**: ★ CHARM-Preserved - ★ PEP-CHF - ★ I-Preserve - ★ TOPCAT - ★ NEAT-HFpEF

DIURETICS: symptoms / congestion control

RISK FACTOR REDUCTION: CAD; HTN (rule out renovascular syndrome in the presence of refractory HTN)

REVASCULARIZATION: if significant ischemia / symptoms

RATE CONTROL during AF (± rhythm control)

CONSIDER: ACE inhibitor or ARB; BB; MRA

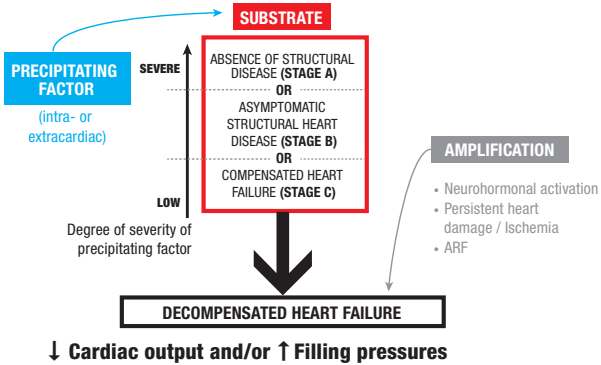
3.4/ DECOMPENSATED HEART FAILURE

Acute or subacute onset or modification of symptoms and signs of heart failure

Decompensated chronic heart failure (80%) vs *de novo* heart failure (20%)

50% of patients have preserved LVEF

PATHOPHYSIOLOGY



↓ Cardiac output and/or ↑ Filling pressures

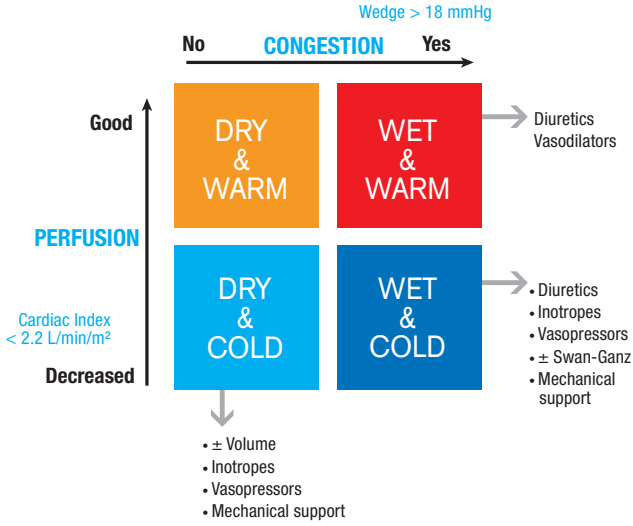
VARIOUS SCENARIOS

TAS > 160; ACUTE PULMONARY EDEMA	NORMAL BP	HYPOTENSION (SBP < 90)
• LVEF often preserved • Acute pulmonary edema • **Treatment**: Vasodilators; Diuretics; BiPAP; Rule out renal artery stenosis	• Systemic congestion • Subacute (often decompensated chronic heart failure) • **Treatment**: Diuretics; ± Vasodilators	• Low output • Renal hypoperfusion • **Treatment**: Positive inotropes (Milrinone; Dobutamine); Vasopressors; Mechanical support
CARDIOGENIC SHOCK	**MYOCARDIAL INFARCTION (KILLIP II OR III)**	**RIGHT HEART FAILURE**
• Acute event (ACS; mechanical complication; fulminant myocarditis) • **Treatment**: Reperfusion; Positive inotropes; Vasopressors; IABP; Mechanical support; Surgery	• Rapid onset • Resolution with treatment of ischemia • **Treatment**: Reperfusion; Nitrates; Ensure good coronary perfusion pressure	• RV infarction; PHT; Pulmonary embolism • Hypotension / systemic congestion • Interventricular dependence: RV dilatation induces ↘ LV filling • **Treatment**: Diuretics; Inotropes; Reperfusion; Pulmonary vasodilators

PRECIPITATING FACTORS

ACUTE DETERIORATION	SUBACUTE DETERIORATION
• Tachyarrhythmia • Bradyarrhythmia - Blocks • Acute coronary syndrome / Ischemia • Mechanical complication of MI • Valvular heart disease (e.g.: ischemic MR) • Pulmonary embolism • Hypertensive crisis • Cardiac tamponade • Aortic dissection • Surgery • Hemorrhage • Endocarditis	• Infection • COPD exacerbation / Asthma • ARF • Nonadherence to treatment • Nonadherence to restrictions • Drugs (NSAID; corticosteroids; Pregabalin) • Arrhythmias - Blocks • Uncontrolled HTN • Hypothyroidism / Hyperthyroidism • Alcohol - Illicit drugs • Anemia • LBBB • Progression of heart disease

MANAGEMENT



- Monitor
- Vital signs - SaO_2
- Urine output
- SVO_2

ACUTE HEART FAILURE

↗ FILLING PRESSURES / CONGESTION
(Wedge > 18 mmHg and/or CVP > 8 mmHg)

and/or

↘ CARDIAC OUTPUT
(< 2.2 L/min/m²)

- Diuretics (Lasix)
- Vasodilators (Nitrates)
- Morphine
- O_2 (target SaO_2 > 92 %)
- BiPAP or Mechanical ventilation if respiratory failure

TARGET ORGAN HYPOPERFUSION

- Cold skin
- Urine output < 20 mL/h
- SVO_2 < 70 %
- Confusion
- Ischemia

Rule out reversible cause

Hemodynamic instability and/or ↘ systemic vascular resistance

Maintain perfusion of vital organs (heart; CNS)
- Vasopressors (Norepinephrine; Dopamine)
- Non-vasodilator inotropes

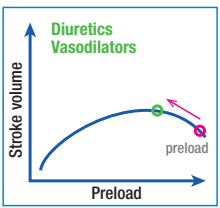
Normal systemic vascular resistance (1000 - 1200 dynes x s/cm⁵)

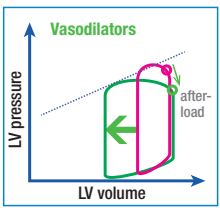
- Inotropes
- Vasodilators

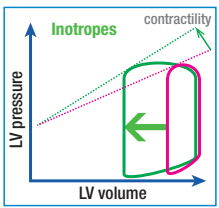
↗↗ systemic vascular resistance

- Vasodilators
- Inotropes

- Intra-aortic balloon pump
- Short-term percutaneous ventricular support (ECMO; Impella; TandemHeart) as "bridge to decision"







VASODILATORS		
Nitroglycerin	Dose: 10-20 µg/min up to 200 µg/min Standard dilution: 50 mg/250 mL D5% = 200 µg/mL	• ↗ cGMP in smooth muscle cells (= vasodilatation) • Venous vasodilator (↘ filling pressures) then arterial (↘ afterload; coronary vasodilatation) • Adverse effects: Tolerance during prolonged use; Hypotension; Headache
Nitroprusside	Dose: 0.3 µg/kg/min up to 5 µg/kg/min Standard dilution: 50 mg/250 mL NS = 200 µg/mL	• Balanced vasodilator • Short half-life • Used for hypertensive emergency or acute MR • Adverse effects: Risk of cyanide toxicity; Hypotension
Nesiritide	• Bolus: 2 µg/kg • Perfusion: 0.01-0.03 µg/kg/min	• Recombinant BNP • Balanced vasodilator • No benefit in ★ ROSE-AHF and ★ ASCEND-HF
INOTROPES		
Dobutamine	Dose: 2-20 µg/kg/min Standard dilution: 250 mg/ 100 mL D5% = 2500 µg/mL	• Beta-1 and beta-2 agonist • Supplementary alpha-1 effect at higher doses (neutralizing the beta-2 vasodilator effect) • **Favor to Milrinone in the presence of significant hypotension** • Arrhythmogenic
Dopamine	• Renal effect (Dopamine) < 3 µg/kg/min • Beta-1: 3-5 µg/kg/min • Alpha-1 (and Beta-1): > 5 µg/kg/min (up to 20 µg/kg/min) Standard dilution: 400 mg / 250 mL D5% = 1600 µg/mL	• Dose-dependent effect • Positive inotrope and vasopressor (vasodilator at low doses) • Norepinephrine precursor • Arrhythmogenic • ↗ Mortality in cardiogenic shock (★ SOAP II)
Milrinone	• Bolus: 25-75 µg/kg x 10-20 min (optional; avoid if hypotension) • Infusion: 0.375 - 0.75 µg/kg/min • Adjustment to GFR Standard dilution: 10 mg/100 mL D5% = 90 µg/mL	• Phosphodiesterase inhibitor (↗ intramyocyte cAMP = ↗ intracellular Ca^{2+}) • Risk of hypotension (vasodilator) • Caution in patients with CAD (hypotension can accentuate ischemia) • Effective despite BB • Favor if BP preserved • Less arrhythmogenic than dobutamine • No benefit in ★ OPTIME-HF study
Levosimendan	• Bolus: 12 µg/kg x 10 min (optional; risk of hypotension) • Infusion 0.05 - 0.2 µg/kg/min	• Calcium sensitizer • Positive inotrope and vasodilator • Equivalent to Dobutamine in ★ SURVIVE

Isuprel	Dose: 0.5 to 10 µg/min Standard dilution: 1 mg / 250 mL D5% = 4 µg/mL	• Beta-1 and beta-2 agonist • Prominent positive chronotropic effect • Risk of hypotension (beta-2 effect)
VASOPRESSORS		
Norepine-phrine	Dose: 0.2 -1 µg/kg/min Standard dilution: 4 mg / 250 mL D5% = 16 µg/mL	• Alpha-1 agonist • Beta-1 effect (but reflex bradycardia secondary to ↗ MAP)
Epinephrine	• Bolus: 1 mg IV every 3-5 min (during resuscitation) • Infusion: 0.05 - 0.5 µg/kg/min Standard dilution: 5 mg / 250 mL D5% = 20 µg/mL	• Alpha-1, beta-1 and beta-2 agonist • Arrhythmogenic
Phenylephrine	Dose: 40 - 60 µg/min Standard dilution: 10 mg / 250 mL NS = 40 µg/mL	• Pure alpha-1 agonist

MONITORING: Cardiac monitoring - Regular vital signs - SaO_2 - urine output; daily weight

LMNOP: IV Lasix; Morphine if anxiety / distress (2.5-5 mg IV); Nitrates (avoid if hypotension); O_2; Position - PEEP

› **Diuretic**: ★ DOSE study → bolus bid equivalent to IV infusion; low-dose IV (equal to usual oral doses) equivalent to high-dose IV (2.5 x usual oral doses)
› **BiPAP**: contraindicated in the presence of hypotension; Vomiting; Impaired level of consciousness; Uncooperative patient

INOTROPES (Dobutamine; Milrinone): **indicated in the presence of peripheral hypoperfusion**

› **Adverse effects**: Hypotension (vasodilator effect); Arrhythmogenic; ↗ O_2 demand; ↗ Long-term mortality

VASOPRESSORS (Norepinephrine): indicated in the presence of severe hypotension

› **Objective**: **redirect cardiac output to vital organs**
› **Adverse effects**: ↗ Afterload; ↗ O_2 demand; Arrhythmogenic

SWAN-GANZ: Indications → **A)** Cardiogenic shock despite inotropes / vasopressors; **B)** Patient refractory to treatment; **C)** Uncertain hemodynamic parameters (filling pressures; SVR); **D)** Hemodynamic assessment prior to transplant / mechanical support

› **Hemodynamic targets**

WEDGE	CVP	BP	SVO_2	SVR	CARDIAC INDEX
< 18 mmHg	< 8 mmHg	MAP > 60 mmHg SBP > 80 mmHg	> 70 %	1000 to 1200 dynes x s/cm^5	> 2.2 L/min/m^2

MONITORING OF TREATMENT: improvement in symptoms / signs of congestion / peripheral perfusion; SVO_2; BP; weakness - OH; urine output; daily weight; CVP; BUN - creatinine - electrolytes

IDENTIFICATION AND TREATMENT OF REVERSIBLE CAUSES: Ischemia; Arrhythmia; Valvular heart disease; Other precipitating factors

DISCHARGE FROM HOSPITAL: congestion resolved; **dry weight achieved**; ACE inhibitors - BB - mineralocorticoid receptor antagonist initiated; stable dose of diuretics and stable labs for > 48 h; restrictions explained; registration in specialized clinic; follow-up < 1 month (vulnerable phase)

SHORT-TERM AND MEDIUM-TERM MECHANICAL SUPPORT

OBJECTIVE: **Maintain adequate target organ perfusion** during acute treatment and/or while waiting for recovery and/or while waiting for heart transplant or long-term ventricular support

SHORT-TERM PERCUTANEOUS MECHANICAL SUPPORT

- **IABP**: increases cardiac output **< 10-15 %**; increases coronary perfusion; contraindicated in the presence of AR or aortic dissection
- **Impella 2.5 and 5.0 L/min**: Femoral artery → Aortic valve
- **TandemHeart**: **A)** Filling cannula: femoral vein → transseptal → LA; **B)** Ejection cannula: femoral artery
  - **Disadvantages** (Impella and TandemHeart): lower limb ischemia; cannula displacement; difficult transport
- **ECMO**: complete cardiopulmonary support
  - **Disadvantages**: anticoagulation; lower limb ischemia; incomplete LV decompression; requires qualified personnel; activation of an inflammatory cascade

MEDIUM-TERM MECHANICAL SUPPORT (LVAD OR RVAD OR PARACORPOREAL BIVAD)

Thoratec VAD; CentriMag; Abiomed BVS5000

CARDIORENAL SYNDROME

Impaired renal function associated with heart failure

MECHANISMS: **A)** Low output; **B)** Venous congestion; **C)** Medications (ACE inhibitors; ARB; contrast agents); **D)** Intravascular hypovolemia (diuretics) = activation of RAA / sympathetic systems; **E)** Underlying renal disease (HTN; DM; PAD); **F)** ↗ Intra-abdominal pressure (ascites)

RENAL PERFUSION PRESSURE = MAP - CVP

NORMAL RENAL FUNCTION	**GFR > 90 mL/min/1.73 m²**
STAGE II CRF	**GFR 60 - 89 mL/min/1.73 m²**
STAGE III CRF	**GFR 30 - 59 mL/min/1.73 m²**
STAGE IV CRF	**GFR 15 - 29 mL/min/1.73 m²**
STAGE V CRF	**GFR < 15 mL/min/1.73 m²**

3.5/ HEART TRANSPLANTATION

INDICATION

Late-stage heart disease after optimal medical / surgical therapy, in presence of an unacceptable quality of life and a poor anticipated survival

Late-stage heart failure; Severe refractory ischemic symptoms; Refractory life-threatening arrhythmias; Complex congenital heart disease...

- **Cardiopulmonary stress testing** to guide transplant listing (reach anaerobic threshold)
  - Peak VO_2 **≤ 12 mL/kg/min** (in the presence of a beta-blocker)
  - Peak VO_2 **≤ 14 mL/kg/min** (patients intolerant to beta-blockers)
  - Percent of predicted peak VO_2 ≤ 50% (in young patients)
- **Heart failure prognosis score** to guide transplant listing
  - Seattle Heart Failure Model: 1-year survival < 80%
  - Heart Failure Survival Score: High / Medium risk

ASSESSMENT

POTENTIAL DONOR: cold ischemia time < 4 h; TTE; coronary angiography (depending on risk factors / age); donor size

IMMUNOLOGICAL WORK-UP: blood group; antibody screening; Panel reactive antibody (PRA); specific HLA antibodies (directed against human leukocyte antigens)

- **PRA > 10 %**: recipient patient sensitized; ↗ risk of humoral rejection
  - **Management**: IV Ig; Rituximab; plasmapheresis

CONTRAINDICATIONS

- **Fixed high pulmonary vascular resistances**
  - **Pulmonary vascular resistances > 5 WU**
  - **Transpulmonary gradient (mPAP – Wedge) > 16-20 mmHg**
  - **Pulmonary vascular resistance index (TPG / CI) > 6**
  - **Pulmonary vascular resistances > 2.5 WU in response to pharmacological challenge while maintaining SBP > 85 mmHg (NO; Nitroprusside; Prostanoids; Inotropes)**
    - High risk of RV failure and mortality after cardiac transplantation
    - Consider aggressive medical therapy (diuretics; inotropes; IV vasodilators; NO) and temporary mechanical support (IABP; LVAD) to improve these parameters
- **Others**: **A)** Irreversible renal dysfunction (GFR < 30 mL/min); **B)** Irreversible significant liver disease (biopsy PRN); **C)** Pre-existing cancer when the risk of tumor recurrence is significant; **D)** Active infection; **E)** Clinically severe symptomatic cerebrovascular disease; **F)** Peripheral arterial disease when it limits rehabilitation; **G)** DM with target organ damage or persistent poor glycemic control (HbA1c > 7.5%); **H)** Active mental illness / Nonadherence; **I)** Active smoking (previous 6 months) or active substance abusers (including alcohol); **J)** Obesity (BMI > 35 kg/m²); **K)** Age > 70 years old (consider selected patients); **L)** Frailty

PRIORITY ALLOCATION SYSTEM

STATUS 4	• Dependent on mechanical support (or mechanical ventilation) and in the intensive care unit
STATUS 3.5	• In-hospital inotrope-dependent (high doses or multiple agents) • Highly sensitized patient • Refractory life-threatening arrhythmia
STATUS 3	• Uncomplicated LVAD / without intensive care • In-hospital on inotropes (low dose / only one agent) • Congenital heart disease › arterial shunt-dependent › with SaO_2 < 65 % › complex with progressive arrhythmia › complex with systemic ventricle decline • Heart-lung transplantation
STATUS 2	• In-patient • Outpatient on inotropes • Congenital heart disease › with SaO_2 65-75 % › with Fontan and exudative enteropathy • Multiple organ transplantation (other than heart-lung)
STATUS 1	• Other

Canadian Cardiac Transplant Network

IMMUNOSUPPRESSION

INDUCTION
- **Anti-IL2 receptor antibodies** (Basiliximab) or **rATG** (antithymocyte immunoglobulins)
- **Precise indications**: high risk of rejection; risk of renal toxicity with calcineurin inhibitors

CORTICOSTEROIDS
- Decrease lymphocyte activation (T cells and B cells)
- Tapering after 6 months
- **Adverse effects:** Cushing; HTN; dyslipidemia; weight gain; DM; ulcers; cataracts; avascular necrosis of the hip; osteoporosis; shingles

CALCINEURIN INHIBITORS: CYCLOSPORINE OR TACROLIMUS
- Decrease T cell activation
- **Adverse effects:** Nephrotoxicity; HTN; DM; Neurotoxicity...

+

PURINE SYNTHESIS INHIBITORS: AZATHIOPRINE OR MMF (MYCOPHENOLATEMOFETIL)
- Inhibit T cell and B cell proliferation
- **Adverse effects:** Bone marrow suppression; Granulocytopenia; Diarrhea; Interaction with Allopurinol (Azathioprine)

M-TOR INHIBITORS: SIROLIMUS (RAPAMYCIN) AND EVEROLIMUS
- **Alternative to calcineurin inhibitors in the presence of renal toxicity**
- Block T cell (and B cell) activation
- Inhibit endothelial cell and fibroblast proliferation
  - › **Decrease the risk of cardiac allograft vasculopathy**
- **Adverse effects:** Altered healing

COMPLICATIONS

TRANSPLANT: bicaval anastomosis

POST-TRANSPLANT HEART FAILURE: optimize coronary perfusion; optimize RV preload (diuretics; UF; minimize transfusions); atrial pacing (junctional rhythm is common post-transplant); avoid hypercapnia - acidosis; inotropes (Milrinone; Dobutamine); pulmonary vasodilators (NO; Prostacyclins; Sildenafil); IABP - ECMO - RVAD - Impella

CELLULAR REJECTION: **Lymphocyte infiltrates (T cells)**; several weeks to several years post-transplant; 40% in the first year
- › **Presentation**: **ranges from asymptomatic to cardiogenic shock**
- › **Diagnosis**: weekly biopsy for 6 weeks - monthly for 6 months - every 3 months for 2 years - every 4 to 6 months
- › **Risk factors**: Young age; female; CMV+; HLA incompatibility
- › **Treatment:** corticosteroids; intensification of immunosuppression

GRADE 0 R	Absence of rejection
GRADE 1 R (MILD)	Interstitial / Perivascular lymphocyte infiltration (≤ 1 zone of myocyte injury)
GRADE 2 R (MODERATE)	≥ 2 zones of infiltration with myocyte injury
GRADE 3 R (SEVERE)	Diffuse infiltration; multiple zones of myocyte injury (± edema; ± bleeding; ± vasculitis)

HUMORAL REJECTION (ANTIBODIES): **anti-donor HLA antibody or anti-endothelial antigen antibody**; absence of lymphocyte infiltrate; acute graft dysfunction (↘ LVEF)

› **Treatment**: Plasmapheresis; Corticosteroids; Rituximab

CLINICAL	• Graft dysfunction; ↘ LVEF; Wall thickening (edema)
HISTOLOGICAL (BIOPSY)	• Capillary endothelial congestion (± interstitial edema) • Macrophages in capillaries (± neutrophils)
IMMUNO-PATHOLOGICAL	• Immunofluorescence: Immunoglobulins + complement (C3d / C4d / C1q) in capillaries • Immunohistochemistry: CD68+ macrophages in capillaries or C4d in capillaries
SEROLOGICAL	• Anti-HLA class I or II antibodies or other anti-donor antibodies

CHRONIC REJECTION: chronic humoral rejection ± cardiac allograft vasculopathy

CARDIAC ALLOGRAFT VASCULOPATHY: 50% at 10 years; **diffuse concentric neointimal proliferation; no angina (denervation)**

› **Complications**: MI; allograft heart failure; arrhythmia; sudden death
› **Risk factors:** number of episodes of rejection; HLA incompatibility; conventional risk factors for CAD; graft ischemia time; donor age; CMV+...
› **Screening**: Dobutamine echocardiography; MIBI-P; Coronary angiography / IVUS
› **Treatment**: Statins; Control of conventional risk factors; Intensification of immunosuppression; m-TOR inhibitors; PCI; re-transplantation

INFECTION: nosocomial (early); fungal (Aspergillosis; Candidiasis); CMV (fever; leukopenia; transaminase elevation); HSV; VZV; PCP; Toxoplasmosis; TB; Nocardiosis; Cryptococcosis; *L. monocytogenes*

› **Prophylaxis (6-12 months post-transplant)**: CMV (Acyclovir / Valganciclovir); *Pneumocystis carinii* and Toxoplasmosis (TMP/SMX); Antifungal agents (Voriconazole / Itraconazole)

NEOPLASIA: 30% at 10 years (lymphoma; cutaneous; solid organs)

OTHER COMPLICATIONS: HTN; Dyslipidemia; DM; CRF (calcineurin inhibitors); sinus tachycardia at rest (parasympathetic denervation); gout

› **Mean survival**: 10 years

3.6/ LONG-TERM VENTRICULAR ASSIST DEVICE

INDICATIONS

ADVANCED HEART FAILURE* • **NYHA IIIb – IV** and • **≥ 2 of these elements:**	• LVEF < 25% and/or VO_2 max < 14 mL/kg/min (or < 50% predicted for age / gender / BSA) • Inotrope dependence • Progressive target organ dysfunction due to hypoperfusion • Repeated hospitalizations (≥ 3 per year) • Progressive discontinuation of beneficial medication (ACE inhibitors; BB) due to hypotension or ARF

***Estimated one-year mortality > 50% on medical therapy** (Seattle Heart Failure Model; Heart Failure Survival Score)

SCENARIOS

BRIDGE TO DECISION	Acute hemodynamic collapse; maintain the patient alive in order to evaluate other therapeutic options; **short-term / medium-term mechanical support** (percutaneous or paracorporeal)
BRIDGE TO RECOVERY	Maintain the patient alive until recovery of sufficient cardiac function to wean mechanical support (by reverse remodeling); acute fulminant myocarditis or sometimes DCM or peripartum cardiomyopathy or following cardiac surgery or myocardial stunning
BRIDGE TO TRANSPLANTATION	Maintain the patient alive while waiting for transplantation
BRIDGE TO CANDIDACY	Improve target organ function to potentially make the patient eligible for transplantation
DESTINATION THERAPY	Use of long-term mechanical support (patient not a candidate for transplantation, but satisfactory life expectancy)

INTERMACS CLASSIFICATION

	INTERMACS PROFILE	TIME TO MECHANICAL SUPPORT
1	CRASHING AND BURNING - Critical cardiogenic shock	Hours
2	PROGRESSIVE DECLINE - Positive inotrope-dependent; continuous deterioration	Days
3	STABLE BUT INOTROPE-DEPENDENT - Stable	Weeks
4	RECURRENT HEART FAILURE - Recurrent decompensation	Weeks - Months
5	EXERTION INTOLERANT - Comfortable at rest	Variable
6	EXERTION LIMITED - Fatigue with the slightest exertion	Variable
7	ADVANCED NYHA III - Comfortable at an acceptable level of exertion	Not a candidate

ASSESSMENT

Refer the patient for assessment before significant irreversible target organ damage (RV dysfunction; Irreversible PHT; irreversible congestive liver disease; irreversible renal failure; coagulopathy; malnutrition) +

- **Target CVP < 15 mmHg** (decreases hepatic congestion; decreases the risk of post-LVAD right heart failure)
- **Right ventricular stroke work index (RVSWI)** = [(mPAP - CVP) x stroke volume] / BSA
  - **Target RVSWI > 300 mmHg x mL/m²**
  - **Mean PAP < 25 mmHg associated with low right ventricular reserve** +
- **Liver disease**: risk of bleeding and post-op transfusion (with deterioration of RV function due to secondary volume overload)

› **Assessments**: Target → BUN < 40 U/dL; creatinine < 221 µmol/L; GFR > 50 mL/kg/min; INR < 1.2; Hb > 100 g/L; Platelets > 150,000/mm³; Albumin > 30 g/L; Prealbumin > 15 g/L; ALT - AST < 2 ULN

› **Valvular heart disease**: correct AR ≥ 3/4 or moderate MS or TR ≥ 3/4 or mechanical AVR

RISK OF POST-LVAD IN-HOSPITAL MORTALITY

PARAMETERS	POINTS	
Platelets < 148 000 / mm³	7	**POST-LVAD IN-HOSPITAL SURVIVAL** • 0-8 points: 87.5 % • 9-16 points: 70.5 % • 17-19 points: 26 % • > 19 point: 13.7 % **If ≥ 17 points: patient optimization prior to LVAD**
Albumin < 33 g/L	5	
INR > 1.1	4	
Ongoing vasodilator therapy	4	
Mean PAP < 25 mmHg	3	
AST > 45 IU/mL	2	
Hematocrit < 34 %	2	
BUN > 51 U/dL	2	
Absence of IV inotrope	2	

Lietz K, Long JW, Kfoury AG, et al. Circulation. 2007;116:497-505

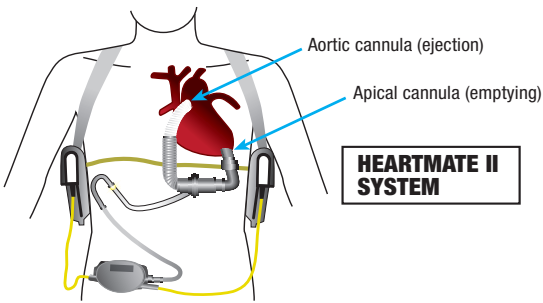
LEFT VENTRICULAR ASSIST DEVICE (LVAD)

"DESTINATION THERAPY" STUDIES: ★ REMATCH (HEARTMATE XVE) and ★ HEARTMATE II → ↘ Mortality compared to conventional medical therapy; Improvement in NYHA class and quality of life; Reverse remodeling

› **2-year survival (registries)**: 65 %

SECOND-GENERATION LVAD PUMPS: **non-pulsatile flow (continuous)**; HeartMate II; Jarvik 2000

› **Flow rate**: up to 10 L/min
› **Pump speed**: adjusted by TTE (LV and RV chambers; position of IV septum; Ao valve opening every 3 beats)
› **Anticoagulation**: Target INR 2 to 3 ± ASA 80 qd
› **BP monitoring (continuous flow pump)**: use sphygmomanometer and Doppler (target mean BP < 80 mmHg)



COMPLICATIONS: bleeding (acquired vWF deficiency; AV malformation); HIT; right heart failure; thromboembolism; stroke; infection; mechanical breakdown; fused aortic valve leaflets (leads to AR or AS); allosensitization; hemolysis; device thrombosis

THIRD-GENERATION PUMPS: HeartWare HVAD (intrapericardial)

MICROPUMPS: CircuLite Synergy (partial support up to 3 L/min; subclavian approach)

3.7/ RIGHT HEART FAILURE

ETIOLOGIES

- Right heart failure secondary to left heart failure (most frequent)
- Precapillary PHT (including pulmonary embolism)
- Cardiomyopathy with RV involvement (including ARVD) (▶▶| Chapter 5 - Cardiomyopathies)
- RV infarction
- Right valvular heart disease
- Congenital heart disease (including ASD and intracardiac shunt)
- Right heart failure post-cardiac surgery
- Constrictive pericarditis (mimics right heart failure)

SYMPTOMS AND SIGNS

- Fatigue; anasarca - edema; anorexia; nausea; RUQ pain
- Hypotension; JVD ± Kussmaul; left parasternal heave ; Harzer's sign; ± signs of PHT; right S3 (↗ inspiration); tricuspid regurgitation; hepatomegaly - pulsatile liver; systemic congestion (ascites; edema)

ASSESSMENT

TTE; radionuclide ventriculography; cardiac MRI; V/Q scintigraphy; Right-Left catheterization

MANAGEMENT

Diuretics (caution in the presence of normal Wedge pressure due to the risk of decreased LV preload); ± mineralocorticoid receptor antagonists

Specific treatment of PHT; Specific treatment of LV HF

Surgical or percutaneous correction of structural abnormality (valvular or congenital malformation)

3.8/ PALLIATIVE CARE

- Discussing the patient's wishes at the stage of advanced heart failure
- Good communication with the patient and family
- Desactivation of the defibrillator
- Analgesia
- ± IV diuretics; ± palliative IV inotropes

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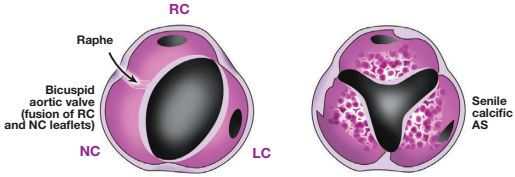
4.1/ AORTIC STENOSIS

ETIOLOGIES

SENILE CALCIFIC AS: Similar risk factors and pathophysiology to CAD and mitral annular calcification (MAC)

BICUSPID AORTIC VALVE

- 1-2% of the population
- **70-80%: fusion of right and left coronary leaflets**
  - 20-30%: fusion of right coronary and non-coronary leaflets
  - Fusion of non-coronary and left coronary leaflets is rare
- **TTE**: Demonstrates valve opening during systole with **only two commissures** (unicuspid valve: only one commissure)
- Screening TTE should be performed in 1st degree relatives
- **Associated aortopathy** (medial degeneration); **aneurysm; dissection**
  - Imaging (TTE; CT angiography; MRI) annually if aorta > 45 mm
  - BB if aorta > 40 mm (in the absence of significant AR)
  - **Ascending aorta replacement if aorta > 55 mm (> 45 mm when AVR is also necessary) or > 50 mm with risk factors for dissection (family history or progression ≥ 5 mm/year)**



RHEUMATIC: fusion of commissures; triangular orifice; concomitant AR and AS; associated mitral valve disease in the majority of cases

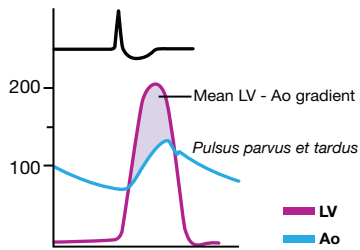
CONGENITAL AORTIC STENOSIS (can be treated by balloon valvuloplasty)

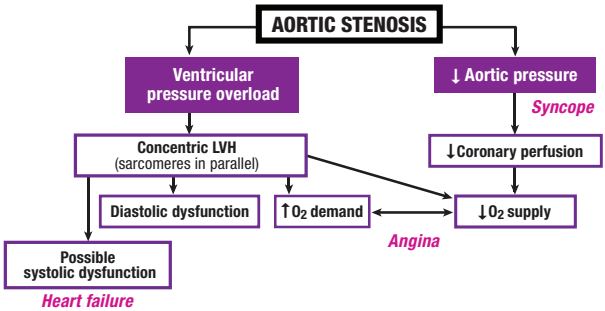
RHEUMATOID AORTIC STENOSIS (rare)

DDx: Aortic sclerosis (calcification but **peak velocity < 2.5 m/s)**; HCM (dynamic obstruction)

- **Supravalvular aortic stenosis: strong A2**; murmur radiates to the right carotid; BP right arm > BP left arm; associated with Williams syndrome
- **Subvalvular aortic stenosis**: membrane or tunnel; combined with AR; absence of systolic anterior motion (SAM) of mitral leaflet

HEMODYNAMIC CONSEQUENCES





SYSTOLIC DYSFUNCTION SECONDARY TO:

1) ↘ **Intrinsic contractility** secondary to remodeling (only slight improvement with surgery)
2) **Mismatch between high afterload and insufficient concentric LVH** (afterload mismatch) (improved by surgery)

SEVERITY

NORMAL AREA: 3-4 cm^2

	MILD	MODERATE	SEVERE	CRITICAL
Jet velocity (m/s)	2.6-2.9	3.0 - 4.0	> 4.0	> 5.0
Mean gradient (mmHg)	< 20	20 - 40	> 40	> 60
Valve area (cm^2)	> 1.5	1.0 - 1.5	< 1.0	< 0.6
Indexed valve area (cm^2/m^2)	> 0.85	0.6 - 0.85	< 0.6	
LVOT VTI / Ao valve VTI ratio	> 0.50	0.25 - 0.50	< 0.25	

SYMPTOMS AND SIGNS

SYMPTOMS: **Heart failure / Dyspnea; Angina; Syncope**

› Bleeding (destruction of von Willebrand factor; Heyde's syndrome)

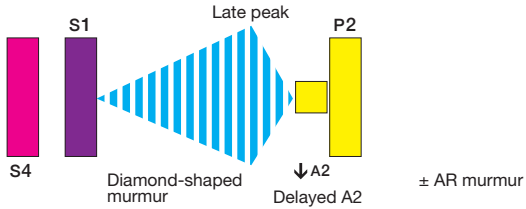
CAROTID: ***pulsus parvus* et *tardus*** (slow ascent; late peak; low amplitude) (absent in the presence of arteriosclerosis); carotid thrill

APEX: sustained; lateralized if LV dysfunction; S4 sometimes palpable; **apical-carotid delay**

AORTIC AREA: look for **thrill**

AUSCULTATION: **crescendo - decrescendo murmur with late peak**; carotid radiation; radiation to apex in the case of Gallavardin phenomenon (high-pitched murmur); accentuation of murmur post-PVC; decrescendo diastolic murmur in the presence of associated AR

› **S2 with a single component: Inaudible A2** or delayed A2 and at same time as P2 with paradoxical expiratory splitting
› **S4**
› **Systolic ejection click** of bicuspid aortic valve disappears in the case of ↘ valve mobility



INVESTIGATIONS

STRESS TEST: To distinguish asymptomatic from symptomatic aortic stenosis; contraindicated if the patient presents symptoms of AS

› Look for symptoms - decreased exercise capacity (< 80% predicted) - abnormal BP response (↗ SBP < 20 mmHg)

ECHOCARDIOGRAPHIC FOLLOW-UP

MILD AS	MODERATE AS	SEVERE ASYMPTOMATIC AS
TTE every 3 to 5 years	TTE every 1 to 2 years	TTE every 6 months to 1 year

HEMODYNAMIC ASSESSMENT - INDICATIONS

a) Inconclusive noninvasive investigation
b) Discordance between clinical findings and noninvasive investigation

PREOPERATIVE CORONARY ANGIOGRAPHY - INDICATIONS

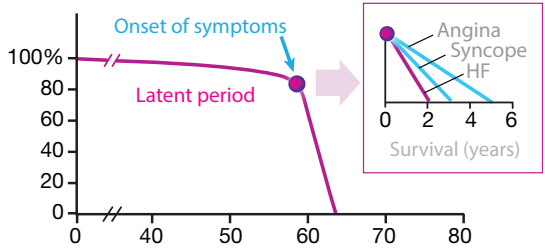
› Angina; documented ischemia; LV systolic dysfunction; known CAD; Male > 40 years; postmenopause; cardiovascular risk factors
- Consider coronary CT angiography in patients with low-to-moderate pretest probability of CAD
- It is reasonable not to perform preoperative coronary angiography in a surgical emergency in the presence of acute valvular regurgitation, acute aortic syndrome or bacterial endocarditis (class IIa recommendation)

OUTCOME

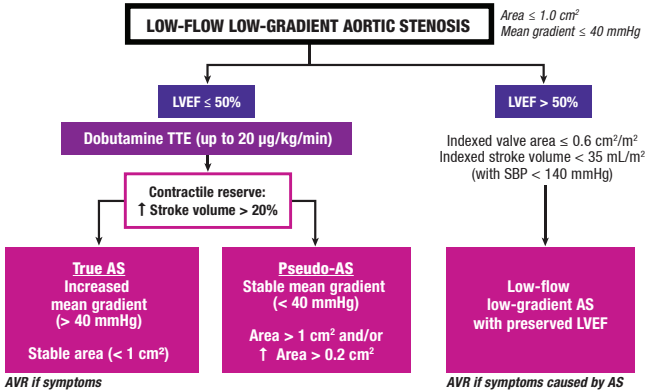
↘ Valve area by 0.1 cm² / year; ↗ Mean gradient by 7 mmHg / year

Asymptomatic AS: risk of sudden death < 1% / year

Symptomatic AS: ↘ survival (sudden death); **2 years in the presence of HF; 3 years in the presence of syncope; 5 years in the presence of angina**



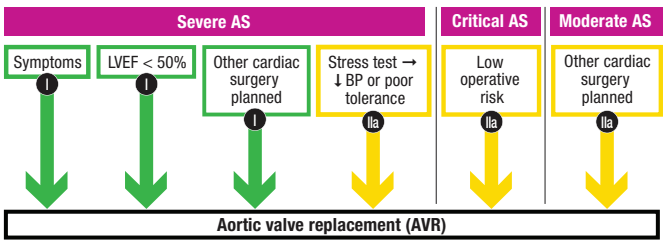
LOW-FLOW LOW-GRADIENT AORTIC STENOSIS



MANAGEMENT

MEDICAL: Patient education - report all symptoms; avoid strenuous physical exertion; echocardiographic follow-up; low-dose diuretics; avoid BB; cautious use of vasodilators (fixed obstruction); treatment of cardiovascular risk factors

SURGERY - INDICATIONS



› **Complication of AVR**: mortality 1-3%; stroke 2%; prolonged ventilation 11%; thromboembolism; bleeding; prosthetic dysfunction

PERCUTANEOUS BALLOON VALVULOPLASTY

Risk of major complications > 10%

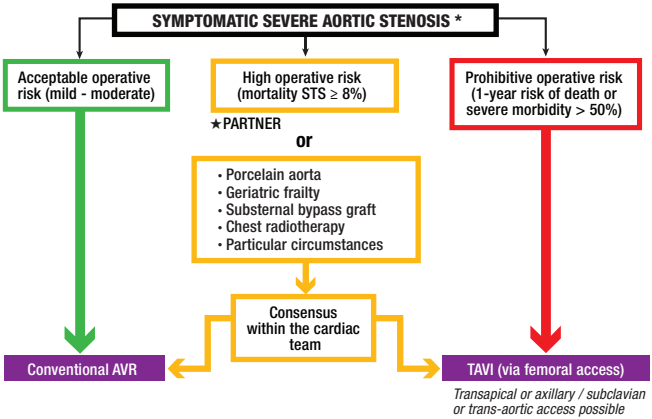
Recurrent symptoms and restenosis at 6 months

Does not constitute a medium-term or long-term alternative to AVR or TAVI

LIMITED INDICATIONS: bridge to AVR or TAVI in a patient with severe symptoms

› Effective in adolescents / young adults with congenital AS in the absence of calcification

TAVI (Transcatheter aortic valve implantation)



* Absence of futility: an operation will probably improve life span and/or quality of life; survival with treatment will probably be ≥ 1-2 years

PRE-TAVI ASSESSMENT: **A)** TTE; **B)** TEE: aortic annulus dimensions at insertion of leaflets on anteroposterior view (PLAX) and side-to-side (short-axis); **C)** CT angiography: Ao; aortic annulus dimensions; aortic-iliac-femoral PAD; distance between coronary ostia and aortic annulus; **D)** Coronary angiography - Aortography - Ventriculography

- Aortic annulus diameter: **> 18 mm and < 29 mm**
- Coronary ostia - aortic annulus distance **≥ 10-11 mm**
- Femoral vascular access: **femoral artery diameter > 6 mm** (to accommodate a 7 mm catheter); evaluate the degree of calcification and arterial tortuosities
- **Geriatric frailty:** increased risk of adverse events during major surgery; **5-meter walking time > 6 s**; Katz index of independence in ADL

STEPS OF THE FEMORAL APPROACH: **A)** Femoral access; **B)** Transvalvular guide; **C)** Delivery catheter; **D)** Pre-dilatation by valvuloplasty during rapid ventricular pacing (180-200 bpm); **E)** Positioning of the valve under fluoroscopic / angiographic guidance and/or by TEE (50% above and 50% below the plane of the aortic annulus); **F)** Valve deployment during rapid ventricular pacing (180-200 bpm) (Sapien valve); **G)** Identification and management of complications; **H)** Closure of access site

LIMITED BENEFIT OF TAVI: Life expectancy < 1 year; 2-year survival with estimated benefit < 25%; STS > 15% (no benefit on survival in ★ PARTNER B); advanced geriatric frailty (dependence for multiple ADL); multiple comorbidities

COMPLICATIONS: 30-day mortality: 3-5%; stroke (6-7%); vascular complications (17%); valve embolization; coronary occlusion (due to migration of a leaflet or calcification); mitral valve disease; perivalvular regurgitation (incomplete apposition); tamponade; AV block requiring PPM (2-9% Sapien; 19-43% Corevalve); arrhythmias; bleeding; aortic rupture

POST-TAVI MANAGEMENT: Long-term ASA; Thienopyridine for 1 to 6 months (except when treated with warfarin); prophylactic antibiotics; annual clinical and TTE follow-up

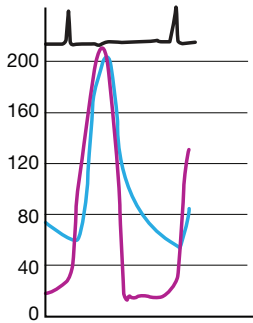
4.2/ CHRONIC AORTIC REGURGITATION

ETIOLOGIES

VALVULAR: **A)** Degenerative (calcification); **B)** Endocarditis; **C)** Leaflet prolapse (loss of support due to aortopathy); **D)** Bicuspid aortic valve; **E)** Rheumatic; **F)** VSD; **G)** Subaortic membrane; **H)** Iatrogenic (post-balloon valvuloplasty); **I)** Myxomatous proliferation; **J)** SLE - RA - ankylosing spondylitis

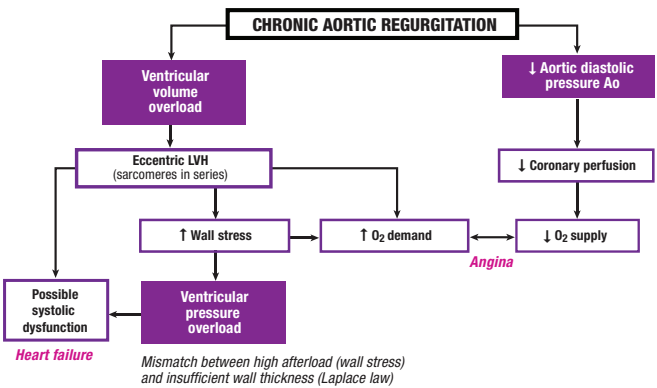
AORTIC: **A)** Aortic dilatation: degenerative / cystic medial necrosis (isolated; Marfan; bicuspid aortic valve); osteogenesis imperfecta; syphilis; Behçet; Takayasu; giant cell arteritis; spondyloarthropathies / ankylosing spondylitis / psoriatic arthritis; polychondritis; HTN; **B)** Dissection: leaflet prolapse following loss of support or presence of intravalvular flap or leaflet perforation by dissection; **C)** Traumatic

HEMODYNAMIC CONSEQUENCES



- Normal or ↑ LVEDP (↑ ↑ ↑ if acute AR)
- ↑ Aortic systolic pressure
- ↓ Aortic diastolic pressure
- ↑ **Pulse pressure**
- ± Pulsus bisferiens
- Femoral systolic pressure > 20 mmHg higher than aortic systolic pressure

LV
Ao



Mismatch between high afterload (wall stress) and insufficient wall thickness (Laplace law)

SEVERITY

	MILD AR (1/4)	MODERATE AR (2 to 3/4)	SEVERE AR (4/4)
Vena contracta (mm)	< 3	3 - 5.9	≥ 6
Regurgitant volume (mL/b)	< 30	2/4: 30 - 44 3/4: 45 - 59	≥ 60
Regurgitant fraction (%)	< 30	30 - 49	≥ 50
Regurgitant orifice (cm²)	< 0.10	2/4: 0.1 - 0.19 3/4: 0.2 - 0.29	≥ 0.30
Jet width (PLAX)	Central; < 25% of LVOT	Intermediate	> 65% of LVOT
Area of regurgitant jet (PSAX)	< 5 % of LVOT area	Intermediate	> 60 % of LVOT area
Pressure half-time (ms)	> 500	200-500	< 200
Diastolic reversal of descending Ao	Brief; Early diastolic	Intermediate	Holodiastolic and prominent (end-diastolic velocity > 20 cm/s)
LV dimensions	Normal		Dilatation
Angiography	1+	2+	3-4+

OTHER MARKERS OF SEVERITY: Holodiastolic reversal of flow in proximal abdominal aorta

SYMPTOMS AND SIGNS

SYMPTOMS: Heart failure - Dyspnea; Angina; Tiredness

- Poorly tolerated bradycardia (↗ regurgitation time)

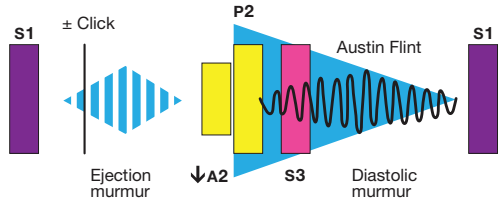
VITAL SIGNS: **↗ pulse pressure (with ↘ DBP)**

PULSE: bounding; ***pulsus bisferiens*** (more accurately assessed in brachial or femoral arteries); carotid thrill (↗ stroke volume)

APEX: large; hyperdynamic; lateralized; ± palpable S3

AUSCULTATION: **decrescendo diastolic murmur starting at A2**; more accurately assessed with the patient seated and leaning forward in forced expiration; duration correlated with severity

- Murmur increases with fists clenched
- **Radiation to left parasternal region indicates a valvular etiology; Radiation to right parasternal region indicates an aortic etiology**
- **Decreased A2** indicates a valvular etiology
- Systolic ejection click (abrupt distension of the aorta)
- **S3**
- **Systolic ejection murmur** (↗ stroke volume) ± thrill
- **Austin Flint murmur**: diastolic rumbling due to aortic reflux onto anterior mitral leaflet
- **Distinguish AR from PR**: AR → murmur starting at A2; peripheral signs; PR murmur ↗ during inspiration

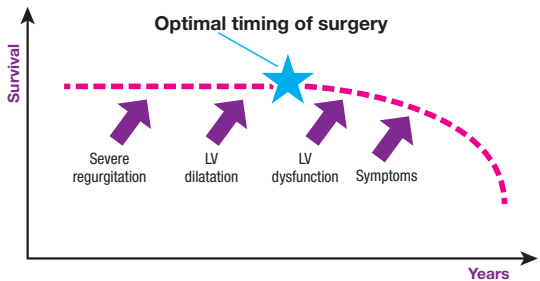


Musset's sign	Systolic nodding of the head
Müller's sign	Systolic pulsation of uvula
Quincke's sign	Capillary pulsation (by pressing lightly on the tip of the nail)
Corrigan's pulse / Water hammer pulse	Abrupt distension with prominent pulse then rapid collapse (more accurately assessed in the radial artery with the arms raised)
Traube's sign (pistol shot)	Systolic and diastolic bruit in the femoral artery
Duroziez' sign	Systolic murmur in the femoral artery with proximal compression and diastolic murmur with distal compression (from the stethoscope)
Hill's sign	SBP in arms > 20 mmHg higher than SBP in legs

OUTCOME AND FOLLOW-UP

Survival rate declines markedly in the presence of symptoms or LV dysfunction

› **Mortality in the presence of symptoms**: > 10 % / year

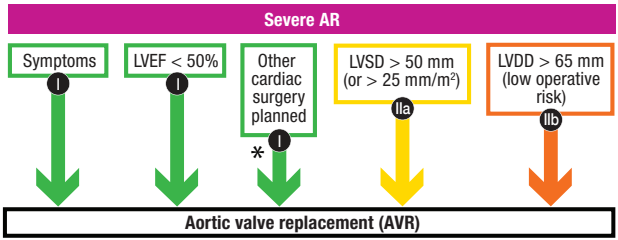


NEWLY DIAGNOSED AR	MILD AR	MODERATE AR	SEVERE AR	SEVERE AR WITH LV DILATATION
TTE at 3 months to ensure stability	TTE every 3 to 5 years	TTE every 1 to 2 years	TTE every 6 to 12 months	TTE every 4 to 6 months

MANAGEMENT

MEDICAL: patient education - report all symptoms; avoid strenuous physical exertion / isometric exercises; echocardiographic follow-up; treat diastolic HTN (ACE inhibitors or Nifedipine); avoid bradycardia; ACE inhibitors and beta-blockers if poor candidate for surgery with severe AR with symptoms and/or LV dysfunction

SURGERY: AVR vs AVR + ascending aorta replacement (Bentall) vs Valve repair vs Ascending aorta replacement + valvular resuspension (David procedure) vs Ross procedure



* IIa if moderate AR

4.3/ ACUTE AORTIC REGURGITATION

ETIOLOGIES: **A)** Endocarditis; **B)** Aortic dissection; **C)** Trauma; **D)** Prosthetic valve dysfunction

HEMODYNAMIC CONSEQUENCES: Regurgitant volume in poorly compliant LV → ↗↗ diastolic pressures → Congestive heart failure

- ↘ Anterograde flow → Systemic hypoperfusion / Shock
- Early mitral valve closure (restrictive diastolic filling pattern)

PHYSICAL EXAMINATION: Tachycardia; shock; pulmonary edema

- ↘ S1 (early mitral valve closure); S3 and S4
- **Brief diastolic murmur** (early pressure equalization on either side of the valve)
- **Austin Flint rumble**
- Systolic murmur (↗ stroke volume)
- Signs of PHT

MANAGEMENT: Urgent surgery

- Positive inotropic agent (Dobutamine) and/or vasodilator (Nitroprusside)

4.4/ MITRAL STENOSIS

ETIOLOGY

RHEUMATIC FEVER: Leading cause of MS

- 25% of patients have isolated MS; 40% have MS and MR; 35% have concomitant aortic valve disease; 6% have concomitant tricuspid valve disease

OTHER RARE CAUSES: **A)** Congenital; **B)** Carcinoid with lung metastases or PFO; **C)** SLE; **D)** RA; **E)** Hunter-Hurler; **F)** Fabry; **G)** Whipple; **H)** Methysergide; **I)** Calcific MS (age related)

DDX (LV INFLOW OBSTRUCTION): LA tumor - Myxoma; LA thrombus; Obstructive vegetation; Cor triatriatum; Severe mitral annular calcification (age); Pulmonary vein stenosis

SEVERITY

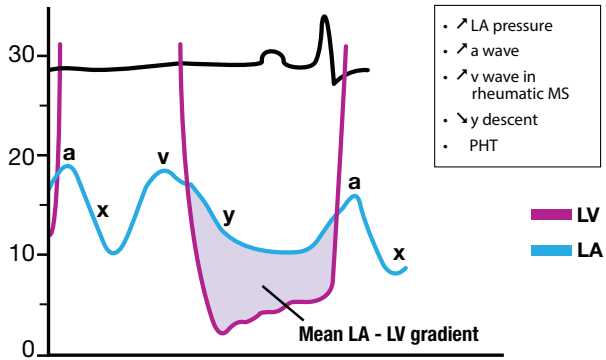
NORMAL AREA: 4-5 cm²

	MILD	MODERATE	SEVERE
Valve area (cm²)	> 1.5	1.0 - 1.5	< 1.0
Mean gradient (mmHg)	< 5	5 - 10	> 10
sPAP (mmHg)	< 30	30 - 50	> 50
Pressure half-time (ms)		150 - 220	> 220 ms

Indices valid for heart rate between 60 and 90 bpm

HEMODYNAMIC CONSEQUENCES

- ↗ LA pressure → pulmonary congestion / PHT / Right heart failure
- LA dilatation → risk of AF / atrial stasis / peripheral embolism
- Intolerance of tachycardia or loss of atrial kick
- Low output state



SYMPTOMS AND SIGNS

SYMPTOMS: Dyspnea; tiredness; poor exercise tolerance; OTP; PND

- **PHT**: Right heart failure; hemoptysis (rupture of bronchial veins; rupture of capillaries; pulmonary edema)
- Palpitations; peripheral embolism
- Recurrent laryngeal nerve compression by dilated LA (Ortner's syndrome)

MITRAL FACIES: secondary to systemic vasoconstriction; pink-purple plaques on cheeks

JUGULAR: JVD; prominent a wave (sinus rhythm)

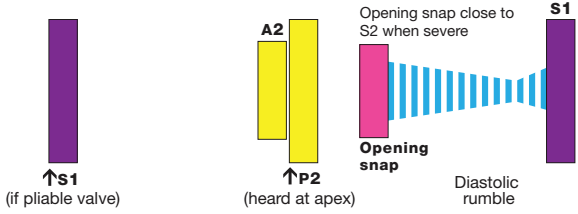
AUSCULTATION: ↗ **S1** when leaflets still pliable and only slightly calcified

OPENING SNAP: Heard more clearly with the diaphragm; absent during significant leaflet calcification

› **A2 - opening snap interval inversely proportional to the severity of MS (severe if < 80 ms)**

DIASTOLIC RUMBLE: Heard more clearly in left lateral supine position with the bell at the apex; look for thrill; murmur increased during tachycardia - exercise

SIGNS OF PHT: **left parasternal heave; P2 increased** (± palpable); ejection click (PA dilatation); TR murmur; Graham Steell murmur; right S3-S4



INVESTIGATIONS AND OUTCOME

TTE: Rheumatic MS → thickening ± calcification of leaflets; hockey stick appearance of anterior mitral leaflet; LA dilatation; commissural fusion with "fish-mouth" mitral orifice (PSAX)

ECHOCARDIOGRAPHIC FOLLOW-UP

MILD MS	MODERATE MS	SEVERE MS
TTE every 3 to 5 years	TTE every 1 to 2 years	TTE annually

STRESS TEST: Evaluate exercise capacity and symptoms

› Combined with TTE to evaluate PAP and mean gradient on exertion when there is a discordance between symptoms and TTE at rest

OUTCOME: **Valve area ↘ by 0.09 cm²/year**

› 5-year survival in patients with symptomatic severe MS without intervention: 44%

MANAGEMENT

MEDICAL: prevention of recurrence of rheumatic fever (penicillin-based prophylactic antibiotics); avoid strenuous exertion; follow-up and decision to operate at the optimal time; aggressive treatment of AF and thromboembolic risk; diuretics PRN; avoid tachycardia

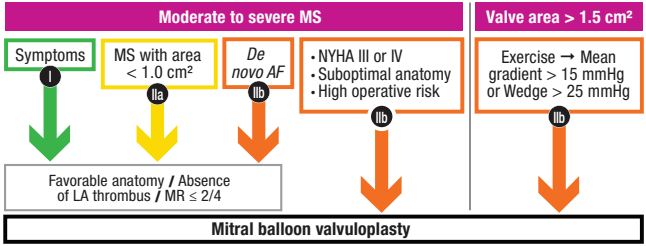
› **Indication for anticoagulation**: **AF; Cardioembolic history; LA thrombus**

BALLOON MITRAL VALVULOPLASTY: transseptal approach; TEE guidance; Inoue 23 to 25 mm balloon; inflation of the balloon inside the valve orifice in order to open commissures

› **Better results in a context of favorable anatomy**: **Wilkins score (BVR) ≤ 8 points**
  - **Success**: valve area > 1.5 cm² and LA pressure < 18 mmHg

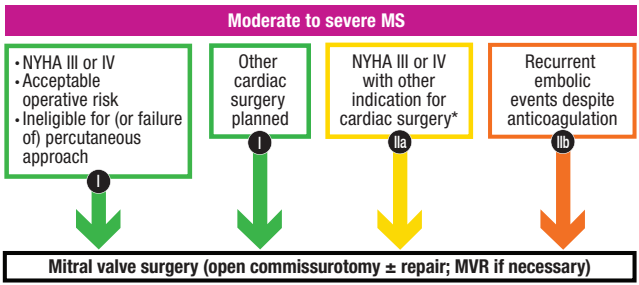
› **Contraindications: moderate to severe MR; LA thrombus (pre-procedure TEE); unfavorable anatomy**

› **Complications**: mortality 1%; stroke - embolism 1-2%; cardiac perforation 1%; MR requiring surgery 2%; iatrogenic ASD; myocardial infarction < 1%



SURGICAL APPROACH: **A)** Closed commissurotomy (obsolete approach); **B)** Open commissurotomy ± mitral valve repair (under CPB); **C)** MVR

› Consider MAZE and LAA amputation during surgery (★ CTSN AF)



* TR; CAD; aortic valve disease; aortic aneurysm, etc.

4.5/ CHRONIC MITRAL REGURGITATION

ETIOLOGY

DEGENERATIVE: **MVP - Myxomatous disease**; Marfan; Ehlers-Danlos; Pseudoxanthoma elasticum; Mitral annular calcification

INFLAMMATORY: **Rheumatic disease**; SLE; Scleroderma; Hypereosinophilia syndrome

INFECTIOUS: Endocarditis

STRUCTURAL: **Ruptured chordae tendineae** (spontaneous - idiopathic; MI; trauma; MVP; endocarditis; rheumatic fever; acute LV dilatation)

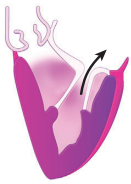
CONGENITAL: Cleft mitral valve; parachute mitral valve (absence of mitral papillary muscle)

FUNCTIONAL MR: associated with LV dysfunction / LV dilatation; **structurally normal valve;** + MR secondary to: **A)** Mitral papillary muscle displacement (malcoaptation of leaflets; tenting area > 6 cm² associated with MR ≥ 3/4; **B)** Annular dilatation; **C)** Loss of the annular systolic contraction; **D)** ± Mitral papillary muscle dysfunction in the presence of concomitant ischemia

› **Ischemic papillary muscle dysfunction**: **posteromedial muscle (perfusion by PDA)** +
>> anterolateral muscle (double perfusion by diagonal and marginal arteries)

CARPENTIER'S CLASSIFICATION

According to movement of the leaflets

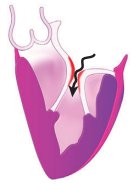


NORMAL MOVEMENT

Endocarditis
Trauma
Annular dilatation

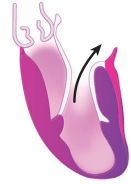
↑ **MOVEMENT**

MVP
Ruptured chordae tendineae



SYSTOLO-DIASTOLIC RESTRICTION

Rheumatic



SYSTOLIC RESTRICTION

Papillary muscle dysfunction

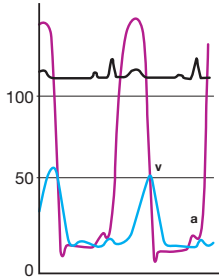
Displaced papillary muscle secondary to RWMA / LV dilatation

SEVERITY

	MILD MR (1/4)	MODERATE MR (2 to 3/4)	SEVERE MR (4/4)
Veina contracta (mm)	< 3	3 - 6.9	≥ 7
Regurgitant volume (mL/b)	< 30	2/4: 30 - 44 3/4: 45 - 59	≥ 60
Regurgitant fraction (%)	< 30	30 - 49	≥ 50
Regurgitant orifice (cm^2) (prognostic value)	< 0.20	2/4: 0.2 - 0.29 3/4: 0.3 - 0.39	≥ 0.40
Jet area	Small central jet < 4 cm^2 or < 20% of LA area	Intermediate	Large central jet > 10 cm^2 (or > 40% of LA area) or eccentric jet along the LA wall (Coanda)
Pulmonary vein flow rate	Systolic dominance	Systolic attenuation	Systolic reversal
Jet envelope on continuous Doppler	Faint; parabolic	Intermediate	Dense; Early, triangular peak
LA dimensions	Normal		Dilatation
LV dimensions	Normal		Dilatation
Angiography	1+	2+	3-4+

FUNCTIONAL MR: severe regurgitation when regurgitant orifice ≥ 0.20 cm^2 or regurgitant volume ≥ 30 mL/b or regurgitant fraction ≥ 50%

HEMODYNAMIC CONSEQUENCES



- **Prominent v wave** (≥ 2-3 x mean LA pressure) except in the presence of significant LA dilatation
- Prominent y descent
- PAP contaminated by v wave
- ± LA-LV diastolic flow gradient

CHRONIC MITRAL REGURGITATION

→ **↓ Anterograde volume** → *Tiredness*

Tolerated for a long time due to low afterload (the LA is a low pressure safety valve) → **Ventricular volume overload** → **Eccentric LVH** (sarcomeres in series) → **Possible systolic dysfunction** → *Heart failure*

- Annular dilatation
- Papillary muscle displacement

LA dilatation → *AF*

↑ LA pressure and Possibly ↑ PAP

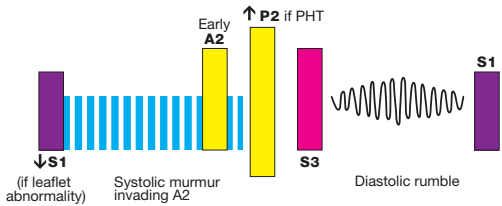
SYMPTOMS AND SIGNS

SYMPTOMS: Dyspnea; OTP; PND; symptoms of low output state; Palpitations (AF); Right heart failure

APEX : hyperdynamic; **dilated; lateralized**; ± palpable S3; palpable wave in left parasternal region (dilated LA kick)

AUSCULTATION : **Decreased S1** in the presence of a leaflet abnormality; early A2 and split S2; P2 > A2 in the presence of PHT; S3; diastolic rumble (↗ inflow)

SYSTOLIC MURMUR: spreads as far as (and invades) A2; **often holosystolic**; ± thrill; high-pitched; maximum at the apex; radiation to the axilla or left scapula (posteriorly directed murmur) or sternum and base (anteriorly directed murmur as in posterior leaflet MVP); not amplified post-PVC; decreased by standing up (increased by squatting); decreased during Valsalva; increased by clenching the fists (in contrast with aortic stenosis)



DDx: **A)** VSD: murmur maximal in left parasternal region; thrill in left parasternal region; **B)** TR: murmur ↗ on inspiration; murmur maximal in left parasternal region; prominent jugular v wave

ISCHEMIC PAPILLARY MUSCLE DYSFUNCTION: mid-systolic or end-systolic murmur

ECHOCARDIOGRAPHIC FOLLOW-UP

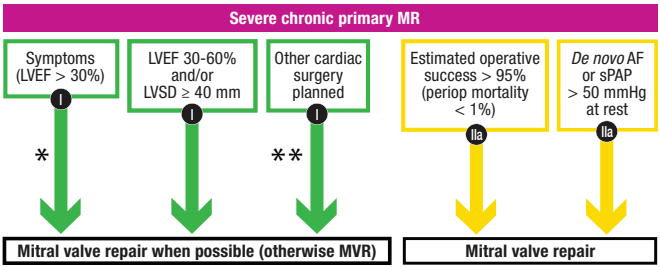
MILD MR	MODERATE MR	SEVERE MR
TTE every 3 to 5 years	TTE every 1 to 2 years	TTE 6 to 12 months

TEE to clarify the anatomy, mechanism, severity and possibility of repair

Stress echocardiography PRN to detect ischemic MR and to measure PAP on exertion

MANAGEMENT

MEDICAL: **little benefit of vasoactive agents in the presence of normal LVEF** (afterload is rarely increased except in HTN); anticoagulation in the presence of AF; aggressive treatment of LV dysfunction in the presence of functional MR (+ resynchronization)



IIb: Consider Mitraclip when surgery is contraindicated in NYHA III or IV with favorable anatomy

*IIb: Symptoms and LVEF < 30% ** IIa: Moderate chronic primary MR (mitral valve repair)

MITRAL VALVE REPAIR / ANNULOPLASTY: Best candidates (in the absence of calcification) → **A)** Degenerative MR - MVP (posterior leaflet easier to repair); **B)** Annular dilatation; **C)** Papillary muscle dysfunction; **D)** Ruptured chordae tendineae; **E)** Leaflet perforation (endocarditis)

- Possible via a minimally invasive approach
- Warfarin for 3 months post-repair; ASA 80 indefinitely

MVR: opt for preservation of the subvalvular apparatus whenever possible (LVEF ↘ by 10% if loss of the subvalvular apparatus due to modification of LV geometry)

MITRACLIP: percutaneous transseptal repair; creation of a double orifice valve using a clip (equivalent to Alfieri procedure)

- ★ **EVEREST**: Mitraclip less effective than conventional surgery to reduce the degree of regurgitation
- **Candidates**: inoperable patient; mitral regurgitation with **regurgitant jet due to malcoaptation of segments A2 and P2**; functional or degenerative regurgitation (MVP or leaflet eversion); depth of coaptation < 11 mm; vertical length of coaptation > 2 mm

FUNCTIONAL MR: ▸▸| Chapter 3

MITRAL VALVE PROLAPSE

2.4% of the population; female predominance

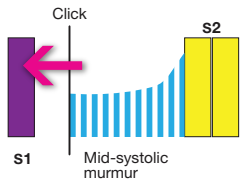
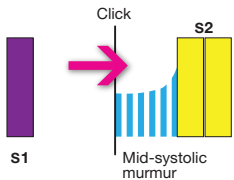
DIAGNOSIS: **A)** Mid-systolic click then murmur; **B) Displacement of one or both leaflets > 2 mm behind the plane of the mitral annulus (PLAX); C) ± Thickening of the leaflets by > 5 mm**

ETIOLOGIES

a) **MVP syndrome**: young woman; benign; associated with OH - palpitations - anxiety; thin leaflets
b) **MVP with myxomatous thickening**: often males aged 40-70 years; thickening / redundancy of the leaflets; significant risk of progression; risk of ruptured chordae tendineae
c) **MVP associated with another disease**: Marfan; HCM; Ehlers-Danlos; osteogenesis imperfecta; *pseudoxanthoma elasticum;* Holt-Oram syndrome; *ostium secundum* ASD; Ebstein's anomaly

CLINICAL FEATURES: **mid-systolic click** then mid- or end-systolic murmur (often crescendo); normal S1; dynamic auscultation

› Mid-systolic click different from the aortic ejection click, as it occurs after the onset of the carotid upstroke

DECREASED LEFT INTRAVENTRICULAR VOLUME	INCREASED LEFT INTRAVENTRICULAR VOLUME
Effect: ↗ duration of MVP murmur  	Effect: ↘ duration of MVP murmur 
Maneuvers: • Tachycardia • ↘ Afterload • ↗ Contractility • ↘ Venous return (standing; Valsalva)	**Maneuvers:** • Bradycardia • ↗ Afterload (clenched fists) • ↘ Contractility • ↗ Venous return (squatting; raising legs)

COMPLICATIONS: Heart failure; Ruptured chordae tendineae; Thromboembolism; Endocarditis; AF; serious complications (including surgery) in 1/100 patient-years

› **TIA**: ASA 80 mg qd
› **AF**: anticoagulation if > 65 years or HTN or MR or history of heart failure
› **Stroke**: anticoagulation if MR or AF or LA thrombus or leaflets > 5 mm

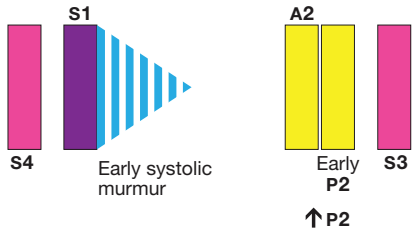
4.6/ ACUTE MITRAL REGURGITATION

ETIOLOGIES: **A)** Endocarditis; **B)** Trauma - Iatrogenic; **C)** Ruptured chordae tendineae (idiopathic-spontaneous; myxomatous degeneration / MVP; Marfan; Ehlers-Danlos; endocarditis; acute rheumatic fever; trauma); **D)** Papillary muscle dysfunction or rupture (ischemia - MI); **E)** Prosthetic valve dysfunction

HEMODYNAMIC CONSEQUENCES: Acute MR → poorly compliant LA (significant v wave) → pulmonary congestion / PHT

› Acute MR → low anterograde flow

PHYSICAL EXAMINATION: **Decrescendo early systolic murmur** due to rapid equalization of pressures on both sides of the valve; **S3 and S4**; signs of PHT; early closure of pulmonary valve (early P2); pulmonary overload; hypotension; tachycardia



MANAGEMENT: Urgent surgery in the presence of heart failure

› **Medical treatment**: Nitroprusside (± Dobutamine) while waiting for surgery; IABP

4.7/ TRICUSPID STENOSIS

ETIOLOGIES: **Rheumatic** (majority); usually associated with MS

› **Other causes (rare)**: Congenital atresia; RA tumor; Carcinoid syndrome (TR >> TS); PPM lead; Extracardiac tumor; Thrombus; Endomyocardial fibrosis; Endocarditis; SLE

SEVERITY: Significant TS when valve area ≤ 1 cm^2 or mean gradient ≥ 5 mmHg or pressure halftime > 190 ms

JUGULAR: Prominent a wave; Loss of y descent

AUSCULTATION: diastolic rumble in lower left parasternal region with ↗ on **inspiration** (± thrill); murmur ↗ on **Mueller maneuver** (inspiration against closed glottis) or during exercise

› Opening snap following that of MS in lower left parasternal region
› Diastolic rumble of the MS; Opening snap

SIGNS OF RIGHT HEART FAILURE (ascites; HSM; peripheral edema; JVD)

MANAGEMENT: operation if **severe symptomatic TS or severe TS with concomitant mitral surgery**

› Open commissurotomy vs TVR (bioprosthesis) vs Balloon valvuloplasty

4.8/ TRICUSPID REGURGITATION

ETIOLOGIES: **Secondary / Functional** (majority); secondary to dilatation of the tricuspid annulus following dilatation of the RV (sPAP > 55 mmHg; RV infarction; PS; DCM; left heart failure...)

› **Primary causes**: Rheumatic; Endocarditis; Ebstein's anomaly; Prolapse (associated with MVP); Carcinoid; Papillary muscle dysfunction / Ruptured chordae tendineae; Trauma; Marfan; RA; Radiotherapy; AV canal defect; Endomyocardial fibrosis; Myxoma; PPM lead; Repeated biopsy (heart transplant); anorectics; SLE

SEVERITY

	MILD TR (1/4)	MODERATE TR (2 – 3/4)	SEVERE TR (4/4)
Jet area (central) cm²	< 5	5 - 10	> 10
Vena contracta (mm)			≥ 7
PISA radius (mm)	≤ 5	6 - 9	> 9
Tricuspid E (m/sec)			> 1
Jet envelope on continuous Doppler	Faint; parabolic	Intermediate	Dense; Early, triangular peak
Hepatic vein flow	Systolic dominance	Systolic attenuation	Systolic reversal

› **Other criteria**: tricuspid annulus ≥ 40 mm (or > 21 mm/m²); D-shaped septal curvature; RV - RA dilatation; EROA ≥ 0.4 cm²; regurgitant volume ≥ 45 mL/b

INSPECTION: Cachexia; Jaundice; Pulsatile orbits

JUGULAR: Prominent c-v wave; loss of x descent; prominent y descent; ± venous thrill; Kussmaul

PALPATION: left parasternal heave; RV lift

AUSCULTATION: **Right S3** (↗ on inspiration); ↗ P2 if PHT; holosystolic murmur in lower left parasternal region (early systolic if primary TR); murmur ↗ on inspiration (Carvallo's sign); **murmur ↗ on Mueller's maneuver**

SIGNS OF RIGHT HEART FAILURE (ascites; pulsatile liver; HSM; peripheral edema; JVD)

MANAGEMENT - SECONDARY TR: Tricuspid annuloplasty during mitral surgery in the presence of: **A)** Severe TR or **B)** Mild-to-moderate TR with dilatation of the tricuspid annulus (≥ 40 mm) or in the presence of PHT or right heart failure

MANAGEMENT - PRIMARY TR: Bioprosthesis TVR or Annuloplasty if severe symptomatic TR or severe TR with progressive RV dilatation / dysfunction or severe TR with concomitant mitral surgery

› **TR secondary to endocarditis in IDU**: total excision of the valve is possible
› **Carcinoid syndrome**: ▶▶| Chapter 5 - RCM

4.9/ PULMONARY STENOSIS

▶▶| Chapter 7 - Congenital heart disease

ETIOLOGIES: Congenital (majority)

› **Fusion of commissures**: thin, dome-shaped valve; treatment by balloon valvuloplasty
› **Dysplastic valve**: thickened leaflets; Noonan syndrome; surgical treatment

OTHER ETIOLOGIES (RARE): Carcinoid; extrinsic compression (tumor; aortic sinus aneurysm); Rheumatic; Supravalvular or subvalvular obstruction (congenital)

SEVERITY: Severe PS if peak gradient > 64 mmHg

4.10/ PULMONARY REGURGITATION

ETIOLOGIES: **A)** Annular dilatation or dilatation of PA (PHT); **B)** Endocarditis; **C)** Following correction of congenital PS - TOF; **D)** Congenital; **E)** Trauma; **F)** Carcinoid; **G)** Rheumatic; **H)** Syphilis

SEVERITY

	MILD PR (1/4)	MODERATE PR (2 TO 3/4)	SEVERE PR (4/4)
Jet envelope on continuous Doppler	Faint; Slow deceleration	Intermediate	Dense; Marked deceleration; early end of diastolic flow (± anterograde diastolic flow)

› **Other criteria**: D-shaped septal curvature; RV dilatation; PHT < 100 ms

PALPATION: left parasternal heave; systolic beat in the 2nd intercostal space (PA dilatation)

AUSCULTATION: Delayed P2; systolic click (PA dilatation); mid-systolic ejection murmur (↗ flow); right S3 and S4 (increased on inspiration)

› **Diastolic murmur:** soft, low-pitched (in the absence of PHT); ↗ on inspiration
› **Graham Steell murmur**: decrescendo high-pitched diastolic murmur in the presence of dilatation of the pulmonary annulus secondary to PHT; accentuated P2; starts after A2; ↗ on inspiration; signs of PHT; TR murmur

4.11/ MULTIVALVULAR HEART DISEASE

AS & MS: Aortic transvalvular gradient underestimated (low flow)

AS & MR: MR increased due to high left intraventricular pressure; the aortic transvalvular gradient can be underestimated (low flow); operate on the mitral valve when MR is severe or in the presence of significant mitral structural disease

AR & MR: MR accentuates AR causing more severe pulmonary congestion; severe LV dilatation (accentuating MR)

4.12/ VALVE PROSTHESES

MECHANICAL PROSTHESES	BIOPROSTHESES
• High thrombo-embolic risk • Excellent durability • **Prefer in patients < 60 years**	• Risk of structural deterioration (Mitral >> Aortic) - Decreased risk in patients > 65 years • **Prefer in the presence of: A) Bleeding risk; B) Difficult anticoagulation; C) > 70 years; D) Small LVOT (stentless bioprosthesis); E) Woman of childbearing potential; F) Patient preference**
• Double-leaflet (St-Jude; Carbo-Medics; ATS Medical) • Tilting-disk (Medtronic-Hall; Omnicarbon)	• Stented porcine bioprosthesis (Mosaic) • Stented bovine pericardium bioprosthesis (Carpentier-Edwards; Mitroflow) • Stentless bioprosthesis - Less obstructive; prefer in patients with small LVOT • Homograft: cadaveric valve - Used for complex aortic valve endocarditis • Ross procedure: autologous transplant of the patient's P valve to the Ao valve; use a cadaveric valve for the P valve - Use in young patients / women of childbearing potential • Percutaneous bioprosthesis (TAVI): - Deployed by balloon (Edwards-Sapien; Sapien XT) - Self-expanding bioprosthesis (Corevalve)

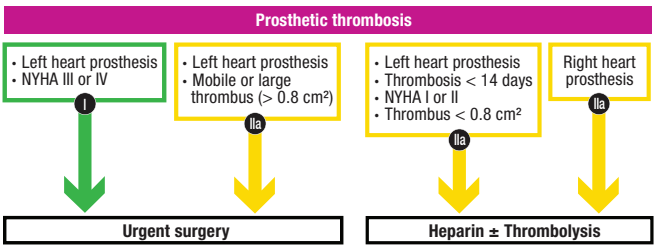
COMPLICATIONS: **A)** Structural deterioration; **B)** Pannus; **C)** Patient-prosthesis mismatch (▸▸| Chapter 1 - Echocardiography); **D)** Thrombosis; **E)** Embolism; **F)** Endocarditis (vegetation; abscess; fistula; dehiscence; destruction); **G)** Periprosthetic leak; **H)** Hemolysis related to periprosthetic regurgitation (↗ LDH; ↗ Bilirubin; ↘ Haptoglobin; Schistocytes); **I)** Dehiscence (rule out endocarditis); **J)** Bleeding secondary to anticoagulants; **K)** Pseudoaneurysm

- **Structural deterioration**: TAVI is possible (valve-in-valve)
- **Periprosthetic regurgitation**: Percutaneous closure with Amplatzer prosthesis (with 3D TEE guidance); indicated if the patient is not a candidate for surgery with significant periprosthetic regurgitation and secondary heart failure or hemolysis (transfusion-dependent); transseptal or transapical approach (M valve); retrograde arterial approach (Ao valve)

MECHANICAL VALVE: thromboembolic risk ⟶ 1-2 per 100 patient-years (aortic) and 2-3 per 100 patient-years (mitral)

PORCINE BIOPROSTHESIS: **structural deterioration** in 30% of patients at 10 years
- 10% at 10 years in patients > 65 years

PROSTHETIC THROMBOSIS: dyspnea; ↘ closing sound; *de novo* murmur
- **Diagnosis**: TTE - TEE - Fluoroscopy
- **Risk**: 0.1%/ year for aortic valve; 0.35%/year for mitral valve (with adequate treatment)



rtPA 10 mg bolus then 90 mg IV over 120 min
Mortality: 4-12% / Embolism: 15%

ANTITHROMBOTIC THERAPY

MITRAL VALVE REPAIR / ANNULOPLASTY	
• Warfarin for 3 months (INR 2-3) • ASA 80 mg qd indefinitely	
BIOPROSTHESIS	
• ASA 80 mg qd indefinitely • ± Warfarin 3 months postoperatively (INR 2-3); Class IIa recommendation for bioprosthesis MVR; • Class IIb recommendation for bioprosthesis AVR	
MECHANICAL PROSTHESIS (MODERN)	
Low risk **AVR with no risk factors*** • Warfarin indefinitely (INR 2-3) • ASA 80 mg qd indefinitely	**High risk** **AVR with risk factors* or MVR** • Warfarin indefinitely (INR 2.5-3.5) • ASA 80 mg qd indefinitely

*** Risk factors: AF / LV dysfunction / History of thromboembolic disease / Hypercoagulability**

EMBOLISM DESPITE WARFARIN THERAPY: **A)** If INR 2-3 → target INR 2.5-3.5; **B)** If INR 2.5-3.5 → target INR 3.0-4.0; **C)** If patient not taking ASA → add ASA

EXCESSIVE ANTICOAGULATION: **A)** Life-threatening bleeding → Prothrombin complex concentrate (or FFP) + vitamin K 5-10 mg IV (max: 1 mg/min); **B)** INR > 10 without bleeding → suspend Warfarin; vitamin K 2.5 mg PO

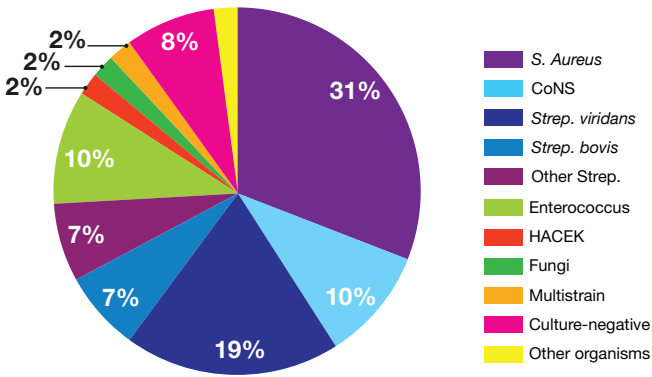
FOLLOW-UP

BIOPROSTHESIS	MECHANICAL VALVE
• Baseline TTE to 2-4 weeks after discharge • Annual follow-up (± TTE if new symptoms and signs) • After 10 years: annual TTE	• Baseline TTE to 2-4 weeks after discharge • Annual follow-up (± TTE if new symptoms and signs)

AT FOLLOW-UP: Physical examination; ECG; CXR; ± Laboratory tests (CBC; BUN / Creatinine; Clotting assessment; INR; Blood cultures); Prophylactic antibiotics

4.13/ INFECTIVE ENDOCARDITIS

MICROBIOLOGY



Culture-negative:

Previous antibiotic; *Coxiella burnetii; Bartonella sp.; Aspergillus sp.; Mycoplasma pneumonia; Brucella sp.; Legionella pneumophila; Tropheryma whipplei; Bartonella sp.;* Fungi (*Candida sp.; Aspergillus sp.*); Antiphospholipid syndrome; Marantic endocarditis; Porcine bioprosthesis allergic response; Rheumatic carditis; Polyarteritis nodosa...

***S.aureus* (including MRSA)**	• Aggressive acute endocarditis; marked toxicity • Metastatic infection; valve destruction • Mortality 25-40% (left heart)
Coagulase-negative Staphylococcus - CoNS ***(S. epidermidis; S. lugdunensis)***	• Foreign body infection / prostheses • Nosocomial infection
Streptococcus viridans (sanguis; mutans; mitis; salivarius...)	• Oropharyngeal flora; alpha-hemolytic • **Subacute endocarditis** • Highly sensitive to penicillin
Streptococcus bovis (gallolyticus)	• GI flora; associated with polyps and colon cancer • **Subacute endocarditis** • Highly sensitive to penicillin
Beta-hemolytic Streptococci (groups A - B - C - G)	• Frequent intracardiac and extracardiac complications; abscess
Enterococci (*faecalis* and *faecium*)	• GI flora • Associated with urinary tract infection/nosocomial infection • Treatment requires bactericidal activity **(synergism with gentamicin)**
HACEK • ***Haemophilus sp.*** • ***Aggregatibacter sp. (previously Actinobacillus)*** • ***Cardiobacterium hominis*** • ***Eikenella corrodens*** • ***Kingella sp.***	• Fastidious Gram-negative bacilli • Upper respiratory tract infections - Oropharyngeal flora • Positive blood culture after 5 days of incubation (sometimes longer) • Large vegetation
Other micro-organisms (can cause culture-negative endocarditis)	• ***Coxiella burnetii* (Q fever)**: subacute endocarditis; elevated IgG titer • ***Bartonella sp.***: Culture-negative endocarditis (perform serology or specific culture technique); cat scratch disease • **Fungi *(Candida)*:** Risk factors: immunodepression - prosthesis - central line - IDU; invasive endocarditis • **Others**: *Brucella sp.; Tropheryma whipplei; Mycoplasma sp.; Legionella sp.*

RISK FACTORS

RISK FACTORS: MVP; congenital heart disease (bicuspid aortic valve; VSD; patent ductus arteriosus); rheumatic disease; degenerative valvular heart disease; IDU; prosthesis or intracardiac device; hospitalization - nursing home; central line; hemodialysis; history of endocarditis

IDU (INJECTION DRUG USERS): *S.aureus* (most frequent organism); mostly involving the tricuspid valve (look for septic pulmonary emboli)

PROSTHETIC VALVE ENDOCARDITIS (PVE)

- **Early (< 12 months post-op): CoNS; *S. aureus*; Gram-negative bacilli; Fungi *(Candida); Corynebacterium* sp; *Legionella* sp**
- **Late (> 12 months post-op): similar microbiology to community-acquired native valve endocarditis**
- Mortality due to *S. aureus* PVE: > 45%

MODIFIED DUKE CRITERIA

DEFINITE ENDOCARDITIS	POSSIBLE ENDOCARDITIS
• 2 major criteria or • 1 major + 3 minor criteria or • 5 minor criteria	• 1 major + 1 minor or • 3 minor criteria

MAJOR CRITERIA

1. Positive blood culture

A) Typical microorganism on ≥ 2 separate blood cultures
- *Strep. viridans; Strep. bovis;* HACEK*; S.areus* or
- Community-acquired Enterococcus with no primary site

B) Sustained bacteremia
- **Slow method**: ≥ 2 positive blood cultures taken at an interval of ≥ 12 h or
- **Rapid method**: 3/3 positive blood cultures or the majority of ≥ 4 blood cultures are positive (taken by different venipunctures); the first and last cultures were taken at an interval of > 1 h

C) *Coxiella burnetii* (Q fever): ≥ 1 positive culture bottle or IgG titer > 1:800

2. Endocardial involvement

A) Positive echocardiography
- Oscillating intracardiac mass (on valve or supporting structures, or in the path of regurgitant jets, or on foreign body) in the absence of an alternative explanation or
- Abscess or
- *De novo* prosthetic dehiscence

B) *De novo* valvular regurgitation

Minor criteria

1. **Predisposition** (heart disease or IDU)
2. **Fever** ≥ 38°C
3. **Vascular phenomenon**: arterial embolism; septic pulmonary infarction; mycotic aneurysm; intracranial hemorrhage; conjunctival hemorrhage; Janeway lesion
4. **Immunological phenomenon** (subacute endocarditis): glomerulonephritis; Osler's nodes; Roth's spot; positive rheumatoid factor; vasculitis
5. **Microbiological evidence**: positive blood culture but not meeting the major criterion or serological evidence of active infection (with organism consistent with infective endocarditis)

Li JS, Sexton DJ, Mick N, et al. Clin Infect Dis 2000;30:633

SYMPTOMS AND SIGNS

SYMPTOMS: fever; chills; night sweats; weight loss; dyspnea; cough; stroke; headache; nausea / vomiting; myalgia; arthralgia; retrosternal chest pain; back pain; abdominal pain; confusion

SIGNS: fever; neurological signs; signs of peripheral embolism; clubbing

- **Cardiac murmur**: in 85% of cases (uncommon in subacute endocarditis)
- **Splinter hemorrhages**: proximal nail fold; red lines
- **Petechiae**: conjunctiva; oral mucosa and palate; extremities
- **Osler's nodes**: small, painful subcutaneous nodule on fingertips (sometimes more proximal)
- **Janeway lesion**: painless, erythematous or hemorrhagic macular lesion on palms and soles
- **Roth's spot**: oval retinal hemorrhage (with central pallor)
- **Splenomegaly**: more frequent in subacute endocarditis

COMPLICATIONS

PERIPHERAL EMBOLISM

- **Risk factors**: vegetation > 10 mm / mobile; mitral valve (anterior leaflet); *S.aureus; Candida*
- **Uncommon after 2 weeks of effective treatment**
- Stroke; digital infarction; septic arthritis; discitis; splenic or renal infarction; splenic abscess; coronary embolism; mesenteric embolism; pulmonary embolism

STROKE: **A) Cardioembolic; B) Intracranial hemorrhage**: ruptured mycotic aneurysm or arteritis with rupture or hemorrhagic transformation of a stroke

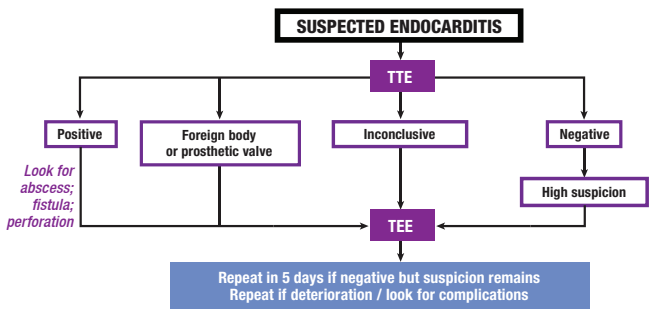
- **Dx**: **A) MRI angiography or CT angiography; B) Conventional angiography** to exclude small aneurysms (< 2 mm) not seen on non-invasive imaging
- **Indication for intervention:** progressing or ruptured aneurysm or > 7 mm
  - **Small aneurysm without rupture**: monitor (possible improvement with antibiotics)
- **When valve surgery is indicated: A) Stroke without bleeding → surgery without delay** (except with extensive brain damage / coma); **B) Intracranial bleeding → wait > 4 weeks**
- **Management of anticoagulation:** stop anticoagulation in patients with mechanical valve > 2 weeks in the presence of stroke (class IIa recommendation)

HEART FAILURE: A) Valve destruction; **B)** Ruptured chordae tendineae; **C)** Fistula; **D)** Purulent myocarditis; **E)** Coronary embolism; **F)** Valve obstruction

ARF: **A)** Immune complex glomerulonephritis (↘ complement); **B)** Renal embolism (renal infarction); **C)** Prerenal ARF; **D)** Gentamicin toxicity; **E)** Interstitial nephritis (secondary to antibiotics)

AV BLOCK / CONDUCTION DISORDERS: perivalvular abscess

ECHOCARDIOGRAPHY



SENSITIVITY: TTE → 70% (50% for prosthesis); **TEE →** 96% (92% for prosthesis)

VEGETATION: Oscillating mass with independent movement; atrial aspect for M and T valves; ventricular aspect for Ao and P valves; on the surface of implanted intracardiac material

- **DDx**: Old vegetation; Non-bacterial thrombotic endocarditis (marantic); Antiphospholipid syndrome / SLE (Libman-Sacks); degenerative changes / myxomatous valve; Lambl's excrescences; ruptured chordae tendineae; Ca^{2+}; nodule - RA; thrombus; fibroelastoma

LOOK FOR: **vegetation; abscess** (not communicating with the lumen) **/ pseudoaneurysm** (pulsatile; colour-Doppler flow detected); **prosthetic dehiscence** (± rocking motion); valvular aneurysm (saccular bulging); intracardiac fistula; valve perforation - channel; purulent pericarditis; obstruction; early mitral valve closure in acute AR (with restrictive diastolic pattern)

MANAGEMENT

ANTIBIOTIC TREATMENT: Target → eradication of microorganisms; bactericidal antibiotic action; sufficient serum concentrations (to penetrate the vegetation by diffusion); minimal toxicity

- **MIC**: Minimum inhibitory concentration (to inhibit growth)
- **MBC**: Minimum bactericidal concentration (to reduce the inoculum)

DURATION: from the first day on which blood cultures ar negatives

- **Positive operative tissue cultures**: entire antimicrobial course after valve surgery

PNC-SENSITIVE *STREP. VIRIDANS* OR *STREP. BOVIS* - MIC < 0.12 µG/ML		
PNC G	12-18 million U / day IV (4-6 doses)	4 weeks
Ceftriaxone	2 g / day IV or IM (1 dose)	4 weeks
PNC G (or Ceftriaxone) + Gentamicin	12-18 million U / day IV (4-6 doses) 3 mg/kg / day IV or IM (1 dose)	2 weeks 2 weeks
Vancomycin	30 mg/kg / day IV (2 doses)	4 weeks

- **Prosthesis: A)** 6 weeks therapy of PNC G (24 million U / day) or Ceftriaxone (with or without gentamicin for the first 2 weeks); **B)** 6 weeks therapy of Vancomycin
- Serum Vancomycin levels: trough 10-15 µg/mL
- Serum Gentamicin levels (3 divided doses): peak serum 3-4 µg/mL; trough < 1 µg/mL

STREP. VIRIDANS OR *STREP. BOVIS* RELATIVELY RESISTANT - MIC 0.12 – 0.50 µG/ML		
PNC G + Gentamicin	24 million U / day IV (4-6 doses) 3 mg/kg / day IV or IM (1 dose)	4 weeks 2 weeks
Vancomycin	30 mg/kg / day IV (2 doses)	4 weeks

- **Prosthesis**: 6 weeks therapy
- Ceftriaxone: consider as an alternative if the isolate is susceptible

METHICILLIN-SENSITIVE STAPHYLOCOCCUS - NO FOREIGN BODY		
Cloxacillin	12 g / day IV (4-6 doses)	6 weeks
Cefazolin	6 g / day IV (3 doses)	6 weeks
Vancomycin (ß-lactam allergy evaluation)	30 mg/kg / day IV (2 doses)	6 weeks

- Uncomplicated right heart endocarditis: 2 weeks

METHICILLIN-RESISTANT STAPHYLOCOCCUS - NO FOREIGN BODY		
Vancomycin	30 mg/kg / day IV (2 doses)	6 weeks
Daptomycin	≥ 8 mg/kg / day IV (1 dose)	6 weeks
METHICILLIN-SENSITIVE STAPHYLOCOCCUS - PROSTHESIS		
Cloxacillin + Rifampicin + Gentamicin	12 g / day IV (4-6 doses) 900 mg / day IV or PO (3 doses) 3 mg/kg / day IV or IM (2-3 doses)	≥ 6 weeks ≥ 6 weeks 2 weeks
METHICILLIN-RESISTANT STAPHYLOCOCCUS - PROSTHESIS		
Vancomycin + Rifampicin + Gentamicin	30 mg/kg / day IV (2 doses) 900 mg / day IV or PO (3 doses) 3 mg/kg / day IV or IM (2-3 doses)	≥ 6 weeks ≥ 6 weeks 2 weeks

- Rifampin: caution in relation to multiple drug interactions

ENTEROCOCCUS SPP.		
Ampicillin + Gentamicin	2 g IV every 4 h 3 mg/kg / day IV or IM (2-3 doses)	4-6* weeks 2-6 weeks (6 weeks with prosthetic valve)
Ampicillin + Ceftriaxone *(E. faecalis)*	2 g IV every 4 h 4 g / day IV or IM (2 doses)	6 weeks 6 weeks
Vancomycin + Gentamicin	30 mg/kg / day IV (2 doses) 3 mg/kg / day IV or IM (3 doses)	6 weeks 6 weeks

* 4 weeks with < 3 months duration of symptoms (6 weeks with ≥ 3 months)

HACEK		
Ceftriaxone	2 g / day IV or IM (1 dose)	4 weeks (6 weeks if prosthesis)

EMPIRICAL TREATMENT (BEFORE PATHOGEN IDENTIFICATION) – COMMUNITY–ACQUIRED NATIVE VALVE OR LATE PROSTHETIC VALVE (> 12 MONTHS)	
Ampicillin + Cloxacillin + Gentamicin	2 g IV every 4 h 12 g / day IV (4-6 doses) 3 mg/kg / day IV or IM
EMPIRICAL TREATMENT (BEFORE PATHOGEN IDENTIFICATION) – EARLY PROSTHETIC VALVE (< 12 MONTHS) OR NOSOCOMIAL ENDOCARDITIS	
Vancomycin + Gentamicin + Rifampin	30 mg/kg / day IV (2 doses) 3 mg/kg / day IV or IM 900 mg / day IV or PO (3 doses)

PROPHYLACTIC ANTIBIOTICS

Candidates

a) Prosthetic valve (or prosthetic valve material)
b) History of infective endocarditis
c) Congenital heart disease
1. Unrepaired cyanotic heart disease (including palliative conduits and shunts)
2. Complete repair with prosthetic material < 6 months
3. Repair with residual defect close to prosthesis / patch (preventing endothelialization)

d) Transplant recipient with regurgitation on a structurally abnormal valve

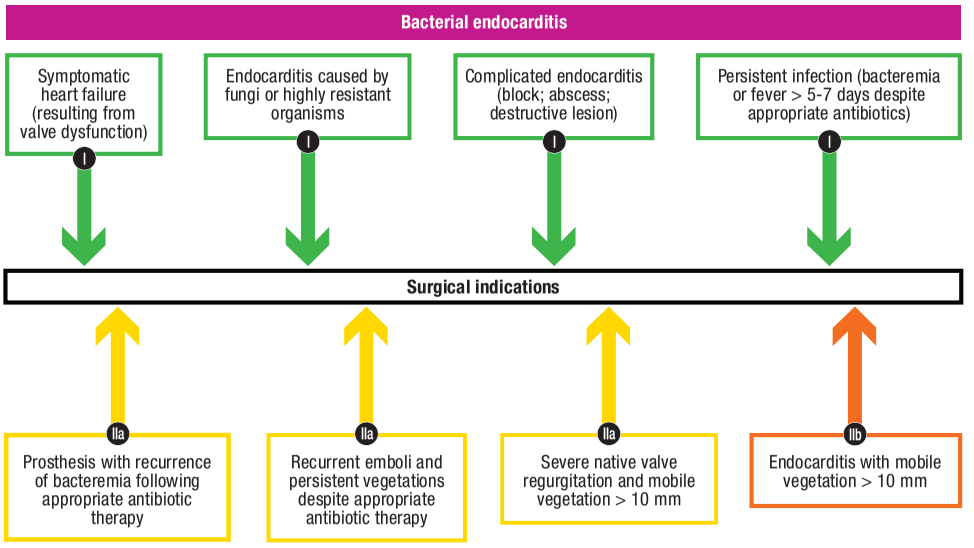
Procedure

- Dental procedure involving the gums or periapical region of the tooth or perforation of the oral mucosa

- **Amoxicillin 2 g PO** (60 min before the operation) or
- Cephalexin 2 g PO or Azithromycin 500 mg PO or Clindamycin 600 mg PO or
- Cefazolin or Ceftriaxone 1 g IM or IV

SURGICAL INDICATIONS

- Coronary CT angiography can provide coronary artery evaluation before cardiac surgery



I: Removal of implantable cardiac device (pacemaker or ICD) if documented infection of the system
IIa: Removal of implantable cardiac device (pacemaker or ICD) if endocarditis due to *S.aureus* or fungi

4.14/ CARDIAC IMPLANTABLE ELECTRONIC DEVICE INFECTION

MICROBIOLOGY: CoNS (42%); Sensitive *S. aureus* (25%); MRSA (4%); Gram-negative bacilli (9%); Multistrain (7%); Culture-negative (7%)

PATHOGENESIS

A) Pocket infection (during procedure or secondary to skin erosion) → ± propagation of infection to intravascular leads → ± intracardiac propagation of infection

B) Bacteremia *(S. aureus)* → hematogenous pocket and/or lead infection

ASSESSMENT: blood cultures x 2; TEE if blood cultures positive (rule out vegetation adherent to the lead and/or the valve); culture of the pocket after explantation of the system; FDG PET-CT (rule out increased FDG uptake)

MANAGEMENT

A) Superficial skin infection without involvement of the pocket and system → oral antibiotics against Staphylococcus for 7 to 10 days

B) Pocket infection and/or skin erosion: complete removal of the system (even in absence of systemic infection) + ATB

C) Documented system infection (lead endocarditis and/or valve endocarditis and/or bacteremia with pocket involvement): complete removal of the system + ATB (risk of clinically significant pulmonary embolism during percutaneous lead removal if vegetation on electrode > 2 cm)

D) Valve endocarditis (without documented system infection): complete removal of the system (± implantation of a new epicardial system) + ATB

E) Occult Staphylococcus bacteremia: complete removal of the system + ATB

EMPIRICAL ANTIBIOTICS: Vancomycin (then according to the organism / sensitivity)

DURATION OF ANTIBIOTICS: **A)** 7-10 days if skin erosion with no inflammatory changes; **B)** 10-14 days if pocket infection; **C)** > 2-4 weeks IV if bacteremia (repeat TEE in 2 weeks in the case of lead vegetation); **D)** > 4-6 weeks if complication (valve endocarditis; septic thrombophlebitis; osteomyelitis)

OPTIMAL TIMING FOR PLACEMENT OF A NEW DEVICE (CONTRALATERAL): **A)** Skin erosion / Pocket infection: in the absence of bacteremia; **B)** Positive blood cultures: absence of bacteremia x > 72 h post-explantation; **C)** Valve endocarditis: wait > 14 days before reimplanting an endovenous system

TEMPORARY PACEMAKER: Use active fixation lead

4.15/ RHEUMATIC FEVER

Autoimmune reaction 2 to 4 weeks after group A beta-hemolytic Streptococcus sore throat *(S. pyogenes)*

JONES' CRITERIA

Major criteria
1) Carditis and valvulitis
2) Migratory arthritis (swollen joints)
3) Sydenham's chorea (CNS inflammation; late manifestation)
4) Erythema marginatum (trunk; proximal limbs)
5) Subcutaneous nodules

Minor criteria
- Arthralgia
- Fever
- Elevation of inflammatory markers (ESR - CRP)
- Prolonged PR

Diagnosis: group A Streptococcal sore throat followed by:
- 2 major criteria or
- 1 major criterion + 2 minor criteria

CARDITIS

PANCARDITIS: **Valvulitis (MR >> AR)**; LV dysfunction; pericarditis

PHYSICAL EXAMINATION (IN A CONTEXT OF ACUTE RHEUMATIC FEVER):
Tachycardia; ↘ S1; ↗ P2 in the case of severe MR; S3; holosystolic murmur; **Carey Coombs murmur** (mid-diastolic murmur secondary to turbulence and increased mitral diastolic flow); early diastolic decrescendo murmur in the case of AR; pericardial friction rub; TR murmur

LONG-TERM SEQUELAE: **Progressive mitral valve disease (MS >> MR)** which becomes symptomatic after several decades; Ao or T valve involvement is possible

PRIMARY PREVENTION

Start antibiotics < 10 days after onset of sore throat

PNC V 500 mg PO bid for 10 days

SECONDARY PREVENTION

Candidate	Agent	Duration
All patients with history of rheumatic fever (with or without carditis) due to the high risk of recurrence (class I recommendation)	• PNC G 1.2 million U IM every 4 weeks (or every 3 weeks if residual cardiac lesion) or • PNC V 200 mg PO bid or • Sulfadiazine 1 g PO daily	• Persistent valvular heart disease: > 10 years since last episode (until age of 40 years minimum; long term if in contact with children) • History of carditis but no sequelae: > 10 years since episode (until age of 21 years minimum) • Absence of carditis: > 5 years since episode (until age of 21 years minimum)

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- UpToDate 2015

Diseases of the Pericardium & Myocardium

05

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5.1/ DISEASES OF THE PERICARDIUM: ETIOLOGIES

IDIOPATHIC (MOST COMMON)

INFECTIOUS

- **Viral:** echovirus; coxsackievirus; adenovirus; EBV; CMV; HCV; HIV; influenza; parvovirus B19
- **Bacterial**: Pneumococcus; Staphylococcus; Streptococcus; Mycoplasma; Lyme; *Haemophilus influenzae;* Meningococcus; Gonococcus; *Coxiella burnetii; Legionella* spp*; Listeria* spp
- **Mycobacteria**: *M. tuberculosis; M. avium*
- **Fungi**: histoplasmosis; coccidioidomycosis
- **Parasites**: toxoplasmosis; echinococcosis
- **Infective endocarditis** (extension)

INFLAMMATORY - IMMUNE

- **Collagen diseases**: SLE; RA; Scleroderma; Sjögren
- **Vasculitis**: PAN; Giant cell arteritis; Churg-Strauss; Takayasu; Behçet
- Sarcoidosis
- Still disease
- **Dressler's syndrome**: late post MI or late post-cardiac surgery or late post-trauma
- Myopericarditis
- Inflammatory bowel disease
- Acute rheumatic fever (pancarditis)
- **Medications:** Procainamide; Hydralazine; Cyclosporine; Doxorubicin; Cyclophosphamide...

NEOPLASTIC

- **Primary:** mesothelioma; angiosarcoma; lipoma; paraganglioma
- **Secondary:** Lung; Breast; Lymphoma; Kaposi sarcoma; GI carcinoma; melanoma; sarcoma...

RADIOTHERAPY

EARLY POST-MYOCARDIAL INFARCTION (2-4 DAYS)

EARLY POST-CARDIAC SURGERY

HEMOPERICARDIUM

- Trauma
- Free wall rupture (infarction)
- Aortic dissection
- **Iatrogenic**: PCI; pacemaker; ablation of arrhythmia; ASD closure; valve repair / replacement; endomyocardial biopsy

TRAUMA

- Contusion; Penetrating injury; Post-CPR

CONGENITAL

- Cyst
- Congenital absence of pericardium

OTHER

- Renal failure - Uremia
- Dialysis
- Anorexia nervosa
- Chylopericardium
- Hypothyroidism or Hyperthyroidism
- Amyloidosis
- Heart failure (transudate)
- Severe PHT (transudate)
- Familial Mediterranean fever; TRAPS syndrome

EARLY POST-MI PERICARDITIS (< 1 WEEK): extension of transmural necrosis to the pericardium (with localized pericarditis); **localized ST elevation; look for ventricular rupture** if effusion associated; treatment with ASA 650 mg PO qid at tapered doses (avoid other NSAIDs) + Colchicine

DRESSLER'S SYNDROME: Late post-MI or post-cardiac surgery or post-trauma pericarditis; **autoimmune phenomenon**; polyserositis; fever; treatment with NSAID + Colchicine

RADIATION-INDUCED PERICARDITIS: A) Acute; B) Late: several months to several years; pericarditis - effusion - constriction - effusion / constriction

METASTATIC PERICARDIAL EFFUSION: Management → pericardiocentesis with drainage; intrapericardial chemotherapy or sclerosing agent; radiotherapy; pericardial window (surgical via left minithoracotomy or percutaneous approach)

CHRONIC PERICARDIAL EFFUSION: Look for and treat an underlying cause; look for systemic inflammation (CRP); **when idiopathic** → monitor by regular TTE **vs.** trial of NSAID / colchicine **vs.** pericardiocentesis (if chronic and > 20 mm; if symptomatic; if suspicion of bacterial or neoplastic aetiology)

DIALYSIS-ASSOCIATED PERICARDITIS: Now more frequent than uremic pericarditis; occurs even with normal plasma urea; consider intensifying dialysis

BACTERIAL PERICARDITIS: Direct extension of pneumonia or endocarditis or hematogenous spread or iatrogenic; **toxic patient;** urgent pericardiocentesis / urgent surgical drainage (± pericardiotomy; ± pericardiectomy)

5.2/ ACUTE PERICARDITIS

Inflammation of the pericardium

Dry vs serous vs fibrinous pericarditis (fibrin; granulation; adhesions; scarring) vs suppurative (bacterial) vs hemorrhagic

PRESENTATION: Retrosternal chest pain **(pleuritic; radiation to trapezius; worse in supine position; relieved by sitting foward)**; dyspnea

CLINICAL FEATURES: ± fever; ± tachycardia; ± signs of tamponade

- **Pericardial friction rub**: **1 or 2 or 3 components (systole; rapid ventricular filling; atrial kick);** evanescent; left parasternal region; patient seated, leaning forward in forced expiration +

ECG: 4 phases

1. **Diffuse ST elevation (concave); PR segment depression; mirror changes in aVR**
2. Normalization of ST segment with depression of the J point
3. T wave inversion
4. T wave normalization

ASSESSMENT: ECG; TTE; Creatinine - BUN; CBC; liver tests; CXR; ESR - CRP; Troponin (if ↗: consider myopericarditis or MI)

- ± ANA; ANCA; RF; PPD; HIV; HCV; TSH; BNP; tumor work-up; chest CT scan and/or cardiac MRI; Ferritin (Still disease); ACE (Sarcoidosis); Serology for *Coxiella burnetii* or for Lyme disease
- ± Pericardial aspiration (looking for cancer cells - cytology; cultures / mycobacterium culture; PCR for TB; Adenosine deaminase); Biopsy (cancer; TB)

DIAGNOSIS: **Clinical diagnosis: ≥ 2 out of 4 criteria**

Pleuritic and positional retrosternal chest pain	Pericardial friction rub (pathognomonic)	Typical ECG changes	Pericardial effusion

MANAGEMENT

IBUPROFEN **600 to 800 mg every 6 to 8 h** > **10 to 14 days (with tapering based on clinical response)**

/or

ASA 650 mg PO qid

⊕

PPI daily

⊕

COLCHICINE **0.5 mg bid for 3 months if > 70 kg (0.5 mg daily if < 70 kg)**

(★ COPE and ★ ICAP studies)

- Look for and treat any specific cause
- Analgesia - Narcotics PRN
- Rest / avoid exercise until complete resolution of symptoms (athletes: 3 months)
- **Corticosteroids: not recommended as first-line therapy**, as risk factor for recurrence
- **Hospitalization: A)** Fever; **B)** Subacute course; **C)** Failure to respond within 7 d to NSAID; **D)** Large pericardial effusion (> 20 mm) and/or tamponade; **E)** Myopericarditis; **F)** Trauma; **G)** Underlying cause; **H)** Immunosuppression; **I)** Receiving anticoagulant

COMPLICATIONS: pericardial effusion; tamponade; constriction

5.3/ INCESSANT AND RECURRENT PERICARDITIS

INCESSANT PERICARDITIS: recurrence of symptoms on withdrawal of treatment

RECURRENT PERICARDITIS: new episode after a symptom-free interval of > 4-6 weeks

- "Self-reactivity" sometimes develops following the first episode

MANAGEMENT

1. **Rule out a specific cause**
2. Resume NSAID with tapering over > 12 weeks; assess the response to therapy with CRP
3. Colchicine (★ CORP; ★ CORP-2) for ≥ 6 months
4. Avoid corticosteroids (in case of contraindications to ASA / NSAID / Colchicine → Prednisone 0.2-0.5 mg/kg daily for several weeks then gradual tapering)
5. **Last resort**: Azathioprine; IV immunoglobulins; anti-IL-1 (e.g. Anakira); Pericardiectomy

5.4/ CARDIAC TAMPONADE

THE PERICARDIUM is a closed sac with a low volume reserve; accumulation of fluid induces increased intrapericardial pressure and **compression of the heart chambers** (R > L)

- **Normal volume of pericardial fluid**: < 50 mL

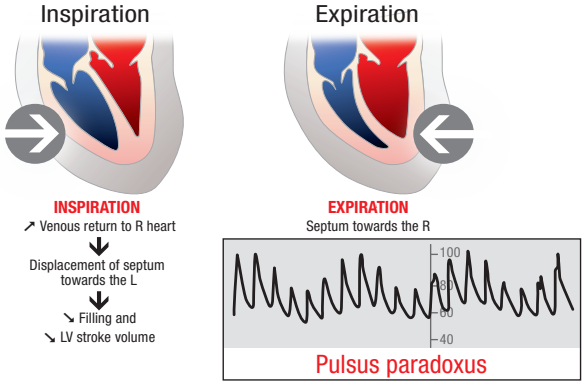
Increase then equalization of diastolic pressures in heart chambers ≈ INTRAPERICARDIAL PRESSURE ≈ 15-20 mmHg

CLINICAL FEATURES: tachypnea; tachycardia; diaphoresis; signs of hypoperfusion

- **Beck's triad**: **hypotension; muffled heart sounds; JVD**
- **Jugular: attenuated y descent**

PULSUS PARADOXUS: ↘ > 10 mmHg of SBP on inspiration

- Difference between the two pressures on sphygmomanometry when:
  1. Onset of Korotkoff sounds (expiration only)
  2. Korotkoff sounds are audible throughout the respiratory cycle
- **Pathophysiology:** cardiac transmission of respiratory variations of intrathoracic pressure is maintained



- **Tamponade and absence of pulsus paradoxus**: AR; ASD; severe LV dysfunction; LVH; RVH; severe hypotension; pericardial adhesions; localized effusion
- **DDx of pulsus paradoxus:** constrictive pericarditis (effusion-constriction); pulmonary embolism; RV infarction; pulmonary disease with marked variations of intrathoracic pressure (asthma; COPD; OSAHS); obesity; ascites; severe hypotension / hemorrhage; pectus excavatum

ECG: low voltage; electrical alternans

CXR: rounded and enlarged heart shadow

FLUOROSCOPY: abolition of cardiac pulsation

TTE: pericardial effusion (anterior to aorta on PLAX); **RA collapse during its relaxation** after the peak of the R wave (very sensitive and specific if > 1/3 of cardiac cycle); **early diastolic RV collapse after T wave** (absent if RVH); abnormal respiratory movement of the septum; plethoric IVC

- **Exaggerated respiratory variations of transvalvular flow**
  - Measure the first E wave following the start of inspiration and expiration
  - **Mitral valve**: **↘ E on inspiration; variation > 30% (Eexp - Einsp / Eexp)**
  - **Tricuspid valve**: **↘ E on expiration; variation > 60% (Exp - Einsp / Eexp)**

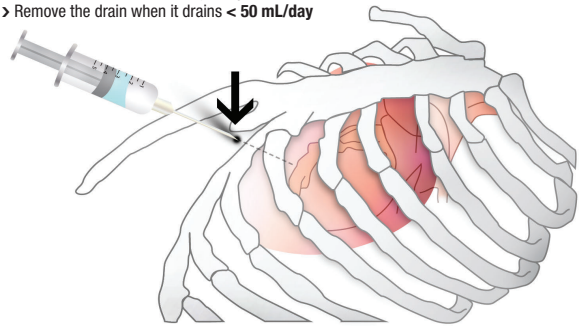
- **Pulmonary veins:** predominance of **systolic** flow (↘ Y wave)
- **Hepatic veins**: **expiration** → ↘ anterograde flow and ↗ diastolic reversal (A wave)

	TAMPONADE	CONSTRICTION
Pulsus paradoxus	Present	Possible (1/3)
Jugular	Attenuation of Y wave	Prominent Y wave "M or W" Pattern
Effect of inspiration on CVP	Reduction (normal effect)	Kussmaul (increase or absence of reduction)

	TAMPONADE	CONSTRICTION
Equalization of diastolic pressures	+	+
Square root sign (ventricular curve)	Absent	+
Ventricular interdependence (discordance of RV and LV systolic pressures during breathing)	Present	Present
Valve flow variations	• M valve: ↘ E on inspiration; **variation > 30 %** • T valve: ↘ E on expiration; **variation > 60 %**	• M valve: ↘ E on inspiration; **variation > 25 %** • T valve: ↘ E on expiration; **variation > 40 %**
Pulmonary vein flow	Systolic	Diastolic
Hepatic vein flow	↗ Diastolic reversal on expiration	↗ Diastolic reversal on expiration

PERICARDIOCENTESIS

1. Patient in 45° supine; subxiphoid approach (1 cm below the xyphoid process and 1 cm to the patient's left); local anesthesia
2. Needle introduced at an angle of 30-45° to the skin aiming for the left scapula while applying negative pressure on the syringe (± echocardiographic guidance)
3. Confirm the correct position of the needle: contrast in the case of echocardiographic guidance; insertion of a guide into the pericardial sac in the case of fluoroscopic guidance
4. Insertion of a dilator followed by a Pigtail catheter
   - › Remove the drain when it drains **< 50 mL/day**



- › **Indications: A)** Tamponade; **B)** Diagnosis of pericardial effusion (metastases; bacterial pericarditis; TB)
- › **Contraindication**: Aortic dissection with hemopericardium; ventricular rupture; coagulopathy; inaccessible effusion
- › **Complications (1-2%)**: Perforation of right heart chambers; coronary laceration; pneumothorax; hepatic puncture; arrhythmia; arterial bleeding
- › **Surgical drainage**: Following trauma or ventricular rupture or loculated / organized effusion or when biopsy is required or bacterial pericarditis
- › **Pericardial window (pericardiotomy)**: During reaccumulation / frequent recurrence; surgical or balloon

5.5/ CONSTRICTIVE PERICARDITIS

Pericardial fibrosis / calcification / adhesions

ETIOLOGIES: Idiopathic; Postoperative; Viral pericarditis; Recurrent pericarditis; Post-radiotherapy; TB; Other (infectious; neoplastic; collagen disease; uremia; post-trauma; sarcoidosis)

CONSEQUENCE: limited filling of heart chambers

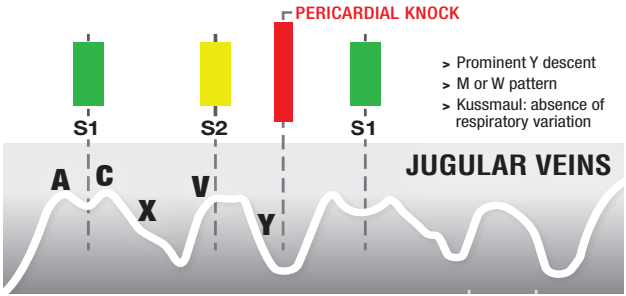
› Rapid early diastolic ventricular filling (prominent Y wave), which then ceases abruptly at mid-diastole (rigid pericardium)

PRESENTATION: systemic venous congestion mimicking right heart failure +

CLINICAL FEATURES: JVD; **prominent Y wave** (normal X descent; "M or W" pattern); **Kussmaul's sign** (increase or absence of decrease of CVP on inspiration); ± pulsus paradoxus (especially in the case of effusion - constriction); anasarca; hepatomegaly; pulsatile liver; signs of liver disease; jaundice; cardiac cachexia; low output state +

› **Pericardial knock:** high-pitched early diastolic sound at the apex or left parasternal region corresponding to the abrupt cessation of ventricular filling (± palpable) +

› **DDx of Kussmaul's sign: RV infarction; pulmonary embolism; RCM; TS; RA tumor; severe right heart failure** +



CXR: Pericardial calcifications

CT SCAN AND MRI: pericardial thickening **> 4 mm** (20% of patients have normal thickness); calcifications (CT scan); pericardial adhesions to the myocardium (MRI) +

TTE: abrupt cessation of ventricular filling at early diastole; abnormal respiratory movement of the septum (septal bounce); restrictive ventricular filling pattern; plethoric IVC

› **Exaggerated respiratory variations of transvalvular flow**
- Measure the first E wave following the start of inspiration and expiration
- **Mitral valve**: ↘ **E on inspiration; variation > 25% (Eexp - Einsp / Eexp)** +
- **Tricuspid valve**: ↘ **E on expiration; variation > 40% (Exp - Einsp / Eexp)**

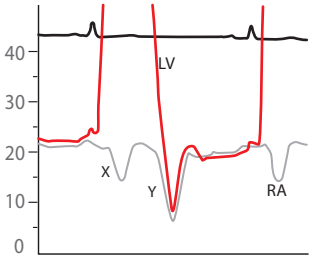
  - Variations masked if ↗ LA pressure (unmasked by asking the patient to sit up)
  - **DDx**: RV infarction; pulmonary embolism; pleural effusion; COPD (COPD: ↗ SVC anterograde systolic flow velocity > 20 cm/s on inspiration)

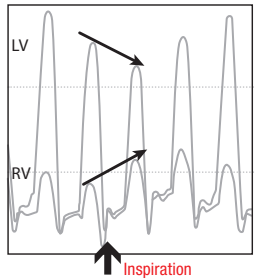
› **Pulmonary veins**: predominance of **diastolic flow** (↗ Y wave)

› **Hepatic veins: expiration →** decreased anterograde flow and increased diastolic reversal (A wave)

› **Tissue Doppler imaging of septal mitral annulus**: **E` > 8 cm/s** (*annulus paradoxus*) +

CARDIAC CATHETERIZATION





ATRIAL CURVE:
- Prominent Y descent
- W or M pattern
- Kussmaul

VENTRICULAR CURVE:
- Square root sign

VENTRICULAR CURVES:
- Equalization of end-diastolic pressures
- Respiratory discordance of ventricular systolic pressures

› **Ventricular curve: square root sign**: rapid initial ventricular filling, then increase and **equalization of end-diastolic pressures** of the chambers (≈ 20 mmHg)
- **LVEDP - RVEDP < 5 mmHg**
  - Can be detected with a bolus in the presence of dehydration

› **Interdependence: RV and LV systolic pressure discordance during respiration**

INSPIRATION

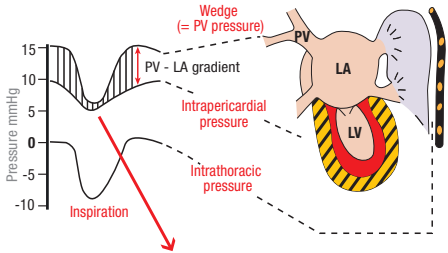
↓ Intrathoracic pressure
↓ Pulmonary venous pressure

(no change of intrapericardial pressure and LA pressure)

↓↓ **PV - LA PRESSURE GRADIENT**

=

↓ venous return to LV (septum shifted to the left)



Absence of transmission of respiratory intrathoracic pressure variations to the intrapericardial compartment (isolated by the thickened pericardium)

Adapted from*: Bunnell IL, Holand JF, Griffith GT, Greene DG. Hemodynamics during induced cardiac tamponade in man. Am J Med 1960;25:640-6*

MANAGEMENT

1. Diuretics (beware of decreased preload)
2. Avoid BB-CCB (compensatory tachycardia to maintain cardiac output)
3. **Pericardiectomy**: the only definitive treatment (perioperative mortality: 5-15%)
4. NSAID in acute effusive / constrictive pericarditis

5.6/ CONGENITAL ANOMALIES OF THE PERICARDIUM

PERICARDIAL CYST

Often adjacent to right chambers

Cardiac MRI PRN; Conservative management (except when compressive)

CONGENITAL ABSENCE OF THE PERICARDIUM

Most often partial absence of the left pericardium

COMPLICATIONS: hernia / strangulation of part of the heart; retrosternal chest pain - syncope - sudden death

ECG: Incomplete RBBB; poor precordial progression of R wave

CXR: Marked levoposition; loss of right heart contour; interposition of lung between Ao and main PA

TTE: Unusual imaging window (PLAX); RV appears dilated; exaggerated heart movements; abnormal movement of interventricular septum

CARDIAC MRI: Marked levoposition; presence of lung parenchyma between Ao and main PA and between inferior heart surface and diaphragm; ± hernia of part of the heart

TREATMENT: Pericardioplasty (in the presence of symptoms or hernia)

5.7/ CARDIOMYOPATHIES - CLASSIFICATION

Myocardial disease (abnormal structure and function) in the absence of CAD - HTN - valvular heart disease - congenital heart disease

▸▸| Classification (following page)

CARDIOMYOPATHIES

HCM

FAMILIAL

SARCOMERIC PROTEIN MUTATIONS
- Myosin-binding protein C
- β myosin heavy chain
- Troponin I
- Troponin T
- α-tropomyosin
- Myosin light chain
- Actin
- α-myosin
- Titin
- Troponin C
- LIM protein

SYNDROMIC HCM
- Noonan's syndrome
- LEOPARD syndrome
- Friedreich's ataxia
- Beckwith-Wiedermann syndrome
- Swyer's syndrome

GLYCOGEN STORAGE DISEASES
- Pompe
- PRKAG2
- Forbes
- Danon (LAMP2)

LYSOSOMAL STORAGE DISEASES
- Anderson-Fabry
- Hurler's

DISORDERS OF FATTY ACID METABOLISM

CARNITINE DEFICIENCY

PHOSPHORYLASE B KINASE DEFICIENCY

MITOCHONDRIAL CYTOPATHIES

FAMILIAL AMYLOIDOSIS (TTR)

FAMILIAL, UNKNOWN GENE

NON-FAMILIAL

OBESITY

ATHLETIC TRAINING

AMYLOIDOSIS (AL / senile)

ACROMEGALY

DCM

FAMILIAL

SARCOMERIC PROTEIN MUTATIONS (see HCM)

Z-BAND
- LIM protein
- TCAP

CYTOSKELETAL GENES
- Dystrophin
- Desmin
- Metavinculin
- Sarcoglycan complex
- CRYAB
- Epicardin

MUSCULAR DYSTROPHY
- Becker (dystrophin)
- Duchenne (dystrophin)
- Emery-Dreifuss

NUCLEAR MEMBRANE
- Lamin A/C (LMNA)
- Emerin

MILDLY DILATED CM

INTERCALATED DISC PROTEIN MUTATIONS (see ARVD)

SCN5A MUTATION

MITOCHONDRIAL CYTOPATHIES

HAEMOCHROMATOSIS

FAMILIAL, UNKNOWN GENE

NON-FAMILIAL

IDIOPATHIC

MYOCARDITIS (infectious / toxic / auto-immune; see Etiologies)

EOSINOPHILIC (Churg-Strauss syndrome)

DRUG-INDUCED CARDIOTOXICITY

CARDIOTOXINS (alcohol, cocaine, amphetamines; anabolic steroids)

PREGNANCY

ENDOCRINE
- Thyroid disease
- Pheochromocytoma
- Acromegaly

NUTRITIONAL
- Thiamine (Beriberi)
- Carnitine
- Selenium
- Hypophosphatemia
- Hypocalcemia

TACHYCARDIOMYOPATHY

KAWASAKI

VIRAL PERSISTENCE

PERIPARTUM CM

HIV

METALS (phosphorus; mercury; cobalt)

SARCOIDOSIS

RCM

FAMILIAL

FAMILIAL AMYLOIDOSIS
- Transthyretin (neuropathy)
- Apolipoprotein (nephropathy)

SARCOMERIC PROTEIN MUTATIONS
- Troponin I
- Myosin light chain

HAEMOCHROMATOSIS

DESMINOPATHY

PSEUDOXANTHOMA ELASTICUM

ANDERSON–FABRY

GLYCOGEN STORAGE DISEASE

HURLER'S SYNDROME

GAUCHER'S DISEASE

FAMILIAL, UNKNOWN GENE

NON-FAMILIAL

IDIOPATHIC

AMYLOIDOSIS (AL / senile)

SARCOIDOSIS

SCLERODERMA

ENDOMYOCARDIAL DISEASES
- Endomyocardial fibrosis
- Hypereosinophilic syndrome (Loeffler)
- Idiopathic
- Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

CARCINOID HEART DISEASE

METASTATIC CANCERS

RADIOTHERAPY

DRUGS (ANTHRACYCLINES)

DIABETES

ARVD

FAMILIAL

INTERCALATED DISC PROTEIN MUTATIONS (DESMOSOME)
- Plakophilin 2 (PKP2)
- Desmoglein 2
- Desmoplakin
- Desmocollin 2
- Plakoglobin

CARDIAC RYANODINE RECEPTOR (RYR2)

TRANSFORMING GROWTH FACTOR-B3 (TGFB3)

FAMILIAL, UNKNOWN GENE

UNCLASSIFIED

FAMILIAL

LV NON-COMPACTION
- Barth syndrome (Tafazzin)
- Lamin A/C
- ZASP
- α-dystrobrevin

NON-FAMILIAL

TAKOTSUBO

Adapted from: *Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the european society of cardiology working group on myocardial and pericardial diseases. EHJ 2008, 29; 270-276.*

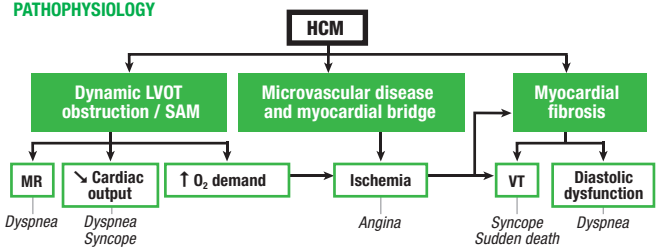
5.8/ HYPERTROPHIC CARDIOMYOPATHY

LV hypertrophy without dilatation and with no identifiable cause (see DDx)

Obstructive HCM (intraventricular gradient at rest or on exercise) versus non-obstructive HCM (gradient < 30 mmHg)

Autosomal dominant; sarcomere protein gene

PATHOPHYSIOLOGY



DIFFERENTIAL DIAGNOSIS

- Valvular heart disease; subaortic membrane; HTN (regression of LVH with tight blood pressure control); amyloidosis (TTR; AL); CRF; isolated basal septal hypertrophy in the elderly; acromegaly; phaeochromocytoma
- Syndromic: Noonan; LEOPARD; Friedreich's ataxia
- Glycogen storage disease; Lysosomal storage disease (Anderson-Fabry); Mitochondrial cytopathy
  - Symmetrical LVH; WPW (Danon and PRKAG2)
- High-level athlete

	ATHLETE	HCM
Genetic test or family history	Negative	Positive
Diastolic dysfunction	Absent	Present
LV end-diastolic diameter	> 55 mm	< 45 mm
SAM	Absent	Present
Asymmetrical LVH	Absent	Present
Severe LVH (> 17 mm)	Absent	Present
Regression of LVH after stopping training	Present	Absent
VO_2 max > 110% predicted	Present	Absent
Scar / fibrosis on MRI	Absent	Present

PRESENTATION: dyspnea; retrosternal chest pain; syncope; AF; malignant arrhythmia; sudden death

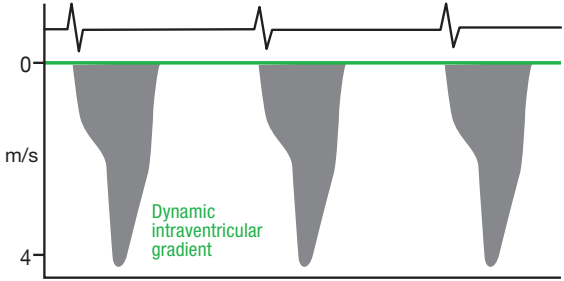
- Progression to DCM with systolic dysfunction ("burn-out" HCM): < 5%

CLINICAL FEATURES: rapid carotid upstroke with **pulsus bisferiens** ("*spike and dome*"); **3 components at apex** (early systolic wave; late systolic wave; S4); paradoxical split S2; **left parasternal systolic ejection murmur (↗ on Valsalva or on standing)**; MR murmur (radiation to axilla)

ECG: LVH; LAH; T - ST abnormalities (diffuse T wave inversion in apical HCM); Q waves; arrhythmias

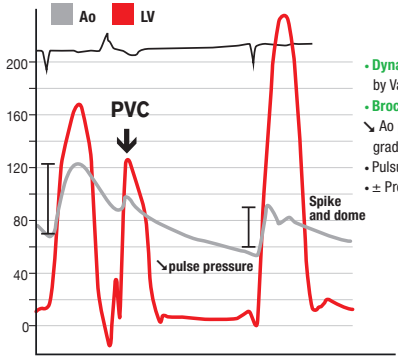
TTE (± CONTRAST): **A)** LV wall **≥ 15 mm** (that is not explained solely by loading conditions); asymmetrical septal hypertrophy (septum / posterior wall **> 1.5: 1**) and/or apical hypertrophy and/or anterolateral hypertrophy or concentric; ↗ LV mass; **B) SAM** (mid-to-late systolic MR with posterior jet); **C)** Dynamic intraventricular gradient **≥ 30 mmHg** amplified by Valsalva maneuver (continuous Doppler shows **a late-peaking dagger-shaped appearance**); **D)** Diastolic dysfunction; **E)** Structural abnormality of the mitral valve (elongated leaflets; abnormal insertion of anterolateral papillary muscle); **F)** LA dilatation; **G)** Apical aneurysm

› **Exercise echocardiography**: in symptomatic patients to detect a significant dynamic intraventricular gradient (≥ 50 mmHg) when absent at rest



› **DDx of Dynamic intraventricular gradient**: Takotsubo; cardiac amyloidosis; anterior myocardial infarction (basal hyperdynamism); post-AVR (AS with LVH); sigmoid septum in eldery people; hypertensive heart disease; small hyperdynamic LV

CARDIAC CATHETERIZATION



- **Dynamic intraventricular obstruction** (revealed by Valsalva or Isuprel or PVC or Nitrates)
- **Brockenbrough-Braunwald-Morrow sign**: ↘ Ao pulse pressure post-PVC (and ↗ LV-Ao gradient)
- Pulsus bisferiens (spike and dome appearance)
- ± Prominent v wave (MR due to SAM)

STRESS TEST: evaluate functional capacity; look for abnormal BP response (**↘ BP > 20 mmHg or absence of increase of BP > 20 mmHg**); combine with echocardiography to demonstrate dynamic obstruction; repeat stress test every 2-3 years in clinically stable patients

CARDIAC MRI: LVH; Rule out apical HCM; late gadolinium enhancement (interventricular septum; free wall; RV insertion sites) with **≥ 10% of LV mass associated with increase SCD risk**

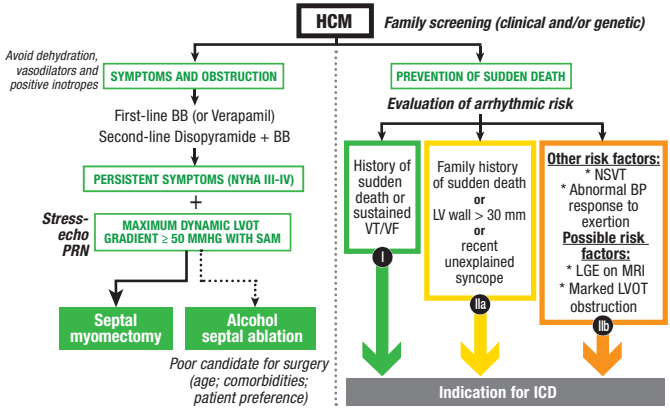
BIOPSY: disorganized myocyte architecture; interstitial fibrosis

GENETIC TEST: indicated routinely (Class I); enables cascade genetic screening of the relatives; positive in 60-70% of cases

MANAGEMENT

- Avoid strenuous exertion / competitive sports
- **Hypotension due to LVOT obstruction**: **volume; BB; Phenylephrine**
- **Anticoagulation** for AF irrespective of CHADSVASc score
- **Family screening:** 1st degree relatives; clinical and/or genetic screening

12 - 18 YEARS OR COMPETITIVE SPORTSMAN	> 18 YEARS
ANNUAL ECG / TTE	ECG / TTE EVERY 5 YEARS



- **Septal myomectomy**: preferable in most cases (especially young patients; septum > 30 mm; other concomitant surgical indication; structural abnormality of mitral valve)
  - **Complications:** mortality (1%); complete AV block (2%); LBBB; iatrogenic VSD (< 1%); Ao valve lesion (AR)
- **Alcohol septal ablation:** selective injection of alcohol into perforating septal coronary branches; under ultrasound guidance (with intracoronary contrast); "controlled" infarction targeting the basal ventricular septum at the site of SAM
  - **Complications:** mortality (2%); complete AV block (10-20%); RBBB; in-hospital VT (5%); repeat procedures (12%); possible long-term arrhythmic risk

PROGNOSIS: cardiovascular death 1-2 % / year; the majority of patients have a **similar life expectancy to that of the general population**; identify patients with increased risk of sudden death

HCM RISK-SCD (5 years): $= 1 - 0.998^{\text{Prognostic index}}$; **consider ICD if 5-year risk ≥ 6%**

- **Prognostic index:** = [0.15939858 x maximal wall thickness (mm)] – [0.00294271 x maximal wall thickness^2 (mm^2)] + [0.0259082 x LA diameter (mm)] + [0.00446131 x maximal LVOT gradient (mmHg)] + [0.4583082 x familial history SCD] + [0.82639195 x NSVT] + [0.71650361 x unexplained syncope] – [0.01799934 x age (years)]

5.9/ DILATED CARDIOMYOPATHY

Ventricular dilatation and systolic dysfunction

Idiopathic in 50% of cases

CLINICAL FEATURES: JVD; lateralized and enlarged apex; S3; S4; AV valve regurgitation

COMPLICATIONS: Heart failure; arrhythmias; conduction disorders; thromboembolism; sudden death

ECG: Sinus tachycardia; arrhythmias; T - ST abnormalities; LVH; poor precordial progression of R wave; conduction disorders

TTE: Spherical LV; thinned walls; dilated chambers; MR (Carpentier I and IIIb); limited aortic valve opening; LVOT VTI < 18 cm; ↘ dP/dT; thrombus; diastolic dysfunction; pericardial effusion; PHT

ASSESSMENT: CXR; CBC; Electrolytes; Phosphorus; Calcium; Renal function; LFTs; TSH; CK; ANA; ESR; CRP; Iron assessment; HIV; Urinalysis; Blood glucose; Lipid profile; ± Lyme antibody titer; ± Urine metanephrines; ± BNP

› **Family screening / Genetic Test**: consider when: **A)** DCM is possibly familial; **B)** DCM with AV block and/or sudden death in the family (LMNA; SCN5A)

SPECIFIC ENTITIES

TACHYCARDIOMYOPATHY: secondary to sustained supraventricular or ventricular tachycardia; recovery of LV function by aggressive rhythm control or rate control within 4 weeks

› **AF**: BB; Amiodarone x 1 month then cardioversion; Digoxin; RF ablation

ALCOHOLIC CARDIOMYOPATHY: improvement of LVEF with abstinence

› **Harmful effects of alcohol (heavy drinking)**: systolic and/or diastolic dysfunction; HTN; CAD **(decreased risk with low consumption / 1 to 2 standard drinks per day)**; stroke; arrhythmia - AF; sudden death; hypertriglyceridemia

OBESITY-RELATED CARDIOMYOPATHY: Secondary to ↗ cardiac output and myocardial fat infiltration; LV dilatation then LV dysfunction

› Suspect when BMI > 40 kg/m^2 (for more than 10 years); Diagnosis of exclusion

CHAGAS DISEASE (TRYPANOSOMIASIS): *Trypanosoma cruzi*; transmission of the parasite by *Triatominae* bugs

› **Early infection**: Acute myocarditis; ± meningoencephalitis / skeletal muscle involvement / nerve involvement
  - **Treatment**: Nifurtimox or Benznidazole
  - **Reactivation**: Immunosuppression / HIV / heart transplant
› **Latent infection**: Mild lymphocytic myocarditis
› **Chagas cardiomyopathy:** 30% of patients; several years after infection; autoimmune myocarditis (little or no residual parasites); dilatation of chambers; ventricular dysfunction (RV then LV); apical and inferolateral aneurysm; thrombus (apex; RAA); embolism; ventricular arrhythmia; blocks; cardiac dysautonomia

5.10/ RESTRICTIVE CARDIOMYOPATHY

High filling pressure secondary to **rigid myocardium** due to **myocardial or endomyocardial fibrosis or following infiltration of the myocardium by a substance**

PRESENTATION: dyspnea; weakness; edema / anasarca; AF

CLINICAL FEATURES: JVD; Kussmaul's sign; S3; S4; palpable apex (contrary to constriction); AV valve regurgitation; hepatomegaly; ascites; peripheral edema

ECG: low voltage; conduction disorders; poor precordial progression of R wave; AF

TTE: bi-atrial dilatation; normal or decreased ventricular volume; normal or slightly increased wall thickness; sparkling myocardium; thickening of valves / interatrial septum; diastolic dysfunction with restrictive pattern; effusion

	CONSTRICTION	RESTRICTION
Y descent	Prominent	Prominent
Pulsus paradoxus	Sometimes present (1/3)	Absent
Palpable apex	No	Yes
Pericardial knock	Present	Absent
LV filling pressure > 25 mmHg	Rare	Frequent
Square root sign	Present	Present
LVEDP - RVEDP (equalization of diastolic pressures)	< 5 mmHg	> 5 mmHg
RVEDP / RVSP (pulse pressure)	> 0.33	< 0.33
sPAP	< 50 mmHg	> 50 mmHg
Ventricular interdependence (discordant respiratory variations of RV and LV pressures)	Present (pressure discordance)	Absent (pressure concordance)
Diastolic pattern	Restrictive	Restrictive
Respiratory variations of transvalvular flow	Exaggerated • **M valve**: > 25 % variation • **T valve**: > 40 % variation	Normal • **M valve**: about 5% variation
Mitral septal annulus E`	> 8 cm/s	< 8 cm/s
Hepatic veins: ↗ diastolic reversal	Expiratory	Inspiratoire
Ventricular wall thickness	Normal	± Increased
Pericardial thickness	± Increased	Normal
Atrial dimensions	± LA dilatation	Bi-atrial dilatation ++
Abnormal respiratory movement of the septum	Present	Absent
BNP	Often normal	Increased

BIOPSY: Rule out infiltration (amyloidosis; sarcoidosis; Gaucher; Hurler's)

MANAGEMENT

- Treatment of underlying cause
- Control of blood volume is difficult (hypotension if ↘ preload)
- Caution with BB and CCB: cardiac output depends on HR (**fixed stroke volume** due to poor filling)

SPECIFIC ENTITIES

SCLERODERMA: microvascular spasm with ischemia and necrosis / fibrosis

HEMOCHROMATOSIS: tissue iron deposits (heart; liver; gonads; pancreas; skin)

- Autosomal recessive; HFE gene mutation
  - **Secondary iron overload:** repeated transfusions; ineffective erythropoiesis
- **Pentad:** heart failure; cirrhosis; impotence; DM; arthritis
- **Cardiac involvement**: **diastolic dysfunction - RCM (possibly followed by systolic dysfunction); LV dilatation - DCM;** conduction disorders
- **Assessment**: ↗ **ferritin (> 200 µg/L in premenopausal women; > 300 µg/L in men or postmenopausal women);** ↗ **transferrin saturation (> 50% in women and > 60% in men)**
- **MRI**: ↘ **relaxation time on T2* (< 20 ms)**
- **TREATMENT**: **Phlebotomies; Chelator (Deferoxamine)**

FABRY DISEASE: X-linked; α-galactosidase A deficiency; accumulation of glycosphingolipids in lysosomes

- **Diagnosis**: ↗ urinary globotriaosylceramide; skin biopsy
- Variable degree of enzyme deficiency: **A) Total deficiency**: neuropathies; renal / skin / cardiac involvement; stroke; **B) Partial deficiency**: isolated cardiac involvement is possible
- **Cardiac involvement**: LVH mimicking HCM; Diastolic dysfunction - RCM; angina / myocardial infarction (endothelial infiltration); HTN; MVP
- **Management**: enzyme replacement therapy

SARCOIDOSIS: multisystem noncaseating granulomas (particularly in lungs / reticulo-endothelial system / skin)

- **Cardiac involvement**: infiltration of cardiac conduction tissue and myocardium (IV septum; LV free wall); blocks; ventricular arrhythmias; RCM; systolic LV dysfunction; LV dilatation; LV aneurysm; RWMA not corresponding to coronary anatomy; pericarditis; valvular heart disease; cor pulmonale (pulmonary fibrosis)
- **Biopsy**: often falsely negative
- **MRI**: late gadolinium enhancement reflecting intramural or subepicardial fibrosis (often anteroseptal or inferolateral)
- **PET-FDG:** demonstrates patchy zones of fibrosis and/or inflammation
- **Management**: Corticosteroids; Plaquenil; Methotrexate; Cyclophosphamide; ICD; Transplant (risk of recurrence)

ENDOMYOCARDIAL FIBROSIS (DAVIES DISEASE): Tropical regions; ± eosinophilia; fibrosis / thrombus / endocardial obliteration (obliteration of apex; papillary muscle fibrosis; AV valve regurgitation); bi-atrial dilatation; diastolic dysfunction with restrictive pattern

LOEFFLER ENDOCARDITIS (HYPEREOSINOPHILIC SYNDROME): Eosinophilia > 1 500 cells/µL with multisystem involvement (lung; CNS; GI; skin)

- **Cardiac involvement**: **myocarditis followed by replacement of the myocardium by thrombus then formation of endomyocardial fibrosis;** fibrosis / thrombus / endocardial obliteration (apex; posterior mitral leaflet; posterobasal wall); RCM; AV valve regurgitation; embolism
- **Management:** anticoagulation; Corticosteroids; Hydroxyurea; Interferon; endocardiectomy; valve replacement / repair

CARCINOID SYNDROME: Gastrointestinal tract (small bowel) or bronchial tumor; release of serotonin by the tumor and liver metastases; ↗ urinary 5-HIAA

- **Symptoms**: skin flushing; diarrhea; bronchospasm; hypotension
- **Cardiac involvement**: **Fibrous endomyocardial plaques in right heart chambers**; tricuspid and pulmonary valve disease with thickening / retraction / rigidity of leaflets (TR and PR due to malcoaptation; ± TS; ± PS); right ventricular dilatation and dysfunction
  - **Involvement of left chambers in the presence of R→L shunt or lung metastases**
- **Management:** Somatostatin analogs; embolization of liver metastases; TVR if severe symptoms and/or dilatation – progressive RV dysfunction (despite adequate control of the cancer)

5.11/ CARDIAC AMYLOIDOSIS

Interstitial infiltration of a protein demonstrating apple-green birefringence when stained with Congo Red

PRIMARY AMYLOIDOSIS (AMYLOIDOSIS AL)

Plasma cell dyscrasia (plasma cell clone); tissue deposits of a portion of **immunoglobulin light chains**

CARDIAC INVOLVEMENT (50% OF PATIENTS): median survival = 15 months; LVH; RCM; progressive LV dysfunction; ischemia (microvascular infiltration); conduction disorders; atrial disease; sudden death (pulseless electrical activity)

SYSTEMIC INVOLVEMENT: OH; peripheral / autonomic neuropathy; carpal tunnel; periorbital purpura; ecchymoses; macroglossia; RUQ pain; onychodystrophy; renal failure / nephrotic syndrome

CLINICAL FEATURES: hypotension / OH; JVD; Prominent X and Y waves; Kussmaul; S4 rarely present (atrial disease); pleural effusions; hepatomegaly; anasarca

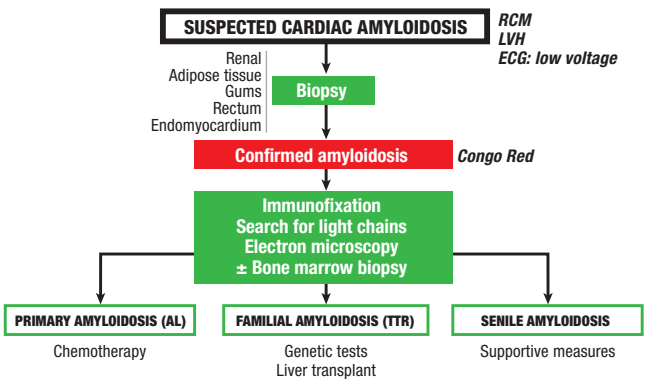
ECG: microvoltage (despite LVH on TTE) ; AF; pseudo-infarction; blocks

TTE: thickened walls; small ventricular chamber; dynamic LVOT obstruction; valvular / interatrial septum infiltration; sparkling myocardium; diastolic dysfunction; possible systolic dysfunction; pericardial effusion; bi-atrial dilatation

CARDIAC MRI: rapid accumulation of contrast in myocardium (**rapid wash-out from blood**); circumferential subendocardial or patchy transmural late gadolinium enhancement; atrial left gadolinium enhancement

DIAGNOSIS: biopsy of abdominal adipose tissue (positive in > 70% of cases) or gums or salivary glands or kidney or rectum or endomyocardial tissue

- If Congo Red positive → **Distinguish primary (AL) from familial (TTR) amyloidosis**
  - Serum and urinary immunofixation (± SPEP and UPEP)
  - Electron microscopy immunohistochemistry techniques
  - Abnormal kappa / lambda light chain ratio
- Bone marrow biopsy: % plasma cells; rule out MM and Waldenström



MANAGEMENT

- Cautious use of Lasix; **particular caution with vasodilators and Digoxin**
- Anticoagulation in the presence of AF or atrial disease (A wave < 20 cm/s)
- **Anti-plasma cell chemotherapy**: Melphalan / Dexamethasone or Cyclophosphamide / Thalidomide / Dexamethasone; High-dose chemotherapy combined with autologous bone marrow transplantation as required

FAMILIAL AMYLOIDOSIS

Mutant transthyretin protein (TTR) (in the majority of cases)

Autosomal dominant; most patients develop clinical features after the age of 40 years

PRESENTATION: various degrees of cardiac / conduction tissue / peripheral nerve / renal involvement

TREATMENT: **liver transplant** (mutant TTR produced by the liver)

SENILE CARDIAC AMYLOIDOSIS

Non-mutant transthyretin protein (TTR)

Rare extracardiac involvement

SUSPECT: in an elderly patient with heart failure + LV wall thickening + normal chamber dimensions; frequent blocks; AF

DIAGNOSIS: endomyocardial biopsy

Median survival: 7.5 years

5.12/ ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA (ARVD)

RV dysfunction (regional or global) secondary to infiltration of the myocardium by fibrous / adipose tissue

- **Triangle of dysplasia**: lesion of the RV inflow tract, RV outflow tract and apex of the RV
- LV is sometimes involved; can mimic DCM

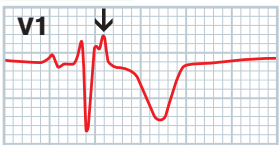
AUTOSOMAL DOMINANT: majority of cases; desmosome protein gene

- **Autosomal recessive**: **Naxos syndrome** (plakoglobin; woolly hair; palmoplantar keratoderma); **Carvajal syndrome** (desmoplakin; palmoplantar keratoderma; predominant LV involvement)

4 PHASES

1. Asymptomatic
2. Arrhythmic (palpitations; syncope; VT – sudden death)
3. Right heart failure
4. Biventricular failure / DCM

DIAGNOSIS: requires the presence of several criteria

MAJOR CRITERIA	MINOR CRITERIA
01. Structural lesion	
TTE a) RV: **regional akinesia or dyskinesia or aneurysm +** b) **PLAX RVOT ≥ 32 mm or PSAX RVOT ≥ 36 mm** (end-diastole) or FAC ≤ 33% **MRI** a) RV: regional akinesia or dyskinesia or dyssynchrony + b) RV end-diastolic volume ≥ 110 mL/m² (M) or ≥ 100 mL/m² (F) or RVEF ≤ 40% **Angiography** • RV: regional akinesia or dyskinesia or aneurysm	**TTE** a) RV: regional akinesia or dyskinesia + b) PLAX RVOT 29 to 32 mm or PSAX RVOT 32 to 36 mm (end-diastole) or FAC 33% to 40% **MRI** a) RV: regional akinesia or dyskinesia or dyssynchrony + b) RV end-diastolic volume 100 to 110 mL/m² (M) or 90 to 100 mL/m2 (F) or RVEF 40 to 45%
02. Tissue characterization (biopsy)	
Residual myocytes < 60% with fibrous replacement of RV free wall with or without fat replacement	Residual myocytes 60 - 75% with fibrous replacement of the RV free wall with or without fat replacement
03. Repolarization abnormalities	
T wave inversion in V1-V2-V3 (absence of cRBBB with QRS ≥ 120 ms)	• T wave inversion in V1-V2 (absence of RBBB with QRS ≥ 120 ms) or V4 or V5 or V6 • T wave inversion in V1-V2-V3-V4 with cRBBB
04. Depolarization / conduction abnormalities	
Epsilon wave in V1-V2-V3 (low amplitude signal between the end of the QRS and the start of the T wave) 	• Late potentials (SAECG): ≥ 1/3 positive parameters (absence of QRS ≥ 110 ms on basic ECG) a) Filtered QRS ≥ 114 ms b) Terminal QRS (< 40 µV) ≥ 38 ms c) RMS (Root mean square) of terminal 40 ms ≤ 20 µV • QRS: S nadir to the end of the QRS ≥ 55 ms in V1- V2-V3 (absence of cRBBB)
05. Arrhythmias	
NSVT or VT with LBBB morphology with superior axis (negative QRS in II - III - aVF and positive QRS in aVL)	• NSVT or VT of RVOT, LBBB morphology with inferior axis (positive QRS in II - III - aVF and negative QRS in aVL) or unknown axis • > 500 PVCs per 24 h
06. Family history	
• **1st degree relative meeting the criteria** • **1st degree relative with histologically confirmed diagnosis** • **Pathogenic mutation**	• History of ARVD in 1st degree relative (but impossible to verify criteria) • Sudden death < 35 years in a 1st degree relative with suspected ARVD • Confirmed ARVD (histology or criteria) in a 2nd degree relative
• **Definitive diagnosis:** 2 major or 1 major + 2 minor or 4 minor (different categories) • **Borderline diagnosis:** 1 major + 1 minor or 3 minor (different categories) • **Possible diagnosis:** 1 major or 2 minor (different categories)	

Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. Proposed Modification of the Task Force Criteria. Circulation. 2010;121; 1533-1541.

OTHER ELEMENTS TO LOOK FOR: A) ↗ QRS duration > 100 ms in V1 (delayed activation of RV; RBBB); **B)** Multiple RV scars on electrophysiological voltage mapping; **C)** Fat infiltration of RV on MRI (marked inter-observer variability)

DDX: A) DCM; **B)** Uhl's anomaly (zones in RV with absence of myocardium; endocardium and epicardium are continuous); **C)** Idiopathic RVOT VT (ECG / SAECG / TTE all normal); **D)** Myocarditis; **E)** Sarcoidosis

MANAGEMENT

- Avoid competitive sports or symptomatic exertion; Screening in 1st degree relatives
- Treatment of heart failure: ACE inhibitors; BB; Heart transplantation PRN
- ICD:
  a) **Secondary prevention**: documented sustained VF / VT
  b) **Primary prevention**: consider ICD → unexplained syncope; frequent NSVT; family history of premature sudden death; extensive disease (extensive RV involvement; LV involvement); marked QRS prolongation; VT induction during EPS
  c) **Frequent shocks**: Sotalol; Amiodarone; VT ablation

5.13/ ISOLATED LEFT VENTRICULAR NONCOMPACTION

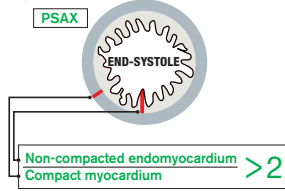
Failure of endomyocardial compaction during embryogenesis

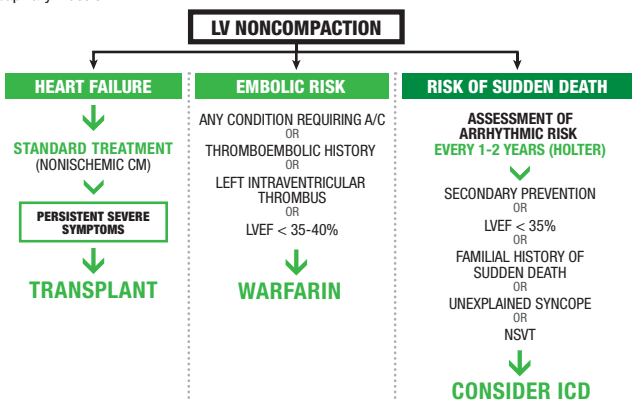
Prominent trabeculations with deep intertrabecular crypts

Isolated (autosomal dominant or sporadic) vs **associated with congenital heart disease** (Ebstein; RVOT or LVOT obstruction; complex heart disease)

PRESENTATION: heart failure; arrhythmia; sudden death; embolism

TTE (± CONTRAST): thin epicardial layer with thick non-compacted endomyocardial layer (predominantly apical and middle portions of inferior and lateral walls); **intertrabecular crypts continuous with the intraventricular cavity** (blood flow on color Doppler); RWMA; LV dysfunction; thrombus; abnormal papillary muscle





MRI: non-compacted endomyocardium / compacted myocardium ratio > **2.3 in diastole**

MANAGEMENT: screening of 1st degree relatives (TTE); avoid competitive sports

5.14/ TAKOTSUBO CARDIOMYOPATHY (STRESS CARDIOMYOPATHY)

Transient systolic dysfunction involving the apex (± midventricular walls) in the absence of any significant CAD; often following an intense emotional or physical stress

- Secondary to catecholamine surge
- Postmenopausal women in > 90% of cases
- **Variants**: isolated midventricular lesion or reverse Takotsubo (basal akinesia)

PRESENTATION: Retrosternal chest pain; ST elevation on ECG or diffuse T wave inversion (with ↗ QT); ↗ troponin (limited); negative coronary angiography

- **Complications**: hemodynamic instability (LVOT obstruction ± SAM secondary to basal hyperdynamism in 15% of cases); heart failure; arrhythmias; thromboembolism; MR (SAM)
- **Complete recovery of LV function in 1 to 3 months; good prognosis**

CARDIAC MRI: myocardial edema; apical akinesia; absence of fibrosis - necrosis

DDX: Intracranial hemorrhage or SAH (often **basal and mid-ventricular akinesia**); major stroke; Pheochromocytoma (rule out if recurrence); Vasospasm; Cocaine; Amphetamines; Myocarditis

MANAGEMENT

- Carvedilol (alpha / beta blocker)
- ACE inhibitor (stop after recovery)
- TTE at 1 and 3 months (consider alternative diagnosis if LV dysfunction persists)
- **Anticoagulation: A)** Anticoagulant therapy if LV thrombi; **B)** Prophylactic anticoagulation may be considered to prevent LV thrombi (class IIb recommandation)
- **Hypotension / Shock**:
  - **Severe systolic dysfunction without LVOT obstruction**: Amines (cautiously); IABP as required
  - **LVOT obstruction:** BB (avoid amines); Volume (in absence of overload); Phenylephrine (cautiously)

5.15/ MYOCARDITIS

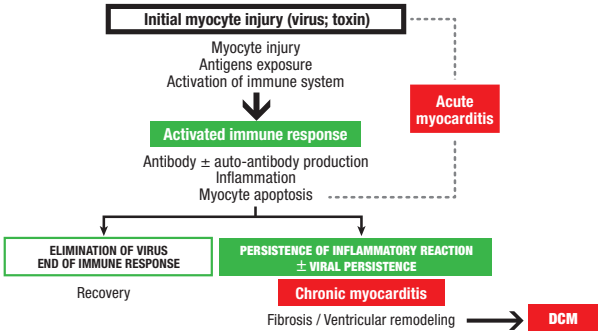
Inflammation of the myocardium

DALLAS CRITERIA: presence of **inflammatory cells** (lymphocytes) ± **myocyte necrosis** on biopsy; poor sensitivity (often falsely negative)

ETIOLOGIES

- **Virus:** Coxsackievirus; echovirus; adenovirus; parvovirus B19; CMV; HSV6; HIV; influenza; HCV; EBV
- **Bacteria / Spirochete:** TB; *Chlamydia pneumoniae; Streptococcus; Mycoplasma pneumoniae; Treponema pallidum; Clostridium*; Diphtheria; Whipple; Lyme
- **Fungi:** *Aspergillus; Candida; Coccidioides; Cryptococcus; Histoplasma*
- **Parasites:** Chagas; Schistosomiasis; Echinococcosis
- **Toxins:** Anthracyclines; Cocaine; 5-FU; phenytoin; cyclophosphamide; arsenic; iron; radiotherapy; alcohol; amphetamines; carbon monoxide; heatstroke; hypothermia; insect / snake bite
- **Hypersensitivity:** clozapine; sulfonamides; cephalosporins; tetracyclines; PNC; tricyclic antidepressants; allopurinol; dobutamine; diuretics
- **Autoimmune:** giant cell myocarditis; Churg-Strauss; Sjögren; inflammatory bowel disease; celiac disease; sarcoidosis; SLE; Takayasu arteritis; Wegener; dermatomyositis; Kawasaki; RA; scleroderma; thyrotoxicosis

PATHOPHYSIOLOGY



PRESENTATION

Compatible symptoms: Acute retrosternal chest pain mimicking myocardial infarction or pericarditis; heart failure; palpitations; syncope; sudden death; cardiogenic shock; viral prodromes; fever

+ ≥ 1 DIAGNOSTIC CRITERION

ECG: AV block (Lyme; giant cell; sarcoidosis); branch block; ST-T abnormalities; PVCs; VT - VF; AF; sinus arrest; low voltage; Q waves	**Myocardiocytolysis:** elevated troponins	**Structural / functional abnormalities (TTE)**: RWMA; systolic dysfunction; ventricular dilatation; wall thickening; effusion; thrombus	**MRI (Lake Louise criteria)** • **Early gadolinium enhancement on T1** indicating inflammation (myocardium vs skeletal muscle enhancement ratio > 4.0) • **Late gadolinium enhancement** indicating fibrosis (intramural or subepicardial; often anteroseptal or inferolateral) • **↗ T2 signal intensity** indicating edema (myocardium vs skeletal muscle signal ratio > 2.0)

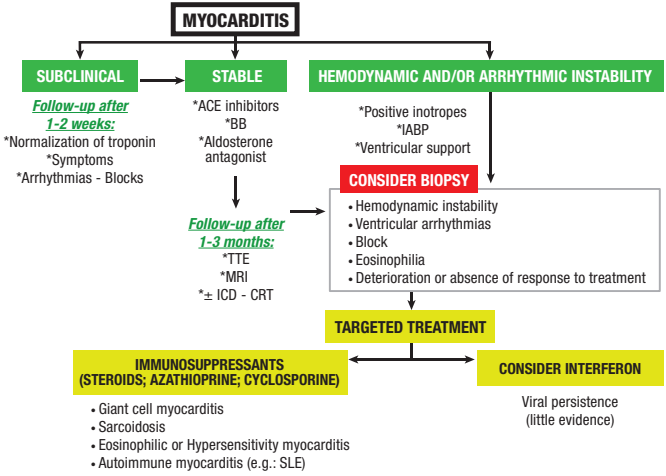
- **Fulminant lymphocytic myocarditis**: < 2 weeks after a viral infection; hemodynamic instability; diffuse LV dysfunction (rarely dilatation); wall thickening (edema); good prognosis with support
- **Giant cell myocarditis**: heart failure (evolving over several weeks to several months); blocks; ventricular arrhythmias; deterioration despite treatment; often underlying autoimmune disease (thymoma; Crohn); median survival < 6 months; Treatment: immunosuppression; transplant
- **Acute lymphocytic myocarditis**: may mimick acute MI (with negative coronary angiography) or may present with progressive LV dysfunction / dilatation or fulminant myocarditis; can progress to DCM
- **Eosinophilic myocarditis**: Hypersensitivity or Loeffler endocarditis or acute necrotizing eosinophilic myocarditis
  - **Hypersensitivity**: drug reaction; rash; fever; multiple organ dysfunction; eosinophilia; Myocarditis; Treatment with corticosteroids
  - **Acute necrotizing eosinophilic myocarditis**: rare; poor prognosis
- **Chronic active myocarditis**: insidious; LV systolic dysfunction (sometimes diastolic with restrictive pattern); ± viral persistence

DEFINITIVE DIAGNOSIS: myocarditis with **histological and/or immunohistological proof** on biopsy

CONSEQUENCES: viral persistence and/or persistent activation of immune system; chronic myocarditis; myocyte necrosis / fibrosis; remodeling; DCM; arrhythmia - sudden death

MANAGEMENT

› Avoid strenuous exertion / competitive sports for ≥ 6 months



5.16/ INDICATIONS FOR ENDOMYOCARDIAL BIOPSY

1.	Heart failure for < **2 weeks** with hemodynamic compromise **(fulminant lymphocytic myocarditis; necrotizing eosinophilic myocarditis; giant cell myocarditis)** (I;B)
2.	Heart failure for **2 weeks to 3 months** with LV dilatation and ventricular arrhythmias or AV block (2nd or 3rd degree) or absence of response to treatment (1-2 weeks) **(giant cell myocarditis or eosinophilic myocarditis)** (I;B)
3.	Heart failure for > 3 months with LV dilatation and ventricular arrhythmias or AV block (2nd or 3rd degree) or absence of response to treatment (1-2 weeks) **(sarcoidosis or Chagas)** (IIa;C)
4.	Heart failure with dilated cardiomyopathy and suspicion of allergic reaction and/or eosinophilia (eosinophilic myocarditis) (IIa; C)
5.	Heart failure with suspicion of anthracycline cardiomyopathy (detect at an early stage of cardiotoxicity) (IIa; C)
6.	Heart failure with unexplained RCM (IIa; C)
7.	Suspected cardiac tumor (with the exception of myxoma), when noninvasive method is inconclusive (IIa; C)

COMPLICATIONS OF BIOPSY: 3%; venous access (arterial puncture; pneumothorax; bleeding); arrhythmia; blocks - RBBB; valve injury; cardiac perforation; tamponade; death; stroke (LV biopsy)

5.17/ CARDIAC TUMORS

METASTASIS

Direct extension; hematogenous; extension via IVC (Hypernephroma; intravenous leiomyomatosis)

Lung; Breast; Lymphoma; Leukemia; Kaposi; Esophagus; Melanoma; Stomach; Mesothelioma; Thyroid; Renal; Extracardiac sarcoma

PRIMARY TUMORS

75 % benign +

SYSTEMIC FEATURES: fever; malaise; weight loss; anemia

EMBOLIC PHENOMENA: tumor embolism or thromboembolism

CARDIAC SIGNS: **depending on the site of the tumor**; blocks - arrhythmia; valve obstruction or regurgitation; SVC syndrome; coronary artery compression; hemorrhagic pericardial effusion (angiosarcoma; lymphoma); heart failure

DIAGNOSIS: TTE; TEE; CT scan or MRI **(mass visible if > 1 cm)**; biopsy; metastatic work-up of malignant tumors; PET scan

- **MRI:** distinction between tumor and thrombus (according to gadolinium enhancement); tissue characterization

MYXOMA

Pedunculated mass with stalk attached to the endocardium (often interatrial septum)

LA (80%); RA (10%); > 90% are solitary

PRESENTATION: Constitutional symptoms; embolisms (tumor fragment or thrombus); valve obstruction (can vary according to the position; look for tumor "plop"); extracardiac metastases

Recurrence in 3% of cases; TTE follow-up for life

Family screening (5 to 10% are familial)

- **Carney complex**: autosomal dominant; multiple intracardiac and extracardiac myxomas; high recurrence rate; cutaneous lentigines; other tumors (testicular; pituitary; thyroid)

TREATMENT: surgical resection

PAPILLARY FIBROELASTOMA

On **valvular endocardium** (80-90%); aortic valve (40%; aortic side); mitral valve (30%; ventricular side); rarely endocardium of LA or LV; solitary (90%)

Friable lesion measuring about 1 cm; resembles a sea anemone; adherent thrombus; 45% have a stalk (1-3 mm)

COMPLICATIONS: thromboembolism

TREATMENT: surgical resection (especially if embolism or mobile or > 1 cm)

LIPOMA

Especially subendocardial (also subepicardial or myocardial)

Predominantly solitary (multiple in the case of tuberous sclerosis)

MRI: fatty mass

COMPLICATIONS: obstruction; pericardial effusion; block; arrhythmias

TREATMENT: surgical resection when symptomatic

LIPOMATOUS HYPERTROPHY OF INTERATRIAL SEPTUM

Excessive fat accumulation in the interatrial septum

Thickening spares the fossa ovale; dumbbell appearance

Associated with obesity and age > 70 years

COMPLICATIONS: Blocks; arrhythmias; SVC obstruction (rare)

RHABDOMYOMA

Children; **associated with tuberous sclerosis** (autosomal dominant; epilepsy; skin lesions; hamartomas)

Ventricles > atria; **multiple lesions; spontaneous regression**

FIBROMA

Children (sometimes adults)

Solitary intramural mass; interventricular septum or LV free wall

TREATMENT: Surgical resection when symptomatic (arrhythmia; blocks; obstruction)

HEMANGIOMA / LYMPHANGIOMA

Intrachamber (ventricle > atrium) / intramural / epicardium / pericardium

Coronary angiography sometimes demonstrates the tumor blood supply

PRESENTATION: asymptomatic; palpitations; heart failure; pericardial effusion; obstruction; embolism; AV block

TREATMENT: echocardiographic follow-up (may increase in size or disappear); surgical resection when symptomatic

MALIGNANT TUMORS

ANGIOSARCOMA

- **RA in 90% of cases** (intramural mass protruding into the chamber)
- Frequent pericardial involvement
- Metastasis at presentation in 70-80% of cases (lung; liver; CNS; bone)
- Mean survival: 10 months
- **Treatment:** Surgery; Radiotherapy; Chemotherapy (Doxorubicin); Neoadjuvant chemotherapy (reduce tumor size prior to surgery); IL-12; autologous transplant (with ex vivo resection); transplant; palliative care

RHABDOMYOSARCOMA

- Children - young adults
- Multiple lesions (60%); no predilection for a particular chamber
- Aggressive, invasive tumor; metastases (lungs; lymph nodes)
- Survival < 1 year

LEIOMYOSARCOMA

- **LA (70-80 %)**; solitary (70%)
- Rapid growth; metastases; mean survival: 6 months

CARDIAC LYMPHOMA

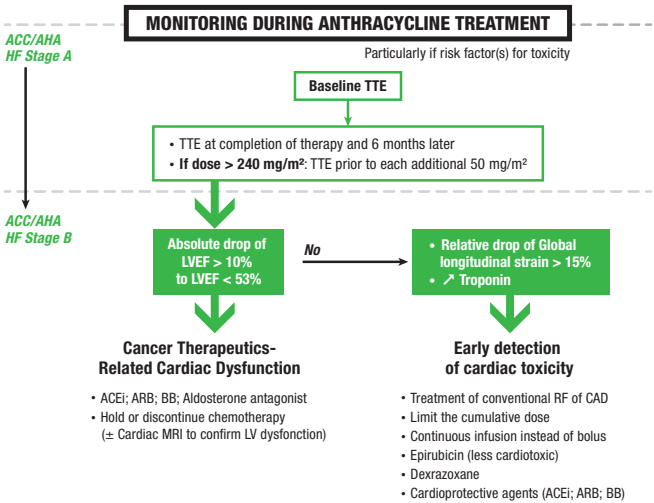
- Right heart (70%); solitary (66%)
- Pericardial effusion (50%)
- Frequent extracardiac disease at the time of presentation
- **Treatment:** Anthracycline; Radiotherapy; Rituximab

5.18/ CARDIAC COMPLICATIONS OF CANCER

COMPLICATIONS: A) Metastases; **B)** Pericardial effusion; **C)** Tamponade; **D)** Constriction (radiotherapy); **E)** SVC obstruction; **F)** Valvular heart disease (metastases; infective endocarditis or non-bacterial thrombotic endocarditis; radiotherapy; obstruction; carcinoid); **G)** CAD (common risk factors; cancer chemotherapy; radiotherapy); **H)** Hyperviscosity (erythrocytosis or thrombocytosis or leukocytosis; ↗ Ig); **I)** Cardiotoxicity of chemotherapy and radiotherapy

ANTHRACYCLINE TOXICITY: (Doxorubicin; Daunorubicin; Epirubicin; Idarubicin)

- **Acute toxicity:** myocarditis; pericarditis; pericardial effusion; arrhythmia; ventricular dysfunction
- **Chronic toxicity: type I cardiotoxicity (irreversible, dose-dependant damage) leading to ↘ LVEF / DCM**
- **Risk factors for toxicity: cumulative dose > 350 mg/m²**; bolus; females; young; > 65 ans; + risk factors for heart disease; history of heart disease; mediastinal radiotherapy; **Trastuzumab (TTE every 3 months during treatment) or Cyclophosphamide or Paclitaxel**; baseline LVEF < 55 %



MEDIASTINAL RADIOTHERAPY: **fibrosis and calcification of cardiac structures;** complications often occur 10-20 years post-exposure; **higher risk with cumulative dose > 30 Gy**

- **Complications**: **A)** Accelerated CAD; **B)** Blocks / Conduction system disease; **C)** Valvular heart disease (thickening / fibrosis / calcification; predominant on left-sided valves; regurgitation > stenosis); **D)** Constrictive pericarditis; Pericardial effusion; **E)** Diffuse myocardial fibrosis with diastolic dysfunction / RCM; **F)** Carotid artery disease (Stroke – TIA); **G)** Aortic calcification / Porcelain aorta; **H)** Recurrent pleural effusions
- **Prevention**: minimize dose to the heart; cardiac shielding; reduction of dose-volume; decreased field; breath-holding; treatment of conventional risk factors of CAD
- **Monitoring after chest radiation exposure**: TTE 5-10 years after exposure then re-assess every 5 years; consider stress-test for CAD detection

SPECIFIC CARDIAC COMPLICATIONS OF CHEMOTHERAPY

LV DYSFUNCTION: Anthracyclines (type I cardiotoxicity; permanent dose-dependant damage); Trastuzumab (type II cardiotoxicity; reversible damage; TTE every 3 months during therapy); Cyclophosphamide; Ifosfamide; Clofarabine; Docetaxel; Paclitaxel (in combination with Doxorubicin); Bevacizumab; Bortezomib; Dasatinib; Imatinib; Sunitinib

ISCHEMIA / VASOSPASM: Capecitabine; 5-Fluorouracil; Paclitaxel; Docetaxel; Bevacizumab (arterial thromboses); Rituximab; Dasatinib; Erlotinib; Sorafenib; Cisplatin; Carboplatin; Interferon

BRADYCARDIA: Thalidomide; Paclitaxel; Docetaxel

HTN: Cisplatin; Docetaxel; Bevacizumab; Rituximab; Trastuzumab; Dasatinib; Sunitinib; Sorafenib; Cyclosporine; Tacrolimus; MMF; Sirolimus

DEEP VEIN THROMBOSIS: Cisplatin; Thalidomide; Bevacizumab; Rituximab; Lenalidomide; Erlotinib; Sorafenib

↗ QT: Anthracyclines; Vorinostat; Arsenic tiroxide; Dasatinib; Lapatinib; Nilotinib; Sunitinib; Lenalidomide; 5-fluorouracil; Cyclophosphamide; Trastuzumab

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Arrhythmias 06

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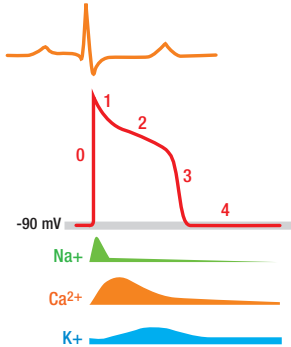
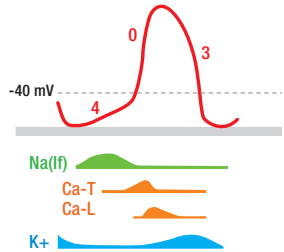
6.1/ PHYSIOLOGY

MYOCARDIAL CELLS / HIS / PURKINJE	SINOATRIAL NODE / AV NODE
	 Inactivated rapid sodium channels (higher resting potential)
• **PHASE 4 (resting potential)**: -90 mV (extracellular Na+; intracellular K+) • **PHASE 0 (action potential)**: brief opening of rapid sodium channels (Na+ influx) • **PHASE 1**: inactivation of sodium channels and K+ efflux • **PHASE 2 (plateau)**: equilibrium between K+ efflux and Ca^{2}+ influx via slow calcium channels • **PHASE 3 (rapid repolarization)**: K+ efflux	• **PHASE 4 (rest)**: spontaneous depolarization → slow sodium influx via If sodium channel › **Intrinsic automaticity**: > 60 bpm (SA node) and 40-60 bpm (AV node) • **PHASE 0 (action potential)**: opening of slow calcium channels (Ca^{2}+ influx) • **PHASE 3 (repolarization)**: inactivation of calcium channels and potassium efflux

ARRHYTHMIC MECHANISMS

1) ABNORMAL AUTOMATICITY: ↗ phase 4 diastolic depolarization

2) REENTRY: two conduction pathways with different conduction velocities and refractory periods; requires one-directional conduction block in one of the pathways of the circuit

3) TRIGGERED ACTIVITY: abnormality during repolarization

› **Early afterdepolarization**: Torsade de pointes
› **Delayed afterdepolarization**: Digoxin poisoning; idiopathic VT; catecholaminergic polymorphic VT

6.2/ BRADYARRHYTHMIAS

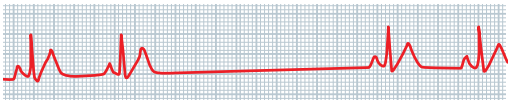
SINOATRIAL NODE

Sinus bradycardia

- **HR < 60 bpm; normal morphology of P wave**
- **Etiologies**: benign; vagal hypertonia; athletes; sick sinus syndrome (SSS); drugs (BB; CCB; Digoxin; Ivabradine; Clonidine; Propafenone; Amiodarone); post-cardiac surgery; ischemia / myocardial infarction; myocarditis; infiltrative cardiomyopathy; Lyme disease; coronary angiography; meningitis; intracranial hypertension; stroke; hypoxia; hypothyroidism; hypothermia; Gram-negative bacillus sepsis; cervical / mediastinal tumor; OSAHS; familial SSS (SCN5A mutation); Chagas, ...
- **Management**: observation; Atropine 0.5 mg; PPM if symptomatic

Sinus arrest / Sinus pause

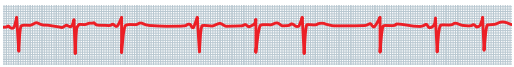
- **Sudden absence of sinus P wave; the duration of the pause is not a multiple of the intrinsic P–P interval**
  - › Ventricular asystole if absence of escape rhythm by latent pacemakers



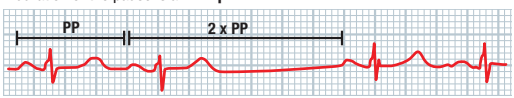
- **Etiologies**: ▸▸| Sinus bradycardia
- **Tachy-bradycardia syndrome**: supraventricular tachyarrhythmia alternating with sinus bradycardia; ± sinus pause following conversion of the tachyarrhythmia; associated with sick sinus syndrome (SSS)
- **Management**: PPM if symptomatic

Sinoatrial block (SA exit block)

- **Sinoatrial block, 2nd degree - Mobitz I**: progressive reduction of P-P interval then absence of P wave; duration of the pause < twice the P-P interval; group beating



- **Sinoatrial block, 2nd degree - Mobitz II**: sudden absence of P wave; the duration of the pause is a **multiple of the intrinsic P–P interval**



Wandering atrial pacemaker

- Passive and gradual shift from a dominant pacemaker focus of the sinoatrial node to a latent atrial pacemaker; a single pacemaker controls rhythm at any one time; possible shift of control back to the sinoatrial node
- **Mechanism**: vigorous vagal tone (benign phenomenon)

Chronotropic incompetence

- **Inability to achieve > 80% HRmax predicted during a stress test (in the presence of sufficient exercise)**
  - › **Chronotropic index**: observed HR reserve (HRmax on stress test - resting HR) / (HRmax predicted for age - resting HR); chronotropic incompetence if **< 80 %**
- **Consequences**: exercise intolerance; factor of poor prognosis

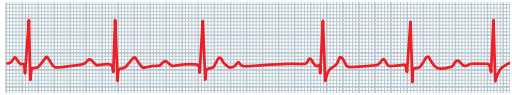
AV CONDUCTION: AV NODE / HIS–PURKINJE SYSTEM

First degree AV block

- **PR > 200 ms** in sinus rhythm
- **Narrow QRS**: delayed AV node conduction (↗ AH)
- **Wide QRS**: delayed AV node conduction (↗ AH) or His-Purkinje conduction (↗ HV)
  - › **Bifascicular block (RBBB + LAHB or RBBB + LPHB or LBBB)**: consider a lesion of the third branch in the presence of prolonged PR

2nd degree AV block, Mobitz I (Wenckebach)

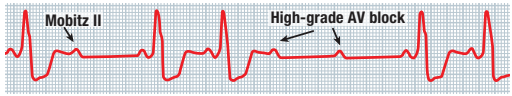
- **Progressive prolongation of the PR interval (with progressive shortening of the RR interval)** until a P wave is blocked; the RR interval including the non-conducted P wave is **less than twice the R–R interval of the previous cycle;** group beating



- **Prognosis**: benign (lesion involving the AV node in the majority of cases)
- **Treatment**: observation if asymptomatic

2nd degree AV block, Mobitz II

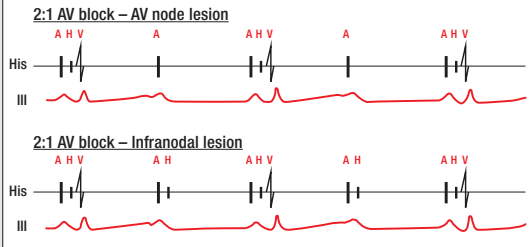
- **P wave suddenly blocked** without any previous prolongation of the PR interval; **the RR interval at the time of the non–conducted P wave = twice the PP interval**



- **Prognosis**: infranodal lesion (His-Purkinje system) in the majority of cases with **high risk of progression to complete AV block**
- **Treatment**: indication for PPM

2:1 AV block

- **P:QRS ratio = 2:1**
- **Suggests AV node lesion (benign)**: **A)** Wenckebach on another ECG; **B)** ↗ PR interval (but narrow QRS); **C)** Improvement of the block with exercise or atropine; **D)** Deterioration of the block with carotid sinus massage
- **Suggests infra-nodal lesion (requires PPM)**: **A)** Wide QRS (underlying intraventricular conduction disorder); **B)** Deterioration of the block with exercise or atropine; **C)** Improvement of the block with carotid sinus massage (↗ PP interval ⟶ ↗ His-Purkinje system recovery time)



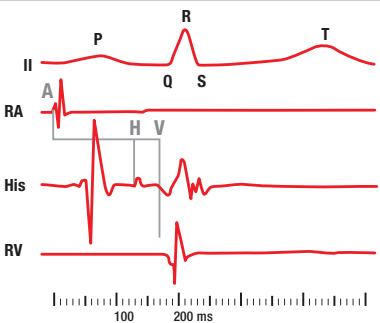
High-grade AV block

- ≥ **2 successive P waves blocked** in sinus rhythm

Complete AV block (3rd degree)	• **Absence of AV conduction** • **Intranodal block**: junctional escape rhythm; narrow QRS; **HR 40–60 bpm** • **Infrahisian block**: ventricular escape rhythm (unreliable and unstable); wide QRS; **HR 15–40 bpm** • **Etiologies**: degenerative; drugs; congenital; ischemia - MI; vagal hypertonia; surgery; calcified AS; progressive familial heart block (Lenègre's disease; SCN5A or TRPM4 mutation); electrolyte disorders; myocarditis; endocarditis; tumor; Chagas; Lyme disease; rheumatoid nodule; AVR; TAVI; hypothyroidism; polymyositis; dilated cardiomyopathy (lamin A/C); infiltrative cardiomyopathy (amyloidosis; sarcoidosis; scleroderma); muscular dystrophy... • **Treatment**: Rule out a reversible cause; PPM

ELECTROPHYSIOLOGICAL STUDY OF CONDUCTION TISSUE

INDICATION: in the presence of a strong suspicion of significant and symptomatic bradyarrhythmia, but in the absence of a clearly documented abnormality

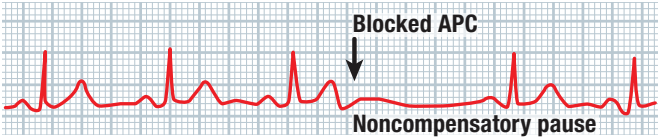
SNRT: Sinus node recovery time	• Continuous rapid atrial stimulation (30 s) then stopped • **SNRT**: interval between last paced beat and the first sinus return beat • **CSNRT (corrected SNRT)**: = SNRT - CL in sinus rhythm › **Normal CSNRT**: < 525 ms • Low sensitivity (65%) but high specificity (95%)
AV conduction	 **Intervals measured** • **AH**: AV node conduction; normal 55-125 ms • **His conduction time**: normal < 25 ms • **HV**: infra-His conduction time; normal: 35-55 ms › **HV > 100 ms**: possible risk of complete AV block › **Short HV**: **A)** Ventricular pre-excitation; **B)** PVC or idioventricular rhythm isorythmic with SR

6.3/ SUPRAVENTRICULAR TACHYARRHYTHMIAS

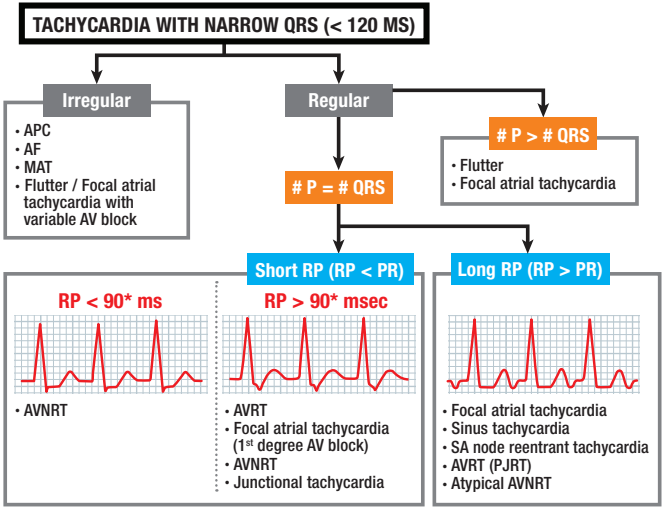
ATRIAL PREMATURE COMPLEXES

ATRIAL PREMATURE COMPLEXES (APC): premature P wave in the cardiac cycle; arises from an atrial focus outside of the sinoatrial node; different morphology from that of the sinoatrial node; sometimes situated in the T wave (look for abnormal morphology of the T wave)

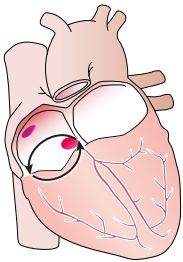
- **Modifiers**: Couplets; Bigeminy; Trigeminy; Salvo
- **Noncompensatory pause**: the APC depolarizes and **resets** the sinoatrial node; the interval between the two P waves before and after the APC **< twice the intrinsic PP interval**
- **Compensatory pause**: failure of the APC to depolarize the sinoatrial node; the interval between the two P waves before and after the APC = **twice the intrinsic PP interval**
- **Blocked atrial premature complex**: the P wave is not followed by a QRS complex (AV-His-Purkinje system in refractory period); the pause is usually noncompensatory



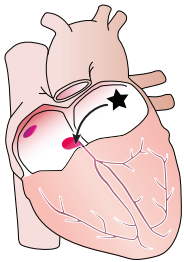
SUPRAVENTRICULAR TACHYARRHYTHMIAS



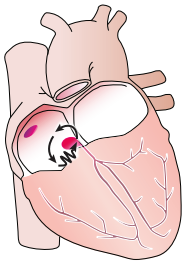
*70 msec for intracardiac VA interval (90 msec for surface ECG VA interval)



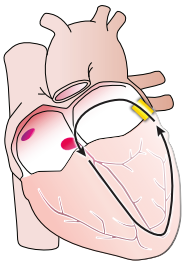
Atrial Flutter



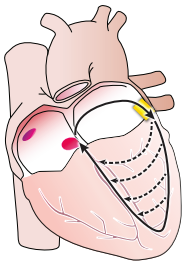
Focal atrial tachycardia



AVNRT: nodal reentry



Orthodromic AVRT



Antidromic AVRT

RESPONSE TO ADENOSINE (OR VAGAL MANEUVER)	
Sudden arrest	**Slowing then re–acceleration**
• AVNRT • AVRT • SA node reentrant tachycardia • (Focal atrial tachycardia)	• Sinus tachycardia • Focal atrial tachycardia • AF; Flutter • Nonparoxysmal junctional tachycardia

SINUS TACHYCARDIA

100-200 bpm (HRmax = 220 - age); nonparoxysmal (progressive onset and termination); normal P waves; secondary to sympathetic stimulation

ETIOLOGIES: fever / sepsis; hypotension; hyperthyroidism; anemia; anxiety; pain; exercise; hypovolemia; pulmonary embolism; ischemia; heart failure; shock; drugs (atropine; catecholamines; adriamycin); alcohol; cocaine; high output state; pregnancy

INAPPROPRIATE SINUS TACHYCARDIA: increased automaticity / sinus dysautonomia

› **Diagnosis**: sinus HR > 100 bpm at rest; mean 24-h HR > 90 bpm; diagnosis of exclusion (rule out physiological sinus tachycardia or focal AT from the high RA)

› **Management**: Rule out an underlying cause (anemia; hyperT4); Ivabradine; BB; radiofrenquency modification of sinoatrial node as last resort

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS): orthostatic intolerance with significant increase of HR during the first 10 min after standing (HR > 120 bpm or HR increased by > 30 bpm)

› **Management**: fluids; NaCl; raise the head of the bed; training; elastic stockings; BB; Fludrocortisone; Midodrine; SSRI

SINOATRIAL NODAL REENTRANT TACHYCARDIA (SANRT): paroxysmal tachycardia; abrupt onset; P wave identical to P wave in SR

› **Management**: vagal maneuver; Adenosine; BB; CCB; RF ablation

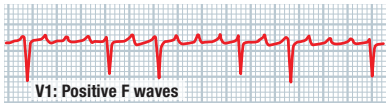
ATRIAL FLUTTER

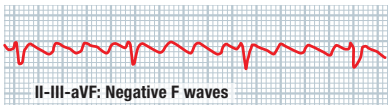
ATRIAL FREQUENCY: **300 bpm** (slowed by class IC AA with risk of 1:1 conduction)

VENTRICULAR FREQUENCY: **150 or 100 or 75 bpm** (2:1 or 3:1 or 4:1 conduction)

TYPICAL ATRIAL FLUTTER

- **Cavotricuspid isthmus-dependent macroreentrant flutter:** atrial flutter counterclockwise around the tricuspid valve annulus (most common) versus clockwise flutter
- **ECG:** sawtooth flutter waves (regular and identical); **negative waves in II-III-aVF and positive waves in V1 in counterclockwise flutter** (and vice versa in clockwise flutter); 2:1 or 3:1 or 4:1 AV conduction





MANAGEMENT

- ECV (50 J biphasic) or atrial overdrive or CCV (IV Ibutilide)
- AV node blocking agents (rate control more difficult than in AF)
- Class IC AAD (combined with AV node blocking agent) or class III AAD
- Thromboembolic prevention (▶▶| AF)
- **RF ablation of cavotricuspid isthmus**: success rate: 90-95%; **first-line long-term treatment;** target bidirectional block; 22-50% will have AF within 30 months

ATYPICAL ATRIAL FLUTTER

- **Cavotricuspid isthmus non-dependent macroreentrant flutter**

1) IART (intra-atrial reentrant tachycardia): macroreentrant circuit arising around a surgical scar following cardiac surgery

2) Left atrial flutter post-AF ablation

- **ECG**: variable morphology of flutter waves (depending on the circuit involved) and different from that of typical flutter
- **Management**: ECV; AV node blocking agents; AAD; RF ablation

FOCAL ATRIAL TACHYCARDIA

ATRIAL FREQUENCY: 150-250 bpm

THREE MECHANISMS: **A)** Automatic (incessant); **B)** Triggered activity; **C)** Microreentrant

ORIGIN: precise focus (pulmonary vein; atrial appendage; *crista terminalis;* SVC or IVC; coronary sinus; mitral annulus; fossa ovale)

ECG: **morphology of P wave different from that in SR**; isoelectric segment between P waves on all leads (unlike flutter); **long RP interval**

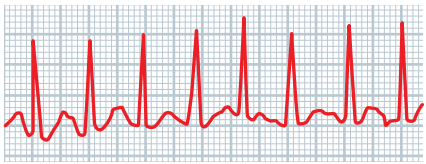
- **V1** - **Positive P wave**: = LA focus (negative P wave in aVL and I)
- **V1** - **Negative or biphasic P wave**: = RA focus (positive or biphasic P wave in aVL)

MANAGEMENT: AV node blocking agent; Class IC or III AAD; ablation of arrhythmogenic focus with 3D electroanatomic mapping (85% success)

MULTIFOCAL ATRIAL TACHYCARDIA (MAT)

ATRIAL FREQUENCY: **100-150 bpm**

IRREGULARLY IRREGULAR RHYTHM: absence of dominant pacemaker; variable morphology of P waves **(≥ 3 different morphologies)**; variable PR interval; abnormal automaticity



RISK FACTORS: COPD; age; Digoxin; Theophylline; hypomagnesemia

MANAGEMENT: correct underlying disease; nondihydropyridine CCB; Amiodarone; Mg^{2+}

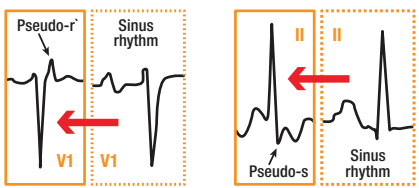
ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA (AVNRT)

AVNRT: **150-250 bpm**; very regular rhythm (except at onset and termination)

ONSET: **sudden; APC with long PR interval (anterograde conduction via the slow pathway)**

SYMPTOMS: palpitations; anxiety; angina; syncope (↘ cardiac output; postconversion sinus pause; vasodepressive response)

TYPICAL AVNRT	ATYPICAL AVNRT
• **Anterograde conduction via the slow pathway; retrograde conduction via the fast pathway (with retrograde atrial activation)** • **ECG**: **Short RP < 90 ms; retrograde P wave hidden in the QRS or just after the QRS (pseudo-r' in V1; pseudo-S in II-III-aVF; absent on baseline ECG in sinus rhythm);** QRS *alternans* if very rapid	• 5-10 % • Anterograde conduction via the rapid pathway; retrograde conduction via the slow pathway; **long RP**



MANAGEMENT: vagal maneuver (Valsalva; carotid sinus massage); Adenosine; CCB; BB; ECV (50 J biphasic); class IC AAD (combined with AV node blocking agent); RF ablation

RF ABLATION: success rate > 95%; **first-line long-term treatment**

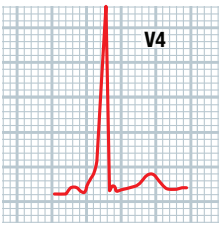
- **Ablation of slow pathway**: inferoposterior to AV node (between the septal aspect of the tricuspid valve annulus and the ostium of the coronary sinus)
- **Complications**: AV block (1%); recurrence (5%); tamponade

ATRIOVENTRICULAR REENTRANT TACHYCARDIA (AVRT) & ACCESSORY PATHWAY

AVRT: **150-250 bpm**; very regular rhythm (except at onset)

ACCESSORY PATHWAY (BUNDLE OF KENT): connection between atrium and ventricle (at the level of the AV sulcus) short-circuiting the AV node - His-Purkinje system; **retrograde conduction only or anterograde (and retrograde) conduction**

1) **Accessory pathway with retrograde conduction only (30%)**: hidden pathway; absence of preexcitation
   - **Associated arrhythmia**: orthodromic AVRT
2) **Accessory pathway with anterograde conduction (70%): ventricular pre-excitation; fusion of ventricular activations by the accessory pathway and by the AV - His-Purkinje system**
   - **Short or negative HV interval**
   - **Associated arrhythmias: A)** Orthodromic AVRT (retrograde conduction); **B)** Antidromic AVRT; **C)** Anterograde conduction of supraventricular arrhythmia (pre-excited AF)
   - **ECG**: PR < 120 ms; wide QRS (> 120 ms) with delta wave; ST-T abnormalities (opposite direction to the QRS); maximized pre-excitation when AV node in refractory period

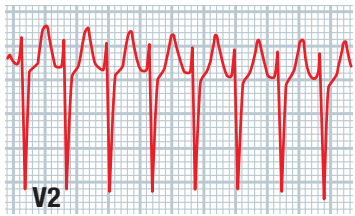
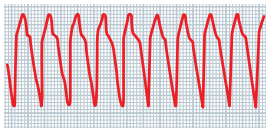


	DELTA WAVE		
SITE OF PATHWAY	**V1**	**AVF**	**AVL**
Left lateral	+	+	-
Left septal or posterior	+	-	+
Right septal or posterior	-	-	+
Anterior or right lateral	-	+	+

WOLFF-PARKINSON-WHITE SYNDROME: symptoms compatible with tachyarrhythmia + ventricular pre-excitation

- **Benign pathway**: inefficient pathway with long refractory period; abrupt disappearance of pre-excitation on stress test (or intermittent loss during ECG or ambulatory monitoring)
- **Malignant pathway**: **refractory period < 250 ms**; able to maintain effective anterograde conduction of possible AF (with risk of VF and sudden death)

DEMONSTRATION OF AN ACCESSORY PATHWAY: **A)** Eccentric retrograde atrial activation during ventricular stimulation or during orthodromic AVRT; **B)** Ventricular stimulation during AVRT induces atrial activation even when the His bundle is refractory; **C)** Ventricular stimulation induces atrial activation before activation of the His bundle; **D)** Ventricular stimulation at various frequencies associated with a stable VA interval (non-decremental VA conduction)

ORTHODROMIC ATRIOVENTRICULAR REENTRANT TACHYCARDIA (AVRT)	ANTIDROMIC ATRIOVENTRICULAR REENTRANT TACHYCARDIA (AVRT) (5–10%)
• **Macro-reentrant tachycardia with anterograde conduction via the AV / His–Purkinje system and retrograde conduction via the accessory pathway** • **ECG**: Narrow QRS; retrograde P wave following QRS **(short RP but > 70 ms intra-cardiac)**; negative retrograde P wave in lead I if left lateral bundle	• **Macro-reentrant tachycardia with anterograde conduction via the accessory pathway and retrograde conduction via the AV / His-Purkinje system; wide QRS tachycardia** +
	
• **If functional branch block ipsilateral to the accessory pathway:** ↗ VA interval and ↗ tachycardia cycle length	

MANAGEMENT OF AVRT: vagal maneuver; Adenosine (can precipitate AF); AV node blocking agent (can precipitate prexcited AF); ECV (50 J); AAD (IC; III); RF ablation of accessory pathway

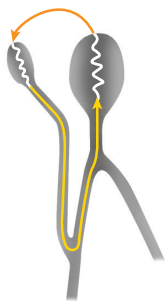
ABLATION OF THE ACCESSORY PATHWAY: **first-line long-term treatment**; success rate: 95%

› **Complications**: 5% recurrence rate; vascular access; microembolism / stroke (left pathway); tamponade; AV block; coronary lesion

› **Asymptomatic pathway**: **EP study or observation is reasonable (IIa recommendation);** ablation if high risk findings during EP study (**R-R < 250 ms** during induced AF; multiple accesory pathways; AVRT precipitating pre-excited AF; pathway with refractory period < 240 ms) or in patients with specific employment (e.g. pilot) +

PERMANENT FORM OF JUNCTIONAL RECIPROCATING TACHYCARDIA (PJRT): incessant supraventricular tachycardia; posteroseptal accessory pathway (R > L); pathway with **slow retrograde one-directional** conduction; **long RP**; **negative P wave in II-III-aVF** +

MAHAIM PATHWAY: accessory pathway in lateral wall of RV; distal connection to RV (atrioventricular connection) or to the right branch (atriofascicular connection); **similar conduction properties to those of the AV node (decremental conduction at higher HR); anterograde conduction only** +


MAHAIM PATHWAY

› **Baseline ECG**: normal (minimal pre-excitation)

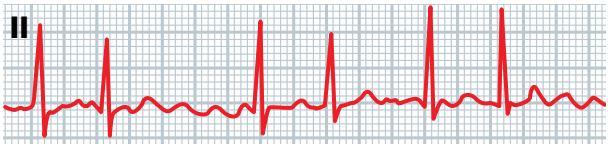
› **Associated arrhythmia**: antidromic AVRT (with **LBBB** morphology); QRS axis 0° and -75°; QRS < 150 ms; late precordial transition; HR 130-270 bpm

JUNCTIONAL TACHYCARDIA

NONPAROXYSMAL JUNCTIONAL TACHYCARDIA	PAROXYSMAL JUNCTIONAL ECTOPIC TACHYCARDIA (JET)
• 70-130 bpm; nonparoxysmal = progressive onset ("warm-up") • **Origin**: origin of AV node or His bundle; narrow QRS; abnormal automaticity • **Etiologies**: Digoxin poisoning; post-cardiac surgery; electrolyte disorder; ischemia; MI; COPD; hypoxia; myocarditis • **Management**: Treatment of underlying cause; BB; CCB	• 110-250 bpm; paroxysmal = sudden onset; more frequent in children; triggered by exercise or stress • **Origin**: AV node or His bundle; narrow QRS; AV dissociation versus VA association • **Management**: BB; AAD (IC; III); RF ablation

6.4/ ATRIAL FIBRILLATION

ATRIAL FREQUENCY: **400-600 bpm**; absence of organized P wave with chaotic atrial fibrillation-rhythm; irregularly irregular ventricular rhythm



› **Lead V1**: sometimes prominent fibrillatory waves (mimicking atrial flutter), but absence of organized waves elsewhere

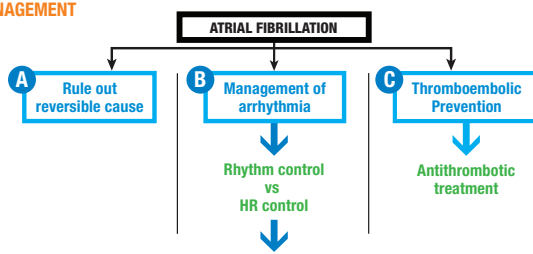
CLASSIFICATION

Paroxysmal AF	Terminates spontaneously or with intervention within < 7 days of onset
Persistent AF	Continuous AF, sustained > 7 days
Longstanding persistant AF	Continuous AF, sustained > 12 months
Permanent AF	No other attempt to restore and/or maintain SR
Nonvalvular AF	Absence of rheumatic MS, prosthetic heart valve or mitral valve repair

SYMPTOMS: palpitations; tiredness; dyspnea; exercise intolerance; faintness; syncope (conversion pause or rapid AF in the presence of structural heart disease); systemic embolism; heart failure (tachycardiomyopathy)

CCS SAF SCALE	
Class 0	Asymptomatic
Class I	Minimal effect on quality of life
Class II	Minor effect on quality of life
Class III	Moderate effect on quality of life
Class IV	Severe effect on quality of life

MANAGEMENT

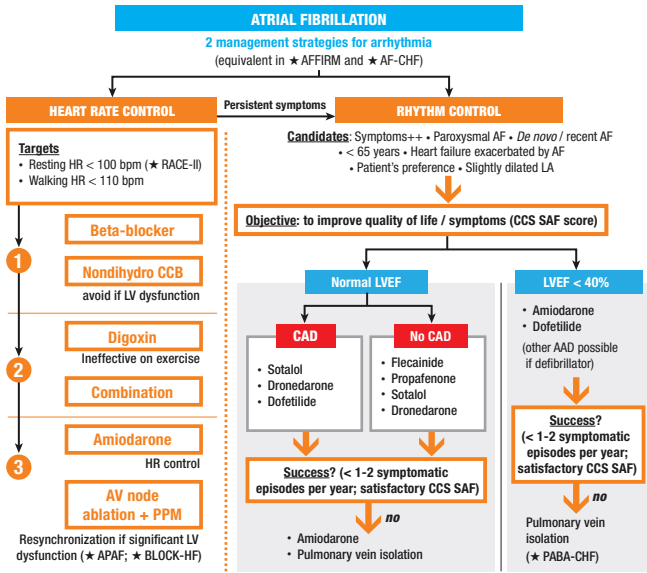


- Target improvement of quality of life and symptoms
- Reduce hospitalizations

RULE OUT REVERSIBLE CAUSE AND RISK FACTORS: Alcohol ("holiday heart syndrome"); ischemia; myocarditis - pericarditis; structural heart disease / heart failure / cardiomyopathy / valvular heart disease / LVH / congenital heart disease / diastolic dysfunction; supraventricular tachycardia (tachycardia-induced AF); SSS; WPW; HTN; pulmonary embolism; hyperthyroidism; frequent V-Pace; OSAHS; vagal hypertonia (athlete; sleep); hyperadrenergism (exercise); postoperative; pneumonia; PHT

› **AF in young patient with structurally normal heart**: consider electrophysiological study to eliminate other supraventricular arrhythmia degenerating to AF (tachycardia-induced AF)

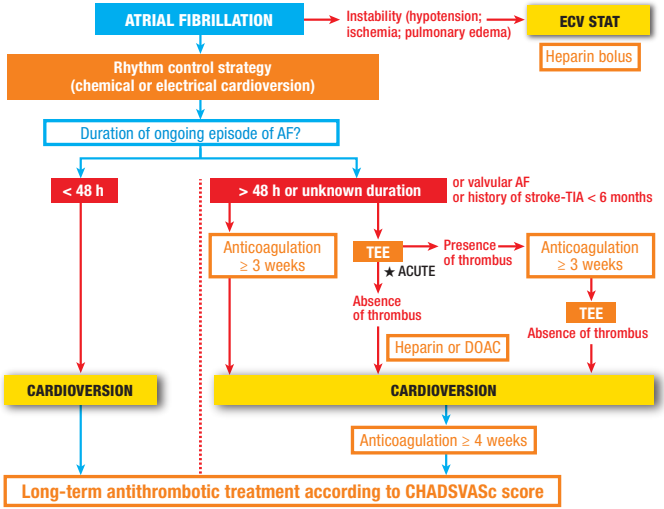
MANAGEMENT OF ARRHYTHMIA



HEART RATE CONTROL STRATEGY			
Diltiazem	0.25 mg/kg IV x 10 min (repeat 0.35 mg/kg PRN)	120 - 480 mg PO qd	Hypotension; bradycardia; edema; negative inotrope; avoid if ↘ LVEF or pre-excited AF
Verapamil	0.075 - 0.15 mg/kg IV x 2 min	120 - 240 mg PO bid	
Metoprolol	2.5 - 5 mg/kg IV x 2 min (3 doses every 5 min PRN)	25 - 200 mg PO bid	Hypotension; bradycardia; tiredness; depression; asthma; negative inotrope; avoid if preexcited AF
Nadolol	10 - 320 mg qd		
Esmolol	**IV bolus**: 500 µg/kg; **Infusion**: 50-300 µg/kg/min (dilution: 2500 mg / 250 mL)		
Digoxin	0.25 mg IV (or PO) every 6 h (4 doses over 24 h; adjustment according to creatinine clearance)	0.0625 to 0.25 mg qd	Digoxin toxicity; Nausea; Vomiting; Visual abnormalities; avoid in the presence of pre-excited AF
HEART RHYTHM CONTROL STRATEGY			
CLASS IC			
Flecainide	50 - 150 mg PO bid * Combine with AV node blocking agent	• **Efficacy at 1 year**: 30-50 % • **Adverse effects**: ↗ QRS (caution if > 25%); VT; bradycardia; 1:1 flutter • **Contraindications**: CAD or LV dysfunction (★ CAST) • Pre-treatment stress test if > 50 years or high Framingham score	
Propafenone	50 - 300 mg PO tid * Combine with AV node blocking agent		
CLASSE III			
Amiodarone	Loading dose of 10 g over several weeks then 100 - 200 mg PO qd	• **Efficacy at 1 year**: 60-70 % (★ CTAF) • **Avantage:** controls HR (BB effect) • **Adverse effects**: ▸▸| Amiodarone	
Dronedarone	400 mg PO bid	• **Efficacy at 1 year**: 40 % • ★ **ATHENA**: Paroxysmal AF; ↘ cardiac mortality with Dronedarone • **Contraindications:** heart failure / LVEF < 40% (★ ANDROMEDA) or permanent AF (★ PALLAS) or Digoxin • Monitor LFTs at 6 months	
Sotalol	40 - 160 mg PO bid	• **Efficacy at 1 year**: 30-50 % (★ CTAF) • **Adverse effects**: ↗ QT; torsade de pointes; bradycardia; asthma (BB effect) • **Avoid**: women > 65 years / CRF / LVEF < 40% / significant LVH / electrolyte disorders / ↗ QTc • Monitoring of QT for 72 h; stop if QTc > 500 ms	
Dofetilide	0.125 to 0.5 mg PO bid (according to CrCl)	• **Complication**: torsade de pointes • **Contraindications**: CrCl < 20 mL/min; hypokalemia; baseline QTc > 440 ms	

"PILL IN THE POCKET" APPROACH: AAD as needed (Flecainide 200 to 300 mg or Propafenone 450 to 600 mg) combined with Metoprolol 50 to 100 mg; indicated in the presence of occasional episodes in subjects with a healthy heart; initiate under cardiac monitoring to demonstrate safety of the approach

CARDIOVERSION



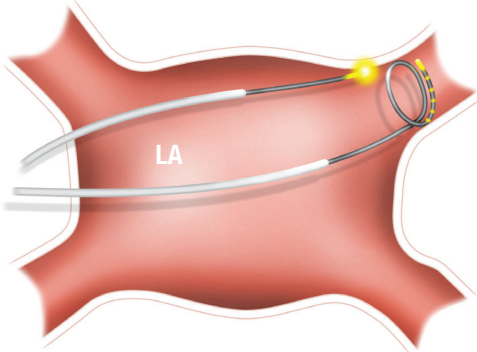
ELECTRICAL CARDIOVERSION: 200 J biphasic

- **Failure (5 %)**: Add AAD followed by another attempt of ECV (Amiodarone; Flecainide; Propafenone; Ibutilide; Sotalol)
- **Conversion then early recurrence of AF (ERAF) post-ECV**: Add AAD followed by another attempt of ECV

CHEMICAL CARDIOVERSION: only minimally effective when AF present for > 7 days

CHEMICAL CARDIOVERSION		
Propafenone	450 to 600 mg PO	• Hypotension; 1:1 flutter; bradycardia; complete AV block • Contraindicated in the presence of CAD or systolic dysfunction; administer with AV node blocking agent
Flecainide	200 to 300 mg PO	
Procainamide	15-17 mg/kg IV x 60 min	• Hypotension • **Efficacy**: 60 %
Ibutilide	1 mg IV x 10 min; may repeat once if necessary	• Torsade de pointes (2-3%) • Contraindicated if LVEF < 30% or significant LVH or ↗ QTc > 440 ms or SSS or hypokalemia • Pretreat with $MgSO_4$
Vernakalant	3 mg/kg x 10 min then observation for 15 min then 2nd bolus of 2 mg/kg x 10 min PRN	• Blocks various atrial ionic channels (↗ refractory period) • **Efficacy**: 50 % (★ ACT; ★ AVRO) • **Adverse effects**: dysgeusia; Nausea; Hypotension; ↗ QT and QRS intervals • **Contraindications**: hypotension; ACS during previous 30 days; NYHA III or IV; Severe AS; non-corrected QT > 440 ms; LVEF ≤ 35%

PULMONARY VEIN ISOLATION



PAROXYSMAL AF	PERSISTENT AF
• Triggered by **premature complexes arising in pulmonary veins** (90% of cases; ★ Haïssaguerre) • **Ablation:** pulmonary vein isolation (electrical disconnection from the rest of the LA by radiofrequency ablation)	• Presence of a substrate **maintaining and perpetuating the arrhythmia** • **Substrate**: structural and electrical remodeling of the atrium; fibrosis - inflammation - ↘ refractory period • **Ablation**: pulmonary vein isolation combined with modification of the substrate (other radiofrequency lesions in the atria) › Linear ablation (roof of LA and mitral annulus; ± cavotricuspid isthmus) › Ablation of complex fractionated atrial electrograms sites (CFAE) › No benefit in ★ STAR-AF

OBJECTIVE: improve symptoms and quality of life

INDICATION: **AF with persistent and harmful symptoms (negative impact on quality of life) despite trial of drug treatment (class I or III AAD)**

SUCCESS RATE: **60-75% after 1 procedure and 75-90% after 2 procedures** (success rate 10-15% lower in the presence of persistent AF); improvement of quality of life; more effective than AAD for maintenance of SR

MAJOR COMPLICATIONS: **5 %;** vascular complication (1-2%); cardiac perforation / tamponade (1%); thromboembolism (1%); PV stenosis (0.5%); atrio-esophageal fistula; phrenic nerve palsy (diaphragmatic paralysis); atypical flutter; death (1/1,000)

CONTRAINDICATIONS: LA > 55 mm; significant structural heart disease; LA thrombus; long-term AF; mechanical MVR

PERIPROCEDURAL CONSIDERATIONS: TEE before the procedure; procedure performed under anticoagulation (continue warfarin; stop DOAC 12-24 h before the procedure); continue anticoagulation for 2 months post-op (then according to CHADSVASc score)

› **Early recurrence of AF post-PVI (< 3 months)**: secondary to acute inflammation; management by rhythm control then re-evaluate at 3 months

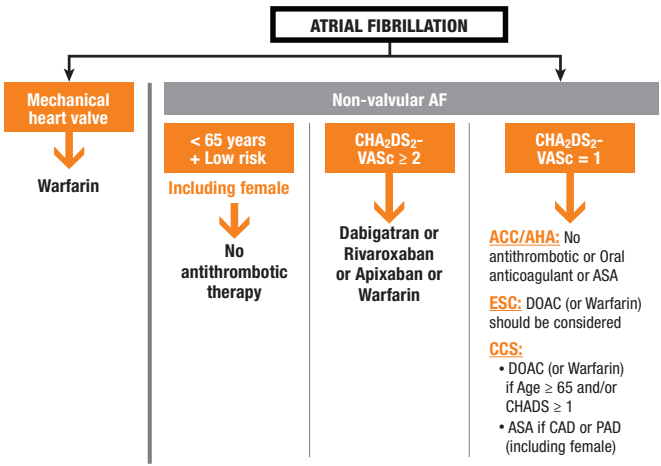
PVI FOR PERSISTENT AF AND HEART FAILURE: more effective than AV node ablation + resynchronization (★ PABA-CHF)

- ★ **AATAC-AF:** PVI superior to Amiodarone in relieving persistent AF in patients with congestive heart failure; PVI associated with ↘ all-cause mortality and ↘ hospitalization

SURGICAL ABLATION OF AF: indicated for symptomatic AF when concomitant cardiac surgery is planned

- **Paroxysmal AF: pulmonary vein isolation** (endocardial or epicardial) ± ablation line to mitral annulus
- **Persistent AF: modified Cox-Maze procedure**; requires bilateral atriotomy; ablation lines in LA to isolate pulmonary veins / isolate the posterior LA / create an ablation line between the pulmonary veins and mitral annulus; ablation lines at the cavotricuspid isthmus and between inferior and superior venae cavae; left atrial appendectomy; one-year success rate: 85% (63% in ★ CTSN AF)

THROMBOEMBOLIC PREVENTION



$CHADS_2$ SCORE		
Congestive heart failure and/or LVEF ≤ 40%	1 point	**Stroke / year** 0 → 1.9 % 1 → 2.8 % 2 → 4.0 % 3 → 5.9 % 4 → 8.5 % 5 → 12.5 % 6 → 18.2 %
HTN	1 point	
≥ 75 years	1 point	
DM	1 point	
Stroke – TIA – Thromboembolism	2 points	

Gage BF, Waterman AD, Shannon W, et al. JAMA 2001;285:2864-70.

CHA_2DS_2-VASC SCORE		
Recent decompensated HF and/or LVEF ≤ 40%	1 point	**Stroke / year** 0 → 0 % 1 → 1.3 % 2 → 2.2 % 3 → 3.2 % 4 → 4.0 % 5 → 6.7 % 6 → 9.8 % 7 → 9.6 % 8 → 6.7 % 9 → 15.2 %
HTN	1 point	
≥ 75 years	2 points	
DM	1 point	
Stroke - TIA - Thromboembolism	2 points	
Vascular disease (history of MI; PAD; Aortic plaque)	1 point	
65-74 years	1 point	
Female	1 point	

Lip GY, Nieuwlaat R, Pisters R, et al. Chest 2010;137:263–272.

BENEFIT OF WARFARIN IN PRIMARY PREVENTION: ★ AFASAK-1 AND 2;★ SPAF-1 and 2 and 3; ★ BAATAF; ★ CAFA; ★ SPINAF

- **Benefit of Warfarin**: **relative risk of stroke ↘ by 64%**
- **Benefit of ASA**: relative risk of stroke↘ by 19%

WARFARIN ANTIDOTE: vitamin K; prothrombin complex concentrate (Octaplex; Beriplex; Cofact; Proplex; factors II - VII - IX - X); FFP (8 units)

★ **ACTIVE-A**: Warfarin impossible; ASA + Plavix vs ASA; ↘ stroke but ↗ major bleeding

- **Indication for ASA-Clopidogrel**: when any form of oral anticoagulation is impossible but acceptable bleeding risk

BLEEDING RISK ASSOCIATED WITH ANTICOAGULATION

WARFARIN: **annual risk of major bleeding ≈ 3%**

HAS-BLED SCORE		
HTN (SBP > 160 mmHg)	1 point	**Major bleeding/year** 0 → 1.1 % 1 → 1.02 % 2 → 1.88 % **3 → 3.74 %** 4 → 8.7 % 5 → 12.5 %
Abnormal (liver or renal function) • Creatinine ≥ 200 µmol/L or Dialysis • AST - ALT > 3 x ULN or Bilirubin 2 x ULN or Cirrhosis	1 point each	
Stroke	1 point	
Bleeding (history; Anemia; Bleeding diathesis)	1 point	
Labile INR	1 point	
Elderly (> 65 years)	1 point	
Drugs (associated with a risk of bleeding) or Alcohol	1 point each	

Pisters R, Lane DA, Nieuwlaat R, et al. Chest 2010;138:1093-100.

HAS-BLED ≥ 3: **high bleeding risk**; try to correct reversible risk factors

OTHER SCORES: $HEMORR_2HAGES$; ATRIA

DIRECT ORAL ANTICOAGULANTS (DOAC)

CONTRAINDICATED: **A)** Mechanical prosthetic valve; **B)** Moderate to severe mitral stenosis (usually of rheumatic origin)

DABIGATRAN (PRADAXA)	RIVAROXABAN (XARELTO)	APIXABAN (ELIQUIS)	EDOXABAN (SAVAYSA; LIXIANA)
Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Dose: 150 mg bid • **110 mg bid**: ≥ 75 years; CrCl 30-49 mL/min with additional bleeding risk factor Not studied in patients with CrCl < 30 mL/min	**Dose: 20 mg qd** • **15 mg qd**: CrCl 30-49 mL/min Not studied in patients with CrCl < 30 mL/min	**Dose: 5 mg bid** • **2.5 mg bid**: ≥ 2 factors (≥ 80 years or ≤ 60 kg or creatinine ≥ 133 µmol/L) Not studied in patients with CrCl < 25 mL/min	**Dose: 60 mg qd** • **30 mg qd**: CrCl 30-49 mL/min Not studied in patients with CrCl < 30 mL/min
★ **RELY** • **150 mg bid**: ↘ **stroke (superior to warfarin);** comparable bleeding • **110 mg bid:** non-inferior for stroke; ↘ **bleeding**	★ **ROCKET-AF** • 20 mg (15 mg if CrCl 30-49 mL/min): **non-inferior to warfarin for stroke**; comparable bleeding	★ **ARISTOTLE** • Apixaban 5 mg bid (2.5 mg bid not extensively studied): ↘ **stroke (superior to warfarin);** ↘ **bleeding;** ↘**all-cause mortality**	★ **ENGAGE-AF** • **60 mg qd**: **non-inferior for stroke** (trend for superiority); ↘ **bleeding** • **30 mg qd**: **non-inferior for stroke** (trend for inferiority); ↘ **bleeding;** ↘ **all-cause mortality**
Renal excretion: 80%	Renal excretion: 33%	Renal excretion: 25%	Renal excretion: 50%

FOLLOW-UP: CrCl (Cockcroft-Gault) prior to initiation / when clinically indicated / ≥ 1 x / year

CONSIDER REDUCED DOSE: high bleeding risk (HAS-BLED ≥ 3); impaired renal function; drug interactions (P-gp and/or CYP3A4)

★**AVERROES**: AF with mean CHADS = 2; Warfarin impossible; Apixaban 5 mg bid versus ASA; early discontinuation (↘ stroke with Apixaban; similar bleeding)

BLEEDING WITH DOAC: Idarucizumab (Dabigatran; ★ RE-VERSE); Andexanet alpha (Rivaroxaban; Apixaban; Edoxaban); discontinue the anticoagulant; local compression; plasma expansion / transfusion; maintain diuresis to promote elimination; seek an opinion from a hematologist / pharmacist; consider prothrombin complex concentrates or activated factor VII or hemodialysis (Dabigatran)

DOAC AND OTHER ANTICOAGULANTS	
Switch from Warfarin → DOAC	• INR < 2.0 → Start DOAC immediately • INR 2.0 - 2.5 → Start DOAC on the following day
Switch from IV Heparin → DOAC	After stopping heparin
Switch from LMWH → DOAC	At the next scheduled dose of LMWH
Switch from DOAC → LMWH or IV Heparin	At the next scheduled dose of DOAC
Switch from DOAC → Warfarin	Stop DOAC when INR > 2.0

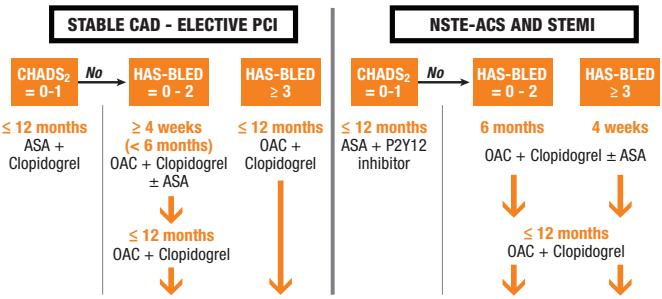
PERIOPERATIVE USE OF DOAC	
Surgery with low bleeding risk (Dental extraction; cataract; endoscopy without biopsy; superficial skin surgery)	Continue DOAC (operate under DOAC) or skip the dose in the morning of the operation
Surgery with intermediate bleeding risk (Endoscopy with biopsy; prostate or bladder biopsy; angiography; electrophysiological intervention; pacemaker)	• **Apixaban – Rivaroxaban:** stop DOAC ≥ 24 h before the operation • **Dabigatran**: stop DOAC ≥ 24 h (CrCl ≥ 80 mL/min) or ≥ 36 h (CrCl 50-80 mL/min) or ≥ 48 h (CrCl 30-50 mL/min)
Surgery with high bleeding risk (Lumbar puncture; spinal / epidural surgery; thoracic / abdominal / neurological / orthopedic surgery; liver or kidney biopsy; TURP)	• **Apixaban – Rivaroxaban**: stop DOAC ≥ 48 h before the operation • **Dabigatran**: stop DOAC ≥ 48 h (CrCl ≥ 80 mL/min) or ≥ 72 h (CrCl 50-80 mL/min) or ≥ 96 h (CrCl 30-50 mL/min)

PERCUTANEOUS OCCLUSION OF LEFT ATRIAL APPENDAGE

★**PROTECT AF**: Watchman system non-inferior to warfarin for thromboembolic prevention; associated procedural complications; requires long-term antiplatelet therapy

INDICATION: high risk of stroke (CHADS ≥ 2) for whom anticoagulation is precluded

ATRIAL FIBRILLATION AND CORONARY ARTERY DISEASE



Beyond 12 months

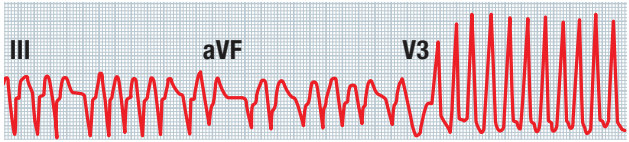
Long term oral anticoagulation

OAC (Oral anticoagulation):
Either Warfarin (INR 2.0 - 2.5) or DOAC (Dabigatran 110 mg bid; Rivaroxaban 15 mg qd; Apixaban 2.5 mg bid)

Proton pump inhibitor if risk of GI bleeding

★**WOEST:** 573 patients with an indication for anticoagulant therapy undergoing PCI (25-30% with ACS); Warfarin + Clopidogrel (versus Warfarin + Clopidogrel + ASA) associated with ↘ bleeding and ↘ mortality

PRE-EXCITED ATRIAL FIBRILLATION



Irregularly irregular tachycardia with wide QRS

COMPLICATIONS: **rapid AV conduction via an efficient accessory pathway (refractory period < 250 ms) → transformation to VF** +

MANAGEMENT: ECV stat; Procainamide or Ibutilide if hemodynamically stable; ablation of accessory pathway

› **Agents contraindicated**: AV node blocking agents predisposing to conduction via the accessory pathway (Digoxin; nondihydropyridine CCB; BB; Adenosine; IV Amiodarone)

AF DETECTED BY PACEMAKER (SUBCLINICAL AF)

★ **ASSERT**: detection of subclinical atrial tachycardia (defined by HR > 190 bpm and duration > 6 min) associated with increased thromboembolic risk

› **Episode > 17.7 h (upper quartile of duration)**: **significantly ↗ risk of stroke (fivefold)**

★ **TRENDS**: atrial tachycardia (probable AF) ≥ 5.5 h associated with increased thromboembolic risk

CONSIDER ANTICOAGULATION: **A)** Episode lasting ≥ 24 h; **B)** Shorter episode in high-risk patient (cryptogenic stroke; TIA)

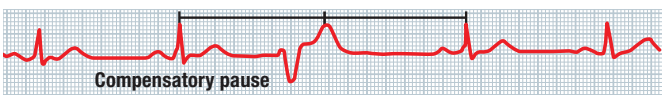
6.5/ VENTRICULAR TACHYARRHYTHMIAS

PREMATURE VENTRICULAR COMPLEXES

Premature ventricular depolarization during the cardiac cycle; wide QRS; T wave in opposite direction to the QRS

MODIFIERS: couplet; bigeminy; trigeminy; monomorphic; polymorphic; associated with compensatory or noncompensatory pause; associated with retrograde atrial activation; interpolated complex; fusion complex; associated with echo (PVC → retrograde atrial activation → anterograde ventricular activation)

› **Compensatory pause**: **interval between QRS before and after PVC = 2 x RR interval** (failure of PVC to reset the sinoatrial node)



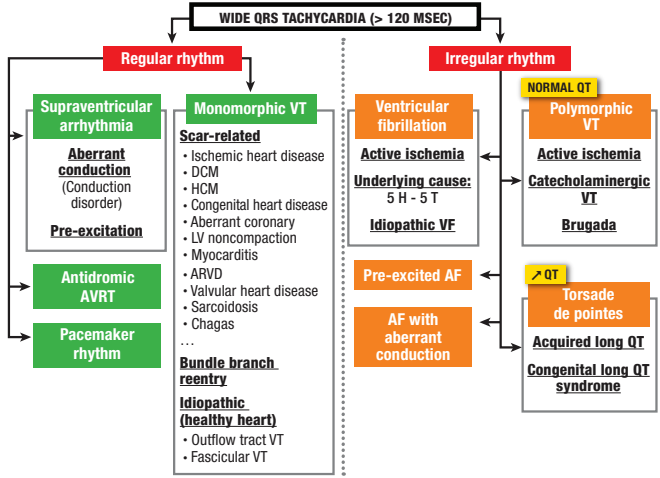
› **Interpolated PVC**: PVC between two beats of baseline rhythm with no modification of rhythm

PVC / MONOMORPHIC NSVT IN STRUCTURALLY NORMAL HEART: benign; risk of **tachy-cardiomyopathy** if frequent **(> 10,000 / 24 h)** and with a short coupling interval (< 300 ms) +

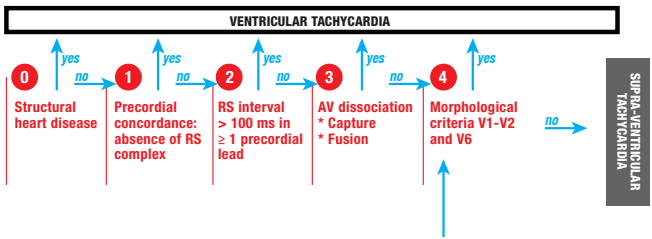
MANAGEMENT: Observation; intervention if symptoms or complications (tachycardiomyopathy); BB; AAD (IC; III); radiofrequency ablation

PVC ASSOCIATED WITH AF: elements in favor of PVCs rather than aberrant conduction → fixed coupling interval / pause after wide QRS / bigeminy

WIDE QRS TACHYCARDIA: DIFFERENTIAL DIAGNOSIS



WIDE QRS TACHYCARDIA: VT VERSUS ABERRANT CONDUCTION



	QRS	V1–V2	V6
RBBB morphology	QRS > 140 ms Left frontal axis	R RSr' QR	R/S < 1 QS
LBBB morphology	QRS > 160 ms Right frontal axis	notch at S R > 30 ms R to S > 70 ms	Any Q wave

OTHER CRITERIA

- **Supraventricular tachycardia with aberrant conduction**: **A)** Onset: Early P wave (APC); **B)** Change of PP interval precedes change of RR interval; **C)** QRS: identical to baseline rhythm; **D)** Stopped by vagal maneuver
- **Ventricular tachycardia**: **A)** Onset: Early QRS (PVC); **B)** Change of RR interval precedes change of PP interval; **C)** QRS: identical to PVC on baseline rhythm; **D)** Canon A wave; variable intensity of S1; variable SBP; **E)** -90° to 180° axis deviation

LOCALIZATION OF VT ON ECG

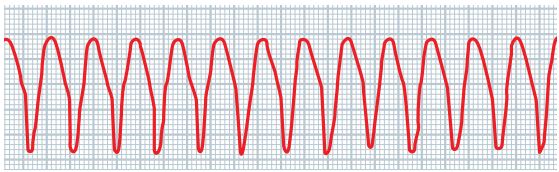
1) **V1 morphology**: LBBB (VT arises in RV and sometimes in LV septum); RBBB (VT arises in LV)
2) **Frontal axis**: Superior (VT arises in inferior wall); Inferior (VT arises in anterior wall)
3) **QRS V1 to V6**: **A)** Positive concordance → basal focus; **B)** Early QRS transition (V1-V2) → apical focus; **C)** Late QRS transition → midventricular focus
4) **QS complexes**: indicate the territory in which the arrhythmia arises (II-III-aVF = inferior; V4-V5-V6 = apical)
5) **Epicardial VT**: pseudo-Delta wave (initial portion of wide QRS)

VENTRICULAR TACHYCARDIA (VT)

≥ 3 consecutive ventricular complexes; HR 110-250 bpm

- **Sustained**: **> 30 s (or ECV necessary)** +
- AV dissociation or VA association (retrograde conduction)

MONOMORPHIC VENTRICULAR TACHYCARDIA: **scar-related in the majority of cases; look for structural heart disease** +



- **Acute management**: cardioversion (100 J biphasic) / defibrillation if absent pulse (200 J biphasic); Procainamide or Amiodarone (150 mg IV x 10 min then 1 mg/min x 6 h then 0.5 mg/min x 18 h) or Sotalol; ventricular overdrive; look for underlying cause
- **Secondary prevention**: First-line ICD; BB; Amiodarone (★ OPTIC); Sotalol; Mexiletine; RF ablation if repeated ICD shocks

VENTRICULAR TACHYCARDIA IN STRUCTURALLY NORMAL HEART

▸▸| Idiopathic ventricular tachycardia

BUNDLE BRANCH REENTRY TACHYCARDIA: **in DCM; macro-reentry with anterograde conduction via the right bundle branch and retrograde conduction via the left bundle branch; Monomorphic VT with LBBB morphology**

- **Management**: right bundle branch ablation

ACCELERATED IDIOVENTRICULAR RHYTHM (AIVR): **50-110 bpm; competition between sinoatrial node and a ventricular ectopic focus**; increased automaticity; progressive onset and termination; associated with MI / reperfusion or Digoxin toxicity

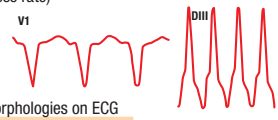
- **Management**: observer; atropine PRN; « overdrive » auriculaire

POLYMORPHIC VENTRICULAR TACHYCARDIA WITH NORMAL QT: **occurs during active myocardial ischemia or in genetic arrhythmia syndrome** (▸▸| Channelopathies)

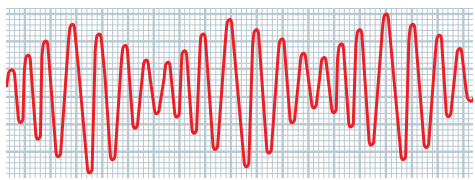
- **Acute management**: defibrillation; Rule out active ischemia; BB; Amiodarone; Lidocaine; correct electrolyte disorders

IDIOPATHIC MONOMORPHIC VENTRICULAR TACHYCARDIA

Absence of structural heart disease; favorable prognosis

Outflow tract VT	**MECHANISM**: myocyte calcium overload inducing triggered activity (delayed afterdepolarization); NSVT > sustained VT; 140-180 bpm; induced by exercise / stress / Isoproterenol **RVOT VT**: **LBBB morphology; inferior frontal axis; V3-V4 precordial transition** › **DDx**: ARVD (abnormal SAECG / TTE / EPS) › **Management**: Adenosine; BB; Verapamil; class IC AAD; RF ablation (90% success rate)  **LVOT VT**: 2 morphologies on ECG **1) RBBB - Inferior axis - S in V6** **2) LBBB - Inferior axis - early precordial R wave transition (V2 LVOT versus ≥ V3 RVOT)** **VT ARISING IN SINUS OF VALSALVA**: **LBBB; inferior axis** › **Left sinus of Valsalva**: rS in I; V1 with "w" pattern or notch; early precordial transition › **Right sinus of Valsalva**: large R wave in V1; early precordial transition
Fascicular VT	**MECHANISM**: reentry in Purkinje system **3 TYPES**: › **Left posterior hemibranch**: **RBBB; Left superior frontal axis** › **Left anterior hemibranch**: RBBB; Right inferior frontal axis › **High septum**: Narrow QRS; normal axis **MANAGEMENT**: Verapamil / Diltiazem; class III AAD; RF ablation
Mitral annulus	**ECG**: RBBB morphology; Dominant R in precordial leads

TORSADE DE POINTES



Polymorphic ventricular tachycardia; HR 200-250 bpm; twisting of QRS around the isoelectric line (axis changes by 180° every 5-20 beats)

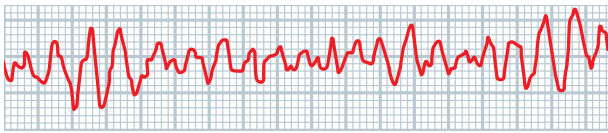
- **Associated with ↗ QT interval**: **prolonged ventricular repolarization; QT > 500 ms; ± prominent U wave** +
- **Mechanism**: triggered activity (early afterdepolarization)
- **Long RR - short RR sequence**

ETIOLOGIES - ACQUIRED LONG QT: Drugs (www.qtdrugs.org); AAD (IA; III); severe bradycardia; electrolyte disorders (hypokalemia; hypomagnesemia); CNS lesion; ischemia; hypothermia; anorexia; hypothyroidism; heart failure

- **Congenital long QT syndrome**: ▸▸| Channelopathies

MANAGEMENT: Mg^{2+} (1-2 g IV); ventricular overdrive; Isoproterenol (pause-dependent TdP); Lidocaine; BB with temporary pacemaker in place; correct underlying cause / correct electrolyte disorders; PPM (in the case of pause-dependent TdP)

VENTRICULAR FIBRILLATION (VF)



Chaotic ventricular rhythm; HR 400-600 bpm; absence of organized QRS - ST - T; fatal within 3-5 min

ACUTE MANAGEMENT: immediate defibrillation (200 J biphasic) ± CPR (▸▸| Chapter 9); rule out ischemia; look for underlying cause ("5 H and 5 T"); AAD to prevent recurrence (Amiodarone; Lidocaine; Procainamide)

- **5 H - 5 T**: Hypovolemia; Hypoxia; Hydrogen (acidosis); Hypokalemia / Hyperkalemia; Hypothermia; Tension pneumothorax; Tamponade; Toxin; coronary Thrombosis; pulmonary Thrombosis

ELECTRICAL STORM: **≥ 3 episodes of VT/VF in 24 hours** +

- **Management**: first-line BB; intubation / sedation; rule out ischemia or underlying cause; magnet over the ICD if inappropriate shocks; Amiodarone or Procainamide or Lidocaine (in the presence of ischemia); ventricular overdrive; reprogramming of ICD therapies; RF ablation; ventricular mechanical support

IDIOPATHIC VENTRICULAR FIBRILLATION

DIAGNOSIS OF EXCLUSION: absence of structural heart disease and absence of an identifiable channelopathy

EARLY REPOLARIZATION (HAÏSSAGUERRE PATTERN): association between VF and early repolarization (J point elevation ≥ 1 mm on 2 contiguous inferior and/or lateral leads)

POSSIBLE MECHANISM: triggered by PVC with short coupling interval (arising in Purkinje system)

MANAGEMENT: ICD; Isoproterenol for electrical storm; Quinidine; cathter ablation of PVCs triggering VF; assessment of first-degree relatives

6.6/ CHANNELOPATHIES

CONGENITAL LONG QT SYNDROME (LQTS)

ABNORMAL QT: **QTc ≥ 450 ms (male) or ≥ 460 ms (female)**

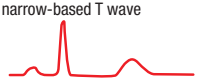
› **50th percentile of LQTS cohorts**: **QTc > 480 ms** +

TRANSMISSION: autosomal dominant form (Romano-Ward syndrome) or recessive form (deafness; Jervell & Lange-Nielsen syndrome)

SCHWARTZ SCORE		
ECG	**Clinical features**	**Family history**
• QTc ≥ 480 ms: 3 points • QTc 460-479 ms: 2 points • QTc > 450-459 ms (male): 1 point • QTc after 4 min of recovery on stress test ≥ 480 ms: 1 point • TdP: 2 points • Alternating T wave: 1 point • Notched T wave on 3 leads: 1 point	• Syncope on exercise / stress: 2 points • Syncope without stress: 1 point	• Family member with LQTS: 1 point • Sudden death in first degree relative before the age of 30 years: 0.5 point

≤ 1 point: low probability
1.5 to 3 points: intermediate probability
≥ 3.5 points: high probability

Schwartz PJ, Moss AM, Vincent GM, et al. Circulation 1993; 88: 782-784.

LQT1	LQT2	LQT3
KCNQ1 mutation	KCNH2 mutation	SCN5A mutation
Trigger: exercise; swimming; stress	**Trigger**: noise / alarms; postpartum	**Trigger**: rest / sleep
Wide-based T wave	Notched or biphasic T wave	Long isoelectric segment then narrow-based T wave 
Management: first-line BB (significant protection); ± ICD	**Management**: BB (moderate protection); ± ICD	**Management**: Mexiletine; Flecainide; Ranolazine; Low protection by BB; ± ICD

COMPLICATIONS: syncope; TdP; sudden death

MANAGEMENT: avoid trigger; avoid drugs that ↗ QT; correct electrolyte; avoid strenuous exercise; BB (first-line); DDD or AAI pacemaker for pause-dependent TdP (especially associated with LQT3); sympathectomy

› **Risk factors for sudden death**: syncope; QTc > 500 ms; complex ventricular arrhythmia; Jervell and Lange-Nielsen

› **ICD**: **A)** Secondary prevention of sudden death; **B)** Syncope on BB therapy

SHORT QT SYNDROME (SQTS)

ECG: **QTc interval ≤ 340 ms with HR < 100 bpm;** high amplitude T wave; short or absent ST segment +

COMPLICATIONS: AF; syncope; VF; sudden death

DIFFERENTIAL DIAGNOSIS: hyperkalemia; hypercalcemia; hyperthermia; acidosis; Digoxin

MANAGEMENT: Quinidine; Sotalol; ICD for secondary prevention

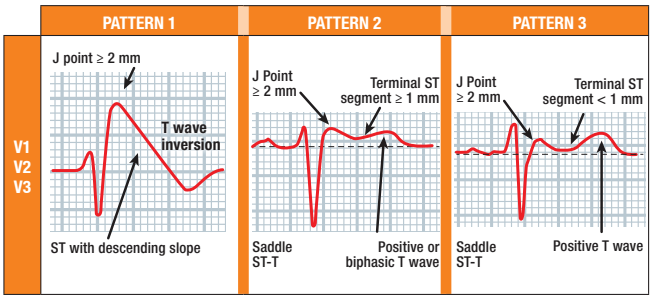
BRUGADA SYNDROME

TRANSMISSION: autosomal dominant; sodium channel gene mutation (SCN5A; 20% of patients) or unidentified mutation

DIAGNOSTIC CRITERIA

• Pattern 1 on ECG (≥ 2 leads: V1-V2-V3); spontaneous or with drug challenge (sodium channel blocking agent) or • Pattern 2 or 3 (≥ 2 leads: V1-V2-V3) with conversion to Pattern 1 with drug challenge	+	**≥ 1 CLINICAL CRITERIA** • Polymorphic VF or VT • Family history of sudden death < 45 years • Pattern 1 in the family • VT during programmed stimulation • Unexplained syncope • Nocturnal agonal respiration

Wilde AA, Antzelevitch C, Borggrefe M et al. Circulation 2002; 106; 2514-2519.



UNMASKED BRUGADA SYNDROME: sodium channel blocking agent (challenge with Procainamide 10 mg/kg IV x 10 min or Flecainide 400 mg PO); Drugs (www.brugadadrugs.org); fever; hypokalemia or hyperkalemia; leads V1-V2-V3 in 2nd or 3rd intercostal space; Cocaine; alcohol

COMPLICATIONS: Polymorphic VT (triggered by rest / sleep) / VF; sudden death (particularly in men in their forties); AF; SSS; conduction disorder

MANAGEMENT: Quinidine and/or Isoproterenol for electrical storm

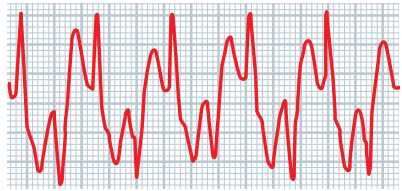
› **ICD**: **A)** Secondary prevention of sudden death; **B)** Spontaneous pattern 1 with syncope

CATECHOLAMINERGIC POLYMORPHIC VT

TRANSMISSION: autosomal dominant (ryanodine receptor gene mutation - RyR2) or autosomal recessive (calsequestrin gene mutation - CASQ2)

MYOCYTE CALCIUM OVERLOAD: triggered activity with delayed afterdepolarization

PRESENTATION: Polymorphic VT induced by exercise / stress; bidirectional VT



DIAGNOSIS: structurally normal heart; normal ECG

› **Exercise** → bidirectional VT and/or polymorphic PVCs and/or polymorphic VT

MANAGEMENT: BB (first-line treatment; Nadolol 1-2 mg/kg); CCB (Verapamil); Flecainide; Sympathectomy; avoid vigorous exercise

› **Titration of drug treatment**: guided by stress test and Holter

› **ICD**: **A)** Secondary prevention of sudden death; **B)** Syncope on BB therapy

GENETIC TESTING FOR FAMILIAL ARRHYTHMIAS

OBJECTIVE: **A)** Family screening; **B)** Establish / confirm a diagnosis

DISEASE	GENE	INDICATIONS FOR GENETIC TESTING
Long QT syndrome	Identification of a causal mutation: 75% (KCNQ1; KCNH2; SCN5A; KCNE1; KCNE2)	a) Cardiac arrest + long QT (family screening) b) Syncope + long QT (family screening / diagnosis / treatment) c) Asymptomatic long QT (family screening / diagnosis / treatment)
Brugada syndrome	Identification of a causal mutation: 20% (SCN5A)	a) Cardiac arrest + Brugada syndrome (family screening) b) Syncope + Brugada syndrome (family screening) c) Asymptomatic + Pattern 1 (family screening)
ARVD – Arrhythmogenic RV dysplasia	Identification of a causal mutation: 50% (PKP2; DSP; ± DSG2 - DSC2)	a) ARVD satisfying diagnostic criteria (family screening) b) Suspected ARVD (diagnostic criterion)
Catecho-laminergic polymorphic VT	Identification of a causal mutation: 50% (RYR2; ± CASQ2)	Suspected catecholaminergic polymorphic VT (family screening)
Hypertrophic cardiomyopathy	Identification of a causal mutation: 50% (MYH7; MYBPC3; ± TNNT2 - TNNI3 - TMP1)	a) HCM with clinical diagnosis (family screening) b) HCM with pre-excitation (PRKAG2; LAMP2; GLA)
Familial dilated cardiomyopathy	Identification of a causal mutation: 20 % (MYBPC3; MYH7; TNNT2; LMNA; SCN5A)	a) Probable familial DCM (family screening) b) Familial DCM + high-grade conduction disorder / atrial arrhythmia: LMNA and SCN5A
Sudden death	**Indication for targeted genetic testing**: negative autopsy in the presence of familial clinical signs of a particular phenotype (for family screening)	

6.7/ SYNCOPE

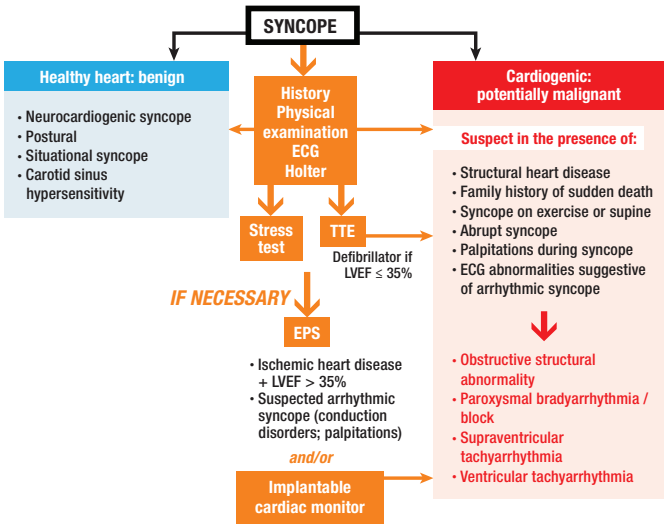
Brief loss of consciousness secondary to transient global cerebral hypoperfusion; resolves spontaneously; rapid recovery

DDX OF LOSS OF CONSCIOUSNESS: Syncope; Aborted cardiac arrest; Epilepsy; Conversion / Psychogenic; Ischemic (vertebrobasilar TIA); Migraine; Metabolic disorder (Hypoglycemia; Poisoning; Hypoxemia; Hyperventilation); Traumatic (cerebral commotion)

DDX OF SYNCOPE: **A)** Neurocardiogenic (vasovagal); **B)** OH (dysautonomia; drugs; dehydration; alcohol); **C)** Cardiogenic syncope; **D)** Carotid sinus hypersensitivity; **E)** Situational syncope (cough; defecation; laughing; micturition; postprandial; deglutition); **F)** Subclavian steal syndrome

DDX OF CARDIOGENIC SYNCOPE: Bradyarrhythmia / Block (AV block; SSS; pause following conversion of supraventricular tachyarrhythmia); Tachyarrhythmia (supraventricular; AF; WPW syndrome; VT; channelopathy; arrhythmogenic drugs; idiopathic VF); Obstructive valvular heart disease; Aortic dissection; Myxoma; Tamponade; HCM; Infarction / Ischemia; Congenital coronary artery anomalies; Massive pulmonary embolism; PHT; Pacemaker dysfunction

ASSESSMENT



Rare syncope and definitive diagnosis necessary

ASSESSMENT: History of the present illness; Physical examination; BP supine - standing; carotid sinus massage; ECG; Holter (weekly syncope) or Loop recorder (monthly syncope); TTE

ECG ABNORMALITIES SUGGESTIVE OF ARRHYTHMIC SYNCOPE: diurnal sinus bradycardia < 40 bpm or diurnal sinus pauses ≥ 3 s; bifascicular block; QRS > 120 ms; Mobitz II or 3rd degree AV block; pre-excitation; NSVT; long QT; short QT; Brugada pattern; epsilon wave / T wave inversion in V1-V2-V3; early repolarization; LVH (dilated cardiomyopathy or HCM); Q waves

ELECTROPHYSIOLOGICAL STUDY: placement of intracardiac catheters to evaluate: **A)** sinoatrial node function (rule out SSS); **B)** AV node and His-Purkinje system function (rule out AV block); **C)** susceptibility to supraventricular and ventricular tachyarrhythmias

- **Indications (syncope)**: **A)** Ischemic heart disease not meeting the criteria for ICD; **B)** Conduction disorder with suspected arrhythmic syncope (not meeting the criteria for permanent pacemaker); **C)** Abrupt syncope or preceded by palpitations with suspicion of an arrhythmic cause
- **Look for**: **A)** CSNRT > 525 ms; **B)** HV interval > 100 ms; **C)** Infra-His block during RA stimulation; **D)** Induced supraventricular tachycardia with hypotension; **E)** Monomorphic VT induced during programmed ventricular stimulation in the presence of ischemic heart disease
- **Programmed ventricular stimulation**: runs of 8 successive impulses (CL between 600 and 400 ms) then 1 or 2 or 3 premature complexes (minimal coupling interval of 200 ms)

ORTHOSTATIC HYPOTENSION (OH)

DEFINITION: **reduction of SBP > 20 mmHg or DBP >10 mmHg on standing up (< 3 min)** +

ETIOLOGIES: Drugs; Dehydration / Hemorrhage; Postprandial; Dysautonomia

- **Primary dysautonomia**: **A)** Pure dysautonomia (Bradbury-Eggleston syndrome); **B)** Multi-system atrophy (Shy-Drager syndrome); **C)** Parkinson's disease
- **Secondary dysautonomia**: DM; amyloidosis; alcohol; CRF; age; Guillain-Barré; mixed connective tissue disease; RA; Eaton-Lambert syndrome; SLE; carcinomatous autonomic neuropathy; multiple sclerosis; Wernicke's encephalopathy; hypothalamic or mesencephalic neoplastic or vascular disease; hereditary neuropathy; HIV; Chagas; Syphilis; botulism; Fabry; Tangier; vitamin B12 deficiency; porphyria; spinal cord lesion

MANAGEMENT: education; stand up slowly; lie down in the case of symptoms; sodium supplement (NaCl 1-2 g tid) and adequate hydration (2-3 L per day); avoid hypotensive drugs / alcohol; elastic compression stockings; Midodrine (alpha-agonist; 2.5-10 mg tid); Fludrocortisone (mineralocorticoid; 0.1-0.3 mg qd); raise the head of the bed by 10° to decrease nocturnal diuresis

NEUROCARDIOGENIC SYNCOPE (VASOVAGAL)

PRESENTATION: Trigger factor (prolonged standing or emotional stress) → prodromal symptoms preceding syncope (nausea; diaphoresis; blurred vision; palpitations; faintness) → brief syncope

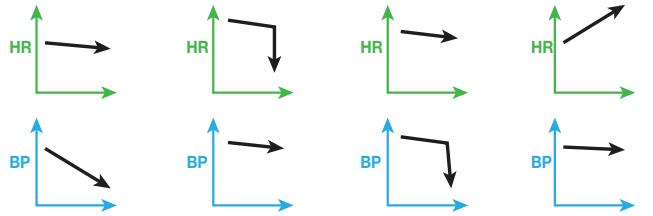
MECHANISM: vigorous ventricular contraction in the presence of low preload (secondary to venous pooling) → activation of cardiac mechanoreceptors → vagal hypertonia

- **Three responses to vagal hypertonia**: **A)** Cardioinhibitory (sinus pause and/or AV block); **B)** Vasodepressor; **C)** Mixed

TILT TABLE TEST: indication → to confirm the diagnosis of neurocardiogenic syncope when in doubt

- **Procedure**: 20 min in horizontal supine position → 30 to 45 min at 70° (± Isoproterenol or TNT)
- **Look for**: syncope + type of response following vagal hypertonia

MANAGEMENT: education; avoid trigger factors; sodium supplement (1-2 g NaCl tid) and adequate hydration; elastic compression stockings (30 mmHg); avoid hypotensive drugs / alcohol; isometric counterpressure maneuvers (handgrip for 2 min; leg crossing) or supine position in the case of prodromal symptoms; orthostatic training; raise the head of the bed by 10°; Midodrine / BB / Fludrocortisone / SSRI (Fluoxetine; Paroxetine; Venlafaxine); consider DDD pacemaker in the case of refractory syncope with dominant cardioinhibitory response (no benefit in ★ VPS-II; positive results in ★ ISSUE-3)

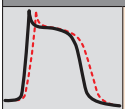


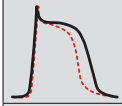
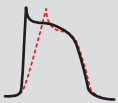
CAROTID SINUS HYPERSENSITIVITY

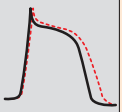
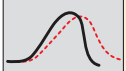
CAROTID SINUS MASSAGE: Apply pressure with 2 fingers (circular movements) for 10 s over the carotid pulse (at the level of the cricoid cartilage) with cardiac monitor

- **Contraindications**: carotid murmur; history of TIA - stroke
- **Cardioinhibitory response**: ventricular asystole > 3 s during massage → indication for DDD or VVI pacemaker in a patient with syncope

6.8/ ANTIARRHYTHMIC DRUGS (AAD)

VAUGHAN WILLIAMS CLASSIFICATION		
CLASS IA – SODIUM CHANNEL BLOCKING AGENTS		
	• Slow phase 0 (↘ conduction velocity) • Prolong the duration of the action potential (↗ QT) • Intermediate kinetics • Act on atria / ventricles / accessory pathway	
Quinidine	• **Indications**: Atrial and ventricular arrhythmias; Brugada; short QT syndrome; Idiopathic VF • **Dose**: 6 to 10 mg/kg IV (0.3-0.5 mg/kg/min); 300 to 600 mg PO qid	• ↗ QRS (avoid ↗ > 25 %) • ↗ QT (TdP) • Hypotension; Nausea; Vomiting; Diarrhea; Thrombocytopenia; Lupus; Fever; Arrhythmogenic
Procainamide	• **Indications**: Atrial and ventricular arrhythmias; CCV AF (combined with AV node blocking agent); Pre-excited AF • **Dose**: 15-20 mg/kg IV x 60 min (max 1 g) then 2 to 6 mg/min IV; stop if hypotension / ↗ QRS > 50% / arrhythmia controlled	• **Metabolite**: N-acetylprocainamide (class III effect; renal elimination) • **Adverse effects**: ANA+; drug Lupus; Arrhythmogenic; Infra-His block; ↗ QT (torsade de pointes); Negative inotropic agent with high-dose; Hypotension
Disopyramide	• **Indications**: Atrial and ventricular arrhythmias; HCM • **Dose**: 100-300 mg PO tid to qid	• Negative inotropic agent • Vagolytic effect (↗ heart rate) • Urinary retention; constipation; ↗ QT (TdP)

CLASS IB – SODIUM CHANNEL BLOCKING AGENTS		
	• Decrease the duration of the action potential • Rapid kinetics • Main effect: ventricular	
Lidocaine	• **Indications**: Ventricular arrhythmias; (enhanced effect in ischemic tissues) • **Dose**: 1 to 3 mg/kg IV (20-50 mg/min) then 1-4 mg/min (dilution: 2 g / 500 mL D5%)	• CNS toxicity (faintness; paresthesia; confusion)
Mexiletine	• **Indications**: Ventricular arrhythmias; long QT syndrome 3 • **Dose**: 150 to 300 mg PO bid to tid	• Sinus bradycardia; hypotension • CNS toxicity (dysarthria; faintness; paresthesia; confusion)
CLASS IC – SODIUM CHANNEL BLOCKING AGENTS		
	• Slow phase 0 (↘ conduction velocity) • Slow kinetics • **Use-dependent effect**: maximum antiarrhythmic effect at high HR (receptor open or inactivated) • ↗ **QRS duration** (avoid ↗ > 25 %) especially at high HR	
Flecainide	• **Indications**: AF; Flutter; PSVT; catecholaminergic polymorphic VT • **Dose**: 50 to 200 mg bid (combine with AV node blocking agent)	• Avoid in patients with CAD (★ CAST) / LV dysfunction • Risk of organization of AF into flutter with 1:1 AV conduction • Negative inotropic agent • ↗ pacemaker stimulation threshold
Propafenone	• **Indications**: AF; Flutter; PSVT • **Dose**: 150 to 300 mg PO bid to tid (in combination with AV node blocking agent)	• Avoid in CAD / LV dysfunction • Hepatic metabolism (7% of patients are slow metabolizers) • Negative inotropic agent • ↗ pacemaker stimulation threshold
CLASS II – BETA–BLOCKERS		
Beta-blockers	• Block beta-adrenergic receptors • **Indications**: supraventricular and ventricular arrhythmias • **Metoprolol**: 2.5 to 5 mg IV every 5 min x 3 • **Esmolol**: 0.5 kg /mg IV bolus then 50-200 µg/kg/min (dilution: 2500 mg/250 mL)	• **Adverse effects**: Negative inotropic agent; bronchospasm; hypotension; bradycardia; block; rebound effect on discontinuation; depression; exacerbation of severe PAD; masking of hypoglycemia symptoms; nightmares; erectile dysfunction

CLASS III – POTASSIUM CHANNEL BLOCKING AGENTS		
	• Increase the duration of the action potential; minimal effect on phase 0 • ↗ QT interval (risk of TdP)	
Amiodarone	• **Indications**: AF; Flutter; VT; VF; PSVT • **Dose**: 150 mg IV x 10 min then 1 mg/min IV x 6 h then 0.5-1 mg/min thereafter (dilution: 450 mg/250 mL D5%) • **PO**: 800 to 1600 mg PO daily x 7-14 days (10 g) then 100 to 600 mg daily • **Adverse effects**: ▸▸| Amiodarone	
Sotalol	• **Indications**: AF; PSVT; ventricular arrhythmias • **Dose**: 80 to 160 mg bid	• ↗ QT (TdP) • **Inverse use-dependent**: maximum antiarrhythmic effect at lower HR (resting receptors); ↗ QT at low HR • ★ **SWORD**: ↗ mortality post-myocardial infarction with LVEF ≤ 40% with d-Sotalol (without BB effect) • Renal excretion
Dronedarone	• **Indications**: Paroxysmal AF (★ ATHENA) • **Dose**: 400 mg bid	• **Contraindication**: NYHA III-IV heart failure (★ ANDROMEDA); permanent AF (★ PALLAS); liver disease
Dofetilide	• **Indications**: AF and Flutter • **Dose**: 0.125 to 0.5 mg PO bid	• ↗ QT (initiate in hospital; avoid if baseline QTc ≥ 440 ms) • Renal excretion • Safe in CAD or LV dysfunction (★ DIAMOND)
Ibutilide	• **Indications**: CCV of AF and Flutter (success: 70%) • **Dose**: 1 mg x 10 min (with $MgSO_4$; repeat x 1 PRN	• ↗ QT - TdP; Monitoring x 8 h post-dose • Contraindicated if QTc > 440 ms or hypokalemia
CLASS IV – CALCIUM CHANNEL BLOCKING AGENTS		
	• Decrease conduction velocity (phase 0) of SA and AV nodes	
Verapamil and Diltiazem	• **Indications**: PSVT; AF Flutter (rate control); fascicular VT • **Diltiazem**: 0.25 mg/kg IV x 2 min (2nd bolus after 15 min); 120-360 mg PO daily	• Negative inotropic agent (avoid in the presence of LV dysfunction) • Hypotension; Bradycardia; Leg edema; Drug interactions

OTHER AAD		
Digoxin	• ↗ Vagal tone • **Indications**: Rate control of HR in AF (at rest) • **Dose**: loading dose of 0.5 to 1 mg x 24 h (PO or IV) then 0.0625 to 0.25 mg PO daily	• **Toxicity**: calcium overload → delayed afterdepolarization / ↗ automaticity • ▶▶| Chapter 9 - Digoxin poisoning • Renal excretion
Adenosine	• Brief inhibition of AV conduction • **Indications**: PSVT; VT RVOT • **Dose**: Adenosine: 6 to 12 mg rapid IV	• **Adverse effects**: precipitates AF (1-15%); flushing; dyspnea; retrosternal chest pain • **Contraindications**: asthma; theophylline • **Transplant recipient or Dipyridamole**: use a dose of 3 mg
Atropine	• Vagolytic • **Indications**: symptomatic bradycardia • **Dose**: 0.5 to 1 mg IV (up to 2 mg)	

6.9/ AMIODARONE

ADVERSE EFFECTS

Pulmonary toxicity (2%)	**Toxicity correlated with cumulative dose** • Interstitial lung disease; Organizing pneumonia / BOOP; ARDS • Cough; Dyspnea; Fever • **PFT:** ↘ DLCO / restrictive pattern • **HDCT**: Interstitial / alveolar opacities; Ground glass; Fibrosis • **Diagnosis of exclusion** (rule out infection and heart failure)	• Permanently discontinue Amiodarone • Corticosteroids if severe • Slow improvement (long half-life of amiodarone)
GI toxicity (30%)	• Nausea; Anorexia; Constipation • ↗ AST ALT 2 x ULN • Symptomatic hepatitis (3%) - Cirrhosis	• Rule out DDx • Consider discontinuation
Hypothyroidism (20%)	• ↗ TSH and ↘ Free T4 • **Risk factors**: Female; underlying autoimmune thyroid disease (positive antibody); failure to escape from the Wolff-Chaikoff effect	• L-Thyroxine • Continue Amiodarone
Hyperthyroidism (10 %)	• ↘ TSH and ↗ Free T4 • ↗ INR if treated with warfarin • Thyroid scintigraphy falsified by the iodine load of Amiodarone **Etiologies** **a)** ↗ **T4 synthesis**: Underlying thyroid disease (Graves; multinodular goiter) exacerbated by iodine load **b)** ↗ **T4 release**: Destructive thyroiditis (fever; painful gland); hypothyroid phase several weeks or months later **c) Mixed** (majority)	**According to etiology** **a)** PTU or Methimazole; Discontinue Amiodarone once hyperthyroid symptoms have been controlled (as Amiodarone blocks conversion of T4→T3) **b)** Prednisone; ± Discontinue Amiodarone **c)** Corticosteroids + antithyroid drugs (then stop antithyroid drugs if good response to corticosteroids in ≤ 1 week of treatment)

Skin	• Photosensitivity (up to 75%) • Blue discolouration (< 10%)	• Avoid exposure to sunlight
CNS	Ataxia; Paresthesia; Polyneuritis; Tremor	Dose-dependent effect
Ophtalmic	Halo; Optic neuropathy; Photophobia; Blurred vision; Corneal microdeposits	Discontinue Amiodarone in the presence of optic neuropathy
Cardiac	Bradycardia; Block; Arrhythmogenic (< 1%); ↗ **defibrillation threshold**; ↘ tachycardia CL	

MAJOR DRUG INTERACTIONS: Digoxin; Procainamide; Disopyramide; Diltiazem; Flecainide; Phenytoin; Cyclosporine; Simvastatin; Atorvastatin

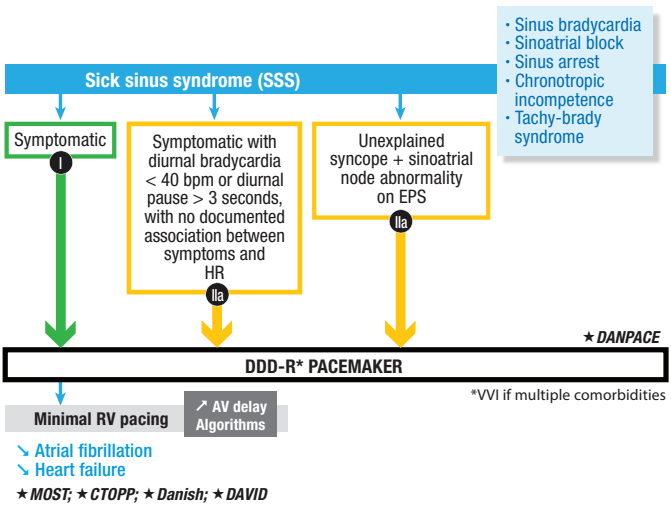
› **Warfarin**: **it is recommended to decrease the dose of warfarin by 30-50% on initiation of Amiodarone**

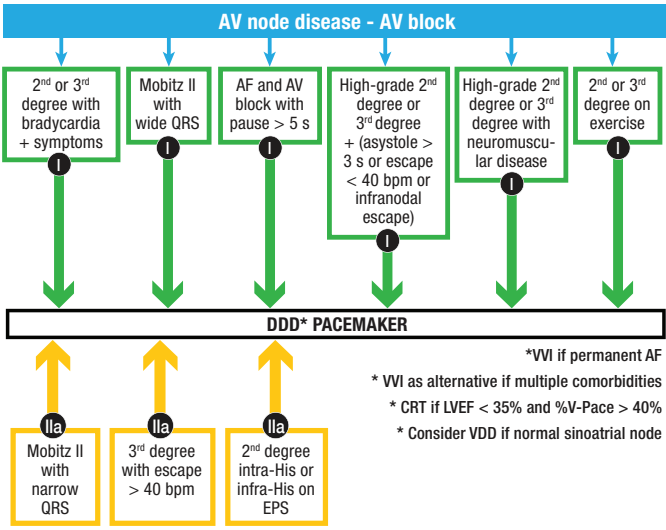
WORK-UP BEFORE STARTING AMIODARONE: TSH - Free T4 - T3; LFTs; CXR; Ophthalmological examination if underlying abnormalities; renal function; ECG

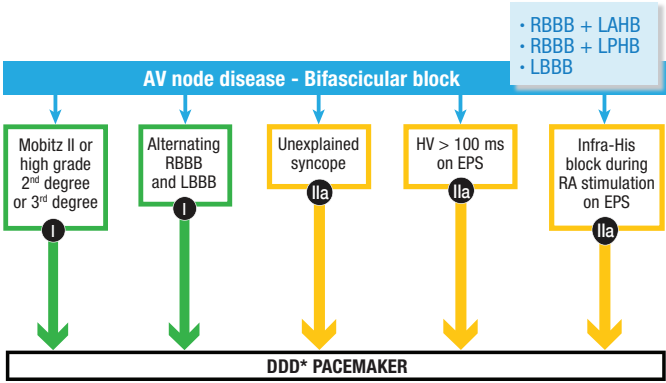
FOLLOW-UP ANALYSES: TSH - Free T4 every 6 months; AST / ALT every 6 months; annual CXR

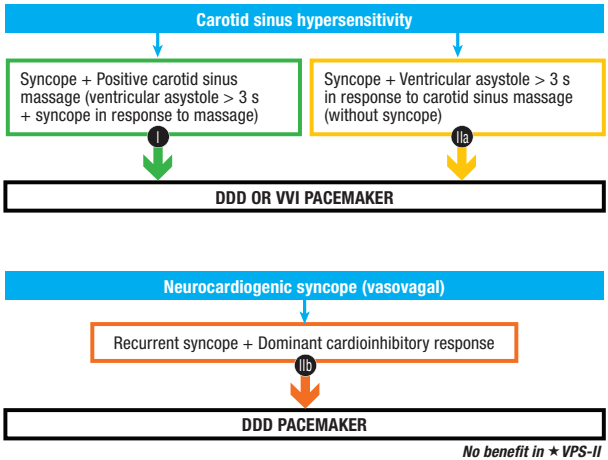
6.10/ PERMANENT PACEMAKER (PPM)

INDICATIONS




AV node disease - AV block
2nd or 3rd degree with bradycardia + symptoms
I
Mobitz II with wide QRS
I
AF and AV block with pause > 5 s
I
High-grade 2nd degree or 3rd degree + (asystole > 3 s or escape < 40 bpm or infranodal escape)
I
High-grade 2nd degree or 3rd degree with neuromuscular disease
I
2nd or 3rd degree on exercise
I
DDD* PACEMAKER
IIa
Mobitz II with narrow QRS
IIa
3rd degree with escape > 40 bpm
IIa
2nd degree intra-His or infra-His on EPS
*VVI if permanent AF
* VVI as alternative if multiple comorbidities
* CRT if LVEF < 35% and %V-Pace > 40%
* Consider VDD if normal sinoatrial node


• RBBB + LAHB
• RBBB + LPHB
• LBBB
AV node disease - Bifascicular block
Mobitz II or high grade 2nd degree or 3rd degree
I
Alternating RBBB and LBBB
I
Unexplained syncope
IIa
HV > 100 ms on EPS
IIa
Infra-His block during RA stimulation on EPS
IIa
DDD* PACEMAKER
*VVI if permanent AF
* VVI as alternative if multiple comorbidities
* CRT if LVEF < 35% and %V-Pace > 40%



TYPES OF PERMANENT PACEMAKERS

NBG CODE				
-1- Chamber paced	**-2- Chamber sensed**	**-3- Response to sensing**	**-4- Rate modulation**	**-5- Multisite pacing**
• O = None • A = Atrium • V = Ventricle • D = Dual (A + V)	• O = None • A = Atrium • V = Ventricle • D = Dual (A + V)	• O = None • T = Triggered • I = Inhibited • D = Dual (T + I)	• O = None • R = Rate modulation	• A = Atrium • V = Ventricle • D = Dual (A + V)

AAI: atrial pacing at the lower rate limit in the absence of sensing of an atrial event; indicated in sick sinus syndrome with preserved AV conduction

VVI: ventricular pacing at the lower rate limit in the absence of sensing of a ventricular event; absence of atrioventricular synchrony; indicated in AV block with permanent AF

DDD: atrial and ventricular pacing; atrial and ventricular sensing; indicated in AV block

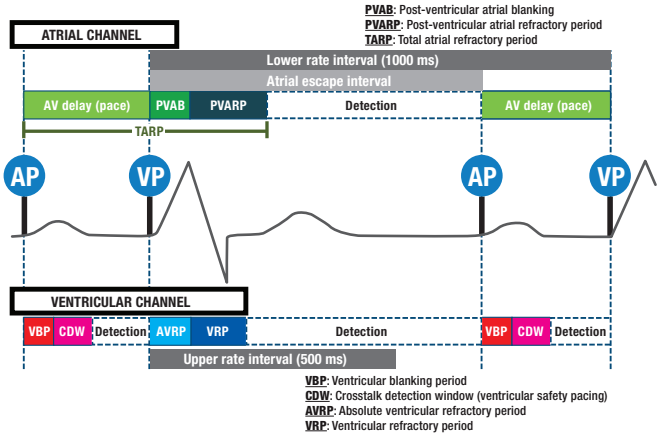
- **4 possibilities**: **A)** A-Sense / V-Sense; **B)** A-Sense / V-Pace (at the end of the AV interval in the absence of sensing of a ventricular event); **C)** A-Pace / V-sense (A-Pace at the end of the atrial escape interval in the absence of sensing of an atrial event); **D)** A-Pace / V-Pace
- **AV delay**: set a long AV delay (not exceeding 250-300 ms) to promote intrinsic AV conduction and minimize ventricular pacing
  - **A-Pace / V-Pace delay > A-Sense / V-Pace delay** (A-Sense: part of the atrium is already depolarized)

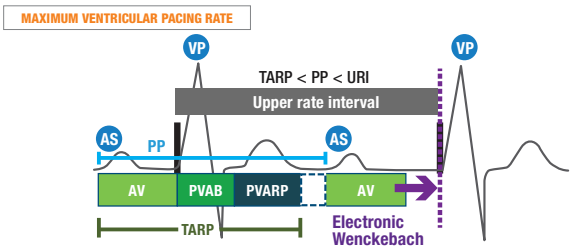
VOO: asynchronous ventricular pacing; mode used in pacemaker-dependent patients submitted to a source of electromagnetic interference (e.g.: electrocautery)

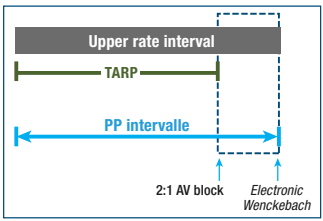
VDD: ventricular pacing with preserved atrioventricular synchrony on sensing of intrinsic P waves; requires a single lead (proximal atrial sensing by a ring; bipolar distal ventricular lead); consider in AV block in the absence of sick sinus syndrome

DDI: absence of "tracking" of sensed atrial events; V-Pace when the "lower rate interval" is reached (and A-Pace when the atrial escape interval is reached in the absence of a sensed event); indicated for atrial tachyarrhythmia with ineffective "mode-switch"

DDD PACEMAKER INTERVALS







RULE : Upper rate interval ≥ TARP

- **If PP interval < URI**
  → electronic Wenckebach
- **If PP interval < TARP** → 2:1 AV block
  - Frequency of 2:1 AV block
    = 60,000 ms / TARP (ms)

SPECIAL FUNCTIONS / ALGORITHMS

RATE ADAPTIVE: DDD-R or AAI-R or VVI-R; increased pacing rate when the patient is active (via activity sensor); activate in the case of symptomatic chronotropic incompetence / sick sinus syndrome

HYSTERESIS: **lower rate interval following V-Sense longer than lower rate interval following V-Pace (e.g.: 50 bpm vs 70 bpm);** promotes intrinsic rhythm

AAI ⟷ DDD MODE (MVP MODE): AAI mode switches to DDD mode when ≥ 2 of the previous 4 A-A intervals do not contain V-Sense

DYNAMIC AV DELAY: AV delay decreases at higher HR **(= ↘ TARP);** useful in patients with AV block and risk of 2:1 block on exercise

MODE SWITCH: DDD mode switches to DDI mode following atrial tachyarrhythmia to prevent tracking of this tachyarrhythmia

VENTRICULAR SAFETY PACING: **following A-Pace →** early ventricular pacing (AV delay: 100 ms) in the presence of a ventricular event detected inside the cross-talk detection window (preventing asystole in the presence of cross-talk or preventing R on T in the presence of a PVC)

POST-PVC EXTENSION OF PVARP: extension to 400 ms; prevents detection of a post-PVC retrograde P wave and therefore **the development of PMT**

RATE SMOOTHING: prevents an abrupt change of HR (during paroxysmal sinus arrest or following a mode switch)

RATE DROP RESPONSE: pacing at a higher rate (100-120 bpm) following an abrupt drop in HR (due to neurocardiogenic syncope)

NOISE RESPONSE: VOO or DOO mode activated following noise (nonphysiological signals)

PACEMAKER MONITORING

Battery	• ↘ Voltage and ↗ Impedance with time • **ERI**: Elective replacement indicator (< 3 months)
Lead	• **Impedance**: significant change > 200 ohms • **Low impedance (< 250 Ohms)**: insulation defect • **Increased impedance (> 1000 Ohms)**: short circuit (lead fracture; loose set screw) • Chest x-ray PRN
Events	• % A-Pace; % V-Pace; Frequency histogram • Saved episodes; AT/AF; Mode switch; Ventricular high rate; PMT
Sensitivity	• **Atrial**: from 0.3 to 0.6 mV • **Ventricular**: from 2 to 3.5 mV
Pacing	• **Safety margin**: programmed amplitude → twice the pacing threshold (or automatic capture) • **Pulse width**: 0.4 to 0.5 ms

MINIMUM FOLLOW–UP FREQUENCY FOR PPM, CRT, OR ICD	
Post-implantation follow-up	• < 72 h post-implant (in person) • 2 to 12 weeks post-implant (in person)
PPM or CRT follow-up	• 3 to 12 months (in person or by remote monitoring) • At least once a year in person
ICD follow-up	• 3 to 6 months (in person or by remote monitoring) • At least once a year in person
Signs of battery depletion	• Every 1 to 3 months (in person or by remote monitoring)

PACEMAKER DYSFUNCTION

Capture failure	• **Early post-implant:** lead migration; myocardial perforation; maturation (inflammatory reaction) • **Late lead maturation:** exit block • **Modified threshold:** myocardial infarction; cardiomyopathy; acidosis; electrolyte disorders; drugs (class IC AAD; Sotalol) • **Ineffective autocapture algorithm** • **Inadequate programming:** insufficient pacing amplitude safety margin • **Lead:** insulation defect; lead fracture; loose set screw • **Battery depletion** • **Failure to capture:** pacing during the refractory period; ± associated undersensing
Output failure	• **Oversensing** (inhibition) • **Lead:** insulation defect; short circuit (lead fracture; loose set screw) • **Hysteresis** • **Battery depletion** • **Post-PVC extension of PVARP** • **Generator dysfunction** (rare)
Undersensing	• **Inadequate intrinsic signal:** PVC or APC • **Signal modification:** myocardial infarction; cardiomyopathy; conduction disorder; metabolic disorder • **Programming:** high sensitivity • **Lead:** migration; maturation; insulation defect; lead fracture; loose set screw • **Magnet** • **Noise response** • **Safety pacing function** • **Battery depletion** • **Pseudofusion** • **Functional undersensing** (refractory period)
Oversensing	• **Cross-talk:** pacing of one chamber induces sensing of an event in the other chamber; minimized by blanking • **Far-field:** QRS detected as atrial event • **Oversensing of T wave** • **Electromagnetic interference:** electrocautery; MRI • **Myopotentials (unipolar electrode)** • **Lead:** insulation defect (internal contact of the two conductors); short circuit (lead fracture; loose set screw)

Pacing at a rate different from programmed rate	**High heart rate** • **Rate-adaptive:** R • **Undersensing** • **Tracking** of intrinsic atrial rhythm (or atrial oversensing) • **Rate smoothing** • **Rate drop** • **Pacemaker-mediated tachycardia** • **Runaway pacemaker** (battery depletion)	**Low heart rate** • **Oversensing** • **Hysteresis** • **AAI ⟷ DDD** • **Sleep mode** • **Battery depletion**

PACEMAKER-MEDIATED TACHYCARDIA (PMT)

- **Risk factors**: **A)** PVC with retrograde conduction; **B)** Atrial capture failure; **C)** Very long programmed AV delay; **D)** Atrial oversensing or undersensing
- **Mechanism**: Retrograde V-A conduction (often post-PVC) → A-Sense (outside of the PVARP) → V-Pace → retrograde V-A conduction → A-Sense (and so on)
- **Diagnosis**: **A)** A-Sense / V-Pace at the maximum pacing rate; **B)** A-Sense following V-Pace with V-A interval < 400 ms; **C)** Discordance between pacing rate and activity sensor; **D)** Modulation of P-V period
- **Prevention / Termination**: **A)** PVARP > retrograde V-A conduction time (while avoiding excessively prolonged TARP, which would lead to low frequency 2:1 block); **B)** Extension of post-PVC PVARP; **C)** 1 cycle without V-Pace following A-Sense during PMT

PACEMAKER SYNDROME: **secondary to loss of AV synchrony** (± atrial contraction on closed AV valve) with VVI pacemaker; tiredness / retrosternal chest pain / dyspnea / cough / confusion / faintness / syncope

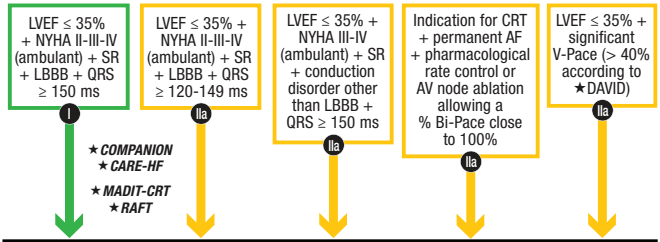
DIAPHRAGMATIC STIMULATION: lead close to phrenic nerve; incorrectly positioned lead (cardiac vein; myocardium perforation; migration); high stimulation amplitude

6.11/ CARDIAC RESYNCHRONIZATION THERAPY (CRT)

HEART FAILURE: altered electromechanical coupling → inter- and intraventricular delays → ventricular asynchrony → ↗ systolic dysfunction → altered myocardial metabolism / functional MR / ventricular remodeling / LV dilatation

SCIENTIFIC EVIDENCE	
• ★ **COMPANION**: LVEF ≤ 35% + NYHA III or IV (ambulant) + SR + QRS ≥ 120 ms + Hospitalization for heart failure during the previous year • ★ **CARE-HF**: LVEF ≤ 35% + NYHA III or IV (ambulant) + SR + QRS ≥ 150 ms (120-149 ms with TTE criteria of asynchrony)	• ★ **MADIT-CRT**: LVEF ≤ 30% + NYHA I (15%) or NYHA II (85%) + SR + QRS ≥ 130 ms • ★ **RAFT**: LVEF ≤ 30% + NYHA II (80%) or NYHA III (20%) + QRS ≥ 130 ms
• ↘ All-cause mortality • ↘ Hospitalization • Improvement of quality of life • Reverse remodeling	• ↘ All-cause mortality (★ RAFT) • ↘ Hospitalization • Improvement of quality of life • Reverse remodeling
MAINLY BENEFICIAL IN LBBB WITH QRS ≥ 150 MSEC	

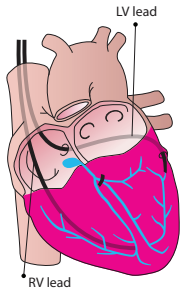
INDICATIONS



*Life expectancy with satisfactory functional capacity > 1 year

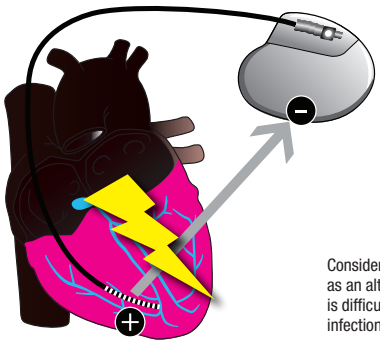
PROGRAMMING

RA pacing	• **Minimal** to avoid interatrial asynchrony • Minimum rate: 50 bpm • Do not activate "R"
AV delay	• **100-120 ms (minimize intrinsic AV conduction; ensure adequate duration of atrial kick)** • Consider echocardiography-guided optimization in the presence of a pseudonormal (grade II) or restrictive (grade III) mitral diastolic pattern
LV lead position	• **Basal posterolateral wall** (site of maximum electromechanical delay) • Avoid scars whenever possible (LGE on MRI); target adequate threshold; avoid phrenic nerve stimulation (electronic reprogramming of vectorial stimulation configuration PRN)
V-V delay	• **Simultaneous or pre-excitation of LV stimulation (30 ms)** • Echocardiographic optimization PRN in non-responders (using aortic VTI and/or deformation imaging and/or RV - LV pre-ejection intervals)
Maximize Bi-Pace	• **Target Bi-Pace > 98%** • AF → AV node blocking agent or RF ablation of AV node • Frequent PVCs → AAD or RF ablation
ECG	• **V1: dominant R wave** • **I: negative** • V4-V5: positive in the case of basal LV stimulation (negative if apical) • Frontal axis: -90° to 180°



V1	I	FRONTAL AXIS
RV apical stimulation		0 to -90°
Resynchronization therapy		-90 to 180°

6.12/ IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR (ICD)



Consider **subcutaneous defibrillator** as an alternative when venous access is difficult; after removal of an ICD for infection; in young patients

SCIENTIFIC EVIDENCE

SECONDARY PREVENTION: ★ AVID; ★ CIDS; ★ CASH

› Reduction of the absolute mortality (vs Amiodarone): 10.5% at 36 months **(NNT 10 patients)** +

PRIMARY PREVENTION: reduction of absolute mortality of 5-8% at 36 months **(NNT 14-18 patients)** +

› ★ **MADIT-I**: Ischemic heart disease; LVEF ≤ 35%; NYHA I-II-III, NSVT; inducible VT → ↘ all-cause mortality

› ★ **MUSTT**: Ischemic heart disease; LVEF ≤ 40%; NYHA I-II-III, NSVT; inducible VT → ↘ all-cause mortality

› ★ **MADIT-II**: Ischemic heart disease; LVEF ≤ 30%; NYHA I-II-III → ↘ all-cause mortality

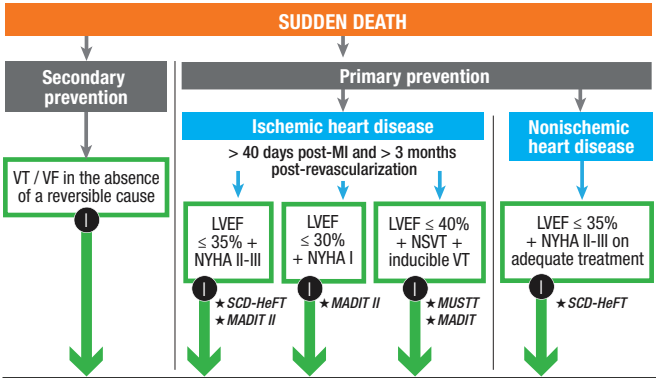
› ★ **DEFINITE**: Nonischemic heart disease; LVEF ≤ 35%; NYHA I-II-III, NSVT (or ≥ 10 PVCs / h) → trend to ↘ all-cause mortality

› ★ **SCD-HeFT**: LVEF ≤ 35%; (ischemic or nonischemic heart disease); NYHA II-III → ↘ all-cause mortality

› ★ **DINAMIT**: LVEF ≤ 35%; **< 40 days post-MI**; decreased HR variability or high resting HR → no benefit

› ★ **IRIS**: LVEF < 40%; **< 30 days post-MI**; HR > 90 bpm or NSVT > 150 bpm → no benefit

INDICATIONS



OTHER CONDITIONS HCM + risk factors • ARVD + risk factors • Long QT syndrome with syncope or VT on beta-blockers • Brugada with syncope or VT • Catecholaminergic polymorphic VT with syncope or VT on beta-blockers • Sarcoidosis or giant cell myocarditis or Chagas • LV noncompaction • Congenital heart disease

PROGRAMMING – PRIMARY PREVENTION

ZONE #1: SLOW VT	ZONE #2: FAST VT	ZONE #3: VF
150 to 188-200 bpm (400 to 320-300 ms)	**188-200 to 250 bpm (320-300 to 240 ms)**	**> 250 bpm (< 240 ms)**
• Monitor (at user discretion)	**a)** ≥ 1 ATP (**burst**) attempt (8 impulses at 84-88% of tachycardia CL) **b)** Maximum energy shock	• Maximum energy shock (> 30 J) x 6 (ATP during charge)

- **Detection duration**: ≥ 30 intervals (≥ 6-12 sec)
- **VT/VF discriminators vs supraventricular arrhythmia (up to 230 bpm)**: **A)** V > A / A-V dissociation; **B)** EGM morphology (vs baseline template); **C)** Abrupt onset; **D)** Stable R-R interval

ANTI-TACHYCARDIA PACING (ATP): interrupt the reentry circuit of monomorphic VT; effective in 70-80% of patients with fast VT (★ PainFREE Rx II)

- **Burst**: 8 impulses with constant inter-stimulus interval (at 88% of tachycardia CL)
- **Ramp**: 8 impulses with decreasing inter-stimulus interval

★ **MADIT-RIT:** primary prevention; administration of therapy only during fast VT (≥ 200 bpm) or following a period of prolonged detection (> 60 s for 170-199 bpm or > 12 s for 200-249 bpm or > 2.5 s for 250 bpm) associated with **↘ all-cause mortality / ↘ inappropriate ICD therapies**

PROGRAMMING – SECONDARY PREVENTION

DETECTION DURATION: ≥ 30 intervals (≥ 6-12 sec)

SLOWEST ZONE: at least 10 bpm below the documented tachycardia rate (but not faster than 200 bpm except for some young patients) → ATP (≥ 1 burst attempt - 8 impulses at 88% of VT CL; 10 ms scan decrement) → Shock

VF: > 250 bpm → ATP while charging → Shock (full output)

MANAGEMENT FOLLOWING AN ICD SHOCK

MEDICAL ASSESSMENT: < 24 h (urgent if multiple shocks or symptoms)

APPROPRIATE SHOCK: VF; monomorphic VT; polymorphic VT

INAPPROPRIATE SHOCK: apply a magnet over the device; reprogram treatment / parameters

- **Supraventricular tachycardia** → modify therapy zones; optimize discriminator programming; AV node blocking agent / AAD; RF ablation
- **T wave oversensing (and small R wave)** → decrease ventricular sensitivity (however, must be sufficient to detect VF; defibrillator test PRN); prolong the ventricular refractory period; modify sensing decay; lead repositioning
- **Atrial far-field** (distal coil of an integrated bipolar electrode close to the tricuspid valve)
- **R-wave double counting** → modify sensing decay; prolong the refractory period; decrease ventricular sensitivity (however, must be sufficient to detect VF; defibrillator test PRN)
- **Electromagnetic interference**
- **Myopotentials**
- **Lead** (insulation defect; lead fracture; loose set screw)

ELECTRICAL STORM: ▶▶| Ventricular fibrillation

PREVENTION OF NEW SHOCKS: BB; Amiodarone; Sotalol; therapy reprogramming; RF ablation

SHOCK APPROPRIATE BUT INEFFECTIVE

- **Increased defibrillation threshold**: ischemia; progressive heart failure; AAD (sodium channel blocking agents; Amiodarone); electrolyte / metabolic disorders; pleural / pericardial effusion
- **Secondary to defibrillator**: insufficient programmed shock amplitude; battery depletion; lead (insulation defect; lead fracture; loose set screw; migration)

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Adult congenital heart disease & Heart disease in pregnant women

07

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7.1/ SEGMENTAL ASSESSMENT & FETAL CIRCULATION

SEGMENTAL ASSESSMENT

POSITION OF THE APEX: A) Levocardia (apex points to the left); **B) Dextrocardia** (apex points to the right); **C) Mesocardia** (apex in the middle)

ATRIAL SITUS (solitus; inversus; ambiguus): according to the position of the atrial appendages, IVC (which drains into the RA) and visceral situs

- **Right atrial appendage morphology:** large base, triangular shape, contains numerous pectinate muscles
- **Left atrial appendage morphology:** narrow base, finger-shaped

AV CONNECTION: A) Concordance: morphological LA connected to morphological LV (and RA connected to RV); **B)** Discordance

- **Right ventricle morphology:** moderator band, extensive trabeculations, infundibulum, tricuspid valve
  - **Tricuspid valve**: 3 leaflets - septal attachments - closer to apex than M valve - absence of distinct papillary muscles
- **Left ventricle morphology**: fine trabeculations; mitral valve
  - **Mitral valve:** 2 leaflets - mitro-aortic continuity - 2 papillary muscles - less apical than the T valve

VENTRICULO-ARTERIAL CONNECTION: A) Concordance: Morphological LV connected to the aorta; morphological RV connected to the PA; **B) Discordance**; **C) Double-outlet** (> 50% of the aorta and PA arise from the same ventricle)

- **Aorta:** "Candy cane"; 3 vessels (innominate artery, left carotid artery, left subclavian artery); always associated with its aortic valve
- **Pulmonary trunk**: rapidly divides into RPA and LPA; always associated with its pulmonary valve

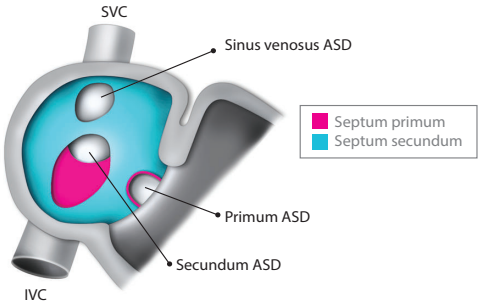
FETAL CIRCULATION

1. **DUCTUS VENOSUS:** allows oxygenated umbilical blood to short-circuit the liver and reach the IVC
2. **FORAMEN OVALE**: allows blood derived from the IVC (part of which is derived from the placenta and is oxygenated) to go directly to the left heart (preferentially perfusing the coronary arteries and CNS)
3. **PATENT DUCTUS ARTERIOSUS**: allows blood (predominantly derived from the SVC) to go from the right heart to the descending aorta (to the placenta)

7.2/ ATRIAL SEPTAL DEFECT (ASD)

4 TYPES

1. **SECUNDUM ASD (80 %):** in the fossa ovale
2. **PRIMUM ASD (15 %):** close to AV valves; associated with AV canal defect
3. **SINUS VENOSUS ASD (5 %):** close to the origin of the SVC (exceptionally IVC); associated with anomalous pulmonary venous connection (R > L)
4. **CORONARY SINUS ASD (1 %):** communication between the coronary sinus and the LA; associated with persistent left SVC



SIGNIFICANT ASD: generally **> 10 mm with Qp/Qs > 1.5: 1**

ACCENTUATION OF L → R SHUNT: in the presence of ↘ LV compliance or ↗ LA pressure (age; LVH; HTN; cardiomyopathy; myocardial infarction; MR...)

LUTEMBACHER SYNDROME: ASD + rheumatic MS

HOLT-ORAM SYNDROME: autosomal dominant; TBX5 mutation; abnormalities of hands; secundum ASD

FEATURES: left parasternal heave; palpable dilated PA (2nd left intercostal space); **fixed split S2**; pulmonary ejection murmur (↗ flow); tricuspid diastolic rumble in the presence of significant shunt; TR murmur in the presence of right heart failure

ECG

- **Secundum ASD: Incomplete RBBB; right axis deviation; RAH; Notch on R wave in inferior leads**
- **Primum ASD: RBBB; left axis deviation; RAH**
- **Sinus venosus ASD: non-sinus rhythm (negative P wave in inferior leads)**

CXR: RA-RV dilatation; ↗ vascularization; prominent central PA

TEE: evaluate pulmonary venous return; ASD dimensions; possibility of percutaneous closure; agitated-saline PRN (R→L shunt = contrast in left chambers; L→R shunt = negative contrast in right chambers)

COMPLICATIONS

a) Right heart failure (± TR) (volume overload)

b) Atrial arrhythmias: typical flutter; IART; AF; SSS after repair

c) Paradoxical embolism

d) PHT (5-9%) (rarely severe)

INDICATIONS FOR ASD CLOSURE

a) Dilatation of right chambers (I;B)

b) Paradoxical embolism (IIa;C)

c) Platypnea-orthodeoxia (IIa;C)

d) PHT with marked L→R shunt > 1.5: 1 or with significant reactivity to vasodilator (IIb;C)

e) Do not close if **irreversible PHT** with sPAP > 2/3 SBP or PVR > 2/3 SVR (III;C)

PERCUTANEOUS CLOSURE: possible if **secundum ASD < 38 mm with adequate margins (distance > 5 mm** from AV valves, coronary sinus, origin of SVC / IVC and right pulmonary veins) **and with normal pulmonary venous return**

› ASA for 6 months after ASD closure; **complications** (1 %) → prosthesis embolization; erosion (atrial wall or Ao); thromboembolism; arrhythmia - AF; endocarditis; tamponade

PACEMAKER LEADS: risk of paradoxical embolism if ASD not repaired

PREGNANCY: generally well tolerated; risk of paradoxical embolism

7.3/ PATENT FORAMEN OVALE (PFO)

Absence of fusion of septum secundum and septum primum at birth

25% of adults

ASSOCIATION WITH CRYPTOGENIC STROKE: possibility of paradoxical embolism

› **Risk factors**: PFO > 5 mm or spontaneous R→L shunt or atrial septal aneurysm or prominent Eustachian valve

DIAGNOSIS: TEE with bubbles: **bubbles in ≤ 3 beats in left chambers**; facilitated by Valsalva maneuver

TREATMENT OF CRYPTOGENIC STROKE: highly controversial

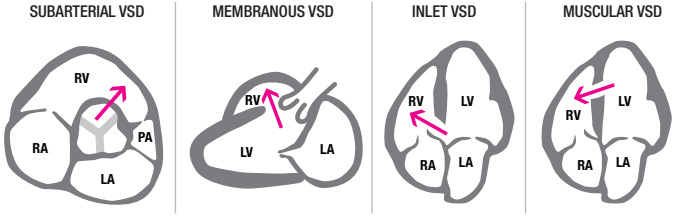
1) First-line ASA; Warfarin if documented DVT (± closure of PFO)
2) If recurrence: anticoagulation vs percutaneous closure
   - No convincing evidence for the superiority of percutaneous closure versus medical treatment (equivocal results in ★ CLOSURE-I, ★ RESPECT and ★ PC)

ANEURYSM OF INTERATRIAL SEPTUM: **redundant and mobile portion of the atrial septum with excursion ≥ 15 mm** from the midline

7.4/ VENTRICULAR SEPTAL DEFECT (VSD)

4 TYPES

1) **SUBARTERIAL** (5%): below the Ao and P valves; associated with AR (due to leaflet prolapse); numerous synonyms (outlet; conal; subpulmonary; subaortic; infundibular; supracristal)
2) **MEMBRANOUS** (80%): membranous septum; adjacent to Ao and T valves
3) **AV CANAL (INLET)**: below the AV valve (see AV canal defect)
4) **MUSCULAR** (15-20%): completely surrounded by muscle



CLINICAL FEATURES AND SEVERITY: **Restrictive VSD** (RV pressure << LV pressure) or **nonrestrictive VSD** (RV pressure similar to LV pressure)

- **Small VSD**: normal LV dimensions; absence of PHT; **holosystolic murmur in left parasternal region (3rd-4th left intercostal spaces) with spoke-wheel radiation ± palpable thrill**; spontaneous closure is possible
- **Moderate VSD**: **LA and LV dilatation (volume overload)**; PHT (reversible); ± mitral diastolic rumble; S3; lateralized apex
- **Large VSD**: Progressive PHT then Eisenmenger; **absence of VSD murmur; signs of PHT (left parasternal heave; ↗ and palpable P2; right S4; ejection click; Graham-Steel murmur and TR)**

COMPLICATIONS

a) Left heart failure (volume overload)

b) PHT (± right heart failure due to pressure overload)

c) Progressive AR due to leaflet prolapse (subarterial VSD or membranous VSD)

d) Double chamber RV (muscle band develops as a result of the VSD jet, inducing subpulmonary stenosis)

e) Progressive subaortic stenosis

f) Arrhythmia: AF; PVCs; NSVT; postoperative AV block

g) Endocarditis

INDICATIONS FOR VSD CLOSURE

a) Significant VSD: symptoms or progressive left ventricular dysfunction (volume overload) or right ventricular dysfunction (pressure overload) or Qp:Qs > 2:1 or sPAP > 50 mmHg (I;B)

b) Subarterial or membranous VSD with **AR ≥ moderate** (I;B)

c) In the presence of **severe PHT** (sPAP > 2/3 SBP or PVR > 2/3 SVR), closure should only be considered in the case of L→R shunt > 1.5:1 or significant reactivity to vasodilators (I;B)

d) **Double chamber RV**: significant obstruction (mean gradient > 40 mmHg or > 30 mmHg with symptoms)

e) Endocarditis (IIa;B)

PERCUTANEOUS CLOSURE IS POSSIBLE: **A)** Trabecular muscle VSD situated away from T or Ao valves; **B)** Membranous VSD situated away from the Ao valve

PREGNANCY: a small VSD is well tolerated in the absence of associated PHT or LV dysfunction

7.5/ ATRIOVENTRICULAR CANAL DEFECT

Developmental anomaly of endocardial cushions

a) **Partial atrioventricular canal defect:** intact interventricular septum; primum ASD; mitral cleft; AV valves inserted at same level (common annulus)

b) **Complete atrioventricular canal defect:** defect of the septum on either side of the cardiac crux: non-restrictive VSD (inlet VSD) and primum ASD; common atrioventricular orifice (one common AV valve with 5 leaflets)

- **Associated Down syndrome** (Trisomy 21): small stature, typical facies, mental retardation, brachydactyly, atlanto-axial instability, hypothyroidism, propensity to PHT, OSAHS

ECG: Complete or incomplete RBBB; **left axis deviation; spontaneous or postoperative AV block;** atrial arrhythmia +

VENTRICULOGRAPHY: **Elongated LVOT (goose neck deformity)**

COMPLICATIONS

a) **Left and right AV valve regurgitation**
b) **Left heart failure** (secondary to VSD and left AV valve regurgitation)
c) **Right heart failure** (secondary to ASD and right AV valve regurgitation)
d) PHT; Eisenmenger if not operated
e) **Arrhythmias: AF; flutter; AV block**
f) Progressive subaortic stenosis
g) Paradoxical embolism
h) Postoperative residual shunt
i) Postoperative mitral stenosis

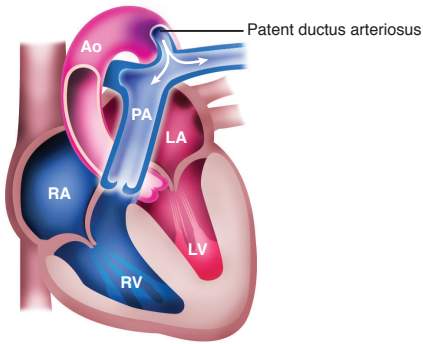
INDICATIONS FOR SURGERY

Patient already operated

a) **Hemodynamically significant** persistent or *de novo* defect (I;B)
b) **Deterioration of LV function** (I;B)
c) **Symptomatic left AV valve regurgitation** (I;B)
d) **Symptomatic left AV valve stenosis** (post-repair) (I;B)
e) **Subaortic obstruction** with mean gradient > 50 mmHg (I;B)
f) Do not operate if **severe, irreversible PHT** (sPAP > 2/3 SBP or PVR > 2/3 SVR) (III;C)

7.6/ PATENT DUCTUS ARTERIOSUS

Connection between proximal pulmonary artery and descending aorta (distal to the left subclavian artery)



A) SILENT DUCTUS ARTERIOSUS: incidental finding on TTE

B) SMALL PATENT DUCTUS ARTERIOSUS: continuous murmur; minimal hemodynamic impact; Qp/Qs < 1.5:1

C) MODERATE PATENT DUCTUS ARTERIOSUS: **continuous machinery murmur in 2nd left intercostal space ± thrill; increased pulse pressure**; bounding pulse; LV dilatation (lateralized, hyperdynamic apex); S3; reversible PHT (induces ↘ duration of the murmur)

D) LARGE PATENT DUCTUS ARTERIOSUS: Severe PHT; Eisenmenger physiology; absence of continuous murmur; **differential hypoxemia and cyanosis (lower limbs cyanosed; clubbing of the toes)**

TTE: flow from aorta to PA visible on PLAX (RVOT/PA view); **diastolic flow reversal** in descending aorta

COMPLICATIONS

a) **Left heart failure (volume overload)**
b) Progressive PHT
c) Arrhythmias (AF)
d) Endarteritis / Ductus aneurysm

INDICATIONS FOR SURGERY

a) **All cases of patent ductus arteriosus** except when silent or large with irreversible PHT (IIa;B)
b) **Endarteritis** (IIa;B)
c) In the presence of **severe PHT** (sPAP > 2/3 SBP or PVR > 2/3 SVR), closure should only be considered in the case of L→R shunt > 1.5:1 or significant reactivity to vasodilators (IIa;B)

PERCUTANEOUS CLOSURE: preferable in the case of ductus arteriosus < 8 mm (without aneurysm) or in the presence of calcification

PREGNANCY: similar considerations to those of VSD

7.7/ LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

SUPRAVALVULAR AORTIC STENOSIS

Fixed obstruction above the sinus of Valsalva

CORONARY ARTERIES submitted to high pressures; risk of dilatation / ostial stenosis / early CAD; requires regular screening for CAD

WILLIAMS SYNDROME: autosomal dominant; 7q11.23 deletion; supravalvular aortic stenosis, peripheral pulmonary artery stenosis, renal artery stenosis, HTN, hypercalcemia, cognitive deficits, "cocktail" personality, elf-like facies

CLINICAL FEATURES: **BP right arm >> BP left arm (Coanda effect with preferential jet to innominate artery)**; crescendo-decrescendo systolic murmur; suprasternal thrill; **increased A2**; absence of ejection click; S4; peripheral PA stenosis can cause end-systolic or continuous posterior murmur

VENTRICULOGRAPHY: **"ballerina foot" pattern of LV**

INDICATIONS FOR SURGERY (patch aortoplasty or ascending aorta replacement or resection with end-to-end anastomosis)

a) **Symptoms and/or mean gradient > 50 mmHg** (I;C)
b) **Doppler instantaneous maximum gradient > 70 mmHg** if mild obstruction (I;C)

VALVULAR AORTIC STENOSIS

BICUSPID AORTIC VALVE (▶▶| Chapter 4 - Valvular heart disease)

ASSOCIATED WITH: CoA; patent ductus arteriosus; ascending aortopathy

ROSS PROCEDURE: replace the aortic valve by the patient's pulmonary valve and replace the pulmonary valve by a cadaveric homologous graft; reimplantation of coronary arteries

› **Complications:** structural deterioration of the homologous P graft; aortopathy (specific to bicuspid aortic valve); AR; coronary stenosis

SUBVALVULAR AORTIC STENOSIS

Discrete membrane or tunnel-shaped LVOT stenosis

ASSOCIATED WITH: AR (valvular damage caused by the high velocity jet); VSD; AV canal defect; Shone complex

› **Shone complex**: multiple stenoses at different levels: **A)** Supravalvular mitral annulus or parachute mitral valve; **B)** Subvalvular aortic stenosis; **C)** Bicuspid aortic valve; **D)** CoA

DDX: HCM (absence of SAM in subaortic stenosis)

CLINICAL FEATURES: crescendo-decrescendo systolic murmur ± thrill; **no radiation to the carotids; absence of ejection click; AR diastolic murmur** +

INDICATIONS FOR SURGERY

a) **Symptoms with Doppler instantaneous maximum gradient > 50 mmHg** or mean gradient > 30 mmHg (I;C)
b) **Associated progressive AR** (I;C)

MEMBRANE: resection of the membrane ± myomectomy ± AVR

TUNNEL: Konno procedure (aortoventriculoplasty ± AVR)

› Complications: recurrence; AV block; iatrogenic VSD

7.8/ COARCTATION OF THE AORTA (COA)

Stenosis in the region of the ligamentum arteriosum (distal to the left subclavian artery)

ASSOCIATED ABNORMALITIES: Bicuspid aortic valve (80% of cases); aneurysm of the circle of Willis; collateral circulation (intercostal and mammary arteries); aortopathy; anomalous brachiocephalic circulation; aortic arch hypoplasia; VSD; Shone complex

› **Turner Syndrome** (45, X): CoA (35%); bicuspid aortic valve; ASD; VSD

SIGNIFICANT COA (IN THE ABSENCE OF COLLATERAL): **HTN in arms with trans-CoA gradient on catheterization > 20 mmHg or with SBP in arms ≥ 20 mmHg higher than SBP in legs** +

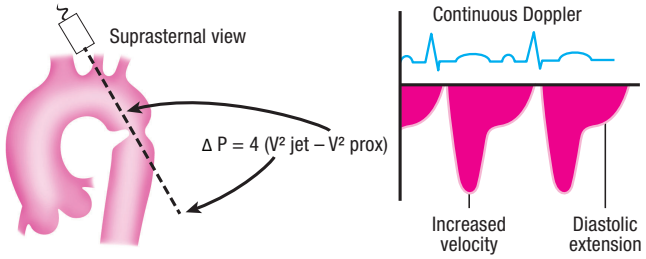
CLINICAL FEATURES

› **In the absence of collaterals**: **HTN in arms; SBP in arms higher than in legs; radiofemoral delay on palpation of pulse; interscapular ejection murmur (rarely continuous); S4; ↗ A2**; systolic click / systolic murmur in the presence of bicuspid aortic valve
› **In the presence of collaterals**: continuous crescendo-decrescendo murmur in left parasternal region or left scapula

CXR: **A) "3" sign:** indentation of the aorta at the site of CoA with distal and proximal dilatation; **B) Erosion of the ribs:** intercostal collaterals +

TTE: turbulence and ↗ velocity in descending Ao (suprasternal view) with diastolic extension of anterograde flow

› **Abdominal aorta:** ↘ velocity of systolic flow and diastolic extension of anterograde flow



MANAGEMENT

a) Congenital cardiology follow-up for life
b) Control of BP (at rest and on exercise) and cardiovascular risk factors
c) BB if aortopathy
d) Imaging of the entire aorta (MRI) with regular follow-up (by TTE for ascending Ao / Ao valve and MRI for entire Ao)
e) Brain MRI (rule out aneurysm of the circle of Willis)
f) Avoid contact sports / isometric exercises if residual CoA or associated aortopathy

COMPLICATIONS

a) **Left heart failure (pressure overload)**
b) Persistent HTN
c) Aortopathy / Aortic dissection
d) Aortic valve disease
e) Early CAD and PAD
f) Intracranial aneurysms / Hemorrhage
g) Endarteritis

INDICATIONS FOR SURGERY

› **In the presence of significant CoA: peak-to-peak gradient ≥ 20 mmHg** on catheterization or less in the presence of collaterals (I;C)

PERCUTANEOUS APPROACH (dilatation + stenting): preferable in the majority of cases (except in the case of a long or tortuous lesion) and preferred technique in the presence of re-coarctation

› **Complications:** aortic dissection / rupture; stroke; aneurysm or pseudoaneurysm; aortobronchial fistula; re-CoA; persistent HTN

SURGICAL OPTIONS: resection with end-to-end anastomosis or graft placement; patch aortoplasty; subclavian flap aortoplasty; bypass graft

› **Complications**: paraplegia; recurrent laryngeal nerve or phrenic nerve paralysis; dissection; aneurysm (post-patch aortoplasty); pseudoaneurysm; claudication of arms (subclavian flap aortoplasty); re-CoA; persistent HTN; endarteritis

POST-REPAIR FOLLOW-UP: Regular MRI and regular TTE

› Consider screening for intracranial aneurysms in the circle of Willis

PREGNANCY: pregnancy contraindicated if CoA not repaired (risk of IUGR - fetal loss - HTN); imaging of the entire Ao is necessary

7.9/ RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

SEVERITY

	MILD	MODERATE	SEVERE
Doppler instantaneous maximum gradient (mmHg)	< 36	36 - 64	**> 64**
Peak velocity (m/s)	< 3	3 - 4	**> 4**

* Doppler measurements not valid in the presence of long stenosis / tunnel stenosis

SUPRAVALVULAR PULMONARY STENOSIS / PERIPHERAL PULMONARY ARTERY STENOSIS

ASSOCIATED WITH: TOF; Williams syndrome; Noonan syndrome; Alagille syndrome; VSD; Congenital rubella

CLINICAL FEATURES: systolic ejection murmur (left parasternal region and posterior; increased by inspiration; sometimes continuous in peripheral pulmonary artery stenosis); absence of ejection click; increased or preserved P2; left parasternal heave

SUBVALVULAR PULMONARY STENOSIS

Associated with VSD or TOF

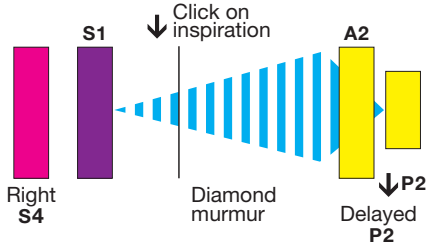
DOUBLE CHAMBER RV: mid-chamber obstruction secondary to a prominent muscle band; associated with VSD

VALVULAR PULMONARY STENOSIS

2 TYPES

1) **Dome-shaped**: thin, pliable, mobile valve; fusion of commissures; post-stenotic dilatation of the PA
2) **Dysplastic (10-15%)**: thickened, immobile leaflets; associated with Noonan syndrome; absence of post-stenotic dilatation

CLINICAL FEATURES: Prominent a wave in jugular vein; left parasternal heave; crescendo-decrescendo systolic murmur ± thrill; **ejection click if the valve is pliable** (early if severe PS; absent in the presence of a dysplastic valve; ↘ **during inspiration** due to premature valve opening); delayed and decreased P2 (absent if severe PS); right S4; ± cyanosis (if ASD or PFO)



Noonan syndrome: autosomal dominant; dysplastic pulmonary valve, pulmonary artery stenosis, ASD, HCM, developmental delay, facial dysmorphism, small stature, congenital lymphedema

LEOPARD syndrome: autosomal dominant; lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genital organs, growth retardation, deafness, LVH

POSSIBLE COMPLICATIONS

- **RVH**
- Right heart failure ± TR
- Pulmonary regurgitation (postoperative)
- Pulmonary artery dilatation (post-stenotic)
- Cyanosis in the presence of associated ASD or VSD
- Atrial arrhythmia (AF / flutter) or ventricular arrhythmia

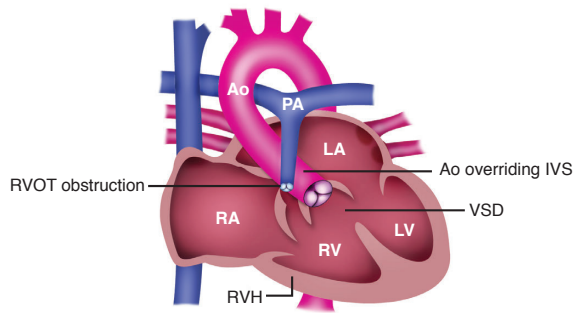
INDICATIONS FOR SURGERY

a) Balloon valvuloplasty for **dome-shaped valvular stenosis with symptoms and maximum Doppler gradient > 50 mmHg** or mean gradient > 30 mmHg (I;C)
b) Balloon valvuloplasty for **asymptomatic dome-shaped valvular stenosis and maximum Doppler gradient > 60 mmHg** or mean gradient > 40 mmHg (I;C)
c) **Surgery if significant RVOT obstruction with:** dysplastic valve or supravalvular stenosis or subvalvular stenosis or associated pulmonary hypoplasia or severe associated PR (I;C)
d) **Severe postoperative PR:** deterioration of functional class or deterioration of RV function or significant TR or flutter / AF or sustained ventricular arrhythmia (I;C)
e) **Valvular stenosis with**: significant arrhythmia or ASD / VSD (with R→L shunt) or recurrent endocarditis (IIa;C)
f) **Double chamber RV** with significant mid-chamber obstruction (gradient > 50 mmHg on catheterization) (IIa;C)

PREGNANCY: well tolerated if RV pressure < 70% of LV pressure; valvuloplasty as required during pregnancy in the presence of severe refractory symptoms (ideally after first trimester)

7.10/ TETRALOGY OF FALLOT (TOF)

COMBINATION OF: A) Non-restrictive (subarterial) VSD; **B)** RVOT obstruction (infundibular, valvular or supravalvular); **C)** RVH; **D)** Aorta overriding the septum



CORRECTIVE SURGERY: **A) Closure of the VSD; B) RVOT disobstruction**; **C)** ± infundibulectomy or subannular patch or transannular patch (induces significant PR) or RV - PA conduit (if congenital coronary artery anomalies crossing over the RVOT) or PVR or pulmonary valvotomy or pulmonary arterioplasty

ASSOCIATED ABNORMALITIES: right aortic arch; secundum ASD (pentalogy of Fallot); pulmonary trunk and peripheral pulmonary artery stenosis / hypoplasia; congenital coronary artery anomalies (LAD with ectopic origin crossing over the RVOT)

- **DiGeorge syndrome** (15% of TOF): 22q11 deletion; facial dysmorphism, hypocalcemia, thymus hypoplasia, immune deficit, psychiatric illness, truncus arteriosus, interrupted aortic arch, double outlet RV

CLINICAL FEATURES (POST-CORRECTION): left parasternal heave; soft ejection murmur (RVOT); subtle and soft diastolic pulmonary murmur (PR); ± absent P2; ± holosystolic murmur in the case of residual VSD; ± AR murmur

ECG: RBBB; wide QRS **(QRS > 180 ms is a risk factor for VT)** +

INVESTIGATIONS: **A)** TTE; **B)** MRI (RV and LV function and dimensions; PR; TR; RVOT; pulmonary arteries; shunt; Ao); **C)** Stress test (exercise capacity); **D)** Holter; **E)** Electrophysiological study PRN

TTE: Severe PR if **the continuous Doppler regurgitation envelope is dense and reaches zero before the end of diastole** (equalization of pressures on either side of the valve) or if PHT < 100 msec +

POST-CORRECTION COMPLICATIONS

- **Pulmonary regurgitation**
- **RV dysfunction / RV dilatation (± TR)**
- Residual RVOT obstruction (subvalvular, valvular or supravalvular) / peripheral pulmonary artery stenosis (causing RV pressure overload)
- Residual VSD
- Infundibular aneurysm
- LV dysfunction
- Aortic root dilatation / Progressive AR
- Arrhythmia: atrial flutter; IART; AF; AV block
- VT (RVOT heavily scarred from surgical intervention); sudden death (0.2% year)
- Endocarditis

INDICATIONS FOR POST-CORRECTION SURGERY (IIA;C)

a) **Severe PR** with: symptoms or moderate-to-severe RV dilatation (**end-diastolic volume > 170 mL/m²; end-systolic volume > 85 mL/m²**) or moderate-to-severe RV dysfunction (**RVEF < 45 %**) or moderate-to-severe TR or atrial or ventricular arrhythmia +
b) **Residual VSD** with shunt > 1.5:1
c) **Moderate to severe RVOT obstruction** (peak Doppler gradient > 50 mmHg)
d) **Severe AR** with symptoms or LV dysfunction
e) **Aortic root > 55 mm**
f) **RVOT aneurysm or false aneurysm**
g) **Combination** of residual VSD and/or residual PS and PR inducing RV dilatation / dysfunction or symptoms

SURGICAL OPTIONS: A) PVR (bioprosthesis or cadaver) ± tricuspid annuloplasty; **B)** Percutaneous pulmonary valve inserted into a pre-existing RV-PA conduit; **C)** Infundibular resection or RVOT patch or transannular patch or valved conduit if obstruction persists

VENTRICULAR ARRHYTHMIA: **Risk factors**: **A)** Inducible VT on EPS; **B)** QRS > 180 ms; **C)** History of palliative shunt; **D)** Significant PR or RVOT obstruction; **E)** Advanced age at the time of complete correction; **F)** NSVT on Holter; **G)** RV or LV dysfunction; **H)** Syncope; **I)** Severe RV dilatation (> 150-180 ml/m²)

- **Secondary prevention**: ICD indicated
- **Primary prevention**: indication for ICD determined on an individual basis according to the risk of sudden death (risk of frequent inappropriate shocks)

PREGNANCY: risk of right heart failure in the presence of RVOT obstruction and/or severe PR and/or RV dysfunction; screen for 22q11 deletion

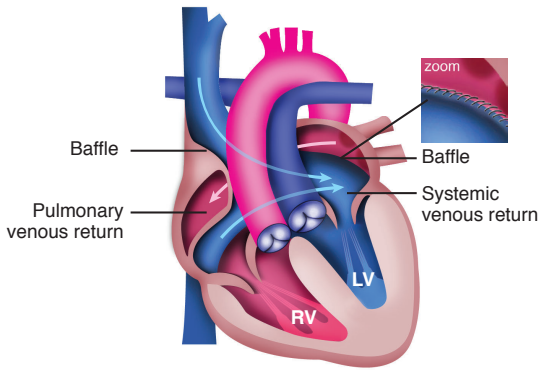
7.11/ TRANSPOSITION OF THE GREAT ARTERIES (D-TGV)

Atrioventricular concordance and ventriculoarterial discordance (the RA is connected to the morphological RV which is connected to the Ao; the LA is connected to the morphological LV which is connected to the PA); incompatible with life in the absence of operation (2 parallel circuits)

POSITION OF THE AORTA: anterior and to the right of the PA (connected to the RV)

ASSOCIATED ABNORMALITIES: VSD; LVOT obstruction; ASD; CoA; congenital coronary artery anomalies

ATRIAL SWITCH: MUSTARD (OR SENNING) PROCEDURE



The majority of adults have undergone this procedure (but this operation was replaced by arterial switch in about 1990); the blood is redirected to the atria by means of a conduit (baffle) made from pericardium or Dacron allowing physiological correction (systemic venous blood is redirected towards the subpulmonary LV; pulmonary venous blood is redirected towards the subaortic RV)

CLINICAL FEATURES: Single S2 (loud A2; P2 is inaudible as the PA is posterior); left parasternal heave; holosystolic murmur of the systemic AV valve

ECG: RVH; block - bradycardia; atrial arrhythmia

CXR: Egg-shaped heart (narrow mediastinum due to parallel great vessels); retrosternal aorta (lateral view)

TTE: Ao and PA are parallel; phasic flow in the baffle with **peak velocity < 1 m/s**; agitated-saline to evaluate baffle leak or stenosis

COMPLICATIONS

a) **Systemic RV failure (+ TR)**
b) Systemic RV ischemia (perfused only by the RCA)
c) Systemic AV valve regurgitation (abnormal septal geometry)
d) Obstruction of the baffle (SVC; IVC)
e) Baffle leak (paradoxical embolism; cyanosis)
f) Subpulmonary obstruction (abnormal LV geometry)
g) Arrhythmias: atrial flutter; IART; SSS; AV block
h) VT - Sudden death (risk factors: RV dysfunction; age; supraventricular arrhythmia; QRS > 140 ms)

INDICATIONS FOR POST-MUSTARD SURGERY (IIA;C)

a) **Moderate-to-severe systemic AV valve regurgitation**
b) **SVC or IVC obstruction** (dilatation + stent in baffle)
c) **Pulmonary vein obstruction** (post-Senning procedure)
d) **Baffle leak with:** significant shunt (Qp:Qs > 1.5:1) or symptoms or PHT or progressive ventricular dilatation / dysfunction or need for pacemaker transvenous lead or R→L shunt with cyanosis (percutaneous closure of the leak)
e) **Symptomatic tachyarrhythmia**: ablation
f) **Bradyarrhythmia:** pacemaker with endovenous lead in the absence of baffle stenosis or baffle leak
g) **Consider transplant** if severe systemic RV dysfunction

PREGNANCY: avoid pregnancy in the presence of moderate-to-severe systemic RV dysfunction and/or severe systemic AV valve regurgitation

ARTERIAL SWITCH: JATENE PROCEDURE

Switching of the Ao and PA; the PA is replaced anteriorly (Lecompte maneuver); the coronary arteries are reimplanted; the LV becomes subaortic

COMPLICATIONS

a) Obstruction of the aorta and pulmonary artery at the sites of surgical anastomosis
b) Subpulmonary or PA or pulmonary arterial branch obstruction following Lecompte maneuver
c) Aortic root dilatation / AR
d) Stenosis of the coronary ostia (regular screening for CAD is indicated)

INDICATIONS FOR POST-JATENE SURGERY (IIA;C)

a) Significant PA obstruction (subvalvular, supravalvular or arterial branch)
b) Coronary artery obstruction
c) Severe AR
d) Severe Ao dilatation > 55 mm

RASTELLI PROCEDURE

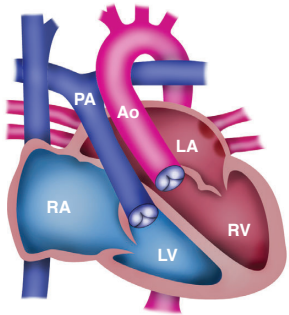
For treatment of D-TGV with VSD and RVOT obstruction

PROCEDURE: **A)** LVOT tunneled to the Ao by an intracardiac patch through the VSD; **B)** RV - PA extracardiac valved conduit

7.12/ CONGENITALLY CORRECTED TRANSPOSITION OF GREAT ARTERIES (L-TGV)

DOUBLE DISCORDANCE (atrioventricular and ventriculoarterial): the circulation is corrected physiologically; the morphological RV is systemic (subaortic)

POSITION OF THE AORTA: anterior and to left of the PA



ASSOCIATED ABNORMALITIES: abnormalities of the systemic T valve (Ebstein-like malformation); VSD; PS; dextrocardia

ECG: AV block (fragile His bundle wich is displaced anteriorly and laterally); septal activation from R to L (septal Q waves absent on left precordial leads, but present on right precordial and inferior leads); accessory pathway

CLINICAL FEATURES: Palpable A2 (anterior Ao); inaudible P2 (posterior PA); holosystolic murmur due to systemic AV valve regurgitation

COMPLICATIONS

a) **Progressive systemic AV valve regurgitation (T valve)**
b) **Progressive systemic RV dysfunction**
c) Systemic RV ischemia (only perfused by the RCA)
d) **Complete AV block (2% / year)**
e) **Atrial arrhythmia:** AF; IART; accessory pathway
f) VT - sudden death

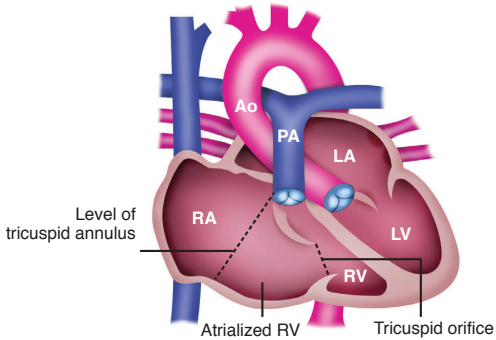
INDICATIONS FOR SURGERY

a) Moderate-to-severe systemic AV valve **regurgitation** (IIa;B)
b) **Deterioration of the systemic RV** (IIa;C): consider heart transplantation

PREGNANCY: avoid pregnancy if RVEF < 40% and/or moderate-to-severe TR

7.13/ EBSTEIN ANOMALY

Apical displacement of the tricuspid valve **> 8 mm/m²** (septal and posterior leaflets) with elongated / redundant anterior leaflet; atrialized RV (small volume functional RV)



ASSOCIATED ABNORMALITIES: A) Accessory pathway(s) (25% of patients; 50% have multiple pathways); **B)** secundum ASD or PFO ± cyanosis (50% of patients); **C)** RVOT obstruction (by T valve); VSD; mitral valve disease

CLINICAL FEATURES: ± V wave in jugular veins (often absent due to severe RA dilatation); left parasternal heave; split S1 with ↗ T1; split S2 (RBBB); right S3; lower left parasternal holosystolic murmur (↗ on inspiration); systolic clicks; ± cyanosis; low output state; signs of right heart failure

ECG: RA dilatation (Himalayan P waves); low voltage; ± pre-excitation; RBBB; Q waves in V1 (as far as V4) and inferior leads; AF - flutter

CXR: "water bottle heart": RA dilatation and left convexity (dilatation of the RV infundibulum); ↘ vascularization

COMPLICATIONS

a) **Severe TR**
b) **Right heart failure / Dilatation of right chambers**
c) Arrhythmias: flutter; AF; AT; accessory pathway(s)
d) Sudden death (pre-excited atrial arrhythmia or VT)
e) Cyanosis - paradoxical embolism in the presence of PFO or ASD
f) RVOT obstruction due to the abnormal tricuspid valve
g) Tricuspid stenosis or prosthetic valve dysfunction post-surgery

INDICATIONS FOR SURGERY (I;B)

a) **Severe TR** with NYHA III - IV or deterioration of functional class
b) **Progressive RV dysfunction or dilatation**
c) **Progressive cardiomegaly** on CXR (cardiothoracic ratio > 65%)
d) **Cyanosis** with resting SaO_2 < 90% (closure of ASD)
e) **Paradoxical embolism** (closure of ASD)
f) **Arrhythmia / WPW**: ablation by catheter or surgical cryoablation

REPAIR: feasibility according to: **A) Length and mobility of the anterior leaflet (creation of a monoleaflet valve); B) Size of the residual RV > 1/3 of total RV**

OTHER SURGICAL OPTIONS

- **Conventional TVR**
- **Bidirectional cavopulmonary connection** (**bidirectional Glenn**): decreases preload and workload of the small RV
- **Fontan procedure in** the presence of a hypoplastic RV
- **Heart transplantation**

PREGNANCY: well tolerated in the absence of cyanosis / right heart failure / arrhythmia

7.14/ MARFAN SYNDROME

Autosomal dominant; FBN1 gene mutation (> 1,000 mutations have been reported)

COMPLICATIONS: Aortic root dilatation; aortic dissection; AR; MVP - MR; left heart failure; tricuspid valve prolapse - TR

MANAGEMENT

a) BB (↘ dP/dT) and ARB
b) Target SBP < 120 mmHg (BB; ARB)
c) Avoid isometric exercise - competitive / contact sports
d) MRI indicated to evaluate all of the aorta; regular follow-up is recommended

TTE FOLLOW-UP	MRI OR CT ANGIOGRAPHY
Annually	Every 3 to 5 years (more frequent if dilatation / imminent indication for surgery / 1 year postop / recent dissection)

INDICATIONS FOR SURGERY (I;B)

a) **Ascending aorta > 50 mm**
b) **Ao > 45 mm**: with: progression > 5 mm/year or progressive AR with probable valve preservation or family history of aortic dissection with Ao < 50 mm or severe MR requiring surgery
c) **Ao > 40 mm before pregnancy**
d) **Other regions of the Ao** between 50-60 mm or progressive dilatation

SURGICAL OPTIONS: A) Bentall procedure: replacement of ascending Ao with valved graft; **B) David procedure:** replacement of the ascending Ao with graft and resuspension of the native aortic valve (valve sparing)

PREGNANCY: risk of transmission (autosomal dominant); MRI imaging of the entire Ao; TTE every 4-8 weeks; BB; avoid ↗ dP/dT during delivery; cesarean section if unstable aorta (> 40-45 mm)

- **Pregnancy contraindicated if Ao > 45 mm** (risk of aortic dissection)
- **If Ao ≥ 40 mm**: referral for sugery is recommended if contemplating pregnancy

GHENT CRITERIA

SYSTEM	MAJOR CLINICAL SIGNS	MINOR CLINICAL SIGNS	DEFINITION OF SYSTEM INVOLVEMENT
Skeletal	• *Pectus carinatum* • Surgical *Pectus excavatum* • Long limbs › Arm span to height ratio > 1.05 or › ↘ Upper segment to lower segment ratio • Long fingers › Wrist sign and thumb sign • Scoliosis > 20° or spondylolisthesis • Maximum elbow extension < 170° • Flat foot • Acetabular protrusion (hip x-ray)	• Moderate *Pectus excavatum* • Joint hypermobility • Arched palate with overlapping teeth • Characteristic facies	**Major** ≥ 4 major signs **Minor** ≥ 2 major signs or 1 major and 2 minor signs
Ocular	• Lens dislocation	• Flat cornea • Elongated eyeball • Myopia	**Major** 1 major sign **Minor** ≥ 2 minor signs
Cardio-vascular	• Aortic root dilatation • Aortic dissection	• MVP • Pulmonary trunk dilatation < 40 years • MAC < 40 years • Dilatation or dissection of the descending thoracic aorta or abdominal aorta < 50 years	**Major** ≥ 1 major sign **Minor** ≥ 1 minor sign
Pulmonary		• Spontaneous pneumothorax • Apical bulla (CXR or CT)	**Minor** ≥ 1 minor sign
Cutaneous		• *Striae atrophicae* (unexplained) • Recurrent incisional herniae	**Minor** ≥ 1 minor sign
Dura mater	• Lumbosacral dural ectasia (CT or MRI)		**Major** 1 major sign
Genetic	• 1 first-degree relative with diagnostic criteria • FBN1 gene mutation causing Marfan		

Diagnosis established:
- **1 system with major involvement + 1 system with minor involvement + 1 genetic criterion**
- **2 systems with major involvement + 1 system with minor involvement**

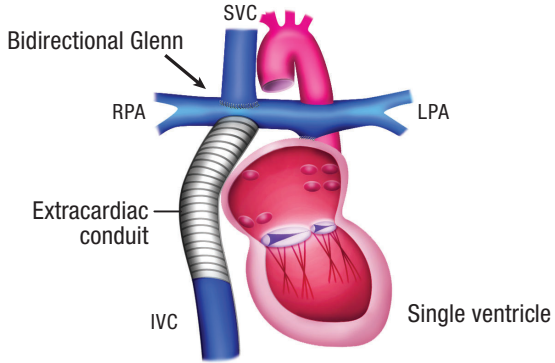
Lœys BL, Dietz HC, Braverman AC, et al. J Med Genet 2010; 47:476-485

7.15/ FONTAN PROCEDURE

Palliative procedure in the presence of a single ventricle (anatomical or functional); systemic venous return redirected to PA, short-circuiting the subpulmonary ventricle

PREREQUISITES: **Mean PAP < 15 mmHg** with normal-sized PA, normal function of the single ventricle, absence of any significant AV valve regurgitation

STEPS OF THE MODIFIED FONTAN PROCEDURE: **1) Bidirectional cavopulmonary connection (bidirectional Glenn)**: connection between the SVC and R or L pulmonary arteries; **2) Connection of IVC to PA** (lateral conduit or extracardiac conduit or intracardiac conduit) with pulmonary trunk ligation



FACTORS OF HEMODYNAMIC DETERIORATION

a) Any ↗ filling pressure of the systemic ventricle
b) Obstruction to systemic venous return (thrombosis or obstruction of Fontan; ↗ PVR; pulmonary arteries stenosis; pulmonary vein compression)
c) Arrhythmia (risk of hemodynamic deterioration and thrombus)

CLINICAL FEATURES: JVD but nonpulsatile; single S1 and S2; absence of murmur (except in the case of AV valve regurgitation or subaortic obstruction); hepatomegaly / leg edema / ascites

COMPLICATIONS

a) **Intra-Fontan thrombus**: predisposed by stasis and atrial arrhythmia; leads to Fontan obstruction / pulmonary embolism / paradoxical embolism
b) **Fontan obstruction** (at anastomotic sites or by thrombus)
c) **Right pulmonary vein compression** by the interatrial septum or the dilated RA
d) **Arrhythmia**: IART; flutter; AF; SSS; AV block
e) **Cyanosis in the presence of a R→L shunt:** systemic venous collateral to pulmonary veins; pulmonary AVM; residual ASD; fenestrated Fontan; hepatopulmonary syndrome
f) **Ventricular dysfunction / systemic AV valve regurgitation**
g) **Protein-losing enteropathy:** anasarca; diarrhea; ↗ fecal alpha-1-antitrypsin and hypoalbuminemia
h) **Congestive hepatopathy** (or even cardiac cirrhosis)

MANAGEMENT

a) **A/C** if thrombus or stasis or thromboembolism or ASD or fenestration or atrial arrhythmia
b) **Single-ventricle failure**: consider ACE inhibitors - BB; sildenafil; transplant; mechanical support
c) **Aggressive treatment of atrial arrhythmias:** look for a hemodynamic cause; TEE prior to ECV; AAD; A/C; catheter ablation; conversion to extracardiac Fontan with intraoperative Maze
d) **When a pacemaker is indicated**: epicardial ventricular lead
e) **Protein-losing enteropathy**: diuretics - aldactone; eliminate obstruction or arrhythmia; dietary support; IV albumin; corticosteroids; sildenafil; Fontan fenestration; transplant

INDICATIONS FOR REOPERATION (I;C)

a) **Obstruction** to systemic venous return (revision of the Fontan or angioplasty / stenting or conversion of Fontan or thrombectomy)
b) **Obstruction** to pulmonary venous return (conversion to extracardiac Fontan)
c) Moderate-to-severe systemic AV valve **regurgitation**
d) **Symptomatic cyanosis** with venovenous collaterals or pulmonary AVM (catheter occlusion)
e) Residual ASD or fenestrated Fontan with significant R→L shunt (percutaneous closure)
f) **Subaortic stenosis** with peak-to-peak gradient > 30 mmHg
g) **Protein-losing enteropathy** with Fontan obstruction (revision of the Fontan or angioplasty / stenting) or with elevation of systemic venous pressures (consider fenestration)
h) **Symptomatic and refractory atrial arrhythmia** (conversion to extracardiac Fontan with intraoperative Maze)

PREGNANCY: increased risk of all Fontan-specific complications; risk of spontaneous abortion / IUGR / prematurity; follow-up by an experienced, multidisciplinary team

7.16/ EISENMENGER SYNDROME

Obstructive pulmonary vascular disease secondary to communication between pulmonary and systemic circulations (L→R shunt), leading in the long term to irreversible elevation of PAP and PVR (to systemic levels) and reversal of the shunt (R→L)

CLINICAL FEATURES: Central cyanosis (differential cyanosis in the presence of patent ductus arteriosus); clubbing; JVD (prominent A wave; prominent V wave in the presence of TR); signs of PHT

ECG: RAH; RVH; right axis deviation; atrial arrhythmia

CXR: dilatation of central pulmonary arteries ± calcification; dilatation of right chambers

COMPLICATIONS

a) **RV dysfunction**
b) **Complications of cyanotic heart disease:** erythrocytosis; bleeding; CRF; hyperuricemia / gout; cholelithiasis
c) Intrapulmonary hemorrhage / hemoptysis
d) Pulmonary artery aneurysm
e) Pulmonary artery thrombosis / Pulmonary embolism
f) Stroke - TIA; paradoxical embolism
g) Brain abscess
h) Arrhythmias: AF; flutter; VT
i) Sudden death
j) Endocarditis

MANAGEMENT

a) Correct iron deficiency, when present
b) Aggressive treatment of arrhythmia
c) Noncardiac surgery: multidisciplinary preoperative assessment in a tertiary institution
d) Pregnancy contraindicated
e) Avoid dehydration - hemorrhage - anemia
f) Avoid NSAID - vasoactive agents (which ↗ the shunt and cyanosis) - estrogens - nephrotoxins
g) Air filter on IV lines
h) Avoid vigorous physical exercise
i) Dental hygiene and prophylactic antibiotics
j) Investigate hemoptysis (CXR; CBC; CT scan; embolization PRN)
k) Influenza - pneumococcus vaccination

TREATMENT OF PHT

a) First-line endothelin antagonists (Bosentan; Macitentan)
b) PDE-5 inhibitors or prostanoids

LUNG ± HEART TRANSPLANT: in the case of refractory symptoms with estimated 1-year survival < 50%; contraindicated in the presence of multiple pleuropulmonary collaterals

7.17/ CYANOTIC HEART DISEASE

R→L shunt (deoxygenated blood enters the systemic circulation); chronic hypoxemia

SECONDARY ERYTHROCYTOSIS (↗ EPO)

- **Hyperviscosity (Hct > 65% and Hb > 20 g/dL)**: headache; faintness; tiredness; disorders of concentration; visual disorders; paresthesia; tinnitus; myalgia; intraoperative bleeding
  - **Treatment:** phlebotomies (if patient is iron-repleted and well hydrated)
  - **Treat any iron deficiency** (as microcytosis can cause hyperviscosity and is a risk factor for stroke); beware of rebound effect
- **Bleeding / clotting abnormalities** (if severe bleeding: FFP; vitamin K; cryoprecipitates; DDAVP; platelets)

OTHER COMPLICATIONS: Stroke - TIA; cerebral hemorrhage; paradoxical embolism; brain abscess; CRF; proteinuria; hyperuricemia; gout; hypertrophic osteoarthropathy (arthralgia); scoliosis; cholelithiasis

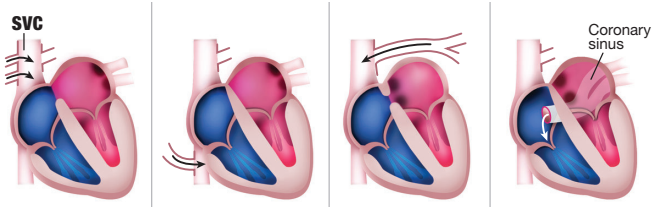
- Beware of nephrotoxic agents, including contrast agents

BASIC WORK-UP: SaO_2; CBC; ferritin; transferrin; iron saturation; ± folate; ± vitamin B12; PT-PTT; renal function; uric acid

PALLIATIVE SHUNTS (systemic to pulmonary): objective: improve pulmonary blood flow and cyanosis

- **Blalock-Taussig**: subclavian artery to pulmonary artery (modern: graft connecting the two arteries, preserving perfusion of the upper limb)
- **Waterston**: Ascending Ao to right PA
- **Potts**: Descending Ao to left PA
- **Physical examination:** Continuous murmur (except in the presence of stenosis / occlusion / significant PHT)
- **Complications**: PHT; distortion of PAs; stenosis / aneurysm at the site of anastomosis; heart failure (volume overload); arrhythmias

7.18/ ANOMALOUS PULMONARY VENOUS RETURN



RPV TO SVC (WITH SINUS VENOSUS ASD) | RPV TO IVC (SCIMITAR) | LPV TO INNOMINATE VEIN | LPV TO CORONARY SINUS

CONSEQUENCES AND CLINICAL FEATURES: similar to ASD

INDICATION FOR SURGERY: dilatation of right chambers

SCIMITAR SYNDROME: **pulmonary veins (right lung) drain into the IVC; scimitar appearance on CXR**; ± hypoplasia of right lung

7.19/ CONGENITAL CORONARY ARTERY ANOMALIES

ECTOPIC ORIGIN OF A CORONARY ARTERY

1 % of the population

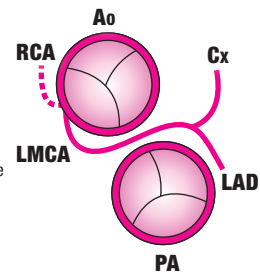
CLINICAL FEATURES: sudden death; retrosternal chest pain; arrhythmia; LV dysfunction; syncope

DETECTION: coronary CT angiography (or cardiac MRI); cholelithiasis

› Look for ventricular arrhythmia during exercise testing

INDICATIONS FOR SURGERY
(reimplantation; marsupialization)

a) Coronary artery coursing between the great vessels with **documented ischemia** (I;B)
b) Ectopic origin of **LMCA** (opposite sinus) coursing between the Ao and the PA (I;B)
c) Ectopic origin of the **right coronary artery** (opposite sinus) coursing between the Ao and the PA with documented ischemia (I;B)
d) Ectopic origin of the **LAD** coursing between the Ao and the PA (IIb;C)



ALCAPA SYNDROME

Anomalous left coronary artery arising from the pulmonary artery

CLINICAL FEATURES: ischemia; LV dysfunction; MI; ventricular arrhythmia; sudden death; may be well tolerated in the presence of collaterals of the RCA

INDICATIONS FOR SURGERY (coronary reimplantation)

› All patients with **ALCAPA syndrome** (I;C)

CORONARY ARTERIOVENOUS FISTULA

Communication between a coronary artery and a heart chamber (RA; RV) or a vein (coronary sinus; vena cava; pulmonary vein) or sometimes the PA

CLINICAL FEATURES: continuous left parasternal murmur

COMPLICATIONS

a) Dilatation of the nutrient coronary artery
b) Rupture - dissection
c) Myocardial ischemia distal to the fistula
d) Endarteritis
e) Left heart failure

INDICATIONS FOR SURGERY (percutaneous closure by embolization or surgical closure)

a) Large fistula - Qp:Qs > 1.5 : 1 (I;C)
b) Small to moderate fistula with: ischemia or arrhythmia or LV dysfunction or LV dilatation or endarteritis (I;C)

CONGENITAL SINUS OF VALSALVA ANEURYSM

RUPTURE: Sudden chest pain and dyspnea; continuous AV shunt with possible left and right heart failure; bounding pulse; continuous murmur ± thrill

a) Ruptured aneurysm of the right sinus of Valsalva: Ao - RVOT fistula
b) Ruptured aneurysm of the non-coronary sinus: Ao - RA fistula
c) Ruptured aneurysm of the left sinus of Valsalva: Ao - LA fistula

DDX: Infectious (endocarditis); Inflammatory - Vasculitis; Marfan; Iatrogenic

MYOCARDIAL BRIDGE ("MILKING")

Intramyocardial coronary segment (usually LAD)

Compression of the coronary segment with each systole

CONSEQUENCES: usually none; sometimes ischemia - angina - LV dysfunction - arrhythmia / VT - sudden death

MANAGEMENT: BB; CCB; PCI or CABG if severe refractory ischemia

7.20/ VASCULAR RING

Malformation of the aortic arch associated with **compression of the esophagus and/or trachea** (dysphagia, respiratory symptoms, stridor)

a) Double aortic arch
b) Right aortic arch; associated with Kommerell's diverticulum compressing the trachea (diverticulum at the junction of the left subclavian artery and the descending aorta)
c) Aberrant origin of the right subclavian artery (posterior to the esophagus)
d) Retroesophageal descending aorta (compression of the trachea)

7.21/ COR TRIATRIATUM

Fibromuscular diaphragm dividing the LA into two chambers

Severity varies according to the degree of stenosis; nonobstructive form (benign) versus obstructive form (leads to PHT)

Management similar to that of MS

7.22/ HEART DISEASE IN PREGNANT WOMEN

HEMODYNAMIC CHANGES DURING PREGNANCY

HEMODYNAMIC CHANGES	CONSEQUENCES
↗ 40-50% of plasma volume	Risk of congestion
↗ 10-20% of HR	Poorly tolerated MS
↗ 30-50% of cardiac output	
↘ Peripheral resistance (especially ↘ DBP)	Tolerated poorly stenotic lesions (increased gradient)
↗ Venous pressure in legs	Risk of stasis / DVT
Hypercoagulability	Increased thromboembolic risk

NORMAL PHYSICAL EXAMINATION OF THE PREGNANT WOMAN

↗ HR; normal or slightly ↗ CVP; Hyperdynamic state (pulse; apex); Apex may be broadened and slightly lateralized; leg edema is frequent

Accentuated S1 - accentuated splitting; S2 may appear to be constantly split at the end of pregnancy; S3 is frequent; left parasternal ejection murmur ≤ 3/6; continuous murmur (cervical venous "hum" or breast murmur)

MATERNAL RISK OF CARDIAC EVENTS

STRESS TEST: high-risk pregnancy if < 70% of predicted functional capacity

CARPREG SCORE (1 point each):

1) History of heart failure - TIA - Stroke - Arrhythmia 2) NYHA ≥ III or cyanosis 3) Mitral valve area < 2 cm² or Aortic valve area < 1.5 cm² or LVOT gradient > 30 mmHg 4) Systemic ventricle systolic function < 40%	Risk of cardiac event during pregnancy: • 0 point: 5 % • 1 point: 27 % • ≥ 2 points: 75 %

* Does not take PHT - mechanical valve - aortopathy into account

Siu SC, Sermer M, Colman JM, et al. Circulation 2001; 104:515–521.

WHO CLASSIFICATION

STAGE I: LOW-RISK PREGNANCY

- Uncomplicated, small or mild PS or patent ductus arteriosus or MVP
- Successfully repaired simple lesions (ASD; VSD; patent ductus arteriosus; anomalous pulmonary venous drainage)
- Isolated APC and PVC

STAGE II: MILD-TO-MODERATE RISK PREGNANCY

- Unrepaired ASD or VSD
- Repaired TOF
- Most arrhythmias

Stage II or III, depending on severity

- Mild LV dysfunction
- HCM
- Valvular heart disease not considered to be WHO stage I or IV
- Marfan syndrome without Ao dilatation
- Bicuspid aortic valve with Ao < 45 mm
- Repaired CoA

STAGE III: HIGH-RISK PREGNANCY (EXPERT FOLLOW-UP RECOMMENDED)

- Mechanical valve
- Systemic RV
- Fontan
- Cyanotic heart disease
- Complex congenital heart disease
- Marfan: Ao 40-45 mm
- Bicuspid aortic valve: Ao 45-50 mm

STAGE IV: PREGNANCY CONTRAINDICATED

- **Severe pulmonary arterial hypertension**
- **Severe LV dysfunction (LVEF < 30% - NYHA III or IV)**
- **Previous peripartum cardiomyopathy with residual impairment of LV function**
- **Severe MS or severe AS**
- **Marfan: Ao > 45 mm**
- **Bicuspid aortic valve: Ao > 50 mm**
- **Unrepaired CoA**

BICUSPID AORTIC VALVE STENOSIS

Pregnancy contraindicated if ascending Ao > 50 mm (or > 25 mm/m²)

› In the presence of Ao dilatation: TTE every 4-8 weeks; BB

SEVERE AORTIC STENOSIS: avoid pregnancy (particularly if symptoms or LV dysfunction or abnormal stress test); risk of hemodynamic instability during delivery; percutaneous valvuloplasty PRN in the presence of severe symptoms

MITRAL STENOSIS

Moderate-to-severe MS is poorly tolerated; deterioration due to tachycardia and ↗ cardiac output; risk of pulmonary congestion and PHT

BB (Metoprolol); valvuloplasty PRN if refractory NYHA III-IV

MITRAL REGURGITATION AND AORTIC REGURGITATION

Generally well tolerated if moderate regurgitation / NYHA ≤ II / normal LV function and dimensions

Diuretics and vasoactive agents PRN; Surgery if refractory NYHA III-IV

PROSTHETIC VALVE

Follow-up by an experienced multidisciplinary team

MECHANICAL VALVE: significant maternal and fetal risks

- Thromboembolic risk (hypercoagulability of pregnancy)
- Risk associated with anticoagulation (fetal loss; placental hemorrhage; insufficient anticoagulation; embryopathy; management during delivery)

UNFRACTIONATED HEPARIN (IV OR SC): less effective than warfarin; adjusted according to aPTT 6h post-injection (> 2 x normal)

LMWH: bid; dose according to **anti-Xa level 4 h post-injection (target: 0.8-1.2 IU/mL);** review once a week; replace by unfractionated heparin > 36 h before delivery

WARFARIN: risk of embryopathy during the first trimester (4-10%); **lower risk with Warfarin ≤ 5 mg daily**

WARFARIN DOSE ≤ 5 MG QD: continue Warfarin; replace by unfractionated heparin at the end of pregnancy prior to planned delivery

WARFARIN DOSE > 5 MG QD: LMWH or IV Heparin during first trimester; replace by Warfarin for 2nd and 3rd trimesters; then replace by unfractionated heparin prior to planned delivery

CYANOTIC HEART DISEASE

Pregnancy contraindicated if SaO_2 < 85 %

R→L shunt increased by ↘ peripheral resistance

Maternal hypoxia alters fetal growth and survival

PULMONARY HYPERTENSION

Pregnancy contraindicated in the presence of severe pulmonary hypertension

EISENMENGER: **maternal mortality as high as 50%**

DILATED CARDIOMYOPATHY

Avoid pregnancy if LVEF < 40%

PERIPARTUM CARDIOMYOPATHY

DEFINITION: "Idiopathic" cardiomyopathy with LV systolic dysfunction occurring around the last month of pregnancy or during the first 5 months post-partum

- Diagnosis of exclusion

RISK FACTORS: twin pregnancy, African American mother, advanced age, pre-eclampsia, smoking

MANAGEMENT: **A)** Hydralazine / Nitrates; **B)** BB (avoid Atenolol and Carvedilol; prefer beta-1 selective BB; Metoprolol is the best studied BB during lactation); **C)** Digoxin; **D)** Diuretics; **E)** Anticoagulate if intracardiac thrombus or LVEF < 35% or concomitant Bromocriptine

- ACE inhibitors (Captopril; Enalapril) are safe while breastfeeding
- Possible benefit of post-partum Bromocriptine (2-5 mg/day)
- Continue therapy with standard HF medications for ≥ 12 months

Normalization of LVEF in 50% of women (2 to 6 months)

Avoid subsequent pregnancy **(30% recurrence rate)**

HYPERTROPHIC CARDIOMYOPATHY

Autosomal dominant; variable penetrance

High-risk pregnancy if symptoms at baseline or significant baseline LVOT gradient

HYPERTENSION

PRE-EXISTING HTN: before pregnancy or < 20 weeks; rule out CoA

GESTATIONAL HYPERTENSION: *de novo* HTN (> 20 weeks after start of pregnancy); BP > 140/90 on 2 occasions; absence of proteinuria; returns to normal during the first 12 weeks postpartum

- **Management**: Labetalol; Methyldopa; Nifedipine

PRE-ECLAMPSIA: gestational HTN with the presence of proteinuria **(> 300 mg/24 h or > 30 mg/mmol on urine spot test**

- **Risk factors:** primiparous; twin pregnancy; ≥ 40 years; BMI ≥ 35 kg/m^2; family history of preeclampsia
- **Clinical features:** headache, blurred vision, abdominal pain, thrombocytopenia, abnormal LFTs, hemolysis, hyperreflexia - clonus, seizures, acute pulmonary edema, stroke
- **Management:** rest; sodium restriction; magnesium sulphate; delivery; IV Labetalol; Methyldopa; Nifedipine; IV Nitroglycerin; target SBP 140 to 160 mmHg and DBP 90 to 105 mmHg

ATRIAL FIBRILLATION

Anticoagulant according to embolic risk

CONTROL HR: Digoxin; BB (Metoprolol); CCB (Verapamil)

CONTROL RHYTHM: ECV; CCV (Procainamide); Flecainide / Sotalol

Continuous fetal monitoring during intervention / AAD

SUPRAVENTRICULAR TACHYCARDIA

ACUTE: Vagal maneuver or Adenosine or ECV; Metoprolol PRN; IV Procainamide; Continuous fetal monitoring during intervention

PROPHYLAXIS: Metoprolol or Digoxin; Flecainide / Sotalol PRN; Verapamil or ablation as 3rd line

CONTRACEPTION

Avoid estrogens in women with cyanotic heart disease, AF or flutter, mechanical prosthetic valve, Fontan, thromboembolic history or LVEF < 40%

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- UpToDate 2015

Peripheral Vascular Disease

08

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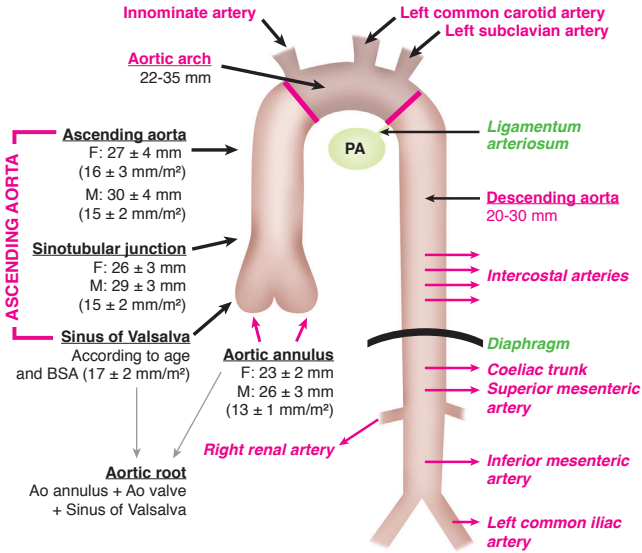
8.1/ ANEURYSM OF THE THORACIC AORTA

ANEURYSM: permanent and localized dilatation of an artery; **diameter > 150 %** of normal diameter (for age / gender / BSA)

- **Ectasia**: arterial dilatation < 150% of normal diameter
- **Pseudo-aneurysm (false aneurysm)**: **rupture** of arterial wall contained by hematoma and adjacent tissues

NORMAL DIMENSIONS



RISK FACTORS

- **Atherosclerotic / Degenerative** (media degeneration): HTN; smoking; COPD; family history
- **Congenital**: Bicuspid aortic valve; Tetralogy of Fallot; CoA; VSD; Transposition of great arteries
- **Genetic**: Marfan; Ehlers-Danlos type IV; Turner; Loeys-Dietz; Noonan; Familial thoracic aortic aneurysm syndrome
- **Inflammatory**: Takayasu; Giant cell arteritis; Behçet; Ankylosing spondylitis; Spondyloarthropathies; SLE; Sarcoidosis
- **Infectious**: Syphilis; Salmonella; Staphylococcus; HIV

PRESENTATION: Asymptomatic; Aortic dissection; Aortic rupture; AR; Infectious aortitis; Compressive symptoms (recurrent laryngeal nerve; trachea; esophagus; SVC syndrome); Pain (neck; jaw; back; interscapular); Embolism (thrombus or cholesterol crystals); Fistula (aortoesophageal; aortobronchial)

ECHOCARDIOGRAPHY: diameter at end-diastole using the leading-edge of the anterior wall to the leading of the posterior wall

CT SCAN AND MRI: measurement of outer diameter

CXR: large mediastinum; prominent aortic knob; trachea deviated to the right

MANAGEMENT

RISK FACTOR CONTROL: HTN; Lipids; Smoking

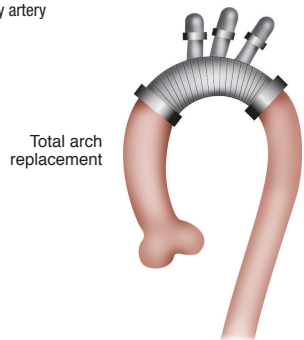
BB AND ACE INHIBITORS / ARB

AVOID ISOMETRIC EXERCISES

INDICATIONS FOR SURGERY – ASCENDING AORTIC ANEURYSM	
Degenerative ascending aortic aneurysm	**≥ 55 mm**
Progressing aneurysm	**> 5 mm / year**
Symptomatic aneurysm	Compressive symptoms; Pain
Ao valve or CABG surgery	**> 45 mm**
Bicuspid aortic valve	**> 55 mm (or > 50 mm with family history of dissection or progression ≥ 5 mm / year)**
Marfan	**40-50 mm** (▸▸| Genetic aortic syndromes)
Marfan or Genetic Syndrome or Bicuspid aortic valve	**Maximum Ao area (cm²) / Patient's height (m) > 10**
Lœys-Dietz	**≥ 42 mm** (TEE) or **≥ 44 mm** (CT or MRI)
Turner	**> 25 mm/m²**
SURVEILLANCE – ASCENDING AORTIC ANEURYSM	
Aneurysm 35 - 44 mm	• Ensure stability with follow-up assessment 6 months after diagnosis • Stable → Imaging every 1-3 years **(progression ≈ 1 - 2 mm / year)**
Aneurysm 45 - 54 mm	Imaging after 3-6 months (stability) then every 6-12 months
Pregnancy	Imaging every 6-8 weeks (until 3 months postpartum)

ANEURYSM OF AORTIC ARCH

SURGERY: requires profound hypothermia and circulatory arrest; temporary cerebral perfusion via the right axillary artery



SURGICAL OPTIONS: Resection of the proximal hemi-arch; Total arch replacement; Stent with reimplantation of innominate arteries...

› **Elephant trunk procedure**: aneurysm of the aortic arch and descending aorta; allows subsequent stenting of the descending aorta

MANAGEMENT – ANEURYSM OF THE AORTIC ARCH	
Isolated aneurysm of the aortic arch > 55 mm or compressive symptoms	Surgery (if acceptable surgical risk)
Aneurysm of the aortic arch < 40 mm	Imaging every 1-2 years
Aneurysm of the aortic arch > 40 mm	Imaging every 6-12 months

ANEURYSM OF THE DESCENDING THORACIC AORTA

MANAGEMENT – ANEURYSM OF THE DESCENDING THORACIC AORTA	
Degenerative or traumatic aneurysm > 55 mm	TEVAR (when technically feasible)
Chronic dissection + [refractory symptoms or aneurysm > 55 mm or progression of diameter > 4 mm/year]	TEVAR (open surgery when TEVAR is contraindicated)

SURGICAL PROCEDURE: CPB with retrograde femoral perfusion

› **Risk of spinal cord ischemia**

THORACIC ENDOVASCULAR AORTIC REPAIR (TEVAR): stent deployment requires a normal aortic segment > 20 mm above and below the aneurysm (with diameter < 40 mm) and adequate vascular access

› **Contraindications**: Severe Ao atherosclerosis (risk of atheroembolism); severe PAD (limiting femoral access)

› **Regular long-term surveillance following TEVAR:** CTscan or MRI after 1, 6 and 12 months and then yearly (or every 2 years if stable course)

› **Complications**: Stroke; Atheroembolism; Spinal cord ischemia; Paraplegia; MI; Ventricular arrhythmia; ARF; Transformation from type B to type A dissection; Stent fracture; Stent migration; Infection; Occlusion of arterial branches (subclavian; mesenteric; celiac trunk; renal)

- **Endoleak**: persistence of blood flow outside of the stent lumen towards the aneurysm sac

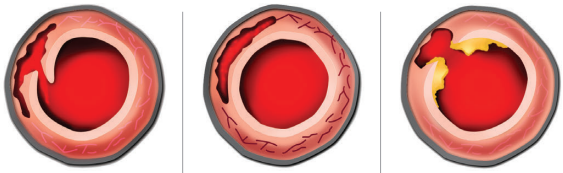
TYPE I ENDOLEAK	Reperfusion and filling of the aneurysm sac via a leak in the proximal or distal portion of the stent (requires treatment)
TYPE II ENDOLEAK	Retrograde flow in the aneurysm sac via a branch artery (intercostal; lumbar; mesenteric) (observation)
TYPE III ENDOLEAK	Separation of stent components (fracture; separation) (requires treatment)

8.2/ ACUTE AORTIC SYNDROME

AORTIC DISSECTION

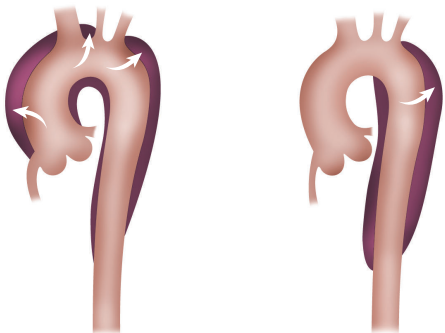
Tear of the media with bleeding inside the media and along the arterial wall

Acute aortic syndrome



Ao dissection | **Intramural hematoma** | **Penetrating atherosclerotic ulcer**

STANFORD CLASSIFICATION	
Type A	Involves the ascending Ao
Type B	No involvement of the ascending Ao
DEBAKEY CLASSIFICATION	
Type I	Ascending Ao → extends at least to the aortic arch (± descending Ao)
Type II	Confined to the ascending Ao
Type III	Confined to the descending Ao



Type A Ao dissection
Involvement of the ascending Ao
(Surgical management)

Type B Ao dissection
No involvement of the ascending Ao
(Initially medical treatment)

RISK FACTORS

↗ AORTIC STRESS	DEGENERATION OF THE MEDIA
• Aortic aneurysm • Aortic valve disease • HTN • CoA • Recent aortic intervention • Trauma / Deceleration • Pheochromocytoma • Cocaine • Weightlifting • Penetrating ulcer • Infectious aortitis	↗ metalloproteinases; ↘ elastic fibers; ↗ proteoglycans • **Degenerative / Atherosclerotic** • **Genetic**: Marfan; Ehlers-Danlos type IV; Bicuspid aortic valve; Turner; Loeys-Dietz; Familial thoracic aortic aneurysm and dissection • **Vasculitis**: Takayasu; Giant cell arteritis; Behçet • **Other**: Pregnancy; Polycystic kidneys; Chronic corticosteroid therapy

PRESENTATION: Acute - severe - tearing pain; Retrosternal pain (type A) or back pain (type B)

- **Target organ ischemia:** Myocardial infarction; Stroke - TIA; Spinal cord ischemia (paraplegia / parapharesis) or mesenteric or renal or lower limbs; Ischemic neuropathy
- **Hemorrhagic**: Tamponade; Hemothorax; Hemomediastinum; Aortopulmonary or aorto-enteric or aorto-esophageal fistula
- **Aortic regurgitation**: Mechanisms: **A)** Aortic root dilatation (malcoaptation); **B)** Dissection involving a leaflet implantation site (leaflet prolapse); **C)** Transvalvular prolapse of the dissection flap; **D)** Underlying AR (bicuspid aortic valve)

CLINICAL FEATURES: Hypotension or Normotension or Hypertension (**measure BP in both arms**); Absent pulses (evaluate pulses in all extremities); **AR murmur**; Signs of tamponade; Neurological deficits; Abdominal signs

TEE: Dissection flap separating the true lumen and the false lumen (with independent movement); two flows on either side of the dissection flap on color Doppler; thrombus in the false lumen; look for the entry site and/or exit site of the dissection; pericardial effusion; myocardial ischemia (RWMA); AR; coronary ostia

	TRUE LUMEN	FALSE LUMEN
Size	True < False	False > True
Pulsation	Systolic expansion	Systolic compression
Direction of flow	Anterograde (systolic)	Retrograde or ↘ Anterograde systolic flow
Thrombus	Rare	Common
Contrast agent	Rapid opacification	Delayed opacification

CXR

a) **Aortic shadow** abnormal and enlarged
b) **Large mediastinum**: **AP CXR → > 8 cm at the carina**
c) **Calcium sign**: separation between calcification of the aortic intima and the lateral wall of the aortic knob **> 10 mm**
d) **Pleural effusion** (inflammatory reaction or hemothorax)
e) **Deviation of the trachea** towards the right (or deviation of the esophagus - NGT)
f) **Pulmonary edema** (AR)

PREOPERATIVE CORONARY ANGIOGRAPHY: it is reasonable not to perform coronary angiography in acute aortic syndrome, which constitutes a surgical emergency (class IIa recommendation)

POSTOPERATIVE COMPLICATIONS: Aneurysm formation (at the site of dissection or at the site of anastomosis or elsewhere); Recurrent dissection; Graft dehiscence; Pseudoaneurysm; AR; Infection; Progression of false lumen

FOLLOW-UP BY CT ANGIOGRAPHY OR MR ANGIOGRAPHY: 1-3-6-12-18-24 months; then annually +

- **Tybe B aortic dissection: TEVAR or surgical repair if aneurysm > 55-60 mm or > 4 mm/year growth or target organ ischemia or recurrent pain**

AVOID ISOMETRIC EXERCISES; CONTROL BP

SPONTANEOUS INTRAMURAL HEMATOMA

Medial tear with bleeding inside the media, but absence of communication with the aortic lumen (absence of false lumen)

- Can propagate in an anterograde or retrograde fashion
- **May have an identical clinical presentation to that of aortic dissection**

IMAGING: Intramural thrombus; Enlarged wall **> 5 mm** (crescent-shaped or circular); Absence of flow (contrast) in wall +

COURSE: Resolution or stabilization or aneurysm formation or progression to aortic dissection or aortic rupture

MANAGEMENT: Similar to aortic dissection (for corresponding segment)

a) **Ascending Ao** → urgent surgery
b) **Descending Ao** → initial medical treatment; Indication for TEVAR (or surgery) according to aortic diameter or persistent symptoms or progression or compromise of branches (with ischemia)

PENETRATING ATHEROSCLEROTIC ULCER

Penetration of the aortic wall by an atherosclerotic ulcer (± secondary intramural hematoma); descending aorta in the majority of cases

COMPLICATIONS: Aortic dissection; Aortic rupture; Distal embolism (thrombus or cholesterol crystals); Aneurysm

MANAGEMENT

a) **Ascending Ao** → Surgery should be considered
b) **Descending Ao** → Initial medical treatment; Indication for TEVAR (or surgery) according to aortic diameter or persistent symptoms or progression or deteriorating associated intramural hematoma

8.3/ ABDOMINAL AORTIC ANEURYSM (AAA)

ANEURYSM: **Abdominal Ao diameter > 30 mm**

- Predominantly occurs in the infrarenal aorta
- Degeneration of the media (↗ metalloproteinases)
- **Risk factors**: Smoking; Family history; Age; Male gender; COPD; dyslipidemia; HTN

PRESENTATION: Asymptomatic; Embolism; Rapid expansion; Pain; Compression or erosion of adjacent structures; Rupture

ABDOMINAL ULTRASOUND: High sensitivity and specificity

- **Screening**: Male, 65 to 74 years with history of smoking; Male ≥ 60 years with family history of AAA

MANAGEMENT: Smoking cessation; treatment of HTN - dyslipidemia - DM; Surveillance of AAA

AAA REPAIR: Surgical or Percutaneous (EVAR) in a patient with **life expectancy > 2 years**

MANAGEMENT – ABDOMINAL AORTIC ANEURYSM	
Indication for aneurysm repair (EVAR or open surgery)	• ≥ 55 mm or • Symptoms (pain) or • Progression > 10 mm per year (> 5 mm over 6 months) or • Infectious or inflammatory
AAA 30-39 mm	Surveillance every 3 years (progression ≈ 3 mm per year)
AAA 40-44 mm	Surveillance every 2 years
AAA > 45 mm	Surveillance every year

EVAR: endovascular AAA repair (for infra-renal AAA); anatomical suitability → proximal aortic neck (segment between the lowest renal artery and the proximal extent of the aneurysm) > 10-15 mm of length (and < 32 mm in diameter); adequate vascular access required

★ EVAR and ★ DREAM: surgical versus endovascular AAA repair; ↘ operative mortality with EVAR; **similar long term mortality; ↗ reintervention with EVAR**

SURGICAL AAA REPAIR SHOULD BE PREFERRED: anatomical criteria for EVAR not met or when regular long-term surveillance is impossible

- **Regular long-term surveillance following EVAR:** CT angiography or MR angiography at 1 month - 6 months - then annually; look for endoleakage, stent position, stability and exclusion of the aneurysm sac, stent fracture
- **Late complications of surgery**: para-anastomotic aneurysm; graft infection; graft-enteric fistula; imaging every 5 years

PATIENTS NOT CANDIDATES FOR SURGERY: significant comorbidities → no benefit of EVAR on long term survival (★EVAR 2)

8.4/ OTHER AORTIC DISEASES

AORTIC ATHEROSCLEROTIC PLAQUE

COMPLEX PLAQUE: Plaque thickness ≥ 4 mm or mobile / pedunculated debris (= thrombus) or ulceration

- ↗ embolic risk
- **Site**: particularly in the distal aortic arch and descending aorta

EMBOLISM: spontaneous or iatrogenic (post-intervention)

- **Thrombus (thromboembolism)**: thrombus forms on an unstable plaque then embolizes to a medium-to-large artery (stroke; TIA; leg ischemia; renal or splenic infarction; mesenteric ischemia)
  - Consider anticoagulation if complex plaque in aortic arch with stroke / TIA (class IIb)
- **Cholesterol crystals (atheroembolism)**: crystal emboli to small arterioles ("blue toe"; retinal ischemia / Hollenhorst plaques; Amaurosis fugax; TIA; Confusion; ARF; HTN; *Livedo reticularis*; Petechiae; Purpura; Intestinal ischemia; Pancreatitis)
  - **Hypocomplementemia; Eosinophilia**
  - **Consider endarterectomy or stent** in the presence of an identified source of embolism and recurrent atheroembolism

MANAGEMENT: Secondary prevention; ASA - Statin - control HTN / DM; smoking cessation

GENETIC AORTIC SYNDROMES

SYNDROME	DETAILS	FOLLOW–UP	MANAGEMENT
Marfan	• FBN1 mutation • Dilatation of aortic root **(annulo-aortic ectasia)** and ascending Ao; **Type A dissection** • Ghent diagnostic criteria ▶▶| - Chapter 7	• TTE at diagnosis and after 6 months (stability) then every 6-12 months • Follow-up by imaging of the entire aorta following repair of the ascending Ao	• BB; Losartan • **Surgery**: **A)** > 50 mm; **B)** Progression > 5 mm/y; **C)** Family history of dissection < 50 mm; **D)** Significant AR • **Desire for pregnancy**: surgery if ≥ 40 mm
Lœys-Dietz	• Autosomal dominant • TGFBR1 or 2 mutation • Tortuosities / aneurysms / artery dissection • Hypertelorism; Cleft palate or bifid uvula • **Aneurysm of the aortic root; Aortic dissection**	• Imaging of the entire aorta at diagnosis and after 6 months (stability) • **Annual MRI of the cerebrovascular circulation and as far as the pelvis**	• **Surgery if ascending Ao ≥ 42 mm (TEE; inner diameter) or ≥ 44 mm (CT or MRI; outer diameter)**
Ehlers-Danlos Type IV	• Autosomal dominant (COL3A1) • **Risk of artery rupture** (including thoracic and abdominal aorta) • **Risk of rupture of the uterus / intestine**		• Role of prophylactic repair remains uncertain (friable tissues) • Follow-up by imaging
Turner	• 45, X • Small stature; Ovarian insufficiency • **Bicuspid aortic valve (20%); CoA (10%); Ao aneurysm; Ao dissection**	• Look for risk factors of aortic dissection (bicuspid aortic valve / CoA / dilatation of thoracic Ao / HTN) • **In the presence of risk factors:** annual TTE • **Otherwise**: TTE every 3-5 years	• Surgery if maximum Ao area (cm^2) / patient's height (m) > 10 • Surgery if diameter > 25 mm/m^2
Non-syndromic familial thoracic aortic aneurysm and dissection	• Non-syndromic • Autosomal dominant • Variable penetrance • **Genes identified:** TGFBR1 and 2; ACTA2; MYH11; MYLK; PRKG1	• **Family screening:** 1st degree relatives of patients with unexplained dissection or aneurysm • **Genetic testing** if several family members are affected	• TGFBR mutation: similar management to that of Loeys-Dietz

VASCULITIS WITH AORTIC INVOLVEMENT

Destruction of vessels (inflammation; ↗ metalloproteinases; granulomas)

Takayasu	• **Vasculitis of the aorta and its branches (stenosis and/or aneurysm)** • **Diagnostic criteria**: < 40 years; Claudication (upper limbs or lower limbs); ↘ Brachial pulse; Aortic or subclavian murmur; sBP Difference > 10 mmHg arms; Stenosis of the Ao or its branches (CT angiography or MR angiography) • **Treatment:** Prednisone 50 mg; MTX; Azathioprine; Anti-TNFalpha
Giant cell arteritis (temporal arteritis)	• **Vasculitis of the aorta and its branches** • **Diagnostic criteria**: > 50 years; *de novo* headache; tenderness over temporal artery (or ↘ pulse); ↗ ESR (> 50 mm/h); Positive biopsy • Constitutional symptoms; Claudication of the jaw; Claudication of upper limbs; Visual symptoms; PMR; Aortic aneurysm / dissection • **Treatment**: Prednisone 50 mg
Behçet	• **Diagnostic criteria**: Mouth ulcers; Genital ulcers; Uveitis or retinal vasculitis; Erythema nodosum; Pseudofolliculitis; Pathergy • **Arterial involvement**: destruction of the media; aneurysm ± rupture (any artery can be affected)
Ankylosing spondylitis	• HLAB27+ • **Diagnostic criteria:** < 40 years; Low back pain; Morning stiffness; Slow progression; Improvement with exercise • AR; Dilatation of the aortic root

TRAUMATIC AORTIC RUPTURE

Predominantly involves the **aortic isthmus** (deceleration injury)

BP in arms > BP in legs; radiofemoral delay; interscapular murmur

CXR: widened mediastinum; displaced nasogastric tube (hematoma); Dilatation of aortic arch / descending aorta; pleural effusion

MANAGEMENT: TEVAR if suitable anatomy (or open surgery)

INFECTIOUS AORTITIS

Contiguous invasion or septic embolism (endocarditis) or hematogenous spread

SITE: on a pre-existing aortic lesion (aneurysm; atherosclerotic plaque; site of iatrogenic injury); predominantly involves the infrarenal aorta

MICROORGANISMS: *S. aureus; Salmonella;* Streptocoque; *E. coli; Neisseria;* Fungi; TB; Syphilitic aortitis (10-25 years post-infection)

COMPLICATIONS: saccular aneurysm; fistula; pseudo-aneurysm; rupture

8.5/ PERIPHERAL ARTERY DISEASE

PAD: cardiovascular risk equivalent to that of CAD

› **5-year mortality**: 10-15% (75% from cardiovascular causes)

RISK FACTORS: Smoking; DM; HTN; Dyslipidemia; Age; CRF; Chronic inflammation

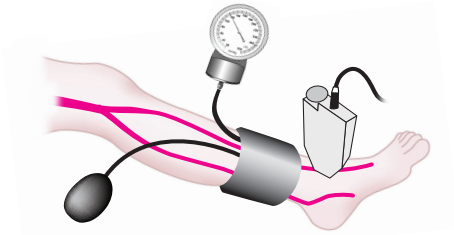
PRESENTATION: Asymptomatic; Intermittent claudication; Critical limb ischemia

CLINICAL FEATURES: ↘ pulse; murmur; pallor on elevation; ↗ erythema of limb in dependent position; coldness; muscle atrophy; hair loss; onychodystrophy; skin fissures; ulcers; devitalization - gangrene

FONTAINE CLASSIFICATION	
I	Asymptomatic
II	Intermittent claudication
IIa	Claudication > 200 m
IIb	Claudication < 200 m
III	Rest pain / night pain
IV	Ulcer / Gangrene

DDX: vasculitis (thromboangiitis obliterans; Takayasu; giant cell arteritis); CoA; fibromuscular dysplasia; external compression; radiotherapy; neurogenic claudication (lumbosacral radiculopathy); arthritis; myositis; venous insufficiency; popliteal artery entrapment syndrome

ANKLE-BRACHIAL INDEX



ABI ≤ 0.90	ABI 0.91 - 0.99	ABI 1.0 - 1.4	ABI > 1.4
Abnormal	**Gray zone**	**Normal**	**Calcified noncompressible artery**
• Mild: 0.8-0.9 • Moderate: 0.5-0.8 • Severe: < 0.5	ABI on exercise if persistent suspicion of PAD: diagnosis of vascular claudication if ABI ↘ by > 20-25 %		DM / CRF / Age → Use toe-brachial index (diagnostic if < 0.7)

ABI: ratio of sBP in ankle (posterior tibial artery or dorsalis pedis artery) / brachial artery

INDICATION FOR ABI: suspicion of PAD in the leg with:

› Suspected claudication; Poor wound healing; ≥ 50 years + [DM or Smoking]; ≥ 65 years; intermediate Framingham score

OTHER EXAMINATIONS: segmental BP measurements; Doppler US; MR angiography; CT angiography; Angiography

MANAGEMENT

MANAGEMENT OF RISK FACTORS: Smoking cessation; Statin; Treatment of DM (HbA1c < 7%); Control of BP; ACE inhibitors (★ HOPE)

ASA: ↘ mortality - stroke - myocardial infarction (★ Antithrombotic Trialists' Collaboration)

› **Indications**
  a) Symptomatic patient (claudication; critical limb ischemia; history of revascularization; history of amputation) (class I recommendation)
  b) Asymptomatic patient with ABI ≤ 0.90 (class IIa recommendation); limited evidence

› **Clopidogrel as alternative treatment**: superior to ASA in ★ CAPRIE; marginal benefit of ASA and Clopidogrel combination in ★ CHARISMA

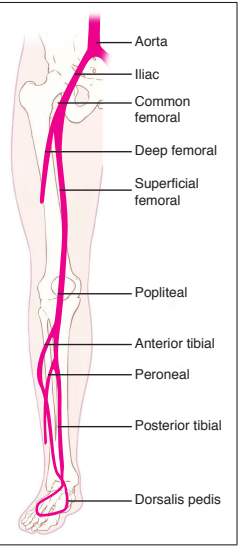
SUPERVISED EXERCISE PROGRAM: 30-45 min; 3 x / week ; > 12 weeks; ↗ exercise capacity

CILOSTAZOL (100 MG PO BID): phosphodiesterase-3 inhibitor; ↘ platelet aggregation; direct arterial vasodilator; contraindicated in the presence of heart failure; beware of drug interactions

PENTOXIFYLLINE (400 MG PO TID): phosphodiesterase inhibitor; ↘ blood viscosity; ↗ erythrocyte deformability; marginal efficacy

REVASCULARIZATION: Indications → **A)** Symptoms refractory to medical treatment with impaired quality of life; **B)** Critical limb ischemia

Aorto-iliac	• First-line endovascular revascularization (with stent) (TASC II type A - B - C) • Surgical revascularization: aortofemoral bypass graft with Dacron or PTFE prosthesis; femorofemoral bypass graft; axillofemoral bypass graft
Femoro-popliteal	• First-line endovascular revascularization (TASC II type A - B - C) • Stenting for intermediate length (TASC type II B) • Surgical revascularization: femoropopliteal bypass graft preferably with autologous venous conduit (or PTFE prosthesis)
Infra-popliteal (below the knee)	• Revascularization in the presence of persistent critical limb ischemia despite proximal revascularization • First-line endovascular revascularization • Stenting if suboptimal result • Surgical revascularization: femorotibial or femoroperoneal bypass graft (autologous venous conduit)



› **Mode of revascularization**: first-line endovascular treatment in most cases; decision by multidisciplinary team according to anatomy / durability / comorbidities / local expertise / patient preference
  • **Percutaneous revascularization**: medium- and long-term patency decreased in the presence of a distal lesion / lesion > 10 cm / multiple lesions / poor distal runoff / DM / CRF

- **Surgical revascularization:** preferred in the case of disseminated disease or technically difficult endovascular revascularization or TASC II type D (± type C)

› **Regular surveillance**: for all patients post-revascularization; history - ABI - physical examination; ± Doppler US (vein graft)

› **Antithrombotic therapy:** ASA for all patients; Clopidogrel 1 to 3 months post-stenting; consider Warfarin after bypass graft with vein graft

CRITICAL LIMB ISCHEMIA

DEFINITION: A) Ischemic pain at rest; B) Ischemic lesion (ulcer; gangrene)

› **sBP at ankle**: < 50 mmHg (rest pain) or < 70 mmHg (ischemic lesion)

ONE-YEAR MORTALITY: 25 %

MANAGEMENT: **A)** Analgesia; **B)** Urgent revascularization if tissues are still viable (endovascular if technically feasible); **C)** Amputation if tissues are devitalized; **D)** Secondary prevention - wound care - adjusted shoes - treatment of infectious complications

› ★ **BASIL**: revascularization by infrainguinal venous bypass graft similar to endovascular revascularization; ↘ reintervention with bypass graft; ↘ **mortality with bypass graft in patients surviving > 2 years**

ACUTE LIMB ISCHEMIA

MECHANISM: embolism (cardiac; Ao; peripheral arteries); thrombosis *in situ*; thromboembolism from a popliteal artery aneurysm (repair of aneurysm as primary prevention if > 20 mm); thrombosis of infrainguinal bypass graft; trauma; dissection; thrombophilia - hyperviscosity; *phlegmasia cerulea dolens*; iatrogenic (endovascular procedure; IABP; extracorporeal cardiac mechanical support)

PRESENTATION: Pain; Coldness; Pallor; Loss of pulse (Doppler PRN); Paresthesia / Sensory deficit; Weakness / Paralysis

MANAGEMENT: Medical emergency; **A)** IV Heparin; **B)** Percutaneous thromboembolectomy and/or direct intraarterial thrombolysis (first-line); **C)** Surgical revascularization (second-line)

ATHEROSCLEROSIS OF THE ARMS

Innominate / subclavian artery stenosis

SUBCLAVIAN STEAL SYNDROME: claudication of the arm; reversal of flow of the vertebral artery (vertigo; syncope; diplopia; dysarthria; ataxia) or of a mammary bypass graft (angina) to perfuse the arm

DETECTION: BP difference in arms ≥ 10 mmHg

TREATMENT: endovascular or surgical revascularization

8.6/ ATHEROSCLEROTIC RENOVASCULAR DISEASE

↘ Renal perfusion → activation of renin-angiotensin-aldosterone system → peripheral vasoconstriction + salt and water retention → HTN

BILATERAL RENAL ARTERY STENOSIS (OR FUNCTIONAL SOLITARY KIDNEY): ↗ BP (renin-angiotensin-aldosterone system) with salt and water retention in the absence of compensatory sodium excretion → flash pulmonary edema

CONSEQUENCES: Asymptomatic; HTN; Flash pulmonary edema - Diastolic dysfunction; Progressive deterioration of renal function (ischemic nephropathy; hypertensive nephropathy in contralateral kidney + proteinuria)

MANAGEMENT

POSSIBLE RENOVASCULAR HTN

a) Onset of HTN < 30 years (FMD) or > 55 years
b) Severe or refractory HTN
c) Underlying atherosclerosis
d) ↗ Creatinine ≥ 30% post-ACE inhibitors - ARB
e) Recurrent flash pulmonary edema
f) Unilateral atrophic kidney (asymmetry > 1.5 cm)

Screening → **DOPPLER US RENAL ARTERIES**

Diagnosis → **MR ANGIOGRAPHY OR CT ANGIOGRAPHY RENAL ARTERY ANGIOGRAPHY**

Renal artery stenosis

SECONDARY PREVENTION + ACE INHIBITORS (EXCEPT WHEN BILATERAL)

INDICATION FOR REVASCULARIZATION?

- Recurrent flash pulmonary edema
- Refractory HTN
- Progressive CRF (bilateral stenoses)

Yes

BENEFIT OF ANGIOPLASTY-STENTING?

	NORMAL PERFUSION	**ISCHEMIA** • FFR < 0.8 • Systolic gradient ≥ 20 mmHg • Technetium scan
NEPHROPATHY • Proteinuria • Atrophy • ↘ GFR • Resistance index > 0.8 (nephrosclerosis)	NO	±
NORMAL PARENCHYMA	NO	++

STUDY: no benefit with stenting in ★ CORAL

8.7/ CEREBROVASCULAR DISEASE

ETIOLOGIES – MECHANISMS

HEMORRHAGIC STROKE (20%)

INTRACEREBRAL HEMORRHAGE

RISK FACTORS: HTN; Trauma; Bleeding diathesis; Amyloid angiopathy; Vascular malformation; Tumor; Drugs

SUBARACHNOID HEMORRHAGE

- Ruptured aneurysm
- Explosive headache
- Blood in CSF

ISCHEMIC STROKE (80%)

ATHEROTHROMBOTIC (LARGE VESSELS)

- Intracranial or extracranial vessels
- Thrombosis *in situ* or Artery → artery embolism or Hypoperfusion
- ± Preceded by TIA in the same territory

CARDIOEMBOLIC

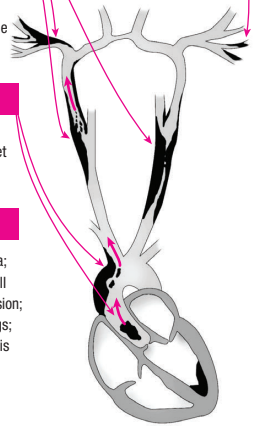
- Sudden onset
- Maximum deficit at onset
- Multiple territories

OTHER

Dissection; Thrombophilia; Hyperviscosity; Sickle-cell anemia; Systemic hypoperfusion; Arteritis; Vasospasm; Drugs; Cerebral venous thrombosis

LACUNAR (SMALL PENETRATING VESSELS)

- Lipohyalinosis (HTN; DM)
- Pure motor; Pure sensory; Hemiparesis / Ataxia; Dysarthria / Clumsy hand



TRANSIENT ISCHEMIC ATTACK (TIA)

TIA: transient episode (often < 1 h) of neurological dysfunction (focal cerebral or retinal or spinal ischemia) **in the absence of CNS infarction / permanent CNS injury**

ASSESSMENT: MRI (diffusion-weighted images - DWI) or brain CT scan; noninvasive imaging of head and neck vessels (carotid Doppler; CT angiography; MR angiography); ECG; TTE; ± TEE (cryptogenic TIA; suspicion of cardioembolic TIA); Holter; ± Evaluation of intracranial arteries (CT angiography or MR angiography or angiography or transcranial Doppler)

- **Evaluation of hereditary thrombophilia**: thrombophilia associated with venous >>> arterial thromboses; consider in the presence of cryptogenic TIA or suspected antiphospholipid syndrome (miscarriages; venous thrombosis; *livedo reticularis*) or personal or family history of systemic thrombosis
  - **Look for**: protein C or S or antithrombin III deficiency; Leiden factor V; prothrombin mutation G20210A; lupus anticoagulant; anticardiolipin antibody

EVALUATION OF THE SHORT-TERM RISK OF STROKE

ABCD² SCORE		
≥ 60 years	1 point	48-hour stroke risk 0-1: 0 % 2-3: 1 % 4-5: 4 % 6-7: 8 %
BP ≥ 140/90	1 point	
Dysphasia without weakness or Unilateral weakness	1 point 2 points	
Diabetes	1 point	
Duration 0-59 min Duration ≥ 60 min	1 point 2 points	

Rothwell OM, Giles MF, Flossmann E, et al. Lancet. 2005; 366: 29-36.
Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Lancet. 2007; 369: 283-92.

CARDIOEMBOLIC SOURCE

ASSESSMENT: ECG; 24-hour monitor / Holter; TTE; TEE

› **Additional ambulatory electrocardiographic monitoring** beyond 24-hour for subclinical AF detection if cardioembolic TIA suspected (★ EMBRACE; ★ CRYSTAL-AF)

HIGH CARDIOEMBOLIC RISK	POTENTIAL CARDIOEMBOLIC RISK
• LA (LAA) or LV thrombus • AF - Flutter • Recent MI (< 1 month) • Rheumatic MS • Prosthetic valve • Severe LV dysfunction • Infective endocarditis • Noninfective endocarditis (Libman-Sacks; Antiphospholipid syndrome; Nonbacterial thrombotic endocarditis) • Myxoma - Fibroelastoma • ASD or VSD	• Complex atherosclerosis of the aorta • Aortic valve disease • Mitral annular calcification • MVP • PFO • Atrial septal aneurysm • LV aneurysm without thrombus • Spontaneous echo contrast in LA • Regional wall motion abnormality • HCM • LV noncompaction

ISCHEMIC STROKE

NIH STROKE SCALE (NIHSS): QUANTIFICATION OF NEUROLOGICAL IMPAIRMENT	
Level of consciousness	0 - Alert; 1 - Drowsy; 2 - Stuporous; 3 - Comatose
Orientation (2 questions)	0 - 2/2; 1 - 1/2; 2 - 0/2
Response to 2 commands	0 - 2/2; 1 - 1/2; 2 - 0/2
Gaze	0 - Normal lateral eye movements 1 - Partial gaze palsy 2 - Complete palsy
Visual fields	0 - No visual loss 1 - Partial hemianopia 2 - Complete hemianopia 3 - Bilateral hemianopia

Facial palsy	0 - Normal 1 - Minor paralysis 2 - Partial paralysis 3 - Complete paralysis
A) Motor function - left arm **B) Motor function - right arm**	0 - No drift 1 - Drift in 5 s 2 - Some effort against gravity; limb falls in 10 s 3 - No effort against gravity 4 - No movement
A) Motor function - left leg **B) Motor function - right leg**	0 - No drift 1 - Drift in 5 s 2 - Some effort against gravity; limb falls in 10 s 3 - No effort against gravity 4 - No movement
Ataxia	0 - Absent 1 - Present in one limb 2 - Present in two limbs
Sensory	0 - Normal 1 - Mild-to-moderate sensory loss 2 - Severe to total sensory loss
Language	0 - No aphasia; normal 1 - Mild-to-moderate aphasia 2 - Severe aphasia 3 - Mute, global aphasia
Dysarthria	0 - Normal 1 - Mild-to-moderate dysarthria 2 - Severe dysarthria
Extinction and Neglect	0 - No abnormality 1 - Visual, tactile, auditory, spatial, or personal inattention or extinction (1 sensory modality) 2 - Profound hemi-inattention or extinction to more than one modality

IMMEDIATE MANAGEMENT: ABC; Cardiac monitor (> 24 h); IV line; O2 (if $SaO_2 < 94\%$); Blood glucose; NPO

EXAMINATIONS: Unenhanced brain CT scan; Blood glucose; ECG; Electrolytes; Renal function; CBC; PT-aPTT; Troponin; ± Lumbar puncture (if suspicion of SAH and in the absence of bleeding on CT scan); ± EEG (rule out seizures)

DDX: Conversion; Hypertensive encephalopathy; Hypoglycemia; Complicated migraine; Seizures; Poisoning

INTRAVENOUS THROMBOLYSIS: **rtPA 0.9 mg/kg IV (max 90 mg) over 60 min** (10% of dose as a bolus over 1 min)

- ★ **NINDS rtPA Stroke Study**: < 3 h after onset of symptoms; improvement of neurological recovery at 3 months; similar mortality to that with placebo; cerebral hemorrhage in 6% of patients
  - **3 to 4.5 h of symptoms:** ★ ECASS-3; improvement of neurological recovery at 3 months
- **Post-thrombolysis**: intensive care; monitoring of neurological signs every 15-30 min for 6 h, then hourly for 24 h; Brain CT scan STAT if suspicion of intracranial hemorrhage; BP every 15-30 min for 6 h then hourly for 24 h; target BP < 180/105; repeat CT scan after 24 h

CANDIDATES FOR INTRAVENOUS THROMBOLYSIS	
< 3 h after onset of symptoms	**3 to 4.5 h after onset of symptoms**
A) Ischemic stroke with measurable neurological deficit (not minor); B) Absence of improvement of neurological deficit; C) Caution in the presence of major neurological deficit (risk of hemorrhagic transformation); D) Absence of SAH; E) Absence of head injury or stroke < 3 months; F) Absence of myocardial infarction < 3 months (risk of myocardial rupture; relative contraindication); G) Absence of GI or urinary bleeding < 21 days; H) Absence of major surgery < 14 days; I) Absence of noncompressible arterial puncture < 7 days; J) Absence of history of intracranial hemorrhage; K) Absence of CNS neoplasm / AVM / intracranial aneurysm; L) Absence of recent intracranial or spinal surgery; M) BP < 185/110; N) Absence of active internal bleeding; O) INR < 1.7; P) DOAC: normal sensitive detection test or last dose > 48 h (with normal renal function); Q) Normal aPTT if heparin received < 48 h; R) Platelet count > 100,000 mm3; S) Blood glucose > 2.7 mmol/L; T) Absence of seizures with residual neurological impairment; U) Brain CT scan: absence of multilobar infarction (1/3 of a cerebral hemisphere)	Same criteria as for thrombolysis < 3 h of symptoms + **Exclusion criteria:** a) > 80 years b) Oral anticoagulants c) NIHSS > 25 d) History of stroke + DM e) Ischemic lesion > 1/3 of the middle cerebral artery territory

INTRAARTERIAL REVASCULARIZATION

- ★ **MR CLEAN**: stroke < 6 h + proximal occlusion in the anterior cerebral circulation; 89% treated with IV tPA before randomization; intraarterial thrombolysis and/or mechanical thrombectomy versus usual care; benefit on the functional outcomes
- ★ **ESCAPE**: stroke < 12 h + proximal intracranial occlusion in the anterior circulation; early thrombectomy associated with improved functional outcome and ↘ mortality

MANAGEMENT OF BP

- **BP > 220/120 mmHg**: 10-15% ↘ BP for 24 h (Nicardipine; Labetalol)
- **Thrombolysis considered**: target BP < 185/110
  - Labetalol 10-20 mg IV x 1-2 min (can be repeated once)
  - Nicardipine: 5 mg/h (titrate every 5-10 min up to 15 mg/h; when target BP has been achieved → 3 mg/h infusion)
- **Post-thrombolysis**: Labetalol 10 mg IV x 1-2 min (then every 10-20 min; max 300 mg) or Labetalol 10 mg IV then 2-8 mg/min infusion or Nicardipine (as above)
- **Post-stroke (long-term)**: target BP < 140/90 (ACE inhibitors and/or diuretics); resume antihypertensives 24 h after stroke

ASA: 325 mg in < 48 h (> 24 h in the case of thrombolysed stroke); benefit on the morbidity - mortality

OTHER TREATMENTS: **A)** Thromboprophylaxis / sequential compression device; **B)** Detection of dysphagia (water swallow test); **C)** Target normothermia and normoxemia; **D)** Nutritional support; **E)** Insulin if blood glucose > 10.3 mmol/L (avoid hypoglycemia); **F)** Rehabilitation

SECONDARY PREVENTION

RISK FACTORS: ▸▸| Chapter 9; Treatment of HTN (from 24 h); Smoking cessation; Treatment of dyslipidemia (★ SPARCL); Treatment of DM; Moderate alcohol intake; Regular moderate physical exercise; Healthy weight; Balanced diet; Treat OSAHS

ANTIPLATELET THERAPY: indicated in a context of noncardioembolic TIA or ischemic stroke; ASA (50 to 325 mg daily) or ASA 25 mg / Dipyridamole 200 mg bid or Clopidogrel 75 mg daily

- **Evidence:** similar outcomes with Clopidogrel versus ASA / Dipyridamole (★ PRoFESS); no benefit of long-term combination of Clopidogrel and ASA (★ MATCH); ↘ adverse events with ASA / Dipyridamole versus ASA (★ ESPS-2; ★ ESPRIT)

ATRIAL FIBRILLATION: Warfarin (★ EAFT) or DOAC for secondary prevention

- **Initiation of A/C in acute stroke**: according to the severity of the stroke (risk of hemorrhagic transformation); anticoagulant therapy initiated < 14 days in ★ EAFT; wait 72 h for small stroke or 1 week for moderate stroke or 2 weeks for large stroke; no benefit of Heparin bridge
- **WATCHMAN**: LAA occlusion device; ★ PROTECT AF (noninferior to warfarin); consider when anticoagulation is contraindicated

LVEF ≤ 35 %: no evidence in support of warfarin for secondary prevention; Warfarin or ASA or Clopidogrel or ASA / Dipyridamole

RHEUMATIC MITRAL STENOSIS: Warfarin

NONRHEUMATIC VALVULAR HEART DISEASE: Aortic or mitral valve disease or mitral annular calcification or MVP; Antiplatelet therapy (IIb; C)

PFO: controversial subject; ▸▸| Chapter 7 - Congenital heart disease

THROMBOPHILIA: associated with venous >>> arterial thromboses; anticoagulation if concomitant DVT; Antiplatelet therapy or anticoagulation in the absence of DVT or an identifiable cause of stroke

- **Antiphospholipid syndrome**: anticoagulation indicated

CAROTID ARTERY REVASCULARIZATION

SYMPTOMATIC CAROTID ARTERY STENOSIS: benefit of surgical revascularization compared to medical treatment (★ NASCET; ★ ECST; ★ VACS); NNT = 6

ASYMPTOMATIC CAROTID ARTERY STENOSIS: benefit of surgical revascularization in selected patients (★ ACAS and ★ ACST; studies conducted prior to the introduction of modern medical treatment); NNT = 33

ANGIOPLASTY-STENTING VERSUS ENDARTERECTOMY: **comparable long-term outcomes** (★ CREST; ★ SAPPHIRE)

- **Angioplasty-Stenting**: increased risk of periprocedural stroke compared to endarterectomy (particularly in patients > 70 years)
- **Prefer angioplasty-stenting**: anatomical / technical considerations (post-radiation; post-surgical; obesity; hostile neck; stenosis at different level); high operative risk - severe comoborbidities
- **Dual antiplatelet therapy**: 4 weeks

REVASCULARIZATION IN THE PRESENCE OF MULTIPLE COMORBIDITIES: little evidence in favor of surgical or endovascular revascularization (NYHA III-IV; CCS III-IV; CAD ≥ 2 vessels or LMCA; LVEF ≤ 30%; recent myocardial infarction; severe lung disease; advanced CRF)

	SYMPTOMATIC (< 6 MONTHS)		ASYMPTOMATIC
	Carotid artery stenosis: 50-69% (angiography)	**Carotid artery stenosis: 70-99% (noninvasive imaging)**	**Carotid artery stenosis > 70%**
Endarterectomy	**I; B**	**I; A**	**IIa; A**
	To be performed within 14 days of the neurological event unless contraindicated (IIa; B)		Mortality - perioperative stroke < 3% Life expectancy > 5 years
	Mortality - perioperative stroke < 6% Life expectancy > 5 years		
Angioplasty-Stenting	Alternative to surgery: I; B	Alternative to surgery: I; B	IIb; B (controversial)
	Mortality - perioperative stroke < 5%		

INTRACRANIAL HEMORRHAGE

MANAGEMENT: Intensive care; Neurosurgical assessment; Target normothermia; Target blood glucose < 10.3 mmol/L; Thromboprophylaxis (sequential compression device; IVC filter PRN); Phenytoin in the presence of seizures; ± Continuous EEG monitoring

ANTICOAGULATION: Discontinue anticoagulation and antiplatelet therapy for more than 1-2 weeks and subsequently reassess the indication; weigh up the thromboembolic risk against the bleeding risk (high in cortical stroke secondary to amyloid angiopathy)

- **Reverse Warfarin**: **prothrombin complex concentrate** (Octaplex; Beriplex; Cofact; Proplex); complex of factors II - VII - IX - X; Target INR < 1.4
  - **Vitamin K**: 10 mg IV (max 1 mg/min)
  - **Fresh frozen plasma**: 8 units when prothrombin complex concentrate is not available

BLOOD PRESSURE: treat if sBP > 180 mmHg in the absence of intracranial hypertension; target BP < 160/90 (labetalol; nicardipine; esmolol; enalapril; hydralazine; nitroprusside; TNT)

CONTROL OF INTRACRANIAL HYPERTENSION: target cerebral perfusion pressure > 60 mmHg (MAP - ICP) and ICP < 20-25 mmHg; raise head of bed by 30°; analgesia; control of BP (target SBP < 180 mmHg and MAP < 130 mmHg, while maintaining adequate cerebral perfusion pressure); ventriculostomy (external CSF drainage); IV mannitol (target plasma osmolality: 300-310 mOsmol/kg); sedation; hyperventilation ($PaCO_2$: 30-35 mmHg); neuromuscular blockade; surgical evacuation of hematoma; barbiturate-induced coma

8.8/ PULMONARY EMBOLISM

RISK FACTORS: Age; Personal or family history of pulmonary embolism; Cancer; Trauma; Surgery; Immobilization; Pregnancy; Hormonal therapy; Oral contraceptive; Nephrotic syndrome; Chemotherapy

- **Thrombophilia**: Homozygous factor V Leiden; Homozygous prothrombin G20210A; Protein C deficiency; Protein S deficiency; Antiphospholipid syndrome / Lupus anticoagulant

PRESENTATION: Dyspnea; Pleuritic pain; Retrosternal chest pain; Cough; Hemoptysis; Paradoxical embolism; Syncope; Sudden death - Pulseless electrical activity

CLINICAL FEATURES: Tachypnea; Tachycardia; ± Shock; ± Cyanosis (R→ L shunt via PFO); ↘ SaO_2; Low-grade fever; JVD; Left parasternal heave; ↗ P2; TR murmur; right S3 or S4; Pleural friction rub (pulmonary infarction); signs of DVT in leg (edema; erythema; heat; pain; difference between legs)

D-DIMERS: **very sensitive but not specific**

ECG: Sinus tachycardia; S1Q3T3; *de novo* RBBB; T wave inversion (V1 to V4; inferior leads); Q in III and aVF; Qr in V1; ST depression or ST elevation in V1-V4; right axis deviation; AF / Flutter

CXR: PA dilatation; Atelectasis; Elevation of the diaphragm; Pleural effusion

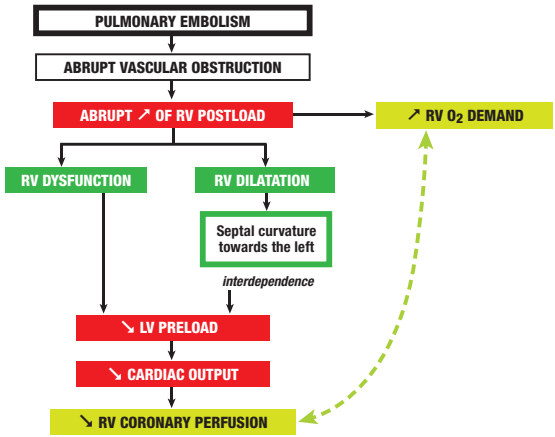
- **Westermark sign:** Segmental oligemia secondary to proximal arterial occlusion
- **Hampton hump**: Triangular hyperdensity adherent to the pleura secondary to pulmonary infarction (consolidation with hemorrhage)

TTE: RV dilatation (↗ acute afterload); RV hypokinesia; PHT (non-preconditioned RV is unable to genereate a mPAP > 40 mmHg); TR; shunt via PFO; thrombus-in-transit visible in right chambers / PA; septal curvature towards the LV; dilated and noncompliant IVC

- **McConnell's sign: hypokinesis of basal / mid RV free wall (preserved apex contractility)** +

LEG ULTRASOUND: look for ↘ vein compressibility

CONSEQUENCES OF PULMONARY EMBOLISM

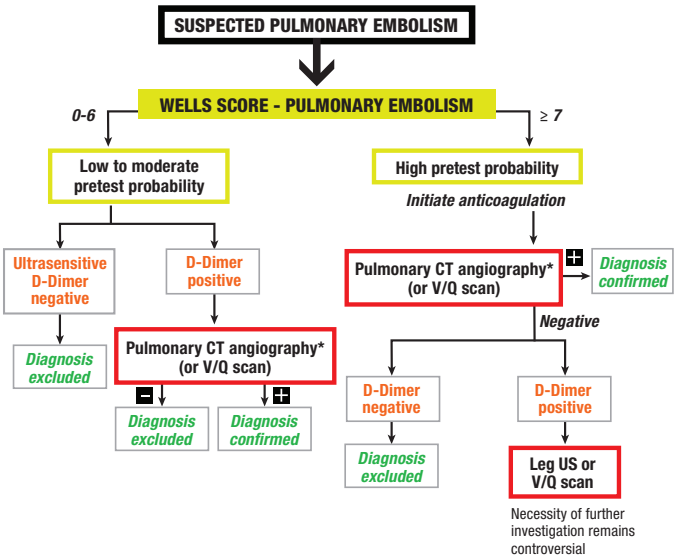


ASSESSMENT

WELLS CRITERIA – PRETEST PROBABILITY – DEEP VEIN THROMBOSIS		
Active cancer	1 point	• **0 point**: low pretest probability • **1-2 points:** moderate pretest probability • **≥ 3 points:** high pretest probability
Paralysis or recent cast immobilization	1 point	
Bedridden > 3 days or surgery < 4 weeks	1 point	
Local vein tenderness	1 point	
Swelling of entire leg	1 point	
Difference between calves > 3 cm	1 point	
Pitting edema	1 point	
Superficial collateral vein	1 point	
Alternative diagnosis at least as likely	- 2 points	

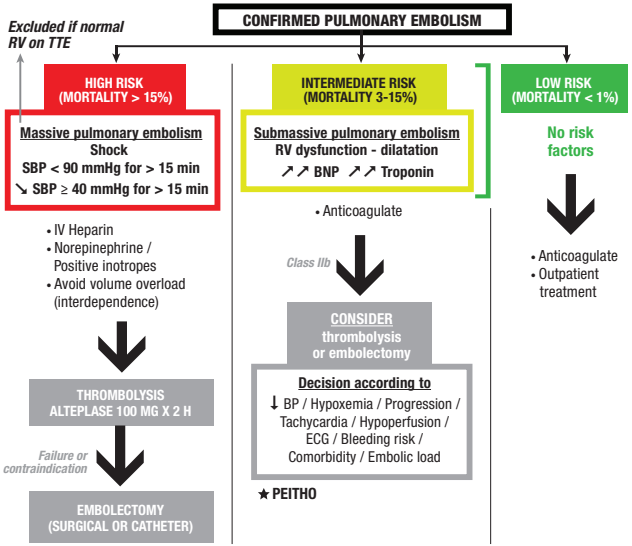
WELLS CRITERIA – PRETEST PROBABILITY – PULMONARY EMBOLISM		
Signs or symptoms of DVT	3 points	• **0-1 point**: low pretest probability (10%) • **2-6 points**: moderate pretest probability (30%) • **≥ 7 points**: high pretest probability (65%)
Alternative diagnosis is less likely	3 points	
HR > 100 bpm	1.5 points	
Immobilization or surgery < 4 weeks	1.5 points	
History of DVT or pulmonary embolism	1.5 points	
Hemoptysis	1 point	
Cancer (< 6 months or metastasis)	1 point	

Wells PS, Anderson DR, Bormanis J, et al, Lancet 1997; 350:1795
van Belle A, et al. JAMA 2006; 295:172



*** Interpret according to:**
A) Pretest probability
B) Site of thrombus (main PA or lobar or segmental versus subsegmental PA)

MANAGEMENT



★ **PEITHO**: PE with RV dysfunction and ↗ Troponin; Tenectaplase + Heparin vs Heparin; ↘ Haemodynamic decompensation; similar all-cause 7-day mortality; ↗ intracranial bleeding; ↗ major hemorrhage

Unfractionated heparin	• IV bolus: 80 IU/kg • IV infusion: 18 IU/kg/h (target aPTT 1.5-2.5 x control or 60-80 s)	
Enoxaparin	• 1 mg/kg SC bid or 1.5 mg/kg qd	**LMWH** • Better bioavailability • More predictable effect • Avoid if GFR < 30 mL/min
Dalteparin	• 100 IU/kg SC bid or 200 IU/kg qd	
Tinzaparin	• 175 IU/kg SC bid	
Fondaparinux	• < 50 kg: 5 mg SC qd • 50-100 kg: 7.5 mg SC qd • > 100 kg: 10 mg SC qd	• Indirect Xa inhibitor • Avoid if GFR < 30 mL/min
History of HIT	Argatroban or Bivalirudin or Lepirudin or Danaparoid	

WARFARIN: **anticoagulant effect in 5 days**

› **Initially procoagulant effect:** due to ↘ proteins C and S

› **Overlapping of warfarin with Heparin ≥ 5 days (and ≥ 24 h with INR ≥ 2.0)**

Provocated pulmonary embolism or proximal DVT (secondary to surgery; trauma; pregnancy; hormonal therapy)	Thromboembolism and active cancer	Idiopathic or recurrent pulmonary embolism (or proximal DVT)
Anticoagulation x 3 months	LMWH (★ CLOT) Continue in the presence of active cancer (warfarin as alternative)	Anticoagulation x ≥ 3 months and consider long-term treatment (according to balance between the risks of recurrence and bleeding)

DOAC IN ACUTE PHASE OF THROMBOEMBOLIC DISEASE: ★ EINSTEIN (Rivaroxaban 15 mg bid x 3 weeks then 20 mg qd); ★ AMPLIFY (Apixaban 10 mg bid x 7 days then 5 mg bid)

SECONDARY PREVENTION (after acute phase): Options → **A)** Warfarin; **B)** Rivaroxaban 20 mg qd (★ EINSTEIN-extension); **C)** Apixaban 2.5 mg bid (★ AMPLIFY-extension); **D)** Dabigatran 150 mg bid (★ RE-SONATE and ★ RE-MEDY); **E)** ASA 100 mg qd (★ ASPIRE and ★ WARFASA)

IVC FILTER: Indications → **A)** Bleeding / Contraindication to anticoagulation; **B)** Recurrent pulmonary embolism despite treatment (in the presence of a proximal thrombosis)

- ↘ Pulmonary embolism recurrence rate; ↗ DVT recurrence rate
- **Complications:** access site complication; recurrent DVT; IVC thrombosis; IVC perforation; migration; post-thrombotic syndrome
- Resume anticoagulation and **remove** the filter as soon as possible

INTRAVENOUS THROMBOLYSIS: ↘ mortality in massive pulmonary embolism

- **Alteplase 100 mg IV x 2 h** (without heparin); resume heparin without bolus at the end of thrombolysis if aPTT ≤ 80 s

CATHETER-ASSISTED THROMBUS REMOVAL

- **Indications**: Hemodynamic instability with → **A)** Contraindication to thrombolysis or **B)** Failure of thrombolysis (rescue)
  - **Consider surgery** in the presence of mobile thrombus-in-transit in right chambers or thrombus-in-transit in PFO

LOCAL CATHETER THROMBOLYSIS FOR DVT: A) Extensive ilio-femoral thrombosis with low bleeding risk (including *phlegmasia cerulea dolens*); **B)** Progression of thrombus despite treatment; **C)** Extensive upper extremity DVT (subclavian and axillary veins)

- **Benefit:** ↘ risk of postthrombotic syndrome
- **Pharmacomechanical approach**: local thrombolysis combined with catheter thrombectomy ± balloon venoplasty (± stent)

UPPER EXTREMITY DVT: Risk factors → central catheter; pacemaker; thoracic outlet syndrome (Paget-Schroetter disease); Cancer

- Risk of complications in the case of proximal DVT (starting at axillary vein)
- **Risk of PE**: 10 %
- **Anticoagulation**: ≥ 3 months
  - It is acceptable to observe upper extremity DVT **distal to the axillary vein**

POSTTHROMBOTIC SYNDROME: varicosities; hyperpigmentation; ulcers

- **Compression stockings**: 30-40 mmHg
- Consider angioplasty ± stenting in the presence of iliac vein obstruction

THROMBOPROPHYLAXIS IN MEDICALLY HOSPITALIZED PATIENTS

- **Unfractionated heparin:** 5000 IU SC bid or tid
- **LMWH**: Enoxaparin 40 mg SC qd or Dalteparin 5000 U SC qd
- **Fondaparinux:** 2.5 mg SC qd (useful in patients with a history of HIT)
- **Intermittent pneumatic compression**: contraindication to anticoagulants or multiple risk factors (with anticoagulant)

8.9/ HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

TYPE 1 HIT: Benign form

TYPE 2 HEPARIN-INDUCED THROMBOCYTOPENIA

Immune form (IgG)

PATHOPHYSIOLOGY: Antibody directed against neoantigens on protein PF4 (protein released by activated platelets)

› Neoantigens are exposed following binding of PF4 with heparin → IgG binds simultaneously to the heparin-PF4 complex and to platelet Fc receptors → platelet activation with release of prothrombotic molecules → platelet consumption + intense thrombin production → multiple thromboses (venous or arterial)

5-10 days post-exposure to heparin (or earlier in the case of re-exposure < 3 months)

↘ > 50% of platelets (compared to baseline count) or thrombosis beginning 5-10 days after the start of heparin

4 T SCORE			
	2 POINTS	**1 POINT**	**0 POINT**
Thrombo-cytopenia	> 50% decrease in platelet count and nadir ≥ 20,000/µL and no surgery in past 3 days	• > 50% decrease in platelet count and surgery in past 3 days or • 30-50% decrease in platelet count or • Nadir 10,000-20,000/µL	• < 30% decrease in platelet count or • Nadir < 10,000/µL
"Timing" (post-exposure)	Day 5 to Day 10 (or ≤ 1 day if prior heparin exposure within 30 days)	Uncertain interval (but probably between Day 5 and Day 10) or after Day 10 (or ≤ 1 day if prior heparin exposure within 30-100 days)	Decrease in platelet count ≤ Day 4 (no other heparin therapy during past 100 days)
Thrombosis	Confirmed new thrombosis; Skin necrosis at injection site; Anaphylactoid reaction to IV heparin bolus	Recurrent venous thrombosis while on anticoagulant therapy or suspected thrombosis or nonnecrotic skin lesions at injection site	None
oTher causes	No alternative cause to explain thrombocytopenia	Possible alternative cause	Probable alternative cause (recent surgery; bacteremia; chemotherapy; drugs…)

6-8 points: high probability (34%)
4-5 points: intermediate probability (11%)
0-3 points: low probability (0.9%)

Lo GK, Warkentin TE, Sigouin CS et al. J Thromb Haemost. 2006; 4: 759-65.

DIAGNOSTIC WORK-UP: to be performed in the case of intermediate to high probability (4 T score)

- **ELISA assay of anti-PF4 antibodies** (excellent NPV but low PPV)
- **Serotonin-release assay** (platelets containing labeled serotonin placed in contact with the patient's plasma and heparin); gold standard diagnostic test

PREVENTION: CBC every 2-3 days (starting on Day 5 of heparin therapy)

MANAGEMENT OF TYPE 2 HIT

1) Stop all forms of heparin
2) Argatroban or Bivalirudin or Fondaparinux or Danaparoid
3) Initiate Warfarin **once the thrombocytopenia has resolved** (with IV co-administration of a direct thrombin inhibitor; overlapping for ≥ 5 days; discontinue after achieving therapeutic INR for 2 days); anticoagulation ≥ 3 months if confirmed thrombosis
   - If the patient is treated with Warfarin at the time of HIT: reverse with vitamin K

8.10/ PULMONARY HYPERTENSION

PHT	GROUP 1–3–4–5 PHT	POSTCAPILLARY (GROUP 2)
mPAP ≥ 25 mmHg	mPAP ≥ 25 mmHg Wedge ≤ 15 mmHg	mPAP ≥ 25 mmHg and Wedge > 15 mmHg
		Isolated postcapillary: dPAP - Mean Wedge < 7 mmHg and/or PVR ≤ 3 WU
		With precapillary component: dPAP - Mean Wedge ≥ 7 mmHg and/or PVR > 3 WU

ETIOLOGIES

	mPAP ≥ 25 mmHg; Wedge ≤ 15 mmHg; PVR ≥ 3 WU
Group 1: Pulmonary arterial hypertension (PAH)	• **Idiopathic PAH** • **Heritable PAH** - BMPR2; ALK1; Endoglin; SMAD9; CAV1; KCNK3 mutation - Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu) • **PAH secondary to drugs - toxins** (Anorectics; Cocaine; Amphetamines) • **PAH associated with** - **Collagen diseases** › Scleroderma - CREST; SLE; Mixed connective tissue disease; RA; Sjögren; Dermatomyositis - **HIV** - **Portal hypertension** (Cirrhosis) › Liver transplantation contraindicated if mPAP ≥ 35 mmHg or PVR > 250 dyn x s / cm^5 - **Congenital heart disease** (Shunt) › VSD; Patent ductus arteriosus; ASD; Anomalous pulmonary venous return; AV canal defect; Complex congenital heart disease - **Schistosomiasis**

Group 1`	• **Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis** - Similar presentation to that of PAH - Suspect in the presence of pulmonary edema following administration of pulmonary artery vasodilators - Characteristic changes on pulmonary HDCT (subpleural thickened septal lines; centrilobular ground-glass opacities; lymphadenopathy)
Group 2: PHT secondary to left heart disease	**mPAP ≥ 25 mmHg; Wedge > 15 mmHg** • LV systolic dysfunction • LV diastolic dysfunction • Left-sided valvular heart disease • Pulmonary veins stenosis
Group 3: Pulmonary hypertension secondary to lung disease	• COPD • Interstitial lung disease • Mixed lung disease • Sleep-disordered breathing • Alveolar hypoventilation • High altitude
Group 4	• Thromboembolic pulmonary hypertension
Group 5: Uncertain mechanism	• **Hematological disease**: Myeloproliferative disease (Polycythemia vera; Essential thrombocytosis; CML); Splenectomy; Chronic hemolytic anemia (Sickle-cell anemia; Hereditary spherocytosis; Homozygous beta-thalassemia) • **Systemic disease**: Sarcoidosis; Langerhans cell histiocytosis; Lymphangioleiomyomatosis; Neurofibromatosis; Vasculitis • **Metabolic disease**: Glycogen storage disease; Gaucher; Thyroid disease • **Other**: Neoplastic obstruction; Fibrosing mediastinitis; Dialysis
Reversible causes of PHT secondary to ↗ transpulmonary blood flow Exercise; Anemia; Pregnancy; Sepsis; Hyperthyroidism; Volume overload	

ASSESSMENT

PRESENTATION: Dyspnea on exertion; Fatigue; Retrosternal chest pain; Syncope; Palpitations; Leg edema; Ortner's syndrome (recurrent laryngeal nerve compression by dilated PA); Hemoptysis

CLINICAL FEATURES: Hypotension; Cold extremities; ± Cyanosis; JVD (↗ A wave; ↗ V wave); left parasternal heave; Pulmonary artery palpable in left second intercostal space; ↗ P2; Ejection click / Systolic ejection murmur at pulmonary site; Holosystolic murmur (TR; ↗ on inspiration); PR murmur (Graham-Steel); Right S3 and/or S4; Pulsatile liver; Anasarca

› Look for signs of collagen disease (sclerodactyly; arthritis; telangiectasias; Raynaud; rash) and liver disease (spider naevi; testicular atrophy; palmar erythema); look for clubbing

ASSESSMENTS: HIV; ANA; RF; LFTs (± liver US); BNP; TSH; Thrombophilia screening (group 4)

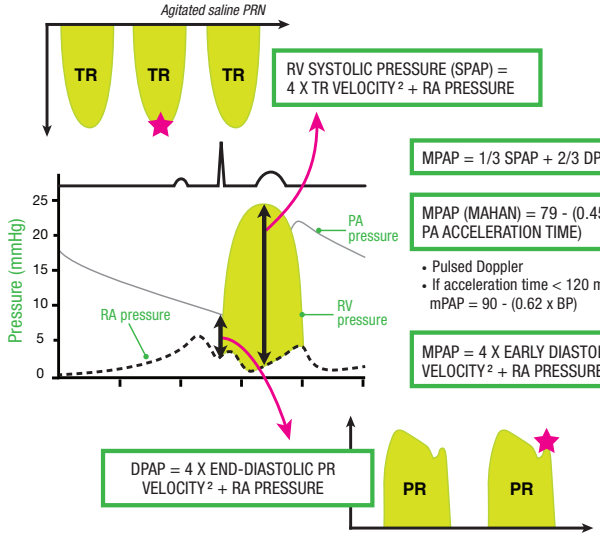
ECG: RAH; RVH; R axis deviation; T wave inversion in R precordial leads; RBBB; Atrial arrhythmias

CXR: central PA dilatation; RA-RV dilatation; pruning (loss) of the peripheral blood vessels (oligemia)

TTE: ↗ PAP; RA and RV dilatation (RV / LV basal diameter ratio > 1.0); PA dilatation (> 25 mm); RVH; RV dysfunction (RIMP - S' - TAPSE - Strain); Curvature of the septum towards LV; Small left chambers; TR; Pericardial effusion; Look for shunt; Look for cause of PHT due to heart disease

› **Screening**: **A)** Scleroderma: annually (+ DLCO / biomarkers); **B)** Sickle-cell anemia: annually

TTE (CONTINUED)



CARDIAC MRI: More favorable prognostic factors → Ejection volume > 25 mL/m² or RV end-diastolic volume < 84 mL/m² or LV end-diastolic volume > 40 mL/m²

PULMONARY ASSESSMENT: CXR; PFTs; Pulmonary high-resolution CT; Arterial blood gases; V/Q scan (± CT angiography / pulmonary angiography); Nocturnal saturometry / Polysomnography

- **PFTs**: PAH associated with mild-to-moderate ↘ lung volumes and ↘ DLCO (40 to 80% of predicted)
- **Rule out thromboembolic PHT (Group 4) in all patients by V/Q scan** +

RIGHT/LEFT CATHETERIZATION

- **Look for a shunt** (oximetry run)
- **Wedge pressure** (end of expiration) ± LVEDP; 500 mL bolus PRN to reveal diastolic dysfunction
- **Cardiac output**: Thermodilution (in the absence of significant TR or low output state or shunt) or Fick
- **PVR (WU)** = **mPAP - Wedge / Cardiac output**
- **Diastolic pressure gradient** = **dPAP - Mean Wedge**
- **Vasoreactivity test** (Idiopathic PAH; Heritable PAH; Drug-induced PAH)
  - **Positive**: **absolute ↘ of mPAP ≥ 10 mmHg (to mPAP < 40 mmHg) in the absence of ↘ cardiac output** +

INHALED NO (FIRST LINE)	IV EPOPROSTENOL	IV ADENOSINE
10 to 20 ppm	2 - 12 ng/kg/min	50 to 350 µg/kg/min

- **Hepatic venous pressure gradient** = **Wedged hepatic venous pressure - IVC pressure;** normal value between 1-5 mmHg (≥ 10 mmHg → portal hypertension / cirrhosis)

MONITORING OF FUNCTIONAL CAPACITY: WHO functional class (equivalent to NYHA); 6MWT; Stress test; Cardiopulmonary test / VO_2 max

MANAGEMENT

O_2 (target: SaO_2 > 90% and PaO_2 > 60 mmHg)

AVOID PREGNANCY

REHABILITATION / AEROBIC EXERCISE PROGRAM

AVOID HIGH ALTITUDE; O_2 in plane when SaO_2 < 92% (or PaO_2 < 60 mmHg)

VACCINATION (Influenza - Pneumococcus)

SODIUM RESTRICTION (< 2.4 g/day) in the presence of volume overload

DIURETICS for volume overload

DIGOXIN (right heart failure or atrial tachyarrhythmias)

DRUG THERAPY FOR GROUP 1 PAH		
Anticoagulation	**Warfarin** Target INR: 2.0 to 2.5	Consider in idiopathic PAH or Heritable PAH or PAH due to anorexigens (class IIb recommendation)
Calcium channel blocking agents	**Nifedipine** (120 - 240 mg) **Diltiazem** (720 - 960 mg) **Amlodipine** (20 - 30 mg PO)	In patients with idiopathic PAH, Heritable PAH or drug induced PAH and positive vasoreactivity test Continue if WHO functional class 1 to 2/4 with marked hemodynamic improvement
Prostanoids (prostacyclins) **Vasodilators** **Antiproliferative agents**	**Epoprostenol** 2 ng/kg/min IV (target 25 - 40 ng/kg/min)	**Only agent demonstrated to ↘ mortality in IPAH** (★ Primary Pulmonary Hypertension Study Group) Need for intravenous administration (risk of local infection and catheter obstruction / sepsis)
	Treprostinil (SC or IV or inhaled) • s/c: 1-2 to 20 - 80 ng/kg/min • Inhaled: 30 - 45 µg qid	Associated with infusion site pain
	Iloprost aerosol 2.5 - 5 µg (6-9 per day)	Associated with flushing and jaw pain
Prostacyclin IP receptor agonist	**Selexipag** 200-1600 µg PO bid	Headache; Diarrhea; Nausea; Flushing
Endothelin receptor antagonist **Vasodilator**	**Ambrisentan** 2.5 - 5 - 10 mg PO qd	Adverse effects: liver function test abnormalities; edema
	Bosentan 125 mg PO bid	Monitor liver function monthly
	Macitentan 3 or 10 mg PO qd	Can cause anemia
Phospho-diesterase-5 inhibitor **↗ NO**	**Sildenafil** 20 mg PO tid	Associated with headache, flushing, epistaxis **Do not combine with soluble guanylatecyclase stimulator**
	Tadalafil 2.5 - 10 - 20 - 40 mg PO qd	
Soluble guanylate cyclase stimulator **↗ NO**	**Riociguat** 2.5 mg PO tid	Approved for group 1 PAH (★ PATENT) and thromboembolic PHT (★ CHEST) Risk of syncope **Do not combine with PDE–5 inhibitor**

BALLOON ATRIAL SEPTOSTOMY FOR RA-RV DECOMPRESSION: creation of a R → L shunt; ↘ RV filling pressures; improvement of LV filling; ↗ cardiac output (**at the cost of hypoxemia**)

› **Indications**: Severe PAH with treatment-refractory right heart failure (including inotropes) or recurrent syncope or bridge to transplant

LUNG TRANSPLANT: Progressive treatment-refractory PAH; WHO functional class 3-4/4

› **5-year survival:** 52-75%; risk of bronchiolitis obliterans - rejection - opportunistic infections

GROUP 2 PHT: left heart disease causing **venous PHT with passive retrograde transmission of increased pressure**

› **Wedge > 15 mmHg; Diastolic pressure gradient < 7 mmHg (dPAP - Mean Wedge)** +

› May be associated with pulmonary hemosiderosis (leakage of RBC from capillaries) with formation of fibrosis

› **Pulmonary artery vasodilators: risk of pulmonary edema in the presence of ↗ LV filling pressures** +

- **PAH-approved therapies are not recommended in group 2 PHT**
- **PDE-5 inhibitors / Macitentan**: awaiting the results of the ★ SIl-HF and ★ MELODY-1

› **Postcapillary PHT with precapillary component**: **development of arterial PHT with ↗ PVR as mechanism of adaptation to pulmonary edema**

- **Active component**: ↗ pulmonary artery vasomotor tone and/or fixed obstructive arterial structural remodeling
- **Diastolic pressure gradient ≥ 7 mmHg (dPAP - Mean Wedge)** +
- **Consider pulmonary artery vasodilators** on an individual basis by the expert PH centre

GROUP 4 PHT: organized thrombus associated with the arterial wall with lobar or segmental or subsegmental perfusion abnormality

› Pulmonary arteriopathy superimposed (similar to idiopathic PAH)

› **V/Q scan:** screening test of choice

- CT pulmonary angiography / Conventional pulmonary angiography for confirmation

› **Thromboendarterectomy:** treatment of choice (deep hypothermia circulatory arrest)

- Consider balloon pulmonary angioplasty if technically non-operable

› **Anticoagulation** for life

› **Consider pulmonary artery vasodilators** when thromboendarterectomy is impossible or gives mixed results; prefer Riociguat (beneficial in ★ CHEST)

PAH ASSOCIATED WITH CONGENITAL HEART DISEASE (SHUNT)

EINSENMENGER	PAH WITH L→R SHUNT	PAH WITH SMALL SEPTAL DEFECT	POST-CORRECTION PAH
• Large defect • Severely ↗ PRV • Reversed shunt (or bidirectional) • Cyanosis; Erythrocytosis; multisystem features	• Moderate-to-large defect • No cyanosis at rest • Do not operate if PVR > 4.6 WU (or indexed PVR > 8 WU/m²)	• VSD < 1 cm • ASD < 2 cm • ↗ PVR disproportional to congenital anomaly • Similar profile to idiopathic PAH	• PAH despite absence of a residual defect

› **Shunt distal to the tricuspid valve** (VSD; patent ductus arteriosus; truncus arteriosus) subjects pulmonary arteries to much higher pressure stress than pre-tricuspid shunt

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Miscellaneous 09

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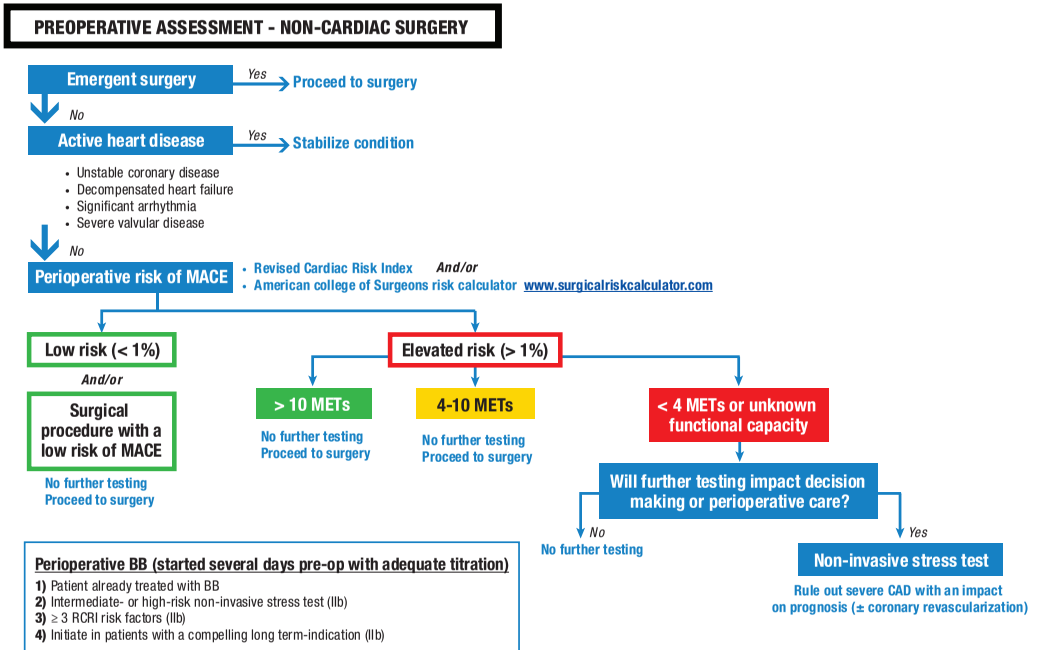

PREOPERATIVE ASSESSMENT - NON-CARDIAC SURGERY
Emergent surgery
Yes
Proceed to surgery
No
Active heart disease
Yes
Stabilize condition
• Unstable coronary disease
• Decompensated heart failure
• Significant arrhythmia
• Severe valvular disease
No
Perioperative risk of MACE
• Revised Cardiac Risk Index And/or
• American college of Surgeons risk calculator www.surgicalriskcalculator.com
Low risk (< 1%)
And/or
Surgical procedure with a low risk of MACE
No further testing
Proceed to surgery
Elevated risk (> 1%)
> 10 METs
No further testing
Proceed to surgery
4-10 METs
No further testing
Proceed to surgery
< 4 METs or unknown functional capacity
Will further testing impact decision making or perioperative care?
No
No further testing
Yes
Non-invasive stress test
Rule out severe CAD with an impact on prognosis (± coronary revascularization)
Perioperative BB (started several days pre-op with adequate titration)
1) Patient already treated with BB
2) Intermediate- or high-risk non-invasive stress test (IIb)
3) ≥ 3 RCRI risk factors (IIb)
4) Initiate in patients with a compelling long term-indication (IIb)

EVALUATION OF FUNCTIONAL CAPACITY

1 MET

- Eating; dressing; going to the toilet
- Walking indoors
- Walking 1-2 blocks (3.2-4.8 kph)
- Light housework (washing dishes; dusting)

4 METs

- **Climbing one flight of stairs**
- Walking at 6.4 kph
- Running a short distance
- Heavy housework (scrubbing floors; moving furniture)
- Golf - Bowling - Dancing - Doubles tennis - Playing ball
- Swimming - Singles tennis - Skiing - Basketball

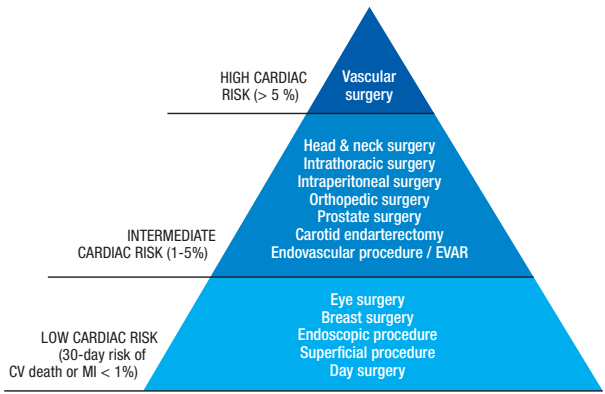
10 METs

REVISED CARDIAC RISK INDEX (RCRI) DURING NONCARDIAC SURGERY

1) History of CAD 2) History of heart failure 3) History of cerebrovascular disease 4) Insulin-treated DM 5) Pre-op Creatinine > 2 mg/dL (> 176 mmol/L) 6) Intrathoracic or intraperitoneal or vascular surgery	**Risk of cardiac events** (MI; pulmonary edema; VF; cardiac arrest; complete heart block) 0 point = low risk (0.5%) 1 point = moderate risk (1.3%) 2 points = moderate risk (3.6%) ≥ 3 points = high risk (9.1%)

Lee TH, Marcantonio ER, Mangione CM. Circulation 1999; 100; 1043-1049

CARDIAC RISK ASSOCIATED WITH SURGERY



NONINVASIVE STRATIFICATION

OBJECTIVE: to exclude the presence of severe CAD with an impact on prognosis and which would require revascularization, regardless of the type of surgery

PREOPERATIVE REVASCULARIZATION: **no benefit on perioperative events,** even in the presence of significant ischemia on noninvasive stratification (★ CARP; ★ DECREASE-V)

INDICATIONS FOR PREOPERATIVE REVASCULARIZATION: identical to stable CAD or unstable angina or NSTEMI or STEMI (▸▸| Chapter 2 - CAD) +

PERIOPERATIVE BETA-BLOCKERS AND STATINS

BB - INDICATIONS: **1)** Patient already treated with BB (Class I recommendation); **2)** Intermediate- or high-risk non-invasive stress test (IIb); **3)** ≥ 3 RCRI risk factors (IIb); **4)** Initiate in patients with a compelling long term indication (IIb)

BB - MODALITIES OF USE: Start BB therapy several days preoperatively; titrate the dose targeting a resting HR of 60-80 bpm; avoid hypotension

› ★ **POISE**: High-dose Metroprolol succinate started **2-4 h preoperatively** versus placebo; ↘ primary outcomes (cardiovascular mortality; MI) but ↗ all-cause mortality and ↗ stroke

STATINS - INDICATIONS: 1) Patient already on statin (I); **2)** Initiate if undergoing vascular surgery (IIa); **3)** Initiate in patients with clinical indications who are undergoing elevated-risk procedures (IIb)

PERIOPERATIVE ECG AND TROPONIN

ECG: Preoperative → CAD, arrhythmia, PAD, cerebrovascular disease or structural heart disease (except for low-risk procedures); **Post-operative** → **A)** Signs or symptoms suggestive of ischemia / MI / arrhythmia; **B)** Usefulness of routine screening in asymptomatic patient is uncertain (IIb)

POSTOPERATIVE TROPONIN: Indications → **A)** Signs or symptoms suggestive of ischemia or MI; **B)** Usefulness of routine screening in asymptomatic patient is uncertain (IIb)

DIAGNOSIS OF PERIOPERATIVE MYOCARDIAL INFARCTION: ▸▸| Chapter 2 (Definition of MI)

› **Consider type 1 myocardial infarction (rupture of fragile plaque) or type 2 (O_2 supply/ demand mismatch); Type 1 MI causes < 5% of troponin elevation postoperatively** +

PERMANENT PACEMAKER AND DEFIBRILLATOR

PACEMAKER-DEPENDENT PATIENT: Reprogram in V00 or D00 mode or apply a magnet during the operation (asynchronous stimulation)

DEFIBRILLATOR: **Temporarily** deactivate tachyarrhythmia therapies or apply a magnet during the operation

› **N.B.**: a magnet applied to a defibrillator deactivates tachyarrhythmia therapies, **but does not change the pacing mode to V00 or D00**; risk of inappropriate inhibition of pacing

SPECIFIC ENTITIES

HCM: avoid dehydration / vasodilators / hypotension / beta-agonists

SEVERE AORTIC STENOSIS

› **Asymptomatic**: complete preoperative clinical reassessment with stress test; consider AVR before elective high-risk non-cardiac surgery; monitor intravascular volume; avoid tachycardia; avoid intraoperative hypotension (treat with phenylephrine)

› **Patient refusing AVR or not a candidate or requiring urgent surgery**: operative mortality ≥ 10%; consider TAVI or balloon valvuloplasty if hemodynamically unstable

POST-PCI SURGERY AND DUAL ANTIPLATELET THERAPY

- **Post-PTCA**: wait **2-4 weeks** (then operate under ASA)
- **Post-BMS**: dual antiplatelet therapy for a minimum of **2-4 weeks** (then operate under ASA)
  - Discontinue Clopidogrel 5-7 days preoperatively
- **Post-DES**: dual antiplatelet therapy for a **strict minimum of 3 to 6 months** with new generation stents (consider bridging with IV tirofiban / eptifibatide / cangrelor if surgery required before this time) then operate under ASA

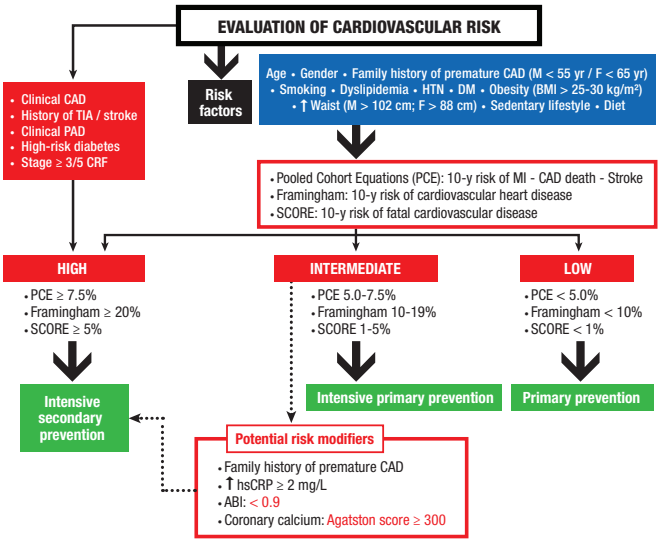
	MECHANICAL VALVE PROSTHESIS	ATRIAL FIBRILLATION	THROMBOEMBOLIC DISEASE
High thrombo-embolic risk (annual risk > 10%)	• Mitral valve prosthesis • Old generation aortic valve prosthesis (cageball; tilting-disk) • Stroke or TIA < 6 months	• CHADS 5 or 6 • Stroke or TIA < 3 months • Rheumatic disease	• Thromboembolism < 3 months • Severe thrombophilia (protein C or S or antithrombin deficiency; antiphospholipid antibodies; multiple anomalies)
	• Stop Warfarin 5 days pre-op + Bridge with IV heparin or LMWH - **Prosthetic Valve or AF** → Enoxaparin 1 mg/kg bid or Dalteparin 100 IU/kg bid; **Venous thromboembolism** → Enoxaparin 1.5 mg/kg qd or Dalteparin 200 IU/kg qd • INR on the day before surgery (vitamin K 1 mg PO if INR > 1.5) • Stop IV Heparin 4-6 h pre-op; Last dose of LMWH 24 h pre-op (Enoxaparin 1 mg/kg or Dalteparin 100 IU/kg administered 24 h pre-op) • Resume Warfarin 12-24 h post-op if adequate hemostasis • Resume Heparin (without bolus) or LMWH 48-72 h post-op depending on hemostasis • Consider IVC filter in the presence of venous thromboembolism < 4 weeks		
Moderate thromboembolic risk (annual risk 5-10%)	**Bileaflet aortic valve prosthesis with ≥ 1 risk factor:** AF • History of stroke or TIA • HTN • DM • Heart failure • > 75 years	CHADS 3 or 4 (no benefit in ★BRIDGE; mean CHADS = 2.3)	• Thromboembolism 3-12 months • Nonsevere thrombophilia: Leiden factor V or prothrombin mutation (heterozygous) • Active neoplasia
	• Case-by-case decision for heparin bridge (thromboembolic risk versus perioperative bleeding risk)		
Low thromboembolic risk (annual risk < 5%)	Bileaflet aortic valve prosthesis with no other risk factor	CHADS 0 to 2 (with no history of stroke or TIA)	Thromboembolism > 12 months (with no other risk factor)
	• Heparin bridge not recommended		

MINOR PROCEDURES: do not discontinue Warfarin for superficial skin or ophthalmic (cataract) or dental procedures (use tranexamic acid)

PERIOPERATIVE DOAC: ▶▶| Chapter 6

9.2/ PRIMARY & SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

EVALUATION OF THE RISK OF ADVERSE CARDIOVASCULAR EVENTS



CARDIOVASCULAR DISEASE - PRIMARY PREVENTION

CONTROL OF CONVENTIONAL RISK FACTORS: ▶▶| Smoking cessation; ▶▶| Dyslipidemia; ▶▶| HTN; ▶▶| DM; ▶▶| Weight & Diet; ▶▶| Physical exercise

ASA: **not recommended as part of routine primary prevention**

- ★ **Antithrombotic Trialists' Collaboration**: **marginal benefit of ASA for primary prevention (high NNT);** bleeding risk
- **Consider ASA for primary prevention**: in the presence of a low bleeding risk but high cardiovascular risk (subclinical atherosclerosis; multiple risk factors; family history of premature cardiovascular disease) (Class IIb recommendation; C)

CARDIOVASCULAR DISEASE - SECONDARY PREVENTION

Smoking	Complete cessation
Dyslipidemia	High dose statin; Target → ≥ 50% ↘ LDL
HTN	Target BP < 140/90 (< 140/85 in the presence of DM)

Antiplatelet therapy	ASA: for life (★ Antithrombotic Trialists') • Clopidogrel as alternative (★ CAPRIE) • No benefit of ASA + Clopidogrel combination (★ CHARISMA)
ACE inhibitors	As secondary prevention for all patients (especially when LVEF ≤ 40% or HTN or DM or CRF)
BB	• LVEF ≤ 40%: Long term • Normal LVEF: can be stop 3 years after ACS • Antianginal: Long term
DM	HbA1c < 7%
Physical exercise	> 30 min moderate exercise 5 x per week
Obesity	• BMI: 18.5 - 24.9 kg/m² • Waist: M < 102 cm and F < 88 cm
Healthy diet	Healthy and balanced diet
Influenza vaccine	Annually
Hormonal therapy; NSAID	Avoid

9.3/ SMOKING CESSATION

30% of deaths related to CAD can be attributed to smoking

BENEFITS: reduction of cardiovascular risk to achieve a similar level to that of nonsmokers after 5 years of smoking cessation

INTERVENTION

1) Confirm that the patient is a smoker; **2)** Strongly recommend smoking cessation; **3)** Ask the patient whether he/she wants to stop smoking (if the patient refuses, suggest reducing consumption ± nicotine replacement therapy); **4)** Establish a plan and a date for complete cessation; **5)** Inform the patient's friends and relatives; **6)** Remove all objects related to smoking; **7)** Cease all activities related to smoking; **8)** Have a plan in the case of temptation / relapse; **9)** Propose drug therapy; **10)** Propose support by a smoking cessation center; **11)** **www.smokefree.gov** ; **12)** Ensure regular follow-up

DRUG THERAPY

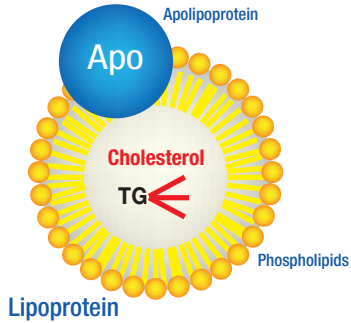
Nicotine gum	**Initially 1 gum every 1–2 h then decrease (maximum: 24 gums per day)** • ≤ 24 cigarettes / day: 2 mg gum • ≥ 25 cigarettes / day: 4 mg gum	• 6-month abstinence rate: 19% • **Adverse effects**: Nausea; Oropharyngeal irritation
Transdermal nicotine patch	• < 10 cigarettes / day: 14 mg patch for 6 weeks then 7 mg patch for 4 weeks then stop • > 10 cigarettes / day: 21 mg patch for 6 weeks then 14 mg patch for 2 weeks then 7 mg patch for 2 weeks	• 6-month abstinence rate: 23% • **Adverse effects**: Local skin reaction; Nausea; Insomnia
Bupropion SR	• Inhibits dopamine and norepinephrine reuptake • Bupropion SR 150 mg PO daily for 3 days then bid for 12 weeks then stop • Start 10 days before smoking cessation • Can be combined with nicotine replacement therapy	• 6-month abstinence rate: 24% • **Adverse effects**: Decreased seizure threshold; Insomnia; Xerostomia; Nightmares

Varenicline	• Partial agonist of acetylcholine nicotinic receptor • Varenicline 0.5 mg PO daily for 3 days then bid for 3 days then 1 mg bid for 11 weeks then stop • Start 1 to 2 weeks before smoking cessation • Can be combined with nicotine replacement therapy	Contraindicated in the case of pregnancy or breastfeeding or CRF or mental illness

9.4/ DYSLIPIDEMIA

DIET: source of triglycerides (glycerol bound to 3 fatty acid chains) and dietary Cholesterol

LIPOPROTEINS: transport TG and cholesterol in the blood



CHYLOMICRONS: large nonatherogenic lipoproteins transporting TG from the gastrointestinal tract; apoB48

VLDL: large nonatherogenic lipoproteins transporting TG from the liver; apoB100

LDL: **atherogenic lipoproteins responsible for atherosclerosis; mainly contain cholesterol; apoB100** +

- **Calculated LDL (mmol/L) = TC - HDL - (0.45 x TG) (valid if TG < 4.5 mmol/L)**
- **Calculated LDL (mg/dL) = TC - HDL - (TG / 5) (valid if TG < 400 mg/dL)**

NON-HDL CHOLESTEROL (= TC - HDL): cholesterol contained in LDL - VLDL - IDL - Lp(a); predictive of cardiovascular risk

- **ApoB**: comprises LDL - VLDL - IDL - Lp(a)

HDL: antiatherogenic properties; contains apolipoprotein **ApoA1**

HYPERTRIGLYCERIDEMIA: **TG-enriched LDL → formation of smaller and denser LDL (due to modification by hepatic lipase) → dense, atherogenic LDL** +

- **HyperTG**: TG-enriched HDL (CTEP) → ↗ recovery of HDL by the liver → **↘ HDL** +
- **HyperTG**: associated with metabolic syndrome **(↗ TG; ↘ HDL; dense, atherogenic LDL)** +
- **HyperTG: risk of pancreatitis** (especially if TG > 10 mmol/L or > 885 mg/dL)

LP(a): apolipoprotein(a) bound to a molecule of LDL; associated with an increased risk of cardiovascular events; plasma concentration is genetically determined

SCREENING FOR DYSLIPIDEMIA

- Male ≥ 40 years
- Female ≥ 50 years (or postmenopausal)
- DM
- HTN
- Smoking
- BMI > 27 kg/m²
- CRF - CrCl < 60 mL/min
- Atherosclerosis
- Family history of premature CAD (M < 55 years; F < 65 years)
- Family history of dyslipidemia
- SLE - RA - Psoriatic arthritis - Ankylosing spondylitis - Inflammatory bowel disease
- COPD
- Erectile dysfunction
- HIV (treated with antiretroviral agents)
- Clinical features of familial dyslipidemia (xanthomas; xanthelasmas; arcus senilis)

DYSLIPIDEMIA: UNDERLYING CAUSES

HYPERCHOLESTEROLEMIA: Hypothyroidism; Cholestasis; Nephrotic syndrome; CRF; Cushing; Corticosteroids; Anorexia; HIV protease inhibitors

HYPERTRIGLYCERIDEMIA: Obesity; DM; Alcohol; CRF; Hypothyroidism; Corticosteroids; Antipsychotics (Clozapine; Olanzapine); Nonselective BB; Thiazides; Cyclosporine; HIV protease inhibitors; Retinoic acid; Hormonal therapy; Sirolimus; Bile acid sequestrants

↘ **HDL**: Smoking; Obesity; Sedentary lifestyle; DM; CRF; HyperTG; Nonselective BB; Corticosteroids; Anabolic steroids; Cyclosporine

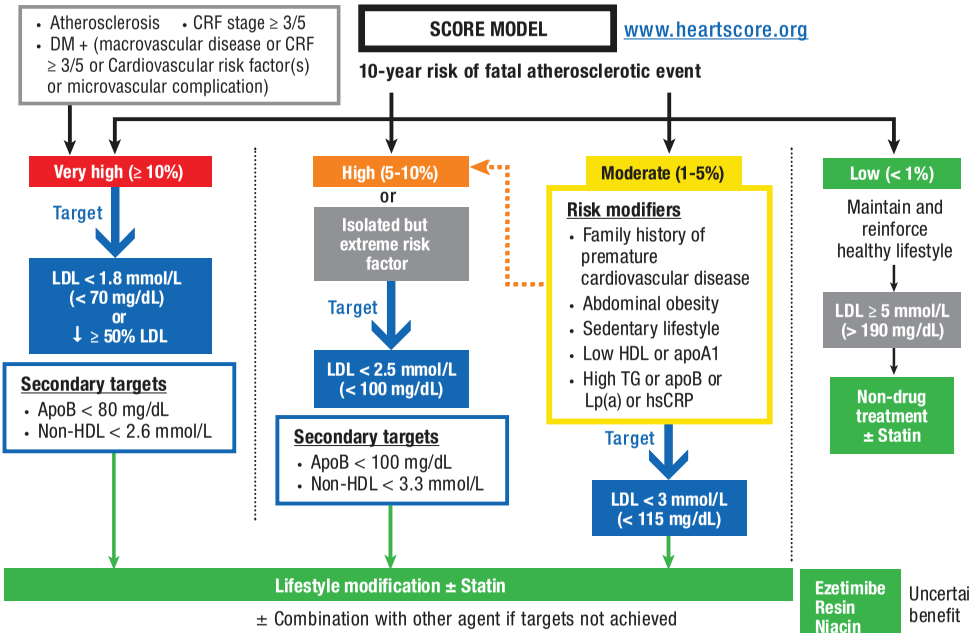
GENETIC DISORDERS OF LIPOPROTEINS

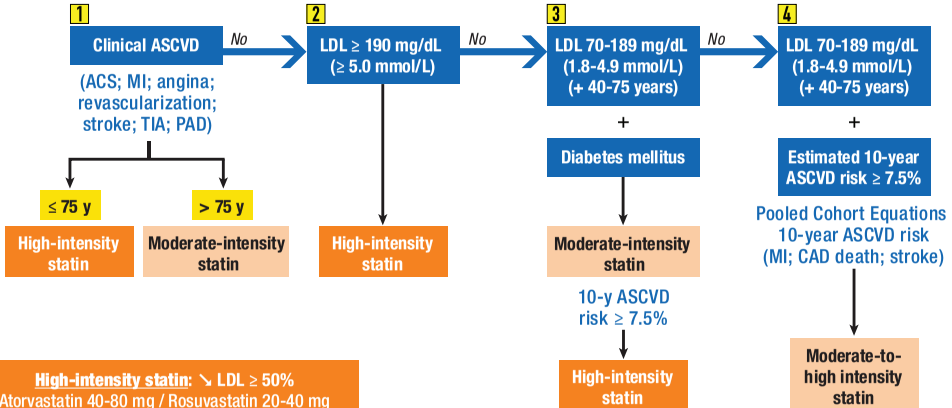
Familial hyper-cholesterolemia	↗ **LDL**	• **LDL–R receptor mutation** • 1,000 mutations identified • Autosomal dominant	• Arcus senilis • Xanthelasmas • **Pathognomonic tendinous xanthomas** (extensor tendons; MCP; Achilles tendon) • Premature CAD
Defective Apo B100	↗ **LDL**	• ↘ Affinity for LDL-R receptor • Autosomal dominant	• Similar presentation to familial hyper-cholesterolemia
Familial LPL deficiency	↗ **TG**	• **Abnormal catabolism of chylomicrons** and VLDL	• **Pancreatitis** • **Lipemia retinalis** • **Eruptive xanthomas** • **Lactescent serum**
Familial Apo-C-II deficiency	↗ **TG**	• **Apo–CII is the LPL activator**	• Similar presentation to familial LPL deficiency
Familial dysbeta-lipoproteinemia	↗ **TC** ↗ **TG**	• **Homozygote for ApoE2** (less effective binding to hepatic receptors) • Accumulation of **remnant lipoproteins** (IDL; remnant chylomicrons)	• Premature CAD • **Tuberous xanthomas** (elbows; knees) • **Palmar xanthomas** • **Consider diagnosis:** ApoB (g/L) / TC (mmol/L) ratio < 0.15

Familial combined hyperlipidemia	A) ↗ **VLDL** (↗ **TG**) or B) ↗ **LDL** (↗ **TC**) or C) ↗ **VLDL** and ↗ **LDL** (↗ **TG** and ↗ **CT**)	• 1-2% of the population • Extremely heterogeneous • Interactions between multiple genes and environment • Hepatic overproduction of lipoproteins apo-B100 (associated with VLDL) • Defective LPL in 1/3 of patients (↗ TG)	• Xanthelasmas • Arcus senilis • Premature CAD • Dense, atherogenic LDL • **Consider diagnosis**: Apo B > 120 mg/dL + TG > 1.5 mmol/L + family history of premature CAD
Familial ↘ HDL	↘ **HDL**	a) Apo A-I deficiency b) Tangier (CERP protein dysfunction) c) Familial LCAT deficiency	

MANAGEMENT - CANADIAN TARGETS

* **Intermediate risk with no indication for treatment**: consider statin if Lp(a) > 300 mg/L or hsCRP > 2.0 mg/L (with ★ JUPITER inclusion criteria) or albumin/creatinine ratio > 3 mg/mmol or positive stress test or carotid IMT > 1.0 mm (or plaque) or ABI < 0.9 or coronary calcium score > 100


• Atherosclerosis • CRF stage ≥ 3/5
• DM + (macrovascular disease or CRF ≥ 3/5 or Cardiovascular risk factor(s) or microvascular complication)
SCORE MODEL
www.heartscore.org
10-year risk of fatal atherosclerotic event
Very high (≥ 10%)
Target
LDL < 1.8 mmol/L (< 70 mg/dL) or ↓ ≥ 50% LDL
Secondary targets
• ApoB < 80 mg/dL
• Non-HDL < 2.6 mmol/L
High (5-10%)
or
Isolated but extreme risk factor
Target
LDL < 2.5 mmol/L (< 100 mg/dL)
Secondary targets
• ApoB < 100 mg/dL
• Non-HDL < 3.3 mmol/L
Moderate (1-5%)
Risk modifiers
• Family history of premature cardiovascular disease
• Abdominal obesity
• Sedentary lifestyle
• Low HDL or apoA1
• High TG or apoB or Lp(a) or hsCRP
Target
LDL < 3 mmol/L (< 115 mg/dL)
Low (< 1%)
Maintain and reinforce healthy lifestyle
LDL ≥ 5 mmol/L (> 190 mg/dL)
Non-drug treatment ± Statin
Lifestyle modification ± Statin
± Combination with other agent if targets not achieved
Ezetimibe
Resin
Niacin
Uncertain benefit



High-intensity statin: ↘ LDL ≥ 50%
Atorvastatin 40-80 mg / Rosuvastatin 20-40 mg

Moderate-intensity statin: ↘ LDL 30-50%
Atorvastatin 10-20 mg / Rosuvastatin 5-10 mg / Simvastatin 20-40 mg / Pravastatin 40-80 mg

Less evidence for statin therapy in NYHA II-IV HF or Hemodialysis

ASCVD: Atherosclerotic cardiovascular disease

Consider statin therapy

- LDL ≥ 160 mg/dL (≥ 4.1 mmol/L)
- Evidence of genetic hyperlipidemia
- Family history of premature ASCVD (< 55 y M - < 65 y F)
- Hs-CRP ≥ 2 mg/L
- CAC ≥ 300 Agatston units
- ABI < 0.9

NONDRUG TREATMENT: healthy diet; diet rich in omega-3 fatty acids; target healthy weight (BMI 18.5 to 24.9 kg/m²); regular physical exercise; smoking cessation; moderate alcohol consumption (maximum: 2 glasses per day for M and 1 glass per day for F)

DRUG TREATMENT: **First-line Statin**

HYPERTRIGLYCERIDEMIA: avoid alcohol and secondary causes; ↘ carbohydrates; increase omega-3 consumption; exercise and weight loss; control of DM

- **› TG > 10 mmol/L (> 885 mg/dL) → Fibrate for prevention of pancreatitis**
- **› TG 5-10 mmol/L (440-885 mg/dL) → Consider Fibrate (undemonstrated benefit)**

↘ **HDL**: smoking cessation; weight loss; exercise; moderate alcohol consumption

- **› Niacin**: no benefit in ★ AIM-HIGH and ★ HPS2-THRIVE studies

STATINS (HMG–COA REDUCTASE INHIBITORS)		
Atorvastatin	10-80 mg	• **↘ LDL (30-50%)** • ↘TG (10-30 %); ↗ HDL (5-10 %) • ↘ intracellular cholesterol synthesis → ↗ expression of LDL-R receptor • **Pleiotropic effects**: stabilization of atherosclerotic plaque; antiinflammatory effect; antithrombotic effect; improves endothelial function • **Adverse effects**: ↗ Transaminases; Myalgia / Myositis / Rhabdomyolysis; Drug interactions; ↗ risk of DM
Fluvastatin	20-80 mg	
Lovastatin	20-80 mg	
Pravastatin	10-40 mg	
Rosuvastatin	5-40 mg	
Simvastatin	10-40 mg	
BILE ACID SEQUESTRANTS (RESINS)		
Colesevelam	4 to 6 tablets (in 1 or 2 daily doses)	• **↘ LDL (15-30 %)** • **Adverse effects:** GI symptoms (constipation; discomfort); ↘ absorption of medications; ↗ TG
Colestipol	1 or 5 g / unit; 2-6 units / days (with meals)	
CHOLESTEROL ABSORPTION INHIBITOR		
Ezetimibe	10 mg	• **↘ LDL (20 %)** • Interferes with NPC1-L1 protein of intestinal epithelial cells • ★ **IMPROVE-IT:** Ezetimibe + Simvastatin vs. Simvastatin post ACS; ↘ MI and Stroke
FIBRATES		
Fenofibrate	200 mg	• **↘ TG (35-50 %)** • ↗ HDL (5-10 %); ↘ LDL (10-20 %) • ↗ LPL activity; ↘ Hepatic secretion of VLDL • **No benefit in ★ ACCORD study** • **Adverse effects**: ↗ Creatinine (adjust according to CrCl); Myotoxicity (avoid Gemfibrozil with statin); Rash; Drug interactions; ↗ Transaminases
Bezafibrate	400 mg	
Gemfibrozil	600 mg bid	

NICOTINIC ACID		
Niacin	1 g tid	• ↗ **HDL (25 %); ↘ TG (30 %); ↘ LDL (20 %)** • ↗ Hepatic production of apo A1 • ↘ HDL catabolism • ↘ Hepatic production of VLDL • **No benefit in ★ AIM-HIGH and ★ HPS2-THRIVE studies** • **Adverse effects**: Flushing (↘ with ASA); Hyperuricemia; Hyperglycemia; Hepatotoxicity; Gastritis
Slow-release niacin (Niaspan)	1-2 g daily	
CETP INHIBITORS		
↗ HDL; Anacetrapib; Dalcetrapib (no benefit in ★ dal–OUTCOMES); Evacetrapib		
PCSK9 INHIBITORS		
↘ LDL ★ **ODYSSEY long term**: ↘ LDL (62 %); ↘ MACE with Alirocumab vs. Placebo ★ **OSLER**: ↘ LDL (61 %); ↘ cardiovascular events and MACE with Evolocumab vs. Placebo		

STATINS

★ **CHOLESTEROL TREATMENT TRIALISTS': each 1 mmol/L (40 mg/dL) ↘ of LDL → 20-25% ↘ RR of cardiovascular mortality or myocardial infarction** +

PRIMARY PREVENTION: ★ WOSCOPS (Pravastatin); ★ AFCAPS/TexCAPS (Lovastatin); ★ HPS (Simvastatin); ★ ASCOT (Atorvastatin); ★ JUPITER (Rosuvastatin)

SECONDARY PREVENTION: ★ 4S (Simvastatin); ★ CARE (Pravastatin); ★ LIPID (Pravastatin); ★ HPS (Simvastatin)

› **Intensive treatment:** ★ A-to-Z and ★ SEARCH (Simvastatin); ★ PROVE-IT, ★ TNT, ★ ALLIANCE, ★ IDEAL and ★ SPARCL (Atorvastatin)

ADVANCED HEART FAILURE (LVEF < 30 %): no benefit (★ CORONA; ★ GISSI-HF)

RENAL FAILURE ON DIALYSIS: no benefit (★4D; ★AURORA)

MONITORING OF STATIN THERAPY

LIPID PROFILE: **At 4 to 12 weeks; then annually when dose adjusted and targets achieved**

DECREASING DOSE: may be considered when LDL < 1.0 mmol/L (< 40 mg/dL) +

MYALGIA: Discontinue Statin then resume several weeks later to **prove toxicity** (+ monitoring of CK)

› **Proven toxicity**: **A)** Reintroduce the same statin at a lower dose; **B)** Fluvastatin; **C)** Rosuvastatin 5-10 mg daily (or every 2 days or once a week); **D)** Ezetimibe - Niacin - Fibrate

› **Consider other conditions**: Hypothyroidism; CRF; liver disease; PMR; steroid myopathy; vitamin D deficiency; primary muscle diseases

MYOSITIS: myalgia + ↗ CK > ULN

RHABDOMYOLYSIS: severe myalgia; CK > 10,000 IU/L; Myoglobinuria; ± ARF

RISK FACTORS FOR MYOPATHY: statin dose; drug interactions; > 75 years; CRF (prefer Atorvastatin); liver disease; alcohol; pre-existing myopathy

AST – ALT		CK	
Baseline measurement and as necessary		Assay as necessary in the presence of myalgia	
↗ < 3 x ULN	↗ ≥ 3 x ULN	↗ ≤ 5 x ULN	↗ > 5 x ULN
• Continue treatment • AST - ALT in 6 weeks • If stable → stop monitoring AST - ALT	• Discontinue Statin • Consider DDx (alcohol; drugs; NASH) • Monitor AST - ALT until normalization **Normalization** a) Reintroduce at a lower dose b) Different statin c) Ezetimibe - Niacin - Fibrate	• Continue statin in the absence of symptoms • Repeat CK in 6 weeks • Discontinue Statin in the presence of symptoms or ↗ CK • If stable and asymptomatic → stop monitoring CK	• Discontinue Statin • Consider rhabdomyolysis (± hydration) • Monitor CK until normalization • Consider DDx **Normalization** a) Reintroduce at a lower dose b) Different statin c) Ezetimibe - Niacin - Fibrate

9.5/ HYPERTENSION

ASSESSMENT

DIAGNOSIS OF HYPERTENSION		
Office	**1st VISIT:** SBP ≥ 140 and/or DBP ≥ 90	
	SUBSEQUENT VISIT: • Diagnosis of HTN if **target organ damage or DM or GFR < 60 mL/min** • Diagnosis of HTN if **SBP ≥ 180 and/or DBP ≥ 110** • Otherwise › **Office**: diagnosis of HTN if **SBP ≥ 160 and/or DBP ≥100** x first 3 visits (mean) › **Office**: diagnosis of HTN if **SBP ≥ 140 and/or DBP ≥ 90** x first 5 visits (mean) › **ABPM or BP measured at home**	
ABPM (24 h)	• Daytime SBP: ≥ 135 or • 24-hour SBP: ≥ 130 or • Night: SBP ≥ 120; ↘ < 10 %	• Daytime DBP: ≥ 85 or • 24-hour DBP: ≥ 80 or • Night: DBP ≥ 70; ↘ < 10 %
BP at home	Daytime SBP: ≥ 135 mmHg	Daytime DBP: ≥ 85 mmHg
	• ≥ 2 readings daily (on getting out of bed and at bedtime) for 7 days (mean of days 2 to 7) • Recommended apparatus: www.hypertension.ca	
Hypertensive emergency	HTN diagnosed immediately	

STAGE OF HTN		
Grade 1 140-159 and/or 90-99	**Grade 2** 160-179 and/or 100-109	**Grade 3** ≥ 180 and/or ≥ 110

BLOOD PRESSURE MEASUREMENT TECHNIQUE

a) After resting for 5 min; no coffee or cigarettes for > 30 min; legs uncrossed; **b)** Patient seated in a chair with a back with the arms level with the heart; **c)** Inflatable cuff covers **> 80% of the arm circumference**; Cuff > 3 cm above the cubital fossa; **d)** Inflate to 30 mmHg above the level at which the radial pulse is lost; **e)** Deflate by 2 mmHg per beat; **f)** ≥ 3 measurements on the same arm (determine the mean of the last 2 measurements); **g)** Measure BP in both arms; **h)** Measure BP 1 min and 3 min after standing (rule out OH)

- **First audible sound = SBP (Korotkoff phase I)**
- **Last audible sound = DBP (Korotkoff phase V)**
  - If sounds persist until 0 mmHg, use the point at which the sounds become softer to define DBP (phase IV)

WORK-UP: Electrolytes; Creat; Urinalysis; Albumin/creat ratio; Fasting glucose; Lipids; CBC; ECG

ABPM (AMBULANT BLOOD PRESSURE MONITORING): verify response to treatment; nocturnal HTN (insomnia; OSAHS; obesity; CRF; OH; dysautonomia); evaluate fluctuating BP

- **White coat syndrome**: high BP in the doctor's office; home BP or daytime ABPM < 130-135/80-85 mmHg; no signs of target organ damage
- **Masked HTN:** normal BP in the doctor's office; ↗ daytime BP (stress; work...)

SEARCH FOR TARGET ORGAN DAMAGE

HEART DISEASE: CAD; Heart failure; LVH (ECG; TTE)

CEREBROVASCULAR DISEASE: stroke; TIA; Intracerebral hemorrhage; SAH; Vascular dementia; Carotid IMT ≥ 1 mm or plaques

PERIPHERAL ARTERY DISEASE (PAD): Aortic dissection; AAA; Claudication - Leg ischemia; ABI < 0.9

RENAL DISEASE: Hypertensive nephroangiosclerosis; CrCl < 60 mL/min; Microalbuminuria (30-300 mg/24 h or albumin/creatinine ratio 3.4-34 mg/mmol or 30-300 mg/g) or Macroalbuminuria

HYPERTENSIVE RETINOPATHY: Hemorrhages; microaneurysms; cotton wool spots or hard exudates; papilledema

UNDERLYING CAUSES OF HYPERTENSION

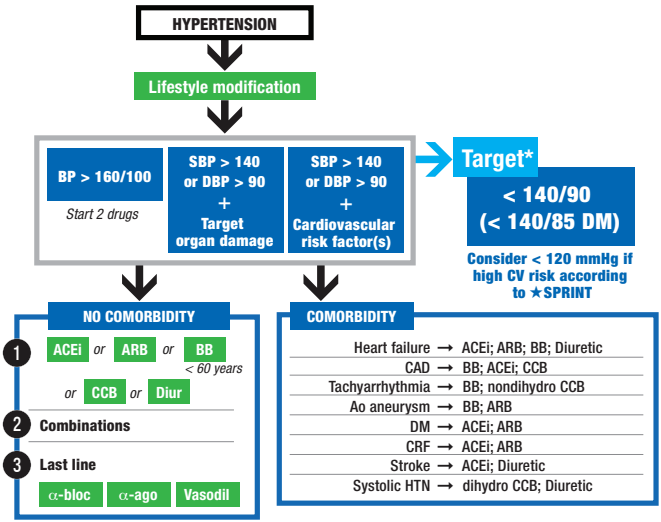
LOOK FOR AN UNDERLYING CAUSE IN THE PRESENCE OF: severe HTN; sudden onset or sudden deterioration of HTH; treatment failure; target organ damage disproportionate to the duration of HTN

Chronic renal disease	• Salt and water retention / Volume overload	• Urinalysis; Creatinine; Renal US; ± biopsy
Renovascular disease	• ▶▶| Chapter 8 (Peripheral vascular disease)	• Doppler renal arteries; MR angiography; CT angiography
CoA	• HTN in arms; ↘ Femoral pulses; Murmur between scapulae	• TTE; MR angiography; CT angiography; Cardiac cath
Primary hyper-aldosteronism	• Adenoma; Adrenal hyperplasia • Hypokalemia (spontaneous or severe diuretic-induced); Refractory HTN; ± Hypernatremia; Muscle weakness	• ↗ Plasma Aldosterone / Renin ratio (high sensitivity) • Suppression test with salt load (absence of ↘ of Aldosterone) • Adrenal CT scan or MRI • Adrenal vein catheterization

Cushing syndrome	• Truncal obesity; Violaceous striae; Thin skin; Muscle wasting; Osteoporosis; Buffalo hump	• Urinary cortisol • Suppression test (1 mg dexamethasone) • CT scan of adrenal glands
Pheochromo-cytoma	• Labile HTN; Headache; Profuse sweating; Palpitations • Exacerbated by stress / anesthesia / BB / caffeine / manipulation of the tumor • ± Dilated CM with HTN • Associated with Von Hippel-Lindau syndrome; MEN; Neurofibromatosis	• Plasma metanephrines (sensitivity 99%) • Urine metanephrines • CT scan or MRI of adrenal glands
Medications – Drugs	NSAID; Corticosteroids; Cyclosporine; Tacrolimus; EPO; Ephedrine; Decongestants; Cocaine; Amphetamines; Oral contraceptive; MAO inhibitors - SSRI; Midodrine; Anabolic steroids	

Other: Acromegaly; Hypothyroidism; Hyperparathyroidism; Pregnancy; Acute glomerulonephritis; Renal crisis (scleroderma); Rebound HTN (nonadherence to treatment); Smoking; Alcohol; Obesity; Sodium; OSAHS; Liquorice; Chronic pain; Intracranial neoplasm

MANAGEMENT



*** AMERICAN TARGETS (JNC 8)**

- < 60 years (or DM or CRF) → < 140/90 mmHg
- > 60 years → < 150/90 mmHg

★ **SPRINT**: sBP ≥ 130 mmHg + ≥ 50 years old + increased CV risk (CV disease; GFR 20-60 ml/min; Framingham > 15% /10-year; ≥ 75 years) + no diabetes / no prior stroke; target → **sBP < 120 mmHg vs. < 140 mmHg**; study terminated prematurely; ↘ **MACCE;** ↘ **Mortality**

NONDRUG TREATMENT: healthy weight (BMI 18.5 to 24.9 kg/m2); waist < 102 cm (M) and < 88 cm (F); regular physical exercise; moderate alcohol consumption; sodium < 2.4 g daily; healthy diet (rich in fruit and vegetables; low-fat; DASH diet); smoking cessation; relaxation techniques

DRUG TREATMENT

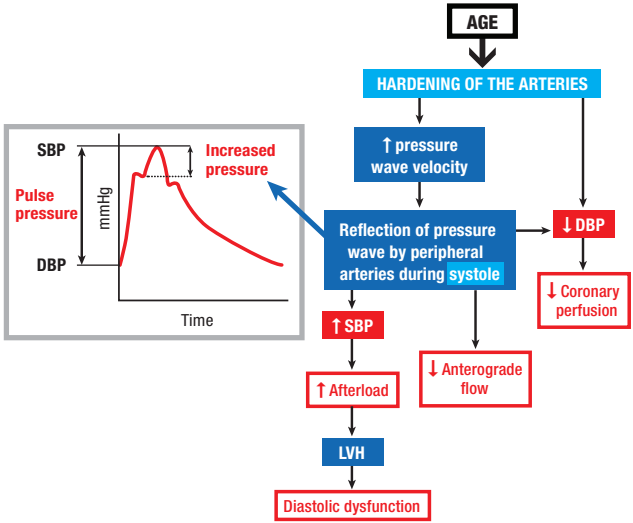
- ★ **ALLHAT**: Chlorthalidone and Lisinopril and Amlodipine are comparable
- ★ **ASCOT**: Hypertensive patients with ≥ 3 cardiovascular risk factors; Amlodipine + Perindopril superior to Atenolol + Thiazide (study terminated prematurely; ↘ stroke, ↘ mortality)
- ★ **ACCOMPLISH**: Hypertensive patients with CAD or high risk of CAD; **Benazepril + Amlodipine superior to Benazepril + HCTZ**

ANGIOTENSIN–CONVERTING ENZYME (ACE) INHIBITORS		
Benazepril	5 mg to 40 mg qd	• ↗ Bradykinin (cough; angioedema) • **Accept ↗ creatinine ≤ 30%** • Deterioration of renal function with bilateral renal artery stenosis • Hyperkalemia
Captopril	6.25 mg tid to 50 mg tid	
Cilazapril	1.25 mg to 10 mg qd	
Enalapril	2.5 mg to 40 mg qd	
Fosinopril	10 mg to 40 mg qd	
Lisinopril	5 mg to 40 mg qd	
Perindopril	2.5 to 10 mg qd (2 to 8 mg in Canada)	
Quinalapril	5 mg to 40 mg qd	
Ramipril	1.25 mg to 10 mg qd	
Trandolapril	0.5 mg to 4 mg qd	
ANGIOTENSIN II RECEPTOR BLOCKERS (ARB)		
Candesartan	8 mg to 32 mg qd	• ARF; Hyperkalemia; OH; Angioedema • Deterioration of renal function with bilateral renal artery stenosis • Do not add ARB to ACE inhibitors (harmful effect in ★ONTARGET)
Irbesartan	75 mg to 300 mg qd	
Losartan	25 to 100 mg qd	
Olmesartan	20 mg to 40 mg qd	
Telmisartan	20 mg to 80 mg qd	
Valsartan	40 mg to 320 mg qd	
DIRECT RENIN INHIBITORS		
Aliskiren	150 mg to 300 mg qd	Adverse effect of pro-renin?
CALCIUM CHANNEL BLOCKERS		
Amlodipine	5 mg to 10 mg qd	• Dihydropyridines (Amlodipine and Nifedipine): OH; leg edema; flushing; headache • Non-dihydropyridines (Diltiazem and Verapamil): negative inotropic agent; negative chronotropic agent
Nifedipine	XL: 30 mg to 120 mg qd	
Verapamil	SR: 120 mg qd to 240 mg bid	
Diltiazem	CD: 120 mg to 360 mg qd	

DIURETICS		
Indapamide	1.25-2.5 mg daily	• Avoid thiazides if CrCl < 30 mL/min • Adverse effects (thiazides): hyponatremia; hypomagnesemia; hypokalemia; OH; glucose intolerance; hypercalcemia; ARF; sulfonamide allergy; gout
Chlorthalidone	12.5-50 mg daily	
Hydrochlorothiazide	6.25-50 mg daily	
Metolazone	2.5-10 mg daily	
Bumetanide	0.5-5 mg daily	
Furosemide	20-600 mg daily	
Torsemide	2.5-10 mg daily	
Eplerenone	25-100 mg daily	
Spironolactone	25-100 mg daily	
Triamterene	50-300 mg daily	
Amiloride	5-10 mg daily	
BETA-BLOCKERS		
Acebutolol	100 mg bid to 400 mg bid	Bronchospasm; Bradycardia; Negative inotropic agent; Exacerbation of PAD; Fatigue; Erectile dysfunction; Rebound effect on withdrawal; Unopposed alpha stimulation (pheochromocytoma); ↗ TG and ↘ HDL (nonselective); Masks symptoms of hypoglycemia; glucose intolerance
Atenolol	25 mg to 100 mg qd	
Bisoprolol	2.5 mg to 10 mg qd	
Carvedilol	3.125 mg bid to 50 mg bid	
Labetalol	100 mg bid to 400 mg bid	
Metoprolol	25 mg bid to 100 mg bid	
Nadolol	40 mg to 240 mg qd	
Nebivolol	2.5 mg to 20 mg qd	
Pindolol	2.5 mg bid to 40 mg bid	
Propranolol	LA: 80 mg to 320 mg qd	
Timolol	2.5 mg bid to 20 mg bid	
ALPHA-BLOCKERS		
Doxazosin	1 mg to 16 mg qd	• Not recommended as first-line • OH; Fluid retention (risk of heart failure) • Doxazosin used as third line in ★ ASCOT
Prazosin	0.5 mg tid to 5 mg tid	
Terazosin	1 mg to 20 mg qd	
CENTRAL ALPHA-ADRENERGIC AGONISTS (VASOMOTOR ACTIVITY CENTER)		
Methyldopa	250-3000 mg daily	Sedation; Dry mouth; Impotence; Galactorrhea; ANA+; Autoimmune anemia
Clonidine	0.1 mg to 0.8 mg bid	Sedation; Dry mouth; Rebound effect on withdrawal

DIRECT VASODILATORS		
Hydralazine	10 mg to 50 mg qid	• Relaxation of precapillary arterioles • Reflex sympathetic activation; Lupus
Nitroglycerin	Imdur: 60-240 mg / 24h Nitrodur: 0.2 to 0.8 mg/h	Nausea; Headache; Hypotension; Tolerance

HYPERTENSION IN THE ELDERLY



★ **HYVET**: > 80 years; SBP > 160 mmHg; Indapamide / Perindopril vs Placebo; Benefit of treatment (↘ all-cause mortality; ↘ adverse events)

INITIATE TREATMENT IF SBP > 160 mmHg (no RCT with SBP < 160 mmHg)

› **Target → SBP ≤ 150 mmHg**
- Caution when DBP < 60 mmHg
- Monitoring of adverse effects: BP supine-standing

PSEUDOHYPERTENSION: HTN on sphygmomanometer, but normal BP on intraarterial measurement; secondary to rigid arteries that are not compressible by the cuff

› **Osler's maneuver**: radial pulse palpable when cuff inflated

TREATMENT-RESISTANT HYPERTENSION

BP > 140/90 mmHg despite ≥ 3 medications at adequate doses (including a diuretic)

ETIOLOGIES: nonadherence; failure to comply with salt restriction; dehydration (↗ stimulation of renin and aldosterone); **insufficient dose of diuretic; HTN secondary to an underlying cause**; hyperaldosteronism; OSAHS

› **Pseudo-resistance**: **A)** White coat syndrome; **B)** Pseudohypertension in the elderly

MANAGEMENT: Combination of ≥ 3 medications; look for underlying cause; use a sufficient dose of diuretic; mineralocorticoid receptor antagonist; alpha-blocking agent (Doxazosin); percutaneous radiofrequency renal denervation (no benefit in ★ Symplicity HTN-3)

HYPERTENSIVE CRISIS

SBP ≥ 180 MMHG OR DBP ≥ 110 MMHG

HYPERTENSIVE URGENCY: absence of target organ damage

› Often associated with discontinuation of treatment, nonadherence to treatment and/or anxiety
› **Management:** gradual treatment (over 24-48 h); consider oral treatment (Captopril; Furosemide; Propranolol; Nifedipine); avoid target organ hypoperfusion

HYPERTENSIVE EMERGENCY: **target organ damage; immediate treatment required; invasive hemodynamic monitoring; target ↘ DBP by 10-15% x 30-60 min**

› **Retinal damage:** hemorrhages; exudates; papilledema
› **CNS damage:** Hypertensive encephalopathy (headache; irritability; altered state of consciousness); thrombotic stroke; hemorrhagic stroke; SAH
  • **Cerebral autoregulation:** ↗ intracerebral blood pressure when DBP > 110-130 mmHg (autoregulatory mechanisms no longer effective); risk of cerebral edema
› **Cardiac damage:** Aortic dissection; acute heart failure; acute coronary syndrome
› **Renal damage:** ARF
› **Other:** Eclampsia / HELLP syndrome; Microangiopathic hemolytic anemia

Nitroprusside	IV infusion: 0.25-10 µg/kg/min (short duration) Standard dilution: 50 mg/250 mL D5 %	Nausea; Vomiting; Cyanide toxicity; Avoid in the presence of CNS damage or ARF or liver failure
IV Nitroglycerin	Perfusion: 5-60 µg/min Standard dilution: 50 mg/250 mL D5 %	Headache; Vomiting; Methemoglobinemia; Tolerance
Labetalol	• IV bolus: 20-80 mg every 10 min • IV infusion: 2 mg/min (max 300 mg / 24 h) Standard dilution: 200 mg/160 mL NS (= 1 mg/mL)	Vomiting; Faintness; Nausea; Block; OH
Esmolol	• Bolus: 0.25-0.5 mg/kg/min x 4 min • IV infusion: 0.05-0.3 mg/kg/min Standard dilution: 2500 mg/250 mL	Hypotension; Nausea; Block
IV Nicardipine	IV infusion: 5-15 mg/h	Headache; Nausea; Flushing; Tachycardia

9.6/ DIABETES

TYPE 1 DM: autoimmune (or idiopathic) destruction of pancreatic beta cells

TYPE 2 DM: insulin resistance and/or abnormal insulin secretion

DIAGNOSIS

DIAGNOSIS OF DIABETES	PREDIABETES		
	Abnormal fasting blood glucose	**Glucose intolerance**	**Prediabetes**
• **Fasting blood glucose:** ≥ 7.0 mmol/L (≥ 126 mg/dL) or • **Random blood glucose**: ≥ 11.1 mmol/L (≥ 200 mg/dL) or • **Blood glucose 2 h after 75 g glucose load**: ≥ 11.1 mmol/L or • **HbA1c**: ≥ 6.5 %	**Fasting blood glucose:** 6.1 - 6.9 mmol/L (110 - 124 mg/dL) Rule out Glucose intolerance	**Blood glucose 2 h after 75 g glucose load:** 7.8 - 11.0 mmol/L (140 - 200 mg/dL)	**HbA1c:** 6.0 - 6.4% Rule out Glucose intolerance
	More intensive management of cardiovascular risk factors; consider Metformin or Acarbose		

GLYCEMIC CONTROL - TYPE II DIABETES

BENEFITS OF GLYCEMIC CONTROL

- **Reduction of microvascular complications**: retinopathy; nephropathy; neuropathy (★ DCCT - ★ UKPDS - ★ ADVANCE)
- **Little evidence concerning the benefit on macrovascular complications**: ★ ADVANCE and ★ VADT; ★ ACCORD demonstrated excess mortality for target HbA1c < 6%

GLYCEMIC CONTROL TARGETS		
HbA1c	**Fasting blood glucose & Preprandial blood glucose**	**2 h postprandial blood glucose**
≤ 7 % every 3 months (every 6 months when target achieved)	**4.0 - 7.0 mmol/L (72 - 126 mg/dL)**	**5.0 - 10.0 mmol/L** (5.0 - 8.0 when target HbA1c not achieved)

1) **NONDRUG TREATMENT**: weight loss (< 5%); balanced diet / follow-up by a nutritionist; regular moderate aerobic physical exercise (30 min; 5 times a week)
   - **Stress test prior to training program:** consider in patients at high-risk of cardiovascular disease (or with microvascular complication) in the case of training with an intensity greater than rapid walking
2) **FIRST-LINE DRUG TREATMENT:** Metformin
3) **SECOND-LINE DRUG TREATMENT:** in combination with Metformin
   - Sulfonylurea (or Meglitinide) and/or Incretins
   - Bedtime basal insulin therapy
4) **INSULIN THERAPY**: 3 approaches
   a) **Bedtime basal insulin therapy**: combined with oral antidiabetic; **starting dose of 10 units at bedtime**; increase by 1 unit per day, targeting a fasting blood glucose of 4.0-7.0 mmol/L (72 - 126 mg/dL); avoid nocturnal hypoglycemia
   b) **Premixed insulin**: **starting dose of 5-10 units bid** (before breakfast and before dinner); increase the morning dose by 1 unit, targeting evening blood glucose before dinner of 4.0 - 7.0 mmol/L (idem for the evening dose, targeting morning fasting blood glucose of 4.0 - 7.0 mmol/L)
   c) **Intensive insulin therapy: total daily dose = 0.3 to 0.5 kg unit**; 40% of the total dose as bedtime basal insulin therapy; 20% of the total dose as bolus doses tid with each meal

Biguanide	Metformin: 250 mg bid to 850 mg tid	Decreases hepatic glucose synthesis	**↘ HbA1c by 0.8%** **Adverse effects:** Nausea; Diarrhea; Lactic acidosis (contraindicated if GFR < 30 mL/min) Weight loss Benefit on the risk of MI and mortality in obese patients in ★UKPDS
Sulfonylureas	• Gliclazide: 60 mg qd to 120 mg qd • Glimepiride: 1 to 8 mg qd • Glyburide: 2.5 mg qd to 10 mg bid	Stimulates insulin secretion by the pancreas	**↘ HbA1c by 0.7%** **Adverse effects:** Hypoglycemia (prefer Gliclazide which is associated with the lowest risk of hypoglycemia); weight gain Benefit on the risk of MI in ★UKPDS
Meglitinide	Repaglinide: 0.5 mg tid to 4 mg qid	Stimulates insulin secretion by the pancreas	**↘ HbA1c by 1-1.5 %** Short duration of action (to be taken < 30 min before the meal) **Adverse effects:** Hypoglycemia; Weight gain
Incretin - GLP-1 analog ("glucagon-like peptide 1")	• Exenatide: 5 to 10 µg SC bid • Liraglutide: 0.6 to 1.8 mg SC daily	**GLP-1:** ↗ insulin secretion; ↘ glucagon secretion; delays gastric emptying	**↘ HbA1c by 1 %** **Weight loss** **Adverse effects:** Nausea; Vomiting
Incretin - DPP-4 inhibitors	• Sitagliptin: 100 mg qd • Linagliptin: 5 mg qd • Saxagliptin: 5 mg qd	Inhibits the breakdown of GLP-1	**↘ HbA1c by 0.7 %** Safe post-ACS (★EXAMINE; Alogliptin) **Adverse effects:** ↗ hospitalization for heart failure with Saxagliptin in ★SAVOR but not with Sitagliptin in ★TECOS
Alpha-glucosidase inhibitor	Acarbose: 25 mg tid to 100 mg tid	Decreases intestinal absorption of carbohydrates	**↘ HbA1c by 0.6 %** **Adverse effects:** Bloating
Thiazolidine-dione (TZD)	Pioglitazone: 15 mg to 45 mg qd	Increases peripheral insulin sensitivity	**↘ HbA1c by 0.8 %** **Adverse effects:** Weight gain; Edema; contraindicated in heart failure (★DREAM); bladder tumor; fracture

SGLT2 inhibitors	Canagliflozin Dapagliflozin Empagliflozin	↘ glucose reabsorption by the renal proximal tubule	↘ **All-cause mortality** with Empagliflozin in ★ EMPA-REG ↘ BP; Weight loss **Adverse effects:** urinary tract infections; candidiasis; ↗ LDL
RAPID ACTING INSULIN • Aspart (NovoRapid) • Lispro (Humalog)		• Onset of action: 10-15 min • Peak action: 1-2 h • Duration of action: 3-5 h	
REGULAR INSULIN • Humulin-R • Novolin ge Toronto		• Onset of action: 30 min • Peak action: 2-3 h • Duration of action: 6.5 h	
INTERMEDIATE-ACTING INSULIN • Humulin-N • Novolin ge NPH		• Onset of action: 1-3 h • Peak of action: 5-8 h • Duration of action: up to 17 h	
LONG-ACTING INSULIN • Detemir (Levemir) • Glargine (Lantus)		• Onset of action: 90 min • Duration of action: up to 24 h	
PREMIXED INSULIN Humulin 30/70; Novolin ge 30/70; Biphasic insulin aspart (NovoMix 30); Insulin lispro / lispro protamine (Humalog Mix25)…			

MANAGEMENT - TYPE II DIABETES

CARDIOVASCULAR RISK: **2- to 3-fold higher prevalence of coronary artery disease than in nondiabetic subjects; coronary artery disease occurs 10 years earlier**

CONTROL OF CARDIOVASCULAR RISK FACTORS: healthy weight; waist < 102 cm (M) and < 88 cm (F); BMI 18.5 - 24.9 kg/m2; healthy diet; regular physical exercise; smoking cessation

CONTROL BP: target BP < 140/85 and prefer ACEi (or ARB) as first-line treatment

› ★ **ACCORD-BP**: no benefit of targeting SBP < 120 versus < 140 mmHg

ANTIPLATELET THERAPY (ASA):

› **Secondary prevention**: indicated for all patients
› **Primary prevention**: uncertain benefit (ongoing ★ ASCEND and ★ ACCEPT-D studies); not recommended routinely; consider if high 10-year risk of cardiovascular events in the absence of bleeding risk (class IIb recommendation); **decision based on clinical judgment**

STATIN: ★ CARDS and ★ HPS studies of primary prevention demonstrated a benefit

› **European guidelines - Indications: A)** Very high risk ⟶ DMI or DMII + (macrovascular disease or CRF ≥ 3/5 or cardiovascular risk factors or microvascular complication); **B)** High risk ⟶ DMII + (absence of cardiovascular risk factors and absence of target organ damage)
› **Canadian guidelines - Indications**: Diabetes + (≥ 40 years or present for > 15 years in a patient ≥ 30 years or macrovascular disease or microvascular complication)
› **American guidelines - Indications**: Diabetes + 40-75 years + LDL ≥ 70 mg/dL (≥ 1.8 mmol/L)

ACEI: cardioprotective effect: (★ HOPE, ★ EUROPA and ★ ADVANCE); indicated in the presence of HTN or clinical macrovascular disease or ≥ 55 years or in the presence of a microvascular complication

› **ARB: when ACEi are not tolerated;** ★ ONTARGET ⟶ Telmisartan non-inferior to Ramipril; ★ TRANSCEND ⟶ no benefit of Telmisartan versus placebo (patients intolerant to ACEi)

NONINVASIVE ASSESSMENT OF CAD (PROGNOSTIC PURPOSES): Indications → **A)** Symptoms (retrosternal chest pain; dyspnea); **B)** Baseline ECG abnormalities; **C)** Atherosclerosis (PAD - TIA - stroke - murmur)

› **Revascularization**: **benefit of revascularization by bypass graft (versus PCI) on mortality and risk of MI (★ FREEDOM)** +

VACCINATION: Influenza (annually); Pneumococcus

OTHER: self-monitoring of blood glucose; screening for retinopathy (every 1-2 years); screening for neuropathy (big toe; Semmes-Weinstein 10 g monofilament test or 128 Hz tuning fork); examination of feet; prevention of diabetic ulcer; PDE-5 inhibitor for erectile dysfunction

HYPOGLYCEMIA: Blood glucose < 4 mmol/L (72 mg/dL) + symptoms (tremor; palpitations; anxiety; profuse sweating; nausea; confusion; weakness); **treatment with 15 g of oral carbohydrate or 1 mg of Glucagon SC (or IM) or 1 ampoule of 50% dextrose IV**

DIABETIC NEPHROPATHY

CHRONIC NEPHROPATHY: GFR < 60 mL/min and/or microalbuminuria or macroalbuminuria

SCREENING: albumin / creatinine ratio and serum creatinine (and GFR) every year

MANAGEMENT: optimal control of blood glucose and BP; ACEi or ARB; Nephrological follow-up if sustained deterioration or GFR < 30 mL/min or significant macroalbuminuria; aggressive treatment of cardiovascular risk factors (high risk of adverse events)

ALBUMINURIA			NEPHROPATHY		
	Albumin / creatinine ratio (mg/mmol)	**Albumin mg / 24h**	**Stage**	**Renal damage**	**GFR (mL/min)**
Normal	< 2.0	< 30	1	Minimal - Absent	≥ 90
Micro-albuminuria	2.0 - 20.0	30 - 300	2	Mild	60 - 89
Macro-albuminuria	> 20.0	> 300	3	Moderate	30 - 59
			4	Severe	15 - 29
			5	End-stage	< 15

9.7/ PHYSICAL ACTIVITY

PHYSIOLOGY OF EXERCISE

1) **↗ CARDIAC OUTPUT:** ↗ up to 4- to 6-fold
   a) ↗ **Stroke volume** (↗ venous return → Frank-Starling law; catecholamines → positive inotropes)
   b) ↗ **HR** (HRmax ≈ 220 - age)
2) **REDISTRIBUTION OF PERFUSION:** vasodilatation in muscles; vasoconstriction of other systems (except for CNS and heart)
3) **↗ O_2 EXTRACTION BY MUSCLES**
4) **↗ CORONARY PERFUSION:** ↗ up to fivefold; vasodilatation of coronary arterioles

› **MVO_2**: myocardial O_2 consumption; determined by **HR / SBP / LV end-diastolic volume / wall thickness / contractility** +

BENEFITS & RISKS

BENEFITS OF EXERCISE ON CONVENTIONAL CARDIOVASCULAR RISK FACTORS

- **HTN**: ↘ 3.4 / 2.4 mmHg
- **Dyslipidemia**: ↗ HDL 0.06 mmol/L (2.3 mg/dL); ↘ TG
- **Obesity**: ↘ 7 kg in 1 year (in combination with diet)
- **Diabetes:** ↘ HbA1c by 0.8%

IMPROVEMENT OF OTHER PARAMETERS: functional capacity; quality of life; mental health; endothelial function; inflammatory state; ischemic threshold

- **Physical activity**: **↘ mortality and ↘ cardiovascular events in patients with CAD** (meta-analyses); ↘ mortality and hospitalizations in patients with LVEF < 35% (★ HF-ACTION; after adjustments)

BENEFITS OF TRAINING: ↗ VO_2 max; ↗ stroke volume; lower HR for the same level of exercise (same HRmax); ↗ arteriovenous O_2 difference; delayed ventilatory threshold; ↘ MVO_2 for the same level of exercise

RISKS OF PHYSICAL EXERCISE

a) **< 35 years**: sudden death / arrhythmia / genetic condition (HCM; congenital coronary artery anomalies; myocarditis; ARVD; Channelopathy; CAD; Acute aortic syndrome; Aortic stenosis; DCM; WPW; *commotio cordis*)
b) **> 35 years:** CAD / MI (especially in sedentary subject performing unusually strenuous exercise)

INTENSITY OF PHYSICAL EXERCISE

1 MET: = O_2 consumption at rest while seated (3.5 mL O_2/kg/min)

< 3 METs	3 – 5 METs	5 – 7 METs	7 – 9 METs	> 9 METs
• Washing • Shaving • Dressing • Washing the dishes • Sewing • Playing a musical instrument • Golf (caddy) • Walking (3.2 kph) • Fishing • Pool	• Washing the windows • Electric lawnmower • Making a bed • Dancing • Golf • Sailing • Tennis (doubles) • Volleyball (6 players) • Ping-pong • Walking (6.4 kph)	• Manual lawnmower • Climbing stairs (slowly) • Badminton • Tennis (singles) • Basketball • Walking (8 kph) • Bike-riding (16 kph) • Swimming (breaststroke)	• Shoveling snow • Climbing stairs (moderate speed) • Canoe • Soccer • Jogging (8 kph) • Swimming (front crawl) • Bike-riding (19 kph) • Mountain-climbing	• Climbing stairs (rapidly) • Shoveling heavy snow • Handball • Squash • Running (> 10 kph) • Bike-riding (> 21 kph)

EVALUATION OF THE RISK OF PHYSICAL EXERCISE

PRE-TRAINING STRESS TEST: **A)** DM; **B)** Symptoms or multiple cardiovascular risk factors or known heart disease; **C)** Strenuous physical exercise by a sedentary subject (M > 45 years and F > 55 years)

CATEGORY	CHARACTERISTICS	MANAGEMENT
Class A: In good health	• M < 45 years or F < 55 years with no symptoms, no heart disease and no major cardiovascular risk factors • M > 45 years or F > 55 years with no symptoms, no heart disease and ≤ 1 major cardiovascular risk factor • M > 45 or F > 55 years with no symptoms, no heart disease with ≥ 2 major cardiovascular risk factors	• No restriction • No supervision required • Physical examination / Stress test as necessary (according to cardio-vascular risk factors / type of strenuous exercise)
Class B: Stable heart disease	• Stable CAD • Nonsevere valvular heart disease • Stable congenital heart disease (according to 36th Bethesda conference) • Stable cardiomyopathy (LVEF ≤ 30%) • Abnormal stress test (no class C abnormalities) **+** **CLINICAL CHARACTERISTICS** NYHA I or II; No decompensated heart failure; ≥ 6 METs; No ischemia < 6 METs; Normal BP response to exercise; No VT on effort - rest; Able to selfmonitor	• Individualized prescription **(50% of HR reserve then increase)** • Medical supervision with monitoring during the initial phase (6-12 sessions) • Nonmedical supervision thereafter until the patient is able to self-monitor
Class C: Moderate to high risk	• CAD • Nonsevere valvular heart disease • Moderate congenital heart disease (36th Bethesda conference) • Cardiomyopathy (LVEF ≤ 30%) • Partially controlled ventricular arrhythmia **+** **CLINICAL CHARACTERISTICS** NYHA III-IV; Stress test < 6 METs; Ischemia < 6 METs; Abnormal BP response to exercise; NSVT on exercise; History of cardiac arrest; Potentially dangerous medical condition	• Individualized prescription **(40% of HR reserve then increase)** • Medical supervision with monitoring until safety is confirmed (> 12 sessions) • Can be classified as class B when exercise is safe
Class D: Unstable condition	• Unstable ischemia • Severe valvular heart disease / symptoms • Severe congenital heart disease • Decompensated heart failure • Uncontrolled arrhythmia • Other condition worsened by exercise	• Exercise contraindicated • Target treatment of the disease

Fletcher GF, Balady GJ, Amsterdam EA. Exercise Standards for Testing and Training; A Statement for Healthcare Professionals From the American Heart Association. Circulation. 2001;104:1694-1740

COMPETITIVE SPORT: according to the 36th Bethesda conference

PRESCRIPTION OF AEROBIC (ISOTONIC) PHYSICAL EXERCISE

FREQUENCY: 5 times a week

DURATION: 30 min (in 10-min fractions if necessary)

INTENSITY: moderate

- **Target**: ideally 450 to 750 METs x min / week (1000 kcal / week)
- **Kcal/min**: = (METs x 3.5 x kg weight) / 200
- **Strenuous aerobic exercise**: 3 times a week; 20 min per session

MODERATE AEROBIC EXERCISE	VIGOROUS AEROBIC EXERCISE
• **% VO_2 max**: 45-59 % • **% HR reserve**: 45-59 % • **% HRmax**: 55-69 %	• **% VO_2 max**: 60-85 % • **% HR reserve**: 60-85 % • **% HRmax**: 70-90 %
• **Borg scale**: 12-13 / 20 Comfortable while talking (≈ ventilatory threshold ≈ 50 % VO_2Max)	• **Borg scale**: 14-16 / 20 Conversation is difficult during exercise
• **METs**: 4 - 6 METs (middle-aged) 5 - 7 METs (young) 3 - 5 METs (elderly) 2 - 3 METs (very elderly)	• **METs**: 6 - 8.5 METs (middle-aged) 7 - 10 METs (young) 5 - 7 METs (elderly) 3 - 4 METs (very elderly)
• **Type of exercise**: rapid walking; bike-riding; swimming; dancing; pool aerobics; elliptic exercise machine	• **Type of exercise**: rapid walking uphill; jogging; rapid swimming; hockey; singles tennis; shoveling snow

- **Target HR according to HR reserve**: = (prescribed % x HR reserve) + resting HR
- **HR reserve**: = HRmax on stress test - resting HR
- **HRmax**: = 220 - age
- **HRmax**: = HRmax on stress test limited by symptoms

- **Ischemia on stress test**: Target HR on exercise must be at least 10 bpm lower than ischemic threshold (or target HR = 70% of HR at the ischemic threshold)

PRESCRIPTION OF RESISTANCE TRAINING (STATIC; ISOMETRIC)

FREQUENCY: twice a week

CONTENT: 1-3 series of 8 to 12 repetitions of the prescribed load (counterweight machine or dumbbells)

8-10 MUSCLE GROUPS: Biceps; Triceps; Shoulders; Pectorals; Back; Abdominal muscles; Leg muscles

PRESCRIBED LOAD: maximum load that can be lifted once → 35% of this maximum load for arms and 45% for legs

9.8/ WEIGHT & DIET

WEIGHT CONTROL

BMI: = Mass (kg) / Height ² (m^2)

Underweight	BMI < 18.5 kg/m²
Healthy weight	BMI 18.5 - 24.9 kg/m²
Overweight	BMI 25.0 - 29.9 kg/m²
Obesity - Class I	BMI 30.0 - 34.9 kg/m²
Obesity - Class II	BMI 35.0 - 39.9 kg/m²
Obesity - Class III (morbid)	BMI ≥ 40 kg/m²

BENEFIT OF WEIGHT CONTROL ON CARDIOVASCULAR RISK FACTORS: ↘ BP; improves lipid profile (↘ TG; ↘ atherogenic lipoproteins; ↗ HDL); ↘ DM; ↘ OSAHS; ↘ inflammatory state; improves endothelial function

WEIGHT LOSS

BMI	**Target 18.5 - 24.9 kg/m²**
WAIST (midpoint between superior iliac crest and costal margin)	**Target < 102 cm M and < 88 cm F** (ideally < 94 cm M and < 80 cm F)

1) LIFESTYLE MODIFICATION: healthy diet; regular physical exercise; behavioral therapy (selfmonitoring; eat more slowly; eat smaller servings; nutritional education...)

- **Targets**: **weight loss of 5% in 3-6 months** (realistic target)
- **Measurements**: **energy deficit of 500 kcal per day** (loss of 1-2 pounds per week); Regular exercise program (30 min; 5 times a week)

2) DRUG TREATMENT: indicated after failure of nondrug treatment for 6 months with BMI > 30 kg/m² (or > 27 kg/m² with comorbidities)

Pancreatic lipase inhibitor	Orlistat 120 mg tid + fat-soluble vitamin supplement	Inhibits digestion and absorption of dietary fat by 30%	Bloating; Steatorrhea; Abdominal cramps; Renal stones
Selective serotonin agonist	Lorcaserin	Early satiety	Faintness; Nausea; Headache; URTI; Uncertain long-term safety (valvular heart disease?)

3) BARIATRIC SURGERY: indicated in the presence of class III obesity (or class II obesity with secondary comorbidities) and failure of other treatment modalities with an acceptable operative risk

- **Options**: Vertical gastroplasty with laparoscopic banding or laparoscopic Roux-en-Y gastric bypass

HEALTHY DIET

DASH diet or Mediterranean diet or AHA diet; emphasize intake of vegetables, fruits, whole grains, nontropical vegetable oils, nuts, low-fat dairy products, fish, poultry; limit intake of sodium - sweets - sugar-sweetened beverages - red meats

BENEFIT ON CONVENTIONAL CARDIOVASCULAR RISK FACTORS: ↘ LDL; ↘ BP; ↘ Weight; ↘ DM

MEDITERRANEAN DIET: rich in olive oil / nuts / fruit and vegetables; ↘ cardiovascular mortality in secondary prevention (★ Lyon diet heart study) and ↘ cardiovascular events in primary prevention (★ PREDIMED)

Total calories - Energy balance	**Intake equal to energy expenditure** **Normal intake: 22 kcal/kg (± 20%)**
Fat	**< 35 % of total energy intake**
Mono- and polyunsaturated fatty acids (fish; vegetable oils; nuts)	• Increase intake • **Omega-3 fatty acids → ↘** cardiovascular mortality (★ GISSI-Prevention)
Saturated fatty acids	< 7% of total energy intake Avoid red meat - high-fat dairy products - tropical oils (palm; coconut)
Trans fatty acids / Hydrogenated oils	Limit to a minimum; < 1% of total energy intake; ↗ LDL and ↘ HDL
Dietary cholesterol	< 200-300 mg daily
Carbohydrates	**45 - 60% of total energy intake** Prefer whole grain products - low-fat dairy products - fruit and vegetables Avoid carbohydrates with a high glycemic index (potatoes; white bread; white rice; soft drinks)
Proteins	**15 -20% of total energy intake**
Fibers (whole grains; fruit; vegetables; nuts)	Increase intake; 25 - 50 g daily
Fruit and vegetables	≥ 8-10 servings per day
Fish	At least twice a week
Sodium	< 2.4 g per day
Alcohol	M: 20 g per day (2 glasses); F: 10 g per day (1 glass) (caution in the presence of DM - HTN - Liver disease - History of alcohol abuse)
Red meat; High-fat dairy products	Limit to a minimum

METABOLIC SYNDROME

CENTRAL OBESITY (WAIST) USA - Canada: M: ≥ 102 cm; F: ≥ 88 cm Europid: M: ≥ 94 cm; F: ≥ 80 cm	+	**≥ 2 OF THE FOLLOWING RISK FACTORS** • TG ≥ 1.7 mmol/L (150 mg/dL) • HDL: M < 1.03 and F < 1.3 mmol/L (40 - 50 mg/dL) • BP ≥ 130/85 (or treated HTN) • Fasting blood glucose ≥ 5.6 mmol/L (100 mg/dL)

↗ risk of cardiovascular disease and DMII

MANAGEMENT: control of cardiovascular risk factor; regular exercise; weight loss

9.9/ OBSTRUCTIVE SLEEP APNEA SYNDROME

OBSTRUCTIVE APNEA: **absence of airflow for ≥ 10 s despite active ventilatory efforts**

OBSTRUCTIVE HYPOPNEA: ↘ airflow < 50% for ≥ 10 s with ↘ SaO_2 ≥ 4 %

APNEA-HYPOPNEA INDEX (AHI): mean number of episodes of apnea and hypopnea per hour (mild if AHI ≥ 5; severe if AHI ≥ 30)

CLINICAL FEATURES: snoring; daytime sleepiness; witnessed apnea during the night; morning headache; disorders of concentration

HARMFUL EFFECTS: sympathetic stimulation; transient hypoxemia; marked fluctuations of intrathoracic pressure (↗ afterload); nocturnal HTN; treatment-resistant HTN; diastolic dysfunction; nocturnal angina

ASSOCIATIONS: obesity; DM; metabolic syndrome; AF; CAD; stroke; heart failure; nonischemic dilated cardiomyopathy; PHT

DIAGNOSIS: Polysomnography (screening by nocturnal saturometry)

TREATMENT: Weight loss; CPAP; Oral device; Surgery

9.10/ DRIVING & AIR TRAVEL

	PRIVATE VEHICLE	COMMERCIAL VEHICLE
STEMI	1 month	3 months
NSTEMI - Significant damage (RWMA)	1 month	3 months
Unstable angina or NSTEMI without RWMA	48 h post-PCI (7 days in the absence of PCI)	7 days post-PCI (30 days in the absence of PCI)
CAD - PCI	48 h post-PCI	7 days post-PCI
CABG	1 month	3 months
LMCA	Disqualified if > 70%	Disqualified if > 50%
VF - Absence of reversible cause	6 months	Disqualified
Unstable VT	6 months	Disqualified
VT or VF - Reversible cause (MI; Electrocution; Drugs)	Disqualified until correction of reversible cause	
Stable sustained VT - LVEF < 30%	3 months	Disqualified
Stable sustained VT - LVEF ≥ 30%; without ICD	4 weeks	3 months
Symptomatic SSS	Disqualified until treatment	
LBBB or Bifascicular block or Mobitz I or Bifascicular block + 1st degree AV block	No restriction in the absence of alteration of LOC	No restriction in the absence of alteration of LOC and in the absence of higher grade of AV block on annual Holter
Mobitz II (infranodal)	Disqualified	Disqualified
Alternating RBBB and LBBB	Disqualified	Disqualified
3rd degree AV block	Disqualified	Disqualified

Pacemaker	1 week post-implantation (no alteration of LOC postimplantation; functioning pacemaker)	1 month post-implantation (no alteration of LOC postimplantation; functioning pacemaker)
ICD - Primary prevention (NYHA I to III)	4 weeks	Disqualified
ICD - Secondary prevention (VF or VT with alteration of LOC)	6 months	
ICD - Secondary prevention (stable VT; NYHA I to III)	1 week + interval associated with VT	
Therapy (ATP or shock) with alteration of LOC	6 months	
Brugada / Long QT / ARVD	6 months after episode with alteration of LOC	Disqualified
EPS (without induced VT) or ablation procedure	48 h	1 week
SVT / AF / Flutter with alteration of LOC	• Ablation: 48 h • Medical treatment: 3 months	• Ablation: 1 week • Medical treatment: 3 months
Classical vasovagal syncope - 1st episode	No restriction	No restriction
Classical vasovagal syncope - Recurrence (< 12 months)	1 week	12 months
Syncope with treated cause (e.g.: pacemaker)	1 week	1 months
Situational syncope	1 week	1 week
Unexplained syncope - 1st episode	1 week	12 months
Unexplained syncope - Recurrence (< 12 months)	3 months	12 months
AS	NYHA I or II; No alteration of LOC	Asymptomatic - NYHA I - Area ≥ 1 cm² - LVEF ≥ 35%
AR - MS - MR	NYHA I or II; No alteration of LOC	No alteration of LOC - NYHA I - LVEF ≥ 35%
Mechanical valve or Bioprosthesis	6 weeks Anticoagulation (if indicated) No thromboembolic complication	3 months NYHA I and LVEF ≥ 35% Anticoagulation (if indicated) No thromboembolic complication
NYHA I or II	No restriction	LVEF ≥ 35%
NYHA III	No restriction	Disqualified
NYHA IV	Disqualified	Disqualified

Heart transplant	6 week NYHA I or II	6 months NYHA I; LVEF ≥ 35% No ischemia on annual noninvasive test
LVAD - continuous flow ventricular assist device	2 months NYHA I-III	Disqualified
HCM	No alteration of LOC	Wall thickness < 30 mm; No syncope; No NSVT (annual Holter); No family history of sudden death; No ↘ BP on exercise

AIR TRAVEL

INDICATION FOR O_2: A) PaO_2 < 70 mmHg; **B)** CCS III/IV angina; **C)** NYHA III/IV heart failure; **D)** Cyanotic congenital heart disease; **E)** PHT - Right heart failure

Stable angina / NYHA I – II – III	O_2 if NYHA III
Post-myocardial infarction / NYHA I	6-8 weeks
Heart failure / NYHA I - II - III	O_2 if NYHA III
Valvular heart disease / NYHA I - II - III	O_2 if NYHA III or PHT
Congenital heart disease / NYHA I - II - III	O_2 if NYHA III or PHT or PaO_2 < 70 mmHg
ICD / NYHA I - II	1 month post-ICD therapy associated with presyncope or syncope

9.11/ CARDIOVASCULAR COMPLICATIONS OF SYSTEMIC DISEASES

HIV

Heart failure - Dilated cardiomyopathy - Myocarditis; Pericardial effusion / Pericarditis; Infective and noninfective endocarditis (non-bacterial thrombotic endocarditis); PHT; Neoplasia → Kaposi sarcoma (epicardial) / NHL; Accelerated atherosclerosis / Endothelial dysfunction; Early-onset cerebrovascular disease; Protease inhibitors → lipodystrophy / ↗ TG - ↗ LDL - ↘ HDL / Glucose intolerance; Arrhythmias - ↗ QT; Dysautonomia; Vasculitis; Drug interactions

VASCULITIS

TAKAYASU - GIANT CELL ARTERITIS - BEHÇET: ▸▸| Chapter 8

KAWASAKI: young children (< 5 years); fever; rash; conjunctivitis; lymphadenopathy; mucosal lesions; erythema of extremities then desquamation

- **Cardiac involvement**: pericardial effusion; myocarditis; MI; aortitis; AR; heart failure; arrhythmias; coronary arteritis
- **Coronary artery stenoses or aneurysms:** < 6 weeks after onset of the disease; proximal lesions; short-term, medium-term and long-term risk of thrombosis
- **Treatment:** ASA; IV Ig; consider anticoagulation if multiple aneurysms or thrombus

CHURG & STRAUSS: pericarditis; myocarditis; coronary arteritis; heart failure; mesenteric ischemia

POLYARTERITIS NODOSA (MEDIUM VESSEL VASCULITIS): HTN; heart failure; arteritis; coronary aneurysms; angina; myocardial infarction; pericarditis

CONNECTIVE TISSUE DISEASES

RHEUMATOID ARTHRITIS: pericarditis; pericardial effusion; constriction; accelerated CAD; blocks (rheumatoid nodules); granulomatous valve lesions with regurgitation (mitral; aortic); rheumatoid aortitis; PHT (rheumatoid lung disease)

HLA-B27-ASSOCIATED SPONDYLOARTHROPATHIES: aortitis / aortic root dilatation; aortic valvulitis; AR; blocks; early CAD

SYSTEMIC LUPUS ERYTHEMATOSUS: pericarditis; pericardial effusion; constrictive pericarditis; coronary arteritis; accelerated CAD; nonbacterial endocarditis (Libman-Sacks; nonmobile vegetations); valvulitis (fibrosis; retraction; regurgitation); myocarditis; sinus tachycardia; congenital AV block; PHT; aortitis

- **Drug-induced lupus**: hydralazine; procaïnamide; quinidine
- **Antiphospholipid syndrome (antiphospholipid antibodies or lupus anticoagulant)**: arterial or venous thrombosis; myocardial infarction; stroke; intracardiac thrombus; PHT; nonbacterial endocarditis; valvulitis (fibrosis; regurgitation)

SCLERODERMA: Raynaud; renal crisis; pericarditis; pericardial effusion; microvascular ischemia; myocardial fibrosis; heart failure (diastolic > systolic); conduction disorders; PHT

POLYMYOSITIS: myocarditis / heart failure; blocks; PHT

ENDOCRINE DISEASES

ACROMEGALY: HTN; LVH; heart failure; diastolic dysfunction; stroke; insulin resistance; aortic root dilatation; mitral regurgitation

CUSHING'S DISEASE: Accelerated CAD; hyperglycemia / insulin resistance; dyslipidemia; HTN; LVH; heart failure; dilated cardiomyopathy; stroke; PAD

HYPERPARATHYROIDISM: ↗ contractility; short QT; calcifications (valvular; aortic)

HYPOCALCEMIA: Prolonged QT; ↘ contractility

HYPERTHYROIDISM: high output; ↘ systemic resistance; systolic HTN (↗ pulse pressure); sinus tachycardia; ↗ plasma volume; angina (↗ O_2 demand); vasospasm; PHT; AF; heart failure

HYPOTHYROIDISM: low output state; ↗ systemic resistance; sinus bradycardia; diastolic HTN; ↗ LDL; hypertriglyceridemia; pericardial effusion; prolonged QT; low voltage; ↗ risk of CAD; diastolic dysfunction

PHEOCHROMOCYTOMA: HTN; tachycardia; concentric LVH; myocarditis; cardiomyopathy similar to Takotsubo

MUSCULAR DYSTROPHIES

PERMANENT PACEMAKER: **A)** Third-degree or advanced second-degree AV block (class I recommendation); **B)** May be considered with any degree of AV block (including first degree) in patients with Steinert disease, Kearns-Sayre syndrome or limb-girdle muscular dystrophy (class IIb)

BECKER DYSTROPHY AND DUCHENNE DYSTROPHY: X-linked; ↗ CK; **progressive dilated cardiomyopathy**; MR; hypertrabeculations; arrhythmias; blocks

- **Duchenne**: **prominent R wave in V1** (↗ R/S ratio); Q wave in left precordials; short PR; RVH

MYOTONIC DYSTROPHY: autosomal dominant; **predominantly affects conduction tissue**; blocks; arrhythmias (AF; flutter; VT; bundle branch reentry VT); systolic and/or diastolic dysfunction; LVH; MVP

› **Follow-up**: Annual ECG and Holter

EMERY-DREIFUSS DYSTROPHY: DCM; arrhythmias (AF; Flutter; atrial asystole with junctional rhythm; VT; VF); conduction disorders (including dystrophy secondary to **lamin A/C** mutation)

LIMB-GIRDLE MUSCULAR DYSTROPHY: **DCM**; prominent R wave in V1; blocks

OTHER NEUROLOGICAL DISEASES

FRIEDREICH'S ATAXIA: autosomal recessive; **concentric HCM** (sometimes localized in the septum); LVOT obstruction; diffuse T wave inversion; possible progression to DCM

MITOCHONDRIAL DISEASES: HCM; DCM; blocks (Kearns-Sayre syndrome); preexcitation

DESMIN-RELATED MYOPATHY: autosomal dominant; conduction disorders; DCM; RCM

GUILLAIN-BARRÉ SYNDROME: HTN; OH; sinus tachycardia; ST abnormalities; tachyarrhythmias / bradyarrhythmias; asystole

MYASTHENIA GRAVIS: myocarditis; arrhythmias; blocks

ACUTE CEREBROVASCULAR DISEASE: ST elevation or depression; T wave inversion; Q waves; ↗ QT (with peaked T wave); neurogenic stunned myocardium; Takotsubo cardiomyopathy; systolic dysfunction; acute pulmonary edema; VT - VF; Torsade de pointes; bradyarrhythmias

CHRONIC RENAL DISEASE

INDEPENDENT CARDIOVASCULAR RISK FACTOR

Accelerated and aggressive CAD; cardiomyopathy; LVH; HTN; valvular heart disease (Ao sclerosis; MAC); vascular calcifications; toxicity of cardiovascular drugs; dyslipidemia (↘ HDL; ↗ TG - ↗ LDL); cardiorenal syndrome; arrhythmias; blocks; infective endocarditis; anemia associated with heart failure; risk of contrast nephropathy; inflammatory state

› To convert serum creatine level mg/dL to mmol/L, multiply by 88.4

› **High output heart failure (AV fistula)**: Nicoladoni - Branham sign → ↘ cardiac output (↘ LVOT VTI) after manual compression of the fistula; predictive improved cardiac output after fistula ligation

9.12/ CARDIOVASCULAR COMPLICATIONS OF TRAUMA

PENETRATING INJURY: knife; bullet

› Tamponade; Ischemia (coronary trauma); Complex lesion (valves; coronary arteries; intracardiac fistula)

NONPENETRATING INJURY: compression or deceleration or contusion; safety belt; airbag; steering wheel; fall; collision; rib fractures; CPR

› Contusion; systolic dysfunction; LV free wall rupture (tamponade or hemothorax); RA rupture; ventricular septal rupture; ruptured chordae tendineae or papillary muscle; ruptured valve leaflet (Ao > M > T); Ao rupture; rupture of pericardium (cardiac hernia); arrhythmias; blocks; myocardial infarction (thrombosis; dissection; coronary laceration); *commotio cordis*

SEVERE BURN: toxic myocardial depression for several days (in addition to significant hypovolemia)

ELECTROCUTION: cardiac arrest (VF; asystole); myocardial necrosis; ischemia; arrhythmias; conduction disorder; ECG abnormalities; dysautonomia

MANAGEMENT

ABC; ACLS; Cardiac monitor; NS Bolus; Transfusion; Ultrasound (FAST); OR - Urgent left anterolateral thoracotomy in the case of structural damage

9.13/ POISONING

COCAINE POISONING

SYMPATHOMIMETIC AGENT: inhibition of presynaptic reuptake of norepinephrine and dopamine

CARDIOVASCULAR COMPLICATIONS: sympathetic stimulation; HTN; LVH; ischemia; MI; DCM (excess catecholamines); myocarditis; heart failure (systolic and/or diastolic); arrhythmia; sudden death; endocarditis; aortic dissection; stroke - intracranial hemorrhage; Takotsubo; Brugada pattern on ECG; ↗ QT (effect on sodium and potassium channels)

MYOCARDIAL INFARCTION: ↗ O_2 demand; vasospasm; accelerated CAD; thrombosis (↗ platelet activation / aggregation); ↗ plaque rupture; coronary dissection

- **Treatment of myocardial infarction:** O_2; ASA; Benzodiazepines; Nitrates; CCB (Diltiazem 20 mg IV); Coronary angiography if persistent ST elevation (thrombolysis if coronary angiography not available and in the absence of contraindication); avoid BB (unopposed alpha-adrenergic stimulation)

BETA-BLOCKER POISONING

PRESENTATION: Symptoms often appear within first 6 h after ingestion: bradycardia; hypotension; cardiogenic shock; altered LOC; seizures; hypoglycemia; bronchospasm

ASSESSMENT: ECG; Glucose; Electrolytes; Ca^{2+}; BUN; Creatinine; Acetaminophen - Salicylate; beta-HCG

- **ECG**: sinus bradycardia; ↗ PR interval; ↗ QRS interval (Propranolol or Acebutolol); bradyarrhythmia; asystole

MANAGEMENT: ABC; Monitor; Atropine (0.5-1 mg IV every 3-5 min up to 0.04 mg/kg); Bolus NS; IV Dextrose; Benzodiazepine if seizures; Activated charcoal (50 g) if patient presents 1-2 h postingestion; Poison Center

IF NECESSARY (IN THE FOLLOWING ORDER)

a) **Glucagon:** IV bolus 5 mg over 1 min (± 2nd bolus in 10 min); if improvement → start infusion (2-5 mg/h); target MAP 60 mmHg; Antinausea treatment (Ondansetron)
b) **IV Calcium:** Calcium chloride (1 g of 10% solution = 10 mL via central line up to a dose of 3 g if necessary) or Calcium gluconate (30 mL of a 10% solution via a central or peripheral line); Monitoring of serum calcium
c) **Vasopressors:** Epinephrine (1-10 µg/min; titrate to achieve MAP of 60 mmHg)
d) **High-dose insulin / Glucose (D5-10%) infusion;** ▶▶| CCB poisoning; K^+ - Mg^{2+} supplement PRN
e) **IV fat emulsion** (parenteral nutrition)
f) **Sodium bicarbonate** (1-2 mEq/kg IV ± infusion) if ↗ QRS interval
g) **Endovenous pacemaker:** frequent capture failure; only slight hemodynamic improvement; consider if failure of drug treatment
h) **IABP / Ventricular assist device** if failure of drug treatment
i) **Consider hemodialysis** if failure of drug treatment (Atenolol; Nadolol; Sotalol; Acebutolol)

CALCIUM CHANNEL BLOCKER POISONING

DIHYDROPYRIDINE CCB: arterial vasodilatation; reflex tachycardia; effects of nondihydropyridine CCB with high-dose ingestion

NONDIHYDROPYRIDINE CCB: peripheral vasodilatation; bradycardia; negative inotropic agent

ASSESSMENT: ECG; Glucose; Electrolytes; Ca^{2+}; BUN; Creatinine; Acetaminophen - Salicylate; beta-HCG

MANAGEMENT: ABC; Monitor; Bolus NS; Atropine (0.5-1 mg IV every 2-3 min up to 3 mg); activated charcoal (50 g) if patient presents in 1-2 h post-ingestion; Poison Center

IV CALCIUM: Calcium chloride (10-20 mL of solution 10% x 10 min via central line; repeat up to 4 x if necessary every 20 min) or Calcium gluconate (30 to 60 mL of a 10% solution via a central or peripheral line); Monitoring of serum calcium

- **Infusion**: Calcium chloride (0.2-0.4 mL/kg/h of a 10% solution) or Calcium gluconate (0.6-1.2 mL/kg/h of a 10% solution) if necessary; serum ionized calcium assay every 2 hours; ECG monitoring

IF NECESSARY (IN THE FOLLOWING ORDER)

a) Glucagon: IV bolus 5 mg over 1 min (± 2nd and 3rd boluses every 10 min); if improvement → start infusion (2-15 mg/h); target MAP 60 mmHg; Antinausea treatment (Ondansetron)

b) High-dose insulin / Glucose infusion; 50 mL D50% if blood glucose < 8.25 mmol/L; Correct potassium

- **Bolus:** 1 unit/kg of regular insulin IV
- **Infusion:** 0.5 U/kg/h IV (titrate up to 2 U/kg/h according to response; increase by 0.5 U/kg/h every 20 min)
  - **D5-10% infusion**: 0.5-1 g/kg/h of dextrose; additional bolus of D50% PRN (capillary blood glucose **every 15-30 min)**
  - **Serum potassium** assay every 30 min (± Mg^{2+}); supplement as necessary

c) IV vasopressor: IV Norepinephrine

d) IV fat emulsion (parenteral nutrition): bolus 1-1.5 mL/kg x 1 min (20% solution); Infusion 0.25-0.5 mL/kg/min (30-60 min)

e) Other measures: Endovenous pacemaker (but does not improve contractility); IABP - Ventricular assist device

DIGOXIN POISONING

EXTRACARDIAC MANIFESTATIONS: visual disorders; GI symptoms (nausea; vomiting); neurological symptoms (confusion; muscle weakness); hyperkalemia

CARDIAC MANIFESTATIONS: sinus bradycardia; sinus arrest; ectopic atrial tachycardia with AV block; "regularized" AF (junctional escape rhythm); junctional tachycardia; AV block; PVCs; ventricular bigeminy; VT; bidirectional VT; VF

- **Mechanisms**: **A)** ↗ **Delayed after-depolarizations** (due to ↗ intracellular Ca^{2+}); **B)** ↗ **Automaticity; C)** ↗ Vagal tone; **D)** Associated hyperkalemia
- **Digoxin impregnation**: flattening / inversion of T waves; ↘ QT; "scooped" ST segment; ST depression (lateral leads); U waves

ASSESSMENT: Plasma digoxin (6 h post-ingestion if acute poisoning); electrolytes; K+; Mg^{2+}; Creatinine - BUN; ECG; Blood glucose

MANAGEMENT: ABC; Cardiac monitoring; Poison Center; Atropine 0.5 mg IV; Bolus NS; Activated charcoal if poisoning < 1-2 h

CORRECT HYPOKALEMIA: as hypokalemia exacerbates the toxic effects; correct hypomagnesemia associated with hypokalemia

- **Do not correct hyperkalemia,** which is corrected by Digibind

ANTIDOTE: Digibind (anti-Digoxin antibody)

- **Indications: A)** Threatening arrhythmia (symptomatic bradycardia; AV block; ventricular arrhythmia; asystole); **B)** Target organ damage (ARF; altered state of consciousness); **C)** Hyperkalemia (> 5 - 5.5 mmol/L)
- **1 vial of Digibind neutralizes 0.5 mg of Digoxin**

EMPIRICAL TREATMENT (ACUTE POISONING WITH UNKNOWN DOSE)	ACUTE POISONING WITH KNOWN INGESTED DOSE	CHRONIC POISONING WITH KNOWN PLASMA DIGOXIN
10 vials (repeat in 30 min if insufficient)	Number of vials = [Ingested dose of Digoxin (mg) x 0.8] / 0.5	Number of vials = [Serum concentration (ng/mL) x patient's weight (kg)] / 100

MAINTAIN ON MONITOR > 72 H if concomitant renal failure (delayed elimination)

HEMODIALYSIS: not indicated

9.14/ SWAN-GANZ CATHETER PLACEMENT

INDICATIONS: A) Cardiogenic shock; **B)** Mixed shock; **C)** Mechanical complication of myocardial infarction; **D)** PHT; **E)** Pretransplantation assessment

1) VERIFICATIONS: patency of ports; test balloon and pressure transducer

2) CENTRAL VENOUS ACCESS: insert the introducer (Cordis) under ultrasound guidance into the internal jugular vein (modified Seldinger technique)

3) SWAN-GANZ CATHETER PLACEMENT: insert the Swan-Ganz catheter by following the natural curvature towards the PA

- Inflate the balloon in the RA (RA hemodynamic curve); keep the balloon inflated while advancing the Swan-Ganz (deflate the balloon on withdrawal)
- Advance the Swan-Ganz while examining changes in the appearance of the hemodynamic curve displayed on the monitor (RA → RV → PA → Wedge)

RA	RV	PA
15-20 cm	**30 cm**	**40 cm**

- Withdraw the Swan-Ganz if **< 1 mL of NS** is necessary to inflate the balloon and obtain a Wedge pressure (the catheter tip is probably too distal)

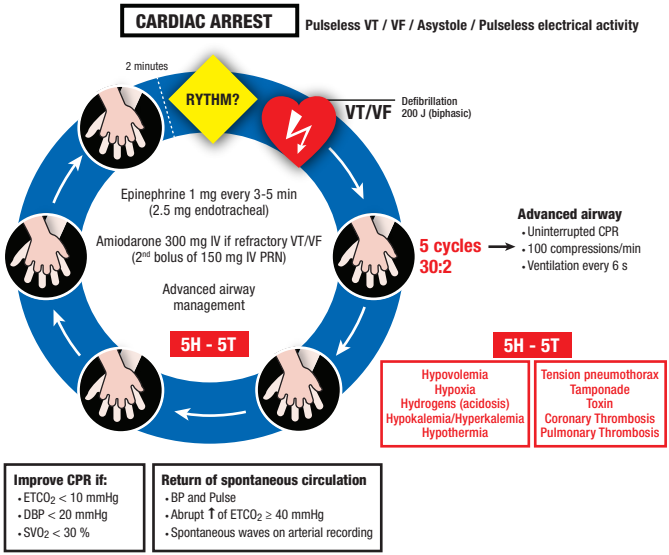
4) CXR: catheter tip < 5 cm from the midline; West zone # 3 preferable

CONSIDER FLUOROSCOPY if chamber dilatation or significant TR

AIR EMBOLISM: left lateral decubitus position (to prevent RVOT obstruction); 100% O_2

9.15/ CARDIOPULMONARY RESUSCITATION

CARDIOPULMONARY ARREST



RECOGNIZE CARDIOPULMONARY ARREST: unresponsive / breathing / pulse

› **Activate the survival chain:** 911 - Blue Code - Defibrillator / AED

CARDIOPULMONARY RESUSCITATION

› **Cycles: 30 compressions : 2 ventilations**

› **Compressions**: lower half of the sternum; 100-120 compressions / min; 5 cm deep (avoid > 6 cm); complete chest recoil between each compression; minimize interruptions

› **Ventilation**: Head tilt / Chin lift ("Jaw thrust" if cervical trauma); avoid excessive ventilation

DEFIBRILLATION: Pulseless VT or VF; perform as rapidly as possible

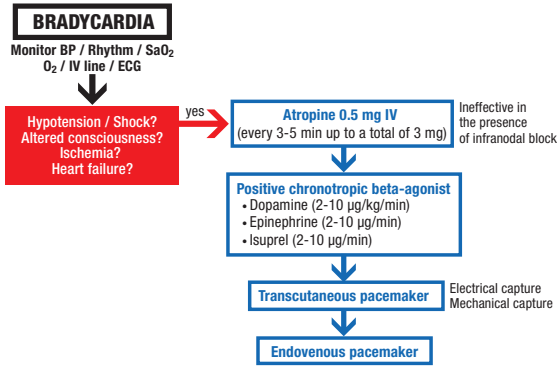
AIRWAY MANAGEMENT

› **Initial ventilation**: Ambu mask; 1 s; elevation of the rib cage; avoid excessive ventilation

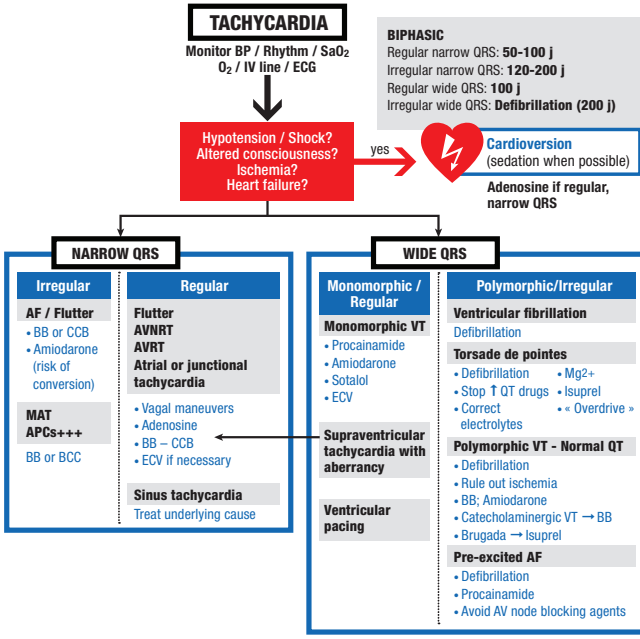
› **Advanced airways support**: allows better ventilation and protects the airways; Endotracheal tube or Laryngeal mask or Combitube

- **Confirmation of position: A)** Physical examination (expansion of rib cage; auscultation); **B)** Capnography / CO_2 detector; **C)** Esophageal detector (syringe); **D)** CXR (distal extremity of ETT > 3 cm from the carina)
- **CPR cycles**: **Continuous compressions at 100 bpm; Asynchronous ventilation every 6 sec**

BRADYCARDIA



TACHYCARDIA



DRUGS USED IN CARDIOPULMONARY RESUSCITATION

Adenosine	• 6 mg IV (push) then 20 mL NS • 2nd bolus 12 mg IV PRN	• Supraventricular tachycardia	Bronchospasm; Hypotension; Flushing; Retrosternal chest pain; Can trigger AF
Amiodarone	• 150 mg IV x 10 min (repeat PRN) • Infusion: 1 mg/min x 6 h then 0.5 mg/min (dilution: 450 mg / 250 mL D5%) • Max: 2.2 g / 24 h	• Supraventricular tachycardia • Stable monomorphic VT • Polymorphic VT with normal QT	Bradycardia; ↗ QT; Long-term toxicity
Beta-blockers	• **Esmolol:** 0.5 mg/kg x 1 min then infusion of 0.05-0.3 mg/kg/min (dilution: 2500 mg / 250 mL) • **Metoprolol**: 5 mg IV x 1 min (repeat every 5 min up to a total of 15 mg)	• Supraventricular tachycardia • Polymorphic VT associated with ischemia or LQTS or catecholaminergic VT	Hypotension: Bradycardia; Negative inotrope; Bronchospasm
Diltiazem	• 15-20 mg IV x 2 min • 2nd bolus (in 15 min): 20-25 mg IV • Infusion: 5-15 mg/h IV • Dilution: 125 mg/100 mL D5 % (= 1 mg/mL)	• Supraventricular tachycardia	Hypotension; Bradycardia; Negative inotrope
Lidocaine	• Bolus: 1-1.5 mg/kg IV • Perfusion: 1-4 mg/min (30-50 µg/kg/min) • Dilution: 2 g / 500 mL D5%	• Stable monomorphic VT	Altered state of consciousness; Seizures; Bradycardia
Procainamide	• 20-50 mg/min (until suppression of arrhythmia or hypotension or ↗ QRS > 50% or total dose 17 mg/kg) • Dilution: 1000 mg / 250 mL NS	• Pre-excited AF • Stable monomorphic VT	Bradycardia; Hypotension; ↗ QT; Torsade de pointes; Avoid in the presence of heart failure
Sotalol	• 1.5 mg/kg IV x 5 min	• Stable monomorphic VT	Bradycardia; Hypotension; ↗ QT; Torsade de pointes; Avoid in the presence of heart failure
Magnesium sulfate	• 1-2 g IV x 15 min	• Polymorphic VT with ↗ QT	Hypotension; Respiratory depression
Epinephrine	• **Dose**: 0.1-0.5 µg/kg/min • **Dilution:** 5 mg / 250 mL D5%		

Dobutamine	• **Dose**: 2-20 µg/kg/min • **Dilution:** 250 mg / 100 mL D5%
Dopamine	• **Dose**: 1-20 µg/kg/min • **Dilution:** 400 mg / 250 mL D5%
Isuprel	• **Dose**: 0.5-10 µg/min • **Dilution:** 1 mg / 250 mL D5%
Milrinone	• **Bolus**: 50 µg/kg x 10 min • **Dose**: 0.375 to 0.75 µg/kg/min • **Dilution:** 10 mg / 100 mL D5% (= 0.09 mg/mL) or 20 mg / 100 mL D5% (= 0.17 mg/mL)
Norepinephrine	• **Dose**: 0.1-0.5 µg/kg/min • **Dilution:** 4 mg / 250 mL D5% (double PRN)
Phenylephrine	• **Dose**: 0.5-2 µg/kg/min • **Dilution:** 10 mg / 250 mL NS

MANAGEMENT POST-CARDIAC ARREST

Look for and treat the cause of the cardiac arrest; Coronary angiography if necessary

VENTILATION: Tidal volume 6-8 mL/kg; $SaO_2 \geq 94\%$; $PaCO_2$ 40-45 mmHg

TARGET ORGAN PERFUSION: NaCl bolus; vasopressors (Epinephrine; Dopamine; Norepinephrine); treat any reversible causes; IABP - Ventricular assist device

- Stunned myocardium x 24-48 h and transient SIRS post-cardiac arrest
- **Targets:** SBP ≥ 90 mmHg; MAP ≥ 65 mmHg; $SVO_2 \geq 70$ %

TARGETED TEMPERATURE MANAGEMENT

- **Indications**: Comatose adult patients (no meaningful response to verbal commands) with return of spontaneous circulation after cardiac arrest
- **Benefits**: improvement of survival and neurological prognosis (★ Hypothermia after cardiac arrest study group)
- **Targets**: uncertain (between 32°C to 36°C for at least 24 h); intensive treatment of hyperthermia; ★ TTM → no demonstrated benefit of 33°C versus 36°C
- **Complications**: coagulopathy; arrhythmias; ↗ QT; bradycardias; hyperglycemia; infectious risk; hypokalemia / hypomagnesemia / hypophosphatemia

NEUROLOGICAL ASSESSMENT: neurological examination; EEG (rule out seizures in the presence of persistent coma); Brain CT / MRI

- **Factors of poor prognosis (valid after > 72 h)**: **A)** Bilaterally absent pupillary light reflex; bilaterally absent corneal reflexes; **B)** Status myoclonus (during the first 72 hours); **C)** EEG with persistent absence of reactivity to external stimuli or with persistent burst supression or with intractable status epilepticus; **D)** Somatosensory evoked potentials (bilateral absence of cortical response to median nerve stimulation); **E)** Imaging (extensive cortical / subcortical lesions; extensive brain edema)
- **Brain death**: consider organ donation

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Abbreviations

A

AAD: Antiarrhythmic drug
AAA: Abdominal aortic aneurysm
ABC: Airway, Breathing, Circulation
ABI: Ankle-Brachial Index
A/C: Anticoagulant / Anticoagulation
ACEi: Angiotensin-converting enzyme inhibitor
ACLS: Advanced Cardiac Life Support
ACS: Acute coronary syndrome
AF: Atrial fibrillation
AIVR: Accelerated idioventricular rhythm
ALT: Alanine aminotransferase
AML: Anterior mitral leaflet
ANA: Antinuclear antibody
Ao: Aorta
APC: Atrial premature complex
Apo: Apoliprotein
aPTT: Activated partial thromboplastin time
AR: Aortic regurgitation
ARB: Angiotensin receptor blocker
ARDS: Adult respiratory distress syndrome
ARF: Acute renal failure
ARVD: Arrhythmogenic right ventricular dysplasia
AS: Aortic stenosis
ASA: Acetylsalicylic acid
ASD: Atrial septal defect
AST: Aspartate aminotransferase
ATL: Anterior tricuspid leaflet
AV: Atrioventricular
AVM: Arteriovenous malformation
AVNRT: Atrioventricular nodal reentrant tachycardia
AVR: Aortic valve replacement
AVRT: Atrioventricular reentry tachycardia

B

BB: Beta-blockers
BID: Twice daily
BMI: Body mass index
BMS: Bare metal stent
BNP: Natriuretic peptide type B
BOOP: Bronchiolitis obliterans organizing pneumonia
BP: Blood pressure
BSA: Body surface area
BUN: Blood urea nitrogen
BVR: Balloon Valvuloplasty Registry

C

CABG: Coronary artery bypass graft
CAD: Coronary artery disease
CBC: Complete blood count
CCB: Calcium channel blockers
CCS: Canadian Cardiology Society
CCV: Chemical cardioversion
CK: Creatinine kinase
CM: Cardiomyopathy
CML: Chronic myeloid leukemia
CNS: Central nervous system
CO: Cardiac output
CoA: Coarctation of the aorta
CoNS: Coagulase-negative Staphylococcus
COPD: Chronic obstructive pulmonary disease
COX-1: Cyclooxygenase-1
CPB: Cardiopulmonary bypass
CRF: Chronic renal failure
CRP: C-reactive protein
CRT: Cardiac resynchronization therapy
CS: Coronary sinus
CSNRT: Corrected Sinus Node Recovery Time
CT: Computed tomography
cTn: Cardiac troponin
cTnT HS: Highly sensitive cardiac troponin T
cTnT: Cardiac troponin T
CTO: Chronic total occlusion
CVP: Central venous pressure
CXR: Chest x-ray

D

DBP: Diastolic blood pressure
DCM: Dilated cardiomyopathy
DDx: Differential diagnosis
DES: Drug-eluting stent
DIC: Disseminated intravascular coagulation
DM: Diabetes
dP/dt: Rate of LV pressure rise in early systole
DTS: Duke Treadmill score
DVT: Deep vein thrombosis

E

ECG: Electrocardiogram
ECMO: Extracorporeal membrane oxygenation
ECV: Electrical cardioversion
EEG: Electroencephalogram
EOA: Effective orifice area
EPO: Erythropoietin
EPS: Electrophysiological study
ESR: Erythrocyte sedimentation rate
EVAR: Endovascular aortic repair

F

FAC: Fractional Area Change

FFP: Fresh frozen plasma
FFR: Fractional flow reserve
FMD: Fibromuscular dysplasia

G

GERD: Gastroesophageal reflux disease
GFR: Glomerular filtration rate
GI: Gastrointestinal

H

HbA1c: Glycosylated hemoglobin
HCM: Hypertrophic cardiomyopathy
HDCT: High-definition computed tomography
HDL: High-density lipoprotein
HELLP: HELLP syndrome
HIT: Heparin-induced thrombocytopenia
HR: Heart rate
HSM: Hepatosplenomegaly
HTN: Hypertension

I

IABP: Intra-aortic balloon pump
IART: Intraatrial reentry tachycardia
ICD: Implantable cardioverter-defibrillator
IDU: Intravenous drug user
IMT: Intima-media thickness
INR: International normalized ratio
ISA: Intrinsic sympathetic activity
IUGR: Intrauterine growth retardation
IVC: Inferior vena cava
IVCT: Isovolumic contraction time
IVRT: Isovolumic relaxation time
IVS: Interventricular septum
IVUS: Intravascular ultrasound

J

JVD: Jugular vein distension

L

LA: Left atrium
LAA: Left atrial appendage
LAD: Left anterior descending
LAH: Left atrial hypertrophy
LAHB: Left anterior hemiblock
LAO: Left anterior oblique
LBBB: Left bundle branch block
LMCA: Left main coronary artery
LDH: Lactate dehydrogenase
LDL: Low-density lipoprotein
LFTs: Liver function tests
LGE: Late gadolinium enhancement
LIMA: Left internal mammary artery
LMWH: Low molecular weight heparin
LPHB: left posterior hemiblock
LPL: Lipoprotein lipase
LQTS: Long QT syndrome
LV: Left ventricle
LVAD: Left ventricular assist device
LVDD: Left ventricular diastolic diameter
LVEDP: Left ventricular end-diastolic pressure
LVEF: Left ventricular ejection fraction
LVH: Left ventricular hypertrophy
LVOT: Left ventricular outflow tract
LVSD: Left ventricular systolic diameter

M

M: Mitral
MAC: Mitral annular calcification
MAO inhibitor: Monoamine oxidase inhibitor
MAP: Mean arterial pressure
MCP: Metacarpophalangeal
MET: Metabolic Equivalent of Task
MIBIP: MIBI-Dipyridamole
MPA: Main pulmonary artery
MR: Mitral regurgitation
MS: Mitral stenosis
MSK: Musculoskeletal
MTX: Methotrexate
MVP: Mitral valve prolapse
MVR: Mitral valve replacement

N

NGT: Nasogastric tube
NIHSS: NIH Stroke Scale
NNT: Number needed to treat
NPO: Nil per os
NPV: Negative predictive value
NSAID: Non-steroidal anti-inflammatory drug
NSVT: Non-Sustained Ventricular Tachycardia
NYHA: New York Heart Association

O

OH: Orthostatic hypotension
OR: Operating room
OSAHS: Obstructive sleep apnea / hypopnea syndrome
OTP: Orthopnea

P

PA: Pulmonary artery
PAD: Peripheral artery disease
PAH: Pulmonary arterial hypertension
PAN: Polyarteritis nodosa
PAP: Pulmonary artery pressure
PAT: Paroxysmal atrial tachycardia
PCI: Percutaneous coronary intervention
PCR: Polymerase chain reaction
PDE-5: Phosphodiesterase-5
PET: Positron emission tomography
PET-FDG: Fluorodeoxy-glucose positron emission tomography
PFO: Patent foramen ovale
PFTs: Pulmonary function tests
PHT: Pressure half time
PHT: Pulmonary hypertension
PISA: Proximal isovolumic surface area
PDA: Posterior interventricular artery
PJRT: Paroxysmal junctional reentry tachycardia
PLAX: Parasternal long axis
PML: Posterior mitral leaflet
PMR: Polymyalgia rheumatica
PMT: Pacemaker-mediated tachycardia
PNC: Penicillin
PND: Paroxysmal nocturnal dyspnea
PO: Per os
POTS: Postural orthostatic tachycardia syndrome
PPD: Purified Protein Derivative (Mantoux test)
PPI: Proton pump inhibitor
PPM: Permanent pacemaker
PPV: Positive predictive value
PR: Pulmonary regurgitation
PRN: As needed
PS: Pulmonary stenosis
PSAX: Parasternal short axis
PSVT: Paroxysmal supraventricular tachycardia
PT: Prothrombin time
PTCA: Percutaneous coronary angioplasty
PTL: Posterior tricuspid leaflet
PTU: Propylthiouracil
PV: Pulmonary vein
PVAB: Post-ventricular atrial blanking
PVARP: Post-ventricular atrial refractory period
PVE: Prosthetic valve endocarditis
PVR: Pulmonary valve replacement
PVR: Pulmonary vascular resistance

Q

QD: Once daily
QID: Four times a day

R

RA: Rheumatoid arthritis
RA: Right atrium
RAA: Right atrial appendage
RAH: Right atrial hypertrophy
RAO: Right anterior oblique
RBBB: Right bundle branch block
RCA: Right coronary artery
RCM: Restrictive cardiomyopathy
RCT: Randomized controlled trial
RF: Radiofrequency
RF: Rheumatoid factor
RF: Risk factor
RPA: Right pulmonary artery
RUQ: Right upper quadrant
RV: Right ventricle
RVAD: Right ventricular assist device
RVG: Radionuclide ventriculography
RVH: Right ventricular hypertrophy
RVOT: Right ventricular outflow tract
RVSP: Right ventricular systolic pressure
RWMA: Regional wall motion abnormality
RWT: Relative wall thickness

S

SA: Sinoatrial
SAECG: Signal-averaged ECG
SAH: Subarachnoid hemorrhage
SAM: Systolic anterior movement of mitral leaflet
SaO_2: Oxygen saturation
SBP: Systolic blood pressure
SIRS: Systemic inflammatory response syndrome
SLE: Systemic lupus erythematosus
SPEP: Serum protein electrophoresis
SQTS: Short QT syndrome
SR: Sinus rhythm
SSRI: Selective serotonin reuptake inhibitor
SSS: Sick sinus syndrome
STS: Society of Thoracic Surgeons
STEMI: ST segment elevation myocardial infarction
STL: Septal tricuspid leaflet
SVC: Superior vena cava

SVO_2: Venous oxygen saturation
SVR: Systemic vascular resistance

T

T: Tricuspid
TARP: Total atrial refractory period
TAVI: Transcatheter aortic valve implantation
TB: Tuberculosis
TEE: Transesophageal echocardiography
TG: Triglycerides
TGV: Transposition of the great arteries
TIA: Transient ischemic attack
TID: Three times a day
TNK: Tenecteplase
TNT: Nitroglycerin
TOF: Tetralogy of Fallot
TR: Tricuspid regurgitation
TTE: Transthoracic echocardiography
TTR: Transthyretin
TVR: Tricuspid valve replacement
TXA-2: Thromboxane-2

U

ULN: Upper limit of normal
URI: Upper rate interval
URTI: Upper respiratory tract infection
US: Ultrasound

V

VAC: Vacuum assisted closure
VF: Ventricular fibrillation
VLDL: Very low density lipoprotein
VO_2: Oxygen consumption
VPC: Ventricular premature complex
VSD: Ventricular septal defect
VT: Ventricular tachycardia
VTI: Velocity-time integral
vW: von Willebrand

W

WMSI: Wall motion score index
WPW: Wolff-Parkinson-White

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Cardiology Board Review

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WILEY Blackwell

This edition first published 2018
© 2018 John Wiley & Sons Ltd

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John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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9600 Garsington Road, Oxford, OX4 2DQ, UK

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Library of Congress Cataloging-in-Publication Data:

Names: Pai, Ramdas G., author. | Varadarajan, Padmini, author. | Pai, Sudha M., 1958- author.
Title: Cardiology board review / by Ramdas G. Pai, Padmini Varadarajan, Sudha M. Pai.
Description: Hoboken, NJ : Wiley, 2017. | Includes index. |
Identifiers: LCCN 2017026562 (print) | LCCN 2017028086 (ebook) | ISBN 9781118699003 (pdf) | ISBN 9781118699010 (epub) | ISBN 9781118699027 (pbk.)
Subjects: | MESH: Heart Diseases | Examination Questions
Classification: LCC RC669.2 (ebook) | LCC RC669.2 (print) | NLM WG 18.2 | DDC 616.1/20076–dc23
LC record available at https://lccn.loc.gov/2017026562

Cover images: inset – © RichHobson/Gettyimages; main – © asiseeit/Gettyimages
Cover design by Wiley

Set in 10/12pt WarnockPro by Aptara Inc., New Delhi, India

10 9 8 7 6 5 4 3 2 1

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Preface

This book is a very comprehensive review of all major topics in cardiology with an intention to help those preparing for initial and recertification exams in cardiology and those who want to review cardiology in an easy-to-do fashion. It is a compilation of over 1300 questions encompassing all the topics in cardiology. This has been edited by an internationally acclaimed teaching physician with an expertise in all aspects of cardiology. The book is organized in a question-and-answer format and is divided into easy-to-follow chapters related to different areas of cardiovascular medicine. The answers are explained in detail and are accompanied by references to major trials in cardiology and guidelines, and some clinical pearls where applicable. The explanations are clear and evidence based. The book highlights a special section on electrocardiograms which are of high resolution. The answers to the questions are given in depth, which will allow the examinees to prepare for this section and take the exam with greater confidence as this section is scored separately from the main exam. The chapters on imaging have questions relating to chest X-ray, cardiac computed tomography, echo, stress echo, cardiac magnetic resonance imaging, nuclear stress testing, and so on. The book also deals with questions relating to topics not usually encountered in similar books: for example, racial disparities in medicine, cardiac emergencies, and so on. The book also facilitates critical review of cardiovascular medicine to enhance one's diagnostic and therapeutic skills.

History and Physical Examination

1

1.1. A 25-year-old woman has a 2/6 ejection systolic murmur best heard in the second left intercostal space with normal S1. The S2 is split during inspiration, and P2 intensity is normal. No apical or parasternal heave. The murmur diminishes during expiration and standing up. What is the murmur likely due to?

A. Physiological or normal
B. Atrial septal defect (ASD)
C. Bicuspid aortic valve
D. Hypertrophic obstructive cardiomyopathy (HOCM)

1.2. A 29-year-old pregnant woman was found to a have a systolic murmur best heard in the second left intercostal space. It is rough and there was a palpable thrill in the same area and in the suprasternal notch. Patient is asymptomatic and has normal exercise tolerance. What is the likely explanation of the murmur?

A. Pulmonary stenosis (PS)
B. Normal flow murmur due to increased cardiac output
C. Posterior mitral leaflet prolapse causing an interiorly directed jet
D. Mammary soufflé

1.3. A 22-year-old patient has a hypoplastic radial side of the forearm and fingerized thumb. What this may be associated with?

A. ASD
B. Tetralogy of Fallot
C. Coarctation of aorta
D. Ebstein's anomaly

1.4. A 28-year-old man presented with a history of shortness of breath on exertion. On examination, the pulse rate was 76 bpm and blood pressure (BP) 126/80 mmHg. The left ventricular apex was prominent and forceful. The S1 and S2 were normal, but there was a 2/6 ejection systolic murmur best heard in the third right intercostal space. There was no appreciable variation with respiration, but there was an increase in intensity with the Valsalva maneuver and standing up. It seemed to be less prominent on squatting. There was no audible click. What is the murmur likely due to?

A. Valvular aortic stenosis
B. HOCM
C. Mitral valve prolapse (MVP)
D. Innocent murmur

1.5. A 36-year-old asymptomatic woman was found to have a systolic murmur best heard in the apex, but also in the aortic area. It was mid to late systolic and was associated with a sharp systolic sound. What is the likely cause of the murmur?

A. Posterior mitral leaflet prolapse
B. Anterior mitral leaflet prolapse
C. Valvular aortic stenosis
D. Aortic subvalvular membrane

1.6. A 78-year-old man with hypertension and diabetes mellitus presented with exertional shortness of breath of 6 months' duration. Examination revealed a 4/6 crescendo–decrescendo murmur best heard in the second right intercostal space.

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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The first component of the second sound was soft. The murmur was also heard along the right carotid artery. What is this patient likely to have?

A. Mild aortic stenosis
B. Moderate or severe aortic stenosis
C. Pulmonary stenosis
D. MR

1.7. A thrill and a continuous machinery murmur in the left infraclavicular area is indicative of what?

A. Patent ductus arteriosus (PDA)
B. Increased flow due to left arm arteriovenous (AV) fistula for dialysis
C. Venous hum
D. Pulmonary AV fistula

1.8. Which of the following is not a feature of aortic coarctation?

A. A continuous murmur on the back
B. Lower blood pressure in legs compared with arm
C. Radiofemoral delay
D. Pistol shot sounds on femoral arteries

1.9. A 22-year-old newly immigrant woman was referred to high-risk pregnancy clinic because of clubbing and cyanosis. Examination in addition revealed a parasternal heave, 4/6 ejection systolic murmur in the third left intercostal space, normal jugular venous pressure (JVP), and oxygen saturation of 75%. What will you recommend after confirmation of the diagnosis?

A. Continue pregnancy with sodium restriction
B. Continue pregnancy, but deliver at 28 weeks
C. Advise termination of pregnancy
D. Perform percutaneous ASD closure and continue pregnancy

1.10. What is the murmur of ASD?

A. Continuous due to flow across the defect
B. Ejection systolic due to increased flow across the pulmonary valve
C. Mid-diastolic due to increased flow across the tricuspid valve
D. Continuous over lung fields due to increased flow in lungs

1.11. What is a systolic click that disappears on inspiration likely due to?

A. Pulmonary valvular stenosis
B. Bicuspid aortic valve
C. MVP
D. Pulmonary hypertension

1.12. A 36-year-old woman presented with an 8-month history of progressive exertional dyspnea. Physical examination revealed heart rate of 74 bpm, regular, BP 126/78 mmHg, no pedal edema. JVP and carotid upstroke were normal. Cardiac auscultation revealed normal S1, an accentuated P2 with narrow splitting of S2, an ejection click, and a 2/6 ejection systolic murmur. What is the likely diagnosis?

A. Pulmonary hypertension
B. PS
C. Aortic stenosis
D. ASD

1.13. Causes of prominent "a" wave in jugular venous pulsations include all of the following except which option?

A. PS
B. Pulmonary hypertension
C. Tricuspid stenosis
D. Aortic stenosis
E. ASD

1.14. What is a 6-year-old Amish boy in Pennsylvania with short stature, polydactyly, short limbs, absent upper incisor teeth with dysplasia of other teeth, and a systolic murmur most likely to have?

A. ASD
B. Ventricular septal defect
C. Aortic coarctation
D. PS

1.15. Which of the following describes ventricular septal defect murmur?

A. Holosystolic
B. Ejection systolic
C. Systolico-diastolic
D. None of the above

1.16. Clubbing and cyanosis in lower limbs, but not upper limbs, is indicative of which of the following?

A. PDA with coarctation of aorta
B. PDA with pulmonary hypertension
C. Ventricular septal defect Eisenmenger's
D. ASD Eisenmenger's with coarctation of aorta

1.17. A 46-year-old man presented with progressive fatigue and leg swelling. He had no significant past medical history except a front-on collision in a car he was driving. Examination revealed 2+ edema, raised JVP, and an enlarged liver, which seemed to expand during systole. What is the likely diagnosis?

A. Severe tricuspid stenosis
B. Severe tricuspid regurgitation (TR)
C. Constrictive pericarditis
D. Restrictive cardiomyopathy

1.18. A 23-year-old has a mid-diastolic rumble and sharp early diastolic sound. What is the likely explanation?

A. Mitral stenosis
B. Constriction
C. Restriction
D. Bicuspid aortic valve

1.19. A 28-year-old man has history of progressive fatigue and exertional shortness of breath over the last 6 months. Examination revealed raised JVP that seemed to increase with inspiration and a sharp precordial sound in early diastole. What is the most likely diagnosis?

A. Right ventricular infarct
B. Tricuspid stenosis
C. Constrictive pericarditis
D. Restrictive cardiomyopathy

1.20. A 66-year-old woman with left breast cancer post mastectomy, radiation, and chemotherapy was admitted with shortness of breath, heart rate of 120 bpm, and BP of 90/60 mmHg. On slow cuff deflation during BP measurement, Korotkoff's sounds started at 90 mmHg during expiration only and throughout the respiratory cycle at a cuff pressure of 70 mmHg. An echocardiogram was obtained. What is this likely to show?

A. Akinesis of left anterior descending area
B. Thick pericardium
C. Large pericardial effusion
D. Large, globally hypokinetic left ventricle.

1.21. Features of restrictive cardiomyopathy may include all of the following except which option?

A. Raised JVP
B. Loud S3
C. Kussmaul's sign
D. A diastolic knock in pulmonary area

1.22. Pulsus paradoxus despite tamponade may not be present in which of the following?

A. ASD
B. Aortic stenosis
C. Mitral stenosis
D. Old age

1.23. Pulsus paradoxus may occur in all of the following except which option?

A. Tamponade
B. Status asthmaticus
C. Pulmonary embolism
D. Aortic stenosis

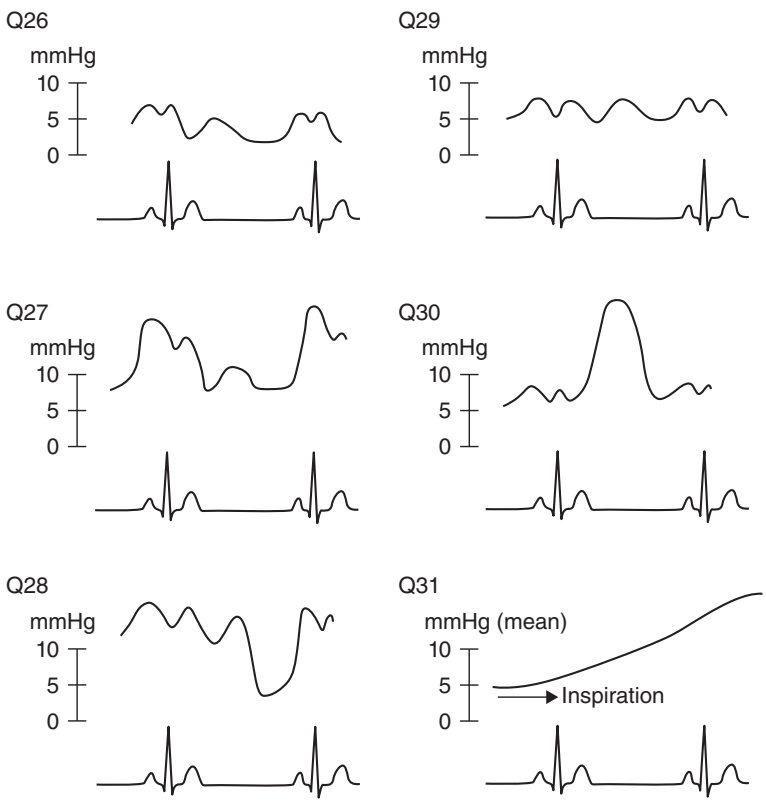
1.24. Square sign during Valsalva maneuver occurs in which of the following?

A. HOCM
B. MVP
C. Aortic stenosis
D. Congestive heart failure

1.25. An abnormal Schamroth's test may be found in all of the following except which option?

A. Tetralogy of Fallot
B. Subacute bacterial endocarditis
C. Left atrial myxoma
D. Aortic stenosis

1.26–1.31. For the jugular vein or RA pressure tracings shown in Figures 1.26–1.31, match with an appropriate clinical scenario from the following choices:

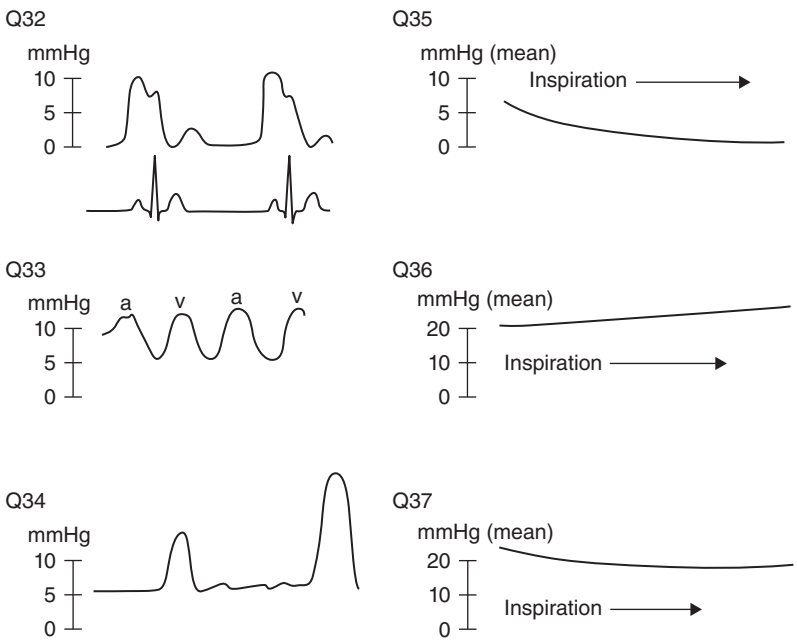


Figures 1.26–1.31

A. Normal
B. Pericardial constriction
C. Restrictive cardiomyopathy
D. ASD
E. Tricuspid stenosis
F. TR
G. Cardiac tamponade
H. Superior vena cava syndrome
I. Heart failure
J. PS

1.32–1.37. For the jugular vein or RA pressure tracings shown in Figures 1.32–1.37, match with an appropriate clinical scenario from the following choices:

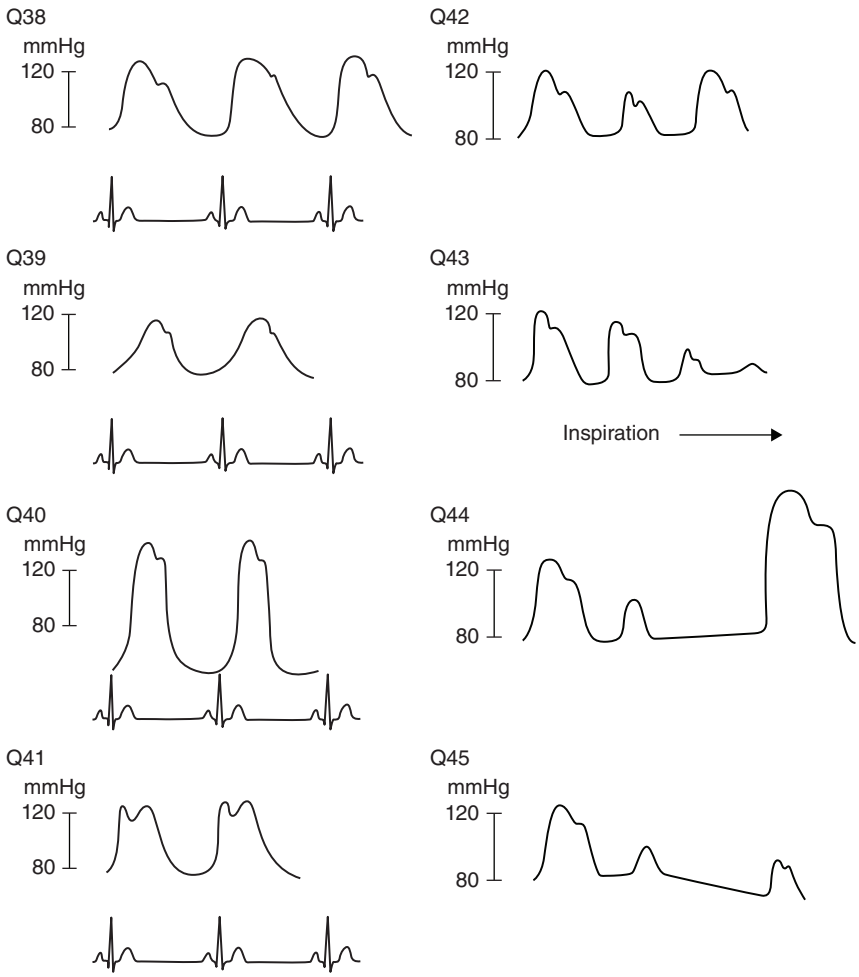
A. Normal
B. Pericardial constriction
C. Restrictive cardiomyopathy
D. ASD
E. Tricuspid stenosis
F. TR
G. Cardiac tamponade
H. Superior vena cava syndrome
I. Heart failure
J. PS
K. Complete heart block



Figures 1.32–1.37

1.38–1.45. For the carotid pulse or arterial pressure tracings shown in Figures 1.38–1.45, match with an appropriate clinical scenario from the following choices:

A. Normal
B. Constriction
C. Aortic stenosis
D. AR
E. Mitral stenosis
F. Mixed aortic stenosis and AR
G. Cardiac tamponade
H. HOCM
I. Heart failure
J. Complete heart block
K. MR
L. Premature ventricular contraction (PVC)



Figures 1.38–1.45

Answers

1.1. A. Physiological or normal.

The murmur is <3/6 in intensity and diminishes with standing, when venous return is less, indicating a flow murmur. S2 split during inspiration only is physiological. During inspiration, increased venous return and pulmonary flow prolongs right ventricular (RV) ejection. This delays P2.

1.2. A. Pulmonary stenosis (PS).

A murmur associated with a thrill indicates that it is pathological and not just due to increased cardiac output. A thrill in the suprasternal notch is pathognomonic of PS. Valvular PS would be associated with an ejection click which diminishes with inspiration. Left parasternal heave would be indicative of RV hypertrophy (RVH).

1.3. A. ASD.

The features are suggestive of Holt–Oram syndrome.

1.4. B. HOCM.

In HOCM, the left ventricular (LV) outflow obstruction is dynamic and is increased by an increase in LV contractility or a reduction in LV size. Standing, Valsalva maneuver, and amyl nitrite reduce venous return, reduce LV filling, and increase systolic anterior motion of the anterior mitral leaflet (SAM), resulting in increased LV outflow tract (LVOT) obstruction. Squatting kinks leg arteries, raising peripheral resistance and hence an increase in LV volume. This reduces SAM and LV outflow obstruction. Valvular aortic stenosis murmur intensity is flow dependent, and hence reduction in venous return with standing or Valsalva maneuver as well as increase in peripheral resistance with squatting would diminish the murmur. In mitral valve prolapse (MVP), an increase in LV volume would reduce prolapse, and a reduction in LV volume would lengthen the murmur by producing earlier prolapse. MVP is generally associated with a mid-systolic click.

1.5. A. Posterior mitral leaflet prolapse.

The systolic click and late systolic murmur indicate MVP. In anterior leaflet prolapse, the mitral regurgitation (MR) jet is directed posteriorly and murmur may be conducted to the axilla. In posterior leaflet prolapse, the jet is anterior wall hugging, along the aortic root, which facilitates its conduction to the aortic area.

1.6. B. Moderate or severe aortic stenosis.

This is a classic aortic stenosis murmur with carotid conduction. Soft A2 (first component of S2 indicates significant aortic stenosis). Features of severe aortic stenosis are late-peaking murmur, absent A2, paradoxic splitting of S2 (i.e. split during expiration instead of inspiration), and slow-rising carotid pulse (pulsus parvus et tardus).

1.7. A. Patent ductus arteriosus (PDA).

Though the other conditions can produce continuous murmurs, they are not associated with a thrill or machinery character.

1.8. D. Pistol shot sounds on femoral arteries.

Pistol shot sounds occur in severe aortic regurgitation (AR). Others are features of aortic coarctation.

1.9. C. Advise termination of pregnancy.

The findings are typical of tetralogy of Fallot, and the murmur is due to PS. Murmur of ASD is due to flow and softer and not associated with clubbing or cyanosis unless associated with Eisenmenger's syndrome. Tetralogy of Fallot is associated with extremely high risk, and pregnancy should be terminated.

1.10. B. Ejection systolic due to increased flow across the pulmonary valve.

Flow across the defect and the lungs does not produce murmurs. It takes a torrential shunt to produce a mid-diastolic flow murmur across the tricuspid valve.

1.11. A. Pulmonary valvular stenosis.

In severe PS, due to low pulmonary artery (PA) pressure, an increase in venous return to right ventricle during inspiration may open the pulmonary valve before systole, eliminating the ejection click.

1.12. A. Pulmonary hypertension.

This is suggested by loud P2. In pulmonary hypertension, P2 moves closer to A2 due to higher pulmonary valve closure pressure, and S2 may be single when PA pressure approaches systemic pressure. Ejection click and soft ejection systolic murmur may occur because of PA dilation. Other features of pulmonary hypertension may include a palpable PA in second left intercostal space, a palpable P2 or diastolic knock, parasternal heave due to RVH and prominent "a" wave in jugular venous pulsation due to RVH resulting in accentuated right atrial (RA) systole. PS results in a louder murmur and diminished P2. ASD results in wide, fixed, splitting of S2.

1.13. E. ASD.

Prominent "a" wave occurs due to forceful RA systole, and this can occur against stenotic tricuspid valve, hypertrophied RV (PS and pulmonary hypertension) or hypertrophied ventricular septum (aortic stenosis, hypertrophic cardiomyopathy, or hypertension). In ASD, defect in the atrial septum would not allow a prominent "a" wave, even in the presence of pulmonary hypertension, as the right atrium would decompress into the left atrium during atrial systole.

1.14. A. ASD.

ASD or common atrium as part of Ellis–van Creveld syndrome or mesoectodermal or chondroectodermal dysplasia is an autosomal recessive inheritance disorder that occurs in old-order Amish population. The *EVC* gene is on chromosome number 4, short arm. It is a form of ciliopathy. Other ciliopathies that result in abnormal organogenesis include Bardet–Biedl syndrome, polycystic kidney and liver disease, Alstrom syndrome, Meckel–Gruber syndrome, and some forms of retinal degeneration, and so on.

1.15. A. Holosystolic.

1.16. B. PDA with pulmonary hypertension.

In PDA Eisenmenger's, the shunt reversal through PDA causes desaturation in lower part of the body only, resulting in central cyanosis and clubbing in lower extremities and not upper extremities.

1.17. B. Severe tricuspid regurgitation (TR).

Liver that is pulsatile (expansile) in systole is indicative of a powerful RA "V" wave, and this suggests severe TR. This can also be seen in the jugular venous pulsation. Sternal compression during the motor vehicle accident likely caused a flail tricuspid valve and severe TR. Liver pulsation in tricuspid stenosis is pre-systolic. Liver pulsations are not seen in constriction or restriction.

1.18. A. Mitral stenosis.

This is typical mitral stenosis with pliable leaflets, which causes opening snap. A2-OS interval is a good measure of mitral stenosis severity. Normally, 70–100 ms (same as isovolumetric relaxation time). Less than 70 ms indicates high left atrial pressure, suggesting severe mitral stenosis.

1.19. C. Constrictive pericarditis.

Rise in JVP is paradoxical (Kussmaul's sign), and sharp protodiastolic sound is pericardial knock – classic features of constriction. Kussmaul's sign occurs because of lack of transmission of negative intrathoracic pressure to the right atrium

through the rigid pericardium. Hence, increased venous return during inspiration causes a rise in RA pressure. In tricuspid stenosis, inspiratory increase in venous return may not readily empty into right ventricle, causing a paradoxical rise in JVP with inspiration. Kussmaul's sign can occur in RV infarct but occurs in the setting of inferior myocardial infarction. Restrictive cardiomyopathy may be associated with S3, which is less sharp (a thud), but no venous paradox.

1.20. C. Large pericardial effusion.

This is typical cardiac tamponade with classic paradoxic pulse, hypotension, and tachycardia. Constriction causes venous paradox.

1.21. C. Kussmaul's sign.

As pericardium is normal, inspiratory negative intrathoracic pressure is transmitted to cardiac chambers, and hence the venous paradox does not occur. Diastolic knock is palpable loud P2, a feature of pulmonary hypertension that is common in restrictive LV physiology.

1.22. A. ASD.

Pulsus paradoxus may not be present when LV filling is not affected by phase of inspiration due to lack of interventricular dependence, as in ASD, or LV filling from other sources, such as severe AR or MR.

1.23. D. Aortic stenosis.

1.24. D. Congestive heart failure.

See explanation in Box 1.1 Clinical Pearls. This is because though a Valsalva maneuver reduces left-sided venous return, it does not affect LV stroke volume as it is already well filled and beyond the peak of Starling's curve. Increase in intrathoracic pressure is transmitted to the aorta, causing an increase in aortic pressure.

1.25. D. Aortic stenosis.

This test is named after South African cardiologist for diagnosis of clubbing. In clubbing, the angle between the nail and nail fold is >165° and when nails of fingers from two sides are apposed, the gap between them disappears. Clubbing is seen in cardiac conditions (in addition to a variety of pulmonary diseases) in subacute bacterial endocarditis, congenital cyanotic heart diseases, and left atrial myxoma.

1.26. A. Normal.

Note the mean RA pressure of <5 mmHg and the "a" wave due to atrial systole is slightly higher than the "V" wave, which occurs because of RA filling on the closed tricuspid valve. A smaller "V" wave indicates a compliant right atrium. The sharp "C" wave that coincides with the QRS complex of the electrocardiogram is due to a combination of tricuspid valve closure and transmitted carotid impulse.

1.27. E. Tricuspid stenosis.

Note the large "a" wave as the RA contracts against a stenosed tricuspid valve; the gradient is reflected as large "a" wave. Note that the mean RA pressure is slightly elevated as well commensurate with transtricuspid gradient. In conditions causing RVH (pulmonary hypertension, PS, aortic stenosis with septal hypertrophy), the "a" wave may be prominent due to noncompliant RV (RV fourth heart sound), but mean RA pressure may not be high unless there is heart failure.

1.28. B. Pericardial constriction.
Note elevated RA pressure with rapid "Y" descent.

1.29. D. ASD.
In ASD, the "a" and "V" waves would be of similar height because the defect leads to equilibration of the LA and RA pressures.

1.30. F. TR.
Large "V" wave is due to TR filling up RA during systole. When the "V" wave pressure is about 25–30 mmHg, it may become palpable to the examining finger and associated with expansile liver.

1.31. B. Pericardial constriction.
The increasing mean RA pressure with inspiration is the venous paradox or Kussmaul's sign. This is because of dissociation between intrathoracic and intrapericardial pressures because of thick pericardium. During inspiration, the intrathoracic pressure drops, increasing venous return to the right atrium, but the intrapericardial and intra-RA pressure does not drop and returning blood increases the pressure further. Kussmaul's sign can occur even in acute pericarditis and RV infarcts, the latter invoking pericardial restraint.

1.32. J. PS.
Note a large "a" wave with near-normal mean RA pressure. Contrast this with tricuspid stenosis.

1.33. G. Cardiac tamponade.
Note the raised RA pressure with prominent "X" and "Y" troughs.

1.34. K. Complete heart block.
The intermittent large waves are "cannon a" waves when atria and ventricles happen to contract simultaneously due to AV dissociation.

1.35. A. Normal.
The RA pressure is <5 mmHg and drops with inspiration.

1.36. H. Superior vena cava syndrome.
Note the high JVP which does not drop on inspiration as superior vena cava is blocked and jugular vein is not in communication with right atrial hemodynamics or pulsatile changes. In contrast to constriction, the JVP in superior vena cava syndrome is nonpulsatile. It would be high in both.

1.37. I. Heart failure.
High JVP that drops with inspiration.

1.38. A. Normal.
This is the typical normal tracing. Note the fairly rapid upstroke, pulse pressure of about 40 mmHg, dicrotic notch and dicrotic wave.

1.39. C. Aortic stenosis.
Note the very slow rise, attributable to high blood flow velocity across the valve which converts pressure to kinetic energy.

1.40. D. AR.
Note rapid upstroke, rapid downstroke (water-hammer pulse), wide pulse pressure, and low diastolic pressure due to peripheral vasodilation. This can also occur in PDA and large AV fistulae.

1.41. F. Mixed aortic stenosis and AR.

This is called pulsus bisferiens or double pulse. Can also occur in HOCM.

1.42. I. Heart failure.

This is pulsus alternans. Alternating strong and weak pulse with regular RR interval due to alternating stronger and weaker myocardial contraction with every other beat attributable to altered calcium handling by contractile proteins. It is a sign of severe systolic dysfunction.

1.43. G. Cardiac tamponade.

BP drop with inspiration is called pulsus paradoxus. An inspiratory drop of >10 mmHg may indicate tamponade.

1.44. L. Premature ventricular contraction (PVC).

With appropriate increase in pulse pressure in the post PVC beat due to a combination of increased preload due to long filling period and increased contractility due to force–frequency relationship.

1.45. H. HOCM.

In this patient, after PVC, instead of an augmented pulse there is a smaller pulse volume. This is due to the fact that increased contractility in the post PVC beat increases dynamic LVOT obstruction and reduces stroke volume. This is called Brockenbrough phenomenon on cardiac catheterization. This contrasts with valvular aortic stenosis, where pulse pressure increases after a PVC.

Box 1.1 Clinical Pearls

- Loud S1 occurs when mitral valve closes forcefully from open position against transmitral gradient or prematurely and occurs in mitral stenosis, short pulmonary regurgitation (PR) interval, and hyperdynamic circulation.
- S1 is soft in MR, long PR interval, and severe AR. In severe AR, mitral valve may move toward closure in presystole.
- P2 can be loud in pulmonary hypertension (higher pulmonary valve closure sound) and dilated PA (better P2 transmission).
- S2 may be paradoxically split when aortic valve closure is delayed and comes after P2 as in left bundle branch block, severe aortic stenosis, severe LV dysfunction, PDA (increased transaortic flow). S2 is split in expiration and not in inspiration when RV filling and ejection time are increased.
- Only right-sided sound/murmur that is attenuated by inspiration is pulmonary ejection click of valvular PS as inspiratory increase in venous return to right ventricle in the presence of RVH may cause an increase on RV end diastolic pressure high enough to open the pulmonary valve as PA pressure is lower.
- Carey Coombs murmur is mid-diastolic mitral murmur due to mitral valvulitis in rheumatic fever.
- Austin Flint murmur is mitral mid-diastolic murmur heard in severe AR. Potential explanations include: AR jet causing anterior mitral leaflet vibration, or mitral/AR jet interaction or AR jet causing partial diastolic closure of anterior mitral leaflet.
- Graham Steel murmur is early diastolic murmur of PR that occurs in severe pulmonary hypertension. Higher PA diastolic pressure causes turbulence of PR jet and the murmur.

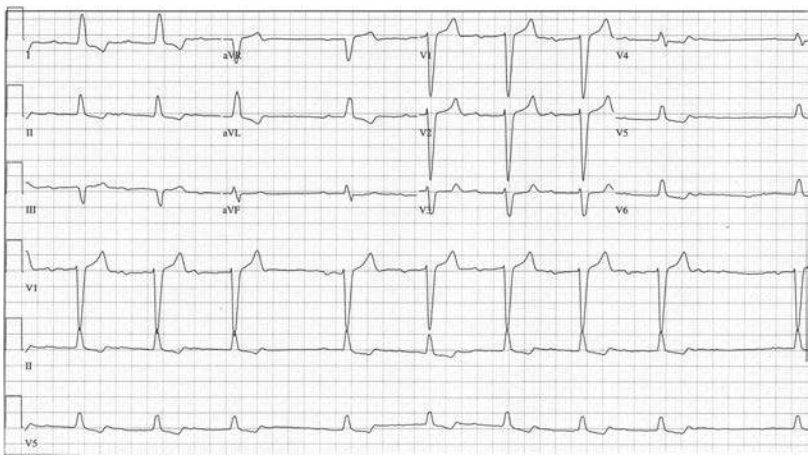
- Mid-diastolic murmur of mitral stenosis is best heard with the bell without much pressure as it is a low-frequency murmur and better heard in left lateral position. Presystolic accentuation indicates atrial contraction.
- Tapping apex typically occurs in mitral stenosis and it is palpable S1.
- Maneuvers are helpful in evaluating murmurs. Inspiration increases right-sided venous return and augments right-sided murmurs. Standing reduces venous return and after three or four beats LV filling as well reduces its size. This may augment HOCM murmur and lengthen MR murmur of MVP. Squatting kinks limb arteries and increases afterload. This may reduce murmurs of valvular aortic stenosis through reduced stroke volume and HOCM murmur through an increase in LV volume and shorten murmur of MVP through increasing LV volume and reducing prolapse.
- The Valsalva maneuver involves expiration against a closed glottis, increasing the intrathoracic pressure. There are four phases of heart rate and BP response. Normal response includes the following:
  - Phase 1. Early during the Valsalva maneuver, pressure on the intrathoracic aorta and pulmonary veins emptying into left heart transiently increases filling, stroke volume, and BP with reflex slowing of heart.
  - Phase 2. With a continued Valsalva maneuver, LV filling diminishes and lowers stroke volume and BP, resulting in compensatory tachycardia. Reflex peripheral vasoconstriction slowly increases BP and lowers heart rate.
  - Phase 3. With release of the Valsalva maneuver, pressure on the aorta drops, and BP drops with some increase in heart rate.
  - Phase 4. Left ventricle fills, with increase in stroke volume with continued peripheral vasoconstriction causing BP to overshoot the baseline value. This will reflexly reduce heart rate below baseline.

  Phase 2 is used in dynamic auscultation.
- In HOCM, the Valsalva maneuver results in smaller left ventricle size causing increased LVOT obstruction and an increase in murmur intensity.
- In MVP, reduced LV volume with phase 2 Valsalva results in earlier and greater prolapse and the MR murmur lengthens.
- Heaving apex denotes LV hypertrophy, forceful apical lift signifies LV volume overload, tapping apex loud S1, and bifid apex with presystolic lift LV occurs due to a combination of LVH with a forceful atrial kick causing S4 as it occurs in hypertrophic cardiomyopathy.
- Left parasternal or precordial bulge indicates RVH occurring before the rib cage ossified (young age), and parasternal lift or heave indicates RVH starting after childhood.
- A downward tug on larynx held up with fingers after deglutition indicates aortic arch aneurysm. Also called tracheal tug or Oliver's sign, occurs with every heartbeat.
- A large, sharp systolic wave in jugular venous pulsation during systole is the cannon wave. This occurs when the right atrium contracts over closed tricuspid valve, as in complete heart block (intermittent) or junctional or idioventricular rhythm with retrograde ventriculoatrial conduction.

Electrocardiography 2

ECG diagnostic criteria are listed in Box 2.1.

For the tracings in the questions/figures in this section, please analyze carefully and list the important findings and possible clinical setting. Answers are found at the end of the chapter.



Question/Figure 2.1

Question/Figure 2.2

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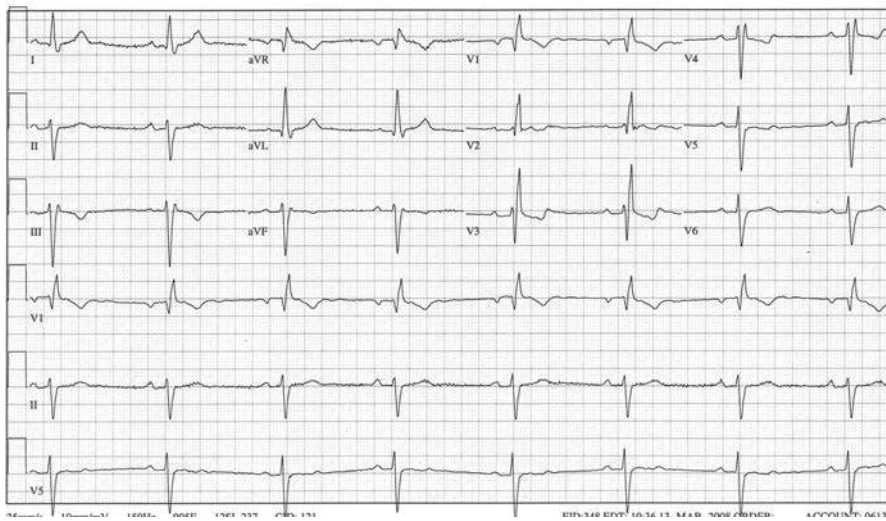

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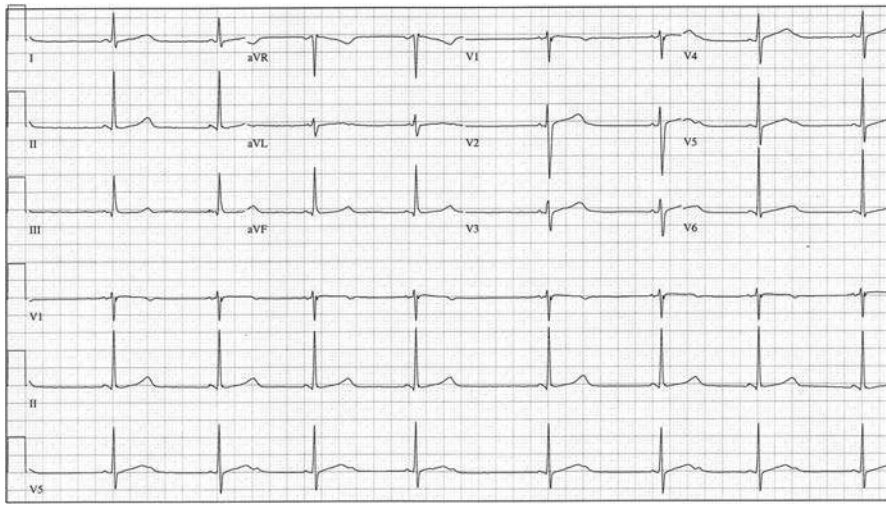

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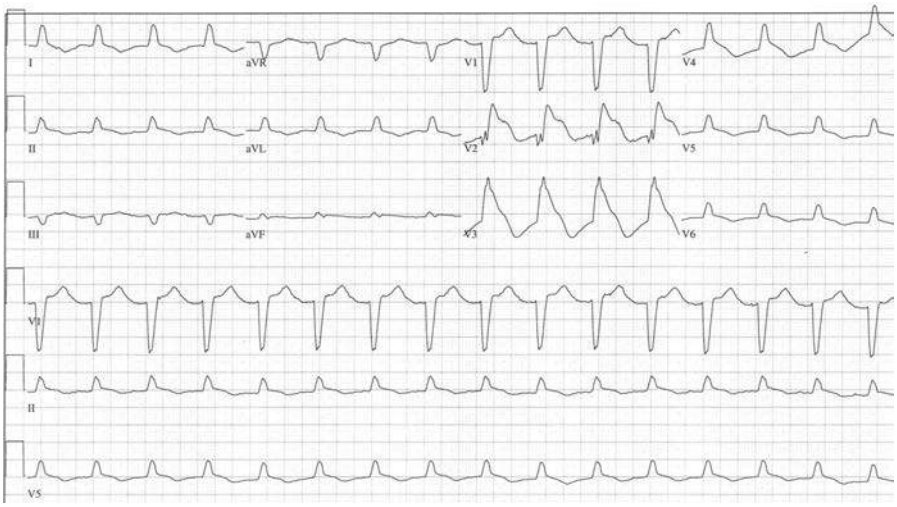

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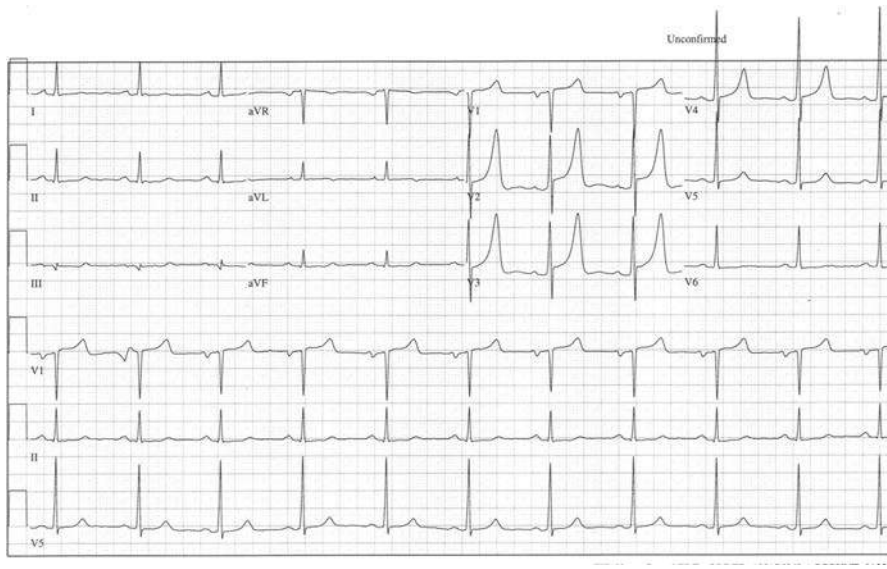

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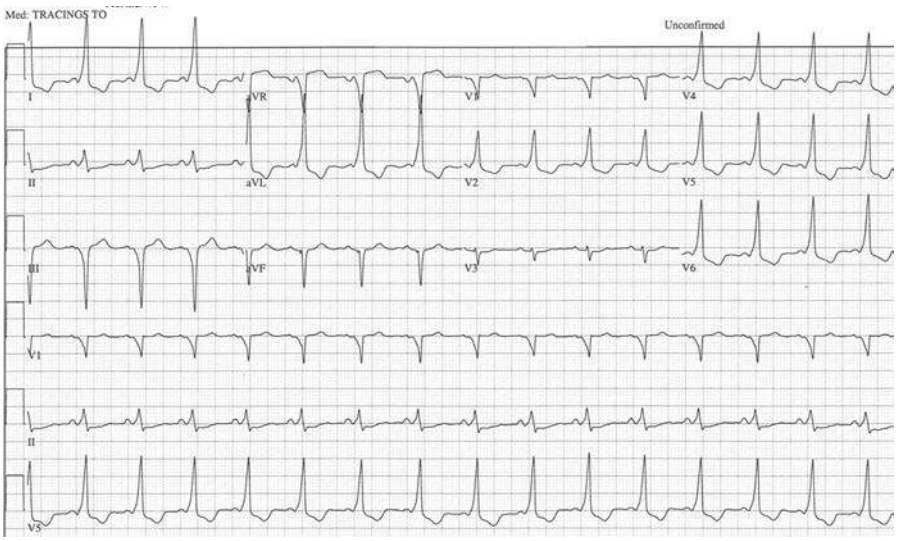

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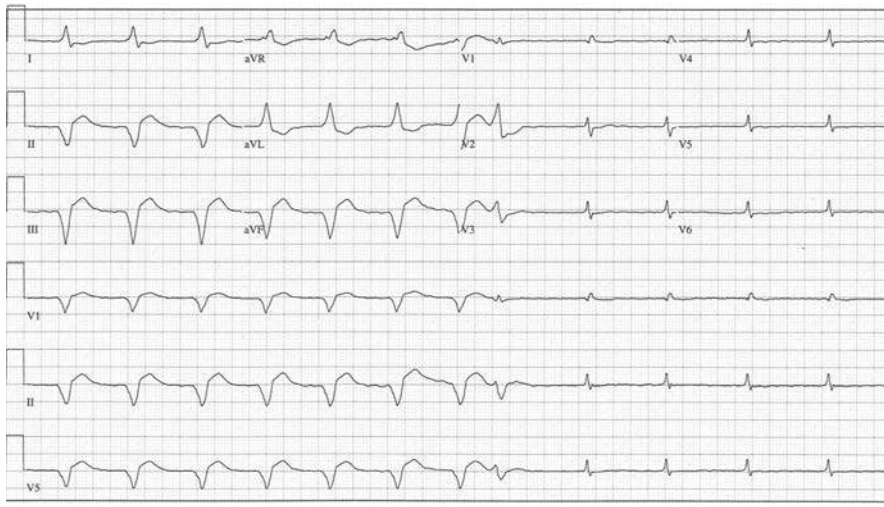

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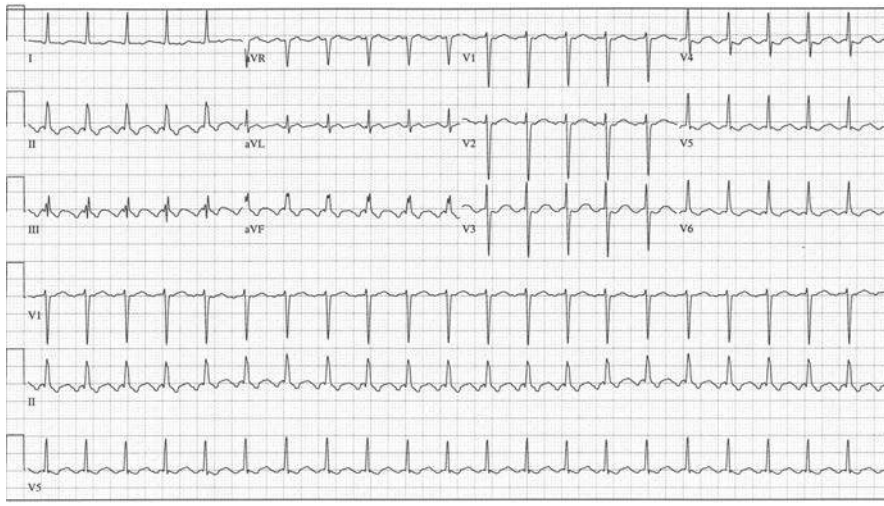

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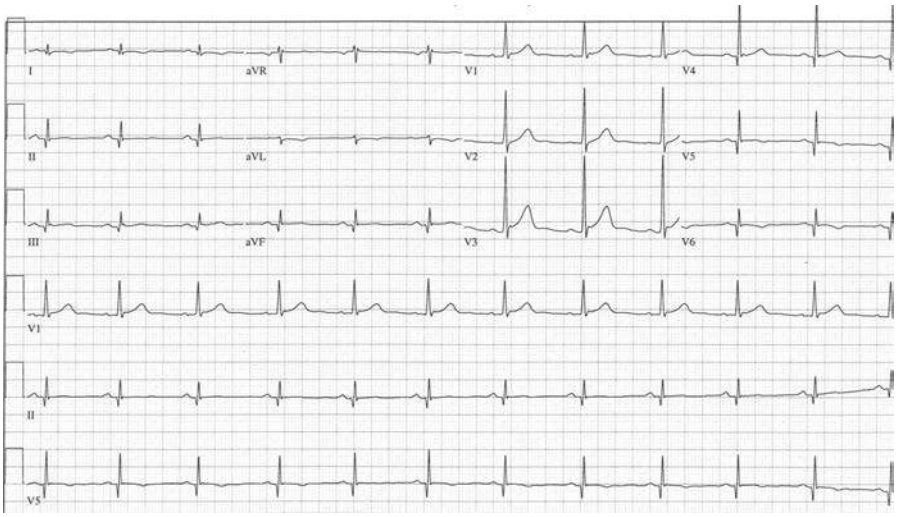

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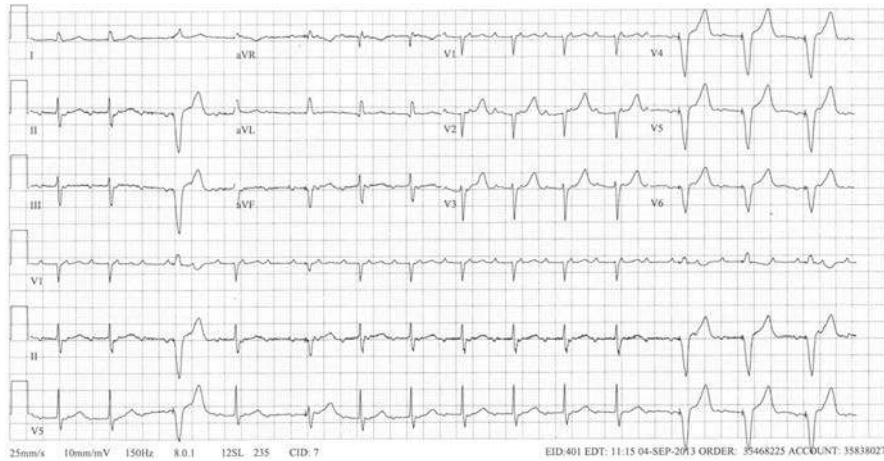

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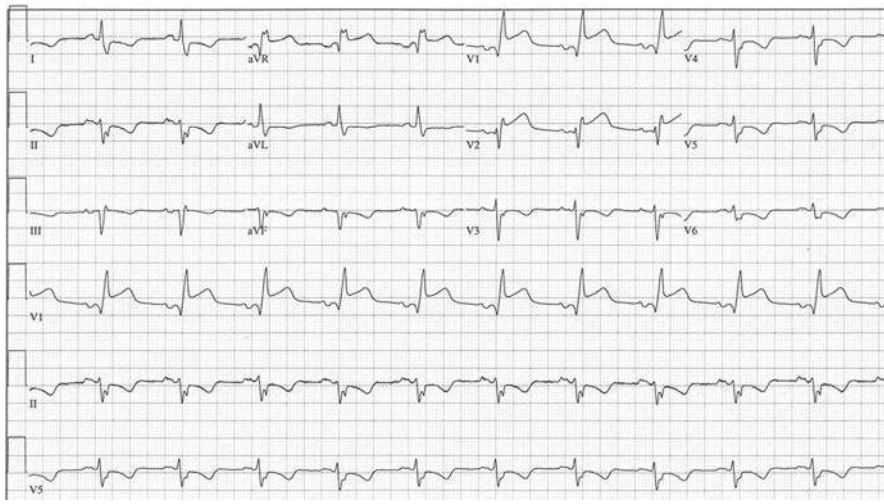

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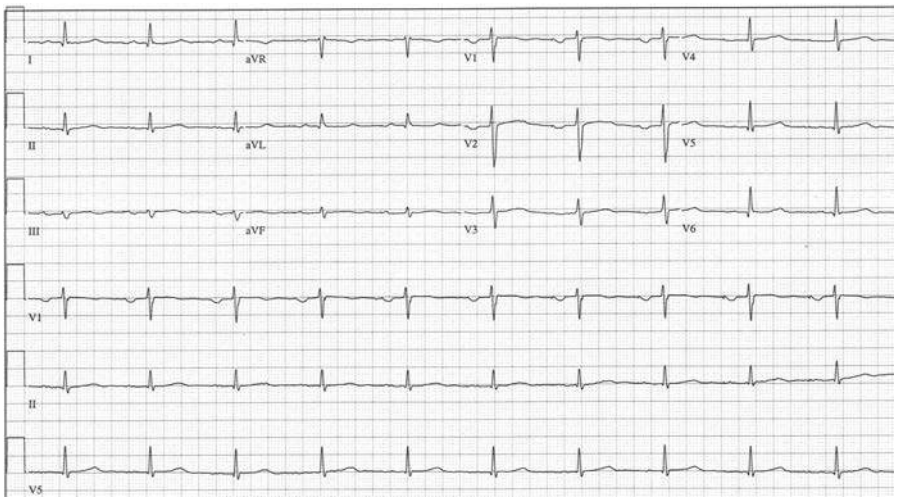

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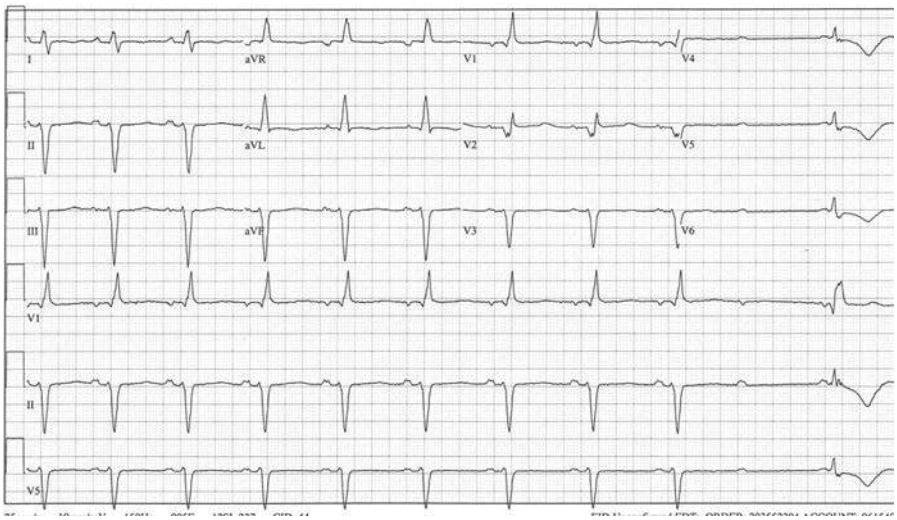

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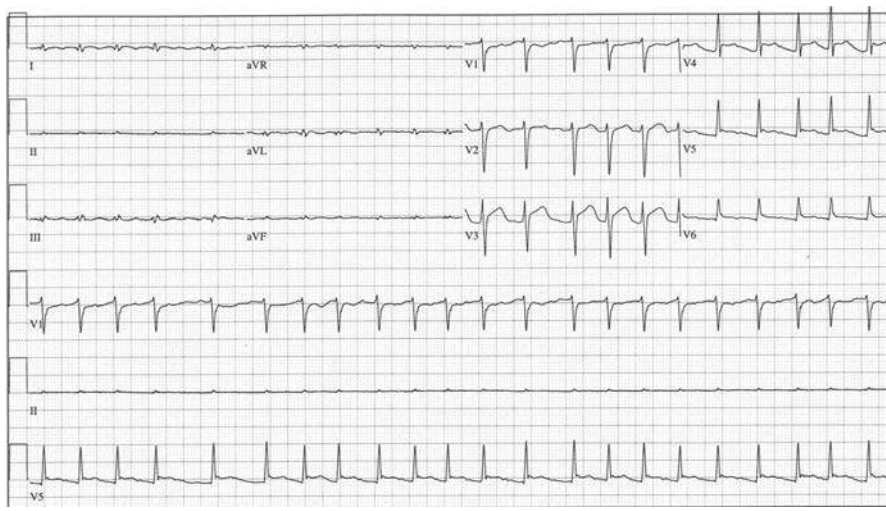

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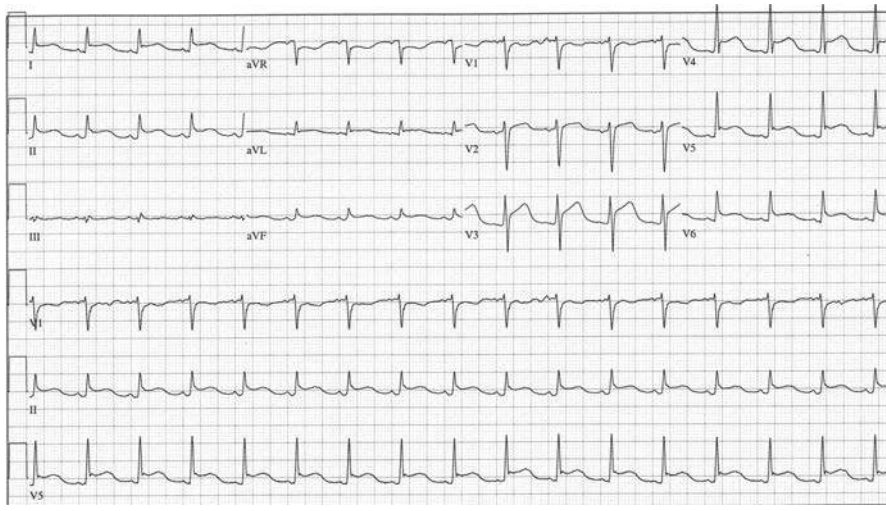

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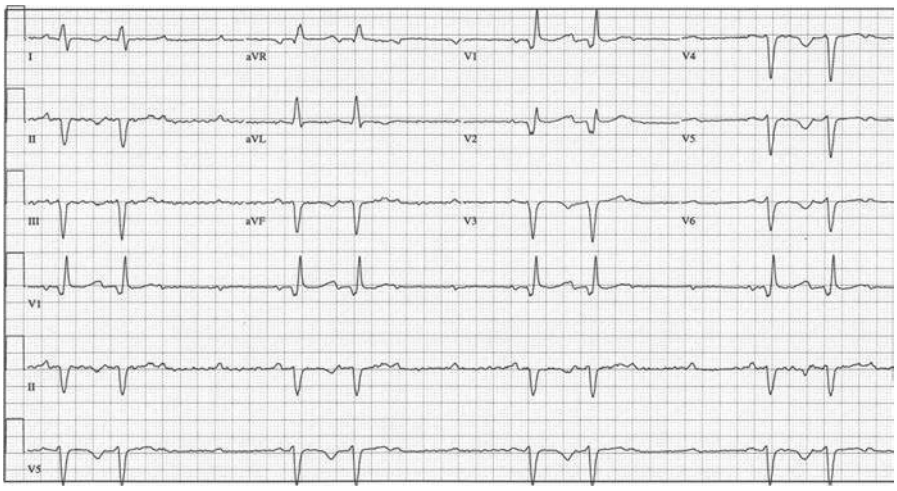

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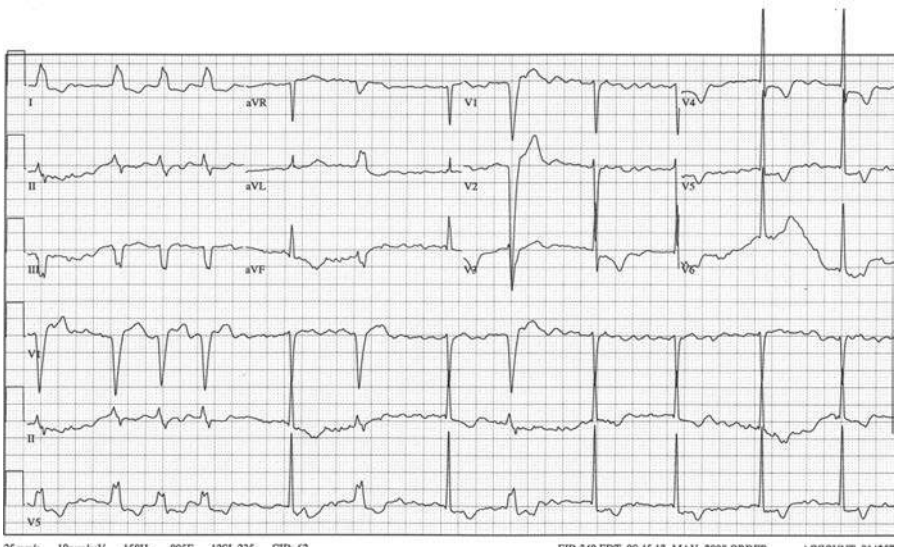

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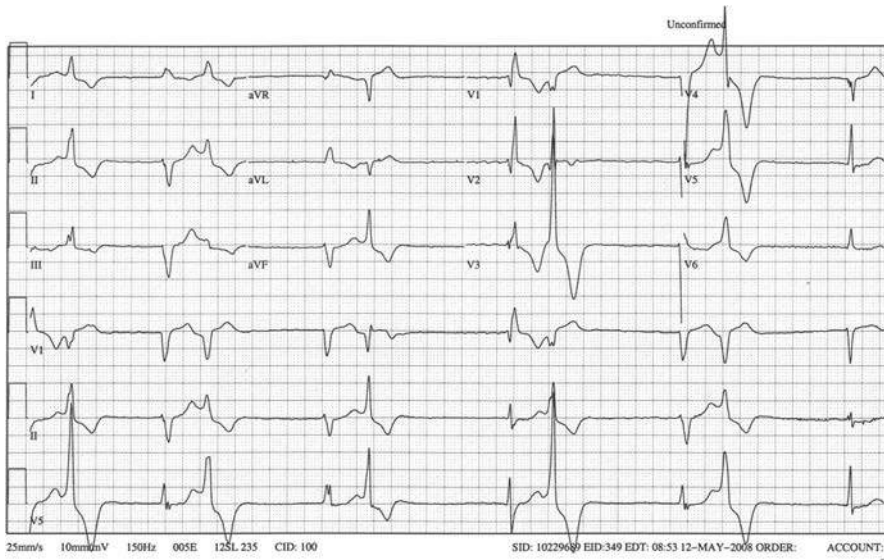

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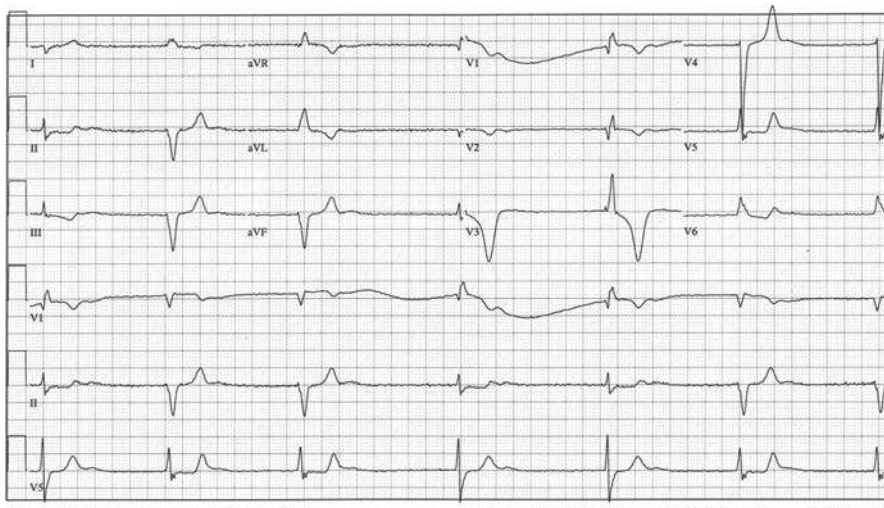

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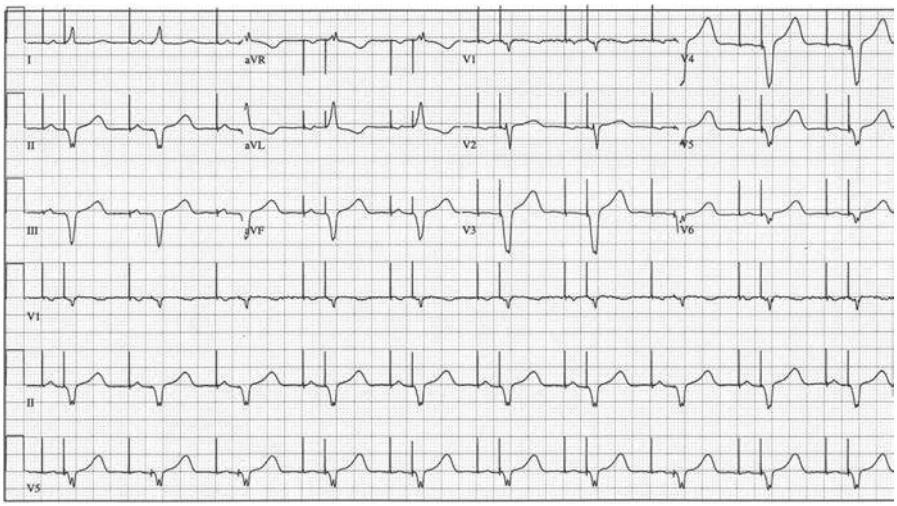

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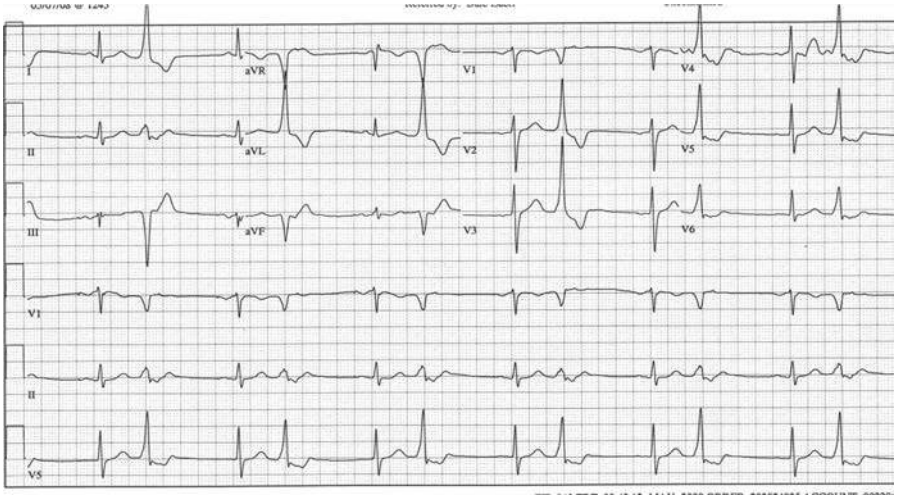

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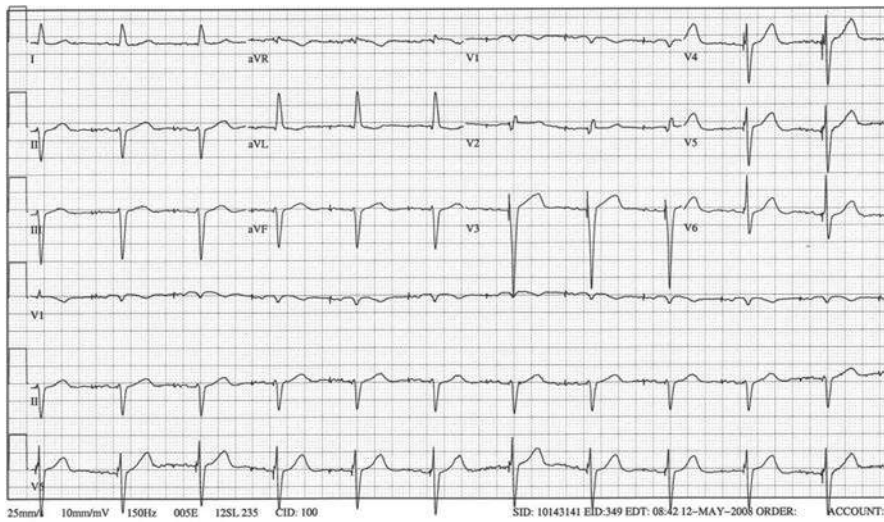

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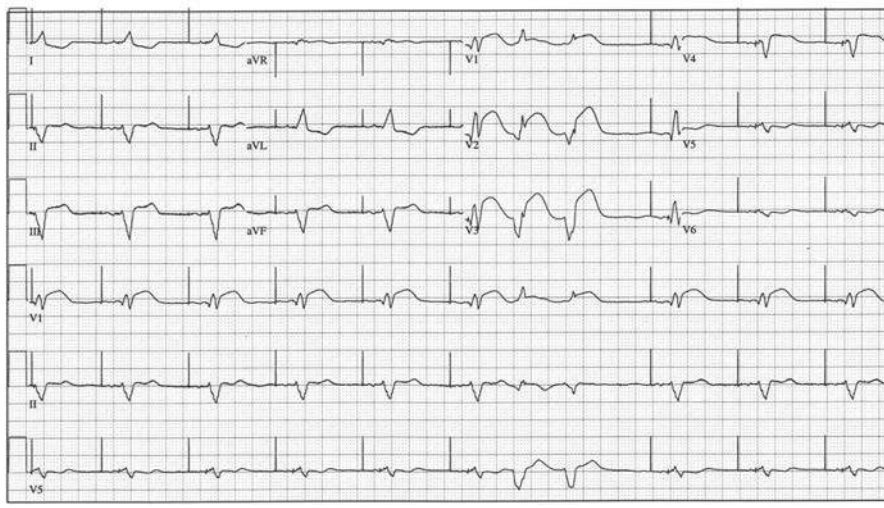

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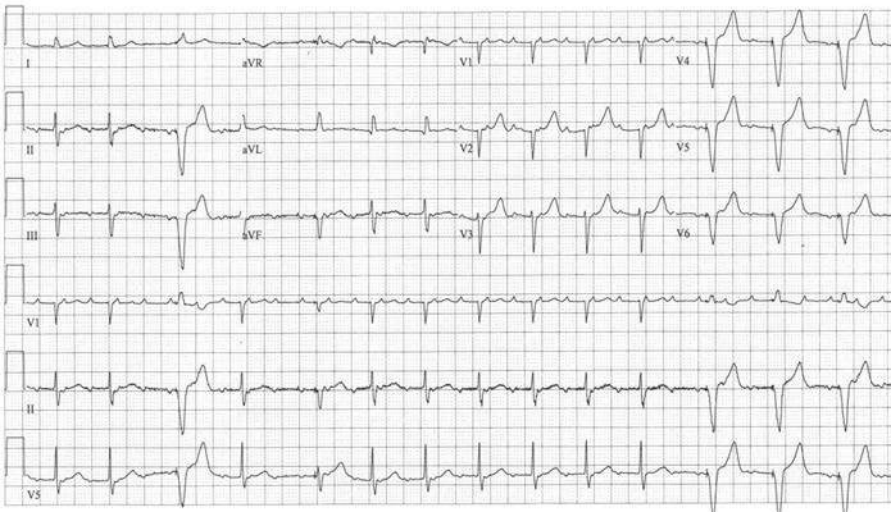

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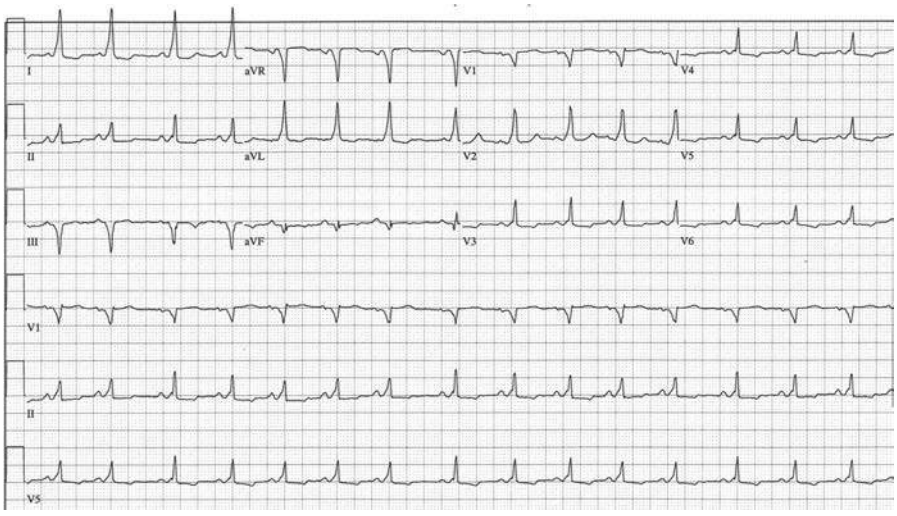

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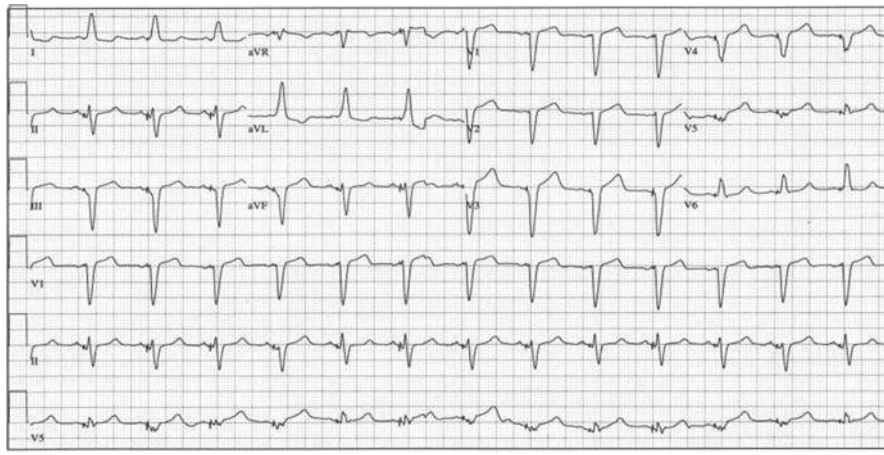

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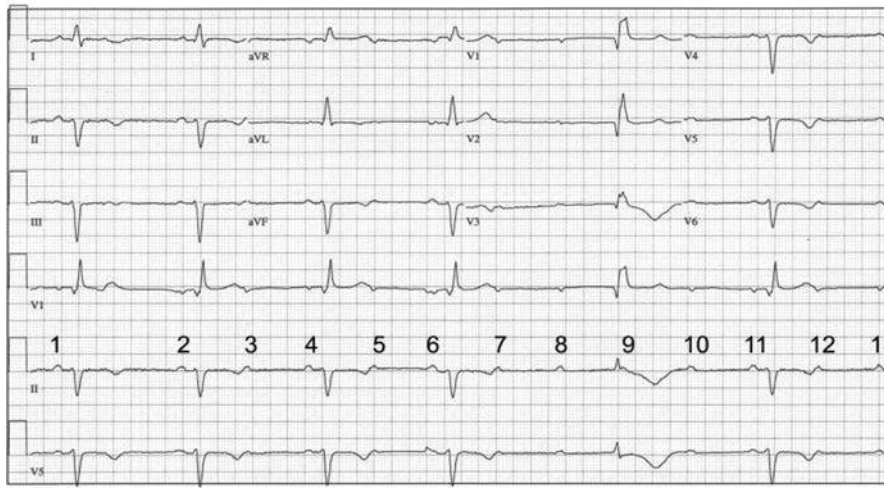

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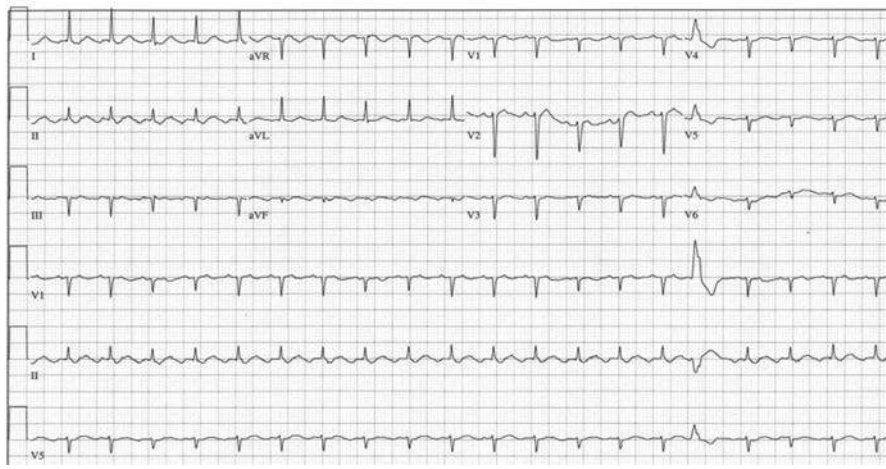

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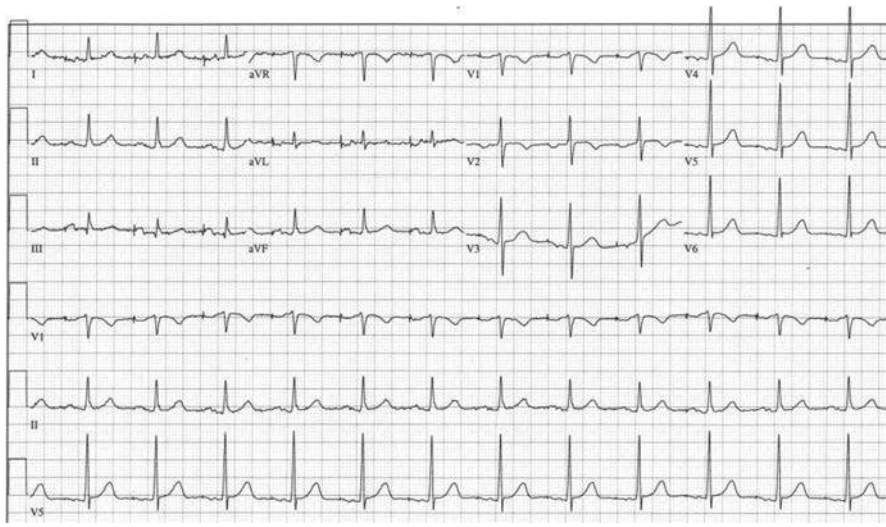

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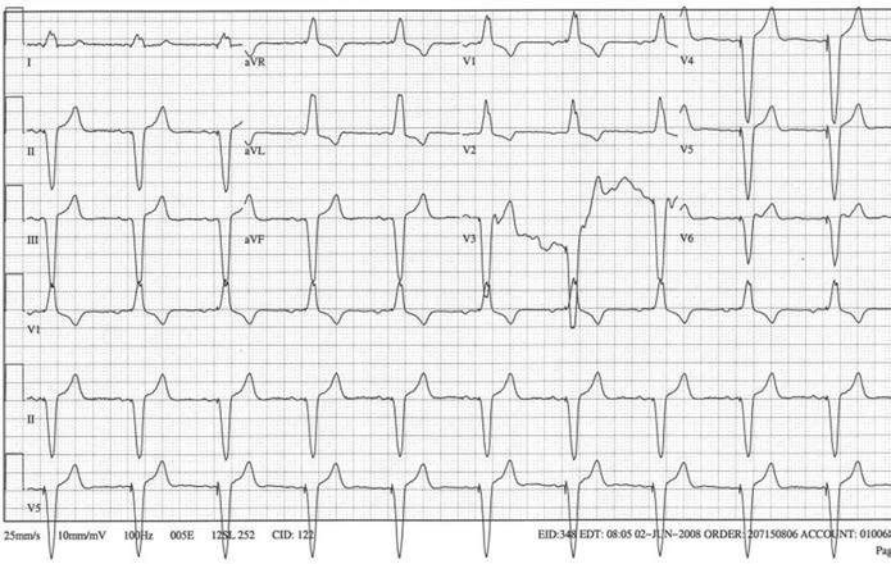

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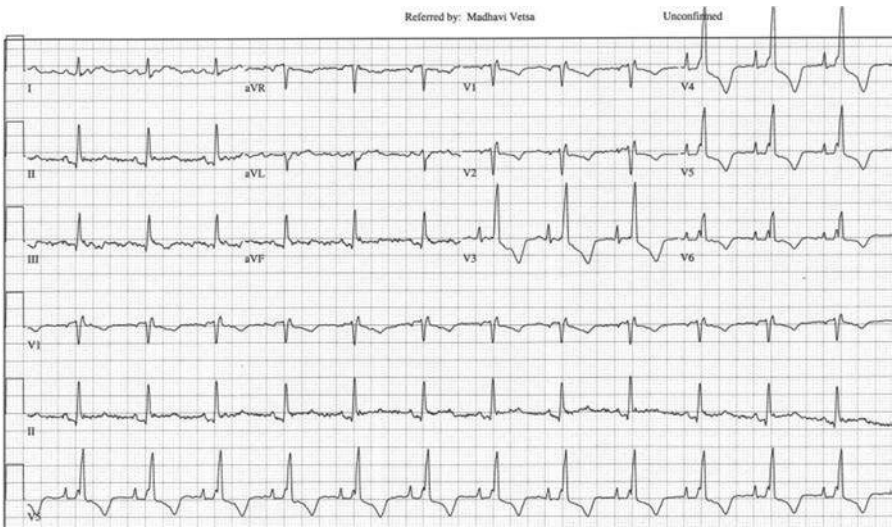

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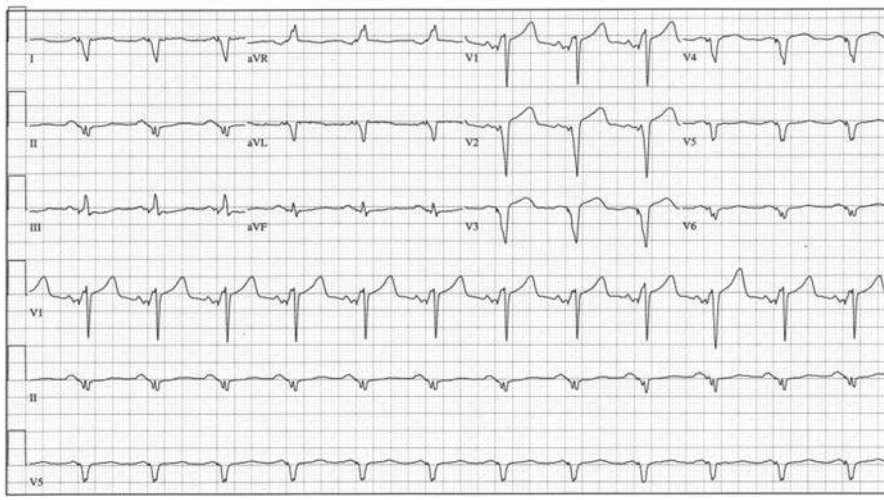

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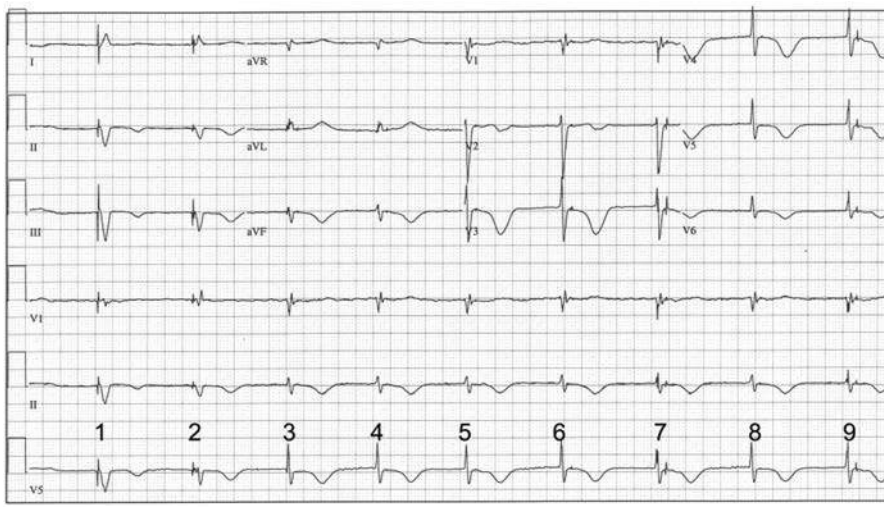

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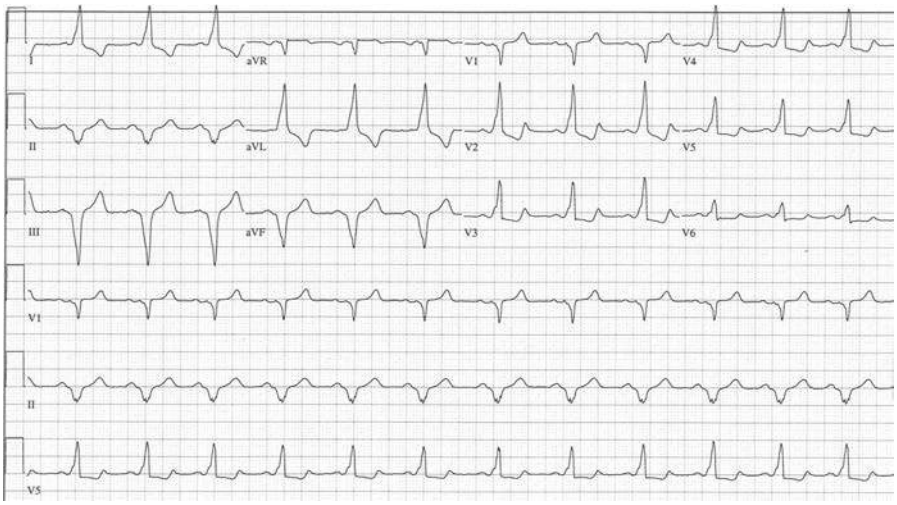

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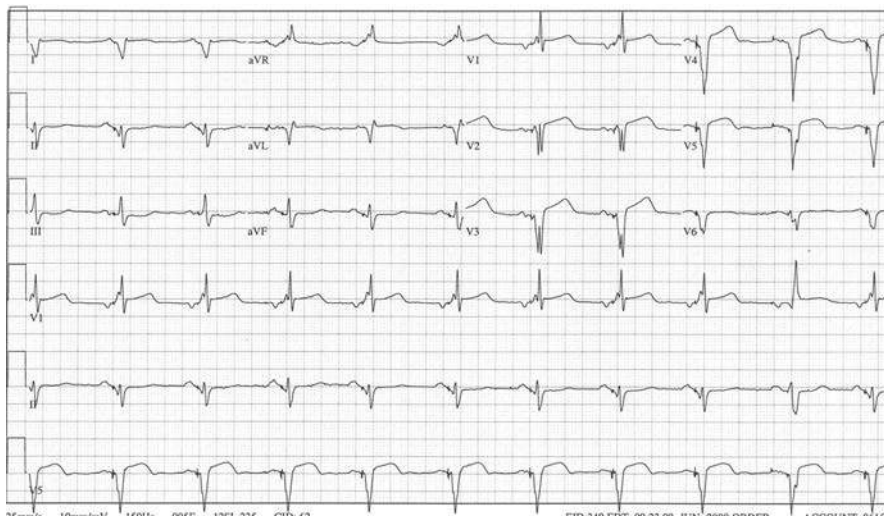

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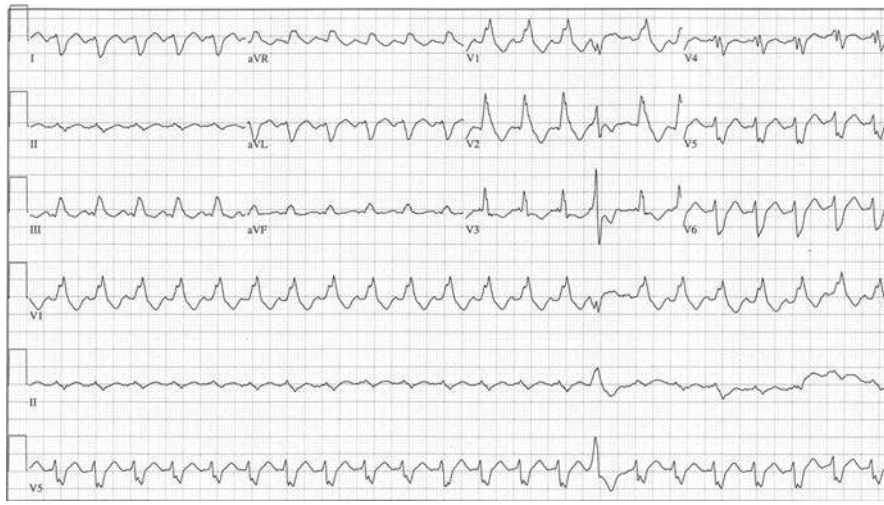

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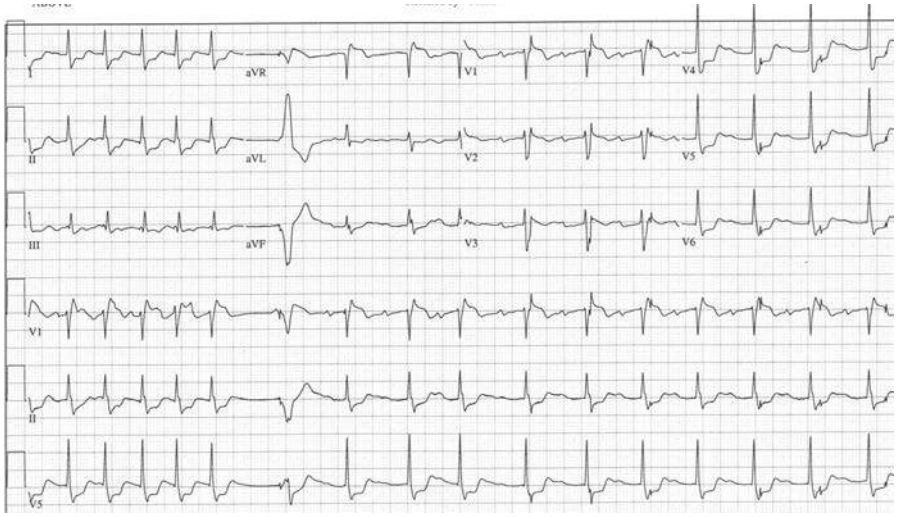

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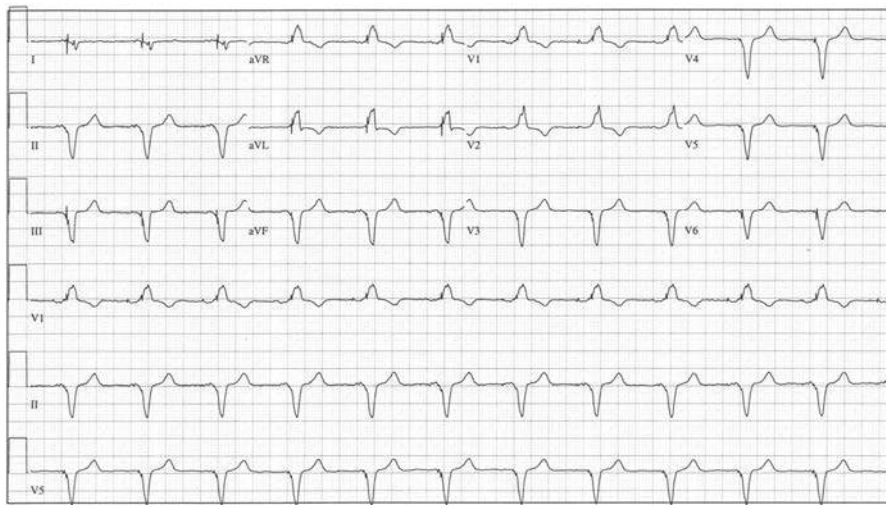

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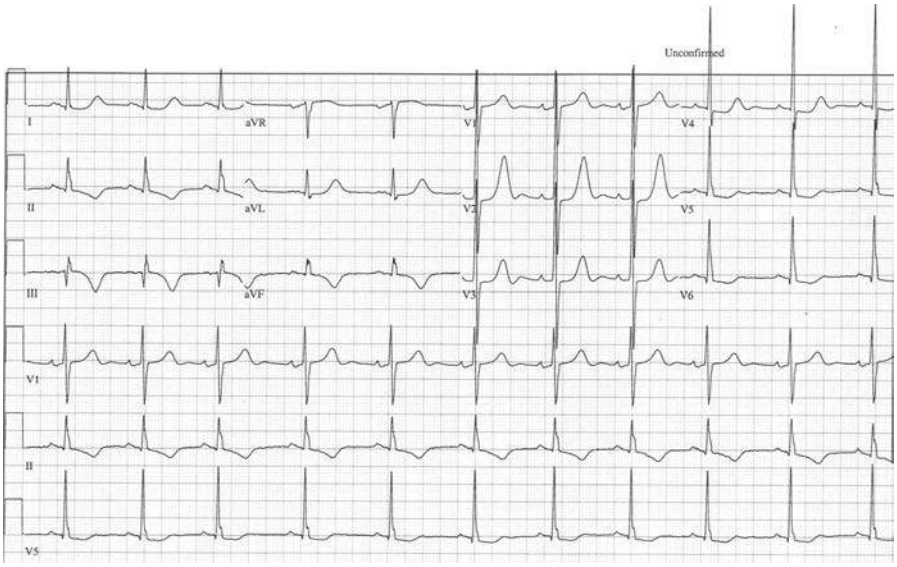
Question/Figure 2.49



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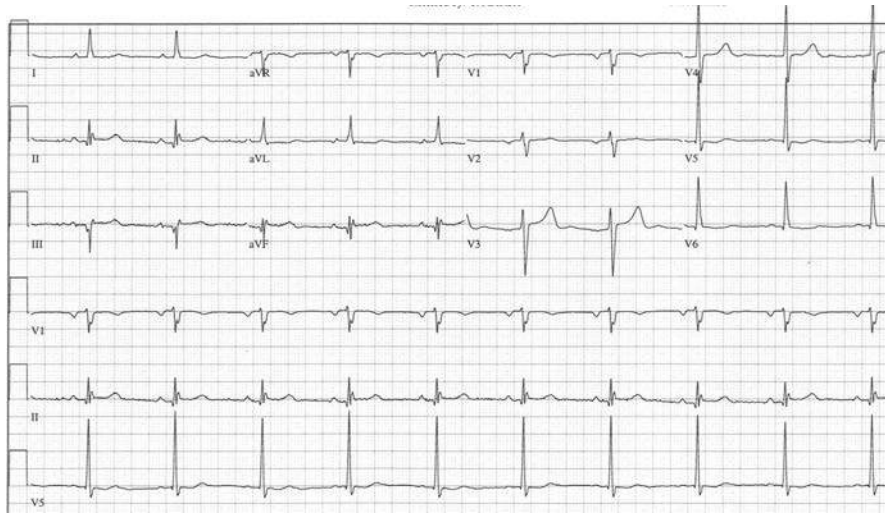

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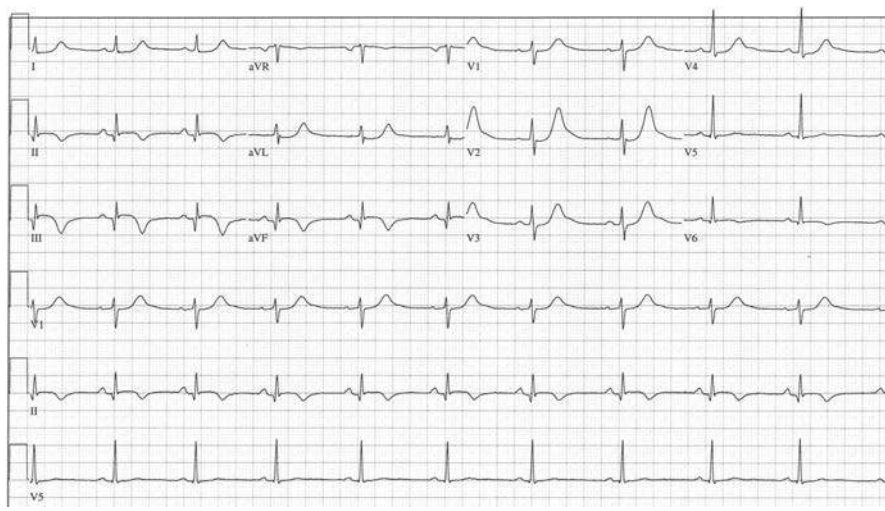

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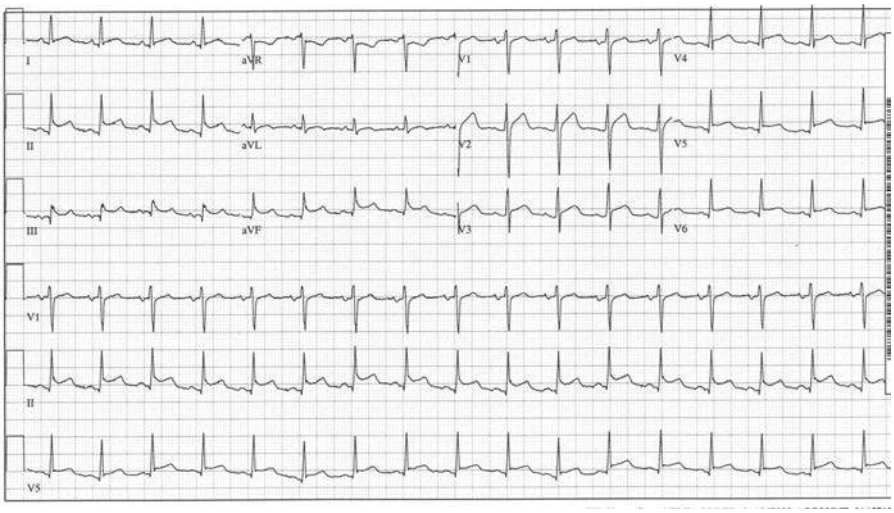

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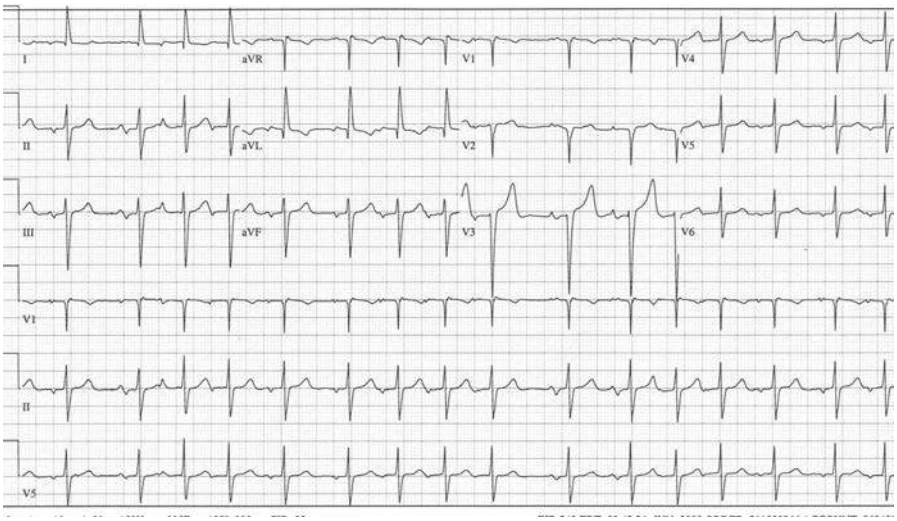

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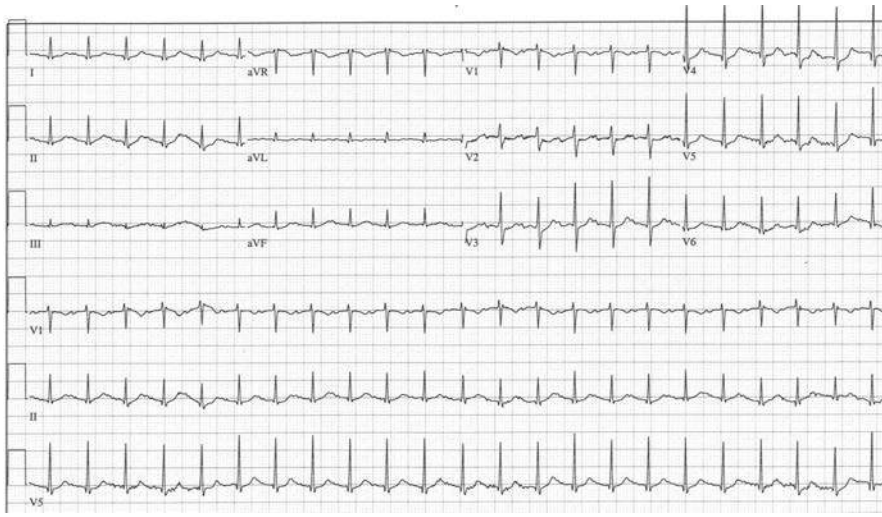

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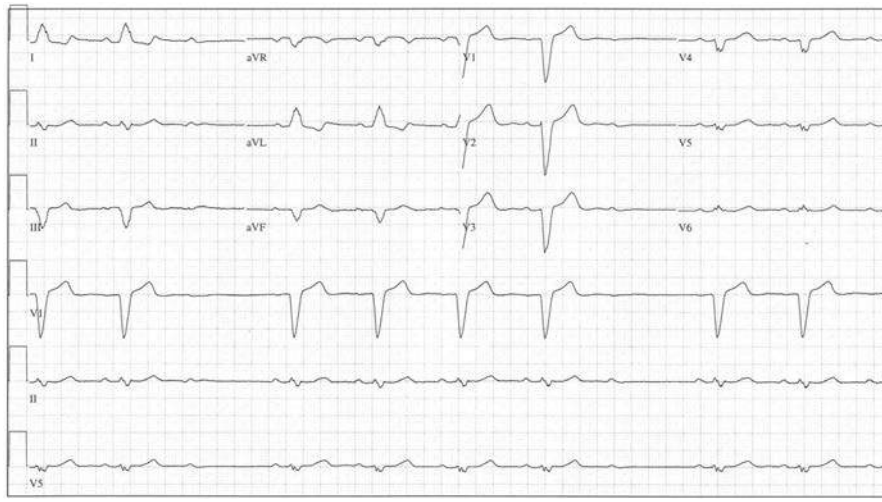

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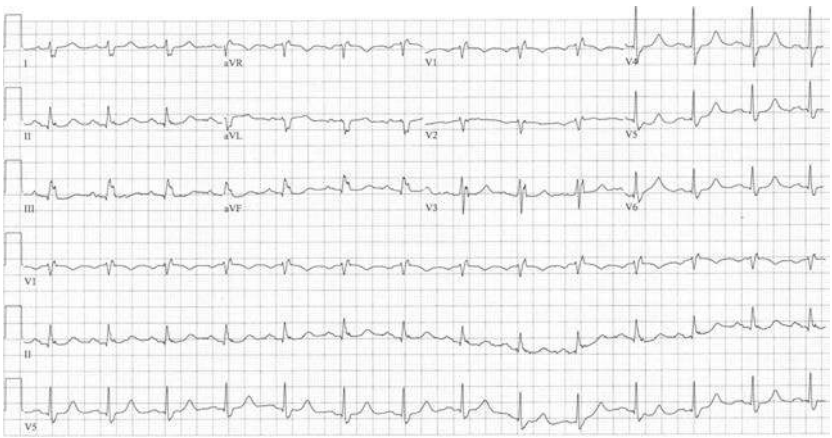

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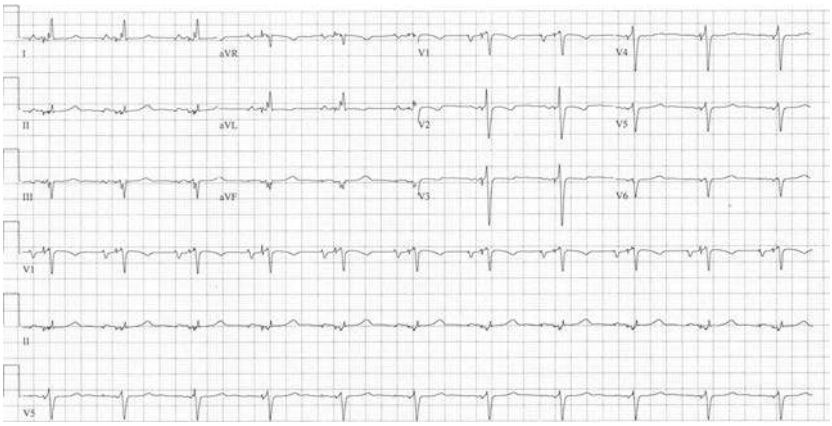

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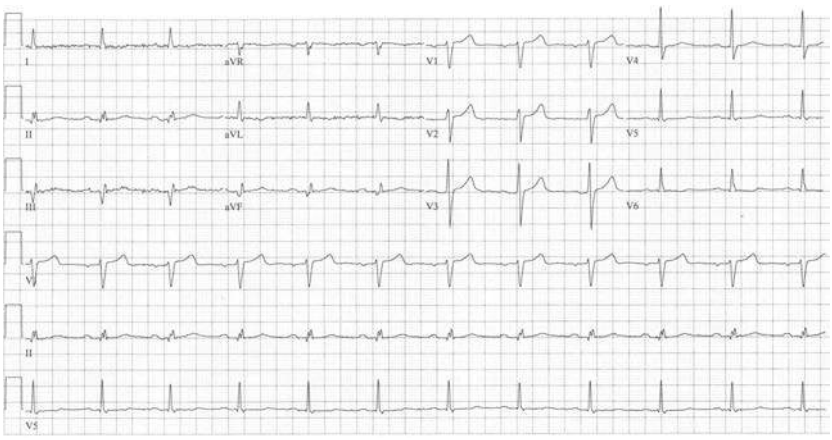

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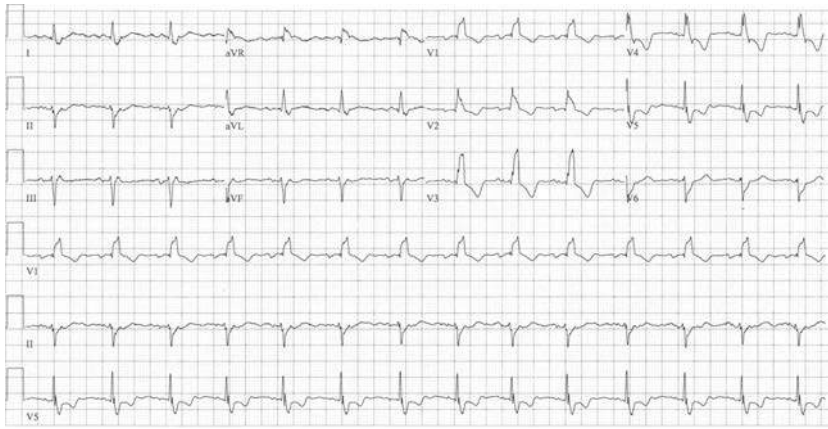
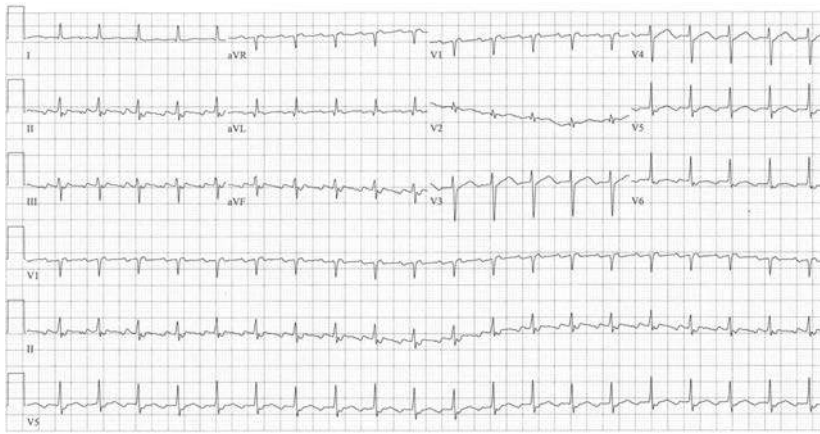


Question/Figure 2.60

Question/Figure 2.61



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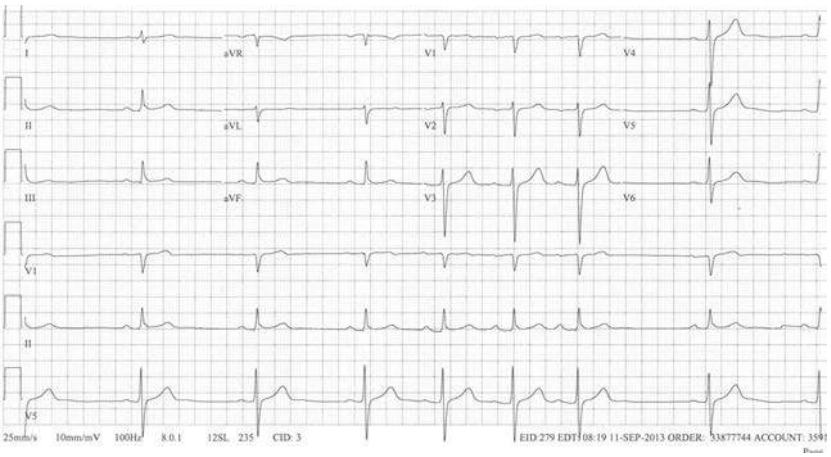

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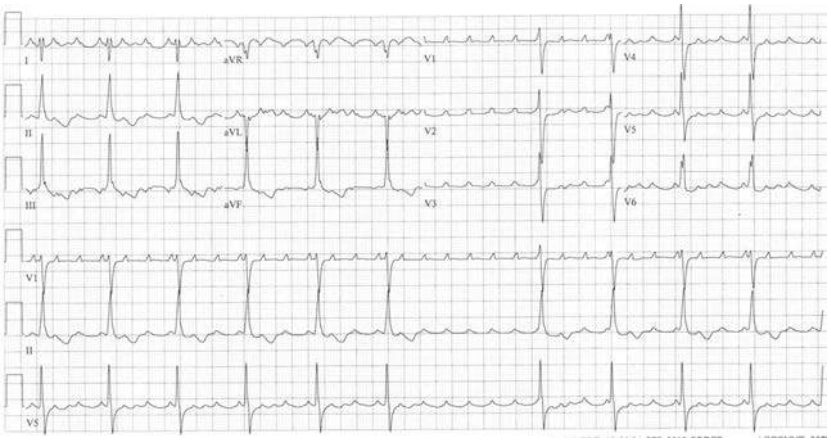

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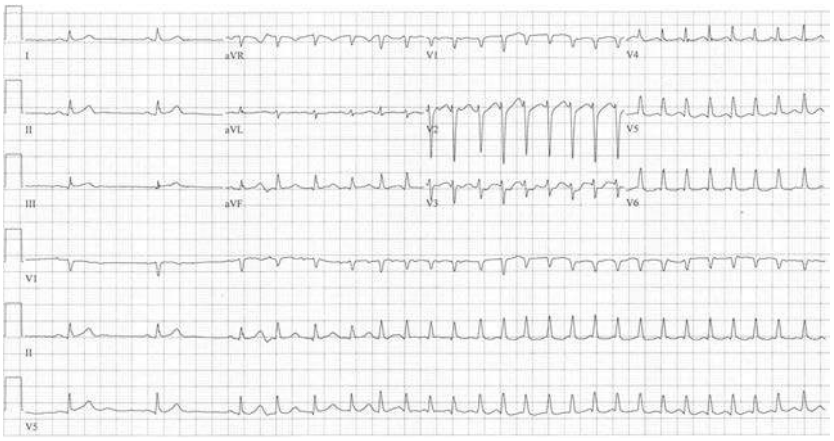

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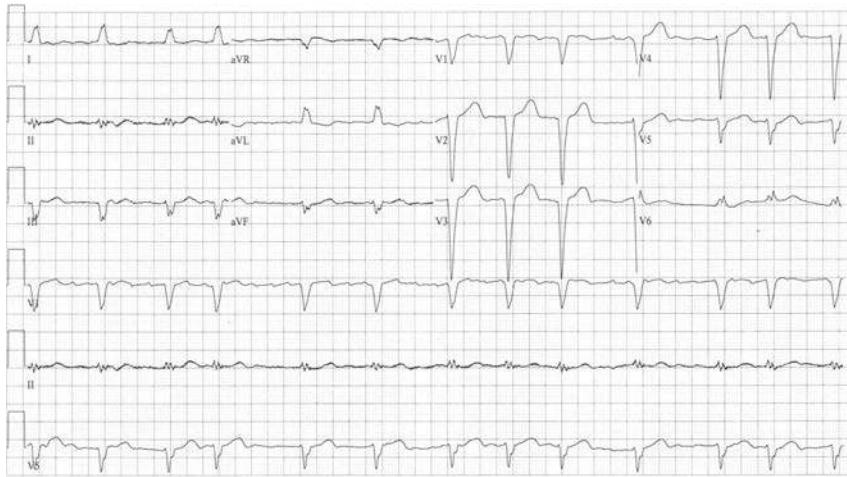

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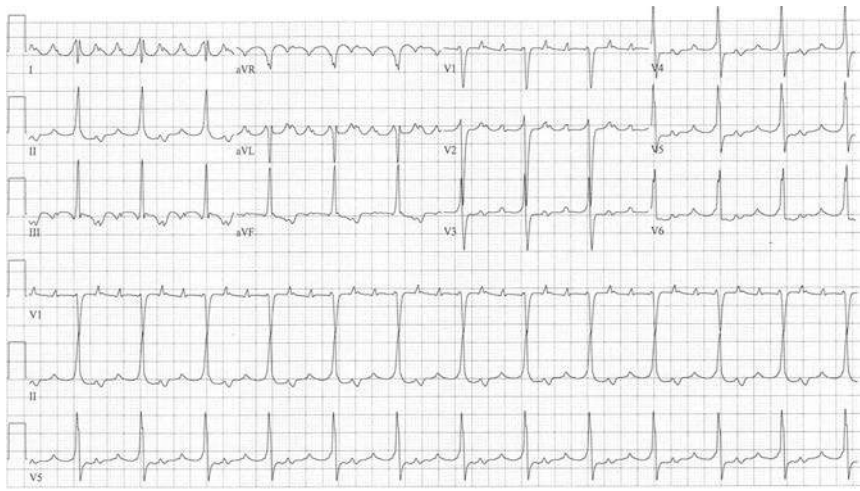

Question/Figure 2.67

Answers

2.1. Second-degree atrioventricular (AV) block, Mobitz type I (AV Wenckebach). Note increasing PR interval and PR interval being the shortest after a dropped beat. Also, note that the patient has intraventricular conduction delay (IVCD) and lateral T wave inversion. Despite IVCD, it is less likely to be trifascicular block as AV Wenckebach is generally a nodal rather than infra-Hisian phenomenon.

2.2. Right ventricular (RV) hypertrophy (RVH) with strain and biatrial enlargement. R in V1 >5 mm with right axis deviation and ST–T changes in right chest leads support RVH. P wave amplitude >3 mm supports right atrial enlargement and P-terminale in V1 > 1 × 1 box supports left atrial enlargement.

2.3. Sinus rhythm with bifascicular block. Note right bundle branch block (RBBB) and left axis deviation with mean QRS axis less than −30° suggesting left anterior fascicular block (LAHB). Also note that the peak of R wave is earliest in III, followed by II, and then I, indicating late activation of left ventricular (LV) lateral wall supplied by anterior fascicle. Inferior wall is supplied by posterior fascicle and R wave peaks early in these leads.

2.4. Sinus arrhythmia with short PR interval suggesting Lown–Ganong–Levine syndrome. Note that there is no delta wave or QRS prolongation indicating Wolff–Parkinson–White (WPW) syndrome. In Lown–Ganong–Levine syndrome, the accessory pathway is atrio-Hisian, shortening the PR interval. In WPW syndrome, AV preexcitation of a portion of ventricular myocardium results in delta wave and QRS prolongation.

2.5. Atrial fibrillation. Note absence of P wave and irregularly irregular ventricular response. Also note low QRS voltage (<5 mm in limb and <10 mm in chest leads), which should raise the suspicion of chronic obstructive pulmonary disease, pericardial effusion, or diffuse myocardial disease.

2.6. Acute anterior ST elevation myocardial infarction (STEMI). Note hyperacute, tombstone ST elevation in V2 and V3.

2.7. Hyperkalemia. Note peaked, tall T waves in V2 and V3.

2.8. Junctional tachycardia. P waves are inverted in inferior leads with superior axis indicating junctional or low atrial origin.

2.9. RVH. qR in V1 with right axis deviation and strain pattern in right chest leads is suggestive of RVH.

2.10. WPW syndrome (? posteroseptal).

2.11. Seven beats of accelerated idioventricular rhythm, followed by a fusion beat and then accelerated junctional rhythm. This is suggestive of digoxin toxicity.

2.12. Atrial flutter with 2 : 1 conduction. Flutter waves are clearly visible in inferior leads.

2.13. Posterior myocardial infarction. Note tall R waves in V1 and V2 with upright T wave associated with Q waves inferolaterally. In RVH, one would expect to see strain pattern in right chest leads.

2.14. Ventricular tachycardia. Broad complexed tachycardia with RBBB morphology with left rabbit ear, QRS duration of 200 ms and indeterminate axis – all suggestive of ventricular tachycardia (VT) rather that supraventricular tachycardia (SVT) with aberrancy.

2.15. Atypical atrial flutter with 3 : 1 conduction, intermittent RV pacing (third and last three beats) and one fusion complex (fifth beat).

2.16. Acute anterior STEMI. Note Q waves and ST elevation of 3–4 mm in V1 and V2.

2.17. Sinus rhythm with low QRS voltage (<5 mm in limb leads or <10 mm in chest leads). Consider pericardial effusion, emphysema.

2.18. Nonconducted P (second from right) followed by a P associated with a ventricular escape beat showing T wave inversion. Consistent with Mobitz type II AV block. Also note anterior Q wave, RBBB and LAFB – a substrate for trifascicular block.

2.19. Atrial fibrillation with rapid ventricular response. Also note low QRS voltage and diffuse ST elevation, suggesting pericarditis with effusion which may result in atrial fibrillation through atrial irritation.

2.20. Acute pericarditis. Note diffuse concave-up ST elevation and PR segment depression in most of the leads and reciprocal PR segment elevation and ST depression in aVR.

2.21. Episodes of complete heart block. Note >1 nonconducted P in a row. Note old inferior and acute anterior STEMI and mechanism of heart block is likely to be infra-Hisian with high risk of lack of escape rhythm.

2.22. Premature ventricular contractions (PVCs), three-beat VT (beats 2–4), accelerated idiojunctional rhythm (fairly regular narrow complex with no preceding P at a rate of 65 bpm, beats 9–12), Afib (lack of a P wave), short QT interval. These are highly indicative of digoxin toxicity. Digoxin toxicity blocks AV node and promotes subsidiary pacemakers at a faster rate.

2.23. Junctional rhythm with ventricular bigeminy.

2.24. Junctional rhythm with RBBB (beats 1, 4, and 5) with intermittent V-pacing (beats 2, 3, 6, and 7). Note a small pacer spike, changed QRS morphology upright in I, and different T wave morphology with paced beats.

2.25. Dual-chamber pacing.

2.26. Ventricular bigeminy.

2.27. Atrial pacing, ventricular tracking with ventricular pseudofusion. The V-spike before QRS is coincidental and QRS has normal conducted morphology. Lengthening AV delay will conserve the battery.

2.28. Dual-chamber pacing with ventricular couplet (beats 7 and 8).

2.29. Atrial flutter with 2 : 1 conduction and intermittent V-pacing.

2.30. WPW syndrome.

2.31. Dual-chamber pacer with atrial sensing and V-pacing producing slightly fused complex. Only very initial part of QRS is slightly slurred, indicating pacer-induced depolarization and rest of the QRS is normally conducted. Note LAFB as well.

2.32. High-grade AV block. The P waves are numbered. The atrial rate is about 86 bpm, and between 1 and 2 (rate 43) a P wave is dropped, indicating 2 : 1 sino-atrial block (produced by a nonconducted premature atrial contraction (PAC) between 1 and 2 through concealed retrograde conduction. The PAC is deforming the ST segment). Then there is 2 : 1 A : V block till 7 followed by two successive Ps being dropped (complete AV block) with a ventricular escape beat at 9 burying a P wave.

2.33. Narrow complex regular tachycardia at a rate of 150 .bpm without a discernible P wave. Likely paroxysmal SVT and possible atrioventricular nodal reentry tachycardia.

2.34. Broad complex tachycardia at a rate of 140 bpm, suggestive of VT. Note negative concordance in chest leads, superior axis, QRS duration of >200 ms, and slow upstroke of QRS complex – all suggestive of VT.

2.35. Atrial flutter with 2 : 1 conduction. Note clear flutter waves in lead II. There is a single PVC.

2.36. Atrial paced rhythm with normal AV conduction and normal QRS.

2.37. Atrial sensed and ventricular paced rhythm. Note that QRS is upright in V1, suggesting probable LV rather than RV pacing. Patient has a biventricular (BiV) pacer.

2.38. WPW syndrome. Note the delta waves in V4 and V5.

2.39. Dual-chamber pacer with atrial tracking and V-pacing producing fusion QRS complexes with initial portion due to pacing and remainder being conducted.

2.40. VOO pacing with pacer competing with junctional rhythm producing fully paced beat (1), fusion complex (2), pseudofusion (3), and lack of sensing (5–9). Also note QT prolongation. T wave inversion can occur because of repolarization memory secondary to V-pacing.

2.41. Dual-chamber pacing.

2.42. WPW syndrome, probably posteroseptal pathway because of inferior Q waves, positive delta waves in anterolateral leads, and rapid transition from V1 to V2.

2.43. BiV pacer with atrial and LV pacing. Note that QRS is negative in lateral leads and positive in V1, indicating LV pacing.

2.44. Broad complex tachycardia at a rate of 140 bpm with QRS duration of 160 ms, RBBB pattern with right rabbit ear and right axis deviation and rapid upstroke of initial part of QRS (in V5/V6) with broadening of latter part suggesting SVT with aberrancy. Note that the PVC did not reset the rhythm.

2.45. Broad complex tachycardia with monophasic RBBB pattern in V1, right axis deviation, and QRS duration of 160 ms. No P waves seen. Note rapid rise of QRS voltage in V5 and V6. The patient had SVT with aberrancy.

2.46. Atrial fibrillation for the first five beats, then V-pacing for a beat followed by sinus rhythm with first-degree AV block and lack of V-sensing in last three beats. Also note acute anterior STEMI.

2.47. BiV pacer. Patient is paced in atrium and left ventricle, producing RBBB QRS morphology.

2.48. Blocked PACs. The pauses are due to nonconducted PACs which occurred on the T wave and during refractory period of AV node. This does not signify AV nodal disease. When there are pauses, always look for nonconducted PACs. Also note QT prolongation.

2.49. Acute inferolateral STEMI. Note reciprocal ST depression in aVR; in pericarditis, there is reciprocal ST and PR segment elevation in aVR.

2.50. BiV hypertrophy. R in V1 is >5 mm and R/S in V1 is 1, suggesting RVH. R in V5 plus S in V2 is 35 mm, and ST depression in V5 and V6 suggests LV hypertrophy (LVH).

2.51. Normal electrocardiogram.

2.52. Acute inferior STEMI with near-complete ST segment resolution and inferior Q waves.

2.53. Acute inferolateral STEMI.

2.54. Multifocal atrial tachycardia. Note three different P wave morphologies and average rate >100 bpm.

2.55. Sinus tachycardia.

2.56. Intermittent dropped QRSs without progressive PR prologation suggesting second-degree Mobitz type II AV block. Also note that patient has left bundle branch block (LBBB), further supporting that the mechanism of AV block is likely infra-Hisian rather than intranodal. High risk of complete heart block.

2.57. Bifascicular block. Patient has RBBB and right axis deviation, suggesting left posterior fascicular block. Note the peaks of R wave in leads II and III follow lead I, suggesting activation spreading from lateral to inferior wall, the region of posterior fascicle.

2.58. Dual-chamber pacing, but QRS is native rather than paced. The V-spike comes before QRS, but QRS is narrow and has near-normal morphology.

2.59. Inferior myocardial infarction, age undetermined, possibly recent (slight ST elevation in leads III and aVF.

2.60. Bifascicular block with RBBB and LAFB. Also note absence of r in leads V1 to V4, indicating anterior myocardial infarction. Hence, the likely mechanism is diffuse conduction system disease through ischemia and signifies high risk because of infra-Hisian mechanism and extent of myocardial involvement.

2.61. Severe hyperkalemia with near sine wave appearance: Note peaked T waves, QRS prolongation, and absent P waves.

2.62. Atrial flutter with 2 : 1 conduction. The atrial rate is 240 bpm and ventricular rate is 120 bpm.

2.63. Marked respiratory sinus arrhythmia. Note that the P wave morphology is constant and cyclical changes in P–P intervals are consistent with frequency of respiration. It is a marker of vagotonia and seems to be more marked in the young and at slow heart rates.

2.64. Atrial tachycardia with variable block.

2.65. Paroxysmal atrial fibrillation with rapid ventricular response.

2.66. Atypical atrial flutter with variable block and IVCD of LBBB morphology.

2.67. Atrial tachycardia with 3 : 1 conduction. Atrial rate is about 225 bpm, and this could also be slow flutter because of antiarrhythmic therapy.

Box 2.1 ECG Diagnostic Criteria

Normal sinus P wave

- P wave duration <120 ms
- Amplitude ≤2.5 mm
- P wave axis between 45° and 75° in frontal plane

Criteria for left atrial enlargement

- P wave duration >120 ms in lead II
- Notched P wave in lead II with inter-notch distance >40 ms (P-mitrale)

- P-terminale in V1 >0.04 mm
- P wave axis between +45° and −30° in frontal plane (left axis deviation)

Criteria for right atrial enlargement

- P wave amplitude >2.5 mm in lead II (P-pulmonale)
- Area under initial positive part of P wave in V1 >0.06 mm
- P wave axis >75° in frontal plane (right axis deviation)

Criteria for LVH

- Sokolov criteria: S in V1 plus R in V5 or V6 >35 mm; R in aVL >11 mm
- Cornell criteria: S in V3 plus S in V1 ≥28 mm for men and ≥20 mm for women
- Romhilt–Estes criteria (LVH if 5 points): R wave in any limb lead ≥20 mm, or S in V1 or V2 ≥30 mm, or R in V5 or V6 ≥30 mm (3 points); left atrial abnormality (3 points); ST–T changes without digoxin (3 points) or with digoxin (1 point); QRS axis <−30° (2 points); QRS duration >90 ms (1 point); intrinsicoid deflection in V5 or V6 >50 ms (1 point)

Criteria for RVH

- R in V1 ≥7 mm
- QR in V1
- R/S in V1 >1 with R at least 5 mm
- R/S in V5 or V6 <1
- $S_1Q_3T_3$ pattern (pulmonary embolism)
- $S_1S_2S_3$ pattern

Criteria for BiV hypertrophy

- Tall R in both left and right chest leads
- LVH with right axis deviation
- LVH with deep S in V5 or V6
- LVH with shift of precordial transition (R/S = 1) to the left of V4

Criteria for LAFB

- QRS axis <−45° with rS in inferior leads (i.e., no inferior Q waves) and qR in high lateral leads plus QRSd <120 ms

Criteria for left posterior fascicular block

- QRS axis >120° with RS in high lateral leads and qR in inferior leads plus QRSd <120 ms

Criteria for LBBB

- Broad notched R wave in lateral leads, absent q in left-sided leads (septal activation will be right to left), QRSd ≥120 ms

Criteria for RBBB

- Broad notched R wave in V1 and V2 with right rabbit ear, deep slurred S in left-sided leads (reciprocal of R′), QRSd ≥120 ms

Causes of tall R wave in V1

- RVH (generally with right axis deviation and secondary ST–T changes or right atrial enlargement)
- True posterior infarct (generally with upright T, inferior or lateral Q)
- Hypertrophic obstructive cardiomyopathy (due to septal depolarization)
- Duchenne muscular dystrophy
- RBBB
- WPW syndrome with posterior or lateral pathways
- Heart shifted to right

Causes of Q waves

- Normal in V1/V2 and III (in lead III will disappear with deep breath which makes heart vertical)
- Myocardial infarction
- Myocardial infiltration (sarcoid, amyloid)
- Myocarditis
- WPW syndrome
- LBBB results in Q in V1/V2
- Hypertrophic obstructive cardiomyopathy (septal hypertrophy causing Q in lateral leads)

Causes of ST elevation

- Normal variant (early repolarization, generally V1–V4)
- Myocardial injury (convex up)
- LV aneurysm (persistent beyond 6 months)
- Pericarditis (concave up, diffuse, ST and PR elevation in aVR, PR depression)
- Brugada syndrome
- Hyperkalemia ("dialyzable current of injury")
- Type IC antiarrhythmic agents
- LVH and LBBB (in right chest leads as reciprocal of ST depression on left chest leads)

Hyperkalemia

- Peaked T wave (early sign)
- Increased QRS duration
- Absent P wave
- Sine wave morphology in late stage

Hypercalcemia

- Shortened QT interval

Hypocalcemia

- QT lengthening (especially ST segment lengthening)

Chest X-Ray in Cardiology

3

3.1. A 52-year-old African American male was admitted with complaints of shortness of breath and edema. He has a history of methamphetamine use. A chest X-ray (Figure 3.1a) was performed in the emergency room (ER). What does the chest X-ray show?

A. Cardiomegaly
B. Cardiomegaly, automatic implantable cardioverter-defibrillator (AICD) lead
C. Normal findings
D. Cardiomegaly, AICD lead, left pleural effusion

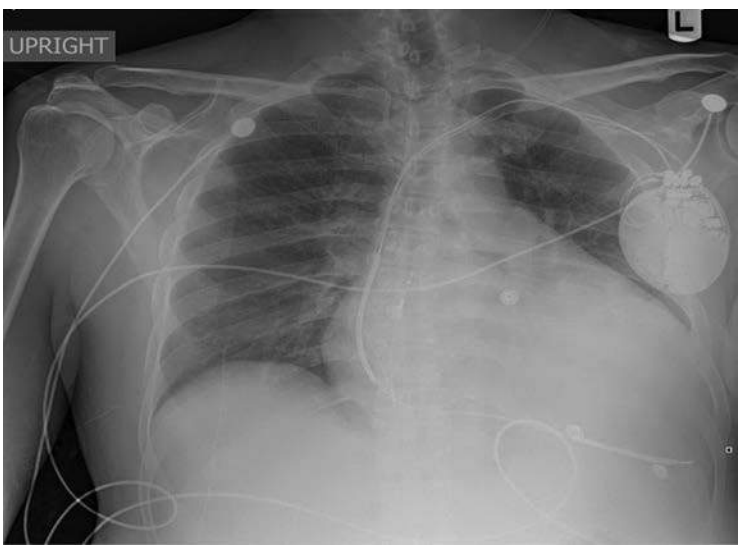

Figure 3.1a

3.2. An 84-year-old male was admitted with shortness of breath. He was diagnosed with left pleural effusion. He underwent thoracentesis. A few hours later he developed increasing oxygen requirements. A chest X-ray was done (see Figure 3.2a). What does it show?

A. Pulmonary edema
B. Right apical pneumothorax
C. Left apical pneumothorax
D. Right-sided pneumonia

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Figure 3.2a

3.3. A 59-year-old male was admitted with a history of subarachnoid hemorrhage. A PA chest X-ray (Figure 3.3a) was performed in the ER. What does the chest X-ray show?

A. Normal chest X-ray

B. Prosthetic valve in the mitral position

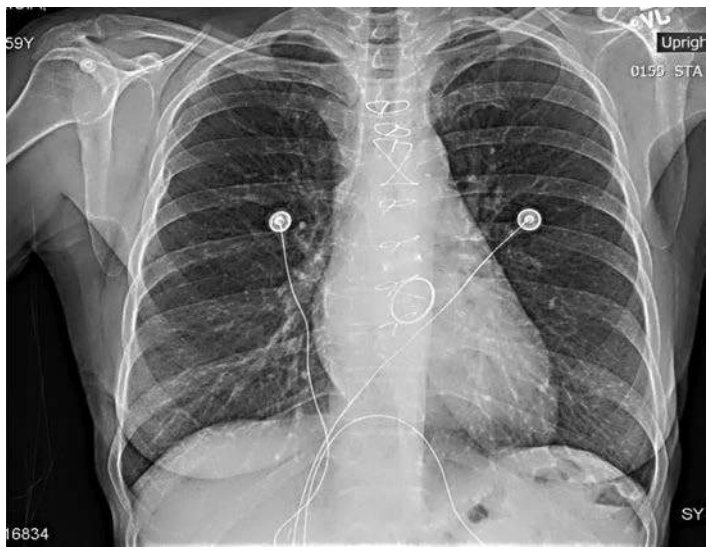

Figure 3.3a

C. Prosthetic valve in the aortic position
D. Prosthetic valves in the aortic and mitral positions

3.4. A 75-year-old male presented to the ER with complaints of shortness of breath. A chest X-ray (Figure 3.4a) was performed in the ER. What does the X-ray show?
A. Left pleural effusion
B. Right pleural effusion
C. Consolidation
D. Pulmonary edema

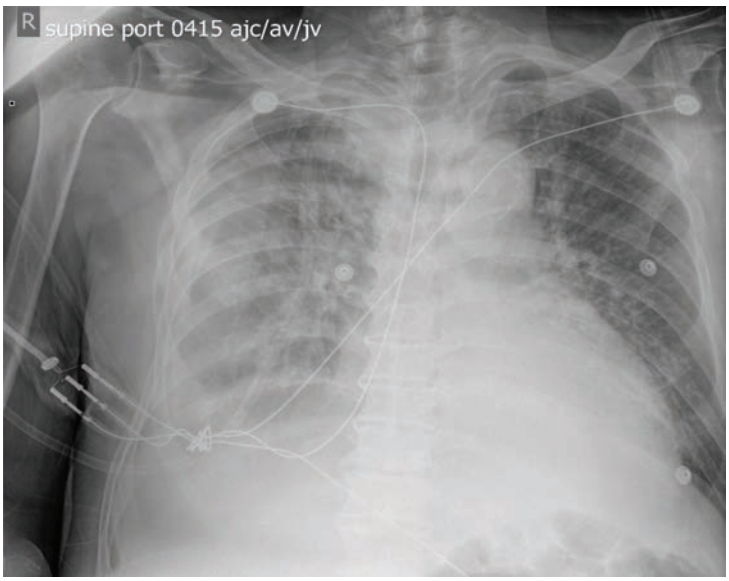

Figure 3.4a

3.5. A 59-year-old Pakistani male presented to the ER with complaints of headache. He had a computed tomography (CT) scan of his head, which showed evidence of subdural hemorrhage. He also had a chest X-ray (Figure 3.5a) in the ER. What does the X-ray show?
A. Bioprosthetic valve in the aortic position
B. Bileaflet mechanical prosthesis in the mitral position
C. Bioprosthetic valve in the mitral position
D. No prosthetic valve is seen

3.6. A 56-year-old male presented to the ER with complaints of shortness of breath on exertion, cough with whitish expectoration, and pedal edema. In the ER he had a chest X-ray (see Figure 3.6a). What is the most important finding on the X-ray?
A. Pneumothorax
B. Right pleural effusion only
C. Left pleural effusion
D. Bilateral pleural effusion
E. No abnormality seen

Figure 3.5a

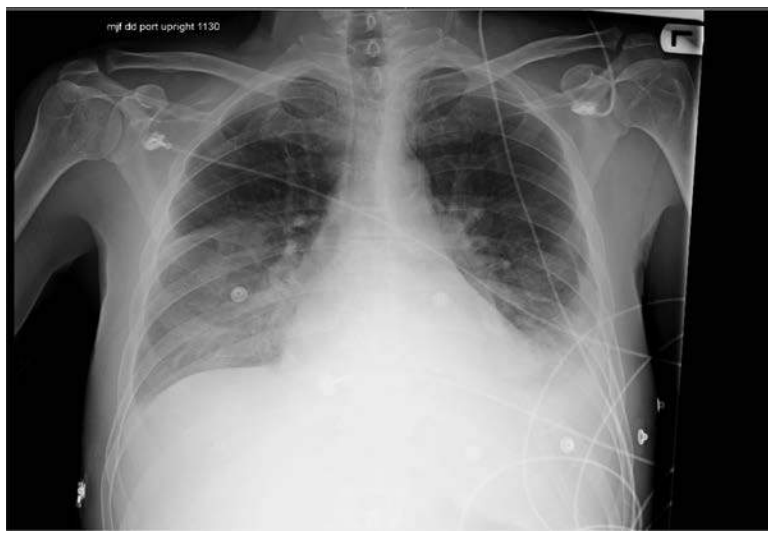

Figure 3.6a

3.7. A 39-year-old male presented to the hospital after a cardiac arrest at home. He was brought to the hospital and had a chest X-ray (Figure 3.7). What does the chest X-ray show?

A. Normal heart size
B. Cardiomegaly
C. Left pneumothorax
D. Right pneumothorax

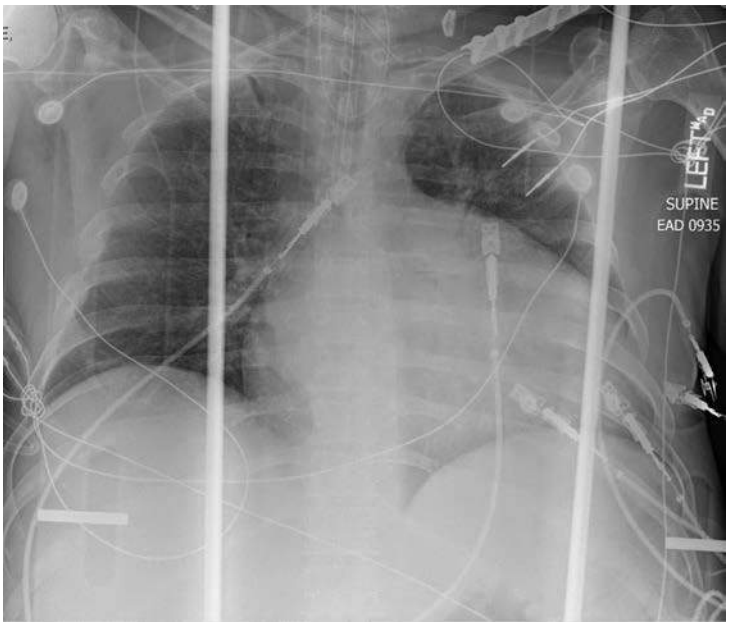

Figure 3.7

3.8. A 51-year-old male came to the hospital with complaints of fatigue, cough. He had a chest X-ray (see Figure 3.8a) in the ER. What does his chest X-ray show?

A. Normal aortic size
B. Prominent aortic knob
C. Prominent main pulmonary artery
D. Prominent left bronchus

3.9. The patient in Question 3.8 then had an echocardiogram. He had mild tricuspid regurgitation, velocity of 4.7 m/s, elevated right atrial pressure of 20 mmHg, and estimated pulmonary artery systolic pressure of 110 mmHg. What are these findings suggestive of?

A. Primary pulmonary hypertension
B. Pulmonary vascular congestion
C. Right to left shunt
D. None of the above

3.10. A 69-year-old male was admitted to the hospital complaining of shortness of breath. His initial chest X-ray showed pulmonary edema and he was started on intravenous diuretics. Two days later he complained of feeling feverish,

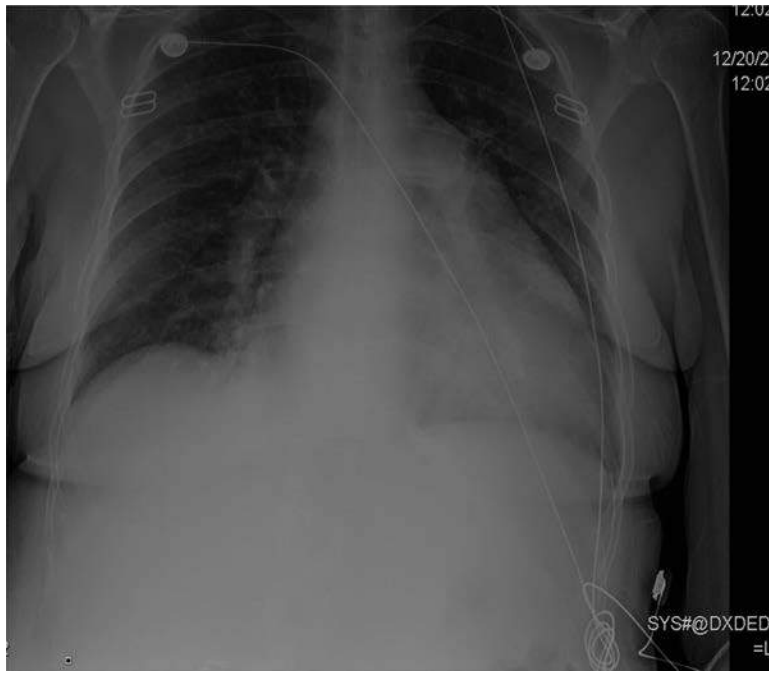

Figure 3.8a

temperature was 101°F, with chills and greenish expectoration. What does the repeat chest X-ray (Figure 3.10a) show?

A. Pulmonary edema
B. Right hilar consolidation with superimposed pulmonary vascular congestion
C. Left hilar consolidation
D. Right hilar consolidation

3.11. A 62-year-old male was admitted with complaints of shortness of breath. What does the chest X-ray in Figure 3.11a show?

A. Left atrial enlargement
B. Right ventricular enlargement
C. Left ventricular enlargement
D. Right atrial and right ventricular enlargement

3.12. An 80-year-old female patient has a history of long-standing systolic murmur at the base. She had a chest X-ray (Figure 3.12a). What is the most important finding?

A. Marked enlargement of main pulmonary artery
B. Marked enlargement of the aorta
C. Marked enlargement of the right pulmonary artery
D. Marked enlargement of the main pulmonary artery and left pulmonary artery

3.13. What does the blue arrow point to on the chest X-ray in Figure 3.13?

A. Enlarged left atrium
B. Aortic knob
C. Enlarged pulmonary artery
D. None of the above

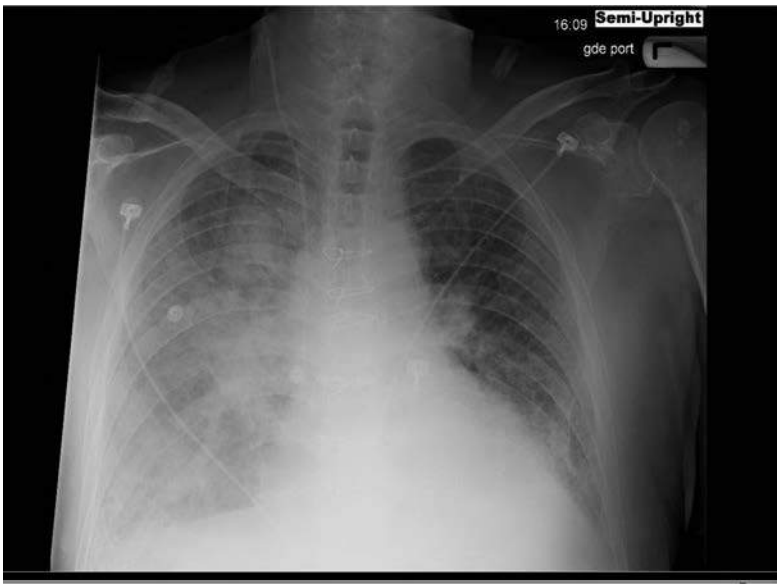

Figure 3.10a

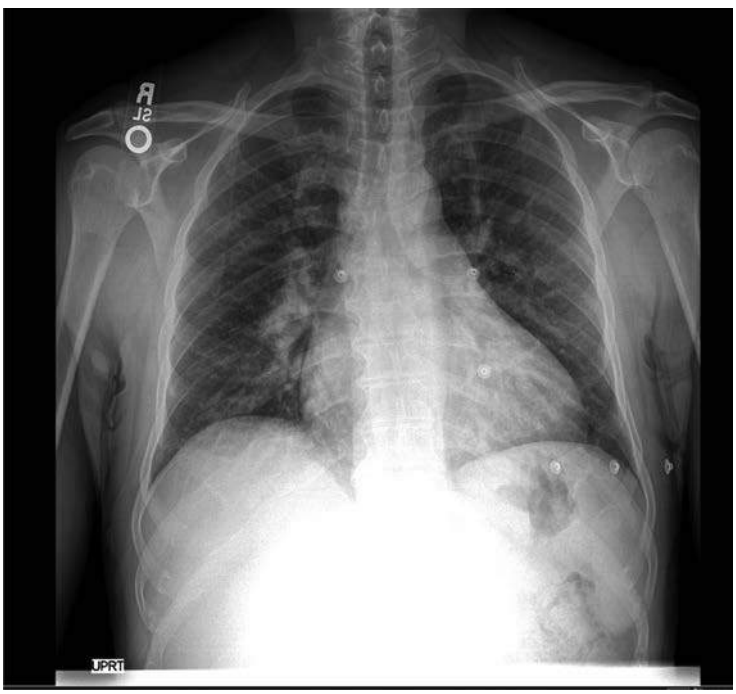

Figure 3.11a

Figure 3.12a

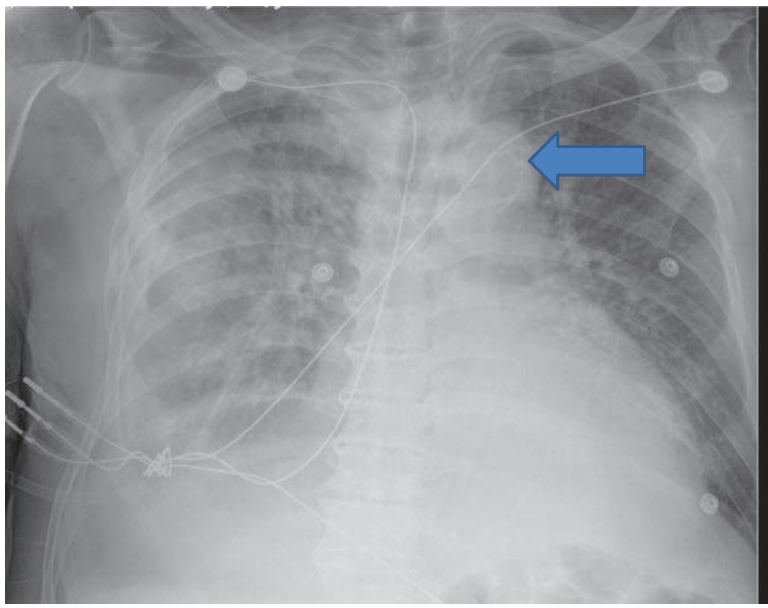

Figure 3.13

3.14. What structure indicated by the blue arrow in Figure 3.14 forms the cardiac boundary:

A. Ascending aorta
B. Arch of the aorta
C. Right pulmonary artery
D. Superior vena cava

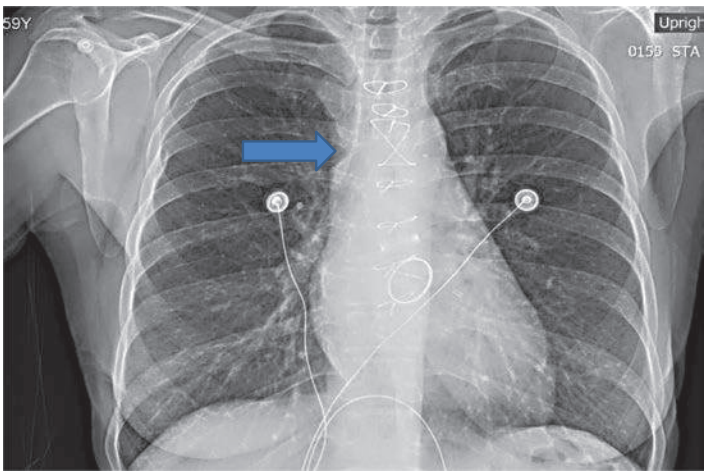

Figure 3.14

3.15. Figure 3.15a shows a 93-year-old female patient with a history of shortness of breath who has undergone what procedure?

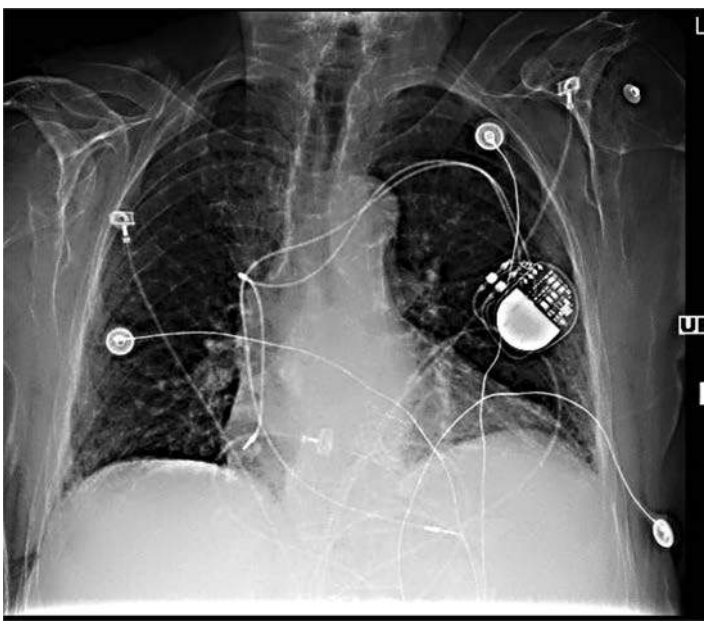

Figure 3.15a

A. Surgical replacement of mitral valve
B. Surgical replacement of aortic valve
C. Transaortic valve replacement (TAVR)
D. None of the above

3.16. The patient in Question 3.15 has also undergone another procedure. What is this other procedure?
A. Permanent single-chamber pacemaker
B. Dual-chamber pacemaker
C. Dual-chamber AICD
D. None of the above

3.17. What does the blue arrow in Figure 3.17 point to?
A. Right atrial pacer lead
B. Right ventricular pacer lead
C. Right ventricular implantable cardioverter-defibrillator (ICD) lead
D. Coronary sinus lead

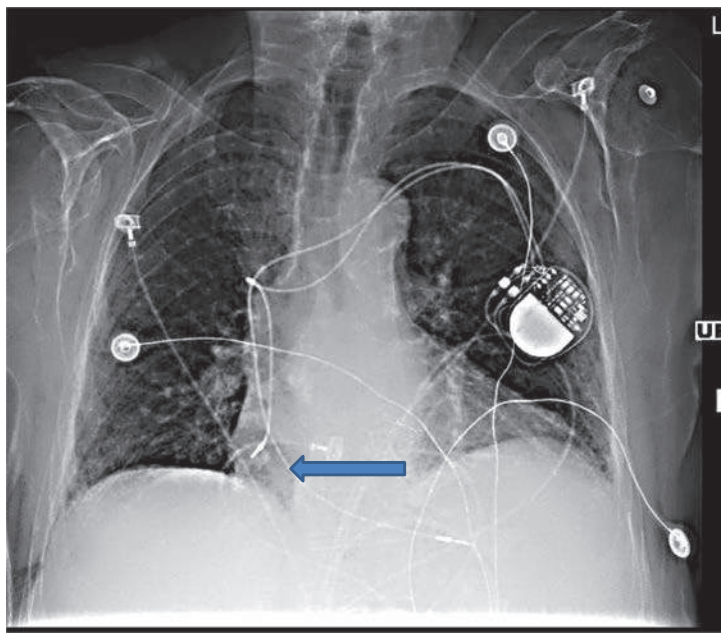

Figure 3.17

3.18. What does the blue arrow in Figure 3.18 point to?
A. Right atrial pacer lead
B. Right ventricular ICD lead
C. Right atrial ICD lead
D. Coronary sinus lead

3.19. What does the blue arrow in Figure 3.19a point to?
A. Right atrial pacer lead
B. Right ventricular ICD lead
C. Right atrial ICD lead
D. Coronary sinus lead

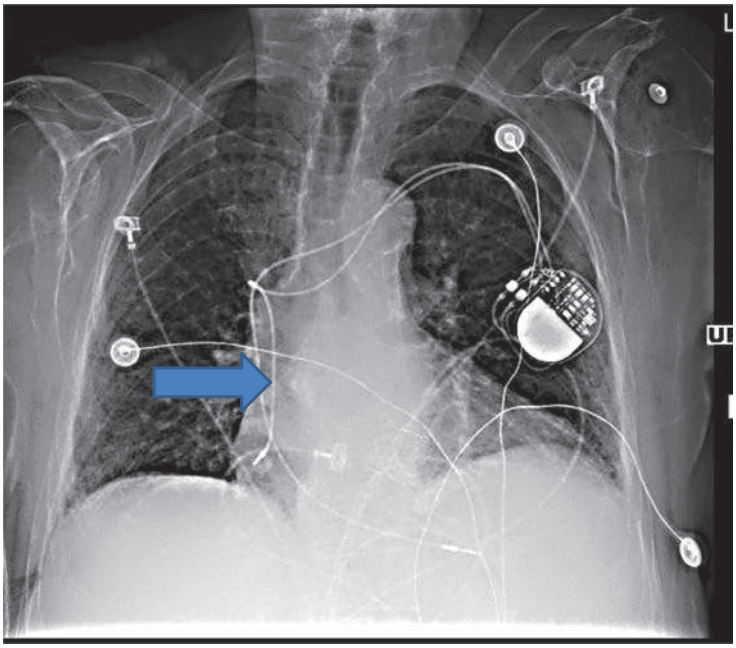

Figure 3.18

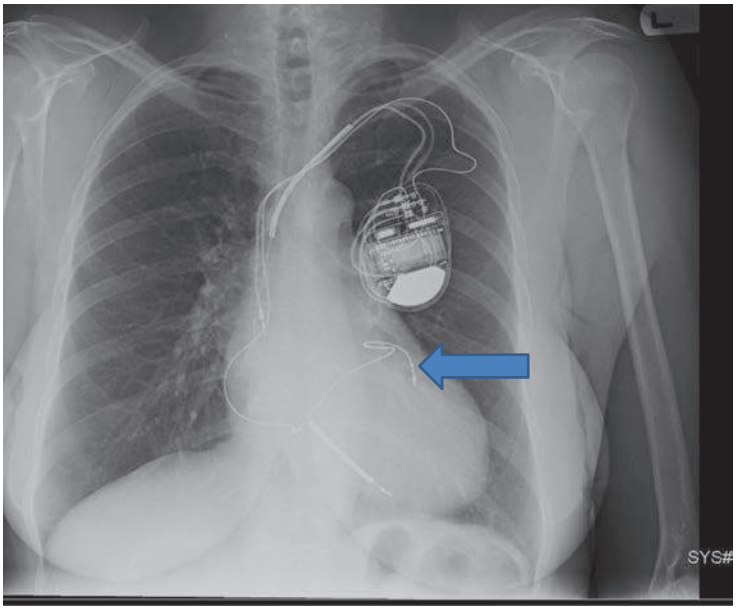

Figure 3.19a

3.20. What does the blue arrow in Figure 3.20 point to?

A. A pacer lead
B. Catheter placed through left subclavian vein
C. Arterial line
D. None of the above

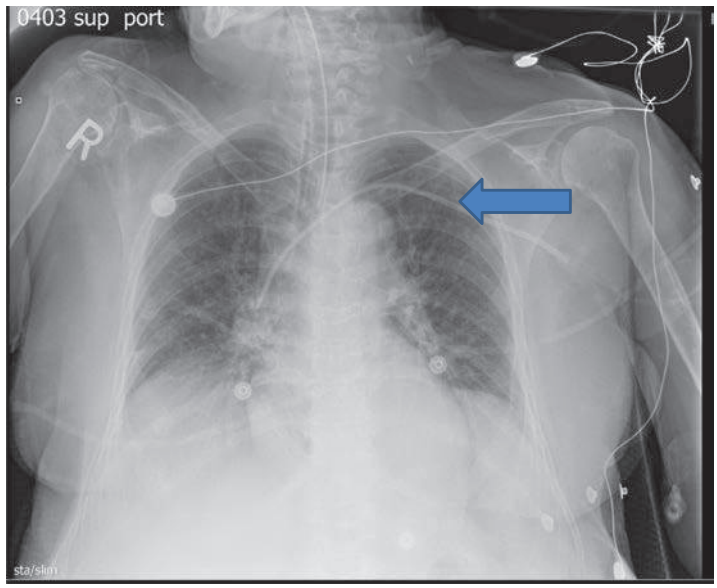

Figure 3.20

3.21. What does the blue arrow in Figure 3.21 point to?

A. Catheter placed through right internal jugular vein
B. Catheter through right subclavian vein
C. Pacer lead
D. None of the above

3.22. An 86-year-old male with history of chronic obstructive pulmonary disease is admitted to the hospital. After a day he was noted to be hypoxic. He also complained of feeling feverish and increasingly short of breath. Referring to Figure 3.22a, what procedure did he undergo?

A. Placement of central line
B. Placement of a pacer
C. Endotracheal intubation
D. Thoracentesis

3.23. The arrow in Figure 3.23 points to which landmark on the chest X-ray from the patient in Question 3.22?

A. Carina
B. Main pulmonary artery
C. Esophagus
D. Aorta

3.24. The arrow in Figure 3.24 points to what structure on the chest X-ray?

A. Nasogastric tube
B. Percutaneous endoscopic gastrostomy tube
C. Central venous catheter
D. None of the above

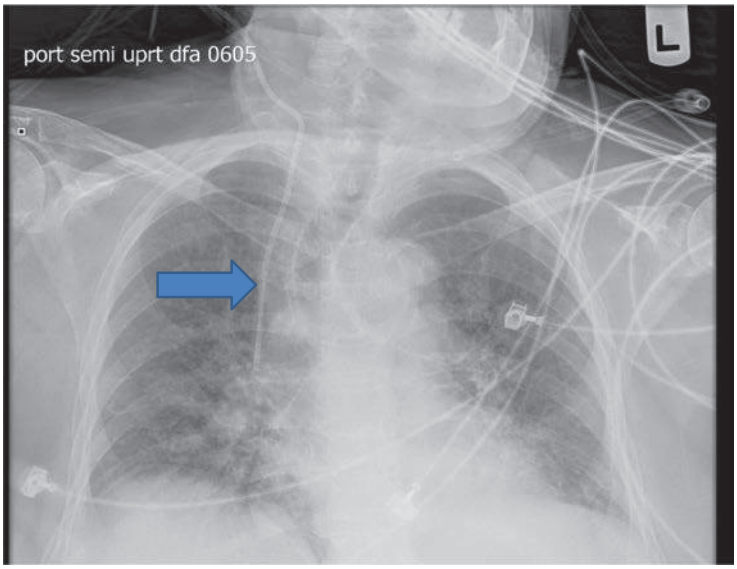

Figure 3.21

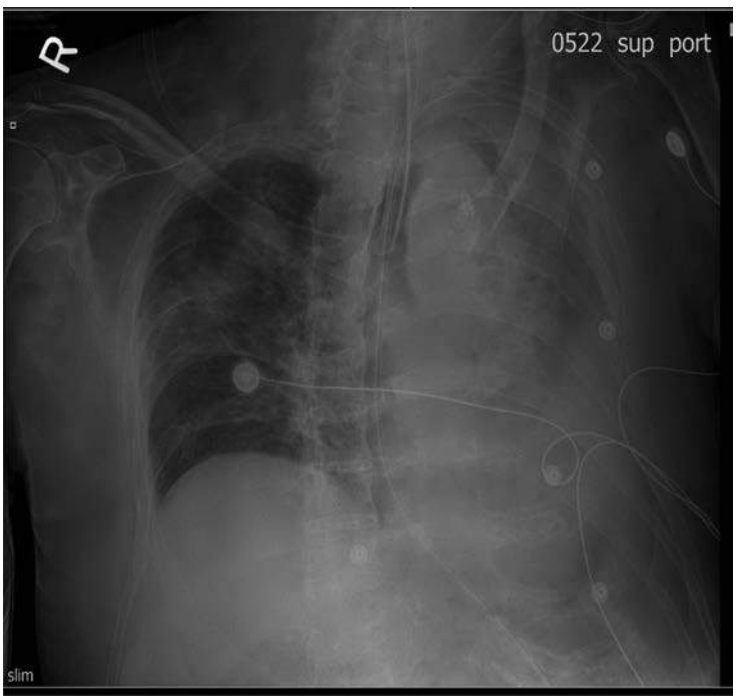

Figure 3.22a

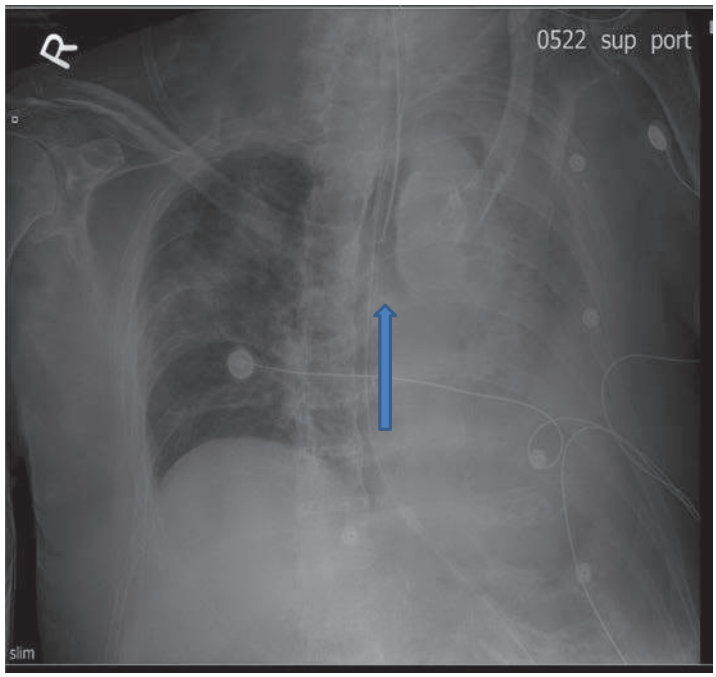

Figure 3.23

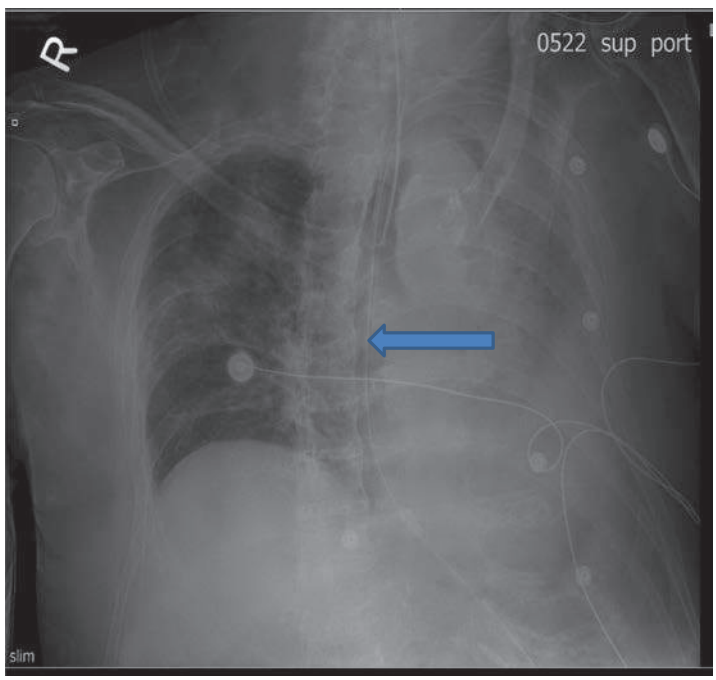

Figure 3.24

3.25. A 59-year-old Hispanic female patient was admitted to the hospital with complaints of fever and shortness of breath. A chest X-ray was performed (see Figure 3.25a) and she had which of the following procedures performed?

A. Pericardiocentesis
B. Placement of a catheter in the right pleural space
C. Placement of a catheter in the left pleural space
D. Right paracentesis

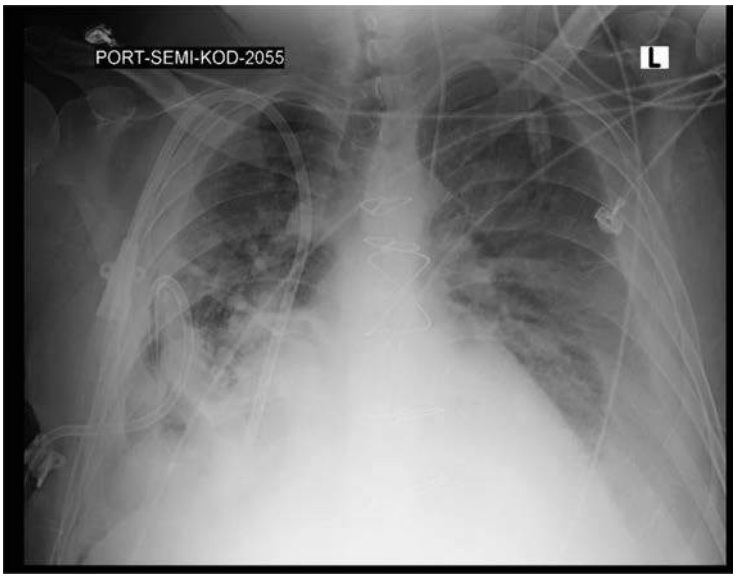

Figure 3.25a

3.26. The chest X-ray in Figure 3.26a shows which of the following:

A. Dextroposition
B. Dextrocardia
C. Levocardia
D. Mesocardia

3.27. A 69-year-old male with a history of heart transplant 10 years ago is complaining of low-grade fever, fatigue, and loss of appetite. He had a chest X-ray (see Figure 3.27a) as part of his work up. What does this chest X-ray show?

A. Normal chest X-ray
B. A rounded opacity in the right lower lobe
C. Patchy consolidation in the left lower lobe
D. Multiple lung nodules

3.28. Plethoric lung fields on chest X-ray are seen in all of the following except:

A. ASD
B. Ventricular septal defect (VSD)
C. Patient ductus arteriosus (PDA)
D. Mitral stenosis

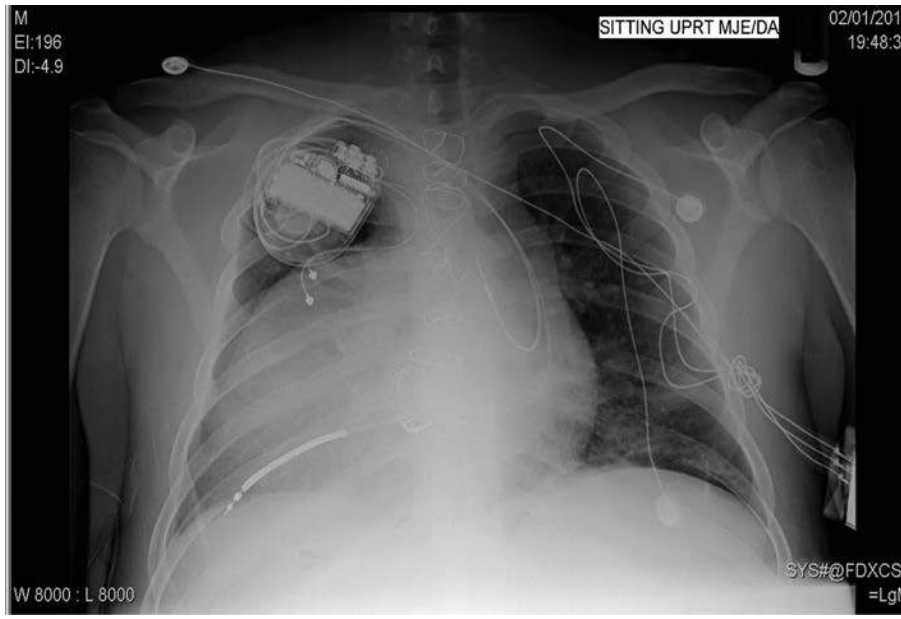

Figure 3.26a

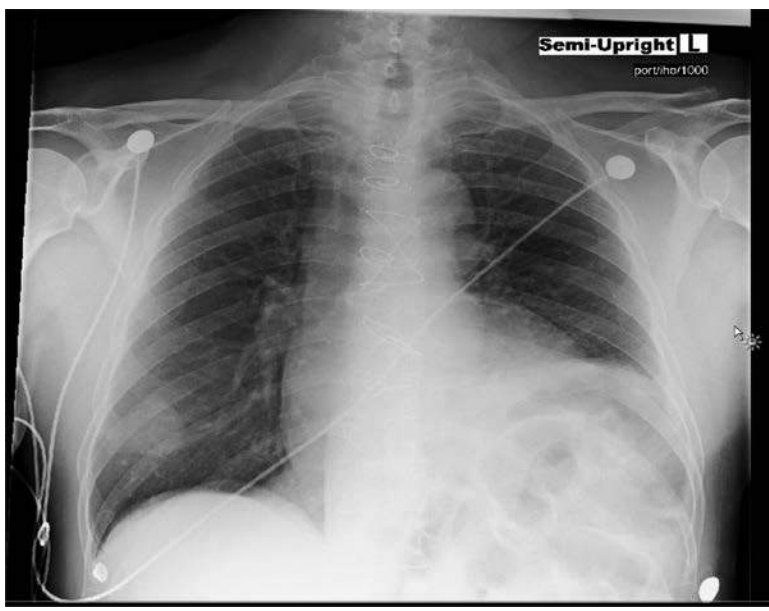

Figure 3.27a

3.29. What is peripheral pulmonary artery pruning a feature of?
- **A.** Pulmonary hypertension
- **B.** Pulmonary stenosis
- **C.** Acute pulmonary embolism
- **D.** Pulmonary regurgitation

3.30. Dilated main pulmonary artery (jug handle appearance) in a patient with Eisenmenger's syndrome is indicative of:
- **A.** ASD Eisenmenger's
- **B.** VSD Eisenmenger's
- **C.** PDA Eisenmenger's

3.31. Straightened left heart border is classically seen in which of the following:
- **A.** Mitral stenosis
- **B.** Aortic stenosis
- **C.** ASD
- **D.** PDA

3.32. Coeur en Sabot is a feature of which of the following:
- **A.** Tetralogy of Fallot
- **B.** Aortic coarctation
- **C.** Dilated cardiomyopathy
- **D.** Hypertrophic cardiomyopathy

3.33. Snowman appearance is a classic description of which of the following:
- **A.** Partial anomalous pulmonary venous drainage
- **B.** Total anomalous pulmonary venous drainage
- **C.** Ebstein's anomaly
- **D.** ASD

3.34. Scimitar sign is seen in which of the following:
- **A.** Partial anomalous pulmonary venous drainage
- **B.** Total anomalous pulmonary venous drainage
- **C.** Ebstein's anomaly
- **D.** ASD

3.35. An increase in subcarinal angle due to lifting of left bronchus is a feature of which of the following:
- **A.** Left ventricular hypertrophy
- **B.** Left atrial dilation
- **C.** Right atrial dilation
- **D.** Pulmonary ectasia

Answers

3.1. D. Cardiomegaly, AICD lead, left pleural effusion.

The cardiomediastinal ratio is increased, which is indicative of cardiomegaly (red arrow in Figure 3.1b). There is also an AICD lead in the right ventricle (blue arrow in Figure 3.1b). The left costophrenic angle is blunted, which is suggestive of presence of pleural effusion.

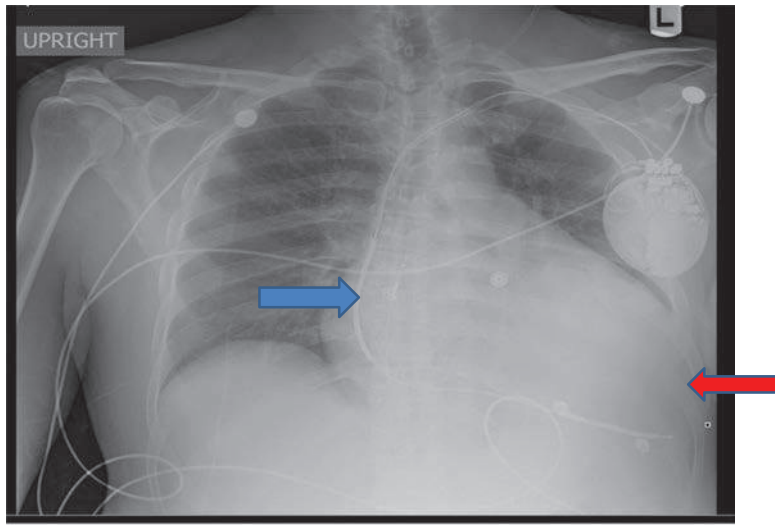

Figure 3.1b

3.2. C. Left apical pneumothorax.

The patient had thoracentesis, which then caused left apical pneumothorax: blue arrow in lateral view (Figure 3.2b); multiple arrows in posteroanterior (PA) view (Figure 3.2c). The pneumothorax was drained with a chest tube.

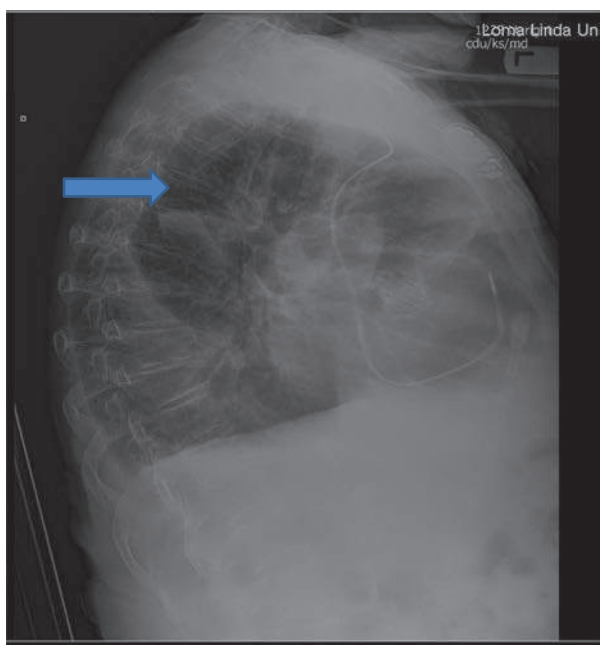

Figure 3.2b

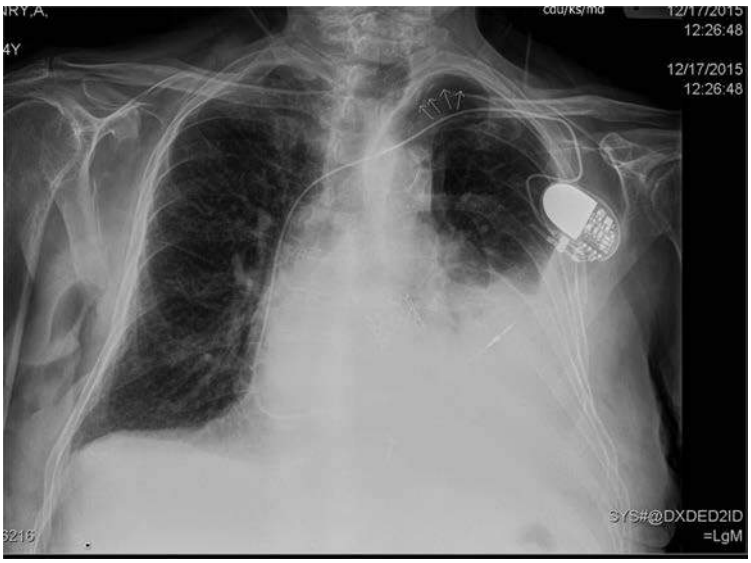

Figure 3.2c

3.3. D. Prosthetic valves in the aortic and mitral positions

The chest X-rays (Figures 3.3b and 3.3c) show two mechanical valve prosthetic rings: one in the aortic (red arrow) and another in the mitral position (blue arrow). Mitral is to the left of the midline, caudal and posterior.

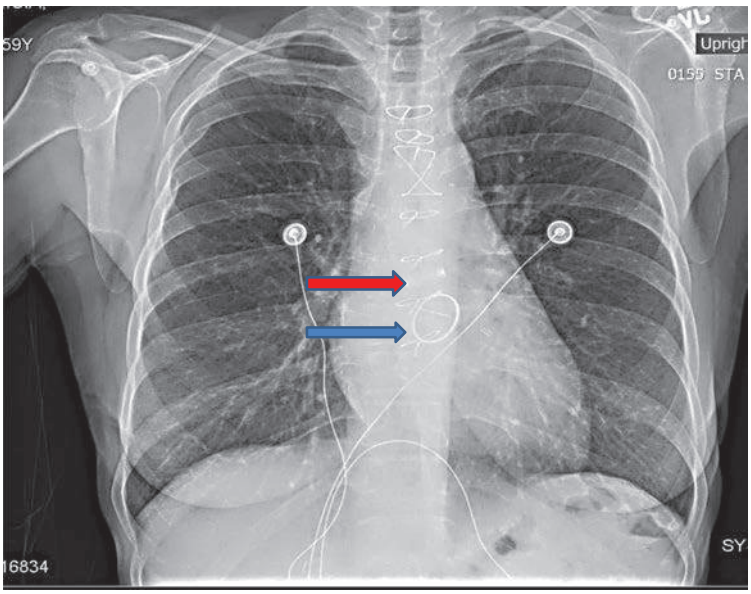

Figure 3.3b

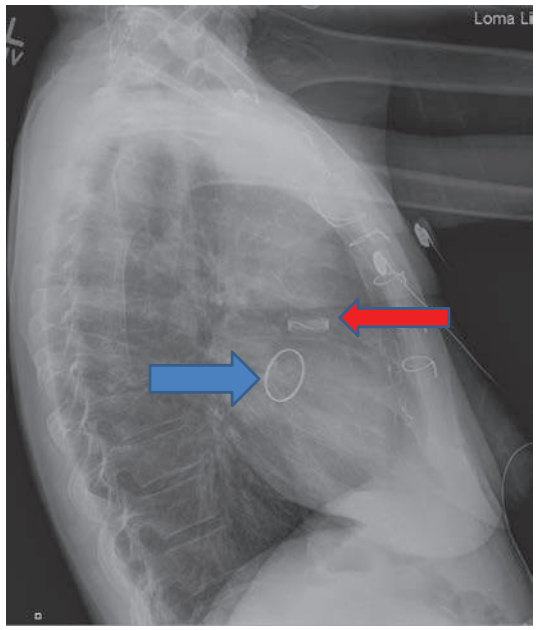

Figure 3.3c

3.4. B. Right pleural effusion.

The right costophrenic angle is blunted. The lower to middle lung zones are indistinct and markings are obscured. The chest X-ray shows the presence of right pleural effusion, shown by the blue arrow in Figure 3.4b.

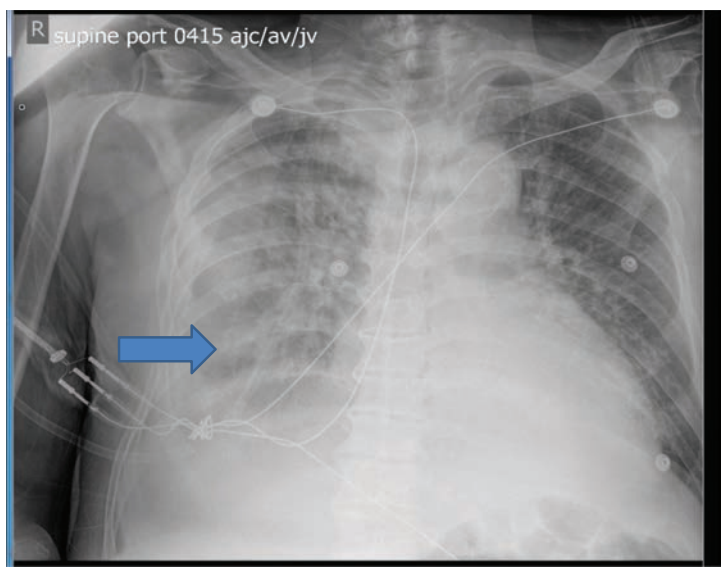

Figure 3.4b

3.5. B. Bileaflet mechanical prosthesis in the mitral position.

The chest X-ray shows sternal wires indicative of previous surgery (red arrow in Figure 3.5b). There is a bileaflet mechanical prosthesis in the mitral position (blue arrow in Figure 3.5b). The patient's international normalized ratio was 13 and probably caused the subdural hemorrhage.

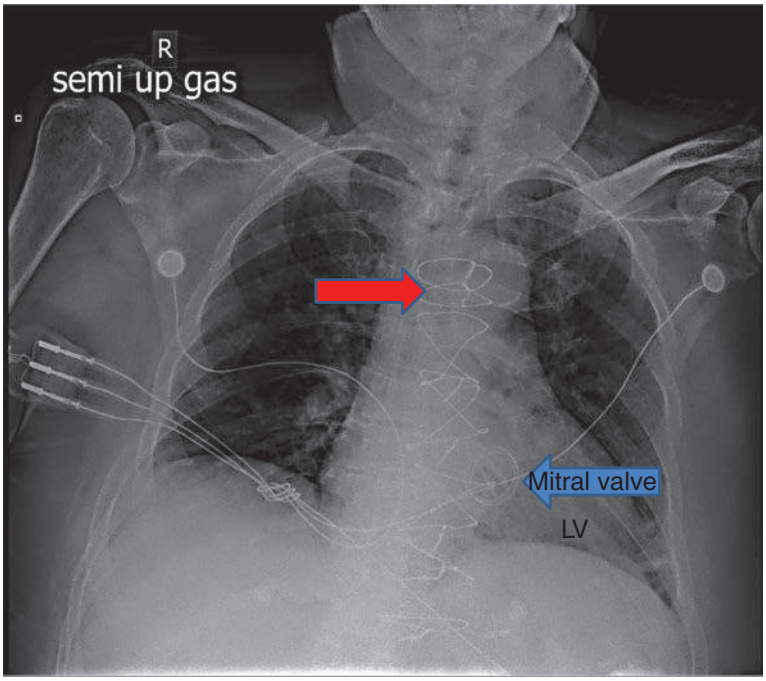

Figure 3.5b

3.6. D. Bilateral pleural effusion.

The chest X-ray shows blunting of both costophrenic angles, which is indicative of bilateral pleural effusion (blue arrows in Figure 3.6b).

3.7. B. Cardiomegaly.

The patient's chest X-ray shows increased cardiomediastinal ratio, which is suggestive of cardiomegaly.

3.8. C. Prominent main pulmonary artery.

The main pulmonary artery is enlarged and is prominent (blue arrow in Figure 3.8b). The red arrow points to the left pulmonary artery, which has a pruned appearance in the peripheral lung zones.

3.9. A. Primary pulmonary hypertension.

The patient is young, and has a prominent main pulmonary artery on the chest X-ray. His echocardiogram reveals pulmonary hypertension. The lungs fields are not plethoric. Given the findings on chest X-ray and echocardiogram, he has primary pulmonary hypertension.

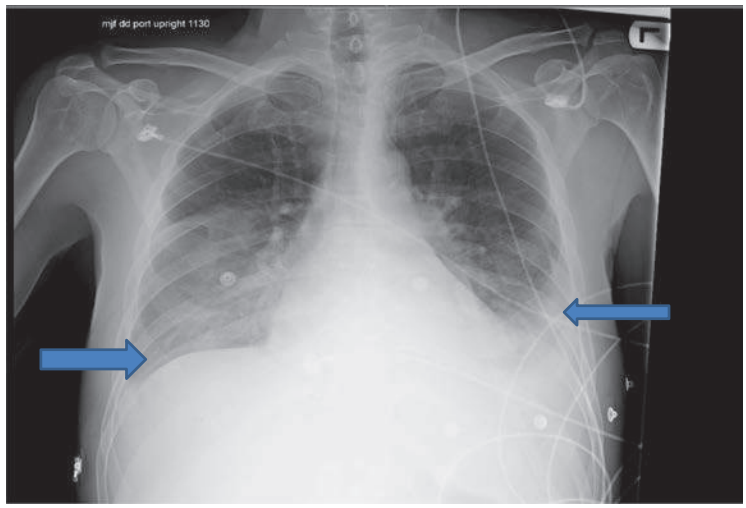

Figure 3.6b

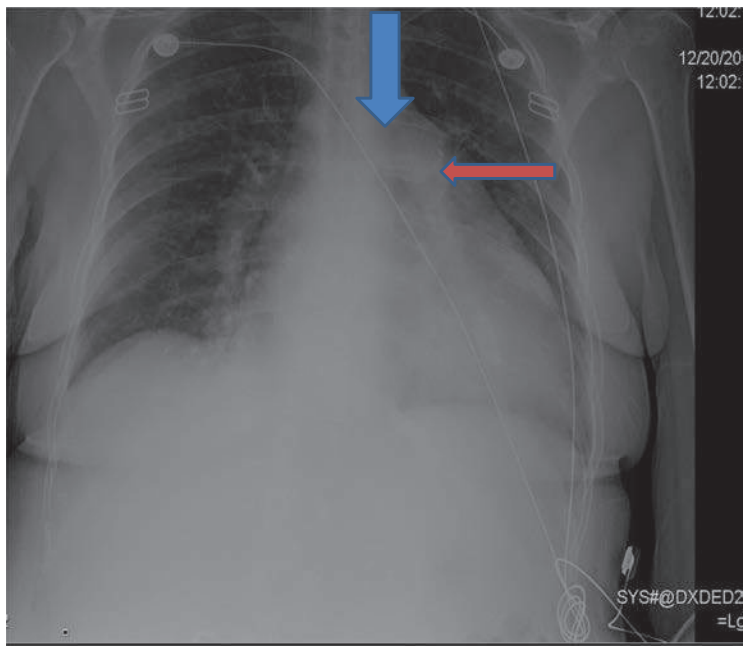

Figure 3.8b

3.10. B. Right hilar consolidation with superimposed pulmonary vascular congestion.

The chest X-ray shows increased pulmonary vascular congestion. But the more striking finding is the presence of right hilar consolidation (blue arrow in Figure 3.10b) suggestive of pneumonia. The less likely differential diagnosis is unilateral right pulmonary edema.

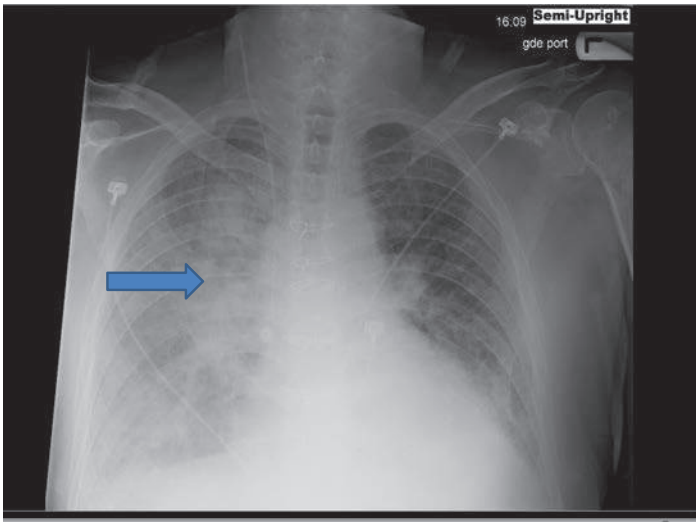

Figure 3.10b

3.11. D. Right atrial and right ventricular enlargement.

This patient's chest X-ray shows enlargement of both right atrium (blue arrow in Figure 3.11b) and right ventricle, as evidenced by lifted apex (red arrow). Enlargement of the right ventricle usually causes the apex to be rounded and uplifted,

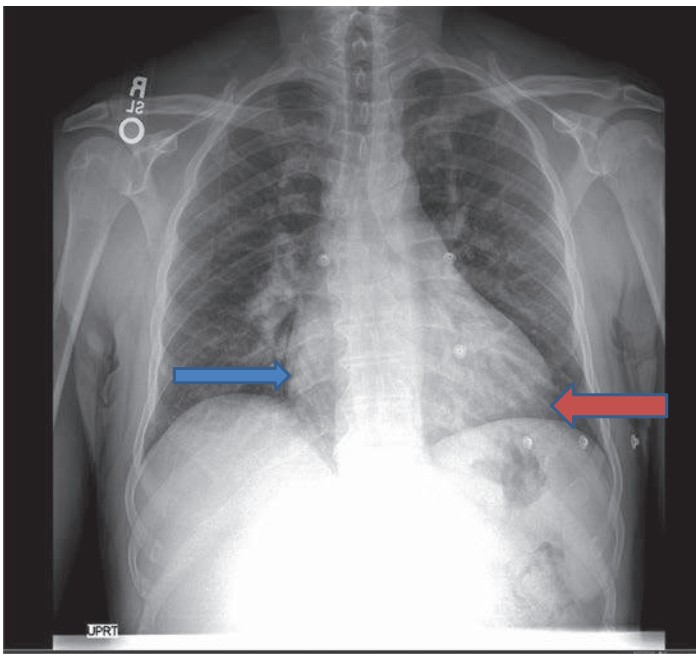

Figure 3.11b

as shown by the red arrow. This patient had an echocardiogram which showed enlargement of the right-sided chambers without any signs of a shunt. He then underwent a transesophageal echocardiogram, which revealed a sinus venosus atrial septal defect (ASD).

3.12. D. Marked enlargement of the main and left pulmonary artery.

In Figure 3.12b, the red arrow points to the enlarged main pulmonary artery and the blue arrow points to the enlarged left pulmonary artery. This is suggestive of pulmonary valve stenosis.

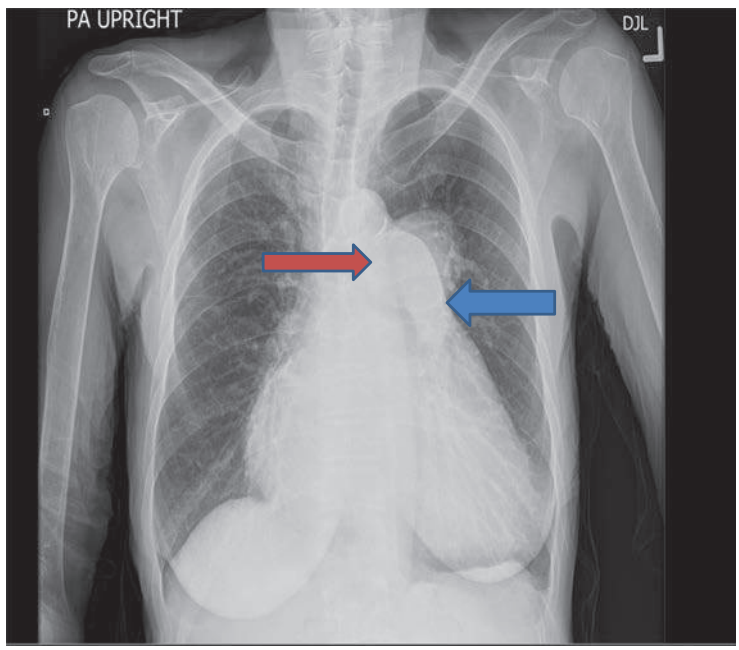

Figure 3.12b

3.13. B. Aortic knob.

3.14. D. Superior vena cava.

3.15. C. Transaortic valve replacement.

This patient with complaints of shortness of breath had severe aortic stenosis. She then underwent a transaortic valve replacement. The bioprosthetic valve is shown by the blue arrow in Figure 3.15b. This is an Edwards valve and has a titanium mesh to hold the leaflets and not just the sewing ring. Also note that there are no sternotomy wires.

3.16. B. Dual-chamber pacemaker.

3.17. B. Right ventricular pacer lead.

3.18. A. Right atrial pacer lead.

This patient has a dual-chamber pacemaker with leads in the right atrium and right ventricle.

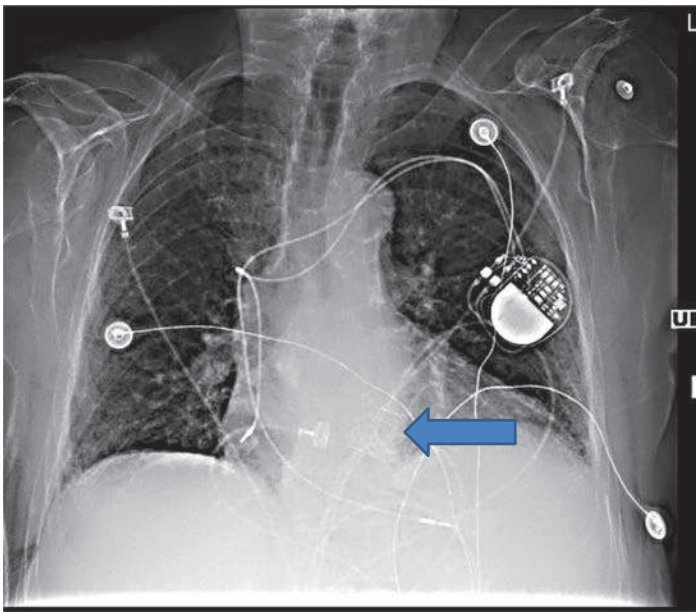

Figure 3.15b

3.19. D. Coronary sinus lead.

In this patient's chest X-ray three leads are visible. In Figure 3.19b, the blue arrow points to the coronary sinus lead. The lead in the right ventricle is thicker than a regular pacing lead and is indicative of an ICD lead (red arrow). The third lead is the right atrial lead (yellow arrow).

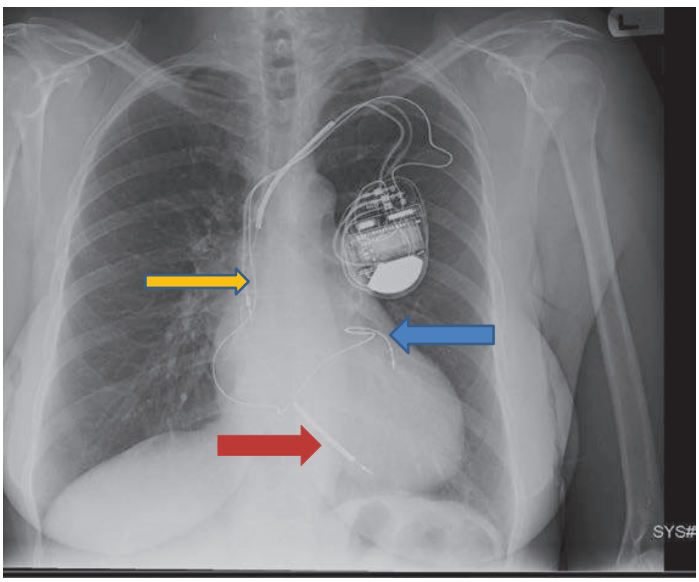

Figure 3.19b

3.20. B. Catheter placed through left subclavian vein.

There is a catheter that has been placed through a left subclavian approach and is terminating at the lower level of the superior vena cava.

3.21. A. Catheter placed through right internal jugular vein.

3.22. C. Endotracheal intubation.

The patient was tachypneic and hypoxic. He had emergent endotracheal intubation and was started on mechanical ventilation. The blue arrow in Figure 3.22b points to the endotracheal tube.

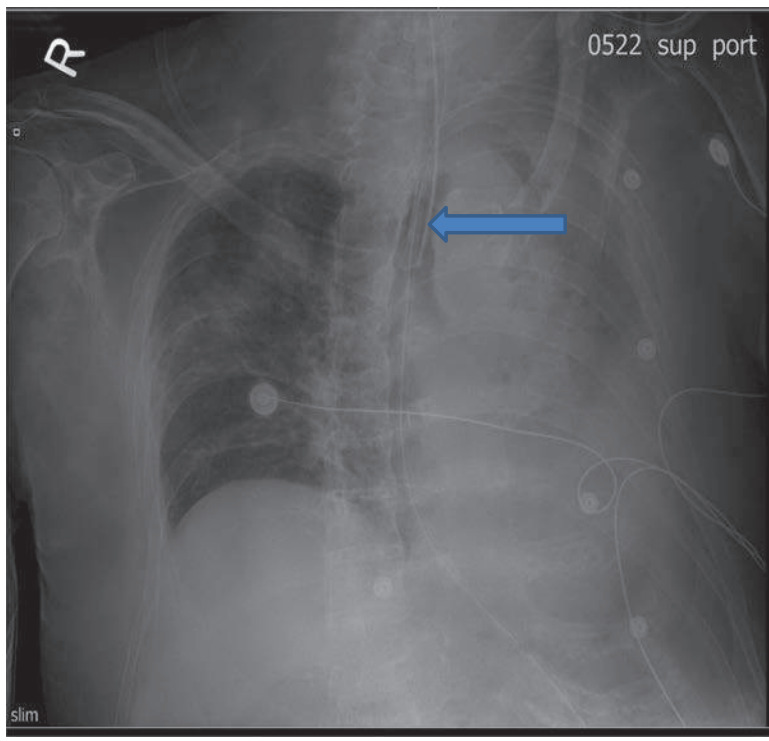

Figure 3.22b

3.23. A. Carina.

The endotracheal tube can be seen terminating about 1 cm above the carina.

3.24. A. Nasogastric tube.

The arrow points to the nasogastric tube, which is terminating below the diaphragm.

3.25. B. Placement of a catheter in the right pleural space.

The arrow in Figure 3.25b points to the catheter in the right pleural space. The right costophrenic angle is still obscured. She probably had right pleural effusion that was drained by placement of a right pleural catheter.

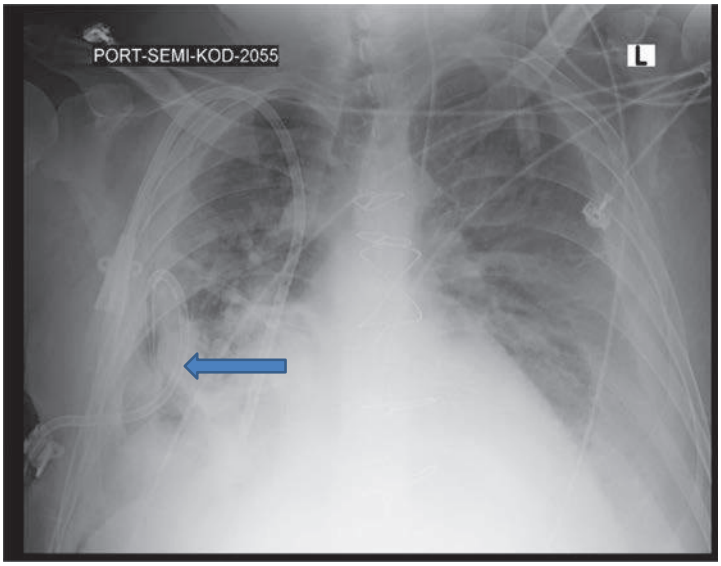

Figure 3.25b

3.26. B. Dextrocardia.

This is a portable chest X-ray. The most striking feature is that the apex of the heart is pointing to the right. This is called dextrocardia. In dextroposition, the apex still points to the left but the heart itself is shifted to the right. The arrow in Figure 3.26b points to the apex of the heart, which is pointing to the right.

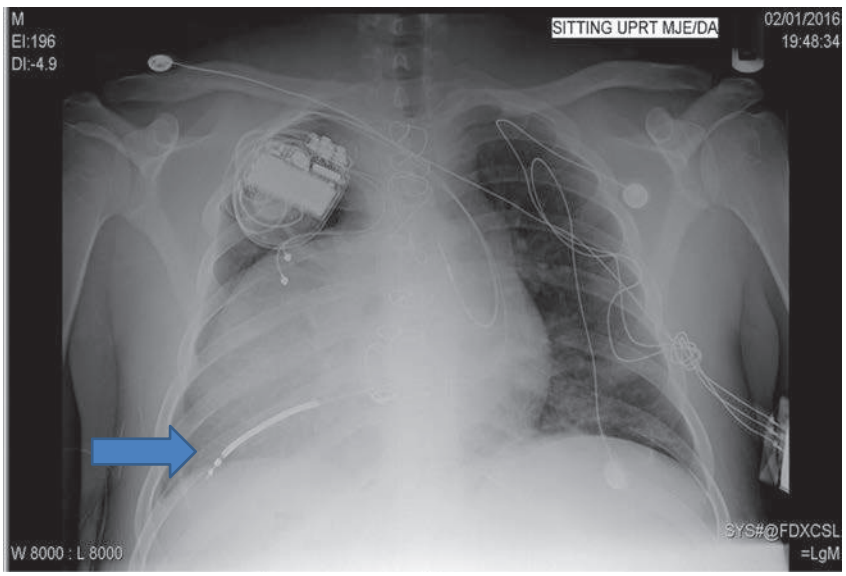

Figure 3.26b

3.27. B. A rounded opacity in the right lower lobe.

The rounded opacity in the right lower lobe is shown by the arrow in Figure 3.27b. Since this patient is status post heart transplant, he is prone to opportunistic infections such as aspergillosis, norcardiosis, and coccidiomycosis. He underwent a CT scan of the lung which again demonstrated the rounded opacity in the right lower lobe. He underwent CT-guided biopsy and pathology was positive for *Norcardia*. Also note the elevated left hemidiaphragm, which may suggest left phrenic nerve palsy.

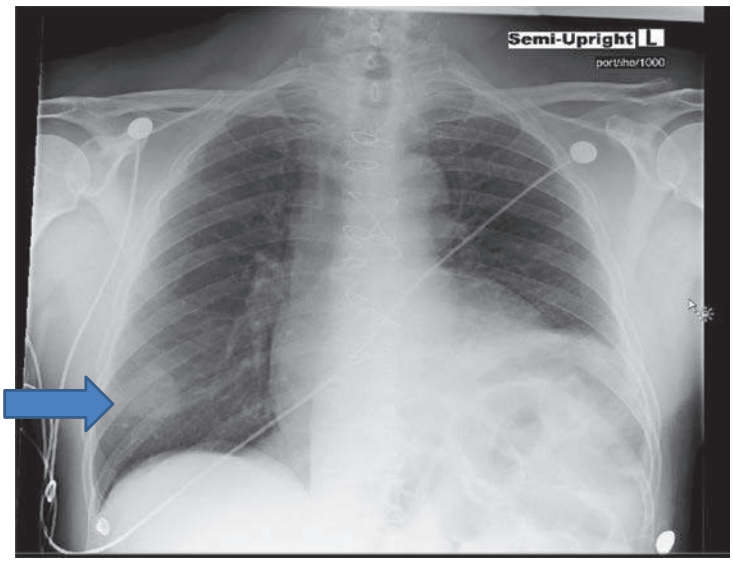

Figure 3.27b

3.28. D. Mitral stenosis.

Plethoric lung fields are indicative of increased pulmonary blood flow and are seen in left-to-right shunts such as ASD, VSD, and PDA. The pulmonary artery branches are prominently seen up to peripheral lung fields and flow is significantly increased.

3.29. A. Pulmonary hypertension.

Peripheral vasoconstriction, along with dilated central pulmonary arteries, results in this appearance in pulmonary hypertension. In pulmonary stenosis, lung fields are oligemic.

3.30. A. ASD Eisenmenger's.

Severely dilated main pulmonary artery is a feature of large ASD. In large VSDs, as pulmonary artery pressure does not regress during childhood, pulmonary artery tends to have thicker walls and hence does not dilate as much.

3.31. A. Mitral stenosis.

Filling of the bay between main pulmonary artery and left ventricle by the dilated left atrial appendage in mitral stenosis causes straightening of left heart border.

3.32. A. Tetralogy of Fallot.

This is due to right ventricular hypertrophy, which lifts the apex up mimicking the wooden boots of Danish farmers.

3.33. B. Total anomalous pulmonary venous drainage.

3.34. A. Partial anomalous pulmonary venous drainage.

Partial anomalous pulmonary venous drainage from right upper pulmonary vein to inferior vena cava results in a scimitar-shaped shadow along right heart border. Diagnosis is confirmed by transesophageal echocardiography.

3.35. B. Left atrial dilation.

This is typically seen in mitral stenosis due to severe left atrial enlargement. Dilated left atrium may also show as a double atrial shadow near right atrial border with acute angulation with right hemidiaphragm, pressure on left recurrent laryngeal nerve causing hoarseness of voice (Ortner's syndrome), and dysphagia due to pressure on esophagus. Pressure on esophagus is best appreciated by performing a barium swallow.

Stress Testing and Risk Stratification of Asymptomatic Subjects

4

4.1. A 45-year-old male comes to your office for evaluation of chest pain. He reports substernal chest pressure, lasts a few minutes, does not radiate to his shoulder or jaw, occurs with exertion sometimes, and is relieved on its own in a few minutes. His risk factors include hypertension controlled on hydrachlorothiazide and amlodipine. He also was a 20 pack a year smoker, but quit a month ago. His electrocardiogram (ECG) shows no abnormalities. To evaluate his chest pain, what should the next step be?

A. Coronary angiography
B. Exercise stress echocardiogram
C. Exercise stress test
D. No testing needed at this time

4.2. The patient walked for 5 min on the treadmill (Bruce protocol) and had to stop the test due to substernal chest pressure. His peak stress blood pressure (BP) dropped to 90 mmHg from a resting pressure of 130 mmHg. His stress ECG shows 4 mm downsloping ST depressions in the anterior chest leads that last 5 min into recovery. He is nauseous and diaphoretic. What is the next step in his evaluation?

A. Nothing at present
B. Adenosine myocardial perfusion imaging (MPI)
C. Coronary angiogram to evaluate for obstructive CAD
D. Modify medical therapy

4.3. A 55-year-old male comes to your office for evaluation of chest pain. He reports no cardiac risk factors other than hypercholesterolemia. He describes his chest pain as a discomfort, in the central chest, occurs at rest, lasts a few minutes, and is relieved with aspirin. A resting ECG done in the office reveals preexcitation. What does the next step in his evaluation include?

A. Exercise stress test
B. Coronary angiogram
C. Referral to an electrophysiologist
D. Exercise myocardial perfusion

4.4. In the evaluation of a patient with chest pain and right bundle branch (RBBB) on ECG, which of the following is true regarding exercise stress testing?

A. Stress test is not useful in patients with RBBB
B. Stress testing should always be combined with imaging
C. Stress testing can be undertaken without affecting the predictive value of stress ECG
D. None of the above

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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4.5. A 50-year-old women presents to the emergency room (ER) with complaints of chest pain. Her chest pain started 3 days prior to presentation and radiates to her jaw, occurs with exertion, and is relieved with rest. Her risk factors include hypertension and hypercholesterolemia. Her ECG at presentation is normal. Three sets of cardiac biomarkers drawn at presentation and then 8 h apart are negative. What is the best next recommended step?

- **A.** She is at low risk for ischemia; hence, discharge her home with advice regarding risk factor modification
- **B.** Refer her for coronary angiography
- **C.** Order a pharmacological stress nuclear study
- **D.** Order an exercise stress test

4.6. Which of the following is not a contraindication to exercise ECG stress testing?

- **A.** 75-year-old male with complaints of chest pain and one episode of frank syncope. On examination, he has slow rising carotid pulse and a harsh 3/6 ejection systolic murmur with radiation to both carotids.
- **B.** A 35-year-old female with complaints of shortness of breath. On examination, jugular venous pressure is elevated, 15 cmH_2O, S3 gallop, and 2+ pedal edema. She has recently delivered her second baby.
- **C.** A 68-year-old male with complaints of chest pain. He describes it as a sharp substernal chest pain, worse on deep inspiration. He gives a history of hip replacement 2 weeks ago.
- **D.** A 44-year-old male with complaints of chest pain brought on by exertion, started a month ago. Physical examination is unremarkable except for an elevated BP of 140/78 mmHg. His ECG shows first-degree atrioventricular block and incomplete RBBB.
- **E.** A 65-year-old male presents to the ER with exertional chest pain. Pain started 24 h prior to presentation. He is currently chest-pain free. His ECG showed sinus bradycardia with Q waves in anterior chest leads V1–V4. An ECG done 1 month ago at his doctor's office was completely normal.

4.7. Which is an indication to stop an exercise treadmill test?

- **A.** Drop of >10 mmHg from baseline BP despite an increase in workload with associated features of ischemia
- **B.** Sustained ventricular tachycardia
- **C.** Moderate to severe angina
- **D.** Signs of cyanosis or pallor
- **E.** All of the above

4.8. Which of the following is a class III indication for exercise stress testing without imaging (echo or nuclear perfusion)?

- **A.** Patients with a high pretest probability of having CAD
- **B.** Preexcitation on baseline ECG
- **C.** Left ventricular hypertrophy with <1 mm ST depression on baseline ECG
- **D.** Patient with vasospastic angina

4.9. A 45-year-old male is being evaluated by his primary care physician as part of his executive health checkup. He reports no risk factors and is asymptomatic. His baseline ECG shows no resting abnormalities. He is able to walk for 14 min (13.5 METS on a Bruce protocol). He reaches an exercise heart rate of 185 bpm, has

no angina, and has no ST segment changes on his ECG. What would his Duke treadmill score be?

A. 9
B. 14
C. 2
D. 3.4

4.10. Based on the test results in Question 4.9, what is the next most appropriate step?

A. Stress imaging study
B. Computed tomography (CT) angiography
C. Coronary angiography
D. No further testing
E. Repeat testing in 1 year

4.11. Which one of the following is a class I recommendation in assessing asymptomatic adults with no known CAD?

A. Genomic testing
B. Obtain global risk score (Framingham)
C. Assessment of lipoprotein and apolipoprotein
D. Measurements of natriuretic peptides

4.12. Which one of the following is a class I recommendation in assessing asymptomatic adults with no known CAD?

A. Genomic testing
B. Obtain family history
C. Assessment of lipoprotein and apolipoprotein
D. Coronary CT angiogram

4.13. Measurement of C-reactive protein (CRP) is not recommended in which of the following?

A. In men over 50 years with a low-density lipoprotein (LDL) of <130 mg/dL
B. In women over 60 years with an LDL <130 mg/dL not on hormone replacement therapy, and without diabetes or chronic kidney disease
C. In asymptomatic high-risk adults
D. In asymptomatic intermediate-risk men 50 years and younger or women 60 years and younger

4.14. With one exception, the following are class III recommendations in assessing low-risk asymptomatic adults with no known history of CAD. Which is the exception?

A. Coronary CT angiogram
B. Magnetic resonance imaging (MRI) for plaque detection
C. Measurement of coronary calcium score
D. Resting ECG

4.15. In patients with diabetes mellitus, which of the following is *not* recommended?

A. Stress echocardiogram
B. Stress MPI
C. Coronary calcium score measurement
D. Measurement of hemoglobin A1C

4.16. In asymptomatic women, all of the following except one are *not* recommended. Which is the exception?

A. Obtaining global risk score
B. Obtaining natriuretic peptides
C. MRI for plaque detection
D. Measurement of lipoprotein

4.17. Stress MPI is recommended in which of the following situations?
A. In the assessment of a low-risk individual
B. In the assessment of an intermediate-risk individual
C. In an asymptomatic adult with diabetes mellitus
D. None of the above

4.18. Which of the following is not true?
A. Echocardiography is recommended to detect left ventricular hypertrophy in patients with hypertension
B. Echocardiography is recommended in risk assessment of asymptomatic adults without hypertension
C. A resting ECG is reasonable in asymptomatic adults with hypertension
D. All of the above

4.19. Which of the following is a class III indication in the assessment of asymptomatic adults?
A. Measurement of arterial stiffness
B. Obtaining a resting ECG
C. Obtaining an echocardiogram in a patient with hypertension
D. Stress MPI in an individual with diabetes mellitus

4.20. Which of the following is not indicated regarding assessment of an asymptomatic adult with diabetes mellitus
A. Measurement of hemoglobin A1C
B. Stress MPI
C. Testing for microalbuminuria
D. Coronary CT angiogram

4.21. The thallium scan in Figure 4.21 (study 2 is a 4 h redistribution) is from a 47-year-old man presenting with chest pain and ejection fraction (EF) of 35%. The coronary angiogram showed origin occlusion of LAD with collaterals from the right. Rest of the vessels were normal. What would you do?
A. Refer for single-vessel coronary artery bypass grafting with possible left internal mammary artery to left anterior descending (LAD) artery
B. Perform a positron emission tomography scan for viability
C. Refer for implantable cardioverter-defibrillator
D. None of the above

4.22. A 55-year-old man with diabetes and prior myocardial infarction with a right coronary artery (RCA) stent presented with chest pain. His cardiac markers were normal and EF on echo was 45% with inferior wall hypokinesis. The results of a stress Sestamibi scan are shown in Figure 4.22. What would you recommend?
A. Coronary angiography
B. Do stress echo
C. Perform stress perfusion scan in 6 months
D. Medical management only at this point

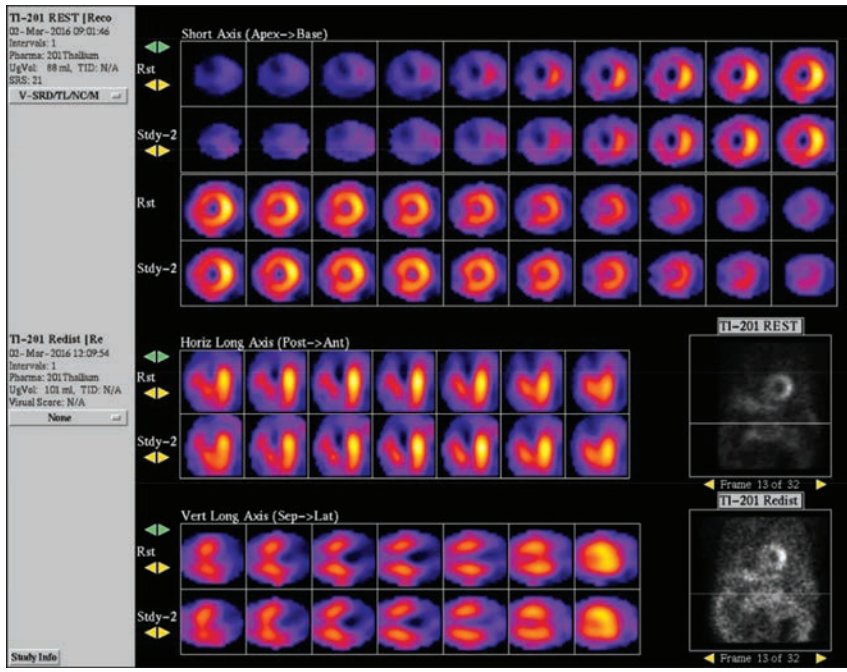

Figure 4.21

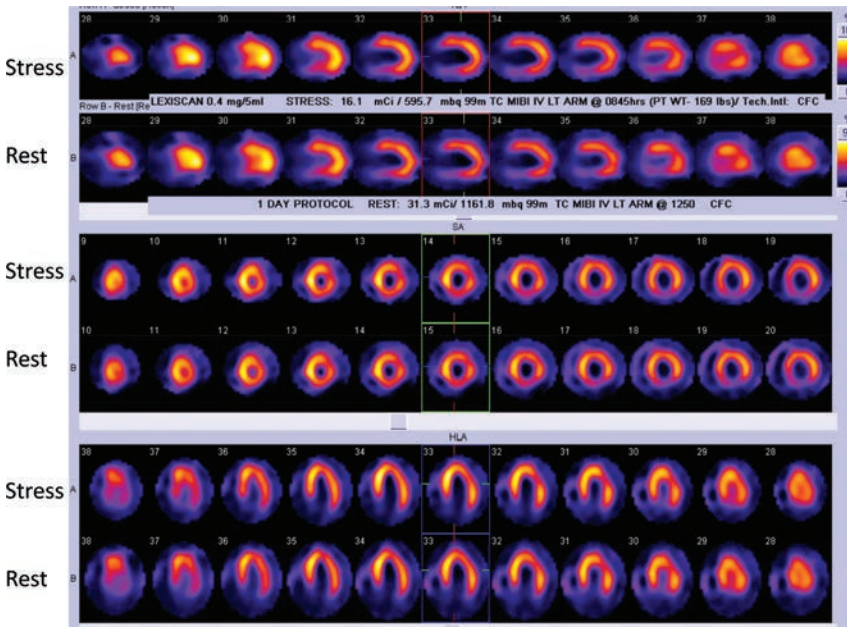

Figure 4.22

4.23. A 67-year-old man with hypertension and diabetes presented with central chest pain lasting 30 min. There were no ECG changes, and cardiac markers were negative. The results of a stress perfusion study are shown in Figure 4.23. What will you recommend?

A. Coronary angiography
B. Medical management only
C. Perform stress echo
D. None of the above

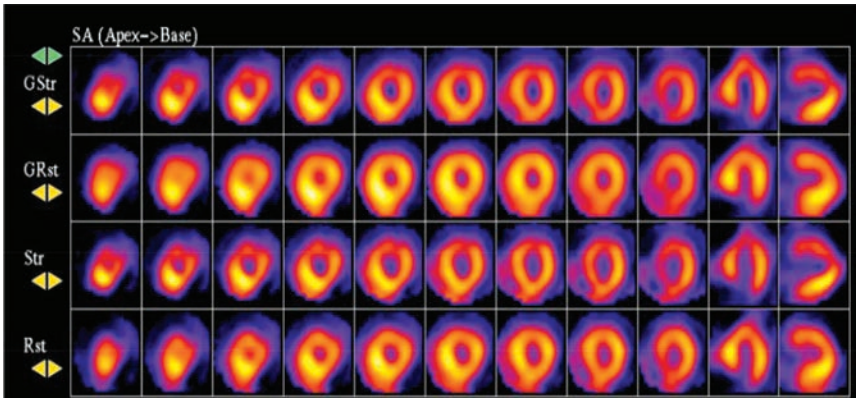

Figure 4.23

4.24. What is the stress perfusion image shown in Figure 4.24 suggestive of?

A. Reversible ischemia of large LAD area
B. Infarct of LAD area
C. Ischemia of RCA area
D. Ischemia of circumflex area

4.25. What does the stress perfusion image in Figure 4.25 show?

A. Reversible apical perfusion defect
B. Reversible defect of entire LAD area
C. Inferior wall ischemia
D. Apical infarct

4.26. What is the stress perfusion scan in Figure 4.26 suggestive of?

A. Perfusion defect in LAD area
B. Ischemia of inferior wall
C. Apical infarct
D. Normal rest and stress perfusion

4.27. The results of stress perfusion only are shown in Figure 4.27 (no rest perfusion shown). What are the results indicative of?

A. Normal stress perfusion and normal left ventricular wall motion
B. Normal perfusion with inferior hypokinesis
C. Anterior perfusion defect with normal wall motion
D. Inferior perfusion defect with inferior hypokinesis

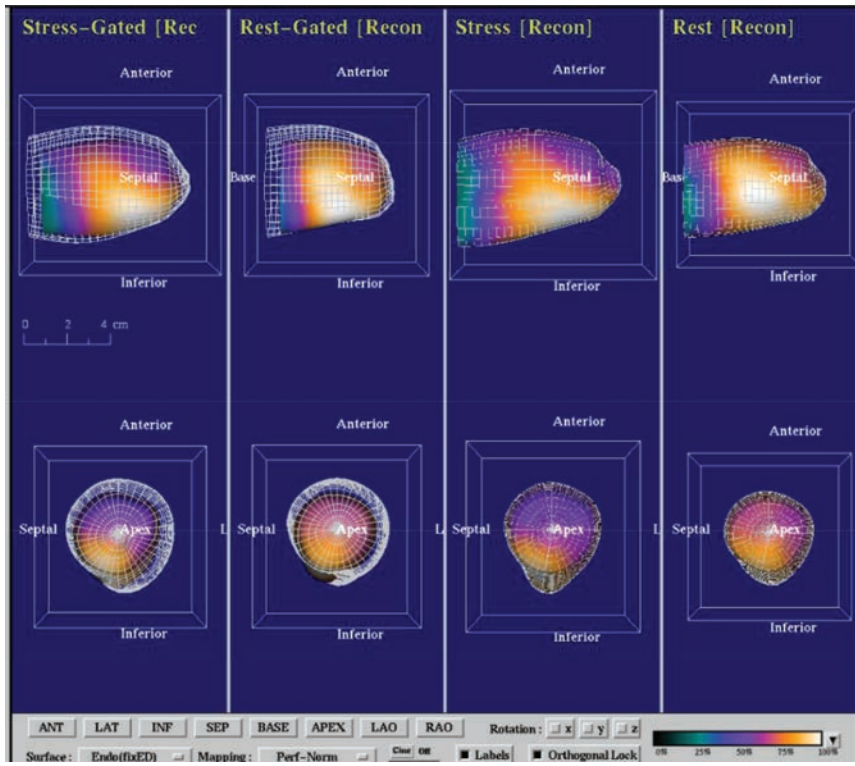

Figure 4.24

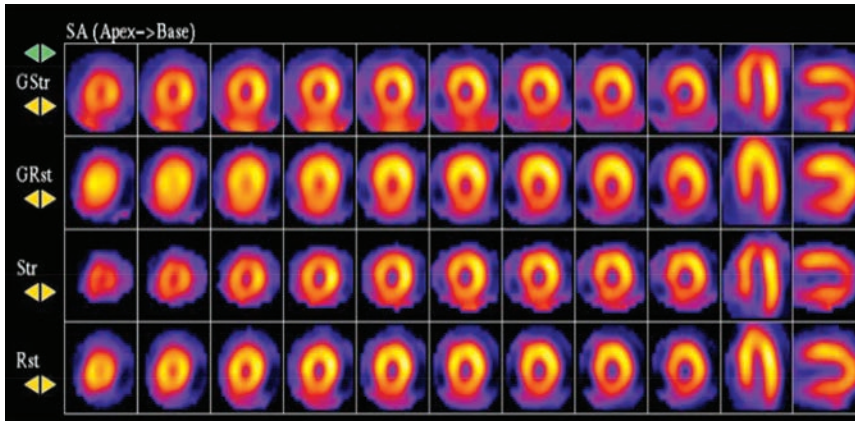

Figure 4.25

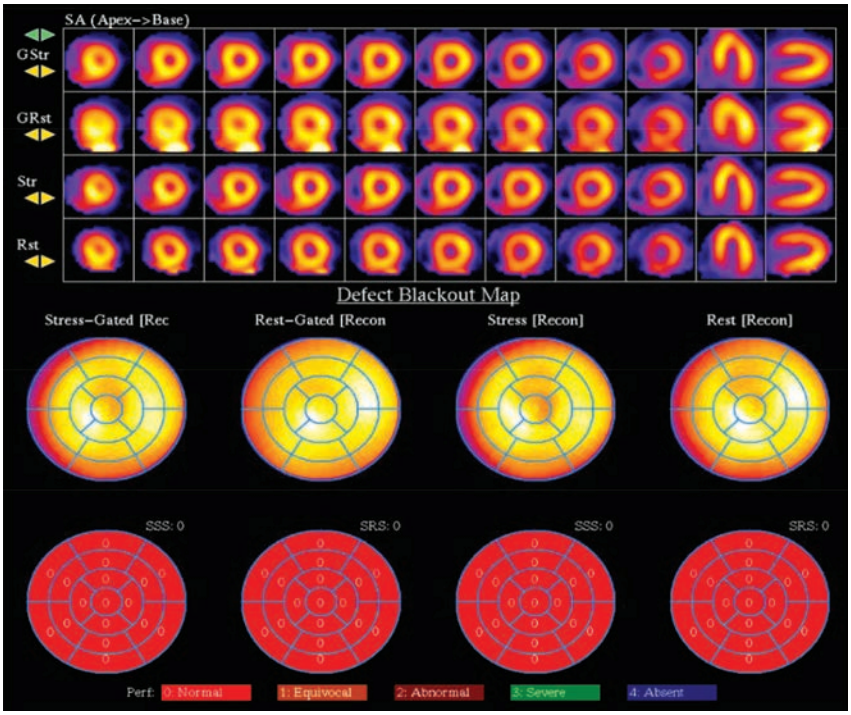

Figure 4.26

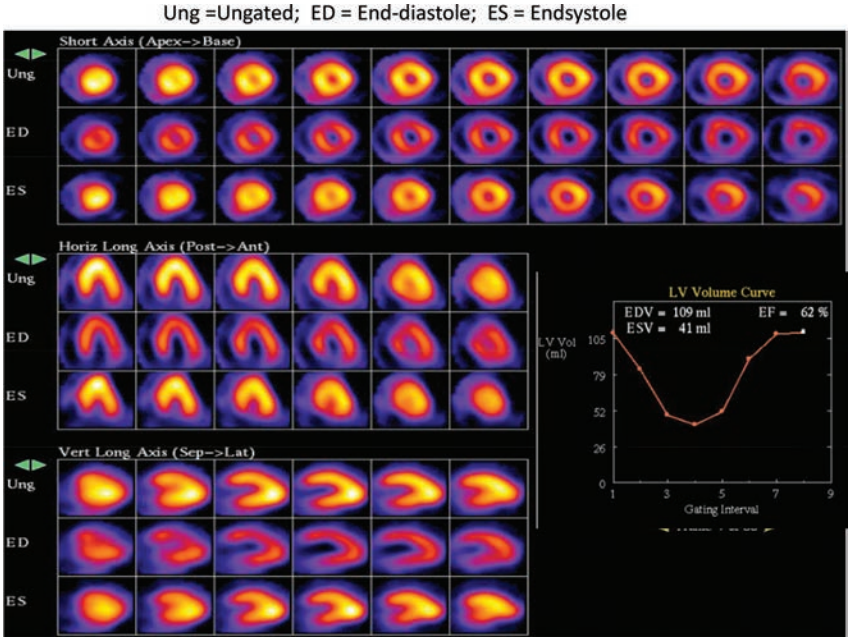

Figure 4.27

4.28. What is the rest/stress perfusion study shown in Figure 4.28 indicative of?

- **A.** Inferior wall infarction
- **B.** Inferior wall ischemia
- **C.** Inferior and anterior ischemia
- **D.** Anterior wall infarct with minor reversibility

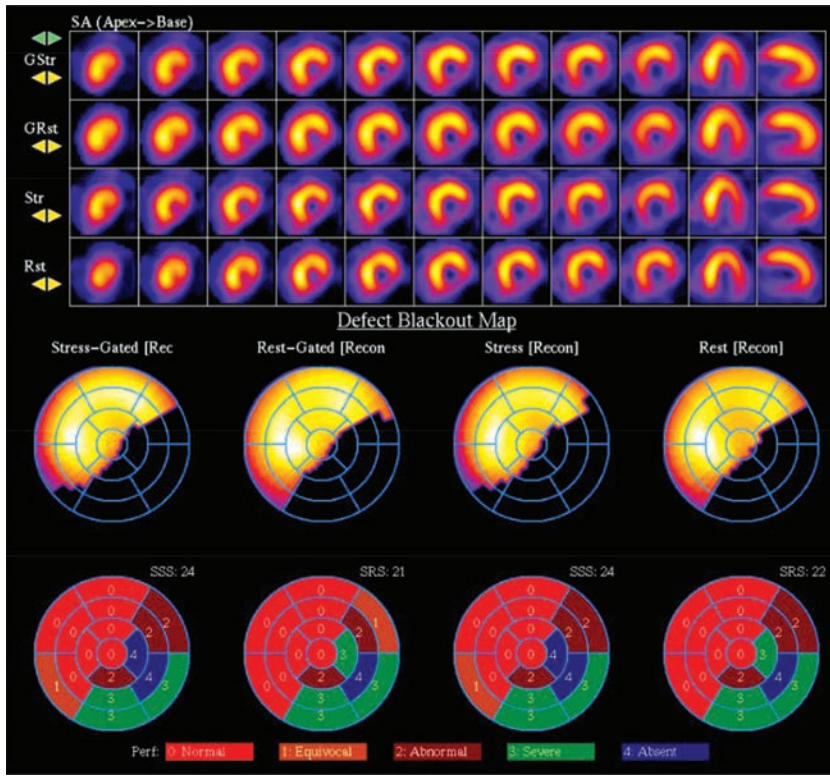

Figure 4.28

4.29. What is the patient whose rest/stress perfusion test results are shown in Figure 4.29 likely to have?

- **A.** Severe LAD artery lesion
- **B.** Left main lesion
- **C.** Circumflex lesion
- **D.** RCA lesion

4.30. A 66-year-old diabetic presented to the ER with chest pain. The resting ECG showed nonspecific ST–T changes, and cardiac markers were negative. The patient was on metformin, aspirin, atorvastatin, and lisinopril, with heart rate of 68 bpm and BP of 123/78 mmHg. Cardiac examination was normal. The patient's nuclear stress test is shown in Figure 4.30. What will be a next logical step?

- **A.** Admit for further observation
- **B.** Refer for coronary angiography
- **C.** Discharge home and continue medical management
- **D.** Perform an echocardiogram

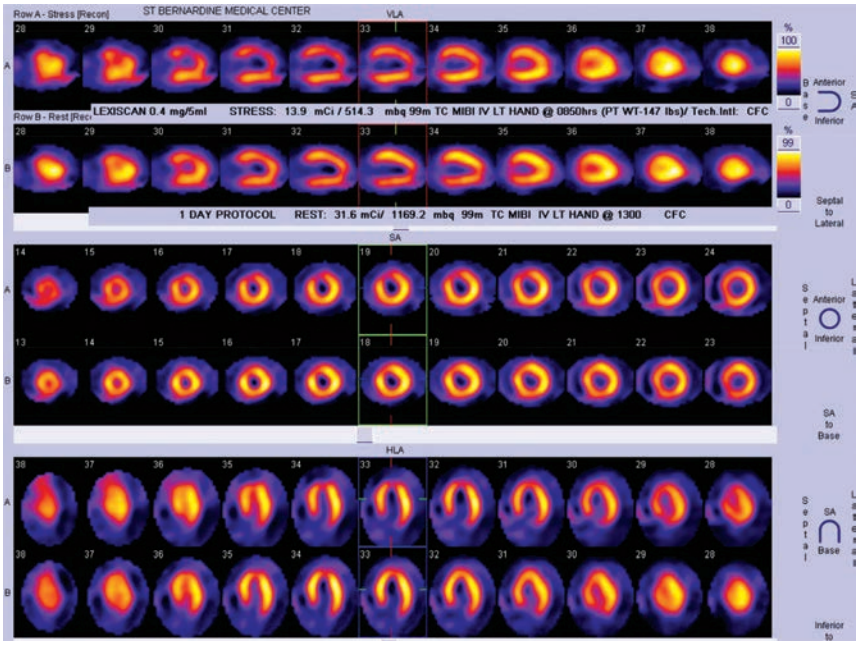

Figure 4.29

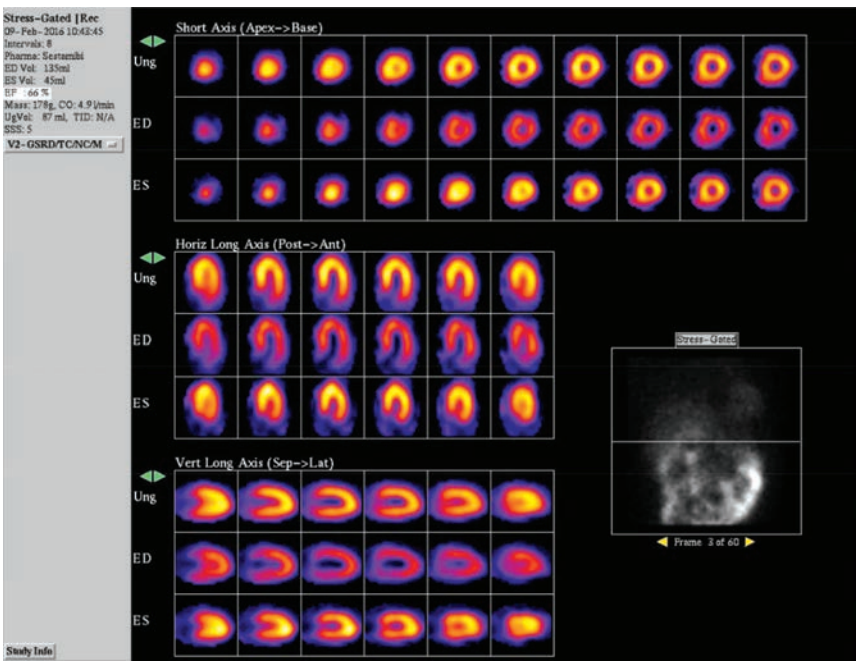

Figure 4.30

4.31. The vasodilator stress study shown in Figure 4.31 is indicative of what?

- **A.** Normal perfusion
- **B.** Ischemia in LAD area
- **C.** Ischemia in RCA area
- **D.** Ischemia in circumflex area

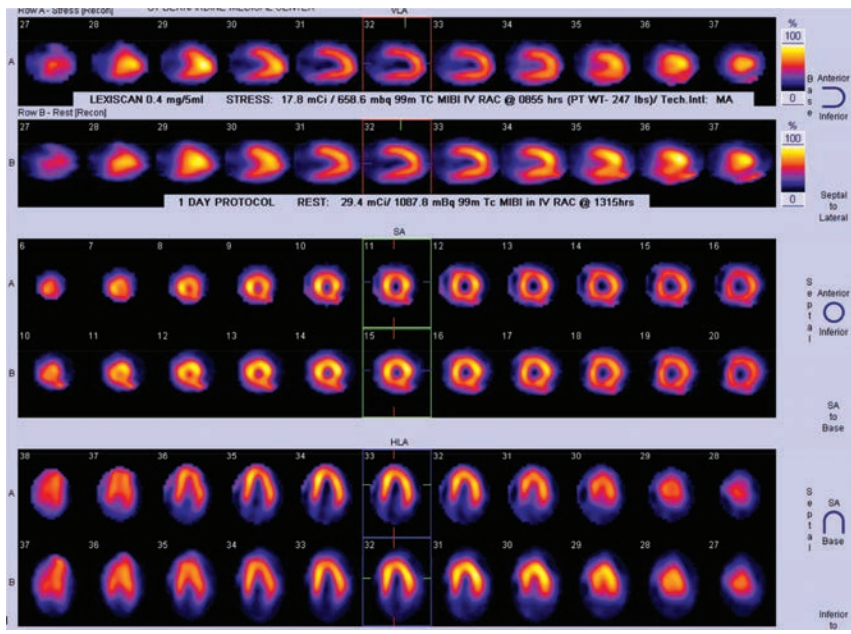

Figure 4.31

Answers

4.1. C. Exercise stress test.

This patient has atypical chest pain. He has risk factors that warrant further testing. His ECG shows no resting abnormalities. If the patient is able to exercise, first step in his evaluation should be exercise stress testing. According to the American College of Cardiology (ACC)/American Heart Association (AHA) 2002 guidelines (Gibbons *et al.*, 2002), if a patient has stable chest pain, has- low to intermediate-risk unstable angina, has symptoms that warrant a diagnosis of coronary artery disease (CAD), is able to exercise, and has an interpretable ECG, then exercise stress testing is the first step.

4.2. C. Coronary angiogram to evaluate for obstructive CAD.

This patient has several high-risk features on his stress test. He walked only 5 min on a Bruce protocol, having to stop due to chest pain. He had significant ST depression at low level of stress that was accompanied by a drop in his systolic BP. These features point to significant CAD. He should be referred for a coronary angiogram.

4.3. D. Exercise myocardial perfusion.

This patient's resting ECG shows preexcitation. According to the ACC/AHA guidelines (Gibbons *et al.*, 2002), class III indications for exercise stress test alone without imaging include preexcitation (Wolff–Parkinson–White) syndrome, electronically paced ventricular rhythm, greater than 1 mm resting ST depression, and complete left bundle branch block.

4.4. C. Stress testing can be undertaken without affecting the predictive value of stress ECG.

With exercise, ST depression usually occurs with RBBB in leads V1–V3. But in leads V4–V6 or the inferior leads, ST changes with stress are similar to those of a normal resting ECG (without RBBB). Hence, the presence of RBBB on resting ECG does not reduce the sensitivity, specificity, or predictive value of the stress ECG in the diagnosis of ischemia.

4.5. D. Order an exercise stress test.

This patient has intermediate probability for CAD based on age, gender, and symptoms. Women have a lower prevalence of obstructive CAD; exercise stress test, which is used to detect focal stenosis, is less sensitive and specific in women. Women tend to have resting ST and T wave changes which can get more pronounced with stress, causing decreased accuracy when used to detect focal disease. Despite the lower accuracy of exercise stress ECG testing, the 2005 ACC/AHA guidelines on the Role of Noninvasive Testing in the Clinical Evaluation of Women Suspected with Coronary Artery Disease recommends exercise ECG as the first test of choice in women with intermediate risk and normal baseline ECG. In women, other parameters, such as poor exercise capacity, low heart rate recovery, and failure to reach target heart rate, are more predictive of outcome than ST changes with stress.

4.6. D. A 44-year-old male with complaints of chest pain brought on by exertion, started a month ago. Physical examination is unremarkable except for an elevated BP of 140/78 mmHg. His ECG shows first-degree atrioventricular block and incomplete RBBB.

The patient in D can safely undergo stress testing. Contraindications to exercise stress ECG testing include severe symptomatic aortic stenosis (scenario A), decompensated heart failure (scenario B), acute pulmonary embolism (scenario C), and within 2 days of an acute myocardial infarction (scenario E).

4.7. E. All of the above.

The scenarios listed are all absolute indications to stop the treadmill test. In addition, ST elevation >1 mm in leads without Q waves, the patient's desire to stop, and technical difficulties in monitoring ECG or BP are all absolute indications to stop the exercise treadmill test.

4.8. B. Preexcitation on the baseline ECG.

It is a class III indication to use an exercise stress test in patients with preexcitation, paced ventricular rhythm, greater than 1 mm resting ST depression, and complete left bundle branch block. It is a class IIa indication to perform an exercise stress test in patients with vasospastic angina and class IIb to perform treadmill stress test in patients with high pretest probability for CAD according to ACC/AHA guidelines (Gibbons *et al.*, 2002).

4.9. B. 14.

Duke treadmill score is calculated as

$$\text{Exercise time (min)} - (5 \times \text{Amount of ST deviation (mm)}) - (4 \times \text{Exercise angina index})$$

(0: none; 1: if exercise angina occurred; 2: if angina was the reason to stop the test). Here, it would be $14 - (5 \times 0) - (4 \times 0) = 14$. Exercise time is based on a standard Bruce protocol.

4.10. D. No further testing.

A Duke treadmill score of >5.5 is suggestive of low risk of death (<1% per year) and hence no further testing is needed. Patients with intermediate score (−10 to +4) have a mortality risk of 1–3% per year and in those with a high risk score (<−10) have a mortality risk of >3% per year.

4.11. B. Obtain global risk score (Framingham).

Obtaining a global risk score in asymptomatic adults without a clinical history of CAD is a class I indication. These scores are helpful in combining individual risk factor measurements into a single quantitative estimate of risk that can be use in prevention strategies. It is not recommended to perform genomic testing or measure lipoprotein or natriuretic peptides in this population; these are considered to be a class III indication (Greenland *et al.*, 2010).

4.12. B. Obtain family history.

Obtaining a family history of atherothrombotic coronary vascular disease is recommended in the assessment of asymptomatic adults (Greenland *et al.*, 2010).

4.13. C. In asymptomatic high-risk adults.

Measurement of CRP is not recommended in asymptomatic high-risk adults (class III). In men 50 years and older or women 60 years and older with an LDL of <130 mg/dL and not on lipid-lowering therapy, hormone replacement therapy, or immunosuppressive therapy, without clinical CAD, diabetes mellitus, chronic kidney disease, severe inflammatory conditions, or contraindications to statin therapy, CRP can be used to select patients for statin therapy (class IIa). It is also deemed reasonable to measure CRP in asymptomatic intermediate-risk men younger than 50 or women younger than 60, for assessment of CAD risk (class IIb) (Greenland *et al.*, 2010).

4.14. D. Resting ECG.

A resting ECG may be reasonable in the assessment of asymptomatic adults with no history of hypertension or diabetes mellitus (class IIb). It is a class III indication to obtain coronary CT angiogram, coronary calcium score, or MRI for plaque detection in low-risk asymptomatic individuals (Greenland *et al.*, 2010).

4.15. A. Stress echocardiogram.

In asymptomatic adults with diabetes mellitus it is reasonable to measure coronary calcium score (class IIa). It is also reasonable to measure hemoglobin A1C and stress MPI (class IIb). Stress MPI may be considered for patients with diabetes or when prior risk assessment suggests high risk, such coronary artery calcium of over 400 (Greenland *et al.*, 2010).

4.16. A. Obtaining global risk score.

It is a class I indication to obtain a global risk score in all asymptomatic women.

4.17. C. In an asymptomatic adult with diabetes mellitus.

Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic individuals with diabetes mellitus or in adults with a strong family history of CAD, or when prior risk assessment such as a coronary artery calcium score of over 400. Stress MPI is not recommended for assessment of low- or intermediate-risk asymptomatic individuals (class III) (Greenland *et al.*, 2010).

4.18. B. Echocardiography is recommended in risk assessment of asymptomatic adults without hypertension.

It is a class III indication to perform echocardiography in asymptomatic adults without hypertension. A resting ECG can be obtained in patients with hypertension or diabetes (class IIa) or an echocardiogram obtained in patients with hypertension to detect left ventricular hypertrophy (class IIb) (Greenland *et al.*, 2010).

4.19. A. Measurement of arterial stiffness.

Measurement of arterial stiffness is a class III indication at the present time (Greenland *et al.*, 2010).

4.20. D. Coronary CT angiogram.

It is a class III indication to obtain a coronary CT angiogram in an asymptomatic adult with diabetes (Greenland *et al.*, 2010).

4.21. A. Refer for single-vessel coronary artery bypass grafting with possible left internal mammary artery to left anterior descending (LAD) artery.

Though there is no redistribution, the resting scan shows significant thallium uptake in the anterior wall and septum, indicating viability and revascularization is appropriate. There is good probability that EF will improve, obviating the need for a primary prevention implantable cardioverter-defibrillator.

4.22. D. Medical management only at this point.

There is only a fixed inferior wall defect attributable to an old myocardial infarction. There are no reversible defects.

4.23. A. Coronary angiography.

Note the fully reversible perfusion defect in the anterior wall and septum suggesting proximal LAD artery lesion. The reversible defect is >30% of the myocardium, indicating high risk.

4.24. A. Reversible ischemia of large LAD area.

4.25. A. Reversible apical perfusion defect.

4.26. D. Normal rest and stress perfusion.

4.27. A. Normal stress perfusion and normal left ventricular wall motion.

4.28. A. Inferior wall infarction.

Inferior wall infarction is indicated by the fixed perfusion deficit.

4.29. A. Severe LAD artery lesion.

4.30. C. Discharge home and continue medical management.

The patient has normal perfusion without any ischemia, normal left ventricular wall motion, and normal EF. This indicates a low risk profile.

4.31. B. Ischemia in LAD area.

References

Gibbons, R.J., Balady, G.J., Bricker, J.T., *et al.* (2002) ACC/AHA 2002 Guideline Update for Exercise Testing: Summary Article. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*, **106**: 1883–1892.

Greenland, P., Alpert, J.S., Beller, G.A., *et al.* (2010) 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults: Executive Summary. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guideline. *Circulation*, **122**: 2748–2764.

Echocardiography

5

5.1. Which of the following manipulations will increase the echocardiographic frame rate (see Box 5.1)?
- **A.** Increase depth
- **B.** Increase transmit frequency
- **C.** Decrease sector angle
- **D.** Increase transmit power

5.2. The lateral resolution increases with:
- **A.** Decreasing transducer diameter
- **B.** Reducing power
- **C.** Beam focusing
- **D.** Reducing transmit frequency

5.3. Axial resolution can be improved by which of the following manipulations?
- **A.** Reducing beam diameter
- **B.** Beam focusing
- **C.** Reducing gain
- **D.** Increasing transmit frequency

5.4. Which of the following is associated with continuous-wave Doppler compared with pulsed-wave Doppler?
- **A.** Aliasing
- **B.** Range specificity
- **C.** Ability to record higher velocities
- **D.** All of the above

5.5. An intraoperative transesophageal echocardiogram (TEE) revealed mitral regurgitation (MR) with the following measurements: regurgitant jet area 4 cm^2, proximal isovelocity surface area (PISA) radius 0.8 cm at a Nyquist limit of 50 cm/s at a heart rate of 82 bpm and arterial blood pressure 80/40 mmHg (see Box 5.2). What does this represent?
- **A.** Mild MR
- **B.** Moderate MR
- **C.** Severe MR

5.6. With one exception, for a given regurgitant volume all of the following result in a reduction in the jet size. Which is the exception?
- **A.** Fast heart rate
- **B.** Doubling the sector angle
- **C.** Increasing the imaging depth
- **D.** Increasing the blood pressure

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5.7. A patient has an LV outflow tract (LVOT) velocity of 1 m/s, time velocity integral (TVI) of 25 cm, LVOT diameter of 2 cm, aortic transvalvular velocity of 1.5 m/s, and heart rate 70 bpm. What is the cardiac output of this patient?

A. 5.5 L/min
B. 4.5 L/min
C. 6.3 L/min
D. Cannot be determined based on the data given

5.8. A patient with aortic stenosis (AS) has an LVOT diameter of 2 cm, LVOT velocity (V1) of 2.5 m/s, and transaortic valve velocity (V2) of 5 m/s; two-dimensional examination showed moderate systolic anterior motion (SAM) of the mitral leaflet. How would you describe the valvular AS in this patient?

A. Mild
B. Moderate
C. Severe
D. Cannot be calculated based on data given

5.9. In a patient with isolated aortic regurgitation (AR), the following measurements were obtained: transmitral flow 80 cm^3/beat, flow across aortic valve 140 cm^3/beat, TVI of AR signal 100 cm. How would you describe the AR in this patient?

A. Mild
B. Moderate
C. Severe
D. Cannot be determined

5.10. The presence of severe AR in a patient with mitral stenosis (MS) is likely to do which of the following to the calculated mitral valve area by the pressure half-time method?

A. Overestimate the valve area
B. Underestimate the valve area
C. Have no effect

5.11. What is this patient in Figure 5.11 likely to have?

A. Severe AS
B. Severe MR
C. Severe pulmonary hypertension
D. Mild AS

5.12. For the patient in question above, the LVOT diameter was 2 cm and the LVOT velocity by pulse Doppler was 1 m/s. What is the aortic valve area by the continuity equation?

A. 0.2 cm^2
B. 0.3 cm^2
C. 0.5 cm^2
D. 0.8 cm^2

5.13. Figure 5.13 is the continuous wave signal obtained from the pulmonary valve at the mid to proximal esophageal location. What is this patient likely to have?

A. Wide-open pulmonary regurgitation (PR)
B. Mild PR
C. Severe valvular pulmonary stenosis (PS)
D. Severe subvalvular PS

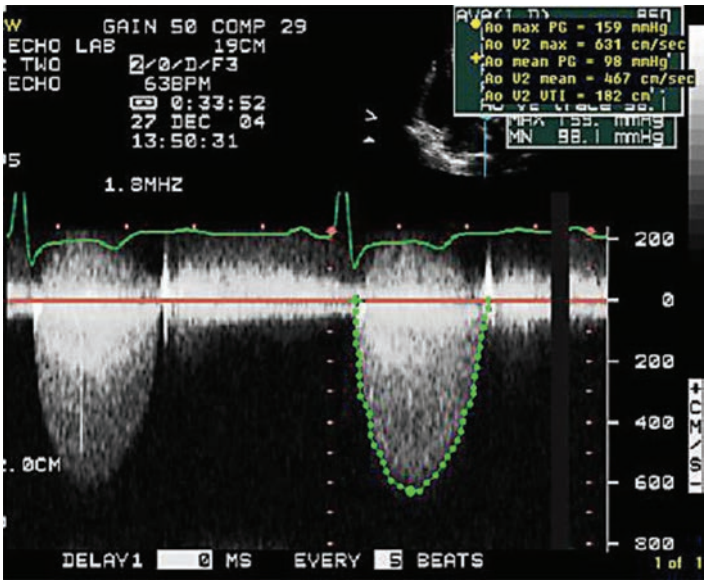


Figure 5.11

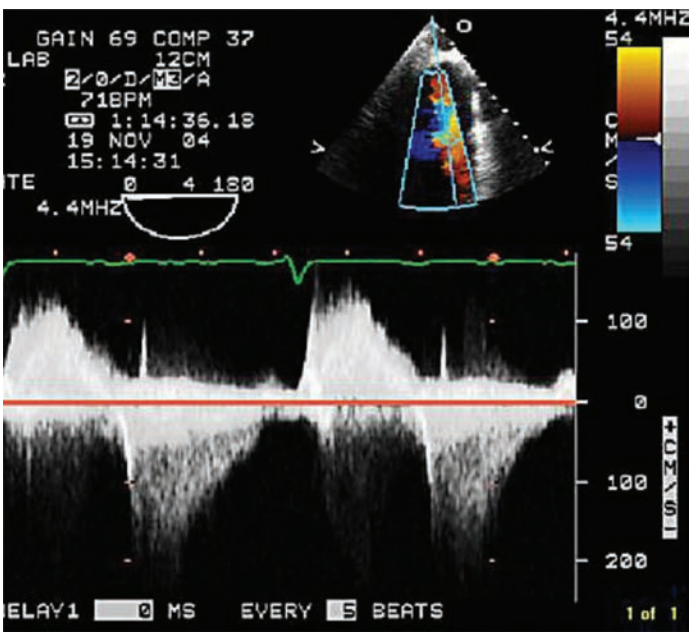


Figure 5.13

5.14. The pulmonary vein flow shown in Figure 5.14 is indicative of what?

A. Elevated LA pressure with normal end diastolic pressure (EDP)
B. Elevated LA pressure with elevated EDP
C. Abnormal LV relaxation with normal EDP
D. Elevated LV EDP with normal LA pressure

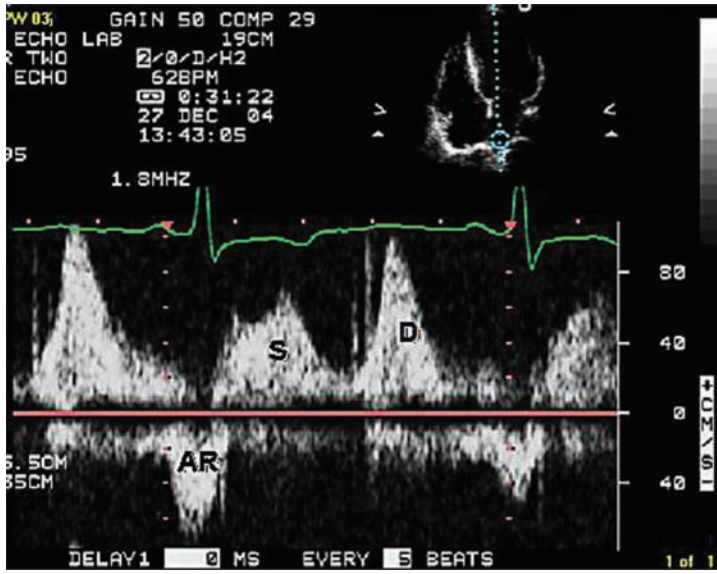


Figure 5.14

5.15. The mitral flow pattern shown in Figure 5.15 is suggestive of what?

A. Normal LA pressure
B. High LA pressure
C. Atrial mechanical failure
D. Abnormal LV relaxation with normal LA pressure

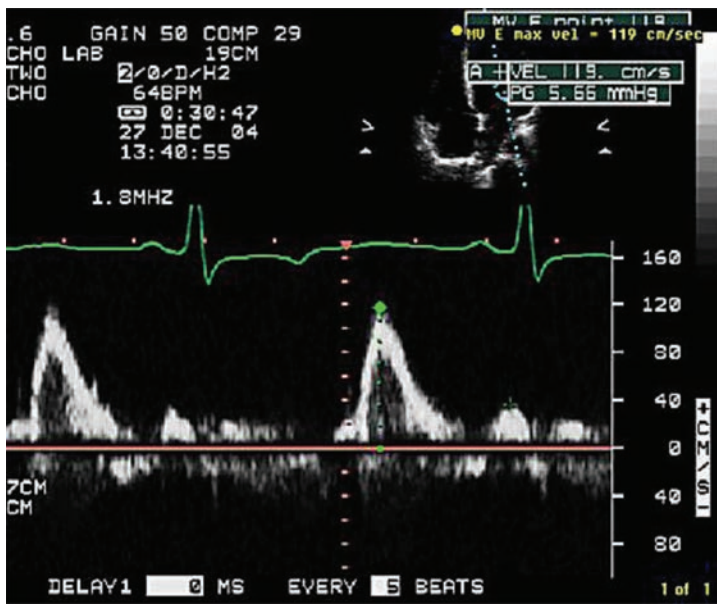


Figure 5.15

5.16. What condition does the patient in Figure 5.16 have?

- **A.** Mitral atresia
- **B.** Tricuspid atresia
- **C.** Transposition of great vessels with atrial baffle
- **D.** Epstein's anomaly

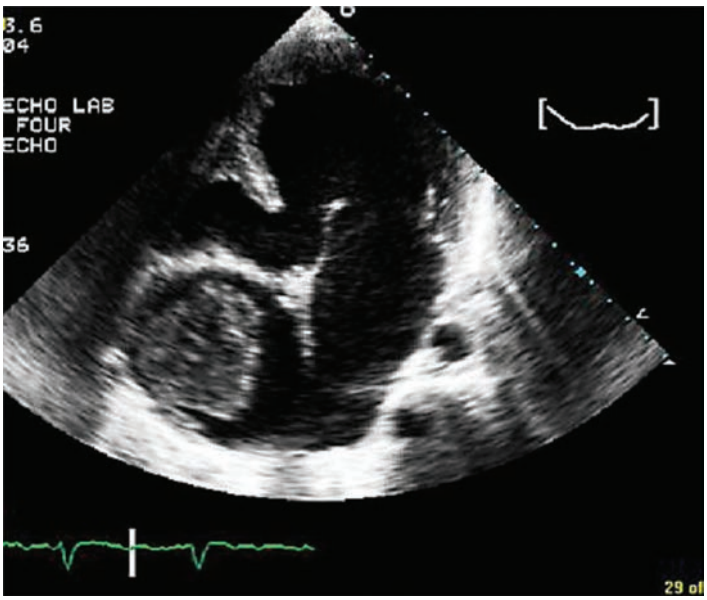


Figure 5.16

5.17. Which of the following does the patient in Figure 5.17 have?

- **A.** Prominent Eustachian valve
- **B.** Ostium secundum ASD
- **C.** Ostium primum ASD
- **D.** Sinus venosus ASD

5.18. What type of flow was recorded from the mid-esophageal position in Figure 5.18?

- **A.** Mitral flow
- **B.** Pulmonary vein flow
- **C.** Superior vena cava flow
- **D.** Flow across ASD

5.19. The patient in Question 5.17 with secundum ASD has ASD dimensions of the defect 3 cm × 2 cm, TVI of flow across the defect is 39 cm, and heart rate of 70/s. What is the approximate shunt flow across the ASD?

- **A.** 12.8 L/min
- **B.** 3 L/min
- **C.** 7 L/min
- **D.** Cannot be calculated

5.20. What is the cause of the patient's mitral valve problem shown in Figure 5.20?

- **A.** Rheumatic heart disease
- **B.** Degenerative valve disease
- **C.** Fen–phen valvulopathy
- **D.** Ischemic heart disease

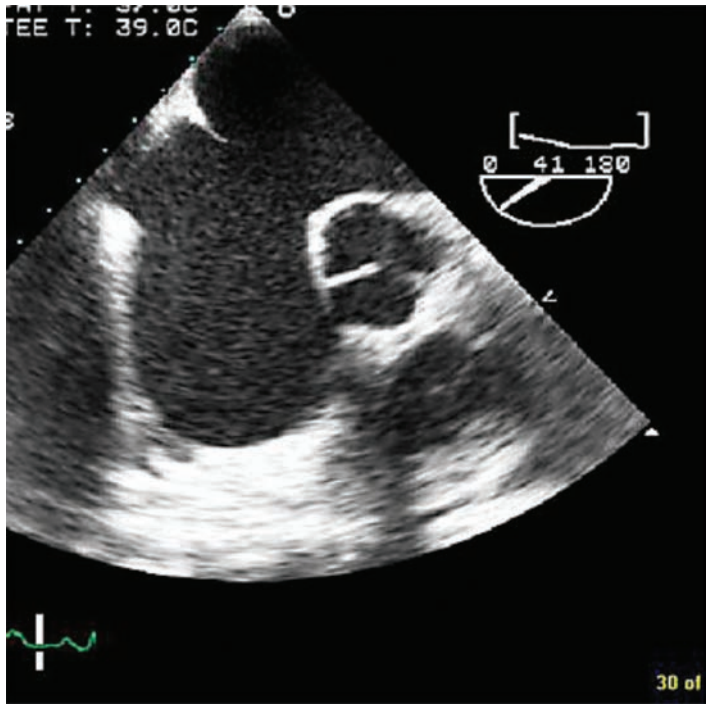


Figure 5.17

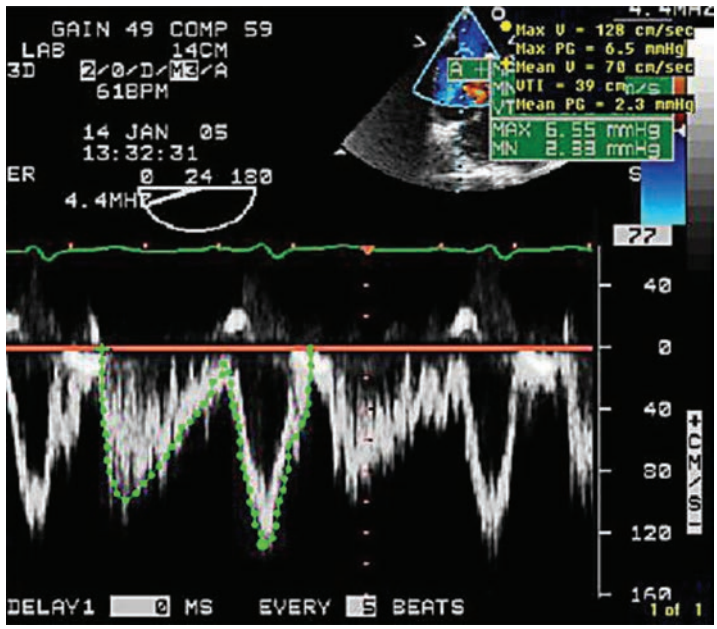


Figure 5.18

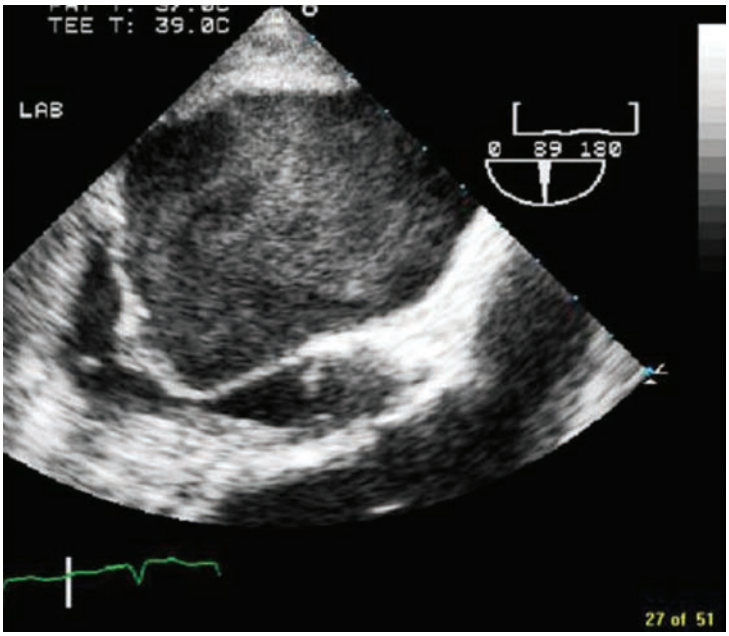


Figure 5.20

5.21. Figure 5.21 shows a patient that may have all of the following except what?
- **A.** Atrial septal defect
- **B.** Wolf–Parkinson–White syndrome
- **C.** TR
- **D.** Bicuspid aortic valve

5.22. The M-mode echocardiogram in Figure 5.22 is suggestive of what?
- **A.** Normal mitral valve motion
- **B.** MS
- **C.** Severe AR
- **D.** High LA pressure

5.23. What is the image shown in Figure 5.23 suggestive of?
- **A.** Mitral annuloplasty
- **B.** Catheter in the coronary artery
- **C.** Biventricular pacemaker or implantable cardioverter-defibrillator (ICD)
- **D.** An artifact

5.24. What is the structure denoted by the arrow in Figure 5.24?
- **A.** LA appendage
- **B.** Left lower pulmonary vein
- **C.** Left upper pulmonary vein
- **D.** Right lower pulmonary vein

5.25. The patient shown in Figure 5.25 has what condition?
- **A.** Valvular AS
- **B.** Subvalvular AS
- **C.** Endocarditis
- **D.** Hypertrophic obstructive cardiomyopathy (HOCM)

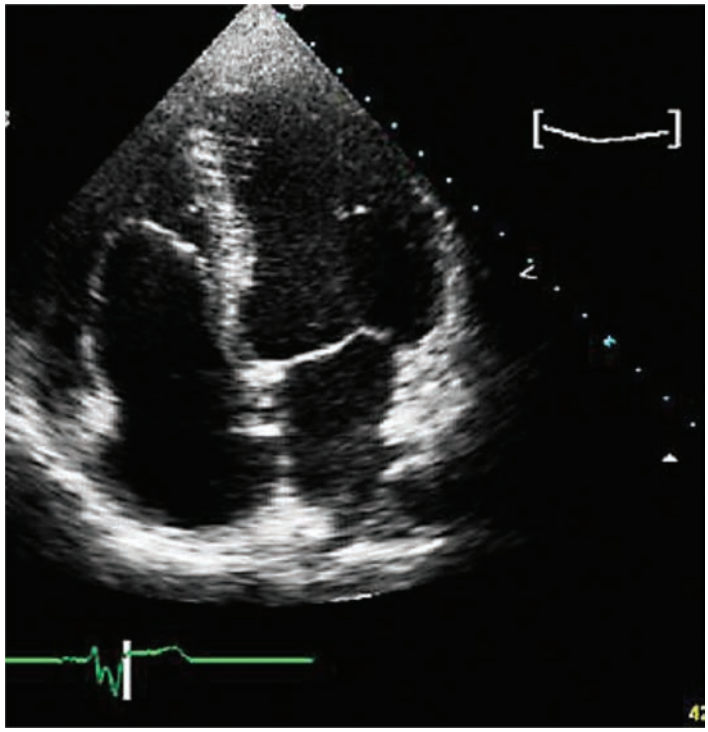


Figure 5.21

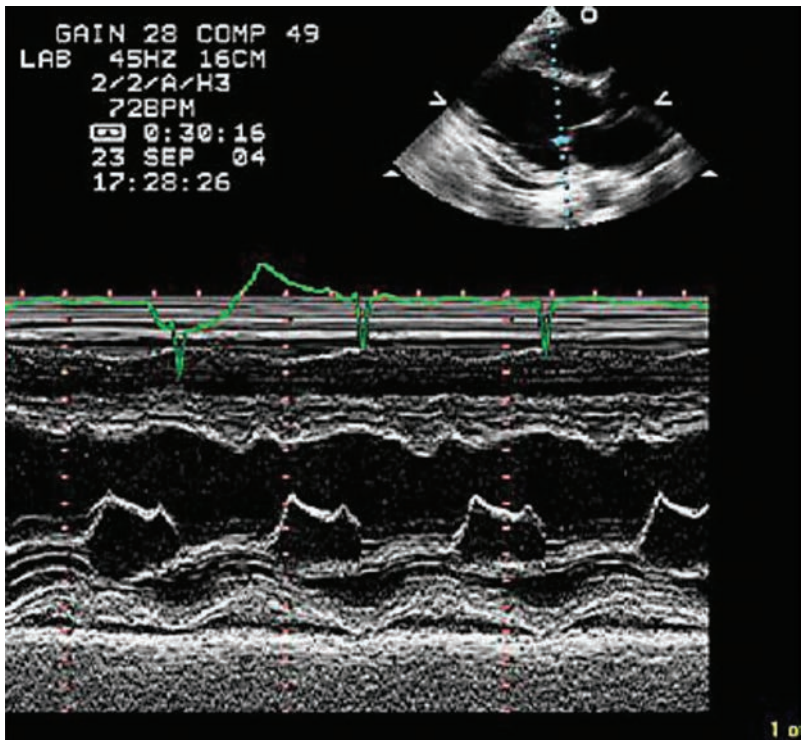


Figure 5.22

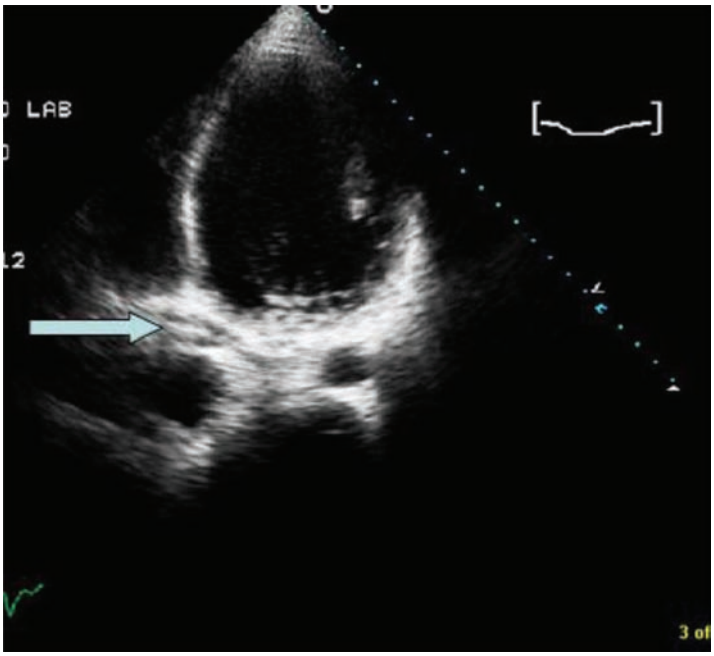


Figure 5.23

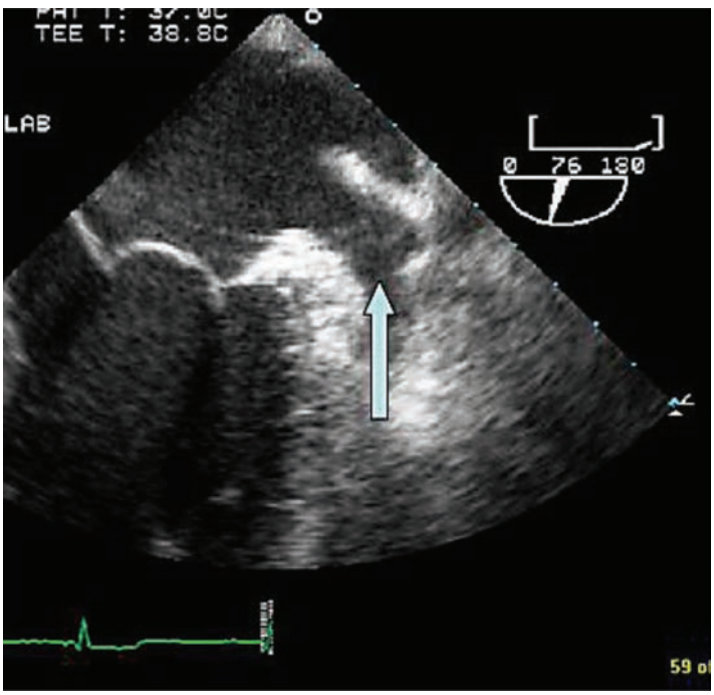


Figure 5.24

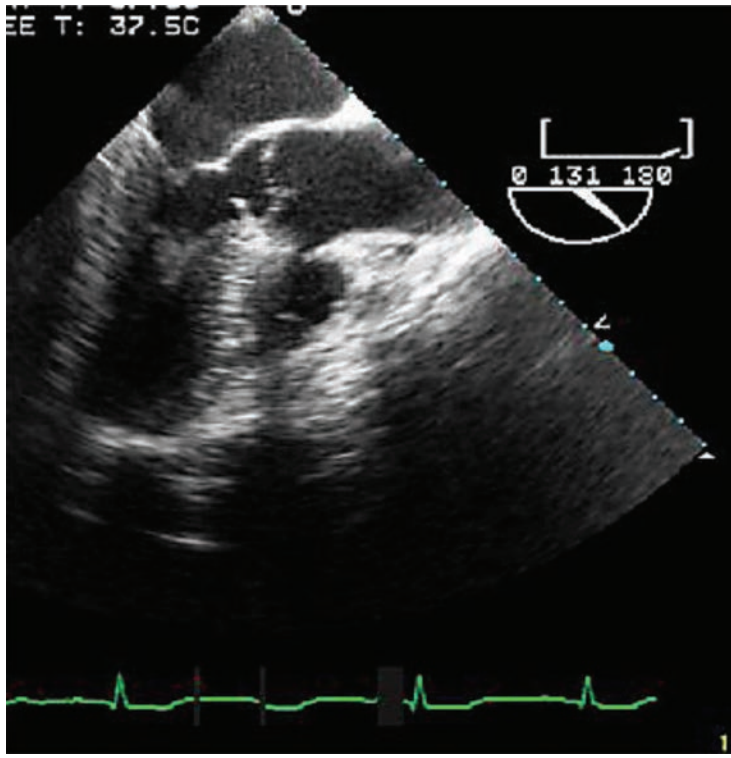


Figure 5.25

5.26. The cause of dyspnea in the patient in Figure 5.26 is likely to be due to what?

- **A.** Left heart failure
- **B.** Primary pulmonary hypertension
- **C.** Chronic obstructive pulmonary disorder
- **D.** None of the above

5.27. Figure 5.27 shows an end systolic frame in a patient with shortness of breath. What is the most likely diagnosis?

- **A.** Ebstein's anomaly
- **B.** Hypertrophic cardiomyopathy
- **C.** ASD
- **D.** Dilated cardiomyopathy

5.28. What is the most likely mechanism of MR in the patient in Figure 5.28?

- **A.** P2 tethering
- **B.** P2 prolapse
- **C.** Bileaflet mitral valve prolapse
- **D.** None of the above

5.29. A 19-year-old patient was stabbed in the precordial area. Examination revealed a loud systolic murmur (Figure 5.29). What is the most likely cause of this murmur?

- **A.** Penetrating injury to the interventricular septum
- **B.** Mitral valve prolapse
- **C.** HOCM
- **D.** None of the above

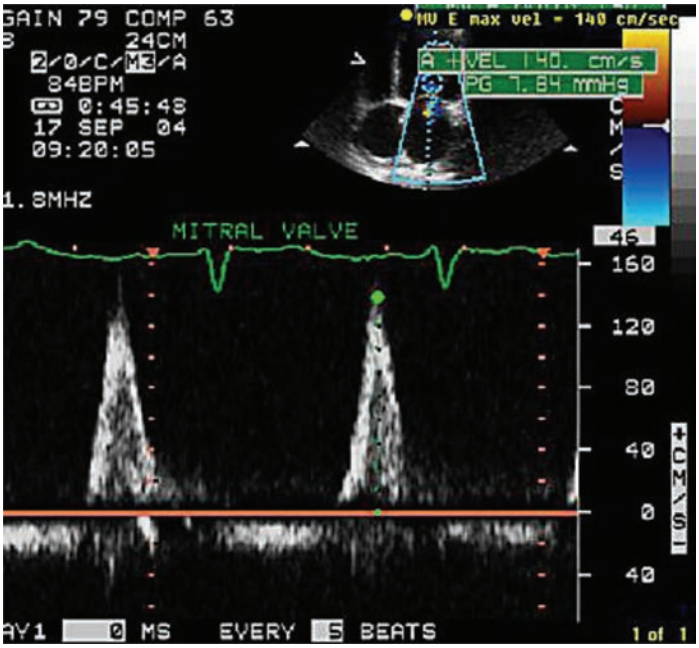


Figure 5.26

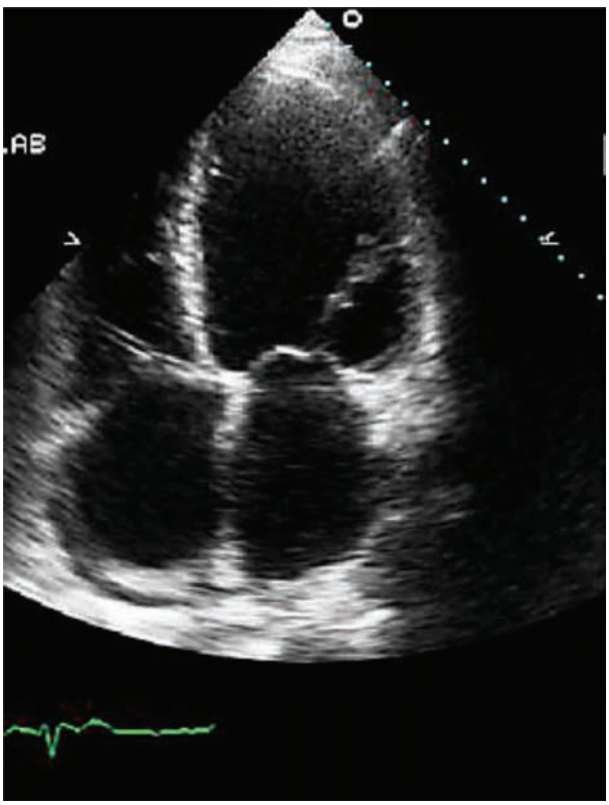


Figure 5.27

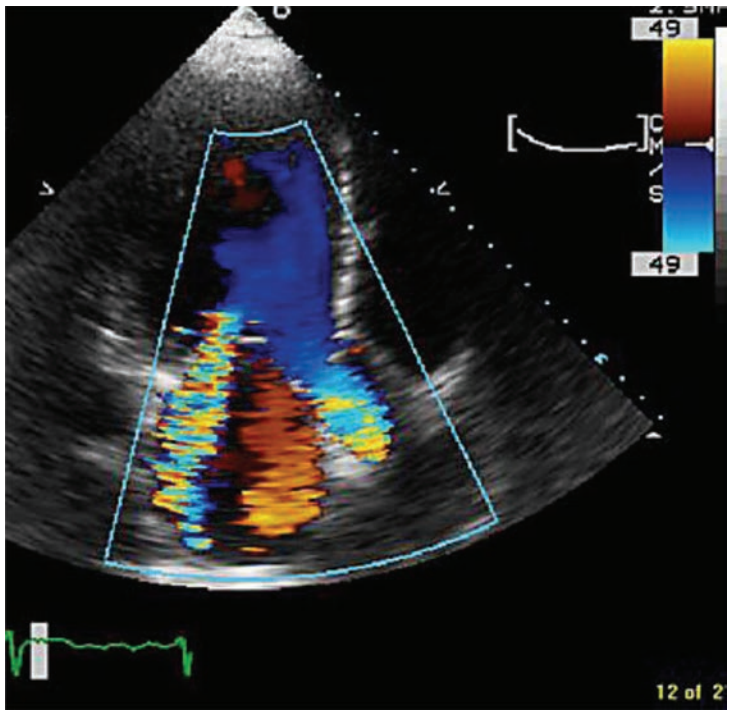


Figure 5.28

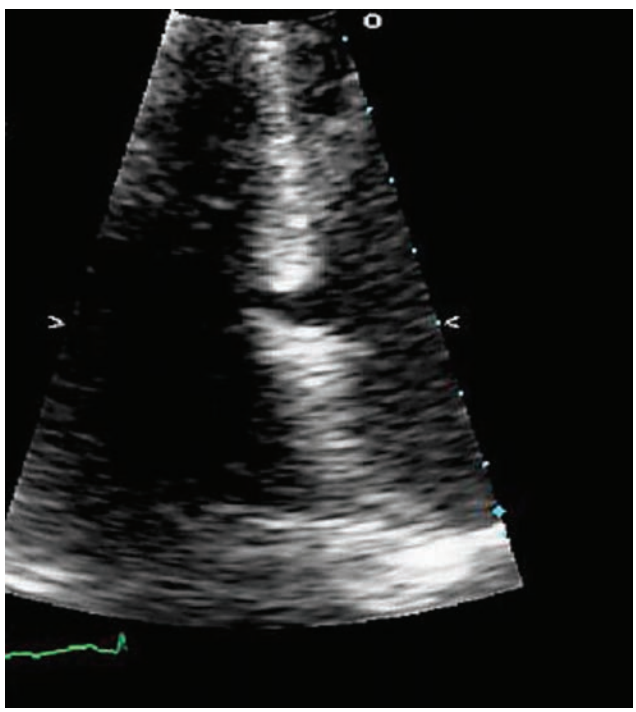


Figure 5.29

5.30. What is the continuous-wave Doppler signal in Figure 5.30 suggestive of?

A. AS and AR
B. MS and MR
C. VSD flow
D. Aortic flow in a patient with coarctation

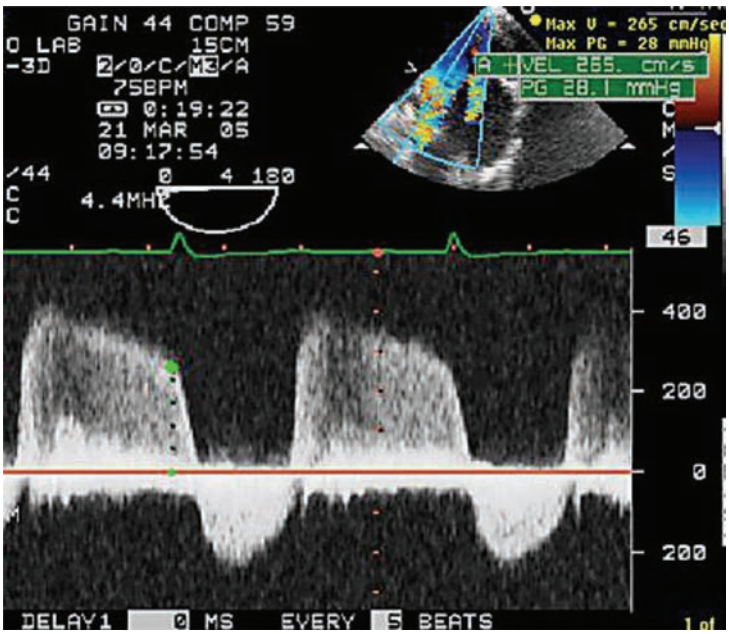


Figure 5.30

5.31. The continuous wave signal in Figure 5.31 was obtained from the mid-transesophageal location. What is it indicative of?

A. AS and AR
B. MS and MR
C. VSD flow
D. None of the above

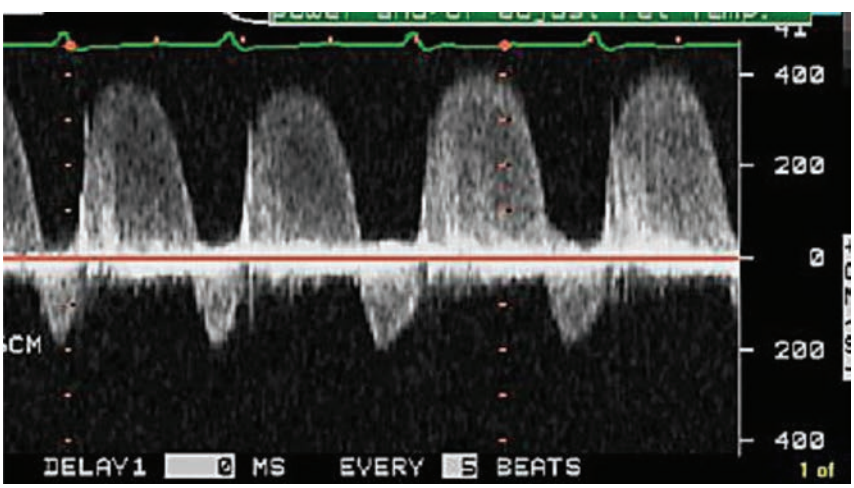


Figure 5.31

5.32. Figure 5.32 shows a TEE image from the mid-esophagus of a late diastolic frame of the aortic valve. What is this patient most likely to have?

A. Severe AR
B. Severe AS
C. HOCM
D. Ascending aortic dissection

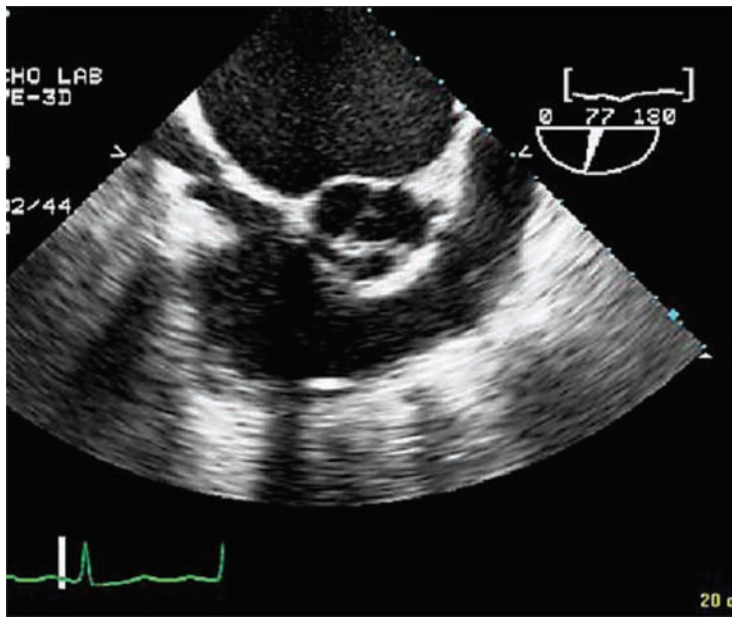


Figure 5.32

5.33. What is the patient in Figure 5.33 most likely to have?

A. Acute severe MR
B. Chronic severe MR
C. Severe MS and mild MR
D. None of the above

5.34. The patient in Figure 5.34 had *Staphylococcus aureus* endocarditis of the aortic valve. What is the most likely cause?

A. Central venous catheter-associated infection
B. Dental work
C. Immunosuppressed state
D. Intravenous drug use

5.35. What is the image of the aortic valve in Figure 5.35 suggestive of?

A. Aortic valve vegetation
B. Node of Arantius
C. Lambl's excrescences
D. Ascending aortic dissection causing prolapse of the noncoronary cusp

5.36. What is the most likely cause of the signal shown in Figure 5.36?

A. HOCM
B. Critical valvular AS
C. Acute MR
D. None of the above

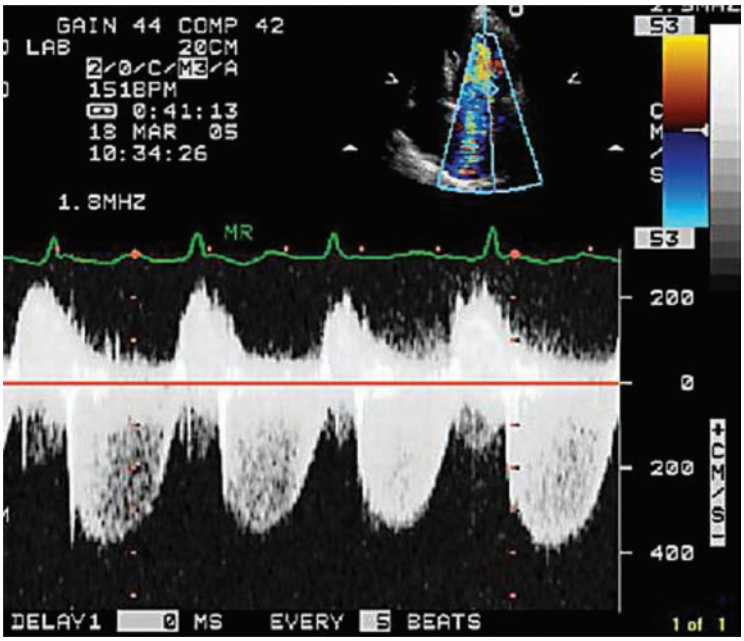


Figure 5.33

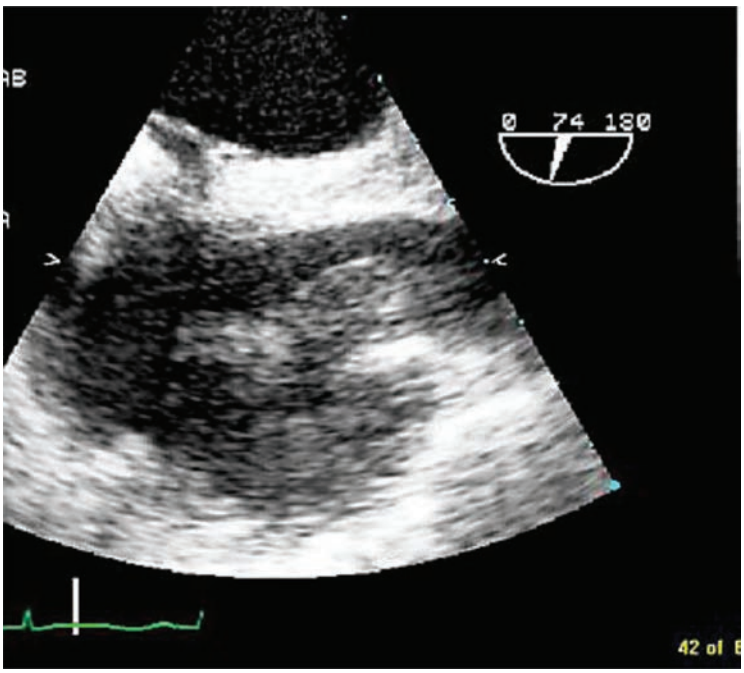


Figure 5.34

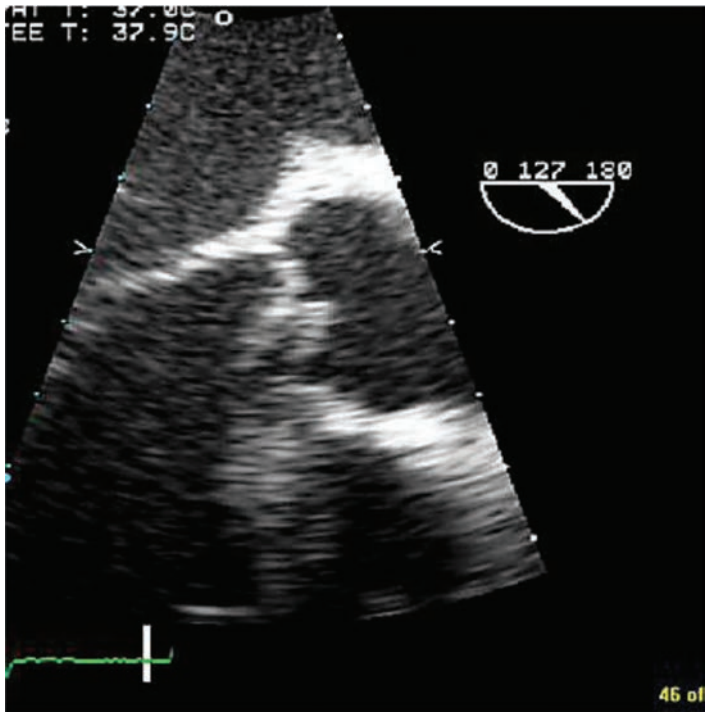


Figure 5.35

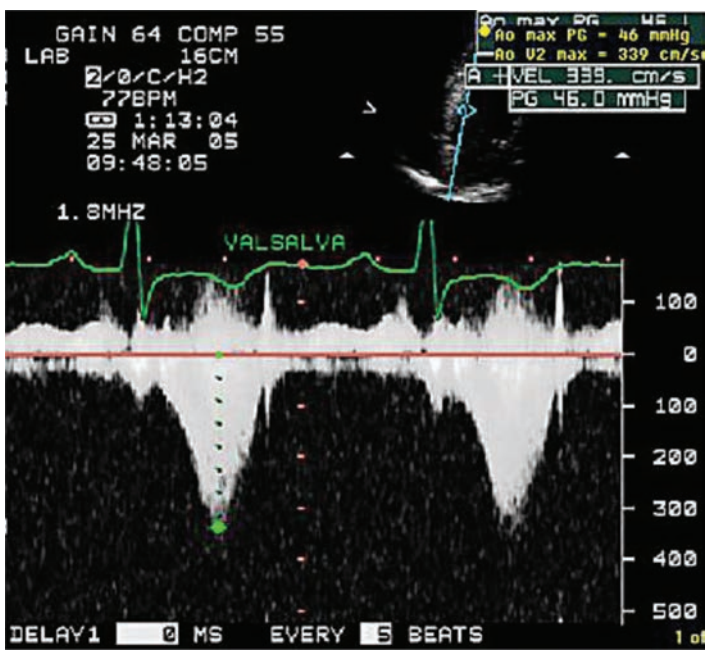


Figure 5.36

5.37. What is the image shown in Figure 5.37 suggestive of?

A. Bioprosthetic tricuspid valve
B. Carcinoid valvulopathy of tricuspid valve
C. Tricuspid annuloplasty ring
D. Large tricuspid vegetation

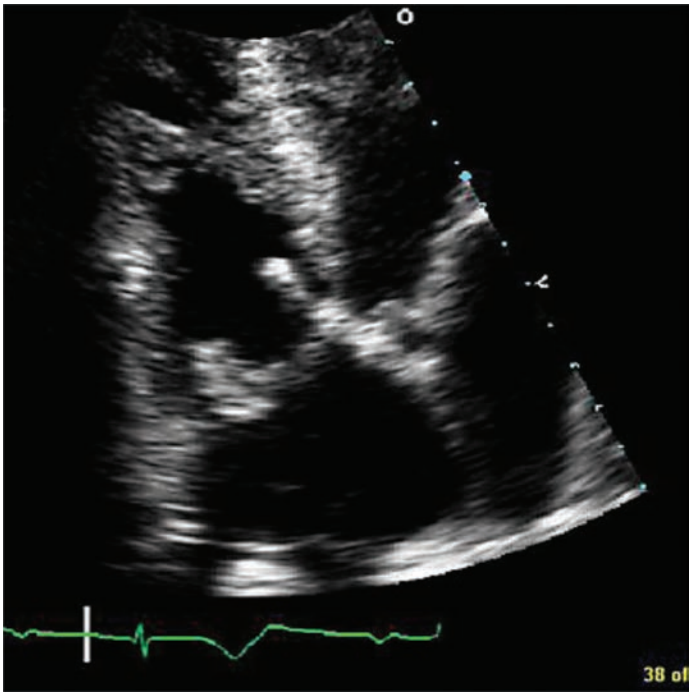


Figure 5.37

5.38. What is the 65-year-old patient with MR in Figure 5.38 likely to have?

A. An opening snap
B. Third heart sound
C. Fourth heart sound
D. Summation gallop

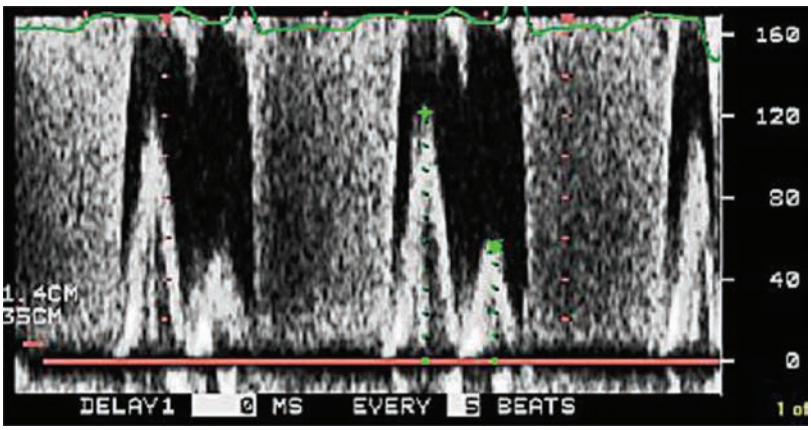


Figure 5.38

5.39. What is the continuous-wave Doppler signal in Figure 5.39 consistent with?

A. Critical AS
B. Severe MR
C. Maladie de Roger
D. None of the above

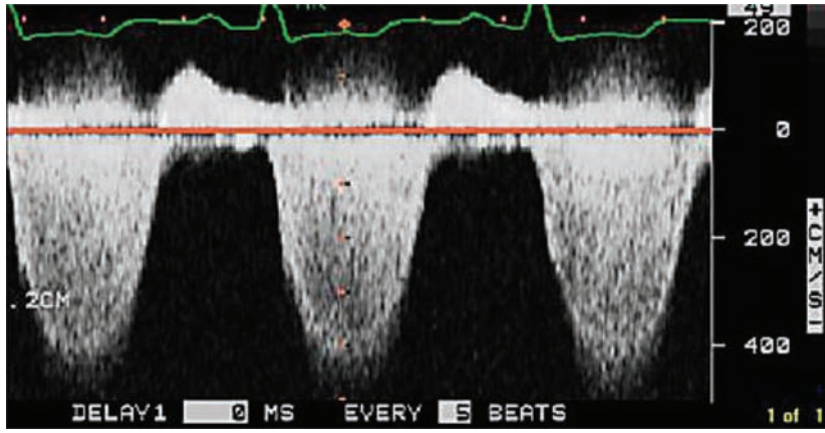


Figure 5.39

5.40. The TR signal in Figure 5.40 was obtained from TEE. The clinically estimated right atrial (RA) pressure in this patient was 20 mmHg and there is no PS. What would the PA systolic pressure in this patient be?

A. 30 mmHg
B. 50 mmHg
C. 80 mmHg
D. Cannot be calculated

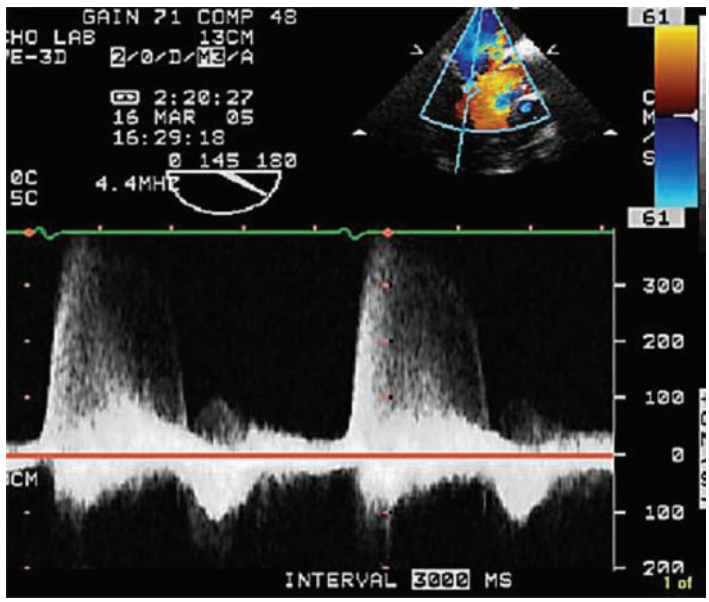


Figure 5.40

5.41. What condition is the patient in Figure 5.41 likely to have?

A. Acute severe AR
B. Mild AR
C. MS
D. None of the above

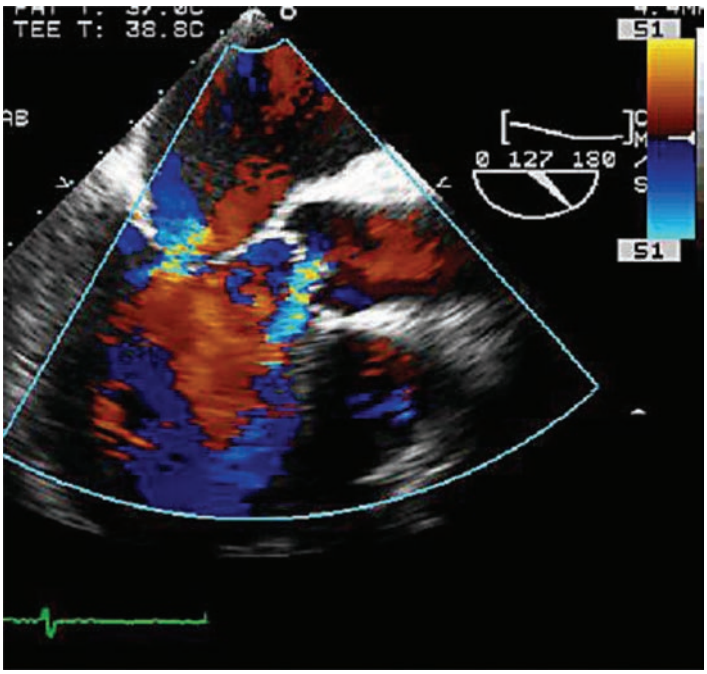


Figure 5.41

5.42. The transmitral flow in Figure 5.42 is obtained from the esophageal transducer location from a patient with *Staphylococcus aureus* bacteremia and acute hemodynamic decompensation. The patient is in sinus rhythm. What is the most likely cause of his decompensation?

A. Acute MR
B. Acute AR
C. Rupture of the ventricular septum
D. None of the above

5.43. The pulse-wave Doppler flow signal in the descending thoracic aorta on a TEE shown in Figure 5.43 is indicative of what?

A. Coarctation of the aorta
B. Middle aortic syndrome
C. Severe AR
D. HOCM

5.44. What is the likely cause of heart failure in the 30-year-old man shown in Figure 5.44?

A. Noncompaction of the left ventricle
B. Hemochromatosis
C. Cardiac amyloid
D. Hypertrophic cardiomyopathy

5.45. What is the structure indicated by the arrow in Figure 5.45?

A. IVC–RA junction
B. Superior vena cava
C. Anomalously draining right upper pulmonary vein
D. ASD

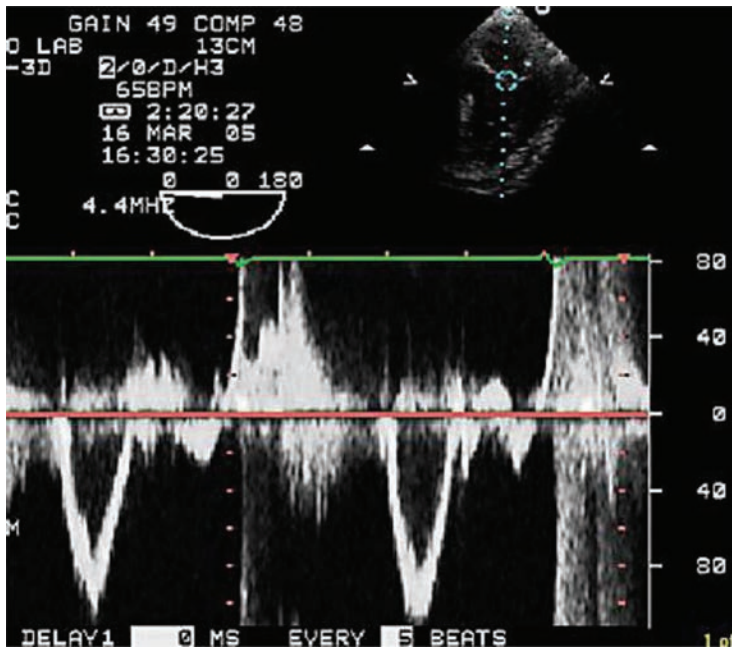


Figure 5.42

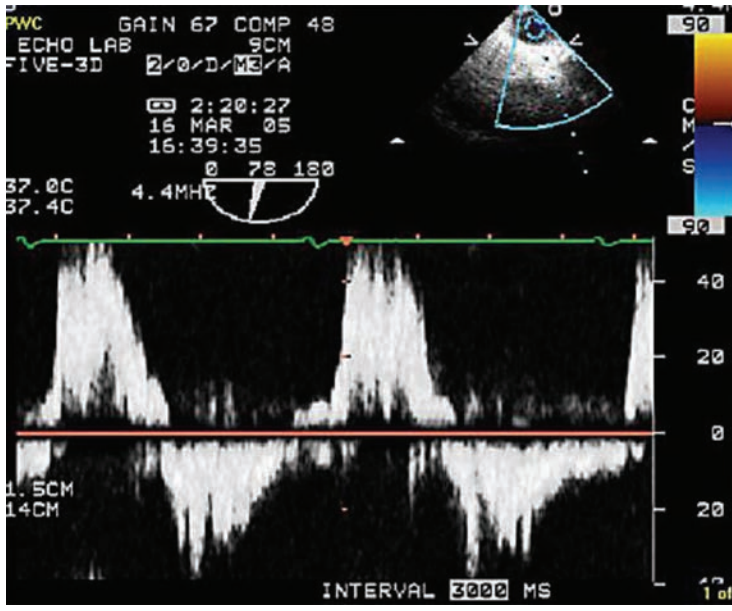


Figure 5.43

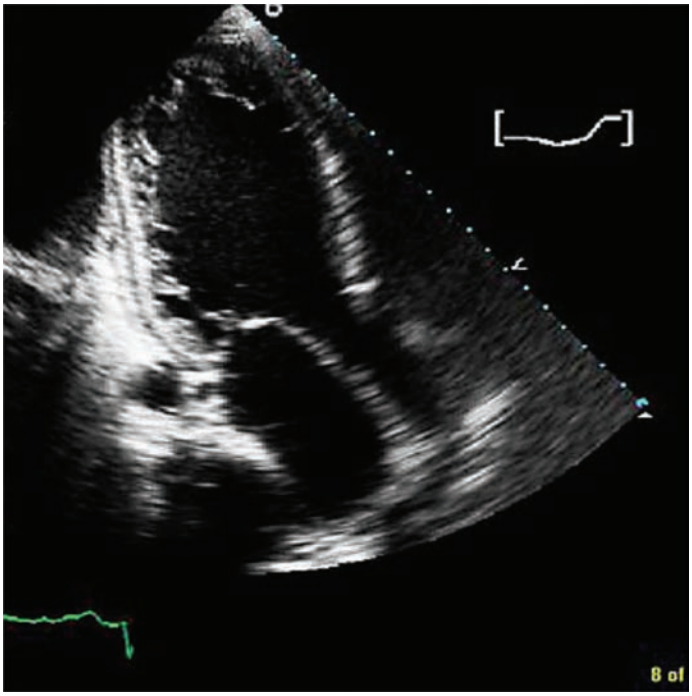


Figure 5.44

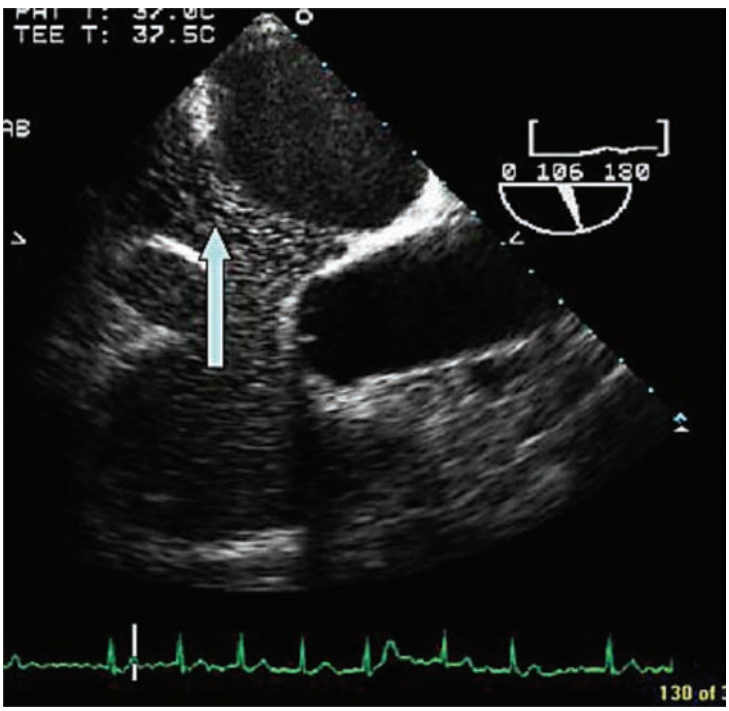


Figure 5.45

5.46. What is the approximate MR flow rate of the patient in Figure 5.46 (PISA radius of 0.9 cm, aliasing velocity of 38 cm/s)?

A. ~200 cm^3/s
B. ~200 cm^3/min
C. ~100 cm^3/min
D. ~100 cm^3/s

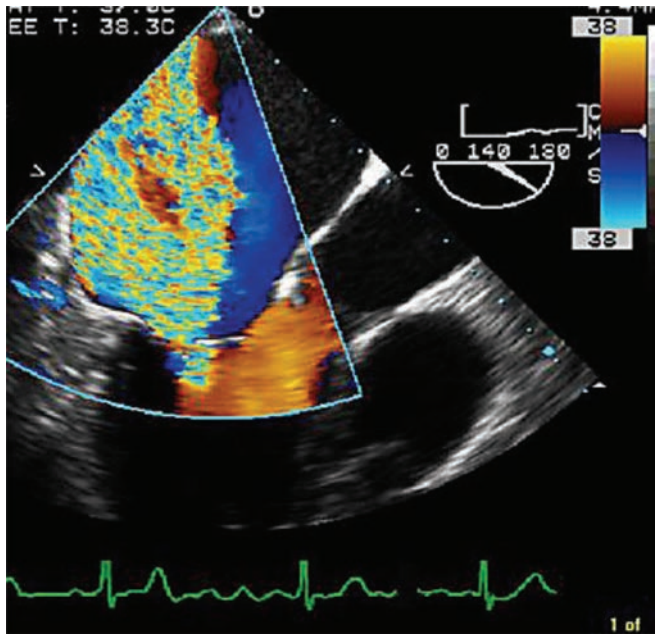


Figure 5.46

5.47. What is the likely diagnosis of the patient in Figure 5.47?

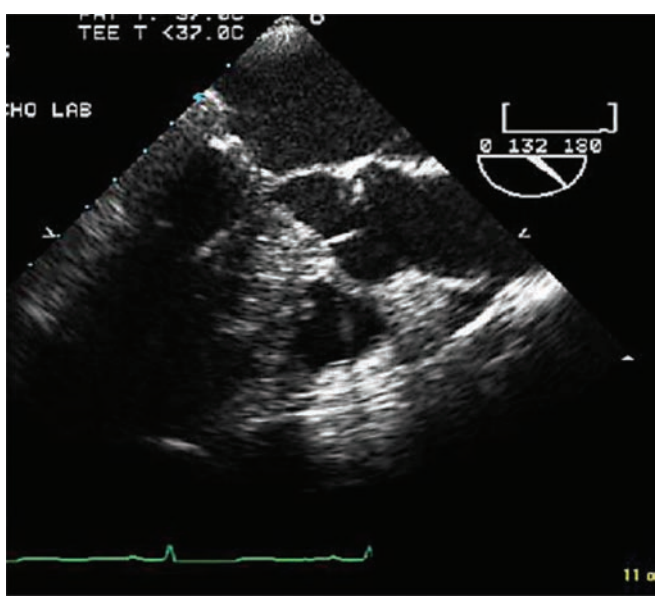
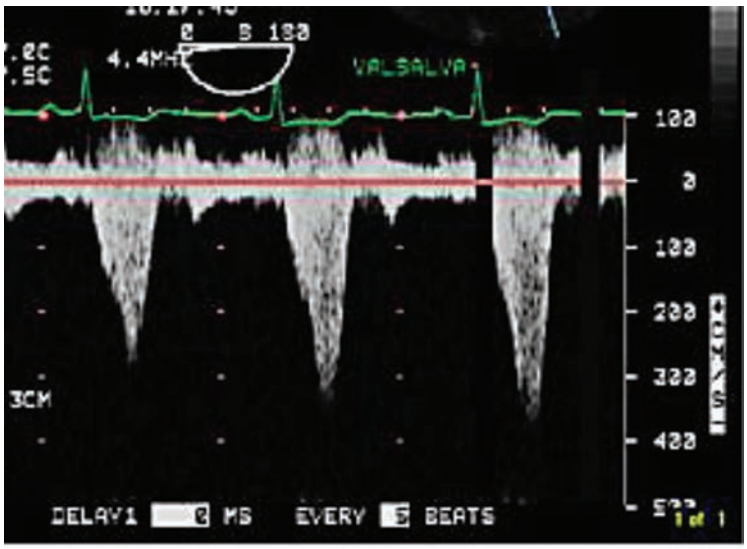


Figure 5.47

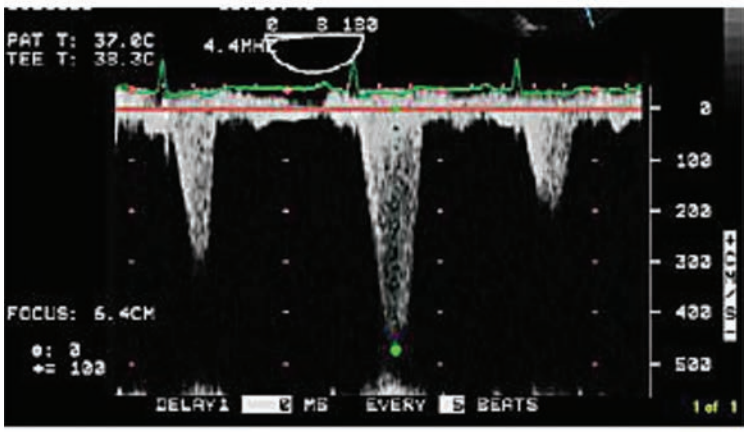
A. An early diastolic murmur
B. Late-peaking systolic ejection murmur with absent A2 component of S2
C. Late-peaking systolic murmur increased by Valsalva's maneuver and normal A2
D. Mid-diastolic murmur

5.48. What is the most likely diagnosis of the patient in Figure 5.48?

A. HOCM
B. Severe AS
C. Mitral valve prolapse
D. None of the above



At rest



With Valsalva

Figure 5.48

5.49. What is the most likely diagnosis of the patient in Figure 5.49?

- **A.** Apical HOCM
- **B.** Hypertensive heart disease
- **C.** Endomyocardial fibrosis
- **D.** None of the above

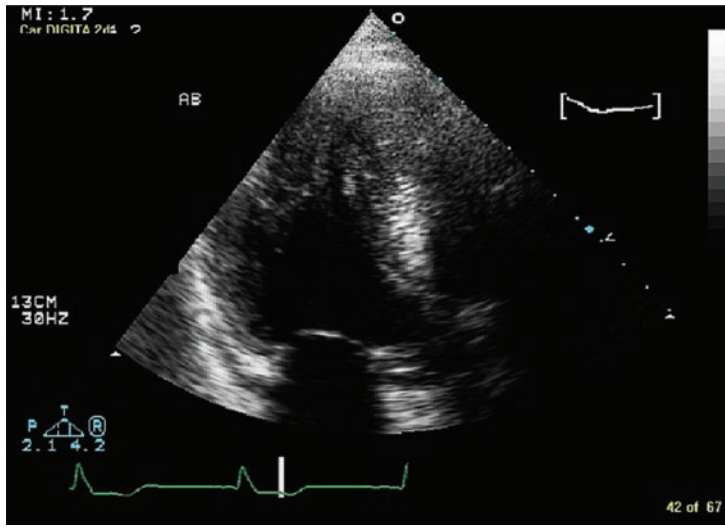


Figure 5.49

5.50. The appearance of the atrial septum in the patient in Figure 5.50 is due to what?

- **A.** ASD repair with a pericardial patch
- **B.** ASD closure device
- **C.** PFO closure device
- **D.** None of the above

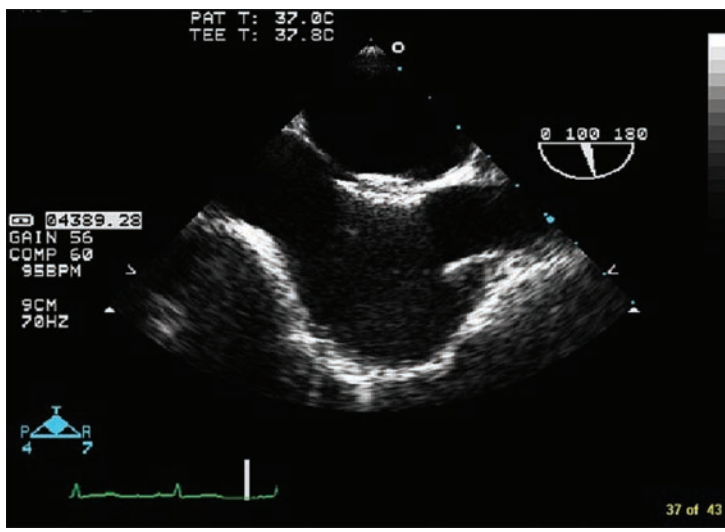


Figure 5.50

5.51. What does Figure 5.51 show?

A. Normal native tricuspid valve
B. Normal bioprosthetic valve
C. Vegetation on a bioprosthetic valve
D. Avulsion of the tricuspid valve

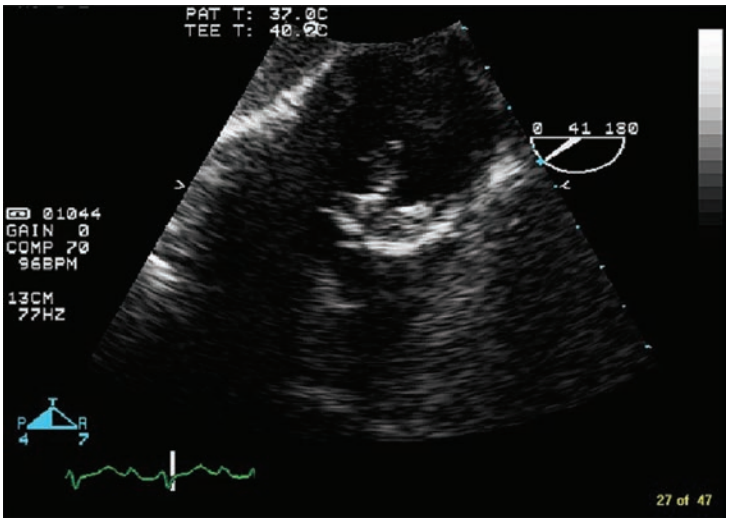


Figure 5.51

5.52. A 31-year-old woman with no other medical history had two episodes of transient ischemic cerebral attacks, the first one after a long duration of air travel and the second one during straining in the rest-room. From the TEE image in Figure 5.52, what is the most likely cause of this patient's attacks?

A. Paradoxical embolism
B. Vagally mediated atrial fibrillation
C. LA thrombus
D. None of the above

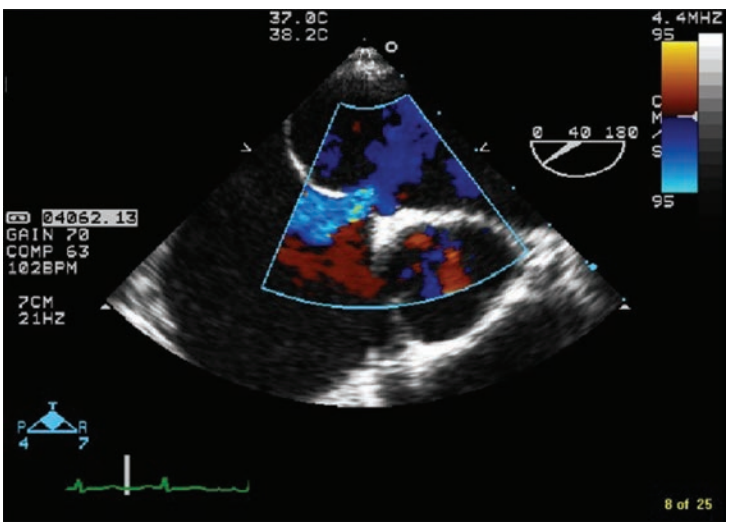


Figure 5.52

5.53. A 35-year-old patient with AIDS and bicuspid aortic valve has *Staphylococcus* bacteremia. What is the parasternal long-axis color flow image in Figure 5.53 suggestive of?

A. Right coronary artery flow
B. Pulmonary vegetation
C. Fistulous communication between aorta and right ventricle
D. None of the above

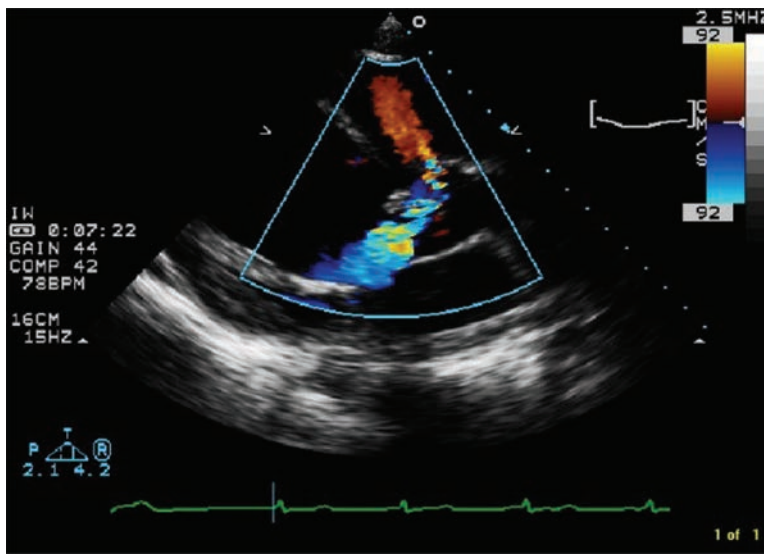


Figure 5.53

5.54. What are the patient's bilateral *Staphylococcus* lung abscesses shown in Figure 5.54 likely due to?

A. Tricuspid valve endocarditis
B. Pulmonary valve endocarditis
C. Catheter-related infection of superior vena cava and right atrium
D. None of the above

5.55. What is the structure indicated by the arrow in Figure 5.55?

A. Coronary sinus
B. IVC
C. ASD
D. None of the above

5.56. Describe the amount of TR in the patient in Figure 5.56.

A. Mild
B. Moderate
C. Severe
D. Cannot quantify

5.57. Which of the following is the patient in Question 5.56 likely to have?

A. Normal PA pressure
B. Mild pulmonary hypertension
C. Moderate or severe pulmonary hypertension

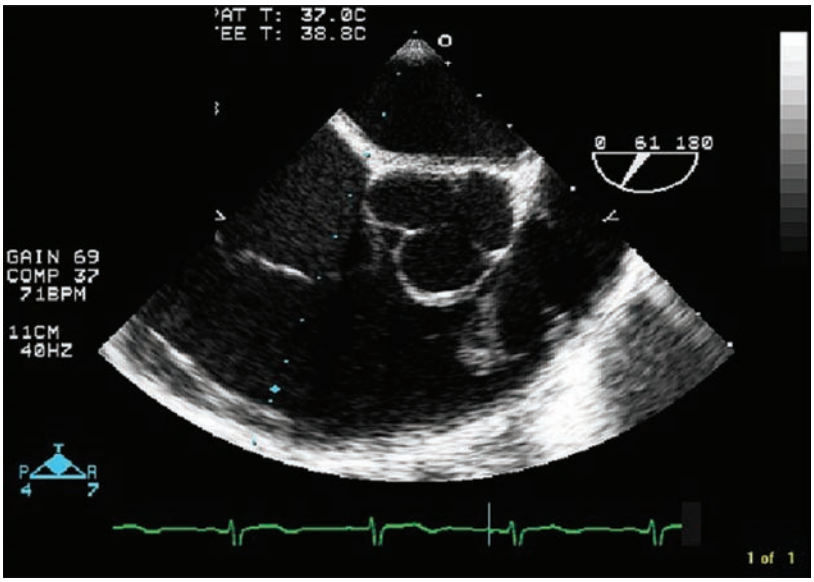


Figure 5.54

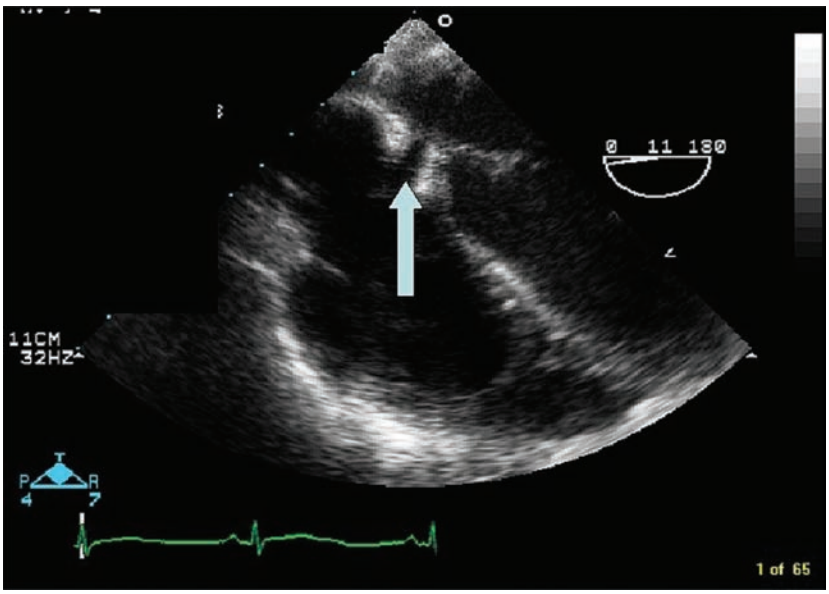


Figure 5.55

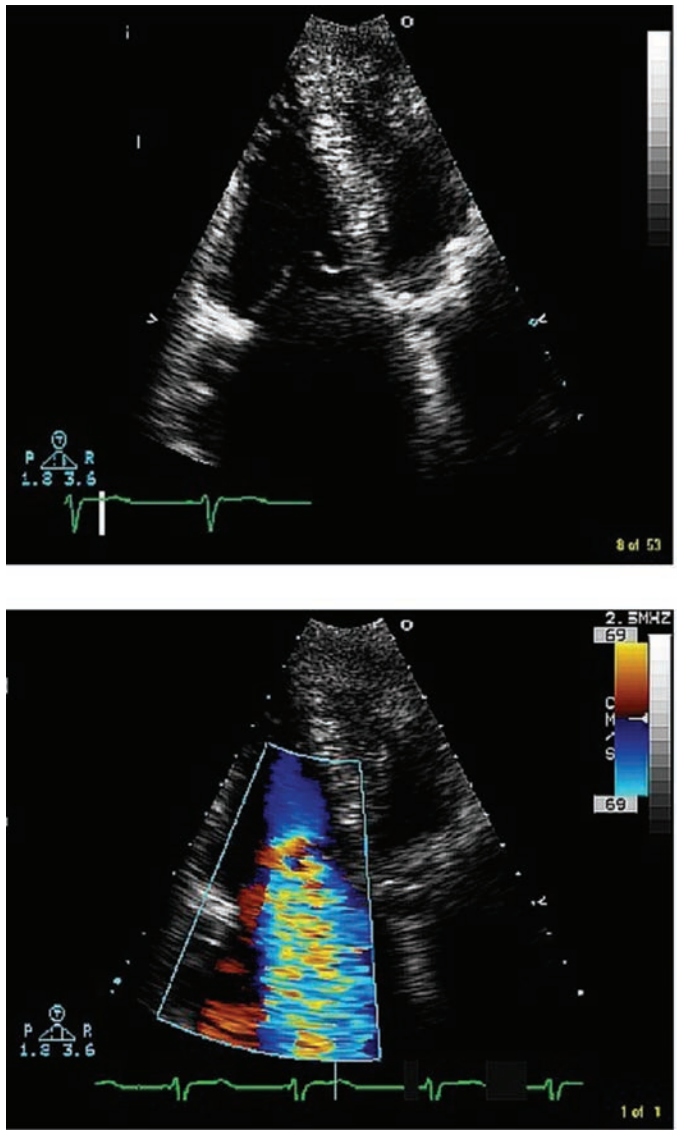


Figure 5.56

5.58. What is the likely type of surgical procedure performed on the mitral valve of the patient in Figure 5.58?

- **A.** Mitral annuloplasty
- **B.** Alfieri procedure
- **C.** Replacement with a bioprosthetic valve
- **D.** Replacement with a mechanical valve

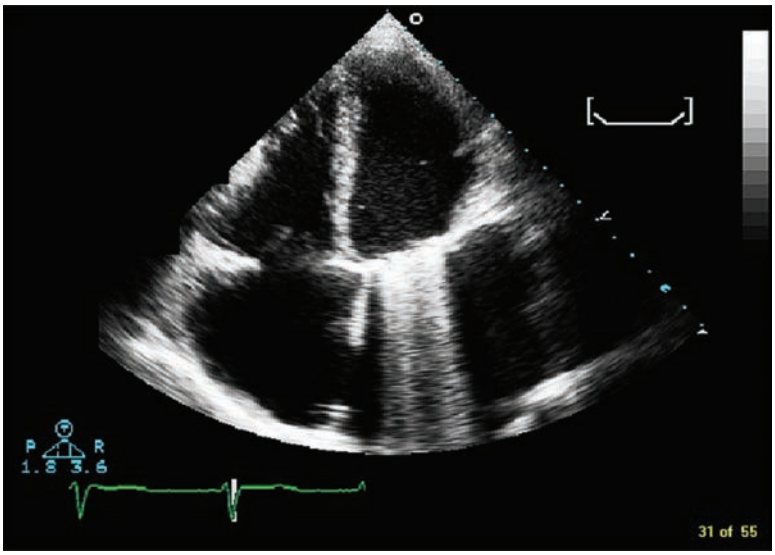


Figure 5.58

5.59. What intervention can potentially change the mitral inflow pattern seen in the images in Figure 5.59?

- **A.** Diuresis
- **B.** Control of severe hypertension
- **C.** Correction of severe anemia
- **D.** All of the above

5.60. What is the abnormality shown in Figure 5.60?

- **A.** Thoracic aortic aneurysm
- **B.** Cor triatriatum
- **C.** Artifact
- **D.** Dilated left PA

5.61. What is the patient in Figure 5.61 likely to have?

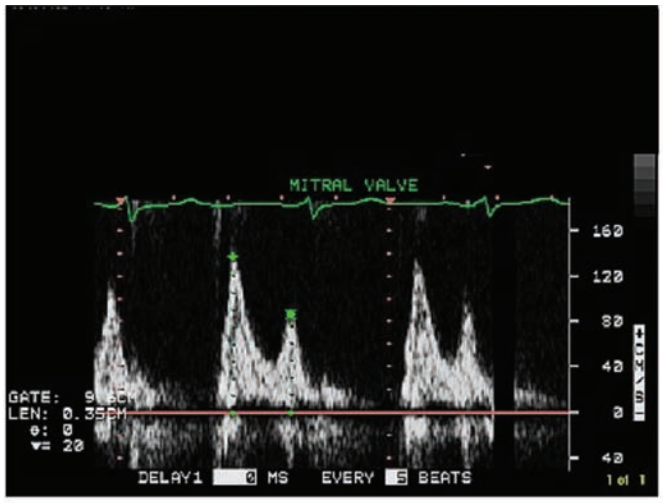
- **A.** Mitral valve prolapse
- **B.** Elevated LV EDP
- **C.** HOCM
- **D.** Severe AR

5.62. What does the mitral valve motion in the patient in Figure 5.62 suggest?

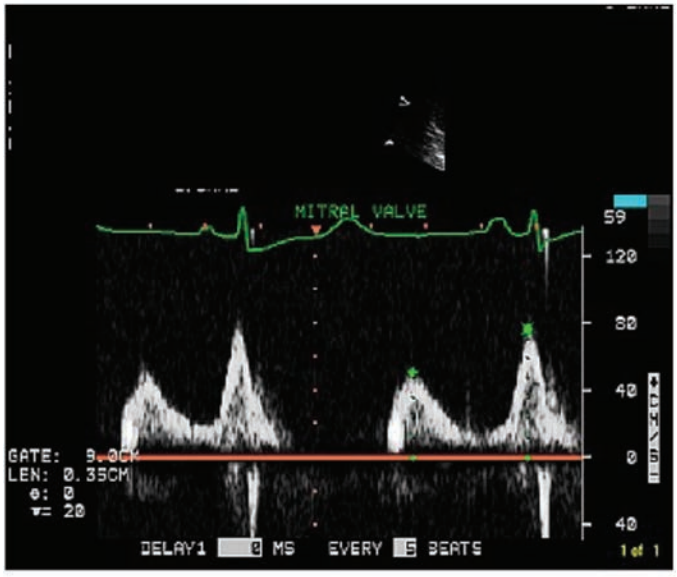
- **A.** Atrial fibrillation
- **B.** Elevated LV EDP
- **C.** Mitral valve prolapse
- **D.** Severe AR

5.63. What is the aortic valve m-mode in Figure 5.63 suggestive of?

- **A.** AS
- **B.** HOCM
- **C.** Congestive heart failure
- **D.** Hypertension



Before



After

Figure 5.59

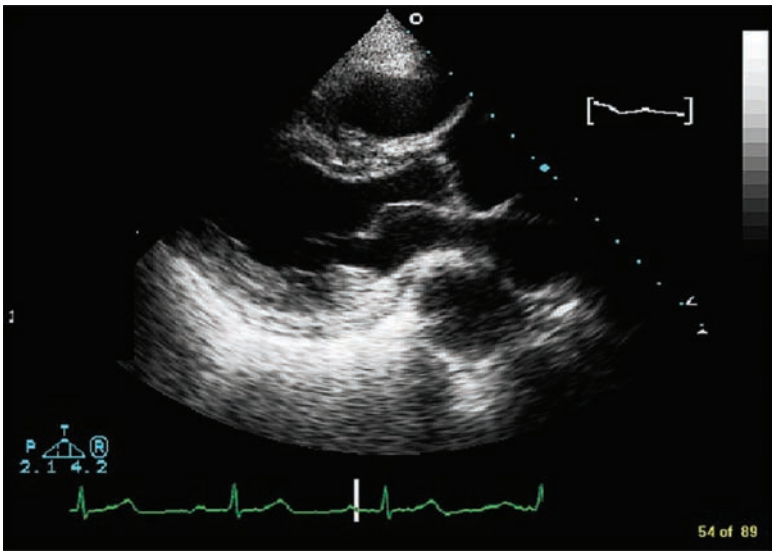


Figure 5.60

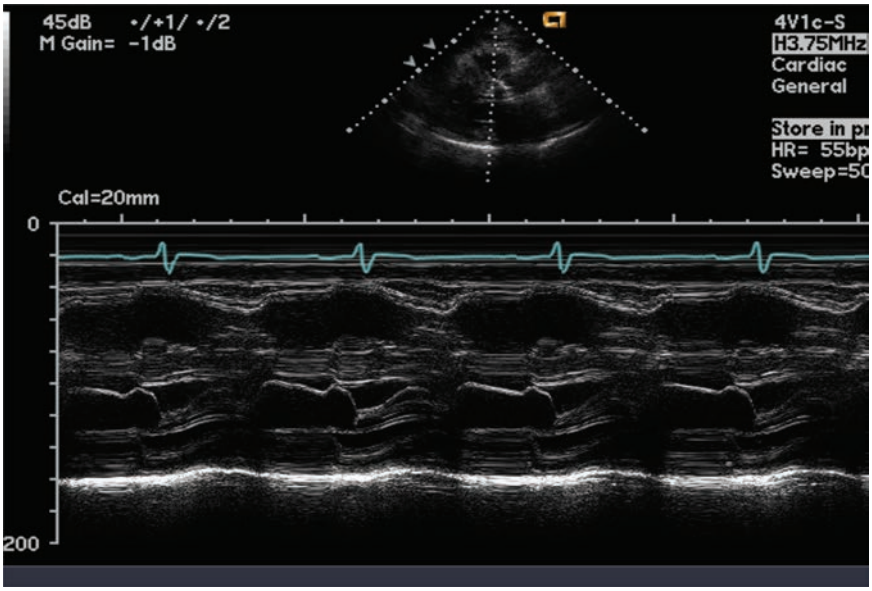


Figure 5.61

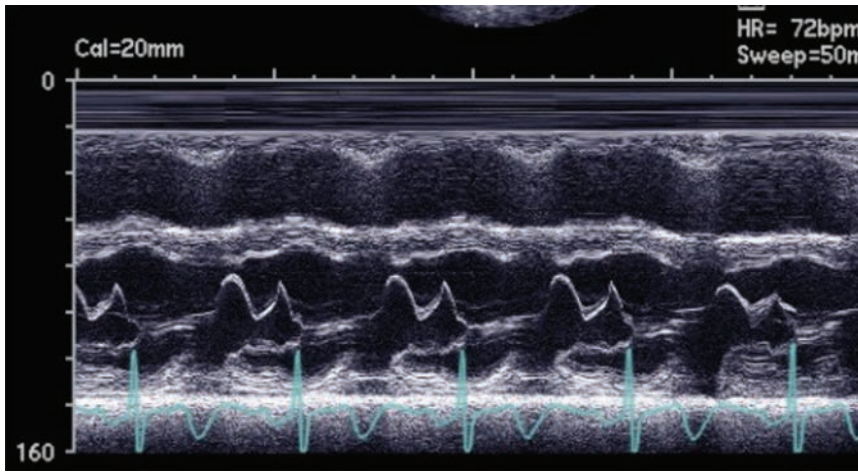


Figure 5.62

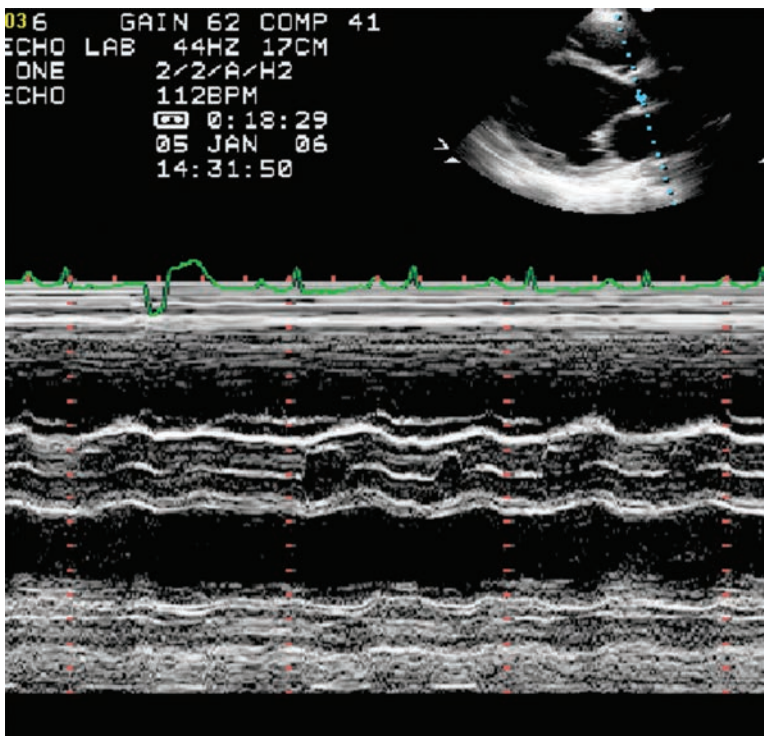


Figure 5.63

5.64. What is the patient in Figure 5.64 likely to have?

- **A.** Mild AR
- **B.** MS with high LA pressure
- **C.** Acute severe AR
- **D.** Severe MR

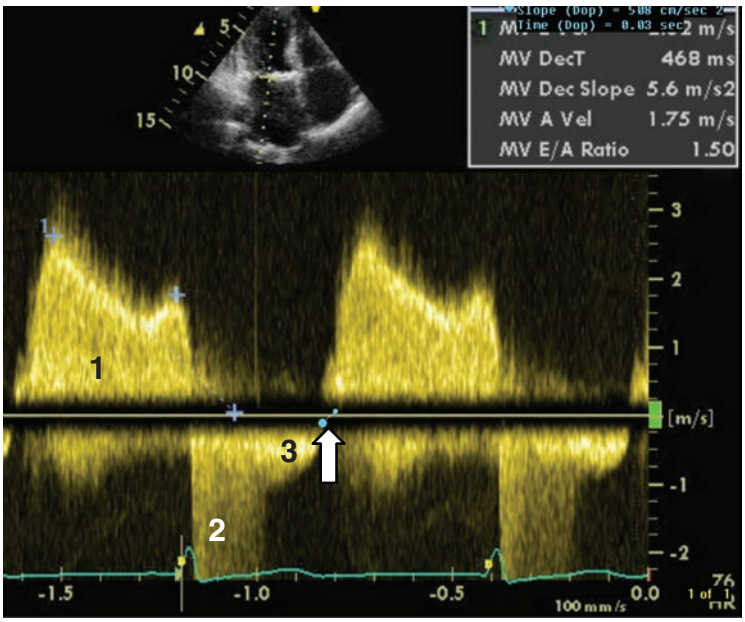


Figure 5.64

5.65. The patient in Figure 5.65 has MS with which of the following?

- **A.** High LA pressure
- **B.** Hyperdynamic LV
- **C.** Severe LV systolic dysfunction
- **D.** MR

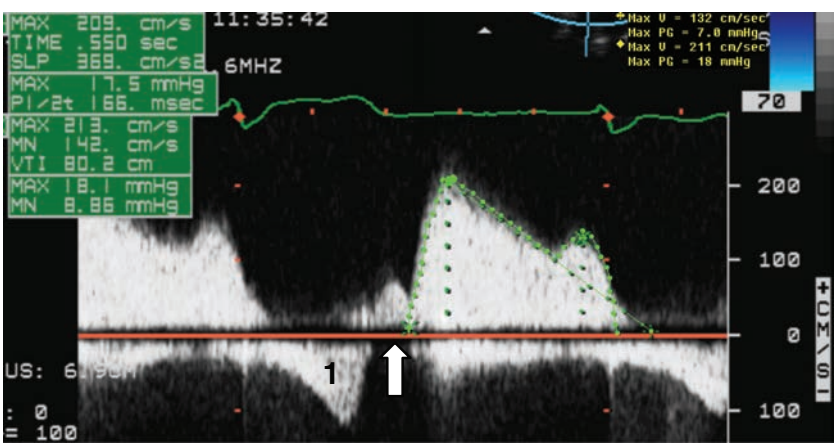


Figure 5.65

5.66. What is the continuous-wave Doppler signal in Figure 5.66 suggestive of?

A. Severe AR
B. MS
C. Pulmonary hypertension
D. Severe PR

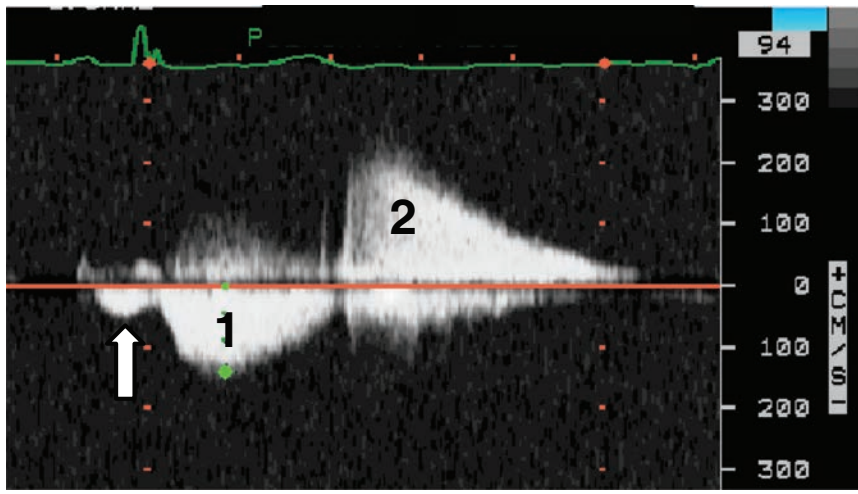


Figure 5.66

5.67. What is the continuous-wave signal in Figure 5.67 from a 22-year-old woman with a history of heart surgery during infancy indicative of?

A. Severe AS
B. Severe PS
C. Severe PS and PR
D. Severe pulmonary hypertension

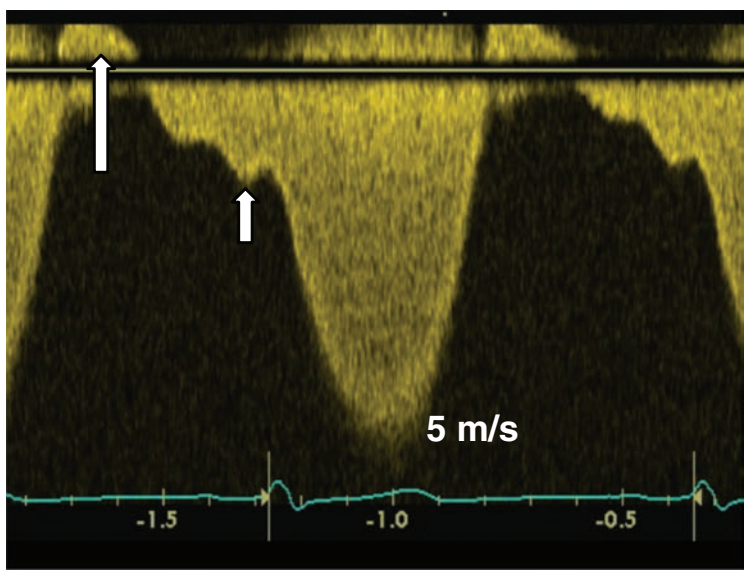


Figure 5.67

5.68. What was the signal in Figure 5.68 obtained from?

A. Apical window
B. Parasternal window
C. Suprasternal window
D. Subcostal window

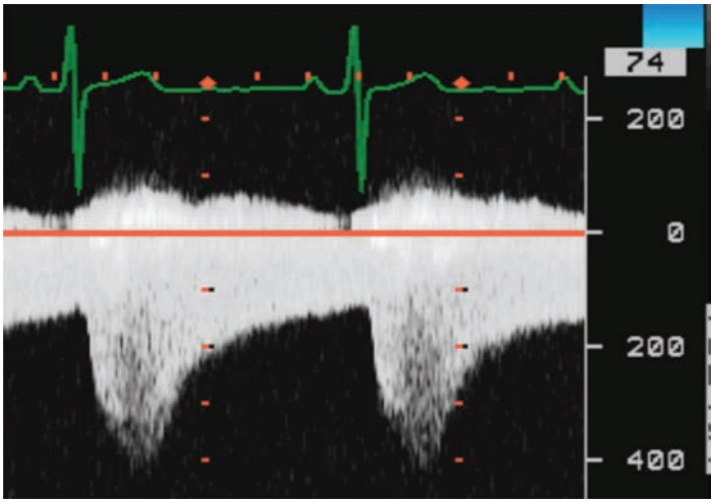


Figure 5.68

5.69. What condition does the patient in Figure 5.69 have?

A. PA branch stenosis
B. PR
C. Patent ductus arteriosus (PDA)
D. None of the above

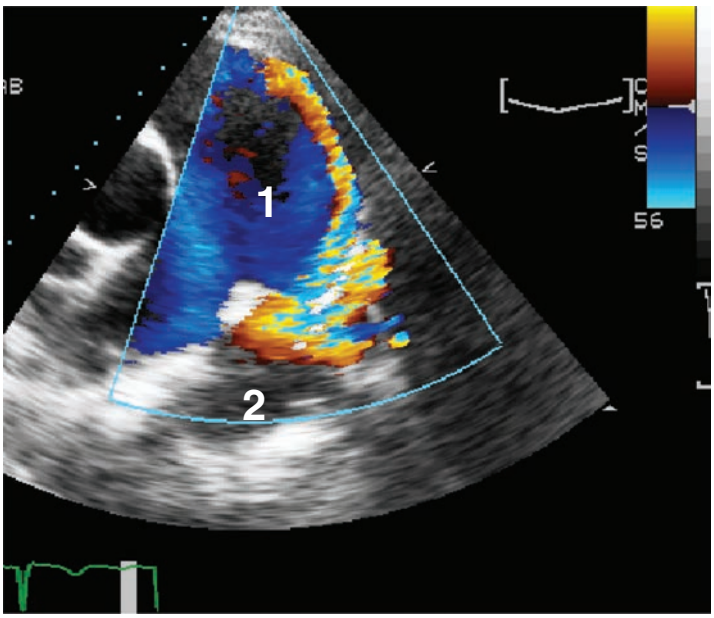


Figure 5.69

5.70. In Figure 5.70, the flow obtained on TEE from the descending thoracic aorta is indicative of what?

A. Aortic coarctation
B. PDA
C. Normal flow in intercostal artery
D. Severe AR

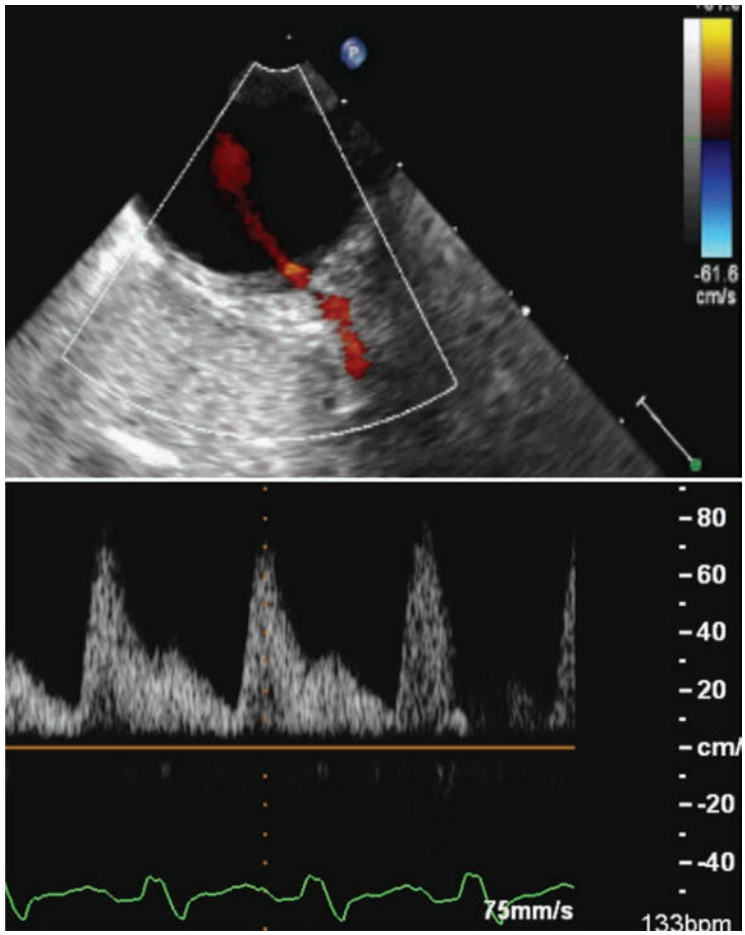


Figure 5.70

5.71. In Figure 5.71, the flow from this subcostal view is indicative of what?

A. Large ASD
B. Severe MR
C. MS
D. Tricuspid stenosis

5.72. Figure 5.72 is a recording of flow across the pulmonary valve using pulsed-wave Doppler in a patient with severe dyspnea. What is the likely diagnosis?

A. Pulmonary hypertension
B. PS
C. PR
D. Large ASD

5.73. Figure 5.73 shows a patient with what condition?

A. LV systolic dyssynchrony
B. LV diastolic dyssynchrony
C. Good LV synchrony
D. None of the above

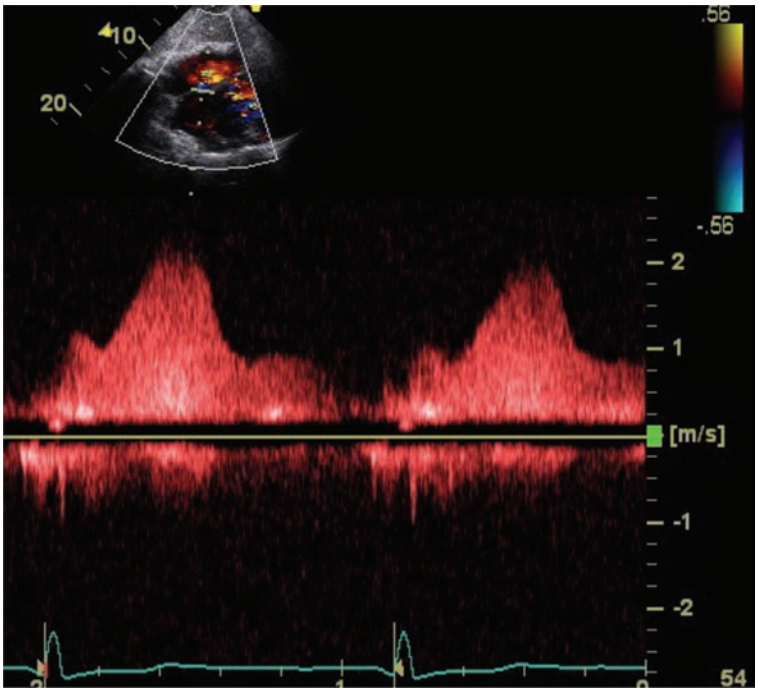


Figure 5.71

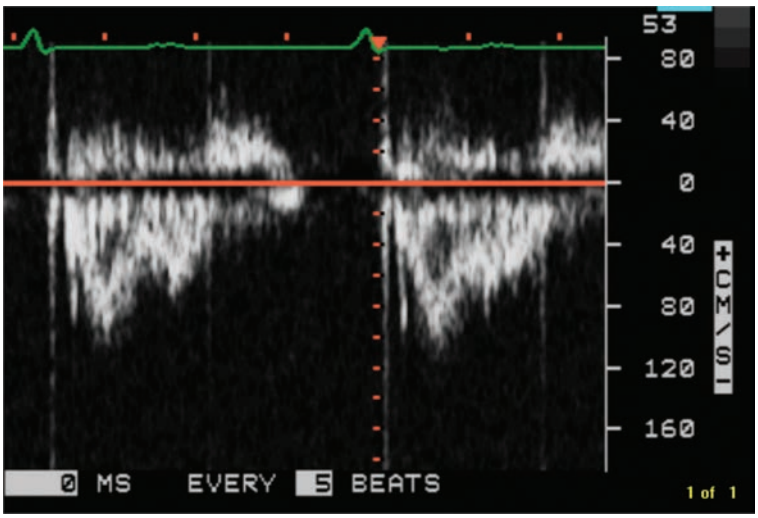


Figure 5.72

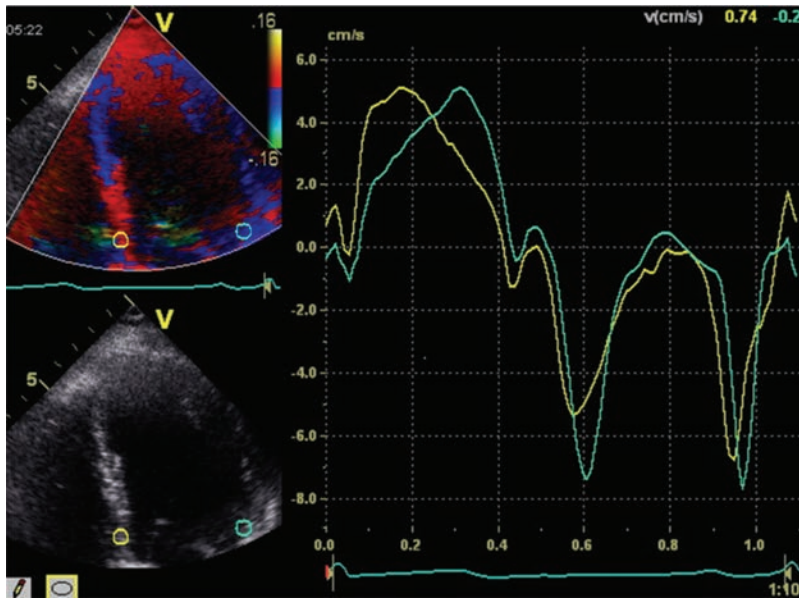


Figure 5.73

5.74. In Figure 5.74, what are the signals from the septum and LV lateral wall of?

- **A.** LV strain
- **B.** Strain rate
- **C.** Velocity
- **D.** None of the above

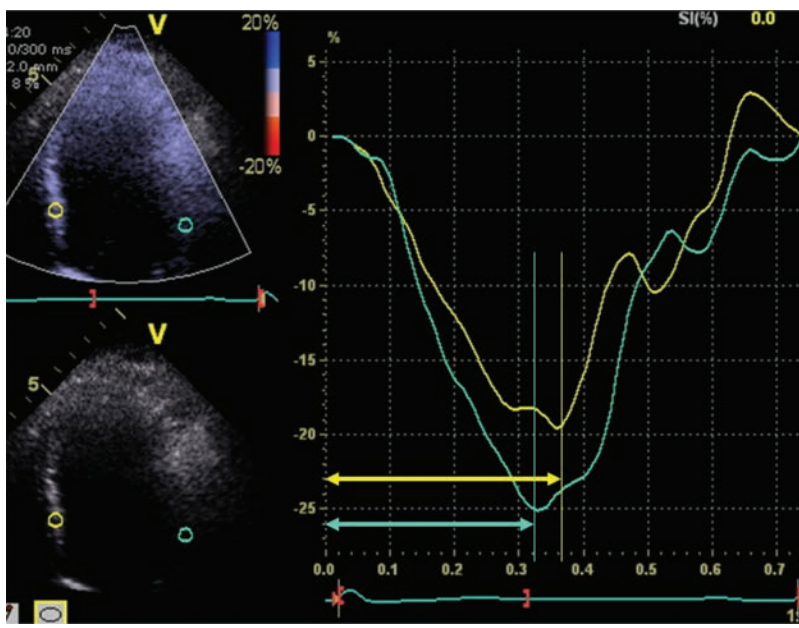


Figure 5.74

5.75. In the TEE image in Figure 5.75, what does the downward-pointing arrow refer to?

- **A.** Aortic valve
- **B.** Vegetation on the aortic valve
- **C.** Aortic subvalvular membrane
- **D.** Aortic dissection

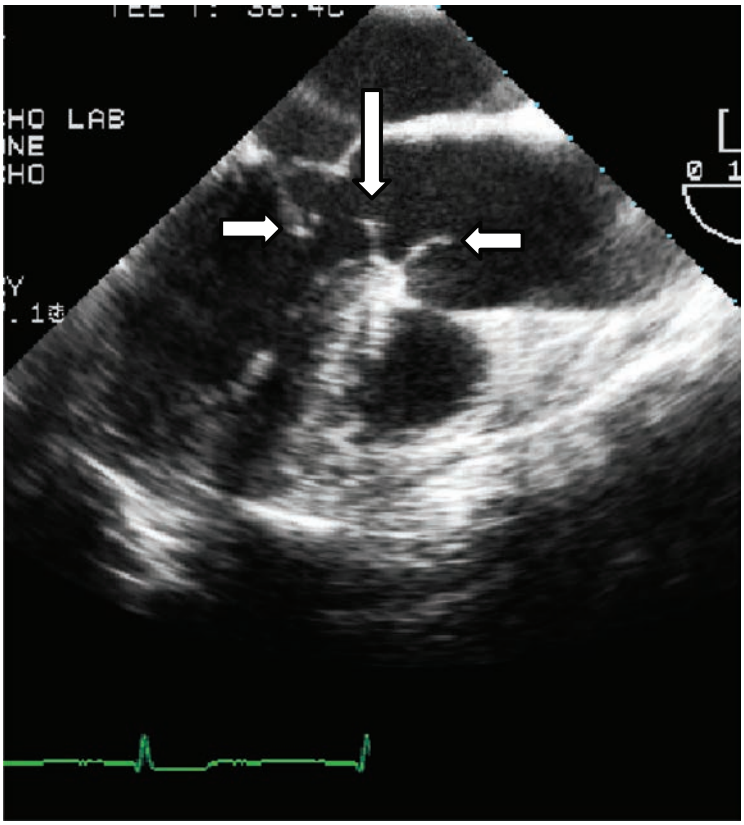


Figure 5.75

5.76. What does the arrow on the TEE image in Figure 5.76 point to?

- **A.** Coronary artery
- **B.** Aortic valve ring abscess
- **C.** Artefact
- **D.** Coronary sinus

5.77. What is depicted for the patient in Figure 5.77?

- **A.** Dilated coronary sinus and dextrocardia
- **B.** Dilated coronary sinus and levocardia
- **C.** Cor triatriatum
- **D.** Aneurysm of circumflex coronary artery

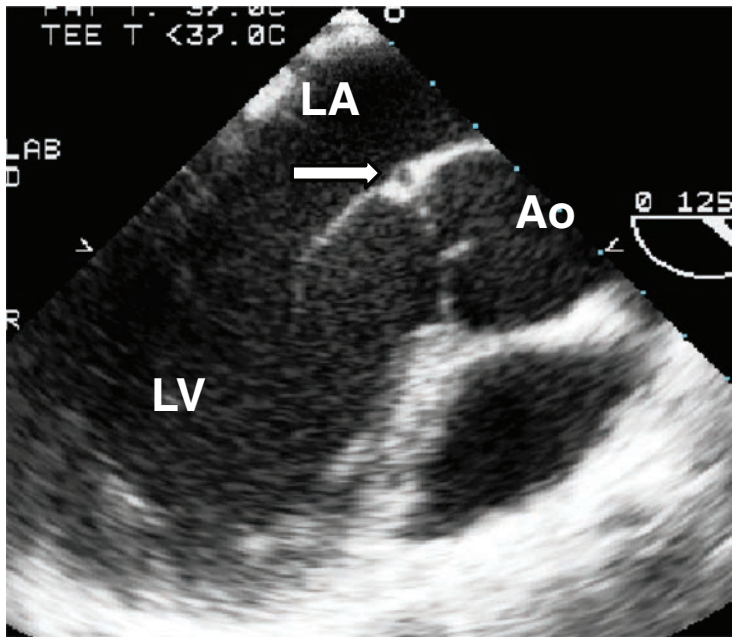


Figure 5.76

(a)

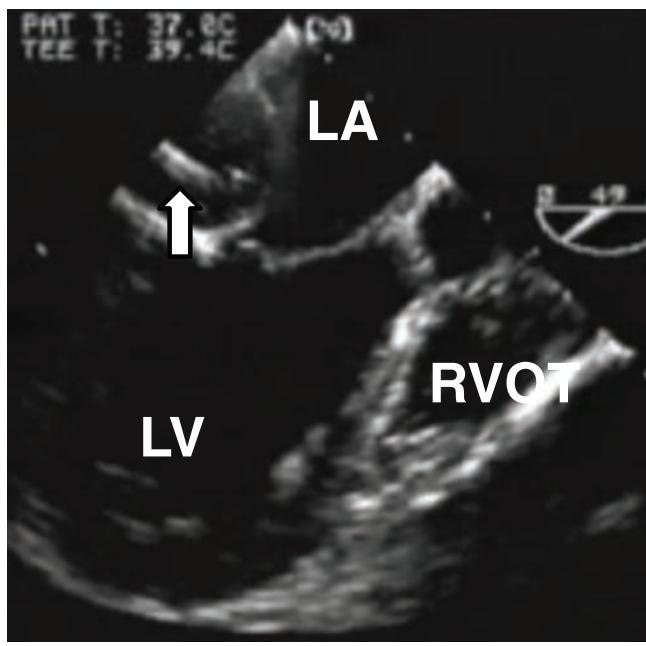


Figure 5.77

(b)

Figure 5.77 (*Continued*)

5.78. What does the arrow point to in Figure 5.78? (DTA: descending thoracic aorta)

A. Aortic aneurysm
B. IVC
C. Dilated azygos vein
D. Mirror image artefact

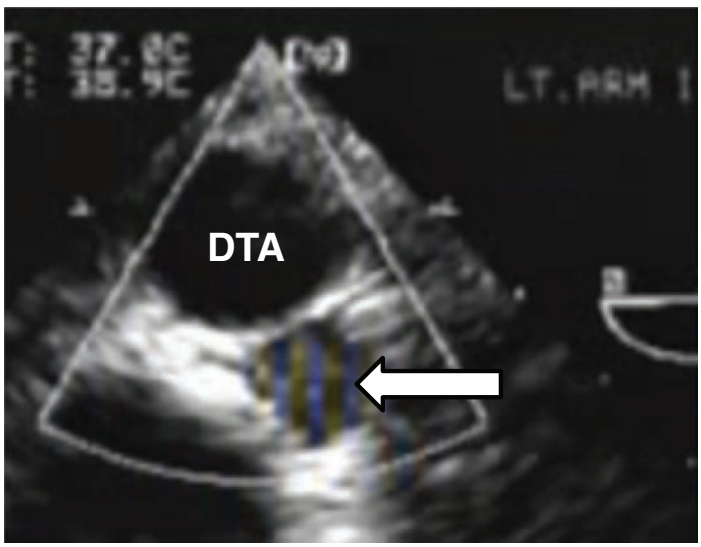


Figure 5.78

Answers

5.1. C. Decrease sector angle.

Increase in frame rate occurs with reducing sector angle and reducing depth, the former by reducing scan lines and the latter by reducing ultrasound transit time. It is independent of transmit frequency and power.

5.2. C. Beam focusing.

Focusing increases lateral resolution. Increasing transducer diameter and increasing frequency also increase lateral resolution.

5.3. D. Increasing transmit frequency.

Increasing the transmit frequency will reduce the wavelength and hence the spatial pulse length. This will increase the pulse repetition frequency and the axial resolution. Beam diameter and focusing have no effect on axial resolution.

5.4. C. Ability to record higher velocities.

Aliasing and range specificity are properties of pulsed-wave Doppler. Continuous-wave Doppler is not associated with range ambiguity. Continuous-wave Doppler will also permit recording of higher velocities than pulsed-wave Doppler will, as it is not limited by the pulse repetition frequency as transmitted ultrasound is continuous.

5.5. C. Severe MR.

Jet area underestimates the severity of MR as the driving pressure is low. The regurgitant flow rate is approximately 200 cm^3/s. Because of low left ventricular (LV) systolic pressure of 80 mmHg, the MR velocity would be in the range of 4 m/s (400 cm/s) assuming a left atrial (LA) pressure of 16 mmHg. Hence, the effective regurgitant orifice (ERO) area would be about 200/400, or 0.5 cm^2. Hence, in an intraoperative setting, it is important to bring up the blood pressure before performing MR quantitation.

5.6. D. Increasing the blood pressure.

Underestimation of MR can occur due to undersampling in the setting of low frame rate (increasing sector angle and depth) and high heart rates. Increasing blood pressure will increase the driving pressure across the mitral valve, and hence the jet size will increase because of a combination of an increase in regurgitation as well as higher kinetic energy in the jet imparted by higher driving pressure. Jet size is proportional to its kinetic energy. Wall-hugging jets tend to be smaller than free jets because of loss of jet energy to the wall.

5.7. A. 5.5 L/min.

The stroke volume equals the cross-sectional area multiplied by the TVI of the LVOT, which is $3.14 \times 1 \times 1 \times 25 = 78$ cm^3. Cardiac output equals stroke volume multiplied by heart rate: $78 \times 70 = 5.5$ L/min.

5.8. D. Cannot be calculated based on data given.

In a patient with serial stenosis in close proximity, the continuity equation cannot be applied because of difficulty in obtaining precise subvalvular velocity and cross-sectional area of the flow in the LVOT. In a person without SAM the cross-sectional area of subvalvular flow is roughly equal to the cross-sectional area of the LVOT. Subvalvular obstruction will result in flow streams such that the cross-sectional area of flow is less than the anatomic LVOT area.

5.9. C. Severe.

Regurgitant volume is $140 - 80 = 60$ cm^3/beat and regurgitant fraction is $60/140 = 43\%$. ERO area is regurgitant volume/TVI of aortic signal: $60/100 = 0.6$ cm^2. The regurgitant fraction in AR depends not only on ERO, but diastolic period and driving pressure. Hence, the ERO area is a more reliable index of AR volumetric severity. An ERO area of ≥ 0.4 cm^2 is indicative of severe AR.

5.10. A. Overestimate the valve area.

In the presence of severe AR, the pressure half-time is decreased due to a rise in LV diastolic pressure produced by AR. Hence, in the calculation of mitral valve area by the pressure half-time method the valve area will be overestimated or MS severity will be underestimated. Pressure half-time is decreased due to increase in late LV diastolic pressure, causing a reduction in the LA–LV pressure gradient.

5.11. A. Severe AS.

This is an AS signal. Please pay attention to the onset of the signal, which is sometime after the onset of QRS indicative of signal arising during ejection. Typically a peak gradient >80 mmHg and a mean gradient of 40 mmHg are indicative of severe AS, though these are flow dependent. Valve area is a better indicator of severity of AS. MR signal starts with QRS. Tricuspid regurgitation (TR) signal in severe pulmonary hypertension also starts with QRS. (See Box 5.3.)

5.12. C. 0.5 cm^2.

By the continuity equation $A1 \times V1 = A2 \times V2$. Hence the aortic valve area ($A2 = A1 \times V1/V2$) is approximately $3.14 \times 1 \times 1 \times 1/6 = 0.5$ cm^2.

5.13. A. Wide-open pulmonary regurgitation (PR).

Note the rapid deceleration of the PR signal with rapid equilibration of late diastolic pulmonary artery (PA) and right ventricular (RV) pressures. The increased systolic flow velocity is due to increased flow secondary to wide-open PR. Note that from this TEE view you are looking at the pulmonary valve from above (i.e., the PA side), unlike a parasternal short-axis view.

5.14. B. Elevated LA pressure with elevated EDP.

The rapid D-wave deceleration with time <170 ms indicates high LA pressure. In addition, the S wave is smaller than the D wave. The atrial reversal wave duration is about 220 ms. The normal duration is about 80–100 ms. This is due to increased duration of atrial systole having to pump against elevated LV EDP. Pulmonary vein atrial regurgitation duration greater than mitral A-wave duration is indicative of high LV EDP.

5.15. B. High LA pressure.

This inflow pattern shows a high E/A ratio. The deceleration time is also short, suggestive of high LA pressure. In pure atrial mechanical failure the E wave is normal, with diminished mitral A-wave amplitude.

5.16. B. Tricuspid atresia.

The atretic tricuspid valve is shown. There was no atrial septal defect (ASD), and outflow from right atrium was through right atrium to PA shunt. Patient also had a superior vena caval-right PA shunt. Both were patent. This would need low pulmonary vascular resistance and low PA pressure. This patient has a nonrestrictive ventricular septal defect (VSD), and hence RV systolic pressure would be the same as LV systolic pressure and to maintain low PA pressure the RV outflow

should be minimal or nonexistent. In this patient this was accomplished surgically with banding of the PA.

Right atrial thrombus in this patient with tricuspid atresia is due to stasis.

5.17. B. Ostium secundum ASD.

Primum ASD would be in the lower part of the septum and may involve anterior mitral leaflet and A–V conduction. Sinus venosus ASD is in the upper septum near the superior vena cava and may also be associated with anomalous drainage of the right upper pulmonary vein. There is also a rare type of sinus venosus ASD in the vicinity of the inferior vena cava (IVC). In unroofed coronary sinus, the shunt is from left atrium to right atrium through a posterior defect into the coronary sinus such that flow goes through the coronary sinus into the right atrium.

5.18. D. Flow across ASD.

This biphasic flow with a systolic–early diastolic component and LA contraction is typical of ASD flow. Pulmonary vein flow and superior vena cava flow would be triphasic, with distinct systolic and diastolic flows with reversal and atrial contraction. Mitral flow has only diastolic components with early and late diastolic components.

5.19. A. 12.8 L/min.

The shunt flow per beat can be calculated as the product of the TVI of the shunt flow and the anatomic area of the defect. This would be $39 \times 3.14 \times 1.5 \times 1$ cm^3/beat (183 cm^3). This multiplied by the heart rate gives the shunt flow per minute.

5.20. A. Rheumatic heart disease.

The patient has classic rheumatic MS. The anterior leaflet is thin with a hockey-stick appearance in diastole, which occurs due to commissural fusion. In degenerative MS there is severe annular calcification, which extends into the leaflets causing stenosis. In fen–phen valvulopathy the leaflets are thick and fibrosed and may result in both MS and MR. Ischemic involvement of the left ventricle without papillary muscle rupture causes restriction of closure and functional MR and not MS. Also note severe smoke-like echo or spontaneous echo contrast in the left atrium and layered thrombus in the body of the left atrium at the top of the image.

5.21. D. Bicuspid aortic valve.

This patient has Epstein's anomaly. Note the downward displacement of the septal leaflet of the tricuspid valve compared with the mitral leaflet attachment. A displacement of >8 mm/m^2 is suggestive of Epstein's. The septal leaflet may be large, sail-like, and adherent to the ventricular septum. This is frequently associated with ASD, right-sided accessory pathway, and TR, but not with bicuspid aortic valve.

5.22. A. Normal mitral valve motion.

This M mode is suggestive of normal mitral valve motion. There is normal mitral valve opening with greater early diastolic opening compared with opening associated with LA contraction. Valvular MS would cause mitral leaflet thickening, reduced opening and reduced ejection fraction (EF) slope, and paradoxical anterior motion of the posterior leaflet during diastole because of commissural fusion. Severe AR may cause fluttering of the anterior mitral leaflet and premature closure of the anterior mitral leaflet as the mitral valve opening is flow dependent. Features

of high LA pressure will include predominant early opening, rapid EF slope, and a smaller opening with atrial contraction mirroring the transmitral inflow pattern.

5.23. C. Biventricular pacemaker or implantable cardioverter-defibrillator (ICD).

The arrow here depicts a lead in the coronary sinus and is consistent with a biventricular pacemaker.

5.24. A. LA appendage.

The structure denoted by the arrow is the LA appendage. This is separated from the left upper pulmonary vein, which is to the posterior with a ridge popularly known as the "coumadin ridge" because of the potential to be misinterpreted as a thrombus. Because this ridge is echo reflective, sometimes one can see thrombus-like artifacts in the appendage as mirror image artifacts. Though the appendage is clearly visualized here, this view alone is not sufficient to rule out a thrombus. Multiple tomographic views have to be obtained through the appendage in its entirety as the appendage may have multiple lobes.

5.25. B. Subvalvular AS.

The structure attached to the septum below the aortic valve is a classic subaortic membrane. Occasionally, vegetations can be seen here due to seeding from the aortic valve. This is a diastolic frame, and hence aortic valve opening cannot be evaluated.

5.26. A. Left heart failure.

The mitral inflow shown here is indicative of high LA pressure. Though the patient is in atrial fibrillation with only E wave, the E wave deceleration is very rapid, with a deceleration time of 100 ms.

5.27. D. Dilated cardiomyopathy.

There is a four-chamber dilatation. There is no increase in wall thickness to suggest HOCM. In ASD both the right ventricle and the right atrium will be dilated due to volume overload with normal LA and LV size. The tricuspid valve position is normal and hence does not support the diagnosis of Ebstein's anomaly.

5.28. A. P2 tethering.

This is an apical long-axis view, showing A2 and P2 scallops of the mitral valve. The MR jet is directed posterolaterally toward P2, consistent with P2 tethering. A similar jet direction can also occur in A2 prolapse, but both leaflets coapt distal to the plane of the mitral annulus. Bileaflet prolapse of equal magnitude will result in a central jet.

5.29. A. Penetrating injury to the interventricular septum.

A defect is seen in the ventricular septum. This patient had a penetrating injury to the septum. The image does not support the presence of mitral valve prolapse or hypertrophic septum.

5.30. A. AS and AR.

Unlike the MR signal, the AS signal occupies only the ejection period and is absent during the isovolumic contraction time. Hence, the signal starts a few milliseconds after the QRS. The diastolic velocity is too high for MS. This order of gradient and LA pressure would be incompatible with life. VSD flow is predominantly systolic with a presystolic component caused by atrial contraction. The gradient across a coarctation is systolic; the duration increases with greater degrees

of stenosis and there may be a diastolic gradient. However, both the systolic and diastolic components will be in the same direction.

5.31. B. MS and MR.

Note that in TEE, from mid-esophageal location, the MR jet is directed toward the transducer.

5.32. A. Severe AR.

The aortic leaflets are thickened with rolled-up edges and a central coaptation defect in end diastole. This anatomy would be associated with wide-open AR, as the regurgitant orifice is visible by anatomic imaging. AS cannot be diagnosed by a diastolic frame. HOCM typically causes mid-systolic closure of the aortic valve, best visualized by M mode. Aortic dissection may cause AR by one of several mechanisms: dilatation of sino-tubular junction, leaflet tethering, extension of hematoma into the aortic leaflet causing it to prolapse, or as a result of a primary problem such as bicuspid aortic valve or annulo-aortic ectasia.

5.33. B. Chronic severe MR.

The MR signal density is more than 60% of the mitral inflow signal. This correlates with a volume of regurgitation. In addition, the mitral inflow velocity is increased without a slow deceleration. A slow deceleration would indicate significant MS. Despite severe MR, the profile of the MR signal is quite rounded without the rapid deceleration that would typically be seen in acute severe MR, because of the large LA V wave, the so-called "V wave cutoff sign." Note that the heart rate is 151 bpm. At rapid heart rates, MR may be grossly underestimated by color Doppler due to limited temporal resolution and continuous-wave Doppler is very helpful.

5.34. A. Central venous catheter-associated infection.

This bicaval transesophageal view shows a large mass in the superior vena cava, which is typically associated with a central catheter-associated thrombus or vegetation. This most likely is the cause of his sepsis and endocarditis. In addition, there is a possible defect at the superior portion of the fossa ovalis, suggesting a patent foramen ovale (PFO). This patient had a large PFO by color and contrast echocardiography, allowing paradoxical embolization of the bacterial mass to cause left-sided endocarditis, escaping the protective filtration mechanism offered by the lung.

5.35. A. Aortic valve vegetation.

The mass on the aortic valve is suggestive of mass on the left ventricular side of the aortic valve. This is suggestive of vegetation. Also, there is prolapse of the noncoronary cusp, causing significant AR, and this is due to leaflet destruction with endocarditis. The other mechanism for prolapse could be a bicuspid aortic valve with prolapse of the larger cusp. Node of Arantius, as the name suggests, is a nodular thickening of the central portion of the leaflet edge and is best visualized from the short-axis view of the valve. Lambl's excrescences are thin filamentous structures attached to the leaflet margin. There is no evidence of aortic dissection or intramural hematoma in this patient.

5.36. A. HOCM.

This late peaking dagger-shaped signal is typical of SAM caused by HOCM. This occurs due to the dynamic LVOT obstruction increasing through systole. Critical

valvular AS is unlikely, as in this case the velocity is likely to be higher (unless cardiac output is very low) and the signal contour would be more rounded. Acute MR gives rise to an early peaking signal with a rapid deceleration because of a large LA V wave, the so-called V wave cutoff sign. In LV cavity obliteration this signal will be much later peaking, with a gradient only in the very late part of systole when there is very little blood left in the distal LV cavity.

5.37. A. Bioprosthetic tricuspid valve.

This patient has Hancock porcine bioprosthetic tricuspid valve. The struts of the bioprosthetic valve are well seen. An annuloplasty ring would be seen as a small rounded structure in cross-section at the tricuspid annulus only.

5.38. B. Third heart sound.

The mitral inflow is suggestive of high LA pressure. The mitral E/A ratio is >2 and deceleration time is 60 ms, indicating very high LA pressure. The calculated E-wave deceleration calculated from the E-wave amplitude and its time (velocity/time) is about 20 m/s^2. A rate of deceleration of >8–9 m/s^2 is likely to result in S3. Age is relevant, as such a filling pattern in young children is normal because they have extremely efficient LV relaxation, which would result in physiological S3. S4 results from a prominent atrial-filling wave in a stiff ventricle, and in a summation gallop the E and A waves are fused. This patient has no MS, and hence opening snap is unlikely.

5.39. B. Severe MR.

The temporal continuity of the systolic signal with the inflow signal suggests its origin at the mitral valve. The AS signal would occupy only the ejection period, being separated from the mitral inflow signal by isovolumic contraction and relaxation periods. A small VSD may result in a holosystolic signal, but generally has a presystolic component associated with LA systole, and generally this flow is directed toward the transducer from most of the imaging windows.

5.40. C. 80 mmHg.

The TR velocity is 4 m/s, yielding an RV–RA systolic gradient of 64 mmHg. With an RA pressure of 20 mmHg the RV systolic pressure would be about 80 mmHg, which would be the same as the PA systolic pressure in the absence of significant PS.

5.41. A. Acute severe AR.

The late diastolic frame in Figure 5.41 shows diastolic MR. There is also AR by color. The mitral valve is closed prematurely. This combination of findings is consistent with acute severe AR. A smaller AR jet in late diastole was due to late diastolic equilibration of aortic and LV pressures. Diastolic MR results from the receipt of AR volume in a left ventricle with high operating end diastolic stiffness.

5.42. B. Acute AR.

The Doppler flow suggests premature closure of the mitral valve with lack of A wave despite being in sinus rhythm. This is pathognomonic of acute AR causing rapidly rising LV diastolic pressure due to failure to accommodate a large acute volume overload. In acute AR the left atrium would still be contracting, but would be unable to eject against an acute increase in afterload. Pulmonary vein flow profile in this patient would show a prominent AR wave, and the tricuspid inflow would still have the A wave. Acute MR and VSD would not eliminate the

A wave unless the patient had a recent episode of atrial fibrillation and the atrium is stunned.

5.43. C. Severe AR.

A prominent holodiastolic flow reversal suggesting retrograde flow in the aorta is seen. This flow would also cause Duroziez's murmur by physical exam due to the turbulence produced by partial occlusion by the finger, which would produce a diastolic murmur in the proximal femoral artery. Coarctation and middle aortic syndrome diminish pulsatility in the distal aortic flow and the flow becomes continuous due to flow through collaterals. Though HOCM can produce mid-systolic closure of the aortic valve, it does not produce any flow disturbance in the distal aorta.

5.44. A. Noncompaction of the left ventricle.

The inferolateral wall of the left ventricle in this patient is heavily trabeculated; noncompacted (trabeculated) to compacted wall thickness ratio is more than 2 : 1. This is highly indicative of noncompaction of LV myocardium, which is a developmental disorder causing congestive heart failure. In the other three conditions the LV myocardium would be thicker, either due to infiltration or increased myocardial mass.

5.45. A. IVC–right atrium junction.

Part of the proximal IVC is seen with entry of saline contrast, in the longitudinal plane from a TEE. With this orientation, caudal structures are seen on the left and cephalad structures are seen on the right. This patient has a prominent Eustachian valve, and in a patient with a prominent Eustachian valve, in a low esophageal view, where left atrium is not seen, this junction may be mistaken for an ASD. This patient was referred from an outside facility with that mistaken diagnosis from a TEE.

5.46. A. ~200 cm^3/s.

The regurgitant flow rate equals $2\pi r^2$ times the Nyquist limit. Here, the PISA radius is 0.9 cm and the Nyquist limit is 38 cm/s. Regurgitant flow rate is $2 \times 3.14 \times 0.9^2 \times 38 \approx 200$ cm^3/s.

5.47. C. Late-peaking systolic murmur increased by Valsalva's maneuver and normal A2.

This patient clearly has SAM of the anterior mitral leaflet causing LVOT obstruction. As the SAM increases in late systole, the gradient velocity and turbulence are more in late systole, causing a late-peaking late systolic murmur. SAM is increased by LV volume reduction and vasodilatation. A2 is preserved in these patients, in contrast to patients with severe AS, who may also have late-peaking systolic murmur.

5.48. A. HOCM.

This patient has HOCM with dynamic LVOT obstruction caused by SAM, which causes a late-peaking systolic gradient, increased by Valsalva's maneuver and amyl nitrate inhalation. The gradient would also be increased by positive inotropic agents and vasodilators and decreased by an increase in afterload, with vasoconstrictors or handgrip. In addition to HOCM, SAM can occur in volume-depleted states with small left ventricle cavity and also after surgical mitral valve repair in patients with long anterior and posterior leaflets, especially if a small annuloplasty ring is used.

5.49. A. Apical HOCM.

This patient has disproportionately thickened LV apical myocardium typical of apical HOCM. This results in a spade-shaped LV cavity in diastole. These patients also have giant T-wave inversions in their chest leads. In hypertensive heart disease, LV hypotension is more uniformly distributed. Endomyocardial fibrosis causes apical obliteration due to endocardial thickening rather than myocardial thickening.

5.50. C. PFO closure device.

The image shows two parallel discs sandwiching the upper atrial septum. The RA disc is larger than the LA disc. This is suggestive of an Amplatzer PFO closure device. In an ASD closure device, the LA disc is larger than the RA disc. Patch repair of the septum will not show the triple-layer morphology as seen here.

5.51. C. Vegetation on a bioprosthetic valve.

This is a short-axis view of the tricuspid valve, best obtained from a proximal gastric location, with clockwise probe rotation at about 20–30°. The sewing ring of the prosthetic valve is clearly seen here, and there is a mass attached to the leaflets indicative of vegetation.

5.52. A. Paradoxical embolism.

Figure 5.52 shows the interatrial septum with a large PFO in its typical location. The color flow shows left to right flow. This flow would reverse under situations of increased RA pressure, such as straining, coughing, and right heart failure. The orientation of the opening is favorable for thrombi originating in the IVC region to traverse the PFO to the left atrium even in the absence of raised RA pressure.

5.53. C. Fistulous communication between aorta and right ventricle.

In addition to the fistulous communication, Figure 5.53 also shows AR. Fistulous communications generally result from rupture of an aortic root abscess. This may result in communications to the right atrium, right ventricle, PA, or the LVOT. Other local complications include abscess of mitral aortic intervalvular fibrosa, leaflet aneurysm, and perforation of the anterior mitral leaflet. One may also get an abscess in the ventricular septum, causing a VSD after rupture.

5.54. B. Pulmonary valve endocarditis.

This is a mid-esophageal image showing the aortic valve in short axis in the center and the RV inflow and outflow wrapped around it akin to the short axis of the aortic valve from a parasternal view. There is a large mass attached to the pulmonary valve consistent with vegetation. This is the likely source of his lung abscesses.

5.55. A. Coronary sinus.

Figure 5.55 is a low esophageal view partially cutting through the posterior A–V groove showing the coronary sinus.

5.56. C. Severe.

This is severe as judged by jet size, vena contract, and PISA radius. In addition, the two-dimensional image shows lack of tricuspid leaflet coaptation, leading to wide-open TR. The mechanism is tricuspid annular dilatation, and hence is functional, probably secondary to previous pulmonary hypertension due to mitral valve disease resulting in RV and RA dilatation, thus stretching the tricuspid annulus. This is repairable with tricuspid annuloplasty. Also note the partly seen mitral

prosthesis. TR quantitations by using the three components of the jet are not well validated.

5.57. C. Moderate or severe pulmonary hypertension.

In patients with wide-open TR, the tricuspid valve may be fairly nonrestrictive, allowing right ventricle and right atrium to behave virtually as a single chamber during systole. In such a situation the TR pressure gradient cannot reliably be calculated using the simplified Bernoulli equation as a considerable amount of energy may be expended in causing acceleration of the TR jet. In addition, RA pressure may be very high, leading to underestimation of PA pressure. In this example, one can count the number of aliases to estimate the TR velocity at the vena contracta. There are four aliases, corresponding to a velocity of 69 cm/s × 4; that is, 2.76 cm/s. Though the pressure gradient is 30 mmHg, the patient is likely to have very high RA pressure (i.e., 20–30 mmHg), and because of wide-open TR the TR pressure gradient would have underestimated the pressure gradient. Hence, the PA systolic pressure is at least moderate but more likely to be in the severe range in the absence of PS. In such patients, careful examination of the pulmonary regurgitant jet to get an estimate of PA diastolic pressure would be helpful.

5.58. D. Replacement with a mechanical valve.

This prosthesis probably is a bileaflet valve in view of the two areas of reverberations seen in the left atrium. A bioprosthetic valve would show struts in the periphery and thin leaflets in the center, unless calcified. An annuloplasty ring is an echo-dense structure at the base of the mitral leaflet on the LA side with intact leaflets. This ring can be partial or complete. An Alfieri stitch can be central or asymmetric and is simply a stitch that focally unites the tips of anterior and posterior leaflets and converts the mitral orifice into a double orifice, best seen in short-axis view.

5.59. D. All of the above.

Pre-intervention mitral flow is indicative of high LA pressure. This pattern is seen despite a heart rate of 92 bpm, as faster heart rates result in atrial predominance of ventricular filling. Post intervention the mitral flow is suggestive of impaired left ventricular relaxation, which is consistent with normal or low mean LA pressure. Note that the heart rate is slower at 62 bpm. This patient had dilated cardiomyopathy with severe functional MR, which responded to diuresis and afterload reduction with a reduction of LV size and elimination of MR. Uncontrolled hypertension will reduce LV ejection performance, increase LV size, and give rise to MR, as myopathic ventricles are exquisitely sensitive to afterload. As these patients have little or no functional reserve, anemia has a serious and deleterious effect on hemodynamics because of a reduction in oxygen-carrying capacity and a demand for higher cardiac output.

5.60. A. Thoracic aortic aneurysm.

The thoracic aorta runs posterior to the left atrium, is rounded, and on dynamic imaging is pulsatile. Turning the imaging plane by 90° would show the long axis of the descending aorta. The membrane of cor triatriatum separates the pulmonary venous chamber from the lower part of the atrium and is best seen from parasternal long-axis and apical views. The location is across the left atrium. Left PA is not seen in the posterior mediastinum.

5.61. C. HOCM.

Note the SAM of the anterior mitral leaflet starting in midsystole. The SAM narrows the LV outflow tract in a dynamic manner, producing LV outflow obstruction and gradient. Elevated LV EDP is not an unreasonable response as deceleration of mitral A wave is slow, though not a classical B hump. Mitral valve prolapse results in late systolic sagging of the mitral valve, not anterior motion. Severe AR with a posteriorly directed jet on to the anterior mitral leaflet results in diastolic fluttering.

5.62. B. Elevated LV EDP.

Note the prominent B hump after the A point of mitral valve motion. In atrial fibrillation, there is loss of A wave. Also see explanation for Question 5.61.

5.63. C. Congestive heart failure.

This is typical of pulsus alternans, which occurs in severe systolic heart failure. Note there is reduced opening and duration of opening of the aortic valve with every other beat, and this results from reduced stroke volume with every other beat. Also note that,in this instance, pulsus alternans was triggered by a premature ventricular complex. In AS, there is leaflet thickening and reduced opening. In HOCM, there may be midsystolic closure of the aortic valve. Hypertension does not produce any characteristic changes in aortic valve motion.

5.64. B. MS with high LA pressure.

The diastolic signal "1" is that of MS, and this patient is in sinus rhythm as there is an A wave. The peak diastolic gradient is about 30 mmHg and mean gradient is 18 mmHg at a heart rate of 76 bpm, and this indicative of severe MS. The arrow points to isovolumic relaxation time (IVRT), which was 30 ms, indicating high LA pressure or large LA "V" wave. "2" indicates partial MR velocity, as it is contiguous with ending of the MS signal, and "3" indicates LV outflow and the gap between that and mitral inflow, which is indicated by the arrow in IVRT.

5.65. B. Hyperdynamic LV.

Systolic signal denoted by "1" is not MR, but due to LV cavity obliteration as it is late peaking and hence indicates a hyperdynamic LV. It also occurs during ejection phase, unlike an MR signal. IVRT indicated by the arrow is 110 ms (time between small marks is 200 ms and two vertical lines is 1 s), and this indicates normal LA pressure. IVRT is the Doppler equivalent of the auscultatory A2–OS interval; that is, interval between aortic component of second heart sound and opening snap in MS. A short A2–OS interval indicates severe MS.

5.66. D. Severe PR.

Signal "2" is early diastolic following an ejection flow "1" suggestive of origin at a semilunar valve. The arrow points to forward flow across the semilunar valve with atrial systole, and this can occur only at the pulmonary valve with normal PA pressure. If the PA pressure is high, atrial systole cannot generate a forward flow even when there is late diastolic equilibration of pressures between PA, right ventricle, and right atrium. For the same reason, you do not get forward flow across the aortic valve in severe AR as aortic diastolic pressure is too high and high LV diastolic pressure may cause premature closure of the mitral valve. The diastolic flow is of low velocity and ends in mid-diastole, indicating severe PR with normal PA pressure.

5.67. C. Severe PS and PR.

This patient in fact had a bovine jugular nonvalved conduit between the right ventricle and PA for pulmonary atresia in a foreign country during infancy and presented with shortness of breath and edema. As the conduit has become too small for her body size and flow requirements, it was functionally stenotic, resulting in a very high systolic gradient. The longer arrow points to the PR signal. The PR is severe and also it rapidly decelerates with equilibration of pressures between PA and right ventricle. Shorter arrow indicates forward flow with RA systole; this indicates normal PA pressure.

5.68. C. Suprasternal window.

This is a classic flow because of severe coarctation of the aorta with systolic and diastolic components. The signals are negative or flow is going away from the transducer. This signal is obtained from the suprasternal window.

5.69. C. Patent ductus arteriosus (PDA).

This is a typical PDA flow obtained from a parastenal short-axis basal view with clockwise rotation of the probe to show PA and branches. "1" indicates dilated main PA and "2" arch/descending aortic junction from which flow is occurring into PA. Note this is a diastolic frame (see marker on electrocardiogram) and flow is into the main PA; hence, not left PA branch stenosis.

5.70. A. Aortic coarctation.

Note that the flow is into the aortic lumen throughout the cardiac cycle, indicative of retrograde flow in the intercostal artery. This occurs in collateral dependent distal perfusion as it occurs in severe aortic coarctation. This patient had interrupted aorta. In severe AR, holodiastolic retrograde flow occurs in the aortic lumen.

5.71. B. Severe MR.

This flow is across the foramen ovale due to excessive stretching produced by high atrial pressures. The flow is from left atrium to right atrium, and note that the highest velocity is in late systole, indicative of a large LA "V" wave which occurs in severe MR. In large ASD, flow will be nonrestrictive across the defect, resulting in very low or transient pressure gradients.

5.72. A. Pulmonary hypertension.

This is a typical "flying W sign" associated with pulmonary hypertension. Midsystolic deceleration occurs because of rapidly returning reflected pressure waves secondary to a stiffer PA that occurs when it operates under high pressure. These is no PR signal and no continuous-wave signal to assess if there is a gradient across the pulmonary valve. The velocity of the signal is under 1 m/s, indicating normal amount of PA flow, and this inconsistent with a large ASD. Large ASD is associated with increased PA flow.

5.73. A. LV systolic dyssynchrony.

Tissue Doppler or tissue velocity images are shown here. Focal velocity profiles of medial (yellow) and lateral annulus (green) are produced offline by placing samples in these regions. Note that the peak of lateral annulus velocity is about 150 ms after the medial annulus velocity peak, suggestive of septolateral mechanical dyssynchrony. A septolateral delay of >65 ms is indicative of LV dyssynchrony. There was good diastolic synchrony, as judged by annular E wave velocity profiles.

5.74. A. LV strain.

Note that the units are in percent, which is percentage shortening compared with original length. Normal myocardial strain is 15–20%, very similar to percentage sarcomeric shortening during contraction of cardiac muscle cell.

5.75. C. Aortic subvalvular membrane.

This is a classic example of membranous subaortic stenosis. Also note part of this circumferential membrane on the LV side of the anterior mitral leaflet. The image also shows the aortic valve (left-pointing arrow) and the SAM of the anterior mitral leaflet (right-pointing arrow).

5.76. A. Coronary artery.

This was anomalous circumflex coronary artery originating from right coronary artery with retroaortic course between aorta and left atrium. Note that it is small and perfectly circular unlike an abscess, which tends to have irregular edges and inflammatory thickening or other sequelae around it. One can study the course of the vessel by imaging this structure in different imaging planes. Coronary sinus would be in the posterior atrioventricular (AV) groove.

5.77. A. Dilated coronary sinus and dextrocardia.

Note opacification of the structure at the AV groove with saline contrast, indicating anomalous connection of left or right or entire superior vena cava into coronary sinus (as it is not specified which arm was injected). Also note a pacemaker lead in the coronary sinus. At an angle of 49°, the LVOT is on the right side, indicating dextrocardia. This view is typically obtained at 120–140° with levocardia – sort of a mirror image.

5.78. C. Dilated azygos vein.

This is a typical appearance. This patient had an interrupted IVC, and the IVC drained through the azygos vein into the superior vena cava. The IVC does not relate to the thoracic aorta. A mirror image artifact looks like a duplicate image of the DTA.

Box 5.1 Key Practical Pearls

- Higher transducer frequency results in better resolution, but reduced penetration. Better color flow images are obtained at lower transducer frequency.
- To increase frame rate, reduce depth or sector angle and eliminate color flow if you can. Reduce the color flow box width as narrow as possible to increase frame rate.
- Regurgitant jets are underestimated at low frame rates and low gain. Wall-hugging jets are smaller for a given severity because of loss of kinetic energy at the jet–wall interface. Jet size depends on kinetic energy contained in the jet, and hence is a function of both regurgitant flow rate and driving pressure.
- In AS assessment: zoom LVOT and clean up to see LVOT boundaries clearly, obtain V1 to minimize spectral dispersion and V2 from multiple window. For peak velocity of V1, get the peak but for TVI trace through modal velocity.
- In obtaining pressure half-time in MS, ignore the initial rapid ski slope, which is affected markedly by LV relaxation and recoil. Mean gradient depends on heart rate: lower at lower heart rate due to longer diastolic filling time. Mean gradient should be given along with heart rate.

- A TEE has a higher spatial resolution than a transthoracic echocardiogram because of higher carrier frequency.
- In the performance of TEE, get the key information first to answer the clinical question, just in case patient becomes intolerant of the procedure and the procedure needs to be abandoned. For example, when the question is rule out acute aortic dissection, examine ascending aorta first as its involvement mandates emergency ascending aortic repair. Then look at pericardial effusion, LV function, AR and its mechanism, extent of dissection, entry point location, coronary and arch vessel involvement, and so on. In suspected endocarditis, examine the left- and then right-sided valves first in a comprehensive fashion from midaortic location, which is most tolerable for the patient.

Box 5.2 Key Guideline Summaries

- Echocardiographic criteria for severe MR include jet area to LA area ratio >40%, jet area >10 cm^2, vena contracta diameter ≥7 mm, regurgitant volume ≥60 cm^3, regurgitant fraction ≥50%, ERO area ≥0.4 cm^2, or systolic flow reversal in any of the pulmonary veins. There may be a large coaptation defect in mitral valve closure mechanism. MR signal by continuous wave may be triangular, the so-called "V" wave cutoff sign due to large LA "V" wave. (Zoghbi *et al.*, 2003). In eccentric wall-hugging jets, jet size may be smaller by as much as 50% for a given regurgitant volume.
- Echocardiographic sign of severe MS is mitral valve area <1.0 cm^2 with or without supporting features of mean diastolic gradient of >10 mmHg or PA systolic pressure of >50 mmHg (Baumgartner *et al.*, 2009).
- Echocardiographic criteria for severe AS include aortic valve area <1.0 cm^2, indexed valve area <0.6 cm^2, V2 >4 m/s, mean gradient >40 mmHg, or velocity ratio (V1/V2) <0.25 (Baumgartner *et al.*, 2009).
- Severe AS with low gradient is said to exist when AV area <1 cm^2 and mean gradient <30 mmHg and can occur in those with both normal and low EF and is associated with high mortality which is reduced by AVR. Low-dose dobutamine echo can be used in these patients to differentiate from pseudo severe AS (increase in AV area with increase in cardiac output), true severe AS (mean gradient increases with increase in stroke volume, but AV area remains unchanged), or evaluate for contractile reserve (EF and cardiac output increase).
- Echocardiographic criteria for severe AR include jet height to LVOT diameter ratio ≥65%, jet area to LVOT area ≥60%, vena contracta diameter >6 mm, regurgitant volume ≥60 cm^3, regurgitant fraction ≥50%, ERO area ≥0.3 cm^2, or prominent holodiastolic flow reversal in descending aorta. AR pressure half-time may be <200 ms (Zoghbi *et al.*, 2003).
- Echocardiographic criteria for severe TR include jet area >10 cm^2, vena contracta diameter >7 mm, PISA radius >9 mm at a Nyquist limit of 50–60 cm/s, or systolic flow reversal in hepatic veins. There may be a large coaptation defect in tricuspid valve closure mechanism. TR signal by continuous wave may be triangular, the so called "V" wave cutoff sign due to large RA "V" wave (Zoghbi *et al.*, 2003).
- Criteria for severe tricuspid stenosis: mean diastolic gradient ≥5 mmHg, diastolic TVI >60 cm, pressure half-time ≥190 ms, tricuspid valve area by continuity equation ≤1.0 cm^2 (Baumgartner *et al.*, 2009).

- Echocardiographic criteria for severe PR include large jet size at origin, steep deceleration of PR signal by continuous wave often stopping in mid-diastole, increased pulmonary flow compared with systemic flow, and RV enlargement. Features are less quantitative (Zoghbi *et al*., 2003).
- Echocardiographic criteria for severe PS: peak systolic velocity >4 m/s or peak systolic gradient >64 mmHg (Baumgartner *et al*., 2009).

Box 5.3 Important Clinical Trial or Outcome Data Summaries

- **Cardiac resynchronization therapy (CRT) in narrow QRS cohort study.** In the Yu *et al.* (2006) study, of the 102 patients with class III or IV heart failure and EF <35%, 51 had QRSd <120 ms but had LV mechanical asynchrony by echo. Both groups had similar response to CRT in terms of 6 min walk test and reduction in LV volumes and MR and improvement in EF. Response rate in both groups was about 70%.
- **RethinQ trial.** In the Beshai *et al.* (2007), 172 patients with standard indication for ICD, QRSd <130 ms, and echocardiographic evidence of LV dyssynchrony were randomized to CRT versus no CRT. Primary endpoint was improvement in peak oxygen consumption. There was no improvement in peak oxygen consumption with CRT. Subgroup analysis showed improvement in those with QRSd >120 ms. The 6 min walk improved significantly in those with nonischemic cardiomyopathy and New York Heart Association class improved in both groups. The trial is criticized for poor echo data quality, three different core labs, lack of standardization, three different vendors, need to drop some data, and poor reproducibility.
- **Echo-CRT trial.** In the Ruschitzka *et al.* (2013) study, 809 patients with heart failure class III or IV, EF <35%, QRSd <130 ms, and echo evidence of LV dyssynchrony were randomized to ICD with CRT turned on or off. Of 1680, 809 patients had LV dyssynchrony. Primary endpoint was all-cause mortality and hospitalization for heart failure. The trial was stopped prematurely because of higher mortality in the CRT arm (hazard ratio 1.8, $p = 0.02$).

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Cardiac Magnetic Resonance Imaging

6

6.1. Magnetic resonance imaging (MRI) makes use of nuclei with unpaired spins. What is the nucleus used in image production?

A. Hydrogen-1
B. Carbon-13
C. Phosphorus-31
D. Sodium-23

6.2. What is the resonance frequency with a 1.5 T scanner?

A. 63 MHz
B. 42 MHz
C. 126 MHz
D. None of the above

6.3. How is spatial localization of signal origin achieved?

A. Magnetic gradient
B. Timing of received RF signal
C. Timing of transmitted RF signal
D. All of the above

6.4. With which of the following is cardiac MRI generally not advisable in patients?

A. Automated implantable cardioverter defibrillator
B. Cerebral aneurysm clips
C. Iron-containing foreign body in the eye that has been there for 6 years
D. All of the above
E. None of the above

6.5. What are the potential effects of a strong magnetic field in a patient with a pacer or implantable cardioverter-defibrillator?

A. May burn the circuits
B. Heat generation at lead tip and tissue coagulation and rise in threshold
C. Reset device
D. All of the above

6.6. Gadolinium (Gd) does which of the following?

A. Shortens T1 and increases signal on T1-weighted images
B. Lengthens T1 and increases signal on T1-weighted images
C. Shortens T1 and reduces signal on T1-weighted images
D. Lengthens T1 and reduces signal on T1-weighted images

6.7. Which of the following can magnetic resonance (MR) coronary angiography be performed with?

A. Single breath hold
B. Multiple breath holds
C. With the use of a navigator pulse
D. None of the above

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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6.8. In the FIESTA or steady-state free precession (SSFP) MR image shown in Figure 6.8, what does "1" refer to?

A. Right ventricle
B. Left ventricle
C. Right atrium
D. Left atrium

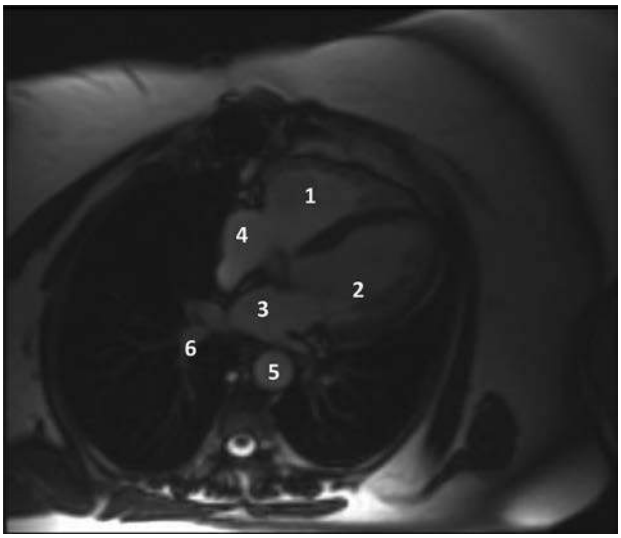


Figure 6.8

6.9. In the FIESTA or SSFP MR image shown in Figure 6.9, what does "2" refer to?

A. Right ventricle
B. Left ventricle
C. Right atrium
D. Left atrium

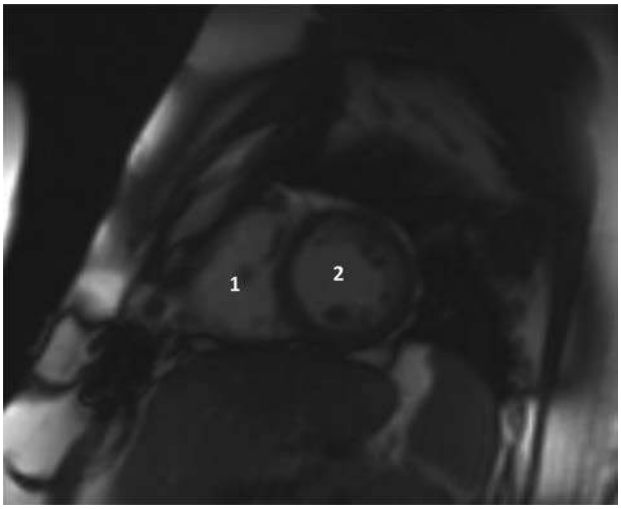


Figure 6.9

6.10. In the T1-weighted black blood MR image shown in Figure 6.10, what does "1" refer to?

A. Right ventricle
B. Left ventricle
C. Right atrium
D. Left atrium

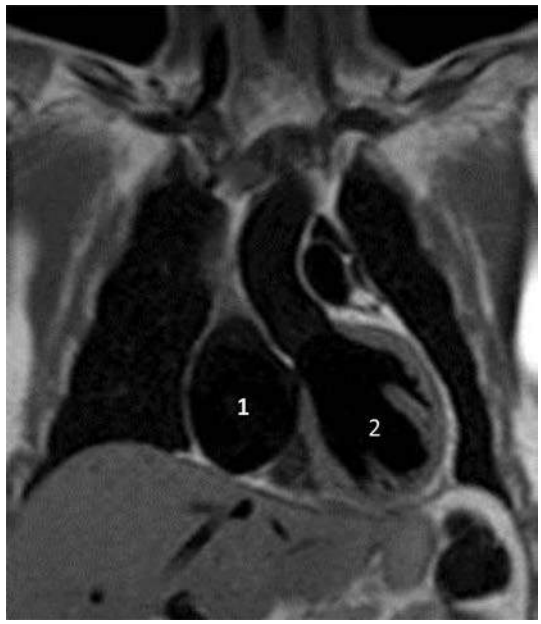


Figure 6.10

6.11. Figure 6.11 shows a delayed Gd-enhanced image in a patient with occluded left anterior descending (LAD) artery. What is the image indicative of?

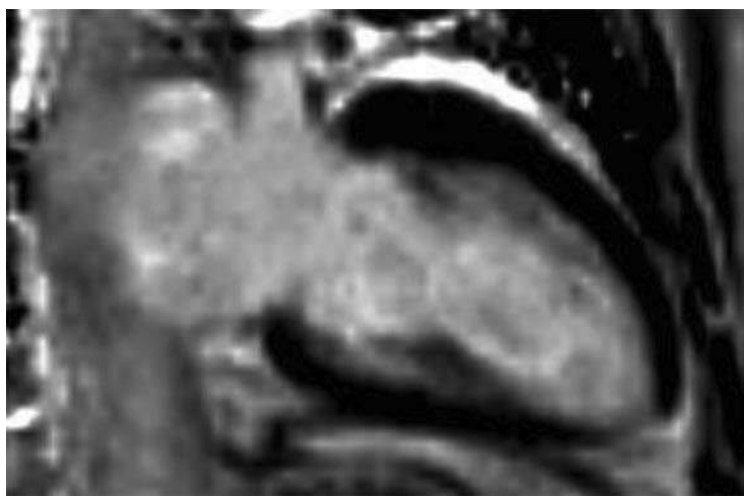


Figure 6.11

A. Scarred left ventricle anterior wall
B. Scarred left ventricle inferior wall
C. LAD area looks fully viable
D. None of the above

6.12. What does the MRA in Figure 6.12 show?
A. Pulmonary artery branch stenosis
B. Pulmonary infundibular stenosis
C. Normal pulmonary veins
D. None of the above

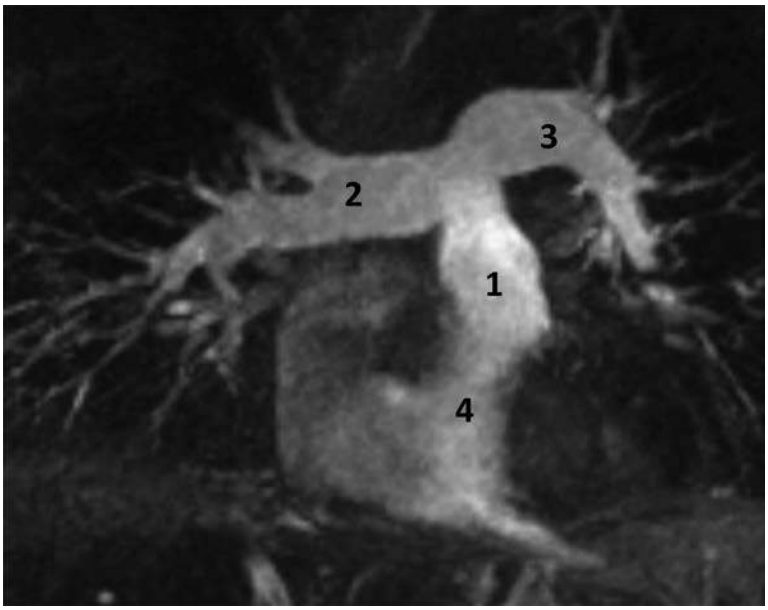


Figure 6.12

6.13. What does the image in Figure 6.13 show?
A. T1-weighted image
B. FIESTA image
C. Contrast-enhanced MRA
D. None of the above

6.14. Which of the following statements about Figure 6.14 are accurate?
A. It is a volume-rendered MRA image
B. Gd contrast was used for imaging
C. 1, 2, and 3 refer to ascending aorta, main pulmonary artery (MPA), and pulmonary veins respectively
D. All of the above

6.15. What does the arrow point to in Figure 6.15?
A. Lipomatous atrial septum
B. Atrial myxoma
C. Sarcoma
D. Artifact

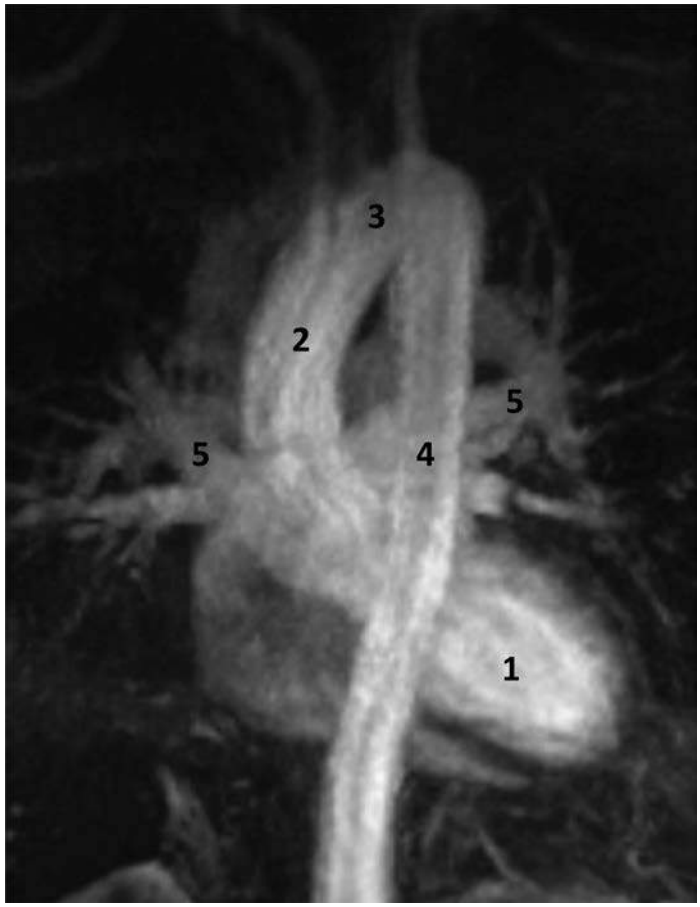


Figure 6.13

Figure 6.14

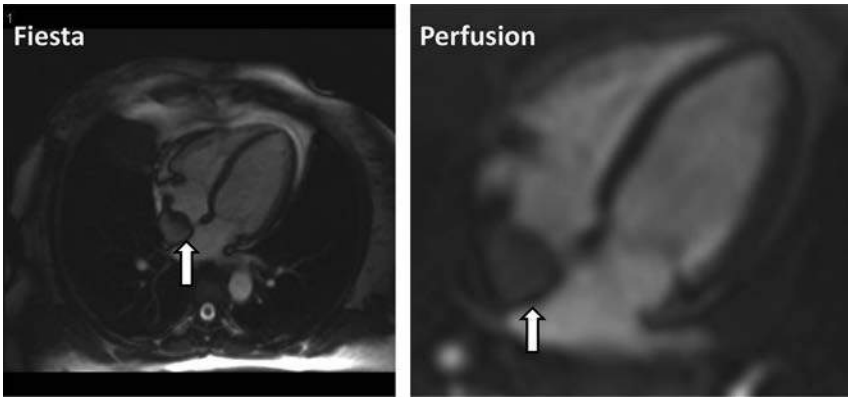


Figure 6.15

6.16. What is the patient in Figure 6.16 likely to have?

A. Heart failure
B. Pneumonia
C. Atrial septal defect
D. Descending aortic dissection

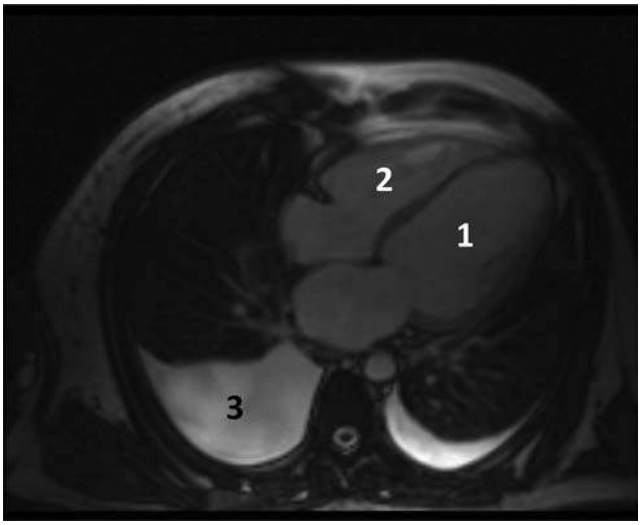


Figure 6.16

6.17. What is the patient in Figure 6.17 likely to have?

A. Multivessel coronary artery disease
B. Single-vessel circumflex disease
C. Extensive myocardial scarring due to prior infarcts
D. Normal coronary artery

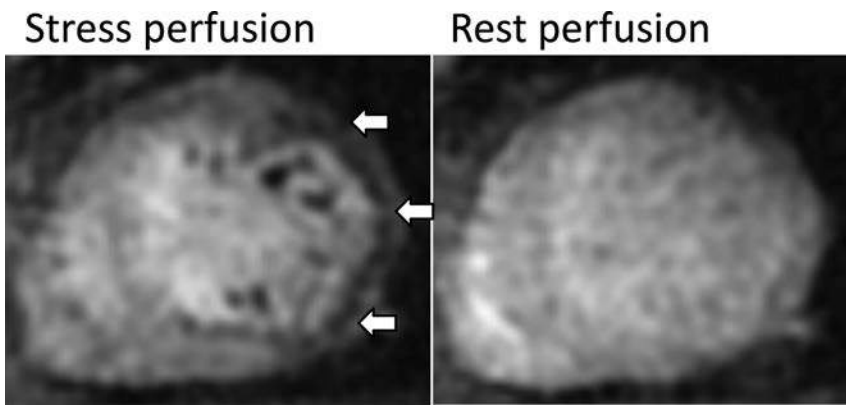


Figure 6.17

6.18. What is the patient in Figure 6.18 likely to have had?

A. Arrhythmogenic right ventricular dysplasia (ARVD)
B. Inferior myocardial infarction
C. Anterior myocardial infarction
D. Myocarditis

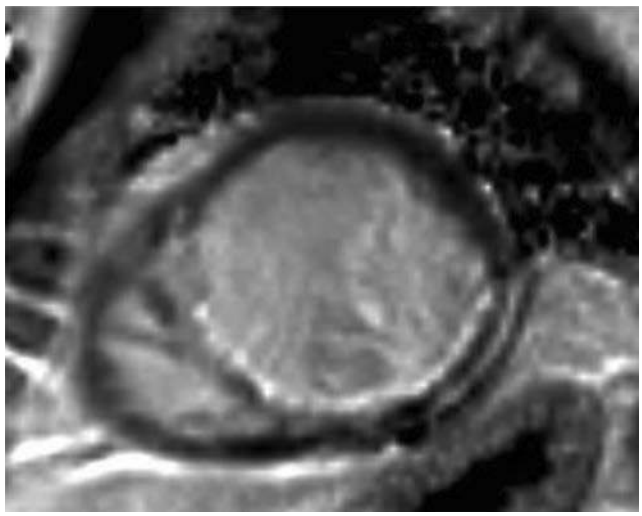


Figure 6.18

6.19. What is the patient in Figure 6.19 likely to have had?

A. ARVD
B. Inferior myocardial infarction
C. Anterior myocardial infarction
D. Myocarditis

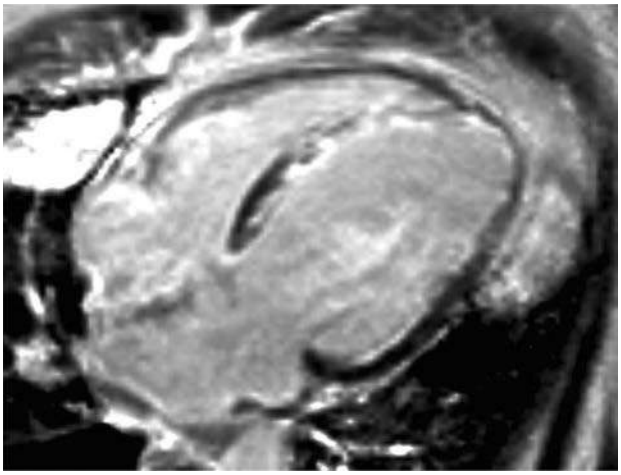


Figure 6.19

6.20. The patient in Figure 6.20 has severe left ventricle dysfunction. What is the etiology likely to be?

A. Left ventricle noncompaction
B. Myocarditis
C. Myocardial infarct with fatty replacement
D. Cardiac amyloid

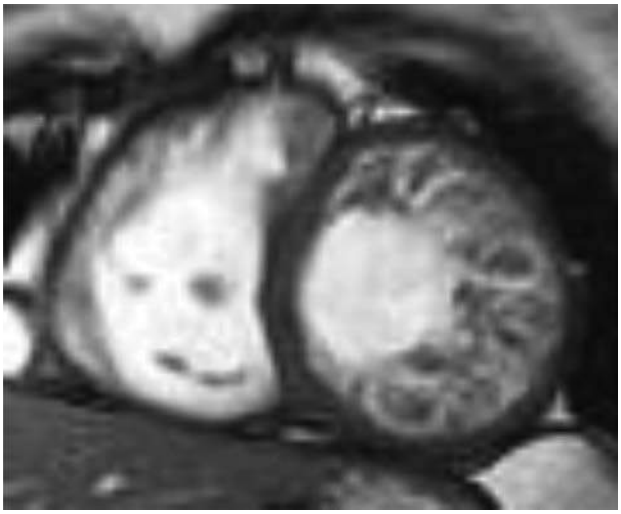


Figure 6.20

6.21. What is the patient in Figure 6.21 likely to have?

A. Bicuspid aortic stenosis
B. Aortic valve vegetation
C. Aortic dissection
D. None of the above

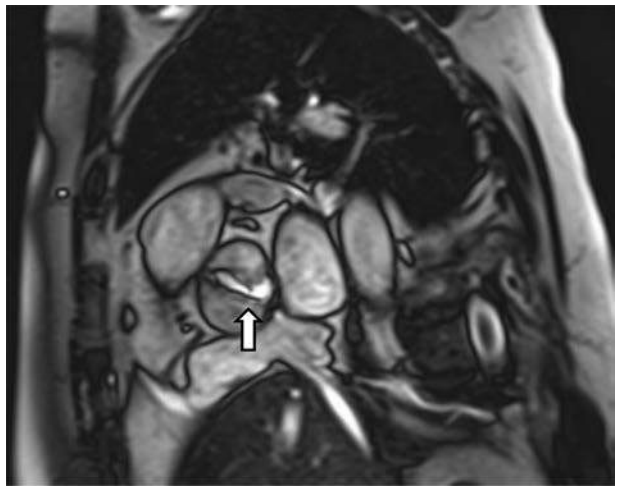


Figure 6.21

6.22. In the black blood cardiac MR image of the chest in Figure 6.22, what does the arrow point to?

A. Trachea
B. Right pulmonary artery
C. Left pulmonary artery
D. Aorta

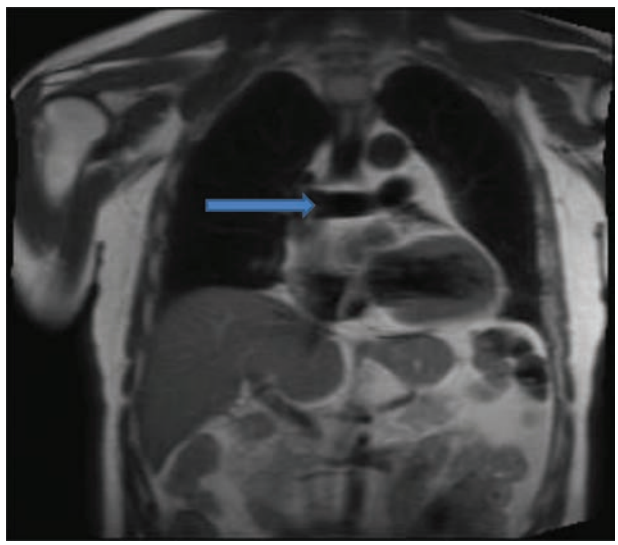


Figure 6.22

6.23. What structure does the arrow point to on the black blood cardiac MR image in Figure 6.23?

A. Trachea
B. Right main bronchus
C. Left main bronchus
D. Pulmonary artery

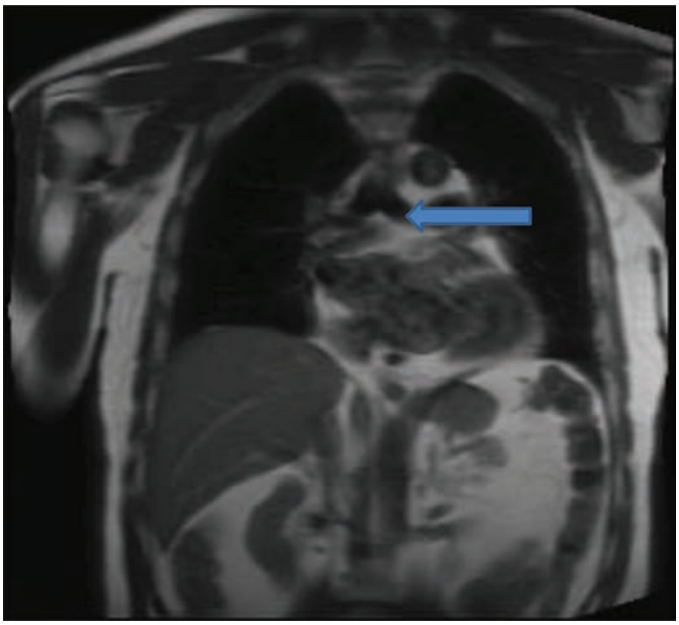


Figure 6.23

6.24. The 58-year-old male seen in Figure 6.24 complained of shortness of breath and palpitations (AO: aorta; LA: left atrium; LV: left ventricle). This patient probably has which of the following conditions?

A. Hypertrophic cardiomyopathy
B. Sigmoid shaped septum
C. Normal myocardium
D. Hypertensive heart disease

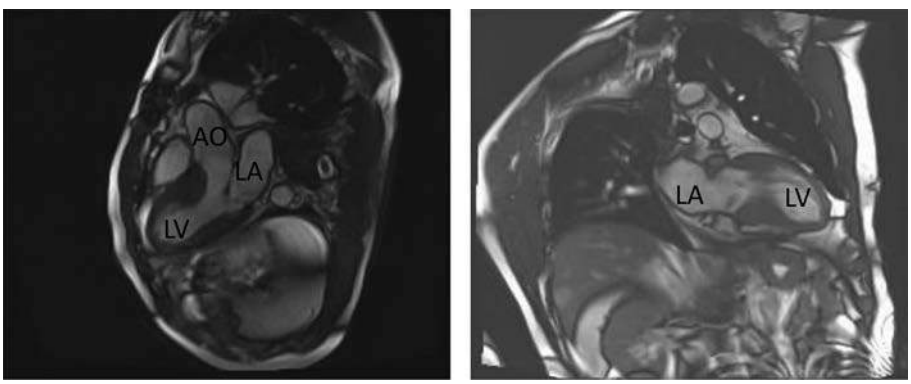


Figure 6.24

6.25. The regions arrowed in the inversion recovery images from the patient in Question 6.24 shown in Figure 6.25 are indicative of what? (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

A. Normal myocardium
B. Transmural LGE of the septum
C. Subendocardial LGE of the septum and lateral wall
D. Midmyocardial patchy LGE of the septum and inferolateral wall

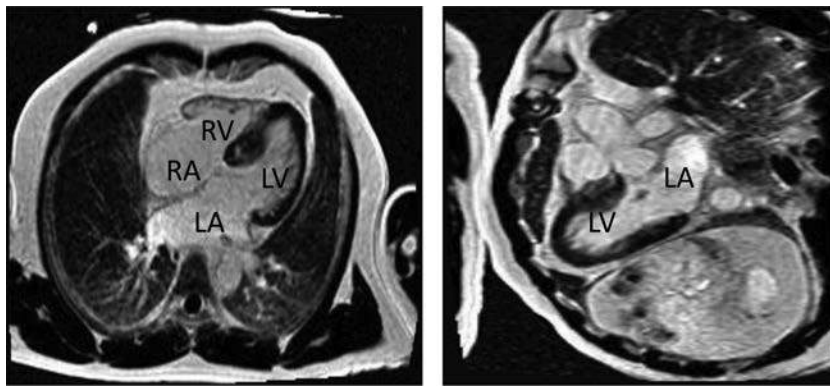


Figure 6.25

6.26. What does the still frame of the short-axis image in Figure 6.26a show?

A. Cleft anterior mitral valve
B. Cleft posterior mitral valve
C. Normal mitral valve
D. Mitral valve vegetation

6.27. What structure does the arrow point to on the bright blood cardiac MR image in Figure 6.27a?

A. Main pulmonary artery
B. Ascending aorta
C. Right pulmonary artery
D. Left pulmonary artery

6.28. What structure does the arrow point to on the bright blood cardiac MR image shown in Figure 6.28a?

A. Main pulmonary artery
B. Ascending aorta
C. Right pulmonary artery
D. Left pulmonary artery
E. Descending aorta

6.29. What structure does the arrow point to in the bright blood cardiac MR image in Figure 6.29a?

A. Superior vena cava
B. Inferior vena cava
C. Pulmonary artery
D. Aorta

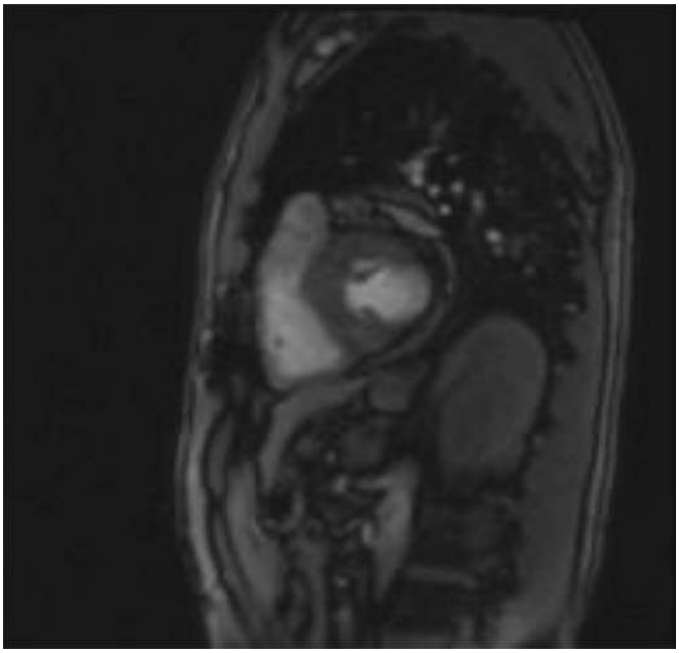


Figure 6.26a

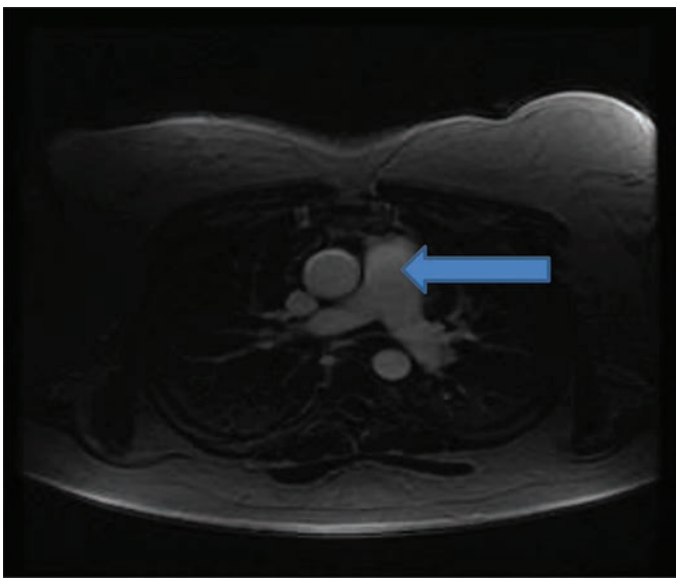


Figure 6.27a

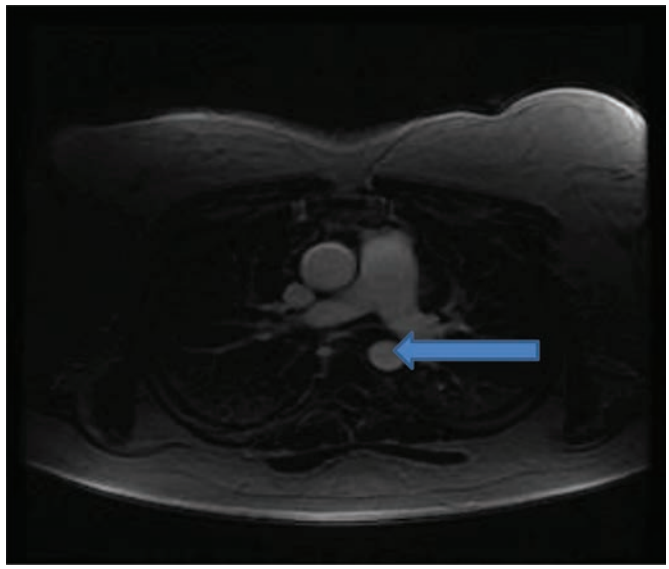


Figure 6.28a

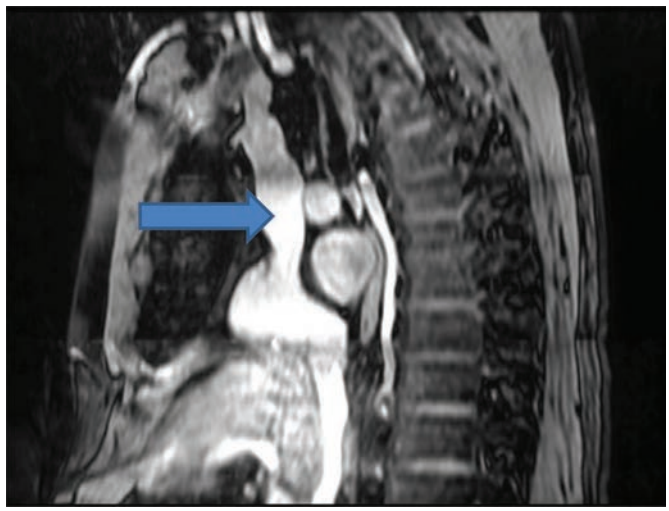
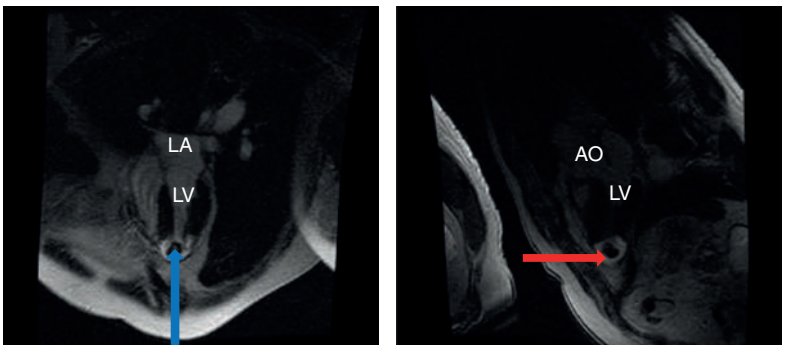


Figure 6.29a

6.30. A 50-year-old male was admitted to hospital with complaints of chest pain. The electrocardiogram obtained at the time of admission showed 3 mm ST elevation in leads V3–V6. He was rushed to the cardiac cath lab, which showed occlusion of the distal LAD artery. He then underwent cardiac MRI to evaluate left ventricle function and scar burden. What do the inversion recovery images in Figure 6.30 show?

A. LGE of the left ventricular apex
B. Transmural LGE of the apex with an apical thrombus
C. Apical thrombus
D. Subendocardial LGE of the apex



LA: left atrium; LV: left ventricle; AO: aorta

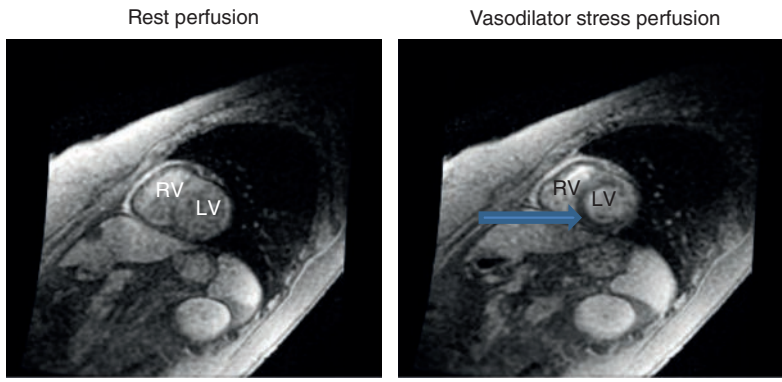
Figure 6.30

6.31. An 18-year-old female with a history of hypertension underwent a procedure. Based on the images shown in Figure 6.31, what procedure did she undergo?
A. Aortoplasty
B. Balloon dilatation of aorta
C. Stent of coarctation of the aorta with restenosis
D. Surgical anastomosis of coarctation of aorta with restenosis

Figure 6.31

6.32. A 50-year-old female patient is referred to the cardiology clinic for complaints of substernal chest pain. She has complaints of palpitations, and a Holter monitor demonstrated premature ventricular complexes. Her family history is significant for premature coronary artery disease. Owing to orthopedic problems, she underwent a Lexiscan stress cardiac MRI. What do the perfusion images in Figure 6.32 show?

A. Stress-induced myocardial perfusion defect in the septum, anterior and inferior walls
B. Rest myocardial perfusion defect in the anterior and inferior walls
C. Global stress-induced perfusion defect
D. Artifact



RV: right ventricle; LV: left ventricle

Figure 6.32

6.33. What do the contrast-enhanced MRA and volume-rendered image of the aorta in Figure 6.33 show?

A. Normal aorta
B. Dissection in the ascending aorta
C. Dissection flap in the descending aorta start just distal to the arch
D. Artifact

6.34. A 58-year-old male patient was admitted to hospital for chest pain. He has a history of hypertension and chronic smoking and his echo images were suboptimal. He underwent a cardiac MRI (Figure 6.34) to evaluate left ventricle function. What is the cause of his chest pain?

A. Myocarditis
B. Constrictive pericarditis
C. Dissection of the aorta
D. Pulmonary embolism

6.35. What does the still-frame long-axis view of the heart in Figure 6.35 show?

A. Normal aortic and mitral valves
B. Normal aortic valve
C. Normal mitral valve and artifact from a prosthetic aortic valve
D. None of the above

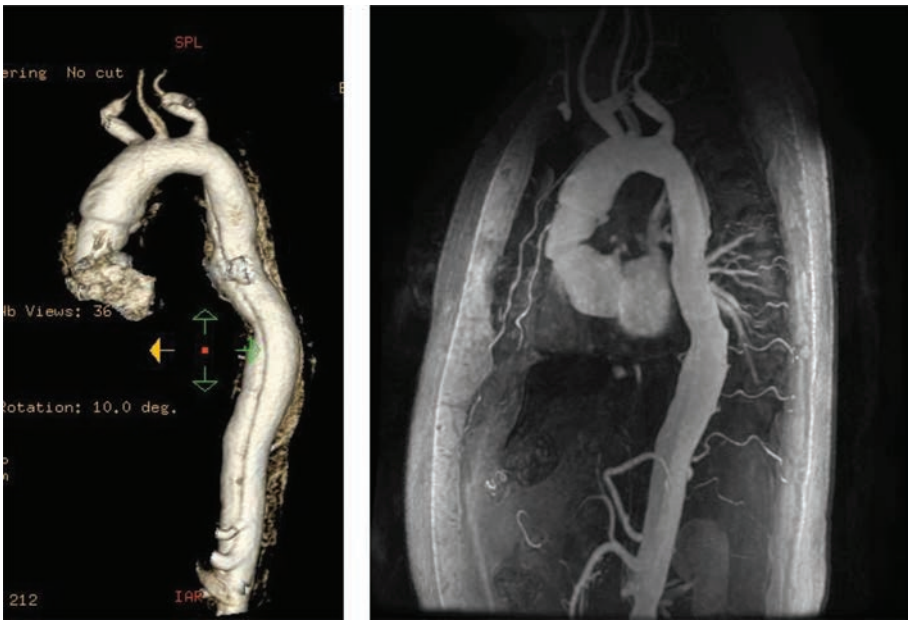


Figure 6.33

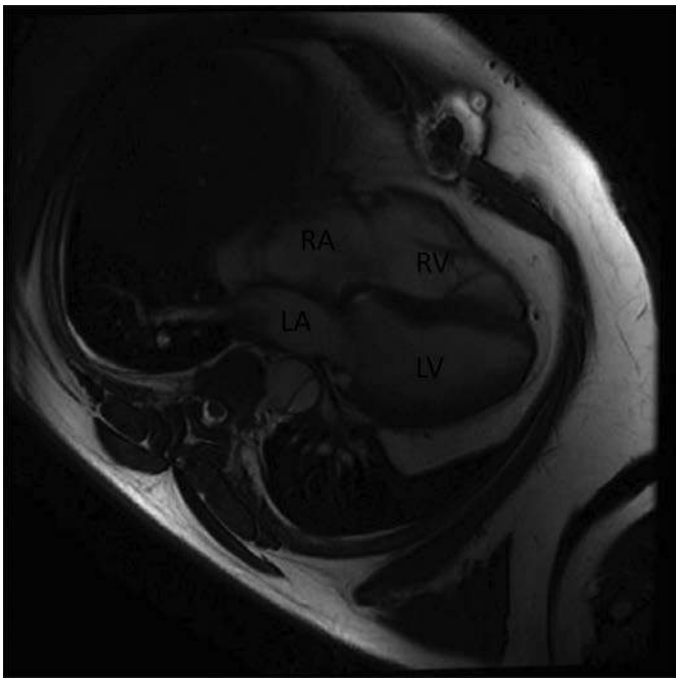


Figure 6.34

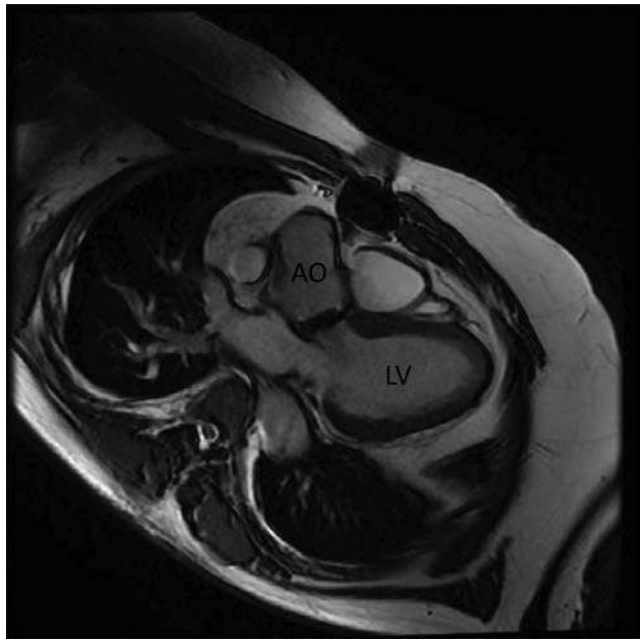


Figure 6.35

6.36. A 50-year-old female had a routine transthoracic echocardiogram. Her cardiologist found a mass in the right atrium. She was then referred for a cardiac MRI (see Figure 6.36) to evaluate this mass further. What is the mass is suggestive of?

A. Right atrial myxoma
B. Right atrial sarcoma
C. Thrombus
D. Lipomatous hypertrophy of the interatrial septum

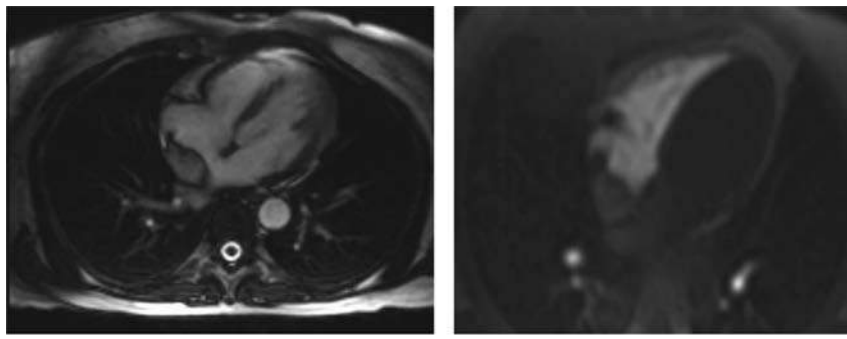


Figure 6.36

Answers

6.1. A. Hydrogen-1.
Hydrogen-1 is most abundant in living tissues.

6.2. A. 63 MHz.
It is 42 MHz multiplied by the magnetic field strength B_o in tesla.

6.3. A. Magnetic gradient.
There is a slight gradient in *X*, *Y*, and *Z* planes (strength of magnetic field varies from slightly above to below 1.5 T in a 1.5 T system) and this helps localize where the signal is coming from.

6.4. D. All of the above.
Spinal cord stimulator is a contraindication as well. Coronary stents, heart valves, artificial joints, and vertebral plates are not contraindications.

6.5. D. All of the above.

6.6. A. Shortens T1 and increases signal on T1-weighted images.
The seven unpaired electrons on Gd couple with excited water spins and hasten relaxation, thereby reducing T1. This property of Gd is used for magnetic resonance angiography (MRA), first-pass perfusion, and late Gd enhancement (LGE) of myocardial scar.

6.7. C. With the use of a navigator pulse.
It takes 15–20 min based on slice thickness and extent needed and hence needs navigator pulse to track the diaphragm so that images can be acquired only at certain phases of the respiratory cycle.

6.8. A. Right ventricle.
The other numbers indicate the following structures: 2, left ventricle; 3, left atrium; 4, right atrium; 5, descending thoracic aorta; 6, pulmonary vein.

6.9. B. Left ventricle.
Structure "1" is the right ventricle.

6.10. C. Right atrium.
Structure "2" is the left ventricle. This is the coronal plane.

6.11. C. LAD area looks fully viable.
The scar looks white on delayed Gd-enhanced imaging. There is no evidence scarring in this image.

6.12. D. None of the above.
This is a normal MRA of the pulmonary artery and branches: 1, main pulmonary artery; 2, right pulmonary artery; 3, left pulmonary artery; 4, right ventricle outflow tract.

6.13. C. Contrast-enhanced MRA.
This is of the aorta. The aorta looks normal. 1, left ventricle; 2–4, aorta; 5, pulmonary veins.

6.14. D. All of the above.

6.15. A. Lipomatous atrial septum.
Its location in the atrial septum and the absence of a perfusion point to a lipomatous septum. There was no delayed enhancement.

6.16. A. Heart failure.

Note the bilateral pleural effusions. The left ventricle seems to be dilated with thinning of the apical area. The atrial septum is intact and bowing to the right, indicating high right atrial pressure. The descending aorta (behind left atrium) is normal (1: left ventricle; 2: right ventricle; 3: left pleural effusion).

6.17. A. Multivessel coronary artery disease.

The dark area pointed by the arrows is a perfusion defect during first-pass perfusion using Gd chelate. The perfusion defect is seen during vasodilator stress in the lateral wall as well as anterior and inferior walls and completely fills in during rest perfusion. Reversible perfusion defect indicates ischemia and not infarct, and extent indicates multivessel disease.

6.18. B. Inferior myocardial infarction.

Subendocardial scar indicates an infarct; involvement of inferior septum and inferior wall is consistent with right coronary artery lesion. In ARVD, scarring may be seen in the right ventricle wall along with fatty deposit, dilation, aneurysm formation, and reduced function. Scar pattern in myocarditis may be patchy, midmyocardial, subepicardial, or even transmural.

6.19. C. Anterior myocardial infarction.

Note the scar distribution in mid and distal septum consistent with LAD artery lesion.

6.20. A. Left ventricle noncompaction.

Note the heavily trabeculated left ventricle with noncompated to compacted myocardial thickness ratio of >2.5. There is a high risk of thrombus formation, and anticoagulation is recommended when there is a thrombus, embolic event, atrial fibrillation, or just EF is <40%. In cardiac amyloid, left ventricle would be thick.

6.21. A. Bicuspid aortic stenosis.

The arrow in Figure 6.21 is pointing to the aortic valve. This is a FIESTA or SSFP cine sequence.

6.22. B. Right pulmonary artery.

6.23. C. Left main bronchus.

The arrow in Figure 6.23 is pointing to the left main bronchus. The carina is shown well where the trachea branches into the right and left main bronchi.

6.24. Hypertrophic cardiomyopathy.

This patient has hypertrophy of his anterior septum and anterior and inferior walls. The upper septum is asymmetrically hypertrophied (arrow) and points more to hypertrophic cardiomyopathy.

6.25. D. Midmyocardial patchy LGE of the septum and inferolateral wall.

The LGE pattern seen here is midmyocardial patchy enhancement, whereas in the setting of coronary artery disease the LGE pattern is either subendocardial or transmural.

6.26. A. Cleft anterior mitral valve.

The short-axis mitral valve view shows a cleft of the anterior mitral valve (arrowed in Figure 6.26b).

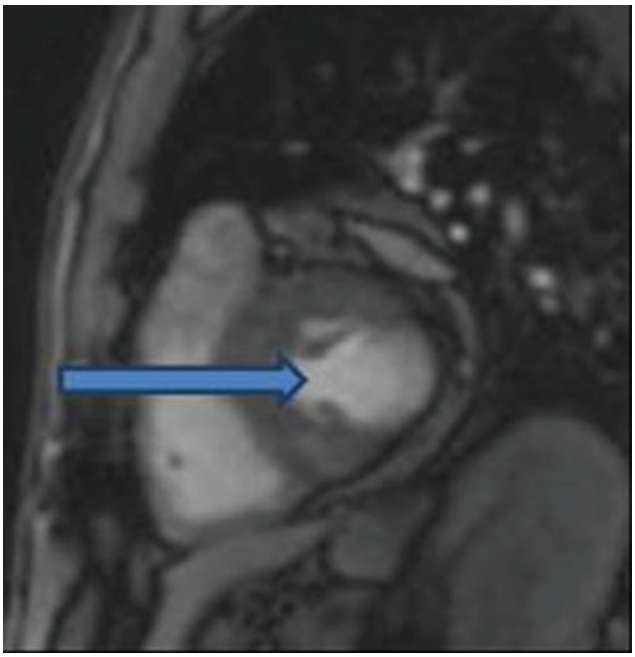


Figure 6.26b

6.27. A. Main pulmonary artery.

Figure 6.27b shows the main pulmonary artery (MPA), along with the aorta (AO).

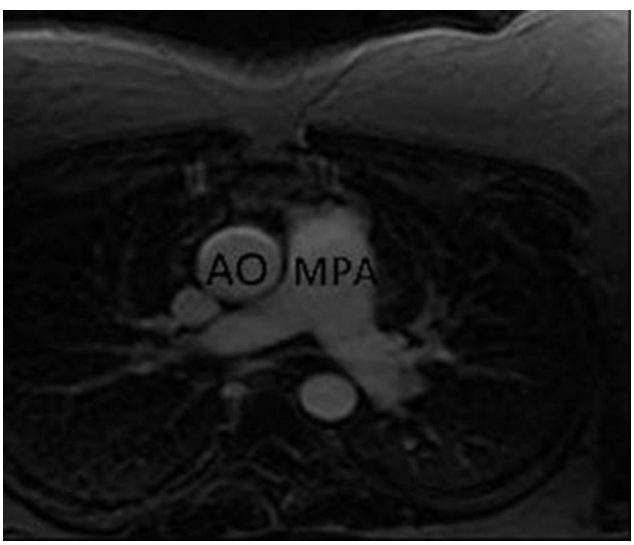


Figure 6.27b

6.28. E. Descending aorta.

Figure 6.28b shows the descending aorta (arrowed), along with the aorta (AO) and main pulmonary artery (MPA).

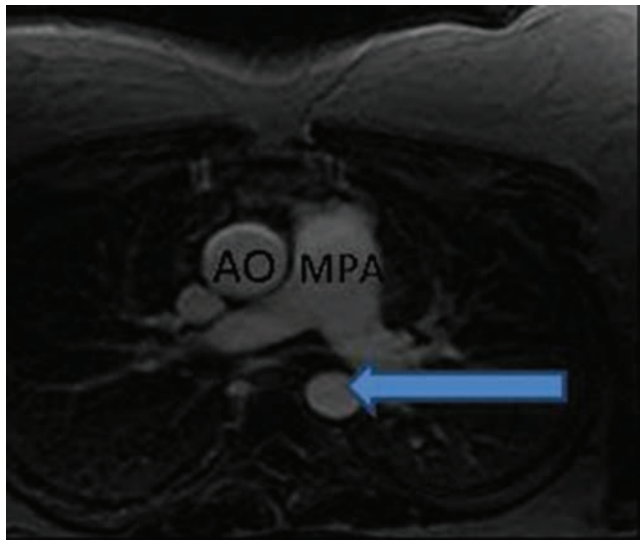


Figure 6.28b

6.29. A. Superior vena cava.

Figure 6.29b shows the superior vena cava (SVC), along with the right atrium (RA).

6.30. B. Transmural LGE of the apex with an apical thrombus.

The red arrow in Figure 6.30 shows transmural LGE of the apex and the blue arrow an apical thrombus. Both the four- and three-chamber views show transmural scar of the apex with a dark filling defect representing thrombus. The scarred areas take up Gd that is not washed out and appears as bright areas on this sequence, whereas thrombus does not take up contrast and appears as a filling defect (LV: left ventricle; LA: left atrium; AO: aorta).

6.31. C. Stent of coarctation of the aorta with restenosis.

The stented segment, which measured 30 mm, is clearly seen on both images in Figure 6.31. The lumen of the stented segment is narrowed up to 50%, representing restenosis.

6.32. A. Stress-induced myocardial perfusion defect in the septum, anterior and inferior walls.

The arrow in Figure 6.32 shows the stress-induced perfusion defect in the septum, anterior and inferior walls (LV: left ventricle). At rest there is homogeneous perfusion of Gd in all myocardial segments. With vasodilator stress there is lack of perfusion in the septum, anterior and inferior walls (dark areas), representing myocardial ischemia.

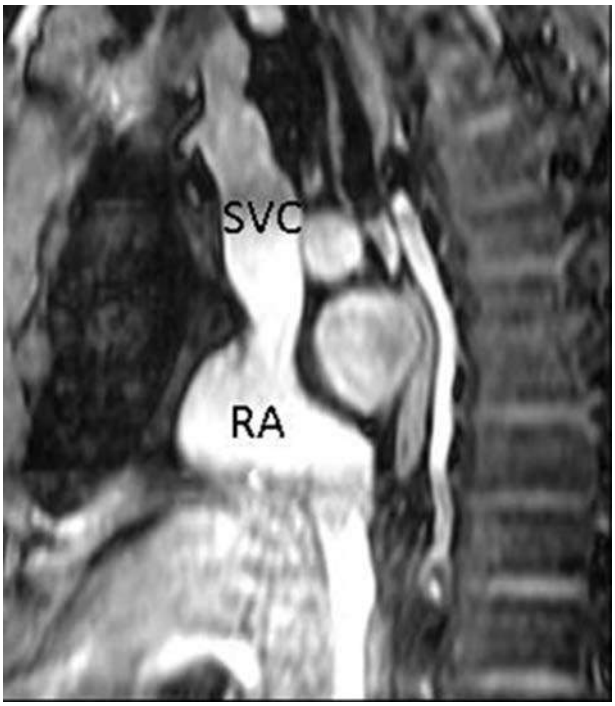


Figure 6.29b

6.33. C. Dissection flap in the descending aorta start just distal to the arch.

The contrast-enhanced image of the aorta shows contrast in the true lumen (T), while the false lumen (F) does not enhance. The blue arrow points to the dissection flap. This patient had a type A dissection and underwent ascending aortic repair including a hemiarch.

6.34. C. Dissection of the aorta.

The size of the heart looks normal. Figure 6.34, a still-frame image, shows a flap in the descending aorta (arrow; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle). The cause of this patient's chest pain is due to dissection of the aorta.

6.35. C. Normal mitral valve and artifact from a prosthetic aortic valve.

This patient has a normal mitral valve but has a prosthetic aortic valve. There is artifact from the mechanical prosthesis indicative of a mechanical aortic valve (arrow; LV: left ventricle; LA: left atrium; AO: aorta).

6.36. D. Lipomatous hypertrophy of the interatrial septum.

The mass is lipomatous hypertrophy of the interatrial septum. The mass is in continuity with the upper part of the interatrial septum. On the perfusion image there is no enhancement indicative of avascularity. On T1-weighted images this mass will appear bright and can be suppressed with fat suppression sequences (LV: left ventricle; RV: right ventricle; RA: right atrium).

Cardiac Computed Tomography

7

7.1. Which of the following scan modes is used for coronary calcium scanning?
- **A.** Prospective gated noncontrast
- **B.** Prospective gated contrast scan
- **C.** Retrospective gated noncontrast
- **D.** Retrospective gated contrast scan

7.2. What is the traditional slice thickness for coronary calcium screening?
- **A.** 0.625 mm
- **B.** 1 mm
- **C.** 3 mm
- **D.** 5 mm

7.3. Which scan mode is used for assessment of left ventricle function?
- **A.** Prospective, gated with contrast
- **B.** Retrospective, gated with contrast
- **C.** Retrospective, gated without contrast
- **D.** Prospective, gated without contrast

7.4. Which of the following imaging procedures is likely to be associated with lowest radiation exposure?
- **A.** Prospectively gated, electrocardiogram (ECG)-triggered cardiac computed tomography angiography (CTA)
- **B.** Retrospectively gated, cardiac CTA
- **C.** Coronary angiography
- **D.** Stress perfusion scan with sestamibi

7.5. Which of the following imaging procedures is likely to be associated with the highest radiation exposure?
- **A.** Retrospectively gated, cardiac CTA with dose modulation
- **B.** Retrospectively gated, cardiac CTA
- **C.** Dual-isotope myocardial perfusion scan with thallium and sestamibi
- **D.** Stress perfusion scan with sestamibi

7.6. Who are at the highest cancer risk with cardiac computed tomography (CT)?
- **A.** Men
- **B.** Women
- **C.** Blacks
- **D.** Caucasians

7.7. During cardiac CTA, which organ gets the highest radiation dose?
- **A.** Heart
- **B.** Lungs
- **C.** Esophagus
- **D.** Breast

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7.8. Which of the following affects radiation dose?
- **A.** Tube voltage
- **B.** Tube current
- **C.** Pitch
- **D.** All of the above

7.9. Pitch is table movement divided by collimated beam width. At a pitch of 1, there is no overlap of data. At a pitch >1 there is a gap, and with a pitch <1 there is overlap. Which pitch is likely to be associated with least amount of radiation?
- **A.** 0.4
- **B.** 0.6
- **C.** 1.0
- **D.** 3.0

7.10. Which one has least amount of radiation?
- **A.** Calcium score with electron-beam CT
- **B.** Calcium score with X-ray CT
- **C.** Chest X-ray
- **D.** Cardiac MRI with gadolinium vasodilator stress

7.11. Which of the following 45-year-old patients presenting to the emergency room (ER) with atypical chest pain are appropriate candidates for coronary CTA?
- **A.** Patient with hypertension, diabetes mellitus, and prior left anterior descending (LAD) artery stent
- **B.** Patient with hypertension, ECG shows nonspecific ST–T changes, negative cardiac enzymes
- **C.** Patient with a prior myocardial infarction followed by coronary artery bypass grafting
- **D.** All of the above

7.12. Which of the following agents are appropriate to slow the heart rate for coronary CTA?
- **A.** Beta blockers
- **B.** Nondihydropyridine calcium channel blocker (e.g., diltiazem)
- **C.** Ivabradine
- **D.** All of the above

7.13. Which of the following is likely to reduce radiation dose the most?
- **A.** Increasing pitch by 25%
- **B.** Decreasing tube current by 25%
- **C.** Decreasing tube current by 25%
- **D.** They are all similar

7.14. Which of the following is the best measure of radiation dose to the patient?
- **A.** CT dose index (CTDI)
- **B.** Dose–length product (DLP)
- **C.** Effective radiation dose (ERD)
- **D.** All of the above

7.15. What is the US legal limit for radiation dose to a pregnant woman for the entire length of pregnancy?
- **A.** 0.05 mSv
- **B.** 0.5 mSv
- **C.** 5 mSv
- **D.** 50 mSv

7.16. During coronary CTA to the mother, how much radiation is the fetus likely to get?
- **A.** 14 mSv
- **B.** 1.4 mSv
- **C.** 0.14 mSv
- **D.** None with shielding

7.17. What is the typical HU value for fat?
- **A.** −1000 HU
- **B.** −50 HU
- **C.** 0 HU
- **D.** 1000 HU

7.18. What is the typical HU threshold for calcium for calcium score is?
- **A.** 100
- **B.** 130
- **C.** 0
- **D.** 400

7.19. Image noise can be reduced by which of the following?
- **A.** Increasing tube voltage
- **B.** Increasing tube current
- **C.** Iterative reconstruction
- **D.** All of the above

7.20. Which of the following statements is correct about iterative reconstruction?
- **A.** It takes longer as it makes multiples passes through the data
- **B.** It increases signal-to-noise ratio
- **C.** It can be performed on any CT scanner
- **D.** All of the above

7.21. What is the image pixel size of a CT image reconstruction with a field of view (FOV) of 256 mm and a 512 × 512 matrix?
- **A.** 0.5 mm × 0.5 mm
- **B.** 0.25 mm × 0.25 mm
- **C.** 2 mm × 2 mm
- **D.** None of the above

7.22. How can the image pixel size be increased during CT image reconstruction?
- **A.** Decreasing FOV
- **B.** Increasing matrix
- **C.** Both
- **D.** Neither

7.23. Spatial and temporal resolution are affected by all of the following except which?
- **A.** Detector width
- **B.** Rotation time
- **C.** Dual-source technology
- **D.** Number of detector rows

7.24. If a reconstructed image is noisy, how can this noise be reduced?
- **A.** Increasing slice thickness
- **B.** Reducing slice thickness
- **C.** Changing window level
- **D.** None of the above

7.25. Which of the following techniques may be helpful for better coronary visualization for those with calcification?
- **A.** Dual-energy CT
- **B.** Reconstruction with sharp filter
- **C.** Both
- **D.** Neither

7.26. How can visualization within a stent be facilitated?
- **A.** Dual-energy CT
- **B.** Reconstruction with sharp filter
- **C.** Wide window
- **D.** Thin slice
- **E.** All of the above

7.27. In a person presenting to the ER with chest pain and suspicion of acute coronary syndrome (ACS), which of the following are appropriate indications for coronary CTA?
- **A.** Normal ECG and biomarkers, low or intermediate probability of CAD
- **B.** Nonspecific ECG changes and normal biomarkers, low or intermediate probability of CAD
- **C.** Nondiagnostic ECG and biomarkers, low or intermediate probability of CAD
- **D.** Normal ECG and biomarkers, low or intermediate probability of CAD, unable to exercise
- **E.** All of the above

7.28. In a person presenting to the ER with chest pain, negative ECG and enzymes, and a history of prior coronary stent, which of the following are appropriate or possibly appropriate indications for coronary CTA?
- **A.** Left main coronary artery drug-eluting stent, 4 mm, 1 year ago
- **B.** LAD coronary artery stent 2 years ago 2.5 mm
- **C.** Mid right coronary artery (RCA) stent, 3.5 mm a year ago
- **D.** All of the above

7.29. It is appropriate to perform coronary CTA in which of the following *asymptomatic* patients?
- **A.** Left main coronary artery stenting with stent size ≥3 mm
- **B.** Left main coronary artery stenting with stent size <3 mm
- **C.** LAD bifurcation stent 4 mm size
- **D.** None of the above

7.30. Which of the following are reasonable indications for coronary CTA?
- **A.** Patient with ejection fraction of 30%, low to intermediate risk for CAD, to rule out ischemic etiology
- **B.** To rule out anomalous origin or coronary artery
- **C.** To monitor for CAD post heart transplant
- **D.** To check for graft patency in a patient with chest pain after prior coronary artery bypass grafting
- **E.** All of the above

7.31. Which of the following does the arrow in Figure 7.31 point to?
- **A.** Anomalous RCA
- **B.** Normal RCA origin, not calcified
- **C.** Normal RCA origin, calcified
- **D.** None of the above

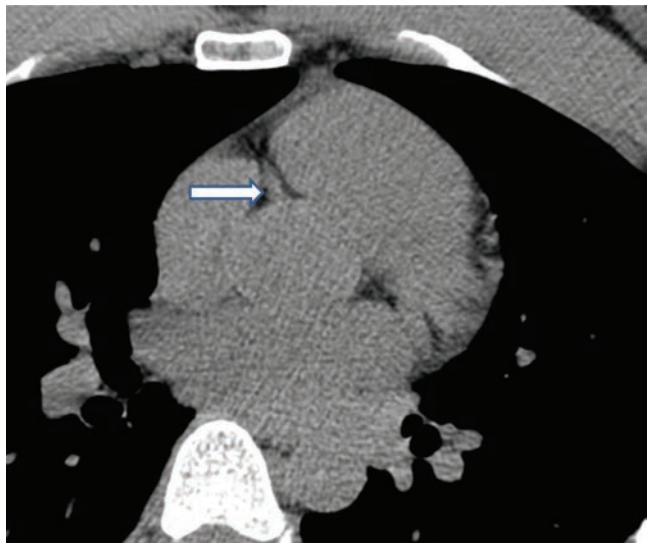

Figure 7.31

7.32. What is the arrow in Figure 7.32 pointing to?

A. Anomalous origin of left coronary artery
B. Normal left main coronary artery origin, not calcified
C. Normal left main coronary artery origin, calcified
D. Anomalous origin of RCA

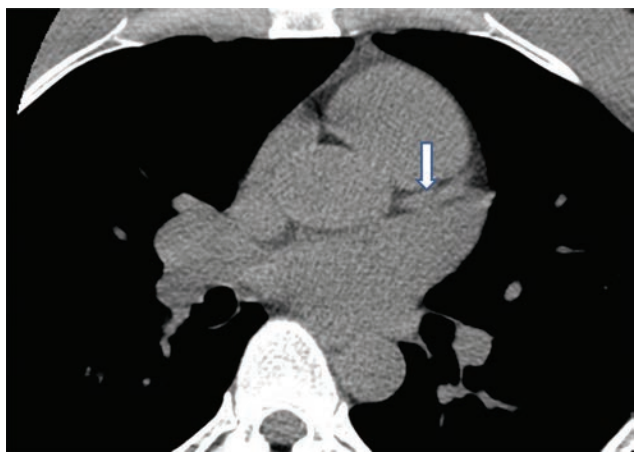

Figure 7.32

7.33. What do the numbers 1, 2, 3, and 4 correspond to in Figure 7.33?

A. Pulmonary veins: left upper, left lower, right upper, right lower respectively
B. Pulmonary veins: LEFT lower, left upper, right lower, right upper respectively
C. Pulmonary veins: right upper, right lower, left upper, left lower respectively
D. None of the above

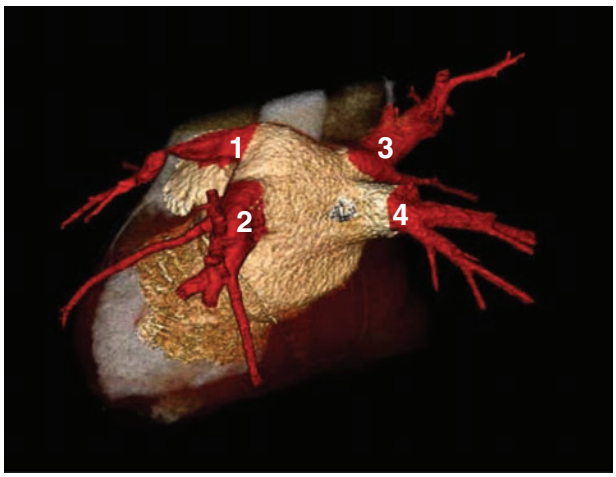

Figure 7.33

7.34. What does the number 1 correspond to in Figure 7.34?

A. Left atrial appendage
B. Left superior pulmonary vein
C. Left inferior pulmonary vein
D. Body of left atrium

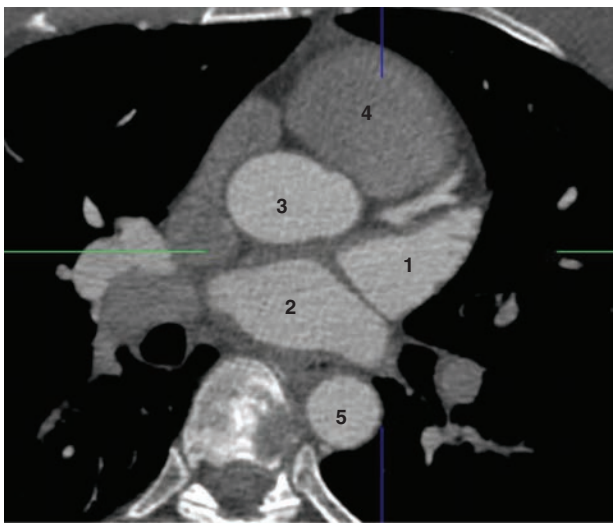

Figure 7.34

7.35. Figure 7.35 shows a volume rendered image viewed from the top. What does the number 1 refer to?

A. Ascending aorta
B. Pulmonary artery
C. Pulmonary vein
D. Body of left atrium

7.36. Figure 7.36 shows a volume rendered image. What does the number 1 refer to?

A. LAD artery
B. Diagonal artery
C. Circumflex artery
D. RCA

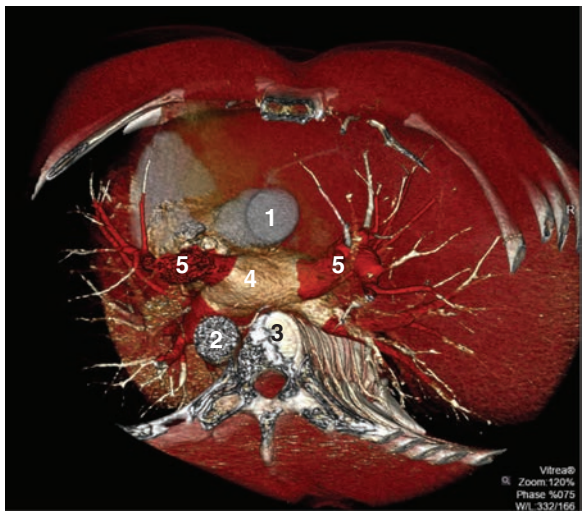

Figure 7.35

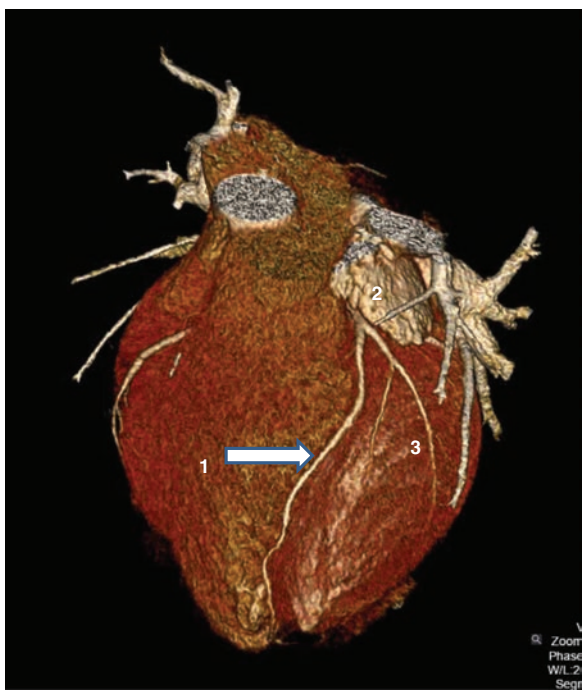

Figure 7.36

7.37. Figure 7.37 shows a volume rendered image. What does the arrow point to?

- **A.** LAD artery
- **B.** Diagonal artery
- **C.** Circumflex artery
- **D.** Right ventricle branch of RCA

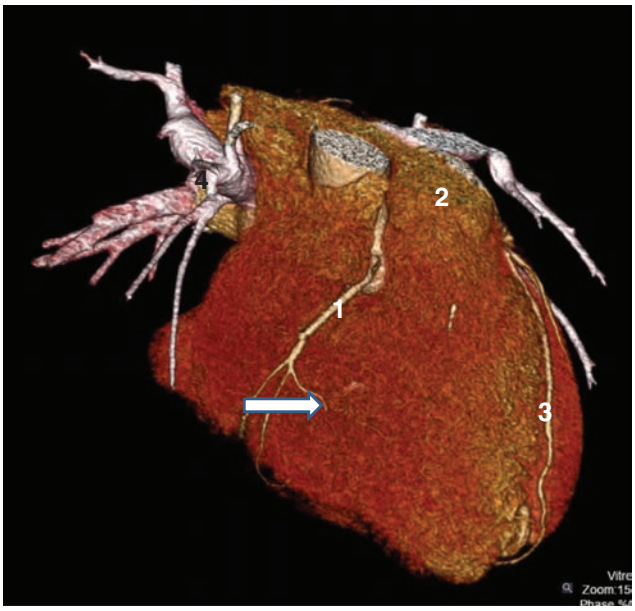

Figure 7.37

7.38. In Figure 7.38, what does the number 1 refer to?

A. RCA
B. Circumflex
C. Mitral annular calcification
D. Pericardiophrenic bundle

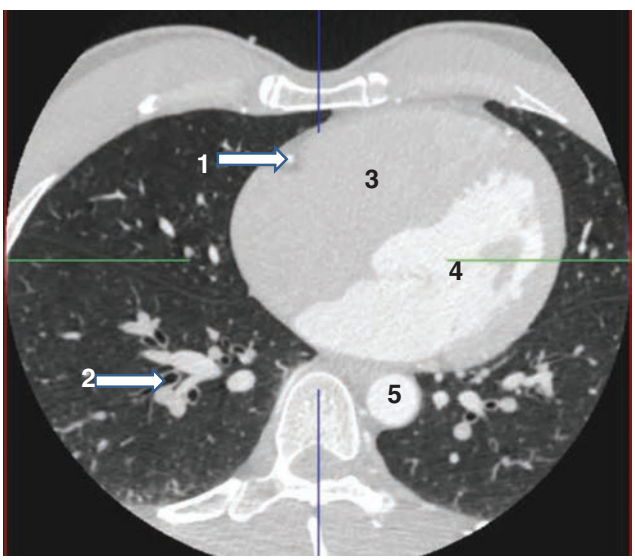

Figure 7.38

7.39. In Figure 7.39, what does the number 2 refer to?

A. Ascending thoracic aorta
B. Descending aorta
C. Inferior vena cava
D. Azygos vein

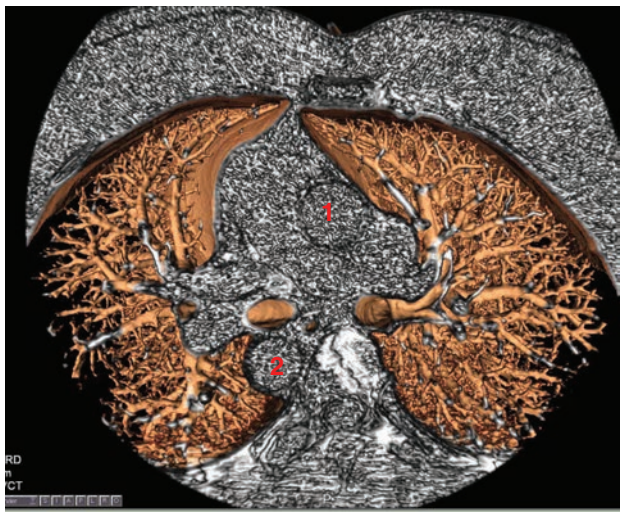

Figure 7.39

7.40. Figure 7.40 shows a volume rendered image. What does the number 1 refer to?

A. Left lower pulmonary vein
B. Left upper pulmonary vein
C. Left pulmonary artery
D. Right lower pulmonary vein

Figure 7.40

7.41. Figure 7.41 shows a volume rendered image. What does the number 1 refer to?

A. LAD artery
B. Left internal mammary artery
C. Diagonal
D. Right internal mammary artery

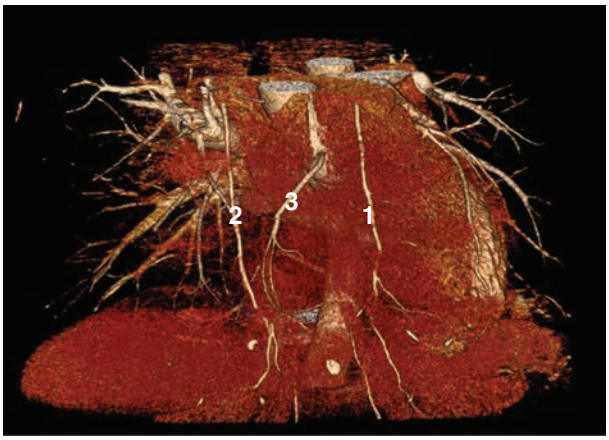

Figure 7.41

7.42. Figure 7.42 shows a volume rendered image. What does the number 1 refer to?

A. LAD artery
B. Left internal mammary artery
C. Aorta
D. Pulmonary vein

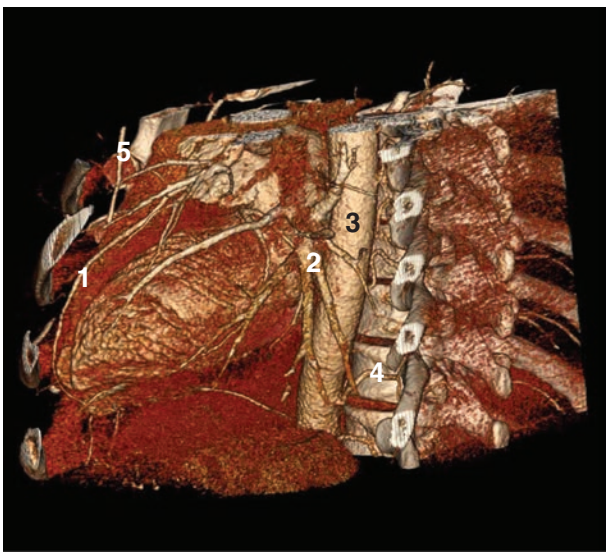

Figure 7.42

7.43. In the axial scan in Figure 7.43, what does the number 1 refer to?

A. Coronary sinus
B. Right coronary artery
C. Circumflex coronary artery
D. Anomalous left circumflex coronary artery

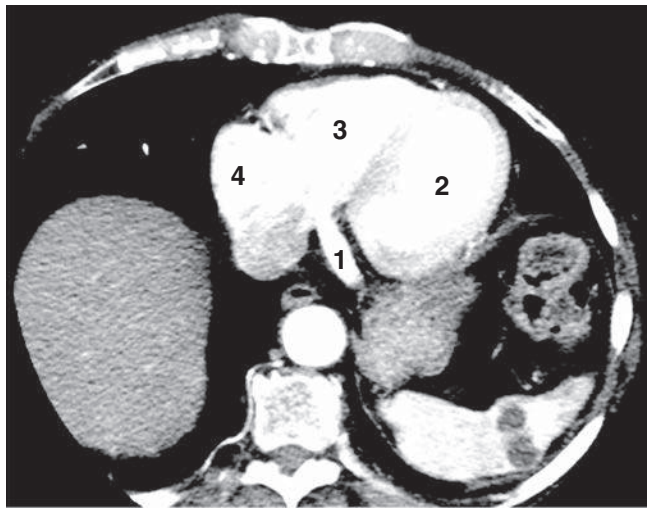

Figure 7.43

7.44. A 44-year-old man with no cardiac risk factors was seen in the ER with exertional chest pain. Axial contrast-enhanced scans are shown in Figure 7.44. What is the possible cause of his chest pain?

A. Left main coronary artery stenosis
B. Anomalous circumflex artery
C. Anomalous RCA from left coronary cusp with interarterial course
D. None of the above

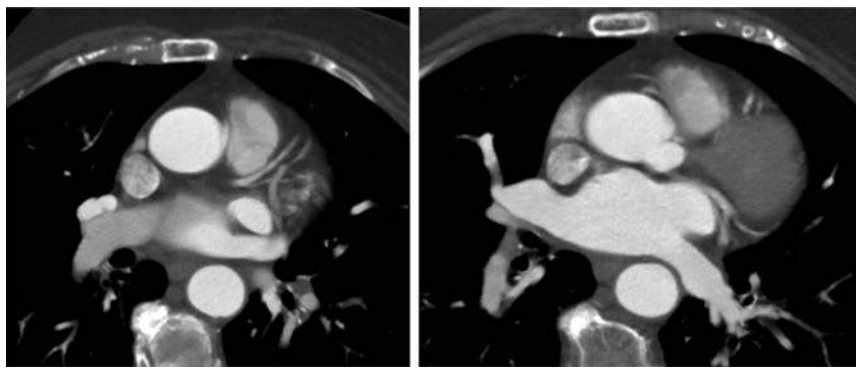

Figure 7.44

7.45. Which of the following options describes the LAD artery segment shown in Figure 7.45?

A. Normal
B. Has severe stenosis in proximal segment
C. Has a large mixed plaque in the cross-section shown
D. Has a large soft plaque in the cross-section shown

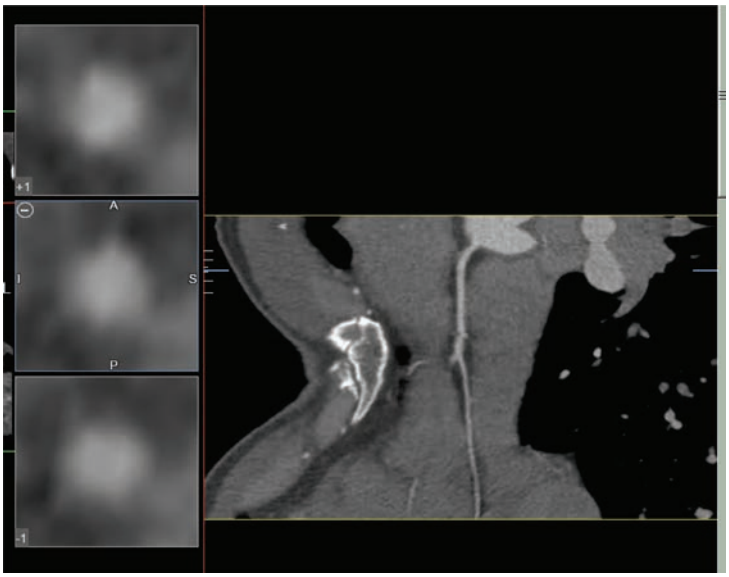

Figure 7.45

7.46. The volume rendered scan in Figure 7.46 shows what?

A. Normal coronary anatomy
B. Anomalous LCA
C. Anomalous RCA from left sinus
D. Saphenous venous graft to RCA

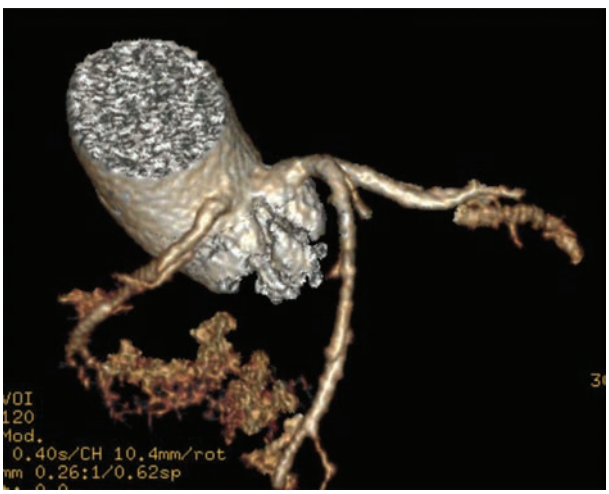

Figure 7.46

7.47. What can be said from the volume rendered scan shown in Figure 7.47?

- **A.** Has normal coronary anatomy
- **B.** Has severe LAD artery stenosis
- **C.** Need to evaluate LAD artery and other vessels using curved multiplanar reformation and centerline methods to comment about the coronaries
- **D.** Has moderate LAD artery stenosis, and stress test is indicated

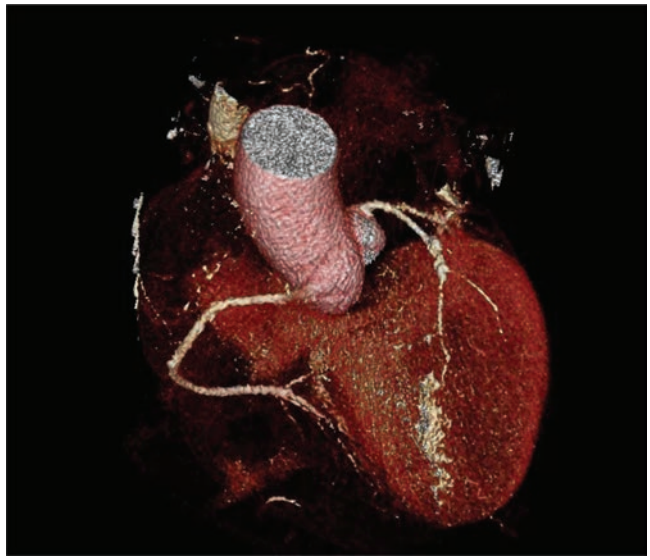

Figure 7.47

7.48. A 48-year-old patient with hypertension and diabetes mellitus was seen in the ER with atypical chest pain. Cardiac enzymes were normal. Coronary calcium distribution is shown in Figure 7.48. What would be a reasonable next step?

- **A.** Cancel coronary CTA in view of severe coronary calcification and order a stress test
- **B.** Go ahead with coronary CTA; if lesions are moderate or indeterminate, consider cardiac catheterization
- **C.** Cancel coronary CTA and treat with aspirin and high-intensity statin
- **D.** Refer for cardiac catheterization

7.49. What does the arrow in the axial scan in Figure 7.49 refer to?

- **A.** Coronary sinus
- **B.** RCA
- **C.** Circumflex coronary artery
- **D.** Anomalous circumflex artery

7.50. For transcatheter aortic valve replacement (TAVR) planning, what type of cardiac protocol is most appropriate?

- **A.** Noncontrast CT with cardiac gating
- **B.** Noncontrast CT without cardiac gating
- **C.** Contrast CT with cardiac gating
- **D.** Contrast CT without cardiac gating

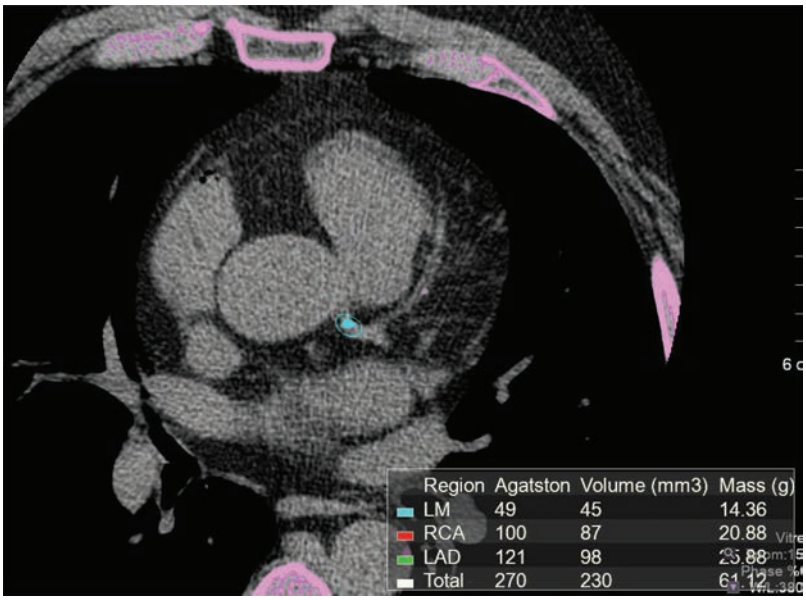

Figure 7.48

Figure 7.49

7.51. What cardiac CT measures are useful for TAVR planning?

- **A.** Aortic annulus size
- **B.** Left and right coronary height from aortic annulus
- **C.** Size of aortic sinus and sinotubular junction
- **D.** Aortic leaflet size and degree of calcification
- **E.** All of the above

7.52. The CT images shown in Figure 7.52 would permit which of the following?

- **A.** Size 23 mm TAVR
- **B.** 26 mm TAVR
- **C.** 29 mm TAVR
- **D.** Coronary height is too low for TAVR

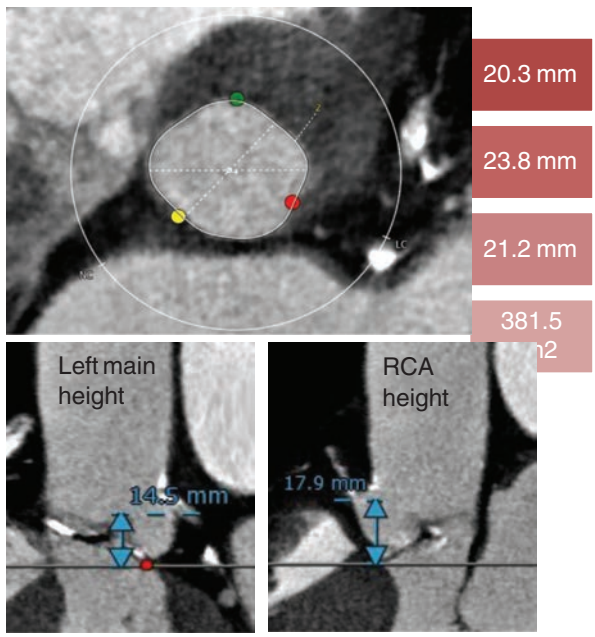

Figure 7.52

7.53. The patient in Figure 7.53 has severe calcific aortic stenosis and TAVR is being planned. Which of the following statements is correct?

- **A.** The aortic annulus is large and may need a 29 mm valve
- **B.** There is severe aortic valve calcification and this may increase risk of coronary occlusion
- **C.** The coronary height and size of the sinus and sinotubular junction are not shown and these are important in planning
- **D.** All of the above

7.54. A peripheral CTA of a patient being considered for TAVR is shown in Figure 7.54 (RCFA: right common femoral artery; RCIA: right common iliac artery; REIA: right external iliac artery). Which of the following conclusions can be drawn?

- **A.** Peripheral vessels are adequate for transfemoral approach
- **B.** Either side can be used for transfemoral approach
- **C.** Both
- **D.** Neither

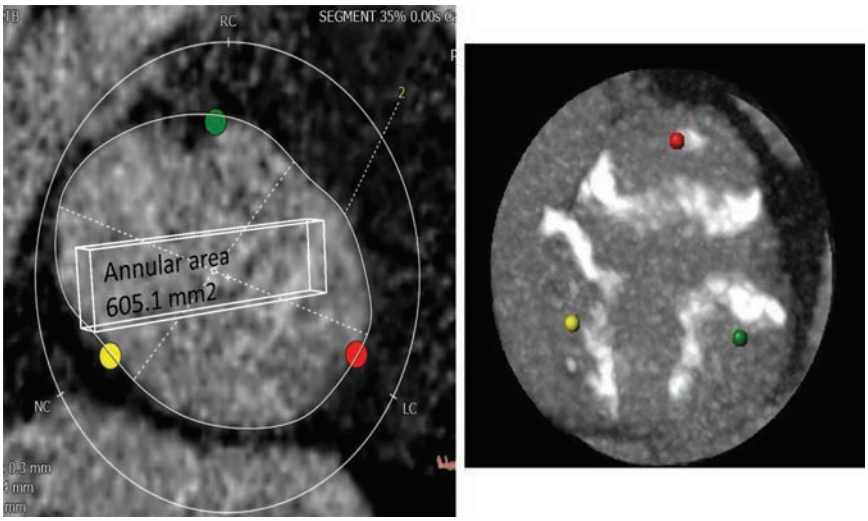

Figure 7.53

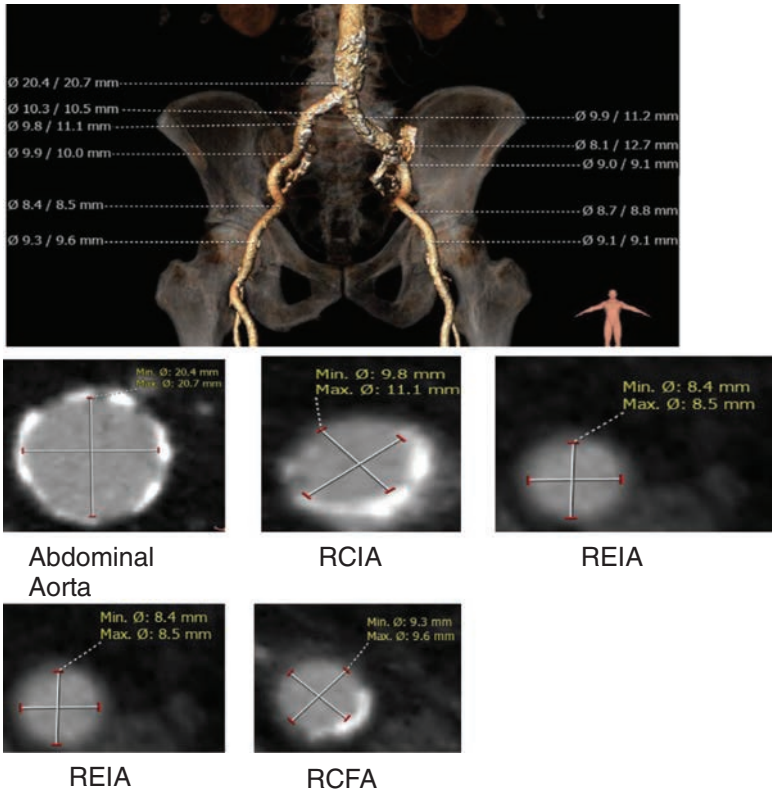

Figure 7.54

7.55. Which of the following techniques has thea potential to evaluate the functional significance of a coronary artery lesion using cardiac CT?

A. Dynamic CT–myocardiac perfusion imaging
B. Static CT–myocardiac perfusion imaging
C. Transluminal attenuation gradient assessment
D. CT–fractional flow reserve
E. All of the above
F. None of the above

7.56. Which of the following characteristics is associated with a potentially severe coronary artery stenosis?

A. Small area of stenosis
B. Greater lesion length
C. Positive remodeling
D. Low-attenuation plaque <30 HU
E. All of the above
F. None of the above

7.57. A 35-year-old patient who had undergone a Bentall procedure 2 months earlier presented with chest pain. A contrast CT axial image is shown in Figure 7.57a. What is the likely explanation for the chest pain?

A. Leaking pseudoaneurysm of the aorta
B. Occluded left coronary anastomosis
C. Occluded RCA
D. None of the above

Figure 7.57a

7.58. The patient shown in Figure 7.58 has a recent implantable cardioverter-defibrillator and presented with chest pain. What is the likely cause of the chest pain?

A. Right ventricular lead perforation
B. Inferior infarct
C. Large pericardial effusion
D. None of the above.

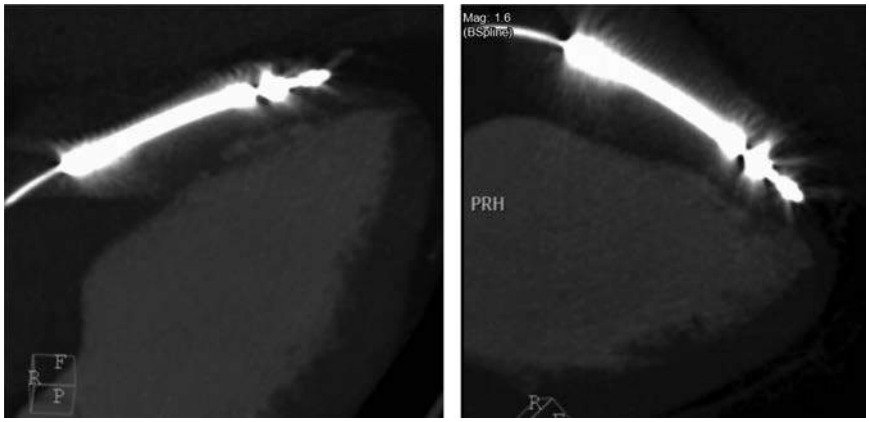

Figure 7.58

7.59. The RCA of the patient shown in Figure 7.59 shows what?

A. Severe RCA classification
B. Severe lesion in mid segment
C. RCA stent
D. Normal RCA

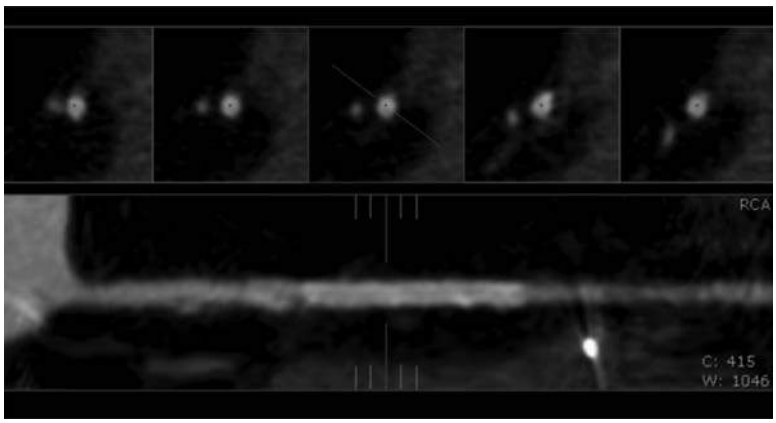

Figure 7.59

7.60. The LAD artery of the patient shown in Figure 7.60 is described by which of the following?

A. Normal anatomy
B. Mid LAD artery lesion.
C. Myocardial bridging
D. None of the above

7.61. A 40-year-old truck driver passed out while loading his truck. There were no other medical problems. A chest CT (Figure 7.61a) was performed in the ER to rule out pulmonary embolism because of his leg swelling and positive D-dimer. Which of the following is a possible cause of his syncope?

A. Pulmonary embolism
B. Large pericardial effusion
C. Anomalous origin of left coronary artery
D. Anomalous origin of RCA.

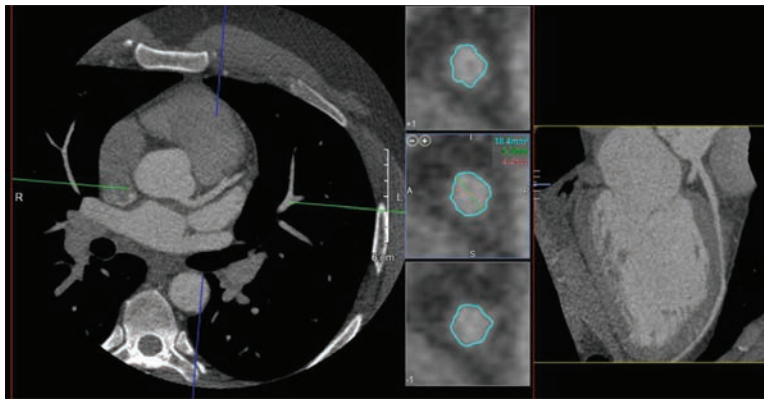

Figure 7.60

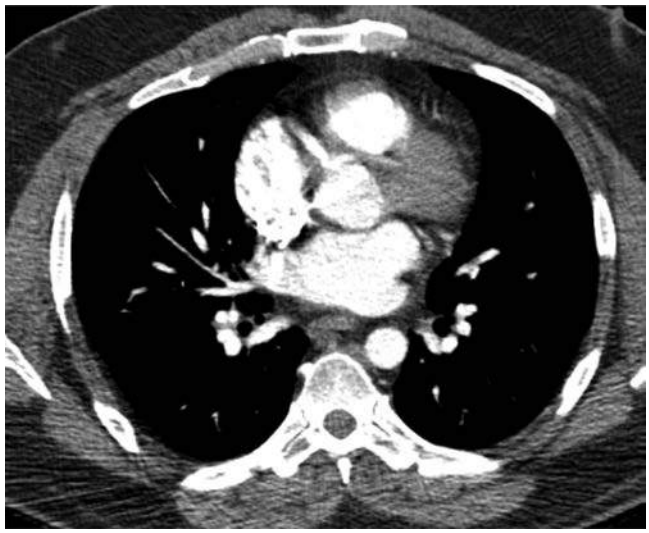

Figure 7.61a

7.62. What would be your recommendation to the patient in Question 7.61?

- **A.** Reassurance
- **B.** Exercise stress test
- **C.** Stress echo
- **D.** Coronary angiography and possible left coronary reimplant

7.63. An 83-year-old woman presented with acute central chest pain. Chest CT with contrast was obtained in the ER (Figure 7.63a). What are the images suggestive of?

- **A.** Stanford type A aortic dissection
- **B.** Stanford type B aortic dissection
- **C.** Pulmonary embolism
- **D.** Intramural hematoma

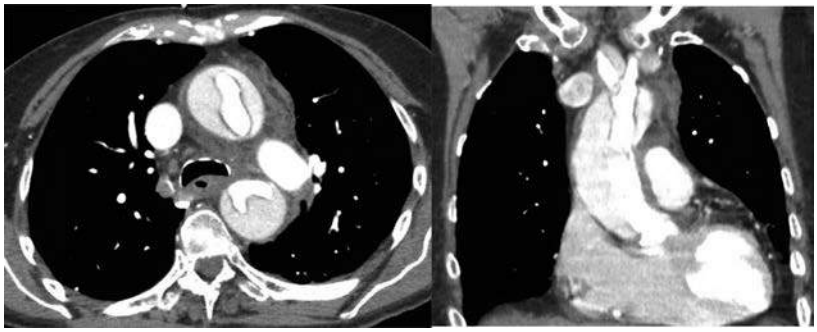

Figure 7.63a

Answers

7.1. A. Prospective gated noncontrast.
Prospective gating reduces radiation exposure. Contrast should not be used. Generally, a Hounsfield unit (HU) threshold of 130 units is used to detect calcium.

7.2. C. 3 mm.
Outcome data are based on this slice thickness.

7.3. B. Retrospective, gated with contrast.
For left ventricle function assessment the left ventricle has to be opacified; scan should be gated and should have all phases.

7.4. A. Prospectively gated, electrocardiogram (ECG)-triggered cardiac computed tomography angiography (CTA).
This is associated with an absorbed radiation dose of about 3 mSv, compared with about 15 mSv for retrospectively gated, cardiac CTA, 7 mSv for coronary angiography, and about 15 mSv for stress perfusion scan with sestamibi.

7.5. C. Dual isotope myocardial perfusion scan with thallium and Sestamibi.
This is associated with a radiation exposure of about 25 mSv. Dose modulation during prospective gating reduces radiation dose by about 40%, but prospective gating reduces by about 85%.

7.6. B. Women.
The young are also at high risk as they have more years to live after radiation exposure, such that cancer phenotype can develop following DNA damage.

7.7. D. Breast.
Breast and skin get the highest radiation dose, and then lung, heart, and esophagus in descending order.

7.8. D. All of the above.
Radiation dose is proportional to tube current and square of tube voltage. It is inversely proportional to pitch.

7.9. D. 3.0.
Radiation is inversely proportional to pitch. Hence, compared with a pitch of 1, 3 is associated with a third of the radiation and a pitch of 0.4 is associated with 2.5 times the radiation.

7.10. D. Cardiac MRI with gadolinium vasodilator stress.
There is no radiation with MRI. It uses radiofrequency pulses.

7.11. B. Patient with hypertension, ECG shows nonspecific ST–T changes, negative cardiac enzymes.
This is a level 4 chest pain patient; that is, atypical chest pain with a thrombolysis in myocardial infarction (TIMI) score <2. The other two scenarios are level 3 and are appropriate for stress testing. Coronary CTA is appropriate in patients with low to intermediate probability of coronary artery disease (CAD). See Box 7.1.

7.12. D. All of the above.
Beta blockers in oral and intravenous form are traditionally used. In those with reactive airway disease, calcium channel blockers are an option. In those with low blood pressure who may not tolerate either of these, ivabradine, which selectively slows the sinus node without lowering blood pressure, is an option. This drug is approved for treatment of heart failure.

7.13. C. Decreasing tube current by 25%.
This will reduce radiation dose by about 40%, whereas A and B options reduce radiation dose by only 25%.

7.14. C. Effective radiation dose (ERD).
ERD is expressed in millisieverts. CTDI is the radiation dose delivered by the machine for a given scan parameter based on phantom simulation. DLP (mGy cm) takes into consideration scan length: DLP = CTDIvol × scan length. ERD = DLP × 0.014 (where 0.014 is a conversion factor) for cardiac CTA. Hence, for a DLP of 1000 mGy cm, the ERD for cardiac CT is 1000 × 0.014 = 14 mSv

7.15. C. 5 mSv.
50 mSv is for adult radiation workers.

7.16. C. 0.14 mSv.
This is very low with low risk. Even with shielding, the fetus will get some scattered radiation.

7.17. B. −50 HU.
Water is 0 HU, air is −1000 HU.

7.18. B. 130.

7.19. D. All of the above.
Decreasing pitch reduces noise as well, but it increases radiation.

7.20. D. All of the above.
Multiple passes and signal averaging improve signal strength and reduce noise.

7.21. A. 0.5 mm × 0.5 mm.

$$\text{Pixel size} = \frac{\text{FOV}}{\text{matrix}}$$

7.22. C. Both.

7.23. D. Number of detector rows.
This affects the amount of coverage during one cardiac cycle, but not temporal or spatial resolution.

7.24. A. Increasing slice thickness.
This gives more photons or energy or signal. To reduce noise by half, you have to increase slice thickness fourfold, as noise is inversely proportional to the square of the number of photons.

7.25. C. Both.
With dual energy, you can subtract calcium from the image. Reconstruction with sharp filter has to be performed on the scanner raw data.

7.26. E. All of the above.

7.27. E. All of the above.

7.28. B. LAD coronary artery stent 2 years ago 2.5 mm.
It is inappropriate to perform coronary CTA when stent size is <3 mm. In others with symptoms, it is of uncertain significance.

7.29. A. Left main coronary artery stenting with stent size ≥3 mm.
It is inappropriate to do in other asymptomatic patients. Presence of symptoms, stent size of ≥3 mm, and left main coronary artery location make coronary CTA increasingly appropriate. Use of techniques such as dual-source CT or appropriate processing with iterative processing and use of sharp filters would be helpful for better quality images.

7.30. E. All of the above.

7.31. B. Normal RCA origin, not calcified.

7.32. B. Normal left main coronary artery origin, not calcified.

7.33. A. Pulmonary veins: left upper, left lower, right upper, right lower respectively.

7.34. A. Left atrial appendage.
2: Body of left atrium; 3: ascending aorta; 4: right ventricle outflow tract, 5: descending thoracic aorta.

7.35. A. Ascending aorta.
2: Descending aorta; 3: vertebral body; 4: roof of left atrium; 5: pulmonary vein.

7.36. A. LAD artery.
2: Left atrial appendage; 3: diagonal artery.

7.37. D. Right ventricle branch of RCA.
1: RCA; 2: right ventricular outflow tract (RVOT); 3: LAD artery; 4: right pulmonary veins.

7.38. A. RCA.
The RCA is in the right atrioventricular groove. The pericardiophrenic bundle would be outside the pericardium. 2: bronchus; 3: right ventricle; 4: left ventricle; 5: descending thoracic aorta.

7.39. A. Ascending thoracic aorta.
1: Ascending aorta.

7.40. A. Left lower pulmonary vein.
2: Descending thoracic aorta; 3: ascending aorta; 4: left upper pulmonary vein; 5: right lower pulmonary vein; 6: right upper pulmonary vein. Figure 7.40 is a view from the back.

7.41. B. Left internal mammary artery.
2: Right internal mammary artery; 3: RCA.

7.42. A. LAD artery.
2: Left lower pulmonary vein; 3: descending thoracic aorta; 4: intercostal artery; 5: left internal mammary artery.

7.43. A. Coronary sinus.
2: Left ventricle; 3: right ventricle; 4: right atrium.

7.44. C. Anomalous RCA from left coronary cusp with interarterial course.
Note that the proximal course is between aorta and RVOT. Circumflex courses normally. No LAD artery stenosis is seen in the images in Figure 7.44.

7.45. A. Normal.

7.46. C. Anomalous RCA from left sinus.
There is an interarterial course between the aorta and pulmonary artery (pulmonary artery not shown).

7.47. C. Need to evaluate LAD artery and other vessels using curved multiplanar reformation and centerline methods to comment about the coronaries.
One cannot comment about stenosis severity from volume rendered images.

7.48. B. Go ahead with coronary CTA; if lesions are moderate or indeterminate, consider cardiac catheterization.
Despite two risk factors, patient is at low to intermediate risk for CAD and coronary CTA (TIMI score 2 and level 4) is appropriate. Coronary calcification may impede lumen visualization, but coronary calcium score is not >400. Use of interactive processing and using sharp filter or dual-source CT would be helpful to better evaluate calcified areas.

7.49. B. RCA.
Distal RCA in right posterior atrioventricular groove.

7.50. C. Contrast CT with cardiac gating.
This could be prospectively gated for midsystolic phase or retrospectively gated so that systolic phase can be reconstructed. The measurements of aortic annulus should be obtained in systole and contrast is essential for blood–wall interface visualization.

7.51. E. All of the above.
Aortic annulus is best sized by CT. Coronary height of >10 mm assures that the aortic leaflets may not occlude coronary ostia after TAVR. Amount of calcification and length of aortic leaflets also have a bearing on potential to occlude coronary ostia. If the aortic sinus is small and coronary height is less, risk of coronary occlusion is high and there may be a need to wire the coronary before TAVR.

7.52. A. Size 23 mm TAVR.
Based on annular dimensions and area. Coronary height >10 mm is adequate.

7.53. D. All of the above.

7.54. C. Both.
The vessels are >7 mm, which would permit any delivery sheath. With the newer generation valves even 5–6 mm vessels are adequate.

7.55. E. All of the above.

7.56. E. All of the above.

7.57. A. Leaking pseudoaneurysm of the aorta.
Anteriorly, as shown by the arrow in Figure 7.57b – possibly related to RCA anatomosis.

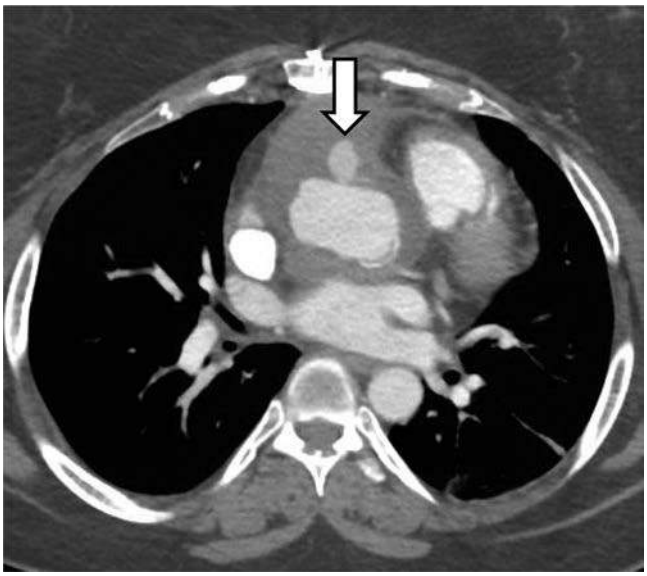

Figure 7.57b

7.58. A. Right ventricular lead perforation.
Note that the tip of the lead is beyond the right ventricle wall and in epicardial fat or beyond.

7.59. C. RCA stent.
The RCA stent is in the middle of the segment shown. CTA is not very optimal to evaluate for lesions within the stent, though the stent looks patent.

7.60. C. Myocardial bridging.
Note the smooth narrowing and intramyocardial course.

7.61. C. Anomalous origin of left coronary artery.
Note that the left coronary artery (arrow in Figure 7.61b) is originating from right coronary sinus and courses in between the aorta and RVOT. This course has elevated risk of sudden death, though it is commonly found at routine autopsies. Ventricular arrhythmia brought on by exertion is a possibility.

7.62. D. Coronary angiography and possible left coronary reimplant.
As the patient had syncope and is in a high-risk occupation, this is very justified. If he was asymptomatic, it is controversial what would be the best management, but most would lean toward coronary reimplant or a graft on the coronary. Reimplant may be associated with recurrent ostial stenosis of the left main coronary artery and needs close monitoring. A stress test would be reasonable if the patient was asymptomatic and had normal left ventricular function. However, the American College of Cardiology/American Heart Association guidelines recommend surgical correction for all coronaries coursing between great vessels.

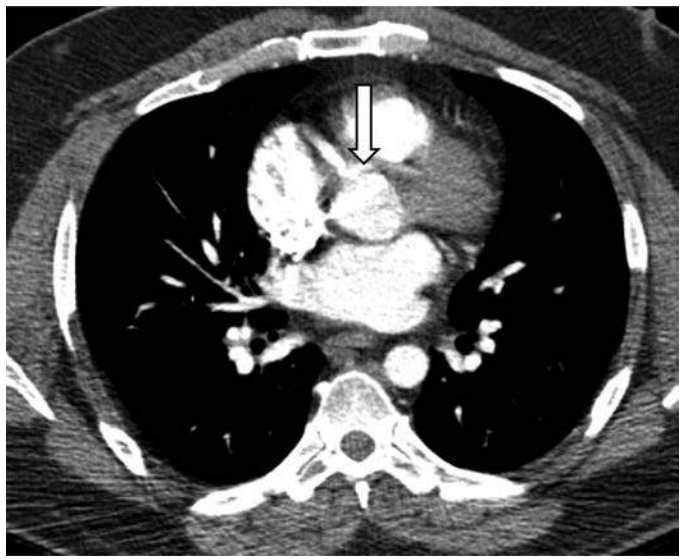

Figure 7.61b

7.63. A. Stanford type A aortic dissection.

This involves ascending and descending aorta (DeBakey type II). The axial image on the left of Figure 7.63b shows the true lumen in the ascending aorta (blue arrow) and descending aorta (red arrow). The coronal scan on the right of Figure 7.63b shows the ascending aorta with both true and false lumens. The false lumen is opacified by the contrast as there is flow in that; intramural hematoma does not get opacified by the contrast. Type B (DeBakey type III) involves descending aorta only and type I involves ascending aorta only. Transesophageal echocardiography, CT, and MRI are equally sensitive and specific for the diagnosis of aortic dissection.

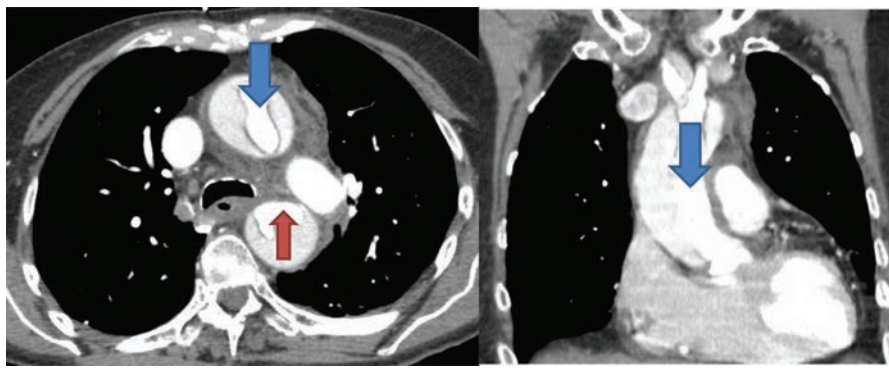

Figure 7.63b

Box 7.1 Suggested Chest Pain Triaging in ER and Role of Coronary CTA

Suggested steps in chest pain triaging in the ER (at discretion of ER physician)

1. Obtain details on prognostic variables
2. Assignment to level in chest pain protocol
3. Choice of testing based on the level
4. Incorporation of coronary CTA test results and disposition
5. Follow-up plan

1. Obtain details on prognostic variables

- Type of chest pain (angina, atypical, noncardiac)
- Age ≥65
- ≥3 coronary risk factors
- Known CAD
- Aspirin use in last 7 days
- ≥2 chest pain episodes in 24 h
- ST deviation ≥0.5 mm
- Elevated cardiac enzymes
- TIMI score (1 point each for age >65, >3 coronary risk factors, known CAD, aspirin use in last 7 days, >2 chest pain episodes in 24 h, ST deviation >0.5 mm, elevated cardiac enzymes)

2 and 3. Assignment to level in chest pain protocol and appropriate testing

See Figure B7.1.

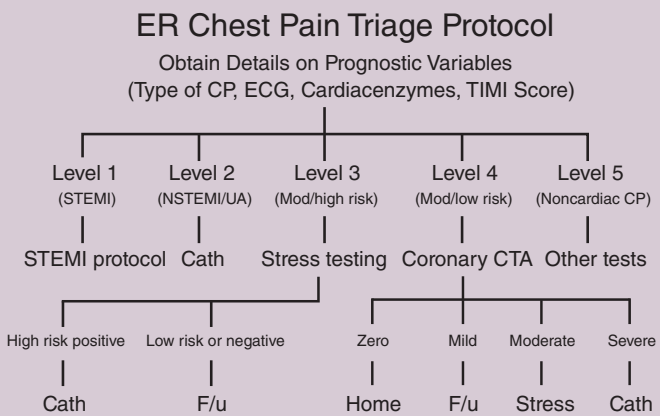

Figure B7.1

- Level 1: ST-elevation myocardial infarction (STEMI) → STEMI protocol
- Level 2: non-STEMI, unstable angina → cardiac catheterization
- Level 3: TIMI score >2, typical angina, moderate ACS risk → stress testing

- Level 4: low to intermediate risk of ACS, TIMI score ≤2 → coronary CTA
- Level 5: noncardiac chest pain → look for noncardiac causes based on presentation

4 and 5. Incorporation of coronary CTA test results and disposition

- Zero: no stenosis → discharge home
- Mild: 1–49% → discharge home with follow-up within a week
- Moderate: 50–69% → noninvasive testing (stress test)
- Severe ≥70%: → admit and catheterization

Choice of Stress Test

- If a patient can walk and ECG is normal → exercise stress ECG
- If a patient can walk and ECG is abnormal (not LBBB or RV paced rhythm) → exercise stress with imaging (echo or nuclear perfusion)
- If LBBBB or paced rhythm → Lexiscan nuclear perfusion preferable (exercise perfusion results in false-positive perfusion defects). Dobutamine or exercise stress echo are acceptable as well
- If a patient cannot walk → pharmacological stress test (dobutamine echocardiogram), vasodilator (Lexiscan) nuclear stress, vasodilator (Lexiscan) cardiac MRI when available

Further Reading

Raff, G.L., Chinnaiyan, K.M., Cury, R.C., *et al.* (2014) SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *Journal of Cardiovascular Computed Tomography*, **8**(4): 254–271. (An excellent review for chest pain triaging and appropriate use of cardiac CT in this situation.)

Taylor, A.J., Cerqueira, M., Hodgson, J.M., *et al.* (2010) ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *Circulation*, **122**(21): e525–e555. doi: 10.1161/CIR.0b013e3181fcae66. (A very useful resource that goes over appropriateness criteria for cardiac CT.)

Cardiac Catheterization

8

8.1. Which of the images A, B, or C in Figure 8.1 depicts the correct anatomic placement of the Kelly to identify the site of sheath entry for transfemoral access?

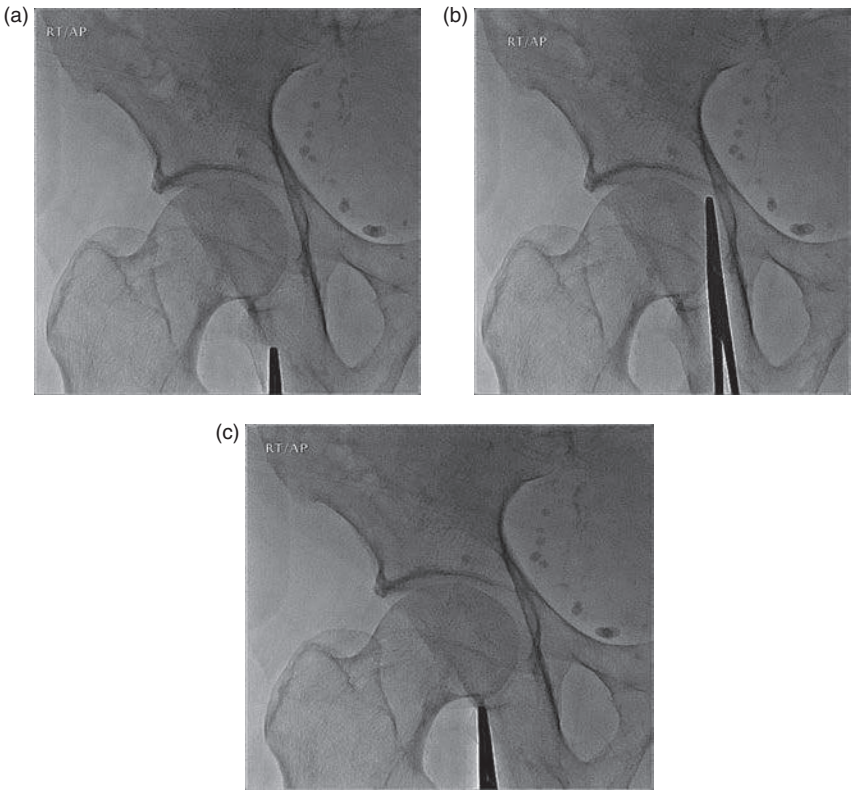

Figure 8.1

8.2. Where should be the ideal location of sheath entry in transfemoral access during cardiac catheterization?

A. Above the inferior epigastric artery to stay as far away from the common femoral bifurcation as possible
B. In the mid common femoral artery above the bifurcation
C. In the proximal profunda femoris
D. In the superficial femoral artery

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8.3. What are the possible complications associated with the access depicted in Figure 8.3?

A. No complications as the access appears appropriate
B. Pseudoaneurysm and arteriovenous malformations
C. Retroperitoneal hemorrhage
D. Intracranial hemorrhage

Figure 8.3

8.4. What physical sign would be expected if a complication occurred from a "low" stick?

A. A continuous bruit over the access site
B. Bruising over the skin
C. A sudden and severe drop in blood pressure
D. Angina chest discomfort

8.5. A 70-year-old man underwent a diagnostic cardiac catheterization via the right transfemoral approach prior to aortic valve replacement. Approximately 1 h later the nurse reports to you that he appears agitated and is complaining of lower abdominal discomfort. His systolic blood pressure is now 90 mmHg. The blood pressure prior to the procedure was 150 mmHg systolic. What is the next best step?

A. Immediately start intravenous fluid and blood transfusion and obtain a non-contrast computed tomography (CT) of the abdomen and pelvis.
B. Immediately start intravenous fluid and monitor blood pressure response
C. Reassure the nurse that his is likely a vagal response and request that she monitor the blood pressure closely
D. Immediately take the patient back to the catheterization laboratory to reevaluate his femoral anatomy.

8.6. Which of the femoral angiograms A or B in Figure 8.6 is most likely to be associated with the patient in Question 8.5?

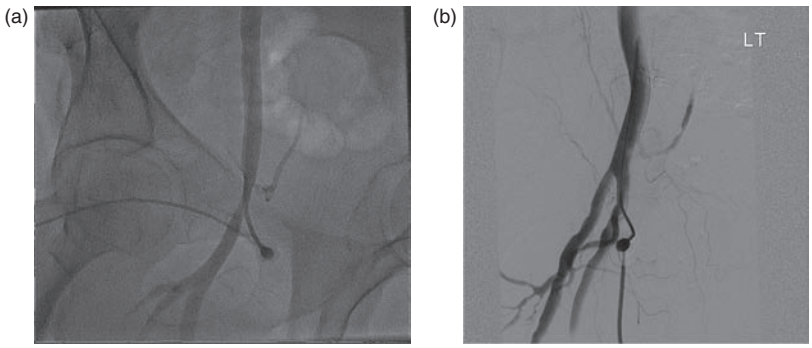

Figure 8.6

8.7. A 68-year old man underwent an uncomplicated percutaneous coronary intervention of the mid left anterior descending (LAD) artery. You are called about 30 min after the procedure that there is a large hematoma over the femoral access site. Manual pressure is applied for 40 min but the hematoma quickly reforms. What is the next best step?

A. Immediately start intravenous fluid and blood transfusion and obtain a non-contrast CT of the abdomen and pelvis
B. Immediately start intravenous fluid, apply a clamp for compression, and monitor blood pressure response
C. Reassure the nurse that his is likely a vagal response and request that she monitor the blood pressure closely
D. Immediately take the patient back to the catheterization laboratory to reevaluate his femoral anatomy

8.8. A 56-year-old man presents to the emergency department complaining of discomfort in the right groin. He underwent a diagnostic cardiac catheterization about 3 days ago. Examination reveals a loud, continuous bruit over the femoral artery. What test should be ordered next?

A. A complete lower extremity angiogram, as this patient likely has concomitant peripheral vascular disease
B. A CT scan of the pelvis
C. An ultrasound evaluation of the right groin
D. No work-up is needed as he likely has chronic peripheral vascular disease and the discomfort is normal in this time frame

8.9. A patient is being evaluated and consented prior to an outpatient cardiac catheterization. He reports that he had a CT angiogram about 2 years ago. After the procedure he developed hives and pruritus. His physician prescribed a medication for a week at that time, the name of which he cannot recall. How should he be managed?

A. Given that the procedure was remote, this is likely an idiosyncratic reaction; proceed with the planned procedure without addition evaluation or medication

B. He may have had a mild contrast reaction, which is unlikely to recur; proceed as planned without addition evaluation or medication
C. He may have had a mild contrast reaction; administer an antihistamine prior to the planned procedure
D. He may have had a mild contrast reaction; administer an antihistamine and a short course of oral steroids prior to the procedure

8.10. You are in the midst of completing a diagnostic cardiac catheterization on a patient. His coronary anatomy is angiographically normal and the left ventricular function is normal. He suddenly becomes profoundly hypotensive. He is fully alert and able to answer questions. A repeat angiography again demonstrates angiographically normal coronary arteries. A stat echocardiogram demonstrates that the left ventricular function is normal and there is no evidence of pericardial effusion. What is the next best step in his management?

A. Reverse the sedation and monitor hemodynamics
B. Administer a bolus of normal saline and monitor hemodynamic response
C. Start intravenous normal saline bolus followed by continued infusion and administer intravenous glucocorticoids
D. Start dopamine infusion immediately and admit to the intensive care unit. Consult cardiothoracic surgery

8.11. Which of the following statement is correct regarding sedation during transradial access?

A. No sedation is required as this is a minimal painful and quick access
B. Moderate sedation to achieve a completely comfortable response
C. Deep sedation, making sure that airway is protected but no response to painful stimuli
D. General anesthesia, as multiple sticks are often required and significant pain may occur

8.12. The right radial artery is successfully accessed for coronary angiography in a 55-year-old woman. The sheath is advanced without difficulty. What is the immediate next step?

A. Proceed with diagnostic catheter advanced under fluoroscopic guidance immediately as access may spasm
B. Administer a pharmacologic cocktail containing heparin only prior to beginning catheterization
C. Administer a pharmacologic cocktail containing heparin and a vasodilator prior to beginning catheterization
D. Administer a pharmacologic cocktail containing only a vasodilator prior to beginning catheterization

8.13. The cardiac catheterization is successfully completed in the patient in Question 8.12. As the sheath was being removed there is significant tension noted and the patient suddenly complained about pain in the forearm? How should you proceed?

A. This is a normal response; continue to steady negative tension and withdraw the sheath
B. Stop immediately, as the sheath is entrapped by arterial spasm; consult vascular surgery immediately

C. Administer a repeat bolus of the pharmacologic cocktail containing vasodilator and heparin; reattempt retraction gently
D. Repeat sedation only and reattempt when the patient is sedated and able to tolerate the discomfort

8.14. A 6-French JL-4 is used to engage the left main coronary artery for coronary angiography. The pressure waveform in Figure 8.14 is recorded. What should you do next?
A. Proceed as usual with coronary angiogram
B. Retract the catheter and reposition the engagement; if the same waveform is present, proceed as usual
C. Retract the catheter and reposition the engagement; if the same waveform is detected then give a small gentle puff of contrast to visualize the anatomy
D. Abandon the procedure, as there may be severe left main stenosis; consult cardiothoracic surgery

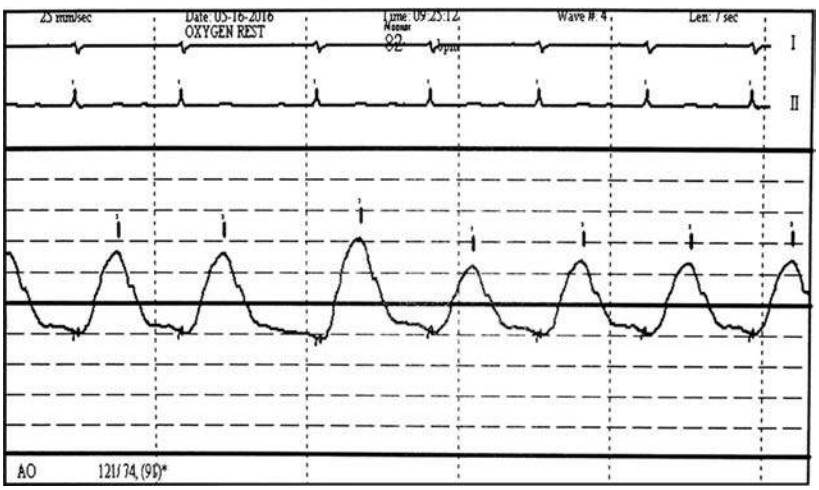

Figure 8.14

8.15. Coronary angiography is performed on a patient. What is depicted in the angiogram shown in Figure 8.15a?
A. Artifact from streaming of the contrast
B. A spiral dissection
C. Injection into the conus branch
D. Occluded right coronary artery

8.16. What should be the next step in treating the patient in Question 8.12?
A. Give a more brisk contrast injection to more forcefully displace the blood with contrast and better image the vessel
B. Advance a wire carefully to the distal vessel followed by a small-caliber over-the-wire balloon to verify intraluminal position
C. Proceed with angiography of the right coronary system, as no treatment is required for vessel tortuosity
D. Advance a floppy wire and treat the individual stenosis with stent implantation

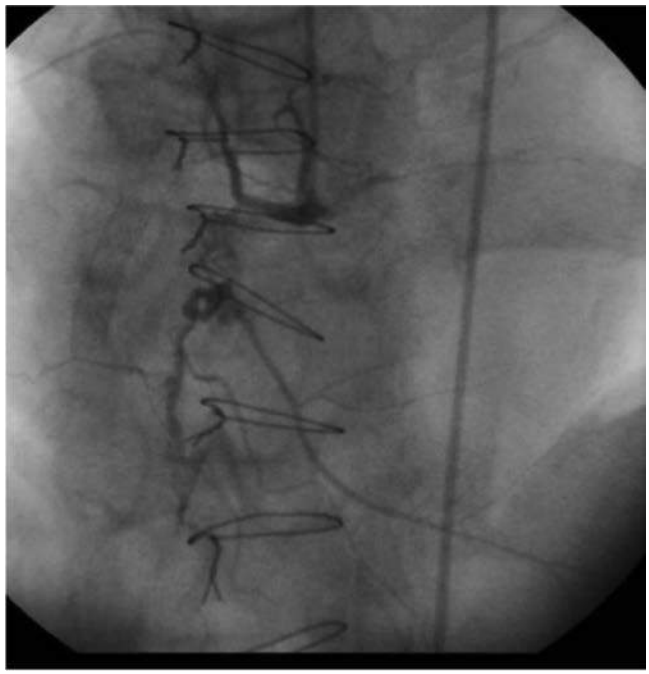

Figure 8.15a

8.17. What is the aortogram in Figure 8.17 suggestive of?
- **A.** Occluded left main artery
- **B.** Occluded RCA
- **C.** Aortic dissection
- **D.** Aortic intramural hematoma

8.18. The patient in Figure 8.18 presented with cardiogenic shock. What does the image show?
- **A.** Impella, RCA stent
- **B.** Intra-aortic balloon pump
- **C.** RCA stent and tandem heart catheter
- **D.** None of the above

8.19. What does the coronary angiogram in Figure 8.19 show?
- **A.** Significant distal left main coronary artery lesion
- **B.** LAD stenosis
- **C.** Severe circumflex lesion
- **D.** None of the above

8.20. What has the patient in Figure 8.20 likely presented with?
- **A.** Acute anterior ST-elevation myocardial infarction (STEMI)
- **B.** Acute inferior STEMI
- **C.** Chronic stable angina
- **D.** None of the above

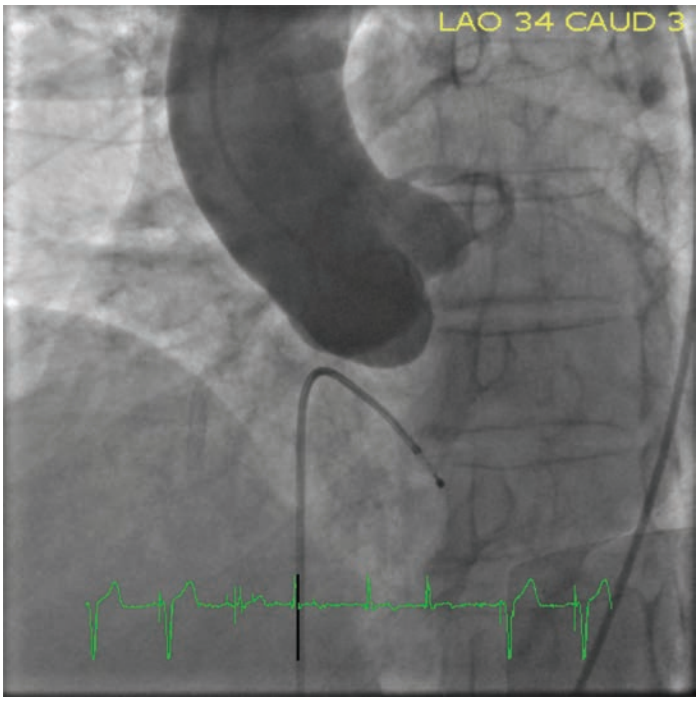

Figure 8.17

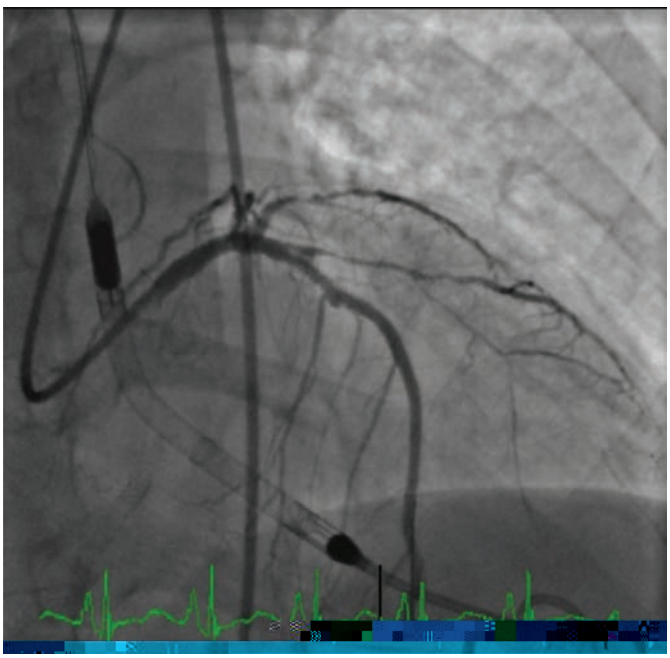

Figure 8.18

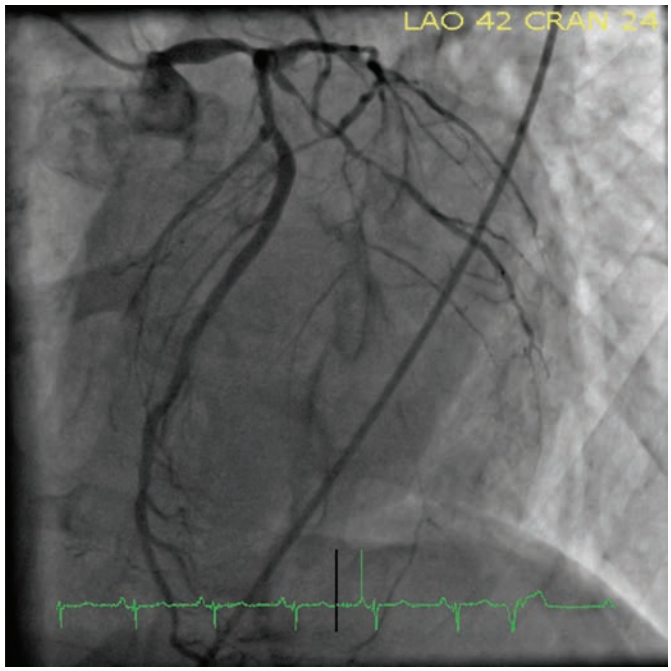

Figure 8.19

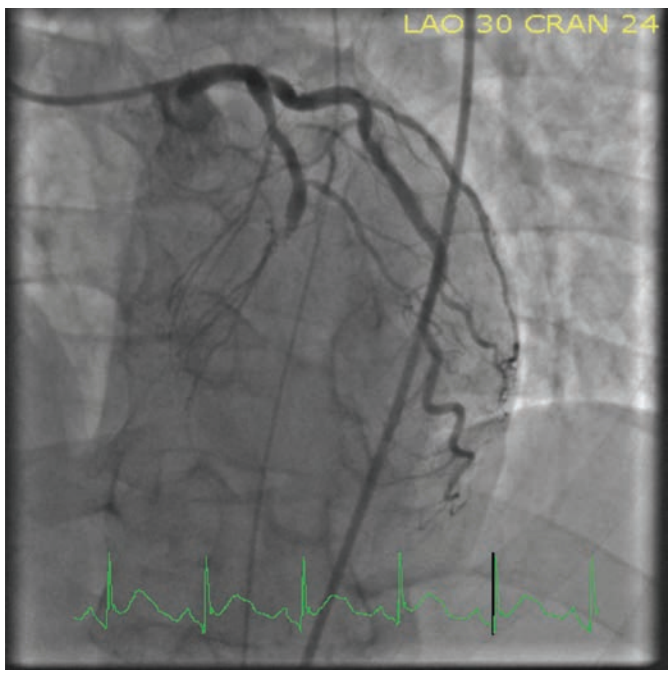

Figure 8.20

Answers

8.1. C.

An instrument such as a Kelly is placed over the patient skin to fluoroscopically identify the inferomedial femoral head. This is the ideal location for the needle to enter the skin at such an angle as to facilitate entry into the common femoral artery below the inferior epigastric artery and above the common femoral bifurcation. Entry at this location minimizes vascular complications.

8.2. B. In the mid common femoral artery above the bifurcation.

The ideal location for sheath entry into the common femoral artery is below the inferior epigastric artery and above the bifurcation to minimize vascular complications.

8.3. B. Pseudoaneurysm and arteriovenous malformations.

This sheath has entered the superficial femoral artery and is considered a low stick. Low sticks are associated with arteriovenous fistulas and pseudoaneurysms as potential vascular complications.

8.4. A. A continuous bruit over the access site.

A low stick could result in an arteriovenous fistula or pseudoaneurysm. Physical examination would reveal a continuous murmur on auscultation over the arteriotomy site.

8.5. A. Immediately start intravenous fluid and blood transfusion and obtain a noncontrast CT of the abdomen and pelvis.

This patient most likely has a retroperitoneal hemorrhage. The sudden drop in blood pressure and the abdominal discomfort are big clues to this diagnosis. He should be immediately resuscitated with intravenous fluids and should receive a blood transfusion. A noncontrast CT scan of the abdomen and pelvis should be ordered when he is hemodynamically stable to confirm the diagnosis.

8.6. A.

The first angiogram demonstrates a "high" stick just at the inferior epigastric artery. A high stick is associated with a retroperitoneal hemorrhage.

8.7. D. Immediately take the patient back to the catheterization laboratory to reevaluate his femoral anatomy.

A hematoma over the arteriotomy may develop from inadequate manual compression, failure of closure device, or vessel trauma. In a patient with a hematoma that is refractory to prolonged attempts at hemostasis with manual compression, the appropriate step would be to reevaluate the femoral anatomy. This allows for efficient decision making in management of any potential vascular complication.

8.8. C. An ultrasound evaluation of the right groin.

An ultrasound is the test with the highest initial yield in this patient. It will identify potential local vascular complications such as a pseudoaneurysm, which is the most likely diagnosis.

8.9. C. He may have had a mild contrast reaction; administer an antihistamine prior to the planned procedure.

This patient likely had a mild contrast reaction and should be pretreated with antihistamines such as diphenhydramine 50 mg about 1 h before the procedure.

8.10. C. Start intravenous normal saline bolus followed by continued infusion and administer intravenous glucocorticoids.

This patient is most likely having an immediate adverse contrast reaction. The angiography should be immediately stopped and he should be resuscitated with intravenous fluids. Glucocorticoids may be administered to suppress the immune response but will not be effective immediately. Epinephrine injection may be needed. In refractory or severe cases, vasopressor infusion may be needed to temporize the situation.

8.11. B. Moderate sedation to achieve a completely comfortable response.

Adequate moderate sedation is essential in transradial access as pain and anxiety may lead to more arterial spasm.

8.12. C. Administer a pharmacologic cocktail containing heparin and a vasodilator prior to beginning catheterization.

The radial artery is small in caliber and prone to spasm; therefore, after radial access, it is generally recommended to administer a pharmacologic cocktail of heparin and a vasodilator. Different regimens and dosages have been recommended. One such option is 2000 units of heparin, 200 μg of nitroglycerine, and 2.5 mg of verapamil.

8.13. C. Administer a repeat bolus of the pharmacologic cocktail containing vasodilator and heparin; reattempt retraction gently.

If there is resistance while maneuvering catheters via the transradial approach, vasospasm should be immediately suspected. Aggressively removing the catheter may result in evulsion of the artery. Therefore, repeating the pharmacologic cocktail of heparin and vasodilators is the most prudent course of action. Sedating the patient is appropriate, though not as a stand-alone therapy.

8.14. C. Retract the catheter and reposition the engagement; if the same waveform is detected then give a small gentle puff of contrast to visualize the anatomy.

The example shown is of a ventricularized arterial waveform. This is recognized at a slight decrease in systolic pressure but a large decrease in diastolic pressure. There is also a loss of or significant smoothing out of the dicrotic notch. It is commonly encountered when the angiography catheter passes through or is against a significant coronary stenosis. Readjusting the catheter to verify positioning is important before continuing on with the angiography. If the same waveform is verified then a gentle "puff" of injection can be performed to visualize the anatomy and the potential cause of the waveform.

8.15. D. Occluded right coronary artery.

The arrow in Figure 8.15b points to occluded proximal right coronary artery with bridging collaterals. The patient had prior coronary artery bypass surgery.

8.16. B. Advance a wire carefully to the distal vessel followed by a small-caliber over-the-wire balloon to verify intraluminal position.

A common technique in treating a coronary dissection is to leave the first wire in place within the dissection plane. A second wire is then attempted to be advanced into the true lumen. The first wire may act both as a guide as to the location of the dissection plane and also may deflect the second wire. Once the wire is advanced successfully a small balloon may be advanced and dye injection performed to confirm intraluminal position.

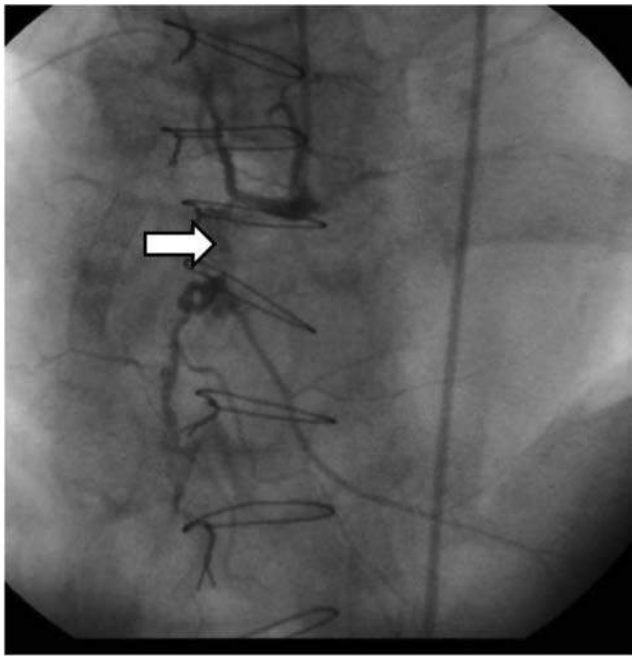

Figure 8.15b

8.17. B. Occluded RCA.
The RCA is calcified as well. The ascending aorta is normal. Note a temporary right ventricular pacer and intermittent pacing.

8.18. A. Impella, RCA stent.

8.19. A. Significant distal left main coronary artery lesion.

8.20. A. Acute anterior ST-elevation myocardial infarction (STEMI).
Note the thrombotic occlusion of the mid LAD artery.

Acute Coronary Syndromes

9

9.1. Of the following statements regarding a patient with multiple cardiac risk factors and angina-like chest pain lasting 30 min, which is the incorrect one?
- **A.** A normal echocardiogram (ECG) in the emergency room (ER) rules out myocardial infarction (MI)
- **B.** Ischemia in circumflex area is more often electrically silent
- **C.** Negative first set of cardiac markers does not rules out MI
- **D.** ECG changes could be dynamic, and it is useful to repeat every 15 min in the first hour of chest pain or when chest pain recurs

9.2. The components of thrombolysis in MI (TIMI) risk score on initial patient evaluation for suspected acute coronary syndrome (ACS) include which of the following?
- **A.** Age >65 years
- **B.** More than three coronary artery disease (CAD) risk factors
- **C.** Prior CAD with >50% lesion
- **D.** More than two anginal events in 24 h
- **E.** Use of aspirin in last 7 days
- **F.** ST deviation on ECG
- **G.** Elevated cardiac markers
- **H.** All of the above
- **I.** Some of the above

9.3. Which of the following types of chest pain rule out ACS?
- **A.** Sharp stabbing chest pain
- **B.** Pleuritic chest pain
- **C.** Chest pain reproduced by palpation
- **D.** None of the above

9.4. Guideline recommendation for ECG for patients presenting with chest pain to the ER is performance of ECG within how much time of arrival?
- **A.** 5 min
- **B.** 10 min
- **C.** 30 min
- **D.** 60 min

9.5. The GRACE risk model predicts in hospital mortality in ACS patients and includes Killip class, systolic blood pressure (BP), heart rate, age, and serum creatinine level. Which one of the following may be negatively correlated with mortality?
- **A.** Heart rate
- **B.** Systolic BP
- **C.** Killip class
- **D.** None of the above

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9.6. Which of the following are contraindications for NTG in patients with ACS and continuing chest pain?
- **A.** Systolic BP <90 mmHg
- **B.** Inferior MI with positive Kussmaul
- **C.** Sildenafil or vardenafil within 24 h
- **D.** Tadalafil within 48 h
- **E.** All of the above
- **F.** None of the above

9.7. Regarding use of traditional nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors in the setting of ACS, which of the following statements is correct?
- **A.** Traditional NSAIDs, but not COX-2 inhibitors can be used
- **B.** Traditional NSAIDs should be used, but COX-2 inhibitors can be used
- **C.** Neither traditional NSAIDs nor COX-2 inhibitors should be used
- **D.** Either can be used with no risk of harm

9.8. Which calcium channel blockers are contraindicated in ACS?
- **A.** Diltiazem
- **B.** Verapamil
- **C.** Short-acting nifedipine without a beta blocker
- **D.** None of the above

9.9. The first dose and route of aspirin use in suspected ACS is which of the following?
- **A.** 162 or 325 mg enteric coated
- **B.** 162 or 325 mg nonenteric coated chewed
- **C.** 81 mg orally
- **D.** None of the above

9.10. Aspirin in suspected ACS is avoided in which of the following patients?
- **A.** Aspirin allergy
- **B.** Recent gastrointestinal bleed
- **C.** Neither A nor B
- **D.** Both A and B

9.11. For patients with ACS, what is the recommended duration of double antiplatelet therapy (DAPT)?
- **A.** 1 month
- **B.** 6 months
- **C.** 1 year
- **D.** Forever, unless at high risk of bleeding

9.12. After NSTEMI, in addition to ASA, Plavix, beta blocker, and high-intensity statin therapy, which other agents are recommended for those with ejection fraction (EF) <40%?
- **A.** Angiotensin-converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs) in those who are ACEI intolerant
- **B.** Aldosterone blocking agent, provided creatinine is <2 mg/dL and K is <5 meq/L
- **C.** Diltiazem to prevent reinfarction
- **D.** A and B
- **E.** A and C

9.13. In a patient with non-ST elevation ACS, early coronary angiography is appropriate in which of the following situations?
- **A.** TIMI score of 5
- **B.** Continuing chest pain
- **C.** EF <40%
- **D.** Anterior wall motion abnormality
- **E.** Dynamic mitral regurgitation (MR) murmur
- **F.** All of the above

9.14. Based on current data, which of the following statements are correct in the setting of ACS?
- **A.** In the setting of ST elevation MI (STEMI), nonculprit vessels should not be stented
- **B.** In the setting of NSTEMI, it is reasonable to perform percutaneous coronary intervention (PCI) on critically stenosed nonculprit vessels as well
- **C.** Both A and B are correct
- **D.** Neither A or B are correct

9.15. Which of the following statements are correct re prasugrel use?
- **A.** It is used 10 mg once a day.
- **B.** It reduces risk of stent thrombosis compared with clopidogrel
- **C.** It has a higher risk of bleeding in those above 75 years of age or weigh <60 kg
- **D.** It is contraindicated in those with prior stroke or transient ischemic attack (TIA)
- **E.** All of the above
- **F.** None of the above

9.16. Which of the following should not be used as the sole anticoagulant during PCI?
- **A.** Fondaparinux
- **B.** Enoxaparin
- **C.** Bivalirudin
- **D.** None of the above

9.17. Which of the following statements are accurate re the duration of stoppage of antiplatelet drugs before elective coronary artery bypass grafting?
- **A.** Clopidogrel for 5 days
- **B.** Prasugrel for 7 days
- **C.** Eptifibatide and tirofiban for 2–4 h
- **D.** Abciximab for 12 h
- **E.** All of the above

9.18. Before coronary artery bypass grafting, which of the following statements is correct?
- **A.** Aspirin should be stopped a week earlier
- **B.** Aspirin should not be stopped
- **C.** Aspirin should be stopped 24 h before
- **D.** None of the above

9.19. Which of the following statements are accurate regarding triple antithrombotic therapy after MI?
- **A.** The duration should be minimized
- **B.** Concomitant proton pump inhibitors should be used

C. Triple therapy should not be used
D. A and B are correct

9.20. Which of the following agents are useful for secondary prevention post MI?
A. Vitamin E
B. Folic acid
C. Beta carotene
D. Fish oil
E. None of the above

9.21. Which of the following statements are true for older patients with non-ST elevation ACS?
A. They may have atypical symptoms
B. Benefit with medical and catheter-based therapies is similar to younger patients
C. They get less guideline-directed medical therapy
D. None of the above
E. All of the above

9.22. Compared with men, women presenting with ACS have which of the following?
A. More atypical symptoms
B. Greater chance of getting discharge from the ER
C. Higher risk of long-term complications such as heart failure (HF), shock, renal failure, stroke, readmission
D. All of the above
E. None of the above

9.23. Compared with men, women presenting with ACS have which of the following?
A. Greater incidence of normal coronary arteries
B. Higher percentage of normal EF
C. Fewer high-risk lesions
D. Same benefit with medicines
E. All of the above
F. None of the above

9.24. In ACS due to cocaine use, it is preferable to avoid which of these agents?
A. Heparin
B. Beta blocker
C. ACEI
D. None of the above

9.25. Which of the following are true re use of early glycoprotein (GP) IIb/IIIa inhibitor in the setting of acute STEMI receiving DAPT?
A. There is no clear benefit in terms of MI or death during follow-up
B. No clear evidence for a decrease in target vessel revascularization
C. There is evidence for rapidity of ST segment resolution, but not for improvement in TIMI grade 3 flow
D. All of the above

9.26. Adjunctive GP IIb/IIIa inhibitors are recommended in addition to DAPT and heparin in acute STEMI setting in which of the following situations?
A. At time of primary PCI
B. Routinely in the ER

C. Those with large thrombus burden
D. All of the above
E. At time of primary PCI or those with large thrombus burden

9.27. For a patient presenting with STEMI to a non-PCI facility, which of the following factors support immediate thrombolytic therapy?
A. Presentation within 4 h of chest pain
B. Low-risk STEMI
C. Low bleeding risk with thrombolysis
D. PCI facility is far away
E. All of the above
F. There is no indication for thrombolysis; transfer to PCI facility

9.28. A 68-year-old man presents to a non-PCI facility with anterior STEMI with ST elevation from V2 to V5. He is short of breath with bilateral rales. Chest pain started 4 h earlier. He had a TIA 6 weeks earlier and is on clopidogrel and statin. Estimated transport time to nearest catheterization laboratory is 75 min. After giving O_2, nitroglycerin (NTG), ASA, and heparin, what is the best next strategy?

A. Immediate transfer to the PCI facility
B. Give half-dose thrombolytic and then transfer
C. Patient is too high risk to transfer; give full-dose thrombolytic
D. None of the above

9.29. A 64-year-old man presents to a non-PCI facility with anterior STEMI with ST elevation from V2 to V4. He is short of breath with bilateral rales. Chest pain started 3 h earlier. He is on aspirin and statin. Estimated transport time to nearest catheterization laboratory is 4 h. There are no contraindications for thrombolytic therapy. After giving O_2, NTG, ASA chewed, and heparin, what is the best next strategy?
A. Full-dose thrombolytic and transfer to PCI facility
B. Half-dose thrombolytic and transfer to PCI facility
C. Immediately transfer to PCI facility
D. Treat medically as the patient is high risk to transfer

9.30. In patients presenting with acute MI, which of the following plasma glucose targets are desirable?
A. Tight control with glucose <110 mg/dL
B. Liberal control with glucose <300 mg/dL
C. Glucose <180 mg/dL
D. None of the above

9.31. A 65-year-old patient with diabetes mellitus and hypertension had an acute anterior MI treated within 4 h of chest pain with drug-eluting stent (DES) in left anterior descending (LAD) artery. He is stable. Serum creatinine is 1.3 mg/dL; creatine clearance 60 mL/min. His home medications include aspirin, glybenclamide, metformin, and lisinopril. What would the appropriate actions be?
A. Start on insulin infusion 1 unit per hour and titrate to blood glucose <180 mg/dL
B. Continue current medications
C. Discontinue metformin
D. Discontinue lisinopril

9.32. Which of the following statements regarding thrombus aspiration are accurate in patients with acute MI undergoing PCI?
- **A.** It is reasonable to perform in those presenting early and have large thrombus burden
- **B.** It may not be useful in those presenting late
- **C.** It is not useful in side branches subtending small myocardial territories
- **D.** All of the above
- **E.** None of the above

9.33. A 52-year-old man with no prior cardiac history presented with chest pain of 4 h and found to have acute anterior STEMI. He lost his job and medical insurance recently. He was on lisinopril and simvastatin. After administering aspirin and NTG, an immediate coronary angiography revealed a 90% lesion in the mid LAD artery with a reference diameter of 4 mm. The lesion length was 6 mm and type B. Other vessels were angiographically normal. What would the most appropriate therapy be?
- **A.** A DES
- **B.** A bare-metal stent (BMS)
- **C.** Either
- **D.** Immediate single-vessel bypass using left internal mammary artery on beating heart

9.34. In acute STEMI qualifying for reperfusion therapy, which of the following options is correct?
- **A.** Desired door to needle is ≤30 min and door to balloon time is ≤90 min
- **B.** Desired door to needle and door to balloon times are ≤90 min
- **C.** There is no indication for thrombolysis
- **D.** None of the above

9.35. Which of the following strategies may reduce time to reperfusion therapy in acute STEMI?
- **A.** Media campaign to educate patients on signs of MI
- **B.** Prehospital ECG
- **C.** Use of 9-1-1 rather than being driven to the ER by a family member
- **D.** An ER MI protocol
- **E.** All of the above

9.36. In acute STEMI, fibrinolysis is preferred over primary PCI in which of the following situations?
- **A.** Early presentation, ≤3 h
- **B.** Catheterization laboratory is not available or expert operator is not available
- **C.** Predicted (door to balloon)–(door to needle) time is greater than 60 min
- **D.** Medical contact to balloon or door to balloon time is likely to be >90 min
- **E.** All of the above

9.37. In acute STEMI, primary PCI is preferred over fibrinolysis in which of the following situations?
- **A.** Late presentation, >3 h of chest pain
- **B.** Heart failure or cardiogenic shock
- **C.** Contraindication to thrombolytics
- **D.** Diagnosis of STEMI is in doubt
- **E.** All of the above

9.38. Absolute contraindications for thrombolytics include which of the following?
- **A.** Prior intracranial hemorrhage
- **B.** Ischemic stroke within 3 months (except acute stroke <3 h)
- **C.** Closed head or facial trauma in last 3 months
- **D.** Cerebral arteriovenous malformation, berry aneurysm, or neoplasms
- **E.** All of the above
- **F.** Above are only relative contraindications and decision depends upon risk/benefit ratio

9.39. Relative contraindication for thrombolytics include which of the following?
- **A.** Systolic BP >180 mmHg or diastolic BP >110 mmHg
- **B.** Prolonged cardiopulmonary resuscitation or major surgery in <3 weeks
- **C.** Pregnancy
- **D.** Current anticoagulant use
- **E.** Noncompressible vascular punctures
- **F.** All of the above
- **G.** Some of the above

9.40. Which of the following statements about tissue plasminogen activator (tPA) are true?
- **A.** It acts more rapidly than streptokinase
- **B.** It acts better in the presence of fibrin; in its absence it is a weak plasminogen activator
- **C.** It is a surface-active agent
- **D.** Generally, dose for STEMI is 15 mg bolus + 50 mg over 30 min + 35 min over 60 min
- **E.** All of the above
- **F.** Some of the above

9.41. GUSTO-1 was a landmark trial that compared front-loaded alteplase with streptokinase in acute STEMI within 6 h. What were the findings?
- **A.** Reduced death with alteplase
- **B.** Reduced myocardial reinfarction with alteplase
- **C.** Trend to increased intracranial bleed with streptokinase
- **D.** All of the above

9.42. A 48-year-old man with acute inferior MI has a heart rate of 74 bpm, BP of 90/60 mmHg. There are no murmurs. The jugular venous pressure is 16 cmH_2O and the column seems to rise during quiet breathing. The lungs are clear. What would the appropriate treatment for low BP include?
- **A.** Intravenous bolus of normal saline
- **B.** Normal saline and dobutamine infusion if BP is still low
- **C.** Intravenous Lasix
- **D.** Infusion of norepinephrine

9.43. A 52-year-old man with reperfused (with PCI with DES) acute anterior MI got recurrent chest pain, more on breathing, associated with an increase in ST elevation leads V2 to V5 on day 3. What may this indicate?
- **A.** Stent thrombosis
- **B.** Dressler's syndrome
- **C.** Chemical pericarditis
- **D.** Potential for myocardial rupture

9.44. In what is left ventricle free wall rupture in the presence of acute MI more common?

- **A.** Elderly
- **B.** Women
- **C.** Those without prior infarcts
- **D.** Large infarcts
- **E.** Reperfusion with lytics rather than PCI
- **F.** All of the above
- **G.** Some of the above

9.45. Which of the following are true about left ventricle free wall rupture?

- **A.** It tends to occur at the junction of infarct and normal muscle
- **B.** Generally occurs after 1–4 days of infarct, but can occur as late as 3 weeks
- **C.** Usually occurs in left ventricle, but may involve right ventricle or atria
- **D.** All of the above

9.46. A 46-year-old patient with inferior STEMI, post primary PCI, became suddenly short of breath, rapidly evolving into pulmonary edema needing endotracheal intubation. On examination, his heart rate was 130 bpm, BP 80/50 mmHg, bilateral rales, and high jugular venous pressure. Cardiac sounds were soft, and there were no murmurs. The ECG showed sinus tachycardia with normal ST segments. What is the most likely diagnosis?

- **A.** Coronary stent thrombosis
- **B.** Acute pulmonary embolism
- **C.** Papillary muscle rupture
- **D.** Large RV infarct

9.47. Which of the following statements are true regarding papillary muscle rupture?

- **A.** It can occur with small subendocardial infarcts affecting tip of papillary muscle
- **B.** More commonly involves posteromedial papillary muscle
- **C.** Anterolateral papillary muscle may derive dual blood supply from LAD and circumflex arteries and is less prone to rupture
- **D.** All of the above

9.48. In the setting of acute MI, prophylactic lidocaine is recommended in which of the following situations?

- **A.** Large anterior MI
- **B.** Routinely in prehospital phase
- **C.** Routinely on arrival to the ER
- **D.** None of the above
- **E.** All of the above

9.49. Patients with acute inferior MI may get which of the following types of atrioventricular (AV) conduction problems?

- **A.** Generally, first degree or Mobitz type I, but sometimes worse
- **B.** Generally intranodal problem due to ischemia or increased vagal tone
- **C.** May respond to atropine
- **D.** Rarely needs permanent pacemaker
- **E.** All of the above

9.50. Patients with acute MI, may get which of the following types of AV conduction problems?

- **A.** Generally, Mobitz type II or complete heart block
- **B.** Generally due to extensive myocardial ischemia
- **C.** In Mobitz type II AV block, atropine can make it worse by dropping the ventricular rate by increasing atrial rate
- **D.** Generally needs permanent pacemaker
- **E.** All of the above

9.51. A 62-year-old patient presents 3 weeks after an acute MI with fever and pleuritic chest pain. There was no cough, and chest X-ray showed blunting of costophrenic angles. ECG showed inferior Q waves with no ST elevation. The white cell count was 20 000 with neutrophilia; erythrocyte sedimentation rate was 100 mm at the end of first hour. What would the best treatment be?

A. Azithromycin
B. Aspirin 650 mg q 6 h
C. NSAIDs
D. Prednisone 40 mg/day
E. None of the above

9.52. In a patient with acute anterior MI, post primary PCI, and an EF of 30%, which of the following may reduce the risk of death in the ensuing 3 months?

A. Beta blocker
B. Amiodarone
C. *d*-Sotalol
D. Flecainide

9.53. Which of the following statements about depression post MI are true?

A. It is common
B. It is associated with an increase in mortality
C. It is associated with poor medication compliance
D. Selective serotonin reuptake inhibitors improve survival
E. All of the above
F. B and D only are correct.

9.54. Which of the following statements are true about DAPT after an acute MI?

A. DAPT reduces mortality only during the first year
B. DAPT may reduce mortality beyond 1 year post MI
C. DAPT reduces mortality beyond 1 year in only those with DES
D. None of the above.

9.55. The results of the DAPT trial support the use of DAPT post MI even after 12 months. Which of the following were additional observations with use of DAPT?

A. The rate of stent thrombosis was reduced beyond 12 months
B. Risk of MI in nonstented areas was reduced
C. There was a higher risk of bleeding
D. All of the above

9.56. The PLATO trial (comparing clopidogrel with ticagrelor after ACS) showed which of the following?

A. Ticagrelor was associated with reduced major adverse cardiac and cerebrovascular events (MACCEs) after ACS compared with clopidogrel
B. Risk of major bleeding was similar for both agents overall
C. Risk of intracranial bleeding was higher with ticagrelor
D. Risk of MI was lower with ticagrelor, but stroke risk was similar
E. All of the above

9.57. The TOTAL trial randomized patients undergoing primary PCI for STEMI to thrombectomy versus no thrombectomy. What were the findings?

A. Thrombectomy did not reduce the primary endpoint of death, MI, stroke, and class IV HF
B. Stroke risk was increased in thrombectomy patients
C. No benefit of thrombectomy in the subset with high thrombus burden

D. Bailout thrombectomy needed in 8% of nonthrombectomy group
E. All of the above.

9.58. The MATRIX-ACCESS trial shows which of the following?
A. The rate of major adverse cardiac events was similar between radial and femoral access approaches
B. Net adverse cardiac events were lower in radial approach strategy
C. Risk of bleeding was lower with a adial approach
D. Major bleeding was associated with higher mortality
E. All of the above are accurate

9.59. The DANAMI 3 trial tested the hypothesis that performing PCI on non-infarct-related artery (IRA) during primary PCI for STEMI may improve outcome. Which of the following were the results?
A. The primary endpoint (death, MI, subsequent revascularization) was reduced by about 50% by performing PCI on non-IRA
B. Only MI was reduced by performing PCI on non-IRA
C. Only angina and repeat revascularization was reduced by performing PCI on non-IRA
D. There was no difference in outcome by performing PCI on non-IRA

9.60. Based on the After Eighty trial, primary PCI for STEMI in the elderly,
A. Increased stroke risk
B. Reduced MACCEs
C. Did not affect outcomes
D. None of the above

Answers

9.1. A. A normal echocardiogram (ECG) in the emergency room (ER) rules out myocardial infarction (MI).

This statement is wrong, as about 10% of acute non-ST-elevation MI (NSTEMI) may have normal ECG. ECG changes could be dynamic, where even ST elevation can come and go.

9.2. H. All of the above.

Each has a score of 1 and the maximum total score is 7. The higher the score, the higher is the 14-day event rate, progressively increasing from 4.7% to 40.9%. Note that ACS despite acetylsalicylic acid (ASA), ST deviation and positive cardiac markers portend high risk (Antman *et al.*, 2000).

9.3. D. None of the above.

In a multicenter chest pain study, ACS was present in 22%, 13%, and 7% respectively for choices A, B, and C.

9.4. B. 10 min.

9.5. B. Systolic BP.

The higher the systolic BP, the lower the risk. For others, higher numbers correlate with higher mortality (Granger *et al.*, 2003).

9.6. E. All of the above.

This is because of risk of serious hypotension. Clinical scenario in B is indicative of right ventricular (RV) infarct.

9.7. C. Neither traditional NSAIDs nor COX-2 inhibitors should be used.
This is because of potential risk of platelet aggregation. Also, these may be associated with higher risk of gastrointestinal bleeding.

9.8. C. Short-acting nifedipine without a beta blocker.
This is because of risk of reflex tachycardia.

9.9. B. 162 or 325 mg nonenteric coated chewed.

9.10. D. Both A and B.

9.11. C. 1 year.

9.12. D. A and B.
That is, ACEIs or ARBs in those who are ACEI intolerant, and aldosterone blocking agent provided creatinine is <2 mg/dL and K is <5 meq/L. Diltiazem reduced reinfarction rate in NSTEMI in the diltiazem reinfarction trial when EF was >40%. Also, in this trial, a beta blocker was not used and this was before the days of statin therapy.

9.13. F. All of the above.
These are all high risk markers.

9.14. C. Both A and B are correct.

9.15. E. All of the above.

9.16. A. Fondaparinux.
This is because of risk of catheter thrombosis.

9.17. E. All of the above.

9.18. B. Aspirin should be not be stopped.
Should continue 81–324 mg/day.

9.19. D. A and B are correct.

9.20. E. None of the above.

9.21. E. All of the above.

9.22. D. All of the above.

9.23. E. All of the above.

9.24. B. Beta blocker.
This is because of possible risk of unopposed alpha action of cocaine on coronary artery worsening spasm. The same principle holds for amphetamine-induced ACS as well.

9.25. D. All of the above.
See discussions on BRAVE-3, ON-TIME 2 and Horizons-AMI trials in Box 9.1.

9.26. E. At time of primary PCI or those with large thrombus burden.

9.27. E. All of the above.
The low-risk patients presenting early are suitable candidates. These patients may even be treated medically and noninvasively risk stratified unless there are high-risk features during hospital stay.

9.28. A. Immediate transfer to the PCI facility.
This is a high-risk patient and rapid PCI is in order. Also, history of TIA poses a contraindication for thrombolytic therapy.

9.29. A. Full-dose thrombolytic and transfer to PCI facility.

This is a high-risk patient with anterior MI, pulmonary edema, and ACS despite aspirin. In view of considerable delay in transfer to PCI facility and presentation within 4 h of chest pain, administering thrombolytic with immediate arrangement to transfer to PCI facility is appropriate as there are no contraindications for thrombolytics. See discussion on TRANSFER-AMI trial in Box 9.1. Early presentation, delay in transfer, and lack of contraindications for thrombolytics support thrombolytic therapy followed by PCI as soon as possible.

9.30. C. Glucose <180 mg/dL.

The 2009 guidelines recommend this conventional target rather than a tight control of normal glucose recommended in the 2004 guidelines. There are no trials comparing these two strategies in acute MI, but a large randomized trial in intensive care unit patients (NICE-SUGAR) indicated higher mortality in the intensive glucose control arm.

9.31. C. Discontinue metformin.

Discontinue metformin in view of radiocontrast agent administration to reduce risk of lactic acidosis. Insulin infusion is no longer recommended for tight glycemic control in acute MI any more as per 2009 guidelines.

9.32. D. All of the above.

The choices are self-explanatory. Benefit is seen in those who present early, have a large thrombus burden, and large territory is jeopardized. The EXPIRA trial, which randomized 175 patients, showed greater myocardial blush, greater 90-min ST segment resolution, and smaller infarct size at 3 months in those undergoing thrombus aspiration.

9.33. B. A bare-metal stent (BMS).

This is in view of the fact that he may not be able to reliably take clopidogrel for 1 year (uninsured) and the fact that stent size is 4 mm and short with low-risk of restenosis. A DES is superior to a BMS in diabetics in those with long lesions and small vessels (<3 mm). There was no difference in outcomes between BMS and DES except rates of later ischemia-driven target vessel revascularization (HORIZONS-AMI trial).

9.34. A. Desired door to needle is ≤30 min and door to balloon time is ≤90 min.

9.35. E. All of the above.

All of these may speed up time to reperfusion.

9.36. E. All of the above.

The first trials to show the benefit of thrombolytics over placebo in STEMI included the British ISIS-2 trial and Italian GISSI trial.

9.37. E. All of the above.

This is provided a catheterization laboratory is available with expert operator and door or contact to balloon time is likely to be <90 min.

9.38. E. All of the above.

In view of high risk of bleeding into brain. In addition, suspected aortic dissection or active bleeding (menses is not) are contraindications.

9.39. F. All of the above.

9.40. E. All of the above.

In addition, there is a risk of allergy with streptokinase and should not be repeated in the next 6-12 months.

9.41. A. Reduced death with alteplase.

There was no difference in reinfarction rates. There was a trend to increased intracranial hemorrhage with alteplase.

9.42. B. Normal saline and dobutamine infusion if BP is still low.

The patient has classical RV infarct with raised jugular venous pressure, Kussmaul's sign, and clear lungs in the setting of inferior MI. Other signs may include ST elevation in right chest leads. Intravenous fluids help improve RV output, and dobutamine will recruit noninfarcted RV myocardium to increase its performance. BP may plummet with diuresis and NTG.

9.43. D. Potential for myocardial rupture.

The focal pericarditis causing recurrent ST elevation may be due to slow seepage of blood through softened myocardium and is a marker of high risk of rupture. Dressler's syndrome occurs after 2–3 weeks. An echocardiogram would be valuable, and this may show intramural hematoma, pericardial fluid, or strands, which are risk factors for threatened myocardial rupture.

9.44. F. All of the above.

All are recognized risk factors for myomalacia cordis. In addition, being on steroids or NSAIDs and hypertension may predispose to it. The rupture could be acute or blowout (which results in immediate death), subacute (causing tamponade), or chronic (causing a pseudoaneurysm).

9.45. D. All of the above.

The rupture generally does not occur in the center of infarct. Adjacent hyperkinesis near a dyskinetic segment may promote rupture.

9.46. C. Papillary muscle rupture.

In view of flash pulmonary edema and hypotension. Hypotension combined with high left atrial pressure and large regurgitant orifice may not result in an MR murmur because of low driving pressure and lack of turbulence in the MR jet. Acute stent thrombosis is unlikely in view of lack of ST elevation. Acute pulmonary embolism and RV infarct do cause pulmonary edema.

9.47. D. All of the above.

Posteromedial papillary muscle has blood supply from right coronary artery only and is more likely to rupture.

9.48. D. None of the above.

There is no benefit for prophylactic lidocaine. The Lown grading of ventricular arrhythmias as a basis for prophylactic lidocaine has not been supported by randomized trials.

9.49. E. All of the above.

9.50. E. All of the above.

9.51. B. Aspirin 650 mg q 6 h.

This is classic Dressler's syndrome, which is thought to be autoimmune, occurring in about 1% of MIs. NSAIDs and steroids are best avoided as they may impair the left ventricle healing process and may promote rupture.

9.52. A. Beta blocker.
See details on CAST, SWORD, CAMIAT, and EMIAT in Box 9.1.

9.53. E. All of the above.

9.54. B. DAPT may reduce mortality beyond 1 year post MI.
Please see results of DAPT and TIMI-54 trials in Box 9.1.

9.55. D. All of the above.
See DAPT trial details in Box 9.1.

9.56. E. All of the above.
See details of PLATO trial in Box 9.1.

9.57. E. All of the above.
See Box 9.1.

9.58. E. All of the above are accurate.
Please see Box 9.1.

9.59. A. The primary endpoint (death, MI, subsequent revascularization) was reduced by about 50% by performing PCI on non-IRA.
See Box 9.1.

9.60. B. Reduced MACCEs.
See Box 9.1.

Box 9.1 Key Trials

- CAST (T C A S T (CAST) I ,): C - A S T . S I (, ,) MI. T .
- SWORD (W *et al.*,): *d*-S MI EF < %. T *d*- .
- CAMIAT (C *et al.*,): C MI. N - .
- EMIAT (J *et al.*,): E MI. N - .
- ISIS- (ISIS- (F I S I S) C G ,): T F I S I S . A - - .I . A .
- ISIS- (ISIS- (S I S I S) C - G ,): T S I S I S . A × - . I . A - .
- ISIS- (ISIS- (T I S I S) C G ,): T T I S I S . A × - , PA, , . A . I . N

- . S PA: PA
, - , . T
PA . F
PA. T
, -
.

- GISSI- (G I S S 'I M (GISSI) ,): MI . T . % SK % , % (p = . , (RR) . , % (CI) . .).
- GUSTO (T GUSTO I ,): MI - , - , , - PA , PA . A PA - .
- PAMI (T G U S O O C A A C S (GUSTO II) A S I ,): STEMI PA . A , , ,
- VANQWISH (B *et al.*,): I NSTEMI, .
- FRISC-II (L *et al.*,): I NSTEMI , .
- SHOCK (H *et al.*,): MI - . E . H , . E - MI .
- PURSUIT (T PURSUIT T I ,): ACS ST . I - MI ST- .
- PRISM-PLUS (P R I I S M P L U S S (PRISM-PLUS) S I ,): ACS . W , GP II /III ACS .
- BRAVE- (M *et al.*,): STEMI DAPT . A ,

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, MI, , -
(% , . %).

- ON-TIME (V ' H *et al.*,): STEMI DAPT. T ST , TIMI . N - - , MI, .
- H -AMI (S *et al.*,). STEMI DAPT UFH GP II /III . A , .
- TRITON-TIMI (W *et al.*,): - - ACS ( ) ( ). A - . . P , MI, (. % . %). D MI. P .T US F D A (FDA) > < . I < , FDA / . P DAPT - TIA .
- ASSENT- (A S E N T S P C I (ASSENT- PCI) I ,): PCI STEMI. F PCI - (% %). S , , GP II /III PCI.
- FINESSE (E *et al.*,): N PCI STEMI.
- TRANSFER-AMI (C *et al.*,): H - STEMI -PCI (, ASA, , , PCI) (- , PCI). P (% %).
- DAPT (M *et al.*,): ASA MI ASA MI . DAPT (. % . %) MACCE (MI) ASA . DAPT .
- TIMI- (B .,): MI ASA , ASA BID ASA BID. MACCE % ASA . % DAPT . I , , , .
- PLATO (W *et al.*,): ACS - . A , , , . % . % (, . ; % [CI], . . ; *P* < .).

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- TOTAL (J *et al.*,): A
  PCI STEMI. R . N
  , MI, , HF IV. B
  % . T
  .
- MATRIX-A (V *et al.*,): -
  , ST- ,
  ( ) ( )
  . (. %)
  , (. %) ([RR]
  . , % CI . . ; *p* = .), - α . . (. %)
  (. %)
  (. , % CI . . ; *p* = .). T
  BARC [B A R C]
  (. % . %, RR . , % CI . . ; *p* = .)
  - (. % . %, RR . , % CI . . ; *p* = .).
- DANAMI (E *et al.*,): D PCI -
  -IRA (> % FFR < . > %) PCI
  STEMI . . P , MI
  , % -IRA PCI %
  IRA- PCI (*p* = .).
- A E (T *et al.*,): STEMI >
  PCI . %
  PCI .

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Chronic Coronary Artery Disease

10

10.1. The resting electrocardiogram (ECG) is normal in what percentage of patients with stable coronary artery disease (CAD)?
- **A.** About 10%
- **B.** About 50%
- **C.** About 75%
- **D.** 100%

10.2. The occurrence of conduction disturbances such as left bundle branch block (LBBB) and left anterior fascicular block (LAFB) are associated with which of the following?
- **A.** Good prognosis
- **B.** Poor prognosis
- **C.** Does not dictate prognosis
- **D.** None of the above

10.3. The presence of LV hypertrophy on the resting ECG in a patient with stable CAD may be suggestive of which of the following?
- **A.** Underlying hypertension
- **B.** Aortic stenosis
- **C.** Hypertrophic cardiomyopathy
- **D.** All of the above
- **E.** None of the above

10.4. In what percentage of patients does the resting ECG become abnormal in patients with stable CAD during an episode of angina?
- **A.** 100%
- **B.** 50%
- **C.** 75%
- **D.** 25%

10.5. What is the most common finding on the ECG in stable CAD patients during an episode of angina?
- **A.** ST segment depression
- **B.** ST segment elevation
- **C.** Normalization of previous ST abnormalities (pseudonormalization)
- **D.** None of the above

10.6. In a patient with chest pain and moderate probability of CAD and a normal resting ECG, what is the best test to order to evaluate for ischemia?
- **A.** Exercise stress ECG
- **B.** Exercise echo
- **C.** Dobutamine stress echo
- **D.** Stress nuclear

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10.7. What is true of a negative stress ECG for a patient receiving anti-anginal medications when evaluating for ischemia?
- **A.** Reduces the sensitivity as a screening tool
- **B.** Does not have any effect on the test
- **C.** Increases the sensitivity as a screening tool
- **D.** None of the above

10.8. A stress nuclear test is helpful in which of the following situations?
- **A.** Abnormal resting ECG changes
- **B.** LBBB
- **C.** LV hypertrophy
- **D.** All of the above

10.9. A pharmacological stress test can be ordered to evaluate for CAD in which of the following situations?
- **A.** Patients unable to exercise and achieve an adequate workload
- **B.** Peripheral vascular disease
- **C.** Patients with pulmonary disease
- **D.** All of the above

10.10. Exercise testing in asymptomatic patients without known CAD may be appropriate in which situation?
- **A.** Patients with diabetes mellitus
- **B.** Severe coronary calcifications on electron beam computed tomography (CT)
- **C.** Evidence of ischemia on ambulatory ECG
- **D.** All of the above
- **E.** None of the above

10.11. Which of the following is a true statement?
- **A.** Stress test in females is associated with higher false-positive results compared with males
- **B.** Stress test in females is associated with low rate of false-positive results compared with males
- **C.** Stress test in females is associated with higher rates of false-negative results compared with males
- **D.** Stress test in females is associated with low rates of false-negative results compared with males
- **E.** The results are similar in both men and women when stratified appropriately

10.12. In a patient with angina, with an intermediate to high pretest probability, with LBBB on ECG and with moderate ability for physical exercise, what is a reasonable diagnostic test to perform?
- **A.** Exercise stress ECG
- **B.** Exercise stress echo
- **C.** Coronary angiogram
- **D.** Adenosine stress cardiovascular magnetic resonance (CMR)

10.13. In a patient with angina, with intermediate pretest probability and able to perform moderate ability to function physically, what would be a reasonable test to perform?
- **A.** Coronary angiography
- **B.** Exercise stress ECG
- **C.** Exercise stress echo
- **D.** Coronary CT angiography (CCTA)

10.14. In a patient with an intermediate to high pretest probability for CAD and who is incapable of at least moderate exertion, what are the recommended tests for the diagnosis of CAD?

A. Dobutamine stress echo
B. Adenosine stress single-photon emission CT (SPECT)
C. Dobutamine stress SPECT
D. None of the above
E. All of the above

10.15. A 40-year-old woman is referred for evaluation of angina. Her physical exam is normal. Based on her history she is at low pretest likelihood. She has severe knee pain and is unable to perform moderate physical activity. What is the best recommended diagnostic test to evaluate her angina?

A. Coronary angiogram
B. Adenosine stress CMR
C. CCTA
D. Dobutamine stress echo
E. B, C, and D

10.16. A 55-year-old male with a history of hypertension, diabetes, smoking, and family history of CAD is referred to you for evaluation of chest pain. He is unable to walk on the treadmill due to back pain. What is a reasonable diagnostic test to perform?

A. Coronary angiogram
B. Dipyridamole stress echo
C. Stress CMR
D. CCTA

10.17. A 65-year-old male is referred for evaluation of exercise-induced angina. He has a history of hypertension, diabetes mellitus, and hypercholesterolemia. He used to smoke one pack of cigarettes a day for 20 years and has quit recently. His father was diagnosed with CAD and underwent coronary artery bypass grafting (CABG) at age 68. He is on aspirin, amlodipine 10 mg daily, lisinopril 20 mg daily and Lipitor 40 mg qd. On exam his heart rate is 60 bpm, BP 120/75 mmHg, and is otherwise unremarkable. He used to walk 2 miles a day. He now has intractable angina and is not able to perform low-intensity exercise. His primary care physician had started him on long-acting nitrates without relief. What is the best test to evaluate this patient's symptoms?

A. Exercise stress ECG
B. Exercise stress SPECT
C. Coronary angiogram
D. Dobutamine stress echo

10.18. A 63-year-old male with a history of hypertension, diabetes mellitus, hypercholesterolemia, and past history of smoking has complaints of angina. His primary care physician has optimized him on guideline-directed medical therapy and has referred him to you for further evaluation. An echocardiogram is ordered and resting LV ejection fraction (EF) is 30%. What is the best test to evaluate this patient?

A. Exercise SPECT
B. Adenosine SPECT

C. Coronary angiogram
D. Exercise treadmill

10.19. A 60-year-old female with cardiac risk factors is being evaluated for IHD. She has complaints of new-onset angina. She is on optimal medical therapy for hypertension, hypercholesterolemia and diabetes mellitus. She is unable to walk due to orthopedic limitations. She then has a dobutamine stress echocardiogram, wherein she achieves 70% of her age-predicted maximum heart rate at peak stress. What is the best approach in further evaluation of this patient?
A. Adenosine stress SPECT
B. Coronary angiogram
C. No further testing
D. Intensify medical therapy

10.20. A 69-year-old male has a history of hypertension, diabetes mellitus controlled on long-acting insulin therapy, hypercholesterolemia, and past history of smoking. He is on optimal medical therapy. He has new onset of exercise-induced angina of 1 month duration. His primary care physician ordered a stress test. His stress test was interpreted as negative. He is now referred to you for further evaluation. What is the best test to order?

A. No further testing
B. Stress nuclear imaging
C. Coronary angiogram
D. Adenosine stress CMR

10.21. A 59-year-old male patient with multiple cardiac risk factors and intractable angina was referred for a coronary angiogram. His coronary angiogram revealed a 60% stenosis in the mid LAD artery. What is the best approach in the treatment of this patient?
A. Percutaneous coronary intervention (PCI) of the 60% stenosis with a bare-metal stent
B. Fractional flow reserve (FFR)-guided PCI of the 60% stenosis
C. No further evaluation
D. PCI with a drug-eluting stent (DES)

10.22. A 71-year-old male underwent coronary angiogram to evaluate suspected IHD. His angiogram revealed 30% lesion in his mid right coronary artery (RCA), 40% lesion in left circumflex artery, and a 60% stenosis of his proximal LAD artery. FFR of the LAD artery lesion was 0.85. What is the best approach in managing this patient?
A. PCI with a DES to his proximal LAD stenosis
B. Intensify medical therapy
C. PCI of left circumflex and LAD stenosis
D. No further therapy

10.23. What is the US annual mortality rate in a middle-aged man with CAD?
A. 1.7–3%
B. 5–10%
C. 10–15%
D. None of the above

10.24. What is the US occurrence of major ischemic events in a middle-aged person with CAD?

A. 5–10%
B. 1.4–2.4%
C. 15–25%
D. None of the above

10.25. What is the 5-year survival in a patient with triple-vessel disease with an LV EF of 30% and on medical therapy?

A. 70%
B. 60%
C. 40%
D. 25%

10.26. There is an increased gradient of risk based on angiographic extent of disease. Which of the following options best describes this statement?

A. True
B. False
C. Not enough information is provided
D. None of the above

10.27. In a patient with symptomatic CAD, with three-vessel CAD on coronary angiography and an EF of 40%, what would the best approach be?

A. Multivessel PCI with DES
B. Multivessel PCI with bare metal stents
C. Coronary artery bypass grafting (CABG) including left internal mammary artery (LIMA) to LAD artery
D. Medical therapy only

10.28. According to the SYNTAX trial, what was a low SYNTAX score?

A. 23–32
B. ≤22
C. ≥33
D. 50

10.29. In the SYNTAX trial, the combined end point of death, myocardial infarction (MI), and stroke for CABG was described as what compared with DES at 5-year follow-up?

A. Equal
B. Lower
C. Higher
D. None of the above

10.30. In the SYNTAX trial, MI and repeat revascularization were described as what in the DES group compared with the CABG group?

A. Lower
B. Higher
C. Equal
D. None of the above

10.31. In the SYNTAX trial at 5-year follow-up, the occurrence of major adverse cardiac and cerebrovascular events (MACCEs) was described as what in the PCI group compared with the CABG group?

A. Equal
B. Lower
C. Higher
D. Do not know

10.32. What is the best approach for revascularization in a patient with 70% distal left main coronary disease?

A. PCI with DES
B. CABG
C. Medical therapy
D. Medical therapy plus CABG

10.33. A 65-year-old male patient has complaints of severe angina. His coronary angiogram reveals a 50% mid RCA stenosis, FFR of 0.85, and a 30% left circumflex lesion. What is the best approach in treating this patient?

A. DES to RCA stenosis only
B. DES to RCA and left circumflex arteries
C. CABG
D. Guideline-directed medical therapy

10.34. In the COURAGE trial, is it true or false that PCI with optimal medical therapy reduced the risk of death or MI compared with optimal medical therapy alone?

A. True
B. False

10.35. A 69-year-old male with hypertension and diabetes mellitus had a coronary angiogram for symptoms of angina. His resting echocardiogram showed an EF of 35%. He underwent PCI with a DES to the mid LAD artery. He is on aspirin, clopidogrel, metoprolol, and high-intensity atorvastatin. Prior to discharge, what other medication is indicated?

A. Hydrochlorothiazide
B. Angiotensin-converting inhibitor
C. Diltiazem
D. Angiotensin receptor blocker

10.36. In the patient mentioned in Question 10.35, what is the optimal duration of dual antiplatelet therapy?

A. 3 months
B. 6 months
C. 12 months
D. 6–12 months

10.37. A 54-year-old male with CAD has complained of angina which occurs two or three times per week. He is on aspirin, long-acting metoprolol, and atorvastatin. What is the next best step to add?

A. Nifedipine
B. Switch metoprolol to atenolol
C. Ranolazine
D. Long-acting nitrates

10.38. The patient in Question 10.37 is started on a long-acting nitrate. He comes back to your office for a follow-up. He indicates that his angina is not completely resolved. He also says that his BP at home is elevated 150/95 mmHg. What is the best course of action to take next?

A. Add nicardipine
B. Start ranolazine
C. No need to add anything at this time
D. Switch metoprolol to atenolol

10.39. By how much does ranolazine increase the plasma concentration of simvastatin?
- **A.** Threefold
- **B.** Twofold
- **C.** Fourfold
- **D.** Does not change the plasma concentration

10.40. How is the absorption rate of ranolazine affected by verapamil?
- **A.** Increased
- **B.** Decreased
- **C.** No change

10.41. How is the plasma concentration of ranolazine affected by ketoconazole?
- **A.** Decreased
- **B.** Increased
- **C.** It is not affected

10.42. Cocaine causes MI due to its effect on what?
- **A.** Alpha adrenergic stimulation
- **B.** Beta adrenergic stimulation
- **C.** Alpha and beta adrenergic stimulation
- **D.** Dopaminergic receptors

10.43. A 65-year-old man was admitted to the emergency room with acute anterior ST elevation MI. He underwent uneventful stenting of the proximal LAD artery within 4 h of chest pain onset. He had mild congestive heart failure, and EF on echo was 30%. In addition to beta blocker, angiotensin-converting-enzyme inhibitor, high-dose statin, aspirin, and clopidogrel, what else is likely to improve his outcome, if done before discharge?
- **A.** Implantation of an implantable cardioverter-defibrillator
- **B.** Eplerenone 25 mg daily
- **C.** Amiodarone 200 mg daily to reduce risk for VT/Vfib
- **D.** Warfarin to get an INR to 2-3 to prevent LV thrombus

10.44. A 38-year-old athletic, very muscular individual is evaluated for numbness in the left arm during exercise and weightlifting. No other medical problems. Examination is normal, as is the resting ECG. He is 68 inches tall, weighs 180 lbs, and has a short muscular neck. On stress test using a ramp protocol, he attained 95% of age-predicted heart rate at 16 METs, there was no chest pain, but had 1 mm of upsloping ST depression in inferior leads resolving within 20 s. What will you recommend?
- **A.** Coronary angiogram
- **B.** Stress nuclear test or stress echo.
- **C.** Adson's test
- **D.** Magnetic resonance imaging of C spine.

Answers

10.1. B. About 50%.

The resting ECG can be normal in about 50% of patients with stable CAD. Nonspecific ST–T changes are most commonly found on the resting ECG in stable CAD patients.

10.2. B. Poor prognosis.

The presence or development of conduction disturbances in stable CAD patients is associated with a poor prognosis. This may be suggestive of reduced left ventricular (LV) function and or multivessel disease (Fihn *et al.*, 2014).

10.3. D. All of the above.

When LV hypertrophy is evident on the resting ECG, further evaluation is needed. Such patients should undergo an echocardiogram to evaluate LV function, wall motion, wall thickness and valve function.

10.4. B. 50%.

The resting ECG becomes abnormal in 50% of patients during an episode of angina in patients with stable CAD.

10.5. A. ST segment depression.

The most common finding on a resting ECG during an episode of angina is ST depression. The most common finding is ST segment depression.

10.6. A. Exercise stress ECG.

Exercise stress ECG is probably the best test to order in this situation. The stress ECG will be very useful to evaluate for ischemia especially when the resting ECG is normal and the patient is able to exercise and achieve a good workload (Fihn *et al.*, 2014).

10.7. A. Reduces the sensitivity as a screening tool.

In the presence of anti-anginal therapy, the sensitivity of stress ECG is reduced and a negative stress test cannot be used to rule out significant CAD. Long-acting nitrates and beta blockers need to be stopped 2–3 days prior to the test.

10.8. D. All of the above.

A stress nuclear test will be helpful in the evaluation of ischemia in the presence of resting ECG changes, LBBB, LV hypertrophy, and in those receiving digoxin. In these patients, ST segments cannot be interpreted accurately during stress. An exercise stress nuclear test is relatively expensive (about three times) compared with a regular stress ECG test. Hence, a stress nuclear test should not be used as a screening tool especially in a patient with low probability of CAD. In patients with chest pain and a normal resting ECG, an exercise stress ECG should be used to screen for CAD. In patients with LBBB, pharmacological stress is preferable as exercise stress may result in false-positive septal perfusion defects.

10.9. D. All of the above.

A pharmacological stress nuclear test can be used to evaluate for ischemia in all of the situations A–C. Though pharmacological stress testing provides diagnostic accuracy comparable to an exercise stress nuclear test, exercise testing should be preferred as the exercise portion of the test provides additional information, such as heart rate and blood pressure (BP) response, amount of exercise and workload achieved, symptoms, and stress ECG abnormalities. Hence, whenever a patient can exercise and has a normal resting ECG, an exercise stress test is preferable (Fihn *et al.*, 2014).

10.10. D. All of the above.

10.11. A. Stress test in females is associated with higher false-positive results compared with males.

Exercise stress ECG was associated with a higher rate of false-positive rates based on earlier studies. But when men and women are appropriately categorized based on their pretest probability, the results of stress test are similar in both men and women, though the specificity may be slightly lower (Fihn *et al.*, 2014).

10.12. D. Adenosine stress cardiovascular magnetic resonance (CMR).

In a person with angina and with moderate physical limitation, a pharmacological stress is recommended. According to the 2012 ACC/AHA guidelines (Fihn *et al.*, 2012), pharmacological stress CMR is useful in the diagnosis of CAD (class IIa) recommendation (Nandalur *et al.*, 2007; Hamon *et al.*, 2010; Schuetz *et al.*, 2010).

10.13. D. Coronary CT angiography (CCTA).

In a person with an intermediate pretest probability of CAD, with ability to exercise moderately a CCTA can be useful to diagnose CAD (class IIb) recommendation according to the 2012 ACC/AHA guidelines (Fihn *et al.*, 2012; Budoff *et al.*, 2008; Schuetz *et al.*, 2010).

10.14. E. All of the above.

In a patient with intermediate to high pretest likelihood of CAD and unable to perform at least moderate exertion, then pharmacological stress with either echo or nuclear imaging is recommended (class 1) according to the 2012 ACC/AHA guidelines (Fihn *et al.*, 2012).

10.15. E. B, C, and D.

In a patient with low pretest likelihood and unable to exercise, pharmacological stress or CCTA are a reasonable diagnostic test (class IIa, level of evidence C) (Fihn *et al.*, 2012).

10.16. C. Stress CMR.

In a patient with intermediate to high pretest likelihood and unable to exercise, stress CMR is reasonable to perform for evaluation of angina (class IIa, level of evidence B). CCTA is reasonable to perform in a patient with low to intermediate likelihood of ischemic heart disease (IHD), who is incapable of at least moderate physical activity (class IIa, level of evidence B) (Fihn *et al.*, 2012).

10.17. C. Coronary angiogram.

This patient has a high pretest likelihood of IHD and has intractable symptoms. Coronary angiogram is the best test to evaluate for CAD (class I, level of evidence C) as he is on optimal guideline-directed medical therapy and may be amenable for coronary revascularization (2014 ACC/AHA guideline update) (Fihn *et al.*, 2014).

10.18. C. Coronary angiogram.

This patient has high probability of multivessel disease based on risk factors, angina, and low EF. His LV EF is 30%, which poses a high risk in the presence of IHD. Patients with high likelihood of IHD based on noninvasive testing will benefit from a coronary angiogram provided they are amenable to revascularization (class IIa, level of evidence C).

Features of high risk (>3% annual mortality rate) include: resting LV EF <35%, high-risk treadmill score ≤11, severe exercise-induced LV dysfunction (<35%), stress-induced perfusion defect, especially anterior wall, multiple perfusion defects of moderate size on stress-induced imaging, large fixed perfusion defect on thallium-201 imaging along with LV dilatation or increased lung uptake, moderate perfusion defect on thallium-201 imaging associated with LV dilatation or increased lung uptake, wall motion abnormality developing in two segments at low dose of dobutamine (<10 μg/(kg min)) or at a low heart rate <120 bpm, or extensive ischemia on a stress echocardiogram.

10.19. B. Intensify medical therapy.

This patient has risk factors for IHD. Her primary care physician ordered a dobutamine stress echo. The results of the noninvasive test are indeterminate as she did not achieve target heart rate. Owing to her symptoms, she should undergo coronary angiogram for further evaluation. According to the 2014 ACC/AHA guidelines (Fihn *et al.*, 2014), coronary angiography is reasonable in patients with suspected symptomatic IHD who cannot undergo diagnostic stress testing, or have indeterminate or nondiagnostic stress tests, when there is a high likelihood that the findings will result in important changes to therapy (class IIa, level of evidence C).

10.20. C. Coronary angiogram.

This patient probably has a false-negative stress test. Based on his risk factors and symptoms his pre- and post-test likelihood of IHD are high. Despite a negative stress test, coronary angiogram is warranted here as the findings on coronary angiogram may result in important changes to therapy. The 2014 update of ACC/AHA guidelines (Fihn *et al.*, 2014) state that "Coronary angiography might be considered in patients with stress test results of acceptable quality that do not suggest the presence of CAD when clinical suspicion of CAD remains high and there is a high likelihood that the findings will result in important changes to therapy" (class IIb, level of evidence C).

There are high-quality clinical data to base recommendations for performing coronary angiography in suspected IHD patients. All prior trials in this subset of patients have required angiography. Additionally, the incremental benefits of detecting CAD by coronary angiography need to be determined. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial is an ongoing trial randomizing patients with at least moderate ischemia on stress testing to a strategy of optimal medical treatment alone versus routine coronary angiogram along with medical therapy. Prior to randomization, patients with normal renal function will undergo CCTA to exclude left main or severe CAD.

10.21. B. Fractional flow reserve (FFR)-guided PCI of the 60% stenosis.

This patient with a 60% stenosis of his mid LAD artery should undergo FFR. If the FFR is <0.80 then that lesion should be intervened on. The FAME-2 trial (see Box 10.1) showed that, in patients with stable CAD and functionally significant stenosis, FFR-guided PCI along with best medical therapy compared with best medical therapy alone decreased the need for urgent revascularization (De Bruyne *et al.*, 2012).

10.22. B. Intensify medical therapy.

This patient has a coronary stenosis that was shown to be not significant for ischemia based on FFR. In the FAME-2 trial, it was shown that the outcomes were favorable with best medical therapy when there was no demonstrable ischemia by FFR. Hence, medical therapy should be intensified in this patient. Please refer to discussion in Question 10.21.

10.23. A. 1.7–3%.

10.24. B. 1.4–2.4%.

Data from the Framingham study before the widespread use of aspirin, beta blockers have shown the annual mortality rate in patients with chronic stable angina was 4%. The use of aggressive medical therapy has improved the prognosis. In recent studies the annual mortality rate in stable patients with CAD has been shown to be 1.7–3% and the occurrence of major ischemic events was around 1.4–2.4% (The PEACE Trial Investigators, 2004).

10.25. C. 40%.

Data from the CASS study (see Box 10.1) have shown that 5-year survival in medically treated patients with severe triple-vessel disease and an LV EF ≤34% was poor at 40% (Emond *et al.*, 1994). If the LV EF was greater than 50% then the 5-year survival was around 80%. As the stenosis severity increases and LV function is reduced below 34%, prognosis is adversely affected.

10.26. A. True.

Studies have shown that there is an increased gradient of risk with increased angiographic extent of disease. It has been shown that in medically treated symptomatic CAD patients the annual mortality rate is 2% when there is a 50% stenosis in only one of the major epicardial coronary vessels. In patients with an obstructive lesion proximal to the first septal perforator the 5-year survival rate is 90%, compared with 98% in patients with more distal LAD stenosis (Califf *et al.*, 1996).

10.27. C. Coronary artery bypass grafting (CABG) including left internal mammary artery (LIMA) to LAD artery.

In the 2014 ACC/AHA guidelines (Fihn *et al.*, 2014), CABG has received a class 1 recommendation in patients with diabetes mellitus and multivessel CAD (three vessel or complex two vessel including proximal LAD artery provided a LIMA graft can be anastomosed to the LAD artery). See Box 10.1 regarding the FREEDOM trial (Faroukh *et al.*, 2012), the SYNTAX trial (Kappatein *et al.*, 2013), and the meta-analysis of eight trials, including the FREEDOM trial (Verma *et al.*, 2013).

10.28. B. ≤22.

A low SYNTAX score was defined as ≤22 in the SYNTAX trial. This score was based on location, severity, and extent of stenosis, with a low score indicating less complicated anatomy. A score of 23 to 32 was defined as intermediate, and a score ≥33 was defined as a high-risk score.

10.29. B. Lower.

In the SYNTAX study (see Box 10.1) the occurrence of combined end point in the CABG group was lower compared with DES (16.7% versus 20.8%, $P = 0.03$ respectively) (Kappatein *et al.*, 2013).

10.30. B. Higher.

In the SYNTAX trial (see Box 10.1) the MI rate and repeat revascularization were higher in the DES group when compared with the CABG group: MI 3.6% in the CABG versus 7.1% in the DES group; repeat revascularization 10.7% for CABG versus 19.7% for the DES group (Kappetein *et al.*, 2011).

10.31. C. Higher.

In the SYNTAX trial (see Box 10.1), at 5-year follow-up the occurrence of MACCEs was higher in the DES group compared with the CABG group: 37.3% versus 26.9% respectively, $p < 0.0001$ (Serruys *et al.*, 2009).

10.32. D. Medical therapy plus CABG.

The best approach to revascularization in this patient is optimizing medical therapy and CABG (class 1, level of evidence B) (Fihn *et al.*, 2012).

10.33. D. Guideline-directed medical therapy.

CABG or PCI in this patient is class III (harm) according to the 2012 ACC/AHA guidelines (Fihn *et al.*, 2012). CABG or PCI should not be performed with the sole intent of improving survival in patients with stable IHD with one or more coronary stenoses that are not anatomically significant (<70% in non-left main coronary artery or FFR >0.80, no or mild ischemia on noninvasive testing, stenosis involving only the RCA or left circumflex artery, or subtend only a small area of viable myocardium.

10.34. B. False.

See Box 10.1 about the COURAGE trial results.

10.35. B. Angiotensin-converting inhibitor.

Since his LV EF is <40%, he should be started on angiotensin-converting enzyme inhibitor.

10.36. C. 12 months.

According to current ACC/AHA guidelines (Fihn *et al.*, 2014), dual antiplatelet therapy with aspirin and clopidogrel or prasugrel should be continued uninterrupted for 12 months, though the benefits and risks of treatment beyond 1 year are uncertain (Mauri *et al.*, 2014). See Box 10.1 about the DAPT study.

10.37. D. Long-acting nitrates.

This patient should be started on long-acting nitrates to help control his angina.

10.38. A. Add nicardipine.

This patient has elevated BP and his angina is persistent despite being on a long-acting nitrate and a beta blocker. The next best medication to add would be nicardipine, as he has elevated BP. The half-life of this drug is 2–4 h, but appears to have greater vascular selectivity. For chronic stable angina, it is supposed to be as effective as verapamil or diltiazem, and when combined with a beta blocker the efficacy is enhanced.

10.39. B. Twofold.

Ranalozine increases plasma concentration of simvastatin twofold.

10.40. A. Increased.

The absorption of ranolazine is increased by verapamil by inhibition of P-glycoprotein system.

10.41. B. Increased.

Ranolazine is metabolized by the cytochrome P450 system. Ketoconazole is a strong inhibitor of cytochrome P450 system. Hence, the concentration of ranolazine will be increased when co-administered with ketoconazole.

10.42. A. Alpha adrenergic stimulation.

Cocaine causes MI by its alpha adrenergic stimulation, which causes coronary vasoconstriction and increased myocardial oxygen demand. Thus, when treating such patients, pure beta blockers are contraindicated and drugs such as labetolol which block both alpha and beta adrenergic receptors should be used.

10.43. B. Eplerenone 25 mg daily.

As the EF is <35%. There is no indication for an implantable cardioverter-defibrillator unless EF after 40 days remains <35%.

10.44. C. Adson's test.

The features are consistent with thoracic outlet syndrome. The stress test is negative at very high workload and there is no indication for further ischemic work-up.

Box 10.1 Clinical Trials

- **FAME-2** (De Bruyne *et al.*, 2012). Hypothesis was that FFR-guided PCI of functionally significant stenosis along with best medical therapy would be superior to best medical therapy alone. A total of 1220 patients were enrolled, 880 were randomized and 332 enrolled in registry. Primary end point was a composite of death, MI, or urgent revascularization. The trial was halted prematurely because of a significant difference in the primary outcome between the two groups: 4.3% in the PCI group and 12.7% in the medical therapy group (hazard ratio with PCI 0.32, 95% confidence interval (CI) 0.19–0.53, $P < 0.001$). The difference was driven by a lower rate of urgent revascularization in the PCI group. In patients without ischemia the outcome appeared to be favorable with best medical therapy alone.
- **CASS trial** (Emond *et al.*, 1994). This study describes the impact of clinical, angiographic, and demographic characteristics on the long-term survival of Coronary Artery Surgery Study (CASS) patients while they were under medical treatment. All CASS patients who had not received heart surgery before enrollment (23 467 patients) were included in this survival analysis while they were under medical treatment or surveillance. Follow-up time ranged from 0 to 17 years (median: 12 years). Overall, 12-year survival for patients with zero-, one-, two-, and three-vessel disease is 88%, 74%, 59%, and 40% respectively. The 12-year survival for patients with at least one diseased vessel and EFs in the ranges 50–100%, 35–49%, and 0–34% is 73%, 54%, and 21% respectively.
- **FREEDOM trial** (Faroukh *et al.*, 2012). In this trial, 1900 patients were randomized to either PCI or CABG. The primary outcome in this trial was a composite of death, nonfatal MI, or nonfatal stroke. The 5-year rates were 18.7% in the CABG group versus 26.6% in the DES group ($p = 0.005$). The benefit of CABG was driven by differences in rates of MI ($p < 0.001$) and death from any cause ($p = 0.049$). Stroke was more frequent in the CABG group, and 5-year survival rates were 5.2% in the CABG group compared with 2.4% in the DES group ($p = 0.03$).

- **SYNTAX trial.**
  - The 5-year update from the SYNTAX trial (Kappatein *et al.*, 2013) did not show a significant survival advantage with CABG over DES in patients with diabetes mellitus (12.9% with CABG versus19.5% with DES, $p = 0.065$).
  - In the SYNTAX, trial the occurrence of MACCEs correlated with the SYNTAX score for DES patients but not for those who had undergone CABG. At 12-month follow-up the primary end point was similar in the CABG and DES groups in patients with a low SYNTAX score. In contrast, MACCEs occurred more often in DES patients when the SYNTAX scores were intermediate or high (Serruys *et al.*, 2009). This difference in MACCEs increased at 5 years between those treated with a DES compared with CABG.
- **Meta-analysis** (Verma *et al.*, 2013). The best evidence supporting the use of CABG in patients with multivessel CAD and diabetes mellitus comes from a meta-analysis of eight trials, including the FREEDOM trial. The study had 3131 patients and at 5 years patients with diabetes mellitus randomized to CABG had a lower all-cause mortality than those randomized to PCI either with bare-metal stent or DES (relative risk 0.67, 95% CI 0.52–0.86, $P = 0.002$).
- **COURAGE trial** (Boden *et al.*, 2007). This was a randomized study which enrolled 2287 patients who had objective evidence of MI and significant CAD. Between 1999 and 2004, 1149 patients were assigned to undergo PCI with optimal medical therapy (PCI group) and 1138 to receive optimal medical therapy alone (medical-therapy group). The primary outcome was death from any cause and nonfatal MIn during a median follow-up of 4.6 years. Cumulative primary-event rates were 19.0% in the PCI group and 18.5% in the medical-therapy group (hazard ratio for the PCI group, 1.05; 95% CI 0.87–1.27, $P = 0.62$). There were no significant differences between the PCI group and the medical-therapy group in the composite of death, MI, and stroke (20.0% versus 19.5%; hazard ratio 1.05, 95% CI 0.87–1.27, $P = 0.62$), hospitalization for acute coronary syndrome (12.4% versus 11.8%; hazard ratio 1.07, 95% CI 0.84–1.37, $P = 0.56$), or myocardial infarction (13.2% versus 12.3%; hazard ratio 1.13, 95% CI 0.89–1.43, $P = 0.33$). The trial concluded that, as an initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy.
- **DAPT trial** (Mauri *et al*., 2014). This enrolled 9961 patients who were either assigned to stop thienopyridine therapy after 12 months or to continue for another 18 months. The coprimary efficacy end points were stent thrombosis and MACCEs (a composite of death, MI, or stroke) during the follow-up period from 12 to 30 months. The primary safety end point was moderate or severe bleeding in this trial. Continued treatment with thienopyridine beyond 12 months, compared with placebo, reduced the rates of stent thrombosis (0.4% versus 1.4%; hazard ratio 0.29, 95% CI 0.17–0.48, $P < 0.001$) and MACCEs (4.3% versus.5.9%; hazard ratio 0.71, 95% CI 0.59–0.85, $P < 0.001$). The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% versus 1.6%, $P = 0.001$). An elevated risk of stent thrombosis and MI was observed in both groups during the 3 months after discontinuation of thienopyridine treatment.

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Heart Failure, Transplant, Left Ventricular Assist Devices, Pulmonary Hypertension

11

11.1. A 62-year-old man with smoking, hypertension, and diabetes mellitus complains of shortness of breath on exertion. He gets short of breath walking up a flight of stairs. There is no chest pain. On physical examination, heart rate 72 bpm, regular; blood pressure 148/90 mmHg, body mass index (BMI) 24. Jugular venous pressure (JVP) and heart sounds are normal. The electrocardiogram shows normal sinus rhythm. The echocardiogram shows mild left ventricular (LV) hypertrophy, normal wall motion, normal valvular function, mitral E/A velocity ratio of 0.7, E/E′ ratio of 7, pulmonary artery (PA) systolic pressure of 50 mmHg. What is the most productive next step?

- **A.** Add calcium channel blocker (CCB) as a lusiotropic agent as it may reduce PA pressure
- **B.** Computed tomography (CT) pulmonary angiography to rule out pulmonary embolism
- **C.** Right heart catheterization (RHC) to evaluate for pulmonary vascular resistance and its response to O_2 and pulmonary vasodilators
- **D.** Diuresis to reduce left atrial (LA) pressure as this may reduce PA pressure

11.2. Which of the following agents are shown to improve survival in heart failure with reduced ejection fraction (HFrEF)?

- **A.** Carvedilol and metoprolol succinate
- **B.** Angiotensin-converting-enzyme inhibitor (ACEI)
- **C.** Spironolactone
- **D.** All of the above
- **E.** None of the above

11.3. Which of the following agents are shown to improve survival in heart failure with preserved ejection fraction (HFpEF)?

- **A.** Carvedilol and metoprolol succinate
- **B.** ACEI
- **C.** Spironolactone
- **D.** All of the above
- **E.** None of the above

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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11.4. A 62-year-old asymptomatic hypertensive had an echocardiogram for a murmur. The rest of the physical examination was normal. Echocardiogram showed normal LV wall thickness and wall motion with ejection fraction (EF) of 65%. Valves were normal. Mitral E/A velocity ratio was 0.7. What does the patient have?
- **A.** Stage A heart failure (HF)
- **B.** Stage B HF
- **C.** HFpEF
- **D.** None of the above

11.5. Diagnosis of HF by Framingham criteria requires which of the following?
- **A.** Two major or one major and two minor criteria
- **B.** Four major criteria
- **C.** Two major criteria and raised serum brain natriuretic peptide (BNP)
- **D.** None of the above

11.6. The major Framingham criteria for HF include:
- **A.** S3
- **B.** Paroxysmal nocturnal dyspnea
- **C.** Basal rales
- **D.** All of the above

11.7. The minor Framingham criteria for HF include which of the following?
- **A.** Shortness of breath
- **B.** Edema
- **C.** Nocturnal cough
- **D.** All of the above

11.8. Which of the following are class I indications for echocardiography, based on American College of Cardiology Foundation and imaging societies' appropriateness criteria in subjects with HF?
- **A.** Clinical HF
- **B.** Family history of cardiomyopathy, but no clinical HF
- **C.** Cardiotoxic chemotherapy
- **D.** All of the above

11.9. In which patients with HFrEF is coronary angiography most appropriate and clearly indicated?
- **A.** A 52-year-old patient with EF of 30%, diabetes, and angina on walking one block
- **B.** A 63-year-old man with prior ST elevation myocardial infarction, scarred left anterior descending artery area on nuclear testing, no reversible ischemia, EF of 30%, but short of breath on exertion
- **C.** A 22-year-old patient with HF, EF of 10%, severely dilated left ventricle
- **D.** None of the above

11.10. Compared with atrial myocyte, ventricular myocyte is which of the following?
- **A.** Longer
- **B.** Broader
- **C.** Has more T tubules
- **D.** All of the above
- **E.** None of the above.

11.11. Which of the following has absent T tubules?
- **A.** Ventricular myocyte
- **B.** Atrial myocyte
- **C.** Purkinje cells
- **D.** None of the above

11.12. Which of the following have the most abundant gap junctions?
- **A.** Ventricular myocyte
- **B.** Atrial myocyte
- **C.** Purkinje cells
- **D.** None of the above

11.13. What is the increase in myocardial contractile force with increase in preload called?
- **A.** Frank–Starling phenomenon
- **B.** Anrep phenomenon
- **C.** Bowditch phenomenon
- **D.** None of the above.

11.14. What is the increase in myocardial contractile force with acute increase in afterload called?
- **A.** Frank–Starling phenomenon
- **B.** Anrep phenomenon
- **C.** Bowditch phenomenon
- **D.** None of the above.

11.15. What is the increase in myocardial contractile force with increase in heart rate called?
- **A.** Frank–Starling phenomenon
- **B.** Anrep phenomenon
- **C.** Bowditch phenomenon
- **D.** None of the above.

11.16. An increase in LV end-systolic size would increase which of the following?
- **A.** LV preload
- **B.** LV afterload
- **C.** None
- **D.** Both

11.17. What would an acute increase in afterload result in?
- **A.** Reduction in LV EF
- **B.** Increase in LV end-systolic volume
- **C.** Increased LV contractility
- **D.** All of the above.

11.18. Which of the following does the LV EF depend upon?
- **A.** LV preload
- **B.** LV afterload
- **C.** LV contractility
- **D.** All of the above

11.19. Which of the following factors affect LV diastolic function?
- **A.** LV relaxation process
- **B.** Modulus of chamber stiffness
- **C.** LV recoil
- **D.** All of the above

11.20. Submassive acute pulmonary embolism may cause all of the following except which option?
- **A.** Increase in intrapericardial pressure
- **B.** Increase in LV end-diastolic pressure
- **C.** Reduced LV filling
- **D.** Increase in stroke volume

11.21. Which of the following is not acceptable as a donor heart for heart transplant?
- **A.** Bicuspid aortic valve
- **B.** History of meth use with normal EF and absence of LV hypertrophy
- **C.** Atrial septal defect with normal right ventricle function
- **D.** History of alcohol abuse and EF of 35% on pressors

11.22. What is your recommendation for a donor heart that is normal except for 3+ functional tricuspid regurgitation (TR)?
- **A.** Reject the heart
- **B.** Assign the heart to alternate list
- **C.** Do DeVega annuloplasty on bench and use the heart
- **D.** Do tricuspid valve replacement and use the heart

11.23. What are the likely outcomes after heart transplant in a patient with preoperative moderate PH and increased pulmonary vascular resistance?
- **A.** Right ventricular (RV) dilation and failure
- **B.** Tricuspid regurgitation
- **C.** Low output state
- **D.** None of the above
- **E.** Options A–C

11.24. Which of the following reduces serum levels of cyclosporine, tacrolimus, and sirolimus?
- **A.** Phenytoin
- **B.** Phenobarbital
- **C.** Rifampicin
- **D.** All of the above

11.25. Which of the following increases serum levels of cyclosporine, tacrolimus, and sirolimus?
- **A.** Erythromycin
- **B.** Ketoconazole and fluconazole
- **C.** Diltiazem and verapamil
- **D.** Amiodarone
- **E.** All of the above

11.26. Which of the following are potential side effects of tacrolimus?
- **A.** Diabetes mellitus
- **B.** Tremor
- **C.** Anemia
- **D.** All of the above
- **E.** None of the above

11.27. Potential side effects of cyclosporine include which of the following?
- **A.** Hypertension
- **B.** Hypertriglyceridemia

C. Hypercholesterolemia
D. Increase in creatinine
E. All of the above

11.28. Which of the following are treatment options for antibody-mediated graft rejection?
A. High dose corticosteroid
B. Intravenous (IV) immunoglobulin
C. Daily plasmapheresis
D. IV rituximab
E. All of the above.

11.29. Which of the following drugs may retard cardiac allograft vasculopathy?
A. Sirolimus
B. Everolimus
C. Statins
D. Mycophenolate mofetil
E. All of the above.

11.30. In an adult patient with heart transplant beyond 6 months, which of the following surveillance regimens for rejection is appropriate?
A. Biannual endomyocardial biopsy for the first 5 years
B. Biannual endomyocardial biopsy for indefinite period of time
C. Echocardiography in place of biopsy
D. Cardiac magnetic resonance imaging with delayed enhancement in place of biopsy
E. All of the above

11.31. Which of the following are not acceptable practices for cardiac allograft surveillance?
A. Monitoring of serum BNP trends
B. Monitoring of troponin I and C-reactive protein
C. Echocardiography in place of biopsy
D. Cardiac magnetic resonance imaging with delayed enhancement in place of biopsy
E. All of the above

11.32. In a patient with heart transplant, pregnancy should be discouraged under which of the following circumstances?
A. Within a year of transplant
B. Evidence of LV dysfunction
C. Evidence of coronary vasculopathy
D. All of the above
E. None of the above.

11.33. Which of the following statements are true in a heart transplant patient who gets pregnant?
A. Discontinue all antirejections medications in the first trimester because of teratogenicity
B. Discontinue all antirejections medications throughout pregnancy because of fetal growth retardation

C. Continue corticosteroids and calcineurin inhibitors (cyclosporine or tacrolimus)
D. Continue corticosteroids, tacrolimus and mycophenolate mofetil

11.34. Which of the following statements are true regarding coronary angiography after heart transplant?
A. Reasonable to perform coronary angiogram at 6 months after heart transplant
B. Reasonable to perform coronary angiogram at 5 years after heart transplant and then annually
C. Both A and B
D. Neither A nor B

11.35. Which of the following patients are reasonable candidates to evaluate for heart transplant?
A. Male, 60 years, EF of 10%, class IV HF, inotrope dependent
B. Female, 57 years, EF 35%, class IV angina, poor targets for percutaneous coronary intervention or coronary artery bypass grafting and refractory to medical therapy
C. Male, 67 years, class III symptoms, EF 20%, V_{O2} max 8 mL/(kg min)
D. All of the above
E. None of the above.

11.36. Which of the following are absolute contraindications for heart transplant?
A. Prostatic carcinoma, status post treatment with persistently elevated prostate-specific antigen
B. AIDS with opportunistic infections
C. Fixed PH with PA systolic pressure >60 mmHg or pulmonary vascular resistance >6 Wood units or transpulmonary gradient >15 mmHg
D. All of the above.
E. None of the above

11.37. Which of the following patients are undesirable candidates for heart transplant for class IV HF?
A. Male, 75 years, with HFrEF and EF 10%
B. Patient on hemodialysis for heart transplant alone
C. Living alone with no social support
D. BMI >35 kg/m^2
E. All of the above

11.38. Which of the following statements are true regarding an implantable left ventricular assist device (LVAD)?
A. In patients with severe class IV HFrEF ineligible for heart transplant, it prolongs survival
B. It may be used as bridge to transplant
C. It may be used as bridge to recovery
D. It may be used as destination therapy
E. All are correct.

11.39. In a patient considered for LVAD, which of the following findings may increase associated risk?
A. Highly trabeculated left ventricle
B. LV apical thrombus

C. LV end diastolic diameter <63 mm
D. All of the above

11.40. Which of the following are red-flag findings in patients undergoing LVAD?
A. LA appendage thrombus
B. Severe RV dysfunction
C. Patent foramen ovale (PFO)
D. Ventricular septal defect (VSD)
E. All of the above.

11.41. Which of the following valvular lesions may be problematic in patients undergoing LVAD?
A. Moderate or severe aortic regurgitation (AR)
B. Moderate or severe mitral stenosis
C. Moderate or severe TR
D. All of the above

11.42. Which of the following valve lesions may not significantly impede LVAD function?
A. Mitral regurgitation
B. Aortic stenosis
C. Pulmonary regurgitation
D. All of the above.

11.43. Which of the following prosthetic valves may need to be explanted before LAVD implant?
A. Mechanical aortic valve
B. Bioprosthetic aortic valve
C. Normally functioning mechanical mitral valve
D. Mechanical mitral valve with 3+ mitral regurgitation (MR)
E. All of the above.

11.44. Which of the following are preferred surgical options to be included for severe AR before LVAD implant?
A. Bioprosthesis
B. Complete sewing and closure
C. Park stitch (central suture)
D. All of the above
E. None of the above

11.45. What is sudden desaturation soon after LVAD implant likely due to?
A. Unmasked PFO
B. AR
C. Unmasked RV dysfunction
D. Pulmonary embolism

11.46. Which of the following options is true about AR quantitation after LVAD?
A. Should be upgraded by one grade based on traditional criteria
B. Should be downgraded by one grade
C. Should be based on aortic flow reversal in diastole
D. None of the above
E. All of the above

11.47. What is a recommended approach if leftward septal shift, severe RV dysfunction, and severe TR occur soon after LVAD implant even at low speed?
A. Reduce the LV cannula size
B. Perform tricuspid valve repair
C. Infuse fluid
D. Change to biventricular mechanical circulatory support

11.48. Which of the following echo findings indicate normal LVAD function?
- **A.** Inflow (LV) cannula velocity of <1.5 m/s without turbulence
- **B.** Ouflow (aortic) cannula velocity of <2.0 m/s without turbulence
- **C.** Intermittent opening of aortic valve
- **D.** Ventricular septum in the middle
- **E.** All of the above

11.49. What may signs of LVAD malfunction include?
- **A.** Diastolic flow reversal in inflow and outflow cannula with pump arrest
- **B.** Reduced response to increase in pump speed
- **C.** LV dilation
- **D.** Low velocities in cannula
- **E.** All of the above

11.50. What may persistent aortic valve closure in a patient with LVAD result in?
- **A.** Aortic root thrombus
- **B.** AR
- **C.** Both A and B
- **D.** Neither A nor B

11.51. What should one not do when aortic root thrombus is seen in a patient with LVAD?
- **A.** Reduce pump speed
- **B.** Increase pump speed
- **C.** Neither

11.52. What might signs of an LV suction event include?
- **A.** LV end diastolic diameter <3 cm
- **B.** Obstruction to inflow cannula
- **C.** Leftward septal shit
- **D.** Increase in TR
- **E.** All of the above.
- **F.** None of the above.

11.53. A patient with an LVAD presents with heart failure. An echocardiogram shows an increase in LV size and greater opening of aortic valve with each beat from 90 to 200 ms. What is the most likely cause?
- **A.** Thrombosis of the LVAD
- **B.** Hypertension
- **C.** Pulmonary embolism
- **D.** None of the above

11.54. With increase in pump speed, which of the following may occur?
- **A.** Reduced opening of aortic valve
- **B.** A diminution of systolic velocity and an increase in diastolic velocity in the aortic cannula
- **C.** A diminution in LV size
- **D.** Septal shit to left
- **E.** All of the above

11.55. Which statin has least interaction with immune suppressants?
- **A.** Simvastatin
- **B.** Pravastatin
- **C.** Atorvastatin
- **D.** Rosuvastatin

11.56. Which immunosuppressant may increase serum creatinine level?
- **A.** Sirolimus
- **B.** Cyclosporine
- **C.** Mycophenolate mofetil
- **D.** Corticosteroid

11.57. A 45-year-old man with heart transplant performed 6 years ago is admitted with shortness of breath and fever. He is on prednisone, tacrolimus, mycophenolate mofetil, diltiazem, and pravastatin Chest X-ray is suggestive of pneumonia. The echocardiogram showed normal LV function, wall thickness, and filling pressures. The white cell count is 16 000, and serum creatinine is 3.2 mg/dL. In addition to treating with appropriate antibiotics, what would you do?
- **A.** Start dobutamine infusion
- **B.** Discontinue tacrolimus
- **C.** Treat with IV immunoglobulin
- **D.** Perform plasmapheresis

11.58. In a patient with systolic heart failure on optimal doses of carvedilol and spironolactone, which drug is likely to produce maximum mortality and HF admission benefit?
- **A.** ACEI
- **B.** Angiotensin receptor blocker
- **C.** Neprilysin inhibitor
- **D.** Diuretic

In Questions 11.59–11.66, match the question's clinical scenario to the indicated risk of PH, if any, and to the type of pulmonary arterial hypertension (PAH) based on the current classification system. See Box 11.2 on the classification of pulmonary hypertension at the end of this chapter. Each option may apply to more than one clinical situation or none at all.

11.59. A 62-year-old woman, with a history of hypertension and obesity (current BMI 31), presents with dyspnea. On echo there is normal LV and valvular function, mitral E/e′ ratio is 6, and PA systolic pressure is 60 mmHg. She has used the appetite-suppressant drug fen-phen for 2 years in the past. Based on the current classification system, which of the following options best describes this patient's condition?
- **A.** No PH
- **B.** Group 1 PH
- **C.** Group 2 PH
- **D.** Group 3 PH
- **E.** Group 4 PH
- **F.** Group 5 PH

11.60. A 27-year-old woman has idiopathic PH. Based on the current classification system, which of the following options best describes this patient's condition?
- **A.** No PH
- **B.** Group 1 PH
- **C.** Group 2 PH
- **D.** Group 3 PH
- **E.** Group 4 PH
- **F.** Group 5 PH

11.61. A patient has PH in systemic sclerosis. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.62. The PA pressure in a patient being evaluated for liver transplant because of end-stage liver disease is 65/40 mmHg. Echo shows normal LV and is consistent with normal left and right atrial pressures. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.63. A 10-year-old boy has severe PH. His mother had a history of severe depression and committed suicide 6 years ago. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.64. The PA pressure in a 37-year-old patient who had VSD patch closure at the age of 15 years is 60/35 mmHg. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.65. A 52-year-old woman with shortness of breath, echo shows EF of 60%, thickened mitral leaflets with diastolic doming, mitral valve pressure half-time of 270 ms, isovolumic relaxation time 30 ms, mild TR with a velocity of 3.9 m/s, dilated inferior vena cava. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.66. A 42-year-old woman presents with protein C deficiency, recurrent deep-vein thromboses and pulmonary embolism. She is uninsured with intermittent compliance with anticoagulation and has increasing dyspnea and bilateral pedal edema. JVP is elevated, and P2 is loud and palpable at left sternal border. Based on the current classification system, which of the following options best describes this patient's condition?

A. No PH
B. Group 1 PH
C. Group 2 PH
D. Group 3 PH
E. Group 4 PH
F. Group 5 PH

11.67. What is the commonest cause of moderate to severe PH worldwide?

A. Idiopathic
B. Mitral stenosis
C. Schistosomiasis
D. Pulmonary embolism

11.68. Which of the following mutations is responsible for the majority of patients with familial PH?

A. *BMPR2* mutations
B. *BMPR1B* mutation
C. *SMAD9* mutation
D. None of the above

11.69. Which is the preferred modality to diagnose thromboembolic PH?

A. V/Q scan
B. CT pulmonary angiography
C. Gd-enhanced MR pulmonary angiography
D. Transesophageal echocardiography

11.70. Is RHC indicated in patients with PH?

A. Yes
B. No
C. Depends upon the situation

11.71. Which of the following statements are true regarding RHC in those with PH?

A. RHC is recommended to confirm the diagnosis of PAH (group 1) and to support treatment decisions
B. In patients with PH, it is recommended to perform RHC in expert centers as it is technically demanding and may be associated with serious complications
C. RHC is recommended in patients with congenital cardiac shunts to support decisions on correction
D. RHC is indicated in patients with CTEPH (group 4) to confirm the diagnosis and support treatment decisions
E. All of the above
F. None of the above.

11.72. Which of the following statements is untrue about vasoreactivity testing in PH?

A. Vasoreactivity testing is recommended in patients with idiopathic PAH, hereditary PAH, and PAH associated with drugs use to detect patients who can be treated with high doses of a CCB

B. A positive response to vasoreactivity testing is defined as a reduction of mean PA pressure ≥10 mmHg to reach an absolute value of mean PA pressure ≤40 mmHg with an increased or unchanged cardiac output
C. Nitric oxide is recommended for performing vasoreactivity testing. IV epoprostenol is recommended for performing vasoreactivity testing as an alternative
D. Adenosine should be considered for performing vasoreactivity testing as an alternative
E. The use of oral or IV CCBs in acute vasoreactivity testing is recommended

11.73. Which of the following are acceptable recommendations in those with PAH?
A. Avoid pregnancy
B. Use flu and pneumococcal vaccines
C. Supervise training program or cardiopulmonary rehab
D. Those needing anesthesia, use epidural rather than general
E. All of the above.

11.74. Which of the following are class I indications in PAH?
A. Diuretic treatment is recommended in PAH patients with signs of RV failure and fluid retention
B. Continuous long-term O_2 therapy is recommended in PAH patients when arterial blood O_2 pressure is consistently <8 kPa (60 mmHg)
C. High doses of CCBs are recommended in patients with idiopathic PAH, hereditary PAH, and drug-induced PAH who are responders to acute vasoreactivity testing
D. Pulmonary vasodilators are generally recommended for group 1 PH
E. All of the above
F. None of the above.

11.75. Which of the following drugs have class I recommendations for treatment of World Health Organization group 1 PH functional class II and III, either alone or sequentially or in combination?
A. Ambrisentan
B. Bosentan
C. Sildenafil
D. Tadalafil
E. All of the above
F. The above are recommended only in class IV

11.76. Which of the following statements are correct regarding CTEPH?
A. Life-long anticoagulation is recommended in all patients with CTEPH
B. It is recommended that in all patients with CTEPH the assessment of operability and decisions regarding other treatment strategies should be made by a multidisciplinary team of experts
C. Surgical pulmonary endarterectomy in deep hypothermia circulatory arrest is recommended for patients with CTEPH
D. Riociguat is recommended in symptomatic patients who have been classified as having persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH by a CTEPH team, including at least one experienced pulmonary endarterectomy surgeon
E. All of the above

11.77. What does the patient in Figure 11.77 have?

A. LVAD
B. Impella device
C. Tandem heart device
D. None of the above

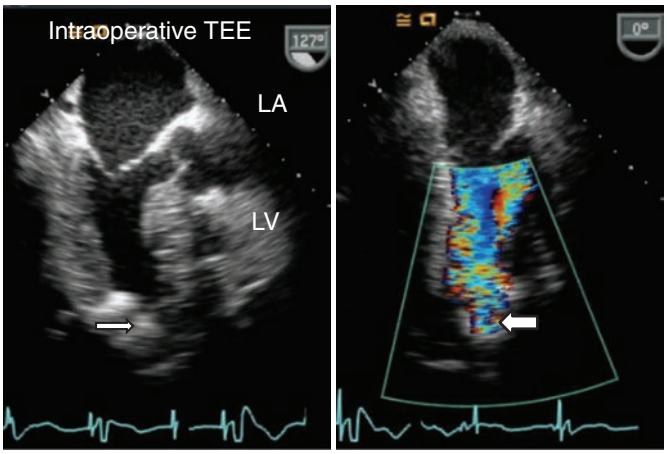

Figure 11.77

11.78. What does the patient in Figure 11.78 have?

A. LVAD
B. Impella device
C. Tandem heart device
D. None of the above

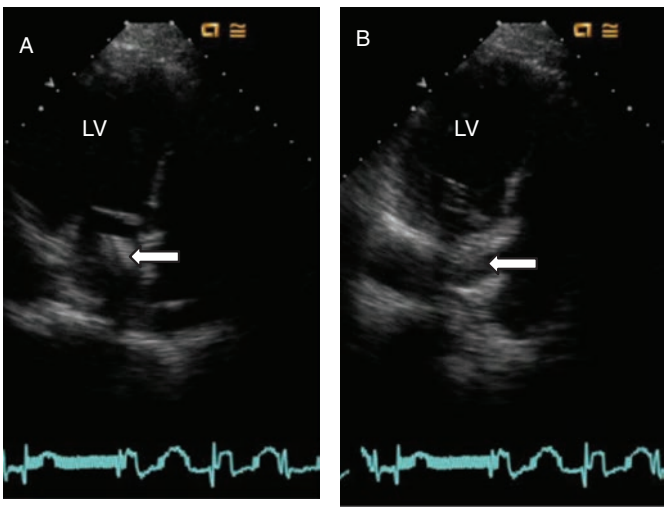

Figure 11.78

11.79. What does the patient in Figure 11.79 have?

A. LVAD
B. Impella device
C. Tandem heart device
D. None of the above

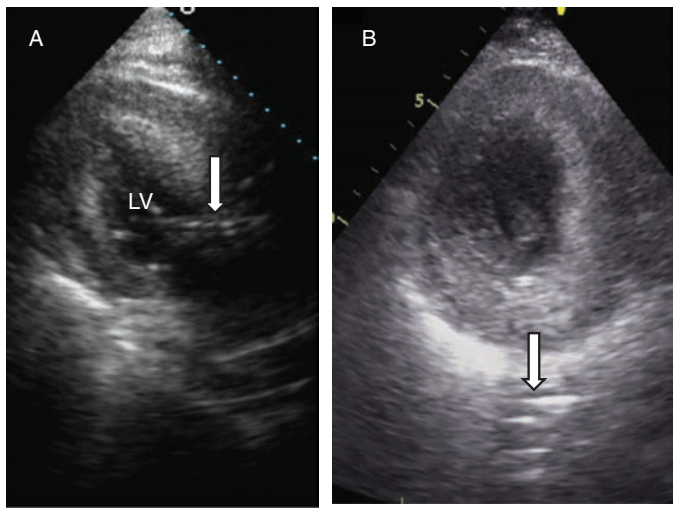

Figure 11.79

Answers

11.1. C. Right heart catheterization (RHC) to evaluate for pulmonary vascular resistance and its response to O_2 and pulmonary vasodilators.

Normal E/E′ ratio indicates normal LA pressure and pulmonary hypertension (PH) being secondary to pulmonary vascular or parenchymal disease. Diuresis would not help. Shortness of breath is unlikely to be due to impaired LV relaxation as LA pressure is normal, and lusiotropic agents do not help hemodynamics in clinical settings apart from in patients with hypertrophic cardiomyopathy. A CT pulmonary angiogram is a poor test for chronic pulmonary emboli – a ventilation/perfusion (V/Q) scan would be better for this purpose.

11.2. D. All of the above.

Note that metoprolol tartrate, which is short acting, is not a good choice in HFrEF because of intermittent blockage of beta receptors, which may expose the patient to intermittent beta blocker withdrawal.

11.3. E. None of the above.

None of these have been shown to improve survival in HFpEF.

11.4. B. Stage B HF.

The pattern of impaired LV relaxation is consistent with stage B HF. He has no clinical HF and is not stage C. HFpEF needs clinical syndrome of HF, generally determined by Framingham criteria.

11.5. A. Two major or one major and two minor criteria.

For the Framingham study, see McKee *et al.* (1971) and Boxes 11.1 and 11.4.

11.6. D. All of the above.

Other major criteria include raised JVP, weight loss of 10 lb with diuresis.

11.7. D. All of the above.

11.8. D. All of the above.

11.9. A. A 52-year-old patient with EF of 30%, diabetes, and angina on walking one block.

In this patient with angina and diabetes, there is a high likelihood of having significant coronary artery disease (CAD) as the basis of LV dysfunction and constitutes class I indication. In scenario B there is no ischemia or chest pain and coronary angiogram would be inappropriate. In C, the likelihood of CAD is very low.

11.10. D. All of the above.

That is, longer, broader, and more T tubules. Ventricular myocytes are about 60–140 μm in length, compared with 20 μm for atrial myocytes. The diameter of a ventricular myocyte is about 20 μm, compared with 5 μm for an atrial myocyte. Atrial myocytes are elliptical, and ventricular myocytes are branched tubules with plenty of mitochondria and sarcomeres.

11.11. C. Purkinje cells.

These have no T tubules as they do not contract and their function is mainly electrical conduction.

11.12. C. Purkinje cells.

To facilitate rapid electrical conduction, as their function is mainly electrical conduction.

11.13. A. Frank–Starling phenomenon.

11.14. B. Anrep phenomenon.

11.15. C. Bowditch phenomenon.

Otherwise known as the force–frequency relationship. Contractile force is maximal at a rate of about 150 bpm.

11.16. B. LV afterload.

LV end-systolic wall stress is a measure of LV afterload and is roughly proportional to blood pressure and LV end-systolic radius and inversely proportional to LV wall thickness (Laplace equation).

11.17. D. All of the above.

An increase in afterload will increase contractility through the Bowditch effect, but this may not be enough to overcome the afterload and hence would cause an increase in LV end-systolic volume and a reduction in EF. Both EF and end-systolic volume are afterload dependent.

11.18. D. All of the above.

11.19. D. All of the above.

The relaxation process affects the early LV filling, chamber stiffness, the late filling, and recoil, which depends upon how well the left ventricle squeezes and then recoils, which affects early filling. In addition, LV filling is affected by pericardial restraint, intrathoracic pressure, and interactions with the right ventricle.

11.20. D. Increase in stroke volume.

Submassive pulmonary embolism may cause right ventricle distention and invoke pericardial restraint (due to noncompliant pericardium) through an acute increase in intrapericardial volume. This will increase intrapericardial pressure, reduced transmural LV diastolic pressure and hence a reduction in stroke volume in the face of reduced LV preload due to reduced transmural LV diastolic pressure.

11.21. D. History of alcohol abuse and EF of 35% on pressors.

The other options are acceptable. Minor defects can always be repaired on the bench.

11.22. C. Do DeVega annuloplasty on bench and use the heart.

11.23. E. Options A–C.

Because of acute afterload mismatch for right ventricle. May be treated with pulmonary vasodilators, diuresis, positive inotropes, and in rare instances atrial septostomy to unload right side and increase cardiac output.

11.24. D. All of the above.

11.25. E. All of the above.

11.26. D. All of the above.

11.27. E. All of the above.

11.28. E. All of the above.

11.29. E. All of the above.

11.30. A. Biannual endomyocardial biopsy for the first 5 years.

11.31. E. All of the above.

11.32. D. All of the above.

11.33. C. Continue corticosteroids and calcineurin inhibitors (cyclosporine or tacrolimus).

Mycophenolate mofetil is a class D drug. Use of azathioprine is controversial.

11.34. C. Both A and B.

11.35. D. All of the above.

11.36. D. All of the above.

11.37. E. All of the above.

11.38. E. All are correct.

11.39. D. All of the above.

The trabeculations may impede flow into inflow cannula and also predispose to thrombus formation. LV thrombus increases stroke risk. A small LV increases the risk of obstruction to inflow cannula.

11.40. E. All of the above.

LA thrombus increases the risk of thrombus as blood is sucked into the LVAD. Suction force also promotes right to left shunting through atrial septal defects or VSDs and systemic desaturation. The PFO should be closed before the LVAD and should be checked for both before and after the LVAD as well, as it may open up with LA unloading. Patients with severe RV dilation and dysfunction may need a biventricular assist device as leftward shift of ventricular septum may aggravate RV dysfunction.

11.41. D. All of the above.

Post LVAD, AR occurs throughout the cardiac cycle and leads to a blind loop type of circulation. Mitral stenosis impedes LV filling. The TR may get worse due to leftward shift of ventricular septum. Hence, all these lesions should be addressed before LVAD implant.

11.42. D. All of the above.

11.43. A. Mechanical aortic valve

Because of risk of thrombosis because of low/absent flow. Bioprosthetic aortic valve is not an issue. The mechanical mitral prosthesis with or without MR has low risk of thrombosis with anticoagulation as flow through it is increased with the LVAD. However, stenotic mitral prosthesis would be a problem and may need to be replaced with a bioprosthesis.

11.44. D. All of the above.

It is important to eliminate AR.

11.45. A. Unmasked PFO.

LA unloading may open up the PFO which was not detected preoperatively even with "ventilator Valsalva" and may cause large right to left shunting and systemic desaturation.

11.46. A. Should be upgraded by one grade based on traditional criteria.

This is because the AR is both systolic and diastolic. In diastole, the aortic flow will all be forward because of LVAD flow and hence this sign is invalid. A vena contracta of >3 mm or jet height to LV outflow tract ratio of >46% is considered to indicate severe AR.

11.47. D. Change to biventricular mechanical circulatory support.

This is a sign of severe RV dysfunction.

11.48. E. All of the above.

11.49. E. All of the above.

11.50. C. Both A and B.

11.51. A. Reduce pump speed.

Reducing pump speed may open the aortic valve and dislodge the thrombus.

11.52. E. All of the above.

11.53. A. Thrombosis of the LVAD.

This would also result in reduced inflow velocity and reduced transpulmonary flow, as evidenced by reduced velocity–time integral of flow across pulmonary valve, which is very useful in monitoring total cardiac output.

11.54. A. Reduced opening of aortic valve.
As flow through the pump increases, there is less flow through aortic valve, greater LV unloading, and less pulsatility in aorta.

11.55. B. Pravastatin.

11.56. B. Cyclosporine.

11.57. B. Discontinue tacrolimus.
This is because it may be the cause of renal dysfunction. The patient has no signs of rejection, and so treatment for antibody-mediated rejection (C and D) is not indicated. You would need to increase corticosteroids to stress dose level.

11.58. C. Neprilysin inhibitor.
LCZ696 has shown a higher efficacy than enalpril in the PARADIGM-HF trial (see Box 11.4; McMurray *et al.*, 2014; Simpson *et al.*, 2015).

11.59. B. Group 1 PH.
PH is attributable to the banned appetite suppressant fen-phen, which causes pulmonary vascular disease. Use for >3 months is a risk factor. E/e′ ratio <8 indicates probable normal LA pressure.

11.60. B. Group 1 PH.

11.61. B. Group 1 PH.

11.62. B. Group 1 PH.
Portopulmonary hypertension is group 1.

11.63. B. Group 1 PH.
This is likely due to *in utero* exposure to selective serotonin reuptake inhibitor, which causes PH in the child.

11.64. B. Group 1 PH.
It is residual PH after late VSD closure due to increased pulmonary vascular resistance.

11.65. C. Group 2 PH.
Clearly due to severe mitral stenosis. Pressure half-time of 270 ms indicates a mitral valve area of <0.7 cm^2 and isovolumic relaxation time of 30 ms indicates very high LA pressure.

11.66. E. Group 4 PH.
Due to pulmonary thromboembolism. Loud, palpable P2 indicates PH. In addition, this patient has features of right HF.

11.67. C. Schistosomiasis.

11.68. A. *BMPR2* mutations.
These account for 75% of the cases of familial type and 25% of cases of idiopathic type. *BMPR2* encodes a type 2 receptor for bone morphogenetic proteins involved in the control of vascular cell proliferation.

11.69. A. V/Q scan.
A V/Q lung scan should be performed in patients with PH to look for chronic thromboembolic PH (CTEPH). The V/Q scan has been the screening method of choice for CTEPH because of its higher sensitivity compared with CT pulmonary

angiogram, especially in inexperienced centers. A normal- or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90–100% and a specificity of 94–100%.

11.70. A. Yes.
All patients should have this to confirm the diagnosis and make treatment decisions.

11.71. E. All of the above.

11.72. E. The use of oral or IV CCBs in acute vasoreactivity testing is recommended.
All the other statements are accurate.

11.73. E. All of the above.
A and B are class I recommendations; C and D are class IIA recommendations.

11.74. E. All of the above.
The statements are self-explanatory.

11.75. E. All of the above.
Recommendation is for group 1 and functional class II or III, rather than too late or too early (i.e., class I recommendation). A and B are endothelin receptor antagonists, and C and D are phosphodiesterase type 5 inhibitors. Prostacyclin analogues epoprostenol (IV), iloprost (inhaled or IV) and treprostinil (subcutaneous or inhaled) also have class I recommendations in this patient category. When combination is used, use drugs from different categories.

11.76. E. All of the above.
These are based on 2015 European Society of Cardiology/European Respiratory Society guidelines (Galiè *et al.*, 2016). See Box 11.3.

11.77. A. LVAD.
Note the inlet cannula in the LV apex (arrow in Figure 11.77). The outflow cannula would be in ascending aorta (not shown).

11.78. C. Tandem heart device.
Note the inlet cannula in the left atrium.

11.79. B. Impella device.
Note the Impella catheter across the aortic valve in Figure 11.79A and in the descending thoracic aorta in Figure 11.79B – both pointed to by the arrow.

Box 11.1 Clinical Pearls, Facts, and Guidelines

Heart Failure Stages

Stage A: risk factors for heart disease such as hypertension, diabetes, or CAD, but no functional or structural changes.
Stage B: structural or functional changes such as LV hypertrophy, low EF, abnormal LV diastolic function, or abnormal valve function, but no clinical HF.
Stage C: ambulatory clinical HF.
Stage D: HF with symptoms at rest.

Framingham Criteria for Heart Failure

HF: two major or one major and two minor criteria.
Major criteria: jugular vein distension, hepatojugular reflux, S3, pulmonary edema, paroxysmal nocturnal dyspnea, 4.5 kg weight loss on diuresis, cardiomegaly on chest X-ray.
Minor criteria: dyspnea, nocturnal cough, bilateral edema, tachycardia >120 bpm, pleural effusions.

Role of Brain Natriuretic Peptide in Heart Failure

1. BNP >400 pg/mL or N-terminal prohormone of BNP (NT-proBNP) >2000 pg/mL supports diagnosis of HF.
2. If BNP <400 pg/mL or NT-proBNP <400 pg/mL in a patient with dyspnea, consider alternate diagnosis.
3. Persistently elevated levels predict poor prognosis and recurrent hospital admissions for HF.
4. Levels are also elevated with LV hypertrophy and atrial fibrillation.
5. May be false negative in obesity because of being metabolized by adipocytes.

Treatment of Heart Failure with Reduced Ejection Fraction

1. Na restriction to <1–2 g/day.
2. Water restriction to <1 L/day in those with hyponatremia.
3. Treatment of underlying cause (e.g., alcohol or drug use, relief of ischemia).
4. Achieve euvolemic status: use JVP and daily weights to monitor.
5. Treatment of acute decompensation with IV diuresis.
6. Digoxin as an inotrope has neutral effect on mortality but may increase mortality in those with renal dysfunction, the aged, and women.
7. Beta blockers are important disease-modifying agents by blocking toxic effects of catecholamines on myocardium and upregulating beta receptors; carvedilol and metoprolol succinate have shown mortality benefit. Maximize doses.
8. ACEIs or angiotensin receptor blockers (ARBs) reduce mortality. Neprilysin inhibitor, LCZ696, was superior to enalapril in PARADIGM-HF trial (McMurray *et al.*, 2014).
9. Spironalactone or eplerenone improve survival.
10. Combination of hydralazine and isorbide dinitrate (BiDil) improves survival incremental to above drugs in black patients.
11. Amiodarone has neutral effect on mortality. May be useful as bridge to beta blockade in acute HF with rapid heart rates (Singh *et al.*, 1995).
12. Inotropes increase mortality; they are used for palliative care and as bridge to heart transplant.
13. An implantable cardioverter-defibrillator (ICD) for primary prevention of death is recommended in those with EF <35%.
14. Cardiac resynchronization therapy (CRT) with biventricular pacer or ICD is recommended for those with EF <35% and QRS duration >150 ms with left bundle branch block morphology.
15. Cardiac transplant improves outcome in end-stage HF patients who are candidates for heart transplant.

16. LVADs improve survival in selected patients with end-stage HF who are not transplant candidates.
17. Treatment of anemia with erythropoietin increased mortality.

Treatment of Heart Failure with Preserved Ejection Fraction

1. Na restriction to <1–2 g/day.
2. Water restriction to <1 L/day in those with hyponatremia.
3. Treatment of underlying cause (e.g., hypertension, relief of ischemia).
4. Achieve euvolemic status: use JVP and daily weights to monitor.
5. Treatment of acute decompensation with IV diuresis.
6. Beta blockers have not shown a mortality benefit.
7. ACEIs and ARBs have not shown a mortality benefit, though ARBs may marginally reduce hospitalization.
8. Aldosterone blockade had no mortality benefit.
9. No role for ICD or CRT devices.
10. Exercise program improves exercise tolerance.

Causes of Acute Heart Failure Decompensation

Keep these in mind.

1. Noncompliance with medical regimen.
2. Acute myocardial ischemia.
3. Uncorrected high blood pressure.
4. Atrial fibrillation and other arrhythmias.
5. Intake of negative inotropic agents (e.g., verapamil, diltiazem, sotalol, disopyramide).
6. Pulmonary embolism.
7. Use of nonsteroidal anti-inflammatory drugs causing fluid retention.
8. Excessive alcohol or illicit drug use.
9. Concurrent infections (e.g., pneumonia, viral illnesses).

Markers of Poor Prognosis in Heart Failure

1. Lower EF.
2. Higher functional class.
3. Hyponatremia.
4. Refractory symptoms.
5. Low blood pressure.
6. Tachycardia.
7. Intolerance to beta blockers and ACEIs.
8. Increasing creatinine.
9. Recurrent admissions.
10. Inotrope dependence.
11. Increasing QRS duration.
12. Higher BNP levels.
13. Anemia.

Box 11.2 Updated Classification of Pulmonary Hypertension

See Simonneau *et al.* (2013).

1. **PAH**
   - 1.1 Idiopathic PAH
   - 1.2 Heritable PAH
     - 1.2.1 *BMPR2*
     - 1.2.2 *ALK-1*, *ENG*, *SMAD9*, *CAV1*, *KCNK3*
     - 1.2.3 Unknown
   - 1.3 Drug and toxin induced
   - 1.4 Associated with:
     - 1.4.1 Connective tissue disease
     - 1.4.2 HIV infection
     - 1.4.3 Portal hypertension
     - 1.4.4 Congenital heart diseases
     - 1.4.5 Schistosomiasis
   - 1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   - 1″ Persistent PH of the newborn (PPHN)
2. **PH due to left heart disease**
   - 2.1 Left ventricular systolic dysfunction
   - 2.2 Left ventricular diastolic dysfunction
   - 2.3 Valvular disease
   - 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. **PH due to lung diseases and/or hypoxia**
   - 3.1 Chronic obstructive pulmonary disease
   - 3.2 Interstitial lung disease
   - 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
   - 3.4 Sleep-disordered breathing
   - 3.5 Alveolar hypoventilation disorders
   - 3.6 Chronic exposure to high altitude
   - 3.7 Developmental lung diseases
4. **CTEPH**
5. **PH with unclear multifactorial mechanisms**
   - 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
   - 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
   - 5.3 Metabolic disorders: glycogen-storage disease, Gaucher disease, thyroid disorders
   - 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Box 11.3 Pulmonary Hypertension Take-home Points

These take-home points are based on ESC/ERS 2015 recommendations (Galiè *et al.*, 2016).

1. RHC is recommended to confirm the diagnosis of PAH (Group 1) and to support treatment decisions.
2. Vasoreactivity testing is recommended in patients with idiopathic PAH, hereditary PAH, and PAH induced by drugs use to detect patients who can be treated with high doses of a CCB.
3. It is recommended to avoid pregnancy in patients with PAH.
4. It is recommended for referral centers to provide care by a multiprofessional team (cardiology and respiratory medicine physicians, clinical nurse specialist, radiologists, psychological and social work support, appropriate on-call expertise).
5. Initial approved drugs monotherapy is recommended in treatment-naive, low-, or intermediate-risk patients with PAH.
6. Initial approved oral drugs combination therapy is recommended in treatment-naive, low-, or intermediate-risk patients with PAH.
7. Sequential drugs combination therapy is recommended in patients with inadequate treatment response to initial monotherapy or to initial double combination therapy.
8. The use of PAH approved therapies is not recommended in patients with PH due to left heart disease or lung diseases.
9. Surgical pulmonary endarterectomy in deep hypothermia circulatory arrest is recommended for patients with CTEPH and it is recommended that the assessment of operability and decisions regarding other treatment strategies (drugs therapy or balloon pulmonary angioplasty) be made by a multidisciplinary team of experts.

Box 11.4 Summary of Pivotal Clinical Trials in Heart Failure

- McKee *et al.* (1971) lists Framingham criteria for HF that serve as the gold standard for its diagnosis.
- The CONSENSUS trial (The CONSENSUS Trial Study Group, 1987) is a large, randomized study that showed a large survival benefit with ACEIs in HFrEF which had been shown before a Veterans Administration randomized trial.
- Packer *et al.* (1996) was a randomized trial that clearly established the role for carvedilol in the treatment of HFrEF.
- The MERIT-HF Study Group (Hjalmarson *et al.*, 2000) randomized trial showed mortality benefit with long-acting metoprolol in HFrEF. Note that short-acting metoprolol does not give the same benefit because of lack of sustained beta blockade.
- Pitt *et al.* (1999) used aldosterone antagonist to improve survival incremental to beta blocker and ACEIs in HFrEF.
- The A-HeFT trial (Taylor *et al.*, 2004) showed a mortality benefit with combination of isosorbide dinitrate and hydralazine (BiDil) in African-American patients with HFrEF and this effect was incremental to beta blocker and ACEIs.

- The DIG trial (The Digitalis Investigation Group, 1997) showed a neutral effect on mortality in HF. But subset analysis has shown a potential reduction in hospitalization in those with severe congestive HF and S3 and potential increased mortality in the elderly, women, and those with renal dysfunction, possibly as a result of digoxin toxicity in these subgroups with lower creatinine clearance rates.
- The CHF-STAT trial (Singh *et al.*, 1995) showed that amiodarone had a neutral effect on mortality in HFrEF. It is possible that a slight reduction in mortality due to malignant ventricular arrhythmias was neutralized by an increase in bradycardiac mortality.
- In the CHARM-Preserved Trial (Yusuf *et al.*, 2003) the ARB candesartan did not reduce mortality in HFpEF, but there was a slight reduction in hospitalization.
- The SENIORS study (Flather *et al.*, 2005) examined beta blockers. They did not reduce mortality in HFpEF.
- The Aldo-HF trial (Edelmann *et al.*, 2013) examined spironolactone, which had a neutral mortality effect in HFpEF.
- In the Ex-DHF study (Edelmann *et al.*, 2011), exercise training was found to improve exercise tolerance and LV filling dynamics in HFpEF.
- In the PARADIGM-HF trial (McMurray *et al.*, 2014) the Angiotensin receptor-neprilysin inhibitor was superior to enalapril in addition to standard therapy in patients with systolic heart failure in terms of mortality and hospitalization. 8442 patients with class II, III, or IV HF and an EF of 40% or less were randomized.
- In the PARADIGM-HF trial (Simpson *et al.*, 2015), MAGGIC (Meta-Analysis Global Group in Chronic Heart Failure) and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) risk scores are described and applied to the trial population. The benefit of LCZ696 was uniform across all risk groups based on these scores.
- The 2015 ESC/ERS Guidelines (Galiè *et al.*, 2016) is an excellent reference resource to understand the current classification, diagnostic approach, and treatment of patients with PH.

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Cardiomyopathies 12

12.1. About 30% of dilated cardiomyopathies are inherited. What modes of transmission are included?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked
D. Mitochondrial
E. All of the above.

12.2. What is the most common mode of inheritance in dilated cardiomyopathy (DCM)?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked
D. Mitochondrial

12.3. A 19-year-old patient has DCM with an ejection fraction (EF) of 10%, complete heart block, junctional escape rhythm with left bundle branch block (LBBB), and muscle weakness. What is the likely mutation in?

A. Lamin A/C gene
B. Troponin T gene
C. Desmin gene
D. Titin gene

12.4. Which of the following gene mutations can cause DCM?

A. Myosin heavy chain
B. Cardiac actin
C. Troponin T
D. Titin
E. Dystrophin
F. All of the above.

12.5. Which of the following is *not* a standard indication for anticoagulation in patients with dilated cardiomyopathy?

A. Male, 30 years, DCM, EF of 10%
B. Male, 30 years, DCM, EF of 25%, apical thrombus
C. Male, 30 years, DCM, EF is 20%, multiple transient ischemic attacks (TIAs), no thrombus seen in left ventricle or left atrium, aorta is clear, no patent foramen ovale
D. Male, 30 years, DCM, EF 35%, no left ventricular (LV) thrombus, no TIA or stroke, left ventricle is hypertrabeculated with noncompacted to compacted ratio of 2.5

12.6. Which of the following mutations may not cause hypertrophic cardiomyopathy (HCM)?

A. Myosin heavy chain
B. Myosin light chain
C. Troponin T
D. Desmin

12.7. Which of the following mutation can cause restrictive cardiomyopathy?

A. Myosin heavy chain
B. Cardiac actin
C. Troponin T
D. Troponin I

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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12.8. A 42-year-old man is diagnosed to have HCM with dynamic LV outflow tract (LVOT) obstruction. He has had two episodes of syncope, and maximum interventricular septal thickness is 30 mm. No genetic testing has been done. Which of the following statements is *not* accurate regarding screening?

A. It is appropriate to screen first-degree relatives with an echocardiogram
B. It is strongly recommended to screen first-degree relatives for high-risk genotypes
C. It is appropriate to perform a physical examination and an electrocardiogram (ECG) in first-degree relatives
D. It is appropriate to screen adult first-degree relatives every 5 years and children every 12–18 months.

12.9. Which of the following statements is inaccurate regarding genetic testing in HCM?

A. Evaluation of familial inheritance and genetic counseling is recommended as part of the assessment of patients with HCM
B. Patients who undergo genetic testing should also undergo counseling by someone knowledgeable in the genetics of cardiovascular disease so that results and their clinical significance can be appropriately reviewed with the patient
C. Genetic testing is reasonable in the index patient to facilitate the identification of first-degree family members at risk for developing HCM
D. Genetic testing is indicated in relatives when the index patient does not have a definitive pathogenic mutation as sporadic mutations may occur.

12.10. A 45-year-old man has HCM and found to have MHC gene mutation. The same mutation is found in one of his sons who is 20 years old. The son had a normal physical examination, ECG, and an echocardiogram. How frequently would you repeat an echocardiogram on this son?

A. No need to repeat
B. Every 12–18 months
C. Every 5 years
D. Only if symptoms occur or ECG becomes abnormal

12.11. Which of the following statements are accurate regarding performance of a 24-h Holter monitor in a patient with HCM?

A. Twenty-four-hour ambulatory (Holter) ECG monitoring is recommended in the initial evaluation of patients with HCM to detect ventricular tachycardia (VT) and identify patients who may be candidates for ICD therapy even if they have no palpitations or syncope
B. Twenty-four-hour ambulatory (Holter) ECG monitoring or event recording is recommended in patients with HCM who develop palpitations or lightheadedness
C. Twenty-four-hour ambulatory (Holter) ECG monitoring, repeated every 1–2 years, is reasonable in patients with HCM who have no previous evidence of VT to identify patients who may be candidates for implantable cardioverter-defibrillator (ICD) therapy
D. All of the above
E. None of the above

12.12. In a patient with known or suspected HCM, which of the following statements regarding echocardiography are accurate?

- **A.** A transthoracic echocardiogram (TTE) is recommended in the initial evaluation of all patients with suspected HCM
- **B.** A TTE is recommended as a component of the screening algorithm for family members of patients with HCM unless the family member is genotype negative in a family with known definitive mutations
- **C.** Periodic (12–18 months) TTE screening is recommended for children of patients with HCM, starting by age 12 years or earlier if a growth spurt or signs of puberty are evident and/or when there are plans for engaging in intense competitive sports or there is a family history of sudden cardiac death (SCD)
- **D.** All of the above

12.13. In a patient with known or suspected HCM, which of the following statements regarding cardiac magnetic resonance (CMR) imaging are accurate?

- **A.** CMR imaging is indicated in patients with suspected HCM when echocardiography is inconclusive for diagnosis
- **B.** CMR imaging is indicated in patients with known HCM when additional information that may have an impact on management or decision making regarding invasive management, such as magnitude and distribution of hypertrophy or anatomy of the mitral valve apparatus or papillary muscles, is not adequately defined with echocardiography
- **C.** CMR imaging is reasonable in patients with HCM to define apical hypertrophy and/or aneurysm if echocardiography is inconclusive
- **D.** In selected patients with known HCM, when SCD risk stratification is inconclusive after documentation of the conventional risk factors, CMR imaging with assessment of late gadolinium enhancement may be considered in resolving clinical decision making
- **E.** All of the above.

12.14. Which of the following drugs may prolong survival in an asymptomatic HCM patient?

- **A.** Beta blocker
- **B.** Verapamil
- **C.** Amiodarone
- **D.** None of the above

12.15. Which of the following therapies are indicated in asymptomatic HCM patients with no outflow obstruction?

- **A.** Beta blocker to reduce atrial fibrillation risk
- **B.** Calcium channel blocker as positive lusiotropic agents to improve cardiac performance
- **C.** Amiodarone to reduce risk of sudden death
- **D.** None of the above
- **E.** All of the above

12.16. A patient with hypertrophic obstructive cardiomyopathy (HOCM) has a resting LVOT gradient of 80 mmHg despite verapamil of 480 mg/day. His heart rate is 58 bpm, blood pressure (BP) 125/70 mmHg and he is still in class III symptoms and short of breath on minimal exertion. Which of the following would you do?

- **A.** Add Nifedipine as a positive lusiotropic agent to improve LV diastolic function
- **B.** Add small dose of frusemide to relieve pulmonary congestion

C. Consider dual-chamber pacer with short atrioventricular delay to cause asynchronous septal contraction and elimination of obstruction
D. Consider disopyramide as a negative inotropic agent

12.17. In a hypotensive patient with HOCM with high outflow gradient, in addition to intravenous fluids, which intravenous drug would be most useful?
A. Phenylephrine
B. Norepinephrine
C. Dopamine
D. Verapamil

12.18. Which of the following statements are accurate regarding septal reduction procedures in patients with HOCM?
A. Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction
B. Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction
C. When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms
D. All of the above

12.19. Which of the following markers may be associated with elevated SCD risk in HCM patients?
A. Family history of sudden death
B. Syncope
C. Nonsustained VT
D. Hypotension on exercise
E. LV wall thickness >30 mm
F. All of the above.

12.20. Which of the following markers may also be associated with elevated SCD risk in HCM patients?
A. Delayed enhancement on CMR imaging
B. Severe LVOT gradient
C. Double and compound mutations
D. All of the above
E. None of the above

12.21. Which of the following statements are accurate regarding use of an ICD for primary prevention in a patient with HCM?
A. An ICD can be useful in select patients with nonsustained VT (particularly those <30 years of age) in the presence of other SCD risk factors or modifiers
B. An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers
C. It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy (LVH), or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation
D. All of the above

12.22. A 42-year-old man presents with shortness of breath, tingling of fingers, vague abdominal pains, and blurred vision. He is hypertensive, creatinine is 2.4 mg/dL, and has corneal opacities. He has reduced touch sensations in hands and feet. An echocardiogram shows moderate LVH with normal wall motion. What is the likely diagnosis?

A. HCM
B. Hypertensive heart disease
C. Fabry disease
D. Hemochromatosis

12.23. A 52-year-old man presented with anginal sounding chest pain. The ECG showed increased voltage and deep T wave inversions V2 to V6. The cardiac enzymes were negative and the coronary angiogram was completely normal. What is the LV gram likely to show?

A. Apical akinesis
B. Severe LVH
C. Dyskinesis distal 2/3 of left ventricle
D. A spade-shaped left ventricle

12.24. A 42-year-old woman presented with abdominal pain, and an abdominal computed tomography scan showed possible LV apical pseudoaneurysm. A TTE was suboptimal. A transesophageal echocardiogram image is shown in Figure 12.24. What is the likely apical abnormality?

A. LV apical aneurysm
B. LV apical pseudoaneurysm
C. LV apical diverticulum
D. LV apex is normal

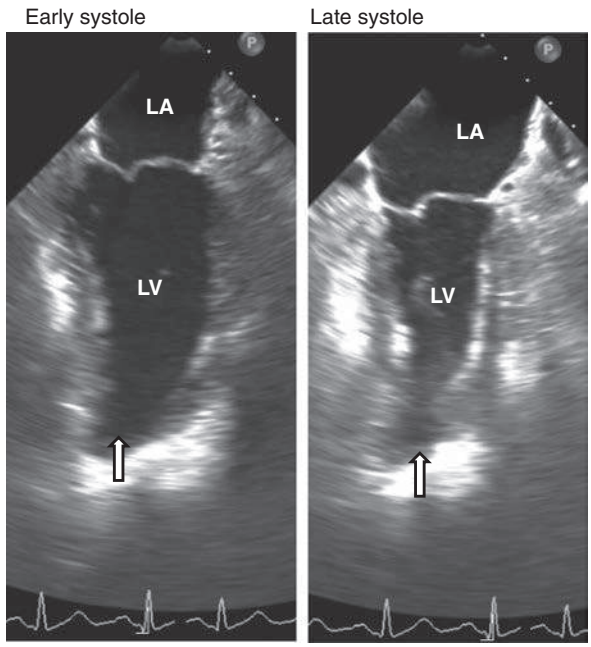

Figure 12.24

12.25. A 42-year-old man with a diagnosis of HOCM has shortness of breath on minimal exertion. He is on verapamil 240 mg BID and disopyramide 100 mg TID. His heart rate is 56 bpm, BP 120/70 mmHg, and examination shows a systolic murmur at the left sternal border increasing with Valsalva. The echocardiogram shows an EF of 75%, severe upper septal hypertrophy, severe systolic anterior motion (SAM) with a resting LVOT velocity of 4 m/s. The septal thickness at SAM–septal contact is 25 mm. What would the most appropriate treatment be?

A. Referral to HCM center of excellence for surgical septal myectomy
B. Alcohol septal ablation
C. Mitral valve replacement
D. Trial with dual-chamber pacemaker with short atrioventricular delay

12.26. A 22-year-old man is admitted with a history of syncope. He had a similar episode 2 months earlier. No other medical history. Family history is unremarkable. His resting ECG is normal and overnight monitoring shows frequent episodes of non-sustained VT of LBBB morphology. An echocardiogram, which is technically difficult, shows normal left ventricle and valvular function. The right ventricle seems to be mildly dilated with a tricuspid annular plane systolic excursion of 15 mm. What would be the most useful test you could recommend at this time?

A. CMR imaging
B. Electrophysiology testing
C. Endomyocardial biopsy
D. A loop recorder

12.27. The 28-year-old patient in Figure 12.27 had syncope. What is the likely underlying cause?

A. LV noncompaction cardiomyopathy
B. HCM
C. Endomyocardial fibroelastosis
D. None of the above

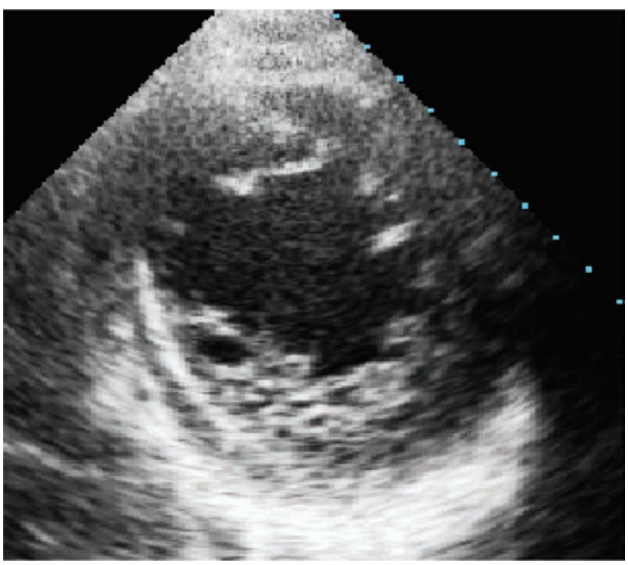

Figure 12.27

12.28. A 28-year-old man with no prior history presented with shortness of breath on minimal exertion. Images from a resting echocardiogram are shown in Figure 12.28. Which of the following may the shortness of breath respond to?

A. Aortic valve replacement
B. Frusemide
C. Beta blocker
D. Digoxin

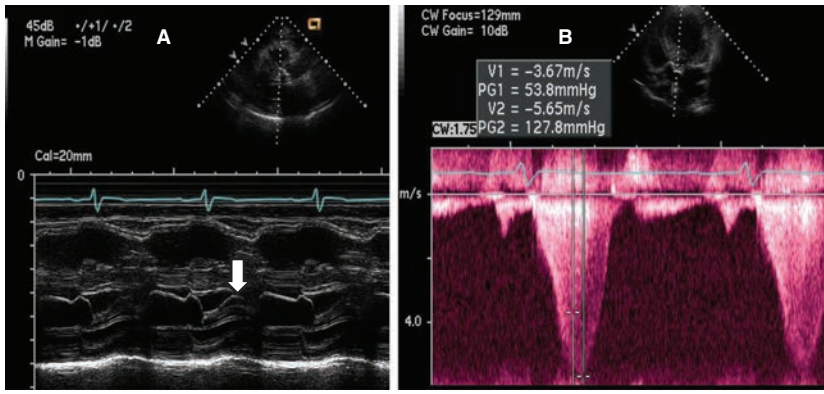

Figure 12.28

12.29. What is auscultation of the patient's heart in Figure 12.29 likely to reveal?

A. Systolic murmur increased by Valsalva maneuver
B. Systolic murmur increased by hand grip
C. Systolic murmur with soft S1
D. Mid diastolic murmur

Figure 12.29

12.30. A 43-year-old woman with no prior medical history presented with a 4 month history of shortness of breath (see Figure 12.30). What could the likely explanation be?

A. Heart failure with reduced EF
B. Heart failure with preserved EF
C. Mitral stenosis
D. Mitral regurgitation

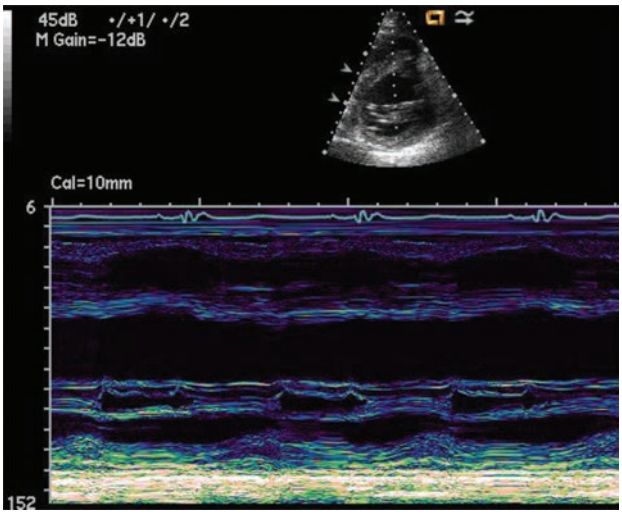

Figure 12.30

12.31. Which of the following is the patient in Figure 12.31 likely to have?

A. HCM
B. Restrictive cardiomyopathy
C. Normal LV size and morphology
D. LV noncompaction

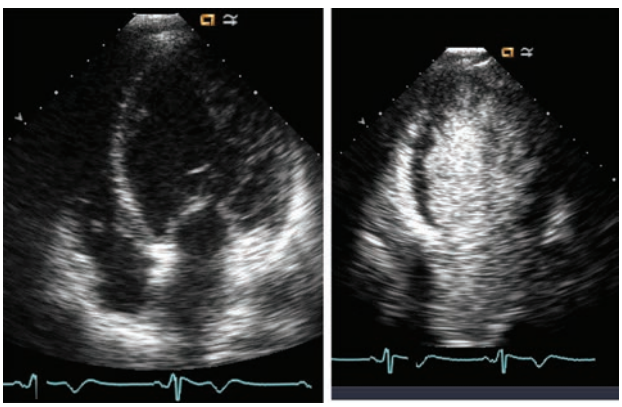

Figure 12.31

12.32. A 66-year-old patient presented with dyspnea and pedal edema. The ECG and an echo image are shown in Figure 12.32. The EF was about 25% and the left ventricle was globally hypokinetic. What is the possible diagnosis?

A. Hypertensive heart disease
B. HCM
C. Cardiac amyloidosis
D. None of the above

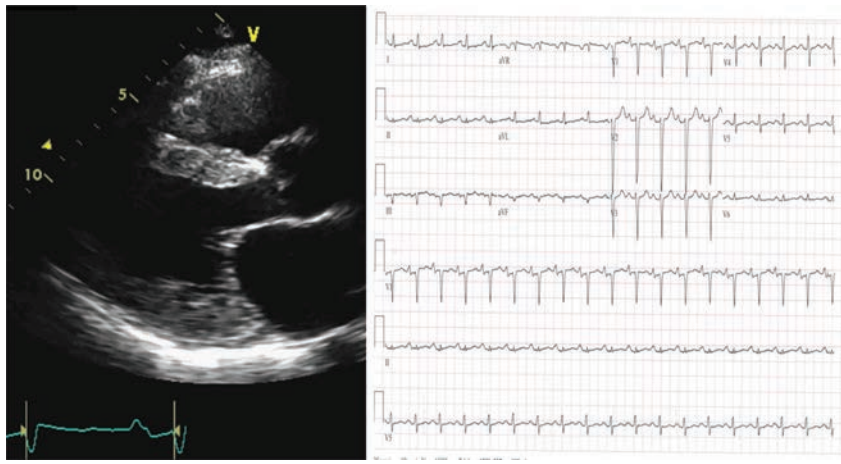

Figure 12.32

12.33. The 33-year-old woman shown in Figure 12.33 presented with shortness of breath and pedal edema of 4 weeks' duration. She also had low-grade fever, dry cough, and wheezing. There was no prior medical history, and she denied use of alcohol or recreational drugs. What does the possible diagnosis include?

A. Hypereosinophilic syndrome
B. Anterior myocardial infarction with large apical thrombus
C. Rib artifact in LV apex
D. Apical HCM

12.34. The 43-year-old African American woman shown in Figure 12.34 (MDE: myocardial delayed enhancement) presented with syncope. What is the possible explanation?

A. LV diverticulum
B. Myocardial infarction
C. Cardiac sarcoid
D. None of the above

12.35. A 42-year-old woman presented with weight loss and diarrhea. A continuous-wave signal through the tricuspid valve is shown in Figure 12.35. What is the likely cause of her symptoms?

A. Hepatic congestion from severe tricuspid regurgitation
B. Protein-losing enteropathy
C. Carcinoid
D. None of the above

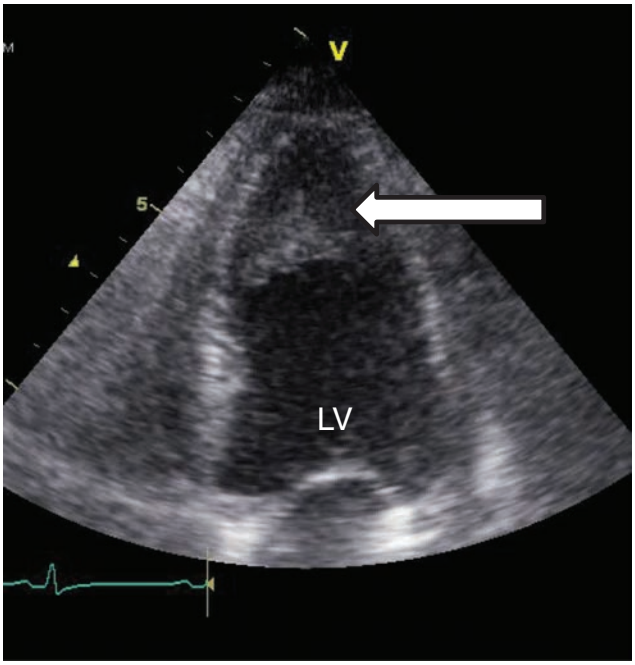

Figure 12.33

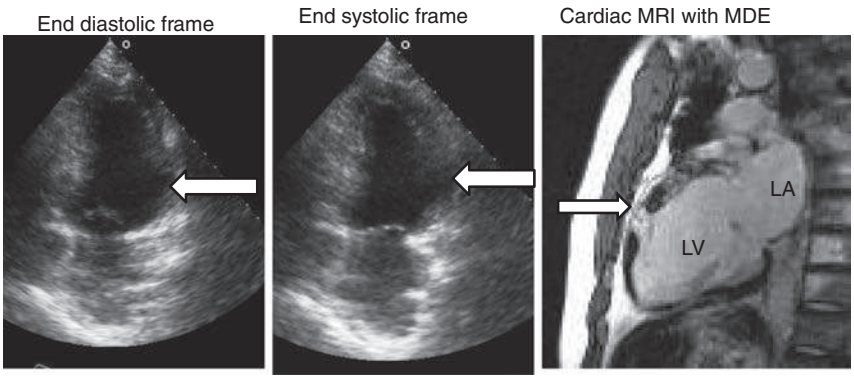

Figure 12.34

12.36. For the diagnosis of ARVD, which of the following criteria are required?

A. Two major
B. One major and two minor
C. Four minor from different categories
D. Any of the above

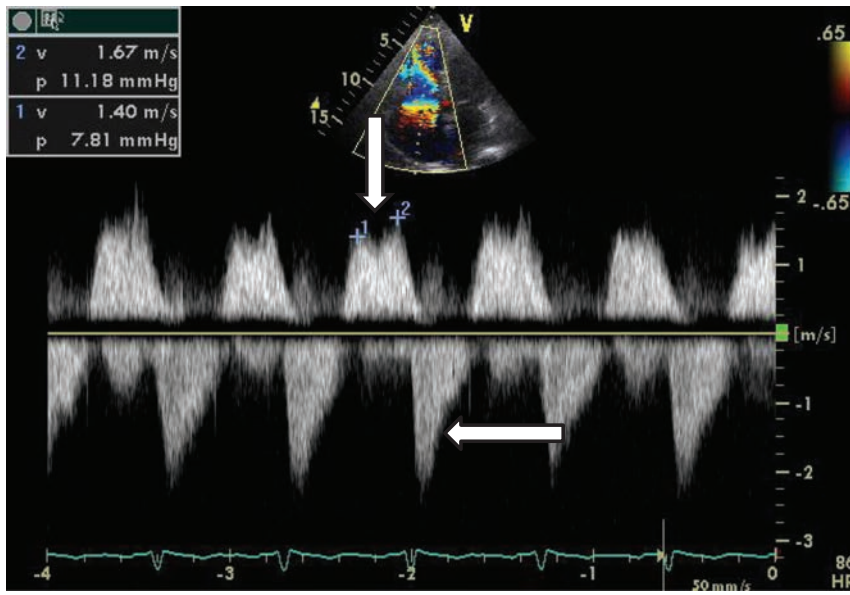

Figure 12.35

12.37. Which of the following are major criteria for ARVD diagnosis?

- **A.** On CMR imaging: RV regional wall dyskinesis plus RV EDV ≥110 mL/m^2 in males/RV EDV ≥100 mL/m^2 in females or RV EF ≤40%
- **B.** Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)
- **C.** Nonsustained or sustained VT of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
- **D.** Arrhythmogenic RV cardiomyopathy (ARVC)/ARVD confirmed in a first-degree relative or identification of a pathogenic mutation categorized as associated or probably associated with ARVC/ARVD in the patient under evaluation
- **E.** All of the above

12.38. Which of the following facts are accurate regarding genetics of ARVD?

- **A.** Inheritance in familial cases is mostly autosomal dominant
- **B.** Mutations affect desmosomes with facilitate cell to cell connections
- **C.** Mutations have been found in plakoglobin (*JUP*), desmoplakin (*DSP*), plakophilin-2 (*PKP2*), desmoglein-2 (*DSG2*), desmocollin-2 (*DSC2*), transforming growth factor beta-3 (*TGF3*), and transmembrane protein 43 (*TMEM43*).
- **D.** Mutations in *RYR2* coding the ryanodine receptor have been reported in ARVC/ARVD in patients with an arrhythmic presentation (stress-induced bidirectional VT) in the absence of significant electrocardiographic or structural abnormalities
- **E.** All of the above

12.39. In the interventional management of HOCM, compared with surgical septal myectomy, alcohol septal ablation has a higher risk of all *except* which of the following?
- **A.** Right bundle branch block
- **B.** LBBB
- **C.** Complete heart block
- **D.** Sustained VT

12.40. What is the general approach for surgical myectomy?
- **A.** Transaortic
- **B.** Transatrial
- **C.** Through right ventricle
- **D.** None of the above

12.41. What is the risk of needing a permanent pacemaker with alcohol septal ablation?
- **A.** 2%
- **B.** 5%
- **C.** 20%
- **D.** 60%

12.42. Which of the following statements is most accurate regarding the amount of residual scar in the ventricular septum after surgical myectomy versus septal ablation?
- **A.** Similar
- **B.** More with surgical myectomy
- **C.** More with alcohol septal ablation
- **D.** None of the above

12.43. Following surgical septal myectomy or septal ablation with relief of obstruction, which of the following statements about LV mass regression are true at 6 months?
- **A.** There is a reduction in septal LV mass only
- **B.** There is a reduction in nonseptal LV mass only
- **C.** There is reduction in both septal and nonseptal LV mass
- **D.** There is no reduction in LV mass

12.44. Regarding residual outflow obstruction after surgical myectomy versus septal ablation, which of the following statements is most accurate?
- **A.** Similar
- **B.** More with surgical myectomy
- **C.** More with alcohol septal ablation
- **D.** None of the above

Answers

12.1. E. All of the above.

12.2. A. Autosomal dominant.

12.3. A. Lamin A/C gene.
The lamin A/C gene causes all these abnormalities.

12.4. F. All of the above.

12.5. A. Male, 30 years, DCM, EF of 10%.
This patient is least likely to benefit in the absence of LV thrombus, TIA, or atrial fibrillation. In option C, though there is no detectable LV thrombus, it is the likely cause of TIA. In D, patient has noncompaction and there is an indication

for anticoagulation if EF is <40% even in the absence of TIA or thrombus as the deep LV crypts may promote thrombus formation and stroke.

12.6. D. Desmin.

Desmin mutation causes DCM. The other three cause HCM. Other mutations leading to HCM include troponin I, myosin-binding protein C, and titin. It is mostly the sarcomeric mutations that cause HCM. But DCM may be caused by mutations in sarcomeric proteins, cytosketetal proteins, as well as Z-disk associated protein.

12.7. D. Troponin I.

12.8. B. It is strongly recommended to screen first-degree relatives for high-risk genotypes.

In the absence of genotyping the index case, it is inappropriate to screen relatives for possible mutations. Genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation.

12.9. D. Genetic testing is indicated in relatives when the index patient does not have a definitive pathogenic mutation as sporadic mutations may occur.

The other statements are correct per ACC/AHA HCM guidelines.

12.10. C. Every 5 years.

In adults every 5 years, and 12–18 months in children. As the genotype is positive, periodic screening for phenotype is indicated even in the absence of symptoms or physical signs as an echocardiogram is a lot more sensitive.

12.11. D. All of the above.

12.12. D. All of the above.

12.13. E. All of the above.

12.14. D. None of the above.

12.15. D. None of the above.

12.16. D. Consider disopyramide as a negative inotropic agent.

This may reduce gradient without slowing heart rate further. As a matter of fact, its anticholinergic properties may increase the heart rate slightly. Diuretic and nifedepine as vasodilator will worsen the gradient by reducing the LV end-systolic volume. Despite initial enthusiasm, subsequent studies have not supported the use of a pacemaker to eliminate gradient.

12.17. A. Phenylephrine.

This is a pure alpha stimulant. Dopamine, dobutamine, and norepinephrine have beta stimulant properties and would worsen outflow obstruction. Digoxin is contraindicated as well. Verapamil, through vasodilation, may drop the BP further.

12.18. D. All of the above.

12.19. F. All of the above.

12.20. D. All of the above.

12.21. D. All of the above.

12.22. C. Fabry disease.

This is an X-linked recessive disease with manifest phenotype in males with wide variation in expressivity and penetrance. It is due to defective alpha glycosidase A deficiency, which leads to its deposition in nerves, vessels, intestines, cornea, heart, and kidneys. Hence, it may lead to cardiac hypertrophy, renal failure, hypertension, visual defects, and neuropathy. It is an orphan disease, and enzyme therapy is available at an annual cost of about $200 000.

12.23. D. A spade-shaped left ventricle.

Indicates apical HCM. The presentation is typical. Option A is consistent with mid left anterior descending coronary artery lesion, and option C with Takatsubo syndrome.

12.24. C. LV apical diverticulum.

The apical tip bulging does contract in systole, indicating it has muscular wall (muscular type of diverticulum). Neither the aneurysm nor pseudoaneurysm contract; aneurysm has a wide neck and pseudoaneurysm has a narrow neck.

12.25. A. Referral to HCM center of excellence for surgical septal myectomy

The patient, an otherwise healthy individual, has exhausted medical options. If the patient had multiple comorbidities and was of advanced age, alcohol septal ablation would have been an option. Both should be done in experienced centers. Mitral valve replacement, though entertained as an option in the past, is not a recommended treatment. Despite some controversial data on the use of dual-chamber pacing in the 1990s, it is not considered an option in the current era.

12.26. A. CMR imaging.

The index of suspicion for right ventricular (RV) dysplasia is significant. CMR imaging would be helpful for assessment of RV volume and EF. An EF <40% or RV end-diastolic volume (EDV) >110 mL/m^2 would serve as a major criterion. VT is also a major criterion and a diagnosis of arrhythmogenic RV dysplasia (ARVD) can be established with two major criteria. Right ventricle biopsy may be negative due to sampling errors and can also be risky in a patient with thin right ventricle wall. Electrophysiology testing or loop recorder would not add much as the patient already has VT with LBBB morphology. ARVD major criteria are listed at the end of the chapter.

12.27. A. LV noncompaction cardiomyopathy.

Note the heavily trabeculated LV myocardium with noncompacted to compacted thickness ratio >2 in systole. CMR imaging and echo with contrast are other useful tools for the diagnosis. LV noncompaction results in cardiomyopathy, heart failure, ventricular arrhythmias, and formation of LV thrombus with embolization. Indications for anticoagulation include: LV thrombus, systemic embolism/stroke/TIA, atrial fibrillation,and EF <40% even without a thrombus. First-degree relatives should be screened as it is mostly transmitted in an autosomal dominant fashion.

12.28. C. Beta blocker.

The m-mode of the mitral valve in panel A shows SAM of the mitral valve (arrow). The continuous-wave Doppler signal in panel B is diagnostic of dynamic

LVOT obstruction with a late-peaking signal. In valvular aortic stenosis the signal would be more rounded as obstruction is present throughout the ejection period. Diuresis and digoxin are likely to worsen the dynamic obstruction. The other useful drugs are nondihydropyridine calcium channel blockers and disopyramide because of their negative inotropic properties.

12.29. A. Systolic murmur increased by Valsalva maneuver.

Note the SAM of the anterior mitral leaflet along with septal hypertrophy, suggesting HOCM.

12.30. A. Heart failure with reduced EF.

The m-mode examination of the left ventricle at the level of mitral leaflet tips shows dilated left ventricle with LV end-diastolic diameter of 62 mm, reduced contractile function, and increased mitral E wave–septal separation. Reduced mitral opening is due to reduced flow – the leaflets are not thickened and posterior leaflet does not move anteriorly during diastole with the anterior leaflet, as would occur with rheumatic mitral stenosis.

12.31. D. LV noncompaction.

Note the hypertrabeculated LV lateral wall. LV contrast is helpful. A noncompacted to compacted ratio of >2 is suggestive of noncompaction. Noncompaction can result in systolic heart failure, ventricular arrhythmias, sudden death, and LV thrombus formation with stroke. Anticoagulation is generally indicated when EF <40% or there is LV thrombus, systemic embolism, or atrial fibrillation.

12.32. C. Cardiac amyloidosis.

Note LVH on echo with low voltage in the limb leads of the ECG. Also note poor R wave progression V1 to V4 despite preserved septal wall thickness; that is, pseudo-anterior infarct pattern. These features are highly suggestive of cardiac amyloidosis.

12.33. A. Hypereosinophilic syndrome.

The patient has obliterative cardiomyopathy with filling of LV apex with fibrous tissue/thrombus. The patient had an eosinophilic count of 65% on the peripheral smear. Treatment with anticoagulation and prednisone resulted in marked improvement in the appearance of the LV apex and symptoms. In late stages, the patient may not respond and may need surgical resection of endocardial thickening or heart transplant.

12.34. C. Cardiac sarcoid.

The arrow points to a focal aneurysm in the mid anterior wall in both the echo and CMR images. The CMR image also shows patchy scarring of the anterior wall. The chest computed tomography scan was suggestive of pulmonary sarcoid. This patient is at high risk of sudden death in view of myocardial scarring and syncope, which may suggest VT. An ICD for primary prevention is indicated. These patients can get scarring in the right ventricle that mimics ARVD, which may cause focal aneurysms, causing severe LV dysfunction, typically in subtricuspid or other areas. They are also at risk for complete heart block. Diagnostic criteria from Heart Rhythm Society (HRS) expert panel are summarized in Box 12.2 at the end of this chapter.

12.35. C. Carcinoid.
Note that the patient has both severe tricuspid stenosis (mean diastolic gradient >5 mmHg) and severe tricuspid regurgitation with "V" wave cutoff sign (arrow). This is typical of carcinoid.

12.36. D. Any of the above.
See Box 12.1 at the end of this chapter for a summary from the 2010 criteria.

12.37. E. All of the above.

12.38. E. All of the above.

12.39. B. LBBB.
With septal ablation, there is higher risk of all except LBBB. Risk of LBBB is higher with surgical myectomy.

12.40. A. Transaortic.
Through the aortic valve.

12.41. C. 20%.
This is a lot higher than for surgical myectomy, where the risk is about 1–2%.

12.42. C. More with alcohol septal ablation.
This is because no muscle is removed and an uncontrolled infarction is produced. Hence, there is a concern for higher sudden death risk and there is a lower threshold to protect with an ICD. Overall survival and sudden death risk are lower with surgical myectomy. Survival of patients after surgical myectomy is fairly similar to the age-matched general population and much better than those with unoperated HOCM patients.

12.43. C. There is reduction in both septal and nonseptal LV mass.
Both regress by about 20%.

12.44. C. More with alcohol septal ablation.
Also, relief of obstruction takes several weeks.

Box 12.1 Most Current and Comprehensive Summary and Guideline

Diagnostic Criteria for ARVD

The following is summarized from Marcus *et al.* (2010).

Diagnostic Terminology for Revised Criteria

Definite diagnosis: two major or one major and two minor criteria or four minor from different categories.
Borderline: one major and one minor or three minor criteria from different categories.
Possible: one major or two minor criteria from different categories.

Major Criteria for ARVD

1. *Echo:* RV regional wall dyskinesis plus RV outflow tract end-diastolic (RVOTd) in long axis ≥32 mm or RVOTd in short axis ≥36 mm or RV fractional area change ≤33%.

2. *Magnetic resonance imaging:* RV regional wall dyskinesis plus RV EDV ≥110 mL/m^2 in males/RVEDV ≥100 mL/m^2 in females or RV EF ≤40% (note that RV scarring and fatty changes on CMR imaging have been removed as criteria).
3. *Histology:* Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy.
4. *Repolarization abnormalities on ECG:* Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms).
5. *Depolarization abnormalities on ECG:* Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3).
6. *Arrhythmias:* Nonsustained or sustained VT of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL).
7. *Family history:* ARVC/ARVD confirmed in a first-degree relative.
8. *Genetic testing:* Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/ARVD in the patient under evaluation.

Minor Criteria for ARVD

1. These are somewhat similar to major criteria, but less stringent or slightly more liberal.

Box 12.2 Expert Consensus Recommendations on Criteria for the Diagnosis of Cardiac Sarcoid

The diagnostic criteria for cardiac sarcoid are from Birnie *et al.* (2014).
There are two pathways to a diagnosis of cardiac sarcoidosis.

1. *Histological diagnosis from myocardial tissue.* Cardiac sarcoid is diagnosed in the presence of non-caseating granuloma on histological examination of myocardial tissue with no alternative cause identified.
2. *Clinical diagnosis from invasive and noninvasive studies.* It is probable that there is cardiac sarcoid if (a) there is a histological diagnosis of extra-cardiac sarcoidosis and (b) one or more of following is present:
   - Steroid ± immunosuppressant-responsive cardiomyopathy or heart block
   - Unexplained reduced LV EF (<40%)
   - Unexplained sustained (spontaneous or induced) VT
   - Mobitz type II second-degree heart block or third-degree heart block
   - Patchy uptake on dedicated cardiac positron emission tomography (in a pattern consistent with cardiac sarcoid)
   - Late gadolinium enhancement on CMR imaging (in a pattern consistent with cardiac sarcoid)
   - Positive gallium uptake (in a pattern consistent with cardiac sarcoid)

References

Birnie, D.H., Sauer, W.H., Bogun, F., *et al.* (2014) HRS Expert Consensus Statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*, **11**: 1304–1323.

Marcus, F.I., McKenna, W.J., Sherrill, D., *et al.* (2010) Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Circulation*, **121**: 1533–1541.

Further Reading

Elliott, P.M., Anastasakis, A., Borger, M.A., *et al.* (2014) 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *European Heart Journal*, **35**(39): 2733–2779. doi: 10.1093/eurheartj/ehu284.

Hypertension 13

13.1. A 61-year-old black gentleman is seen in your office. He denies any cardiac symptoms. He does not have a history of diabetes. His vitals show a heart rate of 75 bpm and blood pressure (BP) of 160/92 mmHg; examination otherwise is normal. You recommend lifestyle modification, including regular exercise and low-sodium diet. What is the initial drug of choice in managing his hypertension?

A. Metoprolol
B. Furosemide
C. Amlodipine
D. Lisinopril

13.2. A 25-year-old female patient comes to your office. She has a history of chronic kidney disease (CKD) stage 2. She denies any cardiac symptoms. Her vitals are heart rate 76 bpm, BP 170/98 mmHg, respiratory rate 14/min. Her physical exam is otherwise normal. She is on furosemide 40 mg daily. What would your add-on drug of choice in this patient be?

A. Amlodipine
B. Clonidine
C. Lisinopril
D. Hydralazine

13.3. A 49-year-old male comes to your office for an evaluation as part of his executive check-up. He reports feeling well. He denies previous history of diabetes or coronary artery disease. Physical examination is unremarkable except for his BP, which was measured at 165/98 mmHg. His BP rechecked after 5 min was 160/98 mmHg. What would your recommendation be to this patient?

A. Reassurance
B. Initiate drug therapy
C. Come back for a follow up in 3 months
D. Come back for a follow up after 6 months

13.4. A 50-year-old female is being evaluated in your office. She reports a history of diabetes mellitus and is taking metformin 500 mg BID. She reports no other history. She denies any cardiac symptoms. She exercises regularly. Her examination is unremarkable except for her high BP, which was measured on two occasions 5 min apart and was 170/92 mmHg. What is the initial drug of choice?

A. Prazosin
B. Clonidine
C. Atenolol
D. Lisinopril

13.5. A 40-year-old female is admitted to the hospital. On examination she is found to have pulmonary edema. Her past history is only significant for hypertension. She is on a medical regimen consisting of a thiazide diuretic, amlodipine, losartan, and carvedilol. Her family also gave a history of recent uncontrolled high BP and one other episode of pulmonary edema 2 months ago. Her BP was 220/110 mmHg. The rest of her examination is unremarkable. What is the initial diagnosis?

A. Pseudohypertension
B. Primary hyperaldosteronism
C. Reno-vascular hypertension
D. Coarctation of aorta

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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13.6. What is the diagnostic test of choice in the patient in Question 13.5?

A. Captopril renogram
B. Intravenous pyelogram
C. Doppler ultrasound of the renal arteries
D. Magnetic resonance angiography (MRA)
E. Captopril-stimulated plasma renin activity (PRA)

13.7. A 60-year-old female is referred to you for uncontrolled hypertension. Her primary care physician was treating her for the last 5 months. She denies any other history in the past. She drinks alcohol socially and is in the habit of chewing tobacco. On examination she weighs 75 kg, BP is 200/100 mmHg. The rest of her examination is unremarkable except for trace pedal edema. Her lab values are as follows:

serum sodium 144 mEq/L
serum potassium 3 mEq/dL
serum chloride 100 mEq/L
serum bicarbonate 29 mEq/L
serum creatinine 0.9 mg/dL
blood urea nitrogen 20 mg/dL
PRA is 1.2 μg/(L h), plasma aldosterone (PA) level is 9.2 ng/L, and aldosterone excretion rate is 8 mg/day (normal is 5–10 mg/day)
urine test after salt loading yields creatinine 1 g, sodium 251 mEq, and potassium 130 mEq.

Which diagnostic test would you order next?

A. Computed tomography of adrenal glands
B. MRA of the renal arteries
C. Serum cortisol and urinary free-cortisol measurement
D. Cosyntropin test

13.8. A 45-year-old male is referred to you for treatment of uncontrolled hypertension. He is on four different antihypertensives at maximal doses, including a thiazide-type diuretic. He denies any other medical history. He is active. His BP is 184/100 mmHg, sitting upright in a relaxed posture. His blood chemistry is unremarkable except for serum potassium of 2.9 mg/dL and a plasma renin level of <1 ng/(mL h). What is the cause of hypertension in this patient?

A. Reno-vascular hypertension
B. Primary aldosteronism
C. Pheochromocytoma
D. Renal parenchymal disease

13.9. What is the best screening test in evaluating the patient in question 13.8?

A. MRA of the renal arteries.
B. Ratio of PA to PRA
C. Urine metanephrine
D. Intravenous pyelogram

13.10. You have been referred a 52-year-old male with refractory hypertension by a primary care physician. The patient gives a history of episodes of headache, sweating,and palpitations. On examination his BP is 198/112 mmHg. Examination is otherwise unremarkable. What is the best screening test in evaluating this patient?

A. Serum cortisol
B. PA to PRA

C. Plasma catecholamines and urinary metanephrines
D. MRA of the abdomen

13.11. What is the BP goal for a 62-year-old patient according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.12. What is the BP goal for a 92-year old patient according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.13. What is the BP goal for a 62-year-old patient with diabetes mellitus according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.14. What is the BP goal for a 42 year old patient with diabetes mellitus according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.15. What is the BP goal for a 62-year-old patient with renal disease according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.16. What is the BP goal for a 42-year-old patient with diabetes mellitus according to the JNC 8 guidelines?
A. <140/90 mmHg
B. <150/90 mmHg
C. <160/100 mmHg
D. <160/90 mmHg

13.17. What is the drug of choice to treat hypertension in a black person with renal disease?
A. Diuretic
B. CCB
C. ACEI or ARB
D. Beta blocker

13.18. What is the drug of choice to treat hypertension in a black person with diabetes mellitus?
A. Diuretic or CCB
B. ACEI
C. ARB
D. Any of the above

13.19. What is the drug of choice to treat hypertension in a nonblack person with diabetes mellitus?
A. Diuretic
B. CCB
C. ACEI or ARB
D. Any of the above

13.20. Which is the most preferred drug to treat hypertension in pregnancy according to the JNC 8 guidelines?
A. Labetalol
B. Nifedipine
C. Methyldopa
D. ACEI

13.21. Which is the most preferred drug to reduce the risk of recurrent stroke according to the JNC 8 guidelines?
A. Diuretic
B. CCB
C. Clonidine
D. Beta blocker

13.22. Which antihypertensive agent may reduce uric acid levels?
- **A.** Diuretic
- **B.** CCB
- **C.** Losartan
- **D.** Candesartan

13.23. Which antihypertensive agent may reduce migraine attacks?
- **A.** Diuretic
- **B.** CCB
- **C.** Losartan
- **D.** Candesartan

13.24. Which antihypertensive agent may result in gynecomastia?
- **A.** Spironolactone
- **B.** CCB
- **C.** Losartan
- **D.** Candesartan

13.25. A 44-year-old man with hypertension received an escalating dose of lisinopril. At the clinic visit his heart rate is 72 bpm and BP is 152/92 mmHg on lisinopril 40 mg/day. What will you recommend?
- **A.** Ask to reduce Na intake to <1 g instead of <2 g per day
- **B.** Add hydrochlorothiazide (HCTZ) 25 mg/day
- **C.** Add losartan 50 mg/day
- **D.** Add beta blocker

13.26. A 75-year-old man with hypertension is on lisinopril 40 mg/day and HCTZ 50 mg/day. His BP is 160/88 mmHg. Previously, he did not tolerate diltiazem because of edema. What would you do?
- **A.** Start losartan 25 mg/day
- **B.** Add amlodipine 5 mg/day
- **C.** Add furosemide
- **D.** Add carvedilol 6.25 mg BID

13.27. What is the recommended daily Na restriction in hypertension?
- **A.** <2400 mg
- **B.** <1200 mg
- **C.** <500 mg
- **D.** None of the above

13.28. What systolic BP (SBP) goal does the Systolic Blood Pressure Intervention Trial (SPRINT) support?
- **A.** <120 mmHg
- **B.** <130 mmHg
- **C.** <140 mmHg
- **D.** <150 mmHg

13.29. The Systolic Hypertension in the Elderly Program (SHEP) showed that, in elderly patients with isolated systolic hypertension, thiazide diuretic reduced which of the following?
- **A.** SBP
- **B.** Stroke risk
- **C.** Cardiac events
- **D.** All of the above

13.30. Which of the following statements are accurate about the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)?
- **A.** The primary outcome was similar in the chlorthalidone, amlodipine, and lisinopril arms. Mortality was similar
- **B.** The SBP was lower in the chlorthalidone group
- **C.** The DBP was lower in the amlodipine group
- **D.** Stroke and cardiac events were higher in the lisinopril group compared with chlorthalidone
- **E.** All of the above

Answers

13.1. C. Amlodipine.

The 2014 hypertension guidelines clearly state that the initial drug of choice in black patients, including those with diabetes, is either a thiazide-type diuretic or a calcium channel blocker (CCB). This recommendation stems from a prespecified subgroup analysis of a single large trial (ALLHAT). In this study, thiazide-type diuretic was shown to be more effective in improving stroke, heart failure (HF), and combined cardiovascular outcomes compared with an angiotensin-converting-enzyme inhibitor (ACEI) in the black subgroup in both diabetic and nondiabetic subjects. Hence, the recommendation to choose a thiazide diuretic over an ACEI. Although a CCB was less effective than a thiazide diuretic in preventing HF in the black population, there were no differences in other outcomes; that is, cardiovascular, cerebrovascular, renal, or combined outcomes. Therefore, either a thiazide-type diuretic or a CCB is the initial drug of choice in black patients.

13.2. C. Lisinopril.

According to the 2014 hypertension guidelines, people aged 18 or older with CKD and hypertension, an initial or add-on medication should include either an ACEI or an angiotensin receptor blocker (ARB) to improve renal outcomes. This recommendation applies to those with and without proteinuria, as studies using an ACEI or an ARB showed improved renal outcomes in both groups. This recommendation is mainly based on kidney outcomes. The African American Study of Kidney Disease and Hypertension study showed benefit of ACEIs in black patients with CKD.

13.3. B. Initiate drug therapy.

The 2014 hypertension guidelines state that in the general population younger than 60 years to initiate pharmacologic treatment to lower diastolic BP (DBP) of 90 mmHg or higher to a goal of lower than 90 mmHg. For ages 30–59 years the recommendations are strong and for ages 18–29 years the recommendations are based on expert opinion. This recommendation is based on data from five DBP trials (Hypertension Detection and Follow-up Program, Hypertension–Stroke Cooperative Study, Medical Research Council trial, Australian National Blood Pressure Study, and VA Cooperative Study), which showed improvements in health outcomes in adults aged 30 through 59 with elevated BP. Initiating treatment at DBP 90 mmHg or higher and reducing the DBP to lower than 90 mmHg reduced cerebrovascular events, HF, and overall mortality. There was no benefit in treating patients to a goal of 80 or 85 mmHg based on the Hypertension Optimal Treatment trial. In patients younger than 30 years there are no good or fair quality randomized control trails and hence is recommendation is start treatment when DBP is 90 mmHg or higher to a goal of less than 90 mmHg.

13.4. D. Lisinopril.

The 2014 guidelines recommendation for initial treatment of the general population with diabetes is thiazide-type diuretic, CCB, ACEI, or ARB (moderate recommendation – grade B). Each of the four drug classes recommended

by the panel yielded comparable effects on mortality and cardiovascular, cerebrovascular, and kidney outcomes, with one exception: HF. Initial treatment with thiazide-type diuretic was more effective than CCB or ACEI, and an ACEI was more effective than a CCB in improving HF outcomes. The panel did not recommend beta-blockers for the initial treatment of hypertension because in one study use of beta-blockers resulted in a higher rate of the primary composite outcome of cardiovascular death, myocardial infraction, or stroke compared with the use of an ARB. Alpha-blockers were not recommended as first-line therapy because in one study the initial treatment with an alpha-blocker resulted in worse cerebrovascular, HF, and combined cardiovascular outcomes than initial treatment with a diuretic.

13.5. C. Reno-vascular hypertension.

Clinical clues that point toward reno-vascular hypertension are: age 30–55 years, accelerated or malignant hypertension, hypertension refractory to triple drug therapy, epigastric bruit, recurrent flash pulmonary edema, unexplained renal insufficiency, or ACEI-induced renal insufficiency.

13.6. D. Magnetic resonance angiography (MRA).

While renal arterial angiography is the gold standard, MRA is equally good. MRA has a sensitivity of 100% and specificity of 96% in diagnosing renal artery stenosis. Computed tomography angiogram has a sensitivity of 98% and a specificity of 94% and can be used if MRA is unavailable. Doppler ultrasound has a sensitivity ranging from 69 to 96% and a specificity of 86–90%. Intravenous pyelogram has a sensitivity of about 75% and a specificity of about 85%, while captopril renogram and captopril PRA have sensitivity of 70–93% and 75% respectively and specificity of 95% and 89% respectively.

13.7. C. Serum cortisol and urinary free-cortisol measurement.

This patient has uncontrolled hypertension, with metabolic alkalosis and hypokalemia. She also has a low normal level of PRA and urinary aldosterone. These are suggestive of mineralocorticoid excess. This can be due to her habit of chewing tobacco. Chewing tobacco can be adulterated with licorice – whichs contain glycyrrhizic acid. This inhibits the inactivation of cortisol by 11-beta-dehydrogenase. This results in increased activation of corticosteroid receptors by cortisol, more so for the renal mineralocorticoid receptors, which causes sodium retention and kaliuresis. Moderate elevation of serum cortisol and urinary level of free cortisol is diagnostic for licorice-induced hypertension.

13.8. B. Primary aldosteronism.

In a patient with refractory hypertension, hypokalemia and inappropriate kaliuresis (urine potassium >30 mEq/24 h), primary aldosteronism should be considered. When serum potassium is <3.5 mg/dL despite ACEI or ARB therapy or potassium supplementation then one should suspect hyperaldosteronism.

13.9. B. Ratio of PA to PRA.

The best screening test for primary aldosteronism is the ratio between PA/PRA. All diuretics should be discontinued 1 week prior to obtaining the levels. Then an elevated PA/PRA alone does not establish the diagnosis. It is confirmed by demonstrating inappropriate aldosterone secretion. During salt loading, a

nonsuppressed aldosterone excretion is diagnostic. A rate of >14 μg/24 h following a salt load (24 mL/kg physiologic saline in 4 h for 3 days or home oral salt load) distinguishes most of the cases.

13.10. C. Plasma catecholamines and urinary metanephrines.
The combination of plasma catecholamines (>2000 pg/mL) and urinary metanephrines (1.8 mg in 24 h) has a diagnostic accuracy approaching 98% in diagnosing both sporadic and familial pheochromocytomas.

13.11. B. <150/90 mmHg.
See the JNC 8 recommendations in Box 13.1.

13.12. B. <150/90 mmHg.
See the JNC 8 recommendations in Box 13.1. Goals are divided depending upon whether the age is above or below 60 years – there is no other age threshold.

13.13. A. <140/90 mmHg.
See the JNC 8 recommendations in Box 13.1.

13.14. A. <140/90 mmHg.
See the JNC 8 recommendations in Box 13.1.

13.15. A. <140/90 mmHg.
See the JNC 8 recommendations in Box 13.1.

13.16. A. <140/90 mmHg.
See the JNC 8 recommendations in Box 13.1.

13.17. C. ACEI or ARB.

13.18. A. Diuretic or CCB.
According to the JNC 8 recommendations. See Box 13.1.

13.19. D. Any of the above.

13.20. A. Labetalol.
Nifedipine and methyldopa are acceptable. An ACEI is contraindicated.

13.21. A. Diuretic.
The other drug is an ACEI.

13.22. C. Losartan.

13.23. D. Candesartan.

13.24. A. Spironolactone.

13.25. B. Add hydrochlorothiazide (HCTZ) 25 mg/day.
That is, add a drug from a different class. Losartan belongs to the same class. Beta blocker is not a preferred drug according to the JNC 8 guidelines unless post myocardial infarction (MI) or angina or has systolic HF. Further reducing Na intake is not a recommendation and is likely to be futile. CCB is another option as well.

13.26. D. Add carvedilol 6.25 mg BID.
Losartan will not help as he is already on an ACEI. Amlodipine is likely to cause edema as he had on diltiazem. Furosemide is not recommended unless in HF or glomerular filtration rate is <40 mL/min. Carvedilol is the best choice.

13.27. A. <2400 mg.

13.28. A. <120 mmHg.
Please see the details for SPRINT in Box 13.2.

13.29. D. All of the above.
See Box 13.2 for details about SHEP.

13.30. E. All of the above.
See Box 13.2 for details about ALLHAT.

Box 13.1 JNC 8 Recommendations

There is a lot of controversy about the JNC 8 recommendations (James *et al.*, 2014), which were not reviewed by the American College of Cardiology, the American Heart Association, or hypertension societies. The recommendations (nine of them) are as follows.

Recommendation 1 In the general population aged ≥60 years, initiate pharmacologic treatment to lower BP at SBP ≥150 mmHg or DBP ≥90 mmHg and treat to an SBP goal of <150 mmHg and a DBP goal of <90 mmHg. (Strong recommendation – grade A.)

Recommendation 2 In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90 mmHg and treat to a DBP goal of <90 mmHg. (For ages 30–59 years.)

Recommendation 3 In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg and treat to an SBP goal of <140 mmHg.

Recommendation 4 In the population aged ≥18 years with CKD, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to an SBP goal of <140 mmHg and a DBP goal of <90 mmHg.

Recommendation 5 In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mmHg or DBP ≥90 mmHg and treat to an SBP goal of <140 mmHg and a DBP goal of <90 mmHg.

Recommendation 6 In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CC), ACEI, or ARB. *Note that beta blocker is not a first-line drug.*

Recommendation 7 In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population:

Recommendation 8 In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.

Recommendation 9 The main objective of hypertension treatment is to attain and maintain a BP goal. If the goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until the BP goal is reached. If the BP goal cannot be reached with two drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If the goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than three drugs to reach the BP goal, antihypertensive drugs

from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom a BP goal cannot be attained using the aforementioned strategy or for the management of complicated patients for whom additional clinical consultation is needed.

Box 13.2 Clinical Trials

- **SPRINT** (The SPRINT Research Group, 2015). About 9000 patients with hypertension and SBP >130 mmHg and at high cardiovascular risk (renal disease, heart disease, stroke), but not diabetes, were randomized to intensive BP control (SBP <120 mmHg) versus traditional control (SBP <140 mmHg). Both the cumulative events and deaths were about 25% lower the in intensive treatment group.
- **Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial** (Margolis *et al.*, 2014). ACCORD enrolled 10 251 type 2 diabetes patients aged 40–79 years at high risk for cardiovascular disease (CVD) events. Participants were randomly assigned to hemoglobin A1c goals of <6.0% (<42 mmol/mol; intensive glycemia) or 7.0–7.9% (53–63 mmol/mol; standard glycemia) and then randomized a second time to either (1) SBP goals of <120 mmHg (intensive BP) or <140 mmHg (standard BP) or (2) simvastatin plus fenofibrate (intensive lipid) or simvastatin plus placebo (standard lipid). Proportional hazards models were used to assess combinations of treatment assignments on the composite primary (deaths due to CVD, nonfatal MI, and nonfatal stroke) and secondary outcomes. Compared with combined standard treatment, intensive BP or intensive glycemia treatment alone improved major CVD outcomes, without additional benefit from combining the two.
- **ALLHAT** (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). A total of 33 357 participants aged 55 years or older with hypertension and at least one other coronary heart disease risk factor were randomly assigned to receive chlorthalidone, 12.5–25 mg/day ($n = 15\,255$), amlodipine, 2.5–10 mg/day ($n = 9048$), or lisinopril, 10–40 mg/day ($n = 9054$) for planned follow-up of approximately 4–8 years. Primary outcome was fatal coronary heart disease or nonfatal MI. Compared with chlorthalidone (6-year rate, 11.5%), the relative risks (RRs) were 0.98 (95% confidence interval (CI), 0.90–1.07) for amlodipine (6-year rate, 11.3%) and 0.99 (95% CI, 0.91–1.08) for lisinopril (6-year rate, 11.4%). The 5-year SBPs were significantly higher in the amlodipine (0.8 mmHg, $P = 0.03$) and lisinopril (2 mmHg, $P < 0.001$) groups compared with chlorthalidone, and 5-year DBP was significantly lower with amlodipine (0.8 mmHg, $P < 0.001$). For amlodipine versus chlorthalidone, secondary outcomes were similar except for a higher 6-year rate of HF with amlodipine (10.2% versus 7.7%; RR, 1.38; 95% CI, 1.25–1.52). For lisinopril versus chlorthalidone, lisinopril had higher 6-year rates of combined CVD (33.3% versus 30.9%; RR, 1.10; 95% CI, 1.05–1.16), stroke (6.3% versus 5.6%; RR, 1.15; 95% CI, 1.02–1.30), and HF (8.7% versus 7.7%; RR, 1.19; 95% CI, 1.07–1.31). Thiazide-type diuretics are superior in preventing one or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.
- **SHEP** (SHEP Cooperative Research Group, 1991). 4736 persons aged 60 years and above were randomized (2365 to active treatment, 2371 to placebo). SBP ranged from 160

to 219 mmHg and DBP was less than 90 mmHg. The 5-year incidence of total stroke was 5.2 per 100 participants for active treatment (HCTZ±atenolol) and 8.2 per 100 for placebo. The RR by proportional hazards regression analysis was 0.64 ($P = 0.0003$). For the secondary end point of clinical nonfatal MI plus coronary death, the RR was 0.73. Major cardiovascular events were reduced (RR 0.68). For deaths from all causes, the RR was 0.87.

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Diabetes Mellitus 14

14.1. Which of the following criteria can be used to diagnose diabetes?
- **A.** Hemoglobin (Hb) A1C >6.5%
- **B.** Fasting glucose >126 mg/dL
- **C.** 2 h glucose >200 mg/dL
- **D.** All of the above
- **E.** None of the above

14.2. Which of the following criteria can be used to identify patients at increased risk for diabetes?
- **A.** Fasting glucose level of 100–125 mg/dL
- **B.** 2 h glucose of 140–199 mg/dL
- **C.** HbA1C of 5.7–6.4%
- **D.** None of the above
- **E.** All of the above

14.3. Studies have established a robust relationship between HbA1C and what conditions in initially nondiabetic patients?
- **A.** Future risk of diabetes mellitus
- **B.** Chronic kidney disease
- **C.** Coronary artery disease
- **D.** All-cause mortality
- **E.** All of the above
- **F.** None of the above

14.4. What type of exercise has been shown to be associated with lowering of HbA1C?
- **A.** Aerobic training
- **B.** Resistance training only
- **C.** Combined aerobic and resistance training
- **D.** None of the above

14.5. Which of the following is not a limitation to using HbA1C?
- **A.** Conditions interfering with interpretation, including hemoglobinopathies, alterations in red cell turnover, such as hemolytic anemia, transfusion, pregnancy, blood loss
- **B.** Lack of standardization in many parts of the world
- **C.** Cost of the assay
- **D.** Less biological variability

14.6. Which of the following is false regarding hypertension control in diabetes mellitus?
- **A.** For most individuals goal should be <130/80 mmHg; lower targets may be appropriate for younger patients
- **B.** Therapy should include an angiotensin-converting-enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB); if intolerant to one class, the other should be substituted

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C. For patients with CKD, treatment should include ACEI or ARB
D. Beta blockers are the first drug of choice

14.7. Which of the following statements is not true regarding cholesterol management in diabetes mellitus?
A. Moderate-intensity therapy is recommended when low-density lipoprotein is between 70 and 189 mg/dL in patients aged 40–75 years of age
B. High-intensity therapy is recommended in patients aged 40–75 years when estimated risk for cardiovascular disease is ≥7.5%
C. Treat patients with fasting triglycerides greater than 500 mg/dL
D. Individualized therapy is recommended in patients <40 or >75 years of age
E. All of the above
F. None of the above

14.8. Which of the following statements is true about when bariatric surgery should be considered?
A. Body mass index (BMI) >40 kg/m^2 or >35 kg/m^2 with an obesity related comorbidity
B. BMI >35–40 kg/m^2
C. BMI >40 kg/m^2 with no comorbidities or BMI >35 kg/m^2 with an obesity-related comorbidity with no response to behavioral or pharmacological treatment
D. None of the above

14.9. Which of the following drugs produce weight gain?
A. Thiazolidinediones
B. Insulin
C. Glinides
D. Sulfonylureas
E. All of the above
F. None of the above

14.10. Which of the following does not produce weight loss?
A. Metformin
B. Pramlintide
C. Exenatide
D. Liraglutide
E. Sodium-glucose cotransporter-2 inhibitors
F. Dipeptidyl peptidase-4 inhibitors

14.11. Which of the following is not true in diabetes mellitus?
A. Overweight and obese patients should be counseled to lose weight through exercise
B. Lifestyle changes can produce a 3–5% weight loss that can be sustained over time
C. For patients with a BMI ≥40 kg/m^2 or a BMI >35 kg/m^2 with an obesity-mediated comorbidity bariatric surgery may improve health when other methods have failed
D. Exercise and lifestyle changes have no benefit in the management of patients with diabetes mellitus

14.12. Which of the following is true regarding aspirin therapy in diabetes mellitus?
A. Low-dose aspirin (75–162 mg/day) is reasonable for those with a 10-year cardiovascular disease (CVD) risk of 10% without an increased risk of bleeding

B. Low-dose aspirin is reasonable in adults with diabetes mellitus with an intermediate risk (10-year CVD risk of 5–10%)
C. In the primary prevention population, aspirin is effective in preventing nonfatal myocardial infarction in men
D. In women, use of aspirin for primary prevention lessens the risk of stroke
E. All of the above
F. None of the above

14.13. Which of the following is true regarding management of hyperglycemia in type 2 diabetes patients?
A. In most patients, to reduce the incidence of microvascular disease, HbA1C should be lowered to <7.0%
B. Reducing HbA1C to <6.5% might be considered in some patients with short disease duration, long life expectancy, and no significant CVD, without causing significant hypoglycemia
C. HbA1c <8% is appropriate for patients with a history of hypoglycemia, limited life expectancy, advanced complications, and cognitive impairment
D. All of the above
E. None of the above

14.14. Which one of the following statements is false?
A. Type 2 diabetes mellitus is associated with a two- to fourfold increased risk of CVD, and event rates correlate with degree of hyperglycemia
B. In a large study, increase in fasting glucose was associated with 17% increased risk of future cardiovascular events or death
C. The correlation between hyperglycemia and microvascular disease is less strong than macrovascular disease with a 37% increased risk for retinopathy or renal failure with 1% increase in A1C
D. After adjustment for CVD risk factors, an increase in A1C of 1% is associated with an increased risk of CVD events, including 19% in myocardial infarction and 12–14% in all-cause mortality

14.15. Which of the following statements is not true regarding renal disease in diabetes?
A. Evidence suggests that presence of diabetic kidney disease in type 2 diabetes is associated with an increased risk of mortality
B. Among adults with diabetes in the USA the prevalence of diabetic kidney disease is 34.5%, 16.8% with albuminuria, 10.8% with impaired glomerular filtration rate (GFR) and 6.9% with both albuminuria and impaired GFR
C. It is recommended to screen yearly for diabetic kidney disease in all type 2 diabetes patients
D. Goals of care for patients with diabetic kidney disease include preventing progression to end-stage renal disease and reducing the risks of cardiovascular events and death
E. Among people with diabetes mellitus, albuminuria and impaired GFR are not associated with increased risks for acute kidney injury, cardiovascular events, and death.

14.16. Which of the following statements is not true regarding glycemic control in medical intensive care unit (ICU) patients?

A. Intensive glycemic control in the ICU targeting blood glucose <110 mg/dL is recommended
B. Intensive glycemic control is associated with excess 90-day mortality
C. Excess mortality was due to moderate to severe hypoglycemia
D. Guidelines suggest a target glucose of 140–180 mg/dL in ICU patients

14.17. Which of the following statements regarding type 1 diabetes mellitus and glycemic control is not true?
A. Strict glycemic control in type 1 diabetes patients can delay the onset of retinopathy, nephropathy, and neuropathy
B. Strict glycemic control can slow the progression of existing microvascular disease
C. The Diabetes Control and Complications Trial (DCCT) was able to demonstrate a reduction in cardiovascular events
D. Strict glycemic control is associated with higher (threefold) risk of hypoglycemia

14.18. Which of the following statements are true?
A. The FREEDOM trial showed that coronary artery bypass grafting (CABG) surgery is superior to percutaneous coronary intervention (PCI)
B. The benefit of CABG was due to lower rates of myocardial infarction and death from any cause
C. CABG was not associated with increased stroke rates
D. PCI was associated with higher strokes

14.19. Regarding sex differences and outcomes in diabetes, which of the following is not true?
A. Women with diabetes have a twofold excess risk for cardiovascular disease compared with men
B. Myocardial infarction usually occurs earlier and is associated with higher mortality in women with diabetes compared with men
C. Revascularization rates are similar in women when compared with men
D. Risk of occurrence of heart failure is higher in women with diabetes when compared to men
E. Long term survival is less in women undergoing revascularization and also have higher post-surgical mortality when compared to men
F. Women with peripheral artery disease respond less well to exercise training when compared with men with and without diabetes

14.20. Which of the following statements is not true regarding the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial?
A. This trial enrolled stable coronary artery disease patients with type 2 diabetes and compared PCI with CABG
B. The majority of patients who underwent PCI had single-vessel interventions
C. There was a difference in survival in the PCI group compared with the CABG group
D. Subgroup analysis of the CABG group showed that those assigned to CABG and optimal medical therapy had more freedom from cardiovascular events compared with optimal medical therapy alone

Answers

14.1. D. All of the above.

14.2. E. All of the above.

14.3. E. All of the above.

Studies have established a link between HbA1C and microvascular and macrovascular complications in initially nondiabetic persons using the new cut points put forth by the American Diabetic Association.

14.4. C. Combined aerobic and resistance training.

In a trial of 262 randomized patients, only combined aerobic and resistance training lowered Hb A1C (mean reduction, 0.34%, $P = 0.03$). The study by Church *et al.* (2010) highlights the importance of type of exercise in patients with type 2 diabetes mellitus to achieve better glycemic control.

14.5. D. Less biological variability.

The strength of using HbA1C is that it has less biological variability, eliminates the need for a fasting sample, and is a stronger predictor of complications compared with fasting blood glucose.

14.6. D. Beta blockers are the first drug of choice.

Beta blockers are not considered the drug of first choice in treating hypertension in patients with diabetes. An ACEI or an RB should be the first drug of choice.

14.7. E. All of the above.

14.8. C. BMI >40 kg/m^2 with no comorbidities or BMI >35 kg/m^2 with an obesity-related comorbidity with no response to behavioral or pharmacological treatment.

Bariatric surgery may be helpful in this case.

14.9. E. All of the above.

14.10. F. Dipeptidyl peptidase-4 inhibitors.

Dipeptidyl peptidase inhibitors are weight neutral, while the rest will result in weight loss when used to treat diabetes.

14.11. D. Exercise and lifestyle changes have no benefit in the management of patients with diabetes mellitus.

Exercise and lifestyle changes can produce a 3–5% rate of weight loss (American College of Cardiology (ACC)/American Heart Association (AHA) class 1 level of evidence A). For very obese patients that have not responded to behavioral treatment with or without pharmacological treatment, bariatric surgery may improve health (ACC/AHA, class II A, level of evidence A).

14.12. E. All of the above.

14.13. D. All of the above.

14.14. C. The correlation between hyperglycemia and microvascular disease is less strong than macrovascular disease with a 37% increased risk for retinopathy or renal failure with 1% increase in A1C.

All the other statements are true (Selvin *et al.*, 2004).

14.15. E. Among people with diabetes mellitus, albuminuria and impaired GFR are not associated with increased risks for acute kidney injury, cardiovascular events, and death.

Albuminuria and impaired GFR portends an independent and additive risk for acute kidney injury, cardiovascular events, and death among people with diabetes mellitus.

14.16. A. Intensive glycemic control in the ICU targeting blood glucose <110 mg/dL is recommended.

Intensive glycemic control is no longer recommended in ICU patients. In the NICE-SUGAR trial (The NICE-SUGAR Study Investigators, 2009), 6104 medical and surgical ICU patients were randomized to intensive glycemic control (blood glucose 81–108 mg/dL) versus conventional control (blood glucose <180 mg/dL). In this study, the intensive glycemic control arm was associated with a higher 90-day mortality. The authors followed up this initial study in 2012 and related the cause of excess mortality to moderate–severe hypoglycemia, especially in patients with distributive shock. Hence, intensive glycemic control is no longer recommended. Although there are no clear glucose targets, guidelines recommend a target glucose of 140–180 mg/dL in the ICU setting. This was true for both surgical and medical ICU patients.

14.17. C. The Diabetes Control and Complications Trial (DCCT) was able to demonstrate a reduction in cardiovascular events.

The DCCT was not able to show a eduction in cardiovascular events with strict glycemic control. This may be due to the study population being young (The Diabetes Control and Complications Trial Research Group, 1993). However, studies have shown a reduction in cardiovascular events with strict glycemic control. All the other statements are true.

14.18. C. CABG was not associated with increased stroke rates.

The FREEDOM trial compared revascularization strategies in patients with advanced coronary artery disease and type 2 diabetes mellitus (Farkouh *et al.*, 2012). The trial showed superiority of CABG over PCI. The primary outcome of all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke occurred more frequently in the PCI group (26.6%) than in the CABG group (18.7%) at 5 years ($p = 0.005$). The benefit of CABG was due to less myocardial infarction ($p < 0.001$) and all-cause mortality ($p = 0.049$). Stroke was more frequent in the CABG group, with 5-year rates of 2.4% in the PCI group versus 5.2% in the CABG group ($p = 0.03$).

14.19. C. Revascularization rates are similar in women when compared with men.

Revascularization rates (PCI, CABG) are found to be lower in women with diabetes compared with men (Regensteiner *et al.*, 2015). All the other statements are true.

14.20. C. There was a difference in survival in the PCI group compared with the CABG group.

The BARI 2D trial showed no difference in survival or freedom from major cardiovascular events at 5 years between the PCI and CABG group (The BARI 2D Study Group, 2009). All other statements are true.

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Lipids

15

15.1. Which of the following are new categories for lipid management outlined in the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (see Box 15.1; Stone *et al.*, 2013)?

- **A.** Individuals with clinical atherosclerotic coronary vascular disease (ASCVD)
- **B.** Individuals with primary elevations of low-density lipoprotein cholesterol (LDL-C) ≥190 mg/dL
- **C.** Individuals 40–75 years of age with diabetes with LDL-C 70–189 mg/dL
- **D.** Individuals without clinical ASCVD or diabetes who are 40–75 years of age with LDL-C 70–189 mg/dL and an estimated 10-year ASCVD risk of 7.5% or higher
- **E.** All of the above

15.2. What is the target goal low-density lipoprotein (LDL) recommendation (primary and secondary prevention) per the new ACC/AHA guidelines in patients with ASCVD?

- **A.** An LDL goal of <100 mg/dL if not diabetic
- **B.** An LDL goal of <70 mg/dL if diabetic
- **C.** No target goal recommendation
- **D.** None of the above

15.3. Which of the following is associated with microalbumnuria?

- **A.** Atorvastatin
- **B.** Metoprolol
- **C.** Amlodipine
- **D.** Lisinopril

15.4. The association of statin-induced microalbuminuria is increased with which of the following?

- **A.** Male gender
- **B.** Diabetes mellitus
- **C.** Coronary artery disease
- **D.** Smoking

15.5. According to the new ACC/AHA guidelines, what is the definition of high-intensity statin treatment?

- **A.** Daily statin dose reduces LDL-C by 30 to <50%
- **B.** Daily statin dose reduces LDL-C by ≥50%
- **C.** Daily statin dose reduces LDL-C by 80%
- **D.** Daily statin dose reduces LDL-C by 70%

15.6. According to the new ACC/AHA guidelines, what is the definition of moderate-intensity statin treatment?

- **A.** Daily statin dose reduces LDL-C by 30 to <50%
- **B.** Daily statin dose reduces LDL-C by ≥50%
- **C.** Daily statin dose reduces LDL-C by 80%
- **D.** Daily statin dose reduces LDL-C by 70%

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15.7. A 67-year-old male with known history of coronary artery disease (CAD) has an LDL-C of 180 mg/dL. Regarding statin treatment, what is the best course of action?

A. No statin treatment
B. High-intensity statin therapy
C. Moderate-intensity statin therapy
D. Low-intensity statin therapy

15.8. A 60-year-old male is referred to you for an evaluation. He has no known history of ASCVD, and his LDL-C is 160 mg/dL. What is the recommendation regarding statin therapy?

A. No statin therapy
B. Lifestyle modification
C. Lifestyle modification and moderate-intensity statin therapy
D. High-intensity statin therapy

15.9. A 45-year-old female has no known ASCVD. Her lab work-up reveals an LDL-C of 220 mg/dL. She has no other cardiac risk factors. What is the current recommendation for statin therapy?

A. Lifestyle modification
B. Lifestyle modification and reassess in 6 months
C. High-intensity statin therapy
D. Lifestyle modification and high-intensity statin therapy

15.10. A 60-year-old male is referred to you for an evaluation. He has no cardiovascular disease. On his lab work-up the triglycerides are 550 mg/dL. Which of the following is not a cause of elevated triglycerides?

A. Oral estrogens
B. Excessive alcohol intake
C. Amiodarone
D. Diabetes mellitus

15.11. Elevated LDL-C is associated with which of the following?

A. Diuretics
B. Cyclosporine
C. Amiodarone
D. Biliary obstruction
E. All of the above
F. None of the above

15.12. Regarding primary prevention, in a person with no diabetes, LDL-C between 70 and 189 mg/dL, and not receiving statin therapy, what is the current recommendation?

A. Initiate statin therapy
B. Estimate 10-year ASCVD risk every 4–6 years
C. Estimate 10-year ASCVD risk every year
D. None of the above

15.13. What is the current recommendation regarding primary prevention when the 10-year ASCVD risk is ≥7.5%?

A. No statin therapy
B. Moderate- or high-intensity statin therapy
C. Moderate-intensity statin therapy only
D. High-intensity statin therapy only
E. None of the above

15.14. What is the current recommendation regarding primary prevention when the 10-year ASCVD risk is 5 to 7.5%?

A. No statin therapy
B. Moderate- or high-intensity statin therapy
C. Moderate-intensity statin therapy
D. High-intensity statin therapy
E. None of the above

15.15. Dyslipidemia, consisting of an increase in LDL and triglycerides and a decrease in high-density lipoprotein (HDL), is not associated with which of the following?

A. Protease inhibitors
B. Non-nucleoside reverse transcriptase inhibitors
C. Nucleoside reverse transcriptase inhibitors
D. Fusion/entry inhibitors

15.16. A 45-year-old woman asks if she should take statins as her father had a myocardial infarction at the age of 60 and she smokes 10 cigarettes a day. She has no diabetes or hypertension and no cardiac history or symptoms and jogs 20 miles a week. Her body mass index (BMI) is 25 kg/m^2. What will be the LDL threshold for starting a statin based on the ACC/AHA guidelines for this patient?

A. >190 mg/dL
B. >160 mg/dL
C. >130 mg/dL
D. >100 mg/dL

15.17. A 45-year-old man post-renal transplant is referred for advice on lipid management. He is diabetic and hypertensive and is on aspirin, beta blocker, angiotensin-converting-enzyme inhibitor, and cyclosporine. HDL-C is 30 mg/dL and LDL-C is 145 mg/dL; BMI is 25 kg/m^2. In addition to lifestyle changes, what else would you recommend?

A. Nothing else
B. Simvastatin 20 mg/day
C. Niacin
D. Pravastatin 40 mg/day

15.18. A 55-year-old man had an ST-elevation myocardial infarction and underwent a successful percutaneous coronary intervention. He has now returned for a follow-up visit after 6 weeks. He is doing well and is on atenolol 50 mg/day, aspirin 81 mg, clopidogrel 75 mg, atorvastatin 80 mg/day, and lisonopril 10 mg/day. His repeat HDL is 40 mg/dL; LDL is 78 mg/dL and triglycerides is 142 mg/dL. What would you recommend?

A. Switch to Crestor® 40 mg/day to achieve LDL of <70 mg/dL
B. Add ezetimibe
C. Add niacin
D. Stay on current therapy

15.19. A 42-year-old woman presents with hypertension and diabetes. Her weight is 320 lbs (145 kg) and BMI is 43 kg/m^2. In addition to treating hypertension and diabetes, what are your other recommendations?

A. Moderate-dose statin therapy
B. Exercise, healthy diet, and target a net calorie deficit of 500–750 kcal/day
C. Lose 30 lbs (~14 kg) of weight over next 6 months
D. All of the above
E. None of the above

15.20. According 2013 obesity guidelines (Box 15.3), weight loss in recommended in which of the following?

- **A.** Individuals with a BMI >30 kg/m^2 even without risk factors
- **B.** Individuals with BMI 25–30 kg/m^2 with risk factors
- **C.** Both A and B
- **D.** Neither A nor B

15.21. Adding US Food and Drug Administration-approved pharmacotherapy as an adjunct to comprehensive lifestyle intervention is reasonable in which of the following conditions?

- **A.** Those with a BMI ≥30 kg/m^2 who are motivated to lose weight
- **B.** Those with a BMI ≥27 kg/m^2 with at least one obesity-associated comorbid condition who are motivated to lose weight
- **C.** Both A and B
- **D.** Neither A nor B

15.22. In the management of obesity, when is it appropriate to refer to an experienced bariatric surgeon for consultation and evaluation of patients who are motivated to lose weight and who have not responded to behavioral treatment (with or without pharmacotherapy)?

- **A.** When BMI ≥40 kg/m^2
- **B.** When BMI ≥35 kg/m^2 with obesity-related comorbidities or complications
- **C.** Both A and B
- **D.** Neither A nor B

15.23. A 42-year-old man comes to see you to assess cardiovascular risk and recommendations. He is obese, but has no other medical history and has started on an exercise and diet program. His height is 70″, weight 220 lbs (~100 kg), BMI 32 kg/m^2, heart rate 70 bpm, blood pressure 130/80 mmHg. His LDL is 135 mg/dL and HDL is 35 mg/dL, glucose is 88 mg/dL, hemoglobin A1C is 6.2%. His 10-year risk of a cardiovascular event is 3%. What will you recommend?

- **A.** A stress test
- **B.** Coronary computed tomography (CT) angiogram
- **C.** Carotid intimal medial thickness with ultrasound
- **D.** No further testing, continue current strategy

15.24. An 80-year-old man had a myocardial infarction 7 years ago and is on atenolol 50 mg/day, aspirin 81 mg/day, and atorvastatin 20 mg/day. What is your recommendation for the statin as he is >75 years old?

- **A.** Stop statin as he is above 75 years
- **B.** Increase statin to 40 or 80 mg/day (high intensity)
- **C.** Ask for patient preference in view of paucity of data in patients >75 years of age
- **D.** Switch to ezetimibe

15.25. A 70-year-old Japanese woman received an left anterior descending coronary artery stent for ST-elevation myocardial infarction. She is doing well and is on atorvastatin 80 mg/day, atenolol 25 mg/day, aspirin 81 mg/day, and clopidogrel 75 mg/day. Her LDL is 85 mg/dL. What would you recommend?

A. Reduce statin
B. Switch to rosuvastatin 40 mg/day
C. Add niacin
D. Add ezetimibe

15.26. Which of the following is a class I recommendation in assessing asymptomatic adults with no known CAD?
A. Genomic testing
B. Obtain global risk score (Framingham)
C. Assessment of lipoprotein and apolipoprotein
D. Measurements of natriuretic peptides

15.27. Which one of the following is a class I recommendation in assessing asymptomatic adults with no known CAD?
A. Genomic testing
B. Obtain family history
C. Assessment of lipoprotein and apolipoprotein
D. Coronary CT angiogram

15.28. Measurement of C reactive protein (CRP) is not recommended in which of the following?
A. In men over 50 years with an LDL of <130 mg/dL
B. In women over 60 years with an LDL <130 mg/dL not on hormone replacement therapy, and without diabetes or chronic kidney disease
C. In asymptomatic high-risk adults
D. In asymptomatic intermediate-risk men 50 years and younger or women 60 years and younger

15.29. Which of the following is not a class III recommendation in assessing low-risk asymptomatic adults with no known history of CAD?
A. Coronary CT angiogram
B. Magnetic resonance imaging (MRI) for plaque detection
C. Measurement of coronary calcium score
D. Resting electrocardiogram (ECG)

15.30. In patients with diabetes mellitus, which of the following is not recommended?
A. Stress echocardiogram
B. Stress myocardial perfusion imaging (MPI)
C. Coronary artery calcium (CAC) score measurement
D. Measurement of hemoglobin A1C

15.31. In asymptomatic women, which of the following is recommended?
A. Obtaining global risk score
B. Obtaining natriuretic peptides
C. MRI for plaque detection
D. Measurement of lipoprotein

15.32. Stress MPI is recommended in which of the following situations?
A. In the assessment of a low-risk individual
B. In the assessment of an intermediate-risk individual
C. In an asymptomatic adult with diabetes mellitus
D. None of the above

15.33. Which of the following is not true?

- **A.** Echocardiography is recommended to detect left ventricular hypertrophy in patients with hypertension
- **B.** Echocardiography is recommended in risk assessment of asymptomatic adults without hypertension
- **C.** A resting ECG is reasonable in asymptomatic adults with hypertension
- **D.** All of the above

15.34. Which of the following is a class III indication in the assessment of asymptomatic adults?

- **A.** Measurement of arterial stiffness
- **B.** Obtaining a resting ECG
- **C.** Obtaining an echocardiogram in a patient with hypertension
- **D.** Stress MPI in an individual with diabetes mellitus

15.35. Which of the following is not true regarding assessment of an asymptomatic adult with diabetes?

- **A.** Measurement of hemoglobin A1C
- **B.** Stress MPI
- **C.** Testing for microalbuminuria
- **D.** Coronary CT angiogram

Answers

15.1. E. All of the above.

The statin randomized controlled trials (RCTs) provide the most extensive evidence for the greatest magnitude of ASCVD event reduction, with the best margin of safety (see Box 15.2). Four statin benefit groups – in which the potential for an ASCVD risk reduction benefit clearly exceeds the potential for adverse effects in adults – have been identified in the new ACC/AHA guidelines. These include all of the scenarios listed in the question.

15.2. C. No target goal recommendation.

The panel makes no recommendations for or against specific LDL-C or non-high-density lipoprotein cholesterol (HDL-C) targets for the primary or secondary prevention of ASCVD. Treating to a target LDL was the most widely used approach for the past 15 years. Three problems were identified in the ACC/AHA guidelines. First, current clinical trial data do not indicate what the target should be. Second, we do not know the magnitude of additional ASCVD risk reduction that would be achieved with one target lower than another. Third, it does not take into account potential adverse effects from multidrug therapy that might be needed to achieve a specific goal. Thus, in the absence of these data, this approach is less useful than it appears, and hence no target goal was set for treatment of LDL in patients with ASCVD (Stone *et al.*, 2013).

15.3. A. Atorvastatin.

It has been show that atorvastatin interferes with tubular reabsorption of albumin, which increases urinary albumin excretion. Robles *et al.* (2013) showed in their study that 27.1% of patients taking atorvastatin had microalbuminuria

compared with 12.3% of patients taking simvastatin ($p = 0.012$). Statin-induced endothelial dysfunction of the glomerulus is the mechanism which induces microalbuminuria.

15.4. B. Diabetes mellitus.

Robles *et al.* (2013) used logistic regression analysis to show an independent relationship between statin treatment and microalbuminuria in diabetic patients.

15.5. B. Daily statin dose reduces LDL-C by ≥50%.

15.6. A. Daily statin dose reduces LDL-C by 30 to <50%.

15.7. B. High-intensity statin treatment.

According to the new ACC/AHA guidelines, if a person is >21 years and has clinical ASCVD and is aged <75 years, then high-intensity statin therapy should be initiated. Moderate-intensity statin therapy should be initiated in patients aged >75 years or if not a candidate for high-intensity statin therapy.

15.8. C. Lifestyle modification and moderate-intensity statin therapy.

In the situation given in the question, moderate-intensity statin therapy should be initiated. If the estimated 10-year ASCVD risk ≥7.5% then high-intensity statin therapy should be initiated.

15.9. D. Lifestyle modification and high-intensity statin therapy.

The new ACC/AHA guidelines state that a person >21 years with no ASCVD and an LDL-C ≥190 mg/dL is a candidates for high-intensity statin therapy along with lifestyle modification.

15.10. D. Amiodarone.

All the options cause elevated triglycerides except for amiodarone. Excessive alcohol intake, refined carbohydrates, oral estrogens, glucocorticoids, bile acid sequestrants, protease inhibitors, retinoic acid, anabolic steroids, sirolimus, raloxifene, tamoxifen, beta blockers (except carvedilol), thiazides, nephrotic syndrome, chronic renal failure, lipodystrophies, poorly controlled diabetes mellitus, hypothyroidism, obesity, and pregnancy can all cause an increase triglycerides.

15.11. E. All of the above.

Saturated fats, anorexia nervosa, diuretics, cyclosporine, glucocorticoids, amiodarone, biliary obstruction, nephrotic syndrome, hypothyroidism, obesity, and pregnancy are all associated with elevated LDL-C.

15.12. B. Estimate 10-year ASCVD risk every 4–6 years.

15.13. B. Moderate- or high-intensity statin therapy.

If the 10-year risk for ASCVD is ≥7.5% then the current guideline recommendation is to initiate either moderate- or high-intensity statin therapy.

15.14. B. Moderate intensity statin therapy.

If the 10 year ASCVD risk is between 5 and 7.5% then the current guideline recommendation is to initiate moderate-intensity statin therapy.

15.15. D. Fusion/entry inhibitors.

All of the options for medications except fusion/entry inhibitors, used in the treatment of HIV/AIDS, cause dyslipidemia, which can be atherogenic. Therefore, the ACC/AHA guideline recommendation is to treat these patients with statins at a higher dose.

15.16. A. >190 mg/dL.

As she has no CAD or diabetes mellitus and her 10-year risk is very low. Of course, she has to stop smoking.

15.17. D. Pravastatin 40 mg/day.

As simvastin metabolism is affected by cyclosporine and may lead to rhabdomyolysis. Niacin does not affect outcomes. As he is a diabetic, he should be on at least a modest dose of a statin.

15.18. D. Stay on current therapy.

Based on the ACC/AHA 2013 guidelines, the patient is already on high-intensity statin therapy and hence no further intervention is needed. Guidelines do not recommend "treat to target."

15.19. D. All of the above.

B and C are weight loss guidelines. The panel recommends as an initial goal the loss of 5–10% of baseline weight within 6 months.

15.20. C. Both A and B.

Risk factors include diabetes, prediabetes, hypertension, dyslipidemia, elevated waist circumference, and obesity-related complications.

15.21. C. Both A and B.

15.22. C. Both A and B.

15.23. D. No further testing, continue current strategy.

The risk is <5% over 10 years and hence no indication for statin either. In the absence of symptoms, A and B are inappropriate. C has not been shown to help risk stratify further.

15.24. C. Ask for patient preference in view of paucity of data in patients >75 years of age.

As per new lipid guidelines.

15.25. A. Reduce statin.

In view of high risk of intracerebral hemorrhage with high-dose statins in Asians.

15.26. B. Obtain global risk score (Framingham).

Obtaining a global risk score in asymptomatic adults without a clinical history of CAD is a class I indication. These scores are helpful in combining individual risk factor measurements into a single quantitative estimate of risk that can be use in prevention strategies. It is not recommended to perform genomic testing or measure lipoprotein or natriuretic peptides in this population and is considered a class III indication (Greenland *et al.*, 2010).

15.27. B. Obtain family history.

Obtaining a family history of ASCVD is recommended in the assessment of asymptomatic adults (Greenland *et al.*, 2010).

15.28. C. In asymptomatic high-risk adults.

Measurement of CRP is not recommended in asymptomatic high-risk adults (class III). In men 50 years and older or women 60 years and older with an LDL of <130 mg/dL and not on lipid-lowering therapy, hormone replacement, or immunosuppressive therapy, and without clinical CAD, diabetes mellitus, chronic kidney disease, severe inflammatory conditions, or contraindications to

statin therapy, CRP can be used to select patients for statin therapy (class IIa). It is also deemed reasonable to measure CRP in asymptomatic intermediate-risk men younger than 50 or women younger than 60 for assessment of CAD risk (class IIB) (Greenland *et al.*, 2010).

15.29. D. Resting electrocardiogram (ECG).

A resting ECG may be reasonable in the assessment of asymptomatic adults with no history of hypertension or diabetes mellitus (class IIb). It is a class III indication to obtain a coronary CT angiogram, coronary calcium score, or MRI for plaque detection in low-risk asymptomatic individuals (Greenland *et al.*, 2010).

15.30. A. Stress echocardiogram.

In asymptomatic adults with diabetes mellitus it is reasonable to measure coronary calcium score (class IIa). It is also reasonable to measure hemoglobin A1C and stress MPI (class IIb). Stress MPI may be considered for patients with diabetes or when prior risk assessment suggests high risk, such CAC of over 400 (Greenland *et al.*, 2010).

15.31. A. Obtaining global risk score.

It is a class I indication to obtain a global risk score in all asymptomatic women.

15.32. C. In an asymptomatic adult with diabetes mellitus

Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic individuals with diabetes mellitus or in adults with a strong family history of CAD, or when there is prior risk assessment, such as a CAC score of over 400. Stress MPI is not recommended for assessment of low- or intermediate-risk asymptomatic individuals (class III) (Greenland *et al.*, 2010).

15.33. B. Echocardiography is recommended in risk assessment of asymptomatic adults without hypertension.

It is a class III indication to perform echocardiography in asymptomatic adults without hypertension. A resting ECG can be obtained in patients with hypertension or diabetes (class IIa) or obtain an echocardiogram in patients with hypertension to detect left ventricular hypertrophy (class IIb) (Greenland *et al.*, 2010).

15.34. A. Measurement of arterial stiffness.

This is a class III indication at the present time (Greenland *et al.*, 2010).

15.35. D. Coronary CT angiogram.

It is a class III to obtain coronary CT angiogram in an asymptomatic adult with diabetes (Greenland *et al.*, 2010).

Box 15.1 What's New in the 2013 ACC/AHA Guideline?

For the complete 2013 ACC/AHA guideline, see Stone *et al.* (2010).

1. Focus on ASCVD Risk Reduction: Four Statin Benefit Groups

- Based on a comprehensive set of data from RCTs that identified four statin benefit groups which focus efforts to reduce ASCVD events in secondary and primary prevention.
- Identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.

2. New Perspective on LDL-C and/or Non-HDL-C Treatment Goals

- The expert panel was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C treatment targets.

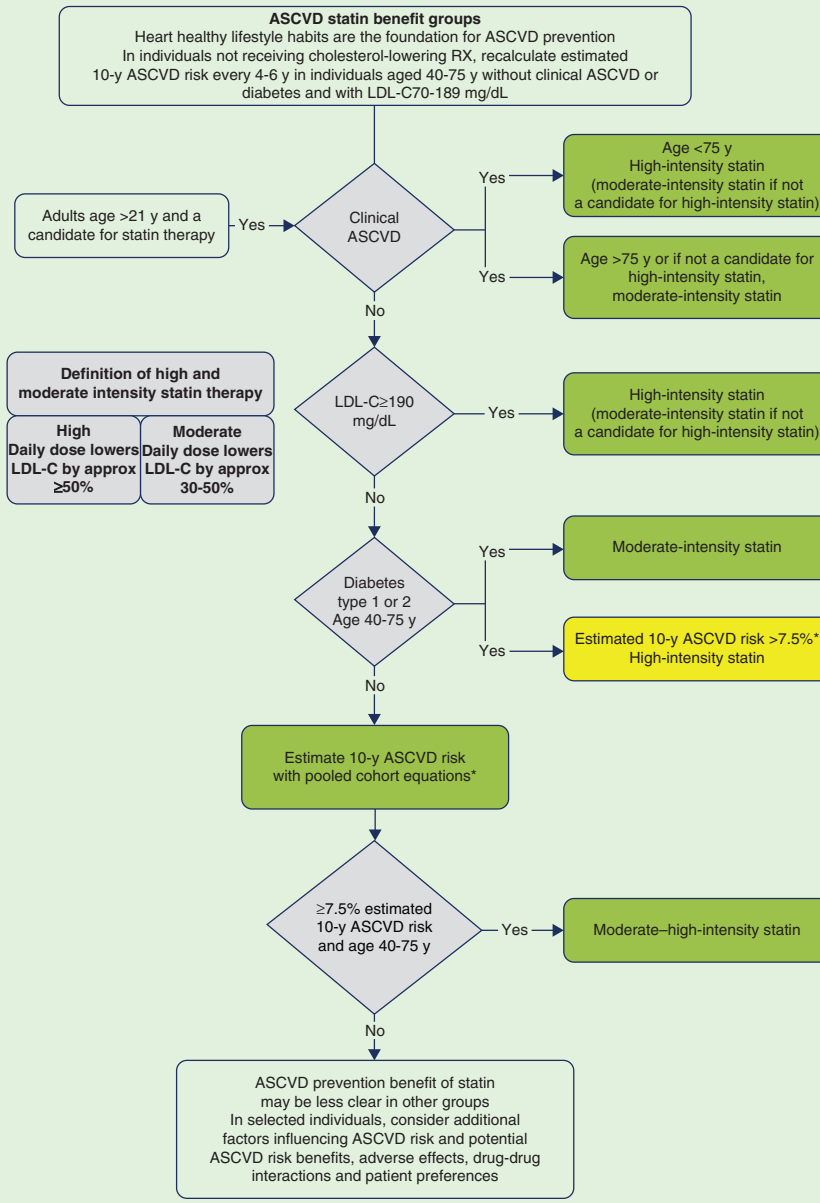

Figure 15.1 Major recommendations for statin therapy for ASCVD prevention.
Source: adapted from Jensen *et al.* (2013).

- The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.
- Non-statin therapies do not provide acceptable ASCVD risk reduction benefits compared with their potential for adverse effects in the routine prevention of ASCVD.

3. Global Risk Assessment for Primary Prevention

- This guideline recommends use of the new pooled cohort equations to estimate 10-year ASCVD risk in both white and black men and women.
- By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, based on RCT data, those high-risk groups that may not benefit.
- Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.

Patient Triaging for Statin Therapy

The flowchart in Figure 15.1 shows the decision process for statin therapy for ASCVD prevention.

Box 15.2 Clinical Trials

- The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial (AIM-HIGH Investigators, 2011). A total of 3414 patients were randomly assigned to receive niacin (1718) or placebo (1696). All patients received simvastatin, 40–80 mg/day, plus ezetimibe, 10 mg/day, if needed, to maintain an LDL-C level of 40–80 mg/dL (1.03–2.07 mmol/L). The trial was stopped after a mean follow-up period of 3 years owing to a lack of efficacy.
- The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (ACCORD Study Group, 2010). 5518 patients with type 2 diabetes who were being treated with open-label simvastatin were randomized to receive either masked fenofibrate or placebo. The primary outcome was the first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke, compared with simvastatin alone.
- The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) (Shepherd *et al.*, 2002). The aim was to test the benefits of pravastatin treatment in an elderly cohort of men and women with, or at high risk of developing, cardiovascular disease and stroke. Pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals. PROSPER therefore extends to elderly individuals the treatment strategy currently used in middle-aged people.
- Cannon *et al.* (2004) enrolled 4162 patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days to compare 40 mg of pravastatin daily (standard therapy) with 80 mg of atorvastatin daily (intensive therapy). An intensive lipid-lowering statin regimen provided greater protection against death or major cardiovascular events than a standard regimen did.

- Shepherd *et al.* (1995). This double-blind study was designed to determine whether the administration of pravastatin to men with hypercholesterolemia and no history of myocardial infarction reduced the combined incidence of nonfatal myocardial infarction and death from coronary heart disease. Treatment with pravastatin significantly reduced the incidence of myocardial infarction and death from cardiovascular causes without adversely affecting the risk of death from noncardiovascular causes in men with moderate hypercholesterolemia and no history of myocardial infarction.

Box 15.3 Primary Care of Patients with Overweight and Obesity

The flowchart in Figure 15.2 shows the chronic disease management model for primary care of patients with overweight and obesity.

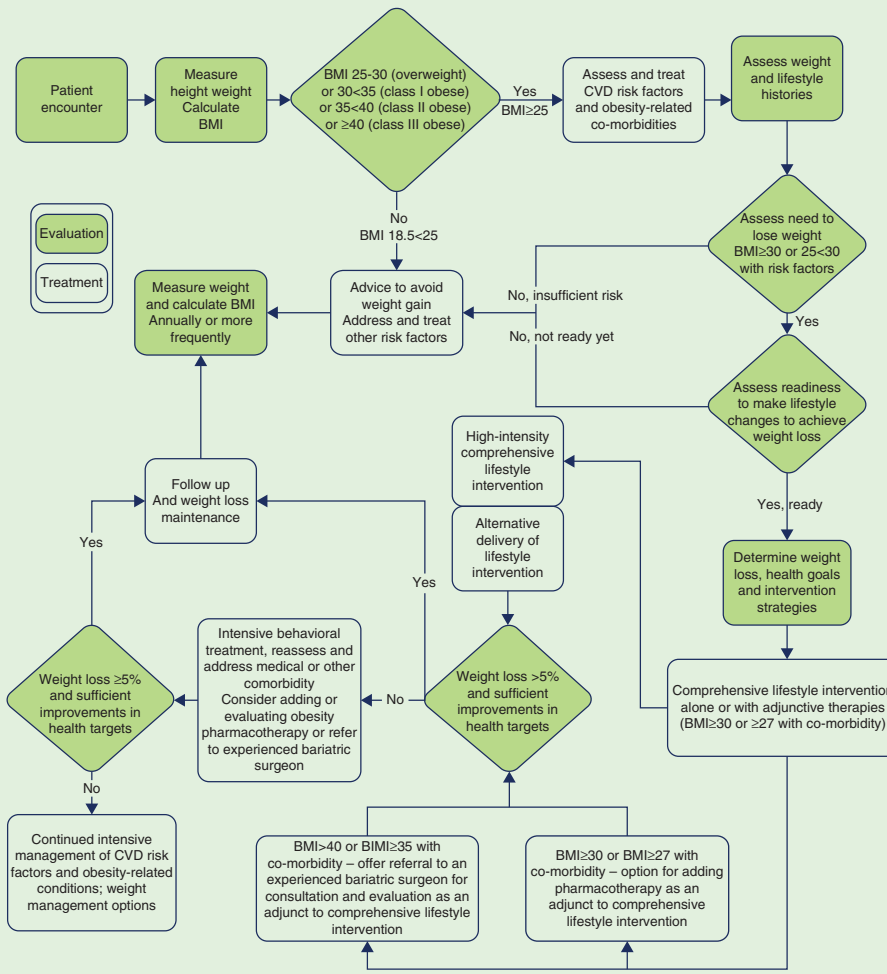

Figure 15.2 Treatment algorithm—the chronic disease management model for primary care of patients with overweight and obesity. *Source*: adapted from Jensen *et al.* (2013).

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Valvular Heart Disease

16

16.1. For a 62-year-old patient with mild aortic stenosis (AS; V2 2–3 m/s) who is asymptomatic, what is the recommendation for follow up echocardiogram?

A. Only when symptoms develop
B. Every 3–5 years
C. Every 1–2 years
D. Every 6–12 months

16.2. For a 72-year-old patient with AS with V2 of 4.2 m/s, aortic valve area (AVA) 0.8 cm^2, ejection fraction (EF) of 65% and normal pulmonary artery (PA) pressure and no symptoms, what would be your recommendation based on current guidelines?

A. Aortic valve replacement (AVR) as patient is likely to become symptomatic soon
B. Follow-up clinic and echo every 1–2 years
C. Follow-up clinic and echo every 6–12 months
D. No follow up till symptoms develop

16.3. A 22-year-old Asian woman presents with shortness of breath and has MS. What will you do about rheumatic fever prophylaxis?

A. Prophylaxis for the next 10 years
B. Prophylaxis till she turns 40 years
C. No prophylaxis as she is >21 years old
D. Prophylaxis for the next 5 years

16.4. Which of the following are acceptable for rheumatic heart disease prophylaxis?

A. Penicillin G benzathine 1.2 million units intramuscularly every 4 weeks
B. Penicillin V potassium 250 mg orally BID
C. Sulfadiazine 1 g orally once daily
D. Any of the above

16.5. Prophylaxis against infective endocarditis (IE) is reasonable for which of the following patients at highest risk for adverse outcomes from IE before dental procedures that involve manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa?

A. Patients with prosthetic cardiac valves
B. Patients with previous IE
C. Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve
D. Patients with congenital heart disease with: (i) unrepaired cyanotic congenital heart disease, including palliative shunts and conduits; (ii) completely repaired congenital heart defect repaired with prosthetic material or device, whether placed by surgery or catheter intervention, during the first 6 months

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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after the procedure; or (iii) repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device.

E. All of the above

16.6. Prophylaxis against IE is indicated in a patient with a prosthetic mitral valve (MV) undergoing which of the following procedures in the absence of local infection in the instrumented area?

A. Transesophageal echocardiogram (TEE)
B. Esophagogastroduodenoscopy
C. Colonoscopy
D. Cystoscopy
E. All of the above
F. None of the above

16.7. Definition of severe AS includes which of the following?

A. Aortic valve area <1.0 cm^2
B. Transaortic velocity >4 m/s on echo
C. Transvalvular mean gradient >40 mmHg
D. Any of the above
E. Need all of the above

16.8. A 75-year-old man with no symptoms has severe aortic valve calcification, aortic valve velocity of 4.5 m/s and EF of 65%. What stage is he in?

A. Stage B
B. Stage C1
C. Stage C2
D. Stage D

16.9. A 72-year-old woman is found to have severe AS with V2 of 4.6 m/s and mean gradient of 47 mmHg. The EF is 60% and PA systolic pressure is normal by echo. She claims she has no symptoms, but the daughter thinks she has slowed down. It is reasonable to do which of the following?

A. An exercise stress test to confirm the asymptomatic status
B. Dobutamine echo to evaluate LV response to stress
C. Refer for cardiac catheterization and AVR
D. Follow up every 6–12 months

16.10. AVR is recommended in which of the following situations of severe AS?

A. For symptomatic patients with severe high-gradient AS who have symptoms (chest pain, shortness of breath, or syncope) by history or on exercise testing
B. For asymptomatic patients with severe AS (stage C2) and LVEF <50%
C. For patients with severe AS (stage C or D) when undergoing other cardiac surgery
D. All of the above

16.11. AVR is reasonable in which of the following situations of severe AS?

A. Asymptomatic patients with very severe AS (stage C1, aortic velocity >5.0 m/s) and low surgical risk
B. Asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in blood pressure
C. Symptomatic patients with low-flow/low-gradient severe AS with reduced LVEF (stage D2) with a low-dose dobutamine stress study that shows an

aortic velocity >4.0 m/s (or mean pressure gradient >40 mmHg) with a valve area >1.0 cm^2 at any dobutamine dose

D. Patients with moderate AS (stage B) (aortic velocity 3.0–3.9 m/s) who are undergoing other cardiac surgery

E. Symptomatic patients who have low-flow/low-gradient severe AS (stage D3) who are normotensive and have an LVEF >50% if clinical, hemodynamic, and anatomic data support valve obstruction as the most likely cause of symptoms

F. All of the above

16.12. Transcatheter AVR (TAVR) is reasonable in which of the following situations?

A. Severe AS patients who meet an indication for AVR who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months

B. As an alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk

C. Neither A nor B

D. Both A and B

16.13. Which of the following statements is not true about balloon aortic valvuloplasty?

A. It is a good treatment for many forms of congenital AS

B. It is a good definitive treatment for calcific AS of the elderly

C. Percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or TAVR in severely symptomatic patients with severe AS

D. It is helpful to predilate the aortic valve just before TAVR

16.14. A 65-year-old woman with no prior cardiac history is short of breath on walking a flight of stairs and doing her daily activities for the last 6 months and is getting worse. Echocardiogram showed an EF of 65%, probable bicuspid aortic valve with V2 of 3.5 m/s, aortic mean gradient of 30 mmHg, V1 0.8 m/s and LV outflow tract diameter (LVOTd) of 20 mm. She walked 4 Mets and ramp II protocol on the treadmill. A TEE confirmed bicuspid aortic valve with a planimetered AVA of 0.7 cm^2 both on 2D and 3D. Normal coronaries on coronary angiography. PA pressure was normal. PFTs were normal. Hemoglobin 13.8 g/dL. What would be your recommendation?

A. Monitor the patient and repeat echo in 6 months

B. Do a dobutamine stress echo (DSE)

C. Enroll in an exercise program

D. Refer for AVR

16.15. A 72-year-old man with history of hypertension and diabetes is short of breath on walking a flight of stairs and doing his daily activities for the last 6 months and is getting worse. Echocardiogram showed an EF of 30%, calcific AS with V2 of 3.5 m/s, aortic mean gradient of 30 mmHg, V1 0.8 m/s, stroke volume index 32 mL/m^2, and LVOTd of 20 mm. Normal coronaries on coronary angiography. What would be your recommendation?

A. AS is not severe; treat with beta blockers and angiotensin-converting-enzyme inhibitor

B. Low-dose dobutamine echo for contractile reserve and hemodynamics

C. Refer for balloon valvotomy to see if the patient improves

D. Refer for TAVR

16.16. In the patient in Question 16.15, what is the approximate AVA by the continuity equation?

A. 0.7 cm^2
B. 0.9 cm^2
C. 1.2 cm^2
D. Cannot calculate with the data given

16.17. In a patient with suspected AR, which is the preferred diagnostic modality?

A. Echocardiography
B. Contrast aortography
C. Cardiac magnetic resonance imaging
D. Radionuclide angiography

16.18. Severe AR is suggested by which of the following echocardiographic measures?

A. Doppler jet width ≥65% of LVOT
B. Vena contracta >0.6 cm
C. Holodiastolic flow reversal in the proximal abdominal aorta
D. Regurgitant volume ≥60 mL/beat, or regurgitant fraction ≥50%, or effective regurgitant orifice (ERO) area ≥0.3 cm^2
E. All of the above

16.19. In a patient with chronic severe AR, which of the following constitute a definite indication for AVR?

A. Symptomatic patients with severe AR regardless of LV systolic function, even if EF is <30%
B. Asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF <50%)
C. Patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications
D. All of the above

16.20. In a patient with chronic severe AR, which of the following constitute a reasonable indication for AVR?

A. Asymptomatic patients with severe AR with normal LV systolic function (LVEF <50%) but with severe LV dilation (LV end-systolic dimension (LVESD) >50 mm, stage C2)
B. Moderate AR (stage B) patients who are undergoing other cardiac surgery
C. Asymptomatic patients with severe AR and normal LV systolic function (LVEF >50%, stage C1) but with progressive severe LV dilation (LV end-diastolic dimension (LVEDD) >65 mm) if surgical risk is low
D. All of the above

16.21. According to the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014), when is MS considered severe?

A. MV area (MVA) <1.0 cm^2 and mean gradient >10 mmHg
B. MVA <1.0 cm^2
C. MVA <1.5 cm^2
D. MVA <1.5 cm^2 and mean gradient >10 mmHg

16.22. A 42-year-old patient is being followed up in valve clinic for rheumatic MS. She is asymptomatic and has no other comorbidities. Her echocardiogram shows an EF of 65%, severe left atrial enlargement, and a calculated MVA of 0.7 cm^2. PA

systolic pressure is 40 mmHg, and Wilkins score is 6 out of 16 without commissural calcification. There was no MR. What would you recommend?

A. Follow up in 6 months
B. Refer for mitral balloon valvotomy
C. Refer for MV replacement and appendage ligation
D. Perform an exercise tolerance test

16.23. A 52-year-old man with rheumatic MS has been having progressive shortness of breath. His LVEF is normal, mean mitral gradient is 8 mmHg at a heart rate of 65 bpm, mitral pressure half-time is 180 ms. There is also moderate MR and the Wilkins score is 7. What would you recommend?

A. Continue to follow up as MS is not severe
B. Refer for mitral balloon valvotomy after coronary angiogram
C. Refer for MV replacement after coronary angiogram
D. Refer for MV repair after coronary angiogram

16.24. What are the echocardiographic indices of severe MR?

A. Central jet with the jet occupying >40% LA area
B. Holosystolic eccentric MR jet, which is wall hugging reaching posterior LA wall
C. Vena contracta >0.7 cm, or regurgitant volume >60 mL, or regurgitant fraction >50%
D. ERO area >0.40 cm^2
E. Systolic flow reversal in pulmonary vein or veins
F. Any of the above

16.25. Which of the following are clear indications for surgical repair of primary severe MR?

A. Symptomatic patients with chronic severe primary MR (stage D) and LVEF >30%
B. Asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30–60% and/or LVESD >40 mm, stage C2)
C. Patients with chronic severe primary MR undergoing cardiac surgery for other indications
D. All of the above

16.26. In a patient undergoing MV surgery for severe MR, which type of anatomy is most suitable for successful repair?

A. Flail P2
B. Flail A2
C. Bileaflet MV prolapse
D. Barlow's disease

16.27. A 62-year-old man with previous anterior myocardial infarction has an EF of 30%, LV dilation, and bileaflet tethering causing MR. The MR jet area is 4 cm^2, vena contracta 5 mm, and the ERO area is 0.25 cm^2. Which of the following describes the state of MR?

A. Mild
B. Moderate
C. Severe
D. Need more data

16.28. Criteria for severe tricuspid regurgitation (TR) include which of the following?

A. Central jet area >10 cm^2
B. Vena contracta width >0.70 cm

C. Continuous-wave (CW) jet density and contour: dense, triangular with early peak
D. Hepatic vein flow: systolic reversal
E. All of the above

16.29. Reasonable indications for tricuspid valve (TV) surgery include which of the following?
A. Patients with severe TR (stages C and D) undergoing left-sided valve surgery
B. Patients with symptoms due to severe primary TR that are unresponsive to medical therapy
C. Asymptomatic or minimally symptomatic patients with severe primary TR (stage C) and progressive degrees of moderate or greater right ventricle dilation and/or systolic dysfunction
D. All of the above

16.30. Indicators of severe tricuspid stenosis include which of the following?
A. Mean diastolic gradient >5 mmHg
B. PHT >190 ms
C. Valve area by continuity equation <1.0 cm^2
D. All of the above

16.31. Indicators of severe pulmonary stenosis include which of the following?
A. Transvalvular velocity >4 m/s
B. Peak gradient >40 mmHg
C. V2 >5 m/s
D. None of the above

16.32. For a 52-year-old man with bileaflet mitral mechanical valve without atrial fibrillation, LV dysfunction, prior thromboemboli, or hypercoagulable state, what is the preferred anticoagulation regimen?
A. Warfarin to an international normalized ratio (INR) goal of 3.0 and aspirin 81 mg daily
B. Warfarin to an INR goal of 3.0 only
C. Warfarin to an INR goal of 3.5
D. Warfarin to an INR goal of 2.5 and aspirin 81 mg daily

16.33. For a 52-year-old man with bileaflet aortic mechanical valve without atrial fibrillation, LV dysfunction, prior thromboemboli, or hypercoagulable state, what is the preferred anticoagulation regimen?
A. Warfarin to an INR goal of 3.0 and aspirin 81 mg daily
B. Warfarin to an INR goal of 3.0 only
C. Warfarin to an INR goal of 3.5
D. Warfarin to an INR goal of 2.5 and aspirin 81 mg daily

16.34. For a 52-year-old man with bileaflet aortic mechanical valve with one of the risk factors such as atrial fibrillation, LV dysfunction, prior thromboemboli,or hypercoagulable state, what is the preferred anticoagulation regimen?
A. Warfarin to an INR goal of 3.0 and aspirin 81 mg daily
B. Warfarin to an INR goal of 3.0 only
C. Warfarin to an INR goal of 3.5
D. Warfarin to an INR goal of 2.5 and aspirin 81 mg daily

16.35. For a patient with mechanical MV undergoing noncardiac surgery needing interruption of anticoagulation, what would you recommend?
- **A.** Minimize nonanticoagulated period; bridge with heparin or LMWH
- **B.** No bridging needed
- **C.** Bridge with novel anticoagulant
- **D.** Use fresh frozen plasma to cover surgery

16.36. For a patient with mechanical aortic valve undergoing noncardiac surgery needing interruption of anticoagulation, what would you recommend? Patient has no risk factors for higher embolic risk.
- **A.** Minimize nonanticoagulated period; bridge with heparin or LMWH
- **B.** Minimize nonanticoagulated period; no bridging needed
- **C.** Bridge with novel anticoagulant
- **D.** Use fresh frozen plasma to cover surgery

16.37. In patients with risk factors for IE presenting with fever of >48 h duration, which of the following guidelines for blood cultures are recommended?
- **A.** At least two sets of blood cultures should be obtained, which may give positive culture rate of about 90%.
- **B.** In patients with a chronic (or subacute) presentation, three sets of blood cultures should be drawn >6 h apart at peripheral sites before initiation of antimicrobial therapy
- **C.** If option B is not feasible or safe in patients with severe sepsis or septic shock, two or more cultures at separate times are acceptable
- **D.** All of the above

16.38. Based on the Duke criteria, a diagnosis of IE can be definitely made with which of the following present?
- **A.** Two major criteria
- **B.** One major and three minor criteria
- **C.** Five major criteria
- **D.** All of the above.

16.39. In a patient with risk factors for IE presenting with persistent fever, a TEE would be appropriate in which of the following situations after obtaining blood cultures and a transthoracic echocardiogram (TTE)?
- **A.** Nondiagnostic TTE
- **B.** Presence of intracardiac lead
- **C.** IE complication is suspected
- **D.** All of the above.

16.40. In a patient with proven endocarditis who also has a pacemaker device, device and lead removal is indicated or reasonable under which of the following situations?
- **A.** Infection of lead or device pocket
- **B.** Needs valve surgery for IE, but leads and pocket look normal
- **C.** IE due to resistant organism such as *S. aureus* or fungi
- **D.** All of the above.

16.41. In a pregnant patient with mechanical valve prosthesis, which of the following anticoagulation regimens are acceptable during the first trimester of pregnancy?
- **A.** Warfarin if therapeutic INR can be achieved with a dose of 5 mg or less
- **B.** Intravenous (IV) UFH to achieve partial thromboplastin time (PTT) twice the control
- **C.** LMWH twice a day to achieve anti-Xa level 0.8–1.2 units/mL 4–6 h after the dose
- **D.** All of the above

16.42. A 52-year-old woman has a history of abdominal bloating and diarrhea of 6 months' duration. The echocardiogram of the TV is shown in Figure 16.42. What is the likely diagnosis?

A. Carcinoid syndrome
B. Rheumatic heart disease
C. Flail TV
D. None of the above

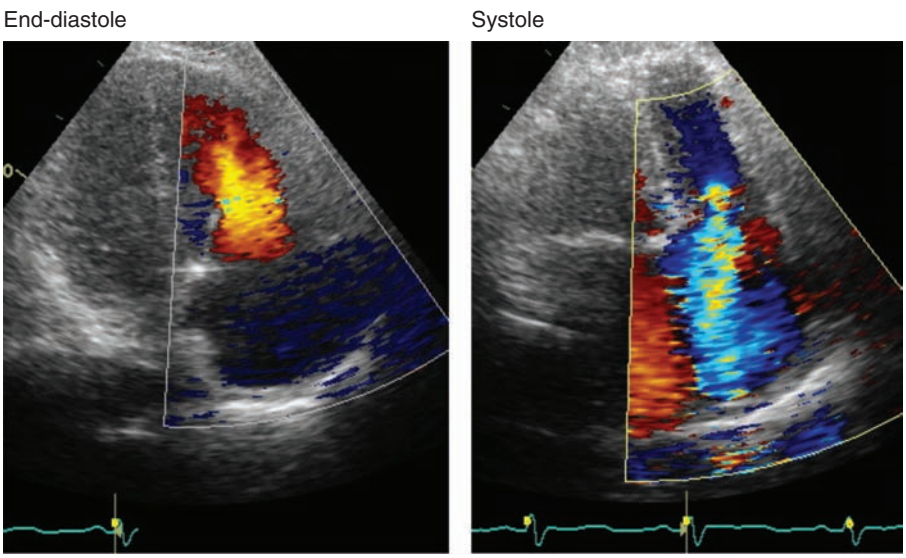

Figure 16.42

16.43. The flow across the mitral bioprosthesis in the patient in Figure 16.43 is indicative of what? (the MV PHT was 120 ms)?

A. Normal function
B. Mild stenosis
C. Moderate stenosis
D. Severe stenosis

16.44. Figure 16.44 is of a patient with a prior bioprosthetic valve. What is the likely cause of dyspnea in the patient?

A. Severe paravalvular AR
B. Severe prosthetic valve stenosis
C. Severe MR
D. None of the above

16.45. What is the m-mode in the patient in Figure 16.45 suggestive of?

A. MS
B. Low cardiac output state
C. Severe AR
D. None of the above.

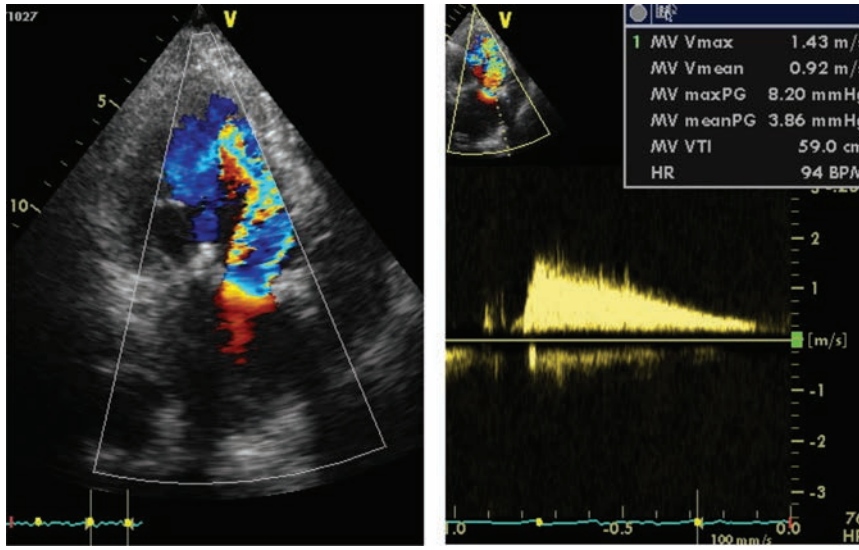

Figure 16.43

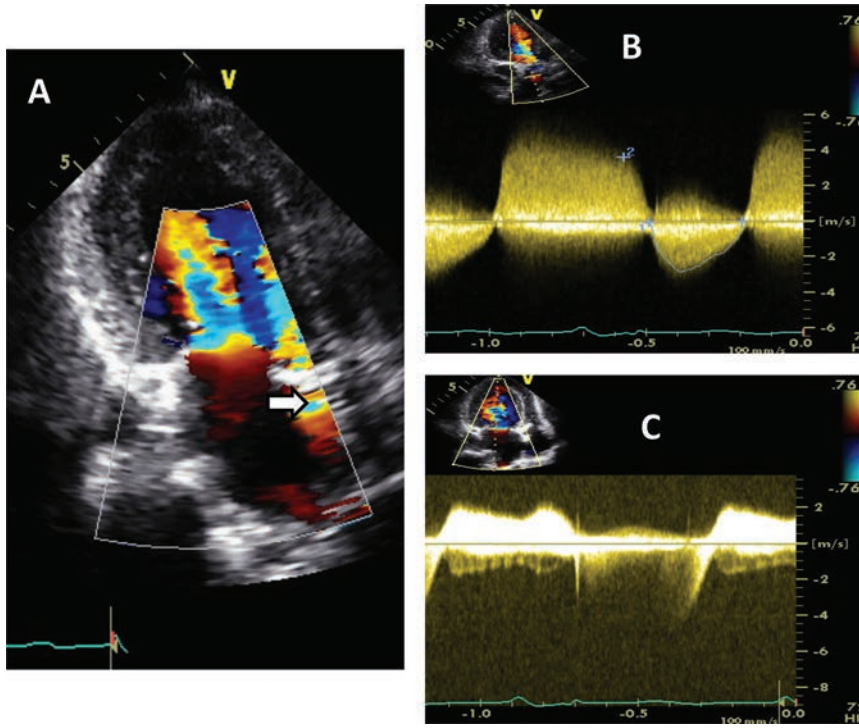

Figure 16.44

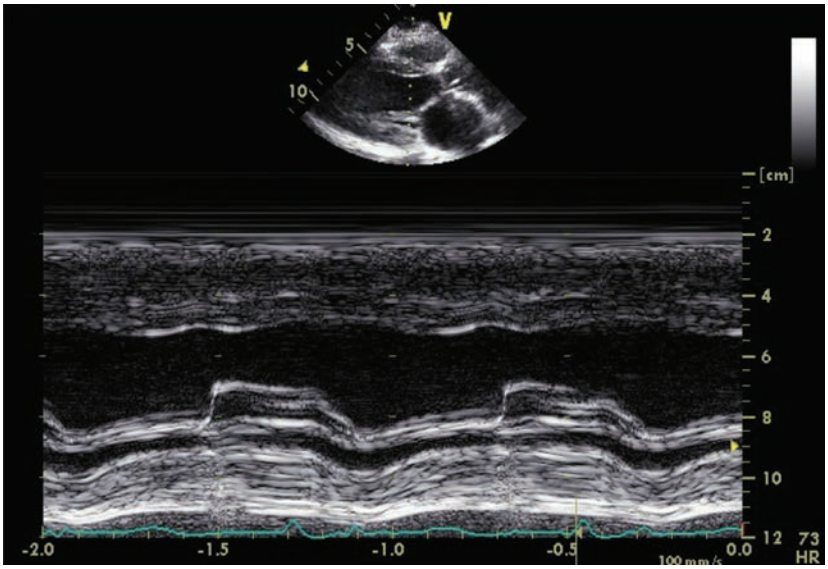

Figure 16.45

16.46. What is the TR velocity profile in the patient in Figure 16.46 with corrected tetralogy of Fallot and pulmonary valve replacement with an V2 of 2.4 m/s suggestive of?

A. Pulmonary hypertension
B. First-degree atrioventricular (AV) block or long AV delay on pacemaker
C. Severe pulmonary regurgitation (PR)
D. None of the above

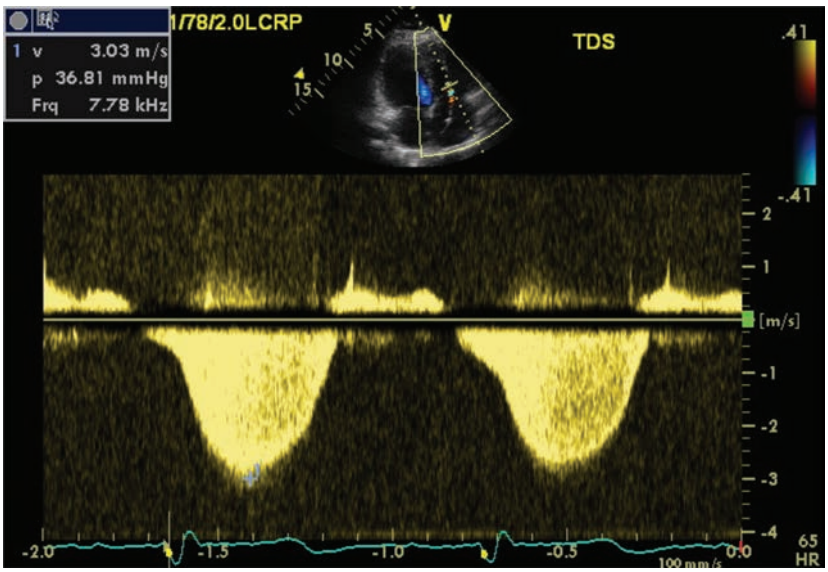

Figure 16.46

16.47. Figure 16.47 shows a CW signal across a bioprosthetic pulmonary valve. What is it suggestive of?

A. Pulmonary valve stenosis
B. Mild PR
C. Moderate PR
D. Severe PR

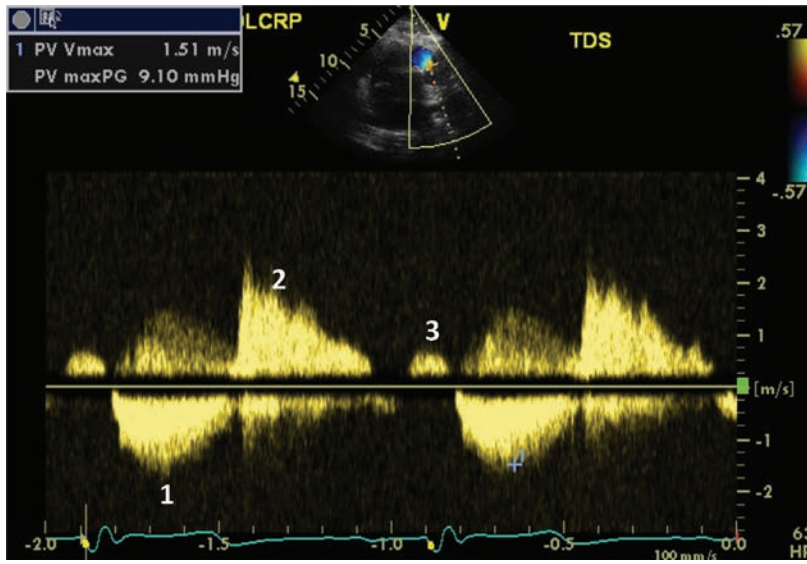

Figure 16.47

16.48. What is the mitral flow in Figure 16.48 suggestive of?

A. Normal flow
B. Severe MR with increased mitral flow
C. MS
D. Severe AR impeding mitral flow

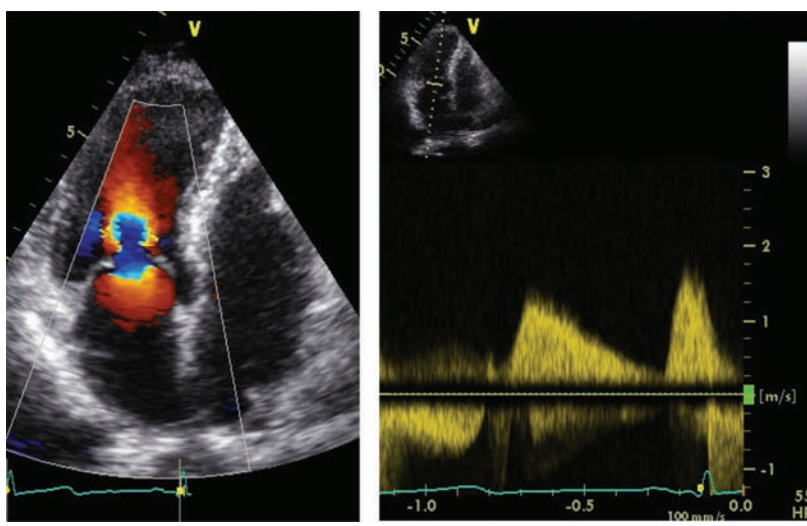

Figure 16.48

16.49. What does the patient in Figure 16.49 have?

A. Acute severe AR
B. Chronic severe AR
C. MS
D. None of the above

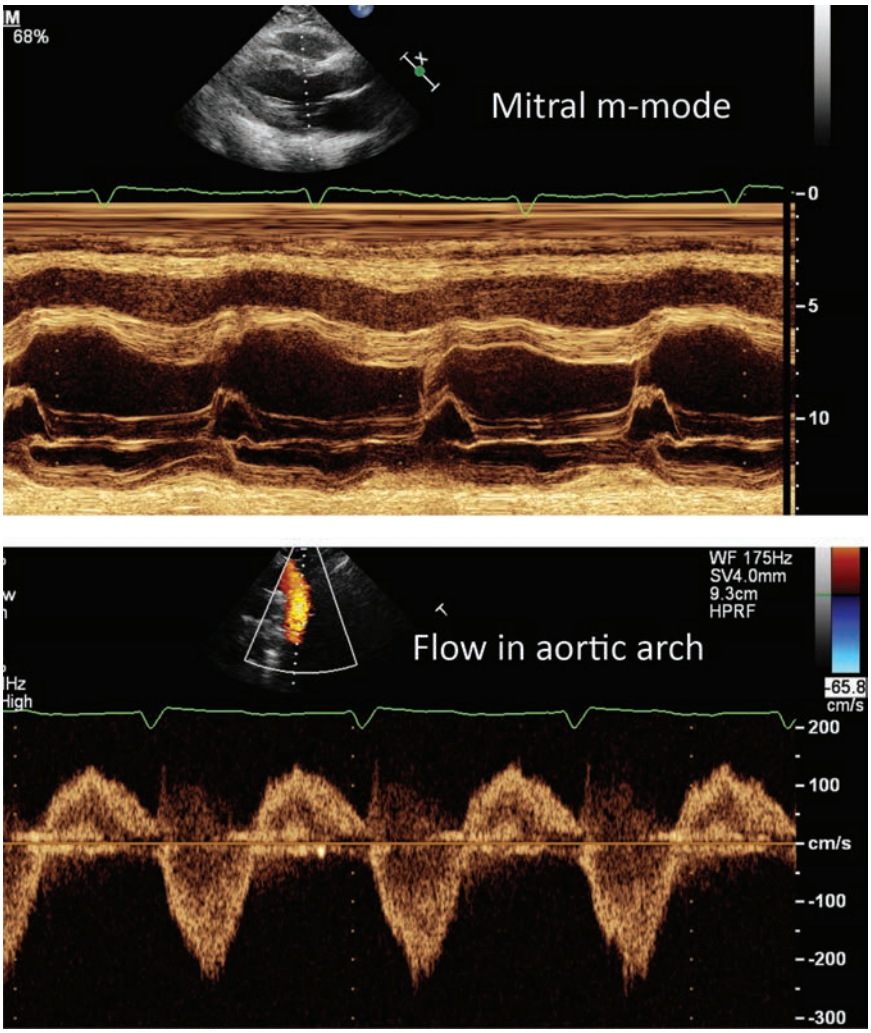

Figure 16.49

16.50. In a patient with suspected endocarditis, what is the Doppler signal in Figure 16.50 diagnostic of?

A. Acute severe AR
B. MS
C. AS
D. None of the above

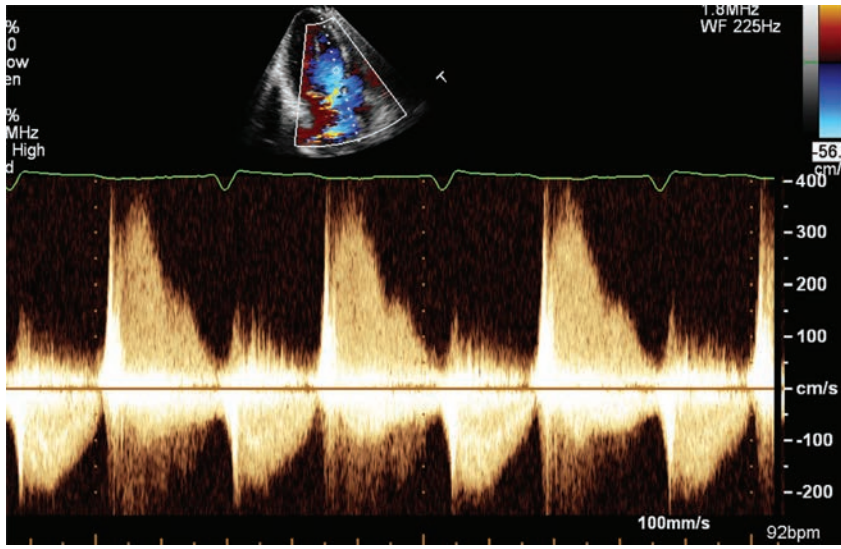

Figure 16.50

16.51. What is the image of the patient with a prosthetic MV and dyspnea in Figure 16.51 indicative of?

A. Severe paravalvular MR
B. MS
C. AR
D. AS

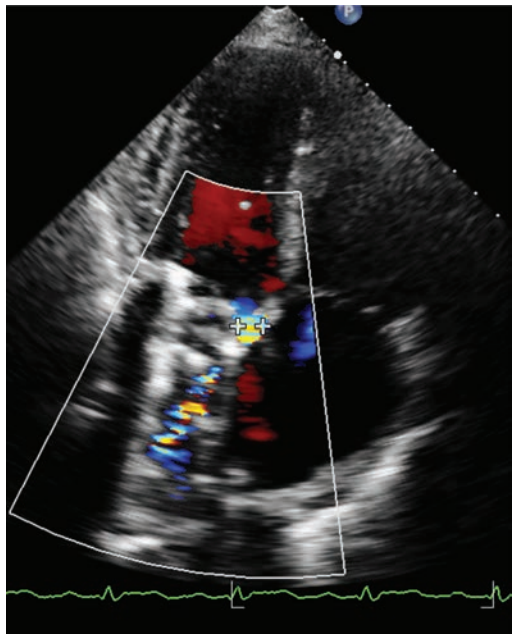

Figure 16.51

16.52. Figure 16.52 shows a 48-year-old man who presented with acute severe shortness of breath. What would be the most optimal treatment?

A. MV repair
B. MVR
C. AVR
D. Prolonged antibiotic therapy

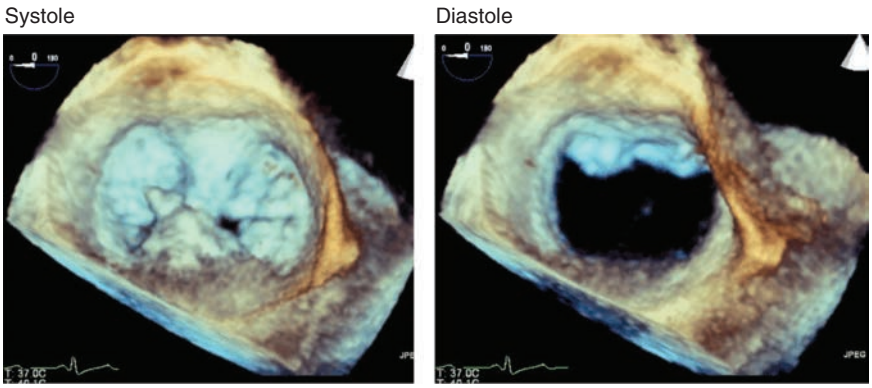

Figure 16.52

16.53. A patient with heart transplant presented with pedal edema and abdominal bloating. Figure 16.53 is of the TV. What is this suggestive of?

A. Severe TR
B. Moderate TR
C. Tricuspid stenosis
D. Normal function of TV in a transplanted patient

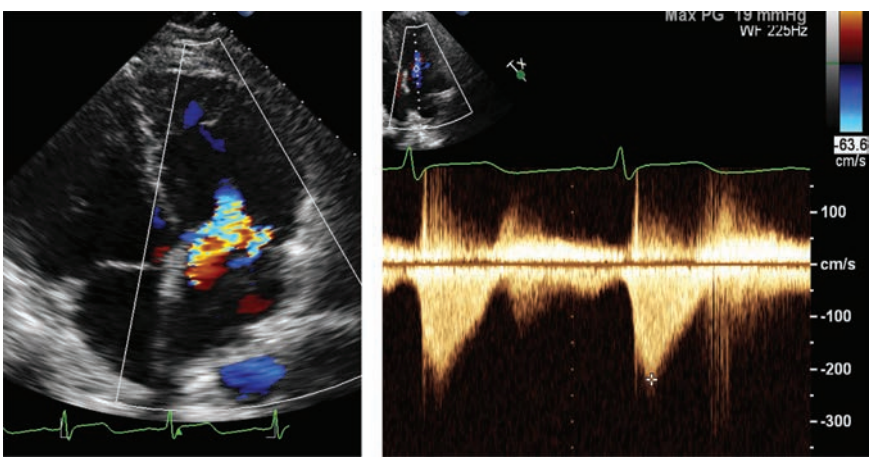

Figure 16.53

16.54. An 88-year-old man with multiple comorbidities and Society of Thoracic Surgeons score of 12 is scheduled for TAVR. Aortic valve images are shown in Figure 16.54. There was no fever, and blood cultures were negative. What would a prudent step be?

A. Proceed with TAVR
B. Proceed with TAVR using carotid protection
C. Cancel TAVR and treat with antibiotic for 6 weeks and repeat TEE
D. None of the above

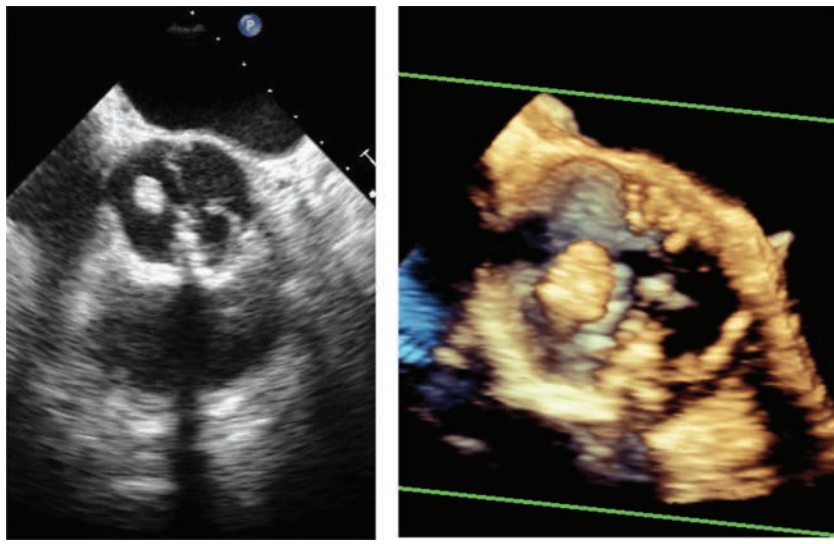

Figure 16.54

16.55. What condition does the patient in Figure 16.55 with a St Jude mechanical MV have?

A. Severe stenosis
B. Mild stenosis
C. Severe MR
D. None of the above

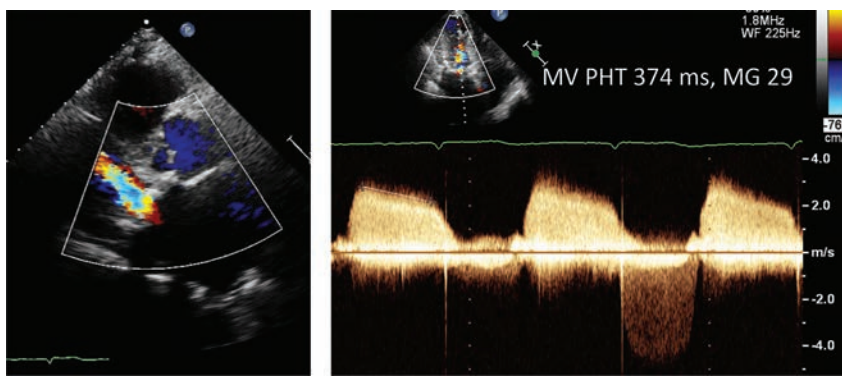

Figure 16.55

16.56. Figure 16.56 shows a patient that presented with shortness of breath. What condition does the patient have?

A. Severe subvalvular AS
B. Severe valvular AS
C. Hypertrophic obstructive cardiomyopathy (HOCM)
D. None of the above

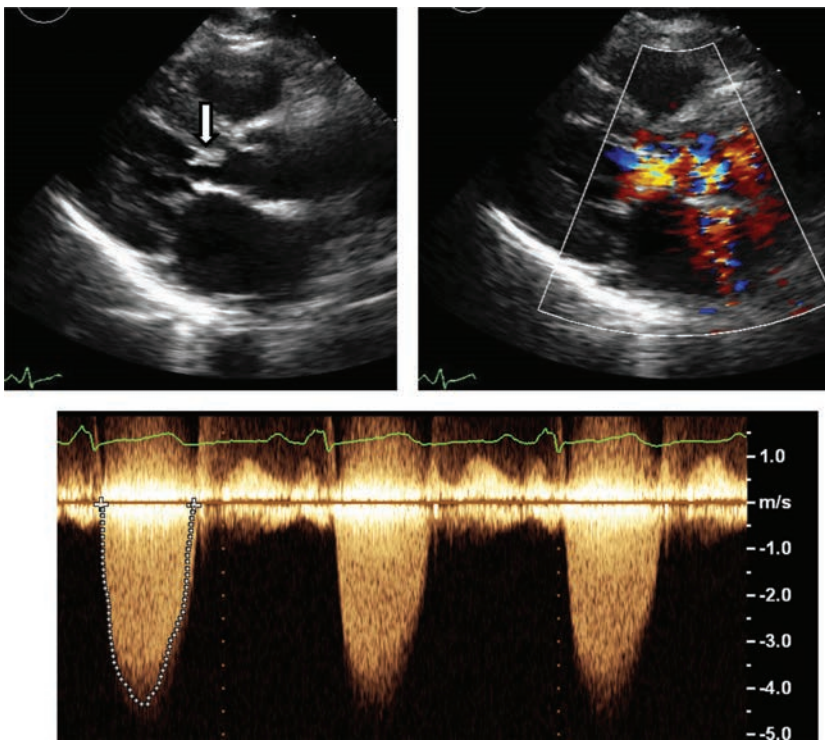

Figure 16.56

16.57. What is the Doppler signal in Figure 16.57 indicative of?

A. Critical AS with high LA pressure
B. Severe AS with atrial fibrillation
C. Severe MR
D. None of the above

16.58. A 19-year-old patient with a mechanical MV was admitted with shortness of breath. Within an hour of admission she had to be intubated and ventilated for respiratory distress. The blood pressure dropped to 60/40 mmHg unresponsive to pressures. The TEE images are shown in Figure 16.58. What would the next logical step would be?

A. IV thrombolytic
B. IV heparin only
C. IV beta blocker to slow the heart rate
D. Wait for the cardiac operating room to be ready, which may take 2–3 h to finish the patient on the table

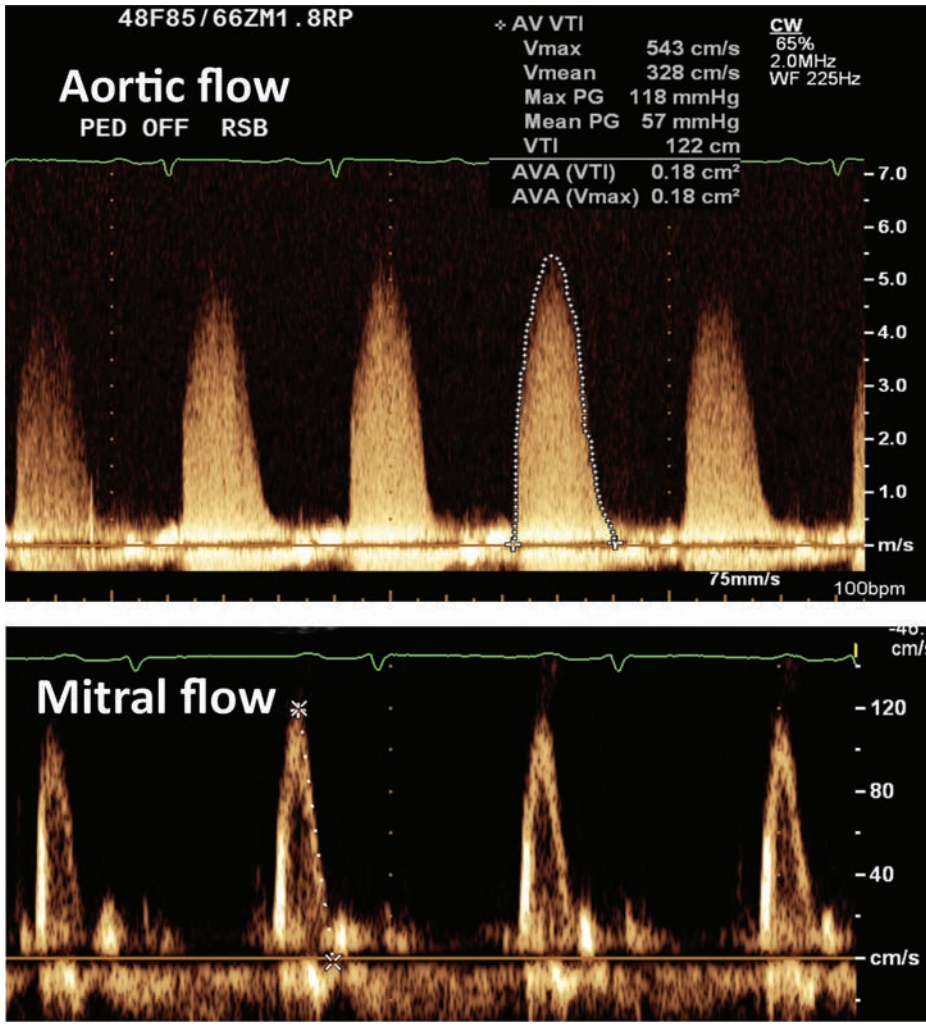
48F85/66ZM1.8RP
Aortic flow
PED OFF RSB
AV VTI
Vmax 543 cm/s
Vmean 328 cm/s
Max PG 118 mmHg
Mean PG 57 mmHg
VTI 122 cm
AVA (VTI) 0.18 cm²
AVA (Vmax) 0.18 cm²
CW
65%
2.0MHz
WF 225Hz
7.0
6.0
5.0
4.0
3.0
2.0
1.0
m/s
75mm/s
100bpm
Mitral flow
cm/s
120
80
40
cm/s

Figure 16.57

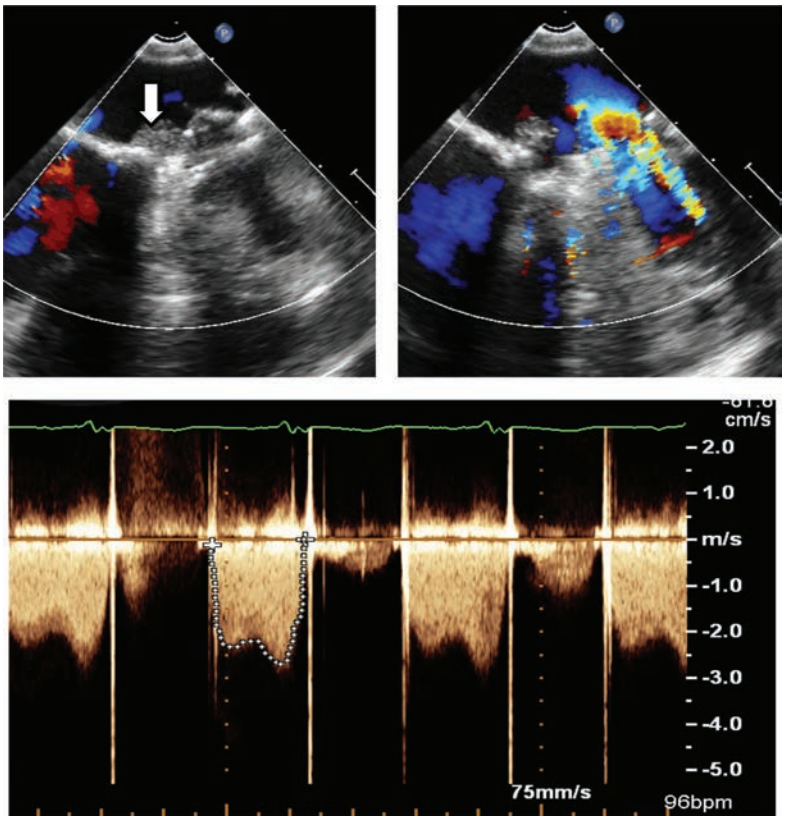

Figure 16.58

16.59. What is the arrow in Figure 16.59 pointing to?

- **A.** Thrombus or pannus on a bileaflet mechanical MV
- **B.** Sewing rim
- **C.** Artifact
- **D.** None of the above

16.60. Figure 16.60 is a pressure tracing of a patient with AS. Which of the following statements are true?

- **A.** A is the peak to peak gradient obtained by catheterization and is not physiological
- **B.** B is the peak instantaneous gradient obtained by Doppler peak velocity V2
- **C.** C is the mean gradient obtained by catheterization or Doppler echocardiography
- **D.** All of the above

16.61. What is the patient whose results are given in Figure 16.61 likely to have?

- **A.** Severe valvular AS
- **B.** Severe subvalvular AS
- **C.** HOCM
- **D.** No AS; has catheter entrapment

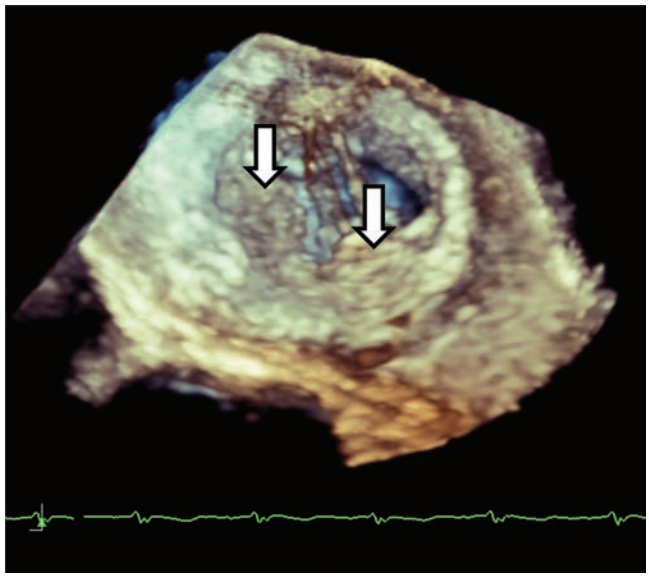

Figure 16.59

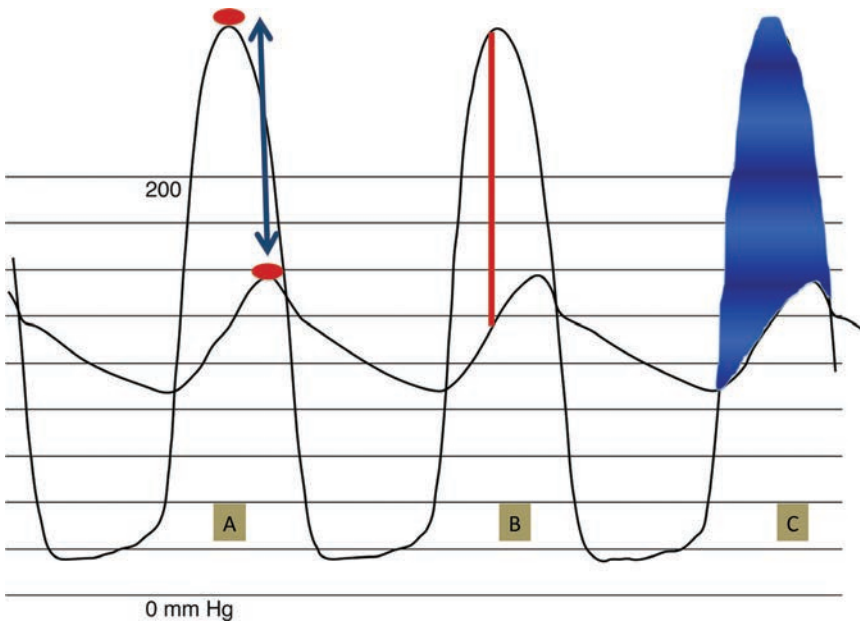

Figure 16.60

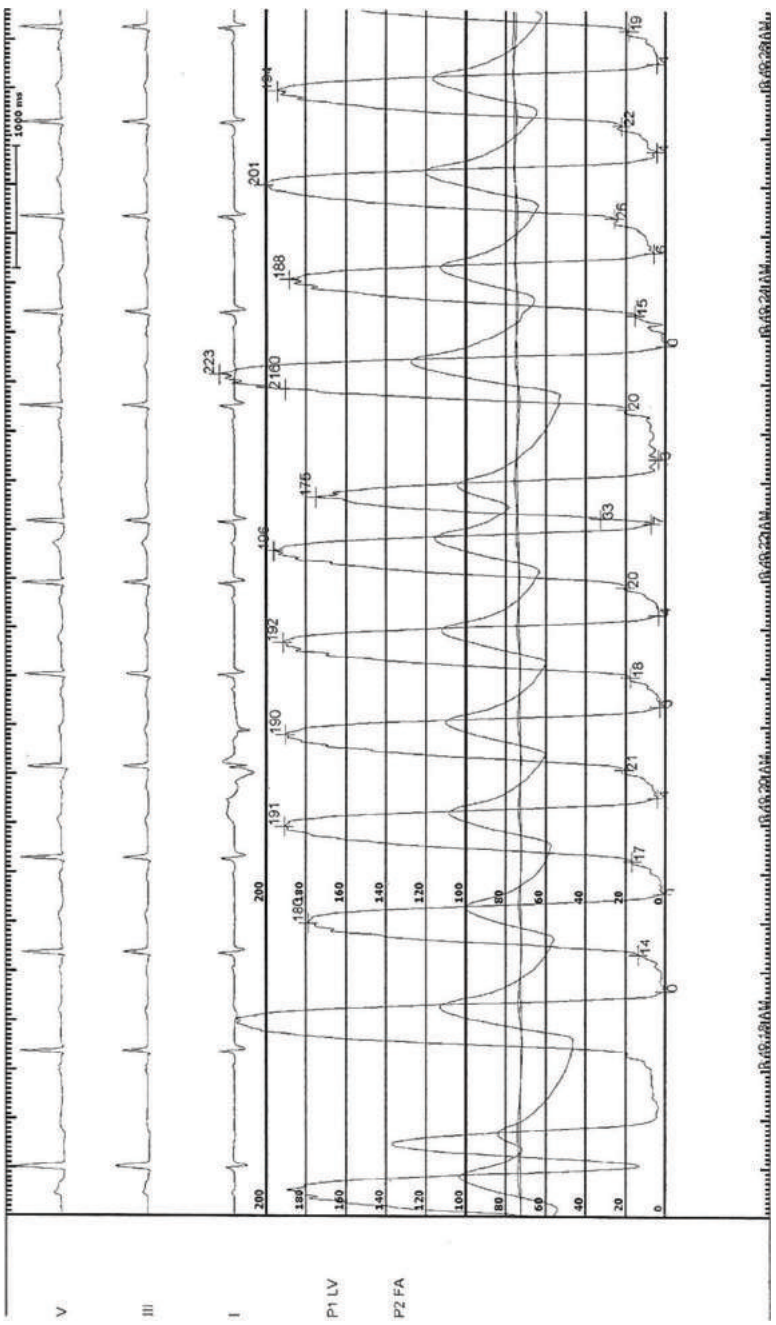

Figure 16.61

16.62. What does the patient (body surface area 1.8 m^2) in Figure 16.62 have?

A. Critical AS, high gradient despite low flow
B. Low-flow, low gradient AS
C. Normal flow, low gradient AS
D. None of the above

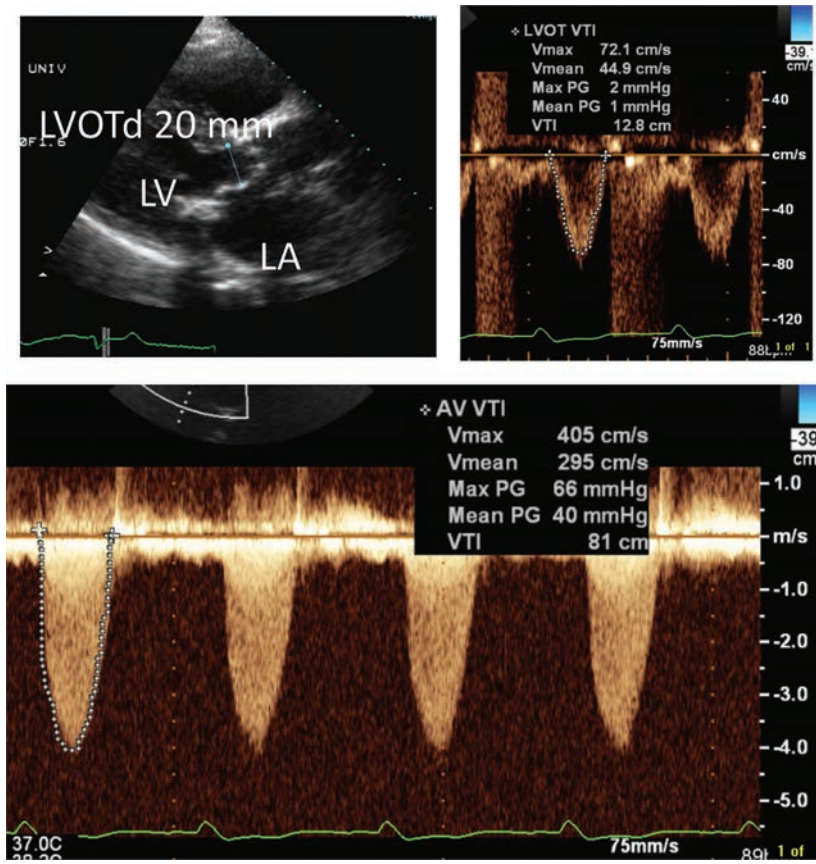

Figure 16.62

16.63. A 32-year-old man has had a history of murmur for several years. On examination he has a 3/6 early diastolic murmur at the left sternal border. He is tall and has skeletal features of Marfan syndrome. He is on atenolol 50 mg/day, and his heart rate is 60 bpm and blood pressure 110/70 mmHg. His echocardiogram shows normal-sized LV with EF of 65%, mild AR, trileaflet aortic valve, and aortic sinus dimension of 51 mm and the ascending aorta 44 mm. What will you recommend?

A. Close monitoring with echo every 6 months for ascending aortic dimensions
B. Add losartan
C. Refer for valve sparing root and ascending aortic replacement with coronary implantation
D. None of the above

Answers

16.1. B. Every 3–5 years.

According to American Heart Association (AHA)/American College of Cardiology (ACC) 2014 valve guidelines (Nishimura *et al.*, 2014) – see Box 16.1. This is mild stage B disease. The same guidelines also apply to mild mitral stenosis (MS), mitral regurgitation (MR), and aortic regurgitation (AR).

16.2. Follow-up clinic and echo every 1–2 years.

According to the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014). This is stage C disease. Evidence, based on natural history studies, is accumulating that option A may be true. Same principle applies to severe asymptomatic AR, MR, and MS.

16.3. B. Prophylaxis till she turns 40 years.

As per AHA/ACC 2014 valve guidelines. The recommendations are as follows. Rheumatic fever with carditis and residual heart disease (persistent valvular heart disease): 10 years or until patient is 40 years of age (whichever is longer). Rheumatic fever with carditis but no residual heart disease (no valvular disease): 10 years or until patient is 21 years of age (whichever is longer). Rheumatic fever without carditis: 5 years or until patient is 21 years of age (whichever is longer).

16.4. D. Any of the above.

16.5. E. All of the above.

16.6. F. None of the above.

16.7. D. Any of the above.

16.8. B. Stage C1.

As he has asymptomatic severe AS with normal left ventricular (LV) function. Stage C2 entails LV dysfunction. Stage D is symptomatic. Stage B is mild or moderate AS, and Stage A is at risk (i.e., calcified aortic valve with V2 <2 m/s).

16.9. A. An exercise stress test to confirm the asymptomatic status.

As there is ambiguity about symptoms (class IIa indication). About 50% of patients who claim to be asymptomatic become symptomatic for the first time on a stress test as patients learn to live within symptoms. If a stress test confirms limitation of exercise tolerance, AVR would be indicated. If patient was clearly asymptomatic, option D would have been reasonable. Dobutamine echo is indicated in patients with low-gradient–severe AS to make sure that it is not pseudo AS and that there is contractile reserve.

16.10. D. All of the above.

These are class I indications for AVR in those with severe AS.

16.11. F. All of the above.

These are all class IIa recommendations for AVR.

16.12. D. Both A and B.

These conclusions are based on the PARTNER trial, where in nonsurgical patients TAVR was superior to medical management alone and in high-risk patients it was equivalent to surgical AVR.

16.13. B. It is a good definitive treatment for calcific AS of the elderly.
The results are only transient in calcific AS.

16.14. D. Refer for AVR.
This patient has an AVA of <1 cm^2 despite normal EF and low gradient and is symptomatic. In such patients, where symptoms are most likely due to AS, AVR is recommended per current guidelines (Nishimura *et al.*, 2014). As the EF is normal, a DSE has limited value. A recent meta-analysis has shown that low-gradient–severe AS patients have a survival advantage with AVR even if there no low flow (Dayan *et al.*, 2015). Low flow is a stroke volume index of <35 mL/m^2.

16.15. B. Low-dose dobutamine echo for contractile reserve and hemodynamics.
Mostly to make sure that it is not pseudo AS; that is, valve opening more fully when the stroke volume is increased. In pseudo AS, with the increase in stroke volume, V2 will not increase proportionately resulting in an increase in V1/V2 velocity ratio or the dimensionless index. Generally, a dimensionless index of <0.25 indicates severe AS. Dobutamine also helps to evaluate the contractile reserve. Based on current valve guidelines, with a DSE, if AVA remains <1 cm^2 and V2 increases to >4 m/s, AVR is indicated (class IIa recommendation). Please see Figure 16.15 from the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014). However, a large meta-analysis shows a benefit even in the absence of contractile reserve (Dayan *et al.*, 2015) – see Box 16.2.

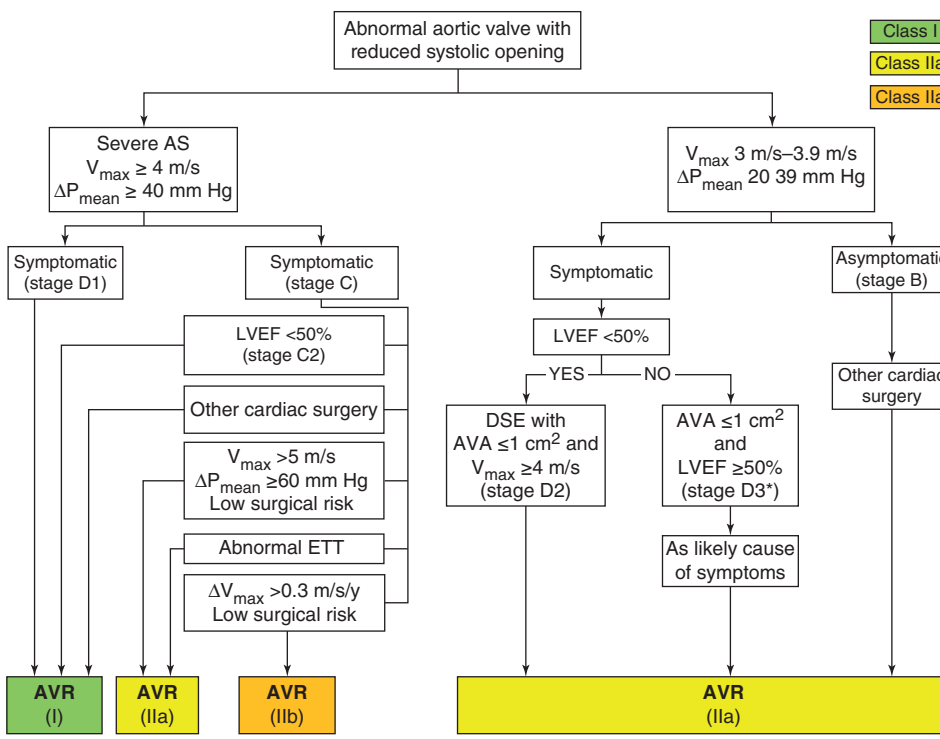

Figure 16.15 Indications for AVR in patients with AS (ETT: exercise tolerance test). *Source:* adapted from Nishimura *et al.* (2014).

16.16. A. 0.7 cm^2.

By the continuity equation, A1 × V1 = A2 × V2 using peak velocities, where A1 is LV outflow tract (LVOT) area (3.14 cm^2 assuming circular geometery), V1 is LVOT velocity, V2 is transvalvular velocity, A2 is AVA. Plugging in the values: 3.14 × 0.8 = A2 × 3.5. Hence, A2 = 0.72 cm^2.

16.17. A. Echocardiography.

This has become the gold standard for assessment of all valvular disorders.

16.18. All of the above.

As per Nishimura *et al.* (2014). In addition, diagnosis of chronic severe AR requires evidence of LV dilation (in acute AR, LV does not dilate).

16.19. D. All of the above.

All are class I indications for AVR in severe AR.

16.20. D. All of the above.

Please refer to the flowchart in Figure 16.20 from the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

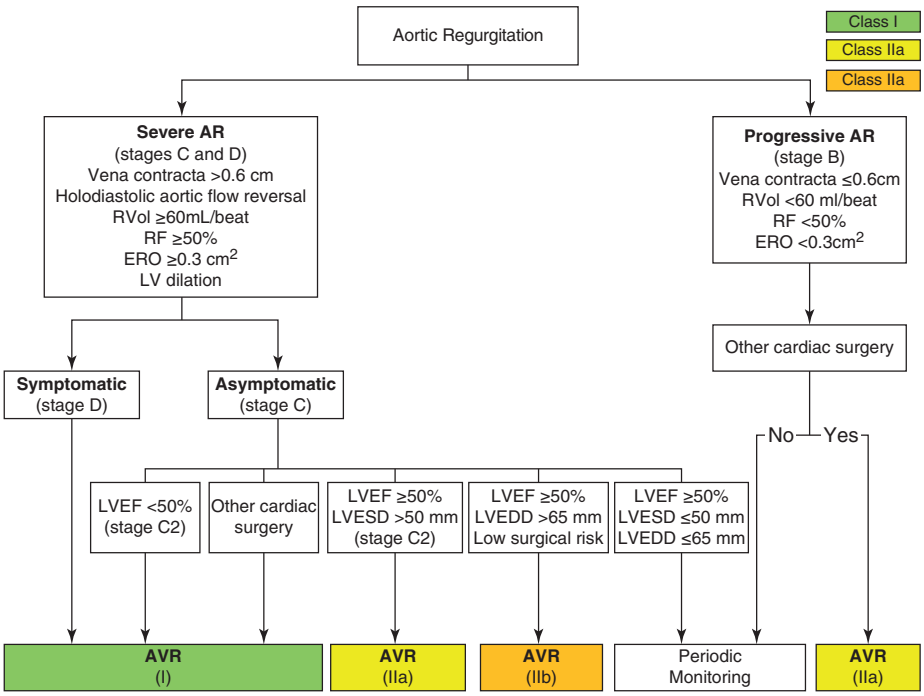

Figure 16.20 Indications for AVR for chronic AR. *Source:* adapted from Nishimura *et al.* (2014).

16.21. C. MVA <1.5 cm^2.

Or pressure half-time (PHT) >150 ms. MVA <1.0 cm^2 or PHT >220 ms is considered very severe.

16.22. B. Refer for mitral balloon valvotomy.

This patient has very severe MS and favorable anatomy for balloon valvotomy with a Wilkins score <8 and no commissural calcification and no MR. Exercise testing is reasonable, but there are no clear guidelines how to incorporate that

data in decision making. Exercise limitation with an exercise-induced PA systolic pressure >60 mmHg are reasonable indications for intervention. Please see the flowchart in Figure 16.22 from the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

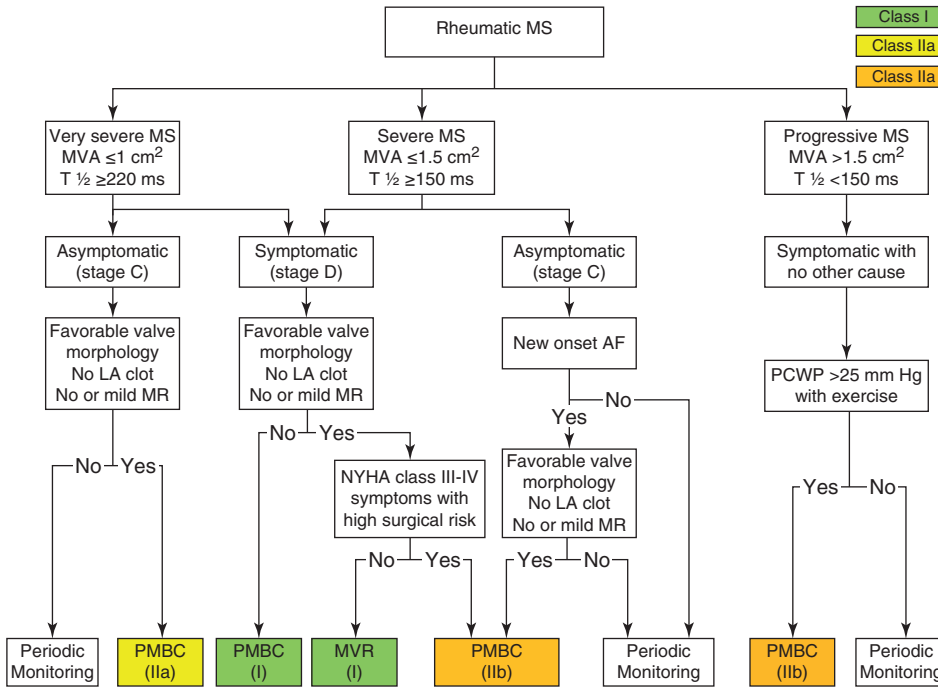

Figure 16.22 Indications for intervention for rheumatic MS (AF: atrial fibrillation; LA: left atrium; NYHA: New York Heart Association; PCWP: pulmonary capillary wedge pressure; PMBC: percutaneous mitral balloon commissurotomy). *Source:* adapted from Nishimura *et al.* (2014).

Chapter 16

16.23. C. Refer for MV replacement after coronary angiogram.

Patient symptomatic and has severe MS (PHT >150 ms). As he has moderate MR, he is not an ideal candidate for balloon valvotomy, though the Wilkins score is low. Rheumatic valves are too scarred to give a good result with repair. Please see the flowchart in Figure 16.22.

16.24. F. Any of the above.

As per AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

16.25. D. All of the above.

Please see the flowchart in Figure 16.25 from the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

16.26. A. Flail P2.

This is most suitable for repair, generally with resection of the segment and ring annuloplasty. Repair of anterior leaflet is more difficult. Barlow's disease will have extensive pathology of both leaflets, annulus, and the chords and the most difficult to repair, if at all, and durability may be compromised because of disease progression.

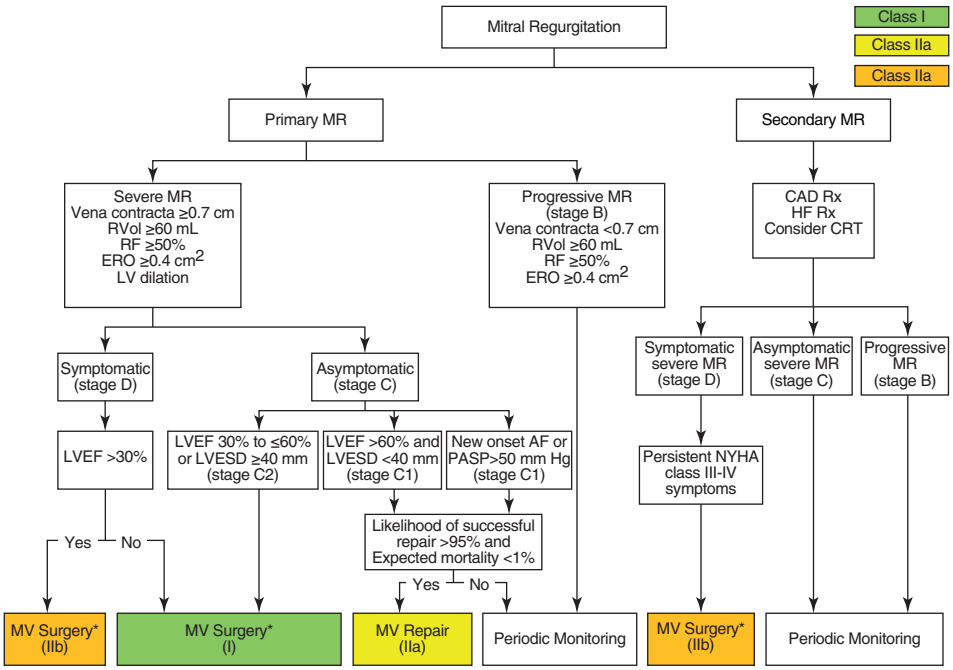

Figure 16.25 Indications for surgery for MR (CAD: coronary heart disease; CRT: cardiac resynchronization therapy; HF: heart failure; Rx: treatment). *Source:* adapted from Nishimura *et al.* (2014).

16.27. C. Severe.

For functional MR, ERO area >0.2 cm^2 or regurgitant volume >30 cm^3 is deemed to be severe. MR due to valve leaflet tethering is functional as there is no leaflet pathology.

16.28. E. All of the above.

16.29. D. All of the above.

See the flowchart from the AHA/ACC 2014 valve guidelines in Figure 16.29.

16.30. D. All of the above.

16.31. A. Transvalvular velocity >4 m/s.

Or peak gradient >64 mmHg.

16.32. A. Warfarin to an international normalized ratio (INR) goal of 3.0 and aspirin 81 mg daily.

Based on AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014). Addition of aspirin further reduces embolic risk by 50–70%. See the flowchart in Figure 16.32.

16.33. D. Warfarin to an INR goal of 2.5 and aspirin 81 mg daily.

Based on the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

16.34. A. Warfarin to an INR goal of 3.0 and aspirin 81 mg daily.

16.35. A. Minimize nonanticoagulated period; bridge with heparin or LMWH.

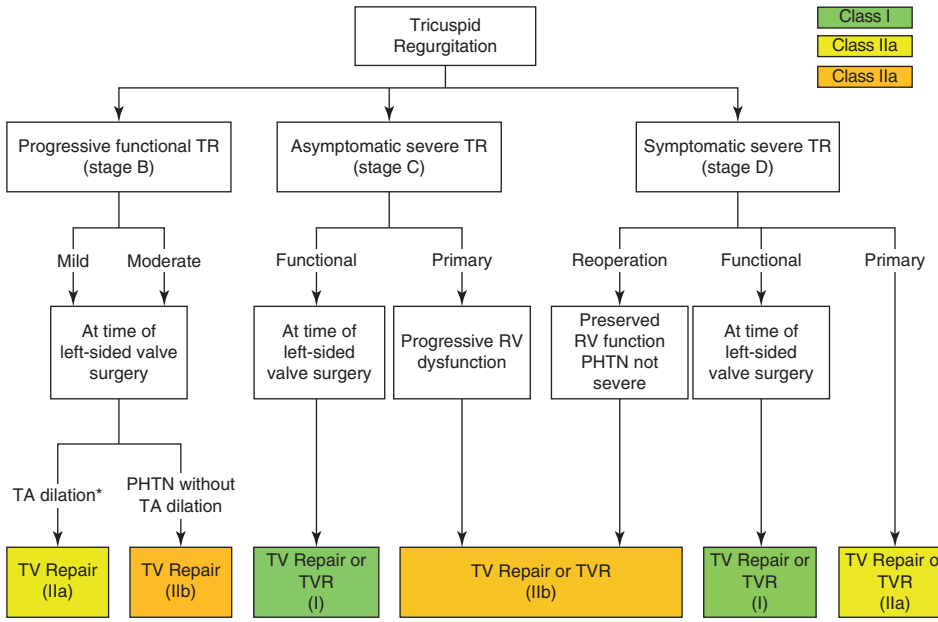

Figure 16.29 Indications for surgery for TR (PHTN: pulmonary hypertension; RV: right ventricle; TA: tricuspid annular; TVR: TV replacement). *Source:* adapted from Nishimura *et al.* (2014).

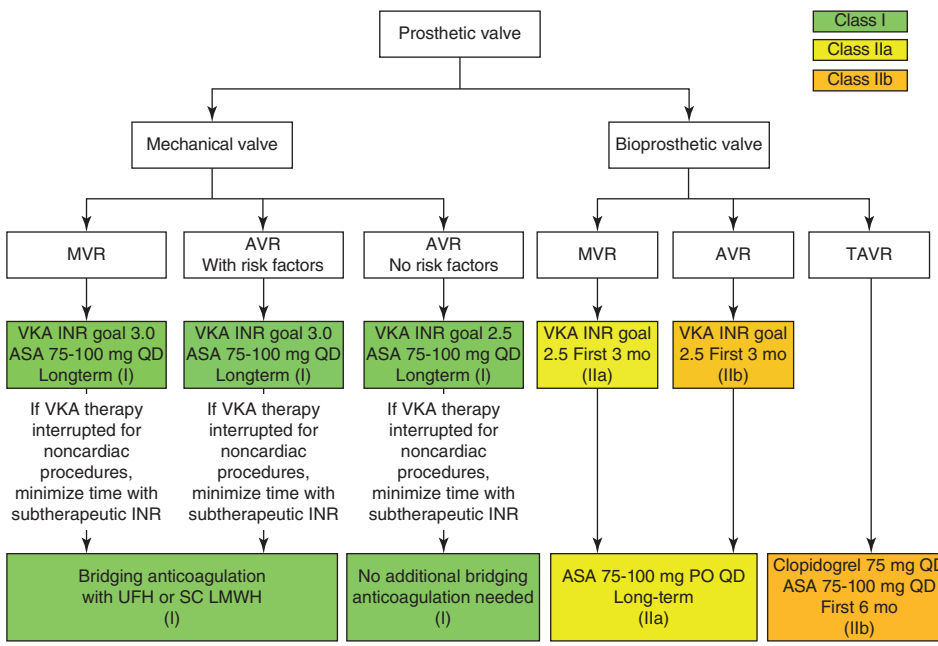

Figure 16.32 Anticoagulation for prosthetic valves (ASA: aspirin; LMWH: low molecular weight heparin; MVR: mitral valve replacement; SC: subcutaneous; UFH: unfractionated heparin; VKA: vitamin K antagonist). *Source:* adapted from Nishimura *et al.* (2014).

Novel anticoagulants are contraindicated for mechanical valves as they increase risk of thrombosis.

16.36. B. Minimize nonanticoagulated period; no bridging needed.
However, bridging is recommended for mechanical aortic valves when risk factors are present.

16.37. D. All of the above.
As per AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

16.38. D. All of the above.
The modified Duke criteria for the diagnosis of IE are as follows.

Major Criteria

1. *Blood culture positive for IE*
   Typical microorganisms consistent with IE from two separate blood cultures:
   - viridans streptococci, *Streptococcus bovis*, HACEK group (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* spp., and *Kingella kingae*), *Staphylococcus aureus*; or community-acquired enterococci, in the absence of a primary focus; or
   - microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
     – at least two positive cultures of blood samples drawn 12 h apart; or
     – all of three or a majority of four separate cultures of blood (with first and last samples drawn at least 1 h apart)
     – single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1 : 800.
2. *Evidence of endocardial involvement*
   - Echocardiogram positive for IE defined as follows:
     – oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation;
     – abscess; or
     – new partial dehiscence of prosthetic valve
     – new valvular regurgitation (worsening or changing of preexisting murmur not sufficient).

Minor Criteria

1. Predisposition, predisposing heart condition, or injection drug use.
2. Fever, temperature >38 °C (100.4 °F).
3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions.

4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor.
5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE.

16.39. D. All of the above.

In addition, it is appropriate if a patient is undergoing valve surgery for IE, there is *S. aureus* bacteremia without a clear source, or there is prosthetic valve with persistent fever. See the flowchart in Figure 16.39 from the AHA/ACC 2014 valve guidelines (Nishimura *et al.*, 2014).

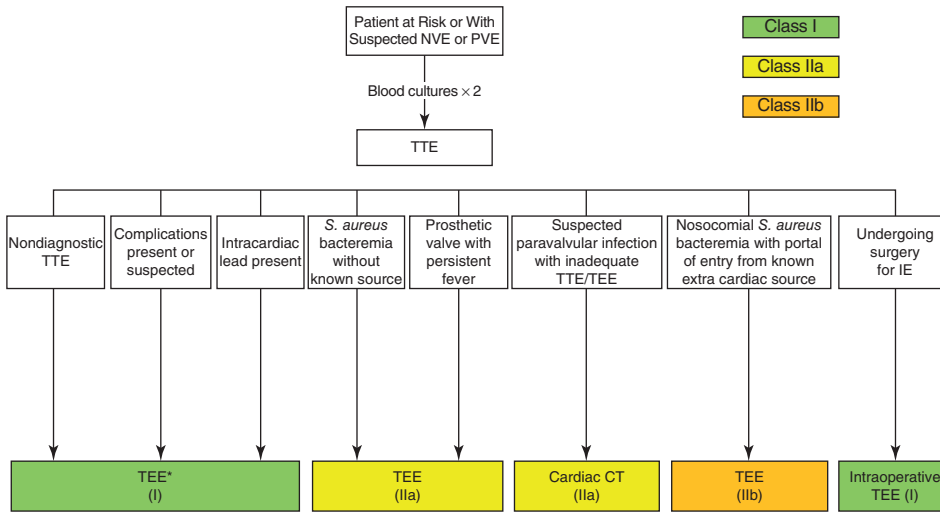

Figure 16.39 Imaging studies in native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE). *Source:* adapted from Nishimura *et al.* (2014).

16.40. D. All of the above.

Option A is a class I indication and other two are class IIa indications. See the flowchart in Figure 16.40.

16.41. D. All of the above.

With LMWH, monitoring is critical. See the flowchart in Figure 16.41.

16.42. A. Carcinoid syndrome.

Note the restricted opening of the TV during diastole suggesting tricuspid stenosis and severe TR. These are diagnostic of carcinoid in this clinical context.

16.43. B. Mild stenosis.

Note flow acceleration across the MV and a mean gradient of only 4 mmHg with pressure equilibration across the valve in end diastole. Normal PHT is generally about 60–80 ms.

16.44. A. Severe paravalvular AR.

Indicated by the arrow with a large proximal isovelocity surface area. The V2 across the aortic valve is about 2 m/s, and hence not stenotic. The MR signal

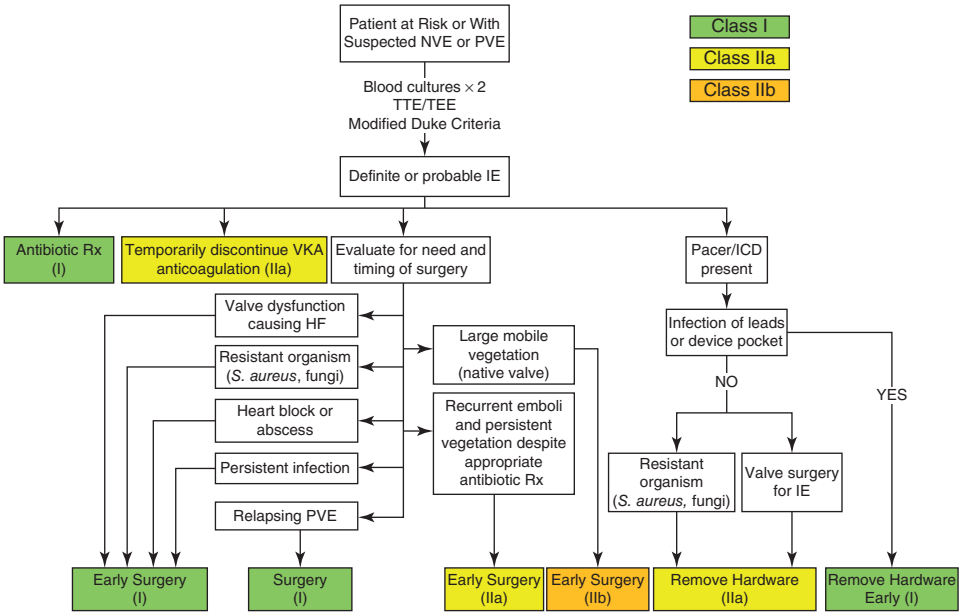

Figure 16.40 Diagnosis and treatment of IE (ICD: implantable cardioverter defibrillator). *Source:* adapted from Nishimura *et al.* (2014).

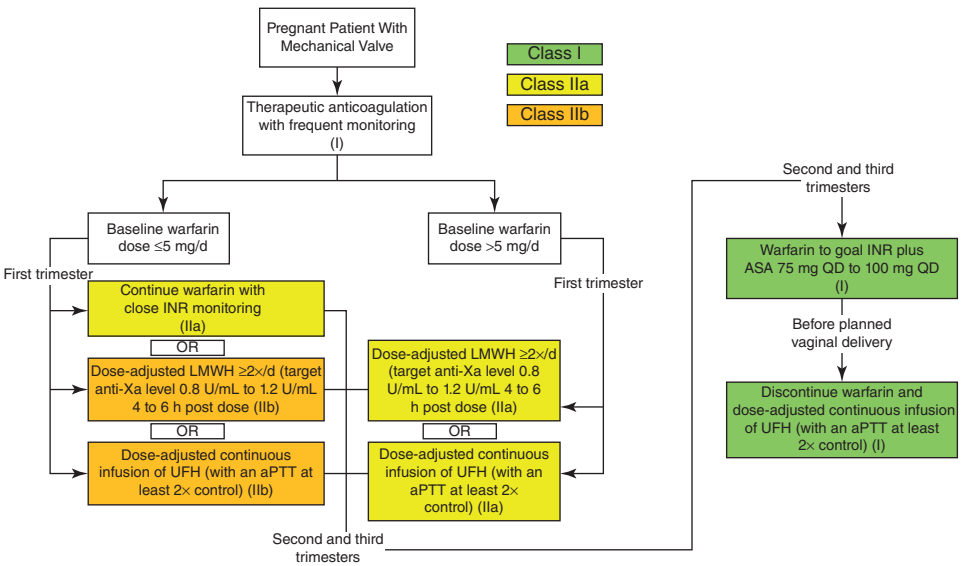

Figure 16.41 Anticoagulation of pregnant patients with mechanical valves (aPTT: activated PTT). *Source:* adapted from Nishimura *et al.* (2014).

on CW is faint, indicating that it is likely mild. The MS, however, seems to be significant and may be contributing to symptoms.

16.45. A. MS.
The m-mode of the MV shows slow EF slope and paradoxical anterior motion of posterior mitral leaflet indicating commissural fusion with posterior leaflet moving anteriorly with anterior leaflet during diastole. This is typical of MS – MS is likely to be severe as the EF slope is very flat and hence MV PHT is likely to be long.

16.46. B. First-degree atrioventricular (AV) block or long AV delay on pacemaker.
Note the diastolic TR indicating long AV delay. Also note the pacer lead.

16.47. C. Moderate PR.
The transvalvular velocity (1) is low, ruling out stenosis. The PR signal is quite dense, indicating that PR (2) is either moderate or severe. However, there is still an end-diastolic PR signal (3) after temporary interruption with right atrial systole. In severe PR, the signal generally ends in mid diastole due to PA/right ventricle diastolic pressure equilibration.

16.48. C. MS.
Note doming of the mitral leaflet and flow acceleration.

16.49. A. Acute severe AR.
Note the premature MV closure on MV m-mode and marked holodiastolic flow reversal in the aorta.

16.50. A. Acute severe AR.
Dense, rapidly decelerating AR signal indicates acute severe AR.

16.51. A. Severe paravalvular MR.
The measurement is of the MR vena contracta. Note that the MR jet reaches the posterior left atrial wall.

16.52. A. MV repair.
This is classical P2 flail, which is very amenable to repair.

16.53. A. Severe TR.
Note the vena contracta diameter of 15 mm and triangular TR signal indicating severe TR. Many times severe TR occurs because of flail TV because of damage to chords during endomyocardial bipospy or dilated tricuspid annulus.

16.54. B. Proceed with TAVR using carotid protection.
We did this. The mobile mass on the aortic valve did not embolize and got crushed against the aortic wall. The patient had no signs of endocarditis. Masses on aortic valve like this seem to embolize very rarely. We avoided aortic valve predilation to minimize embolic risk as well.

16.55. A. Severe stenosis.
Note a mean gradient of 29 mmHg and PHT of 374 ms.

16.56. A. Severe subvalvular AS.
The arrow points to the membrane in the LVOT. Note that the aortic valve opens well.

16.57. A. Critical AS with high LA pressure.

Note that V2 is >5 m/s and the calculated AVA is ≪ 0.7 cm^2, indicating critical AS. The patient is in sinus rhythm, but has no "A" wave and has very rapid E wave deceleration, indicating very high LA pressure.

16.58. A. IV thrombolytic.

As the operating room was not available and patient was worsening very rapidly, we took this approach. The patient had dramatic improvement within 30 min without any neurological sequelae. The arrow points to a large thrombus on the valve, and Doppler signals are indicative of severe obstruction.

16.59. A. Thrombus or pannus on a bileaflet mechanical MV.

This is the LA side of the bileaflet mechanical MV with completely opened discs.

16.60. D. All of the above.

16.61. A. Severe valvular AS.

There is a peak-to-peak gradient of about 80 mmHg. In the post premature atrial contraction beat (though not post premature ventricular contraction), the gradient increases with an increase in aortic pulse pressure, suggesting it is not HOCM. In HOCM, the pulse pressure drops (Brockenbrough phenomenon). In subvalvular AS, as long as the distal catheter is still in the LV, the diastolic pressure would be same as main body of the LV.

16.62. A. Critical AS, high gradient despite low flow.

There is critical AS as the AVA by the continuity equation is 0.5 cm^2 ($3.14 \times 12.8/81$). The gradient is high as the peak gradient is >64 mmHg and the mean gradient is 40 mmHg. The stroke volume is low at 40 cm^3 (3.14×12.8) or 22 cm^3/m^2, but this has not lowered the gradient, suggesting the critical nature of AS. The gradient is proportional to the square of the flow following the Bernoulli equation. Low flow is defined as stroke volume index <35 cm^3/m^2.

16.63. C. Refer for valve sparing root and ascending aortic replacement with coronary implantation.

Ascending aortic dimension >50 mm is an indication for surgery as the risk of rupture and dissection increases markedly at this point. If the aortic dimension was <50 mm, follow-up at 6 months for aortic growth rate would have been appropriate. He is well beta blocked.

Box 16.1 AHA/ACC 2014 Valve Guidelines

Staging of valve disease (A to D) in Nishimura *et al.* (2014) is new compared with the 2008 guidelines. Generally, if the valve disease is severe and symptomatic, there is an indication for intervention; if the valve disease is severe, asymptomatic, and there is no damage to the heart, there is no indication for intervention; if the valve disease is severe, asymptomatic, and there is damage to the heart, then there is an indication for intervention; if the valve disease is severe, asymptomatic, there is no damage to the heart, but the patient is undergoing another heart surgery, there is an indication for intervention. In other words, in asymptomatic severe disease, there is indication for intervention or surgery if there is damage to the heart or the patient is undergoing another heart surgery.

Box 16.2 Meta-analysis of Aortic Valve Replacement

The meta-analysis by Dayan *et al.* (2015) analyzed studies of mortality and survival impact of AVR in patients with low-gradient (LG) AS and preserved left ventricular EF, including paradoxical low-flow (i.e., stroke volume index <35 mL/m^2), low-gradient (LF-LG) and normal-flow, low-gradient (NF-LG), and those with high-gradient (≥40 mmHg) AS or moderate AS. Eighteen studies were included in the analysis. Patients with LF-LG AS have increased mortality compared with patients with moderate AS (hazard ratio (HR): 1.68; 95% confidence interval (CI): 1.31–2.17), NF-LG AS (HR: 1.80; 95% CI: 1.29–2.51), and high-gradient AS (HR: 1.67; 95% CI: 1.16–2.39). AVR was associated with reduced mortality in patients with LF-LG (HR: 0.44; 95% CI: 0.25–0.77). Similar benefit occurred with AVR in patients with NF-LG (HR: 0.48; 95% CI: 0.28–0.83). Compared with patients with high-gradient AS, those with LF-LG AS were less likely to be referred to AVR (odds ratio: 0.32; 95% CI: 0.21–0.49).

References

Dayan, V., Vignolo, G., Magne, J., *et al.* (2015) Outcome and impact of aortic valve replacement in patients with preserved LVEF and low-gradient aortic stenosis. *Journal of the American College of Cardiology*, **66**(23): 2594–2603.

Nishimura, R.A., Otto, C.M., Bonow, R.O., *et al.* (2014) 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*, **63**: e57–e185.

Adult Congenital Heart Disease

17

17.1. What are the most common lesions associated with Noonan syndrome?
- **A.** Pulmonary stenosis (PS) and atrial septal defect (ASD)
- **B.** Ventricular septal defect (VSD)
- **C.** Patent ductus arteriosus (PDA)
- **D.** Coarctation of aorta and aortic stenosis (AS)

17.2. What is the most common lesion associated with Williams syndrome?
- **A.** VSD
- **B.** Supravalvular AS
- **C.** Valvular AS
- **D.** ASD

17.3. What are the most common anomalies seen in DiGeorge syndrome (22q11)?
- **A.** VSD and arch anomalies
- **B.** Pulmonary valve stenosis
- **C.** ASD
- **D.** Supravalvular AS

17.4. What is the most common congenital heart lesion seen in Holt–Oram syndrome?
- **A.** Arch anomalies
- **B.** Coarctation of aorta
- **C.** ASD
- **D.** AS

17.5. What is the most common cardiac anomaly seen in Turner syndrome?
- **A.** Coarctation of aorta
- **B.** Tetralogy of Fallot (TOF)
- **C.** VSD
- **D.** Partial anomalous pulmonary venous drainage

17.6. Bicuspid aortic valves are seen in what percentage of the population?
- **A.** 4–6%
- **B.** 20%
- **C.** 1–2%
- **D.** 10%

17.7. Of the total number of congenital heart defects, simple shunts (ASD, VSD, PDA) are seen in what proportion of them?
- **A.** 75%
- **B.** 25%
- **C.** 50%
- **D.** 90%

17.8. Which of the following congenital cardiac lesions are seen in trisomy 21?
- **A.** VSD
- **B.** Atrioventricular (AV) canal defects
- **C.** ASD
- **D.** All of the above
- **E.** None of the above

17.9. Which of the following congenital cardiac defects are seen in trisomy 13?
- **A.** VSD
- **B.** PDA
- **C.** Dextrocardia
- **D.** All of the above
- **E.** None of the above

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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17.10. Which of the following congenital lesions are not seen in trisomy 18?

A. VSD
B. PDA
C. PS
D. AS

17.11. What is the chamber that dilates in a patient with a significant VSD?

A. Right atrium
B. Right ventricle
C. Left atrium and left ventricle
D. Left ventricle

17.12. What is the most common lesion that is associated with supracristal VSD?

A. AS
B. Aortic regurgitation
C. Pulmonary regurgitation (PR)
D. PS

17.13. A patient has a small restrictive perimembranous VSD. The velocity across the defect is 5 m/s. Blood pressure (BP) recorded at the time of the echocardiogram is 125/75 mmHg. What is the right ventricular (RV) systolic pressure?

A. 40 mmHg
B. 25 mmHg
C. 100 mmHg
D. 125 mmHg

17.14. A patient has a small perimembranous VSD. He is undergoing dental work. His dentist recommends him to see you regarding endocarditis prophylaxis. What would your recommendation be?

A. Amoxicillin 2 g prior to commencement of dental work
B. vancomycin 1 g IV prior to dental work
C. Clindamycin 600 mg prior to dental work
D. No antibiotic prophylaxis is indicated at this time

17.15. The short view of pulmonary artery (PA) branching and continuous-wave Doppler signal through the area of abnormal color flow in Figure 17.15 shows which of the following?

A. ASD
B. VSD
C. PDA
D. Coarctation of aorta

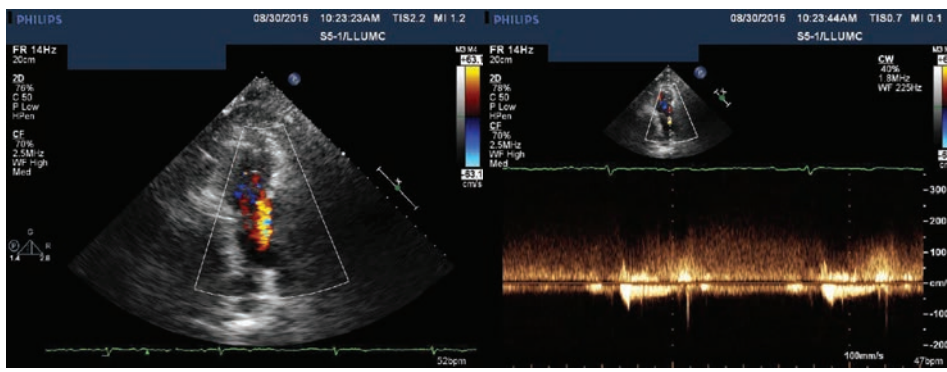


Figure 17.15

17.16. A 26-year-old patient is referred to you for a murmur. A transthoracic echocardiogram (TTE) is performed which fails to show any valvular pathology or a shunt lesion. The TTE is remarkable for dilatation of right atrium and right ventricle. What would the next step be?

A. Reassure the patient; no further test is needed
B. Cardiac catheterization
C. Transesophageal echocardiogram (TEE)
D. Cardiac magnetic resonance imaging (MRI)

17.17. A sinus venosus ASD is commonly associated with which of the following?

A. Cleft mitral valve
B. Partial anomalous pulmonary venous drainage
C. Persistent left superior vena cava (SVC)
D. Goose-neck deformity

17.18. In the patient mentioned in Question 17.16, a TEE was performed which showed a sinus venosus ASD with a partial anomalous venous return of the right upper pulmonary vein. What is the next step in management?

A. Cardiac catheterization to evaluate Qp/Qs
B. Cardiac MRI
C. Cardiac computed tomography (CT)
D. Consultation with a CT surgeon
E. Referral for percutaneous closure of the ASD

17.19. Secundum ASDs make up what proportion of ASDs?

A. 90%
B. 25%
C. 80%
D. 75%

17.20. A primum ASD is associated commonly with which of the following?

A. Left axis deviation on surface electrocardiogram (ECG)
B. Cleft of the anterior mitral leaflet
C. Left axis deviation and cleft mitral leaflet
D. Persistent left SVC

17.21. A patient with hypertension is diagnosed with coarctation of the aorta. What is the most common associated finding one should look for?

A. Pulmonary valve stenosis
B. Bicuspid aortic valve
C. Cleft mitral valve
D. Ebstein's anomaly

17.22. A patient is diagnosed with a PDA. The peak systolic gradient across the defect is 105 mmHg. No other abnormality is noted on the echocardiogram. The BP recorded at the time of the echocardiogram is 130/77 mmHg. Based on the data given, what does the patient have?

A. Suprasystemic RV pressure
B. Normal RV pressure.
C. Systemic RV pressure
D. Cannot tell

17.23. Which of the following does TOF not include?

A. Overriding of the aorta
B. RV hypertrophy
C. PS
D. VSD
E. ASD

17.24. Which of the following is an anomaly that should be sought out in a patient with TOF being referred for surgical repair?

A. Anomalous origin of left anterior descending (LAD) artery from right coronary artery (RCA)
B. Anomalous RCA from LAD
C. Anomalous left circumflex artery from RCA
D. None of the above

17.25. A patient with a history of repaired TOF is referred to you for complaints of fatigue and lack of exercise tolerance. Her echocardiogram shows moderate RV enlargement with mild hypokinesis. What is the probable cause of her right-sided enlargement?

A. Severe tricuspid regurgitation (TR)
B. Severe pulmonary valve regurgitation
C. Severe mitral regurgitation
D. Severe aortic regurgitation

17.26. What is the treatment of choice for the correction of dextro (D)-transposition of great arteries (TGA)?

A. Senning procedure
B. Mustard procedure
C. Jatene arterial switch
D. Rastelli procedure

17.27. What is the position of the aorta in D-TGA?

A. Central
B. Anterior and rightward
C. Anterior and leftward
D. Posterior

17.28. What is the position of the aorta in levo (L)-TGA?

A. Anterior and rightward
B. Anterior and to the left
C. Central
D. Posterior

17.29. In what percentage of patients with L-TGA is complete heart block seen?

A. 90%
B. 30%
C. 50%
D. 10%

17.30. Ebstein's anomaly can be seen in up to what proportion of patients with L-TGA?

A. 100%
B. 90%
C. 80%
D. 25%

17.31. The classic Blalock–Taussig shunt is a connection between which of the following?

A. Ascending aorta to PA
B. Subclavian artery to PA
C. Descending aorta to left PA
D. SVC to right PA

17.32. What is a Rastelli repair?

A. Closure of VSD and placement of right ventricle–PA conduit
B. Balloon atrial septostomy
C. Repair of VSD
D. Repair of ASD

17.33. The Fontan operation is used to repair which of the following defects?

A. Hypoplastic left heart syndrome
B. Triscuspid or mitral atresia
C. Hypoplastic right heart syndrome
D. Double inlet single ventricle
E. None of the above
F. All of the above

17.34. Right aortic arch is associated with which of the following?

A. TOF
B. Truncus arteriosus
C. Pulmonary atresia
D. None of the above
E. All of the above

17.35. A patient with a history of a Fontan operation presents with complaints of edema. On examination he has ascites, and his serum chemistry is significant for a low albumin level. What does this patient have?

A. Celiac disease
B. Pericardial constriction
C. Renal failure
D. Protein-losing enteropathy

17.36. Which of the following is/are a current class I indication regarding surgery for anomalous coronary arteries?

A. An anomalous left main coronary artery coursing between the aorta and PA
B. Ischemia caused by coronary compression (when coursing between the great arteries or has an intramural course)
C. An anomalous RCA between aorta and PA causing ischemia
D. All of the above
E. None of the above

17.37. Which of the following is not a class I indication regarding congenital heart disease in an adult >40 years of age?

A. Atrial level shunts with right ventricle enlargement and without pulmonary arterial hypertension (PAH) are recommended closure to prevent right ventricle failure, improve exercise capacity, and decrease atrial arrhythmia
B. Intervention is recommended for coarctation with obstruction for palliation of hypertension
C. Complex congenital heart disease with de novo presentation should receive comprehensive care at an adult congenital heart disease (ACHD) center with multidisciplinary input
D. In adults with a new presentation of a simple shunt or valve lesion and no hemodynamic compromise, evaluation by a general cardiologist in consultation with an ACHD cardiologist is reasonable
E. Patients with newly diagnosed coronary artery anomalies should be evaluated by an ACHD team with expertise in imaging, coronary artery disease management, intervention, and surgical revascularization

17.38. Regarding hypertension and coarctation of aorta, which of the following is the true statement?

A. The prevalence of hypertension is higher with later repair
B. The prevalence of hypertension is lower regardless of age of repair
C. The prevalence of hypertension is similar to people with no coarctation
D. Hypertension is not a problem after repair

17.39. Regarding the use of angiotensin-converting-enzyme (ACE) inhibitors in coarctation of the aorta, which of the following is the true statement?

A. ACE inhibitors have no known side effect in patients with coarctation of aorta
B. ACE inhibitors have been reported to precipitate acute renal failure in the setting of coarctation
C. Neither A nor B
D. Both A and B

17.40. Regarding screening for diabetes in ACHD, which of the following is the true statement?

- **A.** Screening for diabetes mellitus should be undertaken in patients >40 years, body mass index >25 kg/m^2 with or without risk factors
- **B.** Appropriate screening can include fasting glucose, hemoglobin A1C, or 2-h 75 g oral glucose tolerance test
- **C.** If tests are normal, repeat testing at 3-year intervals
- **D.** All of the above
- **E.** None of the above

17.41. Regarding arrhythmias in ACHD, the following are true except:

- **A.** Wolff–Parkinson–White syndrome and accessory-pathway-mediated tachycardia are associated with Ebstein anomaly
- **B.** The most common arrhythmia facing older adults with congenital heart disease is intra-atrial reentrant tachycardia (IART)
- **C.** The highest incidence of IART is seen in those who have undergone Mustard or Senning repair for D-TGA or the Fontan procedure for single-ventricle physiology
- **D.** In the older adults, ventricular tachycardia (VT) is seen in patients with repaired TOF
- **E.** All of the above
- **F.** None of the above

17.42. Which of the following are true regarding pulmonary disease in ACHD?

- **A.** Clinicians should have a low threshold for assessing patents with ACHD for PAH, with echocardiogram and hemodynamic cardiac catheterization
- **B.** Patients with Eisenmenger's should be followed up closely by an ACHD specialist
- **C.** Treatment of PAH in the setting of ACHD with pulmonary vasodilator drugs can be useful and may lead to functional improvement
- **D.** It is reasonable to consider serial evaluations of lung function in all adults with CHD
- **E.** All of the above

17.43. Which of the following are true regarding recommendations for liver disease in ACHD?

- **A.** Serial evaluation of liver function should be performed in all patients with a previous history of Fontan palliation
- **B.** Patients with palliation for CHD prior to 1992 should be screened for hepatitis C
- **C.** Gallstones necessitating cholecystectomy are seen with increasing frequency in ACHD patients
- **D.** All of the above
- **E.** None of the above

17.44. Which of the following are not true regarding renal disease in ACHD?

- **A.** Renal function should be routinely assessed in all patients with moderate to complex CHD
- **B.** In the presence of renal dysfunction, all effort must be made to minimize additional renal injury

C. Novel biomarkers such as urinary interleukin 18 and neutrophil gelatinase-associated lipocalin may be predictive of acute kidney injury
D. Renal dysfunction is not a poor prognostic marker in patients with ACHD

17.45. Which of the following is not a class I recommendation regarding diagnostic testing in an ACHD patient?
A. Echocardiography in the ACHD patient should be interpreted by physicians with expertise in both acquired and congenital heart disease
B. Echocardiography reporting should include both anatomic diagnoses and quantitative assessment of chambers, valves, and great vessels in a format accessible to physicians caring for ACHD patients
C. Diagnostic cardiac catheterization in the older adult with CHD should use a team approach that includes interventionalists skilled in the evaluation of the physiology associated with CHD, as well as being skilled in selective coronary angiography.
D. Sixty-four detector row or higher computed tomography angiography can be useful in lieu of invasive coronary angiography to exclude important coronary artery disease when the pretest probability is low to intermediate.

17.46. TOF may be associated with which of the following genetic defects?
A. Point mutation in major histocompatibility complex gene
B. 22q11 deletion
C. 9–22 translocation
D. None of the above

17.47. In a patient who had complete repair of TOF, which of the following sequelae may exist?
A. PR or pulmonary stenosis
B. Branch PA stenosis
C. VSD
D. Aortic regurgitation
E. All of the above.

17.48. In a 19-year-old patient with severe asymptomatic PR post TOF repair, what would be the best monitoring strategy in addition to symptoms and heart failure?
A. Serial TTE with monitoring of right ventricle diameter
B. Annual cardiac CT scan for right ventricle volume and ejection fraction (EF)
C. Annual cardiac MRI for right ventricle volume and EF
D. Clinical follow-up alone

17.49. What are the indications for redo surgery in a TOF patient with prior repair?
A. Severe symptomatic PR or severe PR with RV dysfunction
B. Valvular or subvalvular PS with a gradient of >50 mmHg or RVOT obstruction with RV dysfunction
C. Residual VSD with a shunt ratio of >1.5
D. Severe aortic regurgitation with LVEF <50%
E. All of the above
F. None of the above.

17.50. The electrical abnormalities post TOF repair include which of the following?
A. VT and sudden death
B. Atrial flutter or fibrillation
C. Right bundle branch block
D. AV block
E. All of the above
F. None of the above

17.51. Which of the following are predictors of sudden death post TOF repair?

A. Severe PR
B. RV dilation or dysfunction
C. QRS duration of >180 ms
D. Nonsustained VT
E. Syncope
F. All of the above

17.52. An 18-year-old patient with prior Mustard procedure for TGA has developed facial swelling with suffusion. The jugular venous pressure is markedly raised. There is no edema, liver is normal sized, and there are no murmurs. What is the likely explanation?

A. Constrictive pericarditis
B. Failure of subpulmonic ventricle
C. Baffle obstruction
D. Systolic anterior motion (SAM) with dynamic subpulmonic obstruction

17.53. What is the frequency of baffle leaks post Mustard procedure?

A. 5%
B. 25%
C. 50%
D. 90%

17.54. What are the consequences of baffle leaks post Mustard procedure?

A. May be none
B. Systemic desaturation
C. Paradoxical embolization
D. All of the above

17.55. What do the potential consequences of atrial switch operation include?

A. Obstruction to systemic venous baffle
B. Baffle leak
C. Stenosis of pulmonary venous baffle
D. Failure of systemic ventricle and TR
E. Dynamic subpulmonic obstruction due to SAM
F. Atrial arrhythmias and AV conduction defects
G. All of the above.

17.56. Potential complications after arterial switch operation for TGA include which of the following?

A. Stenosis of pulmonary arterial anastomosis site
B. Aortic aneurysm
C. Coronary artery stenosis
D. Neo-aortic regurgitation (native pulmonary valve)
E. All of the above

17.57. What percentage of patients with Ebstein's anomaly may have right-to-left shunt at atrial level?

A. 0%
B. 0%
C. 50%
D. 90%

17.58. Ebstein's anomaly may involve which of the following changes to the tricuspid valve?

A. Adherence of the tricuspid valve leaflets to the underlying myocardium or failure of delamination
B. Apical displacement into the right ventricle of the septal and posterior leaflets of the tricuspid valve below the AV junction resulting in atrialization of right ventricle
C. Redundancy, tethering, and fenestrations of the anterior tricuspid valve leaflet
D. All of the above

17.59. The ECG changes in Ebstein's anomaly may include which of the following
- **A.** Pre-excitation due generally to a right-sided accessory pathway
- **B.** Giant P wave
- **C.** QR pattern in V1 to V4
- **D.** All of the above

17.60. The 19-year-old patient in Figure 17.60 presented with shortness of breath and large RV and RA, PA systolic pressure of 30 mmHg. What would the definitive treatment be?
- **A.** Annual follow-up
- **B.** Surgical repair
- **C.** Percutaneous closure
- **D.** None of the above

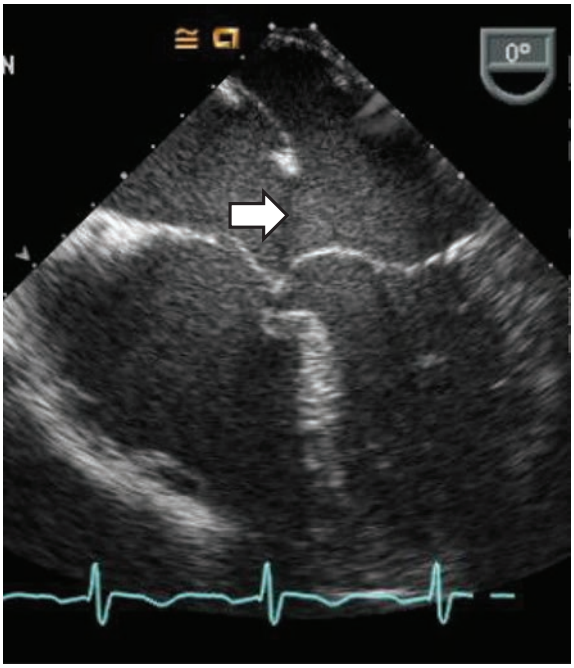


Figure 17.60

17.61. What type of ASD is shown in Figure 17.61?
- **A.** Secundum ASD
- **B.** Primum ASD
- **C.** Sinus venosus ASD of IVC type
- **D.** Sinus venosus ASD of SVC type

17.62. What condition does the patient in Figure 17.62 have?
- **A.** Sinus venosus ASD with anomalous drainage of right upper pulmonary vein
- **B.** Sinus venosus ASD with anomalous drainage of right lower pulmonary vein
- **C.** Secumdum ASD
- **D.** None of the above

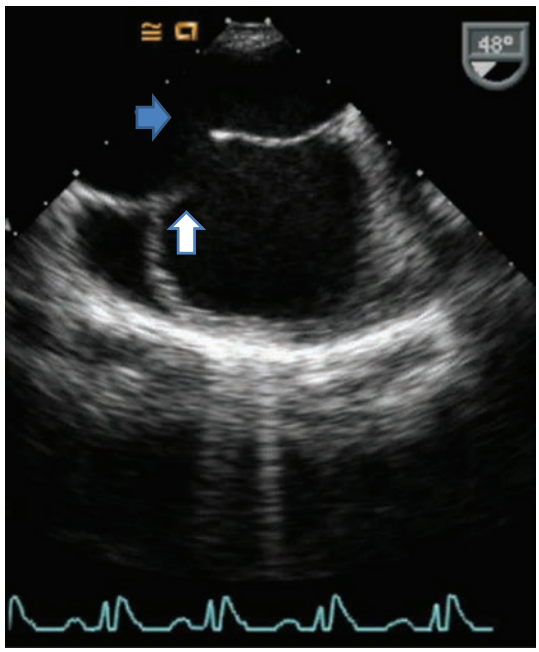


Figure 17.61

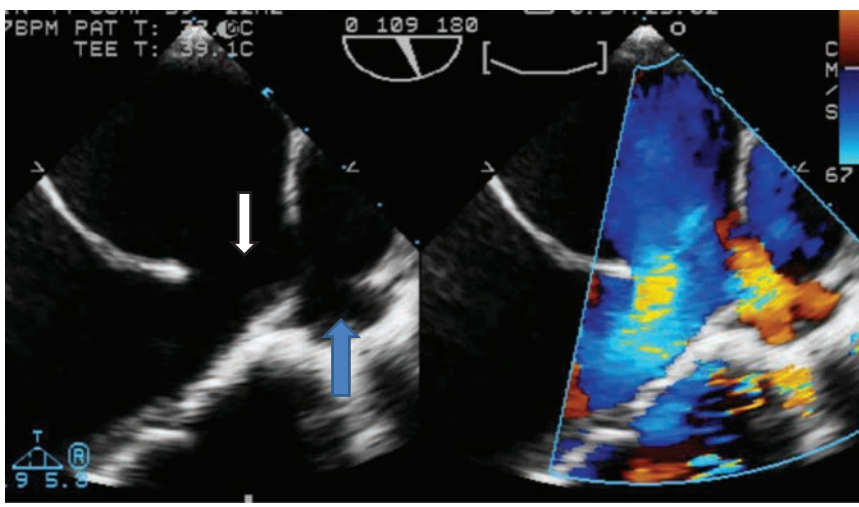


Figure 17.62

17.63. What procedure did the patient in Figure 17.63 have?

- **A.** Closure of secundum ASD with Amplatzer device
- **B.** Closure of patent foramen ovale (PFO) with Amplatzer device
- **C.** Surgical patch of ASD
- **D.** None of the above

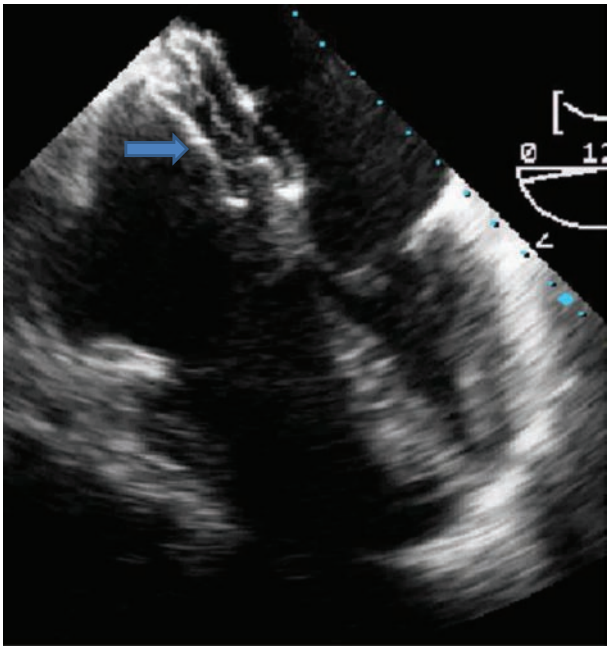


Figure 17.63

17.64. The CW Doppler signal in Figure 17.64 was obtained from a suprasternal window. What is it indicative of?

A. Aortic coarctation
B. PDA
C. Coronary stenosis
D. None of the above

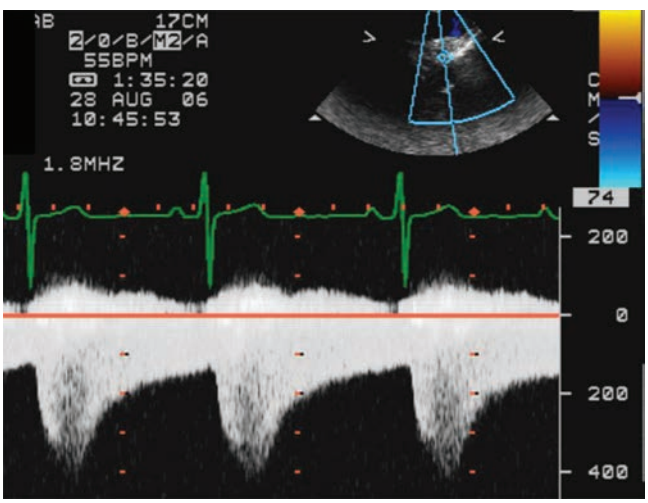


Figure 17.64

17.65. What does the patient in Figure 17.65 have? (DTA: descending thoracic aorta; MPA: main PA; RPA: right PA)

A. PDA
B. PR
C. PS
D. None of the above

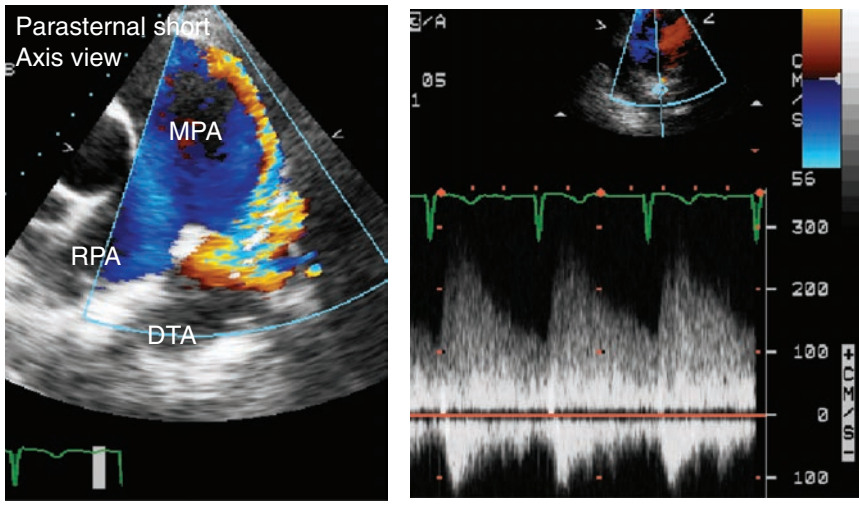


Figure 17.65

17.66. What does the patient in Figure 17.66 have?

A. Congenitally corrected great arteries
B. D-TGA
C. Ebstein's anomaly
D. None of the above

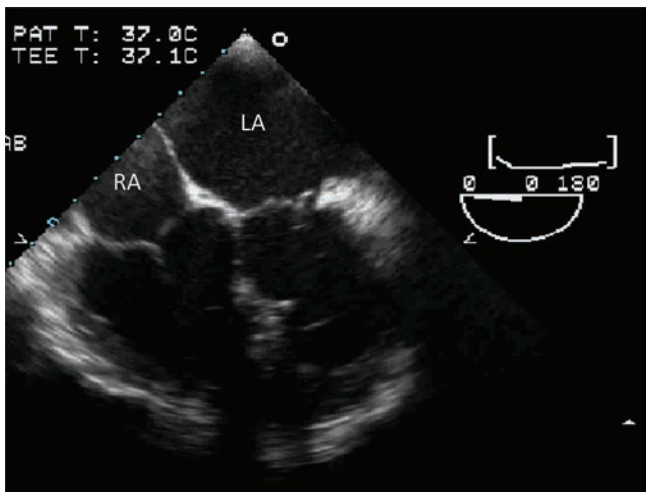


Figure 17.66

17.67. The TEE image in Figure 17.67a (LA: left atrium) is diagnostic of what?

A. Congenitally corrected transposition of great arteries
B. TGA, status post arterial switch
C. Normal anatomy
D. None of the above

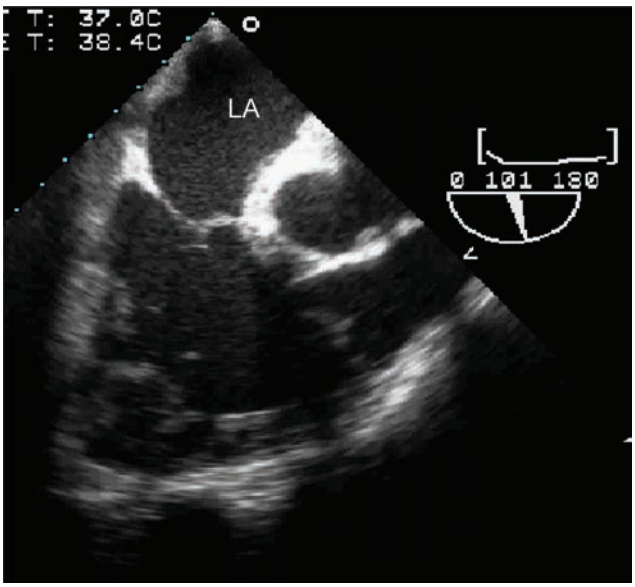


Figure 17.67a

17.68. The patient shown in Figure 17.68 (LA: left atrium; LV: left ventricle; MV: mitral valve; RA: right atrium; RV: right ventricle; TV: tricuspid valve) has what condition?

A. D-TGA with atrial switch
B. L-TGA
C. Cor tiatriatum
D. None of the above

17.69. What procedure is the patient in Figure 17.69 (LV: left ventricle; RV: right ventricle) likely to have had?

A. Congenitally corrected TGA
B. D-TGA with atrial switch
C. D-TGA with arterial switch
D. None of the above.

17.70. Which of the following statements are true about the patient in Figure 17.70a? (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle)

A. The patient may have severe TR and heart failure
B. The patient may be cyanotic
C. The patient may present with atrial arrhythmias and reentrant arrhythmias due to accessory pathways
D. All of the above

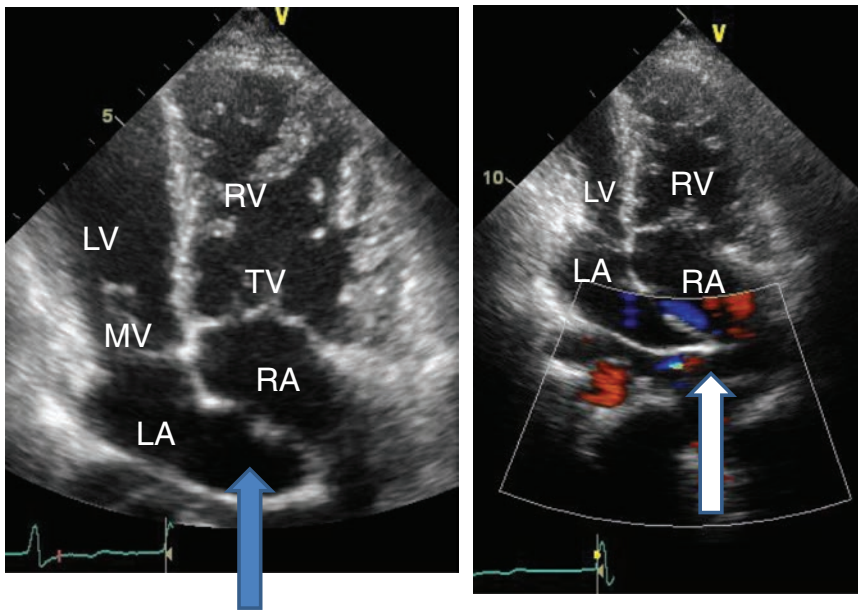


Figure 17.68

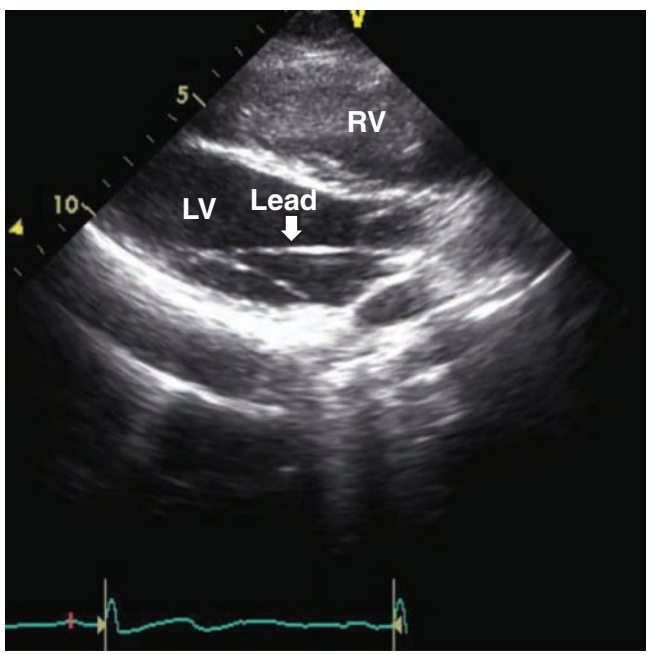


Figure 17.69

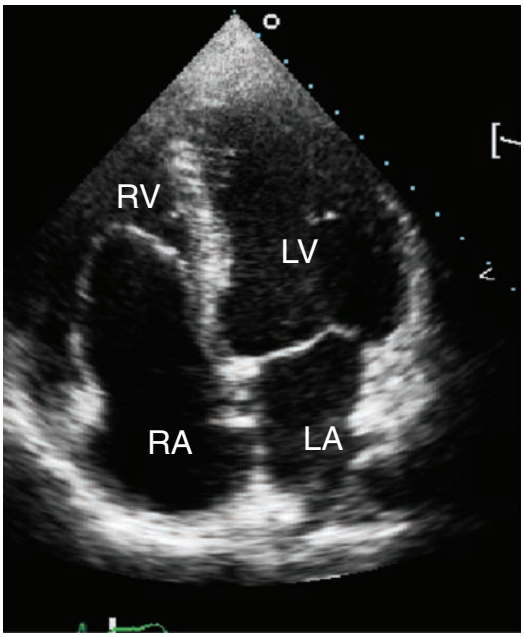


Figure 17.70a

17.71. A patient had surgery for cyanotic heart disease as a child. The CW Doppler signal from the pulmonary valve is shown in Figure 17.71. What has the patient most likely had?

A. TOF
B. Transposition of great vessels
C. Tricuspid atresia
D. Total anomalous pulmonary venous drainage

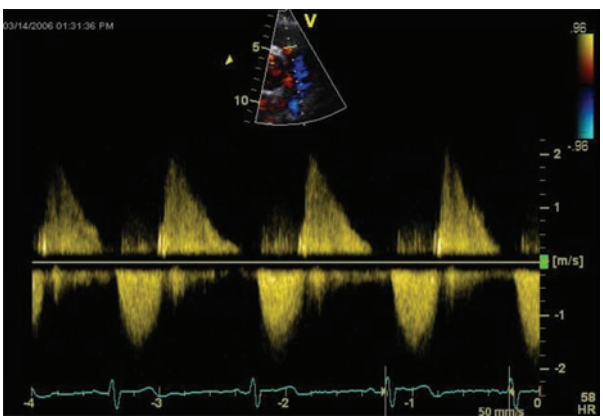


Figure 17.71

17.72. What is Figure 17.72 consistent with?

A. Aortic coarctation
B. Aortic interruption
C. PDA
D. A and B

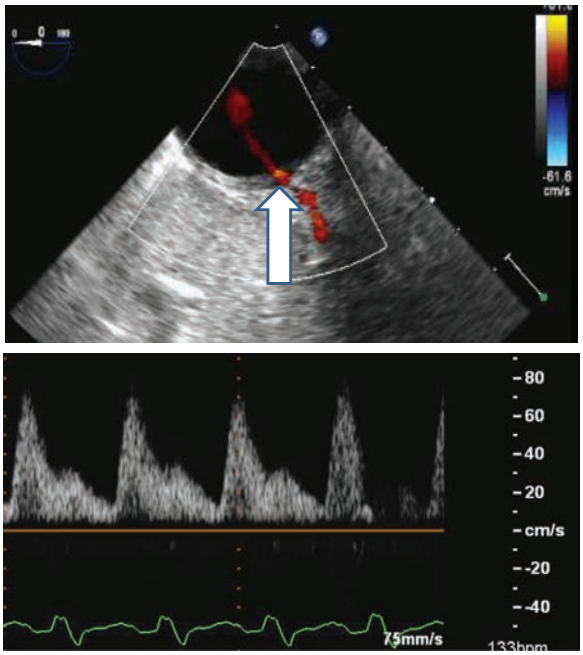


Figure 17.72

17.73. The TEE image in Figure 17.73 (Ao: aorta; LA: left atrium; LV: left ventricle) of the aortic annulus is suggestive of what?

A. Normal aortic annulus
B. Abscess
C. Anomalous coronary artery with retroaortic course
D. None of the above

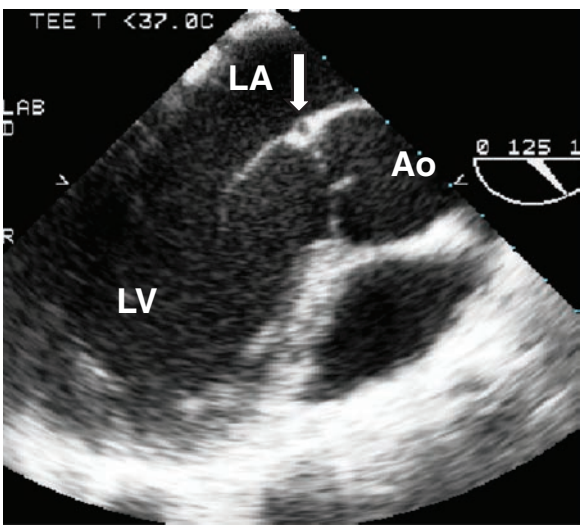


Figure 17.73

Answers

17.1. A. Pulmonary stenosis (PS) and atrial septal defect (ASD).

17.2. B. Supravalvular AS.
The second common associated defect is supravalvular PS.

17.3. A. VSD and arch anomalies.
The most common anomaly seen in DiGeorge syndrome is VSD, followed by arch anomalies. ASD and supravalvular AS are seen in this syndrome.

17.4. C. ASD.

17.5. A. Coarctation of aorta.
The most common congenital cardiac lesion associated with Turner syndrome (45X) is coarctation of aorta, followed by AS and then ASD.

17.6. C. 1–2%.

17.7. C. 50%.
Simple shunts, such as ASD, VSD, and PDA, are seen in about 50% of the congenital heart defects. Simple obstructions such as AS, PS, and coarctation of aorta are seen in about 20%, and complex lesions are seen in 30%.

17.8. D. All of the above.

17.9. D. All of the above.
In trisomy 13, the most lesions seen are VSDs followed by PDAs and then dextrocardia.

17.10. D. AS.
AS does not form a part of syndromic lesions in trisomy 18. The most common lesion noted is VSD, followed by PDA, and then PS.

17.11. C. Left atrium and left ventricle.
A significant VSD will cause enlargement of the left atrium as well as left ventricle. The blood goes across the shunt and is delivered to the lungs and then to the left atrium, which results in dilatation of this chamber.

17.12. B. Aortic regurgitation.
The most common associated finding seen in a supracristal VSD is aortic regurgitation, which occurs due to valve distortion.

17.13. B. 25 mmHg.
The left ventricle–right ventricle gradient across the VSD is $4 \times \text{VSD}^2$ that is, $4 \times 5 \times 5 = 100$ mmHg. The systolic BP is 125 mmHg. Right ventricular systolic pressure is then equivalent to 125–100 mHg, which calculates to 25 mmHg.

17.14. D. No antibiotic prophylaxis is indicated at this time.
According to the new endocarditis prophylaxis guidelines, a simple shunt such as a VSD does not warrant endocarditis prophylaxis (Wilson *et al.*, 2007).

17.15. C. PDA.
There is color flow in the PA and the accompanying Doppler shows continuous flow through systole and diastole, which is suggestive of a PDA.

17.16. C. Transesophageal echocardiogram (TEE).
The patient was referred for a murmur. The TTE is remarkable for dilatation of right-sided chambers. Though the TTE failed to show a shunt lesion, the TEE

should be performed to look for sinus venosus ASD or partial anomalous pulmonary venous drainage that can be easily missed on a TTE. The cause of right-sided dilatation needs to be worked up further, and hence just reassuring the patient is not sufficient.

17.17. B. Partial anomalous pulmonary venous drainage.

Sinus venosus ASD is most commonly associated with partial anomalous venous return of the pulmonary veins. Usually, the right upper pulmonary vein drains anomalously into the right atrium.

17.18. D. Consultation with a CT surgeon.

This patient has a sinus venosus ASD associated with partial anomalous drainage of the right upper pulmonary vein and significant shunt as judged by right ventricle size. This person should be referred to a cardiothoracic surgeon for a complete repair. No need for coronary angiogram as the patient is young.

17.19. D. 75%.

Secundum ASDs are the most common form.

17.20. C. Left axis deviation and cleft mitral leaflet.

A primum ASD is often associated with a left axis deviation on the surface ECG. The most common associated anomaly seen on echocardiogram is a cleft of the anterior mitral leaflet. In this abnormality the AV valves are at the same level and the left ventricular outflow tract is elongated and narrow, giving the characteristic "goose-neck" deformity. Primum ASDs constitute a partial AV canal defect.

17.21. B. Bicuspid aortic valve.

Bicuspid aortic valve is present in 50% of cases with coarctation of the aorta.

17.22. B. Normal RV pressure.

The peak gradient across the PDA is 105 mmHg and systolic BP is 120 mmHg. Right ventricular systolic pressure is 130-105 which is 25 mmHg, which is in the normal range.

17.23. E. ASD.

TOF includes four components: VSD, RV hypertrophy, PS, and overriding of the aorta. ASD is not commonly seen in classic TOF, but when it is present it is called pentalogy of Fallot.

17.24. A. Anomalous origin of left anterior descending (LAD) artery from right coronary artery (RCA).

Coronary artery anomalies are seen in 5% of TOF patients. The most common anomaly one should look out for is anomalous origin of the LAD artery from the RCA. This has great clinical implication. When surgery is performed on the RV outflow tract (RVOT), if an anomalous coronary artery is not identified, the surgeon may inadvertently cut it, leading to catastrophe.

17.25. B. Severe pulmonary valve regurgitation.

Patients who have undergone repair of TOF, especially pulmonary valvotomy or removal of pulmonary valve, will go on to develop severe PR later on. When there is evidence of RV enlargement, severe PR should be sought out on echocardiogram. Owing to the severity of PR, color flow can be misleading, but continuous-wave Doppler can correctly help in identifying severe PR. When severe PR causes

right-sided volume overload, pulmonary valve replacement is the treatment of choice.

17.26. C. Jatene arterial switch.

The procedure of choice to correct D-TGA is the Jatene arterial switch. The Senning and Mustard operations, which are atrial switch procedures, have largely been abandoned. The Rastelli procedure is usually done when there is associated pulmonary or subpulmonary stenosis, wherein a right ventricle–PA conduit is placed. This procedure may require conduit replacement and future operations.

17.27. B. Anterior and rightward.

Normally, the aorta is central and the PA wraps around it. In D-TGA, both the great arteries have a parallel course and the aorta is situated anterior and to the right of a centrally located PA.

17.28. B. Anterior and leftward.

Normally, the aorta is central and the PA wraps around it. In a levo-transposition, the great arteries have a parallel course. The aorta is anterior and to the left of a centrally located PA.

17.29. B. 30%.

Patients with L-TGA can have associated defects. One of them is rhythm abnormalities. The most common rhythm abnormality is complete heart block, which can be seen in 30% of the patients with L-TGA.

17.30. B. 90%.

Ebstein's anomaly of the systemic AV valve (morphologic tricuspid valve) can occur in up to 90% of patients with L-TGA. It is very important to recognize this anomaly as Ebstein's anomaly can result in severe valve regurgitation, which is less well tolerated and needs aggressive early intervention.

17.31. B. Subclavian artery to PA.

When a Gore-Tex interposition graft is used to anastomose the subclavian artery to the PA it is called modified Blalock–Taussig shunt. These two shunts are done to increase pulmonary blood flow in TOF patients. The ascending aorta to PA graft is called the central shunt. A descending aorta to left PA graft is called the Pott's shunt, while an ascending aorta to right PA graft is called a Waterston shunt. An SVC to right PA shunt is called a Glenn shunt, which is designed to provide flow to the PAs under lower pressure.

17.32. A. Closure of VSD and placement of a right ventricle–PA conduit.

Usually, this is undertaken when there is a VSD and associated subpulmonic or pulmonic stenosis. Balloon atrial septostomy is called the Rashkind procedure.

17.33. F. All of the above.

The Fontan operation is used to repair all of the listed congenital heart defects. The goal of the Fontan operation is to separate systemic and pulmonary circulations and also to remove excess load on a single pumping chamber. In this operation, the systemic blood is directed to the lungs either by a modified Fontan–Kreutzer operation using the right atrium to direct blood to the PAs or by total cavo-pulmonary anastomosis, wherein the inferior vena cava (IVC) and SVC are joined directly through a tunnel in the right atrium to the PAs. There is no pumping chamber to the pulmonary circuit, and the single ventricle then is allowed to

pump pulmonary venous blood to the body. The pulmonary flow is passive and depends upon venous pressure and will fail if there is an increase in pulmonary vascular resistance or left atrial pressure.

17.34. E. All of the above.

A right-sided aortic arch can be seen in 25% of cases with TOF and in about 40% of cases with pulmonary atresia.

17.35. D. Protein-losing enteropathy.

Patients with a history of Fontan surgery can present late in life with symptoms such as edema, ascites, and low albumin level, which is characteristic of protein-losing enteropathy. This condition carries a high mortality when present.

17.36. D. All of the above.

All of the above are *class I indications* for surgical intervention in the face of anomalous coronary arteries.

17.37. D. In adults with a new presentation of a simple shunt or valve lesion and no hemodynamic compromise, evaluation by a general cardiologist in consultation with an ACHD cardiologist is reasonable.

Class IIa, level of evidence C. All the others are class I indications.

17.38. A. The prevalence of hypertension is higher especially with later repair.

All the other statements are false (Webb, 2005; Kenny and Hijazi, 2011).

17.39. B. ACE inhibitors have been reported to precipitate acute renal failure in the setting of coarctation.

ACE inhibitors should be used with caution in patients with coarctation, especially if hemodynamically significant. This condition can mimic bilateral renal artery stenosis. ACE inhibitors have been known to precipitate acute renal failure because of already low flow to the renal arteries with significant coarctation (Woodmansey *et al.*, 1994).

17.40. D. All of the above.

According to the current ACHD guidelines (Bhatt *et al.*, 2015).

17.41. E. All of the above.

Association of accessory-pathway-mediated tachycardia is seen with Ebstein anomaly. Catheter ablation is curative in this setting, or intraoperative ablation can be performed when patients are undergoing surgery for valve repair/replacement. IART is the most common arrhythmia seen in older adults with coronary heart disease (CHD), which is a macroreentrant circuit within the atrial tissue that occurs due to patches, atriotomy incisions, and scars. Cavotricuspid-isthmus-dependent atrial flutter may be common, although unusual circuits are often present. Unlike the classic saw-tooth flutter waves occurring at 300 bpm, IART can be associated with varying P wave morphologies at 170–250 bpm, facilitating 1 : 1 conduction causing syncope, hypotension, and even death. Highest incidence of IART is seen post Mustard/Senning or Fontan procedure. Treatment could be elective electrical cardioversion after ruling out atrial thrombi with TEE and chronic AV nodal blockade. If accompanied by bradycardia, a pacemaker is helpful. VT is prototypically seen in patients with TOF. The classic presentation is a macroreentrant tachycardia seen as a late complication of ventriculotomy or VSD patch. These arrhythmias revolve around the RVOT).

Most of the VTs are rapid, causing cardiac arrest. In older adults with repaired TOF, sudden cardiac death is the most common cause of late mortality, with an incidence of 2%/decade, reaching 10% by 35 years after surgery. Older age at the time of repair, advanced RV dilatation, presence of an RVOT patch, QRS interval ≥180 ms, and annual increase in QRS interval are independent risk factors for the development of VT.

17.42. E. All of the above.

A and B are class 1 indications, level of evidence C. Options C and D are class IIa, level of evidence B.

17.43. D. All of the above.

17.44. D. Renal dysfunction is not a poor prognostic marker in patients with ACHD.

Renal dysfunction is actually a marker of poor prognosis in patients with ACHD. Over 6 years, mortality risk was fivefold higher in those with moderate to severe renal impairment and twofold higher with mild impairment compared with those with normal function.

17.45. D. Sixty-four detector row or higher computed tomography angiography can be useful in lieu of invasive coronary angiography to exclude important coronary artery disease when the pretest probability is low to intermediate.

This is class IIa, level of evidence C. The first three options are class I recommendations, level of evidence C.

17.46. B. 22q11 deletion.

Screening for mutations should be offered to all patients with TOF, and all patients, especially those with a heritable mutation, should be offered genetic counseling before a planned pregnancy.

17.47. E. All of the above.

PR jet may be transient when severe and can be missed with color flow imaging. Continuous-wave (CW) signal may show rapid deceleration and equilibration of pressure in PA and right ventricle in mid-diastole.

17.48. C. Annual cardiac MRI for right ventricle volume and EF.

Even in asymptomatic individuals, moderate or severe right ventricle enlargement or dysfunction is an indication for repair. TTE is not reliable, unless 3D echo is performed. Annual cardiac CT exposes the patient to lot of radiation as it has to be retrospectively gated for RV function analysis. In an asymptomatic patient with severe PR, any of the following two may constitute a reasonable indication for valve replacement: RV end-diastolic volume index EDVI >150 cm^3/m^2, RV end-systolic volume index >80 cm^3/m^2, RV/LV end-diastolic volume index ratio >2, RVEF <47%, QRSd >140 ms, RVOT aneurysm, tachyarrhythmias.

17.49. E. All of the above.

For obvious reasons! TOF patients are also prone to ascending aortic aneurysms and need to be monitored for this.

17.50. E. All of the above.

Mechanical correlates of VT include PR and RV dilation; mechanical correlates of atrial arrhythmia include TR.

17.51. F. All of the above.

17.52. C. Baffle obstruction.

The presentation is typical for obstruction to the superior limb of the baffle. This is a lot more common than obstruction to the inferior limb. Constriction would cause hepatomegaly and ascites as well. A small subpulmonic left ventricle may be predisposed to SAM and dynamic outflow obstruction, but this patient does not have any murmurs to suggest this. In addition, the features are not suggestive of heart failure and more of SVC syndrome.

17.53. B. 25%.

17.54. D. All of the above.

The risk of paradoxical embolism is increased by atrial arrhythmias, endocardial pacer leads, and venous thrombosis.

17.55. G. All of the above.

Baffle leak is assessed with saline contrast echocardiography.

17.56. E. All of the above.

17.57. C. 50%.

17.58. D. All of the above.

17.59. D. All of the above.

17.60. B. Surgical repair.

The arrow in Figure 17.60 points to ostium primum ASD in the lower part of the septum. The patient has volume overload with normal PA pressure and has an indication for closure. This is not amenable to percutaneous closure, unlike a secundum ASD.

17.61. C. Sinus venosus ASD of IVC type.

In Figure 17.61, the blue arrow points to the defect and the white arrow to the Eustachian valve, and the IVC is to the left of that.

17.62. A. Sinus venosus ASD with anomalous drainage of right upper pulmonary vein.

The white arrow is pointing to the ASD and blue arrow to right upper pulmonary vein. This is not amenable to percutaneous closure either.

17.63. A. Closure of secundum ASD with Amplatzer device.

The arrow in Figure 17.63 points to the device. In the ASD device the left disc is larger than the right, as in this case. In a PFO closure device, the right disk is larger.

17.64. A. Aortic coarctation.

Note that the systolic gradient is about 64 mmHg and there is a gradient throughout diastole. This is indicative of severe aortic coarctation.

17.65. A. PDA.

The color jet on the left panel coming from the arch–DTA junction into the PA is classic for PDA. Note that the flow is continuous, as shown on the CW Doppler signal on the right.

17.66. A. Congenitally corrected great arteries.

Note that the left AV valve is more apical, indicating that it is the tricuspid valve and the ventricle that goes with it is the right ventricle. Hence, the mitral valve and morphological LV are on the right side. There is AV discordance. This would

in addition be associated with ventriculoarterial discordance (right ventricle to aorta and left ventricle to PA), with the two wrongs making a right, and the circulation would be normal except that the systemic ventricle is morphologically right ventricle and systemic AV valve is a tricuspid valve. There is higher risk of TR and right ventricle (systemic ventricle) failure in these patients.

17.67. A. Congenitally corrected transposition of great arteries.

As shown in the Figure 17.67b and 17.67c (AO: aorta; LA: left atrium; LV: left vent; RA: right atrium; RV: right ventricle), the left atrium is connected to the right ventricle and anterior aorta, and the right atrium is connected to the left ventricle and posterior PA. Also note a pacer lead in the right atrium.

Figure 17.67b

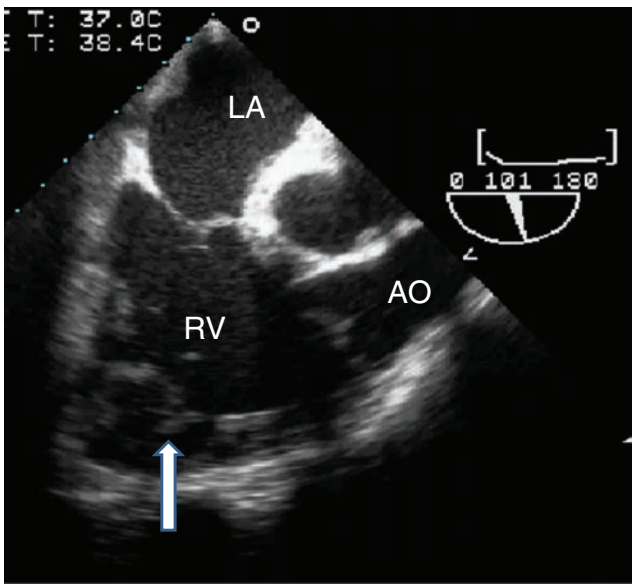
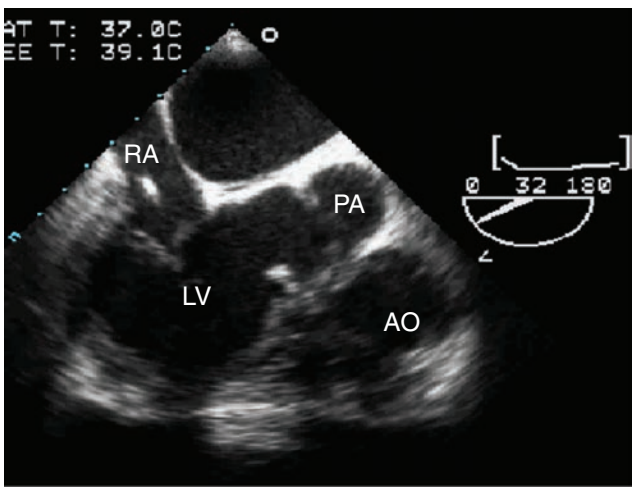


Figure 17.67c



17.68. A. D-TGA with atrial switch.

Note that the right atrium is connected to the right ventricle but gets pulmonary venous blood (white arrow in Figure 17.68) and left atrium is connected to smaller, smoother-walled left ventricle and receives vena caval blood (blue arrow in Figure 17.68). The nature's "wrong" is ventriculoarterial discordance; that is, right ventricle connected to aorta and left ventricle connected to PA. Atrial switch is "man made wrong" and the two wrongs make one right. As the morphological right ventricle is the systemic ventricle, it is prone to dysfunction, and TR can occur as well.

17.69. B. D-TGA with atrial switch.

Note the pacer lead in the left ventricle (smooth walled), indicating that it pumps into the pulmonary circulation. This is indicative of atrial switch. In arterial switch, the left ventricle would pump into the aorta. In L-TGA or congenitally corrected TGA the posterior ventricle would be a morphological right ventricle, which pumps into the aorta.

17.70. D. All of the above.

This patient has Ebstein's anomaly with apical displacement of septal tricuspid leaflet and large sail-like anterior leaflet (arrow in Figure 17.70b). About 25% have accessory pathways, mostly right, and 50% have PFO or ASD, facilitating right-to-left shunting. See Figure 17.70b (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; RVa: atrialized right ventricle; TV: tricuspid valve). Note that a large portion of right ventricle is atrialized (RVa).

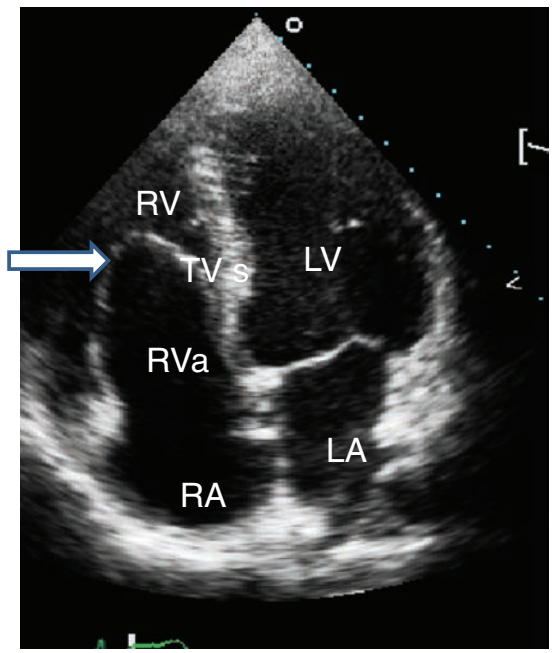


Figure 17.70b

17.71. A. TOF.

Figure 17.71 shows severe PR, which is an important sequela of TOF repair.

17.72. D. A and B.

Note the retrograde flow (arrow in Figure 17.72) into descending thoracic aorta from intercostal arteries suggestive of collateral dependent flow in distal thoracic aorta. This is suggestive of severe aortic coarctation or aortic interruption. This patient had the latter.

17.73. C. Anomalous coronary artery with retroaortic course.

The arrow in Figure 17.73 points to a rounded structure. This was anomalous circumflex originating from the RCA with retroaortic course discovered incidentally during a TEE for suspected endocarditis.

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Pericardial Diseases

18

18.1. What is the normal amount of pericardial fluid?

A. 0
B. 20–50 cm^3
C. 50–100 cm^3
D. 100–200 cm^3

18.2. Which of the following statements about pericardial anatomy is incorrect?

A. Visceral layer is thin and has a single layer of mesothelial cells adherent to epicardial fat and reflected at the base onto parietal pericardium
B. The parietal pericardium is tough and fibrous; it is flask-shaped and has attachments to sternum and diaphragm
C. The visceral and parietal layers are adherent to each other
D. There are two pericardial sinuses
E. The parietal pericardium is continuous with adventitia of great vessels

18.3. Which of the following statements about pericardial sinuses are correct?

A. The transverse sinus is between ascending aorta and pulmonary trunk anteriorly and superior vena cava posteriorly
B. The oblique sinus is posterior to the left atrium and lies between left and right pulmonary veins
C. Both A and B are correct
D. Neither A nor B are correct

18.4. What is the normal intrapericardial pressure?

A. 0 ± 3 mmHg
B. 5 ± 3 mmHg
C. 10 ± 3 mmHg
D. 15 ± 3 mmHg

18.5. A 24-year-old man presents with 5-day history of low-grade fever, malaise, and cough and recent chest pain. He has a triphasic pericardial rub and concave-up ST elevation in most of the electrocardiogram (ECG) leads. Erythrocyte sedimentation rate (ESR) is 96 mm at the end of first hour, and complete blood count is normal. Serum troponin I level is 15 times the normal. What is the most likely cause of his pericarditis?

A. Idiopathic
B. Viral
C. Bacterial
D. Tubercular

18.6. What is the most common type of pericardial rub in acute pericarditis?

A. Triphasic
B. Biphasic
C. Monophasic
D. Quadriphasic

18.7. Some of the characteristics of pericardial rub include which of the following?

A. Scratchy or grating superficial sound that is heard close to the ears; best heard with diaphragm with pressure
B. Best heard sitting up, leaning forward, in expiration
C. May vary with position and heartbeats

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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D. All of the above
E. None of the above

18.8. What is the most common etiology of acute pericarditis?
A. Idiopathic
B. Viral
C. Bacterial
D. Autoimmune

18.9. Some of the acute ECG changes during acute pericarditis include which of the following?
A. Concave-up ST elevation with upright T in most of the leads; ST depression in aVR
B. PR segment depression in most of the leads
C. PR segment elevation in aVR
D. All of the above

18.10. Acute pericarditis can be differentiated from early repolarization by which of the following features?
A. Progressive changes over days
B. PR segment depression
C. ST segment/T wave height ratio of >0.25
D. All of the above

18.11. A 52-year-old man underwent successful left anterior descending artery stent placement for acute anterior ST-elevation myocardial infarction (MI). The next day he complains of left-sided severe chest pain on inspiration and you hear a triphasic, grating sound at low left sternal border. What is the explanation likely to be?
A. Focal pericarditis due to transmural MI
B. Dressler's syndrome
C. Ventricular septal rupture
D. Left anterior descending artery perforation

18.12. Which of the following would you suggest for the patient in Question 18.11?
A. Increase the dose of aspirin
B. Start indomethacin
C. Start corticosteroid
D. Start heparin

18.13. Three weeks after mitral valve repair, a 56-year-old patient presents with features of pericarditis, fever, and normal complete blood count. He is on aspirin 81 mg/day and warfarin for postoperative atrial fibrillation along with low-dose amiodarone. He is in sinus rhythm. What would you recommend?
A. Start corticosteroids
B. Stop warfarin and increase the dose of aspirin to 3 g/day with food, in divided doses for 2 weeks
C. Start colchicine
D. No change in treatment

18.14. A 30-year-old man with no other issues is admitted with a second episode of acute pericarditis in 2 months. The first episode was treated with a 10-day course of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen, 400 mg TID. His autoantibodies were negative. What is your recommendation?
A. Start high-dose NSAID along with colchicine 0.6 mg BID
B. Start indomethacin because of ibuprofen failure

C. Start high-dose steroid with rapid taper
D. Start high-dose steroid with slow taper and low-dose maintenance for 3–6 months

18.15. In a patient with suspected tubercular pericarditis, which test is likely to give the highest diagnostic yield?
A. Acid-fast bacilli culture of pericardial fluid
B. Tuberculin test
C. Pericardial biopsy
D. Adenosine deaminase elevation in pericardial fluid

18.16. On pericardial biopsy, caseating granulomas are seen. What is the likely cause of pericarditis?
A. Tuberculosis
B. Sarcoid
C. Rheumatoid
D. Fungal

18.17. Which of these drugs can potentially result in pericarditis?
A. Hydralazine
B. Methyldopa
C. Penicillin
D. Sodium cromoglycate
E. All of the above
F. None of the above

18.18. What is the most common cause of malignant pericardial effusion with tamponade?
A. Lung cancer
B. Breast cancer
C. Lymphoma
D. Renal cancer

18.19. Indications for pericardiocentesis in a patient with pericarditis include which of the following?
A. Tamponade
B. Suspicion of pyogenic cause
C. Nonresolving, large effusion despite treatment
D. All of the above

18.20. What is the best approach for pericardiocentesis?
A. Subxiphoid with ECG monitoring of a lead connected to the needle
B. Echo guided
C. Magnetic resonance imaging (MRI) guided
D. Surgical

18.21. What is the normal pericardial thickness?
A. <3 mm on echo
B. <2 mm on computed tomography (CT)
C. <4 mm on MRI
D. All of the above

18.22. A 67-year-old patient presents with dyspnea and abdominal swelling. He had coronary artery bypass grafting procedure 5 years earlier. The physical examination reveals raised jugular venous pressure with Kussmaul's sign and ascites. The echocardiogram shows normal LV wall motion, ejection fraction of 60%, septal bounce, a severely dilated inferior vena cava, E/A ratio of 1.3, E/e′ ratio of 10, septal e′ velocity of 15 cm/s and lateral e′ of 12 cm/s. Pericardium looked normal. A gated contrast CT scan was performed and the pericardial thickness was <2 mm with no pericardial thickness. Grafts are patent, and invasive hemodynamics was inconclusive. What will you do?

A. Treat for restrictive cardiomyopathy with diuretics
B. Perform cardiac MRI
C. Refer the patient for pericardiectomy
D. None of the above

18.23. What are the indications for corticosteroids in pericarditis?
A. Unresponsive to NSAID and colchicine
B. Autoimmune etiology
C. Recurrence despite colchicine
D. All of the above
E. None of the above

18.24. Pericardial calcification is best detected by which of the following?
A. Fluoroscopy
B. CT scan
C. MRI
D. Echocardiography

18.25. With which of the following is the risk of constriction the highest?
A. Idiopathic pericarditis
B. Tubercular pericarditis
C. Uremic pericarditis
D. Malignant pericarditis

18.26. Indications for pericardiectomy in pericarditis include which of the following?
A. Multiple recurrences despite chronic NSAID and colchicine
B. Steroid dependence
C. Constriction
D. Effusive–constrictive
E. All of the above

18.27. Prednisone may be helpful to reduce the risk of constriction in which of the following etiologies of pericarditis, in addition to specific antimicrobial therapy?
A. Tubercular
B. Purulent
C. Fungal
D. All of the above

18.28. In a patient with malignant pericardial effusion, which of the following options may reduce recurrence?
A. Intrapericardial tetracycline as sclerosing agent
B. Intrapericardial chemotherapy
C. Pericardial window
D. All of the above

18.29. A patient with end-stage renal disease (ESRD) on hemodialysis has moderate pericardial effusion. What is your recommendation?
A. Intensify dialysis
B. Switch to peritoneal dialysis
C. Start NSAID
D. Perform pericardiocentesis.

18.30. The cause of pericardial effusion in ESRD patients on dialysis includes which of the following?
A. Uremic pericarditis
B. Volume excess
C. Minoxidil
D. Hydralazine
E. All of the above

18.31. Poor prognostic markers in pericarditis include which of the following?
A. Fever >38 °C
B. Subacute onset

C. Large pericardial effusion or cardiac tamponade
D. Lack of response to aspirin or NSAIDs after at least 1 week of therapy
E. All of the above
F. None of the above

18.32. A 27-year-old man with no cardiac symptoms was found to have heart entirely in left chest in left lateral decubitus X-ray and entirely on the right in right lateral decubitus X-ray. What is the patient likely to have?
A. Mesocardia
B. Dextrocardia
C. Congenital absence of the pericardium
D. It is normal

18.33. Which of the following has a higher risk of complications?
A. Total absence of pericardium
B. Partial absence of pericardium
C. They are similar
D. Both are benign

18.34. Which type of pericardial defect is least common?
A. Partial left
B. Partial right
C. Total
D. All are equally common

18.35. Some of the variants of constriction include which of the following?
A. Annular variety with mitral stenosis
B. Annular variety with tricuspid stenosis
C. Pulmonary outflow stenosis
D. All of the above
E. None of the above

18.36. A 54-year-old asymptomatic man was found to have "fluid" around his right atrium on an echocardiogram. Images were difficult, and cardiac MRI was obtained. A FIESTA freeze frame is shown in Figure 18.36. What will you do next?

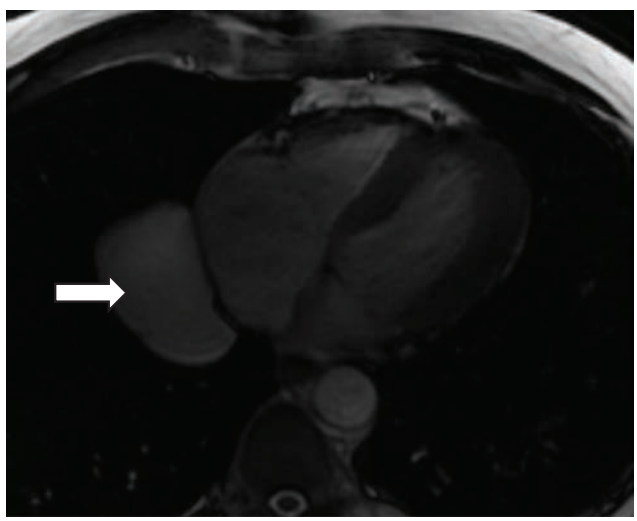

Figure 18.36

A. Reassure, do nothing, monitor for any symptoms
B. CT-guided needle aspiration
C. Surgical resection
D. Positron emission tomography scan

18.37. A 60-year-old man with systolic heart failure and atrial fibrillation presented with shortness of breath. He was on carvedilol, benazepril, amiodarone, and furosemide. Heart rate was 110 bpm. Blood pressure was 85/60 mmHg and jugular venous pressure was severely elevated. A CT scan image is shown in Figure 18.37. What will you do next?

A. Pericardiocentesis
B. Intravenous fluids
C. Intravenous diuresis
D. Refer to cardiothoracic surgery

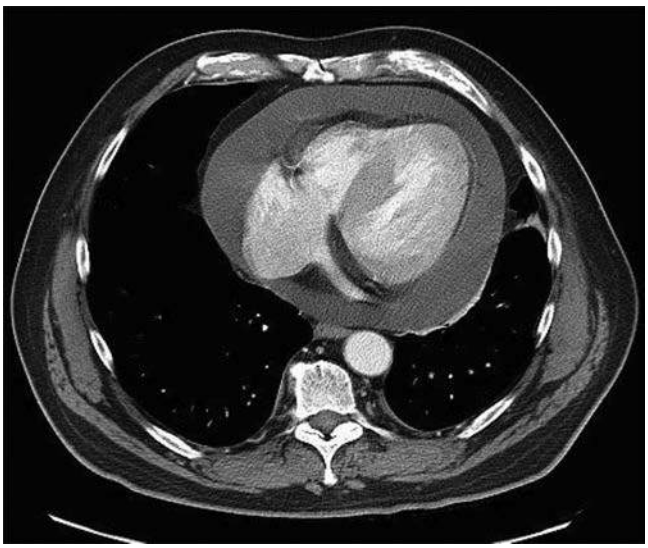

Figure 18.37

Answers

18.1. B. 20–50 cm^3.
It is an ultrafiltrate, acting as a lubricant. Accumulation of >100–150 cm^3 may increase the pericardial pressure, depending upon the rapidity of accumulation.

18.2. C. The visceral and parietal layers are adherent to each other.
The visceral and parietal layers are not adherent to each other. The pericardial fluid lubricates the opposing surfaces such that the layers slide on each other. The other statements are correct.

18.3. C. Both A and B are correct.

18.4. A. 0 ± 3 mmHg.
It is atmospheric or the same as intrapleural pressure, being negative during inspiration and slightly positive during expiration.

18.5. B. Viral.
This is in view of substantial subepicardial myocardial involvement (ECG changes and positive troponin) which generally does not occur with idiopathic causes. Absence of high-grade fever with leukocytosis and short history mitigate against choices C and D respectively.

18.6. A. Triphasic.
In 50–60% of cases when it is heard; the three phases are due to atrial systole, ventricular systole, and early left ventricular (LV) filling, and hence are presystolic, systolic, and early diastolic. Monophasic would be systolic and may be mistaken for a systolic murmur.

18.7. D. All of the above.

18.8. A. Idiopathic.
An etiology may not be discoverable in 60–80% of patients.

18.9. D. All of the above.
Changes in aVR are reciprocal to changes in all other leads. The ECG changes are progressive and progress to ST segment normalization with T wave flattening (stage 2), T wave inversion (stage 3, and normalization of ECG (stage 4).

18.10. D. All of the above.
These are features of pericarditis.

18.11. A. Focal pericarditis due to transmural MI.
This occurs in about 50% of ST-elevation MIs, though getting less frequent with acute revascularization therapies. Dressler's syndrome takes 2–3 weeks to develop.

18.12. A. Increase the dose of aspirin.
For both pain control and anti-inflammatory properties. Indomethacin and corticosteroids may increase the risk of LV rupture. Heparin may cause hemorrhagic pericarditis.

18.13. B. Stop warfarin and increase the dose of aspirin to 3 g/day with food, in divided doses for 2 weeks.
Anticoagulation may make the pericarditis hemorrhagic – as he is in sinus rhythm and has no mechanical valves, the risk of embolic event is rather low.

18.14. A. Start high-dose NSAID along with colchicine 0.6 mg BID.
Colchicine continued for 6 months may reduce pericarditis recurrence by 50% (Colchicine for Recurrent Pericarditis (CORP) trial – see Box 18.1). Use of steroids may increase the recurrence rates. No substantial difference in acute response to any of the NSAIDs used in high dose, though indomethacin is a classic time-honored drug; use of high dose of NSAID is important.

18.15. C. Pericardial biopsy.
The yield is nearly 100%. Yields with acid-fast bacilli cultures and adenosine deaminase test are about 50% and 80% respectively. Tuberculin test could be either false positive or false negative.

18.16. A. Tuberculosis.
Caseation is typical of tuberculosis. The other options listed can result in granulomas.

18.17. E. All of the above.
Options A and B through systemic lupus erythematosus syndrome (isoniazid as well), and options C and D through hypersensitivity reaction.

18.18. A. Lung cancer.
Followed by breast cancer and lymphoma.

18.19. D. All of the above.

18.20. B. Echo guided.
This easy to perform, is bedside, and has the lowest risk. Most often, an apical window is suitable. Echo helps to choose the window, guide the needle, confirm its location in pericardium, and completeness of drainage. A sterile sleeve should be used on the echo probe.

18.21. D. All of the above.
These are approximate.

18.22. C. Refer the patient for pericardiectomy.
Given the clinical and echo features, the probability that he has constriction is >90% and no negative test can reduce it to zero. Hence, surgical exploration is appropriate. A higher septal e′ compared with lateral e is called annulus paradoxus, which is reported in constriction and is attributed to tethered LV lateral wall by pericardium with compensatory increased medial annular motion in early diastole. An e′ of >8 cm/s goes against a primary myocardial restrictive process. In about 25% of patients with constriction following heart surgery, pericardium has normal thickness.

18.23. D. All of the above.

18.24. B. CT scan.
This is the most sensitive. Calcium is not imaged or seen by MRI.

18.25. B. Tubercular pericarditis.
This is >50%. With viral or idiopathic pericarditis it is <1%. In malignancy, the risk is low because of short life span, though the effusion may be hemorrhagic.

18.26. E. All of the above.

18.27. D. All of the above.

18.28. D. All of the above.

18.29. A. Intensify dialysis.
This is likely to be uremic pericarditis. This should cause its resolution in 10–14 days. Both hemodialysis and peritoneal dialysis are equally efficacious. Peritoneal dialysis is not needed unless patient's blood pressure drops during hemodialysis.

18.30. E. All of the above.
These have to be kept in mind in an ESRD patient having pericardial effusion.

18.31. E. All of the above.
See Imazio *et al.* (2007).

18.32. C. Congenital absence of the pericardium.
This is a typical presentation. It is mostly asymptomatic and benign, but excess mobility of the heart may predispose to cardiac contusion and aortic dissection with trauma. On a supine chest X-ray, the apex will be pointing posteriorly.

18.33. B. Partial absence of pericardium.

This is because of herniation of the heart through these defects, resulting in strangulation. Symptoms may include chest pain, shortness of breath, syncope, or sudden death. Surgical pericardioplasty with Dacron, Gore-Tex, or bovine pericardium is indicated in these situations.

18.34. C. Total.

Partial left-sided defect is the most common.

18.35. D. All of the above.

The other variants include left ventricle variety affecting mostly left side, right ventricle variety, global variety, global variety with severe ventricular atrophy (where pericardiectomy is futile and contraindicated), and tubular variety, where both ventricles look like a tube because of constriction from both sides.

18.36. A. Reassure, do nothing, monitor for any symptoms.

Nothing to do as there are no symptoms. This is a typical pericardial cyst, which generally occurs at the right cardiophrenic angle. They have low intensity on T1W imaging and high intensity on T2W imaging. They do not enhance on perfusion imaging. When large or symptomatic, resection or percutaneous drainage is appropriate; recurrence rate with drainage is about 30%.

18.37. A. Pericardiocentesis.

Note the large pericardial effusion. The patient had tamponade, and 1200 cm^3 of fluid was drained with prompt relief of symptoms. The fluid was turbid with high protein content. The thyroid stimulating hormone was 80 mU, suggestive of severe amiodarone-induced hypothyroidism, which likely caused the effusion. The high Hounsfield unit of pericardial fluid was due to high protein content.

Box 18.1 CORP Trial

In the CORP trial (Imazio *et al.*, 2011), 120 patients with a second episode of acute pericarditis were randomized to receive colchicine for 6 months versus placebo. There was about 50% reduction in risk of recurrent pericarditis.

References

Imazio, M., Cecchi, E., Demichelis, B., *et al.* (2007) Indicators of poor prognosis of acute pericarditis. *Circulation*, **115**: 2739–2744.

Imazio, M., Brucato, A., Cemin, R., *et al.* (2011) Colchicine for Recurrent Pericarditis (CORP): a randomized trial. *Annals of Internal Medicine*, **155**: 409–414.

Further Reading

An excellent reference resource for guiding management of all pericardial diseases is:

Maisch, B., Seferović, P.M., Ristić, A.D., *et al.* (2004) Guidelines on the diagnosis and management of pericardial diseases. Executive summary. The Task force on the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology. *European Heart Journal*, **25**: 587–610.

Aortic Diseases 19

19.1. A 50-year-old male with a history of a heart murmur for most of his adult life sees you in the clinic with symptoms of dyspnea on minimal effort and chest pain with minimal effort. Blood pressure (BP) is 130/80 mmHg, heart rate is 72 bpm. Grade III/VI harsh systolic ejection murmur is heard in the right upper sternal border. Echocardiogram showed a bicuspid valve with aortic valve area of 0.6 cm^2. What is the lifetime risk of aortic dissection in this patient?

A. 2–4%
B. 4–6%
C. 6–7%
D. 10–12%

19.2. Aortopathy associated with bicuspid aortic valve is due to which of the following?

A. Abnormal fibrillin
B. Vascular smooth muscle cell apoptosis
C. Matrix metallopeptidase 9
D. All of the above
E. A and C only

19.3. The right/left fusion pathology in a bicuspid valve is seen commonly. What is its incidence?

A. 20%
B. 40%
C. 60%
D. 80%

19.4. The sites of aortic dissection may be (a) just past the left subclavian artery, (b) 3 cm distal to the aortic valve, and (c) at the aortic arch. Which of the following options matches the aortic dissection sites in decreasing order?

A. a, b, c
B. b, c, a
C. b, a, c
D. a, c, b

19.5. The treatment of choice in a 49-year-old male with acute type III aortic dissection, minimally dialted aorta with no leak, good flow in false lumen, BP of 200/100 mmHg, severe interscapular pain, pallor, and tachycardia is which of the following?

A. Emergency surgery
B. Endovascular graft implantation with fenestration
C. Intravenous (IV) nitroprusside
D. IV esmolol

19.6. A 70-year-old patient with a history of three-drug hypertension and tobacco use presents to the emergency room with acute onset of substernal chest pain and electrocardiogram showing St elevation in inferior leads. His BP is 80 mmHg systolic in the left arm and 150 mmHg systolic in right arm. What is your test of choice?

A. Emergency coronary angiography
B. Echocardiography

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C. Computed tomography (CT) of the chest without contrast
D. CT of the chest with contrast

19.7. The angiogram in Figure 19.7 is most likely to be associated with which of the following?
A. 70-year-old African American woman
B. 38-year-old Asian Indian woman
C. 35-year-old Polish male
D. 60-year-old Peruvian male

Figure 19.7

19.8. An 80-year-old woman presents with 20 lb weight loss over the last 6 months. She also reports nausea and diarrhea and states she has to eat small meals as she has abdominal pain if she eats normal portions. She has a history of coronary artery bypass grafting, done 10 years ago. She had traveled to India 6 months ago. What is the test that will have the highest yield?
A. Esophagogastroduodenoscopy
B. Colonoscopy
C. Infectious disease consultation
D. CT with contrast of the chest and abdomen
E. None of the above

19.9. The patient in Figure 19.9 has history hypertension and shortness of breath. Which of the following does the patient have?
A. Hyperparathyroidism
B. Lymphoma
C. Prostate cancer
D. None of the above

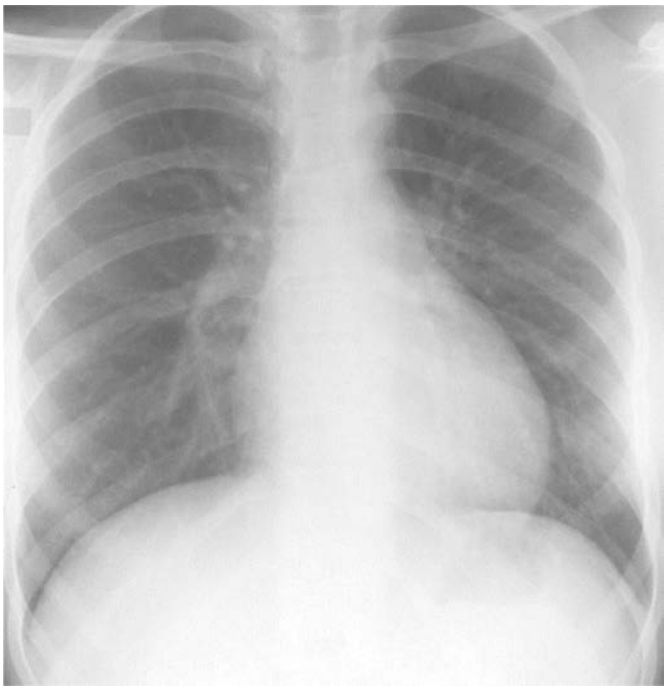

Figure 19.9

19.10. A patient presents with "trash foot" after a cardiac catheterization with the TEE image shown in Figure 19.10. There is a palpable pulse and the foot is warm. Which of the following would you order?

A. IV prostaglandin
B. IV steroids
C. IV heparin
D. IV nitroglycerine
E. None of the above

19.11. What is your test of choice to make the diagnosis of the patient in Question 19.10?

A. Arterial duplex of the lower extremities
B. Venous duplex study of the lower extrenities
C. CT of the abdomen
D. Abdominal ultrasound

19.12. A 53-year-old male presents with symptoms of progressive hoarseness. Figure 19.12 shows the TEE (long-axis view) done. What is the best next step?

A. IV vancomycin and gentamicin
B. Repeat echocardiography in 2 weeks
C. Esmolol drip
D. CT of the chest with contrast

19.13. A 58-year-old male is known to have Marfan syndrome. His echocardiogram shows ascending an aortic aneurysm 4.1 cm in size. What is the next step?

A. CT every 6 months
B. Echocardiogram every 6 months

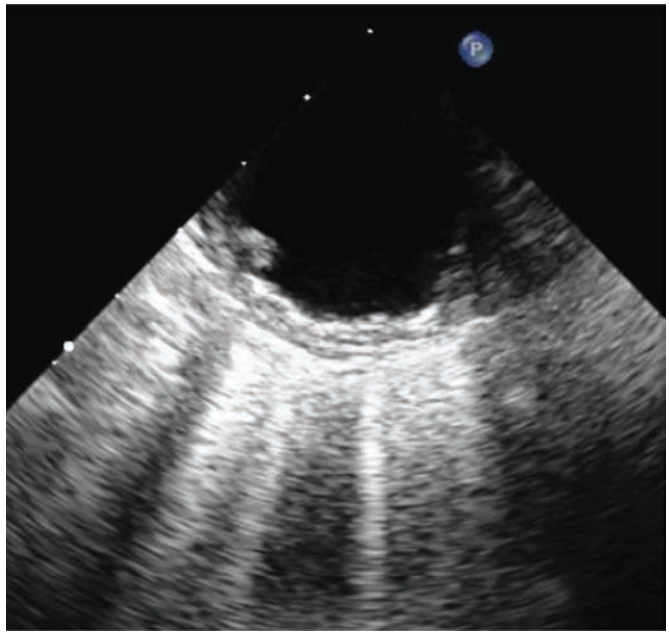

Figure 19.10

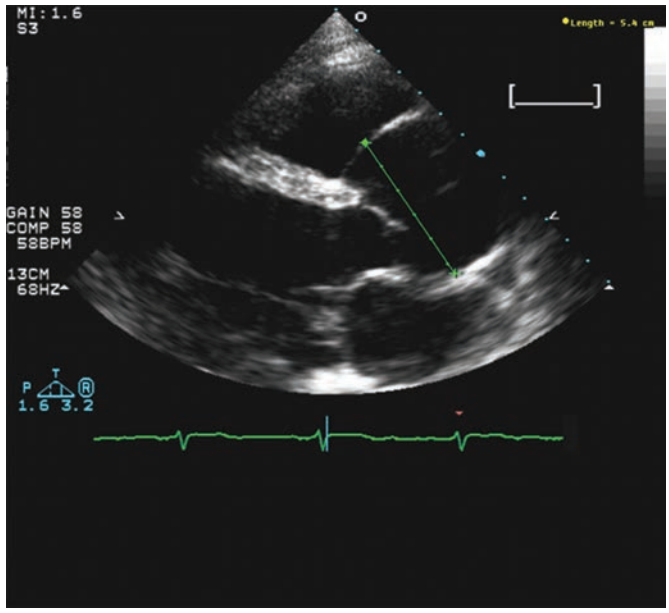

Figure 19.12

C. Annual CT or magnetic resonance imaging (MRI)
D. Echocardiogram every 3 months

19.14. A 43-year-old male had recent surgery for a dissecting aortic aneurysm. Which of the following is/are recommended?
A. CT or echocardiogram at 6 and 12 months after surgery
B. Lifelong beta blockade
C. Use of homografts to replace infected prostheses is contraindicated
D. Control BP to less than 135/80 mmHg
E. B and D
F. A and D

19.15. A 60-year-old male was diagnosed with infrarenal abdominal aortic aneurysm (AAA) of 5.5 cm. What should this patient have?
A. CT every 6–12 months
B. Should undergo repair
C. Monitored by ultrasound every 3–6 months
D. Only A and C

19.16. Endovascular repair of the aneurysm of the descending thoracic aorta is associated with which of the following complications compared with open surgical repair?
A. Higher risk of paraplegia with endovascular repair
B. Lower risk of paraplegia with surgical repair
C. Higher risk of respiratory failure with open repair
D. Higher risk of respiratory failure with endovascular repair

19.17. A 50-year-old woman presents to your office with 6-month history of hypertension that has been difficult to control, headaches, fatigue of the lower extremities on minimal effort, and claudication if she pushes herself. She has had malaise, low-grade fevers, and night sweats. Her BP is 200/105 mmHg in both upper extremities and 100/60 mmHg in both of her ankles. What is the diagnosis?
A. Takatsubo's syndrome
B. Coarctation of the aorta.
C. Mid aortic syndrome
D. Bilateral iliac artery stenosis

19.18. With which of the following is 45,X chromosomal anomaly associated?
A. Development of complete heart block
B. Ventricular septal defect
C. Aortic aneurysm and dissections
D. Tall stature and a violent personality

19.19. "Bamboo" spine is associated with which of the following?
A. Ascending aortic aneurysm
B. Uveitis
C. Arthritis
D. Ulcerative colitis
E. A, B, and C
F. A, C, and D
G. All of the above

19.20. Leriche syndrome is associated with which of the following?
A. Impotence
B. Buttock claudication
C. Atrophy of the lower extremities
D. All of the above
E. A and B only

19.21. Which of the following describes collateral arterial pathways around total occlusions of the infrarenal aorta?

- **A.** Inferior epigastric artery to the internal mammary artery
- **B.** Lumbar artery to the hypogastric artery
- **C.** Inferior mesenteric artery to the hypogastric artery
- **D.** The sacral artery to the hypogastric artery
- **E.** A and B only
- **F.** All of the above
- **G.** A, B, and C only

19.22. A 68-year-old woman presents with severe anterior unrelenting chest pain that radiates to her back. BP is 200/110 mmHg. She has a CT scan of the chest, shown in Figure 19.22a. Which of the following is the next best step?

- **A.** Coronary angiography and aortogram
- **B.** TEE
- **C.** Cardiothoracic surgery consultation and proceed to the operating room
- **D.** MRI of the chest

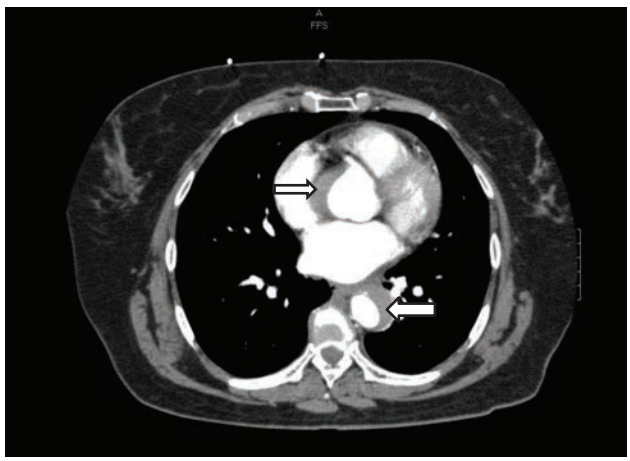

Figure 19.22a

19.23. Which of the following is the treatment of choice in the 80-year-old patient in Figure 19.23a with advanced chronic obstructive pulmonary disease and hypertension? She is status post mastectomy 3 years ago with no residual disease.

- **A.** Endovascular repair
- **B.** Open surgical repair
- **C.** Risk factor modification with conservative therapy

19.24. You successfully repaired a 6.5 cm infrarenal aortic aneurysm a year ago. The aneurysm has continued to grow by 1 cm on a follow-up CT scan. There is no contrast seen within the sac of the aneurysm. What is this an example of?

- **A.** Type I endoleak
- **B.** Type II endoleak
- **C.** Type III endoleak
- **D.** Type IV endoleak
- **E.** Type V endoleak

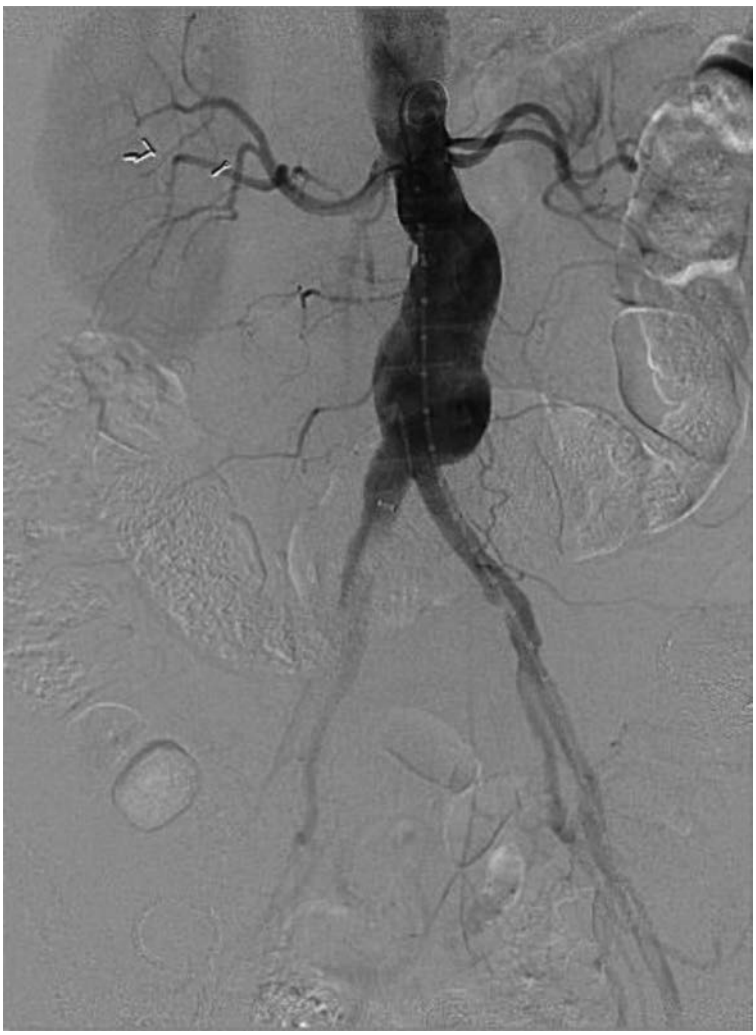

Figure 19.23a

19.25. True or false, "sartans" slow the growth of aneurysms in Marfan syndrome?

- **A.** True
- **B.** False

19.26. Which of the following may 45,X0 be associated with?

- **A.** Brachiofemoral delay
- **B.** Bicuspid aortic valve
- **C.** Dilatation of the aorta
- **D.** Impaired glucose tolerance
- **E.** All of the above

19.27. A bifid uvula is seen in which of the following?

- **A.** Ehlers–Danlos syndrome (EDS)
- **B.** Loeys–Dietz syndrome (LDS)
- **C.** Aneurysms–osteoarthritis syndrome (AOS)

D. Arterial tortuosity syndrome (ATS)
E. Marfan syndrome

19.28. The non-syndromic forms of thoracic aortic aneurysm and dissection (nsTAAD) may be associated with bicuspid aortic valve and/or persistent ductus arteriosus and display typical cystic medial necrosis on pathological examination. Mutations in genes (*FBN1*, *TGFBR1*, and *TGFBR2*) are frequently seen.
A. True
B. False

19.29. The most characteristic and frequently reported clinical presentation of an intimal angiosarcoma of the aorta is the embolic occlusion of the mesenteric or peripheral artery. Leiosarcomas and fibrosarcomas originate from the media or adventitia of the aortic wall. Which rare tumor of the aorta is most common?
A. Angiosarcoma
B. Leiosarcoma
C. Fibrosarcoma

19.30. What structures are the long and short arrows in Figure 19.30 pointing to?
A. Aorta and lateral epigastric artery
B. Aorta and the inferior epigastric artery
C. Aorta and intercostal artery
D. None of the above

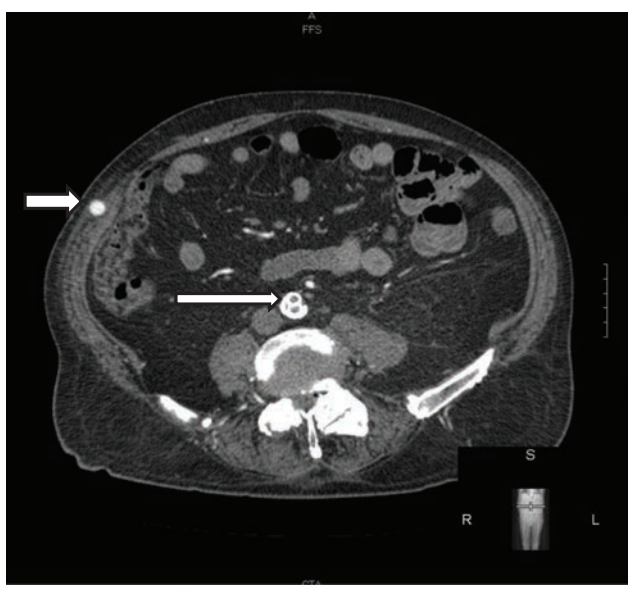

Figure 19.30

19.31. The risk of paraplegia with endovascular thoracic aneurysm repair (Figure 19.31a) is which of the following?
A. 20%
B. 25%
C. 5%
D. 10%

Figure 19.31a

19.32. A 30-year-old Asian female presents with fever, fatigue, and syncopal episode. Examination reveals absent radial pulses. What is the most accurate diagnostic test?

- **A.** Erythrocyte sedimentation rate/C-reactive protein
- **B.** Antineutrophil cytoplasmic antibody (ANCA), antinuclear antibody (ANA)
- **C.** Magnetic resonance angiography (MRA)
- **D.** All of the above

19.33. Takayasu's arteritis affects which of the following?

- **A.** Aorta
- **B.** Pulmonary arteries
- **C.** Renal arteries
- **D.** All of the above
- **E.** A, B, and C

19.34. Treatment of Takayasu's arteritis includes which of the following?

- **A.** Steroid 1 mg/kg of body weight per day
- **B.** Mycophenolate and tocilizumab
- **C.** Bypass grafting
- **D.** Stenting
- **E.** All of the above

19.35. Which of the following is the most accurate to diagnose dissecting ascending aortic aneurysm?

- **A.** TEE
- **B.** CT angiogram
- **C.** MRA
- **D.** All of the above

19.36. Which of the following is/are associated with ascending aortic dissection?

- **A.** Blunt trauma
- **B.** Marfan syndrome
- **C.** Aortic regurgitation
- **D.** Syphilis
- **E.** A, B, and D
- **F.** All of the above

19.37. Severe hypotension at presentation is a grave prognostic indicator in ascending aortic dissection, and is due to which of the following?

- **A.** Pericardial tamponade
- **B.** Severe aortic insufficiency
- **C.** Rupture of the aorta
- **D.** A, B, and C
- **E.** None of the above

19.38. Ascending aortic dissection and aortic regurgitation can be explained by which of the following?

- **A.** The dissection may dilate the annulus of the aortic valve
- **B.** The dissection may extend into the aortic root and detach the aortic valve leaflets
- **C.** Both A and B
- **D.** None of the above

19.39. Which of the following is/are correct regarding myocardial infarction in ascending aortic dissection?

- **A.** Due to involvement of coronary arteries
- **B.** Incidence rate 1–2%
- **C.** Right coronary more commonly involved than left coronary
- **D.** Thrombolytics are indicated
- **E.** A and B
- **F.** A, B, and C

19.40. Pleural effusion in ascending aortic dissection is caused by which of the following?

- **A.** Right more common than left
- **B.** Due to blood from rupture
- **C.** Due to fluid from inflammation around the aorta
- **D.** B and C
- **E.** None of the above

Answers

19.1. C. 6–7%.

See Losenno *et al.* (2012).

19.2. D. All of the above.

All of the factors are part of the extracellular matrix and are abnormal causing cystic medial necrosis.

19.3. C. 60%.

Right and left cusp fusion is seen 60% of the time, followed by right and noncoronary cusps 15–25%, and left/noncoronary cusps 5% of the time.

19.4. C. b, a, c.

The most common site of dissection is the first few centimeters of the ascending aorta, with 90% occurring within 10 cm of the aortic valve. The second most

common site is just distal to the left subclavian artery. Between 5 and 10% of dissections do not have an obvious intimal tear. These often are attributed to rupture of the aortic vasa vasorum, as first described by Krukenberg in 1920.

19.5. D. IV esmolol.

IV beta blockade is to decrease the shear force on the wall of the aorta. If the BP is not controlled on IV beta blockade (first drug of choice per American College of Cardiology guidelines) add other agents to lower BP.

19.6. D. CT of the chest with contrast.

Or emergency transesophageal echocardiogram (TEE). Acute ascending aortic dissection can cause right coronary artery compromise and pericardial tamponade. Unrecognized, the mortality is 1–2% per hour.

19.7. B. 38-year-old Asian Indian woman.

Takayasu's arteritis, or pulseless disease, is most commonly seen in Japan and Asia. Neurological and ophthalmological symptoms are common. Fever, malaise, and loss of upper extremity pulse and a low BP in the upper extremity are common. The angiogram in Figure 19.7 shows severe left subclavian artery stenosis and right innominate artery origin stenosis (Rizzi *et al.*, 1999).

19.8. D. None of the above.

The history is consistent with abdominal angina with weight loss, history of atherosclerosis (see Box 19.1), fear of food, and abdominal pain. Generally, two of the three mesenteric vessels are compromised to manifest these symptoms. The vascular supply of the gut is extensive with robust collateral supply (Hovenwalter, 2009).

19.9. D. None of the above.

There is rib notching due to intercostal artery collateral formation seen with coarctation of the aorta.

19.10. E. None of the above.

19.11. C. CT of the abdomen.

This is "trash foot" from atheroemboli from likely an abdominal aortic aneurysm, though the image shown is from the thoracic aorta, which shows only moderate aortic atheroma without debris. The triad of pain, livedo reticularis, and intact peripheral pulses is pathognomonic for cholesterol embolization. No single therapy has been shown to be clinically beneficial. The CT is the most accurate for diagnosing and sizing the abdominal aortic aneurysm prior to repair.

19.12. D. CT of the chest with contrast.

The echocardiogram in Figure 19.12 exhibits a large proximal ascending aortic aneurysm that may require surgery. Stretch of the recurrent laryngeal nerve by the aortic arch causes hoarseness. The CT will exactly size the aneurysm.

19.13. C. Annual CT or magnetic resonance imaging (MRI).

See guidelines in Table 19.13.

19.14. E. B and D.

See European Society of Cardiology guidelines in Table 19.14.

Table 19.13

Etiology/location	Size (cm)	Time interval/modality
Root or ascending aorta		
• Degenerative	3.5–4.4	Annual CT or MRI
		Echocardiogram to follow valve disease (if needed)
	4.5–5.4	Biannual CT or MRI
		Echocardiogram to follow valve disease (if needed)
Root or ascending aorta	3.5–4.4	Annual CT or MRI
• Marfan syndrome		Echocardiogram to follow valve disease (if needed)
• Bicuspid aortic valve		
• Other genetically mediated disorder	4.5–5.0	Biannual CT or MRI

Table 19.14

Intervention	Recommendations	Level of evidence
Medical therapy	Lifelong beta blockade	Class II
	Control of BP to <135/80 mmHg (130/80 mmHg for Marfan syndrome)	Class I
Surveillance	Imaging at 1, 3, 6, and 12 months, then yearly thereafter (by MRI, CT, or TEE)	Class I
Repeat aortic surgery	Surgery for secondary aneurysm in dissected aorta remote from initial repair	Class I
	Surgery for recurrent dissection or aneurysm formation at previous intervention site	Class I
	Use of homografts to replace infected prostheses	Class IIa
	Endovascular stenting instead of surgery if anatomy is suitable	Class IIa

19.15. B. Should undergo repair.

See Table 19.15. The risk of rupture goes up exponentially as the size of the aneurysm increases.

19.16. C. Higher risk of respiratory failure with open repair.

As the open repair requires a thoracotomy there is a higher risk of respiratory failure. Thoracic aneurysms should be repaired when the size is >6 cm. If a thoracic aneurysm is detected, the rest of the aorta should be imaged to rule out other aneurysms; this applies to aneurysms of the aorta in any location. The popliteal

Table 19.15

Intervention	Recommendations	Level of evidence
Screening	Men ≥60 years who are either the siblings or offspring of patients with AAA should undergo physical examination and screening abdominal ultrasound	Class I
	Men 65–75 years who have ever smoked should undergo physical examination and screening abdominal ultrasound	Class IIa
Surveillance	Patients with AAA 4.0–5.4 cm in diameter should be monitored by ultrasound or CT scans every 6–12 months to detect expansion	Class I
	Patients with AAA <4.0 cm in diameter should be monitored by ultrasound every 2–3 years	Class IIa
Repair	Patients with infrarenal or juxtarenal AAA >5.4 cm in diameter should undergo repair	Class I
	Repair can be beneficial in patients with infrarenal or juxtarenal AAA measuring 5.0–5.4 cm in diameter	Class IIa
	Repair may be indicated in patients with suprarenal or thoracoabdominal AAA measuring 5.5–6.0 cm	Class IIa

arteries should be palpated and imaged with ultrasound to rule out aneurysms. Popliteal aneurysms do not rupture but present with acute limb ischemia. Risk of paraplegia is higher with open surgical repair.

19.17. C. Mid aortic syndrome.

In this patient this is likely a sequel to Takayasu's syndrome with near occlusion of the mid abdominal aorta. Repair is endovascular if focal, otherwise surgical (Delis and Gloviczki, 2005).

19.18. C. Aortic aneurysm and dissections.

Turner syndrome is associated with aortic aneurysm and dissection (Matura *et al.*, 2007).

19.19. E. A, B, and C.

Ankylosing spondylitis is associated with aneurysm of the ascending aorta, uveitis, and arthritis of the spine and the sacroiliac joint. A radiograph shows fusion of the vertebrae and has the appearance of a bamboo tree on X-ray.

19.20. D. All of the above.

Leriche syndrome is due to atherosclerotic total occlusion of the terminal aorta. The triad of symptoms are as noted.

19.21. G. A, B, and C only.

19.22. A. Coronary angiography and aortogram.

According to the guidelines, stable patients over 40 years of age should have coronary anatomy defined prior to going to surgery. Aortic hematomas are treated like a dissection. Type A aortic dissection carries with it a mortality of

1–2% per hour. This patient had a tear in the lesser curve of the arch of the aorta opposite the takeoff of the right innominate artery (Figure 19.22b). The hematoma then advanced in an antegrade and retrograde fashion.

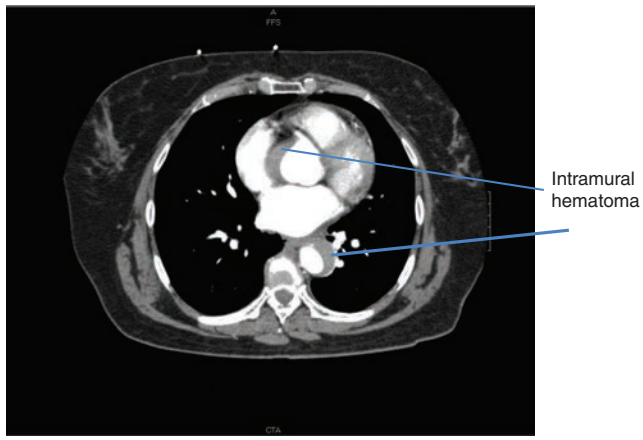

Figure 19.22b

19.23. A. Endovascular repair.

The patient has a life span of more than a year. There is more than 15 mm of infrarenal aortic neck and she is well suited for endovascular aneurysm repair (Figure 19.23b). Open repair carries with it a 4–5% 30-day mortality as opposed to

Figure 19.23b

3% by endovascular repair. The need for re-intervention is higher in the endovascular group.

19.24. E. Type V endoleak.

Type I is a leak from either end of the graft due to a gap between the graft and the aorta; type II is filling of the sac via collaterals – most commonly lumbar; type III is a break in the components of the graft; type IV is leak from the fabric of the graft material; type V is no cause (White *et al.*, 2000).

19.25. A. True.

See Erbel *et al.* (2014).

19.26. E. All of the above.

See Erbel *et al.* (2014).

19.27. B. Loeys–Dietz syndrome (LDS).

These are part of the chromosomal and inherited syndromic thoracic aortic aneurysms and dissection. Type IV EDS has significantly shortened life spans (50% mortality rate by 48 years) due to the spontaneous rupture of visceral organs (colon, uterus) and blood vessels; it affects the entire vascular system and the heart. Fusiform aneurysms are reported. LDS is a triad of arterial tortuosity and aneurysms throughout the arterial tree, hypertelorism, and bifid uvula, as well as features shared with Marfan syndrome. AOS is an autosomal dominant condition combining early-onset joint abnormalities (including osteoarthritis and osteochondritis dissecans) and aortic aneurysms and dissections. ATS is characterized by arterial tortuosity, elongation, stenosis, and aneurysm of the large- and middle-sized arteries; ATS is a very rare autosomal recessive disease.

See Erbel *et al.* (2014).

19.28. A. False.

The first part of the statement is true. The second part is true for the genetic syndrome associated TAAD. Genes for the nsTAAD are not as well defined.

19.29. A. Angiosarcoma.

En bloc resection of the aorta with clean margins is the therapy of choice. Prognosis is poor.

19.30. D. None of the above.

The long arrow points to the aorta with occluded prosthetic graft in it, and the short arrow points to an extra-anatomical Dacron bypass graft – axillofemoral bypass. This was done in a patient with Leriche syndrome.

19.31. C. 5%.

With spinal cord protection, the incidence in contemporary studies shows a risk of cord injury of 5%. As shown in the Figure 19.31b, endovascular repair was performed with a covered stent.

19.32. C. Magnetic resonance angiography (MRA).

This patient has Takayasu's arteritis (pulseless disease, aortic arch syndrome, nonspecific aortoarteritis), which affects young Asian females and is characterized by large-vessel granulomatous vasculitis with massive intimal fibrosis and vascular narrowing. Diagnosis can be made by MRA, CT angiogram, and aortography. It is not associated with ANCA, rheumatoid factor, ANA, or anticardiolipin antibodies.

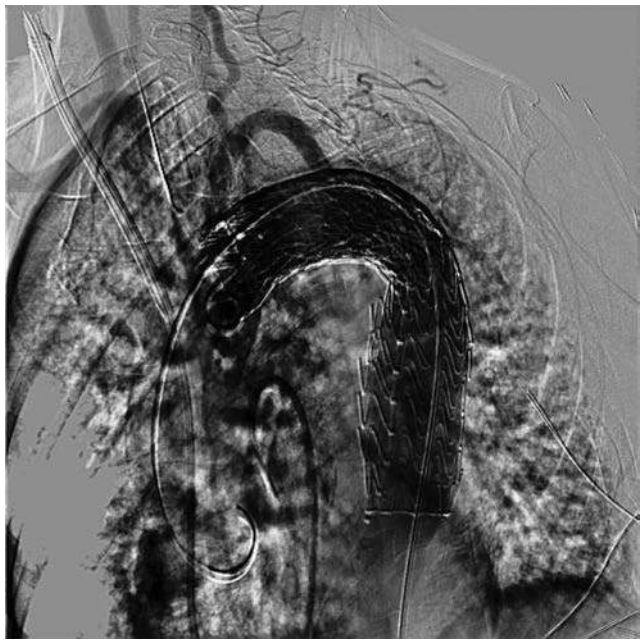

Figure 19.31b

19.33. E. A, B, and C.

Takayasu's arteritis affects the aorta and its branches, the pulmonary arteries, and the renal arteries that can cause renovascular hypertension. It is characterized by segmental and patchy granulomatous inflammation of the aorta and branches, leading to arterial stenosis, thrombosis, and aneurysms.

19.34. E. All of the above.

19.35. D. All of the above.

TEE, CT angiogram, and MRA have equal sensitivity and specificity to diagnose dissecting ascending aortic aneurysm.

19.36. F. All of the above.

Blunt trauma, Marfan syndrome, EDS, congenital bicuspid aortic valve, history of aortic dissection, Turner syndrome, aortic regurgitation, cardiac catheterization, intra-aortic balloon pump, and tertiary syphilis are associated with ascending aortic dissection.

19.37. D. A, B, and C.

Severe hypotension at presentation is a grave prognostic indicator in ascending aortic dissection, and associated with pericardial tamponade, severe aortic insufficiency, and rupture of the aorta.

19.38. C. Both A and B.

Ascending aortic dissection and aortic regurgitation can be due to the following:

- the dissection may dilate the annulus of the aortic valve;

- the dissection may extend into the aortic root and detach the aortic valve leaflets;
- in extensive intimal tear, the intimal flap may prolapse into the left ventricular outflow tract, causing intimal intussusception into the aortic valve, thus preventing proper valve closure.

19.39. F. A, B, and C.

Myocardial infarction in ascending aortic dissection is due to involvement of coronary arteries, with the right coronary more commonly involved than the left coronary with incidence rate 1–2%. Thrombolytics are absolutely contraindicated, as mortality increases to over 70%, mostly due to bleeding into the pericardial sac causing pericardial tamponade.

19.40. D. B and C.

Pleural effusion in ascending aortic dissection is caused by blood from rupture and fluid from inflammation around the aorta. More commonly in the left hemithorax.

Box 19.1 Clinical Pearls

Conditions Affecting the Aorta

- Hypertension
- Atherosclerosis: atheromatous debris
- Genetic conditions such as Marfan syndrome and bicuspid aortic valve
- Infectious causes such as syphilis, mycotic aneurysm
- Trauma
- Inflammatory: vasculitis or arteritis
- Aneurysm, dissection, aortic ulcer, intramural hematoma, aortic rupture, abscess
- Mural thrombi

Aneurysms of the Aorta

- Associated with bicuspid aortic valve and Marfan syndrome due to a defect in fibrillin 1 and other components of the arterial medial wall.
- Operate when ascending and abdominal aorta diameter is >5 cm and thoracic aneurysm diameter is >6 cm. Need close follow up post repair.
- When one aneurysm is detected, look for others, including berry aneurysm of the cerebral arteries and popliteal artery aneurysms.
- Rupture and dissection are the most dreaded complication.
- Stanford type A dissections (entry point proximal to the left subclavian) carries with it mortality of 1–2% per hour and is a surgical emergency. Type B dissections are managed medically with IV beta blockers being the first line of therapy followed by IV vasodilators. Type B dissections require surgery if complicated by organ mal perfusion or rupture. CT and TEE are good initial imaging modalities.
- 15–20% of patients may present with intramural hematoma. Intramural hematoma was found to progress to frank dissection in 45% of patients.

Aortitis

- Inflammation of the aorta. Causes are syphilis, mycotic, giant cell arteritis, Takayasu's, ankylosing spondylitis, rheumatoid arthritis, and relapsing polychondritis.
- Thickness of the wall is increased and may be difficult to differentiate from intramural hematoma.
- Thoracic aortic stenosis is most commonly seen in Takayasu's aortitis; syphillis affects the ascending aorta. Ankylosing spondylitis affects the ascending aorta – thickening of the root and nodularities of the aortic valve.

Atherosclerosis

- Associated with stroke and embolic events. >4 mm plaques are prone to emboli. Aortic penetrating ulcers can lead to intramural hematoma. Most are hypertensive and present with chest or back pain.

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Carotid and Vertebral Artery Disease

20

20.1. The arch angiogram in Figure 20.1a demonstrates which type of aortic arch morphology?

A. Type I
B. Type II
C. Type III
D. Type IV

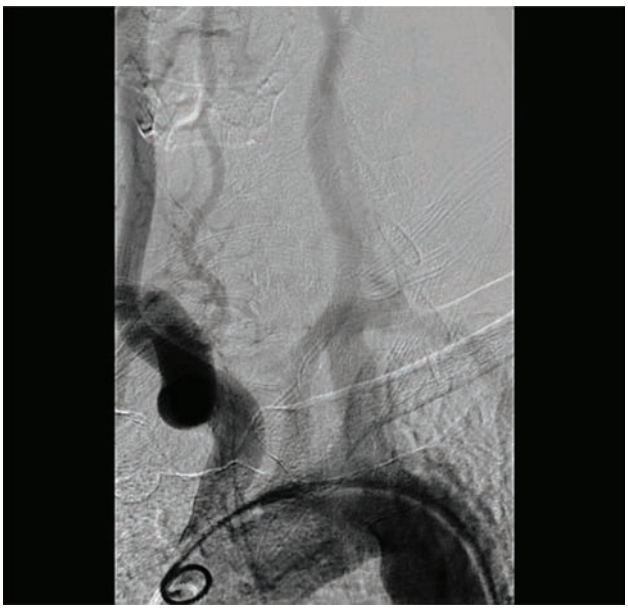

Figure 20.1a

20.2. What does the term "bovine" arch refer to?

A. The aortic arch morphology in cattle
B. A shared common origin of the brachiocephalic and left common carotid arteries
C. A shared common origin of the left subclavian and common carotid arteries
D. A shared common origin of the left and right common carotid arteries

20.3. Which of the following is the most frequent cause of extracranial cerebrovascular disease?

A. Fibromuscular dysplasia
B. Cystic medial necrosis
C. Atherosclerosis
D. Arteritis

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20.4. A 74-year-old man presents for a routine clinical follow-up. He has a 20 pack-year smoking history, having quit smoking 10 years ago, hypertension, and diabetes mellitus. He is clinically asymptomatic and functionally independent. Physical examination is normal with the exception of an audible bruit over the right carotid artery. Which of the following is the most appropriate recommendation?

A. Medication optimization and continued abstinence from cigarette smoking
B. Medication optimization and continued abstinence from cigarette smoking and a carotid duplex ultrasound
C. Medication optimization and continued abstinence from cigarette smoking and a magnetic resonance angiography (MRA) of the head and neck
D. Medication optimization and continued abstinence from cigarette smoking and a computed tomography (CT) of the head and neck

20.5. A 50-year-old woman presents for a routine clinical evaluation. She has a past medical history of gastroesophageal reflux disease and bipolar disorders. She is a nonsmoker. Physical examination is normal with the exception of an audible bruit over the right carotid artery. An electrocardiogram demonstrates sinus rhythm with nonspecific ST–T wave changes. Which of the following is the most appropriate recommendation?

A. Medication optimization and routine health-care maintenance
B. Medication optimization and routine health-care maintenance and carotid duplex ultrasonography
C. Medication optimization and routine health-care maintenance and MRA of the head and neck
D. Medication optimization and routine health-care maintenance and CT of the head and neck

20.6. An 80-year-old right-handed woman with a past medical history of coronary artery disease, sinus node dysfunction status post pacemaker implantation, and hypertension presents to the emergency department. Her laboratory assessment and electrocardiogram are essentially normal. Her daughter reports that she noted that her mother was having some word-finding difficulty on the telephone. She also appeared to be bumping into objects to her left and appeared as though she had not seen them. Ischemia or infarction in which arterial distribution most likely explains this patient's deficits?

A. Left vertebral artery
B. Left internal carotid artery
C. Right vertebral artery
D. Right internal carotid artery

20.7. Bilateral carotid duplex ultrasonography is performed in the patient in Question 20.6. Which criteria are most commonly utilized in assessing the severity of internal carotid artery stenosis by ultrasonography?

A. Visual estimation of the degree of internal carotid stenosis and comparison with the normal-caliber vessel distal to the stenotic segment
B. Measurement of the peak systolic velocity in the internal carotid artery and its ratio with the peak systolic velocity in the external carotid artery
C. Measurement of the peak systolic velocity in the internal carotid artery and its ratio with the peak systolic velocity in the common carotid artery
D. Measurement of the end-diastolic velocity in the internal carotid artery

20.8. The carotid duplex ultrasound performed on the patient in Question 20.6 has equivocal results due to conflicting velocity and ratio data. Which of the following would be most appropriate next step?

A. MRA
B. Repeat carotid duplex ultrasonography with pre-sedation
C. Conventional catheter based angiography
D. CT

20.9. Which of the following treatment strategies is not effective in stroke prevention given the current evidence-based literature?

A. Intensive glucose control and hemoglobin A1c reduction in-patient with diabetes mellitus type 2
B. Interventions aimed at lowering blood pressure below 140/90 mmHg
C. Initiation of high-dose statin medication in patients with recent stroke or transient ischemic attack (TIA)
D. Smoking cessation

20.10. Which of the following antiplatelet regimens is not indicated in reduction of stroke risk in an asymptomatic patient with carotid or vertebral artery atherosclerosis?

A. Aspirin 75–325 mg daily
B. Clopidogrel 75 mg daily
C. Aspirin 75–325 mg plus clopidogrel 75 mg daily
D. Aspirin plus extended-release dipyridamole twice daily

20.11. Which of the following is the recommended method of assessing stenosis severity on angiography?

A. Minimal residual lumen through the zone of stenosis is compared with the estimated diameter of the carotid bulb
B. Minimal residual lumen through the zone of stenosis is compared with the estimated diameter of the common carotid artery
C. Minimal residual lumen through the zone of stenosis is compared with the French size of the diagnostic catheter used during angiography
D. Minimal residual lumen through the zone of stenosis is compared with the diameter of the distal internal carotid artery

20.12. A 68-year-old patient with a past medical history of hypertension and dyslipidemia presents to the hospital with left motor deficit for 7 h. He has a 20 pack-year smoking history. He was previously active. He does not have any active cardiopulmonary disease. A carotid duplex ultrasound demonstrates >70% right internal carotid artery stenosis. Carotid angiography is shown in Figure 20.12. Which of the following is the most effective treatment strategy?

A. Optimization of medical therapy with a target blood pressure less than 140/90 mmHg and initiation of statin therapy in addition to smoking cessation counseling
B. Optimization of medical therapy with a target blood pressure less than 140/90 mmHg and initiation of statin therapy in addition to smoking cessation counseling plus carotid endarterectomy within 2 weeks

C. Optimization of medical therapy with a target blood pressure less than 140/90 mmHg and initiation of statin therapy in addition to smoking cessation counseling plus carotid artery stenting within 2 weeks

D. Optimization of medical therapy with a target blood pressure less than 140/90 mmHg and initiation of statin therapy in addition to smoking cessation counseling and discharge after stabilization; revascularization only if recurrent events

Figure 20.12

20.13. Which of the following patients would not be considered high risk for a carotid endarterectomy?

A. An 84-year-old man with a prior history of stroke. Carotid angiography now demonstrates a complete occlusion of the right internal carotid artery and a high-grade stenosis in the proximal left internal carotid artery.

B. A 75-year-old woman with a prior history of head and neck radiation for previous cancer now presents 2 weeks after an ischemic stroke. Carotid angiography demonstrates a high-grade right internal carotid artery stenosis. The left internal carotid artery is widely patent.

C. A 68-year-old man with a history of inferior wall myocardial infarction 1 year ago which was treated with implantation of a drug-eluting stent in the right coronary artery. He also has a history of diet-controlled diabetes mellitus type 2. He now presents with a left middle cerebral artery territory ischemic stroke. MRA demonstrates a high-grade left internal carotid artery stenosis. The right internal carotid artery is widely patent.

D. A 76-year-old man with a history of coronary artery disease, hypertension, and chronic left ventricular systolic dysfunction presents with dysarthria

and right-sided motor deficit. MRI demonstrates an ischemic stroke. He was discharged from the hospital 3 weeks ago after undergoing coronary artery bypass graft surgery. His post-surgical course was uncomplicated. His estimated left ventricular ejection fraction prior to discharge was 30%.

20.14. A 72-year-old man with a past medical history of hypertension, dyslipidemia, and diabetes mellitus type 2 presents to the hospital with transient left-sided hemiparesis. He is evaluated by neurology, and noninvasive evaluation confirms a high-grade stenosis of the right internal carotid artery. He undergoes carotid endarterectomy with an uncomplicated post-operative course. He now presents to the outpatient clinical for post-discharge follow-up. Which of the following is correct regarding his ongoing management?

- **A.** He should be on aspirin in addition to his antihypertensive and lipid-lowering medication and should have a follow-up carotid ultrasound in 1 month.
- **B.** He should be continued on antihypertensive and lipid-lowering medication and have a follow-up carotid duplex ultrasound in 1 month. Aspirin is not indicated as he does not have a documented history of coronary artery disease and the bleeding risk is too high.
- **C.** He should be on aspirin in addition to antihypertensive medications. A carotid duplex ultrasound should be performed in 1 month. Lipid-lowering medication is not indicated as he has had a successfully uncomplicated carotid endarterectomy unless he has markedly elevated lipid levels.
- **D.** He should be on aspirin in addition to his antihypertensive and lipid-lowering medications. Carotid duplex ultrasound is not indicated for 1 year.

20.15. An 81-year-old man with a prior history of coronary artery disease, chronic obstructive pulmonary disease, hypertension and diabetes mellitus presents to the clinical for post-discharge follow-up. He was recently discharged from the hospital after presenting with a TIA manifested as transient left sided vision loss. He is dependent of 2 liters of oxygen via nasal cannula but is otherwise functioning independently. He had a coronary artery bypass graft surgery about 10 years previously and has not had recurrent angina. Examination reveals a left carotid bruit and carotid duplex ultrasound demonstrates a greater than 70 % left internal carotid artery stenosis confirmed by MRA. What would be the best treatment recommendation?

- **A.** Start aspirin, optimize medical therapy, and follow with serial duplex ultrasound; no carotid intervention is indicated given his age and comorbidities
- **B.** Start aspirin, optimize medical therapy, and refer for carotid endarterectomy
- **C.** Start aspirin, optimize medical therapy, and refer for carotid artery stenting
- **D.** Start aspirin, optimize medical therapy only; order a CT angiogram of the head and neck

20.16. An 85-year old man with a past medical history of hypertension, coronary artery bypass graft surgery, oxygen-dependent chronic obstructive pulmonary disease, and a TIA is referred for carotid angiography. The results are shown in Figure 20.16. He is deemed high risk for carotid endarterectomy and a decision is made to proceed with carotid artery stenting. Which of the following statements is true regarding peri-procedural management?

A. Hemodynamic instability is rare because you are not working on the coronary circulation; therefore, any issues can be addressed on an ad hoc basis as the procedure should be performed quickly
B. If bradycardia develops, a temporary pacemaker should be immediately inserted, as it is likely to be persistent
C. If persistent hypotension develops, intravenous phenylephrine should be easily accessible and immediately administered
D. The patient should be heavily sedated to facilitate rapid completion of the procedure

Figure 20.16

20.17. The patient in Question 20.16 has an uncomplicated post-procedure course and is discharged home the following day. He now presents to the clinic for a follow-up visit. Which of the following is the appropriate post-procedural management strategy?

A. Aspirin and clopidogrel for at least 30 days in addition to antihypertensive medication
B. Aspirin alone in addition to antihypertensive medication
C. No antiplatelet therapy is indicated given the large caliber of the stent and the fact that it is not a drug-eluting device; continue antihypertensive medication
D. Aspirin and clopidogrel for at least 30 days; hold antihypertensive medication to allow systolic hypertension given the history of TIA and carotid stenting

20.18. Which of the following has been demonstrated in the literature regarding the comparative efficacy of carotid artery stenting and carotid endarterectomy?

A. Carotid endarterectomy has a lower risk for death and stroke, while carotid artery stenting has a shorter length of stay and myocardial infarction
B. Carotid artery stenting has a lower risk of myocardial infarction and stroke
C. Carotid endarterectomy and carotid artery stenting have been shown to be equivalent across all endpoints as long as patient selection is performed diligently
D. Carotid endarterectomy is associated with a lower rate of peri-procedural stoke, while carotid artery stenting is associated with a lower rate of peri-procedural myocardial infarction or cranial nerve injury

20.19. A 68-year-old patient with a past medical history of hypertension and coronary artery disease presents for a clinical consultation. He has a 20 pack-year smoking history. He reports that he has intermittent episodes of dizziness and sometimes feels that he has double vision. He thinks that his symptoms are from cervical arthritis because they are more noticeable when he turns his head. He has also noted ringing in his years. These symptoms have been present for several months. He has been seen by an ENT specialist and the evaluation was negative. Which of the following is the best diagnostic test?

A. He likely has benign positional vertigo; therefore, empiric medical therapy should be initiated without any further imaging
B. CT angiography of the head and neck
C. Duplex ultrasound of the great vessels
D. Referral to another ENT specialist for a second opinion

20.20. A 75-year-old man with a past medical history of hypertension, dyslipidemia, and diabetes mellitus type 2 presents to establish himself as a new patient. He quit smoking about 5 years ago but has a 40 pack-year smoking history. He is physically active and has no complaints of chest pain or disproportionate dyspnea. He denies any dizziness or lightheadedness. He is an avid tennis player and denies any limitations during his game. Physical examination demonstrates a loud left infraclavicular bruit. A duplex ultrasound demonstrates a left subclavian artery stenosis with flow reversal in the ipsilateral vertebral artery? What is the most appropriate treatment strategy?

A. Medication optimization and risk factor modification
B. Referral to a vascular surgeon for consideration for subclavian–carotid bypass
C. Referral to an endovascular specialist for consideration for percutaneous intervention on the subclavian artery
D. Instruct him to limit left arm utilization to prevent disease progression

20.21. A 35-year-old patient presents with severe right-sided neck discomfort after a bout of coughing. She also thinks that she may have had transient blindness in the right eye. She has no known past medical history. Physical examination reveals that her right eyelid is drooping. Which of the following is the most appropriate next step in her management?

A. Immediate referral to an ophthalmologist as she likely has a detached retina.
B. Reassurance, as she likely has whiplash with self-limiting symptoms
C. CT angiography of the head and neck
D. Catheter-based angiography of the great vessels

20.22. The patient in Question 20.21 undergoes a CT angiography which demonstrates a right carotid artery dissection. Which is the most appropriate initial therapeutic modality?

A. Surgical bypass
B. Carotid stenting
C. Anticoagulation with heparin followed by warfarin
D. No specific therapy is indicated as, in an otherwise young healthy individual, the dissection will heal over time

Answers

20.1. B. Type II.

The three types of aortic arch morphologies are determined by the relationship of the brachiocephalic trunk to the aortic arch. In the type I morphology, the origin of all three great vessels originates from the same linear plane. In type II, the brachicephalic trunk originates from a plane between the outer and inner curvatures of the aortic arch as demonstrated in Figure 20.1b. In type III, it originates below the inner curvature of the aortic arch.

Figure 20.1b

20.2. B. A shared common origin of the brachiocephalic and left common carotid arteries.

The bovine arch is a variant of normal arch anatomy in which the brachiocephalic artery (black arrow in Figure 20.2) and the left common carotid (brown arrow in Figure 20.2) artery share a common origin from the aortic arch.

Figure 20.2

20.3. C. Atherosclerosis.

Systemic atherosclerosis remains the most frequent cause of extracranial cerebrovascular disease. Other causes, such as fibromuscular dysplasia, cystic medial necrosis, arteritis, and dissection, are much less prevalent.

20.4. B. Medication optimization and continued abstinence from cigarette smoking and a carotid duplex ultrasound.

In a patient with multiple atherosclerotic risk factors and an asymptomatic carotid bruit, a carotid duplex ultrasound should be performed in addition to medication optimization and risk factor modification. However, it should be noted that a bruit itself is more likely a marker of the systemic atherosclerosis rather an of significant carotid artery stenosis.

20.5. A. Medication optimization and routine health-care maintenance.

In an asymptomatic patient without significant risk factors for atherosclerosis, there is no indication for further diagnostic evaluation of a carotid bruit. The positive predictive value for a significant carotid stenosis in such a patient is relatively low. Therefore, the best course of action is to continue with medication optimization and routine health-care maintenance.

20.6. B. Left internal carotid artery.

Ischemia in the left internal carotid artery may lead to right-sided motor and sensory deficit. It may also cause aphasia, often manifested as word-finding difficulty. Left-sided monocular blindness is another manifestation. Vertebrobasilar

system insufficiency most often results is ataxia, a lack of coordination, dizziness, and cranial nerve deficits. Right internal carotid artery ischemia may lead to left-sided motor and sensory deficits, monocular blindness affecting the right eye, and left-sided neglect, among other symptoms. Aphasia may be seen in patients with right internal carotid ischemia in those that are left-handed or ambidextrous.

20.7. C. Measurement of the peak systolic velocity in the internal carotid artery and its ratio with the peak systolic velocity in the common carotid artery.

The consensus is that the peak velocity in the internal carotid artery, the ratio of the systolic velocities in the internal and *common* carotid artery, *as well as* the end-diastolic velocity in the internal carotid artery be used in estimating the degree of stenosis within the internal carotid artery. Table 20.7 provides a rough guideline.

Table 20.7

Degree of stenosis (%)	Peak systolic velocity ICA (cm/s)	ICA : CCA ratio	End-diastolic velocity ICA (cm/s)
50–69	125–230	2–4	40–100
>70	>230	>4	>100

CCA: common carotid artery; ICA: internal carotid artery.

20.8. D. CT.

Although carotid duplex ultrasonography is the most cost-effective first diagnostic test in evaluating carotid stenosis, the possibility of equivocal results often necessitates further testing. Alternatives include conventional catheter-based angiography, MRA, and computed angiography. The choice of testing modality is often dependent on institutional availability and expertise. MRA provides a highly sensitive and specific alternative in assessing the carotid vasculature for stenosis. However, its use is limited in patients with implantable devices such as pacemaker and defibrillators, and those with morbid obesity and claustrophobia. In addition, there is a tendency for overestimation of stenosis severity. CT angiography also provides an excellent alternative and would be the test of choice in this individual given the presence of a pacemaker. Its sensitivity and specificity are comparable to conventional angiography. Heavy calcification leads to a decrease in sensitivity and specificity. In addition, the requirement for use of iodinated contrast material limits its use in those with significant renal dysfunction. Catheter-based conventional angiography remains the gold standard for vascular imaging, but it should be used as the last option given its associated costs and the risks associated with an invasive procedure. It may be used when the aforementioned contraindications preclude the use of noninvasive modalities.

20.9. A. Intensive glucose control and hemoglobin A1c reduction in-patient with diabetes mellitus type 2.

Intensive glucose control and reduction of hemoglobin A1c levels below 6.0–6.5% has not been shown to reduce the risk to stroke in patients with diabetes mellitus type 2 in several contemporary clinical trials. The other modalities stated in this question, including blood pressure reduction, high-dose statin, and smoking cessation, have in fact been associated with significant reductions in strokes. Hyperhomocysteinemia is another biochemical abnormality associated with increased risk of stroke. The administration of vitamins, mainly B vitamins, does lower plasma homocystein levels, but without an effect of stroke risk.

20.10. C. Aspirin 75–325 mg plus clopidogrel 75 mg daily.

Aspirin plus clopidogrel has not been shown to be more effective than either therapy alone in the reduction of stroke risk in clinical trials. Aspirin alone, clopidogrel alone, and the combination of aspirin plus extended-release dipyridamole, on the other hand, have demonstrated efficacy in the reduction in stroke risk.

20.11. D. Minimal residual lumen through the zone of stenosis is compared with the diameter of the distal internal carotid artery.

The North American Symptomatic Carotid Endarterectomy Trial criteria, which compares the zone of stenosis with the diameter of the distal normal segment of internal carotid artery, are the most commonly used criteria for estimating the degree of stenosis. These criteria have led to the delineation of cutoffs of degrees of stenosis most likely to benefit from carotid revascularization.

20.12. B. Optimization of medical therapy with a target blood pressure less than 140/90 mmHg and initiation of statin therapy in addition to smoking cessation counseling plus carotid endarterectomy within 2 weeks.

In patients with symptomatic carotid stenosis of greater than 70% by noninvasive assessment and >50% by invasive assessment, revascularization within 2 weeks is indicated in addition to medical optimization. The rates of death, stroke, or TIA are significantly higher with medical therapy alone in this group of patients.

20.13. C. A 68-year-old man with a history of inferior wall myocardial infarction 1 year ago which was treated with implantation of a drug-eluting stent in the right coronary artery. He also has a history of diet-controlled diabetes mellitus type 2. He now presents with a left middle cerebral artery territory ischemic stroke. MRA demonstrates a high-grade left internal carotid artery stenosis. The right internal carotid artery is widely patent.

Clinical characteristics considered high risk for a carotid endarterectomy include contralateral carotid occlusion or stenosis greater than 50%, significant cardiopulmonary disease, a history of radical neck surgery or radiation, prior history of coronary artery bypass graft, age greater than 80 years, and New York Heart Association class III/IV heart failure. Prior carotid endarterectomy or carotid stenting is also among high-risk features.

20.14. A. He should be on aspirin in addition to his antihypertensive and lipid-lowering medication and should have a follow-up carotid ultrasound in 1 month.

Aggressive secondary prevention measures are indicated in all patients after successful carotid revascularization. This includes antiplatelet therapy with aspirin and continued medical optimization of cardiovascular risk factors.

Carotid duplex ultrasonography is recommended at intervals of 1 month, 6 months, and annually thereafter until serial examinations demonstrate stability.

20.15. C. Start aspirin, optimize medical therapy, and refer for carotid artery stenting

Revascularization is clearly indicated in this symptomatic patient with demonstration of carotid stenosis in the area of cerebral ischemia. Given his multiple risk factors, he would be a candidate for carotid artery stenting.

20.16. C. If persistent hypotension develops, intravenous phenylephrine should be easily accessible and immediately administered.

Transient hemodynamic instability in the form of bradycardia or hypotension is not rare during the carotid stenting procedure. Atropine and phenylephrine should be readily available in the catheterization laboratory and immediately administered in the event hemodynamic instability. A temporary pacemaker should only be inserted in the event of persistent bradycardia not responsive to intravenous atropine. The patient should be minimally sedated so that neurologic status can be assessed throughout the procedure.

20.17. A. Aspirin and clopidogrel for at least 30 days in addition to antihypertensive medication.

Dual antiplatelet therapy with aspirin and clopidogrel is recommended for at least 30 days, as there is a risk for stent thrombosis while the stent endothelializes. In addition, after the acute hospital course, risk factors should be managed as per national guidelines, and there is no role for permissive hypertension after the acute hospitalization.

20.18. D. Carotid endarterectomy is associated with a lower rate of peri-procedural stoke, while carotid artery stenting is associated with a lower rate of peri-procedural myocardial infarction or cranial nerve injury.

Meta-analysis has demonstrated that carotid endarterectomy and stenting have comparable rates of stroke, death, or myocardial infarction over the 30-day and 1-year periods. However, carotid endarterectomy has been associated with a lower risk of peri-procedural stroke, which has translated to a high risk of peri-procedural mortality. Carotid artery stenting, on the other hand, is associated with a lower risk of peri-procedural myocardial infarction and cranial nerve injury.

20.19. B. CT angiography of the head and neck.

This patient's symptoms may be stemming from vertebrobasilar insufficiency. Symptoms of dizziness, diplopia, and tinnitus, although not specific, can be attributable to the vertebrobasilar system when taken together. Ultrasound has a lower sensitivity and specificity for detecting significant vertebral artery disease. The test of choice should be a CT angiogram or MRA. Catheter-based angiography may be needed prior to consideration for revascularization to reliably identify the origin of the vertebral arteries.

20.20. A. Medication optimization and risk factor modification.

This patient has asymptomatic subclavian artery stenosis with steal syndrome as demonstrated by flow reversal in the ipsilateral vertebral artery. There is no indication for revascularization in such a patient, whether surgical or endovascular, unless the ipsilateral internal mammary artery is required for surgical

myocardial revascularization. Medical optimization and risk factor modification should continue to prevent acute cardiovascular events.

20.21. C. CT angiography of the head and neck.

This patient's symptoms are concerning for spontaneous carotid artery dissection and should be further evaluated with a CT angiogram.

20.22. C. Anticoagulation with heparin followed by warfarin.

Initial therapy for a spontaneous carotid dissection is usually anticoagulation with heparin followed by warfarin for 3–6 months. Revascularization is reserved for patients who continue to exhibit recurrent symptoms despite adequate anticoagulation.

Peripheral Vascular Disease

21

21.1. Cigarette smoking increases the odds ratio of peripheral vascular disease by which of the following?

A. Sevenfold
B. Threefold
C. Ninefold
D. Twofold
E. None of the above

21.2. The underlying mechanism(s) of peripheral vascular disease is/are which of the following?

A. Atherosclerosis
B. Hypoperfusion
C. Artery spasm
D. A and C

21.3. The highest incidence worldwide of peripheral vascular disease is seen in which of the following populations?

A. Asian Indians
B. Native American Indians
C. Indo-Caribbeans
D. Eskimo Indians

21.4. Which of the following is/are correct about peripheral vascular disease (PVD)?

A. Framingham risk score >10% has a higher incidence of PVD
B. Aspirin does not appear to help those with mild disease
C. Leg pain that is worsened by standing in one place but better with walking
D. Age over 70 years is associated with higher prevalence of PVD
E. All of the above

21.5. A 30-year-old male 6 ft 8 in tall, myopic, presents with left-sided transient ischemic attack. This patient is at high risk for what other conditions or what features?

A. High incidence of venous thromboembolism in postoperative state.
B. Abnormal lower extremity pulse examination
C. Bony abnormalities
D. Shortened life span
E. Autosomal recessive inheritance
F. Autosomal dominant inheritance
G. A, B, C, D, and E
H. A, B, C, D, and F

21.6. Which of the following statements regarding smoking cannabis is/are correct?

A. Causes arteritis picture like Burger's disease
B. δ-8- and δ-9-tetrahydrocanabinols cause severe vasospasm
C. May cause strokes
D. Venous thrombosis may occur
E. All of the above

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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21.7. Which of the following statement(s) is/are true regarding ankle brachial index (ABI)?
- **A.** An ABI of 1.5 is associated with high cardiovascular mortality
- **B.** Is the first-line study upon suspicion peripheral arterial disease (PAD)
- **C.** A decrease in ABI of 15–20% after exercise would be diagnostic of PAD
- **D.** An ABI of 0.4 is associated with high cardiovascular mortality
- **E.** All of the above

21.8. A 60-year-old male has a history of smoking and hypertension and complains of intermittent claudication. His ABI is 0.7. What is the best next step?
- **A.** Computed tomography (CT) of lower extremities
- **B.** Magnetic resonance angiography (MRA) of lower extremities
- **C.** Doppler ultrasound of lower extremities
- **D.** Angiography
- **E.** Cardiac risk factor modification and a supervised exercise regimen

21.9. Which of the following is used for PAD classification?
- **A.** Trans-Atlantic Inter-Society Consensus (TASC) II
- **B.** Wound, ischemia, and foot infection (WIfI)
- **C.** Fontaine stages
- **D.** Robert B. Rutherford
- **E.** All of the above

21.10. Which of the following is/are correct?
- **A.** Individuals with PAD have an exceptionally elevated risk for cardiovascular events
- **B.** The majority will eventually die of a cardiac or cerebrovascular etiology
- **C.** Prognosis is correlated with the severity of the PAD as measured by the ABPI
- **D.** Large-vessel PAD increases mortality from cardiovascular disease significantly
- **E.** PAD carries a greater than 20% risk of a coronary event in 10 years
- **F.** All of the above.

21.11. Which of the following is the commonest clinical presentation of PAD in patients ≥50 years of age?
- **A.** Asymptomatic
- **B.** Atypical leg pain
- **C.** Classic claudication
- **D.** Threatened limb

21.12. A 57-year-old male with 30-year smoking history and diabetes mellitus presents with buttock pain on walking and erectile dysfunction. He also reports that his legs look thinner than in the past. On examination there is an extremely weak femoral pulse bilaterally. What is the most likely diagnosis?
- **A.** Coarctation of the aorta
- **B.** Leriche syndrome
- **C.** Lumbar spinal stenosis
- **D.** All of the above

21.13. A 56-year-old male with history of smoking and diabetes mellitus presents with calf pain on walking that resolves with resting. Bedside ABI is 0.91. What is the best next step?
- **A.** Doppler ultrasound
- **B.** CT
- **C.** MRA
- **D.** Exercise testing

21.14. A 56-year-old male with history of smoking and diabetes presents with a right cold foot. Ultrasound shows a thrombosed popliteal artery aneurysm. What is the treatment of choice?

A. Tissue plasminogen activator infusion followed by stent implantation
B. Direct covered stent implantation
C. Tissue plasminogen activator infusion of the aneurysm followed by surgical bypass
D. None of the above

21.15. What is/are the indication for popliteal artery aneurysm repair?

A. All popliteal aneurysms should be repaired
B. All symptomatic aneurysms that present with acute limb ischemia regardless of size
C. Patients with patent popliteal aneurysms ≥2.0 cm in diameter
D. B and C

21.16. A 25-year-old female with no significant medical history presents with calf pain upon competitive bicycling. Bedside ABI is 0.91. The popliteal pulse is diminished upon plantar flexion of the foot against the floor. What is the most likely diagnosis?

A. Popliteal aneurysm
B. Popliteal arteritis
C. Popliteal entrapment syndrome
D. None of the above

21.17. A 40-year-old obese male with no medical problem presents complaining of chronic intermittent claudication. ABI is 1.0, and Doppler ultrasound normal. Angiogram shows obstruction of right popliteal artery. What is the most likely diagnosis?

A. Atherosclerosis of the popliteal artery
B. Popliteal artery spasm
C. Adventitial cystic disease
D. Buerger's disease

21.18. A 45-year-old male heavy smoker presents with black skin discoloration and pain in both hands and feet. What is the strongest risk factor?

A. Diabetes mellitus
B. Cigarette smoking
C. Hypertension
D. Hyperlipidemia

21.19. Which of the following is/are an indication for intervention to the infrageniculate arteries?

A. Rest pain
B. Nonhealing ulcerations
C. Severe pain on walking
D. A and B

21.20. Which of the following is/are true about an arterial ulcer?

A. It occurs at tips of toes, heel, and lateral ankle
B. Painful
C. Edema
D. A and B

21.21. Which of the following is/are a feature of a venous ulcer?

A. Minimal pain
B. Large punched-out ulcer
C. Capillary refill >3.0 s
D. None of the above

21.22. A 69-year-old male with history of smoking, diabetes mellitus, hypertension, and paroxysmal atrial fibrillation on aspirin presents with acute severe right foot pain.

Examination reveals delayed capillary refill, weakness, decreased sensation, and inaudible arterial Doppler. What is the best next step?

A. Angiography
B. Thrombolysis
C. Emergency embolectomy
D. Intravenous heparin

21.23. A 56-year-old female presents complaining of leg pain and heaviness. Examination shows varicose veins, with pigmentation and edema. No ulcer. What is the clinical, etiological, anatomical, and pathophysiological (CEAP) class in this patient?

A. C1
B. C2
C. C3
D. C4a

21.24. Which of the following is/are a risk factor for chronic venous disease?

A. Increased body mass index
B. Smoking
C. Presence of arteriovenous shunt
D. Flat feet
E. All of the above

21.25. A 25-year-old obese female with no significant medical history presents with recurrent left lower extremity deep vein thrombosis. Antithrombin III, protein C, protein S, factor V Leiden, and prothrombin G20210A are all normal. What is the most accurate confirmatory diagnostic test?

A. Intravascular ultrasound
B. Venography
C. Venous/interstitial pressure measurement
D. Plethysmography

21.26. Which of the following is/are a contraindication to lower extremity venous ablation?

A. Acute deep vein thrombosis
B. Joint disease that interferes with mobility
C. Klippel–Trenaunay syndrome
D. All of the above

21.27. Which of the following is/are a complication of varicose veins?

A. Stasis dermatitis
B. Pulmonary embolism
C. Carcinoma
D. A, B, and C

21.28. A 78-year-old diabetic male with history of a quadruple coronary artery bypass graft 8 years ago is referred to you by his primary care doctor for difficult-to-control blood pressure (BP). He was admitted to the hospital 3 months ago with acute pulmonary edema. He is currently on benazepril 40 mg/day, amlodipine 10 mg/day, metoprolol 50 mg BID. His BP is 180/110 mmHg. You add clonidine 0.1 mg TID. The creatinine is 1.9 mg/gL. What is the next most appropriate step?

A. Renal vein renin sampling
B. CT angiography
C. Abdominal angiography using carbon dioxide
D. MRA

21.29. What is the gold standard for diagnosing renal artery stenosis (RAS)?

A. CT angiography
B. MRA
C. Renal arteriography
D. Duplex Doppler ultrasonography

21.30. Which of the following describes superior mesenteric artery syndrome?

A. A clinical entity characterized by a decreased acuity of the angle between the aorta and superior mesenteric artery due to the loss of mesenteric fat between the superior mesenteric artery and aorta resulting in compression of the third portion of the duodenum.
B. Present with symptoms consistent with a proximal small bowel obstruction.
C. An aortomesenteric artery angle of ≤40° is the most sensitive measure of diagnosis.
D. A and B
E. A, B, and C

21.31. An 80-year-old female presents with chronic postprandial abdominal pain and weight loss of 30 lb over the last 6 months. She can only eat small portions due to severe abdominal pain. She has prior percutaneous coronary intervention to the left anterior descending and right coronary arteries. She also had a right superficial femoral artery stent 8 months ago. There is a history of a transient ischemic attack in the past, and she has a left carotid bruit. Abdominal examination detects an abdominal bruit. Abdominal ultrasound is normal. What is the most likely clinical diagnosis?

A. RAS
B. Chronic pancreatitis
C. Celiac artery compression syndrome
D. None of the above

21.32. Which of the following is/are types of varicosities?

A. Reticular veins
B. Telangiectasia
C. Varicose veins
D. Venulectasia
E. All of the above

21.33. ACC/AHA guidelines recommend which of the following in critical limb ischemia (CLI)?

A. Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk.
B. Patients with CLI and features to suggest athero-embolization should not be evaluated for aneurysmal disease.
C. Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection.
D. A and C

21.34. In PAD diagnosis, which of the following is/are correct?

A. Exercise treadmill tests are recommended to provide the most objective evidence of the magnitude of the functional limitation of claudication and to measure the response to therapy.
B. Duplex ultrasound of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD.

C. Duplex ultrasound of the extremities can be useful to select patients as candidates for endovascular intervention.
D. Duplex ultrasound can be useful to select patients as candidates for surgical bypass and to select the sites of surgical anastomosis.
E. All of the above

21.35. In treatment of PAD, which of the following is correct?
A. Beta-adrenergic blocking drugs are effective antihypertensive agents and are not contraindicated in patients with PAD.
B. Antiplatelet therapy is indicated to reduce the risk of myocardial infarction (MI), stroke, or vascular death in individuals with atherosclerotic lower extremity PAD.
C. A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure).
D. All of the above.

21.36. Which of the following is/are indications for percutaneous revascularization of RAS?
A. Patients with hemodynamically significant RAS
B. Recurrent, unexplained congestive heart failure
C. Sudden, unexplained pulmonary edema
D. A and B
E. A, B, and C

21.37. Which of the following statements regarding chronic intestinal ischemia is/are true?
A. Should be suspected in patients with abdominal pain and weight loss without other explanation, especially those with cardiovascular disease.
B. Only duplex ultrasound, but not CT angiography, and gadolinium-enhanced MRA are useful initial tests for supporting the clinical diagnosis of chronic intestinal ischemia.
C. Surgical revascularization is indicated for patients with asymptomatic intestinal arterial obstructions.
D. Percutaneous endovascular treatment of intestinal arterial stenosis is not indicated in patients with chronic intestinal ischemia.

21.38. An 80-year-old male undergoes endovascular aneurysm repair uneventfully. The next day he develops severe abdominal pain and a "trash" foot. The next best step is which of the following?
A. Duplex sonography of the abdomen is an appropriate diagnostic tool for suspected acute intestinal ischemia.
B. Surgical consultation
C. Angiography
D. CT angiography

21.39. A 23-year-old female presents with symptoms of hypertension, intermittent claudication, and renal failure. What is the most likely diagnosis?
A. RAS
B. Pheochromocytoma
C. Midaortic syndrome
D. Renal vein thrombosis

21.40. A 70-year-old female presents with several near-syncopal spells and chest pain followed by vigorous mopping. She is status post coronary artery bypass grafting 10 years ago (Figure 21.40a). The right arm systolic BP is 140 mmHg; the left arm systolic BP is 110 mmHg. She smokes one pack per day. The next best step is which of the following?

A. CT angiography of the chest and neck
B. Ultrasound of the carotid and subclavian arteries
C. MRA of the chest and neck
D. Coronary and subclavian angiography and intervention

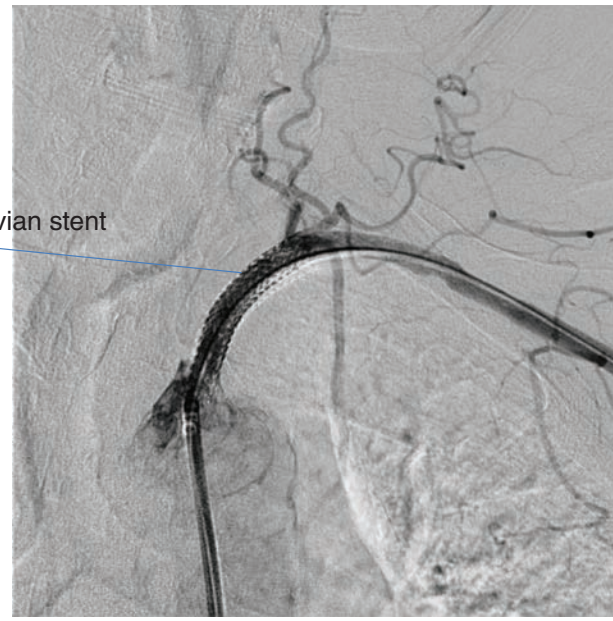

Figure 21.40a

Answers

21.1. A. Sevenfold.

Cigarette smoking increases the odds ratio for peripheral vascular disease by 7.3-fold. Other risk factors include diabetes mellitus, hypertension, and hyperlipidemia (Shammas, 2007).

21.2. D. A and C.

The underlying mechanisms of peripheral vascular disease are atherosclerosis and artery spasm.

21.3. A. Asian Indians.

See Fowkes *et al.* (2013).

21.4. E. All of the above.

21.5. G. A, B, C, D, and E.

Features are suggestive of hyperhomocysteinemia: autosomal recessive inheritance (most enzymatic defects) with Marfanoid features, premature atherosclerosis, downward lens dislocation, and mental retardation. It is a defect of methionine metabolism. Pyridoxine, at a dose of 100–500 mg/day, is the drug of choice for treatment.

21.6. E. All of the above.

See Disdier *et al.* (2001).

21.7. D. An ABI of 0.4 is associated with high cardiovascular mortality.

The first-line study in patient with PAD is the ankle brachial pressure index (ABPI/ABI). Normal ABI range is 1.00–1.40. The patient is diagnosed with PAD when the ABI is ≤0.90. ABI values of 0.91–0.99 are considered "borderline," and values >1.40 indicate noncompressible arteries. PAD is graded as mild to moderate if the ABI is between 0.41 and 0.90, and an ABI <0.40 is suggestive of severe PAD. See Box 21.1 and Figure 21.7.

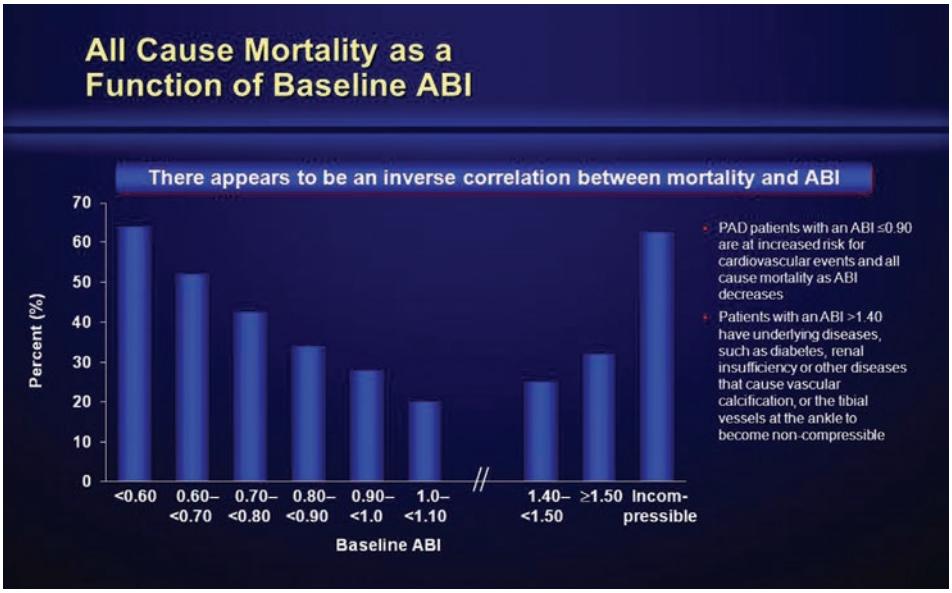

Figure 21.7 All-cause mortality as a function of baseline ABI. *Source:* adapted from Resnick *et al.* (2004).

21.8. E. Cardiac risk factor modification and a supervised exercise regimen.

If ABIs are abnormal the next best step is cardiovascular risk factor modification and a supervised walking regimen.

21.9. E. All of the above.

See Tables 21.9a, 21.9b, and 21.9c.

21.10. F. All of the above.

Table 21.9a Fontaine stages.

Stage	Clinical
I	Asymptomatic
IIa	Mild claudication
IIb	Moderate to severe claudication
III	Ischemic rest pain
IV	Ulceration or gangrene

Table 21.9b Rutherford.

Grade	Category	Clinical
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischemic rest pain
III	5	Minor tissue loss
III	6	Major tissue loss

Table 21.9c TASC II classification of superficial femoral artery occlusion.

Type	Clinical
A	Single occlusion <5 cm in length
B	Single occlusion <5 cm but heavily calcified, or multiple occlusions each <5 cm, or single occlusion <15 cm
C	Multiple occlusion >15 cm
D	Chronic total occlusion >20 cm

21.11. A. Asymptomatic.

The 2005 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on PAD suggested the following distribution of clinical presentation of PAD in patients ≥50 years of age:

- asymptomatic, 20–50%;
- atypical leg pain, 40–50%;
- classic claudication, 10–35%;
- threatened limb, 1–2%.

21.12. B. Leriche syndrome.

Leriche syndrome is the triad of buttock claudication, atrophy of the lower extremities, and erectile dysfunction. Lesion involves truncation of the terminal aorta with collateral formation via the inferior mesenteric artery, the sacral artery, and the iliolumbar arteries (Figure 21.12a). The internal mammary artery can also anastomose with the inferior epigastric artery to supply collaterals. The infrarenal aorta is occluded. Inferior mesenteric artery and lumbar collaterals are seen (arrows in Figure 21.12b).

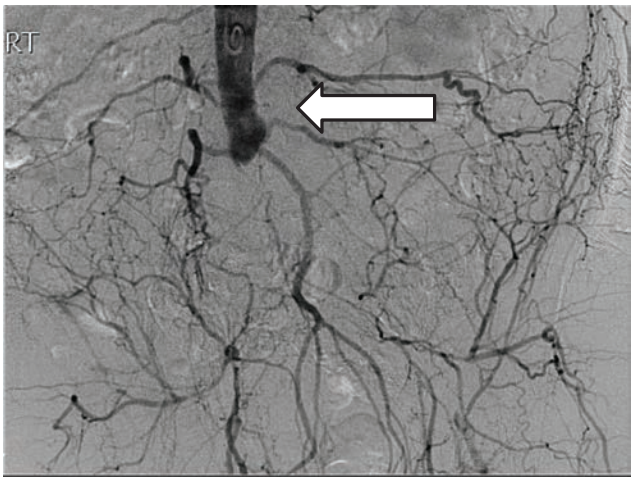

Figure 21.12a Total occlusion of the infrarenal aorta.

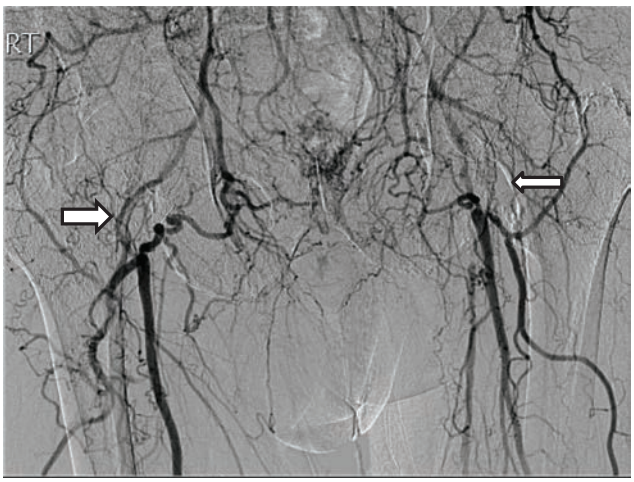

Figure 21.12b Bilateral superficial femoral arteries filling via collaterals.

21.13. D. Exercise testing.

In people with suspected PAD but normal resting ABIs, exercise testing of ABI can be done. A baseline ABI is obtained prior to exercise. The patient is then

asked to exercise (usually patients are made to walk on a treadmill at a constant speed) until claudication pain occurs (or a maximum of 5 min), following which the ankle pressure is again measured. A decrease in ABI of 15–20% would be diagnostic of PAD.

21.14. C. Tissue plasminogen activator infusion of the aneurysm followed by surgical bypass.

Graft patency is improved if thrombus burden is reduced prior to bypass. Also, three-vessel runoff improves long-term graft patency. The popliteal artery is the most common site of a peripheral artery aneurysm that causes symptoms of lower extremity ischemia, which is due to aneurysm thrombosis. The presence of a peripheral aneurysm should prompt evaluation for other aneurysms (Carpenter *et al.*, 1994).

21.15. D. B and C.

The indications for popliteal artery repair are: all symptomatic aneurysms that present with acute limb ischemia regardless of size, to relieve symptoms and minimize the risk of limb loss, and patients with patent popliteal aneurysms ≥2.0 cm in diameter, as these patients have a 30–40% risk of developing acute ischemic complications which are associated with a high risk for limb loss.

21.16. C. Popliteal entrapment syndrome.

This entity results from a developmental defect in which the popliteal artery passes medial to and beneath the medial head of the gastrocnemius muscle or a slip of that muscle, with consequent compression of the artery. Rarely, an anomalous fibrous band or the popliteus muscle deep to the medial head of the gastrocnemius is the compressing structure. Treatment is surgical release of the artery.

21.17. C. Adventitial cystic disease.

Adventitial cystic disease is a rare entity that can lead to arterial obstruction related to mucoid degeneration of the artery due to cyst formation in the adventitia and compression of the popliteal artery. When it occurs in the femoral or popliteal artery, claudication symptoms are indistinguishable from atherosclerotic popliteal disease. Patients tend to be younger, and typical risk factors for cardiovascular disease are often absent. Etiology is unknown.

21.18. B. Cigarette smoking.

Thromboangiitis obliterans (Buerger's disease) is a nonatherosclerotic, segmental, inflammatory disease that most commonly affects the small- to medium-sized arteries and veins of the extremities. Patients are younger than the typical patients with atherosclerotic vascular disease, and are heavy smokers. Digit ischemia is the most common presentation; and although larger artery involvement is uncommon, claudication can occur but is nearly always associated with signs of distal ischemia.

21.19. D. A and B.

Both rest pain and nonhealing ulcer are indication for intervention. Above the knee, intervention is indicated for claudication.

21.20. D. A and B.

Arterial ulcer characterized by

- being painful
- decreased/absent pulses

- pallor on elevation, rubor on dangling
- thin shiny skin with hair loss
- located at tips of toes, heel, lateral ankle, dorsum of the feet
- punched out and well defined
- covered with slough and necrotic tissue
- no edema
- capillary refill >3 s
- ABI <0.75.

21.21. A. Minimal pain.

Features of venous ulcer include:

- painless/minimal pain
- pulses present
- brown varicose vein/pigmentation
- thick, hardened skin
- located at medial gaiter region
- sloping and gradual, covered with slough
- edema present
- capillary refill <3 s
- ABI >0.9.

21.22. A. Angiography.

This patient needs angiography to define the location and extent of the thrombus, and then procced with emergency surgery. See Table 21.22.

21.23. D. C4a.

CEAP clinical classification:
C0 – no visible or palpable signs of venous disease
C1 – telangiectasias or reticular veins
C2 – varicose veins
C3 – edema
C4a – pigmentation or eczema
C4b – lipodermatosclerosis or atrophie blanche
C5 – healed venous ulcer
C6 – active venous ulcer.

Table 21.22 Classification of acute limb ischemia

	Viable	Threatened	Nonviable
Pain	Mild	Severe	Variable
Capillary refill	Intact	Delayed	Absent
Motor deficit	None	Partial	Complete
Sensory deficit	None	Partial	Complete
Arterial Doppler	Audible	Inaudible	Inaudible
Venous Doppler	Audible	Audible	Inaudible
Treatment	Urgent work-up	Emergency surgery	Amputation

21.24. E. All of the above.

The risk factors for chronic venous disease include advanced age, family history of venous disease, smoking, sedentary lifestyle, lower extremity trauma, prior venous thrombosis (superficial or deep), ligamentous laxity (e.g., hernia, flat feet), prolonged standing, increased body mass index, the presence of arteriovenous shunt, high estrogen states, and pregnancy.

21.25. A. Intravascular ultrasound.

This is because the flattened vein may not be noticed on conventional venography.

This patient has May–Thurner syndrome (iliac vein compression syndrome) is a rare condition of compression of left common iliac vein (Figure 21.25) by the overlying right common iliac artery which causes stasis of blood, predisposing the individual to the formation of blood clots. Severe May–Thurner syndrome may require thrombolysis if there is a recent onset of thrombosis, followed by angioplasty and stenting of the iliac vein.

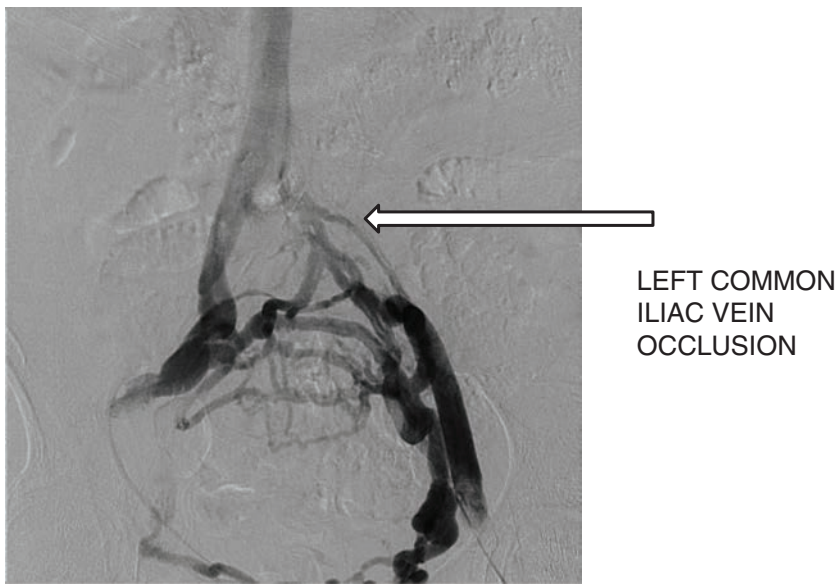

Figure 21.25

21.26. D. All of the above.

Contraindications to lower extremity venous ablation are pregnancy, acute superficial or deep vein thrombosis, moderate to severe peripheral artery disease, joint disease that interferes with mobility, Klippel–Trenaunay syndrome, and advanced generalized systemic disease that limits quality-of-life improvements expected following venous intervention.

21.27. D. A, B, and C.

Varicose veins complications are:

- Pain, tenderness, heaviness, stasis dermatitis, venous ulcers. Development of carcinoma or sarcoma in longstanding venous ulcers is about 0.4–1%.

- Severe bleeding from minor trauma; superficial thrombophlebitis, which is frequently isolated to the superficial veins, but can extend into deep veins, becoming a more serious problem.
- Acute fat necrosis can occur, especially at the ankle of overweight patients with varicose veins.

21.28. C. Abdominal angiography using carbon dioxide.

A CO_2 angiogram is the safest to define anatomy and intervention in this diabetic patient. The following are suggestive of reno-vascular disease:

- An acute elevation in serum creatinine of at least 30% after administration of angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
- Moderate to severe hypertension in a patient with diffuse atherosclerosis, a unilateral small kidney, or asymmetry in renal size of more than 1.5 cm that cannot be explained by another reason.
- Moderate to severe hypertension in patients with recurrent episodes of flash pulmonary edema.
- Onset of stage II hypertension after age 55 years.
- Systolic or diastolic abdominal bruit.

21.29. C. Renal arteriography.

The gold standard for RAS diagnosis is renal arteriography, but duplex Doppler ultrasonography, CT angiography, and MRA are noninvasive tests and reasonable alternatives for initial testing.

Captopril renal scintigraphy (renography), selective renal vein renin measurements, and plasma renin activity (in isolation or after captopril administration)

Figure 21.29 Bilateral RAS.

are not useful as initial diagnostic tests for RAS, although renography is useful to determine the relative function of each kidney.

21.30. D. A and B.

Superior mesenteric artery syndrome (Cast syndrome, Wilkie syndrome, arteriomesenteric duodenal obstruction, and chronic duodenal ileus) is an unusual cause of proximal intestinal obstruction, characterized by compression of the third portion of the duodenum due to narrowing of the space between the superior mesenteric artery and aorta and is primarily attributed to loss of the intervening mesenteric fat pad.

The diagnostic imaging criteria for superior mesenteric artery syndrome are:

- Duodenal obstruction with an abrupt cutoff in the third portion and active peristalsis.
- An aortomesenteric artery angle of $\leq 25°$ is the most sensitive measure of diagnosis, particularly if the aortomesenteric distance is ≤ 8 mm.
- High fixation of the duodenum by the ligament of Treitz, abnormally low origin of the superior mesenteric artery, or anomalies of the superior mesenteric artery.

21.31. D. None of the above.

The patient has mesenteric artery ischemia. Two of the three abdominal branches to the gut are usually compromised to cause these symptoms. CT angiography will usually define these branches and location of stenosis. The treatment is either stent implantation or surgical bypass. Differential includes celiac artery compression syndrome (also known as celiac axis syndrome, median arcuate ligament syndrome, and Dunbar syndrome) is a chronic, recurrent abdominal pain related to compression of the celiac artery by the median arcuate ligament. It is an uncommon disorder that is characterized clinically by the triad of postprandial abdominal pain, weight loss, and sometimes an abdominal bruit.

21.32. D. All of the above.

21.33. D. A and C.

ACC/AHA guidelines recommend the following (see Box 21.2). Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk. Patients with CLI and features to suggest atheroembolization should be evaluated for aneurysmal disease. Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection.

21.34. E. All of the above.

21.35. D. All of the above.

See Box 21.1.

21.36. E. A, B, and C.

ACC/AHA guidelines recommend percutaneous revascularization of RAS in the following (see Box 21.2):

- Patients with hemodynamically significant RAS
- Recurrent, unexplained congestive heart failure
- Sudden, unexplained pulmonary edema

- Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS.
- Accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication.

21.37. A. Should be suspected in patients with abdominal pain and weight loss without other explanation, especially those with cardiovascular disease.

ACC/AHA guidelines (see Box 21.2):

- Duplex ultrasound, but not CT angiography, and gadolinium-enhanced MRA are useful initial tests for supporting the clinical diagnosis of chronic intestinal ischemia.
- Surgical revascularization is indicated for patients with asymptomatic intestinal arterial obstructions.
- Percutaneous endovascular treatment of intestinal arterial stenosis is not indicated in patients with chronic intestinal ischemia.

21.38. B. Surgical consultation.

Acute intestinal ischemia ACC/AHA guidelines (see Box 21.2):

- In contrast to chronic intestinal ischemia, duplex sonography of the abdomen is **not** an appropriate diagnostic tool for suspected acute intestinal ischemia.
- Patients who develop acute abdominal pain after arterial interventions in which catheters traverse the visceral aorta or any proximal arteries or who have arrhythmias (such as atrial fibrillation) or recent MI should be suspected of having acute intestinal ischemia.
- Percutaneous interventions (including transcatheter lytic therapy, balloon angioplasty, and stenting) are appropriate in selected patients with acute intestinal ischemia caused by arterial obstructions that are not surgical candidates.

21.39. C. Midaortic syndrome.

Midaortic syndrome is a condition characterized by segmental narrowing of the abdominal/distal descending thoracic aorta, and frequently accompanied by ostial stenosis of the aorta's branches. If left untreated, it can result in life-threatening complications secondary to severe hypertension.

It can be congenital, caused by a developmental anomaly in the fusion and maturation of the paired embryonic dorsal aortas, **or** acquired secondary to neurofibromatosis, fibromuscular dysplasia, retroperitoneal fibrosis, Williams syndrome, mucopolysaccharidosis, and giant cell arteritis.

21.40. D. Coronary and subclavian angiography and intervention.

Subclavian steal occurs when the left upper extremity is exercised and blood flows retrograde in the left vertebral artery to supply the arm (Figure 21.40b). The blood also flows retrograde in the left internal mammary artery to supply the demands of the left arm (Figure 21.40c). These are the classic indications to intervene. A BP difference in the two upper extremities without symptoms of angina, dizziness, or syncope is **not** an indication to intervene.

Figure 21.40b

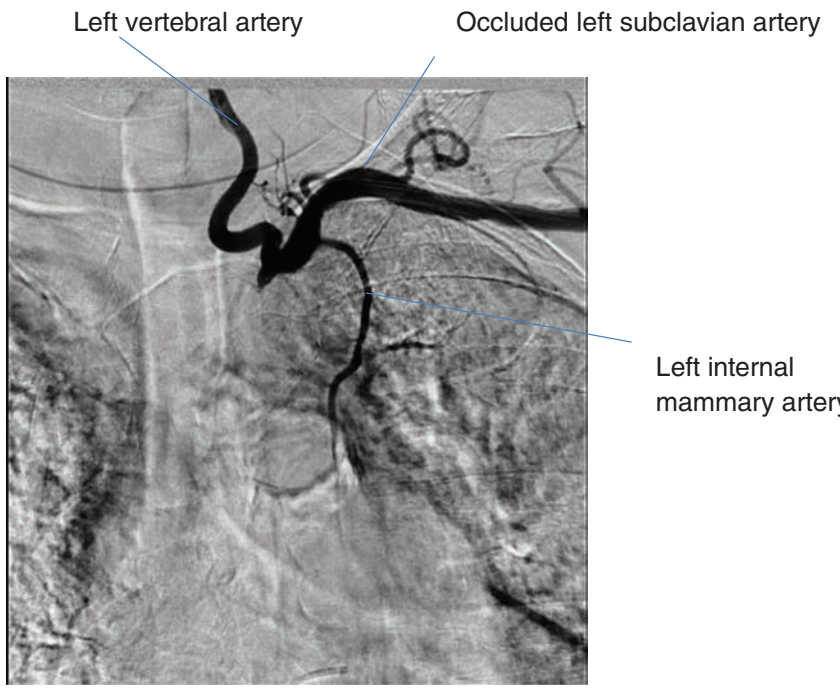

Figure 21.40c

Box 21.1 Clinical Pearls

- Any vascular disease that results in arterial stenosis or occlusion can cause symptoms of extremity pain or tissue loss.
- PAD differential diagnosis: arterial aneurysm, arterial dissection, embolism, popliteal entrapment syndrome, adventitial cystic disease, Buerger's disease, limb trauma, radiation arteritis, vasculitis, and ergot use for migraines.
- Risk factors for PAD are similar to those that promote the development of coronary atherosclerosis (i.e., hyperlipidemia, smoking, hypertension, diabetes).
- Classic claudication is characterized by leg pain that is consistently reproduced with exercise and relieved with rest. The degree of symptoms of claudication depends upon the severity of stenosis, the collateral circulation, and the vigor of exercise.
- To confirm the diagnosis of arterial stenosis or occlusion, which is most commonly due to PAD, the resting ABI should be performed in patients with lower extremity exertional symptoms and in those patients with risk factors for PAD.
- An ABI of $\leq$0.90 has a high degree of sensitivity and specificity for a diagnosis of PAD.
- Visibly dilated lower extremity veins (i.e., telangiectasias, reticular veins, or varicose veins) may be indicative of underlying venous reflux.
- The goals of treatment are improved symptoms and appearance. Initial treatment for most patients with chronic venous disease is conservative and includes leg elevation, exercise, and compression therapy.
- Laser therapy is the only option for treatment of telangiectasias too small to access.

Box 21.2 ACC/AHA Clinical Guidelines

- Individuals with asymptomatic lower extremity PAD should be identified by examination and/or measurement of the ABI so that therapeutic interventions known to diminish their increased risk of MI, stroke, and death may be offered.
- Smoking cessation, lipid lowering, and diabetes and hypertension treatment according to current national treatment guidelines are recommended for individuals with asymptomatic lower extremity PAD.
- Antiplatelet therapy is indicated for individuals with asymptomatic lower extremity PAD to reduce the risk of adverse cardiovascular ischemic events.
- Angiotensin-converting enzyme inhibition may be considered for individuals with asymptomatic lower extremity PAD for cardiovascular risk reduction.
- Patients with CLI in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk.
- Patients with a prior history of CLI or who have undergone successful treatment for CLI should be evaluated at least twice annually by a vascular specialist owing to the relatively high incidence of recurrence.
- Patients with CLI and features to suggest atheroembolization should be evaluated for aneurysmal disease (e.g., abdominal aortic, popliteal, or common femoral aneurysms).
- Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection.
- Duplex ultrasound of the extremities is useful to diagnose anatomic location and degree of stenosis of PAD.
- Duplex ultrasound is recommended for routine surveillance after femoralpopliteal or femoral-tibialpedal bypass with a venous conduit. Minimum surveillance intervals are approximately 3, 6, and 12 months, and then yearly after graft placement.

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Cardiac Arrhythmias

22

22.1. A 45-year-old woman is admitted with syncope while standing in the mall. No premonitory symptoms, no other significant past medical history, and on no medications except contraceptive pill. Her physical examination, electrocardiogram (ECG), and echocardiogram are normal, as is the tilt table test. What is the most likely cause of her syncope?

A. Neurocardiogenic
B. Pulmonary embolism due to hormone-induced hypercoagulable state
C. Catecholaminergic polymorphic ventricular tachycardia
D. Long QT syndrome

22.2. A 55-year-old man with prior myocardial infarction (MI) and coronary stenting 3 years ago is admitted with sudden loss of consciousness while sitting at a desk. He was on aspirin, statin, angiotensin-converting-enzyme inhibitor, and Coreg®. Heart rate was 65 bpm, blood pressure 110/72 mmHg, normal jugular venous pressure, and no murmurs. ECG showed poor R wave progression, echo showed an ejection fraction (EF) of 30% with anterior and apical akinesis and thinning. Left anterior descending artery stent was patent on coronary angiogram. What is the next logical step?

A. Discharge with event monitor
B. Do electrophysiology (EP) testing for inducible arrhythmias
C. Implant an implantable cardioverter-defibrillator (ICD)
D. Perform a stress test for ventricular tachycardia (VT)

22.3. Carotid sinus hypersensitivity is more common in which of the following?

A. 20-year-old female
B. 40-year-old male
C. 40-year-old female
D. 75-year-old man

22.4. Mortality in long QT syndrome depends upon which of the following?

A. Specific genetic defect
B. QT interval
C. History of syncope
D. All of the above

22.5. In a patient with type I Brugada syndrome presenting with syncope, the 2-year risk of sudden death is which of the following?

A. 2%
B. 10%
C. 30%
D. 80%

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22.6. Which of the following statements about Brugada syndrome is correct?
- **A.** It is a genetically determined sodium channelopathy
- **B.** Mortality risk is independent of amount of ST elevation
- **C.** The ECG changes are stable and do not change over time
- **D.** They have underlying left ventricular (LV) dysfunction

22.7. A 78-year-old patient with no prior medical history, not on any medications, is noted to be bradycardic at a routine physical exam. ECG shows complete heart block. Upon further questioning, the patient denies complaining of dizziness, near syncope, or syncope. He admits to noticing a gradual decline in exercise capacity over the last year. What is the next step in the management of this patient?
- **A.** Holter monitor
- **B.** EP test
- **C.** Exercise treadmill test
- **D.** Dual-chamber pacemaker implant

22.8. A 37-year-old patient presents with symptoms of palpitations. Holter monitoring revealed episodes of atrial tachycardia and atrial fibrillation. He was prescribed flecainide 100 mg BID and metoprolol succinate 50 mg daily. He noticed an improvement in symptoms of palpitations but complains of fatigue and inability to return to work as a firefighter. What is the best option for this patient?
- **A.** Continue present management
- **B.** Switch to sotalol
- **C.** EP studies and catheter ablation
- **D.** Lower dose of flecainide and metoprolol

22.9. A 72-year-old woman with history of coronary artery disease, ischemic cardiomyopathy, and paroxysmal atrial fibrillation of 5 years' duration has noticed an increase in frequency and duration of episodes over the last year. Her medications include Tikosyn® 250 μg BID, Coreg 25mg BID, enalapril 10 mg daily, aspirin 81 mg daily, and rivoroxaban 20 mg daily. She would like to consider pulmonary vein antrum isolation procedure if she will be taken off rivoroxaban after the procedure. What do you tell her?
- **A.** She can expect to continue taking aspirin and discontinue rivoroxaban
- **B.** She will need to continue taking rivoraxaban and discontinue aspirin
- **C.** Both medications can be stopped
- **D.** Both medications will be continued

22.10. An ECG (Figure 22.10) is done on a 35-year-old male who is scheduled to undergo knee surgery. The patient has no symptoms of palpitations. What is the next step in the management?
- **A.** No further work-up is indicated
- **B.** Exercise treadmill test
- **C.** Echocardiogram
- **D.** EP studies and ablation

22.11. A 60-year-old patient with history of dilated cardiomyopathy, LVEF 35%, on optimal medical therapy is noted to have frequent premature ventricular complexes (PVCs) on ECG with left bundle branch block (LBBB) morphology and inferior

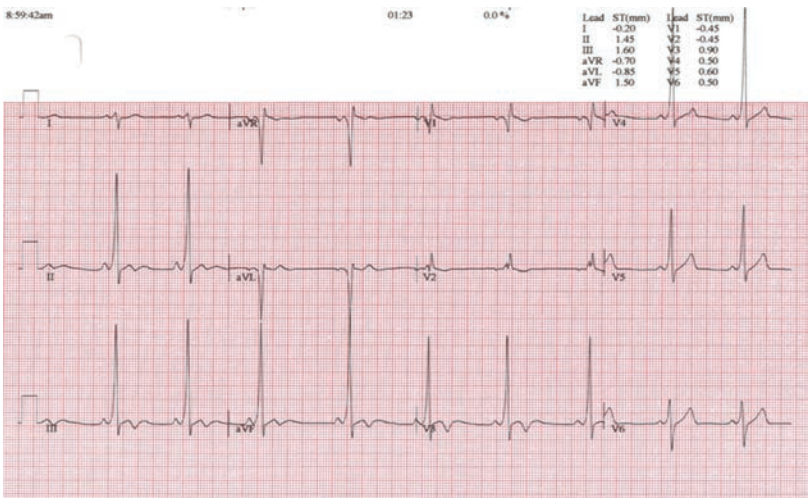

Figure 22.10

axis. She denies symptoms of palpitations. On a 24-h Holter monitor, the PVC burden is 22%. Which of the following options would you offer next?

A. Start amiodarone
B. Repeat echo in 6 months
C. EP studies and catheter ablation
D. ICD implant

22.12. A 40-year-old patient with history of supraventricular tachycardia (SVT) wishes to undergo EP studies and catheter ablation. What is the expected success rate?

A. 70–75%
B. 80–85%
C. 90–95%
D. 100%

22.13. A 65-year-old patient presents with history of prior MI and 5-year history of recurrent palpitations associated with near syncope. He has been on metoprolol and simvastatin. The 12-lead ECG is suggestive of atrioventricular nodal reentrant tachycardia (AVNRT). Which of the following would you recommend next?

A. Continue metoprolol
B. Flecainide
C. Amiodarone
D. EP study/ablation

22.14. A 35-year-old patient presents to the emergency department with 2-h history of rapid heartbeat associated with dizziness. The blood pressure is 90/60 mmHg,; ECG is shows atrial fibrillation with ventricular preexcitation. What is the best treatment option?

A. Intravenous (IV) metoprolol
B. IV digoxin
C. Cardioversion
D. IV amiodarone

22.15. A 60-year-old patient with chronic kidney disease on dialysis has recurrent episodes of palpitations requiring cardioversion. ECG shows counterclockwise atrial flutter. What is the best treatment option?

A. Metoprolol
B. Sotalol
C. Dofetilide (Tikosyn)
D. EP study/ablation

22.16. A 66-year-old female with history of ischemic cardiomyopathy, status post ICD implant, hypertension, and diabetes is detected to have three episodes of paroxysmal atrial fibrillation lasting from 1 to 2 h during a routine device check. She denies symptoms of palpitations. What is the next step in the management of this patient?

A. Observation
B. Holter monitor
C. Echocardiogram
D. Anticoagulation

22.17. A 70-year-old male with history of ischemic cardiomyopathy, hypertension, hospitalized for congestive heart failure exacerbation 3 months ago has four episodes of paroxysmal atrial fibrillation lasting from 8 to 12 h. He reports symptoms of palpitations and fatigue. He has been taking metoprolol and rivaroxaban. What is the antiarrhythmic agent of choice?

A. Dronaderone
B. Dofetelide
C. Flecainide
D. Propafenone

22.18. A 42-year-old patient with no prior medical history presents with palpitations of 5 days' duration. ECG reveals atrial fibrillation with ventricular rate of 120 bpm. He is placed on IV heparin and undergoes transesophageal echocardiography-guided cardioversion the following day. What does this patient have?

A. Lone atrial fibrillation
B. Paroxysmal atrial fibrillation
C. Persistent atrial fibrillation
D. Long-standing persistent atrial fibrillation

22.19. What is the appropriate anticoagulation management for the patient in Question 22.18?

A. Aspirin 75 mg daily for 1 month
B. Aspirin 325 mg daily for 1 month
C. Warfarin for 1 month
D. No aspirin or warfarin is needed

22.20. A 55-year-old patient who is status post coronary artery bypass grafting 3 days ago is noted to be in atrial flutter. He is placed on metoprolol and warfarin and discharged home. He has been followed by his primary care physician. You see him in the office 3 months later. He feels well. He is in atrial flutter with ventricular rate 90 bpm. What would be the next step in the management of this patient?

A. Continue rate control
B. Sotalol
C. Cardioversion
D. EP study/ablation

22.21. A 68-year-old female patient status post mechanical valve 4 years ago on warfarin develops paroxysmal atrial fibrillation. She would like to pursue anticoagulation with a novel oral anticoagulant because of labile international normalized ratio (INR) after she was started on amiodarone. Which of the following do you recommend?

A. Pradaxa
B. Rivaroxaban
C. Apixaban
D. None of the above

22.22. Which of the following is not a factor Xa inhibitor?

A. Apixaban
B. Dabigatran
C. Rivaroxaban
D. Edoxaban

22.23. A 70-year-old patient with paroxysmal atrial fibrillation was started on flecainide 100 mg BID. She has been doing well. An ECG done 1 week later reveals sinus rhythm with LBBB. Which of the following is the appropriate next step?

A. No change
B. Reduce dose of flecainide to 50 mg BID
C. Discontinue flecainide
D. Recommend pacer implant

22.24. A 72-year-old patient with history of atrial fibrillation is on warfarin and digoxin. He was started on dronedarone. The serum creatinine at baseline was 1.3; 1 week later it was 1.7. Which of the following statements is false?

A. The INR is not affected
B. The serum digoxin is unchanged
C. Renal tubular secretion of creatinine is inhibited by dronedarone
D. Reduction in glomerular filtration rate

22.25. When initiating therapy with amiodarone, a reduction in the dose is needed for all of the following agents except which?

A. Digoxin
B. Warfarin
C. Metoprolol
D. Apixaban

22.26. Which of the following statements regarding Tikosyn is false?

A. The dose is determined by creatinine clearance
B. It is contraindicated in patients with heart failure
C. Inpatient monitoring is mandatory while initiating therapy
D. ECG is monitored for QT prolongation

22.27. A 57-year-old patient with no prior cardiac history with symptoms of exercise-induced palpitations undergoes an exercise treadmill test. Sustained wide QRS tachycardia at a rate of 170 bpm occurs during recovery. The ECG is shown in Figure 22.27. The patient is hemodynamically stable. She is given 5 mg of IV metoprolol. Sinus rhythm is restored 5 min later. Echocardiogram reveals normal left and right ventricle function. What is the most likely diagnosis?

A. Ischemic VT
B. Idiopathic RVOT VT
C. Catecholaminergic VT
D. Idiopathic LV VT

Figure 22.27

22.28. A 67-year-old female patient with history of atrial fibrillation, hypertension, and St Jude aortic valve replacement is scheduled to undergo hip replacement. What is the best option for management of anticoagulation?

- **A.** Discontinue warfarin 5 days prior to procedure, bridge with low molecular weight heparin (LMWH) when INR is 2.0, resume warfarin on day of surgery
- **B.** Discontinue warfarin 5 days prior to procedure, no bridging with LMWH is needed, resume warfarin on day of surgery
- **C.** Continue warfarin
- **D.** Discontinue warfarin 2 days prior to procedure, bridge with LMWH after surgery, resume warfarin on day of surgery

22.29. A 70-year-old male patient with history of ischemic cardiomyopathy, status post ICD implant, atrial fibrillation, hypertension, and diabetes is scheduled for ICD generator replacement. What is the best option for management of anticoagulation?

- **A.** Discontinue warfarin 5 days prior to procedure, bridge with LMWH when INR is 2.0, resume warfarin on day of surgery
- **B.** Discontinue warfarin 5 days prior to procedure, no bridging with LMWH is needed, resume warfarin on day of surgery
- **C.** Continue warfarin
- **D.** Discontinue warfarin 2 days prior to procedure, bridge with LMWH after surgery, resume warfarin on day of surgery

22.30. A 55-year-old female patient with history of atrial fibrillation, hypertension, and diabetes is scheduled to undergo biopsy of breast mass. Her renal function is

normal. She is on apixaban 5 mg BID. What is the best option for management of anticoagulation>

A. Discontinue apixaban 24 h prior to procedure
B. Discontinue apixaban 48 h prior to procedure
C. Continue apixaban
D. Reduce dose of apixaban to 2.5 mg BID

22.31. A 22-year-old patient is hospitalized with abdominal pain. She has no cardiac symptoms. Her ECG is shown in Figure 22.31. What does it demonstrate?

A. Intraventricular conduction disturbance
B. Right bundle branch block (RBBB)
C. WPW syndrome
D. Right ventricular hypertrophy

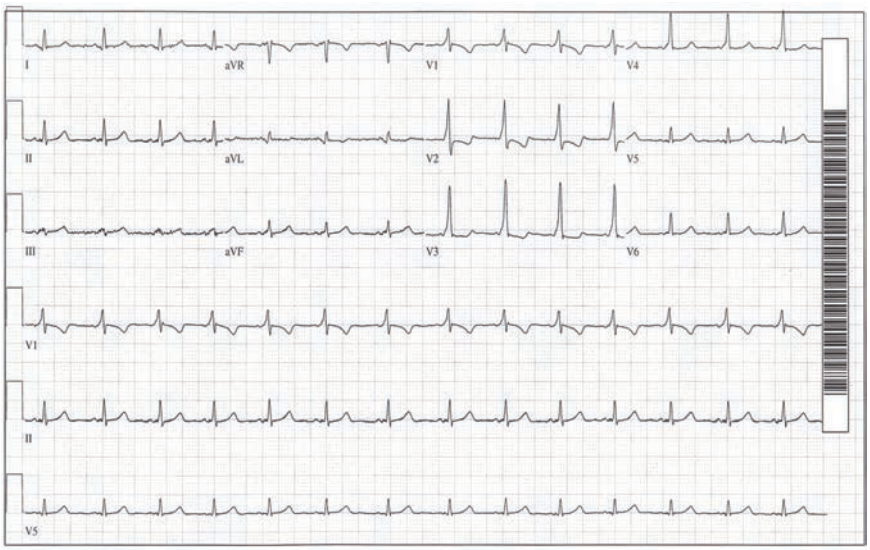

Figure 22.31

22.32. A 28-year-old female patient has had symptoms of palpitations since the age of 5. They are infrequent, occurring once a year, and are brought on by physical activity. Her ECG, done in the office, is shown in Figure 22.32. What is the most likely explanation for her palpitations?

A. AVNRT
B. Orthodromic atrioventricular reciprocating tachycardia (AVRT)
C. Atrial tachycardia
D. Antidromic AVRT

22.33. The ECG in Figure 22.33 demonstrates which of the following?

A. Sinus rhythm with PVC
B. Sinus rhythm with premature atrial complex with aberrant ventricular conduction
C. Sinus rhythm, WPW syndrome with PVC
D. Sinus rhythm, WPW syndrome with two accessory pathways

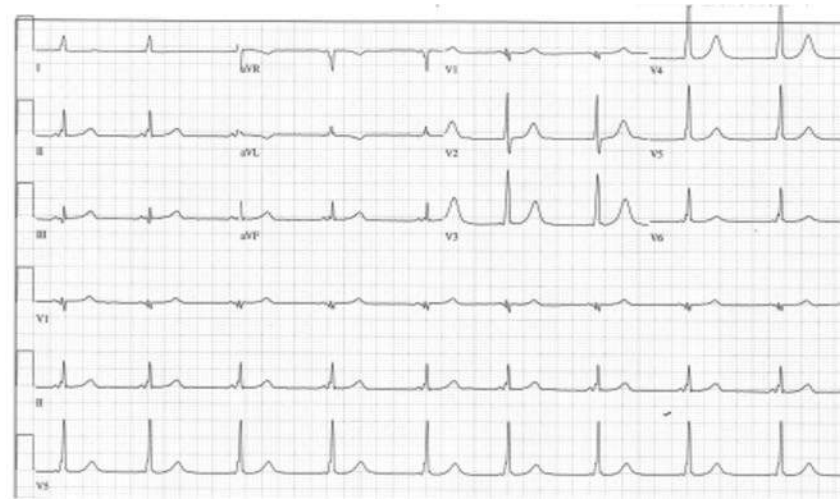

Figure 22.32

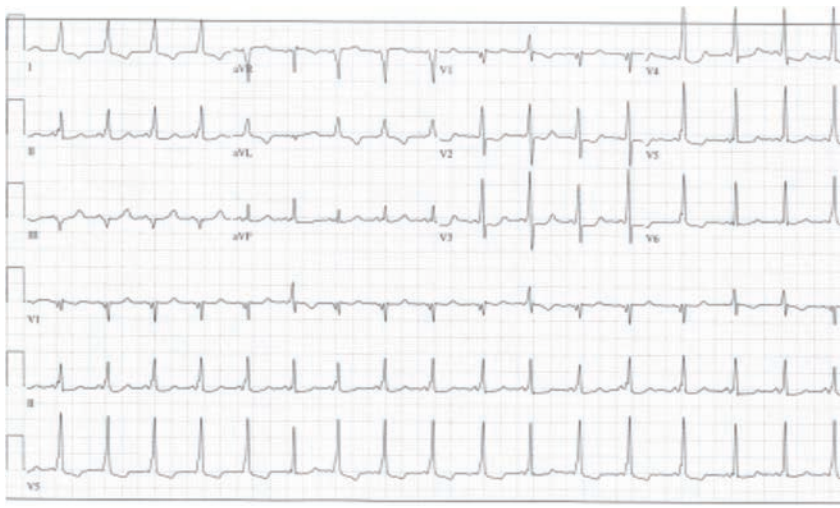

Figure 22.33

22.34. The intracardiac tracing shown in Figure 22.34a demonstrates which of the following?

A. RBBB
B. Short HV interval
C. Normal HV interval
D. Prolonged HV interval

22.35. The wide QRS beats (beats 1 to 6) seen in the tracing in Figure 22.35a are due to which of the following?

A. RBBB
B. Aberrant ventricular conduction
C. Preexcitation
D. Idioventricular rhythm

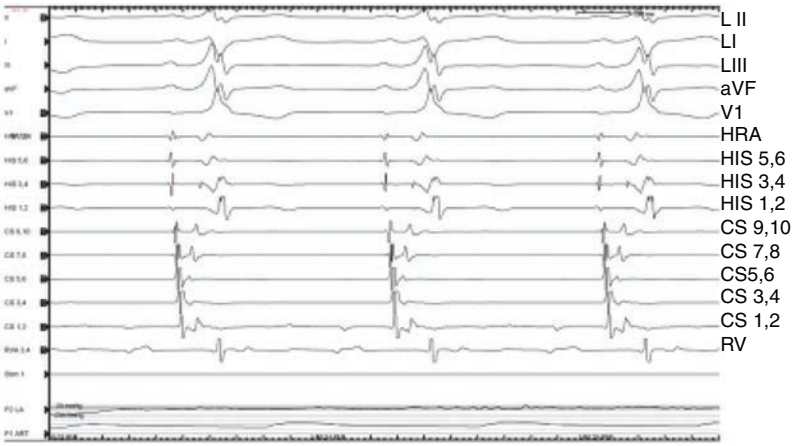

Figure 22.34a

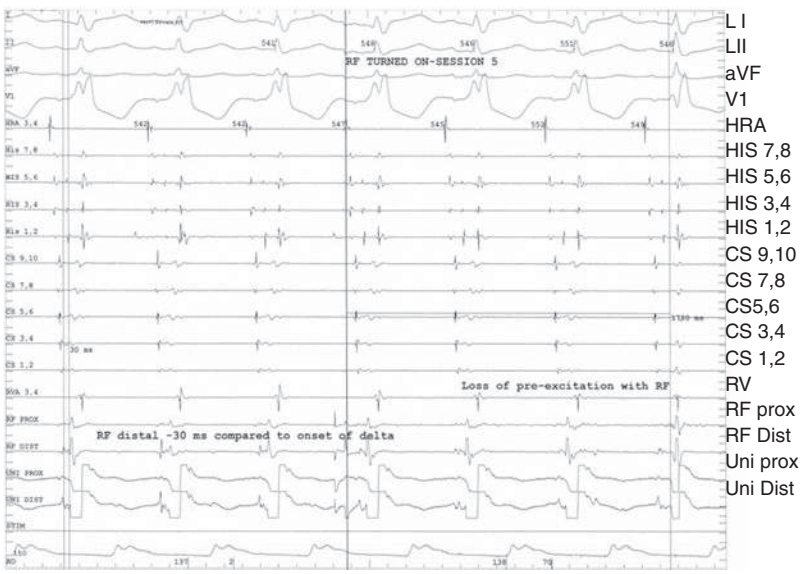

Figure 22.35a

22.36. The 12-lead ECG shown in Figure 22.36 is consistent with which of the following?

A. RBBB
B. Antidromic tachycardia
C. VT
D. None of the above

22.37. The intracardiac tracing in Figure 22.37a is consistent with which of the following?

A. RBBB
B. Antidromic tachycardia
C. VT
D. None of the above

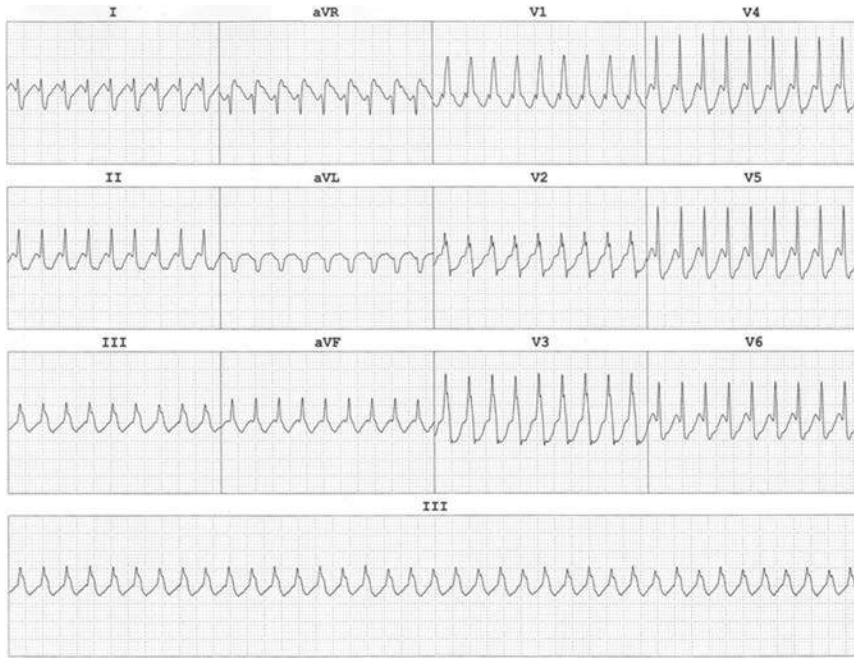

Figure 22.36

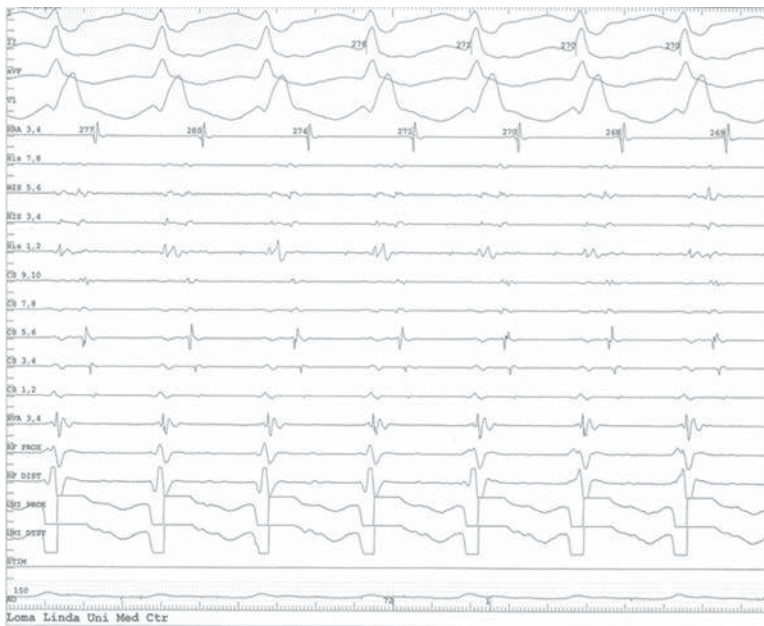

Figure 22.37a

22.38. In Figure 22.38a, the second beat appears different compared with the other beats. The intracardiac electrograms on this beat have a well-defined His spike. What is the most likely explanation for this finding?

A. Beats 1, 3, and 4 are ventricular in origin
B. There is loss of preexcitation on the second beat
C. Beats 1, 3, and 4 are supraventricular in origin with aberrant ventricular conduction
D. None of the above

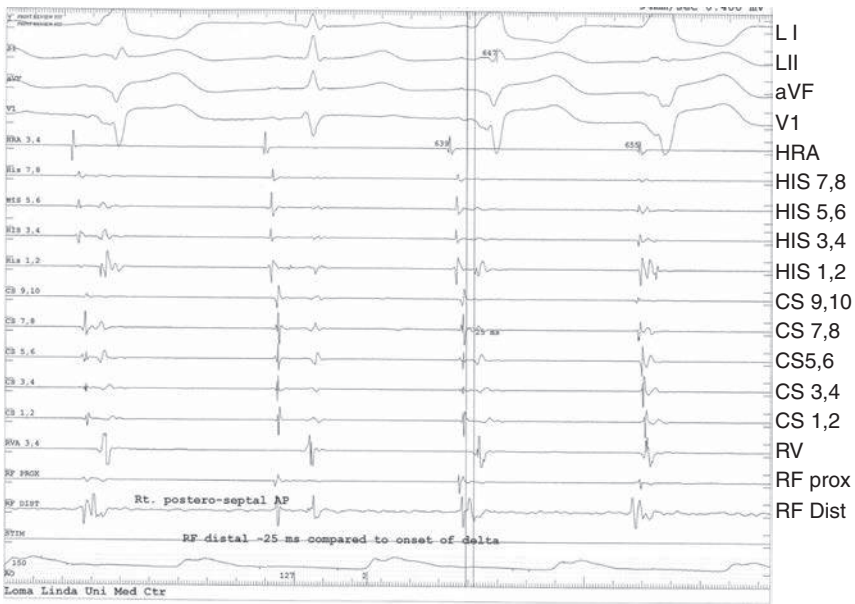

Figure 22.38a

22.39. The intracardiac signals during ventricular pacing are shown in Figure 22.39a. The mapping catheter (RF 1, 2) is positioned at a right postero-septal location. The retrograde atrial activation is most consistent with which of the following?

A. Retrograde VA conduction via AV node
B. Retrograde VA conduction via accessory pathway
C. Atrial signal is not recorded on RF 1, 2
D. None of the above

22.40. Intracardiac signals during sinus rhythm are shown in Figure 22.40. The mapping catheter (RF 1, 2) is positioned in close proximity to poles 3, 4 of the coronary sinus catheter (CS 3, 4). This corresponds to a left lateral position on the mitral annulus. Which of the following statements is correct?

A. A left lateral accessory pathway is present.
B. There is no evidence of an accessory pathway
C. The HV interval is prolonged
D. None of the above

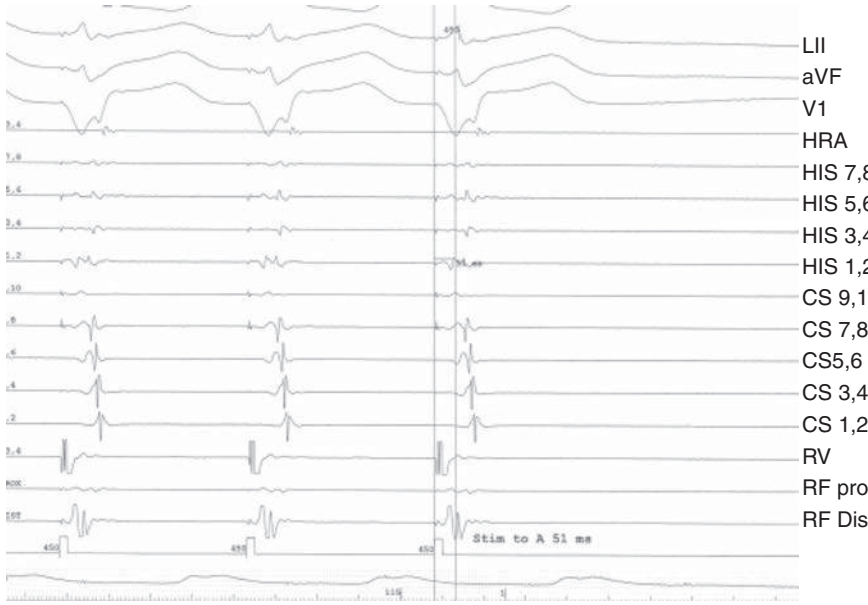

Figure 22.39a

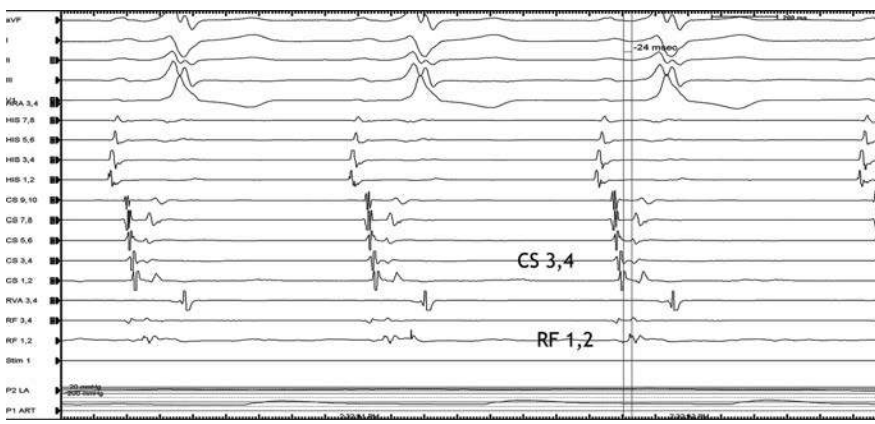

Figure 22.40

22.41. In Figure 22.41, the first four beats are ventricular paced beats and the last four beats are SVT beats. The intracardiac signals with ventricular pacing and SVT are identical. What is the most likely mechanism of SVT?

A. AVNRT
B. AVRT
C. Atrial tachycardia
D. None of the above

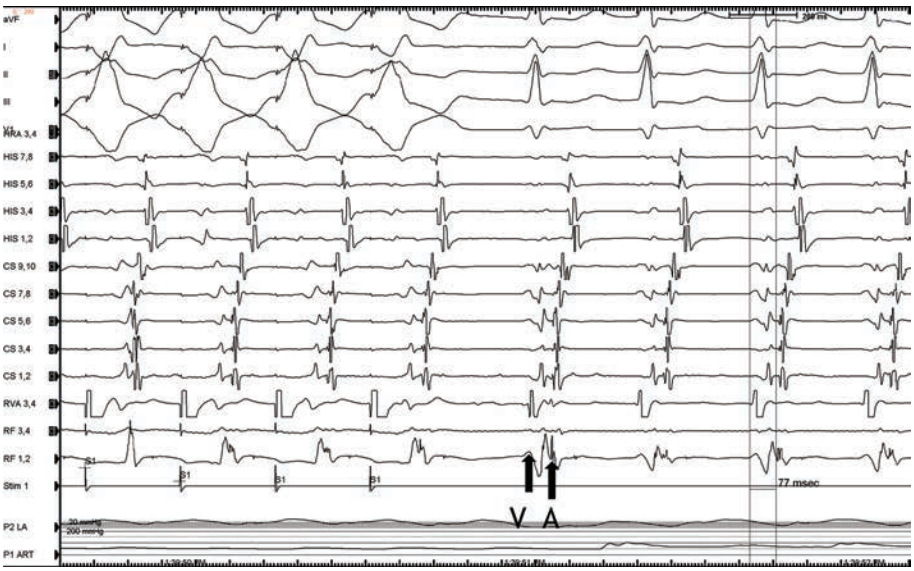

Figure 22.41

22.42. The 12-lead ECG shown in Figure 22.42 is consistent with which of the following?

A. SVT with aberrant conduction
B. VT
C. Paced rhythm
D. Antidromic tachycardia

Figure 22.42

22.43. What is the most likely underlying cardiac condition in the patient whose 12-lead ECG is shown in Figure 22.43?

A. Prior MI
B. Structurally normal heart
C. WPW syndrome
D. None of the above

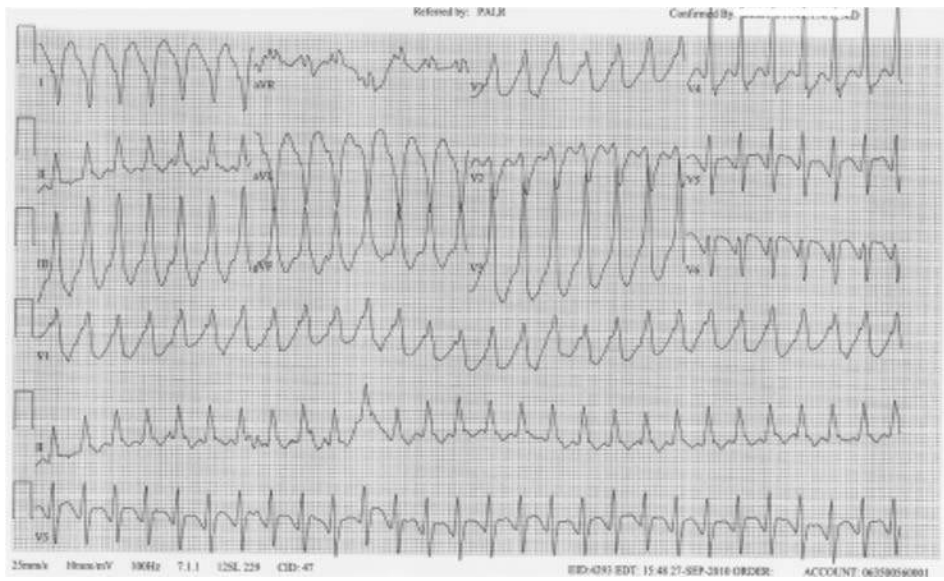

Figure 22.43

22.44. The rhythm strip in Figure 22.44 was obtained in a 25-year-old female patient with symptoms of palpitations and dizziness. The echocardiogram was normal. During a stress test the patient developed sustained wide QRS tachycardia at a rate of 170 bpm with an LBBB morphology and inferior axis which terminated spontaneously. What is the likely diagnosis?

A. Verapamil-sensitive VT
B. Idiopathic RVOT VT
C. Catecholaminergic VT
D. Long QT syndrome

22.45. The intracardiac tracing in Figure 22.45 was obtained during an EP study on a patient with complaints of palpitations and runs of wide QRS tachycardia on an event monitor. What is the likely diagnosis?

A. Idiopathic RVOT
B. Idiopathic LV VT
C. Junctional tachycardia
D. None of the above

Figure 22.44

22.46. The 12-lead ECG in Figure 22.46 demonstrates wide QRS tachycardia. What is the likely diagnosis?

A. SVT with aberrant conduction
B. SVT with underlying bundle branch block
C. VT
D. None of the above

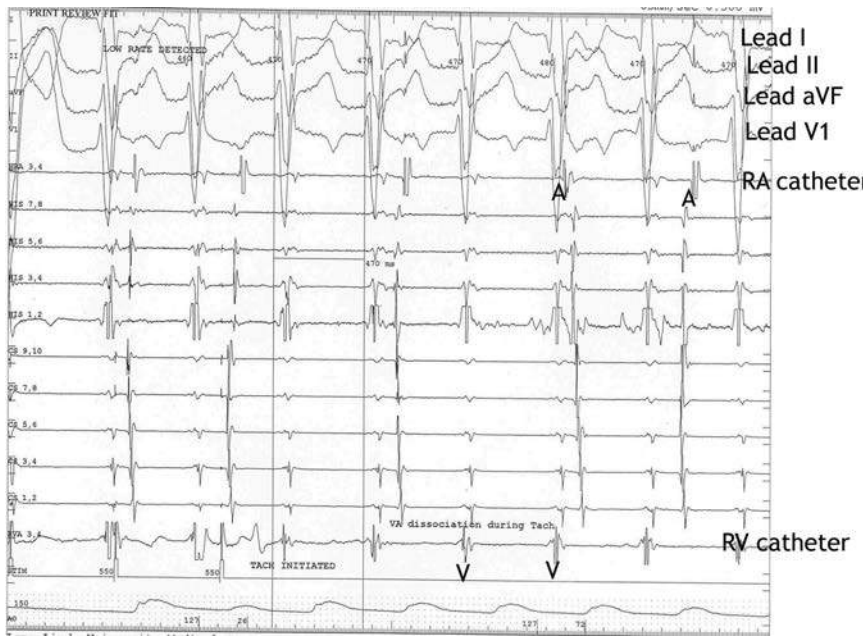

Figure 22.45

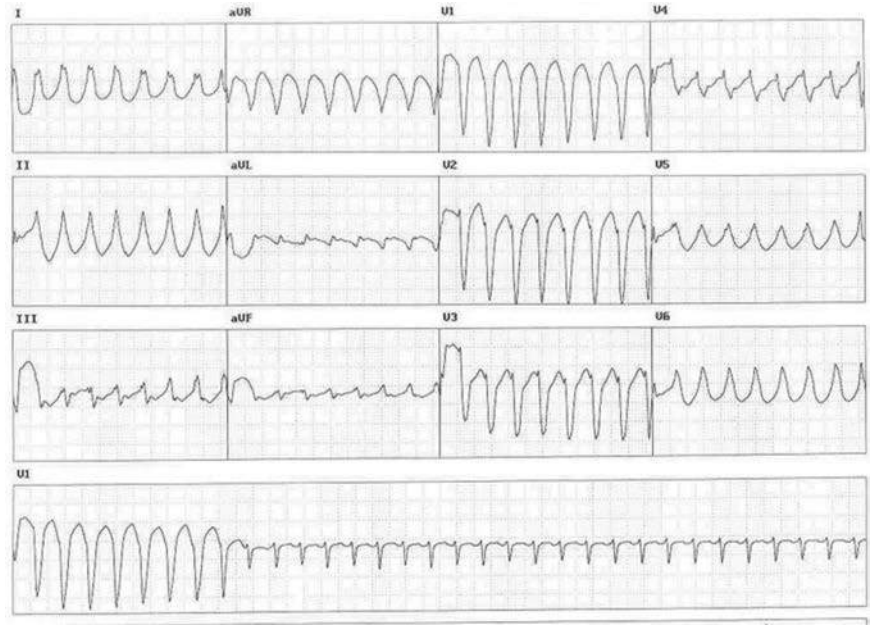

Figure 22.46

22.47. The intracardiac tracing in Figure 22.47 demonstrates wide QRS tachycardia changing to a narrow QRS tachycardia. The cycle length is longer during wide QRS tachycardia. What is this finding consistent with?

A. AVNRT
B. AVRT with bundle branch block ipsilateral to accessory pathway
C. AVRT with bundle branch block contralateral to accessory pathway
D. None of the above

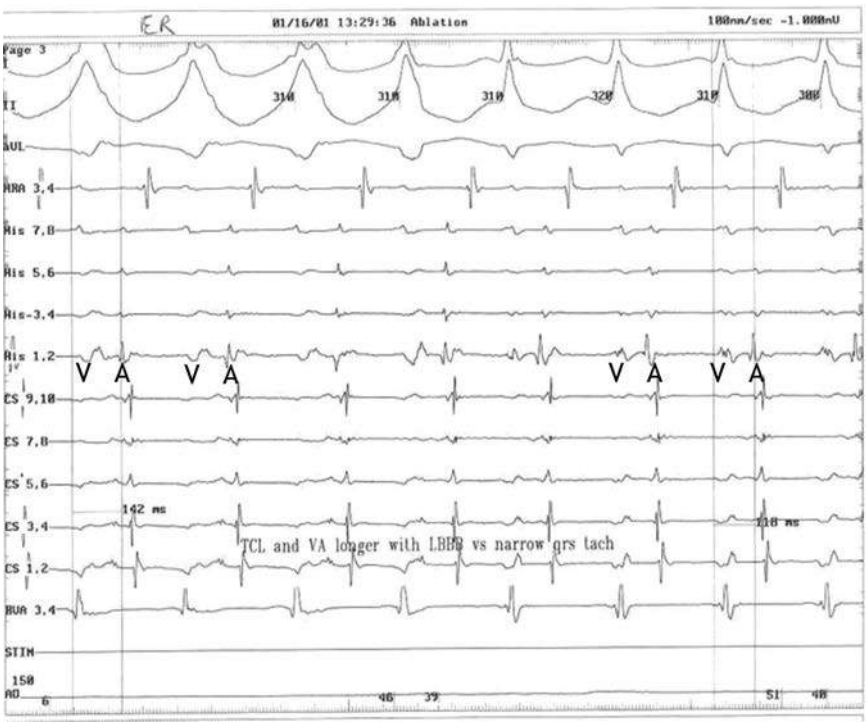

Figure 22.47

22.48. What is the intracardiac tracing shown in Figure 22.48 consistent with?

A. VT
B. Bundle branch reentry
C. SVT with aberrant conduction
D. None of the above

22.49. On the intracardiac tracing shown in Figure 22.49 the first four beats are ventricular paced beats followed by SVT. Which of the following statements is false?

A. The retrograde atrial activation with ventricular pacing is occurring only via the AV node
B. The retrograde atrial activation during SVT is via an accessory pathway
C. The retrograde atrial activation with ventricular pacing and during SVT is via an accessory pathway
D. A left lateral accessory pathway is present

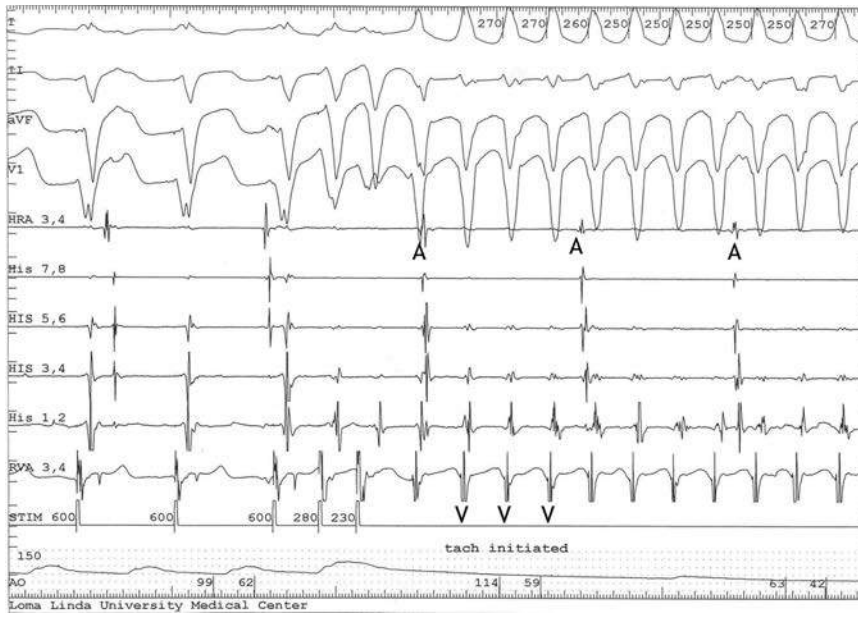

Figure 22.48

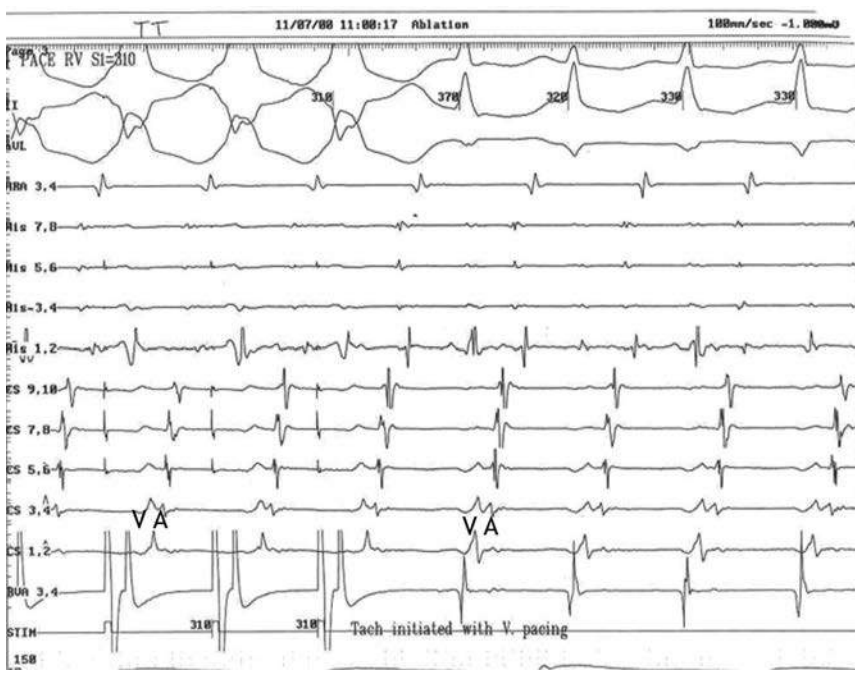

Figure 22.49

22.50. Following the first three atrial paced beats, an atrial extra-stimulus induces tachycardia. The intracardiac tracing shown in Figure 22.50 demonstrates all of the characteristics *except* which of the following?

A. Long AH interval with the extra-stimulus
B. Short VA interval during tachycardia
C. A His spike preceding the ventricular electrogram
D. Short HV interval on the atrial paced beats

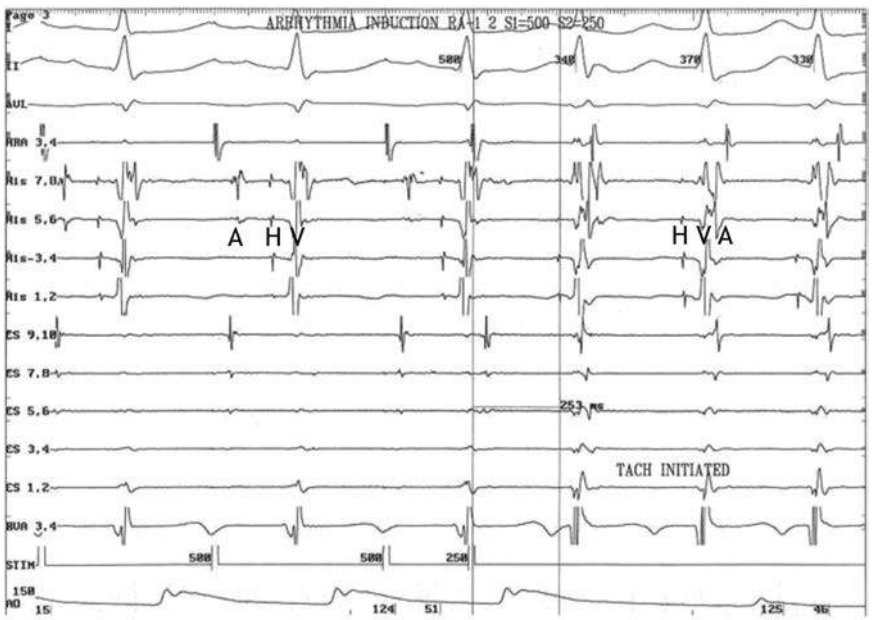

Figure 22.50

22.51. The ECG shown in Figure 22.51 was obtained during an EP study while positioning a catheter in the His bundle region. Which of the following statements is incorrect?

A. The most likely explanation for this ECG pattern is catheter-induced trauma to the right bundle
B. The conduction through right bundle is likely to recover
C. The conduction system is unlikely to recover and a permanent pacemaker implant is indicated
D. A similar situation can be encountered while placing a right ventricular pacing lead in a patient with a preexisting LBBB

22.52. The intracardiac tracing in Figure 22.52 was obtained in a patient with AV block. It demonstrates which of the following?

A. Block at the level of the AV node
B. Infra-His block
C. Intra-His block
D. None of the above

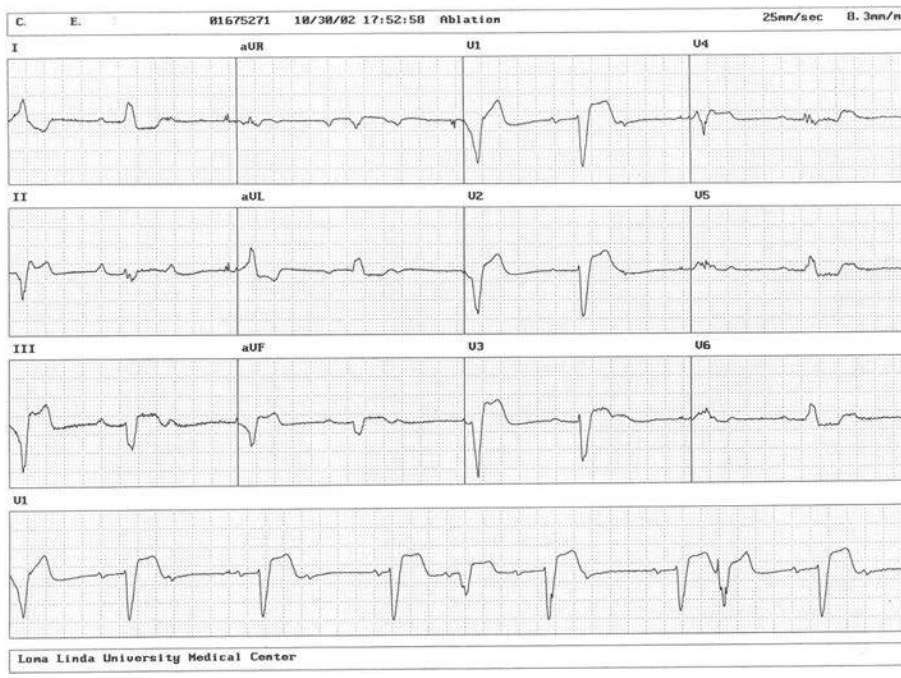

Figure 22.51

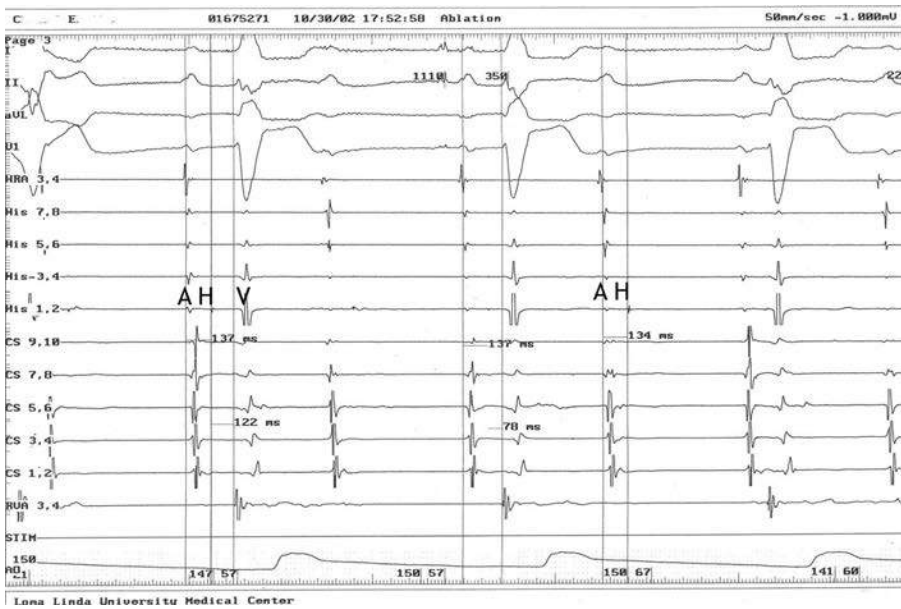

Figure 22.52

Answers

22.1. A. Neurocardiogenic.

Statistically, this is the most common cause of syncope in the middle-aged, even if the tilt table test is negative. The tilt table test has a sensitivity of about 60% and specificity of 90% for the diagnosis of neurocardiogenic or vasovagal syncope. In patients with high pretest probability, a negative test is of limited value. The right ventricle was normal, ruling out submassive pulmonary embolism. Catecholaminergic arrhythmias occur with physical or emotional stress.

22.2. C. Implant an ICD.

A patient with prior MI and extensive scarring with syncope has a high probability of VT as a cause of syncope. Hence, an ICD is indicated and there is no need for arrhythmia monitoring or EP testing to identify the mechanism of syncope. In addition, his EF is <35% on a good medical regimen, and even without syncope would be an indication for ICD for primary prevention.

22.3. D. 75-year-old man.

It occurs in elderly subjects.

22.4. D. All of the above.

The longer the QTc, the higher is the arrhythmic mortality, being about 5% in those with QTc of 450 ms, and 50% in those with QTc >500 ms over lifetime. Syncope in these patients is likely due to runs of polymorphic VT.

22.5. C. 30%.

An ICD is also indicated.

22.6. A. It is a genetically determined sodium channelopathy.

The ECG changes could be dynamic and come and go and can be provoked with procainamide challenge. Type I Brugada with ST elevation of >10 mm has a very high risk of sudden death.

22.7. D. Dual-chamber pacemaker implant.

Complete heart block is a class I indication for permanent pacer implant. A dual-chamber device is indicated in the presence of intact sinus mechanism.

22.8. C. EP studies and catheter ablation.

Patient has side effects related to current medication regimen. He is likely to have breakthrough episodes of arrhythmia on lower dose of flecainide and metoprolol. Trial with a different agent could be tried, but likely to be ineffective. EP studies and ablation is potentially curative.

22.9. D. Both medications will be continued.

Her CHA_2DS_2–VASc score is 4.

22.10. B. Exercise treadmill test.

If there is loss of preexcitation on an exercise treadmill test, accessory pathway conduction is weak and risk of rapid ventricular response if atrial fibrillation occurs is low.

22.11. C. EP studies and catheter ablation.

The PVC burden is high. Morphology is suggestive of right ventricular outflow tract (RVOT) origin of PVCs, which is very amenable to catheter ablation. The LVEF is likely to improve after successful ablation.

22.12. C. 90–95%.

22.13. D. EP study/ablation.
Ablation has a success rate of 90–95%. Patient has history of MI, hence flecainide is contraindicated. Long-term side effects have to be considered with amiodarone.

22.14. C. Cardioversion.
In a patient with Wolff–Parkinson–White (WPW) syndrome and atrial fibrillation, cardioversion is indicated. All other options are contraindicated.

22.15. D. EP study/ablation.
In the presence of chronic kidney disease, options B and C are contraindicated. Metoprolol will not prevent recurrence of atrial flutter.

22.16. D Anticoagulation.
Her CHA_2DS_2–VASc score is 5; hence, she is a candidate for oral anticoagulation.

22.17. B. Dofetilide.
Choices A, C, and D are contraindicated.

22.18. B. Paroxysmal atrial fibrillation.
As the duration is less than 7 days.

22.19. C. Warfarin for 1 month.
Because atrial mechanical function may take 2–21 days to normalize after cardioversion due to atrial stunning. Stunning occurs with chemical or spontaneous cardioversions as well.

22.20. C. Cardioversion.
The patient developed postop atrial flutter; it is unlikely to recur after successful cardioversion. Therapeutic anticoagulation for 3–4 weeks is essential before cardioversion.

22.21. D. None of the above.
The patient has a mechanical valve, which is a contraindication for novel anticoagulants. She will need to continue taking warfarin.

22.22. B. Dabigatran.
This is a direct thrombin inhibitor.

22.23. B. Reduce dose of flecainide to 50 mg BID.
The development of LBBB is due to flecainide. Monitor ECG for prolongation of QRS duration for increase by >25% over baseline.

22.24. D. Reduction in glomerular filtration rate.
The glomerular filtration rate is not affected by dronedarone; it inhibits creatinine secretion, which accounts for higher serum creatinine.

22.25. D. Apixaban.
Dose of apixaban is determined by age, body weight, and serum creatinine.

22.26. B. It is contraindicated in patients with heart failure.
Patients with heart failure *are* candidates for Tikosyn.

22.27. B. Idiopathic RVOT VT.
ECG of VT of LBBB with inferior axis consistent with RVOT origin.

22.28. A. Discontinue warfarin 5 days prior to procedure, bridge with low molecular weight heparin (LMWH) when INR is 2.0, resume warfarin on day of surgery.

CHA_2DS_2–VASc score is 3. Bridging is recommended to reduce risk of thromboembolism.

22.29. C. Continue warfarin.

Bridging is associated with increased risk of pocket hematoma. The procedure can be safely performed while patient is still on warfarin (Birnie *et al.*, 2013).

22.30. A. Discontinue apixaban 24 h prior to procedure.

In the presence of normal renal function, hold apixaban for 24 h.

22.31. C. WPW syndrome.

The delta wave is positive in lead V1, suggestive of a left-sided accessory pathway.

22.32. B. Orthodromic atrioventricular reciprocating tachycardia (AVRT).

The sinus rhythm ECG shows WPW syndrome. The most likely mechanism of SVT in this patient is orthodromic AVRT utilizing the atrioventricular (AV) node for antegrade conduction and accessory pathway for retrograde conduction.

22.33. D. Sinus rhythm, WPW syndrome with two accessory pathways.

The delta wave axis is negative in V1 on majority of the beats; it is positive on the 6th, 11th, 15th, and 16th beats. The patient had right postero-septal and left lateral accessory pathways.

22.34. B. Short HV interval.

This patient has WPW syndrome with antegrade conduction through the AV node as well as accessory pathway. The HV interval is negative due to conduction through the accessory pathway (see Figure 22.34b).

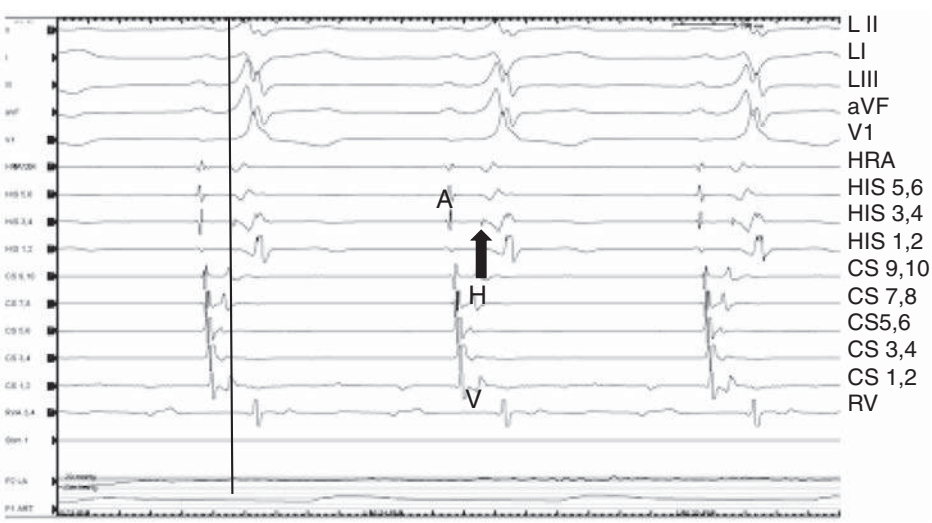

Figure 22.34b

22.35. C. Preexcitation.

The HV interval on beats 1 to 6 is short. Following radiofrequency energy application, on beat 7 there is loss of preexcitation (Figure 22.35b). The QRS is narrow and the HV interval is longer. A and V signals are shown on beat 6 (AV 6) and 7 (AV 7) – note that there is greater separation of A and V in beat 7 compared with beat 6.

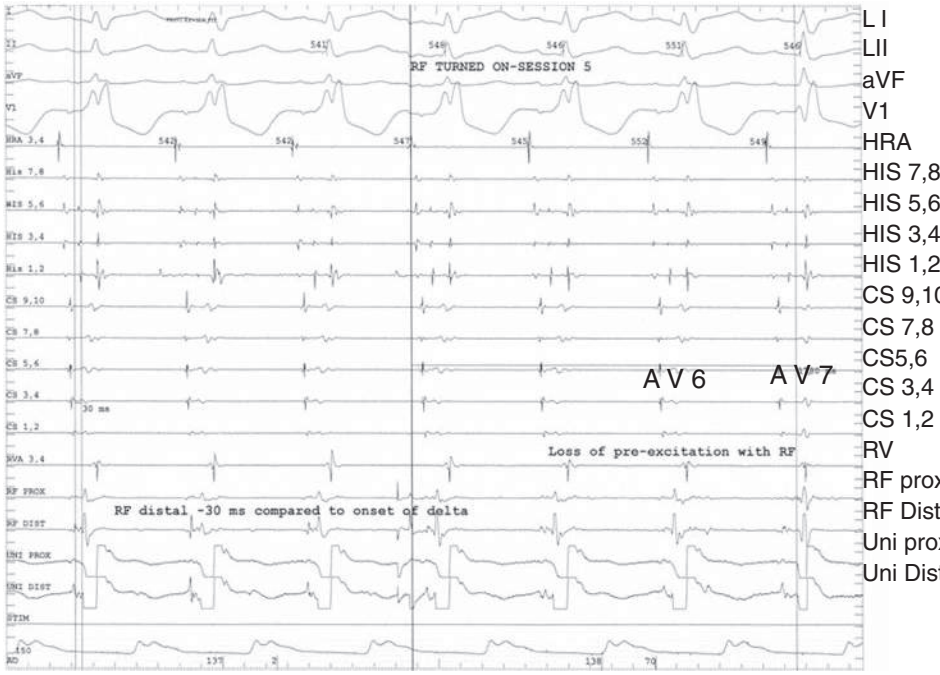

Figure 22.35b

22.36. A. RBBB.

The wide QRS tachycardia is due to the presence of RBBB, which could be present in the baseline state or may occur as a result of rate-related aberrant ventricular conduction. The morphology criteria – rsR in lead V1and rs pattern in leads 1 and V6 – favor supraventricular origin. With antidromic tachycardia, antegrade conduction occurs via accessory pathway which inserts into ventricular myocardium. Subsequent conduction through the ventricular myocardium would be similar to tachycardia which originates in the ventricular myocardium.

22.37. A. RBBB.

A His spike is seen on His 1, 2 (arrow in Figure 22.37b). It precedes the onset of QRS; hence, the rhythm is supraventricular in origin. The retrograde atrial

activation is concentric with earliest atrial activation occurring on His leads, likely due to conduction via the AV node.

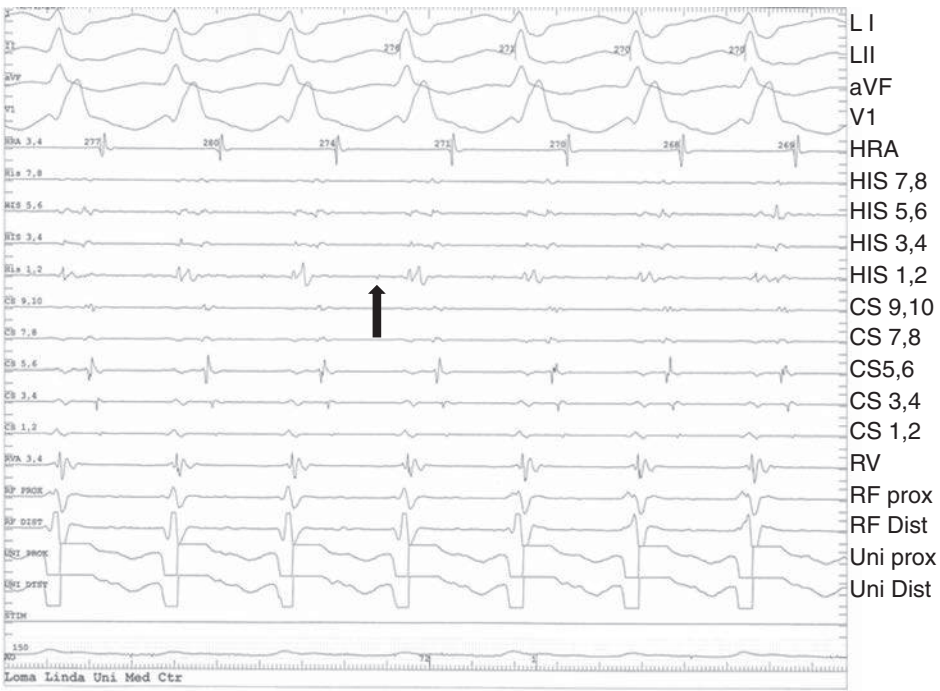

Figure 22.37b

22.38. B. There is loss of preexcitation on the second beat.

Intermittent preexcitation is present. The QRS is narrow and the HV interval is normal with loss of preexcitation on the second beat (see Figure 22.38b).

22.39. B. Retrograde VA conduction via accessory pathway.

The ventricular and atrial signals are fused on RF 1, 2. This is due to retrograde activation via the postero-septal accessory pathway (see Figure 22.39b).

22.40. A. A left lateral accessory pathway is present.

Only a ventricular signal is recorded on the mapping catheter (RF 1, 2) and it precedes the onset of the delta wave. The mapping catheter is recording early ventricular activation via accessory pathway on the mitral annulus at a left lateral location.

22.41. B. AVRT.

The retrograde atrial activation with ventricular pacing and during SVT is eccentric with earliest atrial activation on the mid and distal coronary sinus poles of the coronary sinus catheter. The antegrade limb is the AV node and the retrograde limb is the left-sided accessory pathway.

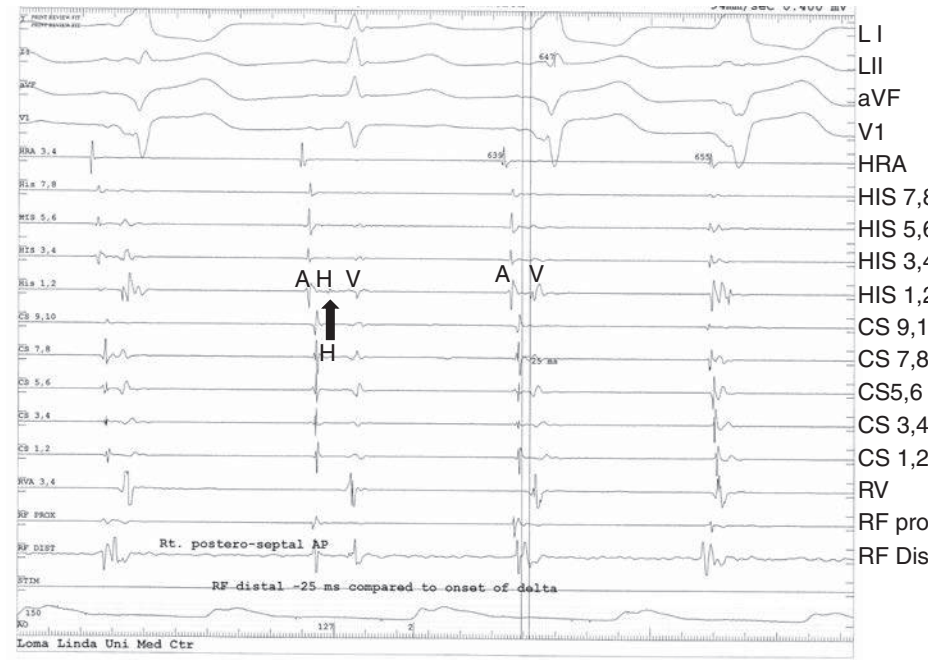

Figure 22.38b

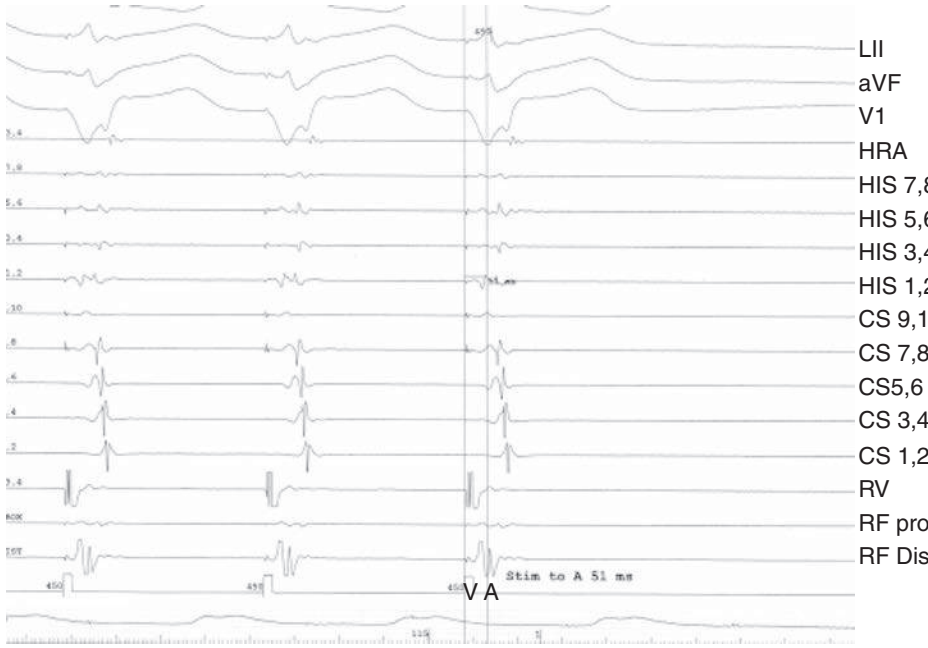

Figure 22.39b

22.42. B. VT.

The morphology is RBBB with monophasic R wave in lead V1. There is evidence of AV dissociation (arrows in Figure 22.42 point to P waves). The axis is in the northwest (left superior) quadrant.

22.43. A. Prior MI.

The ECG is suggestive of VT (wide complex tachycardia with monophasic R in V1 with RBBB morphology, slurred upstroke of QRS). The patient likely had a prior MI.

22.44. B. Idiopathic RVOT VT.

Repetitive monomorphic VT in the absence of structural heart disease and LBBB with inferior axis VT morphology is consistent with RVOT origin.

22.45. B. Idiopathic LV VT.

The tachycardia has RBBB morphology with left axis deviation suggestive of origin in left ventricle in the region of the posterior fascicle.

22.46. A. SVT with aberrant conduction.

On the rhythm strip the tachycardia changes from wide to narrow QRS. Rate-related aberrant conduction during SVT is responsible for wide QRS tachycardia.

22.47. B. AVRT with bundle branch block ipsilateral to accessory pathway.

In the presence of bundle branch block ipsilateral to the accessory pathway, the circuit is larger, which increases the cycle length of the tachycardia. For example, in the presence of LBBB with a left-sided accessory pathway the impulse travels down the AV node, His bundle to right ventricle then left ventricle which then engages the accessory pathway and activates the atrium.

22.48. A. VT.

There is VA dissociation during tachycardia and no His spike recorded in front of the V-signal.

22.49. A. The retrograde atrial activation with ventricular pacing is occurring only via the AV node.

This statement is not accurate. The retrograde atrial activations with ventricular pacing and during SVT are identical. The earliest atrial activation is in the coronary sinus poles 3, 4 of the coronary sinus catheter, which is located at a left lateral site.

22.50. D. Short HV interval on the atrial paced beats.

This is not accurate. All other statements are correct. The HV interval on the first three atrial paced beats is normal. All of the other findings are present on this tracing obtained from a patient with AVNRT.

22.51. C. The conduction system is unlikely to recover and a permanent pacemaker implant is indicated.

This statement is incorrect. This patient has an underlying LBBB. The development of RBBB from catheter-induced trauma results in transient heart block and does not require a permanent pacemaker implant.

22.52. B. Infra-His block.

On the P wave following the third ventricular beat, the distal poles of the His bundle catheter (His 1, 2) has an atrial electrogram followed by a His spike. There is no ventricular electrogram following the His spike.

Reference

Birnie, D.H., Healey, J.S., Wells, G.A., *et al.* (2013) Pacemaker or defibrillator surgery without interruption of anticoagulation. *The New England Journal of Medicine*, **368**: 2084–2093.

Pacemakers and Defibrillators

23

23.1. A 50-year-old patient gives a history of four dizzy spells in the last month, occurring once a week. When she is seen in the clinic, she is not on any medications, is asymptomatic, and pulse is 45 bpm. The thyroid function is normal. What is the next step in the management?

A. Observe
B. 48-h Holter monitor
C. Event monitor
D. Permanent pacer implant.

23.2. A 65-year-old obese male patient with history of hypertension was monitored following colonoscopy. He had sinus bradycardia with heart rate of 45 bpm. A Holter monitor was placed which revealed episodes of second-degree atrioventricular (AV) block with 2 : 1 conduction. The patient did not have any symptoms while he wore the monitor. What is the next step in the management of this patient?

A. Event monitor
B. Sleep studies
C. Electrophysiology (EP) studies
D. Pacer implant

23.3. A 42-year-old patient has noticed fatigue after returning from a trip to the East Coast. He had been hiking in the woods. He denies history of syncope. His ECG shows complete heart block. Which of the following options should be considered next?

A. Observe
B. Lyme serology
C. Temporary pacer
D. Permanent pacer

23.4. A 35-year-old asymptomatic patient with myotonic muscular dystrophy has evidence of first-degree AV block on a routine ECG. Which option should be considered next?

A. Schedule follow up in 6 months
B. Holter monitor
C. EP studies
D. Permanent pacer implant

23.5. In a patient with history of syncope and evidence of right bundle branch block with left anterior fascicular block on one ECG and a right bundle branch block with left posterior fascicular block on an ECG done the following day, what is the next appropriate step?

A. Event monitor
B. EP studies
C. Loop recorder
D. Permanent pacer implant

23.6. A 44-year-old patient is status post cardiac transplant 2 days ago. He develops junctional rhythm at 40 bpm. Of the following treatment options, which one is indicated next?

A. Transcutaneous pacing
B. Temporary trans-venous pacing
C. Permanent pacer implant
D. Observe

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23.7. In patients with cardiac sarcoidosis, which of the following statements is not true?
- **A.** Patients are at risk for developing complete heart block
- **B.** Patients are at risk for developing VT
- **C.** Myocardial involvement occurs in less than 5% of patients
- **D.** Usually affects individuals aged 20–40 years

23.8. Which of the following statements regarding carotid sinus hypersensitivity is not true?
- **A.** Elderly patients may present with unexplained falls without loss of consciousness
- **B.** The reflex has a cardio-inhibitory component
- **C.** There is no vasodepressor component
- **D.** Permanent pacing is indicated in patients who develop pause greater than 3.0 s with carotid sinus massage

23.9. Which of the following statements regarding the role of pacing in neurocardiogenic syncope is not true?
- **A.** It is not the first-line therapy for most patients.
- **B.** It is indicated if there is no prodrome before syncopal event
- **C.** It is indicated in patients with profound bradycardia or asystole during an episode
- **D.** Those patients in whom other therapies are effective, but patient prefers to undergo pacer implant

23.10. In patients with long QT syndrome, which of the following is not an indication for permanent pacer implant?
- **A.** Prevent pause-dependent VT, with or without QT prolongation
- **B.** In high-risk patients with congenital long QT
- **C.** Torsades de pointes VT due to reversible causes
- **D.** Combination of pacing and beta blockade shortens QT interval and reduces the risk of sudden cardiac death

23.11. In a patient with ischemic cardiomyopathy, ejection fraction (EF) 30%, and New York Heart Association (NYHA) class I, all of the following characteristics are contraindications for cardiac resynchronization therapy (CRT) *except* for which option?
- **A.** Left bundle branch block (LBBB) with QRS duration 120–149 ms
- **B.** Non-LBBB with QRS duration 120–149 ms
- **C.** LBBB with QRS duration >150 ms
- **D.** Non-LBBB with QRS duration >150 ms

23.12. A 75-year-old patient with history of sick sinus syndrome, status post pacer implant is scheduled to undergo generator replacement. Pacer diagnostics revealed that patient was V-paced 50% of the time. ECG done with pacer inhibited revealed sinus bradycardia with PR interval of 320 ms, QRS duration 110 ms, and QT interval 420 ms. The left ventricular (LV) EF is 35%. What is the next step in the management of this patient?
- **A.** Replace pacer generator
- **B.** Upgrade to CRT pacer
- **C.** Upgrade to dual-chamber implantable cardioverter-defibrillator (ICD)
- **D.** Upgrade to CRT defibrillator

23.13. A 78-year-old patient with history of nonischemic cardiomyopathy, EF 20%, and permanent atrial fibrillation was recently hospitalized with congestive heart failure exacerbation. In the office she is noted to be in atrial fibrillation with ventricular rate 130 bpm at rest. The patient has been on carvedilol 50 mg BID and digoxin 0.125 mg daily. What is the best treatment option?

A. Single-chamber ICD
B. Dual-chamber ICD
C. Biventricular pacer/ICD and AV node ablation
D. Subcutaneous ICD

23.14. A 55-year-old patient presents with symptoms of epigastric discomfort of 1 h duration. An ECG revealed acute inferior myocardial infarction with complete AV block. The ventricular rate is 50 bpm, and the blood pressure is 80/50 mmHg. He undergoes stent to proximal right coronary artery with resolution of symptoms. The rhythm is unchanged. What is the next step in the management?

A. Observe
B. Transcutaneous pacer
C. Temporary transvenous pacer
D. Permanent pacer implant

23.15. A 48-year-old female patient with no prior cardiac history has an out-of-hospital cardiac arrest. After undergoing prolonged resuscitation measures, including four external shocks, she makes a full recovery. The LVEF is 50%. The cardiac enzymes are mildly elevated, and the coronary anatomy is normal. The cardiac magnetic resonance image is normal. Of the following options, which would you recommend?

A. Beta blockers
B. Life vest
C. Amiodarone
D. ICD implant

23.16. A 64-year-old patient with history of remote myocardial infarction 10 years ago, LVEF 50%, and with inferior wall infarct on echocardiogram gives history of episodes of palpitations associated with dizziness for the last month. He presents to the emergency room following an episode of palpitation of half-hour's duration. ECG reveals wide QRS tachycardia consistent with VT. What is the most appropriate treatment choice for this patient?

A. Metoprolol
B. Sotalol
C. Amiodarone
D. ICD implant

23.17. A 72-year-old patient with history of myocardial infarction 15 years ago is brought to the emergency room following a syncopal spell. He had no warning symptoms. Echocardiogram revealed LVEF 45%, antero-apical infarct. Occluded mid left anterior descending artery is seen on coronary angiogram. EP studies are performed. Sustained monomorphic VT is induced with programmed ventricular stimulation with the introduction of two extra stimuli. What is the next step in the management of this patient?

A. Metoprolol
B. Amiodarone
C. Life vest
D. ICD implant

23.18. A 47-year-old patient is seen by his cardiologist for follow-up. He had an anterior myocardial infarction 6 weeks ago and received thrombolytics. He has been doing well. An echocardiogram is done. The LVEF is 35%, and anterior wall is akinetic. The patient is on aspirin, atorvastatin, metoprolol, and enalapril. Which of the following is recommended for this patient?

A. Spironolactone
B. Amiodarone
C. EP studies
D. ICD implant

23.19. A 65-year-old patient with history of nonischemic cardiomyopathy, diagnosed 1 year ago, and LVEF 30% on recent echo is seen in the office for a routine visit. He has shortness of breath when he walks up an incline. On physical exam, he is euvolemic. Current medications include carvedilol and benazepril. Which of the following therapies would you recommend next?

A. Lasix
B. Digoxin
C. Spironolactone
D. ICD implant.

23.20. An ICD implant for primary prevention is indicated which of the following patients?

A. 50-year-old patient with history of myocardial infarction 6 weeks ago, NYHA class I symptoms, LVEF 30%
B. 40-year-old asymptomatic male with ECG suggestive of Brugada syndrome, whose brother died suddenly
C. 45-year-old asymptomatic patient with history of hypertrophic cardiomyopathy, LV thickness 2.0 cm
D. 18-year-old female with lightheaded spells and QT prolongation on ECG.

23.21. A 64-year-old patient with history of myocardial infarction 12 years ago is hospitalized following elective hip surgery. He has an eight-beat run of nonsustained VT at a rate of 130 bpm. He denies symptoms of palpitations or dizziness. An echocardiogram was done; the LVEF was 40%. He is on metoprolol and enalapril. What is the next step in the management of this patient?

A. Mexilitene
B. Sotalol
C. Amiodarone
D. EP studies

Answers

23.1. C. Event monitor.

It is important to determine that dizzy spells are brought on by bradycardia. As the episodes are not every day, Holter recording may not be fruitful.

23.2. B. Sleep studies.

The patient most likely has obstructive sleep apnea, which is known to be associated with AV block.

23.3. B. Lyme serology.

Lyme disease is a reversible cause of heart block.

23.4. D. Permanent pacer implant.

As the risk of progression of AV block is known to be high.

23.5. B. EP studies.

These are indicated to determine if the patient has inducible ventricular tachycardia (VT), which could account for syncope. Trifascicular disease is indicative of possible diffuse myocardial disease which provides a substrate for VT. If an EP study is negative, trifascular block is the likely cause of syncope and pacer would be appropriate.

23.6. B. Temporary trans-venous pacing.
There is good chance AV conduction will recover.

23.7. C. Myocardial involvement occurs in less than 5% of patients.
About 25% of patients with sarcoid have myocardial involvement, of which 30% develop complete heart block.

23.8. C. There is no vasodepressor component.
In 10–20% of patients a vasodepressor component is present.

23.9. D. Those patients in whom other therapies are effective, but patient prefers to undergo pacer implant.
Pacer implant is contraindicated (class III) in patients who respond to other therapies.

23.10. C. Torsades de pointes VT due to reversible causes.
Pacing is contraindicated (class III) in patients with torsades de pointes VT due to reversible causes.

23.11. C. LBBB with QRS duration >150 ms.
In other situations, patients have to be more symptomatic. Highest benefit is in those with LBBB with QRSd >150 ms.

23.12. D. Upgrade to CRT defibrillator
As EF is 35% and percentage ventricular pacing is >40%.

23.13. C. Biventricular pacer/ICD and AV node ablation
This is a class IIA indication with near 100% biventricular pacing likely following AV node ablation.

23.14. C. Temporary transvenous pacer.
The AV block is likely to resolve in the setting of inferior myocardial infarction.

23.15. D. ICD implant.
For secondary prevention of sudden cardiac death. The patient was defibrillated several times, which explains mild elevation of cardiac enzymes.

23.16. D. ICD implant.
Sustained VT is a class I indication for ICD implant.

23.17. D. ICD implant.
Inducible VT in this patient is a class I indication for ICD implant.

23.18. D. ICD implant.
Class I indication for ICD implant for primary prevention as patient is 40 days post myocardial infarction with LVEF 35%.

23.19. D. ICD implant.
Class I indication.

23.20. A. 50-year-old patient with history of myocardial infarction 6 weeks ago, NYHA class I symptoms, LVEF 30%.
Class I indication for ICD implant.

23.21. D. EP studies.
If VT is induced, it is a class I indication for ICD implant.

Cardiac Masses 24

24.1. An 85-year-old female came in with complaints of chest pain. Her past history is significant for coronary artery disease, diabetes mellitus, and partial left mastectomy for a stage 2 breast cancer 6 years ago. Her lab work was negative for any acute process. She has a history of drug-eluting stent placement to her left circumflex artery 6 months prior to this admission. She has a nuclear stress test which was negative for ischemia. She also underwent an echocardiogram as part of her workup. What does the image in Figure 24.1 show?

A. Normal
B. Enlarged liver
C. Cysts in the kidney
D. Mass in the liver

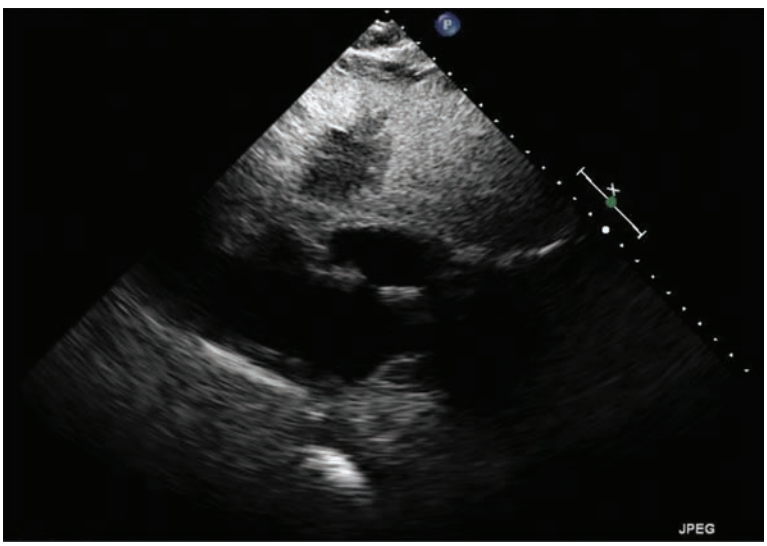

Figure 24.1

24.2. What is the next best step for the patient in Question 24.1?

A. Nothing at this time as she has no abdominal complaints
B. Aspiration biopsy of the liver mass
C. Ultrasound of the liver
D. CT scan of the liver

24.3. A 33-year-old female presented with complaints of shortness of breath, choking sensation, and facial swelling. She has a history of a vaginal delivery 4 weeks ago

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prior to this presentation. She denies any other medical problems in the past. An echocardiogram was performed. What does the image in Figure 24.3 show?

A. Normal echocardiogram from the suprasternal window
B. An artifact
C. Large mass in the superior mediastinum
D. Cannot tell

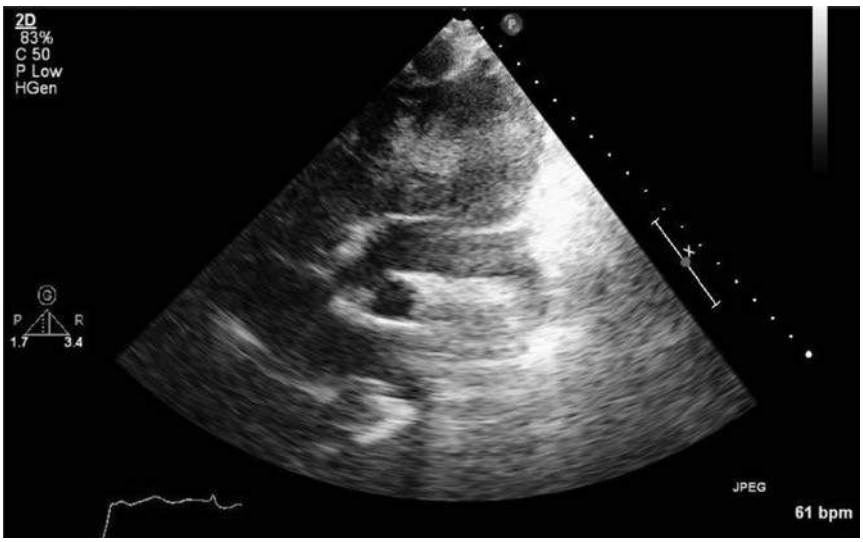


Figure 24.3

24.4. What is the next step for the patient in Question 24.3?

A. Diagnostic imaging with computed tomography (CT) scan
B. Ultrasound of the neck
C. No need for additional imaging
D. PET scan

24.5. A CT scan, shown in Figure 24.5, was ordered for the patient in Question 24.3. What does the image show?

A. Mass in the anterior mediastinum
B. Mass in the posterior mediastinum
C. Mass in the lung
D. Nothing abnormal is seen

24.6. What is the next best step for the patient in Question 24.3?

A. Biopsy of the mass
B. Ultrasound of the mass
C. Consultation with a surgeon
D. Nothing at this time

24.7. A 31-year-old male is admitted to the hospital for complaints of hemoptysis. He is a prisoner, and has a remote history of tuberculosis that was treated. An echocardiogram was performed. What does the still frame obtained from parasternal long axis view and subcostal view in Figure 24.7a show?

A. Mass in the left atrium
B. Mass in the right atrium
C. Large artifact
D. No abnormality is noted

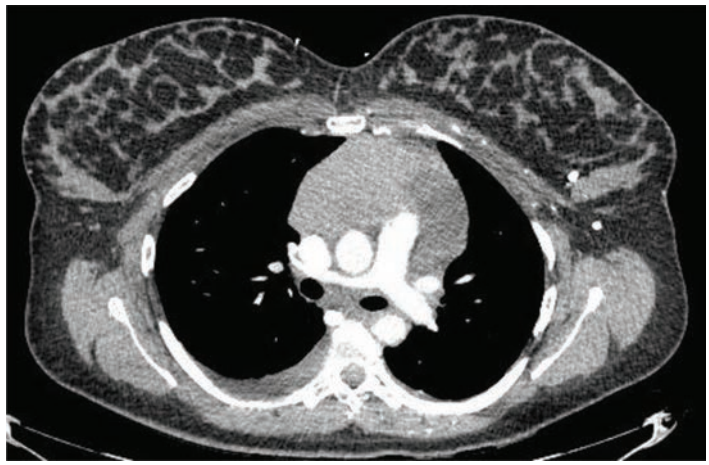


Figure 24.5

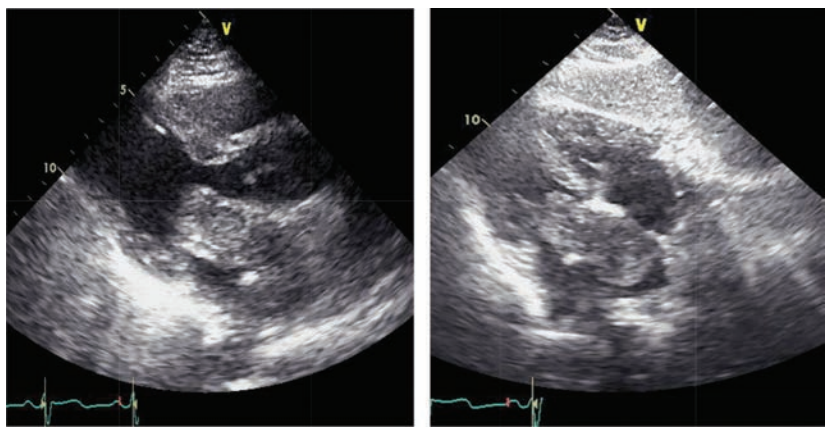


Figure 24.7a

24.8. The patient in Question 24.7 then underwent cardiac magnetic resonance imaging. The SSFP image is shown in Figure 24.8a. What does this image show?

- **A.** Mass in the left atrium
- **B.** Mass in the left atrium with filling defect in the right lower pulmonary vein and bilateral pleural effusions
- **C.** No cardiac abnormality is noted
- **D.** Mass in the right atrium

24.9. The patient in Question 24.7 also then started having hemoptysis, for which a CT scan was done. What does the image in Figure 24.9a show?

- **A.** Normal CT scan of the chest
- **B.** A mass encircling the right bronchus
- **C.** Mass in the pulmonary artery
- **D.** Mass in the liver

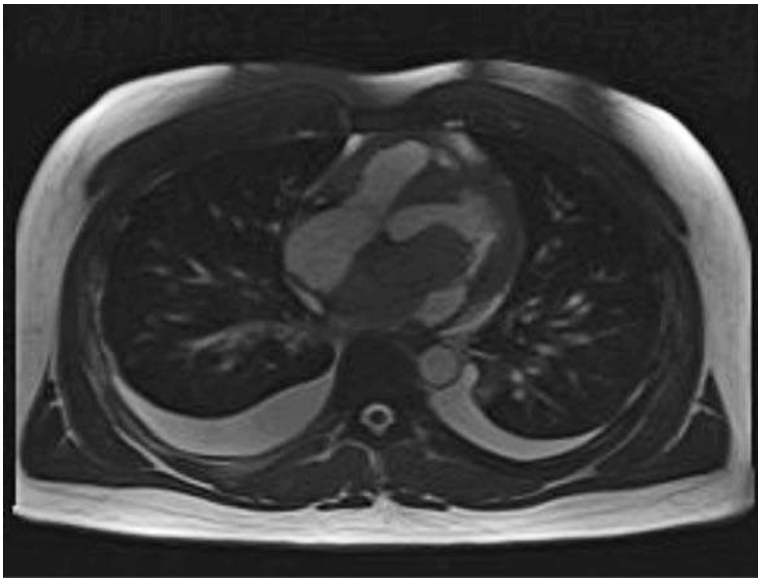


Figure 24.8a

Figure 24.9a

24.10. The patient in Question 24.7 then started complaining of left thigh pain and swelling. A CT scan of the lower extremities was completed; see Figure 24.10a. What does the image show?

A. A normal CT scan
B. Normal right thigh and a large mass in the left thigh
C. A large mass in the lower abdomen
D. Mass in the right thigh

Figure 24.10a

24.11. What is the next best step for the patient in Question 24.7?

A. Consultation with the surgeons to remove the left atrial tumor
B. Biopsy of the left thigh mass
C. Biopsy of the left atrial mass
D. Surgical consultation to remove the left thigh mass

24.12. A 72-year-old male presented with a history of mechanical mitral valve replacement for rheumatic heart disease. He was on a therapeutic dose of warfarin and had subdural hemorrhage. Warfarin was discontinued by his treating physicians. The cardiologist paged late Friday evening for assistance as the patient went into flash pulmonary edema, atrial fibrillation with rapid ventricular response, was intubated emergently and imaging was performed; see Figure 24.12a. What does the image show?

A. Vegetations
B. Pannus
C. Tumor masses
D. Thrombus

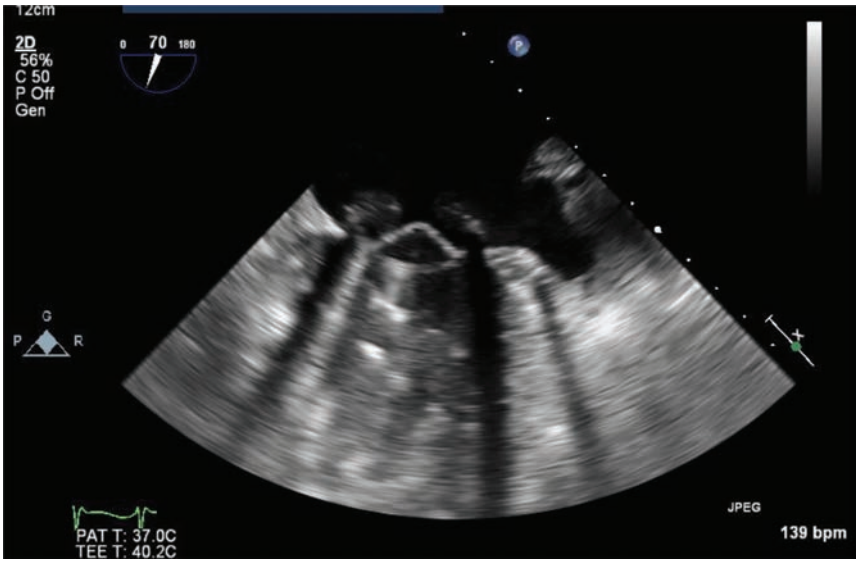


Figure 24.12a

24.13. A 74-year-old male was being evaluated for complaints of shortness of breath. His echo was unremarkable except for the image shown in Figure 24.13a. What does the image show?

A. Normal subcostal view
B. Artifact in the inferior vena cava (IVC)
C. Discrete masses in the IVC
D. Discrete masses in the aorta

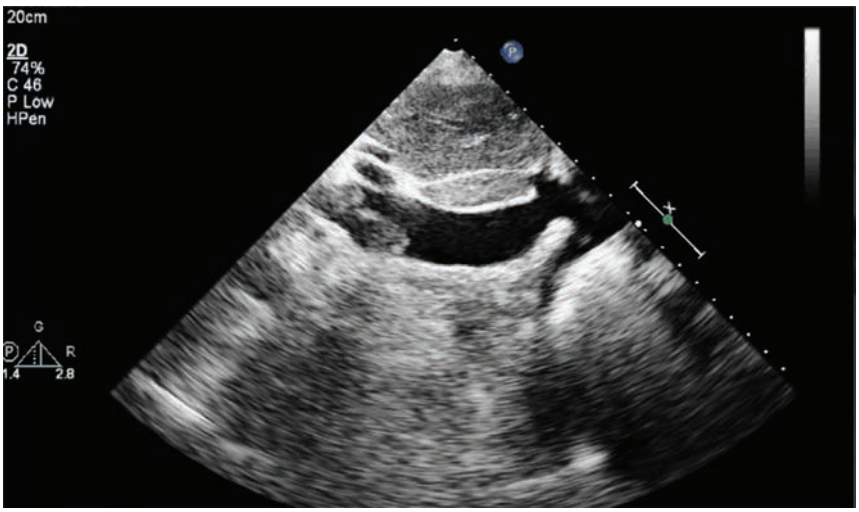


Figure 24.13a

24.14. What is the next best step for the patient in Question 24.12?

- **A.** Do nothing
- **B.** Ultrasound of the abdomen
- **C.** Magnetic resonance imaging of the abdomen
- **D.** Initiate anticoagulation

24.15. A 64-year-old male was admitted to hospital with complaints of fever, fatigue, and night sweats. He had a transthoracic echocardiogram; see Figure 24.15a. What does this left-sided subcostal image show?

- **A.** Normal structures
- **B.** Nephromegaly
- **C.** Hepatomegaly
- **D.** Splenomegaly

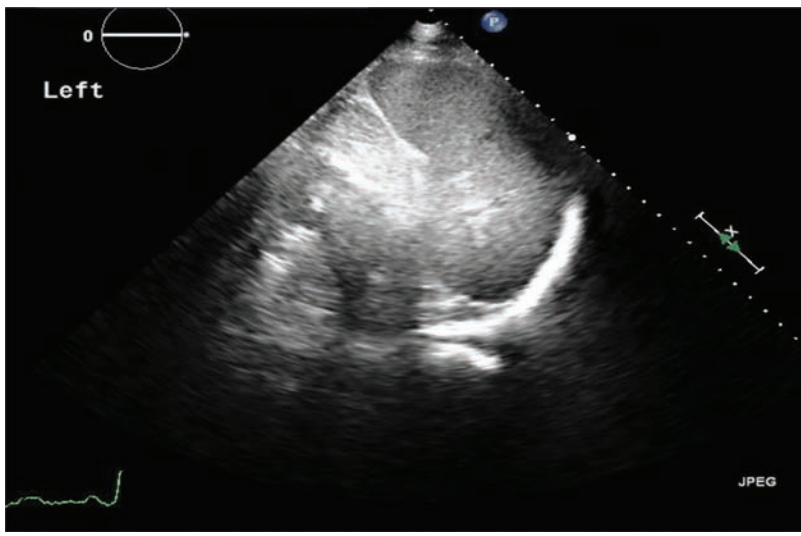


Figure 24.15a

24.16. A 20-year-old male presents to the hospital with complaints of fever, chills, and loss of appetite. He has a history of endocarditis and had a history of tricuspid valve replacement about 2 years prior to this admission. On examination he was febrile and tachycardiac. He had an echocardiogram; see Figure 24.16a. What does the image show?

- **A.** Normal native tricuspid valve
- **B.** Vegetations on the bioprosthetic valve
- **C.** Tumor masses
- **D.** Thrombus on the valve

24.17. A 34-year-old male presents with complaints of malaise and shortness of breath on exertion. Physical examination is otherwise unremarkable. He had an echocardiogram; see Figure 24.17a (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle). What does the image show?

- **A.** Thrombus
- **B.** Myxoma
- **C.** Sarcoma
- **D.** Vegetation

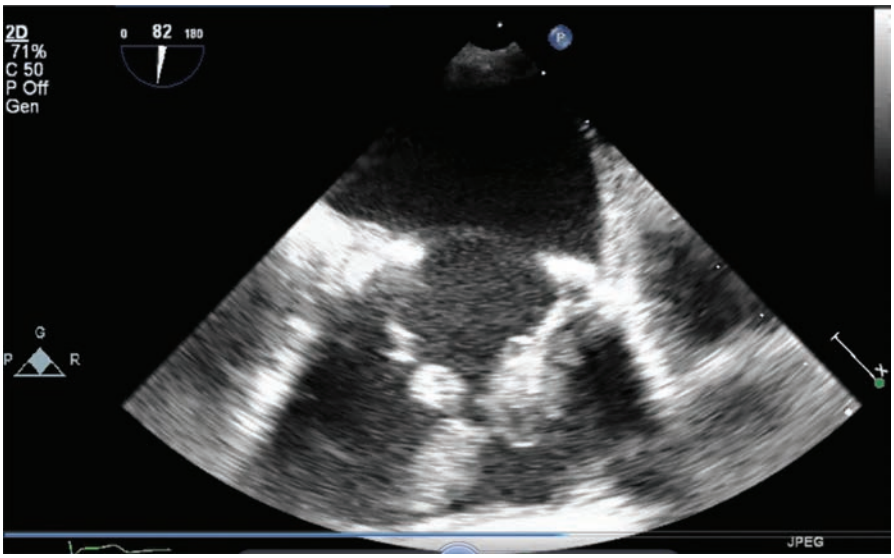


Figure 24.16a

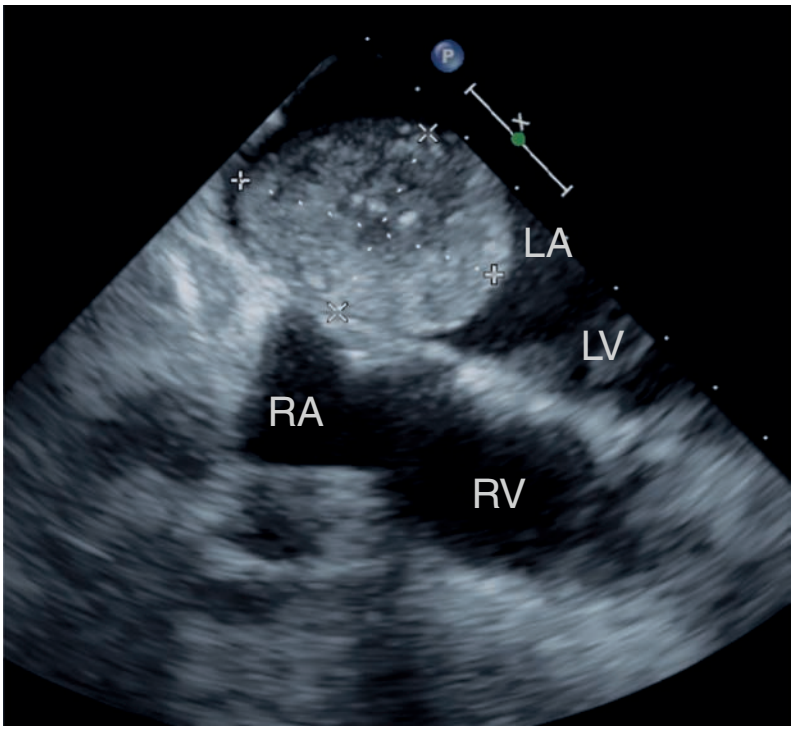


Figure 24.17a

24.18. A 45-year-old female had sudden onset of palpitations and had near syncope. She had no significant past medical history. She had an echocardiogram; see Figure 24.18a (LV: left ventricle; RV: right ventricle). What does the image show?

A. Myxoma
B. Rhabdomyoma
C. Fibroma
D. Lymphoma

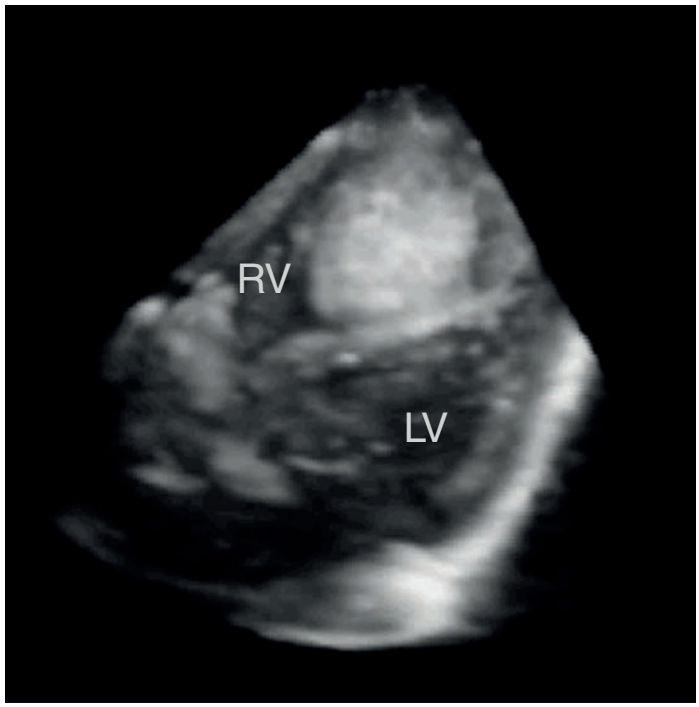


Figure 24.18a

24.19. A 56-year-old male presents to the hospital with a history of transient ischemic attack. On examination he has no motor or sensory deficits. His cardiac examination is normal. He had an echocardiogram; see Figure 24.19a. What does the image show?

A. Vegetation on the mitral valve
B. Papillary fibroelastoma of the aortic valve
C. Papillary fibroelastoma of the mitral valve
D. Thrombus on the aortic valve

24.20. A 35-year-old male with a history of long-standing type 2 diabetes mellitus, hypertension, and end-stage renal disease started dialysis 2 months ago. He presents to the hospital complaining of fever, chills, malaise, nausea, and loss of appetite. He was clammy to touch, tachycardiac, and febrile. The rest of his physical examination was normal. He had blood cultures drawn and had an echocardiogram; see Figure 24.20a. What does the image show?

A. Vegetation on the catheter
B. Thrombus
C. Tumor mass
D. Nothing abnormal is detected

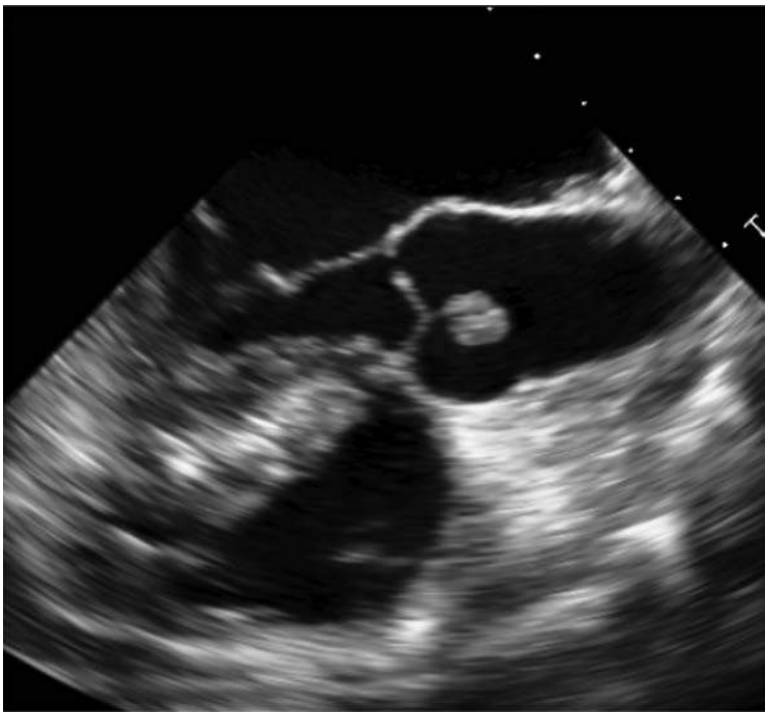


Figure 24.19a *Source:* reproduced with permission of Dr Natesa G. Pandian.

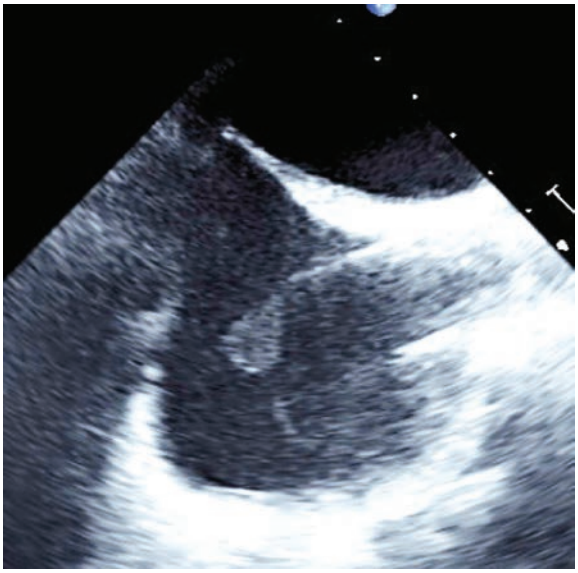


Figure 24.20a

24.21. What is the initial management strategy for the patient in Question 24.20?

A. Start antibiotics
B. Draw blood cultures, one from the periphery and one from the line, and then start antibiotics
C. CT scan of the chest
D. Observation

24.22. What does the image in Figure 24.22a show?

A. Vegetation
B. Thrombus
C. Blood cyst
D. Tumor

Figure 24.22a

24.23. A 75-year-old patient with a history of hypertension had an echocardiogram at an outside hospital. The patient was referred to this hospital for evaluation of a right atrial mass. What does the image in Figure 24.23a (LA: left atrium; RA: right atrium) show?

A. Lymphoma
B. Sarcoma**A.**

Figure 24.25a

24.26. A newborn baby was diagnosed with tuberous sclerosis. She has seizures. She had an echocardiogram; see Figure 24.26a. What does the image show?

- **A.** Multiple small tumors, likely rhabdomyoma
- **B.** Lipomas
- **C.** Sarcoma
- **D.** Fibroma

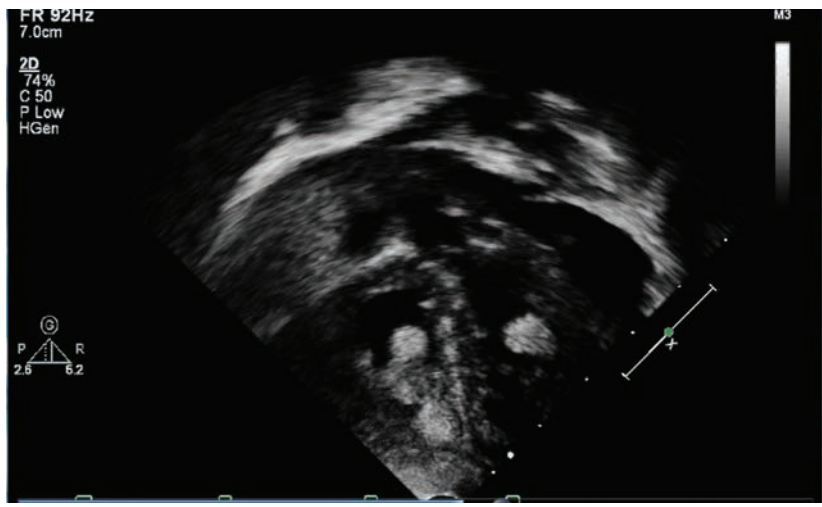


Figure 24.26a

24.27. What is the recommended management strategy for the patient in Question 24.26?

A. Refer for surgery
B. Chemotherapy
C. Do nothing, manage seizures
D. Radiation

24.28. A 59-year-old male presents to the hospital with complaints of acute onset of 9/10 central chest pressure. A 12-lead electrocardiogram showed anterior ST elevation and he was rushed to the cardiac catheterization laboratory. He was found to have a 100% mid left anterior descending artery stenosis for which he had successful coronary intervention and placement of a drug-eluting stent. He then had an echocardiogram the next day, which showed akinesis of the left anterior descending artery territory. What does the apical four chamber image in Figure 24.28a (LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle) show?

A. Tumor in the left ventricular apex
B. A thrombus in the left ventricular apex
C. Artifact from overlying ribs
D. Obliterative myocarditis

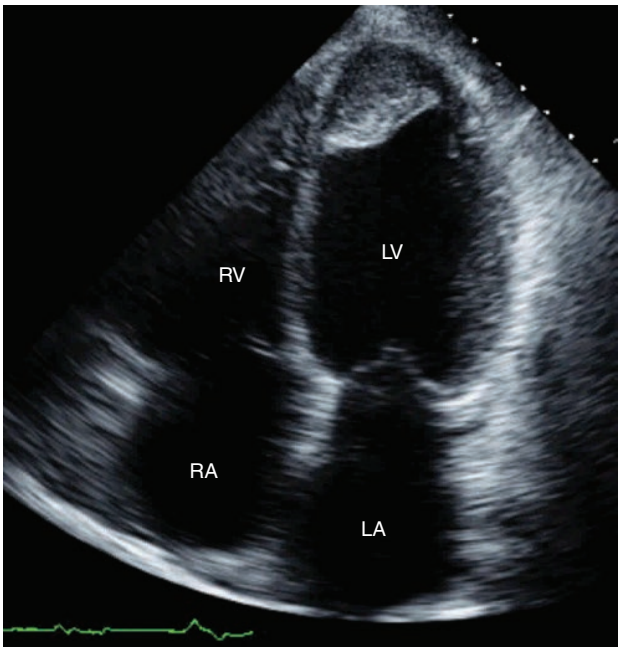
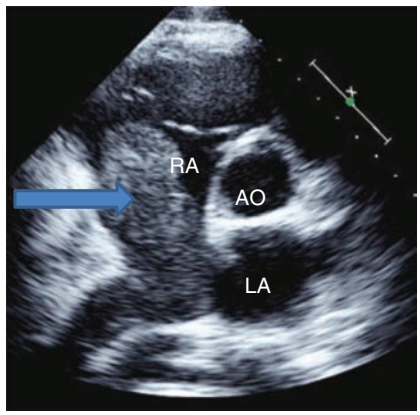
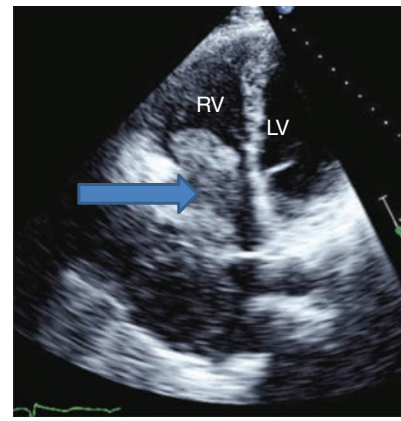


Figure 24.28a

24.29. A 32-year-old male with a previous history of HIV infection is on antiretroviral therapy. He presents to the hospital with complaints of fever, night sweats, loss of appetite, and unintentional weight loss of 12 lb in 2 months. He had an echocardiogram; see Figure 24.29. What is the most likely explanation?

A. Thrombus in the right atrium
B. Renal cell carcinoma
C. Sarcoma
D. Lymphoma





RA-right atrium
LA-left atrium
AO-aorta

RV-right ventricle
LV-left ventricle

Figure 24.29 *Source:* reproduced with permission of Dr Natesa G. Pandian.

24.30. A 67-year-old male had a routine echocardiogram. What does the subcostal view shown in Figure 24.30 demonstrate?

A. Normal findings
B. A mass arising from the superior pole of the right kidney
C. A mass arising from the liver
D. A mass arising from the spleen

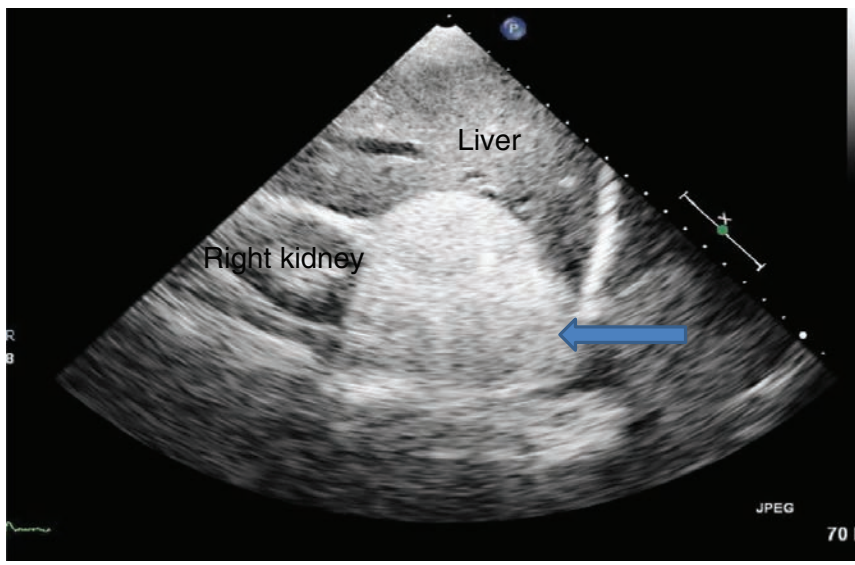


Figure 24.30

24.31. A 28-year-old male has a history of systemic lupus erythematosus and chronic kidney disease stage 2. He had a routine echocardiogram. What does the parasternal long axis view in Figure 24.31a demonstrate?

- **A.** Normal looking mitral valve
- **B.** Inflammatory changes of the mitral valve suggestive of Libman–Sacks endocarditis
- **C.** Papillary fibroelastoma
- **D.** Rheumatic changes of the mitral valve

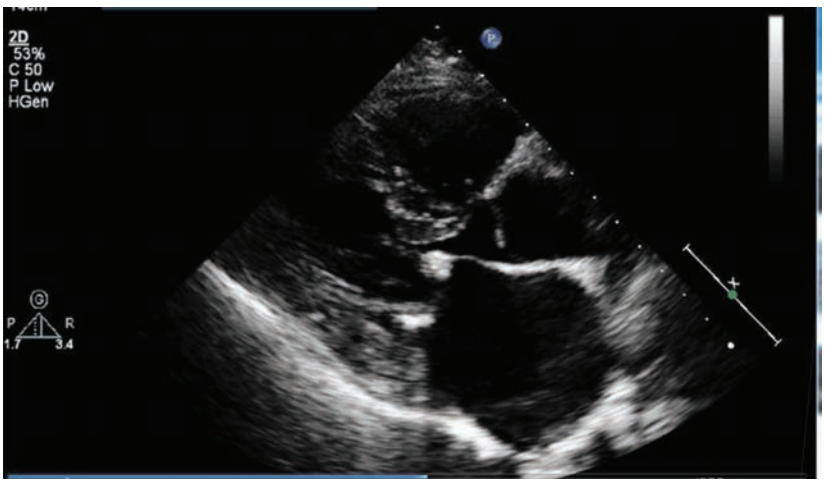


Figure 24.31a

24.32. What does the subcostal view in Figure 24.32a demonstrate?

- **A.** Renal stones
- **B.** Gall stones
- **C.** Hepatic stones
- **D.** None of the above

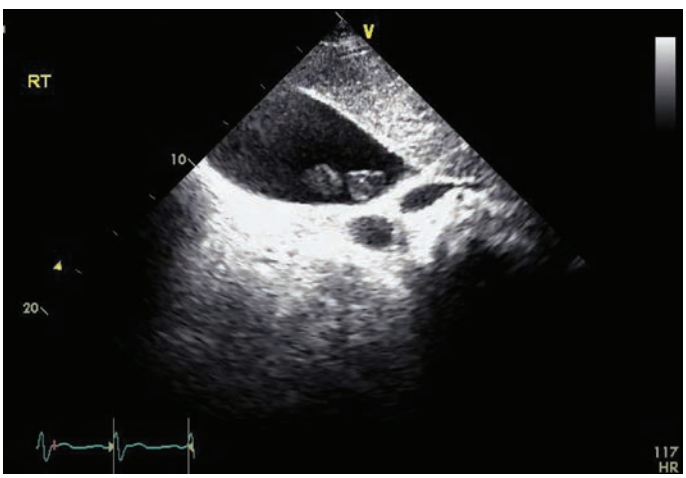


Figure 24.32a

24.33. A 72-year-old male was admitted to the hospital with complaints of fever, chills, night sweats, weight loss of 10 lb in 1 month. He had a routine echocardiogram. What does the subcostal view in Figure 24.33a show?

A. Normal appearance of the liver
B. Cystic lesions in the liver
C. Right renal mass
D. None of the above

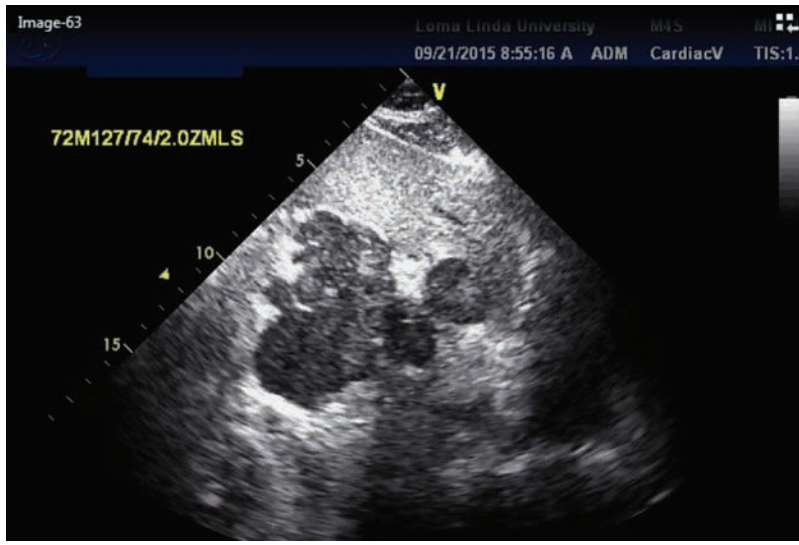


Figure 24.33a

24.34. A 63-year-old male with a history of end-stage renal disease and type 2 diabetes mellitus was admitted to the hospital to manage his dialysis catheter. He underwent a routine echocardiogram. What do the images in Figure 24.34a (LA: left atrium; LV: left ventricle; RV: right ventricle) and Figure 24.34b show?

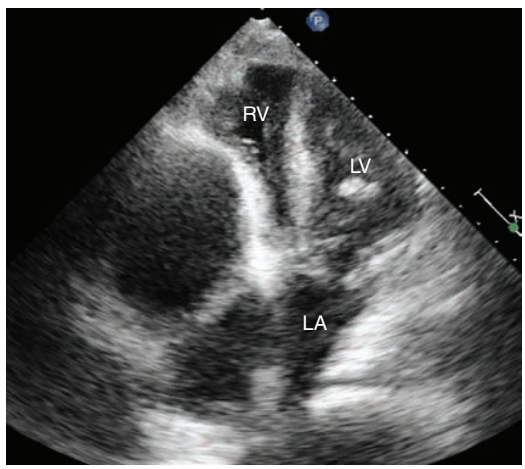


Figure 24.34a

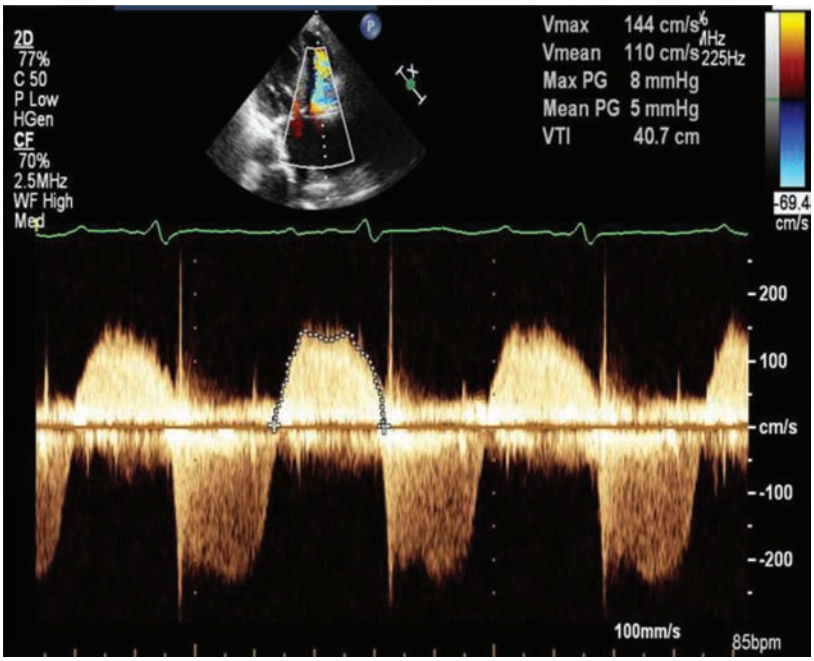


Figure 24.34b

A. Normal apical four-chamber view
B. Apical four-chamber view showing extrinsic compression of the tricuspid valve
C. Apical four-chamber view showing intrinsic compression of the tricuspid valve
D. Apical four-chamber showing compression of the mitral valve

Answers

24.1. D. Mass in the liver.

There is a hypoechoic mass seen in the liver on this subcostal view. The mass measures 45 mm × 34 mm.

24.2. B. Aspiration biopsy of the liver mass.

The liver mass is hypoechoic and is not cystic. She has a previous history of breast carcinoma, which heightens the suspicion for a metastatic mass. She underwent a biopsy of the liver mass which showed metastasis from breast origin. It was positive for both estrogen and progesterone receptors but was negative for HER2 protein.

24.3. C. Large mass in the superior mediastinum.

The image in Figure 24.3 is from the suprasternal window and it shows a large mass in the superior mediastinum. The mass is probably compressing the

superior vena cava (SVC), causing SVC syndrome. The mass may also be compressing her airways, which probably is contributing to her sensation of choking. The mass is seen above the arch of the aorta. Differential diagnosis includes goiter, thymoma, lymphoma, and germ cell tumors. The echocardiogram also showed a medium-sized pericardial effusion with no tamponade, raising the suspicion for malignancy.

24.4. A. Diagnostic imaging with computed tomography (CT) scan.

This patient needs additional diagnostic imaging to ascertain the location and extent of the mass. A CT scan is very appropriate and will help is assessing the size and location of the mass.

24.5. A. Mass in the anterior mediastinum.

There is a large mass in the anterior mediastinum. This mass measured 9.3 mm × 6.4 cm. The mass is seen surrounding the SVC and the airways. This probably represents a large tumor.

24.6. A. Biopsy of the mass.

The patient has a large anterior mediastinal mass, with SVC syndrome. She is symptomatic from this mass. The next best step is to biopsy the mass to characterize it further. The patient underwent a needle biopsy of the mass. The biopsy (Figure 24.6) showed sparse lymphocytic population with features suspicious for mediastinal large B-cell lymphoma. She had further cytological studies and the mass was deemed to be a primary large B-cell lymphoma.

She had other work-up and was negative for metastasis. She was started on R-EPOCH chemotherapy and responded well. Her symptoms of facial swelling and choking sensation had resolved at the time of discharge from the hospital.

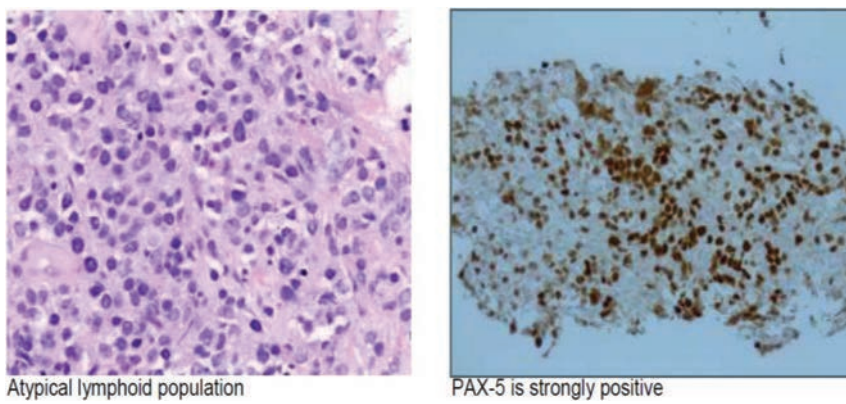


Figure 24.6

24.7. A. Mass in the left atrium.

The parasternal long axis image and the subcostal four-chamber image show a large mass that is probably attached to the interatrial septum and is prolapsing through the mitral valve (Figure 24.7b). Differential diagnosis includes a myxoma.

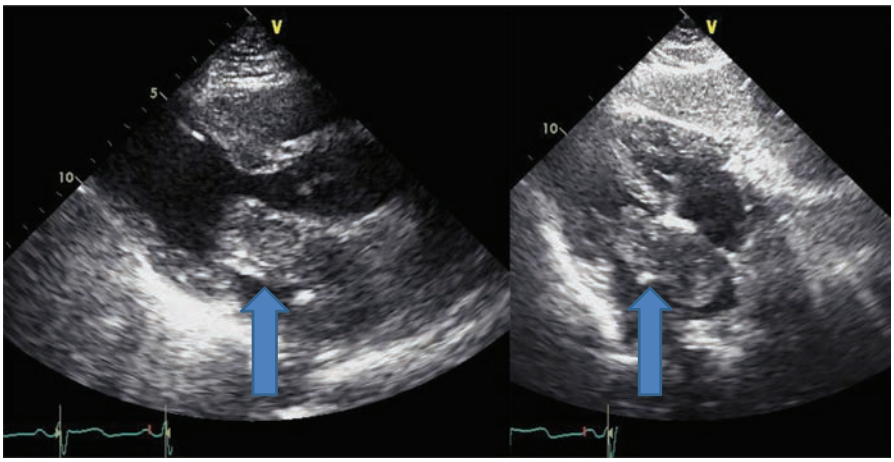


Figure 24.7b

24.8. B. Mass in the left atrium with filling defect in the right lower pulmonary vein and bilateral pleural effusions.

There is a large mass in the left atrium with filling defects in the right lower pulmonary vein (Figure 24.8b). Though the mass appears to be attached to the interatrial septum, this could be a distant metastasis through the pulmonary vein.

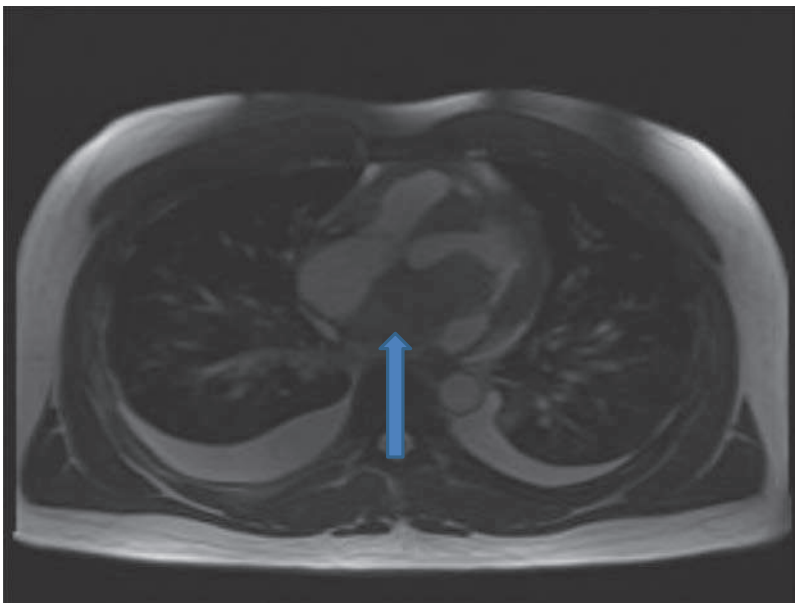


Figure 24.8b

24.9. B. A mass encircling the right bronchus.

There is an abnormal mass seen encircling the right main bronchus (Figure 24.9b). The mass (arrowed) is also seen at the carina infiltrating the airways. This probably is giving rise to hemoptysis.

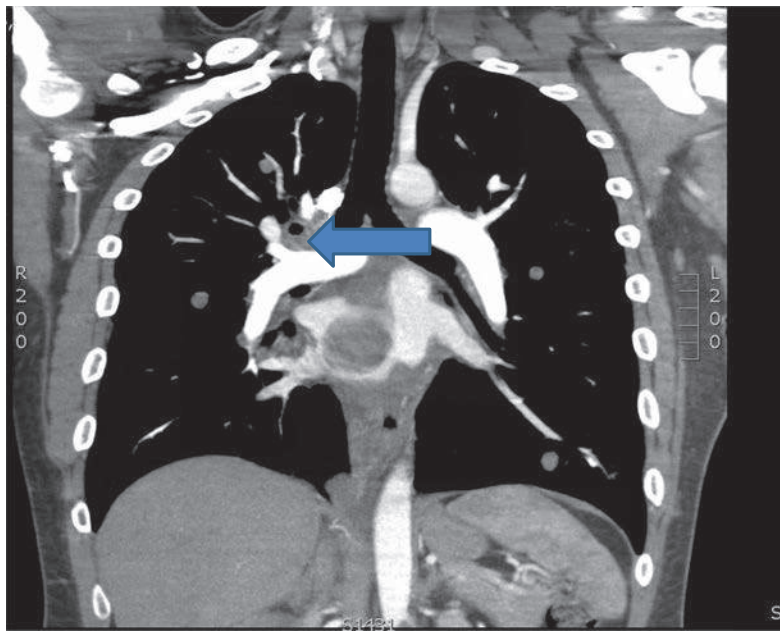


Figure 24.9b

24.10. B. Normal right thigh and a large mass in the left thigh.

This CT scan shows no abnormality in the right thigh. A large mass is seen in the left thigh in the adductor group (arrowed in Figure 24.10b).

24.11. B. Biopsy of the left thigh mass.

Since the patient has a mass in the left atrium, in the chest surrounding the airways, and a in the left thigh, a biopsy of the thigh mass should be undertaken first. This mass is more easily accessible and would provide a tissue diagnosis. He underwent a biopsy of the thigh mass which showed a high-grade sarcoma (Figure 24.11).

His primary tumor was the high-grade sarcoma in his left thigh, which probably then metastasized to the heart though the pulmonary veins and to the chest through the blood. The mass in the chest was also biopsied, which showed evidence of metastasis from his sarcoma. Though the left atrial mass mimicked a myxoma it was essentially a metastasis from the thigh.

24.12. D. Thrombus.

Figure 24.12b (LA: left atrium; LV: left ventricle) shows thrombi attached to the mitral valve sewing ring (blue arrows). The thrombi are preventing the prosthetic valve from opening. The red arrows are pointing to prosthetic valve leaflets.

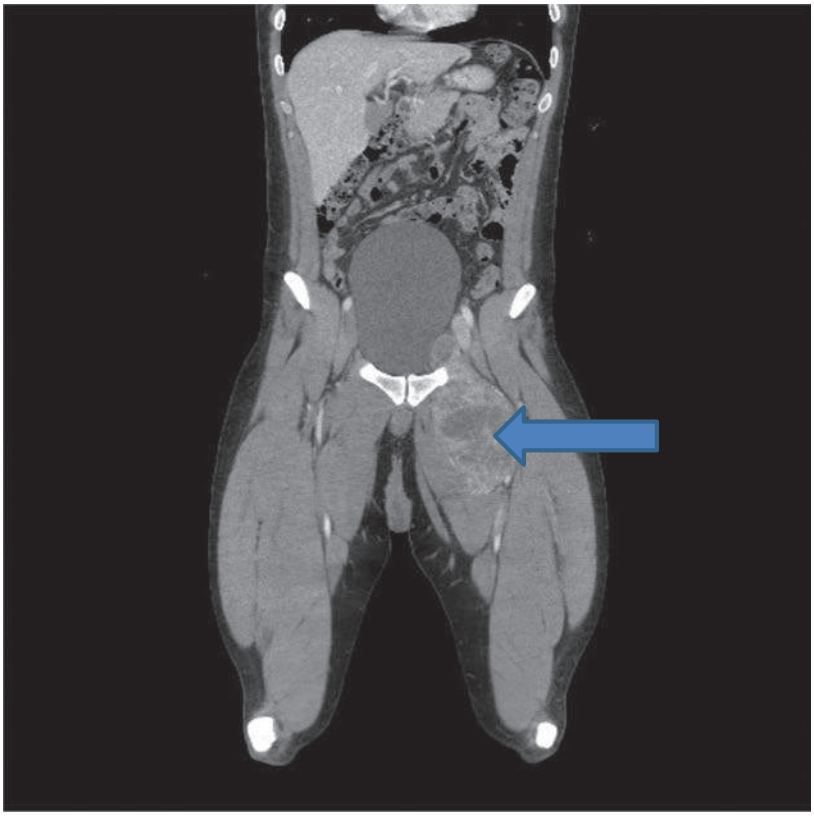


Figure 24.10b

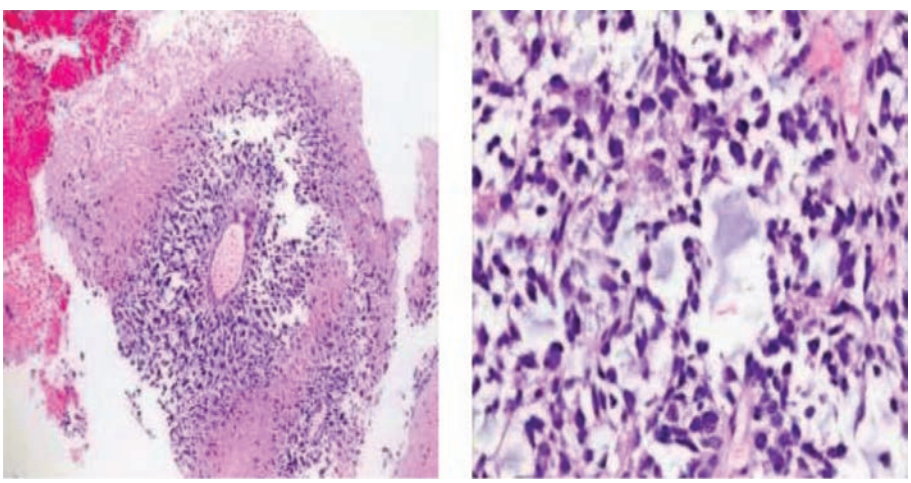


Figure 24.11 Left: spindled tumor cells surrounding vessel. Right: spindled and round cells with occasional mitosis.

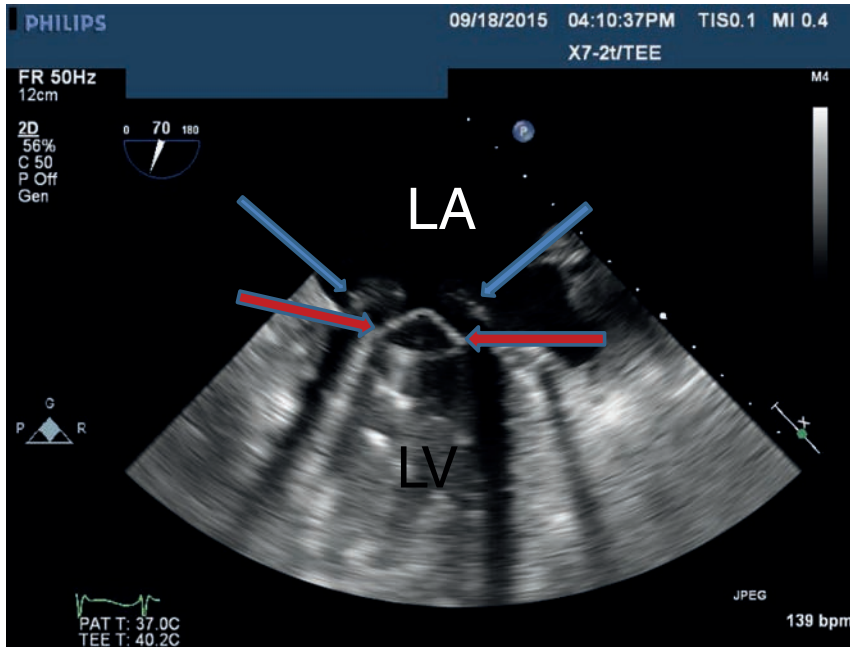


Figure 24.12b

24.13. C. Discrete masses in the IVC.

The subcostal image in Figure 24.13b shows a longitudinal view of the IVC with at least two masses (blue arrow). Differential includes thrombus, tumor masses. The masses are more rounded and discrete and favor thrombi more than tumor.

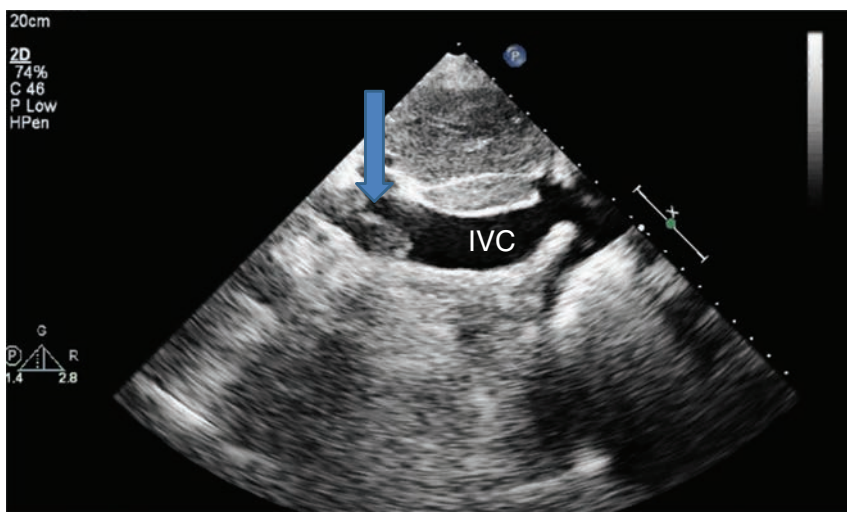


Figure 24.13b

24.14. B. Ultrasound of the abdomen.

The patient underwent an ultrasound of the abdomen, which demonstrated the masses in the IVC. The masses were suggestive of thrombi. The patient then had ultrasound of his lower extremities and was positive for a thrombus in the right popliteal vein. The patient was then initiated on anticoagulants. Though he complained of shortness of breath, he had a negative CT of the pulmonary arteries.

24.15. D. Splenomegaly.

The subcostal image is obtained from the left side. Usual structures seen are the left kidney and spleen when it is enlarged. Figure 24.15b shows an enlarged spleen (blue arrow) and a normal-sized kidney (red arrow). This patient subsequently was diagnosed with acute myeloid leukemia.

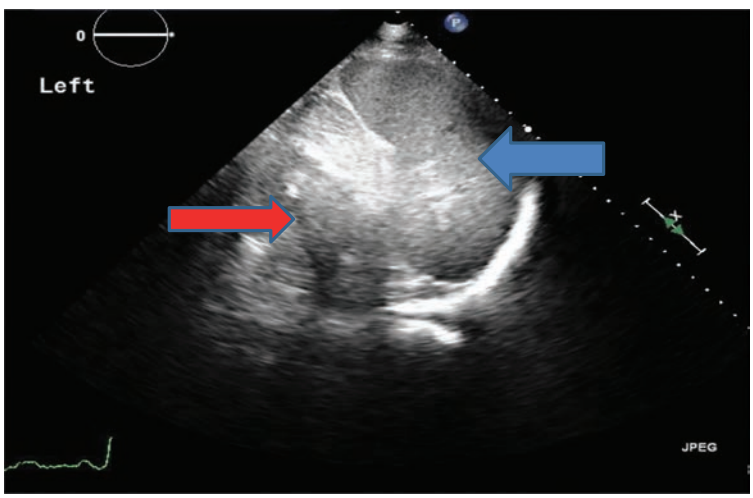


Figure 24.15b

24.16. B. Vegetations on the bioprosthetic.

There is a bioprosthetic tricuspid valve. There are numerous masses on the valve leaflets. Given his clinical picture he probably has recurrent endocarditis. The blue arrow in Figure 24.16b (RA: right atrium; RV: right ventricle) shows the sewing ring of the prosthetic valve. The red arrow points to the masses seen on the valve leaflets.

24.17. B. Myxoma.

Figure 24.17b (RA: right atrium; RV: right ventricle) shows a large mass in the left atrium (blue arrow), probably attached to the interatrial septum. This is the most common location for a myxoma. The patient had surgery and the mass was removed. On histology it was proven to be a myxoma.

24.18. C. Fibroma.

There is a large mass seen in the right ventricle (arrowed in Figure 24.18b). The mass is occupying most of the right ventricle, is discreet and single. It is seen to be extending from the right ventricular wall. Fibromas are known to cause arrhythmias especially ventricular arrhythmias. The arrow points to the fibroma.

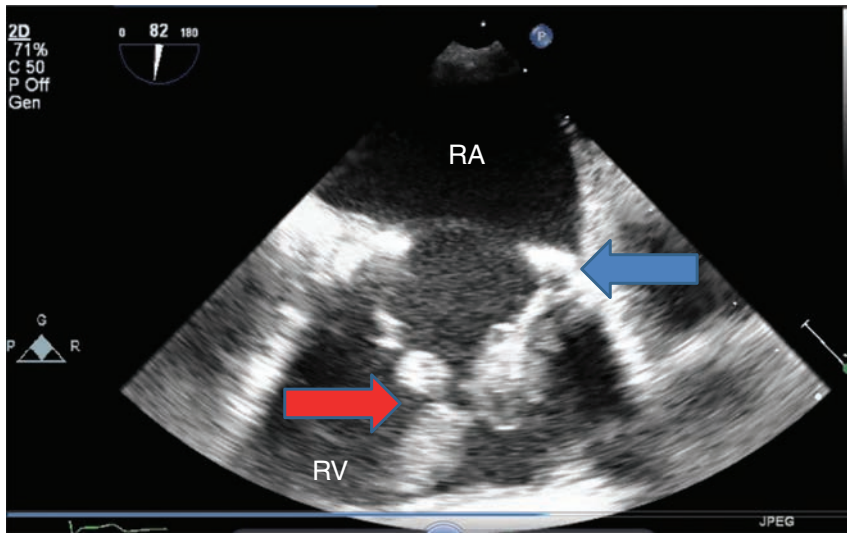


Figure 24.16b

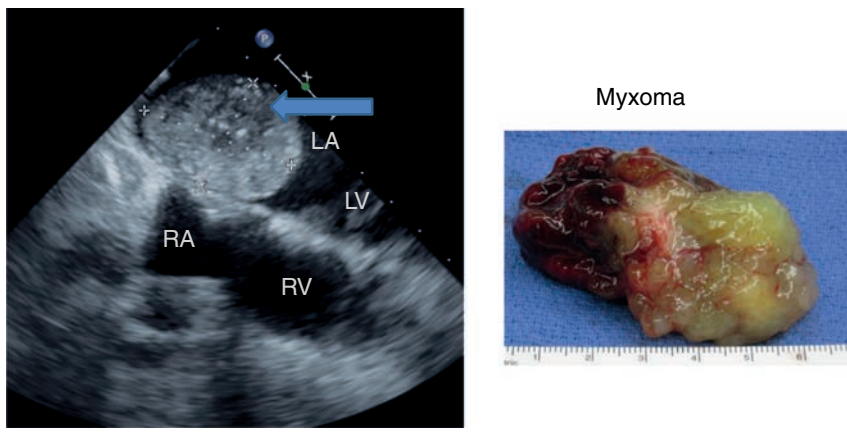


Figure 24.17b *Source:* reproduced with permission of Dr Natesa G. Pandian.

24.19. B. Papillary fibroelastoma of the aortic valve.

Figure 24.19b (LA: left atrium; LV: left ventricle) shows a small mass that appears like a frond arising from a thin stalk from the aortic valve (arrow). This is a characteristic appearance of a papillary fibroelastoma and has been shown to cause a stroke.

24.20. A. Vegetation on the catheter.

There is a mass attached to the end of the catheter in the SVC. The patient's presentation points to endocarditis. This mass most probably is a vegetation. The blue arrow in Figure 24.20b (LA: left atrium; RA: right atrium) points to the catheter and the red arrow shows the mass.

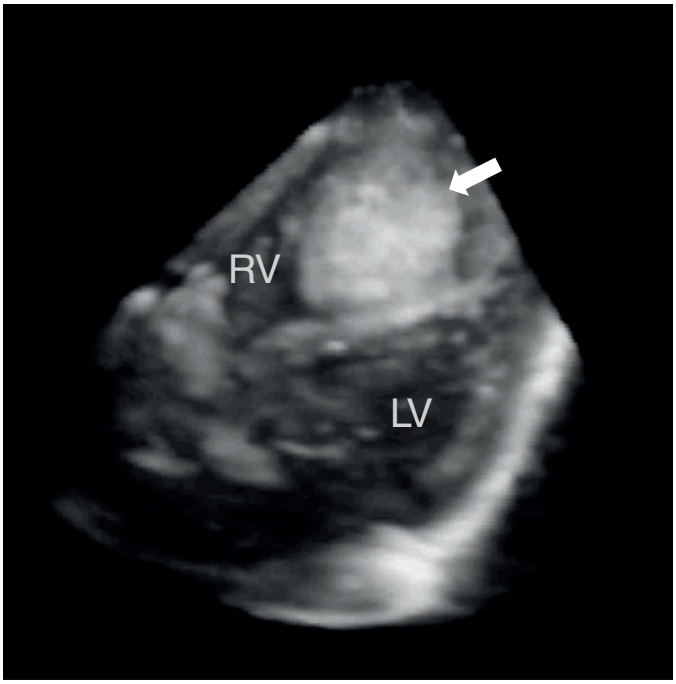


Figure 24.18b

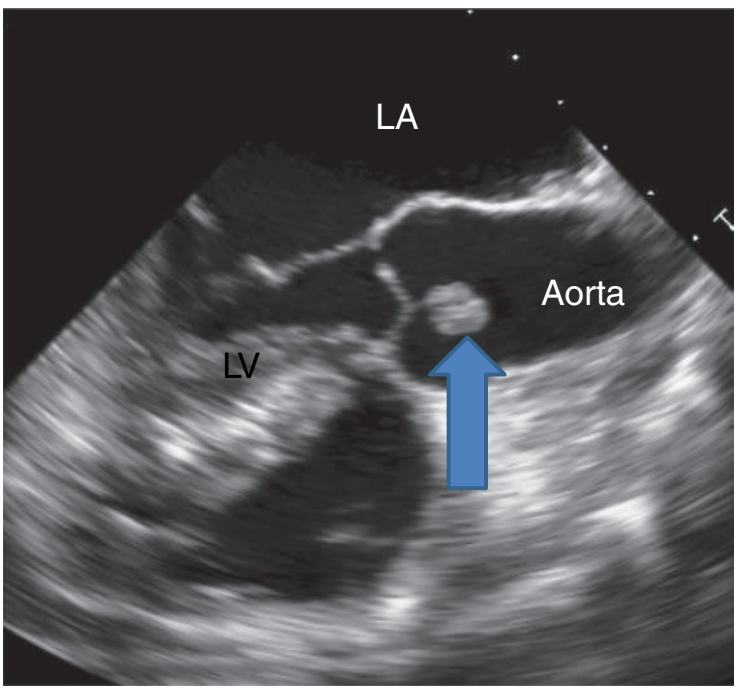


Figure 24.19b

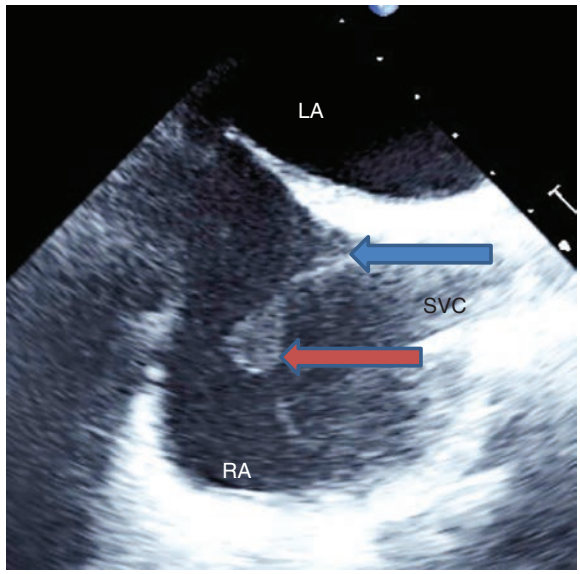


Figure 24.20b

24.21. B. Draw blood cultures, one from the periphery and one from the line, and then start antibiotics.

Since the mass is suspicious for a vegetation, blood cultures should be the initial step. It is recommended that peripheral cultures also be sent along with blood from the suspicious line. Antibiotics can then be initiated and narrowed depending on the organism. This patient probably has endocarditis due to Gram-positive bacteria. The line should then be removed and a new dialysis catheter should be inserted.

24.22. C. Blood cyst.

This small cystic appearing mass (arrow in Figure 24.22b – LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle) is a blood cyst attached to the mitral valve.

24.23. D. Lipomatous hypertrophy of the interatrial septum.

Figure 24.23b (LA: left atrium; RA: right atrium) shows the interatrial septum, which is like a dumbbell. There is a thin fossa ovalis with lipomatous hypertrophy of the interatrial septum on either side. This is a normal finding. When there is extreme lipomatous hypertrophy it can be mistaken for a tumor mass. The red arrow points to the thin fossa and the blue arrow shows the lipomatous hypertrophy of the septum.

24.24. B. Mass in the left atrial appendage which is likely a thrombus.

The patient probably has underlying atrial fibrillation which predisposed her to form a clot in the left atrial appendage. This potentially was the cause for her stroke. In Figure 24.24b (LA: left atrium; LV: left ventricle), the red arrow points to the left atrial appendage and the blue arrow shows the left atrial thrombus.

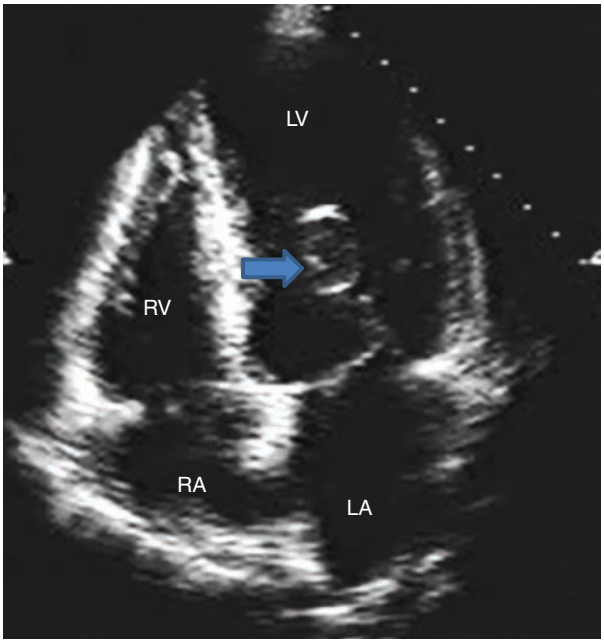


Figure 24.22b

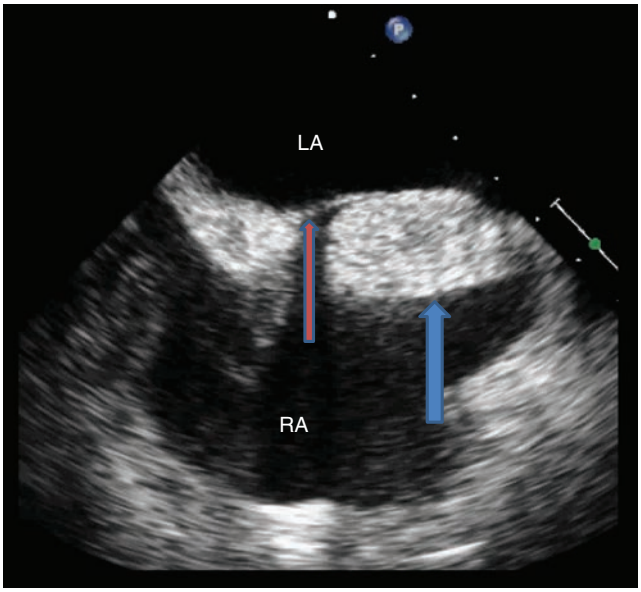


Figure 24.23b

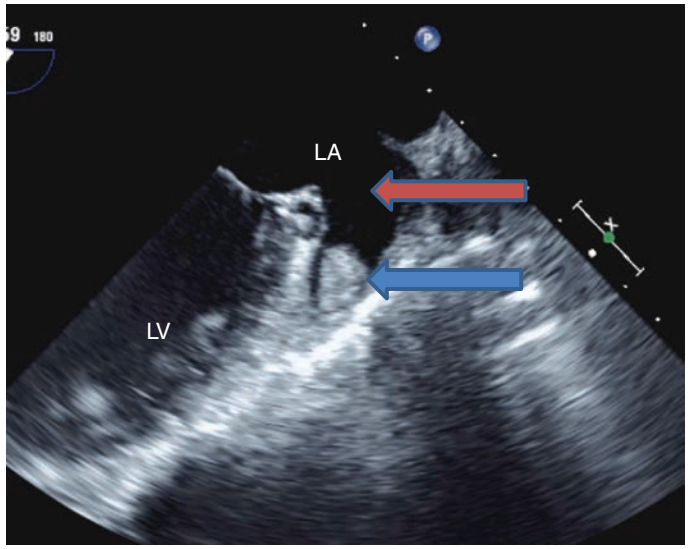


Figure 24.24b

24.25. C. Pericardial cyst.

Figure 24.25b (arrow, left image) shows a large cystic mass outside the right atrium (LA: left atrium; RA: right atrium). This probably represents a large pericardial cyst. The accompanying CT scan (Figure 24.25b, right) confirms the presence of the pericardial cyst.

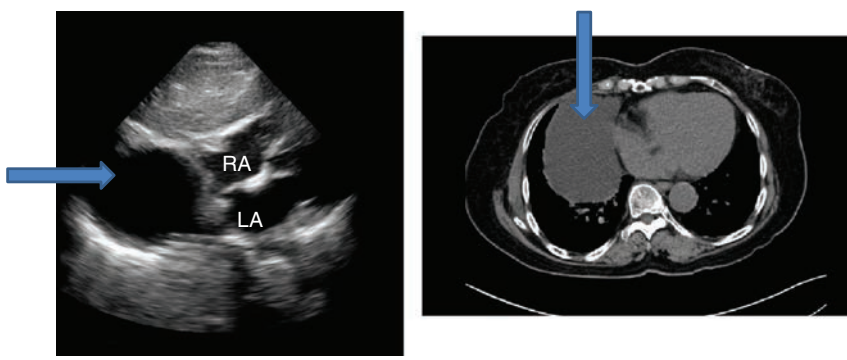


Figure 24.25b *Source:* reproduced with permission of Dr Natesa G. Pandian.

24.26. A. Multiple small tumors, likely rhabdomyoma.

Figure 24.26b is a representative four-chamber view (apex down) showing multiple masses (arrows) in the right ventricle, left ventricle, and right atrium. The patient carries a diagnosis of tuberous sclerosis. Rhabdomyoma, which occurs as multiple small tumors in the heart, is a common association with tuberous

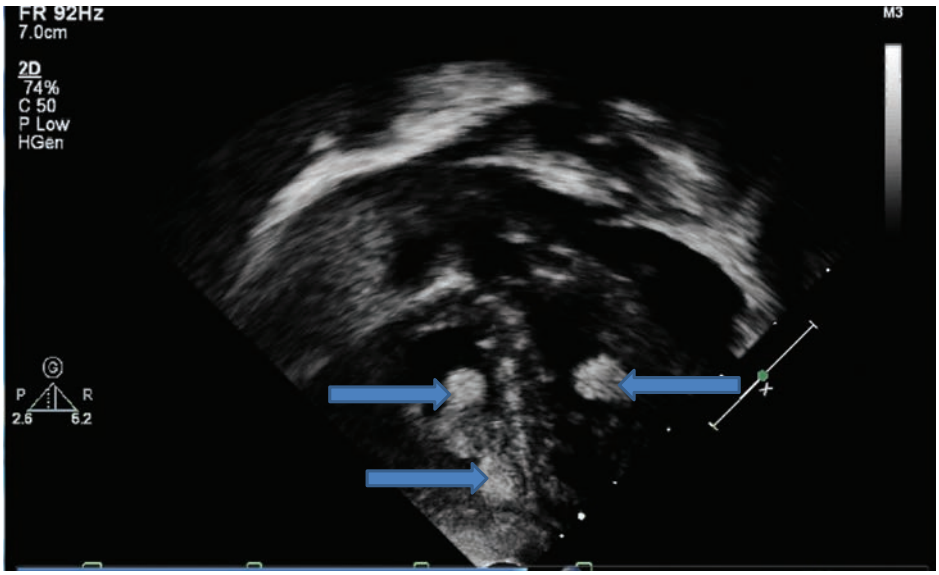


Figure 24.26b

sclerosis and most of them are diagnosed at an early age as they present with seizures.

24.27. C. Do nothing, manage seizures.

Rhabdomyomas present as multiple tumors in the heart. They are benign tumors and usually regress as the child grows. The most common strategy is to do nothing for the tumors. When contrast-enabled studies are undertaken, the tumors will not take up the contrast, suggestive of a lesser amount of vascularity, unlike malignant tumors.

24.28. B. A thrombus in the left ventricular apex.

This patient has presented with an acute ST elevation myocardial infarction involving the left anterior descending artery. The echocardiogram (Figure 24.28b – LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle) showed akinesis of the LV segments subtended by the left anterior descending artery, which then is a good set up for formation of a thrombus (arrow).

24.29. D. Lymphoma.

The echocardiogram shows masses in the right atrium (Figure 24.29, arrow). This patient has HIV infection. These patients are at risk of developing lymphoma. Biopsy from the tumor mass proved to be lymphoma of B cell origin.

24.30. B. A mass arising from the superior pole of the right kidney.

The subcostal view (Figure 24.30) was obtained from the right side of the abdomen. The liver appears to be normal. The kidney on the right is well visualized. There is a homogeneous mass (arrow) arising from the superior pole of the right kidney, probably from the adrenal gland.

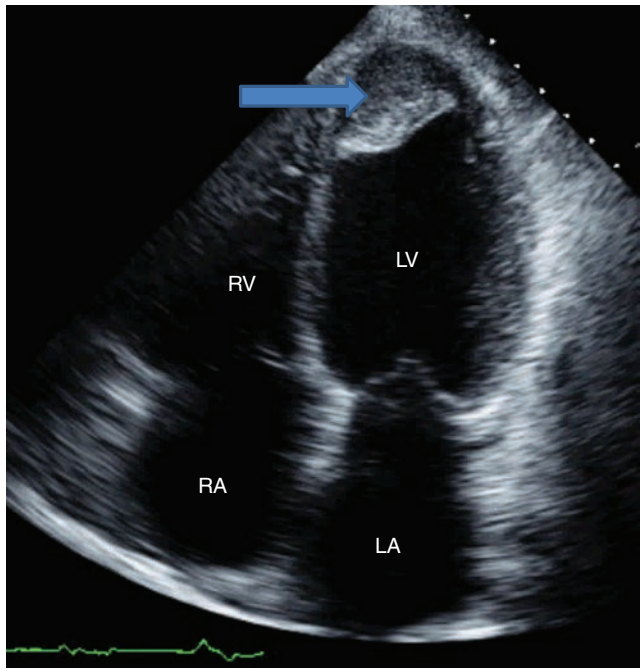


Figure 24.28b

24.31. B. Inflammatory changes of the mitral valve suggestive of Libman–Sacks endocarditis.

This patient with systemic lupus erythematosus is at risk for developing inflammation and development of nonbacterial endocarditis. The mitral leaflet tips are abnormal, probably a result of post-inflammatory changes. Figure 24.31b shows significant mitral regurgitation and moderate amount of mitral stenosis.

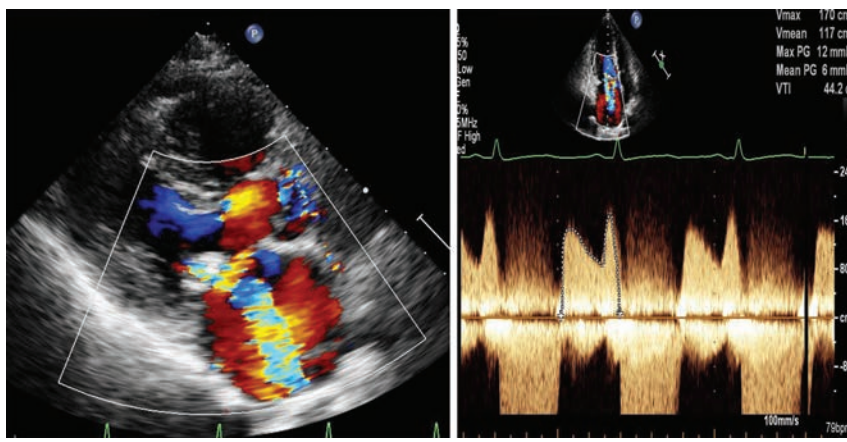


Figure 24.31b

24.32. B. Gall stones.

The subcostal view demonstrates a gall bladder with some gall stones (arrow in Figure 24.32b).

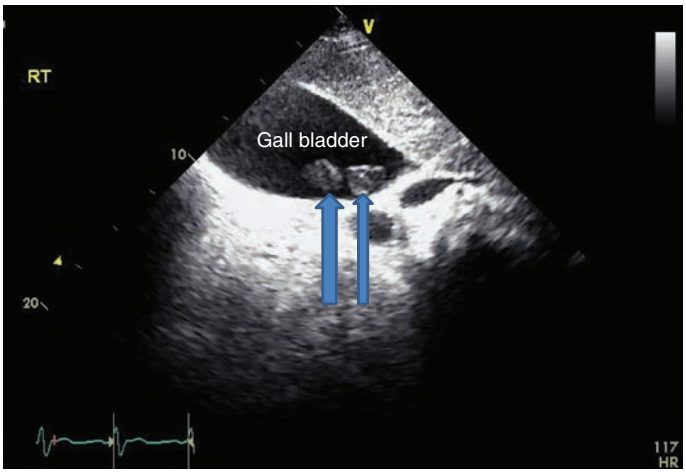


Figure 24.32b

24.33. B. Cystic lesions in the liver.

The cystic lesions in the liver are indicated by the arrow in Figure 24.33b. This patient has a presentation which is suggestive of lymphoma. The subcostal view shows the liver, most of which is replaced by numerous cystic lesions. The patient had a biopsy which proved to be B cell lymphoma.

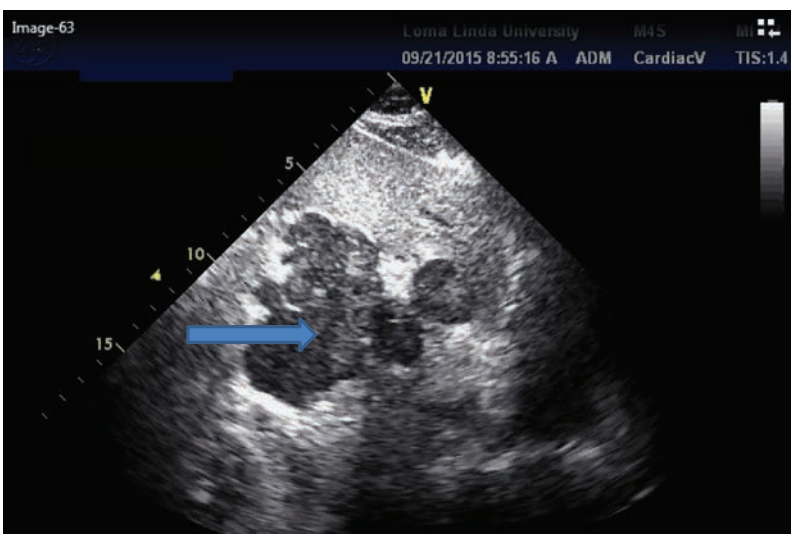


Figure 24.33b

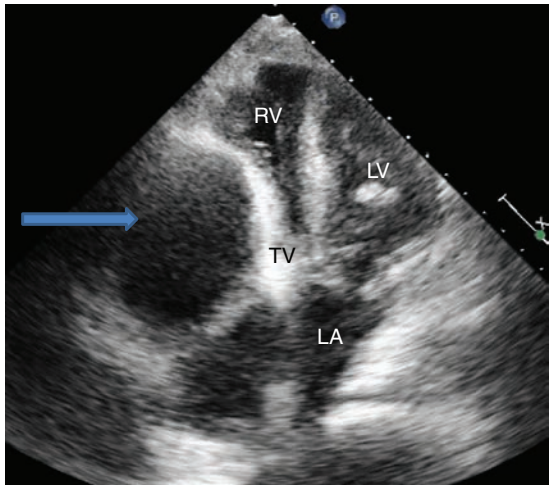


Figure 24.34c

24.34. B. Apical four-chamber view showing compression of the tricuspid valve.

The right side is seen to be compressed. The arrow in Figure 24.34c (LA: left atrium; LV: left ventricle; RV: right ventricle; TV: tricuspid valve) points to a large cystic structure (arrow) outside the right heart and is seen compressing the tricuspid valve. The mean gradient across the tricuspid valve is noted to be 5 mmHg at a heart rate of 85 bpm. This patient has polycystic kidney disease. The cyst is probably a manifestation of his polycystic kidney disease.

Systemic Disorders Affecting the Heart

25

25.1. Cardiovascular effects of acromegaly include which of the following?
- **A.** Left ventricular hypertrophy
- **B.** Hypertension
- **C.** Insulin resistance and diabetes mellitus
- **D.** All of the above

25.2. With which of the following is Cushing's syndrome not associated with?
- **A.** Hypertension
- **B.** Diabetes mellitus
- **C.** Atrial myxomas
- **D.** Mitral regurgitation

25.3. What is the triad of hyperpigmentation, low blood pressure, and hyperkalemia suggestive of?
- **A.** Addison's disease
- **B.** Conn's disease
- **C.** Hypopituitarism
- **D.** Cushing's syndrome

25.4. Cardiac effects of hyperthyroidism include which of the following?
- **A.** Atrial fibrillation
- **B.** High-output heart failure
- **C.** Higher blood volume
- **D.** All of the above

25.5. Which of the following could be cardiac effects of hypothyroidism?
- **A.** Pericardial effusion
- **B.** Cardiomyopathy
- **C.** Elevated serum cholesterol level
- **D.** Low cardiac output and elevated peripheral vascular resistance
- **E.** All of the above

25.6. Which of the following endocrine disorders may be associated with cardiomyopathy?
- **A.** Hyperthyroidism
- **B.** Hypothyroidism
- **C.** Pheochromocytoma
- **D.** All of the above

25.7. Which of the following statements about pheochromocytoma are accurate?
- **A.** About 75% are discovered at autopsy and are commonly missed antemortem
- **B.** Most are >1 cm in size and unilateral
- **C.** 10% could be familial and in such cases may be multicentric and extra-adrenal
- **D.** There is an association with neurofibromatosis
- **E.** All of the above

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25.8. Which of the following statements is not true regarding diagnosis of pheochromocytoma?

- **A.** Plasma catecholamines or 24-h urine metanephrines are good screening tests
- **B.** Clonidine suppression test is positive with pheochromocytoma with >50% suppression of serum norepinephrine
- **C.** Magnetic resonance imaging (MRI) is the more specific imaging modality compared with computed tomography scan
- **D.** Metaiodobenzylguanidine scan is helpful to show that the discovered mass is indeed producing hormones

25.9. Deficiency in the enzyme methionine synthase may result in severe hyperhomocysteinemia manifested by which of the following?

- **A.** Premature atherosclerosis
- **B.** Venous thrombosis
- **C.** Both A and B
- **D.** Neither A nor B

25.10. Which of the following is not a major Jones criterion for the diagnosis of rheumatic fever?

- **A.** Carditis
- **B.** Chorea
- **C.** Erythema nodosum
- **D.** Subcutaneous nodules

25.11. Which of the following is not an acceptable prophylactic antibiotic regimen for rheumatic fever?

- **A.** Benazathine penicillin 1.2 million units once a month
- **B.** Penicillin V 250 mg BID
- **C.** Sulfadiazine 1 g once a week
- **D.** Erythromycin 250 mg BID

25.12. Which of the following statements regarding duration of secondary prevention of rheumatic fever is true?

- **A.** For carditis with residual valvular disease, at least 10 years from last episode and till the age of 40 years
- **B.** For carditis with no residual valvular disease, at least 10 years from last episode and till the age of about 21 years
- **C.** For those with no carditis, at least 10 years from last episode and till the age of about 21 years
- **D.** All of the above

25.13. Patients with giant cell arteritis are more likely to have which of the following?

- **A.** Thoracic aortic aneurysm
- **B.** Abdominal aortic aneurysm
- **C.** Subclavian artery stenosis
- **D.** All of the above
- **E.** None of the above

25.14. Cardiac involvement in ankylosing spondylitis may include which of the following?

- **A.** Atrioventricular conduction blocks
- **B.** Aortitis and aortic root dilation
- **C.** Aortic leaflet nodules and aortic regurgitation
- **D.** All of the above

25.15. Which of the following options is not a cardiac manifestation of scleroderma?
- **A.** Pericarditis and effusion
- **B.** Pulmonary hypertension
- **C.** Patchy myocardial fibrosis and increased risk of sudden death
- **D.** Aortic valve fibrosis resulting in stenosis

25.16. Cardiovascular manifestations of sarcoid do not include which of the following?
- **A.** Complete heart block
- **B.** Myocardial scarring with increased risk of sudden death
- **C.** Cardiomyopathy
- **D.** Pulmonary hypertension
- **E.** Aortic regurgitation

25.17. Which of the following is not a cardiac manifestation of myotonia dystrophica?
- **A.** Conduction blocks such as atrioventricular block and right bundle branch block
- **B.** Myocardial fibrosis and fatty metaplasia
- **C.** Cardiomyopathy
- **D.** Mitral valve prolapse

25.18. Which of the following can occur with acute subarachnoid hemorrhage?
- **A.** Giant T wave inversion
- **B.** Takatsubo-like syndrome with cardiac dysfunction and troponin release
- **C.** Neurogenic pulmonary edema due to capillary leak syndrome
- **D.** QT prolongation and torsades
- **E.** All of the above

Answers

25.1. D. All of the above.

25.2. D. Mitral regurgitation.

This is not an association; the others are. Association with myxoma is called Carney complex. The myxoma generally occurs in the left atrium, but may be multicentric.

25.3. A. Addison's disease.

Hyperpigmentation is due to elevated adrenocorticotropic hormone level. Conn's disease is primary hyperaldosteronism and results in hypertension and hypokalemic alkalosis. Addison's syndrome can occur because of autoimmune disorder, tuberculosis, adrenal bleeding in sepsis, chronic suppressive doses of corticosteroids (prednisone >10 mg/day for >1 month), and so on. Diagnosis is made with the adrenocorticotropic hormone stimulation test.

25.4. D. All of the above.

They also have low peripheral vascular resistance. Increased cardiac output may also precipitate angina. Chronic elevation of heart rate can also result in a myopathic process leading to left ventricular systolic dysfunction.

25.5. E. All of the above.

25.6. D. All of the above.

25.7. E. All of the above.

In addition, they could be part of multiple endocrine neoplasia type 2 (with hyperparathyroidism and medullary carcinoma of thyroid) or multiple endocrine neoplasia type 2B (medullary thyroid cancer and mucosal neurofibromatosis of lips and tongue).

25.8. B. Clonidine suppression test is positive with pheochromocytoma with >50% suppression of serum norepinephrine.

This is not accurate. Norepinephrine suppression occurs in essential hypertension and not in pheochromocytoma. A computed tomography scan is more sensitive than MRI.

25.9. C. Both A and B.

25.10. C. Erythema nodosum.

This is not a major criterion, but erythema marginatum is. Polyarthritis is the other major criterion. Minor criteria include arthralgia, fever, elevated erythrocyte sedimentation rate or C-reactive protein. Two major or one major and two minor criteria make the diagnosis of rheumatic fever very likely.

25.11. C. Sulfadiazine 1 g once a week.

This- is not accurate. It has to be once a day.

25.12. D. All of the above.

25.13. D. All of the above.

25.14. D. All of the above.

25.15. D. Aortic valve fibrosis resulting in stenosis.

This is not accurate. There is no significantly increased risk of valvular abnormalities. Treatment of pericarditis with corticosteroids may increase the risk of scleroderma renal crisis.

25.16. E. Aortic regurgitation.

This is not accurate. All other statements are correct. It can also result in aortitis and systemic vasculitis with aneurysm formation. Cardiac involvement may occur in 30% of patients and is grossly underdiagnosed. Sudden death may be the first cardiac manifestation and cardiac MRI with delayed enhancement may help in screening for scar burden and assess the risk of sudden death.

25.17. D. Mitral valve prolapse.

This is not accurate. The other options are accurate.

25.18. E. All of the above.

Interdisciplinary Consultative Cardiology 26

26.1. Which is the most common cause of sudden death among young athletes?
- **A.** Hypertrophic cardiomyopathy
- **B.** Anomalous origin or coronary arteries
- **C.** Myocarditis
- **D.** Commotio cordis

26.2. A college basketball athlete is found to have anomalous origin of left coronary artery from right sinus of Valsalva with interarterial course on a computed tomography (CT) of the chest performed for an unrelated reason. He has no cardiac symptoms. What will you recommend?
- **A.** Continue with competitive sport as he has no symptoms
- **B.** Perform a stress test and if it is normal allow competitive athletic activity
- **C.** Advise against further competitive activity and refer for further evaluation and possible surgical reimplantation of left coronary artery
- **D.** None of the above

26.3. For a 72-year-old asymptomatic diabetic man scheduled for cataract surgery, which of the following preoperative tests are indicated?
- **A.** Resting electrocardiogram (ECG)
- **B.** Echocardiogram
- **C.** Stress ECG
- **D.** None of the above
- **E.** All of the above

26.4. For a patient with moderate asymptomatic aortic stenosis undergoing an elective high-risk surgery, which of the following statements are accurate?
- **A.** There is a higher risk of perioperative myocardial infarction
- **B.** There is a higher risk of 30-day cardiac event rate
- **C.** There is a higher 30-day mortality
- **D.** All of the above
- **E.** None of the above

26.5. An asymptomatic patient with severe aortic stenosis with normal left ventricular (LV) function and pulmonary artery (PA) pressure is scheduled for knee replacement. What would you recommend?
- **A.** Aortic balloon valvuloplasty before surgery
- **B.** Transcatheter aortic valve replacement before surgery
- **C.** Proceed with surgery with close hemodynamic monitoring
- **D.** Proceed with surgery with beta blockade

26.6. A 76-year-old man with severe symptomatic aortic stenosis is admitted with abdominal pain and diagnosed to have rupture of abdominal aortic aneurysm (AAA) deemed to be unsuitable for endovascular aneurysm repair. What is the right course of action?

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A. Proceed with AAA repair surgery
B. Perform aortic balloon valvotomy before surgery
C. Treat medically
D. None of the above

26.7. Routine use of beta blockers before surgery may result in higher risk of which of the following?
A. Hypotension
B. Stroke
C. Bradycardia
D. None of the above
E. All of the above

26.8. Which of the following statements are accurate regarding elective surgery after percutaneous coronary intervention?
A. Should be postponed >14 days if aspirin (ASA) needs to be stopped and balloon angioplasty was performed
B. Should be postponed >30 days if dual antiplatelet therapy needs to be stopped and bare-metal stent was implanted
C. Should be postponed >1 year if dual antiplatelet therapy needs to be stopped and drug-coated stent was implanted
D. None of the above
E. A, B, and C

26.9. Based on the 2014 American College of Cardiology/American Heart Association guidelines (Box 26.2), which of the following are class I indications for beta blockade perioperatively?
A. Those on chronic beta blockade
B. Those with moderate or high risk myocardial ischemia on preoperative stress testing
C. Those with three or more revised clinical risk index (RCRI) risk factors; for example, diabetes mellitus, heart failure, coronary artery disease (CAD), renal insufficiency, cerebrovascular accident
D. All of the above

26.10. Results of the POISE trial addressing perioperative beta blockade yielded which of the following results?
A. Use of beta blocker reduced risk of atrial fibrillation
B. Use of beta blocker reduced risk of myocardial ischemia
C. Beta blocker use resulted in higher risk of stroke and noncardiac death
D. All of the above

26.11. In a patient with stable CAD on ASA, beta blocker, and statin undergoing AAA surgery, which of the following would you recommend to reduce the risk of perioperative myocardial ischemia?
A. Continue beta blocker
B. Continue statin
C. Continue ASA if possible
D. Administer perioperative prophylactic intravenous nitroglycerine
E. All of the above
F. A, B, and C

26.12. Which of the following is the predominant cause of mortality in patients with end-stage renal disease (ESRD) on dialysis?
- **A.** Cardiac
- **B.** Hyperkalemia
- **C.** Stroke related to hypertension
- **D.** Progressive renal failure

26.13. How does CAD in ESRD differ from patients without ESRD?
- **A.** ESRD patients have more extensive CAD
- **B.** ESRD patients have medial calcification more than intimal calcification
- **C.** ESRD patients have more extensive coronary calcification
- **D.** All of the above
- **E.** None of the above

26.14. A 62-year-old ESRD patient with diabetes and hypertension is being evaluated for renal transplant. The resting ECG and LV wall motion on echo are normal. EF is 65%. He had a stress echocardiogram which was negative for ischemia at a heart rate of 136 bpm and 8.7 METs. On the insistence of the renal transplant committee, he had a coronary angiogram which showed a 70% mid left anterior descending (LAD) artery lesion. What has been shown to reduce the risk of perioperative cardiac events?
- **A.** LAD artery stent drug eluting stent
- **B.** Left internal mammary artery to LAD artery
- **C.** Perioperative beta blockade
- **D.** None of the above

26.15. A 48-year-old patient with ESRD on hemodialysis is seen because of dyspnea. His heart rate is 75 bpm, and blood pressure is 134/80 mmHg. He has no edema, has positive abdominojugular reflux, and no murmurs. Hemoglobin (Hb) is 12.2 g/dL. An echocardiogram shows mild LV hypertrophy, moderate left atrial enlargement, EF of 60% with normal wall motion and normal valves. The calculated PA systolic pressure is 50 mmHg, inferior vena cava is flat, mitral E/A velocity ratio is 1.5, and E/medial Em ratio is 22. Isovolumic relaxation time is 70 ms. What would you recommend?
- **A.** Reduce the dry weight by 4–5 lbs (1.8–2.3 kg) by dialysis
- **B.** Prescribe Coreg®
- **C.** Recommend pulmonary vasodilator
- **D.** Prescribe oral frusemide

26.16. Which medications are recommended for a 63-year-old nondiabetic patient with ESRD and normal blood pressure on hemodialysis?
- **A.** ASA
- **B.** Statin
- **C.** Beta blocker
- **D.** Angiotensin-converting-enzyme inhibitor

26.17. What echocardiographic findings may you encounter in a patient with end-stage liver disease?
- **A.** LA enlargement
- **B.** Hyperdynamic left ventricle with high cardiac output

C. Elevated pulmonary pressure
D. All of the above

26.18. A 46-year-old patient with hepatitis C cirrhosis is short of breath at rest and has an oxygen saturation of 85%. He has normal LV and valvular function and normal PA pressure. What is the most likely cause of dyspnea?
A. Emphysema due α-1-antitrypsin deficiency
B. Pulmonary arteriovenous fistulae
C. Patient foramen ovale
D. Diastolic heart failure

26.19. What is the best way to diagnose hepatopulmonary syndrome?
A. Saline contrast echocardiography
B. Pulmonary CT angiography
C. Contrast pulmonary angiography (invasive)
D. Magnetic resonance angiography

26.20. Which cardiac testing has been shown to improve liver transplant outcomes in end-stage liver disease patients?
A. Dobutamine echo
B. Nuclear stress test
C. Routine coronary angiography
D. None of the above

26.21. Which is not included in the risk calculation using RCRI?
A. Age
B. Creatinine >2 mg/dL
C. CAD
D. Type of surgery

26.22. What is an elevated risk according to RCRI?
A. RCRI ≥2
B. RCRI ≥3
C. RCRI ≥4
D. RCRI ≥5

26.23. A 43-year-old man with mechanical mitral valve on warfarin is admitted with melena and Hb of 10 g/dL. What will predict higher risk of rebleed on emergency upper gastrointestinal (GI) endoscopy?
A. Active bleeding
B. Large ulcer with visible vessel at the ulcer base
C. Adherent clot to ulcer base
D. All of the above
E. None of the above

26.24. What are the high-risk markers in upper GI bleed?
A. Heart rate >110 bpm
B. Systolic blood pressure <90 mmHg
C. Hb <10 g/dL
D. Active bleeding at upper GI endoscopy or rebleed
E. Comorbidities such as CAD and old age
F. All of the above

26.25. In the patient in Question 26.23, with a duodenal-ulcer-related GI bleed, what intervention is likely to shorten anticoagulant-free period?
A. Sclerosant injection to ulcer base
B. Stapling the bleeding site
C. Proton pump inhibitor
D. All of the above

26.26. What is the prevalence with regard to atrial fibrillation after cardiac surgery?

A. 10%
B. 20%
C. 30–50%
D. 80%

26.27. With regard to atrial fibrillation after cardiac surgery, which of the following drugs may not reduce its risk?

A. Beta blocker
B. Sotalol
C. Amiodarone
D. Digoxin

26.28. A 72-year-old man is admitted with a TIA and no signs of infarct in head CT. He is in atrial fibrillation and has normal LV function and no visible thrombi. What is a reasonable timing for starting anticoagulation?

A. 0–2 days
B. 1 week
C. 2 weeks
D. There is no need for anticoagulation

26.29. A 66-year-old woman is admitted with dense right hemiplegia and a large non-hemorrhagic infarct in the left hemisphere occupying 40% of middle cerebral artery area. The patient is in atrial fibrillation and a gated CT of the chest did not show any left atrial thrombus. When would you start therapeutic anticoagulation?

A. Immediately
B. After 1 week
C. After 2 weeks
D. Will not anticoagulate as there is no thrombus

26.30. At what level of doxorubicin therapy do cardiotoxic effects increase exponentially?

A. 300 mg/m^2
B. 450 mg/m^2
C. 600 mg/m^2
D. No threshold

26.31. What factors compound the toxic effects of doxorubicin on the heart?

A. Radiation to chest
B. CAD
C. Age >65 years
D. All of the above

26.32. In addition to Adriamycin®, which other cancer chemotherapeutic agents are potentially cardiotoxic?

A. Herceptin
B. Cyclophosphamide
C. Mitoxantrone
D. All of the above

26.33. Which of the following can 5-fluorouracil potentially cause?

A. Coronary vasospasm, especially in those with CAD
B. Myocarditis
C. Pericarditis
D. None of the above

26.34. Which anticancer drug is associated with arterial or venous thromboembolism?

A. Cisplatinum
B. Cyclophosphamide
C. Adriamycin
D. None of the above

26.35. Angiogenesis inhibitors (anti-vascular endothelial growth factor), cancer drugs angiogenesis inhibitors that target vascular endothelial growth factor with either

antibodies against vascular endothelial growth factor (bevacizumab) or small-molecule tyrosine kinase inhibitors (sunitinib, sorafenib), can produce which of the following side effects?

A. Cardiac dysfunction
B. Heart failure
C. Hypertension
D. All of the above

26.36. Following a hip fracture in the elderly, what is the general consensus regarding recommendation for timing of surgery?

A. Within 48 h
B. Within 4 days
C. Within a week
D. Within a month

Answers

26.1. A. Hypertrophic cardiomyopathy.

This accounts for about 26%. Commotio cordis (ventricular fibrillation with blunt trauma to chest) accounts for about 20%, coronary anomalies about 14%, and myocarditis about 5%. These are the leading causes.

26.2. C. Advise against further competitive activity and refer for further evaluation and possible surgical reimplantation of left coronary artery.

The risk of sudden death is substantial, accounting for 1/7–1/10 deaths in competitive athletes. However, it is not known what percentage of patients with this coronary anomaly will have sudden death as such data are not available. Lots of patients may be asymptomatic, detected incidentally; henc, the denominator is not known.

26.3. D. None of the above.

No further testing is indicated before a low-risk surgery in an asymptomatic patient.

26.4. D. All of the above.

Though the risk has diminished substantially in recent years with better anesthetic techniques and monitoring, still the risk is about twice as high as those without aortic stenosis.

26.5. C. Proceed with surgery with close hemodynamic monitoring.

This is a class IIa indication in those with severe asymptomatic valve lesions. Options A and B are inappropriate in asymptomatic patients.

26.6. A. Proceed with AAA repair surgery.

Proceed with AAA repair surgery with close hemodynamic monitoring in view of need for emergency surgery. Balloon valvotomy would have been appropriate in less urgent situations.

26.7. E. All of the above.

26.8. E. A, B, and C.

See Box 26.1.

26.9. A. Those on chronic beta blockade.
See Fleischer *et al.* (2014). Options B and C are class IIb indications.

26.10. D. All of the above.

26.11. F. A, B, and C.
Option D is a class III indication in a stable patient. It does not reduce the risk of perioperative ischemia.

26.12. A. Cardiac.
Cardiovascular disease is the leading cause of mortality in patients with ESRD. These patients have aggressive forms of CAD, hypertensive heart disease, and heart failure (mostly with preserved ejection fraction (EF)).

26.13. D. All of the above.

26.14. D. None of the above.
This patient has no inducible ischemia at good workload and hence there is no data that any of the options listed would improve the outcome. ASA, statin, and angiotensin-converting-enzyme inhibitor are likely to be beneficial in view of CAD and diabetes.

26.15. A. Reduce the dry weight by 4–5 lbs (1.8–2.3 kg) by dialysis.
The elevated E/Em ratio indicates elevated left atrial (LA) pressure and this is likely responsible for his pulmonary hypertension. It is not uncommon to have normal right atrial pressure despite high LA pressure in these patients. Pulmonary vasodilator is inappropriate for this patient.

26.16. A. ASA.
According to guidelines. Statins have not been shown to improve outcomes in the absence of diabetes or CAD and are not recommended unless low-density lipoprotein >190 mg/dL.

26.17. D. All of the above.
Elevated pulmonary pressure is called portopulmonary syndrome and it is theorized that it may be due to some factors reaching the lungs from the gut bypassing the liver. This is due to increased pulmonary vascular resistance, and treatment with pulmonary vasodilators is indicated. This corrects after liver transplant.

26.18. B. Pulmonary arteriovenous fistulae.
This is called hepatopulmonary syndrome and can result in profound hypoxemia depending upon degree of transpulmonary, right-to-left, shunting. Diastolic heart failure is ruled out by normal PA pressure.

26.19. A. Saline contrast echocardiography.
Saline contrast echocardiography by late appearance of bubbles on the left side (after four beats) and without Valsalva maneuver. The shunt can be qualitatively graded depending upon degree of left-sided opacification. This gets better after liver transplant.

26.20. D. None of the above.
Despite lack of data, it has been a practice to aggressively screen for CAD in these patients in most of the transplant centers, perhaps because of two reasons: high-risk surgery and the fact that a precious donor organ is used.

26.21. A. Age.

Options B, C, and D (if surgery is intra-abdominal, or intrathoracic, or suprainguinal vascular) earn a point each. Other three predictors are heart failure, cerebral vascular accident or transient ischemic attack (TIA), and diabetes mellitus. There are six possible points. These are validated for prediction of perioperative major cardiac adverse events.

26.22. A. RCRI ≥2.

RCRI of 0 or 1 is considered low risk.

26.23. D. All of the above.

Upper GI endoscopy is very helpful to address risk of rebleed, for definitive therapy of bleeding source, and deciding on timing of continuation of anticoagulant therapy.

26.24. F. All of the above.

26.25. D. All of the above.

26.26. C. 30–50%.

26.27. D. Digoxin.

26.28. A. 0–2 days.

As there is no sign of cerebral infarct, it is safe to start anticoagulation right away because of low risk of hemorrhagic transformation. TIA is a risk factor for recurrent stroke in a patient with atrial fibrillation and the patient should be anticoagulated as soon as possible if there is no risk.

26.29. C. After 2 weeks.

The unwritten rule is to anticoagulate in 0–3 days if there is small infarct, in 1 week if medium-sized infarct, and in 2 weeks if large infarct unless need for anticoagulation is urgent. CT is good at ruling out LA thrombus, similar to transesophageal echocardiography, and there is no urgency to anticoagulate. If the infarct is >1/3 of middle cerebral artery area, the risk of hemorrhagic transformation with anticoagulation is high. However, if a thrombus is present with embolic potential, earlier anticoagulation would be indicated. Immediate anticoagulation may be indicated in mechanical valves irrespective of cerebral infarct size for fear of valve thrombosis as well as recurrent embolization despite the risk of hemorrhagic transformation of the infarct. This is a judgement call and there are no guidelines.

26.30. A. 300 mg/m^2.

26.31. D. All of the above.

In addition, very young age and administration of other cardiotoxic agents are risk factors as well.

26.32. D. All of the above.

Cyclophosphamide in large intravenous doses can cause myocardial hemorrhage. Mitoxantrone is an anthracycline.

26.33. A. Coronary vasospasm, especially in those with CAD.

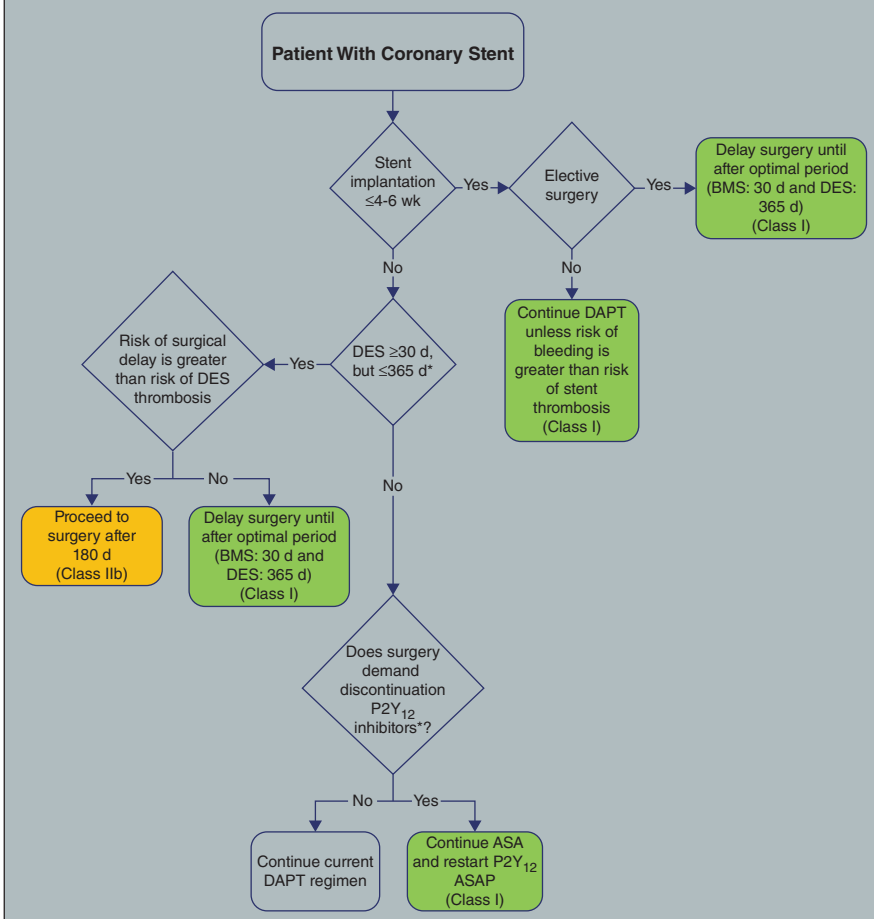
26.34. A. Cisplatinum.

26.35. D. All of the above.

26.36. A. Within 48 h.

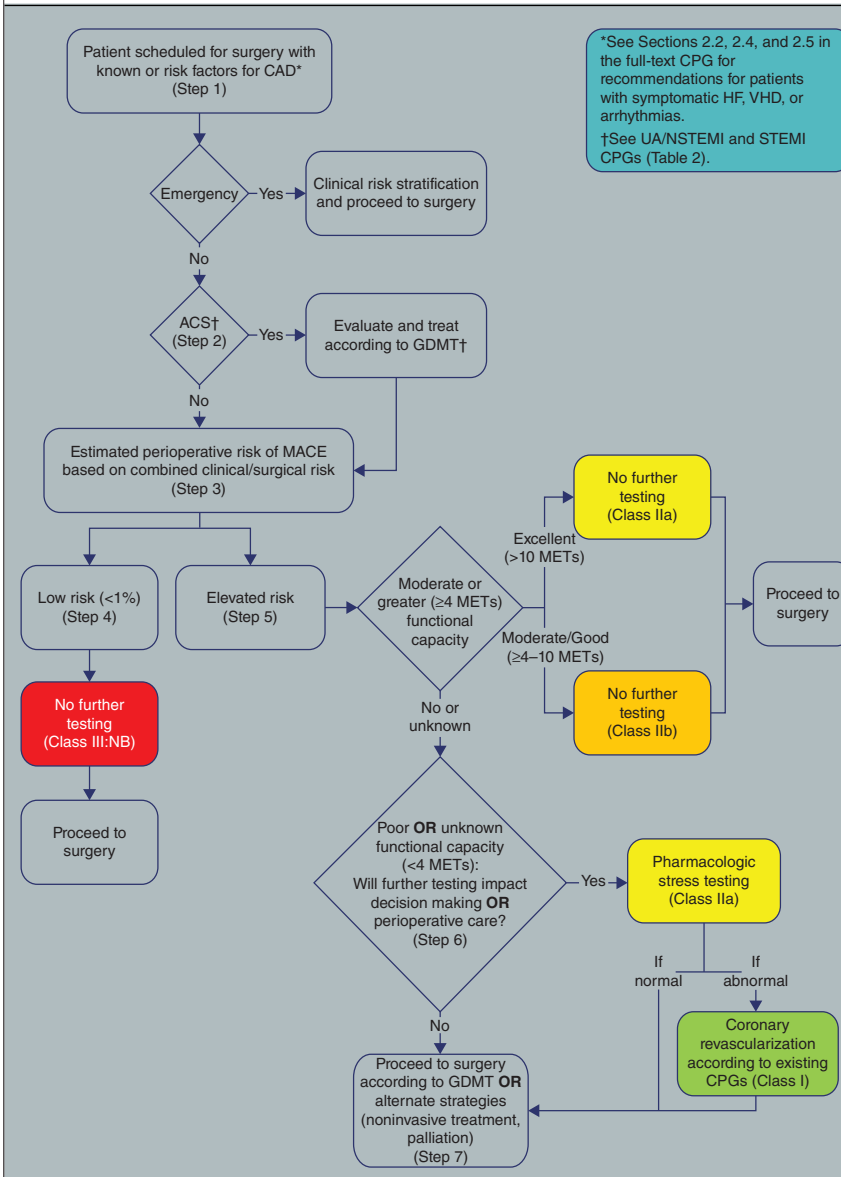
This is important in terms of presurgical cardiac optimization. The data are only observations supporting this; there are no randomized trials. The stated benefits of early surgery include reduced length of stay and cost, reduction of pressure sores, reduction in morbidity (venous thromboembolism, urinary tract infection, atelectasis) and mortality, and improved functional status. But the observation studies are conflicting as well.

Box 26.1 Management of Coronary Stents as per 2014 ACC/AHA Guidelines



Source: Fleischer *et al.* (2014).

Box 26.2 Preoperative Testing Guidelines from 2014 ACC/AHA Guidelines



Source: Fleischer *et al.* (2014).

Reference

Fleischer, L.A., Fleischmann, K.E., Auerbach, A.D., *et al.* (2014) 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Journal of the American College Cardiology*, **64**(22): e77–e137. doi:10.1016/j.jacc.2014.07.944.

Heart Disease and Pregnancy

27

27.1. A 25-year-old female is being seen for genetic counseling. She has a significant family history of Marfan syndrome, with her mother and sister having lens dislocation and aortic aneurysm with dissection. She is asymptomatic, and her aortic root measures 45 mm. She wants to go ahead with pregnancy. What do you recommend?

A. Start a beta blocker before pregnancy
B. Start angiotensin-converting-enzyme inhibitor before pregnancy
C. Avoid pregnancy
D. Start angiotensin-receptor blocker before pregnancy

27.2. A 36-year-old African American female is referred to you. She complains of progressive dyspnea. She denies any prior cardiovascular history. She is 38 weeks pregnant and is her first pregnancy. On examination, she is tachycardiac, blood pressure (BP) is 110/70 mmHg, jugular venous pressure (JVP) is elevated up to her angle of the mandible, apical impulse is diffuse, she has S3 and S4 gallops, 2/6 apical systolic murmur, and crackles up to middle of the back. Electrocardiogram (ECG) confirms sinus tachycardia. Echocardiogram reveals global left ventricular (LV) hypokinesis and an ejection fraction (EF) of 20%. What is the most likely diagnosis?

A. Viral myocarditis
B. Coronary artery disease
C. Peripartum cardiomyopathy
D. Dissection of the coronary artery

27.3. You start the patient in Question 27.2 on diuretics and beta blockers. She complains of persistent shortness of breath. What is your next recommendation?

A. Intra-aortic balloon pump
B. Lisinopril
C. Bromocriptine
D. Ventricular assist device

27.4. The patient in Question 27.2 has a successful vaginal delivery. She is now maintained on anti-failure therapy, which includes a diuretic and beta blocker. Her LV function by echocardiogram is now 40%, which has improved from 20%. She evinces interest in a second pregnancy. What do you recommend?

A. To go ahead with pregnancy
B. Recommend reassessing LV function in 6 months and if normal, then proceed
C. Counsel against pregnancy
D. Recommend addition of angiotensin-receptor blocker and then proceed with pregnancy

27.5. A 30-year-old female, now 34 weeks pregnant, presents to the hospital with acute onset of severe squeezing chest pressure associated with nausea and diaphoresis. She has a prior history of hypertension and is on medications. She used to smoke

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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up until her pregnancy. In the emergency room her heart rate is 76 bpm, BP is 160/80 mmHg, and examination is otherwise unremarkable. Her ECG reveals anterior ST elevation. What do you recommend?

A. Medical management with heparin, aspirin, nitrates, and beta blocker
B. Immediate coronary angiogram with possible intervention
C. Thrombolytic therapy
D. Colchicine and indomethacin

27.6. A 29-year-old Hispanic female is referred to you for complaints of dyspnea. She is 33 weeks pregnant and has recently moved from India. She reports a history of murmur from her childhood. On examination her heart rate is 110 bpm, BP is 120/80 mmHg, JVP is 14 cmH_2O, S1 is increased, S2 is normal with an opening snap, 2/6 diastolic murmur heard along with a holosystolic murmur at the apex. You initiate diuretic therapy. Echocardiogram reveals mitral stenosis with a mean gradient of 17 mmHg. What would your next step would?

A. Beta blocker therapy
B. Amiodarone
C. Synchronized cardioversion
D. Percutaneous mitral balloon valvotomy

27.7. A 26-year-old G2P2 presents to the hospital with complaints of severe substernal chest pressure. She had a normal vaginal delivery 15 days ago. She describes her chest pressure as severe pressure-like, in the central chest, radiating to her jaw, started when she was vacuuming her house. She denies any prior medical history. An ECG performed in the emergency room shows 3 mm ST elevations in V1–V6 with ST depression in leads II, III and aVF. Chest X-ray is unremarkable. What is the most likely diagnosis?

A. Acute pulmonary embolus
B. Coronary artery disease with plaque rupture
C. Spontaneous coronary dissection
D. Acute pericarditis
E. Aortic dissection

27.8. A 27-year-old female is referred to you. She gives a history of murmur from her childhood and is diagnosed with severe aortic stenosis due to a bicuspid aortic valve. She is recommended to undergo aortic valve replacement. She is nulliparous and is planning to have children in the next 1–2 years. What is the best option for her regarding her aortic valve replacement?

A. If she chooses a mechanical valve and is established on daily warfarin of 2.5 mg and achieves a target international normalized ratio of 2–3, then continuation of warfarin until 36th week of pregnancy would be an acceptable option
B. If she gets a bioprosthetic valve, there is about 50% chance of valve degeneration at 10 years
C. Ross procedure could be an option
D. If she proceeds with mechanical prosthesis and chooses to go on low molecular weight heparin during pregnancy, then the low molecular weight he doses should be adjusted based on anti-Xa levels
E. All are true

27.9. What is the condition that is associated with the highest maternal mortality with pregnancy?

A. Marfan syndrome with aortic root measurement of 4.5 cm
B. Family history of cardiomyopathy
C. Severe mitral regurgitation
D. Ventricular septal defect (VSD) with a right-to-left shunt

27.10. A 24-year-old female is referred to you for a murmur. She is pregnant, 10 weeks, and asymptomatic at present. She has no prior cardiac events. She has no cardiac risk factors. On examination, heart rate is 76 bpm, BP 110/70 mmHg, and JVP is normal. Apical impulse is undisplaced, normal S1 and S2, and apical S3 present. There is a 3/6 mid peaking ejection systolic murmur with a click and a grade 1 diastolic murmur at the left sternal border. What is the likely cause of her murmur?

A. Mitral stenosis and mitral regurgitation
B. Pulmonic stenosis
C. Bicuspid aortic valve stenosis and regurgitation
D. Patent ductus arteriosus

27.11. A 32-year-old woman, 10 weeks pregnant, was referred for evaluation of murmur. On examination she had a 5/6 holosystolic murmur at the third left intercostal space with normal S2. No HF. An echocardiogram showed a 4 mm sized perimembranous VSD with normal LV size and PA pressure. What would you recommend?

A. Termination of pregnancy
B. Reassure and follow up
C. Perform cardiac during second trimester for shunt ratio
D. Refer for percutaneous closure

27.12. A 24-year-old primigravida is 14 weeks pregnant and has been having repeated episodes of syncope on minimal exertion. An echocardiogram confirms valvular pulmonary stenosis with a peak gradient of 90 mmHg and a mean gradient of 60 mmHg with moderately hypokinetic right ventricle. What will you do?

A. Recommend termination of pregnancy
B. Recommend balloon valvotomy of the pulmonary valve
C. Surgical replacement of pulmonary valve
D. Treat with pulmonary vasodilators

27.13. A 24-year-old woman who had a heart transplant 5 years earlier is pregnant. What facts would you convey her?

A. Probability of live birth is about 70%
B. There is a higher risk of hypertension, eclampsia, and premature birth
C. Cardiac rejection is rare
D. All of the above

27.14. Cardiac surgery during pregnancy is associated with about what fetal loss?

A. 5%
B. 30%
C. 70%
D. 100%

27.15. Which of the following disorders are associated with the highest risk with pregnancy?

A. Primary pulmonary hypertension with a PA systolic pressure of 110 mmHg
B. Surgically corrected tetralogy of Fallot
C. Severe pulmonary stenosis
D. Large atrial septal defect with a shunt ratio of 3 : 1 and PA systolic pressure of 50 mmHg

Answers

27.1. C. Avoid pregnancy.

She has a significant family history of Marfan syndrome with dissection. She also has significant aortic root dilatation, which puts her at increased risk for rupture. During preconceptual counseling, if aorta is >45 mm then pregnancy should be discouraged. If aorta is <40 mm, pregnancy might be reasonable if low risk. For aortic sizes between 40 and 45 mm, individualized recommendation should be given.

27.2. C. Peripartum cardiomyopathy.

Diagnosis of heart failure due to LV systolic dysfunction that occurs in the last trimester to 6 months postpartum. It is usually a diagnosis of exclusion. The incidence varies. In the USA the incidence is 1 in 3200 deliveries, in South Africa it is 1 in 1000, and in Haiti occurrence is 1 in 300. Frequency is increased with advanced maternal age, multiparity, multifetal pregnancy, African American women, and risk factors such as diabetes mellitus, smoking, and hypertension (Elkayam, 2011).

27.3. C. Bromocriptine.

One of the pathophysiologies of peripartum cardiomyopathy includes defective antioxidant defense mechanism, wherein levels of cathepsin D and prolactin and angiostatic 16 kDa prolactin levels are increased with increasing oxidative stress. This leads to inhibition of endothelial cell proliferation, migration, increases apoptosis, disrupts capillaries, and causes cardiomyocyte dysfunction. In studies on mice, bromocriptine prevented the onset of peripartum cardiomyopathy (Sliwa *et al.*, 2010a,b).

27.4. C. Counsel against pregnancy.

Pregnancy is not recommended when LVEF is <25% at initial presentation or there is persistent decrease in LVEF (Elkayam *et al.*, 2001).

27.5. B. Immediate coronary angiogram and intervention.

Incidence of myocardial infarction is about 1 in 35 700 deliveries. Usually occurs in older females (>35 years), multiparous females, white or African American women, with associated risk factors of hypertension, diabetes mellitus, and smoking (Ladner *et al.*, 2005).

27.6. A. Beta blocker therapy.

The best recommendation is initiation of beta blocker therapy as she is tachycardiac and mitral mean gradient is dependent on the heart rate. Controlling heart rate will reduce the mitral diastolic gradient.

27.7. C. Spontaneous coronary dissection.

Presentation with chest pressure and ST elevations in the anterior leads points to pathology in the left anterior descending artery. Acute aortic dissection usually

results in the dissection flap extending into the right coronary artery. This patient has spontaneous dissection of her left anterior descending artery.

27.8. E. All are true.

A young woman needing valve surgery such as this patient is usually recommended a bioprosthetic valve, but with the understanding that valve degeneration can occur rapidly and the bioprosthesis may need replacement in 10 years. In the case of a mechanical valve, continuing warfarin is the best strategy to prevent valve thrombosis, which is preferred by the European Society of Cardiology guidelines. Warfarin can cause embryopathy in the first trimester, but that risk is minimized if the daily dose of warfarin is <5 mg. Alternatively, if low molecular weight heparin is chosen, it should be adjusted to achieve an anti-Xa level of 1–1.2 U/mL. This is the option chosen by the American College of Chest Physicians. It has been noted that a small minority of patients with mechanical prosthesis on low molecular weight heparin have suffered valve thrombosis despite therapeutic anti-Xa levels. Ross procedure can also be an option in this patient.

27.9. D. Ventricular septal defect (VSD)with a right-to-left shunt.

In this situation there is evidence of Eisenmenger syndrome with a right-to-left shunt. This portends a 30–50% maternal mortality rate and pregnancy is absolutely contraindicated. Uncorrected regurgitant valve lesions are usually well tolerated during pregnancy. Family history of cardiomyopathy is not a contraindication for pregnancy. In Marfan syndrome, an aortic root that exceeds 4.5 cm is associated with a maternal mortality rate of 10%. If diagnosed during pregnancy, therapy with beta blocker should be initiated, serial echocardiograms should be performed, and cesarean section should be performed.

27.10. C. Bicuspid aortic valve stenosis and regurgitation.

27.11. B. Reassure and follow up.

This is small defect and there is neither significant volume overload (normal LV size) nor pulmonary hypertension. This would be well tolerated during pregnancy. There is no indication for VSD closure, and also perimembranous VSDs are not suitable for percutaneous closure (only muscular VSDs).

27.12. B. Recommend balloon valvotomy of the pulmonary valve.

This lesion is very amenable to balloon valvotomy and this should result in good pregnancy outcome.

27.13. D. All of the above.

27.14. B. 30%.

27.15. A. Primary pulmonary hypertension with a PA systolic pressure of 110 mmHg.

Eisenmenger's complex is also associated with one of the highest risks.

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Racial and Gender Disparities

28

28.1. Which of the following statements regarding blacks is not true compared with whites?

- **A.** Age-adjusted cardiovascular death rate is higher in blacks
- **B.** Risk of stroke in blacks is twice as high
- **C.** Blacks are less likely to receive guideline-recommended therapies in heart failure
- **D.** Blacks have a lower risk of left ventricular (LV) hypertrophy

28.2. Which of the following statements are accurate?

- **A.** Black adults are far more likely than white adults to be admitted to the hospital for angina and congestive heart failure
- **B.** Blacks are more likely to be admitted to emergency rooms
- **C.** Blacks are less likely to be insured and get regular medical care
- **D.** All of the above

28.3. Which of the following statements are correct?

- **A.** American Indians die from heart disease much earlier than expected
- **B.** Alaska Natives die from heart disease much later than expected
- **C.** American Indians/Alaska Natives die from heart disease much earlier than expected
- **D.** None of the above

28.4. Which is the leading cause of death in US women?

- **A.** Cancer
- **B.** Heart disease
- **C.** Accidents
- **D.** Alzheimer's disease

28.5. Which of the following statements are correct?

- **A.** Among Hispanic women, heart disease and cancer cause roughly the same number of deaths each year
- **B.** For American Indian or Alaska Native and Asian or Pacific Islander women, heart disease is second only to cancer
- **C.** Two-thirds of women who die suddenly of coronary heart disease have no previous symptoms
- **D.** All of the above

28.6. Which ethnic groups have the highest risk of coronary artery disease (CAD)?

- **A.** White Americans
- **B.** Black Americans
- **C.** Japanese Americans
- **D.** People from South Asian origin

28.7. Among the Japanese, the risk of CAD has been the highest in which of the following groups?

- **A.** Japanese in Japan
- **B.** Japanese settled in Hawaii

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C. Japanese settled in continental USA
D. Risk is similar

28.8. Compared with men, what are women more likely to describe the ischemic chest pain as?
A. Sharp or burning
B. In neck or jaw
C. In abdomen or back
D. All of the above

28.9. Who have the highest prevalence of diabetes mellitus?
A. Native Americans
B. White Americans
C. Black Americans
D. Hispanics

28.10. Regarding patients undergoing cardiac surgery in the USA (STS database), which of the following statements is not accurate regarding blacks compared with whites?
A. Have higher prevalence of hypertension and diabetes
B. Have higher prevalence of preoperative dialysis
C. Have lower preoperative adverse features, such as LV dysfunction, recent myocardial infarction, and 3 or ≥4 mitral regurgitations
D. Have higher adjusted operative mortality and morbidity

28.11. Spontaneous coronary artery dissection (SCAD) is most commonly seen in which of the following groups?
A. Young women
B. Young men
C. Elderly women
D. Elderly men

28.12. In a woman with SCAD, all of the following are recommended except which option?
A. Screen other vascular beds, such as femoral, radial, carotid, and intracranial arteries
B. Avoid pregnancy, as it may precipitate recurrent SCAD; avoid oral contraceptives
C. May use aspirin
D. Use high-dose statin

28.13. A 43-year-old overweight woman is being evaluated for exertional central chest pain. She has no other cardiac risk factors. Her echocardiogram was normal. She walked 7 METs during a stress test, experienced the same chest pain associated with 1.5 mm flat ST segment depression in V3 to V6 lasting 3 min into recovery. What would you recommend?
A. Exercise stress nuclear test
B. Coronary angiogram and, if normal, ergonovine challenge
C. Coronary angiography and, if normal, test for coronary flow reserve
D. Stress cardiac magnetic resonance imaging with rest and stress first-pass perfusion

28.14. Microvascular angina in women may be associated with which of the following?
A. Abnormal stress myocardial perfusion
B. Abnormal stress myocardial energy production demonstrated by ^{31}P myocardial spectroscopy
C. Higher risk of cardiac events and emergency room admission
D. All of the above

Answers

28.1. D. Blacks have a lower risk of (LV) hypertrophy.
This statement is wrong; all others are accurate as per American Heart Association statistics.

28.2. D. All of the above.
According to American Heart Association data.

28.3. C. American Indians/Alaska Natives die from heart disease much earlier than expected.
Some 36% of both these populations are under 65 compared with only 17% for the US population overall.

28.4. B. Heart disease.
In both black and white women.

28.5. D. All of the above.

28.6. D. People from South Asian origin.
That is, people from the Indian subcontinent. The risk is about four times white Americans. They also tend to have premature CAD, diffuse disease, central obesity despite lower body mass index, metabolic syndrome, and diabetes mellitus.

28.7. C. Japanese settled in continental USA.

28.8. D. All of the above.

28.9. A. Native Americans.

28.10. C. Have lower preoperative adverse features, such as LV dysfunction, recent myocardial infarction, and 3 or ≥4 mitral regurgitations.
This is wrong. The preoperative adverse features are higher among blacks. The other statements are correct.

28.11. A. Young women.
Mean age is 42 years. This is not atherosclerotic, but may be associated with fibromuscular dysplasia. There could be genetic and hormonal factors; may occur during pregnancy.

28.12. D. Use high-dose statin.
This is not accurate as the lesions are not atherosclerotic and are due to fibromuscular dysplasia. Also avoid heavy exertion. The artery may remodel, and about 80% of the lesions disappear. Intravascular ultrasound and CT are very useful in making a diagnosis.

28.13. C. Coronary angiography and, if normal, test for coronary flow reserve.
If epicardial coronary arteries are normal, it is likely to be microvascular angina. The microvasculature is best evaluated with coronary flow reserve. The ergonovine challenge is rarely used, and it is a test for coronary spasm which would be nonexertional and is associated with ST elevation rather than depression. Angina in women is microvascular in about 30%.

28.14. D. All of the above.

Pharmacological Principles of Cardiac Drugs

29

29.1. JT is a 45-year-old male who presents to your outpatient clinic for a routine follow-up. His medical history is significant for atrial fibrillation. Upon examination, you learn that JT has been skipping dinner for the past several weeks due to work-related time restraints. The efficacy of which of the following on JT's current medication list will be *least* affected if administered on an empty stomach?

A. Rivaroxaban 20 mg once daily at 1900
B. Carvedilol CR 20 mg once daily at 1900
C. Dronedarone 400 mg twice daily at 0700 and 1900
D. Diltiazem 24H ER 120 mg once daily at 1900

29.2. PJ is a 56-year-old male who is admitted to a percutaneous coronary intervention (PCI)-capable hospital for an ST elevation myocardial infarction (STEMI). Intravenous (IV) cangrelor is bolused prior to PCI, followed immediately by a cangrelor infusion throughout the duration of PCI. An oral $P2Y_{12}$ platelet inhibitor is administered during the cangrelor infusion. Which of the following $P2Y_{12}$ platelet inhibitors would be best to use concurrently with the cangrelor infusion to prevent stent thrombosis?

A. Clopidogrel 300 mg
B. Clopidogrel 600 mg
C. Prasugrel 60 mg
D. Ticagrelor 180 mg

29.3. TW is a 77-year-old female with a history of atrial fibrillation, hypertension (HTN), and heart failure with reduced ejection fraction (HFrEF) who is admitted to the hospital for a total prosthetic-hip-associated infection. Vancomycin and rifampin are initiated for empiric antimicrobial therapy. The team would also like to start oral anticoagulation for stroke prevention. Which of the following oral anticoagulants may be recommended in this patient?

A. Warfarin plus therapeutic enoxaparin
B. Dabigatran
C. Rivaroxaban
D. Edoxaban

29.4. PY is a 42-year-old female admitted to the hospital for worsening dysuria, urinary frequency, flank pain, and intermittent fevers for the past 2 days. PMH includes paroxysmal atrial fibrillation, HTN, and dyslipidemia. Home medications include simvastatin 40 mg oral (PO) QHS, lisinopril 40 mg PO daily, carvedilol 12.5 mg PO BID, and dofetilide 500 μg PO BID. Urinalysis reveals cloudy appearance, large leukocytes, ≥100 white blood cells (WBC), plus nitrites, a 3+ leukocyte esterase, and many bacteria. Which of the following antimicrobials is best recommended for this patient?

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A. Ceftriaxone
B. Ciprofloxacin
C. Levofloxacin
D. Trimethoprim-sulfamethoxazole

29.5. PT is a 72-year-old male who is admitted for new-onset atrial fibrillation, refractory to diltiazem. The team initiates an amiodarone drip for pharmacologic cardioversion. After 4 days on the amiodarone drip, the patient has become stable enough to transition to oral therapy. Which of the following is a reasonable strategy for conversion of IV to PO amiodarone?
A. Stop drip. Initiate 200 mg PO daily immediately after
B. May overlap by 1 day. Initiate 200 mg PO daily
C. May overlap by 1 day. Initiate 400 mg PO TID
D. Stop drip. Initiate 800 mg PO TID 48 h after discontinuation of the infusion

29.6. NM is an 81-year-old female who was started on amiodarone 200 mg PO once daily for maintenance of sinus rhythm approximately 9 months ago. She presents to your cardiology clinic for a routine follow-up. Labs are drawn. Which of the following abnormal labs is *least likely* to be caused from her amiodarone?
A. WBC 28×10^9 cells/L
B. Aspartate aminotransferase 860 U/L
C. Thyroid stimulating hormone 46 mU/L
D. Thyroid stimulating hormone 0.004 mU/L

29.7. A 45-year-old male presents with confusion and visual disturbances. The eectrocardiogram (ECG) reveals third-degree heart block. His wife claims that the patient just picked up a 30-day supply of digoxin 250 μg PO daily this morning. Upon review of the medication vial, you note that there are only 24 tablets remaining. How many vials of digoxin immune Fab may be recommended for this patient in the setting of acute digoxin toxicity?
A. 3 vials
B. 6 vials
C. 10 vials
D. 20 vials

29.8. Rivaroxaban is started inpatient in a 67-year-old female for stroke prevention in the setting of atrial fibrillation. The patient's creatinine clearance is calculated at 62 mL/min. Which of the following is the appropriate dose of rivaroxaban for this patient?
A. Rivaroxaban 20 mg PO daily
B. Rivaroxaban 15 mg PO BID
C. Rivaroxaban 10 mg PO daily
D. Rivaroxaban 15 mg PO daily

29.9. Which of the following genetic tests could you order as a send-out before initiating warfarin in a patient?
A. *VKORC1* genotype
B. HLA-B*5701 allele
C. HLA-B*1502 allele
D. *CYP2C19* genotype

29.10. FL is a 77-year-old male who presents to the emergency department with complaints of fatigue, dizziness, and shortness of breath. Upon further examination, the patient admits to melena for the past several days. A computed tomography scan is concerning for a gastrointestinal hemorrhage. Of note, the patient has been on chronic anticoagulation therapy with warfarin; INR on admission was found to be 11.2. The team would like to use Kcentra for urgent reversal. Which of the following is the best recommended dose for this patient?

A. 50 units/kg of the factor II component (maximum dose 5000 units)
B. 50 units/kg of the factor VII component (maximum dose 5000 units)
C. 50 units/kg of the factor IX component (maximum dose 5000 units)
D. 50 units/kg of the factor X component (maximum dose 5000 units)

29.11. Which of the following statements is correct?
A. Beta-blockers may cause peripheral vasoconstriction through their beta-1 receptor antagonism effects
B. Beta-blockers may cause peripheral vasoconstriction through their beta-2 receptor antagonism effects
C. Beta-blockers may cause peripheral vasodilation through their beta-1 receptor antagonism effects
D. Beta-blockers may cause peripheral vasodilation through their beta-2 receptor antagonism effects

29.12. LG is a 36-year-old female with HFrEF (left ventricular ejection fraction 30%), HTN, diabetes mellitus, and chronic kidney disease stage III. The patient has a reported allergy to valsartan with a reaction of angioedema. Current medications include carvedilol, insulin glargine, insulin lispro, and amlodipine. The team would like to start a medication to optimize the patient's heart failure therapy. Which of the following medications may be started in this patient?
A. Lisinopril
B. Losartan
C. BiDil®
D. Entresto®

29.13. TN is a 40-year-old male with a past medical history that includes asthma and heart failure with preserved ejection fraction. In addition to a rescue inhaler, the patient is currently using fluticasone/salmeterol for maintenance of his asthma. The team would like to start a beta-blocker for this patient but has concerns about concomitant use of a beta-blocker and a beta-agonist. Which of the following beta-blockers would be best to use in this patient?
A. Metoprolol succinate 25 mg PO daily
B. Propranolol 40 mg PO BID
C. Labetalol 100 mg PO BID
D. Carvedilol 6.25 mg PO BID

29.14. Which of the following medications has an active metabolite with the longest half-life?
A. Aspirin
B. Clopidogrel
C. Prasugrel
D. Ticagrelor

29.15. A 36-year-old male presents with chest pain, associated with bilateral nipple tenderness and sensitivity. Cardiac enzymes are negative. Which of the following medications in this patient's profile can mostly likely cause these symptoms?
A. Triamterene/hydrochlorothiazide
B. Spironolactone
C. Labetalol
D. Ranolazine

29.16. Which of the following diuretics may be used in a patient with a confirmed Stevens–Johnson reaction to trimethoprim-sulfamethoxazole?
A. Furosemide
B. Hydrochlorothiazide
C. Metolazone
D. Ethacrynic acid

29.17. TJ is a 54-year-old male who is started on immediate-release isosorbide mononitrate for chronic stable angina, refractory to beta-blocker monotherapy. Which of the following regimens is best to start in this patient?

A. 10 mg PO at 0700 and 1400
B. 10 mg PO at 0700 and 1900
C. 10 mg PO at 0700 and 1900 for 3 days, then 20 mg PO at 0700 and 1900
D. 10 mg PO at 0700 and 1500 and 2300

29.18. WL is a 68-year-old female who is placed in observation awaiting an adenosine stress test. Which of the following statements is false?

A. Chocolate milk, coffee, tea, brownies, and energy bars should be avoided prior to test
B. Patient must remain NPO 4–6 h prior to test
C. The patient is not to take Aggrenox® for at least 24 h prior to test
D. The patient is not to take theophylline-containing medications for at least 12 h prior to test

29.19. A 65-year-old female presents to the emergency department with severe, sharp chest pain, weak pulses, altered level of consciousness, and weakness. BP upon admission was 212/126 mmHg. Upon further examination, the team diagnosed the patient with aortic dissection in the setting of hypertensive emergency. Which agent is best to initiate in this patient to lower blood pressure?

A. IV labetalol
B. IV metoprolol
C. IV nicardipine
D. IV diltiazem

29.20. Which of the following has been proven to be most beneficial for initial treatment in pulmonary arterial HTN (World Health Organization functional class II) to reduce clinical failures, such as death, hospitalization, or worsening pulmonary arterial HTN?

A. Epoprostenol IV 5 μg/(kg min)
B. Ambrisentan 10 mg daily
C. Tadalafil 40 mg daily
D. Ambrisentan 10 mg daily and tadalafil 40 mg daily

29.21. EM is a 60-year-old female diagnosed a year ago with HFrEF. Around that time, she began taking enalapril 10 mg PO BID, carvedilol 25 mg PO BID, and furosemide 20 mg PO BID. Upon further discussion with the patient, it is decided to transition the enalapril to Entresto. Which is the best method in transitioning enalapril to Entresto?

A. Stop enalapril and begin Entresto 49/51 mg PO BID at the time the next dose of enalapril was scheduled
B. Overlap enalapril and Entresto 24/26 mg PO BID by 24 h
C. Overlap enalapril and Entresto 49/51 mg PO BID by 24 h
D. Stop enalapril 36 h before starting Entresto 49/51 mg PO BID

29.22. The team wants to start a moderate-intensity HMG-CoA reductase inhibitor for atherosclerotic cardiovascular disease primary prevention in a patient taking the following current medications: lisinopril 20 mg PO daily, verapamil 120 mg PO QID, metformin 1000 mg PO BID, and glipizide 5 mg PO BID. Which of the following is the best HMG-CoA reductase inhibitor to start in this patient?

A. Simvastatin 40 mg PO QHS
B. Rosuvastatin 10 mg PO QHS
C. Atorvastatin 10 mg PO QHS
D. Lovastatin 40 mg PO QHS

29.23. PT is a 58-year-old male who presents with chest pain for the past 4 months that worsens upon exertion. Vitals include BP of 87/60 mmHg and heart rate of 57 bpm. The team would like to start a medication for chronic stable angina. Which is the best agent to initiate in this patient?

A. Ranolazine
B. Amlodipine
C. Isosorbide mononitrate
D. Nifedipine

29.24. LT is a 24-year-old pregnant female. During her second trimester she presents complaining of excessive fatigue, shortness of breath, palpitations, and swelling in her ankles. She is found to have developed atrial fibrillation on her ECG and on echo her ejection fraction is found to be 25%. Which of the following medications would be deemed safe for the fetus?

A. Enalapril
B. Atorvastatin
C. Digoxin
D. Warfarin

29.25. Which of the following anticoagulants does not require antithrombin III for its anticoagulant effect to work?

A. Heparin
B. Enoxaparin
C. Rivaroxaban
D. Fondaparinux

29.26. XR is an 88-year-old male being treated for a non-STEMI. He is given a 4000-unit bolus of heparin and started at 500 units/h due to his low weight. At 6 h after initiating heparin he develops epistaxis and oozing around the IV site. Upon further investigation, it is found that his heparin drip rate was running at 1000 units/h by accident rather than 500 units/h for the last 6 h since heparin initiation. What dose of protamine is best to reverse the effect of the heparin?

A. 42.5 mg
B. 30 mg
C. 17.5 mg
D. 5 mg

29.27. JG is a 23-year-old patient presenting to the emergency room with palpitations and shortness of breath. An ECG reveals the patient is in atrial fibrillation and delta waves are present. Which of the following agents would be the best choice to help control this patient's atrial fibrillation?

A. Ibutilide
B. Diltiazem
C. Metoprolol
D. Amiodarone

29.28. Which of the following medications would not require monitoring potassium levels in patients?

A. Eplerenone
B. Enalapril
C. Furosemide
D. Amlodipine

29.29. MJ is a 63-year-old patient presenting with acute decompensated heart failure (New York Heart Association (NYHA) class IV), a systolic BP of 84/46 mmHg, and a heart rate of 110 bpm. Which of the following medications would be reasonable to initiate at this time?

A. Dobutamine 2 μg/(kg min)
B. Milrinone 50 μg/kg bolus then 0.75 μg/(kg min)
C. Nesiritide 2 μg/kg bolus, then 0.01 μg/(kg min)
D. Ivabradine 5 mg PO BID

29.30. YT is a 67-year-old female with a past medical history of HFrEF, HTN, diabetes mellitus type 2, atrial fibrillation, and myocardial infarction 4 years ago. She presents today in atrial fibrillation with rapid ventricular response and acute decompensated heart failure with symptoms at rest. Her home medications are lisinopril 40 mg PO daily, carvedilol 25 mg PO BID, pravastatin 40 mg PO daily, digoxin 0.125 mg PO daily, aspirin 81 mg PO daily, warfarin 5 mg PO daily, pioglitazone 30 mg PO daily, and empagliflozin 10 mg PO daily. An amiodarone drip is started to help control the atrial fibrillation. Which of the following statements are false?

A. Empaglifozin has been found to reduce cardiovascular mortality
B. Pioglitazone should be stopped in patients with NYHA class IV heart failure
C. The patient's INR will likely come back with a marked increase on tomorrow morning's lab draw due to the amiodarone inhibiting warfarin hepatic metabolism
D. The patient's digoxin level will likely come back with a marked increase on tomorrow morning's lab draw due the amiodarone drip's effect on the patient's hepatic metabolism

29.31. ML is a 66-year-old female presenting to the catheterization laboratory with a non-STEMI. During the history and physical examination, the patient mentions that previous genetic testing has revealed that she is deficient in the CYP 2C19 enzyme. Which of the following options for antiplatelet therapy during PCI would be best to avoid based upon her genetic profile?

A. Prasugrel 60 mg PO ×1
B. Ticagrelor 180 mg PO ×1
C. Cangrelor 30 μg/kg IV bolus, followed by 4 μg/(kg min) IV continuous infusion
D. Clopidogrel 600 mg PO ×1

29.32. Which of the following antiarrhythmics would require the most dose adjustment when added to a patient already taking a high dose of metoprolol?

A. Propafenone
B. Dofetilide
C. Flecainide
D. Disopyramide

Answers

29.1. D. Diltiazem 24H ER 120 mg once daily.

Coadministration of rivaroxaban with food increases the bioavailability of the 15 mg and 20 mg dose. Administration of carvedilol CR with a high-fat meal results in increases (~20%) in area under the curve and C_{max}. The absolute bioavailability of dronedarone increases from 4% without food to 15% when administered with a high-fat meal. Rivaroxaban 15 mg and 20 mg, carvedilol CR, and dronedarone should all be taken with food.

29.2. D. Ticagrelor 180 mg.

Loading doses of thienopyridines, such as clopidogrel and prasugrel, should not be given until discontinuation of the cangrelor infusion due to a drug interaction related to competitive binding to the $P2Y_{12}$ receptor. However, a loading

dose of ticagrelor may be given at any time during or immediately after discontinuation of the cangrelor infusion.

29.3. A. Warfarin plus therapeutic enoxaparin.

Concomitant use of dabigatran, rivaroxaban, or edoxaban with strong dual *p*-glycoprotein and cytochrome P450 3A4 (CYP3A4) inducers, such as rifampin, should be avoided due to decreased levels of the anticoagulant; it is also unfeasible to determine the extent of reduction of the anticoagulant due to a lack of monitoring assays to test for efficacy. Rifampin may also decrease the effect of warfarin; however, this may be monitored closely through international normalized ratio (INR) readings, and doses may be adjusted accordingly.

29.4. A. Ceftriaxone.

Concomitant use of QT-prolonging agents (i.e., fluoroquinolones) should be avoided with dofetilide. Trimethoprim-sulfamethoxazole has been shown to cause a substantial increase in dofetilide plasma concentrations, which in turn may cause a dose-dependent QT interval prolongation.

29.5. C. May overlap by 1 day, initiate 400 mg PO TID.

The optimal dose for changing from IV to PO amiodarone depends on the dose of the IV amiodarone already administered. In patients who have been on an amiodarone drip for less than 1 week, an initial daily dose of 800–1600 mg of PO amiodarone may be recommended. Amiodarone can cause stomach upset and nausea, which is minimized by giving no more than 400 mg at one time. PO therapy may overlap with IV therapy; however, this is not required. Of note, there are no official recommendations on transitioning from IV to PO amiodarone. Clinical monitoring is recommended.

29.6. A. WBC 28×10^9 cells/L.

Because amiodarone is a potential source of large amounts of inorganic iodine, it can cause hypothyroidism or hyperthyroidism. Liver enzyme elevations and/or hepatotoxicity are also associated with amiodarone use and should be monitored closely. The incidence of leukocytosis due to amiodarone is unlikely.

29.7. A. 3 vials.

Each vial of digoxin immune Fab 40 mg will bind to approximately 0.5 mg of digoxin. The total number of vials required can be calculated by dividing the total body load of digoxin (in milligrams) by 0.5 mg per vial. Total body load is approximately equal to the amount ingested (in milligrams) multiplied by the bioavailability of the tablet preparation, which is 0.8. This patient ingested a total of 1.5 mg of digoxin (0.25 mg × 6 tablets). 1.5 mg × 0.8 = 1.2 mg total digitalis body load. 1.2 mg/0.5 = 2.4 vials. Thus, three vials of digoxin immune Fab may be administered. Alternatively, in the setting of acute ingestion of unknown amounts of digoxin and absence of a serum digitalis concentration level, administer 20 vials of digoxin immune Fab; this may be administered as 10 vials initially, followed by another 10 vials, if needed, to avoid a febrile reaction.

29.8. A. Rivaroxaban 20 mg PO daily.

This is the recommended dose for stroke prevention in non-valvular atrial fibrillation in patients with creatinine clearance >50 mL/min.

29.9. A. *VKORC1* genotype.

Warfarin reduces the regeneration of vitamin K epoxide in the vitamin K cycle through inhibition of VKOR, a multiprotein enzyme complex. Certain single-nucleotide polymorphisms in the *VKORC1* gene have been associated with variable warfarin dose requirements.

29.10. C. 50 units/kg of the factor IX component (maximum dose 5000 units).

Kcentra is composed of factors II, VII, IX, and X, as well as proteins C and S. 50 units/kg of the factor IX component is recommended in pretreatment INRs greater than 6. It should be noted that the dose of Kcentra is based on the actual potency as stated on the carton, which will vary from 20 to 31 factor IX units per milliliter. For patients weighing more than 100 kg, the maximum dose should not be exceeded.

29.11. B. Beta-blockers may cause peripheral vasoconstriction through their beta-2 receptor antagonism effects.

29.12. C. BiDil®.

BiDil (hydralazine/isosorbide dinitrate). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) can both cause angioedema. In patients with a documented reaction of angioedema to an ARB, it is recommended to avoid ACE inhibitors and other ARBs. Entresto is a newly approved heart failure medication that contains a combination of valsartan and sacubitril.

29.13. A. Metoprolol succinate 25 mg PO daily.

It was once recommended to avoid beta-blockers in patients with asthma. However, it has been shown that cardioselective beta-blockers are unlikely to produce unfavorable respiratory symptoms in patients with asthma. Metoprolol succinate is the only cardioselective beta-blocker listed and is likely to target mainly beta-1 receptors when given at a low daily dose of 25 mg.

29.14. D. Ticagrelor.

Ticagrelor has an active metabolite with the longest half-life of approximately 9 h. See Box 29.1.

29.15. B. Spironolactone.

These symptoms are consistent with gynecomastia, which is a dose- and duration-dependent adverse effect of spironolactone. Gynecomastia may be reversible following discontinuation of therapy, but on rare occasions may persist.

29.16. D. Ethacrynic acid.

Ethacrynic acid is the only diuretic listed that does not have a sulfonamide chemical group and may be used in patients with a confirmed sulfonamide allergy.

29.17. A. 10 mg PO at 0700 and 1400.

Immediate-release isosorbide mononitrate is dosed twice daily. Tolerance to nitrate effects develops with chronic exposure. Dose escalation does not overcome this effect. Tolerance can only be overcome by short periods of nitrate absence from the body. Two doses given 7 h apart are recommended to decrease

tolerance development. Of note, hydralazine has been shown to inhibit the development of tolerance to nitrates, which may explain why the combination of hydralazine and isosorbide dinitrate can be dosed TID and is beneficial in heart failure patients.

29.18. C. The patient is not to take Aggrenox® for at least 24 h prior to test.

The patient is not to take the medicine Aggrenox (aspirin/extended-release dipyridamole) for at least 48 h prior to the test. Aspirin alone is not a problem and should be considered if Aggrenox is held.

29.19. A. IV labetalol.

In the setting of acute aortic dissection, BP should be reduced rapidly (generally to a goal systolic BP less than 120 mmHg) with a beta-adrenergic antagonist and a vasodilator within the first 10 min of treatment. As a selective alpha-1 adrenergic and nonselective beta-adrenergic antagonist, labetalol maintains coronary blood flow, minimizes aortic wall stress, and reduces systemic vascular resistance without reducing total peripheral blood flow.

29.20. D. Ambrisentan 10 mg and tadalafil 40 mg daily.

The AMBITION trial was a randomized double-blind, multicenter study that showed the combination of ambrisentan and tadalafil reduced the risk of clinical failure by 50% compared with ambrisentan or tadalafil monotherapy. IV epoprostenol may be considered as first-line therapy in patients with pulmonary HTN and World Health Organization functional class IV.

29.21. D. Stop enalapril 36 h before starting Entresto 49/51 mg PO BID.

Allow a wash-out period of 36 h if switching from or to an ACE inhibitor. For patients receiving a total daily dose of >10 mg of enalapril (or therapeutically equivalent doses), start Entresto 49/51 mg PO BID. For patients receiving a total daily dose of ≤10 mg of enalapril (or therapeutically equivalent doses), start Entresto 24/26 mg PO BID.

29.22. B. Rosuvastatin 10 mg PO QHS.

As a CYP3A4 inhibitor, verapamil may increase the serum concentration of simvastatin, atorvastatin, and lovastatin. Rosuvastatin, on the other hand, is less dependent on CYP3A4-mediated metabolism.

29.23. A. Ranolazine.

Ranolazine exerts antianginal and anti-ischemic effects with minimal change in hemodynamic parameters (heart rate, BP). The other antianginal agents may lower BP in this patient, who is already hypotensive.

29.24. C. Digoxin.

Digoxin is pregnancy category C but is often used in pregnant women with peripartum cardiomyopathy. Warfarin and atorvastatin are pregnancy category X and would not be recommended in this case. ACE inhibitors, such as enalapril, have been shown to be detrimental to the fetus in all three trimesters.

29.25. C. Rivaroxaban.

Rivaroxaban does not require antithrombin III for its anticoagulation effect. Heparin, enoxaparin, and fondaparinux all require antithrombin III for their anticoagulation effect and the effectiveness is greatly diminished in patients with low antithrombin III levels.

29.26. C. 17.5 mg.

Since heparin has a half-life around 60–90 min, after 4 h the preceding amount of heparin has been eliminated. The calculation is 1 mg of protamine for every 100 units of heparin in the first 30 min, 0.5 mg of protamine for every 100 units of heparin given between 30 and 120 min, and 0.25 mg of protamine for every 100 units of heparin given between 2 and 4 h.

Ticagrelor has an active metabolite with the longest half-life of approximately 9 h. See Box 29.1.

29.27. A. Ibutilide.

Ibutilide is an IV class III antiarrhythmic which will convert a patient to sinus rhythm without blocking the AV node. Amiodarone, metoprolol, and diltiazem all block the AV node and could worsen symptoms by allowing increased conduction down the accessory pathway.

29.28. D. Amlodipine.

Amlodipine does not affect potassium levels in patients. Furosemide will lower potassium due to blocking of the Na^+/K^+ channels in the kidney. Eplerenone and enalapril both increase potassium levels in patients.

29.29. A. Dobutamine 2 μg/(kg min).

Dobutamine, starting at a low dose, should not adversely affect the BP. In fact, it would not be unexpected if the BP were to rise due to the increased cardiac output. Milrinone should not be bolused in patients with a systolic BP less than 90 mmHg due to its vasodilatory effects. Both nesiritide and ivabradine are contraindicated in systolic BP less than 90 mmHg. Ivabradine is also not recommended during an acute heart failure exacerbation.

29.30. D. The patient's digoxin level will likely come back with a marked increase on tomorrow morning's lab draw due the amiodarone drip's effect on the patient's hepatic metabolism.

This is false. Digoxin levels will increase on an amiodarone drip due to the P-glycoprotein pump inhibition, not a reduction in hepatic metabolism. An amiodarone drip will often increase INR levels drastically for patients on a stable dose of warfarin; often, even if warfarin is stopped, the INR can trend up for a few days before it starts to normalize. The Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes Mellitus (EMPA-REG) trial demonstrated a reduction in all-cause and cardiovascular mortality in patients using empagliflozin in comparison with placebo. Pioglitazone has a black box warning contraindicating its initiation in patients in NYHA class III or IV heart failure.

29.31. D. Clopidogrel 600 mg PO ×1.

Clopidogrel requires a two-step metabolism to be converted into its active metabolite, and CYP 2C19 is one of the main enzymes required for this conversion. Prasugrel, on the other hand, is converted into its active metabolite primarily by the CYP 3A4 and CYP 2B6 enzymes. Ticagrelor is active in its parent form and is metabolized primarily by the CYP 3A4 enzyme. Cangrelor is active in its parent form and is not dependent on either renal or hepatic enzymes for its metabolism.

29.32. A. Propafenone.

Propafenone possesses independent beta-blocking activity and can also increase metoprolol serum blood levels up to five times normal, increasing the risk of severe hypotension and heart block. If a beta-blocker is needed, one should keep the metoprolol dose low or alternatively use atenolol, since 50% of atenolol is renally cleared.

Box 29.1 Clinical Pearls

Remember that a drug's half-life does not always correlate to how long its effects last in the body. Aspirin has a short half-life, but due to it irreversibly inhibiting platelets its effect lasts until the body can make new platelets rather that how long the drug remains in the body.

Drugs with a large volume of distribution will have a much shorter effective half-life when they are first initiated due to rapid declines in the blood levels. For example, an IV bolus of amiodarone will have a 90% drop in the blood level 45 min afterward due to the drug distributing to the tissues and out of the bloodstream. This is why a drip should be initiated after a bolus dose even though the half-life of the drug is over 1 month long.

There are many ways that drugs can interact: they can have synergistic effects, such as clopidogrel and warfarin; they can affect each other's metabolism, such as metoprolol and propafenone; they can inhibit their excretion through P-glycoprotein pumps, such as with digoxin and amiodarone; and they can both affect similar electrical channels for synergistic QT prolongation, such as methadone and erythromycin.

Drugs can have multiple effects on the body, and it is important to determine which effect will win out. One example are beta-blockers, which cause direct vasoconstriction though blocking beta-2 receptors in blood vessels, reduction of cardiac output through decreases in heart rate, and inhibition of the release of renin from the kidneys, leading to a net effect of lowered BP in patients.

Anticoagulation

30

30.1. A 55-year-old male presents with acute onset of shortness of breath. He has a computed tomography angiogram in the emergency room and is noted to have bilateral segmental and subsegmental pulmonary emboli (PEs). His past medical history is significant for non-small cell carcinoma of the lung, for which he is undergoing treatment. He reports nausea and vomiting. Which of the following would be the choice of anticoagulation?

A. Warfarin
B. Low molecular weight heparin (LMWH)
C. Dabigatran
D. Edoxaban

30.2. In a patient with deep venous thrombosis (DVT) of the leg, not cancer associated, what would not be the choice of anticoagulation for the first 3 months?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. Edoxaban
E. Warfarin

30.3. Initial parentral anticoagulation is a must with what agents, when used to treat non-cancer-associated DVT or PEs?

A. Rivaroxaban and apixaban
B. Dabigatran and edoxaban
C. Rivaroxaban and edoxaban
D. Dabigatran and apixaban

30.4. A patient is on dabigatran 150 mg BID for paroxysmal atrial fibrillation. He is then prescribed dronedarone for rhythm control. What is the recommendation for dabigatran dosing?

A. Continue at 150 mg BID
B. Reduce dosage to 75 mg BID
C. Stop using dabigatran
D. Reduce dosage to 75 mg once daily

30.5. A 65-year-old male is on ketoconazole therapy. He has paroxysmal atrial fibrillation and his CHA_2DS_2–VASc score is 4. His physician decides on starting a novel anticoagulant, dabigatran. What is the recommendation regarding dabigatran dosing in this patient?

A. Start on 150 mg BID
B. Do not use dabigatran
C. Start on 75 mg BID
D. Start on 75 mg once daily

30.6. Which of the novel anticoagulants is mostly excreted through the kidneys?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. Edoxaban

30.7. Which of the following novel anticoagulants is a direct thrombin inhibitor?

A. Rivaroxaban
B. Apixaban
C. Dabigatran
D. Edoxaban

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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30.8. Which of the following drugs has been approved by the US Food and Drug Administration for use to reverse the effect of dabigatran?

A. Idarucizumab
B. Andexanet alfa
C. Aripazine
D. Protamine

30.9. Which of the following drugs is being studied to reverse the effect of apixaban and rivaroxaban?

A. Idarucizumab
B. Andexanet alfa
C. Aripazine
D. Protamine

30.10. Which of the following drugs is being evaluated as a universal anticoagulant reversal agent (anti-direct thrombin inhibitors, anti-Xa inhibitors, unfractionated heparin, LMWH, and fondaparinux)?

A. Idarucizumab
B. Andexanet alfa
C. Aripazine
D. Protamine

30.11. For patients undergoing major orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, what is the current recommendation for thromboprophylaxis from the day of surgery?

A. Thromboprophylaxis in the outpatient period for up to 35 days
B. Thromboprophylaxis for 10 days
C. No need for thromboprophylaxis
D. Thromboprophylaxis for 14 days

30.12. In patients undergoing total hip arthroplasty or total knee arthroplasty, irrespective of the concomitant use of an intermittent pneumatic compression device or length of treatment, what is the recommended choice for thromboprophylaxis?

A. Aspirin alone
B. Unfractionated heparin
C. LMWH
D. Vitamin K antagonist

30.13. For patients undergoing total hip arthroplasty, total knee arthroplasty, and hip fracture surgery, what is the recommended time period to start thromboprophylaxis with LMWH?

A. 4 h preoperatively
B. 4 h postoperatively
C. 12 h or more preoperatively or postoperatively
D. 24 h postoperatively

30.14. For acutely sick hospitalized medical patients who are at increased risk for thrombosis, what is the current recommendation for thromboprophylaxis?

A. LMWH
B. LDUH BID
C. LDUH TID
D. Fondaparinux
E. All of the above
F. None of the above

30.15. Based on the RE-LY trial, which of the following statements is false?

A. Dabigatran 110 mg was noninferior to warfarin in preventing stroke or embolism
B. Dabigatran 150 mg was superior to warfarin in preventing stroke/embolism
C. Dabigatran was associated with more gastrointestinal bleeds
D. Dabigatran was associated with more intracranial bleeds

30.16. Which of the following is not true regarding novel anticoagulants in nonvalvular atrial fibrillation?

- **A.** Rivaroxaban was noninferior to warfarin in preventing stroke
- **B.** Edoxaban was noninferior to warfarin in preventing stroke
- **C.** Apixaban was superior to warfarin in preventing stroke
- **D.** Apixaban was noninferior to warfarin in preventing stroke

30.17. In a patient with acute isolated distal DVT, what is the current recommendation regarding management?

- **A.** Serial imaging of the deep veins in 2 weeks when there are no severe symptoms or risk for extension
- **B.** Serial imaging in 4 weeks
- **C.** No need to image further
- **D.** Start anticoagulation

30.18. In a patient diagnosed with a distal DVT managed with serial imaging, which of the following statements is not true?

- **A.** Anticoagulation if the thrombus has not extended
- **B.** Anticoagulation is recommended if the thrombus has extended but remains confined to distal veins
- **C.** Anticoagulation is recommended if the thrombus extends into the proximal veins

30.19. Which of the following is not true?

- **A.** In patients with acute DVT of the leg, use of compression stockings is not recommended
- **B.** In patients with subsegmental PE (not involving proximal pulmonary arteries) without proximal DVT of legs and a low risk for venous thromboembolism (VTE), clinical surveillance is recommended
- **C.** In patients with subsegmental PE (not involving proximal pulmonary arteries) without proximal DVT of legs and a high risk for VTE, clinical surveillance is recommended
- **D.** In patients with low-risk pulmonary embolism, treatment at home or early discharge is recommended (before 5 days of treatment)

30.20. Which of the following statements are true?

- **A.** In patients with acute PE being managed by thrombolysis, systemic thrombolytic therapy is recommended over catheter-delivered thrombolysis
- **B.** In patients with acute PE associated with hypotension, catheter-assisted thrombus removal is recommended when they are at high risk for bleeding, failed systemic thrombolysis, or in shock
- **C.** In patients with upper extremity DVT involving axillary or more proximal veins, anticoagulation therapy is recommended over thrombolysis
- **D.** In patients with recurrent DVT on therapeutic doses of warfarin or other NOACS, switching to LMWH for at least 1 month is recommended
- **E.** Increasing the dose of LMWH by one-quarter to one-third is recommended if recurrent DVT occurs while on therapeutic dose of long-term LMWH therapy
- **F.** All of the above
- **G.** None of the above

Answers

30.1. B. Low molecular weight heparin (LMWH).

This patient has just been diagnosed with PEs and is related to his underlying cancer. He also reports vomiting. This patient should be treated with LMWH initially (Kearon *et al.*, 2016).

30.2. E. Warfarin.

According to the recent CHEST guidelines (Kearon *et al.*, 2016), in patients with DVT of the leg or PEs, warfarin is not the choice of therapy (for first 3 months) (evidence grade 2B). See Box 30.1.

30.3. B. Dabigatran and edoxaban.

If novel anticoagulants are chosen to treat a DVT or a PE when not associated with cancer, initial parenteral anticoagulation is recommended with dabigatran and edoxaban and is not needed with rivaroxaban and apixaban and is overlapped with warfarin.

30.4. B. Reduce dosage to 75 mg BID.

Dronedarone inhibits P-glycoprotein and cytochrome P450 3A4 and hence increases the plasma concentration of dabigatran, which may lead to increased bleeding. Hence, the current recommendation is to reduce the dose of dabigatran to 75 mg BID in the USA. See Box 30.3.

30.5. C. Start on 75 mg BID.

Ketoconazole, itraconazole, voriconazole, and posaconazole will increase the serum concentration of dabigatran through P-glycoprotein and breast cancer resistance protein competition and cytochrome P450 3A4 inhibition. Hence, it is recommended to start dabigatran dose at 75 mg BID while on any of the aforementioned antifungals in the USA.

30.6. A. Dabigatran.

Among the drugs listed in the question, dabigatran is cleared through the kidneys (80%), while rivaroxaban (66%), apixaban (25%) and edoxaban (50%) have lower rates of renal clearance.

30.7. C. Dabigatran.

Dabigatran is a direct thrombin inhibitor, while all the other agents are factor Xa (FXa) inhibitors.

30.8. A. Idarucizumab.

Idarucizumab is a humanized, monoclonal, antibody fragment that specifically binds with high affinity to dabigatran, an oral direct thrombin inhibitor. It acts by competitively displacing dabigatran from thrombin to reverse anticoagulation and restore fibrin formation. Dabigatran has an affinity for idarucizumab that is 350 times greater than its affinity for thrombin. The dose currently studied in the phase 3 trial is 5 g. A global phase 3 case series study known as RE-VERSE AD is currently enrolling patients treated with dabigatran who have uncontrolled bleeding or require emergency surgery or procedures. A dose of 5 g idarucizumab will be administered intravenously to reverse the effect of dabigatran. The trial will measure plasma-diluted thrombin time

and ecarin clotting time as primary outcome measures. Time to cessation of bleeding will be a secondary outcome. Results from the trial are expected in 2017.

30.9. B. Andexanet alfa.

It is a modified recombinant FXa molecule intended for intravenous (IV) administration. It has been developed as an antidote to reverse anticoagulant activity of oral direct (e.g., apixaban, edoxaban, and rivaroxaban) and injectable indirect (e.g., enoxaparin and fondaparinux) FXa inhibitors. Andexanet alfa acts to target and sequester with high specificity both oral and injectable FXa inhibitors in the blood. Part 1 of the phase 3 ANNEXA-R trial – which was designed to compare the administration of an 800 mg IV bolus of andexanet alfa with placebo in 39 patients pretreated with rivaroxaban 20 mg for 4 days – were presented at the 2015 American College of Cardiology Scientific Sessions on March 16, 2015. Andexanet alfa produced a statistically significant and rapid reduction in anti-FXa activity from baseline (primary outcome); mean percentage change anti-FXa from baseline to nadir was 92% ($P < 0.0001$ versus placebo). Normalization of coagulation parameters was achieved within 2 min of completing the IV bolus infusion; the effect lasted 1–2 h with the IV bolus dose. Part 2 is ongoing and will investigate IV bolus followed by a 2-h continuous infusion to demonstrate sustained reversal.

30.10. C. Aripazine.

It is a small, synthetic molecule designed with broad reversal activity and administered as a single IV bolus dose. It binds to oral FXa inhibitors and direct thrombin inhibitors, as well as to injectable unfractionated heparin and LMWH via noncovalent bonding and charge–charge interactions to neutralize anticoagulation and bleeding. Currently in phase 2 trials.

30.11. A. Thromboprophylaxis in the outpatient period for up to 35 days.

The current guideline recommendation is to extend thromboprophylaxis to 35 days from the day of surgery.

30.12. C. LMWH.

The guidelines recommend the use of LMWH in preference to the other agents recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose unfractionated heparin (LDUH) (all grade 2B), adjusted-dose vitamin K antagonist (VKA), or aspirin (all grade 2C).

30.13. C. 12 h or more preoperatively or postoperatively.

For patients undergoing major orthopedic surgery (total hip arthroplasty, total knee arthroplasty, and hip fracture surgery) and receiving LMWH as thromboprophylaxis, the guidelines recommend starting either 12 h or more preoperatively or postoperatively rather than within 4 h or less preoperatively or postoperatively (grade 1B).

30.14. E. All of the above.

Current recommendations are to use any of the following anticoagulants for thromboprophylaxis: LMWH, LDUH BID, LDUH TID, or fondaparinux (grade 1B).

30.15. D. Dabigatran was associated with more intracranial bleeds.

This is false. In the RE-LY trial, dabigatran was associated with 2.71% (110 mg) and 3.11% (150 mg) major bleeding rates compared with warfarin (3.36%), but was associated with lower rates of intracranial bleeding. See Box 30.2.

30.16. D. Apixaban was noninferior to warfarin in preventing stroke.

This is false. Apixaban was superior to warfarin in preventing stroke (ARISTOTLE trial), while ROCKET AF and ENGAGE AF showed rivaroxaban and edoxaban respectively to be noninferior to warfarin in preventing stroke or embolism. See Box 30.2.

30.17. A. Serial imaging of the deep veins in 2 weeks when there are no severe symptoms or risk for extension.

In a patient with isolated distal DVT without severe symptoms or risk for extension, serial imaging of the deep veins over 2 weeks is recommended.

30.18. A. Anticoagulation if the thrombus has not extended.

The current recommendation for patients with isolated distal DVT managed by serial imaging is to start anticoagulation if the thrombus has extended into the distal veins or into proximal veins.

30.19. C. In patients with subsegmental PE (not involving proximal pulmonary arteries) without proximal DVT of legs and a high risk for VTE, clinical surveillance is recommended.

This is not true. In patients with subsegmental PE (not involving proximal pulmonary arteries) without proximal DVT of legs and a high risk for venous thromboembolism (VTE), anticoagulation over clinical surveillance is recommended.

30.20. F. All of the above.

See CHEST guidelines (Kearon *et al.*, 2016); Box 30.1.

Box 30.1 CHEST Guideline and Expert Panel Report

Kearon *et al.* (2016) updated recommendations on 12 topics that were in the ninth edition of the guidelines and addressed three new topics. The main points taken from Kearon *et al.* (2016), without altering the original language, are as follows (where the asterisks indicate the newly added or changed recommendations since publication of the 9th edition):

*1. In patients with proximal DVT or pulmonary embolism (PE), we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B). For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

*2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).

Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

*3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).

Remarks: Initial parenteral anticoagulation is given before dabigatran and edoxaban, is not given before rivaroxaban and apixaban, and is overlapped with VKA therapy. See text for factors that influence choice of therapy.

*4. In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).

Remarks: It may be appropriate for the choice of anticoagulant to change in response to changes in the patient's circumstances or preferences during long-term or extended phases of treatment.

5. In patients with a proximal DVT of the leg or PE provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (e.g., 6, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

6. In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (e.g., 6, 12, or 24 months) (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B).

Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g., annually).

7. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C), we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g., 6, 12, or 24 months) (Grade 1B), and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B).

Remarks: Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.

8. In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation for at least 3 months over treatment of a shorter duration (Grade 1B), and we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g., 6, 12, or 24 months) (Grade 1B).

Remarks: After 3 months of treatment, patients with unprovoked DVT of the leg or PE should be evaluated for the risk-benefit ratio of extended therapy. Duration of treatment of patients with isolated distal DVT refers to patients in whom a decision has been made to treat with anticoagulant therapy; however, it is anticipated

that not all patients who are diagnosed with isolated distal DVT will be prescribed anticoagulants.

9. In patients with a first VTE that is an unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk (see text), we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk (see text), we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

   Remarks: Patient sex and D-dimer level measured a month after stopping anticoagulant therapy may influence the decision to stop or extend anticoagulant therapy (see text). In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g., annually).

10. In patients with a second unprovoked VTE and who have a (i) low bleeding risk (see text), we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months (Grade 1B); (ii) moderate bleeding risk (see text), we suggest extended anticoagulant therapy over 3 months of therapy (Grade 2B); or (iii) high bleeding risk (see text), we suggest 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 2B).

   Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (e.g., annually).

11. In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).

   Remarks: In all patients who receive extended anticoagulant therapy, the continuing use of treatment should be reassessed at periodic intervals (eg, annually).

*12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B).

   Remarks: Because aspirin is expected to be much less effective at preventing recurrent VTE than anticoagulants, we do not consider aspirin a reasonable alternative to anticoagulant therapy in patients who want extended therapy. However, if a patient has decided to stop anticoagulants, prevention of recurrent VTE is one of the benefits of aspirin that needs to be balanced against aspirin's risk of bleeding and inconvenience. Use of aspirin should also be reevaluated when patients stop anticoagulant therapy because aspirin may have been stopped when anticoagulants were started.

13. In patients with acute isolated distal DVT of the leg and (i) without severe symptoms or risk factors for extension (see text), we suggest serial imaging of the deep veins for 2 weeks over anticoagulation (Grade 2C) or (ii) with severe symptoms or risk factors for extension (see text), we suggest anticoagulation over serial imaging of the deep veins (Grade 2C).

   Remarks: Patients at high risk for bleeding are more likely to benefit from serial imaging. Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging.

14. In patients with acute isolated distal DVT of the leg who are managed with anticoagulation, we recommend using the same anticoagulation as for patients with acute proximal DVT (Grade 1B).
15. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we (i) recommend no anticoagulation if the thrombus does not extend (Grade 1B), (ii) suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C), and (iii) recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).
16. In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT [catheter-directed thrombolysis] (Grade 2C).

    Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.
17. In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an inferior vena cava (IVC) filter (Grade 1B).
*18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS (Grade 2B).
*19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation (Grade 2C) or (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance (Grade 2C).

    Remarks: Ultrasound (US) imaging of the deep veins of both legs should be done to exclude proximal DVT. Clinical surveillance can be supplemented by serial US imaging of the proximal deep veins of both legs to detect evolving DVT (see text). Patients and physicians are more likely to opt for clinical surveillance over anticoagulation if there is good cardiopulmonary reserve or a high risk of bleeding.
*20. In patients with low-risk PE and whose home circumstances are adequate, we suggest treatment at home or early discharge over standard discharge (e.g., after the first 5 days of treatment) (Grade 2B).
21. In patients with acute PE associated with hypotension (e.g., systolic BP <90 mmHg) who do not have a high bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2B).
*22. In most patients with acute PE not associated with hypotension, we recommend against systemically administered thrombolytic therapy (Grade 1B).
*23. In selected patients with acute PE who deteriorate after starting anticoagulant therapy but have yet to develop hypotension and who have a low bleeding risk, we suggest systemically administered thrombolytic therapy over no such therapy (Grade 2C).

    Remarks: Patients with PE and without hypotension who have severe symptoms or marked cardiopulmonary impairment should be monitored closely for deterioration. Development of hypotension suggests that thrombolytic therapy has become indicated. Cardiopulmonary deterioration (e.g., symptoms, vital signs, tissue perfusion, gas exchange, cardiac biomarkers) that has not progressed to hypotension may also

alter the risk–benefit assessment in favor of thrombolytic therapy in patients initially treated with anticoagulation alone.

*24. In patients with acute PE who are treated with a thrombolytic agent, we suggest systemic thrombolytic therapy using a peripheral vein over CDT (Grade 2C).

Remarks: Patients who have a higher risk of bleeding with systemic thrombolytic therapy and who have access to the expertise and resources required to do CDT are likely to choose CDT over systemic thrombolytic therapy.

*25. In patients with acute PE associated with hypotension and who have (i) a high bleeding risk, (ii) failed systemic thrombolysis, or (iii) shock that is likely to cause death before systemic thrombolysis can take effect (e.g., within hours), if appropriate expertise and resources are available, we suggest catheter-assisted thrombus removal over no such intervention (Grade 2C).

Remarks: Catheter-assisted thrombus removal refers to mechanical interventions, with or without catheter directed thrombolysis.

*26. In selected patients with chronic thromboembolic pulmonary hypertension (CTEPH) who are identified by an experienced thromboendarterectomy team, we suggest pulmonary thromboendarterectomy over no pulmonary thromboendarterectomy (Grade 2C).

Remarks: Patients with CTEPH should be evaluated by a team with expertise in treatment of pulmonary hypertension. Pulmonary thromboendarterectomy is often lifesaving and life-transforming. Patients with CTEPH who are not candidates for pulmonary thromboendarterectomy may benefit from other mechanical and pharmacological interventions designed to lower pulmonary arterial pressure

27. In patients with acute upper extremity DVT (UEDVT) that involves the axillary or more proximal veins, we suggest anticoagulant therapy alone over thrombolysis (Grade 2C).

Remarks: Patients who (i) are most likely to benefit from thrombolysis (see text); (ii) have access to CDT; (iii) attach a high value to prevention of PTS; and (iv) attach a lower value to the initial complexity, cost, and risk of bleeding with thrombolytic therapy are likely to choose thrombolytic therapy over anticoagulation alone.

28. In patients with UEDVT who undergo thrombolysis, we recommend the same intensity and duration of anticoagulant therapy as in patients with UEDVT who do not undergo thrombolysis (Grade 1B).

*29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

Remarks: Recurrent VTE while on therapeutic-dose anticoagulant therapy is unusual and should prompt the following assessments: (1) reevaluation of whether there truly was a recurrent VTE; (2) evaluation of compliance with anticoagulant therapy; and (3) consideration of an underlying malignancy. A temporary switch to LMWH will usually be for at least 1 month.

*30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

Box 30.2 Clinical Trials

- **RE-LY trial** (Connolly *et al.*, 2009): a noninferiority study randomizing 18 000 patients with nonvalvular atrial fibrillation with moderate or high risk of stroke to either high-dose dabigatran, low-dose dabigatran, or warfarin. High-dose dabigatran was associated with reduced incidence of stroke 1.11% versus 1.69% (relative risk (RR) 0.66, 95% confidence interval (CI) 0.53–0.82, $P < 0.001$ for superiority) without any major bleeding increase 3.11% versus 3.36% ($P = 0.31$) when compared with warfarin. Even though it was a non-inferiority study, the final analysis showed dabigatran to be superior to warfarin. The US Food and Drug Administration approved the high-dose 150 mg BID for stroke prevention in nonvalvular atrial fibrillation. Subsequently, the lower dose of 75 mg BID was approved for use in patients with renal impairment, though not studied in trials. Both low-dose and high-dose dabigatran were associated with a statistically significant increase in rate of myocardial infarction (0.74% versus 0.72% versus 0.53%).
- **ROCKET AF trial** (Patel *et al.*, 2011): randomized 14 264 patients with nonvalvular atrial fibrillation to rivaroxaban or warfarin. *Results.* Stroke or embolism: intention-to-treat, 2.1 versus 2.4 events per 100 patient-years (hazard ratio (HR) 0.88, 95% CI 0.75–1.03; $P < 0.001$ for noninferiority, $P = 0.12$ for superiority); per protocol, 1.7 versus 2.2 events per 100 patient-years (HR 0.79, 95% CI 0.66–0.96, $P < 0.001$ for noninferiority). Major bleeding 5.6% versus 5.4% (nonsignificant).
- **ARISTOTLE trial** (Granger *et al.*, 2011): randomized 18 201 patients with nonvalvular atrial fibrillation and >1 risk factor for stroke to apixaban or warfarin. Median follow-up 1.8 years, apixaban was superior to warfarin for stroke or systemic embolism reduction (1.27% versus 1.60%, HR 0.79, 95% CI 0.66–0.95; $P = 0.01$ for superiority and $P < 0.001$ for noninferiority). It was also associated with less major bleeding (2.13% versus 3.09%).
- **ENGAGE AF trial** (Giugliano *et al.*, 2013): randomized 21 105 patients to either low-dose or high-dose edoxaban or warfarin in patients with nonvalvular atrial fibrillation. Primary outcome of stroke or embolism: 1.50% with warfarin versus 1.18% with high-dose edoxaban (HR 0.79, 97.5% CI 0.63–0.99; $P < 0.001$ for noninferiority) and 1.61% with low-dose edoxaban (HR 1.07, 97.5% CI 0.87–1.31; $P = 0.005$ for noninferiority). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (HR 0.80, 95% CI 0.71–0.91; $P < 0.001$) and 1.61% with low-dose edoxaban (HR 0.47, 95% CI 0.41–0.55; $P < 0.001$).

Box 30.3 April 2014 AHA/ACC/HRS Atrial Fibrillation Guidelines

See January *et al.* (2014).

- In patients with nonvalvular atrial fibrillation with prior stroke, transient ischemic attack, CHA_2DS_2–VASc score ≥2, recommend oral anticoagulation with:

  a) warfarin, goal INR 2–3 (class 1, level A)
  b) dabigatran (class 1, level B)
  c) rivaroxaban (class 1, level B)
  d) apixaban (class 1, level B).

- In patients with nonvalvular AF unable to maintain INR 2–3 with warfarin, recommend dabigatran, rivaroxaban, or apixaban (class 1, level C).
- In patients with nonvalvular AF with moderate or severe chronic kidney disease with CHA_2DS_2–VASc score >2, consider treatment with reduced doses of dabigatran, rivaroxaban, or apixaban, although safety has not been clearly demonstrated (class IIb, level C).
- In patients with ESRD, dabigatran and rivaroxaban are untested and not recommended (class III, level C).
- In patients with mechanical valve, do not use dabigatran (class III, level B).

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Aspirin and Antiplatelet Therapy

31

31.1. CJ is a 64-year-old female who is transferred to the catheterization laboratory for an emergent PCI following an ST elevation myocardial infarction (STEMI). Two drug-eluting stents are placed. Past medical history includes hypertension (HTN), hyperlipidemia, diabetes mellitus type 2, and gastroesophageal reflux disease. The patient's current medications include lisinopril, simvastatin, metformin, glipizide, and pantoprazole. Which of the following antiplatelets would be best to start in combination with aspirin 324 mg in this patient for prevention of stent thrombosis?

A. Clopidogrel 300 mg loading dose, then 75 mg PO daily
B. Clopidogrel 600 mg loading dose, then 75 mg PO daily
C. Prasugrel 60 mg loading dose, then 10 mg PO daily
D. Ticagrelor 180 mg loading dose, then 90 mg PO twice daily

31.2. What is the proposed rationale behind avoiding concomitant use of ticagrelor with aspirin doses above 100 mg per day?

A. Concomitant use of ticagrelor and aspirin >100 mg daily may result in decreased efficacy of aspirin
B. Concomitant use of ticagrelor and aspirin >100 mg daily may result in decreased efficacy of ticagrelor
C. Concomitant use of ticagrelor and aspirin >100 mg daily may result in intolerable gastrointestinal adverse events that may lead to drug discontinuation
D. Concomitant use of ticagrelor and aspirin >100 mg daily may result in increased hypersensitivity to aspirin

31.3. JP is a 60-year-old female who presents to your outpatient clinic for a check-up. She has been on long-term warfarin therapy for secondary stroke prevention with a history significant for atrial fibrillation and ischemic stroke (2011). From reviewing her electronic profile, it is apparent that JP's warfarin therapy has been difficult to maintain within therapeutic range. You would like to consider transitioning her to rivaroxaban as this is what her insurance company will cover. What is an appropriate method of transitioning JP from warfarin to rivaroxaban?

A. Discontinue warfarin; start rivaroxaban when international normalized ratio (INR) <2
B. Discontinue warfarin; start rivaroxaban when INR <3
C. Discontinue warfarin; start rivaroxaban after 3–5 days of discontinuation of warfarin
D. Start rivaroxaban 3–5 days before discontinuing warfarin

31.4. LT is a 48-year-old male presenting with a new STEMI who is transported from the medical intensive care unit to the catheterizatin laboratory for an emergent percutaneous coronary intervention (PCI). Labs from his current admission

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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observe notable increases in blood urea nitrogen/serum creatinine and decreased urine output, suggesting signs of acute kidney injury. Which of the following intravenous antiplatelet inhibitors would be best to use if the patient is found to require emergency coronary artery bypass grafting surgery?

A. Abciximab
B. Eptifibatide
C. Tirofiban
D. Cangrelor

31.5. RG is a 46-year-old male who presents with swelling, erythema, and pain in his right lower extremity. Past medical history includes HTN, diabetes, and recent hospitalization for a total knee arthroplasty. The patient further admits to a 10-year smoking history. Ultrasound and D-dimer tests suggest that a deep venous thrombosis (DVT) is highly likely. For convenience, the patient indicates that he refuses parenteral agents and wishes to be started on solely an oral anticoagulant for DVT treatment. Which of the following is the best oral anticoagulant for RG?

A. Warfarin
B. Dabigatran
C. Rivaroxaban
D. Edoxaban

31.6. GT is a 66-year-old male on long-term warfarin therapy with a past medical history of atrial fibrillation, HTN, diabetes mellitus type 2, gastroesophageal reflux disease, ischemic stroke, and cirrhosis. He presented to the hospital with sharp, crushing chest pain, shortness of breath, and fatigue. Cardiac enzymes are positive, and she is later diagnosed with non-STEMI and one drug-eluting stent is placed in the right coronary artery. What is the best antithrombotic therapy for GT post-PCI?

A. Stop warfarin. Start aspirin 81 mg daily and clopidogrel 75 mg daily for at least 12 months. Restart warfarin after 12 months
B. Continue warfarin (goal INR 2.0–2.5) lifelong. Start aspirin 81 mg daily and clopidogrel 75 mg daily for at least 12 months
C. Continue warfarin (goal INR 2.0–2.5) lifelong. Start aspirin 81 mg daily and clopidogrel 75 mg daily for 4 weeks. After 4 weeks, stop aspirin and continue clopidogrel 75 mg daily for at least 12 months
D. Continue warfarin (goal INR 2.0–3.0) lifelong. Start aspirin 81 mg daily for at least 12 months.

31.7. What is the rationale behind overlapping warfarin with a parenteral agent for at least 5 days when initiating antithrombotic therapy for venous thromboembolism treatment?

A. Warfarin's effects are dependent on the half-lives of the clotting factors it inhibits the production of
B. It takes approximately 5–10 days for warfarin to inhibit more clotting factors than are being produced
C. Double therapy with warfarin and a parental agent is necessary because it requires two antithrombotic agents to overcome the clot burden
D. A parenteral agent must be used to prevent formation of "white clots," whereas warfarin is used to prevent formation of "red clots"

31.8. MN is a 45-year-old male who is transferred to the coronary care unit post-PCI for a STEMI. Chart review indicates that appropriate doses of heparin, abciximab, and clopidogrel were used in the catheterization laboratory. Hours later, the patient begins to complain of rectal bleeding. Labs are drawn showing hemoglobin/hematocrit 6.2/26.5, platelets 22 000/mm^3, and INR 2.1. The complete blood count prior to PCI the day before was normal. Which of the following statements is true?

A. Pseudothrombocytopenia is a common occurrence of STEMI patients, and thus these labs are of little concern
B. Transient thrombocytopenia is a common adverse event associated with dosing doses of clopidogrel
C. Heparin-induced thrombocytopenia is likely since platelets have dropped suddenly and the patient is exhibiting signs of bleeding
D. Abciximab is associated with sudden profound thrombocytopenia

31.9. TJ is a 59-year-old male who presents with a new STEMI and is transferred to the catheterization laboratory where three drug-eluting stents are placed. Past medical history includes HTN, diabetes mellitus type 2, hyperlipidemia, and transient ischemic attack. Which of the following $P2Y_{12}$ receptor antagonists may not be used with aspirin 81 mg for dual antiplatelet therapy to prevent stent thrombosis?

A. Clopidogrel
B. Prasugrel
C. Ticagrelor
D. Cangrelor

31.10. Which of the following is a common adverse drug reaction to ticagrelor?

A. Leukocytosis
B. Hyperkalemia
C. Weight loss
D. Dyspnea

31.11. Which of the following antiplatelets would be most affected by initiation of phenytoin in a patient with seizures?

A. Aspirin
B. Clopidogrel
C. Prasugrel
D. Ticagrelor

31.12. Which of the follow glycoprotein IIb/IIIa inhibitors is associated with the longest observed platelet antagonism effects?

A. Abciximab
B. Eptifibatide
C. Tirofiban
D. Orbofiban

31.13. Which of the following antiplatelets requires a two-step CYP enzyme=dependent metabolism to become an active drug?

A. Aspirin
B. Clopidogrel
C. Prasugrel
D. Ticagrelor

31.14. Which of the following antiplatelets reversibly binds to platelet receptors on the platelet surface?

A. Aspirin
B. Clopidogrel
C. Prasugrel
D. Ticagrelor

31.15. WM is a 36-year-old male with a past medical history of uncontrolled HTN, diabetes mellitus type 2, and non-STEMI (2014, 2015). He presents to the emergency department with atrial fibrillation with rapid ventricular response, in which intravenous diltiazem is ordered for rate control. Recent labs show Na 135 mEq/L, K 4.1 mEq/L, Cl 100 mmol/L, CO_2 22 mmol/L, blood urea nitrogen 16 mg/dL, and serum creatinine 0.8 mg/dL. Most recent weight is 90 kg and height is 6 ft. The team is considering novel oral anticoagulants that may be started for primary stroke prevention. Which agents may not be used in this patient?

A. Dabigatran
B. Rivaroxaban
C. Apixaban
D. Edoxaban

Chapter 31

Answers

31.1. C. Prasugrel 60 mg loading dose, then 10 mg PO daily.

Clopidogrel, prasugrel, and ticagrelor may all be used in this patient for dual antiplatelet therapy; however, significant benefit was seen with prasugrel, particularly in patients with STEMI and diabetes mellitus.

31.2. B. Concomitant use of ticagrelor and aspirin >100 mg daily may result in decreased efficacy of ticagrelor.

Currently, there is a US black box warning to avoid use of aspirin >100 mg with ticagrelor.

31.3. B. Discontinue warfarin; start rivaroxaban when INR <3.

It should be noted that this specific recommendation is provided in Xarelto's package insert. To date, there is little evidence to show better efficacy and safety outcomes with one method of transition over another method. In contrast, when transitioning from warfarin to either apixaban or dabigatran, the novel oral anticoagulant may be started when INR <2.

31.4. D. Cangrelor.

Eptifibatide and tirofiban are renally cleared and require dose adjustment in renal impairment. Abciximab is metabolized via proteolytic cleavage and its clearance is not dependent on renal function, but its antiplatelet effects can last up to 7–14 days. Cangrelor is not dependent on renal or hepatic function and its antiplatelet effect wears off after 1 h.

31.5. C. Rivaroxaban.

Rivaroxaban is the only agent listed that may be started for DVT treatment and does not require overlap therapy with a parenteral agent. Warfarin, dabigatran, and edoxaban must be started concomitantly with at least 5 days of a parenteral agent, such as enoxaparin or heparin.

31.6. C. Continue warfarin (goal INR 2.0–2.5) lifelong. Start aspirin 81 mg daily and clopidogrel 75 mg daily for 4 weeks. After 4 weeks, stop aspirin and continue clopidogrel 75 mg daily for at least 12 months.

Triple versus dual antithrombotic therapy in patients with atrial fibrillation undergoing PCI remains a controversial topic. There are several different recommendations regarding optimal antithrombotic therapy after stent placement. However, answer "A" is incorrect because warfarin has been shown to be superior over aspirin plus clopidogrel to prevent thromboembolism. Answer "B" is not ideal because triple antithrombotic for over a year puts this patient at increased risk for bleeding. From the information provided in the question, this patient's HASBLED score is at least 3, indicating a high bleed risk. Answer "D" is incorrect because it has been shown that the combination of warfarin plus aspirin after PCI puts patients at increased risk for stent thrombosis.

31.7. A. Warfarin's anticoagulant effects are dependent on the half-lives of the clotting factors it inhibits the production of.

Warfarin inhibits the vitamin K-dependent synthesis of factors II, VII, IX, X and proteins C and S. Because the half-life of factor II may be as long as 48–72 h, it is recommended to overlap initial warfarin therapy with a faster-acting parenteral agent.

31.8. D. Abciximab is associated with sudden profound thrombocytopenia.

This is typically seen within minutes to hours of abciximab administration and is generally associated with bleeding.

31.9. B. Prasugrel.

Of the listed $P2Y_{12}$ receptor antagonists, prasugrel is contraindicated in patients with a history of transient ischemic attack or stroke due to increased risk of significant or fatal bleeding.

31.10. D. Dyspnea.

The incidence of dyspnea associated with the use of ticagrelor has been reported to be as high as 14%. This must be taken into consideration as it may result in noncompliance of the medication and has been found to contribute to hospital readmissions.

31.11. D. Ticagrelor.

Concomitant use of ticagrelor and strong cytochrome P450 (CYP)3A4 inducers, such as phenytoin, must be avoided as it may lead to decreased serum concentrations of ticagrelor.

31.12. A. Abciximab.

Dissociation of abciximab from the glycoprotein IIb/IIIa receptor occurs through proteolytic cleavage, resulting in slow elimination and consequently profound platelet antagonism that can last up to 12 h post-infusion. Platelet function may remain abnormal up to 7–14 weeks after infusion.

31.13. B. Clopidogrel.

Clopidogrel is metabolized extensively via two oxidative steps that are dependent predominantly on CYP2C19 to an active drug. CYP2C19 inhibitors, such as proton pump inhibitors, may lead to reduced serum concentrations of clopidogrel's active metabolite.

31.14. D. Ticagrelor.

Ticagrelor reversibly binds to the $P2Y_{12}$ receptors on the platelet surface, and thus recovery of platelet function is likely dependent on serum concentrations of ticagrelor. Aspirin irreversibly inhibits the COX-1 and COX-2 enzymes, and clopidogrel and prasugrel irreversibly bind to the $P2Y_{12}$ receptors. Thus, aspirin, clopidogrel, and prasugrel inhibit coagulation for the lifespan of the platelet.

31.15. D. Edoxaban.

Edoxaban should not be used in patients with a creatinine clearance (calculated using the Cockcroft–Gault equation) greater than 95 mL/min. In the ENGAGE AF-TIMI 48 trial, patients with creatinine clearance >95 mL/min observed increased rates of ischemic stroke with edoxaban 60 mg daily in comparison with warfarin.

Statistical Concepts

32

32.1. What is the arithmetic average of observations belonging to a continuous variable?

A. Mean
B. Median
C. Mode
D. None of the above

32.2. Which of the following are measures of dispersion around the mean?

A. Standard deviation (SD)
B. Variance
C. Range
D. Interquartile range (IQR)
E. All of the above

32.3. What proportion of values lie between 1SD around the mean in normal distribution?

A. 34%
B. 68%
C. 95%
D. 99%

32.4. Which of the options in Figure 32.4 is likely to have the smallest SD?

A. P
B. Q
C. R
D. All have same SD

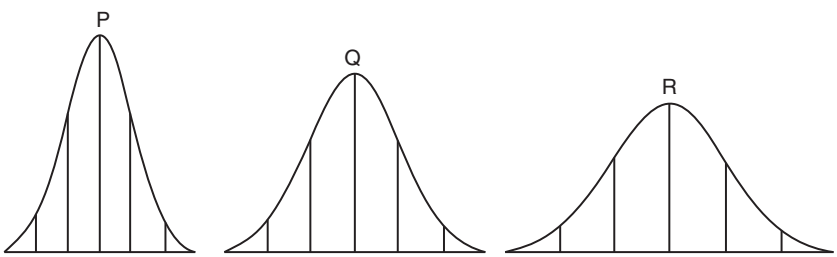

Figure 32.4

32.5. What would be the best test to decide if the mean age of two groups is different?

A. Unpaired *t*-test
B. Paired *t*-test
C. Chi squared test
D. Linear regression

32.6. A group of 40 patients is given a treatment. Measurements of heart rate are taken before and after. What would be the appropriate test to determine if the treatment was effective?

A. Unpaired *t*-test
B. Paired *t*-test
C. Chi squared test
D. Linear regression

Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.
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32.7. Treatment "A" cured 40% of the patients and treatment "B" cured 70% of the patients. What would be the appropriate test to determine if the two treatments are different?

A. Unpaired *t*-test
B. Paired *t*-test
C. Chi squared test
D. Linear regression

32.8. The relationship between age and E/A velocity ratio can be studied best with which test?

A. Unpaired *t*-test
B. Paired *t*-test
C. Chi squared test
D. Linear regression

32.9. Measures of population description include which of the following?

A. Measures of central tendency and dispersion
B. Mean and median
C. IQR and range
D. Median and SD

32.10. The effects of treatments A and B are compared on mortality in a randomized trial. At the end of 2 years the mortality with treatment A was 15% and treatment B was 12%. What was the relative risk reduction with treatment B?

A. 3%
B. 20%
C. 10%
D. 25%

32.11. In Question 32.10, what was the absolute reduction with B compared with A?

A. 3%
B. 20%
C. 10%
D. 25%

32.12. In Question 32.10, what was number needed to treat with B compared with A to save a life over 2 years?

A. 33
B. 7
C. 8
D. 100

32.13. A noninvasive diagnostic test to sort out a symptom is most productive in which patient groups?

A. Low probability of disease
B. Intermediate probability of disease
C. High probability of disease
D. All of these groups

32.14. A group 100 patients with documented disease and 100 without disease got a diagnostic test to detect that disease. Among those with disease 80 had a positive test, and among those without disease 20 had a positive test. What is the sensitivity of the test?

A. 80%
B. 20%
C. 40%
D. 50%

32.15. In the example in Question 32.14, what is the specificity of the test?

A. 80%
B. 20%
C. 40%
D. 50%

32.16. In the example in Questions 32.14 and 32.15, what is the positive predictive value?

A. 80%
B. 20%
C. 40%
D. 50%

32.17. In the example in Questions 32.14 and 32.15, what is the negative predictive value?

A. 80%
B. 20%
C. 40%
D. 50%

32.18. Which of the following measures are affected by pretest probability of disease prevalence in which the test is performed? More than one choice may be correct.

A. Sensitivity
B. Specificity
C. Positive predictive value
D. Negative predictive value
E. All of the above
F. None of the above

32.19. Which of the following test characteristics are ideal for screening of disease?

A. High sensitivity, low cost, minimal risk
B. High specificity, low cost, minimal risk
C. Either A or B
D. Neither A nor B

32.20. Which test characteristics are ideal for confirming the presence of a disease?

A. High sensitivity, low cost, minimal risk
B. High specificity, low cost, minimal risk
C. Either A or B
D. Neither A nor B

32.21. Which of the following will false positives increase with?

A. Higher pretest probability
B. Lower pretest probability
C. Intermediate pretest probability
D. None of the above

32.22. As the test positivity criterion gets more stringent (e.g., increasing ST depression requirement to 2 mm instead of 1 mm), which of the following will happen to the test?

A. Increase in sensitivity and specificity
B. Decrease in sensitivity and specificity
C. Decrease in sensitivity and increase in specificity
D. Increase in sensitivity and decrease in specificity

32.23. What is the positive likelihood ratio (LR+) of a test with 90% sensitivity and 90% specificity?

A. 1
B. 5
C. 9
D. 90

32.24. The pretest probability of disease based on risk factors and presentation in an individual is 10%. If the test described in Question 32.23 is positive, what would be the probability of disease?

A. 30%
B. 50%
C. 90%
D. 99%

32.25. You want to test if treatment "X" prolongs survival in a disease under study. What would be the best study design?

A. A double-blind randomized controlled clinical trial with power >0.8, an outcome adjudication committee, and safety monitoring committee

B. Single blind trial so that you can monitor to make sure that the patient is not harmed
C. A smaller trial with outcome surrogates
D. A nonrandomized trial with propensity score matching

32.26. In the trial in Question 32.25, 1800 patients were enrolled, 900 in the active treatment arm and 900 in the placebo arm. At 2 years there were 200 deaths in the treatment arm and 250 in the placebo arm. The groups are well balanced in terms of baseline characteristics. What is the best approach for outcome analysis?
A. Kaplan–Meier analysis
B. Student's *t*-test
C. Chi squared test
D. None of the above

32.27. A large registry of patients with aortic stenosis was analyzed to see if aortic valve replacement (AVR) would prolong survival in patients with severe aortic stenosis with low gradient and normal ejection fraction. What would be the best statistical approach?
A. Kaplan–Meier analysis
B. Cox regression analysis
C. Propensity score analysis
D. None of the above

32.28. Some of the measures of imprecision or uncertainty around point estimates include which of the following?
A. The 95% confidence interval
B. The SD
C. The standard error of the mean (SEM)
D. All of the above

32.29. Two treatments for BP reduction are tested. The range of systolic BPs qualifying for trial entry is 160–220 mmHg. What will be the best way to analyze the results?
A. Analysis of covariance (ANCOVA)
B. Paired *t*-test
C. Unpaired *t*-test
D. Kaplan–Meir analysis

32.30. Which of the following statements regarding subset analysis of trial results is not true?
A. All subgroup analysis should be prespecified in a statistical analysis plan
B. It is used to look at trends in prespecified subsets and interactions
C. Any deviation from expected trend is hypothesis generating rather than conclusive
D. When the trial is negative and one of the subsets shows a positive result, it confirms benefits in that subset because it is a randomized trial

Answers

32.1. A. Mean.

Median is the middle value, and mode is the most frequent value. All are measures of central tendency. In a normal distribution with number of observations >30, mean, median, and mode are expected to be the same. When the distribution is not normal, the mean, median, and mode are different, as shown in Figure 32.1.

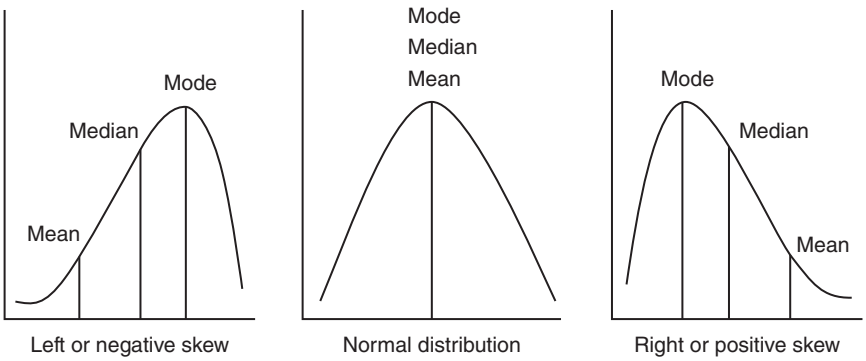


Figure 32.1

32.2. E. All of the above.

The SD is the root-mean-square deviation; that is, the deviation from the mean of each observation that is squared, summated, averaged, and square rooted. Variance is the square of the SD. Range is the difference between maximum and minimum observation. IQR is the difference between observations at the 75th percentile and 25th percentile. All are measures of spread of the observations.

32.3. B. 68%.

See Figure 32.3.

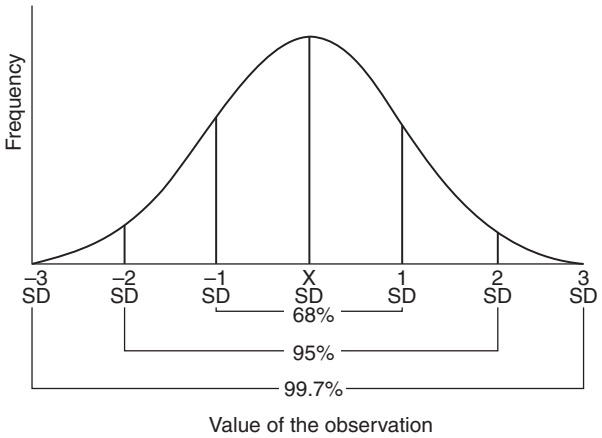


Figure 32.3

32.4. A. P.

A has the smallest SD. C has greater SD and dispersion.

32.5. A. Unpaired *t*-test.

This is the test to compare two group means. Total number and SD are needed for this calculation. Examples: comparisons of age of two groups or ejection fraction of two groups.

32.6. B. Paired *t*-test.

This is because the same group is compared and a change in the same group is analyzed; that is, delta heart rate. Example: heart rate at baseline and after exercise in a group of people.

32.7. C. Chi squared test.

This is used to compare proportions (and not means). Means are compared using a *t*-test.

32.8. D. Linear regression.

This is used to test the relationship between two continuous variable. For example, height and weight, age and blood pressure (BP), age and low-density lipoprotein cholesterol.

32.9. A. Measures of central tendency and dispersion.

A description of any population should include two measures: central tendency (mean, median, or mode) and dispersion (SD, variance, range, or IQR).

32.10. B. 20%.

Relative risk reduction is 3/15 or 20%.

32.11. A. 3%.

This is absolute and relative, over the period of study.

32.12. A. 33.

Treating 100 patients over 2 years saves three lives; hence, to save one life, you have to treat 33 patients.

32.13. B. Intermediate probability of disease.

A positive versus negative test gives the best separation in terms of post-test probability. Example: chest pain and stress test. See Figure 32.13. According to threshold theory of decision making, you test this population (Pauker and Kassirer, 1980).

32.14. A. 80%.

Sensitivity is the percentage of patients with disease who have a positive test. That is, true positives divided by all those with disease. The denominator is all those with disease. Among the 100 people with disease, 80 had positive tests (true positive, TP); 20 had negative tests despite the presence of disease (false negative, FN). Hence:

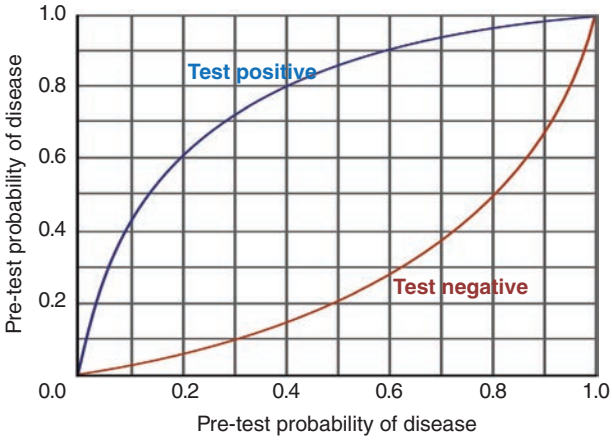
$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} = \frac{80}{100} = 80\%$$

Sensitivity is how well a positive test can detect disease.

32.15. A. 80%.

Specificity is the percentage of subjects without disease who have a negative test. That is, true negatives divided by all those without disease. The denominator is those *without* disease. Among the 100 people without disease, 80 had negative tests (true negative, TN); 20 had positive tests despite no disease (false positive, FP). Hence:

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} = \frac{80}{100} = 80\%$$



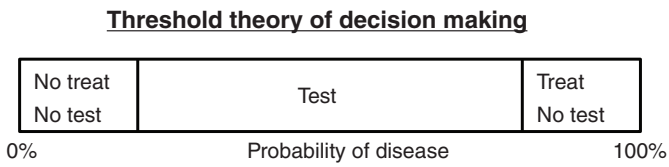


Figure 32.13

Specificity is how well a negative test can detect the absence of disease. To recap: TP is a positive test in those *with* disease ($n = 80$); FP is a positive test in those *without* disease ($n = 20$); TN is a negative test in those *without* disease ($n = 20$); FN is a negative test in those *with* disease ($n = 80$).

32.16. A. 80%.

Positive predictive value (PPV) is the true positives divided by all the positives:

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}} = \frac{80}{80 + 20} = 80\%$$

in this example and population, which is 50% *with* disease (100 out of 200).

32.17. A. 80%.

Negative predictive value (NPV) is the true negatives divided by all the negatives:

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}} = \frac{80}{80 + 20} = 80\%$$

in this example and population, which is 50% *without* disease (100 out of 200).

32.18. C and D. Positive predictive value and negative predictive value.

Sensitivity and specificity are unique test characteristics and are not affected by the population on which they are tested.

32.19. A. High sensitivity, low cost, minimal risk.

The goal is to avoid false negatives so that disease is not missed when it is present.

32.20. B. High specificity, low cost, minimal risk.

The goal is to avoid false positives so that the disease is not diagnosed when it is not present.

32.21. B. Lower pretest probability.

32.22. C. Decrease in sensitivity and increase in specificity.

A stringent criterion will make the test more specific but less sensitive.

32.23. C. 9.

$$\text{LR+} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{0.90}{1 - 0.90} = \frac{0.9}{0.1} = 9$$

An LR+ of 1 indicates that the post-test probability of disease will be higher than the pretest probability of disease.

32.24. C. 90%.

$$\text{Post-test probability} = \text{Pre-test probability} \times \text{LR+} = 10\% \times 9 = 90\%$$

32.25. A. A double blind randomized controlled clinical trial with power >0.8, an outcome adjudication committee, and safety monitoring committee.

This is the best design. With a single blind trial, bias could be introduced.

32.26. A. Kaplan–Meier analysis.

This takes into consideration not only number of deaths, but time to those events, unlike the chi squared test. As the groups are well balanced, adjustment for baseline characteristics using a Cox regression model is not needed.

32.27. C. Propensity score analysis.

Propensity score is a score developed through logistical regression analysis to estimate the probability of performing AVR even in those without AVR by using data from patients with AVR. Then, one can match the AVR population with those without AVR based on the propensity score to make sure that similar populations with and without AVR are compared. This type of analysis can remove about 80% of the bias that might have gone into treatment selection. Hence, it cannot replace a randomized trial, which evens out baseline characteristics of patients with and without AVR.

32.28. D. All of the above.

The 95% confidence interval encompasses the limit inside which the point estimates is likely to lie 95% of the time; this could be for the mean or single estimate. The mean plus/minus 2SD encompasses the 95% confidence interval for all observations in the sample, and the mean plus/minus 2SEM encompasses the 95% confidence interval for the mean of the sample. The SEM is smaller than the SD, and SEM = $\text{SD}/n^{1/2}$, where n is the number of observations.

32.29. A. Analysis of covariance (ANCOVA).

As the BP drop depends upon initial BP as well, this also has to be considered. Generally, the BP reduction is greater in those with higher baseline BPs than those with lower BP (regression to the mean). Treatment comparison as a function of baseline BP is analyzed by ANCOVA. The *t*-tests do not take baseline BP into analysis. Kaplan–Meir analysis is for time to events.

32.30. D. When the trial is negative and one of the subsets shows a positive result, it confirms benefits in that subset because it is a randomized trial.

This statement is wrong. By doing multiple subset analysis, one can find a result just by chance. If you do 20 subset analyses, one should be positive with a p value of 0.05 by chance alone. The other three statements are correct.

Reference

Pauker, S.G. and Kassirer, J.P. (1980) The threshold approach to clinical decision making. *The New England Journal of Medicine*, **302**(20): 1109–1117.

Genetics

33

33.1. Long QT3 is characterized by a defect in which of the following?
- **A.** *KCNQ1*-encoded slow component of the delayed rectifier potassium current (IKs)
- **B.** *KCNH2*-encoded rapid component of the delayed rectifier potassium current (IKr)
- **C.** *SCN5A*-encoded sodium channel
- **D.** None of the above

33.2. Brugada syndrome is associated with a mutation in which of the following?
- **A.** Voltage-gated sodium channel
- **B.** L-type calcium channel
- **C.** *SCN5A*-encoded sodium channel
- **D.** Potassium channel

33.3. Which of the following is not an indication for an implantable cardioverter-defibrillator (ICD) in a patient with long QT syndrome?
- **A.** Aborted cardiac arrest (regardless of genotype)
- **B.** Episode of ventricular tachycardia (VT) despite being on optimal medical therapy
- **C.** Symptomatic with a QTc of greater than 550 ms
- **D.** Symptomatic long QT2, diagnosed with cancer with a life expectancy of 6 months

33.4. A 40-year-old male is being evaluated for symptoms of syncope. He has had three episodes of witnessed syncope. His electrocardiogram (ECG) shows normal sinus rhythm with an incomplete right bundle branch pattern and coved ST segment elevation in the right precordial leads. His father was diagnosed with Brugada syndrome at age 30. His father's ECG was also characteristic for right bundle branch block pattern with coved ST elevation in the right precordial leads. What should his management at this time be?
- **A.** Reassurance and ask to come back for a follow-up in 1 year
- **B.** Beta-blocker therapy
- **C.** Implantable-defibrillator therapy
- **D.** Genetic testing

33.5. A 20-year-old female is being evaluated for syncope. She gives a history of passing out with exercise. Her maternal aunt, who is aged 35 years, also has a history of syncope. Her aunt's symptoms started soon after she delivered her first baby. She also had an aborted cardiac arrest and had an ICD placed. Her cousin, who is aged 25 years, also has a history of syncope. She passes out whenever she hears the doorbell or telephone ring. Her history and physical exam are otherwise unremarkable. What is the best therapy at this time?

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A. Implantable defibrillator
B. Beta-blocker therapy
C. Mexiletine
D. Reassurance and follow-up in 1 year

33.6. Which of the following regarding symptomatic catecholamine-induced polymorphic VT (CPVT) is not true?
A. Type 1 CPVT results from mutations in *RYR2*-encoded cardiac ryanodine receptor
B. Type 2 CPVT results from mutations in *CASQ2*-encoded calsequestrin
C. Characterized by stress-induced syncope with structurally normal heart and normal QT interval
D. First line of therapy is beta blocker or calcium channel blockers

33.7. The mechanism of medications that prolong QT as a cause for acquired long QT syndrome is which of the following?
A. *SCN5A*-encoded sodium channel
B. Voltage-gated sodium channel
C. Inhibition of *KCNH2*-encoded HERG potassium channel
D. Inhibition of calcium channel

33.8. What is the channel that is most commonly affected in long QT syndrome?
A. Potassium channel
B. Sodium channel
C. Calcium channel
D. Transient outward potassium channel

33.9. A 14-year-old male patient gives a history of near drowning. His ECG shows a QTc of 600 ms. What is the most likely cause?
A. Gain of function mutation in the *SCN5A*-encoded sodium channel
B. Loss of function mutation in the *SCN5A*-encoded sodium channel
C. Loss of function mutation in the *KCNQ1*-encoded IKs potassium channel
D. Gain of function mutation in the *KCNQ1*- encoded IKr potassium channel

33.10. A 20-year-old female has symptoms of syncope. Her 12-lead ECG shows notching of the T wave, with a corrected QT of 580 ms. What is the most common genotype associated with this?
A. LQT1
B. LQT2
C. LQT3
D. LQT5

Answers

33.1. C. *SCN5A*-encoded sodium channel.
Long QT3 channelopathy occurs due to a mutation in the *SCN5A*-encoded sodium channel (gain of function). Mutation in the *KCNQ1* (IKs) channel is associated with long QT1, and mutation in the *KCNH2* (IKr) channel is associated with long QT2 syndrome.

33.2. C. *SCN5A*-encoded sodium channel.
Brugada syndrome occurs due to a mutation in the *SCN5A*-encoded sodium channel, and is a loss of function mutation. It should be noted that a gain of function in the same *SCN5A*-encoded sodium channel results in LQT3 syndrome.

33.3. D. Symptomatic long QT2, diagnosed with cancer with a life expectancy of 6 months.

ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year. ICD therapy is otherwise indicated in patients with long QT syndrome in the following situations: (1) In aborted sudden death, regardless of the genotype; and as a secondary prevention measure in (2) breakthrough cardiac events such as VT/ventricular fibrillation, despite being on optimal medical therapy, and (3) intolerance to primary medical therapy (Epstein *et al.*, 2008).

33.4. C. Implantable-defibrillator therapy.

The patient in question probably has Brugada syndrome. His father was diagnosed with Brugada syndrome at a young age. The patient has an ECG showing a type I pattern (coved ST elevation), has multiple episodes of syncope, and has a first-degree relative with Brugada syndrome. It is reasonable to give the patient an ICD (class IIa, level of evidence C) (Epstein *et al.*, 2008).

33.5. B. Beta-blocker therapy.

The patient in question probably has long QT1 syndrome. Given her symptoms of syncope she should be started on beta blockers. It is reasonable to consider an ICD if she continues to have symptoms or breakthrough cardiac events on beta-blocker therapy. Mexiletine is a drug of choice in treating long QT3 patients.

33.6. D. First line of therapy is beta blocker or calcium channel blockers.

This is not true. Pharmacotherapy with either beta blockers or calcium channel blockers is not protective and all symptomatic CPVT patients should receive an ICD.

33.7. C. Inhibition of *KCNH2*-encoded HERG potassium channel.

Most of the medications that prolong QT act by inhibiting the *KCNH2*-encoded HERG potassium channel.

33.8. A. Potassium channel.

33.9. C. Loss of function mutation in the *KCNQ1*-encoded IKs potassium channel.

This patient probably has congenital long QT1 syndrome. His symptoms occurred while exercising and his ECG shows an abnormal prolongation of QT interval. Long QT1 is associated with a loss of function mutation in the *KCNQ1*-encoded IKs potassium channel.

33.10. B. LQT2.

This patient probably has congenital long QT2 syndrome. She has prolongation of her QTc and has notching of her T waves, which is usually seen in LQT2. LQT1 is usually associated with broad-based T waves, and LQT3 is associated with a long isoelectric ST segment with a normal T wave morphology.

Reference

Epstein, A.E., DiMarco, J.P., Ellenbogen, K.A., *et al.* (2008) ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary. *Circulation*, **117**: 2820–2840.

Cardiac Emergencies and Resuscitation 34

34.1. After endotracheal (ET) intubation during witnessed cardiac arrest, which of the following are useful to confirm correct placement of ET tube.

- **A.** Chest rise with breathing
- **B.** Auscultation of abdomen and both lung fields
- **C.** Chest X-ray
- **D.** Waveform capnography
- **E.** All of the above

34.2. What does five-point auscultation after ET intubation consist of?

- **A.** Auscultation of epigastrium, both lung apices, and both axillary areas
- **B.** Auscultation of mitral, tricuspid, pulmonary, aortic, and Erb's areas
- **C.** Epigastric area, front of both chests, backs of both chests
- **D.** None of the above

34.3. In Question 34.1, which is most reliable?

- **A.** Chest rise with breathing
- **B.** Auscultation of abdomen and both lung fields
- **C.** Chest X-ray
- **D.** Waveform capnography
- **E.** All of the above

34.4. With waveform capnography, what is the normal expected p_{CO_2}?

- **A.** 35–45 mmHg
- **B.** 20 mmHg
- **C.** <10 mmHg
- **D.** 0 mmHg

34.5. With waveform capnography, what is the expected p_{CO_2} during adequate cardiopulmonary resuscitation (CPR) in a code setting?

- **A.** 35–45 mmHg
- **B.** 20 mmHg
- **C.** <10 mmHg
- **D.** 0 mmHg

34.6. With waveform capnography, what is the expected p_{CO_2} during CPR in a code setting with a dislodged ET tube?

- **A.** 35–45 mHg
- **B.** 20 mmHg
- **C.** <10 mmHg
- **D.** 0 mmHg

34.7. Which of the following statements are correct for a colorimetric exhaled CO_2 detector?

- **A.** It is not as accurate as capnography
- **B.** Purple means there is CO_2
- **C.** Yellow means no oxygen
- **D.** All are correct

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34.8. Which of the following are contraindications for an esophageal-tracheal tube?

A. Height <4 ft
B. Age <16 years
C. Intact gag reflex
D. Ingestion of caustic
E. All of the above
F. None of the above

34.9. Which of the following statements regarding ventilation during cardiac arrest are correct?

A. 30 : 2 ratio with bag-mask device
B. 8–10 breaths per minute with advanced airway for a patient with cardiac arrest
C. 10–12 breaths per minute with advanced airway for a patient with pure respiratory arrest
D. None of the above
E. All of the above

34.10. For witnessed out-of-hospital cardiac arrest due to ventricular fibrillation, what is the appropriate energy level for defibrillation?

A. 120–200 J with a biphasic shock device
B. 360 J with a monophasic shock device
C. 2–4 J/kg body weight for a child
D. All of the above
E. None of the above

34.11. In a cardiac arrest situation with no access for drug delivery, what is the preferred access?

A. Peripheral intravenous (IV) device
B. Central line
C. ET tube insertion
D. Intraosseous (IO) access

34.12. For ET drug delivery, which of the following statements are accurate?

A. Amount of drug should be about twice as much as IV
B. Dilute in 5–10 cm^3 of fluid
C. Epinephrine, vasopressin, and lidocaine can be given via ET route during cardiac arrest situation
D. All are correct
E. None are correct

34.13. Which of the following can IO access be obtained from?

A. Medial malleolus
B. Upper tibia
C. Iliac crest
D. Sternum
E. All of the above
F. None of the above.

34.14. Which of the following are contraindications for basic life support and advanced cardiopulmonary life support?

A. Rigor mortis
B. Advance directives not to resuscitate
C. Clinical futility due to end-stage disease processes
D. Attempt to resuscitate puts practitioner at risk
E. All of the above

34.15. What is the desired depth of chest compression in adult CPR?
- **A.** ≥2 in
- **B.** 1.5–2 in
- **C.** Enough to produce a pulse
- **D.** Any of the above
- **E.** None of the above

34.16. What is the location for chest compression in CPR?
- **A.** Mid sternum
- **B.** Upper sternum
- **C.** Lower sternum
- **D.** Xiphoid process

34.17. What is the desired rate of chest compression in adult CPR?
- **A.** At least 100/min
- **B.** 80–100/min
- **C.** 60/min in adult, 100/min in a child, 120/min in an infant
- **D.** All of the above

34.18. How often should you rotate the compressors during CPR?
- **A.** 2 min
- **B.** 2–5 min
- **C.** When tired
- **D.** As needed

34.19. What is the desired rate of chest compression in a child?
- **A.** At least 100/min
- **B.** At least 120/min
- **C.** At least 140/min
- **D.** None of the above

34.20. What is the first thing to do when an unresponsive, nonbreathing person is found?
- **A.** Activate emergency response
- **B.** Start CPR
- **C.** Feel the pulse
- **D.** Defibrillate the patient

34.21. In two-rescuer CPR, what is the optimal compression-to-ventilation ratio?
- **A.** 15 : 2
- **B.** 30 : 2
- **C.** 5 : 1
- **D.** 10 : 2

34.22. What do signs of adequate CPR include?
- **A.** End-tidal CO_2 >10 mmHg
- **B.** Diastolic blood pressure (BP) >20 mmHg
- **C.** Both A and B
- **D.** Neither A nor B

34.23. What is the dose of epinephrine in cardiac arrest?
- **A.** 1 mg every 3–5 min rapid push
- **B.** 0.5 mg every 3–5 min rapid push
- **C.** 1 mg every 3–5 min over 2 min
- **D.** 0.5 mg every 3–5 min over 2 min

34.24. What dose of amiodarone can be used in fibrillatory arrest after the first dose of epinephrine?
- **A.** 300 mg IV push
- **B.** 150 mg IV push
- **C.** 300 mg IV slow push over 10 min
- **D.** 150 mg IV slow push over 10 min

34.25. What does a partial pressure of end-tidal CO_2 of >40 mmHg during CPR indicate?
- **A.** Adequate chest compression
- **B.** Adequate ventilation
- **C.** Return of spontaneous circulation
- **D.** All of the above

34.26. What is the dose of IV/IO vasopressin during cardiac arrest?
- **A.** 40 units
- **B.** 80 units
- **C.** 1 unit per kilogram body weight
- **D.** All are correct

34.27. IV/IO vasopressin during cardiac arrest can be substituted for which of the following?
- **A.** First dose of epinephrine
- **B.** Second dose of epinephrine
- **C.** First or second dose of epinephrine
- **D.** After the second dose of epinephrine

34.28. What is the O_2 saturation goal after return of spontaneous circulation?
- **A.** >90%
- **B.** ≥94%
- **C.** 100%
- **D.** None of the above

34.29. Hypotension post arrest is defined as:
- **A.** Systolic BP <90 mmHg or mean arterial pressure <65 mmHg
- **B.** Systolic BP<90 mmHg
- **C.** Systolic BP <90 mmHg and mean arterial pressure <65 mmHg
- **D.** Diastolic BP <40 mmHg

34.30. What is the appropriate volume of IV saline or Ringer's lactate bolus in a hypotensive patient?
- **A.** 250 cm^3
- **B.** 500 cm^3
- **C.** 1–2 L
- **D.** None of the above

34.31. What is the appropriate dose of dopamine infusion in a hypotensive patient?
- **A.** 2–10 μg/(kg min)
- **B.** 7–35 μg/(kg min)
- **C.** 0.1–0.5 μg/(kg min)
- **D.** None of the above

34.32. What is the appropriate dose of epinephrine infusion in a hypotensive patient?
- **A.** 2–10 μg/(kg min)
- **B.** 7–35 μg/(kg min)
- **C.** 0.1–0.5 μg/(kg min)
- **D.** B and C

34.33. What is the appropriate dose of norepinephrine infusion in a hypotensive patient?
- **A.** 2–10 μg/(kg min)
- **B.** 7–35 μg/(kg min)
- **C.** 0.1–0.5 μg/(kg min)
- **D.** B and C

34.34. The initial drug therapy for hypotensive, bradycardic patient includes which of the following?
- **A.** Atropine
- **B.** Dopamine infusion
- **C.** Epinephrine infusion
- **D.** Any of the above

34.35. What is the therapy for VT with no pulse?
- **A.** Synchronized cardioversion
- **B.** Defibrillation (nonsynchronized)
- **C.** Lidocaine bolus IV
- **D.** Any of the above

34.36. The Cincinnati prehospital stroke scale components include which of the following?
- **A.** Facial droop
- **B.** Arm drift
- **C.** Abnormal, slurred speech
- **D.** All of the above

34.37. Which of the following are components of the Glasgow coma scale?
- **A.** Eye opening
- **B.** Best verbal response
- **C.** Best motor response
- **D.** All of the above

34.38. For ischemic stroke with no contraindications, IV recombinant tissue plasminogen activator can be given in which of the following cases?
- **A.** Onset of symptoms <3 h
- **B.** Onset of symptoms <6 h
- **C.** Onset of symptoms <12 h
- **D.** Woke up with stroke symptoms after 8 h of sleep

34.39. Recombinant tissue plasminogen activator in acute stroke is contraindicated in which of the following situations?
- **A.** Head trauma or stroke in the last 3 months
- **B.** Systolic BP >185 mmHg or diastolic BP >110 mmHg
- **C.** International normalized ratio >1.7
- **D.** Platelet count <100 000/mm^3
- **E.** Any of the above

34.40. Contraindications for nitroglycerin in acute coronary syndrome include which of the following?
- **A.** Inferior MI with Kussmaul sign
- **B.** Systolic BP <90 mmHg
- **C.** Use of Viagra® (sildenafil) in the last 24 h
- **D.** Use of Cialis® (tadalafil) in the last 48 h
- **E.** All of the above
- **F.** None of the above

Answers

34.1. E. All of the above.

34.2. A. Auscultation of epigastrium, both lung apices, and both axillary areas.
This is to confirm correct ET tube placement.

34.3. D. Waveform capnography.
It has a sensitivity and specificity of 100%.

34.4. A. 35–45 mmHg.

34.5. B. 20 mmHg.

34.6. D. 0 mmHg.

34.7. D. All are correct.

34.8. E. All of the above.

34.9. E. All of the above.

34.10. D. All of the above.

34.11. A. Peripheral intravenous (IV) device.
With central cannulation, CPR may have to be halted temporarily and there is risk of pneumothorax – hence not desirable.

34.12. D. All are correct.

34.13. E. All of the above.

34.14. E. All of the above.

34.15. A. ≥2 in.

34.16. C. Lower sternum.

34.17. A. At least 100/min.

34.18. A. 2 min.

34.19. A. At least 100/min.

34.20. A. Activate emergency response.

34.21. A. 15 : 2.

34.22. C. Both A and B.

34.23. A. 1 mg every 3–5 min rapid push.

34.24. A. 300 mg IV push.

34.25. C. Return of spontaneous circulation.

34.26. A. 40 units.

34.27. C. First or second dose of epinephrine.

34.28. B. ≥94%.

34.29. A. Systolic BP <90 mmHg or mean arterial pressure <65 mmHg.

34.30. C. 1–2 L.

34.31. A. 2–10 μg/(kg min).

34.32. D. B and C.

34.33. D. B and C.

34.34. D. Any of the above.

34.35. B. Defibrillation (nonsynchronized).

34.36. D. All of the above.

If any of three are present, the probability of a stroke is 72%.

34.37. D. All of the above.

Total possible is 15. For eye opening: spontaneous 4, in response to speech 3, in response to pain 2, none 1. For best verbal response: oriented conversation 5, confused conversation 4, inappropriate words 3, incomprehensible sounds 2, none 1. For best motor response: obeys 6, localizes 5, withdraws 4, abnormal flexion 3, abnormal extension 2, none 1. Score 14–15 is mild dysfunction; ≤10 is severe dysfunction.

34.38. A. Onset of symptoms <3 h.

34.39. E. Any of the above.

34.40. E. All of the above

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Cardiology Board Review, First Edition. Ramdas G. Pai, Padmini Varadarajan and Sudha M. Pai.

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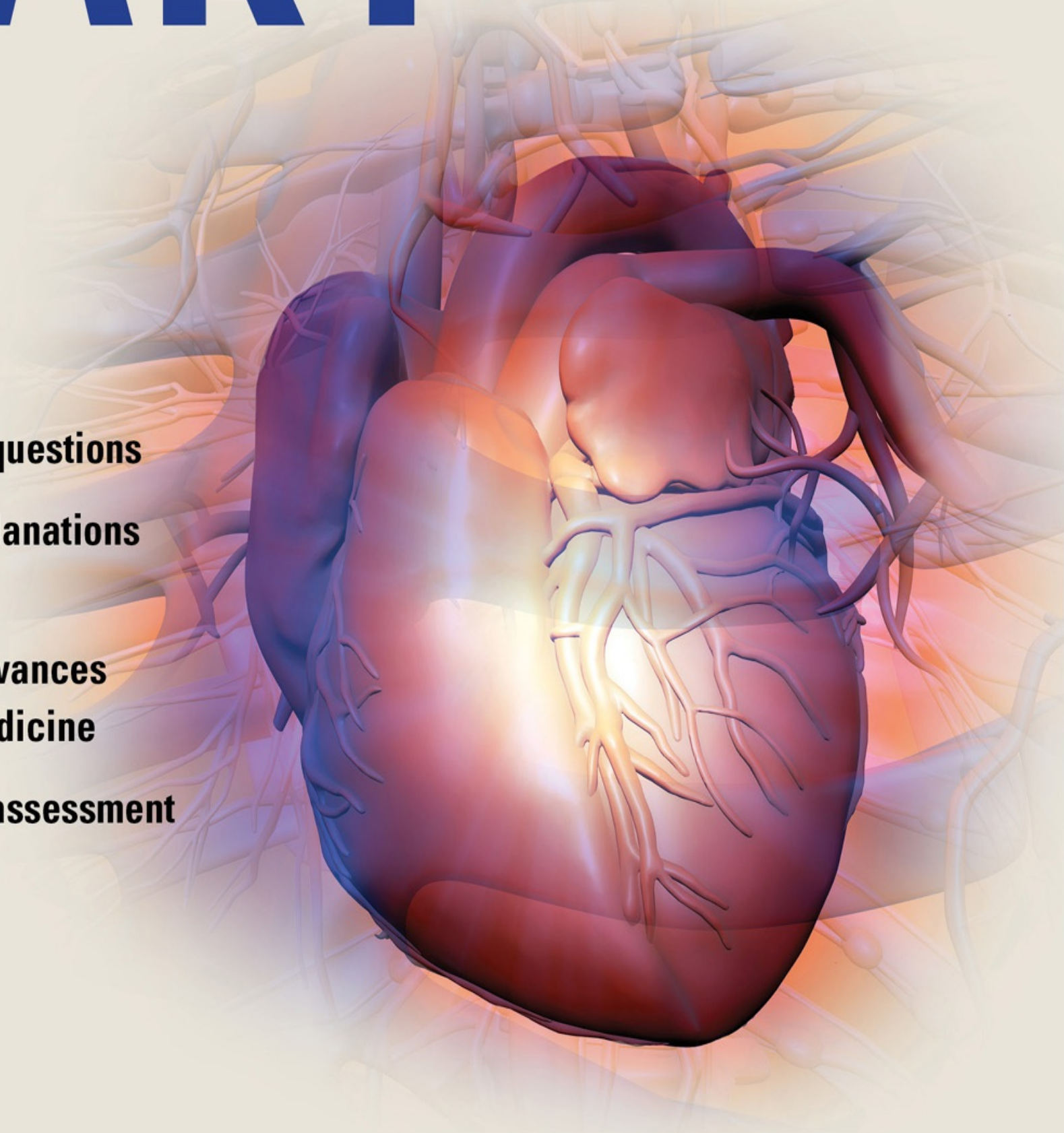
CARDIOLOGY BOARD REVIEW AND SELF-ASSESSMENT

A COMPANION GUIDE TO

HURST'S THE HEART



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CARDIOLOGY BOARD REVIEW AND SELF-ASSESSMENT: A COMPANION GUIDE TO HURST'S THE HEART

For use with the 14th edition of HURST'S THE HEART

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ISBN: 978-1-26-002616-0
MHID: 1-26-002616-7

The material in this eBook also appears in the print version of this title: ISBN: 978-1-26-002615-3, MHID: 1-26-002615-9.

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PREFACE

Cardiology Board Review and Self-Assessment is an all-inclusive study guide written to complement the 14th Edition of *Hurst's The Heart*. Edited by Drs. Valentin Fuster, Robert A. Harrington, Jagat Narula, and Zubin J. Eapen, the 14th Edition of *Hurst's The Heart* is an exhaustive and thorough state-of-the-art review of the entire field of cardiovascular medicine.

Cardiology Board Review contains over 1100 questions and answers presented in a multiple-choice format. Each of the 112 chapters of *Hurst's The Heart* is represented in *Cardiology Board Review* with 10 multiple-choice questions. Detailed answers are provided for each question including not only an explanation of why the correct answer is correct but also why incorrect answers are incorrect. Questions and answers correspond to appropriate sections of *Hurst's The Heart* and include tables, figures, and references. The more than 1100 questions presented in *Cardiology Board Review* span the depth and breadth of the fascinating field of cardiovascular medicine.

Cardiology Board Review is designed to be a study guide for individuals preparing to take the Subspecialty Examination in Cardiovascular Disease given by the American Board of Internal Medicine. Thus, *Cardiology Board Review* will be of particular interest to cardiology fellows preparing to take the board examination for the first time and for practicing cardiologists preparing to take the board examination as part of their recertification process. *Cardiology Board Review* will also be of interest to medical students, residents, fellows, practicing physicians, and other health care professionals who wish to advance their knowledge of cardiovascular medicine.

The current generation of health care professionals increasingly obtains their knowledge from nontraditional formats. To that end, *Cardiology Board Review and Self-Assessment* is available in multiple electronic formats in addition to the traditional print format. The book will be available in print, e-book, and online on McGraw-Hill Education's cardiology web site at www.AccessCardiology.com.

It has been my distinct pleasure to work with four coauthors while preparing *Cardiology Board Review*: Drs. Jonathan Afilalo, Jacqueline E. Joza, Ravi Karra, and Patrick R. Lawler. Each of us contributed original questions and answers corresponding to our particular areas of expertise. We would like to thank the members of the editorial and production departments at McGraw-Hill Education with whom we worked, including Karen Edmonson, Robert Pancotti, and Shivani Salhotra. We would also like to acknowledge the contributions and assistance of a number of other individuals, including Maria L. Alcaraz, Emmanuel E. Egom, Inna Ermeichouk, Caroline Franck, and Sarah B. Windle. Finally, on behalf of myself and my coauthors, we would like to express thanks to our families and colleagues for their encouragement and forbearance during the many months it took to prepare this study guide.

Taking care of patients with cardiovascular disease is an honor and a privilege. Many of these patients have life-threatening conditions that require advanced knowledge and highly technical skills. It is our responsibility, as health care professionals, to ensure that our knowledge and skills match the needs of our patients. It is our hope that you will find *Cardiology Board Review and Self-Assessment* to be an essential and valuable tool in your study of the ever expanding and always fascinating field of cardiovascular medicine.

Mark J. Eisenberg, MD, MPH

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SECTION 1

Cardiovascular Disease: Past, Present, and Future

CHAPTER 1

A History of the Cardiac Diseases, and the Development of Cardiovascular Medicine as a Specialty

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

1-1. All of the following were experimental questions asked by William Harvey *except*:

A. What is the relationship of the motion of the auricle to the ventricle?
B. Do the arteries distend because of the propulsive force of the heart?
C. What purpose is served by the orientation of the cardiac and venous valves?
D. How much blood is present, and how long does its passage take?
E. All were questions asked by William Harvey

1-2. What were the primary component(s) of the clinical examination until the 17th century?

A. Palpating the pulse
B. Palpating the pulse and inspecting the urine
C. Palpating the pulse and percussion
D. Palpating the pulse and auscultation
E. Palpating the pulse, percussion, and auscultation

1-3. Which physician received the Nobel Prize for his work in electrophysiology?

A. Albert von Kölliker
B. Heinrich Müller
C. Augustus Waller
D. Willem Einthoven
E. Thomas Lewis

1-4. Who performed the first cardiac catheterization in a human?

A. Werner Forssmann
B. Claude Bernard
C. Dickinson Richards
D. Etienne Jules Marey
E. André Cournand

1-5. From which Latin word is the term *angina* appropriated?

A. Pain
B. Stress
C. Strangulation
D. Anxiety
E. Discomfort

1-6. Before the defibrillator and coronary care units, the in-hospital mortality associated with acute myocardial infarction was approximately:

A. 10%
B. 15%
C. 20%

D. 30%
E. 40%

1-7. Who first described audible heart murmurs?

A. James Hope
B. John Mayow
C. William Cowper
D. René Laennec
E. Raymond Vieussens

1-8. Which procedure pioneered by Helen Taussig and Alfred Blalock was a pivotal breakthrough in thinking about congenital heart abnormalities?

A. Balloon atrial septostomy
B. Subclavian-pulmonary artery shunt
C. Closure of atrial septal defect
D. Closure of ventricular septal defect
E. Stenting of patent ductus arteriosus

1-9. Who invented the first device for measuring blood pressure?

A. Etienne Jules Marey
B. Jean Poiseuille
C. Scipione Riva-Rocci
D. Karl von Vierordt
E. Carl Ludwig

1-10. Which of the following statements about hypertension is *false*?

A. In 1913, Janeway showed that patients, once diagnosed with hypertensive heart disease and symptoms, lived an average of 4 to 5 years
B. Until the latter half of the 20th century, the asymptomatic state of most patients with hypertension and a prevalent view that lowering the blood pressure would be deleterious to the kidney and brain lulled most physicians into accepting the condition as being normally associated with aging
C. Effective oral treatment was available before President Franklin Roosevelt's death in 1945 from severe hypertension
D. In the 1970s, reports from the Framingham Heart Study showed hypertension to be a major contributing cause to stroke, heart attack, and heart and kidney failure
E. Richard Bright's 1836 discovery of the relationship of cardiac hypertrophy and dropsy to shrunken kidneys introduced the kidneys as a cause of heart failure long before hypertension was known

ANSWERS

1-1. **The answer is E.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Starting in 1603, Harvey dissected the anatomy and observed the motion of the cardiac chambers and the flow of blood in more than 80 species of animals. His experimental questions "to seek unbiased truth" can be summarized in the following questions: What is the relationship of the motion of the auricle to the ventricle? Which is the systolic and which is the diastolic motion of the heart? Do the arteries distend because of the propulsive force of the heart? What purpose is served by the orientation of the cardiac and venous valves? How does blood travel from the right ventricle to the left side of the heart? Which direction does the blood flow in the veins and the arteries? How much blood is present, and how long does its passage take? After many experiments and without knowledge of the capillary circulation of the lungs, which was not known until 1661, Harvey stated, "It must of necessity be concluded that the blood is driven into a round by a circular motion and that it moves perpetually; and hence does arise the action or function of the heart, which by pulsation it performs." This was published in 1628 as *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus*.[1] This revolutionary concept eventually became accepted in Harvey's lifetime and remains the foundation of our understanding of the purpose of the heart.

1-2. **The answer is B.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Until the 17th century, the clinical examination consisted of palpating the pulse and inspecting the urine to reveal disease and predict prognosis. Percussion was first suggested in 1761 by Leopold Auenbrugger, a Viennese physician, who published a book proposing "percussion of the human thorax, whereby, according to the character of the particular sounds thence elicited, an opinion is formed of the internal state of that cavity."[2] It was reintroduced by Jean-Nicolas Corvisart in early 19th-century France and became an essential addition to the chest examination until it was mostly supplanted by the chest x-ray. While auscultation of the chest was first practiced by Hippocrates (460-370 BC), who applied his ear directly to the chest, it was not until the mid-19th century that the stethoscope (first invented by René Laennec in Paris in 1816) moved auscultation to the forefront of the clinical

examination.[3,4]

1-3. **The answer is D.** *(Hurst's the Heart, 14th Edition, Chap. 1)* In 1856, von Kölliker and Müller demonstrated that the heart also produced electricity. Augustus Waller, with a capillary electrometer device (1887), detected cardiac electricity from the limbs, a crude recording that he called an "electrogram." Willem Einthoven, a physiologist in Utrecht, devised a more sensitive string galvanometer (1902), for which he received the Nobel Prize, and the modern electrocardiogram was born. Initially weighing 600 lb and requiring five people to operate, the three-lead electrocardiograph would eventually become portable, 12 leads, routine, and capable of providing both static and continuous recordings of cardiac rhythm.[5] With the electrocardiogram, the activation and sequence of stimulation of the human heart could now be measured, and the anatomic basis for the conduction system confirmed. Thomas Lewis in London was the first to realize its great potential, beginning in 1909, and his books on disorders of the heartbeat became essential for aspiring electrocardiographers.[2,6]

1-4. **The answer is A.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Claude Bernard in 1844 was the first to insert a catheter into the hearts of animals to measure temperature and pressure.[2] In the early 1860s, Auguste Chauveau, a veterinary physiologist, and Etienne Jules Marey, inventor of the sphygmograph, collaborated to develop a system of devices called sounds, forerunners of the modern cardiac catheter, which they used to catheterize the right heart and left ventricle of the horse.[7] Cardiac catheterization in humans was thought an inconceivable risk until Werner Forssmann, a 29-year-old surgical resident in Germany, performed a self-catheterization in 1929.[8,9] Interested in discovering a method of injecting adrenaline to treat cardiac arrest, Forssmann passed a ureteral catheter into his antecubital vein and confirmed its right atrial position using x-ray. The next year he tried to image his heart using an iodide injection. However, he was reprimanded by superiors and did not experiment further. Catheterization began in earnest in the early 1940s in New York and London. André Cournand and Dickinson Richards at Bellevue, interested in respiratory physiology, developed and demonstrated the safety of complete right heart catheterization, for which they shared the Nobel Prize with Forssmann in 1956.[7,10]

1-5. **The answer is C.** *(Hurst's the Heart, 14th Edition, Chap. 1)* On July 21, 1768, William Heberden presented "Some Account of a Disorder of the Breast" to the Royal College of Physicians, London: "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare. The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris."[2,11] Heberden appropriated the term *angina* from the Latin word for strangling. His classic account marks the beginning of our appreciation of coronary artery disease and myocardial ischemia. Edward Jenner and Caleb Parry were the first to suspect a coronary etiology, which Parry published in 1799. Allan Burns, in Scotland, likened the pain of angina pectoris to the discomfort brought about by walking with a tight ligature placed on a limb (1809), a prescient concept that remains relevant today.

1-6. **The answer is D.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Before the defibrillator and coronary care units, the in-hospital mortality associated with acute myocardial infarction was approximately 30%. With the development of the defibrillator by William Kouwenhoven, Claude Beck and Paul Zoll were able to prove that rescue of cardiac arrest victims was possible. Beck's concept that "the heart is too good to die" instilled optimism into the care of coronary patients and aggressiveness into their providers. Myocardial infarction was no longer a disease to be watched but rather one that might benefit from aggressive therapeutic interventions. Zoll reported closed chest defibrillation in 1956 and cardioversion of ventricular tachycardia in 1960. The monitoring of patients in close proximity to skilled nursing personnel who could perform cardiopulmonary resuscitation was a logical next step suggested by Desmond Julian in 1961.

1-7. **The answer is D.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Valvular pathology was described in the 17th and 18th centuries; however, Laennec was the first to describe audible heart murmurs, calling them "blowing, sawing, filing, and rasping."[3] Originally, he attributed the noises to actual valvular disease, but he later decided that they were caused by spasm or contraction of a cardiac chamber. James Hope in England was the first to classify valvular murmurs in *A Treatise on the Diseases of the Heart and Great Vessels* (1832).[12] He interpreted physical findings in early physiologic terms and provided detailed pathologic correlations.[13] Constriction of the mitral valve was recorded by John Mayow (1668) and Raymond Vieussens (1715); the latter also recognized that this condition could cause pulmonary congestion.[14] The presystolic murmur of mitral stenosis was described by Bertin (1824), timed as both early diastolic and presystolic by Williams (1835), and placed on firmer grounds by Fauvel (1843) and Gairdner (1861). Aortic stenosis was first described pathologically by Rivière (1663), and Laennec pointed out that the aortic valve was subject to ossification (1819).[15] Corvisart showed an astute grasp of the natural history of aortic stenosis (1809). Early descriptions of aortic regurgitation were by William Cowper (1706) and Raymond Vieussens (1715),[16] whereas Giovanni Morgagni recognized the hemodynamic consequences of aortic regurgitation (1761). In 1832, Corrigan provided his classic description of the arterial pulse and murmur of aortic regurgitation. Flint added that the presystolic murmur was sometimes heard with severe aortic regurgitation (1862).[4]

1-8. **The answer is B.** *(Hurst's the Heart, 14th Edition, Chap. 1)* The pivotal breakthrough in thinking about congenital abnormalities came from Helen Taussig and Alfred Blalock at Johns Hopkins Hospital with their "blue baby operation." Taussig had observed that patients with cyanotic heart disease worsened when their ductus arteriosus closed. She suggested creating an artificial ductus to improve oxygenation.[17] Blalock, assisted by Vivian Thomas, successfully created a shunt from the subclavian to the pulmonary artery in November 1944. This innovative operation, in which a blue

baby was dramatically changed to a pink one—the Blalock-Taussig shunt—was highly publicized, and other operations soon followed. These include closure of atrial septal defects (1950s), closure of ventricular septal defects (1954), and tetralogy of Fallot repair (1954). In 1966, Rashkind introduced the balloon septostomy, a novel catheter therapeutic technique that bought time for severely cyanotic infants with transposition of the great arteries.[7] In the 1980s, catheters were adapted to dilate stenotic aortic and pulmonic valves as well as aortic coarctation. Today, transcatheter closure of patent ductus arteriosus (1971), atrial septal defects (1976), and ventricular septal defects (1987) has become routine. Indomethacin therapy to enable closure of a patent ductus in the premature infant (1976) and prostaglandin infusion to maintain ductal patency (1981) profoundly changed the medical management of fragile newborns. Stents now help keep the ductus open as well as alleviate right ventricular obstruction in tetralogy of Fallot.

1-9. **The answer is B.** *(Hurst's the Heart, 14th Edition, Chap. 1)* Stephen Hales, an English country parson, reported in his *Statical Essays* (1733) that the arterial blood pressure of the cannulated artery of a recumbent horse rose more than eight feet above the heart—the first true measurement of arterial pressure and the beginning of sphygmometry.[2,18,19] His pioneering efforts stood alone until 1828 when Jean Poiseuille introduced a mercury manometer device to measure blood pressure.[20,21] Over the next 60 years, various sphygmomanometric methods were developed—notably by Ludwig (1847), Vierordt (1855), and Marey (1863)—to refine the measurement of the arterial pressure. An inflatable arm cuff coupled to the sphygmograph, a device small enough to allow measurement outside the laboratory, was invented by Riva-Rocci (1896), who also noted the "white-coat effect" on blood pressure.[22] Nicolai Korotkoff, a Russian military surgeon, first auscultated brachial arterial sounds (1905), a discovery that marked the advent of modern blood pressure recording. This auscultatory approach eventually ensured its widespread use by the 1920s. In 1939, blood pressure recordings were standardized by committees of the American Heart Association (AHA) and the Cardiac Society of Great Britain and Ireland.

1-10. **The answer is C.** *(Hurst's the Heart, 14th Edition, Chap. 1)* President Franklin Roosevelt's death in 1945 from severe hypertension and stroke called international attention to the consequences of hypertension and its inadequate treatment—he had been managed with diet, digitalis, and phenobarbital. Effective oral treatment became possible in 1949, first with reserpine and then with hydrochlorothiazide.[23] Lumbar sympathectomy and adrenalectomy (1925), the last resort, was abandoned. Subsequently, β-adrenergic blockers, calcium channel blockers, ACE inhibitors, angiotensin receptor blocking agents, and direct renin inhibitors have brought antihypertensive relief to many. Severe salt restriction, as practiced earlier with the Kempner rice diet, has taken a lesser role, whereas the Dietary Approaches to Stop Hypertension (DASH) diet, exercise, and alcohol restriction are encouraged. Since 1973, recommendations published by the Joint National Committee (JNC) on Detection, Evaluation, and Treatment of High Blood Pressure have been very helpful.

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CHAPTER 2

The Global Burden of Cardiovascular Diseases

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

2-1. How many deaths worldwide are caused each year by cardiovascular disease (CVD)?

A. 10 million
B. 15 million
C. 17 million
D. 20 million
E. 23 million

2-2. Which of the following statements about global cardiovascular disease (CVD) is *false*?

A. There has been a steady decrease in the age-specific death rate for CVD in both sexes over the past 20 years
B. Women represent 50% of CVD deaths worldwide
C. The total number of deaths from CVD increased more than 40% between 1990 and 2013
D. Increases in gross domestic product are well correlated with reductions in cardiovascular disease mortality
E. A continued increase in the number of CVD deaths is expected as a result of demographic changes worldwide

2-3. What proportion of ischemic heart disease (IHD) patients from low-income world regions are taking *none* of the standard secondary prevention medications?

A. 20%
B. 30%
C. 40%
D. 60%
E. 80%

2-4. Which noncommunicable disease (NCD) is the second most common cause of all disability globally?

A. Stroke
B. Ischemic heart disease
C. Chronic obstructive pulmonary disease
D. Lower back and neck pain
E. Depression

2-5. Which of the following cardiovascular diseases are more commonly diagnosed in men than in women worldwide?

A. Abdominal aortic aneurysm
B. Peripheral arterial disease
C. Atrial fibrillation
D. Both A and B
E. Both A and C

2-6. What is the most common complication of infective endocarditis?

A. Stroke
B. Embolization other than stroke
C. Heart failure
D. Intracardiac abscess
E. Intracardiac fistula

2-7. Which of the following statements about Chagas disease is *false*?

A. Chagas disease is primarily transmitted through the bites of the *Triatoma infestans* insect
B. No rapid diagnostic tests are available to detect the causative parasite
C. The acute phase immediately following infection is often asymptomatic, but it produces fever and malaise in up to 5% of people
D. More than 50% of those infected will not progress to chronic Chagas disease
E. Approximately 30% of those infected will develop chronic cardiovascular Chagas disease

2-8. What percentage of patients with acute rheumatic fever will develop rheumatic heart disease (RHD)?

A. 50%
B. 60%
C. 70%
D. 80%
E. 90%

2-9. Which modifiable cardiovascular risk factor is responsible for the most morbidity and mortality worldwide?

A. Low fruit intake
B. High body mass index
C. High sodium
D. High blood pressure
E. Smoking

2-10. In 2013, the WHO and all member states (194 countries) agreed to a Global Non-Communicable Disease (NCD) Action Plan, which aims to reduce the number of premature deaths from NCDs by 25% by 2025 through nine voluntary global targets. Which of the following is *not* one of the nine voluntary targets?

A. A 20% relative reduction in daily exposure to outdoor and indoor air pollution
B. A 30% relative reduction in the prevalence of current tobacco use in persons aged 15 years and over
C. A 25% relative reduction in the prevalence of raised blood pressure or else containing the prevalence of raised blood pressure, according to national circumstances
D. A halt in the rise of diabetes and obesity
E. At least 50% of eligible people receiving drug therapy and counseling (including glycemic control) to prevent heart attacks and strokes

ANSWERS

2-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 2)* In 2013, more than 17 million people died from CVDs, with an estimated US $863 billion in direct health care costs and productivity losses worldwide.[1] As a result of the large populations in many low- and middle-income countries (LMICs), nearly 70% of CVD deaths occurred in LMICs. CVDs account for 50% of all NCD deaths in the world each year and represent a significant threat to human welfare and sustainable development. CVDs are the leading cause of death in every region of the world, with the exceptions of sub-Saharan Africa—where infectious diseases are still the leading cause of death—and South Korea and Japan, where cancers cause more deaths. The leading cause of CVD-related death was IHD, accounting for more than eight million deaths, followed by ischemic and hemorrhagic strokes, with more than three million deaths each. Rheumatic heart disease, although not the leading cause of death, was a significant contributor to the global burden and a leading cause of highly preventable death, with approximately 275,000 deaths in 2013.

2-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Despite the steady decrease in death rate for both sexes over the past 20 years, the total number of deaths is increasing as a result of population growth and aging, which disproportionately affects low- and middle-income countries (LMICs). Globally, the total number of CVD deaths increased from 12.3 to 17.3 million, a 41% increase between 1990 and 2013.[2] Women represent 50% of these deaths. Although most countries have seen an increased national income per capita over this time, the decrease in the number of CVD deaths cannot be entirely explained by economic growth. The decline in age-specific CVD mortality does not correlate well with increases in country income, except weakly in upper-middle income countries. Therefore, it appears unlikely that economic growth alone will improve a country's burden of CVD. Despite an overall decrease in the global age-specific CVD death rate, a continued increase in the number of CVD deaths is expected as a result of demographic changes. The United Nations estimated that the global population in 2015 was 7.3 billion and will increase to a total of 8.5 billion by 2025 and 9.7 billion by 2050. When population growth slows down as a result of a reduction in fertility, the population ages, and the proportion of older persons aged 60 or older increases over time. In 2015, about 10% of the population was aged 60 or older, and the number of adults in this age group is projected to more than double by 2050 and more than triple by 2100, with more than two-thirds of these older adults residing in LMICs.

2-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Ischemic heart disease is the leading cause of death worldwide, encompassing myocardial infarction and all other acute coronary syndromes as well as long-term sequelae of coronary heart disease, including angina pectoris and ischemic cardiomyopathy. Since the 1990s, the high-income regions, specifically Australasia, Western Europe, and North America, have seen dramatic declines in the age-standardized IHD mortality.[3] However, IHD mortality has increased in other regions, including Central Asia, South Asia, and East Asia. Although IHD burden falls largely on those aged older than 70 years in high-income regions, the age of IHD deaths is much lower in other regions, with a mean age of onset of IHD events before age 50 years in more than 29% of males and 24% of females in North Africa/Middle East and South Asia.[3,4] As more patients with IHD survive their initial event, the IHD death rate and case fatality will no longer be the sole public health benchmark for success; improved symptom control and overall quality of life and access to adequate treatment will be important secondary outcomes.[3] The mainstays of treatment include standard, low-cost medications that are insufficiently used in low- and middle-income countries (LMICs). The Prospective Urban Rural Epidemiological (PURE) study found that only 11% of patients from high-income countries were not taking standard secondary prevention medications, whereas 80% of low-income-region patients were taking none of the recommended medications.[5,6]

2-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Stroke was the second largest contributor to disability globally and in developing countries, whereas it was the third largest contributor to disability in developed countries (after IHD and lower back and neck pain).[7] Globally, the proportional contribution of stroke-related disability-adjusted life years (DALYs) as a proportion of all diseases increased from 3.5% in 1990 to 4.6% in 2013. The deaths caused by stroke also increased from 9.7% in 1990 to 11.8% in 2013. In order to reduce the rising burden of stroke worldwide, urgent prevention and management strategies are needed. Prevention of risk factors remains key to reversing the stroke pandemic, and universal access to organized stroke services must remain a priority, especially in LMICs.[8] In 2013, the top five noncommunicable causes of disability globally (from most to least) were: IHD, stroke, lower back and neck pain, chronic obstructive pulmonary disorder, and depression.[9]

2-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Abdominal aortic aneurysm (AAA) and atrial fibrillation (AF) are more commonly diagnosed in men than in women worldwide, while peripheral arterial disease (PAD) is equally common among men and women in developed countries, and it is more often diagnosed in women than in men in developing countries. AAA is a focal dilation of the abdominal aorta of at least 1.5 times the normal diameter or an absolute value of 3 cm or greater. Risk factors include male sex, smoking, hypertension, atherosclerosis, and history of AAA in a first-degree relative. In 2010, the age-specific prevalence rate per 100,000 ranged from 7.9 to 2274. Prevalence was higher in developed versus developing nations. The age-specific annual incidence rate per 100,000 ranged between 0.83 and 164.6.[10] AF and atrial flutter are irregular heart rhythms that often cause a rapid heart rate and can increase the risk of stroke, heart failure, and other heart-related complications. In 2010, the estimated age-standardized DALYs resulting from AF was 65 per 100,000 population in males and 46 in females, which was an increase of 18.8% and 19% for males and females since 1990, respectively.[11] Higher burden in men compared with women may reflect actual disease rates or poorer access to medical care among women in resource-poor settings. PAD is a circulatory problem in which narrowed arteries reduce blood flow to the limbs and cause symptoms of leg pain with walking (claudication). PAD is defined as an ankle brachial index lower than or equal to 0.90. In developed countries, among adults aged 45–49 years, the prevalence is similar for males and females and is around 5%. The prevalence increases to around 18% for males and females in those aged 85 to 89 years.[12] In developing countries, for the same age groups, the prevalence is around 6% for females and 3% for males and increases to 15% in females and 14% in males.[12]

2-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Infective endocarditis (IE) is an infection caused by bacteria, or other infectious pathogens, that enter the bloodstream and cause inflammation in the heart tissues, often on a valve. Because of the lack of direct blood supply, the heart valves are particularly susceptible to bacterial colonization and are neither protected by the typical immune response nor easily reached by antibiotics. IE is a serious illness, with up to 22% in-hospital and 40% five-year mortality rates.[13] A global collaboration was formed to assess the current characteristics of patients with IE via a large, prospective multicenter registry, called the International Collaboration on Endocarditis (ICE). ICE found that contemporary infective endocarditis is most often an acute disease with a high rate of infection with *Staphylococcus aureus* and involving the mitral (41.1%) and aortic (37.6%) valves. Common complications included stroke (16.9%), embolization other than stroke (22.6%), heart failure (32.3%), and intracardiac abscess (14.4%); these often required surgical intervention (48.2%). In-hospital mortality was high (17.7%).[14] Unfortunately, there were few sites in Asia and Africa included in the registry, which limits the ability to assess geographic differences in patient and microbiologic characteristics in these areas. IE is estimated to have resulted in 65,000 deaths and 1.9 million DALYs in 2013. More complete knowledge and improved surveillance are needed in all world regions.[15]

2-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Chagas disease is a disease of poverty and is localized to Latin America because it is primarily transmitted through bites from the nocturnal "kissing bug," *Triatoma infestans*, which is endemic to this region. The infection can be asymptomatic, but it can eventually lead to premature morbidity and mortality, especially in young women of childbearing age. There are rapid diagnostic tests that can detect the causative parasite, *Trypanosoma cruzi*, in serum and can diagnose chronic infections. Pesticides have been developed for vector control programs, but much is still unknown about this disease. In any case, prevention and elimination of the vector remain the keys to Chagas control. The disease has three phases: acute, indeterminate, and chronic. The acute phase immediately follows infection and is often asymptomatic, but it produces fever and malaise in up to 5% of people. The

indeterminate phase is asymptomatic, with more than 50% of those infected remaining in this phase for life without any long-term sequelae. After a decade or more, approximately 30% of people will experience chronic cardiovascular Chagas disease, with symptoms including heart failure, arrhythmias, and thromboembolism.[16] Deaths are rare in the acute phase, and most deaths attributable to Chagas disease result from downstream cardiovascular sequelae. In addition, approximately 15%–20% of people will experience chronic gastrointestinal disease sequelae, including megaesophagus and megacolon. Between 5 and 18 million people are currently infected, and the infection is estimated to cause more than 10,000 deaths annually.[17]

2-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Rheumatic heart disease is an endemic disease that is common in settings of poverty. It is caused by group A streptococcus infection and leads to mitral stenosis and premature mortality, particularly in young, predominantly female, poorer individuals living in Oceania, South Asia, Central Asia, Africa, and the Middle East. Approximately 60% of all acute rheumatic fever cases will develop RHD, based on data from Aboriginal Australian populations, and 1.5% of patients with RHD will die each year.[18] Globally in 2010, RHD affected more than 34 million people, causing more than 345,000 deaths, almost all in LMICs.[19] The disease can progress to cause moderate to severe multivalvular disease, leading to congestive heart failure, pulmonary hypertension, or AF. RHD also contributes (3%–7.5%) to an estimated 144,000–360,000 incident strokes each year.

2-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 2)* Elevated blood pressure is estimated to be the single largest contributor to the global burden of disease and global mortality. There are gaps in the awareness, treatment, and control of hypertension globally. High blood pressure in populations appears to occur in tandem with economic development, but notably in the highest income countries, individuals with lower socioeconomic status are the group most likely to be untreated.[20,21] In Africa, hypertension is thought to be the leading cause of heart failure, whereas at global levels, hypertension is linked to the development of atherosclerotic vascular disease. In high-income countries, it is estimated to be responsible for 25% of deaths from stroke, 20% of deaths from IHD, and more than 17% of all global deaths.[22] The number of people with uncontrolled hypertension was 978 million in 2008, a substantial increase from 605 million in 1980, largely because of population growth and aging.[23] Other modifiable cardiovascular risk factors are: high body mass index, low fruit intake, smoking, high sodium, and high total cholesterol.[24]

2-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 2)* While a reduction in exposure to outdoor and indoor air pollution is not one of the nine targets, such pollution ranks as the largest single environmental health risk factor, with more than 2.9 million deaths attributed to outdoor air pollution and a similar number attributed to indoor air pollution.[25] Air pollution has been shown to increase preclinical cardiovascular risk factors such as atherosclerosis, endothelial dysfunction, and hypertension. The estimated excess risk of cardiovascular mortality rises 11% per 10 $\mu g/m^3$ rise in levels of particulate matter, with no threshold level below which long-term exposure to urban air pollution has no ill effect on cardiovascular health.[26] Answers B through E: Modeling studies have shown that significant reductions in premature CVD are possible by 2025 if multiple risk factor targets are achieved. Globally, the risk factor change that would lead to the largest reduction in premature mortality would be the decreased prevalence of hypertension, followed by tobacco smoking prevalence for men and obesity for women.

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CHAPTER 3

Assessing and Improving the Quality of Care in Cardiovascular Medicine

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

3-1. Which of the following statements concerning health care expenditures in the United States is *false*?

A. Health care expenditures accounted for nearly 17.5% of the gross domestic product in 2014
B. The United States invested an estimated $3.0 trillion in health care in 2014
C. Expenditures related to cardiovascular disease were estimated to be $656 billion in 2015
D. The United States health system ranked lowest among 11 similar countries with respect to access, equity, quality, efficiency, and healthy lives, despite spending the most on health care
E. Increasing the use of expensive medical care is associated with better quality of care and patient outcomes

3-2. Which of the following factors influences the variability and appropriateness of health care delivery?

A. Patients' clinical status
B. Sociodemographic factors
C. Providers and facilities
D. Geographic location
E. All of the above

3-3. How many years, on average, does it take for guidelines to be incorporated into clinical practice?

A. 4 years
B. 10 years
C. 13 years
D. 17 years
E. 21 years

3-4. Which of the following is *not* generally considered a part of defining quality of care?

A. Cost of care
B. Evidence-based care
C. Improving outcomes
D. Patient satisfaction
E. All of the above are important for defining quality of care

3-5. Which constitute the primary domains of the Donabedian framework for quality assurance?

A. Structure, process, and outcome
B. Process, outcome, and evaluation
C. Research, guidelines, and implementation
D. Research, structure, and outcome
E. Research, outcome, and cost

3-6. Which of the following is *not* a principal thematic dimension in the Institute of Medicine (IOM)'s landmark report on quality improvement initiatives, *Crossing the Quality Chasm: A New Health System for the 21st Century*?

A. Safety
B. Cost

C. Timeliness
D. Efficiency
E. Equity

3-7. What is the specific function of clinical data standards?

A. To measure and improve access to evidence-based care
B. To enable the reproducible collection of data across hospitals and settings
C. To measure physician performance
D. To measure the quality of clinical trial data
E. To enable the assessment of standards of care

3-8. The ACC/AHA guidelines indicate that percutaneous aortic balloon dilation may be considered a bridge to surgical aortic valve replacement or transcatheter aortic valve replacement for symptomatic patients with severe aortic stenosis (Class IIb, level C).[23] A Class IIb level C recommendation could indicate that the intervention is:

A. Probably indicated, based on data from multiple randomized trials
B. Probably indicated, based on expert opinion
C. Probably indicated, based on case studies
D. Possibly indicated, based on expert opinion
E. Possibly indicated, based on a single randomized trial

3-9. Which of the following tools for improving the quality of cardiovascular care involves quantifying a range of health care processes and outcomes, identifying multiple points in the continuum of care for which clinical inertia (the failure to implement or titrate recommended therapies) can occur, and then selecting those with the strongest evidence and highest correlation with clinically meaningful outcomes?

A. Clinical practice guidelines
B. Clinical data standards
C. Performance measures
D. Appropriate use criteria
E. Procedural registries

3-10. Some of the most exciting opportunities to improve care come from the combination of registries and national coalitions to target significant gaps in care. A dramatic example of this is the Door-to-Balloon (D2B) initiative. Which of the following was *not* a performance recommendation in the D2B initiative?

A. Prompt data feedback to the emergency department and cath lab staff
B. Expectations of having the cath lab team assembled within 30 minutes
C. Targeted times to first ECG acquisition for chest pain patients within 15 minutes
D. Emergency medicine physician activates cath lab
E. Single-call activation of the cath lab

ANSWERS

3-1. **The answer is E.** *(Hurst's the Heart, 14th Edition, Chap. 3)* In the United States, health care expenditures accounted for nearly 17.5% of the gross domestic product in 2014 (an estimated $3 trillion) and are expected to reach 19.6% by 2024.[1] Cardiovascular disease (CVD) remains the leading cause of death and disability,[2] with an estimated annual total cost of $656 billion in 2015.[3] In a recent report, the US health system ranked lowest among 11 countries with respect to access, equity, quality, efficiency, and healthy lives,[4] despite spending the most on health care.[5] It is often thought that high-quality health care is dependent on the continued discovery and delivery of novel diagnostic and therapeutic interventions. However, studies suggest that greater use of expensive medical care is actually associated with lower quality and worse outcomes.[6,7] Woolf and Johnson[8] have extended this concept to mathematically quantify the trade-off between the development of new interventions and the more consistent delivery of known therapies. They argue that despite tremendous scientific and technologic advancements, the failure to consistently deliver proven therapies dilutes and reduces the overall quality of a health care system. Thus, money spent on improving this actual delivery of care may be equally or even more critical than money spent on improving technology to result in improved quality of both routine and specialized health care.

3-2. **The answer is E.** *(Hurst's the Heart, 14th Edition, Chap. 3)* A critical goal of efforts to disseminate high-quality care is to ensure rational and efficient use of effective treatment to those who derive the most benefit.[9] Yet surveys evaluating processes of care have shown that, on an average, only one in two US adults receives recommended care when receiving health care services.[10] Several studies have suggested that there are marked variations in the use of evidence-based

treatments of cardiovascular disease (CVD) based on gender, age, race, education, income, and insurance status.[10,11,12,13] A study examining differences in the treatment of myocardial infarction showed that although blacks lived closer than whites to hospitals with revascularization capability that were considered high-quality, they were less likely than whites to be admitted to revascularization-capable and high-quality hospitals.[14] Further emphasizing the need to monitor the quality of care has been the observation of marked variations in the processes of care by geographic region. Pioneering work from the Dartmouth Atlas series, a comprehensive evaluation of health care services provided to Medicare beneficiaries, has documented broad variation in the use of both diagnostic and treatment modalities in CVD as a function of the site of care.[15] Beyond concerns about overall disparities in care, there is emerging evidence that among the patients eligible for treatments, those with the least potential to benefit are preferentially treated, whereas those with the most to gain are systematically undertreated. This finding is referred to as the *risk-treatment paradox*. Many investigators have shown that high-risk patients—who would be expected to benefit more than lower-risk patients—are treated less aggressively, whereas lower-risk patients are treated more aggressively.[16,17]

3-3. **The answer is D.** *(Hurst's the Heart, 14th Edition, Chap. 3)* It is estimated that, on average, it takes about 17 years for guidelines to be incorporated into clinical practice,[9] even with an intervention as simple as aspirin use at the time of myocardial infarction (> 20 years for full adoption). There can be several levels of barriers to the effective implementation of clinical evidence and guidelines in routine practice. These exist at policy, societal, system/organizational, provider, and patient levels. These can be addressed through the use of frameworks for quality metrics and tools to improve quality of care in cardiovascular disease.

3-4. **The answer is E.** *(Hurst's the Heart, 14th Edition, Chap. 3)* Lohr and Schroeder broadly define quality of care as "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[18] The US Agency for Healthcare Research and Quality has proposed a similar definition: "Quality healthcare means doing the right thing at the right time in the right way for the right person and having the best results possible."[19] The Institute for Healthcare Improvement recommends that to improve the United States' health care system requires simultaneous pursuit of three aims, called the "Triple Aim"—improving the patient experience of care (including satisfaction), improving outcomes (of individuals and populations), and reducing the per capita cost of health care.[20] Achieving the best quality of care as marked by highest quality patient outcome and experience with the lowest possible cost is what a health care system usually strives to achieve. Although the concept of quality health care is intuitive and relatively easy to understand, to actually measure, monitor, and improve quality requires the use of a clear conceptual framework that encompasses important, relevant aspects of health care.

3-5. **The answer is A.** *(Hurst's the Heart, 14th Edition, Chap. 3)* One of the earliest approaches to conceptualizing the components of quality assurance was proposed by Donabedian.[21] This framework considers quality to comprise three main domains: structure, process, and outcome. Structure refers to the attributes of settings where care is delivered and includes aspects that exist independently of the patient. Examples of structural attributes include provider training and experience, the availability of specialized treatments, nurse-to-patient ratios, and treatment and discharge plans. Process refers to whether or not good medical practices are followed, and it incorporates concepts such as the medications given and the timing of their administration, the use of diagnostic and therapeutic procedures, and patient counseling. Outcome refers to tangible measures that capture the consequences of care and range from manifestations of disease progression (eg, mortality and hospitalizations) to patient-centered outcomes of health status and treatment satisfaction. As noted by Donabedian, these three components of quality are interdependent and are built on a framework that focuses mainly on linking the delivery of care to outcomes.

3-6. **The answer is B.** *(Hurst's the Heart, 14th Edition, Chap. 3)* The current driving force and roadmap for quality improvement initiatives in American health care is the Institute of Medicine (IOM)'s landmark report, *Crossing the Quality Chasm: A New Health System for the 21st Century*.[9] The IOM recognized the following principal thematic dimensions needed to guide QI in health care:

- Safety—avoiding injuries to patients from the care that is intended to help them
- Effectiveness—providing services based on scientific knowledge to those who could benefit while refraining from providing services to those not likely to benefit
- Patient-centeredness—providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
- Timeliness—reducing waits and sometimes harmful delays in care
- Efficiency—avoiding waste, including waste of equipment, supplies, ideas, and energy
- Equity—providing care that does not vary in quality because of personal characteristics such as sex, ethnicity, geographic location, and socioeconomic status

Cost is not one of the principal themes of the IOM report, but it is considered among the outcomes in the Donabedian framework for quality assurance.

3-7. **The answer is B.** *(Hurst's the Heart, 14th Edition, Chap. 3)* To measure and improve care, one first needs to know both how and what to measure. It is critical to have standardized data definitions that enable the reproducible collection of data across different hospitals and settings. To create the foundation for clear, explicit data capture, the ACC/AHA Clinical Data Standards were developed to serve as a foundation for implementing and evaluating the other ACC/AHA quality

tools.[22] These data standards are a set of standardized definitions of particular conditions and treatments that can and should be applied in both QA/QI activities and, importantly, clinical trials. Inclusion in clinical trials is especially important to support both comparability across studies and their incorporation into guidelines, performance measures, and clinical care. In particular, standardized definitions support the consistent definition of symptoms, comorbidities, and outcomes in many areas of CVD (eg, acute coronary syndromes, congestive heart failure, PCI).[22] The more these data standards are used in clinical trials, observational registries, and QA/QI efforts, the greater the ability will be to translate the emerging knowledge from clinical research to clinical care.

3-8. **The answer is D.** *(Hurst's the Heart, 14th Edition, Chap. 3)* To distill the rapidly expanding body of cardiovascular literature, professional agencies, such as the AHA and ACC, have commissioned expert committees to synthesize the available evidence into clinical practice guidelines.[24-25] The creation of guidelines requires writing committees to systematically review the medical literature and to assess the strength of evidence for particular treatment strategies. This necessitates ranking the types of research from which knowledge is generated. Randomized controlled trials are given the highest weight. When these are not available, other study designs, including preintervention and postintervention studies, observational registries, and clinical experience are used. To transparently communicate the strength of a recommendation and the evidence on which it is generated, a class recommendation (Class I = strongly indicated, Class IIa = probably indicated, Class IIb = possibly indicated, or Class III = not indicated) and strength of the evidence (level A evidence [data derived from multiple randomized trials] through level C [data derived from expert opinion, case studies, or standard of care]) are provided.[25] An intervention that is probably indicated, based on data from multiple randomized trials (option A) is a Class IIa level A recommendation. An intervention that is probably indicated, based on expert opinion (option B) or probably indicated, based on case studies (option C) are both Class IIa level C recommendations. An intervention that is possibly indicated, based on a single randomized trial (option E), is a Class IIb level B recommendation.

3-9. **The answer is C.** *(Hurst's the Heart, 14th Edition, Chap. 3)* At times, the evidence supporting (or for avoiding) a particular diagnostic or therapeutic action is so strong that failure to perform such actions jeopardizes patients' outcomes. Performance measures represent that subset of the clinical practice guidelines (option A) for which the strongest evidence exists and for which their routine use (or avoidance) is felt to be an important advance to elevating quality.[26,27,28] Performance measures are often constructed as a set of measures that quantify a range of health care processes and outcomes; they are designed to identify multiple points in the continuum of care for which clinical inertia—the failure to implement or titrate recommended therapies—can occur.[28,29] Once the relevant domains are identified, then those guideline recommendations with the strongest evidence and highest correlation with clinically meaningful outcomes are selected for performance measure creation. Clinical data standards (option B) are a set of standardized definitions of particular conditions and treatments that can be applied in both quality assurance/improvement activities and clinical trials. Appropriate use criteria (option D) help identify what specific tests and procedures to perform and when and how often, based on estimates of the relative benefits and harms of a procedure or a test for a specific indication. Procedural registries (option E) support the prospective collection of data for assessing performance and guideline compliance within hospitals.

3-10. **The answer is C.** *(Hurst's the Heart, 14th Edition, Chap. 3)* First ECG acquisition for chest pain patients was recommended within 10 minutes. Launched in 2006, the Door-to-Balloon (D2B) initiative sought to increase the proportion of ST-segment elevation myocardial infarction patients receiving primary PCI within 90 minutes of hospital presentation from approximately 50% to more than 75%.[30] This program supplemented data collected through the NCDR CathPCI registry with explicit recommendations about how to improve performance,[31] including (1) activation of the catheterization laboratory (cath lab) by emergency department physicians, (2) single-call activation of the cath lab, (3) expectations of having the cath lab team assembled within 30 minutes, (4) prompt data feedback to the emergency department and cath lab staff, and (5) activation of the cath lab based on prehospital ECGs and targeted times to first ECG acquisition for chest pain patients within 10 minutes. Between January 2005 and September 2010, this effort led to a decline in median D2B time, from 96 minutes in December 2005 to 64 minutes in September 2010.[32] There were corresponding increases in the proportion of patients undergoing primary PCI within 90 minutes (from 44.2% to 91.4%), and within 75 minutes (from 27.3% to 70.4%). The declines in median times were greatest among groups that had the highest median times during the first period.[32]

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SECTION 2

Foundations of Cardiovascular Medicine

CHAPTER 4

Functional Anatomy of the Heart

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

4-1. Which of the following statements is *false*?

A. The main pulmonary artery, portions of both venae cavae, distal pulmonary veins, and nearly the entire ascending aorta are intrapericardial
B. The right and left pulmonary arteries are extrapericardial structures
C. The transverse sinus forms a tunnel-like passageway that separates the great arteries anteriorly from the great veins posteriorly
D. The oblique sinus lies posterior to the right atrium
E. The serous pericardium forms the inner lining of the fibrous pericardium; over the heart, it is referred to as the epicardium

4-2. A 35-year-old woman presents to your clinic for evaluation of a murmur. She describes intermittent regular palpitations that have been associated with lightheadedness. Auscultation reveals a midsystolic click and a crescendo systolic murmur. The S1-click distance increases with squatting and decreases with standing. Regarding this valve or valve defect, which statement is *true*?

A. The valve leaflets are characteristically thin
B. Annular dilatation is not typically present
C. Prolapse of the anterior leaflet occurs more frequently
D. The anterolateral papillary muscle is commonly single and usually has a dual blood supply from the left coronary circulation
E. The posteromedial papillary muscle usually has a single head and is most commonly supplied by the left anterior descending artery

4-3. Regarding Figure 4-1, select the statement that is *false:*

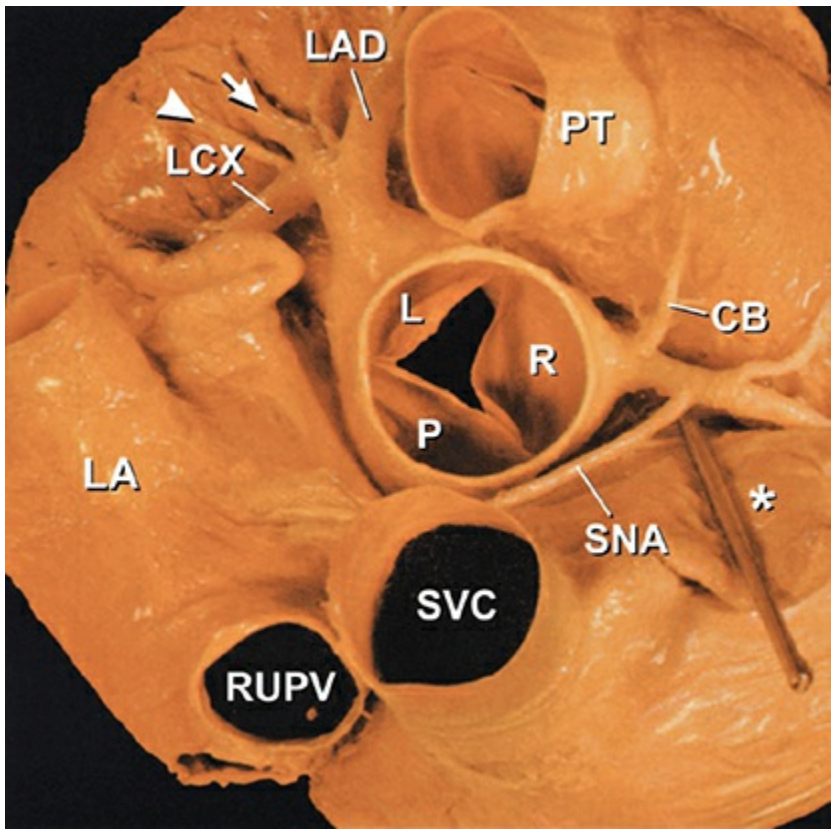

FIGURE 4-1 Superior view of the heart. (Reproduced with permission from McAlpine W. *Heart and Coronary Arteries: An Anatomic Atlas for Radiologic Diagnosis and Surgical Treatment*. New York: Spring-Verlag; 1975.)

A. The central structures labelled L, P, and R are supplied by the conus artery
B. The * depicts the right atrial appendage
C. The arrowhead points to a circumflex marginal branch
D. An ablation catheter positioned at P will reveal atrial electrogram signals
E. The oblique sinus is not visualized in this figure

4-4. All of the following are used to differentiate the right ventricle from the left ventricle *except*:

A. The presence of a moderator band
B. Free wall typically < 0.4 mm thick
C. A prominent arch-shaped muscular ridge known as the crista supraventricularis separates the tricuspid and pulmonary valves
D. The apex is thin and lacks trabeculation
E. The tricuspid valve always follows the morphological right ventricle

4-5. Which of the following statements regarding structures within the right atrium is *false*?

A. The cavotricuspid isthmus is targeted during typical right atrial flutter ablation
B. The cavotricuspid isthmus is a well-defined region of atrial tissue that is bordered by the eustachian ridge and valve posteriorly, and the tricuspid valve annulus anteriorly
C. The right atrial free wall is a very thin structure between pectinate muscles and can perforate during catheter positioning
D. Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve
E. The right atrial appendage abuts the left aortic sinus of Valsalva

4-6. A patient undergoes a transesophageal echocardiography (TEE) as workup for possible left atrial appendage (LAA) closure. Regarding the LAA, which of the following statements is *false*?

A. There is no known relationship between stroke and LAA morphology
B. There are four basic morphologic patterns to the LAA: windsock, cactus, cauliflower, and chicken wing
C. Age is not a determinant for the dimensions of an LAA
D. All lobes of the LAA should be visualized during TEE to rule out a thrombus
E. Both the right and the left atrial appendages are located close to the right ventricular outflow tract

4-7. All of the following are true statements *except*:

A. The left anterior descending artery courses within the epicardial fat of the anterior interventricular groove
B. The first septal perforating branch of the left anterior descending artery supplies the AV (His) bundle and proximal left bundle branch
C. Dominance is left in 70% of human hearts, right in 10%, and shared in 20%
D. A patient who presents acutely with an anterior ST elevation myocardial infarction secondary to a left anterior descending artery occlusion is at risk for a mechanical complication
E. The right coronary artery typically arises nearly perpendicularly from the aorta

4-8. In a typical right-dominant system, which of the following left ventricular segments would most likely *not* be affected in a patient with left anterior descending artery occlusion?

A. Mid anterior wall
B. Mid inferolateral wall
C. Basal anterior septum
D. Basal anterior wall
E. Mid anterolateral wall

4-9. Regarding the great vessels, which of the following statements is *true*?

A. Most coarctations occur just proximal to the left subclavian artery
B. When the eustachian or the adjacent thebesian valve of the coronary sinus is large and fenestrated, it is referred to as the ligamentum arteriosum
C. The ligamentum arteriosum represents the vestigial remnant of the fetal ductal artery, which, when patent, connects the proximal right pulmonary artery to the undersurface of the aortic arch
D. The ostium of the superior vena cava (SVC) is guarded by a crescent-shaped, often fenestrated flap of tissue called the eustachian valve
E. The ligament of Marshall is the vestigial remnant of the vein of Marshall, which forms the terminal connection between a persistent left SVC and the coronary sinus

4-10. Which of the following statements is *false* concerning the triangle of Koch?

A. It is bordered by the coronary sinus ostium, the septal tricuspid annulus, and the tendon of Todaro
B. The AV node is a subendocardial structure that is located within the upper portion of the triangle of Koch

C. The His bundle is located within the triangle of Koch. The apex of the triangle corresponds to the central fibrous body of the heart where the His bundle penetrates
D. The atrial end of the fast pathway in AV nodal reentrant tachycardia inserts near the ostium of the coronary sinus, while the slow pathway lies closer to the apex of the triangle near the AV node
E. AV node displacement occurs in Ebstein malformation and persistent left SVC

ANSWERS

4-1. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 4)* The reflections along the pulmonary veins and venae cavae are continuous and form a posterior midline cul-de-sac known as the oblique sinus. The oblique sinus lies immediately posterior to the left atrium, *not* the right atrium (option D). The main pulmonary artery, portions of both venae cavae, distal pulmonary veins, and nearly the entire ascending aorta are intrapericardial (option A). The right and left pulmonary arteries are extrapericardial structures (option B). The transverse sinus forms a tunnel-like passageway that separates the great arteries anteriorly from the great veins posteriorly (option C). The serous pericardium forms the delicate inner lining of the fibrous pericardium and continues onto the surface of the heart and great vessels at the pericardial reflection.[1] Over the heart, it is referred to as the epicardium, and it contains the epicardial coronary arteries and veins, autonomic nerves, lymphatics, and a variable amount of adipose tissue (option E).

4-2. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 4)* The anterolateral papillary muscle is single and usually has a dual blood supply from the left coronary circulation (option D).[2] Mitral valve prolapse is characterized by *thickened* and redundant leaflets (option A), annular dilatation (with or without calcium) and thickened and elongated chordae tendineae (with or without rupture) (option B). Prolapse of the posterior leaflet occurs more often than that of the anterior leaflet (option C). The posteromedial papillary muscle usually has multiple heads and is most commonly supplied only by the dominant coronary artery (option E).[2] Small left atrial branches supply the most basal aspects of the mitral leaflets.[3]

4-3. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 4)* The figure shows a superior view of the heart, including the aortic and pulmonic valves, the origins of the left and right coronary arteries, the superior aspect of the left atrium, the SVC, and the right upper pulmonary vein. The aortic cusps (labeled L for left aortic cusp; P for posterior aortic cusp; and R for right aortic cusp) form pocketlike tissue flaps that are avascular (option A). The conus artery is the first branch of the right coronary artery in 50%–60% of persons; it supplies the right ventricular outflow tract and forms an important collateral anastomosis (circle of Vieussens) just below the pulmonary valve with an analogous branch from the left anterior descending coronary artery.[1-3] The * symbol (option B) represents the right atrial appendage, which is retracted by the rod to disclose the sinus node artery (SNA). The arrowhead (option C) is pointing to a marginal branch of the left circumflex artery. An ablation catheter positioned at the posterior (or noncoronary) cusp (option D) will reveal atrial electrogram signals due to its close proximity to the interatrial septum. The oblique sinus (option E) is not seen in this figure. It is formed from the reflections along the pulmonary veins and venae cavae that form a posterior midline cul-de-sac that lies posterior to the left atrium.

4-4. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 4)* The right ventricular apex is heavily trabeculated.[1,3] This apical trabecular zone extends inferiorly beyond the attachments of the papillary muscles toward the ventricular apex and about halfway along the anterior wall. This muscular meshwork is the usual site of insertion of transvenous ventricular pacemaker electrodes, and it is the preferred site for positioning the tip of an implantable cardioverter defibrillator lead. The moderator band (option A) forms an intracavitary muscle that connects the septal band with the anterior tricuspid papillary muscle. The right ventricular wall is thin in normal adults, usually less than 0.4 cm (regional variation between 0.2 and 0.7 cm) (option B). A prominent arch-shaped muscular ridge known as the crista supraventricularis separates the tricuspid and pulmonary valves. It is made up of three components (parietal band, infundibular septum, and septal band) that can appear as distinct structures or can merge together (option C).[1,3] The tricuspid valve always follows the morphological right ventricle, which is an important consideration when evaluating patients with congenital heart disease (option E).

4-5. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 4)* The right atrial appendage abuts the right aortic sinus of Valsalva and overlies the proximal right coronary artery (option E). The cavotricuspid isthmus, a frequent target of atrial flutter ablation, is a well-defined region of atrial tissue that is bordered by (1) the eustachian ridge and valve posteriorly and (2) the tricuspid valve annulus anteriorly (options A, B). The right atrial free wall is paper-thin between pectinate muscles and therefore can be perforated easily by stiff catheters (option C).[1-3] The atrial lead of a dual-chamber pacemaker is normally positioned within the trabeculations of the right atrial appendage. Inferior vena caval blood flow is directed by the eustachian valve toward the foramen ovale, and superior vena caval blood is directed toward the tricuspid valve (option D).[4]

4-6. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 4)* The left atrial appendage is usually multilobed and narrower than its right atrial counterpart, and it exhibits more variability in shape.[1-3,5] The chicken wing variety of LAA

morphology has the *least* likelihood for embolic events (option A).[6] There are four basic morphologic patterns: windsock, cactus, cauliflower, and chicken wing (option B).[6] Age and sex are both determinants for LAA dimension (option C).[4] There may be multiple lobes in the LAA; all lobes must be visualized in order to rule out thrombus prior to planned cardioversion, electrophysiology or structural procedure, or percutaneous balloon valvuloplasty procedures (option D). Either atrial appendage may serve as a vantage point from which to access and ablate arrhythmias in the adjacent segment of the right ventricular outflow tract (option E).[7]

4-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 4)* Dominance is right in 70% of human hearts, left in 10%, and shared in 20%.[1-3] In patients with a congenitally bicuspid aortic valve, the incidence of left coronary dominance is 25% to 30%.[3] The left anterior descending artery (LAD) courses within the epicardial fat of the anterior interventricular groove (option A). The first septal perforating branch supplies the AV (His) bundle and the proximal left bundle branch (option B).[3] In patients with symptomatic hypertrophic obstructive cardiomyopathy, nonsurgical septal reduction by percutaneous transluminal occlusion of septal branches of the LAD is a therapeutic approach aimed at reducing the outflow gradient.[8] Anterior infarcts have been shown to be independent predictors of ventricular septal defects post myocardial infarction (option D). Whereas the right coronary artery arises almost perpendicularly from the aorta, the left arises at an acute angle (option E).[4]

4-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 4).* The midventricular inferolateral wall is typically supplied by the *circumflex artery*, not the left anterior descending artery (LAD). In a typical right-dominant system, the LAD supplies the midventricular and basal segments of the anterior (options A and D), anterolateral walls (option E) and anterior septum (option C) and all apical segments. The left circumflex artery supplies the midventricular and basal inferolateral segments, and the right coronary artery supplies the midventricular and basal inferior wall and inferior septum. In the setting of a large obtuse marginal branch of the circumflex artery, the anterolateral or inferior wall may not be supplied by the LAD. However, because the patterns of coronary distribution are so highly variable, these correlations between coronary blood flow and regional anatomy are not precise. For example, a hyperdominant right coronary artery can supply the apex, and a large, obtuse marginal branch of the circumflex artery can supply the anterolateral or inferior wall.[1-3] Ventricular septal defects are more common in the setting of a wrap-around LAD.

4-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 4)* The vein of Marshall forms the terminal connection between a persistent left SVC and the coronary sinus. Its vestigial remnant in normal adults is the ligament of Marshall; it is a potential source of arrhythmias and a common site for recurrences after pulmonary vein isolation (option E). Most coarctations occur just *distal* to the left subclavian artery (option A). The ostium of the inferior vena cava is guarded by a crescent-shaped, often fenestrated flap of tissue, the eustachian valve,[1-3] which is readily seen by echocardiography. Although generally small, the eustachian valve can become so large that it can produce a double-chambered right atrium.[2] Also, when either the eustachian or the adjacent thebesian valve of the coronary sinus is large and fenestrated, it is referred to as a Chiari network (option B).[1-3] The ligamentum arteriosum represents the vestigial remnant of the fetal ductal artery, which, when patent, connects the proximal *left* pulmonary artery to the undersurface of the aortic arch (option C). The ostium of the *inferior* vena cava (not the SVC) is guarded by the eustachian valve. It is an important structure during cavotricuspid isthmus ablation (option D).

4-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 4)* The atrial end of the fast pathway in AV nodal reentrant tachycardia inserts closer to the AV node at the apex of the triangle, whereas the slow pathway (target for radiofrequency ablation) inserts near the ostium of the coronary sinus (option D). The triangle of Koch is bordered by the coronary sinus ostium posteroinferiorly, the septal tricuspid annulus anteriorly, and the tendon of Todaro posteriorly (option A). The tendon of Todaro is a fibrous extension of the Eustachian valve (option B). The body of the AV node is found near the apex of the triangle. The His bundle, also located in the triangle of Koch, penetrates through the central fibrous body separating the atria and ventricles (option C). The bundle of His then bifurcates into right and left main bundle branches, which branch further to become Purkinje fibers that spread conduction to the ventricles. Differences in the conduction system primarily reside in the arrangement of the transitional and compact components of the AV node and in the length and route of the His bundle. In both Ebstein's anomaly and persistent left SVC syndrome with a grossly enlarged CS ostium, the size of the triangle of Koch is reduced, resulting in a shorter distance between the compact AV node and the CS ostium (option E).

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CHAPTER 5

Normal Physiology of the Cardiovascular System

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

5-1. Which of the following is *true* about Figure 5-1?

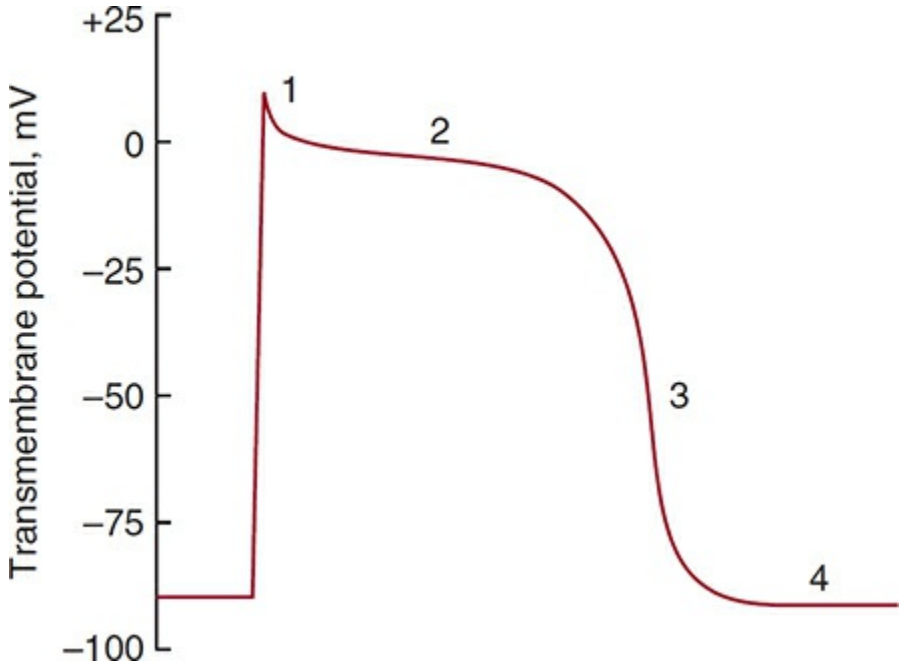

FIGURE 5-1 Phases of the action potential and major associated currents in ventricular myocytes.

A. Sodium influx during phase 1 depolarization is decreased by membrane depolarization
B. Sodium influx is limited after phase 1 by the closure of inactivation gates
C. The phase 2 plateau of the action potential is the result of a decrease in intracellular calcium through the L-type calcium channel
D. Phase 3 repolarization is the result of potassium influx into the cell through the funny channel (I_F)
E. Maintenance of the membrane potential during diastole is an energy-independent process

5-2. Please select the *true* statement about Figure 5-2.

A. Calcium-induced calcium release occurs by calcium influx through ion channel B with release of calcium from the sarcoplasmic reticulum via ion channel C
B. The magnitude of the calcium transient is, in part, determined by calcium influx into the cell via channels B and D
C. The decline in the calcium transient occurs via channel C and is energy-independent
D. Increased cytoplasmic calcium results in contraction, in part, by the binding of calcium to TnI
E. None of the above

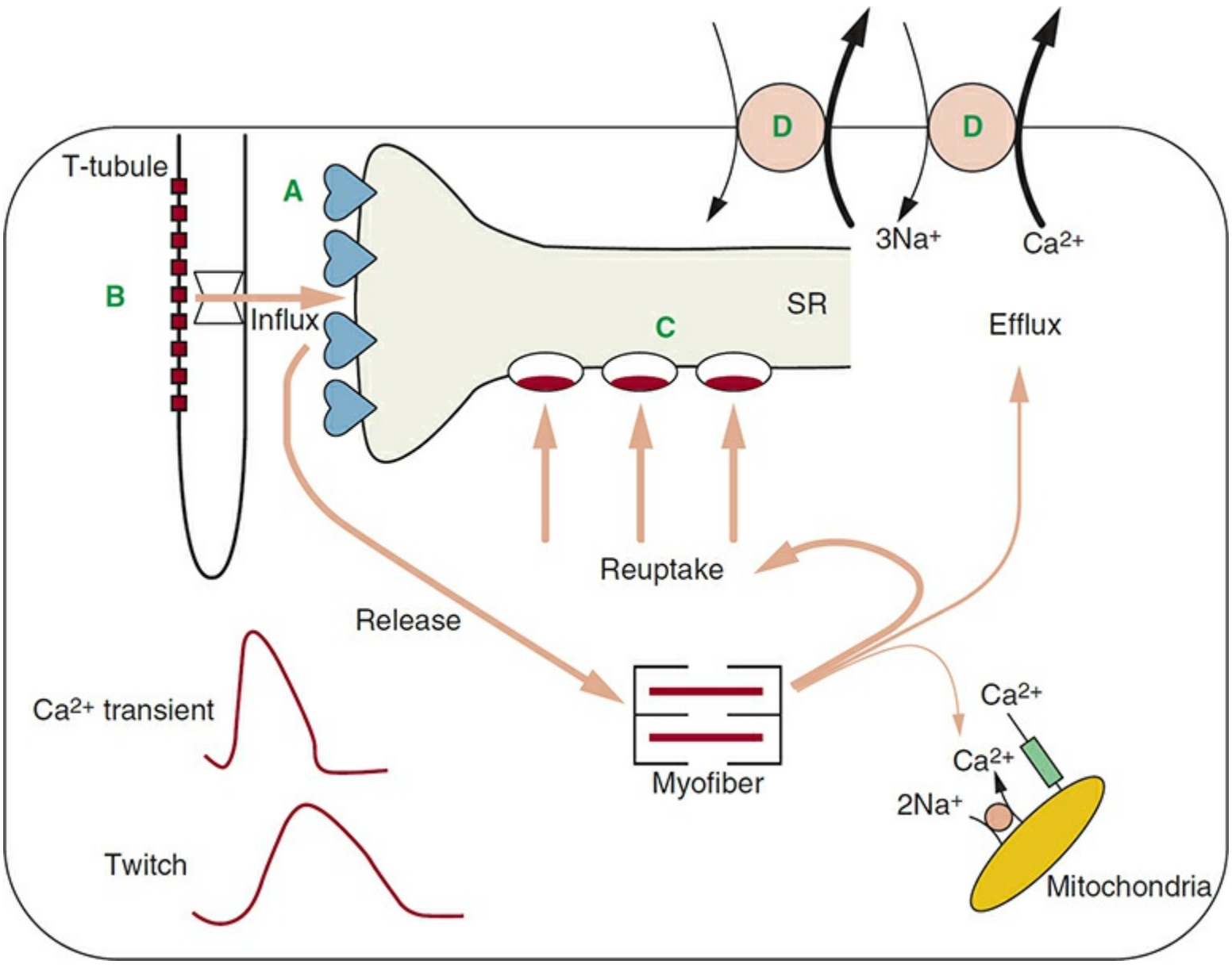

FIGURE 5-2 Major components of excitation–contraction coupling in cardiomyocytes. (Adapted with permission from Scoote M, Poole-Wilson PA, Williams AJ, et al. The therapeutic potential of new insights into myocardial excitation-contraction coupling. *Heart*. 2003 Apr;89(4):371-376.)

5-3. A 54-year-old woman was recently started on furosemide for pedal edema related to prolonged standing. Shortly after starting furosemide, she feels fatigued and confirms dizziness with standing. Her past medical history is notable for hypertension that had not been treated. Her blood pressure is 158/82 sitting and her heart rate is 85. Her physical exam is notable for flat neck veins, a nondisplaced apical impulse, and a soft S4. Which of the following is *not true* for this patient?

A. Discontinuation of her diuretic and increased fluid intake would increase the peak tension in her cardiac muscle fibers following muscle contraction
B. Increasing preload through hydration would increase cardiac output, in part by the increased sensitivity to calcium by myofilaments at longer sarcomere lengths
C. Increased heart rate would result in faster cardiac relaxation
D. Increasing afterload would increase myofilament shortening velocity
E. A cup of coffee could increase contractility

5-4. Which of the following is *true* regarding the cardiac cycle?

A. The *c* wave occurs during isovolumic contraction
B. The *v* wave occurs just after the QRS complex on the ECG, but before the T wave
C. The change in ventricular pressure during ventricular filling is a property of ventricular stiffness
D. Ventricular stiffness is constant during contraction and relaxation
E. The area enclosed within the pressure–volume loop (PVA) is proportional to myocardial oxygen consumption

Questions 5-5 through 5-7 relate to the following vignette.

A 54-year-old woman is brought to the catheterization laboratory to assess her hemodynamics for shortness of breath. A precatheterization echocardiogram revealed normal ventricular function. Moreover, her filling pressures are normal.

5-5. Which of the following is *not true* regarding ventricular function?

A. A modest volume challenge would be expected to increase stroke volume
B. Left ventricular (LV) compliance is determined entirely by the intrinsic elastic properties of the left ventricle
C. A bolus of norepinephrine would be expected to decrease the velocity of LV shortening
D. The rate of LV pressure development (dP/dt) is dependent on preload but relatively independent of afterload
E. Increasing the heart rate from 80 to 95 is unlikely to increase cardiac output

5-6. Which of the following is *true* regarding her diastolic function?

A. Ventricular relaxation is energy-independent
B. Tau, the time constant of LV relaxation, is increased with β-adrenergic receptor stimulation
C. The end-diastolic pressure–volume relationship is influenced by changes in intrathoracic pressure, pericardial constraint, and ventricular interaction
D. The sarcomeric protein titin does not meaningfully contribute to diastolic function
E. The PV relationship during systole reflects the lusitropic state of the heart

5-7. Right heart catheterization revealed a right atrial pressure of 5 mm Hg, a right ventricular (RV) pressure of 25/5 mm Hg, a pulmonary artery (PA) pressure of 25/10 mm Hg, and a wedge pressure of 10 mm Hg. The aortic pressure was 120/85 mm Hg, and heart rate was 85. The cardiac output was calculated to be 6 L/min. Which of the following is correct?

A. The mean arterial pressure (MAP) is 108 mm Hg
B. The mean PA pressure is 15 mm Hg
C. The systemic vascular resistance (SVR) is 14.5 Wood units
D. The pulmonary vascular resistance (PVR) is 2.5 Wood units
E. None of the above

5-8. Which of the following is *true* about the coronary circulation?

A. Collateral vessels around a coronary obstruction have myocardial blood flow during exercise similar to that of the native coronary artery
B. To meet the increased oxygen demands during exercise, the myocardium dramatically increases its extraction of oxygen from the blood
C. Adenosine is a major mediator of coronary autoregulation
D. Coronary vascular resistance is greater in the subendocardial coronary circulation than in the subepicardial coronary circulation
E. The principal endothelial derived relaxing factor is adenosine

5-9. Which of the following is *true* about control of the circulation?

A. Arterial pressure regulation is controlled primarily by the parasympathetic nervous system
B. One result of carotid baroreflex resetting is increased receptor firing for a given mean arterial blood pressure
C. The Bezold–Jarisch reflex occurs with a decrease in ventricular distension and results in bradycardia and hypotension
D. Endothelins constrict arterioles and decrease preload
E. Endocannabinoids increase contractility

5-10. With reference to the venous return curves in Figure 5-3, which of the following is *incorrect*?

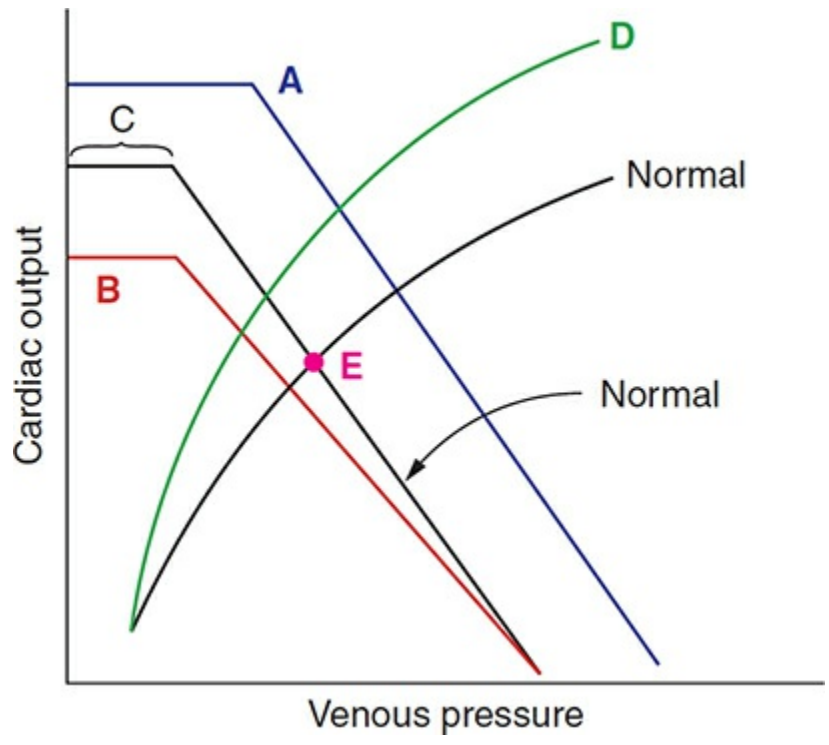

FIGURE 5-3 Venous pressure–cardiac output return curve.

A. Line A is the effect of volume loading or increasing venous pressure
B. Line B is the effect of arteriolar vasodilation
C. The flat portion of the curve in C represents the maximal cardiac output as venous return is reduced
D. The shift in the Frank–Starling curve to curve D is the effect of increased sympathetic tone
E. Point E is the equilibrium point where the ability of the venous system to provide enough return at a given pressure is matched by the ventricle's ability to pump that return when distended to that pressure

ANSWERS

5-1. **The answer is B**. (*Hurst's The Heart, 14th Edition, Chap. 5*). Cardiomyocytes are specialized cells that couple membrane depolarization with cellular contraction. Phase 1 depolarization is the result of sodium influx through Na^+ channels. Sodium influx is *regenerative*, in that increasing membrane depolarization opens more Na^+ channels (option A). Rapid depolarization is limited by K^+ efflux but also by the closure of inactivation gates on Na^+ channels that prevent reopening of individual channels only after the membrane has been fully repolarized (option B). The phase 2 plateau is the result of balanced K^+ efflux and Ca^{2+} influx through L-type Ca^{2+} channels (option C). Phase 3 repolarization is the result of K^+ efflux primarily through the delayed outward K current (I_K). The funny current (I_F) is a specialized channel found in pacemaker cells that results in spontaneous depolarization of the cell during phase 4 and in automaticity (option D). Phase 4 occurs during diastole and requires the Na^+/K^+ ATPase to restore and maintain low intracellular Na^+ and high intracellular K^+ concentrations (option E).

5-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 5).* In Figure 5-2, channel A is the ryanodine receptor on the sarcoplasmic reticulum (SR). Channel B is the L-type Ca^{2+} channel on the sarcolemma. Channel C is the SERCA pump on the sarcoplasmic reticulum, and channel D is the Na^+/Ca^+ exchanged (NCX) on the sarcolemma. Calcium-uptake calcium release is the result of calcium release from the SR through the ryanodine receptor (A) after calcium influx into the cell through the L-type Ca^{2+} channel (B) (option A). The calcium transient is a result of (1) Ca^{2+} influx through the L-type Ca^{2+} channel and the *reverse mode* NCX; (2) the amount of calcium in the SR; (3) the amount of calcium released by the SR for a given calcium current; and (4) intracellular Ca^{2+} buffers. NCX can operate in the reverse mode during cellular depolarization, when the intracellular Na^+ content is high. The net effect is Na^+ extrusion and Ca^{2+} uptake. This is a minor contribution to the calcium transient (option B). The calcium transient declines largely because the SERCA ATPase sequesters calcium into the SR. This requires ATP and is energy-dependent (option C). Calcium concentrations are coupled to contraction. Calcium bound TnC essentially pulls TnI off actin. Thus, TnI can no longer inhibit the formation of myosin-actin crossbridges (option D).

5-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 5)* Options A and B reflect the Frank–Starling mechanism. A key property of healthy cardiac muscle is faster relaxation times with increasing heart rates (option C). This occurs by increased SERCA activity as a result of phospholamban phosphorylation. By the force–velocity relationship, the initial velocity of shortening is inversely related to afterload (option D). Caffeine is a calcium sensitizer and can result in an increased force of contraction (option E).

5-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 5)* The *c* wave is the result of increased atrial pressure as the mitral valve bulges into the atrium during isovolumic contraction (option A). The *v* wave occurs as the atrium fills during ventricular systole and atrial pressure falls with mitral valve opening. The *v* wave occurs after the T wave (option B). During ventricular filling, change in ventricular pressure is a function of ventricular compliance (option C). Isolated, perfused hearts have been instrumental in the development of our understanding of ventricular mechanics. These models have allowed for the determination that ventricular elastance increases during ventricular contraction and decreases with ventricular relaxation (option D). The PVA is proportional to the myocardial oxygen consumption but includes the area within the PV loop as well as the area between the end-systolic pressure relation and the end-diastolic P–V relation (option E).

5-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 5)* The woman in the vignette has a normal right heart catheterization and likely is short of breath for noncardiac reasons. Increasing preload is expected to increase stroke volume (option A). LV compliance in vivo is determined by pericardial pressure, right ventricular pressure and volume, coronary artery perfusion, and the intrinsic elastic properties of the LV (option B). An increase in afterload, such as with a bolus of norepinephrine, is expected to decrease stroke volume and the velocity of LV shortening (option C). Changes in heart rate from 60 to 160 beats per minute are unlikely to increase cardiac output because the small increase in contractility is offset by the decrease in diastolic filling time and the resulting preload (option E).

5-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 5)* Ventricular relaxation is an energy-dependent process requiring ATP for SERCA sequestration of calcium into the sarcoplasmic reticulum, among other processes (option A). β-adrenergic stimulation leads to the activation of PKA and the phosphorylation of phospholamban, resulting in increased SERCA activity. Increased SERCA activity results in faster relaxation, and a decrease of Tau (option B). Chamber stiffness is affected by intrinsic LV factors and extrinsic factors such as pericardial constraint, atrial contraction, intrathoracic pressures, and ventricular interaction (option C). In addition to active relaxation, diastolic function is also related to the viscoelastic properties of the LV. LV recoil is affected by titin and the extracellular matrix (option D). The P–V relationship during diastole reflects the lusitropic state of the heart (option E).

5-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 5)* The MAP is (120 + 2 * 85)/3 = 97 (option A). The PA pressure is (25 + 2 * 10)/3 = 15 (option B). SVR is (97 − 5)/6 = 15.33 Wood units (option C). The PVR is (15 − 10)/6 = 0.83 Wood units (option D).

5-8. **The answer is C**. *(Hurst's The Heart, 14th Edition, Chap. 5)* Collateral vessels that become prominent with obstructive coronary disease cannot augment coronary flow similar to that of the native artery with stress or exercise (option A). Unlike skeletal muscle, the myocardium operates at nearly peak oxygen extraction at rest. Increased oxygen needs are met by increases in blood flow through the coronary circulation (option B). Adenosine levels increase with the breakdown of ATP, and adenosine is a potent coronary vasodilator. If coronary blood flow decreases, local adenosine levels increase, making adenosine an integral component of coronary autoregulation (option C). To maintain equal coronary flow throughout the myocardium, the subendocardial vessels have less resistance than the subepicardial vessels. This is important because subendocardial vessels have a limited ability to further vasodilate in time of stress, and subendocardial zones are more prone to ischemia (option D). The principal endothelial derived relaxing factor is nitric oxide (NO) (option E).

5-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 5)*. Parasympathetic nerves supply only a small portion of the resistance in vessels; the sympathetic nervous system is the primary regulator of vascular resistance (option A). Carotid baroreflex resetting results in decreased receptor firing for a given mean arterial blood pressure (option B). The Bezold–Jarisch reflex is mediated by ventricular C fibers, which are activated by hypovolemia. The net result is a paradoxical bradycardia and hypotension (option C). Endothelin constricts arterioles and venules. The effect on venules serves to increase preload (option D). Endocannabinoids decrease contractility (option E).

5-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 5)*. The venous return curve describes the relationship of cardiac output and venous pressure. Volume loading or venoconstriction shifts the curve up and to the right (option A). By contrast, arteriolar vasoconstriction shifts the curve down and to the left (option B). The flat portion of the curve in C represents the maximal cardiac output as venous return is reduced (option C). The Frank–Starling curve describes the effect of ventricular loading with cardiac output and moves up and to the left at higher levels of contractility (option D). The intersection of the Frank–Starling curve and the venous return curve represents the equilibrium point of venous return and ventricular performance (option E).

CHAPTER 6

Molecular and Cellular Biology of the Heart

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

6-1. A 55-year-old man presents with exertional dyspnea and a 10 lb weight gain. His physical exam is notable for an elevated jugular venous pressure, a soft apical holosystolic murmur, and an S3 gallop. Echocardiography reveals a dilated left ventricle with an ejection fraction of 35%. Which of the following is most likely *true* regarding β-adrenergic signaling in this patient?

A. β2-adrenergic receptors (β2-AR) are the dominant type of β-adrenergic receptor in the heart
B. An increase in GRK2 activity contributes to β-adrenergic receptor desensitization
C. β1-AR density is increased in this patient's myocytes
D. This patient's heart is more sensitive to β-agonists now than before developing decompensated heart failure
E. β1-AR signaling is likely to protect against apoptosis in his cardiomyocytes

6-2. Which of the following is *incorrect* regarding excitation–contraction coupling?

A. Depolarization of the cardiomyocyte membrane results in the opening of L-type calcium channels
B. The SERCA ATPase functions to sequester calcium in the sarcoplasmic reticulum during relaxation
C. In a healthy heart, tachycardia results in decreased calcium in the cytoplasm of the cardiomyocyte and increased contractile force
D. PKA and CaMKII maintain SERCA activity by phosphorylating and inactivating phospholamban
E. The efficiency of the ryanodine receptor response to cytoplasmic calcium is dependent on the ryanodine receptor's proximity to the L-type calcium channel

6-3. A 54-year-old patient with a history of heart failure with reduced ejection fraction is admitted following 3 shocks from his internal cardiac defibrillator. Which of the following could contribute to a proarrhythmic state in this patient?

A. Hyperphosphorylation of the ryanodine receptor contributes to a calcium leak from the sarcoplasmic reticulum
B. Increased systolic calcium concentrations in myocytes
C. An increased force-frequency relationship
D. A shortened relaxation phase
E. Increased SERCA expression and activity

6-4. Which of the following is *not true* regarding signaling pathways in heart failure?

A. An increased intracellular concentration of calcium leads to increased activity of calcineurin in failing myocytes
B. CaMKII contributes to hypertrophy by phosphorylating transcription factors such as MEF2 and class II histone deacetylases
C. Prohypertrophic growth factors tend to work through heterotrimeric proteins of the Gq family
D. Mechanical stretch alone can induce many hypertrophic signaling pathways
E. Hallmarks of a fetal-gene expression program during hypertrophy include the expression of BNP, ANF, and α-MHC

Questions 6-5 through 6-7 refer to the following vignette.

A 52-year-old man presents to your office for a follow-up appointment. He has a long-standing history of hypertension. His ECG is suggestive of left ventricular hypertrophy, and his echocardiogram shows a left ventricular wall thickness of 1.4 cm.

6-5. Which of the following is *not true* regarding signaling pathways in this patient?

A. Protein synthesis is dramatically upregulated through the PI3K and mTOR pathways
B. Extracellular signal-related kinases (ERKs) are activated
C. GSK-3β activity is reduced in cardiomyocytes undergoing hypertrophic growth

D. Hypertrophic signaling has a strong overlap with factors known to broadly regulate organ size
E. mTORC1 has an important role in pathologic, but not physiologic hypertrophy

6-6. Which of the following is *not true* regarding microRNA signaling in this patient?

A. The miR212/132 family of microRNAs promotes hypertrophy by the inhibition of the antihypertrophic transcription factor FoxO3
B. MiR-133 levels are increased and promote hypertrophy and fibrosis
C. Anti-miRs are an approach to pharmacologically modulate microRNA signaling
D. MiRs that promote myocardial glucose utilization are investigational approaches to prevent the progression to heart failure
E. Exosomes secreted from the heart allow for the systemic circulation of miRNAs to other organ beds

6-7. Which of the following is *true* regarding lncRNAs in this patient?

A. The lncRNA CHAST is likely to be upregulated
B. LncRNAs, by definition, are not translated into protein products
C. LncRNAs exert their effects solely through the inhibition of complementary transcripts
D. LncRNAs are found only in intergenic regions
E. LncRNAs are highly conserved across phyla

6-8. Which of the following is *not true* regarding cell death in the development of heart failure?

A. Cytochrome C release marks cells about to undergo necrotic cell death in the failing heart
B. Prolonged ER stress can trigger cell death pathways
C. Apoptotic cell death is programmed cell death that does not typically result in an inflammatory response
D. Necrotic cell death is marked by a loss of membrane integrity, extrusion of intracellular contents, and inflammation
E. Apoptotic cell death is energy dependent, but necrotic cell death is energy independent

6-9. Which of the following is *not true* regarding cardiac fibroblasts?

A. Cardiac fibrosis is the result of collagen production in excess of collagen degradation
B. Cardiac fibroblasts differentiate into myofibroblasts that express contractile proteins
C. The main components of cardiac extracellular matrix are proteoglycans and elastin
D. Pathologic cardiac fibrosis is proarrhythmogenic, in part, because of electrical isolation of regions of the myocardium
E. Cardiac fibroblasts in the adult heart are primarily derived from resident fibroblasts

6-10. Which of the following is *true* regarding cardiac microRNAs?

A. The majority of transcripts in the genome encode proteins
B. MicroRNAs, PIWI-interacting RNAs, and endogenous short interfering RNAs are types of long ncRNAs
C. MiRNAs regulate gene expression by binding to mRNAs, resulting in degradation
D. The number of ncRNAs decreases with increasing complexity of the species
E. Long ncRNAs are more than 2000 base pairs long

ANSWERS

6-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 6)* This patient presents with classic findings of heart failure with reduced ejection fraction. In the normal heart, 60% to 80% of β-adrenergic receptors are of the β1 subtype.[1] With heart failure, β1-AR is downregulated, and the β1-AR/β2-AR ratio nearly normalizes (options A and C).[2] A molecular hallmark of heart failure is the desensitization of the β-adrenergic signaling axis. A failing heart is less sensitive to exogenous β-AR ligands than is a normal heart (option D). At the molecular level, this occurs by a decreased density of β1-AR in cardiomyocytes and increased levels of GRK2. GRK2 phosphorylates β-ARs and reduces their sensitivity (option B).[3] Chronic β-AR signaling through the β1-AR is believed to contribute to cardiomyocyte apoptosis seen in heart failure (option E).[3]

6-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 6)* Following depolarization of the cardiomyocyte membrane, L-type calcium channels open, and calcium influxes into the cardiomyocyte (option A).[4] In response, ryanodine receptors release calcium from the sarcoplasmic reticulum. The net result is an increase in cytoplasmic calcium that leads to increased myofilament contractility. Activation of ryanodine receptors is more efficient when they are in close proximity to the calcium influx through L-type calcium channels (option E).[5] An increase in force with increasing heart rate is due to increased cytoplasmic calcium and is known as the force-frequency relationship (option C). The force-frequency relationship is an important feature of the healthy heart. During relaxation, cytoplasmic calcium is sequestered in the

sarcoplasmic reticulum by the SERCA ATPase (option B). SERCA activity is negatively regulated by phospholamban.[6,7] PKA and CaMKII can phosphorylate and inactivate phospholamban, thus maintaining SERCA activity (option D).

6-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 6)* Intracellular calcium homeostasis is altered in the failing cardiomyocyte. Hallmarks of the failing cardiomyocyte include (1) decreased systolic calcium, (2) increased diastolic calcium, and (3) a prolonged relaxation phase (options B and D).[4] Additionally, the force-frequency relationship is altered such that contractile force decreases with increasing heart rate (option D). Biochemically, the L-type calcium channel does not activate the ryanodine receptor as efficiently, and hyperphosphorylation leads to an increased sensitivity of the ryanodine receptor.[8] Calcium leak from the ryanodine receptor can result in delayed afterdepolarizations, an important contributor to arrhythmogenesis (option A).[4,9] Finally, SERCA expression has been demonstrated to be reduced in animal and human models of heart failure, and the restoration of normal SERCA levels has been a focus of gene therapy efforts for patients with heart failure (option E).[7,8]

6-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 6)* Hypertrophic signaling results from complex inputs at the membrane and within the cell. Mechanical stretch alone can activate many of the signaling pathways involved in hypertrophy through surface-bound integrins and mechanically activated ion channels (option D).[10] Additionally, prohypertrophic growth factors such as angiotensin II work through heterotrimeric G-proteins (option C). The Gq family is particularly important because overexpression of Gq is sufficient to cause hypertrophy.[11] A key feature of hypertrophic signaling is an increase in intracellular calcium that binds to calmodulin, resulting in the activation of calcineurin and CaMKII (option A). Both calcineurin and CaMKII lead to the activation of transcription factors that promote hypertophic gene expression programs. CaMKII activates the transcription factors MEF2 and HDAC2 by phosphorylation (option B).[12] One result of hypertrophic signaling is re-expression of factors from cardiac development, such as BNP, ANF, and β-MHC (option E).[13]

6-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 6)* Hypertrophic cardiomyocytes have dramatic upregulation of protein synthesis via the PI3K and mTORC pathways (option A). Many stimuli that result in cardiac hypertrophy also activate PI3K signaling. mTORC1 signaling is one example of several growth pathways that are activated with cardiac hypertrophy. mTORC1 appears to be broadly related to cardiac growth as inhibition compromises both physiologic and pathologic hypertrophy (options D and E).[14] Additionally, MAPK activity is thought to be increased and GSK-3β activity reduced during hypertrophy (option C).[15]

6-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 6)* The importance of microRNA signaling to the pathologic hypertrophy and the progression of heart failure is being increasingly recognized. MicroRNAs regulate multiple processes, such as hypertrophic signaling pathways, tissue fibrosis, vascular density, and cardiac metabolism (option D).[16] MiR-133 is downregulated with cardiac stress and has protective effects against hypertrophy and tissue fibrosis (option B).[17] By contrast, miR212/132 are increased with cardiac stress and promote hypertrophic signaling by repressing the antihypertrophic transcription factor FoxO3 (option A).[18-20] MicroRNAs are promising therapeutic targets and can be specifically targeted by modified nucleic acids that function as anti-miRs (option C). Finally, the systemic roles of cardiac microRNAs are being increasingly understood because cardiac microRNAs can be found in the circulation within small vesicles called exosomes (option E).[21]

6-7. **The answer is A**. *(Hurst's The Heart, 14th Edition, Chap. 6)* LncRNAs were originally defined as noncoding RNAs greater than 200 base pairs in length.[22] LncRNAs can be found within coding genes and intergenic regions (option D). LncRNAs have emerged as complex molecules with a diverse set of regulatory functions.[23] They can repress transcription by binding transcripts, and they directly interact with proteins to regulate their function (option C). More recently, some lncRNAs have been identified that encode small proteins, such as the protein DWORF that activates the SERCA pump (option B).[24] LncRNAs tend to be poorly conserved across phyla (option E). The lncRNA CHAST is an exception, and elevations have been identified in murine models of pressure overload and in hypertrophied human heart tissue (option A).[25]

6-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 6)* Cardiomyocyte cell death is an important contributor to the progression to heart failure. Cell death can occur via necrotic cell death following injuries to the heart or programmed apoptotic cell death. Necrotic cell death is an energy independent process that is marked by a loss of membrane integrity, resulting in extrusion of intracellular contents and inflammation (option D).[26] Apoptotic cell death, by contrast, is programmed and triggered by both intracellular and extracellular stimuli (options C and E). For example, prolonged ER stress can lead to the triggering of death pathways (option B). In failing hearts, some myocytes exhibit features of apoptotic cell death, such as mitochondrial cytochrome C release, but they can survive and maintain intact nuclei (option A).[27] These cells are thought to undergo reversible damage.

6-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 6)* In response to stress, the heart undergoes pathologic remodeling, with proliferation of resident fibroblasts to make more fibroblasts (option E).[28] These fibroblasts tip the balance of extracellular matrix turnover toward excess production compared to degradation (option A).[28,29] Extracellular matrix is a complex network of collagens, elastin, glycoproteins, and proteoglycans. However, type I collagen is the main component (option C).[30] Cardiac fibrosis stiffens the heart and can be proarrhythmic by electrically isolating parts of the

myocardium (option D).[31,32] In addition to roles in maintaining the balance of cardiac extracellular matrix, cardiac fibroblasts can differentiate into myofibroblasts that express contractile proteins. Myofibroblasts play important roles in contracting the wound following injury (option B).[33]

6-10. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 6)* As a result of widespread sequencing, the vast number of ncRNAs has been recognized. It has now been determined that although about three-fourths of the mammalian genome is transcribed, less than 2% is ultimately translated into proteins (option A).[34] Short ncRNAs are < 200 bp in length and include micoRNAs, PIWI-interacting RNAs, and endogenous short interfering RNAs. By contrast, long ncRNAs are longer than 2 kb in length (options B and E).[35-38] MiRNAs can repress gene expression by binding to target mRNAs, resulting in degradation (option C). MiRNAs are increasingly recognized as important regulators of gene expression and cell identity. The number of ncRNAs increases with increasing organism complexity (option D).[39]

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CHAPTER 7

Biology of the Vessel Wall

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QUESTIONS

DIRECTIONS: Choose the one best response to each question.

7-1. Which of the following is *true* about vascular development?

A. A bipotent hemangioblast is capable of giving rise to endothelial cells and blood cells
B. The primitive vasculature arises from coalesced blood islands
C. Postnatal vasculogenesis requires angioblasts that are active in the adult
D. Collateral arteries that form in the presence of obstructive coronary artery disease are the result of bone-marrow-derived progenitor cells
E. VEGF is a potent inhibitor of angiogenesis

7-2. Which of the following is *incorrect* regarding the role of endothelial cells?

A. The endothelium serves as a prothrombotic surface
B. The endothelium regulates the inflammatory response by affecting leukocyte recruitment and margination
C. The endothelium helps to regulate vascular tone
D. The endothelium regulates signaling by allowing for the selective passage of molecules across the barrier
E. The endothelium serves as a barrier to circulating blood constituents

7-3. Which of the following is *not true* about signaling in endothelial cells?

A. Inflamed endothelium produces tissue factor, which creates a procoagulant surface
B. Water-soluble molecules are transported across the endothelium via caveolae
C. L-selectin, P-selectin, and VCAM-1 are important to the capture of leukocytes by the endothelium during inflammation
D. NO acts as a vasoconstrictor by increasing levels of cGMP, which reduces intracellular calcium concentrations and results in the dephosphorylation of MLCK in smooth muscle
E. PGI2 is made by the endothelium and promotes vascular relaxation by increasing cAMP levels in smooth muscle cells

7-4. Which of the following *do not* promote the conversion of vascular smooth muscle to a synthetic phenotype?

A. PDGF
B. FGF
C. TGF-β
D. NO
E. IGF-1

7-5. Which of the following is *not true* regarding the vascular extracellular matrix (ECM)?

A. Degradation of the ECM is one of the earliest events during angiogenesis
B. Matrix metalloproteinases degrade the ECM
C. Increased MMP activity has been noted in abdominal aneurysms
D. Increased MMP activity is found in the shoulder of an atherosclerotic plaque
E. Secreted MMPs are inactivated by plasmin

7-6. Which of the following is *not* a characteristic of endothelial dysfunction?

A. Endothelial dysfunction is associated with cardiovascular risk factors such as diabetes, smoking, and a family history of atherosclerotic disease
B. A hallmark of dysfunctional endothelium is increased NO production
C. Dysfunctional endothelium recruits monocytes and macrophages to the vessel wall

D. Endothelial dysfunction precedes the morphological presence of atherosclerotic plaque
E. All of the above

7-7. A 64-year-old man is admitted with an anterior ST elevation myocardial infarction. He is taken to the cardiac catheterization laboratory and undergoes successful percutaneous intervention with a drug-eluting stent. Which of the following is *not true* regarding the stent?

A. Drug-eluting stents inhibit intimal smooth muscle proliferation
B. Smooth muscle proliferation is the cause of in-stent restenosis
C. Restenosis occurs in 5% to 10% of older generation drug-eluting stents
D. Newer generation drug-eluting stents with thicker struts and improved drug delivery have worse reendothelialization than older drug-eluting stents
E. None of the above

7-8. Which of the following is *true* about vascular progenitor cells?

A. Endothelial progenitor cells are found only in the bone marrow
B. Pericytes share properties with mesenchymal stem cells
C. Adventitial stem cells give rise to cardiomyocytes
D. Vascular smooth muscle progenitors, unlike other smooth muscle cells within the vascular wall, are proliferative
E. B and C

7-9. A 43-year-old woman presents with progressive shortness of breath. Physical exam reveals elevated neck veins, a right ventricular (RV) lift, and a loud P2. Echocardiography shows normal left ventricular function but elevated pulmonary artery pressures. Right heart catheterization shows a normal pulmonary capillary wedge pressure but markedly elevated pulmonary artery pressures. Which of the following is *not true* regarding therapies for pulmonary hypertension?

A. Epoprostenol, iloprost, and treprostinil result in vasodilation of the pulmonary vasculature
B. Sildenafil and tadalafil cause vasodilation by increasing NO levels
C. Bosentan affects endothelin receptors on smooth muscle cells and endothelial cells
D. Ambrisentan and macicentan are selective ET-A antagonists that inhibit smooth muscle vasoconstriction
E. All of the above are true

7-10. Which of the following is *true* regarding signaling pathways in vascular smooth muscle cells?

A. IP3 increases cytoplasmic calcium by direct inhibition of SERCA
B. DAG inhibits muscle contraction via PKC
C. The initial phase of smooth muscle contraction is the result of the latch-bridge state
D. Rho activation desensitizes MLC to intracellular calcium
E. None of the above

ANSWERS

7-1. **The answer is B**. (*Hurst's The Heart, 14th Edition, Chap.* 7) The notion that a bipotent hemangioblast gives rise to endothelial cells and blood cells has recently been challenged. Instead, blood cells probably develop from hemogenic endothelial cells residing in specialized vascular niches (option A).[1] Early blood vessels are derived from blood islands, which are clusters of mesodermal progenitor cells. These islands are marked by central hematopoietic progenitor cells and peripheral angioblasts (option B). Unlike during development, postnatal vasculogenesis does not rely on angioblasts, but instead occurs by the sprouting of new vessels from preexisting vessels. In the adult, vasculogenesis may be limited. However, in scenarios such as the development of collateral vasculature with obstructive coronary artery disease, arteriogenesis occurs. Arteriogenesis occurs by the sprouting of new vessels from preexisting capillaries or arterio-arterio anastomoses (option C).[2] Much work has gone into understanding cytokines that stimulate vasculogenesis. The prototypical angiokine is VEGF.[3] In fact, VEGF inhibitors are used clinically as anticancer agents to inhibit tumor-related angiogenesis (option E).

7-2. **The answer is A**. (*Hurst's The Heart, 14th Edition, Chap.* 7) Among its many functions, the endothelium is of particular importance for maintaining and protecting the integrity and function of the vascular wall, with specific roles. These include (1) functioning as a metabolic tissue that actively secretes vasoactive factors governing vascular tone (option C); (2) acting as an anticoagulant and antithrombotic surface (option A); (3) serving as a barrier to most circulating blood constituents (option E); (4) regulating the transendothelial passage of specific molecules, proteins, and cells across this barrier (option D), and (5) participating in the inflammatory response via active leukocyte recruitment and facilitation of leukocyte margination from the lumen into the vessel wall and adjacent tissues (option E).

7-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 7)* As a part of its barrier function, the endothelium regulates the transport of molecules from the vascular lumen to tissues. Water-soluble molecules, in particular, are transported across endothelial cells in vesicles called caveolae.[4] The endothelium generally serves as an antithrombotic surface. However, when inflamed, the endothelium expresses tissue factor, factor VIII, PAI-1, and factor Va, which create a procoagulant milieu (option A).[5] The endothelium has important roles in regulating inflammation. These include capture, adhesion, and migration of leukocytes (option C).[6] NO and PGI2 are vasodilators (options D and E).

7-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 7)* Conversion of a vascular smooth muscle cell from a quiescent, differentiated phenotype to a proliferative, synthetic phenotype is a hallmark of pathologic states such as neoinitimal hyperplasia. Agents such as NO, prostacyclin, and heparin inhibit growth and promote a differentiated phenotype (option D).[7-9] By contrast, growth factors such as PDGF, FGF, and IGF-1 promote smooth muscle cell migration and hyperplasia (options A, B, and E).[10] TGF-β can promote either the differentiated or synthetic phenotype, depending on the context (option C).

7-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 7)* MMPs are a diverse class of proteins that degrade the ECM (option B). TIMPs antagonize MMPs and stabilize the ECM. MMPs allow for the growth and proliferation of new blood vessels (option A). Importantly, TIMPs and MMPs play a pivotal role in the pathology of atherosclerotic plaques and aneurysms (option C).[11,12] MMPs are highly expressed in the shoulder regions of atherosclerotic plaques and predipose to plaque rupture (option D).[13] MMPs can either be membrane-spanning or secreted. Secreted MMPs are secreted as zymogens and are activated after cleavage by plasmin (option E).

7-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 7)* Endothelial dysfunction precedes the development of atherosclerotic plaque (option D). Dysfunctional endothelium has an impaired capacity for NO production (option B) and upregulates inflammatory markers that lead to the recruitment of inflammatory cells (option C).[14,15] These inflammatory cells infiltrate the vessel wall and oxidize LDL, triggering atheroma formation.[16] Endothelial dysfunction has been correlated to many clinical factors associated with coronary atherosclerotic disease (option A).[17-19]

7-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 7)* Percutaneous interventions with balloon angioplasty and bare metal stents were plagued with high rates of restenosis. Acute arterial injury results in smooth muscle proliferation. This proliferation is a major feature of restenosis (option B). Stents eluting antiproliferative drugs prevent smooth muscle proliferation, leading to reduced rates of restenosis (option A). Unfortunately, these drugs also prevented reendothelialization of the stents and are associated with acute stent thrombosis. Newer generation drug-eluting stents, with thinner struts and better drug delivery, are associated with less stent thrombosis and have better reendothelialization (option D). In the contemporary era of drug-eluting stents (DES), clinically significant restenosis arises in only 5% to 10% of treated.

7-8. **The answer is B**. *(Hurst's The Heart, 14th Edition, Chap. 7)* Endothelial progenitor cells (EPCs) expand and proliferate to make new endothelial cells. Recent work has identified a local source of EPCs within the vessel wall (option A).[2] Pericytes can differentiate into adipocytes, chondrocytes, and osteocytes and share properties with mesenchymal stem cells (option B).[2,22] Adventitial stem cells are still under investigation but appear to give rise to smooth muscle cells, endothelial cells, and myofibroblasts (option C).[23] The presence of VSMCs in the vessel wall is controversial. Both putative VSMCs and mature SMCs can proliferate (option D).[24,25]

7-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 7)*. Epoprostenol, iloprost, and treprostinil are all prostacyclin analogs and result in pulmonary vasodilation (option A).[26] Sildenafil and tadalafil inhibit phosphodiesterase and increase cGMP levels, leading to vasodilation. They do not directly increase NO levels (option B).[26] Bosentan, ambrisentan, and macicentan are endothelin receptor antagonists. Endothelin causes smooth muscle-mediated vasoconstriction via the ET-A receptor and endothelial cell-mediated vasodilation via the ET-B receptor (option C). Bosentan is a mixed ET-A/ET-B antagonist, but the newer agents ambrisentan and macicentan are more selective for the ET-A receptor (option D).[26,27]

7-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 7)*. Vasoactive agents lead to the hydrolysis of phosphoinositides by phospholipase C. As a result, inositol triphosphate (IP3) and diacylglycerol (DAG) are produced.[28] IP3 binds to IP3 receptors on intracellular organelles to increase intracellular levels of calcium (option A).[29] Increased DAG levels lead to increased PKC activity. PKC works to stimulate contraction in the presence of increased intracellular calcium levels (option B).[30] While the initial phase of smooth muscle cell contraction depends on increased intracellular calcium, the sustained phase is related to the latch-bridge state (option C). Essentially, myosin is dephosphorylated when bound to actin. Although the myosin will not actively cycle, it can maintain tension through its association with actin.[31] The GTPase Rho activates Rho kinase, leading to inactivation myosin phosphatase, type I.[32] As a result, MLC remains phosphorylated and is more sensitive to intracellular calcium (option D).[33]

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CHAPTER 8

Molecular and Cellular Development of the Heart

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

8-1. Which of the following is *not true* about the specification of cardiac precursors during gastrulation?

A. Cardiac precursors are derived from mesoderm following gastrulation
B. The fates of cardiac progenitor cells are already determined at the epiblast stage
C. The fates of progenitor cells are determined by the sequence and intensity of external signals encountered during gastrulation
D. A precursor cell's position within the epiblast determines the complement of external signals it receives
E. Mesoderm is the result of epithelial-to-mesenchymal transition (EMT) in the epiblast

8-2. Which of the following is *true* about the specification of mesoderm that gives rise to cardiac cells?

A. Cells that migrate from the anterior primitive streak give rise to lateral mesoderm
B. Cardiac progenitors are found in the lateral plate mesoderm
C. The heart and liver are the last mesoderm to be produced by the embryo
D. Retinoic acid gradients are important for separating cardiac and forelimb fields, but they do not have a role in determining whether cardiac precursors give rise to atrial cells or ventricular cells
E. The first cardiac cells formed in the lateral plate mesoderm are atrial cells

8-3. You see a 2-year-old child for episodes of cyanosis ameliorated by squatting. She is found to have Tetralogy of Fallot. Tetralogy of Fallot most likely results from defects in:

A. The proliferation of cells in the first heart field
B. Fusion of the primordial heart tubes
C. The addition of cells from the second heart field to the heart tube
D. Cardiac specification during gastrulation
E. Specification of atrial and ventricular cardiomyocytes

8-4. Which of the following is *not true* about signaling pathways during cardiac development?

A. Increased levels of nodal and canonical Wnt signaling promote cardiac specification of pluripotent stem cells to cardiac progenitors
B. Endoderm-derived BMP2 promotes the differentiation of cardiac mesoderm to cardiomyocytes
C. Noncanonical Wnt signaling restricts the differentiation of cardiac progenitors to cardiomyocytes, but canonical Wnt signaling promotes cardiac differentiation
D. Both cardiac progenitors and differentiated cardiomyocytes are equally proliferative
E. The differentiation and expansion of the second heart field occurs by a fine balance of canonical Wnt signaling, Notch signaling, and BMP signaling

8-5. Which of the following is *true* about the transcriptional control of cardiac differentiation?

A. Tbx5 is present mostly in cells from the second heart field
B. Pitx2 is important to anterior-posterior patterning
C. Nkx2.5, in coordination with Isl1, regulates the differentiation of cardiac progenitors to cardiomyocytes
D. Association of p300/CBP with cardiac transcription factors leads to histone deacetylation and the activation of transcription
E. Tissue-specific variants of chromatin complexes are not essential to cardiac differentiation

8-6. Which of the following is *true* about cardiac chamber morphogenesis?

A. The fetal heart begins to approximate the morphology of the adult heart by 6 weeks
B. Cardiac jelly is secreted by the endocardium and prevents blood flow until the valves are functional
C. Tbx2 and 3 are required for chamber maturation, whereas Tbx20 represses chamber maturation
D. Chamber formation and proportion are unrelated to localized regions of proliferation
E. Noncompaction results from the lack of the trabecular myocardium to be packed into the compact myocardium

8-7. A 67-year-old woman presents with right-sided hemiparesis. During her evaluation, she is noted to have a patent foramen ovale (PFO). Which of the following is *true* about atrial septation and her PFO?

A. Her foramen primum failed to close
B. Her septum primum did not migrate properly
C. Her septum primum and septum secundum failed to fuse
D. Her left sinus venosus remains linked to her left atrium
E. Her membranous ventricular septum failed to develop

8-8. An infant presents within 1 week of birth with poor feeding, intermittent cyanosis, and respiratory distress. Her exam is notable for a hyperdynamic precordium, bounding peripheral pulse, and a single S2. Echocardiography reveals a diagnosis of truncus arteriosus. Which of the following is *true* about cardiac development in this patient?

A. Failure to form a truncus could result from defects in neural crest migration or in second heart field precursors
B. There is persistence of the fifth pair of aortic arch artery pairs
C. The left sixth branchial arch artery failed to give rise to the trunk of the pulmonary artery
D. There is persistence of the right sixth branchial arch artery
E. There is persistence of the ductus arteriosus

8-9. Which of the following is *not true* of the epicardium?

A. The epicardium is a mesothelial sheet that covers the heart and has epithelial properties
B. The epicardium is multipotent with contributions to cardiac endothelium, fibroblasts, and coronary artery smooth muscle cells
C. In the adult heart, the epicardium is inert
D. The epicardium arises from the coelomic epithelium, which forms the proepicardium
E. The epicardium is a heterogeneous group of cells

8-10. Which of the following is *true* about cardiac development and homeostasis?

A. Cardiomyocyte renewal does not occur in the adult heart
B. The SA node has contributions from both the first and second heart fields
C. Cardiac innervation occurs independently of coronary vasculogenesis
D. The coronary endothelium has a single source of cells
E. Purkinje cardiomyocytes have more mitochondria than other cardiomyocytes in the ventricle

ANSWERS

8-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 8)* After gastrulation, the cardiogenic area, containing cardiac precursors, is formed by early gastrulating mesoderm (option A). It is located within the mesodermal component of the splanchnopleural layer of the anteriormost lateral plate.[1,2] Mesoderm itself is formed by EMT of cells at the central-posterior position in the epiblast (option E).[3] Although different regions of the epiblast give rise to specific cell types, the fates of the precursor cells themselves at this stage are not yet determined (option B).[4] Transplantation studies have shown, for example, that epiblast regions fated to produce brain transplanted to the cardiac-forming region will form the heart, and vice versa. Ultimately, the history of external signals cells receive during their journey through gastrulation determines the differentiation pathway of precursor cells (option C). The sequence of signals received is determined by the location of precursor cells within the epiblast (option D).[3]

8-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Cells migrate out of the primitive streak, such that the anteriormost cells form the axial mesoderm and the posterior cells form the lateral mesoderm (option A). The cardiac fields are found in the lateral plate mesoderm, and along with the hepatic mesoderm they are among the first types of mesoderm specified (options B and C). The first cardiac mesoderm specified gives rise to the septum transversus (option E). Like with gastrulation, local signaling gradients drive differentiation. Retinoic acid gradients, in particular, have been shown to contribute to the separation of cardiac and forelimb fields in addition to the specification of subtypes of cardiac cells, such as atrial and ventricular cardiomyocytes (option D).[5]

8-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Tetralogy of Fallot is classically characterized by pulmonary atresia, a VSD, an overriding aorta, and right ventricular hypertrophy. Following cardiac specification in the lateral plate mesoderm, two heart fields emerge (options D and E). The first heart field gives rise to the left ventricle and most of the atria (option A). The second heart field is adjacent to the first heart field and gives rise to the right ventricle, the outflow tract, and parts of the atria and inflow tract.[2,6,7] Cells from the first heart field differentiate and contribute to the primitive heart tubes (option B). Cells from the second heart tube differentiate somewhat later and are sequentially added. In humans and chicks, there are two primordial heart tubes that must fuse at the midline to form a single heart tube.[8,9] Defects observed in tetralogy of Fallot are associated with structures derived primarily from the second heart field (option C).

8-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Pluripotent cells are fated to cardiac progenitors by canonical Wnt signaling (option A).[2,10] As cardiac mesoderm, cardiac progenitors differentiate into cardiomyocytes in response to BMP signaling from the extraembryonic tissues and endoderm adjacent to cardiac mesoderm (option B).[1] Progenitor cells are proliferative and tend to expand to cardiac fields, while differentiated cells are less proliferative (option D). In general, canonical Wnt/FGF/Shh signaling promote the specification of cells to cardiac progenitors, while BMP and noncanonical Wnt signaling promote differentiation into cardiomyocytes (options C and E).[10,11]

8-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 8)* The molecular regulation of cardiomyocyte specification and differentiation has been the subject of intense study. Different transcription factors are important to regional specification of the heart. For example, Tbx5 is present in anterior heart field cells (option A), Hand2 in second heart field cells, and Tbx1 in cells of the outflow tract.[12,13] More broadly, Gata, Nkx, and Isl factors are important for cardiomyocyte identity. Nkx2.5 is thought to promote cardiomyocyte differentiation, and the balance of a progenitor state versus a differentiated state is maintained by Nkx2.5 competing with Isl1 and Meis factors (option C).[14,15] In addition, *Pitx2c* is expressed in the left side of the SHF, as part of its general role in left-right patterning of lateral plate derivatives in the embryo (option B).[16] While transcription factors can trigger gene expression, access to a locus occurs at the chromatin level. Recent work has highlighted the role of HDACs to deacetylate chromatin, leading to the repression of expression at a locus. Conversely, p300/CBP acetylate histones lead to gene activation (option D). Further, tissue-specific isoforms, such as the Mel1 isoform of PRC1, are important for dictating tissue-specific gene expression programs (option E).[17]

8-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Cardiac morphogenesis starts at 3.5 weeks. In the 12th week, outflow tract subdivision and complete interventricular and atrial septation lead to a heart bearing the gross morphological organization of a definitive adult heart (option A).[8] The heart initially starts as a tube with an inner endocardium. Cardiac jelly is secreted by cardiomyocytes, and it prevents blood flow through the heart tube until the valves are competent (option B). Localized regions of proliferation lead to chamber ballooning. Tbx2 and 3 are important repressors of differentiation, but Tbx20 is required for chamber maturation (option C).[1,18] Following looping, chamber formation results from localized proliferation and ballooning of the chambers (option D).[19,20] The trabecular myocardium initially preserves cardiac output but is incorporated into the compact myocardium during compaction (option E).

8-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Cardiac septation occurs during the seventh week with the growth of a muscular ventricular septum between the right and left ventricles (option E). Later, a membranous septum grows between the muscular septum and the mesenchyme that contains the AV cushions. Atrial septation occurs first with a septum primum that grows between the atria, but that leaves a foramen primum between the septum primum and the AV cushions (option B). As the foramen primum is closed, a second foramen secundum develops in the septum primum (option A). A second septum secundum develops and occludes the foramen secundum. However, the septum secundum contains the foramen ovale, which allows for right-to-left blood flow but not the reverse. The foramen ovale closes due to fusion of the septum primum and secundum. Failure to fuse can lead to a persistent PFO (option C).[21]

8-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 8)* The aortic arch and pulmonary artery result from extensive remodeling of the embryonic aortic arch arteries. The six aortic arch artery pairs develop into five pairs of branchial arch arteries. The fifth aortic arch artery pair undergoes involution and does not contribute to a branchial arch artery pair (option B). The first two pharyngeal artery pairs and the right VI artery regress and do not produce any definitive contribution to the adult aorta (option D). The left VI artery forms the pulmonary trunk and pulmonary arteries (option C). The III pair of arteries forms the common carotid arteries, and the IV pair of arteries makes small contributions to the right subclavian artery and aortic arch. The pulmonary trunk remains attached to the aorta through the ductus arteriosus, which closes and involutes at birth (option E). Outflow tract septation results from the contribution of migrating neural crest and second heart field precursors (option A).[22] Defects can lead to truncus arteriosus.

8-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 8)* The epicardium is the outer mesothelial layer of the heart that makes important contributions to the noncardiomyocyte cells of the heart. The epicardium is an epithelial sheet that covers the heart and can undergo EMT to become smooth muscle cells or fibroblasts (option A). The epicardium is heterogeneous, and some subsets may contribute to the endocardium and coronary endothelium (options B and E).[23-25] The epicardium forms from the proepicardium, which derives from the coelomic epithelium (option D).[26] In the adult heart, the epicardium is activated following injury. The epicardium proliferates and invades the injured area (option C).[27,28]

8-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 8)* Cardiomyocytes are originally added to the developing heart by the expansion and differentiation of progenitor cells. Over time, additional cardiomyocytes are added to the heart by symmetric division of cardiomyocytes. The capacity for cardiomyocyte proliferation wanes with time, but recent work has suggested a low grade of cardiomyocyte proliferation and renewal in the adult heart (option A).[29] The conduction system is a set of specialized cells that coordinate ordered chamber contraction. Cells of the conduction system, such as the Purkinje cells, have less contractility than the working myocardium. They have decreased numbers of mitochondria and disorganized sarcomeres (option E). The cellular origins of the conduction systems are diverse. For example, the SA node is derived from both first and second heart field progenitors (option B).[30,31] The coronary endothelium starts to develop as cardiac muscle thickens. The coronary endothelium has diverse cellular origins, including the sinus venosus endothelium, the ventricular endocardium, and potentially a subset of epicardial cells (option D).[23,32-36] Finally, coronary development is also important for the innervation pattern of the heart (option C).

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CHAPTER 9

Genetic Basis of Cardiovascular Disease

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

9-1. A 23-year-old woman presents with a long history of muscle weakness. Her past medical history is notable for "hypertrophic" cardiomyopathy (HCM), cryptogenic stroke, and optic neuritis. She was told that she had a dilated cardiomyopathy prior to developing a hypertrophic cardiomyopathy. Physical examination, in addition to findings of HCM, are remarkable for short stature and hearing loss. Labs are notable for an elevated CPK. Her family history includes multiple family members with cardiac problems. Her pedigree is shown in Figure 9-1. Her brother has a similar constellation of findings of similar severity. Her mother, her maternal grandmother, and her maternal uncle also have a similar set of findings but with milder severity. Based on the presentation and pedigree, what is the likely mode of inheritance?

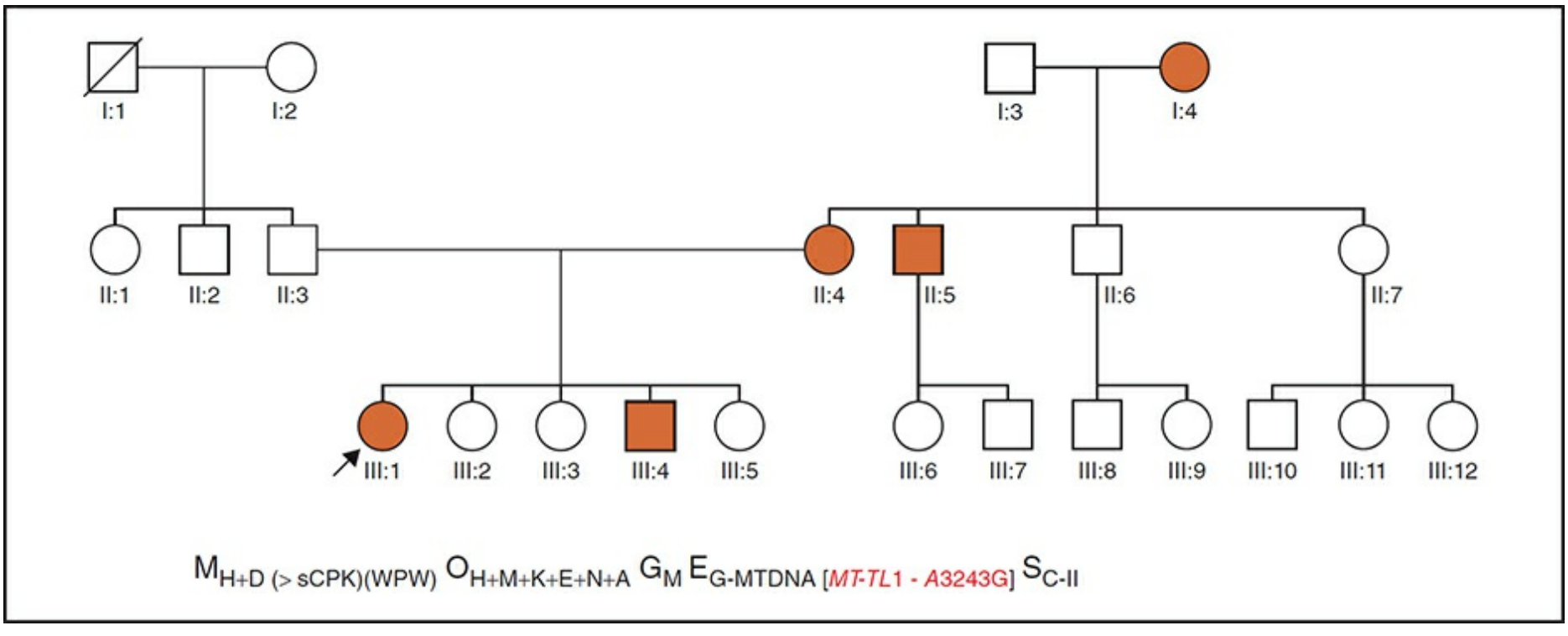

FIGURE 9-1 Pedigree for question 9-1.

A. Autosomal recessive
B. Spontaneous somatic mutation
C. X-linked
D. Mitochondrial inheritance
E. Spontaneous chromosomal translocation

9-2. Which of the following is *true* of heritable cardiomyopathies?

A. About 1 in 500 people carry a gene associated with HCM
B. Patients with sarcomeric mutations can have either a hypertrophic, dilated, or restrictive cardiomyopathy
C. Most heritable cardiomyopathies are autosomal recessive
D. Heritable cardiomyopathies are rare
E. Patients with heritable cardiomyopathies only have mutations in sarcomeric genes

9-3. A 38-year-old man is admitted with acute aortic dissection. Upon inquiry, he is noted to have a strong family history of aortic disease with dissection. Which of the following is *not true* about heritable thoracic aortic diseases?

A. Genetic disorders with increased risk for thoracic aortic dissection are associated with mutations in genes related to extracellular matrix proteins and TGF-β signaling

B. Patients with bicuspid aortic valves are at increased risk for aortic dilation
C. He most likely has an autosomal dominant genetic syndrome
D. A bifid uvula would suggest a diagnosis of Marfan syndrome
E. Translucent skin would suggest a diagnosis of Ehlers–Danlos syndrome

9-4. A 28-year-old woman is sent to you for evaluation of shortness of breath. Her examination reveals elevated neck veins, a right ventricular (RV) heave, and a loud P2. Echocardiography confirms the presence of pulmonary hypertension (PH). Family history is notable for multiple members with PH. Which of the following is *true* about heritable PH?

A. Familial PH is classified as type 2 PH
B. The most common form of heritable PH is associated with a mutation in *BMPR2*
C. Less common mutations in PH include mutations in *FBN1*
D. The presence of multiple telangiectasias would suggest a diagnosis of Gaucher disease
E. Mutations in *BMPR2* are only associated with familial PH

9-5. Which of the following is *not true* of inherited atrial diseases?

A. Mutations of *NPPA* are associated with an autosomal recessive atrial dilated cardiomyopathy
B. Mutations in *SCN5A* are associated with heritable sick sinus syndrome, LQT3, and Brugada syndrome
C. Mutations of *HCN4* are associated with heritable sick sinus syndrome
D. Mutations in the gene *Shugosin-like 1* are associated with chronic atrial and intestinal dysrhythmia (CAID)
E. Having a parent with atrial fibrillation has no effect on one's risk for developing atrial fibrillation

9-6. A 28-year-old man is admitted for syncope following exercise. He has no other prior medical history, and physical examination is normal. Family history is notable for a history of sudden cardiac death. ECG shows evidence of a long QT interval with broad-based T waves. This patient most likely has a mutation in which ion channel?

A. *NPPA*
B. *SCN5A*
C. *KCNQ1*
D. *KCNH2*
E. *HCN4*

9-7. A 34-year-old man presents after resuscitation following cardiac arrest. He is otherwise healthy. ECG shows ST elevation in the anterior precordial leads. Which of the following is *not true* about Brugada syndrome?

A. Brugada syndrome is more common in Southeast Asia
B. Brugada syndrome is associated with mutations in *RYR2*
C. The ECG manifestations of Brugada syndrome can be variable, but they are induced with drugs like ajmaline
D. Arrhythmia can be exacerbated by fevers
E. Arrhythmia can be exacerbated by interactions with certain drugs

9-8. A 35-year-old man presents with atrial arrhythmias. He has a past medical history of thyroid tumors. The physical exam is notable for pigmented skin lesions. Echocardiogram shows the presence of an atrial myxoma. Which of the following is *true* of his syndrome?

A. His syndrome is associated with mutations in the *PTCH1* gene
B. His syndrome is associated with an increased incidence of pancreatic tumors
C. Histologically, the myocytes are round and vacuolated
D. His myxoma will likely respond to rapamycin
E. He is at increased risk for medulloblastoma

9-9. A 21-year-old female presents to you for evaluation of chest pain. She has had recurring bouts of chest pain since she was 8 years old. Her chest pain is worse when lying supine and improves when sitting upright. Her chest pain is also made worse with deep inspiration. In addition to chest pain, she has abdominal pain and fevers during these episodes. The episodes are self-limited and have no specific trigger. Family history of a similar disorder is not known. Which of the following is *true* of familial Mediterranean fever (FMF)?

A. FMF is autosomal dominant
B. FMF is the result of a mutation in the *G6PD* gene
C. The chest pain and abdominal pain are part of a pan-serositis
D. The disease is most common in Western European populations
E. Heterozygous patients are not at risk for the periodic fever syndrome

9-10. Which of the following is *true* about the genetic basis of coronary heart disease (CHD)?

A. Most of the genetic variants that contribute to CHD are known
B. Twin studies show a decreased risk of CHD if the other twin died of premature CHD
C. The 9p21-3 allele is associated with a high risk for CHD

D. Most heritable CHD is due to monogenic disorder
E. Single nucleotide polymorphisms (SNPs) that contribute to CHD are uncommon

ANSWERS

9-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 9)* The patient has a syndrome of mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes (MELAS). MELAS patients can have a dilated cardiomyopathy that transitions to a HCM.[1] MELAS is a mitochondrial myopathy and often is the result of a mutation in transfer RNA (option D). The pedigree shows the phenotype in every generation. Spontaneous mutations would not be in each generation (options B and E). Autosomal recessive mutations skip every generation (option A). Similarly, X-linked mutations tend to involve males because males have a single X chromosome (option C). Autosomal dominant mutations result in affected family members in each generation, but this is not a choice. Mitochondrial DNA is maternally derived, so the disease can only be passed by females. The penetrance of the disease is related to the amount of abnormal mitochondrial DNA that is inherited.

9-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Hypertrophic cardiomyopathy is the most common heritable cardiomyopathy. One in 500 young adults are affected, and 1 in 200 people carry a mutation that is associated with HCM (option A).[2] While patients with HCM primarily have mutations of sarcomeric proteins, sarcomeric mutations can result in either a hypertrophic, dilated, or restrictive cardiomyopathy (option B).[3] While the full complement of mutations leading to heritable cadiomyopathies remains unknown, up to 80% of heritable cardiomyopathies are autosomal dominant (options C and E).[4] Furthermore, heritable cardiomyopathies are common, with more than 50% of patients with dilated cardiomyopathy having evidence for an underlying genetic cause (option D).[4]

9-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Heritable thoracic aortic aneurysm and dissection (TAAD) includes more than 40 genetically different disorders. The genetic basis for these disorders is diverse, and many involve mutations in genes related to extracellular matrix proteins and TGF-β signaling (option A). For example, Marfan syndrome is associated with mutations in the extracellular matrix protein *FBN1*, and mutations of *TGFBR1* and *TGBFR2* cause Loeys–Dietz syndrome type 1 (LDS1) and Loeys–Dietz syndrome type 2 (LDS2), respectively.[5] In 25% of cases, patients with bicuspid aortic valves have dilation of the ascending aorta (option B).[6] Most heritable thoracic aortic aneurysm disorders (TAAD) are autosomal dominant (option C). Different TAAD syndromes are associated with other clinical features. Patients with Marfan syndrome have typical skeletal traits. LDS1 patients have craniofacial traits, including a bifid uvula and craniosynostosis (option D). Patients with Ehlers–Danlos type IV (EDSIV) have a typical skin and face morphology. Facial features include a thin nose, thin lips, prominent eyes, hollow cheeks, a small chin, and lobeless ears. The skin is very thin and nearly translucent, allowing for visualization of the underlying blood vessels (option E).

9-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 9)* The WHO classifies PH in five groups.[7] Group 1 includes idiopathic PH, heritable PH, drug-induced PH, CHD with PH, pulmonary veno-occlusive disease, and pulmonary capillary hemangiomatosis. Group 2 includes PH related to left heart disease (option A). Group 3 includes PH secondary to lung disease. Group 4 includes chronic thromboembolic PAH. Group 5 PH includes miscellaneous disorders that can affect the pulmonary vasculature with unclear or multifactorial mechanisms. Up to 80% of patients with familial autosomal dominant PH have mutations in *BMPR2* (option B).[8] Similarly, up to 20% of sporadic PH is associated with acquired mutations of *BMPR2* (option E). Mutations in *FBN1* are associated with Marfan syndrome (option C). While Gaucher disease can be associated with PH, telangiectasias are associated with Osler–Weber–Rendu syndrome (option D).

9-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Atrial dilated cardiomyopathy (ADCM) is a rare autosomal recessive disease that manifests as biatrial dilation with progression to electrical standstill of the atria. ADCM is associated with mutation of the *NPPA* gene (option A).[9] *SCN5A* encodes a key sodium channel within the heart, and different mutations of *SCN5A* are associated with various arrhythmias, including sick sinus syndrome, LQT3, and Brugada syndrome (option B).[10-14] Mutations of *HCN4* are also associated with a heritable sick sinus syndrome (option C). CAID is associated with mutations in the *Shugosin-like 1* gene and manifests with atrial dysrhythmias and chronic intestinal pseudo-obstruction (option D). The genetic basis for familial atrial fibrillation is not as clear for other arrhythmias, but having an affected parent increases a person's risk for developing atrial fibrillation by 85% (option E).[15]

9-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 9)* This patient has LQT1. LQT1 manifests with exercise-induced arrhythmias. ECG shows broad T waves with a prolonged QT interval. LQT1 involves mutations in *KCNQ1*, and it can be treated with beta blockade (option C). Mutations in *NPPA* are associated with heritable atrial dilated cardiomyopathy (option A). Mutations in *SCN5A* are associated with LQT3, SSS, and Brugada syndrome (option B). Mutations in *KCNH2* are associated with LQT2 (option D). Mutations in *HCN4* are associated with heritable sick sinus syndrome (option E).

9-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Brugada syndrome is a genetic syndrome that is associated with increased risk for sudden cardiac death. Brugada syndrome is heritable, most commonly involving mutations of *SCN5A*, and it tends to occur most commonly in patients from Southeast Asia (options A and B).[16] The ECG typically has ST elevations in the anterior precordial leads. However, these findings are not always readily apparent. Drugs like ajmaline can elicit a more classical pattern in such patients (option C). Arrhythmias can occur with sensitizing factors like fever or drugs (options D and E).

9-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 9)* This patient has Carney syndrome. Type I Carney complex is associated with mutations in the *PRKAR1A* gene (option A). As many as 2.5% of patients with Carney syndrome have pancreatic tumors (option B).[17] Purkinje cell hamartomas, not atrial myxomas, are associated with round and vacuolated myocytes (option C). mTOR inhibitors are used to treat rhabdomyomas associated with tuberous sclerosis (option D).[18] Medulloblastoma is associated with cardiac fibromas and Gorlin

9-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Familial Mediterranean fever is a rare autosomal recessive disorder, most common in patients of Eastern European ancestry (options A and D).[19] FMF is most commonly caused by a mutation in the *MEFV* gene that encodes pyrin, a component of the cellular inflammasome (option B). Patients typically present with abdominal pain and chest pain indicative of serositis (option C). Heterozygous patients can also manifest the disease during stresses, or they can alternatively present with other inflammatory syndromes

9-10. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 9)* Coronary heart disease is a prototypical complex genetic disease (option D). The genetic basis for CHD has been supported by twin studies showing an increased risk for CHD in the second twin when the first twin dies of CHD (option B).[23] Large-scale, genome-wide association studies have identified multiple common SNPs associated with CHD (option E). Together, these SNPs account for about 10% of the heritable basis for CHD (option A).[24] Each SNP generally has a small effect. However, the 9p21-3 allele, in particular, is considered a high risk for CHD (option C).[25,26]

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CHAPTER 10

Stem Cells and the Cardiovascular System

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

10-1. Which of the following is *not true* about mechanisms of cell therapy?

A. Transdifferentiation is when a differentiated cell type commits to becoming a new cell type
B. Angiogenesis is the formation of new blood vessels
C. Bone marrow cell therapy is likely to promote ventricular recovery by transdifferentiation into cardiomyocytes
D. Dedifferentiation likely confers a protective effect for injured cardiomyocytes
E. Transplanted bone marrow cells are transiently retained in the heart following cardiac injury

10-2. Which of the following is *true* of stem cell delivery approaches to the heart?

A. Intracoronary injection of stem cells results in better engraftment of cells than transendocardial injection
B. Transendocardial injection does not require adjunctive imaging modalities to target injured myocardium
C. Intravenous administration of stem cells is a promising approach because stem cell populations evaluated thus far are efficient in their homing to injured myocardium
D. Transepicardial injection of stem cells requires adjunctive imaging modalities to target injured myocardium
E. Activation of resident stem cells has been evaluated in human studies after acute myocardial infarction (MI)

10-3. Which of the following limits the clinical application of skeletal myoblasts to improve cardiac function following injury?

A. Skeletal myoblasts do not share contractile properties with cardiomyocytes
B. Skeletal myoblasts are difficult to isolate
C. Skeletal myoblasts are difficult to expand
D. Skeletal myoblasts do not readily adapt to a hypoxic environment
E. Skeletal myoblasts do not electrically couple to the myocardium and may increase the risk for arrhythmia

10-4. A 54-year-old man presents to your office asking for stem cell therapy. He recently had a large anterior infarct with residual left ventricular (LV) dysfunction. He has read about bone marrow mononuclear cell (BMMNC) therapy and would like some guidance. Which of the following can you tell him?

A. The cells responsible for improving LV function in preclinical models are hematopoietic progenitor cells
B. Early clinical studies after acute MI demonstrate an unequivocal increase in LV function after treatment with BMMNCs
C. BMMNCs can be administered relatively safely, but their efficacy is not proven following acute MI or for chronic heart failure
D. Treatment with BMMNCs improves functional status but not ventricular function
E. None of the above

10-5. The patient from question 10-4 returns to your clinic and is now asking about treatment with mesenchymal stem cells (MSCs). Which of the following can you tell him?

A. Unlike BMMNCs, allogeneic MSCs require immunosuppression
B. MSCs are more effective than BMMNCs for improving ventricular function following acute MI
C. MSCs can differentiate into cardiac progenitors in vivo
D. MSCs from different sources, such as the bone marrow or Wharton's jelly, are equivalent
E. Preliminary data on MSCs for the treatment of cardiovascular disease are promising, but additional studies are needed before routine use can be recommended

10-6. Which of the following is *not true* about angiogenic progenitor cells (APCs)?

A. APCs give rise primarily to endothelial cells

B. Intracoronary injection of $CD34^+$ APCs can reduce angina, but they are associated with small elevations of cardiac biomarkers
C. APCs for the treatment of heart failure have had mixed results
D. Patients with nonischemic heart failure have normally functioning APCs
E. Early studies do not suggest a benefit of APCs for peripheral arterial disease (PAD)

10-7. Which of the following is *true* of adipose stem cells?

A. MSCs derived from adipose tissue are attractive for cell therapy because they are more easily obtained than bone marrow MSCs
B. Adipose-derived MSCs can be differentiated to cardiomyocytes in vivo
C. Adipose tissue can be transdifferentiated to endothelium in vivo
D. The number of adipose-derived MSCs is related to glucose sensitivity
E. Adipose-derived MSCs are limited by adverse events in early clinical trials

10-8. A 65-year-old woman presents to your clinic for advice about stem cell therapy. She brings in a brochure for the use of cardiac stem cells and wants to know your thoughts on stem cell therapy for the heart. She has a nonischemic cardiomyopathy with reduced LV function (LVEF 25%) and class III heart failure symptoms. Her ECG reveals a left bundle branch block with a QRS duration of 150 ms. She has been taking guideline-directed medical therapy for her heart failure and has an implantable defibrillator. She is very intent on going to a stem cell clinic. Which of the following can you use to advise her?

A. Cardiac stem cells are known to promote heart regeneration in preclinical models
B. Current approaches to isolate resident cardiac stem cells include harvest from peripheral blood
C. A resident stem cell population in the heart has been clearly identified, but work regarding clinical efficacy is still preliminary
D. She is more likely to benefit from an upgrade of her ICD to a biventricular pacing system
E. Cardiac progenitor cells are a promising approach to treat heart failure and should be sought out to the best of one's ability

10-9. Which of the following is *not* a limitation to using embryonic stem (ES) cells for cardiac cell therapy?

A. Obtaining ES cells for cell therapy is limited by ethical controversies
B. ES cells would be used as an autologous cell source, requiring immunosuppression after transplantation
C. ES cells are potentially tumorigenic
D. Protocols for robustly differentiating ES cells into cardiomyocytes are lacking
E. Evidence is lacking for the clinical efficacy of ES cells for heart regeneration

10-10. Which of the following is *not true* regarding induced pluripotent stem cells (iPSCs)?

A. iPSCs can be used to generate autologous cardiomyocytes for cell therapy
B. The generation of iPSCs from somatic cells has the potential for tumorigenesis
C. iPSCs can be used to model genetic diseases
D. Like ES cells, the generation of iPSCs remains controversial
E. iPSCs can provide a human model system for fundamental mechanistic work

ANSWERS

10-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 10)* Multiple groups have tested the efficacy of bone marrow cell therapy after MI. Bone marrow cells in preclinical models rarely transdifferentiate into cardiomyocytes (options A and C), are transiently retained in the heart (option E), and most likely exert their beneficial effects on cardiac function through a paracrine mechanism that stimulates new blood vessels through angiogenesis (option B).[1-4] Lastly, a novel concept in cardiac repair is modulation of dedifferentiation. Dedifferentiation is the process by which cardiomyocytes take on a gene and protein expression profile that is more similar to fetal. This phenotype occurs more often in acute and chronic injury of the heart and seems to confer a potential survival advantage of these cardiomyocytes (option D).

10-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 10)* While additional work is needed for cell therapy to be considered a treatment modality, the science of stem cell delivery has rapidly developed. Current approaches include intravenous delivery, but this is limited by poor retention of stem cells in the myocardium (option C). Intracoronary injection of stem cells can be done during percutaneous coronary intervention, but stem cell retention is not as good as with transendocardial injection (option A).[4,5] Transendocardial injection can also be done in the catheterization laboratory, but it requires advanced imaging to identify target areas for injection (option B). Transepicardial injection may be of similar value, but it requires direct visualization of the heart (option D).[6] An alternative to intracardiac

injection is activation of resident stem cells, but this approach remains in preclinical investigation (option E).

10-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 10)* Skeletal myoblasts are skeletal muscle precursor cells derived from skeletal muscle satellite cells. Interest in this population was supported by similarity to adult cardiomyocytes, the potential for autologous utilization, ease of expansion in vitro, and resistance to hypoxic environment (options A through D). However, the MAGIC clinic trial and other pilot studies showed an increased risk for arrhythmia.[7] Functionally, skeletal muscle fails to couple with endogenous cardiac muscle (option E).[8]

10-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 10)* Several preclinical studies showed an improvement in ventricular function after MI with infusion of BMMNCs.[9,10] However, these findings have since proven controversial. Key questions remain as to the mechanism of action and the cell type responsible for the reverse remodeling that has been observed (option A). Nonetheless, human trials have been taking place for nearly two decades. These have been mostly small trials of variable design, and meta-analyses for treatment following acute MI or for ischemic cardiomyopathy have shown mixed results for improving ventricular function or functional status (options B and D).[11] While the science of BMMNCs is still developing, methods of delivery have evolved, and catheter-based delivery of BMMNCs has proven to be relatively safe (option C).

10-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 10)* MSCs are a promising source for cell therapy. MSCs arise from diverse sources and can be differentiated into multiple cell types, including cardiomyocytes, in vitro (option C).[12,13] Unlike BMMNCs, MSCs are thought to be immune privileged, raising the possibility for allogeneic transplantation without immunosuppression (option A). The POSEIDON trial evaluated MSCs in patients with ischemic cardiomyopathy. Interestingly, the autologous MSC group showed improved 6-minute walk distances and Minnesota Living with Heart Failure Questionnaire scores, whereas the allogeneic MSCs group showed a reduction in LV end-diastolic dimension. Both groups showed a reduction in infarct size (option B).[14] MSCs from different sources may have differing efficacies, but MSCs from different sources have yet to be tested for comparative efficacy (option D). Finally, like BMMNCs, clinical studies for MSCs are small, and additional studies are needed before MSCs can be recommended therapeutically (option B).

10-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 10)* APCs are a population of progenitor cells that mainly give rise to endothelial cells (option A).[15] Patients with nonischemic heart failure have functionally impaired APCs (option D). Vrtovec et al. conducted one of the largest randomized trials, with 110 nonischemic cardiomyopathy patients randomized to receive either $CD34^+$ intracoronary infusion or standard therapy. At 12 and 60 months, the $CD34^+$ treatment group showed a significant improvement in LVEF and 6-minute walk distance.[16] However, injection of $CD133^+$ cells led to improved myocardial perfusion but resulted in a lower LVEF, and no difference in functional capacity.[17] This study contradicted findings from prior nonrandomized studies that investigated $CD133^+$ cells (option C).[18] APCs are promising for the treatment of chronic angina, but intracoronary infusion has been associated with small elevations of cardiac biomarkers (option B).[19,20] Patients with nonischemic heart failure have abnormally functioning APCs (option D).[21] Multiple studies have examined the role of APCs in the treatment of PAD, with most showing an excellent safety profile with marginal to no benefit (option E).[19,22-24]

10-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 10)* Adipose tissue harbors a heterogeneous set of progenitor cells, mostly MSCs. These MSCs are attractive because they can be obtained from liposuction, which is easier than bone marrow biopsy (option A). The study of adipose-derived stem cells is still early. MSC cell fates in vivo are still being explored, and conditions for generating MSCs are still being optimized (options B through D). Initial clinical work suggests safety, but additional studies are needed to evaluate efficacy (option E).[25,26]

10-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 10)* Despite nearly two decades of preclinical research, cardiac progenitor cells remain very controversial. Beyond issues of identity, whether the postnatal heart harbors a population of resident progenitor cells has been hotly debated (options A and C).[27,28] Several groups have pushed forward with putative cardiac stem cells. These groups rely on harvest of stem cells from the heart for expansion and then retransplantation (option B).[29,30] Early results are promising, but definitive results for clinical efficacy remain. This patient is the ideal candidate for cardiac resynchronization therapy, and upgrading her device to a biventricular pacing system should be strongly recommended before pursuing less proven approaches (options D and E).

10-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 10)* The isolation and expansion of human ES cells was a formidable scientific achievement. Many groups have used this model to understand mechanisms of development and to develop protocols for robustly differentiating ES cells into specific cell types, such as cardiomyocytes. Current protocols allow for differentiation, expansion, and isolation of cardiomyocytes with greater than 90% purity (option D).[31,32] However, widespread use of ES cells to make new cardiomyocytes remains limited by controversy in obtaining new lines of ES cells, concerns for the tumorigenic potential of transplanted ES cells, and the possible need for immunosuppression after the transplantation of ES cells (options A, B, and C).[33] Initial clinical trials testing ES cells in patients with ischemic cardiomyopathy are underway (option E).

10-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 10)* The ability to transform somatic cells to pluripotency was

a major scientific achievement. The delivery of a cocktail of factors can generate ES-cell–like cells from somatic cellular sources, including fibroblasts and urinary epithelial cells. Thus, iPSCs can be developed to represent individual patients without the ethical concerns surrounding ES cells (option D). As with ES cells, however, concerns remain about the tumorigenic potential of transplanted iPSC cells (option B). Unlike ES cells, because a patient's own cells can be reprogrammed to cardiomyocytes, the possibility exists for autologous cell therapy not requiring immunosuppression (option A). Over the past decade, iPSCs have been used to model genetic cardiovascular diseases and to create platforms for assessing drug safety. Further, iPSC-derived models of disease are being used to better understand the mechanisms that underlie many genetic disorders (option E). Disease modeling is primarily limited to heritable, cell-autonomous disorders (option C).

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SECTION 3

Evaluation of the Patient

CHAPTER 11

The History, Physical Examination, and Cardiac Auscultation

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

11-1. All of the following findings would suggest a diagnosis of hypertrophic cardiomyopathy *except*:

A. Paradoxically split S2
B. Bifid pulse
C. “Triple ripple” apical impulse
D. S4
E. Fixed split S2

11-2. A 35-year-old man with a history of intravenous drug abuse and known bicuspid aortic valve presents with increasing shortness of breath, fevers, and lethargy. All of the following physical examination findings would suggest a diagnosis of aortic insufficiency complicating infective endocarditis *except*:

A. Bisferiens pulse
B. A high-pitched, “cooing,” diastolic murmur
C. A middiastolic rumble
D. Diastolic murmur best heard over the second right intercostal space
E. Arterial pulse that is increased in amplitude

11-3. A 59-year-old man presents with several episodes of substernal chest pressure of 15 minutes’ duration, which was brought on by an argument with his neighbor. His pain is relieved by nitroglycerine. According to the Forrester and Diamond chest pain classification, this patient’s angina would be described as:

A. Noncardiac chest pain
B. Atypical angina
C. Typical angina
D. Dyspnea
E. Walk-through angina

11-4. A 76-year-old woman with severe aortic stenosis presents with dyspnea and worsening functional class in the setting of new-onset atrial fibrillation. Which of the following auscultatory findings would *not* be expected?

A. A late-peaking crescendo-decrescendo systolic murmur
B. A soft S2
C. An apical systolic murmur
D. Delayed and weak carotid upstroke
E. An S4

11-5. The simultaneous left ventricular and aortic pressure tracings (Figure 11-1) are obtained from two different patients undergoing cardiac catheterization for dyspnea. Which of the following diagnoses are suggested in Figure 11-1(*a*) and Figure 11-1(*b*), respectively?

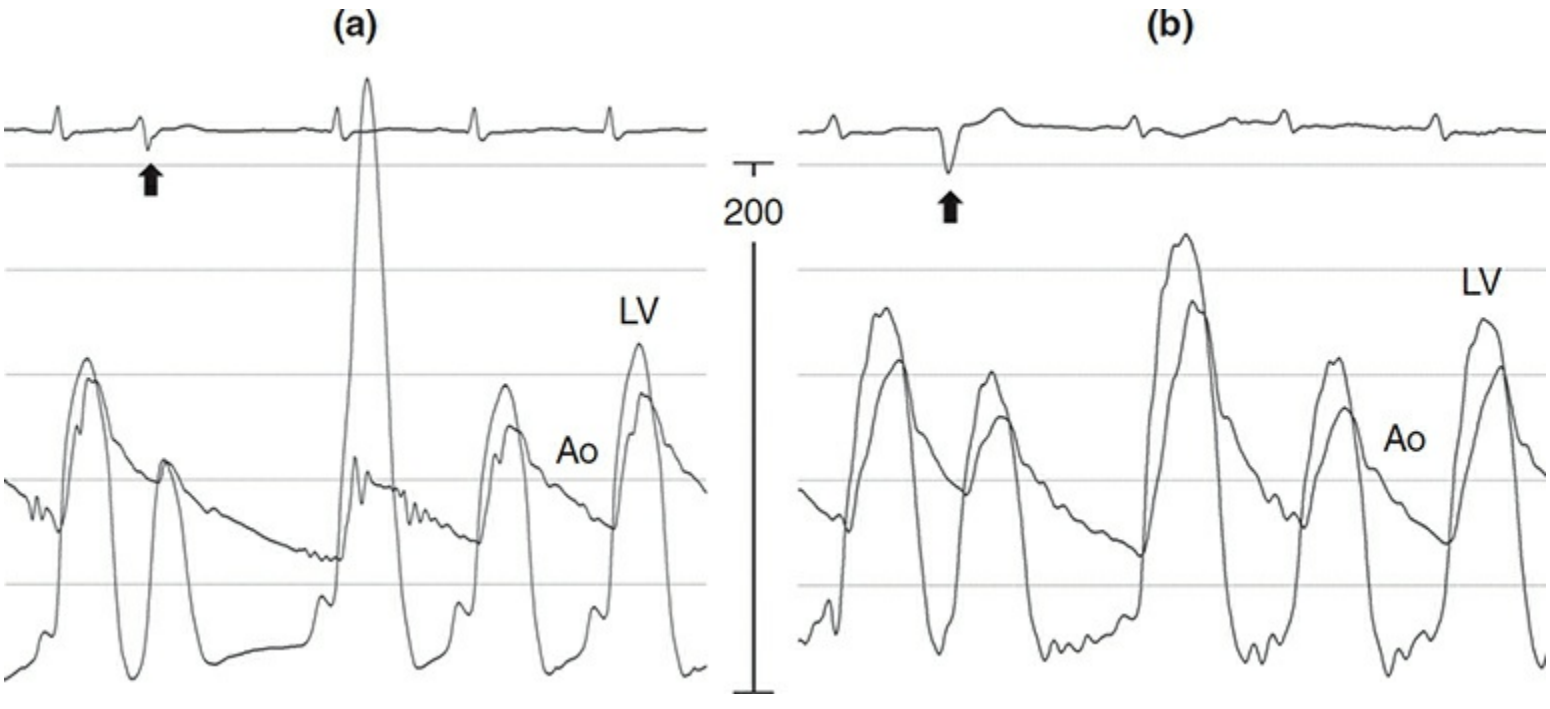

FIGURE 11-1 Simultaneous aortic and left ventricular pressure tracings taken from two patients (*a* and *b*).

A. Aortic stenosis and hypertrophic obstructive cardiomyopathy (HOCM), respectively
B. Hypertrophic obstructive cardiomyopathy and aortic stenosis, respectively
C. Mitral stenosis and aortic stenosis, respectively
D. Mitral regurgitation and mitral stenosis, respectively
E. Hypertrophic obstructive cardiomyopathy and mitral stenosis, respectively

11-6. A 25-year-old woman is referred for a murmur. Transthoracic echocardiography demonstrates mitral valve prolapse. Which of the following is *true* about the click accompanying mitral valve prolapse?

A. This usually occurs in early systole
B. Upon standing, the click will occur earlier in systole
C. It decreases in intensity with inspiration and moves closer to S1
D. This is a lough, high-pitched sound
E. Upon Valsalva maneuver, the click will occur later in systole

11-7. A 34-year-old man presents with a family history of bicuspid aortic valve disease. On auscultation, a loud murmur is heard at the upper sternal border. No thrill is palpable. How should this murmur be graded?

A. Grade I
B. Grade II
C. Grade III
D. Grade IV
E. Grade V or Grade VI

11-8. A 45-year-old woman is referred for a murmur. Which finding on physical examination would be suggestive of a diagnosis of HOCM?

A. A decrease in the intensity of the systolic murmur upon standing
B. A midsystolic click
C. A decrease in the systolic ejection murmur with inspiration
D. A palpable P2
E. An apical holosystolic murmur

11-9. An 18-year-old asymptomatic man is referred for a murmur. The murmur is continuous, present in systole and diastole, and is characterized by a “to-and-fro” sound. The differential diagnosis should include all of the following *except*:

A. Ruptured sinus of Valsalva aneurysm
B. Arteriovenous fistula
C. Patent ductus arteriosus
D. Severe coarctation of the aorta
E. Mixed aortic valve disease (aortic stenosis and aortic regurgitation)

11-10. A 67-year-old woman presents with three days’ duration stuttering chest pressure radiating to her jaw and arm. ECG demonstrates inferior ST-segment elevations. In the emergency room, she suddenly develops worsening shortness of breath. Which of the following physical exam findings could help distinguish acute mitral regurgitation from acute ventricular septal rupture?

A. Assessment of dyspnea in supine and upright positions
B. Soft systolic murmur

C. Cool extremities
D. Increased jugular venous pressure
E. S3

ANSWERS

11-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 11)* Fixed splitting of S2 is classically found in ostium secundum atrial septal defect, where wide splitting of S2 is present at baseline with minimal or no change in the A2-P2 interval during inspiration. Conversely, paradoxical splitting of the S2 is more common in obstructive hypertrophic cardiomyopathy, suggesting severe dynamic left ventricular outflow obstruction. Hypertrophic cardiomyopathy with obstruction is a cause of a bifid pulse, caused by the occurrence of obstruction starting in midsystole. This is seen as a spike-and-dome pattern on aortic pressure tracing. Patients with HOCM might also have a classic apical impulse—the so-called triple ripple—corresponding to the presence of palpable systolic impulse in early and midsystole, separated by withdrawal of the apical impulse related to dynamic outflow obstruction; a palpable atrial contraction corresponds to the third impulse. An S4 is often heard in patients with abnormalities of ventricular relaxation, such as hypertropic cardiomyopathy.

11-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 11)* Aortic regurgitation murmurs heard over the second right intercostal space result from annular dilatation, whereas murmurs heard over the third left intercostal space result from a valvular process. When mixed aortic valve disease is present and the aortic regurgitation is the predominant lesion, an arterial contour with increased amplitude and two palpable systolic peaks can be present—the bisferiens pulse (option A is incorrect). The murmur of aortic regurgitation is a high-pitched "cooing" sound resulting from the high pressure difference between the aorta and left ventricular pressures during diastole (option B is incorrect). A middiastolic rumble, the Austin-Flint murmur, may be heard in aortic regurgitation when an eccentric jet hits the anterior leaflet of the mitral valve, causing it to reverberate and generating the apical rumble (option C is incorrect). In aortic regurgitation, the combination of increased stroke volume and the regurgitation itself gives rise to an arterial pulse that is increased in amplitude ("bounding"), which also collapses very quickly—the so-called water hammer pulse (option E is incorrect).

11-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 11)* Forrester and Diamond categorized chest pain into typical angina (all three criteria were present), atypical angina (two criteria), and noncardiac chest pain (only one criterion). They based this classification on whether the pain (1) was substernal and pressure-like, (2) was precipitated by exertion or emotional stress, and (3) was relieved by rest or nitroglycerin and lasted less than 30 minutes. In certain patient populations (eg, elderly men), this approach yielded such a high pretest probability of coronary artery disease that stress testing was unnecessary for the diagnosis of coronary atherosclerosis. This continues to be of value in clinical practice, particularly for male patients. It is commonly said that women often present with atypical symptoms, and the diagnosis of myocardial ischemia may be missed using these classic criteria. However, data suggest that anginal symptoms might be similar in men and women and that the idea that women often present with atypical symptoms might be misleading.[1] Rarely, patients will report that angina improves with continued exercise (walk-through angina).

11-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 11)* In the early phases of diastolic dysfunction, abnormal (prolonged) ventricular relaxation impairs early diastolic ventricular filling, decreasing the amount of filling in early diastole with a compensatory enhanced atrial contribution of diastolic filling.[2] An audible left heart fourth heart sound (S4) represents this prominent, forceful left atrial contraction into a noncompliant left ventricle. Therefore, although often present in patients with aortic stenosis and sinus rhythm, it is *never* present in atrial fibrillation (due to the loss of the *a* wave). When present, a left-sided S4 is a low-pitched sound, typically only heard at the apex with the bell and easily missed if auscultation in the left lateral decubitus position is not performed. Among the other findings, a late-peaking crescendo-decrescendo systolic murmur, a soft S2, and delayed and weak carotid upstroke (pulsus tardus and parvus) are all signs of *severe* aortic stenosis (options A, B, and D are incorrect). The murmur of aortic stenosis can radiate and, in fact, increase in intensity toward the apex—the Gallavardin phenomenon (option C is incorrect).[3]

11-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 11)* In patients with systolic murmur, attention should be paid to the change in intensity of the murmur on the postectopic beats. There is an increase in ventricular contractility and a decrease in afterload on the postectopic beat; thus, there will be an increase in the intensity of the murmur with both fixed (aortic stenosis) and dynamic (hypertrophic cardiomyopathy) left ventricular outflow tract obstruction. This response is much more striking in the setting of obstructive hypertrophic cardiomyopathy because there will also be an increase in the degree of obstruction (Figure 11-1). Alternatively, in patients with mitral regurgitation, there will be no change in the intensity of the murmur on the postectopic beat due to the decrease in afterload. Aortic and left ventricular pressure tracings illustrate the postectopic beat (arrow) response in dynamic outflow tract obstruction (left) versus fixed aortic stenosis (right). Although systolic gradients increase in both diseases, the response is much more exuberant in hypertrophic cardiomyopathy (the Brockenbrough-Braunwald-Morrow phenomenon).

11-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 11)* Systolic clicks can arise from valvular and nonvalvular

structures (eg, the great arteries). The two most common (and more relevant) clicks are the ones heard in bicuspid aortic valve and mitral valve prolapse. Although the former is typically described as an ejection click and the latter a nonejection click, a description based on timing is more appropriate. The systolic click associated with mitral valve prolapse usually occurs in mid-to-late systole (option A is incorrect), when there is full excursion of the prolapsed mitral leaflet(s) into the left atrium. The click can be single or multiple (salvo of clicks). The timing of the click of mitral valve prolapse occurring later in systole helps to differentiate it from clicks arising from semilunar valves. With increased preload (squatting, supine) the click occurs later in systole, whereas decreased preload (Valsalva maneuver, standing) has the opposite effect (Figure 11-2; option E is incorrect).

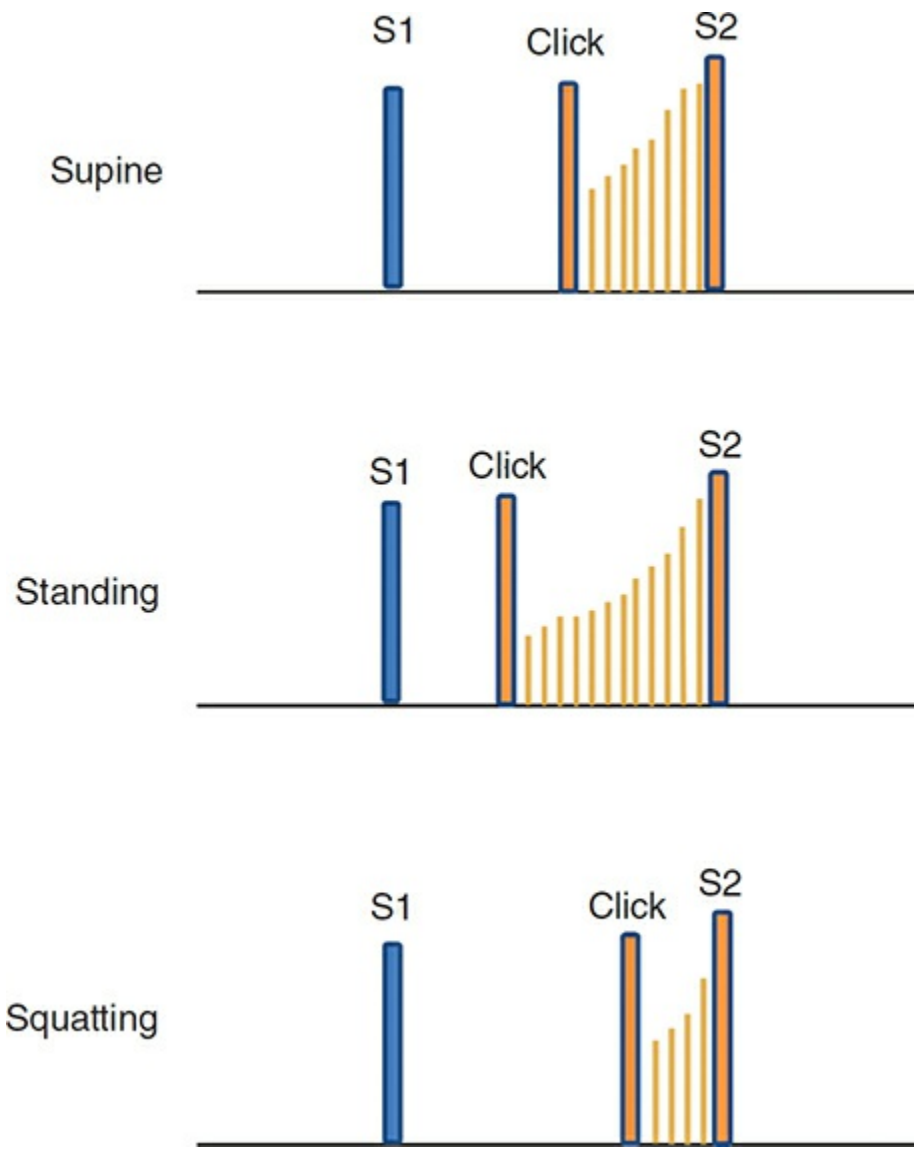

FIGURE 11-2 Positional changes in the systolic click and murmur of mitral valve prolapse. S1, first heart sound; S2, second heart sound.

Conversely, the click of a bicuspid aortic valve (and sometimes of other congenitally abnormal aortic valves such as unicuspid valves) is secondary to the doming of the valve cusps in early systole as the aortic valve opens. The sound is high-pitched (higher than S1) and sometimes quite loud; it should not be confused with a loud split S1 (two components of the same pitch and intensity) or an S4 (low-pitched sound that vanishes if the bell is firmly pressed against the skin) (option D is incorrect). Doming of the cusps is also seen in valvular pulmonary stenosis, and an early systolic click is also typical. As in bicuspid aortic valve, the click of pulmonary stenosis introduces the systolic murmur. However, the click noted in pulmonary stenosis has a unique and important characteristic: it decreases in intensity with inspiration and moves closer to S1 (option C is incorrect). This is the only right-sided auscultatory finding that diminishes with inspiration. Early systolic clicks can also arise from dilated great vessels (aorta or pulmonary artery).

11-7. The answer is C. *(Hurst's The Heart, 14th Edition, Chap. 11)* Systolic murmurs are graded I to VI, as in the following table:

Grade I	Faint murmur; heard only after a few seconds of auscultation
Grade II	Moderately loud murmur heard immediately
Grade III	Loud murmur; not associated with a thrill
Grade IV	Loud murmur associated with a thrill
Grade V	Very loud; can be heard if only the edge of the stethoscope is in contact with the skin
Grade VI	Loudest possible; can be heard with the stethoscope just removed from the chest and not touching the skin

11-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 11)* The simultaneous left ventricular and aortic hemodynamic pressure tracings from a patient with HOCM shown in Figure 11-3 demonstrate characteristic respirophasic hemodynamic changes. Inspiration leads to increased left ventricular afterload; as a result, the systolic gradient between the left ventricle and the aorta decreases with inspiration. At the bedside, this is manifested by a decrease in the systolic ejection murmur noted with inspiration. The presence of this finding suggests dynamic instead of fixed outflow tract obstruction as the source of the murmur. Standing decreases preload and worsens obstruction in HOCM, which will make the murmur louder (option A is incorrect). A midsystolic click is not characteristic of HOCM (option B is incorrect); the approach to a click is reviewed in question 11-6. A palpable P2 can be observed in patients with advanced pulmonary hypertension; although secondary pulmonary hypertension (Group 2) can result from HOCM, this finding is not specific to HOCM (option D is incorrect). An apical holosystolic murmur suggests mitral regurgitation, and it is not specific to HOCM (option E is incorrect).

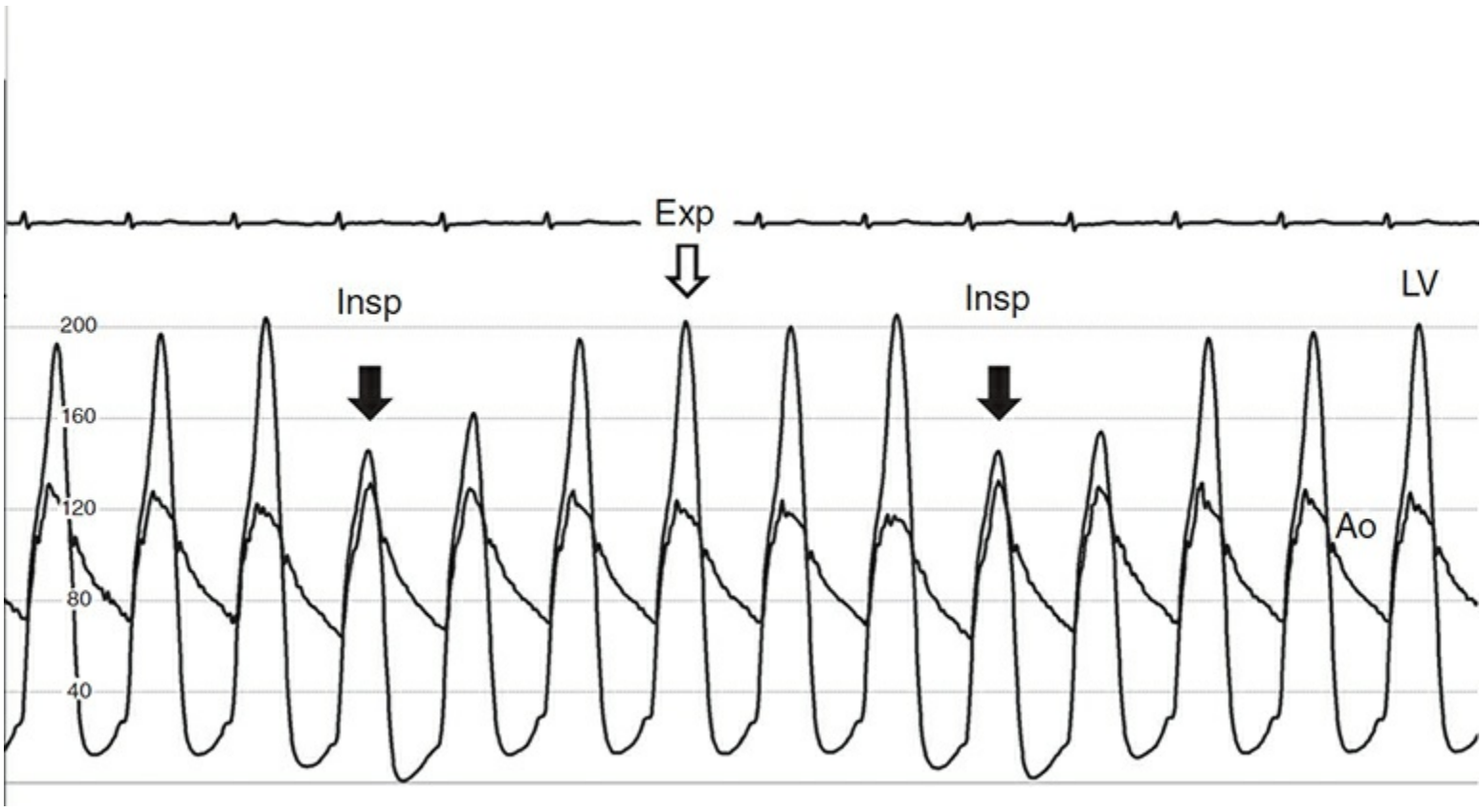

FIGURE 11-3 Simultaneous left ventricular and aortic hemodynamic pressure tracings from a patient with hypertrophic obstructive cardiomyopathy demonstrate characteristic respirophasic hemodynamic changes.

11-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 11)* The continuous murmur is characterized by a to-and-fro sound with no interruption between systole and diastole. The pitch should be similar, but the intensity can vary throughout the cardiac cycle. By definition, the continuous murmur envelops the heart sounds. This is distinctly different from a systolic and diastolic murmur, as noted in mixed aortic valve disease. In that case, one will hear a harsh, diamond-shaped systolic murmur, a second heart sound (which might be single), and a diastolic murmur. These murmurs will have two distinctly different pitches.

The most common continuous murmur seen in current practice is secondary to iatrogenic arteriovenous fistulas (for hemodialysis), which is generally appreciated in the region of the clavicle on the respective side (option B is incorrect). Other causes of continuous murmurs are rare and include patent ductus arteriosus (best heard over the left infraclavicular area), ruptured sinus of Valsalva aneurysm, coronary fistula, intrathoracic arteriovenous fistulae, severe coarctation of the aorta, and a surgically created shunt (eg, Blalock-Taussig, Potts, Waterston) (options A, C, and D are incorrect). The venous hum is a continuous murmur heard on auscultation of the neck. It results from a high flow in the internal jugular vein, which most likely causes a vibration of the venous wall. It is most commonly heard in young, otherwise healthy individuals and is not associated with pathology. The venous hum will disappear with the supine position or with compression of the vein itself.

11-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 11)* In acute severe mitral regurgitation secondary to papillary muscle rupture or mitral valve dehiscence, the left atrium is not accustomed to the severe volume overload. A very large *v* wave is generated because of lack of atrial compliance, and left ventricular and left atrial pressures essentially equalize in systole. The auscultatory result is a very short, early systolic murmur or even absence of a murmur. Accordingly, color-flow and continuous-wave Doppler findings are also often very brief, making the diagnosis of acute mitral regurgitation challenging. Patients with acute severe mitral regurgitation are in frank pulmonary edema and are therefore sitting upright, whereas patients with ventricular septal defect can tolerate the supine position. A soft murmur, cool extremities, increased jugular venous pressure, and an S3 are not specific to either mitral regurgitation or a ventricular septal defect.

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CHAPTER 12

Surface Electrocardiography

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

12-1. Which of the following technical errors may result in an electrocardiogram with farfield signals in lead II?

A. Interchanging of the right arm and right leg leads
B. Interchanging of the right arm and left arm leads
C. Interchanging of the left arm and left leg leads
D. Interchanging of the right arm and left leg leads
E. Interchanging of the right leg and left leg leads

12-2. Which of the following is strongly suggestive of an *atypical* right bundle branch block (RBBB) on electrocardiogram?

A. QRS of at least 0.12 seconds with midfinal slurring
B. RSr' in lead V_1
C. qRS in V_6 with S wave slurring and a positive T wave
D. T wave with an opposite polarity to the QRS slurring
E. QR in aVR with R wave slurring and a negative T wave

12-3. A 42-year-old woman presents to the emergency department with a 12-hour history of worsening dyspnea and weakness. She describes a recent business trip to India. Which of the following represent the *least* likely electrocardiographic sign to be observed in this clinical situation?

A. Right bundle branch block
B. aVL + SV_3 > 20 mm
C. Sinus tachycardia
D. Normal sinus rhythm
E. McGinn-White pattern

12-4. A 24-year-old male with a history of palpitations presents to the emergency department. The following electrocardiographic findings may be observed in a patient with Wolff-Parkinson-White syndrome, *except*:

A. Absence of a right bundle branch pattern in a patient with Ebstein's anomaly
B. Preexcited atrial fibrillation
C. A normal PR interval in the setting of a left-lateral accessory pathway
D. Prolongation of the PR interval
E. A narrow QRS tachycardia with a mid-RP interval

12-5. See Figure 12-1. A 35-year-old woman presents with syncope. The origin of negative T waves in the inferior leads on the electrocardiogram may include which of the following?

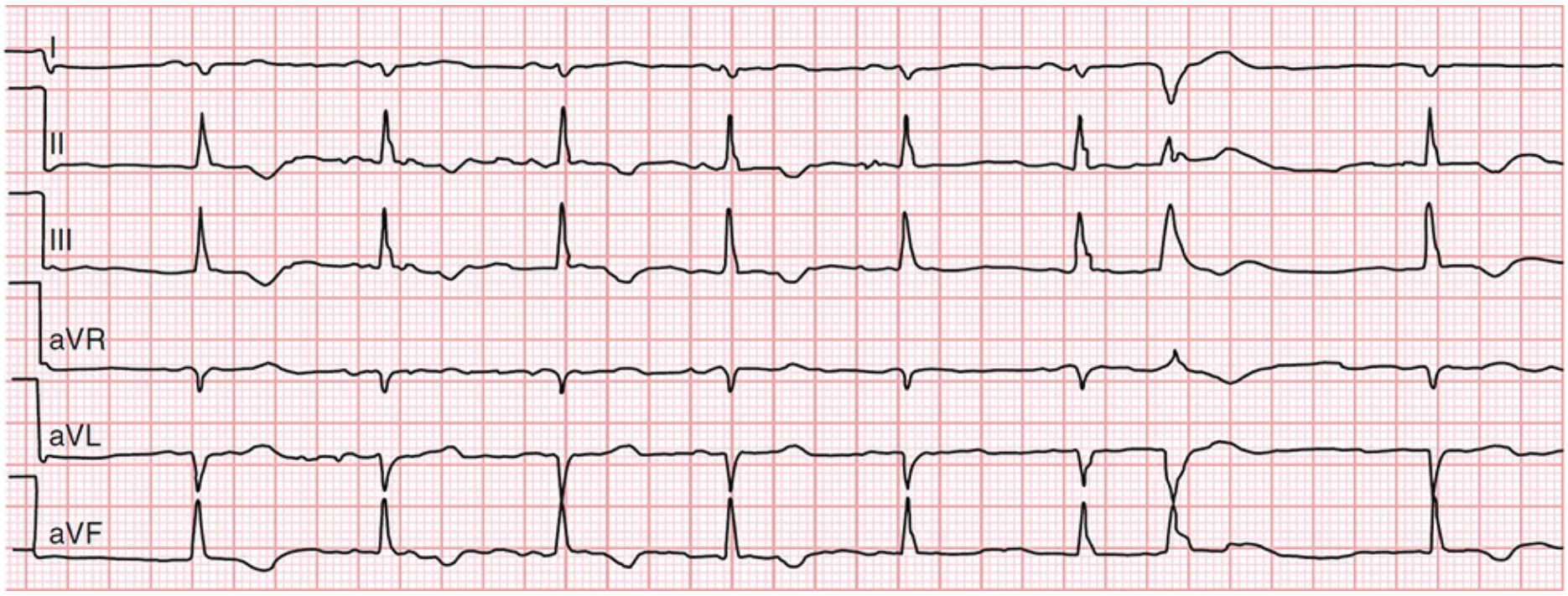

FIGURE 12-1 Electrocardiogram of a 35-year-old woman with syncope.

A. Hyperkalemia
B. Left ventricular hypertrophy
C. Acute pericarditis
D. Advanced atrioventricular block
E. Mitral valve prolapse

12-6. A 75-year-old female presents with nausea and vomiting to the emergency department. Her EKG reveals ST elevation in the inferior leads. Which of the following findings is most likely to suggest the presence of an accompanying right ventricular infarct?

A. Negative T wave in V_4R
B. ST elevations in lead I
C. ST elevations lead II > III
D. ST elevations in lead V_4R
E. ST depression in V_4R

12-7. A 35-year-old woman with a history of rheumatic fever presents to your office in consultation for intermittent palpitations and worsening dyspnea. A physical exam reveals a diastolic murmur over the apex. Thyroid studies are within normal limits. Which of the following ECG findings is *least* likely to be observed in this patient?

A. Atrial fibrillation
B. Atrial tachycardia
C. Biphasic positive-negative p wave in V_1
D. R wave in V_1
E. T-wave inversions in II, III, aVF

12-8. Causes of pathologic Q waves *not* secondary to myocardial infarction include all of the following *except*:

A. Amyloidosis
B. Dilated cardiomyopathy
C. Wolff-Parkinson-White syndrome
D. Cardiac transplant
E. Acute myocarditis

12-9. You are consulted on a 21-year-old female who requires a cardiac workup following a small right middle cerebral artery stroke. She has no other significant past medical history. On questioning, she admits to having a history of breathlessness with maximal exertion for as long as she can remember. All of the following findings may be observed on her electrocardiogram *except*:

A. Leftward QRS axis
B. Left bundle branch block (LBBB)
C. Atrial fibrillation
D. Negative P waves in II, III, aVF
E. Presence of an rsR′ in V_1 with a QRS < 0.12 seconds

12-10. All of the following are associated with a dominant R in V_1 on electrocardiogram *except*:

A. Athlete’s heart

B. Ebstein's anomaly
C. Arrhythmogenic right ventricular dysplasia
D. Wolff-Parkinson-White electrocardiographic pattern
E. Lateral wall myocardial infarction

ANSWERS

12-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 12)* Interchanging of the right arm and right leg leads would result in farfield signals (diminished signals) in lead II. Interchanging of the right arm and left arm leads would result in a pattern of negative P, negative QRS, and negative T waves in lead I (and positive in aVR) (option B). A normal pattern of R wave progression from V_1 to V_6 would argue against dextrocardia in this instance if the leads were placed correctly. Interchanging left arm and left leg leads would result in reversal of leads aVL and aVF, reversal of leads I and II, and inversion of lead III (option C). Interchanging right arm and left leg leads would result in inversion of leads I, II, and III, and reversal of leads aVR and aVF (option D). Interchanging of the right and left leg leads will not result in a different ECG recording compared to one obtained with standard electrode placement (option E).

12-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 12)* The first upward deflection (R) of the QRS should always be shorter than the second upward deflection (r′) in a typical RBBB. Options A, C, D, and E represent diagnostic criteria for a typical RBBB.

12-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 12)* The cause of the patient's dyspnea is most likely secondary to a pulmonary embolus in the context of recent travel. Commonly, the presenting ECG is normal (option D), however the most valuable diagnostic findings for a large pulmonary embolus, which are poorly sensitive but highly specific, are as follows: (1) the McGinn-White pattern (S_I, Q_{III}, negative T_{III} pattern) (option E); (2) RBBB (option A) (3) a rightward-directed QRS axis (typically > 30° to the right of its usual position); (4) negative T wave in right precordial leads; and (5) sinus tachycardia (option C), which is common except in elderly patients or in those with sinus node dysfunction. (Option B) aVL + SV_3 > 20 mm in a woman and > 28 mm in a man (Cornell voltage criterion) is highly specific for left ventricular hypertrophy, which this patient has no indication of having.

12-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 12)* Shortening, as opposed to prolongation of the PR interval is observed in patients with Wolff-Parkinson-White pattern on their resting electrocardiogram. The absence of an RBBB pattern in a patient with Ebstein's anomaly is highly suggestive of the presence of an accessory pathway (option A). In a recent PACES/HRS expert consensus document on the treatment of asymptomatic young WPW subjects, it is recommended that ablation should be considered in subjects between 8 and 21 years with asymptomatic WPW pattern if they have RR intervals shorter than 250 ms during atrial fibrillation due to increased risk of sudden cardiac death (option B).[1] Preexcitation suggesting antidromic conduction in WPW syndrome may still be present with a normal PR interval if the accessory pathway is far from the sinus node (eg, left lateral pathway) (option C). An orthodromic AV reciprocating tachycardia using a retrograde accessory pathway can typically present as a narrow complex tachycardia with either a mid or a long RP (option E).

12-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 12)* Although an infrequent finding, an electrocardiogram with mitral valve prolapse will typically reveal T-wave inversions in the inferior leads and/or V_5 and V_6. This patient had bileaflet mitral valve prolapse with moderate mitral valve regurgitation. She presented after three episodes of high-risk syncope, and she was diagnosed with malignant mitral valve syndrome. The origin of the PVC was from the anterolateral papillary muscle. Hyperkalemia classically causes peaked T waves (option A) (in contrast, hypokalemia may cause T-wave flattening). Left ventricular hypertrophy would cause a more positive than normal T wave (option B). Acute pericarditis would be more likely to show more positive T waves (option C). Advanced atrioventricular block would demonstrate tall and peaked T waves in the narrow QRS complex escape rhythm (option D).

12-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 12)* ST elevations in V_4R would be highly suggestive of a right ventricular infarct. Options A, B, C, and E are more suggestive that the left circumflex is the culprit artery.

12-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 12)* The patient presents with a history and a physical exam suggestive of mitral stenosis (note: a palpable S1 may be noted in mitral stenosis, thyrotoxicosis, anxiety, and in the setting of a short PR interval). Atrial fibrillation (option A), atrial tachycardia (option B), biphasic positive-negative p wave in V_1 (option C), and an R wave in V_1 (option D) are classical electrocardiographic findings of mitral stenosis. T-wave inversions in the inferior leads are not specific for mitral stenosis, but they may be observed in a patient with mitral valve prolapse (option E).

12-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 12)* Pathologic Q waves are not typically seen in a transplanted heart. Patients with cardiac transplant are often observed to have the P wave of both the donor and the

recipient on the same ECG. Generally the donor P wave is of a higher rate than the recipient P wave because there is no vagal control on the donor heart. A pathologic Q wave is wide (≥ 0.04 seconds) and typically exceeds 25% of the following R wave. The presence of abnormal Q waves suggests myocardial necrosis, but it may also be observed in other circumstances, such as amyloidosis (option A), dilated cardiomyopathy (option B), Wolff-Parkinson-White syndrome (option C), and acute myocarditis (option E). Other causes of pathologic Q waves include recording artifacts, normal variants (Q in aVL in a vertical heart, and Q in III in the dextrorotated and horizontal heart), QS in V_1 in septal fibrosis, emphysema, the elderly, and chest abnormalities, some types of right ventricular hypertrophy (chronic cor pulmonale) or left ventricular hypertrophy (QS in V_1-V_2 with a slow increase in the R wave through the precordial leads), left bundle branch conduction abnormalities, infiltrative processes (sarcoidosis, tumors, chronic myocarditis), coronary vasospasm, pheochromocytoma, and congenital heart diseases (coronary artery abnormalities or dextrocardia).

12-9. The answer is B. *(Hurst's The Heart, 14th Edition, Chap. 12)* The question points toward an atrial septal defect (ASD) as a potential etiology for the patient's stroke. An LBBB would not specifically be seen in the presence of an ASD (option B). A leftward QRS axis may be observed in a primum ASD, whereas a normal or rightward axis is more typical of a secundum ASD (option A). Atrial fibrillation, associated with or independent of an ASD, may be the cause of stroke in this patient (option C). Negative P waves in the inferior leads suggest a low/ectopic atrial pacemaker, which can be seen in sinus venosus/SVC defects (option D). A partial or complete RBBB, not an LBBB, may be seen in combination with an ASD (option E).

12-10. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 12)* An athlete's heart is not typically associated with a dominant R in V_1. Options B through E are all causes of a dominant R in V_1. Ebstein's anomaly and arrhythmogenic right ventricular dysplasia present as atypical RBBB. Other causes of a dominant R in V_1 on electrocardiogram include incorrect lead placement, chest anomalies, abnormal variants (post-term infants, scant Purkinje fibers in the anteroseptal region), typical RBBB, Brugada syndrome, and right ventricular or biventricular enlargement.

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CHAPTER 13

Electrocardiographic Exercise Testing

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

13-1. What are the determinants of myocardial oxygen uptake?

A. Minute ventilation and the fraction of ventilation extracted by the tissues
B. Cardiac output and the peripheral arteriovenous oxygen difference
C. Intramyocardial wall tension, contractility, and heart rate
D. Stroke volume and heart rate
E. The maximal heart rate and the maximal systolic blood pressure

13-2. A 65-year-old male is referred to you for evaluation of possible coronary artery disease. He gives a 4-week history of chest discomfort with climbing two flights of stairs, where he had previously been able to climb several flights without difficulty. He denies any dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or syncope. Two weeks ago, he was started on isosorbide mononitrate 30 mg po daily, metoprolol 25 mg po twice daily, and aspirin 80 mg po daily by his primary care physician. Physical exam is within normal limits. You plan to perform an exercise stress test. Which of the following sets of instructions is *false*?

A. Instruct the patient to hold metoprolol for at least 24 hours prior to the test
B. Instruct the patient to avoid vigorous exercise the day of the test
C. Instruct the patient to hold his morning dose of isosorbide mononitrate the day of the test
D. Instruct the patient to continue all medications
E. Instruct the patient to avoid caffeine in the event that a vasodilator stress will be performed at the same time

13-3. A 48-year-old female presents to the emergency department with central chest pain and dyspnea that now occurs after walking one block. The chest pain began six months ago, but the symptoms have become more frequent and occur with even less exertion. She describes an episode of syncope without prodrome. Her family history is significant for a brother having undergone a cardiac surgery at age 52. A systolic ejection click with an associated systolic murmur is noted on exam. Serial troponins are negative. What is the next best course of action?

A. Book an exercise stress test
B. Proceed with transthoracic echocardiography
C. Proceed with coronary angiography
D. Consult cardiac surgery
E. Start a beta blocker and discharge home with follow-up in clinic

13-4. Which of the following is *not* an absolute contraindication to exercise stress testing?

A. Severe mitral stenosis
B. Unstable angina
C. Acute pericarditis
D. Stable, sustained monomorphic VT
E. > 3 mm ST segment depression at rest

13-5. Which of the following statements about exercise stress testing is *false*?

A. The formula MPHR = 220 – age results in an underestimation of maximum heart rate, particularly in older patients
B. The formula MPHR = 220 – age was originally developed to be used for patients' exercise prescriptions
C. The exercise stress test may be terminated when the maximal predicted heart rate reaches 85%
D. Achieving either maximum effort or an ischemic endpoint is crucial for exercise testing performed with or without imaging

E. The maximum predicted heart rate is best achieved by using the formula MPHR = 208 – 0.7 × age

Questions 13-6, 13-7, and 13-8 relate to the following vignette:

A 42-year-old man with diabetes mellitus type II and dyslipidemia is referred for an exercise stress test from the emergency department. He began to complain of dull left shoulder pain 2 weeks prior to presentation. The pain has worsened in the last few days, and it is precipitated by walking up stairs. He remarks that he thinks he may have hurt his shoulder during snow shoveling 2 weeks ago. A physical exam reveals a blood pressure of 138/78 HR 84 regular, oxygen saturation 98% on room air, and respiratory rate of 14. He is afebrile. Normal heart sounds are auscultated, and no murmurs are present. Serial troponins are negative.

13-6. In this patient, all of the following resting electrocardiographic findings may cause reconsideration of an exercise stress test as the primary investigation, *except*:

A. Presence of preexcitation
B. Presence of an LBBB
C. Presence of a paced rhythm
D. Atrial fibrillation with a rapid ventricular response
E. Intraventricular conduction delay

13-7. All of the following parameters should usually prompt exercise stress test termination *except*:

A. 1 mm ST elevation in the anterior precordial leads
B. A decrease in the systolic blood pressure by 10 mm Hg
C. Patient would like to terminate the test
D. Isolated premature ventricular contractions
E. Mobitz type 1 second-degree heart block

13-8. Which of the following results would constitute the worst prognosis?

A. 1 mm of slow upsloping ST depression at 5 METS, with resolution upon termination of exercise
B. 0.5 mm of slow downsloping ST depression at 7 METS, with persistence into 2 minutes of recovery
C. 1.5 mm of horizontal ST depression at 5 METS, with resolution upon termination of exercise
D. 1.5 mm of horizontal ST depression at 5 METS, with persistence into 2 minutes of recovery
E. 1.5 mm of downsloping ST depression at 7 METS, with resolution upon termination of exercise

13-9. Which of the following patients performing an exercise stress test would be identified as a moderate risk for cardiovascular death or nonfatal myocardial infarction over 5 years follow-up?

A. A 45-year-old male performs 7 minutes on EST, limited by chest pain with 2 mm ST depressions during exercise in the inferior leads
B. A 55-year-old female performs 7 minutes on EST, and she stops due to fatigue with 1 mm of horizontal ST depressions into recovery in the anterior precordial leads
C. A 64-year-old female performs 8 minutes on EST, and she stops as a result of leg pain with 0.5 mm ST depressions in the inferior leads during exercise only
D. A 55-year-old female performs 4 minutes on EST, and she stops due to dyspnea, with 3 mm of horizontal ST depressions in the anterior precordial leads during exercise
E. A 70-year-old male performs 7 minutes on EST, limited by leg cramping, with no ST deviation

13-10. Select the *false* statement about EST:

A. Digoxin can produce ST segment depression during exercise even if the effect is not evident on the resting ECG
B. Exercise-induced ST segment elevation is nonspecific for the territory of myocardial ischemia and the coronary artery involved
C. The expected lower sensitivity and specificity traditionally observed in women may be explained by differing CAD prevalence and severity
D. Submaximal exercise testing in which exercise is stopped at a predetermined end point, such as a peak heart rate of 120 beats/min, 70% of MPHR, or a peak MET level of 5, can be used as a class I indication 4 to 7-plus days post-MI for evaluation of medical therapy, prognostic assessment, or development of an activity prescription
E. Exercise-induced ST segment depression does not localize the site of myocardial ischemia, nor does it indicate which coronary artery is involved

ANSWERS

13-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 13)* The determinants of myocardial oxygen uptake are intramyocardial wall tension (left ventricular pressure and end-diastolic volume), contractility, and heart rate (option C). Myocardial oxygen uptake can be estimated by the product of heart rate and systolic blood pressure (the double product or rate pressure product). This information is valuable clinically because exercise-induced angina often occurs at the same myocardial oxygen demand and thus double product. The higher the double product achieved, the better the myocardial perfusion and prognosis. VO_2 max is determined by the maximal amount of ventilation (volume of expired gas [VE]) moving into and out of the lung and by the fraction of this ventilation that is extracted by the tissues: $VO_2 = VE \times (FiO_2 - FeO_2)$ where VE is the minute ventilation and FiO_2 and FeO_2 are the fractional concentration of oxygen in the inspired and expired air, respectively (option A). The determinants of volume oxygen consumption [VO_2] are cardiac output and the peripheral arteriovenous oxygen difference. Because maximal arteriovenous difference behaves more or less as a constant, maximal oxygen uptake serves as an indirect estimate of maximal cardiac output (option B). The product of stroke volume and heart rate is the cardiac output (option D). The rate pressure product is the product of the maximal heart rate (bpm) and the maximal systolic blood pressure (mm Hg), and it represents the internal workload or hemodynamic response (option E).

13-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 13)*. The exercise stress test is being performed to determine if the patient has coronary artery disease. Antianginal medications should be held to minimize their anti-ischemic impact (hold beta-blockers for 24 hours [option A] and hold nitrates and calcium channel blockers the day of the study [option C]). If medications are not held, the test sensitivity may be decreased either by the patient's medical regimen or by the fact that the ischemia was not seen at the level of exertion or double product achieved. If the test is being performed for prognostic reasons (that is, if coronary disease is known to be present), then medications do *not* need to be held. Avoiding vigorous exercise on the day of exercise testing is appropriate to enhance the patient's ability to achieve maximum exercise on the test (option B). Caffeine is a competitive antagonist of adenosine receptors and thus blocks the effect of dipyridamole, adenosine, and regadenoson. It should be withheld for at least 12 hours if there is a possibility of the patient undergoing a vasodilator stress the same day (option E).

13-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 13)* The patient has a probable diagnosis of a stenotic bicuspid aortic valve. Her symptoms are suggestive of a high degree of valve stenosis with possible concomitant coronary artery disease. A transthoracic echocardiogram would be the best first choice (option B). Exercise stress testing would be an absolute contraindication in a patient with possible severe aortic stenosis (option A). Proceeding directly with coronary angiography (option C) or cardiac surgery (option E) would be premature. The patient's symptoms, and particularly that of syncope, are worrisome enough to keep the patient in the hospital until at least a transthoracic echocardiogram is performed (option E).

13-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 13)* >3 mm ST segment depression at rest is a *relative* contraindication to exercise stress testing. Options A through D are all absolute contraindications to exercise stress testing. Other absolute contraindications include patients with acute myocardial infarction, acute myocarditis, Mobitz type 2, second or third degree heart block, known severe left main disease, acutely ill patients, patients with locomotive problems, severe aortic or other valve stenosis, acute pulmonary embolus, and uncontrolled symptomatic heart failure.

13-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 13)* Stopping exercise prematurely once 85% of an estimated maximal heart rate is achieved decreases exercise testing sensitivity and minimizes the opportunity to assess ischemia electrocardiographically and with adjunctive imaging (option C). Bairey and coworkers compared patients undergoing exercise myocardial perfusion imaging with a normal perfusion scan relative to whether they achieved 85% of MPHR. The annual event rate of death, nonfatal MI, or late revascularization was 1.9% for those who reached ≥ 85% MPHR compared to 8.6% for those who achieved < 85%.[1] The formula of MPHR = 220 – age results in an underestimation of maximum heart rate, particularly in older patients (option A), and was originally developed for use in patients' exercise prescriptions (option B). Further, achieving either maximum effort or an ischemic endpoint is crucial (option D). In a meta-analysis of 351 studies involving 18,712 patients, Tanaka and colleagues found that the formula of 208 – 0.7 × age best predicted the maximum heart rate.[2] The formula was predictive in men and women and independent of habitual activity level (option E).

13-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 13*) Exercise stress testing will be difficult to interpret in the presence of a delta wave (option A), LBBB (option B), ventricular pacing (option C), > 1 mm of resting ST depressions, or any atrial arrhythmia with an uncontrolled ventricular response (option D). Accompanying myocardial perfusion imaging, stress echocardiography, or calcium scoring would be other tests of choice.

13-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 13)* The 2002 ACC/AHA guidelines state that exercise should be terminated when premature ventricular contractions occur in pairs with increasing frequency as exercise increases, or when at least three-beat ventricular tachycardia occurs. Other causes for termination include, but are not limited to: ST elevation > 1 mm in precordial or inferior leads that do not have a resting Q wave; onset of Mobitz type 1 or 2 second-degree or third-degree heart block; any decrease in systolic blood pressure during exercise, particularly if accompanied by another indication of ischemia; ST depression ≥ 2 mm; atrial tachycardia, atrial fibrillation, or atrial flutter; patient dyspnea; fatigue or lightheadedness; moderate musculoskeletal pain; patient becomes pale or clammy; and anginal pain increasing to moderate severity.

13-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 13)* The ACC/AHA 2002 exercise testing guidelines classify an abnormal result as ≥ 1 mm of horizontal or downsloping ST depression. In the 2013 AHA scientific statement on exercise standards for testing and training, ≥ 1 mm of slow upsloping is defined as equivocal. There is sufficient evidence to conclude, however, that slow upsloping ST depressions of ≥ 1.5 mm should be included as a criterion for a positive exercise test in addition to the conventional criterion of ≥ 1 mm of horizontal or downsloping ST depression.[3] The earlier during exercise that ST depression occurs, and the lower the rate pressure product of this depression, and the longer it lasts during recovery, the more severe the coronary artery disease, as manifested by the incidence of multivessel and left main disease on coronary angiography.

13-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 13)* This patient's Duke Treadmill score is 2, which falls into the moderate risk category. Duke Treadmill Score (DTS) = Exercise time in minutes on the standard Bruce protocol – 5 × ST deviation (depression or elevation measured in mm in the lead with the greatest degree of ST deviation) − 4 × exercise angina index, where 0 = no angina on the treadmill, 1 = angina occurred, 2 = angina caused termination of exercise. A DTS of +5 or greater constitutes the lowest risk; a DTS of +4 to −10 constitutes a moderate risk; and a DTS of −11 or lower constitutes the highest risk. Option A has a DTS of −11 (high risk). Option C has a DTS of 5.5 (low risk). Option D has a DTS of −11 (high risk). Option E has a DTS of 7 (low risk).

13-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 13)* Unlike ST segment depression, ST segment elevation during exercise in contiguous leads with an R wave localizes to the coronary artery involved. Although ST depression is consistent with subendocardial ischemia, ST elevation is most consistent with transmural ischemia. Options A and C through E are true.

References

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CHAPTER 14

Cardiac Radiography

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

14-1. Radiographic assessment of the lung can often reflect the underlying pathophysiology of diseases of the heart. Which of the following statements regarding the normal radiographic appearance of the pulmonary vasculature of an upright human being is *false*?

A. The pressure differential between the apex and the base of the lung is approximately 22 mm Hg in adult men
B. The number of vessels and their length are more important than their caliber
C. Pulmonary blood volume can be assessed by comparing the size of the pulmonary artery with that of the accompanying bronchus
D. There is caudalization of the pulmonary vascularity because of gravity
E. None of the above

14-2. A 55-year-old man, with no prior cardiac history, presented to the emergency department complaining of acute dypsnea. His chest x-ray revealed cephalad redistribution of the pulmonary vascularity. In which of the following conditions does cephalization *not* occur?

A. Mitral stenosis
B. Pulmonic stenosis associated with ventricular septal defect
C. Aortic stenosis
D. Left ventricular (LV) failure
E. Severe mitral regurgitation (MR)

14-3. A 25-year-old immigrant, with no prior medical history, is referred to your clinic for further evaluation of an abnormal chest radiography, which was discovered incidentally after a positive tuberculin skin test (Mantoux test). Otherwise she had no chest pain, dyspnea, or other specific signs or symptoms. Her chest x-ray is illustrated in Figure 14-1. Which of the following is the most likely radiographic diagnosis?

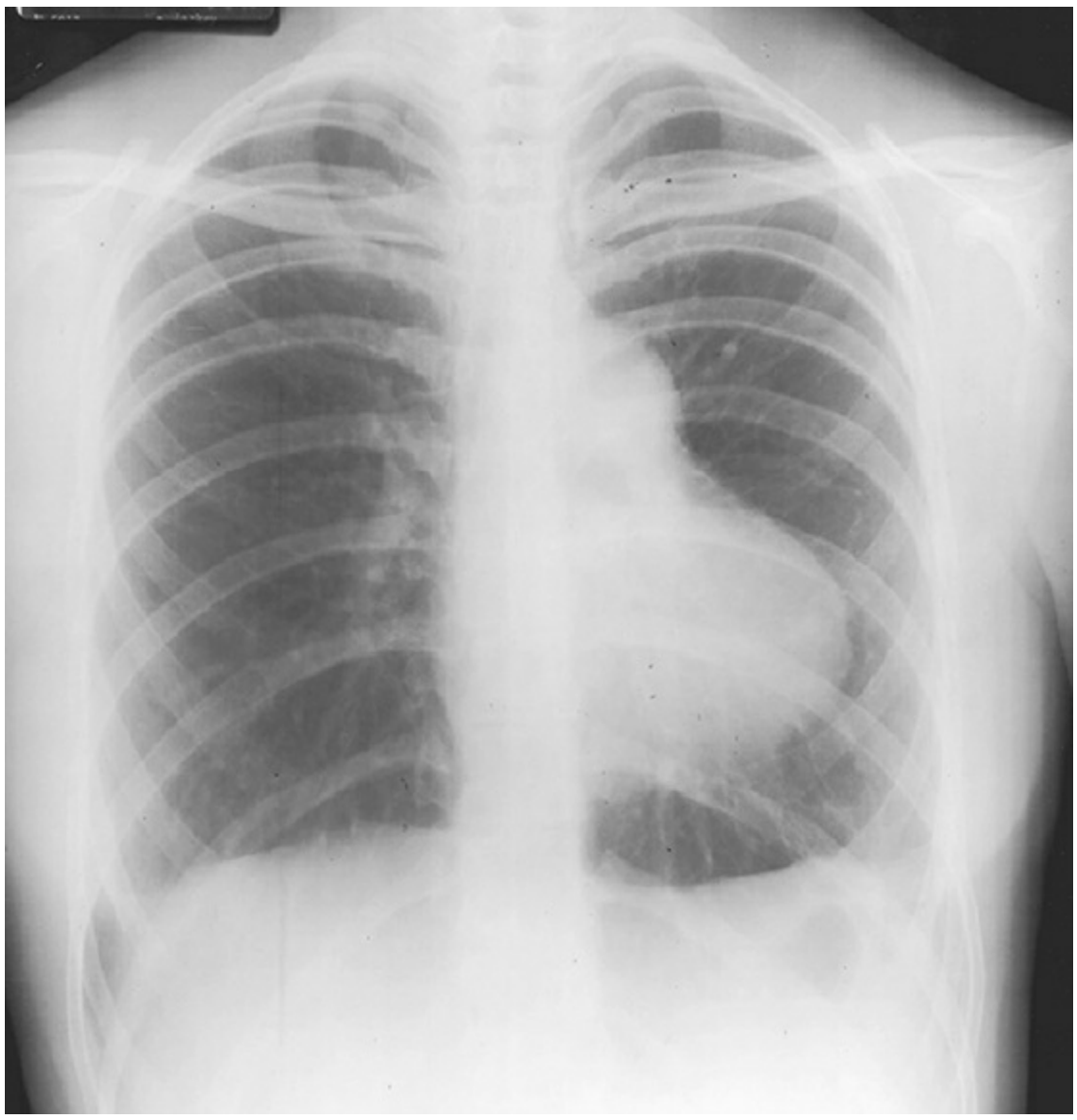

FIGURE 14-1 The heart is normal; however, the cardiac contour is markedly abnormal with elevation of the heart and in particular the cardiac apex. There is a broad band of lucency between the inferior cardiac border and the left hemidiaphragmatic silhouette, caused by normal left lung parenchyma beneath the heart that moves into place below the heart.

A. Congenital absence of the pericardium
B. Late presentation of tetralogy of Fallot
C. Left ventricular aneurysm
D. Severe rheumatic mitral stenosis with tricuspid regurgitation
E. None of the above

14-4. A 64-year-old man, with a 40 pack-year history of tobacco smoking, was admitted to the emergency department with a chief complaint of progressive worsening dyspnea on exertion. A chest radiography was performed, illustrated in Figure 14-2, and was reported as overaeration of the lungs, centralized flow pattern, and a small heart size. Besides chronic obstructive pulmonary disease, which of the following conditions may also present with a smaller-than-average heart on a chest radiography?

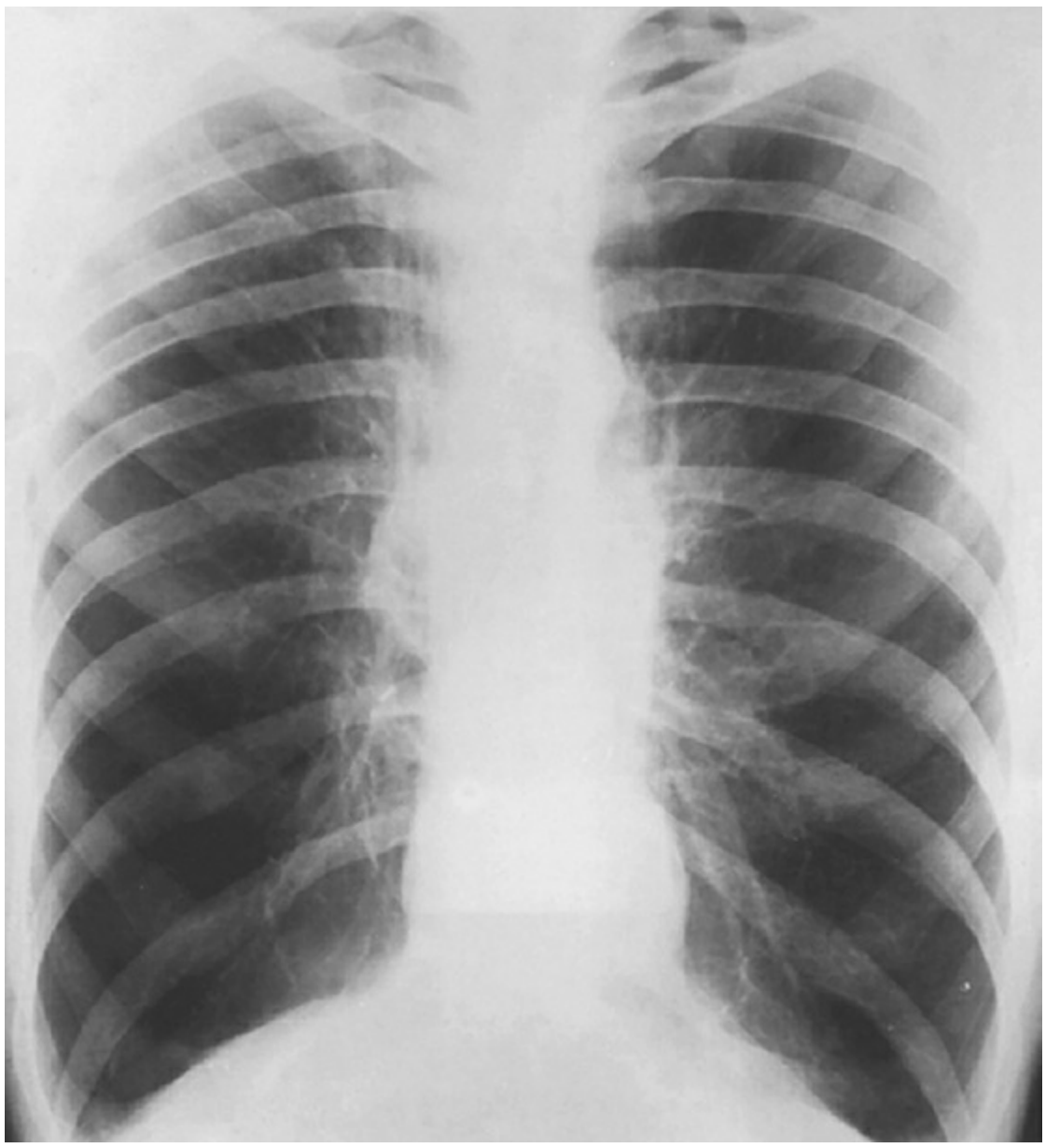

FIGURE 14-2 Severe obstructive emphysema showing overaeration of the lungs, centralized flow pattern, and a small heart size.

A. Addison disease
B. Anorexia nervosa
C. Starvation
D. None of the above
E. All of the above

14-5. A 75-year-old woman underwent a routine preoperative chest radiography prior to surgery for a carcinoma of the sigmoid colon. Her past medical history is significant for type 2 diabetes and arterial hypertension. Her chest x-ray shows linear calcifications within the aortic arch knob. Which of the following statements regarding radiologically detectable calcification in the heart is *false*?

A. Calcification of the coronary artery is almost always associated with flow-limiting luminal stenosis
B. Calcification of the coronary artery is almost always atherosclerotic in nature
C. The extent of valvular calcification tends to be proportionate to the severity of the valve stenosis
D. Mitral annular calcification is rarely indicative of significant disease
E. None of the above

14-6. A 25-year-old man sustained a severe stab wound to the left anterior hemithorax while attempting to break up a domestic fight. On presentation at the emergency department, he was hemodynamically stable. After a left-sided thoracostomy tube was inserted, the patient had a chest x-ray, which showed abnormal lucent areas around the heart. Which of the following conditions may cause abnormal lucent areas in and around the heart?

A. Displaced subepicardial fat stripes
B. Pneumopericardium
C. Pneumomediastinum
D. None of the above
E. All of the above

14-7. A 44-year-old woman with no prior medical history presented to the emergency department complaining of chest pain and palpitations. The admitting physician incidentally noted that the patient had heart sounds on the right side of the chest with no added sounds. A chest x-ray was performed and is illustrated in Figure 14-3. Which of the following diagnoses is consistent with the chest radiography findings?

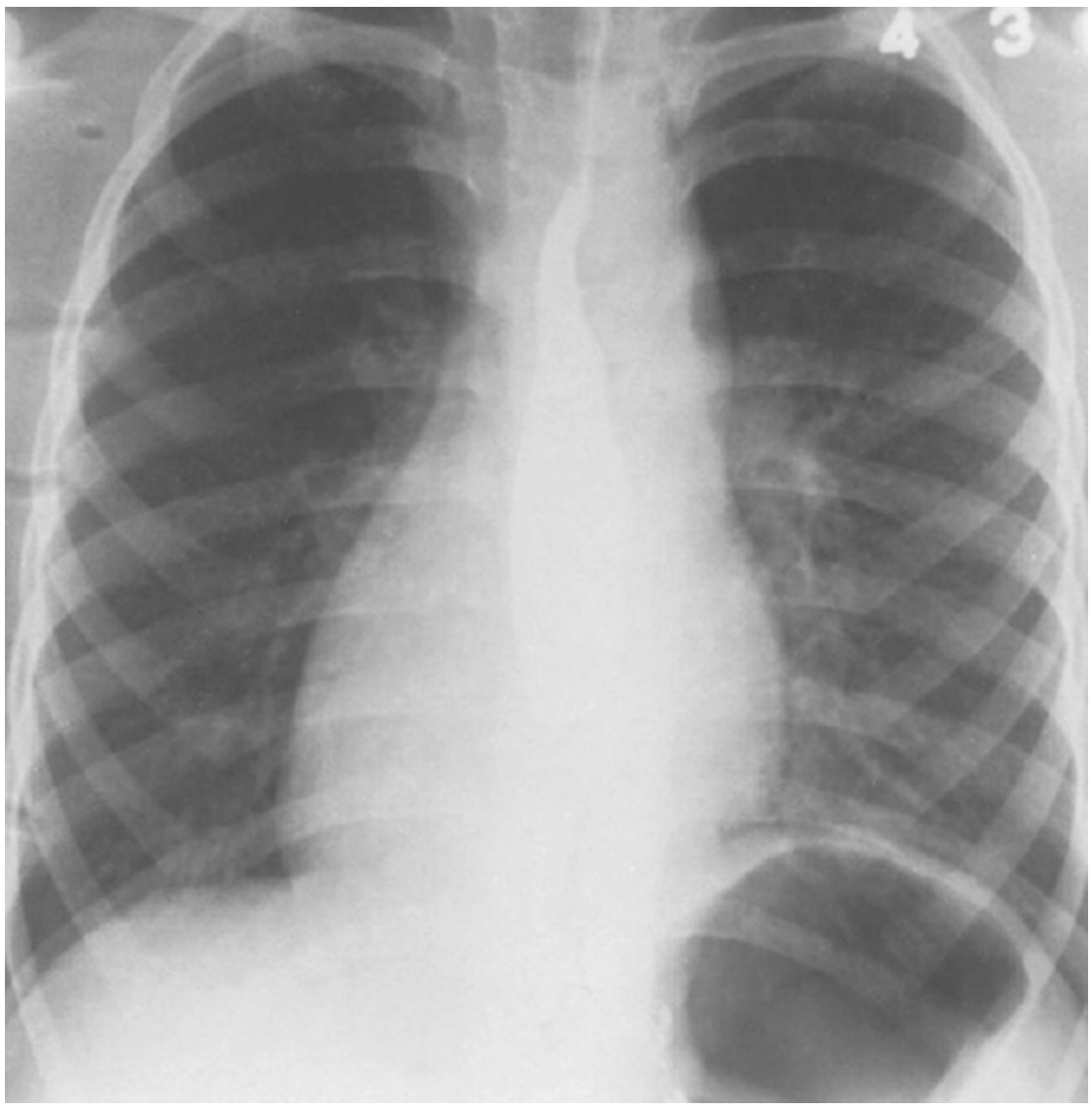

FIGURE 14-3 Note that the aortic arch and the stomach air bubble are both on the left and the apex of the ventricles is pointing to the right inferiorly. This patient had the typical combination of congenitally corrected transposition of the great arteries, ventricular septal defect, and pulmonary stenosis. He was cyanotic. The pulmonary vascularity appears decreased.

A. Dextrocardia with situs inversus
B. Dextrocardia with situs solitus
C. Levocardia with situs inversus
D. Levocardia with situs solitus
E. Cardiac malpositions with situs ambiguus

14-8. The abnormal size and distribution of both the pulmonary and systemic vessels may give important clues to the presence of certain conditions. In which of the following conditions is the prominence of the pulmonary trunk reliably correlated with the degree of enlargement of the right ventricle (RV)?

A. Tetralogy of Fallot
B. Idiopathic dilatation of the pulmonary artery
C. Patent ductus arteriosus
D. Straight-back syndrome
E. None of the above

14-9. A 47-year-old man was admitted to the emergency department complaining of increasing fatigue and dyspnea on exertion. His past medical history is significant for dyslipidemia and poorly controlled hypertension despite being on three antihypertensive medications, including a diuretic. Physical examination was significant for bilateral femoral pulses that were palpable but weak and delayed, as compared with the brachial pulses. The magnified view of the left upper thorax of the chest radiography is illustrated in Figure 14-4. With regard to the radiographic appearance, which of the following statements is *true*?

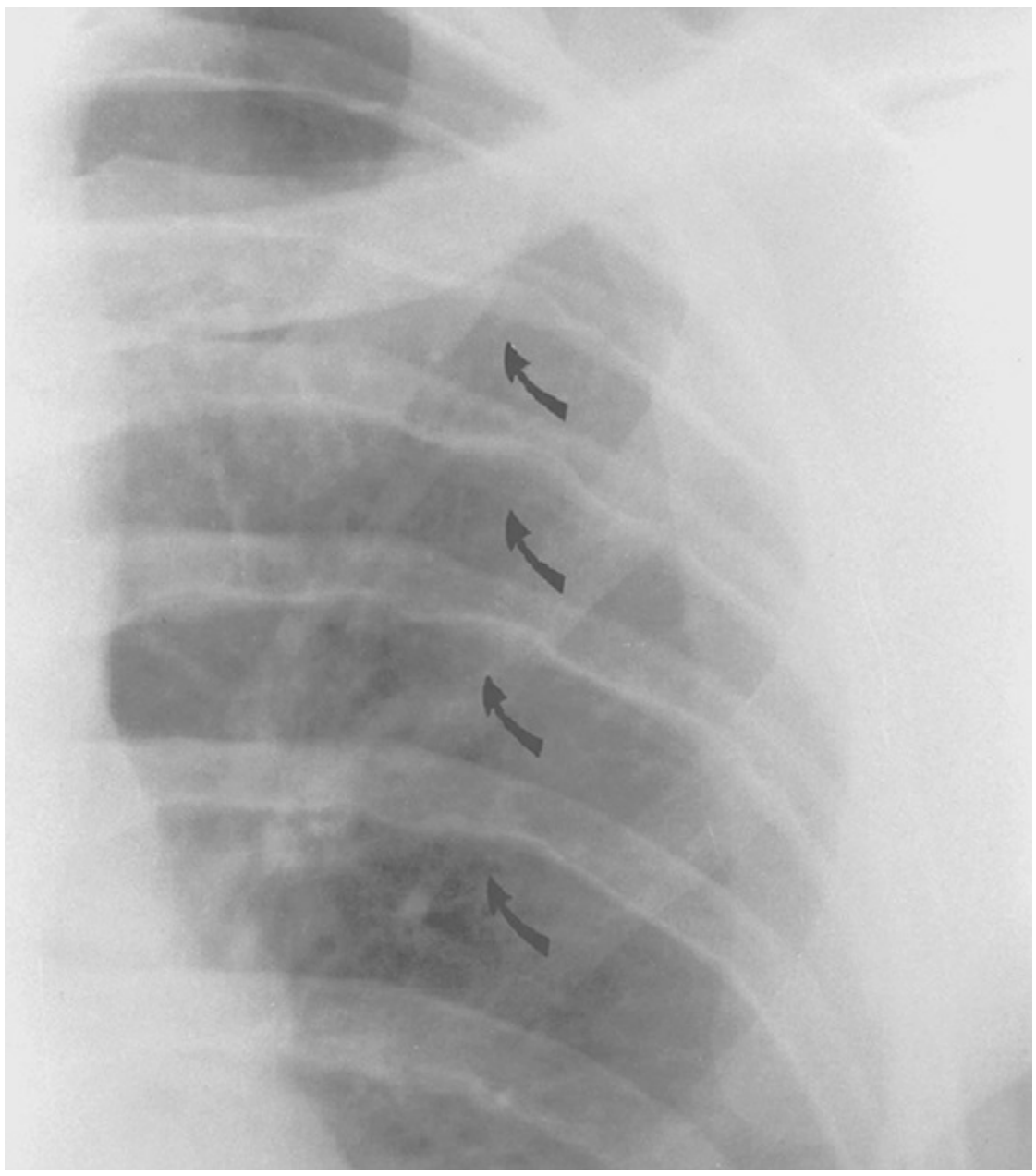

FIGURE 14-4 Magnified view of the left upper thorax showing multiple areas of rib notching (arrows).

A. Rib notching provides important clues to the diagnosis of coarctation of the aorta
B. Notching of the ribs has many origins
C. Superior vena cava (SVC) syndrome can produce a similar radiographic appearance
D. Neurofibromatosis can produce rib notching
E. All of the above

14-10. Cardiac fluoroscopy explores the dynamic features of the heart that are discernible in motion. Which of the following statements regarding cardiac fluoroscopy is *false*?

A. It has been largely displaced by other imaging techniques for the precise evaluation of cardiac size and function
B. It can assess the function of radiodense and echodense prosthetic valves during cardiac catheterization
C. It can be used to guide the positioning of pacemakers or ICDs in the cardiac catheterization laboratory
D. It is routinely used during transcatheter aortic valve implantation to guide the deployment of the prosthesis
E. None of the above

ANSWERS

14-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 14)* In the evaluation of pulmonary vasculature, the caliber of the vessels is more important than the length or the number (option B). As long as the pulmonary blood flow pattern remains normal, with a greater amount of flow to the bases than to the apices, the volume of the flow is proportional to the caliber of the pulmonary arteries. Options A, C, and D are correct.

14-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 14)* Patients with pulmonic stenosis and associated ventricular septal defect (VSD) often show decreased pulmonary vascularity with smaller and shorter pulmonary arteries and veins and more radiolucent lungs. Cephalization tends to occur instead in (1) left-sided obstructive lesions—for example, mitral valvular or aortic valvular stenosis (options A and C); (2) LV failure (option D)—for example, coronary heart disease or cardiomyopathies; and (3) severe MR even before pump failure of the LV occurs (option E).[1] Option B is therefore the correct answer.

14-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 14)* An elevated cardiac silhouette with lucency between the

inferior cardiac border and the left hemidiaphragmatic silhouette is characteristic of congenital absence of the pericardium (option A). A coeur en sabot, a “boot-shaped heart,” is characteristic of tetralogy of Fallot (option B). A bulge along the left cardiac border with a retrosternal double density is virtually diagnostic of LV aneurysm (option C). A markedly widened right cardiac contour with a straightened left cardiac border is often seen in patients with severe MS leading to tricuspid regurgitation (option D).

14-4. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* The cardiothoracic ratio remains the simplest yardstick for assessing cardiac size. A smaller-than-average heart is encountered in patients with chronic obstructive pulmonary disease, Addison disease (option A), anorexia nervosa (option B), and starvation (option C). However, an abnormally small heart size is difficult to define except retrospectively after successful treatment of the underlying pathology.

14-5. **The answer is A.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* Any radiologically detectable calcification in the heart may be clinically important. In general, the heavier the calcification, the more significant it becomes; however, calcification does not imply luminal stenosis, and oftentimes calcification visualized in the coronary arteries is not obstructive (option A). Mitral annular calcification, a commonly encountered cause of cardiac calcification, is rarely indicative of significant disease (option D), but it has been associated with an increased risk of atherosclerotic cardiovascular disease.[2] The extent of valvular calcification tends to be proportionate to the severity of the valve stenosis regardless of the other radiographic signs of the disease (option C).[3-6] Calcification of the coronary artery is almost always atherosclerotic in nature (option B).

14-6. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* The abnormal lucent areas in and around the heart include (1) displaced subepicardial fat stripes caused by effusion or thickening of the pericardium (option A), (2) pneumopericardium (option B), and (3) pneumomediastinum (option C). Pneumomediastinum is differentiated from pneumopericardium in that the former shows a superior extension of the air strip beyond the confines of the pericardium.

14-7. **The answer is B.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* Dextrocardia with situs solitus represents an anomaly with normal situs but a right-sided heart. Radiographically, normal situs (situs solitus) is a certainty when both the aortic knob and the gastric air bubble are on the left side. Situs solitus also means that both the abdominal viscera and the atria are in the normal positions. Dextrocardia with situs inversus indicates the mirror image of normal (option A). Levocardia with situs inversus is a mirror image of dextrocardia with situs solitus (option C). Levocardia with situs solitus is entirely normal (option D). In Cardiac malpositions with situs ambiguus, the patient’s heart can be on either the left or right side, but the site is ambiguous because the aortic arch and the stomach are not on the same side (option E).

14-8. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* Prominence of the pulmonary trunk is a reliable secondary sign of RV enlargement, with the following exceptions: (1) Tetralogy of Fallot with RV hypertrophy but pulmonary trunk hypoplasia (option A); (2) idiopathic dilatation of the pulmonary artery (option B); (3) patent ductus arteriosus with dilated pulmonary trunk but normal RV size (option C); and (4) straight-back syndrome (option D), pectus excavatum, and scoliosis with narrowed AP diameter of the chest. Under the latter conditions, the heart is compressed, displaced, and rotated to the left, giving rise to a falsely enlarged pulmonary artery.

14-9. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* Rib notching provides important clues to the diagnosis of coarctation of the aorta (option A).[7,8] Notching of the ribs has many origins (option B). Basically, any of the three major intercostal structures can enlarge, compress, and erode the lower borders of the ribs, producing areas of notching. They are intercostal arteries, veins, and nerves. Coarctation of the aorta represents the most common cause of rib notching as a result of dynamic dilatation and tortuosity of the arteries. SVC syndrome can produce a similar radiographic appearance (option C), albeit through long-standing venous dilation. Neurofibromatosis also can produce rib notching through the compressive effect of numerous intercostal neurofibromas (option D).

14-10. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 14)* Cardiac fluoroscopy has been largely displaced by other imaging techniques (option A), particularly two-dimensional echocardiography, MRI, and CT, and its use is limited to the cardiac catheterization laboratory, where it can assess the function of radiodense and echodense prosthetic valves (option B) and can guide the positioning of pacemakers or ICDs (option C). With the emergence of transcatheter aortic valve replacement therapy, cardiac fluoroscopy has experienced a resurgence at some centers, where it is commonly used to guide the positioning of the prosthesis (option D).

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CHAPTER 15

Echocardiography

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

15-1. High-quality echocardiographic images require optimal resolution, that is, the ability to distinguish two individual objects separated in space. Which of the following will *not* yield high-resolution images?

A. Short wavelengths
B. High-frequency signal
C. Low-frequency signal
D. Small beam width
E. All of the above

15-2. There has been a great deal of interest in using mitral inflow velocity patterns to evaluate left ventricular diastolic properties. Which of the following variables is *not* capable of influencing transmitral filling velocities?

A. Age
B. Heart rate
C. Respiration
D. Position of the Doppler sample volume
E. None the above

15-3. A 55-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 6-month history of dyspnea. On physical examination, she had jugular venous distension, distended abdomen secondary to hepatomegaly and tense ascites, severe bilateral lower limbs pitting edema, and an S3 gallop. After an initial management she was referred to the cardiologist, who performed an echocardiography, and some of the images are illustrated in Figure 15-1. Based on the echo's findings, which of the following is the most likely diagnosis?

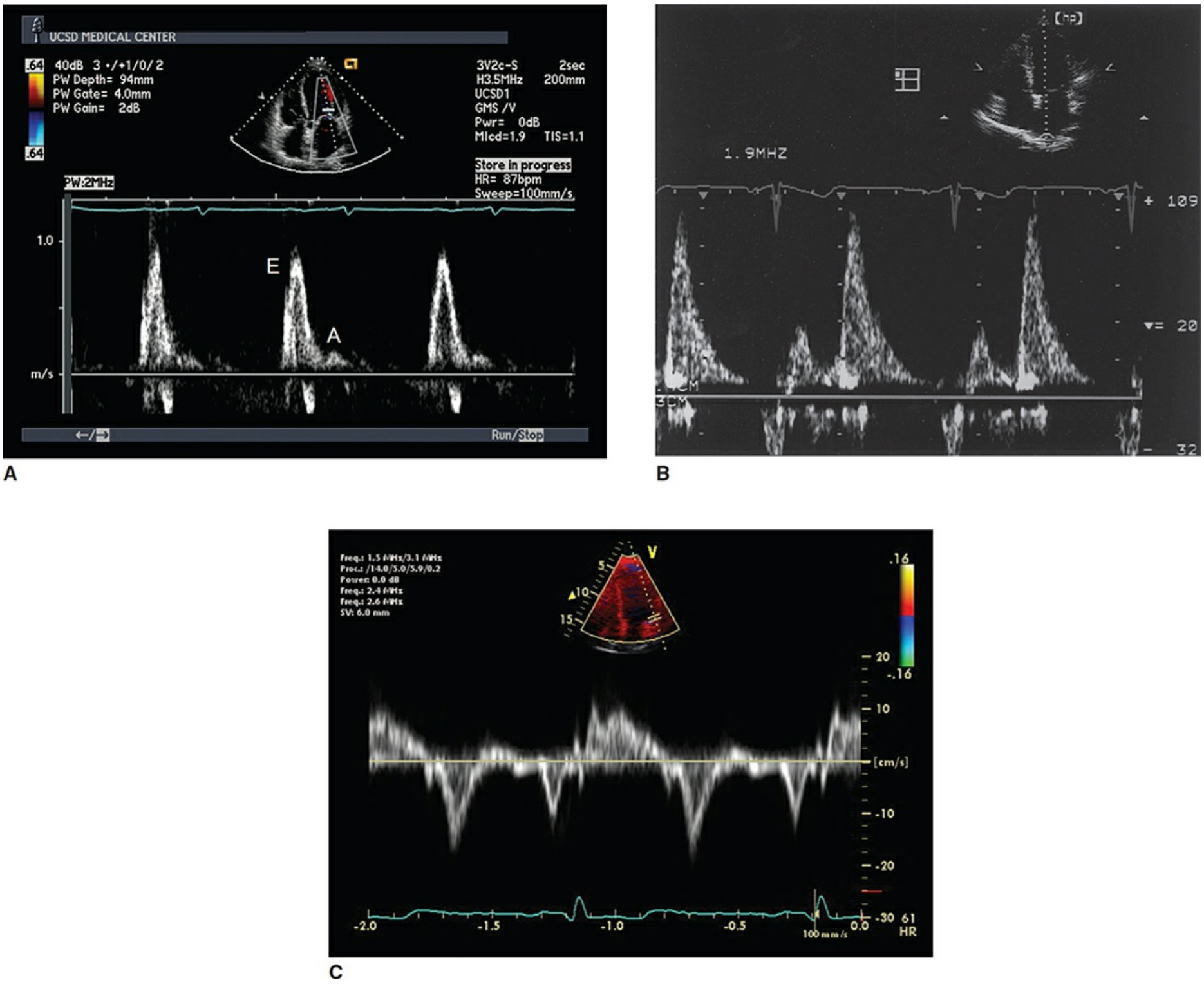
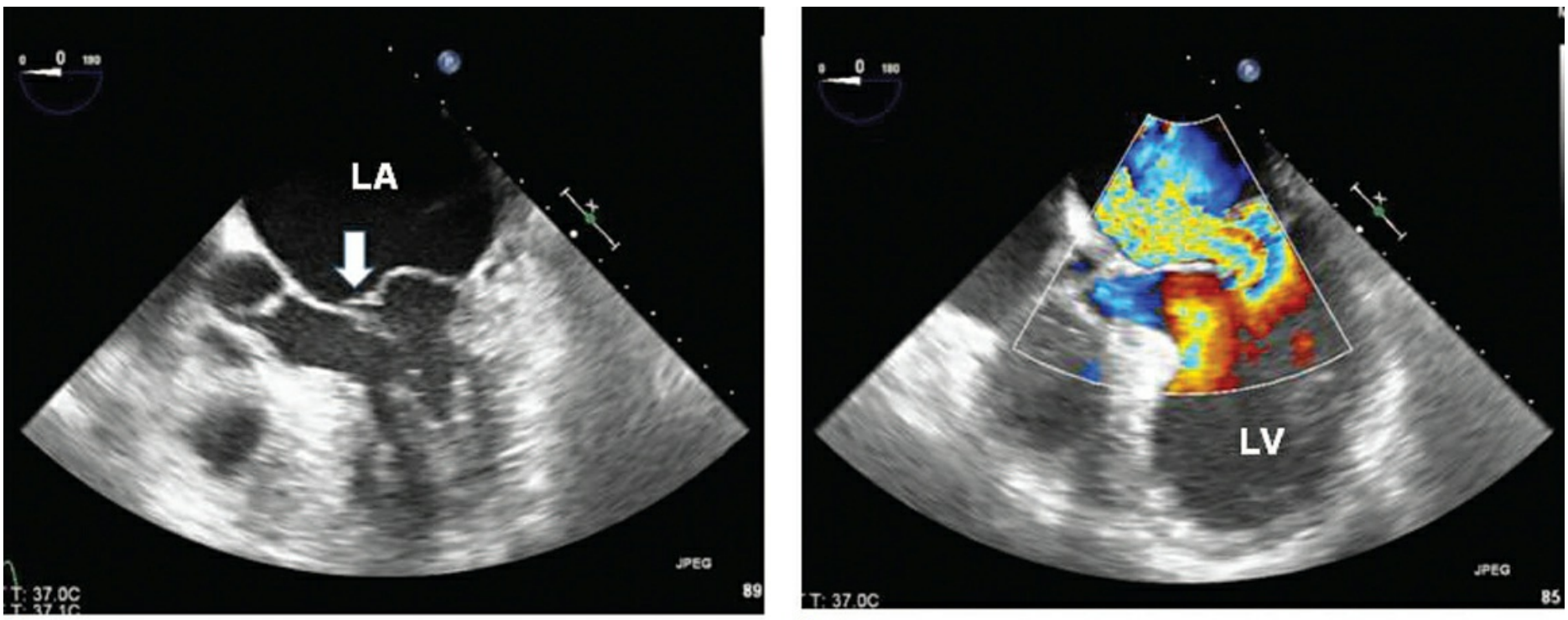


FIGURE 15-1 (A) Pulsed-wave Doppler (PWD) tracing. (B) PWD recording of pulmonary venous flow. The S wave is small, whereas the D wave is prominent. (C) Tissue Doppler recording of lateral mitral annular motion (apical transducer position). Peak early diastolic annular velocity is 17 cm/s.

A. Constrictive pericarditis
B. Amyloid-induced cardiomyopathy
C. Hypereosinophilic cardiomyopathy
D. Endomyocardial fibrosis
E. Idiopathic restrictive cardiomyopathy

15-4. A 54-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 2-week history of progressive chest discomfort and dyspnea. On physical examination, she had a 3/6 holosystolic murmur radiating to the axilla. The initial blood tests, ECG, and chest radiography were all unremarkable. A transthoracic echo showed mitral valve prolapse with a flail posterior leaflet. Transesophageal echo was performed, and some of the images are illustrated in Figure 15-2. Measurements derived from the size of the turbulent jet recorded by color Doppler are often used in clinical practice to assess the severity of mitral regurgitation. Which of the following technical factors *cannot* influence jet size?



A B

FIGURE 15-2 Transesophageal echocardiography image (five-chamber view) demonstrating a flail posterior leaflet of the mitral valve (arrow), and the corresponding color Doppler showing severe mitral regurgitation into the left atrium (LA). LV, left ventricle.

A. Instrument gain
B. Angle of incidence of the interrogating beam
C. Frequency and pulse repetition rate of the transducer
D. The temporal sampling rate
E. None of the above

15-5. An 11-year-old woman was referred to the cardiology clinic for further evaluation of a diastolic murmur. Her past medical history was significant for a surgically closed patent ductus arteriosus at the age of 7 and recurrent chest infections since she was one year old. On general inspection, she appeared thin and slender, and she had an anterior chest deformity as well as a disproportionately long arm span compared to her height. An echo was performed, and a parasternal long-axis view is illustrated in Figure 15-3. Which of the following conditions is the most likely underlying cause associated with this patient's aortic regurgitation (AR) murmur?

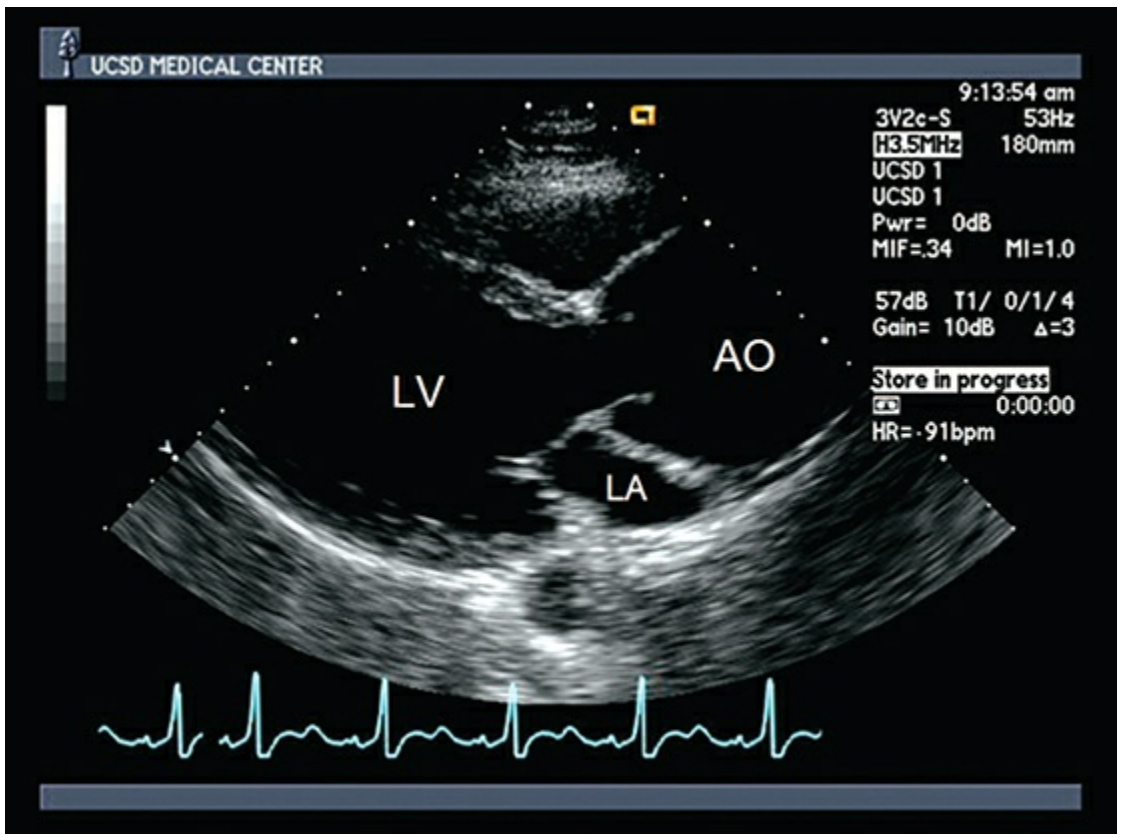


FIGURE 15-3 Parasternal long-axis view. AO, Aorta; LA, left atrium; LV, left ventricle.

A. Marfan syndrome
B. Sinus of Valsalva aneurysm
C. Supravalvular aortic stenosis
D. Coarctation of the aorta
E. None of the above

15-6. A 92-year-old man with a prior history of dyslipidemia, type 2 diabetes, and hypertension was admitted to the emergency department complaining of dyspnea and chest pain. On physical examination, he had a grade 1/6 systolic murmur. An echo was performed, and a continuous-wave Doppler (CW) tracing (from the apical transducer position) through the aortic valve

is illustrated in Figure 15-4. Which of the following factors is *not* a potential source of error in the estimation of the transvalvular aortic gradient by CW Doppler recordings?

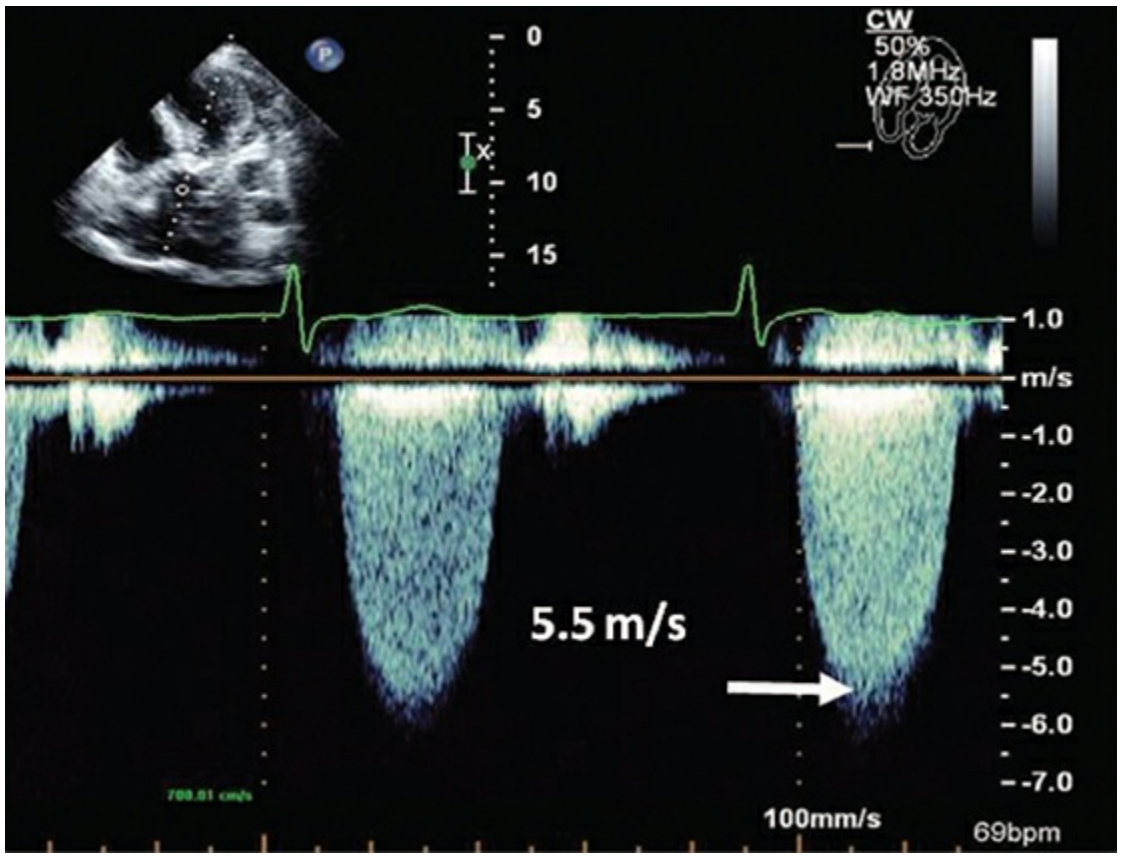


FIGURE 15-4 Continuous-wave Doppler tracing (from the apical transducer position) through the aortic valve in a case of severe aortic stenosis. The peak systolic velocity is 5.5 m/s, corresponding to a maximal instantaneous gradient of 121 mm Hg; the mean gradient is 80 mm Hg.

A. Angle of incidence of the interrogating beam greater than 20 degrees
B. Narrow ascending aorta
C. Concomitant dynamic LV outflow obstruction
D. None of the above
E. All of the above

15-7. A 35-year-old man with no known past medical history was admitted to the emergency department complaining of a 2-day history of acute dyspnea. Upon further questioning, the patient had not been feeling well for the past 2 weeks with fever, malaise, and headaches. On physical examination, he had a diastolic murmur, best heard at the left sternal border, which was confirmed to be AR on transthoracic echo. The patient subsequently underwent a transesophageal echo, and some images are illustrated in Figure 15-5. Which of the following is the most likely cause of this patient's AR?

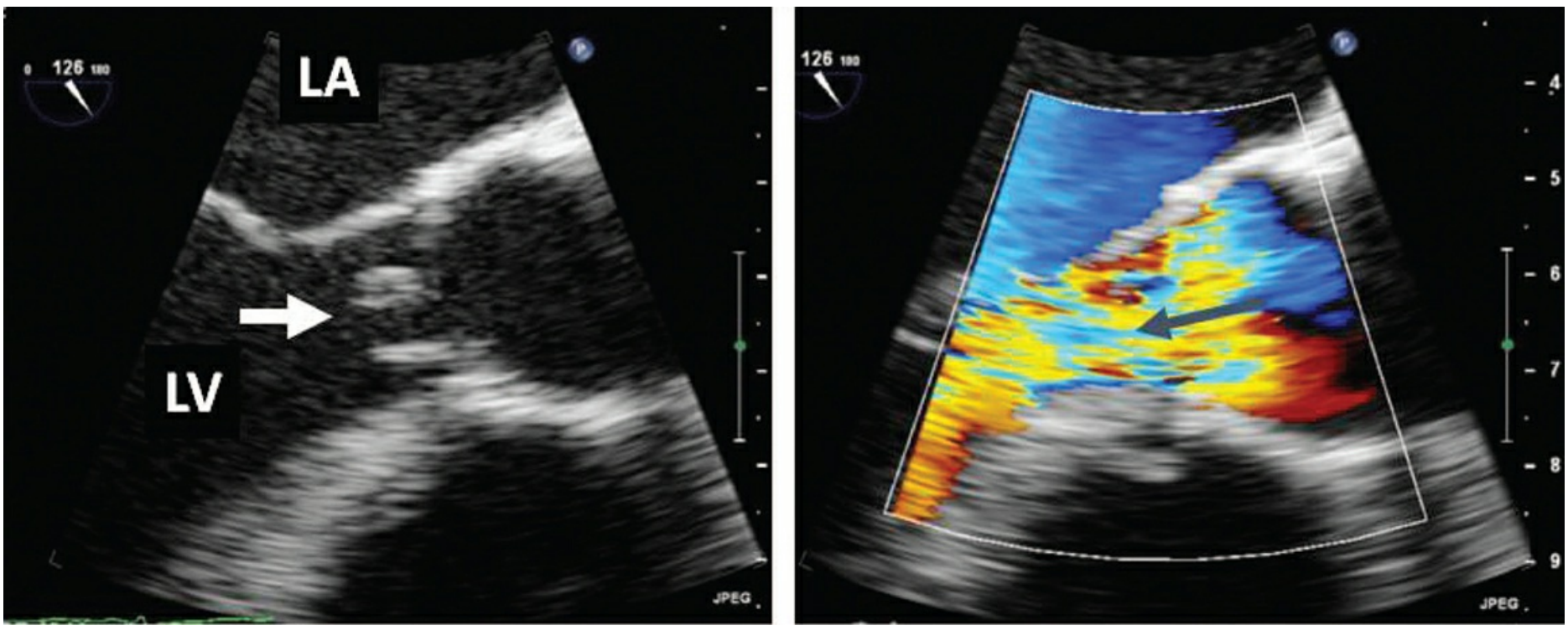


FIGURE 15-5 Transesophageal view depicting the anomaly (white arrow). Color Doppler shows severe aortic regurgitation, with the color jet occupying all of the left ventricle outflow tract. LA, left atrium; LV, left ventricle.

A. Bicuspid aortic valve
B. Aortic dissection
C. Aortitis secondary to vasculitis
D. Aortitis secondary to syphilis
E. Infectious endocarditis

15-8. A 19-year-old man with no personal or family history of sudden cardiac death was admitted to the emergency department following a collapse while playing soccer. On cardiac auscultation, there was a grade 3/6 systolic murmur best heard over the apex. After unremarkable blood tests, ECG, and chest radiography, an echo was performed. An apical four-chamber view is illustrated in Figure 15-6. In which of the following conditions does systolic anterior motion of the mitral valve (SAM) *not* occur?

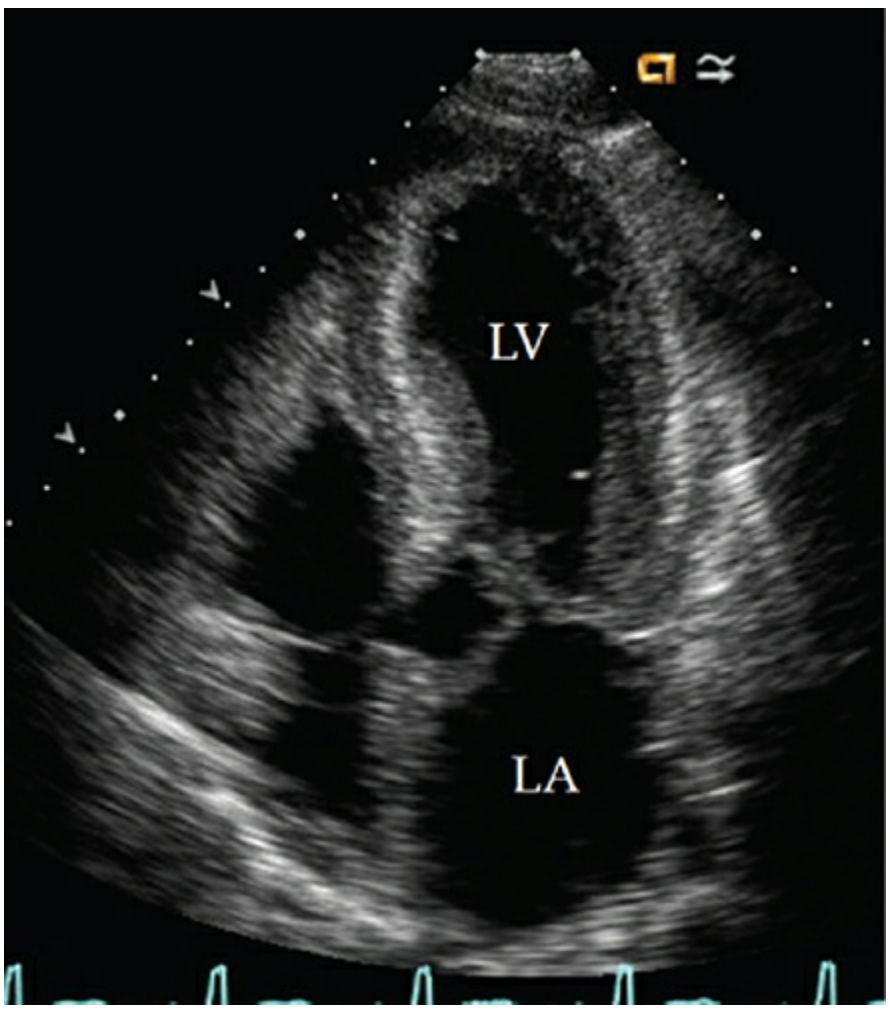


FIGURE 15-6 Apical four-chamber view during systole, demonstrating systolic anterior motion of the mitral valve. LA, left atrium; LV, left ventricle; RA, right atrium.

A. Hypertrophic cardiomyopathy (HCM)
B. Anemia
C. Dehydration
D. Following mitral annuloplasty surgery with a rigid ring
E. None of the above

15-9. An asymptomatic 47-year-old man with a recent history of anterior STEMI was referred to the cardiology clinic by his family doctor because of a persistent ST-segment elevation in the anterior leads. An echo was performed, and an apical four-chamber view is illustrated in Figure 15-7. Based on the echo's findings, which of the following is the most likely diagnosis?

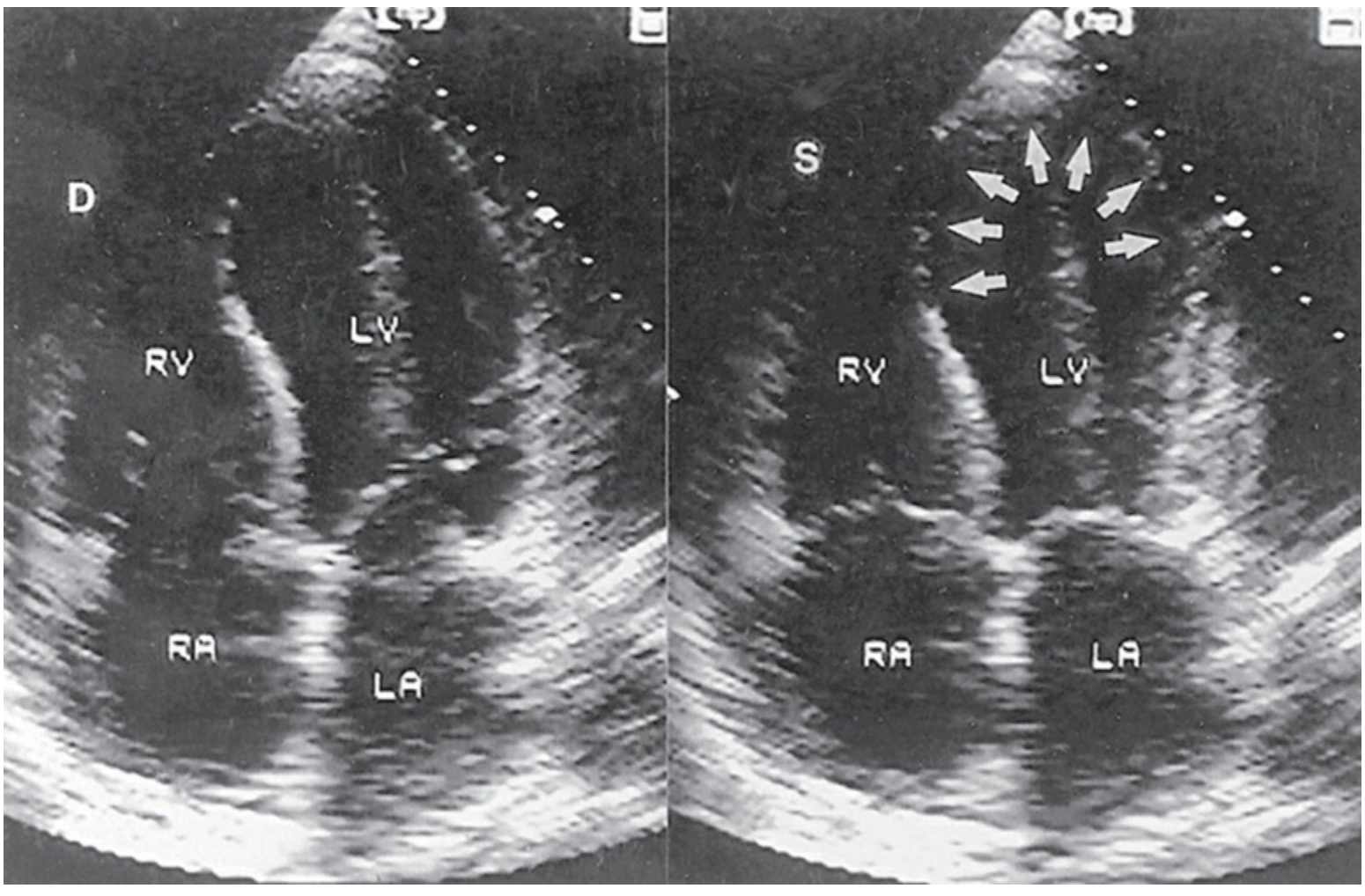


FIGURE 15-7 Apical four-chamber view. Diastole (D) is displayed on the left, systole (S) on the right. During systole, the base of the ventricle contracts, but the apex is dyskinetic (arrows). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

A. LV aneurysm
B. LV pseudoaneurysm
C. Apical ballooning syndrome
D. LV noncompaction
E. Dilated cardiomyopathy

15-10. A 55-year-old woman with a prior history of a modified radical mastectomy for a left breast adenocarcinoma was admitted to the emergency department complaining of acute dyspnea. Chest radiography showed cardiomegaly and left pleural effusion. An echo was performed, and the apical four-chamber view is illustrated in Figure 15-8. With regard to cardiac tamponade, which of the following statements is *false*?

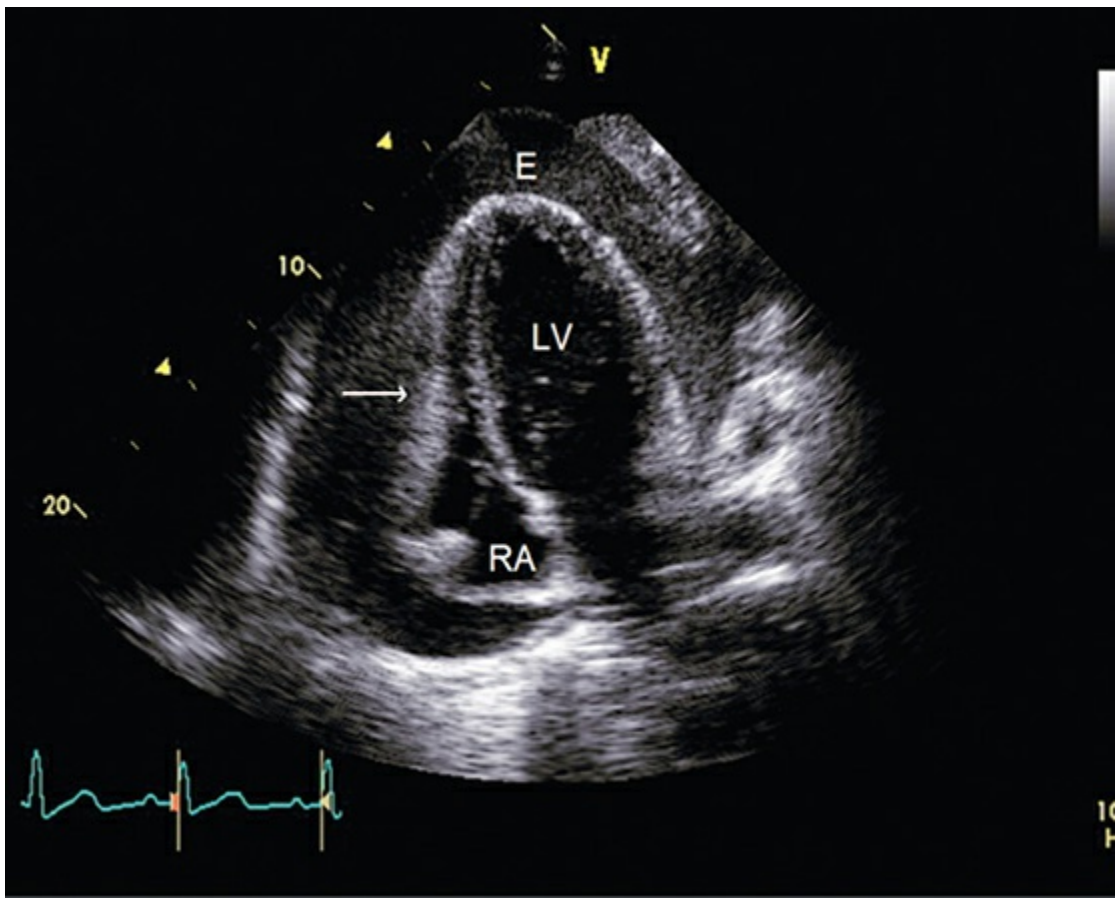


FIGURE 15-8 Right ventricular compression (arrow) in cardiac tamponade (apical four-chamber plane).

A. Right atrium (RA) collapse during atrial systole is the most specific sign of tamponade
B. Diastolic collapse of the right ventricular (RV) free wall is the most sensitive sign of tamponade
C. Left ventricular outflow tract obstruction (LVOT) velocities increase significantly with inspiration
D. Transmitral diastolic gradient during inspiration increases significantly
E. All of the above

ANSWERS

15-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Short wavelengths yield excellent resolution in echo imaging (option A) because the shorter the cycle length, the smaller the object that will reflect the signal and be detected by the echo scanner. Because wavelength is inversely related to frequency, transducers that emit a high-frequency signal (≥ 3.5–7.0 MHz) yield high-resolution images (option B). Because ultrasonic beams diverge as they propagate away from the transducer, the width of the beam can become sufficiently great to encompass multiple targets and decrease resolution (option D). The degree of beam divergence is also less with high-frequency sonic energy than with low-frequency signals.

15-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 15)* The abnormal mitral inflow patterns are often useful in suggesting the presence and severity of diastolic dysfunction. Several variables other than diastolic function, however, are capable of influencing transmitral filling velocities. Transmitral Doppler filling dynamics are affected by the age of the patient (option A), concomitant mitral regurgitation, high-flow states, changes in heart rate (option B),[1] respiration (option C), and the position of the Doppler sample volume within the mitral valve orifice (option D).[2]

15-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Transmitral flow demonstrates a restrictive pattern, with

an abnormally high E/A ratio and a markedly shortened E wave deceleration time (see Figure 15-1*a*). Concomitant pulmonary venous tracings show a very low S velocity and elevated D velocity (S << D) (see Figure 15-1*b*) and a prolonged atrial reversal wave, thus predicting elevated left atrial pressure.[3] In severe LV diastolic dysfunction, tissue Doppler imaging (TDI) of the mitral annulus should show marked blunting of both Em and Am velocities. An exception to this occurs in constrictive pericarditis, where Em is relatively normal at the medial mitral annulus and only mildly reduced at the lateral mitral annulus. Thus when transmitral and pulmonary venous Doppler suggest severe diastolic dysfunction, this TDI pattern suggests constrictive rather than restrictive physiology (amyloid-induced cardiomyopathy [CM], hypereosinophilic CM, endomyocardial fibrosis, and idiopathic restrictive CM).

15-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 15)* A number of technical factors can influence jet size, including instrument gain, the angle of incidence of the interrogating beam, the frequency and pulse repetition rate of the transducer, and the temporal sampling rate.[4] Therefore, measurements derived from the size of the turbulent jet recorded by color Doppler are at best semiquantitative and should not be expected to correlate with the volume of blood contained in the flow disturbance.

15-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Echocardiography is routinely used to assess aortic pathology in patients with Marfan syndrome. The aortic pathology is characterized by symmetrical dilatation of the annulus, sinuses of Valsalva, and aorta (Figure 15-3). Aortic leaflet coaptation may be compromised, leading to AR. In sinus of Valsalva aneurysm, the lesion causes asymmetric dilatation of the aorta. Supravalvular aortic stenosis is recognized as an hourglass narrowing or a discrete fibrous ridge just superior to the aortic valve leaflets, whereas coarctation of the aorta presents a more localized, abrupt luminal reduction in the descending aorta or distal portion of the aortic arch; both of these conditions tend to cause more of a systolic than a diastolic murmur.

15-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Several potential sources of error exist in the estimation of the transvalvular aortic gradient by CW Doppler recordings. It is imperative that Doppler signals from the stenotic jet be obtained with an angle of incidence of less than 20 degrees so as not to underestimate the velocity or gradient. For this purpose, and because two-dimensional techniques rarely reveal the precise direction of the jet, each Doppler examination must use all possible windows and angulations, and the window that provides the highest velocity is chosen. Also, one must be careful to account for the proximal flow velocity in the Bernoulli equation if it is 1.5 m/s or greater. In the adult, CW Doppler can occasionally overestimate peak systolic pressure gradients, especially in patients with narrow ascending aortas (due to pressure recovery). Lastly, in patients with concomitant dynamic LV outflow obstruction, it is usually difficult to separate the increased velocity caused by each of these conditions.

15-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Perhaps the most important contribution of echocardiographic imaging to the assessment of AR is in identifying its etiology and adaptation of the LV to the volume overload. Aggressive vegetations can cause perforation or distortion of the affected leaflet, leading to varying degrees of valvular regurgitation. AR caused by infectious endocarditis can be identified by the presence of valvular vegetations (Figure 15-5), whereas functional AR caused by diseases of the aorta can be identified by anatomic changes of the aortic root or dissection.

15-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 15)* SAM is not pathognomonic for HCM, and it can occur in other conditions involving hyperdynamic LV function (eg, hypovolemia/dehydration, anemia) or anterior displacement of the annulus (eg, use of a rigid mitral ring in mitral valve repair).

15-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Echocardiography is of great value in assessing complications associated with acute myocardial infarction (AMI).[5] Postinfarction LV aneurysms are recognized as wide-mouthed, thin-walled myocardial segments that display dyskinetic expansion during systole (option A). Pseudoaneurysms (most often secondary to a free wall rupture, which is subsequently sealed off by clot and pericardial inflammation) is distinguished from a true aneurysm by the presence of a narrow neck, multilayered thrombi, and characteristic Doppler flow signals at the junction with the ventricle.[6] Because the risk of rupture is high, accurate diagnosis and prompt surgical repair of pseudoaneurysms is important (option B). Takotsubo cardiomyopathy (also called stress cardiomyopathy or apical ballooning syndrome) is a syndrome of sudden-onset chest pain associated with significant LV dysfunction but no occlusive coronary disease and only minor troponin elevations.[7] Echocardiography is well suited for evaluation in this setting and often shows dramatic apical ballooning with preservation (or hyperkinesis) of the LV basal segments (option C). LV noncompaction is a form of cardiomyopathy that is characterized by a prominent noncompacted layer of myocardium lining the cavity of the left ventricle.[8] A ratio of > 2.0 between the systolic thicknesses of the noncompacted and compacted myocardial layers is suggestive of noncompaction (option D).[9] The echocardiographic findings in dilated cardiomyopathy include an increased LV end-diastolic diameter and decreased ejection fraction, in the absence of other features specifically associated with other etiologies (option E).

15-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 15)* Because diastolic pressures are slightly lower in the right heart than in the left, the RA and RV are usually the first chambers to exhibit evidence of increased intrapericardial pressure. High intrapericardial pressure can cause compression or collapse of right heart chambers. Invagination of the RA wall during atrial systole is a sensitive (but not specific) sign of tamponade. Diastolic collapse or buckling of the RV free wall is a more specific sign of tamponade. Doppler echocardiographic recordings in patients with tamponade demonstrate an exaggeration of the normal respiratory variation in ventricular inflow and outflow. Thus transmitral and

LVOT velocities decrease significantly with inspiration, most likely because of enhanced ventricular interdependence and a marked decrease in the transmitral diastolic gradient during inspiration. The latter is caused both by high intrapericardial pressure and by leftward motion of the interventricular septum from increased RV filling.

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CHAPTER 16

Magnetic Resonance Imaging of the Heart

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

16-1. Tissue characterization with mapping or weighted imaging using assessments of T1, T2, or T2* relaxation is increasingly used in cardiovascular magnetic resonance (CMR).[1,2] Which of the following conditions *cannot* be identified by T2 or T2*-weighted imaging?

A. Myocardial edema in the setting of acute myocardial infarction (MI)
B. Myocardial edema in the setting of myocarditis
C. Myocardial hemorrhage
D. Iron-overload cardiomyopathy
E. None of the above

16-2. Although a relatively safe imaging modality, CMR does have the potential for serious and even lethal events. Which of the following statements regarding the safety of common metallic implants and electronic devices commonly found in cardiac patients is *false*?

A. Current coronary stents are safe and can be imaged immediately after implantation
B. Current prosthetic valves are safe and can be imaged immediately after implantation
C. Weakly ferromagnetic implants are safe and can be imaged immediately after implantation
D. Swan-Ganz catheters contain metal and are considered unsafe
E. Transdermal patches may need to be removed before the procedure

16-3. CMR is unique in that, with a single imaging modality, one can identify abnormalities of myocardial perfusion or wall motion with a relatively high spatial resolution and without ionizing radiation. Based on multimodality appropriate use criteria, in which of the following patients is stress CMR considered appropriate?

A. Patients presenting with chest pain at a high pretest probability of coronary artery disease (CAD)
B. Patients at an intermediate pretest probability of CAD with an uninterpretable ECG
C. Patients with an abnormal or uncertain exercise ECG
D. Patients with obstructive CAD of uncertain significance
E. All of the above

16-4. A 54-year-old obese woman was admitted to the emergency department complaining of worsening chest discomfort. After being diagnosed with an acute myocardial infarction, she underwent successful stenting of the left anterior descending artery. An echocardiogram was ordered to assess left ventricular function, but the image quality was suboptimal due to poor acoustic windows. A cardiac magnetic resonance exam was then ordered to provide an assessment of:

A. Myocardial salvage
B. Microvascular obstruction
C. The extent of late gadolinium enhancement (LGE) as a predictor of survival and adverse cardiac events
D. The presence of T2 hyperintensity in the affected territory as an indicator of infarct acuity
E. All of the above

16-5. A 65-year-old man with a 20-year history of poorly controlled diabetes presented to the emergency department complaining of acute dyspnea. After the initial tests, the diagnosis of acute decompensated heart failure (HF) was confirmed. In order to establish the underlying etiology and, importantly, to exclude chronic ischemic heart disease as a potentially reversible cause, a CMR was performed. An LGE image in a two-chamber long-axis orientation is illustrated in Figure 16-1. Which of the following statements regarding LGE is *false*?

FIGURE 16-1 Late gadolinium-enhanced inversion recovery gradient echo image in a two-chamber long-axis orientation in a patient with systolic heart failure. Two areas of prior myocardial infarction are seen: a subendocardial infarct in the basal to midinferior wall and a small apical infarct with an associated apical thrombus.

A. The absence of LGE rules out the diagnosis of underlying CAD
B. Patients without obstructive CAD may have evidence of LGE
C. The presence and amount of LGE is prognostically important in the setting of CAD
D. CMR is considered an appropriate technique for the evaluation of patients with new-onset HF
E. Patients with nonischemic causes of HF may or may not have evidence of LGE

16-6. A 35-year-old man with no prior cardiac history was admitted to the emergency department with chest pain, troponin elevation, and no evidence of angiographically detectable stenoses within the epicardial coronary arteries. The patient underwent CMR, and an LGE image in a basal short-axis orientation is shown in Figure 16-2. Which of the following is the most likely diagnosis?

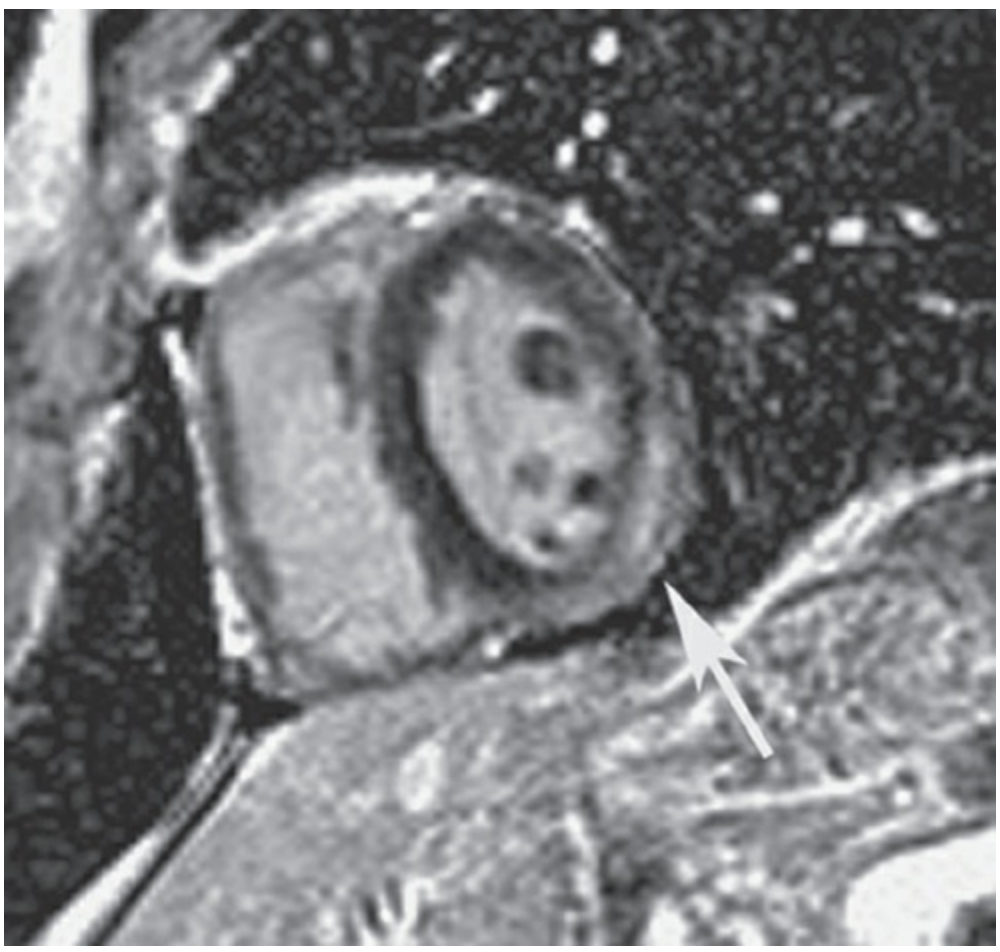

FIGURE 16-2 Late gadolinium-enhanced (LGE) inversion recovery gradient echo image in a basal short-axis orientation. LGE is noted in the midwall and subepicardium in the inferolateral wall (arrow).

A. Noncardiac chest pain

B. Hypertrophic cardiomyopathy (HCM)
C. Acute myocardial infarction
D. Viral myocarditis
E. Takotsubo or stress cardiomyopathy

16-7. A 57-year-old woman with no prior cardiac history was admitted to the emergency department complaining of a 6-month history of dyspnea. On physical examination, she had jugular venous distension, hepatomegaly, tense ascites, severe bilateral lower limb edema, and an S3 gallop. After an initial management she underwent CMR, and a four-chamber T1-weighted image as well as diastolic short-axis images from a real-time cine acquisition during free breathing are illustrated in Figure 16-3. Which of the following statements regarding the diagnosis is *false*?

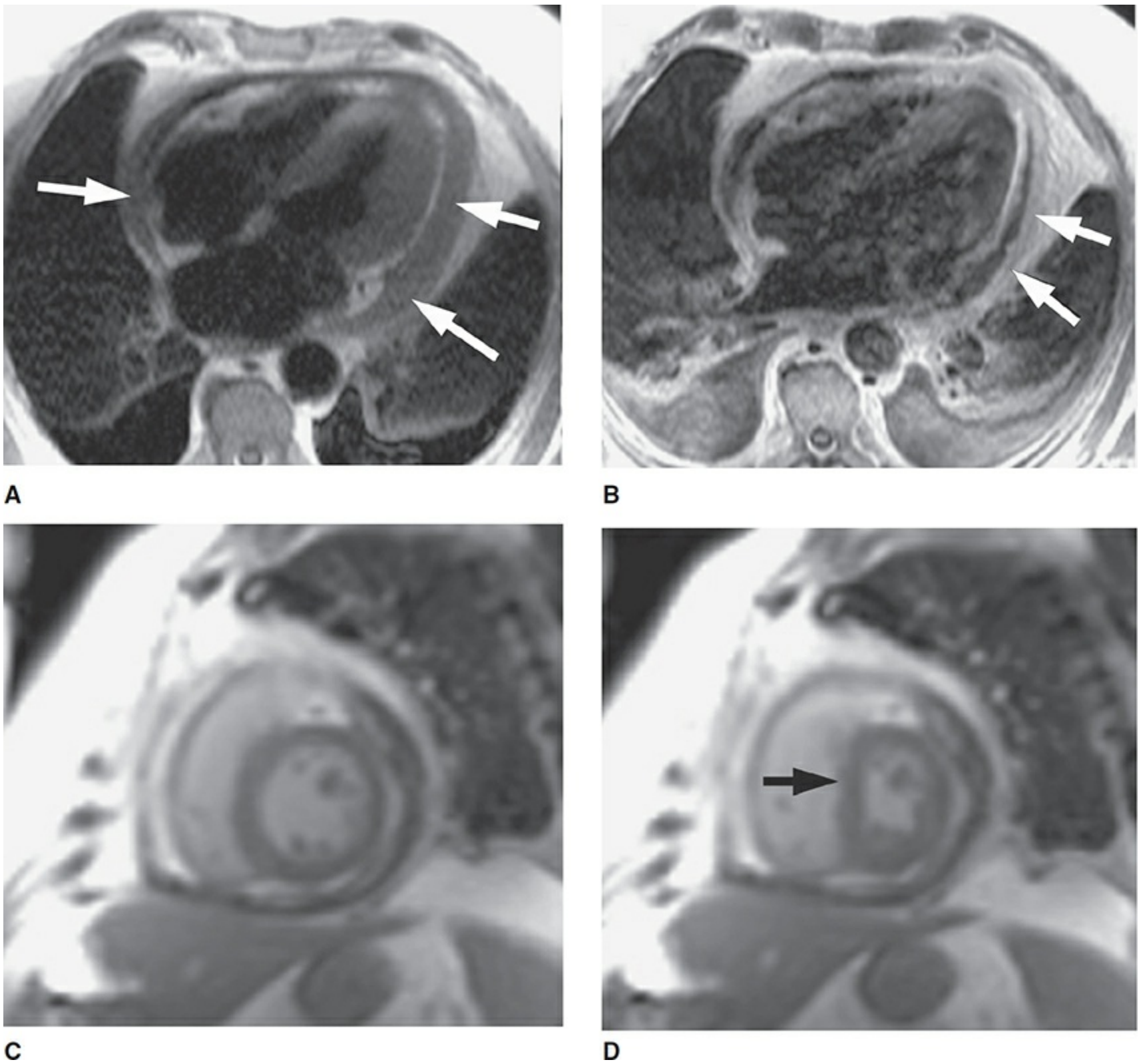

FIGURE 16-3 (A) Four-chamber T1-weighted spin echo demonstrating markedly increased pericardium (dark band, arrows). (B) Same image acquired after contrast showing pericardial enhancement (arrows). (C) and (D) Expiratory and inspiratory, respectively—diastolic short-axis frames from a real-time cine acquisition during free breathing. Note the marked septal flattening during inspiration (arrow) consistent with increased ventricular interdependence.

A. Pericardial thickness of 4 mm or more is considered abnormal
B. Pericardial thickness may not be accurately quantified in the presence of an effusion
C. This disease can occur with normal pericardial thickness
D. The presence of extensive pericardial LGE may identify a subgroup of patients in whom the disease can revert with anti-inflammatory therapy
E. Pericardial LGE is synonymous with pericardial fibrosis

16-8. An 85-year-old woman with no prior cardiac history presented to the emergency department complaining of dizziness. The patient denied any other associated symptoms, and initial test results were within normal range. As part of the dizziness workup, a transthoracic echocardiogram was performed, which showed a large interatrial mass. For further characterization of the mass, the patient underwent CMR, and a T1-weighted image before and after the application of a fat suppression pulse is illustrated in Figure 16-4. Which of the following conditions is the most likely diagnosis?

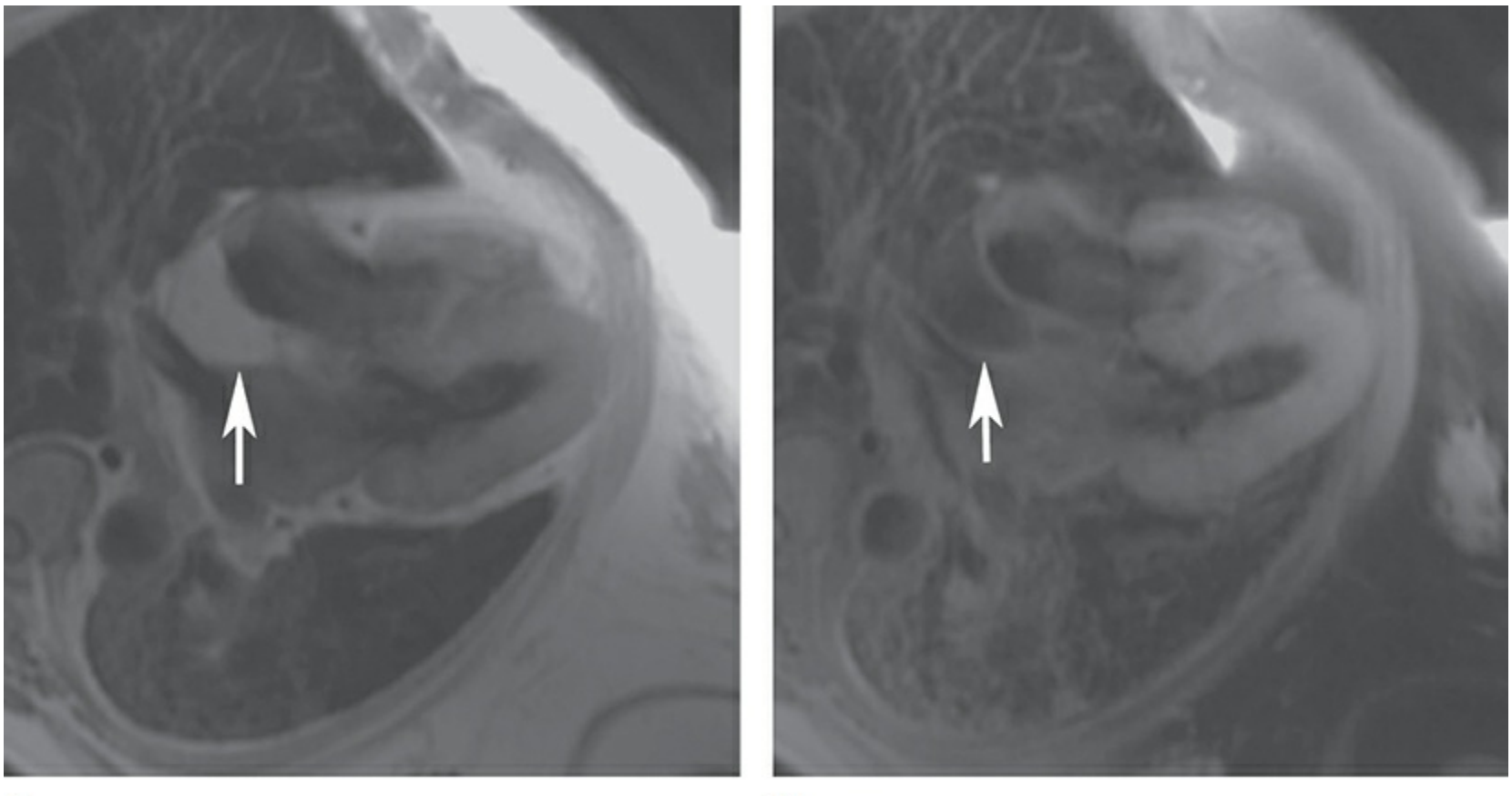

FIGURE 16-4 On standard T1-weighted spin echo images, the lesion is hyperintense (A; arrow). After the application of a fat suppression pulse, the signal from the lesion is nulled (B; arrow).

A. Lymphoma
B. Rhabdomyosarcoma
C. Angiosarcoma
D. Lipoma
E. Myxosarcoma

16-9. A 75-year-old man with a prior history of dyslipidemia, hypertension, and poorly controlled diabetes was referred to cardiology for a CMR exam, three days after his admission to the emergency department for retrosternal chest discomfort. A four-chamber long-axis orientation with different inversion times (TI) is illustrated in Figure 16-5. Which of the following feature does *not* support the diagnosis of a thrombus?

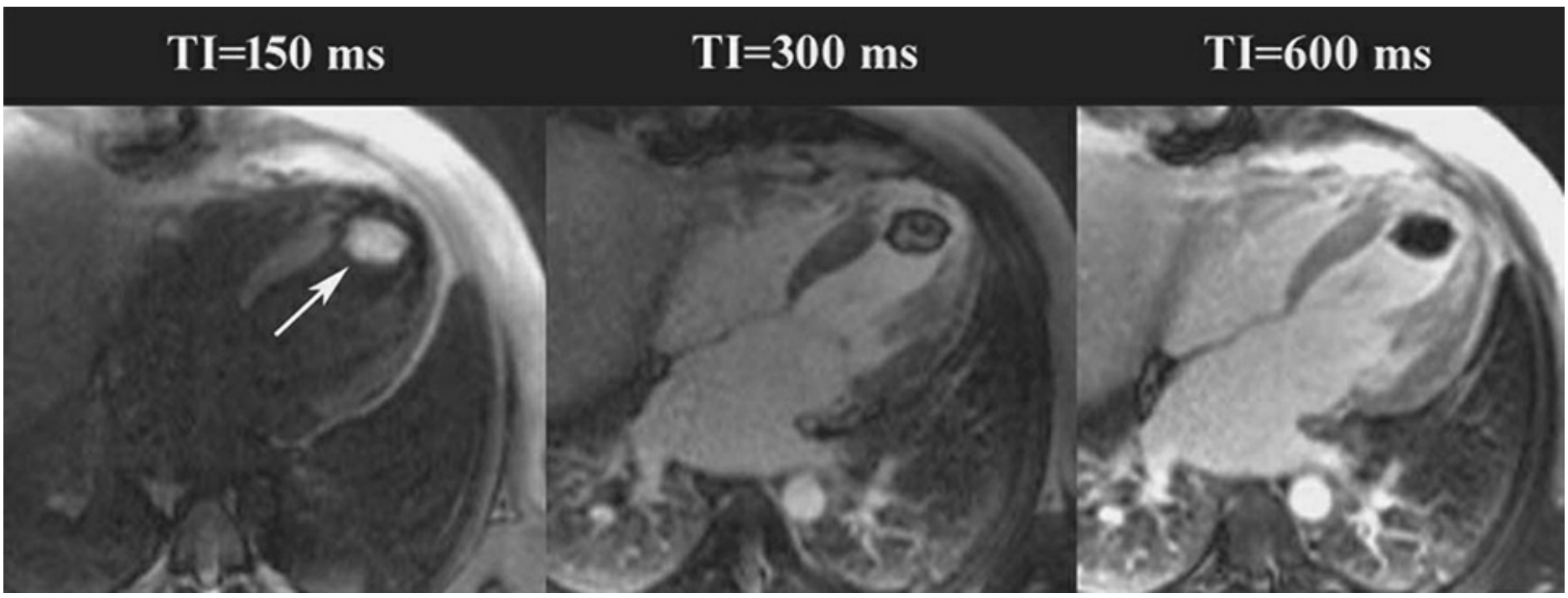

FIGURE 16-5 Four-chamber long-axis orientation with different inversion times (TI).

A. Homogenous appearance
B. Lack of mobility
C. Hyper- or iso-intense with short inversion time (TI) and hypointense with long TI
D. Location in the LV adjacent to areas of scar
E. None of the above

16-10. Although LGE techniques are widely used for identifying myocardial scar and thus inferring viability, dobutamine stress CMR is also used to measure LV myocardial contractile reserve and thus to identify myocardial segments that have the potential to recover systolic function after successful epicardial coronary arterial revascularization. Which of the following is *not* an advantage of using dobutamine stress CMR for assessing myocardial viability?

A. It can be administered to patients with reactive airways disease

B. It can be administered to patients with severe renal dysfunction
C. The prediction of improvements in regional wall motion or radial thickening is incremental above and beyond LGE
D. None of the above
E. All of the above

ANSWERS

16-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 16)* High signal on T2-weighted imaging can demonstrate myocardial edema, such as in the setting of acute MI or myocarditis. T2*-weighted imaging is sensitive to iron in the heart and can identify iron overload cardiomyopathy and myocardial hemorrhage in the setting of acute MI.

16-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 16)* All current coronary stents and prosthetic valves are safe and can be imaged immediately after implantation. Many other cardiac or vascular implants are nonferromagnetic and can also be scanned at any time, or they are weakly ferromagnetic and a delay of 6 weeks before MRI is recommended to allow for endothelialization. Swan-Ganz catheters contain metal and are considered unsafe. Similarly, some medication patches (including transdermal patches) contain metallic foil and may need to be removed before the procedure.

16-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 16)* Based on multimodality appropriate use criteria, stress CMR is considered appropriate for patients at a high pretest probability of CAD or an intermediate pretest probability of CAD with an uninterpretable ECG or inability to exercise.[3] It is also appropriate for patients with an abnormal ECG who are intermediate to high risk as well as those with an abnormal or uncertain exercise ECG or those with obstructive CAD of uncertain significance noted on computed tomography (CT) or invasive coronary angiography.

16-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 16)* Today, perhaps the most widely used imaging method for identifying myocardial injury and fibrosis associated with myocardial infarction is through CMR-based assessments of LGE.[4] LGE has several important uses in the setting of patients with suspected CAD. These include identification of the extent of acute and remote MI, the prediction of recovery of myocardial contractility after successful coronary artery revascularization, characterization of prognosis, visualization of cardiac thrombus or microvascular obstruction and, when combined with T2 imaging methods, localization of the area of myocardial salvage and infarct acuity.

16-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 16)* The first step in the evaluation of the patient with new-onset HF is to establish the underlying etiology and, importantly, to exclude ischemic heart disease as a potentially reversible cause. CMR is considered an appropriate technique for the evaluation of patients with new-onset HF.[5] The presence of LGE in a coronary distribution can support the diagnosis of underlying CAD, but its absence does not rule it out because patients with extensive hibernating myocardium may not have LGE.[6] Patients with HF without obstructive CAD may not have evidence of LGE,[7] or they may have evidence of LGE, usually in a noninfarct pattern, but occasionally in an infarct pattern because of transient thrombotic occlusion of a nonobstructive artery, embolization, or spontaneous coronary dissection. The presence and amount of LGE are prognostically important.

16-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 16)* The pattern of LGE can be quite useful in differentiating causes of cardiomyopathies.[8] The finding of LGE in the midwall and subepicardium of the LV is seen in viral myocarditis and has been validated against histopathology.[8] The finding of "patchy" LGE in myocardial segments with marked hypertrophy, or in the septal insertion points, is suggestive of HCM. The finding of LGE in the subendocardium of the LV following a distinct coronary territory is characteristic of myocardial infarction. Takotsubo or stress cardiomyopathy is a clinical syndrome characterized by chest pain and ECG changes that mimic an acute myocardial infarction, in which there is generally no LGE.

16-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 16)* The hallmarks of constrictive pericarditis are increased pericardial thickness, pericardial inflammation, and ventricular interdependence. The pericardium can be visualized and measured in a number of sequences, although T1-weighted black-blood imaging is usually the standard,[9] where the pericardium appears as a hypointense linear structure surrounded by hyperintense fat layers (Figure 16-3A). Although normal pericardial thickness is less than 1 mm, on CMR, 1 to 3 mm is considered normal because of limitations in spatial resolution,[9] and a thickness of 4 mm or more is considered abnormal. Pericardial thickening may be focal or diffuse. It is important to realize that pericardial thickness may not be accurately quantified in the presence of an effusion (both are hypointense on black-blood imaging), that constriction can occur with normal pericardial thickness, and that increased thickness is not synonymous with constriction. The presence of extensive LGE, which may represent dense inflammation, identifies a subgroup of patients in whom constrictive pericarditis can revert with anti-inflammatory therapy.[10,11]

16-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 16)* High signal intensity on T1-weighted images, besides the presence of recent hemorrhage, can also be caused by fat. Together with signal reduction with fat suppression

techniques, hyperintensity on T2-weighted imaging, a lack of first-pass perfusion, and an absence of LGE, CMR allows for the straightforward diagnosis of lipoma. Although less accurate, CMR can also help differentiate benign from malignant neoplasms (lymphoma, rhabdomyosarcomas, angiosarcomas, and myxosarcomas). Larger sizes, invasion of adjacent structure(s), the presence of pleural or pericardial effusions, prominent first-pass perfusion, or positive LGE are all features seen more commonly in malignancy.[12,13]

16-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 16)* The main strength of CMR in the evaluation of cardiac masses is probably the ability to differentiate between cardiac thrombi from tumors. Features supporting the diagnosis of thrombus include location in the LV adjacent to areas of scar or the left atrial appendage, homogenous appearance, lack of mobility, isointensity or hypointensity on T2-weighted imaging, and absence of perfusion or LGE. A thrombus is hyper- or iso-intense with short TI and hypointense with long TI.

16-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 16)* A particular advantage of low-dose dobutamine infusions for assessing myocardial viability is that they can be administered to patients with reactive airways disease as well as to those with renal dysfunction in whom the use of gadolinium may be contraindicated. In addition, there is some evidence that low-dose dobutamine stress CMR assessments of improvements in regional wall motion or radial thickening are complementary and may even be superior to the assessments of LGE, particularly in those individuals who have an intermediate nontransmural extent of LGE.[14]

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CHAPTER 17

Computed Tomography of the Heart

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

17-1. Advancements in CT technology have made it possible to noninvasively image the beating heart. Which of the following statements regarding cardiac CT is *false*?

A. Cardiac CT can assess left and right ventricular remodeling
B. Cardiac CT can assess regional myocardial wall motion and thickening
C. Cardiac CT is comparable to first-pass radionuclide angiography for the calculation of post-MI LVEF
D. Cardiac CT can detect myocardial iron overload
E. Cardiac CT can detect intracardiac thrombus

17-2. A 35-year-old obese woman with a significant family history of premature coronary heart disease presented to the emergency department complaining of a 2-week history of intermittent chest pain. Initial ECG and biomarkers were within normal limits. After an equivocal stress test, she underwent cardiac CT. Which of the following statements about cardiac CT and coronary artery calcification (CAC) is *false*?

A. The severity of angiographic coronary artery stenosis is directly related to the total CAC
B. Cardiac CT can detect coronary atherosclerosis at its earliest stages
C. CAC is caused by atherosclerosis in the coronary arteries
D. CAC is not found in normal coronary arteries
E. There is a strong linear correlation between total coronary artery plaque area and the extent of CAC

17-3. A 55-year-old woman with a prior history of poorly controlled diabetes, hypertension, and dyslipidemia presented to the emergency department complaining of a retrosternal chest pain radiating to her left arm. In the absence of new ECG changes or cardiac biomarker elevation, she underwent cardiac CT. This patient was scanned with a dual-source CT, and the heart rate during the time of the scan was 105 beats/min. The rendered three-dimensional (3D) image of the heart as well as the maximum-intensity projection (MIP) image of the same patient are illustrated in Figure 17-1. Which of the following would *not* be useful for decreasing motion-related artifacts?

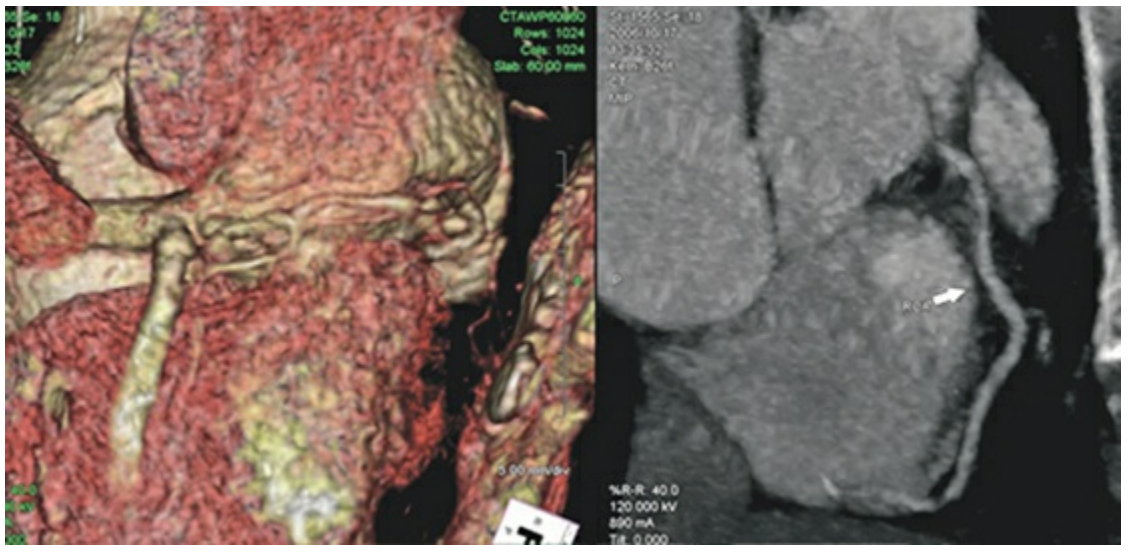

FIGURE 17-1 Left panel: Three-dimensional (3D) rendering image of a heart with significant motion artifact affecting the interpretation of the distal right coronary artery (RCA). Right panel: Maximum-intensity projection (MIP) image of the same patient showing significant transitional motion artifact in the proximal and mid RCA.

A. Image acquisition of less than 50 milliseconds
B. Use of oral and/or intravenous β-blockers prior to scanning
C. Use of sublingual tablets or spray of nitroglycerin
D. Breath-hold strategy during scanning

E. None of the above

17-4. A 64-year-old man with suspected acute coronary syndrome (ACS) was referred to cardiology for coronary CT angiography (CCTA). Which of the following statements about the diagnostic performance of the CCTA is *false*?

A. The diagnostic accuracy for ACS with CCTA is lower than stress echocardiography.
B. The diagnostic accuracy for ACS with CCTA is higher than stress nuclear imaging.
C. The high negative predictive value of CCTA is a valuable tool in the exclusion of obstructive CAD
D. CCTA is useful in the risk stratification of symptomatic CAD
E. CCTA is an accurate tool in the assessment of chest pain in patients with intermediate risk of CAD

17-5. A 78-year-old woman with multivessel coronary artery disease and prior PCI to the left anterior descending coronary artery (LAD) was referred to cardiology for coronary stent evaluation following an episode of severe central chest pain. A CCTA was performed, and it is shown in Figure 17-2. Which of the following factors can potentially *reduce* the diagnostic accuracy of CCTA for the noninvasive evaluation of in-stent restenosis?

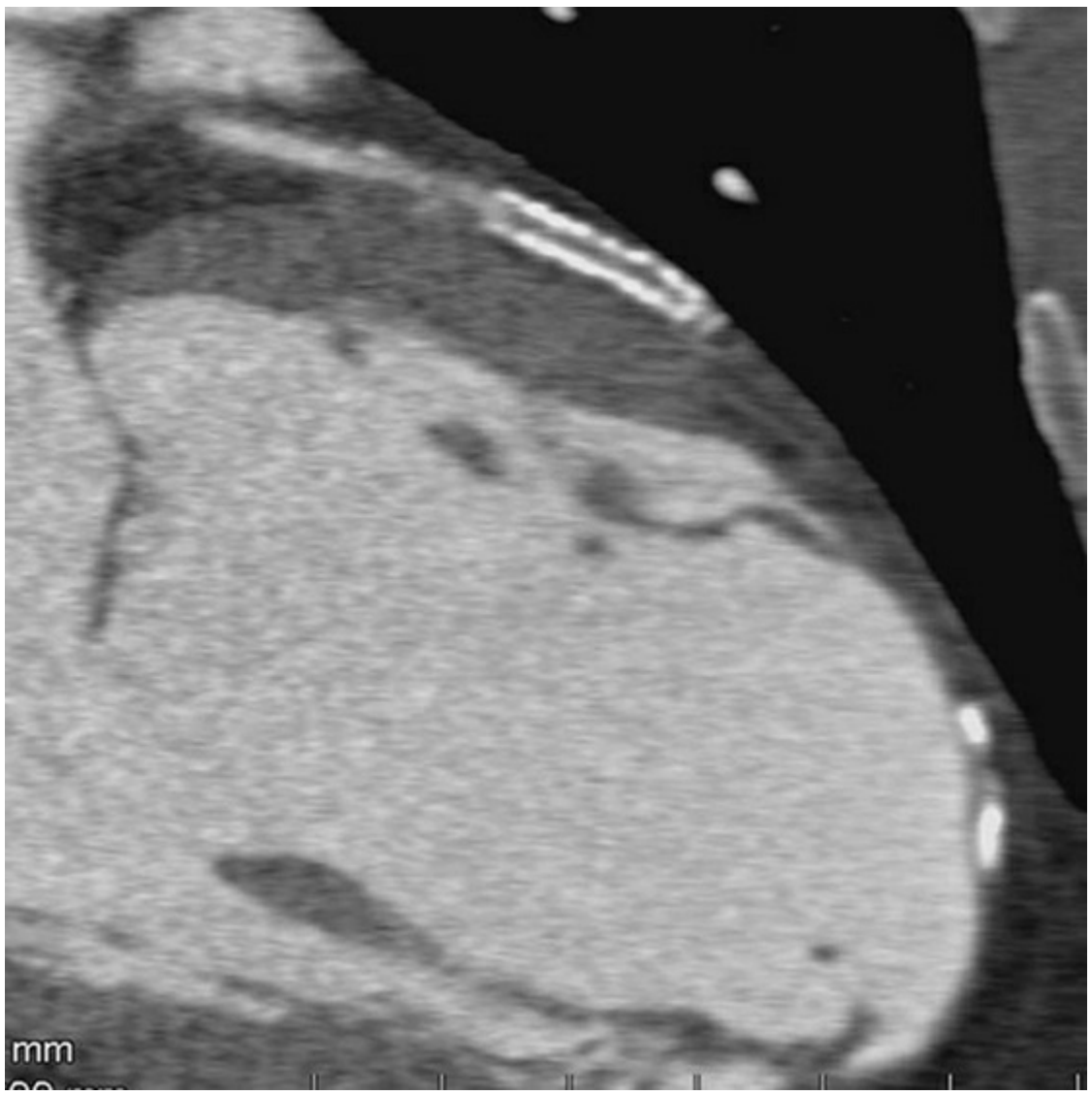

FIGURE 17-2 Evaluation of coronary stents. Occluded stent in the proximal left anterior descending (coronary artery).

A. Imaging artifacts
B. Stent location
C. Heart rate
D. Stent diameter
E. All of the above

17-6. A 37-year-old woman with no prior cardiac history was admitted to the emergency department complaining of atypical chest pain. After the initial ECG and biomarkers were within normal limits, she underwent coronary computed tomography angiography to exclude coronary artery disease. CCTA is illustrated in Figure 17-3. Which of the following statements about congenital anomalies of the coronary arteries is *false*?

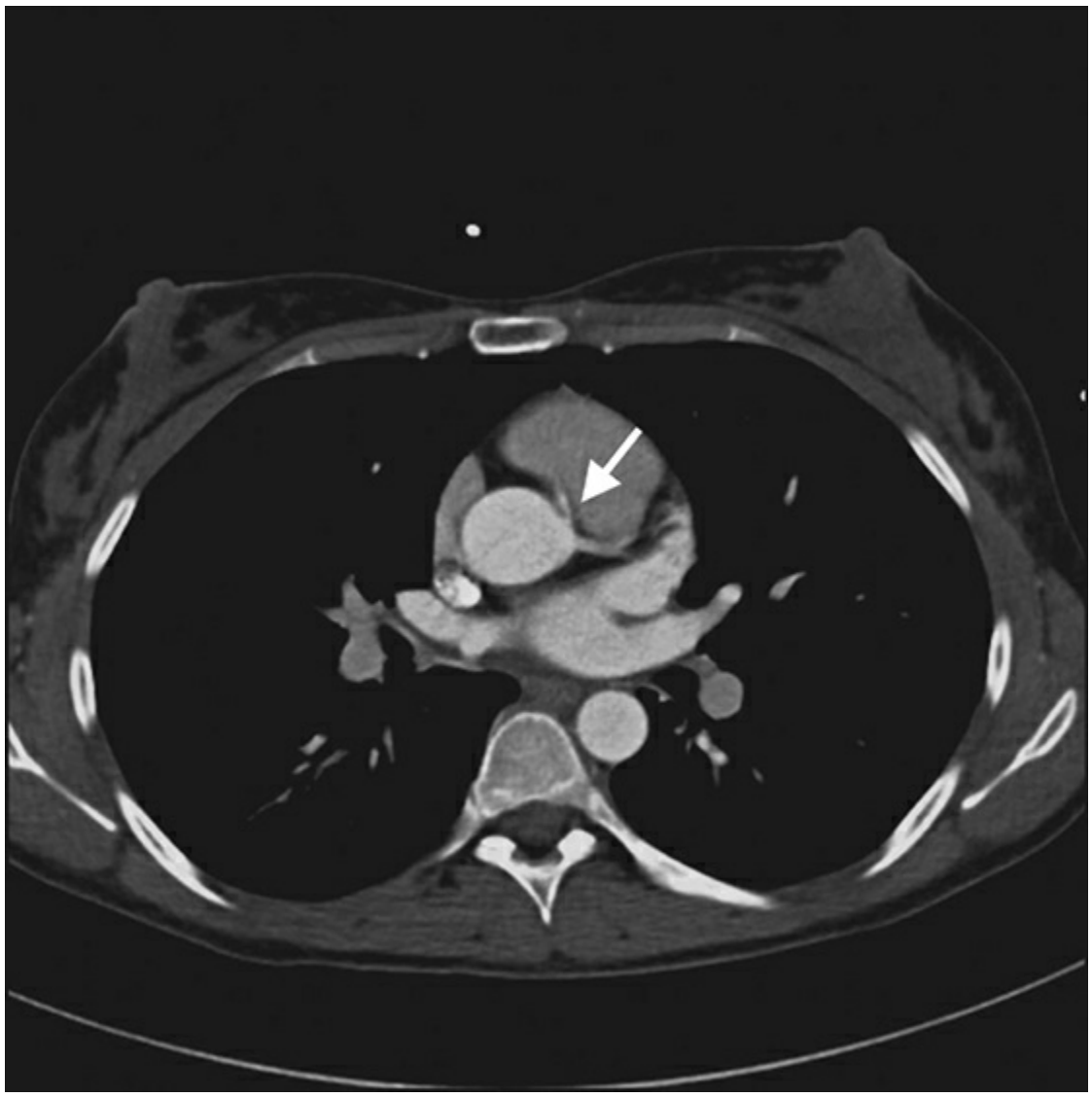

FIGURE 17-3 Anomalous right coronary artery. Note the right coronary artery (arrowhead) arising to the left of midline from the left sinus of Valsalva taking interarterial course.

A. Congential anomalies of the coronary arteries are reported in 0.3% to 1% of the general population
B. Approximately 20% of coronary anomalies can be hemodynamically significant
C. An interarterial course is the coronary anomaly most commonly associated with sudden cardiac death
D. None of the above
E. All of the above

17-7. An 85-year-old woman with a prior history of poorly controlled type 2 diabetes, hypertension, dyslipidemia, rheumatoid arthritis, and multivessel coronary heart disease was admitted to the emergency department with severe symptomatic aortic stenosis. She underwent a contrast-enhanced CTA in advance of the transcatheter aortic valve replacement (TAVR). The left main coronary artery craniocaudal height is illustrated in Figure 17-4. Which of the following factors is predictive of an increased risk of coronary occlusion during TAVR?

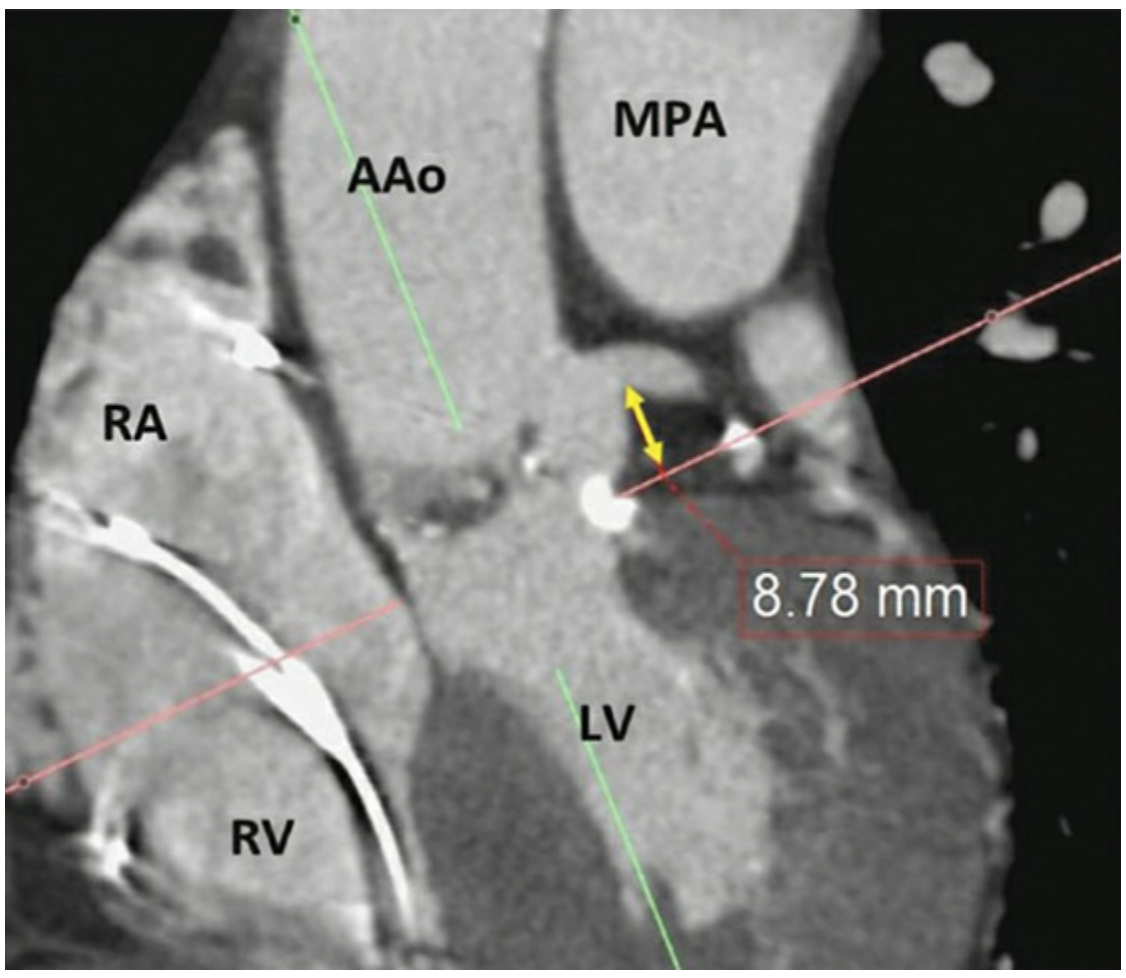

FIGURE 17-4 Left main coronary artery craniocaudal height measured perpendicular to the annular plane. The left main

coronary artery height is 8.78 mm. AAo, ascending aorta; LV, left ventricle; MPA, main pulmonary artery; RA; right atrium; RV, right ventricle.

A. Left main height of lesser than 12 mm
B. A shallow of Valsalva mean diameter (cusp to commissures) of < 30 mm
C. A sinus of Valsalva–to–annular ratio of less than 1.25
D. None of the above
E. All of the above

17-8. The main historical limitation of cardiac CT has been radiation exposure, which was previously reported to be two to four times the radiation dose of diagnostic invasive coronary angiography. Which of the following strategies has been shown to provide the greatest reduction in radiation dose during CCTA?

A. Using prospective ECG-gated or sequential CCTA image acquisition
B. Decreasing the tube voltage in nonobese patients
C. Adopting iterative reconstruction algorithms to allow for significant noise reduction
D. Using scan acquisition modes employing fast helical pitch technique
E. None of the above

17-9. A 75-year-old man with a prior history of dyslipidemia, hypertension, poorly controlled diabetes, multivessel CAD, and multivessel PCI was referred to cardiology for CCTA 3 days after his admission to the emergency department for retrosternal chest discomfort. A CCTA view of the 3 major epicardial vessels is illustrated in Figure 17-5. Which of the following statements regarding the prognostic value of CCTA is *false*?

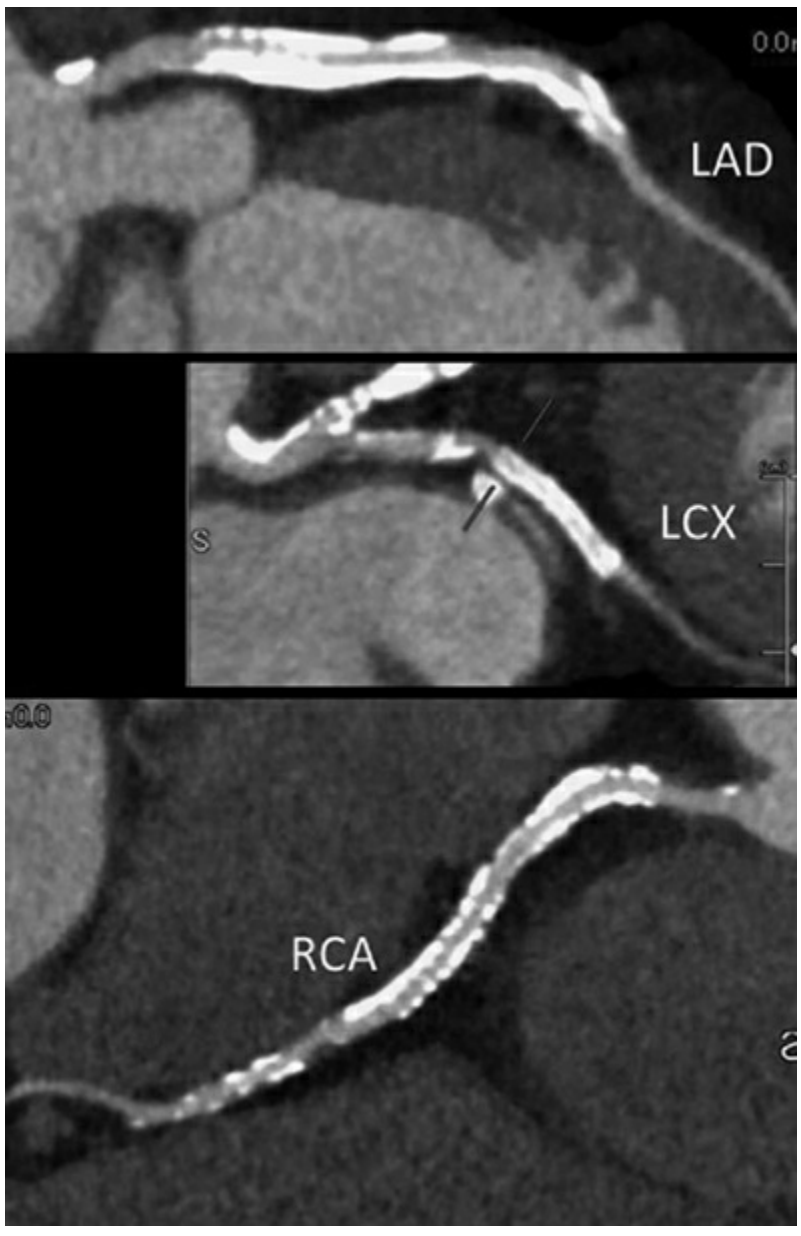

FIGURE 17-5 Conventional cardiac computed tomography angiography (CCTA) for evaluation of all three coronary artery vessels. LAD, left anterior descending (artery); LCX, left circumflex artery; and RCA, right coronary artery.

A. The presence of any stenosis greater than 50% predicts an increased risk of cardiovascular events
B. CCTA is useful for establishing the diagnosis, but not the true extent, of CAD
C. Plaque morphology by CT confers incremental prognostic information beyond that provided by percent stenosis alone
D. CCTA measures of CAD severity and LVEF have independent prognostic value
E. None of the above

17-10. In patients undergoing repeat coronary artery bypass surgery (CABG), CTA scanning has several advantages. Which of the following does *not* support the use of CTA as a primary noninvasive imaging tool for the evaluation of patients prior to CABG?

A. CTA may guide the surgical approach by defining the position of the sternum relative to the underlying right ventricle

and internal mammary artery bypass graft

B. CTA can assess the diameter and calcification of the aorta

C. CTA can assess the presence of coronary stenoses within the bypass graft

D. CTA can assess the presence of coronary stenoses within the native coronary arteries and anastomotic sites

E. None of the above

ANSWERS

17-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 17)* While cardiac CT can provide some information about tissue characterization, it cannot reliably detect iron overload, and this is typically assessed by cardiac MR. Cardiac CT can assess left and right heart size as well as regional myocardial wall motion and thickening (options A and B).[1,2] Cardiac CT is comparable to first-pass radionuclide angiography for the calculation of left ventricular ejection fraction in patients with myocardial infarction (option C).[3] Cardiac CT could effectively detect intracardiac masses such as thrombi and tumors, particularly when these masses are nonmobile or calcified (option E).[4]

17-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 17)* The presence of CAC is clearly indicative of coronary atherosclerosis,[5,6] serving as a marker for CAD; but importantly, the severity of angiographic coronary artery stenosis is not directly related to the total CAC. CAC is thought to begin early in life, and CT can detect coronary atherosclerosis at its earliest stages. Although lack of calcification does not categorically exclude the presence of atherosclerotic plaque, calcification occurs exclusively in atherosclerotic arteries and is not found in normal coronary arteries. A strong linear correlation exists between total coronary artery plaque area and the extent of CAC.

17-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 17)* The coronary arteries move independently throughout the cardiac cycle, and even at relatively slower heart rates (< 70 beats/min), they exhibit significant translational motion of up to 60 mm/s for the RCA and 20 to 40 mm/s for the LAD and circumflex coronary arteries.[7,8] The velocity of coronary artery motion increases significantly with increasing heart rates. Image acquisition of less than 50 milliseconds is truly required to completely avoid cardiac motion artifacts.[7] Cardiac motion is minimized with the use of oral and/or intravenous β-blockers prior to scanning, thereby reducing the heart rate and prolonging the time during the cardiac cycle at which coronary artery velocity is low. Another crucial element for obtaining high-quality coronary images is to maximally dilate coronary vessels with nitroglycerin through the use of sublingual tablets or spray. Respiratory motion can be excluded by performing the scan during a breath-hold.

17-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 17)* Although there is still room for improvement in terms of image quality and elimination of artifacts, the diagnostic performance of the CCTA is now well established. Studies demonstrate higher diagnostic accuracy for ACS with CCTA than with other previously studied modalities, including exercise treadmill, stress nuclear imaging, and stress echocardiography. The high negative predictive value of CCTA makes 64-slice MDCT a valuable tool in the exclusion of obstructive CAD. Therefore, CCTA is useful in the risk stratification of symptomatic patients and can reduce the need for invasive diagnostic coronary angiography in patients without obstructive CAD. A recent scientific statement from the American Heart Association (AHA) on CCTA concluded that "CT coronary angiography is reasonable for the assessment of obstructive disease in symptomatic patients (class IIa, Level of Evidence: B)."[9] In particular, CCTA is an accurate tool in the assessment of chest pain in patients with intermediate risk of CAD or in patients with uninterpretable or equivocal stress tests.[10]

17-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 17)* Imaging artifacts caused by the metallic stent limit the overall visibility of the inner lumen of a deployed stent and can potentially reduce the diagnostic accuracy of CCTA for the noninvasive evaluation of in-stent restenosis. Stent location, heart rate, and stent diameter are also important determinants of accuracy and feasibility for CCTA in this setting.

17-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 17)* Anomalies of the coronary arteries are reported in 0.3% to 1% of the general population.[11] Approximately 20% of coronary anomalies can be hemodynamically significant and manifest as arrhythmias, syncope, MI, or sudden death.[12,13] An interarterial course between the pulmonary artery and aorta is the coronary anomaly most commonly associated with sudden cardiac death.[14]

17-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 17)* Cardiac CT is helpful in reducing the risk of coronary occlusion during TAVR. Coronary occlusion is said to occur in 0.66% of TAVR procedures and is associated with a poor clinical outcome. The mechanism of coronary occlusion relates to calcification on the native aortic valve leaflet being displaced up toward the coronary ostium. CT allows for accurate assessment of both the height of the coronaries and the size and capacity of the sinus of Valsalva.[15] Evidence suggests that a left main height of < 12 mm in conjunction with shallow of Valsalva mean diameter (cusp to commissures) of < 30 mm was associated with more than a fivefold increased risk of coronary occlusion. In addition, a sinus of Valsalva–to–annular ratio of less than 1.25 was also strongly predictive of an increased risk.

17-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 17)* The most significant, and routinely available, radiation reduction strategy (up to 79%) can be achieved through prospective ECG-gated or sequential CCTA image acquisition, which involves the use of axial scanning with the tube current on only during prespecified portions of the cardiac cycle, eliminating tube current (milliampere) during nonimaging portions of the cardiac cycle (ie, systole).[16,17] Additionally, radiation exposure can be further minimized by approximately 46% to 53% by decreasing the tube voltage in nonobese (body mass index < 30 kg/m^2) patients from 120 to 100 kVp.[18,19] More recently, new iterative reconstruction algorithms have been introduced and validated for use in cardiac CT to allow for significant noise reduction, enabling an uncoupling of tube current and image noise and thereby allowing for significant tube current and dose reduction.[20] Finally, new scan acquisition modes employing fast helical pitch technique afforded by dual source dual detector technology allow for rapid scan acquisition and significant dose reduction as a result.[21]

17-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 17)* CCTA yields independent prognostic information in addition to clinical risk factors in patients with suspected or known CAD.[22] In patients with chest pain, CCTA can identify obstructive lesions, such as proximal LAD stenosis, as well as the number of vessels with moderate to severe stenosis, which predict an increased risk for all-cause mortality.[23] The presence of any stenosis greater than 50% at CCTA has been associated with a 10-fold higher risk of cardiovascular events. In addition, the extent of CAD, reflected by the number of coronary segments involved, incrementally increased the risk of adverse outcomes.[24] Plaque morphology by CT confers incremental prognostic information beyond that provided by percent stenosis alone. CCTA measures of CAD severity and LVEF have independent prognostic value. Incorporation of CAD severity had incremental value for predicting all-cause death over routine clinical predictors and LVEF in patients with suspected obstructive CAD.[25]

17-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 17)* CTA may guide the surgical approach by defining the position of the sternum to the RV, establishing patency of existing grafts, and visualizing the aorta, thereby avoiding unnecessary trauma and bleeding.[26] CCTA may be clinically useful for the evaluation of coronary bypass grafts and coronary anatomy in symptomatic patients.[27,28] In the case of reoperation or revascularization, coronary CTA may provide critically important information on the status and anatomic location of the bypass grafts. The AHA Scientific Statement on CCTA states, "It might be reasonable in most cases to not only assess the patency of bypass graft but also the presence of coronary stenoses in the course of the bypass graft or at the anastomotic site as well as in the native coronary artery system (class IIb, Level of Evidence: C)."[9]

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CHAPTER 18

Nuclear Cardiology

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

18-1. The concept that CAD can be detected with radiopharmaceuticals used for SPECT-MPI is based on the ability to detect a relative reduction in myocardial perfusion in a region supplied by a significantly stenosed vessel when compared with a normal region during hyperemia. Which of the following factors beyond focal percent stenosis can affect the degree of hyperemia achievable in diseased vessels?

A. Myocardial mass distal to the stenosis
B. Endothelial dysfunction
C. Nonatherosclerotic microvascular disease
D. B and C
E. A, B, and C

18-2. A 55-year-old double-amputee man with a prior history of ischemic heart disease, migraine, dyslipidemia, and hypertension was admitted to the emergency department with central chest pain. His medications include bisoprolol, amlodipine, isosorbide dinitrate, aspirin, ramipril, rosuvastatin, and the over-the-counter Excedrin Migraine. Initial ECG and biomarkers were within normal limits. Three days after admission, the patient underwent stress nuclear SPECT-MPI for risk stratification. With regard to his medications, which of the following statements is *true*?

A. Bisoprolol should be discontinued for 12 hours before stress imaging
B. Amlodipine should be discontinued for 12 hours before stress imaging
C. Isosorbide dinitrate should be discontinued for 48 hours before stress imaging
D. Excedrin Migraine should be discontinued for 24 hours before stress imaging
E. All of the above

18-3. A frail 89-year-old woman with a prior history of asthma, multiple falls, peripheral vascular disease, and permanent atrial fibrillation was admitted to the hospital following an episode of retrosternal chest pain. Initial ECG and biomarkers were within normal limits. Three days after admission, the patient underwent stress nuclear SPECT-MPI. Which of the following types of stress testing is the preferred approach to stress nuclear SPECT-MPI for this patient?

A. Adenosine
B. Regadenoson
C. Dipyridamole
D. Dobutamine
E. Exercise

18-4. A 75-year-old man with a prior history of myocardial infarction, dyslipidemia, and hypertension was admitted to the hospital following an episode of central chest pain. Initial ECG showed T-wave inversion in the anterior leads with negative biomarkers. Three days after admission, the patient underwent rest thallium-201 (201Tl) SPECT-MPI, which is illustrated in Figure 18-1. Which of the following is the optimal SPECT approach for the assessment of myocardial viability in this patient?

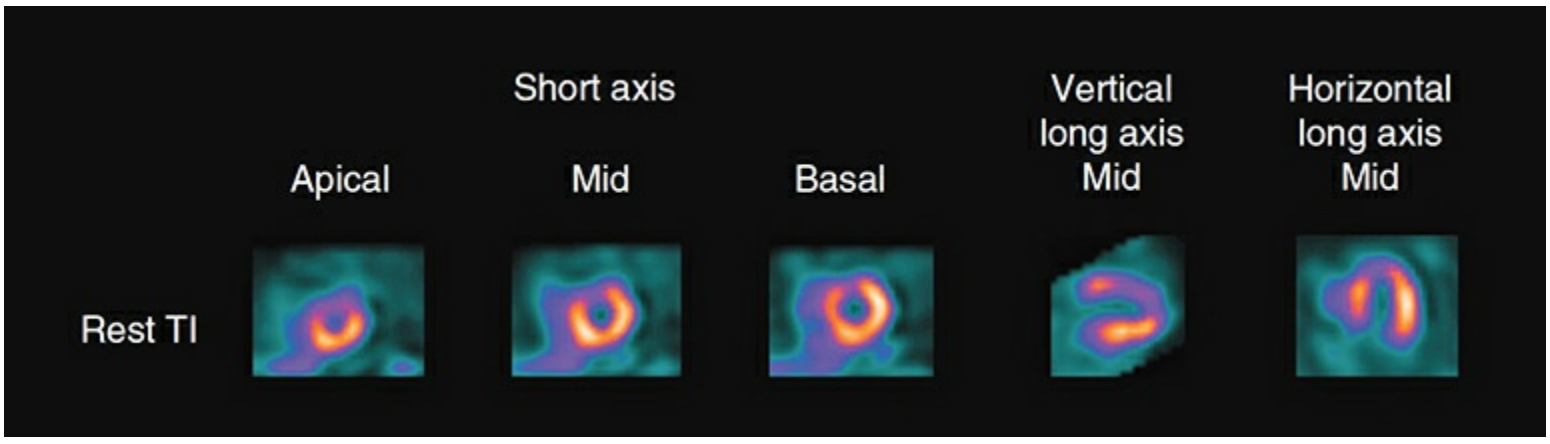

FIGURE 18-1 Rest thallium-201 (201Tl) single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) showing a large amount of resting ischemia in the left anterior descending. The stress SPECT-MPI study was canceled in this patient because of the unexpected perfusion defect.

A. Rest ^{99m}Tc-sestamibi SPECT-MPI
B. Rest ^{99m}Tc-tetrofosmin SPECT-MPI
C. Rest/redistribution thallium-201 (Tl) SPECT-MPI
D. Stress SPECT-MPI
E. Any of the above

18-5. A 65-year-old woman with multiple risk factors for coronary artery disease presented to the emergency department with 2-day history of retrosternal chest discomfort at rest. The patient, whose images are shown in Figure 18-2, was referred for SPECT-MPI after an initial normal ECG and negative biomarkers. With regard to the use of SPECT-MPI in the evaluation of acute chest pain, which of the following statements is *false*?

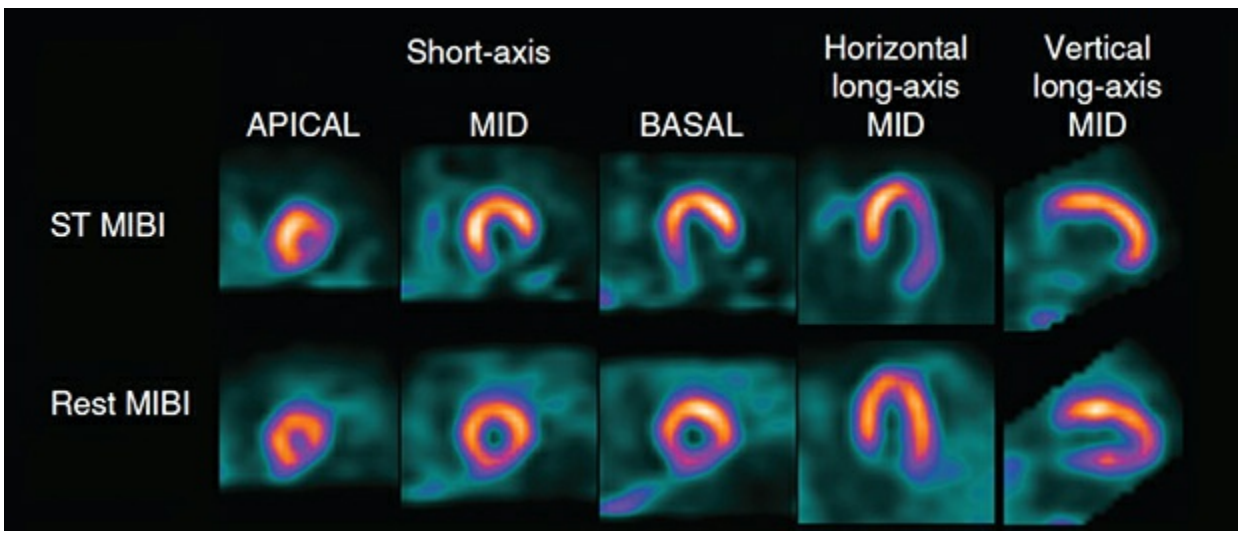

FIGURE 18-2 Adenosine stress/rest myocardial perfusion single-photon emission computed tomography images. Rest sestamibi (MIBI) demonstrated minimal (borderline) perfusion defect in the inferior wall. Stress imaging revealed evidence of severe and extensive ischemia in the inferior and inferolateral wall (41% of the left ventricle).

A. A normal rest SPECT-MPI alone provides strong evidence of the absence of acute MI
B. There is a reduction in hospitalizations when rest SPECT-MPI is incorporated into an ED evaluation strategy of patients presenting with suspected ACS
C. Stress SPECT-MPI study is of no value in ruling out an ACS after a normal rest SPECT-MPI study
D. Stress SPECT-MPI study is safe in low-risk ED patients
E. A normal stress SPECT-MPI study is associated with a very low cardiac event rate

18-6. A 55-year-old man with a prior history of stage IV chronic kidney disease, hypertension, and dyslipidemia presented to the emergency department complaining of central chest pain. Initial ECG revealed an old LBBB, and the laboratory investigations showed negative biomarkers. Which of the following is the best imaging modality for this patient's risk assessment?

A. Vasodilator SPECT-MPI
B. Exercise stress SPECT-MPI
C. CMR imaging
D. CCTA
E. Any of the above

18-7. A 58-year-old morbidly obese woman with a prior history of poorly controlled type 2 diabetes, peripheral vascular disease, stage IV COPD, hypertension, dyslipidemia, and rheumatoid arthritis was admitted to the emergency department with severe retrosternal chest pain. There were no new changes on the initial ECG, and the labs revealed negative biomarkers. Which of the following is the best initial imaging modality for this patient's risk assessment?

A. Exercise stress ECG test
B. Exercise stress CMR imaging

C. Exercise stress nuclear MPI
D. Vasodilator stress nuclear MPI
E. Any of the above

18-8. Applications of nuclear MPI in stable ischemic heart disease are included in the recent ACCF/AHA clinical practice guidelines. Which of the following was assigned a class Ib level of evidence for exercise MPI?

A. Patients with an intermediate pretest risk who have an ECG for which the exercise response cannot be interpreted
B. Patients with an intermediate pretest risk who have an interpretable ECG
C. Patients with ongoing chest pain and uninterpretable ECG (as in old LBBB)
D. None of the above
E. All of the above

18-9. Several large randomized clinical trials have evaluated the application of CCTA to patients with suspected ACS in the ED in comparison to a standard of care approach. In which of the following settings of chest pain in the ED would SPECT-MPI be preferred over CCTA?

A. Elderly patients with known dense coronary calcification
B. Younger patients due to the radiation exposure with CCTA
C. Patients with documented allergy to gadolinium-based contrast agents
D. Patients with valvular heart disease
E. All of the above

18-10. The 2013 ACCF/AHA guideline for the management of heart failure summarized the recommendations for the use of imaging in heart failure patients. Based on this statement, in which of the following clinical applications may nuclear imaging *not* play a role?

A. Patients with ischemic cardiomyopathy who have had a significant change in their clinical status
B. Radionuclide ventriculography for the assessment of LVEF when device therapy is being considered
C. Patients who received treatment that may affect cardiac function
D. Patients with ischemic cardiomyopathy with EF < 35% who are not eligible for revascularization
E. Radionuclide ventriculography for the assessment of LVEF and LV volumes when echocardiography is inadequate

ANSWERS

18-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Multiple factors beyond focal percent stenosis can also affect the degree of hyperemia achievable in diseased vessels. These include stenosis length, myocardial mass distal to the stenosis, plaque composition, diffuse atherosclerosis, nonatherosclerotic microvascular disease, and endothelial dysfunction.[1,2] In general, a significant reduction in maximal hyperemia is usually present when stenosis severity exceeds 70%.[3] However, when compared to assessment of fractional flow reserve (FFR), considered the gold standard, only 35% of vessels visually assessed as having 50% to 70% stenosis manifest a decrease in maximal hyperemia.[4]

18-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 18)* In general, for purposes of diagnosis or initial risk stratification, stress nuclear MPI is performed with the patient off anti-ischemic medications[5] because these medications may limit the development of ischemia during the stress test. When feasible, the use of beta-blockers or long-acting calcium channel blockers should be discontinued for 48 hours before stress imaging, and long-acting nitrates should be discontinued for 12 hours before stress imaging.[5] In general, discontinuation of compounds containing caffeine (Excedrin Migraine) for 24 hours prior to the use of adenosine or dipyridamole and 12 hours prior to the use of regadenoson is recommended.[5,6]

18-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 18)* For patients who cannot exercise (mobility impairment, severe peripheral vascular disease), pharmacologic stress testing is the preferred approach to stress.[7] The preferred pharmacologic stress agents for SPECT-MPI are coronary vasodilators: adenosine, regadenoson, or dipyridamole. Because of the potential adverse effect of severe bronchospasm, dipyridamole is contraindicated for asthmatics. Adenosine is considered contraindicated for patients with second- or third-degree AV block, sick sinus syndrome, or bronchospasm. Regadenoson has the potential to reduce the high frequency of uncomfortable systemic adverse effects and the risk of bronchospasm in asthmatics that are associated with adenosine and dipyridamole. A large phase IV study (999 patients) has reported the safety of regadenoson in patients with stable chronic obstructive pulmonary disease or asthma, but appropriate resuscitative measures should be available in case bronchospasm occurs.[6,8] An alternative to vasodilator stress is inotropic stress with dobutamine. With the increased use of regadenoson, which has fewer contraindications, dobutamine stress nuclear MPI has markedly decreased in many nuclear laboratories. Dobutamine stress results in a lower-rate pressure product than exercise and a lower peak coronary blood flow with vasodilator stress.

Moreover, this patient has atrial fibrillation, and dobutamine may aggravate this arrhythmia.

18-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Although PET and MRI are considered superior for viability assessment, rest/redistribution 201Tl SPECT-MPI is the preferred SPECT approach for the assessment of myocardial viability.[9] Theoretically, the effectiveness of 201Tl SPECT-MPI for viability assessment could be improved by the administration of nitroglycerin prior to the rest injection. Importantly, 24-hour imaging may show additional redistribution compared to 4-hour imaging[10,11] because, in the setting of a critical coronary stenosis with reduced resting blood flow, the time to complete redistribution may be delayed. The stress SPECT-MPI study is not the optimal approach in this patient because of the unexpected perfusion defect at rest. Rest ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin can also be used to assess myocardial viability. However, they are not considered optimal because, unlike 201Tl, they reflect only myocardial perfusion and do not redistribute into the potassium pool. Furthermore, these agents underestimate viability in the presence of myocardial hibernation with resting hypoperfusion.

18-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Because of the very strong relationship between an acute MI and acute closure of a coronary artery, a normal rest MPI alone, without stress imaging, provides strong evidence of the absence of MI (option A). A 99% negative predictive value of rest SPECT-MPI alone for MI was reported in several studies beginning in the mid-1990s.[12] A prospective, randomized, controlled multicenter trial reported a reduction in hospitalizations when rest SPECT-MPI was incorporated into an ED evaluation strategy of patients presenting with suspected ACS (ERASE Trial) (option B).[13] When the radiopharmaceutical is injected after pain has subsided and the SPECT-MPI study is normal, stress SPECT-MPI studies are commonly used to further rule out an ACS because unstable angina might be associated with normal rest perfusion (Figure 18-2). This case illustrates this concept, that is, the value of stress testing when rest MPI is normal in the acute chest pain patient (option C). In fact, rest sestamibi (MIBI) demonstrated minimal (borderline) perfusion defect in the inferior wall, while stress imaging revealed evidence of severe and extensive ischemia in the inferior and inferolateral wall. Based on extensive literature documenting the safety of maximal exercise testing in low-risk ED with a normal ECG and normal serial enzymes (4 to 6 hours apart), a normal stress SPECT-MPI study was safe and associated with a very low cardiac event rate in several studies (options D and E).[14]

18-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Current guidelines support nuclear MPI in symptomatic patients with LBBB.[15] Vasodilator stress SPECT-MPI has been shown to be an excellent predictor of cardiac events in LBBB patients (option A).[16] Guidelines give a class I indication for the use of pharmacologic stress nuclear MPI in the patients with LBBB, regardless of the ability to exercise to an adequate workload (options A and B).[15] Nuclear MPI has a distinct advantage over the use of CMR imaging and CCTA for risk assessment of the CKD patient because there is no organ toxicity associated with the injection of the radionuclide tracers (options C and D). CMR with gadolinium contrast is contraindicated in these patients due to the risks of nephrogenic systemic fibrosis in renal failure patients. With CCTA, the nephrotoxicity of the iodinated contrast results in this study being contraindicated unless the patient is on dialysis. Even in the dialysis patient, the high CAC scores commonly found in the renal failure patient can reduce the diagnostic and prognostic value of the coronary CTA study.

18-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Patients may be categorized as unable to exercise if they are challenged with performing moderate household, yard, or recreational work.[17] In addition, patients with disabling comorbidities are also unable to exercise, and they include patients who are severely frail, markedly obese, with severe peripheral arterial disease, severe chronic obstructive pulmonary disease, or orthopedic limitations. These groups form a large proportion of patients who will be referred and have appropriate indications for nuclear MPI. In patients unable to exercise, guidelines support pharmacologic stress imaging as the initial test in symptomatic male and female patients with intermediate or high pretest likelihood of CAD.[5,18,19]

18-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 18)* The ACCF/AHA SIHD guideline assigned a class Ib level of evidence to exercise MPI for patients with an intermediate to high pretest risk who have an ECG for which the exercise response cannot be interpreted.[20] An exercise stress MPI in this same subset with an intermediate to high risk in the presence of an interpretable ECG was assigned a class IIa level of evidence. Exercise stress is not appropriate in the setting of ongoing chest pain, which may be the manifestation of a high-risk acute coronary syndrome.

18-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Coronary CTA is of value and generally preferred over SPECT-MPI in the ED setting. However, there are certain scenarios of chest pain in the ED in which SPECT-MPI would be preferred. These include patients with known dense coronary calcification (option A), often encountered in the elderly demographic, patients with prior stents causing artifacts within the stent lumen, and patients with contraindications to CCTA.[21-23] CCTA does expose the younger patient to radiation, although the dose with contemporary techniques is lower than that of SPECT-MPI. CCTA does require contrast administration, although this is iodinated contrast (not gadolinium-based contrast as is used for MRI).

18-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 18)* Based on the ACCF/AHA guideline for the management of heart failure, the clinical applications where imaging may play a role include:[24] (i) repeat measurement of LVEF in patients who have had a significant change in their clinical status, received treatment that may affect cardiac function, or are under consideration for device therapy (class I, level of evidence C); (ii) imaging to detect ischemia and viability in

patients with de novo heart failure, known CAD, and no angina, unless the patient is not eligible for revascularization (class IIa, level of evidence C); (iii) viability assessment prior to revascularization in select situations is reasonable in the heart failure patient with CAD (class IIa, level of evidence B); and (iv) radionuclide ventriculography for the assessment of LVEF and LV volumes when echocardiography is inadequate (class IIa, level of evidence C).

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CHAPTER 19

Positron Emission Tomography in Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

19-1. Although the assessment of coronary flow and coronary flow reserve (CFR) is based on absolute rather than relative measures of myocardial perfusion, these measures may still appear reduced in the absence of obstructive epicardial coronary artery disease. Which of the following factors may lower stress perfusion to erroneously low ischemic levels?

A. Caffeine
B. Beta-blockers
C. Inadequate vasodilator stress
D. Small vessel disease
E. All of the above

19-2. The radioligand ^{18}F-FDG is the most important and most widely used for the noninvasive study of the myocardium substrate's metabolism with PET. In which of the following cells does ^{18}F-FDG *not* trace glucose utilization?

A. Mechanical heart valves
B. Skeletal muscle cells
C. Brain cells
D. Tumor cells
E. Inflammatory cells

19-3. Adequate patient preparation during the 24 hours before a ^{18}F-FDG PET scan is essential for reliable results due to the myocardium's ability to shift its energy needs among several fuel substrates, including free fatty acids, glucose, and lactate. Which of the following parameters does *not* affect the myocardium's selection of fuel substrates?

A. Concentrations of the substrates in the blood
B. The availability of adequate oxygenated coronary blood flow
C. Prior carbohydrate or fatty food intake
D. Hormonal influences
E. Neurological innervations

19-4. A 71-year-old woman with a prior history of multivessel PCI and whose images are shown in Figure 19-1 was referred for PET because of recent abnormal ECG and a 6-month history of exertional chest pain and dyspnea. Which of the following statements regarding the rest and stress PET images is *false*?

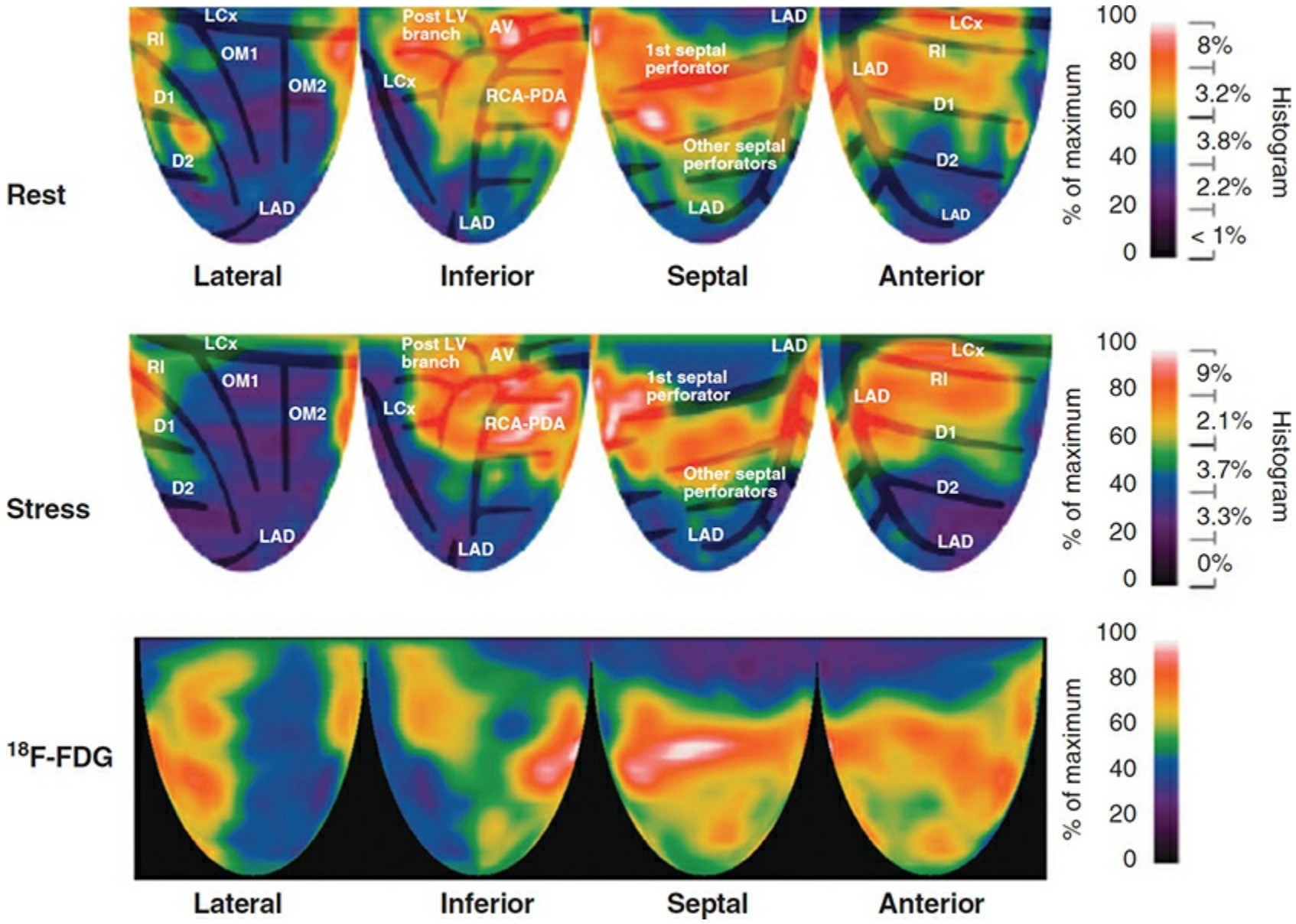

FIGURE 19-1 Relative rest and stress myocardial perfusion and ^{18}F-FDG images are color coded by the scale for relative myocardial uptake. For the rest stress relative perfusion images, the histogram on the right side of the color bar scale gives the relative activity as percent of maximum (100%) and percent of the left ventricle in each range of relative perfusion.

A. There is resting scar or hibernating myocardium in the distribution of the left circumflex
B. There is resting scar or hibernating myocardium in the distribution of the mid-LAD
C. There is a significant worsening of the defect after dipyridamole (stress)
D. There is a substantial mismatch with active FDG uptake in anterior, septal, and apical regions
E. The lateral LV has a predominantly transmural scar

19-5. An 82-year-old hypertensive and diabetic man with prior history of multiple MIs was referred for viability PET to determine his treatment options (revascularization vs. medical treatment). Resting perfusion images are illustrated in Figure 19-2. Which of the following statements regarding rest/viability PET images is *false*?

FIGURE 19-2 Relative rest perfusion and ^{18}F-FDG images are color coded by the scale for relative myocardial uptake. The

histogram on the right side of the color scale gives the percent of the left ventricle in each range of relative uptake.

A. There are apical perfusion defects
B. There are anterior perfusion defects
C. There are lateral perfusion defects
D. Most of the heart is no longer viable
E. None of the above

19-6. An 86-year-old woman was referred for PET scan after refusing a coronary angiography when she presented to the emergency department complaining of retrosternal chest pain after an emotionally stressful event. Initial ECG revealed ischemic-appearing ST changes with elevated biomarkers. Echocardiography showed apical akinesis and hyperdynamic function of the basal segments, with an EF of 28%. Which of the following statements about the stress and rest PET perfusion and ^{18}F-FDG findings of Takotsubo stress cardiomyopathy is *true*?

A. Stress perfusion activity is increased in the basal half of the LV
B. ^{18}F-FDG metabolic activity is decreased in the apical half of the LV
C. "Inverse flow metabolism mismatch" is a characteristic finding
D. B and C
E. A, B, and C

19-7. The assessment of myocardial viability is clinically used in patients with ischemic cardiomyopathy and severely impaired LV function in order to determine prognosis and guide therapeutic decision making. Which of the following clinical outcomes related to myocardial viability is *false*?

A. Revascularization of viable myocardium often leads to increases in LVEF
B. Revascularization of viable myocardium may lead to a reversal of LV remodeling
C. Revascularization of viable myocardium is associated with relief of heart failure symptoms
D. Postrevascularization improvements in physical activity are related to the amount of viable myocardium
E. Revascularization of nonviable myocardium never leads to functional or prognostic improvements in patient outcomes

19-8. A 67-year-old asymptomatic man whose images are shown in Figure 19-3 was referred for PET scan after an abnormal exercise stress test and coronary angiogram. The patient presented on the day of the examination after 16 hours of fasting. With regard to the PET perfusion and glucose metabolism images (Figure 19-3), which of the following statements is *false*?

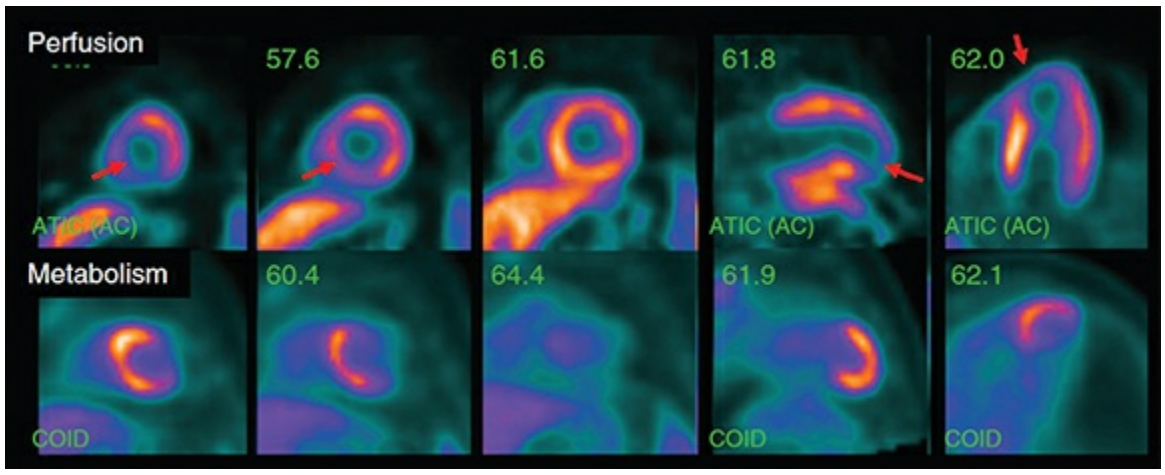

FIGURE 19-3 Positron emission tomography (PET) N-13 ammonia perfusion and glucose metabolism images.

A. Perfusion is severely reduced in the distal anterior wall
B. Perfusion is severely reduced in the apex
C. Perfusion is severely reduced in the mid lateral wall
D. ^{18}F-FDG activity is selectively increased in the region of the perfusion defect
E. ^{18}F-FDG uptake in normal myocardium is absent as a result of prolonged fasting.

19-9. A 37-year-old African-American woman whose images are shown in Figure 19-4 requested a second opinion and PET scan after series of nondiagnostic tests. She complained of a 2-month history of exertional dyspnea. Initial ECG showed a complete left bundle branch block. Echocardiography revealed a severely dilated left ventricle (LV) with an ejection fraction of 45%. Cardiac catheterization demonstrated dilatation of the LV, and the coronary arteries appeared normal. In which of the following conditions can the illustrated patterns of myocardial ^{18}F-FDG uptake occur?

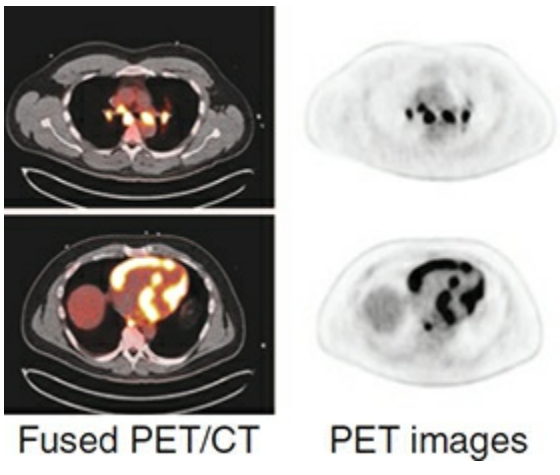

FIGURE 19-4 Axial PET-only and PET/computed tomography (CT) images of the mediastinum (upper row) and the left ventricle (lower row). Multiple foci of intensely increased ^{18}F-FDG uptake are seen in the mediastinum (consistent with mediastinal lymph node involvement) and throughout the left and right ventricular myocardium.

A. Cardiac sarcoid
B. Tuberculous myocarditis
C. Epstein-Barr virus myocarditis
D. Chagas disease
E. All of the above

19-10. The 42-year-old man whose images are shown in Figure 19-5 was referred for ^{18}F-FDG PET/CT imaging after an initial nondiagnostic transthoracic echocardiogram, which was followed by a negative transesophageal echocardiogram for vegetations. The patient had continuing fever, weight loss, and malaise. His cardiovascular examination revealed a grade 3/4 holosystolic murmur that had not been heard before. With regard to the use of ^{18}F-FDG PET/CT for the identification of infective endocarditis in this patient, which of the following statements is *false*?

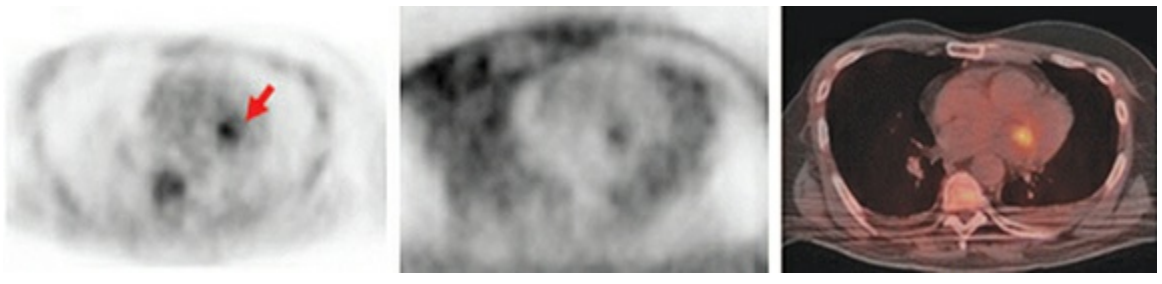

FIGURE 19-5 ^{18}F-FDG positron emission tomography (PET)/computed tomography (CT) imaging of a case of suspected infective endocarditis. The increased ^{18}F-FDG activity (arrow) corresponds to an infected mitral valve. (Reproduced with permission from Kouijzer IJ, Vos FJ, Janssen MJ, et al. The value of ^{18}F-FDG PET/CT in diagnosing infectious endocarditis, *Eur J Nucl Med Mol Imaging.* 2013 Jul;40(7):1102-1107.)

A. Vegetations can be visualized with ^{18}F-FDG PET/CT
B. Vegetations are seen as small foci of increased ^{18}F-FDG activity in the region of the mitral valve
C. ^{18}F-FDG PET/CT is highly sensitive to rule out native valve endocarditis
D. ^{18}F-FDG PET/CT may contribute to the detection of downstream septic emboli
E. None of the above

ANSWERS

19-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Caffeine, beta-blockers, inadequate vasodilator stress, and diffuse or small-vessel disease may lower stress perfusion in cc/min/g to apparently low ischemic levels; therefore, concurrently measuring rest flow and CFR provides integrated diagnostic information for correct clinical interpretation from the coronary flow capacity map.

19-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 19)* As a glucose analog, ^{18}F-FDG tracks the initial transport of glucose from blood into cells and its phosphorylation to glucose-6-phosphate as the initial metabolic step of transformation of exogenously derived glucose. Because phosphorylated ^{18}F-FDG cannot be metabolized further, it is metabolically trapped in the cell, and it accumulates in tissue in proportion to rates of exogenous glucose utilization. However, the radiotracer ^{18}F-FDG is not cell specific for myocardium. It also traces glucose utilization in different organs, such as skeletal muscle and brain, as well as in tumors and inflammatory processes. While ^{18}F-FDG traces glucose utilization around prosthetic heart valves in cases of perivalvular infection, there is no utilization to trace within inert materials such as mechanical valve discs. Therefore, ^{18}F-FDG is clinically useful for imaging regional myocardial

metabolism and for identifying inflammatory disease of the cardiovascular system

19-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 19)* The selection of fuel substrates depends on their concentrations in blood, prior carbohydrate or fatty food intake, availability of oxygenated coronary blood flow, and hormonal influences. Complicating factors include diabetes mellitus and elevated blood catecholamine concentrations, often present in heart failure patients. Neurological innervations do not play a direct role in myocardial fuel utilization.

19-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 19)* The rest and stress PET images showed a large, severe, lateral, apical, mid-anterior, and distal inferior resting scar or hibernating myocardium involving 60% to 70% of the left ventricle in the distribution of the left circumflex, mid-posterior descending, and mid-left anterior descending coronary arteries. After dipyridamole, the defect was minimally worse, indicating a fixed scar or viable, low-flow, hibernating myocardium. The viability ^{18}F-FDG images showed substantial mismatch with active FDG uptake in anterior, septal, and apical regions, indicating hibernating, viable, hypoperfused myocardium in mid to distal LAD and RCA distributions comprising approximately 30% of the LV. The lateral LV had a predominantly transmural scar comprising 25% of the LV with an additional 10% of the anterior, anterolateral wall, apex, and basal inferior wall being viable and hibernating in the distribution of a large first OM branch.

19-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Resting perfusion images showed large, severe, anterior, apical, lateral, and inferior perfusion defects involving 60% of the LV in the distribution of the mid LAD, mid LCX, and RCA coronary arteries. ^{18}F-FDG metabolic images showed myocardial uptake of ^{18}F-FDG, indicating viability of essentially the entire heart, with only a small distal inferior nontransmural scar comprising 3% of the LV taking up less ^{18}F-FDG.

19-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Transient apical ballooning, called Takotsubo (stress) cardiomyopathy, may mimic an acute coronary syndrome; it affects predominantly postmenopausal women and accounts for 1% to 2% of patients with troponin-positive acute coronary syndromes but with angiographically normal coronary vessels. It has been referred to as neurogenic myocardial stunning because it often follows a stressful event.[1] Wall motion is typically impaired in the apical portion of the LV, with concordantly reduced ^{18}F-FDG metabolic activity.[1,2] The typical finding of "inverse flow metabolism mismatch" refers to reduced apical ^{18}F-FDG metabolic activity in the presence of normal or near-normal apical perfusion.

19-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Patients with ischemic cardiomyopathy, severe LV dysfunction, and congestive heart failure symptoms will benefit most from the assessment of myocardial viability. Most studies have reported statistically significant postrevascularization increases in LVEF in patients with viability as compared to no or only minimal improvements in LVEF in patients without viable myocardium.[3] Revascularization of viable myocardium may lead to a reversal of LV remodeling[4] and relief of congestive heart failure symptoms.[5] Postrevascularization improvements in physical activity are related to the amount of viable myocardium with improved physical exercise during daily life prior to and 24 months after CABG.[6] It is important to emphasize that despite the presence of myocardial viability, even involving an adequate amount of the LV, revascularization may not always be followed by a functional improvement or reversed remodeling of the LV, and vice versa—revascularization may be associated with beneficial outcomes even in the absence of apparent viability.

19-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Perfusion is severely reduced in the distal anterior wall, the apex, and the distal inferior wall, suggestive of obstructive disease of the left anterior descending coronary artery. ^{18}F-FDG activity is selectively increased in the region of the perfusion defect, most likely consistent with myocardial viability; the perfusion metabolism mismatch corresponds in location to the distal left anterior descending coronary artery. ^{18}F-FDG uptake in normal myocardium is absent as a result of prolonged fasting. Among several approaches, prolonged fasting for 16 to 20 hours has been proven most effective in consistently suppressing ^{18}F-FDG uptake.[7-9] This is due to the shift of myocardium's substrate selection from glucose to free fatty acid, thereby reducing the accumulation of ^{18}F-FDG in normal myocardium.

19-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 19)* Multiple foci of intensely increased ^{18}F-FDG uptake are seen in the mediastinum (consistent with mediastinal lymph node involvement) and throughout the left and right ventricular myocardium (Figure 19-4), consistent with cardiac sarcoid associated with systemic sarcoid. This pattern of focally increased myocardial ^{18}F-FDG uptake is, however, not specific for cardiac sarcoid but also occurs in other types of granulomatous and nongranulomatous inflammatory processes of the myocardium as, for example, in tuberculous myocarditis,[10] Epstein-Barr virus myocarditis,[11] or Chagas disease.[12]

19-10. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 19)* There is now substantial evidence that ^{18}F-FDG PET/CT contributes to the identification of infective endocarditis, endovascular devices, and prosthetic vascular grafts, and, importantly, the detection of downstream septic emboli. Vegetations and abscesses of native and prosthetic valves can be visualized with ^{18}F-FDG PET/CT, though with a lower and clinically insufficient sensitivity (about 40%) and a specificity of about 70% to 100%.[13,14] They are typically seen as small foci of mildly to intensely increased ^{18}F-FDG activity in the region of the mitral or aortic valve (Fig. 19-5) and do not invariably correspond to findings on

echocardiography. In one investigation in 30 patients with definite prosthetic valve infection, for example, findings by echocardiography and ^{18}F-FDG PET/CT agreed in only half of the patients; in nearly half of the remaining patients, focally increased ^{18}F-FDG uptake was seen in the valve area without corresponding vegetations on echocardiography, possibly because of an early stage of disease when echocardiography may still be negative.[14] Conversely, the absence of abnormal ^{18}F-FDG uptake effectively ruled out the presence of prosthetic valve infection in that study, so the authors proposed to include PET/CT as a major criterion for the diagnosis of infective endocarditis.[14]

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CHAPTER 20

Cardiac Catheterization, Cardiac Angiography, and Coronary Blood Flow and Pressure Measurements

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

20-1. The radial artery approach is associated with reduced bleeding complications and increased patient satisfaction. Which of the following factors is not an additional reason to favor the right radial artery approach over the femoral artery approach?

A. Easy access
B. Direct cannulation of left internal mammary artery grafts in patients with prior coronary bypass
C. Most secure hemostasis in fully anticoagulated patients
D. Radial artery occlusion is generally well tolerated
E. Superficial location

20-2. A 68-year-old man with prior reactions to contrast media, history of type 2 diabetes, chronic kidney disease, and left ventricular systolic dysfunction presented to the emergency department with a 2-hour history of retrosternal chest pain. ECG on arrival showed ST-elevation in interior leads, and the patient was emergently taken to the cardiac catheterization laboratory for primary PCI. Which of the following radiographic contrast agents will be preferred in this case?

A. Iodixanol
B. Diatrizoate
C. Iothalamate
D. Metrizoate
E. Iopamidol

20-3. A 75-year-old woman with a prior history of uncontrolled type 2 diabetes and stage IV chronic kidney disease was admitted to the emergency department complaining of central chest pain and dyspnea. Initial ECG showed T-wave inversions in high lateral leads, and biomarkers were above the upper limit of normal. The patient was brought to the catheterization laboratory within 24 hours. Which of the following pharmacologic regimens has recently been demonstrated to perform better than volume loading with normal saline in reducing the risk for contrast-induced nephropathy (CIN)?

A. IV bolus of furosemide immediately before the procedure
B. Continuous IV furosemide infusion throughout the procedure
C. IV mannitol
D. Calcium channel blockers
E. None of the above

20-4. Intracoronary optical coherence tomography (OCT) is a catheter-based optical imaging modality that produces high-resolution cross-sectional images of the coronary wall. OCT has superior resolution as compared to intravascular ultrasound (IVUS) for all of the following features of the vulnerable plaque, *except*:

A. Plaque rupture
B. Thin-capped fibroatheroma
C. Macrophages within the fibrous caps
D. Plaque burden
E. Intracoronary thrombus

20-5. Myocardial blood flow has been assessed angiographically using the thrombolysis in myocardial infarction (TIMI) score for qualitative grading of coronary flow. Which of the following TIMI flow grades is *false*?

A. Flow equal to that in noninfarct arteries (TIMI-3)
B. Delayed or sluggish antegrade flow with complete filling of the distal coronary bed (TIMI-2)

C. Filling beyond the culprit lesion but faint antegrade flow with incomplete filling of the distal coronary bed (TIMI-1)
D. No flow beyond the occlusion (TIMI-0)
E. Flow faster than that in noninfarct arteries (TIMI-4)

20-6. Unlike fractional flow reserve (FFR), coronary flow reserve (CFR) is subject to variations in hemodynamics that may alter resting flow and limit maximal hyperemic flow. Which of the following clinical situations *cannot* affect CFR?

A. Tachycardia
B. Dyslipidemia
C. Diabetes
D. Age
E. Hypertension

20-7. An 85-year-old woman with a prior history of poorly controlled type 2 diabetes presented to the emergency department complaining of a 2-hour duration substernal chest pain and dyspnea. The initial ECG showed ST-elevation in the high lateral leads. The physical examination revealed a harsh, pansystolic murmur, loudest at the apex and radiating to the axilla. The patient was brought to the cardiac catheterization laboratory, and the left ventricular (LV) and left atrial (LA) pressure tracings are illustrated in Figure 20-1. In which of the following conditions may large *v* waves *not* be present?

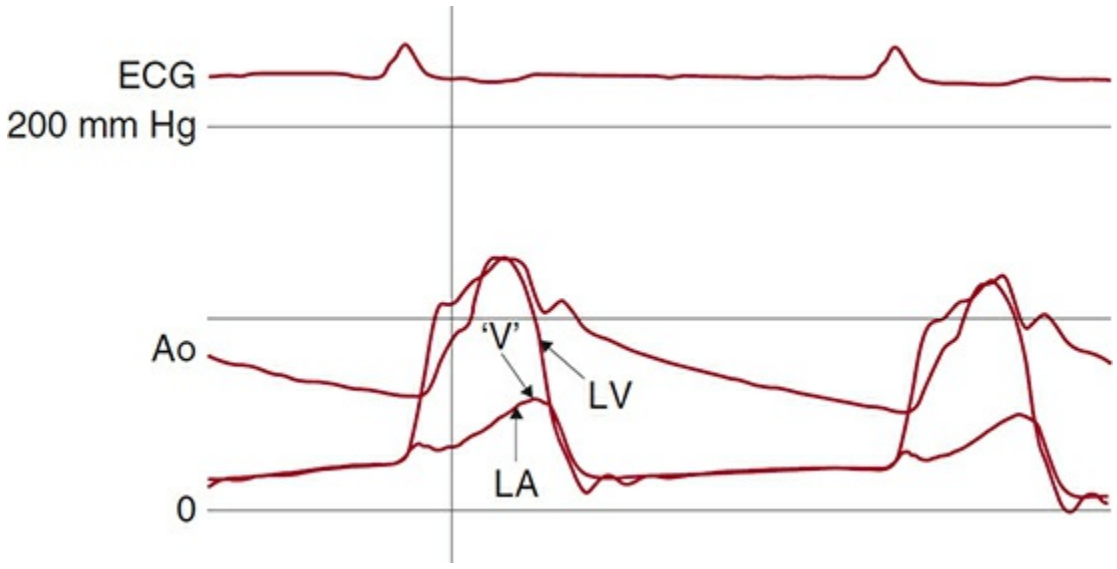

FIGURE 20-1 Left ventricular (LV) and left atrial (LA) pressures showing large V wave.

A. Mitral regurgitation
B. Postcardiac surgery
C. Infiltrative heart disease
D. Mitral stenosis
E. None of the above

20-8. Thermodilution and Fick techniques are the most commonly used methods to assess cardiac output in the cardiac catheterization laboratory. In which of the following clinical scenarios will the thermal dilution cardiac output be unreliable?

A. Severe tricuspid regurgitation
B. Severe pulmonary regurgitation
C. VSD with significant left-to-right shunt
D. Left ventricular heart failure with low output
E. All of the above

20-9. Valvular or vascular obstruction produces a pressure gradient across a stenosis or vascular conduit/chamber narrowing. Which of the following physiologic variables may *not* influence the pressure gradient?

A. Serial lesions
B. Shape of valve orifice
C. Length of valve orifice
D. Proximal chamber pressure
E. None of the above

20-10. In most patients, the pulmonary capillary wedge (PCW) is sufficient to assess LV filling pressure because it closely approximates LA pressure. In which of the following conditions may PCW pressure overestimate LA pressure?

A. Acute respiratory failure
B. Chronic obstructive lung disease with pulmonary hypertension
C. Pulmonary vein stenosis
D. LV failure with volume overload
E. All of the above

ANSWERS

20-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 20)* The radial approach is favored for several additional reasons: (1) The radial artery is easily accessible and is not located near significant veins or nerves; (2) the superficial artery location permits rapid and secure compression band hemostasis; (3) the radial artery access provides the most secure hemostasis in fully anticoagulated patients; (4) because of the collateral flow to the hand through the ulnar artery, the rare case of radial artery occlusion is generally well tolerated; and (5) patient comfort is enhanced by the ability to sit up and walk immediately after the procedure. However, the right radial approach is not directly amenable to cannulation of the left internal mammary artery graft for patients with prior coronary bypass.

20-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 20)* The advantages of the nonionic, low-osmolar agents include less hemodynamic loading, less patient discomfort, less depression of myocardial function and blood pressure, and fewer anaphylactoid reactions. Currently, nonionic, low-osmolar agents are routine for nearly all patients, and they are especially helpful in patients with poor LV function, renal disease, diabetes, or prior reactions to contrast media. Iodixanol is a nonionic, iso-osmolar dimer that is particularly well tolerated and used selectively in patients with peripheral arterial procedures and prior contrast reactions. Diatrizoate, iothalamate, and metrizoate (options B, C, and D) are all high-osmolar ionic contrast agents, whereas iopamidol (option E) is a low-osmolar nonionic contrast agent.

20-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 20)* Dehydrated patients or those with diabetes or renal insufficiency are at risk for CIN. Advanced precautions to limit CIN include hydration, minimizing contrast delivered, and maintenance of large-volume urine flow (> 200 mL/h). These patients should be hydrated intravenously the night before the procedure. After the contrast study, intravenous fluids should be liberally continued unless intravascular volume overload is a problem. Furosemide, mannitol, and calcium channel blockers are not helpful in reducing CIN. No pharmacologic regimen has been demonstrated to perform better than volume loading with normal saline (options A, B, C, and D).

20-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 20)* Compared to IVUS, OCT has superior resolution to evaluate certain features of the vulnerable plaque, such as plaque rupture, intracoronary thrombus, thin-capped fibroatheroma, and macrophages within the fibrous caps. For stent placement, OCT can visualize stent malapposition and tissue protrusion after stenting and neointimal hyperplasia at late follow-up. OCT may replace IVUS for certain applications, such as assessing stent deployment. However, compared to IVUS, OCT has inferior depth of penetration and is therefore less suited to assess total plaque burden.

20-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 20)* TIMI flow grades 0 to 3 have become a standard description of angiographic coronary blood flow in clinical trials. There is no TIMI flow grade 4. In acute myocardial infarction trials, TIMI grade 3 flows have been associated with improved clinical outcomes. The four grades of flow are described as follows:[1]

1. Flow equal to that in noninfarct arteries (TIMI-3)
2. Distal flow in the artery less than in noninfarct arteries (TIMI-2)
3. Filling beyond the culprit lesion but no antegrade flow (TIMI-1)
4. No flow beyond the total occlusion (TIMI-0)

20-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 20)* Tachycardia increases basal flow; therefore, CFR is reduced by 10% for every 15 heartbeats.[2] Increasing mean arterial pressure reduces maximal vasodilatation, thus reducing hyperemia with less alteration in basal flow. CFR may be reduced in patients with essential hypertension or aortic stenosis, myocardial ischemia, and diabetes. The variability in CFR in nonobstructed arteries may also be due to age.[3] Dyslipidemia has no direct physiological effect on CFR.

20-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 20)* The *v* wave on an LA or PCW pressure tracing usually is associated with significant mitral regurgitation (Fig. 20.1). However, large *v* waves are neither highly sensitive nor specific for mitral regurgitation. Large *v* waves also may be present with mitral stenosis with or without mitral regurgitation or any condition in which the LA volume (eg, VSD or LA pressure relationship [the stiffness or compliance] is increased [such as in rheumatic heart disease, postcardiac surgery, and infiltrative heart diseases]).

20-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 20)* If severe tricuspid or pulmonary regurgitation or significant left-to-right shunting is present, the indicator (temperature loss) is attenuated, and the downslope of the temperature curve is prolonged, so the thermal dilution cardiac output will be unreliable. In general, when one uses thermal dilution, a true directional change in cardiac output is reflected by an observed change of ±10%. Thermodilution is also inaccurate in patients with low cardiac output.

20-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 20)* The pressure gradient is influenced by physiologic variables such as rate of blood flow (eg, cardiac output, coronary blood flow); resistance to flow; proximal chamber pressure and compliance; and anatomic variables, such as shape and length of valve orifice, tortuosities of the vessels (for arterial stenosis), or multiple or serial lesions (for both cardiac valves and arterial stenosis).

20-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 20)* PCW pressure closely approximates LA pressure. PCW pressure overestimates LA pressure in patients with acute respiratory failure, chronic obstructive lung disease with pulmonary hypertension, pulmonary vein stenosis, or LV failure with volume overload.

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CHAPTER 21

Coronary Intravascular Imaging

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

21-1. The echogenicity and texture of different tissue components may exhibit comparable acoustic properties. Which of the following items may *not* appear as an echolucent intraluminal image?

A. Thrombus
B. Coronary calcification
C. Atheroma with a high lipid content
D. Retained contrast
E. Air bubble

21-2. Most mechanical limitations of IVUS imaging are specific to the construct of each system. Which of the following parameters is a common cause of nonuniform rotation distortion (NURD) artifacts?

A. Tortuosity
B. Small guide lumen size
C. Slack in the catheter shaft
D. Tightened hemostatic valve
E. All of the above

21-3. Studies comparing optical coherence tomography (OCT) with IVUS suggest that time domain (TD)-OCT is safe and can be performed with success rates at least comparable to those of IVUS. Which of the following adverse effects are *not* empirically associated with the OCT procedure?

A. Chest discomfort
B. Tachycardia
C. ST-T changes on electrocardiography (ECG)
D. Decompensated heart failure
E. All of the above

21-4. Some image artifacts are common to both OCT and IVUS. Which of the following artifacts is specific to the new generation of Fourier-domain (FD-OCT) systems?

A. Foldover artifact
B. Sew-up artifact
C. Multiple reflection artifact
D. Saturation artifact
E. Attenuation artifact

21-5. Near-infrared spectroscopy (NIRS) is a new imaging modality able to detect necrotic core invasively. All of the following limitations of NIRS have considerably reduced its application in the clinical arena, *except*:

A. Inability to quantify plaque burden
B. Inability to assess plaque vulnerability
C. Inability to visualize lumen and outer vessel wall
D. Inability to detect neovascularization
E. Inability to detect microcalcification

21-6. Understanding of the structure of a normal coronary artery is essential to identify its pathologic conditions. Which of the following statements about coronary artery wall is *false*?

A. Normal coronary artery wall appears as a three-layer structure on IVUS
B. A trilayered appearance by IVUS suggests the presence of intimal thickening
C. Visualization of the perivascular structures is common with IVUS
D. Visualization of the perivascular structures is not possible with OCT
E. Normal coronary artery wall appears as a three-layer structure on OCT

21-7. The presence, depth, and circumferential distribution of calcification are important factors for selecting the type of interventional device and estimating the risk of vessel dissection and perforation during PCI. Which of the following statements about the detection of calcification is *false*?

A. IVUS can detect the leading edge of calcium as well as determining its thickness
B. IVUS is superior to fluoroscopy at detecting coronary calcification
C. OCT can depict calcification within plaques as well as quantifying calcium burden
D. OCT is superior to IVUS at estimating calcium component and extent
E. OCT can detect superficial microcalcifications

21-8. Pathologic studies have suggested a relationship between positive vessel remodeling and plaque vulnerability. Which of the following parameters is *not* characteristic of vessels with positive remodeling?

A. Paucity of smooth muscle cells
B. Thinner media
C. Thicker cap
D. Larger lipid cores
E. Increased inflammatory marker concentrations

21-9. Several IVUS studies have been performed to define predictors of restenosis after balloon angioplasty. Which of the following processes is the most important mechanism of long-term failures of nonstented coronary interventions?

A. Negative remodeling
B. Positive remodeling
C. Neointima hyperplasia
D. Neointima thickening
E. None of the above

21-10. Several studies have explored the accuracy of intravascular imaging at detecting hemodynamic significant stenosis. Which of the following parameters may *not* affect the hemodynamic implications of a stenotic lesion?

A. The IVUS minimum luminal cross-sectional area (MLA)
B. Length of the stenosis
C. Physiology of the microvascular bed
D. None of the above
E. All of the above

ANSWERS

21-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 21)* The similar appearance of different materials represents an inherent limitation of all gray-scale IVUS systems. An echolucent intraluminal image, for instance, may represent thrombus, atheroma with a high lipid content, retained contrast, or an air bubble. Calcified structures are, conversely, very echobright.

21-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 21)* Common causes of NURD are tortuosity; severely stenotic segments; small guide lumen size; and guide catheters with sharp secondary curves, slack in the catheter shaft, or tightened hemostatic valve.

21-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 21)* The most frequent complication with TD-OCT using the occlusive OCT technique is transient chest discomfort, bradycardia or tachycardia, and ST-T changes on ECG, all of which tend to resolve immediately after the procedure.[1] Similar transient events were also seen during IVUS imaging procedures. Decompensated heart failure is not a reported complication of the OCT procedure.

21-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 21)* Foldover artifact is specific to the new generation of FD-OCT systems and is the consequence of the "phase wrapping" or "alias" along the Fourier transformation when structure signals are reflected beyond the field of view. This can occur at the site of bifurcations or in large vessels. Sew-up, multiple reflection, saturation, and attenuation artifacts are common to all intravascular imaging technologies.

21-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 21)* Extensive validation studies suggested that NIRS may be superior to IVUS in detecting lipid-rich plaques, but it has limited accuracy in characterizing their phenotype and detecting fibroatheroma (FA) and thin-cap fibroatheroma (TCFA).[2] Other significant limitations of NIRS that have considerably reduced its application in the clinical arena are its inability to quantify plaque burden, to visualize the lumen and outer vessel wall, and to assess plaque characteristics associated with increased vulnerability, such as plaque erosion, neovascularization, and microcalcification.

21-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 21)* A monolayer appearance is a common finding in normal coronary arteries, but a trilayered appearance by IVUS suggests the presence of intimal thickening.[3] The IVUS beam penetrates beyond the adventitial layer, allowing visualization of the perivascular structures, including the cardiac veins and the pericardium. In contrast, the normal coronary artery wall (< 1.5 mm thick) appears as a three-layer structure on OCT, but imaging beyond the adventitial layer is not possible.

21-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 21)* IVUS detects only the leading edge of calcium and cannot determine its thickness. Thus, calcification on IVUS is usually described based on its circumferential angle (arc), longitudinal length, and depth. IVUS has shown significantly higher sensitivity than fluoroscopy in the detection of coronary calcification.[4] OCT can depict calcification within plaques as well-delineated, low-backscattering heterogeneous regions. In addition to circumferential angulation, depth, and longitudinal length, OCT can quantify calcium burden. OCT allows more accurate estimation of the calcium component than IVUS, which significantly underestimates its extent.[5] Superficial microcalcifications can also be identified on OCT images as small calcific deposits separated from the lumen by a thin tissue layer.

21-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 21)* Vessels with positive remodeling showed increased inflammatory marker concentrations, larger lipid cores, a paucity of smooth muscle cells, and medial thinning.[6,7]

21-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 21)* One of the main contributions of intravascular imaging to this field was the realization that negative remodeling, not neointimal hyperplasia, was the most important mechanism of long-term failures of nonstented coronary interventions, namely restenosis. This was initially demonstrated in the peripheral vessels and later reported in the coronary circulation.[8] These studies revealed that more than 70% of lumen loss was attributable to the decrease in external elastic membrane (EEM) area; the neointima accounted for only 23% of the loss.

21-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 21)* The limited value of intravascular imaging in detecting flow-limiting lesions should be attributed to the fact that the hemodynamic implications of a stenosis depend not only on MLA but also on the length of the stenosis and the physiology of the microvascular bed, which cannot be assessed by imaging techniques.

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CHAPTER 22

Magnetic Resonance Imaging and Computed Tomography of the Vascular System

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

22-1. A rare, albeit serious, risk of contrast-enhanced magnetic resonance angiography (CE-MRA) is the association between gadolinium-based contrast agents and nephrogenic systemic fibrosis. In which of the following scenarios may the linear chelates of gadolinium be considered safe?

A. Chronic renal impairment with eGFR < 30 mL/m^2
B. Acute renal impairment
C. Perioperative liver transplantation
D. Neonates
E. Severe heart failure

22-2. Before the advent of CE-MRA, nonenhanced magnetic resonance time of flight (TOF) imaging acquisitions were used to image the carotid arteries, demonstrating good agreement with digital subtraction angiography (DSA). Which of the following statements about the limitations of TOF imaging is *false*?

A. It is sensitive to turbulent flow
B. It tends to understimate the severity of stenoses
C. It has long acquisition times
D. It increases the potential for motion artifacts
E. None of the above

22-3. A 67-year-old man with a prior history of uncontrolled hypertension presented to the emergency department complaining of an acute-onset excruciating and sharp retrosternal chest pain while watching a football game on television. Initial ECG revealed normal sinus rhythm with nonspecific ST changes in the lateral leads. Cardiac biomarkers were within normal limits, and a chest radiography showed moderate mediastinal widening. Which of the following imaging modalities has the highest sensitivity and specificity for detecting this condition?

A. MRI
B. Retrograde invasive aortography
C. Transthoracic echocardiography
D. Transesophageal echocardiography
E. They all have the same sensitivity and specificity for detecting this condition

22-4. Thoracic aortic aneurysms (TAAs) are typically discovered in asymptomatic patients, with symptoms occurring in the setting of either a complication of the disease (eg, a rupture or dissection) or when these complications are imminent. Which of the following statements about the recommendations for surgery is *false*?

A. Diameter of the ascending aorta > 50 mm is the threshold for degenerative aneurysm
B. Diameter of the ascending aorta > 50 mm is the threshold for aneurysm associated with bicuspid aortic valve
C. Diameter of the ascending aorta > 50 mm is the threshold for aneurysm associated with Marfan disease
D. Thresholds can be lowered in case of rapid expansion of TAA (> 5 mm/y)
E. Thresholds can be lowered in select connective tissue diseases (eg, Loeys-Dietz syndrome)

22-5. A 77-year-old man with a prior history of hypertension, type 2 diabetes, and a 150-pack-per-year tobacco smoking habit presented to his cardiologist for a health maintenance examination. He has been feeling generally well and has no particular complaints or concerns. On physical examination, there was an extensive palpable pulsatile abdominal mass. Which of the following represents the preferred imaging modality for preoperative evaluation of abdominal aortic aneurysms (AAA)

before open or endovascular surgery?

A. CTA
B. Ultrasonography
C. TOF sequences MRI
D. CE-MRA
E. Digital subtraction angiography

22-6. A 55-year-old man with a prior history of poorly controlled type 2 diabetes, hypertension, and a 100-pack-per-year tobacco smoking habit, presented to the emergency department with a 6-month history of leg pain upon exertion. He noticed that he had bilateral calf pain (worse on the left) with walking and that it tended to go away when he stopped walking. Which of the following is the best initial investigation for this patient's complaint?

A. Ultrasound imaging
B. Ankle brachial pressure index
C. CTA
D. TOF imaging
E. CE-MRA

22-7. The diagnostic accuracy of CTA for the evaluation of peripheral vessels compares well with MRA and invasive angiography. Which of the following clinical settings does *not* represent one of the main clinical indications of CTA for imaging the lower extremities?

A. Evaluation of arterial and aneurysmal disease
B. Evaluation of patency and integrity of bypass grafts
C. Traumatic arterial injury
D. Acute ischemia
E. None of the above

22-8. Plaques that are at high risk for rupture represent a potential imaging target for identifying vulnerable patients likely to develop unstable manifestations of their atherosclerotic disease. Which of the following features is *not* a key characteristic of vulnerable plaques?

A. A fibrous cap with thickness between 65 μm and 85 μm
B. Few smooth muscle cells
C. Heavy infiltrate of inflammatory cells
D. Microcalcification
E. Large necrotic core

22-9. A key advantage of MRI of the vasculature is the soft-tissue contrast it provides, allowing detailed examination of the composition of individual atherosclerotic plaques. Which of the following features of atherosclerotic plaques *cannot* be directly assessed by MRI?

A. Intraplaque hemorrhage
B. Calcification
C. Luminal thrombosis
D. Angiogenesis
E. Fibrous cap

22-10. ^{18}F-fluoride is a PET tracer increasingly being used to measure the activity of calcific processes in the vasculature. Which of the following statements about ^{18}F-fluoride is *false*?

A. Preferentially binds regions of vascular microcalcification activity
B. The sensitivity of ^{18}F-fluoride/PET is superior to CT for detecting vascular microcalcification
C. Can identify patients with increased metabolic activity in their coronary arteries
D. Can prospectively identify the individual lesions responsible for coronary events
E. None of the above

ANSWERS

22-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 22)* Different gadolinium contrast agents have been divided into low, medium, and high risk for causing nephrogenic systemic fibrosis[1] by the European Medicines Agency. High-risk agents include the linear chelates of gadolinium, and these are contraindicated in patients with an eGFR < 30

mL/m^2, acute renal impairment, and perioperative liver transplantation, as well as in neonates. Low-risk agents include newer cyclic preparations of gadolinium. These are considered safe in patients with an eGFR of more than 30 mL/m^2, and they can be used in patients with an eGFR below this threshold if the benefit of undergoing contrast MRI outweighs the risk. The volume of contrast agent used in this case should be minimized and repetition within 7 days avoided.[2] Gadolinium contrast agents are routinely used, and known to be safe, in the evaluation of patients with (often severe) forms of heart failure.

22-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 22)* TOF acquisitions are sensitive to turbulent flow, can overestimate stenoses, and have long acquisition times, increasing potential motion artifacts.[2] Although TOF MRA remains useful for patients with contraindications to MRI contrast, such as renal insufficiency, CE-MRA has become the technique of choice for imaging the carotid arteries.

22-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 22)* Of all the imaging techniques, MRI has the highest sensitivity and specificity for detecting aortic dissection (98%).[4] However, the use of MRI for the detection of aortic dissection is limited by its lack of availability in urgent situations and by the difficulty of monitoring and managing critically ill patients in the MRI scanner. Therefore, CTA is now considered the mainstay for the accurate and timely diagnosis of acute aortic syndromes.[5] Retrograde invasive aortography has an overall sensitivity of 88% and specificity of 94% for the detection of aortic dissection.[6,7] Transesophageal echocardiography, like CTA and MRA, has demonstrated high accuracy for the diagnosis of aortic dissection and is an alternative diagnostic technique.[8] Transthoracic echocardiography can, in most cases, visualize the aortic root and proximal ascending aorta, but it is not sufficiently comprehensive to rule out this diagnosis.

22-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 22)* When the diameter of the ascending aorta is > 55 mm for degenerative aneurysm (option A) and > 50 mm for aneurysm associated with bicuspid aortic valve (option B) or Marfan disease (option C), surgery is recommended.[9] These thresholds can be lowered in case of rapid expansion of TAA (> 5 mm/y) or in select connective tissue diseases (eg, Loeys–Dietz syndrome) (options D and E).

22-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 22)* Preoperative assessment of AAAs before open or endovascular repair should include determination of the maximum transverse diameter; the relation of the AAA to the renal arteries; the length, diameter, and angulation of the normal-caliber aorta below the renal arteries before the aneurysm (ie, the infrarenal neck); the presence of iliac or hypogastric aneurysms; and serious occlusive disease in the iliac or renal arteries. CTA represents the preferred imaging modality for preoperative evaluation of AAAs before open or endovascular surgery because it allows precise assessment of each of the aforementioned parameters. Ultrasonography remains the most cost-effective imaging technique for detection and follow-up of abdominal AAA expansion. MRI (TOF sequences, CE-MRA) represents an alternative to CTA for the preoperative evaluation of AAA, particularly in cases of renal insufficiency or advanced arterial calcification, although attention should be paid to the risk of developing nephrogenic systemic fibrosis following gadolinium administration in patients with the former. Digital subtraction angiography (DSA) has been largely replaced by the preceding imaging modalities.

22-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 22)* The most common initial investigation in patients presenting with suspected peripheral arterial disease is the ankle brachial pressure index. This is the ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. An ankle brachial pressure index of 0.90 or less should then prompt further investigation to confirm a diagnosis of peripheral artery disease. This is commonly performed with either CTA or MRA.[10]

22-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 22)* The main clinical indications of CTA for imaging the lower extremities include the evaluation of arterial and aneurysmal disease, patency and integrity of bypass grafts, traumatic arterial injury, and acute ischemia.[11]

22-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 22)* Plaques that are at high risk for rupture usually have several key characteristics, consisting of a thin fibrous cap (< 65 μm) with few smooth muscle cells and a heavy infiltrate of inflammatory cells, principally macrophages, microcalcification, and a large necrotic core accounting for more than half of the volume of the plaque. Each of these characteristics therefore represents a potential imaging target for identifying high-risk plaques.

22-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 22)* MRI is useful in detecting intraplaque hemorrhage (option A), a process believed to play a key role in triggering plaque rupture and growth.[12] T2*-weighted sequences have been used to accurately image intraplaque hemorrhage in carotid atherosclerotic plaques.[13,14] Plaque hemorrhage and luminal thrombosis can also be detected on T1-weighted imaging as high-intensity plaques (option C).[15,16] Late gadolinium enhancement detects areas of interstitial edema, angiogenesis, and fibrosis (option D).[17] Late gadolinium enhancement can also improve the visualization of the atherosclerotic fibrous cap, allowing estimation of the carotid cap thickness and the size of its necrotic core (option E).[18] Given that calcification is hypointense on the various MRI sequences, plaque calcification is better assessed by CT and other modalities (option B).

22-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 22)* ^{18}F-fluoride[19-20] preferentially binds regions of vascular

microcalcification activity.[21] These are beyond the resolution of CT, a technique that instead detects macroscopic calcium deposits. ^{18}F-fluoride can identify patients with increased metabolic activity in their coronary arteries, and it retrospectively appears to identify the individual lesions responsible for coronary events.[22]

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SECTION 4

Systemic Arterial Hypertension

CHAPTER 23

Epidemiology of Hypertension

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

23-1. A 48-year-old man presents in follow-up to your outpatient clinic. He has no comorbidities apart from right knee osteoarthritis and obesity. His blood pressure on his initial visit with you was 136/86 mm Hg. After losing 5 lb, today's blood pressure is 132/80 mm Hg. This patient's blood pressure can be labeled:

A. White coat hypertension
B. Benign hypertension
C. Isolated systolic hypertension
D. Prehypertension
E. Pseudohypertension

23-2. Which of the following statements about prehypertension is *false*?

A. The lifetime risk of hypertension approaches 50%, warranting the importance of recognizing the concept of prehypertension to promote lifestyle changes to prevent the onset of hypertension
B. In persons without cardiovascular disease or cancer, the prevalence of prehypertension is 36%, and it is higher in men than in women
C. Prehypertension is associated with abnormalities of cardiac structure and function
D. Approximately 15% of BP-related deaths from coronary heart disease occur in individuals with BP in the prehypertensive range
E. Persons with prehypertension have a 43% higher risk of incident coronary heart disease than those with optimal blood pressure (< 120/80 mm Hg)

23-3. A 56-year-old woman is referred to you for workup of glaucoma. Despite her blood pressure being normal in your office, her home readings have all been above 135/85 mm Hg. Regarding this particular type of hypertension, which of the following is *true*?

A. It is present in approximately 5% of patients not receiving antihypertensive treatment
B. There is a twofold greater risk of future cardiovascular events in those with this type of hypertension as compared to normotensive persons
C. Home BP monitoring is the standard for diagnosing this type of hypertension
D. It is more common in younger persons
E. Persons with prehypertension are less likely to have this type of hypertension

23-4. A 65-year-old man is referred to you from his family physician for the management of hypertension. On history, he admits to snoring when sleeping and describes daytime fatigue. On exam, BP in both arms is 164/98, HR 86 O^2 sat 96% on RA. Normal heart sounds are present, and lungs are clear to auscultation. Which of the following statements is *false*?

A. The most common curable form of hypertension is sleep apnea
B. Treatment with a CPAP mask is most likely indicated
C. Both sleep apnea and hypertension are closely linked to obesity
D. Approximately 60% of sleep apnea patients are hypertensive
E. Approximately 25% of hypertensive patients have sleep apnea

23-5. There is a fundamental difference between the genesis of hypertension in younger and older patients. Which of the following does *not* represent a true difference?

A. In general, the systolic and diastolic BPs are increased in younger patients, whereas in people aged 60 years and older, the diastolic BP starts to fall, but there is a marked increase in systolic BP
B. Younger patients will have an increased peripheral resistance with a normal cardiac output, whereas older patients will

have a selective increase of systolic BP as a result of increased arterial stiffness

C. In younger patients, the increased peripheral resistance is a result of active vasoconstriction that is mediated hormonally, particularly by the sympathetic nervous system and the renin-angiotensin system
D. The benefits of treatment in older patients with systolic pressures below 160 mm Hg remain unproven
E. There is some evidence for BP treatment of the very old (age 85 years or older) to improve mortality

23-6. You are going to counsel your 55-year-old female patient on her risk factors for hypertension. Which of the following statements is *false*?

A. The diastolic pressure will typically increase up to the age of 50, will plateau, and then will decrease throughout the remainder of the life span
B. Increasing body mass index correlates with an increased risk of hypertension
C. The incidence of hypertension is increased in those who smoke 15 or more cigarettes per day
D. There is a strong positive relation between sodium intake and blood pressure
E. Mexican Americans have prevalences that are similar to that of African Americans

23-7. The principal complications of hypertension include all of the following *except*:

A. Left ventricular hypertrophy
B. Peripheral arterial disease
C. Hypothyroidism
D. Stroke
E. Heart failure

23-8. A 58-year-old woman with a history of untreated hypertension presents to your office to discuss the results of her cardiac echocardiogram. Which of the following would be the least likely to be found on her echocardiogram report?

A. Diastolic dysfunction
B. Tricuspid valve regurgitation
C. Increased left atrial size
D. Systolic dysfunction
E. Left ventricular hypertrophy

23-9. Which of the following statements regarding stroke and hypertension is *incorrect*?

A. The linear relationship between stroke and hypertension is stronger for diastolic than for systolic pressure
B. BP typically rises acutely after a stroke, and it is postulated that this helps to maintain cerebral perfusion in the infarct's *penumbra* zone
C. Of all the risk factors for stroke, hypertension has the highest relative risk
D. Hypertension indirectly raises the risk of stroke through its role in atrial fibrillation and left atrial enlargement
E. Treatment of hypertension reduces stroke rates by approximately 35% to 45%

23-10. Your 65-year-old female patient presents to the office to discuss the results of her blood work. You have been treating her for hypertension over the last 10 years. Her creatinine has risen slightly, and you are concerned. Which of the following statements is *true*?

A. There is a twofold greater risk for end-stage renal disease with a systolic BP of > 140 mm Hg compared to a systolic BP of < 117 mm Hg
B. Chronic kidney disease causes remodeling of the arteries and increased stiffness
C. Hypertensive patients with mildly impaired renal function (estimated GFR < 60 mL/min) compared to normal renal function have an equivalent prevalence of target organ damage
D. Diastolic BP is a stronger risk factor for renal death than systolic BP
E. In a patient with chronic kidney disease, it is obvious whether the hypertension or the kidney disease came first

ANSWERS

23-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) 7 classification for hypertension has defined normal BP as < 120 and < 80 mm Hg. What JNC-6 previously labeled as normal (120–129 mm Hg systolic BP or 80–84 mm Hg diastolic BP) and high normal (130–139 mm Hg systolic BP or 85–89 mm Hg diastolic BP) are now combined into a single group called *prehypertension* (option D), to increase the awareness of people with an intermediate level of risk that they may progress to definite hypertension. *White coat hypertension* (or *isolated office hypertension)* (option A) is diagnosed in patients not on any BP-lowering medications when the BP is elevated only persistently in the presence of a

health care worker, particularly a physician. *Benign* hypertension, which alluded to less severe forms of hypertension, is a misnomer and is no longer used (option B). When the average systolic BP is at least 140 mm Hg or more and diastolic BP is < 90 mm Hg, the patient is classified as isolated systolic hypertensive (option C). The term *pseudohypertension* (option E) refers to a falsely elevated diastolic BP when in fact it is low. This condition represents wide pulse pressure isolated systolic hypertension in the elderly and often occurs with diabetes and diabetic kidney disease; it is associated with extensive calcification of many large arteries, including the brachial and elastic aorta.

23-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. The lifetime risk of hypertension approaches 90%[1] (not 50%), which emphasizes the need to recognize prehypertension to help motivate physicians and patients alike to promote lifestyle modifications that will prevent or delay the transition to clinical hypertension. Data from the National Health and Nutrition Examination Survey (NHANES) 1999–2006 in persons without cardiovascular disease (CVD) or cancer shows a prevalence of prehypertension of 36.3%, higher in men than in women, and associated with adverse cardiometabolic risk factors[2] (option B). Prehypertension has recently been shown to be associated with abnormalities of cardiac structure and function, specifically increased left ventricular remodeling and impaired diastolic function[3] (option C). It is estimated that about 15% of BP–related deaths from coronary heart disease (CHD) occur in persons with BP in the prehypertensive range[4] (option D). A recent meta-analysis showed that, compared with optimal blood pressure (< 120/80 mm Hg), those with prehypertension had a 43% higher risk of incident CHD (hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.26–1.63) a risk that was higher in Western subjects (relative risk [RR], 1.70; 95% CI, 1.49–1.94) than in Asian subjects (RR, 1.25; 95% CI, 1.12–1.38), with 24.1% of CHD attributable to prehypertension in Western subjects versus 8.4% in Asian subjects[5] (option E).

23-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. The question refers to a patient with a diagnosis of *masked hypertension*, which is defined as a normal office BP (< 140/90 mm Hg) together with an elevated daytime BP (≥ 135/85 mm Hg). The Dallas Heart Study also showed a twofold greater risk of future cardiovascular events in those with masked hypertension compared to those who were normotensive.[6] Option A is false: masked hypertension is present in approximately 10% to 40% of patients not receiving antihypertensive treatment. Option C is false: Twenty-four-hour ambulatory BP monitoring is the standard for diagnosing masked hypertension; home BP monitoring can also be used, but it is not the standard. Masked hypertension is more common in older persons; those with mental stress; smokers; and those with metabolic syndrome, diabetes, chronic kidney disease, and obstructive sleep apnea (option D). Persons with prehypertension are *more* likely to have masked hypertension and can even develop target organ damage before transitioning to established sustained hypertension (option E).

23-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. The most common curable form of hypertension is renal artery stenosis (not sleep apnea). Sleep apnea is emerging as one of the major causes of hypertension that is of epidemiologic significance. Support for a causal association between sleep-disordered breathing and hypertension includes physiological mechanisms involving vascular dysfunction secondary to altered sympathovagal balance and insulin resistance (option B). Both sleep apnea and hypertension are common, and unsurprisingly there are many people with both conditions. Furthermore, both are closely linked to obesity (particularly central obesity, as seen in the metabolic syndrome), so there is a cluster of related syndromes: hypertension, sleep apnea, diabetes, and the metabolic syndrome (option C). Option D: Approximately 60% of sleep apnea patients are hypertensive[7], and, conversely, approximately 25% of hypertensive patients have sleep apnea[8,9] (option E).

23-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. There is evidence that in the very old (age 85 years or older), mortality may be *higher* in those with the lowest blood pressures.[10] The benefit or harm of treating this patient population is currently being evaluated. In younger patients, whatever the underlying etiology of the hypertension (with a few exceptions), both systolic and diastolic BPs are raised, whereas in people aged 60 years and older, the diastolic BP starts to fall, but there is a marked increase of systolic BP (option A). The underlying hemodynamics are also different: in younger patients, the characteristic changes are an increased peripheral resistance with a normal cardiac output, whereas in older patients, the reason for the selective increase of systolic BP is increased arterial stiffness[11] (option B). In younger patients, the increased peripheral resistance is a result of active vasoconstriction that is mediated hormonally, particularly by the sympathetic nervous system and the renin-angiotensin system. In older patients with systolic hypertension, hormonal mediation is less important, and the changes are mostly mechanical (eg, loss of elastin fibers in the media of the arterial wall[11] (option C). In younger patients, it is clearly established that starting drug treatment when the pressure exceeds 140/90 mm Hg is beneficial. This may also be true in older patients, but the clinical trials that have investigated the benefits of treatment have almost all used an initial systolic BP of 160 mm Hg or greater as an entry criterion and have not lowered the pressure to below 140 or 150 mm Hg[12] (option D).

23-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 23*). African Americans have among the highest prevalences of hypertension compared to other major ethnic groups, and Mexican Americans have prevalences that are similar to that of whites. Age is the factor most strongly associated with hypertension. Systolic BP rises monotonically with age, whereas diastolic BP increases to about age 50, plateaus, and then decreases throughout the remainder of the life span (option A). More than 42% of those with a body mass index of 30 kg/m^2 or greater have hypertension, compared to 28% in those who are overweight (body mass index 25 to less than 30 kg/m^2)[13,14] (option B). Cigarette smoking has an acute effect on increasing blood pressure, primarily through stimulation of the sympathetic nervous system, with adverse effects on arterial stiffness and wave reflection (option C). Dietary sodium is implicated by many genetic,

epidemiological, migrational, and intervention studies to contribute to increasing BP in the population, and higher salt intake is likely to contribute to coronary vascular disease mainly through its effects on BP but also independently by increasing arterial stiffness and albuminuria[15] (option D). The INTERSALT study involved 10,079 persons and found a strong positive relation between sodium intake and BP, with an increase of 6 g/d in salt intake estimated to elevate systolic BP 9 mm Hg over 30 years.[16]

23-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 23)*. The principal complications of hypertension include coronary heart disease, left ventricular hypertrophy (option A), peripheral arterial disease (option B), stroke (option D), heart failure (option E), and chronic kidney disease. The 36-year follow-up data from the Framingham Heart Study show that while the relative impact of hypertension is greatest for stroke and heart failure (RRs, 2.6–4.0), because the overall incidence of CHD is greater than that for stroke or heart failure, the absolute impact of hypertension on CHD is greatest, even though the RR is lower (2.0–2.2).[17]

23-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 23)* There is no direct association between tricuspid regurgitation and systemic hypertension (option A). Approximately half of the patients who present with classic signs and symptoms of heart failure appear to have a normal ejection fraction of more than 50% on echocardiography, termed "diastolic dysfunction," diastolic heart failure," or "heart failure with preserved ejection fraction." Diastolic heart failure is thought to be responsible for as many as 74% of cases of heart failure in hypertensive patients.[18] Left ventricular hypertrophy (option E) and systolic dysfunction and heart failure (option D) are known complications of hypertension. Increased left atrial size (option C) associated with left ventricular hypertrophy can result with systemic hypertension.

23-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 23)* As with coronary events, there is a strong log-linear relationship between both systolic and diastolic pressure and stroke, although the relationship is steeper for strokes than for CHD events and much stronger for systolic than diastolic pressure.[19] BP typically rises acutely after a stroke, and it is postulated that this helps to maintain cerebral perfusion in the infarct's *penumbra* zone (option B).[20] This forms the rationale for avoiding excessive reduction of BP immediately after a stroke. Of all the risk factors for stroke, hypertension has the highest relative risk (4.0 at 40 to 50 years, falling to 2.0 at ages 70 to 80 years), and the highest population attributable risk (40% at ages 40 to 50 years and 30% at ages 70 to 80 years) (option C). Hypertension also indirectly raises the risk of stroke through its role as an important risk factor for atrial fibrillation and left atrial enlargement, which both relate directly to stroke risk (option D). Treatment of hypertension reduces stroke rates by 35% to 44%; this has been shown in both younger patients with systolic and diastolic hypertension and in older patients with isolated systolic hypertension (option E).

23-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 23)* There are two main effects of CKD on the arteries: (1) increased prevalence of atherosclerosis and (2) remodeling of the arteries and increased stiffness, which has been related to increased mortality. The Multiple Risk Factor Intervention Trial showed systolic BP of > 140 mm Hg to be associated with a five- to sixfold (not twofold) greater risk for end-stage renal disease (ESRD) compared to systolic BP of less than 117 mm Hg (option A). Hypertensive patients with mildly impaired renal function (estimated GFR < 60 mL/min) have an increased prevalence of target organ damage, such as left ventricular hypertrophy, increased carotid intima-media thickness, and microalbuminuria (option C). In a large pooled cohort study of more than 500,000 individuals from the Asia-Pacific region followed for a median of 6.8 years, systolic BP was the strongest risk factor for renal death, with each standard deviation increase in systolic BP (19 mm Hg) associated with a more than 80% higher risk (HR, 1.84; 95% CI, 1.60–2.12)[21] (option D). Although chronic kidney disease is certainly a major cause of hypertension, it is often difficult to decide whether the hypertension or the kidney disease came first because a vicious cycle can develop where one condition exacerbates the other (option E).

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CHAPTER 24

Pathophysiology of Hypertension

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

24-1. A 52-year-old man presents to your office for prevention of cardiovascular disease. His examination is notable for a blood pressure (BP) of 153/98 mm Hg. He wants to know about factors that would predispose him to hypertension. Which of the following is *not* associated with hypertension?

A. Excess sodium intake
B. Excess potassium intake
C. Obesity
D. Sedentary lifestyle
E. A and D

24-2. A 23-year-old man is involved in a car accident and is bleeding into his abdomen. Which of the following systems *do not* regulate blood pressure (BP) acutely?

A. Arterial baroreceptors
B. Chemoreceptors
C. Central nervous system (CNS)
D. Renin-angiotensin-aldosterone system (RAAS)
E. Increase in vasodilation

24-3. Which of the following alters pressure-natriuresis in chronic hypertension?

A. Increased tubular resorption
B. Decreased antinatriuretic hormones
C. Decreased activity of the sympathetic nervous system (SNS)
D. A and C
E. None of the above

24-4. Which of the following is *not true* of the two-kidney, one-clip Goldblatt model of hypertension?

A. The clipped kidney is at greater risk for nephron loss than the untouched kidney
B. The clipped kidney produces more renin than the untouched kidney
C. Blood flow through the untouched kidney may be increased compared to the flow before clipping of the contralateral kidney
D. Removal of clipping will restore blood pressure to normal levels, even after the untouched kidney becomes dysfunctional
E. None of the above

24-5. Which of the following are *true* regarding salt-sensitive hypertension?

A. Loss of functional nephrons contributes to salt-sensitive hypertension
B. High levels of Ang II or mineralocorticoids contribute to salt-sensitive hypertension by increasing renal tubular resorption
C. A and B
D. Increased sensitivity of the RAAS is associated with salt-sensitive hypertension
E. None of the above

24-6. A 45-year-old air traffic controller presents to your office for evaluation of hypertension. Which of the following is *not true* about how the SNS contributes to hypertension?

A. Activation of the renal sympathetic nerves causes increases in renin secretion and sodium resorption

B. Radiofrequency renal denervation is an effective way to treat refractory hypertension
C. Epidemiologic studies have suggested a relationship between chronic stress and hypertension
D. Obesity results in increased renal sympathetic activity
E. Renal sympathetic activity is regulated by various regions of the brain

24-7. A 58-year-old man with hypertension presents to your office to establish care. His blood pressure is well controlled with lisinopril. Which of the following is *true* about renin-angiotensin-aldosterone system (RAAS) blockade and hypertension?

A. Blood pressure is very salt-sensitive in the setting of RAAS blockade
B. Angiotensin II (Ang II) elevation promotes sodium and water retention
C. ACE inhibitors can reduce GFR by inhibition of the constrictor effect of Ang II on efferent arterioles
D. RAAS blockade can prevent glomerular injury when the nephrons are hyperfiltering
E. All of the above are true

24-8. A 55-year-old man is being treated with bevacizumab for his lung cancer. He is seeing you for management of his hypertension. Which of the following is *not true* about hypertension associated with VEGF inhibitors?

A. VEGF-inhibitor-induced hypertension is likely to result from decreased NO
B. VEGF inhibition is likely to result from increased endothelin-1
C. VEGF-induced hypertension is solely to be mediated by its effects on the vasculature and is less likely to involve a direct effect on the kidney
D. All of the above are false
E. All of the above are true

24-9. A 53-year-old woman presents with hypertension. Her serum laboratory tests are notable for hypokalemia and metabolic alkalosis. Examination is notable for the absence of acne, adiposity, or hair loss. Which is the next best diagnostic test?

A. Dexamethasone suppression test
B. Plasma renin and aldosterone
C. Serum metanephrines
D. Genetic testing
E. None of the above

24-10. A 35-year-old obese woman presents to you for evaluation of hypertension. She wants to know whether her hypertension would resolve if she were to lose weight. Which of the following is *true* about obesity and hypertension?

A. Central adiposity is more strongly associated with hypertension than subcutaneous fat
B. Obesity results in increased activity of the SNS
C. Obesity results in activation of the RAAS
D. Obesity results in physical compression of the kidneys
E. All of the above are true

ANSWERS

24-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 24)* Although primary hypertension is heterogeneous, some of the main causes of high BP are known. For example, overweight and obesity may account for 65% to 75% of the risk for primary hypertension (option C). Sedentary lifestyle, excess intake of alcohol or salt, and low potassium intake are also known to increase BP in some patients (options A, B, D, and E).[1]

24-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 24)* With rapid blood loss, three important neural control systems begin to function powerfully within seconds: (1) the arterial baroreceptors, which detect changes in BP and send appropriate autonomic reflex signals back to the heart and blood vessels to return the BP toward normal (option A); (2) the chemoreceptors, which detect changes in oxygen or carbon dioxide in the blood and initiate autonomic feedback responses that influence BP (option B); and (3) the central nervous system (CNS) (option C), which responds within a few seconds to ischemia of the vasomotor centers in the medulla, especially when BP falls below about 50 mm Hg. Within a few minutes or hours after a BP disturbance, additional controls react, including (1) a shift of fluid from the interstitial spaces into the blood in response to decreased BP (or a shift of fluid out of the blood into the interstitial spaces in response to increased BP); (2) the RAAS, which is activated when BP falls too low and suppressed when BP increases above normal (option D); and (3) multiple vasodilator systems that are suppressed when BP decreases and stimulated when BP increases above normal (option E).

24-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 24)* In all types of human or experimental hypertension studied thus far, there is a shift of pressure natriuresis that appears to sustain the hypertension. In some cases, abnormal

pressure natriuresis is caused by intrarenal disturbances that alter renal hemodynamics or increased tubular reabsorption (option A). In other cases, altered kidney function is caused by extrarenal disturbances, such as increased SNS activity or excessive formation of antinatriuretic hormones that reduce the kidney's ability to excrete sodium and water and eventually increase BP (options B and C). Consequently, effective treatment of patients with hypertension requires interventions that reset pressure natriuresis toward normal BP either by directly increasing renal excretory capability (eg, with diuretics), or by reducing antinatriuretic influences (eg, with RAAS blockers) on the kidneys.

24-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 24)* In the two-kidney, one-clip Goldblatt model of hypertension, the clipped kidney has reduced blood flow, while the untouched kidney has normal or increased blood flow (option C). This differential in blood flow results in high levels of renin being made by the clipped kidney but almost no renin from the untouched kidney (option B).[1] Over time, the untouched kidney will develop injury from the increased blood flow, leading to nephron loss (option A). Once damage has occurred to the untouched kidney, reversal of clipping will no longer be able to completely reverse hypertension (option D).

24-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 24)* After the loss of entire nephrons, the surviving nephrons must excrete greater amounts of sodium and water to maintain balance. This is achieved by increasing GFR and decreasing reabsorption in the remaining nephrons, resulting in increased sodium chloride delivery to the macula densa and suppression of renin release (option A). This, in turn, impairs the kidney's ability to further decrease renin secretion during high sodium intake, and BP becomes salt sensitive. Factors that increase renal tubular sodium reabsorption, such as excessive levels of mineralocorticoids or Ang II, can also cause hypertension (option B). Reduced sensitivity of the RAAS contributes to salt-sensitive hypertension (option D).

24-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 24)* It is widely believed that chronic stress may lead to long-term increases in blood pressure. Support for this concept comes largely from a few epidemiologic studies showing that air traffic controllers, lower socioeconomic groups, and other groups who are believed to lead more stressful lives also have increased prevalence of hypertension (option C).[2] Even mild increases in renal sympathetic activity stimulate renin secretion and sodium reabsorption in multiple segments of the nephron, including the proximal tubule, the loop of Henle, and distal segments (option A). Obese persons have elevated SNS activity in various tissues, including the kidneys and skeletal muscle, as assessed by microneurography, tissue catecholamine spillover, and other methods (option D). The preganglionic neurons that synapse with the renal sympathetic postganglionic fibers are located in the lower thoracic and upper lumbar segments of the spinal cord and receive multiple inputs from various regions of the brain, including the brainstem, forebrain, and cerebral cortex (option E). Whether renal denervation will prove to be an effective therapy for patients who are resistant to the usual pharmacological treatments remains to be determined (option B).

24-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 24)* Ang II causes salt and water retention by increasing renal sodium reabsorption through the stimulation of aldosterone secretion, by direct effects on epithelial transport, and by hemodynamic effects (option B). Blockade of the RAAS, with Ang II–receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors, increases renal excretory capability so that sodium balance can be maintained at reduced BP. However, blockade of the RAAS also makes BP salt sensitive (option A). The impairment of GFR after RAAS blockade is caused, in part, by inhibition of the constrictor effects of Ang II on efferent arterioles as well as reduced BP (option C). RAAS blockade is often beneficial when nephrons are hyperfiltering, especially if Ang II is not appropriately suppressed (option D). For example, in diabetes mellitus and certain forms of hypertension associated with glomerulosclerosis and nephron loss, Ang II blockade decreases BP, efferent arteriolar resistance, and glomerular hydrostatic pressure, and it attenuates glomerular hyperfiltration.[3]

24-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 24)* VEGF and VEGF receptors are highly expressed in the kidney. VEGF is expressed in glomerular podocytes, and VEGF receptors are present on endothelial, mesangial, and peritubular capillary cells. Signaling between endothelial cells and podocytes is thought to be important for maintenance of the filtration function of the glomerulus, and inhibitors of VEGF signaling have been shown to alter glomerular structure and function (option C). Because the endothelium is a major target for VEGF actions, it is likely that decreases in the production of endothelium-derived relaxing factors such as NO and PGs or enhanced production of vasoconstricting factors such as thromboxane and ET-1 play a role in the hypertensive response to drugs that block the VEGF pathway (options A and B).[4]

24-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 24)* This patient is most likely to have Conn syndrome or primary aldosteronism. Conn syndrome is manifest by expansion of extracellular fluid volume, hypertension, suppression of renin secretion, hypokalemia, and metabolic alkalosis. Therefore, testing of renin and aldosterone levels can be useful to establish a diagnosis (option B). A dexamethasone suppression test can be useful to differentiate ACTH-dependent and ACTH-independent Cushing syndrome (option A). Serum metanephrines can be useful for diagnosing pheochromocytoma (option C). Genetic testing is unlikely to be of high yield at this stage of diagnostics (option D).

24-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 24)* Adipose tissue distribution is important to the risk for obesity-related hypertension. Most population studies that have investigated the relationship between obesity and BP have measured BMI rather than visceral or retroperitoneal fat, which appear to be better predictors of increased BP than subcutaneous fat (option A).[5] Additionally, three mechanisms appear to be especially important in increasing sodium reabsorption and impairing renal-pressure natriuresis in obesity hypertension: (1) increased SNS activity (option B), (2)

activation of the RAAS (option C), and (3) physical compression of the kidneys by fat accumulation within and around the kidneys and by increased abdominal pressure (option D).

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CHAPTER 25

Diagnosis and Treatment of Hypertension

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

25-1. Which of the following statements about hypertension is *false*?

A. Hypertension is a public health problem worldwide
B. Treating hypertension with antihypertensive drugs is effective for the long-term prevention of cardiovascular disease
C. Normal (optimal) pressure is classified as blood pressure < 120/80 mm Hg
D. Blood pressure measurements outside the office or clinic are always identical to office or clinic pressure measurement
E. The prevalence of hypertension is increasing in relation to increased overweight

25-2. During a routine checkup, a 55-year-old male factory worker's recorded blood pressure is 150/90 mm Hg. What is the goal for the initial evaluation of hypertensive patients?

A. Estimate the average blood pressure
B. Consider the overall cardiovascular risk status
C. Determine the presence or absence of target organ pathology
D. Educate the patient on long-term cardiovascular risk reduction
E. All of the above

25-3. Which of the following is considered *correct* blood pressure measurement in the clinic?

A. Using the same cuff size for all patients
B. Taking blood pressures in both arms, in the seated and standing positions
C. Taking the blood pressure in one arm with the patient standing
D. Taking the blood pressure in one arm with the patient seated
E. Using the brachial artery pressure as a substitute for central aortic pressure

25-4. A 36-year-old woman patient has a blood pressure of 140/90 mm Hg in the clinic. An out-of-office ambulatory blood pressure monitor is requested for the next 24 hours. Which of the following is *not* an advantage of this monitoring device?

A. It predicts the risk of morbid events better than clinic blood pressure
B. It can diagnose white coat hypertension
C. It can diagnose masked hypertension
D. It eliminates the need for medical history and physical examination in determining cardiovascular disease risk
E. It can measure systolic and diastolic pressures while the patient sleeps

25-5. After initial assessment in clinic followed by a 24-hour ambulatory pressure monitoring, a 50-year-old male banker is diagnosed with hypertension. Which of the following is *not* an appropriate course of action?

A. Recommendation of the DASH diet
B. Recommendation of an exercise routine
C. Recommendation of smoking cessation and scheduled follow-up in 1 year
D. Prescription of antihypertensive medications
E. Performance of laboratory biochemical testing and imaging to define cardiovascular risk

25-6. Which of the following diuretics used as an antihypertensive drug does *not* cause hypokalemia as a side effect?

A. Spironolactone
B. Thiazides
C. Loop-active diuretics
D. All of the above

E. None of the above

25-7. A 62-year-old female office worker is evaluated for hypertension. She currently takes a beta-receptor blocker for angina, but due to inadequate blood pressure control, a second-line agent is being selected to achieve optimal blood pressure control. Which antihypertensive drug class is *not* appropriate to prescribe?

A. Thiazide diuretic
B. Non-dihydropyridine calcium channel blocker
C. Angiotensin converting enzyme (ACE) inhibitor
D. Angiotensin receptor blocker (ARB)
E. Alpha-receptor blocker

25-8. Which of the following statements about hypertension management is *correct*?

A. Beta-blockers may cause hypoglycemic unawareness
B. The coexistence of diabetes and hypertension increases the risk of future cardiovascular disease compared to hypertension alone
C. The incidence of new hypertension is very low in cancer patients undergoing chemotherapy treatment with vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab
D. Once a stroke has occurred, antihypertensive drug therapy cannot help prevent additional cerebrovascular pathology and disease
E. The prevalence and severity of hypertension are uniform across different ethnic groups

25-9. A 65-year-old man presents to the emergency room with blood pressure of 220/120 mm Hg, altered mental status, and seizures. This hypertensive emergency could be caused by which of the following?

A. Poor adherence to antihypertensive medication
B. Use of NSAIDs
C. Alcohol or substance abuse
D. Underlying pheochromocytoma
E. All of the above

25-10. A 42-year-old woman in her second trimester of gestation requires antihypertensive therapy for her chronic hypertension. Which of the following is *not* safe to prescribe to her?

A. ACEI
B. Methyldopa
C. Labetalol
D. Nifedipine
E. All of the above

ANSWERS

25-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 25)* By current guidelines, normal (optimal) pressure is classified as blood pressure < 120/80 mm Hg (option C). Hypertension is highly prevalent in adult populations throughout the world and is increasing in relation to increased overweight and reduced daily exercise (option E), and it is a growning cause of fatal and nonfatal cardiovascular and renal disease worldwide (option A).[1,2] The benefits of treating hypertension have been firmly established.[3,4]

The introduction of 24-hour ambulatory blood pressure monitoring and systematic home blood pressure monitoring has brought to light the fact that blood pressure measured outside the office or clinic may differ substantially from office or clinic pressure (option D). The importance of out-of-office blood pressures for accurate prognosis is now supported by several national and international guidelines.[5-8]

25-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 25)* Most hypertensive patients are initially identified during office or clinic visits when seen for checkups or nonemergent symptoms. Initial evaluation and classification of these patients is crucial because hypertension is mostly a silent disorder, and patients are often asymptomatic for long periods of time. The goals for the initial evaluation of hypertensive patients include: estimating the average blood pressure (option A), considering the overall cardiovascular risk status (option B), determining the presence or absence of target organ pathology (option C), and beginning the process of education that will lead the patient to recognize and collaborate in long-term risk reduction (option D). It is also an opportune moment to assess the patient for identifiable (secondary) hypertension. Therefore, all of the above are correct (option E).

25-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 25)* Blood pressure measurement in the clinic requires careful

and consistent practice.[9] Choosing an appropriate cuff size is essential for accurate pressure readings; therefore, larger adult cuffs are mandatory for most large or obese patients (option A). In general, a cuff that is too large will underestimate blood pressure. During measurement, the patient should be seated comfortably, and pressures should be taken in both arms due to possible variability. Blood pressures can also be measured in the standing position (option B) to assess for orthostatic hypotension, particularly in the elderly and in those with dizziness.[10] Brachial artery pressures may fail to reflect central aortic pressures (option E), the latter of which is measured directly by invasive catheterization.

25-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 25)* Ambulatory blood pressure measurement is a noninvasive, fully automated technique in which multiple blood pressure measurements are recorded over an extended period (typically 24 hours). It can thus measure blood pressure when a patient is awake during the day, as well as when the patient is sleeping during the night (option E). Studies suggest that the average level of ambulatory blood pressure predicts risk of morbid events better than clinic blood pressure (option A).[11] Ambulatory blood pressure monitoring is valuable for determining whether the patient's usual pressure, in "real life," is either higher or lower than the clinic pressure, thereby enabling the diagnosis of both white coat (option B) and masked hypertension (option C). Nevertheless, a careful and well-focused medical history and physical examination are the foundation for the initial appraisal of a hypertensive patient and his or her risk for cardiovascular disease, and these cannot be substituted by the use of this device (option D).

25-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 25)* After the initial assessment of hypertensive patients, appropriate follow-up reassessment is crucial. Studies have shown that increased cardiovascular event rates were related to failure to intensify treatment, delays of more than 1.4 months for intensification, and delays in follow-up of more than 2.7 months after intensification.[12] In general, the higher the blood pressure, the greater the need for shorter intervals between revisits. Therefore, while smoking cessation is important for cardiovascular prevention, 1 year is too long an interval for follow-up (option C). There is general agreement that in the absence of clues to identifiable hypertension, efficient use and appropriate selection of laboratory resources can be confined to those needed to define cardiovascular risk, to target organ pathology, and to establish a baseline for treatment (option E). Subsequently, appropriate treatment should focus on lifestyle improvement such as adherence to an adequate diet (option A) and increased exercise (option B), as well as prescription of antihypertensive drugs (option D).

25-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 25)* Thiazides have been the mainstay of antihypertensive drug treatment since the 1960s as single agents or in effective two-drug combinations. The most frequent adverse reaction to these drugs is hypokalemia, due to their effect on potassium excretion by the kidneys (option B). Loop-active diuretics are preferred over thiazides when renal function is impaired or in the presence of congestive heart failure, but they share similar adverse reactions, including hypokalemia (option C). Potassium-sparing diuretics, on the other hand, reduce potassium excretion by the kidneys and therefore do not cause hypokalemia (option A). They are valuable for treating primary aldosteronism or thiazide-related hypokalemia.

25-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 25)* The effectiveness of beta-receptor blockers for the prevention of cardiovascular disease in the absence of coronary artery disease is uncertain.[13,14] However, the role of beta-blockers in the management of coronary heart disease, especially angina, remains well accepted.[15] Alpha-blockers may be combined with a beta-blocker for persons with highly variable blood pressure associated with tachycardia (option E). Likewise, ACEIs (option C) and ARBs (option D) can be safely used with beta-receptor blockers as antihypertensive drugs in the context of coronary heart disease. Non-dihydropyridine calcium channel blocker, on the other hand, inhibits cardiac AV conduction and should not be combined with beta-receptor blockers because of the risk of bradycardia (option B).

25-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 25)* The prevalence and severity of hypertension are not entirely uniform in comparing populations with different ethnic status, with increased prevalence in non-Hispanic (black) groups.[16] In addition, the treatment rates and drug responses vary across groups (option E). Beta-blockers may mask the symptoms of hypoglycemia ("hypoglycemic unawareness"), while diuretics and ACEIs have no discernable effect (option A).[17] In addition, the coexistence of diabetes and hypertension confers a two- to threefold greater risk of future cardiovascular disease compared to hypertension alone (option B).[18,19] Antihypertensive drug therapy continues to be important even after a stroke has occurred, as studies have shown that the combination of an ACEI and diuretic is effective for preventing the occurrence of a second stroke (option D).[20] Finally, the occurrence of cancer in hypertensive patients is all too frequent, and the incidence of new hypertension or worsening of previous hypertension in cancer patients may result from chemotherapy with the VEGF inhibitors, varying from 20% to 70% (option C).[21]

25-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 25)* A hypertensive emergency is defined by a rapid increase in blood pressure linked to an immediate threat to target organs.[22,23] Although there is no blood pressure threshold for the diagnosis of hypertensive emergencies, most end-organ damage is noted with systolic blood pressures exceeding 220 mm Hg or diastolic blood pressures exceeding 120 mm Hg. The condition is usually related to a rapid increase in pressure from already high levels in established hypertension, perhaps related to poor adherence to antihypertensive medications. However, abrupt increases in pressure with threat to target organs may appear without prior warning as in some patients with pheochromocytoma or some forms of renal disease (eg, scleroderma renal crisis). The medical history should include queries about the use of nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and substance use.

25-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 25)* The goals and strategy for treating hypertension in pregnancy differ from the usual pattern for nonpregnant women.[24] For women with treated hypertension before pregnancy, pressure should be kept in the range of 120–160/80–105 mm Hg. However, the range of drug classes suitable for treating hypertension in pregnancy is a restricted one, excluding the renin system blockers such as ACEIs (option A) because of the risk of fetal damage.[25,26] Recommended drugs are methyldopa (option B), labetalol (option C), and nifedipine (option D) because these have acceptable evidence of safety in pregnancy.

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SECTION 5

Metabolic Disorders and Cardiovascular Disease

CHAPTER 26

The Metabolic Syndrome

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QUESTIONS

DIRECTIONS: Choose the one best response to each question.

26-1. Which of the following is *not* considered a component of the metabolic syndrome (MetS)?

A. Central adiposity
B. Insulin resistance
C. High serum low-density lipoprotein (LDL) cholesterol
D. High serum triglycerides
E. Hypertension

26-2. Which of the following statements concerning the MetS is *not true*?

A. Insulin resistance and central adiposity are required for a diagnosis of MetS
B. Three of the five criteria are always required for a diagnosis of MetS
C. Between 20% and 35% of the worldwide adult population have MetS
D. Atherosclerotic risk rises in association with the severity of MetS
E. Residual risk describes the remaining increased risk for atherosclerosis after the treatment of a specific risk factor

26-3. Which of the following is *not* a mechanism by which physical activity affects metabolism?

A. Activation of brown fat
B. Improvement in insulin sensitivity
C. Modulation of endothelial and adipose tissue function
D. Gene activation
E. All of the above are mechanisms by which physical activity affects metabolism

26-4. Which of the following concerning sleep is *true*?

A. Six hours of sleep per night is sufficient for the average adult
B. Reduced sleep is associated with hypertension
C. Sleep quality has no known effects on metabolism
D. Shift workers do not differ from the general population in rates of obesity
E. Adults sleep more on average today than 50 years ago

26-5. Which environmental factors could affect the prevalence of MetS?

A. Modern agricultural practices
B. Exposure to endocrine-disrupting chemicals
C. Industrial production of sugars
D. Antidepressant and antibiotic use
E. All of the above

26-6. Which of the following is considered the common starting pathway for the development of MetS?

A. Genetic predisposition
B. Insulin resistance
C. Systemic inflammation
D. Accumulation of fat in adipose or nonadipose tissue
E. Hypertension

26-7. The presence of which of the following would *not* raise a suspicion of MetS?

A. Alzheimer's disease
B. Polycystic ovary syndrome
C. Obstructive sleep apnea
D. Gestational diabetes
E. Family history of hypertension

26-8. What is the approximate annual risk of developing type 2 diabetes in a patient with obesity and MetS?

A. 2.5%
B. 5%
C. 7.5%
D. 10%
E. 12.5%

26-9. What is the most important factor when selecting a dietary intervention for a patient with MetS?

A. Minimization of refined carbohydrates
B. Avoidance of processed foods
C. Consumption of lean meats
D. Consumption of large amounts of vegetables and fruits
E. Ability to maintain the dietary intervention long-term

26-10. Which of the following procedures is associated with the least improvement in type 2 diabetes?

A. Roux-en-Y gastric bypass (RYGB)
B. Sleeve gastrectomy (SG)
C. Laparoscopic gastric banding (LGB)
D. Biliopancreatic diversion with duodenal switch
E. Biliopancreatic diversion without duodenal switch

ANSWERS

26-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 26)* The metabolic syndrome is a theoretical construct from the clustering of interrelated processes to better represent complex pathophysiology for actionable and effective clinical decision making. Specifically, the rationale and practical utility of MetS is to facilitate early diagnosis, risk stratification, and management of cardiometabolic risk factors. This topic is relevant, but it also remains controversial because many aspects remain unproven. Nevertheless, the core principle is that the value of MetS is related to the impact of residual risk (total risk minus the aggregate of known specific risk factors) on cardiovascular disease (CVD). Currently, the diagnosis of MetS is based on a set of commonly measured metabolic markers: abdominal girth (option A), hyperglycemia (option B), hypertriglyceridemia (option D), hypertension (option E), and low high-density lipoprotein (HDL) levels. However, debate still exists over the relative weighting of each of these measures in a predictive model for morbidity and mortality risk. Low-density lipoprotein levels are not among the diagnostic criteria (option C).

26-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 26)* While the diagnostic criteria for MetS vary by organization, either insulin resistance or central adiposity (but not both) are generally required for a diagnosis of MetS (option A). The exception is the criteria of the American Heart Association/National Heart, Lung, and Blood Institute, which do not make a specific requirement for either. By all definitions, three of five criteria (abdominal girth, hyperglycemia, hypertriglyceridemia, hypertension, and low HDL levels) are required for a diagnosis of MetS (option B). Depending on the specific criteria used, approximately 20% to 35% of various reported worldwide adult populations have MetS (option C). Overall, atherosclerotic risk rises in association with the severity of MetS (option D).[1,2] The practical decisions of diagnosis and clinical intervention should take into consideration the continuum of risk imposed by MetS. The term *residual risk* complements the concept of the MetS. Specifically, residual risk describes the remaining increased potential for atherosclerotic CVD, after the treatment of a specific risk factor, such as using cholesterol-lowering agents with dyslipidemia (option E).[3] Factors that contribute to residual risk include lifestyle factors, such as eating patterns and nutrient content, endocrine-disrupting compounds (EDCs), physical activity, sleep hygiene, and others.

26-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 26)* Physical activity has multiple effects on metabolism, including the activation of brown fat (option A), improvement in insulin sensitivity (option B), and modulation of endothelial function and adipose tissue function (option C).[4,5] Shifts in internal energy use among highly active people may also contribute to more efficient carbohydrate processing and reduced insulin resistance.[6] Additionally, gene

activation following physical activity can influence insulin resistance and mitochondrial function (option D).[7] Interventional studies consistently demonstrate a great reduction in the prevalence and severity of MetS among highly active subjects.[1] Most notably, trials that incorporate increased physical activity demonstrate a 29% to 58% reduction in the incidence of type 2 diabetes among at-risk subjects.[8]

26-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 26)* Many studies demonstrate that a reduced amount of sleep, generally 6 hours or less per night (option A), is associated with increased insulin resistance, hypertension (option B), and obesity.[9] One large study demonstrated that reduced time of slow-wave sleep was specifically associated with increased waist circumference.[10] Quality of sleep can also affect metabolism (option C). Shift workers with frequent changes in circadian patterns have higher rates of obesity and type 2 diabetes compared to the general population (option D). Insulin resistance also worsens in the presence of obstructive sleep apnea. Current trends over the past 50 years demonstrate a 1.5- to 2-hour reduction in time spent sleeping each night, which may further contribute to the rising prevalence of MetS (option E).[11]

26-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 26)* The potential adverse metabolic effects of modern agricultural techniques (option A), food processing, and the resultant food chain in the United States with respect to nutrient content and endocrine disruptors are only just becoming clear, but they are still not without controversy. For example, the use of corn for animal feed rather than grass for beef production or seeds for poultry yields a higher n-6 fatty acid content, which may have proinflammatory effects.[12] A number of man-made industrial chemicals have properties that can interrupt normal hormone signaling either through molecular mimicry of natural hormones, blockade of hormone activity, or by affecting hormonal synthesis, transport, binding, or catabolism (option B). Animal models and population exposure studies identify specific endocrine-disrupting chemicals, such as pesticides, plasticizers, preservatives, and artificial sweeteners, among other chemicals that hinder glucose metabolism and cause insulin resistance.[13-16] However, the degree to which endocrine-disrupting chemicals (EDCs) contribute to the high prevalence of MetS is unclear. The high content of fructose within industrially produced sugars (option C), such as sucrose and high-fructose corn syrup, makes this inefficiently metabolized monosaccharide highly available. Multiple longitudinal and cross-sectional studies demonstrate a strong association among high fructose intake and the development of obesity, MetS, and/or vascular disease.[17-20] The rising use of certain antidepressant and other psychotropic medications (option D) that affect metabolic control within the hypothalamus leads to insulin resistance and weight gain. Even the widespread use of antibiotics may influence metabolism through the alteration of intestinal microbiota (option D).[21] The average American adult is given one to two prescriptions for antibiotics annually, which has been associated with the development of obesity.[21] Macrolides confer the greatest risk, perhaps reflecting a greater effect on intestinal microbiota.[21,22]

26-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 26)* It is useful to view a common starting pathway for the MetS as the accumulation of fat in adipose or nonadipose tissue (option D), which increases systemic inflammation (option C) and insulin resistance (option B). Pancreatic β-cell dysfunction ensues via degeneration or transformation to inactive cells.[23] Impaired insulin signaling leads to further accumulation of fat mass.[24] Reduced release and reduced activity of glucagon-like peptide-1 (GLP-1) by L-cells of the distal ileum worsens insulin resistance and drives further increases in adipose tissue.[25] Nutrient sensing within the paraventricular nucleus of the hypothalamus becomes impaired, and resistance to leptin develops within the arcuate nucleus.[26] Adiponectin production within adipose tissue is also diminished, which further promotes insulin resistance.[27] Insulin resistance reduces endothelial and adipose lipoprotein lipase activity, yielding small, dense LDL particles that enter the circulation and are highly atherogenic.[28] Circulating free fatty acids further drive insulin resistance through oxidative stress and accumulation of intracellular derivatives such as ceramides.[29] Visceral fat stores increase, leading to hepatosteatosis and fat accumulation within the pancreas, promoting insulin resistance and β-cell dysfunction.[30,31] Within the vascular endothelium, insulin resistance also impairs nitric oxide (NO) synthase activity, which diminishes NO production, affecting vasodilation and leading to the development of essential hypertension (option E).[32] Low circulating adiponectin and resistance to leptin induce increased expression of endothelin-1, further driving vasoconstriction and promoting hypertension.[32] High levels of circulating lipid particles naturally oxidize and are taken up by macrophages that become activated.[33] Free fatty acids also bind toll-like receptor 4 on macrophage cell surfaces.[34] Both processes trigger the release of inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin (IL)-1, and IL-6. These cytokines promote the degradation of insulin receptor substrate-1, a downstream mediator of insulin activity, further driving insulin resistance.[33] Very few genes have been identified that specifically confer a risk of MetS (option A).[35] However, epigenetic phenomena secondary to behavioral and environmental factors do have great potential to influence the development of obesity and MetS.

26-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 26)* The high prevalence of MetS should trigger aggressive case finding in a large portion of the general population.[36] Signs of obesity, weight gain, hypertension, hyperlipidemia, and hyperglycemia can be early markers of MetS. People with a family history of type 2 diabetes, hypertension (option E), and CVD should also be evaluated for MetS. Additionally, the presence of other conditions associated with insulin resistance, such as polycystic ovary syndrome (option B), hepatosteatosis, obstructive sleep apnea (option C), or gestational diabetes (option D), should raise suspicion for MetS. Diagnosing a person with MetS emphasizes the decision to intervene.

26-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 26)* The annual risk of type 2 diabetes (T2D) is approximately 2.5% when stratified by fasting glucose (option A).[37] In people with obesity and MetS, the annual risk of T2D is nearly 5% (option B), although annual regression of hyperglycemia is about 10%, emphasizing the need for intensive lifestyle changes as part of a preventive care paradigm.[37] By virtue of its syndromic nature, this preventive care approach to people at high risk for MetS should follow the same treatment strategies for MetS. The intensity of intervention should parallel the severity of each MetS component.[36] A striking theme among the major clinical trials investigating individual criteria of MetS is that early, intensive intervention is best at reducing adverse outcomes, especially with the intention of atherosclerotic risk reduction.[8,38-42]

26-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 26)* In early MetS, when the severity of component risks is mild, lifestyle interventions should be implemented that minimize refined carbohydrates (option A), avoid processed foods (option B), favor meats that are lean (option C), and contain large amounts of fruits, vegetables, and fish (option D). Debate continues over the ideal diet, but beneficial dietary pattern examples include the Mediterranean diet, the New Nordic diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Ornish diet. The use of very low carbohydrate diets, such as the Atkins diet, can also be considered. The most important consideration for dietary intervention is the person's ability to maintain this new lifestyle over the long term (option E).[43]

26-10. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 26)* Approved bariatric surgical procedures include the RYGB (option A), SG (option B), biliopancreatic diversion with or without duodenal switch (BPD) (options D and E), and LGB (option C). Surgically induced changes in the gastrointestinal tract affect energy physiology, insulin resistance, hypertension, hyperlipidemia, and other weight-related complications.[44] Additionally, many of the factors contributing to MetS improve, and the risk of cardiovascular events and mortality is reduced.[45] In people undergoing RYGB, SG, or BPD, insulin resistance improves in the immediate postoperative period, signifying the predominance of improved energy regulatory hormone signaling well before weight loss occurs.[46] Following LGB, insulin resistance declines in association with weight loss.[46] The significant improvement and possible resolution of T2D is also substantially higher following RYGB, SG, and BPD, when compared to LGB.[47-49] These observations suggest that the metabolic benefits of RYGB, SG, and BPD may confer additional improvement to people with MetS.

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CHAPTER 27

Obesity and Cardiovascular Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

27-1. What approximate proportion of the adult population worldwide is overweight or obese?

A. 20%
B. 30%
C. 40%
D. 50%
E. 60%

27-2. What proportion of a person's risk for obesity is attributable to genetic factors?

A. < 10%
B. 10% to 20%
C. 30% to 40%
D. 50% to 60%
E. > 60%

27-3. Which of the following does *not* occur in response to weight loss?

A. Increased secretion of ghrelin
B. Increased secretion of leptin, cholecystokinin, glucagon-like peptide-1, amylin, and peptide YY
C. Decreased resting energy expenditure
D. Increased hunger
E. Increased calorie-dense food preferences

27-4. What proportion of body weight must be lost to achieve predictable therapeutic benefits for obstructive sleep apnea?

A. 2.5%
B. 5%
C. 7.5%
D. 10%
E. 12.5%

27-5. Which of the following is *not true* concerning body mass index (BMI)?

A. National Institutes of Health obesity-defined BMI is divided into three classes: obese class I (BMI 30–34.9), obese class II (BMI 35–39.9), and obese class III (BMI ≥ 40)
B. Cutoff values for classifying individuals as underweight, normal, overweight, or obese vary by population
C. BMI will overestimate adiposity in athletes with high muscle mass
D. BMI is a significant independent predictor of cardiovascular disease (CVD)
E. In patients with congestive heart failure, overweight and obesity are protective against mortality

27-6. Which of the following statements concerning the clinical component of the diagnosis of obesity is *not true*?

A. Individuals who meet the anthropometric criterion for overweight or obesity should undergo a clinical evaluation for weight-related complications
B. In many cases, information gathered in the initial examination is sufficient for the diagnosis of certain weight-related complications
C. The goal of weight-loss therapy is to treat and prevent weight-related complications

D. Even metabolically healthy obese patients should be treated aggressively to reduce risk for coronary heart disease
E. BMI does not indicate the impact of excess adiposity on the health of individual patients

27-7. Which of the following is *not true* about the effects of weight loss on CVD risk factors?

A. Weight loss is the most effective therapeutic approach for treating and preventing the progression of cardiometabolic disease
B. If weight loss is not sustained over time, its beneficial effect on type 2 diabetes incidence is lost
C. Weight loss is an effective approach for reducing blood pressure
D. Weight loss decreases triglycerides and LDL, while increasing HDL
E. Weight loss has beneficial effects on LDL subclasses characterized by reductions in small, dense LDL particle concentrations and an increase in medium and large LDL particles

27-8. Which of the following is *not* appropriate for staging cardiometabolic risk in insulin resistant patients?

A. American College of Cardiology/American Heart Association Omnibus risk estimator
B. Framingham Coronary Heart Disease Risk Score
C. Reynolds Risk Score
D. Cardiometabolic Disease Staging System
E. American Heart Association/National Heart, Lung, and Blood Institute diagnostic criteria for metabolic syndrome (MetS)

27-9. Which of the following weight-loss medications is approved for the treatment of obese adolescents?

A. Orlistat
B. Lorcaserin
C. Phentermine/topiramate
D. Naltrexone/bupropion
E. None of the above

27-10. In which of the following patient group(s) could bariatric surgery be considered?

A. BMI of 35 kg/m^2 or more
B. BMI of 35 kg/m^2 or more with at least one associated comorbidity
C. BMI of 40 kg/m^2 or more
D. Both B and C
E. A, B, and C

ANSWERS

27-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Prevalence rates of obesity have increased sharply worldwide over the past 30 years.[1] Worldwide, the proportion of adults with a BMI of 25 kg/m^2 or greater increased between 1980 and 2013 from 28.8% to 36.9% in men, and from 29.8% to 38.0% in women.[2] Prevalence has increased substantially in children and adolescents in developed countries, to the point where 23.8% of boys and 22.6% of girls were overweight or obese in 2013.[2] In the United States, data from the National Health and Nutrition Examination Survey (NHANES) show that roughly two out of three US adults are overweight or obese, more than one-third are obese, and 17% of children are obese.[3,4] This has created a global health crisis with a profound impact on morbidity, mortality, and health care costs largely attributable to weight-related complications.

27-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Like many other chronic diseases, genetic factors constitute a substantial component of disease risk[5] that can explain 50% to 60% of individual variation in body weight in monozygotic/dizygotic twin studies. Monogenic forms of the disease are rare, such as in families with leptin or leptin receptor mutations or deletion of the *SNORD116* gene cluster in patients with Prader–Willi syndrome. Susceptibility to obesity in most people results from the inheritance of multiple genes, with each allele conferring a very small relative risk for the disease. Genomewide association studies have identified more than 100 susceptibility loci for obesity.[6] Particularly strong association signals have been detected for the fat mass- and obesity-associated gene (*FTO*) and the melanocortin-4 receptor (*MC4R*) gene, but even these variants confer odds for obesity of less than 1.7.[7,8] The multiple susceptibility genes interact with each other and with the environment, behavior, and biological factors to produce individual variation in the risks of obesity. The development of excess adiposity is a complex process; however, those individuals who inherit larger subsets of obesity susceptibility genes will tend to be more overweight in any given environment.[9,10] Progressive weight gain is not a lifestyle choice and cannot be viewed in terms of a simple thermodynamic equation of greater energy in than energy out. Rather, gene-environment interactions generate a human biological and behavioral interface unique to each person that not only determines body weight but also explains

individual variation in the net effect on body weight for any given amount of food intake or physical activity.

27-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Homeostatic dysregulation in the hypothalamus adversely affects appetite and satiety as they respond to peripheral hormones that register fuel storage and availability. With obesity, these mechanisms drive an increase in appetite, producing a positive energy balance, which generates and maintains a higher body weight.[11,12] Following a weight-loss intervention, secretion of ghrelin from the stomach is increased above baseline both before and after meals (option A). Ghrelin stimulates neuropeptide Y (NPY) and Agouti-related peptide neurons in the arcuate nucleus of the hypothalamus, causing the release of NPY, which activates orexigenic neural pathways, leading to an increase in appetite (option D). At the same time, hormones from the gastrointestinal tract and pancreas (eg, leptin, cholecystokinin, glucagon-like peptide-1, amylin, and peptide YY) are reduced below baseline levels (option B).[12] These latter hormones circulate to the hypothalamus and stimulate proopiomelanocortin-expressing neurons in the arcuate nucleus to produce α-melanocyte-stimulating hormone (MSH). The α-MSH binds upstream MC4R receptors to activate anorexigenic neural pathways, resulting in suppression of appetite. The fall in these satiety-producing hormones has an additional effect to stimulate appetite. Furthermore, in response to weight loss, resting energy expenditure rates are decreased (option C), and the energy that muscles use for any given amount of work is also decreased (ie, increased muscle energy efficiency). These energetic changes also promote weight regain.[13] Finally, psychological food preferences become oriented to foods of greater caloric density with high fat and sugar content (option E).

27-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Obesity markedly augments the risk of obstructive sleep apnea, which interrupts normal sleep with periods of hypoxia. This establishes a vicious cycle whereby progressive weight gain exacerbates sleep apnea and sleep apnea promotes further weight gain.[14,15] Obstructive sleep apnea adversely affects psychological health, causing fatigue and depression, affects metabolic health by predisposing to MetS and type 2 diabetes, and affects cardiovascular health as an independent risk factor for refractory hypertension, stroke, and CVD.[16-20] The therapeutic options for obstructive sleep apnea include continuous positive airway pressure therapy and weight loss.[21,22] The severity of sleep apnea is quantified by the apnea–hypopnea index (AHI), which reflects the average number of apneic/hypopneic episodes per hour during a polysomnography study.[23] Weight loss, whether achieved by lifestyle therapy[22] or obesity medications,[22] can dramatically improve both AHI scores and symptomatology; however, therapeutic benefits are most predictably achieved with at least 10% weight loss.[21,22]

27-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 27)* The criteria established by the World Health Organization in 1998[24] defines that BMI values 18.5 to 24.9 kg/m^2 are indicative of lean individuals, BMIs 25 to 29.9 kg/m^2 overweight, and BMIs of 30 kg/m^2 or more represent obesity categorized as obese class I (BMI 30–34.9), obese class II (BMI 35–39.9), or obese class III (BMI ≥ 40) (option A). These criteria were soon thereafter adopted by the National Institutes of Health.[25] However, in South Asian, East Asian, and Southeast Asian populations, health is adversely affected at lower levels of BMIs, and alternate criteria have been advocated, with BMIs of 18.5 to 22.9 kg/m^2 indicative of normal weight, 23 to 24.9 kg/m^2 overweight, and 25 or more kg/m^2 obese (option B).[26] BMI is an anthropometric measure that interrelates the height and weight of individuals, and, therefore, is only an indirect measure of adiposity of total body fat mass. BMI incorporates lean mass, fat mass, bone mass, and fluid status, all of which can vary independently from fat mass. BMI will overestimate adiposity in athletes with high muscle mass (option C) and in patients with edema and will underestimate adiposity in elderly patients with sarcopenia. For this reason, patients with elevated BMI measurements must be clinically evaluated to confirm excess adiposity. It is important to consider that the association between BMI and CVD is largely explained by its association with other risk factors, such that independent risk conferred by BMI is usually minimized in multivariate analyses (option D). For example, when adjusted for waist circumference or the presence of MetS, BMI is no longer a significant independent risk factor for CVD or becomes a much weaker predictor.[27-31] Regarding congestive heart failure (CHF), the presence of overweight or obesity may be protective against mortality, referred to as the *obesity paradox* (option E). Elevations in BMI are associated with increased risk of developing CHF in part by predisposing to hypertension, type 2 diabetes, sleep apnea, and CVD. However, once patients present with CHF, the presence of overweight and/or obesity has been observed to be protective regarding risks of future CVD mortality and hospitalizations when compared with lean individuals.[32-34] Better outcomes in overweight or obese subjects may reflect reverse causality resulting from processes that both lower body weight and increase mortality (eg, cardiac cachexia and cigarettes).

27-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Body mass index status as lean, overweight, or obese does not substantially affect coronary heart disease risk in metabolically healthy patients (those with no other MetS traits), so aggressive weight-loss treatment would not be expected to reduce the risk for coronary heart disease in these patients (option D). Metabolically healthy obese individuals exhibit relatively low rates of future type 2 diabetes, cardiovascular events, and mortality.[27,35-38] BMI does not indicate the impact of excess adiposity on the health of individual patients (option E).[39] Therefore, individuals who meet the anthropometric criterion for overweight or obesity must then undergo a clinical evaluation for the presence or absence of weight-related complications (option A).[39,40] The presence and severity of complications or relevant risk factors will indicate the need for more aggressive therapy to improve the health of individual patients. The identification of complications does not involve an extensive or extraordinary degree of testing but can be ascertained in the course of an initial patient evaluation consisting of medical history, review of systems, physical examination, and laboratory studies. In many cases, the information gathered in the initial examination

is sufficient for the diagnosis of certain weight-related complications (option B). For other complications, the initial information augments the degree of suspicion, and additional testing consistent with standards of care is then needed to confirm the diagnosis and to stage the severity of the complication. The goals of weight-loss therapy are to improve the health of patients with obesity by treating and preventing weight-related complications (option C).

27-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Weight loss is perhaps the most effective therapeutic approach for treating and preventing the progression of cardiometabolic disease (option A) via improvements in the core physiological processes that confer risk of future type 2 diabetes (T2D) and CVD events. Three major randomized clinical trials, the Diabetes Prevention Program,[41] the Finnish Diabetes Study,[42] and the Da Qing Study,[43] all demonstrated the impressive efficacy of lifestyle/behavioral therapy to prevent T2D. With observational follow-up after termination of the Diabetes Prevention Program study, there was still a significant reduction in the cumulative incidence of T2D in the lifestyle treatment group at 10 years, despite the fact that BMI levels had equalized among the three treatment arms (option B).[41] Hypertension is an established consequence of overweight and obesity. It is therefore not surprising that one of the associated benefits of weight reduction is lowering blood pressure (option C). A meta-analysis suggests that blood pressure decreases by 1.2/1.0 mm Hg for every kilogram of weight lost. Weight loss of 5% to 10% has been shown to amplify the benefits of changes in macronutrient composition, resulting in a 20% decrease in triglycerides, a 15% reduction in LDL cholesterol, and an 8% to 10% increase in HDL cholesterol (option D). However, greater degrees of weight loss can achieve progressive improvements in dyslipidemia. Meta-analyses have reported that for every kilogram of weight loss, triglyceride levels decrease about 1.9% or 1.5 mg/dL.[44] Furthermore, there are beneficial effects of weight loss on LDL subclasses characterized by reductions in small, dense LDL particle concentrations and an increase in medium and large LDL particles, coupled to a mean increase in LDL particle size and reductions in total LDL particle concentration (option E).[44,45]

27-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Estimates of cardiometabolic disease risk can be used to identify patients at greatest risk for future type 2 diabetes (T2D) and CVD in order to target more aggressive weight-loss therapy to those individuals who will receive the greatest benefit. The clinician should evaluate patients for MetS and prediabetes, because this effectively identifies individuals at high risk for future T2D and CVD. However, MetS and prediabetes have high specificity but low sensitivity for identifying patients with insulin resistance and cardiometabolic disease,[37,46] and these entities alone will not identify significant proportions of at-risk patients (option E). Various indices using information from history and physical examination, such as the American College of Cardiology (ACC)/American Heart Association (AHA) Omnibus risk estimator (option A),[47] Framingham Coronary Heart Disease Risk Score (option B),[48] the Reynolds Risk Score (option C),[49] or commercial products that use clinical laboratory assays, can be used to stage risk in insulin-resistant patients whether or not they meet diagnostic criteria for MetS or prediabetes. Another approach to cardiometabolic disease risk stratification for the patient with obesity is the Cardiometabolic Disease Staging system (CMDS) (option D).[27,28] CMDS defines five stages of risk that are based on established physiological and epidemiological observations to quantitatively stratify the risk of both T2D and CVD.

27-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Orlistat (option A) is the only approved long-term drug for obese adolescents aged at least 12 years, while all others (options B, C, and D) are only approved for adult patients. Since 2012, there have been four new weight-loss medications approved for the chronic treatment of obesity by the FDA.[50,41,51,52] These medications are in addition to orlistat (120 mg), approved in 1999, which was the only preexisting medication for long-term pharmacotherapy and the only one currently permitted in Europe and many other countries. The newer medications include lorcaserin, phentermine/topiramate extended-release (ER), naltrexone ER/bupropion ER, and high-dose liraglutide (3 mg). The availability of these new medications has greatly expanded treatment options for patients with obesity and has led to more robust approaches to patient management.[40] All these medications are approved in the United States as adjuncts to lifestyle modification in overweight patients with BMIs of 27 to 29.9 kg/m^2 having at least one weight-related comorbidity (generally taken to be diabetes, hypertension, or dyslipidemia), or obese patients (BMI $\geq$ 30 kg/m^2) whether or not comorbidities are present.

27-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 27)* Bariatric surgery is the most effective method for treating class II and III obesity[53,54] and can be considered in patients with (1) BMIs of 35 kg/m^2 or more and associated comorbidities (option B) or (2) BMIs of 40 kg/m^2 whether or not accompanied by comorbidities, particularly after failure of lifestyle modification and medical therapies (option C). Bariatric surgery can provide substantial weight loss (15% to more than 40%), but this varies by procedure.[54] The most commonly performed procedures are Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, sleeve gastrectomy, and biliopancreatic diversion with or without duodenal switch. Many patients achieve long-term weight loss; however, it is not uncommon for patients to gradually regain weight over time.[55] Sustained weight loss also depends on ongoing lifestyle therapy, patient reeducation in terms of active lifestyle changes, and long-term medical follow-up.

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CHAPTER 28

Diabetes and Cardiovascular Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

28-1. A 41-year-old woman with a history of atrial fibrillation presents to your office. Which of the following is *incorrect*?

A. A normal glycated hemoglobin should be < 6.0%, while a glycated hemoglobin of 6.0% to 6.5% is considered prediabetes
B. A glycated hemoglobin level of 6.5% or higher on two separate occasions indicates diabetes
C. Prediabetes can be diagnosed by a fasting plasma glucose of 100 mg/dL or more (impaired fasting glucose), a postglucose load of 140 to 199 mg/dL (impaired glucose tolerance), or both
D. Diabetes can be diagnosed by a fasting plasma glucose > 126 mg/dL or a 2-hour postprandial glucose of > 200 mg/dL during an oral glucose tolerance test involving a glucose solution containing the equivalent of 75 grams of glucose dissolved in water
E. Diabetes can be diagnosed in the patient who has a random plasma glucose of > 200 mg/dL with classic symptoms of hyperglycemia

28-2. An obese 17-year-old woman now present with her second pregnancy. Which of the following is *incorrect*?

A. Patients who are overweight or obese with a body mass index (BMI) of > 25 kg/m^2 or in the case of Asian Americans of 23 kg/m^2 or higher should be screened for diabetes
B. Children and adolescents who are overweight or obese should be screened for diabetes
C. With regard to gestational diabetes, patients with risk factors should be tested in the first prenatal visit. At 28 weeks' of gestation, pregnant women who are not previously known to have diabetes should be tested for gestational diabetes
D. Women with a history of gestational diabetes are considered to have prediabetes and should receive lifestyle interventions for the prevention of diabetes
E. All are correct

28-3. Which of the following is *incorrect*?

A. In 1985, an estimated 30 million people worldwide had diabetes
B. It is expected that there will be 350 million people worldwide with diabetes by 2025
C. In the United States in 2012, the unadjusted prevalence of diabetes was 19.3% (95% confidence interval [CI], 7.8%–11.1%)
D. Within the diabetes population, 25.2% (95% CI, 21.1%–29.8%) were undiagnosed
E. All are correct

28-4. A 70-year-old man with a history of diabetes, coronary artery disease (CAD), and hypertension has now developed diabetic nephropathy. Which of the following should *not* be used when treating this patient?

A. Control of hypertension with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
B. Glycemic control
C. Sodium restriction
D. Adjustment of protein intake
E. Renal arteriography if systolic blood pressure is > 170 mm Hg despite treatment with two antihypertensive agents

28-5. Which of the following statements is *not true* regarding type 2 diabetes mellitus and coronary heart disease?

A. Coronary heart disease (CHD) is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease
B. There is a two- to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population. This increase is particularly disproportionate in diabetic women when compared with diabetic

men

C. The protection that premenopausal women have against CHD is not seen if they suffer from diabetes
D. The degree of hyperglycemia and the duration of hyperglycemia are strong risk factors for the development of microvascular but not macrovascular complications
E. Even impaired glucose tolerance increases cardiovascular risk, although there is minimal hyperglycemia

28-6. Which of the following statements is *not true* regarding insulin resistance?

A. The insulin resistance syndrome is a composite of dyslipidemia, hypertension, hypercoagulability, and microalbuminuria
B. Insulin resistance is the predominant defect in > 90% of type 2 diabetes patients and the major pathologic mechanism for the susceptibility to premature cardiovascular disease
C. Hyperinsulinemia is an independent risk factor when adjusted for lipid profile, hypertension, and family history
D. Studies of multiple ethnic groups show increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance
E. Because insulin resistance precedes clinically diagnosed type 2 diabetes by 10 to 15 years in as many as 90% of patients, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics

28-7. One of your patients who has a history of diabetes and multivessel percutaneous coronary intervention (PCI) has a glycated hemoglobin of 7.0%. With respect to intensive (< 7.0% glycated hemoglobin) versus usual care strategies for the treatment of diabetes, meta-analyses of clinical trial results indicate which of the following?

A. For cardiovascular death, there is no difference between the intensive (< 7.0% glycated hemoglobin) and usual care strategies
B. In long-term studies that combine UKPDS, ACCORD, and VADT, myocardial infarction (MI) was reduced by about approximately 15% over the long term
C. Apart from a modest reduction in MI rates, there is no significant benefit of a more intensive lowering of glycated hemoglobin with regard to cardiovascular macrovascular end points
D. One meta-analysis of 27,000 participants with 2370 major cardiovascular events, including hospitalization or death from heart failure, showed no important differences between the more intensive arm compared to the less intensive arm
E. All of the above are true

28-8. Which of the following statements is *not true* about the treatment of diabetic patients with statins?

A. For patients with diabetes and known cardiovascular disease, high-intensity statin therapy is recommended according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 2013
B. For patients with diabetes under the age of 40 with one additional cardiovascular risk factor or those age 40 to 75 without any cardiovascular risk factors, moderate to high-intensity statins are recommended
C. Much of the evidence for the treatment of diabetics with statins comes from subgroup analyses from large randomized trials of lipid-lowering therapies in which diabetic patients represented < 10% of all the patients enrolled
D. In the trials of statin therapy with hyperlipidemia, the relative benefit appears to be increased among diabetic patients compared with nondiabetic patients
E. In a pooled analysis from the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials, patients with prediabetes treated with high-intensity compared to low-intensity statins were more likely to develop new onset diabetes over 5 years

28-9. A 45-year-old man with diabetes and palpitations presents to your clinic. Which of the following statements regarding antiplatelet therapy in patients with diabetes is *false*?

A. For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, it is recommended that aspirin therapy at 81 mg daily be instituted as a primary prevention strategy for type 1 and type 2 diabetic patients
B. For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, clopidogrel can be considered as an alternative to aspirin as a primary prevention strategy for type 1 and type 2 diabetic patients
C. For patients who are under age 50 for men and 60 for women with no additional major risk factors, aspirin therapy is not recommended
D. For diabetic patients with acute coronary syndromes, the evidence suggests that there is no heterogeneity in the response to newer antiplatelet agents and strategies based on diabetes status
E. Clopidogrel is associated with a lower bleeding risk than are prasugrel and ticagrelor

28-10. An asymptomatic 65-year-old man with diabetes is referred to you for screening. With respect to screening for coronary artery disease (CAD) in patients with diabetes, which of the following statements is *true*?

A. Exercise testing in diabetic patients is more likely to be accurate when combined with echocardiography or radionuclide imaging
B. Diabetic patients are less likely to have an appropriate blood pressure and heart rate response to exercise and less likely to experience any pain corresponding to ST-segment changes caused in part by autonomic dysfunction
C. The AHA recommends that the finding of subclinical CAD should prompt clinicians to initiate more aggressive

preventive measures

D. The DIAD study has shown that the prevalence of silent ischemia in the diabetic population is not insignificant, but the annual cardiac event rate is < 1% overall at 4.8 years of follow-up, and routine screening for inducible coronary ischemia did not reduce cardiovascular events

E. All of the above are correct

ANSWERS

28-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 28)* The universally recognized criteria for the diagnosis of prediabetes and diabetes are as follows: (1) a normal glycated hemoglobin should be < 5.7%, (2) a glycated hemoglobin of 5.7% to 6.4% is considered prediabetes, and (3) a level of 6.5% or higher on two separate occasions indicates diabetes (option B).[1] Prediabetes can be diagnosed by a fasting plasma glucose of 100 mg/dL or more (impaired fasting glucose), a postglucose load of 140 to 199 mg/dL (impaired glucose tolerance), or both (option C). Other recognized criteria include a fasting plasma glucose > 126 mg/dL or a 2-hour postprandial glucose of > 200 mg/dL during an oral glucose tolerance test involving a glucose solution containing the equivalent of 75 grams of glucose dissolved in water (option D). Diabetes can also be diagnosed in the patient who has a random plasma glucose of > 200 mg/dL with classic symptoms of hyperglycemia (option E).

28-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 28)* New recommendations identify patients who are at increased risk for diabetes and who require testing. These include patients who were overweight or obese with a body mass index (BMI) of > 25 kg/m^2 or in the case of Asian Americans of 23 kg/m^2 or higher (option A). Recommendations for screening for diabetes have now expanded to screening of children and adolescents who are overweight or obese (option B). With regard to gestational diabetes, patients are tested in the first prenatal visit with risk factors. At 28 weeks' of gestation, there is a test for gestational diabetes in pregnant women who are not previously known to have diabetes (option C). It is recommended that women with a history of gestational diabetes are considered to have prediabetes and should receive lifestyle interventions for the prevention of diabetes (option D).

28-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 28)* The number of people with diabetes has increased alarmingly since 1985, and the rate of new cases is escalating. In 1985, an estimated 30 million people worldwide had diabetes (option A), and this figure is expected to rise to almost 350 million by 2025 (option B).[2] In the United States in 2012, the unadjusted prevalence of diabetes was 12.3% (95% confidence interval [CI], 10.8%–14.1%) (option C). Within the diabetes population, 25.2% (95% CI, 21.1%–29.8%) were undiagnosed (option D).[3]

28-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 28)* There is insufficient evidence to recommend angiotensin-converting enzyme (ACE) inhibitors in normotensive patients without microalbuminuria. Nonetheless, physicians should still recommend screening on at least a yearly basis, because the risk-to-benefit ratio of diagnosing microalbuminuria justifies treatment with an ACE inhibitor, if not for renal disease alone, then for reducing the incidence of myocardial infarction (MI) (option A). Clinical trials evaluating angiotensin receptor blockers (ARBs), including losartan and irbesartan, have demonstrated a significant renal protective effect in the diabetic patient with nephropathy (option A). There were no differences between the ARB and usual care groups with regard to cardiovascular outcomes.[4] An optimal approach toward diabetic nephropathy combines control of hypertension, preferably with an ACE inhibitor or ARB, glycemic control (option B), sodium restriction (option C), and adjustment of protein intake (option D). If increasing macroalbuminuria occurs or if renal insufficiency is progressive despite these measures, the patient should be referred to a nephrologist. It is strongly recommended that renal arteriography be avoided (option E). Dietary protein restriction in patients who have progressive renal insufficiency will reduce the accumulation of nitrogen-containing waste products and can have a beneficial influence on the progression of renal insufficiency.

28-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 28)* Coronary heart disease (CHD) is strongly associated with type 2 diabetes mellitus and is the leading cause of death regardless of the duration of disease (option A). There is a two- to fourfold increase in the relative risk ratio of cardiovascular disease in type 2 diabetes patients compared to the general population. This increase is particularly disproportionate in diabetic women when compared with diabetic men (option B). The protection that premenopausal women have against CHD is not seen if they suffer from diabetes (option C). The degree of hyperglycemia and the duration of hyperglycemia are strong risk factors for the development of *both* microvascular and macrovascular complications (option D). Even impaired glucose tolerance increases cardiovascular risk, although there is minimal hyperglycemia (option E).[5]

28-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 28)* The insulin resistance syndrome is a composite of dyslipidemia, hypertension, and hypercoagulability (option A).[6] The syndrome composite does not require microalbuminuria. It is only now being recognized that insulin resistance is the predominant defect in more than 90% of type 2 diabetes patients and the major pathologic mechanism for the susceptibility to premature cardiovascular disease (option B). Insulin resistance and hyperinsulinemia accelerate the development of atherosclerosis. Hyperinsulinemia is an independent risk factor when adjusted for lipid profile, hypertension, and family history (option C). Studies of

multiple ethnic groups show increased carotid intima-medial thickness (a reliable marker for coronary disease) in subjects with insulin resistance (option D). Impaired glucose tolerance can increase the risk of heart disease. Because insulin resistance precedes clinically diagnosed type 2 diabetes by 10 to 15 years in as many as 90% of patients, this extensive period of atherogenic exposure may account for the higher rates of cardiovascular disease in type 2 diabetics (option E).[7,8]

28-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 28)* Evidence from updated meta-analyses indicates that, for cardiovascular death, there is no difference between the intensive (< 7.0% glycated hemoglobin) and usual care strategies (option A).[9] In long-term studies that combine UKPDS, ACCORD, and VADT, myocardial infarction (MI) was reduced by about 15% over the long term (option B). Apart from this modest reduction in MI rates, there was no significant benefit of a more intensive lowering of glycated hemoglobin with regard to cardiovascular macrovascular end points (option C). One meta-analysis of 27,000 participants with 2370 major cardiovascular events, including hospitalization or death from heart failure, showed no important differences between the more intensive arm compared to the less intensive arm (option D).[10]

28-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 28)* Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors—statins—are the frontline therapy in lowering LDL cholesterol levels in type 2 diabetes patients without having an adverse effect on glycemic control. Important evidence from large randomized trials of lipid-lowering therapies is based on subgroup analyses in which diabetic patients represented < 10% of all the patients enrolled (option C); however, more recently studies have been done exclusively in diabetic patients. In the Cholesterol and Recurrent Events (CARE) Trial, which compared pravastatin with a placebo in secondary prevention, the baseline mean LDL concentration in diabetic patients was 136 mg/dL. LDL was reduced 27% in the group receiving pravastatin, which translated into a 25% reduction in coronary events over 5 years compared with the control group.[11] The Heart Protection Study (HPS), with a subgroup of 5963 diabetic patients, showed a 28% reduction in total coronary heart disease (CHD), including nonfatal myocardial infarction and CHD death, nonfatal and fatal strokes, coronary and noncoronary revascularizations, and major vascular events (total CHD, total stroke, or revascularizations) with simvastatin therapy.[12] *In the trials of statin therapy with hyperlipidemia, the relative benefit appears to be similar between diabetic patients and nondiabetic patients* (option D).

Secondary prevention: For patients with diabetes and known cardiovascular disease, high-intensity statin therapy is recommended according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines of 2013 (option A).[13] Primary prevention: For patients with diabetes under age 40 with one additional cardiovascular risk factor or those age 40 to 75 without any cardiovascular risk factors, moderate to high-intensity statins are recommended (option B). In a pooled analysis from the TNT (Treating to New Targets) and IDEAL (Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering) trials, patients with prediabetes treated with high-intensity compared to low-intensity statins were more likely to develop new onset diabetes over 5 years (HR 1.20, 95% CI; 1.04–1.37) (option E).[14]

28-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 28)* For men over age 50 and women over age 60 with at least one additional major cardiovascular risk factor, aspirin therapy at 81 mg daily is recommended as a primary prevention statin strategy for type 1 and type 2 diabetic patients (option A). *Clopidogrel is not recommended for primary prevention among diabetic patients among patients who can take aspirin* (option B). However, for men under age 50 and women under age 60 with no additional major risk factors, aspirin therapy is not recommended (option C).[1] The use of antiplatelet therapy is the mainstay of management of acute coronary syndromes in diabetic patients. With the advent of newer antiplatelet drugs, there have been recommendations for greater use of prasugrel and ticagrelor. The evidence suggests that there is no heterogeneity in the response to newer agents and strategies based on diabetes status (option D).[15-20] The optimal strategy and regimen in diabetic patients is still elusive and remains the question of ongoing trials focused on limiting the thrombotic burden and not increasing the risk of major bleeding. Clopidogrel is associated with a lower bleeding risk than are prasugrel and ticagrelor (option E).

28-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 28)* The significant increase in major microvascular and macrovascular complications makes it important to begin screening for diabetes at an age younger than 45 years.[21] It has become necessary to implement aggressive screening strategies to be able to identify populations at the highest risk of developing diabetes.[22] Current measures of cardiovascular surveillance for coronary artery disease (CAD) in asymptomatic diabetic patients focus on routine stress testing in accordance with the American College of Cardiology/American Heart Association (ACC/AHA) guidelines. Exercise testing in diabetic patients is more likely to be accurate when combined with echocardiography or radionuclide imaging (option A).[23] Diabetic patients are less likely to have an appropriate blood pressure and heart rate response to exercise and less likely to experience any pain corresponding to ST-segment changes caused in part by autonomic dysfunction (option B). The AHA recommends that the finding of subclinical CAD should prompt clinicians to initiate more aggressive preventive measures (option C). The DIAD study has shown that the prevalence of silent ischemia in the diabetic population is not insignificant, but the annual cardiac event rate is < 1% overall at 4.8 years of follow-up, and routine screening for inducible coronary ischemia did not reduce cardiovascular events (option D).[24]

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CHAPTER 29

Hyperlipidemia

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

29-1. Lipoproteins contain which of the following?

A. Neutral lipid
B. Nonesterified cholesterol
C. Phospholipid
D. Proteins
E. All of the above

29-2. A 40-year-old man with a history of hyperlipidemia has an inferior MI. Multiple members of his family have had coronary events in their early 40s. Which of the following types of studies do *not* provide evidence to support the idea that an elevated plasma LDL is a major risk factor for atherosclerotic cardiovascular disease (ASCVD)?

A. Animal studies
B. Genetic forms of elevated LDL
C. Epidemiological associations
D. Randomized controlled trials
E. All of the above support the idea

29-3. Which of the following steps in the progression of atherosclerosis is *incorrect*?

A. Accumulation of large numbers of foam cells gives rise to fatty streaks
B. Some foam cells die and release their cholesterol esters into the interstitium, and over time the core of extracellular lipid expands
C. Osteoclasts from the medium begin to produce fibrous connective tissue
D. This tissue forms a covering of the fatty streak; here the lesion is called a fibrous plaque (fibroatheroma)
E. Continuous filtration of LDL into the arterial wall leads to several steps to plaque progression

29-4. Which of the following is *not true* about familial hypercholesterolemia (FH)?

A. Heterozygous FH occurs in about one in 500 persons; homozygous FH occurs in only one in a million persons
B. Patients with heterozygous FH commonly develop premature ASCVD, most often between the ages of 30 and 60 years, and estimates are that it accounts for at least 2% of premature myocardial infarctions (MIs). Homozygous FH leads to very premature disease, often in the teens or earlier
C. A clinical feature of FH is the presence of cholesterol deposition in tendons (xanthomas) of the hands, elbows, knees, and feet, especially the Achilles tendon
D. Deposition of cholesterol in the skin about the eyes is called xanthelasma
E. In individuals with hypercholesterolemia, the presence of xanthelasmas is pathognomonic of FH

29-5. One of your patients is morbidly obese and consults you with respect to the advisability of bariatric surgery. Which of the following is *not true* about obesity?

A. Excess body weight can be defined as *overweight* (body mass index [BMI] 25 to 30 kg/m^2) and *obesity* (BMI > 30 kg/m^2)
B. More than one-third (34.9% or 78.6 million) of US adults are obese
C. More than 15% of American children and teens are clinically obese
D. Non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%)
E. Obesity is higher among middle-aged adults (ages 40 to 59 years; 39.5%) than among younger adults (ages 20 to 39

years; 30.3%) or older adults (≥ age 60 years; 35.4%)

29-6. A patient is referred to you with the possible diagnosis of metabolic syndrome. Which of the following is *not true* about the criteria used for the clinical definition of the metabolic syndrome?

A. Increased blood pressure is one of the criteria
B. Dyslipidemia (increased triglycerides and lowered HDL-C) is one of the criteria
C. Increased fasting glucose is one of the criteria
D. Abdominal obesity (increased waist circumference) is one of the criteria
E. Any three of five abnormal findings constitute a diagnosis of the metabolic syndrome, and a single set of cut points are used for all components

29-7. One of your patients has suffered from multiple MIs yet is statin-intolerant. You are considering starting the patient on a PCSK9 inhibitor. Which of the following is *not true* about PCSK9 inhibitors?

A. PCSK9 inhibitors bind PCSK9 from the circulation and thereby prevent the action of PCSK9 to promote the degradation of LDL receptors
B. As a result of PCSK9 inhibition, fewer LDLRs are expressed by the liver, and serum LDL-C levels are reduced
C. US Food and Drug Administration (FDA)–approved PCSK9 inhibitors are evolocumab and alirocumab
D. These drugs must be given systemically once or twice a month, and they cause marked incremental reductions of LDL-C even when given with statins
E. To date, they appear to be safe and have not been reported to cause myopathy

29-8. Which of the following is *true* about cholesteryl ester transfer protein (CETP) inhibitors?

A. CETP inhibitors inhibit CETP, 353 which transfers cholesterol ester from HDL-C to VLDL or LDL. As a result, HDL-C levels are increased, whereas VLDL-C and LDL-C are decreased
B. Three randomized controlled trials with CETP inhibitors have failed to show an ASCVD risk reduction
C. Torcetrapib gave an increase in total mortality, and the trial was discontinued
D. Trials with two other CETP inhibitors, dalcetrapib and evacetrapib, were discontinued before completion because of futility
E. All are true

29-9. A 73-year-old woman who was recently started on a statin comes to you complaining of muscle pain. According to the 2014 National Lipid Association Statin Muscle Safety Task Force, which of the following terms is *incorrect* with respect to statin-associated adverse muscle events?

A. Myalgia: A symptom of muscle discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level. Myalgia symptoms can be described as flu-like symptoms
B. Myopathy: Muscle weakness (not due to pain), with or without an elevation in CK level
C. Myositis: Muscle inflammation
D. Myonecrosis: Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex: Mild: 3- to 5-fold elevation in CK above baseline; moderate: 5- to 10-fold elevation in CK above baseline; severe: 10-fold or greater elevation in CK above baseline or an absolute level of 10,000 U/L or more
E. Clinical rhabdomyolysis: Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of least 0.5 mg/dL [44 μM/L])

29-10. A patient in your practice cannot tolerate high-dose statin therapy. Which of the following statements is *not true* regarding alternatives for patients who are statin intolerant?

A. Efforts should be doubled to start and maintain lifestyle modification, which can lower cholesterol levels by 10% to 15%
B. Both bile acid resins and ezetimibe can lower LDL-C by 25% to 35%
C. Ezetimibe plus a moderate-intensity statin will reduce cholesterol levels as much as high-intensity statins
D. Fibrates and niacin are alternative add-on drugs for patients with hypertriglyceridemia
E. In patients with severe hypercholesterolemia, PCSK9 inhibitors may be an option for patients who are statin intolerant, especially in those with ASCVD or very high LDL-C levels

ANSWERS

29-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 29)* The basic structure of all lipoproteins is similar. They contain a core of neutral lipid (triglyceride and cholesterol ester) (option A) that is surrounded by a polar coat containing nonesterified cholesterol (option B), phospholipid (option C), and proteins (called apolipoproteins) (option D). The major categories of lipoproteins consist of low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), high-

density lipoprotein (HDL), and chylomicrons. These lipoproteins vary in size and density. Because lipoproteins can be separated by electrophoresis, they also have been named according to their migration relative to serum proteins. LDL is called beta lipoprotein, VLDL is pre-beta lipoprotein, and HDL is alpha lipoprotein.

29-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 29)* An elevated plasma LDL is designated a major risk factor for ASCVD. Several lines of evidence support a strong association: animal studies (option A), genetic forms of elevated LDL (option B), epidemiological associations (option C), and randomized controlled trials (RCTs) of LDL-lowering therapies (option D).

29-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Steps in the progression of atherosclerosis have been studied in detail. Accumulation of large numbers of foam cells gives rise to fatty streaks (option A). Some foam cells die and release their cholesterol esters into the interstitium, and over time the core of extracellular lipid expands (option B). Later, smooth muscle cells *(not osteoclasts)* from the medium begin to produce fibrous connective tissue (option C). This tissue forms a covering for the fatty streak; here the lesion is called a fibrous plaque (fibroatheroma) (option D). Continuous filtration of LDL into the arterial wall leads to several steps to plaque progression (option E); after many years, atheromas degenerate into complicated lesions, become unstable, and are prone to rupture. When rupture occurs, plaque material discharges into the lumen of the artery, producing thrombosis and cardiovascular events. At any stage of this process, LDL-lowering therapy reduces plaque progression and decreases the likelihood of plaque rupture and acute ASCVD events.

29-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Classic estimates were that heterozygous FH occurs in about one in 500 persons; homozygous FH occurs only one in a million persons (option A). In some populations, the prevalence of both forms can be higher. Patients with heterozygous FH commonly develop premature ASCVD, most often between the ages of 30 and 60 years, and estimates are that it accounts for at least 2% of premature MIs. Homozygous FH leads to very premature disease, often in the teens or earlier (option B). Another clinical feature of FH is the presence of cholesterol deposition in tendons (xanthomas) of the hands, elbows, knees, and feet, especially the Achilles tendon (option C). Deposition of cholesterol in the skin about the eyes is called xanthelasma (option D); in individuals with hypercholesterolemia, this finding suggests but is not pathognomonic of FH (option E). The same is true for corneal arcus.

29-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Obesity in the general population is associated with an increased risk of ASCVD and other disorders. Among the latter are hypertensive cardiovascular disease, type 2 diabetes, fatty liver disease, gallstone disease, obstructive sleep apnea, and certain forms of cancer (colon, breast, and endometrial). Excess body weight can be defined as *overweight* (BMI 25 to 29 kg/m^2) (*not BMI 25-30 kg/m^2*) and *obesity* (BMI ≥ 30 kg/m^2) (*not BMI > 30 kg/m^2*) (option A). According to the Centers for Disease Control and Prevention (CDC), more than one-third (34.9% or 78.6 million) of US adults are obese (option B). In addition, more than one-third of American adults (35.7%) and 17% (12.5 million) of American children and teens are clinically obese (option C). The CDC notes that non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%), followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%) (option D). Moreover, obesity is higher among middle-aged adults (ages 40 to 59 years; 39.5%) than among younger adults (ages 20 to 39 years; 30.3%) or older adults (≥ age 60 years; 35.4%) (option E).

29-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. A clinical diagnosis of the metabolic syndrome can be made in accord with a clinical definition.[1] The risk factors of this definition include increased blood pressure (option A), dyslipidemia (increased triglycerides and lowered HDL-C) (option B), increased fasting glucose (option C), and abdominal obesity (increased waist circumference) (option D). This diagnosis harmonized previous recommendations from the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute. Any three of five abnormal findings constitute a diagnosis of the metabolic syndrome. A single set of cut points is used for all components *except waist circumference, for which different national or regional thresholds for waist increased circumference were recommended* (option E).

29-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Monoclonal antibody inhibitors of PCSK9 are a new class of LDL-lowering drugs. They bind PCSK9 from the circulation and thereby prevent the action of PCSK9 to promote the degradation of LDL receptors (option A).[2,3] As a result, more *(not fewer)* LDLRs are expressed by the liver, and serum LDL-C levels are reduced (option B).[4,5] US Food and Drug Administration (FDA)–approved PCSK9 inhibitors are evolocumab[4,5] and alirocumab (option C).[6] Another agent (bococizumab) is under investigation. These drugs must be given systemically once or twice a month. They cause marked incremental reductions of LDL-C even when given with statins (option D). To date, they appear to be safe and have not been reported to cause myopathy (option E). Interim reports from randomized controlled trials (RCTs) indicate that they enhance risk reduction in high-risk patients treated with statins.[7,8] Meta-analysis of several smaller trials further suggests ASCVD benefit.[9]

29-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. CETP inhibitors inhibit CETP.[10] The protein transfers cholesterol ester from HDL-C to very-low-density or low-density lipoproteins (VLDL or LDL). As a result, HDL-C levels are increased, whereas VLDL-C and LDL-C are decreased (option A). This exchange theoretically could be beneficial by raising HDL-C, the so-called good cholesterol. However, to date three randomized controlled trials (RCTs) with CETP inhibitors have failed to show an ASCVD risk reduction (option B). One inhibitor, torcetrapib, gave an

increase in total mortality, and the trial was discontinued (option C).[11] Trials with two other CETP inhibitors, dalcetrapib and evacetrapib, were discontinued before completion because of futility (option D).[12]

29-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Although the main concern with statins is the risk of rhabdomyolysis, this is a rare occurrence that affects 0.1% of patients.[13,14] Terminology relating to statin-associated adverse muscle events is variable and has changed over time. According to the 2014 National Lipid Association Statin Muscle Safety Task Force:[13] Myalgia: A symptom of muscle discomfort, including muscle aches, soreness, stiffness, tenderness, or cramps with or soon after exercise, with a normal creatine kinase (CK) level. Myalgia symptoms can be described as flu-like symptoms (option A). Myopathy: Muscle weakness (not due to pain), with or without an elevation in CK level (option B). Myositis: Muscle inflammation (option C). Myonecrosis: Elevation in muscle enzymes compared with either baseline CK levels (while not on statin therapy) or the upper limit of normal that has been adjusted for age, race, and sex: *Mild: 3- to 10-fold elevation in CK above baseline; Moderate: 10- to 50-fold elevation in CK above baseline; Severe: 50-fold or greater elevation in CK above baseline or an absolute level of 10,000 U/L or more* (option D). Clinical rhabdomyolysis: Myonecrosis with myoglobinuria or acute renal failure (an increase in serum creatinine of least 0.5 mg/dL [44 μM/L]) (option E).

29-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 29)*. Statins are first-line cholesterol-lowering therapy, but if they are not tolerated, other ways to achieve cholesterol goals can be considered. Efforts should be doubled to start and maintain lifestyle modification, which can lower cholesterol levels by 10% to 15% (option A).[15] Both bile acid resins and ezetimibe can lower LDL-C by 15% to 25% *(not 25% to 35%)* (option B). Ezetimibe plus a moderate-intensity statin will reduce cholesterol levels as much as high-intensity statins (option C). Fibrates and niacin are alternative add-on drugs for patients with hypertriglyceridemia (option D). Finally, in patients with severe hypercholesterolemia, PCSK9 inhibitors may be an option for patients who are statin intolerant, especially in those with ASCVD or very high LDL-C levels (option E).

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SECTION 6

Cigarette Smoking and Cardiovascular Disease

CHAPTER 30

Epidemiology of Smoking and Pathophysiology of Cardiovascular Damage

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

30-1. At its peak in the 1960s, what proportion of the United States population consumed cigarettes?

A. 35%
B. 45%
C. 55%
D. 65%
E. 75%

30-2. What proportion of the world's 1 billion smokers are male?

A. 50%
B. 60%
C. 70%
D. 80%
E. 90%

30-3. Which of the following statements concerning smoking prevalence and trends in the United States is *false*?

A. The prevalence of smoking among adults in the US decreased by 25% between 1998 and 2013
B. Smoking among US high school students decreased by > 50% between 1997 and 2013
C. A larger proportion of adults 20 to 49 years of age smoke compared to adults age 50 and older
D. Hispanic men are almost twice as likely to smoke as Hispanic women
E. All of the above are true

30-4. By approximately how many years does smoking throughout adulthood reduce life expectancy?

A. 2 years
B. 5 years
C. 7 years
D. 10 years
E. 12 years

30-5. Which of the following statements concerning smoking and cardiovascular disease is *false*?

A. Smoking increases the risk of peripheral arterial disease and abdominal aortic aneurysm by fivefold
B. Smoking increases the risk of ischemic heart disease and stroke by threefold
C. There is a linear and independent relationship between smoking duration and intensity and increasing arterial stiffness
D. Only three constituents of cigarette smoking have been shown to play a role in the initiation and progression of cardiovascular disease: nicotine, carbon monoxide, and reactive oxygen species
E. Cigarette smoking disrupts cardiovascular homeostasis, leading to hemodynamic changes, endothelial dysfunction, inflammation, thrombosis and plaque progression, and abnormalities in lipid and glucose metabolism

30-6. Which of the following statements concerning the effects of cigarette smoking is *false*?

A. Nicotine consumption results in acute, but not chronic, increases in heart rate up to 7 to 10 beats per minute, and elevation in systolic blood pressure up to 5 to 10 mm Hg

B. A combination of nicotine-induced increased oxygen demands and carbon monoxide-associated reduced oxygen availability may lower the threshold for angina onset in smokers
C. The primary mechanism by which smoking leads to vascular and endothelial dysfunction is thought to be suppression of endothelial nitric oxide synthase (eNOS) expression and subsequent decreased bioavailability of NO caused by oxidant chemicals from cigarette smoke
D. Cigarette smoking promotes a prothrombotic state through alterations in platelet activity as well as antithrombotic and prothrombotic factors, including fibrinolytic factors and platelet-mediated pathways
E. Chronic vascular inflammation mediated by cigarette smoking may play an important role in the progression of atherosclerosis

30-7. Smokers are how much more likely to have diabetes than individuals who have never smoked?

A. 0% (incidence of diabetes is not affected by smoking)
B. 25%
C. 45%
D. 65%
E. 100%

30-8. Which of the following statements concerning electronic cigarettes (e-cigarettes) is *false*?

A. There are currently no results from appropriately powered randomized controlled trials examining e-cigarettes for smoking cessation
B. Studies looking at the long-term safety of e-cigarettes are lacking
C. Population-based studies suggest e-cigarette use is associated with 28% lower odds of quitting compared to nonusers
D. The use of e-cigarettes by youth is increasing
E. E-cigarettes are marketed for therapeutic purposes in the United States

30-9. Which of the following statements concerning smoking cessation in cardiovascular patients is *false*?

A. Smokers with myocardial infarction are more likely to quit than similar patients undergoing percutaneous coronary intervention (PCI) who did not present with myocardial infarction
B. Patients with cardiovascular disease who continue to smoke have nearly double the risk of death, myocardial infarction, or stroke compared to patients who quit
C. Patients who quit smoking after PCI have fewer anginal episodes within the first year than patients who continue to smoke
D. Only one in three smokers hospitalized with acute coronary syndrome (ACS) remains abstinent following discharge
E. Varenicline does not increase abstinence following ACS

30-10. What public health intervention has had the largest impact on cigarette consumption?

A. Taxation of tobacco
B. Restrictions on tobacco advertisements
C. Policies to reduce exposure to secondhand smoke
D. Graphic warnings on cigarette packs
E. Public quitlines

ANSWERS

30-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Although the Surgeon General's report in 1957 concluded that cigarette smoking is associated with an increased risk of lung cancer, it was not until publication of the landmark 1964 Surgeon General's report that the adverse relationship between cigarette smoking and cardiovascular disease was seriously recognized. The Surgeon General's report concluded that cigarette smoking is strongly associated with myocardial infarction and coronary heart disease deaths, and it laid the foundation for tobacco control.[1] Unfortunately, health care providers, professional societies, civic bodies, and governments have also played negative or timid roles, largely attributed to the smoking industry's exploitation of the natural skepticism and probabilistic nature inherent in scientific evidence, serious conflicts of interest, and lack of a strong public will. Smoking has claimed more than 20 million lives with premature deaths in the United States alone since the publication of the 1964 report. The annual per capita cigarette consumption in the United States was at its peak in the early 1960s, with a prevalence smoking of about 45% of the population in 1965 (option B). Through concerted efforts over more than half a century, the cigarette consumption in the United States has declined to half of its peak prevalence rates—to about 18% in 2012.[2] Multiple factors, including an improved understanding of the adverse effects of secondhand smoke, policy measures such as a ban on broadcast advertising, increased public awareness, and the increase in cigarette taxes have contributed to this epidemiological transition. Despite years of progress, cigarette smoking remains the leading cause of preventable

cardiovascular morbidity and mortality across the globe.

30-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Globally, about 1 billion individuals smoke. The majority (about 800 million) are males (80%, option D). Although the prevalence of smoking has declined over the past few decades, the total number of smokers has increased globally owing to population growth. The worldwide prevalence of smoking is highly variable by country and region, suggesting a heavy influence of socioeconomic and cultural currents as well as national policies. In 2012, the prevalence of smoking among adults was 49% in eastern Europe, 45% in China, 36% in Japan, 28% in western Europe, 23% in India, and about 18% in Australia, the United States, and Canada.[3] When considering differences by age groups, the highest prevalence of smoking worldwide in 2012 was seen in males aged 44 to 49 (41% prevalence) and females aged 50 to 54 (8.7% prevalence). There is a disproportionately high burden of smoking among males compared to females in countries such as China and India. This is also reflected in the recent estimates of deaths attributable to smoking in China; of the nearly 1 million deaths in 2010, 840,000 were among males in contrast to 130,000 among females.[4] A high burden of smoking among adolescents and young adults (more than 150 million smokers were 25 years or younger) remains a major concern and challenge.[3] During 2012, the prevalence of smoking among 20- to 24-year-old males was above 50% in eastern Europe, Russia, and Indonesia, 41% in China, 37% in Japan, 28% in Latin America, 24% in Pakistan, 21% in Australia, 19% in Canada and the United States, and 13% in India.

30-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 30)* According to the Behavioral Risk Factor Surveillance System (BRFSS) survey, the prevalence of smoking among US adults has declined by 25%, with only 17.9% smokers in 2013 as compared to 24.1% smokers in 1998 (option A).[5] A larger change in smoking prevalence has been seen among US high school students: 15.7% in 2013 compared to 36.4% in 1997 (option B). There are important differences in the smoking prevalence by states and regions in the United States. Similarly, US population-based survey data (National Health and Nutrition Examination Survey [NHANES]) for 2011–2012 showed a much higher smoking prevalence among people 20 to 49 years of age (23.1%) compared to those 50 years of age and older (16.3%) (option C).[5] There is significant heterogeneity in smoking prevalence by race/ethnicity and gender. The smoking rate among Hispanic men (16%) is almost two times higher than it is among Hispanic women (8.3%) (option D).

30-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 30)* A loss of about a decade of life expectancy is estimated because of smoking throughout adulthood among both men and women in various countries, including the United Kingdom, the United States, Japan, and India (option D).[6] Importantly, people who have smoked cigarettes since early adulthood but stopped at 30, 40, or 50 years of age gain back 10, 9, and 6 years of life expectancy, respectively.[6] About 5 to 6 million yearly deaths worldwide and about 0.5 million in the United States are attributable to cigarette smoking each year. This estimate is projected to increase to more than 10 million in a few decades.[6,7] In 1990, smoking was the third-ranked risk factor after childhood malnutrition and indoor pollution from biofuels for loss of disability-adjusted life years (ie, sum of years of life lost and years lived with disability [DALY]). With improvements in nutrition and clean fuel availability, in 2010, it has become the second most common contributor to loss of DALYs (6.3%; 95% confidence interval, 6.2 to 7.7).[8] Smoking is the highest contributor to loss of DALYs in males worldwide and in both males and females in many developing countries. The US societal costs of cigarette smoking per year are around $289 billion; this includes about $151 billion in lost productivity caused by premature deaths and remaining as direct health care costs.[5]

30-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Smoking has been associated with increased and accelerated atherosclerosis and acute plaque rupture and all cardiovascular end points, including myocardial infarction, stroke, and peripheral arterial disease.[9] While smoking causes incremental and independent risk with other risk factors such as hypertension and diabetes on coronary and cerebral vasculature, its prominent role in peripheral vasculature and small-vessel disease has been appreciated: fivefold increased risk of peripheral arterial disease and abdominal aortic aneurysm (option A) compared to a 1.5- to 2-fold increased risk of ischemic heart disease and stroke (option B).[10] A linear and independent relationship of smoking duration and intensity has been reported, with an increase in arterial stiffness measured using brachial-ankle pulse wave velocity (option C).[11] Cigarette smoke is a mixture of more than 5000 toxic chemicals[12] and 1015 to 1017 free radicals.[13,14] It is conventionally divided into two chemically different phases: a tar phase and a gas phase.[15] The tar or particulate phase is material that is trapped when the smoke steam is passed through the glass-fiber (cigarette) filter. The cigarette filter retains 99.9% of all particles larger than 0.1 μm. Nicotine is a major chemical component of the particulate phase of cigarette smoke.[16] The gas (or vapor) phase consists of the material that passes through the cigarette filter.[16] The common chemical components of the gas phase include carbon monoxide (CO), acetaldehyde, formaldehyde, acrolein, nitrogen oxides, and carbon dioxide. Both phases are high in reactive oxygen species (ROS).[17] Despite the presence of many constituents in both phases, only three constituents (nicotine, CO, and ROS) have been shown to play a role in the initiation and progression of cardiovascular disease (option D).[18] The net effect of various endogenous chemicals from cigarette smoke, such as oxidative free radicals and nicotine, together with inflammatory molecules and endogenous-produced ROS released by activated inflammatory cells, is disruption of cardiovascular homeostasis, leading to hemodynamic changes, endothelial dysfunction, inflammation, thrombosis and plaque progression, and abnormalities in lipid and glucose metabolism (option E).[14]

30-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Via sympathetic stimulation, nicotine leads to an increase in cardiac contractility, acute and chronic increase in heart rate up to 7 to 10 beats per minute,[19] and elevation in systolic

blood pressure up to 5 to 10 mm Hg from baseline (option A).[18] Carbon monoxide (CO) is another component of cigarette smoke that has been implicated in cigarette smoke-induced hemodynamic changes. By binding to hemoglobin, CO reduces the oxygen-carrying capacity of hemoglobin, resulting in relative hypoxemia and subsequent dilation of coronary arteries.[20] A combination of nicotine-induced increased oxygen demands on one side and CO-associated reduced oxygen availability on the other side may lower the threshold for angina onset in smokers (option B).[21] Cigarette smoking-induced endothelial dysfunction is an important factor in coronary hemodynamic disturbances and the progression of atherosclerosis. The primary mechanism by which smoking leads to vascular and endothelial dysfunction is thought to be suppression of eNOS expression and subsequent decreased bioavailability of NO caused by oxidant chemicals from cigarette smoke (option C).[22] Cigarette smoking has also been shown to promote a prothrombotic state through several mechanisms. These mechanisms include alterations in platelet activity as well as alterations in antithrombotic and prothrombotic factors, including fibrinolytic factors and platelet-mediated pathways (option D).[15,23] Chronic vascular inflammation mediated by cigarette smoking may play an important role in the progression of atherosclerosis (option E).[24] The exact molecular-pathogenic mechanisms by which smoking induces vascular inflammation are not completely established. Nonetheless, the role of several proinflammatory cytokines as well as activation and interaction between leukocytes and endothelial cells is well recognized in this process.

30-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Cigarette smoking increases the risk of development of diabetes mellitus type 2.[25] A dose-response relationship has been found between the smoking and the incidence of diabetes mellitus in both men and women.[26] Data from the Cancer Prevention Study have shown that there is a 45% higher diabetes rate among smokers than among men who had never smoked (option C). Higher levels of HbA1C have been found in smokers with diabetes than in nonsmokers with diabetes. Smoking also increases requirements for insulin and causes insulin resistance in nondiabetics.[27] Studies have also shown an increased risk of microvascular complications of diabetes such as diabetic neuropathy and faster progression of renal disease.[28] There has been a debate about whether possible weight gain associated with quitting smoking is associated with increased risk, too.[29] Although confounding in observational studies makes it difficult to test this relationship further, the increased risk of weight gain after cessation ameliorates with the duration of smoking cessation.[29] The pathogenesis of smoking and glucose metabolism is not well understood, but nicotine appears to have a central role in this process.[14,30] Nicotine stimulates cathecholamine release from the adrenal medulla and sympathetic nervous system, which may lead to insulin resistance. It also increases the release of corticosteroids, which are known hyperglycemic hormones.[18]

30-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 30)* Invented in the early 2000s by a Chinese pharmaceutical company and patented in 2004, e-cigarettes deliver a nicotine-containing vapor when a solution of nicotine with humectant solution (glycerol or propylene glycol) and flavoring is heated by a battery-powered atomizer. Currently, there are no appropriately powered randomized controlled trials with e-cigarettes to examine their efficacy in smoking cessation (option A).[31] Also, studies looking at the long-term safety of e-cigarettes are lacking (option B). When using population-based studies of smoking cessation in the absence of good randomized controlled trials, e-cigarette users are associated with 28% lower relative odds of quitting compared to nonusers (option C).[32] There are growing concerns about their use due to the absence of studies showing either safety or efficacy. For instance, among high school students, the use of e-cigarettes tripled in 2014 to 2 million (13.4%) from 0.67 million (4.5%) in 2013 (option D).[33] Because of a lack of evidence supporting the safety or efficacy of e-cigarettes at this time, e-cigarette companies cannot advertise them as an alternative for smoking cessation or for therapeutic purposes in the United States (option E).

30-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 30)* In a retrospective analysis of over 2000 patients who underwent percutaneous coronary intervention (PCI) from 1999 to 2009 at Olmsted County, Minnesota, smoking cessation rates at 6 to 12 months were around 50% and did not change over a decade.[34] The odds of cessation were 2.6 times higher among those who had presented with myocardial infarction (option A) and three times among those who participated in cardiac rehabilitation, and cessation was associated with better prognosis.[34] Similarly, a cessation rate of about 60% was seen in Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial participants, and those who continued to smoke had a 1.8 times higher risk of death, myocardial infarction, or stroke compared to those who had quit (option B).[35] Smokers have worse outcomes than nonsmokers after PCI, and those who quit smoking after PCI had fewer anginal episodes at 1-year follow-up than those who continued (option C).[36] It is a big challenge and a big opportunity for us that less than one in three of the current smokers hospitalized with acute coronary syndrome (ACS) remains abstinent following discharge (option D). In a recent study of patients presenting with ACS, varenicline was associated with an abstinence rate of 47.3% versus 32.5% in the placebo group at 6 months (option E).[37]

30-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 30)* The most common and successful step that has been used to reduce tobacco consumption is excise taxes (option A). About a 20% decrease in cigarette consumption has been reported with a 50% increase in inflation-adjusted tobacco price.[38] Tobacco taxes have proven to be more effective among younger adults, and among poor or less educated groups.[6] However, a rapid growth in income and purchasing power parity in developing countries, and the availability of low-priced alternatives such as "bidis," is a challenge. The lower excise tax in the low-income countries makes cigarettes cheaper than in developed countries. Additionally, organized smuggling of cigarettes after excise taxes are raised remains another challenge that will require stricter tax administration.[6] Profits from tobacco manufacturing exceeded 50 billion US dollars in 2012,[39] and beyond the industry's

lobbying effort for keeping a check on excise taxes, the major portal for more than half a century has been the influence and use of mass media. Although a complete or partial ban on tobacco advertisements remains a strong tool to reduce smoking rates, comprehensive bans may be needed to prevent the tobacco industry from using advertising media (option B).[6] Legislative developments to protect people from secondhand smoke (option C), research to continue to study the influence of various interventions to reduce smoking rates, and understanding the counterforces, such as smoking industry activities and human behavior, will be important. Other interventions, such as graphic warnings on cigarette packs (option D) and public quitlines (option E), have been used to reduce tobacco consumption.

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CHAPTER 31

Preventing and Mitigating Smoking-Related Heart Disease

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

31-1. What percentage of smokers interested in quitting are reported to have received tobacco cessation medication during outpatient physician office visits?

A. 69%
B. 50%
C. 21%
D. 8%
E. 75%

31-2. Which of the following statements about the cardiovascular benefits of smoking cessation is *false*?

A. In one year following smoking cessation, half the excess risk of a myocardial infarction is gone
B. Smoking cessation before the age of 30 years eliminates nearly all the risk of death from smoking-related disease
C. The risk of cardiac events drops approximately one month after quitting smoking
D. Those who quit when they are older gain years of life compared to those who continue to smoke
E. The risk of myocardial infarction and other cardiac events drops 15% to 20% by a month after implementing comprehensive smoke-free laws to protect people from secondhand smoke

31-3. Which of the following statements is *not* included within the US Public Health Service "5As" model for smoking cessation intervention and screening for tobacco use?

A. *Advocate* for patients who wish to quit smoking
B. *Advise* tobacco users to quit
C. *Arrange* for follow-up to monitor progress
D. *Assist* patients interested in quitting with counseling and/or pharmacotherapy
E. *Assess* patient interest in and willingness to quit

31-4. A 52-year-old female smoker presents to your clinic and expresses her desire to quit smoking. Which of the following treatment options should *not* be recommended to your patient as a first-line therapy for smoking cessation?

A. Nicotine patch
B. Electronic cigarette
C. Varenicline
D. Bupropion
E. Nicotine inhaler

31-5. A 43-year-old male smoker expresses his desire to quit smoking. He says he has previously tried to quit cold turkey but was unable to abstain from smoking in the long run. What is the maximum recommended duration of nicotine replacement therapy (NRT) use?

A. 8 weeks
B. 10 weeks
C. 12 weeks
D. 24 weeks
E. 52 weeks

31-6. Which of the following interventions has *not* been associated with long-term smoking cessation compared with sham interventions?

A. Motivational interviewing
B. Printed self-help materials
C. Acupuncture
D. Telephone counseling
E. Mobile phone-based interventions

31-7. A smoker with two previous quit attempts is interested in combining NRT with a second form of pharmacotherapy. Which of the following statements about combination therapy is *correct*?

A. Treatment with a combination of long-acting and short-acting NRT is not associated with increased smoking cessation when compared to a single type of NRT
B. Varenicline combined with NRT is associated with higher tobacco abstinence at 12 weeks and 6 months compared to varenicline alone
C. Participants receiving combination therapy do not report more anxiety and depressive symptoms
D. Combination of bupropion and NRT treatment is associated with a significant difference in smoking cessation compared to NRT alone
E. There is no evidence that combination therapy is effective for smoking cessation

31-8. A 30-year-old man who self-identifies as a social smoker (5 or fewer cigarettes per day) presents to your clinic for an unrelated clinical concern. He is unbothered by his smoking, which he does *not* feel compelled to reduce due to his already low number of cigarettes smoked per day. Which of the following statements about the health effects of smoking reduction is *true*?

A. The dose-response relationship between smoking and cardiovascular disease is highly linear
B. Smoking reduction has not been associated with improved levels of biomarkers associated with cardiovascular disease in some studies
C. Smoking as few as five cigarettes a day is associated with a higher risk of death from ischemic heart disease
D. Cigarette smoking at low levels is not associated with an increased risk of cardiovascular disease
E. Complete cessation should not be encouraged in all patients

31-9. The World Health Organization's Framework Convention on Tobacco Control (FCTC) emphasizes the importance of promoting public health through the implementation of policies, including which of the following?

A. Smoke-free environments to protect people from secondhand smoke and to provide an environment that helps people stop smoking
B. Elimination of tobacco advertising and promotion
C. Increased taxes to reduce demand for cigarettes
D. Education of the public on the risks of smoking, such as with large graphic warning labels on tobacco products
E. All of the above

31-10. A 21-year-old smoker is interested in finding alternatives to cigarette smoking and asks about using electronic cigarettes (e-cigarettes) to help him quit smoking. Which of the following statements about e-cigarettes is *false*?

A. E-cigarettes are relatively new products, so their long-term health effects are unknown
B. As of January 2016, e-cigarettes were regulated by the FDA
C. As currently being used in the real world, e-cigarettes are associated with significantly less quitting than NRT or no cessation aids
D. E-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that they assist in smoking cessation
E. Use of e-cigarettes by patients may signal readiness to quit cigarettes, and thus clinicians should be prepared to support patients in their quit attempts

ANSWERS

31-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 31)* Even though 69% of smokers are interested in quitting (option A) and over half report having made a quit attempt in the past year (option B),[1] only 21% of adult current tobacco users received tobacco cessation counseling (option C) and 8% received tobacco cessation medication during outpatient visits (option D).[2] Screening for interest in tobacco cessation is particularly important because physician advice to quit smoking is associated with increased smoking cessation compared to no advice to quit or usual care, with higher cessation seen with more intensive advice compared to minimal advice.[3] It is important that screening be incorporated into all clinical encounters, including those with cardiologists and other specialists, not only to identify and assist patients who are ready to stop smoking, but also to encourage those who are not yet ready to move toward making

the decision to quit.

31-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 31)* In addition to contributing to the long-term development of atherosclerosis, smoking (and secondhand smoke exposure) has immediate effects (within minutes) on endothelial function[4,5] and platelet activation[6] and so can trigger a cardiac event. The risk of cardiac events begins to drop immediately after quitting and declines rapidly (option C). The heart rate drops 20 minutes after quitting, and in a year, half the excess risk of a myocardial infarction is gone (option A). The risk of myocardial infarction and other cardiac events drops 15% to 20% by a month after implementing comprehensive smoke-free laws to protect people from secondhand smoke (option E).[7,8] Smoking cessation before the age of 30 years eliminates nearly all of the risk of death from smoking-related disease (option B), and even those who quit when they are older gain years of life compared to those who continue to smoke (option D).[4] This fact highlights both the importance of encouraging smokers to quit early and the importance of encouraging all smokers to quit, no matter how old they are.

31-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 31)* The US Public Health Service recommends the 5As model for smoking cessation intervention, in which providers (1) *ask* patients about tobacco use to identify current users, (2) *advise* tobacco users to quit (option B), (3) *assess* patient interest in and willingness to quit (option E), (4) *assist* patients interested in quitting with counseling and/or pharmacotherapy (option D), and (5) *arrange* for follow-up to monitor progress (option C). Although current smokers report high rates of being asked about tobacco use (88%), fewer report being advised to quit (66%), and even fewer report being asked if they wanted to quit (43%).[9] If smokers are not properly identified, those interested in cessation cannot be connected with resources that can help them with their quit attempt. Therefore, screening should be incorporated into all outpatient and hospital encounters.

31-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 31)* Various prescription and nonprescription medications approved by the US Food and Drug Administration (FDA) are available to help patients in their attempt to quit, provided patients do not have contraindications to their use.[10] Nicotine replacement therapy, which provides patients with nicotine to manage cravings and nicotine withdrawal symptoms, comes in a variety of forms. Types of NRT include patches (option A), lozenges, inhalers (option E), and nasal sprays. FDA-approved medications include NRT, varenicline (option C), and bupropion (option D). They are all first-line treatments for smoking cessation, and the choice of agent should take into consideration patient preferences, medical comorbidities, and potential drug-drug interactions.

31-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 31)* With respect to treatment duration, a randomized clinical trial of different durations of nicotine patch treatment (8, 24, or 52 weeks) found higher rates of smoking abstinence at 24 weeks in those still using nicotine patches, but no significant difference was seen at 52 weeks.[11] This result suggests that, while nicotine patch treatment can continue longer than 8 to 10 weeks (options A and B), evidence does not support extending treatment past 24 weeks (option D). For the timing of treatment initiation, there is some evidence that starting nicotine patches prior to a patient's quit day is associated with increased smoking cessation compared to starting after the quit day. However, no difference was seen with nicotine gum or lozenges.[12] Thus, it is not necessary to wait until the quit date to initiate treatment with nicotine patches. It is important to note that, while clinical trials have demonstrated the efficacy of NRT when used as part of an organized cessation effort, unsupervised NRT bought over the counter is associated with significantly less quitting than the use of no smoking cessation aids (odds ratio [OR] 0.68, confidence interval [CI] 0.49–0.94).[13] Thus, patients using NRT should be followed and encouraged to maintain their quit attempt. Such combinations of counseling and NRT can be accomplished through telephone quitlines, which also provide certain types of NRT to eligible callers.

31-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 31)* Counseling delivered by telephone (option D), either through telephone quitlines or other sources, is associated with smoking cessation,[14] as are some mobile phone-based interventions (option E),[15] printed self-help materials (option B),[16] and interactive, tailored Internet-based interventions.[17] Motivational interviewing, which consists of counseling to improve one's motivation for and interest in behavioral change, has also been associated with increased smoking cessation compared to brief advice or usual care.[18] In people using pharmacotherapy for smoking cessation, the addition of behavioral support through in-person or telephone contact is also associated with increased smoking cessation compared to control groups.[19] Assistance via telephone is available from state telephone quitlines toll-free at 1-800-QUIT-NOW (1-800-784-8669). Support through text messaging can also be found through the National Cancer Institute's Smokefree TXT program, which is available at smokefree.gov/smokefreetxt, or by texting the word QUIT to 47848 from a mobile phone. Acupuncture, acupressure, or laser therapy has not been associated with long-term smoking cessation compared with sham interventions.[20]

31-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 31)* Treatment with a combination of long-acting and short-acting NRT is associated with increased smoking cessation compared to a single type of NRT (option A).[12] A randomized controlled trial found that varenicline combined with NRT was associated with higher tobacco abstinence at 12 weeks and 6 months compared to varenicline alone (option B).[21] Another randomized controlled trial found that treatment with both varenicline and bupropion for 12 weeks was associated with significantly greater smoking cessation than treatment with varenicline alone at 12 weeks (OR 1.49, 95% CI 1.05–2.12) and 26 weeks (OR 1.52, 95% CI 1.04–2.22)—but not at 52 weeks (OR, 1.32, 95% CI 0.91–1.91).[22] Participants receiving combination therapy, however, reported more anxiety and depressive symptoms (option C). Combination bupropion and NRT treatment is not associated

with a significant difference in smoking cessation compared to NRT alone (option D).[23] While combining different forms of NRT is a recommended, effective strategy for smoking cessation, combination of NRT with bupropion has not proven to be effective, and while combination varenicline and NRT has shown some promise of efficacy at 6 months, further studies on long-term efficacy and safety are needed.

31-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 31)* Cigarette smoking, even at low levels, is associated with an increased risk of cardiovascular disease.[24-26] The dose-response relationship between smoking and cardiovascular disease is highly nonlinear, with more rapid increases in risk at low levels of exposure and flattening of the curve at higher levels of exposure.[24] In fact, smoking as few as five cigarettes a day is associated with a higher risk of death from ischemic heart disease.[26] Smoking a few cigarettes a day should not be promoted as a long-term use pattern, and complete cessation should be encouraged in all patients. Smoking reduction has been associated with improved levels of biomarkers associated with cardiovascular disease in some studies,[27,28] but not in others.[29] It is not clear whether improvements in these biomarkers also result in improvements in the risk of smoking-related disease.

31-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 31)* There is great variability in the prevalence of cigarette smoking worldwide. The World Health Organization's Framework Convention on Tobacco Control (FCTC), the first global public health treaty, adopted in 2003 and implemented in 2005, emphasizes the importance of promoting public health through the implementation of policies, including smoke-free environments to protect people from secondhand smoke and to provide an environment that helps people stop smoking; elimination of tobacco advertising and promotion; increased taxes to reduce the demand for cigarettes; and education on the risks of smoking, such as with large graphic warning labels on tobacco products.[30] Although the FCTC has accelerated the implementation of smoke-free laws[31] and strong health warning labels,[32] only about half of nations report 100% smoke-free restaurants and even fewer smoke-free private workplaces.[33] As of 2016, the United States was one of the few countries that had not ratified the FCTC, and the United States lags behind the rest of the world in several areas, notably strong graphic warning labels on tobacco products, restrictions on advertising and promotion, and tobacco taxation. More comprehensive smoking laws are needed worldwide to ensure the maximum health benefits conferred to both smokers and nonsmokers by such tobacco control legislation.

31-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 31)* As of January 2016, e-cigarettes were not regulated by the FDA. E-cigarettes, a type of electronic nicotine delivery system, are battery-powered devices that heat a solution of humectants such as propylene glycol or glycerol, generally with nicotine and/or flavorings, to form an aerosol that is inhaled by the user. E-cigarettes are relatively new products, so their long-term health effects are unknown (option A). Although many smokers report using e-cigarettes to quit smoking, randomized controlled trials on their efficacy for smoking cessation have been limited, and their results have been equivocal.[34,35] As currently being used in the real world, e-cigarettes are associated with significantly less quitting than NRT or no cessation aids (option C).[36] Data from three studies[37-39] suggest that specific e-cigarette use patterns (daily use of high nicotine delivery devices, which represents the minority of users in these studies) may be associated with increased quitting; as e-cigarette product types and use patterns continue to evolve, this association should continue to be studied. Nevertheless, e-cigarettes should not be recommended as effective smoking cessation aids until there is evidence that, as promoted and used, they assist in smoking cessation (option D).[36,40] A policy statement by the American Heart Association in 2014 encourages the inclusion of e-cigarette use in tobacco screening questions.[41] Use of e-cigarettes by patients may signal readiness to quit cigarettes, and thus clinicians should be prepared to support patients in their quit attempts and to discuss evidence-based practices for smoking cessation, including counseling, NRT, or stop-smoking pharmacotherapy, with these patients (option E).[40]

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SECTION 7

Atherosclerosis and Coronary Heart Disease

CHAPTER 32

Atherothrombosis: Disease Burden, Activity, and Vulnerability

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

32-1. Which of the following statements is *not true*?

A. Causal and modifiable risk factors for atherosclerotic cardiovascular disease are well known but account for < 50% of heart attacks in both sexes
B. Individual susceptibility to conventional risk factors varies greatly, and therefore their predictive value is limited
C. Most first heart attacks occur among people with average or only slightly elevated risk factor levels
D. Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors
E. All of the statements are true

32-2. Which of the following statements is *not true*?

A. Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development
B. Atherosclerosis predominates at sites characterized by high and nonoscillatory endothelial shear stress
C. The speed of disease progression varies greatly, but it usually takes decades to develop the advanced atherosclerotic lesions responsible for clinical disease
D. Plaques are very heterogeneous in size and composition, even plaques located next to each other
E. Most plaques remain asymptomatic, some become obstructive, and a few, if any, become vulnerable

32-3. Which of the following statements is *not true*?

A. Approximately 50% of symptomatic coronary thrombi are caused by plaque rupture
B. Plaque rupture with mural thrombosis is also a common cause of episodic but asymptomatic progression to severe stenosis
C. Of the coronary thrombi not caused by plaque rupture, most are caused by plaque erosion
D. Plaque rupture is a more frequent cause of coronary thrombosis in men than in women
E. All of the statements are true

32-4. Which of the following are characteristics of vulnerable plaques of the erosion-prone type?

A. A plaque that contains a large and soft lipid-rich necrotic core
B. A necrotic core covered by a thin and inflamed fibrous cap
C. Big plaque size and expansive positive remodeling mitigating luminal obstruction
D. Neovascularization (angiogenesis), plaque hemorrhage, and adventitial inflammation
E. None of the above

32-5. Which of the following statements is *not true* regarding the fibrous cap in a fibroatheroma?

A. The fibrocellular part of the plaque located between the necrotic core and the lumen is called the fibrous cap
B. Assessed by microscopic examination postmortem, ruptured caps are typically < 65 μm thick
C. In thin-cap fibroatheroma (TCFA), the necrotic core occupies > 50% of plaque area
D. Thin fibrous caps are usually heavily inflamed, particularly those that have ruptured
E. Apoptosis is common at the site of fibrous cap rupture

32-6. The coronary heart disease (CHD) risk equivalent concept includes all of the following *except*:

A. Symptomatic disease in noncoronary arteries
B. Carotid stenosis of > 50%
C. Ankle-brachial blood pressure index < 0.8
D. Abdominal aortic aneurysm
E. Asymptomatic carotid bruit

32-7. Which of the following statements is *not true*?

A. The total amount of CAC (usually expressed as the *Agatston score*) is a strong predictor of coronary events and provides prognostic information beyond that provided by traditional risk factor scoring
B. Contrast-enhanced CT angiography visualizes not only the lumen but also the arterial wall
C. Intravascular ultrasound (IVUS) can detect and localize plaque as well as quantitate plaque burden, but it requires selective catheterization and motorized pullback in the arteries of interest
D. Serial examinations of well-defined coronary segments have been used to monitor the speed of plaque progression (or regression) over time in patients with established CHD
E. Most acute coronary events originate from angiographically obstructive plaques

32-8. Which of the following is *not* a common characteristic of the TCFA?

A. Large necrotic core
B. Inflamed fibrous cap
C. Uniform pattern of calcification
D. Expansive remodeling
E. Neovascularization

32-9. Which of the following statements is *not true* of coronary CT angiography?

A. Coronary CT may visualize the lumen and detect obstructive and nonobstructive plaques
B. Coronary CT may quantify calcified and noncalcified plaque burden
C. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by large plaque volume
D. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by high CT attenuation
E. Coronary CT may provide additional prognostic information by the detection of higher-risk plaques characterized by the napkin-ring sign and expansive remodeling

32-10. Which of the following catheter-based technologies may have potential for the assessment of coronary atherosclerosis and vulnerable plaques?

A. Conventional grayscale IVUS and virtual histology IVUS
B. Coherence tomography and angioscopy
C. Near-infrared spectroscopy
D. Intracoronary magnetic resonance imaging and thermography
E. All of the above

ANSWERS

32-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 32)* Causal and modifiable risk factors for atherosclerotic cardiovascular disease are well known (eg, smoking, dyslipidemia, high blood pressure, diabetes) and account for most *(not less than 50%)* of heart attacks in both sexes (option A).[1] However, for unknown reasons, the individual susceptibility to these risk factors varies greatly, and consequently, their predictive value is limited (option B).[2,3] Most first heart attacks occur among people with average or only slightly elevated risk factor levels (option C).[4-6] Recurrent events still occur despite lowering of these levels,[7,8] indicating that we need both better detection and better treatment of those who are destined for a heart attack. Better detection of at-risk individuals may be achieved by visualizing the diseased arterial wall rather than just assessing risk factors (option D).

32-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 32)* Atherosclerosis is a chronic, lipid-driven inflammatory disease of the arterial wall leading to multifocal plaque development (option A),[9-11] predominantly at sites characterized by low and oscillatory *(not high and nonoscillatory)* endothelial shear stress (bifurcations, inner wall of curvatures) and preexisting intimal thickenings (option B).[12,13] The speed of disease progression varies greatly, but it usually takes decades to develop the advanced atherosclerotic lesions responsible for clinical disease (option C). Plaques are very heterogeneous in size and composition, even plaques located next to each other and exposed for the same systemic risk

factors (option D). Most plaques remain asymptomatic (subclinical disease), some become obstructive (stable angina), and a few, if any, become vulnerable and lead to atherothrombotic events such as a fatal heart attack or a disabling stroke (option E).

32-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 32)* The great majority of symptomatic coronary thrombi (~75%) *(not approximately 50%)* are caused by *plaque rupture* (option A).[11] Plaque rupture with mural thrombosis (with or without plaque hemorrhage) is also a common cause of episodic but asymptomatic progression to severe stenosis (option B).[14,15] The remaining thrombi are caused by less well-defined mechanisms, of which so-called *plaque erosion* is the most common type (option C).[11] Plaque rupture is a more frequent cause of coronary thrombosis in men (~80%) than in women (~60%) but, except for sex and menopause, no other risk factors have consistently been connected with a particular mechanism of thrombosis (option D).[11] By inference, there are two major types of vulnerable plaques, rupture-prone and erosion-prone, that are presumed to look like the corresponding thrombosed plaques, just without rupture and thrombosis.[16]

32-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 32*) All of the listed characteristics are properties of rupture-prone rather than erosion-prone plaques (option E). Vulnerable plaques of the erosion-prone type are heterogeneous and defined only by their fate (thrombosis, mostly mural).[11,16] The surface endothelium is missing, but whether it vanished before or after thrombosis remains unknown. No distinct morphologic features have been identified, but in general, eroded plaques with thrombosis are scarcely calcified, rarely associated with expansive remodeling, and only sparsely inflamed.[11,16] So, irrespective of plaque type, it is a misconception that vulnerable plaques are heavily inflamed. In contrast with the erosion-prone plaque, the prototype of a presumed rupture-prone plaque contains a large and soft lipid-rich necrotic core covered by a thin and inflamed fibrous cap.[16,17] Associated features include big plaque size, expansive positive remodeling mitigating luminal obstruction (mild stenosis by angiography), neovascularization (angiogenesis), plaque hemorrhage, adventitial inflammation, and a *spotty* pattern of calcifications. Although the macrophage density in ruptured caps is high,[16,17] whole-plaque macrophage density rarely exceeds a small percent because ruptured caps are tiny.

32-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 32)* The fibrocellular part of the plaque located between the necrotic core and the lumen is called the *fibrous cap* (option A). It is extremely thin in coronary plaque rupture.[16,17] Assessed by microscopic examination postmortem, ruptured caps were usually < 65 μm thick (option B).[18] Assessed by optical coherence tomography in vivo, the mean thickness was only 49 μm.[19] If the fibrous cap is thin, the plaque is called a *thin-cap fibroatheroma* (TCFA).[18,20] In TCFA, the necrotic core occupies approximately 23% of plaque area *(not more than 50%)* (option C)**.**[20] Thin fibrous caps are usually heavily inflamed (macrophage density ~14%), particularly those that have ruptured (macrophage density ~26%) (option D),[20] but because they are thin, their ability to accommodate macrophages is limited. Apoptosis is common at the site of fibrous cap rupture, usually confined to macrophages because the vascular SMCs already have vanished when rupture occurs.[20,21] With their ability to synthesize extracellular matrix, including collagen, SMC apoptosis is associated with impaired healing and repair, increasing the risk of plaque rupture.

32-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 32)* Atherosclerosis is a generalized, multifocal arterial disease. However, compared with other arteries, the coronary arteries are in general the most susceptible to atherosclerosis and its thrombotic complications.[22,23] Therefore, if atherosclerosis is present in noncoronary arteries, the coronary arteries will usually also be diseased, irrespective of symptoms.[24] The CHD risk equivalent concept introduced in the previous prevention guidelines included symptomatic disease in noncoronary arteries (option A), carotid stenosis of > 50% (option B), ankle-brachial blood pressure index < 0.9 *(not 0.8)* (option C), and abdominal aortic aneurysm (option D).[25] Asymptomatic carotid bruit is also associated with high CHD risk (option E).[26,27]

32-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 32)* The number and severity of stenoses determined by coronary angiography are signs of atherosclerosis with diagnostic, therapeutic, and prognostic implications.[28-30] However, most acute coronary events originate from angiographically nonobstructive *(not obstructive)* plaques (option E), probably because they are much more numerous.[17,16,31-34] An irregular lumen and/or filling defects indicating plaque disruption and/or thrombosis are associated with worse outcomes.[35] In contrast to coronary *luminography*, CAC detected by computed tomography (CT) imaging reveals the diseased arterial wall directly and correlates strongly with plaque burden.[36,37] The total amount of CAC (usually expressed as the *Agatston score*) is a strong predictor of coronary events and provides prognostic information beyond that provided by traditional risk factor scoring (option A).[38] Contrast-enhanced CT angiography visualizes not only the lumen but also the arterial wall (option B). Because the strong relationship between the CAC score and coronary events is mediated predominantly by coexisting noncalcified or less calcified vulnerable plaques, total or noncalcified plaque burden detected by CT angiography may prove to be an even better marker of risk than the CAC score.[39,40] Intravascular ultrasound (IVUS) can detect and localize plaque as well as quantitate plaque burden, but it requires selective catheterization and motorized pullback in the arteries of interest (option C). Serial examinations of well-defined coronary segments have been used to monitor the speed of plaque progression (or regression) over time in patients with established CHD (option D).[41]

32-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 32)* The TCFA has a distinct microstructure, including a large necrotic core (option A) covered by a thin and inflamed fibrous cap (option B), and other characteristic plaque features are common, such as a large, expansive remodeling (option D), neovascularization (angiogenesis) (option E), and a spotty *(not uniform)* pattern of calcification (option C).[16,17]

32-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 32)* Coronary CT angiography may not only visualize the lumen and detect obstructive and nonobstructive plaques (option A), it may also quantify calcified and noncalcified plaque burden (option B). Furthermore, coronary CT angiography may also provide additional prognostic information by the detection of higher-risk plaques characterized by large plaque volume (option C), low *(not high)* CT attenuation (option D), napkin-ring sign, expansive remodeling (option E), and spotty calcification.[42,43]

32-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 32*) Many catheter-based technologies have been developed or are under development for the assessment of coronary atherosclerosis and vulnerable plaques, including conventional grayscale IVUS, virtual histology IVUS (option A) and other ultrasound-based tissue characterization modalities, optical coherence tomography, angioscopy (option B), near-infrared spectroscopy (option C), intracoronary magnetic resonance imaging, thermography (option D), and vascular profiling.[44-47] Because vulnerable coronary plaques of the rupture-prone type (TCFA) are relatively large, not numerous, and often cluster proximally in the major coronary arteries, their detection in patients undergoing percutaneous coronary interventions might be feasible.[48]

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CHAPTER 33

Coronary Thrombosis: Local and Systemic Factors

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

33-1. Initial atherosclerotic lesions result from the accumulation of inflammatory cells and lipids in which part or layer of the arterial wall?

A. Arterial lumen
B. Intima
C. Media
D. Adventitia
E. All of the above

33-2. Which of the following factors contributes to the attenuation of the proatherogenic state and lesion progression?

A. Vascular cell adhesion molecule-1 (VCAM-1)
B. Matrix metalloproteinases (MMPs)
C. Elevated high-density lipoprotein (HDL)
D. Lipids at injury site
E. Interferon (IFN)-gamma

33-3. Which of the following statements about the coagulation cascade is *correct*?

A. Injury to vessel wall exposes subendothelial proteins such as collagen and von Willebrand factor (vWF) that can potently activate platelets
B. Activated factor Xa is responsible for cleaving fibrinogen to fibrin, which forms a stable hemostatic plug over the injury site
C. Vitamin K is crucial for *de novo* synthesis of four clotting factors, including prothrombin
D. Platelets play an important role in coagulation via their ability to upregulate DNA replication following binding of tissue factor to their surface receptor
E. Upon stimulation, intracellular calcium blocks platelet degranulation, thereby inhibiting platelet activation

33-4. Which of the following is an intrinsic mechanism developed to control coagulation reactions?

A. Hemodilution of coagulation factors
B. Proteolytic feedback by thrombin
C. Protein C
D. Fibrinolysis
E. All of the above

33-5. A 55-year-old female flight attendant with a history of hypertension and atrial fibrillation recently underwent coronary angioplasty, transient ischemic attack, and stenting in the setting of a troponin-positive acute coronary syndrome. Which antithrombotic therapy is recommended for this patient?

A. Aspirin and prasugrel
B. Aspirin and warfarin
C. Aspirin and clopidogrel and warfarin
D. Clopidogrel and warfarin
E. Warfarin alone

33-6. The P2Y and P2X receptors play an important role in platelet activation and thrombus formation. Which of the following statements about these receptors is *false*?

A. $P2Y_1$ is responsible for platelet shape change and calcium mobilization
B. $P2X_1$ is an ADP-gated calcium channel receptor involved in platelet shape change
C. $P2Y_{12}$ is responsible for the platelet aggregation response to ADP
D. $P2Y_1$ is responsible for TXA_2 generation
E. cAMP is an important signaling molecule downstream of $P2Y_{12}$ activation

33-7. Which of the following statements about atherosclerotic plaque neovascularization is *correct*?

A. Vasa vasorum in the intima spreads into the adventitia, where it prompts neovascularization and plaque growth
B. Neovascularization is responsible for stabilizing and strengthening atherosclerotic plaques
C. Promotion of plaque neovascularization is a potential therapeutic strategy to prevent plaque disruption
D. Leaky vasa vasorum in the intima results in macrophage infiltration and plaque destabilization
E. All of the above

33-8. The innate and acquired immune systems are important modulators of inflammation and atherosclerosis. Which of the following associations is *false*?

A. Monocytes and Ly6C/GR-1
B. Dendritic cells and CD4
C. Platelets and CD40L
D. T cells and CD8
E. Mast cell and histamine

33-9. A 60-year-old man is rushed to the emergency room after sustaining a myocardial infarction (MI) during strenuous exercise. What is the *most likely* explanation for this patient's coronary thrombosis?

A. An atherosclerotic plaque rupture led to exposure of subendothelial matrix elements and resulted in a persistent thrombotic occlusion and MI
B. The ruptured plaque had a very small atheromatous core, which increased plaque thrombogenicity and risk of MI
C. A residual mural thrombus resulted in a decreased shear rate, which facilitated the activation and deposition of platelets on the lesion
D. Lack of macrophages in the atherosclerotic plaque led to activation of MMPs that resulted in plaque disruption and thrombus formation
E. None of the above

33-10. A mother brings her 4-year-old daughter to the emergency room with a severe nosebleed. After careful examination and proper testing, she is diagnosed with von Willebrand disease, characterized by a missing or defective vWF. Given what is known about blood clotting, what step in the coagulation cascade is dysregulated in this disease?

A. Proteolytic cleavage of prothrombin to thrombin
B. Platelet degranulation
C. Binding of TF to factor VII
D. Platelet adhesion to injury site
E. Binding of ADP to $P2Y_1$ receptor

ANSWERS

33-1. The answer is B. *(Hurst's The Heart, 14th Edition, Chap. 33)* Atherosclerosis is a systemic disease involving the intima of large and medium-sized arteries that is characterized by intimal thickening caused by the accumulation of cells and lipids (option B).[1] However, secondary changes may occur in the underlying media (option C) and adventitia (option D), particularly in advanced disease stages. The early atherosclerotic lesions might progress without compromising the lumen because of compensatory vascular enlargement (Glagovian remodeling) (option A).[2] Importantly, the culprit lesions leading to acute coronary syndromes are usually mildly stenotic and therefore barely detected by angiography.[3] These high-risk, rupture-prone lesions usually have a large lipid core, a thin fibrous cap, and a high density of inflammatory cells.

33-2. The answer is C. *(Hurst's The Heart, 14th Edition, Chap. 33)* Inflammation is an important process that affects plaque progression, vulnerability, and subsequent thrombus formation. Inflammatory cells (monocyte/macrophages, T cells, and mast cells) present in the core and shoulder of atherosclerotic lesions release inflammatory cytokines and MMPs that affect each step of atherosclerosis from lesion formation, to progression, to disruption and ACS (option B). The circulating monocytes are recruited within the subendothelial space in response to the synthesis and exposure of adhesive proteins triggered by the early accumulation of lipids (option D). The internalized monocytes release inflammatory

mediators, such as netrin-1 and VCAM-1, that are responsible for their retention in the lesions (option A). Mast cells are proinflammatory through the release of histamine, leukotrienes, interleukin (IL)-6, and interferon (IFN)-gamma (option E). Attenuation of the proatherogenic state occurs through HDL-raising and may facilitate the efflux of the wall macrophages (option C).

33-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 33)* The coagulation cascade constitutes a series of molecules that interact with each other in a controlled manner to produce a rapid and amplified response to vessel wall injury. In the case of an atherosclerotic lesion, plaque rupture facilitates the interaction of the inner plaque components with the circulating blood.[4] At the site of vascular lesion, circulating von Willebrand factor (vWF) binds to the exposed collagen that subsequently binds to the glycoprotein (GP) Ib/IX receptor on the platelet membrane (option A). Tissue factor (TF), another plaque component, exhibits a potent activating effect on platelets and coagulation. Platelet activation triggers intracellular signaling via second messengers, such as calcium, that induce shape change and secretion of their granular contents (option E). While platelets are nucleated cells that are devoid of genomic DNA, they contain messenger RNA and have the ability to synthesize proteins following activation (option D). Some clotting factors, namely factors VII, IX, X, and prothrombin, require vitamin K to undergo a posttranslational modification necessary for their ability to bind cell membrane surfaces. Without vitamin K, these factors can be synthesized but will not participate in proper clotting reactions (option C). Finally, clotting factors must be enzymatically cleaved in order to become active. Activated factor Xa is responsible for cleaving prothrombin to thrombin, which can then cleave fibrinogen to fibrin to form the hemostatic plug over the injury site (option B).

33-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Several mechanisms exist to control and limit coagulation reactions and maintain hemostasis. Coagulation is normally restricted to the site of injury by hemodilution of clotting elements, thereby limiting the size of the platelet plug and washing away coagulation factors as blood flows (option A). Although thrombin plays a pivotal role in maintaining the complex balance of initial prothrombotic reparative events, it also controls the subsequent anticoagulant and fibrinolytic pathways through proteolytic feedback mechanisms (option B). Thrombin has a specific receptor in endothelial cell surfaces, thrombomodulin, which triggers a physiologic anticoagulation system. Thrombin generated at the site of injury binds to thrombomodulin, and the complex serves as a receptor for the vitamin K-dependent protein C, which is activated and released from the endothelial cell surface. Activated protein C then inactivates factors Va and VIIIa and limits thrombin effects (option C). Fibrinolysis, the enzymatic breakdown of the fibrin clots, involves catalytic activation of zymogens, positive and negative feedback control, and inhibitor blockade (option D). Blood clotting is blocked at the level of the prothrombinase complex by the physiologic anticoagulant-activated protein C. Activated protein C cleaves factor Va, rendering it functionally inactive, thereby blocking thrombin formation.

33-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Patients presenting with troponin-positive acute coronary syndromes should be considered for treatment with dual antiplatelet therapy to reduce the risk of ischemic complications, irrespective of whether an intracoronary artery stent was used in the management of the patient. Patients treated with intracoronary stenting particularly should receive dual antiplatelet therapy to reduce the risk of stent thrombosis (option A). In addition, oral anticoagulants such as warfarin or NOACs are considered as part of "triple therapy" when an indication for antithrombotic therapy is present (eg, atrial fibrillation, venous thromboembolic disease) (option B). Although such triple therapy increases bleeding risk, this is the current standard of care, although several ongoing clinical trials are examining alternative regimens (options C, D, and E).

33-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Great interest in the platelet ADP receptors (P2Y, P2X) has recently been generated because of available pharmacologic inhibitors. The $P2Y_1$ receptor is responsible for inositol trisphosphate formation through the activation of phospholipase C, leading to transient increase in the concentration of intracellular calcium, platelet shape change, and weak transient platelet aggregation (option A).[5,6] Pharmacologic data have also revealed an essential role for the $P2Y_1$ receptor in the initiation of platelet ADP-induced activation, TXA_2 generation, and platelet activation in response to other agonists (option D). The $P2Y_{12}$ receptor is responsible for completion of the platelet aggregation response to ADP (option C), and it has several important downstream signaling molecules, including cAMP (option E). Pharmacologic approaches have shown a role for the $P2Y_{12}$ receptor in dense granule secretion, fibrinogen-receptor activation, P-selectin expression, and thrombus formation. Although not activated by ADP, platelets possess a third purinergic receptor ($P2X_1$), which is a fast adenosine triphosphate (ATP)-gated calcium channel receptor mainly involved in platelet shape change.

33-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Recent evidence has highlighted the importance of lesion neovascularization in plaque destabilization and plaque growth.[7-9] Preexisting vasa vasorum in the adventitia is thought to spread into the intima, prompting intimal neovascularization (option A).[8] Leaky vasa vasorum with the subsequent red blood cell extravasation is thought to be a major source of macrophage infiltration, and it increases the vulnerability of the atherosclerotic lesions (option D). A recent study using optical coherence tomography has associated vasa vasorum increase with fibrous plaque volume and intraplaque neovessels with plaque vulnerability (option B).[10] Inhibition of plaque neovascularization could thus be seen as a potential new therapeutic intervention to prevent plaque disruption (option C).

33-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Monocytes, dendritic cells, and mast cells are the major

players in innate immunity (Figure 33-1). Mast cells are inflammatory by releasing histamine, leukotrienes, interleukin (IL)-6, and interferon (IFN)-gamma (option E). Dendritic cells are responsible for antigen presentation via human leukocyte antigen (HLA) molecules CD80/86 and CD40 (option B). Monocytes are divided into two major types according to their expression of CD14 and CD16, and can be further classified by their expression of the proinflammatory molecule Ly6C/GR-1 (option A). Platelets also play an important role in the inflammatory environment by secreting various vasoactive chemokines and cytokines such as CD40L (option C). Finally, T cells of the acquired immunity are either $CD4^+$ or $CD8^+$ and likewise play a crucial role in the destabilization of atherosclerotic lesions (option D).

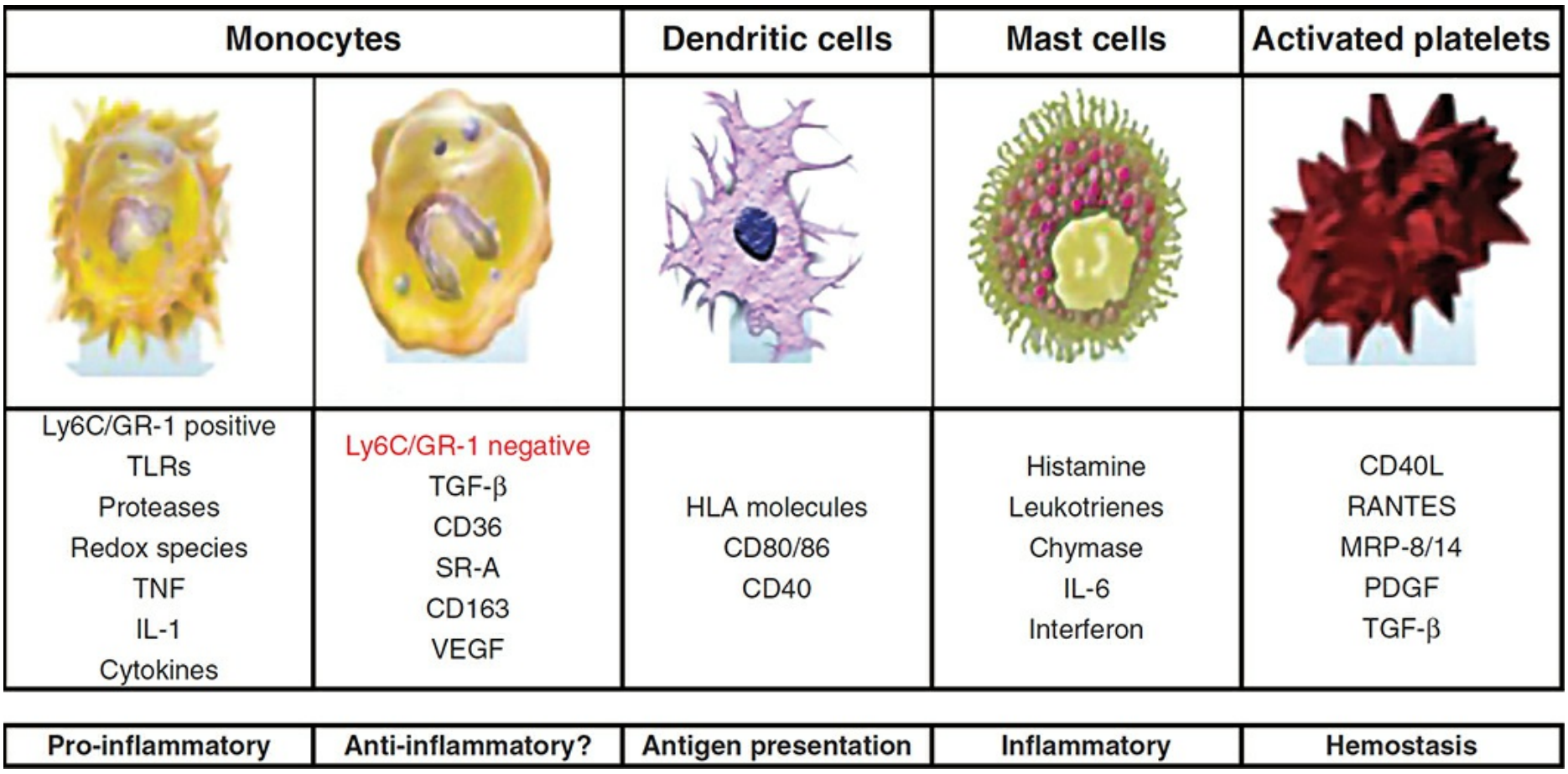

FIGURE 33-1 Major cell players involved in innate immunity.

33-9. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 33)* The mechanisms of platelet deposition and thrombus formation after vascular damage are modulated by the type of injury, the local geometry, and local hemodynamic conditions.[11,12] Tissue factor (TF) readily available in the atherosclerotic intimal space exposed by endothelial loss contributes to the high thrombogenicity of atherosclerotic plaques.[13,14] As such, when injury to the vessel wall is mild, the thrombogenic stimulus is relatively limited, and the resulting thrombotic occlusion is transient, as occurs in UA. On the other hand, deep vessel injury secondary to plaque rupture or ulceration results in exposure of collagen, TF, and other elements of the vessel matrix, leading to relatively persistent thrombotic occlusion and MI (option A). Studies show that the atheromatous core is up to sixfold more active than the other plaque substrates in triggering thrombosis.[11] Therefore, ruptured plaques with a large atheromatous core are at high risk of leading to ACS (option B). Macrophages are suggested to play a key role in inducing plaque rupture by secreting proteases capable of destroying the ECM that provides physical strength to the fibrous cap. Recently, it has been shown that macrophage-mediated matrix degradation by MMPs can induce plaque rupture (option D). Additionally, because platelet deposition increases with increasing degrees of vessel stenosis, residual mural thrombus encroaching into the vessel lumen may result in an increased shear rate, which facilitates the activation and deposition of platelets on the lesion (option C).

33-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 33)* Von Willebrand factor (vWF) is an important clotting factor present in blood plasma, endothelium, and subendothelial connective tissue. Its primary function is binding to other proteins and stimulating platelet adhesion to wound sites (option D). At the site of vascular lesions, circulating vWF binds to the exposed collagen that subsequently binds to the glycoprotein (GP) Ib/IX receptor on the platelet membrane. Under pathological conditions and in response to changes in shear stress, vWF can be secreted from the storage organelles in platelets or endothelial cells, reinforcing the activation process. vWF is not an enzyme, and thus it has no catalytic activity or effect on the conversion of prothrombin to thrombin (option A). Platelet activation by various agonists, such as ADP, leads to the mobilization of calcium and subsequent release of its granular content (option B). Likewise, vWF is not responsible for TF binding to factor VII, which happens physiologically or pathologically following exposure of TF during injury (option C). vWF is also not required for the binding of the ADP agonist to its receptor, $P2Y_1$ (option E). Figure 33-2 highlights the mechanisms involved in platelet adhesion, activation, and aggregation.

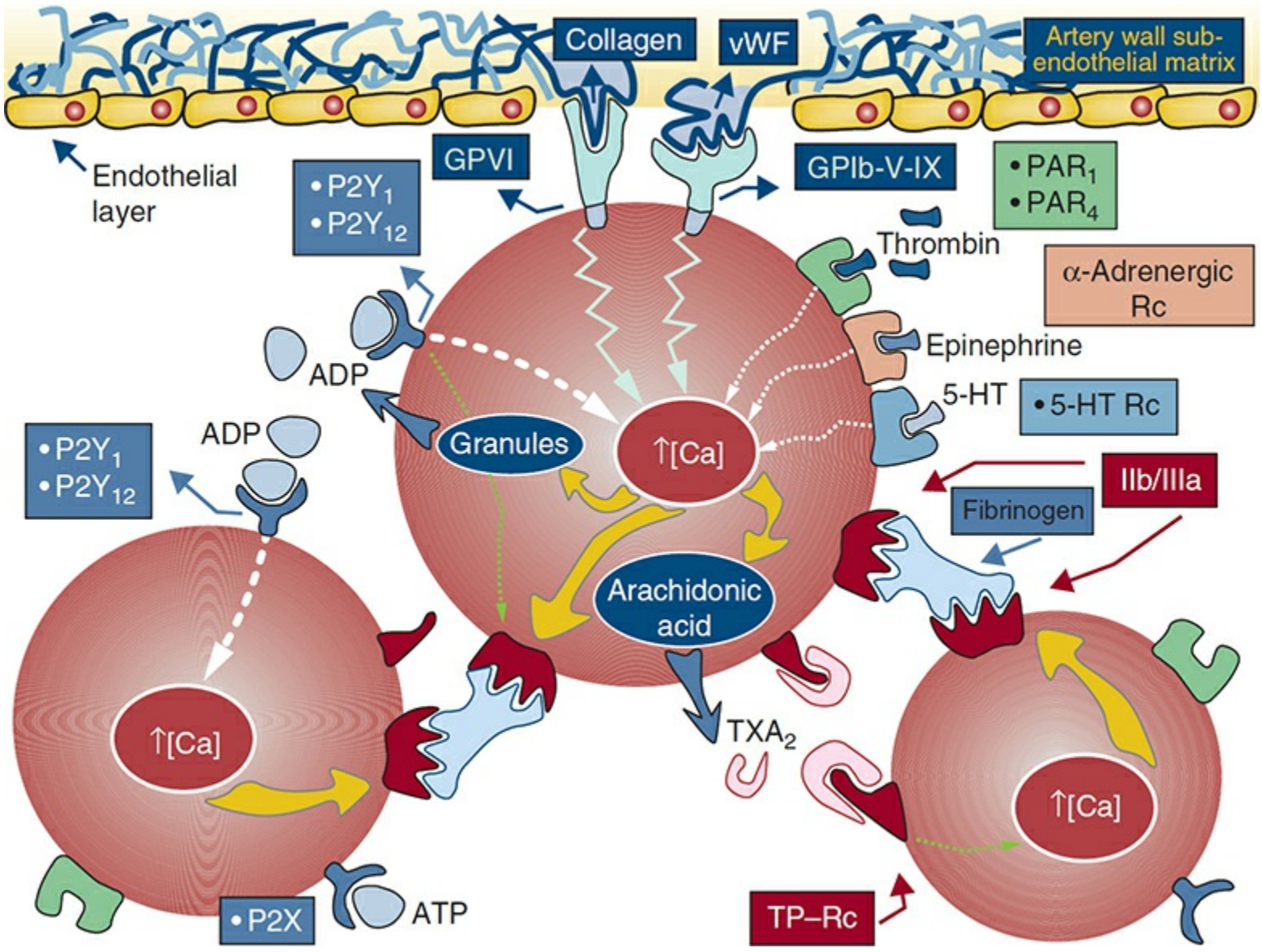

FIGURE 33-2 Mechanisms and agonists involved in platelet adhesion, activation, and aggregation. (Reproduced with permission from Ibanez B, Vilahur G, Badimon J. Pharmacology of thienopyridines: rationale for dual pathway inhibition, *Eur Heart J Suppl.* 2006;8(Suppl G):G3-G9.)

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CHAPTER 34

Coronary Blood Flow and Myocardial Ischemia

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

34-1. Which of the following statements about myocardial ischemia is *true*?

A. Elective revascularization trials driven by ischemia on diagnostic testing has not yet been shown to reduce myocardial infarction despite relief of angina
B. Revascularization of routinely identified coronary stenoses can improve mortality
C. Revascularization is more effective than medical treatment in preventing myocardial infarction and coronary death in stable CAD
D. Immediate percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) fails to reduce the risk of subsequent myocardial infarction
E. All of the above

34-2. A 66-year-old man undergoes exercise testing with myocardial perfusion imaging. What effect will dipyridamole administration have on this patient in the presence of a 95% diameter stenosis in a coronary artery?

A. It will cause progressive coronary narrowing, reducing coronary flow reserve (CFR) but not resting flow
B. A fall in coronary perfusion pressure due to a steal phenemenon and associated subendocardial ischemia
C. Coronary control mechanisms will be activated and will prevent the invocation of maximal vasodilatory capacity
D. Vasodilator-mediated increased coronary flow will cause a rise in coronary perfusion pressure to the epicardium
E. None of the above are correct

34-3. In a fluid dynamic model of stenosis and diffuse narrowing, what is the relationship between arterial radius and coronary flow?

A. Coronary flow is directly proportional to arterial radius
B. Coronary flow is inversely proportional to arterial radius
C. Coronary flow is proportional to the arterial radius divided by four
D. Coronary flow is proportional to the arterial radius raised to the fourth power
E. Coronary flow is independent of arterial radius

34-4. Which of the following statements about coronary blood flow in women is *correct*?

A. Women have larger coronary arteries and higher myocardial perfusion
B. Women have low endothelial shear, which reduces “leaky” endothelial cell junctions
C. Women have high endothelial shear that promotes atheroma formation
D. Women can have high endothelial shear that inhibits low-density lipoprotein transport
E. Women upregulate endothelial NADPH oxidase, thereby increasing oxidative stress

34-5. Which of the following accurately describes the difference in blood flow through a nonstenotic artery compared with a stenotic artery?

A. A stenosis imposes an area of low wall pressure
B. Flow velocity is greater through a nonstenotic section of an artery
C. A section of nonstenosis is an area of high endothelial shear
D. High endothelial shear stress is atherogenic
E. The viscous pressure loss across a stenosis is linearly proportional to flow squared

34-6. Which of the following is *true* about myocardial steal and its mechanisms?

A. Intramyocardial steal refers to blood flow being withdrawn from the subendocardium by the subepicardium

B. As flow increases through a stenosis, the pressure gradient increases, and distal coronary pressure falls
C. Pharmacological vasodilators increase epicardial flow, thereby decreasing the pressure gradient across the stenosis
D. It manifests as stress-induced ST elevations on ECG and angina with reduced average transmural perfusion
E. All of the above

34-7. Which of the following mechanisms regulating coronary blood flow is *incorrect*?

A. Metabolic demand is the primary controller of coronary blood flow
B. Both sympathetic and parasympathetic neurons enervate the coronary arteries
C. Increased coronary blood flow increases endothelial shear and results in vasodilation
D. A sudden rise in coronary pressure results in a sustained increase in coronary blood flow
E. All of the above are incorrect

ANSWERS

34-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 34)* Immediate PCI in ACS reduces the risk of recurrent myocardial infarction (option D). However, elective revascularization trials driven by "ischemia" on diagnostic testing has not yet been shown to reduce myocardial infarction or cardiovascular deaths despite relief of angina (option A; not option B). In addition, the failure of randomized revascularization trials to reduce myocardial infarction or coronary deaths compared to medical treatment alone in "stable CAD" has been demonstrated in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[1] (option C).

34-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 34)* Experimentally and clinically, maximal hyperemic flow for determining CFR is achieved pharmacologically by arteriolar vasodilating drugs such dipyridamole, adenosine, and regadenoson. Progressive coronary narrowing reduces CFR with little change in resting flow until an approximately 80% to 90% diameter stenosis. At these levels of severe stenosis, resting blood flow falls (option A), but some residual CFR capacity remains upon pharmacologic vasodilator stimulus. Stenosis severe enough to reduce resting perfusion does not elicit all remaining reserve vasodilator capacity because of a self-regulating mechanism that protects subendocardial perfusion. At such severe stenosis reducing resting perfusion, any increase in vasodilator-mediated increased coronary flow causes a proportionately greater fall in coronary perfusion pressure, thereby reducing subendocardial perfusion more than subepicardial perfusion, and causing subendocardial (option D is incorrect) ischemia, angina, and ST depression on ECG. When exercise or pharmacologic vasodilation forces greater vasodilation than stable resting conditions, this protective control is overridden (option C), with ensuing subendocardial ischemia (option B).

34-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 34)* The relationship between arterial radius and coronary flow is depicted in Figure 34-1. Coronary flow is a function of the arterial radius raised to the fourth power (option D).

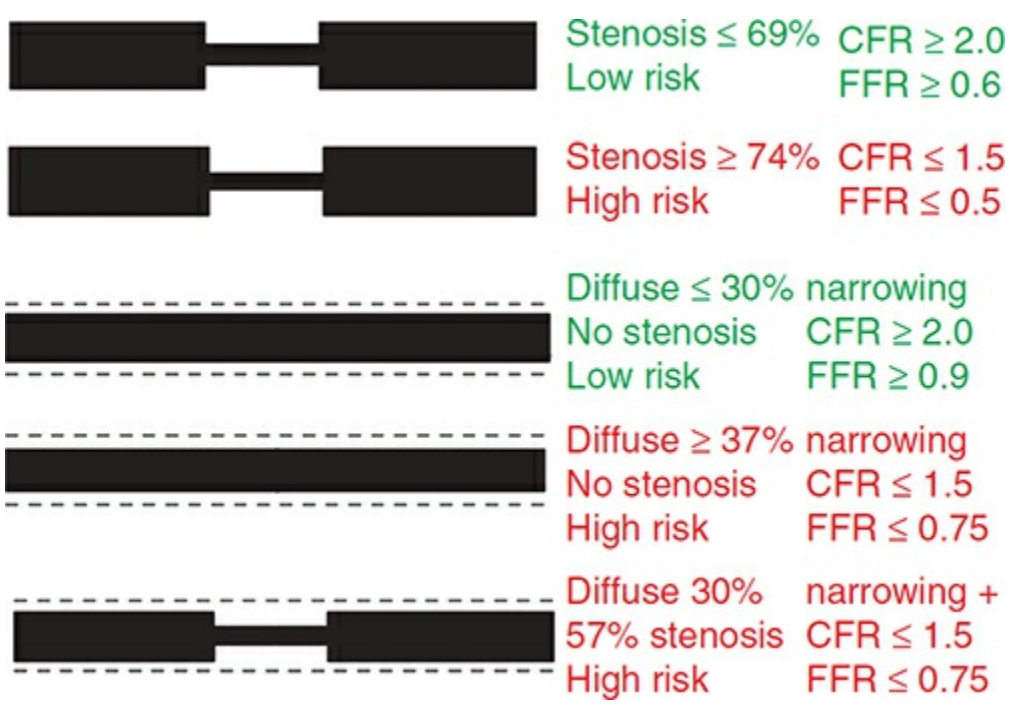

FIGURE 34-1 Computer models of stenosis and calculated coronary flow reserve (CFR) and fractional flow reserve (FFR) based on fluid dynamic analysis of the entire branching coronary artery tree with and without stenosis or diffuse narrowing. (Reproduced with permission from Gould KL, Johnson NP, Kaul S, et al. Patient selection for elective revascularization to reduce myocardial infarction and mortality: New lessons from randomized trials, coronary physiology, and statistics, *Circ Cardiovasc Imaging* 2015 May;8(5). pii: e003099.)

34-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 34)* CAD in women is characterized by atypical chest pain, diffuse epicardial coronary atherosclerosis, microvascular dysfunction, inaccurate diagnostic tests, delayed or late ACS associated with high mortality, and differential responses to medical treatment or invasive procedures in women

compared to men. Coronary arteries in women are smaller than in men (option A), but myocardial perfusion is higher in women. Accordingly, average endothelial shear is higher in women. High endothelial shear stress inhibits low-density lipoprotein transport (option D) by reducing "leaky" endothelial cell junctions (option B); inhibiting inflammation, platelet activation, and thrombosis; retarding oxidative processes; promoting mild stable uniform remodeling; and inhibiting focal atheroma (option C), focal stenosis, and plaque instability. These beneficial effects are mediated by high shear that upregulates endothelial nitric oxide (NO), NO synthase (eNOS) gene expression, eNOS phosphorylation, and manganese superoxide dismutase (Mn-SOD) expression and downregulates endothelial NADPH oxidase, thereby decreasing superoxide ion and oxidative stress (option E).

34-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 34)* Figure 34-2 shows the fluid dynamic equations relating stenosis dimensions, coronary blood flow, pressure gradient, flow profiles, exit vortex shedding, and endothelial shear stress. A normal nonstenotic artery is defined by low flow velocity (option B), high pressure and low shear (option C). Meanwhile, a stenotic artery is defined by high flow velocity, low pressure, and high shear (option A). The quadratic equation has a viscous pressure loss linearly proportional to flow (option E) and an exit separation loss proportional to flow squared. Both viscous and separation pressure losses are related to the arterial radius raised to the fourth power. Consequently, small changes in arterial diameter that are not visible or quantifiable on angiogram may have major effects on coronary flow or CFR, incurring high or low risk. High endothelial shear stress has antiatherogenic effects, whereas low shear stress is atherogenic (option D), with implications for the different manifestations of CAD in women versus men.

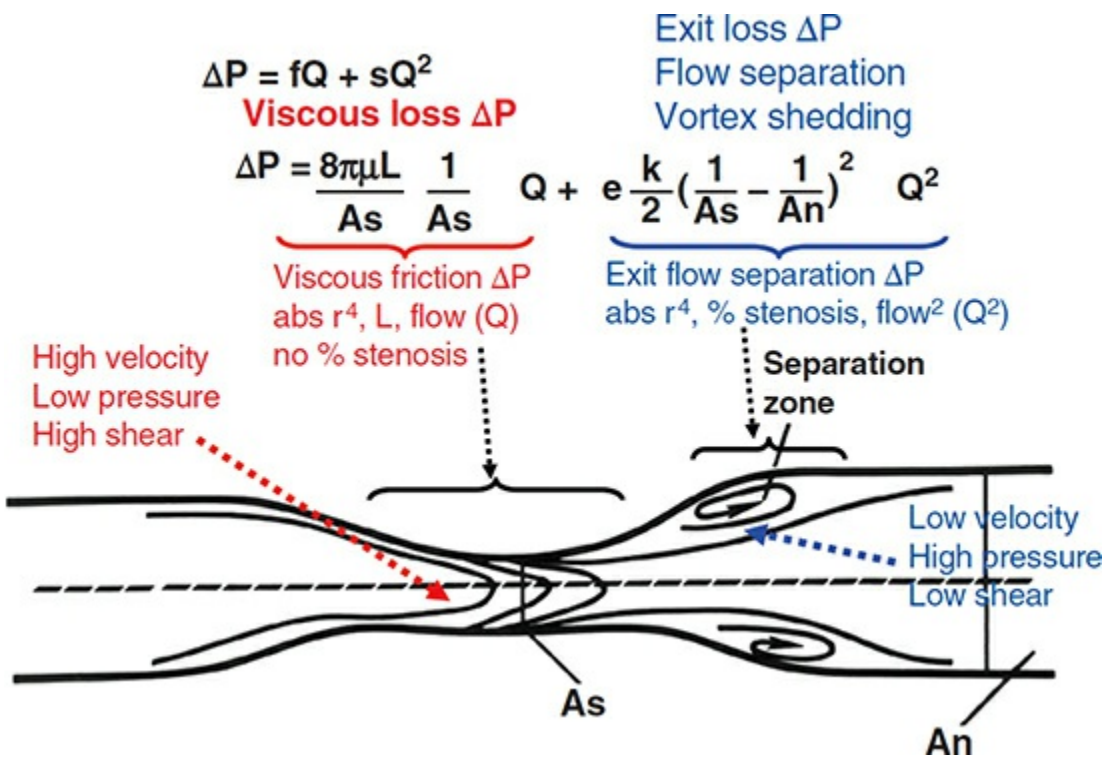

FIGURE 34-2 Schema of blood flow through a stenosis with fluid dynamic equation characterizing stenosis severity. Abbreviations: μ, blood viscosity; ΔP, pressure gradient across the stenosis; An, cross-sectional area of the normal nonstenotic artery; As, cross-sectional lumen area of the stenosis; k, constant; L, stenosis length; ΔP, pressure gradient; Q, flow; fQ, friction coefficient of flow; sQ, separation coefficient of flow squared.

34-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 34)* Intramyocardial steal, also called subendocardial-subepicardial steal, manifests as stress-induced ST depression on ECG and usually angina with reduced average transmural perfusion in cc/min/g to the ischemic threshold of 0.9 cc/min/g (option D). As flow increases through a stenosis, the pressure gradient increases, and distal coronary pressure falls (option B), thereby impairing subendocardial perfusion more than the subepicardium. This subepicardial to subendocardial perfusion gradient is called intramyocardial steal because of the superficial appearance of perfusion being "stolen away" from the subendocardium by the subepicardium (option A). As epicardial perfusion pressure and flow fall because of stenosis, the subendocardium vasodilates maximally as a result of ATP release from red blood cells that prevents ischemia up to a limit. At that level of epicardial perfusion pressure and flow, the subepicardium sees higher pressure and flow, thereby not vasodilating maximally. With added pharmacologic vasodilator stress, the epicardial flow increases, the pressure gradient across the stenosis increases (option C), and perfusion pressure falls, thereby making the subendocardium ischemic.

34-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 34)* Of the many factors affecting coronary blood flow, the primary controller is metabolic demand (option A) that nearly instantaneously regulates regional coronary flow, even in small separate myocardial regions independently. Myocardial oxygen demand regulates coronary blood flow via ATP release from oxygenated red blood cells at low myocardial pO_2. Coronary arterial smooth muscle inherently responds to changes in arterial pressure even with adequate arterial oxygenation and in the absence of myocardium or neural connections. A sudden rise in coronary pressure that initially increases coronary blood flow incurs coronary artery vasoconstriction that reduces flow back toward baseline (option E). Both sympathetic and parasympathetic neural networks enervate the coronary arteries (option B). The direct neural effect of parasympathetic stimulation is coronary vasodilation that would increase coronary blood, while the direct neural effect of beta-sympathetic blockade causes coronary vasoconstriction. As a component of its complex molecular biology, arteriolar vasodilation with increased coronary blood flow also increases endothelial shear stress that normally triggers epicardial coronary artery vasodilation mediated by NO (option C). However, with endothelial dysfunction, shear-induced epicardial vasodilation is lost, or

vasoconstriction occurs.

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CHAPTER 35

Nonobstructive Atherosclerotic and Nonatherosclerotic Coronary Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

35-1. Which of the following statements about normal coronary physiology and function is *correct*?

A. Conductance and flow in the coronary microcirculation are governed by Poiseuille's law
B. Resistance in the conductive vessels of the precapillary coronary tree is primarily responsive to metabolic stimuli
C. Epicardial vessels represent the predominant resistance within the coronary flow circuit
D. All of the above
E. None of the above

35-2. A 45-year-old woman presents to clinic with chest pain and shortness of breath. She had revascularization performed in the past, but her latest angiography results did not demonstrate residual obstructive epicardial coronary stenoses. Which of the following is *correct* about nonobstructive coronary artery disease (CAD)?

A. Nonobstructive CAD is diagnosed much more often in men than in women
B. Results from noninvasive stress testing will likely be normal
C. The patient likely has preserved LV systolic function
D. All of the above are correct
E. None of the above are correct

35-3. A 45-year-old female patient is evaluated for the presence of coronary microvascular dysfunction (CMD). Which of the following measurement techniques and expected outcomes is *not* correct?

A. Administration of adenosine results in smooth muscle relaxation
B. Regadenoson is associated with a reduced risk of bradycardia and bronchoconstriction compared with adenosine
C. Invasive Doppler flow wire can measure coronary blood flow velocity and pressures
D. Acetylcholine has direct effects on smooth muscle relaxation and vasodilation
E. Adenosine has both endothelium-dependent and endothelium-independent effects on smooth muscle cells

35-4. A 65-year-old man complains of new onset dyspnea and presyncopal episodes. He previously underwent heart transplantation six years ago for idiopathic dilated cardiomyopathy. Following a stress test and coronary CT, the patient is diagnosed with cardiac allograft vasculopathy (CAV) with diffuse narrowing of the coronary arteries. Which of the following is expected to be of limited efficacy in this patient without focal stenosis?

A. Repeat heart transplantation
B. Statin
C. Percutaneous coronary intervention (PCI)
D. Calcium channel blocker
E. ACE inhibitors

35-5. Which of the following statements about vasculitides that manifest with coronary arteritis is *correct*?

A. Kawasaki disease affects medium arteries and can result in coronary artery aneurysms
B. Takayasu's arteritis is an autoimmune process affecting the vasa vasorum of large vessels
C. ANCA-associated vasculitides can manifest with myocardial scarring
D. Giant cell arteritis (GCA) may present initially with coronary manifestations
E. All of the above

35-6. A 43-year-old man presents to the emergency room with anginal symptoms. Coronary angiography demonstrates patent coronary arteries, however, a tunneled (bridging) LAD artery is present. Which of the following could account for this patient's symptoms?

A. The tunneled artery is surrounded by epicardial fat, which compresses the lumen and limits blood flow
B. Compression of the tunneled artery occurs during diastole because myocardial blood flow occurs predominantly during systole
C. The tunneled artery runs deep in the myocardium, creating a greater myocardial bridge and accounting for greater compression of the vessel lumen
D. Greater myocardial demand results in increased blood flow during diastole because systole is limited by the increase in heart rate
E. None of the above; a tunneled artery cannot account for this patient's symptoms

35-7. A 43 year old man presents to clinic with exertional dyspnea and is is found to be in clinical heart failure. Angiography revealed a fistula between the LAD and the pulmonary artery. What is the *most* appropriate treatment for this patient?

A. Interventional (transcatheter) closure of the fistula
B. Beta-blocking agent
C. ACE inhibitor
D. Observation and continued follow-up
E. Answers B and C

35-8. Which of the following statements about the pathophysiology of aneurysms is *correct*?

A. The most common cause of aneurysms is dilatation secondary to vessel trauma
B. Dilatation involves the entire vessel wall (intima, media, and adventitia)
C. Aneurysms are often symptomatic and are discovered following patients' complaints
D. A "giant" aneurysm is defined as one having a dilatation diameter > 10 mm
E. All of the above are correct

35-9. A 36-year-old woman presents to the emergency room with chest pains, which started 5 days after delivering her child. A coronary angiography revealed a retrograde dissection of the LAD. Which of the following is *true* regarding this patient's condition?

A. Retrograde dissections should be treated surgically to prevent ischemic complications
B. Pregnancy is unrelated to the coronary dissection
C. Dissections always occur secondary to a triggering event, such as blunt force trauma
D. Coronary dissections are not associated with ischemic ECG changes
E. Retrograde dissections can be treated conservatively without further investigation

35-10. Which of the following characteristics appropriately defines epicardial coronary spasms?

A. Symptoms of angina pectoris occurring at rest
B. ST-segment changes on ECG
C. Minor elevations in serum C-reactive protein
D. Younger age and female predominance
E. All of the above are correct

ANSWERS

35-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 35)* Vessels branch and decrease in size, from prearterioles to arterioles to capillaries. Myocardial blood flow is regulated mostly in the coronary microcirculation, where only small changes in arteriolar diameter can result in large changes in conductance and flow as predicted by Poiseuille's law (option A). Despite a historical focus on the epicardial coronary macrovessels, the microvessels represent the predominant resistance within the coronary flow circuit (option C), and they are innumerable in comparison to the epicardial vessels seen during invasive coronary angiography. The precapillary coronary tree consists of conductive, prearteriolar, and arteriolar vessels. Resistance in these vessel components is primarily responsive to flow, pressure, and metabolic stimuli, respectively (option B) (Figure 35-1).

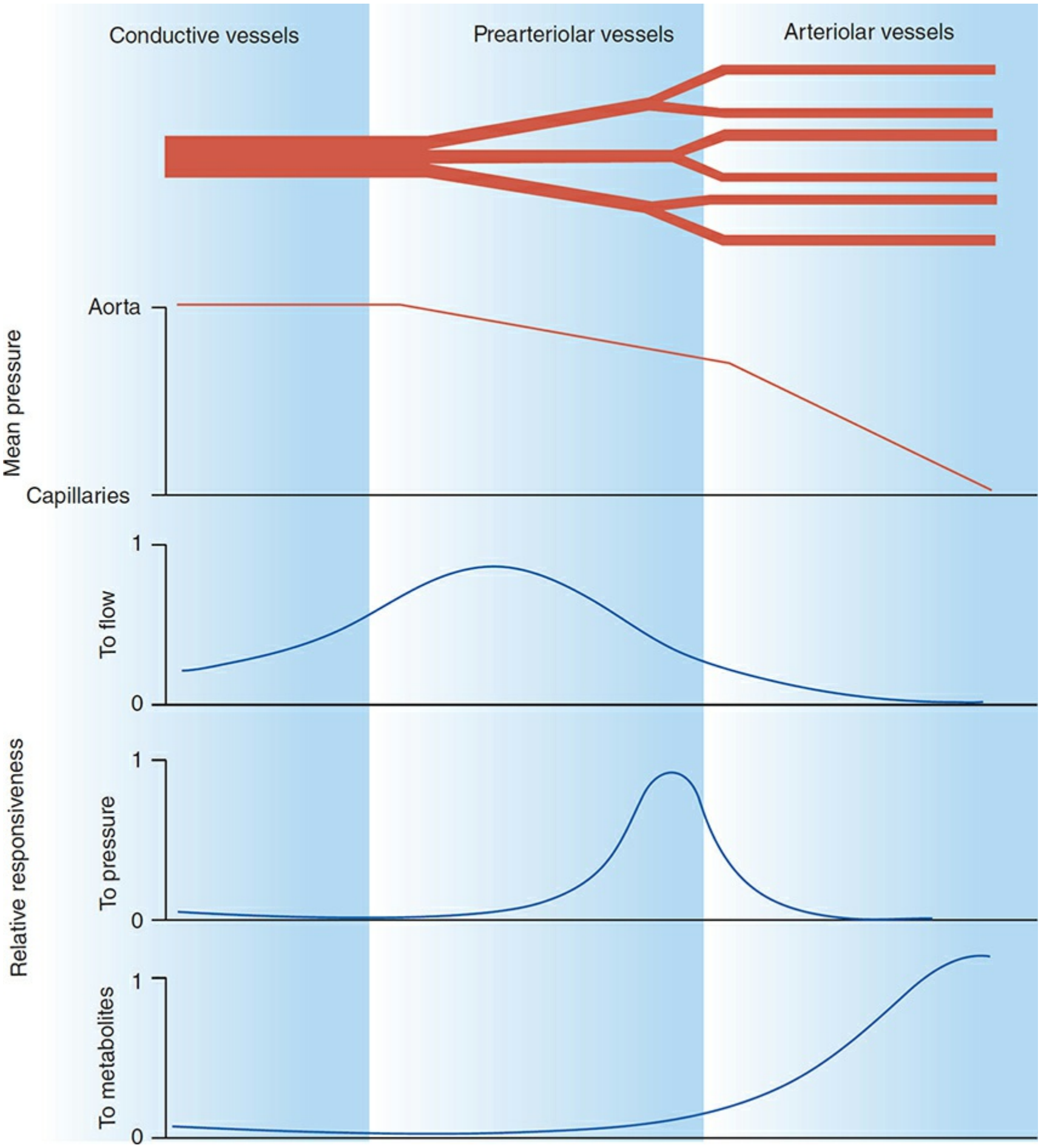

FIGURE 35-1 Components of the coronary circulation. (Reproduced with permission from Maseri A. *Ischemic Heart Disease*. New York: Churchill Livingstone; 1995.)

35-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 35)* A nontrivial proportion of patients with anginal symptoms and ischemia on stress testing (option B) have been noted to have an absence of fixed epicardial coronary arterial stenosis on coronary angiography.[1] The condition of angina with normal angiography, more accurately termed nonobstructive CAD, is being increasingly observed and is significantly more prevalent among women than men (option A).[2] In addition to those without fixed obstructive coronary stenosis, contemporary data suggest that 20% to 30% of patients with angina remain symptomatic despite technically successful revascularization and resolution of fixed epicardial coronary stenosis. In large international registries of patients referred for coronary angiography, the prevalence of nonobstructive CAD in women with angina symptoms may be as high as 65%.[3] Even in the presence of preserved LV systolic function (option C), patients with nonobstructive CAD are at elevated long-term risk when compared to healthy cohorts.

35-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 35)* To evaluate for the presence of CMD, several provocative agents are dependent on functional endothelium, whereas others act directly on vascular smooth muscle and are considered endothelium-independent. The most commonly used pharmacological agent for endothelium-dependent testing is acetylcholine. In normal coronary arteries, acetylcholine releases nitric oxide (NO) from endothelium, overriding its direct effects at the vascular smooth muscle muscarinic receptor to induce vascular smooth muscle contraction, resulting in vasodilation. In arteries with dysfunctional endothelium, insufficient biologically active NO is released in response to acetylcholine, the drug's direct effect to activate vascular smooth muscle predominates, and

vasoconstriction occurs (option D). Adenosine is the most commonly used endothelium-independent pharmacological agent. Activation of adenosine A_{2A} receptors on vascular smooth muscle results in reproducible smooth muscle relaxation (option A). Regadenoson is a selective A_{2A} adenosine receptor agonist also used in pharmacologic stress testing because of reduced side effects (eg, less bradycardia and less bronchoconstriction) (option B). Adenosine receptors are also present in endothelium. As much as 25% of the hyperemic response obtained with intravenous adenosine infusion is the result of endothelial-dependent vasodilation (option E) because it can be blocked by infusion of NG-nitro-L-arginine methyl ester (L-NAME), an inhibitor of NO synthase.[4] Invasive measurement of coronary blood flow and CFR is predominantly performed using an intracoronary Doppler flow wire.[5] The wire directly measures coronary blood flow velocity and can be combined with a pressure sensor (option C).

35-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 35)* CAV is a process whereby the allograft coronary arteries become diffusely and circumferentially narrowed with progressive luminal loss. CAV has few therapeutic options, with repeat transplantation being the only definitive treatment (option A). Statins (option B), calcium antagonists (option D), and angiotensin-converting enzyme inhibitors (option E) have all demonstrated some effect at reducing CAV.[6] Some immunomodulating drugs may be more effective than others at slowing progression. Percutaneous coronary intervention is an option for focal stenoses in patients with advanced disease and compromised ventricular function but is not feasible for diffuse narrowing (option C). Antiplatelet agents may be given to reduce the risk of myocardial infarction, although the evidence supporting this is limited.

35-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 35)* The coronary arteries can be affected by systemic inflammatory conditions. Kawasaki disease is a childhood vasculitis that can manifest with coronary abnormalities. Widespread inflammation of medium-sized arteries results in coronary artery aneurysms (option A) in approximately 25% to 30% of patients who are not treated early. The mainstays of treatment are intravenous immune globulin and aspirin. The pathological cause of Takayasu's arteritis is not precisely known, but it is widely thought to result from an autoimmune process mediated by T cells and to affect the vasa vasorum of large vessels with leukocyte infiltration (option B). The ANCA-associated diseases most commonly affect the kidneys, lungs, eyes, nerves, and skin, and cardiac involvement may not be considered part of the typical presentation. However, up to half of patients may have cardiac abnormalities, and cardiac MRI often demonstrates myocardial scarring (option C).[7,8] Giant cell arteritis is a vasculitis predominantly of older patients. Infiltration of the intima with giant cells can result in granuloma formation and thickening of the internal elastic lamina. In rare cases, GCA may present initially with coronary manifestations (option D).

35-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 35)* Occasionally, coronary artery segments of varying lengths may travel within the myocardium and reappear on the epicardium more distally in the arterial course. This is sometimes referred to as a *tunneled artery*, but the clinical phenomenon is most often referred to as the description of the overlying muscle, a *myocardial bridge*. On pathological specimens, the coronary artery is surrounded, not by epicardial fat, but by myocardium (option A). The degree of bridging and compression of the vessel lumen is variable, possibly relating to the varying depth of the tunneled segment within myocardium, with thicker myocardial bridges being potentially more symptomatic (Figure 35-2) (option C). Conceptually, the compression of a tunneled artery should be limited mostly to myocardial systole because coronary blood flow occurs predominantly during diastole. However, many bridges also restrict expansion of the coronary artery in diastole (option B). Additionally, augmentation of coronary blood flow required to meet increasing demands, such as exercise, is often accompanied by an increase in flow during systole because diastole is progressively limited by the increase in heart rate (option D). Thus ischemia, myocardial infarction, arrhythmias, and sudden death have all been attributed to myocardial bridging (option E).

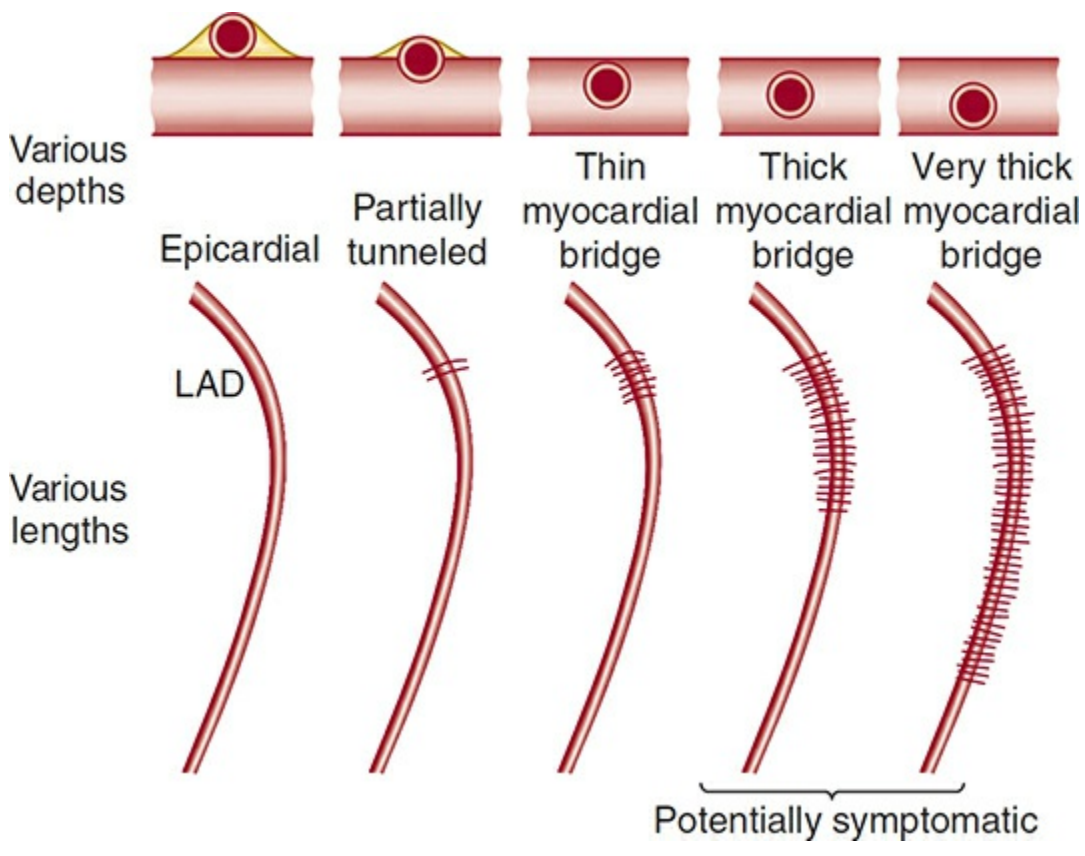

FIGURE 35-2 Diagram of myocardial bridging showing morphologic variations in tunneling (length of tunneled segment, depth

of tunneled segment). (Reproduced with permission from Pepine CJ. *Acute Myocardial Infarction*. Philadelphia: FA Davis; 1989.)

35-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 35)* An abnormal communication between an epicardial coronary artery and a cardiac chamber, major vessel (vena cava, subpulmonary veins, pulmonary artery), or other vascular structure (mediastinal vessels, coronary sinus) is known as a coronary artery fistula. Fistulas that connect the left circulation to left-sided chambers may not result in clinical disease and may be incidentally found on angiography. Fistulas between the left and right circulation result in a shunt of blood flow, which may be clinically relevant, depending on the volume of flow. Fistulas predispose to endocarditis and may present with continuous murmur, myocardial ischemia/angina, acute myocardial infarction, sudden death, coronary steal, congestive heart failure, arrhythmias, or coronary aneurysm formation.[9] If patients present with heart failure or ischemia symptoms, the traditional evaluation often includes coronary angiography, which is the most reliable method of detecting coronary fistulas. Patients with incidentally found, asymptomatic, left-to-left fistulas can be managed conservatively (eg, with beta-blockers) and will often remain stable and symptom-free for long periods of time. Interventional occlusion or surgical repair (option A) is indicated for patients with symptoms attributable to the fistula or heart failure/cardiac remodeling caused by shunting of blood.

35-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 35)* An aneurysm of the coronary artery is a pathological dilation of the entire vessel wall: intima, media, and adventitia (option B). "Giant" aneurysms are often defined as those with diameters more than four times the normal diameter (option D), but dilations of 20, 30, and 40 mm are not uncommon. Aneurysms are present in about 1% of people at autopsy; the most common (up to 50% of cases) etiology is dilation secondary to vessel damage from atherosclerosis (option A). The malformation can be congenital or acquired secondary to atherosclerosis, trauma (external or iatrogenic), or inflammatory illnesses. Aneurysms are typically asymptomatic (option C) and are sometimes incidentally found on CT, angiography or, rarely, on echocardiography.

35-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 35)* Dissection refers to the separation of arterial wall layers and can occur spontaneously or as a secondary event (option C). Depending on the nature and severity of the dissection, the false lumen can compress or occlude the true lumen, resulting in ischemia, infarction, or death. Spontaneous or primary dissections are less common than secondary and are most commonly reported in young women, often associated with pregnancy (option B). Vessels can dissect in antegrade (toward the distal vessel) or retrograde (toward the vessel origin) patterns. The signs and symptoms of dissection are similar to ACS resulting from atherosclerotic disease: chest pain, ischemic ECG changes (option D), and elevated cardiac biomarkers. Antegrade dissections are often treated with stenting to prevent further propagation of the dissection and ischemic complications. Because of the direction of blood flow, retrograde dissections can often be treated conservatively (ie, without further intervention) (option E).

35-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 35)* The syndrome of coronary spasm includes symptoms typical of angina pectoris, but occurring at rest (option A) and typically associated with transient elevation of the ST segments. The clinical findings (symptoms and ECG changes) associated with coronary spasm may occur without ST-segment elevation, and in fact they are often associated with ST-segment depression and/or T-wave changes (option B) and may also at times result from small-vessel or regional coronary dysfunction. Minor elevations of serum C-reactive protein (option C) suggest chronic low-grade inflammation may be involved in the pathogenesis of coronary spasm.[10] Finally, coronary spasm is more common in younger patients and women (option D) than angina pectoris occurring because of obstructive atherosclerosis. So all of the above are correct (option E).

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CHAPTER 36

Definitions of Acute Coronary Syndromes

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

36-1. Coronary artery disease (CAD) accounts for what proportion of all global deaths?

A. 20%
B. 30%
C. 40%
D. 50%
E. 60%

36-2. In 2011, the costs associated with myocardial infarction (MI) and coronary heart disease (CHD) in the United States were $11 billion and $10 billion, respectively. These costs are projected to do what by 2030?

A. Decrease by 100%
B. Decrease by 50%
C. Stay approximately the same
D. Increase by 50%
E. Increase by 100%

36-3. Which of the following concerning acute coronary syndrome (ACS) is *false*?

A. ACS is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis
B. ACS encompasses unstable angina (UA), ST-segment elevation MI (STEMI), and acute non–ST-segment elevation MI (NSTEMI)
C. ACS without myocardial necrosis is defined as UA
D. Myocardial necrosis is a necessary, but not sufficient, component of either STEMI or NSTEMI
E. Classification of ACS as STEMI, NSTEMI, or UA is determined within the initial hours of presentation

36-4. Initial triage of patients suspected of having acute coronary ischemia should include consideration which of the following possible alternative conditions?

A. Myocarditis/myopericarditis
B. Pulmonary embolism
C. Gastroesophageal reflux
D. Sepsis
E. Any of the above

36-5. Which of the following concerning UA is *false*?

A. UA is usually secondary to abrupt reduction in myocardial perfusion as a result of nonocclusive coronary thrombosis
B. UA and NSTEMI have distinct clinical presentations and pathogenesis
C. The incidence of UA has decreased over the last several decades
D. The diagnosis of UA relies primarily on clinical history
E. Patients with UA may present with either rest or minimal exertion angina lasting at least 20 minutes, new-onset severe angina, or crescendo angina

36-6. The risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days in individuals with the highest Thrombolysis in Myocardial Infarction (TIMI) risk scores is:

A. 25%

B. 40%
C. 55%
D. 70%
E. 85%

36-7. Historically, myoglobin, creatine kinase, and the cardiac-specific CK-MB isoform have served as serum biomarkers indicating myocardial injury or necrosis. What is the most significant limitation of these biomarkers for the diagnostic evaluation of patients with presumed cardiac chest pain?

A. Cost of the test
B. Delay in release into the peripheral blood after onset of injury
C. Lack of cardiac specificity
D. Difficulty of use
E. Instability in vitro

36-8. Which of the following concerning biomarkers of cardiac injury is *false*?

A. Both troponin I and troponin T are only found in cardiac tissue
B. Troponin elevation occurs only in the context of ACS
C. Cardiac troponins demonstrate a graded, dose-dependent association with increasing cardiovascular risk
D. Changes in cardiac troponins confer an independent and stronger impact on subsequent risk than clinical symptoms or ECG signs
E. American College of Cardiology/American Heart Association guidelines recommend against the routine measurement of CK-MB for the diagnosis of MI

36-9. Which of the following is *not* one of the criteria that must be present in the proper clinical setting leading to evidence of myocardial necrosis, according to the World Heart Federation's Universal Definition of Myocardial Infarction?

A. Detection of the rise or fall of troponin or CK-MB with at least one value above the 99th percentile of the upper reference limit (URL), in addition to evidence of myocardial ischemia by one of the following: (1) Symptoms of ischemia; (2) ECG changes indicative of new ischemia (new ST/T-wave changes or new left bundle branch block [LBBB]); (3) Development of new pathologic Q waves on ECG; (4) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
B. Sudden or unexpected cardiac death, involving cardiac arrest, often preceded by symptoms of coronary ischemia and accompanied by new ST-segment elevation or new LBBB, with or without evidence of fresh intracoronary thrombus or an expected rise in serum biomarkers
C. For patients with normal baseline biomarker levels undergoing PCI, a periprocedural increase of cardiac biomarkers above the 99th percentile URL is deemed abnormal. An increase of a biomarker greater than five times the 99th percentile URL is defined as a PCI-related MI
D. For patients undergoing coronary artery bypass graft (CABG) with normal baseline biomarker levels, increases greater than five times the 99th percentile URL accompanied by either new pathologic Q waves or new LBBB, angiographically documented graft or native artery occlusion, or new imaging evidence of loss of viable myocardium are labeled as CABG-related MIs
E. Pathologic evidence of MI

36-10. The global task force that introduced the Universal Definition of Myocardial Infarction also added a clinical classification of MI encompassing most of the common etiologies leading to myocardial necrosis. A patient with a history of recent MI who presents with ST-segment elevation and positive troponin is found to have an occlusive stent thrombosis upon emergent angiography. This would be classified as what type of MI?

A. Type 1
B. Type 2
C. Type 4a
D. Type 4b
E. Type 5

ANSWERS

36-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Coronary artery disease accounts for 30% of all global deaths, representing the single most common cause of adult mortality and equivalent to the combined number of deaths caused by nutritional deficiencies, infectious diseases, and maternal/perinatal complications.[1,2] Recent growth in the global burden of cardiovascular disease (CVD) is primarily attributable to the rising incidence across low- and middle-income countries.[3] Among European member states of the World Health Organization (WHO), for example, CVD death

rates for men and women were highest in the Russian Federation and Uzbekistan, respectively, whereas risk was lowest in France and Israel.[4] Conversely, in the United States, over 15 million Americans, or 6.2% of the adult population, have CHD, with an MI occurring once every 43 seconds.[5]

36-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Health care resource utilization for CHD is significant; over 1.1 million hospital discharges in 2010 listed MI or UA as a primary or secondary diagnosis.[5] Health care expenditures are also substantial; costs for MI and CHD were approximately $11 billion and $10 billion, respectively, in 2011.[6] These diagnoses constitute two of the most expensive discharge diagnoses and are expected to increase by 100% by 2030. Despite these sobering statistics, important strides in the diagnosis, prevention, and management of CHD have occurred over the past 50 years. In the United States, for example, several population-based studies have shown a reduction in both the incidence and the case fatality rate associated with MI.[7,8] These favorable trends have been attributed to greater utilization of evidence-based therapies and improvements in the control and burden of risk factors.[9] Concordant changes in the epidemiology of ACS have occurred over the past 10 years as a result of changing demographics and updated definitions of MI.

36-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 36)* The term *acute coronary syndrome (ACS)* is a unifying construct representing a pathophysiologic and clinical spectrum culminating in acute myocardial ischemia. This is usually, but not always, caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis and is associated with an increased risk of myonecrosis and cardiac death (option A).[10] ACS encompasses UA and ST-segment elevation MI (STEMI) or acute non–ST-segment elevation MI (NSTEMI) (option B). Distinguishing these presentations is predicated on the presence or absence of myocyte necrosis coupled with the electrocardiographic tracing at the time of symptoms. ACS without myocardial necrosis is defined as UA (option C), whereas myocardial necrosis is a necessary, but not sufficient, component of either STEMI or NSTEMI (option D). The diagnosis of ACS relies on integrating clinical information from the patient history with the initial ECG and laboratory results. In the initial hours after presentation, distinguishing between STEMI, NSTEMI, and UA may be difficult because biomarkers of myonecrosis can initially be normal (option E). However, as a result of the life-threatening nature of ACS, it is prudent to have a low threshold in suspecting this diagnosis, and therefore, diagnostic sensitivity is usually favored over specificity.

36-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Initial triage of patients suspected of having acute coronary ischemia should identify patients as having (1) ACS; (2) a non-ACS cardiovascular condition such as myocarditis/myopericarditis (option A), stress-related cardiomyopathy, aortic dissection, or pulmonary embolism (option B); (3) a noncardiac cause of chest pain such as gastroesophageal reflux (option C); or (4) a noncardiac condition that is yet undefined, such as sepsis (option D).[11] ACS patients with new ST-segment elevation on the presenting electrocardiogram (ECG) are labeled as having STEMI and should be considered for immediate reperfusion therapy by thrombolytics or percutaneous coronary intervention; those without ST-segment elevation but with evidence of myonecrosis are deemed to have an NSTEMI; and those without any evidence of myonecrosis are diagnosed with UA.

36-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 36)* UA is usually secondary to abrupt reduction in myocardial perfusion as a result of nonocclusive coronary thrombosis (option A). In this event, however, the nonocclusive thrombus that developed on a disrupted atherosclerotic plaque does not result in biochemical evidence of myocardial necrosis. Accordingly, UA and NSTEMI can be viewed as very closely related clinical conditions with similar presentations and pathogenesis but variable clinical severity (option B). Nevertheless, given the increased reliance on highly sensitive biomarkers of myocyte necrosis, the incidence of troponin-negative ACS or UA is decreasing (option C).[12] This shift in ACS epidemiology was illustrated in a report from the US Nationwide Inpatient Sample, which demonstrated an 87% decline in the prevalence of UA between 1998 and 2001 but an increase in NSTEMI.[13] As a result of the lack of objective criteria used to define this condition, UA must be diagnosed from the clinical history (option D) and is thus the most subjective of the ACS diagnoses. There are three principal clinical presentations of UA (option E): (1) rest angina or angina with minimal exertion usually lasting at least 20 minutes; (2) new-onset severe angina (Canadian Cardiovascular Society grade III or higher); and (3) crescendo angina, defined as previously diagnosed angina that has become distinctly more frequent, precipitated by less severe degrees of exertion, or more severe.[14,15] Despite a clear and consistent definition for UA, the subjective nature of these criteria may compromise diagnostic accuracy, thereby leading to misclassification. In one report, for example, 20% of patients diagnosed with UA and referred for coronary angiography did not have any angiographically apparent obstructive epicardial CAD.[16]

36-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Once CAD has been established as the likely cause of chest pain, it is necessary to estimate, or stratify, risk for adverse events using qualitative or quantitative methods. The tempo and severity of chest pain, the extent of electrical abnormality, and the magnitude of serum biomarker elevation all portend a higher risk for adverse events. Among these, biomarker evidence of myocyte necrosis is the strongest and most consistent correlate of risk. Quantitative risk scores provide an alternative and more precise approach to risk stratification. Perhaps the most widely used is the integer-based TIMI risk score, which allots a single point for each of the following in patients with chest pain: age > 65 years; aspirin use within 7 days prior to presentation; ST deviation > 0.5 mm; severe angina; at least three risk factors for CAD; raised cardiac biomarker; and known coronary stenosis.[17] The short-term risk of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization within 14 days varied from 1.4% for patients with very low scores (0–1) to 40% for those with the

highest scores (option B).

36-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Serum biomarkers indicating myocardial injury or necrosis are critical elements in the diagnostic evaluation of a patient with presumed cardiac chest pain and are essential to distinguishing between UA and overt infarction. Ideally, such biomarkers would be specific to cardiac muscle, would be absent from nonmyocardial tissue, would be released quickly into the peripheral blood after onset of injury, and would reflect the magnitude of necrosis. Moreover, the marker should be easy to use, quick and inexpensive to measure, and stable in vitro. Historically, myoglobin, creatine kinase, and the cardiac-specific CK-MB isoform have served this purpose in the diagnosis of MI. The main limitation of these markers is the lack of cardiac specificity (option C) because each may also be variably released from skeletal muscle and other tissues, such as the tongue, small intestine, uterus, and prostate. As a result, earlier definitions of MI did not require the presence of these cardiac biomarkers for diagnosis but rather considered their elevation along with clinical symptoms and electrical signs of myocardial ischemia.[18]

36-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 36)* Troponin I (TnI) and troponin T (TnT) are found only in myocardial tissue (option A), therefore elevated levels of either marker reflect myocyte injury. The advantages to cardiac troponin (cTn) testing (TnI or TnT) notwithstanding, as with any diagnostic test, gains in sensitivity occur at the expense of specificity. Several studies have shown that troponin elevations may occur in non–acute coronary syndrome clinical settings (option B), such as heart failure, renal dysfunction, and pulmonary embolism. Troponin may even be detected in apparently healthy community-dwelling adults, as shown in the Dallas Heart Study.[19] In that report, investigators found the following clinical conditions independently associated with detectable levels of cardiac troponin: left ventricular hypertrophy, diabetes mellitus, chronic kidney disease, and heart failure. As a result, the diagnosis of type 1 MI requires not only the presence of elevated cardiac troponin, but also a clinical context supporting an ischemic etiology. From a prognostic perspective, cTns demonstrate a graded, dose-dependent association with increasing cardiovascular risk (option C). Antman et al[20] illustrated this relationship in a post hoc analysis of a randomized trial evaluating various pharmacologic approaches in patients with ACS, demonstrating that unadjusted mortality rates at 42 days increased from 1.0% to 7.5% among those with the lowest versus highest levels of cTn. In addition, changes in cTn confer an independent and stronger impact on subsequent risk than clinical symptoms, ECG signs, or other biomarkers (option D).[21] Given these benefits of assessing and formulating clinical decisions based on detecting cTn, the Universal Definition of MI considers this biomarker preferentially over CK-MB. In addition, American College of Cardiology/American Heart Association guidelines no longer consider the routine measurement of CK-MB as necessary for the diagnosis of MI, and they provide a class III recommendation against routine use of this test (option E).[11]

36-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 36)* In 2007, the World Heart Federation, in concert with major European and American cardiovascular societies, convened a global task force to introduce the Universal Definition of MI. The result was a clinicopathologic classification of MI that considers five different MI types, each representing a distinct clinical and pathologic entity culminating in myocyte necrosis. The Universal Definition has been updated twice, with the most recent iteration published in 2012.[22] The new accepted universal criteria for diagnosing an acute MI state that one of five criteria must be present in the proper clinical setting leading to evidence of myocardial necrosis. Options A, B, D, and E are four of these criteria. Option C is incorrect; for a diagnosis of MI to be made in the event of sudden or unexpected cardiac death, involving cardiac arrest, often preceded by symptoms of coronary ischemia and accompanied by new ST-segment elevation or new LBBB, evidence of fresh intracoronary thrombus must be detected by angiography or autopsy when death occurred before blood was obtained or an expected rise in serum biomarkers could occur.

36-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 36)* In addition to revising the criteria for MI diagnosis, the global task force added a clinical classification of MI encompassing most of the common etiologies leading to myocardial necrosis. Each etiology of MI differs with respect to short- and long-term mortality rates. Type 1 MI (option A) occurs as a result of a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. Type 2 MI (option B) occurs secondary to ischemia from either increased oxygen demand or decreased supply, for example, coronary artery spasm, embolism, anemia, arrhythmias, hypertension, or hypotension. Type 3 MI occurs in the setting of sudden cardiac death, including cardiac arrest, that may be preceded by ischemic symptoms, accompanied by new ST-segment elevation, new LBBB, or evidence of fresh thrombus by coronary arteriography or autopsy. Death could occur before blood samples are obtained or before cardiac biomarkers appear in the blood. Type 4 MI is associated with PCI and is further classified as Type 4a or 4b. Type 4a MI (option C) is associated with PCI. Type 4b MI (option D) is associated with stent thrombosis as documented by angiography or at autopsy. Type 5 MI (option E) is associated with CABG.

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CHAPTER 37

Pathology of Myocardial Infarction and Sudden Death

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

37-1. Which of the following statements about myocardial energy metabolism is *correct*?

A. Under normal aerobic conditions, most cardiac energy is derived from glycolysis
B. Decreased adenosine triphosphate (ATP) production due to ischemia results in decreased cytosolic Na^+ and cell swelling
C. Myocardial ischemia primarily affects mitochondrial metabolism and oxidative phosphorylation
D. Reversibly injured myocytes are characterized by cell membrane breaks and amorphous densities in the mitochondria
E. Only one-third of the ATP used by the heart goes to contractile shortening

37-2. A 63-year-old man presents to the emergency department with onset of chest pain while washing his car. He has a history of angina and MI due to culprit LAD disease. Which of the following could be a contributor to smaller infarct size?

A. The absence of coronary collateral vessels
B. The extended duration of coronary occlusion
C. The earlier occlusion of the same coronary artery
D. Ventricular remodeling
E. None of the above

37-3. A 67-year-old man has an acute myocardial infarction (MI) with occlusion of the LAD. He receives thrombolysis and coronary artery revascularization by PCI, but in the following months, he develops left ventricular systolic dysfunction. Which of the following is *not correct* about the mechanisms of reperfusion injury?

A. Reperfusion-mediated infiltration of neutrophils into the ischemic region causes inflammation
B. Reperfusion results in decreased intracellular Ca^{2+}, ATP depletion, and cell death
C. Rapid restoration of physiologic pH contributes to reperfusion injury
D. Reperfusion generates oxidative stress that extends the myocardial injury
E. Decreased nitric oxide allows for neutrophil accumulation and reduced coronary blood flow during reperfusion

37-4. Which of the following is *not* a feature of myocardial hibernation?

A. Decreased calcium responsiveness
B. Upregulation of nitric oxide synthase, COX-2, and heat shock protein
C. Decreased number of sarcomeres
D. Upregulation of myosin, titin, and actinin
E. Chronic ischemia with contractile dysfunction

37-5. A 45-year-old woman is recovering in the hospital from a myocardial infarct with ST-segment elevation. Which of the following is *correct* about plaque morphology?

A. The majority of thrombi leading to acute MI are caused by plaque erosion
B. Plaque erosions are more common in men than in women
C. Most plaques occur in the proximal portion of the coronary arteries
D. Most thrombi in plaque rupture are organizing (> 1 day)
E. All of the above are correct

37-6. Which of the following depicts the *correct* pathologic progression of nonreperfused myocardial infarcts?

A. Wavy fibers, neutrophil infiltration, coagulation necrosis, fibroblast activity
B. Fibroblast activity, granulation tissue, neutrophil infiltration, coagulation necrosis
C. Wavy fibers, coagulation necrosis, hypereosinophilic myocyte, neutrophil infiltration

D. Fibroblast activity, wavy fibers, neutrophil infiltration, coagulation necrosis
E. None of the above

37-7. A 59-year-old man presents with chest pain that precipitated while he was mowing the lawn. He did not seek medical attention until 4 hours after the onset of symptoms. Which of the following is *correct* about reperfusion following acute MI?

A. Myocardium is not salvageable 4 hours after the onset of chest pain
B. In perfused infarcts, neutrophils are concentrated at the margins
C. The rate of healing by fibroblasts is greater in nonreperfused infarcts
D. Reperfused infarcts have areas of necrosis at the center mixed with noninfarcted myocardium
E. Reperfusion within 6 hours of the onset of chest pain is likely to result in significant myocardial salvage

37-8. Which of the following is *incorrect* about myocardial remodeling following MI?

A. Myocardial infarction induces a systemic inflammatory response
B. Transition to M2 macrophages causes expansion of the infarcted area
C. M1 macrophages set up the proinflammatory environment following an infarct
D. Prolonged M1 macrophage activation results in expansion of the injured ventricular wall
E. All of the above are incorrect

37-9. A 64-year-old woman developed an aneurysm following an MI caused by occlusion of the LAD. Which of the following is *correct* about aneurysms?

A. Patients receiving reperfusion therapy have a higher incidence of aneurysms
B. Female gender is an independent determinant of aneurysm formation after infarction
C. The wall of a true aneurysm consists of fibrous pericardium
D. Subendocardial infarcts are the most likely to result in true aneurysms
E. All of the above are correct

37-10. Which of the following is *not correct* regarding complications of MI?

A. Right ventricular wall rupture is much more common than left ventricle rupture
B. Anticoagulation should be discontinued or used with caution in the presence of significant (≥ 1 cm) pericardial effusion after MI
C. Cardiogenic shock is caused by decreased systemic cardiac output with adequate intravascular volume
D. Ventricular arrhythmias are associated with decreased survival post-MI
E. Right ventricular cardiogenic shock is associated with younger age

ANSWERS

37-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 37)* The normal function of the heart muscle is supported by high rates of myocardial blood flow, oxygen consumption, and combustion of fat and carbohydrates (glucose and lactate). Under normal aerobic conditions, cardiac energy is derived from fatty acids, supplying 60% to 90% of the energy for ATP synthesis (option A). The rest (10% to 40%) comes from the oxidation of pyruvate formed from glycolysis and lactate oxidation. Almost all of the ATP formed comes from oxidative phosphorylation in the mitochondria; only a small amount of ATP (< 2%) is produced by glycolysis. Approximately two-thirds of the ATP used by the heart goes to contractile shortening (option E), and the remaining third is used by sarcoplasmic reticulum Ca^{2+} ATPase and other ion pumps. Myocardial ischemia primarily affects mitochondrial metabolism, resulting in a decrease in ATP formation by shutting off oxidative phosphorylation (option C). Decreased ATP inhibits Na^{+}/K^{+}-ATPase, increasing intracellular Na^{+} and Cl, leading to cell swelling (option B). Reversibly injured myocytes are edematous and swollen from the osmotic overload. Irreversibly injured myocytes contain shrunken nuclei with marked chromatin margination. The two hallmarks of irreversible injury are cell membrane breaks and the mitochondrial presence of small osmiophilic amorphous densities (option D).

37-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 37)* Myocardial ischemia occurs when oxygen and nutrient supply do not meet myocardial demand, and necrosis or infarction occurs when ischemia is severe and prolonged. The extent of coronary collateral flow is one of the principal determinants of infarct size. Indeed, at autopsy, it is common to see chronic total coronary occlusion and an absence of MI in the distribution of that artery. The absence of myocardial ischemia following coronary artery occlusion is associated with the presence of well-developed collateral vessels (option A). Reimer and Jennings showed that if a canine coronary artery was occluded for 15 minutes, for 40 minutes, for 3 hours, or permanently for 4 days, myocardial necrosis progressed as a "wave front phenomenon."[1,2] The extent of myocardial necrosis therefore depended on the duration of coronary occlusion (option B). Other than the presence of collateral circulation, factors that influence infarct size include preconditioning (option C), which may greatly reduce

infarct size, and reperfusion. Transmural infarcts may increase in size for weeks after the initial event, and the degree of this expansion is associated with a decrease in the survival rate. The processes involved in postinfarction ventricular dilatation are known as ventricular remodeling. In general, the transmural extent of necrosis is a major determinant of infarct expansion (remodeling) based on large infarct size and the persistence of the occlusion (option D).

37-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 37)* The process of restoring blood flow to ischemic myocardium has shown utility in limiting cell death in the presence of severe ischemia. Reperfusion, however, has paradoxical effects on myocardium that can result in adverse reactions, termed reperfusion injury. During reperfusion, the myocardium is subject to abrupt biochemical and metabolic changes governed by several mediators that interact with each other in complex ways. Reperfusion markedly enhances the infiltration of neutrophils into the ischemic region and amplifies the inflammatory response (option A). At the time of myocardial reperfusion, there is an abrupt increase in intracellular Ca^{2+} known as the calcium paradox (option B). This intracellular Ca^{2+} causes opening of the mitochondrial permeability transition pore (PTP), which uncouples oxidative phosphorylation, resulting in ATP depletion and cell death. In addition, studies have shown that reperfusion of ischemic myocardium generates reactive oxygen species (oxygen paradox). This oxidative stress results in the extension of the myocardial injury beyond that induced by ischemia alone (option D). A key mechanism involves the reduction of the bioavailability of the nitric oxide, which normally inhibits neutrophil accumulation, inactivates superoxide radicals, and improves coronary blood flow (option E). Further contributing to reperfusion injury is the rapid restoration of physiologic pH (option C) that occurs after washout of lactic acid and the activation of the sodium-hydrogen exchanger and the sodium-bicarbonate symporter. The final consequence of reperfusion injury is left ventricular (LV) systolic dysfunction leading to increased morbidity and mortality.

37-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 37)* In the early 1980s, Rahimtoola et al.[3] found significant improvement in left ventricular function after coronary revascularization in a subset of patients with depressed ventricular performance. They postulated that the mechanism of poor myocardial contractility was chronic ischemia (option E), which could be improved by revascularization. The premise behind this rationale was dependent on the surviving myocardium being in a functional, albeit depressed, state, suggesting that the myocardium may adapt to chronic ischemia by decreasing its contractility but preserving viability. Chronically hibernating myocardium demonstrates changes in adrenergic control and calcium responsiveness (option A). Substances that are upregulated in chronic hibernating myocardium include heat shock protein, hypoxia-inducible factor, inducible nitric oxide synthase, cyclooxygenase-2, and monocyte chemotactic protein (option B). Morphologically, hibernating myocytes show a loss of contractile elements, the sarcomeres (option C), with increased glycogen. There is a disorderly increase in cytoskeletal desmin, tubulin, and vinculin, with a decrease in contractile proteins myosin, titin, and actinin (option D).

37-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 37)* The vast majority of MIs occur in patients with coronary atherosclerosis, with > 90% associated with superimposed luminal thrombi. Arbustini et al.[4] found coronary thrombi in 98% of patients dying with clinically documented acute MI, and of those thrombi, 75% were caused by plaque rupture and 25% by plaque erosion (option A). There are gender differences in the causation of coronary thrombi leading to acute MI: Arbustini et al.[4] showed that 37% of thrombi in women were erosion compared with only 18% in men (option B). The thrombus age also varies; the majority of acute thrombi (< 1 day) have been observed in plaque rupture, whereas the majority of thrombi in plaque erosion are organizing (> 1 day)[5] (option D). The majority of thin cap fibroatheromas, acute and healed ruptures, and lesions with fibroatheromas occur predominantly in the proximal portion of the three major coronary arteries (option C), and about 50% arise in the midportion of these arteries.

37-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 37)* The earliest morphologic characteristic of MI that can be discerned and observed between 12 and 24 hours after the onset of chest pain is the hypereosinophilic myocyte. It has been suggested in experimentally induced infarction that the appearance of "wavy fibers" (1) may be the earliest change and is thought to be the result of stretching of the ischemic noncontractile fibers by the adjoining viable contracting myocytes. Neutrophil infiltration (2) is present by 24 hours at the border areas. As the infarct progresses between 24 and 48 hours, coagulation necrosis (3) is established with various degrees of nuclear pyknosis, early karyorrhexis, and karyolysis. At 3 to 5 days, the central portion of the infarct shows loss of myocyte nuclei and striations. The influx of inflammatory cells, including mast cells, induces a cascade of chemokines, which suppress further inflammation and result in scar tissue.[6] Macrophages and fibroblasts (4) begin to appear in the border areas. By 1 week, neutrophils decline, and granulation tissue is established with neocapillary invasion and lymphocytic and plasma cell infiltration. By the second week, fibroblasts are prominent, and there is continued removal of the necrotic myocytes as the fibroblasts are actively producing collagen and angiogenesis occurs in the area of healing. Option A is therefore correct.

37-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 37)* If reperfusion occurs within 4 to 6 hours after the onset of chest pain or electrocardiographic (ECG) changes, there is myocardial salvage (option A), and the infarct is likely to be subendocardial without transmural extension (option E). Within a few hours of reperfusion, neutrophils are evident within the area of necrosis, but they are usually sparse. In contrast to nonreperfused infarcts, neutrophils do not show concentration at the margins (option B). However, reperfused infarcts often demonstrate areas of necrosis at the periphery with interdigitation with noninfarcted myocardium (option D). Macrophages begin to appear by day 2 or 3, and stromal cells show enlarged nuclei and nucleoli by days 3 and 4. Neutrophil debris, which may be concentrated at the border areas in cases of incomplete reperfusion, is seen by 3 to 5 days. Fibroblasts appear by days 3 to 5, with an accelerated rate of healing compared with nonreperfused infarcts (option C).

37-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 37)* Myocardial remodeling is defined as changes in size, shape, and function of the heart occurring secondary to molecular, cellular, and interstitial events after MI. Left ventricular remodeling begins within the first few hours after an infarct and continues to progress, and the infarcted myocardium undergoes rapid turnover during the first 1 to 2 weeks after MI. MI generates a systemic inflammatory response (option A), with activation of the complement cascade, transforming growth factor-β, and chemokines and free radical generation. During the healing phase, infiltrating monocytes differentiate into macrophages, which, along with mast cells, accumulate in the healing scar, inducing fibroblast proliferation. Classically activated M1 macrophages are the first line of defense that influences the subsequent phase of the healing process by M2 macrophages. The prolonged presence of M1 macrophages extends the proinflammatory environment (option C) and causes expansion of the infarcted area (option B). A delayed transition to M2 macrophages thus hampers the formation of scar tissue, predisposing to heart failure development as a result of expansion of the injured ventricular wall (negative remodeling) (option D). Improved healing may be attained by modulating macrophage polarization toward the M2 phenotype, thus promoting the resolution of inflammation and improved infarct healing.

37-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 37)* Single-vessel disease, absence of previous angina, total LAD occlusion, and female gender (option B) are independent predictors of left ventricular aneurysm formation after anterior infarction. Patients receiving reperfusion therapy and exhibiting a patent infarct-related artery have a lower incidence of aneurysm formation (option A). A large acute transmural myocardial infarction that has undergone expansion is the most likely infarct to result in a true aneurysm (option D). Morphologically, the wall of a true aneurysm develops after MI, and it consists of fibrous tissue (option C) with or without interspersed myocytes. In contrast, the wall of a false aneurysm is formed by fibrous pericardium (not from the left ventricular MI and healing).

37-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 37)* The complications of MI may manifest immediately or they may appear late, and they depend on the location and extent of infarction. The acute complications consist of arrhythmias and sudden death, cardiogenic shock, infarct extension, fibrinous pericarditis, cardiac rupture, and mural thrombus and embolization. Ventricular arrhythmias are important markers of electrical instability and are associated with decreased survival in the acute post-MI phase. Left ventricular wall rupture is much more common than right ventricle rupture (option A). Although reperfusion therapy has reduced the incidence of cardiac rupture, late thrombolytic therapy may increase the risk of cardiac rupture. Heart failure after MI ranges from pulmonary congestion to profound organ hypoperfusion or cardiogenic shock. Cardiogenic shock is caused by decreased systemic cardiac output in the presence of adequate intravascular volume (option C). Right ventricular cardiogenic shock after acute infarction is associated with younger age, a lower prevalence of previous infarctions, fewer anterior infarct locations, and less multivessel disease (option E). Pericardial effusion after MI usually takes several months to reabsorb. Anticoagulation should be discontinued in the presence of a significant (≥ 1 cm) or enlarging pericardial effusion (option B).

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CHAPTER 38

Molecular and Cellular Mechanisms of Myocardial Ischemia/Reperfusion Injury

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

38-1. Which of the following is *not* a determinant of infarct size?

A. Time to reperfusion
B. The presence of collaterals
C. Blood pressure
D. Temperature
E. Ischemia/reperfusion injury

38-2. Which of the following does *not* contribute to myocyte necrosis after reperfusion?

A. Sarcolemma disruption and calcium overload
B. ATP depletion and reversal of the Na^{+}/Ca^{2+} exchanger, resulting in increased intracellular calcium
C. The no-reflow phenomenon
D. Tissue edema
E. Autophagy

38-3. Which of the following is *true* about intracellular Ca^{2+} during ischemia-reperfusion injury?

A. The Na^{+}/Ca^{2+} exchanger extrudes Ca^{2+} from the cytoplasm
B. Calpains are activated by increases in Ca^{2+}
C. The RyR2 does not contribute to increased intracellular Ca^{2+}
D. Sarcolemma membranes remain intact
E. Calpains are only active at low pH

38-4. Which of the following is *correct* regarding mitochondrial function during reperfusion?

A. Mitochondrial calcium decreases
B. The mitochondrial permeability transition pore (MPTP) is open during acidosis
C. Cyclophilin D closes the MPTP
D. Restoration of DNA synthesis occurs immediately following reperfusion
E. Succinate levels increase during ischemia and scavenge reactive oxygen species (ROS) following reperfusion

38-5. Which of the following is *not true* regarding coronary circulation during reperfusion injury?

A. Interstitial edema occurs in part because of a dysfunctional endothelial barrier
B. Edema peaks at 120 minutes and again at 7 days
C. The release of vasodilators from the culprit lesion dilates the microvasculature
D. Cellular aggregates from the culprit lesion impair flow in the microcirculation
E. Hemorrhage of the microcirculation is associated with an adverse prognosis

38-6. Which of the following is *true* of ischemic preconditioning (IPC)?

A. Repeated episodes of ischemia increase reperfusion injury
B. Ischemic preconditioning results in a cardioprotective phase 7 days after preconditioning
C. Ischemic preconditioning results in the release of protective autacoids
D. Ischemic preconditioning is thought to increase calcium load

E. The presence of angina before an MI is associated with larger injuries following MI

38-7. Which of the following is *true* about ischemic postconditioning?

A. In preclinical models, intermittent reperfusion reduces infarct size
B. Ischemic postconditioning is unlikely to involve the same mechanisms as preconditioning
C. Early clinical studies demonstrate a benefit of ischemic postconditioning on improving outcomes following myocardial infarction in humans
D. Ischemic postconditioning increases myocardial edema
E. Ischemic postconditioning increases infiltration by polymorphonuclear monocytes

38-8. Which of the following is *not correct* regarding remote ischemic conditioning (RIC)?

A. RIC is likely mediated by bloodborne factors
B. RIC requires an intact neural pathway to be effective
C. The mechanism of RIC is likely to involve the RISK and SAFE pathways
D. RIC results in the release of autacoids
E. Treatment with SDF-1 can increase infarct size by mimicking RIC

38-9. Which of the following pharmacologic options may reduce ischemia-reperfusion injury?

A. Cyclosporine A
B. Adenosine
C. Hypothermia
D. Metoprolol
E. Antioxidants

38-10. When does myocardial edema peak after reperfusion following acute myocardial infarction?

A. Immediately after reperfusion
B. 7 days post reperfusion
C. 3 days post reperfusion
D. A and B
E. B and C

ANSWERS

38-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Shorter time to reperfusion and an increased number of collaterals are associated with smaller infarct sizes (options A and B). Lower temperatures and larger ischemia/reperfusion injury are associated with larger infarct sizes (options D and E). Blood pressure by itself is not directly associated with infarct size (option C).

38-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Calcium overload that results from disruption of the sarcolemma and reversal of the Na^+/Ca^{2+} exchanger contribute to reperfusion injury (options A and B).[1] Impairment of the microcirculation via the no-reflow phenomenon or by compression through tissue edema can exacerbate reperfusion injury (options C and D).[2,3] Autophagy is not known to contribute to reperfusion injury (option E).

38-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Altered Ca^{2+} handling is one of the most prominent and relevant aspects of cardiomyocyte reperfusion. Reperfusion causes further Ca^{2+} influx through the Na^+/Ca^{2+} exchanger in response to Na^+ overload (option A). An important consequence of increased Ca^{2+} is activation of the Ca^{2+}-dependent proteases calpains. Calpains translocate to the sarcolemma during ischemia in response to Ca^{2+} overload but are activated only during reperfusion when intracellular pH is normalized because they are inhibited by low pH (options B and E).[4] When the Ca^{2+} capacity of the sarcoplasmic reticulum (SR) is exceeded, Ca^{2+} is released back into the cytosol through the ryanodine receptor channel (RyR2) (option C). Excessive contractile activation may cause hypercontracture, resulting in disruption of cardiomyocyte architecture that can cause sarcolemma rupture and cell death (option D).

38-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Restoration of the mitochondrial membrane potential favors mitochondrial Ca^{2+} uptake through the Ca^{2+} uniporter and Ca^{2+} overload (option A).[5] Mitochondrial permeability transition is caused by the opening of the MPTP. During ischemia, the MPTP does not open because of the inhibiting effect of intracellular acidosis (option B). Cyclophilin D modulates the sensitivity of MPTP to Ca^{2+} (option C).[6] Reperfusion results in immediate restoration of respiration, proton gradient across the inner mitochondrial membrane, and ATP synthesis (option D). Reactive oxygen species levels increase following reperfusion, in part, because of

oxidation of the excess succinate that builds up during ischemia (option E).[7,8]

38-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Interstitial edema develops as a consequence of increased interstitial osmolarity from increased ion and catabolite concentrations and a dysfunction of the endothelial barrier during myocardial ischemia (option A). Edema development during reperfusion follows a bimodal pattern, where an initial maximum of water content after 120 minutes is associated with the beginning of leukocyte infiltration and a secondary peak after 7 days is associated with enhanced collagen deposition (option B).[9,10] The release of vasoconstrictor substances such as thromboxane, serotonin, and endothelin from the culprit lesion into the microcirculation, in conjunction with the impairment of endothelial function by ischemia/reperfusion per se or by tumor necrosis factor-α (TNF-α), can contribute to enhanced vasoconstrictor responsiveness of the microcirculation during myocardial ischemia/reperfusion (option C).[11-13] Cellular aggregates are either released from the epicardial atherosclerotic culprit lesion and dislodged into the microcirculation or are formed in the coronary microcirculation, resulting in impaired flow (option D). No-reflow and hemorrhage carry an adverse prognosis (option E).[14,15]

38-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Repeated episodes of ischemia decrease reperfusion injury (option A).[16,17] IPC has been shown to induce two distinct windows of cardioprotection. The first, usually referred to as classic preconditioning, occurs immediately after the IPC stimulus and lasts 2 to 3 hours, followed by a disappearance of the effect. This is followed by a second window of protection, or delayed effect, appearing 12 to 24 hours later and lasting 48 to 72 hours (option B).[18,19]The sublethal cycles of short bursts of ischemia and reperfusion, which make up the IPC stimulus, produce a number of endogenous biological factors (i.e., autacoids) from the myocyte, including adenosine, bradykinin, endothelin, acetylcholine, and opioids, which can bind to their respective receptors on the plasma membrane. This will direct the appropriate cardioprotective communication pathway that will convey the protective signal to the mitochondria (option C). Although the end effectors of cardioprotection in classical and delayed IPC remain unclear, it has been suggested that preservation of mitochondrial function with less calcium overload, attenuated ROS production, and MPTP inhibition all contribute to the protective effect (option D).[20-22] The presence of angina before an MI is associated with smaller injuries following MI (option E).[23]

38-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Ischemic postconditioning (IPost) confers myriad protective effects, including the preservation of endothelial function, reduced levels of myocardial edema, reduced levels of oxidative stress, and reduced neutrophil accumulation (options A, D, and E).[24] IPost has been shown to reduce myocardial infarction size in rodents, rabbits, pigs, and other species including humans, although the cardioprotective effects of IPost do not appear to be as robust as with ischemic preconditioning.[25,26] Mechanistically, IPost appears to share many of the same signaling mechanisms recruited at the time of reperfusion by ischemic preconditioning (option B).[25,27] While animal data are promising, early phase clinical studies have yielded mixed results (option C).[28]

38-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Remote ischemic conditioning is the phenomenon whereby the application of one or more brief cycles of nonlethal ischemia and reperfusion to an organ or tissue protect the heart against a lethal episode of acute reperfusion injury. Blood taken from a rabbit that has been preconditioned reduces MI size when transfused into a naïve rabbit, suggesting that RIC occurs via bloodborne factors (option A). The generation of this cardioprotective factor has been shown to be dependent on an intact neural pathway.[29] The exact factor remains unknown, but SDF-1 is a candidate (option E).[25] RIC involves the release of autacoid and depends on an intact neural system (options B and D). The mechanism of RIC is likely to involve the RISK and SAFE pathways (option C).[30]

38-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 38)* The history of pharmacologic cardioprotection has been hugely disappointing, with adenosine, antioxidants, magnesium, calcium channel blockers, anti-inflammatory agents, erythropoietin, and atorvastatin all failing to reduce myocardial infarction size or to improve clinical outcomes (options A, B, C, and E).[24,31] Initial clinical trials using early metoprolol in patients with acute myocardial infarction have suggested a reduction in infarct size (option D).[32] Large clinical studies are under way.

38-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 38)* Edema development during reperfusion follows a bimodal pattern, where an initial maximum of water content after 120 minutes is associated with a beginning leukocyte infiltration, and a secondary peak after 7 days is associated with enhanced collagen deposition (options A, B, and C).[9,10,32] It has been proposed that edema during reperfusion reflects the area at risk on cardiac magnetic resonance (CMR), but such a bimodal pattern raises questions about the use of T2-weighted edema measurement for AAR delineation.[33]

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CHAPTER 39

Evaluation and Management of Non–ST-Segment Elevation Myocardial Infarction

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

39-1. Which of the following factors is associated with a low likelihood that chest pain is caused by myocardial ischemia attributable to obstructive coronary artery disease (CAD)?

A. Known coronary disease (particularly recent PCI)
B. Typical angina reproducing prior documented angina
C. Hemodynamic or ECG changes during pain
D. Dynamic ST-segment elevation or depression of ≥1 mm
E. T waves flat or inverted < 1 mm

39-2. A 55-year-old woman with a history of hypertension and obstructive sleep apnea presents with two days of an intermittent "squeezing" sensation in her chest. The last episode was approximately six hours ago. Which of the following is *true* about the use of the electrocardiogram to diagnosis an acute coronary syndrome?

A. Persistent 0.5 mm ST segment depression is strongly suggestive of an acute coronary syndrome
B. T-wave inversions do not localize well the territory of myocardial ischemia
C. The presence of ST depressions confers a higher risk of 30-day mortality
D. The presence of isolated T-wave inversions confers a worse prognosis compared with ST depression
E. None of the above are true

39-3. A 52-year-old woman presents with an episode of substernal chest pressure. An initial conservative ("ischemia-guided") strategy is selected, and she undergoes stress testing. Which of the following findings would be consistent with a low-risk result, supporting ongoing medical management without coronary angiography with the intent to perform percutaneous coronary intervention (PCI)?

A. Duke treadmill score of 6
B. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a heart rate of 120 beats per minute
C. Lung uptake on thallium scanning
D. Large stress-induced perfusion defect
E. Exercise-related left ventricular ejection fraction < 35%

39-4. A 76-year-old man, an active smoker, with a history of diabetes and hypertension, presents with accelerating angina over the past week that is now present at rest. In addition to his age and the presence of ≥3 risk factors for CAD, all of the following would also put this patient at higher risk, according to the TIMI Risk Score, *except*:

A. Known coronary artery stenosis ≥50%
B. Aspirin use within the past 7 days
C. ≥2 episodes of angina within the past 24 hours
D. ST changes ≥1 mm on ECG
E. Positive cardiac biomarkers

39-5. Which of the following is *not true* about ticagrelor?

A. Ventricular pauses are a known side effect of ticagrelor that usually develop early after treatment initiation, tend to decrease in frequency over time, are rarely symptomatic, and are not usually associated with clinically significant bradycardia
B. Dyspnea tends to occur early after starting the drug in 10% to 15% of treated patients, is not associated with evidence of heart failure, and usually lasts less than a week.

C. Dyspnea and ventricular pauses are thought to be mediated by interference with adenosine reuptake in erythrocytes
D. Ticagrelor is a twice daily, reversible ADP antagonist, and hence its antiplatelet effects are no longer present within 12 hours of discontinuation
E. Ticagrelor is preferred over clopidogrel in the management of patients with acute coronary syndromes when possible

39-6. In selecting a parenteral anticoagulant to treat patients with unstable angina/NSTEMI, which of the following is *true* about the evidence base supporting the use of fondaparinux compared with enoxaparin?

A. In clinical trials, fondaparinux has been shown to reduce the composite risk of death, MI, or refractory ischemia when compared with enoxaparin
B. No meaningful differences in bleeding risk have been observed with fondaparinux over enoxaparin
C. The risk of catheter-related thrombotic complications is higher in patients referred for percutaneous coronary artery intervention who were initially treated with enoxaparin versus fondaparinux
D. A criticism of the OASIS 5 trial that compared fondaparinux with enoxaparin was that patients with renal failure were allowed into the trial, and the hazard was driven by this group
E. Fondaparinux has received a class I recommendation for use in patients with unstable angina/NSTEMI by the ACCF/AHA

39-7. A 39-year-old woman presents to the emergency room with chest pain and marked ST segment changes. She continues to complain of crushing chest pain that began abruptly 2 hours ago. Her brother has a history of aortic dissection at a young age. She is referred for urgent coronary angiography, which is shown in Figure 39-1. Based on the angiographic findings and the patient's clinical picture, which of the following is the most likely diagnosis?

FIGURE 39-1 Coronary angiogram for the patient described in question 39-7.

A. Acute plaque rupture (type I) myocardial infarction in the setting of atherosclerotic CAD
B. Coronary artery embolization
C. Coronary artery dissection
D. Aortic dissection with extension into the coronary arteries
E. Takayasu arteritis

39-8. A 52-year-old female cigarette smoker presents with chest pain and ST segment elevations in leads V4 to V6 on a 12-lead ECG, which abruptly resolve accompanied by the resolution of chest pain with a dose of sublingual nitroglycerin in the emergency room. She undergoes coronary angiography, which demonstrates only a 60% stenosis in the circumflex artery. A diagnosis of variant angina is made. All of the following are potentially beneficial treatments *except*:

A. Nifedipine
B. Amlodipine

C. Atorvastatin
D. Isosorbide mononitrate
E. Metoprolol

39-9. A 65-year-old woman presents with two days of chest pain and progressive dyspnea. She has anterolateral ST elevations, and her troponin is 5 times the upper limit for normal. She undergoes coronary angiography and ventriculography, which is shown in Figure 39-2. Which of the following statements is *true* about the underlying diagnosis?

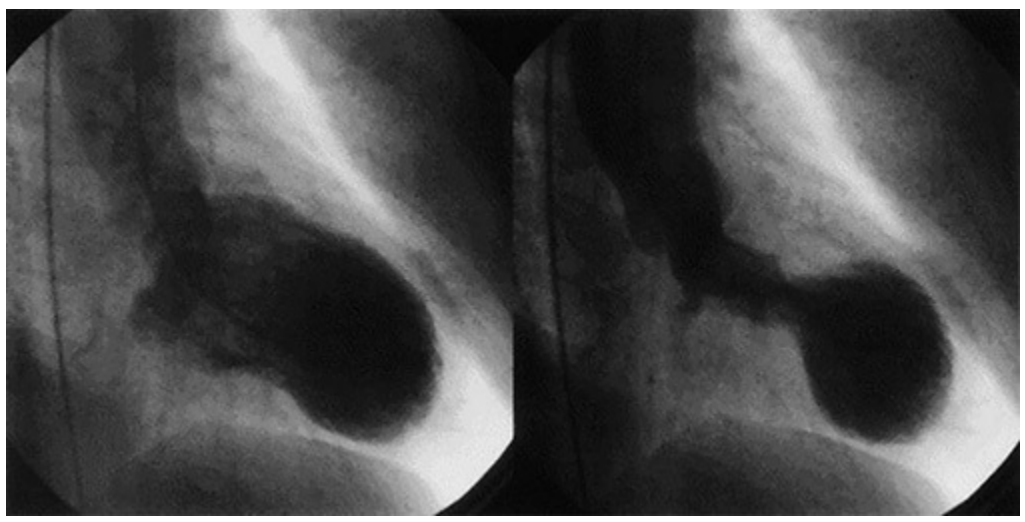

FIGURE 39-2 Left ventriculogram for the patient described in question 39-9. (Reproduced with permission from Abe Y, Kondo M, Matsuoka R, et al. Assessment of clinical features in transient left ventricular apical ballooning, *J Am Coll Cardiol*. 2003 Mar 5;41(5):737-742.)

A. The incidence is rare, approximately 1 in 1000 patients presenting with ACS
B. Emotional stress in the presence of symmetric T-wave inversion in most leads is diagnostic for the condition
C. At angiography, most patients with this condition will not have obstructive CAD
D. Inotropes in this patient are likely to improve hemodynamics
E. The condition is more common in women

39-10. A 67-year-old man presents to the emergency department with chest pain and is diagnosed with NSTEMI. According to the 2014 ACCF/AHA guidelines, all of the following represent class III recommendations *except*:

A. Ibuprofen for early pericarditis
B. Nitroglycerin for pain relief in a patient with recent sildenafil use
C. Immediate release nifidipine in the absence of a beta-blocker
D. Intravenous metoprolol if the oral route is unavailable
E. Withholding oxygen therapy to when SpO_2 is < 90%

ANSWERS

39-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 39)* T wave flattening or low-level inversion (< 1 mm) is associated with a lower likelihood of obstructive CAD as the basis for chest symptoms, whereas more marked symmetric T-wave inversion in multiple precordial leads is highly suggestive of CAD. A number of factors increase or decrease the likelihood of CAD (Table 39-1; answers A through D are incorrect).

TABLE 39-1 Likelihood that Chest Symptoms Are Caused by Myocardial Ischemia Attributable to Obstructive Coronary Artery Disease

High likelihood
Known coronary disease (particularly recent PCI)
Typical angina reproducing prior documented angina
Hemodynamic or ECG changes during pain
Dynamic ST-segment elevation or depression of ≥1 mm
Marked symmetric T-wave inversion in multiple precordial leads
Elevated cardiac enzymes in a rising and falling pattern
Intermediate likelihood
Absence of high-likelihood features and any of the following:
Typical angina in a patient without prior documented angina
Atypical anginal symptoms in diabetics or in nondiabetics with two or more other risk factors
Male gender

Age older than 70 y
Extracardiac vascular disease
ST depression 0.5-1.0 mm or T-wave inversion of ≥1 mm
Low-level troponin elevation that is “flat” and does not rise or fall
Low likelihood
Absence of high- or intermediate-likelihood features but may have:
Chest discomfort reproduced by palpation
T waves flat or inverted < 1 mm
Normal ECG

39-2. **The answer is C.** *(Hurst’s The Heart, 14th Edition, Chap. 39)* Even minor ST depression is associated with a markedly increased mortality rate. Among 9461 patients enrolled in the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) study, mortality at 30 days was 5.1% in patients with ST-segment depression versus 2.1% among those without ST-segment depression.[1]

Transient ST-segment depression of at least 0.5 mm that appears during chest discomfort and disappears after relief provides objective evidence of transient myocardial ischemia. When it is a constant finding with or without chest pain, it is less specific (option A is incorrect). A common but nonspecific ECG pattern in patients with UA/NSTEMI consists of persistent negative T waves over the involved area (option B is incorrect). Deeply negative T waves across the precordial (anterior) leads suggest a proximal, severe, left anterior descending coronary artery stenosis as the culprit lesion and are considered a marker of high risk. However, patients with isolated T-wave inversion have a more favorable prognosis than do those with ST-segment depression (option D is incorrect).[2]

39-3. **The answer is A.** *(Hurst’s The Heart, 14th Edition, Chap. 39)* Stress testing is commonly used for risk stratification in patients with UA/NSTEMI who are managed with an initial conservative (“ischemia-guided”) strategy. The Duke treadmill score (DTS) is used to objectify risk during exercise stress testing. The score is calculated as: DTS = Exercise time (minutes) – (5 × ST deviation in mm) – (4 × angina index). The angina index is scored as: 0 points if no angina occurs, 1 point if nonlimiting angina occurs, and 2 points if angina occurs that limits exercise. Scores are considered low (> 5), intermediate (between 4 and –11), and high (< –11). The other answer choices confer a high risk (Table 39-2; options B through E are incorrect). Stress tests should be symptom limited rather than submaximal, and a stress ECG without adjunctive imaging is appropriate unless baseline ECG abnormalities would preclude adequate interpretation. Those with high-risk findings should undergo coronary arteriography; those with negative or low-risk results can be treated medically. Low-risk patients who complete a stay in a chest pain unit without objective evidence of myocardial ischemia can safely undergo stress testing for diagnosis and prognostic purposes either immediately or, when possible, within 48 hours as an outpatient. In patients who cannot exercise, pharmacologic testing with dipyridamole, adenosine, regadenoson, or dobutamine can be used to provide the stress, and sestamibi imaging or echocardiography can be used as a method of assessment.

TABLE 39-2 American College of Cardiology/American Heart Association Noninvasive Risk Stratification

High risk (> 3% annual mortality rate)
1. Severe resting LV dysfunction (LVEF < 0.35)
2. High-risk treadmill (score ≤ 11)
3. Severe exercise LV dysfunction (exercise LVEF < 0.35)
4. Stress-induced large perfusion defect (particularly if anterior)
5. Stress-induced multiple perfusion defects of moderate size
6. Large, fixed perfusion defect with LV dilatation or increased lung uptake
7. Stress-induced moderate perfusion defect with LV dilatation or increased lung uptake (thallium-201)
8. Echocardiographic wall motion abnormality (involving > 2 segments) developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (≤120 bpm)
9. Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1%-3% annual mortality rate)
1. Mild to moderate resting LV dysfunction (LVEF 0.35-0.49)
2. Intermediate-risk treadmill score (score –11 to +5)
3. Stress-induced moderate perfusion defect without LV dilatation or increased lung intake
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤ 2 segments.
Low risk (< 1% annual mortality rate)
1. Low-risk treadmill (score ≥ +5)
2. Normal or small myocardial perfusion defect at rest or with stress
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress

39-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 39)* The TIMI Risk Score for unstable angina/NSTEMI errs in the risk stratification of patients presenting with suspected acute coronary syndromes. The score allocates points for all of the above risk factors, except for ST changes ≥ 0.5 mm (not 1 mm) on ECG (options A, B, C, and E are incorrect). Patients with unstable angina/NSTEMI at low risk based on TIMI Risk Scores 0 or 1 (or GRACE Risk Score of < 109) can be managed by an "ischemia-guided" strategy.

39-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 39)* Although reversible, ticagrelor still has residual antiplatelet effects for up to 5 days among individuals on chronic therapy, and it should be withheld for at least 5 days if possible prior to nonemergent surgery. Ticagrelor has several known, usually self-limited, side effects, which likely arise from its interference with adenosine uptake (options A through C are incorrect). In the PLATO trial,[3] at the end of the 12-month follow-up period, the primary end point (CV death, MI, and stroke) was reduced from 11.7% in the clopidogrel arm to 9.8% in the ticagrelor arm (HR, 0.84; 95% CI, 0.77–0.92; P < .001). In addition to significant reductions in MI alone, there was also a significant 21% relative risk reduction in vascular mortality and a 22% reduction in total mortality (5.9% vs 4.5%; P < .001).

39-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 39)* Fondaparinux receives a class I recommendation in the most recent AHA/ACC NSTEMI guidelines. In the OASIS 5 trial, which enrolled > 20,000 patients with UA/NSTEMI, 2.5 mg/d of fondaparinux versus 1 mg/kg twice a day of enoxaparin yielded similar rates of the primary end point of death, MI, or refractory ischemia at 9 days (5.8% vs 5.7%; option A is incorrect). However, major bleeding events were reduced by 48% with fondaparinux, and mortality trended lower in the fondaparinux group at 30 days (2.9% vs 3.5%; *P* = .02) and at 180 days (5.8% vs 6.5%; *P* = .05); all but three of the 64 excess deaths with enoxaparin were associated with major or minor bleeding (option B is incorrect). However, several caveats to the OASIS 5 trial merit mention. First, patients were allowed entry with a creatinine up to 3.0 mg/dL. Major bleeding risk was particularly high among patients treated with weight-adjusted enoxaparin who had a creatinine clearance below 30 mL/min (9.9% rate of major bleeding; option D is incorrect). Second, UFH was administered after randomization in a larger proportion of enoxaparin-treated patients, a practice that is thought to increase bleeding risks. Third, the long half-life of fondaparinux may create logistical problems in centers that perform early cardiac catheterization. Finally, among patients undergoing cardiac catheterization, an excess in catheter-related thrombotic complications was observed, a finding that has also been observed in other trials using fondaparinux (option C is incorrect). Finally, it should be noted that, as of the time of writing, fondaparinux has not been approved by the United States Food and Drug Administration for use in patients with acute coronary syndromes, although it received a class I recommendation from the ACCF/AHA Guidelines and is used off-label.

39-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 39)* Figure 39-1 demonstrates the coronary angiogram of a patient with spontaneous coronary artery dissection (SCAD); diffuse irregularity of the left anterior descending artery is noted, along with extension into side branches, including the diagonal artery. SCAD is an increasingly recognized cause of ACS, particularly in women age 30 to 50 years. The pathophysiology of SCAD is unknown; many cases occur in situations such as uncontrolled hypertension, in the puerperium, in those with fibromuscular dysplasia, or as a complication of disorders of collagen integrity, such as Marfan syndrome. The diagnosis of SCAD should be entertained when younger (usually female) patients present with symptoms and signs of acute coronary ischemia in the absence of other risk factors. Diagnostic studies for those with SCAD should be similar to those without the diagnosis; the presence of a coronary dissection plane may be challenging to recognize at the time of coronary angiography, so a high level of suspicion for the presence of the diagnosis should be maintained during such procedures. Standard treatment for SCAD is not established. For many, conservative management may be quite effective, particularly if flow is present in the coronary artery at the time of diagnostic coronary angiography; spontaneous healing of the dissection may be seen at the time of follow-up angiography. Revascularization, by PCI or CABG, is potentially indicated in the presence of an occlusion of a coronary vessel. Given the high prevalence of unrecognized fibromuscular dysplasia in affected patients, some recommend screening for the presence of intracranial aneurysm in those affected by SCAD.

39-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 39)* Variant angina, also called Prinzmetal's angina, is characterized by transient marked ST-segment elevation in the absence of plaque rupture and is thought to be caused by coronary spasm, which is usually focal and often at the site of a coronary artery stenosis. It is thought that coronary spasm is a result of abnormalities in endothelial function and nitric oxide activity at sites of coronary spasm.

Patients with variant angina are often difficult to treat because attacks are unpredictable and often occur without an obvious precipitating factor. NTG relieves variant angina attacks within minutes and should be used promptly; long-acting nitrates are initially effective in preventing variant angina attacks (option D is incorrect). CCBs are very effective in preventing attacks of variant angina (options A and B are incorrect); higher CCB doses are often required. For example, long-acting nifedipine (90 mg/d), diltiazem (360 mg/d), verapamil (480 mg/d), and amlodipine (20 mg/d) are commonly used. Statin therapy is indicated (option C is incorrect), given beneficial effects on endothelial function and the common presence of atherosclerosis underlying focal spasm. There is no documented role for beta-blockers.

39-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 39)* Figure 39-2 demonstrates the characteristic left ventriculogram of a patient with stress cardiomyopathy. Widely recognized as an ACS "mimic," stress cardiomyopathy (also known as "apical ballooning" syndrome or takotsubo cardiomyopathy as a result of the resemblance of the dysfunctional LV to a Japanese octopus pot trap) is found in 1.7% to 2.2% of patients presenting with ACS, and the vast majority (> 90%) are women (option E is correct). Stress cardiomyopathy most often follows an acute emotional stress, such as the death of a loved one, and it may be indistinguishable from a high-risk ACS, with typical angina, rise and fall

of troponin, and onset of heart failure symptoms. Characteristic ECG changes of stress cardiomyopathy include the development of symmetric T-wave inversion in most leads; however, such changes are not specific enough to stress cardiomyopathy to avoid diagnostic coronary angiography (option B is incorrect). At angiography, nonobstructed coronary arteries are the rule (option C is incorrect), along with characteristic myocardial dysfunction of the LV apex, with compensatory basal hyperkinesis. Management of patients with stress cardiomyopathy is typically supportive; patients most often recover rapidly after presentation, though shock at presentation is not uncommon. The use of vasodilating inotropic agents or intra-aortic balloon counterpulsation in those with shock may actually worsen hemodynamics because such treatment may precipitate LV outflow tract obstruction in the context of basal hyperkinesis (option D is incorrect). β-Blockers and ACE inhibitors or ARBs are often used during convalescent periods, but their value in stress cardiomyopathy is unknown.

39-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 39)* A number of pharmacologic strategies are proposed in patients with unstable angina/NSTEMI, as outlined in Table 39-3 (options A through D are incorrect).

TABLE 39-3 American College of Cardiology/American Heart Association Guideline Recommendations for Early Care of Patients with Suspected Acute Coronary Syndrome Treatment Recommendation Level of Evidence

Treatment		Recommendation	Level of Evidence
Oxygen	Administer supplemental oxygen only with oxygen saturation < 90%, respiratory distress, or other high-risk features for hypoxemia	I	C
Nitrates	Administer sublingual nitroglycerin every 5 minutes × 3 for continuing ischemic pain and then assess need for IV nitroglycerin	I	C
	Administer IV nitroglycerin for persistent ischemia, HF, or hypertension	I	B
	Nitrates are contraindicated with recent use of a phosphodiesterase inhibitor	III:Harm	B
Analgesic therapy	IV morphine sulfate may be reasonable for continued ischemic chest pain despite maximally tolerated anti-ischemic medications	IIb	B
	NSAIDs (except aspirin) should not be initiated and should be discontinued during hospitalization	III:Harm	B
β-Adrenergic blockers	Initiate oral β-blockers within the first 24 hours in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to β-blockade	I	A
	Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for β-blocker therapy with concomitant NSTE-ACS, stabilized HF, and reduced systolic function	I	C
	Reevaluate to determine subsequent eligibility in patients with initial contraindications to β-blockers	I	C
	It is reasonable to continue β-blocker therapy in patients with normal LV function with NSTE-ACS	IIa	C
	IV β-blockers are potentially harmful when risk factors for shock are present	III:Harm	B
Calcium channel blockers	Administer initial therapy with nondihydropyridine calcium channel blockers with recurrent ischemia and contraindications to β-blockers in the absence of LV dysfunction, increased risk for cardiogenic shock, PR interval > 0.24 seconds, or second- or third-degree atrioventricular block without a pacemaker	I	B
	Administer oral nondihydropyridine calcium antagonists with recurrent ischemia after use of β-blocker and nitrates in the absence of contraindications	I	C
	Calcium channel blockers are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects	I	C
	Long-acting calcium channel blockers and nitrates are recommended for patients with coronary artery spasm	I	C
	Immediate-release nifedipine is contraindicated in the absence of a β-blocker	III:Harm	B
Cholesterol management	Initiate or continue high-intensity statin therapy in patients with no contraindications	I	A
	Obtain a fasting lipid profile, preferably within 24 hours	IIa	C

Abbreviations: HF, heart failure; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; NSTE-ACS, non–ST-segment elevation acute coronary syndrome.

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CHAPTER 40

ST-Segment Elevation Myocardial Infarction

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

40-1. All of the following electrocardiographic findings can potentially support the diagnosis of a myocardial infarction in the presence of a known old left bundle branch block *except*:

A. Precordial R-wave regression
B. ST-segment elevation ≥ 1 mm concordant with the QRS complex
C. ST-segment elevation ≥ 5 mm discordant with the QRS
D. ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3
E. T-wave inversions in the anterior precordial leads

40-2. A 55-year-old man with a history of coronary artery disease is brought to the emergency room with chest pain by his wife. His ECG demonstrates ST-segment elevation. Which of the following is *true* about his initial management?

A. If he presents to a non–PCI-capable hospital, lytic therapy should be administered promptly, in the absence of contraindications, and the patient should emergently be transferred to a PCI-capable hospital for "facilitated PCI"
B. If the patient presents to a PCI-capable hospital, the desired first medical contact (FMC)-to-device time is < 120 minutes
C. If the patient presents to a non–PCI-capable hospital, and the anticipated FMC-to-device time, including transfer to a PCI-capable hospital, is < 120 minutes, then the patient should be transferred for primary PCI without receiving fibrinolysis
D. When PCI is unavailable, a fibrinolytic should be administered within 90 minutes
E. Patients treated successfully with fibrinolysis do not require follow-up angiography

40-3. All of the following are reasons to preferentially transfer a patient with STEMI for primary PCI rather than administer fibrinolytic therapy *except*:

A. Diagnosis of plaque rupture myocardial infarction in doubt
B. Cardiogenic shock
C. Suspected aortic dissection
D. History of ischemic stroke 6 months prior
E. Anticipated FMC-to-device time of 90 minutes, including transfer

40-4. Which of the following is *true* about the administration of fibrinolytic therapy for patients with STEMI?

A. Reperfusion therapy is reasonable for patients with STEMI and symptom onset within the prior 12 to 24 hours who have clinical and/or ECG evidence of ongoing ischemia. Primary PCI is the preferred strategy in this population
B. Fibrinolysis and primary PCI are associated with equivalent vessel patency rates
C. While there is no mortality benefit associated with primary PCI over fibrinolysis, the lower risk of stroke makes primary PCI the preferred reperfusion strategy in most cases
D. Fibrinolysis should generally be considered up to 6 hours following symptoms onset
E. There are no circumstances under which fibrinolysis should be administered for patients with ST depressions

40-5. A 56-year-old woman presents with crushing chest pain for 30 minutes. Which of the following 12-lead ECG changes would suggest involvement of the left main coronary artery?

A. ST-segment elevation in lead V_1 in the setting of inferior myocardial infarction
B. ST-segment elevation in leads I, aVL, V_5, and V_6
C. Peaking following by a loss of anterior R waves
D. Failure of T waves to invert within 48 hours following the administration of fibrinolysis
E. ST elevation in lead aVR greater than or equal to the extent of ST-segment elevation in lead V_1

40-6. A 67-year-old man is admitted with an anterior STEMI, and he undergoes successful reperfusion with primary PCI. His left ventricular ejection fraction is 35%. All of the following represent potential angiotensin-converting enzyme (ACE) inhibitor regimens to begin ideally within the first 24 hours for this patient *except*:

A. Captopril 6.25 to 12.5 mg 3 times/d to start; titrate to 25 to 50 mg 3 times/d as tolerated
B. Lisinopril 2.5 to 5 mg/d to start; titrate to 10 mg/d or higher as tolerated
C. Ramipril 2.5 mg twice daily to start; titrate to 5 mg twice daily as tolerated
D. Trandolapril test dose 0.5 mg; titrate up to 4 mg daily as tolerated
E. Enalaprilat 1 mg/dose IV over a two-hour period, followed by oral enalopril

40-7. Which of the following is *true* about the epidemiology of cardiogenic shock complicating myocardial infarction?

A. No therapy has meaningfully improved the mortality rate from cardiogenic shock
B. The incidence of cardiogenic shock as a result of severe LV dysfunction complicating MI has decreased over time
C. No trials have successfully demonstrated improvement in outcomes in patients with cardiogenic shock
D. Mortality from cardiogenic shock now is approximately 25%
E. None of the above statements are true

40-8. A 52-year-old man presents with myocardial infarction and undergoes placement of a pulmonary artery catheter, which demonstrated a cardiac index of 2.6 L/min/m^2 and a pulmonary capillary wedge pressure of 22 mm Hg. Which of the following Forrester classifications applies to this patient?

A. Class I
B. Class II
C. Class III
D. Class IV
E. Class V

40-9. A 78-year-old woman presents with chest pain and ST elevation in leads II, III, and aVF. She has ST-segment elevation in lead V4R. Within several minutes of assessment, she becomes progressive hypotensive. The cardiac catheterization team is en route to the hospital. All of the following principles apply to therapy for patients with STEMI and RV infarction and ischemic dysfunction *except*:

A. Nitroglycerine is beneficial to relieve symptoms of chest pain and to decrease endogenous catecholamine release
B. Atrioventricular synchrony should be achieved, and bradycardia should be corrected
C. RV preload should be optimized, which usually requires initial volume challenge in patients with hemodynamic instability provided the jugular venous pressure is normal or low
D. RV afterload should be optimized, which usually requires therapy for concomitant LV dysfunction
E. Inotropic support should be used for hemodynamic instability not responsive to volume challenge

40-10. Which of the following is *true* of patients with acute mitral regurgitation (MR) in the setting of myocardial infarction?

A. The onset of MR due to papillary muscle is usually 14 days following myocardial infarction
B. Acute MR will be detectable at the bedside by the presence of a new-onset, loud, apical systolic murmur
C. When papillary muscle rupture occurs, the posteromedial papillary muscle is more often involved than the anterolateral muscle
D. Echocardiography is often insufficient to make the diagnosis
E. IABP and blood pressure control are used to treat patients acutely and to allow the myocardium to heal; surgery is rarely required

ANSWERS

40-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 40)* New-onset (or not known to be old) LBBB in the setting of chest pain is typically considered and treated as an STEMI. Conversely, the diagnosis of STEMI in the setting of old LBBB can be difficult. Findings suggesting STEMI include (1) a pathologic Q wave in leads I, aVL, V_5, or V_6 (two leads); (2) precordial R-wave regression (option A is incorrect); (3) late notching of the S wave in V_1 to V_4; and (4) deviation of the ST segment in the same direction as that of the major QRS deflection.

An analysis of ECG data from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) I study identified three criteria for diagnosing myocardial infarction in the presence of the LBBB: (1) ST-segment elevation ≥ 1 mm concordant with the QRS complex; (2) ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3; and (3) ST-segment elevation ≥ 5 mm discordant with the QRS (options B through D are incorrect).[1] Such findings are often referred to as the Sgarbossa criteria.

40-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 40)* Primary PCI is superior to fibrinolytic therapy, and when available should be pursued. Patients who present with STEMI to a non–PCI-capable hospital should receive prompt (< 30 minutes; option D is incorrect) fibrinolytic therapy in the absence of contraindications. Such patients should then usually be transferred to a PCI-capable hospital, where follow-up angiography between 3 and 24 hours later (not sooner; option A is incorrect) can be undertaken. If there is evidence of failed thrombolytic therapy (shock, recurrent chest pain, failure of ST segments to decrease by > 50%), then the patient should be transferred more urgently for PCI. On the other hand, for patients who present with STEMI to a PCI-capable hospital, the desired FMC-to-device (eg, coronary stent) time is < 90 minutes (option B is incorrect).

40-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 40)* Patients who present with STEMI to a non–PCI-capable hospital can be managed with fibrinolysis or early transfer to a PCI-capable hospital. If the anticipated FMC-to-device time is anticipated to be < 120 minutes, then transfer should be undertaken (option E is incorrect). Patients presenting with an uncertain diagnosis, such as those with suspected coronary artery dissection, aortic dissection (option C is incorrect), or pericarditis, should be considered for transfer for primary PCI. Additionally, patients with contraindications to fibrinolysis, including ischemic stroke within 3 months (option D is incorrect), should be transferred, as well as those with cardiogenic shock (option B is incorrect).

40-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 40)* While the efficacy of reperfusion declines over time, patients with evidence of ongoing ischemia (ie, chest pain or ongoing ECG changes suggestive of ischemia) can be considered for reperfusion, although in this population the efficacy is anticipated to be lower, and primary PCI is preferred over fibrinolysis. Approximately 95% of patients who are treated with primary PCI obtain complete reperfusion versus 50% to 60% of patients who are treated with fibrinolytics (option B is incorrect). Primary PCI is also associated with a lower risk of stroke than treatment with fibrinolysis, and diagnostic angiography quickly defines coronary anatomy, LV function, and mechanical complications. In meta-analyses, primary PCI is associated with a lower mortality rate (7% vs 9%; $P = .0002$), less reinfarction (3% vs 7%; $P = .0001$), and fewer strokes (1% vs 2%; $P = .0004$) at 30 days when compared with fibrinolysis (option C is incorrect).[2]

Fibrinolysis should be considered up to 12 hours following symptoms onset (option D is incorrect). Fibrinolytic therapy should not be administered to patients with ST depression, except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead aVR (option E is incorrect).

40-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 40)* ST-segment elevation in lead aVR is an ominous sign and is more frequent in patients with left main artery occlusion than in patients with left anterior descending coronary artery or right coronary artery occlusion. In a study of STEMI patients, ST-segment elevation in lead aVR that was greater than or equal to the extent of ST-segment elevation in lead V_1 had 81% accuracy for diagnosing left main occlusion.[3] Generally, ST-elevation myocardial infarction is defined by new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V_2 to V_3 and/or of 1 mm (0.1 mV) in other contiguous chest leads or the limb leads. ST-segment elevation in lead V_1 in the setting of inferior myocardial infarction suggests RV involvement (option A is incorrect). Because no leads on the standard 12-lead ECG directly represent the posterior myocardium, isolated infarction of this area may be difficult to diagnose but is typically manifested by ST-segment depression in V_1 to V_3, a mirror image of anterior myocardial infarct. ST-elevation in leads I, aVL, V_5, and V_6 suggests lateral wall infarction (option B is incorrect). While the R wave may initially increase in height but then soon decrease, this finding is not specific for left main coronary artery disease (option C is incorrect). Failure of the T wave to invert within 24 to 48 hours suggests early postinfarction regional pericarditis (option D is incorrect).

40-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 40)* In the Cooperative New Scandinavian Enalapril Survival Study-2 (CONSENSUS-2) trial, intravenous enalaprilat was administered within 24 hours of presentation followed by oral enalapril. In CONSENSUS-2, mortality was nonsignificantly increased in the treatment group. Conversely, a number of trials demonstrated a benefit with other ACE inhibitor regimens in patients with myocardial infarction, including the Survival and Ventricular Enlargement (SAVE) and Captopril and Thrombolysis Study (CATS) trials of captopril (option A is incorrect), the Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) trial of lisinopril (option B is incorrect), the Acute Infarction Ramipril Efficacy (AIRE) trial (option C is incorrect), and the Trandolapril Cardiac Evaluation (TRACE) trial (option D is incorrect).

40-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 40)* Cardiogenic shock as a result of severe LV dysfunction occurs in approximately 7% of patients with myocardial infarction; it previously had a mortality rate of approximately 80% before the widespread implementation of early revascularization (option A is incorrect). There was a trend toward increased in-hospital survival in the mid- to late 1990s, which correlated with the increased application of reperfusion technologies. The SHOCK II (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock II) trial demonstrated the benefit of early revascularization in patients with MI and cardiogenic shock (option C is incorrect). In most recent studies, the mortality from cardiogenic shock remains approximately 50% (option D is incorrect).

40-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 40)* Forrester described the treatment of patients on the basis of hemodynamic subsets related to pulmonary artery wedge pressure and cardiac output (Table 40-1). The basic goals of this approach include adjustment of the intravascular volume status to bring the pulmonary artery capillary wedge pressure from 18 to 20 mm Hg and optimization of cardiac output with inotropic and/or vasodilating agents. Severely hypotensive patients can be temporarily aided by intra-aortic balloon pumping or possibly by a ventricular assist device.

However, the benefits from these mechanical treatments are often temporary, and there may be a significant risk of complications.

TABLE 40-1 Forrester Classification of Myocardial Infarction

	Cardiac Index ($L/min/m^2$)	Pulmonary Capillary Wedge Pressure (mm Hg)
Class I	> 2.2	< 18
Class II	> 2.2	> 18
Class III	< 2.2	< 18
Class IV	< 2.2	> 18

40-9. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 40)* Patients with right ventricular myocardial infarction should not receive therapies that could deplete preload, such as nitroglycerine. Patients with right ventricular infarction (RVI) present with a mix of left ventricular and right ventricular injury, and the overall balance between the extent of RV and LV dysfunction is a major determinant of long-term outcome. Most patients with RVI and significant hemodynamic compromise have evidence of extensive biventricular infarction and cardiogenic shock. Treatment of RVI initially involves volume loading with normal saline to achieve a pulmonary artery wedge pressure of 18 to 20 mm Hg. In some patients, this alone is sufficient to improve cardiac output and systemic pressure. However, some patients will not respond to fluid loading alone. This may be a result of marked RV enlargement within a relatively noncompliant pericardium, which may result in functional LV compression because of ventricular interaction. In addition to volume loading, the use of dobutamine improves cardiac index. Patients requiring temporary pacing for heart block may also benefit from arteriovenous sequential pacing rather than lone ventricular pacing.

40-10. The answer is C. *(Hurst's The Heart, 14th Edition, Chap. 40)* Severe MR caused by papillary muscle rupture is responsible for approximately 5% of deaths in AMI patients. Rupture may be complete or partial, and it usually involves the posteromedial papillary muscle because its blood supply is derived only from the posterior descending artery, whereas the anterolateral papillary muscle has a dual blood supply from both the left anterior descending and the circumflex coronary arteries. Most patients have relatively small areas of infarction with poor collaterals, and up to half of the patients may have single-vessel disease. The clinical presentation of papillary muscle rupture is the acute onset of pulmonary edema, usually within 2 to 7 days after inferior myocardial infarction (option A is incorrect). The characteristics of the murmur vary; as a result of a rapid increase of pressure in the left atrium, no murmur may be audible (option B is incorrect). Thus a high degree of suspicion, especially in patients with inferior wall infarction, is necessary for diagnosis. Two-dimensional echocardiographic examination demonstrates the partially or completely severed papillary muscle head and a flail segment of the mitral valve (option D is incorrect). LV function is hyperdynamic as a result of the severe regurgitation into the low-impedance left atrium; this finding alone, in a patient with severe congestive heart failure, should suggest the diagnosis. The cornerstones of successful therapy are prompt diagnosis and emergency surgery (option E is incorrect). Emergent placement of an IABP and blood pressure control may be beneficial. The current approach of emergency surgery accrues an overall operative mortality of 0% to 21%, but this appears to be decreasing, and the late results of this approach can be excellent.

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CHAPTER 41

Antiplatelet and Anticoagulant Therapy in Acute Coronary Syndromes

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

41-1. A 45-year-old man undergoes coronary stent implantation for stable ischemic heart disease. He is prescribed clopidogrel and aspirin. Which of the following is *true* about his antithrombotic regimen?

A. The dose of aspirin should be between 75 and 100 mg per day
B. Higher doses of aspirin could be more effective at preventing ischemic events, but at the expense of a higher risk of bleeding
C. Clinical trials support a higher dose (ie, 300 to 325 mg daily) of aspirin in patients with ischemic heart disease
D. When used with newer-generation oral $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor), no preference to aspirin dosing is given
E. None of the above

41-2. All of the following are actions of thromboxane A_2 (TXA_2) *except*:

A. Induces platelet aggregation
B. Potent vasoconstrictor
C. Regulation of renal blood flow
D. Induces proliferation of vascular smooth-muscle cells
E. Proatherogenic

41-3. Which of the following is *true* about clopidogrel?

A. Clopidogrel is approved only in patients receiving percutaneous coronary intervention (PCI) for myocardial infarction
B. All patients with ST-elevation myocardial infarction (STEMI) should receive a loading dose of 600 mg of clopidogrel
C. Renal dose adjustment in the loading and mantainance dose should be undertaken when the estimated glomerular filtration rate (eGFR) is < 30 mL/min per 1.73 m^2
D. In patients scheduled for nonemergent coronary artery bypass graft (CABG) surgery, clopidogrel should be held for 5 days if it is safe to do so clinically
E. Clopidogrel is a bioactive immediately medication

41-4. Which of the following is *true* about intravenous antiplatelet agents?

A. Cangrelor is an intravenous adenosine diphosphate (ADP) analog
B. Cangrelor requires conversion into a bioactive metabolite in the liver
C. Cangrelor's use is experimental only.
D. Parenteral glycoprotein IIb/IIIa inhibitors (such as abciximab, eptifibatide, and tirofiban) have demonstrated an evidence-based reduction in major adverse cardiac events in patients undergoing percutaneous coronary intervention
E. Thrombocytopenia is uncommon with glycoprotein IIb/IIIa inhibitors

41-5. According to the American College of Cardiology Foundation/American Heart Association guidelines for the use of thrombolytics in the management of ST-segment elevation myocardial infarction, all of the following are true *except*:

A. In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated first medical contact (FMC)-to-device time at a PCI-capable hospital exceeds 90 minutes because of unavoidable delays
B. When fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of hospital arrival

C. In the absence of contraindications and when PCI is not available, fibrinolytic therapy is reasonable for patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia within 12 to 24 hours of symptom onset and a large area of myocardium at risk or hemodynamic instability
D. Fibrinolytic therapy should not be administered to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when it is associated with ST elevation in lead aVR
E. Fibrin-specific fibrinolytic agents (tenecteplase, reteplase, alteplase) are preferred over streptokinase if available

41-6. All of the following are *true* about aspirin pharmacokinetics *except*:

A. Peak plasma levels occur 30 to 40 minutes after ingestion
B. Aspirin absorption in the upper gastrointestinal tract occurs within 60 minutes
C. Enteric coating of aspirin has negligible effects on absorption pharmacokinetics
D. COX-mediated TXA_2 synthesis is prevented for the entire life span of the platelet
E. COX-1 and COX-2 are not similarly blocked by equivalent doses of aspirin

41-7. The following are absolute contraindications to fibrinolytic therapy *except*:

A. Structural intracranial disease
B. Previous intracranial hemorrhage
C. Previous ischemic stroke
D. Active bleeding or bleeding diathesis
E. Recent brain or spinal surgery or recent head trauma with fracture or brain injury

41-8. All of the following anticoagulants act by interrupting factor Xa *except*:

A. Enoxaparin
B. Fondaparinux
C. Unfractionated heparin
D. Rivaroxaban
E. Bivalirudin

41-9. According to the American College of Cardiology Foundation/American Heart Association guidelines for the use of anticoagulants in the management of ST-segment elevation myocardial infarction, all of the following are true *except*:

A. Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive enoxaparin administered according to age, weight, and creatinine clearance, given as an intravenous bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to 8 days or until revascularization
B. The recommended dosing for enoxaparin for age < 75 years is 30-mg IV bolus followed by 1 mg/kg SC every 12 h (maximum of 100 mg for the first 2 SC doses) and for age > 75 years is no IV bolus, 0.7 mg/kg SC every 12 h (maximum of 7 mg for the first 2 SC doses)
C. For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last dose of enoxaparin was given < 8 h before PCI, is recommended no additional anticoagulant therapy. If the last dose of enoxaparin was given 8 to 12 h before PCI, is recommended a 0.3mg/kg bolus of IV enoxaparin at the time of PCI
D. For patients receiving alteplase, tenecteplase, or reteplase for fibrinolysis, weight-based IV bolus and infusion of UFH adjusted to obtain aPTT of 1.5 to 2.0 times control are recommended for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization
E. All of the above are consistent with recommendations in the guidelines

ANSWERS

41-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 41)* While some pharmacodynamic studies have suggested high-dose aspirin (eg, 325 mg) may be associated with enhanced antithrombotic effects as a result of COX-1–independent mechanisms, these pharmacodynamic observations do not appear to translate into improved clinical outcomes, and when given in combination with clopidogrel, the maintenance dose of aspirin should generally be lowered to 75 to 100 mg. This is based on a post hoc analysis of data from the CURE[1] (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study in which similar efficacy but less major bleeding was seen in the low-dose (< 100 mg) aspirin group (option B is incorrect). Furthermore, a large-scale prospective randomized study to compare high- versus low-dose aspirin, the CURRENT/OASIS-7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Organization to Assess Strategies in Ischemic Syndromes)[2] trial did not show a benefit to higher dose (300 to 325 mg) versus lower dose (75 to 100 mg) daily aspirin (option C is incorrect). Finally, the introduction into clinical practice of newer-generation oral $P2Y_{12}$ receptor inhibitors (prasugrel and ticagrelor) that are characterized by greater potency than

clopidogrel and are used in combination with aspirin has also led to questions about the optimal dose of aspirin in these patients. Although aspirin dosing did not affect the safety and efficacy profile of patients treated with prasugrel in the TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel) study, a higher dose of aspirin (≥ 300 mg) was associated with reduced efficacy, albeit with no differences in bleeding, in patients treated with ticagrelor in the PLATO (Platelet Inhibition and Outcomes) trial[3] (option D is incorrect).

41-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 41)* The cyclooxygenase (COX) isozymes catalyze the conversion of arachidonic acid to prostaglandin H_2, an unstable intermediate that is the substrate for multiple downstream isomerases that lead to the generation of several prostanoids, including TXA_2 and prostacyclin (PGI_2). Thromboxane A_2 plays roles in platelet aggregation, vasoconstriction, the proliferation of vascular smooth-muscle cells, and the acceleration of atherosclerosis (options A, B, D, and E are incorrect). Conversely, prostacyclin plays a role in regulating renal blood flow, and it functions as a platelet inhibitor and a vasodilator. Only COX-1 is expressed in mature platelets. Importantly, TXA_2 (an amplifier of platelet activation and a vasoconstrictor) is derived largely from COX-1 (mostly from platelets), and its biosynthesis is highly sensitive to inhibition by aspirin, whereas vascular PGI_2 (a platelet inhibitor and a vasodilator) is derived predominantly from COX-2 and is less susceptible to inhibition by low doses of aspirin. Therefore, low-dose aspirin ultimately preferentially blocks platelet formation of TXA_2, diminishing platelet aggregation mediated by thromboxane (TP) receptor pathways.

41-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 41)* In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least 5 days in patients receiving clopidogrel. Clopidogrel is approved for the treatment and prevention of secondary atherothrombotic events across the spectrum of patients with ACS, irrespective of the treatment strategy (invasive or noninvasive; option A is incorrect). This recommendation is independent of whether patients are revascularized or not (ie, medical management) and irrespective of strategy for those undergoing PCI (ie, similar for bare metal stent [BMS], drug-eluting stent [DES], or balloon angioplasty). Clopidogrel is also the only oral $P2Y_{12}$ receptor inhibitor approved for patients with stable CAD undergoing PCI. The recommended loading dose of clopidogrel is 300 to 600 mg. However, in the setting of PCI, a 600-mg loading dose is most commonly used. A 300-mg loading dose of clopidogrel, in addition to aspirin, should also be given in patients under age 75 with STEMI treated with fibrinolytic therapy; patients 75 or older treated with fibrinolytic therapy should be treated with clopidogrel 75 mg (without a loading dose; option B is incorrect). After loading dose administration, a maintenance dose of 75 mg daily should be initiated. No dosage adjustment is necessary for patients with renal impairment, including patients with end-stage renal disease (option D is incorrect). Clopidogrel is an inactive prodrug that requires oxidation by the CYP system to generate an active metabolite (option E is incorrect).

41-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 41)* Glycoprotein IIb/IIIa inhibitors (GPIs) have been shown to reduce major adverse cardiac events (death, MI, and urgent revascularization) by 35% to 50% in patients undergoing PCI. However, their broad use has been limited because they are associated with an increased risk of bleeding complications. Moreover, their use has declined in recent years because of treatment alternatives, such as bivalirudin, associated with a more favorable safety profile (ie, less bleeding) as well as the introduction of potent $P2Y_{12}$ receptor inhibitors. Cangrelor is an intravenous adenosine triphosphate (ATP) analog (option A is incorrect). Due to structural modifications, cangrelor has high affinity for the $P2Y_{12}$ receptor and a higher resistance to ectonucleotidases, does not require hepatic conversion, and is directly active (option B is incorrect). Cangrelor was approved by the FDA in 2015 as an adjunct to PCI for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet receptor inhibitor and are not being given a GPI (option C is incorrect).

Acute coronary syndrome trials tended to report higher incidence of thrombocytopenia among patients treated with abciximab compared with PCI trials (option E is incorrect). Some of this risk may by mediated by the need for longer heparin infusions and an increased risk of heparin-induced thrombocytopenia (HIT). Eptifibatide or tirofiban does not appear to increase mild or severe thrombocytopenia compared with placebo. Severe and profound (< 20,000) thrombocytopenia is more commonly associated with abciximab use and requires immediate cessation of therapy. Pseudothrombocytopenia secondary to platelet clumping and HIT needs to be ruled out. The platelet count returns to normal within 48 to 72 hours in most cases.

41-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 41)* In the absence of contraindications, fibrinolytic therapy should be administered to patients with STEMI at non–PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. The remainder of the statements provided are correct (options B through E are incorrect).

41-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 41)* Enteric-coated aspirin delays absorption, with peak plasma levels at 3 to 4 hours, as opposed to 30 to 40 minutes for non-enteric coated (option A is incorrect). Aspirin is rapidly absorbed in the upper gastrointestinal tract and is associated with measurable platelet inhibition within 60 minutes (option B is incorrect). Because the blockade of COX-1 induced by aspirin is irreversible, COX-mediated TXA_2 synthesis is prevented for the entire life span of the platelet (about 7 to 10 days; option D is incorrect). Therefore, even low doses of aspirin can produce long-lasting platelet inhibition. Higher doses of aspirin are needed to inhibit COX-2 than to inhibit COX-1 (option E is incorrect). These differences explain why very high doses of aspirin are needed to

achieve anti-inflammatory and analgesic effects, whereas low doses of aspirin lead to antiplatelet effects.

41-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 41)* Ischemic stroke within the past 3 months is an absolute contraindication to fibrinolytic therapy; ischemic stroke > 3 months prior is a relative contraindication only. The remainder of the options provided are absolute contraindications to fibrinolytic therapy (options A, B, D, and E are incorrect). In addition to ischemic stroke > 3 months prior, other relative contraindications include: systolic blood pressure > 180 or diastolic blood pressure > 110 mm Hg, recent bleeding (nonintracranial), recent surgery, recent invasive procedure, anticoagulation (eg, vitamin K therapy), traumatic or prolonged cardiopulmonary resuscitation, pericarditis or pericardial fluid, and diabetic retinopathy, among others.

41-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 41)* Anticoagulants act by antagonizing or synergizing various factors along the clotting cascade (Figure 41-1). Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X. Activated factor IX serves as a coenzyme of factor VIIIa to form the intrinsic tenase complex, which further activates factor X. Factor Xa binds with factor Va (released from granules of platelets) to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin is a powerful stimulant of platelet activator, further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot. Factor Xa is antagonized either directly (rivaroxaban, apixaban, or edoxaban; option D is incorrect) or indirectly by agents that synergize antithrombin (unfractionated heparin, enoxaparin, and fondaparinux; options A through C are incorrect). Conversely, direct thrombin inhibitors, including bivalirudin, dabigatran, and lepirudin act to block thrombin (factor IIa) directly.

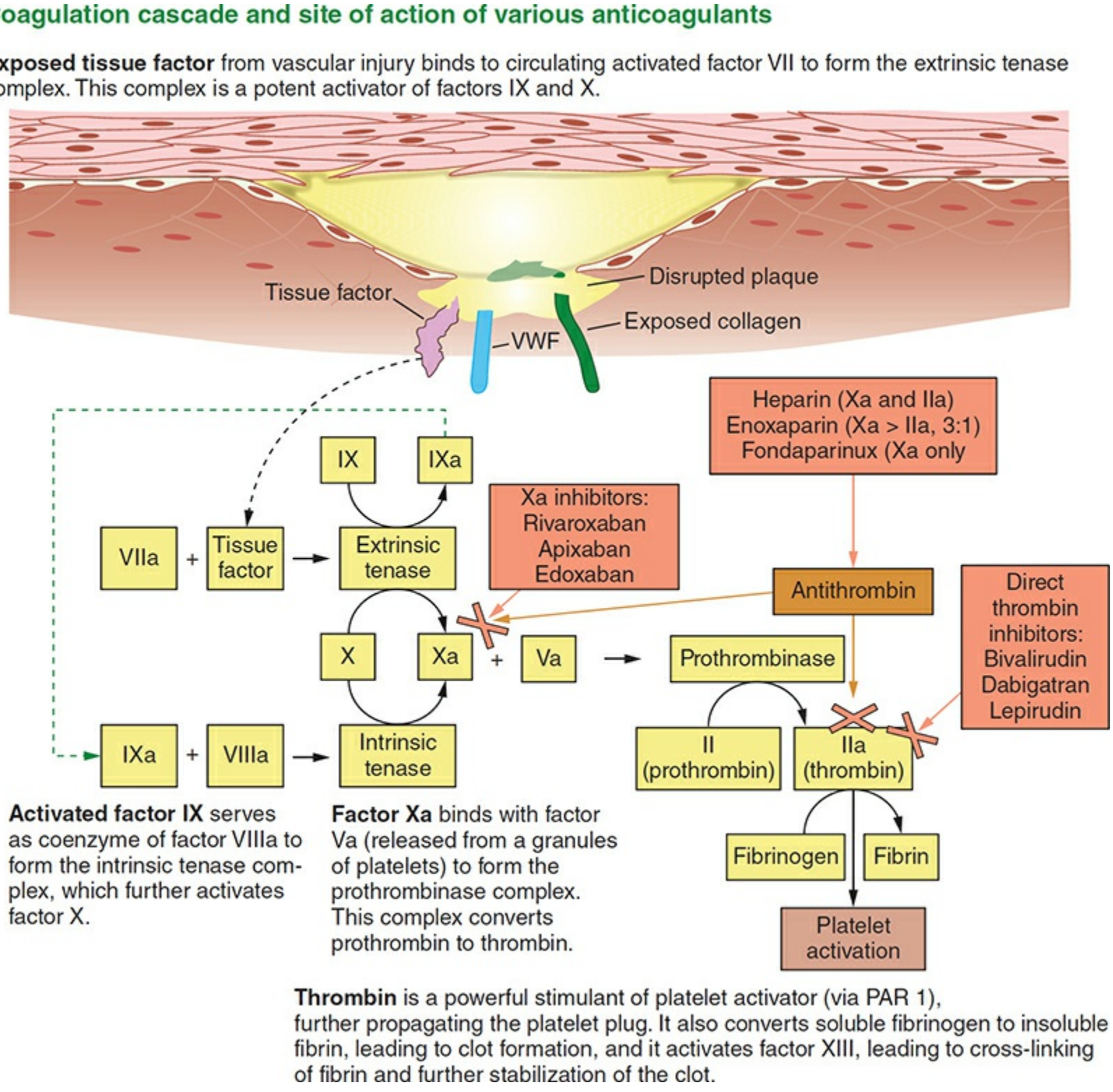

FIGURE 41-1 Coagulation cascade and site of action of various anticoagulants. Exposed tissue factor from vascular injury binds to circulating activated factor VII to form the extrinsic tenase complex. This complex is a potent activator of factors IX and X. Activated factor IX serves as a coenzyme of factor VIIIa to form the intrinsic tenase complex, which further activates factor X. Factor Xa binds with factor Va (released from a granules of platelets) to form the prothrombinase complex. This complex converts prothrombin to thrombin. Thrombin is a powerful stimulant of platelet activator, further propagating the platelet plug. It also converts soluble fibrinogen to insoluble fibrin, leading to clot formation, and it activates factor XIII, leading to cross-linking of fibrin and further stabilization of the clot.

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41-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 41)* All of the options above are consistent with American College of Cardiology Foundation/American Heart Association recommendations as of 2017 (options A through D are incorrect).

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CHAPTER 42

Percutaneous Coronary Interventions in Acute Myocardial Infarction and Acute Coronary Syndromes

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

42-1. Which of the following is *not* an advantage of primary percutaneous coronary intervention (PCI) over fibrinolytic therapy for ST-segment elevation myocardial infarction (STEMI)?

A. Primary PCI is associated with a reduced incidence of intracranial hemorrhage
B. Primary PCI is superior in reducing short-term mortality
C. Primary PCI has a lower overall risk of major bleeding
D. Primary PCI is associated with fewer nonfatal reinfarctions
E. All of the above are correct

42-2. A 58-year-old man begins to experience chest pain that radiates to his left arm while jogging. He initially dismisses the symptoms and is admitted to the emergency department 6 hours later with an anterior myocardial infarction (MI) confirmed by ECG. Which of the following may be associated with smaller infarct size?

A. TIMI grade 1 flow in the infarct artery
B. Remote ischemic conditioning
C. Anterior MI location
D. Reperfusion with PCI at 6 hours
E. None of the above

42-3. A 64-year-old woman with long-standing hypertension is admitted to the hospital with an anterior myocardial infaction. She is promptly reperfused by primary PCI, including stenting of the left anterior descenting coronary artery. Which of the following are associated with reduced infarct size?

A. Baseline TIMI grade 3 flow
B. Total ischemia time < 3 hours
C. Nonanterior MI location
D. Remote ischemic conditioning
E. All of the above

42-4. A 54-year-old woman presents with an anterior STEMI. Which of the following is *not true* about ticagrelor administration in this patient?

A. Ticagrelor is an oral $P2Y_{12}$ inihbitor
B. Ticagrelor is not inferior to clopidogrel in the treatment of patients with STEMI
C. The rates of stent thrombosis are similar with ticagrelor and clopidogrel
D. Crushed oral ticagrelor can increase the time to onset of platelet inhibition
E. Dyspnea is a frequent reason for switching from ticagrelor to clopidogrel

42-5. A 48-year-old man presents with an anterior MI and is found to have complete occlusion of the left anterior descending (LAD) artery, as well as an 80% stenosis in the mid-right coronary artery. He is hemodynamically stable and chest pain free following PCI of the LAD. Which of the following is *correct* about the treatment of multivessel disease?

A. PCI of the infarct artery only has better clinical outcomes than multivessel PCI
B. Primary angioplasty of stenosed vessels with normal blood flow is associated with worse survival
C. Multivessel PCI is associated with increased cardiac mortality
D. Mutivessel PCI in the setting of MI is associated with decreased major adverse cardiovascular events

E. All of the above

42-6. Which of the following is *incorrect* regarding adjunctive thrombectomy methods?

A. Adjunctive aspiration thrombectomy enhances angiographic blush scores and ST-segment resolution
B. Routine thrombectomy before or after stent implantation enhances outcomes for all thrombi sizes
C. There is no benefit to the routine use of rheolytic thrombectomy with primary PCI for STEMI
D. It is reasonable to consider adjunctive thrombectomy in all patients with angiographically large thrombus burden before primary PCI
E. None of the above are incorrect

42-7. Which of the following constitutes a *correct* sequence of events following the arrival of a STEMI patient to the hospital?

A. 12-lead ECG, heparin and $P2Y_{12}$ inhibitor administration, transfer to catheterization lab, revascularization with DES, aspirin treatment indefinitely
B. 12-lead ECG, discontinue anticoagulation, transfer to catheterization lab, routine thrombectomy and PCI, aspirin treatment indefinitely
C. Remote ischemic conditioning, 12-lead ECG, transfer to catheterization lab, revascularization with DES, aspirin treatment indefinitely
D. 12-lead ECG, transfer to catheterization lab, revascularization with DES, heparin and $P2Y_{12}$ administration
E. None of the above are correct

42-8. A 44-year-old man presents to the hospital with ongoing acute chest pain and ST depressions on ECG. He has elevated troponin and a history of coronary artery disease. Which treatment is most appropriate for this patient?

A. "Cool off" the acute thrombotic lesion with antiplatelet and anticoagulant agents for a few days
B. Coronary angiography performed the next working day
C. Immediate Coronary angiography
D. Noninvasive stress testing when troponin is down-trending
E. None of the above

42-9. A 53-year-old woman is admitted with acute chest pain and ECG signs of non–ST-segment elevation MI. Revascularization the following morning is planned. Which of the following adjunctive pharmacological strategies is *incorrect*?

A. Pre-PCI treatment with clopidogrel
B. Aspirin loading dose of 300 to 325 mg
C. Subcutaneous injection of low-molecular-weight heparin
D. Pre-PCI treatment with prasugrel
E. All of the above

42-10. A 70-year-old man is brought to the emergency department with acute chest pain, ST-segment depressions on ECG, and sinus bradycardia. Which adjunctive therapy is *not* appropriate in this patient?

A. IV nitroglycerin
B. Beta-blockers
C. Statin
D. Oxygen therapy
E. Dual antiplatelet therapy

ANSWERS

42-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Over the past 40 years, improvements in the design and development of highly effective antithrombotic and antiplatelet therapy have made PCI a widely used revascularization strategy. This technique gained particular success as it became apparent that a severe residual stenosis persisted in most patients after successful fibrinolysis treatment. A meta-analysis of 23 randomized trials incorporating 7739 patients compared primary PCI with fibrinolytic therapy for STEMI.[1] Primary PCI was superior to fibrinolytic therapy in reducing short-term mortality (option B), nonfatal reinfarction (option D), stroke, and the composite end point of death, nonfatal reinfarction, and stroke. These results were maintained at long-term follow-up and were independent of the type of thrombolytic agent used (streptokinase vs fibrin-specific thrombolytics) and whether patients were directly admitted or transferred emergently for primary PCI. The incidence of intracranial hemorrhage was significantly less with primary PCI (option A), although the overall risk of major bleeding (mostly related to access site bleeding) was not lower with primary PCI (option C).

42-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Once consensus was reached that primary PCI is the superior reperfusion modality, attention turned to limiting infarction size. The last decade has seen many pharmacologic and mechanical strategies to limit infarct size, which are summarized in Table 42-1. Achieving TIMI grade 3 flow has a major impact on short- and long-term mortality. Indeed, there appears to be an inverse relationship between the ability to achieve TIMI grade 3 flow and short-term mortality with either reperfusion strategy (option A). Infarctions involving the LAD artery tend to be larger than left circumflex or right coronary artery infarcts (option C). Symptom onset to balloon time was critically important at up to 3 hours of symptom duration. After 3 hours, MI size did not appear to vary with prolonged times to reperfusion (option D). Experimental models suggest that remote ischemic conditioning, such as transient intermittent limb ischemia, may reduce myocardial infarct size in ischemia-reperfusion models (option B); studies are ongoing.

TABLE 42-1 Infarct Size Reduction.

Proven
1. Baseline TIMI grade 3 flow
2. Total ischemia time < 3 hours
3. Nonanterior MI location
4. Remote ischemic conditioning
Potentially useful in anterior STEMI
1. IV metoprolol
2. SSA O_2
3. IV adenosine (high dose, early treatment)
4. Hypothermia
Ongoing trials
1. LV unloading
2. Steroids
3. Colchicine

Methods or factors associated with small final infarction size are tabulated. Remote ischemic conditioning is the only therapy to appear to decrease MI size and provide lasting clinical benefit.
Abbreviations: IV, intravenous; LV, left ventricular; MI, myocardial infarction; SSA O_2, hyperoxemic oxygen therapy; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

42-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 42)* In addition to proven approaches to reducing infarct size (options A–D), several experimental approaches are currently under development, such as methods to decrease reperfusion injury.[2] Reperfusion injury refers to damage to the myocardial tissue caused when blood supply returns to the tissues after a period of ischemia. In this situation, the restoration of flow results in inflammation and oxidative stress damage. Adenosine can potentially reduce reperfusion injury by suppressing free radical formation and by preventing neutrophil activation. Intracoronary administration of supersaturated oxygen with an arterial oxygen partial pressure of 760 to 1000 mm Hg has been tested in two clinical trials.[3,4] Patients with anterior MI who were treated with less than 6 hours of symptom duration or a 90-minute selective intracoronary infusion of supersaturated oxygen after PCI had a reduction in infarct size. In addition, many experimental studies have documented the effectiveness of systemic hypothermia, initiated before reperfusion, in reducing infarct size. More recently, two small trials have pooled results and demonstrated a reduction of infarct size and a decrease in heart failure for anterior MI. Finally, IV metoprolol has been shown to reduce infarct size in patients with anterior MI presenting < 6 hours after symptom onset, although currently due to the findings from the COMMIT-CCS2 trial, its routine use in STEMI is not recommended.

42-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Ticagrelor is a rapid oral $P2Y_{12}$ inhibitor (option A). Oral ticagrelor has been compared to clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) trial. A total of 18,624 patients with AMI and ACS PCI were randomized to clopidogrel 300 mg or ticagrelor 90 mg loading dose and subsequent therapy of 90 mg twice a day. A total of 7008 patients (37%) were undergoing STEMI intervention. The ticagrelor group had a lower event rate (9.8% vs 11.7%; $P < .0001$; option B). Stent thrombosis was decreased from 3.8% to 2.9% ($P = .01$; option C). An even more rapid onset of platelet inhibition can be achieved by crushing the ticagrelor tablet for oral administration (option D). Time to maximal plasma concentration decreased from 4 to 2 hours, and substantial platelet inhibition occurred within 1 hour of oral administration. Dyspnea is a potential complication of ticagrelor, potentially due to its effects on adenosine reuptake, but this side effect is usually self-limited (option E).

42-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 42)* In initial trials of primary PCTA, plaque dissection and intraluminal thrombosis were difficult to treat with balloon angioplasty and heparin alone. Reocclusion of the infarct-related artery occurred in 5% to 15% of cases and worsened survival. In this context, treating non-culprit stenoses with normal blood flow was considered harmful, and thus the practice of primary angioplasty evolved with treatment of the infarct artery only. However, as antithrombotic, antiplatelet, and coronary stenting improved, the issue of complete revascularization was again raised. Three recently performed well-done randomized trials[6-8] demonstrated that the primary end point of death, recurrent MI, or refractory angina was lower in the multivessel PCI group (option A). Cardiac mortality was also lower (option C). They also showed that major adverse cardiovascular events (MACEs) were lower in patients assigned to multivessel PCI (option D) and that on a background of high usage of $P2Y_{12}$ inhibitors,

multivessel PCI is safe and is associated with improved clinical outcomes compared with culprit-only revascularization.

42-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Primary PCI is effective in restoring normal epicardial coronary flow (TIMI grade 3 flow) in more than 90% of patients with STEMI, but more than half of these patients will have suboptimal flow at the tissue level, as evidenced by poor angiographic blush scores or lack of complete ECG ST-segment resolution. The AIMI (rheolytic thrombectomy) study investigators demonstrated that there is no indication for the routine use of rheolytic thrombectomy with primary PCI for STEMI (option C). However, patients with large thrombus burden often have distal macroembolization, and studies have shown that macroembolization is harmful and leads to impaired myocardial reperfusion and worse clinical outcomes. Therefore, it may be reasonable to consider adjunctive thrombectomy in patients with angiographically large thrombus burden before primary PCI (option D). In another trial involving 1071 patients with STEMI, adjunctive aspiration resulted in enhanced rates of normal angiographic myocardial perfusion (blush) and ST-segment resolution (option A). However, the initial enthusiasm for routine use of aspiration thrombectomy has been dramatically tempered by findings that rates of mortality, TVR, recurrent MI, and stent thrombosis were the same for thrombectomy and primary PCI patients. Only stroke was different and higher in the thrombectomy patients. Thus, routine thrombectomy does not enhance outcomes and should be reserved for large thrombus burden before or after stent implantation (option B).

42-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Regardless of mode of presentation, rapid performance and competent analysis of the 12-lead ECG are the first steps. Skilled reading either on site or by transmission is essential so that "false activations" can be limited. Once a firm diagnosis of STEMI is made, activation of the STEMI team and transport to the catheterization lab are essential. A heparin bolus and a $P2Y_{12}$ inhibitor should be rapidly administered. If logistically feasible, consideration should be given to remote ischemic conditioning while en route to the catheterization lab. Once the infarct artery is identified, intracoronary abciximab may be considered if not already administered. Routine thrombectomy is not useful, but if extensive clot burden exists, it will prevent extensive macroembolization. The use of DESs should be routine. Proper sizing and proper stent opposition are essential to prevent stent thrombosis, and intravascular ultrasound-guided implantation should be strongly considered. After the procedure, anticoagulation is discontinued unless there are other reasons to resume it. All patients without contraindications should be treated with aspirin indefinitely following PCI. The correct sequence of events is therefore described in option A.

42-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 42)* Most patients with non–ST-segment elevation (NSTE)-ACS in the United States undergo cardiac catheterization. The evidence for invasive management is based on several randomized trials that showed improvement in MACE, improved symptoms, improved quality of life, and reduction in readmission. The benefits were greater in patients with higher risk (ie, elevated biomarker, ST-segment changes, higher TIMI or GRACE risk scores).[9] The timing of catheterization has been evaluated in randomized and observational trials. Initially, it was thought that it may be beneficial to "cool off" an ulcerated thrombotic lesion with antiplatelet and anticoagulant agents for a few days (option A). However studies found that earlier intervention is better, particularly in higher-risk patients (option C). Early catheterization was also associated with a reduction in death or large MI at 30 days (option B), and studies consistently favor early invasive strategies over conservative strategies in high-risk patients (option D). In this patient, the presence of ongoing chest pain and the absence of contraindications call for immediate angiography.

42-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 42)* The primary goal of pharmacotherapy for NSTE-ACS is to alleviate ischemia using antiplatelets, antithrombotics, and adjunctive therapies to reduce myocardial oxygen demand. Pharmacotherapy in NSTE-ACS is crucial for management because a substantial portion of patients will not immediately undergo coronary angiography and/or revascularization. Evidence-based guidelines universally advocate that patients with NSTE-ACS should routinely and indefinitely receive low-dose (75 to 100 mg) non–enteric-coated aspirin, after an initial loading dose of 300 to 325 mg (option B). Aspirin is routinely given to all patients with CAD, and it is assumed to equally benefit those undergoing and not undergoing an invasive management strategy.[10,11] The administration of clopidogrel prior to PCI is known to improve outcomes (option A). A study revealed that patients who received pre-PCI treatment with clopidogrel had reduced cardiovascular death, MI, and stent thrombosis when compared with placebo.[12] This can be explained by clopidogrel's slow onset, which is circumvented by early administration. In another trial, pretreatment with prasugrel did not decrease ischemic complications when compared with administration at the time of PCI and was associated with a higher risk for major bleeding.[13] Prasugrel has a very fast onset, thereby rendering pretreatment unnecessary; clinical trials therefore examined its efficacy by administering it at the time of coronary angiography (option D). Finally, anticoagulation is recommended for all NSTE-ACS patients undergoing PCI at the time of diagnosis (class I practice guideline).[11] This is typically administered as an IV infusion of UFH or a subcutaneous injection of low-molecular-weight heparin, or in some countries as subcutaneous fondaparinux (option C).

42-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 42)* In addition to antiplatelets and antithrombotics, adjunctive therapy with oxygen (options D and E are incorrect) is empirically administered in all patients, and especially for patients with oxygen saturation < 90%. If patients are experiencing ischemic chest discomfort, sublingual or IV nitroglycerin can be used (option A is incorrect). Oral beta-blockade should be initiated within 24 hours to reduce heart rate, contractility, and blood pressure, as long as patients are not experiencing heart failure or low output, are at increased risk of cardiogenic shock, or have other contraindications to beta-blockade such as bradycardia or wheezing (option B is correct).[14] Nondihydropyridine calcium channel blockers can be administered to reduce myocardial oxygen demand if beta-blockers are contraindicated, but they would not be indicated here due to bradycardia. Lastly, high-intensity statin

therapy (option C is incorrect) should be administered as soon as possible in patients presenting with NSTE-ACS because it has been associated with reduced rates of recurrent MI, coronary heart disease mortality, need for revascularization, and stroke.[15]

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CHAPTER 43

The Evaluation and Management of Stable Ischemic Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

43-1. A 65-year-old man with a history of obstructive coronary artery disease (CAD) is evaluated in your clinic. He complains that he develops chest pain walking approximately one city block and climbing one flight of stairs. Which of the following Canadian Cardiovascular Society (CCS) angina classes best describes the patient's symptoms?

A. CCS I
B. CCS II
C. CCS III
D. CCS IV
E. None of the above are correct

43-2. All of the following are criteria for defining vulnerable plaque *except*:

A. Active inflammation (eg, monocyte, macrophage, ± T-cell infiltration)
B. Thin cap with large lipid core
C. Endothelial denudation with superficial platelet aggregation
D. Fissured plaque
E. Luminal stenosis > 60%

43-3. A 64-year-old woman presents to your clinic with progressive exertional chest pressure over the past several months. All of the following are advantages of stress echocardiography over stress myocardial perfusion imaging *except*:

A. Higher specificity
B. Versatility; more extensive evaluation of cardiac anatomy and function
C. Greater convenience/efficacy/availability
D. Lower cost
E. Higher sensitivity, especially for single-vessel coronary disease involving the left circumflex artery

43-4. A 54-year-old woman is evaluated for chest pain and dyspnea with noninvasive testing. Which of the following is *not* considered a high-risk finding?

A. Severe resting LV dysfunction (LVEF < 35%) not readily explained by noncoronary causes
B. Resting perfusion abnormalities ≥ 10% of the myocardium in patients without prior history or evidence of MI
C. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
D. Severe stress-induced LV dysfunction (peak exercise LVEF < 45% or drop in LVEF with stress ≥ 10%)
E. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating one vascular territory with abnormalities but without LV dilation

43-5. A 56-year-old man undergoes coronary angiography and is found to have a 70% left main coronary artery (LMCA) stenosis. Which of the following factors would suggest similar efficacy between coronary stenting and coronary artery bypass surgery?

A. Comorbid diabetes mellitus
B. Additional lesions involving the right coronary artery
C. Left main stenosis involving calcified plaque at the bifurcation of the LAD and LCx arteries
D. Reduced ejection fraction

E. SYNTAX score of 20

43-6. All of the following are key angiographic features important for calculating the SYNTAX score *except*:

A. Right, left, or codominant coronary circulation
B. Number of atherosclerotic lesions
C. Number of artery segments involved per atherosclerotic lesion
D. Trifurcation lesion: number of vessel segments diseased
E. All of the above

43-7. Which of the following is *not true* about coronary calcium scoring?

A. Calcification observed on cardiac CT correlates inversely with the overall extent of CAD
B. The coronary artery calcification score is a quantitative measure of overall vascular calcium burden
C. Coronary calcium does not correlate with the degree of luminal obstruction
D. The overall burden may predict future coronary heart disease events
E. Serial screening of patients for progression of CAC is not recommended

43-8. Which of the following are core components of a cardiac rehabilitation/secondary prevention program?

A. Nutritional counseling
B. Blood pressure management
C. Tobacco cessation
D. Lipid management
E. All of the above

43-9. Which of the following is *incorrect* about patients with human immunodeficiency virus (HIV) and cardiac disease?

A. Highly active antiretroviral therapy (HAART) is considered a risk factor for CAD
B. Compared to HIV-negative patients, the prevalence of noncalcified coronary plaques is approximately threefold higher in HIV-positive patients on HAART therapy
C. The risk of incident MI is increased approximately fourfold among those with HIV
D. Lipodystrophy is unlikely to mediate the relationship between HIV and CAD
E. In selected HIV patients at elevated risk for cardiovascular disease, protease inhibitors may be inappropriate

43-10. A 70-year-old man with hypertension is seen in your clinic. Which of the following is *not true* about blood pressure control and the risk of cardiac events?

A. In patients with stable ischemic heart disease, hypertension is a risk factor for recurrent MI
B. In patients with diabetes, uncontrolled hypertension is a strong predictor of premature death, cardiovascular morbidity, and progressive nephropathy
C. Compared to a standard treatment goal SBP < 140 mm Hg, patients treated to intensive blood pressure targets (SBP < 120 mm Hg) have a lower risk for the combination of MI, other ACSs, stroke, HF, and death from cardiovascular causes
D. Blood pressure control in the elderly need not be as rigorous as in younger patients
E. Blood pressure control is an important preventive strategy for incident heart failure

ANSWERS

43-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Canadian Cardiovascular Society (CCS) angina classification is described in Table 43-1. This patient's symptoms are most consistent with class III (option C).

TABLE 43-1 The Canadian Cardiovascular Society Angina Scale

I	II	III	IV
Ordinary physical activity does not cause angina including: Walking and climbing stairs	Slight limitation of ordinary activity including: Walking stairs rapidly Walking uphill Stair climbing after meals	Marked limitation of ordinary physical activity.	Inability to perform any physical activity without discomfort.
Angina occurs: Only with strenuous, rapid, or prolonged exertion at work or recreation	*Angina occurs:* A few hours after awakening Walking > 2 city blocks (level ground) Walking 1 flight of ordinary stairs at a normal pace	*Angina occurs:* Walking ≤ 1 city block (level ground) Climbing one flight of stairs under normal conditions and at a normal pace	*Angina occurs:* With minimal activity May be present at rest

Data from Campeau L. The Canadian Cardiovascular Society grading of stable angina pectoris after a quarter of a century of use, *Can J Cardiol.* 2002 Sep;18(9):941-944.

43-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Major criteria for the defining vulnerable plaque include options A through D.[1] Additionally, luminal stenosis > 90% is also a major criterion. Minor criteria include: superficial calcified nodule, glistening yellow appearance (pathologic diagnosis), intraplaque hemorrhage, outward remodeling, and endothelial dysfunction.

43-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Advantages of echocardiography (options A through D) are outlined. Conversely, advantages of stress myocardial perfusion imaging include: higher technical success rate; higher sensitivity, especially for single-vessel coronary disease involving the left circumflex artery (option E); better accuracy for evaluating possible ischemia when multiple resting left ventricular wall motion abnormalities are present; and more extensive published database, especially in the evaluation of the prognosis.[2]

43-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 43)* High-risk findings on noninvasive testing include options A through D, as well as: stress-induced perfusion abnormalities encumbering ≥ 10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities; stress-induced LV dilation; inducible wall motion abnormality (involving > 2 segments or 2 coronary beds); wall motion abnormality developing at a low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 1 20 beats/min); coronary artery calcium score > 400 Agatston units; and multivessel obstructive CAD (≥ 70% stenosis) or left main stenosis (≥ 50% stenosis) on coronary CT angiography (Table 43-2). Other features are considered low risk, or moderate risk, such as stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating one vascular territory with abnormalities but without LV dilation (option E).

TABLE 43-2 Noninvasive Risk Stratification of Coronary Artery Disease

High risk (> 3% annual death or MI)

1. Severe resting LV dysfunction (LVEF < 35%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities ≥ 10% of the myocardium in patients without prior history or evidence of MI
3. Stress ECG findings including ≥ 2 mm of ST-segment depression at low workload or persisting into recovery, exercise-included ST-segment elevation, or exercise-induced VT/VF
4. Severe stress-induced LV dysfunction (peak exercise LVEF < 45% or drop in LVEF with stress ≥ 10%)
5. Stress-induced perfusion abnormalities encumbering ≥ 10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
6. Stress-induced LV dilation
7. Inducible wall motion abnormality (involving > 2 segments or 2 coronary beds)
8. Wall motion abnormality developing at low dose of dobutamine (≤ 10 mg/kg/min) or at a low heart rate (< 120 beats/min)
9. CAC score > 400 Agatston units
10. Multivessel obstructive CAD (≥ 70% stenosis) or left main stenosis (≥ 50% stenosis) on CCTA

Intermediate risk (1% to 3% annual death or MI)

1. Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
2. Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
3. ≥ 1 mm of ST-segment depression occurring with exertional symptoms
4. Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
5. Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
6. CAC score 100 to 399 Agatston units
7. One vessel CAD with ≥ 70% stenosis or moderate CAD stenosis (50% to 69% stenosis) in ≥ 2 arteries on CCTA

Low risk (< 1% annual death or MI)

1. Low-risk treadmill score (score ≥ 5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
2. Normal or small myocardial perfusion defect at rest or with stress encumbering < 5% of the myocardium*
3. Normal stress or no change of limited resting wall motion abnormalities during stress
4. CAC score < 100 Agaston units
5. No coronary stenosis > 50% on CCTA

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; EEG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.
Reproduced with permission from Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/ PCNA/ SCAI/STS Guidelines for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association of Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society of Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol*. 2012 Dec 18;60(24):e44-e164.

43-5. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 43)* A number of factors are associated with benefit from coronary artery bypass over coronary stenting (options A through D). However, in individuals without such factors, and who have favorable anatomy (option E), disease involving the LMCA can be managed with coronary artery stenting or bypass with similar efficacy (Figure 43-1). Among the strengths of the SYNTAX trial was the use of a numerical score for the objective evaluation of coronary disease severity and the likelihood of revascularization success. The SYNTAX score is generated by summarizing various qualitative plaque features and stenosis locations, and it serves as an objective measure of coronary disease severity that can be used to stratify anticipated patient outcomes (see syntaxscore.com).[3] Patients with high (≥ 33) and intermediate (23–32) SYNTAX scores had lower rates of MACCEs with surgery compared with PCI out to 5 years (high SYNTAX score: 26.8% surgery versus 44.0% PCI; $P < .0001$; intermediate SYNTAX score: 25.8% surgery vs 36.0% PCI). Event rates were similar for patients with low SYNTAX scores (≤ 22). The trial also established that PCI is noninferior to bypass surgery for the treatment of left main CAD (31.0% MACCE rate in the CABG surgery group versus 36.9% in the PCI group; $P = .12$).

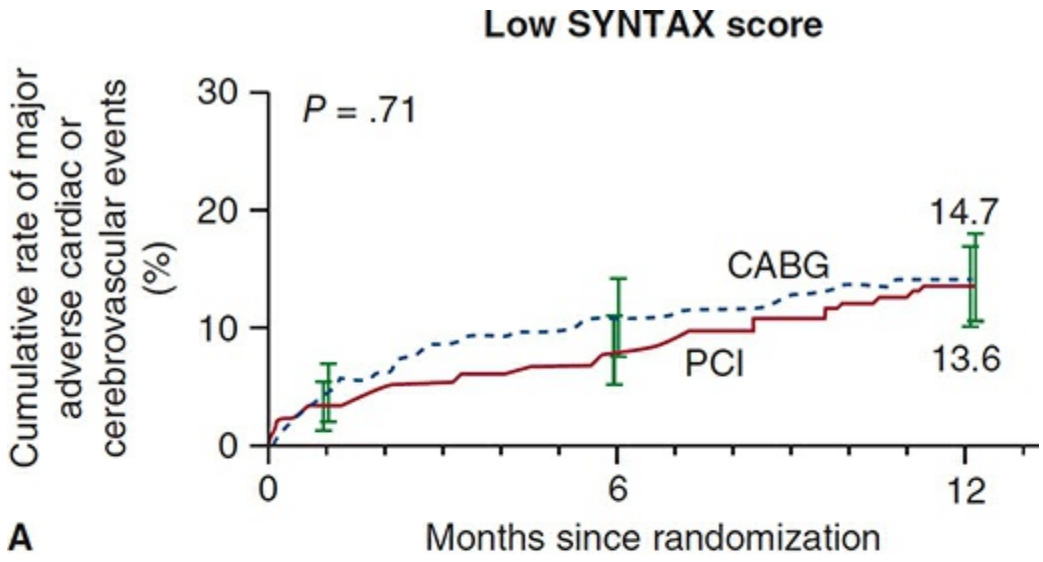

FIGURE 43-1 SYNTAX score and benefit of revascularization strategy. The rates of major adverse cardiac or cerebrovascular events 12 months following therapy are reported for patients with low (A), intermediate (B), or high (C) SYNTAX score. The bars indicate 1.5 standard errors. Note the improved outcomes among patients with high SYNTAX scores who underwent revascularization. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention. (Reproduced with permission from Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease, *N Engl J Med*. 2009 Mar 5;360(10):961-972.)

43-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 43)* The SYNTAX score can support decision making about the optimal strategy for revascularization of left main stenosis. Angiographic features that contribute to the score include options A through D, as well as: total occlusion (number of segments involved, age of total occlusion, presence of a blunt stump, presence of bridging collateral, antegrade versus retrograde filling of the first segment beyond the occlusion, side branch involvement); bifurcation lesion: angulation between the distal main vessel and the side branch < 70°; the presence of an aorto-ostial atherosclerotic lesion; the presence of severe vessel tortuosity at the lesion site; atherosclerotic lesion length > 20 mm; the presence of heavily calcified plaque; the presence of thrombus; and the presence of diffuse or small-vessel disease.

43-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Coronary artery calcification observed on cardiac CT correlates positively with the presence of established atherosclerosis (option A). The coronary artery calcification score is a quantitative measure of overall vascular calcium burden (option B). The presence of calcium in the vessel wall does not correlate with the degree of luminal obstruction (option C), although the overall burden may predict future coronary heart disease events (option D). Serial coronary artery calcification scoring to assess the rate of disease progression is not recommended (option E).

43-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Options A through D represent important, core components of optimal management programs for secondary prevention in those with established CAD. In addition, psychosocial counseling, physical activity, and exercise training are important and beneficial components.

43-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Patients infected with the HIV appear to be at increased risk for a wide range of inflammatory vascular diseases, including CAD. This may occur as a manifestation of HIV itself; low $CD4^+$ T-cell count has been associated with the presence of coronary artery stenotic lesions > 50% of the luminal diameter. Alternatively, CAD in HIV-infected persons could occur as a result of HAART use (option A). Compared to HIV-negative patients, the prevalence of noncalcified coronary plaques is approximately threefold higher in HIV-positive patients on HAART therapy (option B), which may account for parallel findings in similar patients suggesting that the risk of incident MI is increased approximately fourfold (option C). The mechanistic link between HAART and CAD remains speculative, but it may involve cross-reactivity between protease inhibitors and lipid metabolism–regulating proteins that results in dyslipidemia, insulin resistance, central adiposity, and lipodystrophy (option D). In selected HIV patients at elevated risk for cardiovascular disease, protease inhibitors may be inappropriate; under these circumstances, consultation with an infectious disease specialist to determine optimal HIV therapy is advised, as is the early institution of aggressive risk factor control (eg, statin therapy).

43-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 43)* Many observational studies have demonstrated a positive, continuous, and graded relationship between systemic blood pressure and cardiovascular disease risk. In patients with stable ischemic heart disease, hypertension is a risk factor for recurrent MI (option A), an observation that is likely a consequence of the associated endothelial dysfunction and the adverse effects of persistently elevated afterload on myocardial function and oxygen demand. In patients with diabetes, uncontrolled hypertension is a strong predictor of premature death, cardiovascular morbidity, and progressive nephropathy (option B). The Systolic Blood Pressure Intervention Trial (SPRINT) tested whether the conventional systolic blood pressure (SBP) goal of 140 mm Hg is sufficient to reduce cardiovascular events in nondiabetic, nonstroke patients at increased cardiovascular risk. Compared to a standard treatment goal SBP < 140 mm Hg, patients randomized to intensive therapy (SBP < 120 mm Hg) had lower risk for the composite end point of MI, other ACSs, stroke, HF, and death from cardiovascular causes at 1 year (HR, 0.75; 95% CI, 0.64–0.89; $P < .001$; option C). Directionally similar findings were observed for all-cause mortality, although the beneficial effects of intensive therapy were associated with an attendant increase in the number of medications prescribed, systemic hypotension, syncope, electrolyte abnormalities, and acute kidney injury. Studies have affirmed the benefit of treating hypertension in the elderly, although debate continues about the optimal targets and thresholds (option D). Blood pressure control is an important preventive strategy for incident heart failure (option E).

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CHAPTER 44

Coronary Artery Bypass Grafting and Percutaneous Interventions in Stable Ischemic Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

44-1. Which of the following findings on noninvasive testing should prompt referral of a patient for coronary angiography?

A. Exercise treadmill, > 2 mm of ST depression
B. Failure to increase systolic pressure to > 120 mm Hg or a sustained decrease of > 10 mm Hg during exercise
C. Resting perfusion abnormalities > 10% of the myocardium
D. Stress-induced left ventricular dilatation
E. All of the above

Questions 44-2, 44-3, and 44-4 relate to the following vignette:

A 55-year-old man with hypertension, dyslipidemia, and type II diabetes mellitus treated with subcutaneous insulin undergoes coronary angiography following a high-risk stress test with hypotensive blood pressure response. He is found to have proximal left anterior descending coronary artery (LAD) stenosis of 85%, as well as a 70% lesion in the mid-right coronary artery.

44-2. Which of the factors in this patient's history would favor referral for surgical revascularization?

A. A history of diabetes
B. The presence of two or more preexisting risk factors
C. Young age
D. SYNTAX score of 20
E. None of the above

44-3. In this patient, what benefits would be expected from surgical revascularization with coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI)?

A. Reduction in the composite end point of death, nonfatal myocardial infarction, and nonfatal stroke
B. Reduced all-cause mortality risk compared to PCI at 5 years
C. Reduction in the need for repeat revascularization
D. All of the above
E. None of the above

44-4. If this patient were to undergo surgical revascularization, which of the following would be true about the risk of stroke?

A. CABG and PCI are associated with similar risks of stroke
B. Higher stroke risk in patients undergoing CABG is evident only at 1 year follow-up
C. Previous stroke is a risk factor for CABG-related stroke in this population
D. Chronic renal failure is not related to long-term stroke risk in this population
E. The risk of stroke over longitudinal follow-up is fivefold higher in patients undergoing CABG compared with PCI in this population

Questions 44-5 and 44-6 relate to the following vignette:

A 76-year-old man with angina is found to have multivessel coronary artery disease (MV CAD) involving his proximal left anterior descending coronary artery (95%) as well as in an obtuse marginal branch from the left circumflex coronary artery (80%), and distal right coronary artery (75%). An echocardiogram demonstrates no valvular disease, but the left ventricular ejection fraction is 30%.

44-5. Which strategy represents the optimal approach to this patient's management?

A. Optimal medical therapy
B. CABG
C. Multivessel PCI
D. Durable left ventricular device consideration
E. Noninvasive ischemia testing to guide revascularization decisions

44-6. What is the optimal modality of viability testing to inform the decision to undertake surgical revascularization in this patient?

A. Single-photon emission computed tomography (SPECT)
B. Dobutamine stress echocardiography (DSE)
C. Thallium scan
D. Evidence of Q-waves on ECG
E. There is no certain, evidence-based role for viability testing in this setting

Questions 44-7, 44-8, and 44-9 relate to the following vignette:

A 55-year-old man without diabetes presents with typical angina symptoms and no prior history of coronary artery disease. Noninvasive stress testing is positive, and he is referred for coronary angiography, which demonstrates an 80% proximal LAD stenosis as well as a 90% mid-vessel stenosis in a dominant right coronary artery.

44-7. If there is uncertainty as to the hemodynamic significance of this patient's coronary stenoses, which of the following can be undertaken during the catheterization procedure to support a role for revascularization:

A. Fractional flow reserve (FFR) measurement
B. Optical coherence tomography (OCT)
C. Intravascular ultrasound (IVUS)
D. Noninvasive FFR by coronary CT
E. None of the above

44-8. In reviewing this patient's coronary angiogram, which of the following are important elements to ascertain when assessing the anatomic complexity of underlying coronary artery disease?

A. Number of lesions
B. Bifurcation types and angulation
C. Aorto-ostial lesions
D. Severe tortuosity
E. All of the above

44-9. Which of the following statements is true regarding a hybrid approach (percutaneous coronary intervention and surgical revascularization) to revascularization?

A. A hybrid approach is used commonly in all patients without diabetes mellitus where center of expertise is present
B. Insufficient data exist to strongly recommend hybrid revascularization
C. Hybrid approach is strongly preferred in this patient
D. PCI would be preferred in this patient
E. None of the above

44-10. In patients with ischemia identified on noninvasive stress testing, which of the following is true?

A. The role of PCI in the absence of uncontrolled symptoms is uncertain in such patients
B. PCI should be undertaken in all patients with documented ischemia and anatomically amenable disease
C. Optimal medical therapy (OMT) is usually ineffective at controlling angina symptoms
D. PCI is associated with improved mortality in patients with stable coronary artery disease
E. None of the above

ANSWERS

44-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 44)* Patients referred for diagnostic noninvasive stress testing should be considered for coronary angiography in the presence of high-risk findings. A number of such factors are suggested (Table 44-1; options A through D are incorrect).

TABLE 44-1 Criteria for Referring Patients to Coronary Angiography

Exercise Treadmill
Exercise treadmill, > 2 mm of ST depression;
Exercise-induced ST-segment elevation;
Exercise-induced ventricular tachycardia/ventricular fibrillation; and
Failure to increase systolic pressure to > 120 mm Hg or a sustained decrease of > 10 mm Hg during exercise
Myocardial Perfusion Imaging
Severe left ventricular dysfunction, not readily explained;
Resting perfusion abnormalities > 10% of the myocardium;
Severe stress-induced left ventricular dysfunction;
Stress-induced perfusion abnormalities involving > 10% of the myocardium or stress and mental scores indicating multiple territories at risk;
Stress-induced left ventricular dilatation; and
Increased lung uptake.
Stress Echocardiography
Inducible wall motion abnormalities involving > 2 segments or 2 coronary beds
Coronary Computed Tomography
Multivessel obstructive coronary disease or left main stenosis

Modified with permission from Mancini GB, Gosselin G, Chow B, et al. Canadian Cardiovascular Society. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease, *Can J Cardiol*. 2014 Aug;30(8):837-849.

44-2. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 44)* Patients with diabetes mellitus have consistently been found to have more favorable outcomes with surgical revascularization than with percutaneous revascularization (Figure 44-1).[1] This is true even among contemporary trials employing the use of drug-eluting stents. Other clinical variables (options B through E) in this patient would not have an obvious influence on preference for one modality of revascularization over another.

44-3. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 44)* The FREEDOM trial was designed to address the optimal coronary revascularization strategy in patients with diabetes and multivessel CAD in the absence of left main disease, prior CABG, prior stenting within 6 months, and current ST-segment elevation myocardial infarction.[2] In FREEDOM, the overall 5-year Kaplan-Meyer estimates of the primary composite end point of death, nonfatal myocardial infarction, and nonfatal stroke indicated a 26.6% event rate in the first-generation DES group compared to 18.7% in the CABG group ($P < .005$; option A alone is incorrect). Indeed, in FREEDOM, CABG was associated with a significantly reduced all-cause mortality risk compared to PCI at 5 years, and the mortality curves continued to diverge in favor of CABG throughout follow-up (option B alone is incorrect). The results of FREEDOM and subsequent meta-analyses lead to a Class I recommendation in the 2014 ACC/AHA guidelines stating that CABG was associated with improved survival in diabetics with multivessel CAD. This was upgraded from a Class II recommendation in 2012. CABG remains the revascularization treatment of choice for diabetic patients with multivessel disease. This is particularly true if a left internal mammary artery (LIMA) graft to the left anterior descending artery was performed. In general, the need for repeat revisualization is reduced with coronary artery bypass surgery versus PCI (option C alone is incorrect).

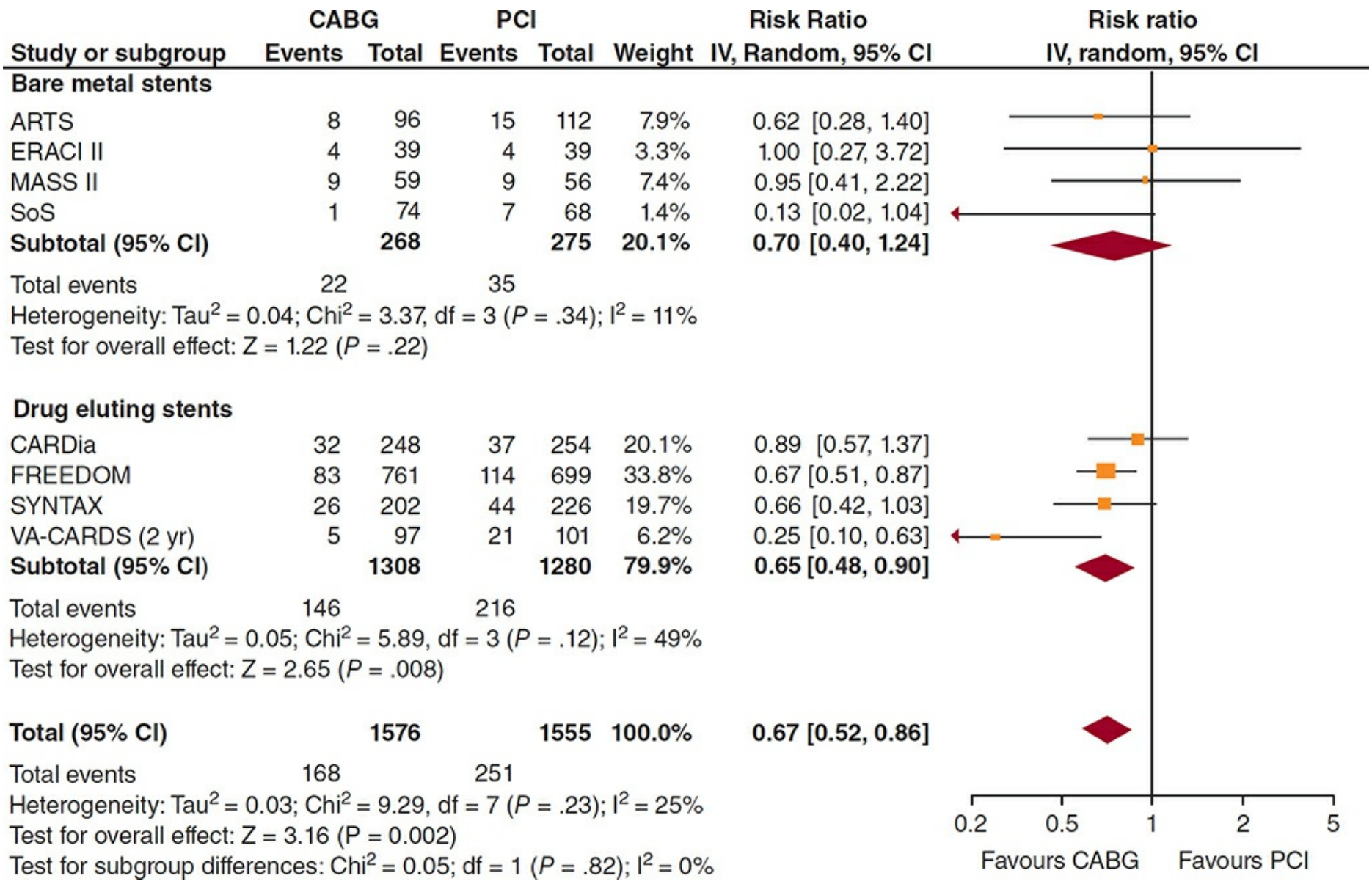

FIGURE 44-1 Forest plots for individual studies and pooled risk ratios for all-cause mortality in randomized controlled trials comparing patients with diabetes and multivessel coronary artery disease who underwent coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI) after 5 years or the longest follow-up. CI, confidence interval. (Reproduced with permission from Verma S, Farkouh ME, Yanagawa B, et al. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials, *Lancet Diabetes Endocrinol* 2013 Dec;1(4):317-328.)

44-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 44)* For patients with diabetes undergoing CABG in the FREEDOM trial, there was an excess of early stroke compared to PCI (option A is incorrect). The difference accrued mostly over the first 30 days after follow-up (option B is incorrect). In an analysis from the FREEDOM CABG cohort, predictors of early stroke included a prior history of stroke, the use of warfarin, and whether CABG was performed outside North America. In long-term follow-up, the strongest predictor of stroke was the presence of chronic renal insufficiency (option D is incorrect). Over 5 years of follow-up, CABG was still associated with a significantly higher stroke rate compared to PCI (5.2% vs 2.4%; $P = .03$; option E is incorrect).

44-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 44)* In the Surgical Treatment for Ischemic Heart Failure (STICH) study, patients with ischemic cardiomyopathy and an ejection fraction of 35% or less were randomly assigned to CABG versus OMT alone and followed for 9.8 years.[3] Although there was no significant difference between OMT alone and OMT plus CABG with respect to the primary end point (death from any cause), there were more cardiovascular deaths in the OMT group (297 deaths, 49.3%) compared to the CABG group (247 deaths, 40.5%; hazard ratio, 0.79; 95% CI, 0.66–0.93; $P = .006$; option A is incorrect). A 2009 meta-analysis has suggested that CABG is the preferred mode of revascularization in patients with left ventricular dysfunction (option C is incorrect),[4] although this analysis was largely limited to patients in the bare metal stent era. The patient does not currently have indications for durable LVAD consideration (option D is incorrect). Noninvasive, ischemia-guided revascularization decisions in patients with left ventricular systolic dysfunction have not been shown to improve outcomes (option E is incorrect).

44-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 44)* In a substudy of the STICH trial, among the 1212 patients enrolled in the overall randomized trial, 601 underwent viability assessment with SPECT or DSE.[5] Of these 601, 298 were randomly assigned to receive OMT plus CABG and 303 to receive OMT alone. There was no significant mortality interaction between viability status and treatment assignment ($P = 0.53$), suggesting that viability assessment did not identify patients with a differential survival benefit from CABG + OMT versus OMT alone. In all patients, while there was an unadjusted association between the presence of viable myocardium and mortality, this was no longer significant after adjusting for potential confounders. Thus, the role of viability testing across modalities (options A through D) remains uncertain in this population.

44-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 44)* The fractional flow reserve (FFR) is a lesion-specific index of stenosis severity defined as the ratio of maximum flow in the presence of stenosis to normal maximum flow. In practice, FFR is estimated as the ratio of coronary artery pressure distal to a lesion of interest to aortic pressure, averaged

over the entire cardiac cycle, with variation in microvascular resistance minimized by pharmacologic induction of maximal hyperemia. FFR is useful to reclassify the functional severity of angiographically indeterminate coronary lesions and to define the utility of PCI. Evidence to date suggests that when a lesion is functionally significant, as defined by an FFR ≤ 0.80, revascularization may be beneficial. For example, in the FAME study, which randomized 1005 patients with multivessel CAD to PCI guided by angiography alone or angiography plus FFR, a strategy of FFR guidance was associated with a reduced rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year (13.2% vs 18.3%; $P = .02$) as well as a reduced usage of stents per patient (1.9 ± 1.3 vs 2.7 ± 1.2; $P < .001$).[6] In the FAME 2 trial, which randomized 888 patients with at least one functionally significant stenosis to PCI plus medical therapy or medical therapy alone, PCI conferred a significant reduction in death, nonfatal myocardial infarction, and urgent revascularization at 2 years.[7] Figure 44-2 depicts the overall decision making regarding revascularization in patients with stable ischemic heart disease, including the role of FFR.

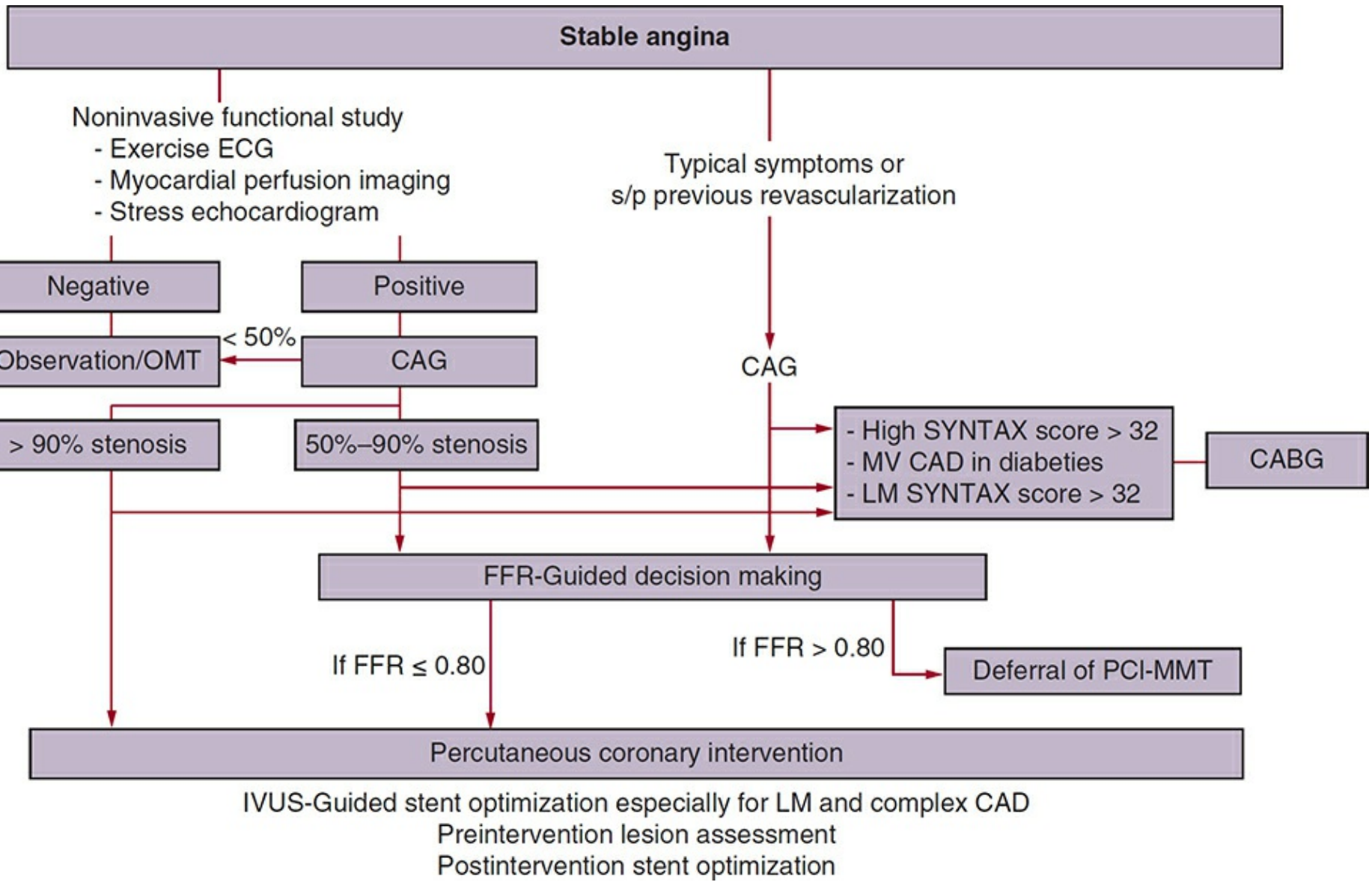

FIGURE 44-2 Proposed algorithm for assignment to revascularization in stable ischemic heart disease. CABG, coronary artery bypass grafting; CAG, coronary angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LM, left main; OMT, optimal medical therapy; MV CAD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

44-8. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 44)* The extent and complexity of CAD are important parameters informing triage to percutaneous coronary intervention (PCI) versus CABG in patients with stable multivessel CAD. The SYNTAX Score (SS), developed for use in the multicenter Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial provides a semiquantitative angiographic measure of disease complexity that is useful for this purpose. For a given patient, the SS represents a sum of scores for every lesion with > 50% diameter stenosis in vessels with a diameter > 1.5 mm. Elements of this score are listed in Table 44-2 (including options A through D; option E is correct).

TABLE 44-2 The SYNTAX Score Algorithm

1. Dominance
2. Number of lesions
3. Segments involved per lesion, with lesion characteristics
4. Total occlusions with subtotal occlusions:
   a. Number of segments
   b. Age of total occlusions
   c. Blunt stumps
   d. Bridging collaterals
   e. First segment beyond occlusion visible by antegrade or retrograde filling
   f. Side branch involvement
5. Trifurcation, number of segments diseased

6. Bifurcation type and angulation
7. Aorto-ostial lesion
8. Severe tortuosity
9. Lesion length
10. Heavy calcification
11. Thrombus
12. Diffuse disease, with number of segments

Adapted with permission from Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX Score: an angiographic tool grading the complexity of coronary artery disease, *EuroIntervention*. 2005 Aug;1(2):219-227.

44-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 44)* The use of a hybrid approach to coronary revascularization is gaining popularity and may be an appropriate alternative for a carefully selected subset of patients with limited CAD involving the proximal or mid LAD and at least one other non-LAD coronary artery. In hybrid coronary revascularization (HCR), a minimally invasive surgical approach is used to bypass the LAD with a LIMA graft in combination with stenting of non-LAD targets. This is believed to leverage the advantages of surgical arterial revascularization of the LAD and substitution of advanced stent technology for saphenous vein grafts for the other targets. HCR is offered in about one third of hospitals in the United States but represents less than 1% of CABG procedures (option A is incorrect). The current body of evidence is limited to observational studies and a small pilot randomized trial (option B is correct). The current ACC/AHA guidelines on coronary revascularization consider HCR only when PCI of the LAD is considered suboptimal, and therefore, it is given a Class IIa recommendation (option C is incorrect).

44-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 44)* Percutaneous coronary intervention is largely reserved for two major groups of patients, namely those who have inadequate symptom relief or persistent reduction in quality of life despite OMT and those with noninvasive testing indicating risk for ischemic events. Currently, the National Heart, Lung, and Blood Institute is sponsoring the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial to evaluate the benefit of PCI in patients with high-risk features on noninvasive testing compared to OMT alone. In a prior pivotal randomized trial (COURAGE), 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease were randomized to undergo PCI with OMT or OMT alone. The primary outcome (death from any cause and nonfatal myocardial infarction during a follow-up period of median 4.6 years) did not differ during the two groups at follow-up (hazard ratio for the PCI group, 1.05; 95% confidence interval [CI], 0.87–1.27; $P = 0.62$). Similarly, there were no significant differences in the composite of death, myocardial infarction, and stroke ($P = 0.62$); hospitalization for acute coronary syndrome ($P = 0.56$); or myocardial infarction ($P = 0.33$). The ISCHEMIA trial will critically inform this ongoing question in the contemporary treatment era, but at the present time the role of routine PCI in the absence of symptoms refractory to OMT is uncertain.

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CHAPTER 45

Rehabilitation of the Patient with Coronary Heart Disease

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

45-1. Which of the following is *not* a benefit of cardiac rehabilitation (CR)?

A. Improved heart rate recovery
B. Decreased levels of high-density lipoprotein (HDL) cholesterol
C. Dose-dependent reduction in mortality
D. Improved left ventricular (LV) function
E. Decreased depression symptoms

45-2. A 54-year-old man recovering from a cardiovascular event is referred to you for medical evaluation prior to initiating CR. Which of the following is a contraindication to enrollment in a CR program?

A. Hypertension
B. Coronary artery bypass graft (CABG) surgery
C. Myocardial infarction (MI)
D. Unstable angina
E. All of the above

45-3. A 59-year-old man with long-standing hypertension is admitted to the ER with a myocardial infarction (MI). Following revascularization with coronary stenting, he improves clinically. Which of the following signs suggests that the patient is ready for a gradual mobilization program and CR?

A. No signs of decompensated heart failure
B. New or recurrent chest pain in the past hour
C. Steadily increasing troponin levels
D. A recent change in cardiac rhythm
E. None of the above

45-4. During a treadmill exercise stress test, a 60-year-old male patient becomes tired and asks to stop the test. Which of the following signs and symptoms is *not* considered an absolute test termination criterion?

A. Cyanosis
B. Dyspnea
C. Ataxia
D. Severe chest pain
E. Dizziness

45-5. Following medical evaluation, a 60-year-old male patient is determined to be in the class C risk category for exercise training. Which of the following statements about his exercise capacity is *true*?

A. His exercise capacity is approximately 10 METs
B. His oxygen uptake during exercise is < 21 mL O_2 uptake/kg/min
C. His maximum HR during exercise (HR_{max}) is 140 beats per minute
D. He is unlikely to develop angina at a workload < 6 METs
E. None of the above

45-6. A 65-year-old woman with stable angina is evaluated for an exercise training program. Which of the following is a *correct* method for determining appropriate exercise intensity?

A. Exercise intensity is determined by the patient's oxygen consumption at rest

B. Exercise intensity is equal to the maximum heart rate achieved during the exercise test
C. Exercise intensity is estimated as the heart rate equal to 220 minus the age in years
D. Exercise intensity is extrapolated from a plot of the heart rate versus oxygen consumption
E. All of the above

45-7. Which of the following is *not* a physiologic effect of smoking on the cardiovascular system?

A. Cell migration to the intima
B. Increased fibrinogen levels
C. Decreased platelet adhesion to the endothelium
D. Smooth muscle proliferation
E. None of the above

45-8. A 57-year-old hypertensive male patient is evaluated following myocardial infarction. Which of the following findings would suggest that this patient has secondary hypertension?

A. Uncontrolled hypertension despite three medications
B. Nocturnal dipping of blood pressure on 24-hour ambulatory monitoring
C. Minimal alcohol consumption
D. Low salt sensitivity
E. All of the above

45-9. Following a psychological evaluation of a 48-year-old woman recovering from a myocardial infarction, you observe that she feels anxious about her cardiovascular health and upcoming CR. Which of the following is *not* a physiologic response to anxiety?

A. Platelet and macrophage cell activation
B. Increased levels of blood lipids
C. Increased heart rate
D. Decreased myocardial oxygen demand
E. Increased blood pressure

45-10. Which of the following is the most common reason for the underutilization of CR programs?

A. Lack of physician referral
B. Higher socioeconomic status
C. Patient age < 65 years old
D. Male gender
E. None of the above

ANSWERS

45-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Clinical trials have demonstrated many clinical benefits of exercise-based CR.[1] A number of mechanistic effects seem to contribute to this clinical benefit. For example, exercise has anti-inflammatory effects by *increasing* HDL cholesterol levels (option B). Heart rate recovery is an indicator of cardiovascular (CV) health, and impaired heart rate recovery predicts mortality. In a study of patients with abnormal heart rate recovery prior to starting CR, the exercise program resulted in a 41% improvement in heart rate recovery (option A).[2] Following MI, exercise training has proven benefits on LV function and remodeling (option D), and the effects were greatest when the exercise training was started 1 week after MI and lasted longer than 12 weeks.[3] It has been estimated that 20% to 45% of patients demonstrate depression following MI.[4] Improved fitness was associated with decreased depressive symptoms and decreased mortality (option E).[5] Furthermore, the relationship between the number of CR sessions completed in older patients and improved outcomes found a dose-dependent reduction in mortality and recurrent MI (option C).

45-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 45)* To establish a safe and effective program of comprehensive CV disease risk reduction and rehabilitation, each patient should undergo a careful medical evaluation and exercise test before participating in an outpatient CR/SP program. CR was initially implemented to reduce hospitalizations after MI (option C), but given the benefits for CV health, the concept was expanded to include patients with several conditions. This includes patients undergoing cardiac surgery and coronary interventions (option B), and those with a high cardiovascular risk, namely hypertensives (option A). Nevertheless, there are absolute contraindications to CR, including all conditions where physical exercise carries a significant risk of adverse effect, such as unstable angina (option D). The indications and contraindications for CR are summarized in Table 45-1.

TABLE 45-1 Clinical Indications and Contraindications for Inpatient and Outpatient Cardiac Rehabilitation.

Indications

- Medically stable after myocardial infarction
- Stable angina
- Coronary artery bypass graft surgery
- Percutaneous transluminal coronary angioplasty or other transcatheter procedure
- Compensated congestive heart failure
- Cardiomyopathy
- Heart or other organ transplantation
- Other cardiac surgery including valvular and pacemaker insertion (including implantablecardioverter defibrillator)
- Peripheral arterial-vascular disease
- High-risk cardiovascular disease ineligible for surgical intervention
- Sudden cardiac death syndrome
- End-stage renal disease
- At risk for coronary artery disease, with diagnosis of diabetes mellitus, hyperlipidemia, hypertension, etc.
- Other patients who may benefit from structured exercise and/or patient education (based on physician referral and consensus of the rehabilitation team)

Contraindications

- Unstable angina
- Resting systolic blood pressure > 200 mm Hg or diastolic > 110 mm Hg
- Orthostatic blood pressure decrease of > 20 mm Hg with symptoms
- Critical aortic stenosis (peak systolic pressure gradient of > 50 mm Hg with an aortic valve orifice area of < 0.75 cm^2 in an average-size adult)
- Acute systemic illness or fever
- Uncontrolled atrial or ventricular arrhythmias
- Uncontrolled sinus tachycardia (> 120 bpm)
- Uncompensated congestive heart failure
- Third-degree heart block (without pacemaker)
- Active pericarditis or myocarditis
- Recent embolism
- Thrombophlebitis
- Resting ST-segment displacement (> 2 mm)
- Uncontrolled diabetes (resting blood glucose > 300 mg/dL [17 mmol/L] or > 250 mg/dL [14 mmol/L]) with ketones present
- Orthopedic problems prohibiting exercise
- Other metabolic conditions such as acute thyroiditis, hypokalemia or hyperkalemia, hypovolemia, etc.

45-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Phase I of CR traditionally begins in the hospital and lasts for the duration of hospitalization. This phase emphasizes a gradual, progressive approach to exercise and an education program that helps the patient understand the disease process, the rehabilitation process, and initial preventive efforts to slow the progression of disease. Simple breathing and leg exercises are commenced with a program of gradual mobilization. The emphasis at this stage is to counteract the negative effects of deconditioning after a cardiac event. A patient is considered appropriate for daily ambulation/mobilization if he or she meets four criteria: there is no new or recurrent chest pain during the previous 8 hours (option B), neither troponin nor creatine phosphokinase (CPK) is increasing (option C), there are no signs of decompensated heart failure (option A), and there is no significant change in ECG or rhythm in the previous 8 hours (option D).

45-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Exercise stress testing in CR is performed to measure the ischemic threshold, assess for arrhythmias, assess exercise tolerance, evaluate hemodynamic response (blood pressure, heart rate), and observe for signs and symptoms of ischemia. The test is traditionally carried out using a treadmill or a cycle ergometer with monitoring of ECG, heart rate, and blood pressure. The RPE Scale and the individual's description of his or her levels of angina and dyspnea (option B) are also assessed. The exercise test usually lasts for 8 to 12 minutes and is terminated when the patient develops symptoms, such as chest pain (option D), or when he or she achieves a physiologic end point, such as 85% of maximal predicted heart rate. The subject's general appearance during the exercise test is also of value and should be carefully observed during the exercise test. Signs of poor perfusion, such as cyanosis (option A) or pallor, and increasing nervous system symptoms, such as ataxia (option C), dizziness (option E), and vertigo, serve as absolute test termination criteria.

45-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 45)* The exercise goals of a CR program are developed based on an individual's baseline ability and limitations. Risk stratification is performed with each patient before the initiation of an exercise program. The guidelines published by the AHA use four categories (A, B, C, and D) according to clinical characteristics. Class C individuals are at moderate or high risk of cardiac complications during exercise due to one of the following: a history of multiple MIs or cardiac arrest, New York Heart Association class III or IV angina, exercise capacity of less than 6 METs (option A), and significant angina or ischemia at a workload < 6 METs (option D). One

MET is defined as 3.5 mL O_2 uptake/kg/min, therefore this patient has an oxygen uptake capacity of < 21 mL O_2 uptake/kg/min during exercise (option B). His maximum HR can be estimated as 220 minus his age in years, therefore his HR_{max} is equal to 160 beats per minute (option C).

45-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 45)* The intensity for exercise training can be calculated from the exercise test (option A), and for cardiac patients, the heart rate is the most common method used. There are three methods of using the heart rate, and these include the direct method, the percentage of HR_{max}, and the heart rate reserve.[6] In the direct method, the heart rate is plotted against oxygen consumption, and the appropriate exercise intensity is extrapolated (option D). The percentage of HR_{max} method uses 65% to 75% of the heart rate achieved during the exercise test, which approximates from 40% to 60% of an individual's maximal oxygen consumption (VO_2 max) (option B). In the heart rate reserve method, the resting heart rate is subtracted from the maximal heart rate (estimated as 220 minus the age in years) to give the heart rate reserve. If an exercise prescription of 60% to 80% of maximal oxygen consumption is required, then 60% and 80% values of the heart rate reserve are calculated, and the resting heart rate is added to each value to give the training heart rate values (option C).

45-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Cigarette smoking, a major risk factor for the development of CHD, remains a leading cause of preventable death worldwide. The causal relationship between smoking and CV disease is well established. The effects of smoking on the CV system include stimulation of smooth muscle proliferation (option D) and cell migration to intima (option A), increase in platelet adhesion to the endothelium (option C), and an increase in fibrinogen levels (increased clotting) (option B). Smoking cessation will reduce the subsequent risk of mortality by up to 9%.[7] Observational studies in post-MI patients suggest that this may be reflected as a halving of long-term mortality.[8]

45-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Evidence exists regarding the importance of hypertension as a risk factor for CV disease and the importance of lifestyle measures and appropriate medication to treat and control hypertension. Ambulatory blood pressure monitoring can confirm the diagnosis of hypertension. A change in lifestyle behaviors may have important effects on BP control. Excessive alcohol consumption (option C) is associated with hypertension, and reduction or cessation of alcohol consumption has been shown to improve blood pressure and to reduce need for medication. Most people with hypertension are salt-sensitive (option D), and reductions in dietary salt are effective. There is a direct link between increasing body weight and blood pressure levels, particularly if fat distribution is central. Stress has a major effect on blood pressure, and recognizing and eliminating this factor may have important effects. Secondary causes of hypertension may be diagnosed if one of the following is noted: blood pressure of ≥ 180/110 mm Hg, uncontrolled hypertension despite three medications (option A), or nondipping of blood pressure during 24-hour ambulatory blood pressure monitoring (option B).

45-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 45)* Psychosocial factors may affect the occurrence and recurrence of CHD and may affect rehabilitation. Anxiety and depression are prevalent in both cardiac patients and their families and are associated with increased morbidity and mortality. Although they may be normal responses after a cardiac event and a natural part of recovery after any life-threatening or stressful event, in excess, they may seriously impede rehabilitation. Anxiety can affect both short- and long-term recovery after a cardiac event. It may relate more to how an individual responds to his or her condition than to its severity. Anxiety may trigger a variety of physiologic responses such as increased levels of circulating lipids (option B), platelet and macrophage cell activation (option A), and increased heart rate (option C), blood pressure (option E), and myocardial oxygen demand (option D), all of which have have implications for the development of atherosclerosis, ischemia, MI, and sudden death.

45-10. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 45)* The most common barrier to CR is a lack of physician referral (option A). Despite national guidelines in the United States designating CR as a Class IA recommendation, Menezes et al.[9] report that up to 80% are not referred. In particular, women (option D), those of lower socioeconomic status (option B), and patients over age 65 (option C) have lower rates of referral.[10] The EuroAspire survey analyzed records and interviews of 9000 patients and reported that only one-third of patients with CHD received any form of CR.[11] Even among those referred to CR, the dropout rate is high among post-MI patients. Importantly, once referred to CR, the reasons for nonattendance were more likely due to personal factors, such as perceptions of heart disease and family influence, versus physical issues.

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SECTION 8

Valvular Heart Disease

CHAPTER 46

Acute Rheumatic Fever

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

46-1. Acute rheumatic fever (ARF) is a multisystem autoimmune response to untreated or partially treated group A *Streptococcus* (GAS) pharyngitis. Which of the following statements about ARF is *false*?

A. First attacks are rare in the very young
B. The peak incidence of ARF occurs in those age 5 to 15 years
C. ARF is rare in adults older than age 35
D. ARF is equally common in males and females
E. No association with ethnic origin has been found

46-2. The incidence of ARF began to decline in developed countries toward the end of the 19th century, and by the second half of the 20th century, ARF had become rare in most affluent populations. Which of the following factors contributed *least* to this decline?

A. More hygienic living conditions
B. Less crowded living conditions
C. Better nutrition
D. Improved access to medical care
E. The advent of antibiotics

46-3. A 31-year-old man with a prior history of rheumatism in every joint at the age of 15 presented to the emergency department complaining of pain in the left hip and right knee. His physical examination revealed a systolic murmur, loudest at the apex and radiating to the axilla. Which of the following statements about the antibodies that contribute to this rheumatic valvulitis is *false*?

A. They target the N-acetyl-β-D-glucosamine–dominant epitope of the GAS carbohydrate
B. They recognize sequences in α-helical proteins (eg, myosin and tropomyosin)
C. They are neutralized by appropriate antibiotic therapy
D. Their serum levels fall significantly after surgical removal of inflamed valves
E. None of the above

46-4. A 29-year-old healthy woman with a past medical history of ARF as a child is seen in the clinic because her 12-year-old daughter has recently been diagnosed with ARF. She is concerned that ARF may be running in her family and that her 2-year-old son may thus be at increased risk of having ARF. Which of the following genetic factors has been associated with the development of ARF?

A. Human leukocyte antigen (HLA) Class II alleles
B. Polymorphisms of transforming growth factor-β1
C. Immunoglobulin genes
D. Certain B-cell alloantigens
E. All of the above

46-5. The long-term clinical consequence of ARF is related to permanent cardiac damage. Which of the following patients is most likely to have permanent cardiac damage from ARF?

A. 15-year-old boy with pleuritic chest pain and diffuse concave-shaped ST-elevation on ECG
B. 25-year-old man with acute heart failure with an EF of 25% and recurrent tachyarrhythmias
C. 27-year-old man with joint pain and a pansystolic murmur loudest at the apex and radiating to the axilla
D. 19-year-old woman with central pleuritic chest pain, positive troponins, and raised inflammatory markers

E. All of the above

46-6. ARF usually has an acute febrile onset and presents with variable combinations of major and minor manifestations. In which of the following presentations is the evidence of a preceding GAS infection *not* needed to diagnose ARF?

A. 12-year-old girl with involuntary, purposeless, rapid, and abrupt movements associated with muscular weakness and emotional lability
B. 13-year-old boy with polyarthritis, temperature of 38.5°C, and ESR of 60 mm in the first hour
C. 9-year-old girl with polyarthritis, temperature of 39.5°C, and ESR of 120 mm in the first hour
D. 12-year-old boy with pleuritic chest pain, arthralgia, fever, and ESR of 72 mm in the first hour
E. None of the above

46-7. A 10-year-old girl was brought by her mother to the emergency department complaining of personality changes, with inappropriate behavior, restlessness, and outbursts of anger or crying. During the physical examination, the patient was asked to squeeze the examiner's hand. This resulted in repetitive irregular squeezes. Which of the following statements about the patient's condition is *false*?

A. It must be associated with other manifestations of ARF in order to confirm the diagnosis
B. It may be the sole expression of the ARF
C. It is a neurologic disorder
D. It occurs in up to 30% of cases of ARF
E. The abnormal movements disappear during sleep

46-8. An 11-year-old girl was brought to the emergency department by her parents complaining of pains in the right hip and left knee. On physical examination, there was a pink rash on the patient's trunk. She had a temperature of 39.5°C, and the ESR was 120 mm in the first hour. Which of the following statements about this rash is *false*?

A. It is itchy and evanescent in nature
B. It affects the trunk predominantly
C. It may be fleeting and disappear within hours
D. It may be brought out by a warm bath or shower
E. It is found in only 4% to 15% of cases

46-9. A 12-year-old boy was brought by his parents to the emergency department complaining of a rash over the bony surfaces of his elbows, wrists, and knees. Three to 4 weeks ago, the patient presented to the same hospital with pleuritic chest pain, arthralgia, fever, and ESR of 72 mm in the first hour. The physical examination revealed some nodules over the bony surfaces of his elbows, wrists, and knees. Which of the following statements about these nodules is *false*?

A. They generally appear later in the course of the disease after several weeks of illness
B. They are seen most commonly in patients with carditis
C. They are firm and painful
D. The overlying skin is not usually inflamed
E. They occur in less than 10% of cases of ARF

46-10. There is no definitive laboratory test for ARF, with the diagnosis based on a combination of clinical manifestations and laboratory evidence of previous streptococcal infection. Which of the following laboratory findings *cannot* be used as evidence of a preceding strep infection?

A. Increased or rising antistreptolysin O titer
B. Increased or rising of other streptococcal antibodies
C. A positive throat swab culture
D. Rapid antigen test for group A β-hemolytic streptococci
E. None of the above

ANSWERS

46-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Acute rheumatic fever is equally common in males and females, but RHD is more common in females in almost all populations.[1,2] First attacks are rare in the very young (option A); only 5% of first episodes arise in children younger than age 5, and the disease is almost unheard of in those younger than age 2 (option A). The peak incidence of ARF occurs in those age 5 to 15 (option B), with a decline thereafter such that cases are rare in adults older than age 35 (option C).[3] No association with sex or ethnic origin has been found (options D and E).

46-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 46)* This decline is attributed to more hygienic and less crowded living conditions, better nutrition, improved access to medical care, and, to a lesser extent, the advent of antibiotics in the 1950s. The decline in the prevalence of RHD in wealthy countries has followed a similar pattern, albeit with a delay compared to ARF incidence, which is explained by the chronic nature of RHD.

46-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 46)* The antibodies that contribute to rheumatic valvulitis target the N-acetyl-β-D-glucosamine–dominant epitope of the GAS carbohydrate,[4] but they also recognize sequences in α-helical proteins (eg, myosin and tropomyosin).[5] These antibodies are elevated in patients with valvular involvement in ARF, significantly reduce after the surgical removal of inflamed valves, and correlate with poor prognosis.[6] At this stage, antibiotics are ineffective and do not reduce the level of circulating antibodies.

46-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Host factors have been considered to be important ever since familial clustering was reported last century. Associations between disease and HLA Cass II alleles have been identified, but the alleles associated with susceptibility or protection differ depending on the population investigated.[7] High concentrations of circulating mannose-binding lectin and polymorphisms of transforming growth factor-β1 and immunoglobulin genes also are associated with ARF.[8-10] Certain B-cell alloantigens are expressed to a greater level in patients with ARF or RHD than controls, with family members having intermediate expression, suggesting that these antigens are markers of inherited susceptibility.

46-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Although rheumatic carditis involves the pericardium, myocardium, and endocardium, fibrinous pericarditis (options A and D) and interstitial myocardial involvement (options B and D) typically resolve without residual damage, whereas verrucous valvulitis (option C) is usually associated with lasting damage. Notably, the pathologic changes also indicate that, unlike in the more common lymphocytic form of myocarditis, heart muscle cells are spared in rheumatic carditis.[11]

46-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 46)* The diagnosis of ARF is made when the patient develops two major manifestations, or one major manifestation and at least two minor manifestations; in addition, evidence of a preceding infection with GAS must be demonstrated using streptococcal serology. The exceptions are patients who present with chorea (option A) or indolent carditis because these manifestations may only become apparent months after the inciting streptococcal infection, so additional manifestations may not be present and streptococcal serology testing may be normal.[12]

46-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Mild chorea may best be demonstrated by asking the patient to squeeze the examiner's hand. This results in repetitive irregular squeezes labeled as the milking sign. Emotional lability manifests in personality changes, with inappropriate behavior, restlessness, and outbursts of anger or crying.[13] Sydenham chorea may be associated with other manifestations of ARF but may also be the sole expression of the disease (options A and B). It is a neurologic disorder characterized by involuntary, purposeless, rapid, and abrupt movements associated with muscular weakness and emotional lability (option C). Chorea occurs in up to 30% of cases of ARF (option D). The abnormal movements disappear during sleep (option E).

46-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Erythema marginatum is a nonitchy (option A), evanescent rash that is pink or slightly red and that affects the trunk predominantly (option B). The rash extends centrifugally, and the skin in the center returns toward normal. The rash may be fleeting and may disappear within hours (option C). It may be brought out by a warm bath or shower (option D). It is reported to be found in only 4% to 15% of cases and may be difficult to detect in dark-skinned patients (option E).

46-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 46)* These nodules generally appear later in the course of the disease after several weeks of illness and are seen most commonly in patients with carditis. They are firm and painless; the overlying skin is not inflamed and may vary in size from a few millimeters to several centimeters. They are most commonly located over bony surfaces or tendons such as elbows, wrists, knees, occiput, and spinous processes of the vertebrae. These occur in less than 10% of cases of ARF.

46-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 46)* Evidence of preceding streptococcal infection may be demonstrated by increased or rising antistreptolysin O titer, other streptococcal antibodies, a positive throat swab culture, or a rapid antigen test for group A β-hemolytic streptococci.

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CHAPTER 47

Aortic Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

47-1. A 65-year-old man was referred for cardiac consultation following a 2-year history of dyspnea on minimal exertion. He had a coronary angiography in the past that revealed normal coronaries. His physical examination revealed a 3/6 systolic ejection systolic murmur across the precordium. An echo was obtained showing left ventricular dysfunction with an EF of 38%, a calcified aortic valve with a mean gradient of 29 mm Hg, and AVA (aortic valve area) of 0.9 cm^2. Which of the following is the best next step in the management of this patient?

A. SAVR after coronary angiography
B. Left and right cardiac catheterization
C. Exercise treadmill testing
D. TAVR
E. Dobutamine stress echocardiography (DSE)

47-2. A 67-year-old man with a prior medical history of hypertension and atrial fibrillation was referred for cardiac consultation following a 2-year history of chest discomfort on minimal exertion. His physical examination revealed a late peaking 3/6 ejection systolic murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 62%, moderate right ventricular dysfunction, moderate mitral regurgitation, a calcified aortic valve with a mean gradient of 29 mm Hg, and AVA of 0.7 cm^2. Which of the following parameters may *not* be a contributor to paradoxical low-flow, low-gradient severe aortic stenosis?

A. Hypertensive heart disease
B. Atrial fibrillation
C. Right ventricular dysfunction
D. Occult aortic regurgitation
E. Mitral regurgitation

47-3. A 52-year-old man with no prior medical history was referred for cardiac consultation following a 1-year history of chest pain and dyspnea on exertion. Palpation of the carotid arteries demonstrated a pulse low in volume and delayed in upstroke. His remaining physical examination revealed a late-peaking 3/6 systolic ejection murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 62%, a calcified bicuspid aortic valve with a mean gradient of 44 mm Hg, and AVA of 0.7 cm^2. Which of the following is the best next step in the management of this patient?

A. SAVR after coronary angiography
B. Stress cardiac magnetic resonance
C. Exercise treadmill testing
D. TAVR
E. DSE

47-4. A 65-year-old man was referred for cardiac consultation following a 2-year history of dyspnea on exertion. He had a coronary angiography in the past that revealed normal coronaries. Palpation of the carotid arteries demonstrated a pulse low in volume and delayed in upstroke. His remaining physical examination revealed a late-peaking 3/6 systolic ejection murmur with a soft and single S2. An echo was obtained showing left ventricular hypertrophy with an EF of 64%, a calcified aortic valve with a mean gradient of 28 mm Hg, and AVA of 1.5 cm^2. Which of the following is the best management approach for this patient?

A. SAVR after coronary angiography
B. Left and right cardiac catheterization
C. Exercise treadmill testing
D. TAVR

E. Observe

47-5. An 89-year-old woman with a prior history of CABG, hypertension, type 2 diabetes, stage III CKD, COPD, and peripheral artery disease presented to the clinic for routine follow-up. The patient appeared frail but denied any cardiovascular symptoms. Her physical examination revealed parvus tardus carotid pulse and a late-peaking 3/6 systolic ejection murmur with a single S2. An echo was obtained showing left ventricular dysfunction with an EF of 44%, a calcified aortic valve with a mean gradient of 48 mm Hg, and AVA of 0.8 cm^2. Which of the following is the best management approach for this patient?

A. SAVR after coronary angiography
B. Left and right cardiac catheterization
C. Exercise treadmill testing
D. TAVR
E. Observe

47-6. A 29-year-old man with no known cardiovascular history presented to the emergency department complaining of acute dyspnea. On arrival, the patient appeared pale with cool distal extremities, peripheral cyanosis, and tachycardia. The physical examination revealed a relatively unsustained left ventricular impulse that was neither hyperdynamic nor significantly displaced to the left, a short and soft diastolic murmur, pulmonary rales, and an elevated JVP. A wide pulse pressure was *not* seen during the examination. An echo was obtained showing a premature mitral valve closure and fluttering of the mitral valve leaflets, most effectively demonstrated using M-mode echocardiography. Continuous-wave Doppler of the regurgitant jet demonstrated a markedly shortened pressure half-time. Which of the following is the best next step in the management of this patient?

A. Aortic balloon counterpulsation
B. Beta-blocker infusion
C. Atrial pacing
D. SAVR
E. TAVR

47-7. Holodiastolic reversal of flow within the descending aorta detected by pulsed-wave Doppler is an abnormal finding typically consistent with at least moderate (present in the proximal descending aorta) or severe (present in the abdominal aorta) AR. In which of the following scenarios can holodiastolic retrograde aortic flow *not* be seen in the absence of AR?

A. Ruptured sinus of Valsalva aneurysm
B. Left-to-right shunt across a patent ductus arteriosus
C. Upper extremity arterio-venous fistula
D. Aortic dissection with diastolic flow into the false lumen
E. None of the above

47-8. A 66-year-old woman with a prior history of type 2 diabetes, depression, and childhood asthma was referred by her GP to the cardiology clinic because of a 2-year history of progressive dyspnea on exertion. Physical examination revealed a holodiastolic murmur best heard along the left sternal border and a 2/4 diastolic rumble noted at the apex. In addition, there was a sharp carotid upstroke followed by a rapid decline. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 52%, and left ventricular end systolic dimension of 49 mm. Which of the following is the best next step in the management of this patient?

A. Nitroprusside infusion
B. Initiation of an angiotensin-converting enzyme inhibitor
C. Angiotensin-converting enzyme inhibitor and follow-up
D. TAVR
E. SAVR

47-9. A 71-year-old man with a prior history of diet-controlled type 2 diabetes and COPD was referred by his GP to the cardiology clinic because of a heart murmur. He was a very active gentleman without any cardiovascular symptoms. Physical examination revealed a diastolic blowing sound best heard along the left sternal border with the patient sitting up and leaning forward and an exaggerated carotid upstroke. In addition, the apical beat was easily visible and palpable, and it was oriented downward and to the left. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 65%, and left ventricular end systolic dimension of 67 mm. Which of the following is the best next step in the management of this patient?

A. Initiation of nifedipine
B. Exercise treadmill testing
C. SAVR
D. Exercise echocardiography
E. Follow-up

47-10. A 61-year-old man with no known cardiovascular history was referred by his GP to the cardiology clinic because of a

heart murmur. He was active and asymptomatic. Physical examination revealed a holodiastolic murmur best heard along the left sternal border. In addition, there was a sharp carotid upstroke followed by a rapid decline. An echocardiogram was obtained demonstrating severe aortic regurgitation, a left ventricular ejection fraction of 45%, and left ventricular end systolic dimension of 37 mm. Which of the following is the best next step in the management of this patient?

A. Initiation of a vasodilator
B. Exercise treadmill testing
C. Follow-up
D. Exercise echocardiography
E. SAVR

ANSWERS

47-1. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 47)* There is a discrepancy between gradient and valve area calculation, and this needs to be sorted out before making any decision with regard to the interventions (options A and D are thus not correct). This patient may have low-flow/low-gradient severe AS with reduced EF. AS severity may be difficult to assess under resting conditions in low LVEF patients,[1-5] and DSE (option E) can help clarify the issue by allowing reassessment of the AVA at a higher flow. With normalized flow, a patient with true severe AS increases the mean transaortic gradient in tandem with valve flow so that AVA remains nearly constant. A patient with pseudo-severe AS, a condition where low flow causes an overestimation of AS severity, increases valve flow with little increase in gradient, resulting in increased AVA. Options B and C would not be useful in resolving the discrepancy between gradient and valve area calculation in this case.

47-2. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 47)* Multiple explanations for low forward flow in the setting of normal EF have been proposed.[6-8] It is generally held that this group has small LV volumes (concentric remodeling), so a normal EF of a small end-diastolic volume produces a small stroke volume and hence a low gradient. Hypertension (option A) has been shown to reduce the transaortic gradients in experimental models and patients, primarily because of changes in transvalvular flow rates and not directly as a result of changes in arterial compliance.[6,7] Right ventricular dysfunction (option C), atrial fibrillation (option B), and mitral regurgitation (option E) are independently associated with low-flow, low-gradient AS.[8] Aortic regurgitation (option D) is associated with higher transaortic flow rates and, consequently, should not cause low-flow, low-gradient AS. Option D is therefore the correct answer.

47-3. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 47)* All evidence (clinical, physical exam findings, aortic gradient, and AVA) points to severe symptomatic AS in a patient with high-flow and normal EF, so SAVR is indicated (option A). No further tests are needed (options B, C, and E). SAVR remains the standard of care in low-risk patients, especially in individuals with a congenital bicuspid aortic valve. (Insufficient data are currently available for the routine use of TAVR (option D) in bicuspid aortic valve patients.)

47-4. The answer is B. *(Hurst's The Heart, 14th Edition, Chap. 47)* There are discrepancies between clinical, physical exam, and echocardiographic findings; and this needs to be sorted out before making any decision with regard to the interventions (options A and D are thus not correct). Invasive hemodynamic measurement is the best next step for such situations when there is discordance in clinical presentation and noninvasive data regarding AS severity (option B). In such cases direct measurement of aortic valve gradient (g) and cardiac output (CO) is indicated. These data are entered into the Gorlin equation: $AVA = CO/44.3\sqrt{g}$, where cardiac output is expressed as flow per systole. Careful attention must be paid to proper pressure and cardiac output measurement.[9] Options C and E would be inappropriate for these reasons.

47-5. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 47)* In the truly asymptomatic AS patient, the risk of sudden death is small, probably less than 1% per year.[10,11] However, AVR is recommended for very rare asymptomatic patients who have developed LV dysfunction and for the patient with severe AS undergoing another cardiac operation where it would be unwise to fail to correct severe AS during surgery.[12,13] Because this is a high-risk patient (elderly, frail, multiple comorbidities and history of a prior CABG), TAVR (instead of SAVR) would be the best option in this case (options A and D). This patient has some indications for AVR, and therefore options B, C, and E would be inappropriate.

47-6. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 47)* This is a case of acute AR. Vasodilator therapy with sodium nitroprusside may stabilize the patient during transport to the operating department. Aortic balloon counterpulsation (option A) is contraindicated because it worsens AR. Beta-blockers (option B) should be avoided in acute AR because they prolong diastole and may worsen AR. Atrial pacing (option C) to increase heart rate might be of theoretical benefit[14]; however, this does not have an established role in clinical practice. Several studies have demonstrated that emergency aortic valve replacement (SAVR, and thus option D) can be performed with low operative mortality and good long-term results in acute AR. The data with TAVR are currently lacking (option E).

47-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 47)* In the absence of AR, holodiastolic retrograde aortic flow can be seen most commonly in hypertensive patients with reduced aortic compliance[15] but also in other conditions such as a left-to-right shunt across a patent ductus arteriosus (option B), upper extremity arterio-venous fistula (option C), a ruptured sinus of Valsalva (option A), or aortic dissection with diastolic flow into the false lumen (option D). It is thus important to assess diastolic flow reversal in the context of these possible confounders. The correct answer is therefore option E.

47-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 47)* As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention (options A, B, and C are thus not correct).[16] In most cases, SAVR is standard therapy (option E). Because TAVR (option D) relies on native valve calcification to hold the TAVR in place, TAVR is not widely used in treating AR, although newer valve designs may overcome this problem. The correct answer is therefore option E.

47-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 47)* As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention.[16] However, some patients develop LV dysfunction without having or noticing symptom onset. To avoid persistent postoperative LV dysfunction, AVR should occur before the LV end-diastolic dimension increases from 50 to 55 mm (option C is thus the correct answer).[17,18] Although adding stress imaging is of uncertain value (option D), if exercise imaging is performed, attention should be focused on LV ejection fraction at exercise. However the utility of imaging LV function during exercise remains controversial (option D). Because afterload is often excessive in AR, there have been attempts to lower afterload using ACE inhibitors, direct vasodilators, or dihyropyridine calcium channel blockers (option A) in the hope of forestalling the need for AVR. These efforts have met with confusing and contradictory results, such that no clear recommendation can be made about their usage.[19-21] Options B and E are not correct for the reasons explained above.

47-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 47)* As with all valve disease, the onset of symptoms represents a negative demarcation in the natural history of the disease, and symptom onset is a clear indication of surgical intervention.[16] However, some patients develop LV dysfunction without having or noticing symptom onset. To avoid persistent postoperative LV dysfunction, AVR should occur before EF declines to 50% to 55% (option E is thus the correct answer) or before LV end-diastolic dimension increases from 50 to 55 mm.[17,18] Although adding stress imaging is of uncertain value (option D), if exercise imaging is performed, attention should be focused on LV ejection fraction at exercise. However, the utility of imaging LV function during exercise remains controversial (option B and D). Because afterload is often excessive in AR, there have been attempts to lower afterload using ACE inhibitors, direct vasodilators (option A), or dihyropyridine calcium channel blockers in the hope of forestalling the need for AVR. These efforts have met with confusing and contradictory results, such that no clear recommendation can be made about their usage.[19-21] Options B and C are not correct for the reasons explained above.

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CHAPTER 48

Degenerative Mitral Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

48-1. A 45-year-old woman with a prior history of diet-controlled type 2 diabetes and chronic obstructive pulmonary disease (COPD) was referred by her GP to the cardiology clinic because of a heart murmur. She was very active and without any cardiovascular symptoms. Physical examination revealed a soft late-systolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating mild prolapse and leaflet thickening with normal coaptation. Left ventricular function and dimensions are normal (ejection fraction 65%). Which of the following is the best next step in the management of this patient?

A. Vasodilator therapy
B. Beta-blocker therapy
C. Elective mitral valve repair
D. Elective mitral valve replacement
E. Observe with echocardiographic annual follow-up

48-2. Mortality after mitral valve repair in patients with degenerative disease correlates with age, with an average risk of 1% for patients below 65 years, 2% for those aged 65 to 80 years, and 4% for octogenarians. Which of the following is *not* an independent predictor of postoperative survival?

A. Severe symptoms (NYHA class III or IV)
B. LV dysfunction
C. A regurgitant orifice area ≥ 40 mm^2
D. A large color Doppler jet appearance
E. The presence of long-standing atrial fibrillation

48-3. A 55-year-old woman with no prior cardiac history was referred by her GP to the cardiology clinic because of a heart murmur. She admitted to living a sedentary lifestyle, and she denied overt cardiovascular symptoms. Physical examination revealed a mid-to-late systolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained, clearly demonstrating moderate to severe mitral valve prolapse and regurgitation without flail segments. Left ventricular function and dimensions were normal (ejection fraction 62%). Which of the following is the best next step in the management of this patient?

A. Exercise Doppler echocardiography
B. Cardiac CT
C. Cardiac magnetic resonance
D. Nuclear perfusion scan
E. Cardiac catheterization

48-4. A 69-year-old man with a prior history of type 2 diabetes and dyslipidemia was referred by his GP to the cardiology clinic because of a heart murmur. He was a very active person without any cardiovascular symptoms. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe prolapse with loss of coaptation, LVEF of 63%, and LVESD of 38 mm. According to the ACC/AHA guidelines, which of the following statements does *not* justify prompt correction of MR in general?

A. Severe MR is not a benign condition
B. Surgical correction in patients with severe MR is unavoidable
C. Patients with severe MR may or may not develop symptoms
D. Mitral valve prolapse is almost always a repairable disease in reference centers
E. The risk of operative mortality in mitral valve repair surgery is, on average, only 10%

48-5. A 59-year-old woman with a prior history of depression and childhood asthma was referred by her GP to the cardiology clinic because of a new onset atrial fibrillation. During the visit, the patient denied any cardiovascular symptoms. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. The ECG showed atrial fibrillation with a controlled ventricular response. An echocardiogram was obtained demonstrating severe mitral valve prolapse with loss of coaptation, LVEF of 66%, and LVESD of 36 mm. Which of the following is the best next step in the management of this patient?

A. Vasodilator therapy
B. Exercise Doppler echocardiography
C. Elective mitral valve repair
D. Elective mitral valve replacement
E. Observe with echocardiographic annual follow-up

48-6. Tricuspid regurgitation does *not* always regress after correction of left-sided valve disease, and reoperations for residual or recurrent tricuspid regurgitation are associated with a higher mortality risk even in experienced centers (up to 15%). Which of the following factors may be used as a guide in deciding on concomitant tricuspid valve repair in patients undergoing mitral valve repair?

A. Degree of TR
B. Annular dimensions
C. Leaflet coaptation or mismatch between leaflet and annulus
D. Presence of atrial fibrillation
E. All of the above

48-7. A 71-year-old woman with a prior history of type 2 diabetes, COPD, and dyslipidemia was referred by her GP to the cardiology clinic because of a heart murmur. She reported otherwise feeling fit and well. Physical examination revealed a holosystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe mitral valve prolapse with loss of coaptation, LVEF of 62%, LVESD of 38 mm, and SPAP of 62 mm Hg. Which of the following is the best next step in the management of this patient?

A. Beta-blocker therapy
B. Exercise Doppler echocardiography
C. Elective mitral valve repair
D. Elective mitral valve replacement
E. Observe with echocardiographic annual follow-up

48-8. Severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem, with the only definitive solution being mechanical (ie, mitral valve repair or replacement). Which of the following factors may be a reason to favor mitral valve replacement over repair?

A. Lower perioperative risk
B. Improved preservation of left ventricular function
C. Improved event-free survival in the majority of patients
D. Greater freedom from prosthetic valve–related complications
E. Greater certitude to correct complex lesions with extensive distortion of multiple scallops

48-9. A 58-year-old man with a history of mitral valve prolapse and mild mitral regurgitation, was referred by his GP to the cardiology clinic because of a 6-month history of exertional dyspnea. Physical examination revealed a pansystolic murmur best heard at the apex and radiating to the axilla. An echocardiogram was obtained demonstrating severe prolapse with a coaptation gap, LVEF of 62%, and LVESD of 38 mm. Which of the following is the best next step in the management of this patient?

A. Immediate admission for management of acute severe MR
B. Exercise Doppler echocardiography
C. Elective mitral valve repair
D. Elective mitral valve replacement
E. Observe with echocardiographic annual follow-up

48-10. An ejection fraction ≤ 60% or a left ventricular end-systolic dimension ≥ 40 mm, though useful at indicating the onset of LV dysfunction, are imprecise and reflect changes in the LV after the negative impact of MR has already been realized. Which of the following new markers indicating an adverse myocardial response to MR has the potential to determine the optimum timing of surgery in the very near future?

A. High brain natriuretic peptide (BNP) levels
B. A lower percentage of age- or sex-predicted metabolic equivalents
C. Lower heart rate recovery after exercise
D. Left atrial dimensions
E. All of the above

ANSWERS

48-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 48)* Currently there is no indication to intervene (options C and D) in less than severe primary mitral regurgitation, except in symptomatic patients where there is a high suspicion that MR grade may be underestimated. The use of beta-blockers (option B) or vasodilators (option A) to treat mitral valve prolapse in normotensive subjects is not recommended. The correct answer is therefore to observe with echocardiographic annual follow-up (option E).

48-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 48)* Some of the identified independent predictors of postoperative survival include severe symptoms (NYHA class III or IV—option A is thus true and therefore incorrect), LV dysfunction (EF < 60% or LVESD > 40 mm—option B is thus incorrect), a regurgitant orifice area ≥ 40 mm^2 (option C is thus incorrect), left atrial dimensions (left atrial index ≥ 60 mL/m^2 or LA > 55 mm), or the presence of pulmonary hypertension or long-standing atrial fibrillation (option E is thus incorrect). The size of the color Doppler jet is subject to many technical parameters, and it is not reliably predictive of outcomes after repair. The correct answer is therefore D.

48-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 48)* Again, currently there is no indication to intervene in less than severe mitral regurgitation, except in symptomatic patients where there is a high suspicion that MR grade may be underestimated. In such patients, exercise testing is useful to clarify the decision making (option A is thus the correct answer).[1] In fact, exercise Doppler echocardiography can be used in asymptomatic patients with moderate to severe primary MR with preserved LV ejection fraction for immediate risk stratification and to guide the timing of mitral valve surgery, especially for those in whom the risk-to-benefit ratio of surgical intervention is uncertain or borderline.[2] Computed tomography (option B), cardiac magnetic resonance (option C), and nuclear perfusion scan (option D) techniques have been compared to echocardiography for MR assessment, but they are not routinely recommended unless there are critical considerations about chamber remodeling or viability.[3,4] Although TEE is more accurate than TTE in locating the site and severity of structural abnormalities and quantifying the severity of MR, TEE during an initial diagnostic evaluation is only indicated in patients with inconclusive or technically difficult TTE examinations. Once the mainstay of evaluation, invasive hemodynamic evaluation (option E) is now reserved for cases in which the diagnosis of the severity and impact of mitral regurgitation is uncertain.

48-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 48)* Prompt correction of asymptomatic mitral regurgitation with preserved left ventricular function (class IIa), in other words before the development of traditional triggers, is based on several axioms: (1) severe MR is not a benign condition (option A is thus incorrect),[5] and if left uncorrected it carries a significant rate of excess mortality associated with increased rates of heart failure and atrial fibrillation[6]; (2) surgical correction in patients with severe MR is unavoidable (option B is thus incorrect); (3) patients with severe MR or ventricular dysfunction may or may not develop classical symptoms (option C is thus incorrect); and (4) mitral valve prolapse is a repairable disease in reference centers (option D is thus incorrect) with excellent operative outcomes (mortality and stroke rates < 1%; not 10% as stated in option E, which is therefore the correct answer) and durability.[7-9]

48-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 48)* According to the 2014 ACC/AHA new classification of the severity of valve lesions, this patient is at stage C1 of degenerative mitral valve disease, and the presence of the new onset of atrial fibrillation[12] is considered a class IIa trigger for mitral surgery in asymptomatic patients with preserved left ventricular function (options B and E are not the best next step in the management of this patient, who needs her valve to be fixed).[13] Severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem with only a mechanical solution (option A is thus not correct); at this time the only definitive treatment is mitral valve repair (option C is thus the correct answer). All prolapsing valves are repairable, and mitral valve replacement should not be an option if appropriate referral patterns are followed (option D is thus not correct).[14]

48-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 48)* The final decision should be guided not only by the degree of regurgitation (≥ moderate) (option A is thus incorrect) but also by annular dimensions (≥ 40 mm when measured by echocardiography in the apical 4-chamber view) (option B is also thus incorrect); leaflet coaptation or mismatch between leaflet and annulus on direct inspection (option C is thus incorrect); and the presence of atrial fibrillation (option D is thus incorrect), pulmonary hypertension, right ventricular dysfunction, and/or left ventricular dysfunction. The correct answer is therefore option E.

48-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 48)* According to the 2014 ACC/AHA new classification of the severity of valve lesions, this patient is at stage C1 of degenerative mitral valve disease, and the presence of pulmonary hypertension[12] is also considered a class IIa trigger for mitral surgery in asymptomatic patients with preserved left ventricular function (options B and E are not the best next step in the management of this patient, who needs her valve to be fixed).[13] Again, severe mitral valve regurgitation in the setting of degenerative mitral valve disease is a mechanical problem (option A is thus not correct) with only a mechanical solution; at this time the only definitive treatment is mitral valve repair (option C is thus the correct answer). All prolapsing valves are repairable, and mitral valve replacement should not be an option if appropriate referral patterns are followed (option D is thus not correct).[14]

48-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 48)* Mitral valve repair is favored over replacement for several reasons, including a lower perioperative risk (option A is thus not correct), improved preservation of left ventricular function (option B is thus not correct), improved event-free survival in most patients (option C is thus not correct), and greater freedom from prosthetic valve–related complications (option D is thus not correct) such as thromboembolism, anticoagulant-related hemorrhage, and endocarditis.[15-17,19] However, in a minority of cases, anatomical factors pertaining to the extent of valvular disruption (eg, perforation) and operator-related factors pertaining to local experience and expertise make replacement more appropriate than repair (option E is thus the correct answer).

48-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 48)* This patient is symptomatic but stable and therefore does not require immediate admission for the management of acute severe MR (option A). The standard class I indications for mitral valve surgery are the onset of symptoms or of left ventricular dysfunction.[19,20] Although guidelines currently contemplate mitral valve replacement (option D) as an acceptable option, mitral valve repair is the preferred option in patients with mitral valve prolapse (option C is therefore the correct answer).[14] Options B and E are not the best next step in the management of this patient, who needs her valve to be fixed.

48-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 48)* In this context, new potential triggers for surgical intervention in asymptomatic patients might include high BNP levels (option A is thus correct),[21] a lower percentage of age- or sex-predicted metabolic equivalents (option B is thus correct), or lower heart rate recovery after exercise (option C is thus correct),[1] the left ventricular ejection index,[22,23] and left atrial dimensions (option D is thus correct).[24,25] The correct answer is therefore option E.

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CHAPTER 49

Ischemic Mitral Regurgitation

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

49-1. A 61-year-old man with a prior history of diet-controlled type 2 diabetes, ischemic heart disease, and COPD was referred for cardiology consultation for a heart murmur. He was a very active man without any cardiovascular symptoms. His physical examination revealed a 2/6 holosystolic murmur loudest at the apex. An echo was obtained showing normal valve leaflets, chords, and annulus; small central MR jet area of 15% LA on Doppler; and mildly dilated LV size with fixed regional wall motion abnormalities. According to the ACC/AHA stages for ischemic MR (IMR), at which of the following stages would this patient be?

A. Stage A
B. Stage B
C. Stage C1
D. Stage C2
E. Stage D

49-2. IMR is an independent predictor of cardiovascular mortality and HF following MI. Which of the following statements about IMR is *false*?

A. The magnitude of risk is proportional to the severity of MR
B. The estimated 1-year mortality for patients with severe IMR ranges from 15% to 40%
C. For patients with moderate IMR undergoing coronary artery bypass surgery, concomitant mitral valve replacement should always be performed
D. Adverse outcomes are associated with a smaller calculated effective regurgitant orifice (ERO) in IMR when compared to primary MR
E. None of the above

49-3. The MitraClip is a transcatheter mitral device for use in high-risk or inoperable patients with severe MR and suitable anatomic criteria. Which of the following characteristics is *not* part of the desirable anatomic criteria for percutaneous edge-to-edge repair of MR using this type of device?

A. Coaptation length ≥ 2 mm
B. Short posterior leaflet
C. Flail width < 15 mm
D. MV orifice area > 4 cm^2
E. MV leaflet length > 1 cm

49-4. IMR is a dynamic lesion, and MR severity can vary over time and during exercise. Which of the following statements about IMR during exercise is *false*?

A. The severity of IMR at rest predictably determines the severity of IMR during exercise
B. Exercise-induced increase in IMR provides additional prognostic information over resting evaluation
C. Exercise echocardiography may be used to further evaluate patients with exertional dyspnea out of proportion to the degree of resting IMR
D. An increase in EROA of ≥ 13 mm^2 during exercise is associated with increased mortality
E. An increase in EROA of ≥ 13 mm^2 during exercise is associated with increased HF hospitalizations

49-5. A 68-year-old man with a prior history of myocardial infarction with PCI to the LAD was referred for cardiology consultation for decreased exercise tolerance. His physical examination revealed a displaced apex beat downward and to the left and a holosystolic murmur loudest at the apex and radiating to the axilla. An echo was obtained showing regional wall motion abnormalities with reduced LV systolic function, LV dilation with severe tethering of mitral leaflets, and a large

wall-impinging jet pattern with an estimated regurgitant volume of 40 mL. Defining severe MR requires the careful integration of multiple echocardiographic parameters. Which of the following echo findings is *not* an indicator of severe MR?

A. Peak mitral valve E-wave velocity < 1.2 m/s
B. A dense triangular continuous-wave Doppler profile
C. Systolic flow reversal in the pulmonary veins
D. Vena contracta width ≥ 0.7 cm
E. MR regurgitant jet area/left atrial area ratio ≥ 40%

49-6. A 75-year-old woman with a prior history of ischemic heart failure was referred for cardiology consultation for a heart murmur. During the visit the patient denied any cardiovascular symptoms. Her physical exam revealed a displaced apex beat downward and to the left and a holosystolic murmur loudest at the apex and radiating to the axilla. An echo was obtained showing LV dilation and systolic dysfunction due to primary myocardial disease, annular dilation with severe loss of central coaptation of the mitral leaflets, and an estimated regurgitant fraction of 55%. In addition, there was systolic flow reversal in the pulmonary veins. According to the ACC/AHA Stages for IMR, at which of the following stages would this patient be?

A. Stage A
B. Stage B1
C. Stage B2
D. Stage C
E. Stage D

49-7. A 65-year-old woman with a prior history of myocardial infarction and multivessel PCI was referred for cardiology consultation for a 3-month history of progressive exertional dyspnea despite optimal guideline-directed medical therapy. Her physical examination revealed an irregularly irregular pulse, a displaced apex beat downward and to the left, an elevated JVP, and a holosystolic murmur loudest at the apex and radiating to the axilla. An ECG was obtained and revealed atrial fibrillation (AF). An echo was also obtained showing regional wall motion abnormalities with reduced LV systolic function and LV dilation with severe tethering of mitral leaflets, and an estimated regurgitant volume of 50 mL. A dense, triangular continuous-wave Doppler profile was also noted. Which of the following statements about this patient's AF is *false*?

A. AF is present in up to 20% of patients undergoing MV surgery
B. AF may be a marker of disease progression in IMR
C. AF may be a marker of worse prognosis in IMR
D. Surgical approaches for AF can be considered in patients undergoing MV surgery
E. The duration of preoperative AF is a risk factor for recurrence after the MAZE procedure

49-8. Although a variety of percutaneous therapies for MR have been developed, the MitraClip system has emerged clinically as the most tolerated and effective approach to date. Which of the following statements about MitraClip is *false*?

A. It may be used in high-risk or inoperable patients with severe MR and suitable anatomic criteria
B. It is currently approved for use in symptomatic patients with primary (degenerative) MR who are at prohibitive risk for surgery
C. It is currently approved for the treatment of IMR in the United States
D. It has already received a class IIb recommendation from the European Society of Cardiology for secondary MR
E. Approximately two-thirds of the MitraClip procedures have been performed in patients with secondary MR worldwide

49-9. A 67-year-old man with a prior history of ischemic heart failure was referred for cardiology consultation for a 2-month history of dyspnea on minimal exertion despite optimal guideline-directed medical therapy for HF. During the visit, the patient had a fast radial pulse with a reduced pulse pressure, the apex beat was displaced downward and to the left, JVP was elevated, and there was a holosystolic murmur loudest at the apex and radiating to the axilla. In addition, an S3 gallop was present. An echo was obtained showing LV dilation and systolic dysfunction, annular dilation with severe loss of central coaptation of the mitral leaflets, a vena contracta width of 0.8 cm, and an estimated regurgitant fraction of 70%. After careful review, the patient's cardiologist decided to refer the patient for surgery as per the ACC/AHA guidelines (class of recommendation: IIb; level of evidence: B).[1] In the setting of severe IMR, which of the following statements about the role of MV repair versus MV replacement (MVR) is *false*?

A. Repair may be safer with lower perioperative mortality and morbidity
B. There is a lower rate of recurrent MR with MV repair than with MV replacement
C. No differences in survival have been reported between the two strategies
D. No differences exist between the two strategies in the incidence of major adverse cardiac and cerebrovascular events
E. More adverse events related to HF and cardiovascular readmissions occur for MR repair

49-10. Many observational studies have identified echocardiographic predictors of recurrent MR following MV annuloplasty. In the randomized trial of repair versus replacement, which of the following factors was significantly associated with recurrent moderate or severe MR in patients following repair for severe IMR?

A. LV end-diastolic diameter > 65 mm

B. Coaptation depth > 1 cm
C. Systolic sphericity index > 0.7
D. Basal aneurysms and dyskinesis
E. All of the above

ANSWERS

49-1. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The clinical presentation and the echo findings are consistent with stage A, which includes asymptomatic patients at risk of MR, as is the case for this patient (option A). Stages B (option B), C (options C and D), and D (option E) typically include patients with progressive MR, asymptomatic patients with severe disease, and symptomatic subjects with severe MR, respectively. Options B through E are therefore not correct. Stages of secondary MR with associated valve anatomy, valve hemodynamics, cardiac findings, and symptoms are presented in Table 49-1.[1]

TABLE 49-1 Stages of Secondary Mitral Regurgitation with Associated Valve Anatomy, Valve Hemodynamics, Cardiac Findings, and Symptoms

Grade	Definition	Valve Anatomy	Valve Hemodynamics*	Associated Cardiac Findings	Symptoms
A	At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	• No MR jet or small central jet area < 20% LA on Doppler • Small vena contracta < 0.30 cm	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• ERO < 0.20 $cm^{2\dagger}$ • Regurgitant volume < 30 mL • Regurgitant fraction < 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥ 0.20 $cm^{2\dagger}$ • Regurgitant volume ≥ 30 mL • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥ 0.20 $cm^{2\dagger}$ • Regurgitant volume ≥ 30 mL • Regurgitant fraction ≥ 50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• HF symptoms due to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea

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*Several valve hemodynamic criteria are provided for the assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

49-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The magnitude of risk is proportional to the severity of MR (option A is thus incorrect).[2,3] Although even mild MR is associated with increased mortality, prognosis is particularly poor for patients with severe IMR, with 1-year mortality estimates ranging from 15% to 40% (option B is thus incorrect).[4] Adverse outcomes are associated with a smaller calculated effective regurgitant orifice (ERO) of > 0.2 cm^2 in IMR compared to primary MR (option D is thus incorrect).[1] The role and expected benefits of concomitant mitral valve replacements remain controversial in moderate secondary mitral valve lesions such as IMR.

49-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The desirable anatomic criteria for percutaneous edge-to-edge repair of MR using MitraClip may include coaptation length ≥ 2 mm (option A), flail width < 15 mm (option C), MV orifice area > 4 cm^2 (option D), and MV leaflet length > 1 cm (option E). A short posterior leaflet is actually among the undesirable criteria for MitraClip. The correct answer is therefore option B. The favorable and unfavorable anatomic criteria are presented in Table 49-2.[5]

TABLE 49-2 Favorable and Unfavorable Anatomic Criteria for Percutaneous Edge-to-Edge Repair of MR

Anatomical MV and LV Characteristics for Percutaneous Edge-to-Edge Repair of MR	
Desirable Criteria	**Undesirable Criteria**
• Moderate to severe MR (≥ grade 3) • Pathology in the A2-P2 zone • Coaptation length ≥ 2 mm • Flail gap < 10 mm • Flail width < 15 mm • MV orifice area > 4 cm^2 • MV leaflet length > 1 cm	• Commissural lesion • Short posterior leaflet • Severe asymmetric tethering • Calcification in the grasping area • Severe annular calcification • MV cleft • Severe annular dilation • Severe LV remodeling • Large (> 50%) inter-commissural extension of regurgitant jet • Severe myxomatous degeneration with multi-scallop prolapse

Reproduced with permission from De Bonis M, Al-Attar N, Antunes M, et al. Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease, *Eur Heart J.* 2016 Jan 7;37(2):133-139.

49-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The severity of IMR at rest does not necessarily reflect nor predict the severity of MR during exercise (option A is thus false, and therefore the correct answer). Exercise-induced increase in IMR provides additional prognostic information over resting evaluation and identifies patients at higher risk of adverse clinical outcomes (option B is thus incorrect).[6] For example, an increase in EROA of ≥13 mm^2 during exercise is associated with increased mortality and HF hospitalizations (options D and E are thus incorrect).[7] Exercise echocardiography has been proposed to evaluate patients with exertional dyspnea out of proportion to the degree of resting IMR (option C is thus incorrect) and LV dysfunction, patients with IMR and unexplained acute pulmonary edema, and patients with moderate IMR at rest who are due to undergo surgical revascularization with CABG.[6,8]

49-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 49)* Indicators of severe MR should be integrated[12] and include a peak mitral valve E-wave velocity > 1.2 m/s (not E-wave velocity < 1.2 m/s as stated in option A, which is thus the correct answer), a dense triangular continuous-wave Doppler profile (option B is thus incorrect), vena contracta width ≥ 0.7 cm (option D is thus incorrect), MR regurgitant jet area/left atrial area ratio ≥ 40% (option E is thus incorrect), and systolic flow reversal in the pulmonary veins (option C is thus incorrect).[10]

49-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The clinical presentation and the echo findings are consistent with stage C, which includes asymptomatic patients with severe MR as is the case for this patient (option D). Stages A (option A), B (options B and C), and D (option E) typically include patients at risk of MR, patients with progressive MR, and symptomatic patients with severe MR, respectively. Options A, B, C, and E are therefore not correct. Stages of secondary MR with associated valve anatomy, valve hemodynamics, cardiac findings, and symptoms are presented in Table 49-1.[1]

49-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 49)* Atrial fibrillation (AF) is commonly associated with MR, and it is present in up to 50% of patients undergoing MV surgery (option A is thus false, and therefore is the correct

answer).[11] LA chamber enlargement as a consequence of increased pressure and volume load to the LA from MR is implicated in the genesis of AF.[12] AF may be a marker of disease progression (option B is thus incorrect) and worse prognosis in IMR (option C is thus incorrect). Surgical approaches for AF with or without left atrial appendage ligation can be considered in patients undergoing MV surgery (option D is thus incorrect). Risk factors for the return of AF after the MAZE procedure include duration of preoperative AF, left atrial size, and reduced LV function (option E is thus incorrect).[13]

49-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 49)* The MitraClip is a transcatheter mitral device for use in high-risk or inoperable patients with severe MR and suitable anatomic criteria (option A is true and thus incorrect). It is currently approved by the US Food and Drug Administration for use in symptomatic patients with primary (degenerative) MR who are at prohibitive risk for surgery (option B is thus incorrect); it is not approved for the treatment of IMR in the United States (option C is thus false, and therefore is the correct answer), but is under investigation for this indication through the Clinical Outcomes Assessment of MitraClip Percutaneous Therapy for Extremely High-Surgical-Risk Patients (COAPT) trial.[10] In contrast, the MitraClip system has already received a class IIb recommendation from the European Society of Cardiology for secondary MR (option D is thus incorrect). Worldwide, it is estimated that approximately two-thirds of the MitraClip procedures have been performed in patients with secondary MR (option E is thus incorrect).

49-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 49)* In the setting of severe IMR, debate has focused on the role of MV repair versus MV replacement (MVR). Repair has been considered safer with lower perioperative mortality and morbidity (option A is thus incorrect), though generally associated with a higher rate of recurrent MR compared with replacement (option B is thus false, and therefore is the correct answer). A randomized multicenter trial assigned 251 patients with severe IMR to undergo either MV repair (n = 126) or chordal-sparing MVR (n = 125) and did not demonstrate any significant difference in LV end-systolic volume indexed to body surface area at 1 and 2 years (primary end point). No differences in survival (option C is thus incorrect) or the incidence of major adverse cardiac and cerebrovascular events (option D is thus incorrect) were found. The rate of recurrence of moderate or severe MR was significantly higher in the repair compared to the replacement group (32.6% vs 2.3% at 1 year, $P < .001$; and 58.8% versus 3.8% at 2 years, $P < .001$), resulting in more adverse events related to HF and cardiovascular readmissions (option E is thus incorrect).[14,4]

49-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 49)* Many observational studies have identified echocardiographic predictors of recurrent MR following MV annuloplasty, including an LV end-diastolic diameter > 65 mm (option A), coaptation depth > 1 cm (option B), and systolic sphericity index > 0.7 (option C).[5] These options (A, B, and C) would be correct in the setting of MV annuloplasty, but this question is about the factors associated with recurrent moderate or severe MR in patients following repair for severe IMR. In the randomized trial of repair versus replacement, only basal aneurysms and dyskinesis were significantly associated with recurrent moderate or severe MR in patients following repair for severe IMR (option D is thus the correct answer).[15] It is important to note that none of the prediction models for recurrent MR have been externally validated. The durability of repair is also influenced by the natural history of underlying ventricular dilation over time; progressive dilation will undermine the integrity of MV repair.

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CHAPTER 50

Mitral Stenosis

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

50-1. Rheumatic heart disease (RHD) remains prevalent in developing countries. Which of the following statements about RHD in developing countries is *false*?

A. The prevalence ranges from 1 to 2 per 1000 school children
B. Ten percent of patients with RHD have isolated MS
C. Only 10% of patients with isolated MS report a past history of rheumatic fever
D. Symptoms occur after at least 4 decades from the initial attack of ARF
E. All of the above

50-2. A 52-year-old woman with a prior history of type 2 diabetes, depression, and SLE presented to her family physician for a routine visit. The patient denied any symptoms such as exertional dyspnea, chest pain, or palpitations. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 1.8 cm^2, and a diastolic pressure half-time of 145 ms. The patient was in normal sinus rhythm and had a valve morphology that was suitable for BMV. According to the ACC/AHA Stages for MS, at which of the following stages would this patient be?

A. Stage A
B. Stage B
C. Stage C1
D. Stage C2
E. Stage D

50-3. A 56-year-old woman with no prior medical history was referred for cardiac consultation following a 6-month history of exertional dyspnea. Physical examination revealed a loud P2 and a middiastolic rumble. A transthoracic echocardiogram was performed that showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 0.9 cm^2, a diastolic pressure half-time of 230 ms, and a PASP of 69 mm Hg. In addition, there was right ventricular dilatation and dysfunction. Which of the following statements about this patient's pulmonary hypertension is *false*?

A. Secondary vasoconstriction in the pulmonary bed may play a role in its development
B. The specific cause of the observed pulmonary vasoconstriction is well established
C. It is almost always reversed by relief of MS
D. It can be improved by the administration of sildenafil
E. The nitric oxide pathway may be involved in the mechanism of pulmonary vasoconstriction

50-4. A 19-year-old man with a prior history of acute rheumatic fever presented to the emergency department complaining of dyspnea on minimal exertion, orthopnea, and paroxysmal nocturnal dyspnea. Physical examination revealed a loud first heart sound and a low-pitched diastolic rumble best heard at the apex. The initial investigations, including a chest x-ray, were consistent with the diagnosis of pulmonary edema. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.2 cm^2 with a PASP of 62 mm Hg. Which of the following statements about this patient is *false*?

A. Juvenile MS is the most likely diagnosis
B. The likely diagnosis may constitute up to a quarter of rheumatic MS cases in developing countries
C. Boys are more commonly affected
D. Atrial fibrillation is uncommon
E. MV calcification and LA thrombi are common findings

50-5. A 28-year-old primigravid woman at 31 weeks' gestation was admitted to the hospital because of NYHA class II heart failure symptoms. Physical examination revealed a loud first heart sound and a middiastolic rumble. An initial ECG revealed AF with fast ventricular response. A transthoracic echocardiogram was performed; it showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and a diastolic pressure half-time of 138 ms. The patient had a valve morphology that was suitable for BMV. Which of the following will *not* be appropriate as an initial next best step?

A. Diuretics
B. Restriction of physical activity
C. Metoprolol
D. Digoxin
E. BMV

50-6. A 55-year-old woman with a prior history of acute rheumatic fever at age 15 presented to the emergency department complaining of exertional dyspnea and intermittent palpitations. Physical examination revealed a loud first heart sound and a middiastolic rumble. In addition, there was an irregularly irregular pulse. Atrial fibrillation was confirmed on the initial ECG. A transthoracic echocardiogram was performed and revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.1 cm^2. In addition there were extensive calcifications and severe subvalvular disease. Which of the following would be the surgical treatment of choice for this patient?

A. Closed mitral valvotomy (CMV)
B. Open mitral valvotomy (OMV)
C. Mitral valve replacement (MVR)
D. BMV
E. All of the above

50-7. A 49-year-old woman with no prior medical history presented to her cardiologist complaining of a reduced exercise tolerance. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 1.1 cm^2, a diastolic pressure half-time of 210 ms, and a PASP of 49 mm Hg. The patient was in normal sinus rhythm and had a valve morphology that was suitable for BMV. According to the ACC/AHA Stages for MS, at which of the following stages would this patient be?

A. Stage A
B. Stage B
C. Stage C1
D. Stage C2
E. Stage D

50-8. Relief of MS by surgery may be done either by CMV, OMV, or MVR. Which of the following is a class 2b indication for MVR?

A. Severely symptomatic MS (MVA < 1.5 cm^2; NYHA class III/IV) who are not high risk for surgery and who are not candidates for BMV
B. Severe symptomatic MS (MVA < 1.5 cm^2; NYHA class III/IV) who are not high risk for surgery and who have failed previous BMV
C. Severe MS (MVA ≤ 1.5 cm^2) with recurrent embolic events despite adequate anticoagulation
D. Severe MS (MVA < 1.5 cm^2) undergoing aortic valve surgery
E. Severe MS (MVA < 1.5 cm^2) undergoing CABG

50-9. A 62-year-old woman with no prior medical history was referred for cardiac consultation following a 6-month history of exertional dyspnea and intermittent palpitations. Physical examination revealed an irregularly irregular pulse, a loud P2 and a middiastolic rumble. In addition, the assessment of the jugular venous pressure revealed absent "a" wave and "x" descent. The initial ECG confirmed AF. A transthoracic echocardiogram was performed, and it showed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, a planimetered MVA of 0.7 cm^2, a diastolic pressure half-time of 240 ms, and a PASP of 79 mm Hg. In addition, there was right ventricular dilatation and dysfunction. Which of the following statements about this patient's AF is *false*?

A. The prevalence in MS patients is approximately 40%
B. Age and the severity of MS are the most important determinants for the development of AF
C. LA enlargement is the cause of AF rather than the result of AF
D. AF in MS may also be secondary to rheumatic scarring and histologic changes in the LA
E. Relief of mitral obstruction may or may not prevent AF

50-10. The echocardiogram is the modality of choice in the assessment of MS. In terms of the assessment of the valve area, which of the following echo modalities has the closest agreement with invasive Gorlin-derived MVA?

A. Direct 2D planimetry
B. Direct 3D planimetry
C. Continuity equation method
D. Pressure half-time technique
E. Proximal isovelocity surface area (PISA) method

ANSWERS

50-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 50)* Using echocardiographic screening, the prevalence of RHD ranges from 20 to 30 per 1000 school children (option A is thus not correct).[1,2] This leads to a large pool of rheumatic MS. Forty percent of patients with RHD have isolated MS (option B is thus not correct) but only 60% of these patients report a past history of rheumatic fever (option C is also not correct).[2,3] In developing countries, the disease may progress much more rapidly, leading to symptoms by the age of 20 (juvenile MS), often within five years of the initial attack of RF (option D is thus not correct).[4] All the above statements are false, and therefore, the best option is E.

50-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 50)* The clinical presentation and the echo findings are consistent with stage B, which includes patients with progressive MS (not severe). Stages A, C, and D typically include patient at risk of MS, asymptomatic patients but with severe disease, and symptomatic subjects with severe MS, respectively. Therefore, options A, C, D, and E are not correct. The stages and severity of MS are presented in Table 50-1.[5]

TABLE 50-1 Stages and Severity of Mitral Stenosis

Stage	Definition	Valve Anatomy	Valve Hemodynamics	Hemodynamic Consequences	Symptoms
A	At risk of MS	Mild diastolic valve doming	Normal transmitral flow velocity	None	None
B	Progressive MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA > 1.5 cm^2	1. Increased transmitral flow velocities 2. MVA > 1.5 cm^2 3. Diastolic pressure half-time < 150 ms	1. Mild-to-moderate LA enlargement 2. Normal pulmonary pressure at rest	None
C	Asymptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS)	1. MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) 2. Diastolic pressure half-time ≥ 150 ms (diastolic pressure half-time ≥ 220 ms with very severe MS)	1. Severe LA enlargement 2. Elevated PASP > 30 mm Hg	None
D	Symptomatic severe MS	1. Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets 2. Planimetered MVA ≤ 1.5 cm^2	1. MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) 2. Diastolic pressure half-time ≥ 150 ms (diastolic pressure half-time ≥ 220 ms with very severe MS)	1. Severe LA enlargement 2. Elevated PASP > 30 mm Hg	1. Reduced exercise tolerance 2. Exertional dyspnea

MVA, Mitral valve area.
(Data from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol.* 2014 Jun 10;63(22):2438-2488.)

50-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 50)* The force needed to overcome the increased LA pressure and to drive blood past the stenotic mitral valve is generated by the right ventricle (RV), such that right ventricular pressure and pulmonary pressure become elevated. As MS becomes severe, secondary vasoconstriction in the pulmonary bed causes a further increase in pulmonary artery pressure (option A is thus incorrect), and pulmonary hypertension may become extreme. The exact cause of pulmonary vasoconstriction in MS is unknown (option B is thus false and is the correct answer). It is known that pulmonary hypertension is usually reversed by relief of MS (option C is thus incorrect)[6] and also that it can at times be improved by the administration of phosphodiesterase inhibitors such as sildenafil (option D is thus incorrect)[7] or by nitric oxide inhalation.[8] These data suggest that the nitric oxide pathway is in some way involved in the mechanism of pulmonary vasoconstriction and pulmonary hypertension in MS (option E is thus incorrect). Occasionally, patients have structural changes in the pulmonary bed, leading to a disproportionate pulmonary hypertension that is not completely resolved with relief of MS.

50-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 50)* This patient suffers from rheumatic mitral stenosis, which when presenting below 20 years is termed juvenile MS as in this case (option A is thus incorrect).[4] This condition is uncommon in developed countries, but it may constitute up to a quarter of cases of all rheumatic MS in developing countries (option B is thus incorrect).[4] Unlike in adults, boys are more commonly affected (option C is thus incorrect).[4] Heart failure/pulmonary edema is a frequent finding, while atrial fibrillation is uncommon (option D is thus incorrect). Severe pulmonary hypertension is common. Although MV calcification and LA thrombi are absent (option E is false and is thus the correct answer), the valve morphology is associated with severe subvalvular disease and thickened leaflets.

50-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 50)* Diuretics can usually be used safely to control mild symptoms; thus they should be administered as part of the initial management (option A). Overaggressive use of diuretics can lead to placental hypoperfusion. Therapy is targeted to reduce heart rate and prolong diastolic filling period. This includes restrictions on physical activity (option B) and the use of beta-blockers (those with selective beta-1 activity is preferred). Metoprolol is preferred over atenolol because it has a lower incidence of intrauterine growth retardation (option C).[5] In patients with atrial fibrillation, digoxin can be safely used (option D). Pregnant patients with severe MS (MVA $\leq$1.5 cm^2) and mild symptoms are best managed medically (options A, B, C, and D are thus true), while those who continue to manifest severe symptoms (NYHA class III-IV) despite medical therapy should undergo BMV if the valve is suitable (option E).[5]

50-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 50)* Relief of MS by surgery may be done either by CMV (option A), OMV (option B), or MVR. CMV, via the transatrial or transventricular route, is still practiced successfully in many developing countries. However, the results of BMV are superior to CMV with lower morbidity. When extensive calcification and severe subvalvular disease make BMV/OMV unfeasible (option D), as in this case, MVR is the surgical treatment of choice (option C).

50-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 50)* The clinical presentation and the echo findings are consistent with stage D, which includes symptomatic patients with severe MS (option E). Stages A, B, and C typically include patient at risk of MS, patient with progressive MS, and asymptomatic patients but with severe disease, respectively. Therefore, options A, B, C, and D are not correct. The stages and severity of MS are presented in Table 50-1.[5]

50-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 50)* The indications for MVR are as follows:[5] (1) Severely symptomatic patients (NYHA class III/IV) with severe MS (MVA < 1.5 cm^2) who are not high risk for surgery and who are not candidates for, or have failed, previous BMV (options A and B, respectively) are class 1 indications, not class 2b; (2) severe MS (MVA < 1.5 cm^2) patients undergoing other cardiac surgery (eg, aortic valve surgery, CABG), which are options D and E respectively, are class 2a indications; and (3) mitral valve surgery and LAA excision may be considered for patients with severe MS (MVA $\leq$ 1.5 cm^2, stages C and D) with recurrent embolic events despite adequate anticoagulation (option C); these are class 2b indications, and therefore C is the correct answer.

50-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 50)* Atrial fibrillation is the most common complication of MS, developing in approximately 40% of patients (option A is thus incorrect).[9] Age and the severity of MS are the most important determinants for the development of AF (option B is thus incorrect).[10] AF is related to LA enlargement, the latter often a result rather than the cause of AF (option C is thus false and is therefore the correct answer for this question).[11] Although it is often hoped that relief of MS will result in restoration of sinus rhythm, AF in MS is due not only to increased LA size but also to rheumatic scarring and histologic changes in the LA.[12] Thus relief of mitral obstruction may[13] or may not prevent AF[14] or allow for a return to sinus rhythm (option E is thus incorrect).

50-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 50)* Valve area can be estimated by direct planimetry (either 2D or 3D), by the continuity equation, by the pressure half-time technique (dividing an empirical constant of 220 by the mitral inflow pressure half-time), and by the PISA method. In some cases these measures are concordant, but in others, all measures must be taken into account and clinical judgment used to decide on MS severity. Planimetry by three-dimensional echocardiography (option B) has better reproducibility than two-dimensional echocardiography (option A) and has the closest agreement with invasive Gorlin-derived MVA.[15] Options C, D, and E are not correct for the above-mentioned reasons.

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CHAPTER 51

Tricuspid and Pulmonary Valve Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

51-1. A 15-year-old boy with a prior medical history of childhood murmur presented to the emergency department after a series of presyncopal episodes. The physical examination revealed a systolic ejection click, a loud systolic murmur peaking in late systole as well as a soft P2. Initial ECG and chest radiography showed evidence of right heart chamber enlargement. An echocardiogram was obtained and showed doming and restricted opening of the pulmonary valve. In addition, spectral and color-flow Doppler revealed high-velocity turbulent flow in the main pulmonary artery consistent with pulmonary stenosis. The patient underwent cardiac catheterization, which revealed an RV–to–pulmonary artery peak-to-peak gradient of 37 mm Hg. Which of the following would be the best step in the management of this patient?

A. Medical therapy with follow-up
B. Surgical valvotomy
C. Percutaneous balloon valvotomy
D. Bioprosthetic valve replacement
E. Mechanical valve replacement

51-2. In which of the following settings is surgical correction of tricuspid valve regurgitation (TR) most commonly performed?

A. Isolated procedure for primary TR
B. Isolated procedure for secondary TR
C. Concomitant procedure during mitral valve surgery
D. Concomitant procedure during aortic valve surgery
E. Concomitant procedure during coronary artery bypass grafting

51-3. A 19-year-old man with no known medical history presented to the emergency department complaining of flushing, diarrhea, and dyspnea. The cardiovascular examination revealed a 2/6 decrescendo diastolic murmur at the left upper sternal border, along with an RV heave and an elevated JVP. An echocardiogram demonstrated thickened barely mobile pulmonary valve cusps, with severe pulmonary regurgitation; subcostal imaging incidentally reveals a hepatic mass. Which of the following is the most likely diagnosis?

A. Infective endocarditis
B. Viral gastroenteritis
C. Congenital pulmonary insufficiency
D. Rheumatic heart disease
E. Carcinoid disease

51-4. An asymptomatic 47-year-old man with a remote history of rheumatic fever as a child is found to have a diastolic murmur during a routine physical examination; the murmur is best heard at the left lower sternal border and increases on inspiration. He is referred for an echocardiogram, which shows a thickened, distorted tricuspid valve with moderate tricuspid stenosis and mild-to-moderate tricuspid regurgitation. Which of the following statements regarding rheumatic tricuspid valve disease is *false*?

A. Rheumatic involvement of the tricuspid valve is more common than the aortic valve
B. Tricuspid stenosis and regurgitation are often seen in combination
C. A Kussmaul sign may be appreciated on examination
D. Valve repair with balloon valvotomy or annuloplasty is preferred in cases where the valve is not severely distorted
E. When valve replacement is needed, a bioprosthesis is preferred over a mechanical prosthesis

51-5. A 25-year-old woman with no significant past medical history was referred to the cardiology clinic complaining of a 6-month history of exertional chest discomfort. The physical examination revealed a systolic murmur peaking in late systole

and best heard over the pulmonary area, and a well-preserved but delayed P2. Initial ECG and chest radiography showed evidence of right heart chamber enlargement. An echocardiography was obtained and showed normal pulmonary valve cusps, midsystolic cusp closure, a prominent presystolic a-wave, and a normal main pulmonary artery diameter. In addition, spectral and color-flow Doppler revealed a late-peaking, high-velocity flow with turbulence in the right ventricular outflow tract. Which of the following is the most likely diagnosis?

A. Pulmonary valve stenosis
B. Infundibular pulmonary stenosis
C. Pulmonary regurgitation
D. Idiopathic pulmonary artery dilatation
E. Pulmonary valve endocarditis

51-6. A 19-year-old woman is followed in cardiology clinic for pulmonary valve stenosis, but she has missed her last appointments because she "felt fine." She now notes progressive exertional dyspnea and can no longer play sports with her friends. Four years ago, the physical examination revealed a systolic ejection click, a preserved but delayed P2, and a 2/6 systolic murmur peaking in early-to-mid systole that was best heard over the pulmonary area. Given the clinical suspicion of worsening pulmonary valve stenosis, which of the following physical examination findings would *not* be expected at this time?

A. Murmur has gotten louder
B. Murmur peaks later in systole
C. Systolic ejection click is more prominent in inspiration
D. P2 has gotten softer
E. All of the above

51-7. A 67-year-old man with a remote history of pulmonary emboli complains of increased abdominal girth. A physical examination revealed elevated JVP, systolic RV heave, a 3/6 pansystolic murmur best heard at the left lower sternal border, and ascites. An echo showed right ventricular dilation, tricuspid annular dilation with loss of central coaptation of the tricuspid leaflets, and a vena contracta width of 0.8 cm. The findings were consistent with severe functional tricuspid regurgitation, and loop diuretic therapy is prescribed. Which of the following statements about tricuspid regurgitation (TR) is *false*?

A. If treated medically, this patient will have a mortality of 26% at 5 years
B. Cardiac MRI may be considered for the assessment of RV size and function
C. Aldosterone antagonists may be of additive benefit, especially in the setting of hepatic congestion
D. Pulmonary vasodilators may be helpful
E. None of the above

51-8. A 55-year-old woman with a prior history of myxomatous mitral valve disease, having been lost to follow-up, presented to the emergency department complaining of dyspnea on minimal exertion and leg swelling. Physical examination revealed a 4/6 systolic murmur best heard at the apex, along with an elevated JVP, pitting leg edema, and mild ascites. An echo was obtained showing biventricular dilation and systolic dysfunction, severe mitral regurgitation, and moderate functional tricuspid regurgitation. The tricuspid leaflets were tethered, but the annular diameter was within normal limits. Which of the following would be the best recommendation according to current guidelines?

A. Mitral valve surgery only
B. Mitral valve surgery with tricuspid valve replacement
C. Mitral valve surgery with tricuspid annuloplasty
D. Medical therapy with aggressive diuresis
E. Isolated tricuspid annuloplasty

51-9. The recommendation to offer surgical correction of the mitral and tricuspid valve lesions is discussed with the patient in Question 8. She asks about the success rate of the additional tricuspid valve procedure being recommended. Which of the following best approximates the probability that this patient will be free from significant tricuspid regurgitation 5 to 10 years post-annuloplasty?

A. 20%
B. 40%
C. 60%
D. 85%
E. 95%

51-10. Because tricuspid regurgitation is a dynamic lesion, tricuspid regurgitation may be graded as moderate or severe on preoperative transthoracic echocardiography under normal loading conditions, but it may appear only mild on intraoperative transesophageal echocardiography under general anesthesia. Other than tricuspid regurgitation severity under normal loading conditions, which of the following parameters should be taken into account when deciding about the need for concomitant tricuspid annuloplasty at the time of mitral valve repair?

A. Annular dimensions
B. Leaflet malcoaptation or leaflet-annulus mismatch on direct inspection
C. The presence of pulmonary hypertension
D. The presence of atrial fibrillation
E. All of the above

ANSWERS

51-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 51)* According to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease,[1] balloon valvotomy is recommended in adolescent and young adult patients with pulmonic stenosis who have exertional dyspnea, angina, syncope, or presyncope and an RV-to-pulmonary artery peak-to-peak gradient greater than 30 mm Hg at catheterization (Class I and Level of Evidence: C). Moderately severe and severe pulmonary valve stenosis is currently treated by percutaneous balloon valvotomy (option C). Surgical valvotomy or replacement is rarely needed (options B, D, E). There is no effective medical therapy for this structural condition (option A).

51-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 51)* Surgical correction of tricuspid valve disease is most commonly performed at the time of mitral valve surgery (option C).[2] Significant TR is less frequently observed in patients with aortic valve or ischemic heart disease, and therefore tricuspid valve surgery is less often needed at the time of these surgeries (options D, E). Furthermore, the majority of patients with TR, whether primary or secondary, are effectively managed medically with diuretics, such that tricuspid valve surgery is not often performed as an isolated procedure, unless it is refractory to medical therapy (options A, B).

51-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 51)* The patient is presenting with cutaneous (flushing) and gastrointestinal (diarrhea) symptoms that are typical of the carcinoid syndrome. The pathognomonic echocardiographic appearance of markedly thickened retracted leaflets is more common on the tricuspid valve but is also observed on the pulmonary valve, as in this case. The gold standard treatment for carcinoid heart disease is usually tricuspid valve replacement and pulmonary valve replacement with patch enlargement of the right ventricular outflow tract. Endocarditis does not have this echocardiographic appearance and is not suspected in the absence of fever (option A). Viral gastroenteritis is not associated with these cardiac findings (option B) whereas congenital pulmonary insufficiency is not associated with these noncardiac findings (option C). Rheumatic involvement of the pulmonary valve may manifest as thickening and restriction at the commissural level, and it would typically be associated with the involvement of other valves without the cutaneous and gastrointestinal symptoms (option D).

51-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 51)* Rheumatic involvement of the tricuspid valve is far less common than with the mitral and the aortic valves (option A), reported in between 10% and 20% of patients. Rheumatic tricuspid valve disease is often predominantly functional, but it is occasionally characterized by leaflet involvement with thickened, fibrosed, and shortened leaflets, and commissural fusion. The resulting clinical syndrome is one of mixed stenosis and regurgitation (option B). Inspiratory increase in jugular venous pressure is common and simulates the Kussmaul sign in constrictive pericarditis (option C). However, the jugular venous pulse with rheumatic tricuspid valve stenosis and regurgitation fails to show rapid "y" descent. Treatment of rheumatic tricuspid valve disease consists of balloon valvotomomy for predominant stenosis, valve repair with annuloplasty (option D), or valve replacement with a low-profile bioprosthetic valve for severely distorted valves (option E).

51-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 51)* Although the valve cusps are normal in infundibular stenosis, a characteristic midsystolic cusp closure (caused by dynamic subvalvular obstruction) and prominent presystolic a-wave are often diagnostic clues, along with high-velocity turbulent flow in the right ventricular outflow tract. The pulmonary valve morphology shows doming and restricted opening in the presence of pulmonary valve stenosis, with high-velocity turbulent flow in the main pulmonary artery (option A). The pulmonary artery and branches are dilated in pulmonary hypertension, idiopathic pulmonary artery dilatation, and severe pulmonary regurgitation (options C and D). In cases of pulmonary valve endocarditis, a mobile vegetation may be observed (option E).

51-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 51)* With progressive pulmonary valve stenosis severity, the murmur gets louder, longer, and peaks later in systole (options A and B). The ejection click is often more prominent in expiration (option C). This seemingly paradoxical behavior of the pulmonary ejection click is explained by an inspiratory increase in right ventricular end-diastolic pressure, which opens the valve in late diastole and hence the absence of systolic ejection clicks during the inspiratory phase. The pulmonary component of the second heart sound (P2) becomes softer (option D), and in very severe cases, the murmur spills past the aortic component, and the pulmonary component is inaudible.

51-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 51)* Several large studies have reported on the adverse effects of longstanding tricuspid regurgitation.[3-5] If treated medically, moderate to severe tricuspid regurgitation carries a

mortality of 26% at 5 years (option A). In addition to echocardiography, cardiac MRI can provide complementary information about the severity of tricuspid regurgitation and its impact on RV dilation and dysfunction (option B). The mainstay of medical management for functional tricuspid regurgitation includes loop diuretics and aldosterone antagonists to decrease volume overload in patients with peripheral edema and ascites (option C).[1] Specific pulmonary vasodilators may be helpful to reduce right ventricular afterload in patients with reversible pulmonary hypertension evaluated with cardiac catheterization (option D).

51-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 51)* According to the American College of Cardiology/American Heart Association Guidelines for the Management of Patients with Valvular Heart Disease,[1] tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional tricuspid regurgitation at the time of left-sided valve surgery, with either (1) tricuspid annular dilatation or (2) prior evidence of right heart failure (Class IIa and Level of Evidence: B). This patient has evidence of right heart failure, and therefore should be considered for tricuspid annuloplasty (option C), which would also be a consideration if she had evidence of annular dilatation.[6] Tricuspid valve replacement (option B) is not indicated for the repair of moderate functional regurgitation because it introduces the additional risks of thromboembolic and hemorrhagic complications inherent with mechanical prostheses, or the risk of structural valve degeneration requiring reoperation inherent with bioprostheses.[7] Isolated tricuspid valve surgery (option E) is not appropriate because this patient has severe symptomatic mitral regurgitation that requires correction. Medical therapy is not a curative option for this patient (option D).

51-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 51)* Data from the surgical literature suggest that 85% of patients having a ring annuloplasty for functional tricuspid regurgitation will be free from moderate or severe tricuspid regurgitation from 5 to 10 years after surgery (option D).[8] Risk factors for recurrent moderate or severe tricuspid regurgitation include: higher preoperative regurgitation grade, poor left ventricular function, permanent pacemaker, and repair type other than ring annuloplasty.[9]

51-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 51)* In this context, the final decision should be guided not only by the degree of regurgitation but also by annular enlargement (diameter > 7 cm from the anteroseptal to anteroposterior commissures when measured by direct inspection, or > 40 mm from the 4-chamber view when measured by echo), leaflet malcoaptation, and the presence of atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, or left ventricular dysfunction.

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CHAPTER 52

Prosthetic Heart Valves

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

52-1. A 62-year-old man with a prior history of infective endocarditis and a porcine aortic bioprosthesis that was implanted 12 weeks ago attended the cardiology clinic for a routine visit. At the clinic, a complete evaluation was unremarkable, including anticoagulation adherence, clinical questioning, physical examination, 12-lead ECG, and transthoracic echocardiography for the assessment of ventricular and prosthetic valve function. Which of the following actions would be the most appropriate at this time?

A. Discharge the patient from the clinic
B. Discharge the patient from the clinic with family physician follow-up
C. Discharge the patient from the clinic and advise him to get in touch if symptoms occur
D. Follow the patient for another year, and if he is stable, discharge him with family physician follow-up
E. None of the above

52-2. Having undergone an echocardiogram before and shortly after his aortic valve replacement surgery, the patient described in Question 52-1 would like to know when the next echocardiogram will be scheduled. Which of the following statements about the use of transthoracic echocardiography after the bioprosthetic valve replacement is *false*?

A. Should be performed annually after the 10th postoperative year
B. Should be performed annually after the fifth postoperative year
C. Should be performed annually after the second or third postoperative year in patients who are at higher risk of accelerated valve dysfunction
D. Should be performed sooner if new symptoms occur
E. All of the above

52-3. A 60-year-old man with a past medical history of a mechanical mitral valve replacement presents to the cardiology clinic and would like to have an expert opinion regarding antibiotic prophylaxis before dental procedures. Which of the following would be the best recommendation regarding antibiotic prophylaxis?

A. 2 g of amoxicillin before any dental procedure
B. 2 g of ampicillin before any dental procedure
C. 600 mg of clindamycin before any dental procedure
D. Antibiotic prophylaxis is no longer recommended
E. Antibiotic prophylaxis only if there is manipulation of gingival or periapical tissue, or perforation of oral mucosa

52-4. You receive a phone call from a urologist for a consultation regarding a 55-year-old man with a past medical history of a bioprosthetic aortic valve replacement. The patient is scheduled to undergo a cystoscopy as part of his investigation for bladder cancer. Which of the following would be the best recommendation regarding antibiotic prophylaxis?

A. 2 g of amoxicillin before the urological procedure
B. 2 g of ampicillin before the urological procedure
C. 600 mg of clindamycin before the urological procedure
D. Antibiotic prophylaxis is no longer recommended
E. Cancel the cystoscopy and advise alternate noninvasive diagnostic testing

52-5. A 79-year-old man with a prior history of arterial hypertension, dyslipidemia, and stage IV chronic kidney disease presented to the emergency department complaining of worsening dyspnea and decreasing exercise tolerance. The patient underwent bioprosthetic aortic valve replacement 8 years earlier for aortic stenosis. The physical examination revealed reduced carotid upstroke bilaterally and a 5/6 systolic ejection murmur across the precordium. A transthoracic echocardiogram was obtained and revealed severe prosthetic valve stenosis. Which of the following may potentially explain

the echocardiographic findings?

A. Bioprosthetic valve degeneration
B. Bioprosthetic valve thrombosis
C. Endocarditis with a large burden of vegetation
D. Pannus
E. All of the above

52-6. A 65-year-old woman with a prior history of arterial hypertension, coronary heart disease, and depression is referred for a routine echocardiogram 4 weeks after having undergone an aortic valve replacement with a 21-mm bioprosthesis. The echocardiogram revealed normal left ventricular function with a mean transprosthetic gradient of 68 mm Hg, and a calculated indexed effective orifice area was 0.61 cm^2/m^2. The mobility of prosthetic leaflets was normal, and there were no findings to suggest prosthetic pannus or thrombus. Patient-prosthesis mismatch was suspected. Which of the following may *not* be a clinical consequence of this diagnosis?

A. Decreased cardiac index
B. Reduced functional improvement
C. Higher risk of stroke in the first 30 days
D. Less left ventricular mass regression
E. More adverse events in long-term follow-up

52-7. A 37-year-old obese man with a history of mechanical mitral valve replacement for congenital mitral valve disease presented to the emergency department complaining of dyspnea. Upon further questioning, the patient also reported a prior history of four embolic strokes with no residual neurologic deficit, all of which were related to poor medication adherence. The physical examination revealed 4/6 systolic ejection murmur across the precordium. A transthoracic echocardiography was obtained and revealed prosthetic valve thrombosis. Which of the following is the strongest independent predictor of nonadherence to an anticoagulation regimen?

A. Age less than 55 years
B. Age older than 55 years
C. Living in a rural geographic area
D. Living in an urban geographic area
E. Pregnancy in the first trimester

52-8. A 42-year-old woman has a history of bioprosthetic mitral valve replacement 12 years ago for myxomatous mitral valve disease (bioprosthesis implanted because of childbearing at the time). She comes to the emergency department complaining of a 2-day history of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. The physical examination revealed bilateral crackles and a pansystolic murmur heard across the precordium. An urgent transthoracic echocardiography was obtained, and it revealed diffuse thickening and reduced mobility of the bioprosthesis. Which of the following is the most likely diagnosis and the most common bioprosthetic valve-related complication leading to reoperation?

A. Paravalvular leak
B. Structural valve degeneration
C. Endocarditis
D. Pannus formation
E. Thrombus formation

52-9. The patient described in Question 52-8 asks whether she should have chosen a mechanical prosthesis at the time of her index surgery (and accepted the risks associated with anticoagulation and childbearing). In counseling her, which of the following statements is *true* regarding the expected long-term risk of reoperation after a mitral valve replacement surgery?

A. The risk is higher with aortic valve replacement than with mitral valve replacement
B. The risk is higher with younger patients
C. The risk is higher with mechanical prostheses than with bioprostheses
D. There is a higher short-term risk with mechanical prostheses but no difference in long-term risk
E. The risk is negligible short- and long-term with newer-generation prosthetic valves

52-10. After initial medical management and discussions with the patient and the heart team, the decision was made to offer reoperative valve replacement to the patient described in Question 52-9. Which of the following may be helpful in preparation for the redo procedure?

A. Transesophageal echocardiography
B. Cardiac catheterization
C. Noncontrast chest CT
D. Prior operative reports
E. All of the above

ANSWERS

52-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 52)* At 6 to 12 weeks after surgery, a complete evaluation including clinical history and examination, 12-lead ECG, and transthoracic echocardiography should be performed to assess functional status, blood pressure and rhythm, ventricular function, prosthetic valve function, gradients, and any paravalvular regurgitation, and anticoagulation adherence should be reviewed. Consensus guidelines recommend annual and symptom-triggered follow-up by a cardiologist for life, with the aim of detecting prosthesis dysfunction and the progression of other valvular heart disease. Follow-up solely by a family physician or as needed is not sufficient (options A, B, C, D).

52-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 52)* Transthoracic echocardiography should be performed annually after the fifth year postoperatively in patients with bioprosthetic valves; earlier in young patients who are at higher risk of accelerated valve dysfunction; and in any patient with a prosthetic valve if any new symptoms occur or there is clinical suspicion of complications based on clinical examination.

52-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 52)* The risk of infectious endocarditis is significantly higher in patients with prosthetic heart valves, but there is insufficient evidence available (1) to define the threshold for and type of prophylaxis required to minimize this risk and (2) to define the incremental risk posed to by adverse outcomes related to antibiotic use, including anaphylaxis and antibiotic resistance.[1,2] Current consensus guidelines recommend antibiotic prophylaxis prior to dental procedures that involve manipulation of gingiva or apical tissue, or breach of the oral mucosa.

52-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 52)* Routine antibiotic prophylaxis is not recommended for patients with prosthetic valves who undergo genitourinary procedures, gastroscopy, colonoscopy, bronchoscopy, transesophageal echocardiography, vaginal or caesarian delivery, or skin or soft-tissue procedures, unless the patient has an active infection or is immunocompromised.[1,2]

52-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 52)* The causes of prosthetic valve stenosis include bioprosthetic valve dysfunction, valve thrombosis, endocarditis with large burden of vegetation, and ingrowth of fibrous tissue (pannus).[3]

52-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 52)* Patient-prosthesis mismatch has been associated with decreased cardiac index, reduced functional improvement, less left ventricular mass regression, worse survival, and more adverse events in long-term follow-up. However, there are several confounding variables associated with a smaller indexed effective orifice area and with worse postoperative outcomes, including advanced age, female gender, and obesity; it is unclear to what extent these confounding variables contribute to the worse outcomes observed in patients with patient-prosthesis mismatch.[4] Stroke is not typically associated with patient-prosthesis mismatch because this is an insidious hemodynamic issue.

52-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 52)* The reasons for anticoagulation nonadherence may include comorbidities and associated side effects, patient preference, socioeconomic barriers, and childbearing. Pregnancy in the first trimester is a contraindication to warfarin therapy. In an analysis of Medicaid patients, age less than 55 years was one of the strongest independent predictors of nonadherence to an anticoagulation regimen.[5] This study also identified inadequate housing and care support, mental illness, and substance abuse as significant barriers to patient adherence with anticoagulation.

52-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 52)* Bioprosthetic structural valve degeneration is defined as any change in function of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Structural valve degeneration is the most common valve-related complication in bioprosthetic valves.[6] It occurs more rapidly in younger patients than in older patients, and earlier in the mitral position compared to the aortic position. Paravalvular leak is common but generally mild, and it infrequently leads to reoperation (option A). Endocarditis is not likely in this case due to the absence of constitutional symptoms or oscillatory mass seen on echo (option C). Pannus and thrombus formation are not suggested by the echo findings (options D and E).

52-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 52)* The risk of reoperation to replace a mechanical or bioprosthetic valve is similar over the first few years (option D), but the risk of having to replace a bioprosthesis after 8 to 12 years is higher (option C) as a result of an increasing incidence of structural valve dysfunction, which is the most common indication for reoperation on bioprostheses.[7-12] Structural valve dysfunction occurs more rapidly in younger patients than in older patients (option B), and earlier in the mitral position compared to the aortic position (option A). Although newer-generation valves have enhanced durability, structural valve dysfunction remains a nonnegligible risk (option E).

52-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 52)* Investigation of the patient requiring reoperative valve replacement should include transesophageal echocardiography to assess native and prosthetic valve function, to evaluate the presence and extent of endocarditis, thrombus, and pannus, and to determine cardiac function, including the presence

of pulmonary hypertension and right ventricular dysfunction.[13,14] Cardiac catheterization should be performed to document native coronary artery anatomy, the presence and patency of coronary bypass grafts, and hemodynamics, including pulmonary artery pressures, cardiac output, and transvalvular gradients. Noncontrast chest CT is helpful to plan sternal reentry, which may be complicated by inadvertent division of structures adherent to the sternum, including the right ventricle, pulmonary artery, aorta, innominate vein, and patent bypass grafts. Prior operative reports are useful to confirm the size and type of previous prosthesis, location of bypass grafts, and technical challenges encountered at first surgery, which may affect the conduct of reoperation.

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CHAPTER 53

Antithrombotic Therapy for Valvular Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

53-1. A 62-year-old man with a prior history of idiopathic dilated cardiomyopathy was admitted to the cardiology unit with advanced heart failure and severe functional mitral regurgitation. During his admission, the patient suffered from recurrent pulmonary edema complicated by intractable hemodynamic instability. After discussing the case with the heart team, the patient underwent percutaneous edge-to-edge repair for mitral regurgitation using the MitraClip device. Which of the following antithrombotic regimens would you recommend to reduce this patient's risk of thromboembolic events post-procedure?

A. Warfarin indefinitely
B. Apixaban indefinitely
C. Aspirin for 6 months along with clopidogrel for 30 days
D. Warfarin indefinitely along with aspirin for 6 months
E. No specific antithrombotic therapy is recommended

53-2. A 75-year-old woman with a prior history of rheumatic heart disease and stage 5 chronic kidney disease presented to the emergency department following a fall complicated by a femoral neck fracture. She denied any history of falls prior to this event, and she had been generally very active and well. Her physical examination revealed an irregularly irregular pulse and a metallic click best heard at the apex. After reviewing her old medical notes, you noticed that the patient underwent a successful mechanical mitral valve replacement (MVR) surgery 15 years ago for which she was taking warfarin. The patient was subsequently evaluated by the orthopedic team, and the plan was to proceed with hip arthroplasty surgery. Which of the following antithrombotic regimens would you recommend during the perioperative period?

A. Stop warfarin 2 to 4 days before surgery, start intravenous unfractionated heparin when the INR falls to < 2.0, and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
B. Stop warfarin 2 to 4 days before surgery, start low molecular weight heparin when the INR falls to < 2.0, and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
C. Stop warfarin 2 to 4 days before surgery and restart warfarin 12 to 24 hours after surgery if bleeding risk allows
D. Do *not* stop warfarin (maintain therapeutic INR), and proceed with hip surgery because the patient's risk for thromboembolic events is very high
E. Cancel the hip surgery and manage the patient conservatively

53-3. A 55-year-old man with a prior history of mechanical MVR, hypertension, and dyslipidemia was admitted to the cardiac unit for a NSTEMI in the anterior territory. The patient underwent coronary angiography, and a drug-eluting stent was deployed in the proximal left anterior descending artery. The patient was discharged on triple therapy with warfarin, aspirin, and clopidogrel. Twelve months later, the patient returned to your clinic as part of follow-up and stated that he had been feeling very well since discharge and denied any cardiovascular symptoms or bleeding events. Which of the following antithrombotic regimens would you recommend at this time?

A. Warfarin only
B. Apixaban only
C. Aspirin and clopidogrel
D. Warfarin and clopidogrel
E. Apixaban and aspirin

53-4. You receive a phone call for an urgent consultation regarding a 31-year-old pregnant woman who was recently found to be pregnant. The patient had a mechanical mitral valve prosthesis implanted 5 years ago and was taking warfarin with a therapeutic INR up to this time. Which of the following anticoagulation regimens would *not* be an acceptable option for this patient?

A. Warfarin for the first 36 weeks with a switch to heparin
B. Low molecular weight heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin
C. Intravenous unfractionated heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin
D. Warfarin restricted to the first 6 to 12 weeks, followed by low molecular weight heparin up to 36 weeks, with a switch to heparin
E. Unfractionated or low molecular weight heparin throughout the pregnancy

53-5. After extensive discussion with the patient described in Question 53-4, since she had an older-generation mechanical mitral valve prosthesis and was taking only 4 mg/d of warfarin, the decision was to continue warfarin throughout the pregnancy (up to 36 weeks). The patient, who is now in her second trimester, had been taking warfarin with an INR of 2.8 and a time in the therapeutic range of 80%. You receive a phone call from her perinatologist seeking advice on the best anticoagulation management at this stage. Which of the following recommendations would be appropriate for the management of this patient?

A. Weekly INR with 2.0 to 3.0 target
B. Weekly INR with 2.5 to 3.5 target
C. Add aspirin and weekly INR with 2.0 to 3.0 target
D. Add aspirin and weekly INR with 2.5 to 3.5 target
E. Add aspirin and weekly INR with 3.0 to 4.0 target

53-6. A 64-year-old man with a prior history of a mechanical aortic valve replacement surgery presented to the emergency department complaining of acute dyspnea. The physical examination revealed a BP of 90/55 mm Hg, bilateral pulmonary crackles, and a harsh 5/6 systolic murmur over the aortic area; the aortic click was not audible. Upon reviewing the patient's old chart, he had been noted to have a softer 2/6 systolic murmur and audible aortic click since his valve replacement surgery. A chest x-ray confirmed the presence of florid alveolar edema and showed a well-positioned mechanical aortic valve prosthesis. The patient was intubated and underwent an urgent transesophageal echocardiogram, which revealed a large thrombus on the aortic valve prosthesis, associated with significant outflow obstruction. Which of the following is the most appropriate next step?

A. Emergency surgery
B. Admission to the cardiovascular ICU for stabilization and surgery in 2 to 3 days
C. Intravenous unfractionated heparin with half-dose fibrinolysis
D. Intravenous unfractionated heparin with fibrinolysis in 1 hour if the patient deteriorates
E. Low molecular weight heparin without fibrinolysis

53-7. You receive a phone call from a family physician seeking advice on the best anticoagulation regimen for 64-year-old woman with a prior history of a mechanical MVR 15 years ago. A couple of years ago, aspirin (81 mg) was added to warfarin by the family physician for a suspected diagnosis of stable angin Which of the following antithrombotic regimens would you recommend at this time?

A. Stop aspirin and continue with warfarin alone
B. Continue with the current regimen (warfarin and aspirin)
C. Switch warfarin to apixaban and stop aspirin
D. Switch warfarin to apixaban and continue aspirin
E. Increase the dose of aspirin to 320 mg daily

53-8. A 27-year-old woman at 36 weeks' gestation, with no significant prior medical history, was admitted to the acute antenatal care unit with symptoms suggestive of acute decompensated heart failure. Upon further questioning, the patient stated that she had had a febrile illness a couple of weeks ago and since then had been feeling generally unwell. An echocardiography was obtained and revealed a myxomatous mitral valve with a mobile vegetation complicated by severe mitral regurgitation. The patient was stabilized on medical therapy and underwent an induced delivery. A few weeks after delivery, the patient experienced recurrent heart failure symptoms and underwent MVR with a bioprosthetic valve, in view of her wishes for future pregnancies. Which of the following antithrombotic regimens would you recommend during the first 3 months after MVR?

A. Warfarin with a target INR between 2.0 and 3.0
B. Warfarin with a target INR between 2.5 and 3.5
C. Warfarin with a target INR between 3.0 and 4.0
D. Apixaban alone
E. Clopidogrel and aspirin

53-9. The patient described in Question 53-8 returned to your clinic 3 months after her bioprosthetic MVR as part of the routine follow-up. Which of the following antithrombotic regimens would you recommend at this time?

A. Stop warfarin
B. Continue warfarin

C. Continue warfarin and prescribe low-dose aspirin
D. Stop warfarin and prescribe low-dose aspirin
E. Switch warfarin to apixaban

53-10. An 85-year-old man with a past medical history of coronary artery disease, arterial hypertension, dyslipidemia, type 2 diabetes mellitus, and severe COPD was diagnosed with severe symptomatic aortic valve stenosis following admission to the cardiology ward with heart failure. Based on his predicted risk of operative mortality, the patient was deemed high risk for surgical aortic valve replacement and underwent transcatheter aortic valve replacement (TAVR). Which of the following antithrombotic regimens would you recommend after TAVR?

A. Warfarin for the first 3 months followed by aspirin indefinitely
B. Aspirin only
C. Clopidogrel for the first 6 months along with lifelong low-dose aspirin
D. Clopidogrel for the first 6 months along with lifelong high-dose aspirin
E. Clopidogrel for the first 12 months along with lifelong low-dose aspirin

ANSWERS

53-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 53)* Following percutaneous edge-to-edge repair for mitral regurgitation using the MitraClip device, aspirin (325 mg/d) is recommended for 6 months along with clopidogrel (75 mg/d) for 30 days after the procedure.[1]

53-2. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 53)* For patients with a mechanical mitral valve, bridging anticoagulation with intravenous unfractionated heparin or subcutaneous low molecular weight heparin is recommended to reduce the risk of adverse effects.[2] Warfarin is stopped 2 to 4 days before surgery. When the INR falls to < 2.0, intravenous heparin infusion or weight-adjusted low molecular weight heparin (twice daily) is initiated. This is stopped 4 to 6 hours (for unfractionated heparin) or 12 hours (for low molecular weight heparin) before surgery. Once bleeding risk allows (usually 12 to 24 hours after surgery), warfarin is restarted. The use of low molecular weight heparin is contraindicated in those with severe renal failure, as in this case (option B).

53-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 53)* After 12 months, stable coronary patients may be managed with oral anticoagulants alone. But in the case of mechanical valves, the addition of low-dose aspirin to anticoagulant therapy has been shown to be beneficial in the long term and is recommended. In select cases such as left main stenting, proximal bifurcation stenting, or proximal LAD stenting, clopidogrel 75 mg/d may be preferred over low-dose aspirin for the long-term treatment.

53-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 53)* Pregnancy with a mechanical heart valve constitutes the WHO risk class III (significantly increased risk of maternal mortality or severe morbidity).[3] There is no ideal anticoagulation regimen. Anticoagulation options are (1) VKA (warfarin) throughout pregnancy with a switch to heparin at 36 weeks; (2) unfractionated or low molecular weight heparin restricted to the first 6 to 12 weeks, followed by warfarin up to 36 weeks, with a switch to heparin; and (3) unfractionated or low molecular weight heparin throughout the pregnancy.[2-5] Warfarin is more efficacious than heparin for thromboprophylaxis, but it is associated with an increased risk of embryopathy, particularly between weeks 6 and 12 of gestation.[6] Warfarin therapy throughout pregnancy is recommended for patients with a daily dose requirement of < 5 mg/d and for those who at are at very high risk of thromboembolism (older generation mitral valve prosthesis or those with previous history of thromboembolism).[2]

53-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 53)* Current guidelines recommend frequent monitoring of anticoagulation therapy during pregnancy irrespective of the antithrombotic regimen chosen.[2,3,5] INR should be measured weekly. For mechanical MVR, older-generation AVR, and those with risk factors for thromboembolism, the target INR should be 3 (range 2.5 to 3.5). For patients with a bileaflet aortic valve and no risk factors for thromboembolism, the recommended target INR is 2.5 (range 2 to 3). Low-dose aspirin (75 to 100 mg/d) is recommended for pregnant patients with either mechanical or bioprosthetic valves in the second and third trimesters.

53-6. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 53)* The ACC/AHA valvular heart disease guidelines recommend emergency surgery (class 1 recommendation) for left-sided prosthetic heart vale thrombosis with moderate to severe (NYHA 3-4) symptoms. Emergency surgery is also preferred in patients with a mobile or large thrombus (> 0.8 cm^2). For patients with mild symptoms (NYHA 1 to 2) of recent onset (< 14 d) and small thrombus burden (< 0.8 cm^2), an initial trial with intravenous infusion of unfractionated heparin may be given. If this is unsuccessful, fibrinolytic therapy is recommended.

53-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 53)* A systematic review found that adjunctive therapy with aspirin in addition to oral anticoagulation was associated with a reduction in overall mortality and thromboembolic

events among patients with mechanical heart valves at the cost of increased bleeding.[7] This increased risk of bleeding was not seen among low-dose aspirin trials (aspirin 100 mg/d) (OR: 0.96, 95% CI: 0.60 to 1.55, $P = 0.87$). On the other hand, the effectiveness of low-dose aspirin (100 mg/d) was similar to that of higher-dose aspirin. Accordingly, the addition of low-dose aspirin (< 100 mg) is recommended by the American College of Cardiology and the American Heart Association for all patients with mechanical valves.[2] The newer oral anticoagulants (dabigatran, apixaban, rivaroxaban) are not indicated for atrial fibrillation associated with rheumatic MS, mechanical or bioprosthetic heart valve, or after mitral valve repair.[2,8]

53-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 53)* Thromboembolic risk associated with bioprosthetic valves appears to be greatest in the first 3 months after implantation.[9] The risk is greater after mitral valve surgery. Based on this risk, antithrombotic therapy with a vitamin K antagonist is recommended for the first 3 months after bioprosthetic MVR to achieve an INR of 2.5 (range 2.0 to 3.0).[2,10]

53-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 53)* After 3 months, the tissue valve and the repaired valve can be treated as native valve and anticoagulation discontinued. After the first 3 months, low-dose aspirin (75 to 100 mg/d), should be continued indefinitely for bioprosthetic AVR or MVR and mitral valve repair patients[2] because this is associated with a reduction in thromboembolic events compared with no antithrombotic treatment.[11]

53-10. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 53)* For patients undergoing TAVR, clopidogrel 75 mg daily is recommended for the first 6 months after the procedure, along with lifelong low-dose aspirin (75 to 100 mg daily).[2]

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CHAPTER 54

Management of Mixed Valvular Heart Disease

Jonathan Afilalo

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

54-1. The general rule for treating secondary tricuspid regurgitation (TR) is to optimize therapy for the underlying cause. Which of the following TR outcomes may be observed after correction of underlying mitral or aortic valve disease?

A. Improvement of TR
B. Worsening of TR
C. No change in TR
D. De novo TR
E. All of the above

54-2. Most TR is secondary to overload caused by left-sided heart disease or by lung disease. Which of the following statements about tricuspid intervention during left-sided surgery is *true*?

A. TR surgery reduces postoperative TR but not RV dilatation
B. TR surgery reduces mortality in this setting
C. TR surgery reduces the risk of postoperative conduction abnormalities
D. 10-year survival is similar for mechanical prostheses versus bioprostheses
E. All of the above

54-3. A 62-year-old man with a history of mitral valve replacement (MVR) 2 years ago presents with increasing leg edema and abdominal girth. A holosystolic murmur is heard at the lower sternal border, with large visible "v" waves noted in the jugular venous pulsation. Echocardiography reveals a normally functioning mitral bioprosthesis, but there is severe functional TR, which was preoperatively graded as mild-to-moderate TR. Which of the following factors may contribute to the variable response of the TR after correction of the mitral valve disease?

A. Right ventricular size and function
B. Pulmonary arterial hemodynamics
C. The underlying etiology of the left-sided valve disease
D. Atrial fibrillation
E. All of the above

54-4. A meta-analysis reviewed the fate of moderate-to-severe MR in a large pool of patients having undergone transcatheter aortic valve replacement (TAVR).[16] In what proportion of patients did the MR severity improve post-TAVR?

A. 10%
B. 30%
C. 50%
D. 70%
E. 90%

54-5. A 90-year-old woman with a history of TAVR 12 months ago presents for routine echocardiographic follow-up. She is feeling well, and her functional class has improved from NYHA III pre-TAVR to NYHA I at the present time. The echocardiogram reveals only trace MR, whereas it was graded as "at least moderate" before TAVR. Which of the following factors may contribute to the MR improvement after TAVR?

A. Secondary MR etiology
B. Aortic mean gradient > 40 mm Hg
C. Sinus rhythm
D. None of the above

E. All of the above

54-6. Irrespective of etiology, it is unusual for mixed aortic valve disease to have equal components of aortic stenosis (AS) and regurgitation (AR). Which of the following statements is *true*?

A. In cases of moderate combined AS/AR, the AS pressure gradients should be lower than expected for isolated moderate AS
B. In cases of moderate combined AS/AR, the LV behaves much more as it would in pure AR
C. In cases of moderate combined AS/AR, outcomes resemble those of AR
D. None of the above
E. All of the above

54-7. Which of the following statements about mixed aortic valve disease, particularly moderate combined AS/AR, is *true*?

A. The outcome compares best with that of severe AS
B. The outcome is substantially worse than moderate AS
C. The outcome is substantially worse than moderate AR
D. Aortic valve replacement should be performed at symptom onset
E. All of the above

54-8. A 51-year-old woman with a prior history of diet-controlled type 2 diabetes and COPD was referred by her GP to the cardiology clinic because of a heart murmur. She was very active and reported no cardiovascular symptoms. A physical examination revealed “a mixed murmur” as described by the examiner. A transthoracic echocardiogram revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, and an MVA of 1.1 cm^2. In addition, there was moderate aortic regurgitation, a left ventricular ejection fraction (LVEF) of 65%, and a left ventricular end systolic dimension of 37 mm. Which of the following statements about the combination of MS and AR is *true*?

A. It is seen almost always in the setting of senile degenerative calcific valvular disease
B. It may lead to underestimation of AR severity during physical examination but not during imaging
C. It may lead to underestimation of AR severity during imaging but not during physical examination
D. It may lead to underestimation of AR severity both during physical examination and during imaging.
E. None of the above

54-9. A 53-year-old woman with no prior medical history was referred for cardiology consultation for a 6-month history of dyspnea on exertion. A physical examination revealed a soft systolic murmur best heard at the apex. A transthoracic echocardiogram revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, an MVA of 1.8 cm^2, and a diastolic pressure half time of 130 ms. In addition, there was significant MR, LVEF of 66%, and LVESD of 35 mm. Which of the following is the best next step in the management of this patient?

A. Immediate admission for IV vasodilators
B. Invasive hemodynamics
C. Elective mitral valve repair
D. Elective mitral valve replacement
E. Elective balloon mitral valvotomy (BMV)

54-10. A 50-year-old woman with a prior history of acute rheumatic fever at the age of 11 was referred for cardiology consultation for a 3-month history of dyspnea on minimal exercise. Physical examination revealed a loud first heart sound and a middiastolic rumble. A transthoracic echocardiogram was performed and revealed rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, an MVA of 0.9 cm^2, and a diastolic pressure half time of 230 ms. In addition, there was moderate MR, LVEF of 62%, and LVESD of 39 mm. Which of the following is the best next step in the management of this patient?

A. IV vasodilators
B. IV beta-blockers
C. Invasive hemodynamics
D. MVR
E. BMV

ANSWERS

54-1. **The answer is E.** *(Hurst’s The Heart, 14th Edition, Chap. 54)* Although it has long been hoped that correction of the hemodynamic load associated with underlying mitral or aortic valve disease would improve secondary TR, observed results remain unpredictable, with TR sometimes improving (option A), sometimes worsening (option B), sometimes

remaining unchanged (option C), and sometimes even arising de novo following left-sided valve surgery (option D).[1-6] All of the options are thus possible TR outcomes after correction of underlying mitral or aortic valve disease. Therefore the best answer is option E.

54-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 54)* It seems clear that tricuspid intervention during left-sided surgery reduces postoperative TR and RV dilatation (option A is thus not correct). However, it has been difficult to show that TR surgery reduces mortality (option B is thus not correct).[5,7-14] Although tricuspid repair reduces postoperative heart failure and TR, it has increased the risk of postoperative conduction abnormalities (option C is thus not correct), requiring permanent pacemaker implantation in some but not all reports. In a large meta-analysis, 10-year survival (about 60%) was nearly identical for bioprostheses versus mechanical prostheses, and this is the correct answer (option D).[15]

54-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 54)* The variable response of TR to correction of left-sided valve disease is in part related to the causes and effects of the left-sided valve disease and its correction. Predictors of TR progression after left-sided valve surgery include: advanced age, right ventricular dilation and dysfunction (option A), tricuspid annular dilation, persistent pulmonary hypertension after surgery (option B), rheumatic or ischemic mitral valve disease etiology (option C), and atrial fibrillation (option D). All of the options are correct, and therefore the best answer is option E.

54-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 54)* In high-risk AS patients, the presence of MR must be considered in the decision of SAVR versus TAVR because the MR is not addressed directly at the time of TAVR but can be repaired at the time of SAVR. Thus it would be important to be able to predict the fate of MR following TAVR in making AVR decisions. In a meta-analysis of observational and randomized studies,[16] MR severity improved in 50% of patients over a median follow-up of 180 days after TAVR. Other studies have shown variable results.[17-29] Options A, B, D, and E are therefore not correct.

54-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 54)* Although the outcome of MR following TAVR still remains difficult to predict, Toggweiler and coworkers[24] found that MR was more likely to improve when it was secondary (option A), when there was an aortic mean gradient > 40 mm Hg (option B), and when atrial fibrillation was absent (eg, sinus rhythm, option C). All of the options are correct, and therefore the best answer is option E.

54-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 54)* In cases of moderate combined AS/AR, the LV behaves much more as it would in pure AS rather than in AR (option B is thus not correct), and outcomes resemble those of AS (option C is thus not correct).[30] Aortic regurgitation causes increased systolic flow through the moderately stenotic valve, thereby increasing jet velocity, pressure gradient, and in tandem, pressure overload on the LV (option A is thus not correct). In turn, the patient and his or her LV respond primarily to the pressure overloads. All of the options are incorrect, and therefore the best answer is option D.

54-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 54)* The outcome for moderate combined AS/AR compares best with that of severe AS (option A), and substantially worse than moderate AS or moderate AR (options B and C).[31] Thus the management of mixed AS/AR should follow the guideline strategy for managing patients with pure AS. Aortic valve replacement should be performed at symptom onset (option D) and might be considered for patients with jet velocity exceeding 5 m/s or patients with abnormal exercise tolerance tests. All of the options are correct, and therefore the best answer is option E.

54-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 54)* The combination of MS and AR is seen almost always in the setting of rheumatic heart disease (and not in the setting of senile degenerative calcific valvular disease—option A). It may be confusing, especially by understating the severity of AR.[32] Because MS limits LV inflow, total LV volumes and the manifestations of volume overload for any degree of AR are lessened, potentially causing underestimation of AR severity both during physical examination and during imaging. Options B, C, and E are therefore not correct.

54-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 54)* Mixed mitral stenosis (MS) and mitral regurgitation (MR) usually occurs in the context of rheumatic heart disease. The management dilemma often presented to clinicians is whether the presence of symptoms in a patient with moderate MS and moderate MR is the result of the valve disease, because neither lesion by itself would probably cause symptoms. Further, if the valve is causing symptoms, current guidelines are unclear with respect to management. Thus although symptom onset in VHD is almost always a cause for mechanical intervention, moderate disease is not (options C, D, and E are therefore not correct). In such cases, invasive hemodynamics performed at rest or during exercise often clarifies the issue. If exercise generates filling pressures that are high enough to cause the patient's symptoms, it is highly likely that MS/MR is the cause of both the clinical and the hemodynamic consequences. This patient, with a history of exertional dyspnea and a moderate VHD, is relatively stable and therefore does not required immediate admission for IV vasodilators (option A).

54-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 54)* This patient is symptomatic, and symptom onset in VHD is almost always a cause for mechanical intervention. Therefore, there is no role for IV vasodilators (option A) and beta-blockers (option B) in this case. Although invasive hemodynamics may be considered in cases of discordance between the clinical presentation and the echo data, this would not be the best next step in the management of this symptomatic patient with severe MS (option C). Balloon mitral valvotomy (BMV) is usually contraindicated because it may worsen

MR (option E), and therefore MVR is indicated for relief of symptoms.

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SECTION 9

Congenital Heart Disease

CHAPTER 55

Mendelian Basis of Congenital and Other Cardiovascular Diseases

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

55-1. A 54-year-old man presents to your office to establish care. His family history is notable for hypertrophic cardiomyopathy in his grandfather, paternal uncle, and sister. His father and his two other brothers are unaffected. He has previously undergone genetic testing and is a carrier for a mutation in the *MYH6* gene that is associated with hypertrophic cardiomyopathy. He is otherwise healthy and denies any functional limitation. His electrocardiogram and echocardiogram are essentially normal. Which of the following concepts explains your patient's lack of a phenotype?

A. Low expressivity
B. Variable penetrance
C. Genetic heterogeneity
D. Spontaneous mutation to a wild type allele
E. The allele is recessive

55-2. A 62-year-old woman presents to your office to establish care. Her past medical history is notable for aortic valve replacement with arch repair for a thoracic aortic aneurysm. Her exam is notable for short stature and low-set ears. She was unable to have children despite trying to become pregnant. Karyotype analysis would likely reveal which of the following?

A. Trisomy 21
B. Trisomy 18
C. Trisomy 13
D. Monosomy of the X chromosome
E. A deletion in the long arm of chromosome 22

55-3. A 45-year-old man presents to your office with exertional dyspnea and palpitations. His exam is notable for brown spots around his lips and eyes. His past medical history is notable for resection of a pituitary adenoma. His cardiac MRI is shown in Figure 55-1. This patient likely has a mutation in which of the following genes?

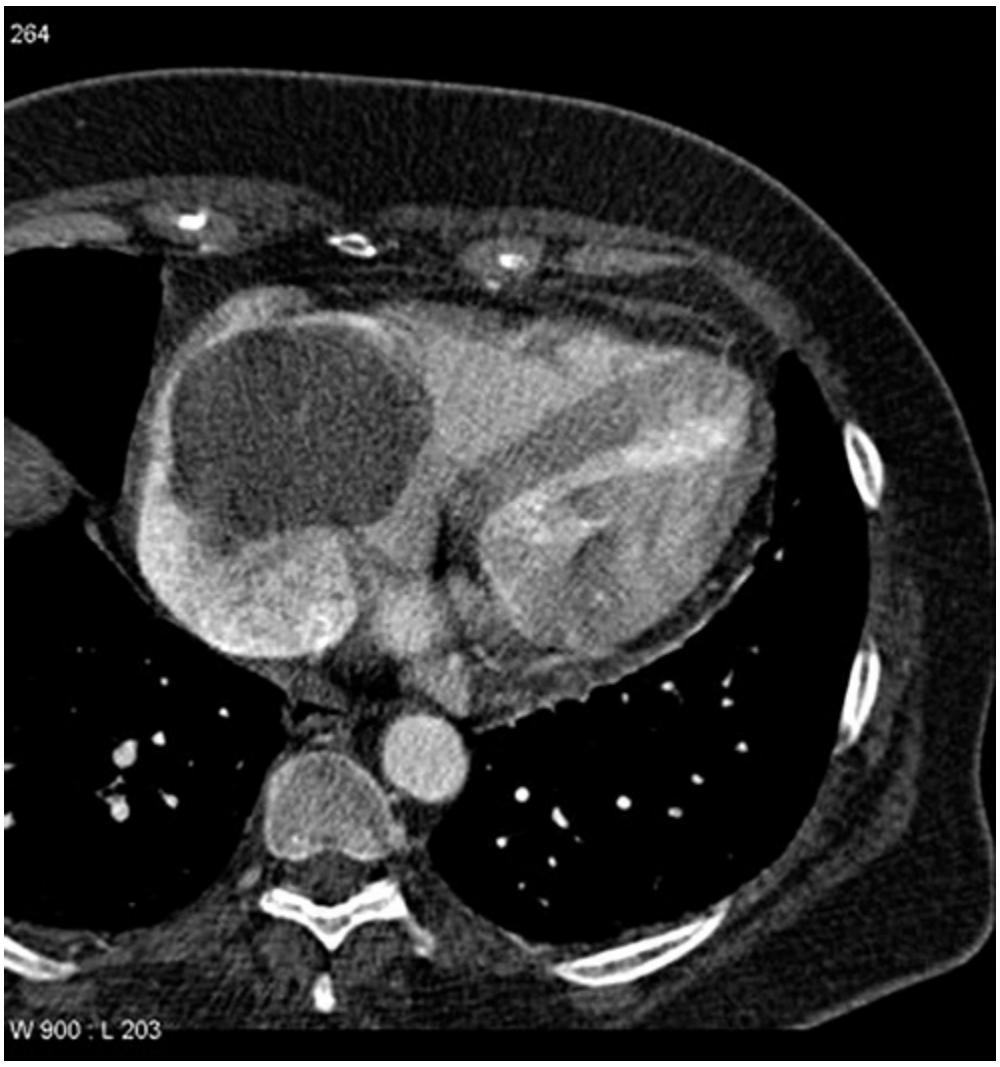

FIGURE 55-1 Cardiac MRI for the patient in Question 55-3. (Case courtesy of A. Prof Frank Gaillard, Radiopaedia.org, rID: 8544)

A. *JAG1*
B. *TBX5*
C. *NKX2.5*
D. *PTPN11*
E. *PRKRA1A*

55-4. You are asked to consult on a 45-year-old man admitted to the neurology service with a stroke. His past medical history includes hypertrophic cardiomyopathy and chronic kidney disease with proteinuria. His family history is notable for multiple family members on his maternal side with enlarged hearts, including his uncle and grandfather. His physical exam suggests normal filling pressures, no inducible obstruction, and right arm weakness. An ECG shows normal sinus rhythm with left ventricular hypertrophy, and an echocardiogram shows hyperdynamic ventricular function with concentric hypertrophy. Which of the following tests would be useful for diagnosing his underlying disorder?

A. Genetic testing for sarcomeric mutations
B. Measurement of α-Gal A levels
C. Genetic testing for *PRKAG2* mutations
D. Genetic testing for *FRDA* mutations
E. A cardiac MRI to evaluate for iron overload

55-5. A 43-year-old woman presents to your clinic for a second opinion regarding her dilated cardiomyopathy. Outside records reveal an ejection fraction of 35% with left ventricular dilation. Clinically, she is well-compensated and on maximally tolerated guideline-directed therapy for her heart failure. Her course has been uncomplicated, and she has no history of arrhythmia. Her past medical history is otherwise unremarkable, but her family history is notable for multiple family members with a similar cardiomyopathy on her maternal side. In which of the following genes is she most likely to have a mutation?

A. *TTN*
B. *LMNA*
C. *CRYAB*
D. *DMD*
E. *SCN5A*

55-6. A 17-year-old basketball player presents to your office for syncopal events. The events have been occurring more often over the past several months. Her exam is unremarkable. Her ECG is notable for an epsilon wave. Cardiac MRI shows a thin right ventricle with prominent fatty infiltration. Which of the following hereditary conditions is she most likely to have?

A. Hypertrophic cardiomyopathy
B. Catecholaminergic polymorphic ventricular tachycardia (CPVT)
C. Arrhythmogenic right ventricular cardiomyopathy (ARVC)

D. Emery–Dreifuss syndrome
E. Brugada syndrome

55-7. A 25-year-old man from Thailand presents to your office for evaluation of recurrent syncopal episodes. The episodes have no prodrome. He has a family history of these episodes, with numerous family members on his paternal side having suffered sudden death, either as infants or as young adults. His ECG is shown in Figure 55-2. A physical examination is unremarkable. In which of the following genes does he most likely have a mutation?

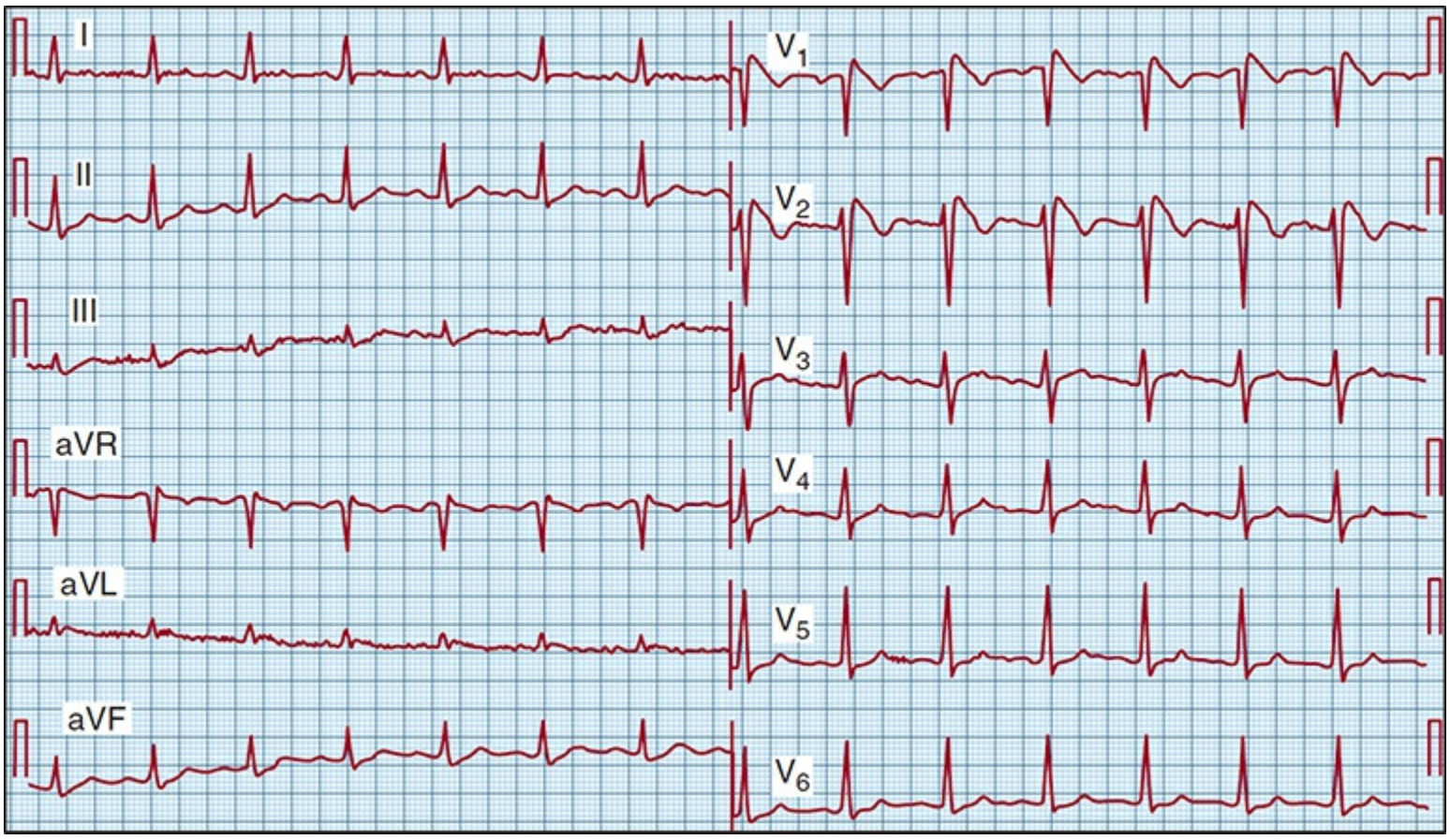

FIGURE 55-2 ECG for patient in Question 55-7.

A. *KCNQ1*
B. *KCNH2*
C. *KCNJ2*
D. *DSP*
E. *SCN5A*

55-8. A 23-year-old woman is referred for evaluation after an abnormal lipid check at an employee health screening fair. Family history is notable for premature coronary artery disease on both sides of her family. She says that her family is known to have a mutation in a gene that affects cholesterol, but she cannot remember the name of the gene. Which of the following mutations is she *unlikely* to have?

A. Loss of function mutations in *LDLR*
B. A mutation of *APOB* that leads to a decreased affinity of APOB for the LDL receptor
C. A mutation of *PSCK9* that causes increased clearance of the LDL receptor
D. A mutation in the *LDLRAP1* that decreases LDL clearance
E. A mutation in *ABCA1* that promotes free cholesterol transport to the extracellular space

55-9. Mutations to which of the following genes are *not* associated with primary pulmonary hypertension (PPH)?

A. *BMPR2*
B. *ACVRL1*
C. *KCNA5*
D. *FBN1*
E. *KCNK3*

55-10. A 35-year-old man is referred to you for management of a thoracic aortic aneurysm. He has a family history of aortic aneurysms and is positive for a genetic mutation in the *FBN1* gene. Which of the following is *not* likely to be observed in this patient?

A. Dislocated lens
B. Aortic regurgitation
C. Arachnodactyly
D. Bifid uvula
E. Mitral regurgitation

ANSWERS

55-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient carries a disease allele but does not have signs or symptoms of the disease, suggesting that the allele is not fully penetrant (option B). Expressivity refers to variable degrees of disease severity in carriers of the disease allele, but all carriers exhibit some signs of the disease (option A). Genetic heterogeneity refers to different disease alleles at different loci that can result in the same phenotypic disease (option C). For instance, multiple mutations in different genes can result in hypertrophic cardiomyopathy. The pattern of inheritance here is consistent with an autosomal dominant allele (option E). Like your patient, his father is likely to also carry the disease allele but not have phenotypic disease. This patient tested positive for the disease allele, so spontaneous mutation to a wild type allele is unlikely (option D).

55-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient has Turner syndrome, which is associated with monosomy of the X chromosome (option D). Patients with Turner syndrome can have a bicuspid aortic valve, often associated with aortic aneurysms.[1] Trisomy 21 is associated with Down syndrome (option A). Trisomy 18 is associated with Edwards syndrome (option B). Trisomy 13 is associated with Patau syndrome (option C). A deletion in the long arm of chromosome 22 is associated with DiGeorge syndrome (option E).

55-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient has Carney complex, manifested by the atrial myxoma shown in the cardiac MRI, lentigines, and endocrine tumors. The Carney complex is associated with mutations in *PRKRA1A* (option E). Mutations in *JAG1* are associated with Alagille syndrome (option A). Mutations in *PTPN11* are associated with Noonan syndrome (option D). Mutations of the cardiac transcription factors *NKX2.5* and *TBX5* are associated with VSDs and Holt–Oram syndrome, respectively (options B and C).

55-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient likely has Fabry's disease. Fabry's disease is an X-linked disorder (note that only males on his maternal side are affected) that involves the heart and kidneys. The diagnosis is established by measuring α-Gal A levels and activity in leukocytes (option B). Fabry's disease is associated with transient ischemic attacks and stroke. Fabry's disease is an example of one of the many disorders that can cause hypertrophic cardiomyopathy, such as glycogen storage diseases with *PRKAG2* mutations and Friedrich's ataxia with mutations in the *FRDA* locus (options C and D). Iron overload is seen in hemochromatosis, but this usually manifests as a dilated cardiomyopathy (option E). Sarcomeric gene mutations are associated with hypertrophic cardiomyopathy (option A).

55-5. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient has an isolated hereditary dilated cardiomyopathy. Up to 25% of these cardiomyopathies are associated with a mutation in the sarcomeric gene *TTN* (option A).[2] Cardiomyopathies involving sarcomeric genes tend to be isolated cardiomyopathies without other organ systems being involved. Mutations in *DMD* (option D) and *CRYAB* (option C), by contrast, are also associated with skeletal myopathies. Hereditary cardiomyopathies due to mutation in *LMNA* (option B) and *SCN5A* (option E) tend to be associated with arrhythmias.

55-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient most likely has ARVC with involvement of the right ventricle and fatty dysplasia of the right ventricle (option C). Hypertrophic cardiomyopathy would be noted by a thickened ventricle by cardiac MRI (option A). CPVT is marked by arrhythmias without structural changes to the right ventricle (option B). Emery-Dreifuss is due to a mutation in the *LMNA* gene that results in cardiac arrhythmia and depressed left ventricular function (option D). Brugada syndrome results in sudden death and cardiomyopathy (option E).

55-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 55)* This patient likely has Brugada syndrome. His ECG has a typical pattern with ST elevations in the right precordial leads. *KCNQ1*, *KCNH2*, *KCNJ2* are all related to long-QT syndromes (options A to C). Mutations in desmoplakin (*DSP*) are related to ARVC (option D). Mutations in *SCN5A* can cause Brugada syndrome, LQT3, and other conduction defects (option E).

55-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 55)* Monogenic syndromes that can lead to premature coronary atherosclerosis include familial hypercholesterolemia, fish eye disease, and Tangier disease. Mutations of the *LDLR*, *APOB*, *PSCK9*, and *LDLRAP1* all can result in familial hypercholesterolemia (options A through D). Mutations of *ABCA1* can cause Tangier disease, by reducing the efflux of free cholesterol to the extracellular space (option E).

55-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 55)* Primary pulmonary hypertension is a familial disease with an autosomal dominant mode of inheritance in 5% to 10% of the cases. PPH is a genetically heterogenous disease. Mutations in bone morphogenic protein receptor type II (*BMPR2*), mapped to chromosome 2q31–33, are responsible for approximately 50% of the familial PPH and 10% to 15% of the sporadic cases (option A).[3,4] Mutations in *ACVRL1*, which codes for a type I receptor of the TGF-β family, cause an autosomal-dominant vascular disorder characterized by pulmonary hypertension, hereditary hemorrhagic telangiectasia (HHT), and visceral arteriovenous malformations (option B).[5] Likewise, mutations in *SMAD9*, *ENG* encoding endoglin, *CAV1* encoding caveolin 1, *KCNA5* and *KCNK3*, both encoding potassium channels, and *EIF2AK4*, coding for eukaryotic translation initiation factor 2 alpha kinase 4, are

causes of PPH (options C and E).[6-8] Mutations in *FBN1* are associated with Marfan syndrome (option D).

55-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 55)* Marfan syndrome is associated with cardiovascular abnormalities, including aortic aneurysm and dissection, aortic regurgitation, and mitral regurgitation (options B and E). In addition to cardiovascular abnormalities, Marfanoid habitus (increased height, disproportionately long limbs and digits), lens dislocation or subluxation, arachnodactyly, thoracic abnormalities, and increased joint laxity are common clinical features (options A and C). Bifid uvula is a classic feature of Loeys–Dietz syndrome (option D).[9]

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CHAPTER 56

Congenital Heart Disease in Adolescents and Adults

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

56-1. A 56-year-old man with a nonrestrictive VSD develops worsening exercise intolerance, pulmonary hypertension, and cyanosis. Which of the following is *not true* of the Eisenmenger syndrome?

A. Survival in patients with Eisenmenger physiology is reduced compared to healthy control subjects
B. Patients with Eisenmenger physiology are susceptible to *in situ* pulmonary arterial thrombosis
C. The risk for hyperviscosity is low, with a hemoglobin < 20 g/dL
D. A pulmonary vasodilator may be indicated
E. Closure of the VSD is indicated

56-2. Which of the following patients *does not* require prophylactic antibiotics prior to bacteremic procedures, such as dental surgery?

A. A 54-year-old man with a mechanical mitral valve prosthesis
B. A 43-year-old woman with repaired patent ductus arteriosus
C. A 43-year-old woman with Eisenmenger complex
D. A 32-year-old man with tricuspid atresia treated with a Fontan conduit
E. A 31-year-old man with a history of infective endocarditis.

56-3. A 31-year-old woman with a history of mechanical mitral valve replacement presents to your office for pregnancy counseling. She has excellent functional capacity. Echocardiography reveals normal ventricular function and a well-functioning mechanical mitral valve. Her medications are notable only for warfarin 3 mg daily. Her INR has been stable on this dose for the past several years. Which of the following would be appropriate advice?

A. If she were to become pregnant, termination of the pregnancy would be recommended
B. She could continue with warfarin during the second and third trimesters of pregnancy
C. She should undergo caesarean section
D. She would have an increased risk for miscarriage
E. None of the above

56-4. A 24-year-old woman presents to your office to establish care. She has a past medical history notable for atrial septal defect (ASD) but does *not* bring prior records. She denies any history of valvular disease. Her ECG shows RSR' and a rightward axis. She is physically fit and exercises regularly without limitation. She wants to know about her prognosis. Which of the following would you tell her?

A. Pregnancy is contraindicated at this stage.
B. She most likely has a primum defect
C. Antimicrobial prophylaxis against endocarditis is recommended with dental procedures
D. She is potentially at risk for right ventricular (RV) failure, pulmonary hypertension, and tricuspid regurgitation over time
E. Systemic anticoagulation is indicated to prevent paradoxical emboli

56-5. A 56-year-old man presents to your office for hypertension. On exam, you note a very loud holosystolic murmur at the lower sternal border. He exercises regularly without limitation. Echocardiography reveals a small restrictive perimembranous VSD and suggests normal pulmonary pressures. Which of the following is the next best step in management?

A. Prophylactic closure
B. Recommendation for antimicrobial prophylaxis against endocarditis with invasive procedures
C. Continued observation
D. A and B

E. None of the above

56-6. A 48-year-old man presents to your office to establish care. He has a history of tetralogy of Fallot repaired with anterior ventriculotomy followed by VSD repair and a pericardial transannular patch. Over his lifetime, which of the following is this patient *not* at risk for?

A. Ventricular arrhythmias
B. Progressive pulmonary regurgitation
C. Eisenmenger physiology
D. A and B
E. B and C

56-7. A 25-year-old with pulmonic stenosis presents to your clinic. She has excellent exercise capacity and is otherwise healthy. Routine echocardiography confirms pulmonic stenosis with dysplastic leaflets and no evidence for infundibular stenosis. The peak gradient across the valve is 45 mm Hg, and the mean gradient is 35 mm Hg. Which of the following would be the next best steps in her management?

A. Continued surveillance
B. Recommendations for endocarditis prophylaxis with bacteremic procedures
C. Percutaneous balloon valvuloplasty
D. Exercise stress testing
E. C and D

56-8. A 42-year-old man presents for evaluation of shortness of breath and chest pain. Physical examination is notable for a harsh late peaking crescendo-decrescendo murmur at the upper sternal border that obscures S2. There is also an early diastolic decrescendo murmur at the mid-right sternal border. An echocardiogram reveals severe aortic stenosis, moderate aortic regurgitation, and a bicuspid aortic valve. Which of the following is also associated with the presence of a bicuspid aortic valve?

A. Perimembranous VSD
B. Parachute mitral valve
C. Dilated ascending aorta
D. Mitral stenosis
E. None of the above

56-9. A 25-year-old man presents for evaluation of hypertension. A physical examination reveals a systolic blood pressure of the right arm of 180 mm Hg and a left lower leg systolic pressure of 150 mm Hg. Which of the following is *not true* of this patient's likely condition?

A. He is at increased risk for intracranial aneurysms
B. Correction of his lesion will cure his hypertension
C. Even with treatment, he would be at risk for atherosclerotic heart disease, heart failure, and stroke
D. He is at increased risk to have a bicuspid aortic valve
E. None of the above

56-10. A 43-year-old woman presents to establish care. She has a history of isolated congenitally corrected transposition of the great arteries (TGA). Which of the following complications is she at increased risk for?

A. Atrioventricular (AV) conduction disturbances
B. Dysfunction of the systemic ventricle
C. Aortic stenosis
D. Aortic dissection
E. A and B

ANSWERS

56-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 56)* This patient has the Eisenmenger complex (a reversed shunt in the presence of a nonrestrictive VSD). Survival in patients with Eisenmenger syndrome is reduced by approximately 20 years compared with healthy control subjects (option A).[1,2] Shunt correction is contraindicated once shunt reversal occurs (option E). Cyanosis is associated with multiple complications, including *in situ* pulmonary arterial thrombosis, hyperviscosity (rarely with a hemoglobin < 20 g/dL), pulmonary arterial atherosclerosis, increased susceptibility to gout, and a heightened risk for infective endocarditis (options B and C).[3-5] Promising advances have occurred over the past decade in the treatment of patients with pulmonary hypertension with pulmonary vasodilators. In the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) trial, patients with Eisenmenger

syndrome who were treated with Bosentan had a significant decrease in pulmonary vascular resistance and systemic vascular resistance, and a significant increase in 6-minute walk distance (option D).[6,7]

56-2. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Certain subgroups are considered at higher risk for infective endocarditis. Guidelines from the European Society of Cardiology and the AHA/ACC on the prevention of infective endocarditis place patients with prosthetic valves, cyanosis, and systemic or pulmonary artery conduits, as well as patients with previous endocarditis, into a high-risk subgroup (options A, C, D, and E).[8,9] Most other congenital cardiac conditions are in a moderate-risk category, except for patients who have undergone surgical or transcatheter repair of ASD, VSD, or PDA (without residua beyond 6 months), who are considered low risk provided there are no sequelae (eg, aortic valve prolapse, aortic regurgitation) (option B).

56-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Pregnancy results in considerable hemodynamic stress on the heart, and delivery is associated with large fluid shifts. Patients with left ventricular dysfunction, stenotic lesions, cyanotic heart disease, and aortic disease tend to have the highest risk for complications during pregnancy (options A and D). For most patients with cardiovascular disease, vaginal delivery is preferred because it results in less blood loss than caesarean section (option C). Pregnant women are inherently hypercoagulable, and their risk of valve thrombosis is increased, thus necessitating appropriate anticoagulation. Oral warfarin accomplishes this task well and is associated with a lower maternal risk, but it is teratogenic to fetuses, especially in the first trimester; the risk of teratogenicity is low after the eighth week of gestation.[10] Therefore, warfarin is recommended by the ACC/AHA guidelines in the second and third trimesters of pregnancy (option B).[11]

56-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Based on the presentation, this patient likely has a secundum ASD. The ECG usually demonstrates a characteristic RSR' complex in the anterior precordial leads with a rightward QRS axis in patients with secundum-type defects and left-axis deviation in those with primum-type ASD (option B). ASDs tend to be well tolerated initially, as in this patient. Thus, pregnancy is not contraindicated (option A). Progressive symptoms of dyspnea on exertion and palpitations often occur in adulthood and are caused by increasing right-sided chamber enlargement, pulmonary hypertension, RV failure, tricuspid regurgitation, and atrial arrhythmias (option D). Patients with large ASDs causing left-to-right shunts develop RV volume overload, which is relatively well tolerated for the first two decades. The risk of infective endocarditis is low unless the patient has coexistent valvular disease (eg, cleft mitral valve) (option C). Paradoxical emboli can occur but are rare, and preventive anticoagulation is not indicated (option E).

56-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 56)* This patient has a small restrictive VSD. For small restrictive defects or defects that have closed partially with time, the pulmonary vascular resistance is not significantly elevated, and the left-to-right shunt magnitude is mild (Qp:Qs ratio ≤ 1.5:1). The intensity of the precordial holosystolic murmur is inversely related to the size of the defect; therefore, a disturbingly loud and harsh precordial holosystolic murmur in a patient with VSD should be viewed as a reassuring sign, not a cause for alarm. Although antibiotics for endocarditis prophylaxis are no longer recommended by the ACC/AHA guidelines, patients are at increased risk for endocarditis.[11] Small restrictive defects of the muscular or membranous septum may be watched conservatively without the need for operative intervention (option C).

56-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 56)* The four characteristic findings in TOF are (1) a malaligned VSD, (2) RV outflow or pulmonary valve or artery stenosis or atresia, (3) a dextraposed over-riding aorta, and (4) RV hypertrophy. Surgical treatment of tetralogy of Fallot is one of the major advances in cardiac surgery. The first generation of intracardiac repairs was performed via a large anterior ventriculotomy and often included incision of the pulmonary valve annulus and placement of a transannular patch made of pericardium or synthetic material. This technique successfully relieved the outflow tract obstruction but resulted in pulmonary valvular incompetence and severe pulmonary regurgitation. Over time, this can lead to RV failure (option B). Ventricular arrhythmias are more likely to occur following such repairs, and they often arise from the region of the transannular patch or ventriculotomy suture lines (option A). This patient has been repaired and no longer has shunting, so he is not at risk for Eisenmenger physiology (option C).

56-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Mild and moderate degrees of pulmonary stenosis (peak gradient ≤ 50 mm Hg) are well tolerated and generally do not require surgical or percutaneous intervention (option A).[12] Asymptomatic patients with severe pulmonary stenosis and a peak gradient ≥ 60 mm Hg or a mean gradient ≥ 40 should undergo intervention to reduce the severity of the stenosis. Symptomatic patients with a peak gradient ≥ 50 mm Hg or a mean gradient ≥ 30 mm Hg should undergo intervention (option C).[13] Infective endocarditis of the pulmonary valve is rare; endocarditis prophylaxis during bacteremic procedures is not recommended (option B).[13]

56-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Options A, B, and D are associated with subvalvular aortic stenosis and the Shone complex. Patients with bicuspid aortic valves often have abnormalities of the aorta similar to patients with Marfan syndrome. The ascending aorta in patients with BAV gradually dilates at a mean of 0.9 mm/year (option C).[14] The risk of dissection in patients with BAV is estimated to be five to nine times that of the general population and is highest in patients with concomitant coarctation.[15,16] Patients with a BAV and ≥ 55-mm aortic root diameter should be referred for surgical aortic root wrapping or replacement.[11]

56-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 56)* This patient is likely to have coarctation of the aorta. A normal patient should have a 5- to 10-mm Hg increase in systolic blood pressure in the lower extremities compared with the upper extremities. Absence of this increase or the presence of a decrease in the lower extremities should arouse suspicion of coarctation. A BAV is present in about half of cases (option D). Intracranial aneurysms, often in the circle of Willis, have been detected in up to 10% of patients (option A).[17] Patients with successfully treated coarctation often continue to have systemic arterial hypertension despite the absence of significant residual coarctation.[18,19] Patients who undergo repair in childhood demonstrate very good long-term survival up to 60 years.[20] Late repair (> 14 years of age) is associated with higher rates of hypertension and decreased survival (option B).[21] Patients with hypertension after late repair are at an increased risk of developing heart failure, atherosclerosis, stroke, and progressive aortic disease (option C).

56-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 56)* Congenitally corrected TGA is characterized by AV and ventriculoarterial discordance. From a circulatory oxygenation standpoint, these patients are "congenitally corrected," essentially "two wrongs make a right," and the pulmonary and systemic circulations run in series, not in parallel, as with dextro-TGA. There is ventricular inversion, and the respective AV valves follow the ventricles. Therefore, the systemic right ventricle (RV) is transposed to the left, and the tricuspid valve goes with it. The left atrium empties into the RV, which then pumps to the leftward and usually anterior aorta. Because the RV is the systemic ventricle, the RV is susceptible to failure over time (option B). The left ventricle (LV) and mitral valve are dextraposed, and the pulmonary artery emerges posteriorly from the LV. Fewer than 10% of patients are free of associated abnormalities, which include VSD (membranous or muscular) in up to 80%, pulmonic stenosis (valvular or subvalvular) in up to 70%, and tricuspid valve abnormalities (usually Ebstein anomaly) in 33% (options C and D).[22] Furthermore, these patients have an increased incidence of AV conduction problems and complete heart block with age (option A).[23]

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SECTION 10

Myocardial, Pericardial, and Endocardial Diseases

CHAPTER 57

Classification of Cardiomyopathies

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

57-1. Which of the following is *true* about the American Heart Association (AHA) classification of cardiomyopathies?

A. Primary cardiomyopathies are limited to cardiomyopathies with systolic dysfunction
B. Secondary cardiomyopathies are cardiomyopathies that are associated with a systemic, multiorgan disorder
C. A patient with hypertrophic cardiomyopathy (HCM) that results in a dilated phenotype would be considered to have a mixed cardiomyopathy
D. Ion channel disorders are *not* considered to be primary cardiomyopathies
E. None of the above

57-2. Which of the following is *not true* of the 2008 European Society of Cardiology (ESC) classification of cardiomyopathy?

A. Ion channelopathies are *not* included in the classification of cardiomyopathies
B. Familial cardiomyopathies are defined by the occurrence of a phenotype in more than one family member that could be caused by the same genetic mutation
C. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is considered a distinct cardiomyopathy, different from dilated cardiomyopathy, HCM, and restrictive cardiomyopathy
D. The genetic basis of cardiomyopathy is emphasized over morphofunctional features in the classification
E. None of the above are true

57-3. Which of the following is *true* regarding the 2013 World Heart Foundation classification?

A. The five attributes to determine classification include morphofunctional phenotype, organ system involvement, genetic pattern of inheritance, etiology, and stage
B. The classification system allows for specific genotypes to be annotated
C. Familial cardiomyopathy should be diagnosed when two or more family members are affected
D. Assessment of functional status incorporates the AHA staging system as well as the New York Heart Association (NYHA) classification system
E. All of the above are true

57-4. A 47-year-old has HCM that progressed from the hypertrophic phenotype to the dilated phenotype. Under the MOGES classification, his M phenotype would be:

A. M_H
B. M_D
C. M_{H+D}
D. M_R
E. None of the above

57-5. The patient in Question 57-4 has an 8-year-old daughter. Genetic testing confirms she is also a carrier for the same sarcomeric mutation. A screening echocardiogram shows no structural abnormalities, and she is otherwise healthy. Which of the following is the best way to describe her morphofunctional description under the MOGES system?

A. MOGES is *not* applicable since she does not have structural abnormalities
B. M_H
C. $M_{E[H]}$
D. $M_{0[H]}$
E. None of the above

57-6. A 34-year-old man presents with 2 weeks of new-onset shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, and pedal edem. He is short of breath with moderate exertion. Prior to experiencing these symptoms, he had an upper respiratory tract illness. He has no family history for cardiomyopathy. Cardiac MRI shows a dilated left ventricle with an ejection fraction of 25%, and a scar pattern consistent with a viral myocarditis. Which of the following is the correct MOGES classification for this patient?

A. $M_D\ O_{H+L}\ G_N\ E_V\ S_{C\text{-}II}$
B. $M_D\ O_H\ G_N\ E_V\ S_{C\text{-}II}$
C. $M_E\ O_{H+L}\ G_N\ E_V\ S_{C\text{-}II}$
D. $M_E\ O_{H+L}\ G_N\ E_V\ S_{B\text{-}II}$
E. $M_E\ O_H\ G_o\ E_V\ S_{B\text{-}II}$

57-7. A 32-year-old woman transfers her care to you. She feels well and denies any cardiopulmonary limitation. She had been previously seen by a cardiologist and was assigned a MOGES classification of $M_0\ O_0\ G_{AD}\ E_{G\text{-}}\textit{LMNA}\ S_{A\text{-}I}$. Which of the following is this patient at risk for?

A. Arrhythmias
B. Stroke
C. Pulmonary hypertension
D. Respiratory failure
E. None of the above

57-8. A 64-year-old man has a MOGES classification of $M_D\ O_0\ G_{AD}\ E_{G\text{-}N\text{-}}\ S_{D\text{-}IV}$. Which of the following is *true* about this patient?

A. He has HCM
B. He has asymptomatic left ventricular dysfunction
C. He has a suspected genetic etiology, but the genetic defect is not known
D. He has a familial etiology that follows an autosomal recessive pattern of inheritance
E. None of the above

57-9. What is the significance of the color code of MOGES classification?

A. Asymptomatic carriers of a mutation
B. Known significance of a mutation
C. Morphofunctional phenotype
D. Functional status
E. None of the above

57-10. A 37-year-old man has a MOGES classification of $M_D\ O_{Lu}\ G_N\ E_{AI\text{-}Sarcoid}\ S_{B\text{-}I}$. Which of the following is *true* about this patient?

A. He has asymptomatic left ventricular dysfunction
B. He has a cardiomyopathy secondary to sarcoidosis
C. He has only cardiac involvement
D. A and B
E. None of the above

ANSWERS

57-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 57)* The AHA classification emphasizes the mechanism for cardiomyopathy, not the morphology.[1] Under the AHA classification, cardiomyopathies are not limited to disorders of systolic dysfunction (option A). Cardiomyopathies were divided into two major groups based on predominant organ involvement. The *primary* cardiomyopathies were those solely or predominantly confined to heart muscle. The primary cardiomyopathies were further categorized into genetic, acquired, and mixed varieties and represented the novelty of the AHA classification (Figure 57-1). Ion channel disorders are included as genetic cardiomyopathies (Figure 57-1) (option D). Thus, a patient with HCM would have a primary genetic cardiomyopathy (option C). The *secondary* cardiomyopathies showed pathologic myocardial involvement as part of systemic (multiorgan) disorders (option B).

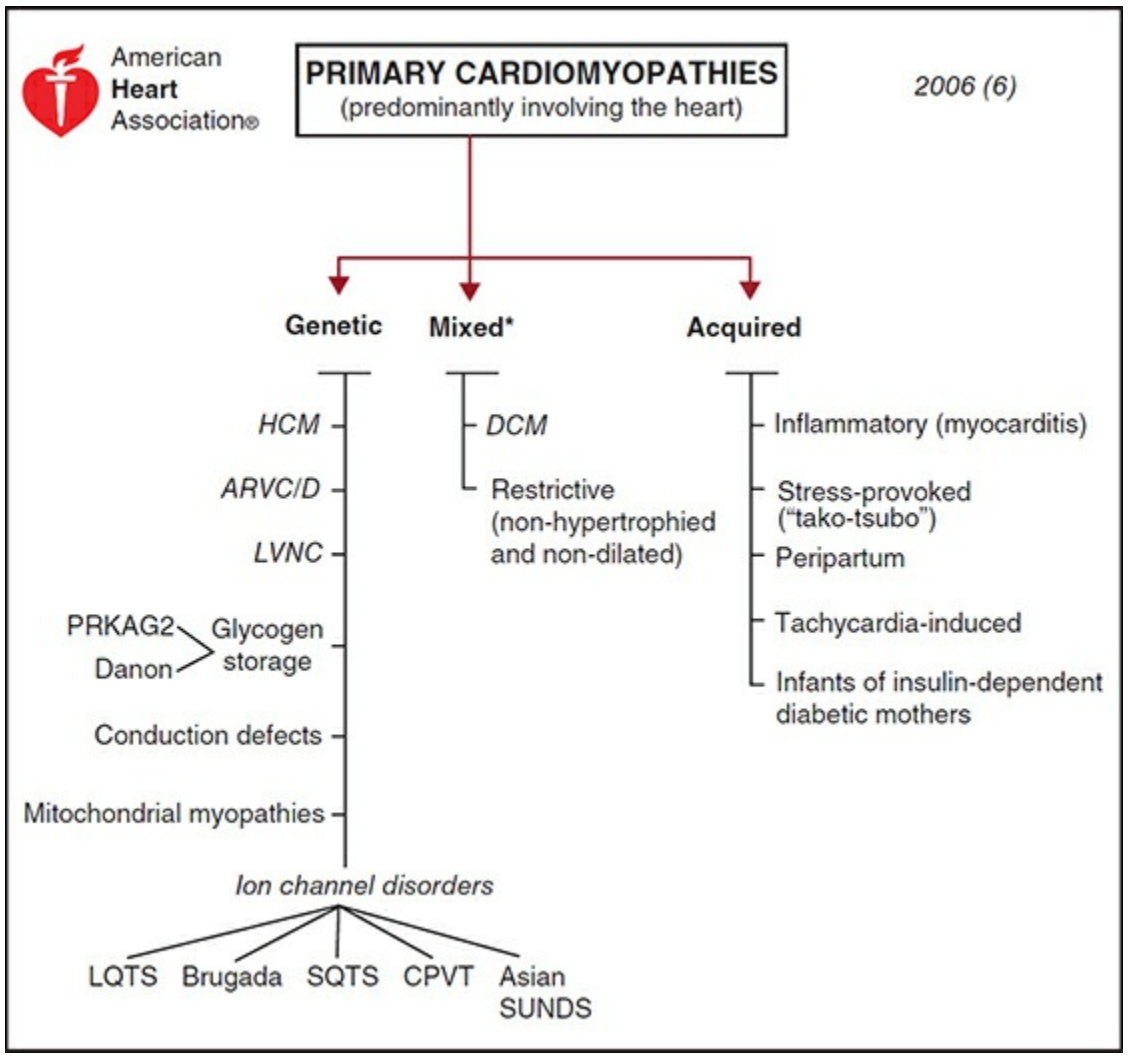

FIGURE 57-1 AHA classification of cardiomyopathy. (Reproduced with permission from Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention, *Circulation*. 2006 Apr 11;113(14):1807-1816.)

57-2. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 57)*. The 2008 ESC classification of cardiomyopathy emphasizes morphofunctional features over the genetic features and thus differs from the AHA classification (Figure 57-2) (option D).[2] Morphofunctional categories include dilated cardiomyopathy, HCM, restrictive cardiomyopathy, ARVC, and idiopathic cardiomyopathy (option C). After morphofunctional classification, cardiomyopathies are classified as familial/genetic or nonfamilial/nongenetic. Familial cardiomyopathies are defined by the occurrence of a phenotype in more than one family member that could be caused by the same genetic mutation (option B). Ion channelopathies, a genetic subtype included in the AHA classification of primary cardiomyopathy, were not accepted as cardiomyopathy in the ESC classification because genes encoding for ion channels might not be associated with overt myocardial dysfunction (option A).

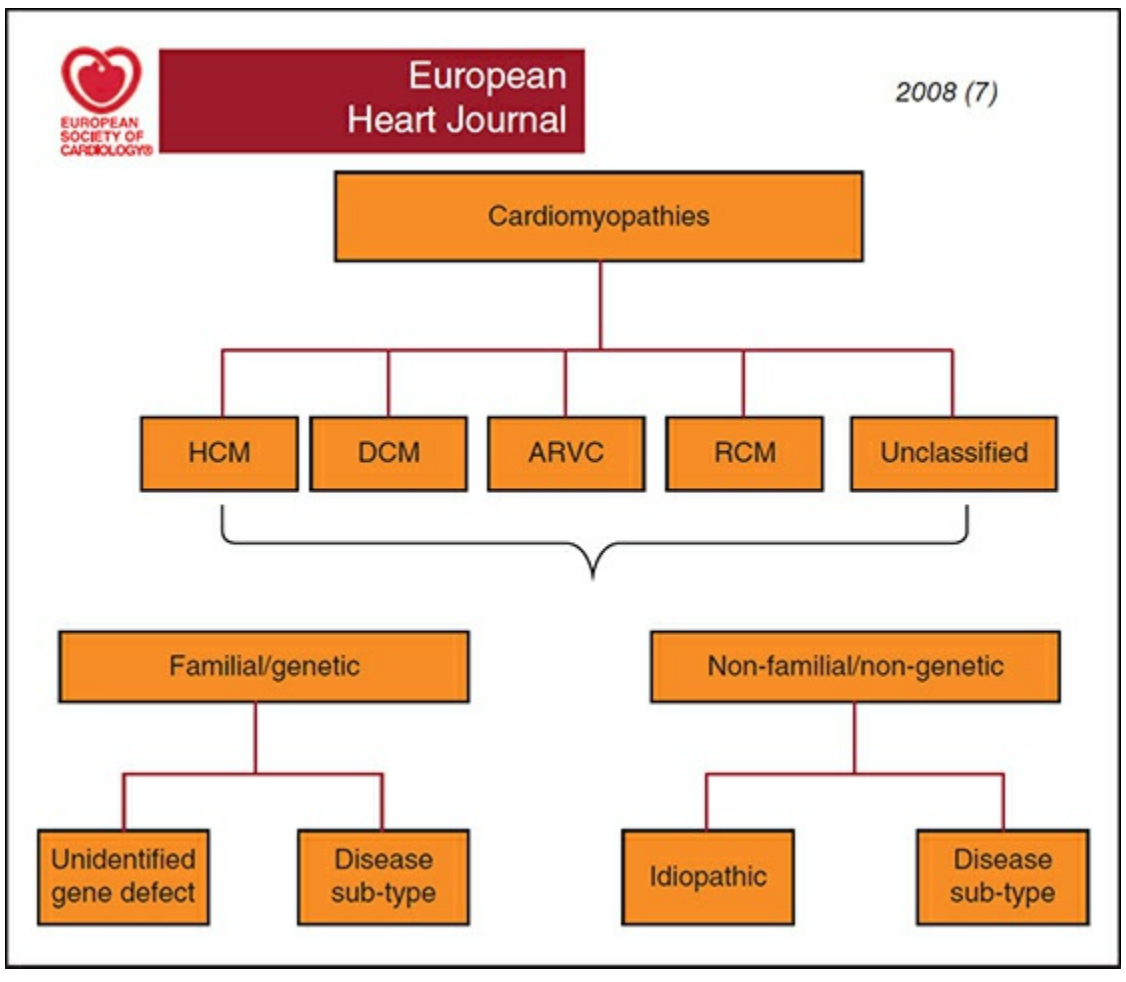

FIGURE 57-2 ESC classification of cardiomyopathy. (Reproduced with permission from Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on

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57-3. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 57)*. The WHF classification system builds on the AHA and ESC systems and is influenced by the TNM convention used in oncology.[3] The five attributes used for classification include morphofunctional phenotype, organ system involvement, genetic pattern of inheritance, etiology, and stage (option A). The system is versatile and even allows for the annotation of specific mutations along with clinical relevant phenotypes such as ventricular morphology and functional status, using the AHA and NYHA staging conventions (options B and D).

57-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chapter 57)* Unlike previous classifications, the mixed or overlapping phenotypes can be easily presented in the MOGES classification system, such as HCM that evolves into dilated congestive phenotype (M_{H+D}) or HCM presenting with predominant restrictive pattern (M_{H+R}) (option C). Option A refers to a purely hypertrophic phenotype; option B refers to a purely dilated phenotype; and option D refers to a purely restrictive phenotype.

57-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 57)*. Under the MOGES system, M allows the description of *early* phenotypes (M_E), such as when the diagnostic criteria for the suspected clinical phenotype (such as DCM or HCM) are not fulfilled and imaging data indicate an increased LV diameter and borderline LV function ($M_{E[D]}$) or possible LV hypertrophy ($M_{E[H]}$) (option C). Clinically healthy mutation carriers are described as $M_{0[H]}$ or $M_{0[D]}$ (0 is for zero) (options A and D). In this case, D and H refer to the phenotype of affected probands (option B).

57-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 57)*. The MOGES classification system is provided in Figure 57-3. He has a dilated cardiomyopathy, so he is M_D (options A, B). His organ involvement is the heart only, so he is O_H (options B and E). He has no family history and a history was taken, so he is G_N (options A through D). The etiology is likely viral, so he is E_v. Finally, he is stage C and has class II symptoms, indicated by $S_{C\text{-}II}$ (options A through C).

SUBSCRIPT NOTATION	M MORPHO-FUNCTIONAL PHENOTYPE	O ORGAN/SYSTEM INVOLVEMENT	G GENETIC INHERITANCE PATTERN	E ETIOLOGY	S STAGE
	D Dilated H Hypertrophic R Restrictive R EMF Endomyocardial fibrosis *LV=left ventricle* *RV=right ventricle* *RLV=biventricular* A ARVC *M=major* *m=minor* *c=category* *LV= left ventricle* *RV=right ventricle* *RLV=biventricular* NC LVNC E Early, with type in parentheses NS Nonspecific phenotype NA Information non available 0 Unaffected*	H Heart *LV=left ventricle* *RV=right ventricle* *RLV=biventricular* M Muscle (skeletal) N Nervous C Cutaneous E Eye, Ocular A Auditory K Kidney G Gastrointestinal Li Liver Lu Lung S Skeletal 0 Absence of organ/system involvement*, e.g. in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G	N Family history negative U Family history unknown AD Autosomal dominant AR Autosomal recessive XLD X-linked dominant XLR X-linked recessive XL X-linked M Matrilineal 0 Family history not investigated* Undet Inheritance still undetermined S Phenotypically Sporadic (apparent or real)	G Genetic cause OC Obligate carrier ONC Obligate non-carrier DN *De novo* Neg Genetic test negative for the known familial mutation N Genetic defect not identified 0 No genetic test, any reason* G-A-TTR Genetic amyloidosis G-HFE Hemochromatosis *Non-genetic etiologies:* M Myocarditis V Viral infection (add the virus identified in affected heart) AI Autoimmune/immune-mediate; suspected (AI-S), proven (AI-P) A Amyloidosis (add type: A-K, A-L, A-SAA) I Infectious, non viral (add the infectious agent) T Toxicity (add cause/drug) Eo Hypereosinophilic heart disease O Other	ACC-AHA stage represented as letter A, B, C, D NA not applicable NU not used *followed by* NYHA class represented as Roman numeral I, II, III, IV

FIGURE 57-3 MOGES system for classification of cardiomyopathies. (Reproduced with permission from Arbustini E, Narula N, Tavazzi L, et al. The MOGE(S) classification of cardiomyopathy for clinicians, *J Am Coll Cardiol*. 2014 Jul 22;64(3):304-318.)

57-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 57)*. This patient is a carrier for a mutation in LMNA. Although she has not developed a morphofunctional phenotype, patients with cardiac laminopathies are at risk for arrhythmias, both ventricular and supraventricular (option A). The other options reflect risks associated with cardiomyopathy in general.

57-8. **The answer is C**. *(Hurst's The Heart, 14th Edition, Chap. 57)* This patient has a dilated cardiomyopathy (M_D) with NYHA class IV symptoms ($S_{D\text{-}IV}$) (options A and B). The patient is believed to have a genetic etiology with an autosomal dominant pattern of inheritance (G_{AD}). However, the genetic defect is not known ($E_{G\text{-}N\text{-}}$) (options C and D).

57-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 57)* The color code describes possible and probable pathologic genetic mutations in red; genetic variants of unknown significance in yellow; and single-nucleotide polymorphisms with possible functional significance in green (option B). The others options are a part of the MOGES system but do not use color.

57-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 57)* This patient has a dilated cardiomyopathy (M_D) secondary to sarcoidosis ($E_{AI\text{-}Sarcoid}$) (options A and B). His sarcoid also involves his lungs (O_{Lu}) (option C). He has stage B heart failure and NYHA class I symptoms and therefore has asymptomatic left ventricular dysfunction (option A).

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CHAPTER 58

Dilated Cardiomyopathy

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

58-1. A 42-year-old man presents to your clinic to establish care for a newly diagnosed dilated cardiomyopathy (DCM). His previous evaluation is notable for the absence of coronary artery disease. Review of his family history reveals that his father also had DCM and his sister has DCM. Which of the following is *not true* about familial DCM?

A. DCM is familial in more than 60% of cases
B. This patient has an X-linked cardiomyopathy allele
C. The most common cause of familial DCM is mutations to sarcomeric genes
D. Of the nuclear envelope genes, mutations to LMNA most often result in DCM
E. Most DCM genes also cause other types of cardiomyopathy

58-2. A 43-year-old woman is found to have a mutation of *LMNA2* associated with DCM. An echocardiogram reveals an ejection fraction of 40%. Which of the following is *true* of cardiac laminopathies that occur due to mutations of *LMNA2*?

A. Conduction system disease often presents prior to DCM
B. Progression of the PR interval is associated with cardiac laminopathies due to mutations of *LMNA2*
C. Patients with cardiac laminopathies due to mutations of *LMNA2* are at high risk for ventricular tachycardia and sudden death
D. Prophylactic ICD implantation would be indicated for this patient if she demonstrated nonsustained ventricular tachycardia on ambulatory ECG monitoring
E. All of the above

58-3. A 24-year-old woman with systemic scleroderma develops exertional dyspnea associated with pedal edema, paroxysmal nocturnal dyspnea, and orthopnea. Which of the following is *not* an associated cardiac manifestation of scleroderma?

A. Hypertrophic cardiomyopathy
B. Pericardial effusion
C. Left ventricular (LV) systolic and diastolic dysfunction
D. Pulmonary hypertension
E. Interstitial fibrosis

58-4. A 37-year-old woman presents with new-onset shortness of breath and orthopnea. She is noted to have an ejection fraction of 30%. Her history is remarkable for having recently delivered a baby boy 4 months ago. Which of the following is needed for a diagnosis of peripartum cardiomyopathy?

A. The cardiomyopathy must be an idiopathic condition
B. The onset of the cardiomyopathy must be related to the timing of pregnancy
C. There should be no preexisting heart disease
D. There must be LV dysfunction
E. All of the above

58-5. A 54-year-old man is admitted for a newly diagnosed cardiomyopathy. His past medical history is notable for heavy alcohol use. Which of the following is *true* of an alcohol-induced cardiomyopathy?

A. Administration of thiamine can reverse the cardiomyopathy
B. A daily alcohol intake of > 80 grams per day (3 drinks) for five years prior to diagnosis is associated with cardiomyopathy
C. A hypertrabeculated phenotype
D. Occurrence of atrial fibrillation is associated with poorer outcomes

E. None of the above

58-6. You are asked to provide a preoperative risk assessment for a 38-year-old man with cirrhosis who is scheduled for transjugular intrahepatic portosystemic shunt (TIPS). Which of the following is *true* of cirrhotic cardiomyopathy?

A. During the early phase of cardiomyopathy, diastolic dysfunction is apparent
B. QT prolongation is present in more than 50% of cases
C. Diastolic dysfunction predicts death after TIPS implantation
D. Latent heart failure is often unmasked by stressors
E. All of the above

58-7. You are asked to consult on the oncology ward for a possible chemotherapy-related cardiomyopathy. Which of the following is *not true* about chemotherapy-related cardiomyopathies?

A. Anthracyclines are associated with type 1 myocardial damage
B. Trastuzumab is associated with type 2 myocardial damage
C. Cyclophosphamide is associated with a hemorrhagic myocarditis
D. Sumatinib is associated with hypertension
E. The incidence of cardiomyopathy increases when trastuzumab is used without an anthracycline

58-8. Which of the following is associated with a reversible cardiomyopathy?

A. Alcohol-induced cardiomyopathy
B. Tachycardia-induced cardiomyopathy
C. Takotsubo cardiomyopathy
D. Viral myocarditis
E. All of the above

58-9. A 37-year-old man is admitted for a new-onset cardiomyopathy. His EKG shows frequent premature ventricular contractions (PVCs). Which of the following is *not* associated with a PVC-induced cardiomyopathy?

A. More than 10,000 PVCs per day are associated with LV dilation
B. More than 20,000 PVCs per day are associated with reduced ejection fraction
C. For patients with a PVC-induced cardiomyopathy, successful termination of the PVCs can reverse the cardiomyopathy
D. Therapy for frequent PVCs in patients with idiopathic LV dysfunction modifies clinical outcomes
E. PVC-induced cardiomyopathy can occur in children

58-10. Which of the following is *not* associated with a mitochondrial cardiomyopathy?

A. Hypertrophic phenotype
B. Dilated phenotype
C. Maternal inheritance
D. Autosomal inheritance
E. Clinical manifestations tend to be restricted to the heart

ANSWERS

58-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 58)* In more than 60% of cases of DCM, the disease is familial, as proven by clinical family screening demonstrating that more than one member is affected or shows traits that predict the development of the disease (option A).[1,2] This patient likely has an autosomal dominant allele. This patient's father is affected, and because he did not inherit an X chromosome from his father, the disease allele cannot be X-linked (option B). Sarcomere genes (*TTN, MYH7, MYBPC3, TNNT2, TNNI3, MYL2, MYL3*) are mutated in 25% to 30% of DCM patients (option C).[3] Nuclear envelope genes (*LMNA, EMD, SYNE1, TMPO*) are mutated in about 7% to 10% of cases, with *LMNA* mutations accounting for the majority of DCM in this subgroup (option D).[4] Most DCM genes also cause other types of cardiomyopathy (HCM, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (option E).

58-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)* The development of conduction system disease usually precedes the appearance of the DCM (option A). The natural history is characterized by a long asymptomatic phase in which regular and slowly progressive LV dilation or dysfunction is demonstrated (option B).[5] The high risk of life-threatening ventricular arrhythmias is one of the characteristics of cardiolaminopathies, and such arrhythmias may manifest even in mildly dilated and dysfunctioning hearts.[6,7] Recent guidelines on the primary prevention of sudden cardiac death (SCD) recommend ICD implantation in patients with DCM and a confirmed disease-causing *LMNA*

mutation and such clinical risk factors (Class IIa level B) as nonsustained ventricular tachycardia during ambulatory ECG monitoring, LV ejection fraction (LVEF) < 45% on initial evaluation, male gender, and nonmissense mutations (insertion, deletion, truncation, or mutations affecting splicing) (options C and D).

58-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 58)* The heterogeneous cardiac manifestations of scleroderma include myocarditis, pericarditis, and pericardial effusion (option B); conduction disturbances; LV systolic and diastolic dysfunction (option C); valve dysfunction; myocardial ischemia and coronary artery disease; and pulmonary hypertension (option D).[8] Histologically, scleroderma is associated with fibrosis (option E). Hypertrophic cardiomyopathy is not typically associated with scleroderma (option A).

58-4. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)* Criteria for diagnosing peripartum cardiomyopathy include: (1) idiopathic condition (no detectable cause of HF) (option A); (2) temporal appearance (the last month of pregnancy or during the first 5 months postpartum according to NHLBI and toward the end of pregnancy or in the months following delivery according to ESC (option B); (3) the absence of preexisting known heart disease (option C); and (4) the presence of LV dysfunction (option D).

58-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 58)* The three criteria for diagnosing alcoholic cardiomyopathy include DCM phenotype, absence of other known and detectable causes of DCM (option C), and a long history of heavy alcohol intake. The toxic effect is expected for daily alcohol consumption over 80 g (three or more standard-sized drinks per day) lasting 5 years or more before the onset or diagnosis (option B).[9] Atrial fibrillation, QRS width > 120 ms, and the absence of β-blocker therapy identify patients with a poor outcome (option D). Thiamine deficiency (beriberi) is no longer confused with alcoholic cardiomyopathy; the former fully responds to thiamine administration, whereas the latter does not (option A).

58-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)* According to the 2005 World Congress of Gastroenterology, cirrhotic cardiomyopathy is defined by "chronic cardiac dysfunction in patients with cirrhosis characterized by impaired contractile responsiveness to stress and/or altered diastolic relaxation with electrophysiological abnormalities in the absence of other known cardiac disease."[10] The impaired diastolic relaxation is more common in early phases, whereas systolic dysfunction and LV dilation are manifest in advanced phases (option A); electrophysiological abnormalities include prolongation of QT interval in more than 50% of cases (option B), electromechanical dyssynchrony, and chronotropic and/or inotropic incompetence.[11] In the complex pathophysiology of cirrhosis-related cardiac and hemodynamic changes, diastolic dysfunction seems to predict death after TIPS implantation (option C).[12] Patients with cirrhosis often demonstrate hyperdynamic circulation and increased cardiac output, decreased systemic vascular resistance, and increased compliance of the arterial vessels. This combination of hemodynamic conditions corresponds to latent left HF where any stressor may clinically unmask the LV dysfunction (option D).

58-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)* Heart muscle toxicity is generally characterized as *nonreversible injury* (type 1) as a result of the presence of structural damage (prototyped by the anthracycline or high-dose cyclophosphamide DCM in acute and chronic forms) and potentially reversible (on cessation of therapy) dysfunction (type 2) in the absence of structural abnormalities, as with targeted therapies (ie, trastuzumab, sunitinib, lapatinib) (options A and B). The 3-year cumulative incidence of cardiomyopathy is 6.6% when trastuzumab is used with anthracyclines and 5.1% when used without anthracyclines (option E).[13] Myocarditis is a rare complication described in patients treated for cancer (ie, cyclophosphamide and hemorrhagic myocarditis) (option C). Hypertension is the most common cardiovascular complication associated with vascular endothelial growth factor inhibitors (option D).

58-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)*. All of the above are associated with a reversible cardiomyopathy (options A through D), although reversal of the cardiomyopathy is not guaranteed with cessation of the cause.

58-9. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 58)* A dose-response relationship has been demonstrated in serial evaluations of LV function among 239 consecutive patients with frequent PVCs and no obvious cardiac disease; > 20,000 PVCs per 24 hours were associated with subclinical deterioration in LVEF whereas >10,000 PVCs per 24 hours showed LV dilation without a change in LVEF (options A and B).[14] For patients with a PVC-induced cardiomyopathy, successful termination of the PVCs can reverse the cardiomyopathy (option C). Randomized trials are ongoing, aimed at assessing whether therapy for frequent PVCs in patients with idiopathic LV dysfunction modifies clinical outcomes (option D). In children, the proportion of PVC-induced cardiomyopathy seems higher than previously expected, especially because ectopy tends to persist throughout follow-up (option E).

58-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 58)* Mitochondrial cardiomyopathies can be caused by mutations both in mitochondrial DNA genes (maternal inheritance) and in nuclear genes (Mendelian inheritance: no male passes down the disease to children) coding mitochondrial proteins (options C and D). They are characterized by either a hypertrophic phenotype evolving through dilated and dysfunctional hearts or DCM (options A and B). They are commonly observed in families in which mutation carriers also express noncardiac traits, such as hearing loss, palpebral ptosis, myopathy, renal failure, cryptogenic stroke, diabetes, optic neuritis, and/or retinitis pigmentosa (option E).

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CHAPTER 59

Hypertrophic Cardiomyopathies

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

59-1. A 25-year-old woman seeks to establish care for hypertrophic cardiomyopathy (HCM). Her family history is notable for multiple affected family members. Which of the following is *not true* regarding the genetics of HCM?

A. She is most likely to have a mutation of a sarcomeric protein
B. 5% to 10% of cases are caused by metabolic or storage disorders
C. Missense single nucleotide variants of *MYH7* are associated with a dominant negative effect
D. Nonsense mutations of MYBC3 are associated with haploinsufficiency
E. Unaffected family members cannot have the causal mutation

59-2. You are asked to be an expert witness at a trial for an 18-year-old man who experienced sudden death while playing basketball. Which of the following autopsy findings are *not* consistent with a diagnosis of HCM?

A. Asymmetric septal hypertrophy with a small left ventricular cavity
B. If left ventricular outflow tract obstruction was present, plaque may be located on the upper septal area
C. Mitral valve abnormalities are rarely present
D. Epicardial arteries can follow an intramural course
E. Histopathologic examination shows cardiomyocyte hypertrophy and disarray

59-3. A 24-year-old woman with HCM is on a maximally tolerated dose of beta-blocker and continues to have class III exertional dyspnea. Which of the following are causes of diastolic dysfunction in patients with HCM?

A. Impairment of ventricular relaxation
B. Increased chamber stiffness
C. Insufficient coronary blood flow
D. Compromised myocardial energy metabolism
E. All of the above

59-4. Which of the following physical examination findings are *not* associated with HCM with obstruction?

A. Pulsus alternans
B. Bifid apical impulse
C. Decrease in murmur quality going from sitting to standing
D. Decrease in the murmur when raising the legs
E. Amyl nitrite will increase the murmur

59-5. A 27-year-old man presents to your office for exertional syncope and shortness of breath. Which of the following would be consistent with a diagnosis of sarcomeric HCM?

A. Left ventricular wall thickness > 10 mm
B. Diffuse subendocardial late gadolinium enhancement on cardiac MRI
C. Systolic anterior motion (SAM) of the mitral valve apparatus to cause obstruction
D. Short PR interval, pre-excitation, and extreme left ventricular hypertrophy (LVH) on ECG
E. Increased serum creatine phosphokinase (CPK) and lactate

59-6. Your patient with HCM is in the cardiac catheterization laboratory for hemodynamic assessment and has the tracing shown in Figure 59-1. Which of the following maneuvers can elicit this phenomenon?

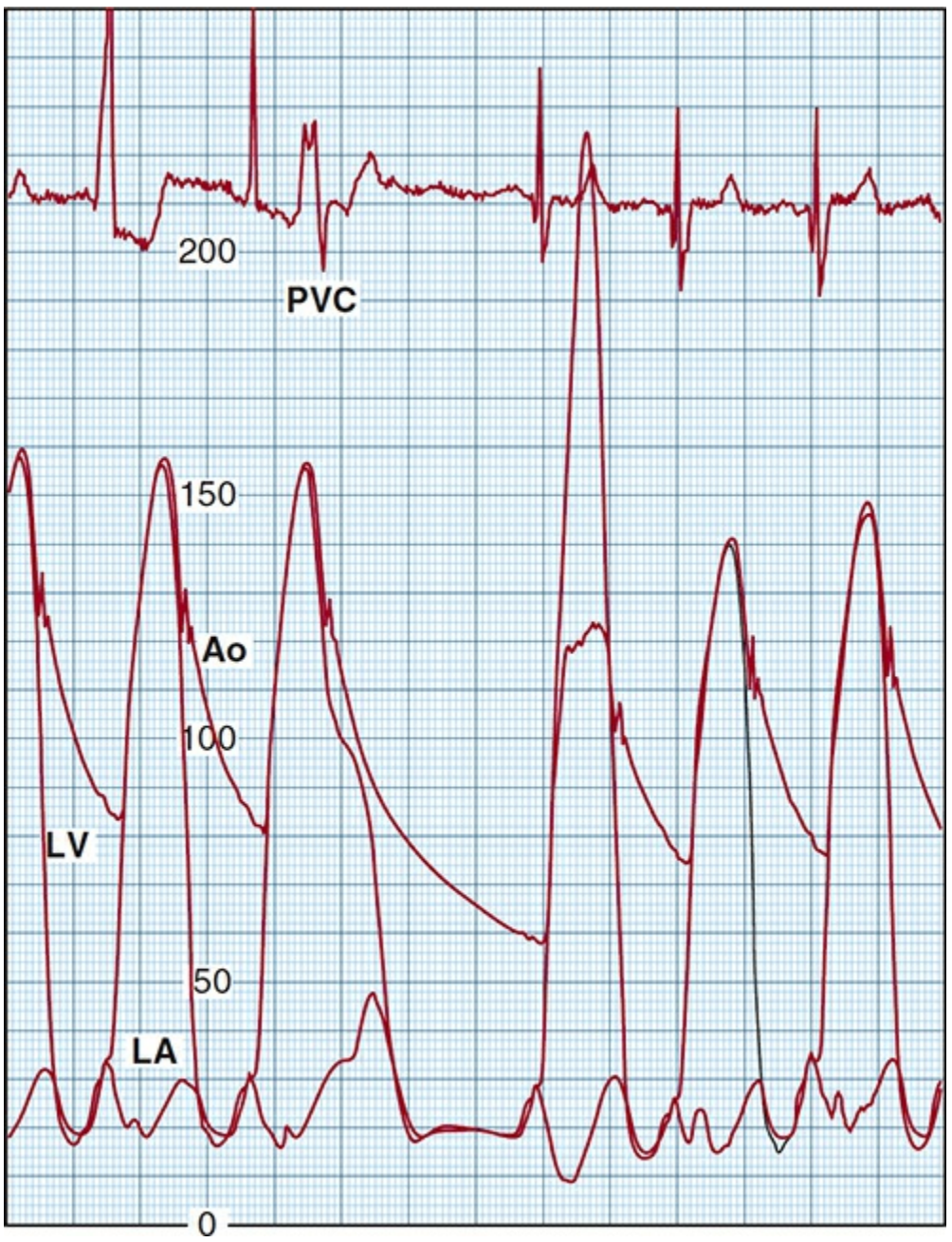

FIGURE 59-1 Invasive hemodynamic tracings for question 59-6.

A. Valsalva
B. Norepinephrine infusion
C. Isooproterenol infusion
D. A and C
E. A and B

59-7. Your patient with HCM has several questions about his risk for sudden death (SCD). Which of the following features are *not* associated with an increased risk of SCD with HCM?

A. History of prior cardiac arrest or spontaneous sustained ventricular tachycardia
B. A family history of premature SCD in a first-degree relative with HCM
C. Nonsustained ventricular tachycardia on ambulatory testing
D. Hypertensive blood pressure response to exercise
E. Extreme LVH > 30 mm

59-8. A 32-year-old man presents for exertional dyspnea. His echocardiogram is diagnostic of hypertrophic obstructive cardiomyopathy (HOCM). He is currently *not* taking any medications. Which of the following could be recommended?

A. Fluid restriction
B. Initiation of a beta-blocker
C. Verapamil
D. Alcohol septal ablation
E. Surgical myectomy

59-9. A 44-year-old woman with HOCM continues to have class 3 shortness of breath despite maximal medical therapy. Which of the following are indications for myectomy?

A. An LV outflow tract obstructive gradient ≥ 50 mm Hg
B. New York Heart Association functional class III-IV symptoms despite maximal medical therapy
C. Recurrent exertional syncope despite maximally tolerated drug therapy
D. A and B
E. All of the above

59-10. A 44-year-old woman with HOCM continues to have class III shortness of breath despite maximal medical therapy and

is interested in myectomy. Which of the following is *not true* regarding complications of myectomy?

A. In large-volume centers, the operative mortality for septal myectomy is < 1%
B. Complications of surgical myectomy (AV nodal block, ventricular septal defect, and aortic regurgitation) of surgery are uncommon
C. The major complication of alcohol septal ablation is complete heart block
D. The risk for complete heart block following alcohol septal ablation is increased if right bundle branch block is present prior to the ablation procedure
E. A maximum LV wall thickness < 16 mm at the point of leaflet-septal contact is a risk factor for ventriculoseptal defects in both alcohol septal ablation and myectomy

ANSWERS

59-1. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 59)* The majority of mutations that cause HCM involve sarcomeric proteins. Between 75% and 80% involve cardiac myosin heavy chain (*MYH7*) and cardiac myosin binding protein C (*MYBPC3*). Mutations in cardiac troponin T (*TNNT2*), troponin I (*TNNI3*), α-tropomyosin (*TPM1*), myosin light chains (*MYL2*, *MYL3*), and cardiac actin (*ACTC1*) account for 15% to 20% of mutation-positive individuals (option A).[1] A further 5% to 10% of cases are caused by metabolic or storage disorders (eg, Anderson-Fabry disease, mitochondrial disorders, glycogen storage diseases), neuromuscular disorders, chromosome abnormalities, and genetic syndromes such as cardio-facial-cutaneous syndromes, including Noonan and LEOPARD syndromes (option B).[2] Two pathogenic mechanisms are thought to account for disease associated with mutations in cardiac sarcomere proteins. Missense single nucleotide variants (a nucleotide change that results in an amino acid being substituted by another amino acid in the protein) predominantly lead to a *dominant negative effect* (described as a "poison peptide" mechanism) in which the mutated protein is not destroyed but rather integrates into the sarcomere, leading to the disease phenotype; this is thought to be characteristic of *MYH7* variants (option C). Alternatively, nonsense single nucleotide variants or small frameshift insertion-deletions can introduce a premature stop codon and cause haploinsufficiency as a result of nonsense mRNA-mediated decay or proteolysis of a truncated (just partially translated) protein. This mechanism is believed to be typical of the majority of *MYBPC3* disease-causing mutations (option D).[3] HCM is characterized by variable intra- and interfamilial expression and incomplete and age-dependent clinical penetrance. Thus, unaffected family members can be carriers of the causal mutation (option E).[4]

59-2. The answer is C. *(Hurst's The Heart, 14th Edition, Chap. 59)* Gross examination of the heart in patients with HCM demonstrates asymmetric septal hypertrophy with a small left ventricular cavity (option A).[5] The mural endocardium may be thickened by fibrous tissue, and if left ventricular outflow tract obstruction is present, there is often a plaque located on the upper septal area where the mitral valve repeatedly has come in contact with the septum (option B). The mitral valve itself may be abnormal, with elongation of the mitral chordae and anterior displacement of hypertrophied papillary muscles. Abnormal attachments of the mitral valve chordae into the septum, insertion of the papillary muscle head directly into the mitral leaflets, myocardial clefts, and increased ventricular trabeculation are also common (option C).[6] Although the epicardial coronary arteries are usually normal, they can follow an intramural course and be compressed during ventricular systole (option D).[7] The classic histopathologic appearance of HCM consists of cardiomyocyte hypertrophy and disarray, interstitial and replacement fibrosis, and dysplastic arterioles (option E).[8]

59-3. The answer is E. *(Hurst's The Heart, 14th Edition, Chap. 59)* Diastolic dysfunction arises from multiple factors that affect both ventricular relaxation and chamber stiffness (options A and B).[9] Patients with HCM have increased oxygen demand as a result of ventricular hypertrophy and abnormal loading conditions but also have compromised coronary blood flow to the LV myocardium because of abnormally small and partially obliterated intramural coronary arteries (option C). In addition, myocardial energy metabolism is compromised as a result of inefficient cardiomyocyte contraction and is an early feature of the disease in carriers of sarcomeric protein mutation (option D).[10]

59-4. The answer is A. *(Hurst's The Heart, 14th Edition, Chap. 59)* The classic carotid pulsation is brisk with a spike-and-dome pattern, characterized by a rapid rise (percussion wave) followed by a midsystolic drop that is, in turn, followed by a secondary wave (tidal wave). Pulsus alternans is alternating strong and weak beats, often associated with severe LV dysfunction (option A). The apical impulse is almost always abnormal in patients with HCM. Typically, it is a sustained systolic thrust that continues throughout most of systole and can be bifid as a result of a forceful atrial systole (option B). From the standing position to a prompt squat, the murmur will markedly decrease in intensity as a result of increases in afterload and preload (option C). Other maneuvers that are used to change the intensity of the murmur include leg-raising to increase preload (and thereby decrease the intensity of the murmur) and inhaling amyl nitrite to decrease afterload (options D and E).

59-5. The answer is C. *(Hurst's The Heart, 14th Edition, Chap. 59)* Increased LV wall thickness measured by any imaging technique is the basis for the diagnosis of HCM. In adults, a wall thickness ≥ 15 mm at end-diastole in one or more

myocardial segments and, in children, a wall thickness more than two standard deviations greater than the predicted mean are sufficient to make the diagnosis (option A). Diffuse subendocardial late gadolinium enhancement on cardiac MRI is suggestive of amyloid. HCM typically has midwall late gadolinium enhancement or late gadolinium enhancement at the insertion zones of the right ventricle (RV) in the septum (option B). Dynamic LV outflow tract obstruction (LVOTO) is characterized by SAM of the mitral valve apparatus and an open ventricular chamber. Most patients have SAM of the anterior leaflet, but it also occurs with the posterior leaflet.[11] Short PR interval, pre-excitation, and extreme LVH on ECG are more consistent with Danon's disease or glycogen storage disease (option D). Increased serum CPK and lactate tend to go along with mitochondrial myopathies (option E).

59-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 59)* Figure 59-1 shows the Brockenbrough phenomenon—the hallmark of latent obstruction. After a premature contraction, an increase in the contractility of the ventricle results in a marked increase in the degree of dynamic obstruction. This is seen as an increase in the outflow gradient and a decrease in the aortic pulse pressure after the pause. When there is little resting obstruction, provocation using the Valsalva maneuver or infusion of isoproterenol can be performed in the catheterization laboratory (options A and C). Norepinephrine infusion would increase afterload and is unlikely to increase obstruction (option B).

59-7. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 59)* Several clinical features are associated with a high risk for SCD in patients with HCM.[12] Patients who have had a prior cardiac arrest or spontaneous sustained ventricular tachycardia are at highest risk (option A). A family history of premature SCD in a first-degree relative with HCM portends a high risk, particularly if there are multiple occurrences (option B). Other risk markers include recent unexplained syncope, nonsustained ventricular tachycardia (option C), hypotensive blood pressure response to exercise (option D), and extreme LV hypertrophy (> 30 mm) (option E).

59-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 59).* Patients with LVOTO should maintain hydration at all times, avoid excessive alcohol consumption, and maintain a healthy weight (option A).[12] Medical therapy should be considered the first-line therapy for the relief of symptoms in patients with obstructive HCM. Beta-adrenergic blocking agents are usually the drugs of choice. Theoretic actions of beta-blockers include decreased heart rate response to exercise, relief of angina by a decrease in myocardial oxygen demand, and improvement in diastolic filling time (option B). Nondihydropyrine calcium channel blockers—specifically, verapamil and diltiazem—are also of value in the treatment of HCM, particularly if beta-blockers are contraindicated or ineffective (option C). A trial of medical therapy should be offered before considering alcohol septal ablation or surgical myectomy (options D and E).

59-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 59)* For patients who have an LV outflow tract obstructive gradient ≥ 50 mm Hg (option A), moderate-to-severe symptoms (New York Heart Association functional class III-IV) (option B), or recurrent exertional syncope despite maximally tolerated drug therapy (option C), other treatment options such as septal myectomy, septal ablation, or dual-chamber pacing should be considered.[12]

59-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 59)* In large-volume centers, the operative mortality for septal myectomy is < 1% (option A).[13] Complications of myectomy (AV nodal block, ventricular septal defect, and aortic regurgitation) of surgery are uncommon (option B).[12] The major complication of alcohol septal ablation is complete heart block, which, with small doses of alcohol and guidance with myocardial contrast echocardiography, occurs in 7% to 20% of patients (option C). The risk for heart block is increased in patients with a preexisting LBBB (option D). A maximum LV wall thickness < 16 mm at the point of leaflet-septal contact is a risk factor for ventriculoseptal defects in both alcohol septal ablation and myectomy.[12]

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CHAPTER 60

Left Ventricular Noncompaction

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

60-1. Which of the following imaging findings is consistent with a diagnosis of left ventricular noncompaction (LVNC)?

A. A ratio of noncompacted myocardium to compact myocardium > 2 in the parasternal short axis by echocardiography
B. A ratio of noncompacted myocardium to compact myocardium > 2.3 in the horizontal long axis by cardiac MRI
C. A ratio of noncompacted myocardium to compact myocardium > 1 in at least two segments of short axis images by multidetector CT
D. All of the above
E. A and B

60-2. A 57-year-old man presents to your clinic to follow up a negative cardiac MRI (CMR) stress test for nonspecific chest pain. He was noted to have an increased ratio of noncompact to compact myocardium with normal left ventricular (LV) function. He is otherwise healthy. Which of the following is *not true* about compact and trabecular myocardium in the normal population?

A. The compacted layer but not the trabeculated layer is thicker in men than in women
B. The compacted layer thickens, whereas the trabeculated layer thins with systole
C. Trabeculated LV segments show increased systolic thinning of trabeculated layers and greater thickening of the compact segments with age
D. There are sex-specific differences in the trabeculated/compacted ratio at end systole or end diastole
E. In end systole, the trabeculated/compacted ratio is lower in older (50–79 years) subjects than in younger (20–49 years) subjects

60-3. Which of the following is *not true* regarding the proposed pathogenesis of LVNC?

A. LVNC may be the result of abnormal cardiac development
B. Polymorphisms of genes affecting the Notch pathway are associated with LVNC
C. The causes of interruption of myocardial compaction during cardiac development are unknown
D. LVNC is always inherited and never acquired
E. LVNC can be regarded as an isolated entity or as one of the traits that may recur in other cardiac and noncardiac diseases

60-4. A 32-year-old woman with a history of Barth syndrome in her family is pregnant with a boy. She wants to know about the risks of Barth syndrome if her son is affected. Which of the following is *true* of Barth syndrome?

A. Barth syndrome is not transmitted from mother to son
B. Barth syndrome is due to a mutation of the *MIB1* gene
C. Hypertrophic cardiomyopathy does not occur with Barth syndrome
D. Among children with a dilated cardiomyopathy (DCM), reverse remodeling can occur with normalization of heart function
E. Arrhythmias are uncommon

60-5. Which of the following is *not true* about the genetic basis for LVNC?

A. LVNC can result from mutations to genes that encode sarcomeric proteins
B. The same mutations that cause LVNC can result in hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and restrictive cardiomyopathy (RCM)
C. LVNC can be seen in patients with neuromuscular disorders
D. LVNC has been associated with mutations of ion channels
E. All of the above are true

60-6. A 34-year-old athlete is referred to you for palpitations. CMR showed a LVNC phenotype with normal left ventricular function. Which of the following is *true* of acquired LVNC?

A. LVNC is a rare finding among athletes
B. The majority of women who develop LVNC during pregnancy will have a regression of trabeculation after delivery
C. Patients with siderosis and LVNC have preferential accumulation of iron in the compact layer
D. LVNC is rare among patients with bicuspid aortic valve disease
E. Patients with acquired LVNC are likely to have an underlying familial syndrome

60-7. Which of the following is a typical finding in the evaluation of LVNC?

A. An abnormal ECG
B. A ratio of > 2:1 of noncompacted to compacted layer at end diastole by echo
C. Myocardial fibrosis is identified by late gadolinium enhancement during CMR
D. Elevation of troponin in the serum
E. All of the above are typical findings

60-8. A 45-year-old man presents for evaluation of LVNC. He is asymptomatic but was found to incidentally have an ejection fraction of 35% and LVNC. Which of the following is *true* about the prognosis for patients with LVNC?

A. Asymptomatic patients or individuals with LVNC and normal LV function have a poor prognosis
B. Patients presenting with heart failure (New York Heart Association class III or IV), sustained ventricular arrhythmias, or left atrial dilation have a favorable prognosis
C. A right bundle branch block is associated with a good prognosis
D. Prognosis depends on the severity of the underlying cardiac disease rather than the trabecular anatomy of the LV
E. None of the above are true

60-9. Which of the following is *not* indicated in patients with Barth syndrome?

A. Consideration of aspirin with severe LV dysfunction
B. Inclusion of uncooked cornstarch in the diet to prevent muscle protein loss
C. Avoidance of succinylcholine
D. Use of prophylactic antibiotics in high-risk clinical situations
E. Empiric administration of warfarin with a goal INR of 2-3

60-10. Which of the following is *true* regarding the epidemiology of LVNC?

A. The incidence of LVNC in children is less than 0.1 per 100,000.
B. Approximately 10% of pediatric cardiomyopathies are associated with LVNC
C. LVNC is more common in women than in men
D. A and B
E. A and C

ANSWERS

60-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 60)* A ratio of noncompacted myocardium to compact myocardium > 2 by echocardiography is consistent with a diagnosis of LVNC (option A).[1] A ratio of noncompacted myocardium to compact myocardium > 2.3 in the horizontal long axis by cardiac MRI is consistent with a diagnosis of LVNC (option B).[2] A ratio of noncompacted myocardium to compact myocardium >2.2 in at least 2 segments of short axis images by cardiac CT is consistent with a diagnosis of LVNC (option C).[2]

60-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 60)* CMR studies in normal adult volunteers demonstrated the following sex- and age-related differences: (1) the compacted but not the trabeculated layer is thicker in men than in women (option A); (2) the compacted layer thickens, whereas the trabeculated layer thins with systole (option B); (3) trabeculated LV segments show increased systolic thinning of trabeculated layers and greater thickening of the compact segments ($P < .05$) with age (option C); (4) total wall thickening is neither sex nor age dependent; (5) there were no sex-specific differences in the trabeculated/compacted ratio at end systole or end diastole (option D); and (6) in end systole, the trabeculated/compacted ratio was lower in older (50–79 years) subjects than in younger (20–49 years) subjects ($P < .05$) (option E).[3] Overall, the application of current diagnostic criteria demonstrates that LVNC may occur in a relevant proportion of healthy individuals.

60-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 60)* The most cited pathogenetic hypothesis for LVNC is embryogenic arrest of the normal process of trabecular maturation during early intrauterine life when the heart undergoes

cardiac chamber maturation (option A).[4] However, LVNC can be heritable or acquired. For example, patients with cardiomyopathies may develop LVNC during the course of their disease (option D).[5,6] While many signaling pathways have been linked to compaction during heart development, only mutations of the *MIB1* gene have been linked to LVNC. The *MIB1* gene encodes a ubiquitin ligase that regulates endocytosis of Notch ligands.[7] To date, mutations in this gene have been reported in individuals with LVNC in two Spanish families (option B).[8] The causes of interruption of myocardial compaction are unknown (option D). LVNC can be regarded as an isolated entity or as one of the traits that may recur in other cardiac and noncardiac diseases. For example, LVNC is associated with tafazzinopathies [caused by mutations in the *TAZ* (*Tafazzin*, or *G4.5*) gene] (option E).[9]

60-4. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 60)* Barth syndrome should be suspected in all male infants with heart failure, DCM, and LVNC, especially when associated with other markers of disease. Barth syndrome is a rare X-linked recessive disorder characterized by cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, and distinctive facial characteristics. As an X-linked disorder, the mutation is passed from mother to son (option A). While mutations of *MIB1* have been associated with LVNC, Barth syndrome is caused by mutations in the *G4.5* gene (*TAZ*) (option B).[9-11] LVNC is commonly associated with LV dilation and dysfunction at onset.[9] Less commonly, Barth cardiomyopathy may present with a hypertrophic or hypertrophic-dilated phenotype (option C). Heart involvement occurs in almost all children before the age of 5 years. Thereafter, the cardiomyopathy may demonstrate an intermittent course during which the heart can undergo remodeling. Improvement can be observed after infancy, with possible stabilization after the toddler years (option D).[12] Overall, however, cardiac function varies and tends to decline over time. Arrhythmias, both supraventricular and ventricular, are more commonly reported in adolescents and young adults than in infants.[9]

60-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 60)* LVNC can result from a diverse set of mutations, including to sarcomeric proteins (option A), ion channels (option D), and neuromuscular disease loci (option C). Mutations to the sarcomeric proteins ACTC1 (cardiac actin alpha) and MHY7 can cause DCM, RCM, and HCM (option B).[13,14]

60-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 60)* The proportion of athletes who develop LVNC under intensive exercise is relevant (about 10%) (option A).[15] Among pregnant women with LVNC, 69.2% showed complete resolution of LV trabeculations over a mean duration of 8.1 ± 4.2 months (option B).[16] Although LVNC can be associated with disorders of red blood cells, in patients with myocardial iron overload and siderosis, a preferential distribution of intramyocyte iron in the compacted or noncompacted layers has not been observed (option C).[17] A high prevalence of LVNC is reported in patients fulfilling the echocardiographic criteria for bicuspid aortic valve (BAV). Specifically, in one study, 12 (11.0%) of 109 patients with BAV fulfilled the criteria for LVNC, with nine of the 12 patients being men. Although the pathophysiologic basis of LVNC in patients with BAV is unclear, special attention should be given to the evaluation of LV trabecular anatomy.[18] All these acquired conditions of LVNC demonstrate that a unique pathogenetic hypothesis of embryogenic defect is unlikely to explain acquired, late-onset, transient LVNC (option E).

60-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 60)* Although a normal ECG finding is rare in LVNC and is observed in a minority of patients (from 6% to 13%), there are no changes specific to LVNC (option A).[19] A ratio of > 2:1 of noncompacted to compacted layer at end systole by echo is characteristic of LVNC (option B). Myocardial fibrosis is not a criterion for the diagnosis of LVNC (option C). There are no specific biomarkers for LVNC (option D).

60-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 60)* Prognosis in LVNC depends on the clinical presentation. Asymptomatic patients or individuals with LVNC and normal LV function have a good prognosis (option A).[20] Alternatively, patients presenting with heart failure (New York Heart Association class III or IV), sustained ventricular arrhythmias, or left atrial dilation have an unfavorable prognosis (option B).[20,21] Adverse outcomes of isolated LVNC occur in patients with advanced heart failure, dilated left heart with systolic dysfunction, reduced systolic blood pressure, pulmonary hypertension, and right bundle branch block (option C).[20] In summary, prognosis depends on the severity of the underlying cardiac disease rather than the trabecular anatomy of the LV (option D).

60-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 60)* Patients diagnosed with Barth syndrome with heart failure should receive standard medications as per guidelines. Aspirin can eventually be added to decrease the risk of stroke in patients with severe LV dysfunction (option A). Empiric warfarin in the absence of thromboembolic events is not recommended (option E). The monitoring of arrhythmias and related prevention strategies should be maintained over the course of the patient's life. Disease-specific treatments can include the administration of granulocyte colony-stimulating factor either routinely or in high-risk clinical situations (eg, infections, surgery) along with prophylactic antibiotics (option D). Diets should include the administration of uncooked cornstarch to prevent muscle protein loss overnight (option B). Succinylcholine, a nondepolarizing neuromuscular blocker that could have a prolonged effect, should be avoided (option C).[12]

60-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 60)* The precise proportion of LVNC remains elusive. Data on the annual incidence of LVNC in children report values < 0.1 per 100,000 (option A).[22] Isolated LVNC accounted for

9.2% of all cases in a population-based retrospective cohort study of primary cardiomyopathies in Australian children.[23] This prevalence was close to that recorded in the Texas Children's Hospital echocardiography database (9.5%) (option B).[24] As for sex, LVNC is reported to be more common in men (56% to 82%) than in women (option C).[25-28]

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CHAPTER 61

Restrictive Heart Diseases

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

61-1. Which of the following echocardiographic findings are associated with restrictive physiology?

A. An increased ratio of early diastolic filling to atrial filling (≥ 2)
B. Decreased E-deceleration time (< 160 ms)
C. Increased isovolumetric relaxation time
D. A and B
E. B and C

61-2. Which of the following features are consistent with the European Society of Cardiology and American Heart Association definitions of restrictive cardiomyopathy?

A. Normal or reduced diastolic volumes of one or both ventricles
B. Increased ventricular wall thickness
C. Normal or reduced systolic volumes of one or both ventricles
D. A and B
E. A and C

61-3. A 43-year-old woman is admitted to your care for acute decompensated heart failure with preserved ejection fraction. The family history is notable for restrictive cardiomyopathy. She has experienced a nearly 25-pound weight gain, is orthopneic, and is short of breath at rest. Which of the following would you *not* expect to observe during her physical examination?

A. Prominent jugular venous pulse and X and Y descents
B. Ascites
C. Crescendo-decrescendo murmur that worsens with Valsalva
D. A filling sound
E. Diminished pulse pressure

61-4. Which of the following findings favor a diagnosis of constrictive pericarditis over restrictive cardiomyopathy?

A. Elevated NT-proBNP
B. Kussmaul's sign
C. Shift of the septum with respiration by echocardiogram
D. Higher lateral e´ velocity compared to the medial e´
E. Prominent y descent on the jugular venous waveform

61-5. Which of the following is *true* regarding the genetic basic of RCM?

A. Most cases are autosomal recessive
B. Mutations of *TNNI3* are associated with RCM
C. EMB demonstrating immunoreactive granulofilamentous material accumulated within myocytes is indicative of a typical RCM desminopathy
D. B and C
E. None of the above are true

61-6. A 32-year-old woman presents to your clinic for volume overload. Her examination is notable for an elevated jugular venous pressure with prominent y descent. Her neck is also notable for the finding in Figure 61-1. She also has ascites marked peripheral edema. Echocardiography shows a RCM. Family history is notable for family members with the same condition. Which of the following genes are associated with this condition?

FIGURE 61-1 Neck of the patient in question 61-6.

A. *MYH6*
B. *MYBC3*
C. *ABCC6*
D. *TNNI3*
E. *TNNT2*

61-7. Which of the following is *not* characteristic of cardiac involvement of hereditary hemochromatosis (HH)?

A. Serum ferritin > 300 ng/mL
B. Low voltage on ECG
C. Longer T2* times with cardiac MRI are associated with a better prognosis
D. Diastolic dysfunction occurs early and is followed by reduced systolic function later in the disease
E. Lower early (E´) diastolic velocity by echocardiography

61-8. A 65-year-old man presents to your office for evaluation of cardiac amyloidosis. He had been having shortness of breath, and a cardiac MRI was suggestive of amyloid deposition. Which of the following would *not* be indicated to resolve the cause of his amyloid?

A. Endomyocardial biopsy (EMB) with mass spectrometry of the sample
B. Serum protein electrophoresis
C. Serum free light chains
D. No further testing, and referral for palliation
E. Pro-BNP levels

61-9. A 54-year-old woman presents with cutaneous flushing, diarrhea, bronchospasm with wheezing and shortness of breath, and volume overload. You suspect carcinoid heart disease. Which of the following is indicated to make a diagnosis?

A. Coronary angiography
B. Serum serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid levels
C. Serum ACE level
D. Cardiopulmonary exercise testing
E. Fecal evaluation for ova and parasites

61-10. A 73-year-old woman is diagnosed with AL amyloid complicated by cardiac involvement. She is referred to you for cardiac clearance prior to treatment consideration. Which of the following has prognostic value for this patient?

A. Serum NT-proBNP
B. Cardiac troponin T
C. Evaluation of NYHA functional class
D. A and B
E. All of the above

ANSWERS

61-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 61)* Restrictive physiology describes a pattern of ventricular filling in which increased myocardial stiffness causes a precipitous elevation of ventricular pressure matched by a limited increase in volume; the resultant diastolic dysfunction is characterized by a pattern of mitral inflow Doppler velocities

with an increased ratio of early diastolic filling to atrial filling (≥ 2) (option A), decreased E-deceleration time (< 160 ms) (option B), and decreased isovolumetric relaxation time (option C).

61-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 61)* According to the definition of the European Society of Cardiology (ESC), "Restrictive cardiomyopathies are defined as restrictive ventricular physiology in the presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, and normal ventricular wall thickness."[1] According to the definition of the American Heart Association (AHA), "Primary restrictive non-hypertrophied cardiomyopathy is a rare form of heart muscle disease and a cause of heart failure that is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular (LV) wall thickness and atrioventricular (AV) valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function."[2] Both definitions emphasize restrictive ventricular physiology, normal or reduced volume of one or both ventricles, and normal wall thickness.

61-3. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 61)* A physical examination of patients with RCM reflects the elevated systemic and pulmonary venous pressures, with prominent jugular venous pulse and X and Y descents. In the advanced course of the disease, the pulse volume is low, the stroke volume declines, and the heart rate increases. A systolic murmur and filling sound reflect AV valve regurgitation and fast early diastolic filling; a fourth heart sound (S4) can be present. Hepatomegaly, ascites, and peripheral edema are common in decompensated patients. A crescendo-decrescendo murmur that worsens with Valsalva is more consistent with a diagnosis of hypertrophic obstructive cardiomyopathy.

61-4. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 61)* It is crucial to distinguish between RCM and constrictive pericarditis (CP) because RCM typically responds only to medical management and carries a poor prognosis, whereas CP may be curable by pericardiectomy and represents a potentially reversible cause of heart failure.[3] Two-dimensional echocardiography, M-mode, and Doppler blood-flow evaluation including respiratory-related ventricular septal shift (option C), preserved or increased medial mitral annular e´ velocity (option D), and prominent hepatic vein expiratory diastolic flow reversal are independently associated with the diagnosis of CP.[4-6] NT-proBNP levels are significantly higher in RCM than in CP (option A).[7] Kussmaul's sign can be observed in CP or RCM (option B). CP is associated with a prominent x descent and y descent, while RCM is associated a prominent y descent but a blunted x descent (option E).

61-5. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 61)* Familial RCM demonstrates autosomal dominant inheritance in the majority of cases (option A). The *TNNI3* gene that encodes the thin filament troponin I is the most common disease gene responsible for RCM (option B).[8] The typical RCM desminopathy is easily diagnosed by EMB demonstrating desmin immunoreactive granulofilamentous material accumulated within myocytes (option C).[9]

61-6. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 61)* This patient has pseudoxanthoma elasticum (PXE). PXE is a rare autosomal recessive systemic disease of the connective tissue that affects the extracellular matrix of multiple organs. PXE involves the cutaneous, ocular, and cardiovascular systems.[10,11] The cutaneous lesions typically occur in flexural areas (Figure 61-1), and the fundi may show angioid streaks radiating out from the optic discs, subretinal neovascularization, and/or hemorrhage. The cardiovascular manifestations are characterized by the development of arterial calcifications, premature coronary artery disease, peripheral vascular disease, and RCM.[12-17] PXE is caused by homozygous or compound heterozygous mutations in the *ABCC6* (ATP-binding cassette subfamily C member 6) gene that encodes a transmembrane adenosine triphosphate (ATP)-driven organic anion transporter (option C). Options A, B, D, and E are sarcomeric genes for which mutations are associated with hypertrophic cardiomyopathy and dilated cardiomyopathy.

61-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 61)* The cardiac phenotype of HH is characterized by early LV diastolic dysfunction with evolution through LV systolic dysfunction and dilation (option D). The diagnosis of HH is established by genetic testing in patients with elevated serum ferritin (> 300 ng/mL) and transferrin saturation values (> 55%) (option A). The ECG is nonspecific and does not significantly contribute to the diagnosis of HH cardiomyopathy; low QRS complex voltage and nonspecific repolarization abnormalities are uncommon in early phases; conduction disease may be present (option B). With cardiac MRI, the T2* method is highly sensitive and specific and is especially useful for detecting, grading, and monitoring iron deposition.[18-20] Patients demonstrating a T2* higher than 20 ms are at low risk for developing heart failure (HF); T2* between 10 and 20 ms indicates the presence of cardiac iron deposition and an intermediate risk of HF; and a T2* less than 10 ms indicates high risk of HF and a need for immediate chelation therapy.[21] Other modalities can suggest HH as well. In a multivariable analysis, echocardiographic spectral tissue Doppler lower early (E´) diastolic velocity was independently associated with hemochromatosis.[22]

61-8. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 61)* The gigantic scientific achievements in advancing our understanding of the biomolecular bases of amyloidogenic processes, and the development of novel drugs that target the different types of amyloidosis, are rapidly helping to change the fate of those with an ominous disease that until recently was hopeless and that is now a prototype of a successful model of precision and personalized medicine (option D). In the patient with unexplained LV hypertrophy and clinical suspicion for amyloidosis, biochemical testing should include evaluation for monoclonal protein production, serum immunofixation and electrophoresis, and serum free light chain

assay (options B and C).[23-26] EMB has the dual advantage of being able to demonstrate amyloid deposition and to allow for the immune characterization of amyloidogenic protein. Recently, mass spectrometry–based proteomics have been introduced as a valuable tool for amyloid typing, with the advantage of not being antibody dependent. This can be performed on whole tissues or after laser capture microdissection of Congo red–positive areas (option A).[27] A high concentration of NT-proBNP allows the detection of AL amyloidosis at presymptomatic stages with a diagnostic sensitivity of 100%. Thus, screening with NT-proBNP has been advocated in patients at risk of developing AL amyloidosis (ie, patients followed by hematologists for monoclonal gammopathy of undetermined significance and altered circulating free light chain ratio).[28] Further, serum NT-proBNP levels are prognostic (option E).

61-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 61)* Carcinoid heart disease (Hedinger syndrome) is a rare condition that affects the right side of the heart in up to 60% of patients with neuroendocrine tumors (NETs) and systemic carcinoid syndrome (CS).[29] CS is caused by vasoactive substances secreted by NET cells; 5-hydroxytryptamine (serotonin) is the predominant peptide, followed by prostaglandins, histamine, bradykinin, tachykinins, and transforming growth factor-β (TGF-β). Both the tachykinins and TGF-β display profibrogenic properties inducing fibromyxoid plaques that affect the right ventricular endocardium, the ventricular side of the tricuspid valve apparatus (leaflets, chordae, and papillary muscles), the ventricular site of the pulmonary valve, and less commonly, the pulmonary artery. Serum serotonin, platelet serotonin, and urinary 5-hydroxyindoleacetic acid levels are elevated (option B).[30] The other options provided are helpful to exclude other causes of heart failure such as coronary artery disease (option A), shortness of breath (option D), sarcoid (option C), and diarrhea (option E). However, none of these are specific to the diagnosis of carcinoid.

61-10. **The answer is E.** (*Hurst's The Heart, 14th Edition, Chap. 61)* With AL amyloid, the criteria for evaluating both hematologic response (decreased amyloidogenic light chains) and organ response (improvement of organ function) are well established and graded. Treatment options depend on eligibility for autologous stem cell transplantation as well as on individual criteria to evaluate the tolerability of chemotherapeutic agents, including novel agent-based treatments with proteasome inhibitors, such as bortezomib, or immunomodulatory drugs such as thalidomide, lenalidomide, and pomalidomide.[31] Elevated cardiac biomarkers (NT-proBNP > 5000 ng/L, cardiac troponin T > 0.06 ng/mL) are considered exclusion criteria for stem cell transplantation (options A and B).[32] Standard chemotherapy requires dose reductions in stage IIIb patients (option C). Non-chemotherapy approaches to the treatment of AL amyloidosis are now rapidly expanding.

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CHAPTER 62

Arrhythmogenic Cardiomyopathy

Jacqueline Joza

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

62-1. A 35-year-old man experiences a sudden-onset syncope while playing soccer, and you are consulted by the emergency department. All of the following represent *major* criteria from the updated Task Force criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) *except*:

A. Regional right ventricular akinesia on transthoracic echo
B. Inverted T waves in leads V1 and V2 in the absence of complete right bundle branch block
C. Nonsustained ventricular tachycardia with LBBB morphology and superior axis
D. Identification of a pathogenic mutation
E. Epsilon wave

62-2. Which of the following regarding the prevalence of ARVC in the general population and the prevalence of clinical manifestations in men versus women respectively is *correct*?

A. 1/1000 – 1/5000; males > females 5:1
B. 1/5000 – 1/10,000; males > females 5:1
C. 1/1000 – 1/5000; males > females 3:1
D. 1/1000 – 1/5000; females > males 3:1
E. 1/5000 – 1/10,000; females > males 5:1

62-3. Classic right-sided ARVC is a genetic disease of the intercalated disks. Which of the following regarding intercalated disks is *incorrect*?

A. Intercalated disks are the units of electromechanical continuity between cardiac myocytes
B. The sarcomere constitutes a component of the intercalated disk
C. Gap junctions constitute a component of the intercalated disk
D. Adherens junctions constitute a component of the intercalated disk
E. Desmosomes constitute a component of the intercalated disk

62-4. A 30-year-old man presents to your clinic with bilateral lower extremity edema that has been progressive over the last few months. His physical exam reveals an elevated jugular venous pressure. In what percentage of ARVC cases do patients present with this physical finding?

A. 5% to 10%
B. 20% to 30%
C. 30% to 40%
D. 50% to 60%
E. 70% to 80%

62-5. A 25-year-old man presents to the hospital with rapid-onset palpitations. These lasted for approximately 10 minutes and were associated with dizziness. No documentation of a sustained arrhythmia was noted on monitoring, but he is noted to have frequent premature ventricular contractions of RBBB morphology, superior axis, and negativity in lead I. On physical exam, you note thickening of the skin on the palms of his hands. A transthoracic echocardiogram is performed and reveals left ventricular (LV) dilatation and dyskinesia. This constellation of findings is *most* consistent with:

A. Anderson–Tawil syndrome
B. Naxos disease
C. Brugada syndrome
D. Catecholaminergic polymorphic ventricular tachycardia

E. Caravajal syndrome

62-6. After you suspect ARVC in a 40-year-old woman, a cardiac MRI is performed. The conclusion in the final report notes, "an affected triangle of dysplasia, a pattern most consistent with ARVC. Correlate clinically." The *triangle of dysplasia* refers to the combination of which of the following structures?

A. Epicardial subtricuspid region, cavotricuspid isthmus, and right ventricular (RV) outflow tract
B. Left, right, and noncoronary cusps of the aortic valve
C. RV apex, interventricular septum, and LV apex
D. Epicardial subtricuspid region, RV basal anterior wall, and posterolateral left ventricle
E. Basal mitral valve region, RV basal anterior wall, and LV apex

62-7. A 45-year-old woman has a diagnosis of nonischemic cardiomyopathy, with signs and symptoms of predominantly right-sided heart failure. You suspect ARVC based on a few minor criteria. She cannot undergo a cardiac MRI due to significant renal dysfunction. Genetic testing does *not* reveal any relevant mutations. You consider endomyocardial biopsy. Which of the following statements is *incorrect* about the use of endomyocardial biopsy in patients with suspected ARVC?

A. The loss of normal RV myocardium with evidence of fibrofatty infiltration supports the diagnosis
B. The risk of cardiac perforation is equivalent for RV septal wall and RV free wall biopsies
C. RV septal wall or LV biopsies are not usually helpful
D. There is a high rate of false negatives and low sensitivity
E. The diagnostic yield may be improved by using electroanatomic voltage mapping to guide biopsy

62-8. You refer your patient with probable ARVC to a specialized center for genetic testing. Which of the following statements is *incorrect*?

A. The predominant inheritance pattern is autosomal recessive with variable penetrance and expressivity, although an autosomal dominant pattern has been described
B. Class I recommendation for mutation-specific screening of family members following the identification of a pathogenic mutation in the proband
C. Class IIa recommendation for genetic testing of confirmed cases of ARVC
D. Class IIb recommendation for genetic testing of borderline cases of ARVC
E. Class III recommendation for genetic testing of patients who fulfill only a single minor Task Force criterion

62-9. All of the following put a clinically confirmed ARVC patient at a higher risk for sudden cardiac death *except*:

A. Unexplained syncope
B. Older age
C. Left ventricular dysfunction
D. Presence of heart failure
E. Sustained ventricular arrhythmias

62-10. A 25-year-old man presents with frequent premature ventricular contractions (PVCs). Twenty-four-hour Holter monitoring reveals a PVC burden of 18%. The morphology of the PVCs is consistent with a left bundle branch pattern with a transition at V5, with an inferior access suggesting an origin at the right ventricular outflow tract (RVOT). Which of the following is more suggestive of ARVC as opposed to RVOT-ventricular tachyardia (VT)?

A. Good response to verapamil
B. Endocardial ablation suppresses the arrhythmia
C. RVOT-VT is difficult to induce by programmed ventricular stimulation
D. QRS duration during VT is shorter (< 120 ms in lead I)
E. A single VT morphology with LBBB pattern and an inferior axis is commonly recorded

ANSWERS

62-1. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 62)* Inverted T waves in the right precordial leads must be present past V2 to constitute a major criterion: including V1, V2, and V3 or beyond in patients > 14 years of age in the absence of complete right bundle branch block. Otherwise, inverted T waves in leads V1 and V2 only is a *minor* finding. Originally dating back to 1994, the Task Force criteria for ARVC were modified in 2010 to improve the diagnosis and management of ARVC. The criteria were aimed at facilitating the recognition and interpretation of the clinical and pathologic features of ARVC, and the modified criteria incorporated new knowledge on the genetic basis of the disease, improving diagnostic sensitivity and maintaining diagnostic specificity. The structural, histologic, ECG, arrhythmic, and genetic features are structured in major and minor criteria. The Task Force document formally introduced the

biventricular variant and the left dominant variant.[1] Options A and C through E represent major criteria from the updated Task Force criteria. A definite diagnosis requires two major, or one major and two minor, or four minor criteria from different categories to be fulfilled.

62-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 62)* The prevalence of ARVC is estimated to range from 1 in 1000 to 1 in 5000 in the general population.[2-5] A small proportion of patients progress to LV dysfunction; in these patients, the clinical hallmark remains ventricular arrhythmias.[6] The prevalence of clinical manifestations of the disease is higher in males than in females (3:1).[7-8] The disease usually manifests in young adults; of 439 index patients described by Groeneweg et al,[7] only 4 presented before the age of 13 years, while none presented before the age of 10 years. The reason could be related to the completion of intercalated disk maturation or the need for prolonged exposure to exercise before the disease becomes manifest.[7]

62-3. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 62)* Intercalated disks are highly specialized cell-cell junctions; they are the units of electromechanical continuity between cardiac myocytes (option A)[9] and are constituted of gap junctions (option C), adherens junctions (option D), and desmosomes (option E). In *dilated* cardiomyopathy, genetic abnormalities in the sarcomere may be causal for disease (option B). *Gap junctions* (nexus, communicating junctions) are located in the lateral parts of the intercalated disks and mediate ionic traffic between the adjacent cells and provide the basis for functional cell coupling. Key structural proteins are connexins; the connexins predominantly expressed by cardiac myocytes are Cx43, Cx40, and Cx45. *Adherens junctions* (fasciae adhaerentes) are located in the transverse parts of the intercalated disks where the actin filaments of the sarcomeres are anchored and connected with the plasma membrane. This anchorage provides the intercellular "mechanical continuity" between the myocytes supporting the transmission of force between cells and synchronous contraction and relaxation. *Desmosomes* (maculae adhaerentes) are located in both the transverse and lateral parts of the intercalated disks: they reinforce the adherens junctions and fix adjacent cells. Desmosomes bind desmin on the intracellular side, span the cell membrane, and bind adjacent desmosomes on the extracellular side. Desmosome-forming proteins include plakophilin-2 (PKP2), desmoglein 2 (DSG2), desmocollin 2 (DSC2), plakoglobin (JUP), and desmoplakin (DSP).

62-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 62)* It is relatively uncommon for patients with ARVC to present with symptoms of right heart failure. Those with ARVC typically present between the second and fifth decades of life.[10] Symptoms are heterogeneous but most commonly reflect the presence of ventricular arrhythmias, which can range from isolated premature ventricular contractions to sustained ventricular tachycardia. Supraventricular arrhythmias also occur in 14% of ARVC patients, with atrial fibrillation being the most frequently reported.[11] In a study of 129 probands, symptoms on presentation included palpitations in 56%, dizziness in 29%, syncope in 26%, chest pain in 19%, and cardiac arrest in 22%.[12] Symptoms related to right heart failure are present in 6% (option A).[13] These findings are consistent with other studies.[4,10,14-15]

62-5. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 62)* Naxos disease (option B) and Carvajal syndrome (option E) are distinctive forms of ARVC that are inherited in an autosomal recessive manner in association with extracardiac manifestations, including wooly hair and plantopalmar keratoderma (thickening of the skin on the palms and soles).[16] Carvajal syndrome is a variant of Naxos disease with predominant LV involvement (option E) as noted in the question stem. Premature ventricular contractions with a right bundle branch morphology typically originate from the left ventricle, and with a superior axis and negativity in lead I they suggest an anterolateral LV origin. Anderson–Tawil syndrome, or long QT type 7 (option A), is characterized by periodic paralysis, ventricular arrhythmias, and prolonged QT interval (specifically polymorphic ventricular tachycardia and premature ventricular contractions), and anomalies including low-set ears, widely spaced eyes, small mandible, fifth-digit clinodactyly, syndactyly, short stature, and scoliosis. Brugada syndrome (option C) can mimic ARVC because both conditions may demonstrate RV conduction delay, and mutations typically recurrent in Brugada syndrome have been found in ARVC patients and vice versa. The demonstration of the presence of structural abnormalities supports the diagnosis of ARVC. Catecholaminergic polymorphic ventricular tachycardia (option D) is another inherited arrhythmia characterized by episodic syncope that occurs during exercise or acute emotion in individuals without structural cardiac abnormalities; the underlying cause is the onset of fast ventricular tachycardia (bidirectional or polymorphic).

62-6. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 62)* The triangle of dysplasia involves the epicardial subtricuspid region, RV basal anterior wall, and posterolateral LV, with the RV apex being mostly spared.[17] Historically, the *triangle of dysplasia* referred to the RV apex, the RV inflow tract, and the outflow tract and was thought only to be present in advanced stages of the disease.[17-18] Although cardiac MRI has emerged as the preferred imaging modality for ARVC, it is also one of the most common reasons for misdiagnosis. Common pitfalls include misinterpretation of variants of normal RV wall motion and inaccurate interpretation of intramyocardial fat infiltration.[19] It is important to note that in pediatric ARVC patients, intramyocardial fat infiltration and myocardial fibrosis are uncommon findings by CMRI.[20]

62-7. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 62)* An increased risk of cardiac perforation and tamponade is present with a biopsy at the RV free wall. Endomyocardial biopsy is rarely performed but may be helpful in establishing a diagnosis of ARVC when the etiology of cardiomyopathy or structural changes are unclear. The American College of Cardiology/American Heart Association consensus guidelines give a Class IIa (level of evidence C) indication for

endomyocardial biopsy in patients with heart failure when a specific diagnosis is suspected that would influence therapy.[21] The demonstration of fibrofatty infiltration with loss of normal RV myocardium supports the diagnosis (option A).[22-23] There is a high rate of false negatives and low sensitivity as a result of the patchy nature of disease and the predilection for specific areas of the RV (option D).[23] Thus, conventional RV septal wall or LV biopsies are not helpful because these areas are commonly spared. Diagnostic yield may be improved by using electroanatomic voltage mapping to guide biopsy (option E).[24]

62-8. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 62)* The predominant inheritance pattern is autosomal dominant with variable penetrance and expressivity, although an autosomal recessive inheritance pattern has been described with the cardiocutaneous syndromes of Naxos disease and Carvajal syndrome (option A).[16] Approximately 60% of probands will have an identifiable pathogenic mutation.[7] Identification of a pathogenic mutation on genetic testing is a major criterion for the diagnosis of ARVC.[22] Currently, one of the major roles of genetic testing in ACM is for mutation-specific screening of family members following the identification of a pathogenic mutation in the proband (option B). The Heart Rhythm Society and European Heart Rhythm Association expert consensus guidelines give this indication a Class I recommendation.[25] Although genetic testing may be useful for confirmed cases (Class IIa)(option C) or considered for borderline cases (Class IIb)(option D), it is not recommended (Class III)(option E) for those fulfilling only a single minor Task Force criterion.[25] The clinical genetic and molecular workup in the proband and his or her family should be performed as in other familial cardiomyopathies and include clinical and genetic screening of first-degree relatives. A positive family history of ARVC is a risk factor for disease, with over a third of family members of affected individuals developing disease.[7,26-27] The cumulative 5-year and 10-year probabilities of developing ARVC in first-degree family members are 7% and 21%, respectively, with siblings of probands having a threefold higher risk compared to parents or children.[26] Pathogenic mutations are identified in 36% to 72% of selected family members, and up to 40% of these individuals will fulfill Task Force criteria for ARVC.[7,28] Disease will still occur in 18% of those who are mutation negative.[7] Also, the presence of symptoms or the occurrence of more than one genetic variant in family members increases the likelihood of Task Force criteria–confirmed disease.[7,26,28] The constellation of findings highlights the complexity of the genetics of ARVC and firmly supports the screening of family members of affected individuals.

62-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 62)* There are no prospective, randomized clinical trials to identify who has the highest risk for sudden cardiac death (SCD) and would benefit most from an implantable cardioverter-defibrillator (ICD). However, based on observational studies in ARVC patients, a history of prior cardiac arrest, sustained ventricular arrhythmias (option E), unexplained syncope (option A), *younger* age (option B), extensive RV dysfunction, LV dysfunction (option C), and the presence of heart failure (option D) are independently associated with subsequent ventricular arrhythmias.[29-37] In a study of patients receiving ICDs for definite or probable ARVC, 48% received an appropriate ICD therapy during a mean follow-up of 5 years.[38] The only independent predictors of ICD therapy were the presence of nonsustained VT and inducibility at electrophysiology study. The role of electrophysiology study for risk stratification is unclear because studies provide conflicting evidence.[31,33,38,39]

62-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 62)* Differential diagnoses of ARVC include idiopathic RV outflow tract VT (RVOT-VT), sarcoidosis, myocarditis, dilated cardiomyopathy, Brugada syndrome, athlete's heart, RV infarction, Chagas disease in endemic areas, pulmonary hypertension, and congenital heart disease. Idiopathic RVOT-VT should be differentiated from early ARVC, when gross structural abnormalities are absent. Differential diagnosis is based on clinical data (Task Force criteria), pathology data (endomyocardial biopsy), and imaging data such as echocardiography and cardiac MRI or positron emission tomography demonstrating or excluding scars and inflammation.[40,41] In general, in RVOT-VT: (1) Twelve-lead surface ECG and SAECG are normal during sinus rhythm, (2) A single VT morphology with LBBB pattern and an inferior axis is commonly recorded (option E),[42] (3) QRS duration during VT is *longer* (≥ 120 ms in lead I) (option D),[43] (4) a notched QRS and precordial transition in lead V6 recur in ARVC but not in RVOT-VT,[44] (5) RVOT-VT is difficult to induce by programmed ventricular stimulation (option C),[41] (6) patients with idiopathic RVOT-VT are good responders to verapamil (option A),[41] and (7) endocardial ablation suppresses the arrhythmia in RVOT-VT (option B).[41]

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CHAPTER 63

Myocarditis

Ravi Karra

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

63-1. A 42-year-old man presents with two weeks of dyspnea on exertion, pedal edema, and orthopnea. One month ago, he had a mild febrile illness. Echocardiography confirms reduced left ventricular (LV) systolic dysfunction. Serologies are suggestive of a viral myocarditis secondary to coxsackievirus B3. Which of the following is *not true* regarding coxsackie-mediated viral myocarditis?

A. Myocardial infection is initiated by the transmembrane coxsackievirus-adenovirus receptor (CAR)
B. Cell damage is induced by direct cytotoxicity and is mediated by viral proteinases
C. Patients with defects of dystrophin and dysferlin demonstrate increased susceptibility to myocardial CV-B3 infection
D. The early innate immune response results in direct myocyte injury
E. All of the above are true

63-2. Which of the following is *not* associated with a poor outcome after a diagnosis of viral myocarditis?

A. New York Heart Association (NYHA) classes III to IV symptoms at 6 months
B. Biventricular dysfunction at the time of diagnosis
C. The presence of late gadolinium enhancement (LGE)
D. High rate of cardiomyocyte apoptosis on biopsy
E. Presentation with heart failure symptoms

63-3. A 67-year-old woman received an orthotopic heart transplant 6 months ago. She presents with generalized malaise and new-onset heart failure. Echocardiography confirms allograft dysfunction, and serum PCR demonstrates human cytomegalovirus (HCMV) viremia. Which of the following is *true* regarding HCMV myocarditis?

A. Myocardial infection with HCMV is usually observed in immunocompetent hosts
B. Myocardial pathology is notable for an infiltrate by eosinophils
C. Viral infection is restricted to myocytes
D. In immunosuppressed patients, infection often occurs by reactivation of a latent infection
E. First-line treatment is with acyclovir

63-4. A 43-year-old woman presents with new-onset heart failure, generalized myalgias, and periorbital swelling. A careful history indicates that she has a predilection for eating raw pork. Which of the following is *not true* regarding *Trichinella* myocarditis?

A. Infection of striated muscles occurs in the first phase of infection
B. A complete blood count can show hypereosinophilia
C. A muscle biopsy would show larvae
D. Treatment is albendazole
E. All of the above

63-5. Which of the following is *true* of cardiac MRI (CMR) findings of acute myocarditis?

A. CMR findings are diagnostic but not prognostic
B. LGE is present in a noncoronary distribution
C. CMR would show decreased myocardial edema
D. Early gadolinium enhancement is normal
E. The presence of a pericardial effusion increases the diagnostic accuracy of CMR for myocarditis

63-6. A 20-year-old college student presents with acute decompensated heart failure. His history is notable for a recent study

abroad in South America. Which of the following is *true* for Chagas myocarditis?

A. The causal agent is *T. gondii*
B. Myocarditis is part of the acute phase
C. The chronic phase can lead to chronic cardiomyopathy
D. Treatment is with trimethoprim-sulfamethoxazole
E. Both B and C are correct

63-7. A 48-year-old woman from Wisconsin presents with syncopal episodes. Approximately three weeks earlier she had been camping and noted a bulls-eye rash. Which of the following is *true* of Lyme carditis?

A. Lyme carditis typically manifests at the same time as erythema migrans
B. Atrioventricular block can occur within a week of infection
C. Patients often recall erythema migrans at the time of presentation
D. Myopericarditis results in focal wall motion abnormalities
E. Both A and D are correct

63-8. A 38-year-old man presents with acute cardiogenic shock and incessant ventricular arrhythmias. After he is stabilized with mechanic circulatory support, an endomyocardial biopsy is performed. The results are shown in Figure 63-1. Which of the following is *true* of this condition?

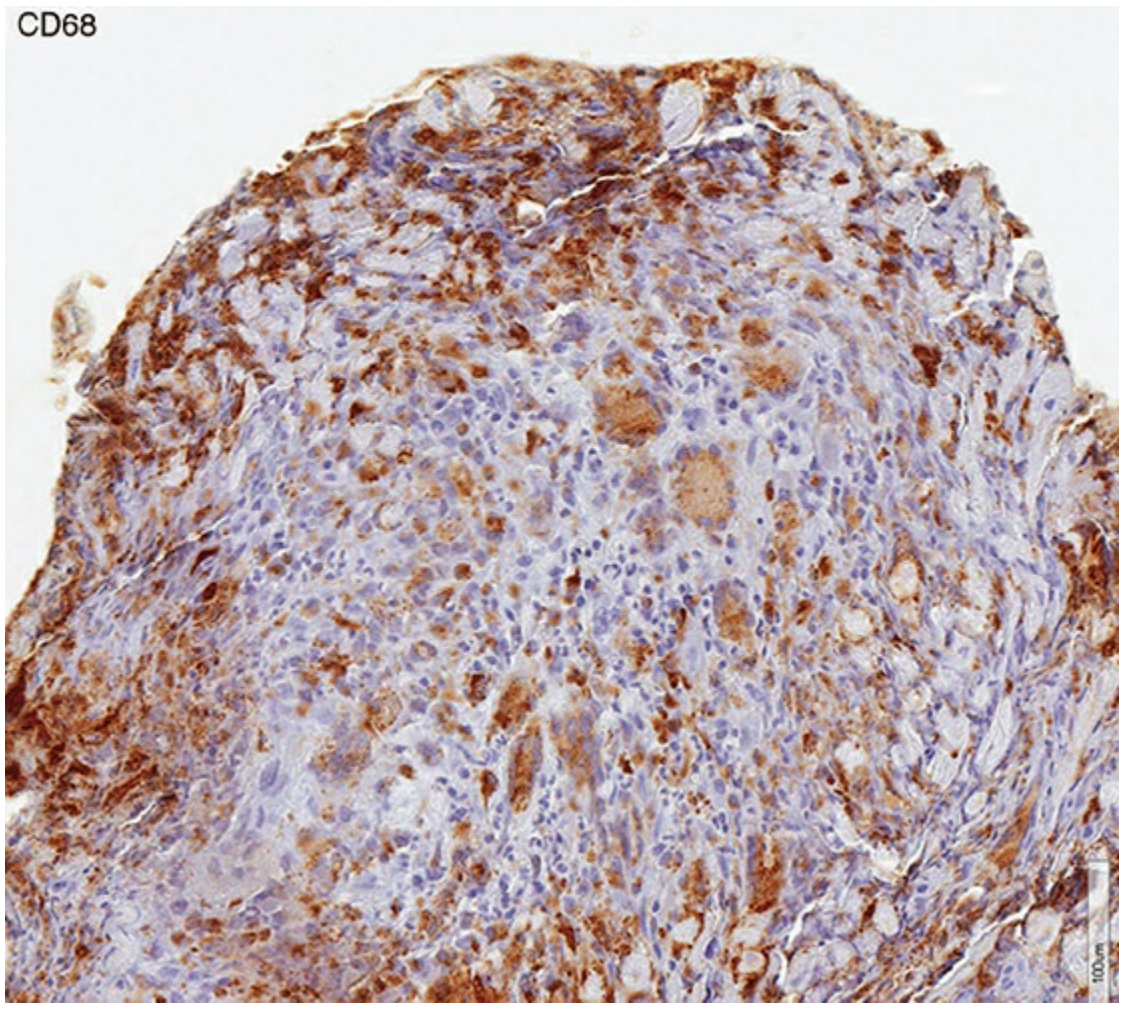

FIGURE 63-1 Biopsy from patient in question 63-8 after staining with anti-CD68.

A. The prognosis is excellent
B. Treatment with muromonab-CD3 may be of benefit
C. Following transplantation, recurrence in the donor heart can occur
D. Mechanical support often requires biventricular support
E. Both C and D are correct

63-9. A 47-year-old woman presents with wheezing and syncope. A chest x-ray shows hilar lymphadenopathy, and an echocardiogram reveals left ventricular dysfunction. Which of the following is *not true* about sarcoidosis?

A. The pathologic hallmark is noncaseating epithelioid granulomas in the affected tissues
B. Endomyocardial biopsy is both sensitive and specific for diagnosing cardiac sarcoidosis
C. Patients with cardiac sarcoid and normal LV ejection fraction (LVEF) continue to be at risk for arrhythmia
D. LGE by cardiac MRI corresponds with biopsy findings of granuloma
E. Cardiac PET can be used to assess arrhythmogenic risk

63-10. Which of the following is *true* of cardiac involvement with hypereosinophilic syndrome (HES)?

A. Affected patients often present with acute decompensated heart failure during the acute necrotic stage
B. During the thrombotic phase, oral anticoagulation is appropriate to prevent major embolic events
C. Late cardiac involvement results in a restrictive cardiomyopathy
D. Both B and C are true

E. All of the above

ANSWERS

63-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 63)* The cardiotropic coxsackievirus B3 (CV-B3) is one of the most common causes of myocarditis.[1] The myocardial infection is initiated by the transmembrane CAR; the ablation of CAR blocks viral affliction of myocardial cells and inflammation in the myocardium in experimental models (option A).[2] In CV-B3–infected myocytes, the cell damage is induced by direct cytotoxicity and mediated by viral proteinases (option B).[3] Patients with defects of dystrophin and dysferlin demonstrate increased susceptibility to myocardial CV-B3 infection by enhancing viral propagation to adjacent cardiomyocytes and disrupting membrane repair function (option C).[4-6] In viral infections, the early innate immune response provides the first defense mechanism and is mediated by cytokines. However, the late adaptive immune response contributes to the myocardial lymphocyte infiltration that must clear virus-infected cardiac myocytes in CV-B3 myocarditis and endothelial cells in parvovirus B19 myocarditis. Although this mechanism clears the virus, it also results in myocyte injury (option D).

63-2. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Predictors of outcome vary in different myocardial biopsy studies. Persistence of New York Heart Association (NYHA) classes III to IV, left atrium enlargement, and improvement in LVEF at 6 months emerged as independent predictors of long-term outcome in one study (option A).[7] Biventricular dysfunction at diagnosis was the main predictor of death/transplantation in another study (option B).[8] High rates of cardiomyocyte apoptosis were associated with functional recovery at 1 year (option D).[9] The presence of LGE emerged as the best independent predictor of all-cause and cardiac mortality, whereas the initial presentation with heart failure was a predictor of incomplete long-term recovery (options C and E).[10]

63-3. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Myocardial infection with HCMV is more commonly observed in immunocompromised hosts (option A). The myocardial pathology is characterized by T-cell inflammatory infiltrate and by the presence of typical intranuclear amphophilic inclusion bodies that specifically immune-stain with anti-HCMV antibodies (option B). The virus infects both myocytes and endothelial cells (option C). Children become infected early in life in developing countries, whereas up to 80% of the adult population is infected in developed nations. The course of primary infection is usually mild or asymptomatic in immunocompetent hosts as HCMV establishes a latent but persistent infection reflecting the inability of the immune system to clear the infection; immune evasion mechanisms allow infected cells to escape both innate and adaptive effector immunity.[11] In immunosuppressed patients (eg, solid organ or bone marrow transplantation recipients), the infection can be reactivated to result in systemic and organ infection; the heart is a possible target for tissue infection, especially in heart transplant recipients (option D). For herpes simplex virus types 1 and 2 and for varicella-zoster virus, acyclovir (or its prodrug valacyclovir) and famciclovir have greatly reduced the burden of disease and have demonstrated a remarkable safety record. Ganciclovir and valganciclovir remain the drugs of choice for HCMV infection in immunocompromised hosts (option E).[12,13]

63-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Eosinophilic myocarditis is a possible complication in patients with trichinosis, a zoonosis caused by nematodes of the genus *Trichinella*. *Trichinella* is endemic in the areas with unregulated slaughter of pigs and particularly in areas where these are in contact with wild animals.[14,15] Symptoms of trichinosis occur in two stages. Intestinal infection is the first stage and develops 1 to 2 days after consuming contaminated meat. The most common symptoms are nausea, diarrhea, abdominal cramps, and fever. The second stage corresponds to larval invasion of muscles and starts after about 7 to 15 days (option A). The diagnosis of trichinellosis should be based on clinical findings; pathology findings of muscle and/or EMB detecting larvae; laboratory findings of specific antibody response by indirect immunofluorescence, ELISA, or Western blot; hypereosinophilia (1000 eosinophils/mL) and/or increased total IgE levels; increased levels of muscle enzymes; and investigation of the possible source and origin of infection (options B and C).[14-16] When the diagnosis is proven, the treatment is based on antihelminthic drugs, such as albendazole or mebendazole, and supportive therapy in patients with heart failure (option D).[15]

63-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 63)* CMR provides a detailed morphofunctional description of ventricular involvement and offers important prognostic information.[17] There is a substantially lower risk of events in patients with suspected myocarditis but normal CMR findings (option A).[18] According to the Lake Louise CMR criteria, acute myocarditis is associated with (1) increased regional or global myocardial signal intensity in T2-weighted images (indicating myocardial edema); (2) increased global myocardial early gadolinium enhancement (EGE) ratio between myocardium and skeletal muscle in T1-weighted images (supporting hyperemia/capillary leakage); and (3) at least one focal lesion with nonischemic distribution in LGE T1-weighted images (suggestive of cell injury/necrosis) (options B through D) .[17] The diagnostic accuracy does not increase with the addition of pericardial effusion (option E).[19]

63-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Chagas disease (CD) is caused by the protozoan parasite

T. cruzi (option A).[20] In the acute phase, the disease can manifest with myocarditis, conduction system abnormalities, and pericarditis (option B). In untreated patients, the disease progresses to the chronic phase.[21,22] In the chronic phase, illness can be severe, with LV dilation and dysfunction, aneurysm, congestive heart failure, thromboembolism, ventricular arrhythmias, and sudden cardiac death, which is the leading cause of death in patients with Chagas heart disease (option C).[23] Two antiparasitic drugs are available for the treatment of CD: benznidazole and nifurtimox (option D).[23,24]

63-7. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Lyme carditis is rare and typically manifests 2 to 5 weeks after the erythema migrans (option A). Patients who develop Lyme disease may first manifest atrioventricular block at 14 days (range, 2–24 days) after the onset; only one-third of patients recall the erythema migrans (options B and C).[25,26] Myopericarditis can present with chest pain, dyspnea, or syncope, and the signs and symptoms of Lyme myopericarditis can mimic acute coronary syndrome, with ECG ST-segment alterations and elevated peripheral blood cardiac biomarkers.[26] In such cases, echocardiography demonstrates diffuse ventricular hypokinesis rather than the focal wall motion abnormalities expected with an acute coronary syndrome (option D).[25]

63-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 63).* The biopsy in Figure 63-1 shows giant cells consistent with a diagnosis of giant cell myocarditis. GCM carries a poor prognosis, with a median survival of 5.5 months from the onset of symptoms; in one report, 89% of patients either died or required cardiac transplantation, and another report showed 1-year survival of 30% to 69% (option A).[27,28] Mechanical circulatory support for bridge to recovery is rare, whereas it is more commonly used as bridge to transplant; biventricular support is often required (option D).[29,30] Heart failure treatment includes standard regimen with beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists as per guidelines.[31,32] The management of GCM has also included the use of muromonab-CD3, pulse steroids, and varying combinations of azathioprine, cyclosporine, and prednisone monitored with surveillance EMB (option B). Post-transplant survival is similar to that of patients who underwent heart transplantation for other diseases; however, GCM may recur in 10% to 50% of transplanted hearts (option C).[27,28,33]

63-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Sarcoidosis is a chronic multisystem inflammatory disease of unknown etiology that carries the pathologic hallmark of noncaseating epithelioid granulomas in the affected tissues (option A).[34] CMR offers a high sensitivity and specificity for the assessment of cardiac involvement. Whereas T2 hyper-enhancement identifies early edema, the LGE in a nonvascular distribution supports myocardial scarring. LGE correlates with cardiac biopsy findings of granulomatous inflammation (option D).[35,36] In patients with preserved LVEF and extracardiac sarcoidosis, major adverse cardiac events, including death and ventricular tachycardia, are associated with a greater LGE and right ventricular involvement; preserved LVEF does not exclude the risk for adverse events (option C).[37] Additionally, PET studies have proved to be clinically useful for diagnostic and prognostic information, especially for the risk of ventricular arrhythmias in patients with cardiac sarcoidosis. The presence of focal perfusion defects (rubidium-82 imaging in this report) and FDG uptake identified a higher risk of death or ventricular tachycardia (option E).[38] Although EMB has low sensitivity (19%–32%) as a result of the inherent sampling limitation for focal epithelioid granulomas, it offers high specificity for the diagnosis (option B).[39]

63-10. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 63)* Cardiac involvement is a major cause of morbidity and mortality in HES.[40] The cardiac pathology is divided into three stages: (1) an acute necrotic stage, (2) a thrombotic stage, and (3) a fibrotic stage. The early, acute necrotic stage is characterized by eosinophilic and lymphocyte infiltration; in the myocardial interstitium, eosinophils undergo degranulation with release of biologically active factors that cause myocyte injury. Clinical presentation may comprise nonspecific manifestations. Patients may *infrequently* present with acute heart failure or cardiogenic shock at onset (option A).[41] In the thrombotic stage, mural thrombi develop on the endocardium. Thromboembolic complications occur in up to 30% of patients; oral anticoagulation is appropriate to prevent major embolic events (option B). In the scarring, fibrotic stage, both ventricles and subvalvular structures of the AV valves are involved. The functional phenotype is typically restrictive as in endomyocardial fibrosis (option C).

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CHAPTER 64

The Athlete and the Cardiovascular System

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

64-1. A 56-year-old woman presents for an exercise stress test. She completes 10.2 METS. The acute response to aerobic exercise includes increases in all of the following *except*:

A. Maximum oxygen consumption
B. Cardiac output
C. Stroke volume
D. Systolic blood pressure
E. Peripheral vascular resistance

64-2. A 29-year-old professional athlete is referred to you with left ventricle (LV) hypertrophy on his echocardiogram. Which criteria favor hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy over the athletic heart syndrome?

A. LV wall thickness ≥ 16 mm
B. LV hypertrophy with an unusual distribution (heterogeneous, asymmetric, or sparing the anterior septum)
C. Persistence of hypertrophy after physical deconditioning
D. LV end-diastolic diameter > 70 mm
E. All of the above

64-3. A 29-year-old Olympic canoeist is referred to you by her family physician with an abnormal ECG pattern. Which ECG abnormality is *not* commonly seen on the ECGs of elite endurance athletes?

A. Incomplete left bundle branch block
B. Early repolarization
C. Increased QRS voltages with diffuse T-wave inversion and deep Q waves
D. Mildly increased P-wave amplitude
E. Increased voltages consistent with right ventricular and LV hypertrophy

64-4. An endurance runner is referred to you by his family physician after a routine ECG shows an arrhythmia. Which of the following arrhythmias are *not* commonly noted among elite athletes?

A. Sinus arrhythmia and sinus bradycardia
B. First-degree and Mobitz type II second-degree AV block
C. Frequent premature beats and couplets
D. Nonsustained ventricular tachycardia
E. Junctional rhythm

64-5. A 22-year-old college football player has a cardiac arrest and sudden death during a championship game. Which of the following statements is *not true* about sudden death in athletes?

A. Sudden death occurs with an incidence of 1 to 2 per 100,000 athletes (12 to 35 years of age) per year
B. The frequency of sudden death is fourfold lower in female athletes
C. In athletes younger than 35 years, inherited diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy, and congenital coronary artery abnormalities of wrong sinus origin are the most common causes of sudden death
D. In athletes older than 35 years, atherosclerotic coronary artery disease is the most common cause of death
E. All of the above are true

64-6. A 17-year-old athlete is referred to you for assessment after a cardiac arrest requiring resuscitation during a high school basketball game. Which of the following statements is *true* about HCM?

A. HCM is the single most common cause of sudden cardiac arrest in athletes in the United States
B. HCM accounts for about one-third of sport-related sudden fatalities
C. HCM is a genetically transmitted disease characterized by genotypic and phenotypic heterogeneity
D. LV hypertrophy is characteristically asymmetric with a variety of patterns of wall thickening
E. All of the above are true

64-7. Which of the following statements is *not true* regarding arrhythmogenic right ventricular cardiomyopathy?

A. Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disorder characterized pathologically by fibrofatty replacement of right ventricular myocardium
B. It is an uncommon cause of sudden death on the athletic field in the United States
C. Clinical manifestations include ECG depolarization and repolarization abnormalities commonly localized to right precordial leads
D. Myocardial aneurysms are localized to the posterobasal, apical, and outflow tract regions
E. Sudden death during physical exercise is likely related to hemodynamic factors, increased right ventricular volume and wall stress, and enhanced sympathetic tone that culminate in ventricular fibrillation

64-8. A 15-year-old lacrosse player who recently had a normal history and physical with his family physician collapses during a game. Which of the following statements is *true* regarding sudden death in athletes with no evidence of structural heart disease?

A. Approximately 10% of young athletes who die suddenly with exercise have no evidence of structural heart diseases
B. Sudden death may be due to ventricular pre-excitation
C. Sudden death may be due to inherited cardiac ion channelopathies, including long QT syndrome, short QT syndrome, and Brugada syndrome
D. Sudden death may be due to catecholaminergic polymorphic ventricular tachycardia
E. All of the above are true

64-9. An amateur boxer collapses shortly after being punched in the chest. Which of the following statements is *not true* about commotio cordis?

A. The most common sports associated with commotio cordis deaths in the United States are those in which projectiles are integral to the game
B. Collapse is almost never instantaneous and is usually delayed to 10 to 20 seconds after the chest blow
C. The most common cardiac arrhythmia documented soon after collapse is generally ventricular fibrillation
D. Survival from commotion cordis has increased to > 50% as a result of more rapid response times and access to external defibrillation as well as greater public awareness
E. The cellular determinants of VF induced by chest wall blows likely include ion channel activation caused by increased LV pressure

64-10. Which of the following is *not true* with respect to the routine use of ECGs during athlete screening in the United States?

A. Routine use of ECG screening has not been supported because of the large number of athletes to be screened
B. Routine use of ECG screening has not been supported because of the low incidence of events
C. Routine use of ECG screening has not been supported because of the substantial number of expected false-negative and false-positive results
D. Routine use of ECG screening has not been supported because of the need for repetitive ECG screening during adolescence
E. Routine use of ECGs is mandated as part of athlete screening in the United States

ANSWERS

64-1. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* The acute response to training for such athletic activities as cross-country skiing, long-distance running, swimming, or bicycling includes substantial increases in maximum oxygen consumption (option A), cardiac output (option B), stroke volume (option C), and systolic blood pressure (option D), associated with decreased *(not increased)* peripheral vascular resistance (option E).[1] With several weeks of endurance training, the chronic adaptations to training include increased maximal oxygen uptake from augmented stroke volume and cardiac output and increased arteriovenous oxygen difference. The response to endurance exercise predominantly produces a volume load on the left ventricle.

64-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* Differentiating the physiologic changes resulting from habitual exercise in the athletic heart syndrome with HCM or dilated cardiomyopathy represents a challenge to the clinician. Physiologic cardiac adaptation from regular exercise leads to an increase in left ventricle (LV) wall thickness.

This can be difficult to distinguish from the pathologic changes of HCM. Criteria favoring HCM include a high degree of LV hypertrophy (wall thickness ≥ 16 mm) (option A) with an unusual distribution (heterogeneous, asymmetric, or sparing the anterior septum) (option B), a small LV cavity (< 45 mm), the presence of striking electrocardiogram (ECG) abnormalities, and the persistence of hypertrophy after physical deconditioning (option C). Although many athletes have increased intracavitary dimensions, LV end-diastolic diameter > 70 mm is distinctly unusual as a manifestation of the athlete's heart (option D). LV wall thickness > 12 mm is unusual even in highly trained athletes but is not uncommon in elite rowers and cyclists. LV wall thickness ≥ 16 mm raises the possibility of HCM. Hypertrophy (> 12 mm) above the normal range is distinctly uncommon in female athletes. Athletes with LV wall hypertrophy may have increased cavity dimensions, which are rarely present in diseases with pathologic wall thickening.[1]

64-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 64)* A spectrum of abnormal 12-lead ECG patterns is present in up to one-half of trained athletes, more commonly in men and in endurance athletes.[2-7] The most commonly observed alterations include early repolarization patterns (option B), increased QRS voltages, diffuse T-wave inversion, and deep Q waves (option C). ECGs in endurance athletes can show mildly increased P-wave amplitude (option D), suggesting atrial enlargement, incomplete right *(not left)* bundle branch block (option E), and increased voltages consistent with right ventricular and LV hypertrophy.[2-7] Among endurance athletes, voltage criteria for right ventricular hypertrophy are present in a substantial proportion. Abnormal and bizarre ECG patterns suggestive of cardiac disease are noted in a minority of elite athletes.[2-7] Most such ECGs represent only extreme manifestations of physiologic athlete's heart. A significant minority of asymptomatic elite athletes show distinctly abnormal ECG patterns usually associated with precordial T-wave inversions but without evidence of cardiac disease.[8] Many uncommon ECG findings in athletes are not considered normal variants and require further evaluation.

64-4. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 64)* Arrhythmias commonly noted in athletes include sinus arrhythmia, sinus bradycardia (option A), and junctional rhythm (option E). They are often accompanied by other manifestations of enhanced parasympathetic tone. Atrioventricular (AV) conduction delays with first-degree and Wenckebach or Mobitz type I (*not Mobitz type II*) second-degree AV block (option B) are common in endurance athletes and attributable to enhanced vagal tone and withdrawal of sympathetic tone at rest.[8] Ambulatory monitoring of athletes has demonstrated ventricular arrhythmias, including frequent premature beats, couplets (option C), and nonsustained ventricular tachycardia (option D). These arrhythmias can be within the spectrum of physiologic athlete's heart.[8] Such arrhythmias are generally not associated with symptoms or an increased risk of sudden cardiac death, and they are generally reduced with exercise or deconditioning.[9]

64-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 64)* The underlying cardiovascular conditions that predispose to the rare and tragic sudden deaths in young athletes are known.[10-16] Available population-based data show that these events occur with an incidence of 1 to 2 per 100,000 athletes (12–35 years of age) per year (option A) with the frequency eightfold lower *(not fourfold lower)* in female athletes (option B).[10-16] In athletes younger than 35 years, inherited diseases such as HCM, arrhythmogenic right ventricular cardiomyopathy, and congenital coronary artery abnormalities of wrong sinus origin are the most common causes of sudden death (option C). In athletes older than 35 years, atherosclerotic coronary artery disease is the most common cause of death (option D).[10-16]

64-6. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* Hypertrophic cardiomyopathy is the single most common cause of sudden cardiac arrest in athletes in the United States in which a definitive cardiac diagnosis can be made postmortem (option A). HCM accounts for about one-third of sport-related sudden fatalities (option B).[10-16] HCM is a genetically transmitted disease characterized by genotypic and phenotypic heterogeneity (option C). Usually, the characteristic hypertrophied, nondilated LV with increased wall thickness manifests during adolescence.[10] LV hypertrophy is characteristically asymmetric with a variety of patterns of wall thickening (option D).[17]

64-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* Arrhythmogenic right ventricular cardiomyopathy is an inherited heart muscle disorder characterized pathologically by fibrofatty replacement of right ventricular myocardium (option A).[18-22] It represents the leading cause of sudden death on the athletic field in the Veneto region of Italy, accounting for approximately 25% of cardiovascular sudden death in young competitive athletes, but it is distinctly uncommon in the United States (5% of athlete deaths) (option B).[18-22] Clinical manifestations include ECG depolarization and repolarization abnormalities commonly localized to right precordial leads (option C). These include inverted T waves in V1-V3 in most patients with arrhythmogenic right ventricular cardiomyopathy. Less commonly, distinctive depolarization waves known as epsilon waves are seen after the QRS complex in the ST segment on the ECG. Cardiac imaging techniques demonstrate right ventricular global or regional morphologic and functional abnormalities.[18-22] Commonly, premature ventricular contractions or sustained monomorphic ventricular tachycardia with left bundle morphology originate from the right ventricle and are associated with exercise.[17-22] Myocardial aneurysms are localized to the posterobasal, apical, and outflow tract regions (option D), resulting in the clinical characterization of these regions as the triangle of dysplasia. Sudden death during physical exercise is likely related to hemodynamic factors, increased right ventricular volume and wall stress, and enhanced sympathetic tone that culminate in ventricular tachycardia (*not ventricular fibrillation*) (option E).[18-23] Physical exercise can acutely increase right ventricular afterload and cavity enlargement, which in turn can trigger ventricular arrhythmias by stretching the diseased right ventricular musculature.[18-23]

64-8. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* Approximately 10% of young athletes who die suddenly with exercise have no evidence of structural heart diseases (option A). In many such patients, the cause of sudden death is likely a primary electrical heart disease. These include primary electrical abnormalities such as ventricular pre-excitation (Wolff-Parkinson-White syndrome) (option B) and inherited cardiac ion channelopathies, including long QT syndrome, short QT syndrome, Brugada syndrome (option C), and catecholaminergic polymorphic ventricular tachycardia (option D).[24] These primary electrical abnormalities and other conditions predisposing to athletic sudden death have ECG changes.[10-16]

64-9. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 64)* In the absence of underlying cardiovascular disease, blunt nonpenetrating chest blows[25-32] during athletic or recreational activities that cause sudden cardiac death are known as commotio cordis. Although first noted a century ago, it is only in the last 15 to 20 years that commotio cordis has been recognized as a not-uncommon occurrence in youth sports, and it is now regarded as the second leading cause of sudden cardiac death in young athletes, with global recognition.[25-32] The most common sports associated with commotio cordis deaths in the United States are those in which projectiles are integral to the game (eg, baseball, softball, ice hockey, football, lacrosse) (option A). Ages of victims range from 1 to 50 years, although the mean age of individuals experiencing commotio cordis is 14 years, with 30% of individuals older than 18 years. Collapse *is usually instantaneous*, although occasionally delayed 10 to 20 seconds after the chest blow (option B). Cardiac arrhythmias documented soon after collapse are generally ventricular fibrillations (VF) (option C); however, as the time to first documented arrhythmia increases, asystole is more frequently evident. Early reports of resuscitated commotio cordis showed poor survival, although more recently, survival from these events has increased markedly to more than 50% as a result of more rapid response times and access to external defibrillation as well as greater public awareness of this condition (option D).[25-32] The mechanism by which commotio cordis occurs is complex and largely unresolved, and a porcine model was developed for study of this syndrome, which demonstrated that the immediate cause of collapse was VF.[25-32] The use of this model has allowed the definition of several important determinants of VF following a chest blow, including, most importantly, an impact delivered directly over the heart and the timing within the vulnerable phase of repolarization (a narrow 10- to 30-millisecond window just prior to the T-wave peak, equivalent to only 1% to 2% of the cardiac cycle) associated with peak LV pressure caused by the blow, although a wide range of individual vulnerability to VF is evident in the model.[25-32] Furthermore, impact velocity appears to have a Gaussian distribution, with a velocity of 40 mph most likely to trigger VF. In addition, hardness and reduced diameter of the impact object have been correlated directly with the risk of VF.[25-32] Sudden cardiac death in commotio cordis appears to be a primary electrical event. The cellular determinants of VF induced by chest wall blows likely include ion channel activation caused by increased LV pressure (option E).[25-29] The potassium–adenosine triphosphate ion channel mediates the initiation of VF in the swine model and has also been shown to be activated by atrial stretch.[25-29] It is possible that more stretch-activated ion channels are also involved.

64-10. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 64)* The routine use of ECGs is *not* mandated as part of athlete screening in the United States (option E). On many occasions, AHA consensus expert panels have evaluated and decided not to support mandatory national athlete screening in the United States with routine use of ECGs.[33-36] Indeed, sudden cardiovascular deaths in athletes are rare (albeit tragic) events insufficient in number to be judged as a major public health problem or justify a change in national health care policy. The most frequently cited obstacles to mandatory national screening of trained athletes are: (1) the large number of athletes to be screened nationally on an annual basis (ie, about 10 to 12 million) (option A); (2) the low incidence of events (option B); (3) the substantial number of expected false-negative and false-positive results in the range of 5% to 20%, depending on the specific ECG criteria used (option C); (4) cost-effectiveness considerations (ie, extensive resources and expenses required vs few events in absolute numbers); (5) liability issues for physicians (ie, charged with both enforcement and the sole responsibility for disqualifying athletes from competition); (6) the lack of resources or physicians dedicated to performing examinations and interpreting ECGs, in contrast to the long-standing sports medicine program in Italy; (7) the influence of observer variability, technical considerations, and the impact of ethnicity/race on the interpretation of ECGs, particularly important for multicultural athlete populations such as those in the United States; (8) the need for repetitive (ie, annual) ECG screening during adolescence (option D), given the possibility of developing phenotypic evidence of cardiomyopathies during this time period or later; (9) the logistical challenges and cost related to second-tier confirmatory screening with imaging and other testing, should primary evaluations raise the suspicion of cardiac disease; and (10) the recognition that even with testing, screening cannot be expected to identify all athletes with important cardiovascular abnormalities, and a significant false-negative rate can be expected.[32-44]

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CHAPTER 65

Cardiovascular Disease in the Elderly: Pathophysiology and Clinical Implications

Mark J. Eisenberg

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

65-1. Which of the following is *not* an effect of aging on the gross anatomy of the heart?

A. Endocardial thickening and sclerosis
B. Increased left atrial size
C. Valvular fibrosis and sclerosis
D. Decreased epicardial fat
E. All of the above

65-2. Which of the following is a cardiovascular effect associated with aging?

A. Thrombosis
B. Bleeding complications with antiplatelet, anticoagulant, and fibrinolytic agents
C. Sarcopenia
D. Altered pharmacodynamics
E. All of the above

65-3. Which of the following statements about multimorbidity is *true*?

A. The most common pattern of multimorbidity is the coexistence of a cardiometabolic condition and osteoarthritis
B. The dyad of hypertension and hyperlipidemia is rare among Medicare beneficiaries
C. Over 50% of Medicare beneficiaries with HF, stroke, or AF have more than seven chronic conditions
D. Noncardiovascular conditions account for almost a quarter of readmissions after HF or MI in older adults
E. All of the above

65-4. Which of the following statements about polypharmacy is *false*?

A. Polypharmacy is defined as concomitant use of three or more medications
B. About 40% of community-dwelling older adults take at least five medications
C. About 20% of community-dwelling older adults take medications that may exacerbate coexisting conditions
D. Medications used to treat arthritis can antagonize the effects of many cardiovascular medications
E. All of the above

65-5. Which of the following statements about frailty is *false*?

A. Frailty is characterized by reduced physiologic reserve in multiple organ systems to maintain homeostasis after a stressful event
B. After functional decline, frailty is considered the second most problematic manifestation of aging
C. When using a comprehensive definition of frailty, more than 50% of the general population is affected
D. Persons with three or more criteria from the *frailty phenotype* are considered frail
E. None of the above statements are false

65-6. Which of the following statements about cognitive impairment is *true*?

A. Dementia affects 25% of adults age 70 years or older in the United States
B. The prevalence of dementia increases from 5% in patients age 71 to 79 years to 37% in those over 90 years of age
C. Mild cognitive impairment is present in 52% of people ≥ 70 years old

D. The prevalence of cognitive impairment is higher in older adults undergoing CABG than in those who are hospitalized with HF
E. Large cerebral infarcts, grey matter lesions, lacunes, and microinfarcts are some of the cerebrovascular pathologies associated with dementia

65-7. Which of the following statements is *true* about the effects of aging on the risk of heart failure (HF)?

A. The high prevalence of HF in elderly patients is *not* solely related to improved survival from acute MI and other CVDs
B. The exponential rise in HF among older people is due to a gradual erosion in cardiovascular reserve
C. The effects of normal aging alter the four major determinants of cardiac output
D. A healthy 90-year-old person has the exercise capacity and cardiovascular reserve equivalent to a younger person with New York Heart Association functional class III HF.
E. All of the above

65-8. Which of the following statements about the use of intravenous antiplatelet therapy in older adults is *false*?

A. Patients at a higher risk of reinfarction tend to benefit the most from intravenous antiplatelet therapy
B. It is difficult to say whether intravenous antiplatelet therapy is beneficial to older adults because few studies have enrolled patients older than 75
C. Current guidelines recommend avoiding intravenous antiplatelet therapy in STEMI patients ≥ 85 years of age
D. The use of glycoprotein IIb/IIIa should be limited to older persons with high thrombosis risk and low bleeding risk
E. All of the above

65-9. Which of the following statements about aortic stenosis (AS) is *true*?

A. The prevalence of AS in patients older than 80 years of age is higher than 20%
B. More than 90% of all aortic valve procedures are performed in the geriatric population
C. AS is an uncommon valvular abnormality in both young and older patients
D. Symptoms of AS are known to be especially prominent in elderly patients with a sedentary lifestyle
E. Older individuals with severe AS are less likely to exhibit delayed upstroke of the carotid pulse wave

65-10. Sinus node pacemaker cells degenerate progressively with age. By age 75, approximately what percentage of sinus node pacemaker cells continue to function normally?

A. 5%
B. 10%
C. 20%
D. 30%
E. 50%

ANSWERS

65-1. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 65)* The effects of aging on the gross anatomy of the heart are: increased left ventricular wall thickness and decreased cavity size, endocardial thickening and sclerosis (option A), increased left atrial size (option B), valvular fibrosis and sclerosis (option C), and increased *(not decreased)* epicardial fat (option D).

65-2. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 65)* With increasing age, changes in the hemostatic system shift the intrinsic balance between thrombosis and fibrinolysis in the direction of thrombosis (option A). As a result, older adults are at increased risk for both venous thromboembolic disease (ie, deep venous thrombosis and pulmonary embolism) and thrombosis in the arterial system, including myocardial infarction (MI), left atrial appendage thrombus in AF, and stroke. Despite these changes, and perhaps paradoxically, older adults are also at increased risk for bleeding complications with all antiplatelet, anticoagulant, and fibrinolytic agents (option B), as exemplified by the increased incidence of intracranial hemorrhage in older adults receiving prasugrel or fibrinolytic agents. In addition, age-associated declines in muscular mass (sarcopenia) and bone mass (osteopenia) contribute to reductions in exercise tolerance, adversely affect balance, and predispose to injurious falls (option C). Further, aging is associated with altered pharmacokinetics and pharmacodynamics of almost all medications (option D), so that drug dosages tested in clinical trials involving predominantly younger and healthier patients may not be appropriate for the majority of older adults.

65-3. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 65)* Multimorbidity often involves CVD—the coexistence of a cardiometabolic condition and osteoarthritis was the most common multimorbidity pattern in several population-based studies (option A).[1] Among Medicare beneficiaries, the dyad of hypertension and hyperlipidemia was most prevalent (53%) (option B), and other common conditions were ischemic heart disease, diabetes, and arthritis.[2,3] In addition, over

50% of Medicare beneficiaries with HF, stroke, or AF have more than five chronic conditions (option C).[4] Prevalent noncardiovascular conditions include arthritis, anemia, chronic kidney disease, cataracts, chronic obstructive pulmonary disease, dementia, and depression.[3] Furthermore, noncardiovascular conditions account for almost half of readmissions after HF or MI in older adults (option D).[5] Therefore, identifying common patterns of multimorbidity may guide clinical decisions by helping clinicians to prioritize interventions that are most likely to have a positive impact on overall outcomes.

65-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 65) Polypharmacy* is typically defined as concomitant use of five or more medications (option A).[6] The use of prescription medications and the prevalence of polypharmacy have increased markedly over the past decade.[7] The number of chronic conditions and prescribing practices aligned with disease-based guidelines are directly correlated with polypharmacy.[6,8] Approximately 40% of community-dwelling older adults take at least five medications (option B),[6] and 20% take medications that may exacerbate coexisting conditions (option C).[9] For example, arthritis is often treated with nonsteroidal anti-inflammatory drugs, which antagonize the effects of many cardiovascular medications (ACEIs, ARBs, diuretics) and also increase the risk for MI, HF, and worsening renal function (option D). The number of medications and treatment complexity are associated with nonadherence, drug-related adverse events, financial burden, and caregiver stress.[6,10-16]

65-5. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 65) Frailty* is a geriatric syndrome that is characterized by a reduced physiologic reserve in multiple organ systems (eg, the brain or the endocrine, immune, musculoskeletal, or cardiovascular systems) to maintain homeostasis after a stressful event and an increased vulnerability to adverse health outcomes (option A).[17] It is the most problematic manifestation of aging and contributes substantially to the heterogeneity in the health status of the aging population (option B). Several criteria for diagnosing frailty have been developed, yielding varying prevalence estimates in the general population, from < 5% using a specific physical performance-based definition to > 50% using a more comprehensive definition (option C).[18] The *frailty phenotype*, derived from the Cardiovascular Health Study, is a widely accepted method for classifying older adults into robust, prefrail, or frail categories based on unintentional weight loss, weak handgrip strength, exhaustion, slow gait speed, and low physical activity.[19] Persons with three or more of these criteria are considered frail (option D); those with one or two criteria are considered prefrail.

65-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 65)* Dementia affects 14% of adults age 70 years or older in the United States (option A), and the prevalence increases with age, from 5% in patients age 71 to 79 years to 37% in those over 90 years of age (option B).[20] Mild cognitive impairment, a less severe form of cognitive limitation with relative preservation of functional status, is present in 22% of people ≥ 70 years old (option C).[21] The annual rate of progression from mild cognitive impairment to dementia is estimated to be about 12%.[21] The prevalence of cognitive impairment in older adults with CVD is higher than that in the general population: 35% in patients undergoing coronary artery bypass graft (CABG) surgery[22] and 47% in hospitalized patients with HF (option D).[23] The underlying mechanisms include hypoperfusion, oxidative stress, and inflammation, which lead to diverse cerebrovascular pathologies, including large cerebral infarcts, white matter lesions, lacunes, microinfarcts, and microbleeds (option E).[24]

65-7. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 65)* Although the high prevalence of HF in elderly patients is partly related to improved survival from acute MI and other CVDs, other age-related factors contribute to the development of HF, including long-standing hypertension (option A) (present in 75% of patients with HF), vascular stiffness, left ventricular diastolic dysfunction, sinus node dysfunction, progressive valvular heart disease, coronary ischemia, and reduced responsiveness to β-adrenergic stimulation.[25] As a result, a gradual erosion in cardiovascular reserve with age results in an exponential rise in HF among older persons (option B). Studies in healthy older adults have confirmed that the effects of normal aging lead to altered preload, afterload, heart rate, and contractility—the four major determinants of cardiac output (option C)—thus resulting in a progressive decline in peak cardiopulmonary performance, even in the absence of clinically evident CVD.[26] Stated another way, an otherwise healthy 90-year-old person is likely to have exercise capacity and cardiovascular reserve equivalent to a younger person with New York Heart Association functional class III HF (option D).

65-8. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 65)* The role of intravenous antiplatelet therapy in ACS is difficult to define, both for younger and older patients. Glycoprotein IIb/IIIa inhibitors appear to reduce reinfarction and overall infarct size at the time of NSTE-ACS, with patients at higher risk deriving the most benefit (option A), but few studies have enrolled patients over age 75 (option B), and the risk of bleeding complications increases with age.[25,27] One study of ACS patients demonstrated higher event rates in octogenarians randomized to glycoprotein IIb/IIIa inhibitor therapy,[28] and current guidelines recommend avoiding these medications entirely in the setting of fibrinolytic therapy for STEMI in patients ≥75 years of age (option C).[29] Because these drugs are associated with greater bleeding risks in the elderly, the use of glycoprotein IIb/IIIa inhibitors should probably be limited to select older individuals with high thrombosis risk and low bleeding risk (option D). The intravenous platelet inhibitor cangrelor has a different mechanism of action than the glycoprotein IIb/IIIa inhibitors, and clinical trials evaluating cangrelor demonstrated similar benefits among patients older and younger than age 75 years.[30] However, the magnitude of the bleeding risk associated with cangrelor remains unclear;[31] thus, the safety of this drug in elderly patients requires further study.

65-9. **The answer is E.** *(Hurst's The Heart, 14th Edition, Chap. 65)* The prevalence of symptomatic aortic stenosis (AS) increases from 0.2% in patients under age 60 to nearly 10% in those ≥80 years of age (option A).[25,32] As a result, over 70% of all aortic valve procedures are performed in the geriatric population (option B), and AS is the most common valvular abnormality requiring surgical or percutaneous intervention (option C). Symptoms may not be as prominent in elderly patients with sedentary lifestyles (option D), resulting in delayed presentation or incidental diagnosis of severe AS at the time of presentation for other medical problems.[25] In addition, although physical findings are generally similar in younger and older patients, older patients with severe AS are less likely to exhibit delayed upstroke of the carotid pulse wave (pulsus tardus et parvus) as a result of increased arterial stiffness (option E).

65-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 65*) The progressive degeneration of sinus node pacemaker cells results in only 10% continuing to function normally by age 75 (option B).[25] Similar processes occur in the tissues surrounding the sinus node and within the conduction pathways, contributing to the development of sinoatrial exit block or atrioventricular nodal block.

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CHAPTER 66

Pericardial Diseases

Patrick R. Lawler

QUESTIONS

DIRECTIONS: Choose the one best response to each question.

66-1. Which of the following is *correct* regarding the normal anatomy and physiology of the pericardium?

A. It allows great distention of the cardiac chambers and increased cardiac filling
B. Congenital absence or surgical removal of the pericardium is fatal
C. The human pericardium consists of two distinct layers, the inner serosa and the outer fibrosa
D. Most of the innervation of the pericardium occurs via the vagus nerves
E. All of the above

66-2. A 49-year-old man presents to clinic with pleuritic chest pain, myalgia, and fever. Which of the following findings is *not* a diagnostic criterion for acute pericarditis?

A. New widespread ST elevation or PR depression on ECG
B. Sharp chest pain that is worse on inspiration
C. Fever > 38°C
D. Pericardial friction rub
E. New or worsening pericardial effusion

66-3. A 63-year-old woman presents with recurrent pericardial disease. Which of the following is a Class I level A recommendation on the proper diagnosis and management of pericardial diseases?

A. Corticosteroids should be prescribed as first choice in patients with acute pericarditis
B. Vasodilators and diuretics are recommended in the presence of cardiac tamponade
C. An absolute contraindication to draining a pericardial effusion includes a suspicion of bacterial etiology
D. Colchicine is a first-choice drug to be used as an adjunct to aspirin/NSAIDs to treat and prevent recurrent episodes of pericarditis
E. None of the above

66-4. Which of the following is *not* a recommended therapeutic option for recurrent pericarditis?

A. High-dose prednisone (1.0 to 1.5 mg/kg/d)
B. Triple therapy of aspirin, colchicine, and corticosteroids
C. Pericardiectomy
D. Low-dose prednisone for patients on oral anticoagulants
E. Aspirin/NSAID and colchicine

66-5. A 40-year-old woman presents to the emergency room with chest pain, fever, and night sweats. She has recently returned from travelling in India and has lost 10 pounds. Which of the following findings is *not* consistent with a diagnosis of tuberculous pericarditis with pericardial effusion?

A. Lack of signs and symptoms of pulmonary tuberculosis
B. Presence of pulsus paradoxus
C. Electrical alternans on ECG
D. Negative acid-fast bacilli staining and mycobacterium cultures on pericardial fluid
E. Elevated C-reactive protein

66-6. Which of the following clinical presentations is consistent with cardiac tamponade?

A. Pulmonary edema
B. Impaired ventricular diastolic filling

C. Third heart sound
D. Decreased central venous pressure
E. All of the above

66-7. A 63-year-old man is brought to the emergency room with altered level of consciousness and is found to be tachycardic and hypotensive. Echocardiography reveals a large pericardial effusion with echocardiographic evidence of tamponade. Which of the following is *not* appropriate in the subsequent management of this patient with cardiac tamponade?

A. If a pericardial catheter is placed, removal of the intrapericardial catheter when the output is < 90 mL over a 24-hour period
B. Prompt needle pericardiocentesis to aspirate all the pericardial fluid
C. Pericardiocentesis should be guided by echocardiography to prevent tissue injury
D. If a pericardial catheter is placed, reassessment of effusion size and areas of loculation before catheter removal
E. All of the above are correct

66-8. Which of the following statements about constrictive pericarditis is *correct*?

A. It is twice as prevalent in women as in men (2:1 ratio)
B. The thickened pericardium has decreased compliance, resulting in ventricular interdependence
C. Orthopnea and paroxysmal nocturnal dyspnea are typically observed
D. Patients often present with features of left-heart failure
E. None of the above

66-9. Which of the following is most likely to provide definitive treatment for symptomatic patients with constrictive pericarditis?

A. Anti-inflammatory therapy
B. Pericardiocentesis
C. Pericardiectomy
D. Close follow-up
E. None of the above

66-10. A 55-year-old woman presents to your clinic with vague chest pain and dyspnea. A chest radiograph reveals a mass in the right costophrenic angle. CT of the chest suggests a pericardial cyst. Which of the following is *correct*?

A. Pericardial cysts are smooth, thin-walled structures usually filled with pus
B. The recommended therapeutic course is observation of the patient
C. Pericardial cysts are usually symptomatic and tend to increase in size over time
D. The patient's symptoms are likely unrelated to the cyst
E. Percutaneous drainage of the cyst is recommended for asymptomatic patients

ANSWERS

66-1. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 66)* The human pericardium has two distinct layers; the serosa is composed of a single column of mesothelial cells that surrounds all four cardiac chambers and the proximal great vessels and reflects on itself to form the inner surface of the fibrosa, a fibrocollagenous structure (option C). This monolayer of serosal cells covering the surface of the heart and epicardial fat is also called the visceral pericardium, whereas the fibrosa and the reflection of the serosa make the parietal pericardium.

Most of the innervation of the pericardium occurs via the phrenic nerves (C4–C6), which course anteriorly (option D); this is particularly relevant during pericardiectomy. No adverse consequences follow congenital absence or surgical removal of the pericardium (option B). However, the pericardium serves many important (although subtle) functions. It limits distension of the cardiac chambers and facilitates the interaction and coupling of the ventricles and atria (option A). Limitation of cardiac filling volumes by the pericardium may also limit cardiac output and oxygen delivery during exercise.

66-2. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 66)* The clinical diagnosis of acute pericarditis is established when two of four clinical criteria are satisfied (Table 66-1). Acute pericarditis is usually characterized by sharp retrosternal pain (option B) that is aggravated by lying down and relieved by sitting up; its onset is often heralded by a prodrome of fever, malaise, and myalgia. The most specific physical sign can be the presence of a pericardial friction rub (option D), which is identifiable in no more than a third of cases. Within a few hours of the onset of chest pain, typical ECG changes include ST-segment elevations and depression of the PR segment (except in lead aVR), which can persist for hours or days (option A). This is the first ECG stage of pericarditis, followed by normalization of the ST segments (stage 2), T-wave inversions (stage 3), and finally, normalization again (stage 4). This is different from myocardial

infarction, wherein T-wave inversions often begin while the ST segments are still elevated. In addition, echocardiographic identification of pericardial effusion confirms the clinical diagnosis of acute pericarditis (option E). Elevated fever (option C) is a major indicator of poor prognosis but is not a diagnostic criterion.

TABLE 66-1 Definition and Diagnostic Criteria for Acute Pericarditis

Inflammatory pericardial syndrome to be diagnosed with at least 2 of the 4 following criteria: (1) pericarditic chest pain (2) pericardial rubs (3) new widespread ST elevation or PR depression on ECG (4) pericardial effusion (new or worsening)
Additional supporting findings: Elevation of markers of inflammation (ie, C-reactive protein, erythrocyte sedimentation rate, and white blood cell count); Evidence of pericardial inflammation by an imaging technique (computed tomography, cardiac magnetic resonance).

66-3. The answer is D. *(Hurst's The Heart, 14th Edition, Chap. 66)* Treatment of pericardial disease is challenging because there is a paucity of randomized, placebo-controlled trials that identify appropriate therapy and help with clinical decision making. Table 66-2 summarizes the main recommendations of the 2015 ESC guidelines.[1] Colchicine is a first-line therapy to be used as adjunct to aspirin/NSAIDs or corticosteroids to treat and prevent pericarditis, either in acute or recurrent cases (Class I recommendation, level of evidence: A) (option D). Corticosteroids should not be prescribed as first choice in patients with acute pericarditis, given the risk of recurrence (Class III recommendation, level of evidence: C) (option A). The essential indications to drain a pericardial effusion include: cardiac tamponade (therapeutic pericardiocentesis), a suspicion of bacterial or neoplastic etiology, and persistent moderate to large pericardial effusion without response to medical therapy (Class I recommendation, level of evidence: C) (option C). Vasodilators and diuretics are not recommended in the presence of cardiac tamponade (Class III recommendation, level of evidence: C) (option B).

TABLE 66-2 Summary of the 2015 European Society of Cardiology Guidelines on the Diagnosis and Management of Pericardial Diseases

	Indication	Evidence
Acute and recurrent pericarditis		
A triage is recommended to identify high-risk patients who should be admitted to hospital. Low-risk patients can be managed as outpatients.	Class I	Level B
Colchicine is now a first-choice drug to be used as adjunct to aspirin/NSAID or corticosteroids to treat and prevent pericarditis either in acute or recurrent pericarditis (weight-adjusted doses are recommended without a loading dose; eg, 0.5 mg twice a day for 3 months in acute pericarditis and 6 months in recurrent pericarditis; colchicine should be given only as 0.5 mg once for patients > 70 kg).	Class I	Level A
Levels of C-reactive protein are useful to guide the treatment duration and assess the response to treatment in acute and recurrent pericarditis; anti-inflammatory therapy should be maintained until symptom resolution and C-reactive protein normalization.	Class IIa	Level C
Corticosteroids should not be prescribed as first choice in patients with acute pericarditis since it may favor chronicization.	Class III	Level C
Pericardial effusion		
The essential indications to drain a pericardial effusion include: (1) cardiac tamponade (therapeutic pericardiocentesis), (2) a suspicion of bacterial or neoplastic aetiology, and (3) persistent moderate to large pericardial effusion without response to medical therapy.	Class I	Level C
A triage system is proposed also for the management of pericardial effusion and is essentially based on the following: (1) recognize cardiac tamponade and possible bacterial of neoplastic etiologies, (2) exclude concomitant pericarditis or treat as pericarditis, (3) identify associated underlying diseases, and (4) if chronic and large (> 20 mm), consider pericardial drainage to prevent cardiac tamponade during follow-up.	Class I	Level C
Treatment of pericardial effusions should be tailored as much as possible to the underlying etiology.	Class I	Level C
Cardiac tamponade		
In a patient with clinical suspicion of cardiac tamponade, echocardiography is recommended as the first imaging technique to evaluate the size, location, and degree of hemodynamic impact of the pericardial effusion.	Class I	Level C

Urgent pericardiocentesis or cardiac surgery is recommended to treat cardiac tamponade.	Class I	Level C
A judicious clinical evaluation including echocardiographic findings is recommended to guide the timing of pericardiocentesis.	Class I	Level C
Vasodilators and diuretics are not recommended in the presence of cardiac tamponade.	Class III	Level C
Constrictive pericarditis		
CT and CMR are indicated for the evaluation of a suspected constrictive pericarditis as second-level imaging techniques after echocardiography.	Class I	Level C
Cardiac catheterization is indicated only in complex cases when noninvasive imaging does not provide a clear-cut diagnosis or provides conflicting results.	Class I	Level C
The mainstay of therapy for chronic constriction is radical pericardiectomy, but it is acknowledged that there is a need to assess the possible presence of pericardial inflammation (eg, elevation of C-reactive protein, pericardial inflammation on CT/CMR) as precipitating cause in new-onset cases in order to treat with empiric anti-inflammatory therapy.	Class I	Level C
Diagnostic workup of pericardial diseases		
First diagnostic evaluation in a patient with a clinical suspicion of pericardial disease should include: focused history and physical examination, ECG, chest x-ray, and routine blood tests, including markers of myocardial inflammation and lesion and renal function.	Class I	Level C
Echocardiography is the first essential diagnostic imaging tool, whereas CT and CMR are second-level imaging techniques for specific indications.	Class I	Level C
Additional diagnostic testing should be targeted and clinically guided.	Class I	Level C
Main specific forms		
Tuberculosis		
Empiric antituberculous therapy is only recommended in countries where tuberculosis is endemic and the disease is highly probable in the setting of a patient with pericarditis and pericardial effusion.	Class I	Level C
In cases with an established diagnosis of tuberculous pericarditis, standard antituberculous therapy is recommended for 6 months and prevents the evolution to constrictive pericarditis.	Class I	Level C
In patients with tuberculous pericarditis with features of constriction and not responding to antituberculous therapy, pericardiectomy is recommended after 4–8 weeks of medical therapy.	Class I	Level C
Neoplastic pericardial diseases		
The definite diagnosis of neoplastic pericardial disease relies on the evidence of neoplastic cells on cytology of pericardial fluid.	Class I	Level B
Pericardial biopsy should be considered for the final etiologic diagnosis in selected cases.	Class IIa	Level B
Tumor markers in pericardial fluid may be helpful to differentiate a benign vs a malignant pericardial effusion.	Class IIa	Level B
In cases with a confirmed diagnosis of neoplastic pericardial disease, systemic antineoplastic treatment is indicated.	Class I	Level B
Extended pericardial drainage is recommended to prevent recurrent cardiac tamponade and pericardial effusion and to provide a way for intrapericardial therapy.	Class I	Level B
Intrapericardial therapy with cytostatic agents should be considered to treat neoplastic pericardial disease.	Class IIa	Level B

Abbreviations: CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; NSAID, nonsteroidal anti-inflammatory drugs.

66-4. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Recurrent pericarditis is one of the most troublesome complications of pericarditis, occurring in one-third of cases. The mainstay of therapy for recurrences is similar to that for acute pericarditis: aspirin or an NSAID plus colchicine at the same doses that are recommended for acute pericarditis (option E). Corticosteroids should be considered as a second-line therapy for patients with contraindications for or failure of aspirin/NSAIDs or patients with specific indications (eg, pregnant patients, patients with a systemic inflammatory disease already on corticosteroids, patients with renal failure, patients on oral anticoagulant therapies to avoid interference with aspirin/NSAIDs) (option D). If used, low to moderate doses (eg, prednisone 0.2 to 0.5 mg/kg/d or equivalent) are indicated because high doses (eg, prednisone 1.0 to 1.5 mg/kg/d) are associated with a high rate of severe side effects (up to 25%) with more drug withdrawals, drug-related hospitalization, and recurrences (option A). In more difficult cases, aspirin or NSAID, colchicine, and corticosteroids may be used together as a triple therapy to achieve better control of symptoms (option B).[2] After failure of medical therapy, pericardiectomy can be considered (option C), although it should be performed in centers with specific expertise in such surgery to achieve the best outcomes.[3]

66-5. **The answer is D.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Tuberculosis is a major cause of pericarditis in nonindustrialized countries but an uncommon cause in developed countries with a low prevalence of tuberculosis. Tuberculous pericarditis results from hematogenous spread of primary tuberculosis or from the breakdown of infected mediastinal lymph nodes, with the result that affected individuals generally lack the typical symptoms and signs of pulmonary tuberculosis (option A). Early signs include fever, weight loss, and night sweats. Essentially, all causes of pericarditis can manifest as pericardial effusion. In developing countries, tuberculosis continues to be the predominant etiology, accounting for 50% to 60% of cases.[4] Findings suggestive of pericardial effusion with tamponade physiology (that are nonspecific to tuberculous pericardial disease, however) include an elevated pulsus paradoxus (option B) and ECG findings of low QRS voltage and electrical alternans (option C). Bacterial and mycobacterial cultures should be

performed if bacterial infection or tuberculosis is suspected, respectively. However, TB is a slow-growing organism, and cultures can take weeks to become positive. Acid-fast bacilli staining (option D), adenosine deaminase, pericardial lysozyme, and interferon-γ levels, as well polymerase chain reaction testing, should be added in the evaluation of tuberculous pericarditis. Nonspecific blood markers of inflammation, such as the erythrocyte sedimentation rate, C-reactive protein (option E), and white blood cell count, usually increase in cases of pericarditis and can support the diagnosis.

66-6. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Cardiac tamponade corresponds to a corollary of hemodynamic derangements that are secondary to increased intrapericardial pressure. As intrapericardial pressure rises in patients with cardiac tamponade, elevated pericardial pressure is transmitted to all four chambers, affecting diastolic filling. Inspection of the jugular veins will show elevation in central venous pressure (option D); venous distention may or may not be present. Analysis of the venous wave contour will reveal absence or blunting of the *y* descent, representing impaired ventricular diastolic filling (option B).

Cardiac auscultation might reveal distant heart sounds. Because early diastolic filling is profoundly impaired, a third heart sound should not be present (option C); its occurrence suggests an alternative diagnosis. For unclear reasons, tamponade does not usually lead to pulmonary edema (option A); the lungs are often clear on auscultation in patients with isolated cardiac tamponade. Rather, hemodynamic compromise is the more striking finding.

66-7. **The answer is A.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Cardiac tamponade is a cardiac emergency and should be treated with prompt needle pericardiocentesis (option B) unless it is caused by aortic dissection. The goal should be aspiration of all pericardial fluid. The procedure should be done with transthoracic echocardiographic guidance by an experienced operator (option C). During echo-guided pericardiocentesis, the largest collection of fluid in closest proximity to the chest wall should be identified, defining the optimal site for needle entry. Echocardiography also confirms the absence of interposed lung or liver tissue. Complications include cardiac or coronary perforation, hemothorax or liver injury, pneumothorax, and pneumopericardium. The daily output of pericardial fluid is recorded. The pigtail catheter should not be removed until the output is < 30 mL over a 24-hour period (option A). Before the intrapericardial catheter is removed, a limited echocardiogram is often repeated to reassess the effusion size and areas of loculation (option D).

66-8. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Constrictive pericarditis results from inflammation and/or scarring of the pericardium, leading to impairment of cardiac filling. The disease also appears to favor men over women (2:1 ratio) (option A). Given the abnormal pericardial compliance, diastolic filling is significantly impaired in patients with constrictive pericarditis (steeper increase in pressure per change in volume in the pressure–volume curve). As a consequence, cardiac filling pressures increase, and cardiac output falls as stroke volume decreases. The thickened pericardium has limited expansion, and cardiac chambers "compete" for pericardial space during diastolic filling. With respiration, an increase in preload in one ventricle occurs at the expense of filling in the other (ventricular interdependence) (option B). Patients with constrictive pericarditis typically present with features of right-sided heart failure (option D), manifested by elevated venous pressure, ascites, and leg edema. Orthopnea and paroxysmal nocturnal dyspnea are not usually observed and suggest another etiology (option C).

66-9. **The answer is C.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Although patients presenting with constrictive pericarditis and evidence of active pericardial inflammation (either by CMR or elevated inflammatory markers) might respond to anti-inflammatory therapy (Class IIb recommendation; level of evidence: C) (option A), therapeutic pericardiectomy is the recommended treatment for symptomatic patients with constrictive pericarditis (Class I recommendation; level of evidence: C) (option C). Pericardiectomy is the surgical removal of the pericardium, and the procedure is applicable to all variants of pericardial disease. Some patients presenting with cardiac tamponade demonstrate features of constrictive pericarditis immediately after pericardiocentesis is performed and tamponade relieved, such as in the case of those with effusive constrictive pericarditis. In such cases, therapy should be focused on treating active inflammation; a subset of patients might develop chronic constrictive pericarditis and require pericardiectomy following the pericardiocentesis (option B). Therefore, close follow-up of patients with effusive-constrictive pericarditis is recommended (option D).

66-10. **The answer is B.** *(Hurst's The Heart, 14th Edition, Chap. 66)* Pericardial cysts are smooth, thin-walled structures filled with clear fluid (hence the term spring water cysts) (option A). Patients with pericardial cysts are usually asymptomatic, and the cysts tend not to increase in size (option C). Some patients with pericardial cysts complain of atypical chest pain or dyspnea, most likely as a result of compression of contiguous structures (option D). For patients with symptoms related to the pericardial cyst, percutaneous drainage or surgical removal can be performed (option E).[5] However, given the risks associated with both procedures and the benign, well-tolerated course of the disease, observation is likely most appropriate for the majority of patients with pericardial cysts (option B).

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Cardiology I

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Learning Objectives

1. Distinguish between the treatment strategies for acute coronary syndrome: ST-segment elevation myocardial infarction and non–ST-segment elevation acute coronary syndrome.
2. Formulate evidence-based treatment strategies for patients with acute decompensated heart failure.
3. Devise a treatment plan for patients presenting with ventricular or life-threatening arrhythmias.
4. Differentiate between goals and treatment for hypertensive emergencies and hypertension without progressive organ damage.
5. Provide evidence-based treatment for a patient given a diagnosis of idiopathic pulmonary arterial hypertension.

Abbreviations in This Chapter

AAD	Antiarrhythmic drug
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome
ACT	Activated clotting time
ADHF	Acute decompensated heart failure
ADR	Adverse drug reaction
AF	Atrial fibrillation
aPTT	Activated partial thromboplastin time
BNP	B-type natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Cardiac index
CO	Cardiac output
CPR	Cardiopulmonary resuscitation
CV	Cardiovascular
DAPT	Dual antiplatelet therapy
ECG	Electrocardiogram
EF	Ejection fraction
GI	Gastrointestinal
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
HF	Heart failure
HIT	Heparin-induced thrombocytopenia
ICD	Implantable cardioverter-defibrillator
IPAH	Idiopathic pulmonary arterial hypertension
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MI	Myocardial infarction
mPAP	Mean pulmonary arterial pressure
NSTE-ACS	Non–ST-segment elevation acute coronary syndrome
NSTEMI	Non–ST-segment elevation myocardial infarctions
PAH	Pulmonary arterial hypertension
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PH	Pulmonary hypertension
SCD	Sudden cardiac death
SHD	Structural heart disease
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
UA	Unstable angina
UFH	Unfractionated heparin
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions can be found at the end of this chapter.

1. A 62-year-old man presents to the emergency department with the chief concern of chest pain that woke him from sleep and radiates to his jaw. An electrocardiogram (ECG) reveals ST-segment depression in leads II, III, and aVF. His blood pressure is 112/62 mm Hg, and heart rate is 60 beats/minute. Cardiac enzymes have been obtained, and the first troponin result was slightly positive. Preparations are under way to take the patient to the cardiac catheterization laboratory for evaluation. Which medication regimen is most appropriate for this patient at this time?
   A. Aspirin 325 mg, clopidogrel 600-mg loading dose, and unfractionated heparin (UFH) infusion 80-unit/kg bolus, followed by 18 units/kg/hour and metoprolol 5 mg intravenously three times.
   B. Aspirin 81 mg; prasugrel 60-mg loading dose; UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour; and intravenous enalaprilat.

C. Aspirin 325 mg, ticagrelor 180-mg loading dose, and UFH infusion 60-unit/kg bolus, followed by 12 units/kg/hour.

D. Aspirin 81 mg, prasugrel 60-mg loading dose, nitroglycerin infusion at a rate of 10 mcg/minute, and bivalirudin 0.75 mg/kg bolus and 1.75 mg/kg/hour infusion.

2. An 81-year-old African American man (weight 90 kg) presents to the emergency department with chest pressure (10/10 on a pain scale). His ECG reveals ST-segment depression in the inferior leads. His medical history is significant for hypertension and chronic kidney disease. Pertinent laboratory results are troponin 5.8 ng/L, serum creatinine (SCr) 3.7 mg/dL, and estimated creatinine clearance (CrCl) 20 mL/minute. The patient has been given aspirin 325 mg single dose; a nitroglycerin drip, initiated at 5 mcg/minute, will be titrated to chest pain relief and blood pressure. The patient consents for cardiac catheterization after adequate hydration. Which anticoagulation strategy is most appropriate to initiate in this patient?

   A. Intravenous heparin 4000-unit intravenous bolus, followed by a 1000-unit/hour continuous infusion.

   B. Enoxaparin 90 mg subcutaneously every 12 hours.

   C. Fondaparinux 2.5 mg subcutaneously daily.

   D. Bivalirudin 67.5-mg bolus, followed by a 157-mg/hour infusion.

3. A 56-year-old man presents to the hospital with the chief concern of chest pain that was unrelieved at home with nitroglycerin. His ECG reveals ST-segment depression and T-wave inversion. Cardiac markers show an elevated troponin I. The cardiologist has requested that the patient go to the cardiac catheterization laboratory for further evaluation. The patient has a history of coronary artery disease (CAD) and had a myocardial infarction (MI) about 6 months ago. During his previous hospitalization, the patient was thought to have developed heparin-induced thrombocytopenia (HIT) because his platelet count dropped to 40,000/mm^3 after his previous catheterization. Given this patient's diagnosis and history, which treatment regimen would be most appropriate during his cardiac catheterization?

   A. Abciximab.

   B. Bivalirudin.

   C. Eptifibatide.

   D. Tenecteplase.

4. A 62-year-old man presents to the emergency department after several hours of chest discomfort. His ECG reveals 1- to 2-mm ST-segment elevation in leads V_1–V_4, with positive troponins. He has also had increasing shortness of breath and swelling over the past 2–3 weeks. His medical history is significant for tobacco use for 40 years, chronic obstructive pulmonary disease, diabetes, and hypertension. His blood pressure is 102/76 mm Hg and heart rate is 111 beats/minute. He has rales in both lungs and 2–3+ pitting edema in his extremities. His ECG reveals an ejection fraction (EF) of 25%. After primary percutaneous coronary intervention (PCI), he is transferred to the cardiac intensive care unit. Which best describes the acute use of β-blocker therapy in this patient?

   A. Give 12.5 mg of oral carvedilol within the first 24 hours.

   B. Give 5 mg of intravenous metoprolol at bedside.

   C. Give 50 mg of oral metoprolol at discharge.

   D. Give no β-blocker at this time.

5. A 60-year-old woman with New York Heart Association (NYHA) class IV heart failure (HF) (heart failure with reduced ejection fraction [HFrEF]) is admitted for increased shortness of breath and dyspnea at rest. Her extremities appear well perfused, but she has 3+ pitting edema in her lower extremities. Her vital signs include blood pressure 125/70 mm Hg, heart rate 92 beats/minute, and oxygen saturation (Sao_2) 89% on 100% facemask. After initiating an intravenous diuretic, which is the best intravenous drug to treat this patient?

   A. Dobutamine.

   B. Milrinone.

   C. Nitroglycerin.

   D. Metoprolol.

6. A 75-year-old woman has a history of NYHA class III HFrEF (left ventricular ejection fraction [LVEF] 25%) and several non–ST-segment elevation myocardial infarctions (NSTEMIs). She had an episode of sustained ventricular tachycardia (VT) during this hospitalization for pneumonia. Her corrected QT (QTc) interval was 380 milliseconds on the telemetry monitor, and her serum potassium and magnesium were 4.6 mEq/L and 2.2 mg/dL, respectively. Which intravenous agent is most appropriate for this patient?
   A. Procainamide.
   B. Metoprolol.
   C. Magnesium.
   D. Amiodarone.

7. A 53-year-old woman is admitted to the hospital after the worst headache she has ever had. Her medical history includes exertional asthma, poorly controlled hypertension, and hyperlipidemia. She is nonadherent to her medications, and she has not taken her prescribed blood pressure medications for 4 days. Vital signs include blood pressure 220/100 mm Hg and heart rate 65 beats/minute. She has a cerebrovascular accident. Which agent is most appropriate for this patient's hypertensive emergency?
   A. Fenoldopam 0.1 mcg/kg/minute.
   B. Nicardipine 5 mg/hour.
   C. Labetalol 0.5 mg/minute.
   D. Enalaprilat 0.625 mg intravenously every 6 hours.

8. A 56-year-old African American man has a long history of poorly controlled hypertension secondary to medication nonadherence and subsequent dilated cardiomyopathy (LVEF 35%). He is assessed in a community health clinic today and reports not having taken his medications for the past week. The patient is asymptomatic, and his examination is unremarkable except for blood pressure 180/120 mm Hg and heart rate 92 beats/minute. All laboratory values are within normal limits except for an SCr of 1.4 mg/dL and a urinalysis with 2+ proteinuria. Which regimen would be best to treat this patient in the clinic?
   A. Nifedipine 10 mg sublingually.
   B. Clonidine 0.2 mg orally.
   C. Captopril 12.5 mg orally.
   D. Labetalol 200 mg orally.

9. A 52-year-old woman experiences a witnessed cardiac arrest in a shopping mall; she is resuscitated with an automatic external defibrillator device. On electrophysiological study, she has inducible VT. Which agent is most appropriate for reducing the secondary incidence of sudden cardiac death (SCD)?
   A. Propafenone.
   B. Amiodarone.
   C. Implantable cardioverter-defibrillator (ICD).
   D. Metoprolol.

10. The Sudden Cardiac Death in Heart Failure trial evaluated the efficacy of amiodarone or an ICD versus placebo in preventing all-cause mortality in ischemic and nonischemic patients with NYHA class II and III HF. There was a 7.2% absolute risk reduction and a 23% relative risk reduction in all-cause mortality at 60 months with an ICD versus placebo. Which option best shows the number of patients needed to treat with an ICD to prevent one death versus placebo?
   A. 1.
   B. 4.
   C. 14.
   D. 43.

11. You are working on a review article about newer treatment strategies for hypertensive crises. You want to ensure that you retrieve all relevant clinical trials and related articles on your subject. Which comprehensive database is most appropriate to search to ensure that you have not missed key articles?
   A. International Pharmaceutical Abstracts.
   B. Iowa Drug Information Service.
   C. Clin-Alert.
   D. Excerpta Medica.

12. A physician on your team asks that you report an adverse drug reaction (ADR) experienced by a patient taking nesiritide. The patient had severe hypotension after the initial bolus dose of nesiritide, although his blood pressure was in the normal range before therapy initiation. The hypotension led to reduced renal perfusion, resulting in oliguric acute kidney injury and subsequent hemodialysis. The patient had no known renal insufficiency before developing this complication. Which statement best describes The Joint Commission requirements for institutional ADR reporting?
    A. A MedWatch form must be completed that explains the situation in which the ADR occurred.
    B. Institutions must create their own definition of ADR with which practitioners will be familiar.
    C. Hospital staff members must use the Naranjo algorithm to assess the severity of the ADR.
    D. Only severe or life-threatening ADRs need to be reported.

13. Your pharmacy and therapeutics committee wants you to perform a pharmacoeconomic analysis of a new drug available to treat decompensated HF. This drug works through a unique mechanism of action. Unlike other available inotropic therapies that can increase mortality, this drug appears to reduce long-term mortality. However, the cost is 10-fold greater than that of other available drugs. Which pharmacoeconomic analysis would be best to determine whether this new drug is a better formulary choice than currently available agents?
    A. Cost minimization analysis.
    B. Cost-effectiveness analysis.
    C. Cost-benefit analysis.
    D. Cost-utility analysis.

BPS Pharmacotherapy Specialty Examination Content Outline

This chapter covers the following sections of the Pharmacotherapy Specialty Examination Content Outline:

1. Domain 1: Patient–centered pharmacotherapy
    a. Tasks 1:1–17, 2:1–5, 7, 3:1–5, 4:1–7, 5:1–5
    b. Systems and patient-care problems:
        i. Acute coronary syndrome
        ii. Acute decompensated heart failure
        iii. Adult cardiac arrest
        iv. Advanced cardiac life support
        v. Basic life support and cardiopulmonary resuscitation (CPR)
        vi. Life-threatening arrhythmias
        vii. Hypertensive crises (urgency and emergency)
        viii. Pulmonary hypertension
2. Domain 2: Drug Information and Evidence-Based Medicine, Tasks 1:2, 3, 2:1, 5, 6, and 3:1, 2
3. Domain 3: System-Based Standards and Population-Based Pharmacotherapy, Tasks 1:4

I. ACUTE CORONARY SYNDROME

A. Definitions
1. Acute coronary syndrome (ACS) is a spectrum of conditions compatible with acute myocardial ischemia or infarction because of an abrupt reduction in coronary blood flow.
2. Atherogenic plaque rupture is the underlying pathophysiology for ACS, causing several prothrombotic substances to be released, which results in platelet activation and aggregation and eventual thrombus formation leading to partial or total occlusion of the coronary artery.
3. ACS can be divided into ST-segment elevation myocardial infarction (STEMI) and non–ST-segment elevation acute coronary syndrome (NSTE-ACS)
    a. STEMI
        i. Defined by characteristic symptoms of myocardial ischemia in association with persistent ST-segment elevation on ECG with positive troponins
        ii. STEMI is an indication for immediate coronary angiography to determine whether reperfusion can be performed.
    b. NSTE-ACS
        i. Suggested by the absence of persistent ST-segment elevation
        ii. NSTE-ACS can be divided into unstable angina (UA) and non-STEMI (NSTEMI) according to whether cardiac biomarkers of necrosis are present. UA and NSTEMI are closely related conditions whose pathogenesis and clinical presentation are similar but vary in severity.
        iii. Abnormalities on the ECG and elevated troponins in isolation are insufficient to make the diagnosis and must be interpreted in the appropriate clinical context (Table 1).
        iv. Optimal inhibition of thrombosis is paramount in the management of ACS.

B. Clinical Assessment and Initial Evaluation
1. A 12-lead ECG should be performed and interpreted within 10 minutes of presentation.
    a. Persistent ST-segment elevation should be treated according to the STEMI guidelines.
    b. Serial ECGs can be performed if initial is nondiagnostic.
2. Serial cardiac troponins (I or T) should be obtained at presentation and 3–6 hours after symptom onset.
3. At initial presentation, the clinical history, angina symptoms and equivalents, physical estimation, ECG, renal function, and cardiac troponin measurements can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events, which is useful for selecting the site of care, antithrombotic therapies, and invasive management. Risk calculators include the following:
    a. Thrombolysis in myocardial infarction (TIMI) risk score (available at www.timi.org [accessed December 13, 2017]) is useful in predicting 30-day and 1-year mortality in patients with NSTE-ACS.
        i. Composed of seven 1-point indicators rated on presentation; 1 point is given for each of the following: 65 years or older, three or more risk factors for CAD, prior coronary stenosis 50% or greater, ST deviation on ECG, two or more anginal events in previous 24 hours, use of aspirin in previous 7 days, and elevated cardiac biomarkers
        ii. Risk of mortality, new or recurrent MI, or severe recurrent ischemia through 14 days; 0–2 is low risk, 3 is intermediate risk, and 4 or more is high risk
        iii. Among patients with higher risk scores (e.g., TIMI of 3 or more), there is a greater benefit from therapies such as low-molecular-weight heparin, glycoprotein (GP) IIb/IIIa inhibitors, and invasive strategies.
    b. The Global Registry of Acute Coronary Events (GRACE) risk model (www.outcomes-umassmed.org/grace/acs_risk/acs_risk_content.html [accessed December 10, 2015]) predicts in-hospital and postdischarge mortality or MI. Patients with high GRACE risk model scores (i.e., GRACE score greater than 140) can be identified for early invasive strategies.

Table 1. ACS Definition

	Subjective Findings	Objective Findings	Extent of Injury
NSTE-ACS UA	Most commonly presents as a pressure-type chest pain that typically occurs at rest or with minimal exertion Pain most often starts in the retrosternal area and can radiate to either or both arms, neck, or jaw Pain may also present with diaphoresis, dyspnea, nausea, abdominal pain, or syncope Unexplained new-onset or increased exertional dyspnea is the most common angina equivalent Less common atypical symptoms[a] (without chest pain) include epigastric pain, indigestion, nausea, vomiting, diaphoresis, unexplained fatigue, and syncope	ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur No positive biomarkers for cardiac necrosis	No myocardial injury; partial occlusion of coronary artery
NSTEMI		ST-segment depression, T-wave inversion, or transient or nonspecific ECG changes can occur Positive biomarkers (troponin I or T elevation)	Myocardial injury; partial occlusion of coronary artery
STEMI	Classic symptoms include worsening of pain or pressure in chest, characterized as viselike, suffocating, squeezing, aching, gripping, and excruciating, that may be accompanied by radiation	ST-segment elevation > 1 mm above baseline on ECG in two or more contiguous leads Positive biomarkers (troponin I or T elevation)	Myocardial necrosis; total occlusion of coronary artery

[a]Up to half of all MIs are silent or unrecognized, and one-third present with symptoms other than chest discomfort.

NSTE-ACS = non–ST-segment elevation acute coronary syndrome; NSTEMI=non-ST segment elevation myocardial infarction; MI=myocardial infarction; STEMI= ST segment elevation myocardial infarction; UA = unstable angina.

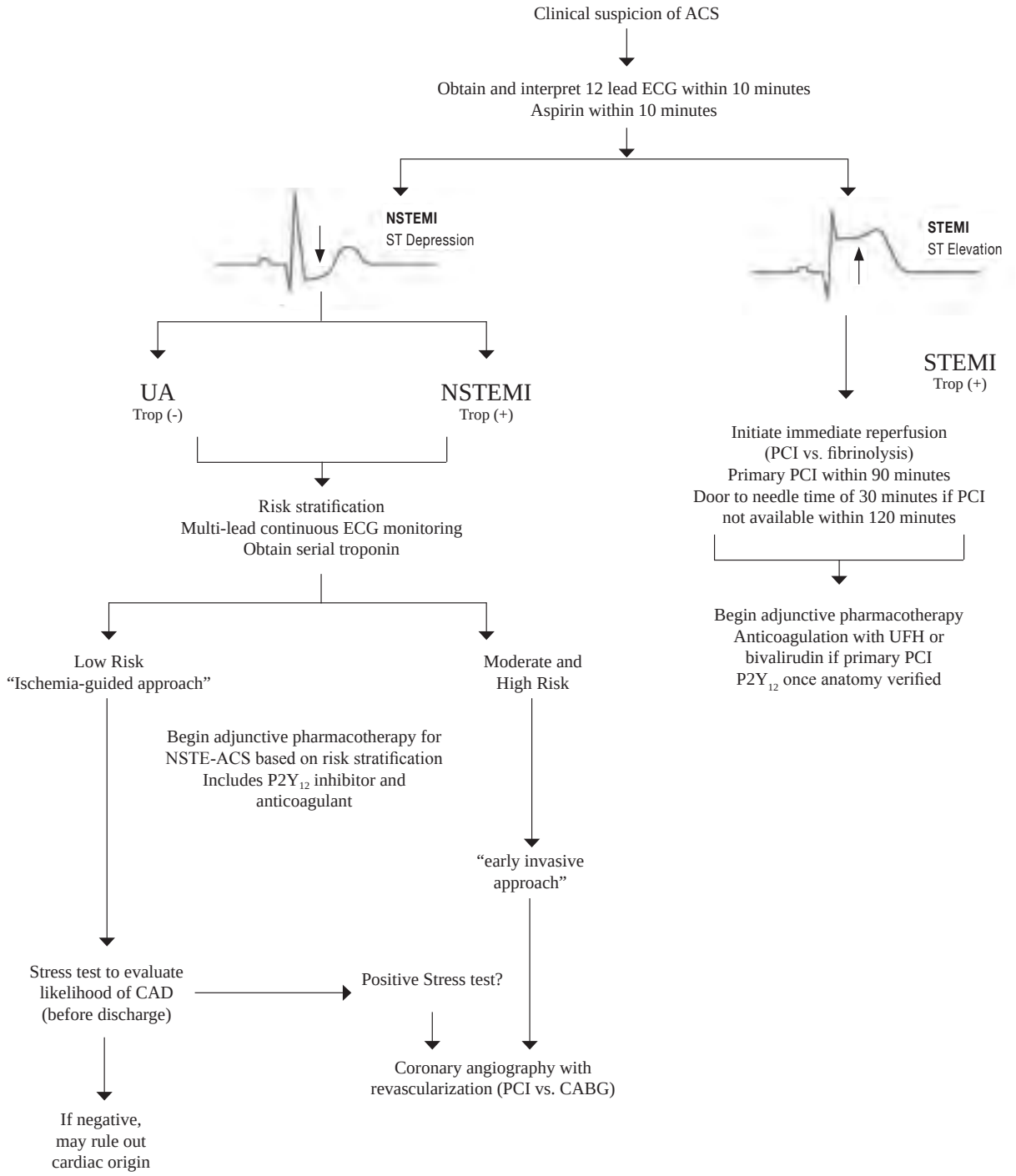

Figure 1. ACS diagnosis and risk stratification.

CABG = coronary artery bypass grafting.

C. Decision for Invasive Management
   1. STEMI
      a. The goal of therapy is to restore patency of the infarct-related artery and minimize infarct size. Secondary goals include prevention of complications such as arrhythmias or death as well as to control chest pain and associated symptoms.
      b. Requires urgent revascularization either interventionally or with drug therapy
      c. Primary PCI is preferred to lytic therapy. Performance measure includes goal of primary PCI within 90 minutes of first medical contact.
      d. Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed (discussed later in chapter). If PCI cannot be performed within 120 minutes, performance measure for lytic administration includes a door to needle time of 30 minutes.
   2. NSTE-ACS
      a. The goal of therapy is to prevent total occlusion of the related artery and to control chest pain and associated symptoms. Patients with NSTE-ACS are treated on the basis of risk (TIMI, GRACE) with either an early invasive strategy (interventional approach) or an ischemia-guided strategy (a conservative management strategy using medications rather than an interventional approach).
      b. Early invasive strategy is a diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy.
         i. Indicated in those with NSTE-ACS who have refractory angina or hemodynamic or electrical instability or those with high risk based on clinical findings
         ii. Routine invasive therapy is generally superior to an ischemia-guided strategy (results in lower rates of recurrent UA, recurrent hospitalization, MI, and death) in patients with one or more of the following risk features: advanced age (older than 70 years), previous MI or revascularization, ST deviation, HF, depressed resting left ventricle (LV) function (i.e., LVEF less than 40%), noninvasive stress findings, high TIMI or GRACE scores, markedly elevated troponins, and diabetes.
         iii. Not for those with serious comorbidities or contraindications to such procedures (hepatic, renal, pulmonary failure, cancer), for whom the risks for the procedure may outweigh the benefits of revascularization
         iv. Ischemia-guided therapy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability.
            (a) Recommended for patients with a low risk score (TIMI 0 or 1, GRACE less than 109)
            (b) Indicated for those with acute chest pain with a low likelihood of ACS who are troponin negative (preferred for low-risk women)
            (c) Can be chosen according to clinician and patient preference
   3. All patients should receive anti-ischemic and analgesic medications early in care: morphine, oxygen, nitroglycerin, and aspirin plus β-blocker (Table 2).

Table 2. Initial Anti-ischemic and Analgesic Therapies in the Management of Acute Coronary Syndrome

Therapy	Comments
M = Morphine or other narcotic analgesic	Provides analgesia and decreased pain-induced sympathetic/adrenergic tone Commonly used because it can also induce vasodilation and mediate some degree of afterload reduction Morphine 1–5 mg IV every 5–30 min is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications[a] Carries a class IIb recommendation and may not be favored more than other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death[b] Slows the absorption of antiplatelet therapy, reduces time to peak antiplatelet activity, and may decrease area under the curve
O = Oxygen	Can help attenuate anginal pain secondary to tissue hypoxia Consider supplemental oxygen if Sa_{O_2} < 90%, respiratory distress, or high-risk features of hypoxemia[c]
N = Nitroglycerin	Facilitates coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by venous capacitance NTG spray or sublingual tablet (0.3–0.4 mg) every 5 min for up to three doses to relieve acute chest pain (if pain is unrelieved after one dose, call 9-1-1); afterward, assess need for IV administration IV administration used in first 48 hr for treatment of persistent ischemic chest pain, HF, and HTN IV NTG 5–10 mcg/min; titrate to chest pain relief or max 200 mcg/min Use should not preclude other mortality-reducing therapies (β-blocker, ACE inhibitor) Contraindications: sildenafil or vardenafil (use within 24 hr) or tadalafil (use within 48 hr); SBP < 90 mm Hg or ≥ 30 mm Hg below baseline, HR < 50 beats/min, HR > 100 beats/min in absence of symptomatic HF or right ventricular infarction
A = Aspirin	Inhibits platelet activation Mortality reducing therapy Chew and swallow non–enteric coated 162–325 mg × 1 dose[c] Clopidogrel if aspirin allergy Performance measure
β-Blocker	Decrease myocardial ischemia, reinfarction, and frequency of dysrhythmias and increase long-term survival Oral β-blocker[c] should be initiated within 24 hr in patients who do not have signs of HF, evidence of low-output state, increased risk of cardiogenic shock, or other contraindications to β-blockade (e.g., PR interval > 0.24 s, second- or third-degree heart block, active asthma, or reactive airway disease) Reasonable to continue in patients with NSTE-ACS with normal LV function[a] Use metoprolol succinate, carvedilol, or bisoprolol in concomitant stabilized HFrEF[c]; add cautiously in decompensated HF Avoid agents with intrinsic sympathomimetic activity (acebutolol, pindolol, penbutolol) IV β-blocker[d] is potentially harmful in patients who have risk factors for shock (age > 70 yr, HR > 110 beats/min, SBP < 120 mm Hg, and late presentation)

[a]Class IIb may be considered.

[b]From: Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016-27; and Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J 2005;149:1043-9.

[c]Class I, should be performed or administered; class IIa, reasonable to be performed or administered.

[d]Class III, not to be administered or harmful.

ACE = angiotensin-converting enzyme; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricle; NTG = nitroglycerin; SBP = systolic blood pressure.

4. Patients with STEMI and NSTE-ACS should be treated with antiplatelet and anticoagulant therapy (Tables 3–9).
   a. Platelets are activated by several different mechanisms, only some of which can be inhibited by medications.
   b. Combination therapy with multiple antiplatelet agents plus a concomitant anticoagulant are the mainstay of acute ACS management, which targets the underlying pathophysiology of thrombus formation in ACS.
   c. The roles and combinations of antiplatelet therapies continue to be refined through clinical trials in varying subsets of ACS presentation (Table 3).
   d. In general, all patients receive aspirin and $P2Y_{12}$ receptor antagonists, and some patients benefit from the addition of GP IIb/IIIa inhibition in the acute management of ACS.

Table 3. Antiplatelet Management Strategies According to ACS Presentation

Antiplatelet	NSTE-ACS Ischemia Guided	NSTE-ACS Invasive	STEMI Primary PCI	STEMI + Fibrinolytic
Aspirin	Aspirin	Aspirin	Aspirin	Aspirin
$P2Y_{12}$ receptor antagonist	Clopidogrel Ticagrelor	Clopidogrel Prasugrel[a] Ticagrelor[a]	Clopidogrel Prasugrel Ticagrelor	Clopidogrel[b]
GP IIb/IIIa inhibitor	Greatest benefit when given to patients and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor[c]			

[a]It may be reasonable to choose ticagrelor or prasugrel (in those who are not at high bleeding risk) over clopidogrel in patients treated with early invasive strategy for NSTE-ACS (class IIa, 2014 NSTE-ACS guideline).

[b]Pre-PCI after fibrinolytic therapy: 300-mg loading dose if within 24 hr of event; clopidogrel 600-mg loading dose if > 24 hr after event.

[c]Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (those with elevated biomarkers, those with diabetes, those undergoing revascularization) and in those not receiving adequate pretreatment with $P2Y_{12}$. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel.

GP = glycoprotein; PCI = percutaneous coronary intervention.

   e. Antiplatelet recommendations
      i. Aspirin
         (a) An irreversible cyclooxygenase-1 inhibitor blocking the formation of thromboxane A_2– and thromboxane A_2–mediated platelet activation
         (b) Given to all patients (class I)
         (c) Established first-line therapy in ACS; reduces the incidence of recurrent MI and death
         (d) Loading dose is necessary for aspirin-naive patients; avoid enteric coated initially because of delayed and reduced absorption.
            (1) Dosing is 162–325 mg for patients at initial presentation of ACS (Table 4).
            (2) Dosing is 81–325 mg for those who are undergoing PCI, depending on chronic aspirin therapy regimen.
         (e) Aspirin is given indefinitely at a preferred dose of 81 mg after ACS with or without PCI (class I).
            (1) High dose (greater than 160 mg) is associated with more bleeding than lower dose (less than 160 mg).

(2) High dose (greater than 160 mg) has not been shown to improve outcomes after ACS more effectively than lower dose (less than 160 mg).

(f) Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ receptor inhibitor is indicated for all patients after ACS for at least 12 months (discussed later). The optimal dose of aspirin in patients treated with DAPT appears to be 75–100 mg daily.

Table 4. Guideline Recommendations for Aspirin Therapy in ACS with or without PCI

Guideline Recommendation	Class/Grade
Initiate 162–325 mg of ASA before PCI; after PCI, give ASA indefinitely • 2013 ACCF/AHA guideline for STEMI	I
Initiate 81–325 mg of nonenteric-coated ASA before PCI in patients already taking ASA; in patients not taking ASA, give 325 before PCI; after PCI, continue ASA indefinitely • 2014 NSTE-ACS guideline • 2011 ACCF/AHA/SCAI guideline for PCI	I
81 mg of ASA preferred to higher maintenance doses • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI • 2011 ACCF/AHA/SCAI guideline for PCI	IIa IIa IIa

Class I, should be performed or administered; Class IIa, reasonable to be performed or administered; Class IIb, may be considered; Class III, not to be administered or harmful.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ASA = acetylsalicylic acid; SCAI = Society for Cardiovascular Angiography and Interventions.

ii. $P2Y_{12}$ inhibitors

(a) Inhibit the effect of adenosine diphosphate on the platelet, a key mediator resulting in amplification of platelet activation

(b) $P2Y_{12}$ inhibitor therapy is given to all patients (class I).

(c) Choice of oral $P2Y_{12}$ inhibitor depends on an ischemia-guided therapy or early invasive approach and pharmacokinetic differences (Tables 5–7).

(1) Prasugrel should not be administered to patients with a history of stroke or transient ischemic attack (class III).

(2) The efficacy or ticagrelor is decreased in patients treated with higher doses of aspirin (greater than 300 mg daily) compared with lower doses (less than 100 mg daily).

(d) Clopidogrel and ticagrelor are preferred for a medical (i.e., ischemia-guided) strategy (Table 5).

(e) Clopidogrel, ticagrelor, and prasugrel are options for an early invasive strategy (Table 5).

(1) It is reasonable to choose ticagrelor over clopidogrel for $P2Y_{12}$ inhibition treatment in patients with NSTE-ACS or STEMI treated with an early invasive strategy or coronary stenting (class IIa).

(2) It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ inhibition treatment in patients with NSTE-ACS or STEMI who undergo PCI who are not at high risk of bleeding complications and have no history of transient ischemic attack or stroke (class IIa).

(f) No randomized data are available on the long-term safety or efficacy of "switching" patients treated for weeks or months with a $P2Y_{12}$ inhibitor to a different $P2Y_{12}$ inhibitor.

Table 5. Guideline Recommendations for $P2Y_{12}$ Inhibitor Therapy in ACS with or without PCI

Guideline Recommendation	Class/Grade[a]
A loading dose of $P2Y_{12}$ receptor inhibitor should be given before PCI. Options include: a. Clopidogrel[b] 600 mg followed by 75 mg daily b. Prasugrel 60 mg followed by 10 mg daily; or c. Ticagrelor 180 mg followed by 90 mg twice daily • 2013 ACCF/AHA guideline for STEMI • 2014 NSTE-ACS guideline	I LOE B LOE B LOE B
For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy: a. Clopidogrel 600 mg followed by 75 mg daily b. Ticagrelor 180 mg followed by 90 mg twice daily • 2014 NSTE-ACS guideline	I LOE B LOE B
For NSTE-ACS patients treated with an early invasive or ischemia-guided strategy: It is reasonable to use ticagrelor in preference to clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
For NSTE-ACS patients treated with PCI who are not at risk of bleeding complications • It is reasonable to choose prasugrel over clopidogrel • 2014 NSTE-ACS guideline	IIa LOE B
Prasugrel should not be administered to patients with a prior history of TIA or stroke • 2014 NSTE-ACS guideline • 2013 ACCF/AHA guideline for STEMI	Class III

[a]Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

[b]Before PCI after fibrinolytic therapy: 300-mg loading dose if within 24 hr of event; clopidogrel 600-mg loading dose if > 24 hr after event.

TIA = transient ischemic attack.

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Mechanism of action	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Thienopyridine; inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor	Inhibits ADP-mediated platelet activation at the $P2Y_{12}$ receptor
Peak platelet inhibition	300 mg load ~6 hr 600 mg load ~2 hr	60-mg load ~30 min[d]	180 mg load ~30 min[d]
% platelet inhibition	30%–40%	60%–70%	60%–70%
Loading dose	300–600 mg[e]	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily; (5 mg if < 60 kg, BW ≥ 75 years)[f]	90 mg BID[g]
Metabolism	Prodrug; converted by two-step process to active metabolite involving 2C19 in addition to other CYP enzymes	Prodrug; converted by one step to active metabolite by several CYP pathways	Not prodrug; reversible, noncompetitive binding; 3A4 (primary), 3A5, P-gp inhibitor
Reversible platelet binding	No	No	Yes
Half-life	8 hr (metabolite)	3.7 hr (metabolite, range 2–15 hr)	7 hr (parent), 9 hr (active metabolite)
Nonresponders	Exposure to active drug affected by *CYP2C19* genetic polymorphisms	No known issues	No known issues

Table 6. Comparison of Oral $P2Y_{12}$ Receptor Inhibitors

Parameter	Clopidogrel (Plavix)[a]	Prasugrel (Effient)[b]	Ticagrelor (Brilinta)[c]
Drug-disease interactions and common nonbleeding-related adverse events	PPIs inhibit *CYP2C19* (concomitant use with esomeprazole/omeprazole is discouraged on package labeling); increased bleeding with NSAIDs, OACs, O3FAs	No clinically significant drug interactions; more bleeding with NSAIDs, OACs	Careful with asthma, bradycardia: More bleeding with NSAIDs, OACs Strong 3A4 inhibitors increase ticagrelor concentrations; strong 3A4 inducers decrease ticagrelor concentrations; do not exceed 40 mg of simvastatin or lovastatin Limit aspirin to < 100 mg; monitor digoxin concentrations
Surgery hold time[h]	5 days	7 days	5 days
Bleeding risk	Less than PRA and TIC with standard dosing	Risk of non-CABG, spontaneous, and fatal bleeds higher than standard-dose clopidogrel	Risk of non-CABG bleeds higher than standard-dose clopidogrel
Box warning	*CYP2C19* polymorphisms	Age-related bleeding CVA	Aspirin dosing > 100 mg
Contraindications		TIA, CVA	ICH, severe hepatic disease
Supporting trials	CREDO, CURE, PCI-CURE, CLARITY, COMMIT	TRITON-TIMI 38, TRILOGY	PLATO, PEGASUS
FDA indication	ACS managed medically or with PCI	ACS with PCI	ACS managed medically or with PCI

[a]Administer clopidogrel indefinitely if aspirin allergy. Avoid loading dose if patient is ≥ 75 yr in STEMI when fibrinolysis is given.

[b]Avoid PRA in patients with active pathological bleeding or a history of TIA or CVA and in patients > 75 yr unless patient has diabetes mellitus or history of myocardial infarction.

[c]Avoid TIC in patients with active pathologic bleeding or a history of ICH. Avoid doses of aspirin > 100 mg daily (exception: first dose of 325 mg).

[d]A significant antiplatelet effect has been observed at 30 min. Onset of effect is quicker, and extent of platelet inhibition is greater than with clopidogrel.

[e]A 600-mg loading dose results in greater, more rapid, and more reliable platelet inhibition than a 300 mg loading dose.

[f]Although using 5 mg in patients weighing < 60 kg should be considered, this dose has not been studied in patients undergoing PCI.

[g]Maintenance dosing of 60 mg BID is FDA approved for reduction of thrombotic events after an initial 12 months of therapy.

[h]In emergency CABG, clopidogrel and ticagrelor should be held for at least 24 hr to minimize the risk of CABG-related bleeding.

ADP = adenosine diphosphate; BID = twice daily; BW = boxed warning; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; ICH = intracranial hemorrhage; NSAID = nonsteroidal anti-inflammatory drug; O3FA = omega-3 fatty acid; OAC = oral anticoagulant; P-gp = P-glycoprotein; PRA = prasugrel; TIC=ticagrelor.

iii. Intravenous $P2Y_{12}$ inhibitor
   (a) Cangrelor, a direct-acting, rapidly reversible, intravenous $P2Y_{12}$ inhibitor, achieves a high level of platelet inhibition (greater than 90% with a 30 mcg/kg intravenous bolus followed by a 4 mcg/kg/minute infusion) within 5 minutes and reaches steady state within 15–30 minutes of administration.
   (b) Rapid onset and offset (half-life less than 5 minutes) allows quick, high degree of platelet inhibition with resolution of normal platelet function within 1 hour of ending treatment.
   (c) Primarily studied in the setting of PCI only and may be considered in those who are not candidates for oral agents

(d) Pivotal trials comparing cangrelor with clopidogrel in ACS have not shown superiority of cangrelor; however, both the CHAMPION PHOENIX PCI and PLATFORM trials were discontinued prematurely.
(e) Cangrelor has had better efficacy than post-PCI clopidogrel with increases in minor bleeding (not major) (CHAMPION PHOENIX).
(f) Cangrelor treatment is associated with risk for dyspnea.
(g) Cangrelor has not been studied in settings with preloaded clopidogrel or compared with prasugrel or ticagrelor.
(h) Cangrelor has a potential use as a bridge therapy after discontinuation of oral $P2Y_{12}$ inhibitor in high-risk patients undergoing coronary artery bypass grafting (CABG) (Angiolillo 2012).
(i) The onset of action of both clopidogrel and prasugrel is delayed when coadministered with cangrelor, suggesting that cangrelor preferentially binds to the $P2Y_{12}$ and prevents irreversible inhibition with prasugrel and clopidogrel's active metabolite. Therefore, clopidogrel and prasugrel should not be initiated until termination of the cangrelor infusion. No such drug interaction exists with ticagrelor.
(j) Expense and lack of evidence demonstrating superiority to other $P2Y_{12}$ agents limits its use.
(k) Cangrelor has not been included in the ACS guidelines to date because FDA approval occurred after guideline release.

iv. Intravenous GP IIb/IIIa inhibitors
(a) Intravenous GP IIb/IIa receptor inhibitors can be added to aspirin with or without an oral $P2Y_{12}$ inhibitor for cardiovascular (CV) benefit in select high-risk patients in the acute management of ACS.
(b) Block the final common pathway of platelet aggregation; achieves 80% inhibition of ex vivo platelet aggregation
(c) GP IIb/IIIa inhibition may be beneficial in patients with high-risk features, particularly in those not adequately pretreated with $P2Y_{12}$ inhibition.
(d) Abciximab, double-bolus eptifibatide, and high-dose bolus tirofiban are class I options for invasive strategy (Table 7). Preferred options are eptifibatide and tirofiban (class IIb).

v. GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through a decrease in documented MI, but they can increase the risk of bleeding.
vi. Most, but not all, data were gathered in the era before routine $P2Y_{12}$ use.
vii. Benefit from adding GP IIb/IIIa inhibitors to aspirin therapy is greatest among those with highest-risk features (elevated biomarkers, diabetes, undergoing revascularization) and in those not receiving adequate pretreatment with clopidogrel or ticagrelor
viii. It is reasonable (class IIa, 2014 NSTE-ACS guideline) to give GP IIb/IIIa inhibitors to high-risk patients with NSTE-ACS treated with UFH and adequately pretreated with clopidogrel or ticagrelor.
ix. Most studies combined GP IIb/IIIa inhibitors with UFH as the anticoagulant.
x. Upstream administration (given before PCI) has not been shown to be superior to delayed administration (given at time of PCI).
(a) Upstream administration is noninferior to delayed timing for reducing ischemic events.
(b) Significantly higher rates of bleeding occur in those receiving upstream GP IIb/IIIa inhibitors than in those receiving delayed administration.
(c) Bolus-only GP IIb/IIIa inhibitor administration has been adopted in clinical practice but not into practice guidelines.

xi. Common adverse events of GP IIb/IIIa inhibitors:
  (a) Most common adverse effect is bleeding, with rates as low as 1.4% and as high as 10.6%, depending on length of therapy and how bleeding rates were accrued in the individual studies.
  (b) Note that the smaller-molecule agents eptifibatide and tirofiban depend on renal clearance; adjustment of the infusion is recommended to decrease risk of bleeding; monitor SCr (CrCl)
  (c) All GP IIb/IIIa inhibitors can cause thrombocytopenia; monitor hemoglobin (Hgb), hematocrit (Hct), and platelets.
    (1) Rates of thrombocytopenia (platelet count less than 50,000 cells/mm^3) with abciximab in clinical trials indicate 0.4%–1.4% incidence
    (2) When administered with UFH, rates of thrombocytopenia with either tirofiban or eptifibatide are no greater than UFH alone
  (d) The antiplatelet effects of abciximab can be reversed by platelet transfusion, whereas those of eptifibatide and tirofiban cannot.
  (e) Secondary to their short half-life, eptifibatide and tirofiban can be reversed within a few hours by discontinuing the infusion and are preferred options (Class IIb) in NSTE-ACS guideline .

Table 7. GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI[a]

Agent	Pretreated with $P2Y_{12}$	Not Pretreated with $P2Y_{12}$	Renal Adjustments
Abciximab (ReoPro)[b]	Of uncertain benefit	PCI: 0.25 mg/kg IVB, then 0.125 mcg/kg/min (max 10 mcg/kg) for 12 hr; ACS without PCI: not recommended	Not necessary
Eptifibatide (Integrilin)	Of uncertain benefit	PCI: 180 mcg/kg IVB × 2 (10 min apart); 2 mcg/kg/min initiated after first bolus for 18–24 hr[c]; ACS without PCI: of uncertain benefit in patients adequately pretreated with a $P2Y_{12}$ receptor inhibitor; single bolus used as above	If CrCl < 50 mL/min/1.73 m^2, reduce infusion 50%; avoid in patients on hemodialysis; not studied in patients with SCr > 4 mg/dL
Tirofiban (Aggrastat)	Of uncertain benefit	PCI: 25 mcg/kg IVB over 3 min; then 0.15 mcg/kg/min for 18 hr ACS without PCI[d]: 0.4 mcg/kg/min for 30 min (LD infusion), then 0.1 mcg/kg/min for 18–72 hr	If CrCl ≤ 60 mL/min/1.73 m^2, reduce infusion 50%

[a]GP IIb/IIIa inhibitors should be used in combination with heparin (either unfractionated heparin or low-molecular-weight heparin) or used provisionally with bivalirudin and aspirin.

[b]Not recommended in those not undergoing PCI because of clinical trial results.

[c]Double bolus is recommended to support PCI in STEMI and NSTE-ACS.

[d]Lower dose used to treat medically managed NSTE-ACS or when there is substantial delay to PCI (i.e., 48 hr).

CrCl = creatinine clearance; IVB = intravenous bolus; LD = loading dose.

xii. Platelet function testing
   (a) Although platelet function can be evaluated by platelet function testing or genotyping, neither is routinely performed in the clinical setting.
   (b) Clinical outcomes with use of platelet function testing to modify antiplatelet therapy (i.e., high-dose vs. standard-dose clopidogrel) in PCI patients with high on-treatment platelet reactivity have been negative to date). Outcomes with prospective genotype-guided antiplatelet therapy (CYP2C19) from large cohorts of PCI patients are forthcoming.
   (c) Routine use of platelet function and genetic testing is not currently recommended (class III: no benefit).

f. Anticoagulant recommendations
   i. Use of anticoagulants is mainly concentrated in the procedural setting, though use may continue for a finite period after the procedure.
   ii. Selection and use among agents may depend on ACS presentation, timing or dose of preprocedural antiplatelet medication, clot burden during procedure, and estimated risk of bleeding during procedure.
   iii. Anticoagulants increase the risk of bleeding and will require some type of monitoring for agent-specific risks.

Table 8. Anticoagulant Management Strategies in ACS

Management Strategy	Class I Recommendations[a]
STEMI (PPCI)	UFH, bivalirudin
STEMI, with fibrinolytic[b] therapy	UFH, enoxaparin, fondaparinux
NSTE-ACS, early invasive strategy	Enoxaparin, bivalirudin,[c] UFH
NSTE-ACS, ischemia-guided strategy	Enoxaparin, fondaparinux[d], UFH

[a]Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

[b]Fibrinolytics preferred when PCI cannot be performed within 120 min of first medical contact (class I). Door-to-needle time was < 30 min. Those who receive fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hr with IV UFH or IV/SC enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or IV/SC fondaparinux during hospitalization, up to 8 days.

[c]If bleeding risk is high, it is reasonable to use bivalirudin monotherapy in preference to UFH plus GP IIb/IIIa inhibitor (class IIa).

[d]Fondaparinux should not be used as the sole anticoagulant to support PCI. Give additional anticoagulant during revascularization if fondaparinux was initially chosen as the anticoagulant strategy. Fondaparinux is given a class I recommendation in the 2014 NSTE-ACS guidelines (for an ischemia-guided strategy) and a class III or harmful recommendation in the 2011 PCI and 2013 STEMI guidelines when PCI is indicated.

PPCI = primary percutaneous coronary intervention; UFH = unfractionated heparin.

g. Anticoagulant agents (see Table 9 for dosing and contraindications)
   i. UFH
      (a) Exerts its effects as an indirect thrombin inhibitor on fibrin-bound clots
      (b) Given as intravenous bolus with or without infusion and adjusted according to activated partial thromboplastin time (aPTT) or activated clotting time (ACT) to maintain therapeutic anticoagulation according to specific hospital protocol, usually continued for 48 hours or until PCI is performed
      (c) Risks include bleeding, thrombocytopenia, and HIT with or without thrombosis.
      (d) Monitoring includes aPTT or ACT, Hgb/Hct, and platelets.
      (e) Unlike other anticoagulants, UFH is not renally cleared and can be used safely in those with renal impairment.
   ii. Enoxaparin
      (a) Molecular weight is one-third of UFH with balanced anti-factor Xa (anti-Xa) and anti-IIa activity.

(b) Given as subcutaneous injection at least 2 inches on either side of the navel at a 90-degree angle into 1 inch of pinched skin (avoid injection into muscle); alternate dosing sites
(c) Does not require routine anti-Xa monitoring; SCr to calculate CrCl for dosing; monitor Hgb, Hct, platelets
(d) Risks include bleeding, injection site hematomas, spinal or epidural hematomas, retroperitoneal hematoma/bleeding, thrombocytopenia including HIT with or without thrombosis, mechanical prosthetic valve thrombosis (in pregnancy)

iii. Fondaparinux
(a) Selective inhibitor of activated factor X
(b) Longest half-life of anticoagulants (17 hours)
(c) Given as subcutaneous injection into fatty tissue, at a 90-degree angle into a pinched skinfold; alternate dosing sites between the left and right anterolateral and posterolateral abdominal wall
(d) Does not require routine anti-Xa monitoring; requires SCr to calculate CrCl to assess for contraindication; monitor Hgb, Hct, platelets
(e) Risks include bleeding, thrombocytopenia, and spinal or epidural hematomas.
(f) No increased risk of HIT

iv. Bivalirudin
(a) A direct thrombin inhibitor; directly inhibits thrombin in both circulating and bound clots and inhibits thrombin-mediated platelet aggregation
(b) Given as an intravenous bolus with or without infusion fixed rate and usually continued until the end of PCI (with or without delay after infusion in some high-risk patients)
(c) Does not require monitoring for adjustment; monitor SCr (adjustment required for infusion in those impaired CrCl), Hgb, Hct, platelets
(d) Can be given in patient with history of or suspected HIT undergoing PCI

v. An anticoagulant should be administered to all patients with ACS in addition to antiplatelet therapy to reduce the risk of intracoronary and catheter thrombus formation (Tables 8 and 9) irrespective of initial treatment strategy.
(a) Enoxaparin: 30-mg intravenous bolus, then 1 mg/kg subcutaneously every 12 hours (or 1 mg/kg subcutaneously once daily for CrCl less than 30 mL/minute), continued for the duration of hospitalization or until PCI is performed
(b) Bivalirudin: 0.1 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients with early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor
(c) Fondaparinux: 2.5 mg subcutaneously daily, continued for the duration of hospitalization or until PCI is performed
(d) Intravenous UFH: initial bolus of 60 units/kg (maximum 4000 units) with initial infusion of 12 units/kg/hour (maximum 1000 units/hour) adjusted on the basis of aPTT to maintain therapeutic anticoagulation according to specific hospital protocol, continued for 48 hours or until PCI is performed

vi. In an ischemia-guided strategy, UFH, enoxaparin, and fondaparinux are class I recommended options.

vii. For an invasive strategy, UFH, enoxaparin, and bivalirudin are class I recommended options.
(a) Fondaparinux should not be used as the sole anticoagulant to support PCI (class III). Give additional 85 units/kg of intravenous UFH immediately before PCI revascularization to reduce risk of catheter thrombosis if fondaparinux was initially chosen as the anticoagulant strategy if no GP IIb/IIIa inhibitor is used and 60 units/kg intravenously if a GP IIb/IIIa inhibitor is used with UFH dosing according to target-activated clotting time.

(b) Use of enoxaparin during PCI may be reasonable in patients treated with upstream subcutaneous enoxaparin with an ischemia-guided strategy.
  (1) An additional dose of 0.3 mg/kg intravenous enoxaparin should be administered at time of PCI to patients who have received fewer than two therapeutic subcutaneous doses or received the last subcutaneous dose 8–12 hours before PCI.
  (2) Patients who have received enoxaparin within 8 hours of the last subcutaneous dose generally have adequate anticoagulation to undergo PCI without supplemental bolus.
  (3) Patients who undergo PCI more than 12 hours after the last subcutaneous dose are usually treated with full-dose de novo anticoagulation with an established regimen (e.g., full-dose UFH or bivalirudin).
  (4) In patients who have not received anticoagulant therapy, a 0.5- to 0.75-mg/kg intravenous loading dose is needed.

(c) In those at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and GP IIb/IIIa receptor antagonist (class IIa).
  (1) For patients who have received UFH, wait 30 minutes and then give a 0.75-mg/kg intravenous loading dose, followed by a 1.75-mg/kg/hour intravenous infusion.
  (2) For patients already receiving bivalirudin infusion, give additional 0.5 mg/kg loading dose and increase infusion to 1.75 mg/kg/hour during PCI.

(d) Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.

viii. In patients undergoing primary PCI, either UFH or bivalirudin is preferred.

ix. When a fibrinolytic agent is given as a reperfusion strategy, UFH, enoxaparin, and fondaparinux are recommended.
  (a) Those given fibrinolytic therapy should receive anticoagulation after fibrinolysis for at least 48 hours with intravenous UFH or intravenous/subcutaneous enoxaparin during hospitalization, up to 8 days (preferred, selected patients), or intravenous/subcutaneous fondaparinux during hospitalization, up to 8 days.
  (b) Bivalirudin is not recommended in this population.

Table 9. Antithrombotic Dosing in ACS with or without PCI

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
Classification	—	LMWH	Factor Xa inhibitor	Direct thrombin inhibitor
NSTE-ACS	60 units/kg IVB (maximum 4000 units), 12 units/kg/hr IV (maximum 1000 units/hr) for 48 hr or until PCI performed; goal aPTT/anti-Xa according to hospital-specific protocol	1 mg/kg SC every 12 hr for 24–48 hr or until PCI performed or throughout hospitalization (up to 8 days); 30 mg IVB	2.5 mg SC daily	0.1 mg/kg IVB; then 0.25 mg/kg/hr IV (only for planned invasive strategy)

Table 9. Antithrombotic Dosing in ACS with or without PCI *(Cont'd)*

	UFH	Enoxaparin (Lovenox)	Fondaparinux (Arixtra)	Bivalirudin (Angiomax)
PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa inhibitors, UFH 50–70 units/kg IVB; if no GP IIb/IIIa inhibitors, UFH 70–100 units/kg IVB	If last dose < 8 hr, nothing additional needed; if last dose > 8 hr, 0.3 mg/kg IVB if last dose 8–12 hr before or < 2 therapeutic doses received before PCI	Fondaparinux should not be used as a sole anticoagulant for PCI	0.75 mg/kg IVB, 1.75 mg/kg/hr IV d/c at end of PCI, or continue for up to 4 hr after procedure if needed; hold UFH 30 min before administration
STEMI ± primary PCI	Supplemental doses to target ACT[a]; if GP IIb/IIIa, UFH 50–70 units/kg IVB; if no GP IIb/IIIa, UFH 70–100 units/kg IVB	30 mg IVB, followed immediately by 1 mg/kg SC every 12 hr; do not exceed 100 mg on first two doses; if > 75 yr, omit bolus; 0.75 mg/kg SC every 12 hr; do not exceed 75 mg on first two doses	2.5 mg IVB; then 2.5 mg SC daily	0.75 mg/kg IVB, 1.75 mg/kg/hr IV
Dose adjustments and contraindications	Avoid if history of HIT	If CrCl < 30 mL/min/1.73 m^2, 1 mg/kg SC daily; avoid if history of HIT	Contraindicated if CrCl < 30 mL/min/1.73 m^2	Adjust infusion dose in severe renal dysfunction If CrCl < 30 mL/min/1.73 m^2, reduce infusion to 1 mg/kg/hr; if on hemodialysis, reduce infusion to 0.25 mg/kg/hr

[a]Target ACT is 250–300 s for HemoTec and 300–350 s for Hemochron without GP IIb/IIIa inhibitors and is 200–250 s in patients given concomitant GP IIb/IIIa inhibitors.

ACT = activated clotting time; aPTT = activated partial thromboplastin time; HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; SC = subcutaneous(ly).

5. Fibrinolytic therapy is indicated for patients with STEMI in whom PCI cannot be performed (Table 10).
   a. In the absence of contraindications (Table 11), fibrinolytic therapy should be given to patients with STEMI (class I when onset of ischemic symptoms is within the previous 12 hours) when it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact, with an ideal door-to-needle time of less than 30 minutes.
   b. Patients undergoing reperfusion with fibrinolytics should receive anticoagulant therapy for at least 48 hours and preferably for the duration of the index hospitalization, for up to 8 days, or until revascularization is performed.
   c. Recommended regimens include the following:
      i. UFH administration of a 60-unit/kg bolus (maximum 4000 units) and 12 units/kg/hour (maximum 1000 units/hour), to obtain an aPTT of 1.5–2.0 times control (about 50–70 seconds)
      ii. Enoxaparin 30 mg intravenously (if 75 years or older, omit bolus), followed in 15 minutes by a 1 mg/kg subcutaneous injection (if 75 years or older, 0.75 mg/kg) every 12 hours for the duration of index hospitalization, for up to 8 days, or until revascularization. Maximum 100 mg for the first two doses. If 75 years or older, maximum 75 mg for the first two doses. If CrCl is less than 30 mL/minute/1.73 m^2, extend dosing interval to daily administration.
      iii. Fondaparinux administered with initial 2.5 mg intravenous dose, followed in 24 hours by 2.5 mg/day subcutaneous injections (contraindicated if CrCl is less than 30 mL/minute/1.73 m^2) for the duration of the index hospitalization, for up to 8 days, or until revascularization

Table 10. Fibrinolytic Therapy

	Dosing
Alteplase (t-PA, Activase)	≤ 67 kg: 15 mg IVP over 1–2 min, then 0.75 mg/kg IV over 30 min (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over 60 min > 67 kg: 15 mg IVP over 1–2 min, then 50 mg over 30 min, then 35 mg over 1 hr (maximum total dose 100 mg)
Reteplase (r-PA, Retavase)	10 units IVP; repeat 10 units IV in 30 min
Tenecteplase (TNK-t-PA, TNKase)	< 60 kg: 30 mg IVP; 60–69 kg: 35 mg IVP; 70–79 kg: 40 mg IVP; 80–89 kg: 45 mg IVP; > 90 kg: 50 mg IVP (~0.5 mg/kg)

IVP = intravenous push; r-PA = recombinant plasminogen activator; t-PA = tissue plasminogen activator.

Table 11. Contraindications to Fibrinolytic Therapy

Relative Contraindications	Absolute Contraindications
BP > 180/110 mm Hg on presentation or history of chronic poorly controlled HTN History of ischemic stroke > 3 mo before Recent major surgery (< 3 wk before) Traumatic or prolonged CPR (> 10 min) Recent internal bleeding (within 2–4 wk) Active peptic ulcer Noncompressible vascular punctures Pregnancy Known intracranial pathology (dementia) Oral anticoagulant therapy	Any prior hemorrhagic stroke Ischemic stroke within 3 mo (except in past 4½ hr) Intracranial neoplasm or arteriovenous malformation Active internal bleeding Aortic dissection Considerable facial trauma or closed-head trauma in past 3 mo Intracranial or intraspinal surgery within 2 mo Severe uncontrolled HTN (unresponsive to emergency therapy) For streptokinase,[a] treatment within previous 6 mo (if considering streptokinase again)

[a]Streptokinase is no longer marketed in the United States but is available in other countries.

BP = blood pressure; CPR = cardiopulmonary resuscitation.

D. Long-term Management After ACS
   1. DAPT: 12 months
      i. Aspirin should be continued indefinitely at a maintenance dose of 81 mg daily in all patients after ACS (class I).
      ii. In patients who were treated with an ischemia-guided therapy, aspirin plus either clopidogrel 75 mg daily or ticagrelor 90 mg twice daily should be continued for up to 12 months.
      iii. After PCI (bare metal stent or drug-eluting stent), aspirin plus clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be continued for at least 12 months.
   2. Early discontinuation of DAPT
      a. Early discontinuation is reasonable when the risk of morbidity exceeds the anticipated benefit (class IIa).
         i. DAPT should be continued after ACS (with or without stent) for at least 12 months (class I)
         ii. Shorter-duration DAPT can be considered for patients with stable ischemic heart disease who have undergone PCI with elective stent placement (class I, 6 months duration for elective PCI).
      b. In general, shorter durations of DAPT are appropriate for those with a lower ischemic risk and a high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischemic risk with a lower bleeding risk.
         i. No trials have compared duration of DAPT specifically in ACS.
         ii. Prior recommendations for DAPT duration for patients treated with drug-eluting stents were based on data from first-generation stents.

iii. Trials comparing shorter durations of DAPT have evaluated newer-generation stents in all patients undergoing PCI (including elective cases).
iv. Compared with first-generation stents, newer-generation stents have an improved safety profile and lower risk of stent thrombosis.

3. Long-term DAPT
   a. In general, longer-duration DAPT may be reasonable for patients at higher ischemic risk with a lower bleeding risk.
   b. Trials evaluating the need for an extended duration in patients with and without ACS undergoing PCI (greater than 12 months) of DAPT therapy after PCI show a reduction in stent thrombosis and ischemia end points with increased bleeding for patients continued on DAPT beyond 12 months.
   c. The risk of stent thrombosis is greater on cessation of DAPT; however, continued DAPT beyond 1 year is unassociated with a reduction in CV or total mortality.
   d. A longer duration of $P2Y_{12}$ inhibitor therapy is an individualized approach according to the patient's risk of ischemia and bleeding.
      i. It is reasonable to consider DAPT beyond 12 months if the patient is tolerating therapy and not at high risk of bleeding (class IIb).
      ii. Durations of DAPT may be reasonable beyond 12 months if patient is at high risk and no significant history of bleeding on DAPT (class IIb).
      iii. A DAPT score derived from the dual antiplatelet study may be useful in making decisions about whether to prolong or extend DAPT in patients treated with coronary stent implantation (Table 12).
         (a) For those with a high DAPT score (2 or greater), prolonged DAPT reduces net (ischemic plus bleeding) events.
         (b) For those with a low DAPT score (less than 2), the benefit-risk ratio for prolonged DAPT is not favorable (increased bleeding without a reduction in ischemic events
         (c) Derived from the DAPT study, which included 11,648 patients with mainly clopidogrel as $P2Y_{12}$ inhibitor
         (d) Duration of DAPT more or less than 12 months should jointly be made by the clinician and the patient, balancing the risks of stent thrombosis and ischemic complications with risks of bleeding.
   e. Ticagrelor has been shown to reduce CV end points of death, MI, and revascularization better than placebo at a reduced dose of 60 mg twice daily (after at least 12 months of 90 mg twice daily) with less bleeding than extended use of 90 mg twice daily. (Bonaca 2015)

4. β-Blockers
   a. Indicated for all patients unless contraindicated
   b. If not started orally within the first 24 hours, reevaluate for possible initiation before discharge.
   c. Continue for at least 3 years (when EF is greater than 40%).
   d. If moderate or severe LV failure, initiate carvedilol, bisoprolol, or metoprolol succinate with gradual titration. Continue indefinitely in patients with EF less than 40%.
5. Angiotensin-converting enzyme (ACE) inhibitors
   a. ACE inhibitors should be started and continued indefinitely for all patients with LVEF of 40% or less and in those with hypertension, diabetes mellitus, or stable chronic kidney disease unless contraindicated.
   b. ACE inhibitors may be acceptable in all other patients with cardiac or other vascular disease.
   c. Angiotensin receptor blocker is indicated if the patient has contraindications to or is intolerant of ACE inhibitors.
   d. Contraindications include hypotension, pregnancy, and bilateral renal artery stenosis.

Table 12. DAPT Score to Determine Favorability of Prolonged DAPT

Factors Used to Calculate DAPT Score	Add Points for Total Score[a]
Age ≥ 75 yr	-2
Age 65–74 yr	-1
Current tobacco user	1
Diabetes mellitus	
NSTEMI or STEMI at presentation	
Prior MI or PCI	
Stent diameter < 3 mm	
Paclitaxel-eluting stent	
CHF or LVEF < 30%	2
Saphenous vein graft PCI	2

[a]A score ≥ 2 favors prolonged DAPT; a score < 2 is of unfavorable risk-benefit.

CHF = congestive heart failure; DAPT = dual antiplatelet therapy; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

From: Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082-115; and Yeh RW, Secemsky EA, Kereiakes DJ, et al. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. JAMA 2016;315:1735-49.

6. Aldosterone receptor blockers
   a. Indicated in patients who are already receiving an ACE inhibitor and β-blocker after MI and who have an LVEF of 40% or less and either symptomatic HF or diabetes, unless contraindicated
   b. Contraindications include hyperkalemia (potassium [K^+] 5.0 or greater), CrCl less than 30 mL/minute/1.73 m^2, and SCr greater than 2.5 mg/dL in men and greater than 2.0 mg/dL in women.
7. Lipid management: High-intensity statins are indicated in all patients after ACS without contraindication. In high-risk patients achieving a less-than-anticipated response to statins (less than a 50% reduction in LDL), or in those who are completely statin intolerant, non-statin therapy may be considered for CV benefit.
   a. Depending on additional desired LDL percentage reduction, consideration can be given to either ezetimibe or a PCSK9 inhibitor in combination with statin therapy in very high-risk patients.
   b. Both ezetimibe and evolocumab (given in combination with statins) have been shown to reduce CV end points.
8. Pain control
   a. NSAIDs and select cyclooxygenase-2 inhibitors (class III) should be discontinued at time of presentation because they have been associated with increased risk of major adverse cardiac events.
   b. Before discharge, the patient's musculoskeletal discomfort should be addressed, and a stepped-care approach should be used for selection of therapy.
   c. Pain should be treated with acetaminophen, nonacetylated salicylates, tramadol, or narcotics at the lowest dose to control symptoms.
   d. It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy is insufficient.
      i. Monitor regularly for sustained hypertension, edema, worsening renal function, or gastrointestinal (GI) bleeding.
      ii. If these occur, consider dose reduction or discontinuation.
9. Vaccination
   a. Pneumococcal vaccination is recommended for patients 65 years and older and in high-risk patients (including smokers with asthma) with CV disease.
   b. An annual influenza vaccination is recommended for patients with CV disease.

10. Patient education
    a. All patients should be counseled on the duration of DAPT and the avoidance of premature discontinuation.
    b. Patients should be educated about appropriate cholesterol management, blood pressure control, smoking cessation, and lifestyle management.
    c. Risk factor modification should be addressed in all patients after ACS.
11. Cardiac rehabilitation: All eligible patients should be referred to a comprehensive CV rehabilitation program.

E. Special Populations
1. Antiplatelet recommendations in patients going on to CABG
    a. Aspirin should be continued preoperatively to patients undergoing CABG (81–325 mg).
    b. In patients referred for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery and prasugrel for at least 7 days before surgery.
    c. In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding.
    d. In patients referred for CABG, short-acting GP IIb/IIIa (eptifibatide or tirofiban) should be discontinued for at least 2 hours before surgery and abciximab for at least 12 hours to limit blood loss and transfusion.
2. Combined oral anticoagulant therapy and antiplatelet therapy in NSTE-ACS
    a. The duration of triple antithrombotic therapy with an oral anticoagulant, low-dose aspirin, and a $P2Y_{12}$ inhibitor (clopidogrel preferred) should be minimized to the extent possible to limit the risk of bleeding.
    b. Proton pump inhibitors should be prescribed to those with a history of GI bleeding (and is reasonable in those without a known history of GI bleeding) who need triple antithrombotic therapy.
    c. Targeting a lower international normalized ratio (INR) of 2.0–2.5 may be reasonable (class IIb in NSTE-ACS guideline; class IIa in STEMI guideline) in patients needing triple therapy.
3. Older patients (i.e., 75 years or older)
    a. Doses should be individualized by weight or CrCl to reduce adverse events caused by age-related changes in pharmacokinetics and dynamics, volume of distribution, comorbidities, drug interactions, and increased drug sensitivity.
    b. Bivalirudin, rather than GP IIb/IIIa inhibitors plus UFH, is reasonable in older patients given similar efficacy but less bleeding (class IIa).
    c. CABG may be preferred to PCI in older patients, particularly those with diabetes mellitus or complex three-vessel disease (e.g., SYNTAX score greater than 22), with or without involvement of the proximal left anterior descending artery.
4. Chronic kidney disease
    a. CrCl should be estimated in patients with ACS, and doses of renally cleared medications should be adjusted accordingly.
    b. Patients with chronic kidney disease undergoing coronary and LV angiography should receive adequate hydration and reduced contrast volume.
    c. In patients with CrCl less than 60 mL/minute/1.73 m^2, ticagrelor was associated with a 4% absolute risk reduction in all-cause mortality compared with clopidogrel in a prespecified analysis from PLATO without increased risk of bleeding.
    d. No clinical trials to date have shown the utility of prasugrel in renal insufficiency.

5. Women
    a. Women of all ages have higher rates of in-hospital and long-term complications from ACS than men.
    b. Women derive the same benefit from aspirin, $P2Y_{12}$ inhibitors, anticoagulants, β-blockers, ACE inhibitors, and statins as men, but women may be at higher risk of adverse events.
        i. Women incur a higher rate of bleeding complications, renal failure, and vascular complications.
        ii. A risk score has been developed to attempt to reduce bleeding risk.
    c. Women with NSTE-ACS and high-risk features (e.g., troponin positive) should undergo an early invasive strategy.
    d. Women with NSTE-ACS and low-risk features should not undergo early invasive treatment because of the lack of benefit and potential for harm (class III).
    e. Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given as new drugs for secondary prevention and should not be continued in previous users unless the benefits outweigh the estimated risks.
        i. Hormone therapy increases the risk of thrombotic events, especially in the first year of therapy, and does not provide CV protection.
        ii. Women who are more than 1 year past the initiation of hormone therapy who want to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of CV events and breast cancer (combination therapy) or stroke (estrogen).

Patient Cases

1. A 66-year-old woman (weight 70 kg) with a history of MI, hypertension, hyperlipidemia, and diabetes mellitus presents with sudden-onset diaphoresis, nausea, vomiting, and dyspnea, followed by a bandlike upper chest pain (8/10) radiating to her left arm. She had felt well until 1 month ago, when she noticed her typical angina was occurring with less exertion. Electrocardiography revealed ST-segment depression in leads II, III, and aVF and hyperdynamic T waves and positive cardiac enzymes. Blood pressure is 150/90 mm Hg, and all laboratory results are normal; SCr is 1.2 mg/dL. Home medications are aspirin 81 mg/day, simvastatin 40 mg every night, metoprolol 50 mg twice daily, and metformin 1 g twice daily. Which regimen is the best treatment strategy for this patient?

    A. Aspirin 325 mg, ticagrelor 180 mg × 1 dose, and UFH 60-unit/kg bolus; then 12 units/kg/hour titrated to 50–70 seconds with an early invasive approach.

    B. Aspirin 325 mg and enoxaparin 70 mg subcutaneously twice daily with an early invasive approach.

    C. An ischemia-guided strategy with abciximab 0.25 mg/kg bolus; then 0.125 mg/kg/minute for 12 hours plus enoxaparin 80 mg subcutaneously twice daily, aspirin 325 mg/day, and clopidogrel 300 mg 1 dose; then 75 mg once daily.

    D. An ischemia-guided strategy with aspirin 325 mg and ticagrelor 180 mg × 1 dose; plus UFH 70-unit/kg bolus; then 15 units/kg/hour.

2. A 45-year-old patient underwent an elective percutaneous transluminal coronary angioplasty and drug-eluting stent placement in her right coronary artery. Which duration best represents the minimum time DAPT should be continued?

    A. At least 1 month.

    B. At least 3 months.

    C. At least 6 months.

    D. At least 12 months.

Patient Cases *(Cont'd)*

3. A 52-year-old man (weight 100 kg) with a history of hypertension and hypertriglyceridemia presents at a major university teaching hospital with a cardiac catheterization laboratory. He has had 3 hours of crushing 10/10 substernal chest pain radiating to both arms that began while he was eating his lunch (seated), which is accompanied by nausea, diaphoresis, and shortness of breath. He has never before experienced chest pain of this character or intensity. He usually can walk several miles without difficulty and smokes 1.5 packs of cigarettes per day. Home medications are lisinopril 2.5 mg/day and aspirin 81 mg daily. Current vital signs include heart rate 68 beats/minute and blood pressure 178/94 mm Hg. Electrocardiography reveals a 3-mm ST-segment elevation in leads V_2–V_4, I, and aVL. Serum chemistry values are within normal limits. The first set of cardiac markers shows positive troponins, 0.8 mcg/L (normal defined as less than 0.1 mcg/L). Which regimen is best to treat this patient's STEMI?

   A. Reperfusion with primary PCI and stenting of occluded artery, together with abciximab 0.25 mcg/kg intravenous push, then 0.125 mg/kg/minute, clopidogrel 300 mg 1 dose, and aspirin 325 mg 1 dose.

   B. Reperfusion with a reteplase 10-unit bolus twice, 30 minutes apart, plus a UFH 60-unit/kg bolus and a 12-unit/kg/hour infusion, clopidogrel, and aspirian.

   C. Reperfusion with tenecteplase 25-mg intravenous push 1 dose, enoxaparin 30-mg intravenous bolus plus 100 mg subcutaneously twice daily, aspirin 325 mg x 1 dose, ticagrelor 180 mg x 1 dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

   D. Reperfusion with primary PCI with stenting, prasugrel 60 mg 1 dose, aspirin 325 mg 1 dose, and bivalirudin 0.75 mg/kg followed by 1.75 mg/kg/hour.

4. A 76-year-old male smoker (weight 61 kg) has a history of hypertension, benign prostatic hypertrophy, and lower back pain. Three weeks ago, he began to experience substernal chest pain with exertion (together with dyspnea), which radiated to both arms and was associated with nausea and diaphoresis. Episodes have increased in frequency to four or five times daily; they are relieved with rest. He has never had an ECG. Today, he awoke with 7/10 chest pain and went to the emergency department of a rural community hospital 2 hours later. He was acutely dyspneic and had ongoing pain. Home medications are aspirin 81 mg/day for 2 months, doxazosin 2 mg/day, and ibuprofen 800 mg three times daily. Vital signs include heart rate 42 beats/minute (sinus bradycardia) and blood pressure 104/48 mm Hg. Laboratory results include blood urea nitrogen (BUN) 45 mg/dL, SCr 2.5 mg/dL, and troponin 1.5 mcg/L (normal value less than 0.1 mcg/L). His ECG reveals a 3-mm ST-segment elevation. Aspirin, ticagrelor, and sublingual nitroglycerin were given in the emergency department. The nearest hospital with a catheterization laboratory facility is 2.5 hours away. Which regimen is best?

   A. Give alteplase 15 units intravenously plus enoxaparin 30 mg intravenous bolus.

   B. Use an ischemia-guided treatment strategy with UFH 4000-unit intravenous bolus, followed by 800 units intravenously per hour.

   C. Give tenecteplase 35 mg intravenously plus UFH 4000-unit intravenous bolus followed by 800 units intravenously per hour.

   D. Transfer the patient to a facility for primary PCI.

II. ACUTE DECOMPENSATED HEART FAILURE

A. Precipitating Factors
   1. Medication related (nonadherence to medications, recent addition of negative inotropic drugs, initiation of medications that enhance salt retention, excessive alcohol or illicit drug use)
   2. Disease related (nonadherence to sodium or fluid restriction, acute myocardial ischemia, uncorrected high blood pressure, pulmonary embolus, atrial fibrillation or other arrhythmias, concurrent infections, other acute CV disorders)

B. Diagnosis
   1. Must include a detailed history and physical examination
   2. B-type natriuretic peptide (BNP) or NT-proBNP useful to support diagnosis and establish prognosis for acute decompensated heart failure (ADHF)
   3. Hemodynamic monitoring (Table 13)
      a. Routine use of hemodynamic monitoring with invasive intravenous lines (e.g., Swan-Ganz pulmonary artery catheters) is not recommended; however, signs and symptoms of congestion and perfusion (Table 14) or noninvasive means to determine hemodynamic values are commonly used to determine status of decompensation.
      b. Hemodynamic monitoring with pulmonary artery catheters is helpful for evaluating patients refractory to initial therapy, for those with unknown or unclear volume status, or for those with clinical significant hypotension or worsening renal function.

Table 13. Hemodynamic Values in Patients with ADHF and Sepsis

Parameter	Normal Value	Typical ADHF Value	Typical Sepsis Value
Mean arterial pressure[a] (MAP; mm Hg)	80–100	60–80	60–80
Heart rate (HR; beats/min)	60–80	70–90	90–100
Cardiac output (CO; L/min)[b]	4–7	2–4	5–8
Cardiac index (CI; L/min/m^2)[c]	2.8–3.6	1.3–2	3.5–4
Pulmonary capillary wedge pressure (mm Hg)[d]	8–12[b]	18–30	5–8
Systemic vascular resistance (SVR; dynes/s/cm^5)[e]	900–1400	1500–3000	300–800
Central venous pressure (CVP; mm Hg)[f]	2–6	6–15	2–6

[a]MAP = diastolic blood pressure + [⅓(SBP − diastolic blood pressure)].

[b]CO = stroke volume × HR.

[c]CI = CO/body surface area.

[d]A range of 15–18 mm Hg is often desired or optimal in patients with HF to ensure optimal filling pressures.

[e]VR = [(MAP − CVP) / CO] × 80.

[f]BP = CO × SVR.

C. Clinical Presentation
   1. Patients with ADHF can be categorized into four subsets on the basis of fluid status and cardiac function (Figure 2).
   2. "Wet or dry" is commonly used to describe volume status.
   3. "Warm or cold" is used to describe cardiac function or ability to perfuse tissues.

Table 14. Signs and Symptoms of ADHF

Congestion (elevated PCWP)	Hypoperfusion (low CO)
Dyspnea on exertion or at rest Orthopnea, paroxysmal nocturnal dyspnea Peripheral edema Rales Early satiety, nausea, or vomiting Ascites Hepatomegaly, splenomegaly Jugular venous distension Hepatojugular reflux	Fatigue Altered mental status or sleepiness Cold extremities Worsening renal function Narrow pulse pressure Hypotension Hyponatremia

CO = cardiac output; PCWP = pulmonary capillary wedge pressure.

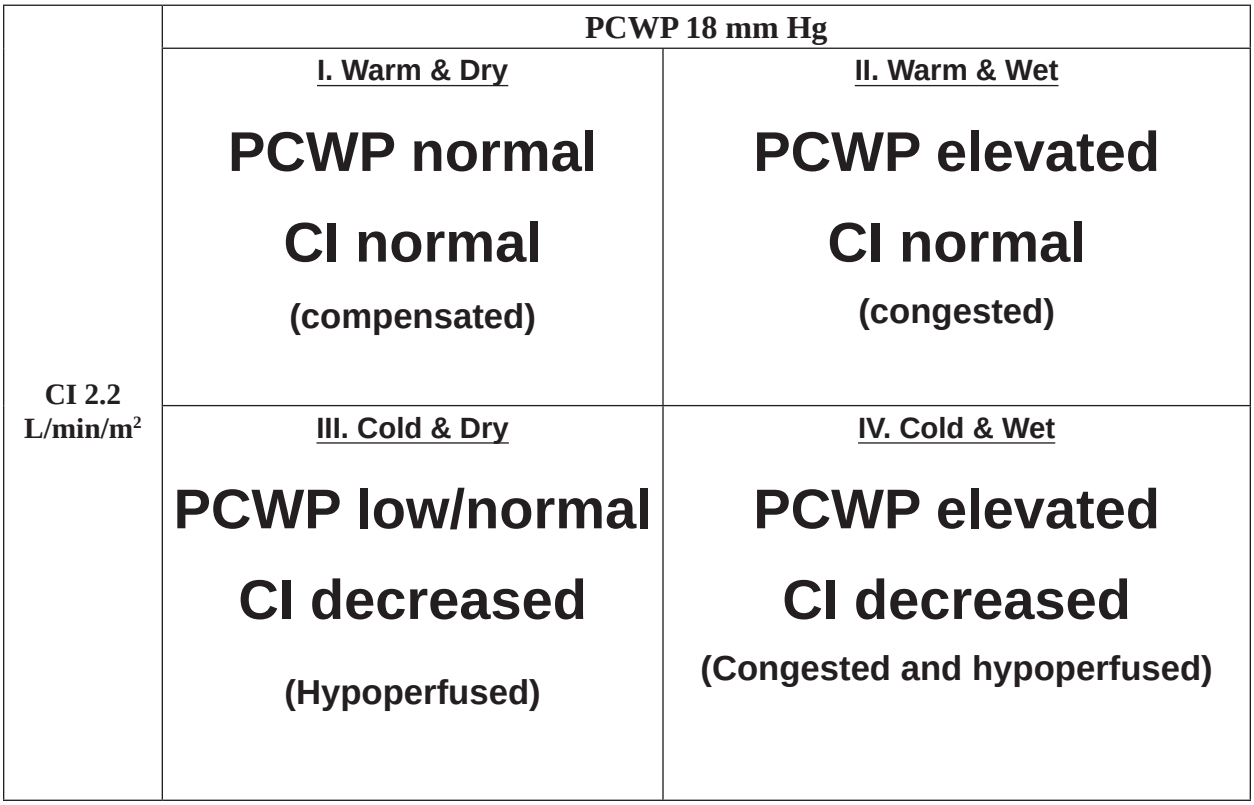

Figure 2. Forrester hemodynamic subsets based on signs and symptoms or hemodynamic parameters in ADHF

Table 15. ADHF Therapy Based on Hemodynamic Subset

Subset and description	Treatment
Subset I: Warm and Dry (normal parameters) (PCWP 15–18 mm Hg[a] and CI > 2.2 L/min/m^2)	Optimize oral medications
Subset II: Warm and Wet (pulmonary or peripheral congestion) (PCWP > 18 mm Hg and CI >2.2 L/min/m^2)	IV diuretics ± IV vasodilators (venous[b]) If symptoms persist, adjunct strategies to overcome diuretic resistance may be necessary.
Subset III: Cold and Dry (hypoperfusion ± orthostasis) (PCWP 15–18 mm Hg[a] and CI < 2.2 L/min/m^2)	If PCWP < 15 mm Hg, IVF until PCWP = 15–18 mm Hg If PCWP ≥ 15 mm Hg, SBP <90 mm Hg, IV inotrope[c] If PCWP ≥ 15 mm Hg, SBP ≥90 mm Hg, IV vasodilator (arterial[d]) ±IV vasopressor[e] if needed
Subset IV: Cold and Wet (pulmonary/peripheral congestion + hypoperfusion) (PCWP >18 mm Hg and CI < 2.2 L/min/m^2)	IV diuretics + If SBP ≥90 mm Hg, IV vasodilator (arterial[d]) If SBP <90 mm Hg, IV inotrope[c] ±IV vasopressor[e] if needed

[a]Goal PCWP is 8–12 mm Hg in a normal patient and 15–18 mm Hg in a patient with HF. If PCWP < 15 mm Hg in a patient with HF, either remove fluid restriction or cautiously administer fluids until PCWP is 15–18 mm Hg and then reassess CI.

[b]Venous vasodilator: Reduces PCWP.

[c]Compelling reason for inotrope = SBP < 90 mm Hg, symptomatic hypotension, or worsening renal function.

[d]Arterial vasodilator: reduce systemic vascular resistance with compensatory increase in CI.

[e]IV vasopressors may be required when marked hypotension precludes the use of traditional IV inotropes (e.g., septic or cardiogenic shock) but are generally avoided in ADHF

CI = cardiac index; IV = intravenous(ly); IVF = intravenous fluids; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

D. Chronic HF Therapy in the Setting of Acute Decompensation
   1. It is recommended to continue guideline-directed medical therapies during decompensation unless hemodynamic instability or contraindications exist (e.g., hypotension, cardiogenic shock).
   2. ACE inhibitors
      a. Caution with initiation or titration during aggressive diuresis
      b. Increases in SCr (decrease in glomerular filtration rate of 20% or more) from ACE inhibitor use are not associated with worse outcomes.
   3. β-Blockers
      a. Do not discontinue in patients who are stable on dose before admission (i.e., recent initiation or titration was not responsible for decompensation).
      b. Initiation is recommended after optimization of volume status and successful discontinuation of intravenous diuretics, vasodilators, and inotropic agents.
      c. Should be initiated at a low dose only in stable, euvolemic patients
      d. Caution should be used when initiating in patients who have received inotropes during their hospital course.
   4. Digoxin
      a. Continue at dose to achieve serum digoxin concentration of 0.5–0.8 ng/mL.
      b. Avoid discontinuation unless there is a compelling reason to do so, because digoxin withdrawal has been associated with worsening HF symptoms.
      c. Caution if renal function begins to deteriorate or often fluctuates

E. ADHF Therapy Overview (Table 15; Box 1)
   1. The main drug classes used to treat ADHF include diuretics, inotropes, and vasodilators.
   2. No therapy studied to date has been shown conclusively to decrease mortality.
   3. Treatments are directed toward relieving symptoms, restoring perfusion, and minimizing further cardiac damage and adverse events.

Box 1. Overview of Acute Decompensated Heart Failure Guideline Recommendations

Diuretic therapy Recommended as intravenous loop diuretics for patients with fluid overload. Change to oral route on day before discharge, if possible. When response to diuretics is minimal, the following options should be considered: • Fluid and sodium restriction • Initiation of increased doses or continuous infusion of loop diuretic • Addition of a second diuretic with a different mechanism of action (metolazone, hydrochlorothiazide, chlorothiazide) • Ultrafiltration
Inotropic therapy May be considered to relieve symptoms and improve end-organ function in patients with reduced left ventricular ejection fraction and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if • Marginal SBP (< 90 mm Hg) • Symptomatic hypotension despite adequate filling pressure • No response to or intolerance of intravenous vasodilators May be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function
Vasodilator therapy May be considered in addition to intravenous loop diuretics to rapidly improve symptoms in patients with acute pulmonary edema or severe hypertension (if symptomatic hypotension absent) May be considered in patients with persistent symptoms despite aggressive diuretics and oral drug therapy When adjunctive therapy is necessary in addition to loop diuretics, intravenous vasodilators should be considered over inotropic drugs

F. Diuretics (Box 2): Used primarily to treat patients with pulmonary and peripheral congestion or wet (subset II or IV) HF
   1. Considered first-line therapy for management of ADHF associated with fluid overload
   2. No difference between bolus and continuous administration of intravenous diuretics
   3. Administering high-dose intravenous diuretic (2.5 times the previous oral dose) is associated with greater fluid removal.

Box 2. Diuretic Therapy for Acute Decompensated Heart Failure

Loop diuretics (ascending limb of loop of Henle)
Most widely used and most potent, effective at low CrCl (< 30 mL/min/1.73 m^2)
Furosemide most commonly used; furosemide 40 mg PO = furosemide 20 mg IV = bumetanide 1 mg IV or PO = torsemide 20 mg IV or PO
Thiazides (distal tubule)
Weak diuretics when used alone, not effective at low glomerular filtration rate (CrCl < 30 mL/min/1.73 m^2)
Reserved for add-on therapy in patients refractory to loops
Diuretic resistance
Increase dose before increasing frequency of loop diuretic (note ceiling effect at ~160–200 mg of IV furosemide)
Add a second diuretic with a different mechanism of action • Hydrochlorothiazide 12.5–25 mg PO daily, metolazone 2.5–5 mg PO daily (30 min before loop diuretic administration) • Chlorothiazide 250–500 mg IV daily; consider if GI edema; generic is very expensive; reserve for NPO or refractory to other alternatives
Continuous infusion of loop diuretic: Furosemide 0.1 mg/kg/hr IV doubled every 4–8 hr, maximum 0.4 mg/kg/hr
Adverse effects: Electrolyte depletion (sodium, K^+, magnesium), worsening renal function

GI = gastrointestinal; NPO = nothing by mouth; PO = oral(ly).

G. Vasodilator Therapy (Table 16)
   1. Used primarily to manage pulmonary congestion or wet (subset II or IV) HF
      a. No data to suggest intravenous vasodilators improve outcomes
      b. Use is limited to relief of dyspnea in those with intact blood pressure.
   2. When adequate blood pressure is maintained, use in preference to inotropic therapy.
   3. Venous vasodilation results in a reduction in PCWP and acute relief of shortness of breath while awaiting the onset of diuretic effects.
   4. Vasodilators with arterial vasodilating properties (nitroprusside and nesiritide) can also be used as an alternative to inotropes in patients with elevated systemic vascular resistance (SVR) and low cardiac output (CO).
   5. Vasodilators should be avoided in patients with symptomatic hypotension.
   6. Frequent blood pressure monitoring is necessary.

Table 16. Vasodilator Therapy for ADHF

	Sodium Nitroprusside (Nipride)	Nesiritide (Natrecor)	IV Nitroglycerin
Mechanism of action	Nitric oxide–induced stimulation of GC to convert GTP to cGMP	Recombinant B-type natriuretic peptide binds to natriuretic peptide receptor A to stimulate GC and production of cGMP; natriuretic mechanism unknown	Combines with sulfhydryl groups in vascular endothelium to create *S*-nitrosothiol compounds that mimic nitric oxide's stimulation of GC and production of cGMP
Clinical effects	Balanced arterial and venous vasodilator	**Hemodynamic effects:** ↓ PCWP and SVR, ↑ CI, minimal changes in HR **Neurohormonal effects:** ↓ NE, ET-1, and aldosterone Natriuretic effects at supratherapeutic doses	Preferential venous vasodilator > arterial vasodilator, arterial vasodilation at high doses (e.g., >100 mcg/min)
Indication	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF, hypertensive crises	Warm and wet ADHF, alternative to inotropes in cold and wet ADHF	Warm and wet ADHF, ACS, or hypertensive crises
Dosing	0.1–0.2 mcg/kg/min IV, increase by 0.2–3 mcg/kg/min every 10-20 min	2 mcg/kg IVB, 0.01 mcg/kg/min IV	5 mcg/min IV, increase by 5 mcg/min every 5-10 minutes up to 200 mcg/min
Typical dose	0.5–1 mcg/kg/min IV	0.01 mcg/kg/min IV; can omit bolus if low SBP	25–100 mcg/min IV, titrated to response
Half-life	< 10 min	18 min	1–3 min
Elimination	Cyanide hepatically metabolized, thiocyanate renally excreted	Natriuretic peptide receptor C (no renal or hepatic adjustment)	Inactive metabolites in urine
AEs	Hypotension or cyanide or thiocyanate toxicity	Primarily hypotension (up to 1 hr), tachycardia (less than inotropes)	Hypotension, reflex tachycardia, headache, tachyphylaxis

AE = adverse effect; cGMP = cyclic guanine monophosphate; CI = cardiac index; ET-1 = endothelin; GC = guanylate cyclase; GTP = guanosine triphosphate; IVB = intravenous bolus; NE = norepinephrine.

H. Inotropic Therapy (Table 17)
   1. Used primarily to manage hypoperfusion or cold (subset III or IV) HF
   2. It is important to confirm that patients in subset III have adequate filling pressures (i.e., pulmonary capillary wedge pressure [PCWP] 15–18 mm Hg) before administering inotropic therapy.
   3. Useful for symptom relief in patients with low systolic blood pressure (less than 90 mm Hg) or symptomatic hypotension
   4. Given risk of sequelae, it is reasonable to consider vasodilators before inotropes.
   5. Monitor continuously for arrhythmias.
   6. Differences in the pharmacologic effects of dobutamine and milrinone may confer advantages and disadvantages.

Table 17. Inotropic Therapy for ADHF

	Dobutamine (Dobutrex)	Milrinone (Primacor)
Mechanism of action	β_1-Agonist: Stimulates AC to convert ATP to cAMP to ↑ CO; slight peripheral vasodilation	PDE inhibitor: Inhibits cAMP breakdown in heart to ↑ CO and in vascular smooth muscle to ↓ SVR
Clinical effects	Positive inotropic, chronotropic, lusitropic effects	Positive inotropic and lusitropic effects, no direct chronotropic effects
Indication	**ADHF: Cold and wet (Forester subset IV) or cold and dry exacerbations (Forester III) (if PCWP > 15 mm Hg)**	
Dosing	Start 2.5–5 mcg/kg/min IV; may titrate to maximum of 20 mcg/kg/min	50 mcg/kg IVB (rarely administered), then 0.1–0.2 mcg/kg/min IV; may titrate to maximum of 0.75 mcg/kg/min
Typical dose	5 mcg/kg/min IV	No bolus, 0.1–0.375 mcg/kg/min IV
Half-life	2 min	1 hr, prolonged to 2–3 hr if HF or CrCl < 50 mL/min/1.73 m^2
Elimination	Hepatically metabolized (inactive), renally eliminated	90% renal
AEs	Proarrhythmia, tachycardia, hypokalemia, myocardial ischemia, tachyphylaxis (> 72 hr); possible increased mortality with long-term use	Proarrhythmia, hypotension (avoid bolus), tachycardia, < 1% thrombocytopenia, possible increased mortality with long-term use
Other comments	Consider if hypotensive	Consider if receiving a β-blocker

AC = adenylate cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CO = cardiac output; PDE = phosphodiesterase.

I. Vasopressin Antagonists
   1. Therapeutic option for managing euvolemic or hypervolemic hyponatremia in those at risk of or having active cognitive symptoms despite water restriction (i.e., serum sodium less than 125 mEq/L or less marked hyponatremia that is symptomatic and resisted correction with fluid restriction, including patients with HF and syndrome of inappropriate secretion of antidiuretic hormone)
   2. Trials show effectiveness in correcting sodium with maintained therapy but no improvement in global clinical status, mortality, or reductions in rehospitalization.
      a. Hyponatremia redevelops after therapy cessation.
      b. Role in long-term management of HF remains unclear.
   3. Tolvaptan is the only vasopressin antagonist indicated for clinically significant hyponatremia associated with HF.
      a. Oral dosing: 15 mg daily, then titrated to 30–60 mg as needed
      b. Pharmacology: Binds to and inhibits the V_2 receptor, located in the renal tubule where water reabsorption is regulated
      c. Initiate only in hospital setting to allow monitoring of volume status and serum sodium concentrations.
      d. Contraindicated with cytochrome P450 3A4 inhibitors (tolvaptan is a substrate of 3A4)
      e. An overly rapid rise in serum sodium (maximum correction in any 24-hour period of chronic hyponatremia should be less than 9 mEq/L) can result in hypotension, hypovolemia, and neurological sequelae.

Patient Case

Questions 5–7 pertain to the following case.

A 72-year-old man is admitted to the hospital for HF decompensation. The patient has progressively increased dyspnea when walking (now 10 ft [3 m], previously 30 ft [6 m]) and orthopnea (now four pillows, previously two pillows), increased bilateral lower extremity swelling (3+), 13 kg of weight gain in the past 3 weeks, and dietary nonadherence. He has a history of idiopathic dilated cardiomyopathy (LVEF 25%, NYHA class III), paroxysmal atrial fibrillation (AF), and hyperlipidemia. Pertinent laboratory values are as follows: BNP 2300 pg/mL (0–50 pg/mL), K^+ 4.9 mEq/L, BUN 32 mg/dL, SCr 2.0 mg/dL (baseline 1.9 mg/dL), aspartate aminotransferase (AST) 40 IU/L, alanine aminotransferase 42 IU/L, INR 1.3, aPTT 42 seconds, blood pressure 108/62 mm Hg, heart rate 82 beats/minute, and Sa_{O_2} 95%. Home medications include carvedilol 12.5 mg twice daily, lisinopril 40 mg/day, furosemide 80 mg twice daily, spironolactone 25 mg/day, and digoxin 0.125 mg/day.

5. Which regimen is best for treating his ADHF?
   A. Carvedilol 25 mg twice daily.
   B. Nesiritide 2 mcg/kg bolus, then 0.01 mcg/kg/minute.
   C. Furosemide 120 mg intravenously twice daily.
   D. Milrinone 0.5 mcg/kg/minute.

6. After being initiated on intravenous loop diuretics with only minimal urine output, the patient is transferred to the coronary care unit for further management of diuretic-refractory decompensated HF. His Sa_{O_2} is now 87% on a 4-L nasal cannula, and an arterial blood gas is being obtained. His blood pressure is 110/75 mm Hg, and his heart rate is 75 beats/minute. The patient's SCr and K^+ concentrations have begun to rise; they are now 2.7 mg/dL and 5.4 mmol/L, respectively. In addition to a one-time dose of intravenous chlorothiazide, which regimen is most appropriate for this patient?
   A. Nitroglycerin 20 mcg/minute.
   B. Sodium nitroprusside 0.3 mg/kg/minute.
   C. Dobutamine 5 mcg/kg/minute.
   D. Milrinone 0.5 mcg/kg/minute.

7. The patient initially responds with 2 L of urine output overnight, and his weight decreases by 1 kg the next day. However, by day 5, his urine output has diminished again, and his SCr has risen to 4.3 mg/dL. He was drowsy and confused this morning during rounds. His extremities are cool and cyanotic, blood pressure is 89/58 mm Hg, and heart rate is 98 beats/minute. It is believed that he is no longer responding to his current regimen. A Swan-Ganz catheter is placed to determine further management. Hemodynamic values are cardiac index (CI) 1.5 L/minute/m^2, SVR 2650 dynes/second/cm^5, and PCWP 30 mm Hg. Which regimen is most appropriate for his current symptoms?
   A. Milrinone 0.2 mcg/kg/minute.
   B. Dobutamine 5 mcg/kg/minute.
   C. Nesiritide 2 mcg/kg bolus, then 0.01 mcg/kg/minute.
   D. Phenylephrine 20 mcg/minute.

III. ACUTE LIFE-THREATENING ARRHYTHMIAS

A. Adult Cardiac Arrest (Box 3)

Box 3. Select Advanced Cardiovascular Life Support Algorithms[a]

1. Start CPR (give oxygen; attach monitor/defibrillator)
2. Rhythm shockable? (If yes, go to Pulseless VT/VF No. 3; if no, go to asystole/PEA No. 11)
Algorithm for Pulseless Ventricular Tachycardia or Fibrillation
3. Defibrillation (shock 1)
4. CPR 2 min Establish IV/IO access
5. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC, go to Asystole/PEA algorithm If ROSC, initiate post–cardiac arrest care
6. Defibrillation (shock 2)
7. CPR 2 min Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
8. Reassess rhythm; shock if appropriate and proceed If no sign of ROSC, go to asystole/PEA algorithm If ROSC, initiate post–cardiac arrest care
9. Defibrillation (shock 3)
10. CPR 2 min Amiodarone[b] 300 mg IV/IO × 1; may repeat at 150 mg bolus × 1 Reversible causes of the event should be identified and corrected[c]
Algorithm for Asystole or PEA
11. CPR 2 min IV/IO access Epinephrine 1 mg IV/IO every 3–5 min Consider advanced airway, capnography
12. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, proceed
13. CPR 2 min Treat reversible causes[c]
14. Reassess rhythm; shock if appropriate and proceed to No. 6 or 7 for pulseless VT/VF If no sign of ROSC, continue steps 11–14 If ROSC, initiate post–cardiac arrest care

[a]If no IV/IO access, endotracheal administration of epinephrine, lidocaine, and atropine is allowed at 2–2.5 times the recommended IV/IO dose. Dilute this dose with 5–10 mL of sterile water or normal saline.

[b]If amiodarone is unavailable, lidocaine may be considered. Lidocaine 1–1.5 mg/kg IV, repeat 0.5–0.75 mg/kg IV/IO every 5–10 min (maximum 3 mg/kg). Lidocaine has not been shown to improve ROSC and hospital admission compared with amiodarone.

[c]Hypovolemia, hypoxia, hydrogen ion (acidosis), hypokalemia or hyperkalemia, hypothermia, tension pneumothorax, tamponade (cardiac), toxins, thrombosis (pulmonary), thrombosis (coronary).

CPR = cardiopulmonary resuscitation; IO = intraosseous(ly); PEA = pulseless electrical activity; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

B. Symptomatic Bradycardia
   1. If unstable, atropine 0.5 mg every 3–5 minutes (maximum dose 3 mg). (Note: Unstable = hypotension, acutely altered mental status, signs of shock, ischemic chest discomfort, acute HF)
   2. If atropine fails, transcutaneous pacing, dopamine 2–10 mcg/kg/minute, or epinephrine 2–10 mcg/minute

C. Symptomatic Tachycardia
   1. If unstable, synchronized cardioversion
   2. If stable, determine whether QRS complex is narrow or wide.
      a. Narrow-complex tachycardia (QRS less than 120 milliseconds); usually atrial arrhythmias
         i. Regular ventricular rhythm: Supraventricular tachycardia (SVT) or sinus tachycardia likely
            (a) Vagal maneuvers or adenosine 6 mg intravenous push, followed by a 20 mL saline flush, then a 12 mg intravenous push (may repeat once)
               (1) Rapid push followed by elevation of arm to increase circulation
               (2) Larger doses may be needed in patients taking theophylline or caffeine.
               (3) Initial dose should be reduced to 3 mg in patients taking dipyridamole or carbamazepine and in patients after heart transplantation, and when the drug is being given by central access.
               (4) Use adenosine cautiously in severe CAD.
               (5) Adenosine should not be given to patients with asthma.
               (6) Do not give adenosine for unstable or for irregular or polymorphic wide complex tachycardias, because it can cause degeneration to ventricular fibrillation (VF).
            (b) If vagal maneuvers or adenosine fails to convert paroxysmal SVT, calcium channel blockers (CCBs) or β-blockers can be used. If Wolff-Parkinson-White syndrome, avoid verapamil, diltiazem, and digoxin
         ii. Irregular (narrow complex) ventricular rhythm: AF (or possibly atrial flutter)
            (a) General management should focus on control of the rapid ventricular rate.
               (1) Usually non-dihydropyridine CCBs (diltiazem, verapamil) or β-blockers; digoxin sometimes useful
               (2) Rate is acceptable if it is less than 110 beats/minute at rest in asymptomatic persistent AF.
            (b) If patient is hemodynamically unstable, synchronized cardioversion is recommended.
            (c) Patients with AF for more than 48 hours are at high risk of cardioembolic events and should not be immediately cardioverted if stable.
            (d) Transesophageal echocardiography before cardioversion is an alternative strategy to ensure the absence of left atrial clot.
            (e) Risk of thromboembolic event surrounding cardioversion (both pharmacologic and electrical) is greatest within the first 10 days.
            (f) Cardioversion
               (1) If AF for up to 7 days, either elective direct current conversion or chemical cardioversion
                  (A) Flecainide, dofetilide, propafenone, ibutilide, or amiodarone (proven efficacy)
                  (B) Digoxin and sotalol are not recommended and may be harmful.
                  (C) Disopyramide, quinidine, and procainamide are less effective or incompletely studied.
               (2) If AF greater than 7 days, administer either elective direct current conversion or chemical cardioversion with dofetilide, amiodarone, or ibutilide (proven efficacy).

b. Wide complex tachycardia (QRS greater than 120 milliseconds): Usually ventricular arrhythmias
   i. Ventricular tachycardia (VT) or unknown mechanism
      (a) Consider adenosine only if regular and monomorphic.
      (b) Intravenous procainamide, amiodarone (or sotalol); lidocaine second line
      (c) Avoid procainamide and sotalol if prolonged QTc.
   ii. Definite SVT with aberrancy: Probably transiently slowed or converted by adenosine
   iii. Polymorphic (irregular) VT
      (a) Induced primarily when the QTc interval is greater than 500 milliseconds (torsades de pointes)
      (b) If unstable, polymorphic (irregular) VT requires immediate defibrillation with the same strategy as VF.
      (c) If stable, intravenous magnesium (Mg^{2+}) 1–2 g intravenous bolus (maximum 16 g every 24 hours) may be given; however, this is supported only by observational studies in the setting of wide QRS.
      (d) Withdrawal of QT-prolonging medications, correction of low Mg^{2+} or K^{+} levels
         (1) Class I and III antiarrhythmic drugs
         (2) Assess for drug interactions by cytochrome P450 3A4 (e.g., azole antifungals, erythromycin).
         (3) Assess for other QTc-prolonging drugs such as haloperidol, ziprasidone, droperidol, promethazine, macrolide and quinolone antibiotics, tricyclic antidepressants, or drugs contraindicated with dofetilide such as sulfamethoxazole/trimethoprim or thiazides.

D. Antiarrhythmic Overview (Tables 18 and 19)

Table 18. Vaughn-Williams Antiarrhythmic Drug Classes

Class/Ion Affected	Agents	Physiological Effect	Result on Electrophysiological Parameters	Clinical Utility
Class I/Na^{+} channel blockers				
Ia (intermediate)	Disopyramide quinidine, procainamide	↓ Conduction velocity; ↑ refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
Ib (fast)	Lidocaine, mexiletine, phenytoin	↓ Conduction velocity; ↓↑ refractory period	↓ QT interval	Ventricular arrhythmias
Ic (slow)	Flecainide, propafenone	↓↓↓ Conduction velocity; Ø refractory period	↑ QRS complex	Supraventricular arrhythmias and ventricular arrhythmias
Class II β-blockers	Metoprolol, esmolol, atenolol	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III K^{+} channel blockers	Amiodarone,[a] dronedarone,[a] sotalol,[b] dofetilide, ibutilide	Ø Conduction velocity; ↑↑↑ refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV Ca^{2+} channel blockers	Diltiazem, verapamil	↓ Conduction velocity; ↑ refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias

[a]Amiodarone and dronedarone have Ib, II, and IV class activity in addition to class III actions.

[b]Sotalol has 50%/50% β-blocking properties/K^{+}-blocking properties.

Ca^{2+} = calcium; Na^{+} = sodium. ↑= increases; ↓decreases; Ø= no effect

Table 19. Antiarrhythmic Drug Properties and Dosing (class I and III agents only)

Drug	AEs, Contraindications, Pharmacokinetics, and Drug Interactions	Dosing by Indication
Class Ia: Na^+ channel blockers		
Quinidine (Quinidex, Quinaglute)	AEs: Nausea, vomiting, and diarrhea (30%), "cinchonism" (CNS and GI symptoms, tinnitus), strong vagolytic and anticholinergic properties, TdP (first 72 hr), hypotension, GI upset PK: Half-life 5–9 hr Potent inhibitor of CYP2D6; substrate and inhibitor of CYP3A4 DIs: Warfarin, digoxin	AF conversion: Avoid use because of GI AEs AF and VT maintenance: Sulfate: 200–400 mg PO every 6 hr Gluconate (CR): 324 mg PO every 8–12 hr Decrease dose 25% if CrCl < 10 mL/min/1.73 m^2
Procainamide (Pronestyl)	AEs: hypotension (IV use, 5%), TdP CI: LVEF < 40% PK: Active metabolite NAPA (class III effects) may accumulate in renal dysfunction	AF conversion: 1 g IV for 30 min; then 2 mg/min (1-hr efficacy 51%) AF maintenance: No oral agent available VT conversion: 20 mg/min IV until 17 mg/kg, arrhythmia ceases, hypotension, or QRS widens > 50% VT maintenance: 1–4 mg/min Reduce dose in renal and liver dysfunction
Disopyramide (Norpace, Norpace CR)	AEs: Anticholinergic effects, TdP, ADHF (potent negative inotropic effect) CIs: Cardiogenic shock, congenital long QT syndrome, second- or third-degree AVB, glaucoma PK: Half-life 4–8 hr Substrate of CYP2D6 DI: May enhance the effect of β-blockers	AF conversion: IR 200 mg (if < 50 kg) or 300 mg (if > 50 kg) PO every 6 hr AF maintenance: 400–800 mg/day in divided doses (recommended adult dose 600 mg/day given as IR 150 mg PO every 6 hr or as CR 300 mg PO every 12 hr) If < 50 kg, moderate renal dysfunction (CrCl > 40 mL/min/1.73 m^2) or hepatic dysfunction, maximum 400 mg/day If severe renal dysfunction (IR only; avoid CR) CrCl 30–40 mL/min/1.73 m^2, 100 mg every 8 hr CrCl 15–30 mL/min/1.73 m^2, 100 mg every 12 hr CrCl < 15 mL/min/1.73 m^2, 100 mg every 24 hr Ventricular tachycardias: Use has fallen out of favor because of the availability of newer agents with less toxicity
Class Ib: Na^+ channel blockers		
Lidocaine (Xylocaine)	AEs: CNS (perioral numbness, seizures, confusion, blurry vision, tinnitus) CI: Third-degree AV heart block PK: Reduce dose in those with HF, liver disease, low body weight, and renal dysfunction and in older adults DI: Amiodarone (increased lidocaine levels)	Pulseless VT/VF conversion or VT with a pulse: 1–1.5 mg/kg IVP; repeat 0.5–0.75 mg/kg every 3–5 min (maximum 3 mg/kg) (If LVEF < 40%, 0.5–0.75 mg/kg IVP) (Amiodarone DOC in pulseless VT/VF; lidocaine acceptable if amiodarone not available) VT maintenance: 1–4 mg/min Reduce maintenance infusion in liver disease
Mexiletine (Mexitil)	AEs: CNS (tremor, dizziness, ataxia, nystagmus) CI: Third-degree AV heart block PK: Half-life 12–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP1A2	VT maintenance: 200–300 mg PO every 8 hr; maximum 1200 mg/day Reduce dose by 25%–25% in hepatic impairment

Table 19. Antiarrhythmic Drug Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, Pharmacokinetics, and Drug Interactions	Dosing by Indication
Class Ic: Na^+ channel blockers (Note: Avoid in patients with HF or after MI; increased risk of sudden death)		
Propafenone[a] (Rythmol, Rythmol SR)	AEs: Metallic taste, dizziness, ADHF, bronchospasm, bradycardia, heart block (negative inotropy and β-blocking properties) CIs: HF (NYHA III–IV), liver disease, valvular disease (TdP), CAD, MI PK: Half-life 10–25 hr Substrate CYP2D6, CYP1A2, CYP3A4 Inhibitor CYP1A2, CYP2D6 DIs: Digoxin ↑ by 70%; warfarin ↑ by 50% as well as drugs that inhibit CYP 2D6, 1A2, 3A4 (increased propafenone)	AF conversion: 600 mg PO × 1 (efficacy 45% at 3 hr) 450 mg PO × 1 (weight < 70 kg) AF maintenance: HCl: 150–300 mg PO every 8–12 hr HCl (SR): 225–425 mg PO every 12 hr Reduce dose 70%–80% in hepatic impairment
Flecainide[a] (Tambocor)	AEs: Dizziness, tremor, ADHF (negative inotropy), vagolytic, anticholinergic, hypotension CIs: HF, CAD, valvular disease, LVH (TdP) PK: Half-life 10–20 hr Substrate CYP2D6, CYP1A2 Inhibitor CYP2D6 DI: Digoxin ↑ by 25%	AF conversion: 300 mg PO × 1 (efficacy 50% at 3 hr) AF maintenance: 50–150 mg PO BID Reduce dose by 50% when CrCl < 50 mL/min/1.73 m^2
Class III: K^+ channel blockers		
Amiodarone (Cordarone)	AEs: Pulmonary fibrosis 3%–17%, hyperthyroidism 3%, hypothyroidism 30%, neurological toxicity 20%–40%, GI upset, photosensitivity, corneal deposits, hepatitis, blue-gray skin 15%, TdP < 1%, heart block 14%, hypotension (IV), phlebitis (IV; Ca^{2+}- and β-blocking properties), bradycardia CIs: Iodine hypersensitivity, hyperthyroidism, third-degree AV heart block PK: Half-life 58 days (average) Inhibits CYP3A4/2D6/2C9/1A2/2C19 and intestinal P-gp Substrate CYP3A4/1A2/2C19/2D6 DIs: Warfarin, digoxin, statins (maximum simvastatin dose 20 mg/day), phenytoin ↑ ≥ 50%, lidocaine, and others Does not increase mortality in patients with HF	AF conversion: IV: 5–7 mg/kg IV over 30–60 min, then 1.2–1.8 g/day continuous IV or divided oral doses until 10 g PO: 1.2–1.8 g/day in divided doses until 10 g AF maintenance: 200–400 mg/day PO Pulseless VT/VF conversion: 300 mg or 5 mg/kg IVB in 20 mL of D_5W or NS; repeat 150 mg IVB every 3–5 min Stable VT: 150 mg IVB in 100 mL of D_5W for 10 min VT/VF maintenance: 1 mg/min × 6 hr, then 0.5 mg/min (maximum 2.2 g/day)
Sotalol (Betapace, Betapace AF)	AEs: ADHF, bradycardia, AVB, wheezing, 3%–8% TdP within 3 days of initiation, bronchospasm (β-blocking effects) CIs: Baseline QTc > 440 ms or CrCl < 40 mL/min/1.73 m^2 (AF only), LVEF < 40% PK: Renally eliminated, half-life 30–40 hr Hospitalization ideal for initiation of therapy because of BW: Do not initiate if baseline QTc interval > 450 ms; if QTc > 500 ms during therapy, reduce the dose, prolong the infusion duration, or d/c use Not effective for AF conversion	AF maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min/1.73 m^2) 80 mg PO daily (40–60 mL/min/1.73 m^2) CI < 40 mL/min/1.73 m^2 VT maintenance (based on CrCl): 80 mg PO BID (> 60 mL/min/1.73 m^2) 80 mg PO daily (30–60 mL/min/1.73 m^2) 80 mg PO every 36–48 hr (10–30 mL/min) 80 mg PO: individualize; every 48 hr minimum (< 10 mL/min/1.73 m^2)

Table 19. Antiarrhythmic Drug Properties and Dosing (class I and III agents only) *(Cont'd)*

Drug	AEs, Contraindications, Pharmacokinetics, and Drug Interactions	Dosing by Indication
Class III: K^+ channel blockers		
Dofetilide (Tikosyn)	AEs: TdP (0.8%; 4% if no renal adjustment), diarrhea CIs: Baseline QTc > 440 ms or CrCl < 20 mL/min/1.73 m^2 PK: Renal and hepatic elimination Half-life 6–10 hr Substrate CYP3A4 DIs: CYP3A4 inhibitors and drugs secreted by kidney (cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine, megestrol), HCTZ BW: Hospitalization mandatory for initiation, obtain QTc 2–3 hr after each of the first 5 doses, reduce 50% if QTc ↑ > 15%; NTE QTc > 500 ms Does not increase mortality in patients with HF	AF conversion (based on CrCl; efficacy 12% at 1 mo): 500 mcg PO BID (> 60 mL/min/1.73 m^2) 250 mcg PO BID (40–60 mL/min/1.73 m^2) 125 mcg PO BID (20–40 mL/min/1.73 m^2) CI < 20 mL/min/1.73 m^2 AF maintenance: Dose as above according to renal function; adjust for QTc NTE 500 ms or > 15% ↑ in QTc
Ibutilide (Corvert)	AEs: TdP 8%, AV heart block (β-blocking properties) CIs: Baseline QTc > 440 ms, LVEF < 30%, concomitant antiarrhythmic drugs PK: Half-life 2–12 hr (average 6) DIs: CYP3A4 inhibitors or QT-prolonging drugs ECG monitoring during and 4 hr after CV	AF conversion: 1 mg IV (≥ 60 kg) or 0.01 mg/kg IV (< 60 kg); repeat in 10 min if ineffective (efficacy 47% at 90 min) BW: Potentially fatal arrhythmias (e.g., polymorphic VT) can occur with ibutilide, usually in association with TdP; patients with chronic AF may not be the best candidates for ibutilide conversion
Dronedarone (Multaq)	AEs: Worsening HF, QT prolongation, hypokalemia or hypomagnesemia with K^+-sparing diuretics, hepatic failure CIs: QTc ≥ 500 ms or PR ≥ 280 ms, NYHA class IV HF or NYHA class II–III HF with recent ADHF, severe hepatic impairment, second- or third-degree AVB, or HR < 50 beats/min PK: Half-life 13–19 hr Substrate 3A4 Inhibitor intestinal P-gp DIs: CYP3A4 inhibitors, QT-prolonging drugs, simvastatin, tacrolimus/sirolimus, warfarin, and other CYP3A4 substrates with narrow therapeutic range, digoxin and other P-gp substrates (dabigatran, rivaroxaban)	AF maintenance: 400 mg orally BID D/C if QTc is ≥ 500 ms BW: The risk of death is doubled when used in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; use is contraindicated in these patients Use in patients with permanent AF doubles the risk of death, stroke, and hospitalization for HF; use is contraindicated in patients with AF who will not or cannot be converted to normal sinus rhythm

[a]Indicates that pill-in-pocket approach can be used for selected patients.

AF = atrial fibrillation; AV = atrioventricular; AVB = atrioventricular block; BW = Boxed Warning CAD = coronary artery disease; CI = contraindication; CNS = central nervous system; CR = controlled release; CV = cardioversion; D_5W = dextrose 5%; DI = drug interaction; DOC = drug of choice; GI = gastrointestinal; HCl = hydrochloride; HCTZ = hydrochlorothiazide; IR = immediate release; LVH = left ventricular hypertrophy; ms = millisecond(s); NAPA = *N*-acetylprocainamide; NS = normal saline; NTE = not to exceed; NYHA = New York Heart Association; PK = pharmacokinetics; QTc = corrected QT interval; SR = sustained release; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

E. Long-term Management of Ventricular Arrhythmias
   1. Nonsustained VT
      a. Asymptomatic
         i. Infrequent ventricular ectopic beats, couplets, and triplets without other signs of underlying structural heart disease (SHD) or inherited arrhythmia syndrome should be considered a normal variant in asymptomatic patients.

ii. No treatment other than reassurance is needed for patients without SHD or inherited arrhythmia disorder.
iii. Treat survivors of MI and HF with reduced EF with β-blockers (class I) unless contraindicated.

b. Symptomatic
i. β-Blockers may be considered for a therapeutic trial in symptomatic patients (class IIb, level of evidence [LOE] C).
ii. Non-dihydropyridine CCBs may be considered as an alternative to β-blocker therapy in suitable patients without SHD.
iii. Antiarrhythmic drug (AAD) therapy (amiodarone, flecainide, mexiletine, propafenone, sotalol) may be considered to improve symptoms associated with arrhythmias in patients on adequate doses of β-blocker or CCB (class IIb; LOE C).
(a) Flecainide and propafenone are not recommended to suppress premature ventricular contractions in patients with reduced LV function (class III).
(b) Sotalol should be used with caution in patients with chronic kidney disease and should be avoided in patients with prolonged QT interval at baseline or excessive prolongation of QT interval (500 milliseconds) on therapy initiation (class I; LOE B).
(c) Amiodarone appears to have less overall proarrhythmic risk than other AADs in patients with HF and may be preferred to other membrane-active AADs unless functioning defibrillator has been implanted (class IIb; LOE C).
iv. Amiodarone, sotalol, and other β-blockers are useful after defibrillator implantation to reduce shocks and to suppress nonsustained VT in patients who are unsuitable for ICD therapy, in addition to optimal medical therapy for patients with HF.

2. Sustained VT
a. Immediate defibrillation (advanced CV life support management)
b. Evaluate cardiac structure and function.
c. ICDs indicated for most patients with SHD

F. Implantable Cardioverter-Defibrillators
1. For primary prevention of SCD
a. Previous MI, at least 40 days earlier and EF of 35% or less
b. Nonischemic dilated cardiomyopathy, LVEF of 35% or less receiving optimal chronic medications for at least 3 months
c. Syncope with SHD and inducible VT/VF during electrophysiological study
d. High risk of life-threatening VT/VF; congenital long QT syndrome with recurrent symptoms or torsades de pointes while receiving β-blocker
e. Must have reasonable survival expectation for more than 1 year
2. For secondary prevention of SCD
a. Previous episode of resuscitated VT/VF, hemodynamically unstable VT with no completely reversible cause, or sustained VT in presence of heart disease
b. Must be receiving optimal chronic medications (β-blockers, ACE inhibitors)
c. Must have reasonable survival expectation for more than 1 year
3. General medication considerations with ICD (Table 19)
a. β-Blockers
i. Considered mainstay therapy
ii. Effective in suppressing ventricular ectopic beats and in reducing SCD in a spectrum of cardiac disorders in patients with and without HF (nonsustained VT)

b. Amiodarone
   i. No better than ICD in reducing SCD as a lone agent; no mortality benefit
   ii. Can be used to treat symptomatic nonsustained VT if β-blockers not effective when ICD not indicated
   iii. Can be used in combination with β-blockers to decrease firing of ICD (defibrillator storm)
c. Sotalol
   i. No mortality advantage
   ii. Can suppress VT and be used to decrease frequency of ICD firing
   iii. Greater proarrhythmic potential; avoid in patients with severely depressed LVEF or significant HF; renal dosing necessary

Table 20. Alteration of Defibrillation Threshold

Threshold Alteration	Medications	Comments
Increase threshold	Amiodarone, lidocaine, and mexiletine	Reprogram ICD, increased energy (joules) needed
Decrease threshold	Sotalol	May decrease energy needed for DCC

DCC = direct current conversion; ICD = implantable cardioverter-defibrillator.

G. Treatment of Arrhythmias in Special Patient Populations
   1. HF
      a. Avoid class Ia and class Ic agents.
      b. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after MI.
      c. Dronedarone (used in atrial arrhythmias only) is contraindicated in patients with symptomatic HF with recent decompensation necessitating hospitalization or NYHA class IV symptoms; risk of death was doubled in these patients.
   2. Acute MI
      a. Avoid class Ia and class Ic agents.
      b. CAST trial with class Ic agents (encainide, flecainide) showed greater mortality when used to treat post-MI non–life-threatening ventricular arrhythmias; avoid class Ic agents in patients with SHD.
      c. Class Ia medications: Increased mortality in MI survivors
      d. Amiodarone and dofetilide (used for atrial arrhythmias only) have a neutral effect on mortality in patients with LV dysfunction after MI.

H. Drug-Induced Arrhythmias: Review all potential drug etiologies and treat appropriately.
   1. Drug-induced QT prolongation
      a. Discontinue offending agent if QT prolongation significant (i.e. > 450 msec)
      b. Ensure proper renal and hepatic dosing adjustments.
      c. Review electrolyte abnormalities and thyroid function tests.
      d. Ensure that all electrolytes are maintained at critical levels: K^+ greater than 4 mmol/L and less than 5 mmol/L and Mg^{++} greater than 2 mg/dL.
      e. Ensure that all ECG parameters are within normal limits (e.g., QT interval less than 500 milliseconds).
   2. Drug-induced bradycardia or atrioventricular block
      a. β-Blocker, CCB, digoxin
      b. Administer antidote if appropriate (e.g., calcium for CCB toxicity).
   3. Review for drug interactions. Antiarrhythmic agents have drug interactions that may cause significant outcomes.

Patient Cases

Questions 8 and 9 pertain to the following case.

A 68-year-old man is admitted after an episode of syncope, with a presyncopal syndrome of seeing black spots and experiencing dizziness before passing out. Telemetry monitor showed sustained VT for 45 seconds. His medical history includes HF NYHA class III, LVEF 30%, two MIs, hypertension for 20 years, LV hypertrophy, DM, and diabetic nephropathy. His medications include lisinopril 5 mg/day, furosemide 20 mg twice daily, metoprolol 25 mg twice daily, digoxin 0.125 mg/day, glyburide 5 mg/day, and aspirin 81 mg/day. His blood pressure is 120/75 mm Hg, heart rate 80 beats/minute, BUN 30 mg/dL, and SCr 2.2 mg/dL.

8. Which is the best therapy to initiate for conversion of his sustained VT?
   A. Amiodarone 150 mg intravenously for 10 minutes, then 1 mg/minute for 6 hours, then 0.5 mg/minute.
   B. Sotalol 80 mg twice daily titrated to QTc of about 450 milliseconds.
   C. Dofetilide 500 mcg twice daily titrated to QTc of about 450 milliseconds.
   D. Procainamide 20 mg/minute, with a maximum of 17 mg/kg.

9. The patient presents to the emergency department 3 months after amiodarone maintenance initiation (he refused ICD placement) after a syncopal episode, during which he lost consciousness for 30 seconds, according to witnesses. He also has rapid heart rate episodes during which he feels dizzy and light-headed. He feels very warm all the time (he wears shorts, even though it is winter), is unable to sleep, and has experienced a 3-kg weight loss. He received a diagnosis of hyperthyroidism caused by amiodarone therapy. On telemetry, he shows runs of nonsustained VT. Which would best predict the duration of amiodarone-associated hyperthyroidism in this patient?
   A. Never.
   B. 1 month.
   C. 6 months.
   D. 1 year.

10. A 64-year-old woman presents to the emergency department with the chief concern of palpitations. Her medical history includes hypertension controlled with a diuretic and an inferior-wall MI 6 months ago. She is pale and diaphoretic, but she can respond to commands. The patient's laboratory values are within normal limits. Her vital signs include blood pressure 95/70 mm Hg and heart rate 145 beats/minute; telemetry shows sustained VT. Although initially unresponsive to β-blockers, the patient is successfully treated with lidocaine. Subsequent electrophysiological testing reveals inducible VT, and sotalol 80 mg orally twice daily is prescribed. Two hours after the second dose, the patient's QTc is 520 milliseconds. Which regimen change would be most appropriate for this patient?
   A. Continue sotalol at 80 mg orally twice daily.
   B. Increase sotalol to 120 mg orally twice daily.
   C. Discontinue sotalol and initiate dofetilide 125 mcg orally twice daily.
   D. Discontinue sotalol and initiate amiodarone 400 mg orally three times daily.

IV. HYPERTENSIVE CRISES

A. Definitions
   1. Hypertensive emergency
      a. Severe elevations in blood pressure (usually greater than 180/120 mm Hg) with evidence of new or worsening target-organ damage
      b. Acute target-organ damage can include hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke or other acute neurological deficit; unstable angina or acute MI; acute LV failure with pulmonary edema; dissecting aortic aneurysm; retinopathy or papilledema; decreased urinary output or acute renal failure; eclampsia.
      c. Actual blood pressure may not be as important at the rate of blood pressure rise.
      d. Requires immediate blood pressure lowering (not necessarily to normal ranges) to prevent or limit further target-organ damage
      e. In general, oral therapy is discouraged for hypertensive emergencies.
   2. Hypertensive urgency
      a. Situations associated with severe blood pressure elevation in otherwise stable patients without acute or impending change in target-organ damage or dysfunction
      b. Short-term risk is not as high; therefore, blood pressure reduction occurs over several days, not immediately.

B. Goals and Treatment
   1. Hypertensive emergency
      a. Goal is to minimize target-organ damage safely by rapid recognition of the problem and early initiation of appropriate antihypertensive treatment.
      b. Patients are usually admitted for intensive care unit care and close follow-up.
      c. Lower mean arterial pressure (MAP) by no more than 25% or diastolic blood pressure to 100–110 mm Hg within first hour, then/100 mm Hg over next 2–6 hours, then to normal over next 24–48 hours.
      d. Compelling conditions requiring rapid lowering of SBP, usually to less than 140 mm Hg, in the first hour of treatment include aortic dissection, severe preeclampsia or eclampsia, and pheochromocytoma with hypertensive crisis.
      e. Intravenous medications used commonly (Table 21)
      f. No randomized evidence to suggest one drug of choice because of small trial size, lack of long-term follow-up, and failure to report outcomes
      g. Two trials have shown that nicardipine is better than labetalol in achieving the short-term blood pressure target.
      h. Agents are chosen on the basis of drug pharmacology, pathophysiological factors underlying the patient's hypertension, degree of progression of target-organ damage, desirable rate of blood pressure decline, and presence of patient characteristics (Table 21-22).
      i. No randomized evidence exists comparing different strategies to reduce blood pressure, except in patients with intracranial hemorrhage.
      j. No randomized evidence suggests how rapidly to reduce blood pressure.
      k. Clinical experience indicates that excessive reductions in blood pressure can cause renal, cerebral, or coronary ischemia and should be avoided.
   l. Oral loading doses of antihypertensive agents can bring about cumulative effects, causing hypotension after discharge.

2. Hypertensive urgency
   a. Treated by reinstitution or intensification of antihypertensive drug therapy
   b. No indication for referral to the emergency department, immediate reduction in blood pressure in the emergency department, or hospitalization
   c. No proven benefit exists from rapid reduction in blood pressure.
   d. The choice of agent used in this setting varies, and in many cases, adjusting chronic oral therapy (increasing doses), reinitiating therapy in the nonadherent, or adding a new agent (i.e., diuretic) to long-term therapy is appropriate.
   e. All patients with hypertensive urgency should be reevaluated within 7 days (preferably after 1–3 days).

C. Treatment Options (Table 21)

Table 21. Commonly Used IV Drugs for Hypertensive Emergencies

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Sodium nitroprusside (Nipride) (immediate, 2–3 min)	0.3–0.5 mcg/kg/min, increase in increments of 0.5 mcg/kg/min to achieve BP target; maximum 10 mcg/kg/min; for infusion rates ≥ 4–10 mcg/kg/min or duration > 30 min, thiosulfate can be coadministered to prevent cyanide toxicity	Intra-arterial BP monitoring recommended to prevent "overshoot"; lower doses required in older adult patients; tachyphylaxis common with extended use AEs: Cyanide or thiocyanate toxicity with prolonged use can result in irreversible neurological changes and cardiac arrest, nausea, vomiting, methemoglobinemia CIs: Renal, hepatic failure Caution: Elevated ICP
Nitroglycerin (2–5 min, 5–10 min)	5–10 mcg/min, increase in increments of 5 mcg/min every 3–5 min to a maximum 20 mcg/min	Use only in patients with ACS and/or acute pulmonary edema; do not use in volume-depleted patients AEs: Headache, nausea, vomiting, tachyphylaxis
Hydralazine (Apresoline) (10 min, 1–4 hr)	5–10 mg via slow IV infusion every 4–6 hr (NTE initial 20 mg/dose)	BP begins to decrease within 10–30 min, and lasts 2–4 hr; unpredictability of response and prolonged duration of action make hydralazine less desirable first agent AEs: Reflex tachycardia, headache, flushing Caution: Angina or MI, elevated ICP, aortic dissection
Enalaprilat (Vasotec) (within 30 min, 12–24 hr)	0.625–1.25 mg over 5 min; doses can be increased up to maximum 5 mg every 6 hr	Should not be used in acute MI; mainly useful in hypertensive emergencies associated with hypertensive emergencies associated with high plasma renin activity; dose not easily adjusted; relatively slow onset (15 min) and unpredictability of BP response AEs: Renal insufficiency or failure, hyperkalemia CIs: Pregnancy, bilateral renal artery stenosis, angioedema (Note: Long half-life)

Table 21. Commonly Used IV Drugs for Hypertensive Emergencies *(Cont'd)*

Drug (onset, duration)	IV Dose	Comments/AEs
Vasodilators		
Fenoldopam (Corlopam) (< 5 min, 30 min)	0.1–0.3 mcg/kg/min, increased by 0.05–0.1 mcg/kg/min every 15 min to a maximum of 1.6 mcg/kg/min	Contraindicated in patients at risk of increased intraocular pressure (glaucoma) or intracranial pressure and those with sulfite allergy AEs: Headache, flushing, tachycardia, cerebral ischemia
Nicardipine (Cardene) (1–5 min, 15–30 min; up to 4 hr if prolonged infusion)	5 mg/hr, increased by 2.5 mg/hr every 5 min to a maximum 15 mg/hr	Contraindicated in advanced aortic stenosis; no dose adjustment needed for older patients AEs: Reflex tachycardia, nausea, vomiting, headache, flushing Caution: Angina or MI, acute HF
Clevidipine (Cleviprex) (2–4 min, 5–15 min)	1–2 mg/hr, doubling every 90 s until BP approaches target, then increasing by less than double every 5–10 min; maximum 32 mg/hr; maximum duration 72 hr	Patients with renal failure and hepatic failure and older adults not specifically studied—use low end range for older adults; contraindicated in soy or egg product allergy, severe aortic stenosis, defective lipid metabolism (e.g. pathological hyperlipidemia, lipoid nephrosis or acute pancreatitis) Caution: HF, concomitant β-blocker use, reflex tachycardia, rebound HTN
Adrenergic Inhibitors		
Esmolol (Brevibloc) (1–2 min, 10–30 min)	LD 500–1000 mcg/kg IVB over 1 min, then a 50 mcg/kg/min infusion; for additional BP lowering, the bolus dose is repeated and the infusion is increased in 50 mcg/kg/min increments as needed to a maximum 200 mcg/kg/min	Contraindicated in patients with concurrent β-blocker therapy, bradycardia, or decompensated HF AEs: Bronchospasm, HF exacerbation, bradycardia or heart block Caution: May worsen acute HF, asthma (higher doses may block β_2 receptors and impact lung function in reactive airway disease), heart block
Labetalol (Normodyne, Trandate) (5–10 min, 3–6 hr)	20–80 mg every 15 min or initial 0.3–1 mg/kg dose (max 20 mg) slow IV injection every 10 min or 0.4–1.0 mg/kg/hr infusion up to maximum 3 mg/kg/hr	Contraindicated in reactive airway disease or chronic obstructive pulmonary disease; especially useful in hyperadrenergic syndromes; may worsen HF and should not be given in patients with second- or third-degree heart block or bradycardia
Phentolamine (2 min, 15–30 min)	IVB dose 5 mg; additional bolus doses every 10 min as needed	Used in hypertensive emergencies induced by catecholamine excess (pheochromocytoma, monamine oxidase inhibitors interactions with food and/or drugs, cocaine toxicity, amphetamine overdose, or clonidine withdrawal)

CI = contraindication; ICP = intracranial pressure.

Table 22. Agents Preferred for Hypertensive Crises According to Comorbidities

Comorbidity	Preferred Agents	Comments
Acute aortic dissection	Labetalol, esmolol	Requires rapid lowering of SBP to ≤ 120 mm Hg; β-blocker should be given before vasodilator (nicardipine or nitroprusside) if needed for BP control or to prevent reflect tachycardia or inotropic effect; SBP ≤ 120 mm Hg should be achieved within 20 min
Acute coronary syndromes	Esmolol or nitroglycerin (preferred), labetalol, nicardipine	Nitrates given in the presence of PDE-5 inhibitors may induce profound hypotension; contraindications to β-blockers include moderate to severe LV failure with pulmonary edema, bradycardia (< 60 beats/min), hypotension (SBP < 100 mm Hg), poor peripheral perfusion, second- or third-degree heart block, and reactive airway disease
Acute pulmonary edema	Clevidipine, nitroglycerin, nitroprusside	β-Blockers contraindicated
Acute renal failure	Clevidipine, fenoldopam, nicardipine	
Eclampsia or preeclampsia	Hydralazine, labetalol, nicardipine	Requires rapid BP lowering; ACE inhibitor, ARBs, renin inhibitors, and nitroprusside contraindicated
Perioperative HTN (BP ≥ 160/90 mm Hg or SBP elevation > 20% of the preoperative value that persists > 15 min)	Clevidipine, esmolol, nicardipine, nitroglycerin	Intraoperative hypertension is most common during anesthesia induction and airway manipulation
Acute sympathetic discharge or catecholamine excess states (e.g., pheochromocytoma, post-carotid endarterectomy status)	Clevidipine, nicardipine, phentolamine (Note: Avoid unopposed β-blockade)	Requires rapid lowering of BP
Acute intracranial hemorrhage	IV continuous infusion	Lower BP in those who present with SBP > 220 mm Hg with continuous IV infusion and close BP monitoring; immediate lowering of SBP < 140 mm Hg is not of benefit and may be harmful
Acute ischemic stroke	No preference of agent	Early initiation or resumption of antihypertensive treatment indicated only in (1) patients treated with tissue-type plasminogen activator to a SBP < 185/110 mm Hg and (2) patients with SBP > 220 mm Hg or DBP > 120 mm Hg; cerebral autoregulation in the ischemic penumbra of the stroke is grossly abnormal and rapid reduction of BP can be detrimental; reinitiate antihypertensive therapies in those with preexisting hypertension after neurological stability

ARB = angiotensin receptor blocker.

Patient Cases

11. A 68-year-old man with a history of chronic kidney disease stage V on hemodialysis, hypertension, CAD post-MI, moderately depressed LVEF, and gastroesophageal reflux disease presents with acute-onset shortness of breath and chest pain. After his recent dialysis, he had a large barbecue meal with salt and smoked some marijuana laced with cocaine. He was nonadherent to medical therapy for 2 days and noticed he had gained 2 kg in 24 hours. His baseline orthopnea worsened to sleeping sitting up in a chair for the 2 nights before admission. He developed acute-onset chest tightness with diaphoresis and nausea, and his pain was 7/10. He went to the emergency department, where a blood pressure of 250/120 mm Hg was noted. He had crackles halfway up his lungs on examination, and chest radiography detected bilateral fluffy infiltrates with prominent vessel cephalization. Electrocardiography revealed sinus tachycardia, heart rate 122 beats/minute, and ST-segment depressions in leads 2, 3, and aVF. He was admitted for a hypertensive emergency. Laboratory results are as follows: BUN 48 mg/dL, SCr 11.4 mg/dL, BNP 2350 pg/mL, troponin T 1.5 mcg/L (less than 0.1 mcg/L), creatine kinase 227 units/L, and creatine kinase-MB 22 units/L. Which medication is best to manage this patient's hypertensive emergency?
    A. Intravenous nitroglycerin 5 mcg/minute titrated to a 25% reduction in MAP.
    B. Labetalol 2 mcg/minute titrated to a 50% reduction in MAP.
    C. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
    D. Clonidine 0.1 mg orally every 2 hours as needed for a 50% reduction in MAP.

12. A 56-year-old white woman with a long history of hypertension because of nonadherence and recently diagnosed HF (EF 35%) presents to the local emergency department with a blood pressure of 210/120 mm Hg and heart rate of 105 beats/minute. She states that she felt a little light-headed but that she now feels okay. She ran out of her blood pressure medications (including hydrochlorothiazide, carvedilol, and lisinopril) 3 days ago. Current laboratory values are within normal limits. Which medication is best for this patient?
    A. Sodium nitroprusside 0.25 mcg/kg/minute titrated to a 25% reduction in MAP.
    B. Labetalol 80 mg intravenously; repeat until blood pressure is less than 120/80 mm Hg.
    C. Resumption of home medications; refer for follow-up within 2 days.
    D. Resumption of home medications; initiate amlodipine 10 mg daily; refer for follow-up in 1 week.

V. PULMONARY HYPERTENSION

A. Definition, Diagnosis, and Treatment Goals
    1. Pulmonary hypertension (PH)
        a. A hemodynamic and pathophysiological condition defined as an increase in mean pulmonary arterial pressure (mPAP) of 25 mm Hg or greater at rest as assessed by right heart catheterization
        b. PH can be found in many clinical conditions.
        c. Current clinical classification
            i. Individualizes different categories of PH sharing similar pathological and hemodynamic characteristics (Table 23)
            ii. Used by the FDA and European Agency for Drug Evaluation for new drugs approved for PH

Table 23. Clinical Classification of PH

Category of PH	Clinical Characteristics
Group 1	PAH; pathological lesions affect the distal pulmonary arteries in particular
Group 2	PH caused by left heart disease; pathologic changes are characterized by enlarged and thickened pulmonary veins, pulmonary capillary dilatation, interstitial edema, alveolar hemorrhage, and lymphatic vessel and lymph node enlargement
Group 3	PH caused by chronic lung disease or hypoxia; pathological changes include medial hypertrophy and intimal obstructive proliferation of the distal pulmonary arteries
Group 4	CTEPH; pathological lesions are characterized by organized thrombi tightly attached to the pulmonary arterial medial layer in the elastic pulmonary arteries, replacing the normal intima; nonoccluded areas may be indistinguishable from PAH; collateral vessels can grow to reperfuse at least partly the areas distal to complete obstructions
Group 5	PH caused by unclear multifactorial mechanisms

CTEPH = chronic thromboembolic pulmonary hypertension; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

2. Symptoms
   a. Dyspnea with exertion (60% of patients), fatigue, chest pain, syncope, weakness (40%); caused by impaired oxygen delivery to tissues and diminished CO
   b. Orthopnea, peripheral edema, liver congestion, abdominal bloating, and other signs of right ventricular hypertrophy and failure occur when disease progresses to involve the heart.
3. Diagnosis and classification: Severity of disease should be evaluated in a systemic and consistent manner through a combination of clinical and functional classifications (Tables 23–25), exercise capacity, and echocardiographic, laboratory, and hemodynamic variables to inform therapeutic decisions.

Table 24. Diagnostic Findings of PAH

Type	Diagnostic Findings
Hemodynamic alterations	mPAP ≥ 25 mm Hg at rest, PAWP ≤ 15 mm Hg, and PVR > 3 Wood units on RHC
ECG	Signs of RV hypertrophy, right-axis deviation, and anterior ST- and T-wave abnormalities consistent with RV strain pattern
Echocardiography	Estimated RV systolic pressure elevation, enlarged RV, RV dysfunction
Chest radiography	Enlarged pulmonary arteries and diminished peripheral pulmonary vascular markings, RV enlargement
Physical examination	Cool or cyanotic extremities, jugular venous distension, pulsatile hepatomegaly, peripheral edema, ascites

mPAP = mean pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RV = right ventricle.

Table 25. World Health Organization Classification of Functional Status for PAH

Class	Definition
I	No symptoms (dyspnea, fatigue, syncope, chest pain) with normal daily activities
II	Symptoms with strenuous normal daily activities that slightly limit functional status and activity level
III	Symptoms of dyspnea, fatigue, syncope, and chest pain with normal daily activities that severely limit functional status and activity level
IV	Symptoms at rest; cannot conduct normal daily activities without symptoms

4. Treatment goals
    a. Relieve acute dyspnea symptoms.
    b. Improve exercise capacity and quality of life and prevent death.
5. Acute vasodilator response testing
    a. Mandatory in patients with idiopathic pulmonary arterial hypertension (PAH) to identify those who will respond favorably to long-term treatment with high doses of CCBs
    b. Inhaled nitric oxide is the compound of choice.
    c. Intravenous epoprostenol and intravenous adenosine are alternatives but carry risk of systemic vasodilatory effects.
    d. Positive response: mPAP reduction of at least 10 mm Hg to an absolute mPAP of less than 40 mm Hg
    e. Positive response predicts mortality reduction with long-term CCB or vasodilator use.

B. Treatment of PAH (Boxes 4 and 5; Table 26-27)
1. All patients with PAH should be evaluated promptly at a center with expertise in the diagnosis of PAH before initiation of therapy.
2. Collaborative and closely coordinated care of patients with PAH should involve the expertise of the local physician and those with expertise in PAH care.
3. Treatment decisions are based on World Health Organization functional classification, prior treatment status, response to CCBs, and mode of administration desired.
4. Use of PAH drugs, particularly tested in clinical trials with PAH, might not be helpful in other forms of PH.
5. Use of PAH drugs in other forms of PH should not be generalized; treatment decisions must be made on an individual basis.

Box 4. Initial PAH Treatment Algorithm: Supportive Care

Supportive care: Treat corrective causes of hypoxemia and avoid dehydration, pain, fatigue, high altitude, smoking, pregnancy, and iron deficiency
Oxygen to maintain Sao_2 > 90%, diuretic if peripheral edema or ascites
Oral anticoagulation, warfarin (INR 1.5–2.5) if IPAH ± diuretics ± digoxin (Anticoagulation to prevent catheter thrombosis [IV prostaglandin use] and venous thromboembolism) (IPAH, heritable PAH, and PAH caused by anorexigens [class IIa; LOE C], APAH)
Immunizations for influenza and *Pneumococcus* spp.
Discuss effective methods of birth control with women of childbearing potential

Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

APAH= associated pulmonary arterial hypertension; IPAH = idiopathic pulmonary arterial hypertension; LOE = level of evidence; PAH = pulmonary arterial hypertension.

Box 5. PAH Treatment Algorithm: Vasoreactive Algorithm

Positive response to acute vasoreactivity testing
Initiate oral CCB (WHO FC I–II)
If sustained response, continue CCB
If no sustained response, initiate non-vasoreactive algorithm in Table 26

CCB = calcium channel blocker; WHO FC = World Health Organization functional classification.

Table 26. PAH Treatment Algorithm: Non-vasoreactive Algorithm

Negative response to acute vasoreactivity testing (or unresponsive to CCB therapy)				
Initiate therapy with approved medications				
Recommendation	**Evidence**	**WHO FC II**	**WHO FC III**	**WHO FC IV**
I	A or B	Ambrisentan Bosentan Macitentan[a,b,c] Riociguat[a] Sildenafil Tadalafil	Ambrisentan Bosentan Epoprostenol IV[c] Iloprost inhaled Macitentan[a,b,c] Riociguat[a] Sildenafil Tadalafil Treprostinil SC, inhaled[a]	Epoprostenol IV[c]
IIa	C		Iloprost IV + treprostinil IV	Ambrisentan Bosentan Iloprost inhaled and IV[a] Macitentan[a,b,c] Riociguat[a] Sildenafil Tadalafil Treprostinil SC, IV, inhaled
IIb	B		Beraprost[a]	
	C		Initial combination therapy	Initial combination therapy
If inadequate clinical response: Consider eligibility for lung transplantation Sequential combination therapy with ERAs, prostanoids, PDE-5 inhibitor, or soluble guanylate cyclase stimulator				
If inadequate response on maximal therapy: Referral for lung transplantation (class I) BAS (IIa; LOE C)				

Class I, should be performed or administered; class IIa, reasonable to be performed or administered; class IIb, may be considered; class III, not to be administered or harmful.

[a]Approved only by the U.S. Food and Drug Administration (macitentan, riociguat, treprostinil inhaled), in New Zealand (iloprost IV), and in Japan and South Korea (beraprost).

[b]Received positive opinion for approval by the European Medicines Agency.

[c]Morbidity and mortality as primary end point in randomized controlled study or reduction in all-cause mortality (prospectively defined).

BAS = balloon atrial septostomy; CCB = calcium channel blocker; ERA = endothelin receptor antagonist; PDE-5 = phosphodiesterase type 5; WHO FC = World Health Organization functional classification.

Table 27. Overview of Pulmonary Arterial Hemorrhage Treatment Options

Drug, Mechanism, and Indication	Dose	Adverse Effects	Considerations
CCBs Class II PAH	Varies by agent and patient tolerance	Hypotension, headache, dizziness, peripheral edema, cardiac conduction delay (diltiazem)	Should not be used empirically without positive response to acute vasodilatory response testing Diltiazem, amlodipine, nifedipine most commonly used Select agent on the basis of HR at baseline If tachycardic, choose diltiazem If bradycardic, choose amlodipine, nifedipine
Epoprostenol (Flolan, Veletri) Prostanoid Class III–IV PAH	2–40 ng/kg/min IV	Jaw pain, nausea, vomiting, flushing, headache, muscle aches and pain, catheter-related thrombosis, and IV line infections; rebound worsening of symptoms if abruptly discontinued	Continuous IV infusion by pump Flolan: Unstable at acidic pH and room temperature (refrigerate or use ice packs before and during infusion) Veletri: Stable at room temperature Drug must be reconstituted in sterile environment Medical emergency if infusion interrupted (half-life, 6 min); spare drug cassette and infusion pump should be kept available
Treprostinil (Remodulin, Tyvaso) Prostanoid Class II–IV PAH	1.25–40 ng/kg/min SC infusion, IV Inhaled	Severe erythema and induration (83%) and injection site pain (85%) limits use; also headache, nausea, diarrhea, rash	Longer half-life (3 hr); longer to seek medical attention Premixed, prefilled syringe easier to administer Local treatments (hot/cold packs or topical analgesics) can be used to minimize infusion site discomfort Moving infusion site every 3 days minimizes irritation
Inhaled iloprost (Ventavis) Prostanoid Class III–IV PAH	2.5 mcg × 1; then 5 mcg/inhalation by nebulizer 6–9 times daily while awake	Mild, transient cough, flushing, headache, syncope	6–9 inhalations daily (15 min each with jet nebulizer) Prodose AAD nebulization system required Inhaled form has fewer systemic adverse reactions Use no more than every 2 hr
Oral treprostinil (Orenitram) Prostanoid	0.25 mg every 12 hr or 0.125 mg every 8 hr; may increase dose in increments of 0.25 mg or 0.5 mg every 12 hr or 0.125 mg every 8 hr every 3–4 days as tolerated to achieve optimal clinical response	Limb pain (14%), hypokalemia (9%), abdominal distress (6%)	Administer with food Swallow tablets whole; do not crush, split, or chew; use only intact tablets Dose reduction in moderate hepatic impairment Contraindicated in severe hepatic impairment (Child-Pugh class C) Alcohol increases absorption of treprostinil

Table 27. Overview of Pulmonary Arterial Hemorrhage Treatment Options *(Cont'd)*

Drug, Mechanism, and Indication	Dose	Adverse Effects	Considerations
Bosentan (Tracleer) Nonselective endothelin receptor antagonist (ET_A and ET_B) Class III–IV PAH	62.5–125 mg PO BID	Peripheral edema 5%–14%, hypotension 7%, increased LFTs 11%, flushing 7%–14%, palpitations 5%	Available only through REMS Severe drug interactions with glyburide (increased LFTs) and cyclosporine (decreased efficacy of both cyclosporine and bosentan) Monitor LFTs monthly Monitor Hgb and Hct every 3 mo Potential teratogen; if childbearing age, use two contraceptive methods (reduced efficacy of hormonal contraceptives); monthly pregnancy test needed Efficacy decreased with inducers and toxicity increased with inhibitors of CYP 2C8/9 and 3A4
Ambrisentan (Letairis) Selective endothelin receptor antagonist (ET_A only) Class II–III PAH	5–10 mg PO once daily	Peripheral edema 17%, hypotension 0%, increased LFTs 0%–2.8%, flushing 4%, palpitations 5%, fluid retention	Available only through REMS Caution with cyclosporine; maximum dose is 5 mg daily Contraindicated in patients with idiopathic pulmonary fibrosis Potential teratogen (see above comments) Periodic Hgb and Hct monitoring No CYP drug interactions documented
Macitentan (Opsumit) Dual endothelin receptor antagonist Class II–III PAH	10 mg once daily	Anemia, nasopharyngitis, bronchitis, headache, influenza, urinary tract infection	Contraindicated in pregnancy; available only through REMS Metabolized by CYP3A4; avoid use with strong CYP3A4 inhibitors Monitor for elevations of aminotransferases, hepatotoxicity, liver failure, and anemia
Sildenafil (Revatio) PDE-5 inhibitor Class II–IV PAH	20–80 mg PO three times daily	Headache, epistaxis, facial flushing, bluish or blurry vision, light sensitivity, dyspepsia, insomnia	Half-life 4–5 hr May augment effects of other vasodilators when used in combination (especially prostacyclin) Contraindicated in patients receiving nitrates Avoid combined use with strong CYP3A4 inhibitors (e.g., ritonavir, cimetidine, erythromycin) and inducers (rifampin)
Tadalafil (Adcirca) PDE-5 inhibitor Class II–IV PAH	20–40 mg PO once daily	Headache, flushing, indigestion, nausea, backache, myalgia, nasopharyngitis, respiratory tract infection	Half-life 17.5 hr May augment effects of other vasodilators when used in combination (especially prostacyclin) Contraindicated in patients receiving nitrates If CrCl = 31–80 mL/min/1.73 m^2, initiate 20 mg PO once daily and titrate as tolerated If CrCl < 30 mL/min/1.73 m^2 or hemodialysis, avoid use If Child-Pugh class A or B, initiate 20 mg PO once daily and titrate as tolerated If Child-Pugh class C, avoid use Avoid use with potent CYP3A4 inhibitors or inducers

Table 27. Overview of Pulmonary Arterial Hemorrhage Treatment Options *(Cont'd)*

Drug, Mechanism, and Indication	Dose	Adverse Effects	Considerations
Riociguat (Adempas) Soluble guanylate cyclase stimulator Chronic thromboembolic PH and class II–IV PAH	1 mg PO three times daily; increase by 0.5 mg no sooner than 2-wk intervals; maximum dose 2.5 mg three times daily	Headache, dizziness, dyspepsia or gastritis, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation Serious bleeding occurred in 2.4%, compared with 0% in placebo in clinical trials, including one fatal event	Contraindicated with nitrates; NO donors in any form or use with any PDE inhibitors (including nonspecific and specific PDE-5 inhibitors) Teratogenic, contraindicated in pregnancy Available only through restricted REMS program for women Not recommended for patients with pulmonary veno-occlusive disease Half-life: 7–12 hr Plasma concentrations reduced in smokers Drug interaction with strong CYP3A4 inhibitors and P-gp/breast cancer resistance protein; may use a lower starting dose of 0.5 mg three times daily; decrease dose by 0.5 mg if hypotension occurs Not recommended in severe renal or hepatic disease (CrCl < 15 mL/min/1.73 m^2 or Child-Pugh class C)
Ambrisentan/ tadalafil combination Class II–III PAH	Initiate ambrisentan 5 mg once daily, with or without tadalafil 20 mg once daily Increase to 20 mg ambrisentan or 40 mg tadalafil at 4-wk intervals	Most common: peripheral edema, headache, nasal congestion, cough, anemia, dyspepsia, and bronchitis	Same considerations for each individual agent as above REMS program Do not split, crush, or chew tablets
Selexipag (Uptravi) Oral non-prostanoid prostacyclin IP receptor agonist Class II–III PAH	Initiate at 200 mcg BID; increase by 200 mcg BID at weekly intervals up to 1600 mcg BID reached	Headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity and flushing	Take with food to improve tolerability. Can cause pulmonary edema with pulmonary veno-occlusive disease. D/C treatment if confirmed Strong CYP2C8 inhibitors should be avoided Decrease dosing to once daily in patients with moderate hepatic impairment and avoid in patients with severe hepatic impairment Not for use in breastfeeding

AAD = adaptive aerosol delivery; d/c = discontinue; ET = endothelin; Hct = hematocrit; Hgb = hemoglobin; LFT = liver function test; NO = nitric oxide; PAH = pulmonary artery hemorrhage; REMS = Risk Evaluation and Mitigation Strategies.

Patient Cases

13. A 38-year-old woman with obesity presents with increasingly severe symptoms of fatigue and shortness of breath. She could walk only 10–20 feet at baseline and is now short of breath at rest. Her arterial blood gas is pH 7.31, P_{CO_2} 65 mm Hg, P_{O_2} 53 mm Hg, and 85% Sa_{O_2}. She has three-pillow orthopnea and 3+ pitting edema in her lower extremities. Her medical history is significant only for AF. Computed tomographic angiography shows that her pulmonary artery trunk is substantially enlarged, with a mean pressure of 56 mm Hg. Echocardiography reveals right atrial and ventricular hypertrophy. Chest radiography detects prominent interstitial markings. Pertinent laboratory test values are BUN 21 mg/dL, SCr 1.2 mg/dL, AST 145 IU/L, alanine aminotransferase 90 IU/L, INR 2.1, and aPTT 52 seconds; vital signs include blood pressure 108/62 mm Hg and heart rate 62 beats/minute. Home medications are warfarin 2.5 mg/day, ipratropium 2 puffs every 6 hours, salmeterol 2 puffs twice daily, and diltiazem 480 mg/day. Her diagnosis is idiopathic pulmonary arterial hypertension (IPAH). Which regimen is the best evidence-based management strategy?

    A. Increase diltiazem to 600 mg/day.

    B. Start sildenafil 20 mg three times daily.

    C. Start epoprostenol 2 ng/kg/minute.

    D. Start bosentan 62.5 mg twice daily.

14. A 48-year-old man with IPAH is admitted to the medical intensive care unit for severe respiratory distress. Medications before admission included bosentan and sildenafil. His vital signs include blood pressure 97/45 mm Hg, heart rate 130 beats/minute, and respiratory rate 24 breaths/minute, and his oxygen requirements are increasing. Recently, during a previous hospital admission, pulmonary artery catheter placement revealed an mPAP of 40 mm Hg, right atrial pressure 16 mm Hg, CI 1.2 L/minute, and PCWP 15 mm Hg. Echocardiography reveals EF 60% with significant right ventricular dilation. Which regimen is most appropriate?

    A. Epoprostenol and add phenylephrine, if needed, for blood pressure support.

    B. Furosemide and add norepinephrine, if needed, for blood pressure support.

    C. Nitroprusside and add epinephrine, if needed, for blood pressure support.

    D. Dobutamine to increase CO.

Special Acknowledgment: ACCP gratefully acknowledges the contribution of previous authors Drs. Jo Ellen Rodgers, Robert Page, and Sheryl Chow to this chapter.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient's atypical symptoms, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggest NSTE-ACS. She has at least three risk factors for CAD, a history of CAD (prior MI), and positive troponins, which places her at high risk of future events. In such high-risk patients, an early invasive strategy (as in Answers A and B) is used to determine whether occluded or partly occluded arteries exist, which ones can be intervened on, and whether to make an intervention. An ischemia-guided approach, also called *medical management*, as in Answers C and D, would not be preferred because of this patient's risk category (i.e., positive troponins). Dual antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) is indicated for an early invasive strategy in the management of an NSTE-ACS. In patients undergoing PCI, clopidogrel, prasugrel, or ticagrelor is an appropriate option (Answer A is correct). After an initial bolus of 60 units/kg and an infusion of 12 units/kg/hour (Answer A is correct; Answer D is incorrect), UFH can be titrated to an aPTT of 50–70 seconds, making Answer A correct. Aspirin alone without a $P2Y_{12}$ agent, as in Answer B, would not provide adequate antiplatelet therapy. Furthermore, enoxaparin would need to be dosed with a 30-mg intravenous bolus before initiating twice-daily subcutaneous dosing because this patient has positive troponins. Glycoprotein inhibitors, as in Answer C, can be useful in high-risk patients, typically those with positive troponins; however, their benefit has been shown mainly when UFH, not low-molecular-weight heparin, is given as the anticoagulant.

2. Answer: D

It is important to understand that this patient case occurs in the context of elective stent placement, not after ACS. In the non-ACS setting, the duration of DAPT is determined by the type of stent placed (bare metal stent vs. drug-eluting stent). After elective drug-eluting stent placement, DAPT is recommended for at least 12 months because the risk of in-stent thrombosis is highest during this time. The recommendation is for at least 1 month—and ideally up to 1 year—after bare metal stent placement because endothelialization of the stent usually occurs early, typically within 1 month after stenting. Bleeding risk may be a reason to consider earlier termination (after a minimum of 1 month) of DAPT after bare metal stent placement.

3. Answer: D

Although this patient presented within 3 hours of chest pain onset and is a candidate for thrombolytic therapy (within 6 hours of onset is preferred), up to 95% of patients can achieve normal, brisk TIMI-3 flow rates with primary PCI, compared with only 50%–60% of patients achieving normal TIMI-3 coronary flow with thrombolytic therapy. Because the patient presents to a hospital that can perform a primary PCI with stent implantation, this is the preferred reperfusion strategy (Answers B and C are incorrect). Answer A is incorrect because an anticoagulant agent must be administered in addition to antiplatelet therapy. Answer D—reperfusion with primary PCI, DAPT with aspirin and prasugrel, and dosing of bivalirudin as an anticoagulant strategy—is correct.

4. Answer: C

Unlike the patient in case 3, this patient presents with a STEMI to a rural community hospital where the nearest hospital with catheterization laboratory facilities is more than 120 minutes away (i.e., lytics are indicated). He presents within the window for fibrinolytic therapy consideration (less than 6 hours after chest pain onset) and has no obvious contraindications. Because he is still having ischemic chest pain and ST-segment elevation, he should benefit from reperfusion therapy. He is experiencing complete heart block and bradycardia, which could indicate an occlusion above the area perfusing his sinoatrial or atrioventricular nodes. Enoxaparin (Answer A) is a treatment option for anticoagulant therapy given in conjunction with fibrinolytics, but the patient is at higher risk of bleeding from impaired enoxaparin clearance and needs a dosage adjustment. Furthermore, he is older than 75 years, beyond the age at which the intravenous bolus should be given, and the alteplase dosing is incomplete. Simply treating this patient conservatively with UFH alone (Answer B) in the setting of ongoing chest pain, shortness of breath, and pulmonary edema is not optimal. Diagnostic catheterization and possible PCI to determine whether an artery can be reperfused (Answer D) may be desirable, but is complicated because the patient's SCr is elevated

(2.5 mg/dL), and he is in a rural hospital, where he cannot be assessed quickly enough (within 90–120 minutes). Because of the shorter half-life and ease of administration of tenecteplase, it may be preferable to alteplase. Clearance of UFH with tenecteplase is not as altered as with enoxaparin, and it would be a more appropriate therapy than enoxaparin in combination with a thrombolytic (Answer C is correct).

5. Answer: C

This patient, who has ADHF, is receiving a β-blocker. Although long-term β-blockers can improve HF symptoms and reduce mortality, they can also worsen symptoms in the short term. It is recommended to keep the maintenance β-blocker therapy at the same or slightly lower dose compared with the outpatient therapy in patients with ADHF; increasing the β-blocker dose before reaching euvolemia might acutely worsen his clinical picture (Answer A is incorrect). In patients admitted with volume overload without substantial signs of reduced CO, it is reasonable to try intravenous loop diuretics initially (Answer C is correct). As gut edema increases, oral loop diuretics (notably furosemide) become less effective because of decreased absorption. Nesiritide is a vasodilatory drug that is FDA approved for the symptomatic relief of acute HF; however, because of its lack of evidence for benefit, adverse effects, and substantial cost, nesiritide is not recommended for routine use in the broad population of patients with acute HF (Answer B is incorrect). Milrinone is an inotropic drug. Because of their adverse effects, inotropes are recommended in cold and wet exacerbations only after vasodilatory medications have failed (Answer D is incorrect).

6. Answer: A

Intravenous vasodilators such as nitroglycerin (Answer A) and sodium nitroprusside (Answer B) are reasonable options if intravenous diuretics fail and the patient progresses to acute pulmonary edema. Both agents rapidly cause venous vasodilation and reduce pulmonary filling pressures, which can relieve acute shortness of breath. Answer A, nitroglycerin, is the optimal choice for this patient, given his declining renal function and the concern about increased risk of thiocyanate toxicity with sodium nitroprusside in this setting (Answer B is incorrect). Dobutamine is typically used in states of low CO decompensation and is counteracted by concomitant β-blocker therapy, making it a poor choice in patients receiving β-blockers (Answer C is incorrect). Although milrinone is a more acceptable inotropic agent in a patient receiving β-blockers, the dosing strategy is inappropriate as an initial dose (Answer D is incorrect). Finally, inotropes are generally reserved for patients when other therapies have failed.

7. Answer: A

Signs of a decreased CO state in HF (e.g., increased SCr, decreased mental status, cool extremities) suggest a cold and wet state, and adjunctive therapy is indicated. Positive inotropic agents such as milrinone will increase CO to maintain perfusion to vital organs. Milrinone will also vasodilate the peripheral vessels to unload the heart (lower SVR). Although dobutamine would be a potential choice in this patient, it is not recommended in patients receiving β-blockers (Answer B is incorrect). Although this patient has low blood pressure, his elevated SVR suggests that he will tolerate the vasodilatory effects of milrinone (Answer A is correct). Although nesiritide would provide venous and arterial vasodilation, it is relatively contraindicated in patients with a systolic blood pressure less than 100 mm Hg and is absolutely contraindicated in patients with a systolic blood pressure less than 90 mm Hg (Answer C is incorrect). Phenylephrine has no positive beta effects; therefore, it will not augment contractility. In addition, it will cause vasoconstriction through alpha stimulation, which will further increase SVR and probably worsen CO (Answer D is incorrect). Vasoconstrictors are reserved for patients in cardiogenic shock. Although this patient has signs of significant hypoperfusion, his blood pressure is not so low that it warrants vasopressor therapy.

8. Answer: A

Treatment options for sustained VT depend on concomitant disease states, particularly LVEF (40% cutoff). In a patient with LV dysfunction, class I agents such as procainamide are contraindicated (Answer D is incorrect). In a patient whose CrCl is less than 60 mL/minute/1.73 m^2, sotalol requires a considerable dose reduction to avoid excess risk of torsades de pointes. Sotalol is not an effective cardioversion drug but is more useful for preventing future episodes of arrhythmias (maintaining sinus rhythm) once sinus rhythm is achieved (Answer B is incorrect). Dofetilide is indicated only for AF, not

for ventricular arrhythmias; similarly, cardioversion rates with dofetilide are low (Answer C is incorrect). Amiodarone is first-line therapy for sustained VT in patients with severe renal insufficiency, HF, and structural heart disease (Answer A is correct).

9. Answer: C

With the prolonged half-life of amiodarone and extensive fat tissue volume of distribution, it would be expected that hyperthyroid adverse effects would last for 3–5 half-lives of the drug, which is anywhere from 5 to 8 months (Answer C is correct; Answer A is incorrect). Although therapeutic concentrations may fall off substantially by then, 1 month is too soon to expect the effects to subside (Answer B is incorrect). Although some iodine and amiodarone molecules will probably remain absorbed in fat stores for years, if not for life, therapeutic concentrations should not exist for longer than what is predicted by the half-life (Answer D is incorrect).

10. Answer: D

This patient is experiencing QT prolongation with sotalol, placing her at an elevated risk of developing life-threatening torsades de pointes. Sotalol should be discontinued immediately (Answer A and B are incorrect). Given the QT prolongation that occurred with sotalol, the same will probably occur with dofetilide (Answer C is incorrect). Amiodarone is associated with minimal risk of torsades de pointes and therefore would be an appropriate alternative agent to prevent ventricular arrhythmias (Answer D is correct).

11. Answer: A

Hypertensive emergency should be treated immediately by a 25% reduction in MAP, followed by a slow reduction to goal for 5–7 days. The patient's comorbidities guide the optimal therapy. His dialysis and SCr of 11.4 mg/dL are a contraindication to sodium nitroprusside (Answer C is incorrect) because of possible thiocyanate toxicity. Labetalol (and β-blockers in general) is controversial in patients who have taken cocaine, but its nonselective nature makes it an option; however, a reduction of 50% initially is too rapid a decrease in blood pressure for safety (Answer B is incorrect). Clonidine is not an appropriate drug for a hypertensive emergency because its oral form is difficult to titrate and can lead to precipitous drops in blood pressure beyond the goal 25% reduction and possibly stroke or worsening MI (Answer D is incorrect). Nitroglycerin is an optimal choice, considering the patient's lack of contraindications to this therapy and his evolving MI (Answer A is correct).

12. Answer: C

In the setting of asymptomatic hypertensive crisis (without acute target-organ damage), giving intravenous medications, as in Answers A and B, and admitting the patient to the hospital are unnecessary (Answer A and B are incorrect). This patient is probably presenting because of a history of nonadherence. Resuming her home medications (Answer C is correct) at this time would be most appropriate, with close follow-up to ensure that her prescribed regimen is working. Adding a fourth agent (Answer D is incorrect) at this time is unnecessary, considering that she could be controlled on her current drug regimen if she were adherent. Follow-up should occur within the first few days rather than waiting 1 week.

13. Answer: C

This patient is already receiving therapy with CCBs to control her heart rate caused by AF. She is taking a large dose of diltiazem, and her heart rate is unlikely to tolerate further increases in therapy (Answer A is incorrect). Sildenafil is indicated for patients to improve symptoms or for patients whose other therapies have failed (Answer B is incorrect). Although bosentan is an attractive oral option to manage her PAH, her liver enzymes are elevated more than 3 times the upper limit of normal. Therefore, in this setting, administering bosentan is not recommended (Answer D is incorrect). If liver transaminases are elevated transiently because of hepatic congestion, bosentan can be reconsidered later. Because this patient is currently in functional class IV with advanced symptoms at rest, epoprostenol is indicated for a survival benefit (Answer C is correct).

14. Answer: A

Epoprostenol (Answer A is correct) is warranted to manage this patient's underlying disease because he has not responded to two oral PAH therapies; he is considered high risk because of his right ventricular dysfunction and low CI. He has normal filling pressures for a patient with right ventricular dysfunction, and diuresis with furosemide might only worsen his low CI (Answer

B is incorrect). The underlying cause of his low CI is not elevated arterial resistance; therefore, nitroprusside would probably worsen his hypotension (Answer C is incorrect). Correcting the elevated pulmonary pressures should correct the low CI; therefore, dobutamine is not indicated at this time because it would probably worsen his tachycardia (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

In this patient, the presence of chest pain, ST-segment depression on ECG, and positive biomarkers for myocardial necrosis suggests NSTE-ACS. Because of his presentation characteristics, he is at a high enough risk to warrant cardiac catheterization (invasive strategy). This invasive strategy is used to determine whether occluded or partly occluded epicardial arteries exist, which ones can be intervened on, and whether to perform PCI (percutaneous transluminal coronary angioplasty with or without stenting). Initial therapy for ACS usually consists of morphine, oxygen, nitroglycerin, and aspirin therapy, but only aspirin has been shown to reduce mortality from these initial treatments. Aspirin should be given as soon as possible after hospital presentation and continued indefinitely, if tolerated. According to clinical trials, guidelines, and experience, an initial dose of 162–325 mg is recommended (Answers B and D are not the best choices of dosing for an acute episode). Aspirin, together with a $P2Y_{12}$ receptor antagonist, is indicated for an early invasive strategy in the management of UA/NSTEMI, improving outcomes. The 2014 NSTE-ACS guidelines give a class I recommendation for clopidogrel, ticagrelor, and prasugrel in the ACS setting for patients undergoing PCI. The choice of which $P2Y_{12}$ receptor antagonist to use in the ACS setting depends on patient presentation, contraindications, and whether PCI is involved; in this case, any of the three $P2Y_{12}$ antagonists would be appropriate. The anticoagulation strategy treatment for ACS generally includes one anticoagulant (UFH, low-molecular-weight heparin, fondaparinux, or bivalirudin). When UFH is chosen as an anticoagulant strategy, the dose used for ACS is a 60-unit/kg bolus and a 12-unit/kg/hour infusion (Answer A is an incorrect dosing strategy). Regarding dosing, bivalirudin (Answer D) would be an appropriate anticoagulation strategy; however, the initial aspirin dose should be higher, and a nitroglycerin drip would not be the best choice, given his right-sided MI (low blood pressure, low heart rate). Intravenous β-blocker therapy (Answer A) is reasonable in patients without contraindications when hypertension or ongoing ischemia is a concern; however, initiating oral therapy within 24 hours is preferred in most patients as long as the patient has no signs of HF, evidence of low output state, increased risk of cardiogenic shock, or other contraindications to β-blockade. β-Blockers should initially be avoided in this patient, given his blood pressure and heart rate. An intravenous ACE inhibitor (Answer B) should not be given to patients within the first 24 hours of ACS because of the increased risk of hypotension. Answer C includes DAPT and an appropriate dose of anticoagulant (Answer C is correct).

2. Answer: A

The NSTE-ACS guidelines recommend the use of one anticoagulant during an acute event. Enoxaparin, UFH, and bivalirudin are all recommended as class I agents for the invasive management of NSTE-ACS. However, fondaparinux (Answer C) is not optimal because increased risk of catheter-related thrombosis has been associated with fondaparinux use in the catheterization laboratory. The NSTE-ACS guidelines advise the use of additional heparin if fondaparinux was chosen as an initial anticoagulant when the patient underwent intervention, whereas the PCI guidelines give fondaparinux a class III or harmful recommendation. Of the remaining three options, UFH (Answer A) is preferred because of its rapid clearance. Both enoxaparin (Answer B) and bivalirudin (Answer D) are appropriate options but would need to be dose adjusted, given this patient's CrCl of less than 30 mL/minute/1.73 m^2. Doses listed in Answers B and D would be appropriate for patients with a normal CrCl, however.

3. Answer: B

Given that this patient had a significantly low platelet count with his most recent heparin exposure and is believed to have HIT, using any of the GP IIb/IIIa inhibitors (Answers A and C) would be unwise for ACS treatment because these agents must be combined with UFH. Thrombolytic therapy (Answer D) is not recommended for treating NSTE-ACS and would be inappropriate in this patient. Bivalirudin (Answer B), a direct thrombin inhibitor, would be the treatment of choice in patients with HIT undergoing PCI.

4. Answer: D

Administration of β-blocker therapy carries a risk of causing HF decompensation, particularly when the β-blocker is titrated too quickly or initiated in

patients who are not euvolemic. Although administering β-blockers within the first 24 hours is beneficial in STEMI, this patient has several risk factors that would be considered contraindications to initial β-blockade. The clinical condition of this patient suggests he is not euvolemic, and aggressive diuresis should be attempted before initiating a β-blocker for him. In addition, intravenous β-blocker therapy (Answer B) would place him at an even greater risk of cardiogenic shock. Answers A and C are inappropriate because the doses are too aggressive for a patient with an EF of 25%. Answer D is correct; however, before discharge, this patient should be reevaluated for the initiation of low-dose β-blocker therapy.

5. Answer: C

This patient is well perfused and can be classified in Forrester hemodynamic subset II (warm and wet). Because the patient has pulmonary congestion (shortness of breath, dyspnea at rest), intravenous diuretics are first-line therapy. Nitroglycerin (Answer C) is the best choice in this setting because vasodilatory agents can be used in conjunction with intravenous diuretics to improve acute pulmonary edema. When adjunctive therapy is needed in addition to loop diuretics, intravenous vasodilators should be considered over inotropic agents. Dobutamine (Answer A) and milrinone (Answer B) primarily increase CO, which is not a problem in warm and wet exacerbations. In addition, the adverse effects of these agents (increased mortality, proarrhythmia) limit their use. Intravenous metoprolol (Answer D) should be used extremely cautiously because of its negative inotropic effects and because this patient is not in a euvolemic state.

6. Answer: D

This patient has a depressed LVEF less than 40%; therefore, her drug therapy options are limited. Procainamide (Answer A) is indicated only in secondary prevention of sustained VT in patients with a normal LVEF greater than 40%; if given to this patient, it could worsen her HF. Metoprolol (Answer B) is indicated for treating patients with asymptomatic nonsustained VT and SVT associated with CAD. This patient had an episode of sustained VT; therefore, therapy beyond β-blockade is warranted. Her QTc interval is not prolonged at 380 milliseconds, and her serum magnesium concentration is within normal limits, so she does not need intravenous Mg^{2+} therapy (Answer C). Amiodarone (Answer D) is a first-line treatment of patients without contraindications because of its efficacy and safety in patients with an LVEF less than 40%.

7. Answer: B

This patient has target-organ damage from poorly controlled hypertension in the form of a cerebrovascular accident. Although fenoldopam (Answer A) is indicated for treating hypertensive emergencies, its use is cautioned in patients with stroke symptoms because its dopamine agonist activity can cause cerebral vasodilation and potentially reduced blood flow to the ischemic areas of the brain. Nicardipine (Answer B) is an appropriate choice for this patient because its calcium channel blocking effects will reduce blood pressure and potentially decrease vasospasm in the cerebral arteries, which can lead to further ischemia or seizure activity. Although labetalol (Answer C) is an effective option for treating this patient's hypertensive emergency, she has a history of asthma and a low heart rate, making labetalol a less-than-ideal option for treating her symptoms. The antihypertensive effects of enalaprilat (Answer D) depend on a patient's renin activity, which is unknown in this case. Therefore, the blood pressure–reducing effects may be more difficult to control than with a drug having a more consistent effect in individuals. In addition, the bolus nature of the drug is not ideal for tightly controlling blood pressure with no more than a 25% reduction in MAP. Continuous infusion drugs are preferable for easier titration to effect in a hypertensive emergency.

8. Answer: C

This patient is experiencing hypertensive urgency, considering that he has no evidence of target-organ damage. Thus, his blood pressure may be reduced over 24 hours using oral medications. Given this patient's concomitant comorbidities, HF, and microalbuminuria, an ACE inhibitor (Answer C) would be considered appropriate. Sublingual nifedipine (Answer A) is no longer recommended for management of hypertensive urgency because of acute blood pressure lowering and association with life-threatening adverse events, such as MI and stroke. Clonidine (Answer B) and labetalol (Answer D) are acceptable options; however, the patient has compelling indications for an ACE inhibitor. Although the patient should receive a β-blocker in addition to an

ACE inhibitor for HF management, labetalol is not one of the three β-blockers recommended for chronic HF management.

9. Answer: C

The Cardiac Arrest Study Hamburg trial compared ICD with AAD in survivors of cardiac arrest for secondary prevention of SCD. The propafenone (Answer A) study arm was discontinued early because of a significantly (61%) higher mortality rate than in the ICD arm (Answer A is incorrect). Although this trial had a small sample size that prevented a statistically significant difference in total mortality in ICD-treated patients versus patients treated with either amiodarone or metoprolol, the incidence of sudden death was significantly lower in patients with an ICD (Answer C is correct; 33% vs. 13%; p=0.005). The Antiarrhythmics Versus Implantable Defibrillators trial also evaluated ICD implantation versus AAD therapy (primarily amiodarone) in survivors of SCD. Patients with ICDs had a significantly higher rate of survival than those treated with drug therapy (89% vs. 82%; p<0.02), making Answer C preferable to all the other options (Answers B and D are incorrect).

10. Answer: C

The number needed to treat can be calculated as 1/Absolute risk reduction. Because the absolute risk reduction in mortality at 60 months was 7.2% with ICD versus placebo, 1/0.072 would be used to calculate the number of patients needed to treat to prevent one death during this time. About 14 patients (Answer C) would need to be treated with ICD to prevent one death in 60 months versus placebo. Other calculations in this fashion, including relative risk reduction and 100% minus the absolute or relative risk reduction, do not provide useful information for interpreting the trial results and yield an incorrect number of patients (Answers A, B, and D are incorrect).

11. Answer: D

International Pharmaceutical Abstracts (Answer A) is a database of primarily pharmaceutical abstracts in more than 750 journals, including foreign and state pharmacy journals, in addition to key U.S. medical and pharmacy journals. Many of the citations are not included on Medline, so a broader search can be performed; however, subject descriptors are not consistently defined in a uniform way, and multiword terms are often cited backward. The Iowa Drug Information Service database (Answer B) offers full-text articles from 1966 to the present in about 200 medical and pharmacy journals (based primarily in the United States). It is updated monthly, and newly available articles may take longer to access from this service. The Clin-Alert database (Answer C) contains more than 100 medical and pharmacy journals focused on adverse events, drug interactions, and medical-legal issues. It is used primarily to look up adverse events (especially recent reports) associated with medications. Excerpta Medica (Answer D) is a comprehensive database of more than 7000 journals from 74 countries dating from 1974 to the present. Recently published articles appear in the system within 10 days of article publication, and it often contains data not found in a typical Medline search.

12. Answer: B

MedWatch is a post-FDA approval program established by the FDA for health care professionals to report the adverse events that occur after a drug is approved. Although it is commonly used only for reporting serious reactions to the FDA and would not be mandatory in this case (Answer A is incorrect), it can be used to report any adverse event. Information recorded on these forms is reported to the manufacturer and used to determine whether black box warnings are necessary or whether new adverse effects are seen with a drug. The Joint Commission requires that all institutions have a definition of an ADR for the institution that can be understood and remembered by all health care professionals (Answer B is correct). In addition, The Joint Commission requires that each drug dose administered be monitored for adverse effects, that each institution have a system in place for reporting ADRs, and that the institution ensure that the reporting mechanism identifies all key ADRs. The Naranjo algorithm is used to determine the likelihood of cause and effect from a presumed drug-induced event, but is not required (Answer C is incorrect). Answer D is incorrect as serious adverse effects are reportable to the FDA, as are severe and life-threatening events.

13. Answer: B

Because the pharmacy and therapeutics committee wants to discover whether the new drug is worth the extra cost for the added mortality benefits it can provide for patients with decompensated HF compared

with available therapies, a cost-effectiveness analysis (Answer B is correct) is the best pharmacoeconomic analysis to perform. Cost-minimization analysis (Answer A is incorrect) is used to determine whether a therapeutically equivalent drug within a class that provides the same therapeutic outcome as other available drugs can be used for less cost. Cost-utility analysis (Answer D is incorrect) is used to determine whether a drug can improve the quality of a patient's life more than other available therapies. Cost-benefit analysis (Answer C is incorrect) is used to evaluate new programs or services to determine whether they provide enough benefit to justify the cost of running the program.

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Cardiovascular Critical Care

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Learning Objectives

1. Describe cardiovascular anatomy, inherent physiologic function, and circulation in relation to hemodynamic assessment.
2. Evaluate patients and devise a treatment strategy for patients with cardiogenic shock, considering pharmacodynamic response to vasopressors/inotropes.
3. Identify cardiovascular disease states associated with cardiogenic shock.
4. Understand the fundamentals in management of cardiovascular diseases in critically ill patients.
5. Recognize the options for and roles of mechanical circulatory support and heart transplantation as advanced therapies for heart failure and/or cardiogenic shock.

Abbreviations in This Chapter

ABG	Arterial blood gas
ACE	Angiotensin-converting enzyme
ACS	Acute coronary syndrome(s)
ACT	
AF	Atrial fibrillation
ARB	Angiotensin receptor blocker
AV	Atrioventricular
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
$CHADS_2$	Congestive heart failure, hypertension, age older than 75, diabetes, and prior stroke or transient ischemic attack
CVP	Central venous pressure
ECHO	Echocardiography
ECMO	Extracorporeal membrane oxygenation
HIT	Heparin-induced thrombocytopenia
HOCM	Hypertrophic obstructive cardiomyopathy
ICU	Intensive care unit
LV	Left ventricle/ventricular
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCS	Mechanical circulatory support
MI	Myocardial infarction
NSTEMI	Non–ST-segment elevation myocardial infarction
OLH	Outlying hospital
PCI	Percutaneous coronary intervention
PVR	Pulmonary vascular resistance
RV	Right ventricle/ventricular
SA	Sinoatrial
STEMI	ST-segment elevation myocardial infarction
SVR	Systemic vascular resistance
VAD	Ventricular assist device
VT	Ventricular tachycardia

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

Questions 1–8 pertain to the following case.

A 58-year-old man (height 71 inches, weight 106 kg) was transferred to the intensive care unit (ICU) from an outlying hospital (OLH) after 24 hours of progressively worsening chest pain and shortness of breath. He arrives on 6 L of oxygen by high-flow nasal cannula, with a heparin infusion at 16 units/kg/hour and dopamine infusing at 15 mcg/kg/minute by peripheral line. Notes show that he was bradycardic (heart rate [HR] ranging from 50 to 58 beats/minute) and hypotensive (78/49 to 86/55 mm Hg) on presentation to the OLH. His 12-lead electrocardiogram (ECG) at the OLH showed ST-segment depression in leads V2 and V3. Given his chest pain and ECG findings, aspirin 324 mg (chewed and swallowed), clopidogrel 600 mg, and morphine 4 mg intravenously once were administered before transfer. Notes also show that β-blockers and nitroglycerin were held because of bradycardia and hypotension.

His medical history is significant for medical nonadherence, hypertension, diabetes, hyperlipidemia, and heart failure with preserved ejection fraction (HF*p*EF), with a last-reported left ventricular ejection fraction (LVEF) of 65% 1 year ago.

- Vital signs on transfer: BP 87/52 mm Hg, HR 85 beats/minute, respiratory rate 19 breaths/minute, temperature 37.6°C
- The team's assessment indicates ongoing distress, radiating chest pain 7 of 10, evidence of rales, absence of any cardiac murmurs, and presence of a right radial arterial line.

- A preexisting urinary catheter with 20 mL of urine in the reservoir is also present (the patient reports that his last void was yesterday morning). According to OLH records, only 30 mL of urine was reported before time of transfer.
- His chest radiography reveals evidence of diffuse patchy opacities; however, the report indicates that an infiltrate cannot be ruled out.
- His serum chemistry panel results are as follows: sodium 132 mEq/L, potassium 4.2 mEq/L, chloride 102 mEq/L, carbon dioxide 22 mEq/L, blood urea nitrogen (BUN) 34 mg/dL, serum creatinine (SCr) 1.9 mg/dL, and glucose 163 mg/dL.
- Results of the complete blood cell count (CBC) are as follows: white blood cell count (WBC) 11.3×10^3 cells/mm^3, hemoglobin 10.9 g/dL, hematocrit 31.1%, and platelet count 213,000/mm^3.
- Additional laboratory values include troponin 3.9 ng/mL, aspartate aminotransferase (AST) 14 IU/L, alanine aminotransferase (ALT) 46 IU/L, hemoglobin A1C (A1C) 8.3%, and brain natriuretic peptide (BNP) of 1423 pg/mL.

1. Which is the most likely cause of this patient's admission and transfer?
   A. Septic shock caused by suspected pneumonia with subsequent myocardial depression and demand ischemia.
   B. Cardiogenic shock caused by acute on chronic decompensated systolic heart failure.
   C. Cardiogenic shock caused by a suspected posterior ST-segment elevation myocardial infarction (STEMI).
   D. Cardiogenic shock caused by a suspected non–ST-segment elevation myocardial infarction (NSTEMI) affecting the lateral wall.

2. Given this patient's presentation, which coronary artery is most suggestive of a culprit lesion?
   A. Left main coronary artery.
   B. Left anterior descending artery.
   C. Left circumflex coronary artery.
   D. Right coronary artery.

3. The interventional cardiologist who is evaluating the patient for potential revascularization asks the ICU team to place a central venous catheter. Which changes/interventions regarding this patient's hemodynamic support would be best to recommend?
   A. Increase dopamine to achieve a mean arterial pressure (MAP) greater than 65 mm Hg.
   B. Convert the patient to norepinephrine, and titrate the dose to achieve a MAP greater than 65 mm Hg while weaning off dopamine.
   C. Initiate milrinone at 0.375 mcg/kg/minute, and continue dopamine at 15 mcg/kg/minute.
   D. Administer 1000 mL of normal saline as a bolus because of low urine output.

4. The patient has been taken to the cardiac catheterization laboratory, and a "code blue" is called overhead for immediate emergency response to this patient's procedural area. On arrival, chest compressions have just been paused for defibrillation, and a single dose of epinephrine has been administered. The interventional team indicates that, when attempting visualization of the right coronary artery, the patient went into ventricular tachycardia (VT). The patient's telemetry monitor now shows a sinus tachycardia with noted ectopy—HR of 113 beats/minute and blood pressure (BP) of 84/52 mm Hg. The cardiologist asks for recommendations for an antiarrhythmic because he is concerned about a VT relapse, given the bigeminy revealed on telemetry. Which agent would be best to recommend?
   A. Lidocaine 100 mg intravenous push over 2–3 minutes, followed by an infusion at 1 mg/minute.
   B. Amiodarone 300 mg intravenous push over less than 1 minute.
   C. Metoprolol 10 mg intravenous push over 1–2 minutes.
   D. Diltiazem 20 mg intravenous push over 2 minutes, followed by a continuous infusion at 5 mg/hour and titrated to maintain a HR less than 110 beats/minute.

5. The patient returns to the ICU after his left heart catheterization, which was performed through the femoral artery. In addition to his acute decompensation, which major procedural complication is of greatest concern during the next 12 hours?
   A. Bleeding (particularly retroperitoneal bleeding).
   B. Dissection/rupture.
   C. Stent thrombosis.
   D. Papillary muscle rupture.

6. The patient is currently on dopamine at 12 mcg/kg/minute and norepinephrine at 0.08 mcg/kg/minute with an HR of 108 beats/minute, a BP of 82/51 mm Hg, a cardiac index of 2.0, a central venous pressure (CVP) of 26 mm Hg, and a pulmonary artery pressure of 29/21 mm Hg. The physician would like to augment management of this patient's hypotension but asks for your recommendation out of concern for the patient's right ventricular (RV) function, as evidenced by the rising CVP despite only mildly elevated pulmonary artery pressures. Moreover, the physician's goal is to wean the dopamine while increasing the patient's systemic vascular resistance (SVR) without affecting the pulmonary vascular resistance (PVR) much, if at all. Which strategy would be best to recommend?
   A. Keep the current infusions and reevaluate later.
   B. Initiate phenylephrine at 1 mcg/kg/minute and wean the dopamine off if MAP is greater than 65 mm Hg.
   C. Initiate vasopressin at 0.04 unit/minute and wean the dopamine off if MAP is greater than 65 mm Hg.
   D. Administer a 1-L bolus of normal saline and wean the dopamine off if MAP is greater than 65 mm Hg.

7. Hours later, this patient goes into atrial fibrillation (AF) with an HR of 126 beats/minute; however, the patient's BP remains 86/56 mm Hg according to the regimen selected in the previous question. Which agent would you most likely administer to manage the patient's AF?
   A. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute.
   B. Amiodarone 150 mg intravenous infusion over 10 minutes, followed by a continuous infusion at 1 mg/minute.
   C. Metoprolol 5 mg intravenous push once, followed by 5 mg intravenous push every 6 hours.
   D. Diltiazem 20 mg intravenous push, followed by a continuous infusion at 5 mg/hour and titrated to maintain an HR of less than 110 beats/minute.

8. If this patient did have a myocardial infarction (MI) during his stay (regardless of intervention or medical management) with an LVEF greater than 40%, which most accurately depicts the medication-related quality metric that would not require initiation or documentation of contraindications at this time?
   A. $P2Y_{12}$ contraindication.
   B. Statin contraindication.
   C. β-Blocker contraindication.
   D. Angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor antagonist (ARB) contraindication

I. CARDIOVASCULAR FUNDAMENTALS OVERVIEW

A. The myocardium has five functions and distinctive properties:
   1. *Chronotropy*: Ability to generate an electrical impulse at an intrinsic rate
   2. *Dromotropy*: The speed and ability to facilitate electrical impulse conduction
   3. *Inotropy*: Ability to contract in relation to a given preload, afterload, and HR
   4. *Bathmotropy*: Demonstration of an intrinsic excitatory threshold
   5. *Lusitropy*: Relaxation of the myocardium, independent from termination of contraction
   6. Other related terms:
      a. *Preload*: Volume of blood (represented in most cases by a pressure) in a *ventricular cavity* at the end of diastole immediately before contraction, imparting stretch on a resting myocardial sarcomere
      b. *Afterload*: The pressure that a *ventricle* must overcome to generate cardiac output. The greater the afterload (vascular resistance or impedance), the greater the amount of energy and force required to enable ejection of blood from a ventricle and vice versa

B. Coronary Artery Circulation
   1. Myocardial perfusion occurs through the coronary arteries during diastole.
   2. Coronary artery anatomy and perfusion are not the same in everyone.
   3. ECG defects, hemodynamic assessment, and patient symptoms may assist with coronary artery disease (CAD) localization.
   4. Circulatory dominance:
      a. Right dominant: Posterior descending artery and atrioventricular (AV) nodal artery arise from the right coronary artery (85% of the population).
      b. Left dominant: Posterior descending artery arises from the circumflex artery (8% of the population).
      c. Codominant: Posterior descending artery arises from branches of the circumflex and the right coronary artery (7% of the population).
      d. Other notable variations: The sinoatrial (SA) node may have variation in the vessels that supply it; it is most commonly perfused by the right coronary artery (about 70%), circumflex (about 25%), and right coronary artery and circumflex (about 5%).

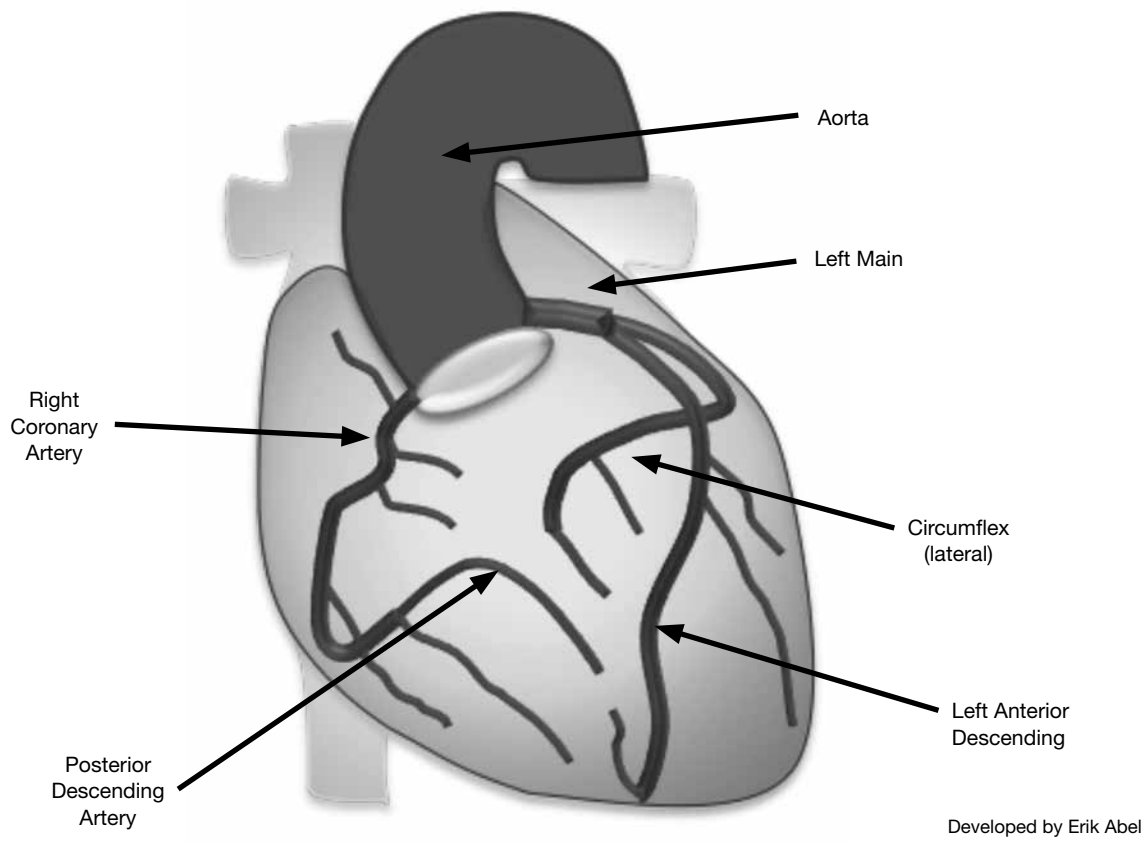
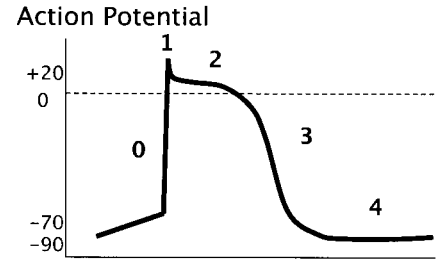
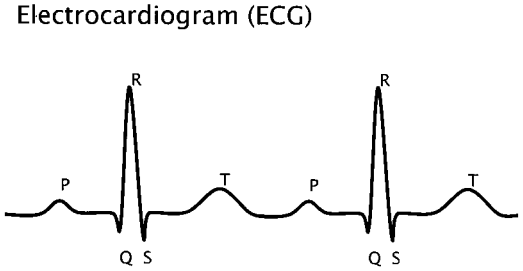


Figure 1. Coronary artery circulation.

C. Anatomy in Relation to the ECG
   1. A single lead of an ECG tracing is a summative representation of the action potentials occurring from a single cell, facilitating myocardial conduction, contraction, and relaxation.
   2. A 12-lead ECG can provide a geographic representation of conduction within the myocardial tissue. Conduction abnormalities within specified leads may indicate perfusion defects in some clinical scenarios (i.e., acute coronary syndromes [ACS]).



Phase	Electrolyte movement	Conduction change
0	Na+ influx into cell	Depolarization
1	Rrefractory Ca^{2+} and C^{l-} into cell	Effective Refractory Period
2	Ca^{2+} into cell and K^{+} out of cell	
3	K+ out of cell	Repolarization
4	Resting Membrane Potential	



ECG point	Representation
P	Sinoatrial (SA) node impulse generation
PR interval	Duration for conduction to occur from the SA node through the AV node, bundle of His, bundle branches and Purkinje fibers
QRS	Concurrent atrial repolarization and ventricular depolarization
ST segment	Ventricular refractory period
T	Ventricular repolarization
QT interval	Duration for atrial and ventricular repolarization
RR interval	Duration between ventricular depolarizations (represents heart rate)
U	No listed or commonly visualized; may be more prominent in hypothermia or in severe electrolyte depletions

12 — Lead Electrocardiogram (ECG)

Limb leads				Precordial Leads			
I	Anterolateral (Circumflex)	aVR		V1	Anteroseptal (LAD)	V4	Anteroapical (Distal LAD)
II	Inferior (RCA)	aVL	Anterolateral (Circumflex)	V2	Anteroseptal (LAD) Posterior (RCA)	V5	Anterolateral (Circumflex)
III	Inferior (RCA)	aVF	Inferior (RCA)	V3	Anteroapical (Distal LAD) Posterior (RCA)	V6	Anterolateral (Circumflex)

adapted from ACLS instructor book

Figure 2. Anatomy in relation to the ECG.

II. HEMODYNAMIC MANAGEMENT AND THE HEART

A. Hemodynamic Assessment Relies on the Clinician's Clinical Interpretation to:
   1. Understand cardiovascular circulation (Figure 3) and pathophysiology contributing to the hemodynamic parameters in isolation and in the context of other hemodynamic parameters
   2. Account for trends in the values in light of end-organ function and surrogates of oxygen delivery, and use VO_2 mismatch
   3. Understand the roles of hemodynamic tools, limitations in use, and interpretation of the devices/technology.
   4. Identify appropriate therapeutic targets (Figure 4), and apply the pharmacologic/pharmacodynamic principles (Table 1) to initiate, modify, or discontinue therapy depending on clinical response

B. Advantages and Disadvantages of Invasive Hemodynamic Monitoring for Assessing Cardiac Output and/or Volume Status
   1. Hemodynamic monitoring techniques facilitate diagnosis, but they should not be mistaken for therapeutic interventions.
   2. Very little evidence has shown improved outcomes with advanced hemodynamic monitoring of any type, likely because patient management is dependent on clinician interpretation and reaction.
   3. Diligent use and skilled interpretation of these technologies, together with patient assessment, can be used to guide therapeutic interventions.
   4. See comparisons of invasive and minimally invasive hemodynamic monitoring devices (see table 2 in the Shock and Resuscitation chapter).

C. Pharmacologic Support in Cardiovascular Critical Illness (see Table 1 and "Shock Syndromes" for hemodynamic basic principles)

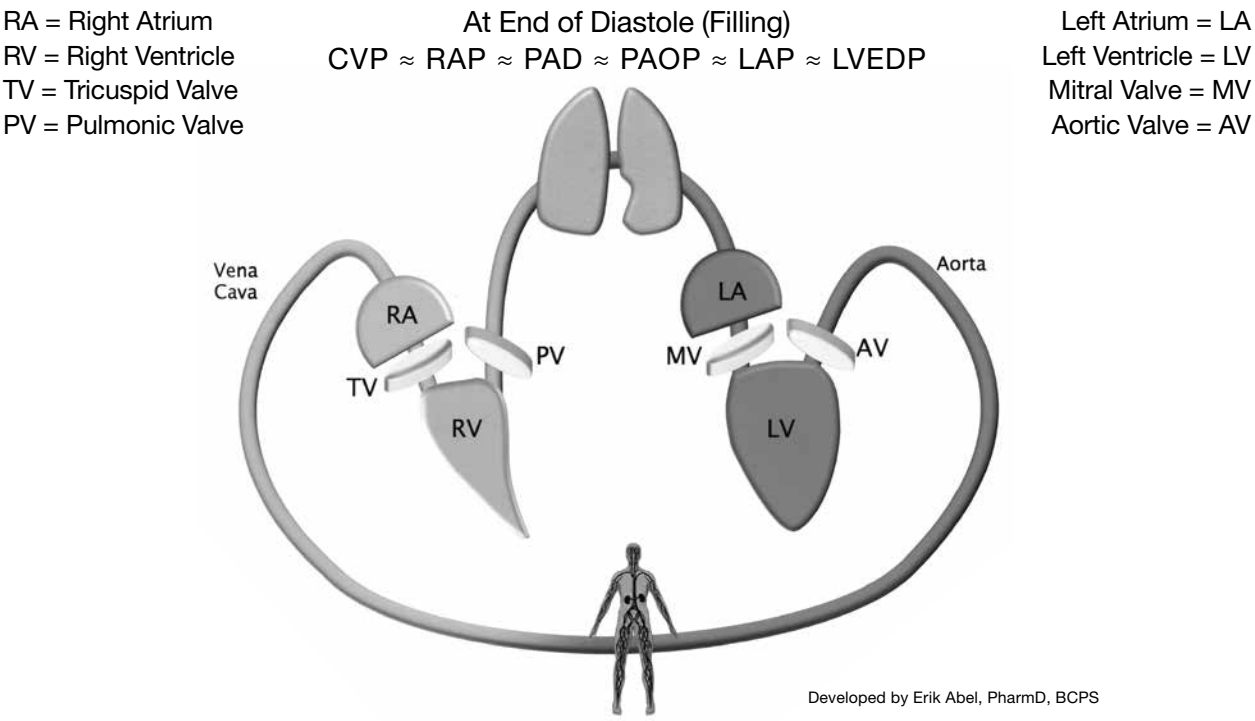


Figure 3. Cardiovascular systemic circulation.

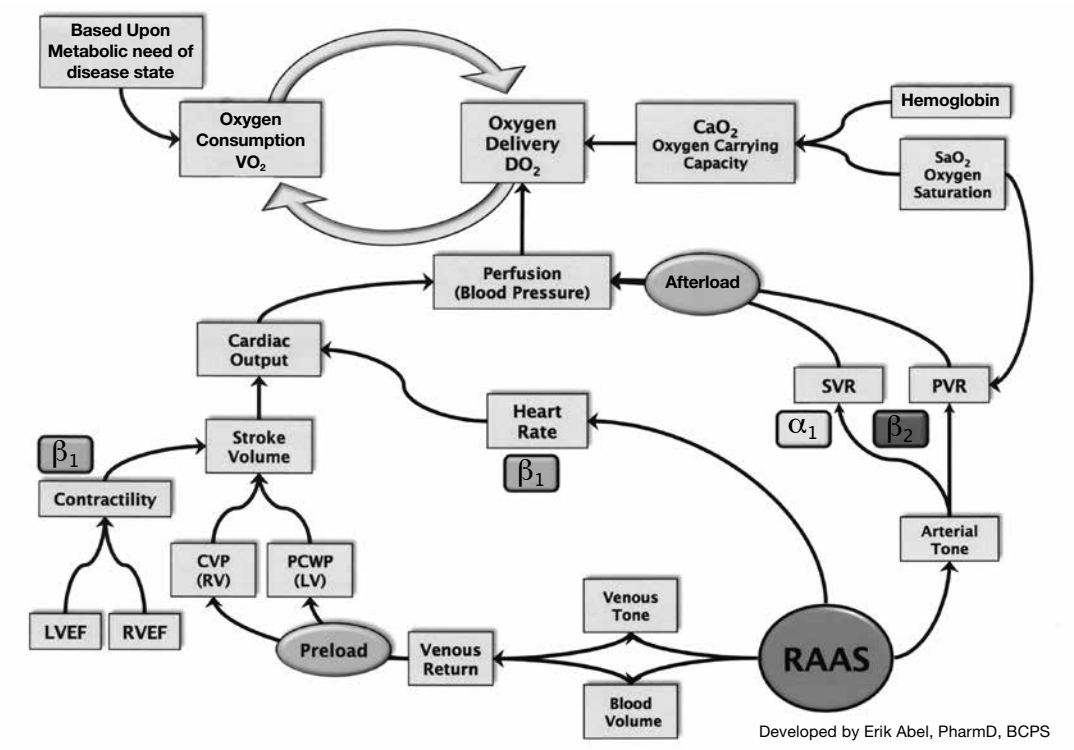


Figure 4. Integrated model of the hemodynamic parameters and therapeutic targets.

Table 1. Pharmacologic Support in Cardiovascular Critical Illness (Br J Pharmacol 2012;165:2015-33; J Am Coll Cardiol 2014;63:2069-78; 2011;xiv, 461 p.; Circulation 2008;118:1047-56; 2014;xix, 1490 p.; J Pharm Pract 2011;24:44-60)

Vasopressors	Dopa	α_1	β_1	β_2	Other Mechanism	HR	CVP	CO	SVR	PVR
Dopamine[a]	+++++	+++	++++	++		↑	↔	↑	↔ or ↑	↔ or ↑
Epinephrine[a]		++++	++++	+++		↑	↔	↑	↑	↑
Norepinephrine[a]		+++++	+++	++		↑	↔	↑	↑	↑
Phenylephrine		+++++				↔ or ↓	↔	↑	↑	↑
Vasopressin	N/A				V_1 and V_2 agonism	↔ or ↓	↔	↔ or ↓	↑	↔ or ↓
Inotropes										
Dobutamine		+	++++	++		↑	↔	↑	↔ or ↓	↔ or ↓
Isoproterenol			+++++	+++++		↑	↔	↑	↔ or ↓	↔ or ↓
Milrinone[b]	N/A				PDE_3 inhibition	↔ or ↑	↔	↑	↓	↓
Vasodilators										
Nitroglycerin					cGMP	↔ or ↑	↔ or ↓	↔ or ↑	↔ or ↓	↔ or ↓
Nitroprusside					cGMP	↔ or ↑	↔ or ↓	↔ or ↑	↔ or ↓	↓
Nesiritide					cAMP	↔ or ↑	↔ or ↓	↔ or ↑	↓	↓
Nitric oxide (inhaled)					cGMP	NA	↔	↔ or ↑	↔	↓
Epoprostenol (inhaled)					cAMP	N/A	↔	↔ or ↑	↔	↓

[a]High doses associated with increasing α1 activity.

[b]Normal half-life is 2.5 hours but is eliminated renally. Loading dose rarely used in routine management.

CVP = central venous pressure; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; N/A = not applicable; PDE3 = phosphodiesterase type 3; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance.

III. CARDIOGENIC SHOCK

A. Characterized by Three Hallmark Attributes:
   1. Sustained hypotension unresponsive to fluid administration alone (SBP less than 90 mm Hg for at least 60 minutes)
   2. Evidence of myocardial dysfunction with reduced cardiac index (less than 2.2 L/minute/m^2)
   3. Signs and symptoms of malperfusion in the setting of elevated cardiac filling pressures (e.g., pulmonary capillary wedge pressure [PCWP] greater than 18 mm Hg)

B. Signs and Symptoms: See Heart Failure section.

C. Epidemiology: Without appropriate diagnosis and management, in-hospital mortality rates as high as 60% have been described Semin Respir Crit Care Med 2011;32:598-606.

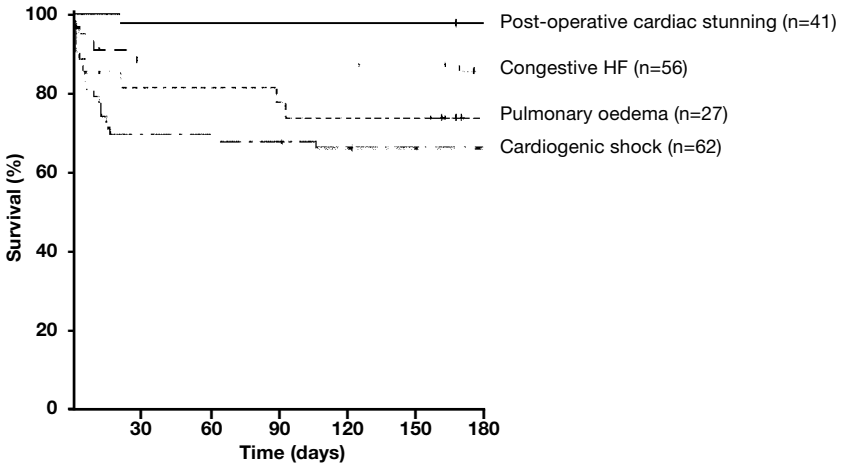


Figure 5. Survival rates of ICU patients over time presenting with different acute heart failure syndromes (Crit Care 2010;14:201).

D. Etiology
   1. Usually caused by left ventricular (LV) failure secondary to an acute MI, but a list of other potential causes can be found in Box 1
   2. May be multifactorial, including one or more of the causative etiologies; however, can also coexist with other types of shock syndromes

Box 1. Potential Causes of Cardiogenic Shock (2014;xix, 1490 p.; Semin Respir Crit Care Med 2011;32:598-606; Cardiol Clin 2013;31:567-80, viii; Cardiol Clin 2013;31:519-31, vii-viii)

Left Ventricular Failure
- Large MI
- Small MI with preexisting systolic heart failure
- Reinfarction
- Septic shock with severe myocardial depression

RV Failure
- RV infarction
- End-stage pulmonary hypertension

Acute Mechanical Dysfunction
- Papillary muscle rupture or chordal rupture with subsequent severe mitral regurgitation
- Free-wall rupture
- Ventricular septal rupture
- Cardiac tamponade

Cardiomyopathy
- End-stage heart failure
- Myocarditis
- Peripartum cardiomyopathy
- Left ventricular outflow tract obstruction
- Stress-induced cardiomyopathy (i.e., takotsubo)

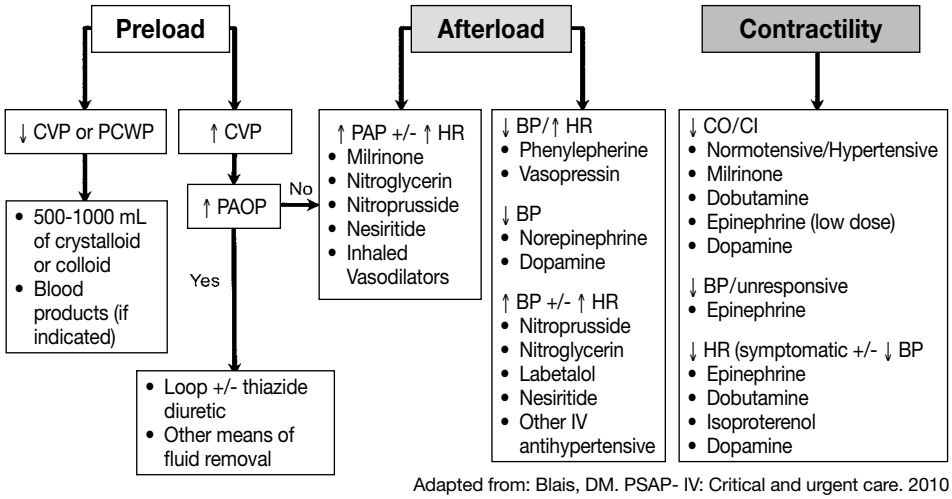
Box 1. Potential Causes of Cardiogenic Shock *(continued)*

Valvular Disease
- Acute aortic regurgitation
- Ischemic mitral regurgitation
- Aortic or mitral stenosis with tachyarrhythmia or other condition causing decompensation
- Infectious endocarditis
- Prosthetic valve dysfunction or thrombosis

Arrhythmia

Other Conditions
- Prolonged cardiopulmonary bypass and/or coronary air embolus
- Cardiac trauma (blunt or penetrating)
- Heart transplant rejection
- Pulmonary embolism
- Medical nonadherence

E. Resuscitation/Treatment
   1. Treatment largely depends on managing underlying chronic or acute cardiovascular disease(s) outlined in Box 1, with consideration given to chronicity of clinical changes before onset of shock.
   2. Means of management will be primarily discussed under the Major Contributing Etiologies heading in sections III–VI.
   3. Hemodynamic management and pharmacotherapeutic considerations
      a. Because cardiogenic shock may have different underlying, contributing etiologies, hemodynamic management requires careful interpretation of clinical values. Treatment strategies could be devised according to the algorithm in Figure 6.
      b. Sepsis Occurrence in Acutely Ill Patients (SOAP) II landmark trial (N Engl J Med 2010;362:779-89)
         i. International multicenter trial (n=1679) that compared the 28-day mortality of norepinephrine with that of dopamine in the management of shock
            (a) Included if signs of malperfusion and MAP less than 70 mm Hg or SBP less than 100 mm Hg, despite adequate fluid challenge (at least 1000 mL of crystalloids or 500 mL of colloids unless the CVP was greater than 12 mm Hg or the pulmonary artery occlusion pressure was greater than 14)
            (b) Allowed titration to maximums of norepinephrine 0.19 mcg/kg/minute versus dopamine 20 mcg/kg/minute, after which open-label norepinephrine was allowed (open-label norepinephrine doses did not exceed 1.1 mcg/kg/minute during the study period)
            (c) Epinephrine and vasopressin were permitted as rescue agents (similar use in both groups).
            (d) Dobutamine use was greater in the norepinephrine group (19.4% vs. 14.8%).
         ii. Showed that dopamine was associated with a significantly higher mortality rate than was norepinephrine with or without dobutamine in patients with cardiogenic shock in subgroup analysis
         iii. Specifically, dopamine was associated with more adverse events than norepinephrine in the management of all shock subtypes, predominantly driven by the incidence of arrhythmias (24.1% vs. 12.1%, $p<0.001$). Tachyarrhythmias with dopamine had the greatest incidence within the first 36 hours after randomization.



Adapted from: Blais, DM. PSAP- IV: Critical and urgent care. 2010

Figure 6. Shock management and treatment considerations based on hemodynamic indices.

Patient Cases

Questions 1–6 and Question 8 pertain to the following case.

J.M. is a 58-year-old man with a history of CAD, type 2 diabetes mellitus, hyperlipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy after a STEMI 2 years ago left him with two drug-eluting stents in his proximal and mid-left anterior descending artery. Records indicate an LVEF of 30–35% and moderate mitral regurgitation from 6 months ago. He is admitted to the cardiac care unit for severe shortness of breath and altered mental status, where he is currently on CPAP (continuous positive airway pressure). He has gained 13 kg during the past 2 weeks (now weighs 121 kg) and has had decreased urine output, despite having had his diuretic dose increased. Home medications include the following: aspirin 81 mg once daily, ticagrelor 90 mg every 12 hours, pantoprazole 40 mg once daily, metoprolol tartrate 25 mg every 12 hours, atorvastatin 40 mg once daily, insulin glargine 10 units every night, metformin 500 every 12 hours, furosemide 40 mg twice daily, and potassium chloride 20 mEq twice daily. His wife states that he was taking clopidogrel until 1 month ago but could not afford it, so his primary care physician provided ticagrelor samples. A physical examination reveals rales throughout his lung fields. He is afebrile, anxious, and alert.

1. Given J.M.'s comorbidities, some drugs or drug classes have proven mortality benefits. Which group of added or modified medications, not on the patient's home medication profile, might best have helped slow the progression of his disease and confer mortality benefits?
   A. Amlodipine, clopidogrel, and sitagliptin.
   B. Spironolactone, lisinopril, and carvedilol.
   C. Pravastatin, amlodipine, and aspirin 325 mg.
   D. Prasugrel, sildenafil, and atenolol.

Patient Cases *(continued)*

2. Given the patient's presentation, which group of diagnostic tests would be most helpful to guide your recommendations to the team for J.M.'s current management? (Assume that a basic metabolic panel [Chem 7], a pulse oximetry, and a capillary blood glucose have already been completed.)

   A. Urine culture, respiratory culture, lactate and procalcitonin.
   B. Chest radiography, arterial blood gas (ABG), liver function tests, and serial troponins.
   C. Chest radiography, echocardiogram (ECHO), lactate, and BNP.
   D. Chest radiography, arterial line, ABG, and lactate.

3. All tests mentioned above have been ordered, and the following results are available. J.M.'s BP is 110/76 (MAP 87) mm Hg and HR is 56 beats/minute.

   - Chest radiography reveals diffuse patchy opacities; however, infiltrate cannot be ruled out; lines are all in appropriate positions.
   - Serum chemistry panel results are as follows: sodium 126 mEq/L, potassium 4.8 mEq/L, chloride 102 mEq/L, carbon dioxide 21 mEq/L, BUN 32 mg/dL, SCr 1.6 mg/dL, and glucose 134 mg/dL.
   - Results of the CBC are as follows: WBC 9.8 × 10^3 cells/mm^3, hemoglobin 11.1 g/dL, hematocrit 32.6%, and platelet count 173,000/mm^3.
   - Additional laboratory values include the following: troponin 0.9 ng/mL, AST 114 IU/L, ALT 102 IU/L, and BNP 1936 pg/mL.
   - Invasive hemodynamic parameters include CVP 28 mm Hg, pulmonary artery pressures 46/22 mm Hg, cardiac index 1.8 L/minute/m^2, and central venous oxygen saturation ($ScvO_2$) 53%; pulmonary artery occlusion pressure is not yet available.
   - ABG results are as follows: pH 7.36, P_{O_2} 93.7, P_{CO_2} 43.2, bicarbonate 23.9, O_2 saturation 89%, and lactate 6.9.
   - ECHO results are pending.

   The patient's physical examination reveals that his extremities are cold to the touch, and capillary refill is poor. The team has ordered furosemide 80 mg intravenously once and discontinued metoprolol; the team would like to initiate a vasopressor or inotrope for this patient. Which would be best to recommend at this time?

   A. Norepinephrine 0.08 mcg/kg/minute.
   B. Epinephrine 0.08 mcg/kg/minute.
   C. Milrinone 0.25 mcg/kg/minute.
   D. Dobutamine 5 mcg/kg/minute.

IV. ACUTE CORONARY SYNDROMES

A. Pathophysiology
   1. Manifestation of prolonged cessation of oxygenated blood supply to a portion of the myocardium that is most commonly caused by an acute thrombus at the site of coronary atherosclerotic stenosis leading to local or regional myocardial ischemia and necrosis
   2. Other disease states leading to an elevated myocardial oxygen demand with a concurrent inability to meet such demands may result in a scenario where "demand ischemia" is considered versus a diagnosis of ACS.

B. Presentation and Diagnosis (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426) – Although other cardiac enzymes assays are available for clinical use, cardiac troponins are usually used as sensitive markers indicative of myocardial necrosis. Troponin is eliminated renally.

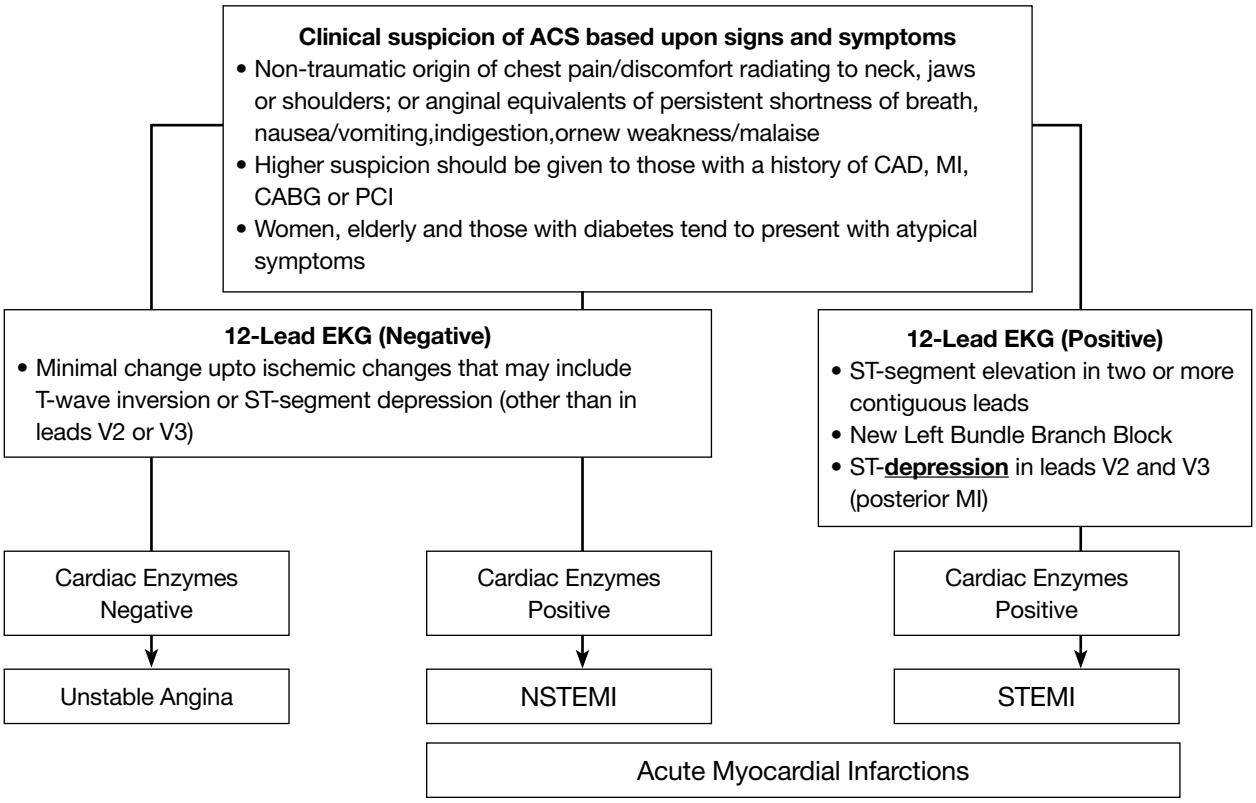


Figure 7. Presentation and diagnosis.

Box 2. Causes of Troponin Elevation (Heart 2006;92:987-93)

Acute MI	Chronic heart failure
Post-PCI	Acute decompensated heart failure
Early post-cardiac surgery	Chest wall trauma
Acute pulmonary embolism	Severe strenuous exercise
Rhabdomyolysis	Cardiotoxic chemotherapy
Tachyarrhythmia	Direct current cardioversion/defibrillation
Aortic stenosis	Cardiac amyloidosis
Pericarditis	Heart transplantation
Myocarditis	Sepsis
Type A dissection	

PCI = percutaneous coronary intervention.

C. Acute Management of MI

Table 2. Acute Management (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426)

MI Type	STEMI	NSTEMI
Goals of care	Reperfusion therapy as soon as possible • Primary PCI preferred if it can be performed within 90 min of medical contact • If primary PCI is unavailable within 90 min of medical contact, thrombolytics should be administered within 30 min of presentation unless contraindications exist • Surgical revascularization may be indicated, depending on severity of CAD, complexity of anatomy, or development of other complications	Prevent total occlusion of the vessel • Decision and need for revascularization (PCI or surgery) vs. medical management should be made on the basis of risk stratification, symptom resolution, and indicators of ongoing myocardial damage/ischemia

PCI = percutaneous coronary intervention.

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426)

Predominant interventions on presentation/onset for stabilization – Any ACS	
Oxygen	• Can help facilitate anginal pain secondary to tissue hypoxia • Supplemental oxygen considered if Sa_{O_2} less than 90%, respiratory distress, or other high-risk features for hypoxemia
Aspirin	• Inhibit platelet activation • Four aspirin 81 mg each (324 mg total) or one 325-mg tablet (non–enteric coated) should be chewed and swallowed immediately
Nitrates	• Can facilitate coronary vasodilation and may also be helpful in scenarios of severe cardiogenic pulmonary edema caused by increased venous capacitance • Nitroglycerin (NTG) 0.4 mg sublingually every minute for total of THREE doses; afterward, assess need for IV NTG • Intravenous NTG is indicated in the first 48 hours after treatment of persistent ischemia, HF, or hypertension but should not preclude therapy such as β-blockers or ACE inhibitors when indicated • **Should NOT be administered:** o If SBP < 90 mm Hg OR if SBP is ≤ 30 mm Hg below baseline o If severe bradycardia (including heart block) with HR ≤ 50 beats/minute o If tachycardia (HR ≥ 100 beats/minute) in the absence of symptomatic HF, or RV infarction o If patient has received an oral phosphodiesterase inhibitor within the past 24–48 hours
Morphine or other narcotic analgesic	• Provides analgesia and decreases pain-induced sympathetic/adrenergic tone • Morphine commonly used because it may also induce vasodilation and mediate some degree of afterload reduction • Morphine now carries a class IIbB recommendation and may be not be favored over other narcotic analgesics, given that at least two large trials have identified an association between morphine administration and risk of death (N Engl J Med 2014;371:1016-27; Am Heart J 2005;149:1043-9)

Table 3. Predominant Interventions on Presentation/Onset for Stabilization – Any ACS *(continued)*

Predominant interventions on presentation/onset for stabilization – Any ACS		
β-Blockade	• Decreases HR and myocardial oxygen demand and increases diastolic filling time of ventricles and thereby the coronary arteries • **β-Blockade should be initiated within the first 24 hr of an ACS <u>unless</u>:** o There are signs of HF o Active evidence of other shock states o If at increased risk of cardiogenic shock (SBP < 120 mm Hg), HR > 110 beats/minute or < 60 beats/minute • ***Relative contraindications* to β-blockade include:** o PR interval greater than 0.24 s, second- or third-degree heart block, and active asthma/reactive airway disease	
Loop diuretic	• May be warranted if patient is develops severe cardiogenic pulmonary edema or other concurrent symptoms of HF with volume overload	
Helpful acronyms	MONA ± BB • Morphine • Oxygen • Nitrates (unless contraindicated) • Aspirin • β-Blocker (unless contraindicated)	LMNOP + aspirin (in reverse) • Aspirin • Positioning (resting upright + ECG) • Oxygen • Nitrates (unless contraindicated) • Morphine • Loop diuretic
Other precautions	• ACE inhibitors/ARBs should be used with caution within the first 24 hours of ACS because of the risk of hypotension and potential contribution to contrast-induced nephrotoxicity • Any NSAID other than aspirin should be avoided and/or discontinued for reasons other than GI bleeding and nephrotoxicity, which may include reinfarction, hypertension, HF exacerbation, myocardial rupture, and overall increased risk of mortality associated with their use	

GI = gastrointestinal; HF = heart failure; LMNOP = lasix-morphine-nitro-oxygen-position/positive pressure ventilation; NSAID = nonsteroidal anti-inflammatory drug.

D. Revascularization
   1. Nonsurgical – Details of interventional cardiology procedures are too broad to be discussed in great detail in this chapter; however, following are some considerations of the intervention that may play a role in postprocedural management during a left heart catheterization and percutaneous coronary intervention (PCI):
      a. Access site
         i. Radial artery (and rarely, brachial artery) (Catheter Cardiovasc Interv 2011;78:840-6)
            (a) Easily accessible
            (b) Increased risk of vasospasm during procedure
            (c) Easily compressible vessel when hemostasis is needed postprocedure
            (d) Does not prevent patient mobility postprocedure
         ii. Femoral artery
            (a) Easily accessible
            (b) More difficult to compress vessel when hemostasis is needed postprocedure and also associated with increased bleeding complications
            (c) Limits patient mobility postprocedure for at least 12–24 hours (bleeding risk after sheath removal)

b. Common interventions performed:
    i. Thrombectomy: Thrombus aspiration generally followed by placement of a stent at site of lesion
    ii. POBA (plain old balloon angioplasty): Balloon expansion and at least temporary displacement of occlusion at site of lesion
    iii. Stent placement
        (a) Important to note the number of stents placed, the types of stents, and the locations of placement
        (b) Bare metal stent
            (1) Requires aspirin for life and a P2Y12 antagonist for at least 1 month (12 months preferred) to allow adequate time for endothelialization of the stent(s)
            (2) Longer therapy durations may be considered, depending on the number of stents and/or location(s) of the stent(s).
            (3) Higher risk of in-stent stenosis over time as reendothelialization occurs
        (c) Drug-eluting stent
            (1) Requires aspirin for life and a P2Y12 antagonist for at least 12 months. Longer therapy durations may be considered, depending on the number of stents and/or location(s) of the stent(s). Ongoing investigations are evaluating the optimal duration of dual antiplatelet therapy, but many questions are currently unanswered.
            (2) Associated with a higher risk of stent thrombosis; the rate of endothelialization over the stent is slowed by the drug coating on the stent, thus leaving metal exposed that can potentiate thrombus formation
    iv. Ventriculogram: Means of assessing the ejection fraction using a larger volume of intravenous contrast dye delivered directly into the ventricle to estimate the volume of blood ejected during systole

2. Surgical revascularization – Details of coronary artery bypass grafting (CABG) procedures, including conduit type and use of cardiopulmonary bypass (or performing off-pump), are too broad to be discussed in greater detail in this chapter. According to the STS/ACC/AHA CABG guidelines, emergency CABG is recommended in patients with an acute MI in the following scenarios: (J Am Coll Cardiol 2011;58:e123-210)
    a. Primary PCI has failed or cannot be performed
    b. Coronary anatomy is more suitable for CABG
    c. Persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present
    d. Requirement of surgical repair of a postinfarction mechanical complication of MI (i.e., ventricular septal rupture, mitral valve insufficiency caused by papillary muscle infarction and/or rupture, or free wall rupture)
    e. Patients with cardiogenic shock who are suitable for CABG, irrespective of the time interval from MI to onset of shock and time from MI to CABG
    f. Patients with life-threatening ischemic ventricular arrhythmias in the presence of a left main stenosis of 50% or more and/or three-vessel CAD
    g. CABG use is reasonable as a revascularization strategy in patients with multivessel CAD with recurrent angina or MI within the first 48 hours of STEMI presentation as an alternative to a more delayed strategy
    h. Early revascularization with PCI or CABG is reasonable for select patients older than 75 years with ST-segment elevation or left bundle branch block who are suitable for revascularization irrespective of the time interval from MI to onset of shock

3. Medical management – No revascularization:
    a. Less invasive strategies may be opted for rather than revascularization in some patients. Considerations reinforce a patient-centered approach driven by evidence of ongoing/recurrent ischemia and feasibility of revascularization, including myocardial viability, patient frailty, and comorbid disease states.
    b. Ongoing care outlined in section E remains the focus of optimizing aggressive medical management.

E. Antithrombotics in MI
1. The roles and combinations of antithrombotics continue to be refined in select populations (those with NSTEMI/ACS, STEMI, and PCI). For the most current guidelines and landmark trials, please see www.acc.org/guidelines.
2. Oral antiplatelet therapy
    a. Platelets can be activated by several different mechanisms, only some of which can be inhibited by medications.
    b. In the critically ill, our ability is currently limited to assess and interpret the adequacy of antiplatelet therapies. Clinical evidence with platelet function testing has not been well-studied with durable clinical endpoints such as cardiac events and/or mortality.
    c. Common clinical obstacles in the critically ill are without evidence-based solutions at this time; these include variability in drug response that could be owing to absorption and metabolism variability in patients with hepatic insufficiency. Furthermore, therapeutic alternatives are limited and without evidence when enteral administration is not an option.

Table 4. Oral Antiplatelet Therapy[a] (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-5)

Medication	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Role/mechanism of inhibition	Inhibits thromboxane A_2–mediated platelet activation and aggregation	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor	Inhibits ADP-mediated platelet aggregation ($P2Y_{12}$ receptor) to prevent conformational change of GPIIb/IIIa receptor
Loading dose	324–325 mg	600 mg	60 mg	180 mg
Maintenance dose	81 mg	75 mg QD	10 mg QD	90 mg BID
Route	Oral	Oral	Oral	Oral
Prodrug	No	Yes	Yes	No
Reversible platelet binding	No	No	No	Yes
Onset	30 min	2 hours	30–60 min	30–60 min
% Platelet inhibition	~20	40	70	95
Recommended holding duration before CABGb	Do not hold	5 days	7 days	7 days
Other notable adverse effect(s) or clinical pearls		• Pharmacogenomic variance has been noted and may contribute to drug response	• Black box warning against use in patients with a history of stroke or TIA, and warning of use in patients > 75 years or weight < 60 kg	• Adenosine-induced bradycardia and dyspnea • Elderly patients and patients with moderate or severe hepatic impairment may be at increased risk of bleeding • Concomitant doses of ASA > 100 mg should be avoided

[a]Note: Ticlopidine is not widely used in therapy anymore or discussed in the most current ACS guidelines.

[b]Decisions to hold these agents before other invasive procedures must consider indications for use, risk of thrombosis (i.e., stent type, locations, and number), and risk of bleeding associated with intended procedure/surgery. (J Am Coll Cardiol 2011;58:e44-122; JAMA 2013;310:1451-2; Catheter Cardiovasc Interv 2013;82:1113-4; JAMA 2013;310:189-98; J Am Coll Cardiol 2007;49:734-9; N Engl J Med 2013;368:2113-24; Reg Anesth Pain Med 2010;35:64-101).

ADP = adenosine diphosphate; ASA = acetylsalicylic acid; BID = twice daily; GP = glycoprotein; QD = once daily; TIA = transient ischemic attack.

3. Parenteral antithrombotics
   a. Use of these agents is most intensive in the procedural setting, although may continue for a finite period postprocedurally
   b. The selection and use among the agents in Table 5 may depend on presentation, timing/dose of preprocedural antiplatelet medication administration, clot burden during procedure, and estimated bleeding risk of the procedure.

Table 5. Parenteral Antithrombotics (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2011;58:e123-210; J Am Coll Cardiol 2011;58:e44-122; Br J Clin Pharmacol 2011;72:647-57)

Medication	Heparin (UFH)[a]	Bivalirudin	Abciximab	Eptifibatide	Tirofiban
Role in therapy	Indirect thrombin inhibition mediates decreased propagation of clot	Direct thrombin inhibitor – mediates decreased propagation of clot	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen	Binds to GPIIb/IIIa platelet receptor, preventing platelet binding to fibrinogen
Loading dose	50–100 units/kg bolus	0.75 mg/kg	0.25 mcg/kg	180 mg/kg	25 mcg/kg
Continuous infusion	Variable (if used)	1.75 mg/kg/hr	0.125 mcg/kg/min (max 10 mcg/min)	2 mcg/kg/min	0.15 mcg/kg/min
Platelet inhibition	N/A	N/A	Irreversibly inhibits for the life of the platelet (7–10 days)	Restoration of platelet function within 6–8 hours of discontinuation	Restoration of platelet function within 6–8 hours of discontinuation
Elimination	• Hepatic and reticulo-endothelial system	• 80% plasma proteolysis • 20% renal	• Plasma elimination	• 50%–71.4% renal	• Renal
Removed by dialysis	No	Yes	No	Yes	Yes
Other notable adverse effect(s) or clinical pearls	• Cannot be used in patients with a history/suspicion of heparin – induced thrombocytopenia (HIT) • Target activated clotting time (ACT) or 200–250 s during procedure	• Requires renal dose adjustment • Can be used in patients with or without a history or suggestion of HIT • May be preferred in patients with higher bleeding risk • Target ACT or 200–250 s during procedure	• Murine monoclonal antibody – may produce antigenicity	• Requires renal dose adjustment	• Requires renal dose adjustment

[a]Enoxaparin may be used rather than UFH.

HIT = heparin-induced thrombocytopenia; UFH = unfractionated heparin.

- o If age younger than 75 years: 30 mg intravenous push within 15 minutes, followed by 1 mg/kg subcutaneously, followed by every 12 hours (max 100 mg for the first two doses)
- o If 75 years or older: 0.75 mg/kg subcutaneously every 12 hours (max 75 mg for the first two doses)

F. Postintervention Complications
   1. Bleeding (particularly retroperitoneal bleeding)
      a. Several antithrombotic agents are used during PCI to inhibit both the platelets and the clotting cascade, causing potential coagulopathies.
      b. In addition to antithrombotic use, the catheterization access site (radial vs. femoral) has been identified as a major contributor to post-PCI bleeding complications.
   2. Dissection/rupture of free wall, coronary artery, or aorta: Although this may be spontaneous, it may also be caused by vessel trauma from the catheter itself.
   3. Stent thrombosis
      a. When antiplatelet therapy is discontinued early (aspirin, P2Y12, or both), stent thrombosis may occur in up to 25% of coronary artery stents, irrespective of type of stent (drug-eluting stent or bare metal stent).
      b. Almost 1 in 7 patients may discontinue $P2Y_{12}$ inhibitors within 30 days post-PCI, thus increasing mortality risk (adjusted hazard ratio 9.0; 95% CI, 1.3–60.6). (JAMA 2013;310:189-98)
      c. Mortality rates associated with stent thrombosis can be as high as 45%.
      d. Despite bleeding risks in critically ill patients, careful consideration should be given to correlating these risks with the risk of stent thrombosis.
   4. Papillary muscle rupture and mitral regurgitation
   5. Arrhythmias (particularly after reperfusion)
   6. Contrast-induced nephropathy

G. Ongoing Care – Quality measures for NSTEMI or STEMI independent of revascularization or medical management
   1. Medications that should be initiated before discharge or contraindications should be documented in the medical record.
      a. Aspirin
      b. Statin
      c. $P2Y_{12}$ inhibitor
      d. β-Blocker
      e. If LVEF is less than 40%, ACE inhibitor or ARB and spironolactone
   2. Interventions and/or referrals
      a. LV function assessment (by imaging or during catheterization)
      b. Cardiac rehabilitation
      c. Smoking cessation counseling
      d. Measurement of a lipid profile, including the LDL (low-density lipoprotein) cholesterol, should preferably be obtained within 24 hours of admission. Any lipid profile measured between 6 months before first medical contact and hospital discharge qualifies for this quality measure.
   3. For more information on cardiology-related quality measures and registries, see https://www.ncdr.com/.

Patient Case *(see p. 1-190 for case information)*

4. J.M.'s ECG results reveal no notable evidence of ST-segment changes. The resident is still considering a diagnosis of an ACS, given the patient's shortness of breath and troponin elevation. Which would be most accurate regarding whether any other potential explanations exist for these diagnostic criteria?
   A. No, this is most likely an NSTEMI.
   B. Yes, it is likely undiagnosed chronic obstructive pulmonary disease.
   C. Yes, it is likely early sepsis.
   D. Yes, it is likely decompensated heart failure.

5. J.M. has been experiencing intermittent HR pauses on telemetry. The team has consulted the cardiac electrophysiology team. In the meantime, which statement most accurately reflects whether any other underlying correctable/contributing causes can be addressed?
   A. Ticagrelor should be discontinued, and J.M. should be switched to clopidogrel.
   B. Ticagrelor should be discontinued; only aspirin is needed for J.M.'s CAD at this time.
   C. There are no other identifiable causes, and this is likely a reflection of J.M.'s heart failure disease progression.
   D. J.M.'s hyperkalemia should be treated.

V. ARRHYTHMIAS AND ANTIARRHYTHMICS

A. Pathophysiology: Arrhythmias are generally caused by impulse formation and/or conduction abnormalities.

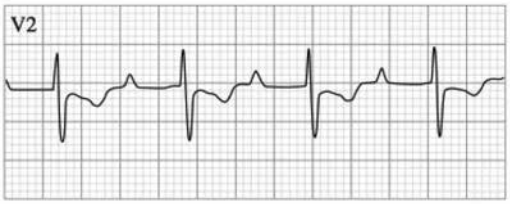
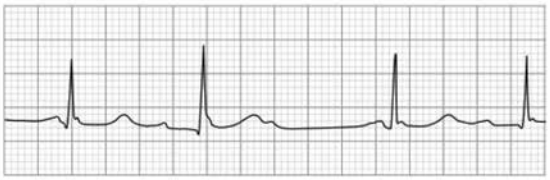
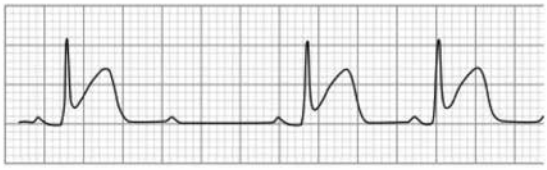
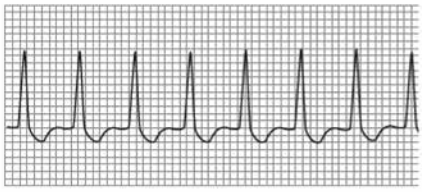
B. Bradyarrhythmias and Types of Heart Block (beyond sinus) (2011;xiv, 461 p.; 2014;xix, 1490 p.; BMJ 2002;324:662-5; BMJ 2002;324:415-8)
   1. Etiologies of heart block

Box 3. Causes of Bradycardias

- Drug toxicity
- CAD
- Degenerative conduction disease
- Surgery (particularly cardiac surgery)
- Endocarditis
- Electrolyte disturbances (particularly hyperkalemia)
- Vagal nerve mediated heart block
- Tumors
- Myocarditis

   2. When evaluating ECGs in the presence of heart block, QRS complex evaluation can guide some differential diagnoses to the source of conduction problems (see Table 6).
      a. Narrow QRS complexes commonly indicate AV nodal dysfunction.
      b. Wide QRS complexes may indicate dysfunction in either the AV node or the His-Purkinje system.

Table 6. Bradyarrhythmias and Types of Heart Block (2011;xiv, 461 p.; 2014;xix, 1490 p.; BMJ 2002;324:662-5; BMJ 2002;324:415-8)

Type	ECG Example	Description
First degree		• Delayed conduction from the sinoatrial (SA) node to the atrioventricular (AV) node characterized by a P-R interval > 0.2 s • Relatively benign, however underlying contributors should be evaluated and minimized (i.e., β-blockers and other agents)
Second-degree Mobitz type 1 (Wenckebach)		• Consistent P-P interval with progressive prolongation of the P-R (indicating impaired SA to AV node conduction) eventually resulting in absence of a QRS complex because of the lack of AV node conduction of atrial impulse • Of most concern in elderly patients where this may be indicative of progressive conduction disease; may be more benign in younger patients • "Longer, longer, longer, drop....must be Wenckebach"
Second-degree Mobitz type 2	 (in a post-ACS setting)	• Consistent P-P interval and consistent P-R interval duration with spontaneous absence of a QRS complex because of the lack of AV node conduction of atrial impulse • Usually indicative of more significant conduction disease and be associated with syncope, heart failure, and increased mortality rates
Third degree		• Characterized by consistent P-P intervals, R-R intervals, and variable/random P-R interval representing independent, uncoordinated atrial and ventricular conduction
Junctional rhythm		• Manifested when sinus node dysfunction allows the AV node to take over as the active cardiac pacemaker resulting in retrograde conduction through the atria

3. Management of bradyarrhythmias includes three principal strategies (see also Figure 5). Stabilize the patient, if symptomatic.
   a. Consider atropine for temporary correction to decrease vagal tone.
   b. Consider pacing strategies (temporary transvenous pacer, transcutaneous pacer, pacing pulmonary artery catheter). Interrogate permanent pacemaker for malfunction/optimization.
   c. Consider chronotropic β-agonist infusion.
      i. Isoproterenol
      ii. Dobutamine
      iii. Epinephrine
      iv. Dopamine
   d. Identify and treat underlying causes/toxidromes.

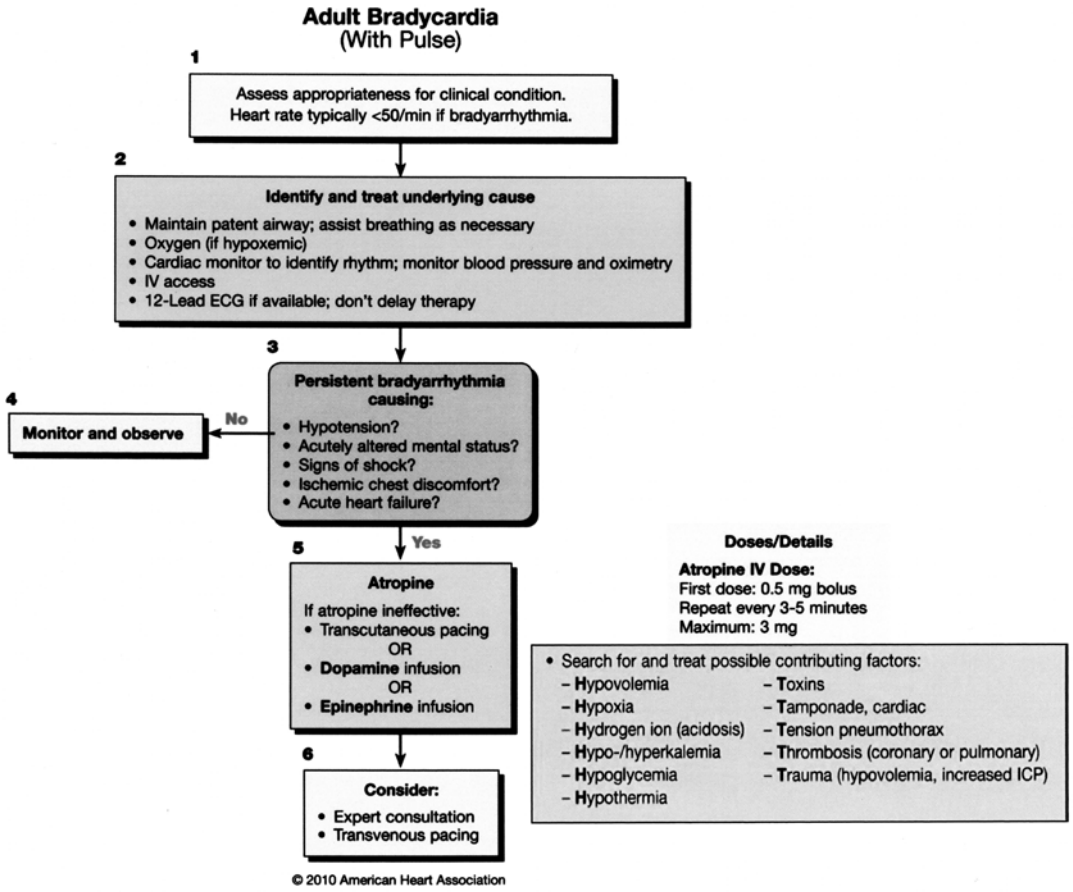


Figure 8. Advanced cardiac life support bradycardia algorithm. (Circulation 2010;122:S729-6)

C. Tachyarrhythmias (beyond sinus) – Etiologies and hemodynamic consequences
   1. Etiologies of tachyarrhythmias
      a. Usually related to enhanced automaticity, reentry, or triggered activity
      b. A history that includes ischemic heart disease or congestive cardiac failure is 90% predictive of VT.
   2. In evaluating ECGs for tachyarrhythmias, some fundamental considerations include:
      a. Evaluate for the presence of P waves.
      b. Evaluate the width of the QRS complex.

Table 7. Tachyarrhythmias (beyond sinus)[a] (Circulation 2014;130:2071-104; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93)

Supraventricular Tachyarrhythmias				
Type	**Rhythm**	**P-wave Attributes**	**Atrial Rate (bpm)**	**Description**
Premature atrial contractions (PACs)	Irregular	N/A	N/A	• Generally benign but may be more evident with increased sympathetic tone, stress, and pericarditis or with sympathomimetic use • In some cases, can lead to an AV block or initiate an reentrant SVT or AF
Supraventricular tachycardia (SVT)	Regular	Hidden or can be retrograde	140–250	• Usually sudden onset/offset with narrow QRS complexes • Often caused by reentry within the atrium or AV node, or by means of an accessory conduction pathway • Can be subcategorized as: o AV nodal reentrant tachycardia (AVNRT) o AV reentrant tachycardia (AVRT) o Sinus node reentry tachycardia
Atrial flutter (AFl)	Regular	Saw-tooth appearance	180–350	• Generally conducts through the ventricles in a 2:1 fashion, resulting in ventricular rates of 100–150 beats/min • In some scenarios, slowing the atrial rate may increase the number of conducted beats leading to rapid ventricular rates and potential hemodynamic compromise • Associated with increased risk of stroke
Atrial fibrillation (AF)	Irregular	No distinct P wave visible	Unable to determine	• Most common arrhythmia, characterized by irregular ECG appearance because of multiple reentry circuits and ectopic foci • Often associated with structural heart disease and potentiated by increase left atrial pressures among other influencing contributors such as age, inflammation, and sympathetic tone • Associated with increased risk of stroke
Multifocal atrial tachycardias (MATs)	Irregular	> 3 different types of distinct P waves	100–130	• Can be misdiagnosed as AF • Commonly associated with respiratory disease, heart failure, critical illness • May be exacerbated by electrolyte abnormalities or toxicity with digoxin or theophylline

Table 7. Tachyarrhythmias (beyond sinus)[a] *(continued)*

Ventricular Arrhythmias	
Type	**Description**
Premature ventricular contractions (PVCs)	• Results from an ectopic ventricular focus conduction that can be identified by the lack of a preceding P wave. Commonly benign or asymptomatic, but may be of concern if present in patterns or in patients with advanced heart disease o Bigeminy: Every other beat is a PVC o Trigeminy: Every third beat is a PVC o Couplets: Patterns of two consecutive PVCs o Triplets: Patterns of two consecutive PVCs
Ventricular tachycardia (VT)	• Potentially lethal wide QRS complex tachycardia characterized according to morphology and duration. Can degenerate into VF or asystole o *Monomorphic VT:* When every QRS complex appears the same and the rate is regular (100–200 beats/min). Commonly caused by reentry circuit related to myocardial scar or fibrosis o Polymorphic: When the QRS complexes continually vary in shape and rate. May be related to multiple ectopic foci, myocardial ischemia, or torsades de pointes o *Non-sustained VT:* Self-terminating episodes lasting for < 30 s o *Sustained VT:* If VT persists for more than 30 s, produces severe symptoms, including syncope, or requires termination by administration of an antiarrhythmic drug or direct cardioversion/defibrillation
Ventricular fibrillation (VF)	• Life-threatening arrhythmia with a chaotic ECG with no discernible QRS, representing rapid disorganized conduction with no resultant coordinated ventricular contractions

[a]Other arrhythmias beyond the scope of this review include sick sinus syndrome (tachy-brady syndrome) and Wolfe-Parkinson-White.

3. Management of tachyarrhythmias with a pulse includes the following strategies:
   a. Stabilization of patient: See Figure 6 and Cardiovascular Emergencies chapter.
   b. Long-term control strategies
      i. Atrial tachyarrhythmias
         (a) HR control typically with class II agents, class IV agents, and/or digoxin (see Table 8)
         (b) Heart rhythm control
            (1) Catheter-based ablation
            (2) Surgical ablation
            (3) Antiarrhythmic therapy typically with class IC or class III agents (see Table 8)
      ii. Ventricular tachyarrhythmias
         (a) Catheter ablation
         (b) Antiarrhythmic therapy
         (c) Evaluation for implantable cardioverter-defibrillator.
   c. Overall considerations for antiarrhythmics (see Table 8) (Circulation 2014;130:2071-104; BMJ 2002;324:594-7; BMJ 2002;324:776-9; BMJ 2002;324:1264-7; BMJ 2002;324:1201-4; Circulation 2012;125:381-9; Heart Fail Rev 2014;19:285-93)
      i. Abrupt discontinuation of chronic antiarrhythmics (i.e., chronic medication before ICU admission) should be done with caution and awareness of antiarrhythmic indication as well as risks-benefits of continuation/cessation.

ii. Appropriate monitoring and potential adjustment may be warranted with many of these agents in the critically ill patient.
   (a) QT/QTc prolongation increases the risk of torsades de pointes. This risk can be influenced not only by the absolute duration of the QT/QTC, but also by the rate at which the QT/QTc is changed (i.e., faster change may also increase risk).
   (b) The class III antiarrhythmics sotalol and dofetilide can be used for both atrial and ventricular tachyarrhythmias and, because of some notable characteristics, should be watched closely when used in the critically ill.
      (1) Both are renally eliminated.
      (2) Both have notable interactions with several other medications in addition to their effect on the QT/QTc interval.
      (3) ECG monitoring should be performed for safety and tolerability 2–3 hours after the first five doses when initiating, reinitiating, or introducing another interacting or QT-prolonging agent.
      (4) Electrolyte abnormalities may place a patient at increased risk of torsades de pointes (particularly magnesium and potassium).

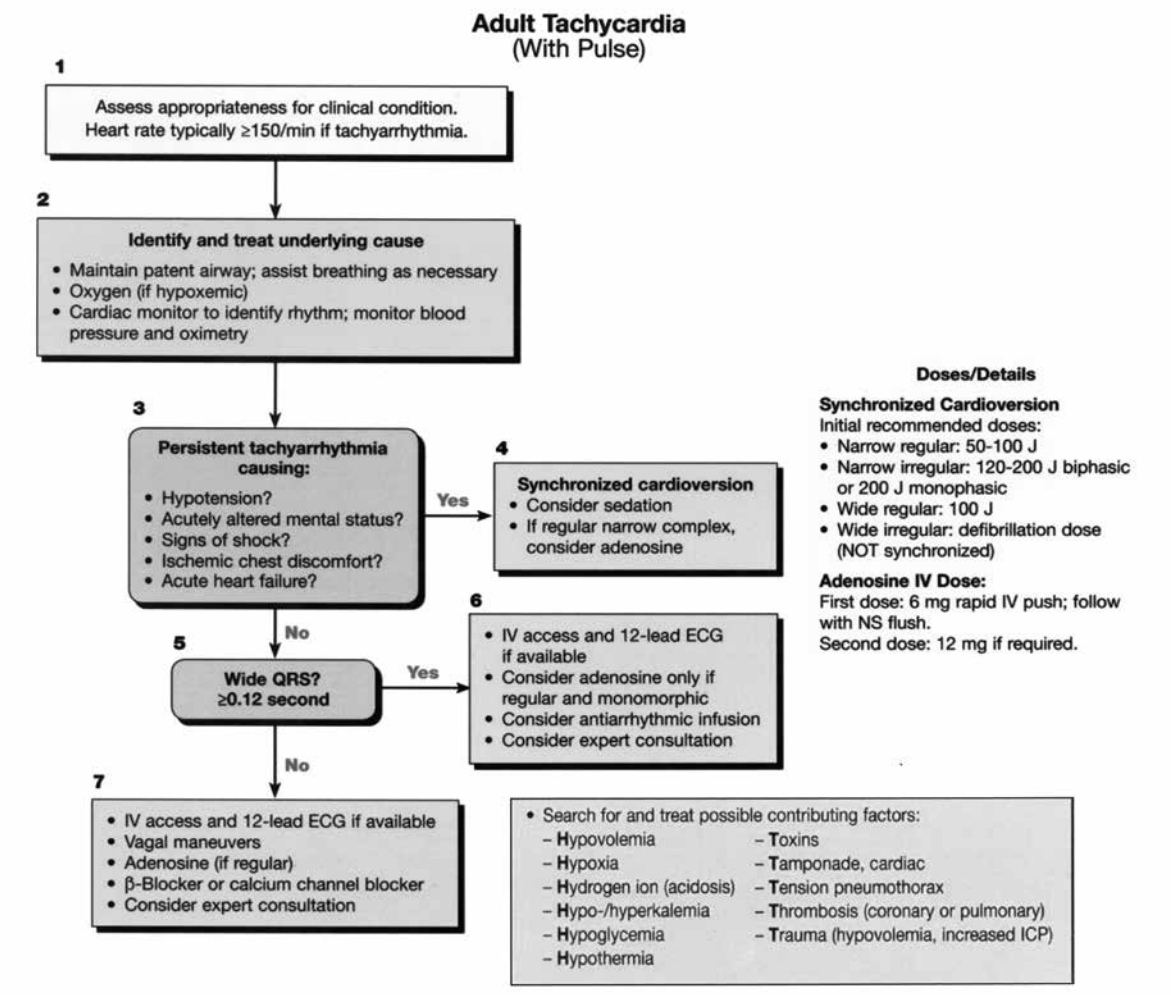


Figure 9. Advanced cardiac life support tachycardia algorithm (Circulation 2010;122:S729-67).

iii. Common agents in the ICU
  (a) β-Blockade
    (1) May be of limited use in patients receiving vasopressors, but can be used for both atrial and ventricular tachyarrhythmias
    (2) Esmolol has the shortest half-life (cleared by plasma esterases), and administration rates commonly coincide with high volumes of fluid.
    (3) Agents with combined α_1-antagonism and non-selective β-antagonism will have greater effects on BP compared with their β_1-specific antagonist counterparts.
      - β_1-specific antagonist examples:
        - Esmolol (intravenous), metoprolol tartrate (oral/intravenous)
      - Combined α1- and non-selective β-antagonist examples:
        - Carvedilol (oral) – 1α:10β receptor activity
        - Labetalol (intravenous) – 1α:7β receptor activity
        - Labetalol (oral) – 1α:3β receptor activity
  (b) Diltiazem
    (1) May be of limited use in patients on vasopressors, but can be used for both atrial and ventricular tachyarrhythmias
  (c) Non-dihydropyridine calcium channel blockers are not recommended in patients with heart failure with reduced ejection fraction (HF*r*EF) (systolic heart failure) (class III C). (J Am Coll Cardiol 2013;62:e147-239)
  (d) Amiodarone
    (1) Widely versatile and commonly used for both atrial and ventricular tachyarrhythmias
    (2) Affects all phases of the action potential (Na, Ca, K channel and provides some α- and β-antagonism)
    (3) Severe hypotension can occur because of the solvent polysorbate 80 (Tween 80) used in some formulations. This transient hypotension in patients with a pulse can be associated with rapid infusions, particularly of undiluted drugs, and is best avoided by dilution and slower administration. However, in pulseless patients, rapid administration of undiluted amiodarone is commonly indicated.
    (4) Among common agents used in the ICU, amiodarone has one of the largest volumes of distribution (about 60 L/kg) and prolonged half-lives (50–55 days).
    (5) In adults, common total intravenous or oral loading doses over several days are about 8–10 g before switching to a maintenance dose.
      - 7.2–12 g = (1.5–2.5 mg/L) × (60 L/kg) × (80 kg)
    (6) Extensive metabolism by CYP3A4 and CYP2C8 and enzyme inhibitor of CYP3A4, CYP1A2, CYP2C9, and CYP2D6, resulting in several drug-drug interactions
    (7) Therapeutic drug monitoring by levels of amiodarone or its metabolite, *N*-desethylamiodarone, is rarely warranted unless trying to confirm suspected toxicity
    (8) If patients are to be continued on amiodarone for a prolonged duration, thyroid and liver function tests, pulmonary function tests, chest radiographs, and ophthalmic examinations should be evaluated periodically. (Heart Rhythm 2007;4:1250-9)
  (e) Lidocaine
    (1) Indicated only for ventricular tachyarrhythmias and is particularly useful if the tachyarrhythmia is caused by active ischemic myocardial tissue
    (2) Efficacy and toxicity are both concentration-dependent.

(3) Metabolism is largely dependent on hepatic blood flow; the primary metabolites are monoethylglycinexylidide (MEGX) and glycine xylidide (GX) and are mediated by CYP1A2. Both lidocaine and MEGX contribute to therapeutic effect and toxicity, whereas GX has predominantly toxic adverse effects. Lidocaine's metabolites are eliminated renally.
(4) Concentration-dependent protein binding includes about 25% bound to albumin and about 50% bound to α_1-acid glycoprotein (AAG).
(5) As AAG increases and decreases as an acute-phase reactant within the first 12–72 after certain stresses (i.e., acute MI, heart failure exacerbation, trauma), an unsuspected variation can occur in free lidocaine levels. Because of the toxicity profile and concentration-dependent efficacy, routine levels should be monitored in most patients if lidocaine is to be continued beyond 24 hours (particularly in patients with heart failure, liver disease, and renal dysfunction).

Box 4. Lidocaine Levels and Toxicity Symptoms

Total Serum Concentration	Toxicity
< 1.5–5 mg/L	Typical therapeutic goal level with idiosyncratic reactions
> 5–8 mg/L	Increasing risk of light-headedness, confusion, dizziness, tinnitus, twitching, tremor, blurred or double vision, hypotension, and bradycardia
> 8 mg/L	High risk of seizures, respiratory depression, hypotension, bradycardia, AV nodal blockade, decreased cardiac output

(f) Digoxin
(1) Commonly, a last-line rate control therapy for patients whose rhythm control strategies have failed and who cannot tolerate, or have contraindications to, β-blockers and/or calcium channel blockers. Some interest has also been revived in its use for heart failure to avoid hospitalization.
(2) Use for AF should be done with caution. Two recently published retrospective trials have shown considerable evidence for increased hospitalization rates and risk of death.
- 71% increased risk of death (hazard ratio 1.71; 95% CI, 1.52–1.93) and 63% increased risk of hospitalization (hazard ratio 1.63, 95% CI, 1.56–1.71) (Circ Arrhythm Electrophysiol 2015;8:49-58)
- Digoxin-treated patients had higher mortality rates (95 vs. 67 per 1000 person-years; p<0.001), and use was independently associated with mortality, despite multivariate adjustment (hazard ratio 1.26; 95% CI, 1.23–1.29, p<0.001). (J Am Coll Cardiol 2014;64:660-8)
- Eliminated renally; thus, may pose risks of digoxin toxicity in patients with acute or chronic renal failure

(3) Although the volume of distribution is relatively large (7–10 L/kg in healthy adults), only a small percentage of total body stores are present in the serum.
(4) Digoxin has a smaller volume of distribution in patients with renal failure (around 4.5 L/kg); thus, loading doses are commonly lower in these patients.

(5) Digoxin efficacy and toxicity do not correlate well with drug levels.
- Common therapeutic targets for HR control are 0.8–1.5 ng/mL, although many clinical laboratories report therapeutic levels within a 0.5–2.0 ng/mL.
- Toxicity, which can present at any serum level, should be evaluated according to clinical manifestations, including mental status changes, visual disturbances, nausea, vomiting, ventricular arrhythmias, bradycardia, and hyperkalemia.
- Efficacy is largely based on clinical control of the HR; steady-state levels (more than 5–7 days after initiation) are typically used only to validate that levels are not supratherapeutic.

4. Anticoagulation for AF or atrial flutter
   a. According to the 2014 AHA/ACC/HRS AF guidelines, all patients with atrial flutter or paroxysmal, persistent, or permanent AF should be evaluated for anticoagulation needs, preferably using the CHA_2DS_2-VASc score to approximate stroke risk (Circulation 2014;130:2071-104).
      i. Patients with a $CHADS_2$ score (congestive heart failure, hypertension, age older than 75, diabetes, and prior stroke or transient ischemic attack) and a CHA_2DS_2-VASc score of 2 or greater should be evaluated for anticoagulation.
      ii. It is reasonable to omit anticoagulation in patients with a $CHADS_2$ and CHA_2DS_2-VASc score of zero.
      iii. For patients with AF and a mechanical prosthetic heart valve or valves, bridging with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) should be performed in the context of bleeding versus stroke risk. Warfarin anticoagulation and international normalized ratio (INR) goals should be consistent with the type and location of the prosthetic valve.
      iv. Although the $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used to estimate annual stroke risk, these scoring systems were not founded in the context of critically ill patients.

Box 5. $CHADS_2$ and CHA_2DS_2-VASc Stroke Risk Scores in AF (Circulation 2014;130:2071-104)

Risk Assessment	Score	Total Patient Score	Adjusted Annual Stoke Rate
$CHADS_2$		0	1.9%
• Heart failure	1	1	2.8%
• Hypertension	1	2	4.0%
• Age ≥ 75	1	3	5.9%
• Diabetes	1	4	8.5%
• Stroke, TIA, thromboembolism	2	5	12.5%
		6	18.2%
CHA_2DS_2-VASc		0	0%
• Congestive heart failure	1	1	1.3%
• Hypertension	1	2	2.2%
• Age ≥ 75	2	3	3.2%
• Diabetes	1	4	4.0%
• Stroke, TIA, thromboembolism	2	5	6.7%
• Vascular disease	1	6	9.8%
• 65–74 years	1	7	9.6%
• Sex category (female)	1	8	6.7%
		9	15.2%

TIA = transient ischemic attack.

b. Anticoagulation decisions should balance the risk of stroke versus the risks of bleeding in the context of duration of bridging and/or lack of anticoagulation. Two scoring systems for bleeding risk systems have been described to help assess bleeding risk in anticoagulation decisions for patients with AF on **warfarin** anticoagulation. Not unlike stroke risk scoring systems, these scoring systems were not founded in the context of critically ill patients.

Box 6. HASBLED or $HEMOR_2RHAGES$ Bleeding Risk Scores in AF

Risk Factor Assessment	Score	Total Patient Score	Bleeds/100 Patient-Years of Warfarin
HASBLED			
• Hypertension	1	0	1.13
• Abnormal renal or liver function (1 point each)	1 or 2	1	1.02
• Stroke	1	2	1.88
• Bleeding	1	3	3.74
• Labile INRs	1	4	8.70
• Elderly (> 65 years)	1	5	12.5
• Drugs or alcohol (1 point each)	1 or 2	6	0
		Any score	1.56
$HEMOR_2RHAGES$			
• Hepatic or renal disease	1	0	1.9
• Ethanol abuse	1	1	2.5
• Malignancy	1	2	5.3
• Older age	1	3	8.4
• Reduced platelet count or function	1	4	10.4
• Rebleeding risk	2	≥ 5	12.3
• Hypertension (uncontrolled)	1	Any score	4.9
• Anemia	1		
• Genetic factors	1		
• Excessive fall risk	1		
• Stroke	1		

c. In the critically ill, parenteral anticoagulation with UFH or LMWH may be more favorable if the benefit of anticoagulation exceeds the risk of bleeding. UFH infusions would be favored over LMWH in renal failure (creatinine clearance [CrCl] less than 30 mL/minute).

d. For anticoagulation of most critically ill patients, oral anticoagulation may be less favorable or even detrimental compared with parenteral anticoagulation.
   i. Elimination of apixaban, dabigatran, and rivaroxaban is significantly affected in renal compromise, and these agents currently lack data for safety in patients with a CrCl less than 30 mL/minute at any dose. These agents interact and are currently irreversible in a controlled, expeditious fashion if the patient needs an invasive procedure or develops an acute bleed.
   ii. Warfarin presents potential difficulty because of its influence on malnutrition, drug interactions, and unpredictable dose response in the critically ill. Complications with this agent are more predictably managed compared with those with other oral anticoagulants if a patient needs an invasive procedure or develops an acute bleed, but warfarin use is still not without risk.

e. For patients with AF/flutter for 48 hours or more (or if undetermined) without therapeutic anticoagulation, absence of thrombus on the left side of the heart should be confirmed by transesophageal ECHO before pharmacologic or direct current cardioversion.

f. If AF/flutter for more than 48 hours or an unknown duration that requires direct current or pharmacologic cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated

Patient Cases

Question 6 pertains to the case on 1-190.
The appropriate intervention has been made from question 5, and the patient has not required any pacing device intervention. For the next 48 hours, J.M. continues on inotrope therapy and is being diuresed (he has been 1250 and 900 mL negative, respectively, over these two days). The transthoracic ECHO results have revealed that J.M.'s ejection fraction is 15–20%, with a dilated, hypokinetic LV; severe mitral regurgitation; and dilated atria. No evidence of intracardiac thrombus is seen, but cannot be ruled out.

6. J.M. has had increasing premature atrial contractions on telemetry, and his HR has consistently been between 83 and 96 beats/minute; he is currently taking dobutamine at 5 mcg/kg/minute and a furosemide infusion at 10 mg/hour. The team is notified that J.M. has gone into AF with rapid ventricular response and an HR of 132 beats/minute (he has been in AF for about 30 minutes). His BP is now 83/52 mm Hg. Which treatment plan would be most favorable for this patient?
   A. Synchronized cardioversion.
   B. Metoprolol 5 mg intravenous push.
   C. Adenosine 6 mg rapid intravenous push through the most proximal port on the central venous catheter.
   D. Amiodarone 150 mg intravenous push, followed by a continuous infusion at 1 mg/minute.

7. M.B., a 76-year-old woman, is now in sinus rhythm with an HR of 98 beats/minute after being cardioverted this morning by direct current cardioversion for AF with rapid ventricular response and hemodynamic instability. Her medical history includes an unspecified arrhythmia, hypertension, frequent epistaxis, and diabetes. Her calculated CHA_2DS_2-VASc score is 5, and her HASBLED score is 4. The physician is considering anticoagulation with a heparin infusion while the patient is in the ICU and asks for a recommendation. Which is the most appropriate response?
   A. According to these scores, the patient's risk of bleeding exceeds her risk of stroke; thus, it would be reasonable to withhold anticoagulation.
   B. According to these scores, the patient's risk of stroke exceeds her risk of bleeding; therefore, it would be reasonable to initiate heparin anticoagulation.
   C. The HASBLED score is less relevant because it is derived from warfarin anticoagulation; however, anticoagulation is likely warranted, given the patient's CHA_2DS_2-VASc score and cardioversion this morning.
   D. The HASBLED score, CHA_2DS_2-VASc score, and cardioversion are irrelevant to this patient's current care, and because she remains in sinus rhythm, anticoagulation is not warranted.

VI. HEART FAILURE

A. Clinical Syndrome – Manifested because of congenital or acquired structural or functional myocardial dysfunction that impairs filling and/or emptying of the heart
   1. Mortality rate of 50% with 5 years of diagnosis
   2. Predominantly descriptive of LV and its pump performance and the ejection fraction
   3. Prognosis and treatment of heart failure are largely dependent on the etiology and symptomology.

Table 8. Diastolic Dysfunction vs. Systolic Dysfunction in Heart Failure

Type	Heart Failure with ***preserved*** EF (HF*p*EF)	Heart Failure with ***reduced*** EF (HF*r*EF)
Dysfunction	• Diastolic – blood filling the heart	• Systolic – blood emptying from the heart • May also coexist with impaired diastolic filling
Characteristics	• LVEF ≥ 50% • Impaired relaxation and filling of the ventricle before contraction • Commonly described as a "stiffened" ventricle • Contractility remains "normal"	• LVEF ≤ 40% • Impaired contraction and emptying of the ventricular cavity • Commonly described as a "dilated" ventricle
Clinical management pearls	• PRELOAD (volume optimization) is essential • As diastolic dysfunction worsens – ventricular PRELOAD and diastolic filling time must be maintained • Conditions acutely decreasing PRELOAD may lead to decompensation (such as tachyarrhythmias) • Keep HR "slow" and ventricles "full"	• PRELOAD optimization essential – at high risk of volume overload • As systolic dysfunction worsens, cardiac output becomes increasingly AFTERLOAD-sensitive • Conditions acutely decreasing or increasing PRELOAD or increasing AFTERLOAD may lead to decompensation • Volume overload and increasing myocardial dilation may contribute to decreased valvular coaptation and regurgitant flow
Common medications to avoid	• NSAIDS with the exception of aspirin	• NSAIDS with the exception of aspirin • Class 1C antiarrhythmics • Calcium channel blockers (in some scenarios, amlodipine may be considered – no proven morbidity or mortality effect)

EF = ejection fraction; LVEF = left ventricular ejection fraction.

B. Heart Failure Etiologies
   1. Ischemic cardiomyopathy
      a. Accounts for about two-thirds of heart failure cases
      b. Caused by myocardial damage/death owing to CAD
   2. Non-ischemic
      a. Accounts for about one-third of heart failure cases
      b. May be attributed to other causes (Table 9)

Table 9. Non-ischemic Cardiomyopathies

Non-ischemic Cardiomyopathies	
• Amyloidosis • Cardiac sarcoidosis • Drug induced o Alcohol o Anabolic steroids o Chemotherapy § Anthracyclines § Cyclophosphamide § Fluorouracil § Bevacizumab § Trastuzumab o Clozapine o Cocaine o Methamphetamine o Tricyclic antidepressants o Weight-loss agents	• Familial • Hypertension • Hyper/hypothyroidism • Hypertrophic obstructive (HOCM) • Idiopathic • Myocarditis o Autoimmune o Eosinophilic o Giant cell o Viral o Other infectious cause • Noncompaction • Peripartum • Obesity • Stress induced (takotsubo)

C. RV Dysfunction and/or Failure (J Am Coll Cardiol 2010;56:1435-46; Exp Clin Cardiol 2013;18:27-30; Circ Heart Fail 2010;3:340-6; Anesth Analg 2009;108:422-33; Anesth Analg 2009;108:407-21)
   1. Less well characterized than LV heart failure
   2. No guidelines to direct management of acute RV failure
   3. RV physiology
      a. The RV normally has only about one-sixth the myocardial mass of the LV. Primary means of compensation is HR increase.
      b. Normal right ventricular ejection fraction is about 40–45%.
      c. Conduit to a low pressure system in the pulmonary vasculature (normally)
      d. RV output should approximate LV output.
      e. Physiologic deficits:
         i. Preload-dependent
         ii. Interdependent on LV and septal contribution to contraction
         iii. Highly sensitive to acute increases in afterload. PVR elevations may be:
            (a) Drug induced (e.g., α_1 agents, protamine)
            (b) Caused by ventilator settings (high PEEP [positive end-expiratory pressure], high tidal volumes)
            (c) Caused by hypoxia
            (d) Caused by hypercarbia
            (e) Caused by pulmonary embolism
         iv. Poor elastic response to acute preload increases compared with LV
         v. Atypical geometric form contributes to:
            (a) Difficultly in objective assessment of RV function by ECHO
            (b) Increases susceptibility to further inefficiency/dysfunction when severely dilated
   4. Etiologies of RV failure

Box 7. Etiologies of RV Failure (J Am Coll Cardiol 2010;56:1435-46; Exp Clin Cardiol 2013;18:27-30)

- LV dysfunction
- Right coronary artery infarction/ischemia
- RV overload
- Pulmonary hypertension (primary or secondary)
- Hypoxia
- Sepsis
- Mitral valve disease
- Tricuspid regurgitation/stenosis
- Pulmonary regurgitation
- Hypovolemia
- Post-cardiac surgery
- Pulmonary embolism
- Cardiac tamponade
- Congenital heart disease
- Arrhythmias
- Heart transplantation (particularly if prolonged ischemic time)

D. Diagnostic Tests for New or Worsening Heart Failure – In addition to routine chemistry and CBC tests, additional testing may include:
   1. Liver function tests (may be indicative of congestive hepatopathy if elevated)
   2. 12-lead ECG
   3. Troponin
   4. Left heart catheterization if suspected new ischemic contribution
   5. BNP or NT-proBNP (N-terminal pro-brain natriuretic peptide) (elevations may help in the diagnosis of acutely decompensated heart failure in scenarios of uncertainty)
   6. Transthoracic or transesophageal ECHO
   7. Invasive hemodynamic monitoring (to guide volume optimization and dosing response to inotropes or vasopressors)
   8. For less common cardiomyopathies, noninvasive imaging (i.e., cardiac MRI [magnetic resonance imaging]) and/or myocardial biopsy may be required.

VII. VALVULAR DISEASE AND MECHANICAL DYSFUNCTION

A. Valvular heart disease is an important comorbid condition that must be considered in hemodynamic management of the critically ill. Valvular heart disease can also independently lead to the presenting critical illness.

B. Among the four cardiac valves, several etiologies[a] contribute to the manifested pathology; however, the depth and breadth of these etiologies are beyond the scope of this chapter. Nevertheless, conditions that may require repair/replacement include:

Stenosis	Narrowing at the opening of the valve(s) Can lead to concurrent regurgitation
Regurgitation	"Leaky" valve(s) resulting in less blood pumping forward through the heart
Prolapse	"Floppy" valve(s) with part of valve not working
Endocarditis	Infection of one or more valves
Malformation	Often occurs at birth when the valve (or valves) is defective

[a]Valvular disease secondary to rheumatic heart disease is a rare, but is a possible contributor

Table 10. Valvular Disease Characteristics and Management Considerations[a,b]

Valvular Disease Type	Management Considerations
Aortic stenosis (AS)	• One of the most common and serious valvular diseases seen in the ICU • As stenosis and disease progresses, severe/critical AS limits the heart to a fixed stroke volume. This inability to increase stroke volume occurs despite intrinsic or extrinsic attempts to compensate (i.e., increased chronotropy or inotropy) and often only increases myocardial oxygen demand without the improving delivery o Must be extremely cautious in approaching and reacting to invasive hemodynamic parameters (particularly cardiac output and cardiac index) – adding agents with inotropic/chronotropic effects may expedite demand ischemia and an acute MI because of the physiologic inability to increase cardiac output with a fixed partial LV outflow tract obstruction o For reasons similar to those listed above, treating hypertension with afterload-reducing agents must be done judiciously because as afterload (SVR) decreases, cardiac output cannot increase • Can coexist with concurrent aortic insufficiency/regurgitation because the stenotic or calcified valve leaflets may no longer move and come together (coapt) well • These patients may be at risk of developing mitral regurgitation and subsequent increases in left atrial pressures (increasing risk of AF) because of increased LV filling pressures • Must be cautious in decreasing HR in sinus tachycardia because this can be a primary means of compensation • Patients need adequate preload; however, they can become symptomatic, even with slight volume overload. This being understood, atrial fibrillation can be very detrimental, simply because it decreases preload to the ventricle • Patients with severe aortic stenosis and systolic heart failure (described as low output – low gradient) have a poorer prognosis
Aortic regurgitation (AR)	• Also known as aortic insufficiency (AI) • Must be cautious in decreasing HR in sinus tachycardia as this can be a primary means of compensation to maintain adequate cardiac output • Patients need adequate preload but the predominant target is to maintain decreased afterload (SVR) to facilitate forward blood flow and cardiac output

Table 10. Valvular Disease Characteristics and Management Considerations[a,b] *(continued)*

Mitral stenosis (MS)	• Contributes to decreased LV filling and increased left atrial pressures; can increase risk of AF and secondary pulmonary hypertension • Increasing diastolic filling time and avoiding tachycardias can facilitate stabilization until valve is corrected • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Mitral regurgitation (MR)	• Primary clinical target is to decrease LV afterload (SVR) to minimize augmentation of MR and to facilitate forward blood flow. If SVR is too high, blood will travel in the path of least resistance until an adequate LV pressure is generated to open the aortic valve (must exceed the systemic diastolic BP) • Can coexist with concurrent mitral regurgitation because the stenotic or calcified valve leaflets may no longer move and coapt well • Use of selective pulmonary vasodilators (i.e., inhaled nitric oxide or inhaled epoprostenol) may be detrimental because these agents can facilitate pulmonary congestion, given the preexisting pulmonary venous hypertension and elevated left atrial pressures
Tricuspid regurgitation (TR)	• Likely to influence pulmonary artery catheter assessments of cardiac output • Can be influenced by infectious causes and presence of indwelling transvenous catheters or leads, but moderate or severe TR is more commonly a marker of RV overload and dysfunction

[a]Infective endocarditis can cause progressive valve disease leading to regurgitant flow and impaired valve leaflet coaptation; however, it can also lead to near-obstruction in some cases.

[b]Degree of valvular disease is graded as mild, moderate, or severe, as defined by objective ECHO or catheter-based assessments.

SVR = systemic vascular resistance.

C. Procedural Correction

Table 11. Procedural Correction

Balloon valvuloplasty	• Performed by percutaneous intervention as a temporizing intervention
Valve repair	• May entail direct surgical repair of a damaged valve leaflet or other scenario may require use implantation of a ring at the valve annulus to facilitate improved coaptation of a regurgitant valve
Tissue (bioprosthetic) valve	• Made of animal or human tissue • Usually does not require long-term anticoagulation (see Table 11) • Does not last as long as a mechanical valve (may last 10–15 years)
Mechanical valve[a]	• Made of manmade materials (newer valves use ceramic or carbon) • They are durable and last a long time (unlikely to need replacement) • Require lifelong anticoagulation • Warfarin is currently the only anticoagulant approved for use by the FDA in patients with mechanical heart valves (see Table 11)
Transcatheter aortic valve replacement (TAVR)	• Made of animal tissue (bioprosthetic) and attached to a wire frame stent and placed using catheter inside the old aortic valve • This may be considered in patients who are at a higher risk of surgical aortic valve replacement or when surgery is not an option • Anticoagulation and/or antiplatelet agents are required for at least a short time after TAVR

[a]St. Jude manufactures mechanical and bioprosthetic valves.

FDA = U.S. Food and Drug Administration.

Table 12. Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations (Circulation 2013;127:e362-425; Circulation 2014;130:e344-426; J Am Coll Cardiol 2012;59:1200-54; Circulation 2014;129:e521-643; Chest 2012;141:e576S-600S; Arch Cardiovasc Dis 2012;105:465-7; The Ohio State University Wexner Medical Center. Clinician's Guide to Anticoagulation Recommendations Post-Valve Replacement. Available from https://evidencebasedpractice.osumc.edu. Accessed January 20, 2015)

Prosthetic Valve Anticoagulation: Levels of Evidence to Support Recommendations

Must consider relative risk of bleeding vs thrombosis given the patient's current clinical status when initiating or continuing anticoagulant therapy

Procedure		Antiplatelet Therapy		Warfarin Target INR‡		Parenteral Anticoagulation
		NO Risk Factors	With Clotting Risk Factors†	NO Clotting Risk Factors	With Clotting Risk Factors†	UFH: Unfractionated Heparin LMWH: Low Molecular Weight Heparin
Mechanical AVR		**ASA 81 mg**	**ASA 81 mg**	**2 – 3**	**2.5 – 3.5**	**Bridging until warfarin therapeutic for 2 days**
Level of Evidence	*CHEST*	1B*	1B*	2C	2C	2C for intermittent UFH subQ Q8H# or LMWH over continuous IV UFH
	ACC/AHA	I	I	I	I	B
	EACTS	IIaC	IIaC	IB	IB	IC
Bioprosthetic AVR		**ASA 81 mg**	**ASA 81 mg**	**2 – 3**	**2 – 3**	**Bridge with UFH until warfarin therapeutic for 2 days**
Level of Evidence	*CHEST*	2C	2C			2C
	ACC/AHA	I	I	IIa - If less than 3 months IIb – Don't use warfarin	I	Discussed but not graded
	EACTS	IIaC	IIaC	IIbC	IIbC	IC
Transcatheter AVR		**ASA 81 mg and clopidogrel 75 mg daily**	**ASA 81 mg and clopidogrel 75 mg daily**			
Level of Evidence	*CHEST*	2C	2C			
	ACC/AHA					
	EACTS	Discussed but not graded	Discussed but not graded			
Mechanical MVR		**ASA 81 mg**	**ASA 81 mg**	**2.5 – 3.5**	**2.5 – 3.5**	**Bridge with UFH until warfarin therapeutic for 2 days**
Level of Evidence	*CHEST*	1B*	1B*	1B	1B	2C for intermittent UFH subQ Q8H# or LMWH over continuous IV UFH
	ACC/AHA	I	I	I	I	B
	EACTS	IIaC	IIaC	IB	IB	IC
Bioprosthetic MVR		**ASA 81 mg**	**ASA 81 mg**	**2 – 3**	**2 – 3**	**Bridge with UFH until warfarin therapeutic for 2 days**
Level of Evidence	*CHEST*	2C	2C	2C	2C	2C
	ACC/AHA	I	I	IIa - If less than 3 months	I	Discussed but not graded
	EACTS	IIaC	IIaC	IIaC	IC	IC
Other Statements	*CHEST*		For patients who have systemic embolism despite a therapeutic INR, the addition of ASA 81 mg/day is recommended if not previously provided and/or upward titration of warfarin to achieve a higher target INR. For a previous target INR of 2.5 (range 2 to 3), it is suggested that the warfarin dose be increased to achieve a target INR of 3.0 (range 2.5 to 3.5). For a previous target INR of 3.0, it is suggested that the warfarin dose be increased to achieve a target INR of 3.5 (range 3.0 to 4.0).			
	ACC/AHA	Discussed; Not graded				

* Except in patients with a history of GI bleeding or who are more than 80 years of age.
† Risk factors for increased risk of thromboembolism include atrial fibrillation, previous thromboembolism, hypercoagulable state, left ventricular dysfunction, older generation thrombogenic valve, mechanical tricuspid valve, greater than one mechanical valve.
# Dosing cited is UFH 15,000 units/kg subQ Q12H or 166 units/kg sub Q8H adjusted therapeutic PTT goals; Enoxaparin 1 mg/kg subQ Q12H

D. Anticoagulation
   1. Three guidelines exist regarding valve anticoagulation, with varying agreement in the recommendations.
   2. Prosthetic mitral valves have increased risk of thrombosis (blood flow across the valve is passive and occurs during diastole) versus aortic valves, where blood flow across the valve is active occurring during systole.

E. Valve Thrombosis
   1. Highest risk within the first year after replacement
   2. Most predominant risk is in mechanical prosthetic valves, but can also occur with bioprosthetic valves
   3. Treatment involves systemic thrombolytic treatment or surgical reoperation with varying success rates – Both carry significant risks of morbidity and mortality, including:
      a. Thrombolysis (predominantly recommended for right-sided valve thrombosis)
         i. Cardiac tamponade
         ii. Stoke/transient ischemic attack
         iii. Systemic embolization
         iv. Major bleeding
         v. Death
      b. Surgery (predominantly recommended for left-sided valve thrombosis)
         i. Cardiac tamponade
         ii. Stoke/transient ischemic attack
         iii. Renal failure
         iv. Heart block
         v. Systemic embolization
         vi. Prolonged ventilation
         vii. Major bleeding
         viii. Death

F. Other Cardiac Functional Defects
   1. Left ventricular outflow tract (LVOT) obstruction (Circulation 2008;117:429-39; J Am Coll Cardiol 2000;36:1344-54)
      a. Hypertrophic obstructive cardiomyopathy (HOCM)
         i. Genetic disease leading to hypertrophy of the left ventricle (particularly the ventricular septum) with or without the presence of LV outflow tract obstruction
         ii. LVOT obstruction is of greatest concern when HOCM exists with systolic anterior motion (SAM) (see below); however, in HOCM, LVOT obstruction can exist in the absence of SAM because of septal hypertrophy; nonetheless, acute clinical management is predominantly the same as outlined in 1.a.i–iii above and in 1.b.i below.
         iii. Treatment of HOCM without SAM relies heavily on the management of contributors to myocardial hypertrophy and diastolic heart failure.
            (a) β-Blockers are first-line agents in the treatment of patients with HOCM and are commonly titrated to HR goals of 60–65 beats/minute.
            (b) Dihydropyridine calcium channel blockers (particularly verapamil) are recommended in patients with contraindications to β-blockade or in those without advanced heart failure or bradycardia.
            (c) For recommendations specific to HOCM (patients also with SAM), see “b” below.
            (d) Patients with HOCM may be at increased risk of sudden cardiac death. Evaluation should consider the patient’s candidacy for implantable cardioverter-defibrillator placement by ambulatory ECG (Holter) monitoring at least biannually.
         iv. Treatment may be indicated by surgical septal myectomy or catheter-directed alcohol ablation.

b. SAM of the mitral valve
    i. SAM and LVOT obstruction results in a systolic outflow tract obstruction and is commonly associated with HOCM, but can also occur in other clinical scenarios, particularly after cardiac surgery
    ii. Can lead severe cardiogenic shock with a low (or no) cardiac output
    iii. SAM is more of a dynamic obstruction in which the degree of obstruction and flow gradient is dependent on HR (systoles per minute), cardiac contractility, and ventricular preload volume.
        (a) In an under-filled LV, there is physically less distance between the mitral valve and septum, thus generating an increased risk of obstruction because the LVOT is generally narrower at the onset of systole, particularly if the mitral valve leaflet is affected.
        (b) Increasing cardiac contractility and HR increases LVOT obstruction and gradient by inducing a stronger contraction, increasing the contact between the septum and mitral leaflets, and increasing the rate of systolic attempts.
    iv. For patients with SAM who have shown a potential for obstructive physiology, management involves maintaining normal or increased LV preload and low HRs.
        (a) Acute hypotension is best managed with phenylephrine or vasopressin (pure vasoconstrictors) to selectively increase SVR without increasing contractility or HR.
        (b) Inotropes and vasopressors that mediate increases in heart rate or contractility should be avoided, if possible, because they may be harmful and worsen the LVOT.
        (c) Afterload-reducing agents (e.g., ACE inhibitors, ARBs, non-dihydropyridines) should be used with caution (if at all).

2. Septal defects (atrial or ventricular)
    a. Septal defects can be acquired (i.e., postinfarction ventricular septal defect) or can be congenital in nature.
    b. Diagnosed predominantly by ECHO using a bubble study. If the patient presents in a seeming low cardiac output state, a left-to-right intracardiac shunt should be suspected if mixed venous oxygen saturation (SvO_2) saturations are greater than $ScvO_2$ saturations.
    c. Important principles
        i. Goals include minimizing the degree of intracardiac shunt while maintaining adequate cardiac output. It is generally favored to accept a right-to-left intracardiac shunt while recognizing that Pao2 saturations will be somewhat decreased and reflective of venous and arterial blood mixing in the LV before ejection.
        ii. Decreasing right-sided cardiac filling pressures can augment left-to-right intracardiac shunting of blood. Administration of venodilators (i.e., nitrates) or aggressive diuresis could augment left-to-right intracardiac shunts and lead to clinical deterioration.
        iii. Intravenous medications should preferably be filtered to minimize the risk of air /particulate embolus traveling through to the left side of the heart and being ejected and causing a potential stroke.
    d. Treatment may include surgical correction or percutaneous catheter placement of a closure device.

Patient Case

Question 8 pertains to patient case on p. 1-190.

8. J.W. is no longer in AF but remains in cardiogenic shock. The cardiac care unit team has consulted the cardiothoracic surgeons for evaluation of his mitral valve disease and has considered advanced heart failure therapies. In the patient's decompensated state, he would likely need additional optimization if he were to undergo surgery. Which temporary means of mechanical circulatory support (MCS) might be most favorable to help stabilize this patient's cardiogenic shock and afterload-sensitive valvular disease?

   A. Venoarterial extracorporeal membrane oxygenation (ECMO).
   B. Venovenous ECMO.
   C. Intra-aortic balloon counterpulsation.
   D. None; the patient likely needs urgent surgery.

VIII. ADVANCED THERAPIES FOR HEART FAILURE AND CARDIOGENIC SHOCK

A. The goals behind advanced therapies can be thought of as dynamic, depending on patient progression and resolution or presentation of comorbid conditions.

B. Dynamic Progression of Heart Failure Advanced Therapies

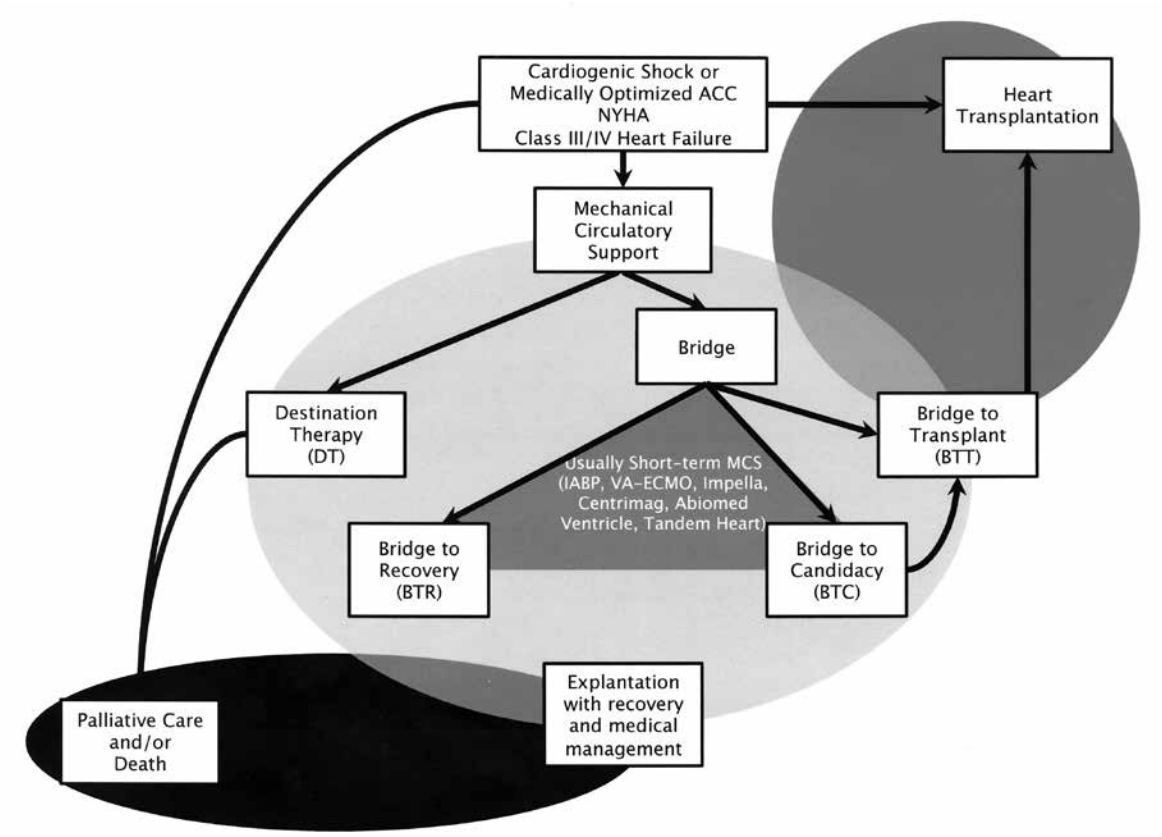


Figure 10. Dynamic progression of heart failure advanced therapies.

C. Mechanical Circulatory Support (MCS) (J Heart Lung Transplant 2013;32:157-87)
   1. Intent, duration, and type of MCS support depend on several factors, including patient acuity, comorbidities, and prognosis.
   2. Common terms
      a. Destination therapy – Formal designation for patients who meet the criteria for long-term mechanical support but who are not a transplant candidate because of relative or absolute contraindications
      b. Bridge to transplant – Formal designation for patients eligible to be listed as candidates for heart transplantation
      c. Bridge to candidacy and bridge to recovery – Used in concept and are not formally recognized abbreviations but describe the approach to temporary MCS when short-term left ventricular assist devices (LVADs) are used to support a patient until a long-term prognosis can be determined, which may include explantation with recovery, implantation of long-term durable LVAD support, heart transplantation, or palliative care.

Table 13. Short to Intermediate Term

Short to Intermediate Term	
Intra-aortic balloon pump (IABP) counterpulsation	• Placed by femoral arterial catheter and advanced up the aorta • Deflation facilitates selective afterload during systole to ease cardiac output (does not technically increase cardiac output) • Inflation enables diastolic augmentation of systemic BP to improve vital organ and coronary perfusion pressures • Can be set to trigger from ECG, pacer, or arterial line pressure or can be manually set • Tachyarrhythmias and aortic regurgitation/insufficiency are not well supported with this means of MCS • Level of support coincides with timing of inflation/deflation per related heartbeat; for example: o 1:1 = one inflation/deflation per every heartbeat (maximal support) o 1:4 = one inflation/deflation for every fourth heartbeat (less support) • When setting duration in deflated state increases (providing less support), the thrombosis risk associated with the IABP increases, commonly requiring anticoagulation
Percutaneous VAD	Example is Impella (Abiomed) • May be considered in cardiogenic shock or as temporary support during high-risk interventional cardiology procedures • Anticoagulation regimen is a common topic of debate and/or medication safety discussion • Management can be complicated by migration and/or malposition of catheter/cannula within the LV, leading to arrhythmias or hemolysis complications
Extracorporeal or paracorporeal VAD	Examples include CentriMag, TandemHeart, BVS 5000, and AB5000 ventricle

Table 13. Short to Intermediate Term *(continued)*

Short to Intermediate Term	
Extracorporeal life support (ECLS) or extracorporeal membrane oxygenation (ECMO)	• Similar cardiopulmonary bypass in which large-bore cannulas drain venous blood that is pumped through an oxygenator, where it is oxygenated and/or cleared of carbon dioxide and then actively pumped back into the body • Modality of support depends on the means of vascular cannulation o *Venoarterial:* Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery in retrograde fashion up the aorta. Potentially indicated for primary cardiogenic shock, cardiopulmonary failure, and post-cardiopulmonary circulatory shock o *Venovenous:* Removal of venous blood from the vena cava with circulation through the ECMO circuit and delivery back to the right atrium. Potentially indicated for hypoxic respiratory failure owing to any cause, hypercarbic respiratory failure with bronchospastic disease or other cause of CO_2 retention, or severe air leak syndromes
Long term	
Implantable LVADs	Examples include the Heartmate II, HeartWare
Total artificial heart	

LVAD = left ventricular assist device; VAD = ventricular assist device.

3. Anticoagulation considerations
   a. Anticoagulation strategies are specific to the proprietary device, and many institutions have standardized protocols. Comparative example approach to postoperative anticoagulation for some LVADs
   b. Safety and efficacy of apixaban, dabigatran, rivaroxaban, enoxaparin, or other anticoagulants in patients with ventricular assist devices (VADs) have not been established.

Table 14. Example of Initial Postinsertion Antithrombotic Regimen

LVAD	Aspirin	Heparin Infusion (once hemostasis achieved)	Initial Warfarin INR Goal
Long-term Devices			
Heartmate II	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• By POD 2: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 3: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	2–3
HeartWare	• POD 0: 325 mg × 1 • Ongoing: 325 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	2–3

Table 14. Example of Initial Postinsertion Antithrombotic Regimen *(continued)*

Short-term Devices			
CentriMag	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	N/A
Abiomed ventricle	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Sliding Scale," titrating to institutional PTT goal	N/A
Abiomed BVS 5000	• POD 0: 325 mg × 1 • Ongoing: 81 mg daily	• Within 12 hr postop: – Initiate "Heparin – no dose escalation at 5 units/kg/hr" • By POD 1: – Increase to "Heparin Cardiac Sliding Scale," titrating to institutional PTT goal	N/A

LVAD = left ventricular assist device; POD = postoperative day; postop = postoperatively; PTT = partial thromboplastin time.

4. Complications of MCS (other than device failure)
   a. Bleeding
      i. Common sources
         (a) Nasal/upper airway
         (b) Gastrointestinal (GI)
         (c) Arteriovenous malformations in one of the above locations
         (d) Hemolysis
      ii. Workup and/or acute treatment options
         (a) Laboratory workup
            (1) Prothrombin time/INR/partial thromboplastin time
            (2) Increase frequency of hemoglobin/hematocrit evaluation.
            (3) Multimeric von Willebrand testing for acquired von Willebrand factor deficiency (some clinicians believe that all patients with prolonged continuous flow MCS develop acquired von Willebrand disease)
            (4) If no overt sign of bleeding – Consider hemolysis workup.
         (b) If suspected/confirmed bleeding, hold anticoagulation and consider reversal with caution. Consider any history of bleeding/clotting-related problems and indications for antithrombotic therapy in addition to MCS.
         (c) Obtain appropriate consults, and consider common interventions. Ear, nose, and throat:
            • Evaluate for source control and/or cauterization.
            • Mupirocin 2% (Bactroban) every 12 hours to each nostril to maintain moist nasal passages
            • Oxymetazoline 0.05% (Afrin) to each nostril every 12 hours as needed for epistaxis

(d) Gastroenterology
(1) Proton pump inhibitor continuous infusion at least until location of GI source identified
(2) Enteroscopy with or without colonoscopy; may consider one or more of the following
- Angiography and cautery
- Balloon-assisted enteroscopy
- Video-capsule enteroscopy
- Surgery

iii. Long-term management
(a) Consider decreasing anticoagulation/antiplatelet therapy intensity.
(b) Refractory bleeding despite interventions above
(1) Consider role of oral antifibrinolytics (i.e., aminocaproic acid).
(2) Consider role of desmopressin or von Willebrand factor replacement if confirmed acquired von Willebrand disease and if LVAD speed cannot be further decreased
(3) If GI arteriovenous malformations are present that are unamenable to intervention, octreotide 50 mcg subcutaneously every 8 hours may be considered.

b. Hemolysis and/or thrombosis
i. Hemolysis may be the presenting symptom of an underlying process, including infection, pump thrombosis, or other mechanical or physiologic dysfunction.
ii. Common presentation includes:
(a) Nonhemorrhagic anemia
(b) Urine color changes with appearance of hematuria or, in severe cases, can be brown or black
(c) Hyperkalemia
(d) LVAD pump alarms
iii. Workup for contributing factors:
(a) Evaluate LVAD and cardiac function for contributing factors, including documentation and alarm history for suction events, power spikes, speed changes, volume status, RV function, arrhythmias
(1) Evaluate cannula(e) position and evaluate for obstruction/thrombus by ECHO or computed tomography (CT).
(2) Evaluate RV function by ECHO.
(3) Evaluate for intra-device thrombosis by ECHO ramp testing (Echocardiography 2014;31:E5-9; J Am Coll Cardiol 2013;62:2149-50; J Am Coll Cardiol 2012;60:1764-75).
(b) Ensure adherence with anticoagulation regimen according to patient's established goals.
(c) Evaluate laboratory values to establish the presence and degree of hemolysis and to identify any other potential contributors.
(1) LDH (lactate dehydrogenase; commonly normal values are 300–600 IU/L for most forms of MCS)
(2) Haptoglobin
(3) Plasma-free hemoglobin
(4) Blood cultures (an association has been identified with bacteremia and hemolysis in patients with LVADs – in some cases, presenting as thrombosis)
(5) Urine assessment – Send baseline urinalysis, urine culture, and appearance of changes daily to assess for improvement. Likely hemolysis, as evidenced by the presence of casts and color changes (darkened tea, red, or black are highly suggestive of hemolysis)

(d) Other laboratory values/considerations
(1) Hypercoagulable states (i.e., HIT [heparin-induced thrombocytopenia])
(2) CBC with differential
(3) Reticulocyte count

iv. Treatment
(a) Address any evidence of mechanical dysfunction by adjusting speed/flow rates, if possible.
(b) Consider medical optimization of RV function.
(c) If hypovolemic, give volume challenge. Consider alkalinization of urine and optimize fluid status (sodium bicarbonate 150 mEq/1000 mL of sterile water) at 0.5-1 mL/kg/hour; treat to a goal urine pH of greater than 7.5 to avoid additional hemolysis/hemoglobinuria-related acute kidney injury.
(d) Evaluate and optimize anticoagulation strategy.
(1) Ensure therapeutic anticoagulation with heparin or warfarin.
(2) Antithrombotic therapy that is more aggressive may be appropriate. Optimal acute antithrombotic strategies, although not yet defined, may include heparin infusion, glycoprotein (GP) IIbIIa infusions, parenteral direct thrombin inhibitors, or thrombolytics.
(3) Severe hemolysis can potentiate platelet activation – Can consider GP IIbIIIa antagonist therapy (see Table 5), depending on bleeding risks and potential surgical plan
(e) Reassess long-term antithrombotic strategy.
(1) Consider augmentation of antiplatelet therapy, or increase the INR therapeutic goal range.
(2) If thought to be related to a concurrent infection, can consider acutely increasing anticoagulation goals until infection control is gained

c. Infection
i. LVAD infections are often complex and have been characterized by the International Society for Heart & Lung Transplantation in the following manner (J Heart Lung Transplant 2011;30:375-84):
(a) VAD-specific infections
(1) Pump and/or cannula infections
(2) Pocket infections
(3) Percutaneous driveline infections
- Superficial infection
- Deep infection

(b) VAD-related infections
(1) Infective endocarditis
(2) Bloodstream infections that may be VAD related or non-VAD related
(3) Mediastinitis
- Sternal wound infection: Surgical site infection-organ space
- VAD pocket infection (continuous with mediastinum or already situated in the mediastinum, depending on the device used)
- Other causes of mediastinitis, perforation of the esophagus

(4) Non-VAD infections
- Lower respiratory tract infection
- Cholecystitis
- *Clostridium difficile* infection
- Urinary tract infection

ii. Antibiotic treatment
(a) Antibiotic coverage should account for site of suspected infection, previous pathogens and susceptibilities, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. Prophylactic antibiotic coverage for VAD-related or non–VAD-related surgical procedures should account for site of procedure, previous infections, proximity to driveline site or VAD pocket, and any other potential exposure or bacteremia secondary to the procedure. In some circumstances, this requires broader prophylactic antibiotic coverage.Interact Cardiovasc Thorac Surg 2012;14:209-14
(b) Treatment duration depends largely on the nature of the infection. However, if the infection is VAD-related or VAD-specific, prolonged antimicrobial therapy (more than 4 weeks) is commonly used.
(c) Because LVAD change-out is not without considerable risk, long-term oral antibiotic suppression therapy may be considered for some infections.

D. Heart Transplantation (J Heart Lung Transplant 2010;29:914-56)
1. Transplantation remains the gold standard treatment for end-stage heart failure.
2. Many variables limit the utility of heart transplantation, foremost of which is donor availability and donor-recipient tissue compatibility. These limitations (and potentially others) may make long-term MCS a more viable option until heart transplantation becomes an option.
3. Other limitations may include recipient characteristics of:
a. Mental health
b. Social support
c. Adherence to medication and appointments
d. Severe pulmonary hypertension
e. Cancer
f. Infection
g. Tobacco or ethanol use
h. Illicit drug use history
4. Considerations of thoracic transplantation for ICU management immunosuppression, rejection, and other complications are widely complex and beyond the scope of this review.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Given this patient's CAD, type 2 diabetes mellitus, hyperlipidemia, gastroesophageal reflux disease, hypertension, obstructive sleep apnea, and ischemic cardiomyopathy, only option B consists of the three agents shown to reduce morbidity and mortality among these comorbidities: carvedilol (heart failure and potentially diabetes), spironolactone (heart failure progression post-MI), and lisinopril (heart failure and diabetes). Thus, Answer B is correct, and Answers A, C, and D are incorrect.

2. Answer: C

Although many of these tests might be helpful in this patient's differential diagnosis, the most likely consideration would be respiratory decompensation or a heart failure decompensation, given the patient's presentation; thus, a chest radiograph, ECHO, BNP, and lactate would be most appropriate, making Answer C correct. Answer A is incorrect; although an infectious etiology cannot be ruled out, it is less likely than non-infectious cardiorespiratory differentials. Answer B is not the best answer; although serial troponins and an ABG could be argued for, liver function tests are unlikely to provide additional insight into this patient's differential. Answer D also is not the best answer; although it provides additional information for hemodynamic assessment, it is lacking in an assessment of cardiac function, which is a likely contributor to the patient's presentation. Answer C is correct, and Answers A, B, and D are incorrect.

3. Answer: D

Dobutamine would be the ideal choice, given the patient's acutely worsening cardiac index and malperfusion and its rapid onset; this would facilitate β_2 arterial vasodilation (both SVR and PVR reduction) as well as increase chronotropy and inotropy. Milrinone, although likely benficial for both cardiac index and PVR reduction, would be less favorable given that its time to peak effect will exceed 6 hours (the time required to achieve greater than 87.5% of steady state, even in normal renal function). Neither norepinephrine nor epinephrine would be favored (particularly at these doses) because the patient's MAP is currently elevated, and these agents would contribute to increased α_1-mediated afterload increases, causing increased myocardial workload in a patient who already has decompensated systolic heart failure. Answer D is correct, and Answers A, B, and C are incorrect.

4. Answer: D

The patient's troponin elevation is most likely a result of the patient's decompensated heart. Given the patient's chemistry and ABG results, chronic obstructive pulmonary disease is highly unlikely. Although this presentation could be attributed to the patient's NSTEMI, his presentation is more consistent with a heart failure exacerbation. Sepsis is also a potential contributor to troponin elevation; by comparison, an infectious etiology is less likely in this patient's case. Answer D is correct, and Answers A, B, and C are incorrect.

5. Answer: B

Ticagrelor has been associated with adenosine-mediated dyspnea and bradycardia and should therefore be evaluated as a contributing cause. According to the current ACC/AHA guidelines, this patient no longer has a direct indication for $P2Y_{12}$ therapy because his stent was placed more than 12 months ago, but the patient should continue aspirin therapy indefinitely. The patient has no evidence of hyperkalemia. Answer B is correct, and Answers A, C, and D are incorrect.

6. Answer: A

Because of this patient's hypotension and ongoing cardiogenic shock, synchronized cardioversion would be preferred. Metoprolol would be unfavorable because of the patient's concurrent dobutamine use and his hypotension; likewise, amiodarone 150 mg intravenous push could contribute to further hypotension. The primary of role of adenosine is to slow AV nodal conduction when patients are tachycardiac with a regular rhythm (i.e., supraventricular tachycardia) to break the arrhythmia or to differentiate atrial from ventriclular sources. However, adenosine plays only a small role in this scenario. Answer A is correct, and Answers B, C, and D are incorrect.

7. Answer: C

The physician is considering heparin anticoagulation while the patient is in the ICU. While valuable to consider for long-term anticoagulation the HASBLED

score is not validated for bleeding risk specific to heparin anticoagulation. Nonetheless, given the patient's CHA_2DS_2-VASc score (annual stroke risk of 6.7%) and cardioversion, anticoagulation should be considered. Answer C is correct and Answers A, B, and D incorrect.

8. Answer: C

The patient is unlikely to remain stable without intervention, given his ongoing cardiogenic shock. To help stabilize this patient, intra-aortic balloon counterpulsation would best facilitate selective afterload reduction during systole (augmenting cardiac output in a patient with a low ejection fraction and severe mitral regurgitation) while providing augmented diastolic pressures. Venovenous ECMO is unlikely to help because this means of MCS is dependent on a functional LV and RV to provide forward blood flow. A venoarterial ECMO would stabilize the patient; however, it would increase afterload on the aortic valve, which could worsen the patient's mitral regurgitation. Furthermore, this degree of MCS may not be warranted at this time unless the patient develops progressive hypoxic cardiopulmonary failure.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

A diagnosis of cardiogenic shock is most likely, given the patient's history, presentation, and ongoing vasopressor requirement; elevated BNP; and lack of infectious symptoms. Furthermore, this patient has positive troponins and ST-segment depression in leads V2 and V3 (anterolateral or posterior leads), which may represent ST-segment elevation equivalent if evaluated in the context of the posterior part of the heart. The SA and AV nodes are usually supplied by the right coronary artery (in 70% and 85% of the population, respectively); thus, the patient's significant bradycardia and hypotension further increase the suggestion of a posterior infarct. Answer C is correct, and Answers A, B, and D are incorrect.

2. Answer: D

The SA and AV nodes are most commonly supplied by the right coronary artery (in 70% and 85% of the population respectively); thus, the patient's significant bradycardia and hypotension further increase the suggestion of a posterior infarct. Answer D is correct, and Answers A, B, and C are incorrect.

3. Answer: B

According to the SOAP II investigation, dopamine is associated with increased rates of adverse events in patients with cardiogenic shock compared with norepinephrine. Milrinone, although helpful in some patients with heart failure, would not be favored, given the patient's current hypotension and acute renal failure. Normal saline administration would likely be detrimental because of the patient's signs of fluid overload, including BNP elevation, hyponatremia, and rales on examination. Answer B is correct, and Answers A, C, and D are incorrect.

4. Answer: A

Lidocaine would be most favorable in patients with ischemia-mediated ventricular arrhythmias, and although the patient is not currently in VT, he is having persistent premature ventricular contractions (bigeminy), further increasing concern for ongoing ischemia and myocardial irritability. Metoprolol and diltiazem would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Amiodarone 300 mg intravenous push is no longer appropriate because the patient has a pulse and BP and is currently not in VT. Furthermore, rapid administration of amiodarone may lead to worsening hypotension. Answer A is correct, and Answers B, C, and D are incorrect.

5. Answer: A

The patient's heart catheterization was performed through the femoral artery, a vessel that it much harder to compress to facilitate hemostasis. Hematomas can occur at the access site; however, the most serious bleeding complication associated with this access site is a retroperitoneal bleed. Answer A is correct, and Answers B, C, and D are incorrect.

6. Answer: C

Vasopressin would be favored because when administered at normal physiologic doses because it mediates predominant increases in SVR while minimally affecting the PVR. Phenylephrine, however, will increase both PVR and SVR by the α_1-receptors. Given the patient's ongoing hypotension, low cardiac index, and rising CVP, inaction would be inappropriate, and additional volume administration would be detrimental in this already volume overloaded and failing RV. Answer C is correct, and Answers A, B, and D are incorrect.

7. Answer: B

Amiodarone boluses would be safest if administered slowly over 10 minutes to avoid additional hypotension, followed by a continuous infusion. Metoprolol and diltiazem would be contraindicated because of ongoing cardiogenic shock and vasopressor requirements. Answer B is correct, and Answers A, C, and D are incorrect.

8. Answer: D

Regardless of the means of medical management or revascularization, current quality registries and measures would require initiation or documentation of contraindication, except for ACE inhibitors/ARBs because the patient still has an LVEF greater than 40%. Answer D is correct, and Answers A, B, and C are incorrect.

APPENDIX A

Class	MOA	Drug (available dosage forms)	ECG Effects: AV Conduction PR	ECG Effects: Ventricular Conduction QRS	ECG Effects: Repolarization QT/QTc	Management Considerations and Pearls	Notable Drug Interactions	Therapeutic Levels (mcg/mL)	Defibrillation Threshold	TdP risk (%)
IA	High-potency vs. fast sodium channel blockade	Quinidine (PO)	↑ ↓	↑	↑	• Different formulations available (no exact conversions) • α-Blockade may contribute to hypotension • Prolonged half-life in CHF and hepatic dysfunction • May require dose adjustments in renal and/or hepatic dysfunction • Enhanced AV node conduction usually requires combination with AV node-blocking agent • > 85% protein bound	• CYP2D6 (inhibitor) • CYP3A4 (substrate and inhibitor)	2–6	↑	2–8
		Procainamide (IV)	↑	↑	↑	• Only available in intravenous form • May contribute to hypotension • Metabolized by hepatic acetylation • Active metabolite (NAPA) renally eliminated and has increased class III properties • Dialyzable	• QT-prolonging drugs	Procainamide: 4–8 NAPA: 10–20	↑ ↓	
		Disopyramide (PO)	↑ ↓	↑	↑	• May require dose adjustments in renal and/or hepatic dysfunction • Potent anticholinergic adverse effects	• CYP3A4 (substrate)	2–8	↑	1–3
IB	Least-potent vs. fast sodium channel blockade	Lidocaine (IV)	N/A	N/A	N/A or ↓	• **Ventricular arrhythmias only** • Increased risk of toxicities in hepatic dysfunction • Binds to AAG (acute-phase reactant) - increased levels of unbound drug present, leading to risk of toxicity as AAG dissipates • Enhanced efficacy in ischemic tissue	• CYP3A4 (substrate)	Total: 1.5–5 Free: 0.5–2	↑	
		Mexiletine (PO)				• **Ventricular arrhythmias only** • Prolonged half-life in CHF and hepatic dysfunction • Decrease dose in CrCl < 10 mL/min	• CYP2D6 (substrate) • CYP1A2	0.5–2	↑	
IC	Most-potent vs. fast sodium channel blockade	Flecainide (PO)	↑	↑	N/A or ↑	• May require hepatic dosing or renal dosing at CrCl < 35 mL/min • Increased risk of mortality post-MI (CAST) • Avoid in CHF because of its potent negative inotropic effects • Combine with AV node blocker to prevent rapid atrial flutter	• CYP2D6	0.2–1	↑	
		Propafenone (PO)				• Hepatic dosing • Increased risk of mortality post-MI (CAST) • Avoid in CHF because of its potent negative inotropic effects • Combine with AV node blocker to prevent rapid atrial flutter • SR and IR formulations not equivalent	• First-pass metabolism • CYP2D6, CYP3A4 CYP1A2 substrate	0.06–1	↑ ↓	
II	β-Blockade	Ex. Carvedilol (PO) Labetalol (PO/IV) Metoprolol (PO/IV) Esmolol (IV)	N/A or ↑	N/A	N/A or ↓	• Sinus bradycardia • AV block • Hypotension more likely with nonselective agents • Continuous infusions of esmolol or labetalol may contribute to large amounts of fluid	• Predominantly CYP2D6		N/A	

APPENDIX A *(continued)*

III	Potassium channel blockade ± other means	Dofetilide (PO)	N/A or ↑	N/A or ↑	↑	• Requires ECG monitoring for initiation, dose titration, reinitiation, or introduction of new interacting agents • Requires renal dosing adjustments	• CYP3A4 (mild) • Trimethoprim, verapamil, and thiazide diuretics contraindicated • QT-prolonging drugs	——	↓	1–8
		Ibutilide (IV)				• Only indicated for cardioversion of AF or enhancement of electrical cardioversion	• QT-prolonging drugs	——		1–8
		Sotalol (PO/IV)				• Requires renal dosing adjustments • Bradycardia	• QT-prolonging drugs	1–3.2	↓	1–6
		Amiodarone (PO/IV)				• Monitor liver and thyroid function tests • Average half-life 53 days; highly lipophilic • Bradycardia • High protein binding	• Inhibits CYP3A4, CYP2D6, CYP2C9	1–2.5+	↑	< 1
		Dronedarone (PO)				• Avoid in persistent AF • Monitor hepatic function tests • Avoid in CHF, particularly NYHA class III/IV • Bradycardia	• Inhibits CYP3A4, CYP2D6, CYP2C9			< 1
IV	Calcium channel blockade	Verapamil (PO/IV)	↑	N/A	N/A	• Hepatic dosing • Sinus bradycardia • Negative inotrope – avoid in patients with systolic heart failure	• CYP3A4 (substrate and inhibitor)	——	↑	
		Diltiazem (PO/IV)				• Decreased dosing in elderly patients and patients with hepatic dysfunction • Bradycardia • Negative inotrope - avoid in patients with systolic heart failure	• CYP3A4 (substrate and inhibitor)	——	N/A	
Misc.	Others	Digoxin (PO/IV)	↑	N/A	N/A	• Junctional rhythms • Decreased dosing in elderly patients and patients with HF, renal dysfunction	• Many interactions	AF: 0.8–2 ng/mL CHF: 0.5–1 ng/mL Toxic > 2.5 ng/mL		
		Adenosine (IV)	↑			• Half-life < 10 s • Used for acute treatment of AV node reentrant tachycardias	• ——	——		
		Magnesium (IV)				• Used to treat TdP and cardiac glycoside-induced arrhythmias				

AF = atrial fibrillation; AV = atrioventricular; CHF = congestive heart failure; HF = heart failure; IR = immediate release; IV = intravenous(ly); MI = myocardial infarction; MOA = mechanism of action; N/A = not applicable; NYHA = New York Heart Association; PO = oral(ly); SR = sustained release; TdP = torsades de pointes.

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Arman T. Askari
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ISSN 2196-8969 ISSN 2196-8977 (electronic)
Contemporary Cardiology
ISBN 978-3-030-19130-6 ISBN 978-3-030-19131-3 (eBook)
https://doi.org/10.1007/978-3-030-19131-3

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This Humana imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To our families for their unwavering support.

Preface to the Second Edition

For any cardiovascular care provider, an understanding of physiology is absolutely essential for delivering patient care. Whether sitting in the echocardiography reading room, performing procedures in the catheterization laboratory, or rounding in the coronary care unit, such an understanding is equally vital. While the underpinnings of cardiovascular physiology from a systems perspective have changed little in recent time, there have been substantial advances in the ability to apply these concepts to newer technologies.

Our primary goal for this second edition of *Cardiovascular Hemodynamics: An Introductory Guide* is not only to expound on the fundamental education of cardiovascular physiology but also to focus additionally on the clinical application of these hemodynamic principles. In order to achieve this, we have updated all of the first edition chapters and have added a new section, "Effects of Selected Interventions on Cardiovascular Hemodynamics."

Born out of the huge economic burden of heart failure is an increased pressure on the healthcare system to decrease the often-avoidable readmissions for those patients with heart failure. We believe that a solid knowledge of heart failure physiology will arm those charged with the care of these patients with the tools necessary to decrease these costly readmissions. In addition, we have added another chapter, "Objective Evaluation of Hemodynamics in the Outpatient," that aims to familiarize the reader with the recent advancements (medical and technological) that have proven helpful with regard to optimizing patient care.

Of course, an emphasis on the basic tenets of cardiovascular physiology remains our central focus, and we use numerous figures, hemodynamic tracings, tables, board style review questions, and hemodynamic "pearls" in order guide our readers. We believe this manual will be of immense value and interest to every student and practitioner of cardiovascular medicine who wishes to fully learn the hemodynamic foundation of cardiovascular medicine.

Beachwood, OH, USA — Arman T. Askari, MD
Lexington, KY, USA — Adrian W. Messerli, MD

Acknowledgment

We would like to acknowledge the authors, who, in many cases, were also mentors.

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resistance, VTI velocity time integral, LVOT left ventricular outflow tract, D diameter, LA left atrial pressure, SBP systolic blood pressure, V_{MR} peak mitral regurgitation velocity, PCWP pulmonary capillary wedge pressure, LVEDP left ventricular end-diastolic pressure, DBP diastolic blood pressure, V_{EDAI} end-diastolic aortic insufficiency velocity, SVR systemic vascular resistance, Q_p pulmonary flow, Q_s systemic flow. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011) 177

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$$\frac{Q_p}{Q_s} = \frac{\text{CSA RVOT} \times \text{VTI RVOT}}{\text{CSA LVOT} \times \text{VTI LVOT}}, \quad \frac{Q_p}{Q_s} = \frac{3.14 \times (2.3/2)^2 \times 21.1}{3.14 \times (1.8/2)^2 \times 17.1}, \quad \frac{Q_p}{Q_s} = \frac{87.6}{43.5} = 2.$$

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Part I

Components of Myocardial Performance

Preload

1

Amanda R. Vest

Understanding the Concept

The four major determinants of cardiac output are cardiac preload, myocardial contractility, heart rate, and afterload. Of these four elements, preload is the primary determinant. Cardiac preload is a semiquantitative composite assessment that is variously described in different cardiovascular physiology texts and articles as end-diastolic myocardial fiber tension, end-diastolic myocardial fiber length, ventricular end-diastolic volume, and ventricular end-diastolic filling pressure [1]. There is a general recognition that preload is not synonymous with any one of these measurable parameters, but is rather a physiological concept that encompasses all of the factors that contribute to passive ventricular wall stress at the end of diastole.

Cardiac preload may be expressed as a mathematical concept based upon the Law of LaPlace. This law states that, for a thin-walled spherical structure, $T = PR/2$, where T is wall tension, P is chamber pressure, and R is chamber radius. In the case of a thick-walled structure such as the left ventricle, the relationship is better described by $\sigma = PR/2w$, where σ is wall stress, and w is wall thickness, and where $T = \sigma w$. From the structure of the LaPlace's equation, the preload for the ventricle can be described as the left ventricular σ, whereby $\sigma\text{LV} = (\text{EDPLV})(\text{EDRLV})/2w\text{LV}$, with EDPLV representing the left ventricular end-diastolic pressure and EDR as the left ventricular end-diastolic radius. Thus, the parameters of pressure, radius (a surrogate for volume), and wall thickness are all demonstrated to contribute to this mathematical definition.

Clinically, a more tangible and measurable representation of preload has been sought from invasive hemodynamic monitoring. A measurement of end-diastolic pressure – the ventricular pressure measured after atrial contraction just before the onset of systole – is the most relevant representation of preload to many clinicians. Noninvasive assessments of end-diastolic chamber volume are also possible, but volume assessments rely on geometric assumptions that can be undermined by arrhythmias, changes in heart rate, localized wall motion abnormalities, and the chronic ventricular dilatation that occurs in many forms of heart failure. The passive pressure–volume relationship within a chamber, which is a reflection of the passive length–tension curve in isolated myocardium, is exponential and not linear. This fact poses one of the greatest limitations to the use of pressure as a surrogate for preload, with the ratio of change in chamber pressure to

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© Springer Nature Switzerland AG 2019

A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_1

volume being greater at higher volumes compared to lower volumes. In addition, the relationship between pressure and volume will also be distorted by various cardiac pathologies, such as the presence of pericardial constriction. Overall, it should be remembered that preload as a physiological concept encompasses more than just a single value on a pressure tracing (Fig. 1.1).

The concept of preload can be applied to either the atria or the ventricles. In the structurally normal heart, the preload experienced by the right atrium will determine the subsequent preloads in the right ventricle and ultimately the left side of the heart. The other determinants of cardiac output will be addressed in later chapters of this section.

Preload Physiology and Theory

Chamber Anatomy and Function

Cardiac preload will increase with a rise in total circulating volume or greater venous return, which increases myocardial wall stress and the pressure within a chamber at the end of its diastolic phase. Conversely, hypovolemia or decreased venous return will result in decreased chamber filling and wall stress and hence a decreased end-diastolic pressure. The chamber most easily and frequently accessed for invasive monitoring of cardiac preload is the right atrium. A central venous catheter, commonly employed in intensive care settings, can contribute useful

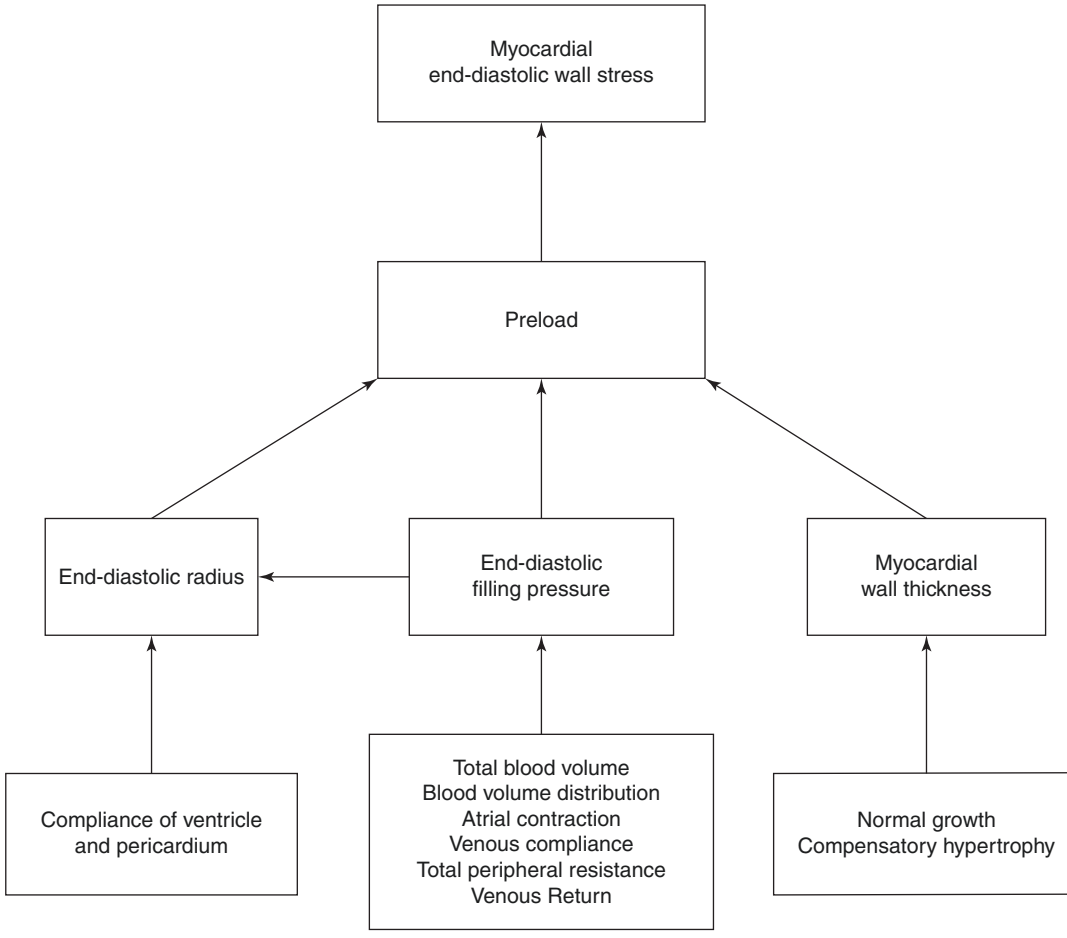

Fig. 1.1 Factors determining preload. (From Norton [1])

information for the clinician when assessing the patient's preload status.

The cardiac cycle comprises diastolic ventricular filling, augmentation by atrial systole to achieve the end-diastolic volume, isovolumic contraction, and then aortic (and pulmonary) valve opening, and stroke volume ejection. Meanwhile, atrial pressure progressively increases during ventricular systole as blood continues to enter the atrium while the atrioventricular valves are closed. Once the ventricle reaches its end-systolic volume, there is a period of isovolumic relaxation, which brings about mitral and tricuspid opening and diastolic filling from the atrium into the ventricle to begin the next cycle. Throughout the diastolic ventricular filling period, the pressure gradient between the atrium and ventricle is minimal. This is because a normal open mitral or tricuspid valve offers little resistance to flow; there is also significant passive filling of both the atrium and ventricle as blood returns from the systemic or pulmonary venous system. At a normal resting heart rate, diastole occupies approximately two-thirds of the cardiac cycle. With increased heart rate, both systolic and diastolic intervals will shorten (Fig. 1.2) [2].

The main difference between the left and right pumping systems is the pressure magnitude. In the normal heart, the pressures developed in the right heart are significantly lower than those on the left side, because resistance across the pulmonary vasculature is far less than the resistance to flow offered by the systemic vascular system. Normal pulmonary artery systolic and diastolic pressures typically do not exceed 30 mmHg and 15 mmHg respectively; the maximal right atrial pressure is generally 8 mmHg (Fig. 1.3).

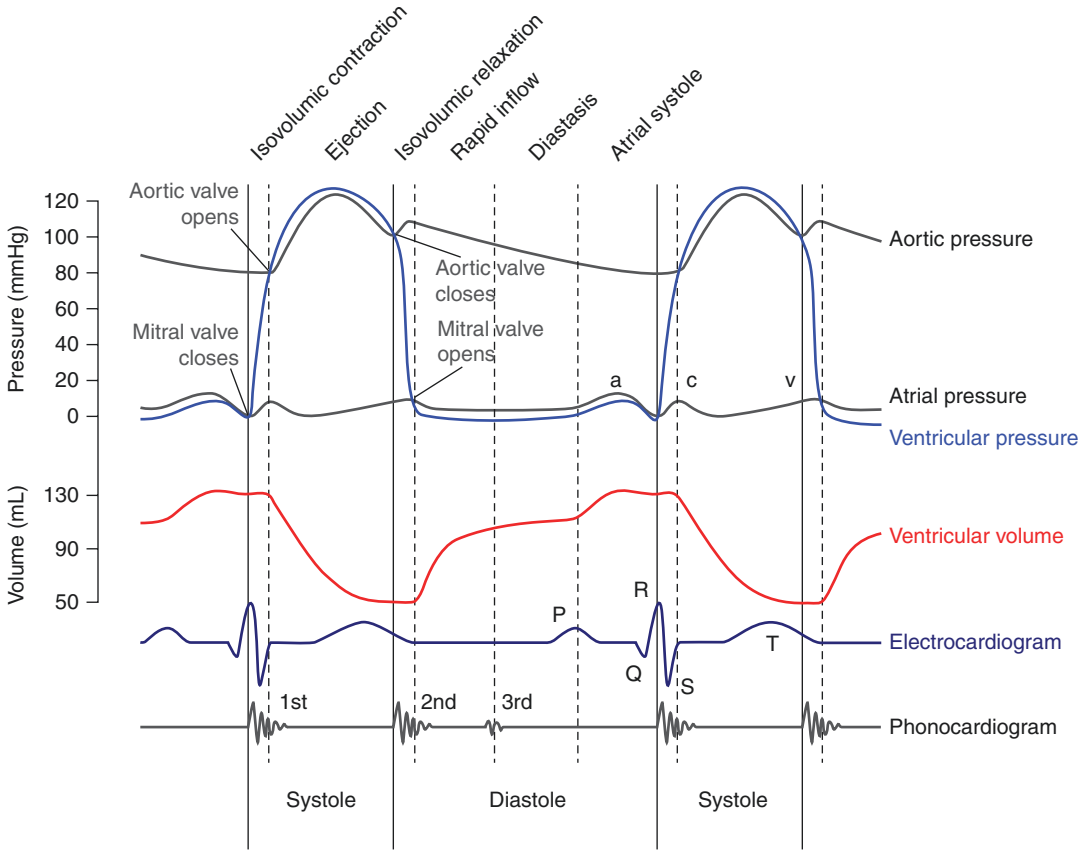

Fig. 1.2 The cardiac cycle. (From Wikipedia: DanielChangMD revised original work of DestinyQx; Redrawn as Xavax)

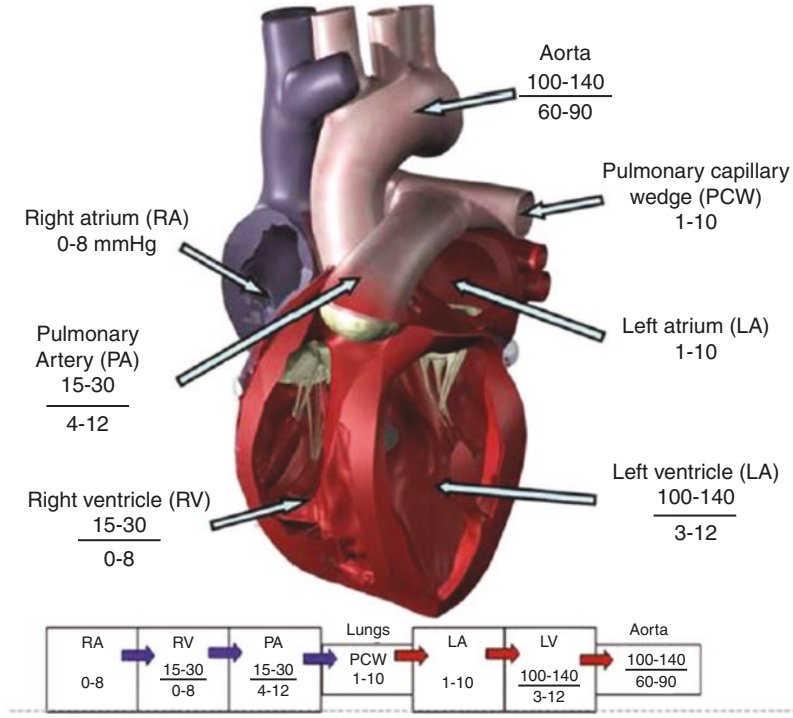

Fig. 1.3 Average pressures within the chambers and great vessels of the heart. (From Iaizzo [48])

The Right Atrial Pressure Waveform

A central venous catheter is correctly placed when its tip is situated in the distal superior vena cava [3]; at this position it approximates pressures within the right atrium. As illustrated above, right atrial pressure also approximates the right ventricular end-diastolic pressure, because minimal pressure gradient exists across the normal tricuspid valve. In turn, the right ventricular end-diastolic pressure reflects the right ventricular end-diastolic volume and, due to the conservation of volume passing through the right and left ventricles, will also mirror left ventricular end-diastolic pressure (LVEDP) and volume. Hence, the right atrial pressure alone can serve as a useful surrogate for cardiac preload while requiring slightly less invasive catheter insertion than pulmonary artery catheterization. However, it is also evident that abnormalities of cardiac structure and function will interfere with the assumptions by which central venous pressure monitoring can approximate left ventricular preload. Therefore, the central venous pressure has a greater role in preload assessment in the medical and surgical intensive care units for patients with structurally normal hearts, than in critically ill cardiac patients. The right atrial pressure waveform demonstrates pressure elevations concurrent with atrial contraction (the *a* wave), reflection of ventricular systole as transmitted by the tricuspid valve (the *c* wave), and venous filling of the right atrium against a closed tricuspid valve (the *v* wave). The *x* descent probably arises from right ventricular contraction pulling the tricuspid annulus downward, whereas the *y* descent corresponds to blood emptying from the right atrium into the ventricle [4] (Fig. 1.4).

As illustrated, there is generally an electromechanical delay of approximately 80 ms between the atrial depolarization of the P wave and the pressure deflection of atrial systole represented by the *a* wave. The degree of delay is dependent upon the length of tubing used for pressure transduction.

The normal right atrial pressure, or central venous pressure, ranges from 0 to 8 mmHg (approximately 0–10 cmH_2O if measured with a water manometer). The atrial pressure is usually taken to be the mean of the *a* waves on the pressure

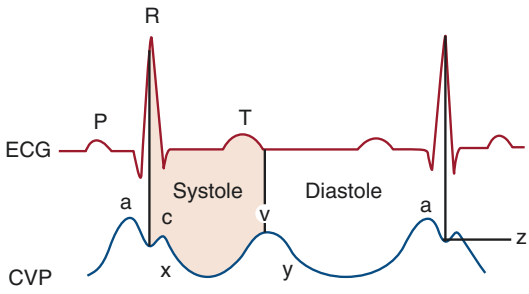

Fig. 1.4 Example of a typical central venous pressure waveform. (From Atchabahian and Gupta [49]). The base of the "c" wave represents the onset of right ventricular contraction and is therefore the best estimate of the final right ventricular filling pressure and preload.

Table 1.1 Variations of the right atrial waveform and their implications

Finding	Implication
Absence of the *a* wave	Atrial fibrillation or atrial standstill
Cannon waves	Atrioventricular dissociation – atrial contraction against a closed tricuspid valve
Elevation of all chamber pressures, with prominent *x* descent	Cardiac tamponade
Elevation of all chamber pressures, with steep *y* descent	Constrictive pericarditis
Large systolic wave	Tricuspid regurgitation

tracing. When the atrial wave is not present (due to atrial fibrillation or atrial standstill), the pressure tracing correlating with the R wave that occurs just before the *c* wave, referred to as the *z* point, is the most appropriate point for central venous pressure measurement. Because the central veins lie within the thorax, the waveform obtained will be influenced by intrathoracic pressure changes during inspiration and expiration. Inspiration is achieved by creating a negative intrathoracic pressure (by expansion of the thoracic cavity) which will be reflected by a downward shift of the central venous tracing. Exaggerated spontaneous inspirations may magnify this deviation. Therefore, it is customary to read the mean pressure at end-expiration, just before the inspiratory drop. The relationship is reversed in patients who are mechanically ventilated because inspiration is typically achieved by applying positive pressure and hence, the pressure at end-expiration is often at the low point of the respiratory nadir. The electronic transducer should always be leveled and zeroed in line with the right atrium, with the fourth intercostal space in the mid-axillary line often used as the anatomical landmark for leveling.

Other variations of the waveform that should be taken into account are listed in Table 1.1. Of particular relevance is the large systolic wave seen in tricuspid regurgitation. In the setting of significant tricuspid regurgitation, the *c* wave and *x* descent will be replaced by a prominent upward deflection (the systolic wave) occurring just before the *v* wave would be expected. This wave represents the regurgitant flow of blood back into the atrium with ventricular contraction.

Assessing Preload from the Right Atrial Pressure

The mean right atrial pressure, or central venous pressure, is primarily a reflection of venous return to the heart and thus the volume status of the patient. Lower pressures will be seen in the hypovolemic patient, as well as those in vasodilatory shock, e.g., due to sepsis or anaphylaxis. Elevated right atrial pressures are seen in cases of right ventricular failure (such as right ventricular infarction, pulmonary embolus), pulmonary hypertension (currently defined as mean pulmonary artery pressure at rest ≥25 mmHg [5]), tricuspid stenosis or regurgitation, cardiac tamponade, pericardial constriction, and hypervolemia (during anuric renal failure for example). The right atrial pressure may also be elevated in chronic or acutely decompensated left ventricular failure with either systolic or diastolic failure mechanisms.

Preload Reserve and the Venous System

In one of the early studies of preload dependence on human subjects, individuals with both normal

hearts and diseased hearts were observed to sustain a reduction in LVEDP and a reduction in cardiac index upon inflation of an occlusive balloon in the inferior vena cava, just caudal to the liver [6]. Conversely, it has been demonstrated in various settings that passive leg raising (PLR) from the horizontal plane in the supine subject increases the volume of blood returning to the right heart and, for a heart that is under filled and demonstrates preload reserve, this additional volume will boost left ventricular stroke volume. The venous system contains the major portion of circulating volume – up to 75% in some situations – because of the greater capacitance of veins than arteries. Therefore, venoconstriction has the potential to displace significant quantities of blood from the peripheral vasculature to the central circulation.

Venous return is the rate of blood flow from the periphery to the right atrium and depends upon the pressure gradient and the resistance to venous return. If blood were removed from a subject's circulating volume until there was no pressure within the venous system (i.e., no outward luminal force distending blood vessel walls), the volume of blood still contained within the system would be called the unstressed volume. The unstressed volume can be modulated by altering the contractile state of the venous smooth muscle. Venoconstriction decreases unstressed volume and, all other parameters being equal, will increase venous return and right atrial pressure. Venodilation increases unstressed volume and decreases right atrial pressure. In experiments using hexamethonium chloride, the unstressed volume has been seen to increase by almost 18 mL/kg, demonstrating the range of reflex compensation available [7]. During exercise, such as running, reflex venoconstriction of vascular beds in the spleen and skin, in combination with the action of the skeletal muscle pump, all help to increase venous return to the higher output heart and hence maintain sufficient pressure in the right atrium to support ventricular filling. In response to a sudden reduction in cardiac output, passive recoil of the veins will redistribute blood to the heart and act to restore adequate stroke volume. Conversely, sequential reductions in cardiac pump output lead to consequent decreases in arterial pressure and increases in venous pressure [8].

Movement of a volume of blood from the arterial system to the venous system will lower arterial pressure and raise venous pressure. However, due to the differing capacitances in these two systems, the arterial pressure change will be 19 times greater than that in the veins [9]. If cardiac output were to fall suddenly, the drop in pressure in the arterial system would far exceed the small rise in pressure in the venous system. Likewise, a large rise in arterial pressure will cause only a small reciprocal fall in venous pressure. All other factors being equal, the relationship venous pressure and cardiac output is reciprocal. Therefore, a constant interplay occurs between the heart and venous system to accommodate changes in posture and volume status. An equilibrium state can be reached at a right atrial pressure where venous return equals cardiac output. The reflex control of venous tone, and the signals governing this primary reservoir for cardiovascular homeostasis, are still incompletely understood.

Preload and the Respiratory Cycle

During inspiration, the negative intrathoracic cavity pressure is transmitted to the thoracic structures resulting in a decrease in the observed intravascular and intracardiac pressures. As previously described, right atrial and pulmonary wedge pressure tracings will be seen to fall. Inspiration will be followed by an increase in right atrial filling as an increased venous blood volume moves down the pressure gradient toward the heart. This leads to increased right ventricular volume and end-diastolic pressure in relation to the pleural pressure, although overall the expansion of the thoracic cavity causes the absolute right ventricular end-diastolic pressure to fall. Increased right-sided flow results in a slight increase in transmural pulmonary pressure during spontaneous inspiration. Events on the left side of the heart are inconsistent, as they are influenced by potentially contradictory changes in several parameters. However, the augmented blood volume moving through the right ventricle has been shown in closed-chest animal models to transiently decrease left ventricular stroke volume, likely due to deviation of the intraventricu-

lar septum into the left ventricular cavity which decreases its end-diastolic volume [10]. The respiratory relationship is reversed in patients who are mechanically ventilated with positive pressure during inspiration and calculation of the transmural pressure, by subtraction of the pleural pressure from the measured hemodynamic pressure, would show a more complex sequence of changes during the respiratory cycle. Intrapleural pressures can be measured with esophageal catheters, or roughly estimated based on the pressure settings of a patient's mechanical ventilation mode.

The Pulmonary Capillary Wedge Pressure Waveform

A key tenet of using the central venous pressure to assess cardiac preload is the relationship of right ventricular end-diastolic pressure to the left ventricular end-diastolic pressure. Experience has shown that there are many situations in which this pressure relationship does not hold true [11]. Pulmonary artery catheterization was previously a procedure limited to the research laboratory, but it made the transition to the bedside in the 1970s following the advent of the Swan-Ganz catheter. This is a multiple lumen catheter that permits pulmonary artery pressure measurement at the distal injection port and right atrial pressure at the proximal injection port. The balloon inflation port is used to inflate and deflate a small air-filled balloon at the distal catheter tip, which is introduced into a pulmonary artery branch. When the balloon is inflated and advanced within a pulmonary arterial branch, a column of static blood will exist between the left atrium and the catheter tip, enabling measurement of the downstream pressure in the left atrium (Figs. 1.5 and 1.6).

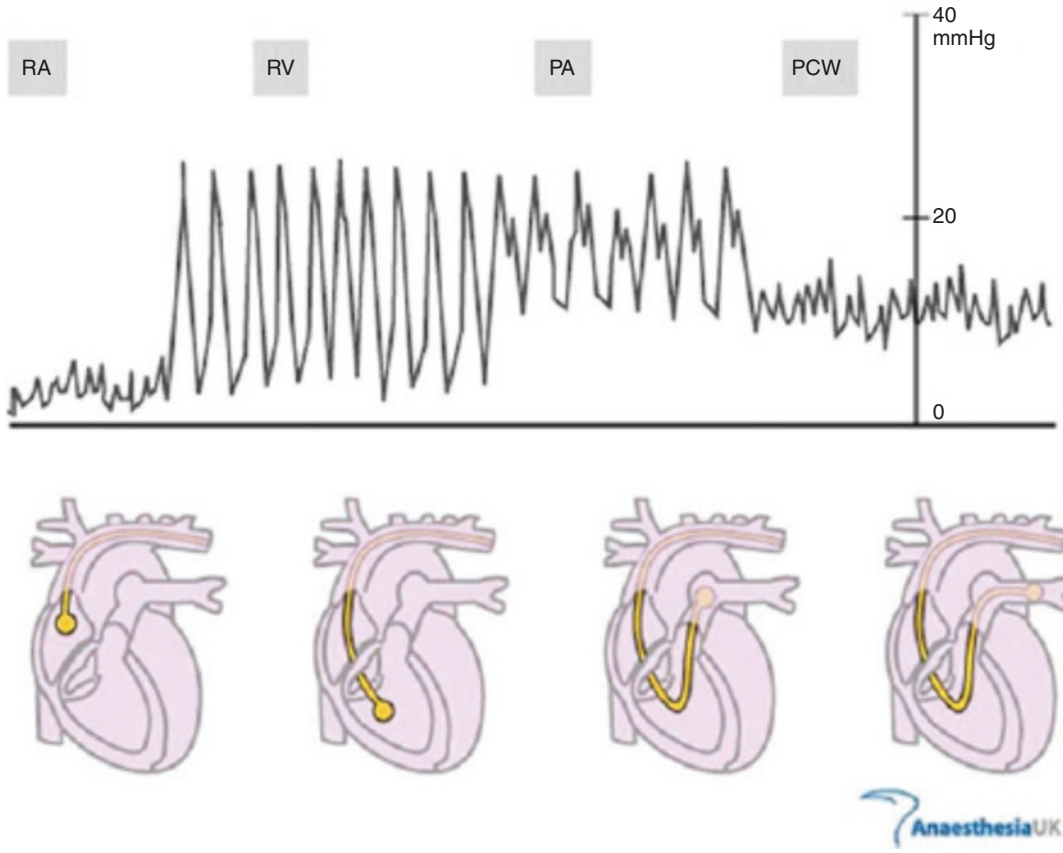

Fig. 1.5 Characteristic intracardiac pressure waveforms derived from the pulmonary artery catheter. (From Anesthesia UK, frca.co.uk)

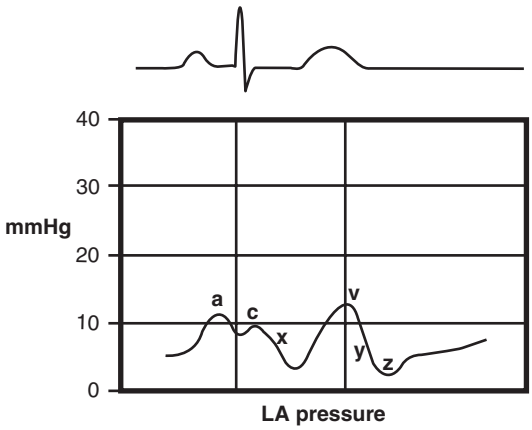

Fig. 1.6 Example of a typical pulmonary capillary wedge pressure waveform. (From The ABCs of A to V: Right Atrial/Left Atrial (PCW) Pressures, CathLabDigest.com). Note the occurrence of the "*a*" wave of left atrial contraction shortly after the electrocardiographic "*P*" wave and the occurrence of the "*v*" wave after the electrocardiographic "*T*" wave. The "*v*" wave falling after the "*T*" wave can be of help when distinguishing a prominent "*v*" wave in pulmonary capillary wedge profile from the systolic deflection of a pulmonary artery waveform, which occurs before the "*T*" wave and means the catheter is not in the wedge position

The waveform obtained at balloon inflation is a reflection of the left atrial pressure and therefore it will show a similar contour as the right atrial tracing with *a*, *c*, and *v* waves produced by the corresponding left-sided physiological events, although the wedge pressure is normally higher than the right atrial pressure. The pulmonary capillary wedge pressure (PCWP) is the key parameter in the clinical assessment of preload in heart failure patients, because in the absence of mitral stenosis, it will approximate left ventricular end-diastolic pressure (LVEDP), and therefore correct measurement technique is essential. The *a* wave will occur near the end of, or just after, the QRS complex, and the *v* wave follows the T wave. The PCWP pressure is measured as the mean amplitude of the *a* wave, or alternatively at the *z* point near the end of the QRS complex if an atrial contraction is not present. If a large systolic wave (*v* wave) is present, suggesting mitral regurgitation, a ventricular septal defect or diastolic dysfunction with impaired atrial compliance, the amplitude should also be recorded. If there is any uncertainty as to whether a true PCWP waveform has been attained, it should be ensured that the v wave falls after the T wave; in the catheterization laboratory, a blood sample can be withdrawn from the distal catheter port in the wedge position and should be the same as the arterial saturation is a true PCWP position has been attained. The PCWP should be measured at end-expiration if the waveform has respiratory variation.

The total electromechanical time delay is greater for the wedge waveform than for the right atrium as the changes in left atrial pressure have to be transmitted back through the pulmonary vasculature to the catheter tip. A balloon-tipped pulmonary artery catheter typically shows a mechanical time delay of 150–160 ms. A pressure gradient should exist between the mean pulmonary artery and the PCWP, with a gradual drop in PCWP occurring as the balloon is inflated. Indeed, there is usually a gradient of approximately 1–4 mmHg between the pulmonary artery diastolic (PAD) pressure and the mean PCWP to ensure forward movement of blood through the pulmonary vasculature, although sometimes the PAD and PCWP can be measured as almost equal [12]. However, a wedge pressure that exceeds PAD suggests an error in measurement, such as misidentification of a dampened PA tracing in place of a PCWP waveform or balloon inflation into a very small branch vessel, called overwedging. The difference between PAD and PCWP will be greater in the setting of pulmonary arterial hypertension, where elevated pulmonary artery pressures are seen without a concurrent PCWP elevation.

Assessing Preload from the Pulmonary Capillary Wedge Pressure

The value in the PCWP lies in its ability to represent (a) the volume status of the patient and (b) the adequacy of left ventricular function. If correctly obtained, the PCWP measures the capillary hydrostatic pressure that will tend to force movement of fluid out of the capillaries and into the pulmonary interstitium. This force is normally 6–12 mmHg

and is opposed by the capillary plasma colloid oncotic pressure at approximately 20–25 mmHg and acts to retain fluid in the vessel [13]. An imbalance of these opposing forces, or a change in the filtration coefficient, can promote the movement of fluid into the interstitium resulting in pulmonary edema. When the only altered parameter is hydrostatic pressure, there is a useful correlation between PCWP and the chest X-ray. From 18 mmHg, features of pulmonary edema may be seen; once hydrostatic pressure exceeds oncotic pressure around 25 mmHg, frank pulmonary edema would be expected. Therefore, a PCWP cut-off of 18 mmHg is often used as the hemodynamic numeric correlate of pulmonary edema [14]. A normal PCWP is usually quoted as 8–12 mmHg [12].

The gold standard invasive clinical assessment of cardiac preload is the left ventricular end-diastolic pressure (LVEDP), which is measured with a catheter retrogradely via the arterial system by crossing the aortic valve into the left ventricle. The correlation of PCWP with the left ventricular end-diastolic pressure, but not pulmonary artery pressures, has previously been demonstrated in settings such as acute myocardial infarction [15]. Although the PCWP is a good surrogate of left ventricular preload, one study showed that LVEDP was >5 mmHg higher than the PCWP in approximately 30% of heart disease patients [16].

It is important to understand situations in which the PCWP will not accurately assess preload. As previously mentioned, there is an exponential relationship between left ventricular end-diastolic pressure and volume. Therefore, the same volume change will cause a small pressure change at a low ventricular volume and a large pressure change in a more distended ventricle. The relationship between left ventricular volume and pressure may also be skewed in pericardial tamponade or constriction. Other scenarios where the PCWP can potentially misrepresent the LVEDP are outlined in Table 1.2. Mitral regurgitation causes a systolic regurgitant wave with onset just before the *v* wave, with similar morphology to that seen in tricuspid regurgitation in the central venous waveform. In pure mitral stenosis, the *a* wave will be prominent and elevated due to the resistance to blood flow through the narrowed valve orifice during atrial systole. The *y* descent is usually prolonged, indicative of the increased resistance to passive left ventricular filling. It is also important to remember that PCWP measured in the resting state may not adequately represent the hemodynamic etiology of dyspnea on exertion. Right heart catheterization during bicycle exercise is increasingly utilized when evaluating patients with potential heart failure with preserved ejection fraction, in whom the left atrial pressure may only rise to abnormal levels during exertion [17].

Table 1.2 Situations where pulmonary capillary wedge pressure (PCWP) may inaccurately represent left ventricular end-diastolic pressure (LVEDP)

PCWP lower than LVEDP	PCWP higher than LVEDP
Aortic regurgitation	Positive pressure ventilation
Highly compliant left atrial chamber	Mitral stenosis
	Mitral regurgitation
	Pulmonary venous obstruction between pulmonary capillary and left atrium
	Left atrial myxoma

Another recent advance in clinical heart failure management is the ability to measure ambulatory pulmonary artery pressures and attain a daily assessment of cardiac preload that guides outpatient therapies. The CHAMPION trial led to the approval of the CardioMEMS device (Abbott, St. Paul, Minnesota, USA) for which a pressure sensor is implanted into the pulmonary artery and wirelessly transmit PA systolic and diastolic measurements to their care providers. The CHAMPION trial showed a 30% reduction in heart failure hospitalizations in the 6 months following randomization to the monitoring strategy versus control, although the single-blind design of the trial and the lack of a comprehensive heart failure disease management comparator arm have left questions about the clinical impact of this approach [18]. However, the ability to assess ambulatory cardiac preload from a PA diastolic surrogate and identify an uptrend in volume status prior to clinical congestion manifestation is clearly a technological advance in the application of hemodynamic principles to clinical care.

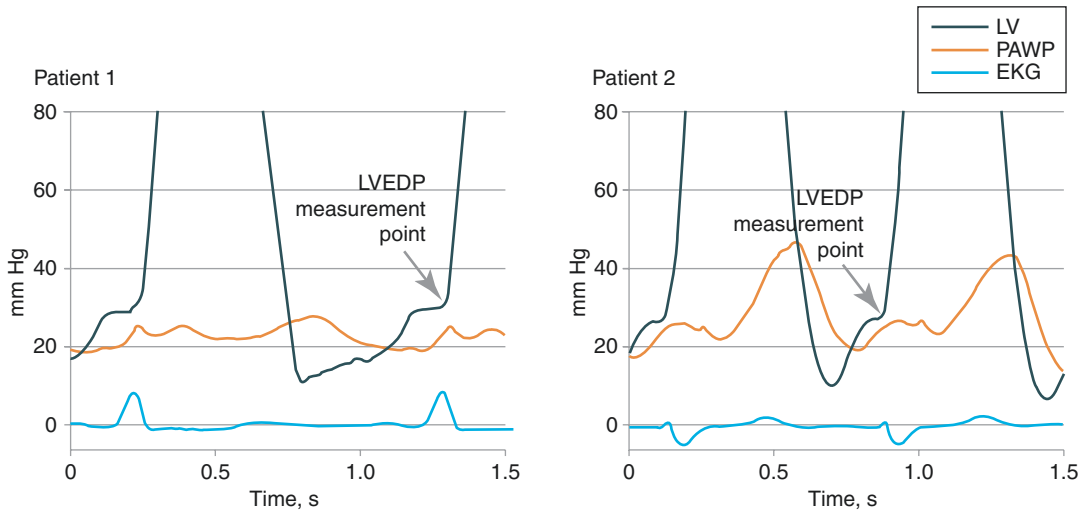

Fig. 1.7 Examples of two patients with similar left ventricular end-diastolic pressures, but differing pulmonary capillary wedge pressures, with patient 1 showing better left atrial compensation for the elevated LVEDP. (From Reddy et al. [50])

In the absence of any of these complicating factors, the wedge pressure should reflect the end-diastolic filling pressure in the left ventricle. The LVEDP is considered the gold standard single parameter in quantifying cardiac preload with the caveat that, as defined above, preload is a composite of several elements that contribute to passive ventricular wall stress at the end of diastole. In situations where it is essential to know the left ventricular preload precisely, such as in the evaluation of pulmonary hypertension etiologies, a left ventricular catheter for direct LVEDP measurement may be necessary. The downside is that the LVEDP requires arterial cannulation and retrograde passage of the catheter across the aortic valve into the left ventricle. This procedure is associated with risks and is usually performed only as a component of a more extensive left heart catheterization procedure. In addition, as the catheter enters the left ventricle for only a matter of minutes, usually only a single measurement of LVEDP is obtained during a patient's hospitalization. This is in contrast to the Swan-Ganz catheter which may remain in place for many days, with many critically ill patients having serial PCWP measurements throughout their intensive care admission. It should, however, be remembered that the LVEDP only reflects the LV operating compliance and can be higher than the PCWP if the left atrium is highly compliant and able to compensate for a chronically elevated LVEDP (Fig. 1.7).

A normal LVEDP is often quoted as 8–12 mmHg, with 16 or 18 mmHg usually being used as the threshold for significant elevation in clinical trials [19]. As illustrated in Fig. 1.3, chamber pressures on the left side of the heart are normally higher than those in the low-pressure system on the right.

Preload Dependency and Pressure–Volume Loops

Having successfully obtained an accurate hemodynamic estimate of preload, the next challenge is to interpret the impact of that parameter on overall cardiac function. The first concept is the preload dependency of ventricular performance. Carl Ludwig is reported as being the first to describe the dependence of cardiac work on diastolic filling, when he wrote in 1856 "… a strong heart that is filled with blood empties itself more or less completely, in other words, [filling of the heart with blood] changes the extent of contractile power" [20]. This relationship of preload to

performance was described in detail by Ernest Henry Starling, who published this relationship in a series of papers between 1912 and 1914 and in his 1915 Linacre Lecture at Cambridge University [21]. The relationship between ventricular pressure and volume during the cardiac cycle can be illustrated by pressure–volume loops, as depicted in Fig. 1.8. End-diastole is located at the lower right corner of the loop. The subsequent upstroke (the vertical line on the right of the graph) is isovolumic contraction. This is followed by ejection, with end-systole located in the upper left corner, and then the downstroke of isovolumic relaxation. As illustrated, increases in preload will result in a greater volume of blood ejection during systole – at least up until a point. Controversy exists as to whether the nondiseased human heart reaches a point of preload at which further end-diastolic stretch will result in decreasing blood ejection [22]. The so-called descending limb of the Frank–Starling curve is better described in the failing heart and will be discussed elsewhere in this book (Fig. 1.8).

At this point, it is valuable to reflect on the myocardial cellular mechanics that underlie the preload concept. The term preload originally arose from the isolated myofiber studies where myocytes were physically loaded with defined forces in the form of a weight applied to one end of a quiescent muscle sample, such as papillary muscle. The other end remains tethered and the force applied prior to contraction is the preload. By varying preload, the relationship between initial length and shortening (isotonic contraction), or developed force (isometric contraction), can be recorded. The maximal force developed at any sarcomere length is determined by the degree of overlap of thick and thin filaments and therefore the number of available actin-myosin cross bridges. Forces increase linearly until a sarcomere length with maximal overload (approx. 2.2 μm) is achieved [23]. Structural proteins constitute a strong parallel elastic component within the myocardium and prevent an increase in developed force beyond this maximal degree of preload. The ascending limb of the myofiber length–tension relationship, which is analogous to the increase in stroke volume with increasing preload in the whole heart, is also modulated by length-dependent increases in myofilament calcium sensitivity [24]. Proposed mechanisms include enhanced calcium binding to troponin C, narrower interfilament gaps at longer sarcomere length, and increased sarcoplasmic reticulum calcium release and uptake at longer sarcomere lengths.

Returning to the whole heart, the major determinants of the left ventricular pressure–volume relationship are the initial ventricular volume, chamber geometry, wall thickness, and myocardial stiffness. Pressure–volume loops highlight the nonlinear pressure and volume relationship during diastolic filling. The instantaneous slope of the curve in the filling phase (i.e., change in pressure/

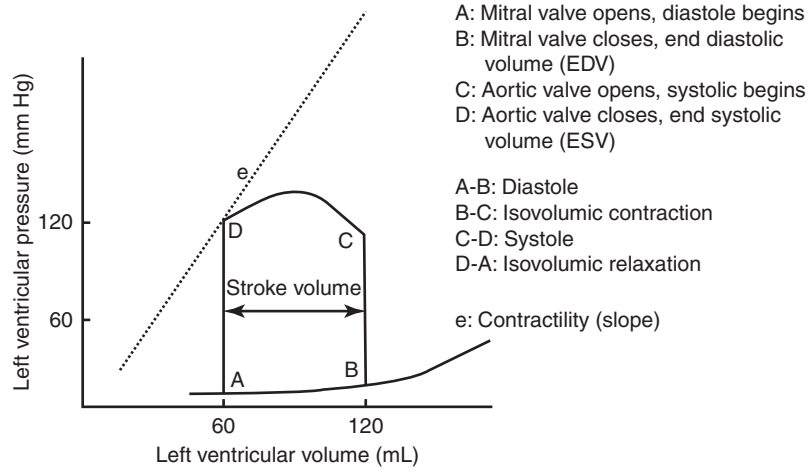

Fig. 1.8 Pressure–volume loop for a single cardiac cycle. (From Loushin et al. [51])

change in volume) represents diastolic stiffness. This parameter is correctly termed as elastance and can be conceptualized by the ventricle behaving as a spring with a stiffness (the inverse of compliance) that increases during contraction and decreases during relaxation. Elastance can be calculated at any point during the ventricle's diastole by calculating the gradient of the curve. Beyond a volume of approximately 140 mL (the exact volume will depend on individual heart dimensions), the chamber becomes progressively more difficult to fill, requiring a greater pressure increase to effect volume changes than earlier in diastole. A thicker, stiffer ventricle, for example in an individual with left ventricular hypertrophy, will show a steeper gradient to the diastolic curve, and hence a greater elastance. The mathematical inverse of elastance (i.e., change in volume/change in pressure) is compliance. The thicker, stiffer ventricle would be described as having reduced compliance. It should be remembered that diastole is an active process that consumes energy; ATP is hydrolyzed to break the actin-myosin crosslink and permit sarcomere lengthening. Therefore ventricular compliance also often falls during ischemia. In the setting of low compliance, a high LVEDP may actually reflect a relatively small LVEDV. Conversely in the normal left ventricle, compliance is high within the typical physiological range, because the chamber operates on the flatter region of the curve where reasonably small pressure rises give significant volume increases, promoting optimal stroke volume.

The importance of the physiological pressure–volume relationship is its role in modulating ventricular performance by the changes in preload. This heterometric regulation occurs on a beat-by-beat basis and ensures matching of the right and left ventricular output with changes in respiration and body posture [25]. In response to myocardial pathology, rises in end-diastolic pressure and volume can also provide a longer term compensatory increase in stroke volume due to increased myocardial fiber length in the remaining functional myocardium. However, the scope of this compensation is limited, as the dilated failing heart will also develop fibrosis, adverse remodeling, and unfavorable metabolic status. This explains the disparity between acute increases in end-diastolic volume resulting in augmented stroke volume, vs. the chronically dilated heart generating a poorer stroke volume.

These considerations illuminate the inherent difficulties in judging preload adequacy. The level of preload at which the heart will show its optimal stroke volume will be dependent on not only the intravascular volume status but also the ventricular compliance and geometry unique to the individual heart. Clinical experience has shown that some dilated, failing ventricles perform optimally at a higher wedge and LVEDP than would be judged normal. However, this cannot be assumed to be the case, as many heart failure patients show improved symptom status and cardiac output following aggressive diuresis and return of their wedge pressure to a value that would be considered to lie in the normal range (Fig. 1.9).

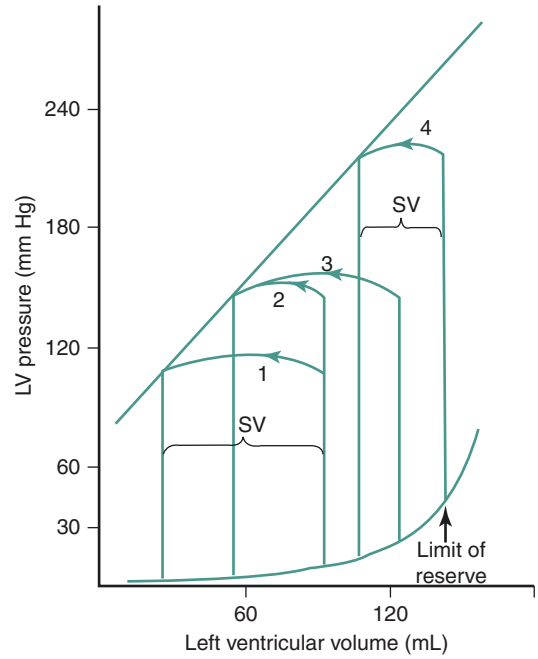

Fig. 1.9 Effects of acutely increasing preload on the pressure–volume loop, to the point of maximal preload reserve. (From Ross [52] and Kaplan [53]). When the ventricle reaches the limit of preload reserve, it is unable to distend any further and the preload is fixed; at this point (loop 4), any further increases in afterload will lead to a reduction in stroke volume

Preload in Clinical Practice

Invasive Hemodynamics

Assessment of preload reserve and preload adequacy is of particular relevance to the management of hypovolemic or septic shock patients. The use of invasive hemodynamic monitoring, with either a central venous catheter or pulmonary artery catheter, is generally the standard technique in the intensive care unit or operating room. Fluid resuscitation is titrated to right atrial or pulmonary wedge pressure, or to the central or mixed venous saturation which serves as a reflection of tissue oxygenation adequacy. Various goal-directed algorithms have been developed in the research setting and have demonstrated the value of early effective volume resuscitation in trauma, surgical, or sepsis patients [26]. However, since its introduction to clinical care almost 40 years ago, the limitations of the pulmonary artery catheter in actual clinical practice have been well documented. As described earlier, for the pulmonary wedge pressure to accurately reflect LVEDP, the following criteria must be met: (a) the catheter is correctly positioned with a valid and accurate wedge tracing obtained, (b) the wedge pressure is correctly interpreted, (c) the wedge pressure is an accurate reflection of LVEDP, and (d) there is a linear and predictable relationship between left ventricular end-diastolic pressure and volume. In an assessment of the technical adequacy of 2711 pulmonary wedge recordings, the authors reported that 31% of these recordings were technically inadequate [27]. Even if a valid waveform is obtained, it is estimated that in approximately a third of cases, data will be incorrectly interpreted by the physician making management decisions [28]. These issues, and the added difficulties brought by positive pressure ventilation, changes in myocardial compliance, and ventricular interdependence, can severely impact on the utility of the pulmonary capillary wedge pressure in accurately reflecting cardiac preload. Such factors may partially explain why randomized controlled trials have, to date, not shown improved outcomes with pulmonary artery catheterization in critically ill patients.

Noninvasive Preload Assessment Techniques

Alternative techniques for assessment of preload adequacy, and responsiveness of the stroke volume to further preload delivery, have also been trialed over recent years (Table 1.3). Various transthoracic and transesophageal echocardiographic measurements have been experimented with. One simple strategy is assessment of venal caval collapse during positive pressure ventilation, with the goal being to identify those patients with a RA pressure less than 10 mmHg who would benefit from further intravenous volume before being subjected to positive pressure ventilation [29]. Another related technique is passive leg raising (PLR) which has gained interest as a maneuver for assessing functional hemodynamic status and assessing potential fluid responsiveness. As described above, passive leg raising from the horizontal position effects a transient increase in preload and acts as an endogenous fluid challenge. Radiolabeled erythrocyte studies to determine venous blood volume in the lower extremities have demonstrated a reduction of approximately 150 mL in each leg when this maneuver is performed [30]. If the right ventricle is preload responsive, the 300 mL increase in venous return will augment right ventricular output and hence left ventricular filling. A small number of studies have proven increases in pulmonary wedge pressure and LVED dimensions with PLR, supporting the theory that the transfer of this volume of blood into the right atrium does significantly contribute to cardiac preload. However, in situations where the preload reserve of the heart is limited, meaning that further diastolic filling will not raise left ventricular stroke volume, the increased venous return will not result in greater cardiac output. The transient increase in cardiac output seen in the preload responsive heart has been observed to be greater after withdrawal of 500 mL blood [31], suggesting that the effect of this maneuver is dependent upon the volume status of the individual. The clinical utility of this observation was highlighted in a study of mechanically ventilated patients judged to be requiring volume expansion, with recording of aortic blood flow after PLR and then a 500 mL intravenous fluid

Table 1.3 Techniques for clinical assessment of cardiac preload

Technique	Pros	Cons
Pulmonary capillary wedge pressure (PCWP) [15]	Multiple right heart and pulmonary pressures, cardiac output, and index all measurable	Invasive, inaccurate with some structural diseases, requires interpretation
Left ventricular end-diastolic pressure (LVEDP) [15]	Gold standard for preload measurement	Requires arterial cannulation, traversing the aortic valve
Ambulatory pulmonary artery diastolic pressure sensor [18]	Enables ambulatory monitoring to detect preload increases	Relies on PA diastolic, further clinical validation required
Vena caval ultrasound assessment	Noninvasive and simple to perform	Sensitivity may be poor
Passive leg raising (PLR) [7]	Noninvasive and simple to perform	Requires bed that performs appropriate movements
Right ventricular end-diastolic volume index (RVEDVI) [33]	Predicts change in stroke volume in response to fluids	Requires a rapid response thermistor and PA catheterization
Left ventricular end-diastolic area (EDA) [36]	No vascular access required	Requires a transesophageal echocardiogram study
Intrathoracic blood volume assessment (ITBV) [38]	Stronger predictor of preload than PCWP or CVP	Requires femoral artery cannulation
Esophageal Doppler [41]	Esophageal probe is minimally invasive	Role in medical intensive care is still to be defined
Deuterium oxide and sodium bromide dilution techniques	Accurate estimation of total body water and extracellular water, respectively	Requires isotope ingestion or injection and blood or urine collections
Radioisotope blood volume analysis (red cell mass and plasma volume measurement) [44]	Measures intravascular volume	Requires isotope injection and blood collections
Bioimpedance spectroscopy [45]	Noninvasive	Does not differentiate intravascular fluid from total body water
Thoracic impedance measurement [46]	Noninvasive	Imperfect representation of invasive hemodynamics

challenge. The PLR was achieved by taking the patient from a semirecumbent position with 45 ° head elevation, through a negative 45 ° tilt of the bed, so that the upper body lay parallel to the horizontal with the lower extremities elevated at a 45 ° angle. An increase in aortic blood flow of at least 10% by PLR predicted a volume expansion-induced increase in aortic blood flow of at least 15% with a sensitivity of 97% and specificity of 94% [32]. Thus, an initial trial of PLR appears to offer a potentially useful noninvasive clinical tool for assessing which critically ill patients will be preload responsive and should receive further volume expansion.

Additional Invasive Preload Assessment Techniques

The use of a pulmonary artery catheter with a rapid response thermistor and an ECG electrode allows computation of the right ventricular ejection fraction, from which right ventricular end-diastolic and end-systolic volumes can be calculated. Right ventricular end-diastolic volume index (RVEDVI) is by dividing right ventricular end-diastolic volume by body surface area, and has been evaluated in surgical critical care settings in mechanically ventilated patients. One such study aimed to determine preload status in acute respiratory failure patients. The degree of positive end-expiratory pressure (PEEP) was titrated and corresponding serial measurement of RVEDVI, wedge pressure, and cardiac index were recorded. They found that, at all levels of PEEP, cardiac index correlated significantly better with RVEDVI than with wedge pressure – at high levels of PEEP, cardiac index inversely correlated with wedge pressure, but remained positively correlated with the RVEDVI [33]. The value of RVEDVI is its ability to predict the change in stroke volume in response to a

fluid challenge, and has been demonstrated to be a superior predictor of recruitable cardiac output than wedge pressure [34]. Of note, though, some authors suggest that the RVEDVI overestimates the preload in comparison to echocardiographic techniques [35].

Left ventricular dimensions have also been employed in the assessment of preload adequacy (Table 1.3). Transesophageal echocardiography is also increasingly used to assess left ventricular filling, with the LV end-diastolic area (EDA) in the transgastric mid-papillary short axis view proving to be a useful parameter that correlated with cardiac preload. In a cohort of heterogeneous medical intensive care unit patients, the left ventricular EDA was significantly lower in those patients who showed a good response to volume challenge [36]. However, the utility of EDA assessment was felt to be lower in this study than in several others evaluating EDA and preload in cardiac surgery patients. Nonetheless, at least one intensive care center has had such success with left ventricular echocardiographic assessment of preload reserve that it has become the primary method for hemodynamic [37].

Another technique that features in the anesthesiology and surgical literature is transpulmonary thermal-dye indicator dilution, which enables bedside measurement of intrathoracic blood volume (ITBV). ITBV has been shown to be a stronger predictor of preload than PCWP and CVP [38]. Transpulmonary double indicator dilution measurements of cardiac output and ITBV can be performed using a catheter positioned in the descending aorta (via the femoral artery) that simultaneously measures thermodilution and dye-dilution. The two indicators are the freely diffusible cold saline and a plasma bound indicator such as indocyanine green (ICG). When injected simultaneously, the cold indicator will equilibrate with the interstitium whereas the ICG will remain in the intravascular space. Based upon the conservation of mass, intrathoracic blood volume (ITBV) can then be calculated from cardiac output and the mean transit time of the dye tracer between the site of injection – the right atrium – and the site of detection. A study in 10 anesthetized patients observed significant decreases in ITBV after a standardized change from supine to sitting body position, which correlated with changes in the stroke volume index. This study found ITBV and EDV to be equivalent indices of cardiac preload in their small sample of anesthetized patients [39]. Another group that compared preload variables in the early phase of hemodynamic stabilization of 57 critical care patients found ITBV to be a more reliable indicator of preload than CVP or PCWP [40]. However, femoral artery catheterization is required for this technique.

An invasive technique for assessing preload adequacy that may be appropriate in high-risk surgical patients is esophageal Doppler. This is a minimally invasive method of measuring real-time descending aortic blood flow that employs the Doppler shift phenomenon as a marker for blood cell velocity. A probe situated in the esophagus is in close proximity to the descending aorta and provides an excellent window for obtaining Doppler flow signal from which cardiac output can be calculated. The left ventricular ejection time (or flow time) corrected for heart rate correlates well with left ventricular preload. In general, a corrected flow time of less than 0.35 s suggests a potential to respond to volume expansion, whereas reading above 0.45 s suggests that volume expansion will not stimulate further increases in cardiac output [41]. Esophageal Doppler has been demonstrated to be effective in guiding nurse-led, protocolized resuscitation in the early postoperative hours, resulting in reduced complications and shorter hospital stays for cardiac surgery patients [42]. Its promise has also been recognized in the medical intensive care setting, where the continuous real-time monitoring could be of use in gaining instantaneous feedback on interventions. Probe insertion takes only minutes, requires minimal technical skill, and is not associated with any major complications [43]. However, the calculations that generate measurements of aortic blood flow do depend upon aortic geometric assumptions.

Finally, a range of techniques for ambulatory assessment of blood volume, as a surrogate for cardiac preload, have been developed to inform the clinically management of heart failure patients

who are at risk of developing congestion years (Table 1.3). Techniques range from the research-only use of deuterium oxide and sodium bromide, to measure the total body water and extracellular volumes, respectively, to the radioisotope measurement of red cell mass and plasma volume in a blood volume analysis test [44]. The relationship between elevated preload and increased tissue edema is harnessed for the techniques of bioimpedance spectroscopy, which involves the placement of voltage and current electrodes at landmarks on the body [45], and for thoracic impedance measurements either via implantable pacemaker-defibrillator devices or from measurement on the chest wall [46]. There is much current interest in the potential for left ventricular assist device (LVAD) flow waveforms to offer a noninvasive assessment of preload for mechanically supported end-stage heart failure patients, with a recent publication showing correlation between the PCWP and the ventricular filling phase slope of the Heartware LVAD flow waveform [47].

Bullet Point Summary

- Preload is a composite assessment of cardiac filling that represents the primary determinant of cardiac output.
- End-diastolic left ventricular pressure and volume are common surrogates for preload.
- However, the passive myocardial length–tension relationship is exponential rather than linear, limiting the role of pressures as a direct surrogate for preload.
- Preload increases with greater circulating volume, venoconstriction, exercise, arteriovenous fistulae, increased ventricular compliance, increased ventricular filling time, left ventricular systolic failure.
- Preload decreases with volume depletion, decreased venous return, impaired atrial contraction, tricuspid or mitral stenosis, less compliant ventricles.
- The atrial pressure waveform comprises *a*, *c*, and *v* waves, with *x* and *y* descents.
- Atrial pressure is usually measured as the mean of the *a* waves.
- Inspiration normally decreases all intracardiac pressures.
- Inflation of the Swan-Ganz catheter balloon within a pulmonary artery branch enables measurement of downstream pressure in the left atrium.
- Pressure–volume loops are orientated with end-diastole located at the lower right corner of the loop.
- The instantaneous slope of the pressure–volume curve in the filling phase elastance.
- Invasive methods of assessing left ventricular preload adequacy include: central venous pressure, pulmonary artery diastolic pressure, and pulmonary capillary wedge pressure. Left ventricular end-diastolic pressure is considered the gold standard.
- Noninvasive methods of assessing left ventricular preload adequacy include vena caval collapse, right ventricular end-diastolic volume index, left ventricular end-diastolic area, esophageal Doppler evaluation of left ventricular inflow, and intrathoracic blood volume.

Review Questions

1. Which of the following has *not* been used as surrogate parameter for cardiac preload?
   (a) Left ventricular end-systolic pressure
   (b) Pulmonary capillary wedge pressure
   (c) Intrathoracic blood volume
   (d) End-diastolic myocardial fiber tension
   (e) Degree of venal caval collapse
   Answer is (a). However, left ventricular end-*diastolic* pressure is a commonly used clinical surrogate for cardiac preload.
2. Which one of the following statements is true regarding central venous pressure monitoring?
   (a) The normal central venous pressure in a healthy adult ranges from 5 to 12 mmHg
   (b) The central venous pressure should be taken to be the lowest point between the *a* and v waves as measured during inspiration
   (c) Central venous pressure rises during deep inspiration
   (d) The *x* descent is absent in cardiac tamponade

(e) Significant tricuspid regurgitation will cause a prominent upward deflection just before the *v* wave would be expected

Answer is (e). The normal central venous pressure is 0–8 mmHg, although a higher rage may well be an appropriate target for a critically ill individual in whom maintenance of preload is important. The pressure is usually read as the mean peak of the *a* waves, ideally at the end of expiration, just before the inspiratory fall in central venous pressure. Cardiac tamponade causes absence of the *y d*escent, and often results in a prominent *x d*escent.

3. Which of the following does *not* generally cause the pulmonary capillary wedge pressure to be unrepresentative of the left atrial pressure?
   (a) Pulmonary venous hypertension
   (b) Balloon inflation in a very small branch vessel
   (c) Aortic stenosis
   (d) Mitral regurgitation

   Answer is (c). Pulmonary venous hypertension, overwedging of the Swan-Ganz balloon and an atrial myxoma can all cause the pulmonary capillary wedge pressure to read higher than the actual left atrial pressure. Severe mitral regurgitation causes a large systolic regurgitant wave with onset just before the *v* wave, and so care must be taken to correctly interpret the pressure waveform and estimate the pressure as the peak of the a waves, because inclusion of the regurgitant upward deflection will cause overestimation of the true pressure. The presence of mitral stenosis and aortic regurgitation can also cause the pulmonary capillary wedge pressure to misrepresent the left ventricular end-diastolic pressure.
4. Which one of the following statements is true regarding ventricular "elastance"?
   (a) This is an expression of the ease of diastolic stretching of the myocardium.
   (b) Can be a calculated as the change in pressure divided by change in volume, which is the instantaneous slope of the pressure–volume curve in the filling phase.
   (c) Beyond a volume of 40 mL in the adult heart, the left ventricle becomes more difficult to fill, and shows lower elastance.
   (d) A heart with left ventricular hypertrophy shows lower elastance than normal.
   (e) In the setting of low elastance, a high LVEDP may actually reflect a relatively small LVEDV.

   Answer is (b). Elastance is a measure of the diastolic stiffness of the myocardium, and is the inverse of compliance. Elastance is decreased above approximately 140 mL in the adult left ventricle. Left ventricular hypertrophy results in higher elastance and lower compliance than normal. It is a higher elastance ventricle in which a high LVEDP may actually reflect a relatively small LVEDV.
5. A 74-year-old female with long-standing hypertension and diabetes presents with confusion, fever and hypotension, with a blood pressure of 88/48. She is diagnosed with urosepsis and admitted to an intensive care unit. A prior outpatient echocardiogram showed severe left ventricular hypertrophy, most marked in the upper septal region, with a left ventricular ejection fraction of 65%. Are the following statements true or false?
   (a) The concentric hypertrophy confers greater elastance, compared to a normal left ventricle.
   (b) Preload is increased in a stiffer left ventricle.
   (c) This individual may be particularly sensitive to volume depletion.
   (d) After recovery from sepsis, beta-blockers and nitrates should be included in this individual's outpatient medication regimen.
      (a) True. A stiffer ventricle has greater elastance, and lesser compliance – these two parameters are inversely related.
      (b) False. As a ventricle becomes less compliant, the preload will decrease as the end-diastolic volume achieved with the same degree of venous return and filling time will be less.

(c) True. Due to the decreasing end-diastolic volume with worsening left ventricular hypertrophy, this heart becomes more "preload dependent," meaning that the same reduction in preload will cause a greater fall in stroke volume compared to a structurally normal heart. An individual such as the one described can show significantly reduced stroke volumes in the setting of volume depletion or distributive shock, due to the development left ventricular outflow tract obstruction, with or without systolic anterior motion of the mitral valve. This patient's blood pressure will likely improve markedly when the preload is augmented, for example, by intravenous volume resuscitation.

(d) False. Beta-blockers are often indicated in patients with significant left ventricular hypertrophy, or hypertrophic cardiomyopathy. By reducing heart rate, the diastolic ventricular filling period is increased, so improving the preload. Conversely, nitrates cause venodilatation and a reduction in preload, and hence may decrease this patient's preload and induce a left ventricular outflow tract gradient.

6. A 60-year-old male with coronary artery disease, hypertension, and active tobacco use presents with chest pain and inferior ST elevations. He was also noted to be in complete heart block with a heart rate of 48 bpm. At emergent cardiac catheterization, there was an acute right coronary occlusion, which was successfully intervened upon. However, the peak troponin T was 28 ng/mL, signifying a significant inferior myocardial infarction. On arrival in the coronary intensive care unit, the blood pressure was 90/72, with a right atrial pressure of 21, PA pressure 27/17, pulmonary capillary wedge pressure 14, cardiac index 1.8 l/min/m^2. Are the following statements true or false?

(a) Passive leg raising could be used as a measure of preload dependence.

(b) Positive end-expiratory pressure will not affect the cardiac index as the pulmonary capillary wedge pressure is normal.

(c) Atrioventricular pacing would be expected to improve the cardiac index.

(d) Use of dobutamine in this setting will increase the preload.

(a) True. Passive leg raising provides an "endogenous fluid challenge" and temporarily enhanced venous return and therefore preload. If the blood pressure and/or cardiac index improves immediately after this maneuver, it suggests that the patient will be responsive to volume resuscitation. The scenario described is consistent with a right ventricular infarction. In this setting, the blood pressure and cardiac index often improve with judicious use of small fluid boluses, as the patient is highly preload dependent.

(b) False. Mechanical ventilation with positive end-expiratory pressure will hinder venous return to the thorax during inspiration and hence may decrease stroke volume, especially in the heart with inadequate preload.

(c) True. The loss of atrial contraction, which usually supplies approximately 20% of ventricular filling, may be particularly detrimental for the preload-dependent right ventricle in this individual. Restoration of atrioventricular coordination with temporary pacing wires can significantly augment ventricular performance.

(d) False. Use of dobutamine in this setting would be expected to enhance contractility and decrease the right ventricular afterload by inducing some vasodilatation in the pulmonary vasculature. The preload may be slightly decreased by systemic peripheral vasculature dilatation.

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Afterload

2

Amanda R. Vest

Understanding the Concept

As discussed in Chap. 1 regarding preload, cardiac afterload is also a semiquantitative composite assessment of a determinant of cardiac output. The four major determinants of cardiac output are cardiac preload, myocardial contractility, heart rate, and afterload. Afterload is the force against which the heart pumps to expel blood into the vasculature. In isolated myofiber experiments, myocytes are physically loaded with defined forces in the form of a weight, to the lower end of a vertically mounted quiescent muscle sample. The opposing end of the myofiber remains tethered. The muscle is then electrically stimulated to contract and lift the additional weight. Once stimulated, the muscle develops tension, or force, until it meets and then overcomes the opposing force of the applied load, which is termed the afterload. Once the afterload is exceeded, the weight will be physically lifted and fiber shortening occurs. The degree and velocity of myofiber shortening is inversely related to the afterload applied. If both ends of the muscle sample are tethered and immobilized, or if the afterload applied is in excess of the myofiber's maximal force generation, the resulting contraction will remain isometric, meaning that the fiber length will be unchanged when tension is generated during contraction [1].

An alternate expression of the afterload is as a stress (defined as unit force per cross-sectional area) enabling comparison of differently sized samples of myofiber. It also permits transfer of the concept to the intact ventricle. Afterload in the whole heart can be understood as the stress encountered by left ventricular myofibers as they contract against the end-diastolic volume. Ventricular wall forces are difficult to directly measure, but the wall tension can be described by LaPlace's equation through $\sigma = PR/2w$, where σ is wall stress, P is pressure, R is ventricular radius, and w is wall thickness. This equation applies to a spherical chamber, whereas the equation is modified toward $\sigma = PR/w$ for a cylindrical vessel. More complex mathematical calculations can also be used to quantify end-systolic wall stress that take into account variations on chamber geometry. It can be seen from the law of LaPlace that, at a given intraventricular

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_2

pressure, a dilated left ventricle (increased ventricular radius) will have to develop a greater inward force than a smaller heart to generate the same systolic pressure. This makes the ventricle vulnerable to an "afterload-contractility mismatch" and explains why stroke volume may be augmented by reducing the afterload of a dilated left ventricle. Conversely, a hypertrophied left ventricular wall will achieve a lower wall stress and more easily generate a systolic pressure that overcomes ventricular afterload.

Another concept for defining afterload is in terms of the impedance to blood flow entering the aorta, known as arterial input impedance. This parameter quantifies the ratio of change in pressure to change in flow. It can be calculated using values for arterial pressure, elasticity, vessel dimension, and blood viscosity, and it requires invasive instantaneous aortic pressure and flow measurements which render it a research tool only. With the two principal determinants of ventricular afterload being systolic pressure and ventricular radius, and because the ventricular dimensions are assumed to remain relatively consistent, the systolic arterial pressure is the parameter most commonly used as a surrogate for afterload in clinical practice. In the absence of aortic or pulmonic stenosis, the maximum systolic pressure beyond the valve reflects the maximum pressure generated by the corresponding ventricle. Hence, the peak aortic pressure and peak pulmonary pressure can be measured to estimate the left and right ventricular afterloads, respectively.

An inverse relationship exists between stroke volume and the afterload [2]. As above, this is a consequence of the fact that muscle cannot shorten in excess of the length determined by the total load acting upon it. When this load is increased, sarcomere shortening will stop at a greater length, and so the extent of thick-thin filament overlap and cross-bridge formation will be diminished compared to a lower afterload (Fig. 2.1).

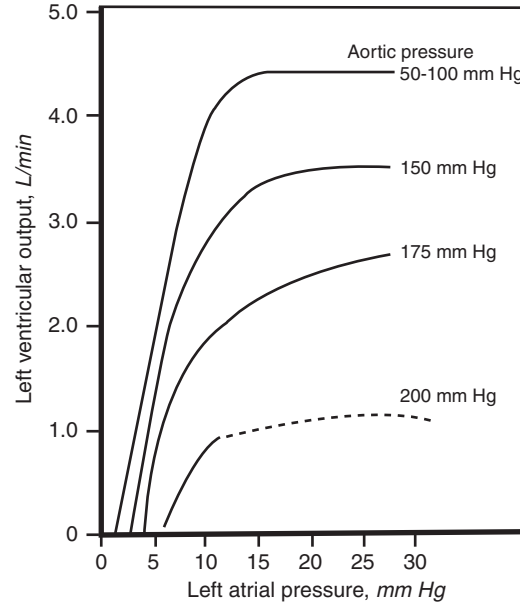


Fig. 2.1 The inverse relationship between afterload and cardiac performance. (Adapted from Sagawa [31])

Afterload Physiology and Theory

Afterload and Arterial Vasculature

The forces that oppose ventricular shortening are a summation of factors encountered throughout the arterial tree and can be referred to as arterial impedance. The total systolic load includes not only the impedance to flow from the large arteries but also the impedance provided by the medium peripheral arteries and smaller arterioles. Stephen Hales (1677–1761) suggested a simplistic model for the function of the arterial system, with the functions of cushion, conduit, and resistance being fulfilled by the proximal elastic arteries, medium-sized muscular arteries, and peripheral arterioles, respectively [3]. This classic model is useful in defining the differing properties of vessels along the arterial tree and in highlighting the peripheral arterioles as the site of the majority of peripheral resistance.

The three major determinants of arterial impedance are resistance, inertia, and compliance.

Resistance in a vessel is described by the Poiseuille equation $R = 8 \times \eta \times l/\pi r^4$, where R is resistance, η represents the viscosity of blood, l is vessel length, and r is vessel radius. Thus, it can be seen that elevated viscosity, such as in polycythemia, will increase resistance to flow. Importantly, resistance is inversely proportional to the fourth power of the radius, enabling small changes in arteriolar diameter to have profound changes on total peripheral resistance [4]. Total peripheral resistance can be expressed with regard to the ascending aorta as $R = P_o/\mathrm{CO}$, where P_o represents the mean arterial pressure, CO is the cardiac output, and R is the total peripheral vascular resistance. This can be re-arranged to $P_o = (\mathrm{CO})R = (\mathrm{SV})(\mathrm{HR})R$ by inputting the equation for cardiac output. This expression allows appreciation that the mean aortic pressure is directly related to both the cardiac output and the peripheral resistance. Inertia, which is related to the mass of the blood column, opposes acceleration of blood flow and is dependent upon the heart rate. Compliance is a property of the vascular walls, with highly compliant vessels being more distensible. Elastance is the reciprocal of compliance. Compliance is also heart rate dependent; the rate dependence of both inertia and compliance leads to phase shifts between instantaneous pressure and flow within the pulsatile arterial system [1]. The arterial pulse waveform begins with the upstroke imposed by ventricular systole, with a rapid increase in aortic pressure in early systole. The peak proximal aortic flow velocity slightly precedes the peak pressure. The aorta and large arteries expand during systole to accommodate some of the pressure fluctuation. This intermittent input into the proximal system is translated to an almost constant flow into the distal capillary bed, fulfilling the cushion function of the Hales model. This is achieved by absorption of stroke volume by the large elastic vessels, with conversion of the energy of systole into stretch of the arterial walls. The walls recoil as pressure within the vessel falls, and the stored energy is returned during diastole to maintain the blood pressure and distal blood flow during this period of the cardiac cycle. This is termed the Windkessel effect and is dependent both upon the capacitance of the aorta and large arteries, and the resistance to flow in the smaller vessels that do not show systolic expansion. However, this now considered an overly simplistic model and contemporary modeling incorporates elements of wave propagation and reflection.

Reflected Pressure Waves

An additional potential contributor to the afterload, not accounted for in the Hales model, is the phenomenon of retrogradely reflected pressure waves traveling from the periphery back toward the ventricle. The speed of propagation, known as the pulse wave velocity, is high enough for the reflected wave to arrive in the proximal aorta within the same cardiac cycle and so the reflection overlays the incident wave with both contributing to the arterial waveform. A reflected wave occurring during systole will increase the afterload; a reflected wave arriving in the proximal aorta during diastole is more advantageous as it will augment coronary blood flow. Major sites of reflection are arterial branch points, particularly the renal artery branches off the abdominal aorta, and the iliac bifurcation. The degree of wave reflection can change the pressure and flow waveforms seen in older subjects and in hypertensive individuals. Aging in industrialized societies is accompanied by increased systolic pressure and decreased arterial compliance; diastolic pressures tend to fall slightly. Intima-media thickening occurs, which causes progressive stiffening of the aging larger elastic arteries, resulting in elevation of aortic systolic and pulse pressures due to a combination of a rise in the forward incident wave and early return of the reflected wave [5] (Fig. 2.2).

A Framingham substudy documented the increases in arterial stiffness (elastance, the inverse of compliance) with advancing age [6]. The result is increased velocity of both the incident and retrograde reflection waves, with an

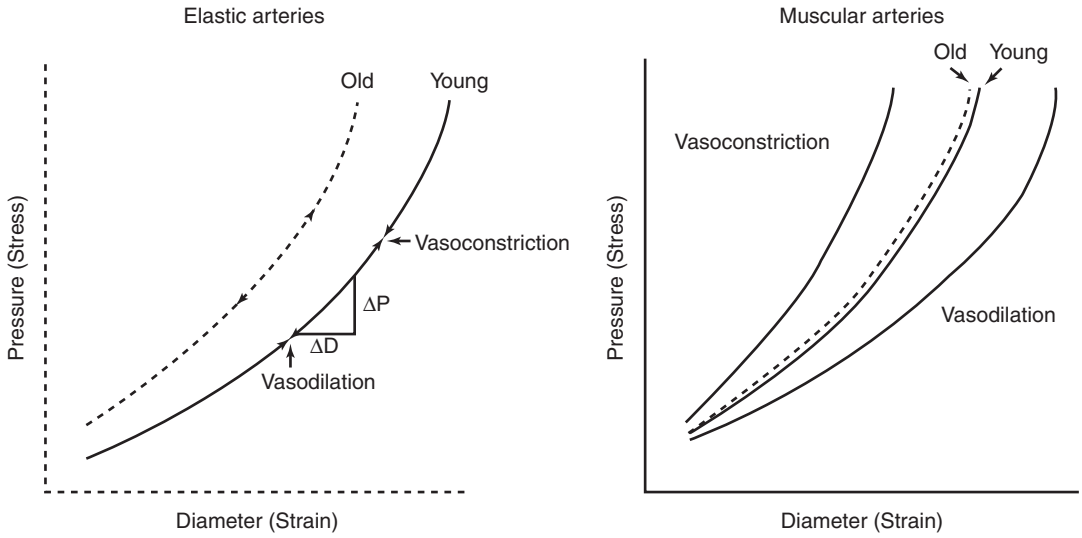


Fig. 2.2 Pressure-diameter relations for elastic and muscular arteries. (From Nichols and Edwards [5])

increase in systolic and pulse pressures. The enhanced incident wave raises myocardial oxygen demand, which can induce ventricular hypertrophy over time. In addition, the early return of reflected pressure waves adds to the afterload by augmenting late systolic pressure and removes the diastolic support of coronary blood flow; hence, the favorable ventriculo-arterial coupling is progressively lost [7]. It is the large central arteries, rather than the peripheral vasculature, that undergo the greatest capacitance changes with age. These changes in reflected waves contribute toward diastolic dysfunction, decreased exercise capacity, and an increased long-term risk of heart failure onset, especially heart failure with preserved ejection fraction (HFpEF) [8]. Large artery stiffness, as measured by carotid-femoral pulse wave velocity, predicts cardiovascular events and mortality, even after accounting for other established cardiovascular risk factors [9].

Decreased compliance in the large arteries may also induce macrovascular damage in organs such as the kidneys and the brain once the cushion effect that absorbs systolic pulsations is lost, causing the microvasculature to be subjected to pulsatile flow. The microvasculature is generally considered to include the small arteries of less than 400 μm diameter, arterioles of less than 100 μm diameter, and the capillaries with their single layer of endothelial cells. It is hypothesized that a more pulsatile microvasculature flow induced by age-related decline in the Windkessel effect is a contributor to end-organ damage [10].

Input Impedance and Characteristic Impedance

Parallels have been suggested between the flow of blood in the arterial system and the flow of current within an alternating current (AC) electrical circuit [11]. An analogous electrical circuit would contain capacitors and resistors, with the alternating storage and discharge of the capacitor separating peak pressure and flow. Impedance is a vector consisting of two components: the magnitude (modulus) and the phase angle, representing the number of degrees by which the sinusoidal pressure is separated from the sinusoidal flow. Electrical impedance occurs as current and voltage fluctuate with AC cycles and can be conceptionally translated into arterial impedance (Z_{in}). However, it should be remembered that blood does not behave sinusoidally, and so biological pressure and flow values must be converted into a fundamental sine wave and a series of harmonic waves using Fourier analysis. A value for impedance is derived from each pair of sine waves of pressure and flow (i.e., harmonics) at their specific phase angle. To validly apply Ohm's law in

this setting, the system should be in the steady state (vasomotor tone should be constant), time invariant (free of beat-to-beat changes in resistance), and linear. The nonlinearity of the ventricle during contraction does somewhat limit this technique, with the variations in elastance of the chamber during contraction being unaccounted for. Therefore, it would not be accurate to derive input impedance from invasive values for the left ventricular pressure and aortic flow, because the intervening aortic valve adds significant nonlinearity. However, when considering the arterial tree, the variations in pressure and flow are minor enough to enable systemic and pulmonary arterial input impendence to be considered valid mathematical descriptions of the systemic and pulmonary arterial trees, respectively.

When using the impedance concept in a compliant vascular system, the flow will be advanced with respect to the pressure sine wave. This is depicted as −90 ° in the phase angle. With inertance the flow is delayed, giving a +90 ° phase angle. The modulus of impedance will decrease with increasing frequency. In a large elastic artery, the compliance and inertia effects interact to keep pressure and flow sine waves in phase. This gives a pulsatile, or characteristic, impedance with a phase angle of 0. In this setting, the modulus will be constant and independent of changes in frequency. If the system were without reflection waves, the input impendence would equal the characteristic impedance. However, the reflected waves moving retrogradely toward the proximal aorta result in a significant difference between arterial input impedance and the characteristic impedance, which incorporates the reflected waves. This difference is more apparent at lower frequencies, where reflected waves return out of phase. Conversely, at high frequencies, the wavelengths are less than the arterial system length and so reflected waves are out of phase and cancel each other out. Therefore, at high frequencies, input impedance is almost equal to characteristic impendence [12]. The aortic input impedance spectrum gives information in the frequency domain about the arterial elastance, pulse wave reflectance, and the peripheral resistance. The clinical relevance is that increases in the pulsatile components – the elastance and reflectance – will lead to ventriculo-arterial mismatch and are, therefore, detrimental to cardiac efficiency (Fig. 2.3).

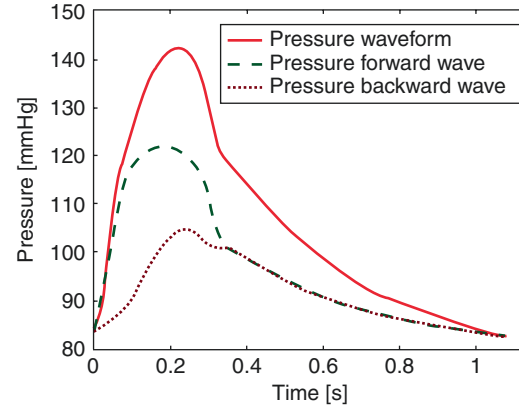


Fig. 2.3 The effects of wave reflection on the systolic pressure profile. (From Chirinos and Sweitzer [32]). Wave separation analysis showing the contributions of the forward (green dashed line) and backward (red dotted line) pressure waves to the systolic pressure profile

Assessing Afterload from Invasive Hemodynamics

Efforts to apply the impedance concept as a clinically measurable tool have been hampered by the complexity of the many advanced analytic functions required to derive values, and hence, the much simpler mean aortic pressure or mean systolic pressure remains the more commonly used surrogate of afterload. Clinically, the invasive measurement of cardiac afterload is usually achieved with a pressure tracing from a fluid-filled catheter with its tip lying just above the aortic valve in the ascending aorta. One phenomenon that the clinician must bear in mind in this setting is the possibility of pressure recovery. This describes the increase in pressure downstream from a stenosis caused by reconversion of kinetic energy to potential energy and can be a source of discrepancy between catheter and Doppler valvular pressure gradients. Bernoulli's theorem, from which Doppler evaluations of flow across a stenosis can be derived, requires that the sum of the pressure head, potential energy, and kinetic energy must be equivalent throughout all parts of the flow system. Therefore, in the setting of aortic

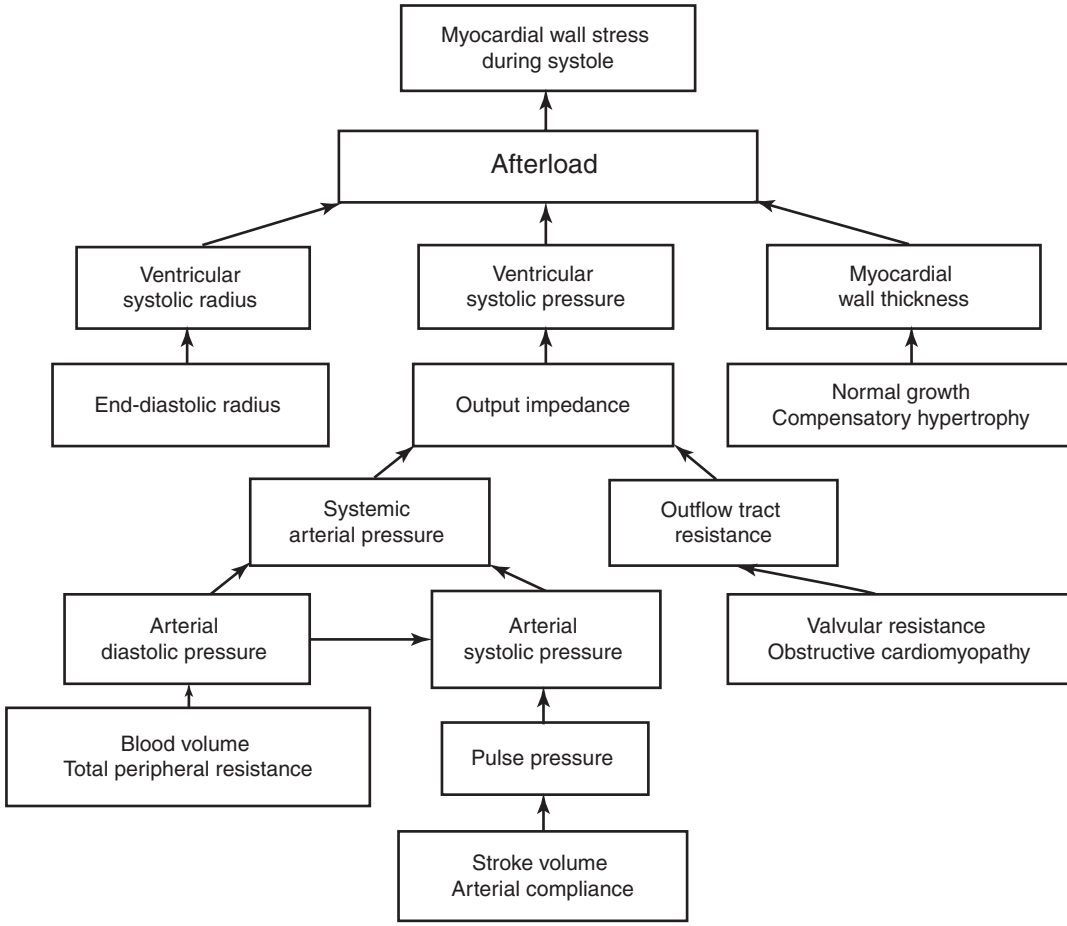


Fig. 2.4 Factors determining afterload. (From Norton [33])

stenosis, the lowest pressure is found where the velocity is highest and hence where the valve orifice is the smallest. Beyond the stenosis, velocity decreases and so pressure will increase, with the total amount of pressure increase (pressure recovery) being dependent upon the dissipation of kinetic energy due to flow separation and vortex formation across the valve. The consequence is that when Doppler gradients are measured at the point of minimal diameter of the stream of blood flow (the vena contracta), they will be higher than the invasive catheter measurements obtained in the proximal aorta, where pressure has been recovered. It has been noted that in milder aortic stenosis, the cusps of the valve form a funnel-shaped orifice and cause greater pressure recovery than in a more severely stenosed valve [13]. The extent of the phenomena is also dependent on the relationship between the dimensions of the valve orifice and the ascending aorta. A smaller aorta will lead to a lesser pressure loss and hence increased pressure recovery, compared to a larger aorta with the same degree of aortic stenosis.

The complexity of the relationship between the contracting ventricle, the arterial system, and its blood flow is such that finding a single parameter to fully encompass the cardiac afterload is probably impossible (Fig. 2.4).

Ventricular Wall Stress Versus Arterial Input Impedance

As previously introduced, aortic input impedance is only one of two biophysical concepts available to define afterload; the other is ventricular wall

stress, defined by LaPlace as $PR/2w$. Wall stress also carries with it some clinical limitations, as the values for pressures and dimensions are instantaneous and cannot account for rapidly changing loads encountered during the cardiac cycle. The calculations are also highly dependent upon ventricular geometric assumptions. The two differing afterload approaches of input impedance and wall stress have been compared in their validity as indicators of ventricular performance. Ross et al. constructed an animal model protocol to elucidate the relative importance of wall stress and impedance in negatively impacting ventricular stroke volume. These early experiments concluded that the dominant factor in regulating ventricular performance, as demonstrated by reduced fractional shortening, was the level of wall stress, rather than input resistance or pulsatile impendence [14].

Afterload Mismatch

Allied to this observation is the recognition that when pulsatile impedance is greater, changes in mean resistance produce greater changes in wall stress. This is presumably the result of the large increase in ventricular volume when pulsatile resistance rises, again emphasizing the impact of ventricular geometry on the outcome of these maneuvers. This appreciation led to the concept of afterload mismatch in 1976, a framework for assessing the matching between the afterload and the inotropic state in the whole heart. Under normal physiologic circumstances, an increase in afterload is usually accompanied by increased venous return (due to movement of blood from the arterial to venous systems) and hence increased end-diastolic volume. This helps to maintain stroke volume in the face of an increased afterload. A mismatch can be induced acutely in a normal heart if end-diastolic volume is not allowed to compensate for the increase in afterload [15]. The result will be a fall in stroke volume, ejection fraction, and ventricular circumference. An example of mismatch creation could be a scenario with sudden infusion of vasopressor into a volume depleted vascular system. An afterload mismatch can also be induced in a normal left ventricle in the opposite hemodynamic situation of volume overload, when the limit of preload reserve has already been reached and the average sarcomere length exceeds 2.2 μm. Additional afterload applied to the ventricle already working at a maximal end-diastolic volume will cause a sharp drop in stroke volume, unless contractility is also enhanced by an inotrope. Thus, an applied afterload stress can serve as an indicator that a heart is operating near either the upper or lower limits of preload [16]. The concept that afterload mismatch can exist even in the basal state explains why therapeutic afterload reduction in conditions such as severe left ventricular dysfunction or mitral regurgitation can significantly improve cardiac output, so long as preload is maintained and the ventricle can achieve an increased end-diastolic volume.

In addition to the acute afterload response studies on the intact heart in unanesthetized large animal subjects, the longer term effects of a sustained increase in afterload have also been extensively studied in animal models. Ross et al. instrumented 12 dogs with ultrasound transducers placed across the left ventricle for measuring the extent and velocity of wall shortening and a micromanometer measuring left ventricular cavity pressure. Transaortic constriction was performed using an inflatable rubber cuff around the proximal aorta to maintain an average systolic blood pressure of 210 mmHg. Ventricular pressures and dimensions were recorded prior to constriction, immediately after constriction, at an early phase after constriction (average 9 days), and a later phase (average 2.5 weeks). Calculations of wall forces relied on a spherical model. Immediately after constriction, there was a decrease in ventricular wall thickness and a 55% increase in calculated peak wall stress above control. Percentage shortening fell by 24% acutely and mean circumferential shortening velocity (V_{CF}) decreased by 39% from control. In the acute phase (mean 9 days), the ventricles were seen to dilate with a 4% increase in end-systolic diameter and peak wall stress fell to 37% above control despite a constant peak systolic left ventricular pressure averaging 210 mmHg. Percentage shortening and

mean V_{CF} remained below control levels at −12% and −20%, respectively. By the later phase at mean 2.5 weeks, the left ventricular walls had significantly hypertrophied with a 15% increase in ventricular wall cross-sectional area above control, with the increased wall thickness successfully reducing peak wall stress to 22% above control. End-diastolic diameter and percent shortening returned to normal [16]. The ventricle was considered to have successfully compensated at this time point by resuming its baseline fractional shortening in the face of a marked sustained elevation in afterload. This study reinforces the concept that the initial afterload mismatch, which causes an acute reduction in stroke volume, can be overcome by the development of physiological hypertrophy with thickened walls once again generating baseline stroke volumes. However, the limited duration in this early proof of concept study does not permit observation of the rapidly hypertrophied heart as it continues to maintain the higher degree of pressure generation against an increased afterload over time. The technique of transaortic banding has been applied to many species of experimental animal models, most commonly mice, enabling investigators to study the development of physiological hypertrophy and subsequent progression to heart failure, so elucidating the myocardial signaling pathways that govern the hypertrophic response [17].

Ventriculo-Arterial Coupling and Pressure–Volume Loops

The relationship between the ventricle and its afterload is key to the concept of ventriculo-arterial coupling and can be illustrated by pressure–volume loops. The effective arterial elastance (E_a) describes the ability of the vessel to accommodate pulsatile flow. E_a can be calculated by dividing the end-systolic pressure by the stroke volume and is, therefore, the slope of the stress/strain or pressure/diameter graphs ($\Delta P/\Delta D$), also known as the end-diastolic pressure–volume relationship. Elastance is the reciprocal of compliance, compliance being the ease of distension. At lower levels of arterial pressure, the arterial wall is supported by compliant elastin fibers, whereas the stiffer collagen fibers predominate at higher pressures. Therefore, the slope of the curve will be greater at higher levels of arterial pressure. Collagen in the human aorta is at least 500 times stiffer than elastin, and the aortic wall collagen content more than doubles from age 20 to 70 years (Fig. 2.5).

During the left ventricular ejection phase of the cardiac cycle, as ventricular volume decreases, the potential for the ventricle to develop pressure also drops. The smallest volume reached is the end-systolic volume, which marks the point of full stroke volume ejection. The aortic valve subsequently closes and the diastolic phase begins. The end-systolic volume at a certain degree of contractility and preload will, therefore, be determined by the afterload. A rise in aortic pressure, all else being equal, will correlate with a decreased stroke volume and a lower aortic pressure with an increased stroke volume. For example, in an individual with aortic stenosis, the pressure–volume loop may show a higher peak pressure, a lesser stroke volume, and an increased end-systolic volume, so shifting the curve into a taller and narrower configuration. Over time, compensatory hypertrophy will mitigate the high wall stress and improve the ventricle's ability to overcome the high afterload and increase the stroke volume, thus causing the loop to increase in width. With a sudden increase in afterload, the stroke volume will be diminished, which causes the end-systolic volume to rise. Over the following few beats, the increase in end-systolic volume predominates over the increased end-diastolic volume (which usually augments ventricular function), with the net change being a decrease in stroke volume and hence a decrease in the width of the pressure–volume loop. With a reduced afterload, the left ventricle ejects blood with greater ease, so augmenting the stroke volume and decreasing end-systolic volume. With less blood remaining in the ventricle after the ejection phase, the ventricle will fill to a lesser end-diastolic volume compared to prior the afterload reduction. Despite this mild reduction in preload, stroke volume shows a net increase because the reduction in end-diastolic volume is less than the reduction in end-systolic volume.

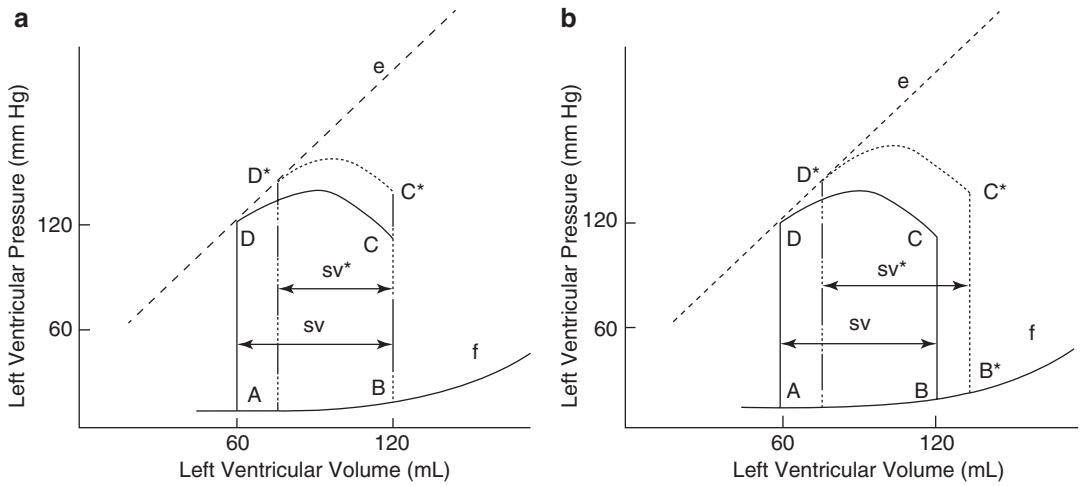
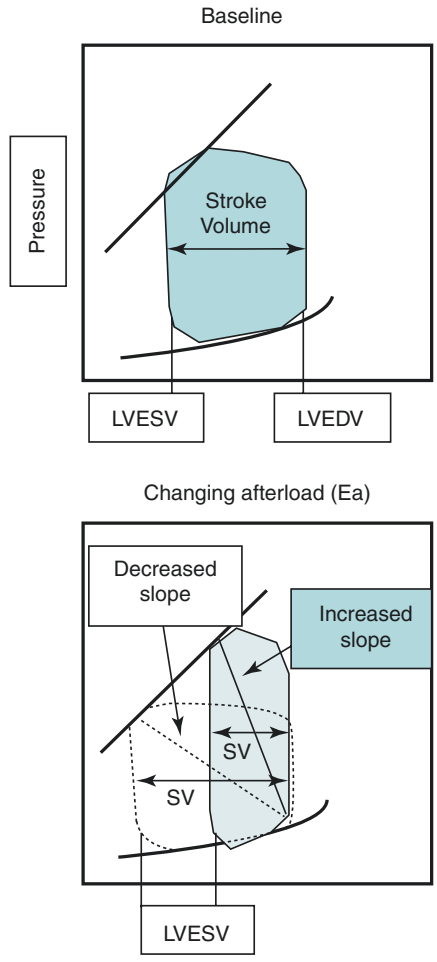


Fig. 2.5 Effects of acutely increasing afterload on the pressure–volume loop. . *A* mitral valve opens, *B* mitral valve closure, *C* aortic valve opens, *D* aortic valve closure, *e* end-systolic pressure–volume relationship, *f* end-diastolic pressure–volume relationship (or ventricular elastance). The dotted loop represents the effect of increasing afterload. Panel b demonstrates the impact of afterload plus (dotted loop) increased preload, increased end-diastolic volume, and therefore preservation of stroke volume. (From Iaizzo [19])

The ratio of the effective arterial elastance to the E_{es} (the slope of the ventricular end-systolic pressure–volume relationship) represents a measure of pump efficiency in expelling blood into the vasculature. This value can be used as a reflection of the ventriculo-arterial coupling and helps conceptualize the relationship between the pump and the vasculature. As E_a increases initially, the arteries accommodate greater blood flow, permitting a greater stroke work. If E_a were to continue to increase, the stroke work would reach a maximal plateau value where arterial and ventricular properties are equal, meaning that $E_a = E_{es}$. The E_a also increases with improvements in ventricular efficiency, which is defined by external stroke work/MVO_2/beat. Ventricular efficiency is maximal at $E_a = E_{es}/2$, meaning that the most favorable ventriculo-arterial coupling occurs when the E_a/E_{es} ratio lies in the range 0.5–1.0 [18] (Fig. 2.6).

Afterload and Cardiac Efficiency

The heart requires significant energy generation to perform its functions. Cardiac metabolism is predominantly aerobic, and hence, the work performed by the heart is typically gauged in terms of myocardial oxygen consumption (MVO_2). Myocytes are densely packed with mitochondria to generate sufficient ATP, predominantly from fatty acid breakdown, to fulfill the required cellular mechanics to sustain the cardiac cycle. The energy required for development and maintenance of systolic wall tension is a key factor in determining myocardial energy expenditure. One hallmark of the failing heart is its disordered and inefficient myocardial metabolism. The degree of afterload is also highly relevant in the ischemic heart, where reducing afterload and reducing heart rate are the major strategies in reducing myocardial oxygen consumption. A systolic pressure increase of only 20–30 mmHg can have a dramatic negative impact on function in a failing or ischemic left ventricle, both by inducing a lower stroke volume and by raising myocardial oxygen demands. Oxygen extraction in the capillary bed is near-maximal, and hence, the capacity to meet the oxygen demands of the myocardium may not be possible in the setting of a high afterload, especially if coronary blood flow can no longer be increased due to flow-limiting stenoses. The other determinants of myocardial oxygen demand are the heart rate, preload, and contractility. The MVO_2 in the rest-



$$EF = \frac{SV}{LVEDV} = \frac{\text{Width of PV Loop}}{LVEDV}$$

Fig. 2.6 The pressure–volume relationship and elastance. Increased elastance, as illustrated by the steeper diagonal slope, leads to smaller stroke volume. (From Bashore [35])

ing heart is approximately 8 mL O_2/min per 100 g [19]. The instantaneous cardiac oxygen consumption can be measured in a human heart by employing the Fick principle; however, this does require catheterization of the coronary sinus to directly measure the venous oxygen saturation and coronary blood flow. Therefore, indirect assessments of the MVO_2 are necessary. Relative changes can be estimated by calculating the pressure-rate product. A simple method, described as early as 1912 using isolated cat and rabbit myocardium, is multiplication of the heart rate with the systolic blood pressure [20]. This noninvasive hemodynamic determinant of oxygen consumption has been validated by other investigators using the isolated dog heart, with the aortic pressure being shown to be the dominant influence in determining myocardial oxygen requirement. A 175% increase in work with afterload elevation was matched with a 178% increase in oxygen consumption as calculated by the product of coronary flow and coronary arteriovenous oxygen difference [21]. These investigators also established the use of the time-tension index/beat in mmHg seconds, derived from the area under the systolic portion of the aortic pressure curve, as an alternate metric of oxygen consumption. They also point out, by the Law of LaPlace, that the generation of the same intraventricular time-tension index will require greater myocardial fiber tension in a large radius heart compared to a smaller one. This fact highlights the inherent mechanical inefficiency of the dilated failing heart. Also of note is a study using healthy humans that demonstrated a corre-

lation of 0.88 between MVO_2 and heart rate alone and 0.90 using the rate–pressure product [22] although some authors have emphasized the limitations of these indirect indices of MVO_2 which do not capture all potentially important changes in myocardial contractility and ventricular dimensions, particularly in less healthy subjects [23].

The Law of LaPlace can also be used to explain why the pressure-overloaded left ventricle (such as that associated with aortic stenosis) will incur a higher myocardial oxygen demand than the volume-overloaded ventricle (as in aortic regurgitation). LaPlace stated that wall tension is proportional to $PR/2$, where P is chamber pressure and R is chamber radius. The pressure-overloaded ventricle shows a large increase in the pressure variable, which will equate to much higher wall tension, and hence MVO_2. Conversely, in the volume-overloaded ventricle, the radius will increase, but not as dramatically as the pressure in the pressure-overload model. Hence, the rise in wall stress in the volume-overload setting will be less substantial, and the corresponding MVO_2 less dramatically elevated.

Afterload in Clinical Practice

Afterload in the Pulmonary Vasculature

Afterload is most frequently discussed in reference to the left ventricle, but can also be applied to the right ventricle and the pulmonary vasculature into which this chamber pumps. It should be noted that significant differences exist in the manners in which the right and left ventricle handle increases in their afterloads. Normally, the resistance to flow in the pulmonary vascular system is much lower at about one-tenth of the resistance met by the left ventricle for the same stroke volume. The thicker walled left ventricle is able to generate much greater pressures and usually successfully generates unchanged stroke volumes in the face of afterload increases. The right ventricle operates much nearer to its full contractility capacity, because it has only a sixth of the muscle mass of the left ventricle and yet performs a quarter of the work. It succeeds in pumping the same cardiac output as the left ventricle due to the much lower resistance in the pulmonary vasculature than the systemic circulation. Operating within this closely matched ventriculo-arterial framework, the right ventricle is extremely sensitive to elevations in its afterload. Even a structurally normal right ventricle may decrease its stroke volume to small elevations in pulmonary vascular resistance. However, the right ventricle can also remodel and adapt to higher pulmonary pressures with time, with the maximal mean artery pressure normally accommodated without right ventricular failure being in the order of 40 mmHg. Severe right ventricular dilatation and dysfunction usually result from its attempts to compensate and maintain stroke volume as the pulmonary pressures rise beyond this [24].

- The pulmonary arterioles also serve as the site of major resistance to flow; however, the pulmonary arterioles receive a more pulsatile input of blood flow than their systemic counterparts. Within this much smaller vascular system, the roles of cushion, conduit, and resistance are not as clearly ascribed to certain generations of vessels as in the systemic circulation. Pulmonary hypertension is currently defined as a mean pulmonary artery pressure of greater than 25 mmHg, with a pulmonary capillary wedge pressure less than 15 mmHg indicating that the hypertension is not secondary to left-sided heart disease [25]. The various etiologies of pulmonary hypertension all tend to show common histopathology features, namely, initial fibrosis, medial thickening, and pulmonary arteriolar occlusion [26]. Right ventricular afterload reduction with pulmonary vasodilators is key to the management of pulmonary hypertension and right ventricular failure. Inhaled nitric oxide has a role during the invasive assessment of pulmonary vascular pressures to help determine the potential for pulmonary vasodilatation, and the use of continuous oxygen therapy can help reduce the degree of hypoxic vasoconstriction. Pulmonary hypertension therapeutics include calcium channel antagonists (nifedipine, amlodipine), prostacyclin analogs (epo-

prostenol, treprostinil, iloprost), endothelin receptor antagonists (bosentan, ambrisentan, macitentan), phosphdiesterase-5 inhibitors (sildenafil, tadalafil), and soluble guanylate cyclase simulators (riociguat) [27].

Afterload and the Respiratory Cycle

The potential for mechanical ventilation to affect invasive assessments of preload (such as the right atrial and pulmonary capillary wedge pressures) and possibly reduce preload by decreasing the pressure gradient into the thorax was discussed in Chap. 1. Positive pulmonary pressures during mechanical ventilation also affect afterload. The degree of pulmonary vascular resistance, and hence RV afterload, is proportional to the degree of airway pressure elevation. With significant RV afterload elevations, the right ventricle will dilate and induce intraventricular dependence, with shifting of the septum into the left ventricle, which reduces left ventricular filling and stroke volume. Conversely, the direct effect of positive airway pressure on the left ventricle is to increase stroke volume by increasing the intrathoracic aortic pressures relative to peripheral arterial pressure. Also worth mentioning in the consideration of valvular lesions and afterload is the effect of mitral regurgitation on the degree of cardiac afterload. Mitral regurgitation will decrease afterload because, during ventricular systole, a fraction of the left ventricular end-diastolic volume will take a retrograde route and flow back into the left atrium through the incompetent valve. Hence, the left ventricle will be working against a reduced afterload, as some blood ejection is into the lower-pressure atrium rather than the usual anterograde flow into the higher-pressure aorta.

Total Peripheral Resistance

The term "total peripheral resistance" (TPR) encompasses the sum of all regional resistances in the systemic circulation. It is sometimes used to infer the total afterload faced by the heart, although as we have already seen the resistance to flow, largely imposed by the arterioles, is actually only one component of the complete cardiac afterload. TPR can be approximated from Ohm's law. In the patient with Swan-Ganz calculations of cardiac output, values for systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) are routinely derived in Wood units from:

$$\text{SVR} = 80 \times \left(\text{mean arterial pressure} - \text{mean right atrial pressure}\right) / \text{cardiac output}$$

$$\text{PVR} = 80 \times \left(\text{mean pulmonary artery pressure} - \text{pulmonary capillary wedge pressure}\right) / \text{cardiac output}$$

These equations give values in dyn s cm^{-5}. Other units for measuring vascular resistance are pascal seconds per cubic meter (Pa s/m^3), or for convenience when using pressure in mmHg and cardiac output in l/min, resistance can be expressed in mmHg min/L. This equates to hybrid reference units (HRU), also known as Wood units, favored by pediatric cardiologists. Multiplying by a factor of 8 converts from Wood units to MPa s/m^3 or by a factor of 80 converts from Wood units to the international unit of dyn s cm^{-5}.

The resistances imposed by the arterial system are arranged in both serial and parallel orientations. In a circuit where resistances lie in series, the total resistance will be the sum of the individual resistive components. Conversely, a parallel circuit will have a total resistance equaling the sum of the reciprocals of the individual resistive components, thus creating a much lower overall resistance than in a series circuit. Therefore, most organ arterial supplies are configured in a parallel arrangement, so limiting the pressure generation required by the ventricle to perfuse all organs. A rise in resistance within one organ bed will have minimal impact on the other arterial beds.

The majority of the resistance component of arterial input impedance lies in the arterioles.

These vessels range 10–150 μm in diameter and are under constant vasoactivity regulation from the sympathetic nervous system and local mediators, thus controlling the flow of blood into specific capillary beds. Local vasodilators include platelet-derived substances, such as serotonin, and endothelium-derived mediators, such as nitric oxide.

Therapeutic Afterload Reduction

The concept of therapeutic afterload reduction was initially clinically applied in the form of intra-aortic balloon counterpulsion to support patients with cardiogenic shock post myocardial infarction. This technique was demonstrated to unload the left ventricle, enhance left ventricular ejection fraction, and improve coronary artery perfusion. Pharmacological afterload reduction strategies for unloading the left ventricle, principally the use of a sodium nitroprusside infusion, are useful tools in acute cardiac care. Nitroglycerin, which combines more venodilation with arteriolar vasodilation in comparison to nitroprusside, may also be used for afterload reduction. The angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, hydralazine, and dihydropyridine calcium channel blockers are additional options, and clevidipine, an intravenous dihydropyridine drug, is increasingly used in critical care settings.

Vasodilating drugs have minimal direct effect on the large elastic arteries, but can markedly reduce reflected wave amplitude from the periphery by decreasing elastance of the smaller muscular arteries. The decreased amplitude and velocity of the reflected wave decreases systolic arterial pressure and increases proximal aortic flow during the deceleration phase. The resulting afterload reduction can help to optimize cardiac output and clinical status in patients with cardiogenic shock, severe mitral or aortic regurgitation, or even aortic stenosis with decompensated left ventricular dysfunction [28], by correcting the afterload mismatch. The afterload tends to be high in decompensated heart failure due to activation of the renin–angiotensin–aldosterone system, as well as a higher effective blood velocity due to slow forward flow. Although the sympathetic activation causing vasoconstriction in heart failure is compensatory to maintain arterial blood pressure despite low output, these adaptations can be counterproductive and impose further afterload on the failing ventricle. Pharmacological afterload reduction can, therefore, achieve marked improvements in cardiac output and symptoms for patients with a dilated left ventricle and sufficient preload reserve (Fig. 2.7).

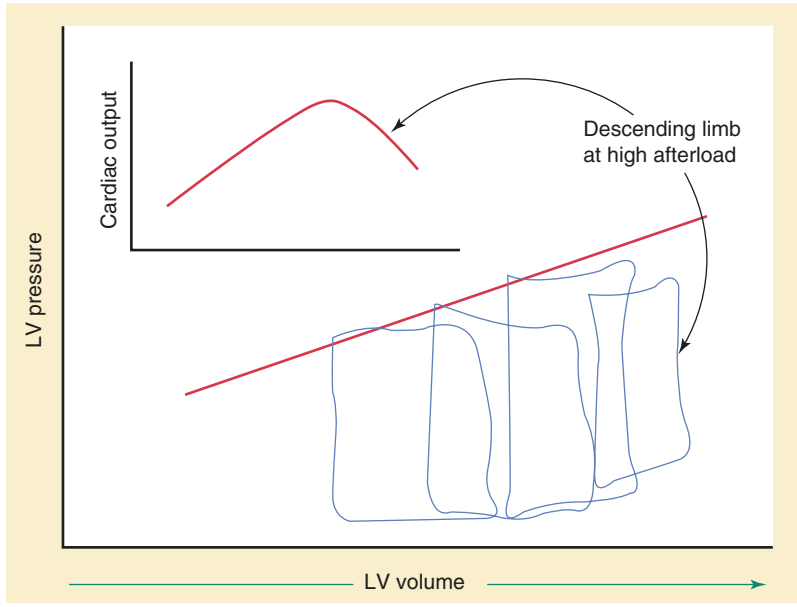


Fig. 2.7 Conditions for afterload mismatch in systolic heart failure. (From Ross [15]). The stroke volume is seen to decrease (decreased width of the pressure–volume loop) as afterload increases

The use of afterload reduction in patients with aortic stenosis may initially seem counterintuitive as the cardiac output across a stenotic aortic valve has traditionally been considered to be fixed with a risk of hypotension without improvements in output if the blood pressure is lowered. However, this scenario underlines the complexity of afterload, because the aortic stenosis in not actually the sole factor determining the force against which the ventricle must pump. Resistances in series are additive, and so the resistive component of aortic input impedance can still be lowered by reducing the most distal resistances in the arterioles despite the proximal resistance across the valve remaining constant. The reduction in total peripheral resistance and hence mean arterial pressure with nitroprusside can, therefore, successfully reduce the afterload mismatch of the dysfunctional ventricle pumping against a high afterload despite the presence of severe and fixed aortic stenosis. Conversely, the administration of nitroprusside to a relatively normal cardiovascular system, or to the heart with aortic stenosis but a preserved ejection fraction, would be expected to lower the cardiac output. This is due to some concurrent venodilation, which will reduce preload and actually induce an afterload mismatch. Another setting where pharmacological afterload reduction can precipitate a worsened clinical status is in the setting of a significant pulmonary shunt. Nitroprusside can inhibit the hypoxic vasoconstriction in a region of pulmonary vasculature, thus supplying blood flow to an area of the lung not receiving good oxygenation (e.g., due to lobar consolidation). This will exaggerate a perfusion–ventilation mismatch and potentially worsen the arterial oxygen saturation. The use of nitroprusside as a lone afterload reducer in the setting of ischemia should also be avoided. Nitroprusside has been shown to decrease myocardial perfusion in the setting of coronary stenoses, whereas nitroglycerin can enhance myocardial perfusion, largely through dilatation of coronary collateral vessels [28, 29].

Bullet Point Summary

- Afterload consists of the forces against which the heart pumps to expel blood into the vasculature.
- Afterload can be defined in terms of wall stress, using the law of LaPlace.
- Alternatively, afterload can be conceptualized as arterial input impedance, drawing parallels from electrical circuits.
- An inverse relationship exists between stroke volume and afterload.
- The aorta and proximal large arteries have a higher ratio of elastic to collagen and are, therefore, highly compliant.
- These elastic arterial walls absorb the systolic pulsations in blood flow, converting stored energy into recoil that maintains the pressure and flow during diastole – the Windkessel effect.
- The arterioles are the site of the majority of arterial resistance, with arteriolar tone being highly dependent on the sympathetic nervous system and local mediators.
- Reflected waves from bifurcations and arterial discontinuities can increase afterload when they return to the proximal aorta during systole.
- With aging, or pathological processes such as hypertension, afterload rises due to increased magnitude of the incident systolic wave and also early return of the reflected wave.
- Afterload mismatch is a scenario in which the ventricular performance is not well coupled to the afterload it encounters, which increases myocardial oxygen consumption and decreases cardiac energy efficiency.
- Over time, an afterload mismatch can induce ventricular hypertrophy.
- Intra-aortic balloon counterpulsion, and drugs such as nitroprusside, hydralazine, and ACE inhibitors, can decrease systemic afterload.
- Pulmonary vasodilators are the cornerstone of pulmonary hypertension management and decrease the afterload faced by the right ventricle.

Review Questions

1. The primary determinant of cardiac output is:
   (a) Preload
   (b) Myocardial contractility
   (c) Heart rate
   (d) Afterload
   Answer is (a).

2. Which one of the following statements regarding the vasculature is *false*?
   (a) With aging, changes in the media of the large elastic arteries cause them to stiffen.
   (b) Vascular compliance is heart rate dependent.
   (c) The small peripheral vessels show a prominent Windkessel effect.
   (d) Retrogradely reflected pressure waves usually arise from arterial branch points such as the iliac bifurcation.
   (e) A reflected wave falling during diastolic is more advantageous to the cardiovascular system,

   Answer is (c). It is the proximal elastic arteries that show the Windkessel effect. The smaller peripheral arteries and arterioles have the capacity to vasoconstrict substantially, but they are not exposed to highly pulsatile blood flow and do not have the elastic properties to permit significant recoil if the pressure within the vessel falls. A reflected wave falling within diastole can help to augment coronary blood flow.
3. Which one of the following statements is true regarding the concept of afterload mismatch?
   (a) Afterload mismatch can occur when the patient is vasodilated.
   (b) An increase in afterload is usually accompanied by a decrease in venous return, due to decreased availability of blood in the venous system.
   (c) Afterload mismatch may occur with sudden infusion of vasopressor in the setting of volume depletion.
   (d) Afterload mismatch can be induced in a normal left ventricle with high preload, when a sudden increase in both afterload and myocardial contractility occurs.
   (e) A chronic afterload mismatch does not result in structural myocardial changes.

   Answer is (c). Under normal physiologic circumstances, an increase in afterload is usually accompanied by increased venous return, due to movement of blood from the arterial to venous systems. A mismatch can be induced acutely in a normal heart if end-diastolic volume is not allowed to compensate for the increase in afterload. Alternatively, additional afterload applied to a ventricle already working at a maximal end-diastolic volume will cause a sharp drop in stroke volume, unless contractility is also enhanced.
4. Which one of the following statements is true regarding potential strategies to reduce afterload clinically?
   (a) The goal of intra-aortic balloon counterpulsion is to lower systolic blood pressure and hence reduce afterload.
   (b) In the setting of some pulmonary conditions, nitroprusside can cause hypoxia.
   (c) Afterload reduction is strictly contraindicated in the setting of a fixed obstructive lesion such as aortic stenosis.
   (d) The sympathetic activation causing vasoconstriction in heart failure is compensatory to maintain blood pressure despite low cardiac output, and hence, afterload reduction should be avoided.
   (e) Sildenafil is a selective pulmonary arterial vasodilator and has no effect on the systemic vasculature.

   The answer is (b). Nitroprusside can inhibit the hypoxic vasoconstriction in a region of pulmonary vasculature, thus supplying blood flow to an area of the lung not receiving good oxygenation (e.g., due to lobar consolidation). This will exaggerate a perfusion–ventilation mismatch and potentially worsen the arterial oxygen saturation. Intra-aortic balloon counterpulsion augments diastolic blood pressure, thus reducing left ventricular wall stress. Afterload reduction with an IABP or nitroprusside may be indicated in acutely ill patients with severe aortic stenosis and a reduced left ventricular ejection fraction. Vasodilation in the setting of decompensated systolic heart failure can correct an afterload mismatch and improve the cardiac output. Sildenafil does have some peripheral vasodilating affects, and hence, dosage may be limited by systemic hypotension.

5. A 70-year-old male with severe aortic stenosis (peak/mean pressures by echocardiography 68/42 mmHg, aortic valve area by continuity equation 0.6 cm^2) presents with worsening dyspnea, lower extremity edema, oliguria, and a 15-lb. weight gain. The blood pressure is 88/74. He is peripherally cool and mildly confused. The left ventricular ejection fraction on his most recent echo was 25%. Are the following statements true or false?
   (a) Due to the severity of the aortic valve stenosis, the only option for reducing afterload is valvuloplasty or valve replacement.
   (b) There is an afterload mismatch.
   (c) Pressure recovery may lead to overestimation of the valve gradient by Doppler measurements and is more likely to occur with smaller ascending aorta diameter.
   (d) The calculated SVR is likely to be elevated; a lower than expected SVR may suggest a septic component to the hypotension.
      (a) False. The total resistance presented by the arterial system is the sum of the many components arranged in series through the vasculature. The significant resistive contribution provided by the arterioles is additive to the resistance imposed by the stenotic valve. Therefore, the afterload can be reduced by vasodilatation of the arterioles.
      (b) True. Although we do not have invasive hemodynamics provided for this patient, the cool peripheries, delayed mentation, and oliguria strongly suggest a low cardiac output state. Therefore, the poor ventricular performance is not well matched to the high afterload imposed by the aortic stenosis plus peripheral vasoconstriction due to the activation of the renin–angiotensin system in cardiogenic shock. Better matching of the low stroke volume may be achieved through peripheral vasodilatation, if this can be tolerated by the low blood pressure. Aortic balloon counterpulsion and/or low doses of intravenous nitroprusside may be successful in improving the cardiac output and stabilizing the decompensated patient ahead of definitive aortic stenosis management.
      (c) True. Pressure recovery is a phenomenon arising from the decrease in velocity and increase in pressure in the proximal aorta, beyond the stenotic aortic valve. This can lead to overestimation of the valve gradient by Doppler measurements and is more likely to occur with smaller ascending aorta diameter.
      (d) True. As described above, the systemic vascular resistance would be expected to be at the higher end, or above, the normal range for SVR. A value in the range of 1200–2500 dyn s/cm^5 would be consistent with the scenario. If the calculated value lies much below this, consideration should be made of an additional distributive shock process, such as sepsis. Of note, a patient with cardiogenic shock and a poor cardiac output can sometimes be seen to have an encouraging rise in their mixed venous saturation, cardiac output, and a fall in the SVR, with the actual etiology being early sepsis causing peripheral vasodilatation.
6. A 55-year-old female with hypertension, diabetes, and chronic kidney disease presents acutely dyspneic. Her blood pressure is 210/110 mmHg, right atrial pressure 15 mmHg, and heart rate is 92 bpm. Her examination is consistent with pulmonary edema. A diagnosis of hypertensive emergency is made. Are the following statements true or false?
   (a) The decrease in arterial compliance associated with hypertension and diabetes is most pronounced in the arterioles.
   (b) Effective arterial elastance is calculated by dividing the stroke volume by end-systolic pressure.
   (c) If the mean arterial pressure is known to be 143 mmHg and the cardiac output

4.0 L/min, the systemic vascular resistance will calculate in the region of 2500 dyn s/cm5.

(d) If this patient receives an arteriovenous fistula in preparation for future hemodialysis, the afterload would be expected to fall and the preload increase.

(a) False. The arteriosclerosis associated with hypertension and diabetes is most prominent in the large elastic arteries. The enhanced incident wave increases afterload, as does the early return of reflected pressure waves.

(b) False. Effective arterial elastance is calculated by dividing the end-systolic pressure by the stroke volume. It is visualized as the slope on the stress/strain graph.

(c) True. MAP = (2 × diastolic pressure + systolic pressure)/3 = 143. SVR = 80 × (MAP − RA pressure)/cardiac output = 80 × (143 – 15)/4 = 2560.

(d) True. Creation of a shunt from the arterial to venous system would be expected to decrease the afterload by directing blood flow away from the high resistance arterioles into the lower resistance venous system, and so enhancing venous return to the heart. The decreased afterload has been shown to slightly reduce myocardial oxygen demand, but also negatively impacts the coronary blood flow [30].

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Contractility

3

Jordan S. Thomas and Justin M. Dunn

Introduction

Myocardial contractility—often referred to as inotropy—is the inherent capacity of the myocardium to contract *independent* of loading conditions, that is, preload and afterload (discussed in Chaps. 1 and 2, respectively). Thus, for a given preload and afterload, contractility is a manifestation of all other factors that influence the interactions between contractile proteins. The incorporation of all these factors makes a simple definition of "contractility" difficult, and it is more easily understood through discussions of *changes* in contractility. Clinically, a change in left ventricular contractility can be defined as a change in the work performed per beat at a constant end-diastolic volume and aortic pressure.

Contractility is best understood by assessing the rate of rise of left ventricular pressure or dP/dt (Fig. 3.1). The contours of these left ventricular pressure curves provide a reasonable index of myocardial contractility. The slope of the ascending limb of each curve indicates the maximal rate of force development by the ventricle. The maximal rate of change in pressure over time, also referred to as the maximum dP/dt, is shown by the tangents to the steepest portion of the ascending limb of each curve. This slope is maximal during the isovolumic phase of early systole in the cardiac cycle, from closure of the mitral valve until opening of the aortic valve (Fig. 3.2).

Accurate clinical measurement of contractility is difficult. In the cardiac catheterization lab, the maximum rate of pressure development (dP/dt_{max}) can be measured during isovolumetric contraction by placing catheters directly in the ventricle. This measurement is often used as an index of contractility [3]. Decreases in left ventricular dP/dt_{max} below the normal value of 1200 mmHg/s suggest depressed myocardial contractility.

The ejection fraction (EF), defined as the ratio of stroke volume to end-diastolic volume, is widely used clinically as a noninvasive surrogate index of cardiac contractility [4]. In current practice, EF is most often measured noninvasively with echocardiography, but alternative methods including nuclear imaging and, more recently, cardiac MRI also exist with each having their own relative strengths and weaknesses. Normal ejection fraction reference values vary depending on gender and the imaging modality used. In clinical practice, however, a range of approximately 50–70% can be considered normal by the majority of imaging modalities, while an EF less than 50% suggests at least some degree of depressed myocardial contractility.

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_3

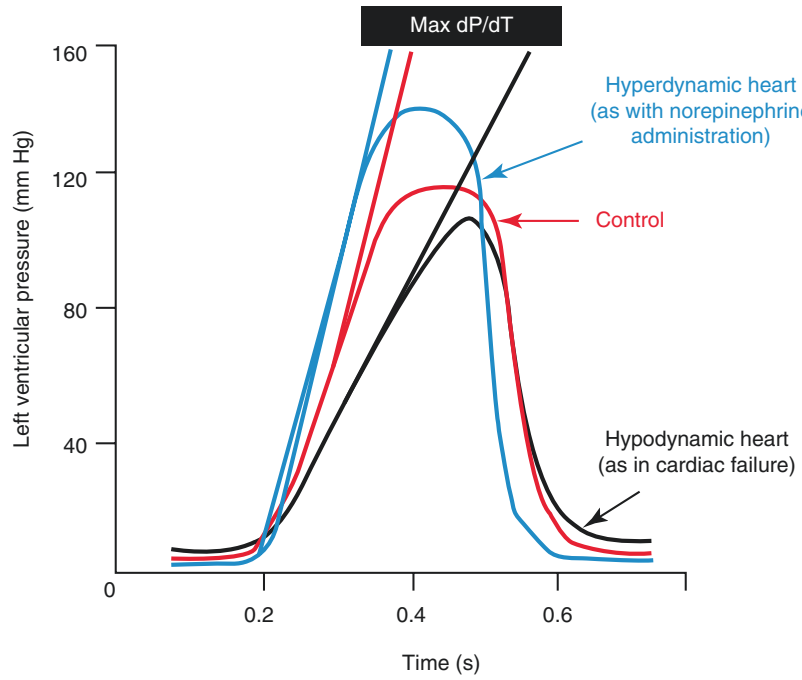

Fig. 3.1 Left ventricular pressure curves with tangents drawn to the steepest portions of the ascending limbs to indicate maximal dP/dt values. *Red*: Control. *Blue*: Hyperdynamic heart, as with norepinephrine administration. *Black*: Hypodynamic heart, as in cardiac failure. (Adapted from Berne and Levy [1], p. 313, Fig. 16.9)

With recent advancements in imaging techniques, 2D speckle tracking echocardiography (STE) with strain imaging has become a key noninvasive tool and is one of the most direct measurements of both global and segmental myocardial tissue deformation and underlying contractility. With its high sensitivity and reproducibility, strain echocardiography has been validated in multiple cardiovascular disease states and holds tremendous promise in both clinical and research settings [5].

Physiology of Contraction

Contraction of cardiac muscle begins when a wave of excitation spreads via gap junctions along the myocardial sarcolemma and into the cells via T tubules. During phase 2 of the action potential, calcium permeability in the sarcolemma increases, and calcium enters the cell via calcium channels in the sarcolemma/T tubules (invaginations in the sarcolemma). This extracellular calcium triggers the release of a much larger store of calcium from the sarcoplasmic reticulum within the cell. This calcium then binds to troponin C forming the calcium–troponin complex, which subsequently interacts with tropomyosin to unblock active sites between the thin actin and thick myosin filaments and allows cross-bridge cycling and thus contraction to occur.

To understand the concept of contractility, it is important to revisit the underlying mechanisms by which contractility changes, beginning at the cellular level. This discussion must begin with the fundamental role of calcium in cardiac contraction and relaxation. With each spontaneous wave of excitation in the myocardium, sodium channels in the sarcolemma are opened by an action potential. Sodium moves into the cytosol depolarizing the membrane. Depolarization opens voltage-gated L-type calcium channels in the sarcolemma/T tubules, allowing an influx of calcium from the extracellular space. Each calcium channel controls a number of calcium release channels which are composed of four ryanodine receptors in the membrane of the sarcoplasmic reticulum. The influx of calcium through the L-type calcium channels triggers a conformational change in the ryanodine receptors, which allows calcium to flow from the sarcoplasmic reticulum into the cytosol via the

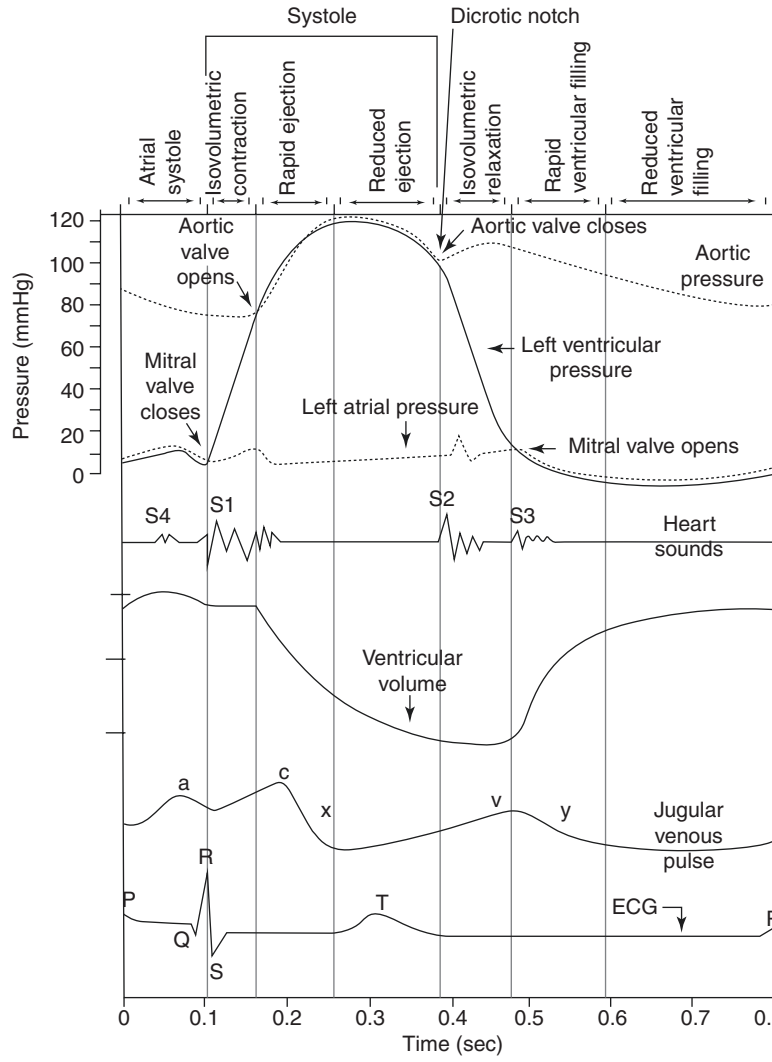

Fig. 3.2 Left atrial, aortic, and left ventricular pressure pulses correlated in time with aortic flow, ventricular volume, heart sounds, venous pulse, and the electrocardiogram for a complete cardiac cycle. (Adapted from Berne and Levy [2], p. 313, Fig. 16.10)

calcium release channels. The amount of calcium released from the sarcoplasmic reticulum is approximately 10 times the amount entering from the extracellular space (Fig. 3.3).

During systole, calcium in the cytosol binds to troponin C, initiating myocardial contraction by relieving the baseline inhibition of the contractile proteins (thin actin filament and thick myosin filament) by troponin I. When cytosolic calcium levels are low, the troponin complex (troponin C/I/T) holds tropomyosin in a position on the thin actin filament that prevents interaction between the cross-bridges on the thick myosin filament and the myosin-binding sites on the thin actin filament. When calcium binds to troponin C, a conformational change occurs, which weakens the bond between troponin I and actin. This conformational change moves the tropomyosin away from the myosin-binding sites and allows the myosin cross-bridges to interact with actin (Fig. 3.4).

At the end of systole, the calcium influx from the extracellular space ceases and the sarcoplasmic reticulum is no longer stimulated to release calcium. The sarcoplasmic reticulum then begins to avidly take up calcium via an ATP-dependent process. A cAMP-dependent protein kinase A (cAMP-PKA) phosphorylates phospholamban, which in turn stimulates the sarcoendoplasmic reticulum calcium ATPase (SERCA) pump in the membrane of the sarcoplasmic reticulum to take up calcium

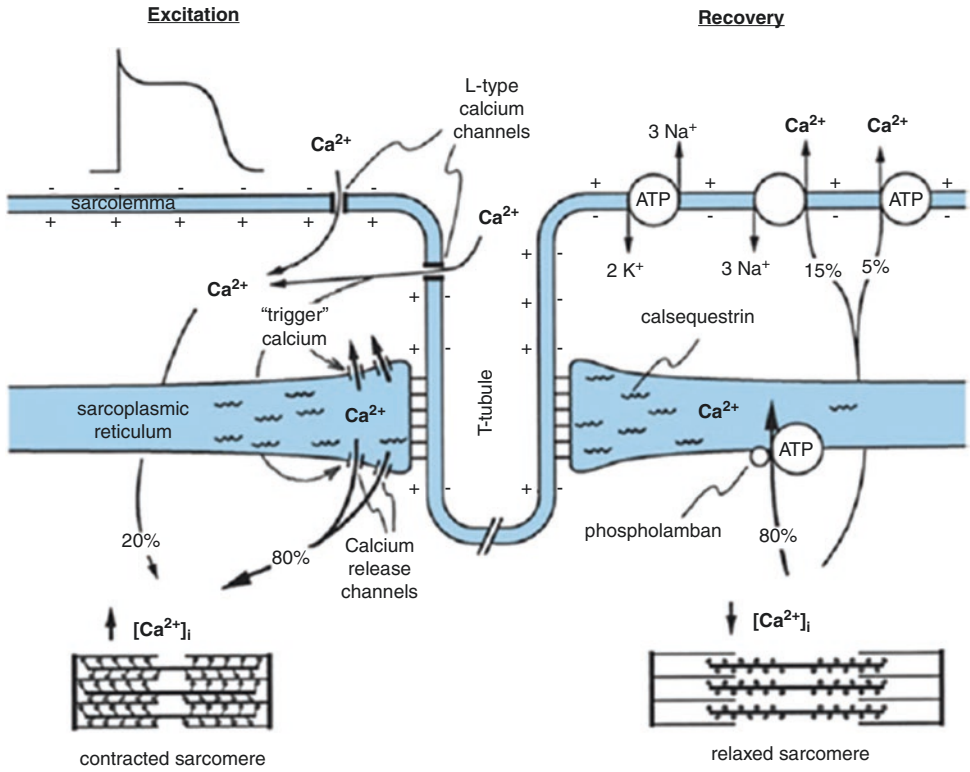

Fig. 3.3 Schematic diagram of the movements of calcium in excitation–contraction coupling in cardiac muscle. The influx of calcium (Ca^{2+}) from the interstitial fluid during excitation triggers the release of Ca^{2+} from the sarcoplasmic reticulum. The free cytosolic Ca^{2+} activates contraction of the myofilaments (systole). Relaxation (diastole) occurs as a result of uptake of Ca^{2+} by the sarcoplasmic reticulum, by extrusion of intracellular Ca^{2+} by Na^+–Ca^{2+} exchange, and to a limited degree by the Ca^{2+} pump. (Adapted from Berne and Levy [2], p. 365)

and facilitate relaxation. Phosphorylation of troponin I by cAMP-PKA also inhibits the calcium binding to troponin C, allowing tropomyosin to return to its resting inhibition of the myosin-binding sites and allowing diastole.

Cardiac contraction and relaxation are both enhanced by catecholamines, a physiologic phenomenon which has important clinical implications. Catecholamines (primarily endogenous norepinephrine, but also endogenous epinephrine) acting at the β receptor in the myocardial sarcolemma lead to the formation of cAMP from ATP and activation of PKA, which in turn increases the influx of extracellular calcium via increased opening of L-type calcium channels in the sarcolemma as discussed above. Catecholamines also enhance myocardial contractile force by increasing the rate of calcium release from the ryanodine receptor in response to calcium entry. The inotropic and lusitropic (relaxation) effects of catecholamine stimulation are mediated by the phosphorylation of phospholamban, accelerating calcium uptake into the sarcoplasmic reticulum by the SERCA receptors. Phosphorylation of phospholamban by cAMP-PKA removes its baseline inhibitory effect on SERCA receptors. While less physiologically significant, catecholamine stimulation of $\alpha 1$ receptors increases the formation of inositol 1,4,5-triphosphate (IP3) in the cytosol, which also stimulates some calcium release from the sarcoplasmic reticulum.

The parasympathetic nervous system has a much smaller effect on contractility as the vagus nerve fibers, mediated via acetylcholine at muscarinic (M2) receptors, are primarily distributed to the atria with very few to the ventricles. This explains the primary effect of parasympathetic stimulation on heart rate rather than contractility. However, under normal circumstances, there is a

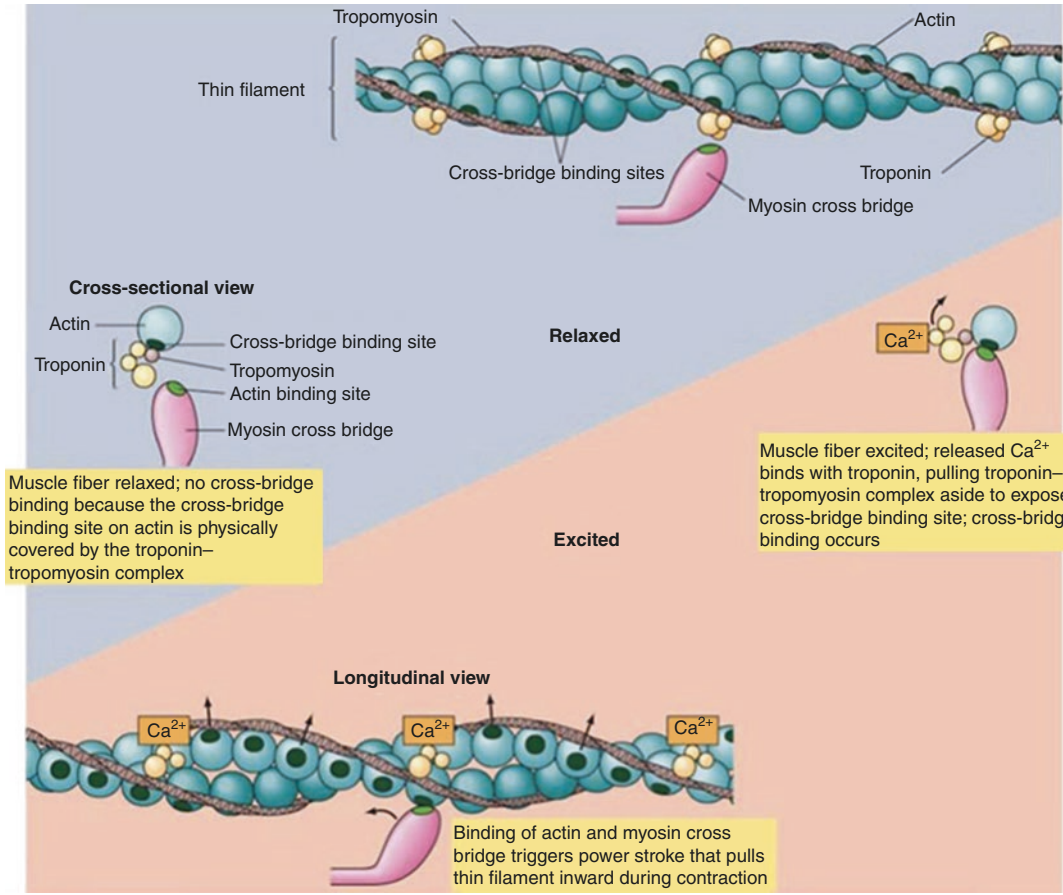

Fig. 3.4 Organization of the thin filament in both the relaxed and excited states. In the relaxed state, the myosin-binding site on actin is covered by the troponin–tropomyosin complex. In the presence of elevated calcium (Ca^{2+}), the troponin–tropomyosin complex is pulled away from the myosin-binding site when Ca^{2+} binds to troponin, allowing the myosin cross-bridge to interact with actin. Hydrolysis of ATP causes a conformational change in the myosin molecule, which pulls the actin filament toward the center of the sarcomere. A new ATP binds to myosin causing the release of the cross-bridge. If Ca^{2+} levels are still elevated, the cycle repeats. If Ca^{2+} are low, relaxation results

complex interplay between the sympathetic and parasympathetic nervous systems such that the sympathetic nerve fibers discharge continuously against tonic vagal inhibition.

There are two factors which affect inotropy that are worth mentioning despite the fact they are poorly understood: the Anrep effect and the Bowditch effect. The Anrep effect is the intrinsic ability of the heart to increase inotropy in response to abrupt increases in afterload [6]. This is seen in denervated hearts, suggesting it is an intrinsic mechanism. The other factor is the Bowditch or treppe effect, also called frequency-dependent activation. This is the ability of the heart to increase contractility slightly in the setting of an increase in heart rate [7]. This phenomenon is likely due to the inability of the Na/K-ATPase to keep up with the sodium influx at high heart rates, leading to an increase in intracellular calcium via the sodium–calcium exchanger.

Contractility in Cardiac Disease

Ischemia

Myocardial ischemia causes a decrease in contractility primarily by reducing ATP production in the mitochondria secondary to inadequate oxygen delivery [8]. This reduction in aerobic

ATP formation results in dysfunctional contractile shortening and reduced sarcoplasmic reticulum calcium pump function. Under these conditions, there is an increase in glycolysis, glucose uptake, and glycogen breakdown resulting in an increase in pyruvate [9]. Pyruvate is not readily oxidized in the mitochondria and is converted to lactate in the cytosol, resulting in a fall in intracellular pH [10]. When the intracellular pH falls, the sarcoplasmic calcium pump requires even more ATP to function properly [11]. In addition, the calcium concentration required for a given amount of myocyte force generation increases as the pH falls [12]. This leads to more ATP use in order to pump calcium back into the sarcoplasmic reticulum, leaving even less ATP to be used for contraction.

Heart Failure

At low inotropic states, the force-generating capabilities of ventricular muscle strips from normal and failing human hearts are similar [13]. As the inotropic demand increases, however, the ability of the failing heart to maintain its contractility reserve (the ability to increase contractility with heart rate or sympathetic stimulation) is severely depressed [14].

One of the major mechanisms of poor contractile reserve in heart failure is blunted adrenergic effects on myocyte contractility compared to normal myocardium [15]. Myocardium from heart failure patients shows significant reduction in beta-adrenergic receptor density, isoproterenol-mediated adenylyl cyclase stimulation, and contractile response to beta-adrenergic agonists [16]. The poor pump performance of the failing heart produces a reflex-mediated, sustained increase in sympathetic activity to maintain blood pressure [17]. It is this sustained sympathetic activity and an increased concentration of norepinephrine at the beta-adrenergic receptors that induce significant changes in beta-adrenergic signaling and downregulation of beta-adrenergic receptors [18]. In dilated cardiomyopathy, the $\beta 1$ receptor density is selectively reduced compared to the $\beta 2$ receptor which maintains its density but appears to be uncoupled from some downstream effector molecules. It is yet unclear whether adrenergic signaling abnormalities are adaptive or maladaptive in heart failure. By reducing LV contractility, desensitization may be detrimental; however, it may also be advantageous by reducing energy expenditure and protecting muscle from the effects of sustained adrenergic stimulation.

A second major mechanism contributing to altered contractility in the failing heart is abnormal calcium regulation within the myocyte. The sarcoplasmic reticulum is altered in heart failure such that the peak systolic cytosolic calcium level is decreased and the uptake of calcium into the sarcoplasmic reticulum is slowed. These abnormalities can explain features of systolic dysfunction including reduced force-generating capacity and slower rates of force decay [19] as well as diastolic dysfunction due to rate-dependent elevations in diastolic calcium levels [20]. There is some evidence to suggest that alterations in SERCA, L-type calcium channels, the ryanodine receptor, Na/K-ATPase, and the Na/Ca exchanger may all play some role in the initiation and progression of heart failure. Research continues in order to further elucidate the mechanisms of heart failure in the hope that targeted therapies may be developed.

Medications and Contractility [21, 22]

Dobutamine ($\beta 1 > \beta 2 > \alpha$)

Dobutamine is a synthetic sympathomimetic amine that approximates the hemodynamic profile of a pure $\beta 1$ agonist. The clinically available formulation is a racemic mixture of enantiomers. Both the (+) and (−) enantiomers stimulate $\beta 1$ receptors and, to a lesser degree, $\beta 2$ receptors. The (+) enantiomer, however, acts as an $\alpha 1$ antagonist, while the (−) enantiomer acts as an $\alpha 1$ agonist. Thus, the enantiomers essentially negate one another in their effect on the $\alpha 1$ receptor. The aggregate effect is that of an agonist at the $\beta 1$ receptor, leading to increased heart rate,

contractility, and diastolic relaxation. Dobutamine does have a modest agonist effect at peripheral β2 receptors causing mild peripheral vasodilation. Due to the increase in stroke volume secondary to its effects on contractility, however, blood pressure often does not change and can even increase despite the peripheral vasodilatory effects. Dobutamine is often used for short-term management of low output heart failure. Usual dosage: 2.5 μg/kg/min is initial dose, titrated to desired effect. Max dose is 20 μg/kg/min, though doses over 10 μg/kg/min are rarely needed. Onset of action is within 1–2 min, with a peak effect in 10 min. Drug effects cease very shortly after the drug infusion is discontinued. Tachycardia and ectopy are seen at higher doses, though these side effects are seen more frequently with dopamine.

Dopamine (D → β → α)

Dopamine is an endogenous sympathomimetic amine that functions as a neurotransmitter. It is a biosynthetic precursor of norepinephrine and epinephrine, and unlike dobutamine, it releases endogenous norepinephrine from stores in the nerve endings in the heart (this is overridden peripherally by prejunctional dopaminergic receptors which inhibit norepinephrine release). At low doses (<3 μg/kg/min), it has a peripheral vasodilatory effect by activating D1 receptors in the renal and mesenteric vascular beds. At intermediate doses (3–10 μg/kg/min), dopamine stimulates β1 and β2 receptors increasing heart rate, contractility, and peripheral vasodilation. At high doses (>10 μg/kg/min), dopamine begins to activate peripheral α1 receptors. This effect leads to a progressive increase in peripheral vasoconstriction with increasing doses. At these higher doses, the actions of dopamine become more like norepinephrine. Higher doses can also cause pulmonary vasoconstriction, and PCWP may be an unreliable estimate of LVEDP in the setting of a high-dose dopamine infusion. Dopamine is typically not recommended for patients with pulmonary edema because its venoconstrictor effects can increase venous return.

Onset of action is within 1–5 min and lasts for approximately 10 min. Tachycardia and ventricular arrhythmias are common at higher doses.

Norepinephrine (β1 > α > β2)

Norepinephrine (noradrenaline) is an endogenous neurotransmitter and is a potent β1 receptor agonist in the heart, with positive inotropic and chronotropic effects. It is also a potent peripheral α1 receptor agonist (more than epinephrine) and causes a dose-dependent increase in systemic vascular resistance. Due to these potent alpha effects, the resultant vasoconstriction limits the inotropic benefit of norepinephrine. It does have a small effect on β receptors. It is synthesized from dopamine and is precursor of epinephrine. Norepinephrine can be used in cardiogenic shock and is considered safer than epinephrine in ischemic disease, though it is still not a first-line choice.

Dosing: Typically start with 8–12 μg/min and titrate or wean to desired effect. Effects are seen within 1–2 min and duration is approximately 1–2 min.

Epinephrine (β1 = β2 > α)

Epinephrine (adrenaline) is an endogenous neurotransmitter synthesized from norepinephrine which is relatively nonselective at all receptors, but it primarily gives mixed β1 and β stimulation with some added α-mediated effects at higher doses. A low physiologic infusion rate (<0.01 μg/kg/min) increases contractility and speeds impulse generation via β activation, but often decreases peripheral resistance and blood pressure via β2 activation. Higher doses (>0.2 μg/kg/min) increase peripheral resistance when α-medicated constriction dominates over β2-mediated vasodilation. The positive inotropy, positive chronotropy, and vasoconstriction act together to raise blood pressure.

Epinephrine should typically be avoided in patients with cardiogenic shock due to myocardial ischemia because of the dramatic increases

in cardiac work and myocardial oxygen consumption. Usual dosing: for ACLS 1 mg IV (10 mL 1:10,000), for anaphylaxis 0.1 mg SQ/IM (0.1 mL 1:1000) or 0.1 mg IV (1 mL 1:10,000) over 5–10 min. The effects are seen within seconds of administration and last for 1–2 min.

Isoproterenol ($\beta 1 > \beta 2$)

Isoproterenol (isoprenaline) is a synthetic epinephrine analog. It is a pure β-agonist with almost no α effect. It has positive inotropic and chronotropic effects in the heart. In the peripheral vessels, $\beta 2$ stimulation leads to a decrease in peripheral resistance and often causes a drop in blood pressure. This drug causes a significant increase in myocardial work and oxygen consumption, so it is rarely used in patients with ischemic heart disease. Its use is typically limited to temporary treatment of bradyarrhythmias, refractory torsades de pointes, refractory bronchospasm, and in cardiac transplant patients to increase heart rate. Dosing: Initially 0.5 μg/min, with most patients responding to 2–20 μg/min. Onset is seen within 30–60 s and lasts anywhere from 8 to 50 min.

Milrinone (PDE-3 Inhibitor)

Milrinone exerts its positive inotropic actions by inhibiting phosphodiesterase in cardiac myocytes. This inhibition reduces the breakdown of intracellular cAMP, ultimately leading to enhanced calcium entry into the cell and increased force of contraction. It also causes some peripheral vasodilation. Milrinone, therefore, has inotropic, vasodilatory, and minimal chronotropic effects. It is used for short-term management of low output heart failure, similar to dobutamine. Dosing: Initial loading dose of 50 μg/kg over 10 min followed by 0.25–0.75 μg/kg/min. The effect is usually seen within 5–15 min. Milrinone is primarily excreted unchanged by the kidney, so dose adjustments may be necessary in patients with significant renal dysfunction.

Digoxin

It is theorized that digoxin (digitalis) improves contractility via inhibition of the sarcolemmal Na^+K^+-ATPase pump, normally responsible for maintaining transmembrane Na^+ and K^+ gradients. Inhibiting this pump causes intracellular Na^+ to rise, which then reduces Ca^{++} extrusion from the cell by the Na^+–Ca^{++} exchanger. This leads to more Ca^{++} being pumped into the sarcoplasmic reticulum with higher amounts of Ca^{++} being released into the myofilaments with each action potential. Increased Ca^{++} release from the sarcoplasmic reticulum enhances the force of contraction. The magnitude of the positive inotropic effect correlates with the degree of Na^+ K^+-ATPase inhibition.

Digoxin is a relatively weak inotropic agent and is used primarily for the treatment of chronic symptomatic systolic dysfunction, especially if accompanied by atrial arrhythmias.

Bullet Point Summary

- Contractility, or inotropy, is the inherent capacity of the myocardium to contract *independent* of preload and afterload.
- Contractility can be evaluated through assessing the rate of rise of left ventricular pressure, or dP/dt. With advancements in echocardiography, 2D speckle tracking with strain imaging now represents an effective method of noninvasive assessment of both global and segmental myocardial contractile function and has been well-validated in multiple cardiovascular disease states.
- In relation to a normal heart, a hypodynamic heart has an elevated end-diastolic pressure, a slowly rising ventricular pressure, and a prolonged ejection phase. A hyperdynamic heart has a reduced end-diastolic pressure, a fast-rising ventricular pressure, and a brief ejection phase.

- Contractility is primarily determined by the way calcium is processed and utilized in the cardiac myocyte.
- Ischemia causes reduced contractility primarily via a decrease in ATP production.
- The failing heart loses its contractile reserve via multiple mechanisms, including blunting of the response to adrenergic stimulus and abnormalities in the handling of calcium within the cardiac myocyte.
- Exogenous inotropic agents work to enhance cardiac contractility via several different mechanisms.

Review Questions

1. An influx of calcium into the cell triggers a conformational change in which receptors to allow calcium release from the sarcoplasmic reticulum?
   A. SERCA
   B. L-type
   C. Calcium release channels
   D. Na/Ca exchanger
   E. Ryanodine

   Answer: E. Depolarization of the myocyte membrane causes calcium inflow via voltage-gated L-type calcium channels. This calcium inflow then triggers a conformational change in ryanodine receptors in the sarcoplasmic reticulum membrane, which allows calcium to flow out into the cytosol via the calcium release channels.
2. The ability of the heart to increase inotropy in response to abrupt increases in afterload is known as the:
   A. Bowditch effect
   B. Lusitropic effect
   C. Anrep effect
   D. Chronotropic effect
   E. Treppe effect

   Answer: C. The Anrep effect is the intrinsic ability of the heart to increase contractility in response to an acute increase in afterload. This is even seen in denervated hearts. The Bowditch or treppe effect is the ability of the heart to increase contractility in the setting of an increasing heart rate.

Special thanks to Frederick Heupler Jr., MD, for his contributions to the previous version of this chapter.

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Cardiac Output

4

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Definition and Determinants of Cardiac Output

Cardiac output is defined as the volume of blood ejected from the heart every minute. At rest the normal adult cardiac output is approximately 5–6 L/min [1] and the normal cardiac output indexed to body surface area is 2.6–3.2 L/min/m^2. Cardiac output is the product of stroke volume and heart rate [2]. The three major determinants of stroke volume, and thus cardiac output, are preload, afterload, and contractility, which are discussed in depth in the three preceding chapters. Preload and contractility are directly correlated to stroke volume, while afterload is inversely correlated [2]. Cardiac output can also be affected by structural abnormalities of the heart such as valvular regurgitation and intracardiac shunts, which reduce the volume of forward flow. These will be discussed in later chapters.

Preload contributes to cardiac output by its effects on stroke volume and heart rate (see Chap. 1). Preload is most directly associated with the ventricular end-diastolic pressure or simply the "filling pressure." The effect of preload on stroke volume is described by the Frank-Starling mechanism [3] (Fig. 4.1). As more volume fills the left ventricle, the pressure at end-diastole increases, and there is greater stretch of the left ventricular walls. The walls behave like a spring, so the greater the stretch of the walls, the more forceful their recoil, and thus the greater the amount of ejected blood [3]. However, as seen in isolated heart preparations, if the stretch on the myocardium exceeds a certain point, the opposite occurs, and stroke volume as well as cardiac output can decrease. Preload also affects heart rate. Although the common conception is that volume depletion leads to tachycardia due to a reduction in baroreceptor firing, an increase in the effective circulating volume may also lead to an increase in heart rate. With increased stretching in the right atrium, the heart pumps at a faster rate due to stretch of the sinus node. The stretching of the right atrium also causes the Bainbridge reflex, a sympathetic nervous system-mediated reflex that increases heart rate in response to this stretching [4].

Afterload is a force that opposes myocardial contraction (see Chap. 2). It is equal to the tension across the ventricular wall during systole.

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_4

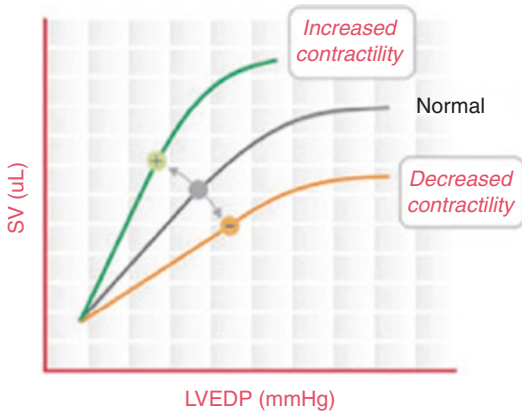

Fig. 4.1 Relationship between cardiac output, preload, and contractility. (*SV* stroke volume, *LVEDP* left ventricular end-diastolic pressure, a measure of preload). (Adapted from http://scisense.com/education/cv-application.html)

The Law of Laplace describes the relationship between the determinants of ventricular wall tension, or afterload, by the equation: $\sigma = (P \times r)/(2w)$, where σ is wall stress, P is chamber pressure, r is the radius of the chamber, and w is the wall thickness. In other words, wall stress (afterload) is directly proportional to ventricular pressure and size (radius) and indirectly related to wall thickness. Ventricular dilation increases afterload, and left ventricular hypertrophy (LVH) is a compensatory mechanism that attempts to decrease afterload [4]. A major component of afterload is captured by forces exerted on the ventricle by the vasculature, which is well estimated by vascular resistance.

Please refer to Chap. 3 for an in-depth discussion of the relationship between contractility and cardiac output. Increases in contractility increase the cardiac output for any given preload or afterload.

Circulatory Hemodynamics

The heart is at the center of two interrelated cardiovascular systems: the systemic, or peripheral, cardiovascular system and the pulmonary cardiovascular system. The flow through each of these systems is fundamentally described with the same equation that describes flow through any tube, wherein the pressure gradient across the tube is equal to the flow across the tube multiplied by the resistance of that tube.

$$\Delta P = Q \times R$$

The abovementioned equation is applied to the circulatory system by defining Q as the cardiac output, R as either the systemic vascular resistance (SVR) or the pulmonary vascular resistance (PVR), and ΔP as the change in pressure across either of the two circuits. In general terms, it is the difference between the average blood pressure before the circuit and the average blood pressure after the circuit. Specifically, the change in pressure across the pulmonary circulation is estimated as the mean pulmonary artery pressure minus the pulmonary capillary wedge pressure (mPAP – PCWP) while the change in pressure across the systemic circulation is estimated as the mean arterial pressure minus the right atrial pressure (MAP – RAP). Right atrial pressure is also referred to as the central venous pressure (CVP). Thus, systemic cardiac output is equal to (MAP – RAP)/SVR. As discussed previously, the noted pressures can easily be determined from a combination of a Swan-Ganz catheter and either invasive or noninvasive blood pressure monitoring [3].

Physiologically, it is useful to see Ohm's law expressed as written above because it reminds us that the pressure gradient across a vascular circuit is the *result* of flow and resistance. Clinically, this means that blood pressure depends both on cardiac output and vascular resistance. Perturbations in blood pressure, either from illness or medications, are the result of changes to one or both of these two factors. It also highlights that a normal blood pressure can occur in the setting of a low cardiac output with a compensatory increase in vascular resistance. Normal blood pressure does not mean that there is normal tissue perfusion!

Despite the fact that the pressure change is the result of changes in cardiac output and resistance, resistance is not measured directly. Instead, we measured the pressures and cardiac output using a variety of tools which will be discussed in detail in this chapter (but most commonly a Swan-Ganz catheter), and calculated the resistance from

Table 4.1 Hemodynamic parameters

Hemodynamic parameter	Formula	Normal range
CO	HR × SV	4–6 L/min
CI	CO/BSA	2.6–4.3 L/min/m^2
SVR	(MAP-CVP)/CO × 80	800–1400 dyn s/cm^5
SVRI	(MAP-CVP)/CI × 80	1500–2300 dyn s/cm^5/m^2
PVR	(PAP-PCWP)/CO × 80	140–250 dyn s/cm^5
PVRI	(PAP-PCWP)/CI × 80	240–450 dyn s/cm^5/m^2

CO cardiac output, *CI* cardiac index, *BSA* body surface area, *SVR* systemic vascular resistance, *SVRI* SVR index, *PVR* peripheral vascular resistance, *PVRI* PVR index

Ohm's law. Normal values for cardiac output, filling pressures, and vascular resistances are listed in Table 4.1.

Hemodynamic Disturbances: The Failing Heart and Shock

Heart failure is defined as either: (1) inadequate cardiac output to support normal organ function, or (2) maintenance of adequate cardiac output at elevated filling pressures. The majority of encountered clinical heart failure falls into the latter category. These patients often present with signs and symptoms of volume overload which are the result of such elevated filling pressures (see Chap. 10). The volume overloaded state can be managed with fluid removal either by diuresis or dialysis. However, a variety of insults can push a heart which functions adequately (either with normal or elevated filling pressures) into a state in which cardiac output is inadequate, assuming the body's demand is held constant. These insults must affect one or more of the four factors of cardiac output (Table 4.2).

Table 4.2 Selected hemodynamic insults to cardiac output

	Examples of insults that predominantly affect listed factor
Preload	Hemorrhage, cardiac tamponade, pulmonary embolism
Afterload	Increase in sympathetic tone, vasopressors
Contractility	Ischemia, systemic acidemia, negative inotropes (calcium channel blockers, beta-blockers)
Heart rate	Heart block, sinus, or AV nodal blocking agents

AV atrioventricular

Inadequate tissue perfusion is a clinical state known as circulatory shock. Human tissues require a constant supply of oxygen to maintain aerobic metabolism. When this supply is impaired, the body tissues slowly revert to anaerobic metabolism, producing toxic metabolic breakdown products, such as lactic acid. By this mechanism, shock leads to end organ dysfunction and eventual failure. Shock resulting from low cardiac output, as described above, is one possible cause of inadequate tissue perfusion. From a hemodynamic standpoint, the three major types of circulatory shock are cardiogenic, hypovolemic, and vasogenic (also known as distributive). Cardiogenic shock and hypovolemic shock are low cardiac output states, whereas vasogenic shock is a high output type of shock [5].

Differentiating these states can be achieved by determining the hemodynamic parameters already discussed. Cardiogenic shock and hypovolemic shock are both associated with low cardiac output and high SVR, but may be differentiated by PCWP, which is elevated in cardiogenic shock but decreased in the hypovolemic shock. Vasogenic shock is a low SVR state due to vasodilation, and with causes including sepsis, thyrotoxicosis, anemia, anaphylaxis, and AV fistulas [6]. Vasogenic shock is typically accompanied by a high cardiac output. Management of heart failure and shock will be discussed more extensively in Chaps. 19 and 21, respectively.

Methods of Determining Cardiac Output

In critically ill patients, differentiating the shock states described above is essential to management, especially when inadequate cardiac output may be related to increased morbidity and mortality [7]; therefore, it is essential to have reliable methods to measure cardiac output.

There are multiple bedside indicators that help estimate the adequacy of cardiac output and/or tissue perfusion. Mental status, specifically, patients falling asleep during their interviews, and decreased urine output are early indicators of inadequate perfusion of the brain and kidneys. Cool forearms and legs also signal low cardiac output as vascular resistance increases and blood is shunted away from the extremities in favor of internal organs [8]. The proportional pulse pressure is another useful bedside marker, and can be calculated as the difference between the systolic and diastolic blood pressures divided by the systolic blood pressure ((SBP-DBP)/SBP). A ratio of less than 25% suggests a cardiac index of less than 2.2 L/min/m^2 [9].

There are also several methods of actually measuring cardiac output. These include invasive methods such as thermodilution and Fick methods, which require the use of a Swan-Ganz pulmonary artery catheter, and noninvasive methods such as transpulmonary thermodilution [10]. Noninvasive clinical measures may help determine whether a patient is in a low output state; however, invasive methods of measuring cardiac output in the intensive care unit are mainstays for precise monitoring to guide therapeutic management.

Thermodilution

With the use of a pulmonary artery catheter, cardiac output may be measured directly by the thermodilution method (introduced in 1953 by Fegler) or indirectly by means of the Fick principle [1]. The thermodilution method of measuring cardiac output involves injection of cold fluid into the Swan-Ganz catheter positioned in the pulmonary artery. This injectate flows through the catheter and exits into the right ventricle where it mixes with blood, which is warmer than the injected fluid. This mixture of blood and indicator fluid then moves into the pulmonary artery, where a thermistor at the catheter tip senses temperature changes [6]. With each beat, the blood temperature rises as the cold fluid is washed out of the right side of the heart [1]. A time-temperature curve is electronically obtained, and the cardiac output is calculated using the Stewart-Hamilton Formula. The key components of this formula are cardiac output, amount of indicator, and the integral of the amount of indicator concentration over time. The cardiac output is inversely related to the area under the thermodilution curve as measured by the integral of the amount of indicator concentration over time [3, 6]. When cardiac output is low, it takes longer for the cold fluid to wash out of the right ventricle and thus for the temperature of the blood to return to baseline, producing a low amplitude, prolonged curve with a large area underneath it. On the other hand, the blood temperature returns to baseline quicker when the injection fluid moves at a faster rate through the heart, as it does with higher cardiac output [3]. This produces a higher amplitude, shorter curve with a smaller area Fig. 4.2. The advantage of this method is the use of computer calculations to give quick measurements as well as less need for blood draws. However, this method becomes less useful in patients with cardiac output less than 2.5 L/min as it tends to overestimate the cardiac output in these cases [3]. It also miscalculates cardiac output in patients with tricuspid regurgitation because the indicator fluid is recycled, thus producing a curve that is similar to the low cardiac output curve and thus underestimates cardiac output [5]. On the other hand, left-to-right shunts tend to overestimate the cardiac output as a portion of the injectate crosses through the shunt and thus the temperature change that is detected downstream occurs quickly as would occur in a true high cardiac output state [5].

Another thermal method of measuring cardiac output is the continuous cardiac output method. This method uses a warm indicator rather than a cold one in the standard thermal dilution [11]. A thermal filament on the right ventricular portion of the pulmonary artery catheter releases small amounts of heat, which is measured by the thermistor at the tip of the pulmonary artery catheter.

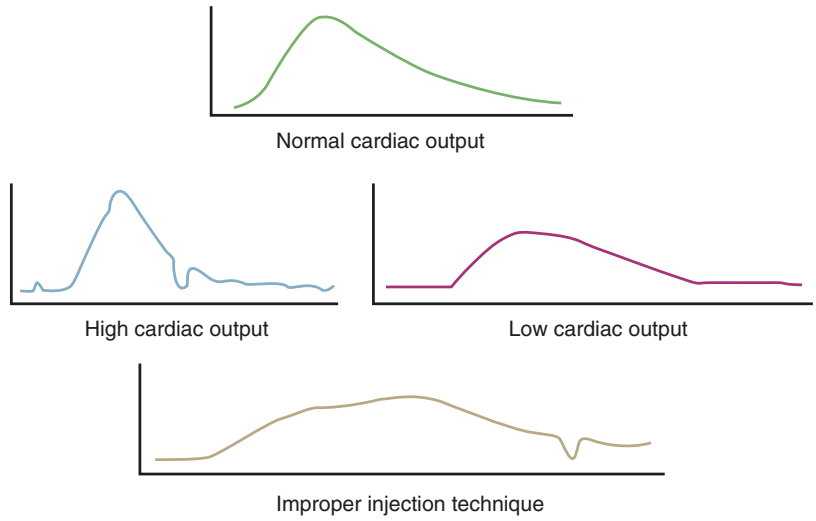

Fig. 4.2 Thermodilution cardiac output curves. (Adapted from Braunwald et al. [3])

The cardiac output is automatically calculated and updated every 30–60 s, giving an average cardiac output over 3–6 min. The major disadvantage of this method is that it does not respond quickly in unstable hemodynamic conditions, such as fluid resuscitation or hemorrhage [12].

The Fick Cardiac Output

The Fick principle is employed to provide an indirect measurement of cardiac output that is based on the oxygen saturation of blood samples obtained through a Swan-Ganz catheter. This method was developed by Eugene Fick in 1870, and is based on the principle that the rate of oxygen consumption by the peripheral tissues is equal to the cardiac output multiplied by the change in oxygen concentration between the arterial and venous system [1]. In other words, when blood volume arrives to tissues at a lower rate, tissues must extract a greater percentage of the available oxygen in each mL of blood to meet their rate of oxygen consumption. This principle is expressed:

$$\text{oxygen consumption} = \text{cardiac output} \times \text{arteriovenous oxygen difference}$$

To calculate the *exact* concentration of oxygen in either the arterial or venous blood, one must calculate the amount of oxygen carried by the red blood cells and the very small amount dissolved in the blood. The following equation is used:

$$\text{Oxygen content} = \text{Hgb}\left(\text{g/dl}\right) \times 1.34\left(\text{mL O}_2\text{/g of Hgb}\right) \times \text{SO}_2\left(\%\right) + 0.0032 \times \text{PO}_2$$

where Hgb is the hemoglobin concentration, SO_2 is the oxygen saturation, and PO_2 is the partial pressure of oxygen not bound to hemoglobin and freely dissolved in the blood. The freely dissolved oxygen is extremely small compared to oxygen bound to hemoglobin and is frequently ignored. Therefore, the arteriovenous oxygen difference can be expressed as:

$$\text{Arteriovenous oxygen difference} = \left(\text{SaO}_2 - \text{SvO}_2\right) \times 1.34 \times \text{Hgb}$$

where SaO_2 and SvO_2 are the arterial and venous oxygen saturations respectively. SaO_2 is measured from either an arterial line or a pulse oximeter with a reliable tracing. SvO_2 is measured as the oxygen saturation in the main pulmonary artery, and is also referred to as the mixed venous oxygen saturation. Together, the entire Fick equation can then be rewritten as:

$$\text{Cardiac output}\left(\text{L}/\text{min}\right) = \frac{\text{VO}_2\left(\text{mL}/\text{min}\right)}{\left(\text{SaO}_2 - \text{SvO}_2\right)\times 1.34 \times \text{Hgb}} \times 10$$

where VO_2 is oxygen consumption. Cardiac output is usually corrected for body size using this equation: cardiac index (CI) = CO/BSA where CI is the cardiac index and BSA is the body surface area. CI is commonly used in the ICU setting to monitor a patient's hemodynamic status and guide therapy. The normal CI is 2.6–4.3 L/min/m^2 [13], and it is normally lower in elderly persons. In healthy adults, the normal value for VO_2 is 200–300 mL/min, or 110–160 mL/min/m^2 when adjusting for body size [5].

The Fick method is more accurate when VO_2 is measured using a calorimeter rather than estimated, as is the usual practice, especially in hyperdynamic states such as sepsis [10]. However, in general practice, even if the calculated CI is not exactly precise, the trend in the estimated CI indicates clinical changes from therapies or insults. The disadvantages of the Fick method are similar to other invasive methods including risk of infection or pulmonary hemorrhage.

Other Methods of Assessing Cardiac Output

An alternate, but still invasive, method of measuring cardiac output is ventriculography [1]. This method requires placement of a catheter in the left ventricle and subsequent injection of contrast dye. The cardiac cycle is recorded in a cine loop, and the stroke volume is calculated by subtracting the end systolic volume from the end-diastolic volume. This method is particularly useful in the setting of valve stenosis or regurgitation. However, the CO may be miscalculated in patients with enlarged ventricles [1]. It is more invasive, requiring arterial access, and catheter placement in the left ventricle with associated risks of structural damage and arrhythmia.

A less invasive method of measuring CO is called the transpulmonary thermodilution technique, which is used by the PICCO monitor. There is no need for catheter placement into the heart using this method [10]. Instead, a central venous catheter is placed along with an arterial catheter with a thermistor at the tip. Indicator fluid is injected into the central line, and the arterial catheter thermistor senses the blood as it passes through the thorax, producing a similar thermodilution curve as the standard thermodilution method. The advantage of this method is that it is less invasive and less influenced by the respiratory cycle than the thermodilution technique, which employs a pulmonary artery catheter [14]. However, it may be inaccurate in patients with aortic stenosis, aortic aneurysm, and intracardiac shunts.

Other noninvasive or minimally invasive methods (See Chap. 13) of measuring CO include esophageal Doppler analysis of aortic blood flow, the indirect Fick method which uses partial carbon dioxide rebreathing, thoracic electrical bioimpedance, and pulse contour analysis of the arterial pressure waveform [6]. Each of these methods has disadvantages that make them less practical in the clinical setting. Esophageal Doppler analysis requires sufficient training to obtain accurate measurements. The indirect Fick method, which is applicable to intubated patients, is less accurate in severe lung injury or when there is variability in tidal volume (as is seen with spontaneous breathing) [6]. Thoracic electrical bioimpedance is less accurate in patients with peripheral edema or pleural effusions, and pulse contour analysis requires that another method of measuring CO be used in order to calibrate the pulse contour device [6].

Summary

- Cardiac output is defined as stroke volume multiplied by heart rate, and the determinants of stroke volume are afterload, preload, and contractility.
- Cardiogenic shock is a low cardiac output, high wedge pressure state that is often associated with hypotension. In cases of impending cardiogenic shock, blood pressure may be preserved. It is important to measure cardiac output in patients who are extremely hemodynamically unstable in order to guide therapy.
- Cardiac output is most commonly measured with a Swan-Ganz catheter using either the thermodilution or the Fick method.
- The Fick principle states that cardiac output is inversely proportional to the arteriovenous oxygen difference and directly proportional to oxygen consumption.

Equations

$$CO = SV \times HR$$

$$CI = CO / BSA$$

$$\text{Fick Principle}: CO = VO_2 / 1.34 \times 10 \times Hgb\left(SaO_2 - SvO_2\right)$$

$$CO = \left(MAP - CVP\right) / SVR$$

Review Questions

1. A 65-year-old male with a history of coronary artery disease status post CABG 5 years prior and known ischemic cardiomyopathy with an ejection fraction of 35% on his last echocardiogram, presents to the ER with palpitations and shortness of breath. His vital signs are blood pressure 120/95, heart rate 130 in sinus rhythm, and oxygen saturation 88% on room air. During his medical interview, he falls asleep between questions. On physical examination, his JVP is estimated to be 14 cm, he has an audible S3, bilateral crackles, and his extremities are cool to the touch. A Swan-Ganz catheter is placed. What is his most likely hemodynamic profile?
   (a) CI = 3.5, PCWP = 24, SVR = 400
   (b) CI = 1.8, PCWP = 30, SVR = 2500
   (c) CI = 2.5, PCWP = 10, SVR = 1800
   (d) CI = 2.0, PCWP = 10, SVR = 800
   - *Answer*: (b) This patient is cold and wet on physical exam and is in severe, decompensated HF.
2. Nitroprusside, a potent vasodilator, is administered to the abovementioned patient. What is the expected effect on blood pressure when it is given?
   (a) The blood pressure will increase
   (b) The blood pressure will decrease
   (c) The blood pressure will stay exactly the same
   (d) The change in blood pressure is uncertain
   - *Answer:* (d) While vascular resistance will drop, the reduction in afterload will increase cardiac output. The percent change in each of these factors will determine the direction and magnitude of blood pressure change, but this cannot be predicted beforehand. Administering a vasodilator to a patient in acute decompensated heart failure can make the blood pressure increase!
3. A 40-year-old female presents with shortness of breath 6 weeks after giving birth. A Swan-Ganz catheter is placed to calculate her cardiac output. Her SvO_2 is 40%, Hgb is 11, and SaO_2 is 98%. What is her cardiac output in L/min output using the Fick equation? Assume a VO_2 of 250 ml/min.
   (a) CO = 2.9 L/min
   (b) CO = 4.2 L/min
   (c) CO = 3.9 L/min
   (d) CO = 6.2 L/min
   - *Answer:* (a) *The Fick cardiac output is calculated as follows*:

$$CO = \left(VO_2\left(\text{assumed}\right) / 1.34 \times Hgb \times \left(SaO_2 - SvO_2\right)\right) \times 10.$$

4. In which of the following situations would the thermodilution method overestimate the cardiac output?
   (a) A 55-year-old woman with carcinoid syndrome associated with severe tricuspid regurgitation.
   (b) A 48-year-old male who presents with an acute inferior myocardial infarction associated with right ventricular failure.
   (c) A 40-year-old male who had an acute ST elevation myocardial infarction 1 week ago who now presents with acute cardiogenic shock due to ventricular septal rupture (VSR).
   (d) A 66-year-old female who presents with a type A dissection associated with severe aortic insufficiency.
   - *Answer:* (c) Shunts tend to overestimate CO when the thermodilution technique is used as a portion of the injectate crosses through the VSR and thus the temperature change that is sensed downstream occurs at a rate similar to a high CO state. Severe TR (choice a) tends to underestimate the cardiac output when using their modulation.
5. In which of the following situations is the estimated oxygen consumption (VO_2) (rather than a direct measurement) most likely to be inaccurate?
   (a) A 60-year-old female with right ventricular infarction.
   (b) An 80-year-old male with sepsis due to *Clostridium difficile* colitis.
   (c) A 48-year-old male with acute ischemic mitral regurgitation.
   (d) A 90-year-old male with severe aortic stenosis.
   - *Answer*: (b) The estimated VO_2 is inaccurate in hyperdynamic states such as sepsis.

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Part II

Effects of Selected Interventions on CV Hemodynamics

5 Renin–Angiotensin–Aldosterone Axis Modulators and Other Vasodilators

Chirag Bavishi, Roberto Ramirez, and Franz H. Messerli

Introduction

The renin–angiotensin–aldosterone system (RAAS) is a complex system that plays an important role in maintaining hemodynamic stability in the human body through regulation of arterial blood pressure, water and electrolyte balance, as well as cardiovascular hemodynamics. Both over- and under activation of the RAAS can result in loss of vital cardiac and vascular functions leading to pathological consequences. Blockade of the RAAS has been shown to be beneficial in patients with hypertension, acute myocardial infarction, and chronic systolic heart failure.

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Mechanism of Raas Inhibitors

The renin–angiotensin–aldosterone system (RAAS) plays an integral role in the homeostatic regulation of arterial pressure, tissue perfusion, and extracellular volume. This pathway is initiated by the secretion of renin synthesized by the juxtaglomerular cells in the afferent arteriole of the renal glomerulus. Renin secretion is modulated through interplay of pathways such as renal baroreceptor mechanism, changes in sodium and chloride delivery in distal tubule, sympathetic stimulation through beta-1 adrenergic receptors, and negative feedback by direct action of angiotensin II. Once activated, renin cleaves angiotensinogen to angiotensin-I, which is then hydrolyzed by the circulating and local angiotensin-converting enzyme (ACE) to the active angiotensin II. Angiotensin-converting enzyme also inactivates bradykinin with its nitric oxide and prostacyclin stimulating and vasodilatory activity. Angiotensin II acts mainly via angiotensin type 1 (AT-1) and angiotensin type 2 (AT-2) receptors. Angiotensin II also stimulates the release of aldosterone from the adrenal cortex. Aldosterone enhances the reabsorption of sodium and water in the distal tubules and collecting ducts and promotes potassium excretion. Like Angiotensin II, aldosterone is an effector hormone of the RAAS, principally involved in volume and blood pressure regulation. It also facilitates cardiovascular and renal inflammation, fibrosis, and remodeling.

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_5

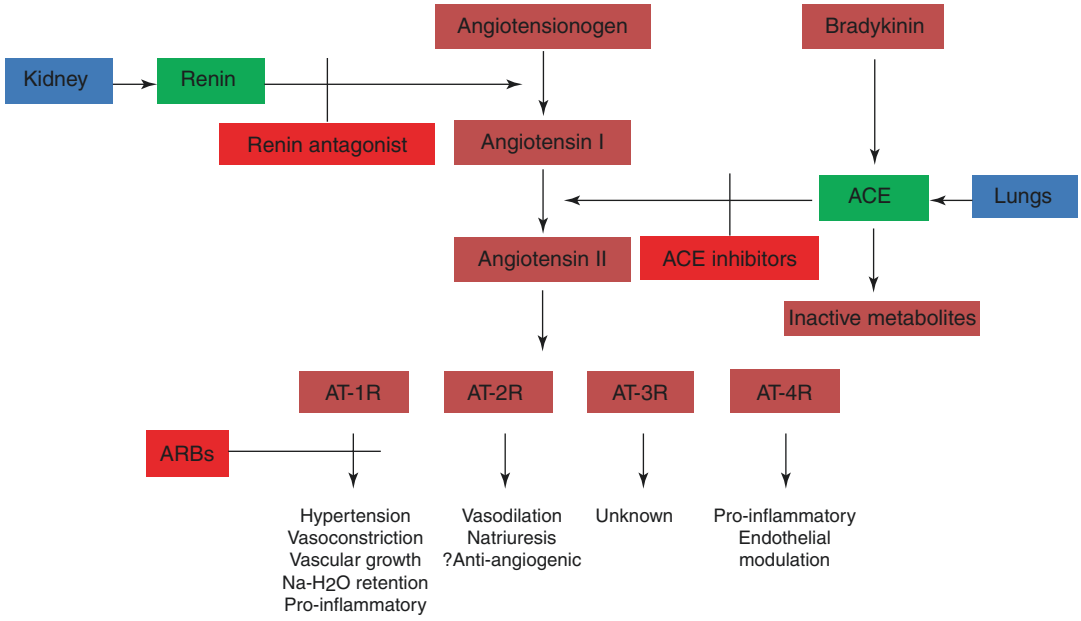

Fig. 5.1 The renin–angiotensin–aldosterone system. Mechanism of action of ACEIs, ARBs, and DRIs

ACE inhibitors (ACEIs) competitively inhibit the enzyme ACE, thereby preventing the conversion of angiotensin I into angiotensin II (Fig. 5.1) and blocking downstream activity of angiotensin II via both AT-1 and AT-2 receptors. They also reduce aldosterone, vasopressin, and plasminogen activator inhibitor-1. ACEIs increase the concentration of bradykinin which contributes to their vasodilatory action; however, this mechanism is also implicated in the occurrence of side effects such as cough and angioedema. Moreover, chronic ACEI use triggers ACE escape pathways; hence, angiotensin II is produced despite blockage of ACE. Angiotensin receptor blockers (ARBs) prevent the binding of angiotensin II to AT-1 receptors, leading to inhibition of all the deleterious effects modulated by angiotensin II, yet preserving the potential beneficial effect of angiotensin II via the AT-2 receptor pathway. Like ACEIs, ARBs reduce BP by decreasing systemic vascular resistance through selective AT-1 receptor blockade. Due to direct receptor blockade, ARBs do not demonstrate angiotensin II escape phenomenon and bradykinin-associated effects.

Table 5.1 Mechanistic differences between ARBs and ACEIs

Principle mechanism of action	ARBs	ACEIs
Plasma angiotensin II	↑	↓
Plasma renin activity	↑	↑
Bradykinin	–	↑
Prostaglandin E_2 and prostacyclin	–	↑
Nitric oxide release	–	↑
Uric acid levels	↓[a]	–
Cough	Not observed	Class specific

[a]Losartan potassium only. Table adapted from Messerli et al. Angiotensin II receptor inhibition. A new therapeutic principle. *Arch Intern Med*. 1996

However, stimulation of the AT2 receptor may result in some bradykinin release. Direct renin inhibitors, DRI (aliskiren), bind to renin with high affinity and prevent the conversion of angiotensinogen to angiotensin I, thereby blocking the synthesis of all angiotensin peptides downstream. These different modes of RAAS inhibition may explain some of the clinical differences between these agents (Table 5.1).

Cardiovascular Hemodynamics

Angiotensin-Converting Enzyme Inhibitors

The cardiovascular effects of ACEIs are evident immediately after the first dose. Single oral dose causes decrease in pulmonary capillary wedge pressure, mean arterial blood pressure, total systemic vascular resistance and increase in cardiac output [1]. Chronic oral dosing produces sustained beneficial hemodynamic effects translating into considerable improvement in LV function and symptoms in patients with systolic heart failure. In patients with systolic heart failure, ACEIs cause dose-dependent reduction in cardiac preload and afterload preventing progressive left ventricular dilatation and systolic dysfunction. These effects probably result from a combination of altered remodeling and sustained reduction in preload and afterload [1], causing leftward shift of the pressure-volume loop (Fig. 5.2). ACEIs also decrease renal vascular resistance, increase renal blood flow, and promote sodium and water excretion mainly though cellular effects in the kidney and alteration in glomerular hemodynamics. All these mechanisms underline the beneficial effects of these agents in heart failure.

ACEIs decrease Ang II and aldosterone formation and potentiate the vasodilatory effects of the kallikrein-kinin system, causing reduction in total peripheral vascular resistance without significant change in heart rate [2]. Moreover, improvement in stroke volume and cardiac output, seen in systolic heart failure patients, is also seen in patients with essential hypertension [3]. The hemodynamic effect of ACEIs in hypertension extends to the regional circulation. During acute or prolonged ACE inhibition, renal and coronary blood flow is increased in patients with heightened RAAS activity [4, 5]. Thus, ACEIs may augment myocardial perfusion both by preventing the vasoconstrictor effect of angiotensin II and by reducing coronary vasoconstriction induced by cardiac sympathetic activation. ACEI also affects arterial compliance and wave reflections in patients with hypertension [6] (Fig. 5.3). ACEIs reduce pulse wave velocity and augmentation index which are markers of arterial stiffness, and this effect is at least partly independent of changes in blood pressure [7]. ACEIs also cause regression of left ventricular hypertrophy, independent of their effects on blood pressure reduction [8]. Inhibitors of the RAAS permit regression of pathologic LVH more effectively than other antihypertensive agents. Table 5.2 summarizes key landmark trials of ACEI in patients with heart failure, hypertension, and myocardial infarction.

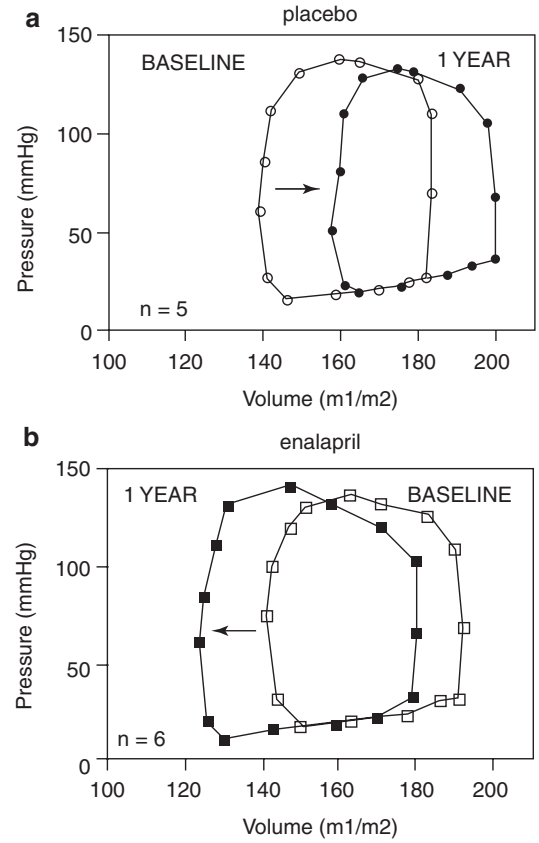

Fig. 5.2 Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo (panel A) and to enalapril (panel B) in SOLVD trial. At 1 year, there was a rightward shift in placebo group and leftward shift in enalapril group. (Reprinted from Konstam et al. with permission of the publisher)

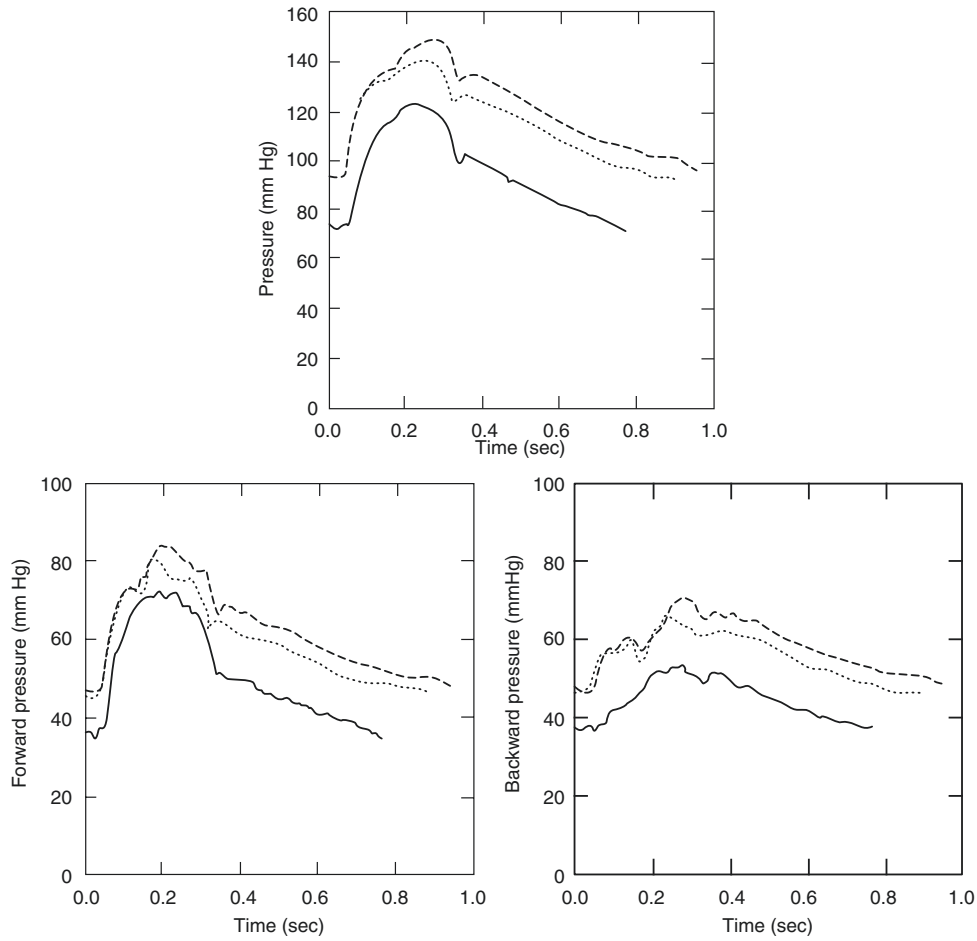

Fig. 5.3 Plots showing ascending aorta pressure waveforms (top) along with their forward (bottom left) and backward (bottom right) components in a representative normotensive (solid line) and hypertensive patient (dashed line). After captopril infusion (dotted line), attenuation of the higher backward wave and prominent late systolic peak in hypertensive patient was seen. (Reprinted from Ting et al. with permission of the publisher)

Angiotensin Receptor Blockers

The cardiovascular hemodynamic effects of ARBs are similar to ACEIs due to similarity in their mechanism of action. However, unlike ACE inhibitors, ARBs do not directly modulate the formation of bradykinin. Due to more downstream inhibition by ARBs and lack of angiotensin II escape phenomenon, they may exert more potent antihypertensive effects compared to ACEIs. Table 5.3 summarizes key landmark trials of ARBs in patients with heart failure, hypertension, and myocardial infarction. Although head-to-head trials comparing ACEIs and ARBs have shown equivocal results, ARB trials had lower rates of events in the placebo arm due to better use of contemporary medications (statins). Moreover, due to fewer adverse events with ARBs, the risk-to-benefit analysis should favor use of ARBs, particularly in patients with hypertension [9].

Aldosterone Antagonists

The pathophysiological effects of hyperaldosteronism on the cardiovascular hemodynamics extend beyond increased intravascular fluid reten-

Table 5.2 Key clinical outcome trials of ACEI in cardiovascular diseases

Trial and year	Active arm (N)	Comparator (N)	Patients	Primary outcome	Follow-up	Major findings
ALLHAT, 2002	Lisinopril (9054)	Chlortalidone (15,255), Amlodipine (9048)	Hypertension	Combined fatal coronary heart disease or nonfatal MI	4.9 years	No difference in primary outcomes
ANBP-2, 2003	Enalapril (3044)	HCTZ (3039)	Hypertension	All CV events or all-cause mortality	4.1 years	Enalapril showed 11% reduction in all CV events or mortality
Pilot HYVET, 2003	ACEI (usually Lisinopril) (431)	Diuretic (usually Bendroflumen-thiazide) (426), Placebo (426)	Hypertension	Stroke, all-cause mortality	1.12 years	No difference in all-cause mortality. Diuretic showed 69% reduction in stroke compared to placebo
SOLVD, 1991	Enalapril (1285)	Placebo (1284)	Chronic heart failure	All-cause mortality	3.5 years	Enalapril showed 16% reduction in all-cause mortality
CONSENSUS, 1987	Enalapril (127)	Placebo (126)	Chronic heart failure	All-cause mortality	6 months	Enalapril showed 40% reduction in mortality
CONSENSUS II, 1992	Enalapril (3044)	Placebo (3046)	MI	All-cause mortality	6 months	No difference in all-cause mortality
SAVE, 1992	Captopril (1115)	Placebo (1116)	MI and left ventricular dysfunction	All-cause mortality	1.8 years	Captopril decreased all-cause mortality by 19%
EUROPA, 2003	Perindopril (6110)	Placebo (6108)	Stable coronary artery disease	Composite of CV mortality, nonfatal MI, and cardiac arrest	4.2 years	Perindopril reduced composite primary end point by 20%
HOPE trial, 2000	Ramipril ($n = 4645$)	Placebo ($n = 4652$)	Multiple CV risk factors	Composite of MI, stroke, or CV death	5 years	Ramipril showed 22% reduction in primary end point

ACEI angiotensin-converting enzyme inhibitor, *CV* cardiovascular, *MI* myocardial infarction

tion and volume overload. Hyperaldosteronism alters fibrinolysis by increasing plasminogen activator inhibitor-1 expression and promotes tissue fibrosis and inflammation [10]. Increased aldosterone activity leads to endothelial dysfunction and arterial stiffness [11]. Moreover, aldosterone is intriguingly involved in sympathetic nervous system activation, decreased baroreceptor sensitivity, increased electrolyte excretion, and cardiomyocyte apoptosis. These effects exerted by aldosterone, one of the final mediators of the RAAS pathway, are only partially inhibited by ACEIs/ARBs. Thus, in addition to modulating volume status, some of the clinical benefits of aldosterone antagonists come from abrogating these adverse effects to limit target organ dysfunction.

Aldosterone antagonists improve LV structural remodeling and performance by increasing LV ejection fraction and decreasing LV end-diastolic and end-systolic volumes, particularly in patients with systolic heart failure and myocardial infarction. Experimental studies have shown that early use of aldosterone antagonist after myocardial infarction could improve myocardial healing as well as both electrical and structural remodeling [12, 13]. Table 5.4 summarizes key

Table 5.3 Key clinical outcome trials of ARBs in cardiovascular diseases

Trial and year	Active arm (N)	Comparator (N)	Patients	Primary outcome	Follow-up	Major findings
LIFE, 2002	Losartan (4605)	Atenolol (4588)	Hypertension	Death, MI, or stroke	4.8 years	Losartan caused 13% reduction in primary end point compared to atenolol
SCOPE, 2003	Candesartan (2477)	Placebo (2460)	Hypertension	CV death, nonfatal stroke, and nonfatal MI	3.7 years	No difference in primary end point, candesartan cause 28% reduction in nonfatal stroke
Val-HeFT, 2001	Valsartan ($n = 2511$)	Placebo ($n = 2499$)	Chronic heart failure	All-cause mortality; combined end point of all-cause mortality, cardiac arrest with resuscitation, heart failure hospitalization, IV inotropic or vasodilator drugs	1.9 years	No difference in all-cause mortality, valsartan showed 23% reduction of combined end point
VALIANT, 2003	Valsartan ($n = 4909$)	Valsartan + captopril ($n = 4885$); captopril ($n = 4909$)	MI	All-cause mortality	2.1 years	No difference in all-cause mortality among the three groups
OPTIMAAL, 2002	Losartan ($n = 2744$)	Captopril ($n = 2733$)	MI	All-cause mortality	2.7 years	No difference in all-cause mortality between the two groups

ARB angiotensin receptor blocker, *CV* cardiovascular, *IV* intravenous, *MI* myocardial infarction

Table 5.4 Key clinical outcome trials of aldosterone antagonists in cardiovascular diseases

Trial and year	Active arm (N)	Comparator (N)	Patients	Primary outcome	Follow-up	Major findings
RALES, 1999	Spironolactone (822)	Placebo (841)	Chronic systolic heart failure	All-cause mortality	2 years	Spironolactone showed 30% reduction in all-cause mortality
EMPHASIS-HF, 2011	Eplerenone (1364)	Placebo (1373)	Chronic systolic heart failure	CV mortality or heart failure hospitalization	1.8 years	Eplerenone showed 37% reduction in primary end point
TOPCAT, 2014	Spironolactone (1722)	Placebo (1723)	Chronic heart failure and ejection fraction ≥45%	CV mortality, aborted cardiac arrest or heart failure hospitalization	3.3 years	No difference in primary composite end point between the two groups
EPHESUS, 2003	Eplerenone (3313)	Placebo (3319)	MI	All-cause mortality and CV mortality or hospitalization or events	1.3 years	Eplerenone reduced all-cause mortality by 15% and CV mortality or hospitalization or CV events by 13%

CV cardiovascular, *MI* myocardial infarction

landmark trials of aldosterone antagonists in patients with heart failure and myocardial infarction.

Direct Renin Inhibitors

Direct renin inhibitor, Aliskiren, is a potent competitive renin inhibitor that binds strongly to renin, resulting in very low circulating levels of angiotensin II and other peptides, thereby rendering the RAAS quiescent. Aliskiren has been as effective as other RAAS inhibitors in reducing blood pressure and left ventricular remodeling [14, 15]. In patients with systolic heart failure, Aliskiren has a potent vasodilatory effect on the efferent arteriole in the glomerulus, leading to marked reduction in renal blood flow and a drop-in filtration fraction [16]. Overall, the lack of incremental benefit in reducing cardiovascular outcomes over ACEI/ARBs, coupled with the noteworthy incidence of adverse effects (diarrhea, hypotension, hyperkalemia, and renal dysfunction), has placed this drug out of favor.

Dual RAAS Blockade

In theory, combination of an ACEI and ARB should result in enhanced RAAS blockade. Conceivably, combination therapy has been shown to be more effective in reducing BP compared with monotherapy alone [17]. In spite of this, dual therapy of ACEI and ARBs were not found superior compared to individual therapy. Multiple studies have also documented increased risk of adverse events such as worsening renal function, hyperkalemia, symptomatic hypotension, and increased medication discontinuation due to adverse effects with combination therapy of ACEIs and ARBs. Based upon the clear evidence of possible harm, ACEIs should not be combined with ARBs. With the advent of the Aliskiren, dual RAAS blockade could now be achieved by combining an ACEI or an ARB with Aliskiren. However, such dual RAAS blockade also has not proven safe, and should be avoided. Table 5.5 summarizes key landmark trials of dual RAAS blocking agents in patients with heart failure and myocardial infarction.

Table 5.5 Key clinical outcome trials of dual RAAS blockade in cardiovascular diseases

Trial and year	Active arm (N)	Comparator (N)	Patients	Primary outcome	Follow-up	Major findings
ALOFT, 2008	Aliskiren + ACEI/ARB (156)	Placebo (146)	Chronic heart failure	Between treatment difference in N-terminal pro-BNP	3 months	Aliskiren added to ACEI/ARB decreased NT-proBNP by 25%
ATMOSPHERE, 2016	Enalapril +Aliskiren (2340)	Aliskiren (2340), Enalapril (2336)	Chronic heart failure	Composite end point of CV death or heart failure hospitalization	3.1 years	No difference in primary end point
CHARM-Added, 2003	Candesartan + ACEI (1276)	Placebo (1272)	Chronic heart failure	CV mortality or heart failure hospitalization	3.4 years	Candesartan added to ACEI showed 15% reduction in primary end point
ONTARGET, 2008	Ramipril + Telmisartan (8502)	Ramipril (8576), Telmisartan (8542)	CV disease	Composite end point of CV death, MI, stroke, or heart failure hospitalization	4.6 years	No difference in primary outcomes among the three groups
VALIANT, 2003	Valsartan + Captopril (4885)	Valsartan (4909), Captopril (4909)	MI	All-cause mortality	2.1 years	No difference in all-cause mortality among the three groups

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BNP* brain natriuretic peptide, *CV* cardiovascular, *MI* myocardial infarction

Other Vasodilators

Several physiological studies demonstrated the dependence of cardiac function on vascular resistance, so vasodilator therapies that reduce systemic vascular resistance should improve cardiovascular hemodynamics. Vasodilators are broadly subclassified into venodilators (e.g., nitrates), which reduce left ventricular filling pressure and relieve pulmonary congestion; arteriolar dilators (e.g., hydralazine), which enhance cardiac output; and balanced vasodilators (e.g., nitroprusside, nitroglycerine), which dilate both resistance and capacitance vessels. Seminal work conducted by Franciosa et al. in the early 1970s showed that intravenous infusion of sodium nitroprusside produced a marked reduction in the elevated left ventricular filling pressure and systemic arterial pressure, resulting in a modest increase in cardiac output [18]. A subsequent study in patients with refractory heart failure revealed even more striking improvements in systemic vascular resistance and cardiac output, with reduced left ventricular filling pressure [19]. Similar effects of nitroprusside were seen in patients with myocardial infarction and depressed left ventricular ejection fraction [20]. Despite being a potent vasodilator, sodium nitroprusside is seldom used these days as prolonged infusion has been associated with thiocyanate toxicity, particularly in those with severe renal dysfunction and systemic hypotension. Currently, intravenous nitroglycerine is the preferred vasodilator in acute conditions. It has comparable hemodynamic effects compared to nitroprusside and likely has more beneficial effects on intercoronary collateral blood flow in the setting of regional ischemia [21]. Although vasodilators are effective in relieving congestion and improving symptoms in patients with acute heart failure, their role in improving cardiac indices has not been demonstrated consistently. The increase in stroke volume and cardiac output with intravenous vasodilators is modulated by several factors such arterial elastance, ventricular function, preload dependence, presence of mitral regurgitation etc. In patients with severely impaired ventricular function, isolated reduction in preload may not translate into higher stroke volume due to markedly reduced cardiac contractility [22] (Fig. 5.4). Combination therapy of dobutamine and nitroglycerin can result in greater overall hemodynamic improvement than either drug alone in such cases.

The hemodynamic benefits of intravenous vasodilators led to the evolution of various oral agents with vasodilatory properties. Combination

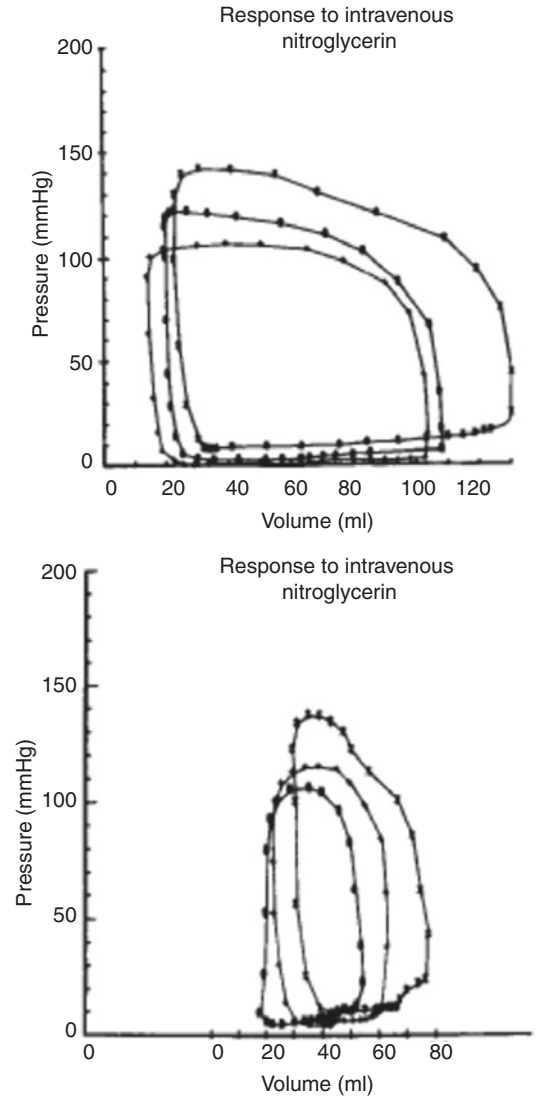

Fig. 5.4 Sequential left ventricular pressure-volume loops after administration of sodium nitroglycerine showing with leftward and downward shift due to changing loading conditions. (Reprinted from McKay et al. with permission of the publisher)

therapy of hydralazine and isosorbide dinitrate (H-ISDN) is one of the common agents used widely in management of chronic systolic heart failure. There is simultaneous reduction of preload with isosorbide dinitrate and afterload with hydralazine (Fig. 5.5). H-ISDN reduce left ventricular filling pressure and pulmonary capillary wedge pressure, increase cardiac index, and

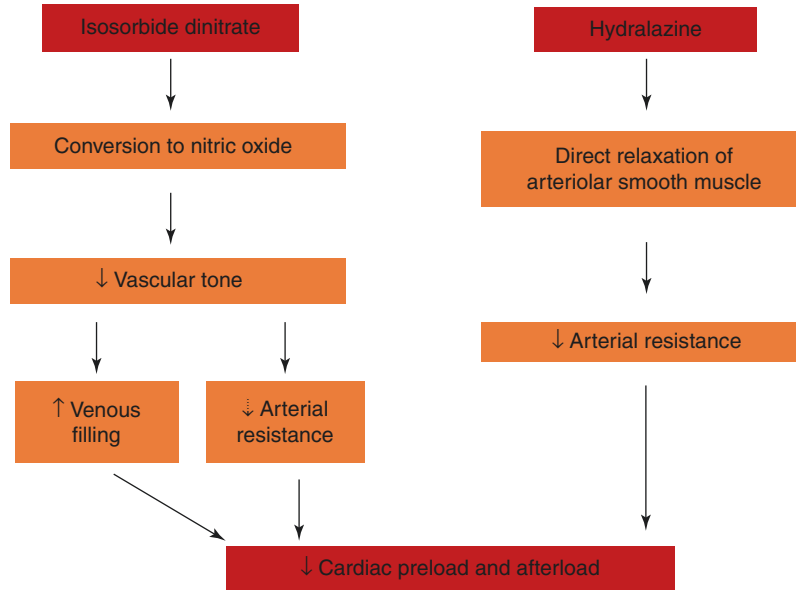

Fig. 5.5 Schematic diagram of mechanism of action of hydralazine and Isosorbide dinitrate

Table 5.6 Key clinical outcome trials of vasodilators in cardiovascular diseases

Trial and year	Active arm (N)	Comparator (N)	Patients	Primary outcome	Follow-up	Major findings
V-HeFT I, 1986	Hydralazine-Isosorbide dinitrate	Placebo	Chronic heart failure	All-cause mortality	2.3 years	Hydralazine-Isosorbide showed 36% reduction in all-cause mortality
A-HeFT, 2004	Hydralazine-Isosorbide dinitrate	Placebo	Chronic heart failure	Composite all-cause mortality, heart failure hospitalizations, and change in quality of life	10 months	Hydralazine-Isosorbide showed 43% reduction in all-cause mortality
WMAC, 2002	IV nesiritide (204), IV nitroglycerin (143)	Placebo (142)	Acute decompensated heart failure	Change in PCWP or dyspnea	3 h, 24 h	Nesiritide improved PCWP at 3 and 24 h than IV nitroglycerin or placebo. Nesiritide resulted in improvement in dyspnea compared with placebo but not IV nitroglycerin
ROSE, 2013	IV dopamine (122), IV nesiritide (119)	Placebo (119)	Acute decompensated heart failure	72-h cumulative urine volume, change in serum cystatin C	72 h	Low-dose dopamine or low-dose nesiritide showed no benefit when added to diuretic therapy

IV intravenous, *PCWP* pulmonary capillary wedge pressure

reduce systemic vascular resistance [23]. These properties make H-ISDN an effective therapy in patients with systolic heart failure. When compared to enalapril, H-ISDN resulted in greater improvements in ejection fraction, peak exercise oxygen consumption, and exercise tolerance [24]. Nesiritide, a synthetic natriuretic peptide, is an intravenous vasodilator with diuretic properties. In patients with heart failure, nesiritide produces dose-dependent balanced arterial and venous vasodilatation leading to reduction in pulmonary capillary wedge pressure, with minimal effect on cardiac contractility or output. Nesiritide also possesses anti-fibrotic, anti-hypertrophic, anti-inflammatory, and aldosterone-inhibiting properties, and may prevent adverse left ventricular remodeling. In a small study, low-dose nesiritide showed reduction of cardiac dilatation and improvement in ejection fraction in patients with acute myocardial infarction. The role of intravenous vasodilators is predominantly limited to management of acute decompensated heart failure. For oral agents, H-ISDN is a part of guideline-directed medical therapy for patients with chronic systolic heart failure. Hydralazine and long-acting nitrates are occasionally used in management of resistant hypertension. Table 5.6 summarizes key landmark trials of vasodilators in management of patients with acute and chronic systolic heart failure.

Review Questions

Question 1: Angiotensin-converting enzyme inhibitors:

A. Decrease preload
B. Decrease afterload
C. May cause hyperkalemia
D. Improve long-term outcome for patients with HFrEF
E. All of the above are correct

Answer 1: E. ACEIs are associated with all of the listed choices.

Question 2: 4. An elderly, nonverbal male is admitted to your facility after initial treatment for a heart attack. You notice that over the past 3 days, he has become lethargic. His appetite has decreased. His urine output has decreased. His blood pressure has been 190/100. His weight has increased 2 pounds. He has rales on his lung examination. His lower extremities are cold with trivial swelling.

Given the above scenario what would be the best way to improve his current state?

A. Decrease his afterload with an ACE inhibitor
B. Decrease his afterload with a beta-blocker
C. Decrease his afterload with a pure vasodilator
D. Decrease his preload with a diuretic
E. Both A and B
F. Both A and D

Answer 2: C. This patient is already exhibiting a decreased CO (cold extremities) and evidence of congestion at rest (rales on examination). A pure afterload-reducing agent would be optimal at this point. Any agent that may decrease this patient's preload will make an already low cardiac output worse. ACEI decrease preload and afterload. Beta-blockers do not decrease afterload but negatively impact contractility and heartrate. Giving a diuretic alone to this person will decrease an already low CO further through a decrease in preload.

Question 3: The mechanism(s) by which ACEIs decrease preload is:

A. Venodilation
B. Inhibition of bradykinin breakdown
C. A direct effect on sodium reabsorption
D. Both A and B
E. Both A and C

Answer 3: D. ACEI decreases both preload and afterload. The mechanism(s) by which these agents decrease preload are thought to be the following: Decrease breakdown of bradykinin and through its effect on decreasing angiotensin II levels. Bradykinin is a potent venodilator and the increase in bradykinin with ACEI use is a major contributor to the reduction in preload seen with these agents.

Question 4: A 68-year-old male presents with an acute anterior MI. After a successful PCI of the proximal LAD, he is started on statin, dual antiplatelet therapy, an ACEI, and beta-blocker. What would be an indication to initiate an aldosterone antagonist?

A. He is a nondiabetic with depressed ejection fraction and no heart failure

B. He is a diabetic with depressed ejection fraction and no heart failure
C. He is a nondiabetic with depressed ejection fraction, heart failure and a serum creatinine of 2.8
D. He is a diabetic with a depressed ejection fraction, heart failure and a serum potassium of 5.1 mmol/liter

Answer 4. B. In the Ephesus trial, patients with an acute MI and the presence of a reduced EF (≤40%) and heart failure (rales, pulmonary venous congestion, or an S3) were randomized to eplerenone or placebo. Diabetic patients could be randomized without any evidence of heart failure. Exclusion criteria included a potassium >5 mmol/liter and a serum creatinine >2.5 mg/dl.

Question 5: ARBs and ACEIs:

A. Both decrease angiotensin II levels
B. Both decrease plasma renin activity
C. Both increase levels of bradykinin
D. Both increase plasma renin activity

Answer: D. Both ACEI and ARB increase plasma renin activity. ACEI decrease angiotensin II levels while ARBs are associated with increased levels. ACEI block the breakdown of bradykinin while ARBs do not.

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6 Beta Blockers and Calcium Channel Blockers

Alexandra-Maria Neagoe, Emrush Rexhaj, Ehud Grossman, and Franz H. Messerli

Introduction

In this chapter, we present pharmacological characteristics and hemodynamic effects of beta blockers (BBs) and calcium channel blockers (CCBs) as well as their main therapeutic indications. These classes of medications are two of the most frequently used for the treatment of cardiovascular diseases such as arterial hypertension, arrhythmia, and heart failure. The main clinical studies will be summarized.

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Beta Blockers

Introduction

Propranolol was the first BB discovered in 1964 by Sir James Black while he was working on the effects of adrenalin on heart in patients with angina pectoris [1]. Ever since, BBs have been the most prescribed drug class in cardiovascular disorders, especially in patients after myocardial infarction. The term "cardioprotection" was extensively used to describe their benefits. As their name indicates, BBs block the action of adrenaline and noradrenaline at β-adrenergic receptors. Table 6.1 summarizes the distribution and the main responses of activation of β-adrenergic receptors. Depending on the selectivity of their actions, they are divided in two groups: cardioselective and non-cardioselective. The stimulation of β1-receptors increases heart rate (chronotropy) and myocardial contractility (inotropy) and speeds up atrioventricular node conduction (dromotropy), while the stimulation of β2-receptors induces vasodilation and bronchodilation and stimulates glycogenolysis in the liver. Thus, inhibition of β1-receptors by BBs results in decreased chronotropy, inotropy, and dromotropy and increased relaxation (lusitropy). At low doses β1-selective BBs act more selectively at a cardiac level, with insignificant effects on vascular and bronchial β-receptors,

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_6

reducing in that way the risk of vasoconstriction and bronchospasm. These cardioselective effects are dose dependent and may disappear with high doses.

Table 6.1 Distribution of α- and β-receptors and mediated effects

Receptor subtype	Organ system	Effect
α	Blood vessel	↑ Constriction
	Uterus	↑ Contraction
	Pancreas	↓Insulin secretion
β1	Heart	↑ Heart rate
	Kidneys	↑ Contractility
	Adipose tissue	↑ Conduction
	Parathyroid glands	↑ Excitation
		↑ Automaticity
		↑ Renin secretion
		↑ Lipolysis
		↑ Secretion
β2	Heart	↑ Heart rate
	Blood vessels	↑ Contractility
	Skeletal muscle	↑ Conduction
	Liver	↑ Excitation
	Lungs	↑ Automaticity
	Pancreas	↑ Vasodilation
	Uterus	↑ Glycogenolysis
	Urinary bladder	↑ Contractility
	Gastrointestinal	↑ Potassium uptake
	Gall bladder and ducts	↑ Bronchodilation
	Nerve terminals	↑ Insulin and glucagon secretion
	Thyroid	↑ Relaxation
	Parathyroid glands	↑ Adrenaline release
		↑ T4-T3 conversion
		↑ Secretion

Pharmacological Characteristics of Beta Blockers

Some specific *pharmacological* properties of BBs distinguish one agent from another (Table 6.2): (1) cardioselectivity and relative affinity for the β1- and/or β2-receptors; (2) intrinsic sympathomimetic activity (slow heart rate less than other BBs by partially acting as β-agonist); (3) lipid solubility; (4) half-life elimination and the way of elimination; (5) additional effects of the drug such as vasodilation.

As Poirier et al. have pointed out in an excellent review [2], the following are of clinical significance:

1. Cardioselectivity

By definition, cardioselectivity represents the property of an agent to block β1-receptors, predominantly present in the heart and renal juxtaglomerular apparatus. Nebivolol and bisoprolol are the agents with the highest β1-selectivity. The β2-inhibition is also dose related, so agents with β1-inhibition can also inhibit β2-receptors at higher doses. Bronchial reactivity in asthma appears to be less enhanced with more cardioselective BBs and is a concern with nonselective agents.

2. Vasodilation

Some agents such as nebivolol and carvedilol exert their effects through vasodilatory properties. Nebivolol administration in healthy subjects

Table 6.2 Pharmacological properties of selected beta blockers

β-Blocker	β-Receptor activity	Membrane stabilizing activity	Intrinsic sympathomimetic activity	Vasodilatation	Elimination half-life (hours)	Route of elimination	Lipid solubility
Propranolol	No	Yes	No	No	3.5–6	Hepatic	High
Atenolol	β1	No	No	No	6–7	Renal	Low
Bisoprolol	β1	No	No	No	9–12	Renal	Low
Carvedilol	No	No	No	Yes	7–10	Hepatic	Moderate
Metoprolol	β1	At high levels	No	No	Tartrate 3–4 Succinate 3–7	Hepatic	Moderate
Nebivolol	β1	No	No	Yes	12	Hepatic	Low
Sotalol	No		No	No	12	Renal	Low

decreased systolic and diastolic blood pressure, and heart rate at rest and during submaximal and maximal exercise [3]. BBs with vasodilation effect (carvedilol via α1 blockade and nebivolol via stimulation of NO release) significantly decrease central blood pressure and wave reflection (augmentation index) as compared to atenolol [4]. Carvedilol and nebivolol have been shown to improve left ventricular systolic function in patients with nonischemic heart failure [5].

3. Lipophilicity/Hydrophilicity

Lipophilic agents such as propranolol, metoprolol, and nebivolol have the ability to cross the blood-brain barrier and have a shorter half-life. They are mainly eliminated through hepatic metabolism and are more susceptible to drug interaction. Due to crossing of blood-brain barrier, one of the most common side effects is vivid dreams and nightmares. Hydrophilic agents are eliminated mainly through renal metabolism, and their dosage needs to be adjusted in renal failure. Special attention needs to be given to sotalol in patients with renal failure since its accumulation might lead to torsade de pointes.

Hemodynamic Effects of Beta Blockers

Due to different properties, there is a difference in the cardiovascular hemodynamics of different BBs.

Intravenous administration of propranolol in anesthetized dogs decreased heart rate, myocardial contractile force, and cardiac output, whereas it increased LV end-diastolic pressure, left atrial pressure, and total and pulmonary peripheral resistances [6]. As shown by Nakano and Kusakari, acute administration of cumulative doses of propranolol results in a shift to the right of the left ventricular function curves, resulting in a reduction of cardiovascular performances. In a small study published in 1967 [7], it was showed the administration of propranolol to healthy subjects while exercising was associated with a reduction of cardiac output, mean arterial pressure, left ventricular minute work, and maximal O_2-uptake and increased the calculated arteriovenous O_2 difference and the central venous pressure. The administration of the same medication in patients with heart disease showed the same effect, although the cardiac outputs achieved during exercise were usually lower than in normal subjects. The cardiac output in patients under propranolol decreased 18%. At the same time, in all patients the heart rate as well as the pulmonary arterial O_2 saturation decreased. The reduction of cardiac output by only 18% with beta blockade suggests there are also other mechanisms through which the cardiac output is increasing during exercise, not only sympathetic stimulation.

The decrease of cardiac output with BBs was noted in another study [8]. Carvedilol, propranolol, bopindolol, and celiprol have each showed a decrease in cardiac output. The maximum decrease was induced by administrating propranolol, whereas the minimum through administrating celiprol. At the same time, in comparison to propranolol, improved coronary flow through coronary vasodilatation as well as reduced peripheral resistance has been demonstrated with carvedilol.

Nebivolol on the other hand has been proven to maintain the cardiac output while concomitantly reducing the arterial stiffness, vascular resistance, blood pressure, and heart rate and increasing the systolic function and stroke volume. Peripheral vasodilatation is caused by nitric oxide release [9].

To conclude, the non-vasodilating beta blockers increase the afterload through increase of the peripheral resistance, while the beta blockers with vasodilating properties cause a decrease of afterload through reducing the peripheral resistance and therefore reducing the blood pressure. At the same time all beta blockers cause bradycardia which consequently decreases the myocardial oxygen consumption and increases the duration of diastole, thereby increasing preload.

Effect on Central Pressure

Studies have shown the carotid and aortic blood pressure (BP) curves are a result of the summation of two different waves: a forward wave coming from the heart during ventricular ejection and a backward wave that has been reflected at the periphery back toward the heart. Normally, when there is physiological ventricular-vascular coupling, the reflected pulse wave returns to the left ventricle in diastole and serves to increase coronary perfusion. When resting heart rate (RHR) is slowed down by a negative chronotropic drug, the reflected pulse wave may return during ventricular systole. The resulting ventricular-vascular mismatch will augment central systolic pressure. To maintain cardiac output when RHR is low, the stroke volume has to increase in parallel with the fall in RHR. An elevated stroke volume will increase pulse pressure, which, in turn, is prone to increase systolic and decrease diastolic BP, particularly when aortic Windkessel function is impaired. For obvious reasons not all BBs are created equal; the vasodilating agents have little if any effect on central pressure [10].

The Therapeutic Indications of Beta Blockers

Hypertension

The mechanism of lowering BP is not clear; no single mechanism can explain the effect for all agents in this class of medication. One possibility is that lowering the cardiac output results in lower blood pressure and increased peripheral resistance [6]. Continuous therapy results in a decrease in peripheral resistance, but still above pretreatment levels and in consequence cannot be the only mechanism responsible for blood pressure lowering [11]. The second possibility is the decrease in sympathetic activity in the central nervous system results in a reduced sympathetic activity in the periphery. This is however only true for agents that cross the blood/brain barrier. Hydrophilic agents like practolol and sotalol do not decrease peripheral sympathetic activity while lowering blood pressure [12]. The reduction of renin secretion, and the consequent reduction of angiotensin II in plasma, is another possible mechanism [13–15]. The BBs with ISA such as pindolol have been shown to increase plasma renin levels while simultaneously reducing the blood pressure [11]. Blocking the β2-receptors diminishes the release of norepinephrine which consequently reduces the BP. This is obvious with nonselective agents such as propranolol, whereas β1 selective agents such as atenolol seemingly are good blood pressure lowering agents [16] However, as already described before, there is a pseudo-antihypertensive effect due to elevation (or lesser decrease) of the central aortic pressure. The slower the heart rate, the greater the pseudo-antihypertensive effect, and the less the reduction in morbidity and mortality [17].

The American, British, and most other formal hypertension guidelines no longer recommend the use of BBs as first-line therapy, except in some patients with ischemic heart disease or heart failure. In older patients, BBs have never been shown to reduce the risk of heart attack, stroke, and/or death [18].

The European guidelines for hypertension still consider the use of BBs as a class I indication for monotherapy or combined therapy. The preferred combination consists of thiazide diuretics, calcium antagonist, and ACE inhibitors/angiotensin receptor blockers with addition of BB in specific situations. Thus we should consider BBs in certain clinical conditions (e.g., aortic dilatation or patients who are symptomatic in case of excessive sympathetic activity). In the young, both atenolol and non-atenolol BBs have been proven to reduce the cardiovascular endpoints for hypertension without other indication. Atenolol is associated with an increased risk for stroke in the elderly, but whether this extends to other non-atenolol BBs is uncertain [19]. The availability of vasodilating BBs with both alpha and beta effect influences positively the cardiac output, heart rate, blood pressure, and systemic vascular resistance. Carvedilol may be superior to traditional BBs in several regards, it has a lower rate of new-

onset diabetes, it has a beneficial effect on lipid profile, and it increases plasma flow to the kidneys [20]. Due to well-documented adverse effects as well as different responses in different patient population, the use of BBs should be used selectively if at all in hypertension.

Arrhythmia

BBs have not only an antihypertensive effect but also an antiarrhythmic effect. They are considered to be class II agents in the Vaughan Williams classification. They act by blocking the effects of catecholamines at the site of β1-receptor, thereby decreasing the sympathetic activity in the heart.

The European guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death recommend BBs as a first-line therapy in the management of ventricular ectopic beats and ventricular tachycardia and the prevention of sudden cardiac death in patients with or without heart failure. Furthermore, the same guidelines recommend the use of BBs in patients with long QT-syndrome.

BBs are also used as rate control therapy in patients who have atrial fibrillation (AF). Importantly, a mortality benefit in patients with atrial fibrillation receiving BBs in comparison with placebo in patients with heart failure with reduced ejection fraction (HFrEF) has not been shown [21]. In general, BBs do not reduce the risk of AF or recurrent AF after ablation. However, in patients with HFrEF in sinus rhythm pretreated with ACE inhibitors/ARBs, BBs were shown to reduce the incidence of AF [21].

Sotalol is the only BB used as a rhythm control therapy in patients with atrial fibrillation and normal ventricular systolic function. However, there is a risk of torsades de pointes so the benefits and risks have to be taken into consideration when administrating sotalol.

Heart Failure

BBs are part of the standard therapy for HFrEF along with ACE inhibitors and diuretics since it has been proven to reduce the mortality and morbidity in such patients [22–28]. BBs should be started in stable patients and gradually up-titrated to the maximum tolerated dose. In patients admitted due to acute heart failure, BBs should be initiated under medical surveillance once the patient is stable.

Coronary Artery Disease

BBs have been shown to reduce the cardiovascular mortality after a myocardial infarction [29–31]. The reduction in mortality was shown to be smaller in Afro-Americans, patients 80 years old or older, and those with an ejection fraction below 20% or patients with renal insufficiency or diabetes. After a myocardial infarction, even in patients with relative contraindications such as pulmonary disease, BBs have shown a benefit [32]. The necessity as well as the duration of BBs after a non ST-elevation myocardial infarction in patients where the ejection fraction is normal or close to normal still needs to be assessed [33, 34].

Beta blockers are also used in stable coronary artery disease to treat patients with stable angina. The antianginal effect is explained through a reduction in myocardial oxygen demand.

Conclusion

After five decades of clinical experience, heart failure with reduced EF remains the only iron-clad indication for BBs in cardiovascular disease – the very indication that decades ago was considered to be the only contraindication for BB therapy. Many of so-called cardioprotective effects of BBs were mostly based on old studies and on hearsay and have never been documented in contemporary prospective randomized trials [35, 36].

Calcium Channel Blockers (CCBs)

Introduction

The observation made by Fleckenstein in 1967 that a reduction of calcium movement into cardiac myocytes determined a negative inotropic effect facilitated the development of calcium antagonist drugs, currently called calcium channel blockers (CCBs). CCBs were introduced for the treatment of hypertension in the 1980s. Their

use was subsequently expanded to disorders such as angina pectoris, paroxysmal supraventricular tachycardia, hypertrophic cardiomyopathy, coronary spasm, Raynaud phenomenon, pulmonary hypertension, esophageal spasms, migraine, and cerebral vasospasm. In this chapter, the main hemodynamic and cardiovascular effects of CCBs will be summarized.

Mechanism of Action

The mechanism of action is reducing the cytosolic free calcium concentration by blocking calcium entry into cells, acting on the L (long-lasting) subtype. There is a difference in selectivity for L-Type and T-Type channels, although all calcium blockers act on both subtypes. Mibefradil has showed the highest selectivity on the T-Type channels, whereas lacidipine was showed to have the highest selectivity on the L-Type channels [37].

Classification

According to their chemical structure, CCBs can be subdivided into dihydropyridines (nifedipine, amlodipine, nitrendipine) and non-dihydropyridines. The non-dihydropyridines are divided into two major groups: (1) phenylalkylamines (verapamil) and (2) benzothiazepines (diltiazem) (Table 6.3). CCBs act on different receptor sites on Ca channels due to their different molecular structure. Since their discovery, there has been an evolvement of different CCB generations. The first generation is characterized by a rapid onset of action and very short half-life, whereas the second and third generations provide a longer duration of action or extended-release mechanisms, poor activation of the sympathetic nervous system, and fewer side effects [38–40] (Fig. 6.1).

Cardiovascular Hemodynamics

CCBs vary in their effects on cardiovascular hemodynamics. Dihydropyridines such as amlodipine and nifedipine are potent arterial vasodilators, whereas non-dihydropyridines work primarily on the heart; phenylalkylamines (verapamil) have a negative chronotropic, dromotropic, and inotropic effect with a positive lusitropic effect, while benzothiazepines (diltiazem) have intermediate chronotropic, dromotropic, and inotropic effects (Table 6.4 and Fig. 6.2).

All CCBs lower arterial pressure when given over the short term and with prolonged administration [41–46]. Head-to-head comparisons of five different calcium antagonists reveal little, if any, difference in blood pressure lowering potency among the various agents, provided that adequate doses are given.

Table 6.3 CCB classification, recommended uses, and adverse effects

Calcium channel blockers	Amlodipine, clevidipine, nicardipine, nifedipine, nimodipine (dihydropyridines, act on vascular smooth muscle); diltiazem, verapamil (non-dihydropyridines, act on heart)
Mechanism	Block voltage-dependent L-type calcium channels of cardiac and smooth muscle → ↓ muscle contractility
	Vascular smooth muscle – amlodipine = nifedipine > diltiazem > verapamil
	Heart – verapamil > diltiazem > amlodipine = nifedipine (verapamil = ventricle)
Clinical use	Dihydropyridines (except nimodipine): hypertension, angina (including Prinzmetal), Raynaud phenomenon
	Nimodipine: subarachnoid hemorrhage (prevents cerebral vasospasm)
	Nicardipine, clevidipine: hypertensive urgency or emergency
	Non-dihydropyridines: hypertension, angina, atrial fibrillation/flutter
Adverse effects	Non-dihydropyridine: cardiac depression, AV block, hyperprolactinemia, constipation
	Dihydropyridine: peripheral edema, flushing, dizziness, gingival hyperplasia

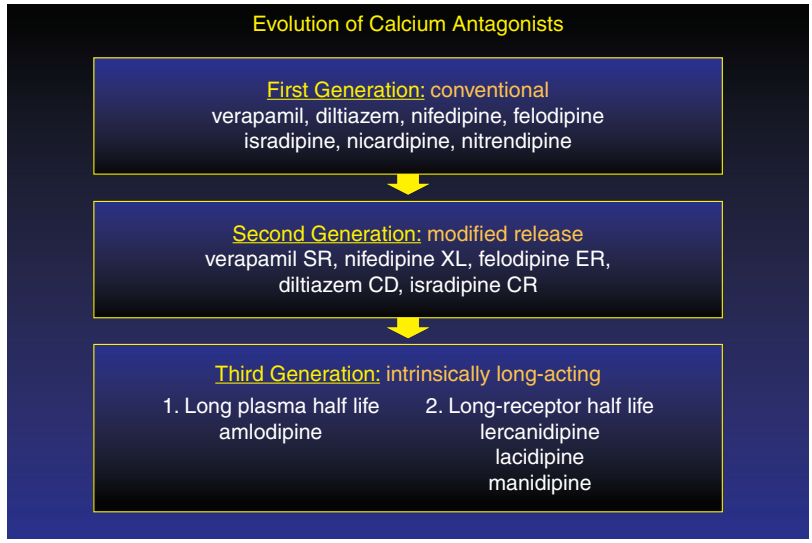


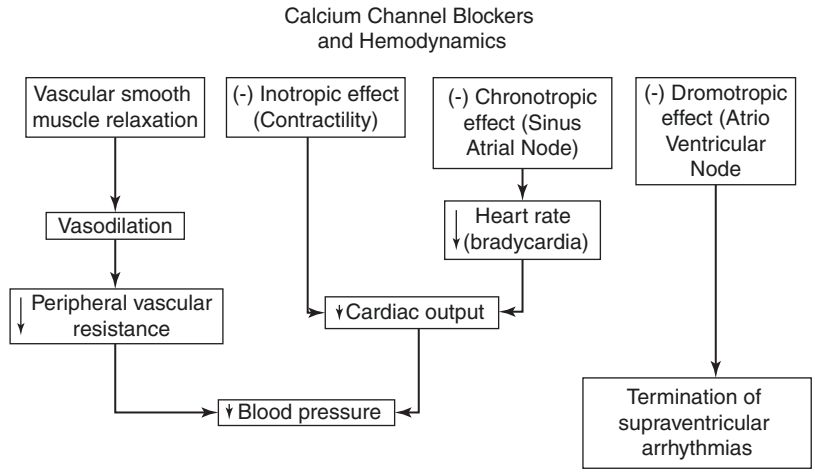
Fig. 6.1 Evolution of CCBs

Table 6.4 Effect of calcium channel blockers

	Dihydropyridines	Non-dihydropyridines	
		Benzothiazepines	Phenylalkylamines
	Amlodipine	Diltiazem	Verapamil
(−) Chronotropic effect	–	↓	↓
(−) Dromotropic effect	–	↓	↓
(−) Inotropic effect	↓/–	↓↓	↓↓
(+) Lusitropic effect	↑	↑↑	↑↑
Peripheral dilatation	↑↑	↑	↑
Coronary dilatation	↑	↑	↑
Cardiac output	–	↓	↓
Blood pressure	↓	↓	↓

(−) negative effect, ↑ increase, ↓ decrease, – no difference

Fig. 6.2 Effect of CCBs on hemodynamics



Left Ventricular Hypertrophy

Most CCBs tend to reduce left ventricular mass (LVM) when given for a sustained period [41–43, 45, 47–85]. In a meta-analysis of 80 randomized, double-blind trials, calcium antagonists decreased LVM by 11% compared with a 10% decrease by ACE inhibitors, 8% decrease by diuretics, 6% decrease by β-blockers, and 13% decrease by angiotensin receptor blockers [85]. The decrease in LVM documented with CCBs is associated with improved ventricular filling, diminished ventricular ectopy, and preserved LV contractility. Evidence from experimental studies indicates that nifedipine, nisoldipine, and amlodipine additionally lead to regression of interstitial and perivascular myocardial fibrosis, which may contribute to the improvement of diastolic function (see below) and coronary reserve.

Effects on Cardiac Contractility

By and large, CCBs are negative inotropic agents and, therefore, are likely to impair cardiac pump function to some extent [86–98]. The most profound negative inotropic effect is seen with verapamil and diltiazem. To some extent this effect is overridden by afterload reduction and reflexive sympathetic activity elicited predominantly by the dihydropyridine derivatives. Favorable hemodynamic responses such as a decrease in pulmonary wedge pressure and end-diastolic ventricular pressure were documented when isradipine, felodipine, and amlodipine were given over the short term. However, improvement of hemodynamics in patients with heart failure did not translate into an increased survival rate. In the Prospective Randomized Amlodipine Survival Evaluation (PRAISE I) [99] study, retrospective subgroup analysis suggested that amlodipine prolonged survival only in patients with nonischemic dilated cardiomyopathy; there was no beneficial effect on cardiovascular morbidity or mortality in patients with ischemic cardiomyopathy. A follow-up trial, PRAISE-2 was specifically crafted to test the hypothesis observed in the prespecified subgroup analysis of a secondary outcome in the original PRAISE study; that is, that amlodipine would reduce the rates of death from all causes in patients with heart failure. The results of PRAISE-2 did not validate the favorable association of amlodipine with improved survival for patients with nonischemic heart failure observed in the initial PRAISE-1 trial. Combined analysis of both trials suggests that amlodipine has no appreciable harmful or beneficial effect on mortality in patients with severe chronic heart failure. Similarly, in the Vasodilator-Heart Failure Trial (V-HeFT) III study, felodipine was safe but not clearly efficacious in patients with heart failure [100].

Left Ventricular Filling

In simplistic terms, left ventricular filling consists of an early diastolic active relaxation phase and a late diastolic passive distensibility phase. CCBs have been documented to have a favorable effect on both. This effect may be heart rate – dependent and appears to be most pronounced with verapamil, less pronounced with diltiazem, and even less so with the dihydropyridine CCBs. However, with prolonged administration of most CCBs, late diastolic passive distensibility is improved as well. The clinical significance of decreased left ventricular filling in patients with hypertension and of its improvement by CCBs is unclear. Certain patients with long-standing hypertension have been documented to have latent or overt heart failure, primarily as a result of impaired filling. In such patients, CCBs that lower heart rate may be helpful because they not only lower arterial pressure but also improve ventricular filling.

Endothelial and Anti-atheromatous Effects

Various experimental studies have documented that CCBs exert anti-atheromatous effects in certain animal models, such as cholesterol-fed rab-

bits. CCBs, particularly of the dihydropyridine class, can reverse endothelial dysfunction in various vascular beds, including subcutaneous, epicardial, and peripheral arteries and forearm circulation. In the Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial [101], the slowest rate of progression of coronary atherosclerosis was observed in those patients whose BP fell within the "normal" JNC-7 category (i.e., systolic BP <120 mm Hg and diastolic BP <80 mm Hg). Administration of amlodipine (but not of enalapril) to patients with CAD and normal blood pressure resulted in reduced adverse cardiovascular events. Intravascular ultrasound imaging noted evidence of slowing of atherosclerosis progression in the amlodipine cohort.

Outcome Data

In a meta-analysis of 15 studies evaluating 47,694 patients with coronary heart disease, Bangalore et al. [102] showed that long-acting CCBs (either dihydropyridines or non-dihydropyridines) were associated with a reduction in the risk of stroke, angina pectoris, and heart failure, with similar outcomes for other cardiovascular events as the comparison group. When compared with placebo, CCBs resulted in a 28% reduction in the risk of heart failure (95% CI, 0.73–0.92). Similarly, in a recent Cochrane meta-analysis on first-line therapy in hypertension, first-line ACE inhibitors and CCBs were similarly effective as low-dose thiazides to reduce all morbidity and mortality outcomes in adult patients [103]. Of note, the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study showed that in combination therapy with benazepril, amlodipine was superior to hydrochlorothiazide in reducing morbidity and mortality [104]. Even in diabetes which was for years a primary indication for blockers of the renin-angiotensin system, a meta-analysis of 19 randomized controlled trials that enrolled 25,414 participants revealed no superiority of ACE inhibitors or ARBs compared to other drug classes such as CCBs in reducing the risk of hard cardiovascular and renal endpoints [105]. Finally, Wang et al. [106] looking at amlodipine specifically in head-to-head studies concluded that compared with other drug regimens, amlodipine-based antihypertensive regimen, as evidenced by the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [107] and Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) [108], the two largest-ever trials in hypertension, might confer more outcome benefit, possibly by better lowering central systolic pressure or ambulatory pressure over 24 hours (Fig. 6.3).

Dihydropyridine CCBs

The most commonly used dihydropyridine CCBs are amlodipine and nifedipine. These drugs induce a selectively transmembrane influx of Ca++ into vascular smooth muscle and cardiac cells, thus causing vasodilation and decreasing the peripheral vascular resistance of coronary arteries and peripheral vasculature (Fig. 6.2). As a result of this effect, blood pressure will be reduced, while coronary blood flow and myocardial oxygen delivery will be increased [109]. The slow-onset, long-acting formulations such as amlodipine, lacidipine, and lercanidipine exert their hemodynamic effects over days and induce long-acting smooth and graded changes of blood pressure.

One of the primary indications for dihydropyridines is blood pressure reduction; many clinical trials have shown that this class of CCBs offers an equivalent reduction in blood pressure when compared to other antihypertensives, which translates into comparable cardiovascular events reduction. These studies include Syst Eur [110], Syst China, ASCOT, ALLHAT, Valsartan Antihypertensive Long-term Use Evaluation (VALUE), and ACCOMPLISH.

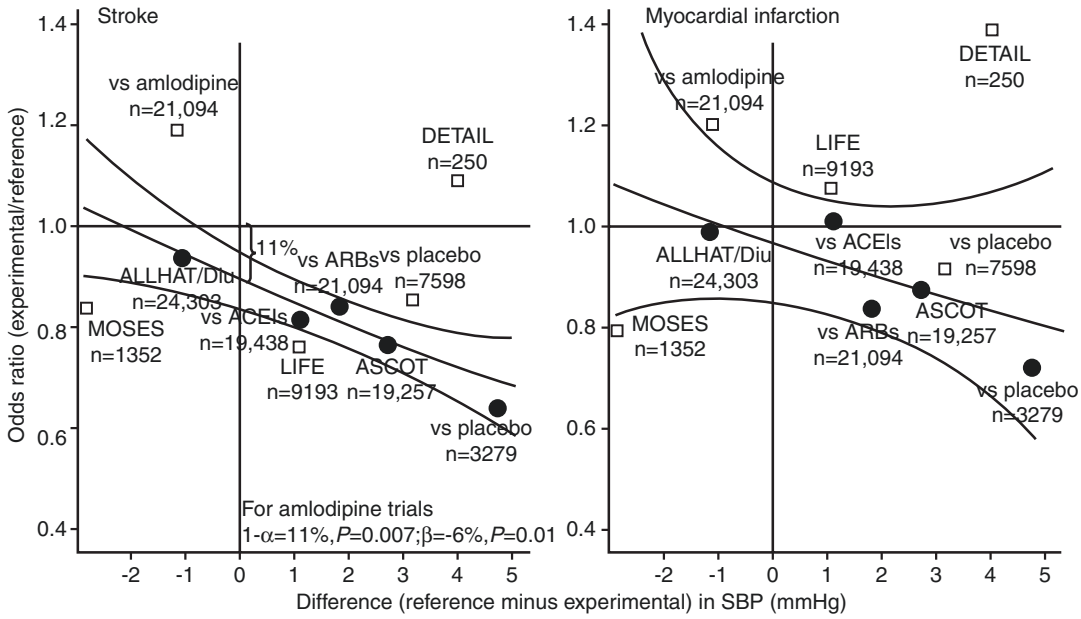


Fig. 6.3 Odds ratios for fatal and nonfatal stroke (left) and fatal and nonfatal myocardial infarction (right) in relation to corresponding differences in systolic blood pressure. Odds ratios were calculated for the amlodipine group vs placebo or other classes of antihypertensive drugs including ARBs (dots) or for the angiotensin receptor group vs placebo or other classes of antihypertensive drugs including amlodipine (squares). Blood pressure differences were obtained by subtracting the mean change in the amlodipine or ARB group from the corresponding mean change in the reference group. When a group of trials was pooled, the blood pressure difference was calculated by averaging the between-group blood pressure difference within each trial with the number of randomly assigned patients as weighting factor. Positive values indicate tighter blood pressure control in the experimental group. The regression line was drawn for trials involving an amlodipine group and weighted by the inverse of the variance of the individual odds ratios [105]

Non-dihydropyridine CCBs

1. *Phenylalkylamines*

The most commonly prescribed CCB in this subclass is verapamil; less commonly used are gallopamil and tiapamil. The systemic vasodilation is moderate and less strong in comparison to dihydropyridines. However, the negative inotropic and negative chronotropic effects induced by verapamil depress sinoatrial (SA) node and atrioventricular (AV) node conduction. As a result, there is commonly a decrease in heart rate. The cardiac output remains stable however due to the increase in stroke volume [111].

Verapamil is most commonly used for decreasing blood pressure and attenuation of angina pectoris. Moreover, verapamil offers similar efficacy as adenosine in reversing supraventricular tachycardia [112–115]. The effects of dihydropyridines and verapamil on atheromatous plaque have been studied in the Verapamil in Hypertension and Atherosclerosis Study (VHAS) trial [116]; in brief, no significant differences between verapamil and chlorthalidone on progression/regression of the atheromatous plaque were appreciated [117]. Studies such as the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) [118] and the International Verapamil SR/Trandolapril Study (INVEST) ([119]) showed the reduction in cardiovascular events was not significantly different compared with drugs such as beta blockers or diuretics. Verapamil should be used with caution in combination with any beta blocker due to the additive negative inotropic and chronotropic effects [120].

2. *Benzothiazepines*

Diltiazem causes vasodilatation, especially in the coronary arteries [121, 122]. Overall, diltiazem has similar hemodynamic properties as verapamil. In atrial fibrillation or flutter without heart failure, diltiazem is preferred over digoxin for control of the heart rate [123]. Due to its moderate negative inotropic and chronotropic effect, the use of diltiazem is contraindicated in patients who have heart failure with reduced ejection fraction [124], sick sinus syndrome [125], and second-degree or third-degree atrioventricular block [126]. For the same reason, combination therapy with beta blockers is also relatively contraindicated.

In the Nordic Diltiazem (NORDIL) trial, the arm treated with diltiazem lowered the risk for stroke compared to the diuretics and β-blocker arm, despite the fact that the systolic pressure was higher in the group treated with diltiazem [127].

Questions

Question 1: A person presents with an anterior MI. Current vital signs are blood pressure 100/60 mmHg, heart rate of 120 beats per minute, rales are noted bilaterally. Extremities are cool with 1+ bilateral lower extremity edema.

Which of the following class of medications should not be initiated acutely?

A. ACEI
B. ARB
C. Beta blocker
D. Diuretic

Answer 1. C. Of all the agents listed, beta blockers would have the most acute deleterious effects. Given CO = HR ∗ SV. The HR in this person is what is maintaining the cardiac output.

Question 2: The optimal time to initiate beta blockers in the above person would be:

A. Immediately
B. Upon initiation of discharge planning
C. Once the person is stable
D. At the same time dobutamine (if required) is being administered
E. Not during this admission

Answer 2: C. Beta blockers should be initiated in patients once they are in a stable state.

Question 3: Beta blockers:

A. Increase contractility, increase heart rate, and decrease dromotropy
B. Increase contractility, decrease heart rate, and decrease dromotropy
C. Decrease contractility, increase heart rate, and increase dromotropy
D. Decrease contractility, decrease heart rate, and decrease dromotropy

Answer 3: D. Beta blockers affect hemodynamics in many ways including negative inotropy, negative chronotropy, and negative dromotropy. The result is decreased contractility, decreased heart rate, and decreased dromotropy.

Question 4: The Prospective Randomized Amlodipine Survival Evaluation (PRAISE 2) trial revealed the following about amlodipine in patients with chronic, severe heart failure:

A. A beneficial effect of amlodipine on mortality in ischemic cardiomyopathy patients
B. A reduction in mortality in nonischemic cardiomyopathy patients
C. No appreciable harmful or beneficial effect in patients with chronic severe heart failure
D. Both A and B

Answer 4: C. Analysis of trials suggests that amlodipine has no appreciable harmful or beneficial effect on mortality in patients with severe chronic heart failure.

Question 5: Arrange the following CCBs in order of their negative inotropic effects:

A. Diltiazem, verapamil, amlodipine
B. Amlodipine, verapamil, diltiazem
C. Verapamil, diltiazem, amlodipine
D. Amlodipine, diltiazem, verapamil

Answer 5: C

Parts of this chapter are modified and updated from Grossman E and Messerli F, Calcium Antagonists, Progress in Cardiovascular Diseases [40].

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Beta Blockers

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CCBs

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7 Pressor Agents, Pure Inotropes, Mixed Function Agents

Paul Anaya and Tracy E. Macaulay

Introduction

In critically ill patients presenting with shock, hemodynamic stability can be achieved using mechanical support with intra-aortic balloon pumps, ventricular assist devices, or extracorporeal membrane oxygenation (ECMO); however, an initial pharmacologic approach is typically undertaken and often preferred. The primary objective of using vasoactive medications is to maintain adequate tissue perfusion and optimize oxygen delivery by improving mean arterial pressure and cardiac output [1, 2]. When considering the use of vasodilators, inotropes, and vasopressors, it is important to be mindful of the balance sought in providing adequate oxygen delivery by maintaining the minimal effective perfusion pressure while simultaneously limiting myocardial oxygen demand and preventing tissue ischemia.

A working knowledge of the hemodynamic effects of these vasoactive agents is the key to guide therapeutic decision-making regarding the choice of vasoactive agent for any given clinical setting. A detailed discussion of basic hemodynamic principles is provided in Part I of this book. To briefly review, cardiac performance is dependent on the physiologic elements of preload and afterload. According to the Frank-Starling principle, stroke volume (or cardiac output) will increase with an increase in preload (Fig. 7.1).

Left ventricular (LV) preload can be estimated by measures of left atrial pressure, pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure. Right ventricular (RV) preload can be estimated by measuring right atrial pressure, central venous pressure, or right ventricular

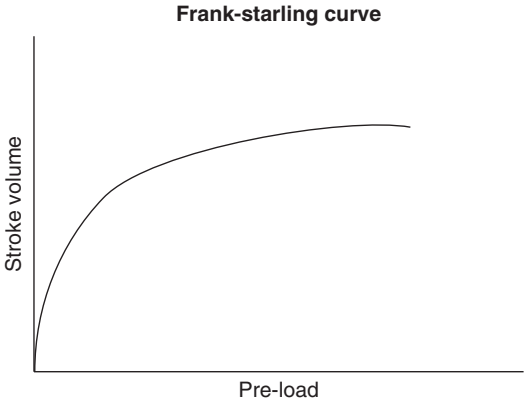

Fig. 7.1 The Frank-Starling curve as it applies in cardiac hemodynamics depicts the relationship between preload and stroke volume or cardiac output

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_7

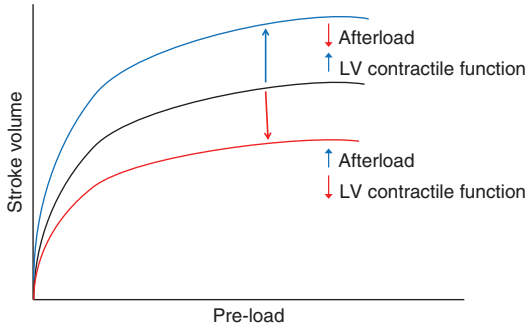

Fig. 7.2 The effects of afterload and intrinsic LV contractility on the Frank-Starling relationship

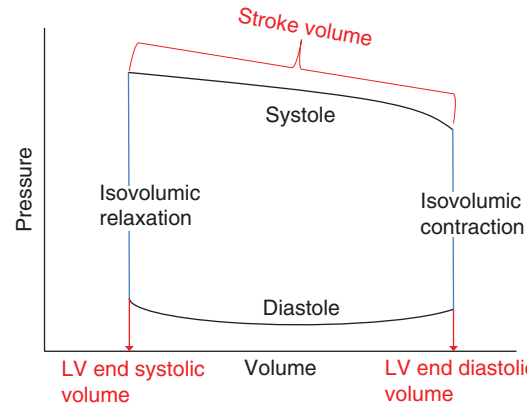

Fig. 7.3 The pressure-volume relation depicts the volumetric and pressure changes that occur through a single cardiac cycle. As is illustrated, the phases of the cardiac cycle include diastole (or filling phase) which begins at the time of mitral valve opening, isovolumetric contraction defined as the time from mitral valve closure until aortic valve opening, systole (or ejection phase) which begins at the time of aortic valve opening, and isovolumetric relaxation defined by the time between aortic valve closure until mitral valve opening heralds the next diastolic phase. Stroke volume is defined as the difference between the volume contained within the ventricle at end diastole and the volume contained at the end of ejection

end-diastolic pressure. In simple terms, preload can be viewed as the distending capacity of the ventricle, and is often referred to as the ventricular filling pressure. An important concept to understand is that in an intact heart surrounded by pericardium, there is a physical limit imposed on the degree of ventricular distention achieved with progressive increases in preload. Furthermore, the distending pressure of the LV is counteracted by, and therefore, determined in part by the surrounding pericardial (or RV) pressure [3]. In mathematical terms, the distending pressure is equal to the ventricular filling pressure minus the pericardial pressure. Under normal physiologic circumstances, the pericardial pressure is negligible and can be ignored such that the distending pressure is equal to the filling pressure. In the setting of acute decompensated heart failure associated with volume overload, the pericardial pressure rises and can no longer be ignored. Thus, while measures of left atrial pressure (or PCWP) may be elevated, the actual distending pressure (i.e., preload) is lower, thereby shifting the relationship of stroke volume to preload leftward along the Frank-Starling curve, resulting in a lower stroke volume. Additionally, as illustrated in Fig. 7.2, regardless from where a patient lies on their specific Frank-Starling curve, a shift of the curve downward for any given preload would imply either an increase in afterload forces or a decrease in the intrinsic contractility of the ventricle. Conversely, a shift of the curve upward for any given preload state would imply either a decrease in afterload or an increase in the intrinsic contractility of the ventricle. Afterload influences cardiac performance in a reciprocal manner such that increases in afterload result in lower cardiac output whereas reduced afterload generally results in improved cardiac output. Left ventricular pressure-volume relations contain information regarding cardiac performance, intrinsic contractile function, preload, and afterload (Fig. 7.3). Historically, these have been generated in the cardiac catheterization laboratory using intracardiac pressure sensors and altering intracardiac volume by pharmacologic or mechanical means. Such alterations in volume produce a series of pressure-volume loops whereby the end-systolic pressure-volume points align (Fig. 7.4). This linear relation is known as the left ventricular end-systolic elastance and defines the intrinsic contractile function of the left ventricle. Additionally, a line drawn from the end-systolic pressure-volume point to the end-diastolic pressure-volume point is known as the arterial elastance and defines the ventricular afterload.

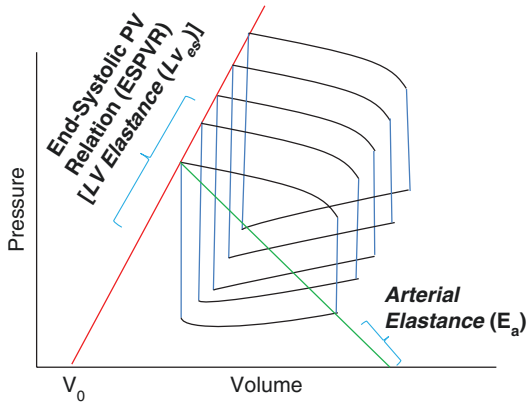

Fig. 7.4 By altering preload, a series of pressure-volume loops can be generated. These can be used to define ventricular end-systolic elastance (LV E_{es}). This end-systolic pressure-volume linear relation is generally accepted as a measure of LV contractility with steeper slopes indicating greater contractility and less steep slopes indicating reduced contractility. Similarly, a linear relationship between the end-systolic pressure-volume point and the end-diastolic pressure–volume point defines arterial elastance (Ea) from which the LV afterload is derived. Black = diastolic and systolic phases of the cardiac cycle; blue = isovolumetric phases; red = LV elastance (LV contractility); green = arterial elastance (afterload)

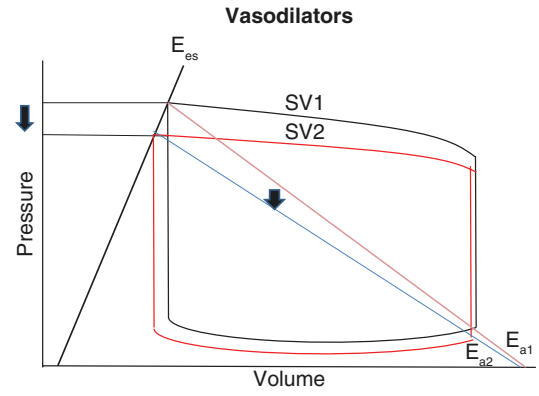

Fig. 7.5 Hemodynamic effects of vasodilators. A reduction in afterload is depicted as a downward shift in the arterial elastance ($E_{a1} \rightarrow E_{a2}$) and a decrease in the end-systolic pressure. This results in an increase in the stroke volume (SV2 > SV1). Vasodilators do not affect the LV contractility. Black = baseline hemodynamic profile; red = hemodynamic profile after intervention

Pharmacologic Fundamentals and Hemodynamic Effects

Vasodilators

Vasodilator therapy is most frequently used in the treatment of hypertension. It is also useful in patients with left ventricular systolic dysfunction (LVSD) with or without pulmonary edema, and has demonstrated a mortality reduction in both acute and chronic management [4, 5]. The primary site of action for vasodilators is the peripheral vasculature where they facilitate the effects of nitric oxide (NO), or act as direct NO donors, to potentiate vasodilatation. Vasodilators used in acute decompensated heart failure or cardiogenic shock include nitroprusside and nitroglycerin. While ace inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, hydralazine, and long-acting oral nitrates can also achieve vasodilatation, these are more typically used in the management of chronic heart failure or hypertensive crisis [6–8]. Since the primary effect of vasodilators is to reduce the systemic vascular resistance, the expected pressure-volume relation would yield a tracing in which stroke volume is augmented simply by decreasing the LV afterload (Fig. 7.5). These agents also have variable effects on venodilation and therefore may also cause a slight reduction in preload. No change to LV contractility occurs, so the end-systolic pressure-volume relation remains constant.

Nitroglycerin

Nitroglycerin (NTG) is a direct NO donor, providing an exogenous source of NO which increases vascular cGMP resulting in smooth muscle relaxation (Table 7.1). Nitroglycerin acts as a preferential venodilator, thereby reducing cardiac preload. It also is an effective coronary artery vasodilator, making it an ideal choice for the patient with myocardial ischemia, hypertension, and/or elevated pulmonary capillary wedge pressure. Contraindications include right ventricular failure, hypertrophic cardiomyopathy, pericardial disease, or pericardial tamponade. Despite favorable hemodynamic effects, no mortality reduction from the use of intravenous nitrates has been demonstrated in large clinical trials [6, 7].

Table 7.1 Vasodilators

Generic (brand)	Starting dose	Maintenance and titration	Adverse drug Rxn	Precautions and contraindications	Uses
Nitroglycerin (Nitrostat IV)	5 mcg/min	Increase every 3 min to max 200 mcg/min	Headache, tachyphylaxis	RV failure, pericardial dz, restrictive cardiomyopathy	Used to treat symptoms of ischemia (low doses), hypertension (high doses), and pulmonary edema
Nitroprusside (Nipride)	0.5 mcg/kg/min	Increase every 5 min to max 5–10 mcg/kg/min; ideally 48 h	Cyanide toxicity and methemoglobinemia with prolonged use and/or high dose	Severe renal, liver impairment	Acute decompensated heart failure due to high afterload, cardiogenic pulmonary edema
Diltiazem (Cardizem)	Arrhythmias – 10 mg IVP (0.25 mg/kg)	5–20 mg/h infusion	AV nodal blockade	Congestive heart failure, bradycardia, sick sinus syndrome, WPW	Atrial fib/flutter, PSVT
Verapamil (Isoptin)	Arrhythmias – 2.5–5 mg IVP	N/A	AV nodal blockade	Congestive heart failure, bradycardia, sick sinus syndrome, WPW	Atrial fib/flutter, PSVT
Nicardipine (Cardene)	No bolus	3–15 mg/h	Low BP, tachycardia, edema	Aortic stenosis	Hypertensive crisis
Nesiritide (Natrecor)	2 mcg/kg IV	0.01 mcg/kg/min; max 0.03 mcg/kg/min; titrate by 0.005 mcg/kg/min q3 h	Low BP, renal failure	Valvular heart dz, pericardial dz, hypotension, restrictive cardiomyopathy	Acute decompensated heart failure with volume overload

Tachyphylaxis can develop within 24 h of continuous therapy, but can generally be overcome by increasing the dose or providing a nitrate-free interval if possible [8].

Sodium Nitroprusside

Sodium nitroprusside is an endothelium-independent vasodilator like nitroglycerin, serving as a direct NO donor within the vasculature. Unlike nitroglycerin, nitroprusside is associated with preferential arterial vasodilating properties [9]. Therefore, while capable of reducing cardiac preload much like nitroglycerin, it has a more potent afterload reducing capability. Unlike other vasodilators, nitroprusside causes only mild increases in heart rate and an overall decrease in myocardial oxygen demand. The molecular composition of sodium nitroprusside includes five cyanide ions which can accumulate as either cyanide or thiocyanate in patients with liver or renal failure, respectively, thereby limiting its applicability. Patients receiving high doses (10 mcg/kg/min) for a prolonged time (>2 days) are particularly at risk of toxicity. Despite this, nitroprusside is considered to be the gold standard intravenous antihypertensive for its remarkable effectiveness and rapid onset of action (Table 7.2).

Other Vasodilators

Intravenous calcium channel blockers, specifically diltiazem, have several important roles in the management of various clinical conditions. Blockade of calcium entry into coronary and peripheral arterial smooth muscle cells results in vasodilation and has a negative chronotropic and negative inotropic effect on the myocardium. The negative chronotropic effects are useful for the management of rapid ventricular heart rates, particularly in patients with supraventricular tachycardia. It is important to note that the significant negative inotropy means diltiazem is only recommended in patients with normal ejection fraction and absence of clinical heart failure. Diltiazem may also play a role in the management of hypertensive urgency and emergency; however, its long biological half-life of 3–4.5 h, makes it less useful than medications with a more rapid onset and easier titration. Also, due to the delayed onset of action, an intravenous bolus of IV diltiazem would typically precede initiation of a continuous infusion.

Esmolol is a β-1 selective adrenergic receptor blocker that has a very rapid onset and short duration of action, making it easily titratable. Unlike labetolol and carvedilol, esmolol exhibits very weak vasodilator effects and therefore is *not* clinically useful as a vasodilator. Rather, its negative chronotropic effect predominates, hence its utility in the treatment of tachyarrhythmias. A resurgent interest in use of esmolol in the treatment of septic shock, mainly due to his negative chronotropic effects, has recently emerged and is a topic of current investigations [10].

Nesiritide is a recombinant B-type natriuretic peptide. Early studies demonstrated that the main clinical effect of nesiritide is peripheral vasodilatation [11]. Nesiritide also induces a

Table 7.2 Comparison of intravenous vasodilators

	NTG	Nitroprusside	Diltiazem	Verapamil	Nicardipine
Mech. of action	Nitric oxide donor, ↑cGMP	Nitric oxide donor, ↑cGMP	Calcium channel blocker	Calcium channel blocker	Calcium channel blocker
Hemodynamic effect	Venodilation>arterial	Arterial and venous vasodilator	Decrease HR, vasodilator	Decrease HR, vasodilator	Vasodilator
Contractility	No effect	No effect	Decrease	Decrease	No effect
Heart rate (HR)	No direct effect (possible reflex tachycardia)	↑ (reflex)	0/↓	0/↓	↑ (reflex)
SA automaticity	No effect	No effect	Decrease	Decrease	No effect
AV conduction	No effect	No effect	Decrease	Decrease	No effect
Vasodilation	↑↑	↑↑↑↑	↑↑↑	↑↑↑↑	↑↑↑↑↑

cGMP cyclic guanosine monophosphate

Table 7.3 Inotrope overview

Generic name	Brand name	Starting dose	Maintenance and titration	Pharmacokinetic properties	Adverse effects
Dobutamine	Dobutrex	1 mcg/kg/min	20 mcg/kg/min	Metabolized by methylation and conjugation, inactive metabolites are renally excreted, *t*1/2 ¼ 2 min	Angina, hypertension, tachyarrhythmia, headache
Isoproterenol	Isuprel	0.01 mcg/kg/min	Increase every 5 min to maximum 0.3 mcg/kg/min	Hepatic metabolism, *t*1/2 ¼ 3–7 h	Syncope, tachyarrhythmia, confusion, tremor
Milrinone	Primacor	0.25 mcg/kg/min	0.75 mcg/kg/min	Renally excreted (83% unchanged), *t*1/2 ¼ 2.3 h (prolonged in renal failure)	Ventricular arrhythmias, hypotension, headache
Levosimendan	Simdax	6–12 mcg/kg IVP	0.05–0.2 mcg/kg/min	Hepatic metabolism with over 10 min active metabolite; $t_{1/2}$ 70 h (prolonged in renal failure)	Hypotension

natriuresis and enhances diuresis, which is associated with a reduction in the PCWP. The combined effects would be expected to improve cardiac performance and increase ventricular stroke volume through a reduction in ventricular afterload and preload. Although initially touted for its clinical effect at reducing dyspnea, subsequent randomized clinical trials failed to demonstrate any meaningful clinical outcomes in terms of renal function or rates of death or rehospitalization [11–13].

Inotropes

Intravenous inotropic therapy is indicated for the treatment of low-output heart failure and cardiogenic shock [14]. In cardiogenic shock, the decrease in cardiac output results in inadequate tissue perfusion, thereby increasing adrenergic drive. Although the release of endogenous catecholamines is temporarily effective acutely, chronic adrenergic stimulation ultimately leads to down-regulation of β_1-receptors and reduced contractile function. The use of inotropic agents such as dobutamine, milrinone, or levosimendan through the direct stimulation of existing β_1-receptors, inhibition of phosphodiesterase III, or calcium sensitization, respectively to augment cardiac output and achieve adequate tissue perfusion may be necessary. Adverse effects of inotropic agents include both supraventricular and ventricular tachyarrhythmias. Therefore, these agents should only be used in acutely ill patients and only for the shortest duration necessary. Additionally, despite their beneficial hemodynamic effects, these agents have not been shown to provide a mortality benefit [15, 16].

The net physiologic effect of inotropic support is an increase in myocardial contractile function and an increased heart rate, resulting in an increased cardiac output. While these effects improve cardiac performance, this occurs at the expense of an increased myocardial oxygen demand (Table 7.3). Pressure-volume relation plots would result in a leftward shift of the LV end-systolic elastance (pressure-volume linear relation) (Fig. 7.6). This leads to an increase in the stroke volume and hence the cardiac output. Despite an increased cardiac output, the blood pressure changes minimally, and any expected increase in the pulsatile pressure is offset by the afterload reduction derived from the peripheral effects of these agents, particularly milrinone.

Dobutamine

Dobutamine is a synthetic catecholamine that acts as a pure inotrope. It binds with high affinity to the β_1- and β_2-receptors in a 3:1 ratio and with lesser affinity to alpha-receptors (B1 > B2 > alpha) [8, 14, 15]. The overarching effect of dobutamine is to augment myocardial contractile function through direct binding of the Gs-protein-coupled β_1-receptor which activates

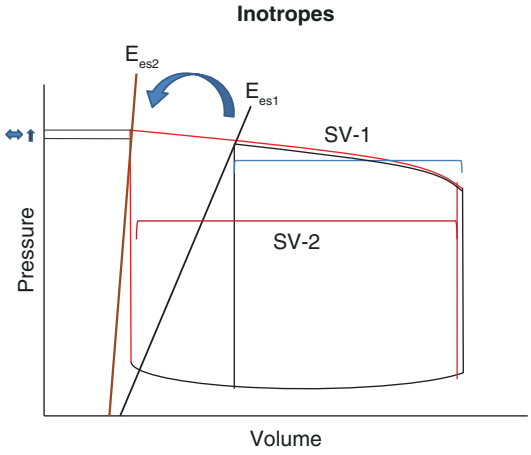

Fig. 7.6 The hemodynamic effect of inotropes. The net effect is a leftward shift in the end-systolic pressure-volume relation (LV end-systolic elastance ($E_{es1} \rightarrow E_{es2}$)) indicating augmented contractility, which results in improved cardiac performance as indicated by the increased stroke volume (SV2 > SV1). Black = baseline hemodynamic profile; red = hemodynamic profile after intervention

adenylate cyclase to produce cyclic AMP (cAMP). The generation of cAMP in turn stimulates calcium influx into the cytoplasm, facilitating actin-myosin interactions with the troponin complex to increase inotropy. In the setting of left ventricular heart failure, dobutamine doses as low as 1 mcg/kg/min and up to 20 mcg/kg/min have been used. At infusion rates of dobutamine above 5 mcg/kg/minute, peripheral vascular effects are seen. Binding of dobutamine to β_2-receptors in the smooth muscle cells of the vasculature also leads to the generation of cAMP. In contrast to its actions on the heart, cAMP activates cAMP-dependent protein kinase (CAMK) within the smooth muscle cells of the vasculature, which causes intracellular reuptake of cytoplasmic calcium by the sarcoplasmic reticulum, thereby leading to vessel relaxation [15]. This effect is counteracted to some extent by the stimulation of alpha-receptors within the vessel wall, which causes peripheral vasoconstriction. The overall effect of dobutamine, however, favors increased myocardial contractility and mild vasodilatation. Advantages of dobutamine include its short half-life (2 minutes) and minimal peripheral effects, which allows infusion through a peripheral vein. It is metabolized by the liver without known active metabolites and is safe to use in patients with renal dysfunction.

Isoproterenol

Isoproterenol is a non-selective beta-receptor agonist which acts as a potent chronotropic and inotropic agent. It is most often used in the setting of cardiogenic shock due to bradycardia in post cardiac transplantation patients. It is also effective in suppressing some ventricular tachycardia arrhythmias [17]. While isoproterenol can augment cardiac output, it has peripheral vasodilatory effects, so no significant change in blood pressure is noted. Therefore, it is not indicated as monotherapy for cardiogenic shock. Like dobutamine, isoproterenol possesses minimal alpha-receptor activity and may therefore be administered through a peripheral vein.

Milrinone

Milrinone is a selective phosphodiesterase (PDE) III inhibitor that prevents the degradation of cAMP and therefore increases intracellular cAMP in cardiac tissue [14, 18]. Hence, this agent operates downstream of the ß-receptor pathway but through its effects results in an increase in intracellular calcium, which augments myocardial contractile function. Compared to dobutamine, milrinone has slightly more potent vasodilatory effects in the periphery through the inhibition of PDE III actions within the pulmonary and peripheral vasculature. Thus, in addition to its positive inotropic effects on the heart, milrinone also reduces afterload and left atrial pressure and enhances LV diastolic relaxation effects. Like dobutamine, milrinone is indicated for severe left ventricular dysfunction. Milrinone may be more beneficial than dobutamine in patients already receiving chronic beta-blockade therapy [19]. In patients with resolving cardiogenic shock, milrinone allows the addition of beta-blocker oral therapy when patients are clinically better compensated, thereby ensuring a more optimal transition to oral heart failure medical management [20]. However, short-term use of milrinone for mild-to-moderate heart failure

exacerbations has not been shown to decrease hospital length of stay and has been associated with an increase in arrhythmias [14]. Compared to dobutamine, no difference in clinical outcomes or arrhythmogenicity has been demonstrated [19]. One disadvantage of milrinone is that it is eliminated by the kidneys, so it should be avoided or administered at a reduced dose in patients with severe renal dysfunction.

Levosimendan

Levosimendan is a calcium-sensitizing agent indicated for the short-term treatment of severe acute decompensated heart failure. It is associated with increased calcium sensitivity of the troponin protein complex, thereby improving myocardial contractility [21, 22]. This is achieved without altering the intracellular concentration of calcium, which minimizes any effects on diastolic relaxation properties. Additionally, it activates potassium-ATP channels in the smooth muscle cells of the vasculature and mitochondria, promoting vasodilatation and possibly affording cardioprotection from myocardial ischemia (although this latter property is controversial and requires further study) [21]. The drug is contraindicated in the setting of severe liver or kidney impairment, and is limited by its side effects, which include an increased risk of atrial fibrillation, ventricular arrhythmias, hypotension, and hypokalemia. Although used in many countries it is not yet approved by the federal drug administration (FDA) for use in the United States.

Vasopressors

Vasopressor agents act predominantly in the peripheral vasculature to achieve vasoconstriction. Consequently, use of these agents typically requires administration through a central line to avoid tissue ischemia that can arise when administered through a peripheral intravenous line or as a consequence of extravasation. These agents include dopamine, norepinephrine, epinephrine, and phenylephrine (Table 7.4). The hemodynamic effects of vasopressor agents are illustrated in Figs. 7.7 and 7.8. The predominant vasoconstrictive properties of these agents results in an increase in cardiac afterload via increased systemic vascular resistance. Thus, while capable of increasing the systemic blood pressure, they do

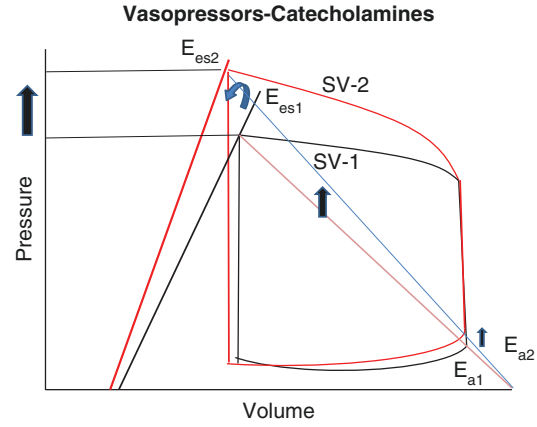

Fig. 7.7 Hemodynamics of catecholamine vasopressor agents. The actions of catecholaminergic vasopressors result in improved contractile function denoted by the slightly leftward shift in the end-systolic pressure-volume relation ($E_{es1} \rightarrow E_{es2}$). However, the dominant effect from these agents is peripheral vasoconstriction leading to an increase in afterload ($E_{a2} > E_{a1}$). Depending on the inotropic effect that these agents confer in comparison to the increased afterload, stroke volume might be expected to increase although to a lesser extent as compared to pure inotropic agents, remain unchanged, or in the setting of an overwhelming increase in afterload, actually decrease (SV1 ≈ SV2). These agents are therefore best suited in cases of vasodilatory shock where their effect in maintaining adequate tissue perfusion pressure is required. Black = baseline hemodynamic profile; red = vasopressor effect; pink = arterial elastance (afterload) at baseline; blue = arterial elastance (afterload) vasopressor effect

Table 7.4 Vasopressor agents

Drug	Brand name	Starting dose	Maintenance and titration
Dopamine	Intropin	3–10 mcg/kg/min	20 mcg/kg/min
Epinephrine	Adrenalin	0.05 mcg/kg/min	0.2–0.8 mcg/kg/min
Norepinephrine	Lovephed	0.02–0.04 mcg/kg/min	0.4–1 mcg/kg/min
Phenylephrine	Neo-Synephrine	100 mcg/min	40–60 mcg/min
Vasopressin	Pitressin	0.01 units/min	0.04 units/min

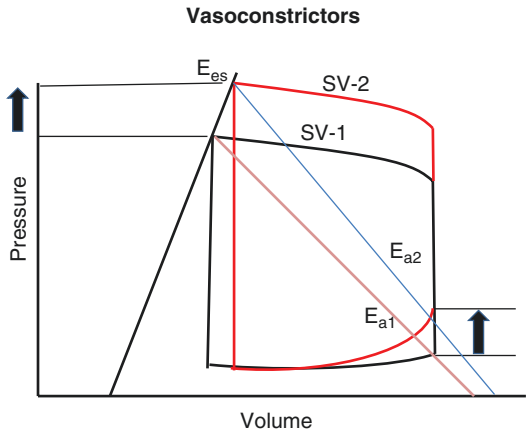

Fig. 7.8 Hemodynamics of pure vasoconstrictors. These agents act primarily to increase the systemic vascular resistance resulting in an upward shift of the pressure-volume relationship. The increase in afterload does not affect intrinsic contractile function but does result in an increase in the end-systolic blood pressure, increased LV end-diastolic pressure, and an increase in the LV afterload ($E_{a1} \rightarrow E_{a2}$). The combined effects result in elevated myocardial oxygen demand and a reduced stroke volume (SV2 < SV1). Therefore, while systemic blood pressure is improved, it comes at the expense of the cardiac output. Black = baseline hemodynamic profile; red = vasoconstrictor effect; pink = arterial elastance (afterload) at baseline; blue = arterial elastance (afterload) vasoconstrictor effect

so at the price of an increased myocardial oxygen demand through elevated heart rate and increased afterload, thereby potentially reducing stroke volume. In the case of the endogenous catecholamine agents such as dopamine, norepinephrine, and epinephrine, these effects are somewhat ameliorated by the slightly enhanced cardiac inotropy.

Catecholamines

Dopamine

Dopamine is an endogenous catecholamine that exhibits unique, dose-dependent pharmacologic actions. Low doses (<5 mcg/kg/min) primarily have dopaminergic receptor (DA1) activity, resulting in vasodilation and increased renal, mesenteric, and coronary blood flow [15]. Historically, low-dose (≤5 mcg/kg/min) dopamine infusion was thought to be renal protective and could aid in the prevention of contrast-induced nephropathy. However, study results have been conflicting and overall show no evidence of a true renal-protective benefit or clinical outcome improvement with renal-dose dopamine [23–25]. Dopamine doses of 3–10 mcg/kg/min will stimulate β_1- and β_2-receptors ($\beta 1 > \beta 2$), enhancing inotropy and chronotropy. At maximal doses of 10–20 mcg/kg/min, alpha-receptor stimulation is dominant and overrides the inotropic effects thereby providing blood pressure support through peripheral vasoconstriction and increased systemic vascular resistance. Due to the increased systemic vascular resistance with doses in this range, myocardial oxygen demand is increased. Pulmonary vein vasoconstriction can occur in patients receiving dopamine, which might compromise the reliability of PCWP measurements as an estimate of left ventricular end-diastolic filling pressures [14, 15].

Norepinephrine and Epinephrine

Norepinephrine and epinephrine are endogenous catecholamines derived from dopamine and characteristically demonstrate mixed receptor activity. Norepinephrine has β_1- and alpha-receptor activity, with lesser affinity for β_2-receptors. This translates clinically into more potent vasoconstrictive properties and less inotropic effects at all dose ranges as compared with dopamine. For this reason, norepinephrine remains the initial catecholamine of choice for septic or vasodilatory shock. Epinephrine is the most potent agonist for the β_1-, β_2-, and alpha-receptors. Use of continuous epinephrine infusion is limited by adverse effects such as cardiac arrhythmias, tissue ischemia, tachycardia, hyperglycemia, cerebral hemorrhage, pulmonary edema, and diminished splanchnic blood flow. As such, epinephrine should be reserved for patients who are unresponsive to dopamine or norepinephrine [8, 14, 26].

Epinephrine bolus dosing in the range of 0.5–1 mg IV (0.1–0.5 mg intracardiac or 0.1 mg/kg via endotracheal tube) has a role in advanced cardiac life support algorithms such as treatment of pulseless ventricular tachycardia, ventricular fibrillation, asystole, or pulseless electrical activity. Another emergent use is in anaphylactoid

reactions to medications, or more commonly contrast. In this setting, depending on the degree of compromise, different doses and routes of epinephrine administration may be appropriate. For systemic anaphylactoid reactions (i.e., hypotension, vasodilatory shock), epinephrine should be given emergently as an intravenous bolus dose of 10 mcg. This dose should be repeated in 1-minute intervals until an intravenous infusion of epinephrine can be initiated or until the patient's hemodynamics have been adequately stabilized. For less severe reactions, epinephrine 0.3–0.5 mg (0.3–0.5 mL of 1:1000 solution) can be given subcutaneously or intramuscularly. Repeated doses are often necessary while steroids and other symptomatic treatments take effect.

Pure Vasoconstrictors

Phenylephrine

Phenylephrine acts as a pure alpha-receptor agonist with almost no β-receptor activity. Consequently, it is a potent vasoconstricting agent and is ideal for the treatment of anesthetic- or vasovagal-induced hypotension as well as vasodilatory shock. Dosing typically begins at 100–180 mcg/min until blood pressures are stable and then infusion is decreased to a maintenance dose of 40–60 mcg/min. The potent vasoconstrictor activity may cause a reflexive decrease in adrenergic drive. Hemodynamically, the dominant effect is an increase in afterload (Fig. 7.8). Therefore, caution should be used in patients with myocardial ischemia or heart failure-induced shock, where inotropy and reduced afterload is needed. Table 7.5 summarizes the hemodynamic effects of vasopressors and inotropes.

Vasopressin

Vasopressin is an endogenous non-catecholamine vasopressor agent secreted primarily by the pituitary gland in response to various physiological stimuli including hypotension, intravascular volume depletion, increased serum osmolality, pain, and hypoxia [8, 14]. It can also be released to a lesser extent by the adrenal glands and myocar-

Table 7.5 Hemodynamic effects of vasopressors and inotropes[a]

Drug type, generic (brand)	HR	MAP	PCWP	SVRI	CO	Receptor activity
Vasopressors						
Dopamine	↑↑					
<3		0	0	0	0	D > b1
3–10		↑	↑	0	1	b1 > b2 > D
>10		↑↑	↑↑	↑	↑	a1 > b1 >> b2
Epinephrine	↑↑↑					
<0.05		0	0	0/↓	↑↑↑	b1 >> b2
0.05–0.15		↑	↑↑	↑	↑↑↑	b1 > a1 > b2
>0.15		↑↑	↑↑	↑↑↑	↑↑	a1 > b1
Norepinephrine	↑↑	↑↑↑	↑↑↑	↑↑↑	0	a1 >> b1
Phenylephrine	0	↑↑	↑↑	↑	0	a1
Vasopressin						
Inotropes						
Dobutamine (Dobutrex[1])	↑					b1 > b2 > a1
2–10		↑	↓	↑	↑	
10–20		0/↓	↓	0/↓	↑↑	
Isoproterenol (Isuprel[1])		↓↓	↓↓	↓↓↓	↑↑↑	b1 >> b2
Amrinone (Inocor[1])	↑	0	↓	↓↓	↑	PDE III inhibitor
Milrinone	↑	↓↓	↓	↓↓	↑↑	PDE III inhibitor
Levosimendan	0	↓↓	↓	↓↓	↑↑	Ca sensitizer

[a]All listed doses are in mcg/kg/min

D dopamine receptor, *b1* beta 1, *b2* beta 2, *a1* alpha, *v1* vasopressin receptor; *PDE* phosphodiesterase, *Ca* calcium

dium in response to circulating catecholamines and increased wall stress, respectively. Vasopressin binds to two receptors, V_1 and V_2. The V_1 receptors are further classified into V_{1a} and V_{1b} subtypes depending on their localization. For example, V_{1a} receptors are primarily found in the smooth muscle cells of the blood vessels, and V_{1b} receptors are localized to the pituitary gland. V_2 receptors are found exclusive in the renal collecting duct. Whereas stimulation of V_{1a} receptors through binding by vasopressin results in vasoconstriction, binding of V_2 receptors causes retention of water by the kidney. These effects result in an increase in both afterload and preload, thereby raising systemic blood pressure and potentially augmenting cardiac output by invoking Frank-Starling forces on the heart [26, 27]. The effect on afterload, however, predominates and limits any potential increase in cardiac output. Additionally, its vasoconstrictive effects on the coronary and cerebral circulations are relatively mild in comparison to catecholaminergic vasopressor agents. Its primary utility is in the treatment of vasodilatory shock and advanced cardiac life support for cardiac arrest algorithms [28]. One potential advantage of vasopressin, over epinephrine is in patients with acidosis, as catecholamine response is diminished in patients with low pH and in hypoxic environments. Fixed-dose vasopressin infusions are recommended as add-on therapy to norepinephrine in patients with vasodilatory shock as vasopressin may augment the vascular sensitivity to norepinephrine and improve its vasopressor effect.

Conclusion

Although advances in mechanical circulatory support have greatly aided the management of patients presenting with cardiogenic shock, vasoactive pharmacologic agents remain the mainstay of treatment. Therefore, it is imperative that cardiac critical care practitioners understand the pharmacologic and hemodynamic effects of these agents in order to provide better patient care.

Bullet Point Summary

- Intravenous vasodilators, such as nitroglycerin, nitroprusside, and nesiritide play an important role in the management of patients with acute decompensated heart failure associated with volume overload and elevated systemic vascular resistance.
- Inotropic agents dobutamine and milrinone operate at different levels along the ß-receptor pathway to augment ventricular contractility.
- Vasopressors should be used for short-term improvement in perfusion pressures in patients with shock (following adequate fluid resuscitation).
- Selection between vasoactive agents is based on the differences in pharmacology, hemodynamic expectations, and specific clinical scenarios.
- Vasopressin provides only mild vasoconstriction as monotherapy but the effect is magnified when co-administered with IV catecholamine in patients with vasodilatory shock.
- Epinephrine is versatile and may be administered IV, via ET tube, or intracardiac in ACLS, as continuous infusion in certain patients with shock, or IM or SQ in anaphylaxis.
- Esmolol is not a vasodilator and currently has a very limited role in the management of patients presenting with shock.

Case 1

A 57-year-old man with a history of non-ischemic cardiomyopathy (LVEF 30%) presents to the emergency department after 4 weeks of progressive dyspnea, non-productive cough, leg swelling, and reduced urine output. He had been treated at urgent care facilities for community acquired pneumonia but his symptoms persisted and worsened. On presentation, his vital signs are BP 120/95 mmHg, HR 104 bpm. He is afebrile and breathing at a rate of 30 breaths per minute. Oxygen saturation on room air is 90%. Physical examination findings show a well-developed male in respiratory distress. Neck examination shows jugular venous distension and bilaterally

diminished carotid upstrokes. The chest reveals bilateral crackles up to the middle lung fields bilaterally. Cardiac examination demonstrates a regular rate, tachycardia, with a sustained and displaced PMI, soft S1S2, audible S3 gallop, and 3/6 systolic murmur heard best at the apex. The abdomen shows evidence of hepatoabdominal reflux and hepatomegaly. The extremities are warm. An ECG shows diffusely low voltage, sinus tachycardia, 105 bpm, a left anterior fascicular block and no evidence of acute myocardial ischemia. A chest x-ray shows bilateral pulmonary edema. An arterial line and central line are placed and nitroprusside is administered. He is placed on supplemental oxygen and given IV diuretics. Within several minutes, the BP is now 100/60 mmHg, HR 90 bpm and the patient reports being able to breath easier. His urine output and his oxygenation have improved.

Question 1:

In the triage of this patient, which of the following hemodynamic profiles would best describe this patient?

A. Warm, dry
B. Warm, wet
C. Cold, dry
D. Cold, wet

Question 2:

The hemodynamic effect of the treatment given is expected to result in which of the following?

A. Shift the end-systolic pressure-volume relation leftward, thereby increasing stroke volume.
B. Shift the end-systolic pressure-volume relation rightward, thereby increasing stroke volume.
C. Reduce afterload and thereby increase stroke volume.
D. Reduce preload more than afterload and thereby increase stroke volume.

Question 3:

The patient develops a fever on hospital day 2 and becomes hypotensive and tachycardic. Physical examination demonstrates resolved jugular venous distention, improved peripheral edema, and warm extremities. Laboratory studies show a mild leukocytosis. Blood cultures are drawn although results are not yet available. The next best course of action would be which of the following:

A. Start broad-spectrum IV antibiotics, continue IV nitrate and diuretic therapy for decompensated heart failure.
B. Discontinue IV nitrate and diuretic therapy. Withhold antibiotics until culture results are returned.
C. Obtain a procalcitonin level and continue with IV nitrate and diuretic therapy.
D. Start broad-spectrum IV antibiotics, discontinue IV nitrate and diuretic therapy, and consider the need for vasopressor support.

Case 2

A 70-year-old man with CAD and ischemic cardiomyopathy returned from a trip abroad with complaints of fatigue, chest pressure, and progressive dyspnea with minimal exertion. At his last clinic visit 6 months ago prior to his trip, the patient was able to play golf and climb 2 flights of stairs without difficulty. He has been compliant with his medical therapy which includes carvedilol 25 mg BID, sacubitril/valsartan 49/51 mg BID, hydralazine 50 mg TID, isosorbide mononitrate 30 mg daily, and spironolactone 25 mg daily. He was hospitalized with acute decompensated heart failure and pulmonary edema, and treated with IV diuretics. Although he responded initially to this treatment, by hospital day 2 he no longer responded to treatment and his urine output declined precipitously. He developed respiratory failure and was ultimately placed on mechanical ventilatory support. A right heart catheterization was performed which showed the following: SBP 85/50 mmHg, HR 110 bpm, RAP 18 mmHg, RV 68/15, PA pressure 70/30/43, PCWP 28 mmHg, CO 3.6 L/min by thermodilution, CI 1.8 L/min/m^2.

Question 4:

The most appropriate next step in the management of this patient would be which of the following?

A. Discontinue oral medications and begin IV inotropic support.
B. Stop beta-blocker and begin dopamine IV infusion.

C. Discontinue oral medications except carvedilol; add milrinone infusion for inotropic support; continue IV diuresis.
D. Continue oral medications, begin milrinone infusion, and continue IV diuresis.

Question 5:
The combined effect of inotropic support and vasodilator medical therapy would be expected to cause which of the following hemodynamic profiles?

A. A shift of the end-systolic pressure-volume relation leftward, causing stroke volume to increase.
B. A reduced afterload and shift of the end-systolic pressure-volume relation leftward.
C. A reduced afterload and no net change in the end-systolic pressure-volume relation.
D. A reduced preload and afterload and a shift of the end-systolic pressure-volume relation to the left.

Case 3

A 60-year-old woman with a history of diabetes mellitus, HTN, and CKD4 is admitted with an acute anterior ST elevation myocardial infarction. She is immediately transferred to the cardiac catheterization laboratory where she undergoes an emergent diagnostic cardiac catheterization and percutaneous coronary intervention to a thrombotic occlusion of the proximal left anterior descending coronary artery. The patient is noted to have obstructive coronary artery disease in the right coronary artery and a large obtuse marginal branch of the left circumflex coronary artery as well, but these were not intervened upon. A right heart catheterization is also performed and shows the following: RAP 10, RV 35/12, PA pressure 40/25/30, PCWP 25, CO 4.1 L/min/m^2, CI 2.3 L/min/m^2. The patient emerges from the cardiac catheterization lab intubated and sedated. She is receiving infusions of dobutamine, norepinephrine, dopamine, and phenylephrine. Her vitals are as follows: BP 100/70 mmHg, HR 120 bpm, T 37C. An echocardiogram is performed demonstrating severe LV systolic dysfunction with an estimated LV ejection fraction of 20% and global hypokinesis.

Question 6:
In order to optimize cardiac performance, which of the following strategies is most appropriate for this patient?

A. Continue current medical therapy.
B. Wean vasopressor agents while maintaining inotropic support.
C. Add IV diuretic therapy.
D. Prepare for mechanical circulatory support.

Answers

1. B

   The clinical profile that best describes this patient is warm and wet. Clinical findings indicate signs of volume overload are present, and hence, the patient is wet. Furthermore, the patient is warm to palpation, a clinical finding that suggests adequate perfusion. This information can be further supplemented by laboratory and imaging studies. In contrast, a warm/dry profile implies either a normal hemodynamic profile or a patient with adequate perfusion who is intravascular volume depleted. A cold/wet profile implies grossly inadequate tissue perfusion and volume overload, whereas a cold/dry profile suggests inadequate perfusion and intravascular volume depletion.

2. C

   The primary hemodynamic effect of IV vasodilator therapy is a reduction in afterload. This reduction in afterload improves cardiac performance, which may result in an increased stroke volume. This is accomplished without changing the end-systolic pressure-volume relation and without appreciably altering preload. Although the improved cardiac performance can enhance diuresis and therefore reduce preload, the dominant effect of vasodilator therapy is a reduction in afterload.

3. D

   A change in the patient's clinical status is often accompanied by a change in hemodynamics. Therefore, recognition of these changes is imperative to guide changes in treatment strategy. In the case scenario, the patient has developed a bacteremia and clinical signs of septic shock. Thus, despite the

fact that the patient presented initially with signs of acute decompensated heart failure associated with volume overload and was treated with IV vasodilator therapy and diuretics, the clinical circumstances now dictate that the patient requires treatment for septic shock which includes IV antibiotics, volume resuscitation, and potentially vasopressor therapy.

4. D

This patient presents with cardiogenic shock characterized by abnormally low cardiac output and elevated right and left heart filling pressures. The calculated systemic vascular resistance is normal, likely a manifestation of the patient's chronic heart failure therapy. Therefore, the patient is most likely to be helped by an augmentation of LV contractility with the use of inotropes. The elevated right and left ventricular filling pressures are consistent with a volume-overloaded state and suggest that aggressive diuresis is indicated. Discontinuation of the patient's chronic heart failure therapy would likely increase afterload and compromise any potential gain from using inotropic agents. In the event that oral therapy cannot be administered, IV vasodilators may be given. Several studies have also shown that abrupt discontinuation of beta-blockers is associated with adverse clinical outcomes, including an increased risk of ventricular arrhythmias.

5. B

The expected hemodynamic effects of combined vasodilator and inotropic effects include a leftward shift in the end-systolic pressure-volume relation (steeper slope) indicating an improvement in LV contractile function. Simultaneously, the predominant effect of vasodilator therapy would be to reduce afterload, resulting in a reduction of end-systolic pressure. The combined effect is to improve cardiac performance and increase cardiac output.

6. B

According to the right heart catheterization findings, the patient is maintaining a cardiac index, which is borderline normal. Calculated systemic vascular resistance is elevated and the patient is normotensive and tachycardic. Together, these findings suggest that the patient's afterload is inordinately high and is likely due to the effects of the vasopressor agents the patient is receiving. Therefore, the gradual removal of these agents would be expected to further improve cardiac performance and may allow for the eventual discontinuation of inotropic support as well. Ultimately, revascularization of the remaining non-culprit obstructive CAD lesions identified at the time of diagnostic cardiac catheterization prior to hospital discharge will provide the best chance for recovery of LV systolic function.

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8 Recently Approved Pharmacologic Agents to Improve Outcomes in Heart Failure

David C. Booth and Navin Rajagopalan

Introduction and Background

Over the past 5 years, two novel FDA-approved agents for the treatment of heart failure have been introduced, the angiotensin receptor-neprilysin inhibitor (ARNi), sacubitril/valsartan (Entresto), and the funny current (I_f) inhibitor ivabradine (Corlanor). Prior to the approval of these agents, hemodynamic optimization – using vasodilators including hydralazine and isosorbide [1, 4, 5] – and neuro-humoral inhibition, combining angiotensin-converting enzyme inhibition, ß-blockade, and mineralocorticoid-receptor antagonism [2, 3, 6–11], have been the evidence-based pharmaceutical approaches to improve outcome in chronic systolic heart failure. The majority of the agents tested in the referenced trials rested on a background of proven hemodynamic benefit. There is a relative paucity of published hemodynamic data for sacubitril/valsartan and ivabradine, as randomized trials for these agents in systolic heart failure have been endpoint-driven. This chapter summarizes the outcome data, quality of life results, and available hemodynamic data for these two drugs. Other modalities which have been shown to improve survival in systolic heart failure include the implantable cardioverter defibrillator, cardiac resynchronization therapy, and left ventricular assist device implantation, but these are not discussed here.

Rationale and Research Leading to Sacubitril/Valsartan

Heart failure activates the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS), leading to vasoconstriction and increased sympathetic tone, in turn resulting in downregulation of the ß-receptors. Activation of RAAS leads to increased secretion of angiotensin II and aldosterone, which also results in increased ADH secretion. These neurohormonal maladaptations result in fluid retention, perpetuating the cycle of heart failure. ACE inhibition, or angiotensin receptor blockade, ß-blockade, and mineralocorticoid antagonism modulate the effects of the SNS and RAAS.

Since the early 1980s, the natriuretic peptide system (NPS) began to receive attention as a potential target in heart failure treatment. Within the NPS are three hormones, atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP),

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_8

and C-type atrial natriuretic peptide (CNP). While CNP is secreted from endothelial cells and cardiac fibroblasts and has vasodilatory and anti-remodeling effects, ANP and BNP are secreted, respectively, from the atria and the ventricles, are released in response to fiber stretch and volume overload and promote diuresis, natriuresis, and vasodilation, counteracting the maladaptive effects of SNS and RAAS activation [12]. With the development of angiotensin receptor blockers, which exert their effects primarily at the Type 1 angiotensin II receptor, there was hope that a more specific RAAS antagonist would result in further survival improvement in heart failure outcomes. However, while the Valsartan Heart Failure Trial (Val HeFT) [13] (2001) demonstrated reduced heart failure hospitalizations, leading to an FDA-approved indication in heart failure, overall mortality in the valsartan and placebo groups was similar. The demonstration of the beneficial effects of the natriuretic peptides led to the development of human recombinant BNP, namely nesiritide, which was FDA-approved for use in 2001 on the basis of improvement in dyspnea in decompensated heart failure. However, a larger randomized trial released in 2011, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) [14], demonstrated no improvement in dyspnea, 30-day mortality, or readmission rates in the nesiritide group. Hypotension was significant in the nesiritide group. As a result, nesiritide is used rarely in practice today, but natriuretic peptide levels remain well established as biomarkers.

Research efforts have been directed at toward identifying agents that could inhibit the enzyme that breaks down endogenous natriuretic peptides, namely, neprilysin. Neprilysin (NEP) is a neutral endopeptidase, and its inhibition increases bioavailability of natriuretic peptides, bradykinin, and substance P, resulting in natriuretic, vasodilatatory, and anti-proliferative effects. The natural hypothesis was that combined inhibition of the RAAS and NEP would result in a better heart failure treatment (Fig. 8.1). This led to the development of omapatrilat, a combined ACEi/NEPi. Several trials of the agent were conducted in heart failure, culminating in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) Trial [15] in patients with NYHA Functional Class II–IV heart failure. While post hoc analyses appeared to demonstrate potential benefit, there was an increased incidence of life-threatening angioedema, which was substantiated in a subsequent study of the agent in hypertension. These results effectively thwarted ACEi-NPi as a treatment in heart failure.

An important advantage of ARBs over ACE is is that ARBs do not block the degradation of bradykinin, the principal instigator of cough, a side effect noted in at least 10% of patients on an ACE, and do not cause angioedema which can occur in about 0.1% of patients on an ACE [16]. Omapatrilat was subsequently demonstrated to inhibit an enzyme responsible for bradykinin metabolism. A logical solution to the adverse effects of omapatrilat was to combine an ARB with an NEPi, termed ARNI or angiotensin receptor-neprilysin inhibitor – LCZ696, Sacubitril/Valsartan. Sacubitril is a prodrug which is converted in the body to sacubitrilat, which inhibits neprilysin and thereby the degradation of NPs. A Phase III trial [17] published in 2010 comparing sacubitril/valsartan to valsartan showed greater reduction in systolic, diastolic, and pulse pressures with sacubitril/valsartan. The Prospective Comparison of ARNI with ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) Trial [18], published in 2012 was a Phase II randomized trial that assessed NT-proBNP after 12 weeks of sacubitril/valsartan compared to valsartan in patients with heart failure with preserved left ventricular ejection fraction (HFpEF). At 12 weeks, NT-proBNP was significantly lower in the sacubitril/valsartan group, and an echocardiographic reduction in left atrial volume and size was also demonstrated. The NT-proBNP lowering effect appeared to be independent of a blood pressure lowering effect of the drug.

Published in 2014, the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized 8399 patients with HFrEF (LVEF $\leq$40%) and NYHA Class II–IV symptoms to sacubitril/valsartan 200 mg PO BID or enalapril 10 mg PO BID (the

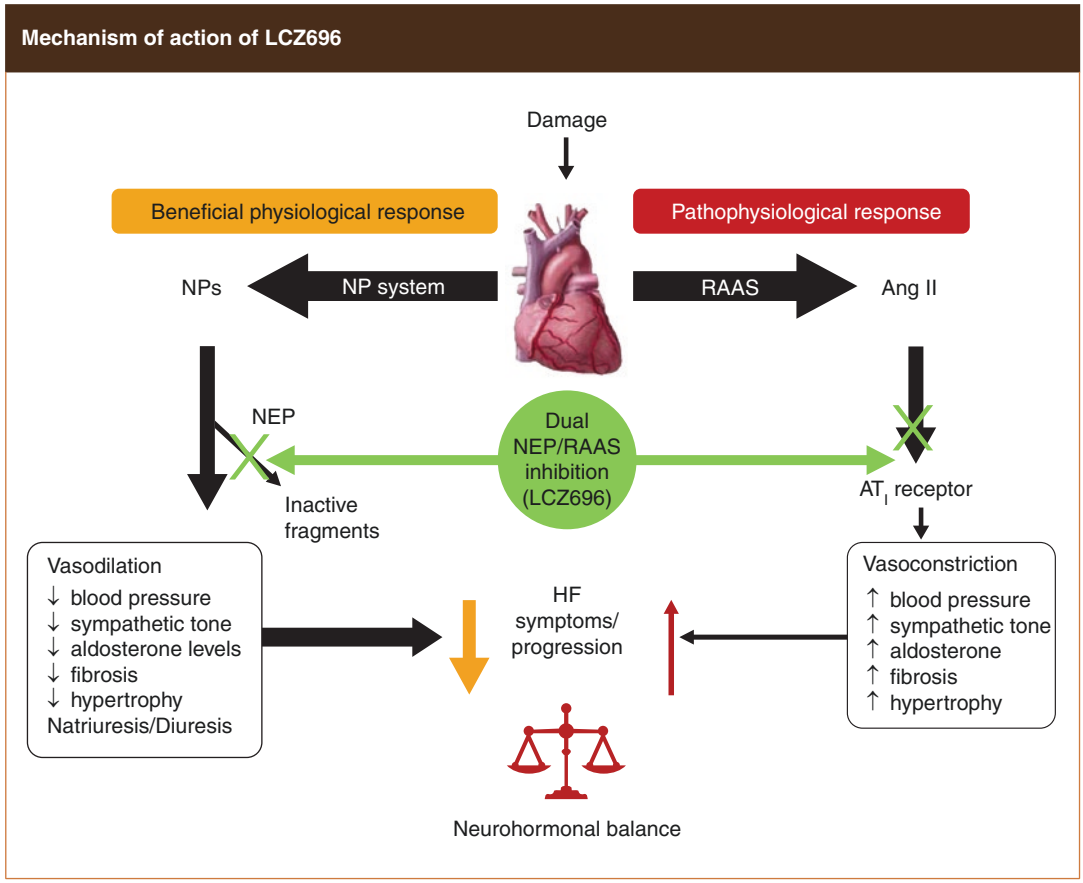

Fig. 8.1 Angiotensin receptor-neprilysin inhibitors have the potential to modulate two counter-regulatory neurohormonal systems in HF: the renin-angiotensin-aldosterone system and natriuretic peptide system. ANG angiotensin, AT1 angiotensin type 1, HF heart failure, NP natriuretic peptide, RAAS renin-angiotensin-aldosterone system. (Indian Heart Journal Volume 70, Supplement 1, July 2018, Pages S102–S110)

goal dose from CONSENSUS and SOLVD), in addition to standard therapy for chronic systolic heart failure. The majority of the study population was receiving ß-blockers and mineralocorticoid antagonists. The primary end point of the trial was the combination of death from cardiovascular causes and heart failure hospitalization. There being insufficient Phase II safety data for sacubitril/valsartan, the PARADIGM protocol stipulated safety and tolerability run-ins for all participants in the trial. If participants tolerated both sacubitril/valsartan and enalapril, they were randomly assigned to the two study arms. This approach allowed assessment not only of the end point of the trial but also provided safety and tolerability data. The study was stopped early, after median follow-up of 27 months, when the study met the prespecified cutoff for significant benefit. The ARNI combination resulted in a 20% decrease in the primary end point, HR = 0.80, $P < 0.001$, giving a Number Needed to Treat of 21. The study drug also reduced the individual components of the combined end point, death from cardiovascular cause by 20% and heart failure hospitalizations by 21%, both $p < 0.001$. All-cause mortality in the sacubitril/valsartan arm was reduced by 16%, HR = 0.84, $p < 0.001$. While sacubitril/valsartanb resulted in 14% experiencing hypotension as compared to 9% in the enalapril arm, the discontinuation rate was not significantly different (sacubitril/valsartan 0.9%, enalapril 0.7%). No significant difference was noted in the occurrence of non-serious angioedema between the two groups.

In secondary analyses, sacubitril/valsartan demonstrated clinical benefits in other indices of heart failure progression, including improved NYHA class, reduced need for intensification of medical treatment, and reduction in the need for emergency department visits, intensive care, and inotropic support. Other findings from PARADIGM-HF include significantly lower NT-proBNP and troponin levels in the sacubitril/valsartan group, significant reduction in the incidence of sudden cardiac death and death from worsening heart failure independent of cardioverter defibrillation implantation, and a nonsignificant reduction in the need for left ventricular assist device implantation and cardiac transplantation. The PARADIGM-HF investigators also carried out a comparison of the sacubitril/valsartan arm with the treatment arms of the SOLVD Trial (enalapril) and the CHARM-Alternative Trial [19] (candesartan) and found substantial relative risk reductions for both the composite end point and for cardiovascular death. Using the Kansas City Cardiomyopathy Questionnaire, the PARADIGM-HF investigators [20] demonstrated remarkable improvement in physical and social activity limitations with sacubitril/valsartan compared to enalapril. The largest improvements were reported in household chores ($p < 0.001$) and sexual relationships ($p = 0.002$); these benefits persisted through 36 months of assessment. In another secondary analysis [21], the PARADIGM-HF investigators found the frequency of episodes of hyperkalemia to be significantly greater in the enalapril arm compared to ARNI, (3.1 versus 2.2 incidents per 100 patient-years, HR = 1.37, CI 1.06–1.76, $p = 0.02$) for patients already taking a mineralocorticoid antagonist.

Criticisms of the PARADIGM-HF Trial include that the study was predominantly white (66%), male (78%), and enrolled predominantly NYHA Functional Class II (70%) patients. Only 5% of the study population was black, perhaps limiting the ability of the study to accurately detect the incidence of angioedema. It has also been suggested that the enalapril dose in PARADIGM-HF was too low [22]. Narrowly defined, only patients with systolic heart failure and an ejection fraction of ≤35% would be candidates for the drug, based on PARADIGM-HF entry criteria. An additional criticism is that neprilysin has been shown to have a role in maintaining homeostasis of amyloid-ß peptide, raising the issue that a neprilysin inhibitor might lead to increased deposits of this protein in brain [11]. However, in a randomized, double-blind trial measuring sacubitril/valsartan levels in cerebrospinal fluid in healthy human subjects [23], sacubitril/valsartan did not cause changes in aggregable amyloid β isoforms compared with placebo, despite achieving CSF concentrations of a metabolite of sacubitril/valsartan sufficient to inhibit neprilysin.

The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF Trial) [24], a prospective randomized trial of the impact of sacubitril/valsartan in HFpEF, has completed enrollment and has an estimated study completion date of March 15, 2019 (clinicaltrials.gov). Serial cognitive testing is being carried out in PARAGON-HF in an effort to assess the impact of sacubitril/valsartan on cognition.

In summary, in prespecified measures of nonfatal clinical deterioration of heart failure, the PARADIGM-HF investigators demonstrated that the combination of sacubitril/valsartan prevented the clinical progression of surviving heart failure patients more effectively than did enalapril alone [25]. On the basis of the PARADIGM-HF Trial, sacubitril/valsartan was FDA-approved in July 2015 to reduce the risk of death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction.

The comParIson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an acute Heart Failure (PIONEER-HF) trial (PMID:30415601) enrolled 881 patients with heart failure with reduced ejection fraction who were hospitalized for acute decompensated heart failure at 129 sites in the United States. After hemodynamic stabilization, patients were randomly assigned to receive either sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or enalapril (target dose, 10 mg twice daily). The primary efficacy outcome was the time-averaged proportional change in the N-terminal pro–B--type natriuretic peptide (NT-proBNP) concentra-

tion from baseline through weeks 4 and 8. Key safety outcomes were the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema.

The investigators noted that time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril–valsartan group than in the enalapril group. In addition, the two drugs appeared to be equally safe; the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly. In an analysis of exploratory clinical outcomes, the in-hospital initiation of sacubitril–valsartan therapy was associated with a lower rate of rehospitalization for heart failure at 8 weeks than enalapril therapy.

Pharmacokinetics of Sacubitril/Valsartan

Absorption of sacubitril/valsartan is rapid, with maximum levels of sacubitril, sacubitrilat, and valsartan all achieved by 2–3 h [26]. With twice-daily dosing, steady-state concentrations are reached within 3 days. Sacubitril is eliminated as predominantly sacubitrilat by the kidney, while valsartan is eliminated by the biliary route. In heart failure patients, area under the concentration-time curves for sacubitril, sacubitrilat, and valsartan was higher. Renal impairment had no impact on sacubitril or valsartan, but increased the area under the concentration-time curve for sacubitrilat. Moderate hepatic impairment increased the area under the concentration-time curve of valsartan and sacubitrilat approximately two-fold. Regarding drug-drug interactions, sacubitril/valsartan increased plasma concentrations of atorvastatin. Pharmacokinetics of the drug were not affected by age, sex, or ethnicity.

Hemodynamic Impact of Sacubitril/Valsartan

Surprisingly little specific functional and hemodynamic data are available regarding sacubitril/valsartan. A post hoc analysis of the PARAGIGM-HF demonstrated that the drug was effective at reducing cardiovascular death and heart failure hospitalization across the spectrum of left ventricular ejection fraction (LVEF), when assessed in stepwise 5-point reductions in LVEF [27]. Addition of sacubitril/valsartan in patients with advanced systolic heart failure may be a useful strategy to improve hemodynamics and to potentially facilitate the transitioning from intravenous HF therapies.

Ivabradine

Background and Pharmacology

The search for a direct sinoatrial node inhibitor began four decades ago. Ivabradine was the first drug specifically developed as a heart rate lowering agent, and in Europe was initially considered for the treatment of angina pectoris. Sinoatrial myocytes have the capacity to develop slow diastolic depolarizations, driving membrane voltage toward the threshold for initiating an action potential (Fig. 8.2). Sinoatrial node activity involves several ionic currents flowing through channels, including the funny or hyperpolarization-activated cyclic nucleotide-gated channel that regulates the I_f current, so-called for its unusual properties compared with other channels at the time of its discovery. The I_f current is carried across the sarcolemma by both sodium and potassium ions, is directly activated by cyclic adenosine monophosphate (cAMP), and is related to I_h neuronal channels. Ivabradine has substantial selectivity for inhibiting the I_f channel at doses that allow heart rate slowing [28]. Studies in experimental models have demonstrated that ivabradine has a pure heart rate lowering effect, does not affect LV contractile state [29], and does not have negative lusitropic properties. In healthy volunteers, equipotent doses of ivabradine (30 mg) and propranolol (40 mg) had similar effects on heart rate and heart rate variability, whereas propranolol was associated with significant systolic and mean blood pressure lowering, and a greater decrease in cardiac output measured noninvasively, compared to ivabradine, placebo, or both [30]. Under fasting conditions, peak plasma ivabradine concentrations are reached in approximately

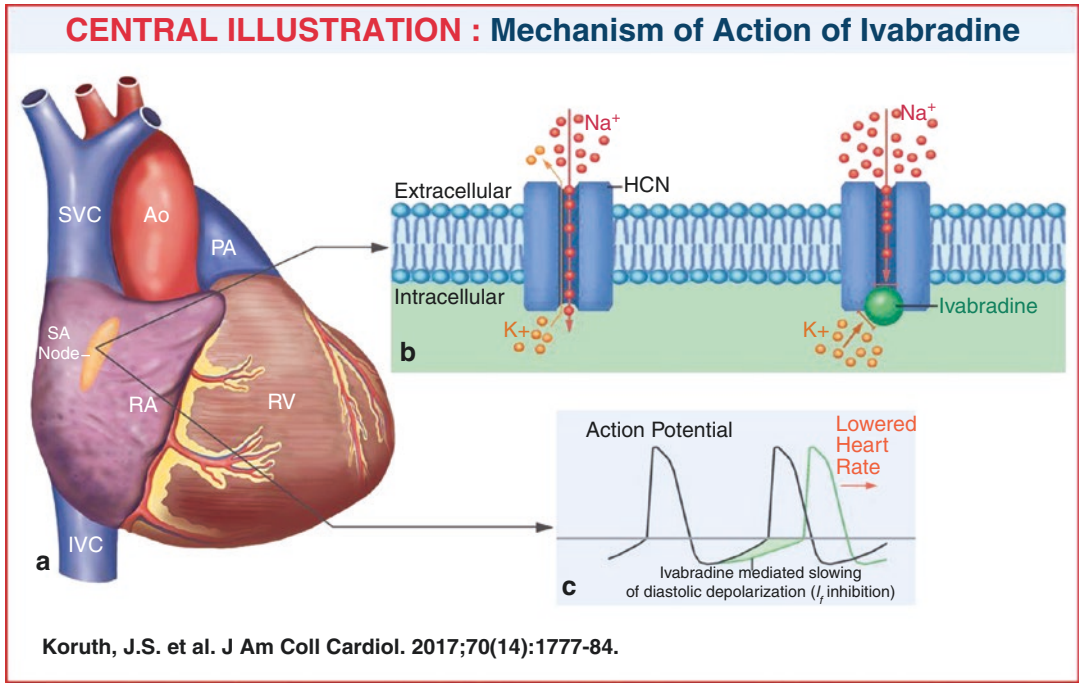

Fig. 8.2 Ivabradine's primary mechanism of action on cardiac tissue is on the sinoatrial (SA) node, which occupies a predominantly subepicardial position at the junction of the superior vena cava (SVC) and the right atrium (RA). (**a**) Heart with position of the Sinoatrial (SA) node. (**b**) In the sinoatrial node, ivabradine blocks the intracellular aspect of the hyperpolarization-activated cyclic nucleotide-gated (HCN) transmembrane channel, which is responsible for the transport of sodium (Na^+) and potassium (K^+) ions across the cell membrane, in the open state. This results in the inhibition of the inward funny current ($\mathbf{I_f}$), which is specifically activated at hyperpolarized membrane potentials. (**c**) By selectively inhibiting $\mathbf{I_f}$, there is a reduction in the slope of diastolic depolarization of the pacemaker action potential (shaded region) and an increase in the duration of diastole, without altering other phases of the action potential. This results in heart rate reduction. Ao aorta, IVC inferior vena cava, PA pulmonary artery, RV right ventricle. (PMID:28958335)

1 hour. Food delays absorption by approximately 1 hour but appears to increase plasma levels of the drug. Ivabradine is extensively metabolized in the liver. The excretion of ivabradine and its metabolites is both renal and hepatic. The half-life of ivabradine and its metabolites requires twice-daily dosing. There is no direct effect of ivabradine on the QT interval. Phosphenes, the off-target effect of ivabradine, are bright sensations not mediated by retinal stimuli, due to effects on hyperpolarization-activated channels in the retina.

While ivabradine was initially targeted as a drug for heart rate control, randomized data failed to demonstrate a significant advantage in patents with stable coronary artery disease without clinical heart failure [31]. Similarly, ivabradine compared to placebo did not significantly improve the change in physical limitation score at 1 year in patients with anginas pectoris [32], although ivabradine patients had better angina scores compared to placebo on the Seattle Angina Questionnaire on every visit to 36 months. Ivabradine did not result in significant exercise tolerance testing benefit, compared to low-dose atenolol, and no advantage was noted when added to full-dose amlodipine [33, 34].

Because of the documented beneficial effect of heart rate lowering in heart failure with reduced ejection fraction, ivabradine was tested in this setting, beginning with the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL) Trial [35], a randomized double-blind, placebo-controlled trial of

10,917 patients. Enrollment characteristics included LVEF <40%, 85% NYHA Class II and III, 83% male, and 87% were taking ß-blockers. At a median of 19 months of follow-up, no difference was found between the ivabradine and placebo groups for the composite end point of cardiovascular death, hospitalization for myocardial infarction (MI), or hospitalization for worsening heart failure. A subgroup analysis of 14% of patients with activity-limiting angina had reduction in hospitalization for MI and borderline reduction in the composite end point ($p = 0.05$); the difference was statistically significant for patients in this subgroup with baseline heart rate ≥ 70 [36].

To investigate the potential benefits on ischemia seen in this subgroup, the SIGNIFY [37] Trial was undertaken, enrolling 19,102 patients with stable coronary artery disease who did not have clinical heart failure. This study again enrolled predominantly male patients; 75% had angina pectoris, and the mean LV ejection fraction was 56%. While heart rate was significantly reduced by ivabradine, there was no significant benefit of ivabradine on the primary composite end point of cardiovascular death or nonfatal MI after median follow-up of 28 months. When the prespecified subgroup with activity-limiting angina was analyzed for the composite outcome, there was in fact evidence of harm with ivabradine therapy; an absolute increase in the composite end point of 1.1% ($p = 0.02$). The reason or reasons for this adverse outcome remain unclear, but the conclusion to be drawn from trials of ivabradine in angina pectoris without LV systolic dysfunction is that no benefit occurs, and even though there may be symptomatic improvement, those patients appear to be at greater risk of an adverse effect of the drug.

The Systolic Heart Failure Treatment with the I_f-inhibitor Ivabradine (SHIFT) Trial [38] randomized 6505 patients with ischemic and nonischemic heart failure, NYHA Class II–IV but predominantly Class II–III, LVEF ≤35%, to ivabradine or placebo. The trial randomized no patients from the United States; most patients were male, 89% taking ß-blockers, 91% ACEi or ARB, 60% aldosterone antagonists, 22% a digitalis preparation. More than two-thirds achieved the target dose of 7.5 mg ivabradine twice daily. Compared to placebo, the composite end point of cardiovascular death or first hospitalization for heart failure was significantly reduced (hazard ratio 0.82, $p < 0.0001$, driven primarily by reduction in HF hospitalization) (Fig. 8.3) Trends were detected for less benefit in patients also receiving ß-blockers and greater benefit for nonischemic patients. There were significant improvements in the NYHA Class and Kansas City Cardiomyopathy Questionnaire summary scores [39]. When patients with baseline heart rate ≥70 from BEAUTIFUL and SHIFT were pooled, no significant impact on mortality could be demonstrated. An echo substudy [40] from SHIFT of 275 patients demonstrated a small but significant increase on LVEF after 8 months of ivabradine therapy (4 ± 10%, $p = 0.004$).

Shortcomings of the SHIFT Trial include that 25% of trial participants were not taking a ß-blocker for HRrEF and that ivabradine did not significantly reduce any end point in patients with baseline HR ≤ 75 bpm. Whereas trials of carvedilol, metoprolol succinate, and bisoprolol demonstrated consistent survival benefit, a similar heart rate reduction by ivabradine resulted in no all-cause survival benefit. Another SHIFT subgroup analysis demonstrated that a statistically significant improvement for the primary end point occurred only for patients <50% of target ß-blocker doses [41]. Thus, ivabradine appeared to exert a beneficial effect only in patients who were also being treated with ß-blockers in whom a heart rate goal of ≤75 bpm had not been achieved. Regarding adverse effects, ivabradine increased the frequency of bradycardia, both asymptomatic and symptomatic, was associated with an increased incidence of atrial fibrillation, and resulted in some ivabradine withdrawals due to phosphenes, which resolved upon discontinuation of drug. The 1.7% increase in the risk of atrial fibrillation noted in pooled BEAUTIFUL and SHIFT data underscore the importance of observing patients on ivabradine for this rhythm disturbance, especially in view of the negative prognostic impact of atrial fibrillation on systolic heart failure. The FDA approved ivabradine in April 2015 for patients with HFrEF

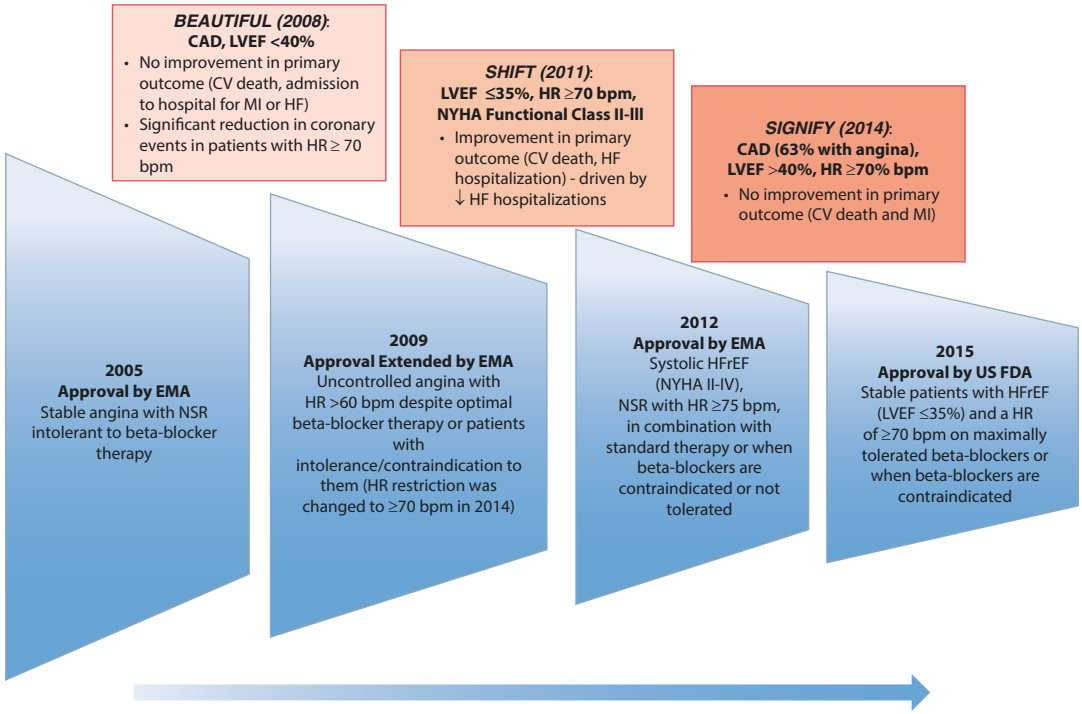

Fig. 8.3 Approval timeline of ivabradine across Europe and the United States. The indications for the use of ivabradine have evolved over time and differ based on region. Since it was first approved for use in angina by the European Medicines Agency (EMA) in 2005, the findings of several randomized controlled trials have resulted in expanded indications to include select heart failure patients and only recent approval by the US Food and Drug Administration (FDA) for this indication. BEAUTIFUL Morbidity-Mortality Evaluation of the I_f-Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction, CAD coronary artery disease, CV cardiovascular, HFrEF heart failure with reduced ejection fraction, LVEF left ventricular ejection fraction, MI myocardial infarction, NYHA New York Heart Association, NSR normal sinus rhythm, SHIFT Systolic Heart Failure Treatment with the I_f-Inhibitor Ivabradine Trial, SIGNIFY Study Assessing the Morbidity-Mortality Benefits of the I_f-Inhibitor Ivabradine in Patients With Coronary Artery Disease. (PMID:28958335)

with LVEF ≤35% on a ß-blocker at the maximum tolerated dose, with HR ≥ 70 bpm (Fig. 8.4). The drug is contraindicated in patients with sinus node dysfunction or atrioventricular block. The FDA approval underscores the prerequisite for guideline-based treatment with maximally tolerated ß-blockers proven effective in HFrEF. In such patients in whom HR remains >70–75 beats per minute, the addition of ivabradine is reasonable. For patients with HFrEF who are proven intolerant of ß-blockers, treatment with ivabradine appears reasonable, keeping in mind that while ivabradine results in decreased heart rate, the exact mechanism of benefit remains uncertain.

Questions remain regarding the efficacy of ivabradine. From a recent meta-analysis of the ivabradine trials [42], the authors concluded that while use of ivabradine in patients with HFrEF in sinus rhythm with HR ≥ 70 to reduce HF hospitalization was supported by the literature, the strength of the evidence was such that more widespread adoption of ivabradine in HF would require additional randomized trials. Recent guideline updates [43] emphasize adherence to the ivabradine FDA package indication.

On the other hand, the guidelines advise that for any patient in NYHA Class II–IV HFrEF not on an ARNI, the threshold to consider discontinuing an ACEi or ARB in favor of sacubitril/valsartan should be low [44]. The number of women and ethnicities different from white in many of the foregoing trials is low enough that one might

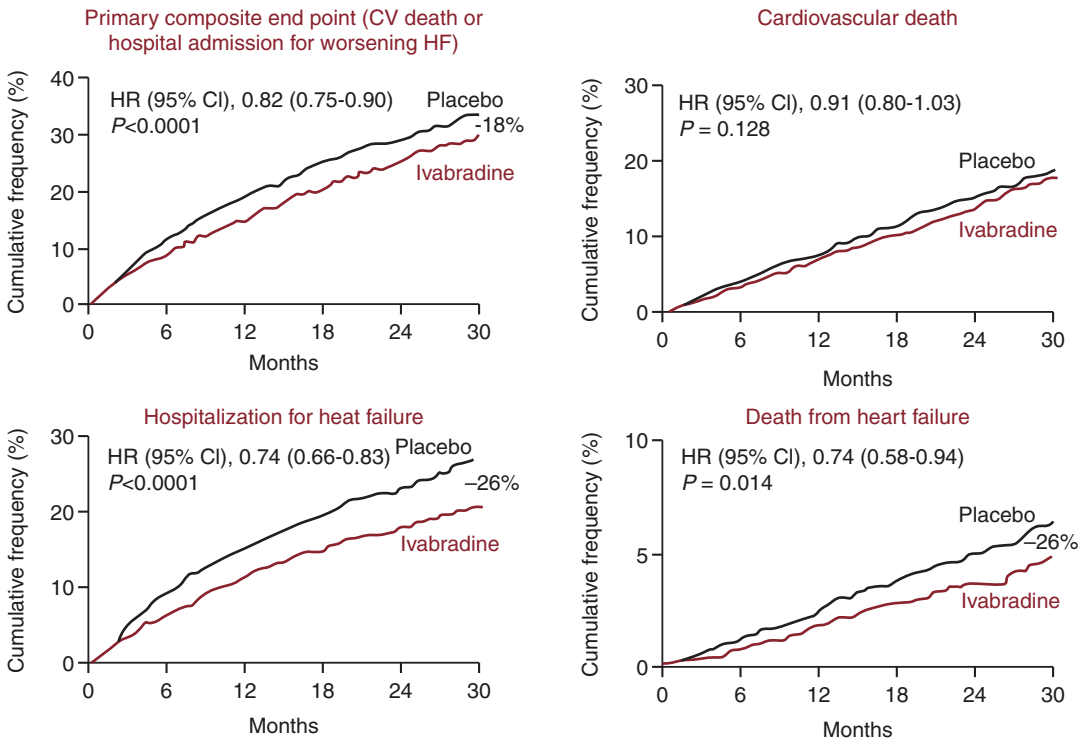

Fig. 8.4 Kaplan-Meier cumulative event curves for different end points in SHIFT. Primary composite outcome (**Panel A**); cardiovascular mortality or heart failure hospitalization and its two components cardiovascular mortality (**Panel B**); heart failure hospitalizations (**Panel C**) and heart failure deaths (**Panel D**) in the ivabradine and the placebo arms. CV cardiovascular, HF heart failure, SHIFT Systolic Heart Failure Treatment with the I_f-Inhibitor Ivabradine Trial. (Swedberg et al.; SHIFT Investigators. Lancet. 2010;376:875–885)

question scientific efficacy of these agents in these populations. For further guidance on the use of sacubitril/valsartan and ivabradine, the reader is referred to the 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure [43] and the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment [44].

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Mechanical Circulatory Support

9

Daniel H. Katz and Marwa A. Sabe

Hemodynamics of Cardiogenic Shock

A clear understanding of the unique hemodynamic changes in CS is critical to understanding the downward spiral of CS (Fig. 9.1) and the unique benefits of various MCS devices. The loop in Fig. 9.2a shows a standard pressure-volume loop for a normal heart. As a reminder, the end-systolic pressure-volume relationship (ESPVR) represents the intrinsic systolic function of the heart, and the slope of the ESPVR, the end-systolic elastance (Ees), is an approximation of contractility. The end-diastolic pressure-volume relationship (EDPVR) defines the diastolic function of the heart. The specific pressure-volume loop assumed by the heart depends on the preload and afterload at any given time but is bounded by the ESPVR and EDPVR. The shift in Fig. 9.2b represents the expected change when the heart suffers an acute insult to intrinsic contractile function, such as an AMI. In general, the contractile function of the heart decreases, which manifests as a drop in the slope of the ESPVR. The resulting pressure-volume loop represents a dilated left ventricle (increased end-diastolic volume) and a weak contractile force that produces a much smaller stroke volume.

A critical problem that drives cardiogenic shock can be demonstrated by considering the energetics of the normal heart compared to the acutely insulted heart. The heart requires energy according to the space bounded by the ESPVR, EDPVR, and the pressure-volume loop. It can be divided into the energy needed to maintain the heart shape and electrical function, termed potential energy (PE), and the energy of actually pumping blood, termed stroke work (SW). Together these make up the pressure-volume area which is directly proportional to myocardial oxygen demand. As you can see by comparing Fig. 9.2c, d, in an acute insult, SW may decrease substantially, but PE remains relatively high. Since SW represents not only a demand for oxygen, but also the supply of oxygen, it is easy to see how such a change in the energetics of the heart could precipitate an imbalance in myocardial demand and supply. This imbalance leads to further ischemia, even in the absence of further coronary obstruction, and drives the downward spiral of CS.

To intervene on this pathophysiologic process, clinicians have several tools at their disposal. In the setting of an AMI, urgent reperfusion remains

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_9

the standard of care [1]. However, several CS states are not driven by coronary occlusion, so thrombolysis and/or percutaneous coronary intervention will offer limited benefit. Traditionally, vasopressors and inotropes have formed the basis of management in CS, as these agents are widely available, have rapid onset of action, and require minimal staff resources to uti-

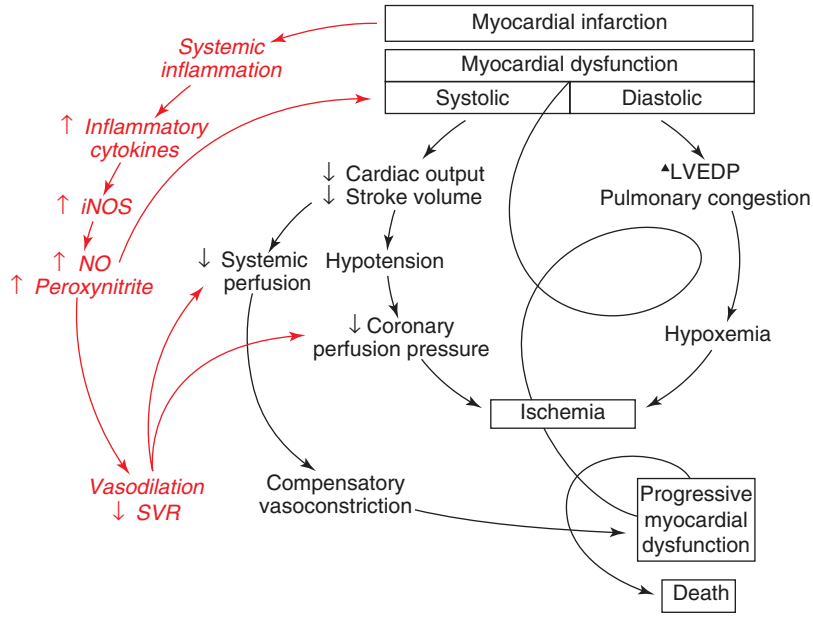

Fig. 9.1 Cardiogenic shock paradigm. Red indicates the effects of inflammatory pathways (Reproduced with permission from Judith Hochman and Harrison's Principles of Internal Medicine)

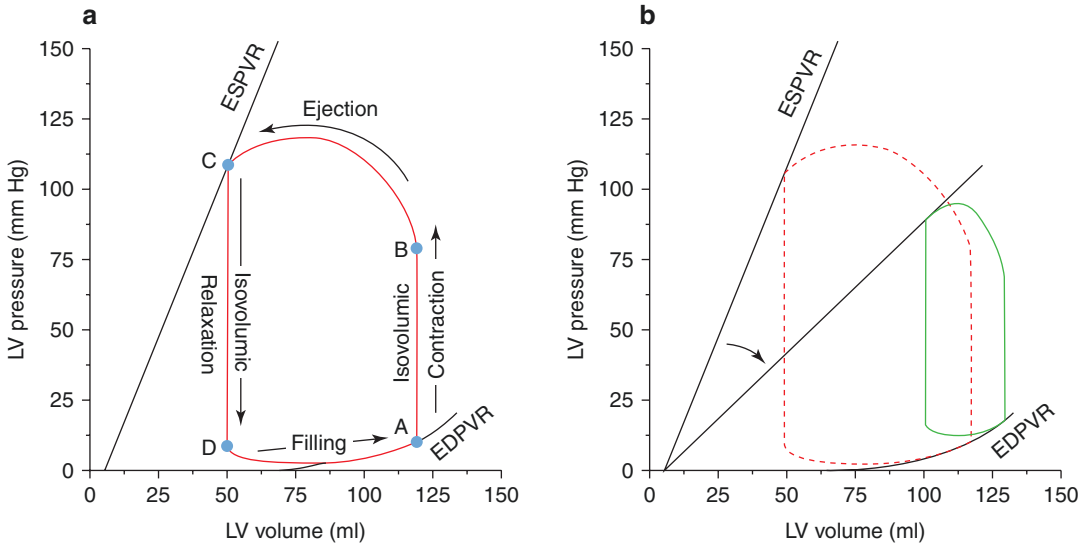

Fig. 9.2 (**a**) The standard pressure-volume loop for a normal heart is shown. The process from point A to point B represents isovolumic contraction where pressure increases without a change in volume. The aortic valve opens at B and ejection occurs with a drop in volume. Ejection occurs until point C when the aortic valve closes, which is followed by isovolumic relaxation to point D. The mitral valve opens at point D and the left ventricle fills. (**b**) In an acute insult, the systolic function of the heart weakens and the ESPVR decreases in slope. This results in a smaller volume of ejection and dilation of the ventricle overall. (**c**) Highlights the components of the pressure-volume area (PVA), which is made up of the stroke work (SW) and the potential energy (PE). (**d**) Shows the change in PE and SW when there is an acute insult to the heart. (Adapted from Uriel et al. JACC 2018 with permission [2])

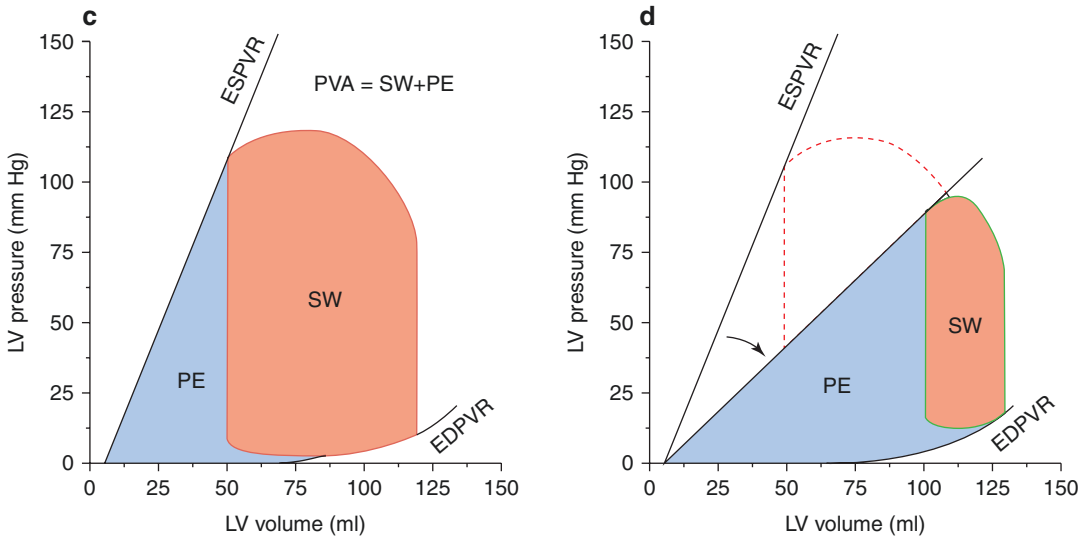

Fig. 9.2 (continued)

lize. However, they also increase myocardial oxygen demand, and may impair end-organ microcirculation, and, thus far, no randomized trials have in fact shown benefit [3]. While these agents are useful for short-term stabilization of hemodynamic collapse, MCS provides a therapeutic intervention that not only supports cardiac output and improves tissue perfusion but also *reduces* myocardial oxygen demand by unloading the ventricle and therefore directly interrupts the spiral of ischemia and myocardial dysfunction that leads toward death [2].

Systems for Temporary Mechanical Circulatory Support

There are numerous devices that provide direct left ventricular (LV) unloading in the setting of CS. They vary in the degree of cardiac output they contribute, and each has unique benefits and challenges. What follows is a general review of the most commonly used devices in clinical practice.

Intra-Aortic Balloon Pump (IABP)

The IABP is the most commonly used form of MCS [4], likely due to the ease of implantation and familiarity in practice. It consists of a conical balloon loaded on a catheter, which is then inserted peripherally so that it may sit in the descending aorta between the left subclavian artery and the renal arteries [5]. Insertion is typically through the femoral artery, but can also be done via the axillary artery directly or through a conduit [6]. Balloon sizes range from 25 cc to 50 cc, and the inflation of the balloon, typically with helium gas, is timed along with the intrinsic heart rate, guided either by the ECG or with fiber-optic monitoring of blood flow. The access cannula is usually 7.5F, the smallest of the various MCS systems.

Hemodynamic Effects

The IABP performs two useful functions in each cardiac cycle. During diastole, the balloon inflates (Fig. 9.3a). This significantly enhances the diastolic pressure within the proximal aorta and therefore enhances the coronary perfusion pressure and the resulting coronary flow [7], thereby directly improving myocardial oxygen supply. The balloon deflates during systole, which results in a significant decrease in afterload. The decrease in afterload allows for earlier opening of the aortic valve, which decreases oxygen demand during isovolumic contraction. In a heart with available contractile reserve, this

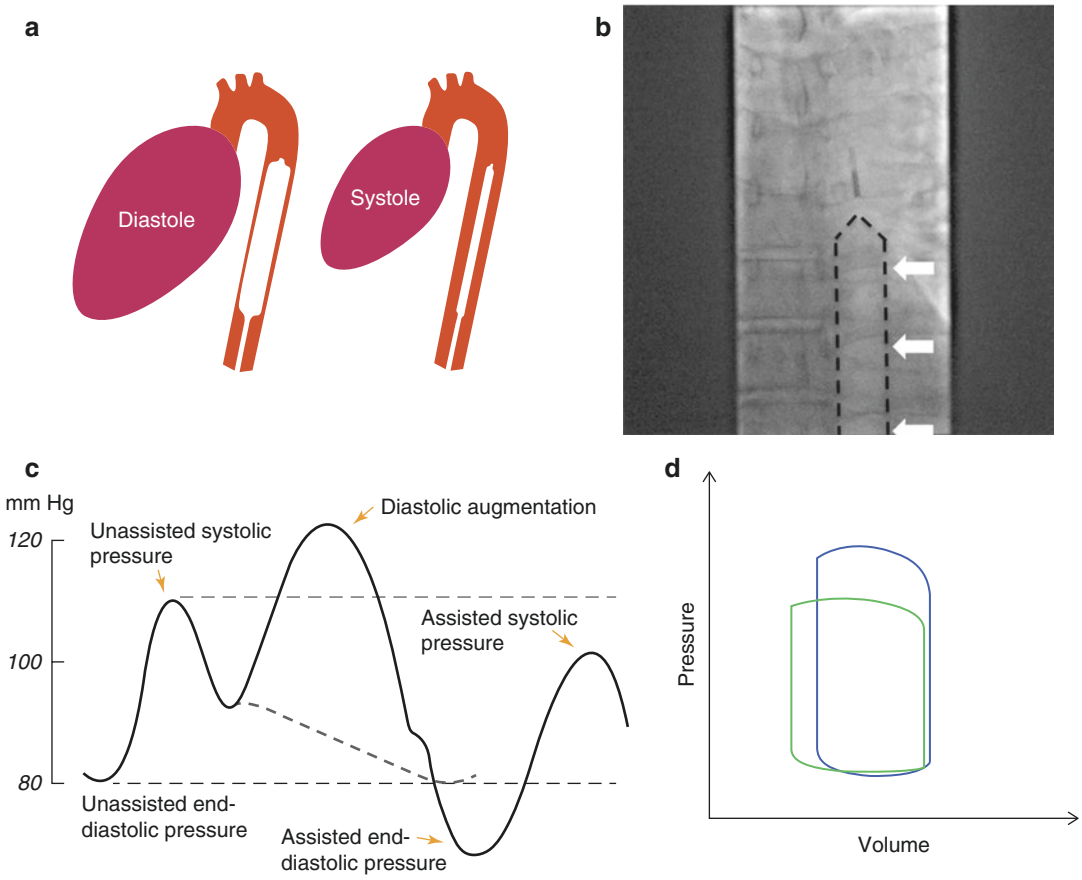

Fig. 9.3 (**a** and **b**) The Intra-aortic balloon pump is peripherally inserted in the descending aorta under fluoroscopy. It inflates during diastole and deflates during systole. (**c**) Diagram of the IABP's effects on systemic blood pressure. When the balloon inflates during diastole, it augments the diastolic pressure, ideally above the normal (unassisted) systolic pressure. Then, with deflation during systole, the systolic pressure is reduced slightly below what it is normally. This is referred to as the assisted systolic pressure. (**d**) Pressure-volume loop with insertion of the IABP is shown in green. Note that with reduction in the afterload, the aortic valve opens at a lower pressure and there is greater volume of ejection. (Reproduced with permission from Briceno et al. [8])

unloading leads to greater stroke volume (Fig. 9.3) [2, 5]. The decrease in systemic vascular resistance without a significant decrease in systemic blood pressure can be extremely useful in cases of acute severe mitral regurgitation or when systemic vascular resistance is high but blood pressure remains low, a state that limits use of afterload reducing medications such as sodium nitroprusside.

Limitations

IABPs are estimated to increase cardiac output somewhere between 0.5 and 1.0 L/min, although this augmentation can be variable in different individuals [5]. However, IABPs themselves provide little intrinsic cardiac output. The LV unloading they provide can enhance LV systolic ejection, similar to vasodilators in acute heart failure (without the side effect of peripheral hypotension, as noted above), but the increase in cardiac output is quite modest. IABPs are also more limited in patients with very high heart rates and arrhythmias due to issues with inflation timing, although this is somewhat mitigated in newer devices that operate by fiberoptic monitoring rather than ECG. IABPs also are contraindicated in patients with any more than mild aortic insufficiency, as inflation during diastole will

exacerbate the degree of aortic insufficiency. Access site bleeding is a present but controllable risk, as the insertion sheath is modest in size.

Study Data

The most important randomized clinical trial of IABPs was the IABP SHOCK II trial which compared IABP to standard treatment in approximately 600 patients with CS related to AMI. There was no benefit in mortality seen at 30 days; however, the trial is noted to have substantial issues with crossover with ~10% of patients in the conventional group receiving IABP, and there are ongoing questions regarding timing of placement, particularly in AMI [3, 8, 9]. This has decreased the strength of recommendations for the use of IABP, but in practice the hemodynamic benefits and the caveats of the IABP-SHOCK II trial have led to continued high-volume use of IABPs.

Ultimately, IABPs are likely to be best suited for situations when the need to increase systemic perfusion is modest, coronary ischemia is a predominant driver of CS, or when a reduction in afterload is expected to be of substantial benefit. IABPs continue to be used for temporizing patients with AMI awaiting CABG, acute mitral regurgitation awaiting surgery, and in selected chronic heart failure patients presenting with cardiogenic shock.

Impella

The Impella (Abiomed, Danvers, Massachusetts) is a percutaneously implanted left ventricular assist device that utilizes an axial flow impeller to pump blood from the LV to the aorta. There are three models presently used in practice which include the Impella 2.5, the Impella CP (3.5), and the Impella 5.0. Access site cannulae are 12F, 14F, and 21F respectively. The model numbers correspond to the upper limit of flow rate achievable, with the CP achieving a maximum of ~4.0 L/min, though actual flow rates are usually somewhat lower than these maximums. The impeller is fixed to a pigtail catheter which is advanced across the aortic valve to the LV either through the femoral artery or through the axillary artery (used frequently for the 5.0 model given the much larger size) (Fig. 9.4).

Hemodynamics

Unlike the IABP, which only reduces afterload, the Impella actively reduces the LV pressure and volume, reducing both preload and afterload. As can be seen in Fig. 9.4, the Impella reduces both wall stress (afterload) and end-diastolic pressure (preload), which leads to a dramatic reduction in both myocardial stroke work and potential energy. This leads to a reduction in myocardial oxygen demand. At the same time, the Impella directly increases cardiac output, which can increase myocardial oxygen supply (Fig. 9.4d). The resulting change in the balance of supply and demand suggests a direct interruption of myocardial ischemia that improves the dangerous spiral of CS.

Limitations

Impella use is growing, though operator familiarity and adequate staff training remain a barrier to use in some care settings. Impellas also use larger access cannulae compared to IABPs, which can lead to an increased bleeding risk. This can be exacerbated by hemolysis related to the axial pump [10], acquired von Willebrand syndrome [11], as well as the necessity of anticoagulation, which is not always necessary for IABPs when the balloon inflates with every beat (1:1). The limitations of duration for Impella use are somewhat uncertain. The FDA has approved the device for 6 days, but some sites have used the Impella 5.0 up to a maximum of 35 days [12]. Femoral access duration is more limited than axillary access due to immobility issues.

Study Data

The small ISAR SHOCK trial observed that even the Impella 2.5 had superior hemodynamic effects compared to the IABP [13]. As a corollary of the benefit of greater cardiac output achieved with this device, registry data also suggested a benefit for patients who received an upgrade from Impella 2.5 to Impella 5.0 [14]. Unfortunately, randomized data for hard out-

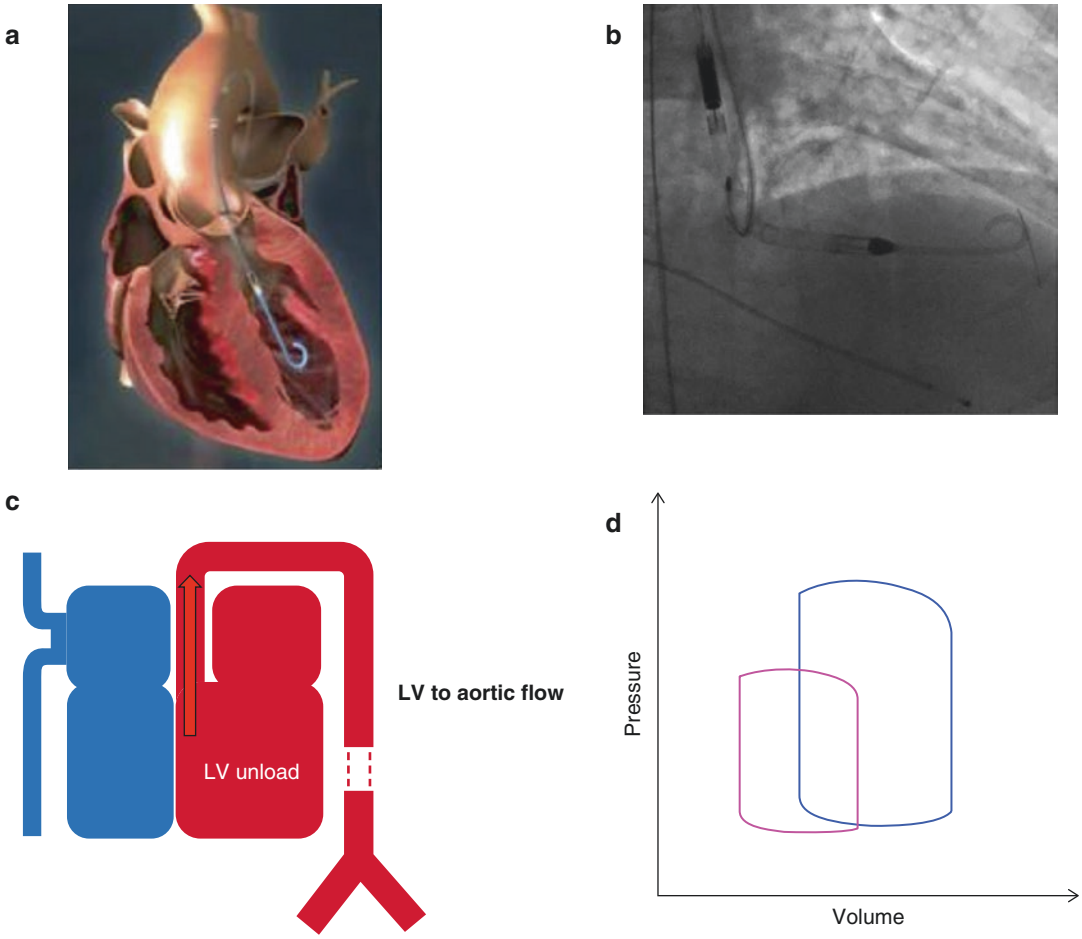

Fig. 9.4 (**a** and **b**) The Impella is inserted fluoroscopically across the aortic valve. (**c**) The Impella directly unloads the LV into the aorta. (**d**) The resulting pressure-volume loop (purple) reflects the unloading of the Impella, as the left ventricular end-diastolic volume significantly decreases. Note that the loop reflects a lower LV stroke volume; however, overall global cardiac output is supported by the Impella. (Reproduced with permission from Briceno et al. [8])

comes are lacking. The Impella CP and IABP were compared in 48 patients with AMI and CS, with no observable difference in 30-day mortality [15]. There is registry data to suggest that for those patients in whom an AMI is the trigger for CS, Impella use prior to coronary intervention was superior to its use afterward [16]. As a result of the experience with Impella at the time of coronary intervention, these devices are frequently deployed in AMI complicated by CS. However, there are some data for use in acute decompensated heart failure, as a bridge to a decision regarding heart transplantation or left ventricular assist device (LVAD) implantation [17, 18].

Extracorporeal Pumps

IABPs and Impellas are both peripherally placed, intracorporeal pumps. As a result, the volume of flow they can deliver, the durability of their use, and their anatomic flexibility are limited. Extracorporeal pumps, on the other hand, use large, robust centrifugal pumps capable of higher flow rates. The inflow and outflow cannulae can be placed in numerous orientations, either peripherally or centrally, depending on anatomy and the desired effect on hemodynamics. A membrane oxygenator can also be placed in-line with an extracorporeal pump to provide blood oxygenation if needed. Like the Impella, these

systems require anticoagulation to reduce the risk of thromboembolism. This section covers the more commonly encountered platforms.

TandemHeart

In many ways, the TandemHeart (CardiacAssist Inc., Pittsburgh, Pennsylvania) mimics the Impella. It is percutaneously placed and directly unloads the LV; however, it uses an extracorporeal centrifugal pump. A 21F inflow cannula is inserted into the femoral vein up to the right atrium and passes across the septum (by transseptal puncture) into the left atrium. The blood is pumped directly into the femoral artery through a 17F cannula (Fig. 9.5) [19]. The hemodynamic profile is similar to that of the Impella. In addition to the routine risks of percutaneous femoral access (bleeding, infection, limb ischemia, etc.), trans-septal puncture increases the possibility of tamponade. Trans-septal puncture is also more technically difficult, and thus this system is not as widely used as the Impella [8]. When compared to IABP, the TandemHeart improved hemodynamic parameters but showed no mortality benefit [20, 21].

CentriMag

The CentriMag (Abott Laboratories, Abbott Park, Illinois) is quite similar to the TandemHeart. It also consists of an extracorporeal centrifugal

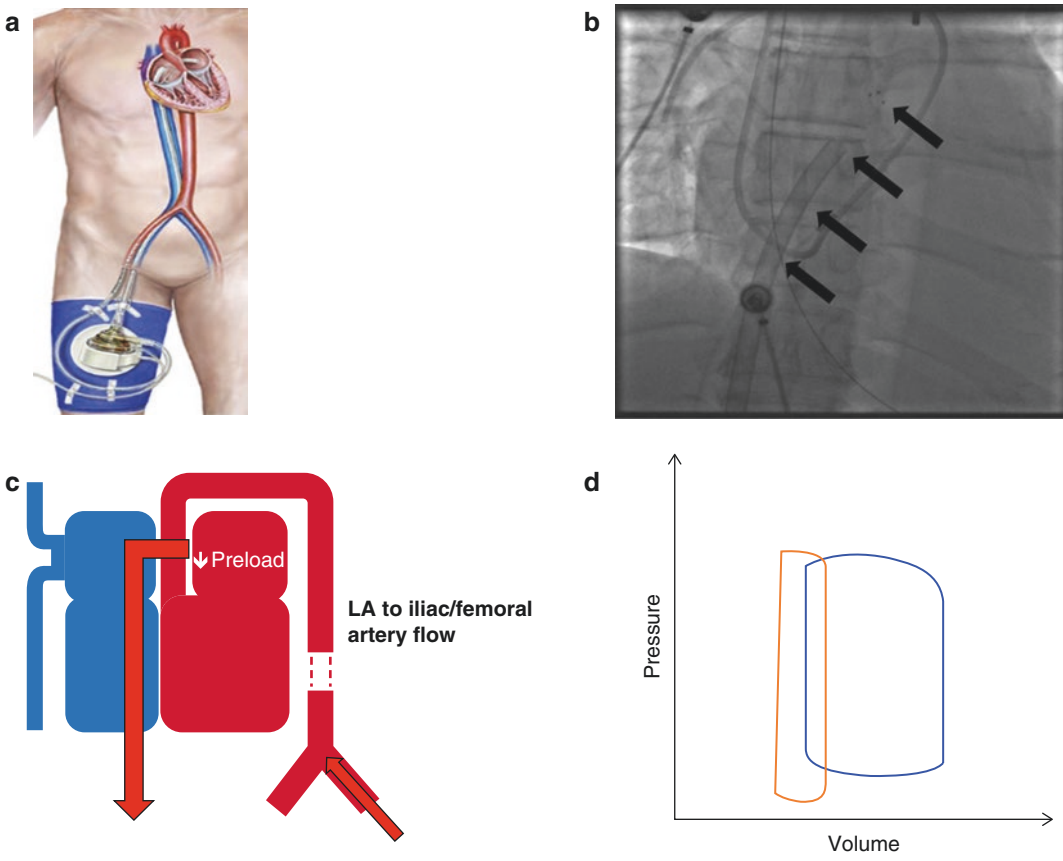

Fig. 9.5 (**a** and **b**) The TandemHeart is placed percutaneously under fluoroscopic guidance. (**c**) The inlet cannula advances up the femoral vein to the right atrium, and crosses to the left atrium, where it drains blood and reduces LV preload. (**d**) Hemodynamic benefits include reduction in preload and reduction in the left ventricular end-systolic volume. Note that the TandemHeart increases afterload on the LV by delivering blood to the femoral artery (Reproduced with permission from Briceno et al. [8])

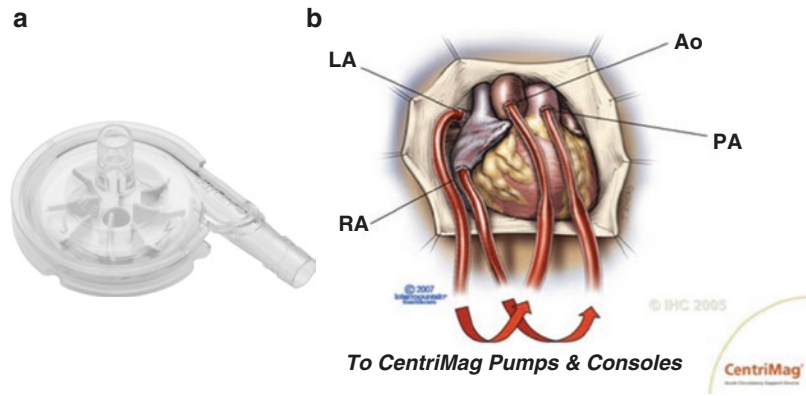

Fig. 9.6 (**a**) The CentriMag is a high flow centrifugal pump. (**b**) The CentriMag can pump blood from the right atrium to the pulmonary artery or the left atrium to the aorta. Other configurations are possible. (Images reproduced with permission from Abbott Laboratories)

pump. The key difference is that the system is implanted through central cannulation (usually by a cardiothoracic surgeon), rather than peripherally. Most commonly the inflow cannula is in the left atrium, and the outflow cannula is in the aorta (Fig. 9.6). However, depending on the situation, the inflow cannulae can be placed in the pulmonary vein or in the left ventricle directly, and for right-sided support can be placed in the right atrium. It is noted that CentriMag is somewhat more flexible in the cannulae it can use and the range of flows it can provide (up to 10 L/min). As a result, surgeons find it useful in post-pericardiotomy syndrome, and the extended duration makes it useful in patients for whom extended mechanical support is needed, as either a bridge to recovery, durable LVAD, or orthotopic heart transplantation [22].

Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO)

ECMO is any system that uses an external membrane to provide oxygenation and removal of carbon dioxide, and is thus suitable for refractory respiratory failure. If that is all that is required, and the patient does not need hemodynamic support, then veno-venous ECMO (VV-ECMO) is adequate. In the setting of CS complicated by respiratory failure, where support of cardiac output is also needed, the membrane oxygenation is paired with a high flow centrifugal pump, and oxygenated blood is pumped from the venous system into the arterial system, hence, venoarterial ECMO (VA-ECMO). Blood is typically removed from the right atrium and returned to the femoral artery after oxygenation, although central cannulation of the aorta by a surgeon is also possible. Alternately, if needed, the inflow can come via the right internal jugular vein and the outflow returned to the right subclavian artery. The venous cannulae range from 19F to 25F and the arterial cannulae are 15F to 24F. Whatever the orientation, the heart and lungs are all bypassed and replaced by the system, such that VA-ECMO is essentially the same as cardiopulmonary bypass (Fig. 9.7). This arrangement takes over the work of both ventricles and therefore is most commonly used in the setting of acute biventricular failure, also complicated by hypoxemic respiratory failure. This is most often seen in AMI, myocarditis, or primary graft failure following orthotopic heart transplant [23].

Hemodynamics

The hemodynamic effects of VA-ECMO are notably different than other MCS systems discussed thus far. Because VA-ECMO drains the venous system, usually from the right atrium, the right ventricle is unloaded, but the LV is not; blood still crosses the pulmonary and coronary vascular circuits and drains into the LV. In fact, not only does ECMO not unload the LV, it then delivers blood flow to the aorta, which in fact increases the afterload on the LV. If left unmanaged, an LV incapable of unloading itself against the afterload of ECMO may develop increased filling pressures and LV distension, which can lead to both increased myocardial oxygen demand and ischemia, as well as pulmonary edema. Furthermore, if the ventriculo-aortic

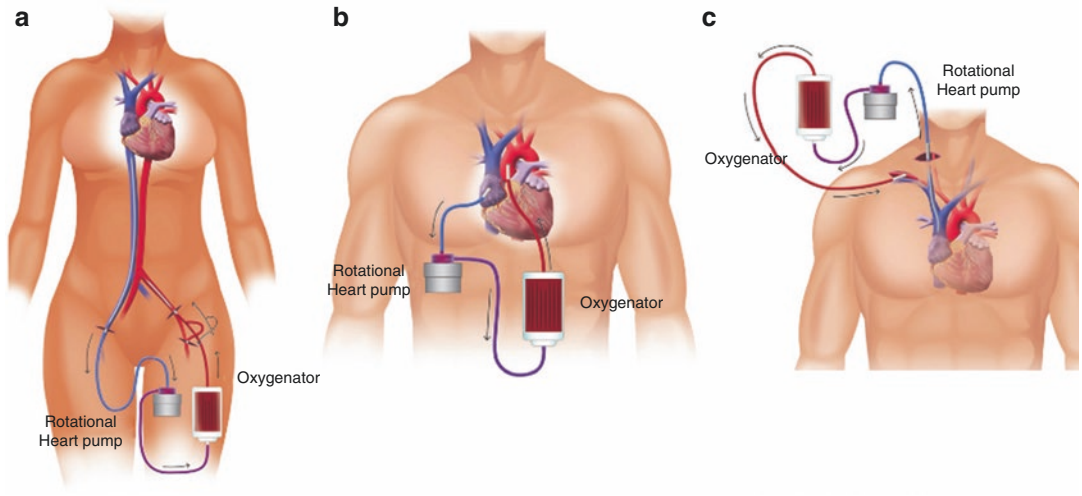

Fig. 9.7 Three possible configurations for VA ECMO. The heart pump and the oxygenator connect a venous inflow to an arterial outflow. Configurations include (**a**) femoral vein to femoral artery, (**b**) right atrium to aorta ("central cannulation"), or (**c**) right internal jugular vein to right subclavian artery. (Reproduced with permission from Rao et al. [23])

coupling is so adverse that the aortic valve does not open, stasis of blood in the LV can increase the patient's risk for thromboembolic events [23].

To manage this problem, ECMO flows could be reduced, though this is limited by the demands of adequate tissue perfusion. Instead, a variety of left ventricular venting options can be employed (Fig. 9.8). Venting options include inotropes or vasodilators, IABP or Impella placement, atrial septostomy (to allow for left atrial to right atrial shunting), or simply a cannula placed directly in the left atrium or LV that drains into the ECMO circuit [23]. Impellas are a frequently used ventilation strategy in patients on VA-ECMO, and simultaneous use of Impella with ECMO support ("ECPELLA") has been shown to be associated with improved 30-day mortality and lower inotrope use in patients requiring VA-ECMO [24].

While it is critical for the LV to be adequately vented to prevent the aforementioned complications, it should also be noted that in patients with substantial respiratory compromise, the blood coming from the LV is poorly oxygenated. If the LV vents itself vigorously, or is supported by any of the strategies listed, enough flow can be generated such that deoxygenated blood preferentially finds its way into the peripheral circulation.

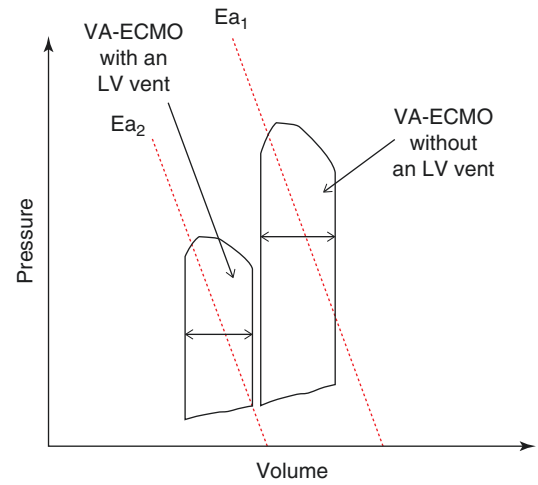

Fig. 9.8 Effect of an LV vent on LV hemodynamics. The vent reduces LV end-diastolic volume and also reduces end-systolic pressure. (Reproduced with permission from Kapur et al. [25])

The at-risk organs are those most proximal, namely, the heart, upper extremities, and head. Thus, this phenomenon is known as North-South syndrome, or Harlequin syndrome (Fig. 9.9) [26]. The phenomenon is best monitored using pulse oximetry or radial artery access in the right arm, wherein arterial supply comes from the

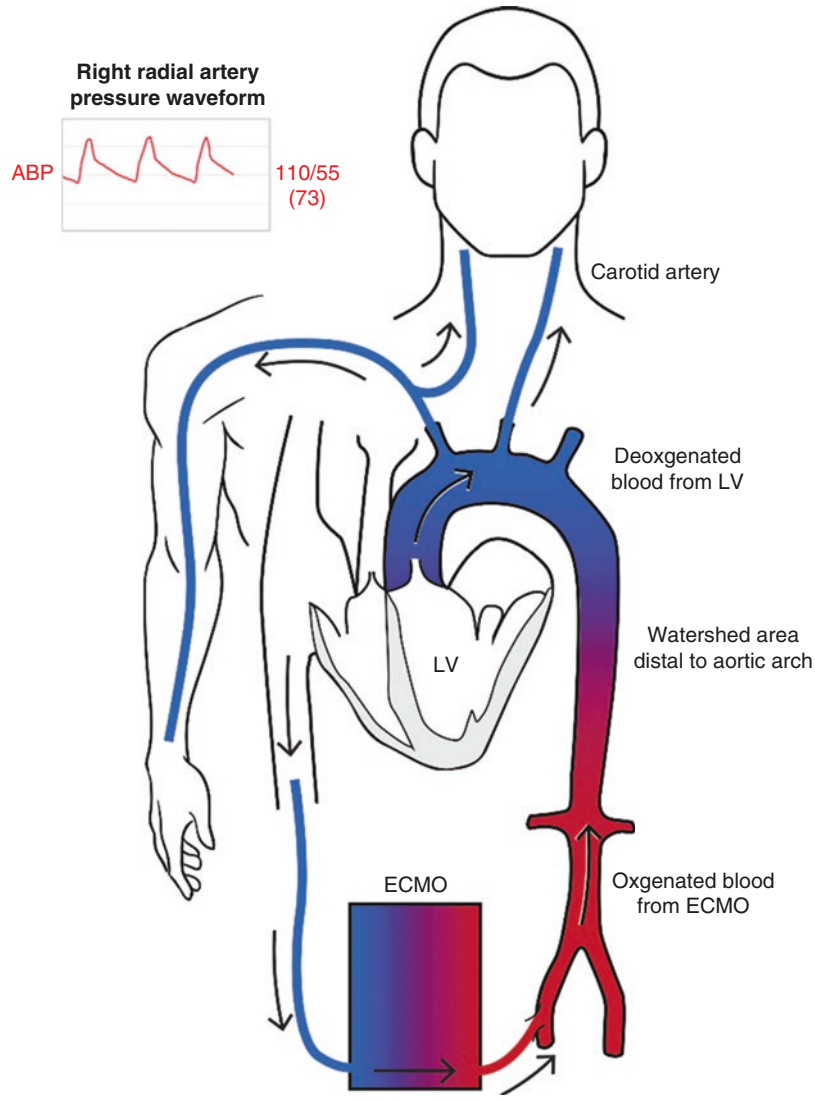

Fig. 9.9 North-South syndrome or Harlequin syndrome. Oxygenated blood from the ECMO circuit mixes with deoxygenated blood from the LV. If this mixing occurs distal to the aortic arch, oxygen to the upper extremities and head can be compromised (Reproduced with permission from Rao et al. [23])

most proximal branch of the aortic arch. If oxygen saturation dips relative to the left arm, or the arterial wave form looks more like the pulsatile work of the LV rather than the continuous flow of ECMO, this can indicate North-South syndrome (or Harlequin syndrome) [23]. If it occurs, increasing ECMO flows can be helpful. Alternative solutions include weakening the stronger LV with an esmolol drip or returning some oxygenated blood back to the RA (which would then make its way to the LV by the normal route), a system referred to as veno-arterio-venous ECMO (VAV-ECMO) [27].

Risks and Limitations

Here again the risks of peripheral cannulation and anticoagulation must be considered: infection, bleeding, and limb ischemia. Because of the particularly large cannulae used with ECMO, the leg distal to the insertion site is frequently cannulated to provide direct antegrade flow and prevent limb ischemia [28]. The ECMO circuit also tends to be more thrombogenic and inflammatory than systems with just a pump, and as a result, peripheral vasodilation and thrombotic events are an ever-present concern [29].

Indications and Contraindications

The principal indication for VA-ECMO is in patients requiring biventricular support as well as respiratory support. The membrane oxygenator carries much of the added risk of ECMO compared to other forms of MCS discussed above, so adding this element should only be done if it is necessary to support the patient. The most important contraindication to initiation of VA-ECMO is the absence of an exit strategy to allow removal of the circuit, whether that is recovery of the heart, durable MCS (discussed below), or heart transplant. Relative contraindications include coagulopathy, obesity, age, and other life-limiting comorbidities particularly malignancy. These issues factor into the likelihood of the patient surviving their time on the ECMO circuit.

Durable Mechanical Circulatory Support

The MCS systems described above are temporary interventions in the setting of cardiogenic shock. In this sense, they are utilized as a bridge to some other more permanent outcome. In some cases, this is a bridge to myocardial recovery, for example, following reperfusion, or of certain types of myocarditis by means of immunosuppressive therapy. However, in patients with CS due to acute on chronic decompensated heart failure or in whom myocardial recovery does not occur, temporary MCS should not even be initiated unless some sort of exit strategy is possible. For more and more patients, that exit strategy is a durable LVAD, and for those who are not heart transplant candidates, durable LVADs represent destination therapy.

Durable LVAD Systems

In general terms, the continuous flow LVADs that are most commonly used in clinical practice are not substantially different from the extracorporeal systems covered above. A high flow pump directly unloads the left ventricle and pumps blood into the proximal aorta. The critical difference is that the pump is surgically implanted in the chest or abdomen. Only a driveline, which powers the pump, is tunneled externally to the skin.

Two categories of pumps are in common use: centrifugal and axial flow pumps, both of which are continuous flow pumps. The HeartWare HVAD (Medtronic, Minneapolis, Minnesota) and the HeartMate 3 (HM3) (Abbott Laboratories, Abbott Partk, Illinois) use centrifugal flow pumps which are implanted with a short inflow cannula into the LV apex, while the HeartMate II (HMII) is an axial flow pump that is implanted just below the diaphragm with a slightly longer inflow cannula connected to the LV apex (Fig. 9.10) [30]. All three systems have a driveline that tunnels out through the abdominal wall and connects externally to a controller which can be powered by

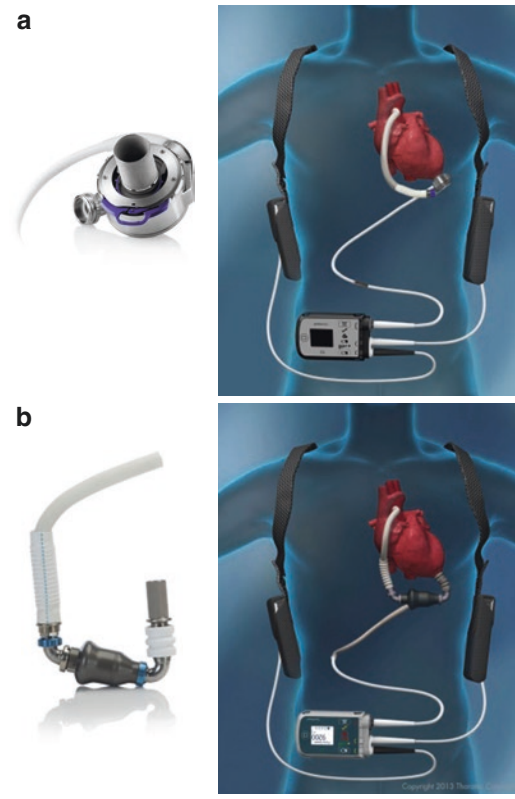

Fig. 9.10 Left ventricular support devices. (**a**) Shows the centrifugal flow pump the HeartMate 3 device. HeartWare (not shown here) is also a centrifugal flow pump. (**b**) Shows the axial flow pump HeartMate II device. Both are connected to external systems with a driveline. Inflow cannulas sit in the LV and outflow cannulas in the aorta. (Reproduced with permission from Abbott Laboratories)

battery or wall outlet. These devices support cardiac output, allowing patients to leave the hospital and resume daily living.

Hemodynamics

In the acute setting, LVADs are hemodynamically similar to other LV-to-aorta MCS systems discussed, such as Impella. However, because the patient's total cardiac output is a combination of their intrinsic LV function, which is pulsatile, and part continuous flow pump, it is worth considering how the two interact. The only externally controllable setting on the LVAD is the speed, measured in rotations per minute. The actual flow that this generates, however, depends on multiple factors, including the preload, afterload, and viscosity of the blood. More directly, as seen in Fig. 9.11, the flow generated by the device is indirectly proportional to the head pressure, which is the pressure gradient between the LV and the aorta. In diastole, the head pressure is high, since LV pressure is relatively low. The high head pressure means flow across the LVAD is lower. During systole, the head pressure is much lower as the LV generates higher pressures at the LVAD inflow cannula. With the low head pressure, LVAD flow increases. Therefore the actual flow generated by the device fluctuates with the cardiac cycle. Because of this effect on flow, increases in the afterload experienced by the LVAD lowers the flow generated by the LVAD, while increases in preload increases flow based on their effect on the head pressure [30]. In fact, the LVAD is more sensitive than the heart to these changes, and it is therefore critical to tightly control blood pressure and volume status in LVAD patients.

The unloading that the LVAD provides manifests in several ways. First, it directly reduces the LV volume and pressure, with subsequent decrease in LV size on echocardiogram. There is evidence that the unloading of the LV myocytes can have long-term beneficial effects on LV remodeling [2]. The direct unloading of the LV also means that the LV itself provides a reduced component of the cardiac output. As a result, the peripheral arterial flow is less pulsatile and more continuous; the greater the LVAD's contribution to the total cardiac output, the lower the pulsatility observed in peripheral arteries [30]. Because of this hemodynamic effect, LVAD patients often do not have blood pressure that can be measured by a typical cuff. Rather a Doppler probe is used to determine the pressure at which flow returns to a peripheral artery. This is commonly referred to as the opening pressure, and it is recommended to keep this below 80 mmHg, given the afterload sensitivity of these devices [31].

LVADs also directly impact the RV. LV unloading reduces left-sided filling pressures, resulting in a drop in RV afterload. However, there are negative consequences for the RV as well. The increased flow from the LVAD can return to the RV and cause RV distension and dysfunction. At the same time, the intraventricular septum can be pulled toward the inflow cannula by the pump, decreasing the septal contribution to RV contractility, and weakening RV performance. For those at risk, these issues can cause early RV failure after LVAD implantation. There is also evidence for late RV failure, the cause of which remains unclear, but may be related to chronic impacts of the above phenomena [30].

Pump Parameters

When in clinic or in the hospital, the HeartMate and HeartWare systems are connected to interfaces that display relevant information about function. Each system uses a different interface for displaying these pump parameters, but in general, pump speed, pump power, pump flow, and some indication of the degree of pulsatility should be readily apparent. The pump speed is set directly. The pump power is directly measured by the VAD and is directly proportional to the amount of actual flow through the VAD. Flow itself is not directly measured by the VAD, but rather calculated from pump power, pump speed, and blood viscosity, with viscosity derived from the hematocrit which has to be entered into the interface (in the HeartWare and HM3 device; this option is not available in the HMII device). For this reason, entering a new hematocrit can cause a sudden shift in the calculated flow.

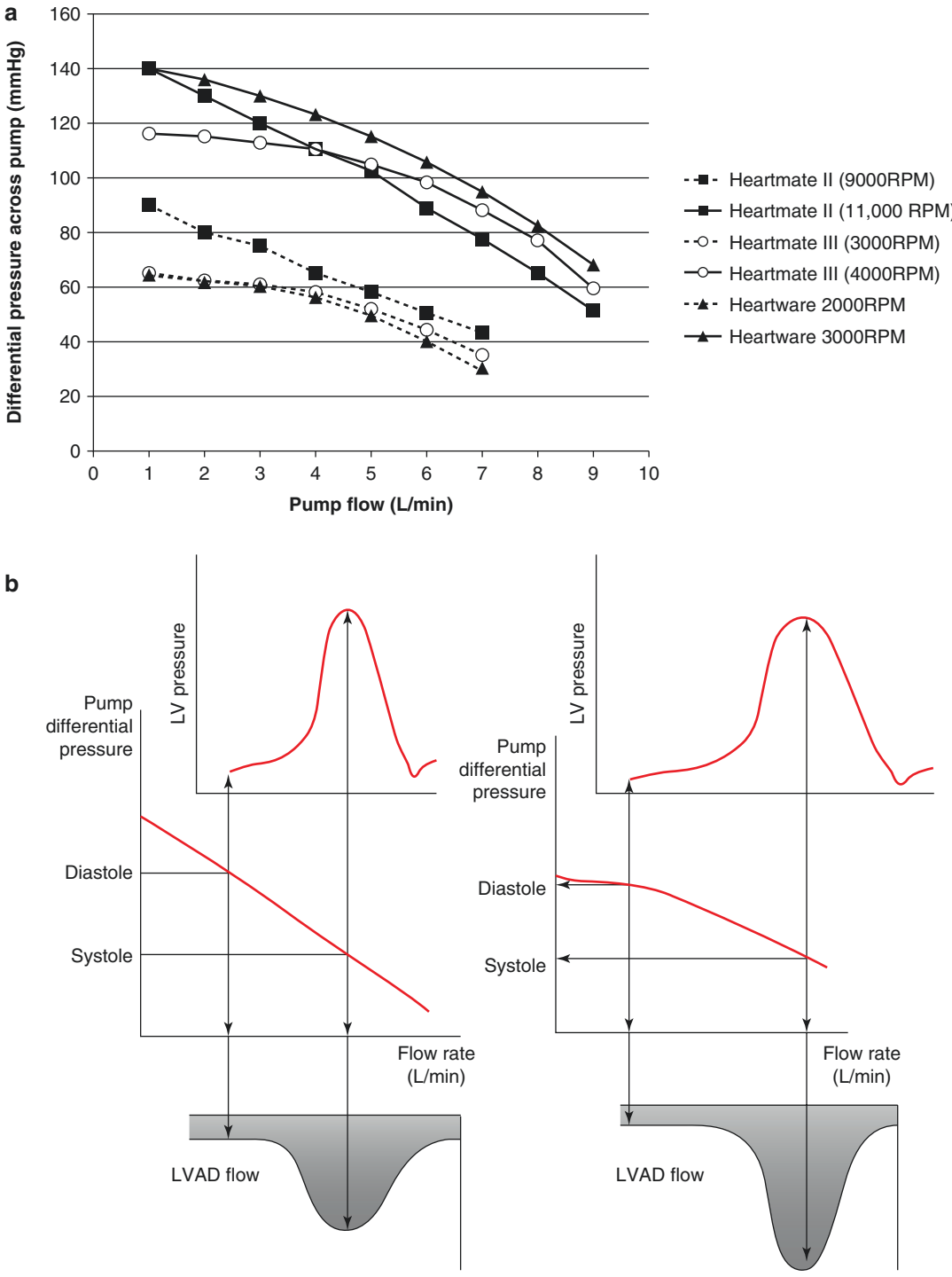

Fig. 9.11 LVAD hemodynamics. (**a**) The actual flow generated by an LVAD varies by the type, speed, and head pressure. (**b**) Actual flow rates in an LVAD vary throughout the cardiac cycle. During systole, the pressure gradient between the LV and the aorta shrinks, so flow increases. The right panel shows an LVAD that is more sensitive to changes in head pressure, with larger fluctuations in flow rate. (Reproduced with permission from Lim et al. [30])

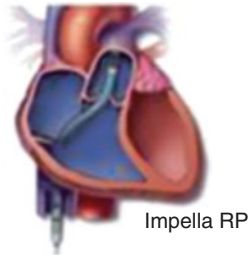

Fig. 9.12 Impella RP. The impeller pumps blood from the inferior vena cava to the pulmonary artery. (Reproduced with permission from Kapur et al. [32])

Right Ventricular Support

The above examples of MCS all focused on left ventricular support, save for ECMO which provides biventricular support. RV support, either in addition to LV support or in isolation can also be achieved with many of the systems already covered. Percutaneous VADs can be placed with cannulae in the right atrium and pulmonary artery, thereby unloading the right heart. There is also an Impella RP, specifically designed for RV support (Fig. 9.12) [25, 32]. Simultaneous use of Impella 2.5, CP, or 5.0 and Impella RP can be used for hemodynamic support in patients with biventricular shock [33]. Durable RVAD is also an option, both in patients with RV failure related to LVAD implantation and in patients with biventricular failure requiring bridge support prior to orthotopic heart transplantation.

Review Questions

Case 1: A 34-year-old female with no past medical history presents with 4 days of progressive dyspnea. She had a mild upper respiratory infection 2 weeks ago. Her vital signs show a temperature of 37 °C, heart rate of 132 in sinus rhythm with frequent ventricular ectopy, blood pressure of 78/59, and an oxygen saturation of 82% on BiPAP with 60% FiO2. On exam, she has an elevated jugular venous pulsation to 14 cm H_2O, crackles in both lung fields, an S3 gallop, and cool, mottled extremities. She is in visible distress. Bedside echocardiogram shows biventricular systolic dysfunction, 2+ mitral regurgitation and no aortic insufficiency. During the echocardiogram, she becomes unresponsive and a code is called for PEA arrest. She is intubated, and after two rounds of CPR and one dose of epinephrine, she has return of spontaneous circulation, though her oxygen saturation remains 83% on appropriate ventilator support and her blood pressure is 76/58.

1. What type of support would be most appropriate at this time?
   A. Dobutamine and norepinephrine
   B. Transfer to the OR for emergent durable RVAD and LVAD
   C. Impella 5.0 via axillary cutdown
   D. VA-ECMO

This patient presents with likely myocarditis with profound biventricular failure and respiratory compromise. This situation favors VA-ECMO. Inotropes and vasopressors are less likely to provide adequate support, and an Impella fails to support the RV. While durable RVAD and LVAD could offer adequate circulatory support, it fails to address the respiratory failure and is potentially unnecessary as near term recovery is possible.

2. The above patient is started on VA-ECMO via right femoral vein and left femoral artery cannulation. Twelve hours after initiation the patient is noted to have frothy secretions in the endotracheal tube. Bedside echo shows a markedly dilated LV with 4+ mitral regurgitation without flail. The aortic valve is not noted to open.

   What is the next best step in management?

A. Placement of an Impella CP
B. Transfer to the OR for emergent mitral valve repair
C. Increasing ECMO pump speed
D. Increasing ventilator oxygenation support

This patient needs LV unloading given their very poor LV function, which can be achieved with an Impella device, acting as a direct LV vent. The mitral regurgitation is a functional con-

sequence of LV dilation, and is not the primary driver of the situation. Increasing ECMO pump speed will increase flow in the proximal aorta and worsen the situation. Increasing ventilator oxygenation support may increase overall oxygenation to a small extent, but does not address LV unloading.

Case 2: A 59-year-old man with a history of hypertension and diabetes presents after 4 days of intermittent chest pressure at rest. Today his chest pressure has persisted for several hours, and he is markedly short of breath prompting his presentation. Vital signs show a heart rate of 95, blood pressure of 92/68, and an oxygen saturation of 92% on room air. His EKG shows ST elevations in V1-V4 with associated q-waves and reciprocal ST depressions. He is given aspirin, ticagrelor, and a bolus of heparin. The catheterization laboratory is activated. Via right radial artery access, he is found to have a proximal LAD occlusion. As the intervention is about to begin, blood pressure is noted to be 75/55, and the patient becomes less responsive.

3. What is the next best action?
   A. Complete the procedure while closely monitoring vital signs
   B. Place an Impella CP
   C. Start a norepinephrine drip
   D. Cannulate for VA-ECMO

This patient is developing cardiogenic shock from an AMI. The primary need is for rapid left ventricular support. Fixing the lesion without support could allow the cycle of CS to continue. It is preferred to start some form of hemodynamic support and then complete the procedure. Norepinephrine would not be an ideal agent as it does not decrease myocardial demand or increase coronary perfusion. VA-ECMO is not necessary as the patient does not have RV or respiratory failure.

Case 3: A 52-year-old male with diabetes, hypertension, and hyperlipidemia with infrequent medical care presents with 3 days of progressive dyspnea and fatigue. He has noted 10 lbs weight gain in the last week. He is noted to be tachycardic to 105 bpm and his blood pressure is 85/56. His extremities are cool to the touch and he is noted to have trouble paying attention during the history. EKG shows inferolateral T-wave inversions with ST depressions. Troponins are sent. Bedside echocardiogram shows EF 15% with wall motion abnormalities. He is given 325 mg aspirin and bolused with 5000 U of IV heparin for presumed acute coronary syndrome. He is started on a dopamine drip and transferred to the cath lab which shows severe three vessel coronary disease with small distal vessels. There is no culprit vessel on which to intervene.

4. What is the next best intervention?
   A. Start sodium nitroprusside
   B. Place an IABP
   C. Book the OR for placement of a left atrium to aortic CentriMag
   D. Book the OR for placement of a durable LVAD

The patient has exacerbation of likely long-standing ischemic coronary disease. He is developing CS and reperfusion is not an option. Temporary MCS with an IABP would be valuable here. It would help to unload the struggling ventricle and increase coronary perfusion pressure to the likely ischemic heart. Sodium nitroprusside would be risky given low blood pressure. A CentriMag would provide hemodynamic support, but is much more invasive than an IABP and may not be necessary at this point. Similarly durable LVAD would be premature as LV recovery is possible in the near term.

After 3 days on the IABP, his mentation has improved and he is diuresed back to his dry weight. However, there is no improvement in the patient's intrinsic LV function, and the cardiothoracic surgeons have decided his coronaries are insufficient for coronary artery bypass surgery. The IABP is unable to be weaned without decrease in blood pressure. He and his family would like to know what further options he has at this point.

5. What option would be best at this time?
   A. Continued monitoring on IABP
   B. Upgrade to CentriMag

C. Evaluate for LVAD/orthotopic heart transplant
D. Transition to comfort care

This patient should begin an urgent evaluation for LVAD and/or heart transplant. Upgrading to CentriMag at this time is not necessary as the patient is adequately supported on IABP, but further monitoring on IABP is unlikely to yield further improvement in his LV function, and is not worth the daily risk for complications from IABP. Transitioning to comfort care is not appropriate as LVAD support is an option and the patient and family are seeking further care.

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Part III

Methods of Hemodynamic Evaluation

Key Clinical Findings

10

Sachin S. Goel and William J. Stewart

From inability to let well alone;
from too much zeal for the new and contempt for what is old;
from putting knowledge before wisdom, science before art, and cleverness before common sense;
from treating patients as cases;
and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us.

– Sir Robert Hutchison MD FRCP (1871–1960)

Case 1

A 65-year-old male, with history of coronary artery disease, anterior wall myocardial infarction 10 years ago, and ischemic cardiomyopathy with left ventricular ejection fraction of 30%, presents to the emergency room with worsening dyspnea on exertion and orthopnea for 1 week. On examination, his heart rate is 88 beats per minute and regular, blood pressure is 126/74 mm Hg, and respiratory rate is 18 per minute with oxygen saturation measuring 94% at room air. The jugular venous pressure is elevated to 14 cm of water. Examination of the lungs is notable for bibasilar rales. Cardiovascular exam reveals a laterally displaced apical impulse. The S1 is normal, S2 is physiologically split, and there is a moderately loud S3. There is no audible murmur. Abdominal examination reveals mild hepatomegaly, with the edge 2 cm below the costal margin, with no evidence of ascites. The lower extremities demonstrate moderate pitting edema to the mid-calf bilaterally.

This patient is in acute decompensated heart failure (ADHF), which, even today, remains a clinical diagnosis performed at the bedside, based primarily on history and physical examination, rather than on laboratory data. The most important clues to this diagnosis are symptoms related to dyspnea and signs related to biventricular congestion and volume overload. Of the symptoms, orthopnea correlates best with elevated pulmonary capillary wedge pressure (PCWP), with a sensitivity approaching 90% [1]. Clinically evident edema usually indicates a volume excess of at least 3–4 L. Measuring blood pressure is of critical importance in patients with ADHF since hypotension is one of the strongest predictors of poor outcomes [2] and has important implications for therapy.

Jugular venous pressure (JVP) is a cardinal aspect of the cardiovascular examination in the assessment of volume status in patients in general, and in those with ADHF in particular. However, estimation of JVP is highly dependent on examiner skill, experience, and patience. An abnormally elevated JVP is a pressure defined as >5 cm of water. If the patient is sitting at a 45 degree angle to the bed, there should be no visible pulsations above the angle of Louis. JVP reflects right atrial (RA) pressure. It is often used

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_10

as a surrogate for left ventricular filling pressure; however right heart failure is often absent in patients with left-sided heart failure. The most common cause of right ventricular failure is left ventricular failure. In a study consisting of 1000 consecutive patients with advanced heart failure undergoing right heart catheterization, RA pressure was found to somewhat reliably predict PCWP (r = 0.64), and the positive predictive value of RA pressure >10 mm Hg for PCWP >22 mm Hg was 88% [3]. Hepatojugular reflux (HJR) is jugular venous distension induced by firm pressure over the liver. An increase in JVP >3 cm by this maneuver is a positive HJR, which is a sign of right-sided volume overload. The presence of jugular venous distension, at rest or inducible, is the bedside clinical sign that has the best combination of sensitivity (81%), specificity (80%), and predictive accuracy (81%) for prediction of elevation of PCWP (≥18 mm Hg) [4].

The third heart sound (S3) occurs in early diastole due to abrupt cessation of rapid early diastolic left ventricular inflow as a consequence of increased LV filling pressures and an abnormally stiff, non-compliant left ventricle [5]. It is a fairly specific marker for LV dysfunction and correlates with BNP levels [6]. However, it is not as sensitive as other bedside findings. In a comprehensive analysis evaluating all studies published between 1966 and 2005 which assessed the precision and diagnostic accuracy in diagnosing the cause of dyspnea, the S3 was found to increase the likelihood of ADHF more than any other part of the physical examination (likelihood ratio 11, 95% Confidence Interval 4.9–25.0) [7]. The S3 is associated with elevated LV filling pressures [8]. In a comprehensive study of the physiology of the S3 comparing findings from phonocardiography, tissue Doppler echocardiography, BNP, and invasive LV hemodynamics, patients with an audible S3 were found to have a higher early mitral inflow velocity (E), a more rapid deceleration time (DT) of early mitral inflow, reduced mitral annular velocity (e'), and therefore higher E/e' ratio. The E/e' ratio has been correlated with elevated LV filling pressures [9, 10].

Hepatomegaly results from increased central venous pressure and is often accompanied by right upper quadrant tenderness. Based on various components of the history and physical examination, patients with ADHF can be assigned to one of the quadrants of a 2 × 2 table, each of which represents a distinct hemodynamic profile defined by the presence or absence of congestion (wet or dry) and low or normal perfusion (cold or warm) (Fig. 10.1) [11]. This strategy is very useful in selecting initial therapy and identifying prognosis in patients with ADHF.

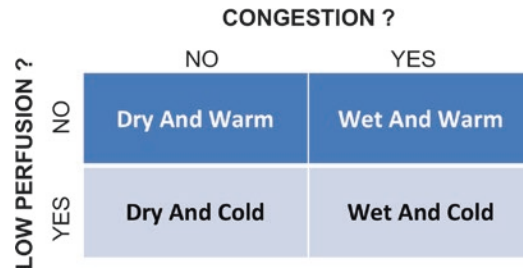

Fig. 10.1 Hemodynamic profiles in ADHF. Evidence for *congestion* (the "yes-no" delineation of the two columns) includes orthopnea, elevated JVP, hepatojugular reflux, S3, rales, hepatomegaly, ascites, peripheral edema, and a loud P2. Evidence *for low perfusion* (the "yes-no" delineation of the two rows) includes narrow pulse pressure, cool and clammy extremities, altered mentation, and oliguria

Case 2

A 54-year-old lady with known history of a heart murmur for over two decades presents with symptoms of worsening fatigue, dyspnea on exertion, and palpitations for the last 2 years. On examination, her pulse is irregular with a heart rate of 110 beats per minute and her blood pressure is 132/84 mm Hg. The jugular venous pressure is elevated to 12 cm of water. Cardiovascular exam reveals laterally displaced, brisk, enlarged, and hyperdynamic apical impulse. The S1 is normal and there is a loud 3/6 holosystolic murmur radiating to the axilla and to the left paravertebral region. In addition, a parasternal right ventricular heave is palpable and a loud P2 is audible. The pulmonary exam is notable for bibasilar rales. Abdominal examination is unremarkable and there is trace bilateral pedal edema.

This patient has chronic severe mitral regurgitation (MR), likely secondary to mitral valve

prolapse (MVP). Although this patient's history and physical findings are classic, clinical findings in MR vary depending on acuity, severity, and the mechanism. For example, in acute severe MR, sometimes caused by acute papillary muscle rupture or endocarditis, the apical LV impulse is not displaced because the LV has not had a chance to dilate. In acute severe MR, the systolic murmur may be early in timing and decrescendo in configuration due to rapid systolic equalization of pressures between the left ventricle and the left atrium (LA). The LA pressure would have a large "V" wave during ventricular systole. MVP is sometimes associated with (1) one or more systolic clicks, produced by sudden tensing of the elongated chordae tendineae as the leaflets prolapse, and (2) a holosystolic or late systolic murmur. In less than severe MR, it is useful to observe the onset of the murmur and the timing of systolic click in MVP, both of which move earlier in systole with maneuvers which reduce left ventricular end diastolic volume (such as standing and the Valsalva maneuver), while the murmur becomes louder. Conversely, the onset of the murmur and the timing of systolic click in MVP are delayed later in systole with maneuvers that increase left ventricular end diastolic volume (such as squatting) and the murmur becomes softer (Fig. 10.2) [12]. Severe MR is often associated with a holosystolic murmur that radiates

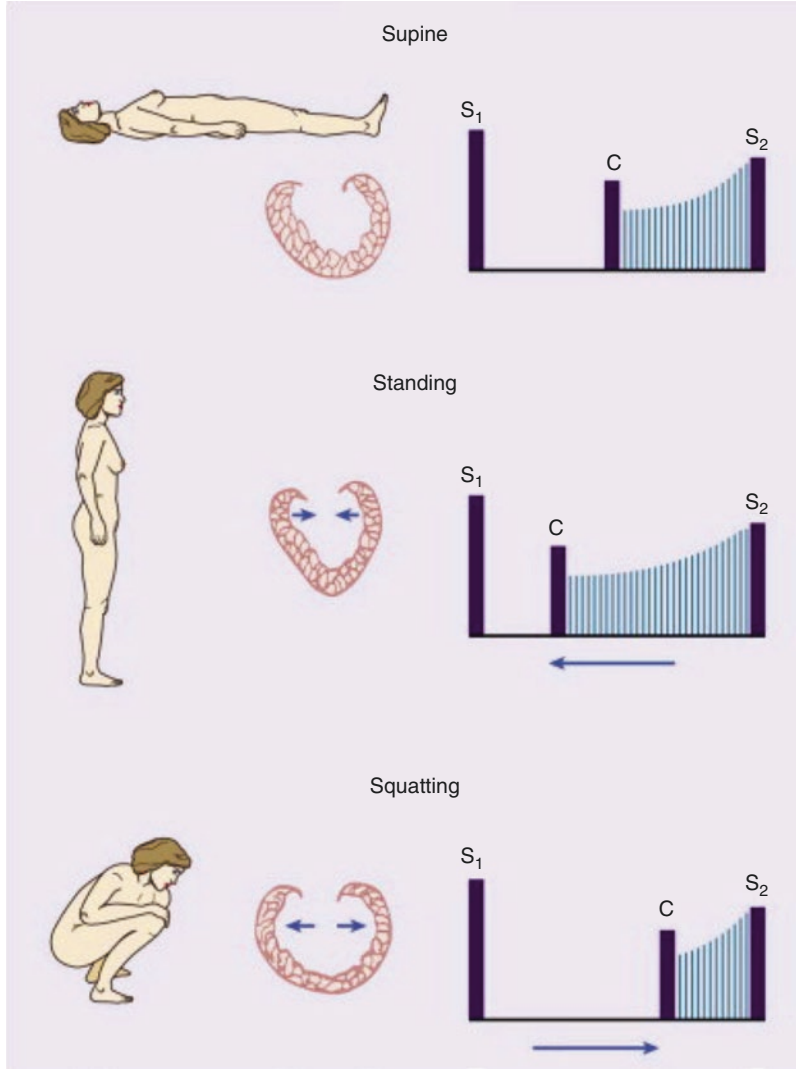

Fig. 10.2 Behavior of the nonejection click (C) and systolic murmur of mitral valve prolapse. The top panel shows the first heart sound (S1), the mid-systolic click (C), and the second heart sound (S2), with the late systolic murmur of moderate mitral regurgitation while the patient is supine. With standing, (middle panel) venous return decreases, the heart becomes smaller, and the prolapse occurs earlier in systole. The click and murmur move closer to S1. With squatting, (lower panel) venous return increases, causing an increase in left ventricular chamber size. The click and murmur occur later in systole and move away from S1. (From Shaver et al. [27])

posteriorly to the axilla and around to the left paravertebral region in the back, irrespective of which mitral leaflet is involved. As mitral regurgitation becomes chronic, left ventricular volume overload leads to left atrial enlargement and atrial fibrillation is common. With development of pulmonary hypertension, the P2 component of the second heart sound becomes louder. The S2 splitting may widen with more severe MR, due to a combination of early A2 as a result of decrease in left ventricular ejection time and delay in P2.

Case 3

A 64-year-old man with history of coronary artery bypass grafting (CABG) 15 years ago presents with complaints of increasing dyspnea on exertion over the last 12 months. Recently he has also noted worsening leg edema and increasing abdominal girth. On examination, his heart rate is 90 beats per minute and regular, and his blood pressure is 108/74 mm Hg. The jugular venous pressure is elevated to 14 cm of water with a prominent, rapidly collapsing *y* descent and a positive Kussmaul sign. The apical impulse is not displaced. The S1 and S2 are normal and there is a high-pitched early diastolic sound, corresponding with the prominent y descent seen in jugular venous waveform, which is heard best at the LV apex. Abdominal examination reveals pulsatile hepatomegaly with evidence of ascites. Bilateral lower extremity edema is present.

This patient likely has pericardial constriction, based on his history and physical findings. Subsequent imaging and cardiac catheterization confirmed this diagnosis. Constriction is characterized by thickened, scarred, and/or calcified pericardium that markedly limits diastolic filling of the heart. The jugular venous waveforms help clarify hemodynamics in constrictive pericarditis. Jugular venous pressure contour normally has two distinct positive waves (*a* and *v* wave) and two negative waves (*x* and *y* descent) (Fig. 10.3a). The *a* wave occurs with right atrial systole and follows the P wave on EKG and precedes the first heart sound (S1). The *x* descent normally occurs as RA pressure falls after the *a* wave and ventricular systole pulls the tricuspid valve and the RA downward. The *c* wave interrupts the *x* descent

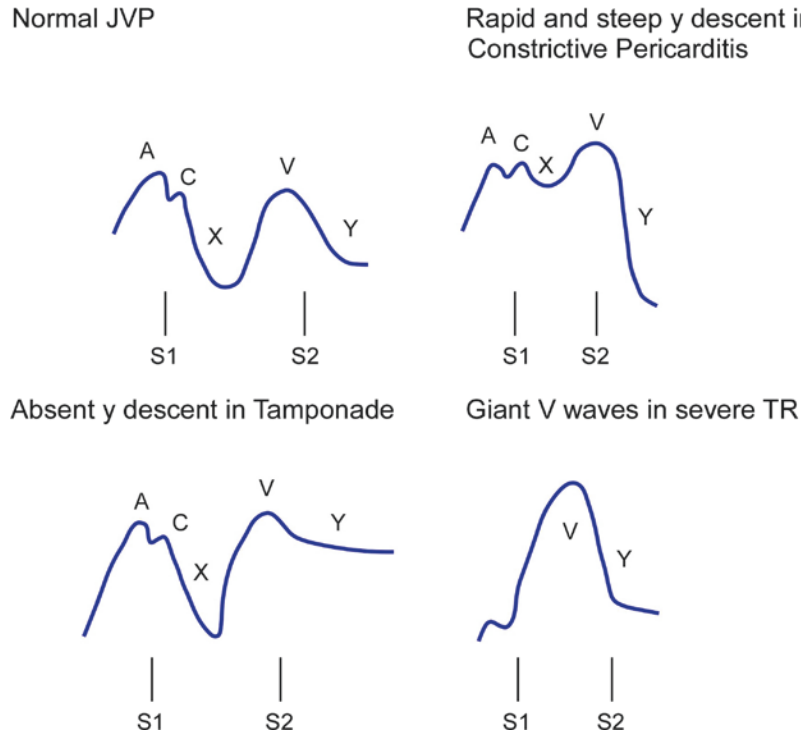

Fig. 10.3 Jugular venous waveform patterns – (**a**) normal patients, (**b**) (constrictive pericarditis), (**c**) pericardial tamponade and (**d**) (severe tricuspid regurgitation) (TR). JVP jugular venous pressure, S1 first heart sound, S2 second heart sound. The A, C, and V positive waves, and the X and Y negative waves, are explained in the text

during early ventricular systole as the tricuspid valve is briefly pushed in to the right atrium as the ventricle begins contracting, thereby elevating RA pressure briefly. The *v* wave occurs with RA filling at the end of ventricular systole, just after the second heart sound (S2). The *y* descent follows the v wave and occurs with fall in RA pressure after the tricuspid valve opens and fills the RV in diastole. Regarding the abnormal jugular venous pressure waveform in constrictive pericarditis, the most prominent wave is the rapid *y* descent, as the ventricles fill rapidly during early diastole due to elevated atrial pressures. Once the pericardial constraining volume is reached, however, ventricular filling slows abruptly due to the development of high ventricular pressure, which is manifested as the characteristic dip and plateau in ventricular diastolic pressures. The JVP contour therefore has an M or W-shaped contour (Fig. 10.3b), with a prominent, rapidly collapsing *y* descent, along with a normal or reduced *x* descent. Another feature of constriction is the respirophasic changes in jugular venous pressure. In normal individuals, JVP falls with inspiration as a reflection of the reduction in the intrathoracic pressure; the increased venous return is accommodated by the compliant right ventricle. In constrictive pericarditis, the increased venous return is not accommodated well; the increased venous return meets the stiff and inelastic pericardium, resulting in a rise in jugular venous pressure with inhalation, characteristically referred to as Kussmaul sign [13]. The classic (sometimes the only) auscultatory finding in constrictive pericarditis is a high-pitched early diastolic sound, referred to as pericardial knock, which occurs due to the abrupt cessation of blood during early diastolic ventricular filling. The pericardial knock corresponds in timing with the prominent y descent in JVP [14].

Case 4

A 66-year-old lady with history of metastatic breast carcinoma presents with worsening dyspnea on exertion for the last 3 days. On examination, her heart rate is 110 beats per minute, blood pressure is 88/56 mm Hg, and there is a paradoxical pulse of 20 mm Hg. The jugular venous pressure is markedly elevated to the angle of the jaw, with an absent *y* descent. The apical impulse is reduced and the heart sounds are muffled and distant. Pulmonary examination reveals clear breath sounds bilaterally.

The triad of hypotension, elevated JVP, and muffled heart sounds, also known as Beck's triad, should alert one to the possibility of cardiac tamponade. This was first described in 1935 by Claude Schaeffer Beck, who was Professor of Cardiovascular Surgery at Case Western Reserve University. Cardiac tamponade occurs when fluid of any kind accumulates in the pericardial space, to an extent where high intrapericardial pressure limits cardiac filling. This leads to markedly elevated venous pressures and reduced cardiac output, which can be rapidly fatal if not treated promptly. A relatively small amount of fluid that accumulates rapidly in the pericardial space can lead to tamponade. In case of a slowly accumulating pericardial effusion, a much larger volume of fluid may be necessary to cause tamponade as the pericardial pressure-volume relation shifts to the right, with greater compliance of the parietal pericardium [15, 16]. In either situation, once a critical amount of fluid has accumulated in the pericardial space, the intrapericardial pressure rises significantly even with relatively smaller rises in volume. The increased intrapericardial pressure may impair cardiac filling and reduce cardiac output. As a compensatory mechanism for maintaining cardiac output and blood pressure, tachycardia is nearly always present in tamponade. One exception to this rule is when the underlying cause for pericardial effusion and resultant tamponade is hypothyroidism. The JVP in pericardial tamponade is almost always elevated, and is sometimes associated with venous distension in the forehead and scalp. The jugular venous waveform is characterized by an absent *y* descent (Fig. 10.3c) due to restricted or diminished ventricular filling even in early diastole with the markedly elevated pericardial pressure. This pattern is in contrast to constrictive pericarditis where ventricular filling in early diastole is rapid and abbreviated prior to its cessation in mid-diastole due to the pericardial constraint.

Pulsus paradoxus, described by Adolf Kussmaul in 1873, is a helpful sign of cardiac tamponade. Pulsus paradoxus is defined as an abnormally large (>10 mm Hg) decline in systolic blood pressure during inhalation and is a consequence of exaggerated ventricular interdependence and exaggerated effects on left- and right-sided filling due to changes in intrathoracic pressure (Fig. 10.4). Normally, the inspiratory decrease in intrathoracic pressure causes an increase in systemic, venous return and a decrease in pulmonary venous return, with a small movement of

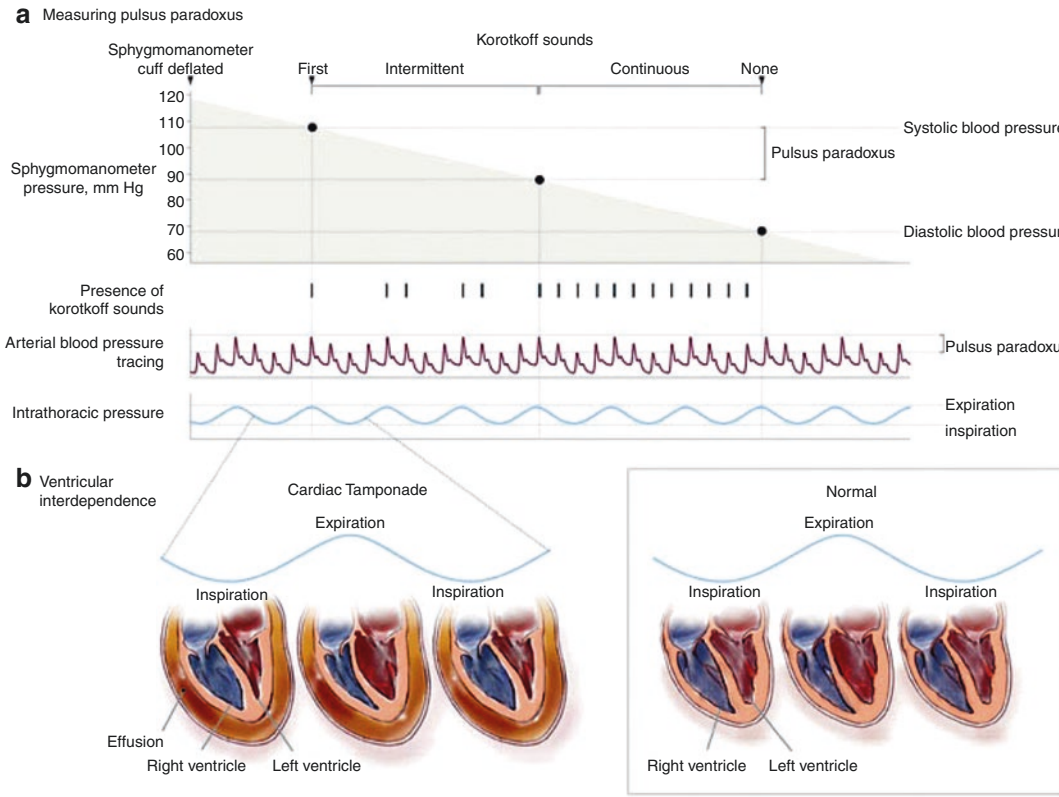

Fig. 10.4 Measurement and mechanism of pulsus paradoxus (**a**) The examiner inflates the sphygmomanometer cuff fully, listens for Korotkoff sounds as the cuff is slowly deflated, and then notes the pressure at which Korotkoff sounds are initially audible only during expiration. As the cuff is further deflated, the examiner notes the pressure at which Korotkoff sounds become audible during expiration and inspiration. The difference between these two pressures is the pulsus paradoxus, which can normally be from 0 to 10 mm Hg. In cardiac tamponade, the pulsus paradoxus measures greater than 10 mm Hg. Inspiratory diminution in the arterial blood pressure tracing represents the pulsus paradoxus. A similar phenomenon may be observed on a pulse oximeter waveform. (**b**) During inspiration in the normal heart, negative intrapleural pressures increase venous return to the right ventricle and decrease pulmonary venous return to the left ventricle by increasing the pulmonary reservoir for blood. As a result of increased right ventricular distention, the interventricular septum bows slightly to the left, and the filling and stroke volume of the left ventricle are mildly reduced. In expiration, these changes are reversed, resulting in the septum bowing to the right and a mild reduction in right ventricular filling. In the presence of cardiac tamponade, the reciprocal changes seen in the normal heart are exaggerated when the pericardial sac is filled with fluid, thus limiting distensibility of the entire heart. This results in a more dramatic reduction in filling of the left ventricle during inspiration, exacerbating the normal inspiratory decrease in stroke volume and blood pressure. (From Roy et al. [28])

the interventricular septum toward the left. The small decrease in left ventricular stroke volume and aortic peak systolic blood pressure results primarily due to inspiratory decrease in LV filling from the decrease in intrathoracic pressure. With tamponade, in presence of pericardial fluid compressing all the walls of the heart, these respiratory changes in venous return are exaggerated. With inhalation, the drop in left-sided filling reduces left ventricular stroke volume and the systemic systolic blood pressure drops by a greater extent than in normal physiology, i.e., more than 10 mm Hg. In patients with true tamponade, pulsus paradoxus can be masked by the presence of numerous conditions, including severe hypotension, pericardial adhesions, right ventricular hypertrophy, severe aortic regurgitation, a stiff left ventricle or other conditions which elevate LV filling pressure, and atrial septal defect [16].

Case 5

A 78-year-old male with history of hypertension, hyperlipidemia, and diabetes mellitus presents with worsening dyspnea on exertion over the last 2 years. On examination, he has a slow-rising, late-peaking, low-amplitude carotid contour by palpation. His heart rate is regular at 88 beats per minute and blood pressure 108/66 mm Hg. The jugular venous pressure is normal. The apical impulse is sustained and non-displaced. Cardiac auscultation reveals normal S1, a soft S2 without splitting, and a 3/6 late peaking systolic ejection murmur, best heard in the right second intercostal space and radiating to the carotids. Pulmonary examination reveals clear breath sounds bilaterally. Abdominal examination is unrevealing and he has no pedal edema.

Based on clinical findings, this patient likely has severe aortic stenosis (AS). Hemodynamically, AS is characterized by a pressure gradient between the left ventricle and aorta during systole (Fig. 10.5a), and the magnitude of this pressure gradient is an indication of the severity of AS. Several physical findings have been shown to correlate with severity of AS, including the characteristic carotid pulse contour, a reduced or absent S2, and the timing and intensity of murmur (Table 10.1) [17]. The quality of carotid pulse in severe AS has classically been described as "parvus et tardus," i.e., weak and slow-rising and delayed. This can be best assessed best by simultaneously palpating the carotid pulse and auscultating the heart. In severe AS, the weak and delayed carotid pulse reflects severe obstruction, with a reduced early systolic rate of blood flow across the aortic valve into the arterial circulation. Delay between brachial and radial pulse (brachioradial delay) has also been described as a clinical indicator of severe AS [18]. With worsening AS, the aortic valve leaflets become increasingly calcified and immobile, leading to a soft or inaudible A2 component of the second heart sound. A normal intensity of A2 implies flexible and mobile aortic valve leaflets and can essentially be very helpful in ruling out severe senile AS. However, the A2 may still be normal in severe AS in young people whose stenosis reflects more congenital fusion of the cusps and less calcific restriction. The gradient between the left ventricle and aorta in AS is greatest in mid-systole and is relatively small early and late in systole. The murmur therefore has a diamond shape; it starts soft and builds to a peak in mid-systole and then becomes quiet in late systole immediately before S2 (Fig. 10.5a). It is referred to as a systolic ejection murmur, since it begins after S1 and ends before S2. The intensity of murmur correlates generally with severity of AS, but there are many exceptions to that correlation. It is best heard at the base of the heart in the second right intercostal space and radiates to the carotids. The timing of the peak intensity of systolic ejection murmur also corresponds to the severity of AS. With mild AS, the maximum instantaneous gradient between the left ventricle and aorta occurs early in systole;

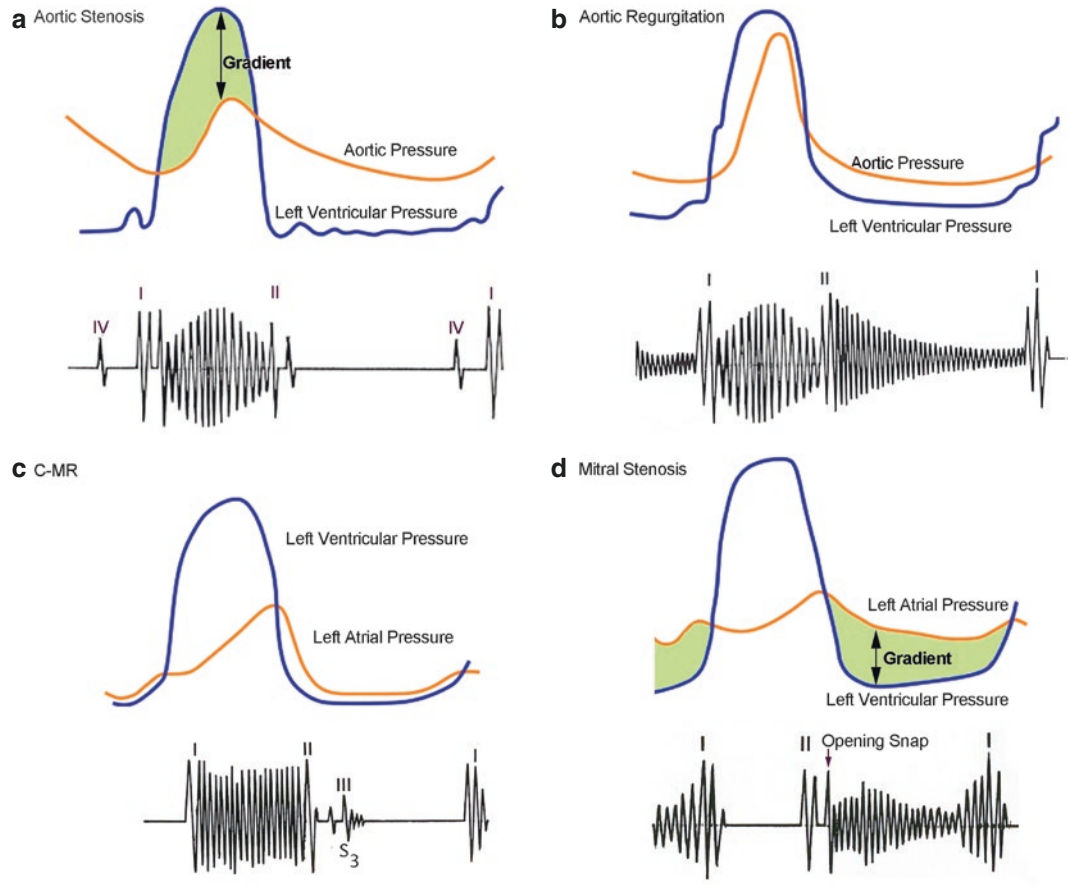

Fig. 10.5 Relationship of murmurs to LV, aortic, and LA pressure waveforms and hemodynamics in various valve diseases. (**a**) *Aortic stenosis (AS).* The gradient between the left ventricle and aorta in AS is greatest in mid-systole and is relatively small early and late in systole. The murmur therefore has a diamond shape, i.e., starts soft and builds to a peak in mid-systole and then becomes quiet in late systole immediately before S2. In young AS patients, there may be an early ejection sound. In senile AS, A2 becomes diminished or absent. An S4 is common due to LV noncompliance. (**b**) *Aortic regurgitation (AR)*. The early diastolic murmur (EDM) begins with S2 and has a decrescendo contour. The duration of the murmur continues for a variable time in diastole, depending on severity and acuity of AR. Notice that aortic diastolic pressure is low. (**c**) *Mitral regurgitation*. There is a pansystolic murmur with a flat profile due to the regurgitant flow into the left atrium. Note that the left atrial pressure rises during systole, a "v" wave. An early diastolic S3 or flow rumble may occur. (**d**) *Mitral stenosis (MS)*. A loud S1 is heard since the mitral gradient is high and the leaflets are not very thickened or calcified. An important indicator of the severity of MS is the time interval between the S2 and opening snap (OS), which is the time it takes for LV pressure to fall from late systolic aortic pressure to early diastolic left atrial pressure. The mitral valve snaps open due to the increased gradient, causing an opening snap (OS). The diastolic murmur correlates with the gradient across the mitral valve, which is largest in early diastole, and increases again in late diastole in this patient in sinus rhythm

hence the systolic murmur peaks in early systole. As the severity of AS worsens, the maximum instantaneous gradient between the left ventricle and the aorta occurs progressively later in systole, and correspondingly the murmur peaks late. No single physical examination finding rules in or rules out severe AS; however, a combination of slow and delayed carotid impulse, reduced intensity of S2, and mid to late peaking systolic ejection murmur at the base radiating to the neck is fairly accurate in diagnosing severe AS clinically [19].

Table 10.1 Physical findings in severe aortic stenosis

Examination	Finding
Carotid pulse	Weak, slow rising, and delayed carotid pulse (pulsus parvus et tardus)
Second heart sound (S2)	Soft or inaudible A2 component of S2
Murmur	Mid to late peaking in systole, radiating to the neck

Case 6

A 56-year-old asymptomatic male is referred for evaluation after his primary care physician heard a heart murmur. On examination, he has a rapidly collapsing pulse with a regular heart rhythm, heart rate of 90 beats per minute and blood pressure of 144/40 mm Hg, and therefore a pulse pressure of 104 mm Hg. Cardiac examination reveals a wide and hyperdynamic apical impulse that is displaced laterally and inferiorly. A high-frequency, blowing decrescendo diastolic murmur is heard, best at the left sternal border in end expiration with the patient sitting up. There is also a short early systolic murmur of moderate intensity. In addition, a systolic and diastolic bruit is heard when the femoral artery is partially compressed and popliteal systolic cuff pressure is >170 mm Hg. Pulmonary and abdominal exam are unremarkable.

No other disease condition in cardiovascular medicine has more eponymous signs associated with it than chronic aortic regurgitation (AR) (Table 10.2). The principal hemodynamic abnormality in chronic AR responsible for these signs is the wide pulse pressure (Fig. 10.5b). The low diastolic arterial pressure results from the rapid run-off of blood from the aorta back into the left ventricle. There is an increase in left ventricular end diastolic volume and hence an increase in left ventricular stroke volume and the pulse pressure. The arterial pulse contour has a rapidly rising and collapsing pulse referred to as "water hammer" pulse, or Corrigan's sign, first described by Sir Dominic Corrigan in 1832. The carotid upstroke is rapid resulting from the increased stroke volume. Few studies have systematically assessed the predictive value of these eponymous signs in Table 10.1; however Duroziez's sign, Corrigan pulse, and Hill's sign are perhaps most important useful signs in detecting severe chronic AR [20]. In a literature review, the presence of a diastolic decrescendo murmur as heard by a cardiologist was the most useful finding for detecting AR (positive likelihood ratio of 8.8), and its absence was most useful in ruling out AR [21]. The diastolic murmur of chronic AR is high-pitched and blowing in character and is best heard along the left sternal border at the left third or fourth intercostal space, with the patient sitting up and leaning forward, with held exhalation. The severity of chronic AR correlates somewhat with the duration of the murmur, while its intensity varies widely. With severe chronic AR, the murmur can be holodiastolic. However, in very severe AR, particularly sudden onset acute AR, the murmur may be early diastolic and short, due to rapid equilibration of LV and aortic pressure. Most patients with severe AR also have an early peaking systolic flow murmur which results from the increased stroke volume even in the absence of concomitant AS. Finally, an apical mid-late diastolic rumble, referred to as the Austin-Flint murmur is audible

Table 10.2 Eponymous signs of chronic aortic regurgitation

Sign	Description
Hill's sign	Exaggerated difference in lower and upper extremity blood pressure
Corrigan's sign	Rapidly collapsing arterial pulse
Duroziez's sign	Systolic and diastolic bruit heard on partial femoral artery compression
Quincke's sign	Exaggerated capillary pulsations of the nail beds
deMusset's sign	Head bobbing with each heart beat
Traube's sign	Pistol shot sound heard over the femoral artery
Mueller's sign	Pulsatile uvula
Becker's sign	Pulsatile retinal arteries
Rosenbach's sign	Pulsatile liver
Gerhard's sign	Pulsatile spleen
Mayne's sign	More than 15 mm hg drop in diastolic blood pressure with arm elevated compared to arm in standard position

in occasional patients with chronic severe AR, reflecting the impact of the AR jet on the anterior mitral valve leaflet; this should not be confused with the diastolic rumble of mitral stenosis.

Case 7

A 62-year-old male with 30 pack-year history of smoking, hypertension, hyperlipidemia, and diabetes mellitus presents to the ER after experiencing worsening substernal chest discomfort radiating to the left arm for 8 hours. On arrival, he appears diaphoretic with a heart rate of 104 beats per minute, blood pressure of 90/68 mm Hg and he is tachypneic with a respiratory rate of 20 per minute and an oxygen saturation of 94% on room air. He is drowsy and somewhat disoriented. Stat 12 lead EKG reveals widespread 3 mm ST segment elevation in precordial leads V1 through V6 and reciprocal ST segment depression in inferior limb leads. Cardiovascular examination reveals elevated JVP at 12 cm and normal heart sounds with no murmurs, rubs or gallops. Pulmonary examination reveals bibasilar rales. Abdominal examination is unrevealing and he has no lower extremity edema, but his extremities are cold and clammy. With a diagnosis of acute ST segment elevation myocardial infarction (STEMI) and cardiogenic shock, he is emergently taken to the cardiac catheterization laboratory. The proximal left anterior descending coronary artery (LAD) is found to be totally occluded, so it is opened and stented. Pulmonary artery catheterization shows a PCWP of 28 mm Hg, with a cardiac index of 1.7 L/min per m^2, and an intra-aortic balloon pump (IABP) is placed. Emergent echocardiogram did not show any evidence of mechanical complications of MI.

Cardiogenic shock is characterized by end-organ hypoperfusion due to cardiac dysfunction and is hemodynamically defined by persistent hypotension (systolic blood pressure <80 to 90 mmHg or mean arterial pressure 30 mmHg lower than baseline) with severe reduction in the cardiac index (<1.8 L/min per m^2 without support or <2.0 to 2.2 L/min per m^2 with support) and adequate or elevated filling pressures [22]. The most common cause of cardiogenic shock is acute myocardial infarction (MI) with left ventricular failure. In the setting of MI, it is very important to rule out mechanical complications such as acute severe MR secondary to papillary muscle dysfunction, ventricular free wall rupture, or ventricular septal defect, all of which can contribute to cardiogenic shock. Other causes of these alarming hemodynamics include acute severe LV or RV dysfunction of any etiology, valvular heart disease such as acute mitral or aortic regurgitation, pericardial tamponade, massive pulmonary embolism, acute aortic dissection, hypertrophic obstructive cardiomyopathy, and acute myocarditis. The hallmark of cardiogenic shock is hypoperfusion of the extremities and vital organs. Loss of cardiac output from any cause increases sympathetic activation, which increases arteriolar constriction and systemic vascular resistance, in an attempt to maintain blood pressure and tissue perfusion. Clinically, cardiogenic shock manifests with signs of reduced end-organ perfusion such as altered mental status, oliguria, respiratory distress due to pulmonary congestion, and cool, clammy extremities. Such patients are typically in the bottom right on the hemodynamic profile chart presented in Fig. 10.1, i.e., wet and cold. However, not all patients in cardiogenic shock have vasoconstriction and elevated systemic vascular resistance. Almost a fifth of patients with cardiogenic shock studied in the SHOCK trial had hemodynamic findings of low systemic vascular resistance, similar to patients with sepsis. This probably results from inappropriate vasodilation, which may represent a systemic inflammatory response state (SIRS) similar to sepsis [22, 23]. Cardiogenic shock can be diagnosed based on clinical findings, but invasive hemodynamic monitoring helps confirm and quantify the degree of vasoconstriction or vasodilation, quantifying filling pressures and cardiac output and ultimately guiding therapy.

Case 8

A 78-year-old woman is brought to the ER with fever, cough, shortness of breath, and altered mental status. She has had intermittent fever

and cough with productive sputum for the last 3 days. On arrival to the ER, she is drowsy but arousable and confused. She is febrile with a temperature of 39 °F, heart rate of 120 beats per minute and regular, blood pressure of 80/50 mm Hg, tachypneic with a respiratory rate of 22 beats per minute, and an oxygen saturation of 90% on room air. Cardiovascular examination reveals no jugular venous distension and rapidly collapsing jugular vein distension even when supine. She has normal heart sounds and no murmurs, rubs, or gallops. Pulmonary exam reveals bronchial breath sounds and rales in the right lower zone with egophony and dullness on percussion. Abdominal exam is unrevealing, and peripheral extremities are warm to touch with capillary refill >3 seconds and mottling of skin. Chest X-ray confirms right lower lobe consolidation.

This patient is in septic shock. It is similar to the patient in case 7; however the mechanism and pathophysiology are different. Also called distributive or vasodilatory shock, the hallmark of septic shock is profound vasodilation and inadequate tissue extraction of oxygen. Vasodilation is mediated by three mechanisms: activation of ATP-sensitive potassium channels in the vascular smooth muscle cell plasma membranes, activation of inducible nitric oxide synthetase, and deficiency of vasopressin [24]. This is followed by leukocyte migration and activation and release of pro-inflammatory markers such as tumor necrosis factor (TNF) and interleukins, which lead to tissue damage and organ dysfunction, which manifest as a systemic inflammatory response state (SIRS).[25] SIRS is defined by the presence of one of the following:

- Temperature >38.5 °F or <35 °F
- Heart rate >90 beats per minute
- Respiratory rate >20 per minute or PaCO2 <32 mm Hg
- WBC >12,000 cells/mm^3, <4000 cells/mm^3, or >10% immature band forms

Sepsis is defined as SIRS in presence of an infection. Similarly, severe sepsis and septic shock are largely clinical diagnoses [25]. Severe sepsis is defined as the presence of sepsis and one of the following signs of organ dysfunction:

- Areas of mottled skin.
- Capillary refilling requires 3 seconds or longer.
- Urine output <0.5 mL/kg for at least 1 hour, or the need for renal replacement therapy.
- Elevated blood lactate levels >2 mmol/L.
- New decrease in mental status.
- Platelet count <100,000 platelets/mL.
- Disseminated intravascular coagulation.
- Acute lung injury or acute respiratory distress syndrome (ARDS).
- Cardiac dysfunction, as defined by echocardiography or direct measurement of the cardiac index.

Septic shock is defined by the presence of severe sepsis and one of the following:

- Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension) after adequate fluid resuscitation or PCWP between 12 and 20 mm Hg
- Need for dopamine >5 mcg/kg per min or norepinephrine or epinephrine <0.25 mcg/kg per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Thus sepsis has a continuum of severity ranging from sepsis manifesting as SIRS to severe sepsis and septic shock. Despite optimal management, mortality from severe sepsis and septic shock can range from 40% to 50% or higher. The key for successful outcome is early identification of the severity of this continuum and of a potential infectious focus.

Case 9

A 54-year-old man with history of chronic alcohol abuse and liver cirrhosis presents with hematemesis. On examination, he is afebrile with a heart rate of 78 beats per minute and blood pressure of 130/80 mm Hg when supine and 110 beats

per minute and 102/60 mm Hg when standing. He feels dizzy on standing. His tongue, axillae, and mucous membranes are moist. Cardiac, pulmonary, and abdominal exams are unrevealing.

This patient has hypovolemia likely secondary to blood loss, in this case, bleeding esophageal varices. Hypovolemia occurs when extracellular sodium and fluid are lost at a rate greater than intake. This may occur by way of gastrointestinal losses (hemorrhage, vomiting, diarrhea), renal losses (diuresis, salt wasting), loss from skin (burns), or third space sequestration (acute pancreatitis, acute intestinal obstruction, fracture). One of the most common causes of hypovolemia is excessive use of diuretic medications. History and physical examination are important in identifying the presence, etiology, and severity of hypovolemia, perhaps even more so than laboratory testing. For example, the initial hemoglobin correlates poorly with the degree of blood loss, even in patients whose hypovolemia is due to gastrointestinal hemorrhage. Similarly prerenal azotemia is a late finding in acute dehydration. Postural assessment of systolic blood pressure is the most rapid and reliable bedside tool, in the absence of autonomic neuropathy or over-use of antihypertensive drugs. A drop of more than 10 mm Hg when the patient goes from supine to standing is indicative of at least a 10% deficit in intravascular volume. In a systematic review of physical findings in assessment of patients with blood loss and hypovolemia, severe postural dizziness and an increase in pulse rate $\geq$ 30 beats per minute were found to be the most sensitive and specific findings for large blood loss [26]. In the same study, the presence of dry axilla supported the diagnosis of hypovolemia in patients with vomiting, diarrhea, or decreased oral intake. Moist mucous membranes and a normal furrowed appearance of the tongue were found to argue against it. It is important to remember that postural blood pressure and heart rate should be measured with the intervention of the patient standing still for 1 minute. Jugular venous pressure is usually low in patients with hypovolemia, and it may be necessary to lay the patient down to see the venous pulsations above the clavicle. Normal skin has elasticity or turgor, i.e., it immediately returns to its normal position after being pinched and released. This is due to elastin content in the subcutaneous tissue, which is affected by moisture content and age. In younger individuals, poor skin turgor may represent hypovolemia.

Case 10

A 53-year-old lady with history of rheumatic heart disease with long-standing history of mitral stenosis, s/p balloon mitral valvotomy 15 years ago, and mitral valve replacement 8 years ago presents with worsening fatigue, exercise intolerance, abdominal distension, and lower extremity swelling. On examination, she has an irregularly irregular pulse with a heart rate of 80 beats per minute, blood pressure of 110/68 mm Hg, and respiratory rate of 16 per minute. Jugular venous pressure is elevated to 14 cm of water with a prominent V wave and a sharp y descent. Cardiac exam reveals a palpable right ventricular heave. On auscultation, the P2 is loud and a 3/6 holosystolic murmur is audible at the left lower sternal border. The murmur increases in intensity with inspiration. Abdominal examination reveals a pulsatile and enlarged liver with evidence for ascites. Moderate bilateral pedal edema is also present.

Tricuspid regurgitation (TR) is a valve lesion that occurs commonly, as a result of right ventricular dilatation from any cause, through the effects of secondary pulmonary hypertension. The most frequent cause is left-sided heart failure due to mitral valve disease or left ventricular dysfunction. TR also occurs in the setting of cor pulmonale, from intrinsic lung disease, or from primary pulmonary hypertension. Pathophysiologically, long-standing pulmonary hypertension causes right ventricular pressure overload, which causes dilatation of the right ventricle and tricuspid annulus. In patients with chronic severe TR, the JVP waveform is characterized by the loss of x descent and a prominent systolic V wave (or C-V wave) caused by markedly increased right atrial pressure during ventricular systole, which is followed by a rapid y descent (Fig. 10.3d). Auscultation usually reveals a loud P2 in pres-

ence of pulmonary hypertension. There may be a pansystolic murmur, loudest in about the fourth intercostal space in the left or right parasternal region. Classically, the systolic murmur intensity increases with inspiration (Carvallo sign) as the venous return on the right side of the heart increases; however, this finding is inconsistent. Many patients with significant TR do not have respirophasic variation, and some have an unimpressive murmur. In the absence of pulmonary hypertension, TR may also occur as a primary valve abnormality, due to trauma, or endocarditis classically in patients who have used intravenous drugs, but increasingly in patients with infected pacemaker leads. In severe TR, there is an increase in diastolic flow, so many patients have a diastolic rumble (sometimes quite loud) along the left sternal border and/or a right sided S3. With severe long-standing TR, the pressure gradient between the right atrium and right ventricle is minimized, and the TR murmur may be short early systolic, barely audible, or absent. A pulsatile liver is often present in severe TR, and ascites and extremity edema are commonly present.

Case 11

A 52-year-old male, with no risk factors for coronary artery disease, presents with symptoms of shortness of breath on exertion and two episodes of near syncope. He has family history of sudden death. On examination, his carotid pulse has a rapid upstroke, followed by a second peak. His heart rate is 60 beats per minute and blood pressure 120/80 mm Hg. His jugular veins are not distended. The apical impulse is wide, sustained, and laterally displaced. On cardiac auscultation, S1 is normal and S2 is paradoxically split. A harsh crescendo-decrescendo 3/6 systolic murmur, heard best at the left sternal border, increases in intensity with the Valsalva maneuver, breath holding with increased abdominal pressure. His lungs are clear on auscultation, and abdominal examination is unrevealing.

Based on physical findings, this patient has hypertrophic cardiomyopathy (HCM). HCM is a common genetic cardiovascular disease and is defined as significant myocardial hypertrophy in the absence of an identifiable cause. The most common sites of ventricular hypertrophy are, in decreasing order, the septum, apex, and mid ventricle. It is further classified as obstructive or non-obstructive, depending on whether a dynamic left ventricular outflow tract (LVOT) gradient is present, either at rest or with provocative maneuvers. LVOT obstruction is the main pathophysiologic mechanism in HCM. The hypertrophied proximal interventricular septum combines with systolic anterior motion (SAM) of the mitral valve leaflets toward the septum, which causes LVOT obstruction and also mitral regurgitation. LVOT obstruction in HCM is dynamic, in contrast to valvular or membranous AS where obstruction to LV outflow is fixed. In dynamic LVOT obstruction, the degree of obstruction varies with cardiac contractility and loading conditions, whereas in case of fixed obstruction such as AS, the degree of obstruction doesn't vary as much with maneuvers. Purposeful alterations in cardiac hemodynamics can be very useful at the bedside in differentiating systolic murmurs of HCM and AS (Table 10.3). Almost all cardiac murmurs decrease in intensity with the Valsalva maneuver except the murmur of HCM. The Valsalva maneuver decreases preload which results in reduced filling of the left ventricle and hence an increase in LVOT obstruction, thus increasing the intensity of systolic murmur in HCM. Similarly, change in position from squatting to standing reduces venous return and preload, thus increasing

Table 10.3 Effect of maneuvers on hypertrophic cardiomyopathy and aortic stenosis

Maneuver	Hemodynamic effect	AS murmur intensity	HCM murmur intensity
Valsalva	Decreased preload	Decreases	Increases
Squat to stand	Decreased preload	Decreases	Increases
Stand to squat	Increased preload	Increases	Decreases
Amyl nitrite inhalation	Decreased preload	No change	Increases

murmur intensity in HCM. Inhalation of amyl nitrite results in vasodilation and decreased preload, which again worsens LVOT obstruction in HCM and the murmur intensity increases. The gradient also increases in the beat after a premature ventricular complex (PVC) and during other types of positive inotropic activity, such as intravenous or endogenous catecholamines. Presence of a loud murmur of at least grade 3/6 usually implies LVOT outflow gradient of greater than 30 mm Hg. The carotid pulse in patients with HCM is characterized by an initial rapid upstroke as no LVOT obstruction exists in early systole. This is followed by a collapse in the pulse as LVOT obstruction develops, followed by a second peak as left ventricular pressure increases to overcome the obstruction. This is referred to as bisferiens pulse, which contrasts markedly from the carotid contour in valvular AS, as mentioned above. The second heart sound in HCM is normal in intensity, and can be paradoxically split due to prolonged ejection time with severe LVOT obstruction.

Case 12

A 45-year-old female, who immigrated from India, presents with new onset palpitations and dyspnea on exertion. She recalls having a prolonged febrile illness during childhood, followed by a murmur. On examination she has an irregularly irregular pulse with a heart rate of 84 beats per minute at rest and a blood pressure of 110/70 mm Hg. Her jugular veins are not distended. The apical impulse has a tapping quality and is undisplaced. A parasternal RV heave is felt along with a palpable P2. On auscultation, S1 is loud, P2 is loud, and an opening snap is heard just after the second heart sound. A low-pitched "rumbling" early diastolic murmur is heard at the apex with the bell of the stethoscope, with the patient in left lateral decubitus position, in held exhalation. Bibasilar rales are heard on lung auscultation. Abdominal and lower extremity exam is unrevealing.

This patient likely has significant mitral stenosis (MS) secondary to rheumatic heart disease. MS is characterized by a pressure gradient between the left atrium and left ventricle during diastole (Fig. 10.5d). The transmitral pressure gradient for any given valve area depends on the transvalvular flow rate. Increase in transmitral flow, most commonly due to exercise, leads to increased pressure gradient and elevated left atrial pressure, which in turn raises pulmonary venous and pulmonary capillary pressures, resulting in dyspnea. Atrial fibrillation or any pathologic state involving an increased heart rate, such as anemia, hyperthyroidism, or others, shortens diastole more than systole. Because the time available for flow across the mitral valve is shorter, the heart spends more percentage of the time in the early phase of diastolic mitral valve flow, when gradients are higher, contributing to marked elevation in left atrial pressure. Chronic pulmonary venous and capillary hypertension leads to pulmonary arterial hypertension and often right-sided heart failure, though not yet in this patient. Atrial fibrillation with rapid ventricular response is often a precipitating or exacerbating factor of the onset of symptoms in patients with MS and may result in pulmonary edema. In fact, MS with rapid AF is a condition where pulmonary edema responds well to beta blocker therapy. Diastolic filling time increases with reduction in heart rate, which reduces the left atrial pressure (because the mitral flow spends more time in "mid to late diastole" when the gradient is lower) and hence the pulmonary venous and capillary pressures are lower.

The physical findings in MS are attributable to two aspects of the inflammatory rheumatic process that leads to fibrosis: (1) thickening and fibrosis of the valve cusps and (2) commissural fusion. The classic auscultatory signs in mild MS, before the leaflets are very thickened, calcified, or markedly immobile, include a loud S1 and an audible opening snap (OS) after S2. The intensity of S1 and presence of the opening snap (OS) reflect the pandiastolic pressure gradient. An important indicator of the severity of MS is the time interval between the S2 and OS, which is the time it takes for LV pressure to fall from late systolic aortic pressure to early diastolic

left atrial pressure. With more severe MS, the left atrial pressure is higher and mitral valve opening occurs closer to S2, causing the S2-OS interval to decrease (Fig. 10.5d). With marked calcification and immobility of the mitral valve leaflets, both S1 and the OS become softer. The murmur of MS is a low-pitched rumbling diastolic murmur at the apex, best heard with the bell of the stethoscope with the patient in left lateral decubitus position. Listening in held exhalation brings the heart closer to the stethoscope and stops the interference of respiratory sounds. The diastolic murmur of MS can be accentuated by brief period of exercise, even just walking or running in place, due to the increased heart rate and the increase in cardiac output. In severe MS, the murmur is usually longer. In patients in sinus rhythm, the rumble is loudest when the gradients are highest, in very early and late diastole (during the atrial kick). The pre-systolic (late diastolic) accentuation of the diastolic murmur is lost when atrial fibrillation occurs.

Self-Assessment Questions

1. A 40-year-old asymptomatic lady presents for evaluation of a murmur that was heard by her primary care physician. On examination, her vital signs are normal. Her jugular veins are not distended and carotid upstrokes are normal. There is a systolic click followed by a 2/6 mid-late systolic murmur at the apex. In order to confirm your suspicion of mitral valve prolapse, you ask the patient to perform squatting and standing maneuvers. What happens to the click and the murmur with squatting and standing maneuvers in a patient with mitral valve prolapse?
   A. The click and murmur move closer to S1 with squatting and away from S1 with standing.
   B. The click and murmur move closer to S1 with standing and away from S1 with squatting.
   C. There is no change in the click or the murmur with standing or squatting.
   D. The click and the murmur decrease in intensity with standing and increase in intensity with squatting.
2. Each of the following statements regarding the JVP waveform and cardiac hemodynamics is true *except*:
   A. Constrictive pericarditis is characterized by a prominent and steep or rapidly collapsing y descent.
   B. Cardiac tamponade is characterized by an absent y descent.
   C. Cannon A wave is present in severe tricuspid regurgitation.
   D. The x descent is lost in severe tricuspid regurgitation.
3. A 52-year-old lady with history of rheumatic heart disease, with history of open mitral commissurotomy 20 years ago, presents with new onset dyspnea on exertion and worsening palpitations. On examination she has an irregularly irregular pulse with a heart rate of 118 beats per minute and a blood pressure of 100/60 mm Hg. Her jugular veins are distended. The apical impulse has a tapping quality and is undisplaced. A parasternal RV heave is felt along with a palpable P2. On auscultation, a low-pitched rumbling mid-diastolic murmur is heard at the apex with the bell of the stethoscope, with the patient in left lateral decubitus position. Bibasilar rales are heard on lung auscultation. What is the next best step in the management of this patient?
   A. Sodium nitroprusside for afterload reduction
   B. Intravenous nitroglycerin infusion for preload reduction
   C. Intravenous morphine
   D. Intravenous beta blocker therapy for rate control
4. All of the following increase the murmur intensity in patients with hypertrophic obstructive cardiomyopathy, except:
   A. Squatting
   B. Standing
   C. Valsalva maneuver
   D. Inhalation of amyl nitrite
5. Each of the following is a finding in severe aortic stenosis, except:
   A. Pulsus parvus et tardus
   B. Soft or inaudible A2
   C. Mid-late peaking systolic murmur
   D. Bisferiens pulse

Answers to Self-Assessment Questions

1. B.
   Standing leads to reduction in venous return and preload. The left ventricle therefore becomes smaller, and prolapse occurs earlier in systole, i.e., closer to S1. Concurrently the intensity of the murmur increases. Squatting leads to increase in preload, causing an increase in LV chamber size; therefore the click and murmur occur later in systole and move away from S1.
2. C.
   Cannon A wave is present in tricuspid stenosis or complete heart block where the right atrium contracts against a closed tricuspid valve due to atrio-ventricular dissociation. All other statements are true.
3. D.
   This patient has rheumatic mitral stenosis and is in heart failure secondary to atrial fibrillation with rapid ventricular response. Tachycardia shortens diastole more than systole, thus reducing the time available for flow across the mitral valve and contributing to marked elevation in left atrial pressure and pulmonary edema. Pure mitral stenosis is the only condition where acute heart failure is treated with beta blocker therapy for heart rate control.
4. A.
   Decrease in preload, secondary to any maneuver (valsalva, standing, and inhalation of amyl nitrite) results in reduced filling of the left ventricle and hence LVOT obstruction increases, thus increasing the intensity of systolic murmur in HCM. Squatting on the other hand increases preload, increasing ventricular volume and reducing the LVOT gradient, hence making the murmur softer in intensity.
5. D.
   In severe AS, the weak and delayed (parvus et tardus) carotid pulse reflects severe obstruction of blood flow across the aortic valve into the peripheral circulation. With worsening AS, the aortic valve leaflets become increasingly calcified and immobile, leading to a soft or inaudible A2 component of S2. With mild AS, the maximum instantaneous gradient between the left ventricle and aorta occurs early in systole; hence the systolic murmur peaks in early systole. As the severity of AS worsens, the maximum instantaneous gradient between the left ventricle and the aorta occurs progressively later in systole, and correspondingly the murmur peaks late. Bisferiens pulse is seen in patients with severe AR or HOCM.

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Echocardiography

11

Omeed Zardkoohi and Richard A. Grimm

Introduction

Echocardiography is a powerful, noninvasive imaging tool that can provide useful hemodynamic information to guide patient management. Intracardiac pressures, cardiac output, vascular resistance, shunt fractions, and valve lesions can be assessed by using a combination of two-dimensional imaging, color Doppler, pulse and continuous wave Doppler, and tissue Doppler. While echocardiography can provide data complementary to catheter-derived measurements and in some situations has even supplanted invasive monitoring, its application requires meticulous technique, an understanding of basic principles of physics, and an appreciation of potential limitations of the method.

Basic Physics of Echocardiography

Doppler Principle

The Doppler principle explains that the frequency of a wave increases as the source of the wave moves toward an observer, while the frequency of a wave decreases as the source moves away from an observer [1]. The change in the frequency of the sound wave depends on the velocity of the moving object, the velocity of sound, and the angle at which the sound wave hits the object. Echocardiography extrapolates this principle of frequency shift to determine the velocity of blood flow in the heart. When a sound wave is transmitted from the transducer crystal at a given frequency, it is reflected by a red blood cell at a certain frequency back to the transducer (Fig. 11.1). If the red blood cell is moving toward the sound waves, the frequency will increase, but if the red blood cell is moving away from the sound wave, the frequency will decrease. The Doppler shift is the change in frequency between the transmitted sound and the reflected sound and is expressed in the following Doppler equation [2]:

$$\Delta f = f_r - f_0 = \frac{2 f_0 (\cos\theta)(v)}{c}$$

where f_0 = transmitted frequency; f_r = reflected frequency; θ = angle between the ultrasound beam and blood flow; v = velocity of red blood cells; and c = speed of ultrasound in blood (1540 m/s).

Algebraic rearrangement of the equation allows one to solve for velocity:

$$v = \frac{(c)(\Delta f)}{2(f_0)(\cos\theta)}$$

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_11

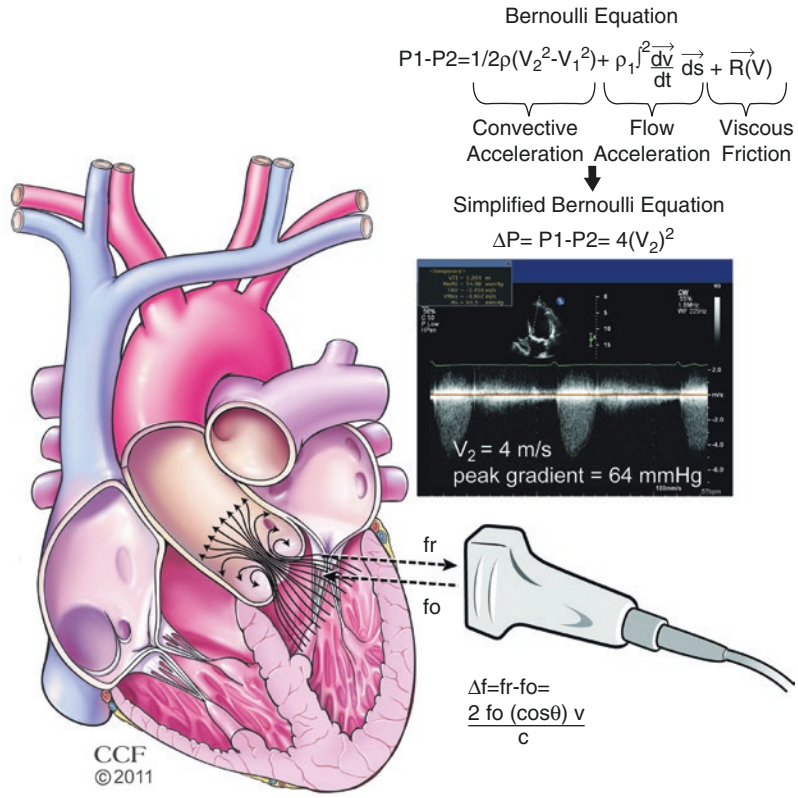


Fig. 11.1 The Doppler principle and Bernoulli equation. *Bottom right*: The echo transducer sends ultrasound waves at a given frequency (f_0) to the heart, and the sound waves are reflected back to the transducer at a different frequency (f_r). The difference between (f_0) and (f_r) is the *Doppler shift*. As shown in the equation, the Doppler shift is directly proportional to the transmitted frequency (f_0), the cosine of the angle of incidence θ (angle between the ultrasound wave and vector of the red blood cell), and the velocity of the red blood cells, however, is inversely proportional to the speed of ultrasound in the medium (c). Rearrangement of the equation allows one to determine the velocity of the red blood cells. *Top right*: The Bernoulli equation enables one to determine the pressure gradient across a stenosis, in this case, a stenotic aortic valve. Flow accelerates just before and at the level of the stenosis. The velocity proximal to the stenosis is V_1, and the velocity distal to the stenosis is V_2. Based on certain assumptions (see text), the Bernoulli equation can be simplified to $P1 - P2 = \Delta P = 4(V_2)^2$. In this case, the peak gradient is 64 mmHg based on the peak velocity across the aortic valve (V_2) of 4 m/s. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011

Note that the number "2" in the equation results from the fact that there are actually two Doppler shifts: one when the sound wave sent from the transducer strikes the red blood cell, and the other when the wave reflected from the red blood cell is sent back to the transducer. Doppler echocardiography is highly angle-dependent. *The angle should ideally be <20 ° which results in <10% underestimation of true flow velocity* [2]. When the ultrasound beam is ideally oriented parallel to the direction of blood flow, that is, when the angle θ is 0 °, the equation is simplified since the cosine of 0 ° is 1. Using the simplified Bernoulli principle (Fig. 11.1), it follows that velocity can be used to estimate pressures.

Continuous Wave Versus Pulse Wave Doppler

Two forms of Doppler echocardiography are pulse wave (PW) Doppler and continuous wave (CW) Doppler. Pulse wave Doppler employs a single crystal that emits short bursts or pulses of

ultrasound at a certain rate per second, known as the *pulse repetition frequency (PRF)*, which is dependent on the depth of interrogation. These pulses are sent to a particular sampling location or depth, and the same crystal waits for the reflected frequency (Fig. 11.2a). Because the same crystal sends and receives the ultrasound wave, the maximum velocity that can be measured is limited by the time it takes to send and receive the wave. This is called the *Nyquist limit*, which is one-half the PRF. *The PRF and the Nyquist limit are solely determined by the depth of the sample volume and not by the transducer frequency*. The shallower the sample volume, the higher the PRF or number of pulses sent per second by the transducer. If the Doppler frequency shift is greater than the Nyquist limit, then the velocities above this limit are cut off the spectral

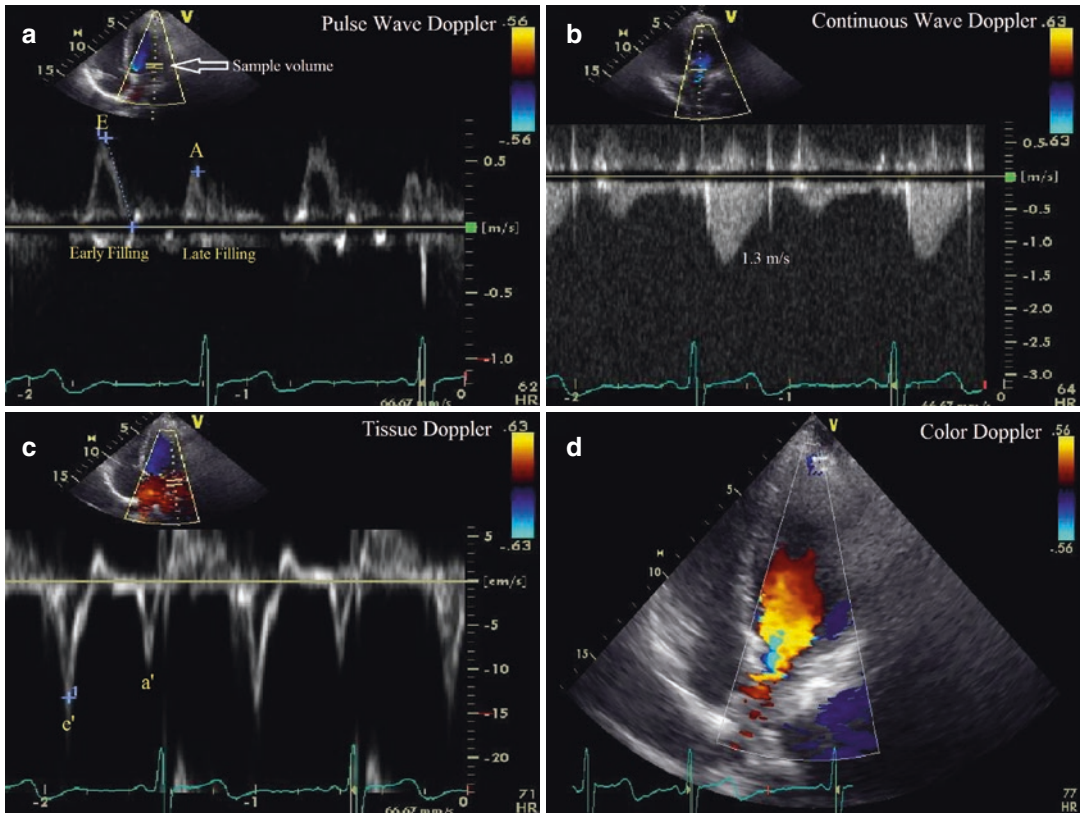


Fig. 11.2 Various forms of Doppler in echocardiography. (**a**) Pulse wave (PW) Doppler of the mitral inflow with the sample volume placed at the leaflet tips. In PW, the same transducer crystal sends and receives waves to determine the Doppler shift at a particular sample volume, marked by the *white arrow*. Because PW obtains information about a particular location, it is said to have "range specificity or range resolution," but it is prone to aliasing. Note that in diastole there is early filling (*E* wave) and Late Filling (*A* wave). Diastasis is known as the period between the *E* and the *A* wave. The *E* velocity is 68 cm/s. (**b**) Continuous wave (CW) Doppler across the aortic valve. In CW, one crystal sends sound waves continuously and another crystal receives the sound waves. Because the CW profile represents all the velocities along the path of interrogation (represented by the *dotted line*), the peak velocity cannot be localized based on the CW signal alone. This phenomenon is known as "range ambiguity." The *y* axis is velocity and the *x* axis is time, and therefore the area under the curve is the velocity time integral (VTI), or the aortic valve VTI, in units of distance (cm). In this example, the peak velocity is 1.3 m/s and the Aortic Valve VTI is 22 cm. (**c**) Tissue Doppler of the mitral annulus characterizes annular velocities, with the corresponding annular e' and a' waves. These waves correspond temporally with the *E* and *A* waves of the mitral inflow. Because $E = 68$ cm/s and $e' = 13$ cm/s, the ratio E/e' is roughly 5, suggesting normal PCWP pressures. (**d**) Color Doppler in which the color pixels represent the mean velocity vector at a particular location

Doppler profile and wrap around to the opposite direction, a phenomenon known as aliasing [1]. Anyone who has watched a wagon wheel in a Western movie appreciates this phenomenon. As the wagon starts to move away, the wheel appears to be moving clockwise. But as the wagon wheel picks up speed and exceeds the "Nyquist limit" of the movie camera, the wheel appears to be moving counterclockwise, which is the equivalent of aliasing. An example of aliasing in echocardiography can be found in Fig. 11.4c, in which PW is used to determine the right ventricular outflow tract (RVOT) velocity. Note that during diastole, the pulmonary regurgitation jet velocity exceeds the Nyquist limit of 1 m/s and wraps around (aliases) to the negative portion of the spectral Doppler profile. Therefore, PW *is suited for measuring low velocity flow (<2 m/s) at specific locations in the heart*, such as the left ventricular outflow tract (LVOT), right ventricular outflow tract (RVOT), mitral inflow, tricuspid inflow, and hepatic vein inflow. PW has the property of "range specificity" in that it provides information at a specific location. Figure 11.2a shows PW of the mitral inflow with sample volume at the leaflet tips, demonstrating the three phases of diastole: early filling (*E* wave), diastasis, and late filling (*A* wave).

Because continuous wave (CW) Doppler employs two crystals, one continuously emitting ultrasound waves and the other continuously receiving reflected waves, it does not fall under the Nyquist limitation (Fig. 11.2b). This allows for interrogation of higher velocities without aliasing. *In CW, all the velocities along the ultrasound beam are recorded, rather than the velocities at one particular location. The peak velocity cannot be localized based on the CW signal alone, a phenomenon known as* "range ambiguity." CW is used to assess gradients in aortic stenosis and mitral stenosis, peak mitral regurgitation velocity, peak tricuspid regurgitation velocity, and intracardiac shunt velocity.

Finally, tissue Doppler is a specialized form of PW that allows the interrogation of myocardial and annular velocities by focusing on lower velocities of higher amplitude with a high frame rate (Fig. 11.2c). Tissue Doppler imaging is employed in the estimation of intracardiac pressures, quantification of wall motion in stress echo, detection of diastolic dysfunction, and intraventricular dyssynchrony, among other applications.

Color Doppler

Color Doppler provides a visual representation of intracardiac flow by translating the velocity vector into color: red and yellow represent flow moving toward the transducer while blue hues represent flow moving away from the transducer (Fig. 11.2d). Note that in the color scale which appears to the right of Fig. 11.2d, the darker the color shade, the closer to zero the velocity becomes, with black representing 0 m/s. The color image is constructed by the summation of multiple scanning lines which translates Doppler shifts into mean velocity, and then the mean velocity into a color based on the color scale. To determine real-time, accurate blood velocities along the path of multiple scanning lines, the transducer must rapidly send multiple groups of pulses or "packets" with pulse wave Doppler. While having more pulses per "packet" increases the accuracy of velocity measurements, this occurs at the expense of temporal resolution because more time is needed to acquire the information from the pulses. Because color Doppler relies on PW, if the velocity of flow is greater than the Nyquist limit, color aliasing occurs, in which color may reverse from blue to yellow, for example.

Bernoulli Equation

The *Bernoulli equation* has applications for echocardiography-based hemodynamic assessment. It is used to calculate the gradient across a stenosis, a regurgitant valve, or a septal defect between two cardiac chambers, and it consists of three components: *convective acceleration, flow acceleration*, and *viscous friction* (Fig. 11.1) [3].

$$P1 - P2 = \underbrace{\frac{1}{2}\rho\left(V_2^2 - V_1^2\right)}_{\text{Convective acceleration}} + \underbrace{\rho\int_1^2 \frac{\overrightarrow{dV}}{dt}\overrightarrow{ds}}_{\text{Flow acceleration}} + \underbrace{R\left(\vec{V}\right)}_{\text{Viscous friction}}$$

where $P1$ = pressure proximal to stenosis; $P2$ = pressure distal to the stenosis, ρ = mass density of blood (1.06×10^3 kg/m^3); V_1 = velocity at proximal location; V_2 = velocity at distal location; ds = acceleration distance; and R = viscous resistance.

Convective acceleration is the increase in kinetic energy that corresponds to the pressure drop across the orifice, and is analogous to the conversion of potential energy to kinetic energy that occurs when an object falls by gravity [3]. The *flow acceleration* component describes the pressure drop required to accelerate the blood by overcoming the blood's inertial forces. Finally, the *viscous friction* component describes the frictional, viscous force that results from neighboring blood cells moving at different velocities.

There are some features of blood flow in the human heart that allow for simplification of the Bernoulli equation. First, the *viscous friction* term is negligible because the velocity profile of blood through a stenotic valve is relatively flat (little variation in blood velocity and therefore little friction), as well as because orifice diameters in the heart are relatively large, minimizing the effect of friction at the center of the orifice. In addition, previous studies have indicated that in most clinical situations the *flow acceleration* component is negligible [3]. In single, stenotic lesions, the proximal velocity term V_1 is typically small (<1 m/s) and can be ignored. Therefore, because in most clinical scenarios the *viscous friction*, *flow acceleration*, and V_1 components are negligible, the Bernoulli equation is simplified to $P1 - P2 = \Delta P = 4(V_2)^2$ (Fig. 11.1).

Intracardiac Pressures

The guide through echocardiographic assessment of various cardiac chamber pressures will follow the same sequence as during a diagnostic right heart catheterization, beginning with the right atrium. A summary of the equations discussed is presented at the end of the chapter (Fig. 11.10).

Right Atrium

Right atrial pressure is reflected in the size of the inferior vena cava (IVC), its response to changes in intrathoracic pressure, and the hepatic vein Doppler profile. Interrogation of the IVC by transthoracic echocardiography can be performed with the subcostal view (Fig. 11.3a, c). An *IVC diameter ≤2.1 cm that collapses >50% with sniffing (which causes an acute drop in intrathoracic pressure resulting in decreased venous return) suggests a normal RA pressure of 3 mmHg (range 0–5 mmHg)* [4]. *An IVC diameter >2.1 cm that collapses <50% with a sniff suggests a high RA pressure around 15 mmHg (range 10–20 mmHg)*. IVC profiles that do not fit into these two categories (i.e., IVC ≤ 2.1 cm but <50% collapse or IVC > 2.1 cm but >50% collapse) can be designated as an intermediate RA pressure of 8 mmHg. Other additional parameters such as hepatic vein profile can be used to further refine this estimated pressure. Young healthy adults may have dilated IVCs but normal RA pressure, and estimation of RA pressure using the IVC index may not be reliable in patients who are intubated [4]. An additional estimate of right atrial pressure is derived from the ratio of the tricuspid inflow diastolic E wave velocity and the right ventricular annular e' velocity, which is the right-sided correlate of estimating left atrial pressure by tissue Doppler. A ratio of $E/e' > 6$ is suggestive of high right atrial pressures. This method can be used in situations where IVC measurements are unobtainable or inaccurate [5].

Because the hepatic vein drains into the IVC, which then drains into the RA, the hepatic vein Doppler profile can provide complementary information regarding right atrial and ventricular hemodynamics. The hepatic vein profile consists of two main antegrade flow waves (systolic (S) and diastolic (D) waveforms) and a retrograde atrial wave (a) (Fig. 11.3b). The S, D, and a waves correspond to the x, y, and a waves of the jugular venous pressure waveform, respectively.

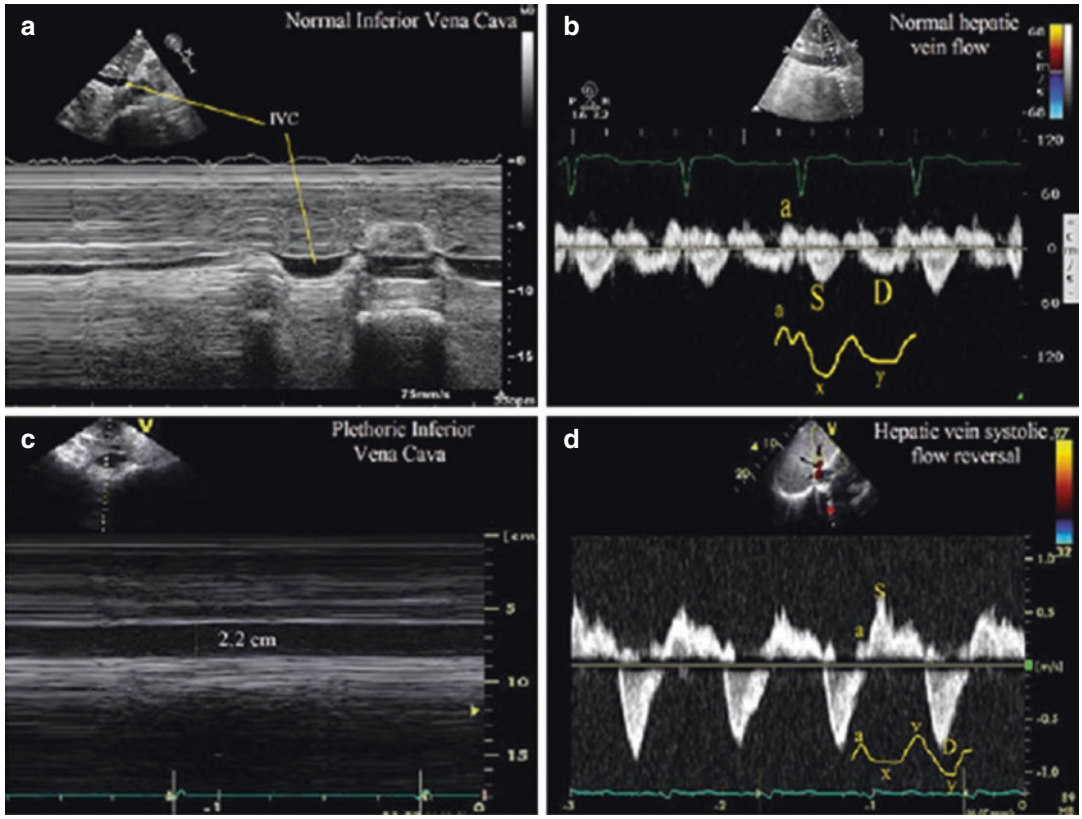


Fig. 11.3 Right-sided pressures. (**a**) M-mode through the IVC from the subcostal view. Note that the IVC size is <2.1 cm and collapses greater than 50%, suggesting normal right atrial pressure (0–5 mmHg). (**b**) Pulse wave (PW) Doppler of the hepatic vein showing normal hepatic vein flow. Note that there are two antegrade waves (*S* and *D*) and one retrograde wave (*a* reversal). The representative portions on the JVP waveform are shown (*S* corresponds to the *x* descent, and *D* corresponds to the *y* descent). The onset of the *S* wave corresponds to the onset of the QRS (isovolumic contraction), although the peak occurs in mid to late systole. In this example, the velocity of the *S* wave is larger than the *D* wave, indicating normal right atrial pressures. (**c**) A plethoric IVC greater than 2.1 cm in width which does not collapse, suggesting a right atrial pressure between 10 and 20 mmHg. (**d**) Systolic flow reversal in the hepatic veins in severe tricuspid regurgitation. Notice that the *S* wave is above the baseline, indicating flow reversal. This corresponds to the blunted *x* descent and tall *v* wave in the JVP waveform

Flow in the hepatic vein is sensitive to respiration, with increasing antegrade flow during inspiration and decreasing flow during expiration. With normal RA pressure, there is a predominance of the *s* wave in the antegrade waveform, whereas with elevated RA pressure, because the pressure gradient between the RA and the hepatic vein is lower, the *s* wave is blunted and the *d* wave predominates. *More quantitatively, a ratio of the s wave velocity divided by the sum of the s and d wave velocity* $[V_s/(V_s + V_d)]$ *less than 55% is highly correlated with an elevated RA pressure* [6]. In addition, in severe tricuspid regurgitation, there may even be systolic wave reversal, which is the echocardiographic equivalent of the loss of the *x* descent in the jugular venous waveform (Fig. 11.3d). In pulmonary hypertension, there may be prominent flow reversal during atrial systole (prominent *a* wave) due to high pulmonary pressures transmitting back to the atrium during diastole. Utilizing the ECG to accurately differentiate systolic flow reversal in the hepatic vein (which should occur coincident with isovolumic contraction) from a prominent (*a*) wave can be

key to avoiding misinterpretation of quite different hemodynamic conditions.

Right Ventricle

In the absence of tricuspid stenosis, the right ventricular end-diastolic pressure should equal the RA pressure as estimated from the IVC measurement. If tricuspid regurgitation (TR) is present, the peak velocity (v_{TR}) measured at end-expiration can be used to estimate the pressure gradient between the right ventricle and right atrium during systole ($\Delta P = 4V_{TR}^2$) (Fig. 11.4a). This pressure gradient can be added to the RA pressure to estimate the right ventricular systolic pressure (RVSP = RA + $4V_{TR}^2$). A TR velocity greater than 2.8–2.9 cm/s, in the setting of a normal RA pressure (0–5 mmHg), corresponds roughly to an RVSP of 36 mmHg, which

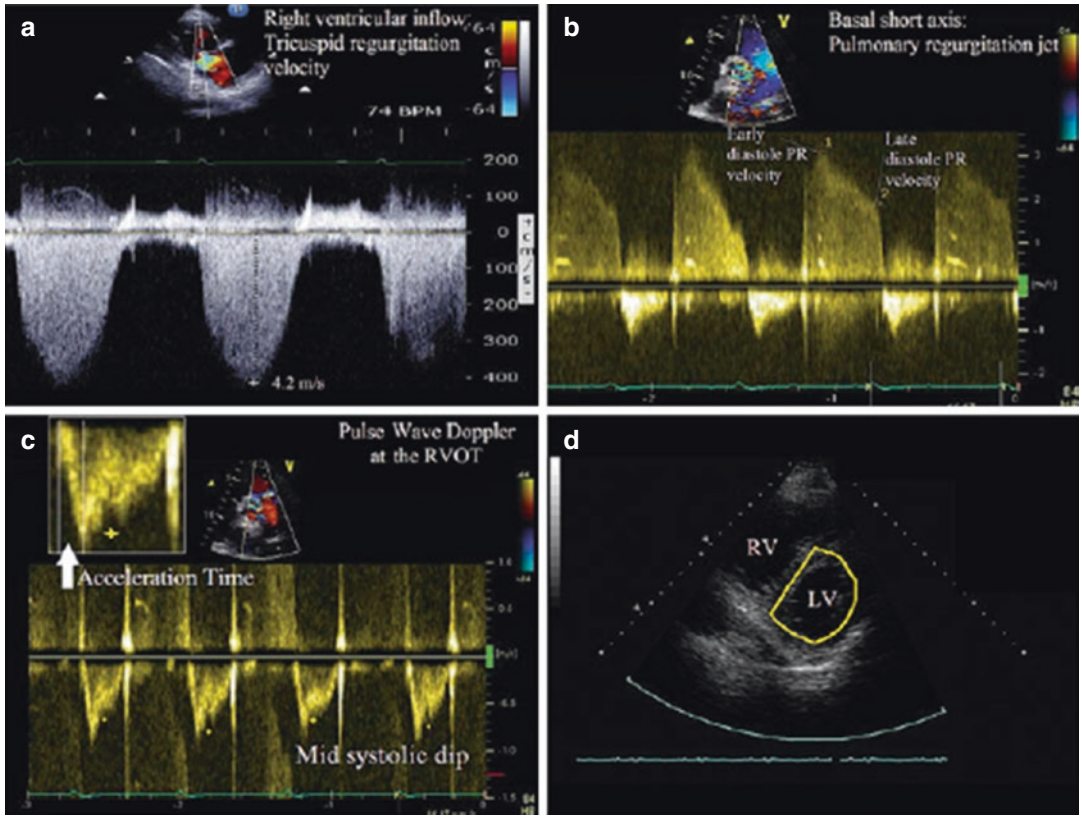


Fig. 11.4 Pulmonary pressures and signs of pulmonary hypertension. (**a**) The right ventricular systolic pressure can be estimated from the peak tricuspid regurgitation velocity obtained in the right ventricular inflow view (*see Question 1*). (**b**) The continuous wave (CW) Doppler profile of the pulmonary regurgitation jet. The early peak velocity can be used to determine the mean pulmonary artery (PA) pressure by the following formula: Mean PA Pressure = $4v_{EarlyDPR}^2$. In this case, early pulmonary regurgitation (PR) jet velocity is 3.9 m/s and the end-diastolic PR velocity is 1.9 m/s. Therefore, the mean PA pressure is roughly 39 mmHg. Also, the pulmonary artery end-diastolic pressure (PAEDP) can be determined from the end-diastolic velocity and estimated right atrial (RA) pressure: PAEDP = RA + $4v_{EDPR}^2$ (*see Question 2*). Note that in pulmonary hypertension, there is absence of the typical end-diastolic dip in the pulmonary regurgitation CW profile that normally corresponds to atrial systole. (**c**) The sample volume is in the RVOT, just below the pulmonic valve. In pulmonary hypertension, there is a steep slope in early systole (acceleration phase becomes shorter, *upper left corner*) and there can be a mid-systolic dip in the RVOT profile (*yellow stars*), due to high afterload. A simplified formula to calculate the mean pulmonary artery pressure (MPAP) is MPAP = 80 − 0.5 (acceleration time (ms)). Acceleration time is roughly 90 ms, yielding a MPAP of 35 mmHg. (**d**) Note the D-shaped septum during systole, suggestive of RV pressure overload

indicates the presence of mild pulmonary hypertension [4].

In cases of severe TR, in which the tricuspid valve is essentially "wide-open" during systole and there is no longer a fixed orifice with a significant pressure drop across the orifice, the RVSP may be underestimated. This is due to the fact that the flow acceleration (inertance) component of the Bernoulli equation is no longer negligible (a pressure drop must occur to overcome the inertance of the large volume of blood), while the convective flow component is less important (large orifice). Therefore, the simplified Bernoulli equation, which includes only the convective component, typically underestimates the RVSP in this scenario [4, 7].

If there is no RVOT obstruction or pulmonary stenosis, then the RVSP should be equal to the pulmonary artery systolic pressure (PASP). In the presence of pulmonary stenosis, because the peak gradient across the pulmonary valve during systole represents the pressure drop from the RV to the pulmonary artery (PA), the PASP can be derived from subtracting the peak gradient across the pulmonary valve during systole (obtained by CW) from the RVSP obtained from the TR jet [8].

Pulmonary Artery

As stated above, the PASP is equal to the right ventricular systolic pressure in the absence of RVOT obstruction. The end-diastolic pressure gradient between the pulmonary artery and the right ventricle is extrapolated from the end-diastolic velocity of the pulmonary regurgitation jet ($\Delta P = 4V_{\mathrm{PRed}}{}^2$) (Fig. 11.4b). Because this jet represents the difference between pulmonary artery end-diastolic pressure (PAEDP) and RVEDP (i.e., $\Delta P = 4V_{\mathrm{PRed}}{}^2 = \mathrm{PAEDP} - \mathrm{RVEDP}$), and RVEDP equals RA pressure in the absence of tricuspid stenosis, it follows by algebraic manipulation that $\mathrm{PAEDP} = \mathrm{RA} + 4V_{\mathrm{EDPR}}{}^2$ [9]. Also, the mean PA pressure can be estimated from the peak pulmonary regurgitation jet velocity (Mean PA Pressure = $4V_{\mathrm{EarlyDPR}}{}^2$) or the RVOT flow measured by PW Doppler using the formula $80 - 0.5 * (\text{pulmonic acceleration time(ms)})$ (Fig. 11.4c) [10]. These formulae can be useful when TR velocity signal is weak and unreliable. Estimation of pulmonary vascular resistance can be made by determining the ratio of the Peak TR velocity and the RVOT VTI (right ventricular outflow tract velocity time integral) in the following formula [11]:

$$\mathrm{PVR}\ (\text{Woods units}) = \frac{10 * (\text{peak TR velocity}(\mathrm{m/s})}{\text{RVOT VTI}(\mathrm{cm})) + 0.16}.$$

Echocardiographic signs of pulmonary hypertension include a D-shaped left ventricle, loss of the atrial systolic dip in the pulmonary regurgitation jet, and a mid-systolic decrease in the pulmonary outflow velocity (Fig. 11.4).

Pulmonary Capillary Wedge/Left Atrial Pressure

One method of estimating the left atrial (LA) pressure is to determine the peak mitral regurgitation velocity (V_{MR}), from which one can derive the pressure gradient between the left ventricle (LV) and LA (LV systolic pressure − LA pressure = $4V_{\mathrm{MR}}{}^2$) [12]. Because the LV systolic pressure equals the systolic blood pressure (SBP) in the absence of LVOT obstruction, the LA pressure = $\mathrm{SBP} - 4V_{\mathrm{MR}}{}^2$. A more common method of estimating the left atrial pressure is to determine the ratio of the mitral inflow *E* velocity to septal mitral annular velocity (*e′*), or *E/e′* [13]. *An E/e′ ratio of >15 is highly correlated with a pulmonary capillary wedge pressure (PCWP) >20, while an E/e′ ratio less than 8 corresponds to a normal PCWP* [13]. This method is valid for patients with

normal and abnormal systolic function. Tissue Doppler-derived estimates of PCWP can be used in patients with atrial fibrillation as well. However, in patients with constriction the exaggerated e' velocity, which corresponds to the rapid y descent on JVP waveform, yields a low E/e' ratio in spite of the fact that the left atrial pressures are elevated. This is the so-called *annulus paradoxus* [14].

Finally, in patients with aortic insufficiency, because the end-diastolic velocity of the aortic regurgitation jet ($4V_{AI}^2$) represents the pressure gradient between the aorta (diastolic blood pressure or DBP) and the LV end-diastolic blood pressure (LVEDP), one can estimate the LVEDP using the following formula: $\text{LVEDP} = \text{DBP} - 4V_{EDAI}^2$. Measurement error inherent with sphygmomanometric readings provides the primary limitation of this method. In the case of severe acute AI, where the end-diastolic velocity of the aortic insufficiency jet approaches zero, the LVEDP approaches the DBP.

Cardiac Output and System Vascular Resistance

The flow rate through a vessel is the product of the cross-sectional area of the vessel and the velocity of blood. However, because velocity varies over time throughout the cardiac cycle due to pulsatility, one cannot take an instantaneous velocity to measure overall flow rate. Rather, an integral of the velocities over time, called the VTI from the Doppler profile, is used to characterize integrated velocity in a given time period to determine flow (volume), rather than flow rate (volume/time) (Fig. 11.5a, b). VTI is essentially a measure of stroke distance. When the VTI (distance) is multiplied by the cross-sectional area (distance squared), the product is a volume (distance cubed). Therefore, stroke volume of the left ventricle can be estimated by multiplying the cross-sectional area of the LVOT ($\pi r^2 = \pi(D/2)^2 = \pi D^2/4 = D^2 * 0.785$, where r is radius and D is diameter) obtained in the parasternal long axis view and multiplying it by the VTI of the PW Doppler profile obtained in the apical long axis view (Fig. 11.5a). The PW cursor is typically placed about 0.5–1 cm below the valve to obtain a laminar flow curve. It is important to measure the PW Doppler profile at the same location as the measured cross-sectional area to maintain accuracy. This stroke volume can be multiplied by the heart rate to give an estimated cardiac output (in the absence of significant aortic regurgitation). If there is no regurgitation or intracardiac shunts, then the stroke volume through the tricuspid, pulmonary, mitral, and aortic valves should be equivalent, and therefore, the principle of multiplying the cross-sectional area of these valves by the VTI of flow across the valves can be applied throughout the heart. Practically speaking, however, stroke volume is typically measured in the LVOT.

If a left to right shunt is present (i.e., ASD or VSD), then it is clinically relevant to estimate the severity of the shunt by determining the ratio of pulmonary blood flow (Q_p) to systemic blood flow (Q_s). Figure 11.6 shows an example of a secundum ASD with left to right flow. Systemic stroke volume is measured by multiplying the LVOT area ($D^2*0.785$) by the LVOT VTI from the parasternal long axis views and the apical long axis views, respectively. The pulmonary stroke volume is measured by multiplying the RVOT Area by the RVOT VTI, measured in the basal short axis view across the pulmonary valve. The ratio of Q_p/Q_s, which equals [(RVOT VTI) (RVOT $D^2*0.785$)]/[(LVOT VTI) (LVOT $D^2*0.785$)], gives an estimate of the shunt fraction (Fig. 11.6). The term 0.785 cancels, and the ratio simplifies to (RVOT VTI) (RVOT D^2)/(LVOT VTI) (LVOT D^2). A ratio greater than 1.5 is considered a significant left to right shunt.

Just as pulmonary vascular resistance correlates with the TR velocity/RVOT VTI, systemic vascular resistance (SVR) correlates relatively well with *MR velocity/LVOT VTI*. A ratio of *MR velocity/LVOT VTI > 0.27* has a relatively high sensitivity and specificity for *SVR > 14 Woods units* [15].

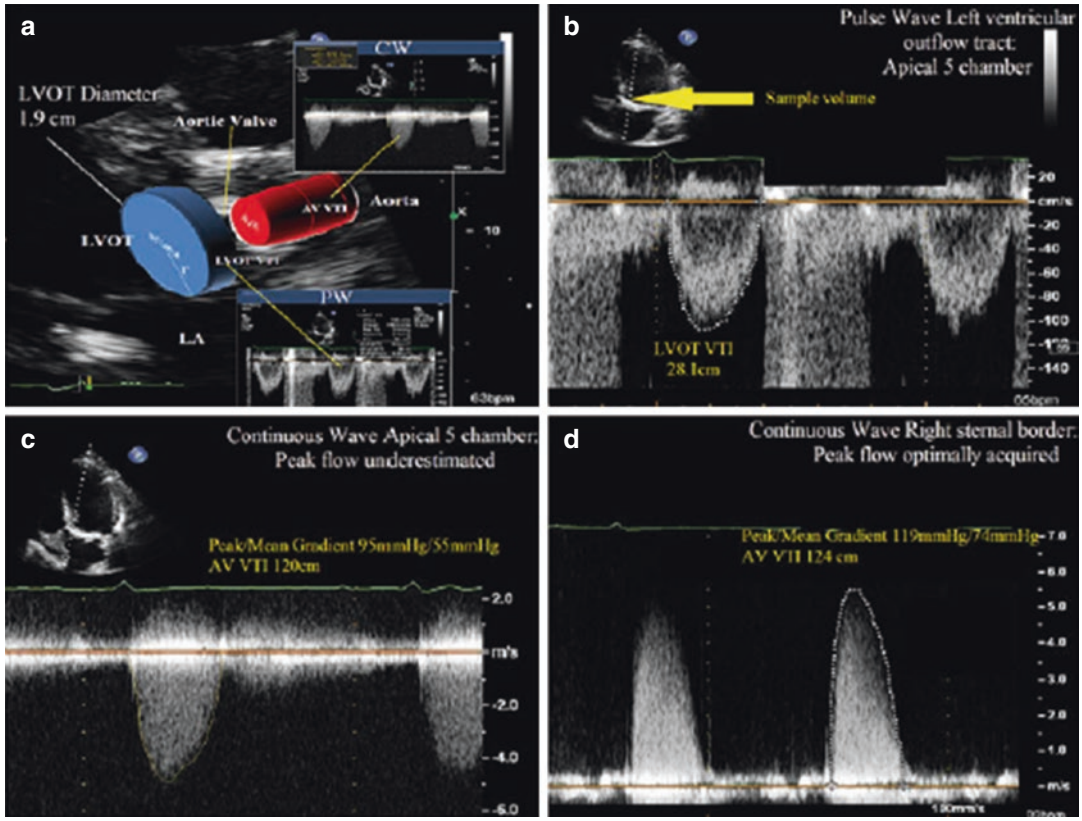


Fig. 11.5 Stroke volume and aortic valve area (AVA) calculation using the continuity equation. (**a**) Based on the continuity equation, the flow through the left ventricular outflow tract (LVOT), or the volume of the *blue cylinder*, must equal the flow through the aortic valve, or the volume of the *red cylinder*. The stroke volume (represented by the *blue cylinder*) is estimated by multiplying the LVOT area by the LVOT VTI. The LVOT area is obtained using the equation Area = πr^2 = (Diameter)^2∗0.785, with the diameter measured in the parasternal long axis view. Because the LVOT diameter in this case is 1.9 cm, the LVOT area is 2.84 cm^2. From the apical 5 chamber or apical long axis view, the LVOT VTI is obtained, which in this case is 28.1 cm (*bottom right* and (**b**)). Therefore, the stroke volume = 28.1 cm∗2.84 cm^2 = 79.8 cm^3. The product of the stroke volume and the heart rate (SV∗HR) can give an estimate of cardiac output. The volume of the *red cylinder* is the product of the AVA and the AV VTI (**c**, **d**). Because the volume of the *blue cylinder* (LVOT Area∗LVOT VTI) must equal the volume of the *red cylinder* (AVA∗AV VTI) to satisfy the continuity equation, it follows that AVA = [LVOT VTI ∗ (LVOT diameter)^2 ∗ 0.785]/[AV VTI] = Stroke volume/AV VTI (*see Question 3*). (**b**) Pulse wave Doppler Sample volume is placed just below the aortic valve in the 5 chamber view, and the LVOT VTI is traced. (**c**) Continuous wave Doppler measures the highest velocity along its path to estimate the peak and mean gradient across the aortic valve. The peak and mean gradients are 95/55 mmHg from the 5 chamber view, which is an underestimation of peak flow in this particular patient. Multiple views are necessary to obtain the highest, most representative jet velocity, as seen in (**d**). Right sternal border view obtains peak and mean gradients of 119/74 mmHg, higher than the peak gradient of 95 mmHg from the apical 5 chamber view

Valve Disease

It is important to recognize that an integrated approach using multiple echocardiographic methods of analysis and clinical context to determine severity of valve lesions is crucial, rather than relying on one specific measurement.

Aortic Stenosis

Echocardiography is currently the standard method to evaluate aortic valve stenosis. Application of the continuity equation is central to the calculation of aortic valve area (AVA). Based on the conservation of mass, the flow in

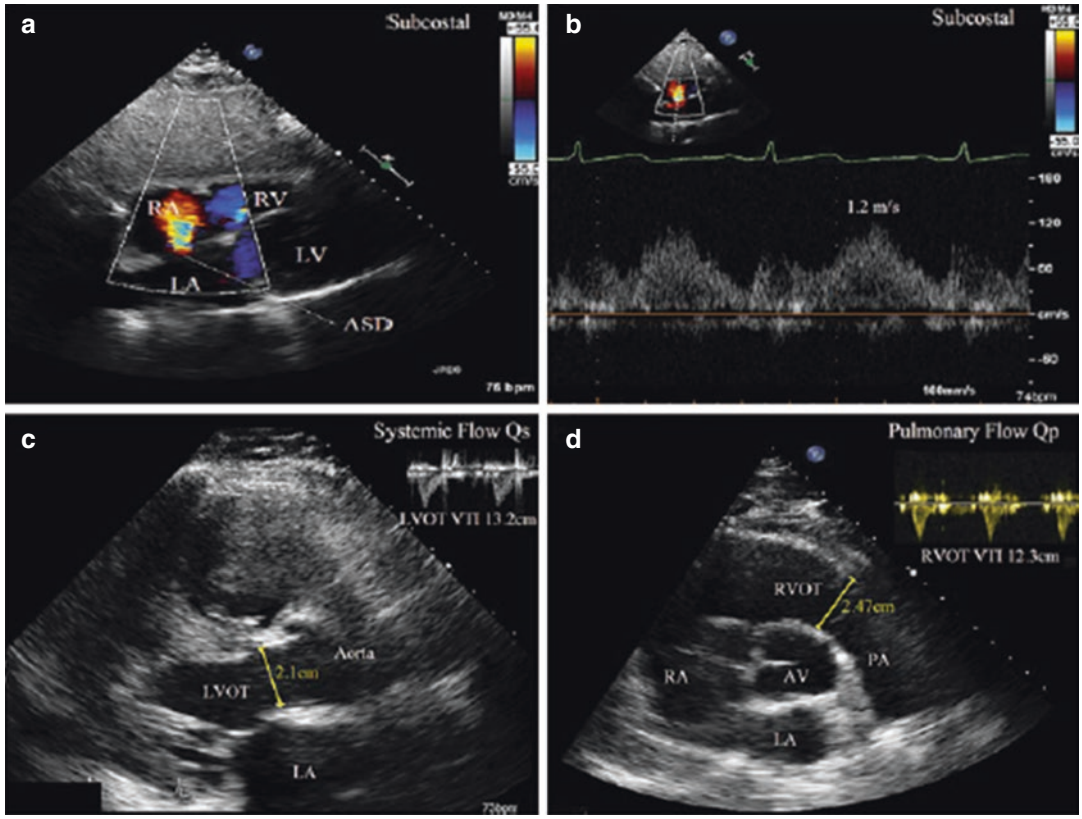


Fig. 11.6 Shunt calculation in a patient with a secundum atrial septal defect (ASD). (**a**) Color flow Doppler demonstrates left to right flow across the ASD in this subcostal view. (**b**) Pulse wave Doppler at the level of the ASD confirms that there is left to right continuous flow. During peak systole, based on the velocity of 1.2 m/s, the pressure gradient between the right atrium (RA) and the left atrium (LA) is $4v^2 = 4(1.2)^2 = 5.8$ mmHg. The RA pressure was estimated at 10 mmHg, so the LA pressure during systole is estimated at 15.8 mmHg (LA = RA + $4v^2$). (**c**) Measurement of systemic flow (Q_s) based on the LVOT area and LVOT VTI (pulse wave Doppler from the apical 5 chamber view, *right upper corner*). (**d**) Measurement of pulmonary flow (Q_p) based on the RVOT area and the RVOT VTI (pulse wave Doppler from the basal short axis view, *right upper corner*). The Q_p/Q_s or shunt fraction is 1.3:1 (*see Question 4 for calculation of Q_p, Q_s, and shunt fraction*)

the left ventricular outflow tract (LVOT) should be equal to the flow through the aortic valve orifice. First, one must determine the flow in the LVOT, or the stroke volume, by multiplying the cross-sectional area of the LVOT by the LVOT VTI determined by PW Doppler in the apical long axis or 5 chamber view (Fig. 11.5a, b). The PW sample volume should be located in the LVOT beneath the valve, and a crisp laminar Doppler signal with no contamination from the pre-stenotic flow acceleration should be sought. This is typically 0.5–1.0 cm from the aortic valve. The LVOT diameter should be measured from the septum to the anterior mitral leaflet in mid-systole, roughly 0.5–1.0 cm from the aortic valve in the parasternal long axis view to approximate the location where the PW was measured in the other echocardiographic view [16]. This flow should equal the product of the cross-sectional area of the aortic valve (AVA) and the AV VTI as determined by CW Doppler, typically the highest VTI obtained from a given view (suprasternal, apical, right parasternal) (Fig. 11.5c, d). The volume of blood in the cylinder in the LVOT (blue cylinder) must equal the volume of blood in the cylinder at the aortic valve (red cylinder) to not violate the law of mass conservation. The AV VTI obtained by CW Doppler is highly dependent on technique and the ability to obtain a good signal that is parallel to flow. Occasionally the right parasternal approach is used to obtain the highest gradient (Fig. 11.5d).

Based on the continuity equation:

$$\text{LVOT Cylinder Volume or Stroke Volume} = \text{AV Cylinder Volume}$$
$$\text{LVOT VTI} * \text{LVOT area} = \text{AV VTI} * \text{AVA}$$
$$\text{LVOT VTI} * (\text{LVOT diameter})^2 * 0.785 = \text{AV VTI} * \text{AVA}$$

Rearrangement yields [17] (Fig. 11.5):

$$\text{AVA} = \frac{\left[\text{LVOT VTI} * (\text{LVOT diameter})^2 * 0.785\right]}{\left[\text{AV VTI}\right]}$$

This equation gives a reliable estimate of the AVA; less than 1.0 cm^2 is considered severe aortic stenosis [16, 18]. Because the LVOT diameter is squared and measurements can vary, this is the greatest source of error in the formula.

The AVA is just one method among many to assess severity of aortic stenosis. Other methods include identifying the peak and mean gradient across the aortic valve, peak velocity across the aortic valve, and dimensionless index [17]. The peak velocity across the aortic valve is obtained from the CW Doppler profile, from which the peak gradient is calculated (from the peak velocity using $\Delta P = 4V^2$), and the mean gradient is calculated by averaging the instantaneous gradients during the ejection period [17]. A mean gradient >40 mmHg is considered severe. Echocardiographic assessment of peak gradient provides the instantaneous gradient between the LV and the aorta, which is different from cardiac catheterization in which often a peak to peak gradient is reported, a less physiologic value. Importantly, the mean gradient on cardiac catheterization correlates well with the Doppler-derived mean gradient. Table 11.1 shows the stages of severity of aortic stenosis based on the AHA/ACC 2014 Valve Guideline Update [16].

Although the peak velocity and estimated AVA are usually concordant (i.e., either velocity >4 m/s and AVA <1.0 cm^2 or velocity <4 m/s and AVA >1.0 cm^2), there may be scenarios in which the jet velocity and AVA may be discordant. In the case of velocity >4 m/s and AVA >1.0 cm^2, possibilities include a high stroke volume, concomitant moderate-to-severe aortic regurgitation, and a large body size. In the case of velocity <4 m/s and AVA <1.0 cm^2, possibilities include low stroke volume, severe concomitant mitral regurgitation, and small body size [16]. In either situation, the peak velocity is the better predictor of clinical outcome, and it is suggested that it be used to determine valve stenosis severity [16].

In patients who have left ventricular dysfunction (LVEF <40%) with concomitant aortic stenosis, the calculated AVA may be severe (<1.0 cm^2), but the mean gradient may not be severe (<30–40 mmHg). It is important to then determine if the aortic stenosis is truly severe and causing left ventricular dysfunction, which would imply improved left ventricular function with valve replacement, or if the aortic stenosis is only moderate in the presence of LV dysfunction from another cause (i.e., coronary disease, nonvalvular cardiomyopathy, etc.), in which the perceived small AVA is related to the inability of the left ventricle to generate the necessary valve opening forces (pseudostenosis). In the latter scenario, valve replacement would not be expected to improve left ventricular dysfunction. Low-dose dobutamine stress protocols (described in detail elsewhere [16]) can distinguish the two clinical scenarios. Recall from the continuity equation that the AVA is proportional to the *LVOT VTI/AV VTI*. If the patient truly has severe aortic stenosis, with the administration of dobutamine, the LVOT VTI and AV VTI should increase proportionally due to increased flow across a fixed,

Table 11.1 Aortic stenosis stages based on the recent AHA/ACC 2014 valve guidelines update [16]

Stage	Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequences	Symptoms
A	At risk of AS	Bicuspid aortic valve, aortic valve sclerosis, or other congenital anomaly	Aortic V_{max} <2 m/s	None	None
B	Progressive AS	Mild-to-moderate leaflet calcification with some reduced systolic motion or rheumatic commissural fusion	Mild AS: Aortic V_{max} 2.0–2.9 m/s or mean ΔP < 20 mmHg Moderate AS: Aortic V_{max} 3.0–3.9 m/s or mean ΔP 20 - 39 mmHg	Early LV dysfunction may be present but LVEF is preserved	None
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet motion	Aortic $V_{max} \geq 4$ m/s Mean $\Delta P \geq 40$ mmHg AVA ≤ 1.0 cm^2 Very severe AS is an aortic $V_{max} \geq 5$ m/s or Mean $\Delta P \geq 60$ mmHg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None: exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet motion	Aortic $V_{max} \geq 4$ m/s Mean $\Delta P \geq 40$ mmHg AVA ≤ 1.0 cm^2	LVEF <50%	None
D1	Symptomatic severe high gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet motion	Aortic $V_{max} \geq 4$ m/s Mean $\Delta P \geq 40$ mmHg AVA ≤ 1.0 cm^2	LV diastolic dysfunction, LVH, pulmonary HTN may be present	Exertional dyspnea, angina, or reduced exercise tolerance, syncope or presyncope
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤ 1.0 cm^2 with resting aortic $V_{max} < 4$ m/s or mean $\Delta P < 40$ mmHg Dobutamine stress echo shows AVA ≤ 1.0 cm^2 with $V_{max} \geq 4$ m/s at any flow rates	LV diastolic dysfunction, LVH, LVEF <50%	HF, angina, syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤ 1.0 cm^2 with aortic V_{max} <4 m//s or mean ΔP < 40 mmHg Indexes AVA ≤ 0.6 cm^2/m^2 *Stroke volume index <35 mL/m^s* *Measured when patient is normotensive*	Increased relative wall thickness with preserved ejection fraction Small LV chamber with low stroke volume Restrictive diastolic filling	HF, angina, syncope, or presyncope

stenotic orifice, so the AVA should remain relatively unchanged. However, if the aortic stenosis only appears severe because of concomitant left ventricular dysfunction, dobutamine infusion will increase the LVOT VTI without a concomitant increase in AV VTI because of improved valve opening, thereby resulting in an increased calculated AVA. It follows that if the AVA increases above 1.0 cm^2 with dobutamine infusion, it is not likely to be severe aortic stenosis. Severe AS is suggested by a peak jet velocity >4.0 m/s provided that the valve area does not increase to >1.0 cm^2 [16]. In addition, the presence of contractile reserve (increase in EF or

SV ≥ 20%) during dobutamine stress predicts a lower mortality rate (<10%) with AVR than if contractile reserve is absent (>30%) [19].

The velocity ratio, also known as the dimensionless index, which is flow independent, is the ratio of the LVOT peak velocity and the AV peak velocity (can also use VTI ratio). A velocity index <0.25 is considered severe. This is used to compare aortic stenosis severity over time in patients who may have different loading conditions.

Accurate estimation of aortic stenosis severity depends on meticulous technique to obtain both an accurate LVOT diameter assessment, as well as the highest velocity jet which may require multiple echocardiographic views. In general, inaccuracies in measuring gradients by echocardiography typically err on the side of underestimation. However, there are two situations in which echocardiography may overestimate severity of stenosis. First, as stated earlier, the peak gradient estimated by the simplified Bernoulli equation ignores the velocity in the LVOT (V_1) as it is usually very small (<1 m/s). Scenarios in which the proximal velocity is >1.5 m/s or the peak velocity is <3 m/s, the flow velocity and gradient may be overestimated since the V_1 is ignored. Therefore, a more accurate estimate of peak gradient across the valve is $\Delta P = 4\left(V_2^2 - V_1^2\right)$ [16]. Another scenario in which the stenosis severity may be overestimated is the pressure recovery phenomenon. This occurs when some of the potential energy which was converted to kinetic energy at the level of the aortic stenosis is converted back to potential energy as flow decelerates (i.e., increasing pressure distal to the valve in the aorta). This pressure recovery is typically negligible, except in the case of small aortas with gradual widening after the stenosis (typically less than 3 cm in diameter). With larger aortas, much of the kinetic energy is converted to heat due to turbulence and viscous friction, so pressure recovery is not an issue [16]. Pressure recovery can be quantitatively calculated as $\Delta P = 4V^2 * 2(\text{AVA/aorta area}) * (1 - \text{AVA/Aorta area})$. As can be seen by the equation, if the AVA is small, and the aorta area is large, the AVA/aorta area ratio is small, and pressure recovery is minimal [16].

One collateral method to confirm the pressure gradient across the LVOT or aortic valve is to assess the peak mitral regurgitation velocity. As described previously, LV systolic pressure − LA pressure = $4V_{MR}^2$. If the LA pressure is estimated to be between 10 and 20 mmHg, then the LV systolic pressure can be estimated by 10–20 mmHg + $4V_{MR}^2$. If the SBP is known, then the difference between the estimated LV systolic pressure and SBP approximates the peak pressure gradient across the LVOT or aortic valve.

Mitral Stenosis

The most common cause of mitral stenosis (MS) is commissural fusion as a result of rheumatic fever. Several echocardiographically derived measurements can be used to assess mitral stenosis, including pressure gradient, pressure half-time, continuity equation, proximal isovelocity surface area (PISA) method, and planimetry. Although planimetry may well provide the most accurate measurement of the mitral valve area (MVA) provided that the images are acquired at leaflet tip level and are a true on-axis view, this section will focus on the pressure gradient, pressure half-time, and continuity equation to assess the valve area. PISA method and planimetry are discussed in detail in another reference [16]. Peak and mean pressure gradients across the mitral valve in diastole are measured by CW from the apical 4 chamber view (Fig. 11.7). It is essential to interrogate the mitral valve during a regular rhythm and normal heart rate (60–80 bpm). If the patient is in atrial fibrillation, then several cardiac cycles (6–8) should be averaged. Mean gradient is preferred to the peak gradient, since the peak gradient may be influenced by mitral regurgitation, atrial compliance, and left ventricular diastology. One cause of a very high peak gradient out of proportion to the mean gradient, for example, is severe mitral regurgitation. While pressure gradients are important parameters in the assessment of mitral stenosis severity, they are highly influenced by heart rate, cardiac output, and mitral regurgitation [16]. Mean pressure gradients supportive of mild, moderate, and

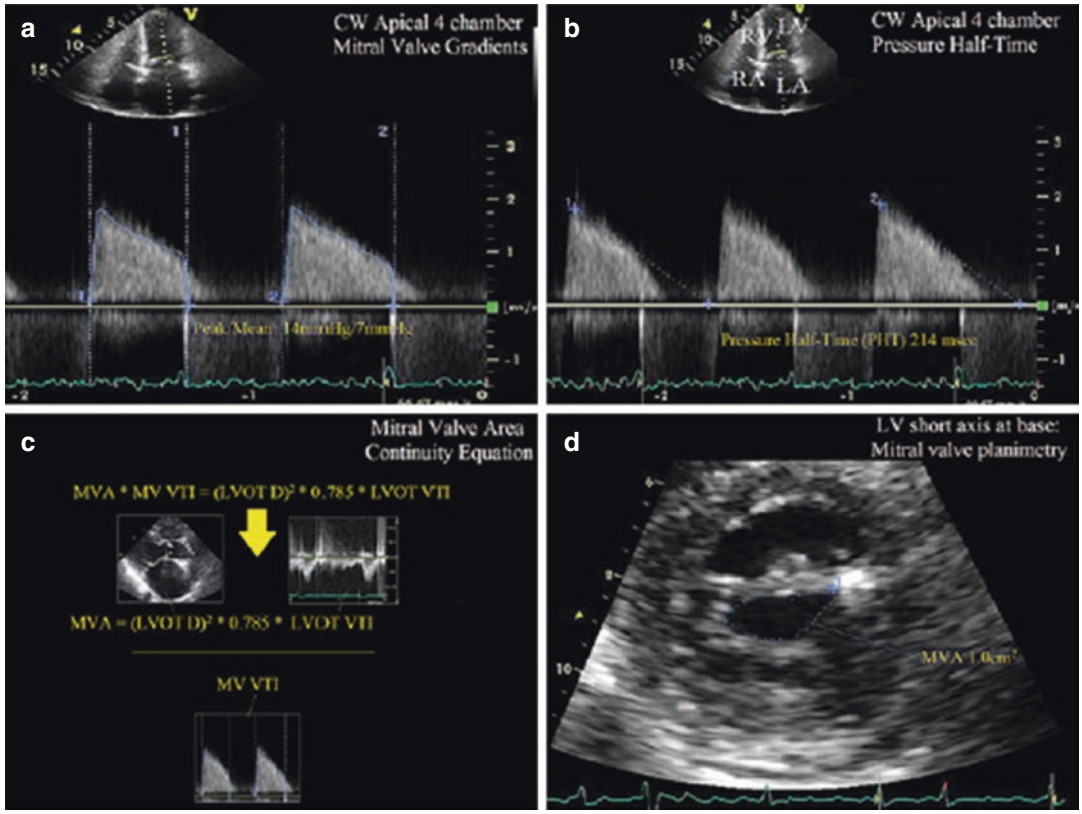


Fig. 11.7 Assessment of mitral stenosis. (**a**) Continuous wave Doppler across the mitral valve yields the peak and mean gradient (14/7 mmHg). Given the irregular heart rhythm, 6–8 beats are measured and averaged to obtain the peak and mean gradient. (**b**) The pressure half-time (PHT) is the time for the pressure gradient to decrease by 50%, and is equal to 0.29∗Deceleration time. Again, multiple beats are averaged (6–8) to obtain the PHT of 214 ms. The mitral valve area (MVA) is estimated by the following empiric equation: MVA = 220/PHT, giving a MVA of 220/214, or 1.0 cm^2, by the PHT method. (**c**) Calculation of MVA using the continuity equation. The flow across the mitral valve must equal the flow across the aortic valve, and therefore, MVA ∗ MV VTI = LVOT a ∗ LVOT VTI. In this case, the LVOT diameter is 1.9 cm, the LVOT VTI is 20 cm, and the MV VTI is 56.4 cm. Therefore, the calculated MV area is 1.0 cm^2. Note that the MV VTI is measured using CW and the LVOT VTI is measured using PW in this situation. (**d**) Planimetry is another method of estimating the MVA. Note the commissural fusion and "fish-mouth" appearance of the mitral opening, characteristic of rheumatic mitral valve disease. In this example, planimetry yields a MVA of 1.0 cm^2, concordant with the PHT and continuity methods

severe MS are <5 mmHg, 5–10 mmHg, and >10 mmHg, respectively [20].

Pressure half-time (PHT) is the time (in ms) it takes for the peak pressure gradient across the mitral valve in diastole to decrease by 50%. Based on the relationship between pressure and velocity, it is also the time in ms it takes for the peak velocity to decrease by 29%. This measurement is obtained by tracing the slope of the *E* wave during early diastole (Fig. 11.7b). It has been found that there is an inverse relationship between PHT and MVA by the following equation: MVA (cm^2) = 220/PHT [21]. In addition, the MVA (cm^2) = 759/Deceleration Time (ms). See Table 11.2 for measurements and valve stenosis severity.

Pressure half-time may be low even in severe MS if atrial compliance is low. In severe aortic insufficiency, due to the increase in the LVEDP during diastole as a result of regurgitation, the pressure between the LV and LA will equilibrate sooner, so the PHT will be reduced and the MVA estimate using the PHT will be inaccurate.

Table 11.2 Stage of mitral stenosis

Stage	Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequences	Symptoms
A	At risk of MS	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
B	Progressive MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets, MVA > 1.5 cm^2	Increased transmitral flow velocities MVA > 1.5 cm^2 Diastolic pressure half-time <150 msec		None
C	Asymptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2 MVA ≤ 1.0 cm^2 with very severe MS	MVA ≤ 1.5 cm^2 MVA ≤ 1.0 cm^2 with very severe MS Diastolic pressure half-time >150 ms, or >220 ms with very severe MS	Severe LA enlargement Elevated PASP>30 mmHg	None
D	Symptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2	MVA ≤ 1.5 cm^2 MVA ≤ 1.0 cm^2 with very severe MS Diastolic pressure half-time > 150 ms, or ≥220 ms with very severe MS	Severe LA enlargement Elevated PASP>30 mmHg	Decreased exercise tolerance Exertional dyspnea

MVA mitral valve area, *PASP* pulmonary artery systolic pressure

The continuity equation estimates the MVA if there is no aortic insufficiency or mitral regurgitation. The flow through the mitral valve should equal the flow through the LVOT by conservation of mass. The formula for flow through the LVOT (i.e., stroke volume), as described previously, is LVOT VTI ∗ (LVOT diameter)^2 ∗ 0.785. Again, this can be thought of as a cylinder, in which the base of the cylinder is the area of the LVOT and the height is the LVOT VTI. The flow through the mitral valve equals the product of the cross-sectional area of the mitral orifice (base of the cylinder) multiplied by the MV VTI (height of the cylinder). The MV VTI is determined by the computer package from the tracing of the CW mitral inflow from the 4 chamber view (Fig. 11.7c).

$$\text{LVOT Cylinder Volume or Flow} \quad \text{MV Cylinder Volume or Flow}$$

$$\text{LVOT VTI} * \text{LVOT area} = \text{MV VTI} * \text{MVA}$$

$$\text{LVOT VTI} * \left(\text{LVOT diameter}\right)^2 * 0.785 = \text{MV VTI} * \text{MVA}$$

$$\text{MVA} = \frac{\left[\text{LVOT VTI} * \left(\text{LVOT diameter}\right)^2 * 0.785\right]}{\left(\text{MV VTI}\right)}$$

Because MS elevates LA pressures, pulmonary hypertension may result. In general, the more severe the MS is, the more severe the pulmonary hypertension becomes. Pulmonary artery (PA) pressures can be assessed using the estimated RVSP, assuming there is no RVOT obstruction or pulmonic stenosis. A resting PASP > 50 mmHg or exercise-induced pulmo-

Table 11.3 Mitral regurgitation severity [16]

Grade	Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequences	Symptoms
A	At risk of MR	Mild mitral valve prolapse Mild valve thickening and leaflet restriction	No MR jet or small central jet <20% LA on Doppler Small vena contracta <0.3 cm	None	None
B	Progressive MR	Severe mitral valve prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior infective endocarditis(IE)	Central jet MR 20–40% LA or late systolic eccentric jet MR Vena contracta <0.7 cm Regurgitant volume <60 mL Regurgitant fraction <50% ERO <0.40 cm^2 Angiographic grade 1–2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
C	Asymptomatic severe MR	Severe mitral valve prolapse with loss of copatation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise C1 LVEF >60% and LVESD <40 mm C2 LVEF ≤60% and LVESD ≥40 mm	None
D	Symptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR >40% LA or holosystolic eccentric jet MR Vena contracta ≥0.7 cm Regurgitant volume ≥60 mL Regurgitant fraction ≥50% ERO ≥0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreaesd exercise tolerance Exertional dyspnea

nary hypertension (PASP > 60 mmHg) in the absence of other causes implies hemodynamically significant mitral stenosis [22].

Mitral Regurgitation

Echocardiographic assessment of mitral regurgitation severity relies on a "weighted average" of the information obtained from multiple modalities (Table 11.3). Color Doppler is the most readily apparent and visualized method of assessing mitral regurgitation. The jet area in the atrium on color Doppler is highly dependent on PRF and color scale. Typically, a large jet area spanning more than 40% of the atrium is considered severe MR. However, there are many caveats to using jet area. The appearance of the color is highly

technique-dependent, and can be affected by hemodynamic changes and atrial size. In addition, a very eccentric jet may "hug" the wall and appear to be smaller than a more central jet, giving the false impression that the eccentric MR is not severe. In addition, in the case of acute, severe mitral regurgitation, the jet duration may be very short given the acute rise in LA pressure, and technical factors such as insufficient color resolution may lead to underestimation [23]. Given its many limitations, jet area should not be the sole method used for quantification of mitral regurgitation.

Another method of MR assessment is the flow convergence or PISA method, which is an extension of the continuity principle and has been shown to correlate well with angiographically determined severity [24]. As flow converges toward a regurgitant orifice, the flow organizes into several concentric hemispheres, each with a specific velocity (Fig. 11.8a). As blood approaches the regurgitant orifice, the radius of the hemisphere decreases, while the velocity of blood at the surface of the hemisphere increases. Since the surface area (cm^2) of the hemisphere can be derived from the radius (surface area of hemisphere = $2\pi r^2$), and the velocity of the blood cells (cm/s) at the surface of the hemisphere (aliasing velocity, V_a) can be obtained from the color scale, the product of these two values (in units of cm^3/s) gives the flow rate proximal to the orifice (Fig. 11.8a). The flow rate distal to the orifice, which must equal the flow rate proximal to the orifice, can be calculated from the effective regurgitant orifice area (EROA) multiplied by the peak mitral regurgitant velocity, obtained from the CW Doppler in the 4 chamber view (Fig. 11.8c). To determine the velocity of the hemisphere of the proximal flow convergence, the color baseline or Nyquist limit are shifted downward toward the direction of flow (Fig. 11.8a). As shown in the figure, this maneuver increases the radius of the hemisphere, allowing easy visualization of color transition from blue to yellow, which is the location where the velocity is equal to the aliasing velocity. By having a larger radius and a lower aliasing velocity, propagation of error in radius measurement is reduced.

It follows that:

$$\text{Flow rate proximal to orifice} = \text{Flow rate distal to the orifice}$$

$$\text{Hemisphere surface area} * V_a = \text{EROA} * \text{peak mitral velocity}$$

$$2\pi r^2 * V_a = \text{EROA} * V_{MR}$$

$$\text{EROA} = \frac{\left(6.28 r^2 * V_a\right)}{V_{MR}}$$

This, of course, assumes that the hemisphere radius is measured at the time that the peak MR velocity occurs, so attempts must be made and standardizing the timing of measurement (i.e., mid-systole). As seen in Table 11.2, ERO > 0.4 is severe MR, and <0.2 is mild MR. The PISA method is not very accurate in situations of very eccentric MR jets (may overestimate severity) and noncircular orifices. A geometric correction factor for eccentric jets that create a wedge of a hemisphere instead of a full hemisphere has been described [25]. The angle created by the wedge (α) is divided by 180° and multiplied by the EROA to obtain the geometrically corrected EROA. Therefore, Geometrically corrected ER OA = $(\alpha/180) * (6.28r^2 * V_a)/V_{MR}$. Furthermore, flow velocity calculated by the PISA method represents an instantaneous flow rate. For instance, in mitral valve prolapse, the instantaneous EROA may be large but if the regurgitation only occurs in mid to late systole, the total regurgitant volume may not be very large. So perhaps a more accurate measurement of MR severity in this situation would be regurgitant volume.

To determine the regurgitant volume (RV), the EROA is multiplied by the MV VTI.

$$\text{RV} = \text{EROA} * \text{MV VTI}$$

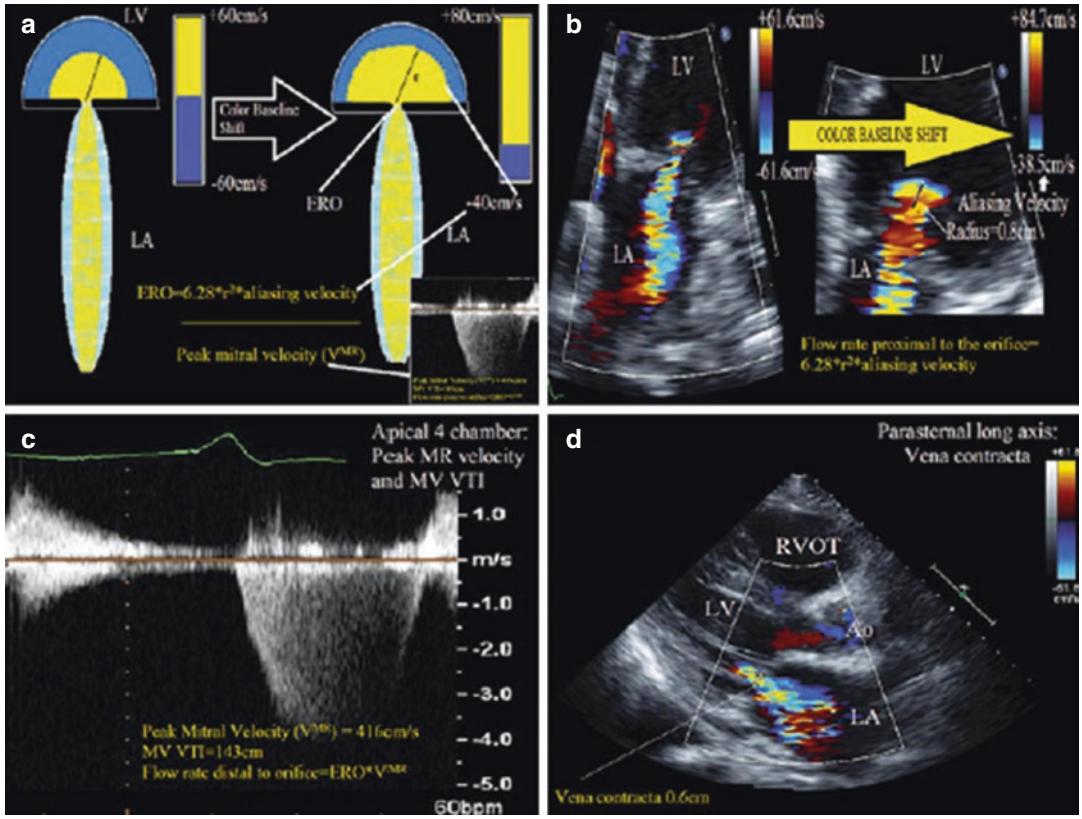


Fig. 11.8 PISA (proximal isovelocity surface area) method for mitral regurgitation and vena contracta. (**a**) Artistic rendition of the PISA concept. As flow converges during systole toward the regurgitant orifice, it accelerates and forms concentric hemispheres of increasing velocity and decreasing radius. For example, the velocity at the edge of the *yellow hemisphere* is higher than the velocity at the edge of the *blue hemisphere*. First the image should be optimized and zoomed. Next, the color baseline is shifted downward toward the direction of flow, from −65 to −40 cm/s, creating the *larger yellow hemisphere* with a lower velocity on the right. The velocity at the boundary between the *yellow* and *blue hemisphere* is the aliasing velocity (V_a = −40 cm/s). The flow proximal to the orifice equals the product of the hemisphere surface area ($2\pi r^2$) and the aliasing velocity (V_a). This proximal flow should equal the flow distal to the orifice, which is the product of the regurgitant orifice area (EROA) and peak MR velocity (V_{MR}). Therefore, EROA = $(2\pi r^2 * V_a)/V_{MR}$. (**b**) Similar to *panel A*, after creating a zoomed-in image, the color baseline is shifted toward the direction of flow, and a larger hemisphere with a known radius (0.8 cm) and aliasing velocity (V_a = 38.5 cm/s) is created. Based on the above equation, the proximal flow rate is 154.7 cm^3/s. (**c**) Continuous wave Doppler across the mitral valve to obtain the peak mitral regurgitant velocity (V_{MR}) = 416 cm/s and MV VTI. The distal flow rate is V_{MR}*EROA. The EROA, which is equal to $(2\pi r^2 * V_a)/V_{MR}$, is 0.37 cm^2, consistent with moderately-severe MR. Regurgitant volume can be calculated with the information in this figure (*see Question 5*). Using the simplified PISA formula, $r^2/2$, estimated EROA is 0.32 cm^2, likely slightly underestimated because the aliasing velocity is 38.5 cm/s, not the 40 cm/s assumed in the simplified formula. (**d**) The vena contracta, the narrowest jet width at the orifice, measured in the parasternal long axis view, is 0.6 cm, consistent with moderately-severe MR

EROA calculation using the PISA may be cumbersome, which can discourage its routine use. A simplified formula can be used if certain assumptions are made [26]. First, one assumes a pressure gradient between the LV and LA of 100 mmHg, which yields a mitral velocity (V_{MR}) of 5 m/s or 500 cm/s (from the Bernoulli equation, LV systolic pressure − LA pressure = $4V_{MR}^2$). If aliasing velocity (V_a) is set to 40 cm/s, then plugging these into the equation:

$$\text{EROA} = \frac{\left(6.28r^2 * V_a\right)c}{V_{MR}}$$

$$\text{EROA} = \frac{\left(6.28r^2 * 40\ \text{cm/s}\right)}{500\ \text{cm/s}}$$

$$\text{EROA} \oplus \frac{r^2}{2}$$

The vena contracta is the narrowest color flow at or upstream of the valve orifice [16]. For mitral regurgitation, it is typically assessed in the parasternal long axis view, and is considered to be independent of flow and pressure for a fixed orifice, even for eccentric jets (Fig. 11.8d). A vena contracta width of <0.3 cm is considered mild MR, and >0.7 cm is considered severe [16]. This parameter, when measurable, should always be considered a key component to the integrated approach to determining mitral regurgitation severity.

Other signs of severe MR are a triangular shape in the CW profile of the mitral regurgitant (early peaking) rather than a smooth parabolic profile, which implies rapid equilibration of LV and LA pressure from severe MR [16]. In addition, in the mitral inflow PW profile, severe MR is typically associated with a tall *E* wave >120 cm/s. Stage 1 diastolic dysfunction pattern on mitral inflow virtually excludes severe MR. In severe MR, the elevated LA pressures during systole decrease the gradient between the LA and the pulmonary veins, so the pulmonary vein *s* wave may be blunted or even reversed.

Aortic Insufficiency

In the parasternal long axis view, the percentage of the LVOT width that the regurgitant jet occupies has been correlated with aortic insufficiency (AI) severity [16]. If the jet width in diastole occupies more than 65% of the LVOT diameter, then it is considered severe. However, just as with jet area in MR, jet width in AI is not valid for eccentric jets in which severity may be underestimated (Fig. 11.9a) [27]. The vena contracta is the narrowest neck of the jet at the level of the valve. The width of the vena contracta correlates with regurgitant orifice area and is unaffected by jet eccentricity [28]. To accurately measure the vena contracta width, a zoomed-in parasternal long axis view should be obtained that shows the flow convergence zone, the vena contracta, as well as the regurgitant jet in the LVOT. A vena contracta width ≥6 mm suggests severe AI (Table 11.4). The utility of this method is limited if there are multiple jets [16]. The PISA method has been applied for the calculation of the aortic regurgitant EROA. This measurement should be made in the apical 5 chamber or apical long axis view in early diastole but is technically more difficult to obtain than the PISA for MR. The same principle applies as with MR, in that the flow rate proximal to the orifice (aorta) which is the product of the hemisphere area and the aliasing velocity ($2\pi r^2 * V_a$) equals the flow rate distal to the orifice in the LVOT (EROA∗peak aortic regurgitant velocity). However, the color baseline is shifted up rather than down, as this is toward the direction of flow. EROA ≥0.3 cm^2 correlates with severe AI (Table 11.4). The simplified PISA method used for MR ($r^2/2$) does not apply to AI.

Pulse wave Doppler in the upper descending thoracic aorta from the suprasternal view can both qualitatively and quantitatively assess aortic regurgitation severity [27]. Holodiastolic flow reversal in the proximal descending aorta is specific for at least moderately-severe aortic insufficiency, and is considered to be the echocardiographic equivalent of the *Duroziez's sign* [16] (Fig. 11.9b). This is a much more specific finding if there is flow reversal is present when sampling in the abdominal aorta. The ratio of the reverse flow (diastolic VTI∗cross-sectional area of the aorta in diastole) to the forward flow (systolic VTI∗cross-sectional area of the aorta in systole) is proportional to the regurgitant fraction [29].

PHT of the aortic regurgitation jet reflects the rate of equalization between the aortic and LV pressures (Fig. 11.9c). Therefore, this PHT is not only influenced by the severity of aortic insufficiency but also by LV pressure, LV compliance, and afterload conditions. Hence, it may be the least reliable method for assessing regurgitation

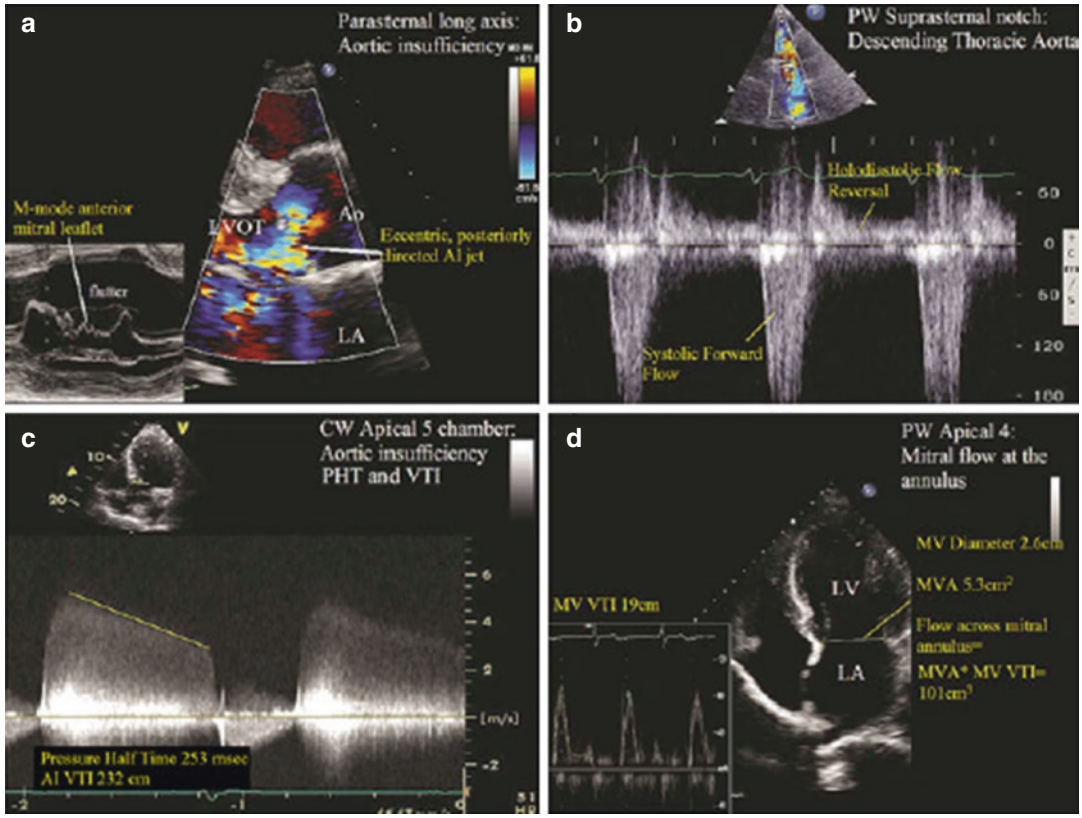


Fig. 11.9 Severe aortic insufficiency (AI). (**a**) Parasternal long axis view color Doppler demonstrates a very severe, eccentric, and posterior directed jet. Note that the M-Mode across the mitral leaflet shows fluttering of the anterior leaflet due to the aortic insufficiency jet (*lower left corner inset*). Given the eccentricity, one cannot use the LVOT jet area to assess severity. (**b**) Pulse wave Doppler with sample volume in the upper descending thoracic aorta, demonstrating holodiastolic flow reversal, a sign of severe AI. (**c**) Continuous wave Doppler across the aortic valve in the apical 5 chamber view. The PHT is 253 ms, consistent with severe AI. The aortic insufficiency VTI is 232 cm based on the CW profile. (**d**) Application of the continuity equation allows for the calculation of the regurgitant AI volume. Flow across the mitral valve plus the regurgitant volume should equal the flow across the aortic valve (Stroke volume). The MVA is determined by measuring the mitral valve diameter, and this area (5.3 cm^2) is multiplied by the MV VTI at the annulus (19 cm) to yield a flow of 101 cm^3. Flow across the aortic valve is determined by the product of the LVOT VTI and LVOT area, which yields a volume of 169 cm^3, calculation not shown. Therefore, the aortic insufficiency regurgitant volume is 169 cm^3 − 101 cm^3 = 68 cm^3, consistent with severe AI. The regurgitant orifice area (EROA) of the aortic valve is calculated by dividing the regurgitant volume (68 cm^3) by the AI VTI (232 cm), which equals 0.3 cm^2, also consistent with severe AI

severity [16]. A PHT <200 ms is supportive of severe aortic insufficiency, and a pressure half-time greater than 400 ms is unlikely to represent more than moderate AR. However, even in severe AI, if the LV has dilated as a chronic adaptation to the increased preload and afterload, then the pressure half-time could be normal since the LV and aorta pressures would not rapidly equilibrate. If vasodilators are given or LV pressures increase for a given degree of AI, the PHT would decrease.

The continuity equation can also be applied to aortic insufficiency if there is no more than mild mitral insufficiency. Think of the flow across the aortic valve as gross income, the regurgitant volume as the tax, and the flow across the mitral valve as the net income. The difference between the flow across the aortic valve ("gross" systolic stroke volume) and the flow across the mitral valve ("net" forward stroke volume) is equal to the "tax" or regurgitant volume per beat. The "gross"

Table 11.4 Stages of aortic insufficiency [16]

Stage	Definition	Valve anatomy	Valve hemodynamics	Hemodynamic consequences	Symptoms
A	At risk for AR	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis Diseases of the aortic sinuses or ascending aorta History of rheumatic fever or known rheumatic heart disease IE(infective endocarditis)	AR severity: none to trace	None	None
B	Progressive AR	Mild-to-moderate calcification Dilated aortic sinuses Rheumatic valve changes Previous IE	Mild AR: jet width <25% of LVOT; vena contracta <0.3 cm; RVol <30 mL/beat; RF <30%; ERO <0.10 cm^2; angiography grade 1+ Moderate AR: Jet width 25–64% of LVOT; vena contracta 0.3–0.6 cm; RVol 30–59 mL/beat; RF 30–49%; ERO0.10–0.20 cm^2;angiography grade 2 + _	Normal LV systolic function Normal LV volume or mild LV dilation	-None
C	Asymptomatic severe AR	Calcific aortic valve disease Bicuspid valve Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	Severe AR: Jet width ≥65% of the LVOT Vena contract>0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3–4+ LV dilation	C1: Normal LVEF ≥50% and mild-to-moderate LV dilation (LVESD ≤ 50 mm) C2: Abnormal LV systolic function with depressed LVEF (<50%) or severe LV dilatation(LVESD > 50 mm or indexed LVESD > 25 $mm.m^2$)	None, exercise testing is reasonable to confirm symptom status
D	Symptomatic Severe AR	Calcific aortic valve disease Bicuspid valve Dilated aortic sinuses or ascending aorta Rheumatic valve changes IE with abnormal leaflet closure or perforation	Severe AR: Jet width ≥65% of the LVOT Vena contract > 0.6 cm Holodiastolic flow reversal in the proximal abdominal aorta RVol ≥60 mL/beat RF ≥50% ERO ≥0.3 cm^2 Angiography grade 3–4+ LV dilation	Symptomatic severe AR may occur with normal systolic function (LVEF ≥50%), mild-to-moderate LV dysfunction(LVEF 40–50%), or severe LV dysfunction(LVEF <40); Moderate-to-severe LV dilation is present	Exertional dyspnea or angina or more severe HF symptoms

EROA effective regurgitant orifice area, *RV* regurgitant volume, *RF* regurgitant fraction, *DA* descending aorta, *LV* left ventricle

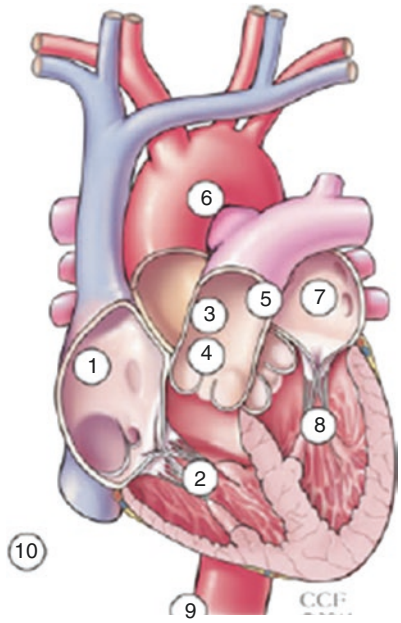
stroke volume can be obtained either from the LVOT VTI method or from the difference between the LV volumes in systole and diastole. To calculate "net" forward flow across the mitral valve, it is important to use PW and place the sample volume at the annulus of the mitral valve to measure and accurate flow across the mitral valve during diastole (Fig. 11.9d).

$$\text{Regurgitant volume}(\text{RV}) = \text{Stroke volume across aortic valve} - \text{Flow across mitral valve annulus}$$

$$\text{RV} = (\text{LVOT VTI} * \text{LVOT area}) - (\text{MV VTI}(\text{diastole}) * \text{MV annulus area})$$

$$\text{RV} = \left[\text{LVOT VTI} * (\text{LVOT diameter})^2 * 0.785\right] - [\text{MV VTI} * (\text{MV diameter})^2 * 0.785]$$

Once the regurgitant stroke volume is obtained, it can be divided by the regurgitant jet VTI obtained from CW in diastole to calculate the EROA [16]. If the EROA is in the severe range but the RV is not, it may be because in acute AI, the rapid increase in the LVEDP shortens the time for regurgitation, so the regurgitant volume may not be as large as expected from the EROA (Fig. 11.10).



1. RA=(0-5 mmHg) if IVC ≤ 2.1 cm and collapses > 50%
   RA=(10-20 mmHg) if IVC>2.1 cm and collapses <50%
2. RVSP=$4V_{TR}^2$+ RA
3. PASP=RVSP if no RVOT obstruction or PS
4. PAEDP=RA + $4(V_{EDPR})^2$
5. Mean PAP=$4(V_{Early\ DPR})^2$ OR 2(PADP)/3 + PASP/3
   PVR(Woods Units)=$10*(V_{TR}/\text{RVOT VTI}) + 0.16$
6. CO=(LVOT VTI)(LVOT D)^2(0.785)(Heart Rate)
7. LA=SBP+ $4(VMR)^2$ if no outflow tract obstruction or Aortic stenosis
   E/e'> 15 = PCWP >20; E/e'<8 =normal PCWP
8. LVEDP=DBP-$4(V_{EDAI})^2$
9. SVR>14 Woods Units if V_{MR}/LVOT VTI>0.27
10. Q_p/Q_s=[(RVOT VTI)(RVOT D)^2]/[(LVOT VTI)(LVOT D)^2]

Fig. 11.10 Summary of intracardiac pressure calculations. RA right atrial pressure, IVC inferior vena cava, RVSP right ventricular systolic pressure, V_{TR} peak tricuspid regurgitation velocity, PASP pulmonary artery systolic pressure, RVOT right ventricular outflow tract, PS pulmonic stenosis; PAEDP pulmonary artery end-diastolic pressure, V_{EDPR} end-diastolic pulmonary regurgitation velocity, PAP pulmonary artery pressure, $V_{EarlyDPR}$ early diastolic pulmonary regurgitation velocity, PVR pulmonary vascular resistance, VTI velocity time integral, LVOT left ventricular outflow tract, D diameter, LA left atrial pressure, SBP systolic blood pressure, V_{MR} peak mitral regurgitation velocity, PCWP pulmonary capillary wedge pressure, LVEDP left ventricular end-diastolic pressure, DBP diastolic blood pressure, V_{EDAI} end-diastolic aortic insufficiency velocity, SVR systemic vascular resistance, Q_p pulmonary flow, Q_s systemic flow. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011)

3D Echocardiography

The advent of 3D echocardiography has provided clinicians with more anatomic detail regarding valve structure and function. One arena in particular in which 3D echo provided value is the assessment of valves during valve interventions, either surgical or in the catheterization lab. For instance, 3D echo assists the operator in the transcatheter placement of the Mitra-clip for the treatment of mitral regurgitation. Beyond informing the clinical regarding anatomic structure and function, 3D echo has some limited clinical applications in the assessment of valve hemodynamics. In mitral stenosis, 3D echo can be used for measuring valve area. In addition, in the same way that a PISA is calculated using 2D echo, 3D Doppler can be used to assess the radius of the proximal isovelocity surface area. The 2D PISA assumes a hemispheric shape of the PISA, which may not be true in all regurgitant lesions, and, for example, in functional mitral regurgitation, the geometry may be more ellipsoid. By applying the hemi-ellipsoid formula for instance, the mitral regurgitation severity can be more accurately measured [30, 31]. *Although its current clinical application in valve hemodynamics is somewhat limited, with time this method will likely receive wider adoption.*

Review Questions

1. What is the estimated right ventricular systolic pressure (RVSP) in the patient in Fig. 11.4a if the inferior vena cava (IVC) measures 2.5 cm and there is no collapse with sniff?
   A. 60 mmHg
   B. 70 mmHg
   C. 30 mmHg
   D. 85 mmHg
2. What is the estimated end-diastolic pulmonary artery pressure in Fig. 11.4b?
   A. 14.4 mmHg
   B. 14.4 mmHg + RA pressure
   C. 38.5 mmHg
   D. 38.5 mmHg + RA pressure
3. Based on the continuity equation, what is the estimated aortic valve area (AVA) in Fig. 11.5? Is this severe AS or moderate AS?
   A. 1.2 cm^2, moderate AS
   B. 1.2 cm^2, severe AS
   C. 0.6 cm^2, severe AS
   D. 0.6 cm^2, moderate AS
4. The patient in Fig. 11.6 has a known secundum atrial septal defect, and as shown in panel (a), there is left to right flow across the atrial septal defect. The echocardiogram was performed to estimate the shunt fraction. Based on the information provided in Fig. 11.6, what is the estimated Q_p/Q_s ratio?
   A. 1:1
   B. 1.3:1
   C. 0.5:1
   D. 2:1
5. In Fig. 11.8, the regurgitant orifice area is 0.37 cm^2. Based on the information in panel (c), what is the estimated regurgitant volume per beat?
   A. 143 mL/beat
   B. 416 mL/beat
   C. 53 mL/beat
   D. 100 cc/beat

Answers

1. The peak TR velocity is 420 cm/s, or 4.2 m/s. Based on the simplified Bernoulli equation, the difference between the RV and RA pressure is $4V_{TR}^2$, or $4*(4.2)^2 = 70.56$ mmHg, roughly 70 mmHg. The RA pressure is estimated at 15 mmHg based on the dilated IVC that does not collapse greater than 50% with the sniff. Therefore, because the RVSP is equal to RA pressure plus the $4V_{TR}^2$, RVSP = 70 mmHg + 15 mmHg = 85 mmHg, compatible with severe pulmonary hypertension.
2. In Fig. 11.4b, the spectral Doppler shows the CW across the RVOT and pulmonic valve. From the pulmonary regurgitation jet, the late diastolic pulmonary regurgitation velocity represents the pressure difference between the pulmonary artery and the right ventricle at end diastole (note the timing just at the onset of the QRS). Therefore, the $4v_{PRed}^2$ = RVEDP − PAEDP. It

follows that PAEDP = RVEDP + $4v_{PRed}^2$. Because the RVEDP is equal to RA pressure, PAEDP = RA + $4v_{PRed}^2$. Here the end-diastolic velocity is 1.9 m/s. Therefore, PAEDP = RA + $4(1.9)^2$ = 14.4 mmHg + RA pressure.

3. Based on the continuity equation, AVA = [LVOT VTI ∗ (LVOT diameter)^2 ∗ 0.785]/[AV VTI]. The LVOT VTI from Fig. 11.5b is 28.1 cm, and the LVOT diameter from Fig. 11.5a is 1.9 cm. The highest AV VTI was obtained from the right sternal border view, which is 124 cm. Note that this corresponded to a peak and mean gradient of 119/74 mmHg, severe aortic stenosis (AS) by gradients. Using the continuity equation, AVA = [28.1 ∗ $(1.9)^2$ ∗ 0.785]/[124] = 0.6 cm^2, also compatible with severe AS.
4. The ratio of pulmonary blood flow to systemic blood flow is the Q_p/Q_s, or shunt fraction. The systemic blood flow (Q_s) is estimated by multiplying the LVOT area, (LVOT D)^2∗0.785, by the LVOT VTI. As shown in Fig. 11.6c, the LVOT diameter is 2.1 cm and the LVOT VTI is 13.2 cm. Therefore, the systemic flow is $(2.1)^2$ ∗ 0.78 5 ∗ 13.2 = 45.7 cm^3. The pulmonary blood flow (Q_p) is estimated by multiplying the RVOT area, (RVOT D)^2∗0.785, by the RVOT VTI. As shown in Fig. 11.6d, the RVOT diameter is 2.47 cm and the RVOT VTI is 12.3 cm. Therefore, the pulmonary blood flow is $(2.47)^2$ ∗ 0.785 ∗ 12.3 = 58.9 cm^3. The Q_p/Q_s ratio is 45.7/58.9 = 1.3:1. Note that because the 0.785 constant is present in both the numerator and denominator, the Q_p/Q_s calculation can be simplified to [(RVOT D)^2 ∗ (RVOT VTI)]/[(LVOT D)^2 ∗ (LVOT VTI)].
5. The regurgitant volume is equal to the product of the regurgitant orifice area (EROA, cm^2) and the MV VTI (cm). In this case, the product of the EROA (0.37 cm^2) and the MV VTI (143 cm) gives a regurgitant volume of 53 mL/beat, which is consistent with moderately-severe MR.

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CT and MRI Cardiovascular Hemodynamics

12

Andrew O. Zurick

Introduction

Noninvasive cardiac imaging has experienced dynamic improvements over the past several decades. Multiple, complementary technologies, including magnetic resonance imaging (MRI), computed tomography (CT), echocardiography, nuclear scintigraphy, fluoroscopy, and angiography, are now capable of directly or indirectly providing information on cardiac and great vessel anatomy, volumes and function, myocardial perfusion, valvular morphology and function, coronary artery blood flow, and presence or absence of myocardial fibrosis or scar. Further, several of these technologies now are capable of providing a noninvasive hemodynamic assessment, which has otherwise primarily in the past been the domain and strength of echocardiography and invasive catheterization. Both CT and MRI have been proven to be accurate and reproducible, with each now capable of providing noninvasive hemodynamic information which is capable of enhancing clinical decision-making and impacting patient care. However, the use of this information must be based on a thorough knowledge of the strengths and weaknesses of the various noninvasive methods of hemodynamic assessment. Understanding the applications and limitations of these modalities will permit their effective and efficient usage in the future (Table 12.1).

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General Overview of MR and CT Physics and Techniques

Physics Overview

MRI is based on the resonance, or increased amplitude of oscillation of a system exposed to a periodic force, of atomic nuclei. Following the application of radio waves, MRI measures the electromagnetic signals that are emitted from atomic nuclei. Hydrogen is the most simple and abundant element in the human body, consisting of a single proton and electron, and therefore, it represents an ideal substrate for clinical MRI. There exists a unique relationship between electricity and magnetism, namely moving electrical charges are capable of generating a magnetic field, and a time-varying magnetic field can create electric fields that can promote the flow of electrical charges. Atomic nuclei of several atoms behave as small magnets with angular momentum, and when placed within a magnetic field, they have a tendency to align with the direction of an electric field applied, and process, or rotate, about their own axis, as would a top.

Most current clinical MRI involves superconducting magnets, where a magnetic field is

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_12

Table 12.1 CT and MRI advantages and disadvantages

	Advantages	Disadvantages
Computed tomography	Rapid image acquisition	Radiation exposure
	Excellent spatial resolution (<1 mm)	Potential need for iodinated contrast dye
	3D dataset acquisition for ability for post-processing/reconstruction	Limited temporal resolution (best temporal resolution with current generation scanners on order of 75 ms)
	Typically well tolerated by patients	Limited hemodynamic assessment options currently
	Not contraindicated in patients with ferromagnetic/metallic implants	
Magnetic resonance imaging	Tissue characterization	Increased image acquisition time
		Potential for patient claustrophobia
	Excellent spatial resolution (1–2 mm)	Possibility, although rare, for NSF following gadolinium contrast administration
	Temporal resolution better than CT (typically 25–50 ms)	Inability to image patients with absolute contraindications including those with ferromagnetic implants (i.e., pacemakers, ICDs, intracerebral vascular coils, etc.)
	Unlimited imaging plane orientation and ability to acquire 3D datasets	
	No need for contrast (i.e., can be performed on patients with decreased GFR)	
	Increased ability to assess cardiovascular hemodynamics noninvasively via volumetric and phase-contrast analysis	

generated perpendicular to an electrical current flowing along a cylindrical coiled wire. The creation of MR images involves the excitation of protons, within a magnetic field, using pulses of radiofrequency energy, which can be specifically applied to body parts of interest through the concurrent application of magnetic field gradients. Following excitation of a tissue, a signal is created within a "receive" coil, which subsequently undergoes analog-to-digital conversion (ADC), which is then processed by the MRI computer as raw data into "k-space." The "Fourier transform" of the raw data ultimately generates 2D or 3D MR images that can be viewed for interpretation. MR imaging of the heart must contend with both cardiac and respiratory motion, conflicting requirements for both high temporal and spatial resolution, and do all of this both accurately and reproducibly in the clinical setting, in a timely fashion.

As with CMR, the small dimensions of the coronary arteries and rapid motion of cardiac structures pose significant challenges to effective imaging with cardiac computed tomography (CT). Current generation multirow detector CT (MDCT) scanners involve a rotating X-ray source, which emit photons, which pass through a patient, as they are moved through the machine gantry. Due to continued improvements in gantry rotation times, and the development of dual-source CT, temporal resolution has improved. Slice collimation, or thickness, has also continued to improve, resulting in greater spatial resolution. Increased X-ray tube strength has also resulted in decreased image noise and recent generation scanners have continued to improve simultaneous slice acquisition, now up to as many as 320 slices per rotation, which allows one to cover a larger volume per rotation, decrease overall data acquisition time, and reduce duration of required breath hold. Through the simultaneous registration of the ECG, it is possible to synchronize image reconstruction with the relative cardiac phase. Ongoing developments in tube-current modulation, prospective ECG-gated scanning, and improved table pitch (speed with which the patient table is advanced through the scanner) continue to lower patient radiation exposure (effective dose).

MRI Techniques

Phase-Contrast Imaging

Phase-contrast imaging (PCI) is an MRI technique for quantifying velocity and blood flow in the heart, across valves, and through great vessels. By measuring the phase shift, or change in precessional frequency, of protons in blood as they move through a magnetic field with a bipolar gradient, velocity, direction, and volume of blood flow can be determined. The amount of relative phase difference is proportional to the velocity of the moving spin, and these phase shifts are measured in degrees within a range of ±180°. Similar to aliasing velocity in Doppler echocardiography, the encoding velocity (VENC) chosen for this technique should optimally be chosen to correspond to a phase shift of 180°. If the phase shift exceeds 180°, then the spins will be interpreted as having a different orientation, which would therefore result in abnormal velocity interpretation. Ultimately, phase-contrast MR imaging produces velocity-encoded images where signal intensity is proportional to the velocity of blood moving through or within the slice plane. Unlike echocardiography, which is constrained by acoustic windows, PCI, utilizing a single imaging plane that is most commonly perpendicular to the direction of blood flow, generates a velocity-encoded image of multiple phases of the heart cycle either with or without breath-holding. No intravenous contrast is necessary to generate these images. Quantification of blood flow is subsequently determined by various software applications that require the user to manually outline the vessel of interest for each cardiac phase, which then produces time-velocity and time-flow curves (Fig. 12.1a,b). Many studies have now demonstrated the reliability of PCI with CMR; however it must be noted that the accuracy of the technique can be significantly affected by the presence of eddy currents [1].

Myocardial Tagging

Myocardial tagging is a series of techniques that impose a saturation grid or series of saturation lines across the myocardium [1]. Deformation of these lines due to myocardial contraction and relaxation are then monitored and can be used to assess myocardial function by tracking the motion of the myocardium during the various phases of the cardiac cycle [2] (Fig. 12.2). When combined with cine imaging, myocardial tagging can provide complementary information regarding myocardial contraction, performance, and can be used to measure myocardial strain in three dimensions. In clinical practice, myocardial tag lines are typically evaluated subjectively to differentiate normal and hypokinetic myocardial segments. While predominantly used as a supplementary technique to cine imaging to evaluate cardiac wall motion, the research applications of myocardial tagging are continuing to evolve, particularly with recent advances in image acquisition speed and improved signal-to-noise ratios.

Volumetric and Functional Assessment

Through continued improvement in hardware and software, MRI has evolved into the "gold standard" for ventricular volumetric and function assessment owing to its excellent accuracy and reproducibility. With manual or automated contours of multiphase, ECG-gated epi- and endocardial contours, ventricular volumes, function, and mass can be determined. In addition, while Doppler echocardiography has typically been considered the reference standard for assessment of diastolic dysfunction, recent studies have also demonstrated the utility and reproducibility of CMR techniques for flow and phase-contrast data analysis to extract velocity-related diastolic parameters [3]. The degree of myocardial fibrosis is related to the degree of left ventricular stiffness. Malaty et al. evaluated 50 patients with dilated cardiomyopathy (DCM) with Doppler echocardiography and breath-hold segmented inversion recovery sequence imaging following intravenous gadolinium administration to determine amount of left ventricular scar burden. Hyperenhancement (HE) was present in 31 patients with a mean scar burden of 4 ± 7.6%, and patients with DCM without HE had significantly higher septal E/E' ratio than patients with scar ($p = 0.05$) suggesting that factors other than scar burden likely contribute to LV stiffness to a greater extent than replacement fibrosis in this

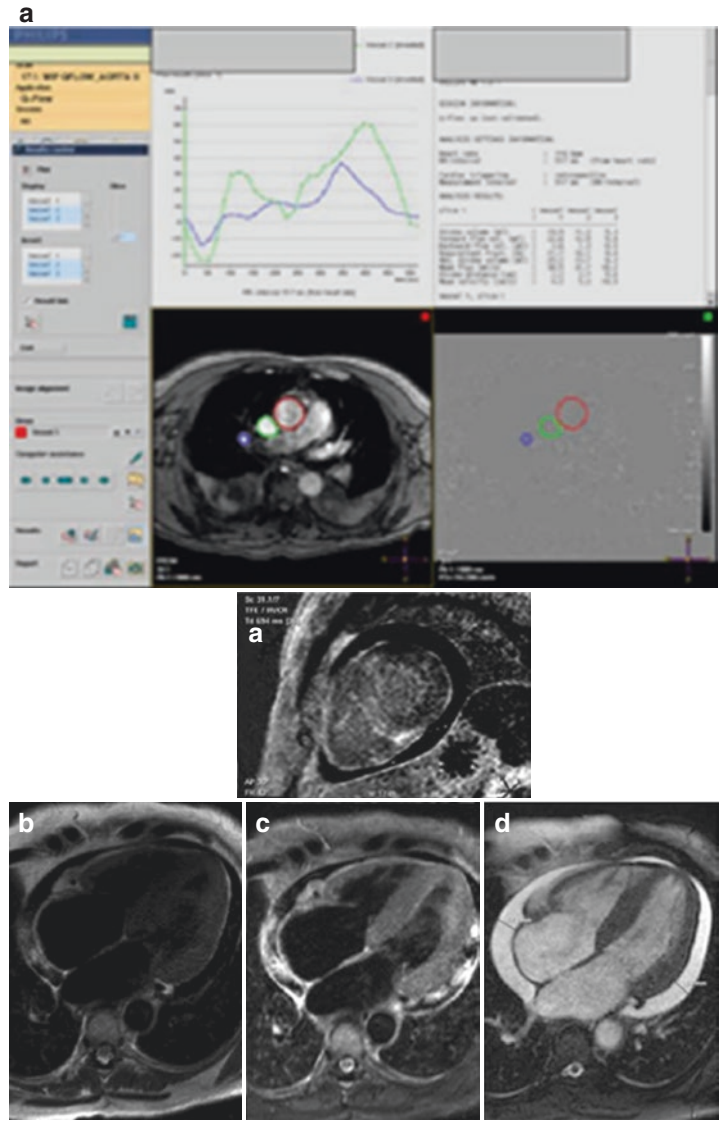

Fig. 12.1 (**a**) Cardiac amyloidosis. Image at *top* are from representative phase-contrast image demonstrating manual contouring of the ascending aorta, superior vena cava, and right upper pulmonary vein. Flow curves in *upper left panel* demonstrate systolic blunting consistent with diastolic dysfunction. Images at *bottom* demonstrate tissue characterization of myocardium in cardiac amyloidosis, with associated circumferential pericardial effusion, through multiple different cardiac MRI pulse sequences. (**b**) Hypertrophic cardiomyopathy with severe systolic anterior motion of the mitral valve (SAM). Representative phase-contrast image (*top*) demonstrating manual contouring of the left ventricular outflow tract. Contours are propagated to images from multiple cardiac phases. Image at *bottom left* represents single cardiac-phase magnitude gradient echo image at end-systole. Peak left ventricular outflow tract velocity can be measured and converted to pressure gradient through utilization of modified Bernoulli equation

b

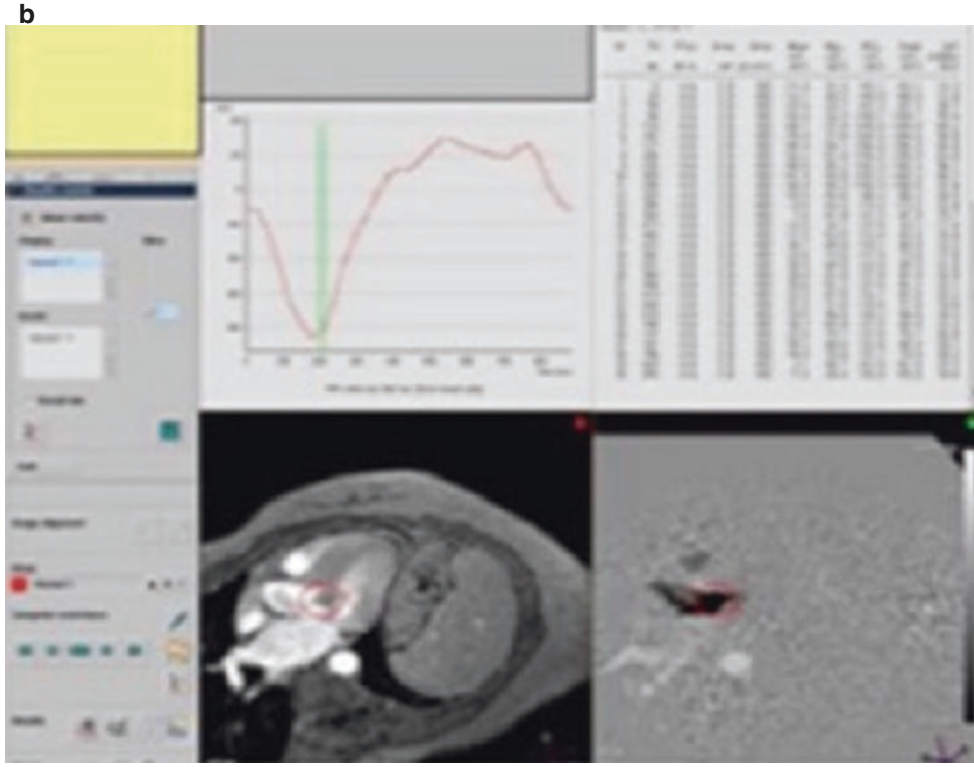

Fig. 12.1 (continued)

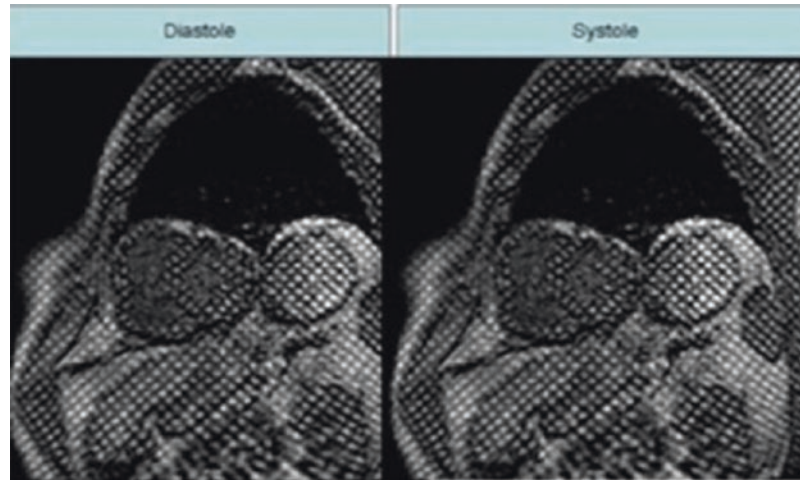

Fig. 12.2 Myocardial tagged image (short axis orientation) with saturation lines depicted across the myocardium in both systole (*right*) and diastole (*left*)

patient population [4]. However, other groups have also shown that cardiac fibrosis correlates with impaired LV diastolic function and functional capacity, elevated NT-pro BNP, and adverse cardiac remodeling in patients with non-ischemic DCM [5]. Other groups have utilized CMR phase-contrast velocity mapping (i.e., tissue phase mapping) to evaluate regional wall motion patterns and longitudinally and circumferentially directed movements of the left ventricle [6]. The complex pattern of ventricular twisting and longitudinal motion in the normal

human heart can be better understood through applications such as these, ultimately helping to provide a better understanding of the complex mechanics of the normal heart.

Stress cardiac MRI has continued to evolve and is capable of providing a multiparametric examination of cardiac function, perfusion, and valvular function and assessing for interstitial fibrosis or myocardial scar. Lipinksi M et al. performed a meta-analysis to understand the role that stress cardiovascular MRI plays in the assessment of patients with known or suspected coronary artery disease [7]. A total of 11,636 patients were evaluated, and those with ischemia were noted to have a higher rate of myocardial infarction or cardiovascular death compared with patients that had a non-ischemic study.

The combined outcome annualized events rates were 4.9% for a positive versus 0.8% for a negative stress CMR ($p < 0.0001$), 2.8% versus 0.3% for cardiovascular death ($p < 0.0001$), and 2.6% versus 0.4% for MI ($p < 0.0005$). The presence of late gadolinium enhancement was significantly associated with a worse prognosis. More recently, Liu A et al. published the first prospective validation of stress T1 mapping against invasive coronary measurements for detecting obstructive coronary artery disease [8]. Sixty patients with angina and 30 normal patients were imaged with CMR adenosine stress/rest T1-mapping. Ischemic viable myocardium downstream from obstructive CAD showed nearly abolished T1 reactivity, while myocardium downstream from non-obstructive coronary artery disease with microvascular dysfunction showed a lesser degree of blunting of T1 reactivity. This method of evaluating patients with coronary artery disease for ischemia may prove to obviate the need for routine intravenous gadolinium contrast administration.

Delayed Enhancement Imaging

The intensity of voxels in an MR image is a direct result of the amount of signal that can be measured by a receiver coil. MR intravenous contrast agents are useful for depicting anatomy and physiology, evaluating vascular supply to both normal and pathologic tissues, and assessing myocardial viability. Most MR contrast agents work by shortening T1 relaxation times, which results in increased signal intensity. The most commonly used MR contrast agents are chelates of gadolinium (Gd3+), a lanthanide heavy metal ion.

Inversion recovery imaging is capable of selectively suppressing signal from certain tissues based on their T1 recovery times and is useful for assessing myocardial infarction and viability. Following gadolinium administration, infarcted myocardium demonstrates a delayed pattern of gadolinium washout, and through the use of inversion recovery techniques, normal myocardium is "nulled" so that infarcted myocardium appears bright by comparison.

Tissue Characterization (T1- and T2-Weighted Imaging)

One of the unique features of cardiac MRI is the ability to characterize normal and pathologic tissues through the use of various pulse sequences. In addition to fat suppression and gadolinium contrast enhancement, T1- and T2-weighted imaging are the most widely utilized techniques. Tissues that tend to appear brighter on T1-weighted images include lipid, hemorrhagic products, proteinaceous fluid, and gadolinium. T2-weighted images of the heart help to characterize tissues with longer T2-times and are typically performed with concurrent blood nulling.

CT Techniques

ECG-Triggering

Through the simultaneous registration of the ECG, it is possible to synchronize CT image reconstruction with the relative cardiac phase. Due to cardiac and respiratory movements, motion artifacts can significantly affect cardiovascular CT images. Appropriate collimation size and image acquisition speed are important to obtain images free from artifacts. Currently, the collimation size for coronary artery calcium screening and angiography is 0.6–3 mm and acquisition speed ranges from 50 to 250 ms. Currently, two ECG-trigger techniques are utilized in cardiac CT

imaging, retrospective and prospective triggering. Prospective triggering can be performed with R wave triggering, end-systolic triggering, and both end-systolic and end-diastolic combined triggering. Alternatively, retrospective triggering is widely used and synchronized to an ECG signal that is recorded simultaneously with images. Changes in heart rate or rhythm can induce misregistration artifact in both prospective and retrospective triggered images.

Contrast Media

The primary purpose of contrast media injection is to increase contrast between the structure of interest and surrounding tissues by increasing the CT Hounsfield units. Care must be taken regarding circulation time for contrast media, the time interval that it takes blood to move from the point of venous access, the structure/region of interest, with several factors having influence, including cardiac output, injection rate, and venous anatomy. Circulation time can be measured using a small contrast bolus injection with serial scanning of a single image slice to obtain peak enhancement time through the time density curve. Alternatively, automatic bolus triggering utilizes a monitoring scan obtained 10–12 s following the start of contrast injection, and when the Hounsfield unit (HU) reaches a pre-specified threshold (typically 120 HU), imaging is initiated.

Clinical Applications

Shunts

Cardiac MRI has become a valuable tool in the evaluation of both cardiac anatomy and quantification of physiologic function. CMR can detect, provide morphologic information about, and quantify both intra- and extra-cardiac shunts. Shunt volume can be calculated through the use of volumetric cine MR imaging or PCI. Provided that there is absence of concurrent valvular regurgitation, total forward flow through the proximal ascending aorta and main pulmonary artery can be utilized to determine shunt fraction (Shunt fraction % (Q_p/Q_s) = total PCI pulmonary artery volume flow (mL)/total PCI ascending aortic volume flow (mL)). Alternatively, shunt severity can be calculated by comparing the ratio of right ventricular to left ventricular stroke volumes (Q_p/Q_s), again provided that there is not significant simultaneous valvular regurgitation. In addition, MR angiography can provide excellent 3D anatomic examination of vessels including the presence of anomalous pulmonary veins.

Cardiac CT is a useful adjunctive imaging modality in the assessment of intra- and extracardiac shunts. It is typically reserved for patients with contraindications for CMR or when there are issues associated with severe claustrophobia. Excellent spatial resolution provides the ability to visualize interatrial and interventricular septal defects (VSDs) [9]. Cardiac CT permits detailed imaging the heart, but also affords additional assessment of several noncardiac structures including mediastinum, lungs, pulmonary artery system, aorta, esophagus, chest wall, and airways [10]. Previous studies have shown that cine CT, through evaluation of indicator dilution curves, provides a precise, noninvasive technique for measuring shunt lesions in congenital and acquired heart diseases [11].

Atrial Septal Defect

Atrial septal defect (ASD) is the most common shunt lesion detected de novo in adulthood [12]. Sinus venosus, septum secundum, and primum defects can clearly be identified with MR imaging in the transverse plane or along the short axis. Further, spin-echo MR imaging has been found to have a greater than 90% sensitivity and specificity for identification of atrial septal defects [13]. PCI enables more precise evaluation of both size and shape of atrial septal defects and permits more accurate quantification of the degree of shunting present [14, 15]. In addition, cardiac CT has been also shown to detect and characterize ASDs with high sensitivity (66–100%) and specificity (86–100%) [16] (Fig. 12.3).

Ventricular Septal Defect

VSD is the second most common congenital defect of the heart, accounting for nearly 20% of

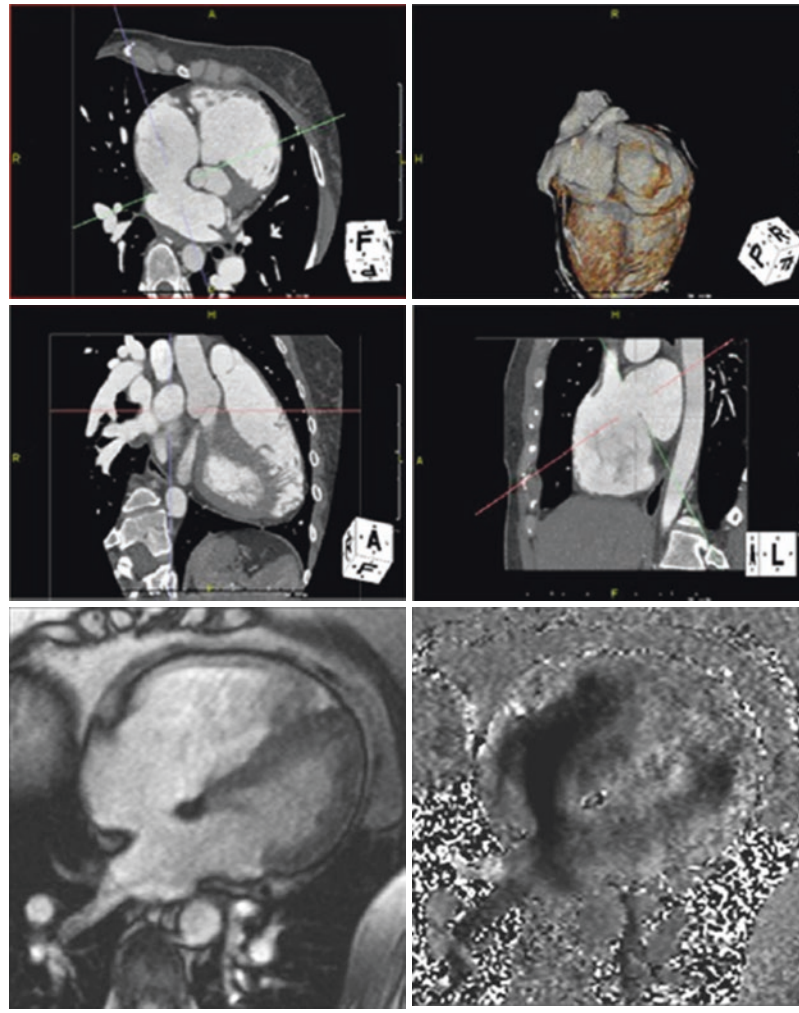

Fig. 12.3 ECG-gated cardiac computed tomography with iodinated contrast axial image demonstrating atrial septal defect (ASD), ostium secundum type (*top*). Cardiac MRI (*bottom*) steady-state free precession 4-chamber image demonstrating ASD, ostium secundum type (*right*), and phase-contrast image demonstrating left to right shunt across ASD (*left*)

all cardiac malformations [12]. VSD can be further categorized into four groups based on location and margin: outlet, membranous, trabecular, and inlet [17]. Membranous is the most common. MR imaging possesses greater than 90% sensitivity for the detection of VSD [18].

Atrioventricular Septal Defect

Atrioventricular septal defects present as a common atrioventricular valve with abnormal arrangement of the valvular leaflets, and variable defects in the primum atrial septum and ventricular inlet septum [19]. In the most severe form of atrioventricular septal defect, there exists bidirectional shunting, where all four chambers of the heart communicate. CMR is a particularly valuable tool in the evaluation of atrioventricular septal defects to delineate anatomical features which are important for surgical planning, cardiac chamber dimension, and presence and size of ventricular component of defects.

Patent Ductus Arteriosus

Before birth, the ductus arteriosus allows blood to bypass the baby's lungs by connecting the pulmonary arteries with the aorta. Patent ductus arteriosus (PDA) is a congenital disorder within the great vessels wherein a neonate's ductus arteriosus fails to close after birth. PDA accounts for 10–12% of all congenital heart disease [12].

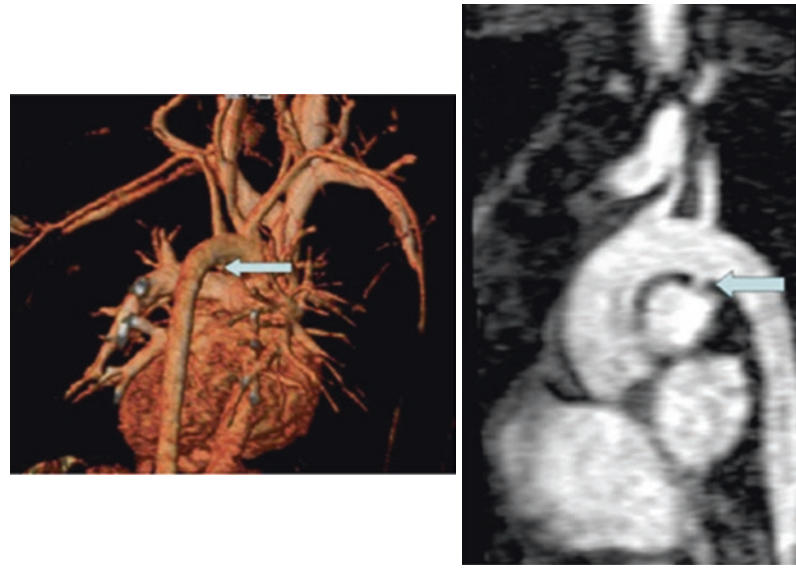

Fig. 12.4 Patent ductus arteriosus. Image at right is 3D, volume rendered MR image of PDA (*arrow*). Image at *left* is MR angiography sagittal image demonstrating PDA in an alternate orientation (*arrow*)

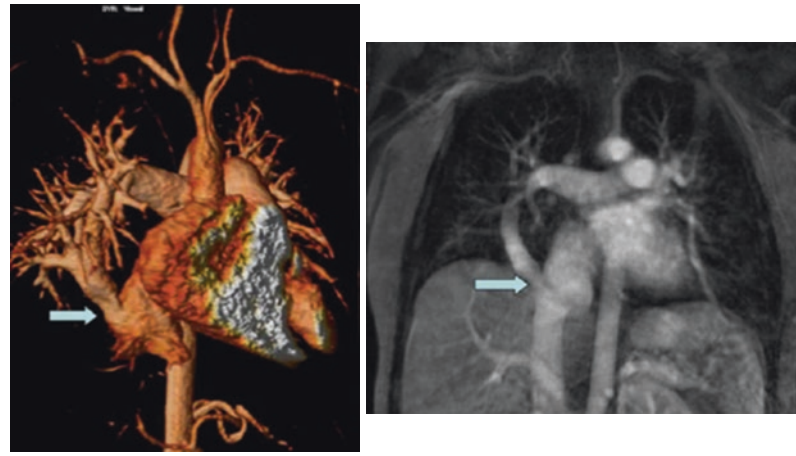

Fig. 12.5 Scimitar syndrome patient (partial anomalous pulmonary venous drainage). Image at *left* demonstrates 3D volume-rendered MR image of anomalous pulmonary venous return with right inferior pulmonary vein draining via antrum on inferior vena cava. Image at right is coronal MR maximum intensity projection (MIP) depicting same

CMR is capable of clearly demonstrating the persistent communication between the aorta and pulmonary artery; however due to the often small size of these defects (<3 mm), echocardiography remains the primary diagnostic tool for their identification and evaluation (Fig. 12.4).

Partial Anomalous Pulmonary Venous Return

Partial anomalous pulmonary venous return (PAPVR) involves one or more pulmonary veins returning aberrantly to the superior or inferior vena cava, right atrium, or coronary sinus. PAPVR is present in 10–15% of patients with secundum-type atrial septal defects and 100% of patients with sinus venosus-type defects [19]. Children with PAPVR are typically asymptomatic, whereas adults with the condition will typically present with dyspnea and palpitations. CMR is a particularly attractive imaging modality for identifying PAPVR as it provides a large field of view and can be performed without ionizing radiation or contrast material. CMR has been reported to have greater sensitivity (95%) for identification of PAPVR compared with echocardiography and angiography [20] (Fig. 12.5).

Diastology

CMR is now playing an increasing role in understanding the physiology of diastolic function. CMR is capable of evaluating myocardium in both active and passive phases, providing insight into relaxation and compliance characteristics. Further, CMR through PCI can assess inflow and myocardial velocities. Previous studies comparing CMR to TTE in the assessment of diastolic function have shown that velocities of mitral valve flow (E and A wave) measured by CMR correlated well with TTE ($r = 0.81$; $p < 0.001$), but also demonstrated systematic underestimation by CMR compared to TTE [21, 22]. Myocardial tagging with CMR can provide complementary information regarding myocardial contraction performance and can be used to measure myocardial strain in three dimensions.

While not typically thought of as a reliable source for assessment of diastolic function, recent studies have demonstrated that CT is capable of providing information regarding cardiac diastolic function. Boogers et al. evaluated 70 patients who had undergone CT and 2D echocardiography with TDI. Good correlations were observed between cardiac CT and 2D echocardiography for assessment of E ($r = 0.73$; $p < 0.01$), E/A ($r = 0.87$; $p < 0.01$), E_a ($r = 0.82$; $p < 0.01$), and E/E_a ($r = 0.81$; $p < 0.01$). In addition, a good diagnostic accuracy (79%) was found for detection of diastolic dysfunction using cardiac CT [23]. Other groups have evaluated the arterial enhancement of the aortic-root lumen on contrast-enhanced CT and plotted its change over time to determine the time-enhancement curve. Nakahara et al. evaluated 30 patients with suspected coronary artery disease who underwent MDCT and echocardiography. On univariate analysis, the slope of the time-enhancement curve was found to correlate with the e' ($r = 0.686$; $P = 0.000$) and E/e' ($r = -0.482$; $P = 0.007$) ([24]).

Valvular Heart Disease

While echocardiography remains the primary first-line imaging modality for the assessment of valvular heart disease, over the past several years, complementary uses of cardiovascular MRI and CT for the assessment of valvular heart disease have been demonstrated. MRI and CT can provide a comprehensive assessment of cardiac valvular anatomy and function. MRI offers the additional capability of assessing blood flow through a variety of imaging sequences.

The unlimited imaging planes offered by cardiac MRI are advantageous for assessment of the complex mitral valve anatomy. The primary benefit of MRI for the assessment of mitral regurgitation is the ability to quantitate regurgitant volume in conjunction with ventricular volumes and function. The primary method for quantification of mitral regurgitation involves subtracting aortic forward flow (calculated from aortic phase-contrast imaging) from the left ventricular stroke volume. Quantification of mitral regurgitation with MRI correlates only modestly with echocardiography but offers lower inter- and intra-observer variability [25]. More recently however, some data has demonstrated discrepancy between mitral regurgitation severity calculated by echocardiography compared with MRI [26]. Some have argued that since LV volume reductions following mitral valve surgery were more closely related to regurgitant volumes measured by MRI rather than echocardiography, that MRI should be the preferred method of mitral regurgitation assessment [26].

Multi-slice computed tomography (MSCT), while not able to provide information of blood flow like MRI, can provide additional or complementary information on the assessment of mitral valve anatomy. Delgado V et al. evaluated 151 patients with MSCT to assess the anatomy of the mitral valve subvalvular apparatus, mitral valve tenting height, and leaflet tethering [27]. The anatomy of the subvalvular apparatus was noted to be highly variable, particularly the posterior papillary muscle, involving multiple heads and insertion sites. Mitral valve tenting height at the central level and mitral valve sphericity index were the strongest determinants of FMR severity. With the continued growth in structural heart transcatheter therapies, MSCT will certainly play an increasing role in the pre-procedural planning of these complex cases over the coming years.

Further, MRI PCI has been demonstrated to help in the stratification of aortic regurgitant (AR) severity. Holodiastolic reversal in the mid-descending thoracic aorta using PCI has been shown to indicate severe AR and can be used with quantified regurgitant values obtained from PCI to further stratify AR severity [28].

One measure of severity of a valvular stenosis involves the peak transvalvular pressure gradient that is generated across the area of narrowing. For stenotic valvular lesions, PCI can be positioned through-plane or in-plane to estimate the maximum transvalvular velocity (V_{max}). As is seen with spectral Doppler echocardiography, if the imaging slice does not pass through the area of maximum velocity, then the pressure gradient, estimated using the modified Bernoulli equation (pressure gradient (mmHg) = $4 \times V_{max2}$), will be underestimated. Aliasing will have a similar appearance as in Doppler echocardiography, and if this is seen at the time of image acquisition, this sequence must be repeated using an alternate phase encoding velocity (V_{enc}). Additionally, PCI can also evaluate volume flow rates by measuring the mean velocity of blood across its lumen (V_{mean}) and multiplying by the cross-sectional area of the vessel lumen (volume flow (mL/s) = V_{mean} (cm/s) × area (cm^2)).

Aortic valve stenosis continues to be one of the most common valvular disorders in older adults with a prevalence of 8% at age 85 [29]. Open surgical aortic valve replacement is the only treatment that has been demonstrated to improve symptoms, survival, and functional status [30]. However, certain patient subsets are deemed high-risk for surgical repair, which lead to the development of transcatheter aortic valve replacement (TAVR). CT now plays a vital role in assessing patients prior to percutaneous aortic valve implantation. 3D reconstructed multi-planar images allow assessment of the aortic valve in multiple phases of the cardiac cycle and permit direct valve and annular area planimetry (Fig. 12.6). These measurements tend to be slightly larger than what is reported by 3D transesophageal echocardiography. Additionally, cardiac CT permits estimation of optimal valve implantation angles via fluoroscopy in the catheterization laboratory. Further, ECG-gated imaging of the thoracic aortic permits accurate assessment of aortic anatomy and morphology. Contrasted imaging of the abdominal aorta and peripheral arteries is also very important for determining whether the peripheral arteries are large enough to accommodate the large diameter of the delivery catheters. The results of the PARTNER trial have shown that at 1 year, the rate of death from any cause was 30.7% with TAVR, compared to 50.7% with standard therapy. However, at 30 days, TAVR as compared to standard therapy was associated with a high incidence

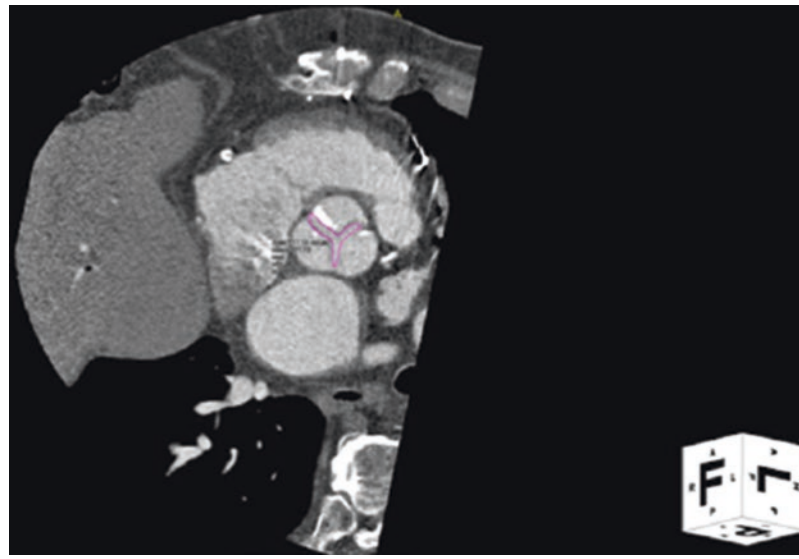

Fig. 12.6 Aortic stenosis. Cardiac CT 3D reconstructed multi-planar image of the aortic valve in short axis at end-systole with planimetry of aortic valve area

of major strokes (5 vs. 1.1%, $p = 0.06$) and major vascular complications (16.2 vs. 1.1%, $p < 0.001$) [31]. With the continued expansion of structural and valvular heart disease therapies in the coming years, CT will continue to play a larger role in pre-procedural planning.

CT is also capable of assessing ventricular volumes on multiphase-gated images to help in the determination of ventricular dilatation with regurgitant valvular lesions. Further, in patients with mechanical valves, CT provides a rapid, low-radiation exposure technique to image the valve in multiple phases of the cardiac cycle to determine opening and closure angles.

Cardiomyopathies

CMR provides excellent qualitative as well as quantitative assessment of ventricular function. When compared with Doppler echocardiography, phase-contrast measurements correspond well, and show fair correspondence when compared with invasive techniques utilizing the Fick principle, indicator-ink method, or thermodilution [32, 33]. Volumetric and functional assessment of the ventricles typically involves retrospectively gated steady-state free precession imaging of the chambers either in short- or long-axis orientations. Utilizing post-processing software, contours of the epi- and endocardium are typically drawn manually for each imaging slice, though more recently with progressive developments in artificial intelligence (AI), contouring can now more commonly be done automatically and edited by a reviewer for accuracy. Post-processing software generates quantitative data regarding cardiac function (ejection fraction, stroke volume, cardiac output), mass, and volumes. Alternatively, determination of cardiac output can be performed with phase-contrast imaging. By comparing cardiac output of the left ventricle in the ascending aorta with the cardiac output of the right ventricle in the main pulmonary artery, there is an internal control of these measurements, with gross differences typically indicating either unknown intra- or extra-cardiac shunt or more commonly, error in the initial prescription of the phase-contrast technique with either incorrectly selected imaging plane or phase encoding velocity.

CMR is now evolving as an important imaging modality in the assessment of patients with hypertrophic cardiomyopathy [34]. Cine imaging provides anatomic and morphologic assessment, allowing for measurement of myocardial wall thickness, papillary muscle anatomy, and left ventricular outflow tract obstruction. Phase-contrast imaging has proven useful in the assessment of gradients in patients with hypertrophic obstructive cardiomyopathy [35]. In patients with left ventricular outflow tract obstruction, PCI (both in plane and through plane) is useful to determine the peak velocity in a manner similar to Doppler echocardiography [34]. Post-gadolinium contrast delayed enhancement imaging also permits assessment of myocardium for scar. CMR also has proven useful in the evaluation of myocardial sarcoidosis [36], amyloidosis [37–39], and hemochromatosis [39, 40].

Through the simultaneous registration of the ECG, it is possible to synchronize image reconstruction with the relative cardiac phase with cardiac CT imaging. In patients with suspected or documented heart disease, precise, accurate quantification of cardiac function is vital for diagnosis, risk stratification, treatment, and prognosis. The same data that is acquired for coronary arterial evaluation, as part of coronary CT angiography, can also be used for evaluation of cardiac function. Previous studies have demonstrated that multiphase, gated cardiac CT demonstrates good correlation when compared with 2D surface echocardiography [41, 42].

Pericardial Disease

CMR is an excellent modality for assessing pericardial disease. CMR can accurately demonstrate pericardial thickness, effusion, pericardial cysts and through various pulse sequences, also demonstrate pericardial edema and/or inflammation. Real-time gradient-echo CMR in a single imaging slice can evaluate ventricular function with simultaneous respiration visualization and assess for

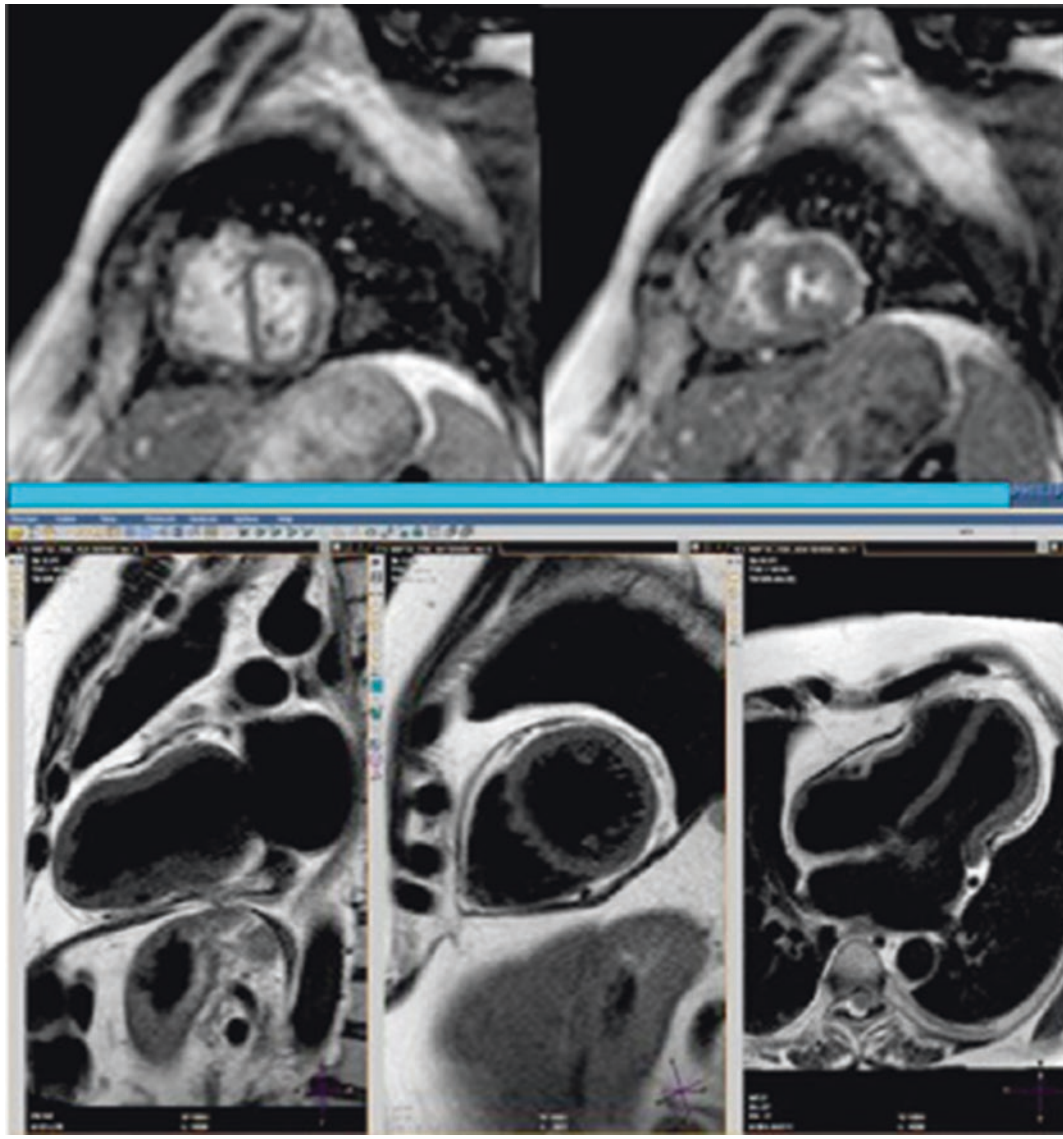

Fig. 12.7 Constrictive pericarditis cardiac MRI. Images at *top* demonstrate real-time free-breathing gradient echo short axis image of the left ventricle demonstrating ventricular interdependence in patient with constrictive pericarditis. Images at *bottom* are spin-echo "dark-blood" images in multiple orientations demonstrating pericardial thickening

ventricular interdependence that might suggest tamponade or constrictive physiology (Fig. 12.7). One area where CMR has significant limitations is in the assessment of pericardial calcification. Pericardial calcium causes significant susceptibility artifact on bright-blood cine MRI sequences.

Cardiac CT provides the ability, whether gated or non-gated, with iodinate contrast or without, to visualize the pericardium and assess and quantify pericardial thickening, calcification, or effusion. Multiphase, retrospectively ECG-gated cardiac CT imaging with iodinated contrast also allows for a functional assessment of interventricular septal motion and ventricular interdependence, although with a somewhat lesser temporal resolution (Fig. 12.9).

Vascular Hemodynamics

Vascular anatomy and pathology can be imaged using CMR with or without gadolinium-based contrast. Black-blood imaging provides excellent vascular anatomic detail with nulling of the blood pool. Alternatively, cine bright-blood CMR imaging provides additional information about vascular wall pathology and flow dynamics. First pass gadolinium-enhanced magnetic resonance angiography (MRA) can now be performed on nearly any MR scanner and produces high-spatial resolution images with broad anatomic coverage (Fig. 12.8). Artifacts with MRA may occasionally result in misdiagnosis of pseudostenosis in a vessel due to metal artifacts, susceptibility artifact from concentrated gadolinium, and volume averaging.

Phase-contrast imaging has also proven useful in the assessment of gradients across aortic coarctation [5]. With aortic coarctation, collateral flow can be assessed by measuring blood flow within 2 cm of the coarctation and above the diaphragm. In patients with significant coarctation, the flow within the coarctation increases toward the diaphragm due to retrograde perfusion of the dilated intercostal arteries, which are providing collateral circulation [43]. Additionally, measurements within the coarctation can help determine peak velocity and therefore pressure gradient within the stenosis. Pressure gradients greater than 20 mmHg measured during cardiac catheterization have been previously considered an indication for intervention [44].

Alternatively, CT angiography can also provide excellent spatial resolution when imaging arterial phase vascular images. Typically, vascular imaging with CT angiography does not necessitate ECG-gating, unless there is specific concern regarding the aortic root, which will typically be affected by cardiac motion artifact on non-ECG-gated images.

Fig. 12.8 3D volume rendered MR angiography image of aortic coarctation (*arrow*) with significant collateral vessels

Coronary Angiography

Through the simultaneous administration of intravenous iodinated contrast material, oral and intravenous beta-blockers to lower the heart rate, and sublingual nitroglycerin for coronary vasodilation, imaging of the coronary arteries has become increasingly feasible (Fig. 12.9). Several multicenter clinical studies have now shown the high diagnostic yield with coronary CT angiography, with sensitivities reported between 83% and 99% and specificities ranging from 93% to 98% [45]. Further, due to very high negative predictive values (95–100%), modern CCTA can be used to reliably rule out the presence of significant coronary artery stenoses.

While the strength of coronary CT is its excellent spatial resolution and anatomic definition, its most commonly cited weakness had been its inability to provide hemodynamic data. Coronary artery stenosis severity does not always correlate well with lesion functional severity at time of invasive FFR. Several studies have now been performed with coronary CT angiography that not only assess anatomy and morphology, but also provide functional physiologic information on coronary flow. New methods have been developed that utilize the anatomic data provided by CCTA in conjunction with computational fluid dynamic modeling that can calculate coronary fractional flow reserve (CT-FFR) from resting CCTA datasets [46], under estimated hyperemic flow conditions (Figs. 12.10 and 12.11). This provides for lesion-specific decreases in FFR, noninvasively. HeartFlow CT-FFR analysis uses an off-site, supercomputer, three-dimensional modeling technique and has now been validated against invasive FFR measurements and was approved by US Food and Drug Administration (FDA) for clinical use in 2014. Siemens Healthcare has also developed a one-dimensional analysis (cFFR) that can be performed at on-site workstations, but this technology is not yet commercially available as of the time of this writing.

During the past several years, multiple studies have been published that evaluated the diagnostic performance of CT-FFR and cFFR compared with invasive FFR as the reference standard [47–53]. Compared with CCTA anatomic assessment of stenosis severity alone, cFFR and CT-FFR

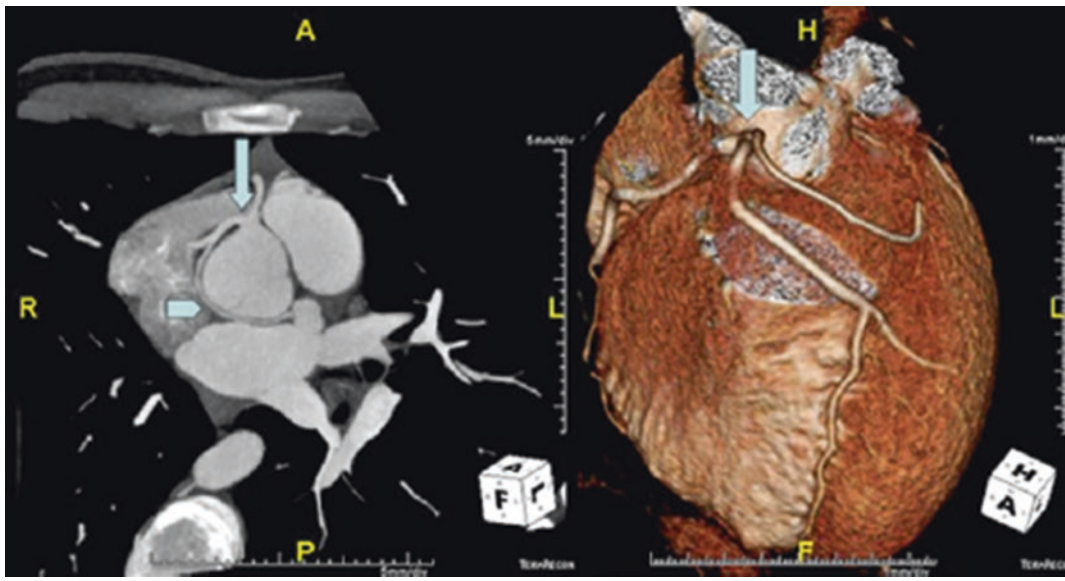

Fig. 12.9 Anomalous origin of the coronary arteries. Image at left demonstrates a maximum intensity projection (MIP) image of a common origin of both the left and right coronary arteries from a single, common ostium with the circumflex coronary artery passing retro-aortic (*arrowhead*). Image at left is a 3D volume-rendered image depicting same (*arrow*)

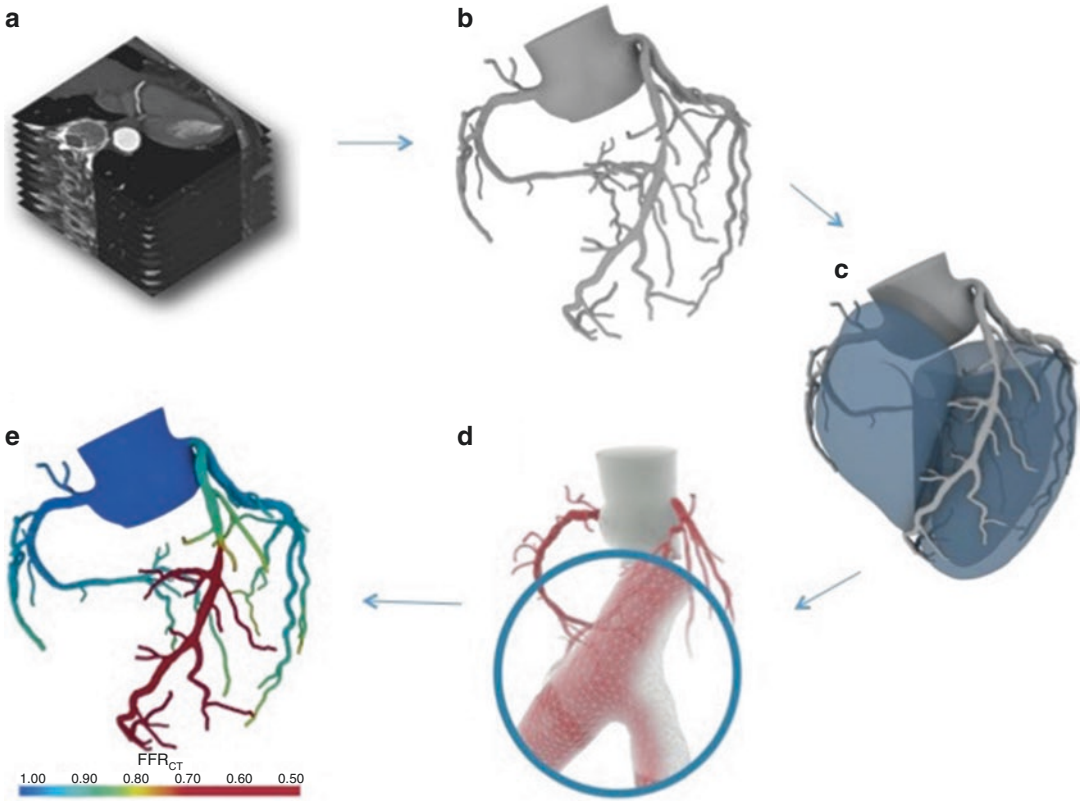

Fig. 12.10 (**a**) Coronary CT angiography image dataset, acquired using standard imaging protocol. (**b**) Image segmentation produces an anatomic model of the root of aorta and epicardial coronary arteries including all second and third order branchings to approximately 1 mm in diameter. (**c**) Physiologic model of coronary flow with specified inflow and outflow boundary conditions is created. Resting coronary flow is based on left ventricular myocardial volume extracted from CT image data and the microcirculation model is based on epicardial vessel size. (**d**) Computational fluid dynamics methods are used to simulate coronary blood flow under maximal hyperemia with simultaneous computation of coronary pressure and flow at millions of discrete points throughout the coronary tree. (**e**) Three-dimensional display of FFR_{CT} values in each coronary artery and its branches with color coding of numerical FFR_{CT} values as shown on the scale. (Images courtesy of Dr. Christopher Zarins, HeartFlow)

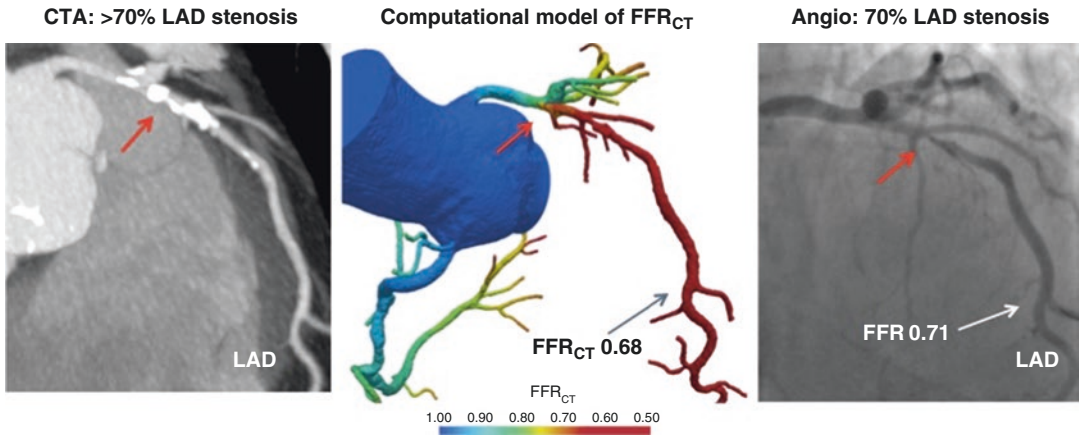

Fig. 12.11 CT-FFR. Case example. CCTA demonstrates heavily calcified LAD lesion with >70% stenosis. HeartFlow FFR_{CT} analysis shows functionally significant proximal LAD stenosis with FFR_{CT} 0.68. Coronary angiogram confirms 70% LAD stenosis with measured FFR 0.71. (Images courtesy of Dr. Christopher Zarins, HeartFlow)

both demonstrated improved test specificity. Good correlations with both cFFR and CT-FFR compared to invasive FFR were reported, ranging from 0.63 to 0.82. Certainly, overall image quality plays a vital role in overall CCTA imaging, and prior studies evaluating cFFR and CT-FFR have demonstrated that 10–13% of cases could not be utilized due to suboptimal image quality. In a sub-analysis of the NXT trial, among patients with CAC score 400, the accuracy, sensitivity, and specificity of FFR_{CT} for the determination of lesion-causing pressure drop were 75% (95% CI, 62%–84%), 88% (95% CI, 64%–97%), and 69% (95% CI, 54%–81%), which were higher than those of CCTA with 44% (95% CI, 31%–56%), 94% (95% CI, 79%–100%), and 23% (95% CI, 11%–37%), respectively [50].

Several groups have now started to look at the potential role of stress and rest myocardial perfusion imaging with CT [54–56]. Pontone G et al. evaluated 100 consecutive symptomatic patients scheduled for invasive coronary angiography with resting coronary CCTA and stress static computed tomography myocardial perfusion (CTP). Patients were evaluated for overall diagnostic accuracy and overall effective dose compared with those of invasive coronary angiography and FFR. Coronary CTA alone demonstrated a per-vessel and per-patient sensitivity, specificity, negative predictive value, positive predictive value, and accuracy of 98%, 76%, 99%, 63%, and 83% and of 98%, 54%, 96%, 68%, and 76%, respectively. Combining coronary CTA with stress CTP, per-vessel and per-patient sensitivity, specificity, negative predictive value, positive predictive value, and accuracy were 91%, 94%, 96%, 86%, and 93% and 98%, 83%, 98%, 86%, and 91%, with a significant improvement in specificity, positive predictive value, and accuracy in both models. The mean effective dose for coronary CTA and stress CTP were 2.8± 1.4 mSv and 2.5± 1.1 mSv [53].

Coronary artery disease remains the leading cause of morbidity and mortality in the industrialized world. While conventional coronary angiography remains the "gold standard" for evaluation of coronary arterial disease, it does possess limitations, namely its invasive nature, cost, and need for radiation and iodinated contrast exposure. Due to these limitations, alternative noninvasive imaging modalities have evolved for the evaluation of coronary artery disease that can avoid some of these undesirable attributes. While CT coronary angiography provides excellent spatial and temporal resolution, its use still requires patient breath-holding, exposure to radiation, and use of iodinated contrast agents. MR imaging of the coronary arteries does not require radiation exposure, can be performed either with or without administration of contrast material, and is capable of being accomplished with or without patient breath-hold. Similar to other noninvasive modalities, MR imaging of the coronary arteries is limited by both cardiac and respiratory motion. In addition, the small size and tortuosity of the coronary vessels, coupled with rapid spatial displacement and increased distance from the body or surface coils, present challenges for accurate imaging.

Initial studies with coronary MRA demonstrated that this technique was capable of accurate diagnosis of left main coronary artery and three-vessel disease [57]. With the continued development and improvement in MRI software and hardware, improvements in spatial resolution and image quality have been possible. Additional studies have now reported that contrast-enhanced MRA (CE-MRA) at 3.0 T is able to depict significant coronary artery stenoses with high sensitivity (94.6%), and negative predictive values of 98.5% and 97.7% on a per-segment and per-vessel basis respectively [58]. Additional studies have compared the visual and quantitative analysis high-spatial resolution CMR perfusion at 3.0 T against invasively determined fractional flow reserve (FFR) [59]. At an FFR threshold <0.75 to define hemodynamically significant lesions, visual CMR analysis reported sensitivity and specificity of 0.82 and 0.94 ($p < 0.0001$), respectively.

Further developments in coronary artery imaging have come through the use of ECG and respiratory triggered, segmented, 3D data acquisition. During free-breathing, monitoring of diaphragmatic motion is performed by a unique navigator echo, and the decision to accept or

reject image data are made based on the position of the diaphragm [60]. In addition, stress-induced myocardial ischemia can now be assessed noninvasively with the use of blood oxygen level-dependent (BOLD) CMR [59]. Perfusion CMR imaging has been compared with quantitative coronary angiography (QCA) and fractional flow reserve (FFR). Futamatsu et al. evaluated 37 patients with perfusion CMR imaging, quantitative coronary angiography, and FFR. Myocardial perfusion reserve (MPR) using a cutoff of 2.06 was found to have sensitivity and specificity for identification of hemodynamically significant CAD (defined as FFR ≤0.75) of 92.9 and 56.7% respectively. Sensitivity and specificity of anatomically significant CAD (>50% diameter stenosis) were 87.2% and 49.2% respectively [61].

Future Directions

The future of cardiac imaging is dynamic. With ever-increasing advances in both hardware and software, cardiac MRI and CT will continue to evolve and improve. Increasing magnetic field strength coupled with multiphased array coils promises to improve CMR spatial resolution. Continued improvements in gantry rotation times, table pitch, X-ray tube strength, and improved simultaneous slice acquisition are all promising areas of improvement in cardiac CT technology at present. Additionally, the coming decade will likely see continued advancements in artificial intelligence and software processing algorithms. With these continued advancements, cardiac CT and MRI will continue to play an ever-increasing role in the noninvasive hemodynamic evaluation of our patients.

Review Questions

1. A 47-year-old female has developed increasing shortness of breath over the preceding 6 months. Transthoracic echocardiogram has demonstrated severe ventricular hypertrophy. Subsequent cardiac MRI is performed to assess LVOT gradients and papillary muscle morphology.

   Among the following, CMR can best evaluate diastolic dysfunction via:

   A. Phase-sensitive inversion recovery imaging (PSIR) post-gadolinium contrast.
   B. Phase-contrast imaging.
   C. Non-breath-hold T2-weighted axial images of the myocardium.
   D. Magnetic resonance angiography.

   Answer B: Phase-contrast imaging (PCI) is capable of assessing both inflow and myocardial velocities, and plotting flow curves relative to the various phases of the cardiac cycle. This modality can provide insight into both myocardial relaxation and compliance characteristics. PCI has been shown to correlate well with TTE in the assessment of diastolic function; however, it tends to underestimate velocities of mitral valve flow (*E* and *A* waves) compared to TTE.

2. A 69-year-old African American male previously underwent coronary artery bypass graft surgery and mitral valve repair 10 years ago. Over the past 9 months, he has developed increasing shortness of breath, lower extremity edema, and abdominal fullness. Transthoracic echocardiogram demonstrates septal bounce and tubular shaped left ventricle with atrial tethering. Subsequent cardiac MRI is performed to evaluate for constrictive pericarditis.

   Among the following, which method is most useful for evaluating for ventricular interdependence?

   A. Real-time gradient echo CMR.
   B. Breath-hold, four-chamber steady-state free precession cine imaging.
   C. Short-axis, breath-hold delayed-hyperenhancement imaging post-gadolinium contrast.
   D. Short-tau inversion recovery imaging (STIR).

   Answer A: Real-time gradient echo CMR typically provides a single image slice, the short axis left ventricle is most often chosen. Through simultaneous evaluation of both ventricular function with respiration, it is possible to assess for ventricular interdependence. Breath-hold, four-chamber steady-state free precession cine imaging is a good method for assessing ventricular function. Short-axis, breath-hold delayed-hyperenhancement

imaging post-gadolinium contrast has been shown to be an effective method for evaluating for active pericardial inflammation; however, this in and of itself does not necessarily reflect evidence of constriction. Short-tau inversion recovery imaging (STIR) is an effective method for evaluating for myocardial and/or pericardial inflammation.

3. With cardiac CT, it is possible to synchronize image reconstruction with the relative cardiac phases via:
   A. Iterative reconstruction.
   B. ECG-triggering.
   C. Filtered back-projection.
   D. Myocardial tagging.

   Answer B: ECG-triggering, through the simultaneous registration of the ECG at the time of image acquisition, can allow for image reconstruction that is synchronized to the relative cardiac phase. ECG-triggering can be performed both prospectively and retrospectively. Iterative reconstruction is a method or group of algorithms used in 2D and 3D image sets. Filtered back-projection is also a reconstruction technique used for CT that applies a filter to the raw data collected during CT and attenuation information is simultaneously collected that are then utilized in image creation. Myocardial tagging is a cardiac MRI technique that applies saturation grid lines to the myocardium, and their subsequent deformation can be used to assess myocardial contraction and relaxation.
4. Shunt volume and shunt fraction (Q_p/Q_s) using MRI can be calculated through use of:
   A. Volumetric cine MRI.
   B. Phase-contrast imaging (PCI).
   C. Neither.
   D. Both A and B.

   Answer D: Both volumetric cine MRI and PCI can be used to calculate shunt volume and shunt fraction (Q_p/Q_s) provided that there is no significant concurrent valvular regurgitation. Specifically, total forward flow through the proximal ascending aorta and main pulmonary artery can be used to determine shunt fraction (Shunt fraction % (Q_p/Q_s) = total PCI pulmonary artery volume flow (mL)/total PCI ascending aortic volume flow (mL)) Alternatively, by using the ratios of the right ventricular to left ventricular stroke volumes, acquired by use of volumetric cine MRI, the shunt fraction can be calculated—provided there is again no significant simultaneous valvular regurgitation.
5. A 17-year-old girl is found to have bicuspid aortic valve by echocardiography. What imaging modality, among those listed below, would be best suited to assess for a common associated cardiovascular anomaly with this condition?
   A. CT.
   B. Chest X-ray.
   C. PET.
   D. MRI.

   Answer D: Patients with bicuspid aortic valve often have other congenital aortic and cardiac abnormalities [62]. The most common association is with coarctation of the aorta, which in autopsy series has been reported to be found in 6% of cases. Alternatively, 30–40% of patients with coarctation are subsequently found to have a bicuspid aortic valve. MRI not only is an excellent modality for assessing the aortic valve morphology and function, but also provides excellent spatial resolution and a large field of view (see Fig. 12.7) to evaluate noncardiac thoracic anatomy. While CT also is a versatile modality with excellent spatial resolution and broad field-of-view, the radiation exposure in this young patient is less than desirable. Chest X-ray is an indirect method of assessing for additional complications associated with coarctation such as notching noted along the ribs. PET has no significant role in imaging coarctation.

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13 Objective Evaluation of Hemodynamics in the Outpatient Setting

Gbolahan Ogunbayo and Ahmed Abdel-Latif

Introduction

Noninvasive hemodynamic (HD) monitoring offers a safer and relatively accurate means of monitoring patients' hemodynamics when performed appropriately. Beyond the potential benefit of determining volume status, noninvasive HD monitoring can be of value in evaluating the adequacy of cardiac perfusion and indirect assessment of cardiac index. Some of these HD parameters have been shown to predict or reduce heart failure admissions [1–6]. It can further reduce the complications associated with invasive hemodynamic monitoring [7, 8]. In the outpatient setting, noninvasive hemodynamic assessment helps to optimize medical therapy, titrate mediations, and identify heart failure patients who will require more aggressive therapies and mechanical support. Accordingly, the current American College of Cardiology Foundation/American Heart Association (ACC/AHA) guidelines for the diagnosis and management of patients with heart failure designates hemodynamic assessment in patients with heart failure a Class I indication [9].

Ambulatory hemodynamic monitoring can be done remotely or in an outpatient setting. Continuous remote monitoring usually requires implantation of a device and external equipment for remote (home) monitoring and transmission or on-site (office) measurement. Instantaneous monitoring can be done in an ambulatory (office) setting. Compared to standard scheduled office visits/audible device alerts, remote monitoring has been shown to reduce emergency department or unplanned/urgent office visits by allowing early and rapid detection of events requiring attention and action [10, 11].

History and Physical Examination

Assessment of volume status is an integral part of management and begins with a thorough and systematic history and physical examination. History focuses on severity and changes in symptoms, response to therapy and inquisition about possible etiologies. Although the cardinal symptom of left ventricular failure is shortness of breath (SOB), a patient may present with a myriad of other symptoms in isolation or combination with SOB including cardiac symptoms such as chest discomfort, palpitations, progressive/worsening dyspnea on exertion or at rest, orthopnea, or paroxysmal nocturnal dyspnea. Exertional dyspnea may not be

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_13

evident in sedentary patients. A (usually productive) cough is not uncommon due to pulmonary edema and irritation. Downstream effects of congestion include symptoms related to hepatic congestion such as jaundice and other features of resultant hepatic dysfunction as well as pedal edema and resultant symptoms including skin changes. Additional presentations/complaints of cardiac decompensation include weakness, fatigue, symptoms of cerebral hypoperfusion including mental status changes, weight loss (cardiac cachexia), nausea, anorexia, bloating, and early satiety.

Physical findings of volume overload may be subtle or overwhelming depending on the degree of volume overload. Vitals may reveal low blood pressure and even low body temperature from reduced cardiac output. Decompensated patients may have a fast and thread-like pulse. Cardiac signs may include inability to lay flat even during the examination, displaced apical impulse that suggests cardiomegaly, elevated jugular venous pressure (JVP), S3 gallop, pulsus alternans, murmurs, or mitral and tricuspid regurgitation from ventricular enlargement. Pulmonary signs include wheezing, rhonchi, reduced air entry, and crackles. Patient with severe heart failure may exhibit signs of reduced cerebral perfusion and include SOB with use of accessory muscles, anxiety, somnolence or confusion. Other signs on physical examination are cachexia with evidence of malnutrition, cyanosis, distended neck veins, exophthalmos jaundice, ascites, and hepatomegaly that may be tender and pedal edema.

Chest X-Ray

Chest X-ray is a quick and noninvasive tool to assess for pulmonary edema in patients with heart failure. The classic signs of pulmonary edema on a chest X-ray include pulmonary vascular congestion and pleural effusion. However, it is important to note that patients with advanced heart failure may not exhibit the classic signs of pulmonary congestion on chest X-ray despite elevated pulmonary capillary wedge pressure. Thus, chest X-ray is not always a sensitive tool in assessing heart failure and could lag behind other methods such as invasive assessment and physical examination.

Echocardiography

Echocardiography is another noninvasive and quick methods to assess cardiac function and estimate hemodynamics in patients. Classical findings of elevated left ventricular filling pressure include high E/e' ratio (the ratio between the velocity of blood inflow through mitral valve and the tissue Doppler velocity at the mitral valve annulus). This concept has been challenged in new studies and the consensus is to avoid complete reliance on this finding specially in patients with advanced heart failure [12]. Dilated inferior vena cava (IVC) on echocardiography has the highest predictive value for decompensated heart failure and elevated PCWP compared to clinical congestion, elevated JVP, and elevated biomarkers. The addition of echo to the clinical and laboratory tests has an extremely high correlation with invasive PCWP assessment [13].

Biomarkers

Natriuretic peptides are a group of plasma peptides that have been measured routinely in clinical practice to guide the diagnosis and management of patients with heart failure. This family includes B-type natriuretic peptide (BNP) and the N-terminal portion of the pro-brain natriuretic peptide (NT-proBNP). NT-proBNP is the biological inert byproduct of the degradation of pre-proBNP. NT-proBNP has been established as a biological marker in the diagnosis and staging of heart failure and has been recommended as a diagnostic tool by the American College of Cardiology/American Heart Association guidelines [14]. Additionally, BNP and NT-proBNP are important prognostic markers in patients with chronic heart failure [15]. Functionally, NT-proBNP hormone acts to promote natriuresis, diuresis and induce vasodilation [15]. The clearance of NT-proBNP occurs primarily in the

kidneys and the plasma levels are therefore affected by renal dysfunction. Careful consideration should be taken when using NT-proBNP levels for hemodynamic assessment in obese patients in which NT-proBNP levels tend to be low. On the other hand, NT-proBNP levels should be evaluated within the clinical context in patients with other conditions that could elevate their levels such as pulmonary disease. Nonetheless, the addition of NT-proBNP level to careful physical examination and history taking increases the clinical accuracy in diagnosing and managing patients with heart failure [15].

As detailed above, none of these methods provide ideal sensitivity and specificity for hemodynamic assessment in patients with heart failure. Therefore, multiple investigators and clinicians have utilized composite scores combining some or all of the above parameters to achieve better clinical decisions when treating heart failure patients. These scores have been shown to be highly predictive of mortality in heart failure patients and improve the specificity of clinical assessment [16, 17].

Continuous Pulmonary Vascular Pressure Monitoring

Continuous monitoring devices include pulmonary artery measurement, right ventricular (RV) pressure monitoring, left atrial (LA) pressure measurements and measurement of thoracic or cardiac (electrical) impedance via intracardiac device leads. Instantaneous hemodynamics may be obtained in the ambulatory/outpatient setting by thoracic bioimpedance, bioreactance, partial carbon dioxide rebreathing technique, portable Doppler flow measurement, and photoelectric plethysmography.

Implantable (Continuous) Sensors/ Monitoring Devices

Pulmonary Artery Monitoring

Changes in pulmonary artery pressure are good predictors of adverse clinical outcomes and hospital readmission in patients with heart failure [3, 18, 19]. In the absence of mitral valve stenosis, PCWP reflects the left ventricular filling pressure. Chronic pulmonary artery pressure monitoring can be achieved using the CardioMEMS™ HF System (CardioMEMS, Inc./St Jude Medical, Inc., USA) implanted in the pulmonary artery connected to a monitoring device by acoustic ultrasonic signals [20]. Multipe reports have confirmed the feasibility, ease of use, accuracy, and predictive ability in long- and short-term large-scale outcome studies [3, 18, 21–25]. This led to FDA approval of wireless implantable hemodynamic monitors for use in patients with New York heart association II–IV symptoms with a recent hospital admission. The goal of these devices in heart failure patients is to reduce heart failure admissions. This system consists of a sensor, an antenna, and interrogating devices (Fig. 13.1). The sensor is made of a coil and a pressure-sensitive capacitor, which both form a pressure-sensitive electric circuit that resonates at a specific frequency. Pressure applied to this unit causes a deflection that shifts the device's frequency which is electromagnetically coupled through an antenna held against the patient's body either with a wand for outpatient pressure measurement or through a pillow for ambulatory or home use [26].

Pulmonary artery pressure tracings from this system can be used as a marker of volume status to monitor and treat patients. Patients with heart failure and dilated left ventricles function at the end of the pressure-volume curve. Therefore, smaller increases in volume are more likely to cause significant and measurable increase in left ventricular end-diastolic and pulmonary pressures, leading to pulmonary edema. Similarly, heart failure patients with preserved ejection fraction and noncompliant ventricles respond to volume changes as described above, although through a different mechanism. Pulmonary artery pressure measurements can detect these small changes days before the onset of heart failure symptoms and need for heart failure admission. Implantation of the CardioMEMS™ device is safe and requires the initial use of dual

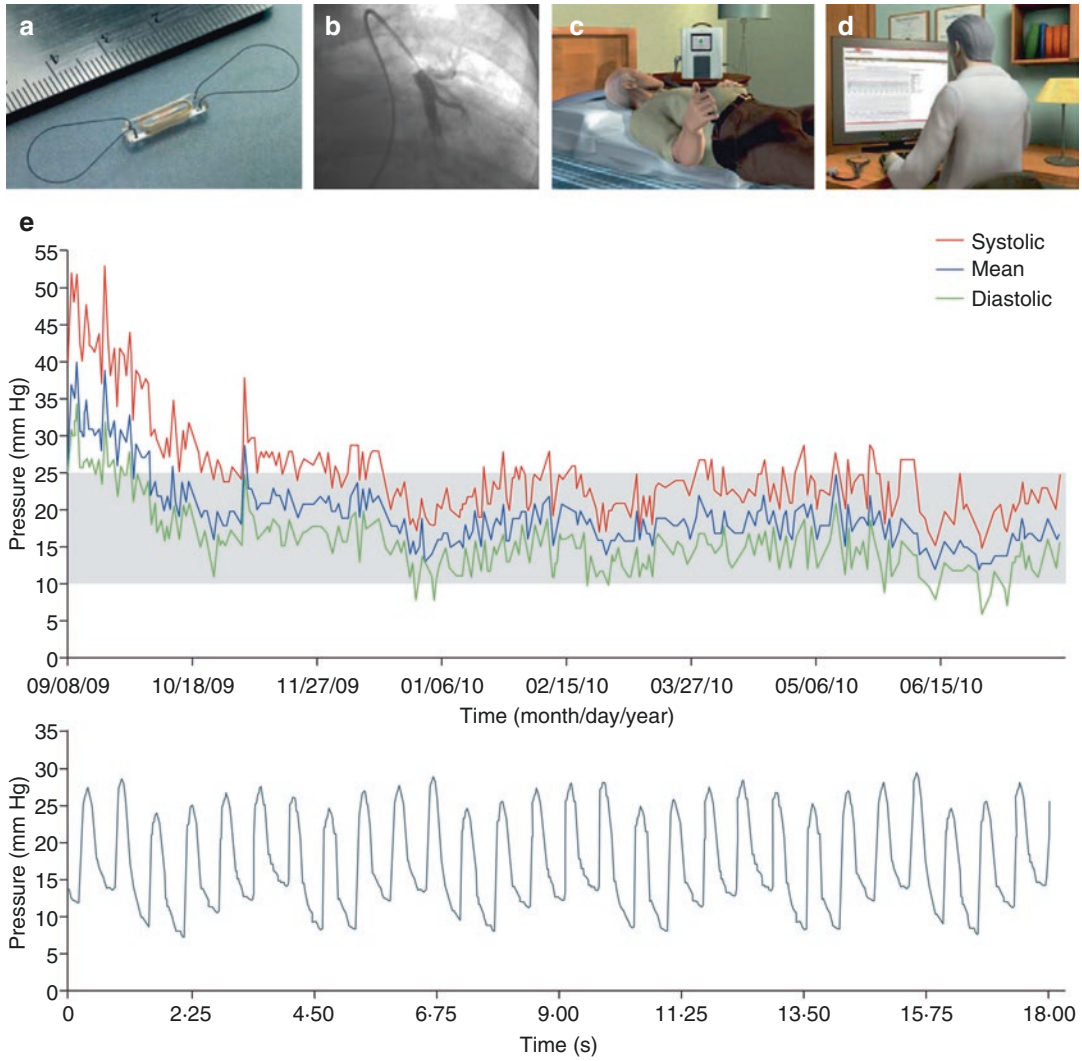

Fig. 13.1 The CardioMEMS™ HF implantable hemodynamic monitoring system. (**a**) CardioMEMS sensor or transmitter; (**b**) transcatheter implantation of the device into a distal branch of the descending pulmonary artery; (**c**) patient is instructed to take daily pressure readings from home using the home monitoring unit; (**d**) information transmitted from the monitoring system to the database is immediately available to treating physicians for review; (**e**) transmitted information consists of pressure trend information and individual pulmonary artery pressure waveforms and are available on the online portal for healthcare providers. (Adapted from Abraham et al. [3])

antiplatelet therapy for 1 month followed by lifelong aspirin use [27–29].

Advantages of this system include accuracy, reproducibility, ease of use, and the relative safe insertion and operation. The sensor does not require a battery and does not need to be replaced or refitted with a battery. Patient compliance with monitoring and medication adhesion are essential to achieve the proposed benefit.

Intracardiac Sensors/Monitoring Devices

Right Ventricular Pressure Sensors

There is no stand-alone right ventricular (RV) sensor device approved by the Food and Drug Administration (FDA). A trial of an implantable monitoring system, the Chronicle® ICD and

Chronicle® implantable hemodynamic monitor (Medtronic, Inc., USA) to measure RV hemodynamics and other parameters showed no clinical effectiveness and therefore it was not approved by the FDA [22].

Left Atrial Pressure Sensors

As with stand-alone RV sensors, there is no FDA-approved left atrial (LA) pressure sensor. An outcomes trial of an investigational LA pressure monitoring device, the HeartPod® (St Jude Medical, Inc., USA) showed feasibility and favorable short- and long-term performance. However, enrollment stopped early because of an excess of implant-related complications [30–32]. These studies, however, show that LA pressure monitoring devices have some promise in the ambulatory and remote management of patients with heart failure.

Intrathoracic Impedance to Measure Volume Status

Intrathoracic impedance is inversely related with volume status and pulmonary capillary wedge pressure. Aortic blood flow is the major determinant of thoracic impedance and therefore, impedance can be used to non-invasively assess cardiac stroke volume and cardiac output/index. These measurements correlate with invasive cardiac output/index [33]. Changes in intrathoracic impedance are noted days or weeks before the onset of symptoms or hospital admission in patients with heart failure [34]. The inverse relationship between intrathoracic impedance and volume accumulation is due to the increased electrical conductance through fluid medium. Feasibility of measuring thoracic congestion by thoracic impedance with the use of an implantable system was almost simultaneously described in human and canine models (Figs. 13.2 and 13.3) [34, 35].

Pacemakers and implantable cardioverter defibrillators (ICDs) are able to measure intrathoracic impedance in humans using the RV bipolar electrode, the LV lead, or ICD electrode. This is done

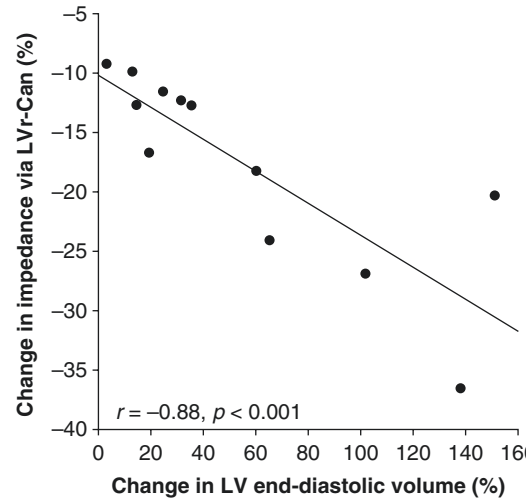

Fig. 13.2 Relationship between LVEDP and impedance. Data shown are for impedance recorded by left ventricular (LV) r–Can in 12 dogs. Correlation coefficient is calculated using Spearman rank order. (Adapted from Khoury et al. [36])

by injecting low-voltage, non-stimulating currents between the device casing and the electrodes. The LV lead has been shown to be the most sensitive to impedance changes in left atrium and left ventricular end-diastolic pressures (LVEDP) [36]. Different devices have patented software that monitor changes in impedance by establishing a baseline using sampling obtained over a period of time. Some programs are able to alert a patient and/or care provider when a predetermined or preset volume threshold is met. Monitoring this parameter has been shown to reduce hospital admissions in patient with heart failure [4, 23, 37, 38]. A 12-week period is required from implantation to impedance measurement. Shorter periods are required for replaced devices.

Advantages of intrathoracic impedance monitoring include the ease of use and the simplicity of the device without the need for additional equipment. When used appropriately and integrated in the clinical management of patients with heart failure, intrathoracic impedance can help reduce hospital admissions due to heart failure (Fig 13.6) [34]. It gives the patient and caregiver the opportunity to be proactive about alteration of hemodynamics and fluid status. Currently, with advances in battery technology,

the impact of impedance monitoring on battery life is small. Instantaneous (ambulatory) impedance measurement is usually inaccurate in settings where there are sources of electrical noise and body motion. Additionally, the system is very sensitive to positioning of the electrodes, body size, humidity, and temperature.

Impedance can also be measured in the ambulatory setting by placing electrodes/sensors on either side of the neck and thorax, two on either side (Fig 13.4). A pair of electrodes inject/transmit alternating electric current while the other pair senses and determines the thoracic impedance. There are two components of impedance: base impedance, which is based on tissue and air in the thoracic cavity and dynamic impedance, which is determined by changing blood volume and velocity in the thoracic aorta. All these parameters have different electrical properties, causing variations in electrical conductance. Ventricular function causes blood flow through the compliant arteries to be pulsatile, thus causing changes in blood volume in the aorta and the thoracic arterial system that results in changes in electrical conductance and impedance.

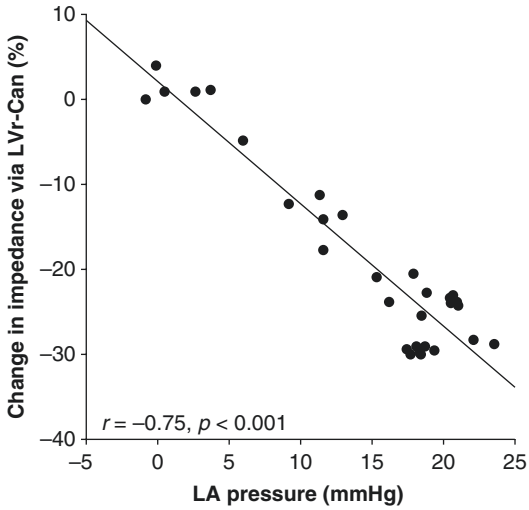

Fig. 13.3 Relationship between LA pressure and Impedance. Data shown are for impedance recorded by left ventricular (LV) r–Can in 1 dog at different time points of the experiment. Correlation coefficient is calculated using Spearman rank order. (Adapted from Khoury et al. [36])

These dynamic, beat-to-beat changes in electric conductance and impedance are used to calculate the stroke volume and other hemodynamic parameters (Fig 13.5). Parameters that can be measured include the stroke volume (SV), cardiac output (CO), central fluid volume, cardiac time intervals, contractility/ejection fraction (EF), acceleration index, total peripheral resistance, aortic compliance, pulmonary capillary wedge pressures (PCWP), and total fluid index (Table 13.1) [40].

The concept of impedance is based on Ohm's Law:

$$\left(I = \frac{E}{R} \right)$$

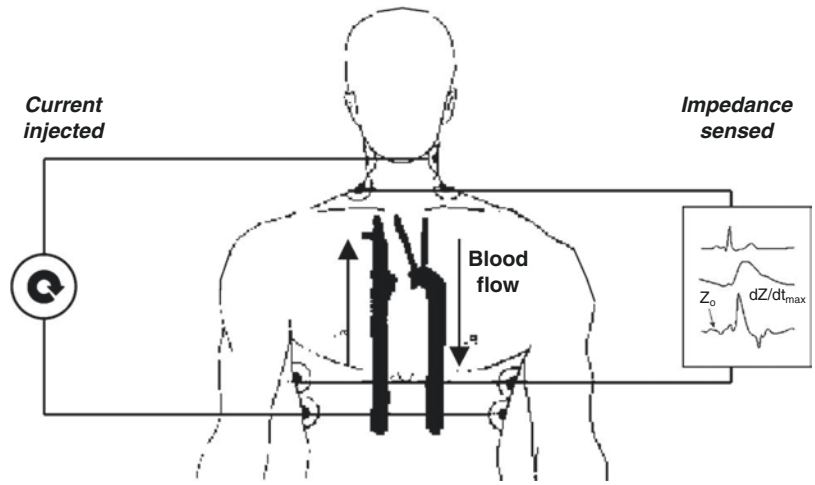

Fig. 13.4 Tetrapolar system of electrodes, separating the current pathway from the sensing pathway. After transmitting electricity by way of the outer electrodes, the impedance to flow of the current through the thorax along the path of least resistance (i.e., the great vessels) is sensed by way of the inner electrodes. (Adapted from Summers et al. [39])

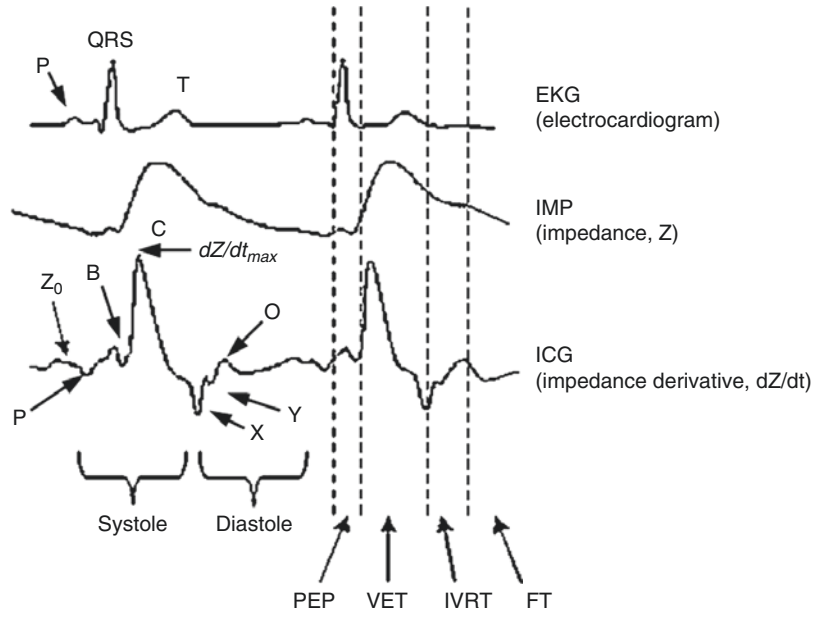

Fig. 13.5 Definition of cardiac and impedance waveforms during the cardiac cycle. *Waveforms* Z_0 baseline impedance, A atrial wave, Baortic valve opening, Cmaximum aortic flow (dZ/dt_{max}), X aortic valve closing, Y pulmonic valve closing, O mitral valve opening, PEP pre-ejection period, VET ventricular ejection time, IVRT isovolumic relaxation time, FT ventricular filling time. (Adapted from Summers et al. [39])

Table 13.1 Electric conductance-based methods for calculating cardiac hemodynamics

Parameters calculated	Formula	Units
Stroke volume (SV)	PF∗ × VET	mL
Stroke index	SV/BSA	mL/beat/m^2
Systolic time ratio	PEP/LVET	
Cardiac output (CO)	SV × HR	L/min
Cardiac index (CI)	CO/BSA	L/min/m^2
Left cardiac work index	(MAP − PCWP) × CI × 0.0144	Kg/m/m^2
Systemic vascular resistance	[(MAP − CVP)/CO] × 80	dyne s cm^5
Systemic vascular resistance index	[(MAP − CVP)/CI] × 80	dyne s cm^5/m^2

BSA body surface area, *CVP* central venous pressure, *HR* heart rate, *LVET* left ventricular ejection time, *MAP* mean arterial pressure, *PEP* pre-ejection period, *PF* peak flow, *PCWP* pulmonary capillary wedge pressure, *VEPT* volume of electrically participating tissue, *VI* velocity index, ∗ derivatives in text

where I is the flow of electric current, E is the voltage drop between the two ends of a circuit, and R is the resistance or impedance [41]. Given a constant current in the circuit, the relationship of changes in voltage across the circuit will be inversely proportional to the impedance. Impedance is related to the resistivity ($_{\varrho}$) (measured in Ωcm), length (L), and cross-sectional area of the conducting medium/material:

$$Z = {}_{\varrho}\left(\frac{L}{A}\right).$$

Since volume is equal to the product of cross-sectional area and length, impedance can be related to changes in the volume according to the following equation [39, 41]:

$$Z = {}_{\varrho}\left(\frac{L^2}{V}\right).$$

In 1940, Nyboer examined the changes in blood volume and flow in the extremities by impedance plethysmography and related the change in impedance (ΔZ) to the change in volume (ΔV) [39, 42]:

$$\Delta V = {}_{\varrho}\left(\frac{L^2}{Z_0^2}\right)\Delta Z$$

With regard to time (t), the equation can be simplified by:

$$\Delta V(t) = {}_{\varrho}\left(\frac{L^2}{Z^2}\right)\Delta Z(t)$$

Changes in impedance in a conductor (thorax) will reflect changes in the volume within the great vessels of the thorax since current will flow through the path of least resistance (resistivity of plasma 65 Ωcm; whole blood 300 Ωcm and muscle, fat, bone and air 200–5000 Ωcm). Using these formulas, the stroke volume can be estimated using a derivative of the impedance waveform $(\delta Z/\delta t)_{max}$, the peak volume change during peak current flow (PF), and the ventricular ejection time (VET) [39, 41, 42]:

$$\mathrm{PF} = {}_{\varrho}\left(\frac{L^2}{Z_0^2}\right)\left(\frac{\delta Z}{\delta t}\right)_{\max}$$

where Z_0 is the baseline impedance of all thoracic tissue, fluid, and air, about 25 Ω for the average adult.

$$\Delta V = \mathrm{SV} = \mathrm{PF} \times \mathrm{VET}$$

$$\Delta V = \mathrm{SV} = {}_{\varrho}\left(\frac{L^2}{Z_0^2}\right)\left(\frac{\delta Z}{\delta t}\right)_{\max} \mathrm{VET}$$

${}_{\varrho}\left(L^2 / Z_0^2\right)$ can be represented by a constant of proportionality, C. Therefore,

$$\Delta V = \mathrm{SV} = \mathrm{C} \times \left(\frac{\delta Z}{\delta t}\right)_{\max} \times \mathrm{VET}$$

The basic assumption of this method is that the change in thoracic impedance is primarily due to increases in the aortic volume. Because the electrical field distribution in the thorax is actually closer to a cone than a cylinder, the initial model was changed from a cylinder to a cone, and therefore the formula was revised [39, 43, 44]:

$$\Delta V = \mathrm{SV} = {}_{\varrho}\left(\frac{L^3}{4.2}\right)\left(\frac{\delta Z}{\delta t}\right)_{\max} \frac{\mathrm{VET}}{Z_0}$$

To avoid the length measurements, the average distance of the thorax (L) is determined to be 17% of the total body height (H); therefore, the equation is revised to:

$$\Delta V = \mathrm{SV} = \left(\frac{(0.17\mathrm{H})^3}{4.2}\right)\left(\frac{\delta Z}{\delta t}\right)_{\max} \frac{\mathrm{VET}}{Z_0},$$

where $(0.17\mathrm{H})^3/4.2$ is defined as the volume of electrically participating thoracic tissue (VEPT).

Finally, when this equation is normalized to an ideal body weight by a factor, δ, the equation would become [39, 44, 45]:

$$\mathrm{SV} = \delta(\mathrm{VEPT})\left(\frac{\delta Z}{\delta t}\right)_{\max} \frac{\mathrm{VET}}{Z_0}$$

Although very sensitive, other changes and pathologies like changes in blood viscosity from anemia and lung pathologies such as pleural effusion or pneumothorax can significantly alter impedance, therefore increasing false positives and reducing its specificity [39, 46]. A study reported that in order to achieve a low false-positive rate, FDA-approved intrathoracic impedance models resorted to algorithms with lower sensitivity for predicting heart failure exacerbation. This may limit the use of thoracic impedance for the prediction/detection of heart failure episodes [47]. More recently, intrathoracic impedance has been used to monitor intravascular volume, aiming to apply knowledge of this method to guide volume therapy in patients with heart failure (Fig. 13.6). Optimal determination of stroke volume by impedance requires patient weight between 67 and 341 pounds and a height of 4–7 feet. Impedance may not be accurate in patients with sepsis, severe aortic regurgitation, and tachycardia (HR > 250 bpm) or patients on intra-aortic balloon pumps [40]. Table 13.2 summarizes the correlation coefficients of different impedance measurements compared to the standard for normal variants and pathologic states.

Intracardiac Impedance Monitoring

Intracardiac impedance has been discussed as an alternative, or a complimentary tool, to other hemodynamic parameters and surrogates in patients with heart failure [46, 48, 49]. It has been used to measure the volume status in patients with cardiac resynchronization therapy (CRT) devices. Intracardiac impedance is a reflection of volume changes in the LV during the entirety of the cardiac cycle. It reduces the false positives encountered with intrathoracic

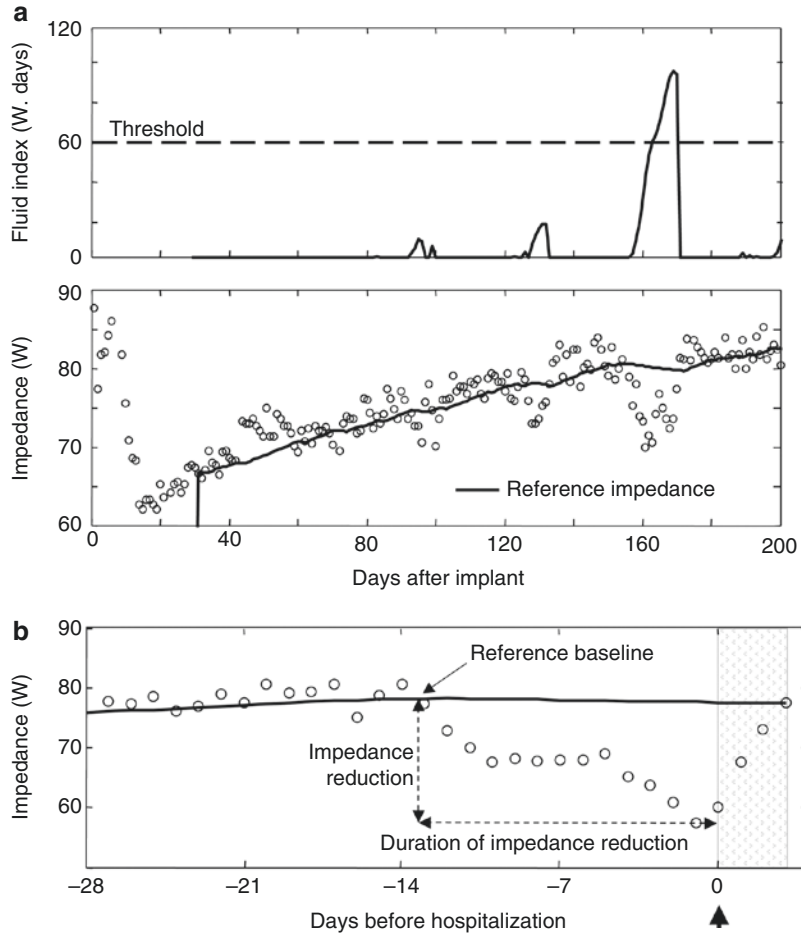

Fig. 13.6 Operational algorithm for detecting changes in impedance over time. (**a**) Differences between measured impedance (bottom; o) and reference impedance (solid line) are accumulated over time to produce fluid index (top). Threshold is then applied to fluid index to detect sustained decreases in impedance. (**b**) Example of impedance reduction before heart failure hospitalization (arrow) for fluid overload and impedance increase during intensive diuresis during hospitalization. Label indicates reference baseline (initial reference impedance value when daily impedance value consistently falls below the reference impedance line before admission). Magnitude and duration of impedance reduction are also shown. Days in hospital are shaded. (Adapted from Yu et al. [34])

impedance measurements associated with other thoracic pathologies. Other theoretical advantages over intrathoracic impedance measurements include reduced delay needed for device pocket maturation and the potentially earlier detection of volume overload as changes in the LVEDP typically occur before pulmonary edema. It can however only be used in patients with CRT devices and these measurements are dependent on lead position which renders them relative rather than absolute values. Additionally, adjustments are needed for postural and diurnal changes commonly encountered with intracardiac impedance measurements.

A combination of multiple parameters that can be recorded from intracardiac devices to form a diagnostic algorithm have been described. These algorithms include various parameters and surrogate markers and have been used to predict heart failure admissions [50, 51]. A list of the devices described above and their proprietary names are summarized in Table 13.3.

Table 13.2 Cumulative correlation coefficients of different impedance measurements compared to a standard for normal variants and pathologic states: How they could affect accurate estimation of cardiac output

Patient	Average correlation	Possible issues with CO estimation
Heathy	0.81 (0.50–0.98)	Hyperdynamic/overestimates
Animals	0.86 (0.41–0.98)	Anatomic landmarks/underestimates
CAD/AMI	0.79 (0.22–0.95)	Weak pulse/underestimates
Chest tubes	0.35	Noise/variable estimates
CHF	0.83 (0.63–0.99)	Lung edema/underestimates
COPD	0.92	Conduction/overestimates
Elderly	0.95	Atherosclerosis/underestimates
Gunshot wound	0.72	Noise/variable estimates
Hemorrhagic shock	0.88 (0.84–0.98)	Low flow/underestimates
Intubated	0.84 (0.1–0.98)	Noise/variable estimates
Obesity	0.76 (0.58–0.94)	Conduction/underestimates
Obstetric patients	0.81 (0.28–0.97)	Anatomic landmarks/underestimates
Pediatric/neonatal patients	0.83 (0.28–0.97)	Lower current/underestimates
Sepsis	0.56 (0.36–0.75)	Runoff/underestimates

Modified from Summers et al. [39]

Table 13.3 Overview of intracardiac impedance monitoring devices

Device	Primary indication	FDA status	Primary measured variable(s)	Implant location	Pertinent contraindications or restrictions
OptiVol® fluid status monitoring system (Medtronic, Inc., USA)	Ambulatory HF surveillance in patients who also meet indication for ICD therapy	Approved Nov 2004	Intrathoracic impedance and heart rate variability	Pectoral muscle region	Patients without an indication for ICD therapy or limited thoracic venous access
Chronicle® ICD and Chronicle® implantable hemodynamic monitor (Medtronic, Inc., USA)	Ambulatory HF surveillance in patients who also meet indication for ICD therapy	Not approved	RV systolic pressure, RV diastolic pressure (an estimate of PADP), maximum change in pressure over time (dP/dt and −dP/dt)	Right ventricle	Patients without an indication for ICD therapy or limited thoracic venous access
HeartPod® (St Jude Medical, Inc., USA)	Ambulatory HF surveillance	Not approved	Mean left atrial pressure	Left atrium	Patients unable to perform Valsalva maneuvers and maintain an airway pressure >39 mmHg for 8 s (required for periodic device calibration)
CardioMEMS™ HF system (CardioMEMS, Inc./St Jude medical, Inc., USA)	Ambulatory surveillance in HF patients with NYHA III symptoms who have preserved EF or reduced EF on OMT, who have had a HF hospitalization in the previous year	Approved May 28, 2014	Systolic, diastolic, and mean pulmonary artery pressure	Left pulmonary artery (ideally, basal segmental branch)	Based on CHAMPION trial criteria (REF), patient should not have any of the following: History of recurrent (>1) pulmonary embolism or deep vein thrombosis inability to tolerate a right heart catheterization recent major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of monitoring

RT cardiac resynchronization therapy, dP/dT rate of rise of left ventricular pressure (mmHg/sec), *EF* left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *HF* heart failure, *ICD* implantable cardioverter defibrillator, *NYHA* New York Heart Association functional class, *OMT* optimal medical therapy, *PADP* pulmonary artery diastolic pressure, *RV* right ventricle
Adapted from Mooney et al. [29]

Bioreactance

Bioreactance is another noninvasive method of measuring cardiac hemodynamics, much like impedance cardiography, but unlike impedance, uses change in signal amplitude of blood flow (Fig. 13.7). Accordingly, bioreactance measures relative phase shifts of the received signals (alternating currents) in comparison to transmitted signals (ΔΦ). These phase shifts are categorized by changes in capacitive and inductive properties of changes in blood flow and intrathoracic volume. This system is less susceptible to noise, and theoretically can be more widely used with fewer limitations compared to impedance cardiography. Also, Unlike hemodynamic measurements by impedance cardiography, bioreactance neither needs static impedance nor utilizes the distance between electrodes for calculation of SV and CO, making hemodynamic calculation less prone to uncertainty [52]. This method has been shown to be accurate and show close overall correlation with hemodynamic measurements obtained using the thermodilution method [53].

Despite the advantages of bioreactance and its improvements over bioimpedance, both methods have similar underlying concepts and hence similar limitations. Changes in aortic dynamics including diseases of the aorta and aortic valve would affect the accuracy of readings. Arrhythmias and heart rates above 150 beats per minute, as well as shunts, edema, abdominal/thoracic pathologies that involve rapid volume shifts between intravascular and extravascular spaces could also make recordings inaccurate.

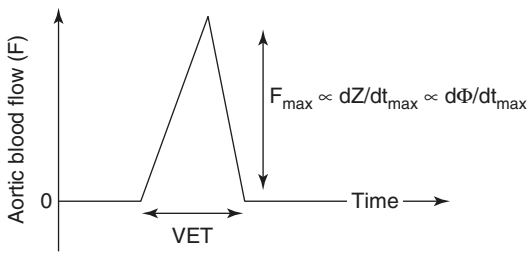

Fig. 13.7 Overview of aortic flow as a function of time and its use to measure cardiac hemodynamics. The basic principle of stroke volume (SV) estimation from changes in the bioimpedance ($\delta Z/\delta t$) or phase shift ($\delta\Phi/\delta t$)

Similar to the cardiac impedance underlying method of measurement, bioreactance is governed by the following physics equation:

$$\Delta V = \mathrm{SV} = {}_{\varrho}\left(\frac{L^2}{Z_0^2}\right)\left(\frac{\delta Z}{\delta t}\right)_{\max} \mathrm{VET}$$

given the tight correlation between rate of blood flow and change in phase shifts, ($\delta\Phi/\delta t$), therefore [52]:

Using a constant of proportionality (C):

$$\Delta V = \mathrm{SV} = \mathrm{C} \times \left(\frac{\delta\Phi}{\delta t}\right)_{\max} \times \mathrm{VET}$$

Partial Carbon Dioxide Rebreathing Technique

This method of hemodynamic measurement uses the carbon dioxide method of the Fick principle which is based on mass conservation [54]:

$$Q = \frac{\mathrm{VCO_2}}{\left(\mathrm{CvCO_2} - \mathrm{CaCO_2}\right)},$$

where Q = cardiac output; VCO_2 = CO_2 elimination (ml/min); $CvCO_2$ = venous CO_2 content (ml/ml of blood); and $CaCO_2$ = arterial CO_2 content (ml/ml of blood). This calculations assume that CO_2 concentrations remain relatively constant.

Since only the pulmonary capillary (nonshunted) blood flow (PCBF) is used in this calculation, accurate measurement of cardiac output requires adding the estimated amount of blood flow not passing through the lungs. In the CO_2 rebreathing method, subjects rebreathe air from a bag, allowing CO_2 to accumulate such that the mixed venous partial pressure is calculated. In the partial rebreathing method, however, in addition to measurements during the rebreathing, measurements are obtained during a non-rebreathing period. These measurements are applied to the Fick equation to obtain cardiac outputs [54].

$$Q_{PCBF} = \frac{VCO_{2NR} - VCO_{2R}}{\left(CvCO_{2NR} - CaCO_{2NR}\right) - \left(CvCO_{2R} - CaCO_{2R}\right)},$$

where NR = non-rebreathing phase and R = rebreathing phase.

Since it is assumed that CO_2 concentrations remain relatively constant during both phases,

$$Q_{PCBF} = \frac{VCO_{2NR} - VCO_{2R}}{CaCO_{2NR} - CaCO_{2R}} \text{ or :}$$

$$Q_{PCBF} = \frac{\Delta VCO_2}{\Delta CaCO_2}$$

Several systems exist for this method of cardiac output calculation. Each one consist of CO_2 measurements, processing of CO_2 signals and several hardware modifications to increase accuracy.

Generally, the first phase is non-rebreathing when baseline measurements are obtained. This lasts about a minute and is followed by a rebreathing phase which lasts for about another minute. During this period, there is repeated inhalation of expired CO_2. The amount of CO_2 inhaled is regulated by a valve attached to the mouthpiece. CO_2 in the rebreathing phase of the test is stored from the preceding exhalation period by the valve system in the mouthpiece, therefore making sure that the inhaled CO_2 is actually from the patient. Repeated inhalation of CO_2 during the rebreathing period increases alveolar CO_2 concentration, arterial CO_2 content and reduces alveolar diffusion of CO_2 and CO_2 clearance from the lungs. In the third and final phase, there is restoration of the patient's CO_2 stores, called the stabilization phase. This also lasts approximately 1 min and restores CO_2 parameters to normal [54].

Although this method is noninvasive, safe, convenient, and applicable in an ambulatory/outpatient setting, it assumes constant cardiac output, partial pressure of mixed venous oxygen, and shunt fraction. Changes during measurements of any of these parameters can significantly change the test results. Also, It is assumed that subjects' hemoglobin concentration is 11 g/dl. A drop of 3 mg/dl can change the estimated cardiac output by about 10%. It may also be inaccurate in patients with lung disease and resultant abnormalities of gas exchange or in patients with a $PaCO_2$ greater than 30 mmHg. Additionally, this method will be technically difficult to use in patients who cannot tolerate the rebreathing phase [7, 54, 55].

Conclusion

Noninvasive cardiac hemodynamic assessment and long-term monitoring have proven beneficial in patients with heart failure. Advances in monitoring devices and technology is allowing accurate and reliable remote monitoring of patients with heart failure. This concept is helping clinicians to manage patients and reduce unnecessary hospital admissions.

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14 Cardiac Catheterization: Right- and Left-Heart Catheterization

Michael D. Faulx and Khaled M. Ziada

Introduction

Myocardial performance is determined by the combined effects of preload, afterload, and contractility [1]. *In vivo,* myocardial performance is represented by the cardiac output, while loading conditions are defined by the interplay between volume, pressure, and vascular resistance within the cardiac chambers and great vessels. Catheterization remains the gold standard for cardiovascular hemodynamic assessment because it provides direct, "real-time" hemodynamic information. Catheterization plays a major role in the diagnosis and management of conditions such as valvular heart disease, complex congenital heart disease, acutely decompensated heart failure, shock, and pulmonary hypertension.

Cardiac catheterization is widely available, and in most centers these procedures are performed quite safely. However, one must always respect the fact invasive procedures are inherently risky. In most cases invasive hemodynamic assessment should be pursued only after noninvasive modalities have failed to furnish the desired results.

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Invasive Hemodynamic Assessment: Fundamental Concepts

The goal of invasive hemodynamic assessment is to accurately replicate real cardiovascular physiology. The accuracy of the data depends on the means through which it is obtained. A basic understanding of how hemodynamic information is acquired in the laboratory is essential to its correct interpretation.

Pressure Measurements

Complex pressure waves generated by the heart and great vessels are periodic, meaning that each cycle repeats itself at a fundamental frequency determined by the heart rate (expressed as cycles/second or Hertz, Hz). The French physicist Jean Baptiste Fourier (1786–1830) demonstrated that complex periodic waves can be expressed as the sum of any number of simpler sinusoidal waves, each with its own frequency and amplitude. These are referred to as *harmonics* and the frequency of each harmonic is an integral multiple of the fundamental frequency (Fig. 14.1). Fourier's theorem is important because the physical properties of a monitoring system must be configured to accurately reproduce pressures across a broad range of harmonic frequencies.

The challenge of constructing a practical hemodynamic monitoring system was tackled by the

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_14

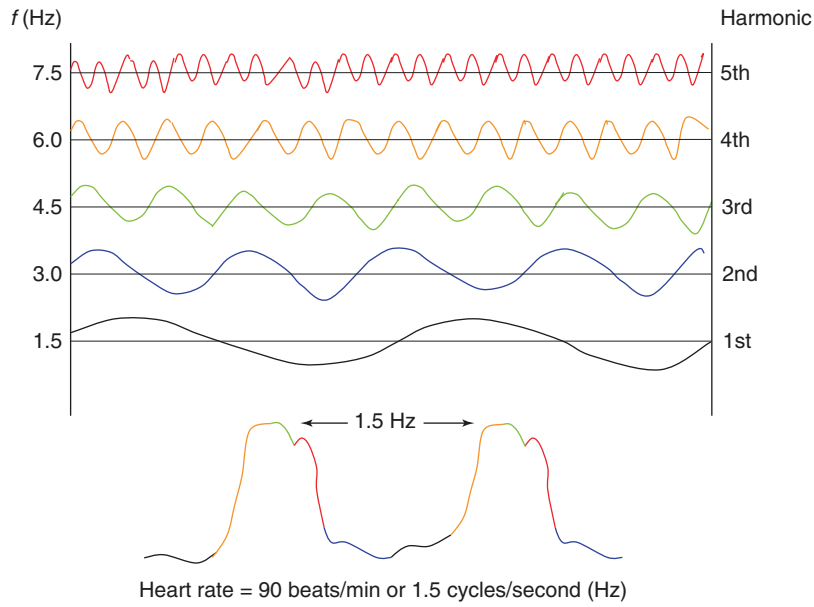

Fig. 14.1 Harmonics in hemodynamic assessment. The aortic pressure waves shown at the bottom are composed of simpler sinusoidal harmonic waves. Each harmonic is a multiple of the fundamental frequency, in this case 1.5 Hz. The data contained within each harmonic contributes in some way to the reconstructed waveform, depicted in this illustration by color. Exclusion of one or more harmonics by a monitoring system can produce a distorted, inaccurate pressure tracing

American physician Carl J. Wiggers (1883–1963). Wiggers employed a fluid-filled catheter system in contact with a rubber diaphragm coupled to a recording device and this design, after several refinements, is still used in monitoring devices today.

The fidelity of pressure measurements obtained by fluid-filled catheters is heavily dependent on the characteristics of the transducer membrane. Flexible membranes are *sensitive* because they can accurately reflect most received amplitudes but they do not respond well to higher frequency harmonics. Conversely rigid membranes respond to a wide range of harmonic frequencies (have better *frequency response*) but tend to be less sensitive. Recording systems used in modern clinical practice tend to have stiffer membranes in order to capture the range of harmonics expected in human physiology, sacrificing sensitivity to some degree.

Another major hindrance to accurate pressure measurement is the fact that transducer membranes resonate in response to stimulation, generating their own pressure waves at a fundamental frequency called the *natural frequency*. When the harmonic frequency of a recorded wave approaches the natural frequency of the monitoring system the amplitudes reflected to the monitor at or near that frequency will be greatly exaggerated. The ability of a catheter system to attenuate the pressure waves produced by the transducer membrane is referred to as *damping*. An ideally damped system is one in which the ratio of input amplitude to output amplitude is maintained close to 1:1 across a broad range of frequencies. Natural frequency (and also frequency response) increases with membrane stiffness and catheter diameter and decreases with catheter length, catheter stiffness, and fluid viscosity. Damping responds in the opposite manner to these factors. Thus, catheters with high-fidelity, tip-mounted transducers (Millar Instruments, Houston, TX) have excellent frequency response and are well suited for capturing high-frequency pressure changes over short time intervals (i.e., measurement of left ventricular dP/dt). Longer, stiffer, fluid-filled catheters coupled to a transducer at the hub are well damped and reasonably sensitive across most of the harmonic frequencies encountered in human studies.

The basic equipment required for pressure measurement in the catheterization lab includes a fluid-filled hollow catheter, multi-port manifold, transducer membrane in contact with an electrical strain gauge, signal amplifier, and a monitor. The catheter tip is placed in the cardiac chamber of interest and connected to the transducer via a dedicated port on the manifold. Pressures at the catheter tip are transmitted through the fluid medium (saline, blood, or contrast) to the transducer membrane, which stretches and vibrates in response to the pressure it sees. The membrane is coupled to a tiny strain gauge contained within a housing unit that has been equilibrated to atmospheric pressure (referred to as *zeroing*). Movement of the piston across the wires of the strain gauge produces an electrical current that is subsequently amplified, reconfigured, and displayed on the monitor.

Hemodynamic waveforms obtained from fluid-filled catheters are subject to a variety of artifacts. Common encountered artifacts are demonstrated and extensively reviewed in Fig. 14.2a–e.

Blood Flow Measurements

Accurate measurement of cardiac output is vital not only as an index of myocardial performance but also as a component in the quantification of valvular stenoses, vascular resistances, and shunts. In clinical practice, cardiac output is assessed by two methods: Fick method and thermodilution.

Oxygen Extraction and Utilization: The Fick Method

The German physiologist Adolph Fick (1829–1901) theorized that the utilization of any substance by an organ can be expressed as the product of the blood flow to the organ and the difference between the arterial and venous concentrations of the substance. When this principle is applied to the lungs, oxygen uptake (VO_2) would be equal to pulmonary blood flow x the difference between pulmonary arterial ($A[O_2]$) and venous ($V[O_2]$) oxygen content. Assuming that there is no pulmonary-systemic shunt and that flow through the pulmonary and systemic circuits are equal, the Fick equation can provide a measure of cardiac output (CO):

$$\text{Fick equation} \quad \text{CO}\left(\text{L/min}\right) = \frac{\text{VO}_2 \ \left(\text{mL/min}\right)}{\text{A}\left[\text{O}_2\right] - \text{V}\left[\text{O}_2\right] \ \left(\text{mL/L}\right)}$$

Oxygen consumption for an individual patient can be directly measured by devices that employ a closed rebreathing circuit with a CO_2 detector. However, this approach is expensive and technically cumbersome and many laboratories assume a resting VO_2 of 1.25 mL/m^2. The reader should be aware that assumed VO_2 values are based on studies of basal metabolic activity in predominantly young subjects. Measured VO_2 can significantly vary from baseline in subjects with underlying cardiopulmonary disease so the use of assumed oxygen consumption values can introduce significant error in the calculation of cardiac output.

Hemoglobin binds approximately 1.36 mL of elemental oxygen per gram and oxygen bound to the hemoglobin molecule accounts for over 98% of the total oxygen content of human blood. Oxygen dissolved in plasma accounts for the rest and is represented by the product of oxygen solubility in plasma (0.003 mL/dL/mmHg) and the partial pressure of oxygen in plasma, PaO_2. The oxygen content of blood is represented by the following equation:

$$\text{Cb}\left[\text{O}_2\right] = \left\{\left[\text{hemoglobin}\right] \times 1.36 \times \text{SaO}_2 \times 10\right\} + 0.003 \times \text{PaO}_2 \times 10.$$

SaO_2 is the percent oxyhemoglobin as detected by oximetry. For the sake of simplicity the content of dissolved O_2 is often omitted from this calculation, but the reader should be aware that under certain circumstances (i.e., high FiO_2 with positive pressure ventilation) the amount of dissolved oxygen in blood can become clinically relevant.

The Fick method is generally an accurate method of cardiac output measurement but error can be introduced at several levels. The Fick method relies on several key assumptions such as the absence of an intracardiac shunt and the notion that oxygen consumption and cardiac output are constant during measurement. In critically

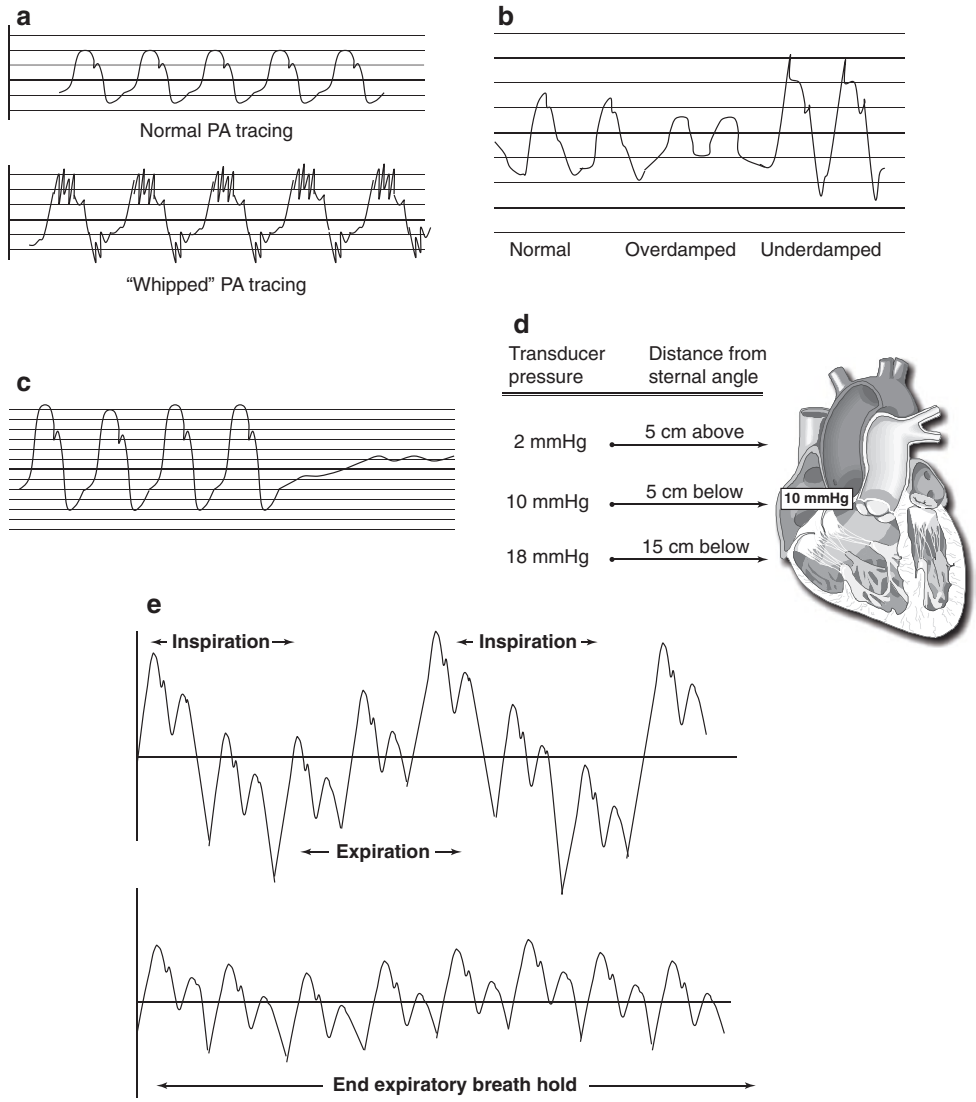

Fig. 14.2 (**a**) Catheter whip in a pulmonary artery (PA) pressure tracing. Whip occurs when the catheter tip vibrates in response to ventricular contraction or valvular motion. Whip causes high-frequency distortion of the waveforms, particularly at the high and low points of the complex. Since the extremes of the waveform are equally affected, the mean pressure obtained from a "whipped" tracing is generally accurate. Whip can be attenuated by catheter repositioning, the use of a high-frequency filter, or increased damping. (**b**) Damping-related artifacts. Overdamping results in a flat, low-amplitude waveform that lacks contour detail. Overdamping can be caused by catheter kinking, air bubbles or blood in the transducer circuit, and the use of long, small-caliber catheters. It can be overcome by removing kinked tubing, flushing of the catheter and manifold, and use of shorter, large-caliber catheters. Under-damping produces exaggerated waveforms with overestimated amplitudes. It occurs when the natural frequency of the catheter system approximates a harmonic frequency in the pressure wave. This can be offset by lowering the natural frequency of the catheter system (longer, smaller-caliber catheters) or the patient (treat tachycardia). (**c**) Positional artifact. This is characterized by flattening of the pressure tracing with a gradual rise in pressure. It most often occurs when the catheter tip is pressed against the wall of a vessel or chamber. Gentle withdrawal and redirection of the catheter typically solves the problem. (**d**) Transducer malposition. In this example, the true mean right atrial pressure is 10 mmHg. When the transducer is zeroed at a level 5 cm below the sternal angle the catheter recording is accurate. When the transducer is zeroed at a level above the chest, the pressure is underestimated. When the transducer is zeroed at a level well below the right atrium, the pressure is overestimated. (**e**) Respiratory variation of right atrial pressure. The thin-walled right-sided chambers are subject to respiratory variation, particularly in subjects with underlying obstructive lung disease. Pressure measurements taken during a few seconds of breath holding at the end of normal expiration (when intrathoracic pressure is theoretically zero) are much less variable

ill patients with pulmonary disease, oxygen consumption can be overestimated since the delivery of oxygen from the lungs to the blood is not uniform. The Fick equation also requires several measurements, each with its own degree of measurement error. The use of an assumed value for oxygen consumption, as mentioned previously, is a major potential source of error; hence, the use of the term "estimated Fick cardiac output" may be the more accurate description of what is actually measured in the routine catheterization laboratory practice.

Indicator Dilution over Time: The Thermodilution Technique

Thermodilution measures the rate of change of blood temperature over time. By injecting a fixed volume (10 mL) of chilled or room air temperature injectate (5% dextrose or 0.9% saline) into the right atrial port of the catheter and continuously measuring temperature with a thermistor located at the catheter tip, we can estimate the rate of flow from the right atrium to the catheter tip. Thermodilution calculations are mathematically complex as they account factors such as the expected degree of catheter warming during injection and the specific heat and gravities of blood and the injectate. Numerical cardiac outputs are provided by computerized analysis of temperature versus time curves and the final cardiac output is typically reported as an average of several injections.

Thermodilution correlates reasonably well with other measures of cardiac output but there are several contributors to measurement error. Pulmonary artery temperature can vary with respiration so injection during the same portion of the respiratory cycle (i.e., end expiration) each time reduces the potential for error. Shorter injection periods (<3 seconds) are preferable to longer ones for similar reasons and the injection periods should be as uniform as possible. Smaller injectate volumes with warmer injectate temperatures (i.e., 5 mL injected at room temperature) produce more measurement error than colder, larger volume injections because the signal-to-noise ratio is lower. Thermodilution is not reliable in the presence of significant tricuspid regurgitation or in low output states because the injectate tends to cycle between the right atrium and right ventricle, resulting in a flattened temperature-time curve.

A recent comparative study indicates that the correlation between thermodilution and estimated Fick methods for the calculation of cardiac output is modest ($r = 0.65$), with a difference of >20% demonstrated in about 38% of patients. Low output by the thermodilution method correlated more closely with 3 and 12 months mortality, indicating that it maybe the preferred method of cardiac output calculation.

Risk of Cardiac Catheterization

Proper informed consent should be obtained from the patient or a designated medical decision maker prior to cardiac catheterization. The major risks related to right and left cardiac catheterization appear in Table 14.1. Decompensated heart failure, shock, acute coronary syndromes, left ventricular dysfunction, morbid obesity, depressed mental status, and advanced kidney disease are all associated with increased procedural risk. The risk for stroke increases significantly with cannulation of the left ventricle. Although debilitating strokes are rare the incidence of small, clinically silent strokes assessed by MRI was found to be 22% in one series of patients with severe aortic stenosis who underwent left ventricular cannulation [2]. For this reason, routine left ventricular catheterization should be avoided in favor of a selective approach, reserving left ventricular cannulation for patients with nondiagnostic or conflicting noninvasive test results.

The most common catheterization complications are related to problems with the vascular access site or subsequent hemostasis. When feasible ultrasound or radiographic guidance should be employed to localize landmarks and guide cannulation of large arteries and veins. Morbid obesity is a common contributor to access-related complications, particularly when femoral access is attempted.

Table 14.1 Complications associated with diagnostic left- and right-heart catheterization[a]

Complication (% risk)	Contributing factors	Prevention
Death (0.11%)	High acuity illness	Reassess necessity of the procedure
	Emergency procedure	Have ACLS equipment on stand by
Myocardial infarction (0.05%)	Acute coronary syndromes	Appropriate medical therapy for ACS
	Profound hypertension	Medical management of hypertension
	Profound tachycardia	Medical management of tachycardia
Stroke (0.07%)	Cannulation of left ventricle	Avoid crossing aortic valve unless absolutely necessary
	Atrial fibrillation	Over-the-wire catheter exchanges
	Ascending aortic atheroma	
Access complications (0.43%)	Anticoagulation	Correction of coagulopathy
Major hematomas	Morbid obesity	Radial artery access
Retroperitoneal bleeds	Agitation	Imaging-guided vascular cannulation
Arteriovenous fistulas		Appropriate conscious sedation
Major arrhythmias (0.38%)	Electrolyte disturbances	Correct metabolic derangements
Ventricular fibrillation	Hypoxemia	Supplement oxygen
Ventricular tachycardia	Right coronary conus branch injection	Cautiously injection of right coronary
Complete heart block		
	Catheter-induced endocardial trauma	Use pigtail catheter in left ventricle
	Underlying bundle branch blocks	
Other embolic events (rare)	Pre-existing deep vein thrombosis	Exclude thromboses prior to study
Pulmonary embolism/ infarction	Prolonged immobility	Limit duration of PA catheterization over-the-wire catheter exchanges
Distal atheroembolism	Aortic atheromatous disease	
Contrast nephropathy (variable)	Pre-existing kidney disease	Adequate hydration
	Diabetes	Use of N-acetylcysteine
	Dehydration	Minimize use of contrast
	Large contrast volume	
Serious allergic reactions	Pre-existing allergies	Pretreatment with corticosteroids and antihistamines
Contrast agents (0.37%)		
Local anesthetic (ester agents)		Use of amide anesthetic agents
Respiratory arrest (variable)	Underlying pulmonary disease	Limit the use of sedatives
	Altered mental status	Optimize heart failure and lung disease prior to the study
	Decompensated heart failure	Frequent airway assessment
	Morbid obesity	Anesthesiology consultation
Other vascular complications (0.28%)	Balloon inflation in small arteriole	Avoid inflation in distal PA
Pulmonary artery perforation	Catheter trauma	Cautious catheter removal
Coronary artery dissection		
Perforation of cardiac chamber	Sub-intimal guide wire route	Use flexible J-tipped wires

[a]Adapted from Noto et al. [4]

ACLS advanced cardiac life support, *ACS* acute coronary syndrome, *PA* pulmonary artery

Right-Heart Catheterization Technique

Right-heart catheterization is generally performed using a 7- or 8-French vascular sheath placed in the common femoral vein or right internal jugular vein using modified Seldinger technique and typically under ultrasound guidance. A balloon tipped pulmonary artery catheter is inserted through the sheath and the balloon is inflated once the tip of the catheter has cleared the sheath. The catheter tip, guided by flow and the manipulation of the operator, traverses the heart from the great veins to the pulmonary artery and the pulmonary artery wedge position [3]. The catheter is then connected to the pressure transducer via a multi-port manifold. Blood can also be withdrawn from the catheter for oximetry and chemistry sampling. There is a proximal lumen at the level of the right atrium to allow for thermodilution assessment of cardiac output. Rarely, situations arise where direct measurement of left atrial pressure is desirable, such as in the evaluation of severe native or prosthetic mitral stenosis. Left atrial cannulation can be performed from the right atrium by fluoroscopy-guided needle puncture of the interatrial septum at the level of the fossa ovalis and the use of a Brockenbrough catheter.

Left-Heart Catheterization Technique

Left-heart catheterization is performed by placing a 4-, 5-, or 6-French sheath into a large artery using Seldinger or modified Seldinger technique. Most contemporary laboratories utilize radial artery access as the preferred choice for arterial access for diagnostic procedures, although the traditional right or left common femoral artery approach remains an important alternative, when radial access is not feasible or when larger bore devices are planned or needed. Ultrasound and fluoroscopic guidance are important tools to optimize the technique and safety of arterial access. Brachial artery access remains as an option for left-sided catheterization, although usually a last resort. Once vascular access is obtained the arterial catheters are advanced retrogradely through the aorta preceded by a J-tipped flexible guidewire. The catheters are controlled by the operator and there are numerous specialized catheters available for use. Endhole catheters are useful for pressure measurements and contrast injection during coronary angiography. They are not ideal for opacification of the aorta or left ventricle because they promote contrast streaming and ventricular ectopy. Multi-hole pigtail catheters record the pressure and are better for the opacification of large structures because they uniformly distribute a larger volume of pressured contrast within a chamber. Aortography and ventriculography should be performed using a pigtail catheter. Some pigtail catheters have proximal and distal transducer ports to allow for simultaneous pressure measurements across a given structure such as the aortic valve.

Data Derived from Right- and Left-Heart Catheterization

Pressure Measurements

When intracardiac pressure measurements are gated to the surface electrocardiogram, systolic and diastolic performance of the heart can accurately be assessed (Fig. 14.3). Pressure measurements are obtained by advancing the catheter to the chamber of interest and recording waveforms over several cardiac cycles. Right-sided pressures can vary greatly with respiration in some patients (see Fig. 14.2e), making interpretation difficult. In this case, a several-second end-expiratory breath hold will maintain thoracic pressure at its theoretical "zero point" for a few cardiac cycles. Normal cardiovascular waveforms and their descriptions follow.

Right Atrial Pressure (Fig. 14.4a)
The normal right atrial pressure wave includes the "a" wave, produced by atrial contraction and the corresponding "x" descent during atrial relaxation. Early in the "x" descent there may be a small positive reflection called the "c" wave which represents closure of the tricuspid valve.

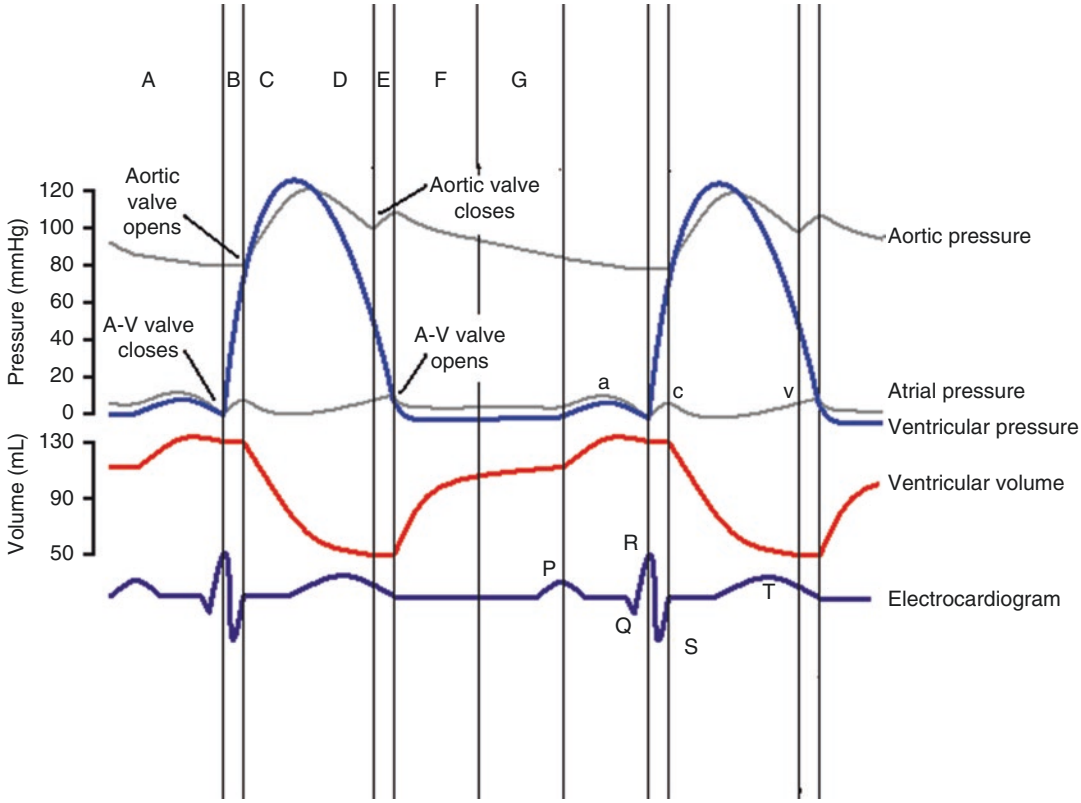

Fig. 14.3 Schematic representation of the major electrical and mechanical events during the cardiac cycle: (**a**) atrial contraction; (**b**) isovolumic contraction; (**c**) rapid ejection; (**d**) reduced ejection; (**e**) isovolumic relaxation; (**f**) rapid ventricular filling; and (**g**) reduced ventricular filling

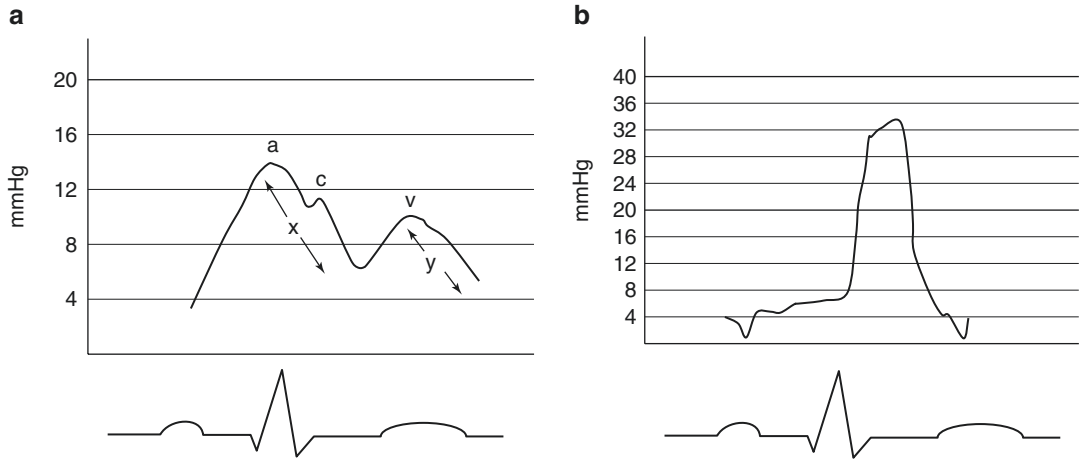

Fig. 14.4 (**a**–**f**) Normal cardiac pressure tracings. Descriptions of each tracing are found within the chapter text. (**g**) Abnormal pressure tracing obtained during selective coronary angiography. In the presence of severe ostial stenosis, the endhole catheter transmits a distorted waveform due to the reflected coronary wedge pressure and appears as a hybrid between aortic and ventricular pressure (ventricularized pressure) waveform

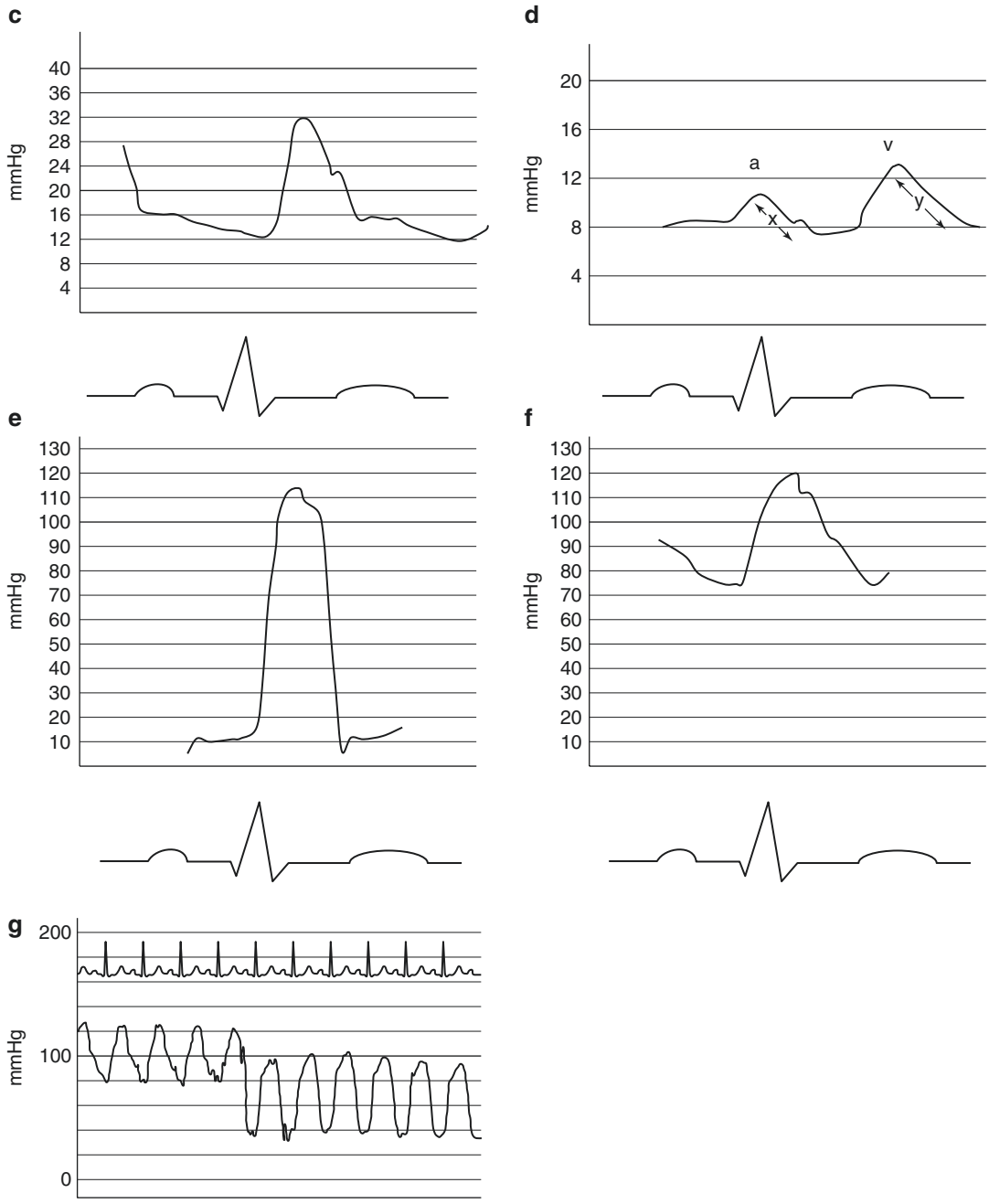

Fig. 14.4 (continued)

The second major wave in the right atrial tracing is the "v" wave, produced by the combination of vena cava flow into the atrium and the upward displacement of the closed tricuspid valve during right ventricular contraction. Once the tricuspid valve opens, the right atrial pressure drops in early diastole, producing the "y" descent. Normal mean right atrial pressure is between 1 and 10 mmHg.

Right Ventricular Pressure (Fig. 14.4b)

The normal right ventricular wave is characterized by a rapid pressure rise during systole followed by

a rapid fall during isovolumic relaxation. Diastolic pressure gradually increases until late systole when the right atrium contracts and right ventricular end-diastolic pressure rises to the level of the atrial "a" wave. Normal right ventricular systolic and diastolic pressure is 15–30 mmHg and 1–10 mmHg, respectively.

Pulmonary Artery Pressure (Fig. 14.4c)

The normal pulmonary artery pressure tracing is a typical arterial waveform with a rapid systolic upstroke. There is a dicrotic notch produced by closure of the pulmonic valve and the diastolic pressure gradually decreases as blood flows from the main pulmonary artery to the lungs. Normal pulmonary artery systolic and diastolic pressure is 15–30 mmHg and 5–10 mmHg, respectively. In intensive care settings, it is common practice to follow the PA end-diastolic pressure as an indirect measure of left atrial pressure. However, this assumption is only true if the pulmonary vascular resistance is close to normal.

Pulmonary Capillary Wedge Pressure, PCWP (Fig. 14.4d)

The PCWP is commonly used as a surrogate for left atrial pressure. This pressure is obtained by cautiously advancing the catheter tip through the pulmonary artery with the balloon inflated until the balloon will no longer advance and appears fixed or "wedged" in the pulmonary bed by fluoroscopy. Inflating the balloon with the catheter tip in the distal pulmonary arterial tree increases the risk for pulmonary artery rupture. The PCWP reflects left atrial pressure because when the balloon is properly wedged there is no longer flow from the proximal PA to the catheter tip. The catheter tip only "sees" the left atrial pressure waves that are reflected back to it through the pulmonary artery capillary bed (Fig. 14.5).

The normal PCWP is analogous to left atrial pressure, with "a" and "v" waves that correspond to left atrial contraction and left ventricular contraction, respectively and their corresponding "x" and "y" descents. It is important to know that left

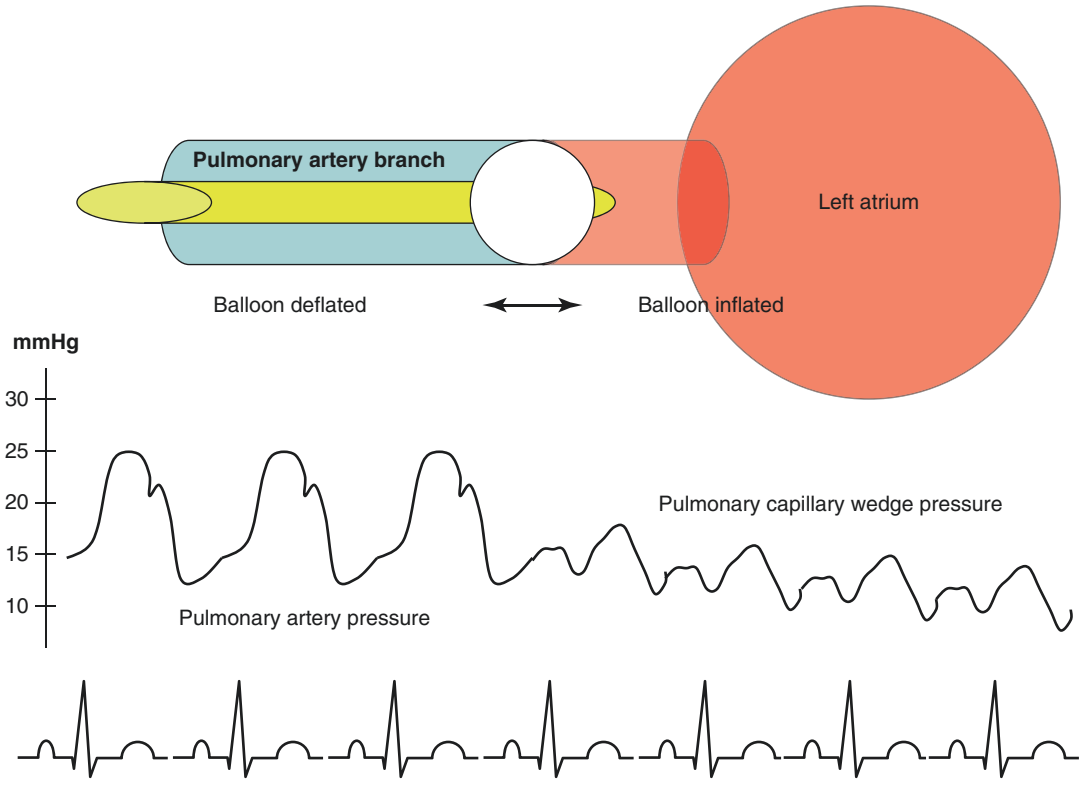

Fig. 14.5 Diagram of the pulmonary capillary wedge technique

atrial activity precedes the reflected wedge pressure by a few milliseconds. This causes the PCWP "v" wave to appear later than the left atrial "v" wave. When the PCWP and left ventricular pressures are superimposed during assessment for mitral stenosis, the result may be overestimation of the transmitral pressure gradient. Normal mean PCWP pressure is between 5 and 12 mmHg, and in the absence of mitral stenosis, it approximates left ventricular end-diastolic pressure.

Left Ventricular Pressure (Fig. 14.4e)
Left ventricular pressure has a rapid upstroke during early systole followed by a rapid descent. Diastolic pressure is low in early diastole and rises slowly until the left atrium contracts. The left ventricular end-diastolic pressure (LVEDP) represents the true preload for the left ventricle, and it is typically measured just prior to abrupt rise in systolic pressure. Normal LVEDP is 5–12 mmHg.

Aortic Pressure and Waveform
(Fig. 14.4f)
Aortic pressure is measured with the catheter tip in the proximal aorta. Central aortic pressures are usually 10–20 mmHg lower than femoral artery pressures due to the greater size and elasticity of the normal aorta. In a normal, high fidelity system, the aortic waveform is characterized by a dicrotic notch which occurs at the closure of aortic valve.

Endhole catheters used for selective coronary angiography should normally transmit a normal waveform of central aortic pressure. In the presence of severe ostial coronary stenosis, the waveform is distorted by the reflected coronary wedge pressure and appears as a hybrid between aortic and ventricular pressure (ventricularized pressure) waveform. The systolic pressure is decreased and the diastolic pressure is markedly decreased, compared to the normal aortic waveform. This should immediately raise concern about severe ostial right or left main coronary stenosis, although the differential diagnosis can simply be a non-coaxial catheter position, with the tip against the wall of the artery (Fig. 14.4g).

Cardiac Output

The Fick method requires sampling of blood from both sides of the pulmonary vascular bed, namely, the pulmonary artery and pulmonary veins or left atrium. Pulmonary artery blood is obtained via aspiration from the distal port of the right-heart catheter. Direct sampling from the left atrium requires transseptal puncture which is impractical for routine diagnostic testing. For this reason, an arterial blood sample (i.e., from the femoral artery sheath) is typically used as a substitute. The thermodilution technique has been previously described.

Normal cardiac output is between 5.0 and 7.5 L/min but varies broadly with patient size and gender (men generally have higher cardiac outputs than women). The human heart can augment its cardiac output over fivefold in certain disease states (i.e., severe anemia, thyrotoxicosis). The cardiac index (cardiac output divided by body surface area, BSA) is a better measure of myocardial performance than cardiac output. The normal range for cardiac index is 2.5–4.0 L/min/m^2. A cardiac index <1.0 L/min/m^2 is not compatible with life.

Vascular Resistance

In a fluid-filled system, resistance (R) is proportional to the pressure difference across the system (ΔP) and inversely proportional to flow (Q); $R = \Delta P/Q$.

By measuring mean aortic pressure (AoP) and mean right atrial pressure (RAP), we can calculate systemic vascular resistance (SVR) in the following manner:

$$\text{Systemic vascular resistance}$$
$$\text{SVR} = \frac{(\text{mean AoP} - \text{mean RAP})}{\text{Cardiac Output}}$$

Similarly, by measuring the mean pulmonary artery pressure (PAP) and left atrial pressure (LAP), either directly or with its surrogate (wedge pressure), we can calculate the pulmonary vascular resistance (PVR):

$$\text{Pulmonary vascular resistance}$$
$$\text{PVR} = \frac{\left(\text{mean PAP} - \text{mean LAP / PCWP}\right)}{\text{Cardiac Output}}$$

Vascular resistances can be expressed in Wood units (mmHg/L/min) or dynes∗s/cm^{-5}. A dyne is the amount of force required to accelerate a 1 gram mass to 1 cm/s^2. 1 Wood unit = 80 dynes∗s/cm^{-5}. Normal systemic vascular resistance is between 8 and 20 Wood units. Normal pulmonary vascular resistance is between 0.25 and 1.6 Wood units.

Shunt Assessment

Shunt flow from the systemic circulation to the pulmonary circulation can be localized and quantified during right-heart catheterization by performing an oximetry saturation run. As the catheter is passed through the great veins to the pulmonary artery, small (2 mL) aliquots of blood are obtained for oximetry from the proximal and distal superior vena cava (SVC), proximal and distal inferior vena cava (IVC), right atrium (low, mid, and high), right ventricle (proximal, mid, and apex), pulmonary artery (main, left, and right), left ventricle, and aorta distal to the ductus arteriosus.

A left-to-right shunt is detected by an oximetry "step-up," where oxygenated left circulation blood mixes with deoxygenated right circulation blood. A "step-up" of ≥7% is considered significant at the level of the great veins and right atrium. A step-up of ≥5% is considered significant at levels distal to the right atrium. Right-to-left shunts are difficult to locate and quantify, and oximetry to detect a "step-down" is generally not performed.

The degree of left-to-right shunting can be quantified by calculating the ratio of pulmonary blood flow (Qp; oxygen consumption divided by the difference in arteriovenous oxygen content across the lungs) to systemic blood flow (Qs; oxygen consumption divided by the difference in arteriovenous oxygen content across the systemic circulation). Systemic mixed venous saturation (MVO_2) is defined as:

$$\text{Mixed venous saturation} \quad \text{MVO}_2 = \frac{\left[(3)\text{SVC saturation} + \text{IVC saturation}\right]}{4}$$

If we assume constant oxygen consumption, hemoglobin concentration, and atmospheric pressure, then many of the terms in this complex calculation cancel out, leaving only the oximetry saturations:

$$\text{Shunt fraction} \quad \text{Qp / Qs} = \frac{\left(\text{Arterial sat}\right) - \left(\text{MVO}_2\text{sat}\right)}{\left(\text{Arterial sat}\right) - \left(\text{pulmonary artery sat}\right)}$$

The pulmonary venous saturation cannot be obtained without transseptal puncture or retrograde catheterization through the mitral and aortic valves. In the absence of a significant right-to-left shunt at the level of the left atrium, ventricle, or proximal aorta, we would expect systemic arterial saturation and pulmonary venous saturation to be the same; thus pulmonary venous saturation is often replaced by systemic arterial saturation in this equation.

Small shunts are defined by Qp/Qs < 1.5 and are often asymptomatic. Large shunts are defined by Qp/Qs > 2.0 and often require closure. Frequently, the location of the shunt is known or suspected from an alternative study such as an echocardiogram, CT scan, or MRI, and catheterization is used to quantify the shunt fraction. In this case, it is not necessary to sample from multiple levels in the same chamber or vessel.

Assessment of Valvular Stenosis

The invasive assessment of valvular stenosis requires measurement of the cardiac output and measurement of the pressure difference across the valve in question. Ideally, pressure measurements should be made simultaneously with two catheters, each coupled to its own transducer and neither crossing the affected valve. The catheters should be placed in the chambers or vessels on either side of the valve, and the pressure tracings should be superimposed to accurately calculate

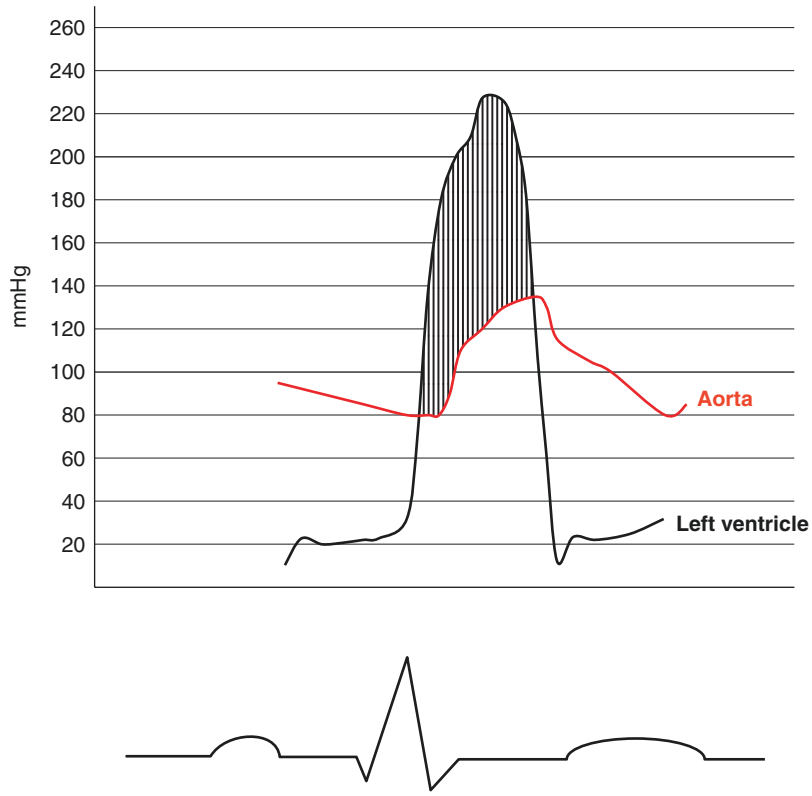

Fig. 14.6 Estimating the transaortic pressure gradient. The pressure waves produced by simultaneous catheterization of the left ventricle and proximal ascending aorta are superimposed. The shaded area under the curve (AUC) is calculated, providing the mean transvalvular gradient

the mean pressure gradient (area under the curve, AUC) (Fig. 14.6).

Assessment of mitral stenosis is performed by measuring simultaneous left ventricular and left atrial pressures. If transseptal puncture is not desired, the pulmonary capillary wedge pressure may be used as a surrogate for the left atrium; however, this may overestimate the magnitude of the gradient since the wedge pressure lags behind true left atrial pressure by a few milliseconds. Assessment of aortic stenosis involves simultaneous measurements in the left ventricle and ascending aorta. Two arterial sheaths can be placed, but this increases the risk for access site complications. Dual lumen pigtail catheters have proximal (ascending aorta) and distal (left ventricle) ports that require two transducers but one arterial access site. Another method is the "pull-back method," where the catheter is withdrawn from the left ventricle into the ascending aorta during continuous recording. This allows for a peak-to-peak measurement of the systolic pressure difference that is not simultaneous and provides a crude approximation of the integrated or mean pressure difference. When aortic stenosis is severe, the catheter itself promotes stenosis, resulting in a higher gradient and potential overestimation of stenosis severity.

The Gorlin formula is typically used to calculate valve areas in the catheterization lab:

$$\text{Gorlin formula} \quad \text{Valve Area}\left(\text{cm}^2\right) = \frac{\text{CO}/[\text{HR}][\text{EP}]}{44.3\times(\text{K})\times\sqrt{\Delta P}},$$

where CO is the cardiac output (L/min), HR is the heart rate (bpm), EP is the ejection period (systolic or diastolic as calculated from the ECG, in seconds/beat), 44.3 is a constant that accounts for energy loss due to acceleration and gravity (cm/s/s), K is a unit-less correction factor (1.0 for the aortic valve and 0.85 for the mitral valve), and $\sqrt{\Delta P}$ is the square root of the mean pressure gradient across the valve. An abbreviated version of

Table 14.2 Criteria for the angiographic assessment of mitral regurgitation

Severity	Grade	Criterion
Mild	1+	Incomplete opacification of left atrium
Moderate	2+	Complete opacification of left atrium but with less relative intensity than the left ventricle
Moderately severe	3+	Complete opacification of left atrium with intensity equal to the left ventricle after 4 beats
Severe	4+	Complete opacification of left atrium with intensity equal the left ventricle within 3 beats

the Gorlin formula, called the Hakki formula, provides a reasonable estimate of valve area as well.

$$\text{Hakki formula} \quad \text{Valve area}\left(\text{cm}^2\right) = \frac{\text{CO}}{\sqrt{\Delta P}}$$

The normal aortic valve orifice area is 3.0–4.0 cm^2. The normal mitral valve orifice area is 4.0–6.0 cm^2.

Assessment of Valvular Regurgitation

The invasive assessment of valvular regurgitation is largely subjective. The severity of aortic and mitral regurgitation can be estimated by applying qualitative criteria to the appearance of aortography and ventriculography, respectively (Table 14.2). The severity of tricuspid and mitral regurgitation can be estimated from the relative magnitude of the "v" waves in the right atrial and PCWP tracings, respectively. However, atrial compliance and ventricular function also influence the amplitude of "v" waves, making this approach fairly non-specific.

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Part IV

Specific Hemodynamically Compromised Situations

Tamponade

15

Olcay Aksoy, Begum Sezer,
and Leonardo Rodriguez

Case Presentation

A 47-year-old female with history of systemic lupus erythematosus (SLE) presents with exertional dyspnea. She reports development of peripheral edema in the past month and has had onset of exertional dyspnea in the past few days.

Salient physical examination findings include a heart rate of 92, blood pressure of 136/72, elevated JVP at 16 mmHg, and grade I/VI early systolic murmur at left lower sternal border. The lung fields are clear. There is 2+ pitting lower extremity edema. Pulsus paradoxus is measured to be 8 mmHg.

A chest X-ray shows an enlarged cardiac silhouette. An ECG shows electrical alternans (Fig. 15.1). An urgent echocardiogram shows increased respirophasic variation across mitral and tricuspid valves (Fig. 15.2a, b).

The patient is admitted to the hospital for further evaluation and management. Over the course of the admission, the patient becomes gradually confused. Laboratory evaluation reveals evidence of mild renal dysfunction and a mild transaminitis. She now has a heart rate of 108 and her blood pressure is 92/56. She is transferred to the Intensive Care Unit and a pulmonary artery catheter is placed, which notes right atrial tracings showing blunted *y* descent (Fig. 15.3a). She subsequently receives a pericardiocentesis with improvement in hemodynamics (post-pericardiocentesis tracings shown in Fig. 15.3b). The patient improves clinically and subsequently is discharged on an intensified treatment regimen for SLE. A follow-up echocardiogram is scheduled.

Introduction

Anatomy

The myocardium is encased in a relatively rigid and noncompliant sac called the pericardium. The pericardium is formed by two layers. The outer sac, called the fibrous pericardium, is composed of fibrous tissue and encases the inner layer of pericardium and the heart. The inner sac has two layers – called the parietal and visceral pericardium. The parietal pericardium is attached to the internal surface of the fibrous pericardium and is contiguous with the visceral pericardium as it gets reflected on the cardiac surfaces. In between the visceral and the parietal pericardium is the pericardial space. This space

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_15

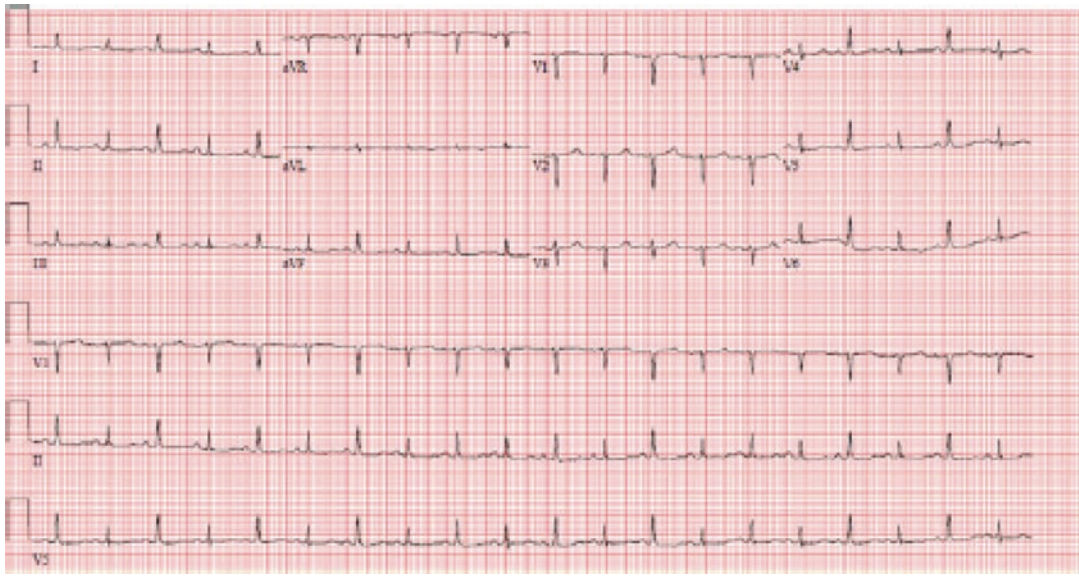

Fig. 15.1 ECG demonstrating electrical alternans

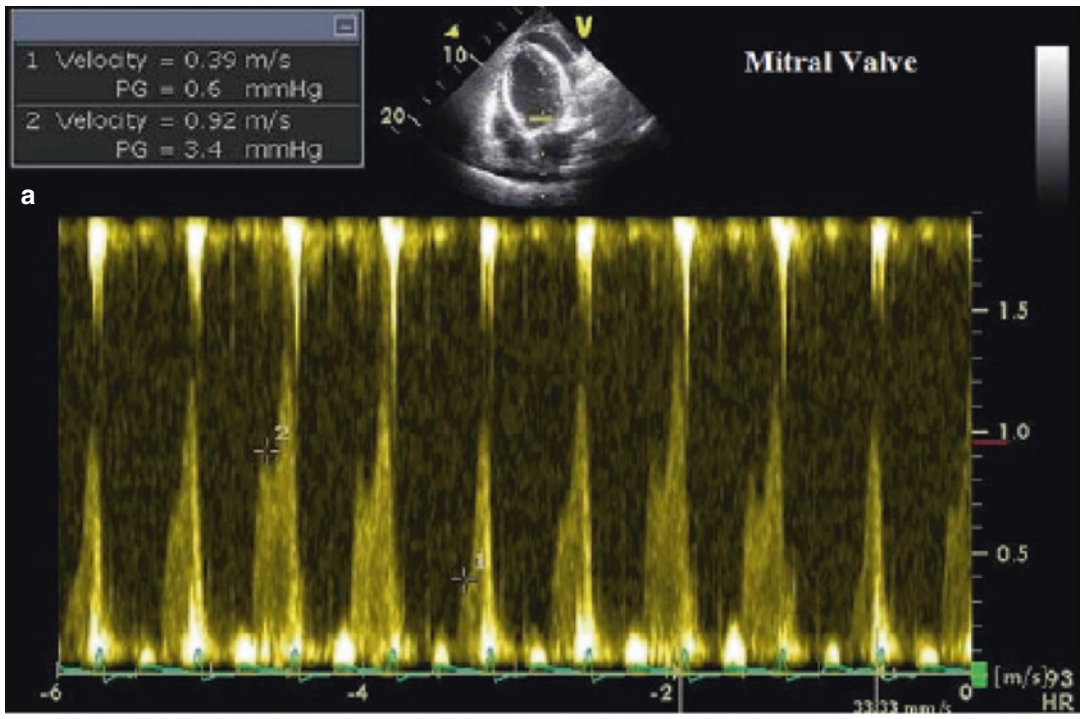

Fig. 15.2 Echocardiogram with Doppler evaluation demonstrating respiratory flow variation across mitral (**a**) and tricuspid valves (**b**)

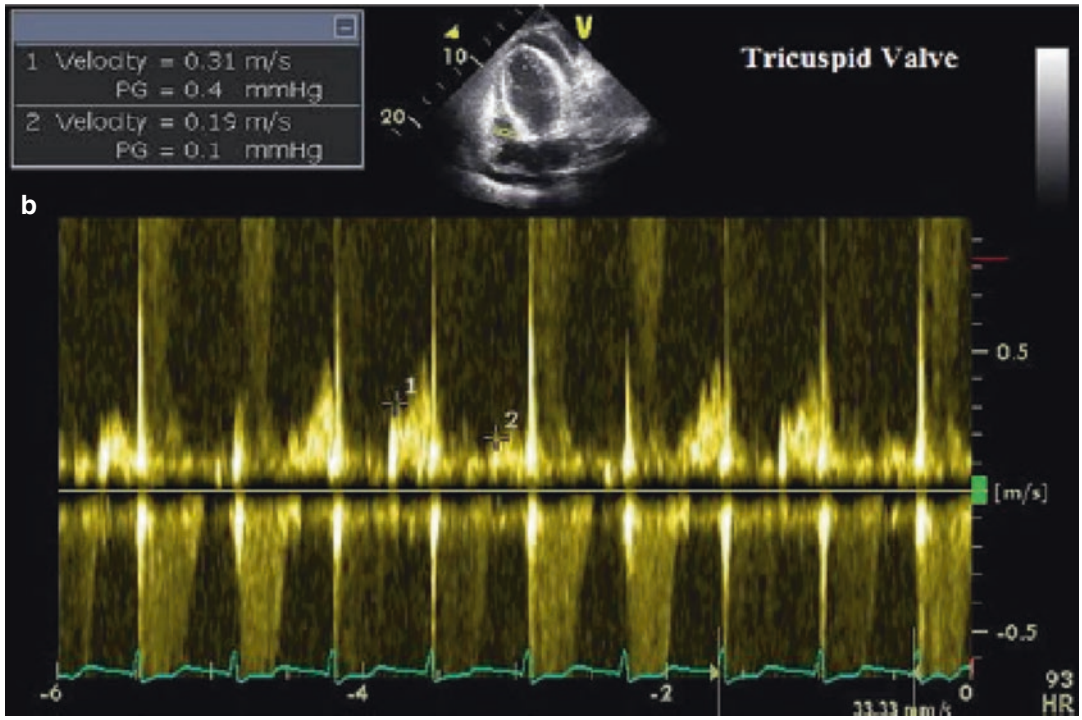

Fig. 15.2 (continued)

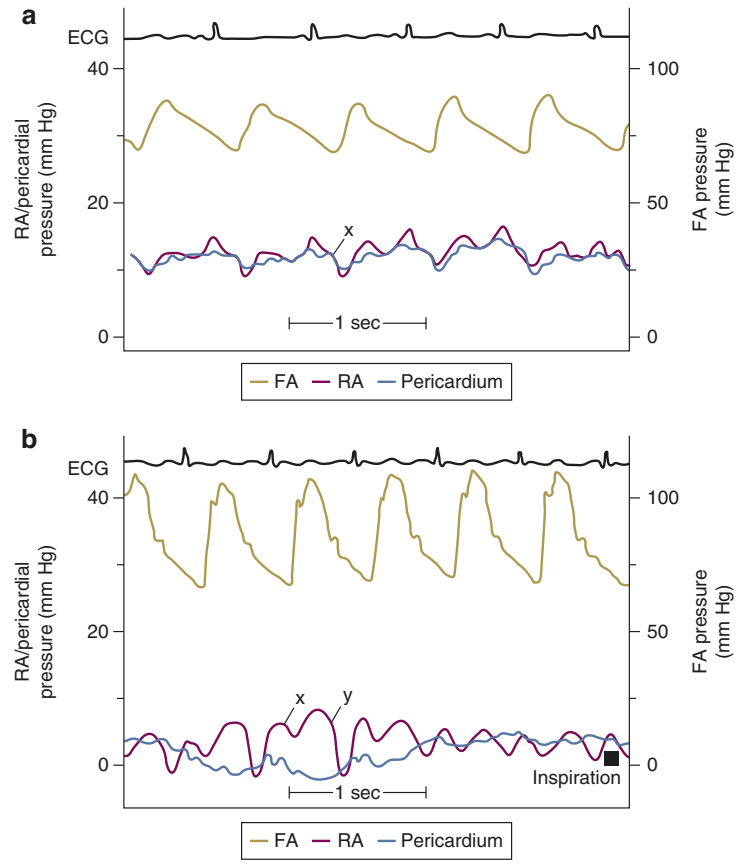

Fig. 15.3 Pre-pericardiocentesis (**a**) and post-pericardiocentesis (**b**). (Reprinted from modification by LeWinter [9])

normally contains up to 50 mL of serous fluid to maintain a low friction environment for the myocardium as it contracts and relaxes within the pericardium throughout the cardiac cycle. The pericardium effectively restrains the cardiac chambers to a confined space and due to this pericardial constraint, any change in the volume of one chamber of the heart is reciprocated by changes in other chambers in the opposite direction [1]. It is this complex interaction of pericardial space with the intracardiac chambers that leads to the hemodynamic consequences of pericardial effusions.

Several diseases and complications of invasive procedures may lead to pathologic accumulation of fluid in the pericardial space, which may impact cardiac output. When the accumulation of pericardial fluid interferes with diastolic filling of the heart, hemodynamic consequences associated with varied clinical presentations including tamponade ensue.

Pathophysiology of Tamponade

Pericardial effusion can be classified according to its onset, size, distribution and composition. The onset can be acute, subacute or chronic (>3 months). The size is based on echocardiogram assessment and is classified as mild (<10 mm), moderate (10–20 mm), or large (>20 mm). Pericardial fluid (exudate, transudate or blood) may distribute in a circumferential or loculated fashion. A variety of different processes can cause pericardial effusion which may eventually lead to cardiac tamponade. Some of these etiologies include malignancy, acute pericarditis, trauma, uremia, iatrogenic, idiopathic, post-acute myocardial infarction, other causes (infection, collagen vascular disease, radiation, heart failure, hypothyroidism).

Progression of a pericardial effusion to tamponade depends on several factors. These include the rate of fluid accumulation, tensile properties of the pericardium, intracardiac pressures, and tensile properties of the myocardium. Ultimately, it is the intrapericardial pressure and its interaction with intracardiac pressures (transmural pressure) that determines the presence of tamponade.

$$\text{Transmural pressure} = \text{intracardiac pressure} - \text{intrapericardial pressure}$$

When the intrapericardial pressure equalizes or exceeds that of the intracardiac chambers, the transmural pressure is then <0, and impaired filling occurs. In patients with pericardial effusions, negative transmural pressure is more often due to increased pericardial pressure but decreased intracardiac pressures also contribute to the development of tamponade.

In cardiac tamponade, increased pericardial pressure from fluid accumulation leads to compression of the cardiac chambers. Hemodynamics of the left and right heart chambers are greatly influenced by each other, which is commonly known as ventricular interdependence. During inspiration, intrathoracic pressure decreases which gets transmitted through the pericardium to the right side of the heart and pulmonary vasculature, causing increased venous return to the right heart. Normally, the free wall expands to accommodate the increased venous return; however, in cardiac tamponade, the free wall cannot expand properly. Hence, the interventricular septum bulges toward the left ventricle to allow right-sided filling, thereby reducing left ventricular compliance and filling during inspiration.

Determinants of intrapericardial pressure include the volume of pericardial fluid and the compliance of the pericardium. The relationship between the size of the effusion and the associated increase in pressure is not linear and is modified by the compliance of the pericardium itself. As such, a larger but chronic effusion might be better tolerated than a smaller but rapidly accumulating one, due to a higher pericardial compliance that develops in the chronic setting (Fig. 15.4). Therefore, the size of the effusion should not be used as a sole criterion for the presence of tamponade.

Progression of a pericardial effusion to tamponade also depends on the intravascular volume status of the patient as well as the compliance of the myocardium. Patients who are intravascularly depleted are more likely to present with compromised hemodynamics due to diminished filling pressures in the cardiac chambers. On the

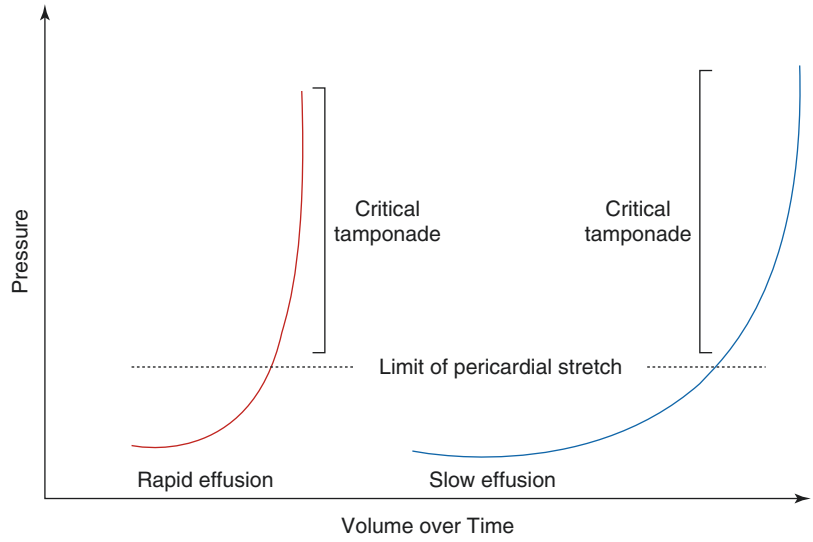

Fig. 15.4 Intrapericardial pressure that is critical in determining the transmural pressure is affected by the time course of fluid accumulation. Rapidly developing effusions reach the limits of the pericardial stretch sooner, whereas slowly developing effusions are better tolerated due to the time allowed for the pericardium to adapt to the changes imposed by the effusion. (Adapted from Spodick [10])

contrary, those with ventricular hypertrophy or restrictive heart disease may not present with tamponade physiology for a given intrapericardial pressure as this pressure is not readily transmitted to the intracardiac chambers due to the diminished compliance of the myocardium.

Table 15.1 Three stages of tamponade

1. Pre-tamponade: no clinical evidence of tamponade as transmural pressure >0; however exaggerated tricuspid and mitral inflow patterns noted
2. Early tamponade: right-sided chambers are affected as the pericardial pressure increases. Clinical presentation might become apparent
3. Tamponade: both right and left-sided chambers are affected as there is equalization of pressures with pericardium. Clinical tamponade is evident

Stages of Pericardial Tamponade

Pericardial tamponade was previously thought of as an "all or none" clinical disorder [2]. However, it is now recognized that patients might present at different stages along the spectrum of tamponade physiology (Table 15.1). The first stage (pre-tamponade) occurs when the pressure in the pericardium is less than right and left ventricular end diastolic pressures (transmural pressure still >0). In this stage, the effusion does not have a clinically significant hemodynamic impact; however, there may be subtle changes in echocardiographic respiratory flow variation across mitral and tricuspid valves and minimally increased pulsus paradoxus pressure (<10 mmHg). In the second stage, the pericardial pressure equals the right ventricular diastolic pressure leading to collapse of the right ventricle during early diastole. In this case, while there is no collapse in the left ventricle, clinical and hemodynamic evidence for tamponade is present with decrease in right ventricular stroke volume. Hypotension, compensatory tachycardia, and elevated pulsus paradoxus might be present. Finally, the most severe stage presents when left ventricular filling is also affected by the increased pericardial pressure. In this case, there is equilibration of pericardial, right ventricular and left ventricular diastolic pressures leading to severely impaired filling of the ventricles and low stroke volume (Fig. 15.5) [3]. Patients in the final stage of tamponade require expeditious diagnosis with direct intervention to drain the pericardial fluid and reestablish hemodynamic stability.

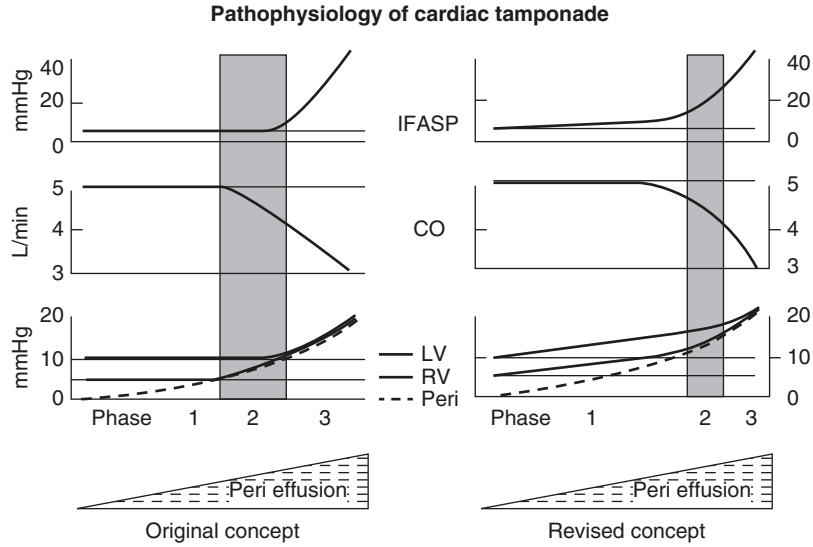

Fig. 15.5 Stages of pericardial tamponade showing pressures in the right atrium, right ventricle, pulmonary capillary wedge pressure, and intrapericardium (peri pericardium, RV right ventricle, LV left ventricle, CO cardiac output, IFASP inspiratory decrease in arterial systolic pressure). Initial concept and its revision with further data are shown below detailing changes in the pressures across stages of tamponade. (Adapted from Reddy et al. [3])

Low-Pressure Tamponade

This condition has been described as a form of tamponade in which relatively low intrapericardial pressure causes cardiac chamber compression in patients with low diastolic pressures (6–12 mmHg). Reported to be present in 20% of patients with tamponade physiology, this condition might be associated with hypovolemia and/or vasodilator and diuretic use [4]. Overall, findings from pulmonary artery catheterization are similar, with equalization of diastolic pressures noted, albeit at lower pericardial and diastolic pressures. Characteristic respiratory fluctuations in transvalvular diastolic Doppler flows are also typically noted. Given the low pressures, patients might not present with typical physical examination findings (elevated JVD, tachycardia); however, they do benefit from pericardiocentesis [4]. When evaluating a patient with a pericardial effusion and hypotension, this clinical entity should be kept in mind.

Diagnosis

Physical Exam Findings

While physical exam might vary in patients with tamponade, there are certain classic findings as defined by Dr. Claude Beck in 1935: low blood pressure, jugular venous distention, and muffled heart sounds. While all three might not be present even in the most advanced cases of tamponade, hypotension and tachycardia, with a narrow pulse pressure, should alert the clinician to its presence.

Pulsus Paradoxus

Originally described by Kussmaul in 1873, pulsus paradoxus is defined by a $\geq$ 10–12 mmHg or a > 9% decline in arterial systemic pressure with inspiration [5]. While the etiology of this drop is debatable, the most widely accepted explanation has to do with intrathoracic pressure changes with

inspiration and the fact that the total volume within the pericardium is fixed. Intrapericardial pressure normally ranges from −5 to +5 cm of water and fluctuates significantly with respiratory cycle. The drop in the intrathoracic pressure with inspiration is transmitted to the pericardium and the right atrium which results in increased venous return to the right side of the heart. The opposite occurs in the left heart, where there is diminished filling of the left ventricle in early inspiration and slightly reduced systemic stroke volume. The reverse is true in expiration: As the intrathoracic pressure increases, the right-sided filling diminishes resulting in improved filling of the left ventricle leading to a higher systemic stroke volume. In a normal individual, these respiratory changes result in a 3–4 mm change in systolic pressure as measured peripherally. When there is a hemodynamically significant tamponade, however, there is interventricular dependence of LV and RV, which leads to exaggeration of the above-described pressure changes with respiration. This is due to the fixed space that the myocardium is constrained within as the increased filling of the RV compromises the filling of the LV, which subsequently leads to the diminished systemic stroke volume with the next contraction. As the underfilled LV cannot generate the normal stroke volume, the blood pressure drops >10 mmHg, which is recognized as pulsus paradoxus on physical exam.

While checking for the presence of pulsus paradoxus allows for quick assessment of patient at the bedside, several coexisting conditions might diminish the accuracy of this test. In patients who have lung disease and shock, pulsus paradoxus might already be present without tamponade. Also, this finding might be absent despite a hemodynamically significant tamponade in the presence of coexisting LV dysfunction with elevated LVEDP, severe aortic insufficiency, pulmonary hypertension, and right ventricular hypertrophy [6, 7].

ECG Findings

Sinus tachycardia, low QRS voltage and electrical alternans are possible ECG findings in tamponade. Sinus tachycardia is the most common finding as heart rate increases to help maintain cardiac output. The amplitudes of the QRS complexes can be low as the fluid collection between the heart and the recording electrodes have a damping effect. Electrical alternans is a phenomenon where QRS complexes alternate in height as the heart swings back and forth within a large fluid filled pericardium (Fig. 15.1). This is a relatively specific finding for tamponade; however, it is not very sensitive.

Echocardiographic Findings

Although tamponade is a clinical diagnosis, echocardiographic evaluation of the patient is a very useful adjunct as it provides direct visualization of the pericardium, the cardiac chambers, and early hemodynamic signs of tamponade physiology. Several echocardiographic parameters may be used to evaluate for evidence of tamponade including M-mode, Doppler interrogation, and 2D visualization. While 2D and M-mode provide visual confirmation of the effusion and the collapse of chambers, Doppler evaluation can be useful in determining the abovementioned flow variations in tamponade (Table 15.2).

Exaggerated diastolic right atrial free wall collapse and diastolic right ventricular outflow tract collapse are early signs of elevated intrapericardial pressure. Brief inversion of the atrial wall can be seen during atrial contraction and does not represent tamponade physiology. Prolonged atrial wall inversion (>1/3 of cardiac cycle) is more indicative of increased intrapericardial pressures. The right ventricular outflow tract is the most easily compressible component of the right ventricle, and may also be affected early

Table 15.2 Evidence of tamponade on echocardiogram

Presence of an effusion. Size, while predictive, is not a reliable determinant of clinical tamponade
Early diastolic collapse of right ventricle
Late diastolic right atrial inversion
Dilated inferior vena cava (>2.5 cm) with failure to collapse of the vessel with inspiration >50%
Respiratory inflow variations across the tricuspid valve (>40%) and the mitral valve (>25%)

Table 15.3 Typical order of findings in tamponade

Tricuspid inflow variation with respiration increased
Mitral inflow variation with respiration increased
Right atrial exaggerated late diastolic collapse (sensitive, nonspecific finding on echocardiogram)
Right ventricular outflow tract collapse (specific finding on echocardiogram)
Right ventricular free wall collapse
Left ventricular free wall collapse

from elevated intrapericardial pressure. As the intrapericardial pressure increases, the right ventricular free wall may also collapse in diastole. Collapse of these above right-sided chambers is indirect evidence that the intrapericardial pressure has exceeded the intracardiac pressures, leading to the inversion of the free walls [1]. As tamponade progresses, further collapse of the left ventricle can also be seen due to similar mechanisms (Table 15.3). Both 2D and M-mode techniques may be used to identify these anatomic manifestations of tamponade.

Doppler evaluation is very helpful in assessing the hemodynamic impact of the pericardial effusion. Outflow across aortic and pulmonary valve (Velocity Time Integral) and inflow across mitral and tricuspid valves (peak velocity) can be measured. In a normal patient, these parameters of flow demonstrate minimal respiratory variation, with the pulmonic and aortic valve velocity time integral varying <10% and the mitral and tricuspid valve peak inflow velocities varying <15% and <25%, respectively. In patients with tamponade, however, respiratory variation across the mitral valve is usually >25% and that across the tricuspid valve >40% (Fig. 15.6). This exaggerated variation in flow across valves provides indirect evidence for ventricular interdependence and suggests a hemodynamically significant effusion.

Also helpful, although often ignored, is the Doppler flow pattern of the hepatic vein. The hepatic vein flow pattern reflects the venous pressure. The normal hepatic vein flow has three major waves: positive systolic and diastolic flows (toward the atrium) and a negative flow corresponding to the atrial contraction (away from the atrium). The systolic flow wave corresponds to the *x* descent and the diastolic flow wave to the *y* descent. In patients with tamponade physiology, blood enters the right atrium only or mostly during ventricular systole. This is reflected in the hepatic vein flow as a predominant systolic wave with decreased or even absent diastolic flow wave (i.e., corresponding to blunted *y* descent on the RA tracing). After pericardiocentesis, the diastolic flow is reestablished (Fig. 15.7).

Pulmonary Artery Catheter Findings

While not routinely used for diagnosis, insertion of a pulmonary artery catheter may provide insight into the pathophysiology of tamponade as it can help clarify the diagnosis.

The cardinal finding on PA catheterization during tamponade is diastolic equalization of pressures of the right atrium, RV diastolic pressure, pulmonary arterial diastolic pressure, and pulmonary capillary wedge pressure. A difference <5 mmHg suffices to establish this equivalency. This pressure is felt to be the passive pressure in the intra-cardiac chambers and should be equal to the intrapericardial pressure in severe tamponade (Fig. 15.8).

As mentioned above, the other abnormal finding is blunted *y* descent following the *v* wave in the right atrial tracing. In tamponade, the *a* wave, *x* descent, and *v* wave remain unaffected as the contraction of the atrium, its relaxation, and rapid filling remain unchanged. The *y* descent, which represents the rapid emptying of the atrium into the right ventricle, is blunted. This is due to the impaired RV relaxation in early diastole due to the effusion-related elevation in RV diastolic pressure. Thus, the rapid emptying of atrium to ventricle, i.e., the *y* descent is blunted (Fig. 15.9). This finding is readily reversed when pericardiocentesis is performed and the intrapericardial pressure is reduced. As the right ventricle is able to relax more efficiently, there is improved flow from the atrium to the ventricle hence a normalized *y* descent.

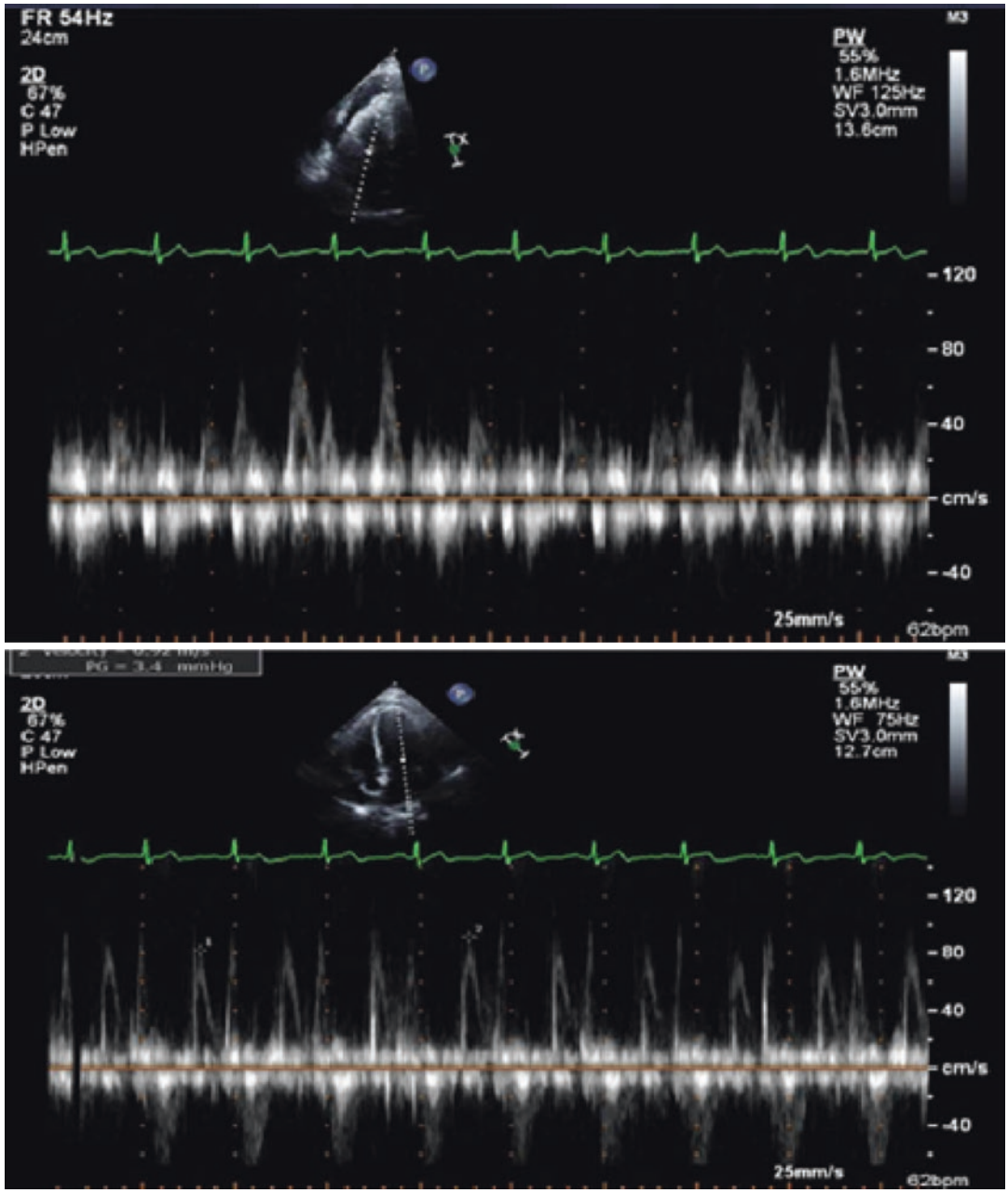

Fig. 15.6 *Top panel* showing tricuspid and *bottom panel* showing mitral valve inflow pattern

Distinction from Constriction

Intrathoracic pressures and changes during inspiration are readily transmitted to the pericardium and the intracardiac chambers in the case of a pericardial effusion with a relatively normal pericardium. In patients who have constrictive pericardium, these pressures are not transmitted, which as a result leads to differences in physical exam and invasive hemodynamic findings. Constriction is notable for lack of decreased right-sided pressure with inspiration, leading to the Kussmaul's sign, a finding not seen in

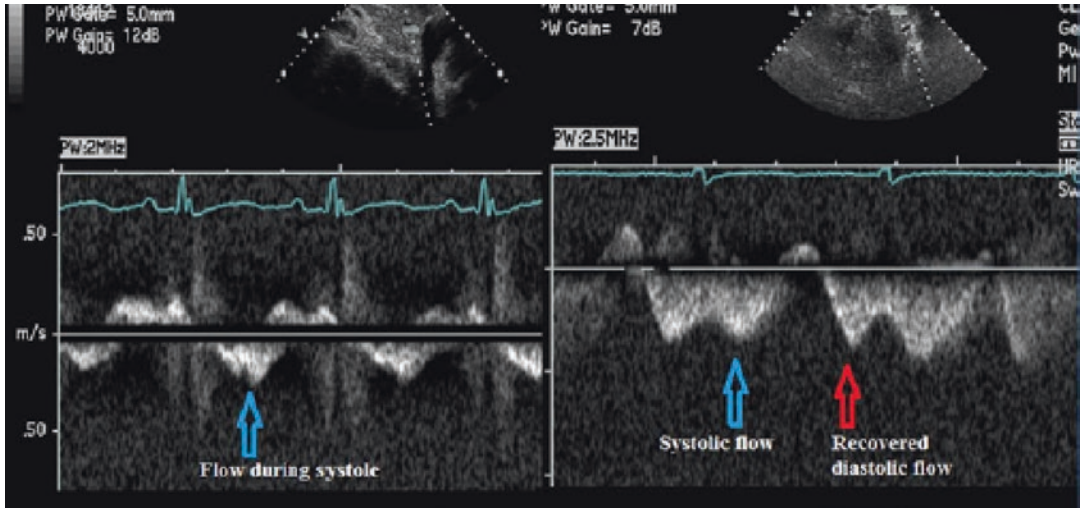

Fig. 15.7 Hepatic vein tracing showing flow to the atrium predominantly during systole and blunted return in diastole. After pericardiocentesis, flow to atrium during diastole is recovered

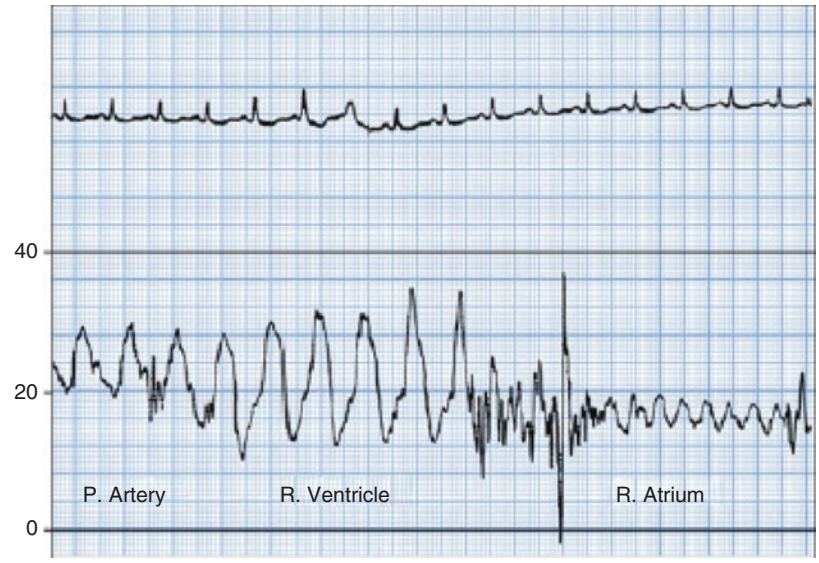

Fig. 15.8 Diastolic equalization of right atrial (mean), right ventricular end diastolic, pulmonary arterial diastolic pressures demonstrated as the PA catheter is pulled back from the pulmonary artery

tamponade. Furthermore, in patients with constriction, there is rapid ventricular filling in early diastole, which is recognized as a prominent *y* descent with a "dip and plateau" appearance (square-root sign) on pulmonary artery catheterization. Such is not the case for tamponade where ventricular filling in early diastole is in fact impaired leading to a blunted *y* descent.

Computed Tomography and Magnetic Resonance Imaging

Advanced imaging such as CT and MRI may be useful to evaluate chronic pericardial effusions but should not be used in the setting of tamponade.

Pericardial effusion might be incidentally diagnosed with these imaging modalities. CT

Fig. 15.9 Right atrial pressure waveform with blunted *y* descent

findings of tamponade include enlargement of the inferior vena cava (IVC) with possible reflux of contrast material within the IVC, enlargement of the vena cava, reflux of contrast material within the azygous vein, flattening of the anterior surface of the heart, and enlargement of hepatic and renal veins [8]. These findings are not specific but collectively can suggest tamponade.

When cardiac tamponade is suspected, clinical assessment of the patient should be performed. In the event that there is a question of tamponade, hemodynamic assessment with a focused physical exam and echocardiography should not be delayed. MRI, in fact, can provide further hemodynamic information in these patients; however, when tamponade is suspected, testing and treatment should not be delayed for performing this test.

Pericardial Tamponade in the Postsurgical Patient

While most effusions seen in clinical practice are circumferential, loculated effusions may be seen in postoperative settings and post trauma. Chronic effusions, though initially circumferential, might organize into loculated effusions as well. In this setting, the aforementioned discussions about hemodynamics might not hold true. There may be focal compression of a cardiac chamber that might only be visible by 2D echocardiography. Doppler findings are also less helpful in postsurgical effusions; it is not uncommon to see exaggerated respiratory flow variation even in patients with small effusions. This may be due to increased respiratory effort secondary to pleural effusions or abnormal respiratory dynamics. When a case of focal tamponade is suspected, the clinical status of the patient and location of the effusion should be carefully assessed for further management.

Management

Patients who present with clinical tamponade should be treated emergently. While preparing the patient for removal of the pericardial fluid, intravenous administration of fluids to maintain adequate perfusion pressure is necessary. The administration of fluids improves the intracardiac filling and might stabilize the patient's hemodynamics by increasing the transmural pressure. Either a pericardiocentesis or a pericardial window might be necessary to resolve the compression of the cardiac chambers. Typically anterior,

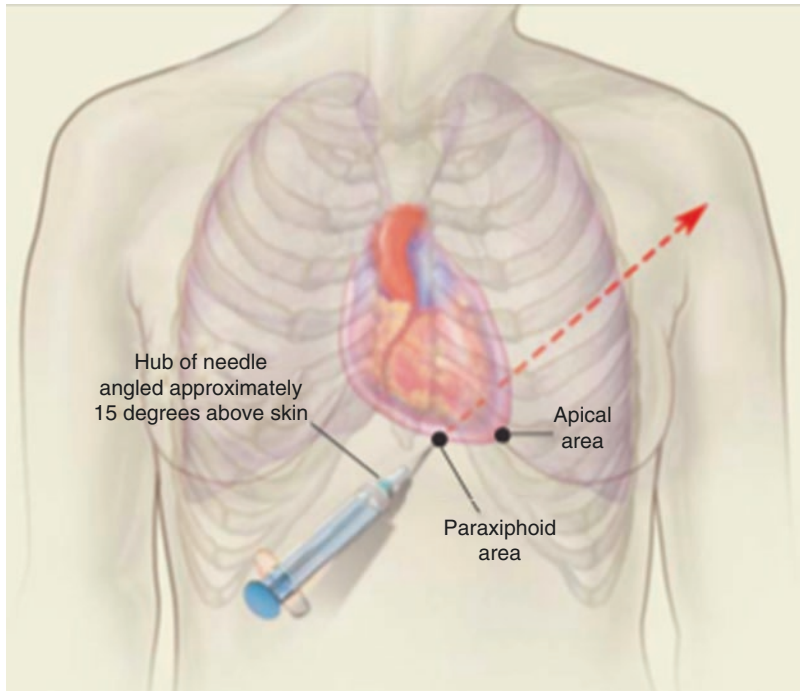

Fig. 15.10 Pericardiocentesis can be performed using paraxiphoid approach where the needle is inserted between xiphoid process and left costal margin at a 15° angle above the skin. In apical approach, the needle is inserted 1–2 cm lateral to the apex within the fifth, sixth, or seventh intercostal space. (Adapted from Spodick [10])

lateral, and apical effusions might be drained by a percutaneous approach; however, surgical drainage is preferred for postoperative patients, loculated, and posterior effusions. The risks and benefits of both approaches in conjunction with the clinical scenario should be taken into account (Fig. 15.10).

Pearls of Assessment

- Pericardial tamponade is a clinical diagnosis.
- Tamponade occurs when transmural pressure is <0.
- When tamponade is in question, all measures for accurate diagnosis and stabilization of the patients should be undertaken.
- Echocardiography is the primary modality to establish the presence of an effusion and support the clinical diagnosis of tamponade.
  - Right atrial and/or ventricular wall inversion.
  - Increased respiratory variation in mitral and tricuspid flows.
  - IVC plethora – dilated IVC with blunted diastolic hepatic vein flow is the most sensitive early echocardiographic finding in tamponade. This may be absent in patients with low-pressure tamponade.
- Pulmonary artery catheterization might be useful to confirm the clinical suspicion in select cases.

Board-Style Questions

1. A 72-year-old man presents with exertional dyspnea and work up including an echocardiogram shows a large pericardial effusion. Which of the following is more specific sign of tamponade?
   A. Systolic flow reversal in hepatic veins
   B. Early diastolic collapse of right atrium
   C. Diastolic collapse of right ventricle
   D. Hypotension in a patient with pericardial effusion
   E. Presence of a large pericardial effusion

2. A 67-year-old female with morbid obesity and rheumatoid arthritis presents with hypotension of unclear etiology. An echocardiogram is performed; however, parasternal and apical windows are difficult to interpret due to body habitus, but there is a moderate circumferential pericardial effusion. Best Doppler hemodynamics are only obtained in the subcostal views. What's expected in the hepatic vein flow pattern in the setting of tamponade?
   A. Diminished forward flow during systole
   B. Diminished forward flow during diastole
   C. Flow reversal during systole
   D. Hepatic vein flow pattern is not expected to change with tamponade
   E. Exaggerated forward flow during diastole
3. Which of the following is not a part of Beck's triad?
   A. Muffled heart sounds
   B. Hypotension
   C. Elevated JVD
   D. Kussmaul's sign
4. A 39-year-old female with a history of tuberculosis as a child presents with pitting peripheral edema and increased fatigue. Echocardiographic evaluation shows pericardial thickening with a moderate effusion. Her heart rate is 102 and blood pressure is 94/64. Which of the following can be helpful in distinguishing tamponade from constriction?
   A. Presence of a pericardial effusion
   B. Absence of Kussmaul's sign
   C. Pericardial thickening seen on CT
   D. Exaggerated flow across tricuspid valve during inspiration
   E. None of the above
5. What's the initial treatment strategy in a hypotensive and tachycardic patient with a pericardial effusion if tamponade is suspected?
   A. Pericardiocentesis
   B. IV fluid infusion
   C. Inotrope infusion
   D. Consultation with cardiothoracic surgery for a pericardial window
   E. Beta blocker administration

Answers to Board-Style Questions

1. Correct answer is C. Systolic flow reversal in hepatic veins is seen in severe tricuspid regurgitation. While options other than C can be seen in tamponade, they are not specific to tamponade.
2. Correct answer is B. Diastolic forward flow is expected to be reduced in the hepatic veins due to elevated right ventricular pressures. Other options do not apply in tamponade.
3. Correct answer is D. Beck's triad consists of muffled heart sounds, hypotension, and elevated neck veins.
4. Correct answer is B. Other options can be seen with both conditions; however, Kussmaul's sign is specific to constriction and is not seen with tamponade.
5. Correct answer is B. An unstable patient in tamponade needs to be fluid repleted emergently in attempt to overcome the pericardial pressure. Further treatment modalities might include pericardiocentesis or a surgical window placement. Beta blockers are contraindicated in compensatory tachycardia.

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Constructive Pericarditis and Restrictive Cardiomyopathy

16

Chun Pong Wong and Allan Klein

Introduction

Despite being different disease processes, constrictive pericarditis (CP) and restrictive cardiomyopathy (RCM) are often discussed together due to their similar clinical and hemodynamic features. Physiologically, both processes lead to diastolic dysfunction but mechanisms are different; a rigid, adherent pericardium is noted in constriction while abnormal myocardium is the culprit in restriction. CP is usually a chronic process, and variant forms do exist (effusive-constrictive, subacute, transient, occult) which share many of the clinical findings, but have subtle clinical differences that distinguish each type. In RCM, the pericardium is merely normal, and the pathological process occurs in the myocardium which is often associated with infiltrative diseases such as amyloidosis, hemochromatosis, sarcoidosis, etc. Given the spectrum of disease and the various clinical manifestations of CP and RCM, initial history and physical examination along with hemodynamic considerations and newer non-invasive imaging criteria now lead the way in making the diagnosis. However, using all available data in distinguishing between the two diseases becomes important, as the treatment is very different.

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Pathophysiology

Constrictive Pericarditis

Constrictive pericarditis is a form of diastolic heart failure caused by an inelastic pericardium that inhibits cardiac filling. Because its treatment differs markedly from all other forms of heart failure, accurate diagnosis is imperative.

The overall incidence of clinical CP is rare. After an episode of acute pericarditis, only 1.8% of patients have been found to develop chronic CP. The incidence was lower in patients with idiopathic or viral pericarditis when compared with other etiologies such as rheumatologic disease, malignancy, or bacterial infection. In patients after cardiac surgery, the incidence of chronic, symptomatic CP appears to be similarly low, with the reported rates of 0.2–2.4%. It is unknown how often constrictive physiology is detected on imaging in these diseases.

In Europe and North America, most cases are idiopathic, related to prior cardiac surgery or chest irradiation. There are also increasing number of cases of post cardiac injury syndrome especially in patients after invasive cardiac procedures, e.g. cardiac surgery, radiofrequency

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_16

ablation for atrial fibrillation, automated implantable cardioverter defibrillator implantation, etc.

However, in other parts of the world, tuberculosis still remains a dominant cause of CP. Other possible causes include connective tissue disease, infection, malignancy, trauma and asbestosis [1].

Hippocrates (c. 460–370 BC) described the normal pericardium as "a smooth mantle surrounding the heart and containing a small amount of fluid resembling urine" [2]. The pericardium, a roughly flask-shaped membranous sac, envelops almost the entire heart except the region of left atrium around the pulmonary venous ostia. It consists of fibrous and serosal component. The outer fibrous sac is composed primarily of collagen fibers with interspersed short elastic fibrils. The serosal component consists of a single layer of mesothelium that forms a parietal and a visceral layer enclosing the pericardial cavity. The parietal layer lines the fibrous pericardium, and together, these structures form the parietal pericardium (Fig. 16.1a, b). The visceral layer is also known as the epicardium and covers the heart (Fig. 16.1c, d). Between the visceral pericardium and the myocardium is a variable amount of epicardial fat. The pericardial cavity normally contains <50 mL of serous fluid which serves as a lubricant during cardiac motion between the adjoining layers to prevent irritation.

The fibrous pericardium is relatively elastic at low volumes but when stretched it becomes rapidly inelastic. The pericardial pressure-volume relationship is non-linear; initially the slope is flat but subsequently becomes very steep, and this also depends on the rate of fluid accumulation (Fig. 16.2). When a scarred or calcified, noncompliant pericardium becomes adherent to various areas on the surface of the heart, in the case of constriction, the cardiac chambers are unable to relax completely during diastole due to extrinsic limits placed by the pericardium. As a result, in the ventricles, mid- and late-diastolic filling occurs earlier in diastole as the constraining force on the ventricle prevents further expansion and filling of the cavity leading to elevation in end-diastolic pressures and decrease in cardiac output. Once identified, pericardial "stripping"/pericardiectomy is the treatment of choice, as medical therapy alone will typically not provide symptomatic relief.

During inspiration, negative intrathoracic pressure is developed (−6 to 0 mmHg), and it is transmitted to the heart via the pericardium and pericardial space of right atrium (RA). This negative pressure results in increased systemic venous return to the right heart as well as augmenting passive filling of the right ventricle (RV). In the presence of a normal pericardium, as the RV fills, the free walls are able to expand and allow for the capacitance of RV. In CP, this process is impeded as the rigid encasement of the ventricles prevents transmission of the negative intrathoracic pressure to the heart. As the stiff outer shell limits capacitance, the RV free walls are unable to expand and accommodate the increased systemic venous inflow during inspiration. This leads to bowing of the septum toward the left ventricle (LV) to accommodate the volume of the RV inflow. The pulmonary venous circulation, which sits outside of the pericardium, behaves similarly to changes in intrathoracic pressure as the systemic venous system, thus leading to changes in LV filling during the respiratory cycle. On inspiration, the pulmonary venous pressure decreases; however, the negative intrathoracic pressure is not transmitted to the LV, leading to decreased flow gradient across the LV and thus limiting LV filling. During expiration, positive intrathoracic pressure reduces systemic venous return leading to decreased RV end-diastolic pressure. Passive filling of the LV now overcomes RV pressure and the interventricular septum shifts rightward into the RV. This phenomenon is known as *ventricular interdependence*; it occurs to a lesser extent in normal physiology but is exaggerated in CP.

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is a myocardial disorder that usually results from increased myocardial stiffness leading to impaired ventricular relaxation with restricted filling. Biventricular chamber size and systolic function are usually normal or near normal until later stages of the

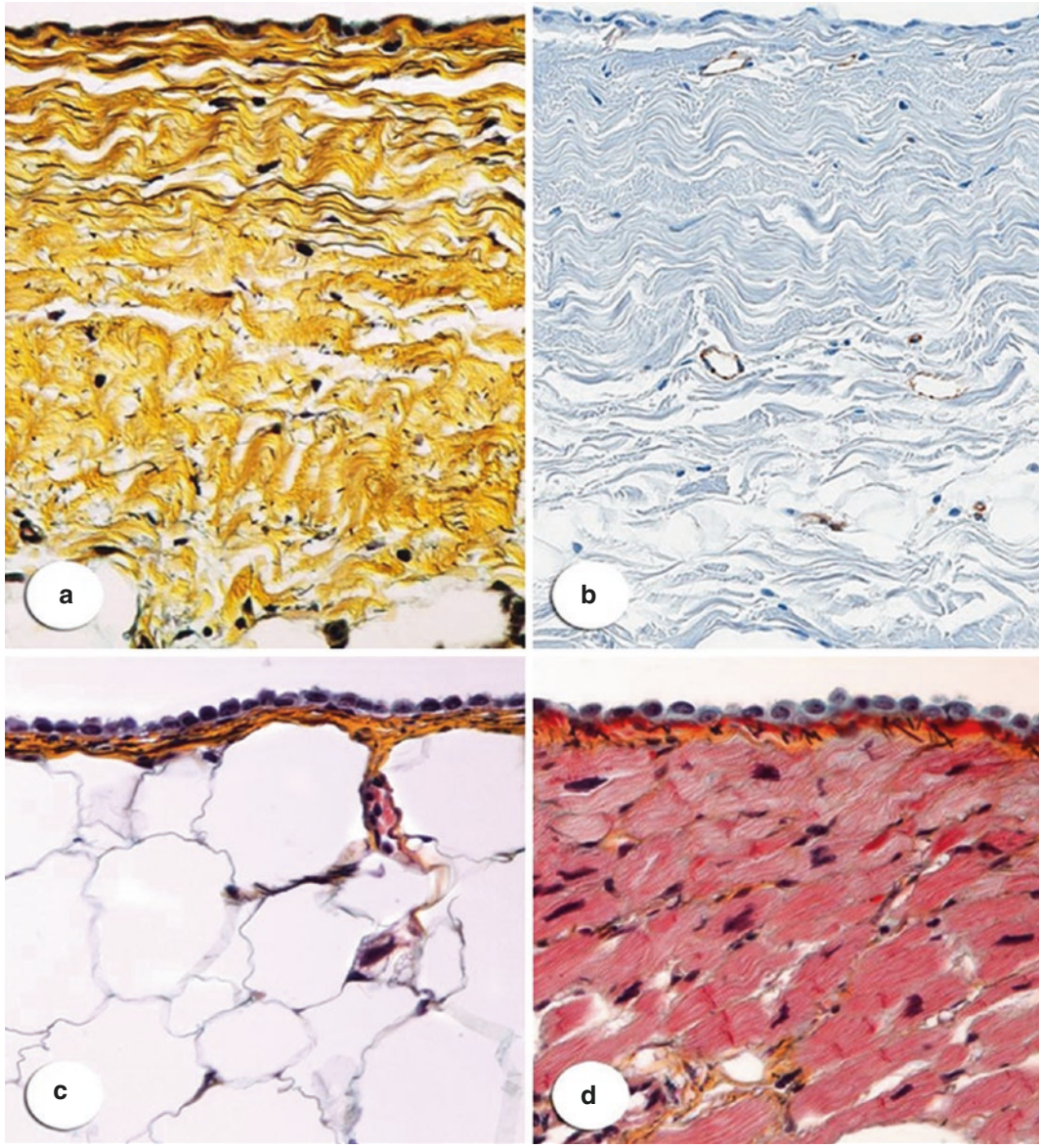

Fig. 16.1 (**a**) Normal, full-thickness parietal pericardium is shown. It consists of a layer of mesothelial cells and compact layers of dense wavy collagen (yellow) with interspersed short elastic fibers (black). (**b**) Fibroblasts with elongated nuclei and scant thin blood vessels are normally present in the parietal pericardium. CD34 immunostaining highlights the endothelial cells of capillaries. (**c**) The visceral pericardium (also called epicardium) consists of a mesothelial cell layer and a thin subepithelial layer of collagen with elastic fibers. The mesothelial cells show distinct microvilli. Beneath the visceral pericardium is epicardial adipose tissue. (**d**) In other areas of the visceral pericardium (or epicardium), only a thin layer of fibrous tissue (yellow) separates the mesothelial cells from the myocardium with absence of epicardial fat. Original magnifications 400×; (**a**, **c**, and **d**): Movat pentachrome stain; (**b**): CD34 immunoperoxidase. (From Klein et al. [9])

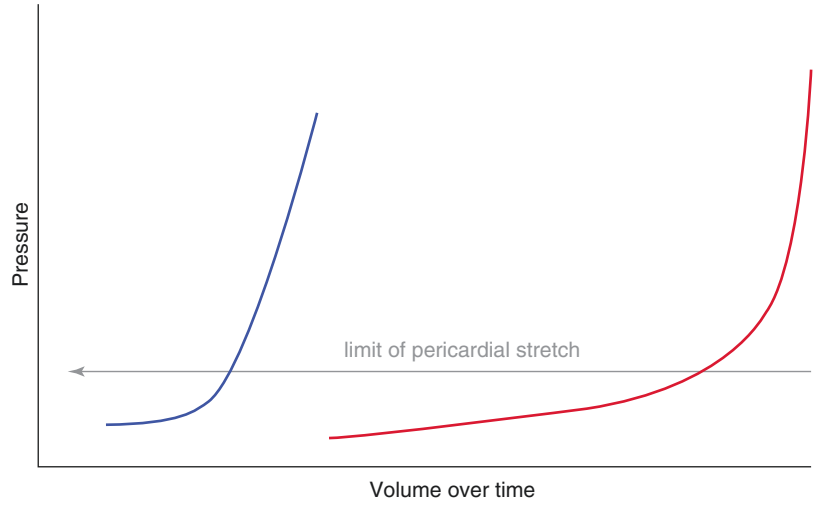

Fig. 16.2 Pericardial pressure-volume curves are shown in which the volume increases slowly or rapidly over time. (Blue curve) Rapidly increasing pericardial fluid first reaches the limit of the pericardial reserve volume (the initial flat segment) and then quickly exceeds the limit of parietal pericardial stretch, causing a steep rise in pressure, which becomes even steeper as smaller increments in fluid cause a disproportionate increase in the pericardial pressure. (Red curve) A slower rate of pericardial filling takes longer to exceed the limit of pericardial stretch, because there is more time for the pericardium to stretch and for compensatory mechanisms to become activated

disease. Affecting either or both ventricles, RCM may cause signs or symptoms of left and/or right heart failure. There may be associated arrhythmias and conduction disturbances. RCM may result from inherited or acquired predispositions and disease or a combination; thereof, which broadly can be classified as infiltrative, storage disease, non-infiltrative, and endomyocardial. Histologically, the infiltrative disorders are associated with deposits in the interstitial space between myocytes, while storage disorders focus primarily on accumulation within the cardiac myocytes. Due to the heterogenous nature of the origins and manifestations of RCM, and the concomitant challenges in diagnosing these diseases, the incidence and prevalence of RCM cannot be accurately estimated.

RCM can also be classified as genetic/familial or non-genetic/non-familial. Familial RCM is often characterized by autosomal dominant inheritance, which in some families is caused by mutations in the desmin gene; in others, familial RCM is associated with conduction defects, caused by mutations in the desmin gene, usually associated with skeletal myopathy. Rarely, familial cases can be associated with autosomal recessive inheritance, e.g. hemochromatosis or glycogen storage disease, or with X-linked inheritance, e.g. Fabry disease [3].

RCM is the least common type of cardiomyopathies [4]. The pericardium and pericardial compliance are normal in pure restrictive cardiomyopathies; however, depending on the cause (e.g. radiation), features of both restriction and constriction can coexist.

Pathophysiologically, the increased stiffness of the LV leads to rapid changes in LV pressure with incremental volume increases. This leads to the characteristic hemodynamic "dip-and-plateau" filling pattern, due to rapid early diastolic filling (dip) and cessation or diastasis of flow in mid- and late-diastole (plateau).

Evaluation

History/Clinical Presentation

Distinguishing between constriction and restriction is often difficult due to similar presenting

symptoms and physical findings. However, there are subtle findings in the history and physical examination that can help to differentiate which process is responsible for the patient's symptoms. The history should be aimed at elucidating any etiologies for either constriction or restriction. For example, an antecedent history of cardiac trauma, cardiac surgery/procedure, or pericarditis would favor constriction, while a prior history of infiltrative or glycogen storage diseases, e.g. amyloidosis, sarcoidosis, or hemochromatosis, suggests restriction. More importantly, a history of radiotherapy especially mantle radiation can lead to symptoms via a myriad of physiological processes including constriction, restriction, pulmonary fibrosis, as well as valvular heart disease. Patients will present with a varying degree of symptoms depending on how advanced the disease process is. Dyspnea on exertion or at rest, edema (lower extremity, ascites, and effusions), pulmonary congestion, and eventually symptoms of low cardiac output are noted in both processes. Late stages of both are heralded by severe heart failure. Table 16.1 lists the different etiologies of CP and RCM.

Physical Examination

Most patients with CP and RCM have elevated jugular venous pressure (JVP). Kussmaul's sign is a paradoxical rise in JVP on inspiration, or a failure in the appropriate fall of the JVP with inspiration. Due to the inability of the RA to accommodate increased venous return, JVP paradoxically increases with inspiration. Kussmaul's sign can be seen in both conditions; however, it is more common in CP. A steep/rapid *Y*-descent of the JVP, i.e. Friedreich's sign, along with peripheral edema, ascites, hepatic congestion, and pleural effusions can also be seen in both conditions as the markers of right-sided heart failure. Physical findings suggestive of CP are the presence of a pericardial knock which occurs at the nadir of the Y-descent and is the diastolic gallop usually heard before S3 consistent with abrupt cessation of ventricular filling; friction rub if active pericarditis; and apical retraction which is secondary to the inability to transmit a palpable ventricular impulse due to a calcified pericardium. An audible S3 and prominent apical impulse are more indicative of restriction. Pulsus

Table 16.1 Causes of constrictive pericarditis and restrictive cardiomyopathy

Constrictive pericarditis	Restrictive cardiomyopathy	
Idiopathic	*Infiltrative*	*Storage diseases*
Viral	Amyloidosis	Fabry disease
Post-surgical	Sarcoidosis	Gaucher disease
Post-radiotherapy	Primary hyperoxaluria	Hemochromatosis
Connective tissue disease	*Endomyocardial*	Glycogen storage disease
Post-MI (Dressler's syndrome)	Carcinoid heart disease	Mucopolysaccharidosis type I (Hurler syndrome)
Post-infectious	Endomyocardial fibrosis	Mucopolysaccharidosis type II (Hunter syndrome)
Uremia	Hypereosinophilic syndrome	Niemann–Pick disease
Sarcoidosis	Chronic eosinophilic leukemia	*Non-infiltrative*
	Drugs (serotonin, methysergide, ergotamine, mercurial agents, busulfan)	Diabetic cardiomyopathy
	Endocardial fibroelastosis	Scleroderma
	Consequence of cancer/cancer therapy	Myofibrillar myopathies
	Metastatic cancer	Pseuxanthoma elasticum
	Drugs (anthracyclines)	Sarcomeric protein disorders
	Radiation	Werner's syndrome

Adapted from Muchtar et al. [4]

paradoxus, which is defined as an abnormal (>10 mmHg) decrease in systolic blood pressure with inspiration, is seen occasionally in CP cases involving pericardial effusion, such as effusive-constrictive pericarditis.

Chest Radiography and Electrocardiography

Pericardial calcification is often seen on chest X-ray and is indicative of CP; however, it is not always present (Fig. 16.8a, b). Cardiomegaly due to biatrial, rather than ventricular enlargement is seen in cases of restrictive cardiomyopathy. Electrocardiography (ECG) findings, such as atrial fibrillation and repolarization abnormalities, are often seen in both conditions, while LV hypertrophy, low voltage QRS, and conduction abnormalities may be a clue to the presence of restriction.

Echocardiography

Echocardiography (TTE) is the first-line and most essential tool in establishing a diagnosis of CP and RCM. In the context of the other diagnostic information, the ability to obtain both anatomic and hemodynamic information is useful in making the diagnosis.

2D and M-Mode

TTE can be used to image the pericardium, regarding the appearance of the pericardium and also the presence of concomitant pericardial effusion. However, measurement of pericardial thickness using TTE is not recommended. Pericardial thickness can also be obtained by transesophageal echocardiography (TEE), though Computed tomography (CT) and cardiac magnetic resonance imaging (CMR) are the gold standard. 2D echocardiography is also useful in assessing atrial and ventricular cavity sizes as well as in characterizing the myocardium. Depending on the etiology, different morphological characteristics can be present, such as thickened myocardium with speckling or a granular pattern which is found in amyloidosis (Fig. 16.3a, b). In RCM, biatrial enlargement, which is less frequent in CP, can be seen on TTE along with a tendency for inter-atrial septal bulging to the right due to increased pressure in the left atrium (LA) as compared to RA (Fig. 16.3b). The characteristic findings of CP on TTE are ventricular septal bounce, myocardial tethering, as well as inferior vena cava (IVC) and hepatic vein plethora. However, ventricular septal shift (VSS) is different from septal bounce. The presence of VSS is defined as any degree of cyclic movement of the ventricular septum toward the left ventricle with inspiration and toward the right ventricle with expiration, which resembles ventricular interdependence. VSS is a sensitive sign of CP with a sensitivity of 93% and specificity of 69% [5]. The features of VSS, septal shudder, and bounce in CP are better appreciated using M-mode imaging due to its high temporal resolution (Fig. 16.4).

Doppler Echocardiography and Tissue Doppler Imaging

Physiologically, both CP and RCM lead to diastolic dysfunction. Information obtained from Doppler echocardiography and tissue Doppler imaging (TDI) has been vital in diagnosing diastolic dysfunction. In additions, TDI information on mitral annular velocities has improved the overall sensitivity and specificity of echocardiography in diagnosing CP while also distinguishing cases of CP from RCM. Doppler has been beneficial by allowing a hemodynamic assessment non-invasively. Specifically, it looks at ventricular filling, i.e., mitral and tricuspid inflow velocities, pulmonary and hepatic venous flow, and especially the respiro-phasic changes brought by CP and RCM in these parameters.

In both CP and RCM, the trans-mitral flow velocity pattern is characteristic of markedly elevated LV filling pressure, i.e. restrictive pattern. The high left atrial pressure (LAP) is associated with high LA–LV gradient at the time of mitral valve opening; therefore, E wave velocity is high, A wave velocity is low, and E/A ratio is high, usually >2.0. However, A wave may not be visible in patients with atrial fibrillation or flutter. Poor LV compliance results in rapid rise of LV

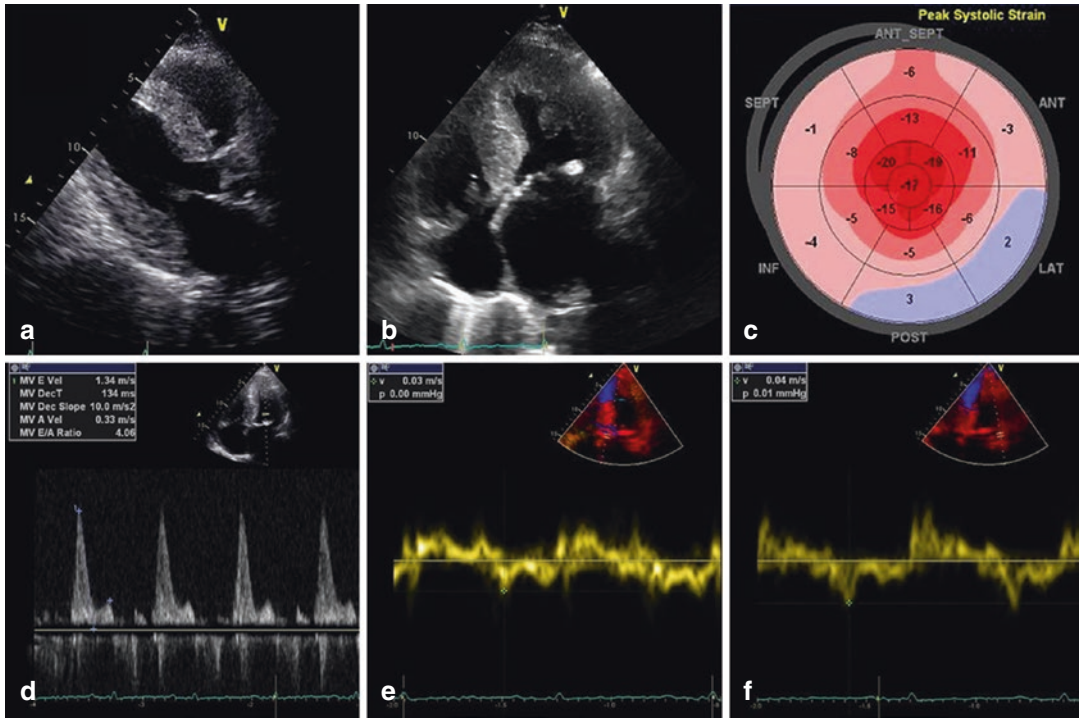

Fig. 16.3 Echocardiography of patient with amyloidosis shows (**a**) thickened myocardium with speckling or a granular pattern and (**b**) biatrial enlargement with inter-atrial septal bulging to the right. (**c**) Global longitudinal strain (GLS) study shows a pattern of apical sparing suggestive of amyloidosis. (**d**) The pulsed wave Doppler study of the mitral inflow shows high E/A ratio of ~4.1 and short deceleration time of ~134 ms. Tissue Doppler imaging (TDI) of mitral annulus shows markedly reduced velocities in both (**e**) septal e' of 3 cm/s and (**f**) lateral e' of 4 cm/s

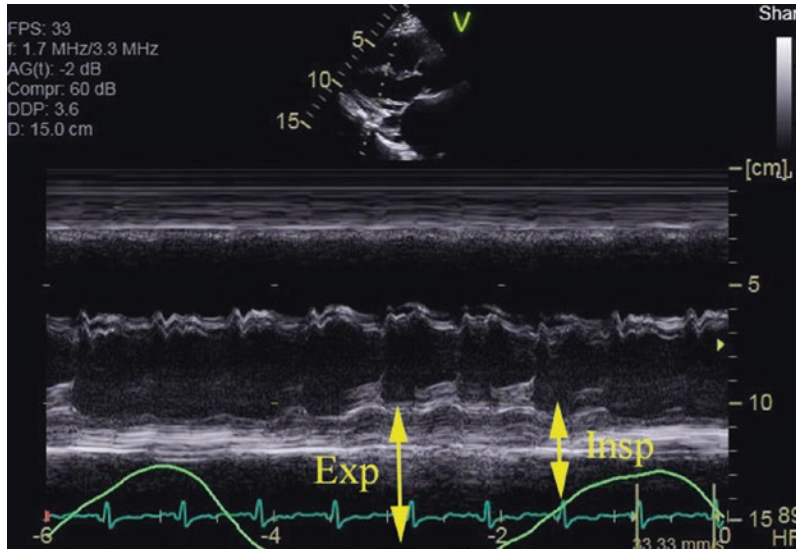

Fig. 16.4 Midventricular septal M-mode recording (parasternal long axis) in a patient with constrictive pericarditis. There is leftward ventricular septal shift in inspiration. Exp indicates expiration and Insp inspiration

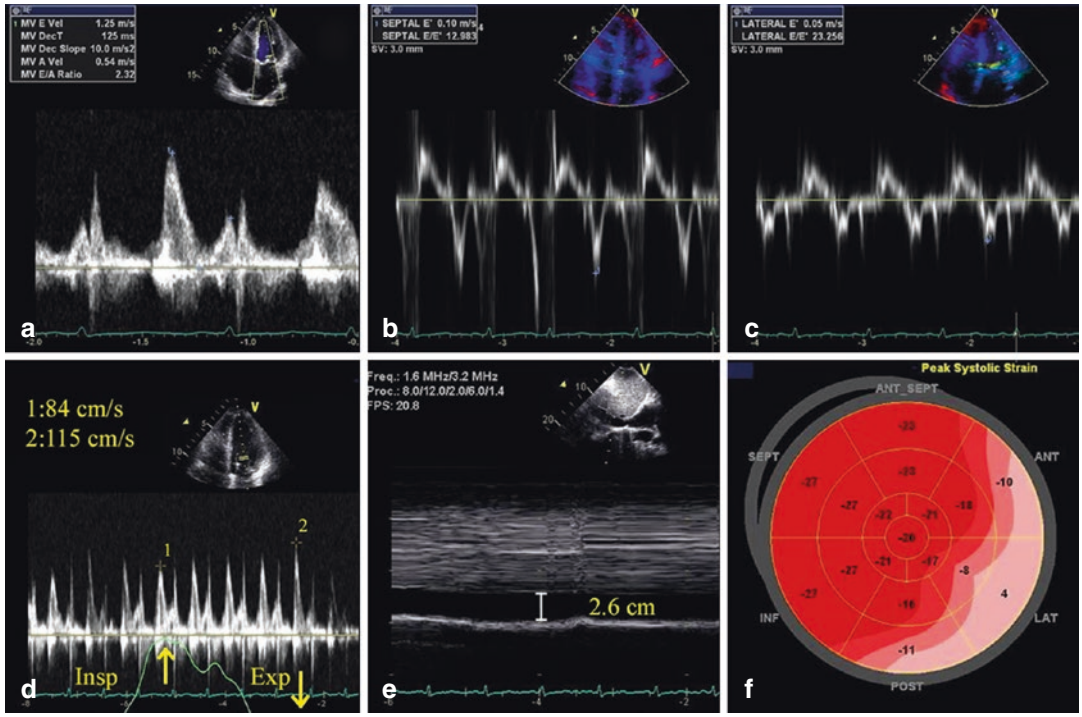

Fig. 16.5 Echocardiography of a patient with constrictive pericarditis. (**a**) The pulse wave Doppler study of the mitral inflow shows high E/A ratio which is ~2.3 and short deceleration time of 125 ms. Tissue Doppler imaging (TDI) of mitral annulus shows "annulus reversus" with (**b**) septal e' of 10 cm/s and (**c**) lateral e' of 5 cm/s. (**d**) There is significant respiratory variation in the mitral inflow [(expiration – inspiration)/expiration; (115–84)/115 × 100% = ~27.0%]. Insp indicates inspiration and Exp, expiration. (**e**) M-mode image shows plethoric inferior vena cava (IVC) with diameter of 2.6 cm and <50% change in diameter during respiration. (**f**) Global longitudinal strain (GLS) study shows LV antero-lateral wall shortening strains were lower than the septal shortening strains

diastolic pressure, which leads to rapid decline of LA–LV pressure gradient. As a result, there is a rapid, early diastolic deceleration of trans-mitral inflow, with shorter than normal deceleration time, i.e., <160 ms (Figs. 16.3d and 16.5a).

Pulmonary artery systolic pressure (PASP), provided pulmonary vascular disease is excluded, can be served as an indirect estimate of LAP and identify patients with increased LV filling pressures. A significant correlation exists between PASP and noninvasively derived LAP. In the absence of pulmonary disease, increased PASP suggests elevated LAP. Calculation of PASP can be done by measuring the peak tricuspid regurgitation (TR) velocity, then applying the modified Bernoulli equation to convert this value into pressure values and adding the estimated right atrial pressure. The American Society if Echocardiography (ASE) recommends the cutoff value for peak TR velocity of >2.8 m/s for diagnosing diastolic dysfunction [5].

TDI of mitral annular velocities have become an integral part of the diastology assessment as well as the diagnosis of CP and restriction. The mitral annular velocity (e′) is measured at the septal/medial and lateral annulus – both of which give information regarding the motion of the annulus with respect to the axis of measurement, i.e., cursor line. These measurements give information about myocardial relaxation and longitudinal motion of the heart, which are affected in CP and restriction. In cases with abnormal relaxation, i.e., restriction, tissue Doppler velocities are predictably reduced (septal e' velocity <7 cm/s or lateral e' velocity <10 cm/s). In RCM, both septal and lateral e' velocities are diminished. In pure CP without myocardial involvement, the septal mitral annulus velocity can be

normal or mildly elevated, i.e., septal e' ≥ 9 cm/s [5]. This is due to the limited lateral expansion of the heart during filling secondary to pericardial encasement which results in a compensatory increase in longitudinal movement of the septum in order to accommodate filling. In patients without pericardial disease, the septal e' is typically lower than the lateral e'. In CP, this relationship reverses; the septal e' velocity is greater than the lateral one, and hence this phenomenon is called "annulus reversus." Tissue Doppler E/e' is a non-invasive estimate of LAP. The ASE guidelines for assessment of diastolic dysfunction recommend using an average of the septal and lateral e' velocities, whereas an average E/e' of >14 indicates elevated LAP [6]. Although LAP is increased in both CP and RCM, E/e' does not increase despite elevated pulmonary capillary wedge pressure (PCWP) in CP, i.e., "annulus paradoxus." However, this only occurs in pure constriction rather than in constriction with myocardial disease [7–8].

The respiratory variation of diastolic inflow velocities across both the mitral and tricuspid valve, i.e., E wave velocities, is different in CP and RCM and can provide compelling evidence for either diagnosis while ruling out other processes. The ASE recommends the calculation of percentage of respiratory variation in CP for mitral and tricuspid inflow as follows:

$$\left(\text{expiration} - \text{inspiration}\right) / \text{expiration} \times 100\%$$

For peak mitral E inflow, the maximal drop occurs with the first beat of inspiration and the first beat of expiration. It usually exceeds 25% respiratory variation (Fig. 16.6d). For peak tricuspid E inflow, the maximal drop is on the first beat in expiration at the same time as the hepatic vein atrial reversal and usually exceeds 40% respiratory variation. The calculated % will be a negative value [9]. These phenomena are manifestations of greatly enhanced ventricular interaction and are not present in either normal subjects or patients with restrictive cardiomyopathy. In restriction, the mitral *E* velocities vary with respiration but to a much lesser degree (usually <10%). These findings can be affected by preload conditions in the LA; an increase in left atrial pressure will diminish the variation with respiration, while volume depleted states will exaggerate it.

Pulmonary and hepatic venous flows represent left and right-sided filling and are also another important measurement in distinguishing constrictive and restrictive physiology. Pulmonary vein systolic flow (*S* wave) is diminished and diastolic flow (*D* wave) is increased irrespective of respiration in restriction. In CP, however, there is increase in both systolic and diastolic flow during expiration as compared to blunted *S* and *D* during inspiration, which is a distinguishing feature (Fig. 16.6).

Hepatic vein flows, designated by *S* and *D* waves can also be used to further identify patients sus-

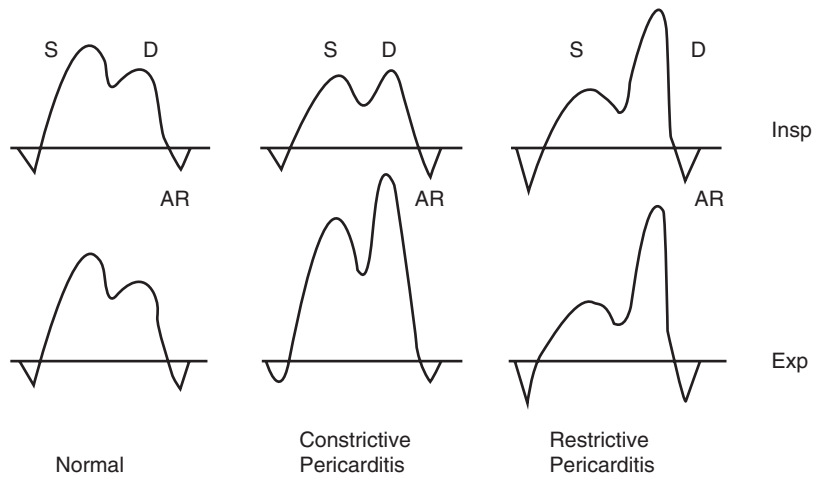

Fig. 16.6 Pulmonary venous flow during different phases of respiration in different conditions. S indicates pulmonary vein systolic flow; D pulmonary vein diastolic flow; AR atrial reversal; Insp inspiration; Exp expiration

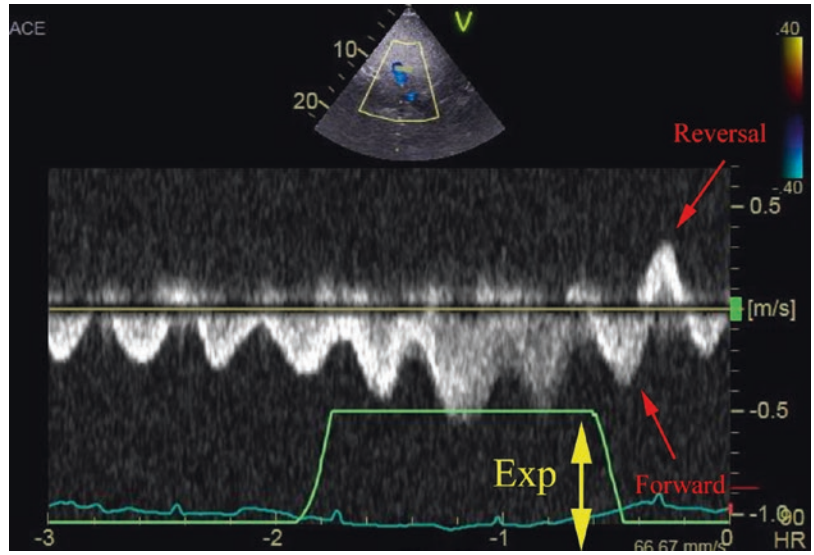

Fig. 16.7 Pulsed-wave Doppler recording (subcostal window) within the hepatic vein in a patient with constrictive pericarditis. Note prominent diastolic flow reversals in expiration, with the diastolic reversal ratio defined as reversal velocity divided by forward velocity (~0.35 m/s reversal velocity divided by ~0.40 cm/s forward flow velocity yields a diastolic reversal ratio of 0.875). Exp indicates expiration

pected of having CP or restriction. Normal patients will have a more prominent *S* wave as compared to the *D* wave; however, there is little to no respiratory variation. In those with CP, there is a significant increase in the diastolic flow, i.e. *D* wave during inspiration and marked blunting during expiration with diastolic flow reversal, whereas restriction patients have an increased diastolic flow, i.e. *D* wave as compared to *S* wave without respiratory variation. However, this is better expressed as the hepatic vein expiratory diastolic reversal ratio, which is defined as follows:

$$\left(\text{diastolic reversal velocity / forward velocity}\right)\text{in expiration.}$$

The finding of a reversal ratio ≥0.79 has a specificity of 88% for CP [5] (Fig. 16.7).

Global Longitudinal Strain (GLS)

Strain in the myocardium can be measured by TDI or speckle-tracking echocardiography (STE). Nowadays, STE is the most widely used strain modality. STE utilizes the phenomenon in which natural acoustic markers in gray scale ultrasound images form interference patterns, i.e., speckles within myocardial tissue. These patterns are quite stable over the short period of time between two consecutive frames, and the 2D displacement for each point in the myocardium is found by automatic search for similar patterns in the two frames (block matching). This process is repeated for all frames through the cardiac cycle to produce a 2D displacement curve for each point in the myocardium. Subsequently, strains are calculated from each LV segment in circumferential, longitudinal, or radial directions [10]. When the information obtained from conventional echocardiography is adequate, GLS is usually not necessary for diagnosis. However, GLS can provide more information in order to exclude other differential diagnosis.

In the cases of RCM, there are often findings of normal or near normal LV systolic function, diastolic dysfunction and left ventricular hypertrophy. The pattern of apical sparing in GLS (Fig. 16.3c) can be an assurance for the diagnosis of amyloidosis in RCM; whereas in hypertrophic cardiomyopathy, myocardial longitudinal deformation is typically reduced at the site of hypertrophy [11]. Due to the tethering of LV free wall in CP, LV septal shortening strains are seen to be higher than the lateral wall shortening strains (Fig. 16.5f), which depends on the location and extent of pericardial calcification. Moreover, the average GLS value is higher in patients with CP than in those with RCM [12].

In distinguishing CP and RCM, Welch TD et al. suggest a relatively simple approach. In the article of the Mayo Clinic diagnostic criteria of constrictive pericarditis, respiration-related ventricular septal shift, preserved or increased septal mitral annular e' velocity, and prominent hepatic vein expiratory diastolic flow reversal are the echocardiographic features which are independently associated with the diagnosis of CP. The presence of VSS with either septal mitral annular e' velocity of ≥9 cm/s or hepatic vein expiratory diastolic reversal ratio of ≥0.79 yields the diagnostic sensitivity of 87% and specificity of 91% for CP [5].

Transesophageal Echocardiography

Given some of the limitations of TTE, TEE may be useful whenever TTE is non-diagnostic or image quality is affected by body habitus or positioning. It can be used in the post-op setting to assess localized effusive-constrictive disease. TEE can be used to image the pericardium to assess thickness and the areas of adherence, as well as to obtain higher fidelity Doppler signals through the MV/TV (*E* velocity) and pulmonary vein flows. Often TEE evaluation is useful as an adjunctive modality since it is better for imaging the posterior aspect of the heart, as well as the RA, RV, and IVC which improves the accuracy of the overall assessment. However, TDI measurement of mitral annulus velocities has not been validated in TEE.

Computed Tomography and Magnetic Resonance Imaging

CT and CMR imaging offer higher resolution and additional information as compared to echocardiography in the evaluation of CP and RCM. CT can assess pericardial thickening (>4 mm) and calcification better than TTE or TEE (Fig. 16.8c, d), though the absence of either does not rule out CP. Talreja DR et al. reported 18% of patients had normal pericardial thickness on histological examination, and 28% of patients had normal pericardial thickness on CT in a study of 143 patients with surgically confirmed CP [13]. It also offers information regarding IVC volume status, as well as ventricular and septal contours associated with constriction. In patients with a prior history of cardiothoracic surgery, CT is useful in assessing the location of important vascular structures prior to surgery as well as assessing for any lung injury or entrapment especially with prior history of radiation exposure.

Gated CMR provides better visualization and resolution of the pericardium than either CT or echocardiography. CT still offers a better assessment of pericardial calcification, but CMR is superior in the evaluation of tissue characterization including pericardial inflammation and edema, pericardial scarring, small pericardial effusions, and myocardial tethering as well as resolving hemodynamic correlates such as IVC plethora and VSS (Fig. 16.9). The ability of CMR for tissue characterization has been used to diagnose and monitor both constrictive physiology and pericardial inflammation in transient CP. Transient CP is an increasingly recognized sub-type of the more typically known CP. It was first described back in 1987, when a small group of subjects with CP demonstrated spontaneous and permanent resolution of constrictive physiology on serial echocardiograms and CMR [14]. Pathologically, transient CP is usually a result of fluctuating pericardial edema, inflammation and fibrin deposition, rather than more fixed pericardial fibrosis or calcification [15]. It may resolve spontaneously or with the assistance of anti-inflammatory therapy. It is likely that in some cases, transient CP may actually represent an early manifestation in the spectrum of CP disease, before chronic inflammation leads to accumulation of fibroblasts and collagen and constrictive physiology becomes irreversible. For the inter-atrial septum (IAS), a thickness of >6 mm is considered significant. This finding is virtually diagnostic of cardiac amyloidosis. Lipomatous hypertrophy can also cause increased thickness of IAS, but it can be easily differentiated by its hyperintense signal on T1-weighted sequence due to fat content [16].

Besides, the delayed enhanced inversion recovery imaging in CMR is the most valuable

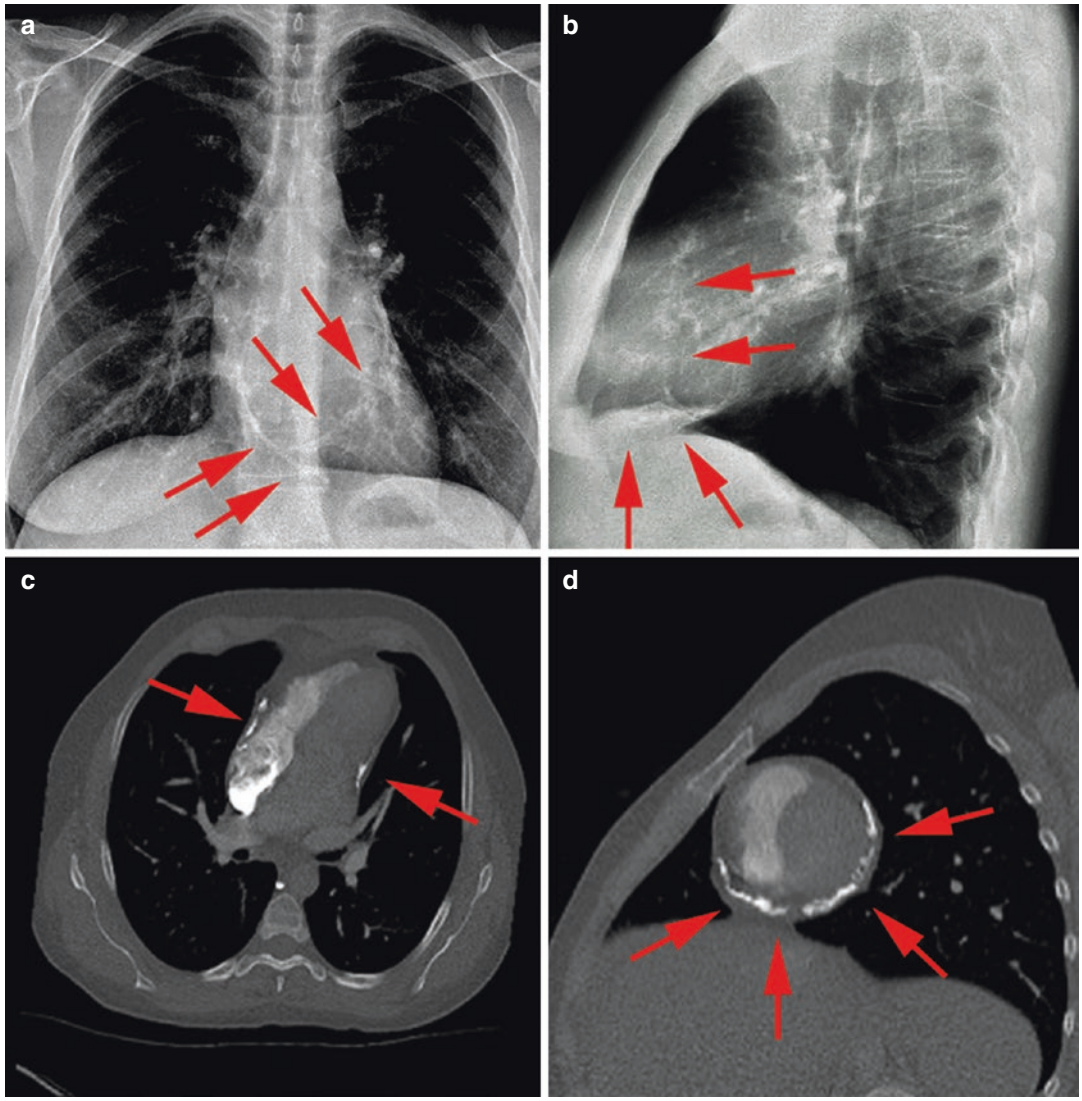

Fig. 16.8 Pericardial calcification seen on CXR (**a** and **b**) and CT scan (**c** and **d**). Red arrows indicate the location of pericardial calcification

sequence for tissue characterization and providing clues as to the underlying cause, especially in the cases of RCM. In cardiac amyloidosis, the late gadolinium enhancement (LGE) is usually global in distribution and predominantly subendocardial but may be transmural. CMR also provides some information about amyloid load (intramyocardial T1 gradient) in the heart, which is helpful in the non-invasive follow-up of patients on treatment [17]. Cardiac sarcoidosis is pathologically characterized by patchy and focal myocardial involvement by granulomatous inflammation, which can leave scar tissue after healing. There are three successive histological stages: edema, non-caseating granulomatous infiltration, and patchy myocardial fibrosis. CMR has been shown to accurately reflect these changes. The acute inflammatory phase shows the presence of focal increased signal on T2-weighted images with myocardial thickening reflecting edema (Fig. 16.10a). Well-formed granulomas are seen as foci of decreased T1 and T2 signal within the area of increased T2 signal. A central low signal area reflects hyaline fibrotic

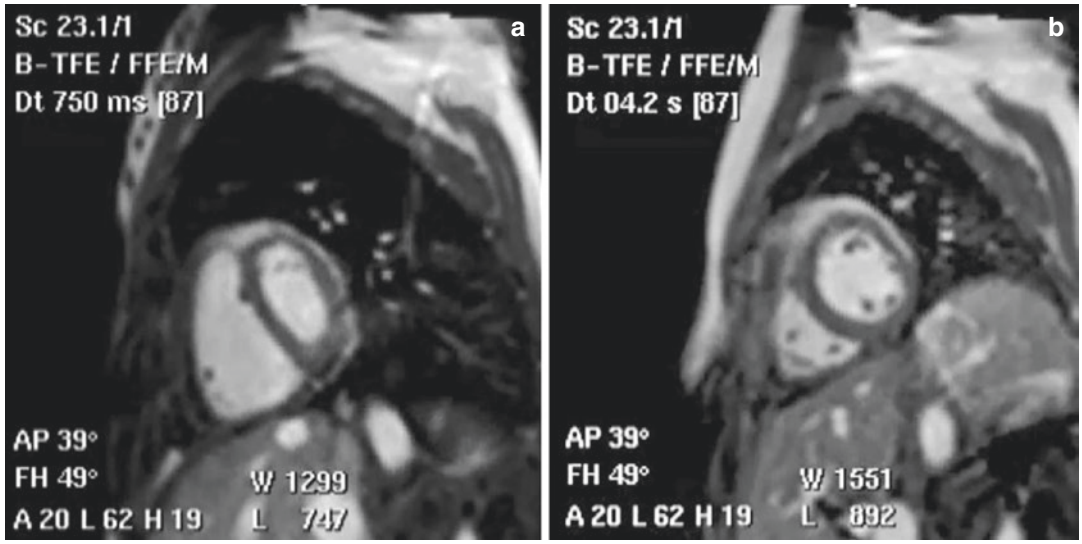

Fig. 16.9 CMR free breathing sequence shows the presence of ventricular septal shift. The ventricular septum moves toward the left ventricle with inspiration during diastole (**a**) and toward the right ventricle with expiration during diastole (**b**)

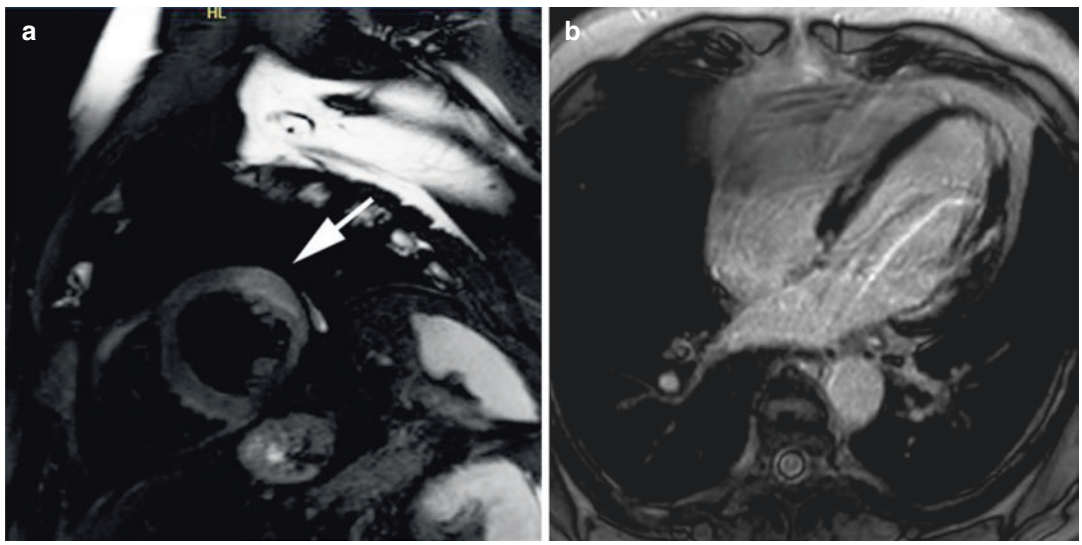

Fig. 16.10 CMR of a patient with sarcoidosis. (**a**) There is increased myocardial signal intensity on T2-STIR imaging to suggest myocardial edema (white arrow). (**b**) Delayed-enhancement imaging reveals late gadolinium enhancement (LGE) in a non-ischemic pattern. There is near transmural LGE in the basal and mid inferoseptum (sparing the endocardium) and mid-myocardial LGE in the mid-anterolateral and transmural LGE at the inferolateral apex

change and peripheral high signal area denotes edema due to granulomatous inflammation. LGE imaging shows hyperenhancement in areas of fibrosis, which does not correspond to any particular coronary artery distribution. These are also more linear in appearance (Fig. 16.10b), compared to the focal, more rounded lesions in the inflammatory stage [16].

In hemochromatosis, CMR is also vital in the detection and quantification of cardiac involvement. Deposition of iron in the myocardium causes a decrease in T2∗ relaxation time, which

can be detected by multi-echo gradient sequences [16]. The ability of CMR to detect myocardial iron overload at an early stage, direct timely institution of chelation therapy, and monitor treatment follow-up have been shown to reduce the morbidity as well as mortality in hemochromatosis [18].

Catheterization/Hemodynamic Assessment

Left and right heart catheterization has been used in the past as the gold standard in distinguishing between CP and RCM. Improvements in non-invasive imaging have helped in increasing the early diagnosis of CP and restriction. Although there are many similar hemodynamic characteristics in CP and RCM, certain unique findings, if present, can help to differentiate the diagnosis.

Hemodynamic findings often seen in patients with CP are increased RA pressure due to the adherent pericardium around RA prevents expansion, Kussmaul's sign (usually present), as well as prominent *x* and *y*-descents of RA pressure tracings because of rapid atrial emptying and underfilled RV (M/W pattern) (Fig. 16.11a). The presence of an increased RV end-diastolic pressure (usually greater than or equal to one-third of the RV systolic pressure) is due to constraint of the RV leading to higher filling pressure. Constriction is generally not known to cause pulmonary hypertension; thus, the RV systolic pressure is not affected. The "dip-and-plateau"/"square-root" sign is seen in the RV and LV pressure tracings as a result of rapid early diastolic flow (dip) and diastasis once pressure equalization occurs (plateau) during mid- and late-diastole. Another key feature is found in the diastolic (plateau) pressures of the LV and RV, which equalize due to the rigid non-elastic pericardium (Fig. 16.11b). This finding is relatively common in patients who undergo catheterization and have constriction; however, in some patients, it is only seen on inspiration, secondary to increased systemic venous return. Lastly, RV and LV systolic pressures exhibit an inverse relation as a result of ventricular interde-

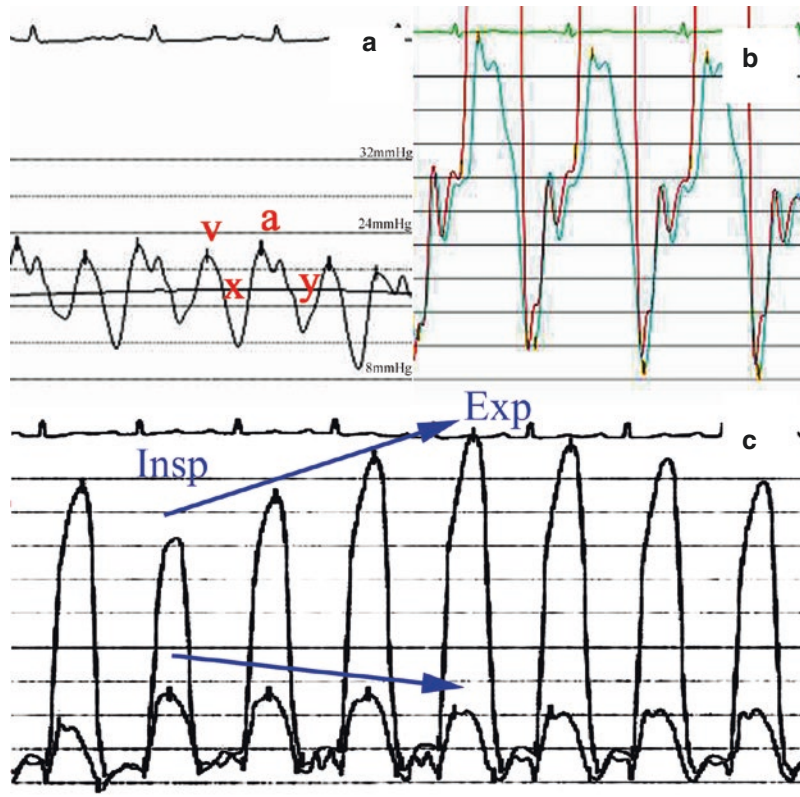

Fig. 16.11 Left and right heart catheterization of a patient with constrictive pericarditis. (**a**) Pressure tracing of the right atrium shows prominent x- and y-descents. v indicates v wave; a, a wave; x, x-descent; and y, y-descent. (**b**) Simultaneous recording of LV and RV pressure tracings shows "dip-and-plateau"/"square-root" sign and equalization of both ventricular diastolic pressures. (**c**) Simultaneous recording of LV and RV pressure tracings with respiratory variation shows ventricular interdependence. LV indicates left ventricle and RV, right ventricle

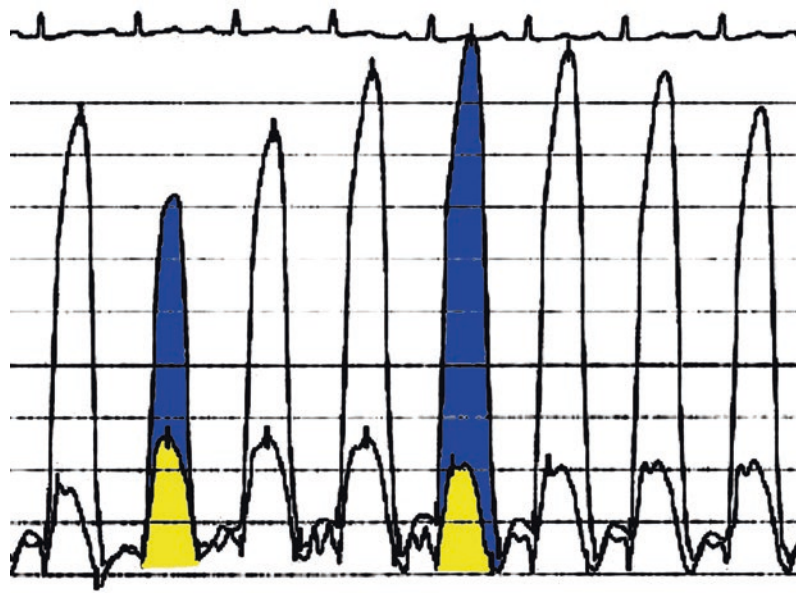

Fig. 16.12 A patient with constrictive pericarditis. During inspiration there is an increase in the area of the RV pressure curve (yellow-shaded area) compared with expiration. The area of the LV pressure curve (blue shaded area) decreases during inspiration as compared with expiration

pendence. With inspiration, the LV systolic pressure falls and the RV systolic pressure rises and vice versa with expiration (Fig. 16.11c). Patients with restrictive cardiomyopathy have ventricular concordance. Systolic area index is used to further quantify this hemodynamic difference. The area under the ventricular pressure curve was used to determine the change in the relative volumes of the LV and RV, which is a better determinant of beat-to-beat stroke volume than the peak pressure alone. The systolic area index is defined as the ratio of the RV area (mmHg × s) to the LV area (mmHg × s) in inspiration versus expiration. An index of greater than 1.1 has been shown to have 97% sensitivity in predicting patients with CP [19] (Fig. 16.12).

Clinical Examples

Calcific Constrictive Pericarditis

A 45-year-old female presented with a history of increasing dyspnea on exertion and progressive heart failure symptoms. She had a history of recurrent pericarditis, otherwise unremarkable. On physical exam, she had bilateral pitting LE edema, elevated JVP, and a pericardial knock. Chest radiography (CXR) showed no pulmonary edema or effusion but was significant for scattered calcification of the pericardium (Fig. 16.8a, b). Echocardiogram showed preserved LV and RV functions, but grade III diastolic dysfunction, VSS and IVC plethora (Fig. 16.5e). Grade III diastolic dysfunction was diagnosed as the LA was dilated with indexed LA volume of ~36 ml/m^2. Transmitral inflow showed high E/A ratio was ~2.3 (Fig. 16.5a). Moreover, the TDI of mitral annulus velocities demonstrated "annulus reversus" with septal e' of 10 cm/s and lateral e' of 5 cm/s (Fig. 16.5b, c), and the average E/e' was ~18.8. The TR signal was insufficient to estimate PASP. Significant respiratory variation in mitral inflow was also present, i.e., >25% respiratory variation in peak mitral E inflow (Fig. 16.5d). GLS study showed LV lateral wall shortening strains were lower than the septal shortening strains (Fig. 16.5f).

Left and right heart catheterization showed normal coronary arteries and confirmed the diagnosis of CP with the hemodynamic finding of CP. There were diastolic equalization of pressures in both the LV and RV and ventricular interdependence (Fig. 16.11b, c).

The patient was referred for pericardiectomy in view of the above findings and persistent symptoms despite medical therapy. She had marked improvement in her symptoms after surgery.

Effusive-Constrictive Pericarditis

A 39-year-old female presents with a history of chest and dyspnea. She had medical history of systolic lupus erythematosus and interstitial lung disease with pulmonary fibrosis. On physical examination, pericardial rubs could be heard. ECG showed sinus tachycardia with diffused ST elevations and PR depressions in lead II. ESR and CRP were both raised. Echocardiography showed large circumferential pericardial effusion with features of cardiac tamponade. Pericardiocentesis was then performed and found exudative pericardial effusion with negative culture and cytology. However, the echocardiography repeated after pericardiocentesis showed small residual pericar-

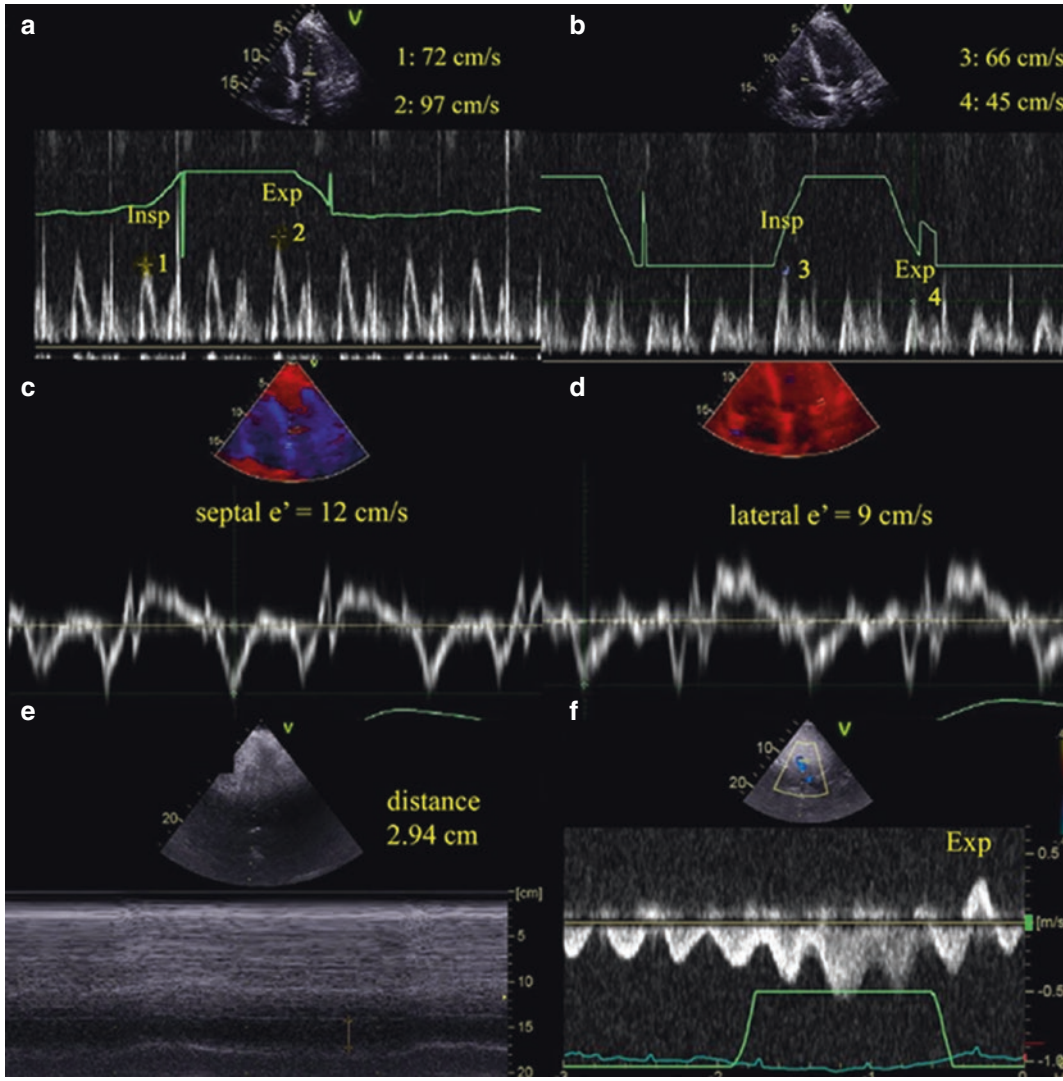

Fig. 16.13 Echocardiography of a patient with effusive-constrictive pericarditis. (**a**) There is significant respiratory variation in the mitral inflow [(expiration – inspiration)/expiration; (97–72)/97 × 100% = ~25.8%]. Insp indicates inspiration and Exp expiration. (**b**) There is significant respiratory variation in the tricuspid inflow [(expiration – inspiration)/expiration; (45–66)/45 × 100% = ~ −46.7%]. Tissue Doppler imaging (TDI) of mitral annulus shows "annulus reversus" with (**c**) septal e' of 12 cm/s and (**d**) lateral e' of 9 cm/s. (**e**) Inferior vena cava is plethoric with diameter of ~2.9 cm and <50% variation in size during respiration. (**f**) Pulsed wave Doppler of hepatic vein flow showed significant end expiratory diastolic flow reversal with hepatic vein expiratory diastolic reversal ratio of ~0.9

dial effusion with features of constriction. There were ventricular septal shift and significant respiratory variation in both mitral and tricuspid inflows, 25.8% and −46.7%, respectively (Fig. 16.13a, b). "Annulus reversus" was present (Fig. 16.13c, d). IVC was still plethoric (Fig. 16.13e). Hepatic vein flow showed significant end expiratory diastolic flow reversal with the hepatic vein expiratory diastolic reversal ratio of ~0.9 (Fig. 16.13f). Since the central venous pressure before and after pericardiocentesis were still >20 mmHg, the diagnosis of effusive-constrictive pericarditis (ECP) is confirmed.

ECP is an uncommon clinical syndrome characterized by the coexistence of tense pericardial effusion and constriction of the heart by the visceral pericardium. Incidence ranges from 2% to 15% of patients with pericarditis, depending on the difference in patient populations, methodologies, and definition. The hallmark of ECP is the presence of the persistently elevated right atrial pressure measured by invasive hemodynamic assessment after intra-pericardial pressure is reduced to a normal level by pericardiocentesis.

Patient was treated with steroids and colchicine. The repeated echocardiography 1 year later did not reveal any more feature of constriction.

Restrictive Cardiomyopathy (Cardiac Amyloidosis)

A 72-year-old male initially presented with new onset atrial fibrillation and dyspnea at rest. Echocardiogram performed was performed during sinus rhythm and showed a depressed ejection fraction of ~40%, marked biatrial enlargement with grade III diastolic dysfunction, moderate pulmonary hypertension, increased left ventricular wall thickness and a speckling pattern of myocardium. GLS study showed the pattern of apical sparing (Fig. 16.3c). The patient was treated with beta-blockers and diuretics presumptively, while serum and urine electrophoresis were negative. The bone marrow biopsy was significant for plasma cell population, and Congo red staining was consistent with amyloidosis. Given the diagnosis of systemic amyloidosis and severe diastolic dysfunction, the patient was presumed to have cardiac amyloidosis and started on treatment for amyloidosis with prednisone and intra-venous melphalan. Due to the chronic nature of the condition and the late presentation as well as the lack of efficacious treatment options, the patient did not respond to therapy and continued to deteriorate over the next few months. Cardiac amyloidosis usually presents later in life with an insidious onset and often is diagnosed as a result of key echocardiographic features. In this case, further testing including CT, MRI, or catheterization was not warranted for diagnosis.

Pearls of Assessment

When assessing a patient with suspected CP or RCM, a focused history and physical examination with emphasis on symptoms as well as clues or signs that suggest either diagnosis is essential. Chest X-ray and ECG are also useful in the initial workup to assess for cardiomegaly and pericardial calcification as well as voltage pattern for possible RCM. Non-invasive imaging is the mainstay and first line of the workup and echocardiography with respirometer to assess for changes in filling velocity and pressures, as well as pericardial thickening is usually the next step. Depending on the echocardiographic results and suspicion for a pericardial or myocardial process, further non-invasive imaging including either a cardiac CT or CMR can be useful to obtain more information that cannot be provided by echocardiography, e.g. pericardial calcification, pericardial inflammation, myocardial fibrosis, etc. If the diagnosis is still inconclusive, left and right heart catheterization with a focus on the hemodynamic findings of "dip-and-plateau" on RV and LV pressure tracings as well as ventricular interdependence which point to a specific diagnosis of CP. Table 16.2 summarizes the key distinguishing features of constrictive pericarditis and restrictive cardiomyopathy. Treatment of symptoms with diuretics is usually a temporizing measure and often patients require surgical pericardiectomy for symptomatic relief of CP. Treatment of RCM depends on the underlying etiology.

Table 16.2 Key distinguishing features of constrictive pericarditis and restrictive cardiomyopathy

	Constrictive pericarditis	Restrictive cardiomyopathy
Physical examination	Pericardial knock	S4 (early) and S3 (late presentation)
	Apical retraction	Prominent apical impulse
Echocardiography		
2D images	Pericardial thickening	Biatrial enlargement
	Ventricular septal shift	Ventricular hypertrophy (usually present)
	Pericardial effusion (may be present)	Myocardial speckling (amyloidosis)
PW mitral inflow	*E*/*A* ratio ≥ 2	*E*/*A* ratio ≥ 2
	>25% respiratory variation in E wave[a]	<25% respiratory variation in *E* wave[a]
PW tricuspid inflow	>40% respiratory variation in E wave[a, b]	<40% respiratory variation in E wave[a, b]
TDI	"Annulus reversus" – lateral e' velocity is reduced, whereas septal e' velocity is normal or higher than normal	Both septal and lateral e' velocities are reduced
PW hepatic vein flow	Hepatic vein flow reversal ratio ≥ 0.79	Hepatic vein flow reversal ratio < 0.79
GLS	LV septum > free wall	Apical sparing (amyloidosis)
Left and right heart catheterization	Diastolic equalization of pressure between LV and RV	LVEDP may be equal to or greater than RVEDP
	Ventricular interdependence	Ventricular concordance
	Systolic area index >1.1	Systolic area index <1.1
	Pulmonary pressure usually normal	Pulmonary hypertension (RVSP >50 mmHg)

GLS Global longitudinal strain, *LV* left ventricle, *LVEDP* left ventricular end-diastolic pressure, *PW* pulse wave Doppler, *RA* right atrium, *RV* right ventricle, *RVEDP* right ventricular end-diastolic pressure, *RVSP* right ventricular systolic pressure, *TDI* tissue Doppler imaging

[a]Respiratory variation = (expiration – inspiration)/expiration × 100%

[b]This is negative value

Review Questions

1. Which of the following(s) is/are cause(s) of pericardial constriction?
   A. Infection
   B. Prior cardiac surgery
   C. Mantle radiation for lymphoma
   D. A and B
   E. All of the above

   Answer: E. Infection, prior cardiac surgery, and mantle radiation for lymphoma are established causes of constrictive pericarditis.
2. Which of the following features of left and right heart cardiac catheterization are seen in constriction?
   A. Diastolic equalization of pressure between LV and RV
   B. Ventricular interdependence
   C. M (or W) pattern on right atrial waveform
   D. Steep or rapid *y*-descent
   E. All of the above

   Answer: E. All of the findings listed above are typically seen in constrictive pericarditis.
3. Which of the following statement is false regarding constrictive pericarditis?
   A. "Annulus reversus" results from a compensatory increase in longitudinal movement of the septum in order to accommodate filling secondary to the limited lateral expansion of the heart during filling secondary to pericardial encasement.
   B. "Pulsus paradoxus" means there is an abnormal (>10 mmHg) decrease in systolic blood pressure with inspiration.
   C. A pericardial knock occurs at the nadir of the x-descent and is consistent with abrupt cessation of ventricular filling.
   D. The American Society of Echocardiography recommends the calculation of percentage of respiratory variation in constrictive pericarditis for mitral and tricuspid inflow is (expiration – inspiration)/expiration × 100%.
   E. Measurement of pericardial thickness using transthoracic echocardiogram is not recommended.

   Answer: C. A pericardial knock occurs at the nadir of the y-descent and is consistent with abrupt cessation of ventricular filling.

4. Which of the following echocardiographic findings is not consistent with restrictive physiology?
   A. Large atria
   B. Blunted *S*/*D* ratio in pulmonary and hepatic vein flows
   C. Low septal and lateral e' velocity on TDI (i.e., septal e' velocity <7 cm/s; lateral e' velocity <10 cm/s)
   D. Decreased mitral inflow velocity (*E* wave) with inspiration
   E. E/A ratio >2

   Answer: D. Decreased mitral inflow (*E* wave) is found in constrictive pericarditis, whereas in restrictive cardiomyopathy, mitral inflow is not changed with respiration. The other findings are all seen in restrictive cardiomyopathy.
5. Which of the following is not the distinguishing features of constrictive pericarditis and restrictive cardiomyopathy?
   A. Ventricular septal shift
   B. Kussmaul's sign
   C. Ventricular interdependence
   D. Hepatic vein flow reversal ratio ≥0.79
   E. Annulus reversus

   Answer: B. Kussmaul's sign can be present in both constrictive pericarditis and restrictive cardiomyopathy.

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Valvular Heart Disease

17

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Introduction

The diagnosis and management of valvular heart disease are challenging and require a knowledge of the relevant historical clues, appreciation of salient physical exam findings, and the ability to critically interpret imaging and invasive hemodynamic data. This chapter will focus on diagnosis of the valve disorders most frequently encountered in the care of patients on the cardiac ward.

Aortic Stenosis

Case Presentation

The patient is a 78-year-old man with a history of hypertension, hyperlipidemia, and percutaneous coronary intervention with drug-eluting stent to the mid-left anterior descending artery 4 years prior. He noted the development of exertional dyspnea over the past 6–12 months, as well as mild chest discomfort over the past 3 months that resolved with rest. Initially attributed to "old age," he finally decided to seek medical attention due to progression of his symptoms.

Salient physical examination findings included mild hypertension (BP 145/90 mmHg) and a normal heart rate (70 bpm). The PMI was not displaced and an S4 gallop was appreciated. A 2/6 systolic crescendo/decrescendo murmur was heard at the upper sternal border peaking late in systole, radiating to the carotids bilaterally. The carotid artery upstrokes were mildly delayed and weak.

Given the symptoms and physical exam findings, transthoracic echocardiography (TTE) was performed. The TTE revealed normal left ventricular function with moderate concentric hypertrophy, a moderately thickened and calcified aortic valve, and severe aortic stenosis (AS) with peak and mean gradients of 85 and 50 mmHg, respectively. With a diagnosis of severe, symptomatic aortic stenosis, the patient was referred for coronary angiography in anticipation of open-heart surgery. Angiography revealed only mild CAD and a patent stent in the mid-LAD, and the patient went to have uneventful valve replacement with an aortic bioprosthesis.

Epidemiology and Pathophysiology

Aortic stenosis (AS) is present in almost 5% of individuals over the age of 75 years [1]. AS may develop due to a congenital valve disorder

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_17

(unicuspid or bicuspid valve), as a result of rheumatic valvular heart disease, as a complication of chest radiation, or most commonly due to degenerative ("senile") thickening and calcification. Over time, AS causes increased pressure on the left ventricle (LV) and leads to a chronically increased afterload state. In order to compensate, the ventricle hypertrophies. Due to increased LV mass and worsening diastolic filling mechanics, diastolic dysfunction ensues. With worsening and long-standing stenosis, LV systolic function eventually falls. Furthermore, impaired LV diastolic and/or systolic function may lead to pulmonary hypertension due to left-sided heart disease. Since senile AS shares many risk factors with coronary artery disease (CAD), the clinical presentation may reflect progressive coronary stenosis in these patients in addition to increased myocardial oxygen demand due to the valvular stenosis.

Patients with aortic stenosis may live for years with a "known murmur" that is clinically silent, especially in cases of bicuspid or rheumatic valve disease. It is estimated that the valve area decreases by approximately 0.12 cm^2/year in patients with senile disease, providing a long period of asymptomatic disease [2]. On the other hand, the development of symptoms portends a grave prognosis: without treatment, angina, syncope, and heart failure are associated with a 50% mortality at 5 years, 3 years, and 2 years, respectively [3].

Physical Examination

The physical examination of patients with AS provides a number of characteristic findings. A systolic murmur is best heard in the aortic position (right upper sternal border) and radiates to the carotid arteries. As stenosis worsens, the peak of the murmur moves closer to the second heart sound (S2) since LV ejection across the valve requires a longer ejection time. With very severe disease, the S2 may be almost inaudible due to the proximity of the murmur's peak to the closing of the valve. With severe AS, a murmur mimicking mitral regurgitation (MR) may also be heard at the apex, but does not radiate to the axilla; this is known as Gallivardin's phenomenon. Palpation of the pulse (preferably at the carotid arteries) in patients with severe AS reveals the characteristic slow ascent (*parvus*) and delayed (*tardus*) peak. Additionally, palpation of the pulses at the upper extremity may reveal a "brachio-radial" delay in patients with severe AS that often presents prior to LV failure or clinical symptoms. Of note, the finding is subtle, with a measured delay of 53.5 msec [4]. An S4 gallop may be heard in the setting of left ventricular hypertrophy (LVH) and a stiffened ventricle.

An important differentiation to be made is between the murmur of AS and that of hypertrophic cardiomyopathy (HCM). In patients with AS, a reduction in preload (i.e., with the Valsalva maneuver or moving from squatting to standing) will reduce flow across the stenotic valve and therefore lessen the murmur. Conversely, a reduction in preload causes decreased filling of the LV cavity resulting in a smaller left ventricular outflow tract (LVOT) diameter and worsening systolic anterior motion (SAM) of the mitral valve and therefore augments the murmur in patients with HCM.

Echocardiography

Transthoracic echocardiography (TTE) is the cornerstone of AS assessment and provides information on left ventricular function, aortic valve morphology, degree of stenosis, and an assessment of pulmonary pressures. Rarely, transesophageal echocardiography (TEE) may be necessary for diagnosis if TTE images are limited or for precise planimetry of the valve area (discussed below). In the early stages of AS, LV systolic function is preserved, with varying degrees of compensatory LVH. Over time, with LV stiffening, diastolic filling becomes more dependent upon atrial systole and diastolic dysfunction ensues. Eventually, the chronically afterloaded LV dilates, and left ventricular systolic function declines.

The degree of valvular stenosis can be assessed both qualitatively and quantitatively. The presence of congenital disorders (i.e., unicuspid, bicuspid, etc.) is assessed in the parasternal long-axis (the valve does not coapt in the center line or may have a "doming" appearance) and short-axis

views (the number of cusps can be identified along with the presence of a "raphe"), as well as the degree of thickening and calcification. The short-axis view is also useful for performing planimetry of the aortic orifice.

Hemodynamic assessment of AS by TTE requires an assessment of the following: jet velocity, peak and mean gradients, and the dimensionless index (DI) (Table 17.1) [5]. Peak jet velocity gives a rough estimate of stenosis severity; velocity >4 m/sec is considered severe. The peak gradient is calculated using the peak velocity via the Bernoulli equation ($\Delta P = 4v^2$).

Table 17.1 Echocardiographic evaluation of aortic stenosis severity

	Mild	Moderate	Severe
Peak jet velocity (m/sec)	<3.0	3.0–4.0	>4.0
Mean gradient (mmHg)	<25	25–40	>40
Valve area (cm^2)	>1.5	1.0–1.5	<1.0
Dimensionless index	*	*	<0.25

The mean gradient is calculated using the velocity time integral (VTI), which sums the velocities over an entire cardiac cycle and is provided by tracing the continuous-wave Doppler aortic outflow envelope. The dimensionless index is a ratio of the velocity (or VTI) in the left ventricular outflow tract (LVOT) to that in the aorta; a ratio <0.25 implies an AVA that is <25% of the LVOT area. The DI is helpful in patients for whom LVOT diameter is difficult to measure.

Calculation of aortic valve area (AVA) may be performed by planimetry as above or by using the continuity equation. The continuity equation makes the assumption that flow and volume are constant. Since flow = cross-sectional area (CSA) × velocity, the relationship can also be described as stroke volume = CSA × VTI, and since volume is constant, the equation can be rearranged as $A_{AV}V_{AV} = A_{LVOT}V_{LVOT}$. Calculation of the AVA is demonstrated in Fig. 17.1. Common mistakes in calculation of the AVA

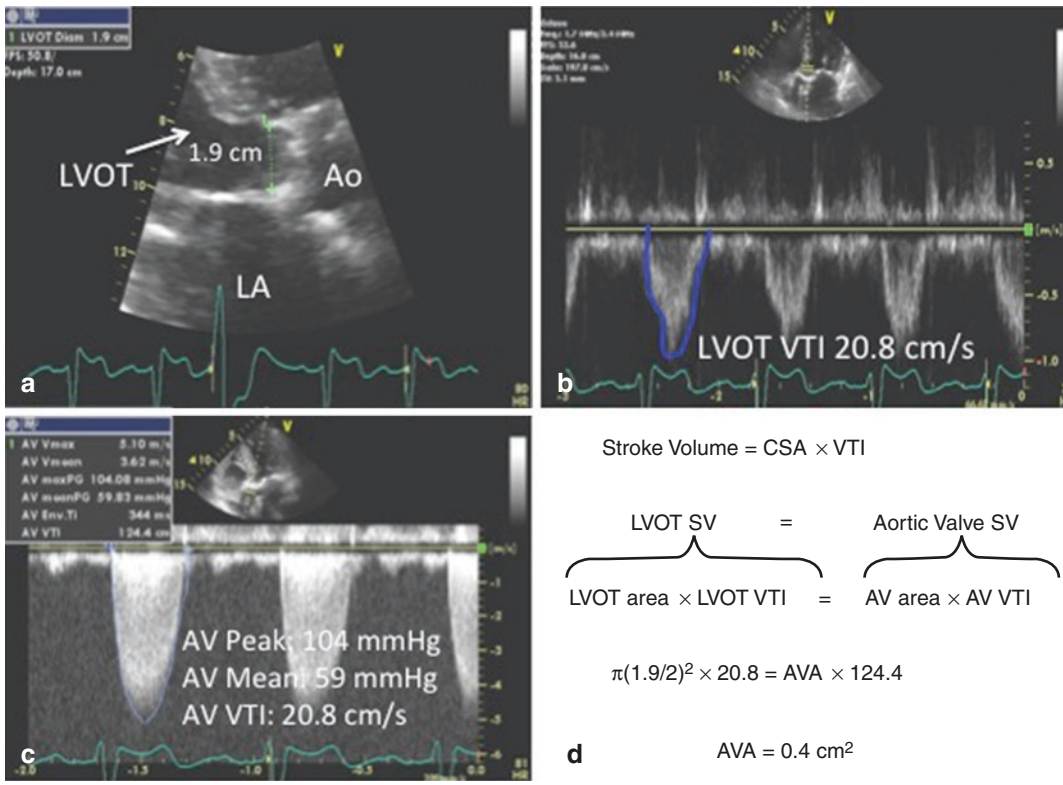

Fig. 17.1 Calculation of aortic valve area (AVA) using the continuity equation. Measurement of the left ventricular outflow tract (LVOT) diameter (**panel A**), velocity time integral (VTI) in the LVOT (**panel B**), and aortic valve (AV) VTI (**panel C**) is necessary to calculate the AVA (**panel D**)

include incorrect measurement of the LVOT diameter (underestimation of the LVOT leads to an underestimation of the AVA) or LVOT/AV outflow gradients.

Low-Flow, Low-Gradient Aortic Stenosis

Patients with chronic pressure overload from AS, CAD, or intrinsic myocardial dysfunction may present with depressed LV function and aortic stenosis with a low gradient. Low-flow/low-gradient (LF/LG) AS is defined as an LVEF <35%, mean gradient <30 mmHg, and AVA < 1.0 cm^2. Evaluation of the true degree of AS in these patients presents a common clinical quandary, as patients may have truly severe AS or "functional" AS caused by poor leaflet excursion in the setting of a low cardiac output (pseudo-AS).

Dobutamine stress echocardiography (DSE) is a common diagnostic tool in this setting. With infusion of increasing doses of dobutamine (DBA; 5–20 mcg), the stroke volume, peak velocity, mean gradient, and AVA are measured/calculated. An increase in SV >20% implies contractile reserve. Increases in peak velocity and/or mean gradient imply true AS; the increased flow across the valve is limited by intrinsic valve disease and results in higher gradients and does not simply cause increased leaflet excursion. An increase in AVA > 0.3 cm^2 implies pseudo-AS; increase in LVOT velocity is greater than the increase in AV velocity due to increased leaflet excursion, providing a higher calculated AVA. The potential outcomes of DSE and the clinical diagnosis are summarized in Table 17.2 [6].

For patients with pseudo-AS, treatment is directed toward the medical management of heart failure. Studies on AVR in patients with LF/LG true AS have shown that perioperative mortality is only mildly increased (5%) in patients with contractile reserve on DSE. On the other hand, patients with LF/LG true AS but without contractile reserve face a significant perioperative mortality (32%) [7]. However, survival thereafter is reasonable, and improvement in ejection fraction is similar in both groups [8].

Table 17.2 Possible outcomes of dobutamine stress echocardiography in low-flow, low-gradient aortic stenosis

Dobutamine response	Diagnosis
Increase in CO and gradient	Contractile reserve present
	True AS
Increase in CO and AVA with constant/decreased gradient	Contractile reserve present
	Pseudo-AS
No response to DBA	No contractile reserve
	Indeterminate re: AS

CO cardiac output, *AVA* aortic valve area, *AS* aortic stenosis, *DBA* dobutamine

Cardiac Catheterization

Outside of the evaluation for coronary artery disease, cardiac catheterization in patients with AS is reserved for situations when the degree of symptoms and severity of AS are contradictory based on noninvasive testing [5]. Catheterization may be used to measure intracardiac pressures, cardiac output, and valve gradient and calculate the AVA.

Historically, measurements of the valve gradient were taken by placing a catheter in the aortic root and another in the LV via transseptal puncture, but this is rarely performed now. Valve gradient may be measured with a dual-lumen pigtail catheter that simultaneously measures pressures in the LV and aorta, or by placing a catheter in the LV and then quickly pulling it back to the aortic root ("pullback gradient"). It should be noted that this "peak-to-peak" gradient is generally lower than the peak gradient obtained by Doppler echocardiography, which is sampled as the peak instantaneous velocity (Fig. 17.2). The peak-to-peak gradient correlates well to the mean gradient.

The valve area is usually calculated using the *Gorlin equation*:

$$\mathrm{AVA} = \mathrm{CO} \div \left(\mathrm{HR} \times \mathrm{SEP} \times 44.3 \times \sqrt{\text{mean gradient}} \right)$$

[CO, cardiac output; HR, heart rate; SEP, systolic ejection period]

Since the Gorlin method is dependent on flow across the aortic valve, patients with LF/LG AS will have a significantly underestimated AVA. In these cases, dobutamine infusion during catheterization may reveal pseudo-AS similar to that

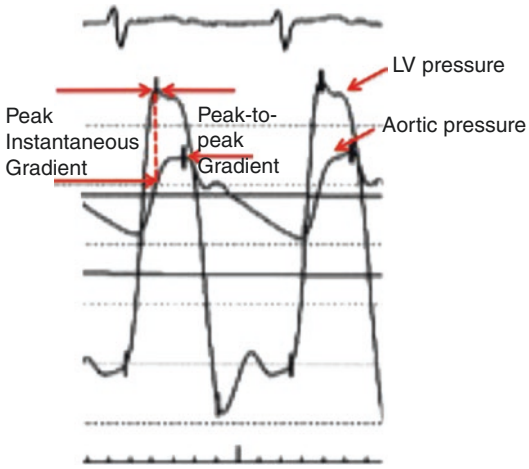

Fig. 17.2 Simultaneous LV and aortic pressure tracing. Peak-to-peak gradient is measured as the difference between peak LV and aortic pressures during cath; peak gradient by echocardiography is an instantaneous peak. Mean gradient is calculated as the average pressure difference between LV and aorta pressures (area between the curves)

described during DSE above (increased cardiac output with increased AVA and stable or decreased gradient).

A simplification of the Gorlin equation is the *Hakki equation*, based upon the assumption that the (HR × SEP × 44.3) approximates 1 under normal conditions [9]:

$$\text{AVA} = \text{CO} \div \sqrt{\text{mean gradient}}$$

For patients with a heart rate >100 bpm, the AVA obtained using the Hakki method should be divided by 1.35 for increased accuracy.

Aortic Regurgitation

Case Presentation

A 42-year-old man presented with progressive dyspnea over a 6-month period. He was quite active previously, running 3 miles every other day, but now required a break after just 2 miles due to dyspnea. He also noticed some dyspnea with walking the three flights of stairs to his apartment, which was new over the prior 1–2 months. He had not experienced orthopnea but has had a few episodes of paroxysmal nocturnal dyspnea over the prior 3 months. He denied chest discomfort or lower extremity edema.

On physical examination, cardiac auscultation was significant for a long, decrescendo, holodiastolic murmur heard best at the left sternal border as the patient leaned forward. Palpation of the brachial pulse revealed a brisk and forceful upstroke and wide pulse pressure. Gentle pressure applied at the tip of the fingernails revealed a "to-and-fro" filling of the nailbeds.

TTE performed revealed a bicuspid aortic valve with fusion of the right and left coronary leaflets and with minimal calcification. There was mild anterior leaflet prolapse resulting in severe, posteriorly directed aortic regurgitation (AR). The aortic root and ascending aorta were normal in size without evidence of dilation. LV systolic function and chamber size were normal.

Given a diagnosis of severe, symptomatic aortic regurgitation, the patient underwent preoperative coronary angiography that revealed minimal atherosclerosis. He then underwent successful aortic valve repair.

Epidemiology and Pathophysiology

Aortic regurgitation (AR) is present in up to 12% of men and may complicate rheumatic valve disease, radiation valvular disease, or bicuspid aortic valve. Infective endocarditis may cause AR due to valve degeneration, leaflet perforation, or paravalvular leakage. Anorectic drugs, such as fenfluramine and phentermine ("fen-phen"), may cause AR through a serotonin-mediated pathway that results in degenerative changes in valve morphology. Additionally, aortic pathology such as ascending dissection or aortic root dilation can cause malcoaptation of the valve and resultant AR. A rare cause of AR is the supracristal VSD, which can result in AR due to prolapse of the noncoronary leaflet.

Of the causes listed above, aortic dissection and endocarditis often cause acute severe AR. This is usually poorly tolerated from a hemodynamic perspective, primarily due to a degree of LV compliance that does not accommodate the

massive increase in volume and leads to acute volume overload and diminished cardiac output. As a result, acute AR is usually a surgical emergency.

The degree of regurgitation is dependent on the diastolic pressure gradient between the aorta and LV, duration of diastole, size of the regurgitant orifice, and LV compliance. In chronic AR, compensatory LV cavity dilation, increase in LV compliance, and LV wall hypertrophy ensue to accommodate the increased filling and afterload. Maintenance of an adequate heart rate (i.e., judicious use of negative chronotropic agents) is also important to minimize diastolic regurgitation time. Together, these changes allow the LVEDP to stay relatively normal and stroke volume to increase. Patients may therefore remain asymptomatic for long periods of time and develop symptoms or LV dysfunction at an average of 4.3% per year [5].

It should also be noted that since diastolic pressure in the aorta is reduced in patients with AR, coronary perfusion pressure is also reduced. Patients may therefore develop symptoms of coronary insufficiency, even in the absence of flow-limiting coronary stenoses, due to decrease coronary flow and increased LV oxygen demand.

Physical Examination

In acute AR, the hallmark diastolic murmur of AR may not be appreciated as easily, since the aortic diastolic and LV diastolic pressures equalize rapidly, and patients are often quite tachycardic due to hemodynamic instability. This also highlights the importance of the judicious use of agents that decrease chronotropy (i.e., beta blockers, non-dihydropyridine calcium-channel blockers, etc.), as slower heart rates allow a longer period of regurgitation.

With chronic AR, however, the long-standing increase in LV volume and concomitant hypertrophy allow the ventricle to accommodate a long period of diastolic backflow through the regurgitant lesion, providing the classic auscultatory diastolic murmur. The murmur is best heard at the aortic position (left sternal border) and may be more easily appreciated with the patient leaning forward. Typically, AR due to aortic dilation is heard at the right sternal border, and that due to valvular disease is heard at the left sternal border. A murmur resembling mitral stenosis (MS) may also be heard at the apex. It is thought that this *Austin Flint* murmur is the result of premature closure of the anterior mitral leaflet due to pressure from the regurgitation jet of AR.

Measurement of the blood pressure often reveals a widened pulse pressure (SBP – DBP). This is due to the fact that the SBP is increased in the setting of higher stroke volume and DBP is decreased due to the regurgitation of blood into the LV.

The peripheral examination in AR provides a number of eponymous findings that have variable degrees of sensitivity and specificity for diagnosis (Table 17.3) [10]. Most of these findings are the result of an increase in stroke volume accompanied by a sudden drop in aortic pressure due to the valvular regurgitation (i.e., wide pulse pressure). Although the majority of these clinical findings lack significant clinical relevance, two signs, Durozier's sign and Hill's sign, have demonstrated clinical correlation with the severity of AR.

Table 17.3 Physical findings in the peripheral examination of severe aortic regurgitation

Physical sign	Description
Corrigan's pulse ("water hammer pulse")	Rapid rise and fall of the arterial pulse
Duroziez's sign	"To-and-fro" murmur heard at the femoral artery elicited with femoral artery compression
Quincke's sign	Capillary pulsations at the nail bed elicited by gentle compression of the distal nail
de Musset's sign	Bobbing of the head
Mueller's sign	Pulsation of the uvula
Hill's sign	Lower extremity BP > upper extremity BP
Rosenbach's sign	Pulsatile liver
Gerhard's sign	Pulsatile spleen

Adapted from Babu et al., Ann Int Med 2003, with permission

Echocardiography

When suggested by history and physical examination, echocardiography provides the definitive diagnosis of AR and provides an assessment of valve morphology, LV size and function, aortic root structure, and of course regurgitation severity.

An assessment of valve anatomy is important to define the etiology of AR. Congenital bicuspid valve disease is responsible for most cases of valvular AR in the developed world, though rheumatic disease remains the most common cause worldwide. In patients with a bicuspid valve, an assessment of the degree of leaflet degeneration and calcification is important to determine whether valve repair may be feasible or whether valve replacement will be necessary. Similarly, assessment for endocarditis is important for antibiotic management and planning the treatment strategy (i.e., large vegetation, presence of abscess, leaflet perforation, etc.).

LV size and systolic function are important to the treatment algorithm. In patients with severe, asymptomatic AR, surgery is not indicated unless there is evidence of LV dilation (end-diastolic dimension >7.5 cm or end-systolic dimension >5.5 cm) or systolic dysfunction (LVEF <50%). It is therefore recommended that patients with chronic AR have close echocardiographic surveillance in the absence of symptoms (every 1 year with mild/moderate AR and every 6 months with severe AR) [5].

Evaluation of ascending aorta and root structure is important for diagnosis and also may dictate the course of management. For instance, in patients with bicuspid AV, dilation of the aorta beyond 5 cm is considered an indication for surgery, and concomitant AV surgery may therefore be performed even in the absence of symptomatic AR. Aortic dissection involving the ascending aorta is a surgical emergency and should be managed accordingly as appropriate.

An accurate assessment of AR severity is nuanced and requires a critical appraisal of numerous parameters taken together. Considerations include regurgitant jet width/LVOT height, vena contracta (VC), calculation of the proximal isovelocity surface area (PISA), subjective appearance of AR jet density and pressure half-time (PHT) of the AR jet on continuous-wave (CW) Doppler, and evidence of diastolic flow reversal in the descending aorta using pulsed-wave (PW) Doppler (Table 17.4).

Table 17.4 Echocardiographic characteristics of severe aortic regurgitation (AR)

Vena contracta	>0.6 cm
Jet width/LVOT height	>60%
PISA	ERO > 0.3 cm^2
Pressure half-time	<250 msec
Descending aorta pulsed-wave Doppler	Pandiastolic reversal of flow with velocity >20 cm/sec

LVOT left ventricular outlflow tract, *ERO* effective regurgitant orifice

The regurgitant jet width is measured in the LVOT in the parasternal long-axis view and compared to the height of the LVOT; a ratio of >60% indicates severe AR. The VC is usually measured in the same view (though the apical five-chamber view may be used) and is the width of the jet at its narrowest point at the AV; a width of >0.6 cm signifies severe AR. By definition, the VC is smaller than the regurgitant jet width.

The PISA method is used most commonly in the assessment of mitral regurgitation (discussed in detail later in this chapter) but can be applied in AR as well to calculate the effective regurgitant orifice (ERO). An ERO >0.3 cm^2 is considered severe.

The basis for measuring PHT (the time required to reduce the gradient across the valve by ½) is as follows: with worsening AR, the aortic diastolic pressure and LVEDP equilibrate more quickly, resulting in a shorter PHT. A PHT < 250 msec signifies severe AR and PHT > 400 msec mild AR. While this method is used clinically, it should be noted that changes in loading conditions (i.e., alterations in SVR, LV compliance) may have effects on the PHT that are contrary to the regurgitant fraction measured. Furthermore, patients with chronic AR may have modified their LV compliance enough that the LV accommodates a long period of diastolic filling (i.e., long PHT). Therefore, the PHT should be used only as a piece of the diagnostic puzzle [11]. Evaluation of the AR jet density on

CW is a subjective measure, and pitfalls include a lack of coaxial alignment of the Doppler signal with the regurgitant flow. Nevertheless, a dense jet with a short PHT may increase the suspicion of severe AR. It should also be noted that due to the large stroke volume ejected by the LV in chronic severe AR, there may be a small outflow gradient measured though this does not reflect true AS.

The presence of some regurgitant flow in the descending aorta in early diastole is common and is due to closure of the AV. Persistent holodiastolic flow reversal with a velocity >20 cm/sec, however, is a marker of severe AR (Fig. 17.3). The presence of diastolic MR (appreciated on the CW or PW Doppler in the apical four-chamber view) may be seen in patients with severely elevated LV pressures, such as in acute severe AR.

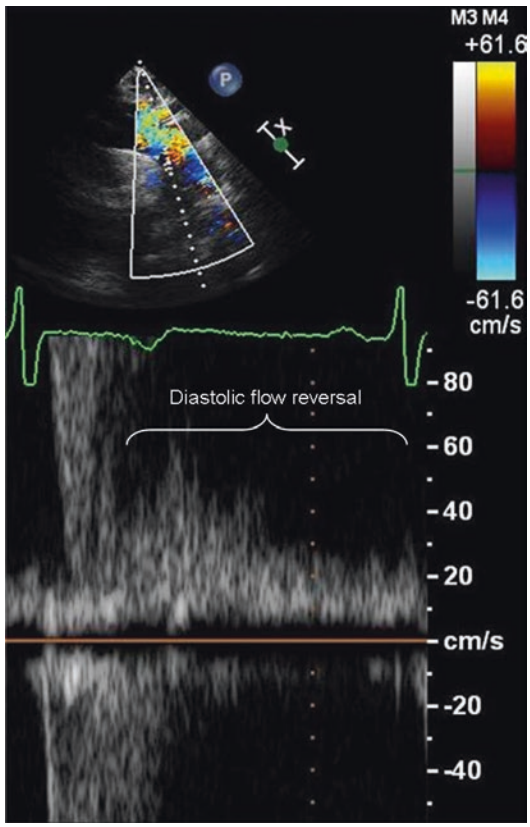

Fig. 17.3 Pulsed-wave Doppler demonstrating pandiastolic flow reversal in the descending thoracic aorta in a patient with severe aortic regurgitation

Cardiac Catheterization

Invasive catheterization holds a diminishing role in the diagnosis of AR. Similar to patients with AS, it is recommended only when the clinical scenario is not substantiated by noninvasive testing. Catheterization can be used to measure the LVEDP, examine the aortic pressure tracing, and quantify the degree of AR.

The aortic pressure tracing reveals elevated SBP (due to increased stroke volume) and a rapid systolic upstroke due to heightened LV contractility. The pulse pressure is widened (as discussed above), and diastolic aortic pressure approximates LVEDP near the end of diastole. In patients with chronic AR, increased LV compliance results in an LVEDP that is near-normal or only mildly elevated. In acute AR, there is a steep, marked rise in LVEDP. The SBP is reduced due to a decline in stroke volume.

The degree of AR is measured using ascending aortography by placing a pigtail catheter in the aortic root, 2 cm above the AV. A left anterior oblique (LAO) projection is selected to properly visualize the ascending aorta and branching arch vessels. Use of a power injector is mandatory, and generally 40 cc of dye is necessary to properly opacify the aorta. The AR is evaluated over two cardiac cycles and quantified as follows: incomplete LV opacification (1+); moderate LV opacification < aortic root opacification (2+); LV opacification = aortic root opacification within two cycles (3+); immediate LV opacification > aortic root opacification (4+).

Mitral Stenosis

Case Presentation

A 48-year-old woman presented to the emergency department with complaints of progressive dyspnea over the past 3 weeks associated with orthopnea and mild lower extremity edema. She had not noticed any chest discomfort or palpitations. She had been having less urine output over the past week, despite a relatively stable diet. She reported a history of rheumatic fever as a teenager, but had

not been followed by a physician for a number of years. She was therefore unaware of any other medical problems.

On examination, she was in mild distress manifest as tachypnea and labored breathing. She was tachycardic with an irregular heart rate of 120 bpm and a BP of 100/65 mmHg. The cardiovascular exam was significant for an opening snap (OS) heard at the left lower sternal border just after the S2, with a short interval between the S2 and OS, followed by a mid-diastolic murmur at the apex heard best in the left lateral position. The JVP was elevated to the angle of the jaw while sitting upright. Examination of the periphery revealed 2+ lower extremity edema bilaterally to the shins and cool extremities.

An ECG revealed atrial fibrillation with a ventricular rate of 125 bpm and no evidence of ischemic changes. Given the examination findings, urgent bedside echocardiography was performed and revealed a low-normal LV ejection fraction (50%) and mild aortic valve thickening and calcification. Most significant was a doming appearance of the anterior mitral leaflet, restricted motion of the posterior mitral leaflet, and fusion of the leaflets at both commissures. The peak and mean gradients across the mitral valve were 34 and 20 mmHg, respectively.

With a clinical diagnosis of suspected cardiogenic shock due to decompensated heart failure and severe mitral stenosis complicated by rapid atrial fibrillation, the patient was moved urgently to the cardiac intensive care unit. Pulmonary artery catheterization (Swan-Ganz) confirmed the diagnosis with a cardiac index of 1.5, PCWP of 35 mmHg, and mixed venous oxygen saturation of 40%. Urgent cardioversion was performed and was successful in restoring a normal sinus rhythm of 70 bpm. With restoration of the rhythm, the patient's urine output increased immediately, and treatment of her volume overload was continued. Repeat TTE revealed a decrease in the mean mitral gradient to 12 mmHg. After successful management of her acute episode, the patient went on to have successful percutaneous mitral balloon valvotomy which decreased her mean mitral gradient to 4 mmHg.

Epidemiology and Pathophysiology

Mitral stenosis (MS) was the first valvular lesion to be diagnosed echocardiographically and treated surgically. Rheumatic heart disease is the leading cause of MS worldwide (prevalence of 6 per 1000 children, compared with 0.5 per 1000 in the United States) [12]. In developed countries, other etiologies such as severe mitral annular calcification due to end-stage renal disease (ESRD), endocarditis, inflammatory disorders (i.e., lupus and rheumatoid arthritis), radiation therapy, and LA myxoma causing MV obstruction are more often considered. MS is a slowly progressive disease that eventually leads to atrial fibrillation (AFib), pulmonary hypertension, and decreased cardiac output. Once symptoms develop, patients face a dismal prognosis, with a 10-year mortality of 70% [13].

In rheumatic fever, inflammation results in nodule formation at the leaflet edge, followed by leaflet thickening, commissural fusion, and chordal thickening and shortening. Smoldering inflammation coupled with turbulent flow across the valve leads to progressive valvular dysfunction [14]. Patients with end-stage kidney disease have disordered calcium metabolism and resultant mitral annular calcification (MAC). As calcification of the annulus progresses to involve the leaflets, obstruction to flow across the valve may occur due to the smaller mitral orifice and restricted leaflet motion [15]. In contrast to rheumatic MS, in which the smallest valve area is at the leaflet tips, obstruction in non-rheumatic MS is predominantly at the annular level.

Physical Examination

The classic findings of MS include the opening snap and mid-diastolic murmur. The source of the OS is mobility of the anterior mitral leaflet and is usually heard best at the LLSB; it is generally not appreciated at the apex. The OS may be differentiated from physiologic splitting of the S2 during exhalation (when the presence of two sounds indicates the OS of MS). A short interval

between the S2 and OS indicates severe MS, as a high LA pressure causes quick opening of the mitral valve in diastole.

The murmur of MS is best heard in the left lateral decubitus position with the stethoscope placed at the ventricular PMI. As with other valve lesions, a louder murmur signifies a large degree of flow (and hence a higher gradient) across the valve. Similarly, in patients with atrial fibrillation, a diastolic murmur leading up to the S1 during a long R-R interval implies severe MS with a persistent gradient even at the end of diastole.

Echocardiography

A subjective assessment of the mitral valve apparatus involves an appraisal of leaflet mobility (typically "doming" of the anterior leaflet and restriction of the posterior leaflet) and thickness, as well as the degree of thickening, calcification, and/or fusion of the commissures and subvalvular apparatus. The systematic scoring system provided by Wilkins and colleagues takes these factors into consideration and is also useful in assessing the feasibility of percutaneous balloon mitral valvotomy (Table 17.5) [16].

The objective evaluation of MS includes a measurement of valve area, valve gradient, and pulmonary artery pressure (PAP) (Table 17.6) [17]. The mitral valve area (MVA) can be assessed using planimetry in the parasternal short-axis projection, though a common pitfall of this method is measuring proximal to the true orifice and thereby overestimating the MVA. Valve area is also estimated using the PHT method, which as with AR is a measure of the time it takes for the gradient across the valve to fall by one-half (Fig. 17.4). Notably, the PHT method is unreliable in patients with severe AR or significant LV diastolic dysfunction since the pressure gradient between the LA and LV equalizes rapidly, providing an abnormally short PHT (thereby overestimating MVA).

The valve gradient in MS is best assessed by tracing the mitral inflow Doppler signal obtained in the apical four-chamber view (Fig. 17.5). The main consideration is the mean gradient, which is automatically calculated by summing the gradient over the cardiac cycle. As shown in the figure,

Table 17.6 Echocardiographic evaluation of mitral stenosis severity

	Mild	Moderate	Severe
Mean gradient	<5 mmHg	5–10 mmHg	>10 mmHg or >15 mmHg with stress
Valve area	>1.5 cm^2	1.0–1.5 cm^2	<1.0 cm^2
Pulmonary artery systolic pressure	<30 mmHg	30–50 mmHg	>50 mmHg or >60 mmHg with stress

Table 17.5 Echocardiographic scoring system for mitral valve stenosis. A score ≤8 is generally associated with favorable outcome from percutaneous mitral balloon valvotomy

Grade	Mobility	Subvalvar thickening	Thickening	Calcification
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	A single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one-third of the chordal length	Mid-leaflets normal, considerable thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid-portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

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a shorter R–R interval results in a marked increase in mitral gradient and highlights the need for appropriate heart rate control in patients with MS, particularly those with concomitant atrial fibrillation.

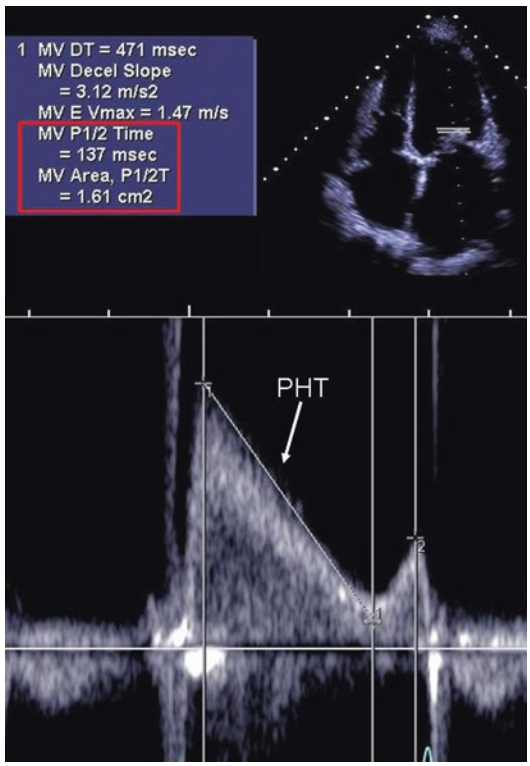

Fig. 17.4 Pulsed-wave Doppler of mitral inflow demonstrating calculation of the mitral valve area (MVA) using the pressure half-time (PHT) method. MVA = 220/PHT

An estimation of pulmonary pressures using the right ventricular systolic pressure (RVSP) is an important part of the evaluation of MS. An RVSP >50 mmHg at rest or > 60 mmHg on exercise TTE is consistent with significant pulmonary hypertension and provides an indication for intervention of MS.

Cardiac Catheterization

As with other valve disorders, catheterization is recommended in the diagnosis of MS when there is discrepancy between the clinical scenario and noninvasive methods [5]. Right heart catheterization (RHC) is often indispensable in the critical care unit to guide management of volume status in patients presenting with pulmonary congestion, depressed cardiac output, and severe mitral stenosis.

The mitral valve gradient is measured by taking simultaneous pressure tracings via an LV catheter and either a pulmonary artery catheter in the wedge position (PCWP) or a direct left atrial catheter (Fig. 17.6). Use of the PCWP is unreliable in patients with pulmonary veno-occlusive disease. It is also important to remember that the "true" wedge pressure is the measured PCWP minus the mean mitral gradient.

As discussed above, the mean gradient is exquisitely sensitive to heart rate, since a faster heart rate leaves less time for diastolic emptying

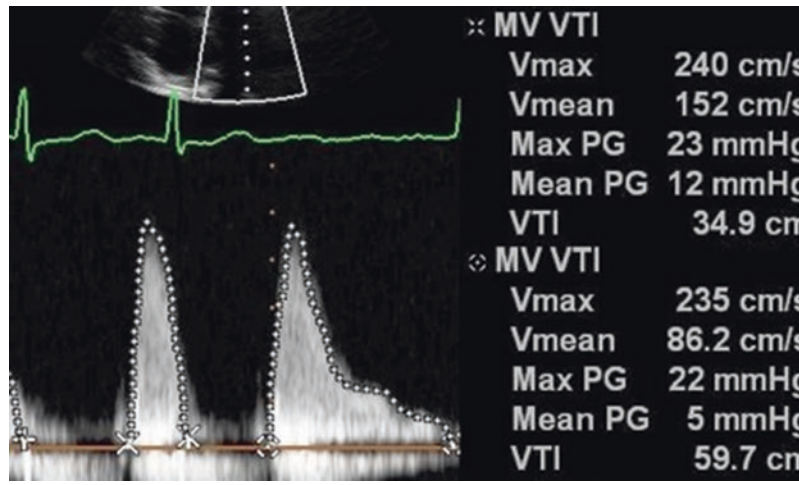

Fig. 17.5 Patient with moderate mitral stenosis and atrial fibrillation. The mean gradient across the mitral valve is significantly increased in the setting of decreased diastolic filling time (i.e., increased heart rate) (beat 1:12 mmHg vs. beat 2:5 mmHg)

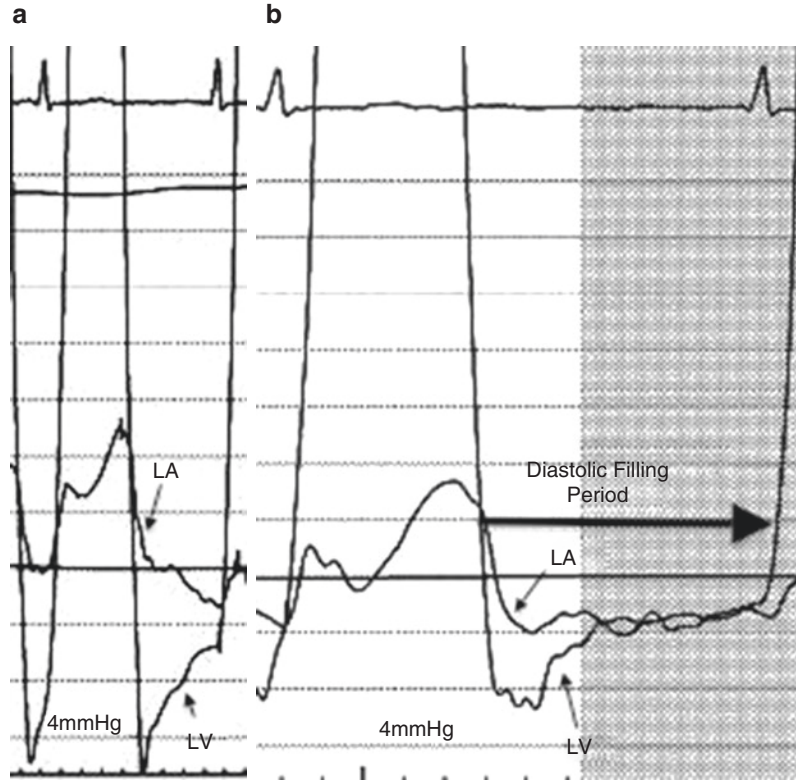

Fig. 17.6 Simultaneous measurement of left atrial (LA) and left ventricular (LV) pressures in a patient with mitral stenosis before (**a**) and after (**b**) percutaneous mitral balloon valvuloplasty. Prior to PMBV, a substantial gradient is present until the end of diastole. In this patient, the pre-procedural resting gradient was 10 mmHg, and post-procedural gradient was 4 mmHg. Paper speed is faster in panel A

of the atrium and results in a higher gradient. In patients with atrial fibrillation, it is therefore recommended to average the gradient over ten cardiac cycles.

The valve area is estimated using the Gorlin formula as follows:

$$\text{MVA} = \left(\text{SV} \div \text{DFP}\right) \div \left(37.7 \times \sqrt{\text{mean gradient}}\right)$$

[SV, stroke volume; DFP, diastolic filling period]

Of note, calculation of the SV using the thermodilution method is not accurate in patients with low cardiac output or significant tricuspid regurgitation. As in patients with AS, the valve area can also be calculated using the Hakki equation:

$$\text{MVA} = \text{CO} \div \sqrt{\text{mean gradient}}$$

In patients with a HR <75 bpm, the value above is divided by 1.35 to provide greater accuracy.

Mitral Regurgitation

Case Presentation

The patient is an 87-year-old man with prior history of diabetes, hypertension, hyperlipidemia, and chronic kidney disease (Stage IV, GFR 25 mL/min/1.73 m^2). He had undergone two prior coronary bypass graft operations, with recent angiography showing patent grafts to the left anterior descending, circumflex, and right coronary arteries. He noted worsening exertional dyspnea over the past 12 months, with recently increasing orthopnea and lower extremity edema. He had initially experienced relief with an increasing dose of diuretics and hydralazine, but his symptoms again worsened.

Physical examination revealed atrial fibrillation with a controlled heart rate of 80 bpm and BP 110/75 mmHg. The PMI was laterally displaced to the mid-axillary line, and there was a 3/6 systolic murmur heard best at the apex and

radiating to the axilla as well as the spine posteriorly. The JVP was elevated at 12 cm H_2O. TTE revealed severely depressed LV function (EF 25%) with moderate LV cavity dilation and moderate LA enlargement. There was severe, posteriorly directed mitral regurgitation due to MV annular dilation, apical displacement of the mitral leaflets, and restriction of the posterior mitral valve.

Given the patient's age, co-morbidities, and two prior open-heart surgeries, he was deemed an inoperable risk for surgical mitral valve repair. He therefore underwent percutaneous mitral valve repair using the MitraClip device (approximating the Alfieri stitch method of surgical repair), which provided a substantial reduction in his degree of MR and improvement in his clinical symptoms.

Epidemiology and Pathophysiology

Mitral regurgitation (MR) affects more than two million people in the United States [18]. Classification of MR is broadly defined by two groups: primary and secondary MR. Primary MR, which is a disorder of the valve itself, is most commonly due to myxomatous (degenerative) disease or mitral valve prolapse (MVP; Barlow's Disease) in the developed world and rheumatic disease in developing countries. Secondary MR is the result of a disordered left ventricular geometry and is usually referred to as "functional" or "ischemic" MR. In secondary MR, annular dilation, apical tethering of the MV leaflets, and/or excessive leaflet motion due to chordal avulsion or papillary muscle rupture lead to the regurgitant lesion.

Acute MR is most often caused by myocardial infarction that leads to papillary muscle rupture or chordal avulsion, supranormal contraction of the non-infarcted papillary muscle, or regional LV dysfunction. Similar to acute AR, it is a severe volume overload state that results in pulmonary edema and depressed cardiac output. Management requires urgent pharmacologic and mechanical afterload reduction and timely surgical referral. Chronic MR, over time, results in a volume overloaded state for the LV and leads to LV dilation and dysfunction, LA enlargement, atrial fibrillation, and pulmonary hypertension.

Physical Examination

A salient physical finding in patients with MR includes the classic high-pitched, holosystolic murmur heard at the apex with radiation to the axilla. If the MR is due to MV prolapse, the murmur may not start until mid-systole, after prolapse of the affected leaflet(s). In patients with severe, posteriorly directed MR (i.e., functional MR or patients with anterior leaflet prolapse), the murmur may also be appreciated by auscultation at the thoracic spine. With posterior prolapse, the regurgitant jet is directed anteriorly and may be best heard at the upper sternal border (similar to AS). The severity of the murmur does not correlate well with the severity of the MR, as other factors including LV cavity dilation and depressed cardiac output can diminish the murmur in the setting of severely decompensated disease. Similar to the murmur in AS, the sound is augmented by increasing afterload (i.e., handgrip) and diminished by reducing venous return (i.e., Valsalva maneuver).

The S1 sound is often diminished due to poor coaptation of the MV leaflets, and the S2 sound may be widely split due to a premature closure of the aortic valve (A2 component) in the setting of poor forward output. In patients with MV prolapse, a mid-systolic click may be appreciated at the time of maximum leaflet prolapse. With heart failure and a dilated LV, an S3 gallop may be also heard. The peripheral exam in severe MR often reveals a prominent upstroke and reflects the increased left ventricular ejection volume, similar to severe AR. In contrast to the pulse in AR, however, the pulse pressure with severe MR is normal.

Echocardiography

Echocardiography is used to quantify MR, evaluate the presence of valve pathology and define

the specific nature of the lesion, and evaluate LV size and systolic function. Quantification of MR is based on a number of parameters including color Doppler, continuous and pulsed-wave Doppler, and pulmonary venous flow pattern (Table 17.7) [19]. Color Doppler imaging can provide an overall impression of the degree of regurgitation based upon the visual estimation of the regurgitant jet in the LA. Slightly more quantitative methods include measurement of the vena contracta (thinnest portion of the regurgitant jet at the regurgitant orifice) and measurement of the regurgitant jet area (RJA) relative to the LA area.

Table 17.7 Echocardiographic determinants of mitral regurgitation severity

	Mild	Moderate	Severe
Color flow mapping			
RJA/LAA	<20%	20–40%	>40%
VC (cm)	<0.40	0.40–0.69	>0.70
ERO (cm^2)	<0.20	0.20–0.40	>0.40
RV (ml/beat)	<30	30–60	>60
Pulsed-wave Doppler			
Mitral E-wave velocity			>1.2 m/sec
PV flow pattern			Systolic blunting or reversal

Reproduced with permission from Krishnaswamy et al. Coron Art Dis 2011

RJA regurgitant jet area, *LAA* left atrial area, *VC* vena contracta, *ERO* effective regurgitant orifice, *RV* regurgitant volume, *PV* pulmonary vein

The proximal isovelocity surface area (PISA) method, as discussed previously in the evaluation of AR, provides the most precise echocardiographic estimation of MR. Briefly, the technique is based upon the idea that as blood converges toward a regurgitant orifice, velocity increases and forms a series of hemispheric shells with the same velocity (hence isovelocity). The velocity at a given shell can be set on the machine as the "aliasing velocity," and calculation of the area bounded by the shell (by measuring the radius) provides the flow at the surface of the shell. Since flow is constant (i.e., conservation of flow principle), the ERO can be calculated as in Fig. 17.7 using the color flow Doppler envelope and the continuous-wave (CW) Doppler tracing to measure MR velocity. If the MR velocity is assumed to be 5 m/sec, and the aliasing velocity set at 40 cm/sec, the PISA formula can be simplified as follows: ERO = $r^2/2$. The regurgitant volume can also be calculated using the

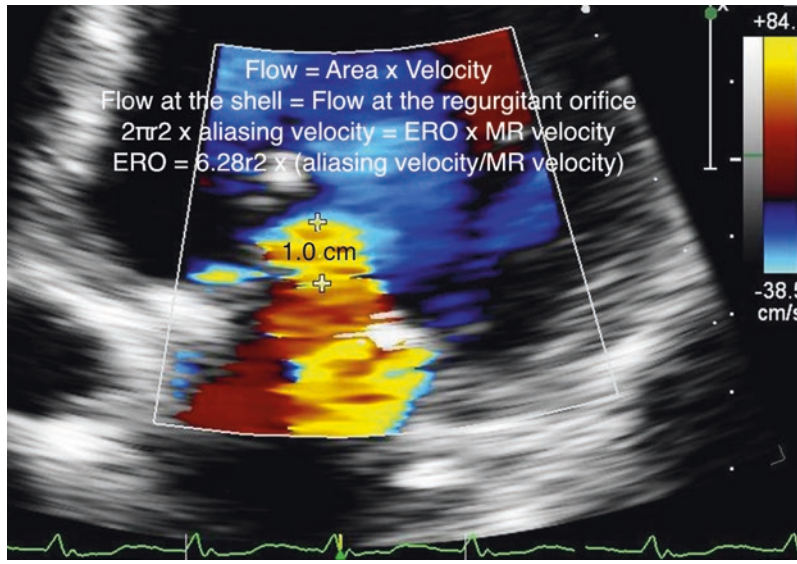

Fig. 17.7 Demonstration of the mitral regurgitation (MR) jet and calculation of the proximal isovelocity surface area (PISA). In this patient with an aliasing velocity set at 38.5 cm/sec and a MR velocity of 500 cm/sec (not shown), the simplified effective regurgitant orifice (ERO) calculation can be used ($r^2/2$), providing an ERO of 0.5 cm^2, which is consistent with severe MR. (Adapted with permission from Krishnaswamy et al., Coron Art Dis 2011)

following: $R_{vol} = ERO \times MR_{VTI}$ (MR_{VTI} is obtained by tracing the MR envelope on CW Doppler).

Pulsed-wave (PW) Doppler is used to interrogate the mitral inflow and stage diastolic function. In the setting of MR, assessment of the peak inflow velocity is useful in quantification. Severe regurgitation results in a higher LA–LV gradient and therefore a higher E-wave velocity during mitral inflow. Use of PW Doppler is also important to evaluate the pulmonary vein flow, specifically for the presence of systolic blunting or reversal in the pulmonary veins that signifies elevated LA pressure (assumedly due to severe MR).

Cardiac Catheterization

Invasive hemodynamic assessment in patients with MR is rarely necessary but may be performed when noninvasive testing is not definitive. In acute MR, the PCWP tracing (or direct LA measurement) demonstrates a large "v" wave due to the large volume of regurgitant blood into a low-compliance LA, and the amplitude of the "v" wave and the LV systolic pressure may be nearly equivalent (Fig. 17.8). It is important to keep this in mind during percutaneous balloon mitral valvotomy as an indicator of complications. The volume overload of the regurgitant lesion on the LV results in elevated LV pressures as well.

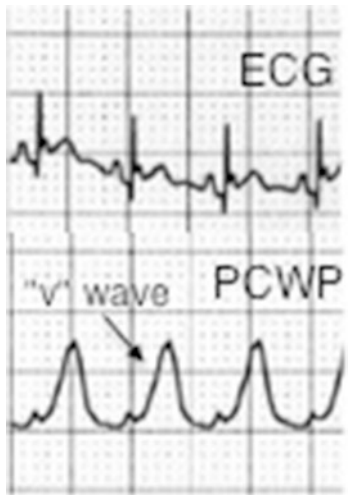

Fig. 17.8 Pulmonary artery catheter pressure tracing in the wedge position (PCWP) in a patient with acute severe mitral regurgitation due to papillary muscle rupture complicating acute myocardial infarction demonstrates a large v-wave

In patients with chronic MR, compliance of the LA increases over time (as does the LV in chronic AR). The "v" wave is therefore smaller than that seen with acute MR. The use of vasodilators in chronic MR produces a similar result. The LV responds to the chronic volume overload of MR as it does in chronic AR and compliance increases, resulting in a less drastic increase in LV pressures than in acute MR.

Ventriculography can also be used to assess the severity of MR. Grading of the regurgitation employs a similar scale as in AR: 1+ = brief LA opacification without LA enlargement; 2+ = moderate LA opacification less than LV opacification and without LA enlargement; 3+ = equal LA and LV opacification that clears over many cycles and with LA enlargement; and 4+ = immediate LA > LV opacification with pulmonary vein filling and LA enlargement. Caution should be exercised in performing ventriculography in patients with MR, in light of the contrast load that it requires in patients who may already be volume overloaded.

Review Questions

Q1. A 74-year-old man presented with exertional dyspnea and orthopnea. Echocardiography revealed a moderately thickened and calcified trileaflet aortic valve with severely restricted motion and an LVEF 20%. Results of interrogation of the AV were performed at rest and with infusion of dobutamine as follows:

Rest		*DBA*	
LVEF	20%	LVEF	25%
LVOT diameter	2.4 cm	LVOT diameter	2.4 cm
LVOT VTI	15.9 cm/sec	LVOT VTI	20.2 cm/sec
Calculated AVA	0.6 cm^2	Calculated AVA	0.9 cm^2

What is the appropriate next step?

(a) Refer for aortic valve replacement
(b) Refer for invasive hemodynamic study
(c) Medical management of LV dysfunction
(d) Refer for balloon aortic valvuloplasty

A1. C. This case demonstrates the diagnosis of "pseudo-AS," for which management of the underlying LV systolic dysfunction is appropriate. In patients with low-flow, low-gradient AS, provocative testing with DBA infusion may be helpful to distinguish true- and pseudo-AS. In this patient, the stroke volume (LVOT area x LVOT VTI) is 71 mL and at stress is 91 mL. This increase of >20% implies the presence of contractile reserve. The increase in calculated AVA of 0.3 cm^2 with stress provides evidence of improved AV leaflet excursion with higher SV; i.e., the "stenosis" is not fixed due to an intrinsic leaflet issue. Surgical intervention or valvuloplasty is not helpful in this setting. An invasive study is not necessary as the diagnosis is clear by echocardiography alone.

Q2. A 45-year-old woman with a history of rheumatic fever presents with worsening exertional dyspnea. Physical examination reveals a regular rate and rhythm. Cardiac auscultation reveals an opening snap and diastolic murmur heard at the apex. There is no lower extremity edema, and the JVP is appreciated at 5 cm above the sternum. Transthoracic echocardiography reveals a normal LVEF, doming of the anterior MV leaflet with restriction of the posterior MV leaflet, and a mean gradient across the MV of 7 mmHg. The estimated RVSP is 40 mmHg. What is the next step in management?

(a) Evaluate noncardiac causes of dyspnea
(b) Perform exercise echocardiography to evaluate the MV
(c) Refer for invasive cardiac catheterization to evaluate the MV
(d) Return for follow-up echocardiogram in 6 months

A2. B. This patient with a history of rheumatic fever presents with exertional dyspnea and a typical echocardiographic appearance of rheumatic mitral valve disease. The mean valve gradient is moderate at best, with a suggestion of borderline pulmonary hypertension (RVSP 40 mmHg). Given the patient's exertional symptoms, however, exercise echocardiography would be the next appropriate step in order to evaluate the MV gradient and pulmonary pressures with exertion. In this patient, TTE during stress revealed a mean MV gradient of 16 mmHg and RVSP of 65 mmHg. She subsequently underwent percutaneous balloon mitral valvuloplasty and was symptom-free with significant exertion afterward. Cardiac catheterization is considered to be less accurate in the evaluation of MS than echocardiography, and is therefore not yet indicated in this patient.

Q3. A 42-year-old man with bicuspid aortic valve seeks to establish a new cardiologist after many years of loss to follow-up. He does not take any medications. He feels well and exercises on a treadmill for 45 minutes 4 times per week. He has no exertional or positional dyspnea. On exam, his HR is 70 bpm and BP 115/50 mmHg. He has a holodiastolic murmur heard best at the left sternal border, and peripheral exam reveals bounding pulses with rapid collapse. TTE reveals normal LVEF 60% with LVIDd 7.2 cm and LVIDs 5.7 cm and a bicuspid aortic valve, and quantification of the degree of AR provides a vena contract of 0.7 cm, PHT 200 msec, and holodiastolic flow reversal in the descending aorta. What is the best next step?

(a) Routine clinical follow-up with TTE in 6 months
(b) Initiation of an ACE-inhibitor
(c) Referral for aortic valve surgery
(d) Exercise stress testing

A3. C. This patient with asymptomatic severe AR demonstrates LV cavity dilation (LVIDd >7.5 cm or LVIDs >5.5 cm), which is a criteria for aortic valve repair or replacement in patients with asymptomatic but severe AR (ACC/AHA Class IIa). For patients with severe AR and normal LV cavity size but without symptoms, follow-up echocardiography is indicated every 6 months (ACC/AHA Class I). Vasodilators are reasonable for symptomatic relief in patients with severe AR (Class IIa), but should not supersede definitive treatment in the setting of LV cavity dilation. Exercise stress testing may be helpful to distinguish whether or not the "asymptomatic" patient is truly asymptomatic (ACC/AHA Class

IIa), but the patient described here has LV cavity dilation and therefore symptoms are not necessary to make the recommendation for surgery.

Q4. A 67-year-old man with hypertension and hyperlipidemia presents with an inferior STEMI and undergoes primary percutaneous coronary intervention to a proximally occluded right coronary artery. The procedure is uneventful, and he is transferred to the cardiac ICU in stable condition. Fourteen hours later, he develops sudden hypotension and dyspnea. There are no new ECG changes. Which of the following would be expected of diagnostic testing:

(a) Large "v"-wave on a PCWP tracing
(b) LA > LV opacification within 1 cycle on a ventriculogram
(c) Pulmonary vein flow reversal during systole on TTE
(d) All of the above

A4. D. The patient above provides a classic presentation of mechanical complication after acute MI, in this case with severe MR due to papillary muscle rupture. Choices A–C all provide diagnostic evidence for severe MR. Appropriate management consists of emergent afterload reduction (using intra-aortic balloon counterpulsation and/or vasodilators if tolerated) and surgical referral for mitral valve surgery.

Q5. A 40-year-old man presents with worsening exertional dyspnea over the past 1 week, along with fevers to 102 degrees. He admits to regular intravenous drug use and claims to have had a "murmur" since childhood. His bedside echocardiogram suggests severe AR. What other diagnostic findings would be expected?

(a) Holodiastolic murmur at the left sternal border
(b) Bradycardia
(c) AR Pressure half-time <250 msec
(d) Systolic murmur resembling MR heard at the apex

A5. C. In acute AR, the rapid rise in LV pressure due to a noncompliant chamber results in rapid equilibration of aortic and LV pressures and results in a short pressure half-time. The hallmark diastolic murmur of AR may not be appreciated as easily in the acute setting for the same reason. Patients with acute AR are often quite tachycardic due to the poorly tolerated hemodynamic consequences of the lesion. The *Austin Flint* murmur of AR resembles the murmur of MS, and is thought to be due to premature closure of the anterior MV leaflet by the regurgitant AR jet.

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Pulmonary Hypertension

18

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Introduction

The pulmonary circulation is normally a low-pressure, low-resistance, and highly compliant system. Pulmonary hypertension (PH) is a pathologic state characterized by an elevation in the mean pulmonary arterial pressure (mPAP). PH may occur as a primary process, though it is most often a complication of other chronic disease states, particularly heart failure and chronic lung disease. Globally, it is helpful to dichotomize PH into precapillary PH, or pulmonary arterial hypertension (PAH), and postcapillary PH, the so-called pulmonary venous hypertension (PVH). Patients may also present with a combination of both. Patients with PAH, regardless of etiology, share common pulmonary vascular changes that define this form of PH. Vasoconstriction and progressive endothelial dysfunction lead to pulmonary vascular remodeling that ultimately results in the obliteration of the pulmonary vasculature and increased pulmonary vascular resistance (PVR) [1].

Right heart catheterization (RHC) remains the gold standard for diagnosing PH and differentiating pre- from postcapillary forms of PH. Classification systems have evolved over time and currently recognize five major etiologies of PH (Table 18.1) [2]: Group 1, PAH; Group 2, PH owing to left-sided heart disease; Group 3, PH due to pulmonary disease or hypoxia; Group 4, chronic thromboembolic PH (CTEPH) and other pulmonary artery (PA) obstructions; and Group 5, PH due to multifactorial mechanisms. PH is hemodynamically defined by a resting mPAP of ≥25 mmHg. Previous definitions have also made reference to mPAP elevation during exercise (to >30 mmHg), but exercise-induced PH in patients with normal resting pressures remains a poorly characterized phenomenon, and recent guidelines have removed this from the definition [3, 4]. PAH is further defined by (1) a PVR >3 Wood units (Wu) and (2) a normal pulmonary capillary wedge pressure (PCWP) (≤15 mmHg).

Epidemiology of Pulmonary Hypertension

The global burden of PH throughout the world has become increasingly recognized [5]. Estimated the prevalence of PH in 2015 at 50–70 million individuals worldwide (about 1% of the global population). Left-sided heart diseases and chronic lung diseases are the most common causes in both industrialized and developing countries. However, the majority of PH is seen in the developing world, where associated diseases including schistosomiasis, rheumatic heart dis-

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_18

Table 18.1 World Health Organization classification system for pulmonary hypertension[a] [2]

Group 1: Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK-1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″ Persistent pulmonary hypertension of the newborn (PPHN)
Group 2: Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)
Group 5: Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

[a]Reproduced with permission of publisher [2]

ease, human immunodeficiency virus (HIV), and sickle cell disease are more commonly seen. PH in developing countries predominantly affects a much younger population, whereas it is primarily seen in older patients (above age 65) in industrialized countries.

PAH is overall a rare disease, although it has been the primary focus of most clinical investigation and treatment. Based on registry data primarily from Europe and the United States, the prevalence of PAH is around 12–15 cases per million [4, 6]. The majority of cases (40–50%) are idiopathic (iPAH) or are inheritable/familial forms. Twenty percent of sporadic cases of PAH and 80% of heritable PAH have been linked to mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene [7]. Presence of the BMPR2 mutation in patients with PAH is associated with increased mortality, and these patients typically present at a younger age with more severe disease [8]. Historically, iPAH commonly affected people in their fourth decade of life, but contemporary registries have demonstrated that the mean age of this population has increased to 50–65 years old [9]. Women are affected 3–4 times as often, though men diagnosed with iPAH have an overall worse prognosis [10]. Prior to the era of targeted PAH pharmacotherapies, long-term survival in iPAH was grim, with a median survival of 2.8 years and 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively [11]. In the current treatment era, those rates have improved to 91%, 74%, and 65% for the same time intervals [12].

Additional important causes of PAH include connective tissue disease (CTD) and congenital heart disease (CHD). Approximately 15–25% of PAH is associated with CTDs. Systemic sclerosis is the most common cause of CTD-associated PAH in the majority of the world, and survival in patients with CTD-PAH is overall worse compared to those with iPAH [5, 12]. CHD-associated PAH accounts for approximately 10% of cases of PAH. The development of PAH in patients with CHD is generally due to the presence of a hemodynamically significant left-to-right (systemic-to-pulmonary) shunt exposing the pulmonary vascular bed to excessive blood flow and, in some cases, chronically elevated pressures. The risk of PAH developing in this population is related to both the chronicity of the shunt as well as its location, with lesions

distal to the tricuspid valve posing the greatest risk, as they permit the transmission of systemic blood pressures to the pulmonary vascular bed. Thus, PAH may also develop in patients with repaired CHD, particularly when the defect is corrected later in life. If CHD is unrepaired, PAH can progress and ultimately result in Eisenmenger syndrome, characterized by shunt reversal, cyanosis, and right heart failure. Interestingly, patients with Eisenmenger syndrome demonstrate better long-term survival in comparison with untreated iPAH patients, with a 77% 3-year survival [4].

Clinical Presentation

The suspicion for PH requires an astute clinician, especially in iPAH, where patients are comparatively younger and typically otherwise healthy. Many patients are often diagnosed years after the onset of symptoms [13]. Initial symptoms are often nonspecific and may be discounted by both the patient and their physician or attributed to other causes such as deconditioning. The clinician must also be proactive in screening for PAH in patients who have associated chronic illnesses, such as systemic sclerosis or HIV infection.

Dyspnea is the most common presenting symptom, seen in 60% of patients diagnosed with PAH [14]. Patients may also complain of fatigue and weakness early in the course of the disease. When untreated, symptom severity will progress as patients develop right heart dysfunction, and patients may present with syncope, arrhythmias, or overt heart failure [4]. The World Health Organization (WHO) functional classification (FC) schema provides one of the most powerful clinical tools for assessing disease severity and prognosis [4]. WHO FC I patients have no physical limitations. FC II patients are asymptomatic at rest but will experience symptoms with ordinary physical activities. FC III patients continue to be asymptomatic at rest but have marked limitations in physical activity. Patients who are FC IV are unable to carry out any physical activity without significant symptoms. They often have rapid progression of symptoms, may be symptomatic at rest, and have signs of right heart failure on exam; frank syncope may occur with exertion and helps define patients between FC III and IV as being FC IV. Patients who are FC IV have a poor prognosis, and when newly diagnosed generally require hospitalization and initiation of IV prostaglandins.

A measured 6-min walk distance (6MWD) performed in clinic provides an objective assessment of functional status. Using the modified Borg dyspnea scale (see Fig. 18.1 – below) to assess for patient effort and monitor oxygen saturation with noninvasive pulse oximetry may add additional prognostic value. Although baseline numbers provide predictive insight into survival, the significance of changes over time remains controversial. Patients who initially walk >440 m demonstrate improved 1-year survival, whereas those who walk <165 m have significantly worse outcome [15]. Formal exercise testing with measurement of oxygen consumption is also an independent predictor for survival and closely correlates with 6MWD.

Physical exam findings vary with disease severity, although most patients will have an

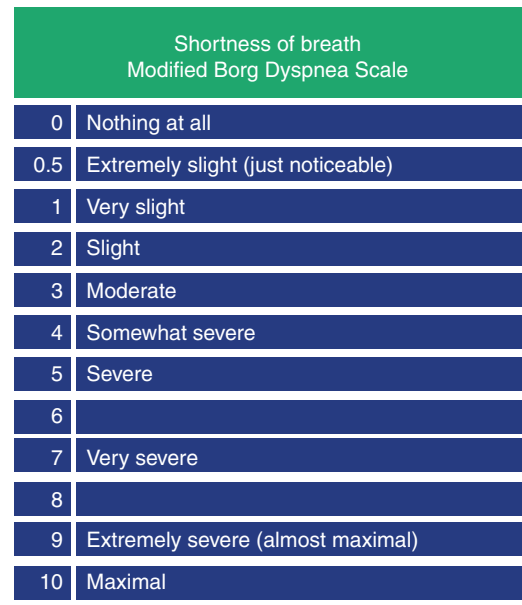

Fig. 18.1 The modified Borg scale has the potential to provide quick, easy, and rapid information about a patient's subjective state of dyspnea

accentuated P2 component of their second heart sound, even with mild disease. Additional auscultatory findings that become present with increasing right heart failure include the low-frequency holosystolic murmur of tricuspid regurgitation (TR), best heard over the left lower sternal border, and a right ventricular (RV) gallop (an S3 and/or S4 may be present). With increasing RV dilation, the patient will develop a palpable parasternal lift. Signs of fluid overload will also become evident with worsening RV failure, including jugular venous distension with prominent *a*- and *v*-wave pulsations associated with decreased RV compliance and worsening TR respectively. The lungs should be dry in isolated PAH; the presence of pulmonary edema suggests postcapillary PH is present, and an alternative diagnosis should be explored.

Noninvasive Testing in PH

The initial evaluation of patients with suspected PH typically involves multiple diagnostic modalities. Laboratory assessments are rarely helpful in the diagnosis of PAH, but may be important when other etiologies of PH, such as rheumatologic diseases, are suspected. Trending brain natriuretic peptide (measured as either BNP or NT-proBNP) values may be helpful to the clinician, as they are correlated with RV dysfunction and prognosis in patients with known PAH [4].

Chest radiography (CXR) is abnormal in 90% of patients presenting with PAH [4]. Right heart dilation, PA enlargement, and loss of distal pulmonary architecture with clear lung fields may all be seen on CXR [14]. A ventilation-perfusion (V/Q) scan should be performed in all patients with suspected PAH to rule out CTEPH, as patients with this disorder may be candidates for curative intervention (pulmonary thromboendarterectomy) or balloon pulmonary angioplasty. The sensitivity and specificity of V/Q scan for both diagnosing and excluding CTEPH approaches 95–100% [4, 16]. Computed tomography (CT) is often performed in patients with known or suspected underlying parenchymal lung disease. Pulmonary function testing (PFT) can elucidate underlying airway disease, such as chronic obstructive pulmonary disease (obstructive pattern) or interstitial lung disease (restrictive pattern). It is important to note, however, that the severity of lung disease as judged by PFTs is often poorly correlated with the presence or severity of PH [17]. A hint to the presence of PH itself is a low diffusing capacity (DLCO) that is out of proportion to the degree of lung disease suggested by the PFTs.

Transthoracic echocardiography should be performed in all patients with suspected PH. It is an excellent screening tool and can also be used assess the severity of PH. Quantifying right ventricular systolic pressure (RVSP) is most traditionally done by measuring the peak velocity of the TR jet, which provides an estimate of the RV systolic pressure (RVSP), a surrogate for pulmonary systolic pressure (in the absence of right ventricular outflow obstruction). There is a high probability of PH in the presence of a TR velocity > 2.8 m/s [4]. However, the absence of a measurable TR jet does not exclude PH and additional echocardiographic parameters can be helpful in this regard. These include dilation of the main PA, increased pulmonary regurgitant velocities, systolic flattening of the intraventricular septum, the presence of RV dilation and/or RV hypertrophy, and elevated right atrial pressure. Tricuspid annular plane systolic excursion (TAPSE) should be measured in all PH patients, with a distance <1.8 cm associated with increased mortality [18]. The presence of a pericardial effusion is an ominous sign in advanced PAH. The echocardiogram is also useful to evaluate for potential cardiac etiologies of PH, including significant valvular disease, left-sided heart failure (systolic and diastolic dysfunction), and the presence of an intracardiac shunt.

Cardiac magnetic resonance (CMR) can provide high-resolution structural information and with phase-contrast studies hemodynamic data as well. However, because of the limited availability and the high cost involved, this modality should not be used for screening.

Hemodynamic Evaluation

The cornerstone for the diagnosis of PH remains the RHC. Measurement of right heart and particularly PA pressures, cardiac output/cardiac index (CO/CI), PVR, and assessment of vasoreactivity are key elements for establishing diagnosis, collecting prognostic indicators, and assisting in the selection of therapy. RHC is recommended in all patients with PAH to confirm the diagnosis, evaluate severity of PH, and assess the need for PAH-specific drugs [4]. RHC is also recommended in patients diagnosed with PAH at 6–12 months surveillance intervals, 3–6 months after a change in therapy and when there is clinical deterioration [4]. There is often trepidation about performing RHC in patients with PAH, who are frequently viewed as being fragile. At experienced PH centers, cardiac catheterization is performed safely, and the risk of major complications is under 1% [19].

PH assessment is best performed in euvolemic states of low or normal CO. Transient high cardiac output states such as anemia, pregnancy, or sepsis will lead to elevated pulmonary pressures, but the PVR should remain normal. Current guidelines recommend that CO be measured by thermodilution, the reliability of which has been validated even in patients with low CO and severe TR [4, 20]. However, this method is prone to errors in measurement in the setting of intracardiac shunting. The direct Fick method is the gold standard for measuring CO, but is rarely performed today due to the cumbersome nature of directly measuring oxygen consumption (VO_2). The indirect Fick method has become the most widely accepted measure of CO; it is less reliable and results should be interpreted cautiously, particularly in patients who are severely obese [21].

We recommend performing a full oxygen saturation run to rule out CHD in all patients undergoing initial RHC for PAH. A left-to-right shunt should be suspected when the absolute PA saturation is >75% or if a step-up of >7% is seen between the superior vena cava (SVC) and PA. A shunt run should consist of measurements from the innominate vein, SVC, inferior vena cava (IVC), RA, RV, and PA. Both high and low SVC saturations should be obtained to identify the presence of anomalous pulmonary venous drainage to the SVC. Whenever a full saturation run is performed, it is important to recognize that the RA receives three different sources of blood return (SVC, IVC, and coronary sinus). The mixed venous saturation is thus estimated by adding three times the SVC saturation to the IVC saturation and dividing by four. Treatment decisions of which shunts benefit from repair and the timing of repair in the setting of PAH are beyond the scope of the chapter (see Chap. 20), but these patients should ideally be referred to cardiologists with expertise in managing adults with congenital heart disease.

The RA pressure waveform (and consequently the central venous waveform) of PH may have several distinctive features. A prominent *a*-wave is common when the RV diastolic pressure is elevated, and the normal *y*-descent may be attenuated reflecting reduced RV compliance. A prominent *v*-wave suggests the presence of significant TR and a fused *cv*-wave is sometimes seen. Severe elevation in mean RA pressure (>20 mmHg) has been associated with increased mortality [22]. Additionally, the expected decrease in RA pressure with inspiration may not occur in patients with severe PH and significant TR; on occasion RA pressure may even increase with inspiration creating confusion that pericardial disease (effusive or constrictive physiology) is present. Pulsus alternans in the RV and PA tracing can occasionally be seen in severe PH and suggests considerable RV dysfunction. It is characterized by alternating strong and weak beats, resulting from the altered Frank–Starling relationship and dyssynchrony of the noncompliant RV.

In normal adults the resting mPAP should not exceed 20 mmHg. PH is defined by a resting mPAP ≥25 mmHg. There remains uncertainty about patients with "borderline" mPAPs of 21–24 mmHg; these patients may simply be early in the disease process [23], though it is reasonable to suspect that future guidelines will lower the threshold of mPAP for defining PH. Previous definitions of PH also included a mPAP of >30 mmHg during exercise. However,

this has been removed from recent guidelines, as further understanding is needed to determine the best methodology for exercising these patients in the catheterization lab [4, 23]. Aging also plays a role in the degree of exercise-induced mPAP elevations; patients >50 years old may demonstrate significantly higher mPAPs, even with slight levels of exertion [23]. In general, however, severe elevations in mPAP (>45 mmHg) are typically only seen in patients with PAH and CTEPH.

Obtaining an accurate assessment of the PCWP is critical in patients with PAH. The PCWP allows for a direct measurement of mean LA pressure, a surrogate for the left ventricular end diastolic pressure (LVEDP) in the absence of mitral valve stenosis or pulmonary venous occlusive disease (PVOD). It is recommended that wedge pressures be sampled in several different segments of the pulmonary vasculature, preferably in the lower lobes of the pulmonary vasculature (West Zone 3). Zone 3 is the only location in the pulmonary circulation where one can be certain that the PA pressure is both greater than the pulmonary venous and pulmonary alveolar pressures, thus minimizing their contribution to the measured PA pressure. Multiple samples should also be obtained in patients with suspected or confirmed CTEPH; obstructive thrombi in some PA segments may lead to the erroneous interpretation of an elevated wedge pressure. An elegant way to document whether PAH is present is continuous recording of the PCWP and then the PAP after balloon deflation and careful withdrawal of the catheter (Fig. 18.2a, b). A significant step-up in the pressure waveform should be noted, resuming the PAP waveform almost immediately after deflation.

If the PCWP waveform has large v-waves, this suggests increased left atrial stiffness or possibly significant mitral regurgitation. In severe pulmonary hypertension, accurate measurement of PCWP may be difficult due to hybrid tracings resulting from incomplete seal of the balloon against the arterial wall. One must be careful not to overinflate the balloon or when performing repeat inflations and deflations in the wedge position, as these can cause rupture of the pulmonary artery, a rare but potentially fatal complication [23].

Measurement of the PCWP should take place during end-expiration (PCWP-exp), when the effects of intrathoracic pressure are minimized. This has been shown to be particularly important in obese and hypoxemic patients, who tend to generate larger intrathoracic pressure changes [23]. A mean pressure will typically be calculated by most cath lab software; however this represents a derived calculation measured over several seconds [24]. The discrepancies between the measured end-expiratory pressure and the digitally calculated mean pressure can be significant and lead to misclassification of patients with pre- and postcapillary PH, with potentially deleterious results (Fig. 18.3) [24]. If the PCWP is normal but clinical concern remains for impaired LV diastology, a small fluid bolus of 500 mL over 5–10 min can be safely administered to help unmask heart failure with preserved ejection fraction (HFpEF) [4, 23]. It is also possible that obtaining hemodynamics during exercise may help to uncover patients with diastolic heart failure, but this is not currently recommended for similar reasons as noted above for testing for PH with exercise [23]. If doubt exists about the accuracy of the PCWP measurement, direct measure of the LVEDP should be performed via retrograde crossing of the aortic valve.

PVR in the normal individual increases with age and decreases with elevations in cardiac output. PVR may be expressed either as Wood units (Wu; mmHg/L/min) or dynes (dyn/s/cm^{-5}),[1] with normal PVR being <1.1 Wu (88 dynes) [25]. PVR is calculated by dividing the transpulmonary pressure gradient (mPAP-PCWP) by the pulmonary blood flow (Qp), which is equal to CO in the absence of intracardiac shunting. A PVR >3 Wu is required for the definition of PAH. Pre- and postcapillary PH may coexist and can be difficult to distinguish clinically when seen together. When precapillary PH is present, the transpulmonary gradient will be higher, at least >12 mmHg, and often markedly elevated. The diastolic pressure

[1] Values given in Wu may be multiplied by 80 to convert to dynes.

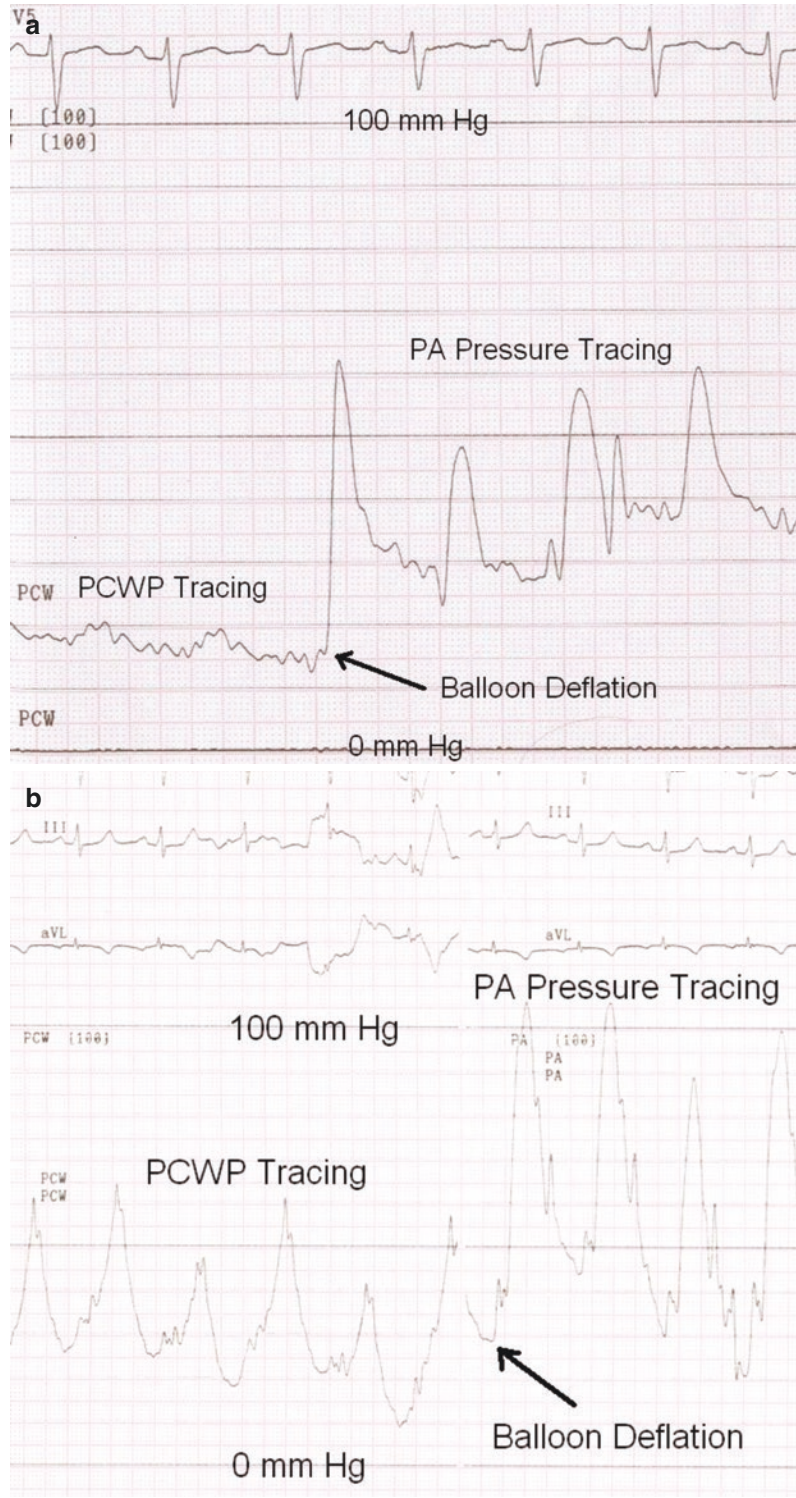

Fig. 18.2 (**a**) Deflation of the wedged pulmonary capillary balloon catheter results in a rapid increase in the pressure recordings identifying the pulmonary artery pressure. In this case the mPAP is >25 mmHg and PCWP is <15 mmHg consistent with a diagnosis of PAH. (**b**) Identification of pulmonary venous hypertension using continuous right heart pressure monitoring during acute balloon inflation and deflation. The PA pressure is elevated but the mPCWP is well in excess of 15 mmHg with large *v*-waves, reflecting the impact of severe mitral regurgitation in this case

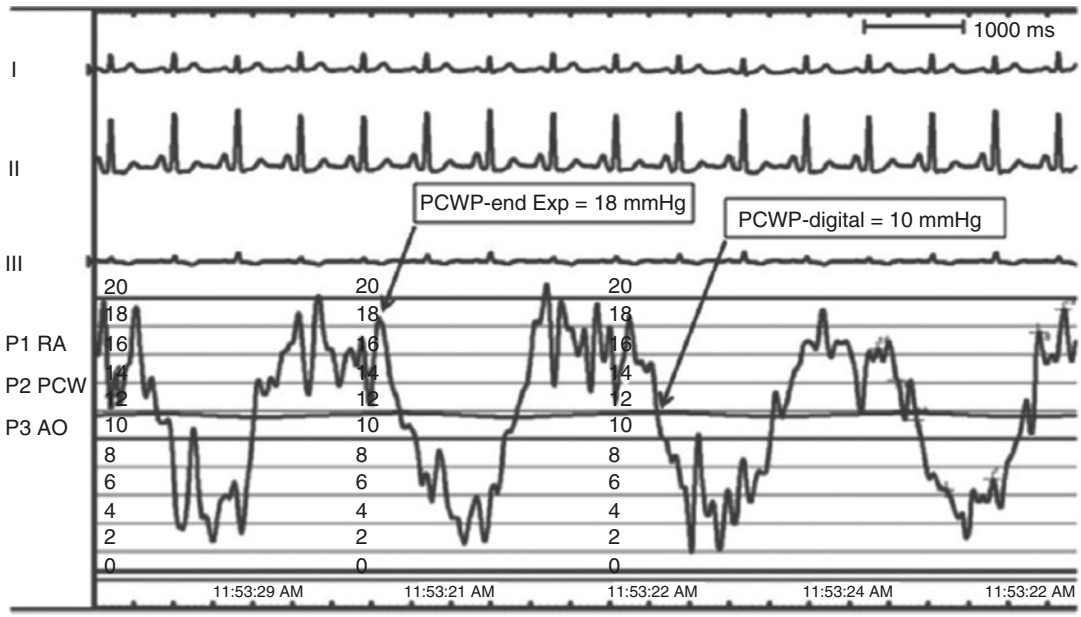

Fig. 18.3 This wedge tracing illustrates the respirophasic waveforms with the digitized means and the difference between PCWP–exp versus the automatically derived mean PCWP, thereby resulting in misclassification. (Reprinted with permission of publisher [24])

gradient (diastolic PAP – PCWP) is also very helpful. In pure postcapillary PH, this difference is typically close to 0, whereas a gradient ≥7 mmHg is consistent with the presence of precapillary PH.

All patients with suspected idiopathic, hereditary or drug-induced PAH should undergo pulmonary vasoreactivity testing as part of their initial RHC. Only a small minority of PAH patients (5–10%) will be vasoresponsive; however responders demonstrate a more favorable prognosis with a 5-year survival rate of 90% when treated with calcium channel blockers (CCBs) [26]. Responsiveness suggests the pulmonary vasculature has satisfactory amounts of vasodilatory reserve, likely representing an earlier stage of disease.

Inhaled nitric oxide (iNO) is most commonly used for vasoreactivity testing because of its specificity in targeting the pulmonary vasculature and neutral effects on coronary blood flow (intravenous prostacyclin and adenosine administration, alternative agents for vasodilatory testing, can reduce coronary blood flow). Also beneficial is the extremely short half-life of iNO, which is particularly important in the event a patient with masked LV diastolic failure or PVOD develops acute pulmonary edema. A substantial increase in the v-wave of the PCWP tracing during inhalation suggests that this may be occurring.

Unfortunately, the equipment used for the setup of iNO administration is cumbersome, and it requires the patient to wear a full facemask for delivery, which can be difficult to tolerate. Newer inhalation agents and smaller delivery devices are being developed (such as modification of the iNeb device to be able to deliver iloprost in a reusable circuit) that may be equally safe and at least as sensitive as iNO.

The maximal effect of iNO is obtained following 5–10 min of inhalation at 40 ppm, after which time the operator should repeat measurements of mPAP and PCWP, and collect PA and systemic saturations to reassess the cardiac output [27]. A positive response has most recently been defined as a reduction in mPAP by 10 mmHg to an absolute value of ≤40 mmHg with preserved CO. Although vasoreactivity testing has traditionally been used to identify patients with iPAH who may be candidates for CCB therapy, recent

studies have suggested that testing may also provide independent prognostic information that extends to other WHO Group I PH patients (PAH) and even those with non-Group I PH [28–30].

Our Approach to Hemodynamic Assessment of PH

1. Patients are taken to the catheterization laboratory in the fasting state and under minimal sedation (to prevent any adverse effect on oxygen saturation or CO).
2. Femoral venous and arterial access is obtained for the initial RHC and brachial, neck or femoral access (based on patient preference) for repeat assessments. If initiation of IV therapy is anticipated, neck access is preferred, as this facilitates leaving the right heart catheter in place after the procedure for more prolonged hemodynamic monitoring in an intensive care setting. In such cases radial access can be considered for left heart requirements. Arterial access permits measurement of the LVEDP if PCWP is questionable or grossly elevated. It also facilitates trouble-free arterial blood gas collection during the shunt run and provides for arterial pressure monitoring and arterial blood gas collection during AVT. It also allows for coronary angiography or ventriculography as necessary.
3. Ideally two transducers should be utilized – this facilitates monitoring of the pulmonary arterial and aortic pressures simultaneously during AVT.
4. A full oxygen saturation run is performed for the initial RHC. This includes innominate vein (or high SVC), SVC, IVC, RA, RV, PA, and aortic saturations. Saturations should immediately be reviewed and repeated if any measurements are questionable. The Fick CO should also be calculated at this time.
5. As the saturations are collected, pressures should be measured in each chamber as the catheter is advanced forward. Collected pressures include RA mean; RV systolic and diastolic; PA systolic, diastolic, and mean; PCWP systolic, diastolic, and mean; and aortic systolic, diastolic, and mean.
6. Measurement of the PCWP should be taken at end-expiration in West zone 3. If there is any question about the validity of the PCWP measurement or if the PCWP is unexpectedly >15 mmHg, measurement of the LVEDP should be performed.
7. Before AVT is performed, thermodilution CO should be performed if that modality is being utilized. At least three measures should be performed with individual results that do not vary more than 15%. If not the case, measures should be repeated until three measures that vary ≤15% have been collected.
8. AVT with iNO (or appropriate alternative agent) should be performed in all patients for whom initiation of advanced medical therapy for PAH is being considered. An increase in the PCWP during testing is generally a contraindication to use of these therapies. A positive response (decrease in mPAP of ≥10 mmHg to a mPAP ≤40 mmHg, without a decrease in CO) may permit initiation of calcium channel blocker therapy in iPAH. If this therapy is selected, very close follow-up is advised, as treatment failure is common.
9. Immediate communication of the results to the referring and treating physicians is essential for prompt recognition and initiation of therapy.

Treatment of PAH

A detailed discussion of the treatment of PAH is beyond the scope of this chapter. The goals of medical management are to achieve normal hemodynamics and a good quality of life – WHO FC I or II symptoms [31]. Treatment must be individualized to the patient and is best undertaken at centers with expertise treating PAH. Most patients will require diuretics to optimize volume status and may require supplemental oxygen to maintain saturations >90% [31]. Vasodilator testing responders should be started on high-dose CCBs (typically amlodipine, diltiazem, or nifedipine). There has been tremendous growth in the field of targeted PAH pharmacotherapies since IV epoprostenol was first approved in 1995. The major classes of PAH drugs currently include phospho-

diesterase type 5 inhibitors (PDE5), endothelin receptor antagonists (ERA), prostaglandins, guanylate cyclase stimulators, and selective prostacyclin IP receptor agonists. Lower-risk patients can be started on a single agent, though it is now common to initiate combination therapy with agents from different classes, particularly in higher-risk patients. Additionally, non-Group 1 patients with precapillary PH, including some with combined pre- and postcapillary PH, may derive benefit from these therapies [32, 33]. These uses should be considered off-label, however, and should be limited to carefully monitored clinical investigations. Ultimately, patients who progress despite advanced therapies may require lung or combined heart-lung transplant to survive.

Several interventional cardiology procedures may be considered to palliate patients with severe, medically refractory PAH and RV failure. Balloon atrial septostomy (BAS) creates an atrial-level right to left shunt that decompresses the RV and increases CO at the expense of worsening hypoxia. BAS has been shown to improve hemodynamics and functional capacity in the short term, although data on long-term survival benefits following the procedure are lacking [34]. The procedure should only be performed at experienced centers and is contraindicated in patients with a mean RA pressure > 20 mmHg or resting oxygen levels <85% on room air [4]. In 2013, Esch et al. [35] described the first-in-human experience, creating a transcatheter pulmonary-to-systemic shunt between the left pulmonary artery and descending thoracic aorta (Potts shunt). Surgical Potts shunts were previously utilized to palliate cyanotic congenital heart disease, but recent interest in their use in the pediatric and adult PAH populations is growing. The advantage of the Potts shunt over a BAS is that the former maintains fully oxygenated blood flow to the head and coronary arteries [34]. An emerging area of research is PA denervation via catheter-based ablation as a treatment of PAH. This is based on experimental evidence showing increased adrenergic signaling is present in patients with PAH and is linked to the development of pulmonary vascular disease and maladaptive RV remodeling [36]. A recent study of 66 patients with PH (39 with Group 1 PAH) demonstrated a >10 mmHg decrease in mPAP in 94% of patients immediately after the procedure, and sustained reductions in mPAP and improvements in CO and WHO FC at 1 year [37]. Though early data looks promising, extensive further studies will be necessary before this paradigm-shifting therapy can be approved.

Case Examples

Case 1

M.H. is a 53-year-old gentleman with scleroderma diagnosed 10 years ago and well-controlled essential hypertension who presented with complaints of worsening exertional dyspnea. A pulmonologist evaluated him 5 years ago and diagnosed him with mild interstitial lung disease. His fatigue and dyspnea had progressively worsened over the previous 3 months to the point of WHO FC III symptoms. There was no prior cardiac history.

His examination showed a JVP of 12 cm, a mildly prominent P2, a II/VI holosystolic murmur consistent with TR and 1+ peripheral edema. An echocardiogram revealed a dilated IVC, right heart enlargement, and mild RV systolic dysfunction with an estimated RVSP of 60 mmHg. There was grade 1 LV diastolic dysfunction; LA size was normal. He was taken to the cardiac catheterization laboratory where pressures included: mean RA 12 mmHg, RV 66/12 mmHg, PA 71/41 with a mean of 51 mmHg, PCWP of 41 mmHg, CI of 2.3 L/min/m^2 and a calculated PVR of 1.9 Wu. He was treated with diuretics by his physician but then developed hypotension and mild acute renal failure resulting in hospitalization.

After seeing the patient in consultation, we felt that the hemodynamics (suggesting PVH) did not match the clinical story (suggesting PAH). We then reviewed the hemodynamic tracings, which brought the measured PCWP into question (Fig. 18.4). It had been measured in only one position and the tracing suggested incomplete balloon occlusion of the PA. The patient begrudgingly agreed to repeat catheterization, where data revealed RA mean 8 mmHg,

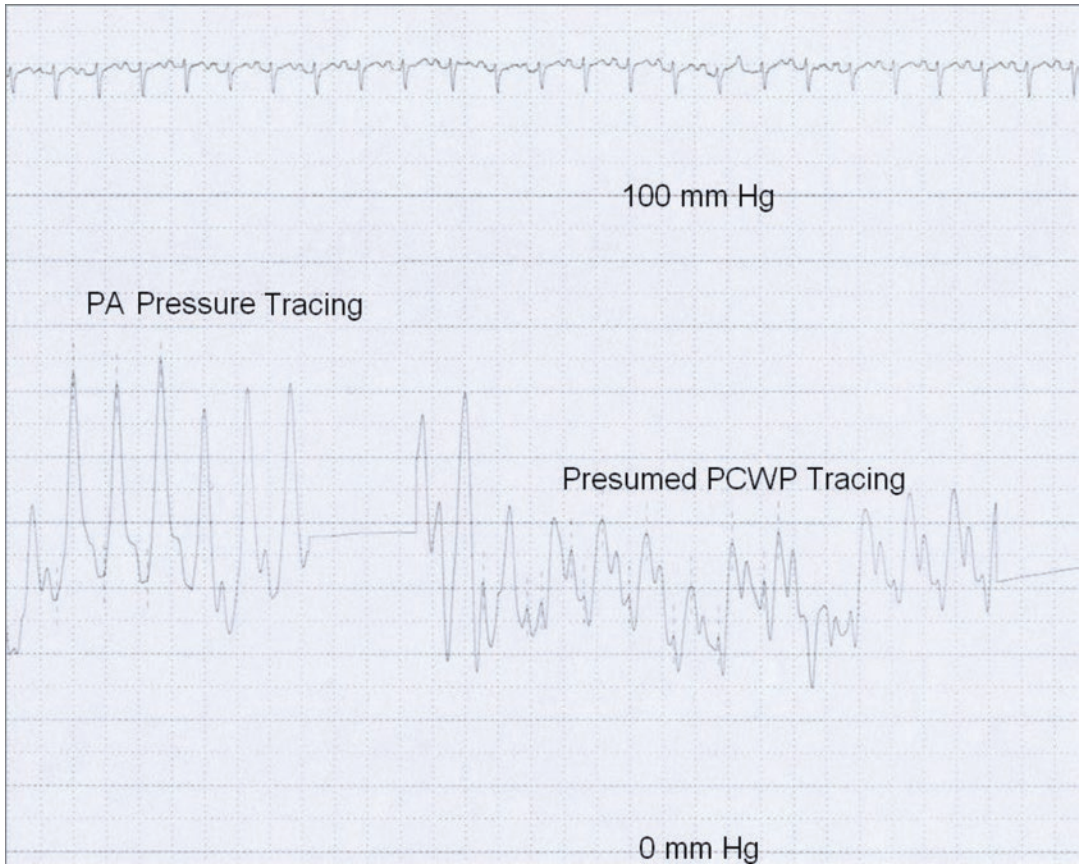

Fig. 18.4 Initial RHC in a patient with scleroderma that suggests the presence of PVH. There is limited respiratory variation in the PCWP tracing and the tracing appears to be a hybrid (fusion of PAP and PCWP waveforms) suggesting incomplete balloon occlusion of the pulmonary artery. These tracing were not consistent with the expected findings. In such cases multiple measurements should be obtained in different locations, and the LVEDP should then be measured for confirmation. This patient required repeat hemodynamic assessment to obtain proper measurements

RV 60/8 mmHg, PAP 60/33 with mean 40 mmHg, PCWP 12 mmHg, CI 2.2 L/min/m^2, and PVR 6.4 Wu (Fig. 18.5). LVEDP was also directly measured via retrograde left heart catheterization and was 11 mmHg. Vasodilatory testing was performed and resulted in a mPAP drop to 36 mmHg with stable PCWP pressure and CI and a decrease in PVR to 5.4 Wu. He was started on an ERA, and on follow-up he experienced a 50 m increase in 6MWD and had improved to WHO FC II.

This patient presents the dilemma of an RHC where data has not been properly collected. In cases like this, it is important to review the actual waveforms and assess if measurements were appropriately performed. In this case the initial RHC evaluated a hybrid PCWP waveform that grossly overestimated the PCWP. With repeat RHC and confirmation with measurement of the LVEDP, the appropriate diagnosis of PAH was made and proper therapy was initiated. Other techniques to ensure appropriate PCWP measurement include repeat measurements in both lung fields in different segments, assurance of appropriate respiratory variation in the tracing, collection of a wedge saturation (which should be ≥95%) and a small (2–3 cc), gentle injection of contrast dye, which should not be washed out until the balloon is deflated (Fig. 18.6).

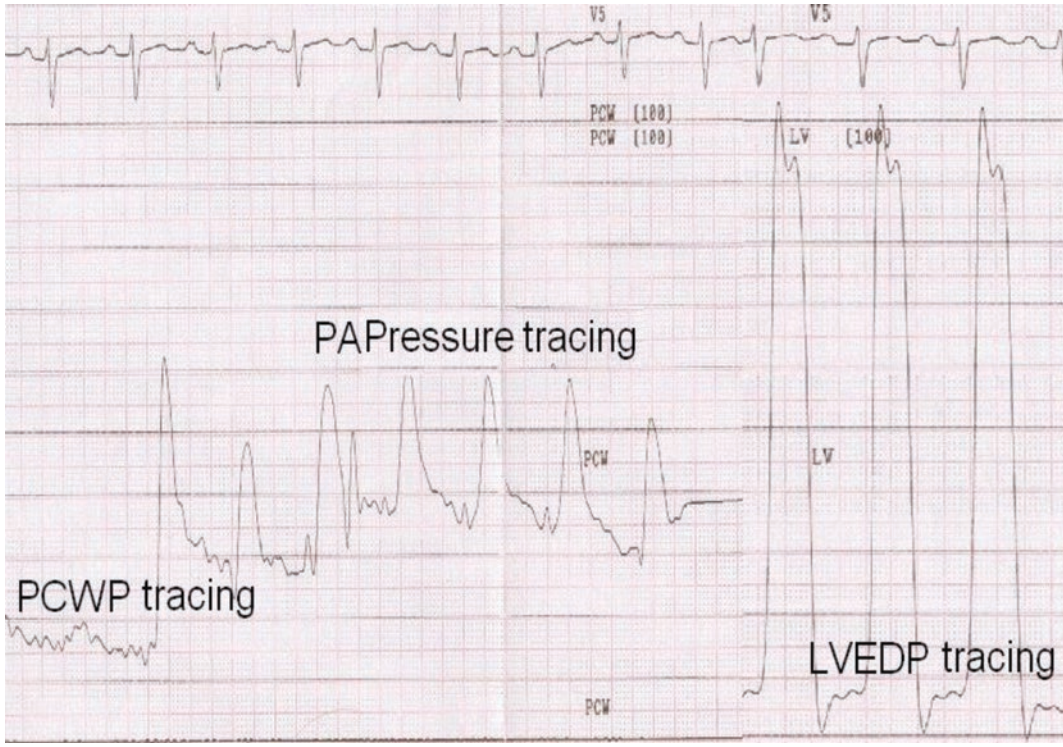

Fig. 18.5 Repeat RHC which indicates the presence of PAH (the expected finding given the clinical history). The LVEDP confirms that the PCWP is low in this case

Fig. 18.6 Gentle contrast injection into the right pulmonary artery under balloon inflation (pulmonary wedge angiogram). The tip of the balloon is highlighted by the arrow. Dye is seen filling a branch pulmonary artery proximal to the balloon and suggests incomplete occlusion. In such a case, a hybrid tracing would be present and would lead to an inappropriately high PCWP recording

Case 2

R.B. is a concerned 36-year-old gentleman who presented with progressive exertional dyspnea and fatigue that had significantly limited his ability to work in construction over the last few years. A recent echo suggested right-sided enlargement and borderline elevated RVSP. A bubble study was performed that suggested the presence of a patent foramen ovale (PFO). His right heart catheterization revealed mean RA pressure 10 mmHg, RV 40/9 mmHg, PA 40/18 with mean 25 mmHg, PCWP mean 12 mmHg, cardiac index 4.0 L/min/m^2, and PVR 1.3 Wu. O_2 saturation measurements were SVC 75%, IVC 76%, RA 89%, RV 88%, and PA 88% and a systemic saturation of 98%.

This case highlights the diagnostic capability of a properly performed shunt run. In this case there is a clear increase in saturation at the RA

level. A contrast injection was subsequently performed that showed an anomalous right upper pulmonary vein draining into the border of the SVC and RA and the presence of a right-to-left shunt in the superior septum. This was most consistent with a sinus venosus atrial septal defect and concomitant partial anomalous pulmonary venous return (PAPVR). It is important to recognize that PAPVR can also be present in isolation, and in such cases the echo bubble study may be negative. Performing a shunt run or at least SVC and PA saturations during RHC ensures that such a shunt will not be missed. The anomalous vein can be entered quite easily and safely (providing a careful technique using a flexible wire is utilized), and a gentle contrast injection can delineate its entry point into the heart (Fig. 18.7). A blood gas drawn in the vein should demonstrate a saturation ≥95%.

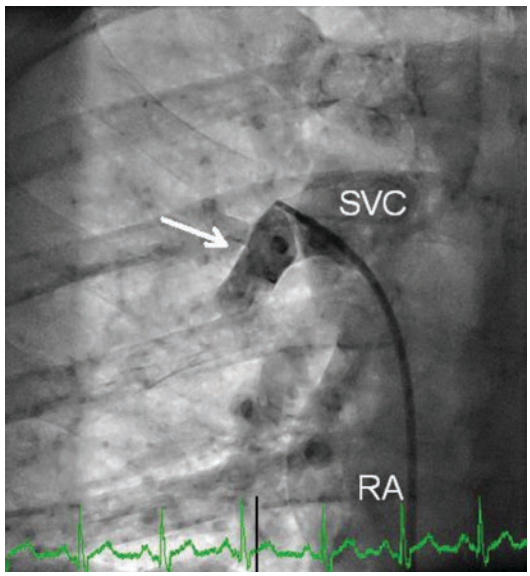

Fig. 18.7 Limited pulmonary vein angiogram (AP projection) of an anomalous right upper pulmonary vein performed via right femoral vein access (hand injection via end-hole catheter). The white arrow highlights the distal segment of the pulmonary vein which drains into the SVC at the RA junction. Samples drawn from this vein showed oxygen saturations >95%. A high CO at catheterization in the presence of right heart enlargement and a negative bubble study should prompt careful assessment for possible anomalous pulmonary venous return

A major clue to the presence of an underlying shunt is revealed in the cardiac index. Most patients with PH will have at least slightly reduced CO (if not grossly decreased). If the CO/CI is normal or high in a patient with echocardiographic evidence of right-sided enlargement (as it was in this case), a shunt is probable and should be carefully sought out. A PFO does not usually result in left-to-right shunting and would certainly not be expected to result in right heart enlargement. The patient in this case was referred to cardiac surgery and underwent successful repair. Repeat echocardiography has demonstrated normalization of his right-sided pressures and chamber sizes after repair.

Case 3

J.T. is a 66-year-old woman with multiple medical problems including advanced renal disease, dilated cardiomyopathy (LVEF~20%), and resultant severe mitral and tricuspid regurgitation. She was admitted to the coronary care unit for further management of worsening congestive heart failure and hemodynamic instability. On examination she was severely volume-overloaded and in respiratory distress with JVD above the angle of the jaw at 45° and a large cv wave. There was a prominent P2 present and a III/VI holosystolic murmur heart best over apex, a laterally displaced point of maximal impulse and a palpable RV heave. Lungs showed bibasilar rales and there was 2+ pitting peripheral edema.

Echo showed four chamber dilatation with severe mitral and tricuspid regurgitation. Estimated RV systolic pressure was 80 mmHg. RHC at the bedside revealed RA pressure 24 mmHg, RV 96/22 mmHg, PA 96/40 with mean 62 mmHg, mean PCWP 34 mmHg, CI 1.8 L/min/m^2, and PVR 10 Wood units. She was seen in consultation for possible initiation of pulmonary-selective therapies, and we instead recommended continued aggressive diuresis and afterload reduction with hydralazine and nitrates (baseline creatinine was 2.5 mg/dl) with the plan

for repeat hemodynamic assessment when stable.

RHC in the cath lab 10 days later showed RA pressure 15 mmHg, RV 73/15 mmHg, PA 73/28 with mean 44 mmHg, PCWP 16 mmHg, CI 1.5 L/min/m^2, and PVR 12.2 Wood units (Fig. 18.8). During inhalation of 40 ppm of nitric oxide, the PA pressure remained essentially unchanged (73/30 with mean 46 mmHg), but the pulmonary capillary wedge increased to a mean of 30 with v-waves to 65 mm Hg (Fig. 18.9). The team was instructed that the patient was not a candidate for selective pulmonary vasodilator therapy and surgical consultation for consideration of mitral and tricuspid valve repair was recommended.

This patient had long-standing RV dysfunction that likely arose from pulmonary venous hypertension consequent to high left-sided filling pressures from left ventricular dysfunction and mitral regurgitation. The PH in this case is therefore the offshoot of long-standing left heart disease and is likely compensatory to "protect" the left ventricle. AVT provides some insight into what would happen with pulmonary-selective therapy and the results suggest that the patient would be poorly tolerant of this therapeutic approach. In such cases this type of therapy could worsen her clinical course and precipitate decompensation and even death. Thorough assessment of hemodynamics in this case led to better understanding of the physiology and avoided a potential pharmacologic misadventure.

Pearls of Assessment of Pulmonary Hypertension

- Clinical suspicion for PH should remain high, especially in young patients with vague complaints such as dyspnea. Family and social history can provide important clues to a possible diagnosis.
- PAH is a diagnosis of exclusion, and patients must undergo a complete workup before a diagnosis of PAH is entertained. Secondary causes resulting in PVH are a far more common cause of PH.

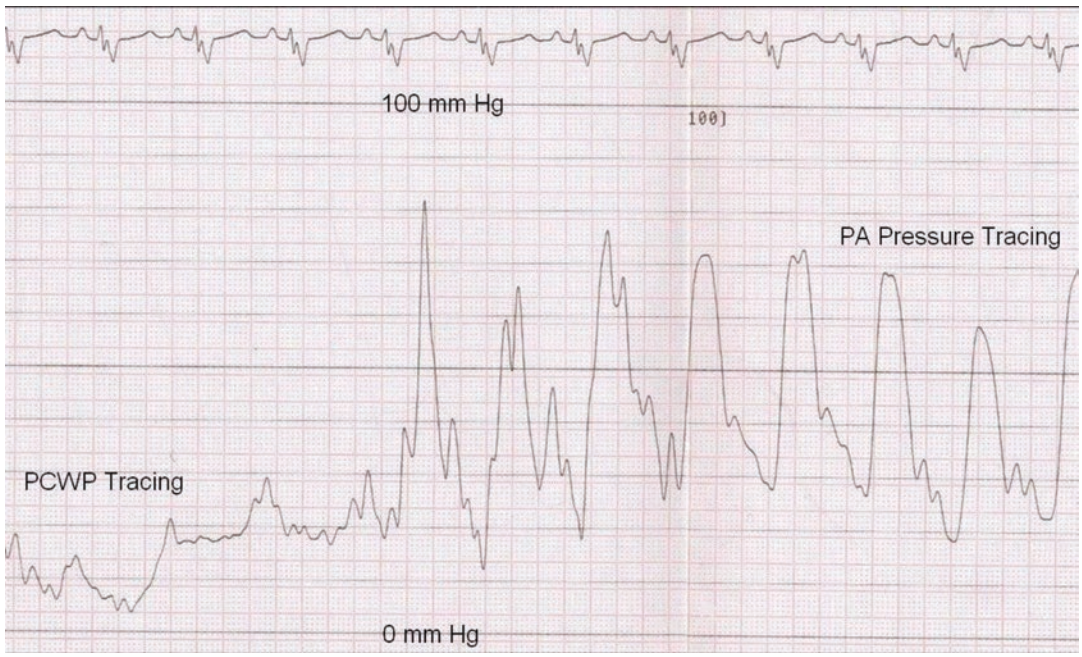

Fig. 18.8 Collected right heart catheterization waveforms in patient with heart failure and severe mitral regurgitation leading to pulmonary hypertension after aggressive diuresis. These suggest the presence of PAH and initially supported a potential role for selective pulmonary vasodilator therapy in this patient

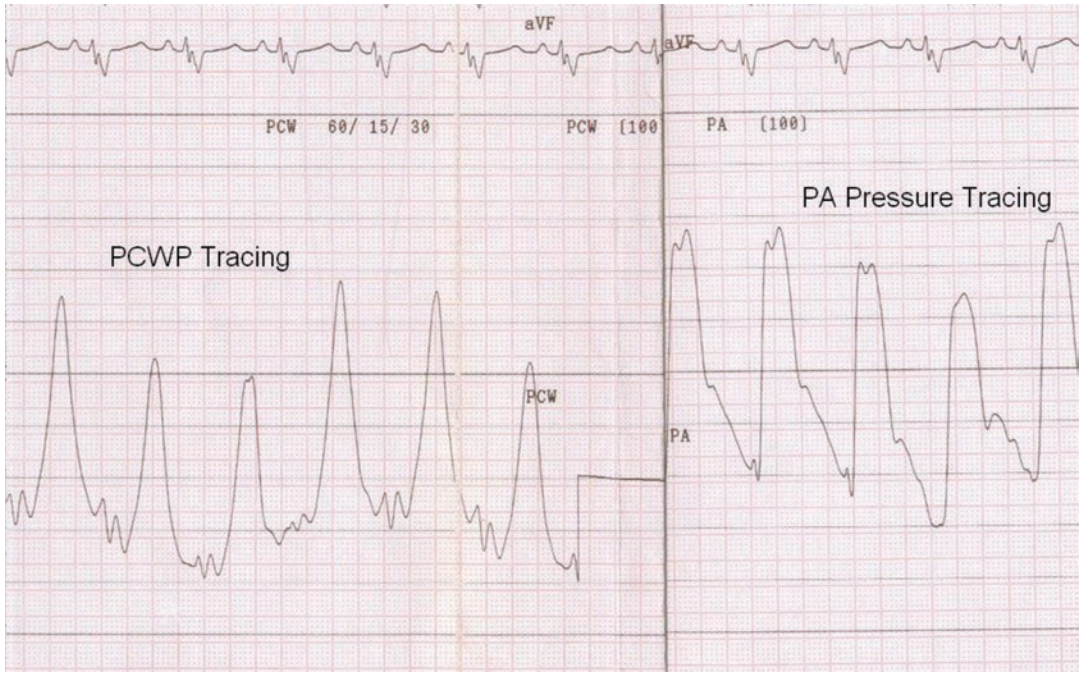

Fig. 18.9 Collected right heart catheterization waveforms during inhalation of 40 ppm of inhaled nitric oxide. Note the dramatic increase in mPCWP to ~30 mmHg and prominent *v*-waves to >65 mmHg. The PA pressure remained essentially unchanged (73/30 with mean 46 mm Hg) compared to baseline (Fig. 18.7). In this case acute vasodilator testing unmasked the left heart pathology leading to pulmonary venous hypertension in this patient

- The use of echocardiography is not adequate for evaluating mild to moderate PH. Only in severe PH does Doppler echocardiography provide reliable data for estimating RVSP. Echocardiography is essential for exclusion of left heart disease.
- The diagnosis of PAH can only be confirmed with RHC. Guidelines define PAH as mPAP >25 mmHg, PCWP ≤15 mmHg, and PVR >3 Wu in the absence of other causes of precapillary PH (e.g., CTEPH, chronic lung disease).
- Appropriate patients undergoing RHC should be further evaluated with vasodilator testing. This aids in selecting therapy and helps determine prognosis.
- Beware of hybrid tracings and confirm that an accurate PCWP measurement has been recorded. For patients in whom PCWP is not believed to be reliable, LVEDP should be directly measured.
- PCWP measurements should be taken at the end of the expiratory phase and in multiple PA segments to confirm accuracy, particularly in the setting of CTEPH or PVOD.
- Prognostic information and therapeutic decision-making are dependent on hemodynamics. Thus, appropriate techniques and proper and immediate interpretation are vital to performing RHC in patients with PH.
- Communication with referring and treating physicians is essential to streamline appropriate patient therapy in this very serious clinical disorder.

Review Questions

1a. A 46-year-old African American woman presents to clinic complaining of cough, lower extremity edema, and dyspnea on exertion over the last 3 months. Her medical history is significant for sarcoidosis diagnosed at 35 years of age and she has a 30-pack year history of smoking. Vitals are blood pressure 135/78 mmHg, pulse 87,

respiratory rate 20, and oxygen saturation 88% on room air. Her cardiac exam is notable only for a prominent P2. EKG shows sinus rhythm with right axis deviation. An arterial blood gas demonstrates a PO_2 of 49 mmHg and a PCO_2 of 35 mmHg. A chest x-ray demonstrates bilateral infiltrates, perihilar lymphadenopathy, and pulmonary vascular dilatation.

What is the best next step in the management of this patient?

A. PFTs
B. Transthoracic echocardiogram
C. CT angiography of chest
D. RHC
E. NT-pro-BNP

Answer C is correct. Although clinical suspicion for PH remains high, other more acute causes of hypoxemia must be ruled out. A CT scan can evaluate the lung parenchyma, which is likely to be abnormal, given this patient's history, and obtaining a contrasted angiography study will evaluate for acute pulmonary embolism or CTEPH as potential causes of hypoxia and PH, respectively. Subsequent evaluations with echocardiogram, PFTs, laboratory testing, and ultimately RHC are all appropriate if other workup is suggestive of PAH.

1b. The patient's CT scan shows the expected findings of sarcoidosis and no pulmonary embolism. An echocardiogram is obtained revealing an RVSP of 70 mmHg with enlargement of right-sided heart structures and normal left heart function. She desaturates to 83% on 6MWT and is only able to complete 280 m. RHC is scheduled.

Which of the following hemodynamics is most consistent with PAH?

A. mPAP 28 mmHg, PCWP 15 mmHg, CO 4.9 L/min, PVR 4.7 Wu
B. mPAP 40 mmHg, PCWP 26 mmHg, CO 5.2 L/min, PVR 2.7 Wu
C. mPAP 52 mmHg, PCWP 14 mmHg, CO 13.4 L/min, PVR 2.8 Wu
D. mPAP 18 mmHg, PCWP 12 mmHg, CO 5.5 L/min, PVR 1.1 Wu
E. mPAP 54 mmHg, PCWP 10 mmHg, CO 5.1 L/min, PVR 8.6 Wu

Answer E is correct. The hemodynamics for this patient are most consistent with the current guidelines for a diagnosis of PAH. Answer B is more indicative of postcapillary PH such as would be seen in patients with heart failure with preserved ejection fraction (HFpEF). The transpulmonary gradient is grossly elevated in answer C, but the CO is also grossly elevated suggesting the presence of an acute high output state such as sepsis or an intracardiac shunt. This patient should have a full saturation run performed to investigate the latter possibility more thoroughly. Answer D is consistent with completely normal hemodynamics. Answer A would have been correct if the PVR had not been calculated incorrectly. The actual PVR is (28–15)/4.9 = 2.7 Wu, which does not meet the formal criteria for PAH.

1c. Acute vasoreactivity testing with iNO at 40 ppm is performed. After 5 min, which of the following hemodynamics is most consistent with a positive response (baseline mPAP 54 mmHg, PCWP 10 mmHg, CO 5.1 L/min)?

A. mPAP 42 mmHg, PCWP 10 mmHg, and CO 5.1 L/min
B. mPAP 38 mmHg, PCWP 10 mmHg, and CO 5.6 L/min
C. mPAP 50 mmHg, PCWP 25 mmHg, and CO 4.9 L/min
D. mPAP 68 mmHg, PCWP 8 mmHg, and CO 4.8 L/min

Answer B is correct. The current definition of a positive test is a drop in mPAP $\geq$10 mmHg to an absolute value $\leq$40 mmHg with the CO remaining stable or increasing. Answer A shows a substantial drop in mPAP, but not to $\leq$40 mmHg. Answer C shows a slight drop in mPAP but also an increase in PCWP and slight decrease in CO. Her PVR calculates as (50–25/4.9) = 5.1 Wu, consistent with combined pre- and postcapillary PH with the predominant driver being left-sided diastolic dysfunction. Although some patients with combined pre- and postcapillary PH benefit from initiation of targeted PAH therapies, this patient's left-sided heart failure should first be optimized and RHC

then repeated to determine the best next steps. Answer E is illogical as the mPAP is not expected to rise, or the PWCP to fall, during vasodilatory testing.

2. A 45-year-old man undergoes RHC for suspected mild PAH. He weighs 80 kg, is 1.75 m tall and his body surface area is 1.97 m^2. His hemoglobin is 12.5 g/dL. Systemic saturation on arterial blood gas is 95%. A shunt run is performed. Which of the following would be most suspicious for PAH secondary to a congenital heart lesion?
   A. SVC saturation 75%, IVC saturation 77%, and PA saturation 74%
   B. SVC saturation 78%, IVC saturation 84%, and PA saturation 68%
   C. SVC saturation 70%, IVC saturation 74%, and PA saturation 72%
   D. SVC saturation 74%, IVC saturation 77%, and PA saturation 90%
   E. SVC saturation 69%, IVC saturation 72%, and PA saturation 71%

   Answer D is correct. The mixed venous saturation is estimated by (3 × SVC + IVC)/4. If the PA saturation is at least 7% greater than the mixed venous saturation, a shunt is highly likely. In answer D, the estimated mixed venous saturation is (3 × 74 + 77)/4 = 75% with a PA saturation of 90%. The pulmonary venous saturation (if not collected) is estimated at 95%. The degree of shunting can be calculated by dividing the Qp by the systemic blood flow (Qs). A rough estimate of the shunt can be calculated using the obtained saturations: (systemic-mixed venous saturations)/(pulmonary vein-PA saturations), which in this case yields a calculated Qp:Qs of (95–75)/(95–90) = 5:1, consistent with a large left-to-right shunt. None of the other choices show a step-up in saturation. The PA saturation in B must be incorrect as a step-down in saturation in the right heart is not possible. This saturation should be repeated ensuring to tap out any residual air bubbles from the syringe (which can lead to aberrant readings) before analysis.
3. A 44-year-old man with vasoresponsive iPAH has been stable on a regimen of 20 mg amlodipine daily for the past 3 years. He presents for follow-up and reports increasing dyspnea and fatigue over the last 3 months. He is comfortable at rest and able to perform some activities of daily living but has fatigue and light-headedness with repetitive actions such as brushing his teeth while standing up. On 6MWD, he desaturates to 83% after 50 m. One year ago, he desaturated to 92% after 100 m. What FC should he be classified as and what is the next step in the care of this patient?
   A. FC II: Change CCB therapy to verapamil or diltiazem
   B. FC III: Change CCB therapy to verapamil or diltiazem
   C. FC III: Repeat RHC for consideration of starting targeted PAH therapies
   D. FC VI: Change CCB therapy to verapamil or diltiazem
   E. FC VI: Admit to the hospital for initiation of IV prostacyclin therapy

   Answer C is correct. This patient presents with clinical worsening consistent with WHO FC III symptoms. It is important to note that the currently utilized definition of responsiveness was derived from a cohort of patients with iPAH with the goal of identifying patients who did well treated solely with CCBs [38]. In this cohort, only ~5% of patients did well with CCB monotherapy long-term. With the proliferation of targeted PAH therapies in the modern era, such a strategy is hard to justify. As such, the modern use of vasoresponsiveness helps to identify, by lack of a response, a high-risk cohort that may only benefit from the most aggressive of therapies. As such, this patient should undergo RHC and initiation of targeted PAH therapies should be considered. There is no evidence to suggest a benefit from switching to an alternative CCB agent as suggested in answers A, B, and D; verapamil is typically avoided in PAH patients out of concern for negative inotropic effects. Answer E is incorrect as the patient's FC is not yet at a VI. Although patients with FC VI often do require admission and initiation of IV prostacyclin therapy, an RHC should also be performed first and prior to a step-up in PAH therapy.

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19 Acute Decompensated Heart Failure

Andrew D. M. Grant, Michael A. Hanna, and Mazen A. Hanna

Epidemiology of Acute Decompensated Heart Failure (ADHF)

Heart failure is estimated to affect 2% of the adult population. There are over one million hospitalizations for ADHF in the USA per year, and, among the Medicare population, it is the leading discharge diagnosis [1, 2]. About 25% of these patients present as de novo heart failure, and 75% present as an exacerbation of chronic heart failure. When not due to an arryhthmia or primary valvular disease, heart failure may arise in those with either reduced (≤40%), preserved (≥50%), or mid-range (40–50%) left ventricular ejection fraction [3, 4]. The inpatient mortality ranges from 3% to 25% depending on associated comorbidites and clinical characteristics [5]. The readmission rate at 30 days is a staggering 20–25% [6].

Hemodynamics of Decompensated Heart Failure

The hemodynamic perturbations in the syndrome of decompensated heart failure are characterized by elevated intracardiac filling pressures, normal or reduced cardiac output, and abnormalities in the systemic and pulmonary vascular resistance (PVR). Although there are syndromes in which the cardiac output is abnormally elevated, these will not be discussed in this chapter.

Intracardiac Filling Pressures

When volume overload (increased preload) and increased afterload occur, there is an elevation of left ventricular end-diastolic pressure from baseline (which may already be elevated). This leads to a rise in left atrial pressure and thus pulmonary capillary wedge pressure (PCWP). The elevation in the PCWP leads to passive *pulmonary hypertension* (pulmonary venous hypertension, WHO Group 2). Either volume overload or pulmonary hypertension (or both) leads to elevation of the right atrial pressure (RAP). The extent of pulmonary hypertension depends on the degree and chronicity of elevation of the PCWP and the degree of superimposed pulmonary vasoconstriction and vascular remodeling (see section "Vascular Resistance").

In patients with ADHF, PCWP is usually >22 mmHg and right atrial pressure >10 mmHg; such a patient is typically classified as "wet." In the average ADHF patient, a RAP >10 mmHg correlates to a PCWP >22 mmHg about 80% of the time [7–10]. In these "concordant" cases, PCWP

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_19

is usually about 2–2.5 times RAP. About 20% of the time, there is "discordance" in this relationship; one example is in patients with disproportionate RV failure in whom RAP is significantly elevated with a normal or only mildly elevated PCWP. The other example is when RAP is normal with a significantly elevated PCWP as one may see in acute left-sided heart failure without volume overload or a very noncompliant LV with high resting filling pressure despite euvolemia. These are important hemodynamic concepts to understand as they may affect management.

Cardiac Output

Cardiac output is a product of stroke volume and heart rate (see Chap. 4). Stroke volume is determined by preload (filling pressure), myocardial contractility, and afterload (mainly systemic vascular resistance). In patients with ADHF, a decrease in cardiac output is more likely due to low stroke volume but occasionally can be due to an inappropriately low heart rate. It is important to note that in the majority of cases of ADHF, the cardiac output remains normal. Low cardiac output, as measured by Fick or thermodilution (we more often use the Fick method at our institution), occurs in a minority of patients who have advanced heart failure or excessively low filling pressures due to overdiuresis. Arbitrarily, a cardiac index (cardiac output/body surface area) of <2.2 is considered low, and such a patient is typically classified as "cold" while a patient with a cardiac index >2.2 is classified as "warm [11]." A patient with a low cardiac index may be compensated and have no signs or symptoms of low perfusion at rest; thus, it is important to consider the overall clinical picture in addition to the calculated cardiac index when deciding treatment options and prognosis.

When evaluating a patient with ADHF, it is useful to categorize the patient according to the estimation or measurement of left-sided filling pressures and cardiac output. The classification scheme shown in Fig. 19.1 is a simple and efficient way to clinically categorize patients and help guide appropriate treatment strategies.

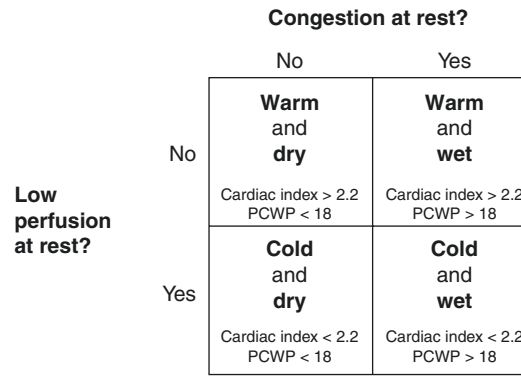

Fig. 19.1 Hemodynamic profiles in patients with left-sided heart failure

Vascular Resistance

Systemic vascular resistance (SVR) is measured as the difference between mean arterial pressure and right atrial pressure divided by cardiac output. Classically, in ADHF, SVR is high as a result of an increased level of vasoconstricting neurohormones such as norepinephrine, angiotension II, and endothelin. However, in the contemporary era in which treatment with agents that block the renin angiotensin aldosterone system (ACE inhibitors/angiotensin receptor blockers/angiotensin receptor blocker + neprilysin inhibitors) and beta blockers is common, the SVR can be normal or sometimes even low. Patients with right-sided heart failure and renal insufficiency are more likely to have normal or low SVR. Knowing the blood pressure and/or the SVR is important with respect to determining treatment options.

Pulmonary vascular resistance (PVR) is measured as the difference between mean pulmonary artery pressure and PCWP (left atrial pressure surrogate) divided by cardiac output. It is important to note that in some patients, in addition to passive pulmonary hypertension due to elevated left atrial pressure, there is an additional component of pulmonary arterial vasoconstriction, raising pulmonary vascular resistance and thus further raising pulmonary artery pressure (pulmonary arterial hypertension). Long-standing elevation of PCWP can also lead to pulmonary vascular remodeling. This component of pulmonary vascular resistance

cannot be reversed by acutely lowering PCWP or with the use of pulmonary vasodilators. Reversal of pulmonary vascular remodeling can be accomplished by long-term consistent lowering of left atrial pressure (e.g., correction of mitral stenosis, left ventricular assist device placement). Patients with an elevated PVR that cannot be reversed have a worse prognosis.

Hemodynamic Evaluation of Decompensated Heart Failure

There are many ways to evaluate hemodynamics in heart failure. The initial and most practical strategy is starting with the clinical history and the physical examination (H&P). Further important hemodynamic information can be gleaned from echocardiography. The most invasive and accurate way to assess hemodynamics is with right heart catheterization using a pulmonary artery catheter, which is reserved for special situations.

Clinical Assessment

The H&P, together with a chest X-ray and basic labs, provides the majority of the hemodynamic information needed to treat patients with acute decompensated heart failure (ADHF). The shortcomings of an H&P are important to acknowledge however, and some of these will be highlighted as we discuss each of the clinical cases at the end of the chapter.

Clinical Estimation of Filling Pressures

Using the H&P, experienced clinicians can estimate, with reasonable accuracy, the intracardiac filling pressures [12, 13]. Some of the important signs and symptoms of elevated filling pressures are outlined in Table 19.1. Symptoms of elevated right atrial pressure, depending on the degree and chronicity, include abdominal bloating and discomfort, early satiety, and RUQ pain that can mimic an abdominal etiology. Signs of elevated right atrial pressure include lower extremity edema, hepatomegaly, and, in advanced right heart failure, ascites. However, the most reliable sign of elevated right atrial pressure is elevation of the jugular venous pressure (JVP), and depending on the skill of the examiner, the right atrial pressure can be reliably assessed at the bedside in most heart failure patients. Indeed, patients with elevation of right atrial pressure may have no edema or ascites, and the only sign may be elevated jugular venous pressure. It is in these patients that congestion is often missed and the patient is incorrectly assumed to be euvolemic.

Table 19.1 Symptoms and signs of elevated intracardiac filling pressures

	↑ RA pressure	↑ PCWP
Symptoms	Leg swelling	Dyspnea at rest or on exertion
	Abdominal bloating	Orthopnea
	Early satiety	PND
	Nausea, anorexia	Positional cough
	RUQ pain	
Signs	Elevated JVP[a]	S_3gallop
	Ascites	+ Abdominojugular reflux
	Enlarged/tender liver	Rales[b]
	Lower extremity edema[c]	

[a]Most specific and sensitive sign of elevated RA pressure and may often be the only sign
[b]Rare in chronic heart failure
[c]Nonspecific and can be due to venous insufficiency, DVT, calcium channel blockers, etc.

Elevation of left atrial pressure/PCWP pressure leads to symptoms of exertional/resting dyspnea, dry cough (worse in the recumbent position), orthopnea, and paroxysmal nocturnal dyspnea. In fact, orthopnea and particularly paroxysmal nocturnal dyspnea are the most specific symptoms of elevated PCWP. The physical exam finding that is most specific for an elevated PCWP (in the absence of mitral stenosis) is an S3 gallop; however, it is not a sensitive finding as most patients with an elevated PCWP do not have an S3 gallop. One of the best clues that a heart failure patient has an elevated PCWP is elevation in the jugular venous pressure. This is because elevated right

Table 19.2 Signs and symptoms of low cardiac output

Symptoms	Fatigue
	Decreased memory/mentation
	Lightheadedness
Signs	Cool extremities
	Sleepy/obtunded
	Narrow pulse pressure
	Oliguria

atrial pressure is predictive of an elevated PCWP in most chronic heart failure patients (see section "Intracardiac Filling Pressures").

Clinical Estimation of Cardiac Output

Estimating cardiac output is more difficult at the bedside [12], but there are several clues to low cardiac output (see Table 19.2). General fatigue, impaired mentation, cool extremities, low urine output, and increased lactate level are useful clues. An objective measure is to calculate the "proportional pulse pressure" which is the systolic blood pressure minus the diastolic blood pressure divided by the systolic blood pressure. A proportional pulse pressure <25% suggests a cardiac index of <2.2 [11].

Echocardiography

The echocardiogram is an important tool in the assessment of heart failure. In patients presenting with a new diagnosis, it is essential in establishing the mechanism of heart failure (preserved versus reduced ejection fraction or valvular etiology; see Chap. 6). Performing a baseline echocardiogram is given a Class I (should be performed) recommendation in patients with a new diagnosis of heart failure according to the ACC/AHA guidelines [14]. For patients with an acute exacerbation of chronic heart failure, it is not always necessary to obtain an echocardiogram. This is particularly true when there is an obvious precipitant for the change in clinical status. When the patient is critically ill or the symptomatic decline is precipitous, the echocardiogram can exclude new structural abnormalities. This is given a IIa (reasonable to perform) recommendation by the ACC/AHA guidelines [14] and has been shown to provide reliable estimates of invasive hemodynamics in this setting [15].

Echo Assessment of Filling Pressures

The measured size of the inferior vena cava (IVC) and its changes with respiration is traditionally used to estimate right atrial pressure [16]. Using this method, there is an assumption that there is continuity between central veins and the right atrium, the same assumption used in interpreting the jugular venous pressure as a reflection of right atrial pressure. Patients with an IVC measuring ≤2.2 cm in diameter that collapses by 50% or more with a sniff are designated as having a low RA pressure (assigned a value of 3 mmHg for the purposes of calculations). Patients with a distended IVC that does not collapse with sniff are designated as having a high RA pressure (15 mmHg). Patients with intermediate findings are assigned an RA pressure of 8 mmHg [16]. An example of this technique is given in Case 3.

Echocardiographic estimation of left ventricular end-diastolic pressures is a continued area of active investigation. The ratio of early diastolic inflow velocity across the mitral valve (E) to the early peak velocity of the mitral valve annulus (E′) has been shown to have a reasonably good correlation with LVEDP [17, 18]. This technique is used in a semiquantitative fashion. An E:E′ ratio of <8 suggests a normal LVEDP. An E:E′ ratio of >15 suggests an LVEDP of greater than 15 [17]. The E:E′ ratio was shown to be less predictive among patients with advanced heart failure admitted to the ICU [19]. Research is underway to find more consistent and precise echocardiographic predictors of LVEDP.

Echo Estimation of Pulmonary Pressures

The most well-accepted means of estimating pulmonary pressures with echocardiography is to

calculate the pressure gradient across the tricuspid valve using the peak velocity of the tricuspid regurgitation jet [16]. Using a simplified Bernoulli equation, the pressure gradient between the right ventricle and the right atrium can be estimated as $P=4v^2$. This is also discussed in detail in Chap. 6, and an example will be reviewed in Case 3.

Echo Assessment of Cardiac Output

Stroke volume (and therefore cardiac output) can be estimated by echocardiography, although it requires several important assumptions be made [20]. The technique for making this estimation is as follows (see also Chap. 6).

The Doppler profile of flow through the LV outflow tract is a graph of velocity vs. time. Taking the integral of this curve gives a unit of distance. When this distance is multiplied by the surface area of the left ventricular outflow tract (LVOT), the resulting number (a volume) is the stroke volume. The LVOT area can be estimated by using 2D echo measurements of its diameter in long axis and then assuming that it is a circle. Although this method is not frequently employed, it should yield a reasonably accurate estimate of stroke volume and therefore of cardiac output (when multiplied by heart rate).

Right Heart Catheterization

Right heart catheterization remains the gold standard for measuring many of the hemodynamic parameters important in the management of heart failure. As noninvasive methodology has improved, however, there are now fewer situations in which this information is necessary [14]. Additionally, a large randomized study showed no benefit to the routine use of a pulmonary artery catheter to manage patients with ADHF in terms of the combined endpoint of mortality and days outside of hospital at 6 months [21].

Right heart catheterization should be considered in a patient who is refractory to initial therapy, whose volume status and cardiac filling pressures are unclear, who has clinically significant hypotension (typically SBP <80 mmHg) or worsening renal function during therapy, or who is being considered for cardiac transplant and needs assessment of the degree and reversibility of pulmonary hypertension and PVR [14, 22]. This latter issue will be discussed further in Case 3.

In each of Cases 1–3, pressures in the right atrium (RA) and pulmonary artery (PA) as well as PCWP as derived from right-heart catheterization are displayed. RA pressure and PCWP are commonly used clinically as descriptors of right and left ventricular "preload" respectively (see Chapter 1). The PA pressure is reported as systolic PA pressure/diastolic PA pressure (mean PA pressure). The cardiac index, as estimated using the Fick principle (see Chap. 4), is also shown. The cardiac index is calculated by dividing the cardiac output by the patient's body surface area. This factor in the size of the patient which is clearly important as normal cardiac output varies with size.

Implantable Hemodynamic Monitoring

There has been recent interest in the use of implantable hemodynamic monitoring systems in the management of heart failure. The CardioMEMS HF system (St. Jude Medical), approved by the FDA in 2016, is a small device implanted in a branch of the pulmonary artery allowing for continuous monitoring of PA pressure. A large randomized clinical trial using this device in patients with chronic NYHA III heart failure demonstrated a reduction in heart failure hospitalizations [23].

General Principles of Management

The majority of patients who present with ADHF are congested and have elevated filling pressures. The central goal of therapy is to decongest the patient and optimize filling pressures to normal or near normal levels. This is most effectively

achieved with the use of an intravenous loop diuretic. In instances of diuretic resistance, combining a loop diuretic with a thiazide, amiloride, and/or spironolactone can be highly effective. If this approach is not successful, as can be the case in advanced renal dysfunction, ultrafiltration may be considered [24, 25].

To further optimize hemodynamics, vasodilators which reduce filling pressures can be used in conjunction with diuretics. Vasodilators, in addition to lowering filling pressures, improve cardiac output by reducing afterload, decreasing functional mitral regurgitation (and thereby increasing forward cardiac output), and reducing wall stress [26–28]. The patients who benefit the most from vasodilators are those with elevated blood pressure and high SVR. It is important to note, however, that a patient with "normal" blood pressure may still have an elevated SVR and benefit from vasodilator therapy. Both "wet and warm" and "wet and cold" patients may be treated with vasodilators.

Intravenous vasodilators used in heart failure are nitroprusside, nitroglycerin, and nesiritide. The vasodilator of choice at our own institution is nitroprusside, which should be administered in an ICU setting with hemodynamic monitoring using a right heart catheter and, in most instances, a blood pressure cuff (as opposed to an arterial line). This is well tolerated and the incidence of cyanide or thiocyanate toxicity is extremely rare to nonexistent [29, 30]. A mean arterial pressure of approximately 65 mmHg is targeted, but this depends on the patient and may need to be higher if renovascular or coronary artery disease is present or suspected, or if the patient is chronically hypertensive with an altered renal autoregulatory threshold. Excessive or overexuberant vasodilation with decrease in blood pressure beyond the renal autoregulatory threshold often leads to decreased renal perfusion, worsening renal function, and should be avoided. Once patients have clinically and hemodynamically improved on intravenous vasodilators, they may be transitioned to an oral vasodilator regimen of either ACE inhibitors, the combination of hydralazine and isosorbide dinitrate, or a combination of all three agents [31].

Intotropic therapy (milrinone or dobutamine) should be reserved for low output states associated with hypotension and end-organ hypoperfusion [32]. The typical patient has advanced systolic dysfunction, a low proportional pulse pressure, cool extremities, and worsening renal function despite adequate filling pressure (need to rule out hypovolemia) and is unresponsive to or intolerant of intravenous vasodilators. These patients constitute no more than 5% of the total ADHF population. Inotropes can also be used as palliative therapy for end-stage heart failure or as a bridge to transplantation.

It is important to note that inotropes increase myocardial oxygen consumption by increasing heart rate and myocardial contractility and can precipitate atrial and ventricular arrhythmias as well as myocardial ischemia. In contrast to dobutamine, milrinone has a long half-life (2.5 h) and is renally excreted, and the dose should be adjusted for renal function. Also, given that milrinone is a more powerful vasodilator, hypotension is more common with this agent and therefore should be used with caution or even avoided when the systolic blood pressure is <90 mmHg. In the setting of background beta blocker therapy, dobutamine will be ineffective unless used in high doses, and milrinone is favored [33, 34]. In rare circumstances, vasopressors are used (dopamine, norepinephrine, vasopressin), when the patient is vasodilated with a low SVR and profound hypotension.

In patients who are managed on a telemetry floor without invasive monitoring, the goal of therapy is to normalize intravascular volume as reflected by relief of edema and normalization of the jugular venous pressure (<8 cmH_2O). When this is achieved, most patients will no longer have orthopnea or dyspnea. Signs of overdiuresis consist of orthostatic decrease in blood pressure and worsening renal function. A common clinical error is incorrectly assuming euvolemia has been achieved when edema has resolved yet unrecognized elevation of the jugular venous pressure persists. By the same token, one may have normalized the jugular venous pressure and achieved intravascular euvolemia but may still have residual edema due to low albumin, venous

insufficiency, or drug side effect (e.g., calcium channel blockers) and wrongly assumed to be intravascularly volume overloaded.

In patients managed with hemodynamic monitoring with a right heart catheter, vasodilator therapy (both intravenous and oral) and diuretics are "tailored" to certain hemodynamic goals. Typically a PCWP of ≤16 mmHg, an RA pressure of ≤8 mmHg, and an SVR of about 1000–1200 dyn are targeted. A common misconception that patients with dilated dysfunctional ventricles require higher filling pressures to maintain cardiac output based on the Starling curve has been dispelled by data showing that most of these patients can maintain and even improve cardiac output with normal or near normal PCWP [30, 35]. As far as RA pressure goals, patients with primarily RV failure may require a higher RA pressure than 8 mmHg to maintain cardiac output and renal perfusion. It has been shown that patients with very elevated RA pressure can have worsening renal function on the basis of renal venous congestion. By lowering RA pressure with diuretics and vasodilators, the kidney is "decongested" or decompressed and renal function often improves [36–38] (see Fig. 19.2).

The goal of cardiac index is usually >2.2, but one has to acknowledge that using the Fick equation, oxygen consumption is estimated and not measured and that up to a 20% variation in cardiac output can be seen [39]. Thus, targeting a specific number per se is simplistic, and the entire clinical picture needs to be considered (e.g., a patient with a cardiac index of 1.8 who with normal PCWP feels well may not need further intervention). Although cardiac output frequently improves, the cardiac output is not the primary target of therapy, rather the reduction of the filling pressures [40]. The general principles of management for the different presentations of heart failure are shown in Fig. 19.3.

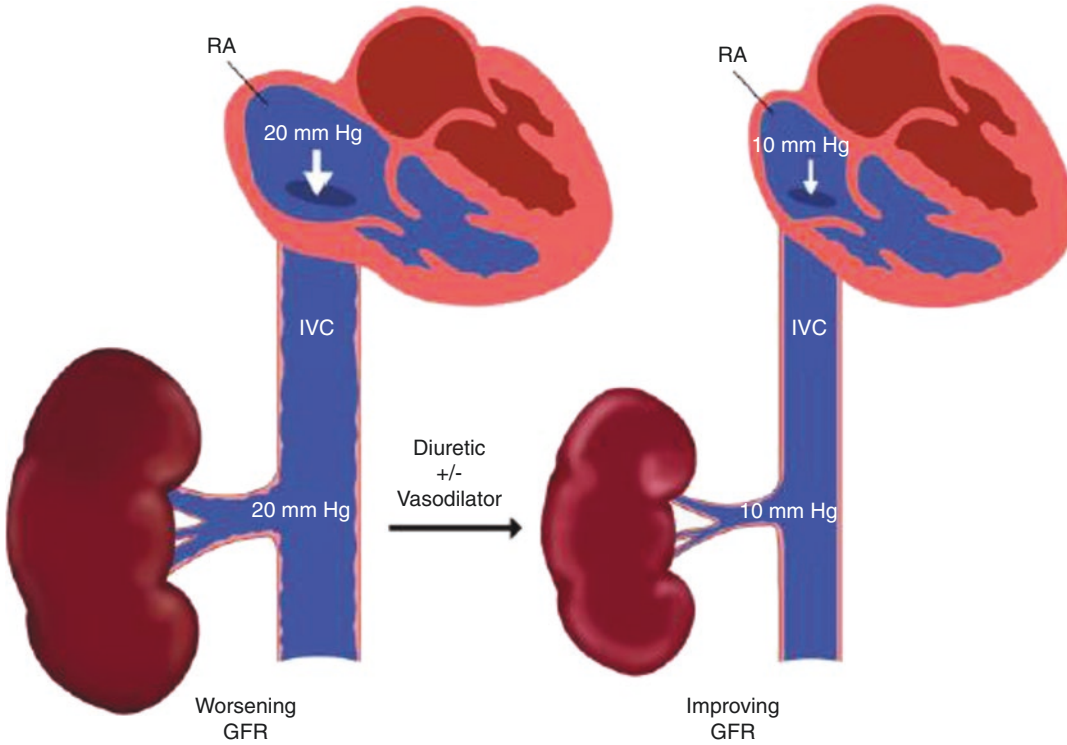

Fig. 19.2 Renal venous congestion: increased right atrial pressure leading to elevated pressure in the IVC and thus the renal vein (especially when coupled with low mean arterial pressure) can lead to worsening renal function by "congesting the kidney." Decreasing right atrial pressure and thus the renal venous pressure can lead to improved renal function

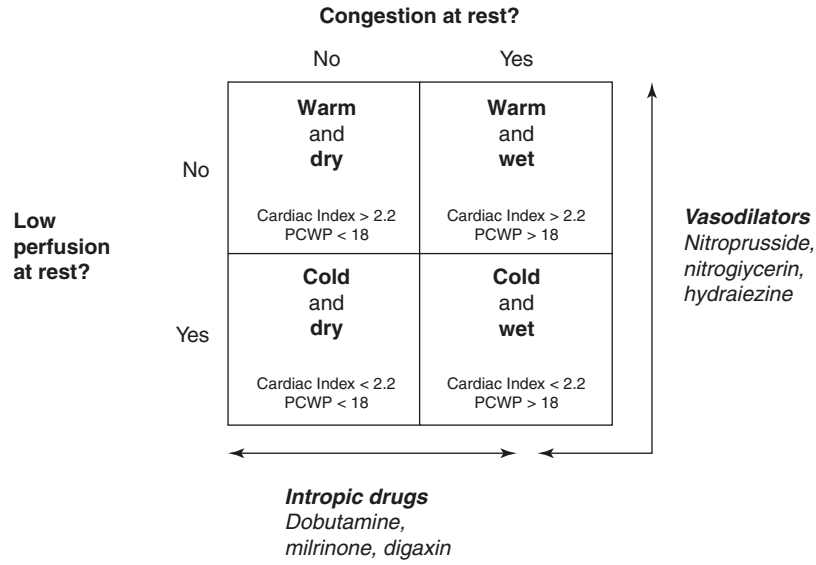

Fig. 19.3 Treatment paradigm in patients with left-sided heart failure

Clinical Presentations of Acute Heart Failure

Case 1

A 46-year-old male with a history of diabetes and hypertension presents with sudden onset of retrosternal chest pain. He is brought by emergency medical services to the hospital where he is found to have an elevated jugular venous pressure, bilateral rales, and edematous and well-perfused extremities. His electrocardiogram reveals ST segment elevation in the inferior leads (ECG leads II, III, and aVF). He is transferred to the cardiac catheterization laboratory but becomes dyspneic and hypoxic lying flat on the table. On examination, his HR is 90 bpm and BP measures 130/90 mmHg. His oxygen saturation is 93% on a high-flow oxygen mask.

A left heart catheterization is performed. The right coronary artery is found to be completely occluded, and the patient undergoes successful angioplasty and stenting to the vessel with good results. A pulmonary artery catheter is placed yielding the following hemodynamics:

RA	PA	PCWP	Cardiac index
12	38/25 (30)	24	3.2

Fig. 19.4 Case 1: left ventricular pressure tracing

A sample from his left heart catheterization is shown in Fig. 19.4. The LVEDP is elevated and correlates closely with the PCWP obtained with right heart catheterization. An echocardiogram is performed which demonstrates severe akinesis of

the inferior wall from base to apex. The overall left ventricular systolic function is described as mildly decreased. Right ventricular function is reported as normal.

Case 1: Hemodynamic Assessment

This is an example of so-called "warm and wet" heart failure (based clinically on his JVP, lower extremity edema and warm extremities, and hemodynamically on an elevated PCWP with a cardiac index in the normal range). Occlusion of the right coronary artery led to systolic and diastolic dysfunction of the left ventricle. This resulted in elevation of the left-sided filling pressures with pulmonary edema.

The orthopnea and hypoxia suggested an acute rise in PCWP. The relationship between PCWP and clinical signs of pulmonary congestion has been well characterized in patients with acute myocardial infarction. The onset of pulmonary congestion generally occurs at a PCWP between 18 and 20, and acute pulmonary edema generally correlates with a PCWP of greater than 30 [41]. These data have been challenged, however [42], and were collected prior to the use of reperfusion techniques such as fibrinolysis and primary percutaneous coronary intervention.

In this case, the importance of echocardiography was to confirm that the main problem was a left ventricular wall motion abnormality and not acute mitral regurgitation, which can be a mechanical complication of inferior myocardial infarction. Suspicion was low for this patient as such cases generally present with cardiogenic shock. However, a high index of suspicion is important. Another known complication of inferior myocardial infarction can be right ventricular infarction. This occurs in some patients when there is proximal occlusion of the right coronary artery but would generally be manifested by an elevated JVP and hypotension without pulmonary congestion. The right heart catheterization provided accurate measurement of cardiac output which has important prognostic implications [43].

In this case, the underlying cause of left ventricular dysfunction is acute coronary occlusion. This is best treated by promptly opening the culprit vessel (here with emergent PCI) in efforts to improve contractility by restoring flow to the compromised ischemic myocardium. Diuretic therapy was also provided to facilitate reduction of volume overload and clearance of pulmonary edema. This is generally considered to be a mainstay of the treatment of decompensated heart failure with increased RA pressure and PCWP. The patient was treated with intravenous furosemide with excellent response. After several days, he no longer required supplemental oxygen, and clinical and radiographic evidence of pulmonary congestion had improved.

Case 2

A 19-year-old G_1P_1 female presents to the emergency department with profound fatigue and right upper quadrant discomfort. Two weeks prior, she gave birth to a healthy baby boy via an uncomplicated vaginal delivery. Since the delivery, she has noticed gradual progression of tiredness to the point where she is no longer able to carry out basic activities of daily living and is short of breath at rest. There is no orthopnea or leg swelling but occasional paroxysmal nocturnal dyspnea. She complains of a dull aching discomfort in the right upper quadrant of her abdomen.

On examination, she is tachycardic with a HR of 120 bpm and BP of 106/88 mmHg. Her extremities are warm. The JVP is elevated to 8 cm above the sternal angle at 60°. The chest is clear to auscultation. In addition to loud first and second heart sounds, a prominent S3 is heard. There is right upper quadrant abdominal tenderness with no rebound tenderness or guarding. A chest X-ray is performed and shows an enlarged cardiac silhouette. An ECG shows sinus tachycardia with low voltages and a nonspecific ST abnormality. Labs are notable for elevated liver enzymes.

Echocardiography shows severe left ventricular dysfunction with an LVEF of 10%, moderate mitral regurgitation, and moderate right

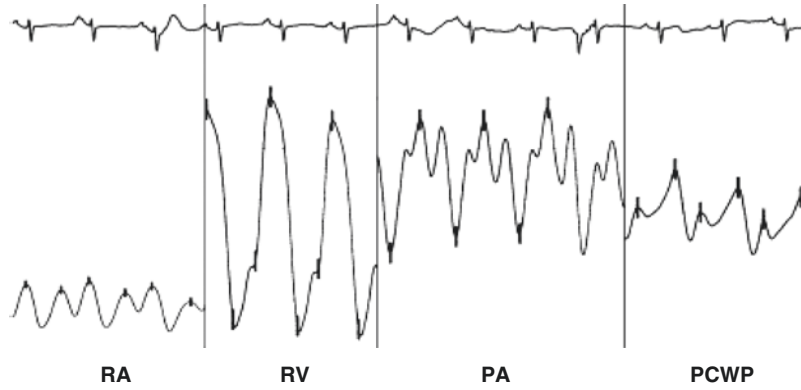

Fig. 19.5 Case 2 sample hemodynamic tracings: Pressures were recorded with the catheter positioned in the right atrium (RA), right ventricle (RV), and pulmonary artery (PA) as well as with pulmonary capillary "wedging" (PCWP). The following pressures were noted: RA mean pressure of 10 mmHg (normal, 0–8 mmHg); RV, pressure of 46/10 mmHg (normal 15–30/0–8 mmHg); PA, pressure of 46/30 mmHg (normal 15–30/4–12 mmHg); and PCWP, mean pressure of 32 mmHg (normal 1–10 mmHg)

ventricular dysfunction. She is given a presumptive diagnosis of a peripartum cardiomyopathy. She is admitted to a heart failure intensive care unit and a pulmonary artery catheterization is performed. Samples from the tracings are seen in Fig. 19.5. Note the somewhat exaggerated waveforms on the section of the tracing labeled pulmonary artery, a commonly encountered artifact.

Her reported hemodynamics are as follows:

RA	PA	PCWP	Cardiac index
10	46/30 (35)	32	2.0

Case 2: Hemodynamic Assessment

This is a case of a patient with so-called "cold and wet" heart failure. The cardiac index is reduced, and both the RA pressure and the PCWP are increased. When accompanied by findings of impaired end-organ function, this state would be termed cardiogenic shock (see Chap. 14). For this patient, there is no clinical evidence of a low perfusion state, such as hypotension, decreased level of consciousness, cool extremities, or renal failure.

The right upper quadrant pain and elevated liver enzymes reflect passive congestion of the liver. The physical examination disclosed an elevated JVP which corresponds to the elevated RA pressure. Note that there were no rales on chest examination and only minimal pulmonary edema on chest X-ray. These findings may have led the clinician to suspect that PCWP was not elevated. Unfortunately, such findings of elevated PCWP are frequently not present among chronic heart failure patients when the time-course of the decompensation is gradual. In such cases, pulmonary lymphatic drainage is enhanced and sufficient to prevent the accumulation of interstitial edema in the lungs. The finding of an S3 should definitely steer the clinician in the right direction, however. The low cardiac output was not recognized at the bedside due to the lack of cool extremities, altered mentation, and low urine output underscoring the insensitivity of these findings [12, 44]. However, if one calculates the proportional pulse pressure in this patient (106–88/106), a value of 17% is obtained suggesting a low cardiac index of <2.2 (see section "Clinical Estimation of Cardiac Output") [11].

The presence of a significant resting sinus tachycardia is ominous however. It suggests that the patient is compensating for a reduced stroke volume by increasing heart rate to maintain cardiac output.

The echocardiogram was crucial in confirming that severe biventricular dysfunction was the cause of the heart failure syndrome. The right heart catheterization was performed because of a concern that the patient was potentially unstable

and needed invasive monitoring. In this case, the right heart catheterization also shows mild elevation in pulmonary artery pressure. The calculated pulmonary vascular resistance (see Chap. 12 for more details) is normal at 1.0 Wood unit:

$$\text{PVR} = \frac{(\text{Mean PA pressure} - \text{PCWP})}{\text{Cardiac output}}$$

$$\text{PVR} = \frac{35-32}{3*} = 1$$

*Cardiac index of 2.0 corresponded to cardiac output of 3 L/min because of body surface area of 1.5 m^2.

This suggests that the patient's pulmonary hypertension is passive and there is no element of pulmonary vasoconstriction or pulmonary vascular remodeling.

The patient was treated with diuretic therapy, ACE inhibitors, and digoxin and observed carefully in an ICU setting. *Beta blockers should not be initiated in such a patient until they become euvolemic and hemodynamically stable*. She was discharged from the hospital 7 days later. Over the next 6 months, the patient was followed closely as an outpatient and had dramatic improvement in symptoms and complete resolution of LV dysfunction. She was advised to avoid pregnancy in the future due to the high risk of recurrent heart failure.

Case 3

A 58-year-old male is referred to a specialized heart failure clinic for evaluation. He has been followed for several years for a non-ischemic dilated cardiomyopathy with severe limitation of his exercise tolerance. His physician sends him for evaluation for the possible need for heart transplantation due to end-stage heart failure. When questioned, he reports that over the past 3 weeks, he has had worsened symptoms of weight gain and leg swelling. These symptoms began after he had started taking a nonsteroidal anti-inflammatory drug for arthritis. On examination, his HR is 90 bpm and his BP measures 98/70 mmHg. He is grossly edematous with pitting edema of both legs as well as scrotal edema. His JVP is elevated with prominent *v* waves. Auscultation of the chest reveals normal breath sounds with no rales or wheeze. On examination of the precordium, there is a loud pulmonic component of the second heart sound and an S3 gallop.

Echocardiography shows severe left ventricular dysfunction with an LVEF of 10% and moderate mitral regurgitation. Severe right ventricular dysfunction is also noted. The estimated RVSP by echocardiography is 88 mmHg (see Fig. 19.6).

The patient is admitted to the hospital, and a right heart catheterization is performed with the following results:

RA	PA	PCWP	Cardiac index
19	88/44 (59)	39	1.5

Case 3: Hemodynamic Assessment

This is another case of so-called "cold and wet" heart failure with reduced cardiac output and elevated right- and left-sided filling pressures. Note again that the patient was not hypoxic and auscultation of the chest did not reveal rales despite a very high PCWP. In contrast to the previous case, the pulmonary hypertension is severe with pulmonary artery pressures approaching the systemic pressures. The loud pulmonic component of S2 is consistent with these high pressures, although it is not a sensitive finding.

The calculated pulmonary vascular resistance is very high (see calculations below) suggesting that there is a pulmonary arterial component to the pulmonary hypertension that would not be immediately reversed if the PCWP was lowered.

$$\text{PVR} = \frac{(\text{Mean PA pressure} - \text{PCWP})}{\text{Cardiac output}}$$

$$\text{PVR} = \frac{59-39}{2.5} = 8 \text{ Wood units}$$

Note how closely the PA pressure was estimated by the transthoracic echocardiogram. Studying the parasternal short-axis images from the echocardiogram also gives us some idea of the relative left- and right-sided intracardiac pressures (Fig. 19.7). The flattened configuration of the interventricular septum during both systole

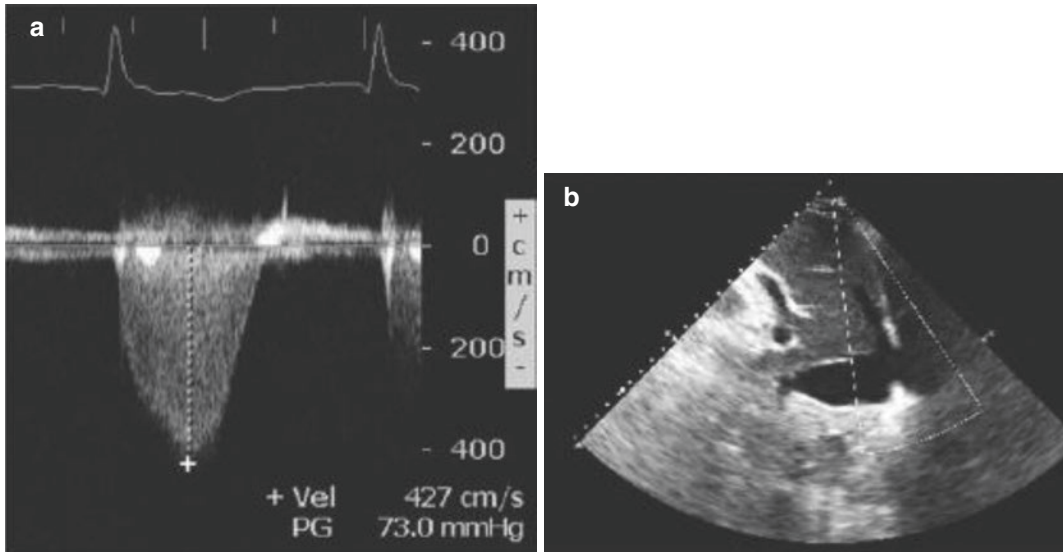

Fig. 19.6 Case 3: estimation of pulmonary artery systolic pressure by echocardiography. Peak velocity of the tricuspid regurgitation jet is 4.27 m/s (**a**) – this suggests a gradient from the RV to the RA of ~73 mmHg. [RV to RA gradient = $4v^2 = 4 \times (4.27)^2 = 72.9$ mmHg. The IVC is dilated (**b**) with a diameter of 2.8 cm and less than 50% variation with respiration – these findings suggest an RA pressure of 15 mmHg. Estimated peak pulmonary artery pressure is 88 mmHg (assuming no pulmonary valve stenosis) (73 + 15 = 88)

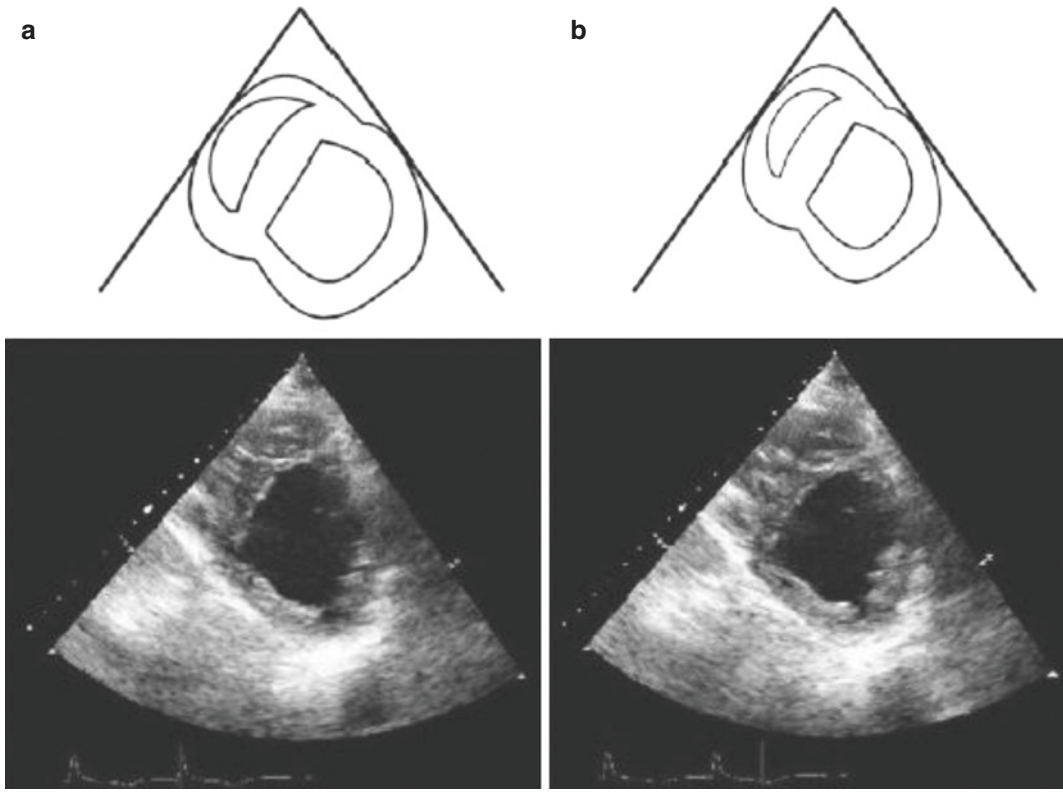

Fig. 19.7 Case 3: parasternal short-axis echo images showing pronounced flattening of the interventricular septum during diastole (**a**) which is still present during systole (**b**). This produces a "D-shaped appearance" of the left ventricle as emphasized in the cartoon above. Severe left ventricular dysfunction is suggested by the minimal change in area of the left ventricular cavity

and diastole suggests that the pressure in the right ventricle (and hence the pulmonary artery) is very high during both systole and diastole.

The patient was treated with inotropic therapy using milrinone, as well as a continuous infusion of furosemide. He was felt to have advanced heart failure, but his high pulmonary vascular resistance precluded heart transplantation because of the risk that the transplanted heart would develop acute right ventricular failure. He underwent placement of a left ventricular assist device which functions as an additional mechanical pump that reroutes blood from the left ventricle into the aorta. With this intervention, he had a dramatic improvement in symptoms and exercise tolerance as well as a marked reduction in PCWP and pulmonary artery pressure.

Pearls of Assessment

- The history and physical examination provide the majority of the hemodynamic information required to manage acute decompensated heart failure.
- No single symptom or sign is perfectly sensitive or specific for the diagnosis of acute decompensated heart failure.
- The most reliable sign of elevated right atrial pressure is elevation of the jugular venous pressure.
- Paroxysmal nocturnal dyspnea is a specific symptom for elevated PCWP.
- Transthoracic echocardiography is an important means of establishing the mechanism of newly diagnosed heart failure and of excluding new structural problems as the trigger for heart failure exacerbation.
- Echocardiography is not needed in routine heart failure exacerbations when a cause for decompensation is clear.
- Need for right heart catheterization is being obviated by noninvasive means of estimating hemodynamic parameters in most situations.
- Right heart catheterization in acute decompensated heart failure is indicated when volume status and cardiac filling pressures are unclear and clinically significant hypotension or worsening renal function during therapy occurs and for the evaluation of pulmonary vascular resistance.

Review Questions

1. A patient with known chronic systolic heart failure is admitted with acute decompensated heart failure. The patient has orthopnea and paroxysmal nocturnal dyspnea. On exam, the jugular venous pressure (JVP) is elevated and estimated to be 10 cm above the sternal angle while the patient is seated upright. Auscultation reveals an S3 gallop. Which of the following suggests an elevated pulmonary capillary wedge pressure (PCWP)?
   A. Orthopnea
   B. S3 gallop
   C. Elevated JVP
   D. All of the above
   Answer D
   Orthopnea and paroxysmal nocturnal dyspnea are the most specific symptoms for elevated PCWP. Although an S3 gallop is not sensitive, it is the most specific sign of left ventricular filling pressure. Elevated jugular venous pressure, although directly estimates right atrial pressure, is a surrogate for elevated PCWP in the vast majority of cases.
2. A patient admitted with decompensated heart failure undergoes right heart catheterization. The right atrial pressure is 5 mmHg, the pulmonary capillary wedge pressure is 10 mmHg, and the cardiac output is 4.0 L/min with cardiac index 1.9 L/min/m^2.
   This is an example of:
   A. Warm and wet heart failure
   B. Warm and dry heart failure
   C. Cold and wet heart failure
   D. Cold and dry heart failure
   Answer D
   The cardiac output of 4 L/min is close to normal. However, this patient has a large body surface area, and his calculated cardiac index is low. The PCWP and RA pressure are both in the normal range.

3. A 72-year-old male presents to the emergency department with a 2-week history of progressive shortness of breath with orthopnea and paroxysmal nocturnal dyspnea. On exam, he has peripheral edema and an elevated JVP at 12 cm above the sternal angle while seated upright. A prominent third heart sound is heard. The patient has inspiratory rales to the mid lung zones bilaterally. A chest X-ray confirms the presence of pulmonary congestion with vascular redistribution, Kerley B lines, and small bilateral pleural effusions.

   The most appropriate next study to assess this patient's etiology of heart failure and hemodynamics is:

   A. 2D echocardiogram with Doppler
   B. Right heart catheterization
   C. Computed tomography with IV contrast
   D. Magnetic resonance imaging

   Answer A

   Echocardiography is a noninvasive, readily available and relatively inexpensive tool for evaluation of left ventricular function, valvular disease, and hemodynamics. It is recommended as a first-line investigation for patients with a new diagnosis of heart failure.

4. The following are all appropriate indications for use of a pulmonary arterial catheter in heart failure except:

   A. Distinction of pulmonary edema related to heart failure from other causes of hypoxia in a critically ill patient in the intensive care unit
   B. Assessment of a patient in shock when intracardiac filling pressures cannot be adequately estimated by noninvasive means
   C. Monitoring of response to beta blocker therapy on routine annual follow-up
   D. Measurement of pulmonary pressures and calculation of pulmonary vascular resistance prior to planned heart transplantation

   Answer C

   For reasons discussed in the section on hemodynamic assessment, the use of pulmonary artery catheters in heart failure should be limited to certain scenarios such as those outlined in answers A, B, and D.

5. A patient admitted with decompensated heart failure undergoes right heart catheterization. The right atrial pressure is 10 mmHg, and the pulmonary arterial pressures are 59/32 mmHg with a mean of 40 mmHg. The pulmonary capillary wedge pressure is 34 mmHg, and the cardiac output is 4.0 L/min.

   The pulmonary pressure in this case could be described as:

   A. Normal – no evidence of pulmonary hypertension
   B. Elevated on the basis of pulmonary venous hypertension
   C. Elevated on the basis of pulmonary arterial hypertension
   D. Representing a mixture of pulmonary venous and pulmonary arterial hypertension

   Answer B

   A pulmonary pressure in this range is clearly abnormal. Determining the extent to which these pressures are elevated due to elevated left-sided pressures alone hinges on the calculation of the pulmonary vascular resistance. The pulmonary vascular resistance calculates out to be 1.5 Wood units, which is within the normal range. This suggests that if the LVEDP could be brought down to normal (with diuresis for example), the pulmonary pressures would become normal. This is the definition of pulmonary venous hypertension.

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Intracardiac Shunts

20

Olcay Aksoy, Alper Ozkan, and E. Murat Tuzcu

Introduction and Epidemiology of the Disease State

In the normal circulation, deoxygenated blood comes into the right heart and passes through the pulmonary circulation to become oxygenated. Then oxygenated blood goes through the left heart to the systemic circulation. An abnormal communication between two heart chambers resulting in an intracardiac (IC) shunt may take place from systemic to pulmonary circulation (left to right) or from pulmonary to systemic circulation (right to left) or may be bidirectional. In this chapter, we review the evaluation and treatment of intracardiac shunts.

While congenital heart diseases are the most common causes of intracardiac shunts, acquired pathologies may also result in IC shunts. Left to right (L → R) shunt in postmyocardial infarction VSD and right to left (R → L) shunt in platypnea-orthodeoxia syndrome (POS) are two examples of acquired IC shunts.

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Detection, localization, and quantification of intracardiac shunts are clinically important in the management of IC shunts and can be performed using noninvasive and invasive techniques. Noninvasive techniques include transthoracic or transesophageal echocardiography, cardiovascular magnetic resonance (CMR), and radionuclide tests. Invasive techniques apply catheter insertion and selective blood sampling of oxygen saturation to diagnose and quantify IC shunts.

Noninvasive Assessment of Intracardiac Shunts

Transthoracic echocardiography (TTE) is a safe, reproducible, and relatively inexpensive method that is widely used in the assessment of intracardiac shunts. Transesophageal echocardiography (TEE) is an excellent tool for defining the anatomy of IC shunts and provides additional information; however, its incremental value in shunt assessment is limited. Magnetic resonance imaging (MRI) allows precise measurement of cardiac volumes and flows yielding accurate IC shunt calculations.

Echocardiographic Assessment of Intracardiac Shunts

Echocardiography has been the primary diagnostic tool and plays an essential role in providing

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_20

morphologic assessment and hemodynamic evaluation in congenital heart disease. TTE permits comprehensive anatomic information regarding the location and the size of the defect. TEE may be needed as a complementary imaging tool particularly in lesions located posteriorly and in patients who will undergo percutaneous or surgical intervention. Color flow Doppler plays a critical role in the detection and localization of IC shunts as well as in determining the direction of shunting—though the sensitivity of echocardiographic evaluation with color Doppler or 2D imaging only is limited. The use of contrast echocardiography with agitated saline together with Valsalva maneuver will increase right atrial pressure and may allow for increased sensitivity when diagnosing intracardiac shunting, when a patent foramen ovale is present. If microbubbles from agitated saline injected from a peripheral vein is seen to enter the left heart chambers within 3 beats; this is consistent with an intracardiac communication between right and left chambers of the heart. If there is delayed appearance of microbubbles in the left chambers (>5 beats), this is associated with intrapulmonary shunting. TEE and transcranial Dopplers with microbubble administration have also enhanced the detection of shunts not otherwise visualized by TTE techniques [1].

In addition to the detection of shunts, echocardiographic techniques can also provide quantification of the degree of shunting. Pulmonary blood flow (Q_p) to systemic blood flow (Q_s) ratio can be calculated using Doppler and 2D echocardiography.

Comprehensive evaluation of a patient with IC shunt is not limited to the detection and quantification of the shunt flow. It also involves the evaluation of the associated abnormalities and secondary findings. For example, in a patient with ASD, the evaluation of right atrial and right ventricular size and septal motion and for other associated anomalies such as anomalous pulmonary venos return is as important as the quantification of the defect.

The hemodynamic significance of intracardiac shunts can be evaluated based on volumetric flow calculations using cross-sectional area (CSA) and velocity time integral (VTI) across the outflow tracts of both ventricles. Pulmonary flow (Q_p) equals systemic flow (Q_s) in the absence of shunt. Formulas are used to calculate volumetric flow with two important assumptions. The first assumption is blood flow has a uniform pattern and constant velocity. The second assumption is that the shape of the outflow tract is circular.

Flow formula is as follows:

$$Q = \mathrm{CSA} \times \mathrm{VTI}$$

(Q = flow, CSA = cross-sectional area, VTI = velocity time integral)

CSA is calculated based on circular shape assumption:

$$\mathrm{CSA} = \pi \times r^2$$

(π = pi constant, which is 3.14; r = radius of the outflow tract)

For the pulmonary flow, the formulas are as follows:

$$Q_p = \mathrm{CSA}_{\mathrm{RVOT}} \times \mathrm{VTI}_{\mathrm{RVOT}}$$

$$Q_p = \pi \times \left(\frac{\text{RVOT Diameter}}{2} \right)^2 \times \mathrm{VTI}_{\mathrm{RVOT}}$$

$$Q_p = \pi \times \frac{\left(\text{RVOT Diameter}\right)^2}{4} \times \mathrm{VTI}_{\mathrm{RVOT}} \quad \text{with} \left(\frac{\pi}{4} = 0.785 \right)$$

$$Q_p = 0.785 \times \left(\text{RVOT Diameter}\right)^2 \times \mathrm{VTI}_{\mathrm{RVOT}}$$

For the systemic flow, the formula would be simplified as follows:

$$Q_s = 0.785 \times \left(\text{LVOT Diameter}\right)^2 \times \text{VTI}_{\text{LVOT}}$$

After simplification, the formula of Q_p/Q_s is

$$\frac{Q_p}{Q_s} = \frac{\left(\text{RVOT Diameter}\right)^2 \times \text{VTI}_{\text{RVOT}}}{\left(\text{LVOT Diameter}\right)^2 \times \text{VTI}_{\text{LVOT}}}$$

See the example in Fig. 20.1. (Q_p = pulmonary flow; Q_s = systemic flow; RVOT = right ventricle outflow tract; LVOT = left ventricle outflow tract).

Potential Source of Errors and Pitfalls

Precise measurements of LVOT and RVOT diameters require appropriate site selection. LVOT diameter should be measured at the level of the aortic annulus during systole in parasternal long axis view of the LV, whereas RVOT is measured at the level of pulmonary valve annulus in parasternal short axis view (see Fig. 20.1). It is important to note that CSA is calculated as if it is a perfect circle even though the shape of the outflow tracts change throughout the cardiac cycle as these are dynamic structures. Positioning of

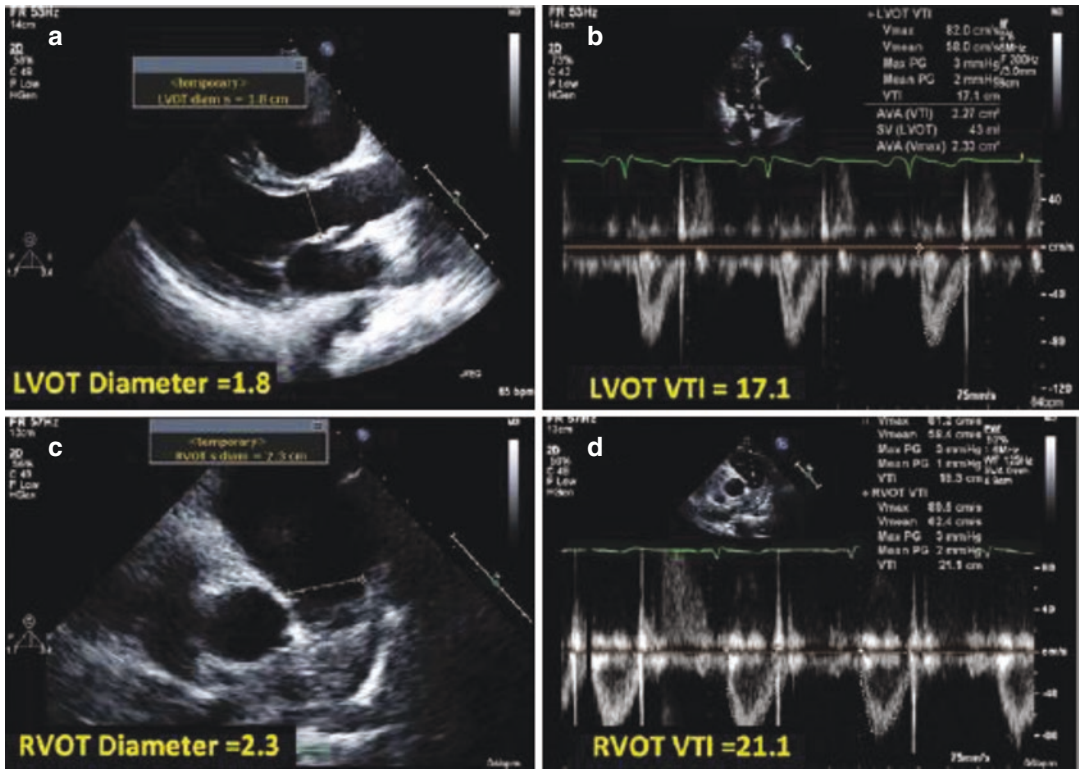


Fig. 20.1 Quantification of IC shunts using transthoracic echocardiography. Systemic stroke volume or flow (Q_s) can be calculated by using CSA of LVOT, which is derived by LVOT diameter at the end of systole (**a**), and LVOT VTI (**b**) pulmonary stroke volume or flow (Q_p) can be measured using CSA of RVOT, which is derived by RVOT diameter at the end of systole (**c**) and RVOT VTI (**d**)

$$\frac{Q_p}{Q_s} = \frac{\text{CSA RVOT} \times \text{VTI RVOT}}{\text{CSA LVOT} \times \text{VTI LVOT}}, \quad \frac{Q_p}{Q_s} = \frac{3.14 \times (2.3/2)^2 \times 21.1}{3.14 \times (1.8/2)^2 \times 17.1}, \quad \frac{Q_p}{Q_s} = \frac{87.6}{43.5} = 2.$$

CSA cross-sectional area, *LVOT* left ventricle outflow tract, *VTI* velocity time integral, and *RVOT* right ventricle outflow tract

sample volume of pulsed wave Doppler signals should be obtained at the levels where RVOT and LVOT diameters were measured. Optimal Doppler signals must be acquired for accurate velocities and VTI. Respiratory variations can affect the position of PW sample location or Doppler velocities.

Many other pitfalls such as arrhythmia, heart rate variability, and presence of valvular heart disease in particular aortic and mitral regurgitation may also complicate shunt assessment. A small error in the diameter measurement is magnified in the calculation of cross-sectional area translating into large errors in flow calculations.

Assessment of Intracardiac Shunt with Cardiovascular Magnetic Resonance

Although echocardiography provides the clinician with an initial screening tool for the assessment shunts, cardiovascular magnetic resonance (CMR) has become a complementary tool for the noninvasive evaluation of the size and morphologic features of the congenital cardiac defects. MRI provides not only the exact visualization of cardiac anatomy but also allows accurate and reproducible quantification of IC shunts. Studies have demonstrated that MRI measurements of IC shunts correlate with those obtained by invasive methods in children [2–5] as well as in adults [5] using different MRI applications [6, 7]. Volumetric MRI and phase contrast cine MRI are the commonly used protocols for the assessment of IC shunt. With these techniques, ventricular stroke volume can be calculated for each ventricle with short axis and/or four chamber views (Fig. 20.2). In the absence of significant valvular regurgitation or ventricular septal defect (VSD), the ratio of the RV to LV stroke volumes yields the Q_p/Q_s ratio. Velocity-encoded (VENC) cine MR is another application for the measurement of IC shunt [6]. Each voxel has its own velocity across the vessel in the gray scale images. Flow can be estimated using the cross-sectional area of the vessel and integrated into the velocity of the blood at the same level. Magnitude images provide an accurate measurement for the cross-sectional areas of the vessel, and phase cine MR images offer reliable quantification for mean flow velocity [3] (Fig. 20.3a, b).

MRI has many advantages when compared to other noninvasive imaging modalities. Unlike echocardiography, MR allows visualization of vascular structures in addition to cardiac chambers. It is possible to make reliable and reproducible measurements of blood flow velocities and assess stenotic and regurgitant valvular lesions by CMR. These can be accomplished with much less subjectivity compared with echocardiography. In contrast to radionuclide technique or cardiac computed tomography (CT), MR does not have any ionizing radiation. In addition to the accurate quantification of IC shunts, MRI is a promising technique for the guidance of transcatheter closure of congenital heart defects [8]. After the closure of such defects, MRI can clearly show the anatomic location of the device and can quantify its effectiveness [9–11]. However, MRI requires more patient compliance, and a comprehensive MR exam takes time and is relatively expensive. Many stents, devices, and vascular filters are MR compatible. Whereas implantable cardiac devices have previously been considered as absolute contraindications, MRI-conditional and MRI-safe pacemakers are now available.

Other Noninvasive Imaging Modalities

Radionuclide techniques can also be used for the assessment of IC shunt. Radionuclide scintigraphy can be considered as an alternative noninvasive method for the quantification of IC shunt and evaluation of LV function in patients with post-MI VSR [12].

Cardiac CT can provide comprehensive anatomic information in the assessment of congenital cardiac defects. Although cine CT makes some hemodynamic measurements possible such as cardiac output, quantification of IC shunts with CT has not been well established.

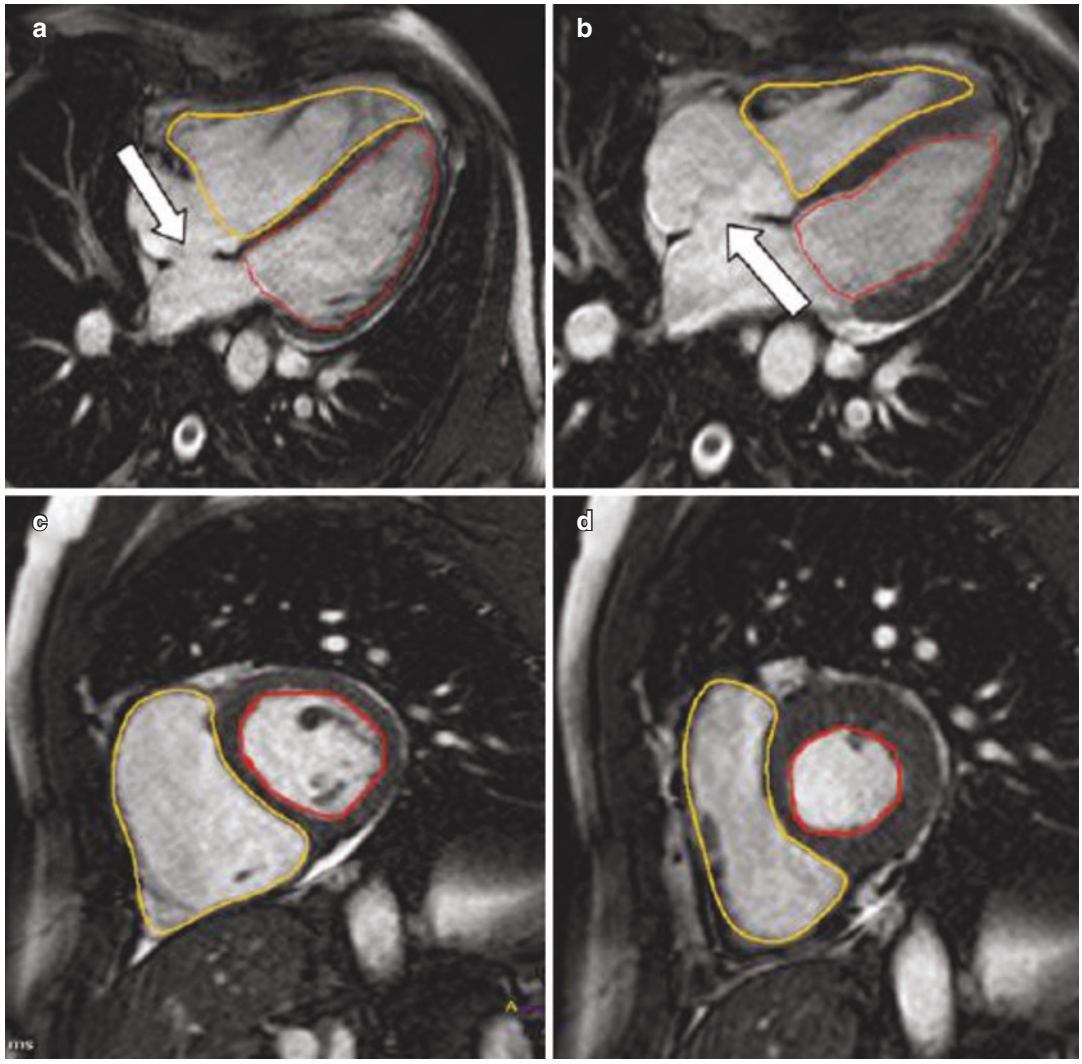


Fig. 20.2 Volumetric method for the quantification of IC shunt. Diastolic (**a**) and systolic (**b**) four chamber cine MR images of both ventricles demonstrate moderately dilated RV with normal systolic function. Diastolic (**c**) and systolic (**d**) short axis cine MR images of both ventricles. The ratio of the RV to LV stroke volumes gives shunt ratio (Q_p/Q_s). LV EDV = 194 cm^3; LV ESV = 102 cm^3; LV SV = 92 cm^3; LV EF = 48%, RV EDV = 289 cm^3; RV ESV = 124 cm^3; RV SV = 165 cm^3; and RV EF = 57%. Shunt ratio can be therefore calculated for this ASD case (*white arrows* show the defect); Q_p/Q_s = 165/92 = 1.8 (ASD atrial septal defect, EDV end diastolic volumes, ESV end systolic volumes, LV left ventricle, RV right ventricle)

Invasive Quantification of Intracardiac Shunts

IC shunts have been calculated using various invasive methods. Indocyanin dilution and/or dye curve technique have been used in the past. Contrast angiography provides qualitative evaluation and localization of the shunts but is not suitable for precise shunt quantification. The widely used invasive technique is the oxymetric study, which is based on blood sampling from different locations in the circulation.

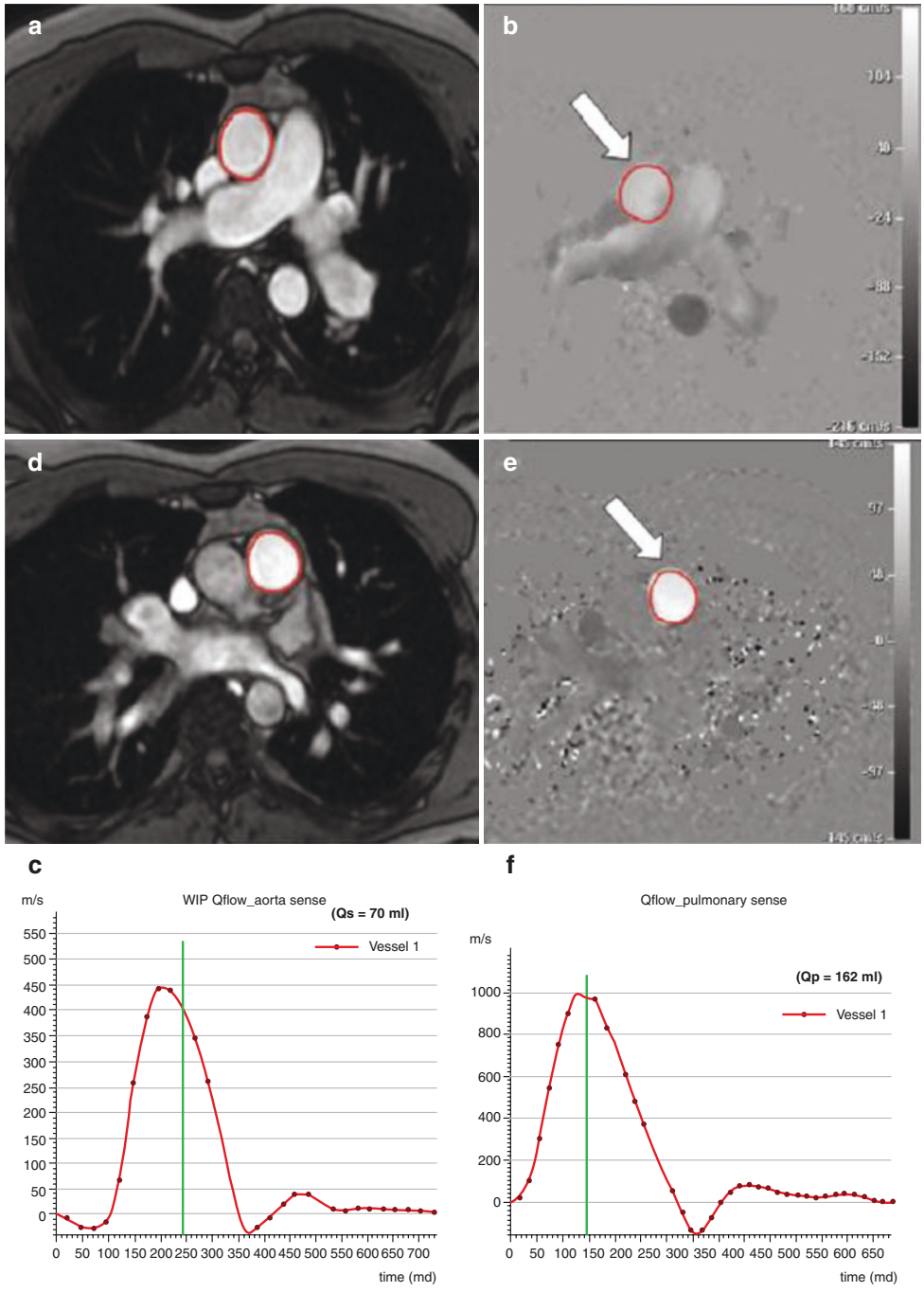


Fig. 20.3 (**a**–**c**) Velocity-encoded (phase contrast) cine MR imaging for the quantitation of systemic flow (Q_s). (**a**) Magnitude image of the ascending aorta for the measurement of cross-sectional area of the vessel. The plane is positioned at the level of the bifurcation of the main pulmonary artery. (**b**) Phase contrast image perpendicular to the ascending aorta (*white arrow*). (**c**) Through-plane velocity mapping creates flow vs. time curves. The area under the curve represents stroke volume of the ascending aorta (Q_s), which was measured 70 mL/beat for this case. (Q_s = 70 mL). (**d**–**f**) Phase contrast cine MR imaging for the quantitation of pulmonary flow(Q_p). (**a**) Magnitude image of the main pulmonary artery. (**b**) Phase contrast image perpendicular to the main pulmonary artery (*white arrow*). (**c**) Through-plane velocity mapping demonstrates flow vs. time curves across the main pulmonary artery. The area under the curve represents stroke volume of the pulmonary artery (Q_p), which was calculated 162 mL/beat for this case. The shunt ratio was therefore calculated Q_p/Q_s = 162/70 = 2.2, which indicates significant left to right shunting

Oxygen Saturation Run

Knowledge of basic principles of Fick's method is fundamental to understanding how IC shunts are calculated in catheterization laboratory.

Blood Sampling

Blood samples should be obtained after a "steady state" of heart rate, respiratory rate, and blood pressure is reached on room air if tolerated by patient. A large hole catheter should be used for easy blood draw. It should be kept in mind that very rapid aspiration or a faulty connection may allow the entry of microbubbles into the syringe, resulting in erroneously increased O_2 saturation and overestimation of Q_p [13]. Sites for blood sampling must be carefully chosen depending on the underlying pathology (Fig. 20.4) Blood sampling procedure should be completed within 5–10 min (or at the same time that oxygen consumption is calculated) in order to minimize the variability in oxygen consumption. After each sample is obtained, the catheter must be cleared with a saline flush. Obtaining blood samples from distal to proximal during catheter "pull-back" from pulmonary artery (PA) is more practical. If possible, the patient should not be receiving supplemental oxygen greater than 30%, as the increased dissolved O_2 in the right heart might cause increased pulmonary flow resulting in overestimation of the shunt ratio.

Variability of oxygen measurements and oxygen content should be taken into account during the sampling process, particularly in the right-sided heart chambers. In a study with 980 patients [14] without shunting, differences of O_2 saturation were found between SVC and RA, RA and PA, and SVC and PA, 3.9 ± 2.4%, 2.3 ± 1.7%, and 4.0 ± 2.5%, respectively. In another study [15], 102 adults without left to right shunt were assessed in order to find the limits of normality of O_2 content differences. The outcomes were from right atrium to mixed venous, right ventricle to right atrium, and pulmonary artery to right ventricle, 0.5 mL/dL, 0.6 mL/dL, and 0.9 mL/dL, respectively.

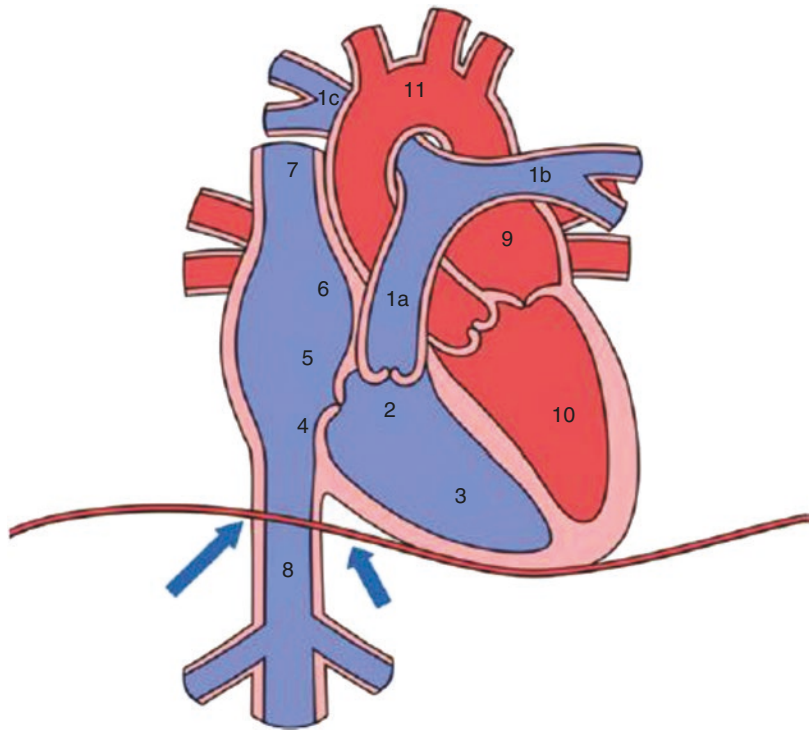


Fig. 20.4 Exact localization for the blood sampling in oxymetric run study. *1a* main pulmonary artery, *1b* left pulmonary artery, *1c* right pulmonary artery, *2* right ventricular outflow tract, *3* right ventricle, *4* low right atrium, *5* mid right atrium, *6* high right atrium, *7* superior vena cava, *8* inferior vena cava (sample should be obtained just below the diaphragm (*blue arrows*); hepatic vein must be taken into account while obtaining inferior vena cava blood), *9* left atrium, *10* left ventricle, *11* aorta or femoral artery

Mixed Venous Oxygen Saturation

In the normal circulation, deoxygenated blood is mixed in the pulmonary artery (PA). However, in the setting of left to right shunt, the site of mixed venous blood would vary according to the location of the lesion. Unfortunately, there is no practical way to measure mixed venous oxygen (MVO_2) because the various sources of MVO_2 (superior vena cava, inferior vena cava, coronary sinus) have different amounts of blood with varying saturations. As a general rule, blood samples should be obtained proximal and distal to the lesion and blood from the chamber(s) proximal to the shunt site is used for MVO_2 measurement. For instance, in the case of patent ductus arteriosus (PDA), arterial blood mixes with venous blood at the pulmonary artery at the level of the aorta. Thus, venous samples should be taken from RV, which is the proximal chamber to the shunt site. In patients with a ventricular septal defect, RAO_2 saturation can represent MVO_2 site. In the case of an atrial septal defect, the location where the arterial shunt mixes with venous blood is not constant. Different formulas are used for the calculation of MVO_2. The most commonly used formula in the estimation of MVO_2 is ((3 × SVC + 1 × IVC)/4) [16]. Other formulas may also be considered for an estimation of MVO_2 as follows:

$$\begin{bmatrix} = \dfrac{\left(\left(1\times \mathrm{SVC_{Sat}}\right)+\left(2\times \mathrm{IVC_{Sat}}\right)\right)}{3} \\ \mathrm{MVO_2} = \dfrac{\left(\left(2\times \mathrm{SVC_{Sat}}\right)+\left(3\times \mathrm{IVC_{Sat}}\right)\right)}{5} \end{bmatrix}$$

where MVO_2 = mixed venous oxygen saturation, SVC_{Sat} = superior vena cava saturation, and IVC_{Sat} = inferior vena cava saturation [15, 17].

Calculation of Shunt Size "Pulmonary to Systemic Flow Ratio (Q_p/Q_s)"

In the absence of a shunt, pulmonary blood flow (Q_p) is equal to the systemic blood flow(Q_s). Q_p/Q_s ratio is calculated based on Fick's principle as follows:

$$\text{Cardiac output} = \frac{\text{Oxygen consumption}}{\left(\text{Arterial } O_2 - \text{Venous } O_2\right)\times \text{Hemoglobin concentration}\times 1.36\times 10}$$

Since the pulmonary circulation occurs between pulmonary veins and pulmonary artery, the formula is adapted as follows:

$$Q_p = \frac{\text{Oxygen consumption}}{\left(\mathrm{PVO_2} - \mathrm{PAO_2}\right)\times \text{Hemoglobin concentration}\times 1.36\times 10}$$

where Q_p = pulmonary blood flow, PVO_2 = pulmonary vein oxygen saturation, and PAO_2 = pulmonary artery oxygen saturation.

Systemic circulation takes place between the aorta and the point where the venous blood is assumed to be fully mixed. Therefore, the formula corresponds to:

$$Q_s = \frac{\text{Oxygen consumption}}{\left(\mathrm{AoO_2} - \mathrm{MVO_2}\right)\times \text{Hemoglobin concentration}\times 1.36\times 10}$$

where Q_s = systemic blood flow, AoO_2 = aortic or systemic arterial oxygen saturation, and MVO_2 = mixed venous oxygen saturation).

These formulas can be simplified to calculate Q_p/Q_s as follows:

$$\frac{Q_p}{Q_s} = \frac{(AoO_2 - MVO_2)}{(PVO_2 - PAO_2)}$$

For right to left or bidirectional shunts:

Effective pulmonary blood flow must be calculated. The net difference of systemic flow to shunt flow should be considered as effective pulmonary flow.

Clinical Utility of the Shunt Ratio in Practice

Shunt ratio (Q_p/Q_s) can help clinicians to better understand the hemodynamic importance of the IC shunt and is clinically very important in decision-making about the requirement of possible intervention. If the ratio is less than 1.5, it generally indicates a "small lesion," a ratio of 1.5–2.0 indicates "likely to require intervention," and a ratio of 2 or more is usually considered to be "severe." Nevertheless, each case should be evaluated individually with its clinical presentation, and shunt ratio should be determined within the clinical context of the disease state. If there is inconsistency between invasive and noninvasive measurements, symptoms attributable to shunt defect, possible associated congenital abnormalities, as well as measurement pitfalls should be carefully reviewed. Secondary findings such as the quantification of chamber enlargement or ventricular function can also help in decision-making.

Review Questions

Q1—A 30-year-old woman presented with dyspnea on exertion. Echocardiographic examination revealed enlargement of right-sided heart chambers with an increased pulmonary flow. Left to right shunt was detected by color flow Doppler assessment in the interatrial septum. Which one of the following echocardiographic measurements is *not* necessary for the quantification of atrial shunt in this patient?

A. Diameter of LVOT
B. Diameter of RVOT
C. Diameter of defect
D. RVOT VTI
E. LVOT VTI

Q2—In which of the following congenital heart diseases, volumetric MRI measurement is *not* an appropriate method for the quantification of the intracardiac shunt?

A. Muscular type VSD
B. Secundum type ASD
C. Patent ductus arterious
D. Partial anomalous pulmonary venous return
E. Aorticopulmonary window

Q3—Which one of the following formulas can be used to estimate mixed venous blood (MVO_2) saturation during cardiac catheterization?

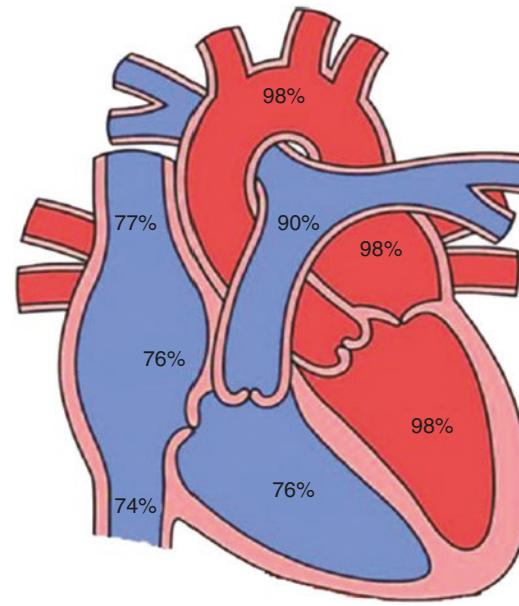
A. $MVO_2 = \frac{(3\times SVC_{sat} + 1\times IVC_{sat})}{4}$

B. $MVO_2 = \frac{(SVC_{sat} + IVC_{sat})}{2}$

C. $MVO_2 = \frac{(2\times SVC_{sat} + 3\times IVC_{sat})}{5}$

D. $MVO_2 = SVC_{sat}$

E. All of the above



Q4—A 16-year-old patient underwent cardiac catheterization for further investigation with the suspicion of congenital heart disease. Her hemoglobin level is 13 g/dL and calculated O_2 consumption is 190 mL/min. According to the saturation run study results, shown below, which is the correct diagnosis?

A. Muscular type VSD − Q_p/Q_s = 1.5
B. Ostium primum type ASD − Q_p/Q_s = 2.8
C. Ostium secundum type ASD − Q_p/Q_s = 2.8
D. Patent ductus arteriosus − Q_p/Q_s = 2.8
E. Patent ductus arteriosus − Q_p/Q_s = 1.5

Q5—A 36-year-old man who was diagnosed secundum type ASD with left to right shunting. Calculated Q_p/Q_s ratio was reported as 2.1 with right atrial and ventricular enlargement. There was no associated significant valvular abnormality and he was still on normal sinus rhythm (68 beats/s). He was complaining of palpitations and exertional dyspnea and referred to you for further investigation and treatment. The following oxygen saturations were measured in catheterization room while the patient was breathing 21% oxygen room air O_2 cont; IVCsat: 69%, SVCsat: 73%, PAsat: 80%, femoral artery sat: 98%.

What would you do for the next step in the evaluation of this patient?

A. Invasive Q_p/Q_s ratio cannot be calculated with these data; hemoglobin and cardiac output should have been reported.
B. Echocardiographic shunt ratio indicates significant left to right shunting with an enlargement of right-sided heart chamber, which is enough for the decision on closure of this ASD.
C. Room oxygen level is not enough; oxymetric study should be repeated while the patient is breathing 80% oxygen.
D. Invasive Q_p/Q_s indicates significant left to right shunt so the defect should be closed as soon as possible.
E. Invasive Q_p/Q_s indicates nonsignificant left to right shunt; therefore, the patient should be treated medically and must be closely monitored.

Answers of the Questions

A1—The correct answer is C.

Echocardiography is the primary tool for the assessment of congenital heart disease. Although echocardiography can provide sizing of the defect, it is not required in the quantification of shunt ratio. The defect size, however, cannot give an idea about the shunt ratio. Small lesion can be associated with small shunt ratio, whereas big lesions can be complicated by Eisenmenger physiology with right to left or bidirectional shunting.

A2—The correct answer is A.

Gradient echo cine MR can provide comprehensive volumetric assessment for both ventricles. The shunt volume can be easily calculated as net difference between LV and RV stroke volumes. In the setting of VSD, however, IC shunt occurs at the ventricular level and quantification of Q_p/Q_s is impossible using this method. On the other hand, if there is severe valvular regurgitation, due to substantial back flow into the atria, stroke volumes can be underestimated.

A3—The correct answer is E.

Although the most common formula is (3 × SVC + IVC)/4, in the estimation of saturation MVO_2 blood**,** other formulas can be considered.

A4—The correct answer is D.

The diagnosis is PDA with L → R shunt. O_2 step up can be clearly seen in the main pulmonary artery. Hence, we can easily calculate Q_p/Q_s using simplified formula, which is

$$\frac{Q_p}{Q_s} = \frac{\left(AoO_2 - MVO_2\right)}{\left(PVO_2 - PAO_2\right)}$$

$$\frac{Q_p}{Q_s} = \frac{\left(98-76\right)}{\left(98-90\right)} = \frac{\left(22\right)}{\left(8\right)} = 2.75$$

Step-by-step approach for the assessment of intracardiac shunt quantification:

Step 1: Compute oxygen content for main locations

$$\text{Arterial oxygen content} = 0.98 \times 1.36 \times 13 \times 10 = 173$$
$$\text{Pulmonary vein oxygen content} = 0.98 \times 1.36 \times 13 \times 10 = 173$$
$$\text{Pulmonary artery oxygen content} = 0.90 \times 1.36 \times 13 \times 10 = 160$$
$$\text{Mixed venous oxygen content} = 0.76 \times 1.36 \times 13 \times 10 = 134$$

(As this is a PDA case, RVsat can represent MVO_2)

Step 2: Compute systemic flow (Q_s)

$$\frac{190}{173-134} = 4.87$$

Step 3: Compute pulmonary flow (Q_p)

$$\frac{190}{173-160} = 14.6$$

Step 4: Compute Q_p/Q_s

$$\frac{14.6}{4.87} = 3$$

A5—The correct answer is B.

Invasive oxymetric measurement of the Q_p/Q_s ratio is 1.5, which is inconsistent with echocardiographic shunt ratio. This is not an uncommon situation in daily practice. Although Q_p/Q_s ratio is clinically very important in decision-making, if there is strong clinical suspicion or laboratory evidence of a significant shunt (this patient is symptomatic and TTE revealed right-sided heart chamber enlargement), then the defect should be closed. On the other hand, it should be kept in mind that atrial shunts can easily be affected by ventricular filling patterns such as compliance or stiffness and might be underestimated in the setting of severe tricuspid regurgitation or atrial fibrillation.

Hemoglobin and oxygen contents are not exactly necessary for an estimation of Q_p/Q_s ratio. Because same parameters are used in the denominator and nominator of the equations, simplified method can be used practically.

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Shock

21

Jose Mariano T. Tan and Michael P. Brunner

Epidemiology of Shock

Shock is a pathophysiological state characterized by inadequate tissue oxygenation. It is a life-threatening condition that may lead to cellular death and vital organ dysfunction. Common clinical manifestations of shock include tachycardia, hypotension, oliguria, and confusion. Laboratory tests often demonstrate signs of end-organ damage such as acute liver or kidney injury, metabolic acidosis, and lactic acidosis.

There are four major categories of shock: cardiogenic, hypovolemic, distributive, and obstructive shock. However, it is important to note that these major categories of shock are not mutually exclusive and combinations with other form(s) of shock may occur.

Cardiogenic shock (CS) is often depicted as shock due to pump failure. The primary disorder in CS is low cardiac output due to intrinsic cardiac dysfunction. It is often a complication of myocardial infarction, but it may also be due to arrhythmia, congestive heart failure, or a primary valvular disorder. CS is estimated to complicate 3–8% of cases of acute myocardial infarction [1–3]. The mortality rate associated with CS in patients with acute myocardial infarction historically approached 80% [1]. Due to contemporary strategies in the management of acute coronary syndrome, the adjusted mortality rate ranges from 45 to 66% [4].

Hypovolemic shock is shock due to hemorrhagic or nonhemorrhagic volume loss. It is often related to traumatic injury, gastrointestinal bleeding, vomiting, or diarrhea. The incidence of hypovolemic shock varies depending on its underlying etiology.

The most common etiology of *distributive shock* is sepsis, a dysfunctional systemic response to an infection. Every year, 1.6 million patients are diagnosed with sepsis in the United States [5]. In its severe form, septic shock may ensue. The mortality associated with severe sepsis and septic shock is estimated to be 14.7–29.9% [6]. These figures are likely underestimated as severe sepsis and septic shock often occur concomitantly with other leading causes of mortality including pneumonia, urinary tract infection, gastrointestinal tract infection, skin infection, and malignancy.

The primary disorder in *obstructive shock* is low cardiac output due to extrinsic cardiac dysfunction. The incidence of obstructive shock varies according to its etiology which includes pulmonary embolism, cardiac tamponade, and tension pneumothorax.

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_21

Clinical Presentation of Shock: A Case-Based Approach

Understanding the pathophysiology associated with each category of shock is essential in performing an appropriate clinical assessment and guiding appropriate therapy. Examples of different conditions associated with each major category of shock are listed in Table 21.1. The following cases are examples from each category of shock.

Case 1: Cardiogenic Shock

A 55-year-old male with hypertension, dyslipidemia, and a family history of coronary artery disease presents to the emergency department

Table 21.1 Etiologies of shock

Cardiogenic[a]	**Distributive**
Myopathic	Sepsis; pancreatitis
Acute myocardial infarction	Pancreatitis
Left ventricular failure	Anaphylaxis
Right ventricular failure	Bacterial toxins
Acute myocarditis	Acidosis
Idiopathic cardiomyopathy	Adrenal crisis
Restrictive/constrictive cardiomyopathy	Myxedema coma
Stress-induced (Takotsubo) cardiomyopathy	Iatrogenic
Acute heart transplant rejection	Neurogenic insult
Iatrogenic (negative inotropic or vasodilatory medications)	Post-resuscitation syndrome
Post-cardiac arrest	Post-cardiopulmonary bypass
Mechanical	**Hypovolemic**
Ventricular septal rupture	Hemorrhagic
Ventricular Free Wall rupture	Trauma
Hypertrophic obstructive cardiomyopathy	Gastrointestinal bleeding
Dynamic left ventricular outflow tract obstruction	Ruptured hematoma
Atrial myxoma	Hemorrhagic pancreatitis
Traumatic	Fractures
Valvular	Ruptured aortic aneurysm
Papillary muscle/chordal rupture	Acute aortic dissection
Acute mitral regurgitation	Plasma extravasation related
Prosthetic valve obstruction	Systemic inflammatory response
Severe aortic regurgitation	Sepsis
Critical aortic stenosis	Major surgery
Severe mitral stenosis	Pancreatitis
Arrhythmic	Major surgery
Tachycardia	Fluid loss related
Sustained ventricular tachycardia	Dehydration
Ventricular fibrillation	Severe burns
Bradycardia	Emesis
High-grade AV block	Diarrhea
Complete heart block	Diaphoresis
	Insensible losses
	Inadequate fluid intake
	Obstructive
	Cardiac tamponade
	Pulmonary embolism
	Pulmonary hypertension
	Tension pneumothorax

[a]*Causes that may complicate acute myocardial infarction are italicized*

with severe substernal chest pain and shortness of breath. Initial vital signs demonstrate tachycardia and hypotension. A third heart sound (S3) is auscultated. He has inspiratory rales in both lung bases, and his internal jugular vein is appreciated above the clavicle in an upright position. His extremities are cool, mottled, and cyanotic. An electrocardiogram reveals ST segment elevation across the anterior precordial leads.

This case describes a patient with CS caused by acute myocardial infarction. CS is a clinical condition in which inadequate tissue perfusion is the consequence of intrinsic cardiac dysfunction. It is characterized by a reduction in cardiac output despite adequate filling pressures. Causes of CS include myopathic, mechanical, valvular, and arrhythmic processes (Table 21.1). The criteria typically used to define CS include systolic blood pressure less than 90 mmHg for at least 30 min or the need for a vasopressor or mechanical circulatory support to maintain a systolic blood pressure greater than 90 mmHg; pulmonary capillary wedge pressure greater than 15 mmHg; and cardiac index less than 2.2 L/min/kg/m^2 [7].

Tachycardia, hypotension, oliguria, confusion, cyanosis, and cold extremities typically characterize the clinical presentation of CS. Tachycardia occurs in an effort to maintain cardiac output when the stroke volume is reduced. Oliguria and confusion are the result of poor tissue perfusion. Cool, mottled, and cyanotic extremities are manifestations of peripheral vasoconstriction.

Peripheral pulses are often diminished in CS due to decreased pulse pressure (*pulsus parvus*). In a failing left ventricle, the strength of every other beat may alternate, a phenomenon known as *pulses alternans*. Delayed pulses (*pulsus tardus*) may be seen in cardiogenic shock in the setting of severe aortic stenosis.

CS due to left ventricular failure may present with pulmonary congestion; patients may complain of orthopnea and paroxysmal nocturnal dyspnea (PND). Examination may demonstrate bilateral inspiratory rales, S3 gallop, and laterally displaced apical impulse due to left ventricular dilatation. Chest radiography may demonstrate cardiomegaly, pulmonary vessel cephalization, Kerley B lines, and parenchymal edema. If right ventricular failure is also present, evidence of venous congestion may be observed including jugular vein distention, hepatojugular reflux, and bilateral lower extremity edema.

Of note, a significant proportion of patients in the SHOCK (SHould we emergently revascularize Occluded Coronaries in cardiogenic shocK?) trial had no pulmonary congestion [8]. Neither auscultation nor chest radiograph detected pulmonary edema in 28% of patients.

Right ventricular infarction complicates up to half of all transmural inferior-posterior myocardial infarctions [9]. Patients with hemodynamically significant right ventricular infarction classically present with hypotension, clear lung fields, and jugular venous distention. Right ventricular failure may be associated with a holosystolic tricuspid regurgitation murmur at the left lower sternal border, jugular venous distension, liver engorgement, pulsatile liver, and peripheral edema. Patients with patent foramen ovale and acute right ventricular infarction may present with profound hypoxia due to decreased compliance in the infarcted right ventricle and right-to-left shunting.

Mechanical complications of acute myocardial infarction may result in CS and can sometimes be evident on physical exam. Acute mitral regurgitation, tricuspid regurgitation, and ventricular septal rupture are associated with holosystolic murmurs. However, if there is rapid equalization of pressure in the atria and ventricles, acute regurgitant lesions may not cause a significant murmur. Prominent jugular *v*-waves suggest severe tricuspid regurgitation. Jugular cannon *a*-waves suggest complete heart block. Ventricular free wall rupture will frequently result in fulminant cardiac tamponade (see section "Case 4: Obstructive Shock").

In CS, a compensatory increase in systemic vascular resistance (SVR) typically occurs through peripheral vasoconstriction in an effort to maintain tissue perfusion. However, this classic paradigm has been challenged. Data from the SHOCK trial demonstrated that many patients with CS instead have low systemic resistance, similar to patients with septic shock [10]

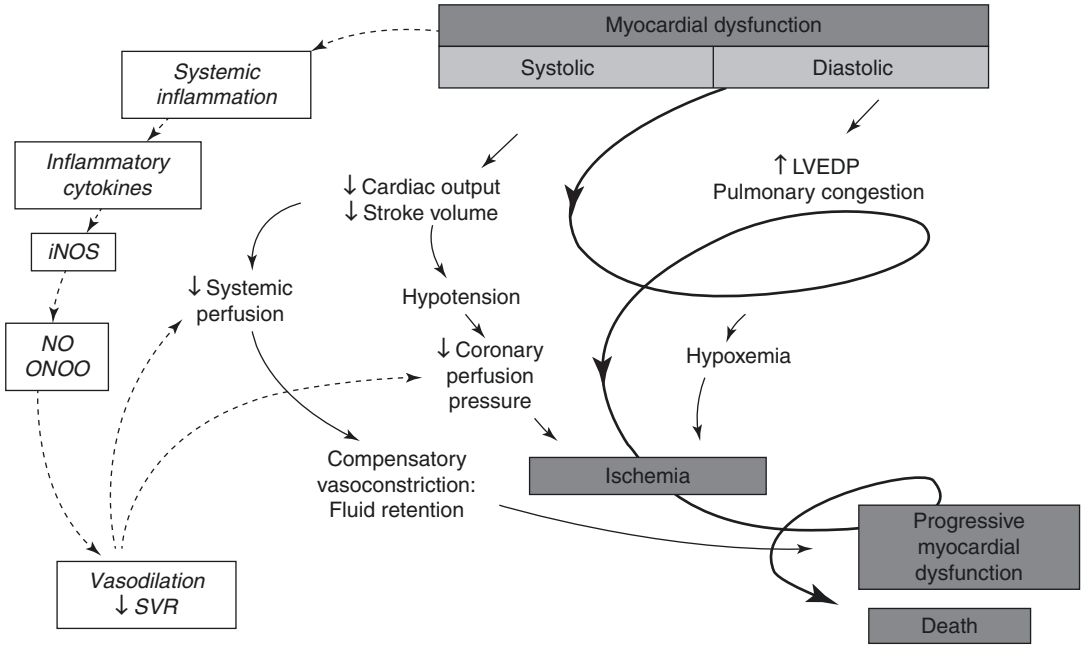

Fig. 21.1 Expansion of the pathophysiological paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. LVEDP left ventricular end-diastolic pressure; NO nitric oxide; iNOS inducible nitric oxide synthase; ONOO− peroxynitrite; SVR systemic vascular resistance. (Reprinted with permission from Hochman and Ohman [26])

(Fig. 21.1). It has been postulated that a systemic inflammatory response-like syndrome with a low SVR may be encountered in up to one-fifth of patients with acute myocardial infarction complicated by CS [11].

The clinical presentation can be utilized to risk-stratify patients with acute myocardial infarction complicated by CS. Killip described a case series of 250 patients presenting to an academic university intensive care unit with myocardial infarction [12]. He divided the patients into four classes according to the clinical presentation. Class I had no clinical signs of heart failure; class II presented with basilar rales and/or S3 gallop and/or elevated jugular venous pressure; class III had frank pulmonary edema; and class IV had cardiogenic shock. Reported mortality was 6%, 17%, 38%, and 67% for each class, respectively.

Current mortality with reperfusion therapy is dramatically lower than that observed in the original observation. However, Killip Class II, III, and IV continue to identify a high-risk subset of patients.

Therapeutic measures for CS often need to be implemented before invasive hemodynamic data are available. The clinical presentation may guide the most effective therapy. For example, patients with a clinical presentation consistent with myocardial infarction require urgent revascularization. A profile consistent with left ventricular failure may require inotropic or vasoactive agents and/or mechanical circulatory support in the form of an intra-aortic balloon pump, percutaneous left ventricular assist device, or extracorporeal membrane oxygenation. Patients with findings consistent with right ventricular infarction may require rapid fluid resuscitation and/or percutaneous right ventricular assist device placement.

Case 2: Hypovolemic Shock

A 25-year-old male patient presents shortly after a gunshot wound to the abdomen. He has experienced profound bleeding. He is tachycardic, hypotensive, and confused. Neck veins are

flat and lung fields are clear. The mucus membranes and skin are dry. Extremities are cool and clammy. He has a large drop in blood pressure and is more tachycardic when changing from supine to standing position.

The second case describes a patient with hypovolemic shock related to traumatic hemorrhage. Hypovolemic shock is characterized by inadequate intravascular volume. Etiologies are generally related to hemorrhage, plasma extravasation, or fluid loss (see Table 21.1). Hemorrhagic etiologies include trauma, gastrointestinal bleeding, ruptured hematoma, hemorrhagic pancreatitis, fracture, and ruptured abdominal aortic aneurysm. Etiologies related to plasma extravasation include systemic inflammatory response, major surgery, and severe pancreatitis. Fluid loss may be due to severe burns, emesis, diarrhea, diaphoresis, other insensible losses, and inadequate oral intake.

Hypotension, tachycardia, confusion, oliguria, and cold extremities typically characterize the clinical presentation of hypovolemic shock. Cardiac output generally falls as a result of decreased ventricular preload. Compensatory tachycardia and an increase in SVR, mediated by peripheral vasoconstriction, occur in an effort to improve tissue perfusion. Increased sympathetic activity may cause narrow pulse pressure and diaphoresis. Peripheral vasoconstriction results in cool, mottled, and cyanotic extremities.

The clinical history will generally suggest the underlying etiology. However, clinical findings may overlap with cardiogenic shock. A key difference is that the intracardiac filling pressure is adequate or elevated (PCWP greater than 15 mmHg) in CS, whereas it is generally low in hypovolemic shock due to inadequate intravascular volume. In hypovolemic shock, the lung fields are generally clear, and there is no evidence of jugular venous distension or peripheral edema.

The physical diagnosis of hypovolemia has been systematically reviewed in adults [13]. The most helpful physical findings include severe postural dizziness or a postural pulse increment of at least 30 beats/min, a systolic pressure decrement of at least 20 mmHg, or a diastolic pressure decrement of at least 10 mmHg for measurements obtained 2 min after assuming an upright posture (orthostasis). Supine hypotension and tachycardia were frequently absent, even after up to 1150 mL of blood loss [13]. In patients with vomiting, diarrhea, or decreased oral intake, the presence of a dry axilla supports the diagnosis of hypovolemia. In adults, the capillary refill time and poor skin turgor have no proven diagnostic value.

Case 3: Distributive Shock

An 80-year-old female with recurrent urinary tract infection presents with fever, tachycardia, hypotension, decreased urine output, and confusion. She is diaphoretic and has foul smelling urine. Her neck veins are flat and the lung fields are clear. The extremities are warm and hyperemic. Capillary refill is brisk. Her hypotension does not improve despite aggressive fluid resuscitation.

This third case describes a patient with distributive shock related to severe sepsis. Inappropriate vasodilation, decreased SVR, hypotension, and poor tissue oxygenation characterize distributive shock. Etiologies of distributive shock include systemic inflammatory response syndrome, severe sepsis, bacterial toxins (e.g., staphylococcal toxic shock), anaphylaxis, adrenal insufficiency, myxedema coma, neurogenic insult, post-resuscitation syndrome, and post-cardiopulmonary bypass (see Table 21.1).

Septic shock is the most common presentation of distributive shock. Septic shock is defined by sepsis-induced hypotension that persists despite adequate fluid resuscitation (20–30 mL/kg starch or 40–60 mL/kg saline or PCWP 12–20 mmHg) [14].

Clinical presentations of distributive shock vary by etiology but are generally characterized by tachycardia, hypotension, oliguria, confusion, and warm, well-perfused extremities. Compensatory tachycardia, oliguria, and confusion are manifestations of poor tissue perfusion. Warm and hyperemic extremities with brisk capillary refill time are the result of inappropriate

vasodilatation and decreased SVR. The cardiac output is typically elevated in distributive shock and may manifest as bounding pulses. The lungs are typically clear, and there is no jugular venous distension or peripheral edema.

Patients with severe sepsis and shock may have fever or hypothermia, diaphoresis, and rigors. Findings associated with an infectious process (e.g., pneumonia) may be present. Tachypnea is common and occurs in an effort to compensate for severe metabolic acidosis caused by elevated lactate. Hoarseness, stridor, wheezing, pruritus, flushing, hives, and abdominal pain may accompany anaphylactic shock. Hypothermia, hypoventilation, and somnolence are associated with myxedema coma (severe hypothyroidism). Profound orthostatic hypotension and skin hyperpigmentation may be presenting signs of adrenal insufficiency. Although most patients with distributive shock present with tachycardia, patients with neurogenic shock may have bradycardia due to sympathetic denervation.

Case 4: Obstructive Shock

A 65-year-old female patient with metastatic breast cancer presents with dyspnea and palpitations. Although she is tachycardic, her heart sounds seem distant. Her initial blood pressure is 80/50 mmHg. Her internal jugular vein is distended, but her breath sounds are clear to auscultation. Careful examination of her blood pressure demonstrates an exaggerated dissipation of Korotkoff sounds during inspiration. She has no leg edema and has not observed any recent fever, bleeding, vomiting, or diarrhea. Chest radiography revealed cardiomegaly with no significant parenchymal disease.

The fourth case is representative of obstructive shock due to cardiac tamponade. In the setting of breast cancer, pericardial metastasis is suspected. Classic findings of cardiac tamponade include distant, muffled heart sounds, jugular venous distension, and hypotension. Ventricular interdependence, manifested by an inspiratory drop in blood pressure (*pulses paradoxus*) greater than 10 mmHg, may also be observed.

Other causes of obstructive shock include tension pneumothorax and pulmonary embolism. Tension pneumothorax may be accompanied by dyspnea with tympany and decreased breath sounds in the affected hemithorax. Pulmonary embolism may be associated with cough, hemoptysis, and limb asymmetry in the context of prolonged immobilization. Both may present with desaturation.

Diagnostic Evaluation of Shock

The etiology of shock can often be determined using data acquired from the medical history, physical examination, basic laboratory evaluation, and radiographic findings. However, additional diagnostic tests may be needed in the optimal assessment and management of shock. Intra-arterial pressure monitoring, echocardiography, and pulmonary artery catheterization are frequently utilized diagnostic modalities.

Brachial cuff measurements are often inaccurate in states of shock. Intra-arterial pressure monitoring provides a continuous assessment of the blood pressure and heart rate and allows for safe and effective titration of vasoactive medications.. Additional data may also be obtained by assessing the arterial waveform. Further, the pulse pressure (systolic blood pressure − diastolic blood pressure) may be helpful in differentiating various shock states.

The 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with ST segment elevation myocardial infarction state that intra-arterial pressure monitoring should be performed (class I indication) for severe hypotension (systemic arterial pressure less than 80 mmHg), during the administration of vasopressor and/or inotropic agents, and for cardiogenic shock [15]. Although the 2016 ACC/AHA guideline does not make any reference to intra-arterial pressure monitoring, it continues to be employed frequently for the same indications. Potential complications of intra-arterial pressure monitoring include pain, infection, hematoma, arterial obstruction, and arterial embolus.

Echocardiography is an invaluable tool in the assessment of shock. It may help determine the etiology of shock and guide management. Echocardiography can be utilized to assess left and right ventricular function and can detect tamponade, restrictive/constrictive physiology, severe valvular regurgitation or valvular stenosis, ventricular septal or free wall rupture, and proximal aortic dissection. Echocardiographic findings of a clot-in-transit and right ventricular dysfunction may suggest the presence of a hemodynamically significant pulmonary embolism.

Echocardiography using agitated saline is a sensitive diagnostic modality for detecting intracardiac and pulmonary vascular shunting. Hemodynamic parameters such as central venous pressure, pulmonary artery pressure, and left ventricular end-diastolic pressure can be estimated using conventional echocardiographic methods.

The pulmonary artery catheter can be valuable in determining the etiology of shock and may help in guiding management. Data obtained from the pulmonary artery catheter includes central venous pressure, right atrial pressure, right ventricular pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure. Obtaining a mixed venous oxygen saturation permits the calculation of the cardiac output, cardiac index, and systemic venous resistance. Furthermore, important diagnostic information may also be determined by analyzing the pressure waveforms.

The hemodynamic data gathered with a pulmonary artery catheter can be utilized to titrate vasopressor therapy, assess hemodynamic effects of changes in mechanical ventilation (e.g., positive end expiratory pressure), and guide fluid resuscitation. In addition, the data may help differentiate between cardiogenic and noncardiogenic pulmonary edema when a trial of diuretic and/or vasodilator therapy has failed.

Pulmonary artery catheterization may aid in determining if pericardial tamponade is present when clinical assessment is inconclusive and echocardiography is not available. Findings of cardiac tamponade include diastolic equalization of pressures and blunted y descent of the arterial waveform (see Chap. 15). Other uses of pulmonary artery catheterization include assessment of valvular heart disease severity and reversibility of pulmonary vasoconstriction in patients being considered for heart transplant. An oximetry run may also be performed using a pulmonary artery catheter. This is important in the investigation of cardiac shunts, which may occur as a complication of myocardial infarction.

Despite its potential advantages, pulmonary artery catheterization has not been shown to broadly improve patient outcomes. Its use is therefore controversial and is not favored in some centers. Whether the lack of benefit on important outcomes is a result of the severity of illness in the patients for whom the use of this tool is contemplated, or a result of incorrect interpretation and use of the data obtained, is a debated topic. It is important to note that the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial showed no significant difference in endpoints of mortality and days out of hospital in the management of congestive heart failure refractory to standard medical therapy [16]. However, this trial demonstrated that the use of the pulmonary artery catheter for this group of patients was safe.

In ESCAPE, the addition of pulmonary artery catheterization to careful clinical assessment was associated with a higher frequency of adverse events but did not affect overall mortality and hospitalization. Adverse events included implantable cardioverter-defibrillator firing, cardiogenic shock, ischemia/angina, pulmonary artery catheter infection, myocardial infarction, stroke or ischemic attack, cardiac arrest, and infection. The only individual event that was statistically different (p value < 0.05) between the groups was pulmonary artery catheter infection (p value $= 0.03$).

The external validity of the findings of the ESCAPE trial has been debated [17]. Many of the registry patients did not get randomized into the trial because pulmonary artery catheterization was deemed necessary for management by a study investigator. Subsequently, only patients with clinical equipoise in whom physicians were comfortable managing heart failure decompensation with or without hemodynamic monitoring were included in the study. As such, the study is not applicable to the critically ill heart failure

patients who are often considered for pulmonary artery catheterization.

The routine use of pulmonary artery catheterization in intensive care units is also controversial. A 2005 meta-analysis of 13 randomized trials including over 5000 critically ill patients showed that the use of pulmonary artery catheters was not associated with benefit or increased mortality [18]. However, the meta-analysis included patients who were critically ill from a wide variety of causes.

There have not been any randomized studies aimed at directly evaluating the utility of pulmonary artery catheters in patients presenting with CS. There were 2968 patients with cardiogenic shock enrolled in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial. Mortality among patients (n = 995) managed with PA catheters (45.2%) was less than that among patients (n = 1406) not managed with PA catheters (63.4%) [19].

A potential limitation of pulmonary artery catheter hemodynamic monitoring is that many physicians do not know how to correctly interpret findings from the device [20]. A 31-question multiple-choice exam was administered to 496 medical doctors at 13 different institutions to assess their knowledge and understanding of the use of the pulmonary artery catheter and interpretation of data derived from it. The examination was given unannounced at general meetings in the departments of medicine, anesthesiology, and surgery. The mean score was 67%; almost half of the responders (47%) could not read a pulmonary capillary wedge pressure from a clear tracing.

The 2013 ACCF/AHA guidelines for the management of heart failure provide guidance for appropriate pulmonary catheter use in hemodynamic assessment [21]. It is a class I indication to use pulmonary artery catheter monitoring to guide therapy in patients with respiratory distress or clinical evidence of impaired perfusion when intracardiac filling pressures cannot be determined by clinical assessment. The guidelines also state that pulmonary artery catheters "can be" useful (class IIa indication) in acute heart failure with persistent symptoms despite seemingly appropriate adjustments of standard therapies if fluid status, perfusion, systemic vascular resistance, or pulmonary vascular resistance is uncertain. Similarly, pulmonary artery catheters can be useful in the setting of renal dysfunction, vasoactive agent use, or mechanical circulatory support. The 2017 ACC/AHA/HFSA Focused Update of the aforementioned guideline did not provide additional guidance on the use of pulmonary artery catheterization.

Routine invasive monitoring of hemodynamics is not recommended in normotensive patients with acute decompensated heart failure responding appropriately to therapy [21]. Potential complications of pulmonary artery catheter use include infection, right bundle branch block, ventricular tachycardia, pulmonary artery rupture, and pulmonary infarction. Over time, pulmonary artery catheters tend to soften and migrate distally, leading to spontaneous wedging even when the balloon tip is not inflated.

Hemodynamic Assessment of Shock

A fundamental understanding of the hemodynamics of shock is critically important. The etiology of shock may not be evident despite the data acquired from the medical history, physical examination, basic laboratory evaluation, and radiographic findings. Hemodynamic data can help diagnose the correct etiology of shock and guide appropriate management.

Systemic tissue perfusion (blood pressure) is determined by the cardiac output (CO) and SVR. Similar to Ohm's law, whereas electrical current through a circuit is directly proportional to the potential difference across the circuit and inversely proportional to the resistance, cardiac output (CO) is directly proportional to the blood pressure difference across the systemic circulation (mean arterial pressure [MAP] − mean right atrial pressure [mean RAP]) and inversely proportional to SVR. Therefore [CO = (MAP − mean RAP)/SVR].

Cardiac output can be measured with a pulmonary artery catheter by utilizing either the Fick method or thermodilution technique (see

Table 21.2 Hemodynamic patterns classically associated with different categories of shock

	RA (mmHg)	RV (mmHg)	PA (mmHg)	PCWP (mmHg)	CI (L/min/kg/m^2)	PP (mmHg)	HR (bpm)	SVR (dynes)	SVO_2 (%)
Normal values	<6	<25/0–12	<25/0–12	<6–12	>2.5	40–50	60–100	800–1600	70
Cardiogenic	↑	↑	↑	↑ (>15)[a]	↓ (<2.2)	↑↓	↑	↑[b]	↓
Distributive	↑↓	↑↓	↑↓	↑↓	↑[c]	↑	↑[d]	↓	↑↓[e]
Hypovolemic	↓	↓	↓	↓	↓	↓	↑	↑	↓

RA right atrium, *RV* right ventricle, *PA* pulmonary artery, *PCWP* pulmonary capillary wedge pressure, *CI* cardiac index, *PP* pulse pressure, *HR* heart rate, *SVR* systemic vascular resistance, *SVO_2* mixed venous oxygen saturation

[a]In the SHOCK trial, 28% of patients had no auscultatory or radiographic evidence of pulmonary edema suggestive of elevated PCWP

[b]A systemic inflammatory response-like syndrome with a low SVR may be encountered in up to one-fifth of patients with acute myocardial infarction complicated by cardiogenic shock

[c]Cardiac output can be reduced in distributive shock due to myopathic processes such as severe acidosis or when preload is decreased because of inadequate intravascular volume

[d]Patients with neurogenic shock may have bradycardia due to sympathetic denervation

[e]SVO_2 is generally increased in sepsis due to poor oxygen utilization

Chap. 4). Different categories of shock can be discriminated using the calculated cardiac output. Whereas cardiac output is low in cardiogenic shock and hypovolemic shock, it is generally elevated in distributive shock (Table 21.2). However, cardiac output can also be reduced in distributive shock due to myopathic processes such as severe acidosis or when preload is decreased because of inadequate intravascular volume.

Systemic vascular resistance (SVR) can be calculated if the blood pressure, right atrial pressure, and cardiac output are known. The drop in arterial pressure across the systemic circulation divided by cardiac output is equal to SVR. [SVR = [MAP − mean RAP]/CO]. The units for SVR are mmHg/mL/m^2 (Woods units) and are typically multiplied by 80 to convert to dynes/cm^5 (dyn). Pulmonary vascular resistance can be calculated by substituting the drop in pressure across the systemic circulation with that of the pulmonary circulation (mean pulmonary artery pressure − mean pulmonary capillary wedge pressure). SVR is reduced in distributive shock but is generally elevated in CS and hypovolemic shock [22].

Mixed venous oxygen concentration (SVO_2) may help differentiate shock from its different categories. In distributive shock related to sepsis, SVO_2 is generally elevated because the mitochondria are unable to utilize oxygen appropriately. As a result, there is a higher than expected venous oxygen saturation. In other states of shock, SVO_2 is generally low.

Elevated pulmonary capillary wedge pressure (greater than 15 mmHg) has classically been used to distinguish CS from noncardiogenic causes of shock. However, in the SHOCK trial, 28% of patients had no auscultatory or radiographic evidence of pulmonary edema to suggest elevated PCWP [8]. Severe sepsis can cause myocardial depression and may elevate left-sided pressures as well. CS related to right ventricular infarction may be associated with marked hypotension, low cardiac output, and shock despite a normal pulmonary capillary wedge pressure.

The intra-arterial pressure waveform can help differentiate various shock etiologies. Pulse pressure equals the difference between systolic and diastolic blood pressure and is normally 40–50 mmHg (Fig. 21.2). The pulse pressure is a reflection of the stroke volume and the strength of each ventricular contraction.

In patients with CS related to left ventricular failure, the pulse pressure is reduced (see Fig. 21.3). A narrow pulse pressure, defined as a pulse pressure <25% of the systolic blood pressure, has a sensitivity and specificity of 91% and 83% for a cardiac index of <2.2 L/min/m^2 [23]. Other causes of narrow pulse pressure include profound intravascular volume loss, cardiac tamponade, and aortic stenosis.

Fig. 21.2 Normal aortic waveform

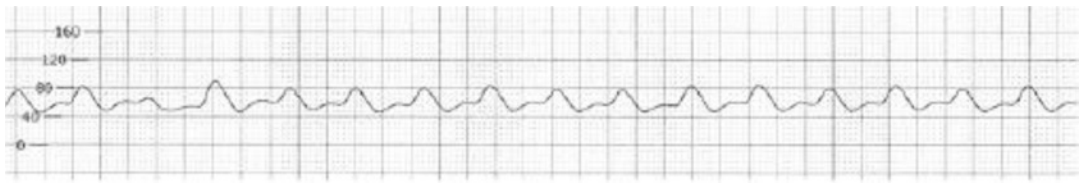

Fig. 21.3 Example of narrow pulse pressure in a patient with cardiogenic shock

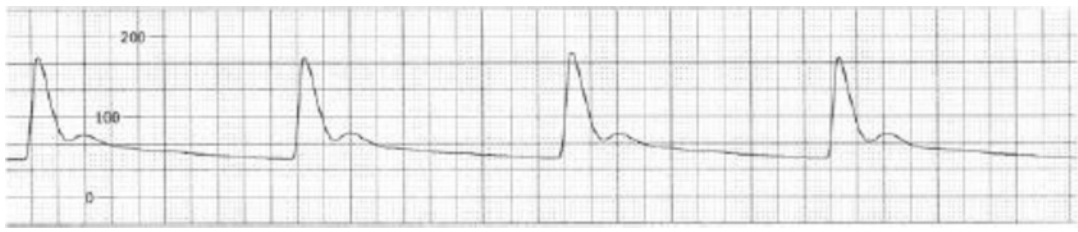

Fig. 21.4 Example of wide pulse pressure in a patient with complete heart block

Fig. 21.5 Example of narrow pulse width in a patient with acute aortic dissection

Widened pulse pressure is a physiological response to exercise and can be seen pathologically with atherosclerosis, aortic insufficiency, complete heart block, aortic dissection, arteriovenous fistula, fever, anemia, thyrotoxicosis, pregnancy, and elevated intracranial pressure (see Fig. 21.4).

The pulse width is also a reflection of stroke volume. Patients in shock with normal or hypercontractile ventricles often have aortic waveforms with narrow pulse widths but normal pulse pressures. Both noncardiac (e.g., anaphylaxis and severe sepsis) and cardiac (e.g., tamponade, acute mitral regurgitation, post-myocardial infarction ventricular septal defect, and aortic dissection) etiologies of shock may be associated with narrow pulse widths. A narrow pulse has a spike appearance with a dicrotic notch that appears low (see Fig. 21.5).

Pulsus alternans occurs when there is an alternating rise and fall in systolic pressure

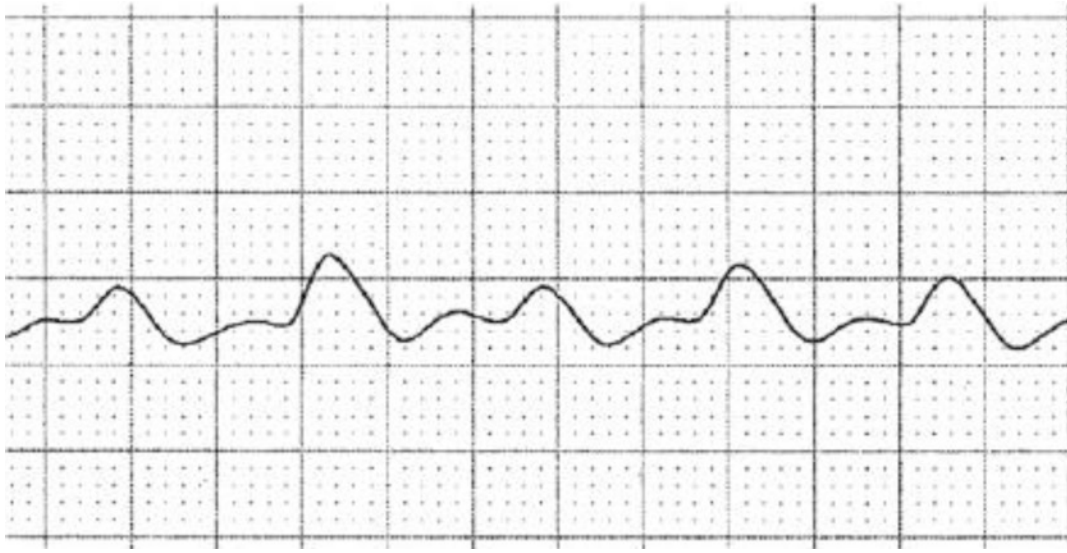

Fig. 21.6 Example of pulses alternans in a patient with advanced left ventricular failure

from beat to beat despite a regular rhythm (see Fig. 21.6). *Pulsus alternans* implies severe myocardial dysfunction and is most often seen in left ventricular failure. It may also occur in association with severe aortic stenosis and severe coronary artery disease. *Pulsus alternans* is thought to be due to variability in myocardial contractility on a beat-to-beat basis because of abnormal intracellular calcium cycling [24].

Pulmonary artery catheter intravascular waveform tracings can also help differentiate various etiologies of shock. Large *v*-waves on the pulmonary capillary wedge pressure tracing suggest shock from acute, severe mitral regurgitation. Likewise, large *v*-waves may be seen on the RAP tracing with severe tricuspid regurgitation. Cannon *a*-waves suggest complete heart block. Elevated and equalized diastolic pressures with loss of y descent suggest cardiac tamponade. Markedly elevated right atrial and right ventricular diastolic pressures and a normal pulmonary capillary wedge pressure suggest CS related to right ventricular infarction. An increase in right-sided pressures with inspiration (Kussmaul's sign) may be observed in right ventricular infarction due to decreased ventricular compliance.

Data obtained from the pulmonary artery catheter may reveal complications of acute myocardial infarction that occur in association with CS. For example, an oxygen step-up upon advancing the catheter from the right atrium to the right ventricle suggests left to right shunting related to ventricular septal rupture.

Arterial hypoxia may complicate shock. Evaluation of hypoxia begins with calculation of the alveolar-arterial (A-a) oxygen gradient. A normal A-a gradient equals 4 + (age/4) or 2.5 + (0.21 × age). Alveolar oxygen is calculated using the alveolar air equation: partial pressure alveolar oxygen (P_AO_2) = oxygen concentration (F_iO_2) × (barometric pressure at sea level (760 mmHg) − partial pressure water vapor (43 mmHg)) − (partial pressure carbon dioxide (P_ACO_2)/respiratory exchange ratio (0.8)). [$P_AO_2 = (F_iO_2 \times (760 - 43)) - (P_ACO_2/0.8)$]. Arterial partial pressure of oxygen is measured using conventional blood gas analysis.

If the A-a gradient is normal and P_aCO_2 is increased, hypoventilation is the suggested cause of hypoxia. With an elevated A-a gradient, proceed to check the mixed venous oxygen saturation. A low mixed venous oxygen saturation suggests hypermetabolism, anemia, or decreased cardiac output. If mixed venous oxygen is normal, administer 100% oxygen. If hypoxia corrects, ventilation/perfusion mismatch is suggested. Ventilation/perfusion mismatch

is caused by airway (e.g., asthma and chronic obstructive pulmonary disease), alveolar (e.g., pneumonia and congestive heart failure), and vascular (e.g., pulmonary embolism) phenomenon. Shunting is suggested if hypoxia does not correct with oxygen supplementation and may be physiological or vascular. Physiological shunting occurs with alveolar collapse (e.g., atelectasis) or decreased alveolar filling (e.g., pneumonia and congestive heart failure). Vascular shunting occurs with right-to-left intracardiac shunts (e.g., atrial or ventricular septal defect) and intrapulmonary shunts (e.g., arteriovenous malformation and hepatopulmonary syndrome).

Hemodynamic data can also be utilized to risk-stratify patients with acute myocardial infarction complicated by CS. In the SHOCK trial, cardiac power (cardiac power = MAP × CO/451) was the strongest independent correlate of in-hospital mortality in patients with CS [25].

Pearls of Assessment

There can be considerable overlap in the clinical presentation of the various categories of shock. Although classically associated with vasoconstriction and cold extremities, patients with CS can present with peripheral vasodilation and warm extremities. Indeed, in the SHOCK trial, the average SVR was not elevated, and the range of values was wide, suggesting that compensatory vasoconstriction is not universal [8].

Patients with distributive shock typically have increased cardiac output. However, in sepsis, depressed myocardial function may occur due to metabolic acidosis and other factors. Acidemia is detrimental to LV contractility and may result from decreased clearance of lactate by the liver, kidneys, and skeletal muscle, further compounded by an anaerobic metabolic state. Inadequate intravascular volume may complicate distributive shock and result in decreased cardiac preload and cardiac output.

Review Questions

1. Which of the following types of shock is typically associated with a high mixed venous oxygenation saturation?
   (a) Septic
   (b) Cardiogenic
   (c) Hypovolemic
   (d) Anaphylactic
   - Answer: (a) In severe sepsis, the mitochondrial respiratory chain does not utilize oxygen effectively. As a result there is more oxygen than expected in the venous blood.
2. Which of the following hemodynamic profiles is most consistent with cardiogenic shock?
   (a) Systolic blood pressure 120 mmHg, pulmonary capillary wedge pressure 10 mmHg, cardiac index 3.5 L/min/m^2, systemic vascular resistance (SVR) 1000 dyn, and mixed venous oxygen 75%
   (b) Systolic blood pressure 80 mmHg, pulmonary capillary wedge pressure 5 mmHg, cardiac index 1.3 L/min/m^2, SVR 1800 dyn, and mixed venous oxygen 60%
   (c) Systolic blood pressure 80 mmHg, pulmonary capillary wedge pressure 10 mmHg, cardiac index 3.5 L/min/m^2, SVR 600 dyn, and mixed venous oxygen 85%
   (d) Systolic blood pressure 80 mmHg, pulmonary capillary wedge pressure 20 mmHg, cardiac index 1.3 L/min/m^2, SVR 1800 dyn, and mixed venous oxygen 60%
   - Answer: (d) Hemodynamic criteria typically associated with cardiogenic shock include systolic blood pressure less than 90 mmHg for at least 30 min or need for vasopressor or intra-aortic balloon support to maintain systolic blood pressure greater than 90 mmHg, pulmonary capillary wedge pressure greater than 15 mmHg, and cardiac index less than 2.2 L/min/kg/m^2 [7].
3. An 85-year-old male presents with hypotension, oliguria, and confusion. An electrocardiogram reveals inferior ST segment elevation. A pulmonary artery catheter is inserted, and the hemodynamic parameters are consistent with cardiogenic shock. His lung fields are clear, and the jugular venous pulse is elevated.

A transthoracic echocardiogram reveals normal left ventricular function. What is the cause of this patient's clinical presentation?
(a) Right ventricular infarct
(b) Ventricular septal rupture
(c) Acute mitral regurgitation
(d) Tamponade
- Answer: (a) The classic findings of right ventricular infarction are hypotension, jugular venous distension, and clear lung fields.

4. An 85-year-old female presents 1 week after developing severe chest pain. She has dyspnea with minimal activity. She is hypotensive and has pulmonary rales. An electrocardiogram reveals anterior *q*-waves. Troponin is elevated but CK-MB is within normal limits. Other laboratory analysis reveals renal and liver injury. Pulmonary artery catheter hemodynamic findings are consistent with cardiogenic shock. An oxygen saturation run reveals an increased oxygen gradient upon advancing from the right atria to the right ventricle. Which complication of acute myocardial infarction is the cause of this patient's shock?
(a) Ventricular free wall rupture
(b) Ventricular septal rupture
(c) Acute mitral regurgitation
(d) Tamponade
- Answer: (b) Ventricular septal rupture may complicate myocardial infarction. An oxygen step-up upon advancing from the right atria to the right ventricle is typical.

Acknowledgments We would like to thank Venu Menon for his contribution to the previous edition of this chapter.

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Intracoronary Hemodynamics

22

James E. Harvey and Stephen G. Ellis

Selective coronary angiography is the gold standard for evaluating the presence and extent of epicardial coronary artery disease. Despite advances in fluoroscopic imaging and catheterization techniques, the evaluation of the intermediate coronary stenosis (luminal diameter narrowing between 40% and 70%) remains a challenge for invasive cardiologists secondary to multiple issues. Angiography provides only a two-dimensional projection of the arterial lumen along the length of the vessel. Vessel characteristics (e.g., significant angulation and tortuosity) and limitations related to image acquisition (e.g., vessel overlap, inability to obtain a true perpendicular projection of the lesion, and the visualization of a focal short stenosis) impair the accuracy of lesion severity assessment despite obtaining coronary angiograms in multiple fluoroscopic views. Studies comparing coronary angiography and postmortem histopathological analysis have demonstrated the discrepancy between angiographic and actual anatomic findings [1–3]. Significant intra- and interobserver variability is also a factor when determining the percent narrowing of a stenosis by angiography [4]. The application of quantitative coronary angiography (QCA) may minimize this discrepancy, but it does not eradicate the limitations of coronary angiography. Intravascular visualization techniques such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), augment anatomical analysis but do not necessarily provide information on the functional significance of a lesion. Thus, cardiologists have focused on physiologic assessment of a lesion to aid in management decisions. Noninvasive testing (i.e., stress testing) to determine objective evidence of ischemia is frequently conducted prior to performing coronary angiography and subsequent percutaneous coronary intervention (PCI). However, these studies are not always feasible nor are the results always reliable; therefore a physiologic method of evaluating an intermediate coronary lesion while in the catheterization suite is desirable.

Sensor-tipped 0.014″ diameter guidewires have been manufactured to accurately and safely measure flow velocities or pressure within a coronary artery. By employing this technology, three methods [coronary flow reserve (CFR), fractional flow reserve (FFR), and instantaneous wave-free ratio (iFR)] have been developed to evaluate the physiologic or functional significance of coronary lesions in the cardiac catheterization suite.

Case Vignette #1

A 58-year-old woman with history of diabetes mellitus (DM) and family history of premature CAD presents with a 7-month history of exertional chest

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3_22

discomfort. Exercise nuclear stress test revealed reversible perfusion defects in the apical anterior and anteroseptal wall and in the mid inferior wall. Coronary angiography revealed "normal coronary arteries" and intravenous infusion of ergonovine did not precipitate coronary vasospasm. Coronary flow reserve (CFR) of the left anterior descending artery was 1.2 consistent with severe microvascular dysfunction.

Coronary Flow Reserve (CFR)

CFR is defined as the ratio of mean blood velocity at maximal hyperemia to mean blood velocity at rest for a given coronary artery [5]. Developed in the 1970s, it is based on the principle that the volume of blood flow in a healthy coronary artery will increase with hyperemia to a greater extent than that of an artery with a physiologically significant stenosis (Fig. 22.1). Since blood flow as volume per time cannot be directly measured in the cardiac catheterization suite, blood velocity is measured as a surrogate because it is proportional to blood volume flow for a constant lumen area. CFR is assessed by placing a Doppler-tipped guide wire into a coronary artery distal to the epicardial stenosis in question. One then measures the flow velocities at rest and at maximal hyperemia. Hyperemia is pharmacologically induced typically by intravenous infusion of adenosine. The Doppler-derived CFR, which is inversely proportional to lesion severity [6], has been validated with good correlation to nuclear stress testing. A CFR value of ≤2.0 indicates a physiologically significant stenosis (Fig. 22.2) [7–10].

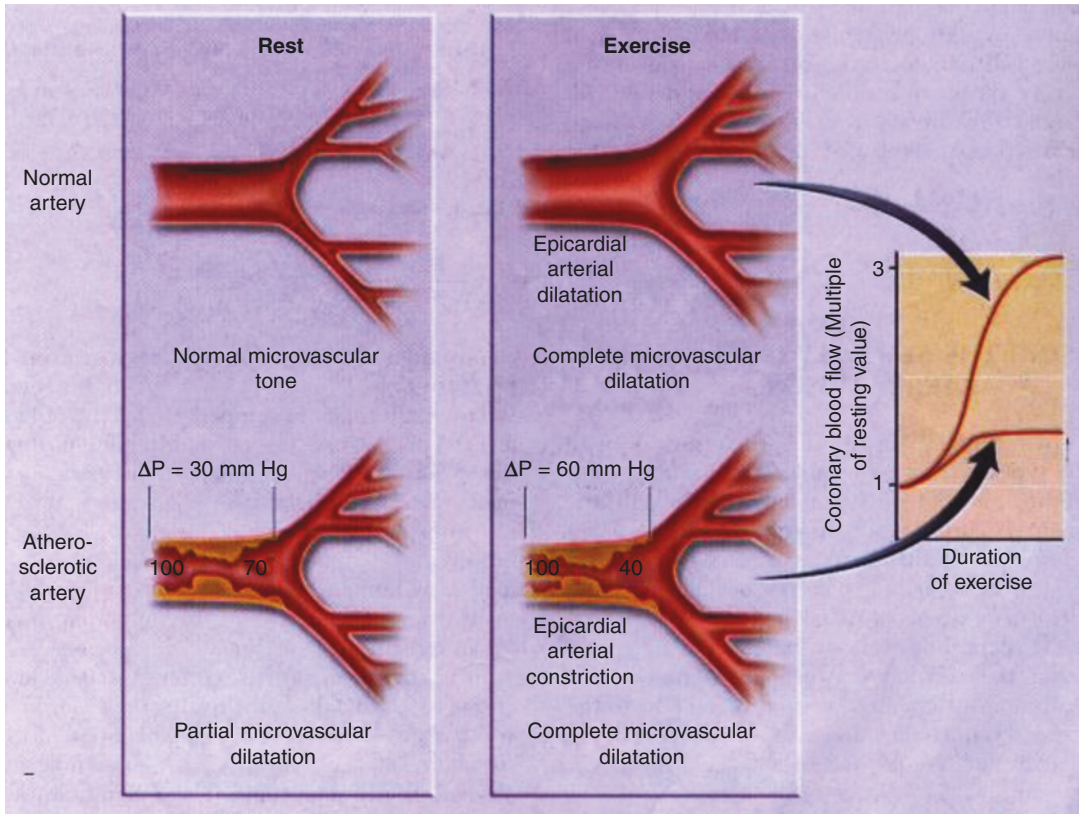

Fig. 22.1 Depiction of coronary blood flow at rest and at maximal hyperemia. A normal coronary artery will have a larger increase in blood flow than a diseased artery with a hemodynamically significant stenosis. By measuring the blood velocity or pressure proximal and distal to the stenosis, one can calculate the relative increase in blood flow or decrease in pressure caused by inducing maximal hyperemia

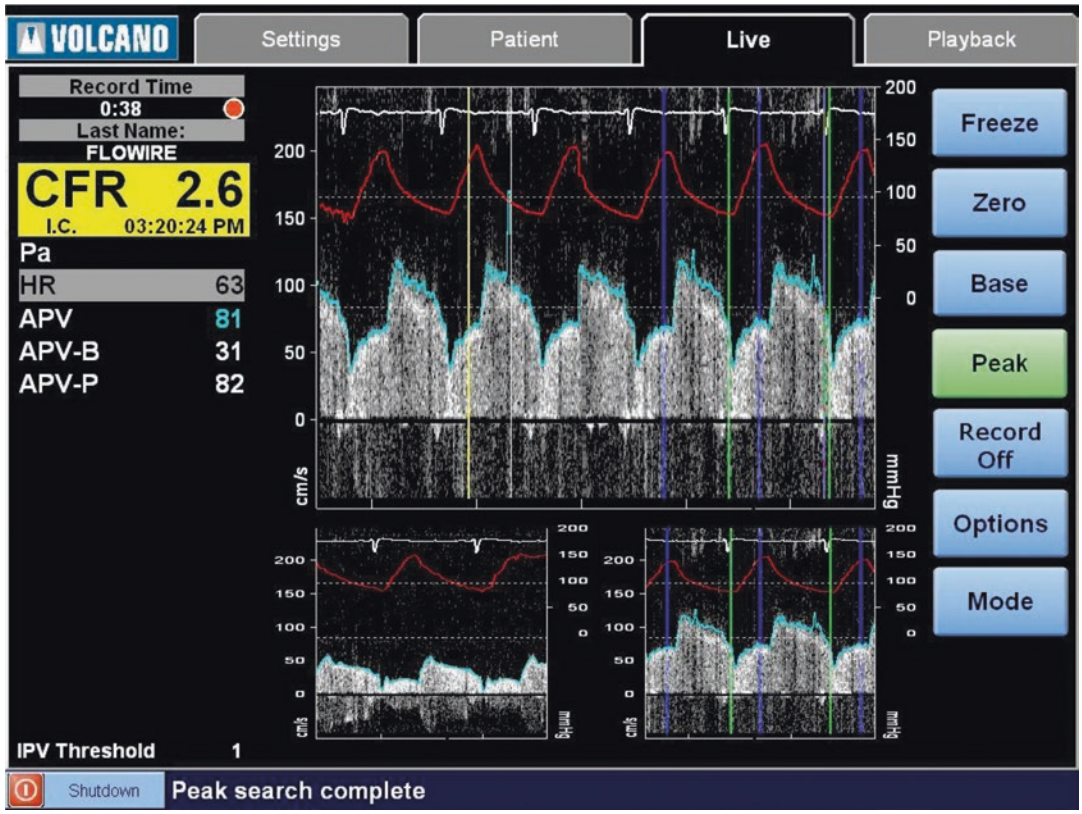

Fig. 22.2 A typical CFR display screen. Intracoronary Doppler blood flow velocity waveforms before intracoronary adenosine are shown on the small graph on the lower left portion of the display screen. Intracoronary Doppler blood flow velocity waveforms after intracoronary adenosine are shown on the small graph on the lower right portion of the display screen and on the large graph in the center of the display. CFR is the ratio of the average peak velocities before and after adenosine; here it is reported as 2.6 on the top left portion of the display. This is suggestive of normal microvascular function

Unfortunately, CFR is affected by both the severity of an epicardial stenosis and the extent of microvascular resistance. Microvascular resistance is influenced by common conditions such as diabetes mellitus, age, and ventricular hypertrophy. Each of these can significantly affect the CFR value regardless of the severity of epicardial stenosis [11–14]. In an effort to overcome this inherent limitation, the concept of relative CFR was developed. Relative CFR is determined by dividing the CFR of the diseased vessel by the CFR of another undiseased coronary vessel and accounts for the contribution of microvascular resistance to the CFR value. This improved the correlation in the detection of ischemia by stress myocardial perfusion imaging [15]. Use of this method requires increased time and risk of evaluating an additional vessel. Due to these inherent limitations of CFR and relative CFR, these modalities are now rarely used to evaluate the severity of an epicardial arterial stenosis. Instead, FFR has become the method of choice for determining the physiologic significance of an epicardial arterial stenosis.

Cardiac Syndrome X

Despite its limitations in the interrogation of epicardial stenoses, CFR is the modality of choice for evaluation of coronary artery microvascular dysfunction. Cardiac syndrome X, or angina with an abnormal cardiac stress test and angiographically normal coronary arteries, is an increasingly

recognized disorder with significant prognostic implications [16]. Diminished coronary flow velocity reserve in response to intracoronary adenosine, defined as a CFR ≤ 2.0, is suggestive of microvascular dysfunction and seen in up to 47% of patients with angina and no significant epicardial stenoses [17]. The patient described in *Clinical Vignette 1* has findings consistent with cardiac syndrome X. Patients with this condition have a rate of adverse cardiac events (myocardial infarction, congestive heart failure, stroke, and sudden cardiac death) of 2.5% per year [16].

Case Vignette 2

A 62-year-old man with past medical history of hypertension, hyperlipidemia, and cigarette smoking presents with 1 month of worsening exertional chest discomfort that radiates down his left arm. Left heart catheterization reveals a focal 70% stenosis in the proximal left circumflex artery (LCx) and a long 60% stenosis in the mid right coronary artery (RCA). A pressure sensor-tipped 0.014″ coronary wire was advanced down the LCx and FFR was performed with a value of 0.83. The pressure sensor-tipped 0.014″ coronary wire was withdrawn and then advanced down to the distal RCA. FFR was 0.72. Percutaneous coronary intervention (PCI) was performed on the mid RCA lesion. No PCI was performed on the LCx, but rather aggressive medical management was employed.

Fractional Flow Reserve (FFR)

FFR is a method to invasively assess the hemodynamic significance of an intermediate coronary stenosis while in the catheterization suite. It is defined as the ratio of the mean distal coronary artery pressure to the mean aortic pressure while at maximal hyperemia [18–20]. It is performed by advancing a 0.014″ pressure-sensor tipped coronary wire across an epicardial stenosis and simultaneously recording the pressure distal to the stenosis (via the coronary wire) and proximal to the stenosis (via the guide catheter) while at maximal hyperemia (Fig. 22.3). Adenosine is the pharmacologic agent typically used to achieve maximal hyperemia because of its safety profile and low cost; however, papaverine or dobutamine can also be used [21–23].

As opposed to CFR, FFR measurement is baseline independent of blood pressure, heart rate, prior infarction, or contribution of collateral circulation [20, 24]. A normal FFR value is 1, while a value of <0.75 is associated with provocable ischemia; this has been shown to correlate well with ischemia demonstrated on noninvasive stress testing [19, 20, 25, 26]. Mortality and adverse cardiovascular event (MACE) rates have been shown to be very low in patients with an FFR >0.75 [27, 28], and multiple studies have demonstrated that PCI can be safely deferred in such patients [19, 27, 29].

Multivessel CAD

FFR is "lesion specific" and can be used to assess intermediate lesions in patients with single-vessel or multivessel CAD. [30] This is particularly useful in clinical scenarios in which patients present with symptomatic CAD and are found to have multivessel disease with multiple intermediate stenoses. In this subset of patients, noninvasive stress testing can demonstrate "balanced ischemia," and thus interpretations of culprit lesions are often inaccurate. Because of this, it has become commonplace to perform multivessel PCI for complete revascularization in this group, although this approach is not proven to be associated with improved outcomes. It was hypothesized that utilization of FFR could aid in the better identification of culprit lesions and thus more appropriate management. To assess the utility of FFR in this group of patients, 1005 patients with multivessel coronary artery disease were randomized to PCI with drug-eluting stents of all stenoses ≥50% versus FFR-guided PCI of stenoses with a value ≤0.80. At 1 year, the rate of death, non-fatal myocardial infarction, and repeat revascularization was significantly lower in the FFR-guided group than in the angiography-guided group (13.2% versus 18.3%), and the FFR group received a significantly fewer number of stents [31]. Eighty percent of patients in both groups

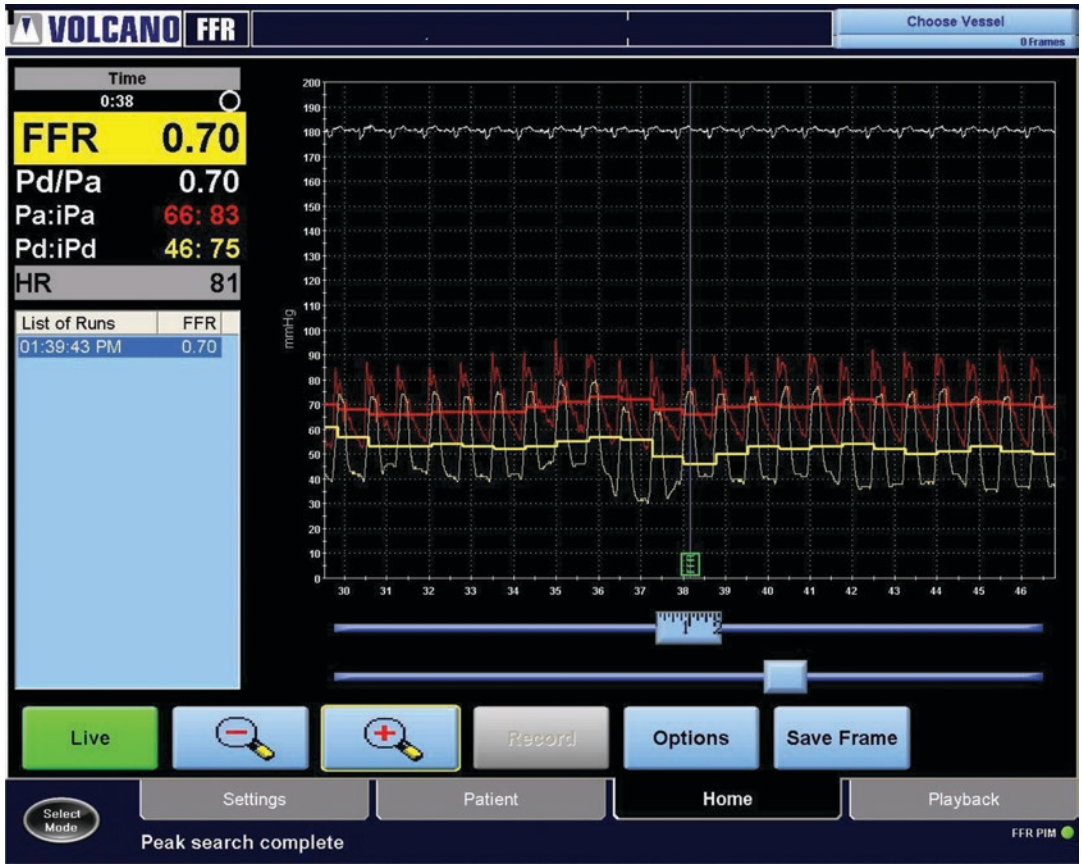

Fig. 22.3 A typical FFR measurement display screen. The aortic pressure is measured through the guiding catheter (red line). The pressure distal to the coronary lesion is measured by the 0.014″ pressure sensor-tipped wire (yellow line). In this example, the ratio of the distal coronary pressure to proximal coronary pressure is 0.70 and consistent with a hemodynamically significant stenosis

were angina-free at 1 year; however, the FFR-guided strategy was significantly less expensive than the angiography-guided group ($14,315 versus $16,700) [31].

Diffuse CAD or Long Coronary Lesions

Another subset of patients in which FFR can be helpful to guide the decision for PCI is in patients with diffuse disease or long coronary lesions. Similar to the assessment of multiple lesions in a single vessel, the pressure-sensor tipped wire can be slowly withdrawn from a vessel during maximal hyperemia and concomitant fluoroscopy can be used to precisely indicate where hemodynamically significant lesions exist. A gradual loss of pressure is consistent with diffuse disease and may suggest that PCI is technically less favorable and that possibly coronary artery bypass grafting (CABG) or medical management should be considered. However, an abrupt decrease in pressure is consistent with a focal hemodynamically significant stenosis and suggests that PCI may be more favorable [32, 33].

Left Main Coronary Disease and Bifurcation Lesions

Angiographic assessment of a left main coronary artery stenosis poses a great challenge for operators. As previously mentioned, factors such

as vessel overlap and unfavorable vessel orientation in relation to achievable camera angles often result in a suboptimal angiographic assessment of the vessel and significant intra-observer variability [34]. In this subset of patients, the use of FFR to further assess the vessel has been shown to be beneficial. One study demonstrated that patients with an intermediate left main stenosis and an FFR >0.75 had superb 3-year outcomes suggesting that PCI can safely be deferred in this subgroup [35].

Similar to left main coronary artery lesions, the evaluation of bifurcation lesions poses a significant challenge to the angiographer. By performing a separate FFR of each branch of the bifurcation, the hemodynamic significance of the lesions can be reliably determined and can assist the operator in deciding the most appropriate course of action for the patient [36].

Coronary Bypass Grafts

There is a paucity of data regarding the utility of FFR in assessing the physiologic significance of intermediate stenoses in a saphenous vein graft (SVG). A small study observed 10 veterans who had a stress myocardial perfusion imaging (MPI) study and were referred for PCI of an SVG stenosis. The sensitivity, specificity, and accuracy of FFR <0.75 for the detection of ischemia on stress MPI were 50%, 75%, and 70%, respectively. The authors concluded that the use of FFR to assess the physiologic significance of SVG lesions was feasible and provided acceptable sensitivity and specificity in comparison to stress MPI.

Acute Myocardial Infarction and Post Myocardial Infarction

While FFR does provide valuable information regarding intermediate coronary lesions in patients with stable and unstable angina, it should not be used in the acute phase of a myocardial infarction (MI). Animal studies have shown that even after reperfusion of an epicardial coronary occlusion, significant perivascular edema and capillary leukocyte plugging occur causing microvascular dysfunction and incomplete restoration of myocardial perfusion [37]. This has been shown to result in up to a 5% overestimation of FFR in humans [38]. Six days after an MI, however, FFR has been shown to be accurate and can be used to identify hemodynamically significant coronary lesions that supply areas with significant remaining ischemic but viable myocardium [39]. Myocardial perfusion SPECT imaging and FFR were performed in 57 patients who had sustained a myocardial infarction at least 6 days prior. Patients with demonstrable ischemia on SPECT imaging had a significantly lower FFR value than those who had evidence of scar without ischemia. When using a cutoff FFR value of 0.75, this demonstrated a sensitivity and specificity of 82% and 87%, respectively. However, when only truly positive and truly negative stress tests were considered, the sensitivity and specificity rose to 87% and 100%, respectively. When sensitivity and specificity were plotted against FFR, the value of FFR for which sensitivity and specificity were equal (88%) was 0.78; however, this value did not show a statistically significant difference in accuracy when compared to a cutoff value of 0.75.

FFR Post PCI

FFR has been shown to have significant prognostic value after PCI has been performed [40–42]. An FFR $\geq$ 0.90 is considered a successful result for balloon angioplasty, and an FFR $\geq$0.94 is successful post stent deployment. FFR values lower than these predict adverse outcomes.

Another area where FFR can be helpful is in the evaluation of jailed side branches after stenting. One study observing the feasibility of FFR for the assessment of jailed side branches showed that only 20% of lesions with QCA >75% had an FFR <0.75 and no lesion with QCA <75% had an FFR <0.75 [43]. These data suggest that most jailed side branches do not have hemodynamically significant stenoses and that PCI of

the daughter vessel can likely be safely deferred. This information is particularly useful given the higher rate of restenosis and stent thrombosis associated with dual stenting of bifurcation lesions [44].

Limitations of FFR

While several randomized controlled trials have demonstrated the clinical benefit of FFR-guided coronary revascularization, certain limitations do exist. FFR is not always accurate in AMI and will often show a falsely elevated value due to microvascular dysfunction. Also, animal studies have suggested that up to 16% of subjects undergoing FFR with adenosine or papaverine do not achieve maximal hyperemia [45]. This suggests that the physiologic significance of some lesions may be underestimated when using standard current vasodilator doses and that higher doses may be needed in order to achieve maximal hyperemia.

Instantaneous Wave-Free Ratio (iFR)

Recently, a new method of invasively assessing the severity of intermediate coronary stenoses has been introduced called the Instantaneous Wave-Free Ratio (iFR). Unlike FFR, coronary lesion assessment with iFR is performed during the resting, or non-hyperemic state, such that the administration of adenosine or other vasodilating agents is not necessary.

iFR is based on the finding that there are multiple distinct pressure waves that occur throughout the cardiac cycle that affect the instantaneous flow and pressure in a coronary artery. The relationship between intracoronary pressure and flow varies throughout the cardiac cycle and is different in the region proximal to a coronary stenosis than it is in the region distal to a coronary stenosis [46]. However, there is a period of time in diastole called the wave-free period (WFP) where there is an absence of new intracoronary pressure waves. During this period, the intracoronary pressure and the intracoronary flow decline in a parallel linear fashion and the microvascular resistance is significantly lower and more stable than that over the remainder of the cardiac cycle [47]. As such, this provides an ideal set of circumstances to allow for the assessment of the hemodynamic significance of a coronary stenosis in a non-hyperemic state.

Similar to FFR, iFR is performed by advancing a 0.014″ pressure-sensor tipped coronary wire across an epicardial stenosis and simultaneously recording the pressure distal to the stenosis (via the coronary wire) and proximal to the stenosis (via the guide catheter) (Fig. 22.3). However, unlike FFR, the iFR measurement is recorded during the instantaneous wave-free period of diastole. As such, this is done with the patient in the resting state without inducing hyperemia.

iFR and the Hybrid Approach

Initially, it was proposed that the use of iFR would complement that of FFR via a "hybrid approach" for the assessment of intermediate intracoronary lesions. With this strategy, iFR would be performed with the patient in the resting state. An iFR value of more than 0.93 would be considered not significant and revascularization would be deferred, while an iFR value of less than 0.86 would be considered ischemic and revascularization would be pursued. However, the values ranging between 0.86 and 0.93 would be considered in the "gray zone." In these patients, adenosine would be administered to calculate the FFR to determine whether or not the lesion should be revascularized. Utilization of this strategy was able to reduce the unnecessary use of adenosine in 60 to 70% of patients [48]. While this strategy provided a practical way to integrate the use of iFR into current clinical practice, two large randomized clinical trials have recently demonstrated the non-inferiority of iFR when compared to FFR such that utilization of the hybrid approach is no longer necessary.

iFR Versus FFR in Clinical Trials

Two large randomized clinical trials have demonstrated that the use of iFR with a single cut-off value of ≤0.89 to guide revascularization is a safe and feasible alternative to FFR. With a primary endpoint of MACE at 1 year, the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) trial was a double-blinded, controlled trial that randomized 2492 patients to iFR vs. FFR for guidance of coronary revascularization for intermediate lesions [49]. The primary endpoint occurred in 78 of 1148 patients (6.8%) in the iFR group and in 83 of 1182 patients (7.0%) in the FFR group ($p < 0.001$ for non-inferiority). In addition, the number of patients with adverse procedural symptoms or clinical signs was significantly lower in the iFR vs. FFR group (3.1% vs. 30.8%, respectively; $p < 0.001$) as was the median procedural time (40.5 min vs. 45.0 min; $p = 0.001$). Similarly, the Instantaneous Wave-free Ratio versus Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR SWEDEHEART) trial was an open-label randomized trial comparing iFR to FFR guided revascularization in patients presenting with stable angina or an acute coronary syndrome. Among the 2037 patients enrolled, the primary endpoint of MACE at 1 year occurred in 68 of the 1012 patients (6.7%) in the iFR group and in 61 of the 1007 patients (6.1%) in the FFR group ($p = 0.007$ for non-inferiority) [50]. The secondary endpoint of adverse procedural symptoms was again significantly higher in the FFR group with chest pain occurring in 68.3% of these patients compared to only 3.0% in the iFR group ($p < 0.001$).

Despite the demonstration of non-inferiority of iFR to FFR, the DEFINE-FLAIR and iFR SWEDEHEART trials demonstrated that the deferral of revascularization occurred more frequently in patients undergoing iFR as compared to those undergoing FFR [51]. In a pooled analysis of the two trials, revascularization was deferred in 1119 of the 2240 patients (50.0%) in the combined iFR groups and in 1015 of the 2246 patients (45.0%) in the combined FFR groups. Most importantly, the primary outcome between the groups was similarly low despite the higher rate of deferral in the pooled iFR group. As a result, the resultant healthcare costs for the iFR group were significantly lower than that of the FFR group.

In addition to the benefits of decreased adverse procedural symptoms, procedural time, and procedural cost of iFR vs. FFR, another potential benefit exists. In the hyperemic state such as that during FFR, coronary flow distal to a stenosis begins to decrease once the stenosis is 40–50% narrowed. As such, when multiple sequential intermediate lesions are present, the hyperemic flow through the proximal stenosis is affected by that of the distal stenosis and vice versa. Thus, it is not possible to determine the severity of an individual stenosis in the hyperemic state [52]. Conversely, coronary flow in the resting state is preserved distal to a coronary lesion until a critical stenosis develops [46]. As a result, there is minimal interaction between sequential intermediate stenoses. This allows for accurate assessment of individual lesion severity in the presence of tandem stenoses with slow pullback of the 0.014″ pressure-sensor tipped coronary wire.

Conclusions

CFR and relative CFR can be used to invasively measure flow velocity in a coronary artery and thus evaluate the hemodynamic significance of epicardial stenoses or microvascular dysfunction. Due to the limitations of CFR and increased time requirements and risk of relative CFR, these methods are now rarely used to assess epicardial lesions. However, CFR is still the test of choice to evaluate for microvascular dysfunction.

FFR is the current method of choice to evaluate the physiologic significance of an intermediate epicardial stenosis. Designated as "lesion specific," it compares the ratio of distal to proximal pressure across an epicardial stenosis. This technique adds important functional information that augments the anatomic information provided by angiography and intravascular imaging modalities (i.e., IVUS and OCT). It has been validated

to improve clinical outcomes when used to guide PCI in patients with single and multivessel CAD and also has been shown to provide useful information when examining a variety of coronary lesions. Furthermore, the use of FFR to guide PCI has been shown to significantly reduce the cost of treatment when compared to PCI guided by angiography alone.

iFR is the newest method of invasively assessing the severity of intermediate coronary stenoses. There are several advantages of iFR over FFR including decreased procedural time and cost and reduced adverse procedural symptoms. With the completion of two large randomized trials, the use of iFR is supported by more than twice the outcome data of that of FFR. Although slowly being adopted by practitioners worldwide, it is believed that iFR will become the method of choice for the evaluation of intermediate coronary stenoses in the years to come.

Review Questions

Questions 1–2

A 62-year-old patient undergoing left heart catheterization for chest pain has a 65% stenosis in a large first diagonal branch. While performing an FFR measurement, the aortic pressure is 102/77 mmHg and the distal diagonal branch mean pressure is 60 mmHg.

1. What is the FFR of the diagonal branch?
   A. 0.779
   B. 0.588
   C. 0.703
   D. Cannot be determined with the information provided.
2. Is PCI of the diagonal branch indicated?
   A. Yes. The FFR was >0.75
   B. No. The FFR was <0.75
   C. Yes. The FFR was <0.75
   D. It depends on the severity of the stenosis in the artery.

Questions 3–4

A 63-year-old hypertensive patient presents with 12 months of intermittent exertional chest pain. An exercise nuclear stress test performed at an outside hospital reported a reversible perfusion defect involving the anteroseptal and lateral walls; however, left heart catheterization revealed angiographically normal coronary arteries. You perform CFR of the LAD which gives a result of 1.6.

3. What is the diagnosis does this patient have?
   A. Non-cardiac chest pain.
   B. Cardiac chest pain due to missed coronary stenosis.
   C. False-positive nuclear stress test.
   D. Cardiac syndrome X.
4. What is the risk of this patient having an adverse cardiovascular event in the next year?
   A. 2.5%
   B. 1%
   C. 10%
   D. 15%
5. You perform a left heart catheterization on a 59-year-old man with worsening exertional angina. Coronary angiography of the RCA reveals a mid 60% stenosis followed by a distal 60% stenosis; the left main trunk, LAD, and LCx have mild disease. You perform iFR of the RCA with slow pullback of the pressure sensor-tipped 0.014″ coronary wire. You obtain the following results:

   - iFR of the right posterior descending artery: 0.76
   - iFR of the RCA between the mid and distal lesions: 0.81
   - iFR of the proximal RCA: 1.00

   What is the most appropriate management decision at this time?

   A. Perform PCI on both the mid and distal RCA lesions.
   B. Perform PCI on the mid RCA lesion.
   C. Perform PCI on the distal RCA lesion.
   D. None of the above.

Answers

1. The Answer is **C**. In order to calculate the FFR you first need to calculate the mean pressure (MP) in the aorta. This can be calculated by the following equation: MP = Diastolic

pressure + (Systolic pressure − diastolic pressure)/3. Plugging the numbers into the equation, the MP = 85.3 mmHg. FFR = MP_{distal}/MP_{aorta} = 60/85.3 = 0.703.

2. The Answer is **C**. PCI is indicated based on the DEFER (FFR <0.75) and FAME (FFR <0.80) studies.
3. The Answer is **D**. Cardiac syndrome X, or angina with an abnormal cardiac stress test and angiographically normal coronary arteries. A CFR ≤2 is suggestive of microvascular disease, the underlying pathophysiology of this syndrome.
4. The Answer is **A**. This patient has a 2.5% chance of having a myocardial infarction, stroke, sudden cardiac death, or developing congestive heart failure over the next year.
5. The Answer is **B**. Performing a slow pullback across multiple serial stenoses in a single vessel during iFR allows the operator to determine the hemodynamic significance of each individual stenosis. In this example, the hemodynamic contribution of the distal RCA stenosis was 0.95 ((1 − (0.81 – 0.76) = (1 – 0.05) = 0.95). The hemodynamic significance of the mid RCA stenosis was 0.81. Thus, the most appropriate management decision is to perform PCI on the mid RCA lesion only.

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A. T. Askari, A. W. Messerli (eds.), *Cardiovascular Hemodynamics*, Contemporary Cardiology,
https://doi.org/10.1007/978-3-030-19131-3

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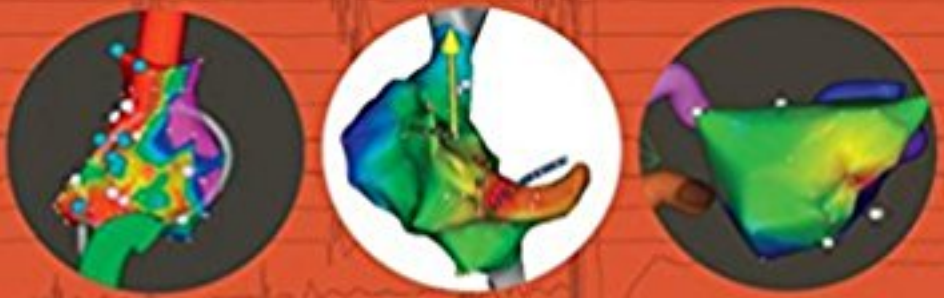

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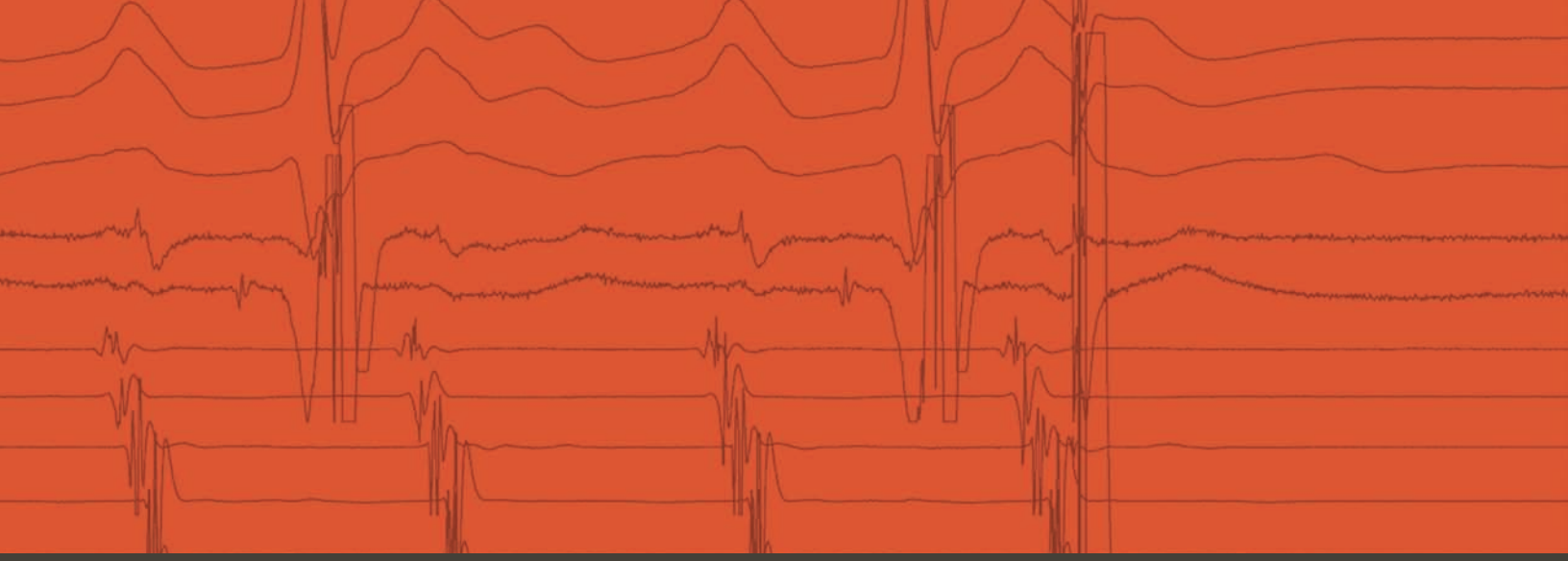

Case Studies in Clinical Cardiac Electrophysiology

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CASE STUDIES IN CLINICAL CARDIAC ELECTROPHYSIOLOGY ISBN: 978-0-323-18772-5

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Library of Congress Cataloging-in-Publication Data

Names: Miller, John M. (John Michael), 1954- author. | Das, Mithilesh K., author. | Zipes, Douglas P., author.
Title: Case studies in clinical cardiac electrophysiology / John Miller, Mithilesh Das, Douglas Zipes.
Description: Philadelphia, PA : Elsevier, [2018] | Includes bibliographical references and index.
Identifiers: LCCN 2016053043 | ISBN 9780323187725 (hardcover : alk. paper)
Subjects: | MESH: Heart Diseases--diagnosis | Electrophysiologic Techniques, Cardiac--methods | Case Reports
Classification: LCC RC683.5.E5 | NLM WG 141.5.F9 | DDC 616.1/2075--dc23
LC record available at https://lccn.loc.gov/2016053043

Content Strategist: Maureen Iannuzzi
Senior Content Development Specialist: Janice Galliard
Publishing Services Manager: Catherine Jackson
Project Manager: Kate Mannix
Design Direction: Brian Salisbury

Printed in China

Last digit is the print number: 9 8 7 6 5 4 3 2 1

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Keenly aware of the time and energy diverted from our families that was required to perform these procedures and assemble the recordings into a form accessible by readers, we dedicate this volume to our beloved wives (Jeanne, Rekha, and Joan), who have allowed us the privilege of putting this work together. We also dedicate this work to the readers, who we hope will benefit from the lessons we have tried to convey, and finally to their patients, who we hope will in turn benefit from their learning.

Foreword

The practice of clinical cardiac electrophysiology is one of clinical exploration that starts with integration of the patient's symptoms and cardiac evaluation with electrocardiographic interpretation. One of the most gratifying experiences for patient and physician is when this process culminates in the electrophysiology laboratory with confirmation of the diagnosis and implementation of effective therapy for the arrhythmia with catheter ablation. Mastery of each component is needed, and the knowledge that is gained from each step can be applied to the previous step to refine one's diagnostic acumen. We became much better electrocardiographers by applying the knowledge gained from the pioneering work that defined cardiac activation patterns and arrhythmia mechanisms using cardiac mapping and programmed electrical stimulation. Expertise in the last step, interventional electrophysiology, is the most challenging to acquire. It requires assimilation of complex patterns of cardiac activation, interpretation of spontaneous changes in patterns, and application of maneuvers to confirm a diagnosis, and this confirmation is critical for guiding catheter ablation.

Drs. Miller, Das, and Zipes have assembled a wonderful book that captures the spirit of clinical exploration leading to effective therapy. They use cases to describe pathophysiologic concepts that start with fundamentals and proceed to complex concepts. From the electrophysiology laboratory they incorporate findings ranging from those that are classic to those that are only recently described and that require a nuanced interpretation and understanding, but that are critical to arriving at the correct diagnosis. Examples include the newest technologies that are now being applied for delineation of arrhythmia mechanisms and substrate.

The authors are renowned teachers who apply their wealth of experience in communicating complex scenarios and concepts to make the cases accessible for the complete range of students of clinical electrophysiology, from the trainee to the advanced practitioner. The cases clarify concepts and provide fundamentals for the new student, but also provide insights that will expand the knowledge of experienced clinicians. Dr Miller's hand is evident throughout in the superb graphics, for which he is widely known among teachers of cardiology.

One of the amazing aspects of biology, medicine, and certainly extending to cardiac electrophysiology, is the variability that one encounters from patient to patient. After years in the field, one still encounters new arrhythmia problems. A solid basis in understanding mapping and diagnostic maneuvers is required for solving new puzzles in the electrophysiology laboratory, and this learning is acquired from the study of cases. You can never analyze too many cases. I congratulate the authors of *Case Studies in Clinical Cardiac Electrophysiology* on a wonderful book.

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Preface

The understanding and care of patients with heart rhythm disturbances (clinical cardiac electrophysiology [EP]) has evolved in the last three decades from simple diagnostic studies of the conduction system using a few electrodes, to complex diagnostic and therapeutic procedures involving recording and stimulation from a large number of electrodes, for the purpose of finding and ablating arrhythmogenic tissue. With this dramatic change in the character of EP studies has come the critical need for careful analysis and thorough understanding of the meaning of recordings that are made and results of stimulation in order to achieve optimal results from ablation. At the same time, EP training programs have come under increasing pressure to perform more procedures in a shorter amount of time, resulting in compromising time for careful and methodical study of and learning from these procedures that are rich with teaching material. Although many excellent texts in our field explain the principles of recording and stimulation in treatment of arrhythmias, for example, *Clinical Arrhythmology and Electrophysiology*, few are structured to show their practical application in a case-study format. In light of this, the purpose of this volume is to take the reader through a representative series of EP procedures from start to finish, evaluating results of diagnostic pacing maneuvers, sampling and comparing characteristics of electrograms, and selection of appropriate sites for ablation. It is our hope that readers will benefit from this mode of presentation, highlighting some of the limitations of techniques that are used on a daily basis, with the aim of improving the efficacy and safety of procedures they perform on their patients.

Acknowledgments

We gratefully acknowledge the role played by our nursing and technical staff with whom we performed the procedures reviewed in this work, as well as electrophysiology fellows, whose patience in keeping catheters in place during long procedures contributed greatly to the quality of the figures. We also acknowledge our patients, who provide a constant source for learning.

1 Sinus Node and Atrioventricular Conduction Disease

Case Presentation

A 56-year-old man experienced syncope while walking at work. Coworkers called emergency medical services (EMS). Upon the arrival of EMS, he was awake and feeling normal but was convinced to go to the emergency room (ER). The patient had a history of anterior wall myocardial infarction (MI), percutaneous coronary intervention (PCI), to left anterior descending coronary artery (LAD) several years before, and a negative stress test within the last 6 months. Examination results were normal except for obesity. ECG showed sinus rhythm, long PR, right bundle branch block (RBBB), left anterior fascicular block (LAFB), and anterior scar. Echocardiogram revealed ejection fraction (EF) 40% and anterior hypokinesis. The patient was referred for electrophysiology (EP) study.

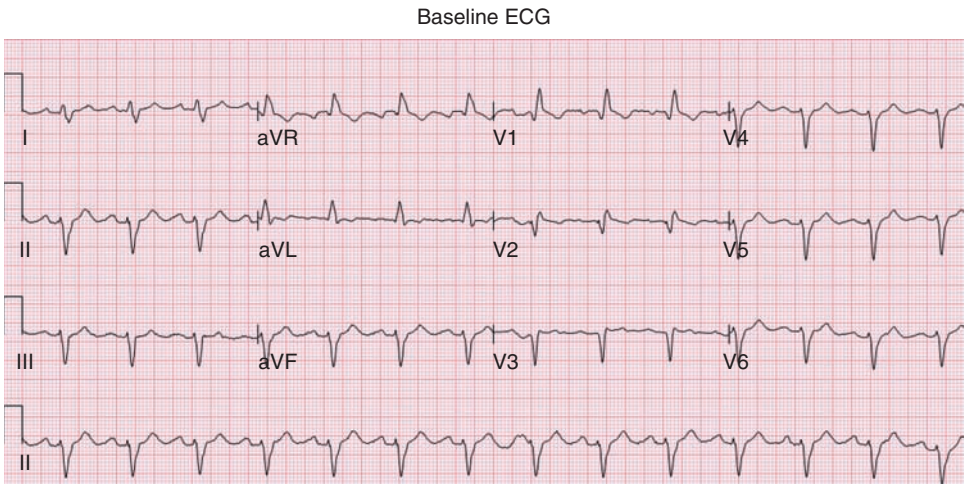


Figure 1-1

The ECG in Fig. 1-1 shows sinus rhythm with a prolonged P wave (left atrial abnormality), slightly prolonged PR interval, RBBB and left anterior fascicular block, and an extensive anterior infarction. On the basis of this, there are many possible causes of syncope—atrial arrhythmias (atrial flutter and fibrillation, other reentrant atrial tachycardias), heart block (either in AV node or His-Purkinje system), or ventricular arrhythmia (ventricular tachycardia or fibrillation). There is nothing in the ECG to favor one cause of syncope over another, and because treatment strategies are very different depending on the cause (medications or ablation for atrial arrhythmias; pacemaker for heart block; implantable defibrillator for ventricular arrhythmias), further investigation is needed.

Evaluation

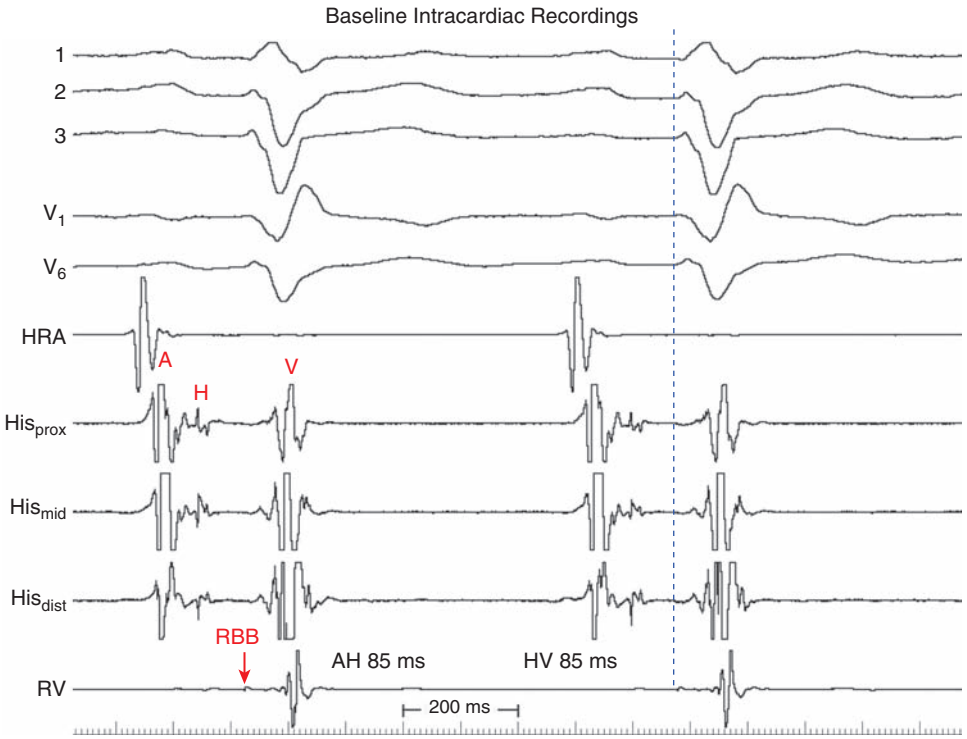


Figure 1-2

Intracardiac recordings during sinus rhythm (Fig. 1-2) show atrial (A), His (H), and ventricular (V) recordings as noted. This confirms the presence of His-Purkinje disease, with an HV interval of 85 ms—prolonged (normal, 40 to 55 ms), but not enough to implicate His-Purkinje dysfunction as a cause of heart block. Surprisingly, though the PR interval is somewhat prolonged, the AH interval is normal (85 ms [normal, 60 to 125 ms]). Usually, prolongation of the PR interval is caused by the AV nodal (AH) component, because to prolong the PR even 60 ms from His-Purkinje disease would require a lengthening of the HV to a degree (that is, from 40 ms to 100 ms) that 1:1 conduction would be unlikely. Note also that there is a delay between the distal His recording and right bundle branch (RBB)—there is usually <10 ms between these—and that the RBBB is further caused by delay or block between the RBB and RV apical electrogram, with a QRS onset *(dashed blue line)* to RV electrogram of 75 ms (normal, 10 to 35 ms).

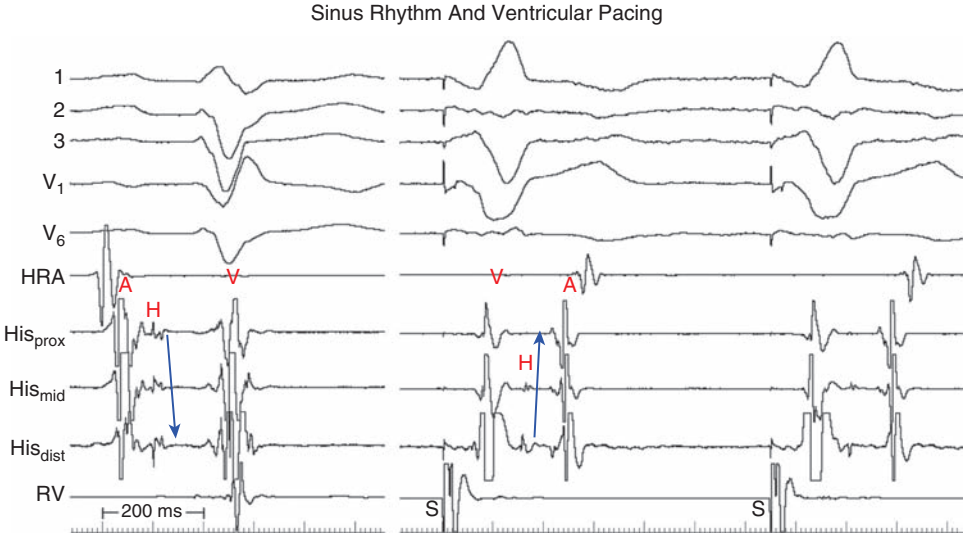


Figure 1-3

The left side of Fig. 1-3 shows a sinus rhythm complex as in the previous figure for reference, whereas the 2 complexes on the right are during pacing from the right ventricular apical region. Note that there is retrograde conduction to the atria, with the His bundle activated from distal to proximal as expected. Usually, the timing of the His potential is before the local ventricular electrogram in the His recoding, because conduction proceeds more rapidly up the RBB to the His than does muscle-to-muscle propagation from apex to base. Because there is RBBB in this case, the impulse cannot ascend the RBB as it normally would and instead must traverse the interventricular septum, enter the left bundle branch, and then activate the His retrogradely. These findings just confirm the His-Purkinje disease but give no further insight as to the cause of syncope.

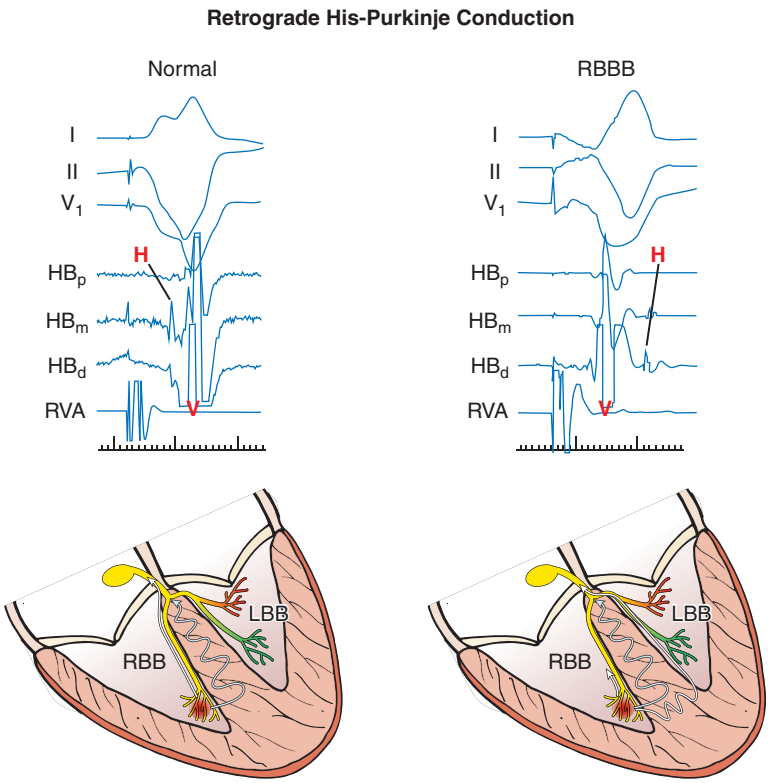


Figure 1-4

As illustrated in Fig. 1-4, in patients with normal His-Purkinje function (at *left*), pacing from the right ventricular apex *(red circle)* results in retrograde conduction over the RBB *(white line)* that is more rapid than muscle-to-muscle conduction (*wavy line* in septum), resulting in a His potential (H) inscribed before the larger local ventricular recording (V). At right, in the presence of anterograde RBBB, the paced wavefront cannot ascend the blocked right bundle and instead crosses the interventricular septum *(wavy horizontal line)* to engage the left bundle, and then proceeds rapidly to the His that now appears after the local ventricular recording (that is again generated after muscle-to-muscle spread).

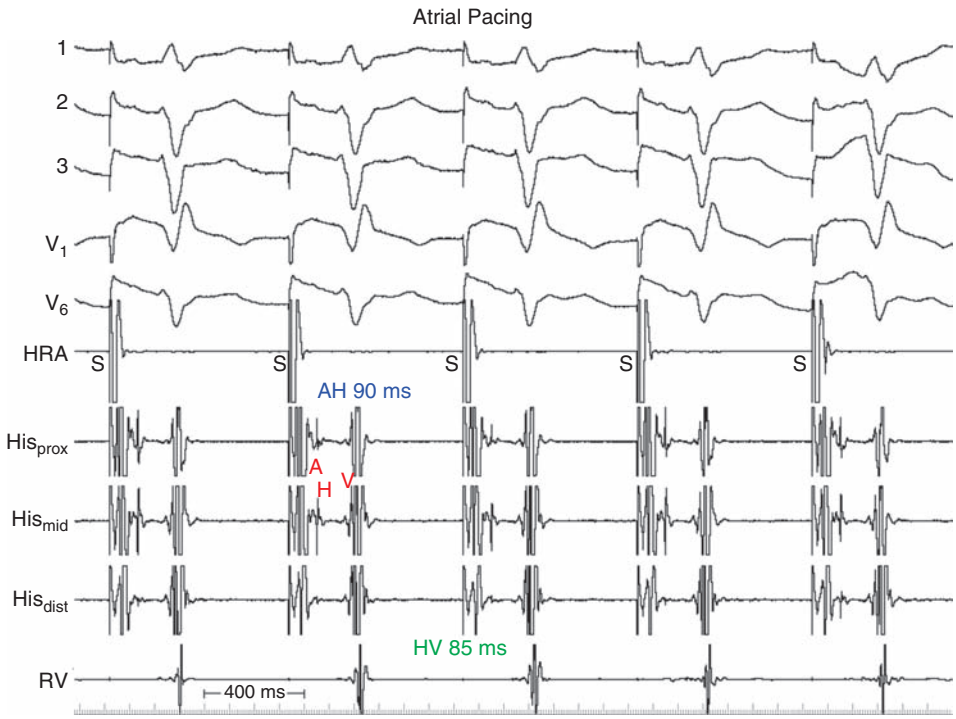


Figure 1-5

Rapid pacing can often reveal abnormalities of AV conduction that were not very evident at rest. In Fig. 1-5, pacing the atrium (S) slightly faster than the sinus rate shows minimal change in either AH (90 ms) or HV (85 ms) intervals. It is useful to display multiple electrode pairs of His recordings because the signal amplitude may vary enough between complexes that the His potential may be poorly visible or even absent in one electrode pair (His_{dist} in this case), whereas it is readily visible in other electrode pairs.

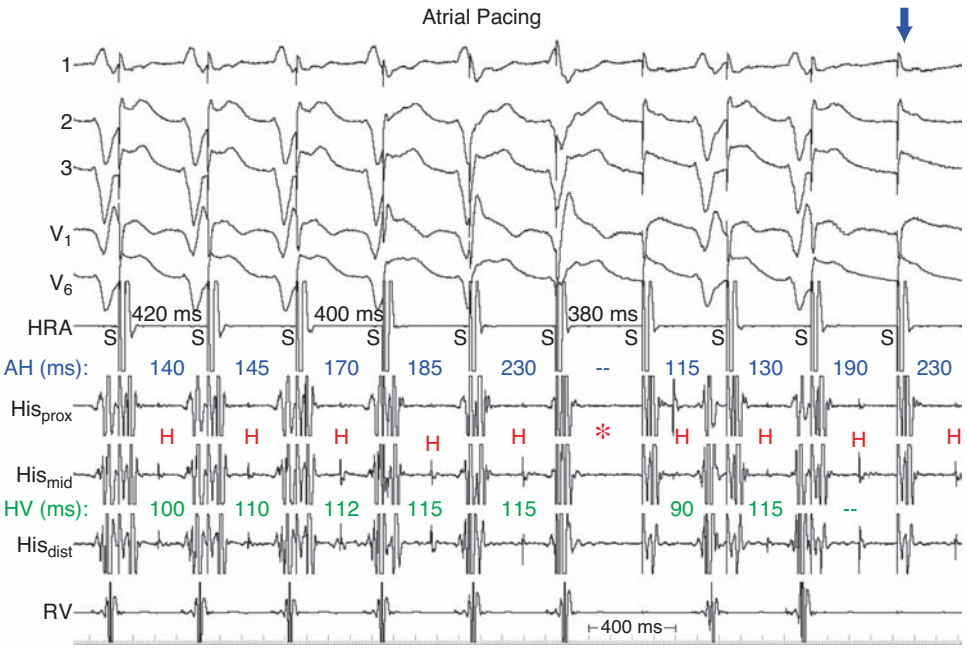


Figure 1-6

More rapid pacing starts to reveal some abnormalities. As the pacing rate increases (cycle length decreases), the AH is expected to prolong but the HV interval usually remains constant. In Fig. 1-6, the AH (in *blue*) does prolong, but so does the HV interval (in *green*). The *asterisk* denotes where AV nodal block occurs (no subsequent His potential), but three cycles after this, there is a His potential not followed by a QRS (infra-His block; *green dash*)

and the HV intervals on the prior two cycles had prolonged (thus, infra-His Wenckebach). This is distinctly abnormal and likely warrants pacemaker implantation. However, this may not be the reason that syncope had occurred (there may be other abnormalities that have not yet been uncovered during the study).

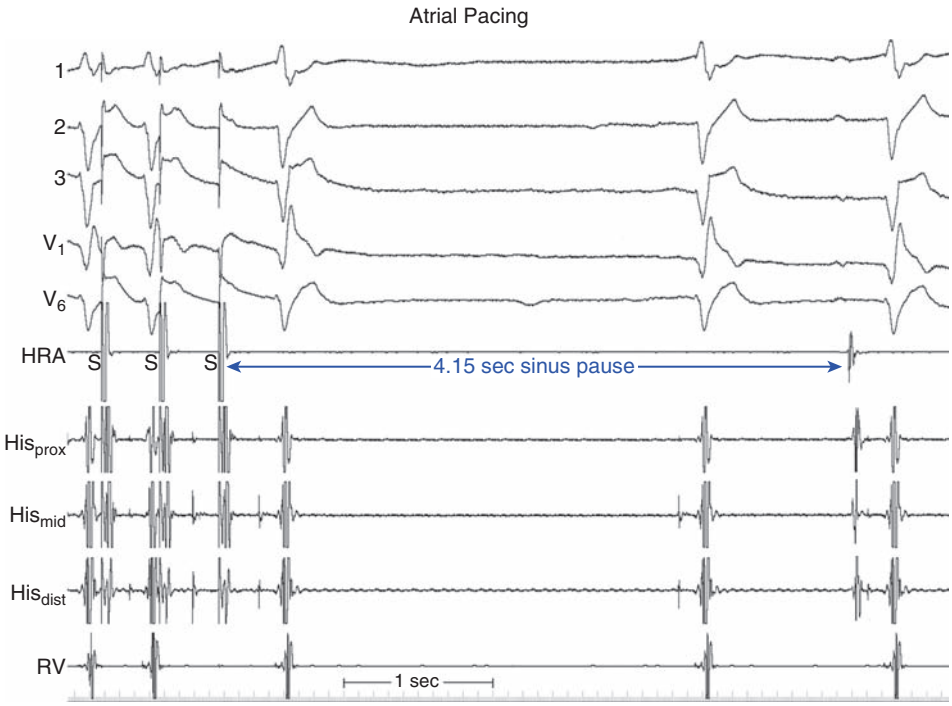


Figure 1-7

In Fig. 1-7, pacing is repeated for 1 min at the same cycle length as shown in the prior figure to stress the sinus node. Upon cessation of pacing, a prolonged sinus pause (4.15 seconds) is observed; a junctional escape complex occurs after 3 seconds. This is another potential cause of syncope (sinus node dysfunction).

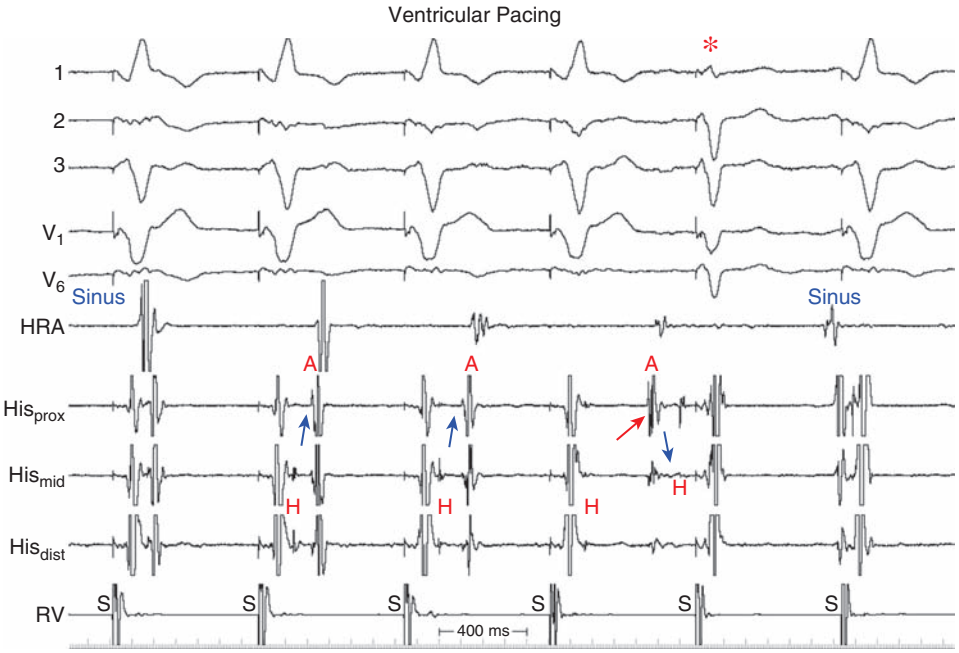


Figure 1-8

Turning to the ventricles (Fig. 1-8), slow ventricular pacing again shows that there is retrograde conduction; the first and last atrial complexes are sinus in origin (HRA before His atrial recordings) but the middle three complexes are retrogradely conducted. The first two of these *(blue arrows)* are over the fast pathway, but after the fourth ventricular stimulus, the ventriculoatrial interval suddenly increases, signifying a switch to a slow pathway *(red arrow)*. Immediately after this, there is a QRS complex that is not fully paced *(asterisk)*; this is because of fusion between the paced wavefront and one over the normal conduction system (see His potential). This is the result of an atypical AV nodal echo (retrograde slow pathway, anterograde fast—*blue arrow*). This is a common finding and, unless accompanied by sustained atypical AV nodal reentrant SVT, has no relevance for the diagnosis of syncope.

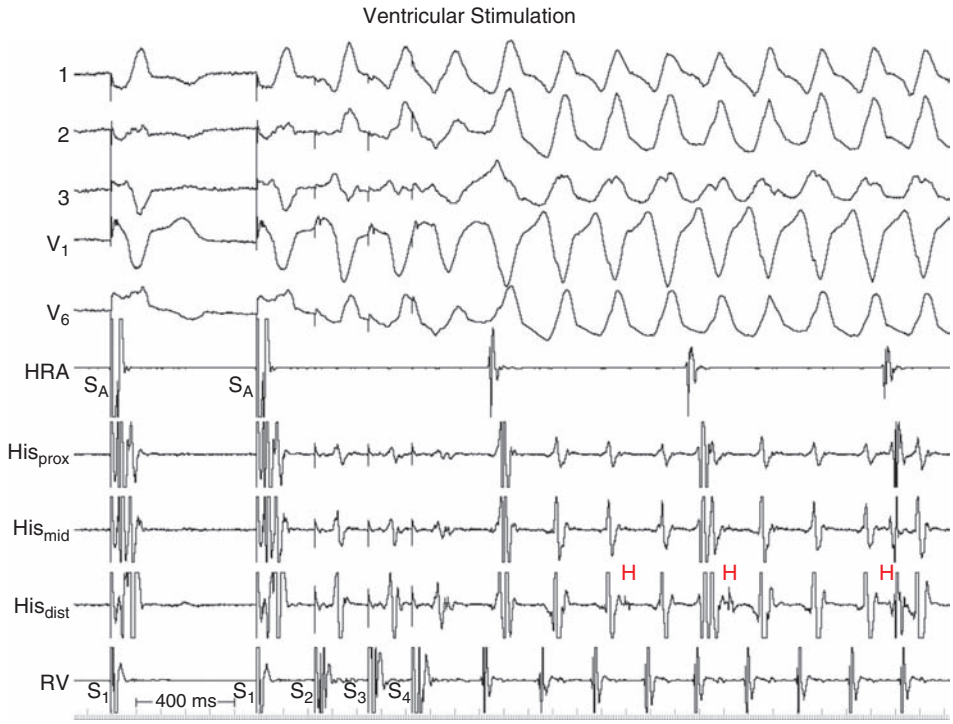


Figure 1-9

The last part of the syncope evaluation consists of programmed ventricular stimulation. As shown in Fig. 1-9, standard stimulation (here, with triple extrastimuli, S2 to S4) initiates a rapid, hemodynamically unstable ventricular tachycardia (CL 250 ms) that stopped spontaneously after 15 seconds. Given the presence of a prior MI and "serious" syncope, this arrhythmia was deemed a reasonable candidate for the cause of his syncope. He received a dual-chamber ICD later that day. Note that a His potential is seen on occasion but not with every complex—excluding bundle branch reentry as a possible cause of the tachycardia (S_A = atrial stimulus).

Summary

- This man had syncope in the presence of structural heart disease—which always needs further evaluation.
- Multiple potential causes of syncope may be present in the same patient; in this case,
  - Sinus node dysfunction
  - His-Purkinje dysfunction
  - Ventricular tachycardia
- Judgment must be used to determine which possible cause(s) of syncope should be treated and how.

Typical ("Slow-Fast") Atrioventricular Nodal Reentry

2

Case Presentation

A 48-year-old woman had a history of palpitations for ~5 years. Her episodes started and stopped suddenly, lasted 1 to 2 minutes, and were associated with lightheadedness. She came to a local emergency room with a prolonged episode: ECG showed a narrow QRS tachycardia (by report; no ECG available) that was terminated with adenosine. She was treated with oral diltiazem and metoprolol but continued to have supraventricular tachycardia (SVT) episodes. She had a normal physical exam; non-invasive evaluation showed no structural heart disease. She was referred for catheter ablation of her SVT.

Baseline ECGs and Intracardiac Recordings

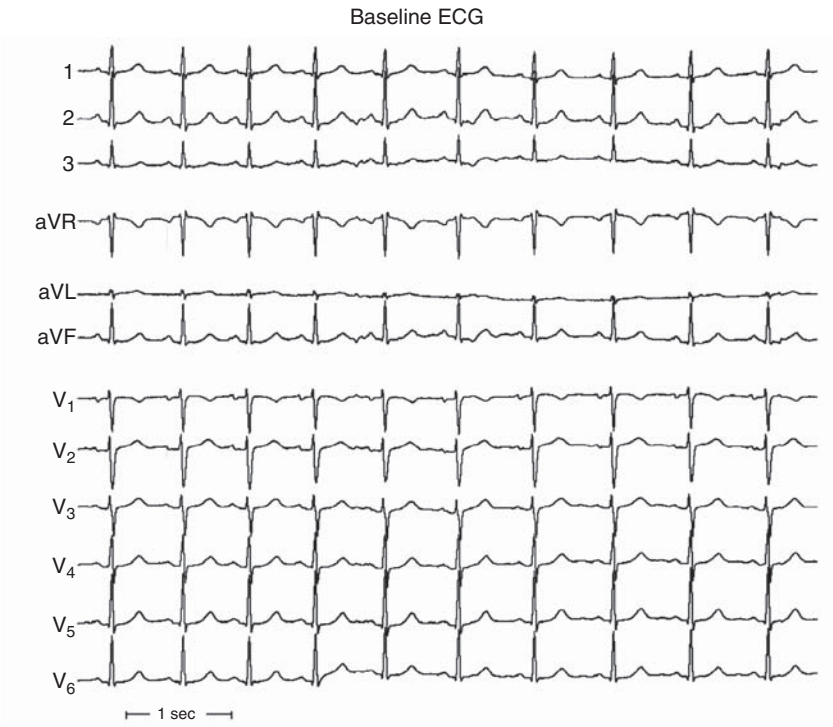


Figure 2-1

Fig. 2-1 demonstrates normal sinus rhythm without delta waves, fractionation, or prolongation of the P wave or QRS and normal QT. ECG is normal.

Figure 2-2

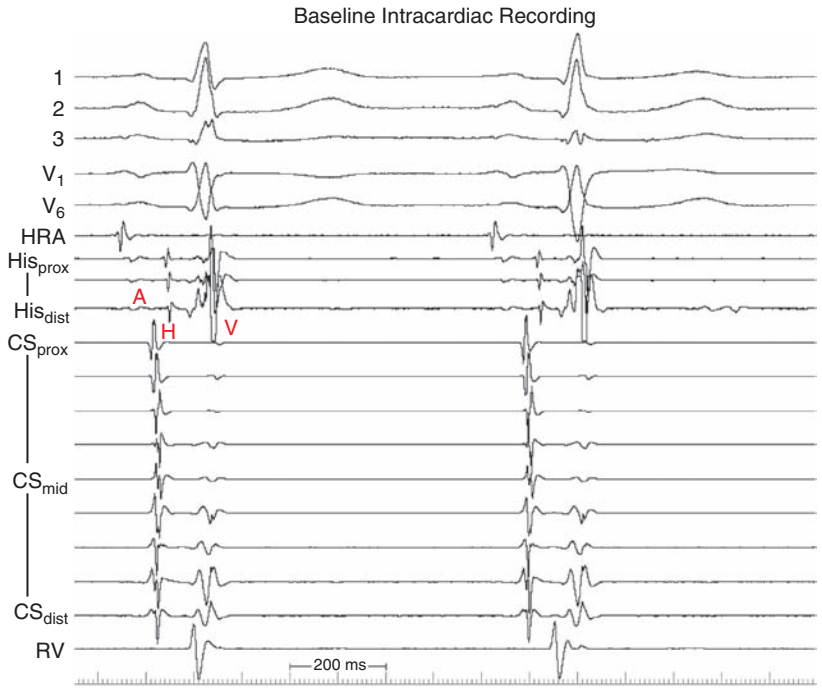
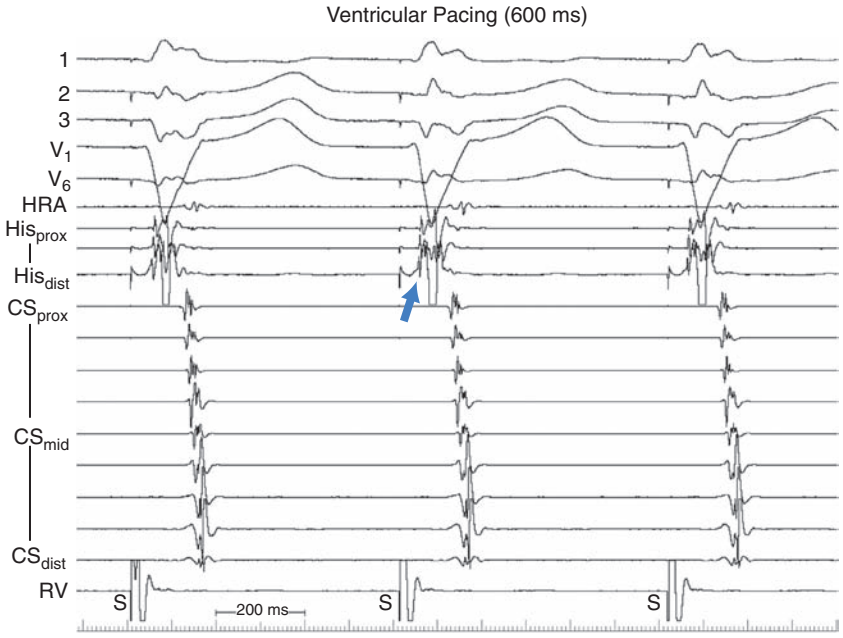


Fig. 2-2 shows normal intracardiac intervals (AH, HV); there is no evidence of preexcitation on intracardiac recordings. Normal progression of atrial activation is seen from right atrium to His to coronary sinus proximal to distal.

Ventricular Pacing

Figure 2-3



In Fig. 2-3, with ventricular pacing at 600 ms, retrograde conduction is present with a concentric activation pattern; a retrograde His potential *(arrow)* is seen between stimulus artifact and local ventricular electrogram.

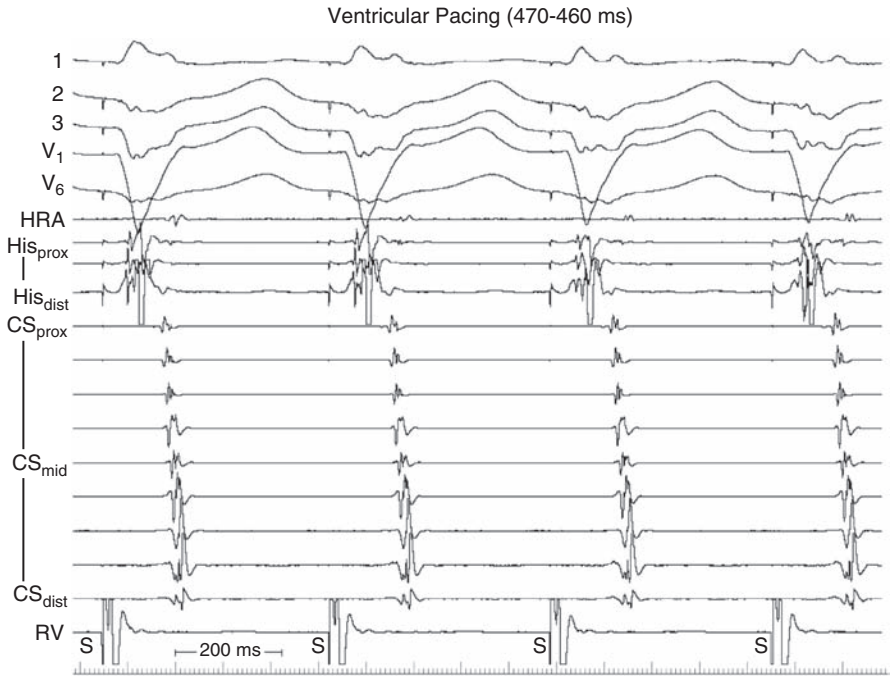


Figure 2-4

With more rapid ventricular pacing (470–460 ms) the same activation sequence is seen in Fig. 2-4, with a longer VA interval—most consistent with AV nodal conduction.

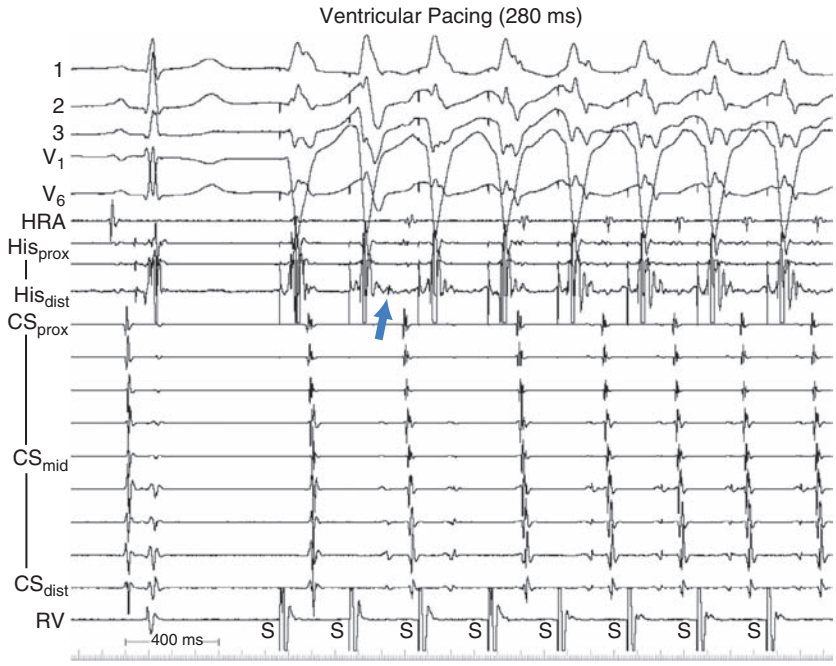


Figure 2-5

In Fig. 2-5, with the sudden onset of ventricular pacing (280 ms), a His "out the back" *(arrow)* is seen after second stimulus, with atrial activation dependent on His (ie, no bypass tract). Retrograde block occurs after the third stimulus likely because of block in the His-Purkinje system, which recovers by the fourth stimulus (after which 1:1 retrograde conduction resumes).

ECGs Compared

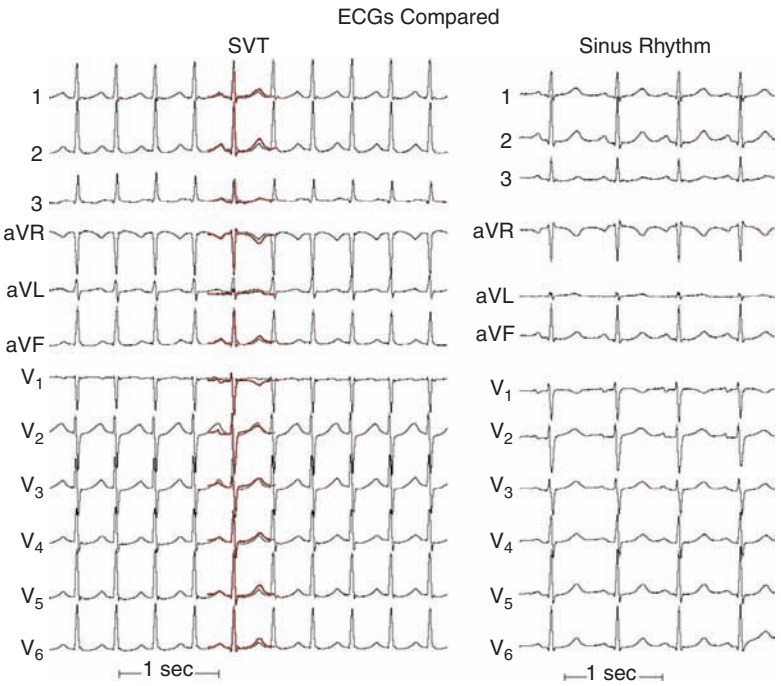


Figure 2-6

SVT was induced ((*left)*; sinus rhythm is shown at right in Fig. 2-6. A superimposed sinus complex *(red)* overlaid on SVT shows no clear difference, implying that the P wave must be hidden within the QRS complex.

Ventricular Pacing in SVT

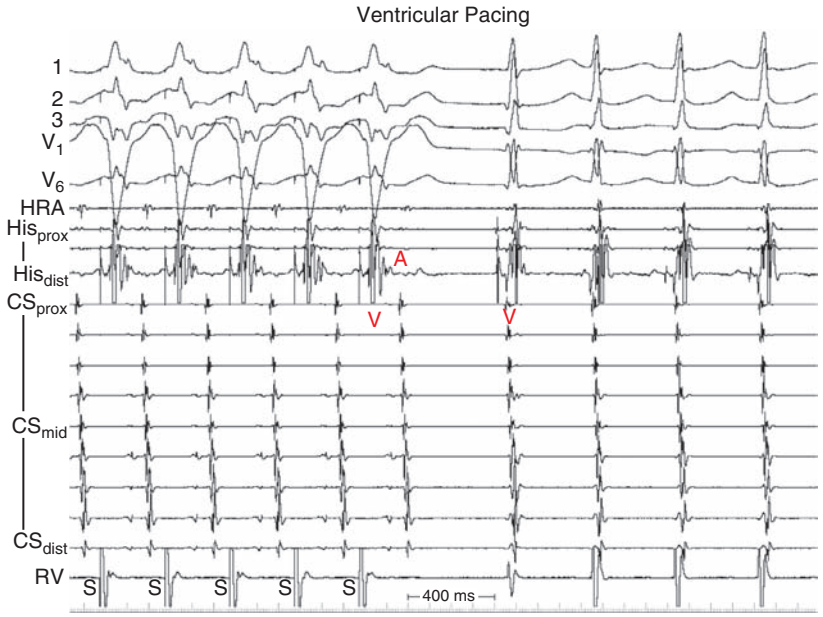


Figure 2-7

In Fig. 2-7, ventricular pacing during SVT conducts retrogradely to atrium with the same activation pattern as during SVT. During SVT that resumes on cessation of pacing, atrial activation appears concentric and within (even before) the QRS complex, excluding orthodromic SVT. The long pause after pacing suggests conduction down an AV nodal slow pathway. The "VAV" response is consistent with typical atrioventricular nodal reentry (AVNRT), not atrial tachycardia (AT).

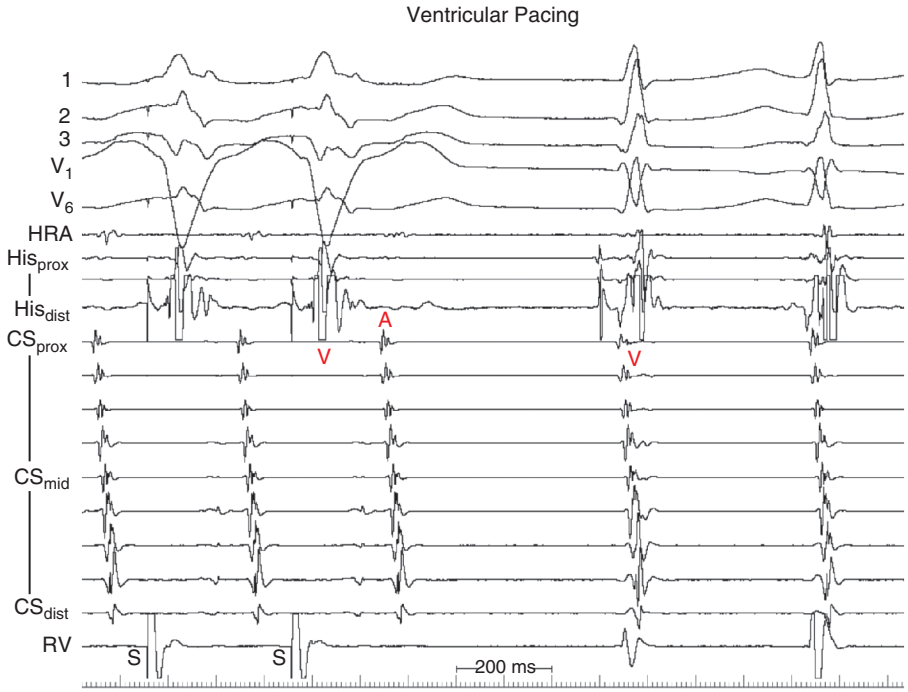


Figure 2-8

Fig. 2-8 is a faster sweep speed of Fig. 2-7, showing the same findings.

Para-Hisian Pacing

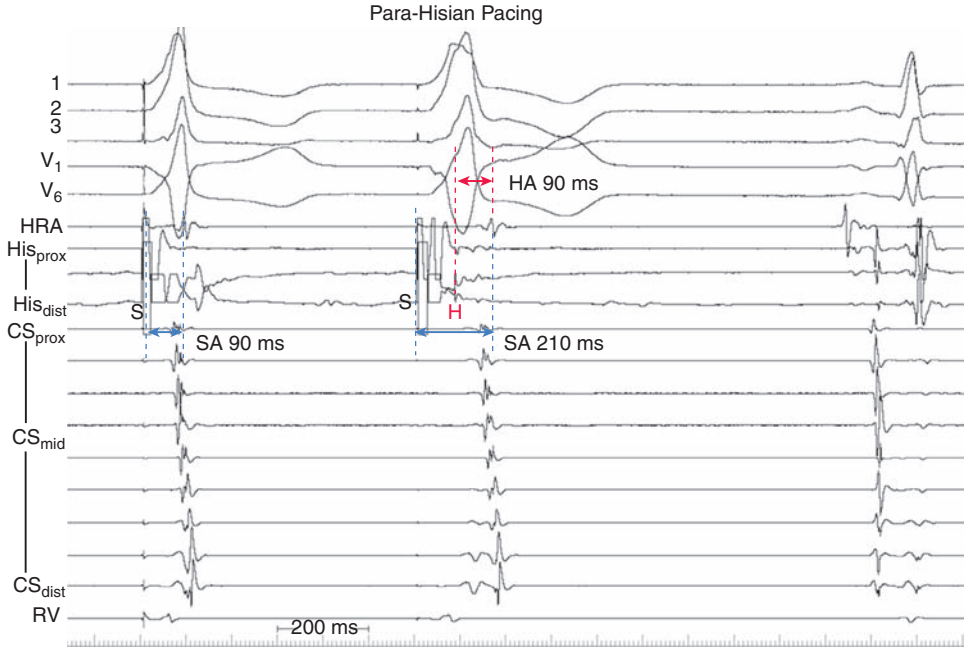


Figure 2-9

The complex at right of Fig. 2-9 shows a normal sinus complex. The complex in middle has a wide QRS suggesting pure ventricular capture. Retrograde conduction is evident. The complex at left is relatively narrow, indicating some element of His capture, though not pure His capture (His + V capture); retrograde conduction is evident with the same pattern as during the wider complex and S-A interval is 90 ms; in the wide complex (V capture only), the S-A interval is 210 ms, indicating conduction only over AV node. The retrograde His is visible (H), with HA still 90 ms.

Ventricular Extrastimuli in Sinus Rhythm

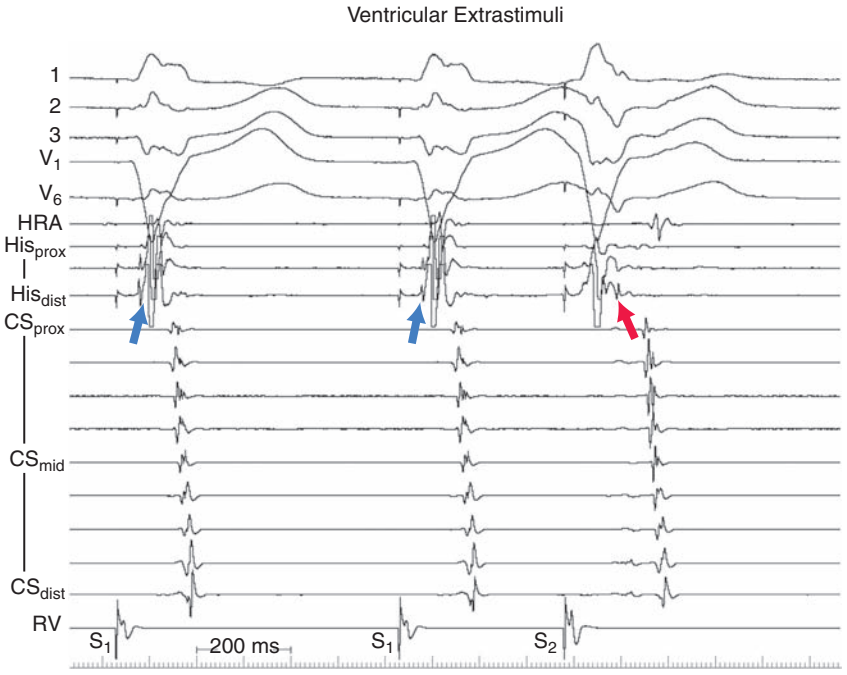


Figure 2-10

A single ventricular extrastimulus at a drive of 600 ms is shown in Fig. 2-10. A retrograde His *(blue arrow)* is seen before the local ventricular electrogram on drive complexes, whereas the His is "out the back" *(red arrow)* after the extrastimulus complex, as a result of block in the right bundle branch with transseptal conduction to and then up the left bundle to the His. If this relationship (atrial activation dependent on prior His activation) remains constant over a range of coupling intervals, a bypass tract is excluded.

Ventricular Extrastimuli in SVT

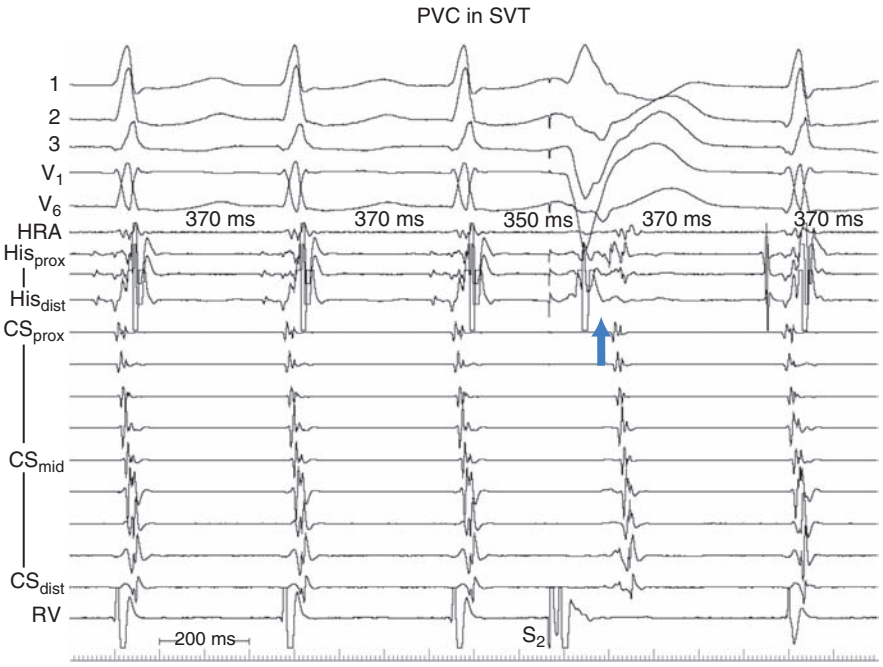


Figure 2-11

In Fig. 2-11, a ventricular extrastimulus is given during SVT. The A-A interval surrounding the extrastimulus is shorter than the rest of the A-A intervals, but the His was not refractory (*blue arrow*

shows where it would be expected if not for the extrastimulus). Advancement of the timing of atrial activation surrounding a *His-refractory* ventricular extrastimulus demonstrates the existence of a path of conduction extrinsic to the normal conduction system (bypass tract). If the extrastimulus occurs at a time when the His is not refractory (as here), it is feasible that conduction could occur through the His to the AV node and atrium, and would not implicate a bypass tract.

Atrial and Ventricular Pacing and Extrastimuli During SVT

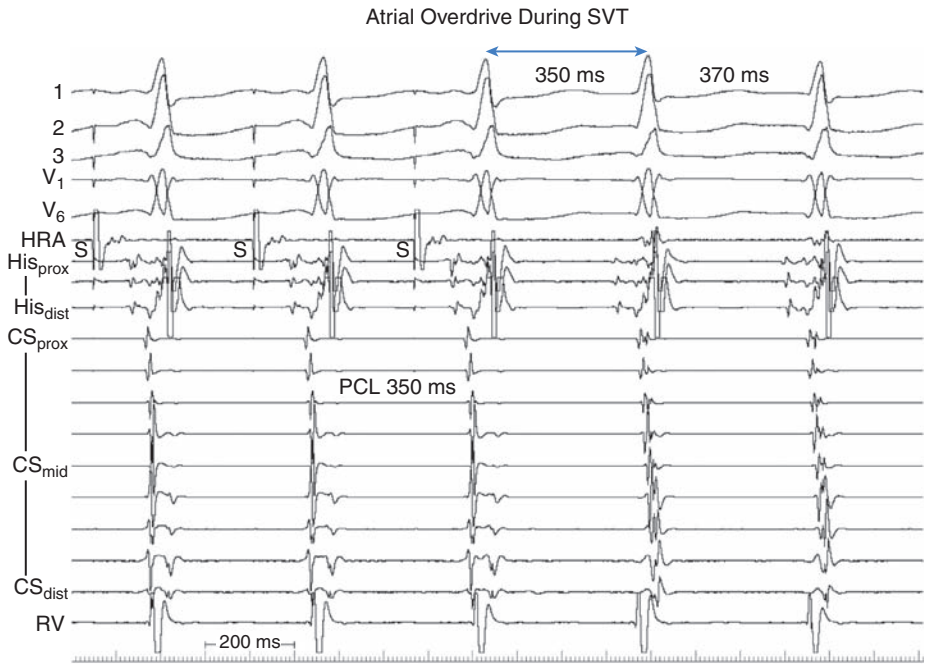


Figure 2-12

Overdrive atrial pacing during SVT is shown in Fig. 2-12. At first glance, the third QRS complex appears to result from the third stimulus. On closer inspection, it is clear that the third stimulus causes the fourth QRS complex because the V-V interval there is the same as the paced cycle length (350 ms). This indicates the presence of slow AV nodal conduction (no surprise, because this type of AV nodal reentry uses an anterograde slowly conducting pathway).

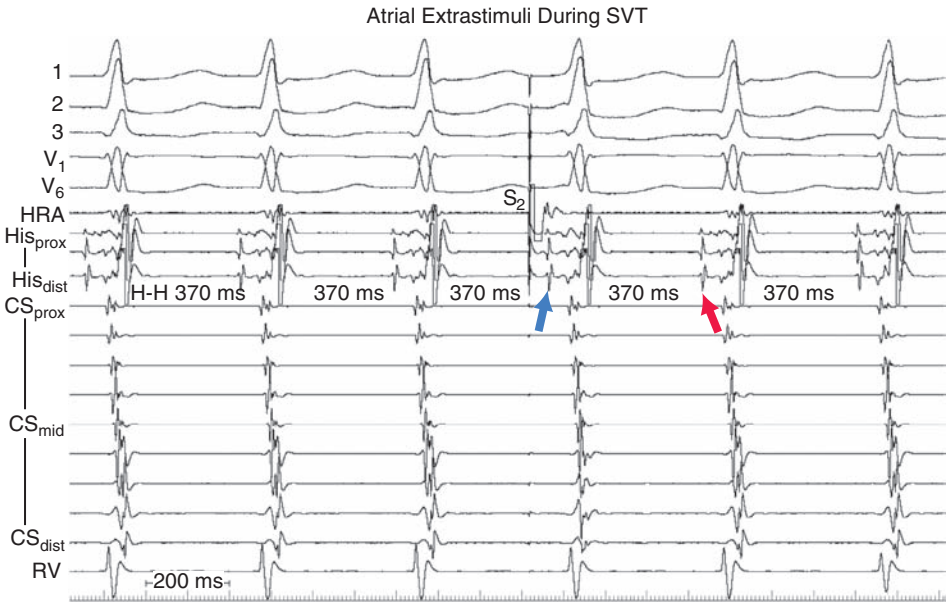


Figure 2-13

In Fig. 2-13, a single atrial extrastimulus is given during SVT. His-His intervals are as indicated; the His immediately after the extrastimulus *(blue arrow)* is on time and unaffected by the stimulus. Thus, if this were a focal junctional tachycardia, it would have already "fired" for that complex and its next occurrence should be right on time. Although this is exactly what happens—the next His *(red arrow)* occurs on time—this finding is also consistent with AV nodal reentry or even AT conducting over a slow AV nodal pathway (the impulse is already on its way down the slow pathway and is unaffected by the atrial extrastimulus). Thus this finding by itself is not diagnostic of focal junctional tachycardia.

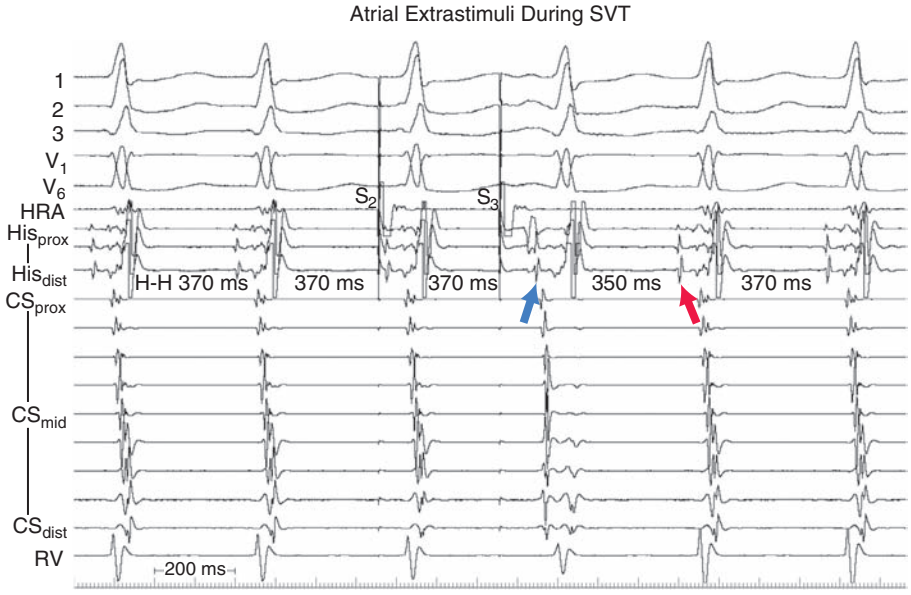


Figure 2-14

Double atrial extrastimuli are now given during SVT (Fig. 2-14). The His potential after second extrastimulus *(blue arrow)* is on time (370 ms), unaffected by the first atrial stimulus (S_2). However, the next His *(red arrow)*, driven by the second atrial stimulus (S_3) is advanced by 20 ms. This shows that focal junctional tachycardia cannot be the diagnosis, because a focal discharge from the His at the red arrow cannot be advanced by an atrial stimulus that did not affect the prior His.

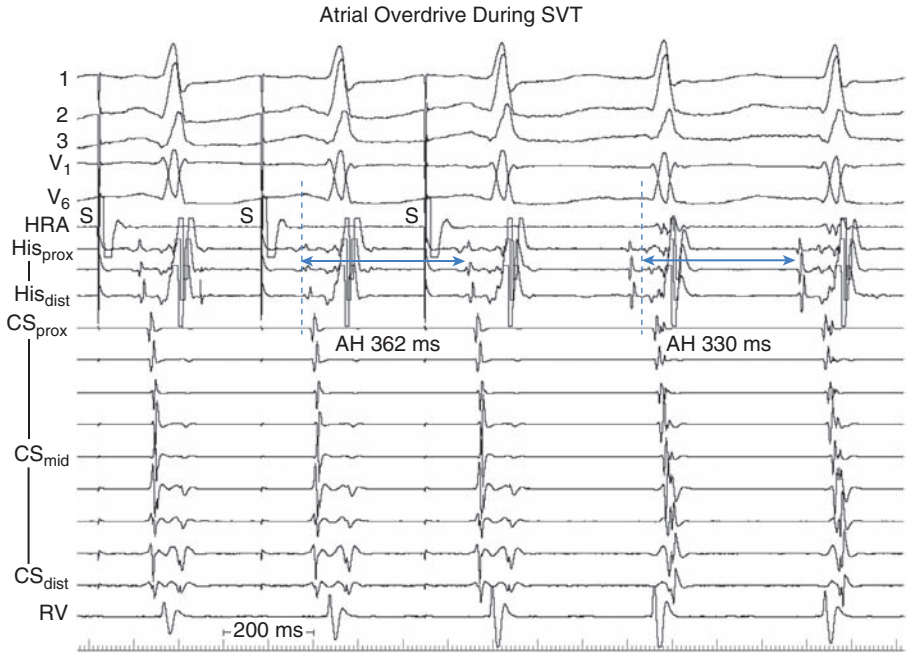


Figure 2-15

Atrial overdrive pacing during SVT is performed again, as shown in Fig. 2-15; the AH interval with pacing (362 ms) exceeds the AH in SVT (330 ms); this is consistent with AV nodal reentry and inconsistent with right AT (in which case the AH intervals should be similar between pacing and SVT).

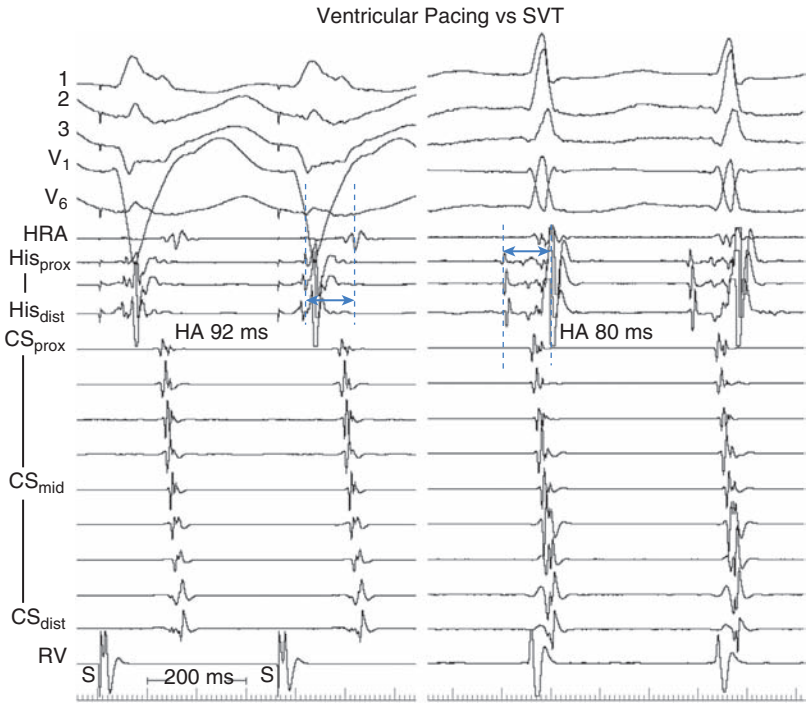


Figure 2-16

The HA interval with ventricular pacing at the SVT cycle length (92 ms) is always the same as or longer than HA in SVT (80 ms), when measured as shown in Fig. 2-16 (end of His to A during pacing, onset of His to A during SVT, with standard 5-mm interelectrode recording catheters). This is not found with very closely spaced, very proximal His recordings, however, where the difference between HA intervals with pacing and SVT narrows as the point of turnaround between anterograde slow and retrograde fast pathways occurs.

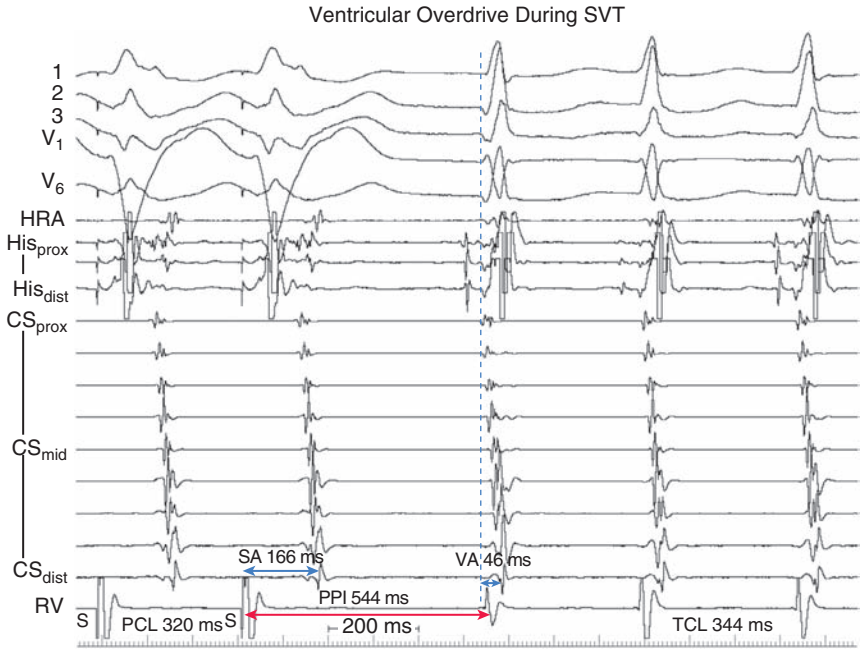


Figure 2-17

Ventricular overdrive pacing during SVT is shown in Fig. 2-17, with intervals as indicated; the SA-VA difference (120 ms) exceeds 85 ms, and the postpacing interval (PPI)–tachycardia cycle length (TCL) difference (200 ms) exceeds 115 ms; both indices indicate AV nodal reentry rather than orthodromic SVT.

Cartoons and Ladder Diagrams of Pacing

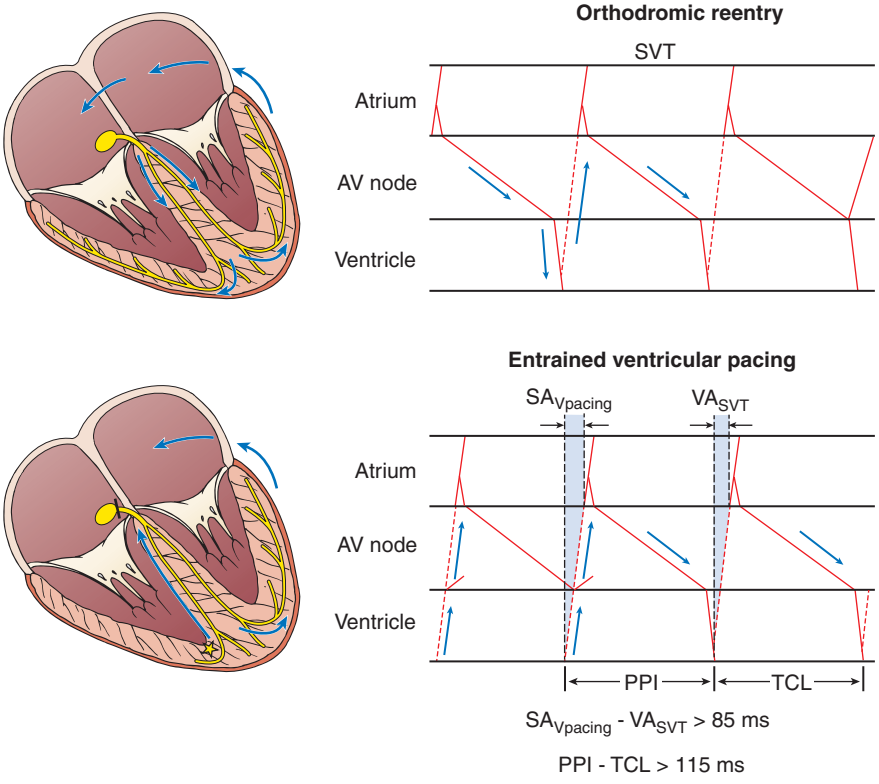


Figure 2-18

Fig. 2-18 displays entrained ventricular pacing during orthodromic SVT; the bypass tract shown here (connecting left atrium and left ventricle) is indicated in the ladder diagrams as a *dotted line*.

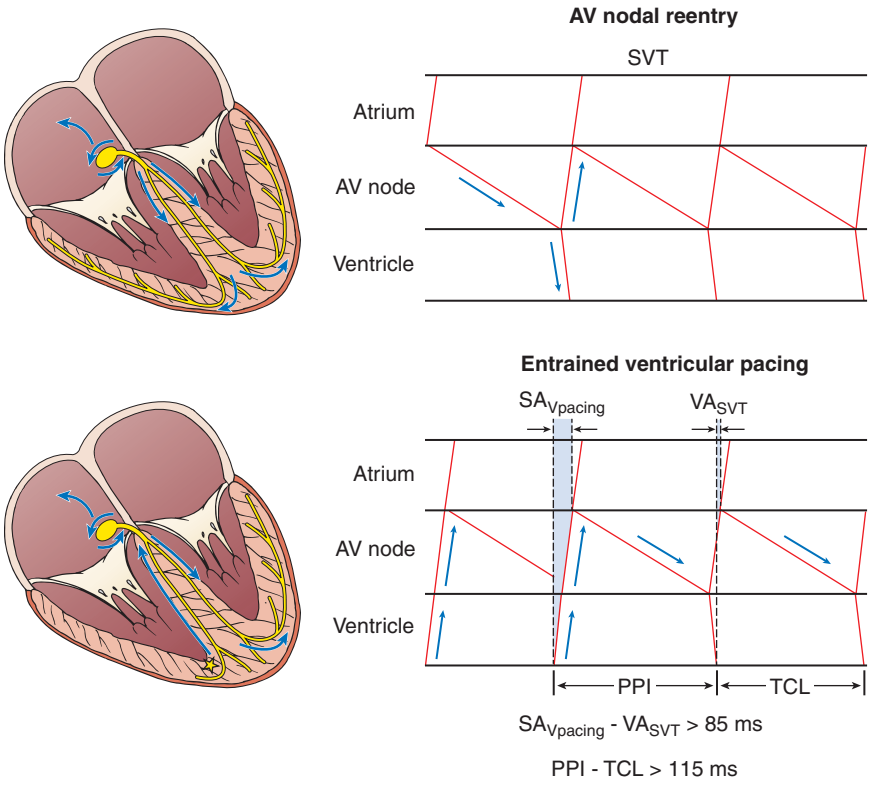


Figure 2-19

Fig. 2-19 shows entrained ventricular pacing during AV nodal reentry.

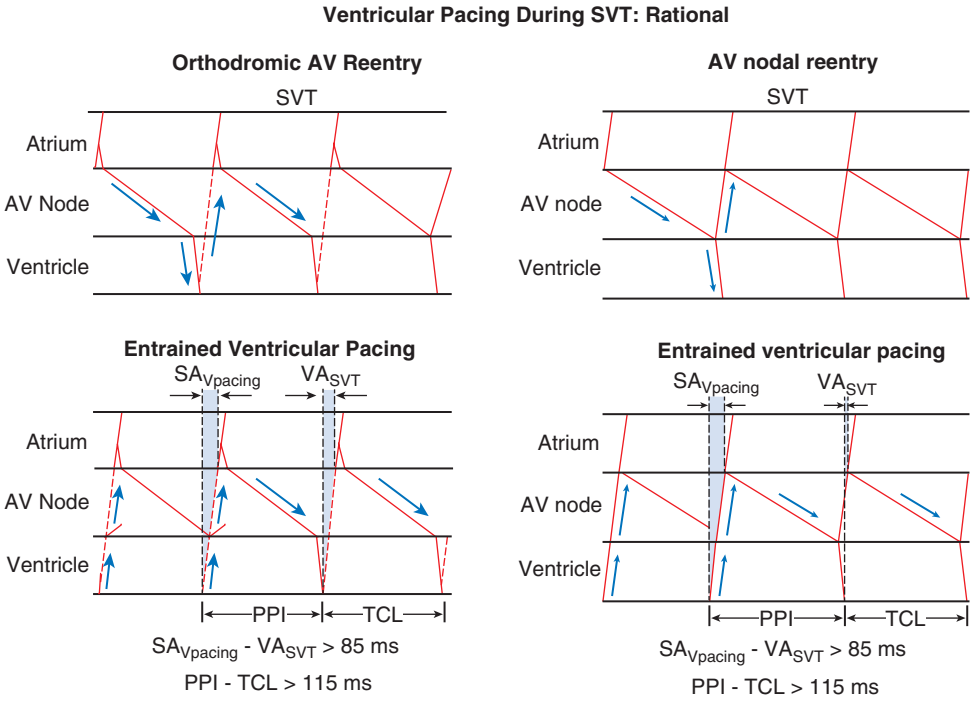


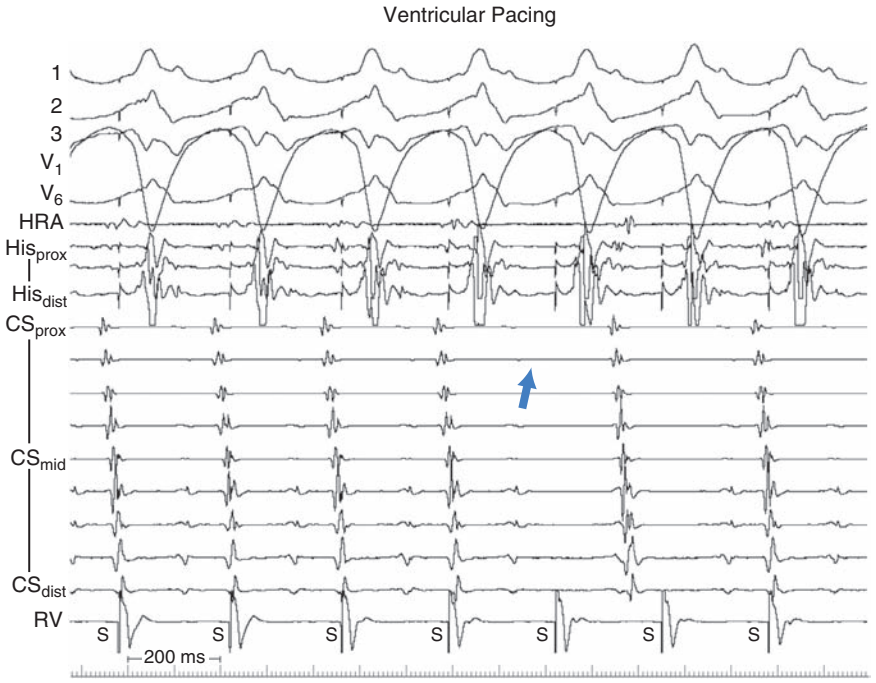
Figure 2-20

(From Michaud et al. Differentiation of atypical atrioventricular node reentrant tachycardia from orthodromic reciprocating tachycardia using a septal accessory pathway by the response to ventricular pacing. *JACC* 2001;38:1163-7.)

Fig. 2-20 is a comparison of SVT and responses to overdrive ventricular pacing in orthodromic reentry with a bypass tract versus AV nodal reentry. In each case, the paced wavefront must travel from the pacing site to the circuit (stimulus-atrial interval, SA) and back to the pacing site (PPI). Fundamentally, because a right ventricular pacing site is relatively near an orthodromic tachycardia circuit, the SA-VA and PPI-TCL differences are shorter than similar indices in cases of AV nodal reentry, in which the ventricular pacing site is remote from the circuit.

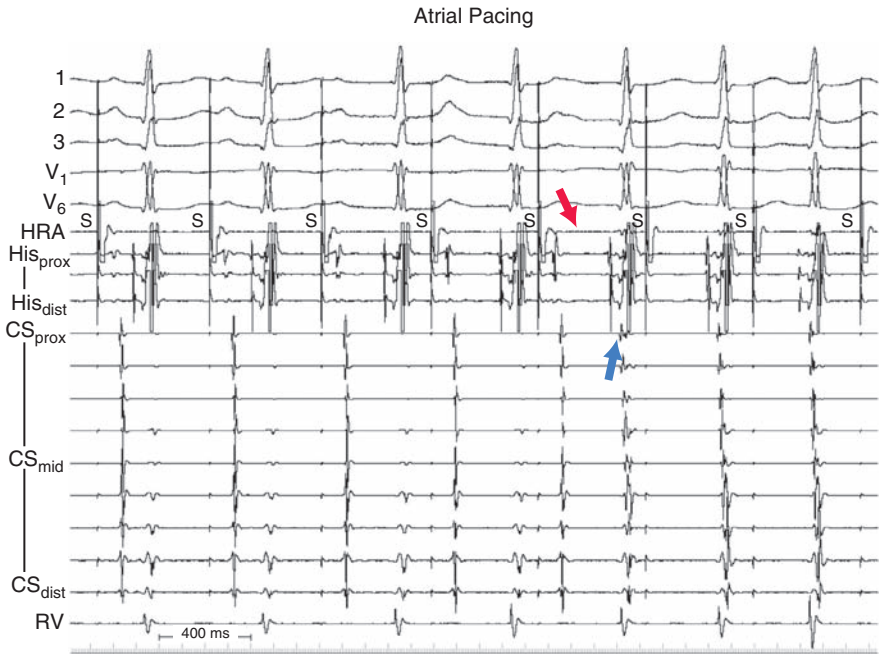
Ventricular and Atrial Pacing in Sinus Rhythm

Figure 2-21



Ventricular pacing to retrograde block in a pattern of Wenckebach is shown in Fig. 2-21 *(blue arrow)*.

Figure 2-22



In Fig. 2-22, burst atrial pacing shifts from fast to slow pathway *(red arrow)* and initiates SVT *(blue arrow)*. Subsequent stimuli do not capture because SVT has superseded them.

Atrial Extrastimulus Testing

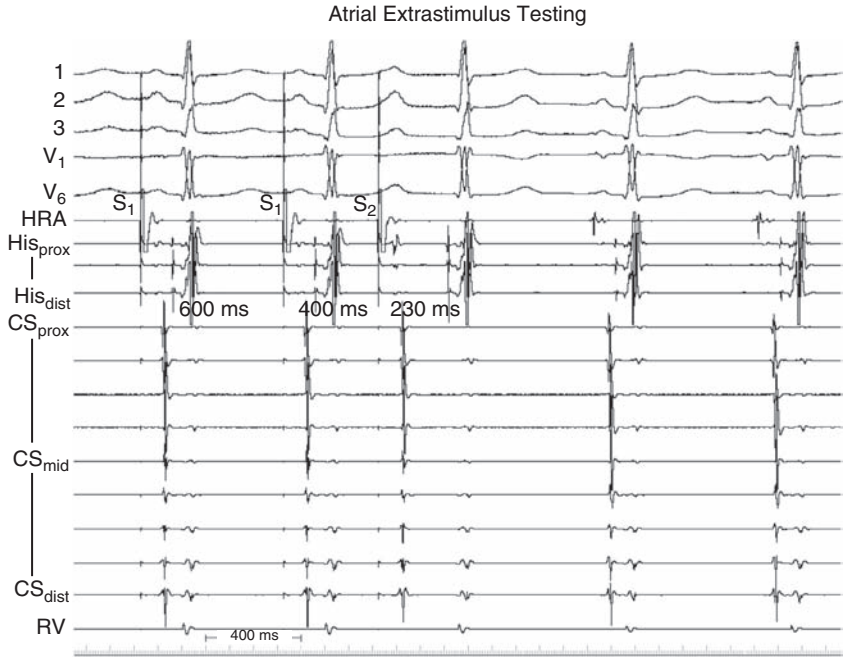


Figure 2-23

Atrial extrastimulus testing 600/400 ms (Fig. 2-23) yields an AH of 230 ms.

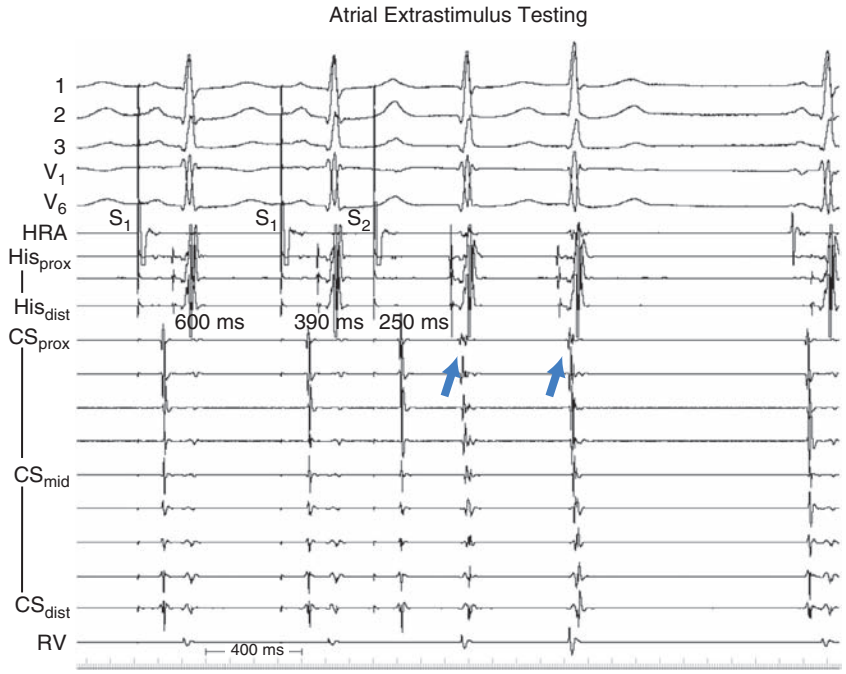


Figure 2-24

Atrial extrastimulus testing 600/390 ms (Fig. 2-24) yields an AH of 250 ms; though not a classic AH "jump" (because the difference in AH intervals resulting from extrastimuli 10 ms apart is <50 ms), the extrastimulus is followed by two echoes *(arrows)*.

Ablation Sites and Assessments

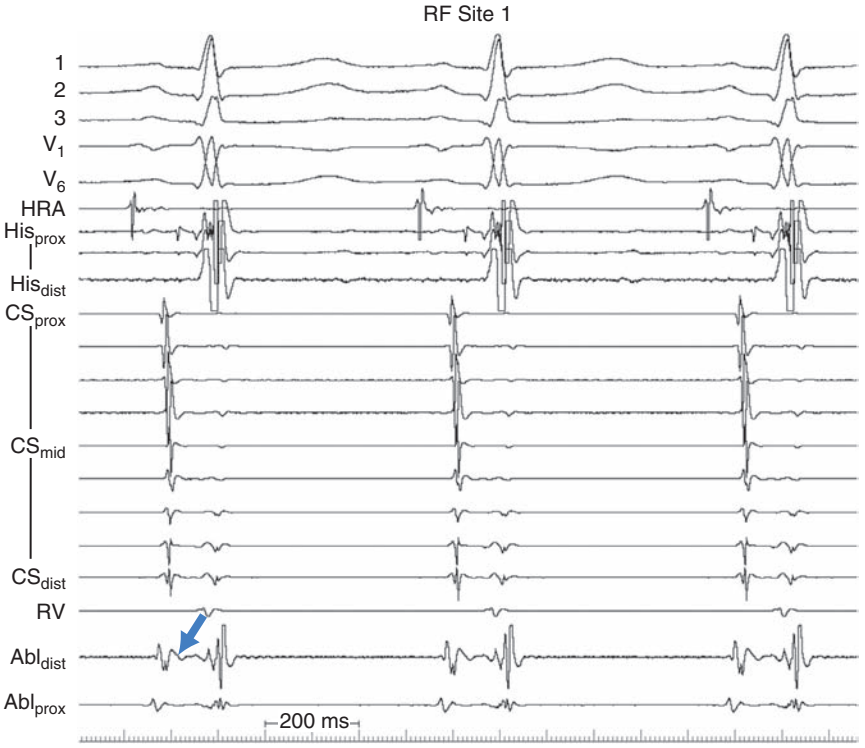


Figure 2-25

Having established AVNRT as the diagnosis, slow pathway ablation commences, as shown in Fig. 2-25. A typical slow pathway potential *(arrow)* is evident.

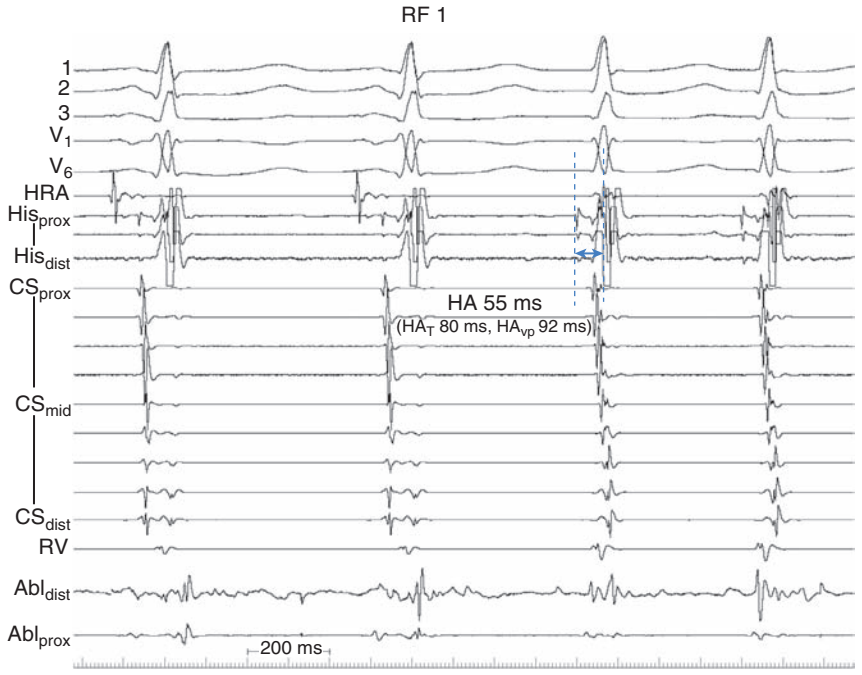


Figure 2-26

During radiofrequency (RF) energy delivery, accelerated junctional rhythm is seen on the last two complexes at right of Fig. 2-26; the HA interval during junctional rhythm is almost always less than the HA in SVT. This is one way to determine whether a rapid 1:1 VA rhythm during RF energy delivery is caused by accelerated junctional rhythm (successful ablation site) versus initiation and continuation of SVT (unsuccessful ablation site).

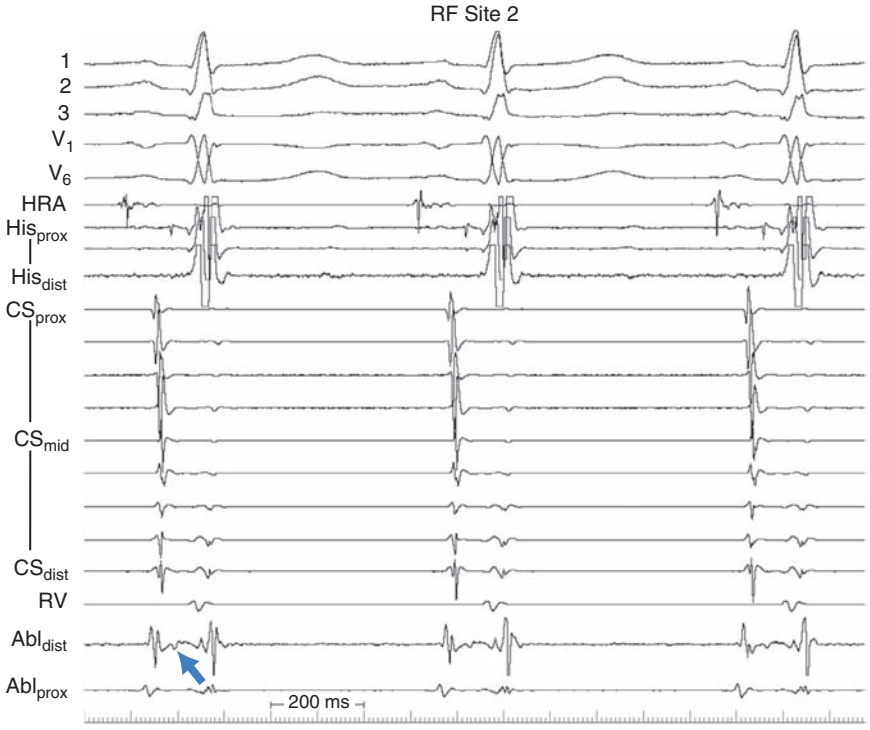


Figure 2-27

After RF 1 (Fig. 2-27), evidence of dual pathways persisted; another site was chosen as shown with another signal compatible with slow pathway activation *(arrow)*.

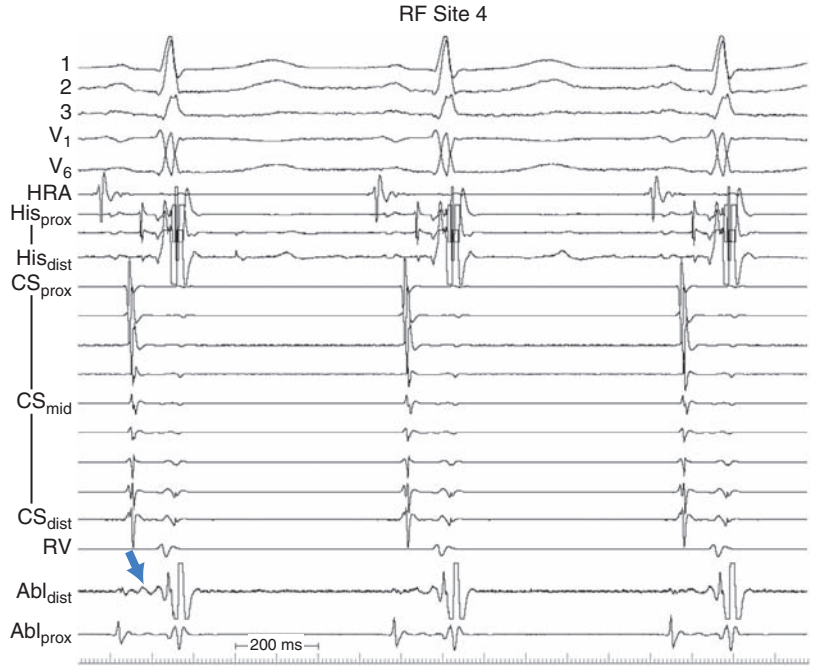


Figure 2-28

As shown in Fig. 2-28, because of persistence of dual pathway physiology, another site of ablation was chosen, with a different type of slow pathway potential *(arrow)*.

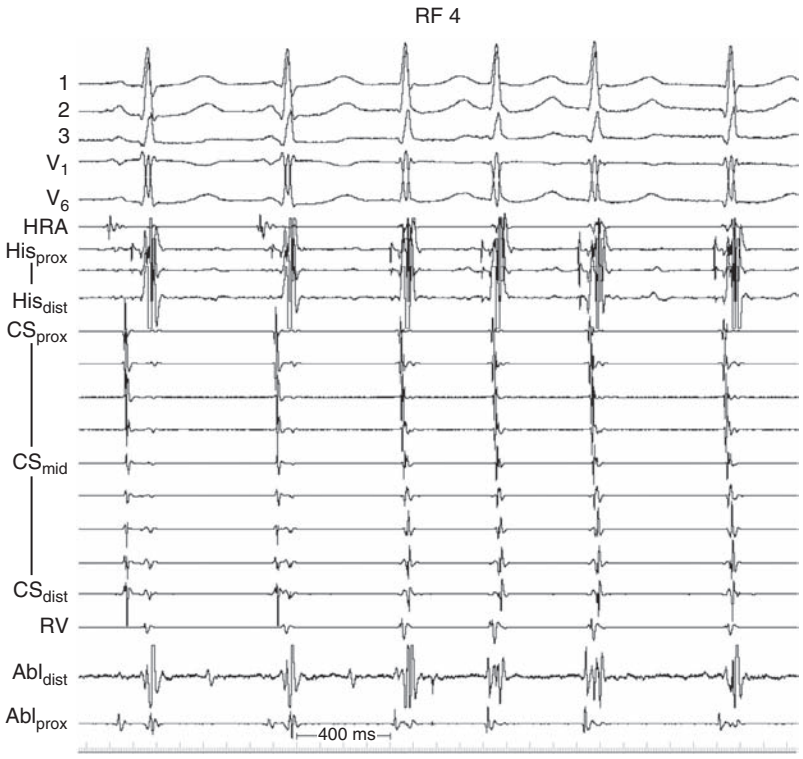


Figure 2-29

At this site in Fig. 2-29, junctional rhythm during RF ablation occurs rather early in the energy application.

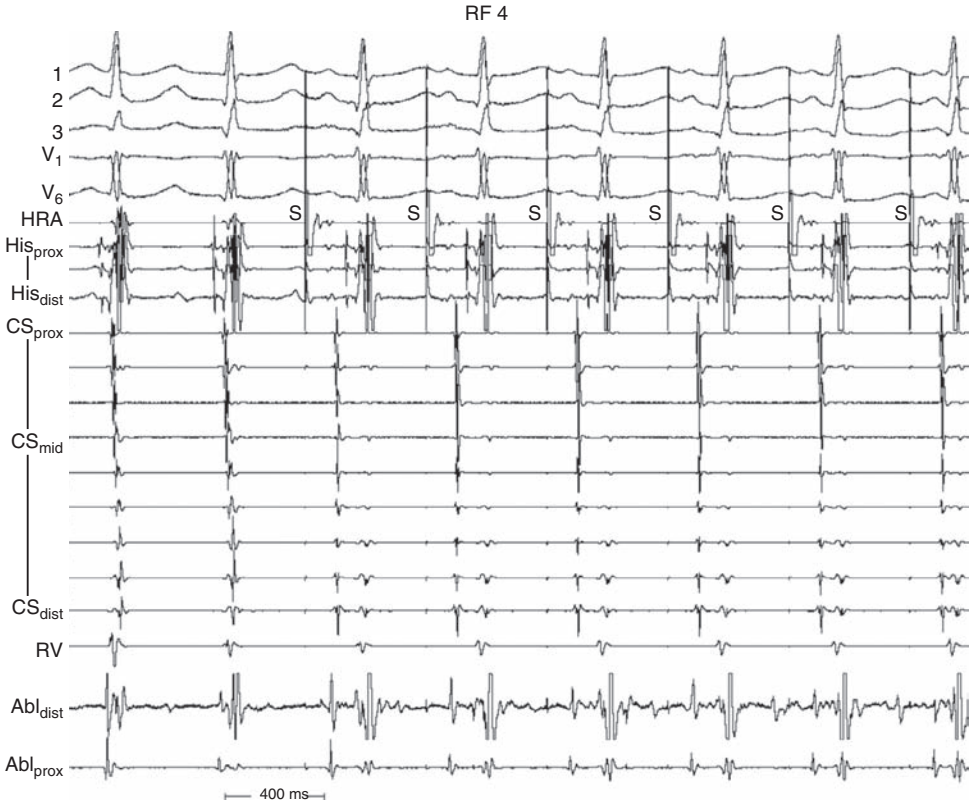


Figure 2-30

Once stable accelerated junctional rhythm is seen, it can be followed by overdrive atrial pacing to ensure the integrity of AV conduction during a more rapid infranodal rhythm (Fig. 2-30). If the PR interval prolongs or AV block occurs, RF delivery can be immediately stopped and almost always conduction returns to what it was before that RF delivery.

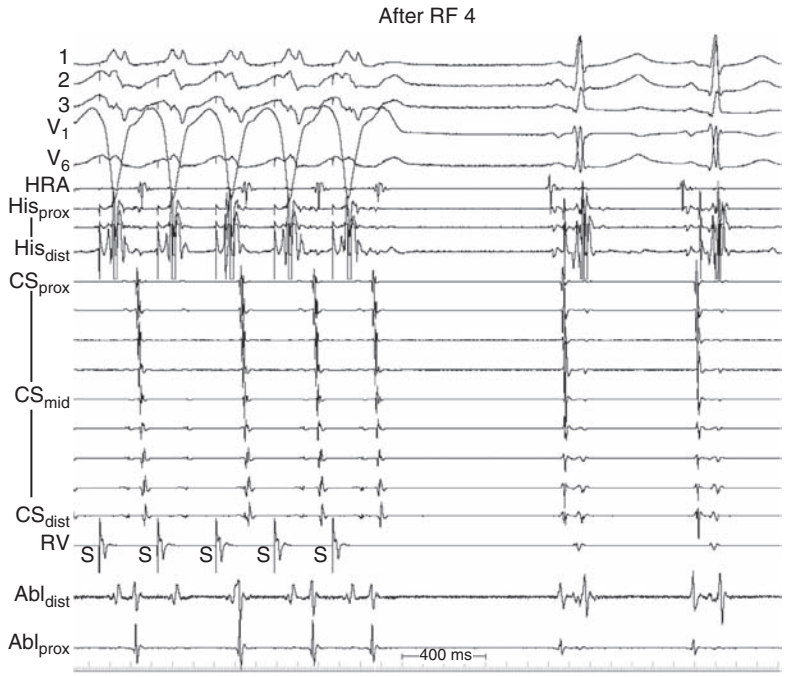


Figure 2-31

Retrograde conduction after RF No. 4 is still good, as is anterograde conduction during sinus rhythm (at right of Fig. 2-31).

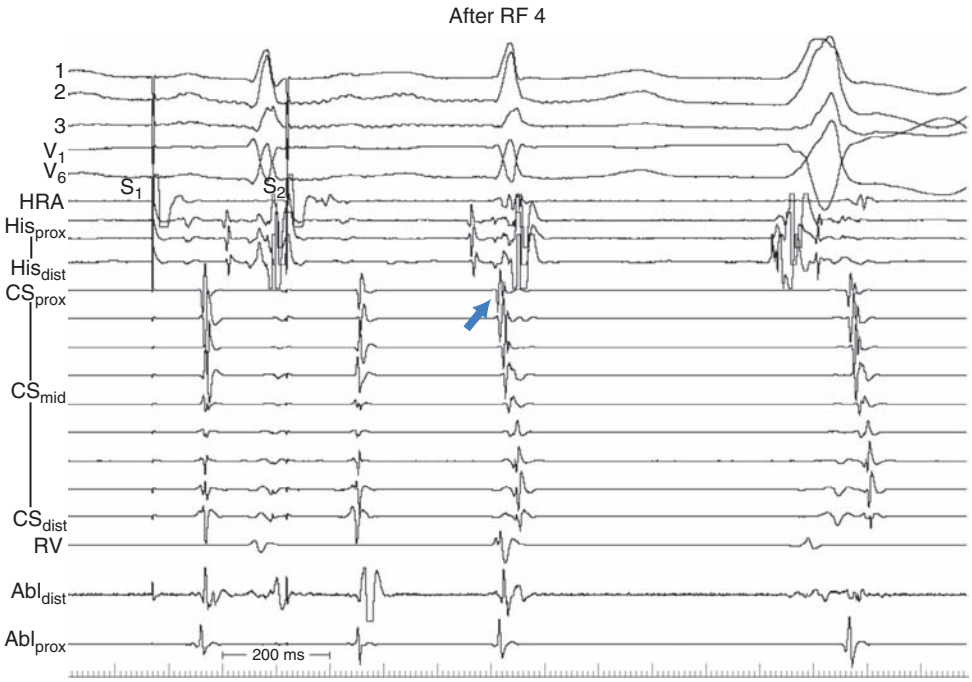


Figure 2-32

Atrial extrastimulus testing after RF 4 still shows an AV nodal echo (only one, *arrow*). A premature ventricular complex (PVC) at the right of Fig. 2-32 shows retrograde His and atrial activation.

SVT Repeatedly Initiated with Atrial Stimulation After Four Attempts at Slow Pathway Ablation,

- No inducible SVT
- Anterograde dual AV nodal pathways and single echoes still
- Preserved AV conduction

What Should You Do Now?

- Try to eliminate dual pathways and echoes?
- End the procedure, risk of AV block is too high?

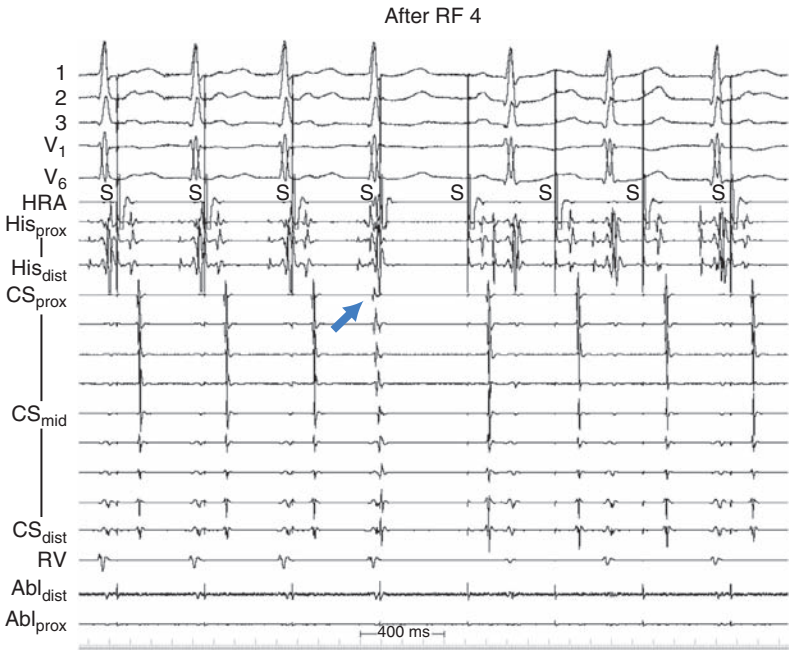


Figure 2-33

In Fig. 2-33, single echoes *(arrow)* remain on atrial drive train; what should be done now? As review, in the baseline state, sustained SVT was easily and repeatedly initiated with atrial pacing, but the slow pathway is still present (although only single echoes are inducible) after four RF applications to the AV nodal slow pathway region. Normal AV conduction is preserved. Is this a good endpoint of the procedure? It would be reasonable to stop here, anticipating a good clinical outcome without risking heart block with additional ablation. We elected to try a little more to eliminate the slow pathway and echoes, however.

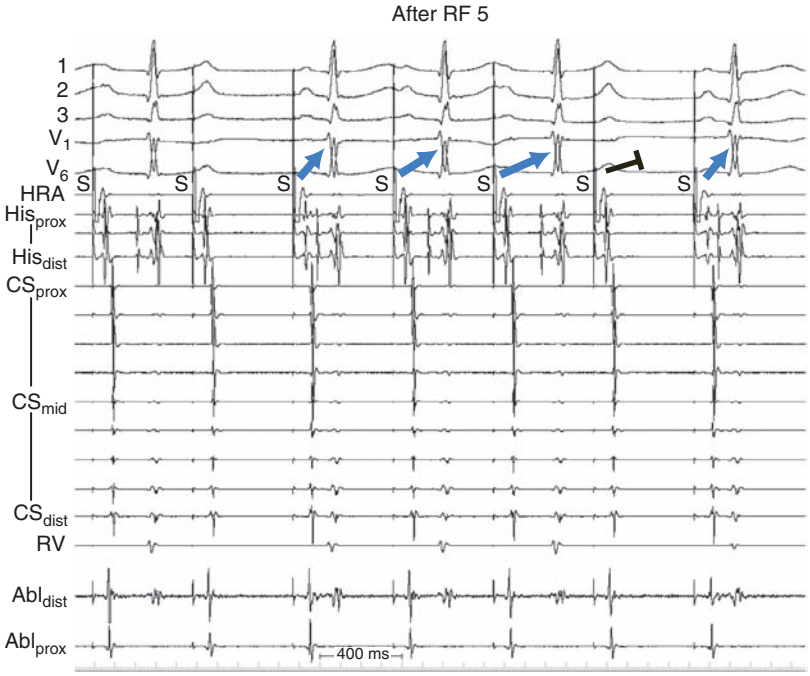


Figure 2-34

In Fig. 2-34, another RF application was given in a similar area, resulting in complete elimination of anterograde slow pathway conduction. (Of note, electroanatomic mapping was not used in this procedure.)

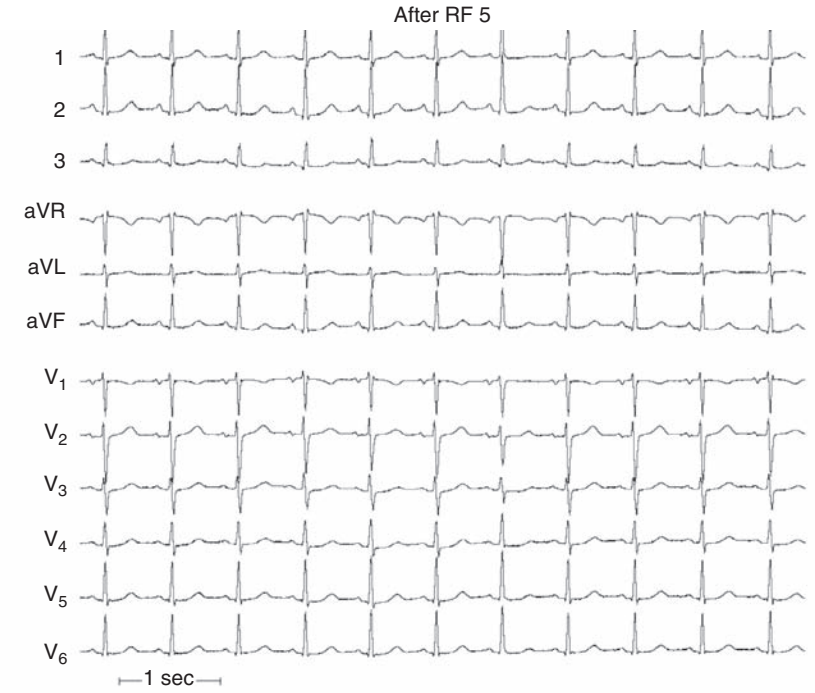


Figure 2-35

Fig. 2-35 demonstrates sinus rhythm after all ablations remains, with normal intervals.

Summary

- AV nodal reentry should be readily distinguished from other SVTs in order to select the appropriate RF targets.
- The vigor of slow pathway ablation should be (Table 2-1)
  - Proportional to the amount of clinical impact SVT has
  - Inversely proportional to the ease of SVT initiation
  - Inversely proportional to the risk of heart block

TABLE 2-1 How Aggressive to be with Slow Pathway Ablation?

Finding	Vigor of Slow Pathway Ablation
Clinical Importance of SVT	
Very bothersome	Relatively safe to be aggressive
Occasional mild nuisance	Be very careful!!!
Ease of SVT Initiation	
Easily reproducible sustained SVT	Eliminate sustained SVT (dual pathways, echoes OK)
Dual pathways + reproducible echoes	Eliminate slow pathway if possible
Dual pathways only	Eliminate slow pathway
Distance from CS os to His Bundle	
Long (≥10 mm)	Relatively safe to be aggressive
Short (<10 mm)	Be very careful!!!

3 Atypical ("Fast-Slow") Atrioventricular Nodal Reentry

Case Presentation

- A 44-year-old man had palpitations for about 2 years. Episodes often occurred during exercise, lasting a few minutes to hours. With one prolonged episode, he went to the emergency room (ER). There, an ECG showed a regular, narrow QRS tachycardia at 180/min, with a long RP interval, which was terminated with intravenous adenosine. Subsequently, metoprolol in tolerated doses was ineffective at preventing recurrent episodes. Findings of physical examination and the resting ECG were normal. Echocardiogram revealed mild global left ventricular hypokinesis. He was referred for EP study and possible ablation.

Baseline ECG and Intracardiac Recordings

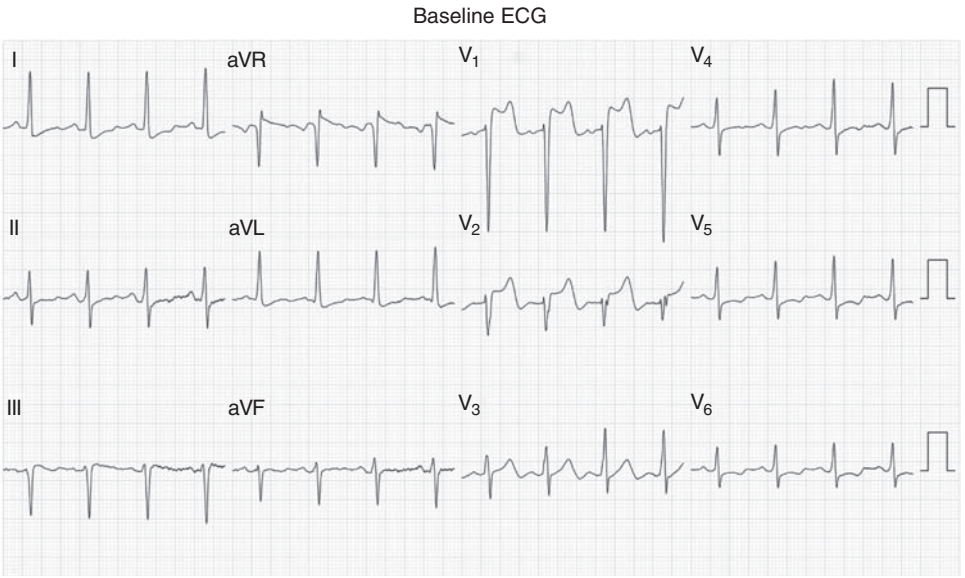


Figure 3-1

There are no clues from the sinus rhythm ECG (Fig. 3-1) as to what the patient's supraventricular tachycardia (SVT) is. ST elevation in V1-V2 is an artifact of the recording system.

Any Clues as to SVT Diagnosis? [Fig. 3-2]

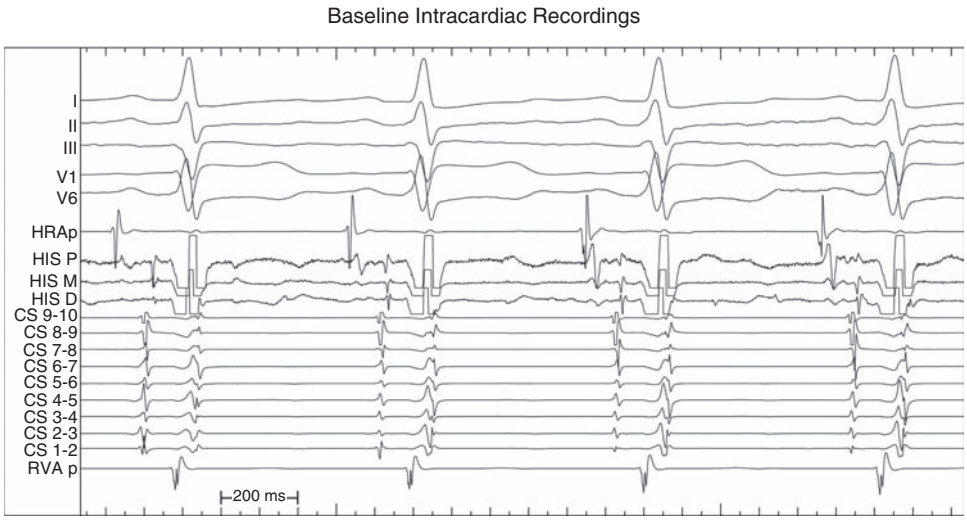


Figure 3-2

There are likewise no clues from the intracardiac recordings (Fig. 3-2), such as subtle preexcitation, as to the cause of the patient's SVT.

Baseline Ventricular Pacing

Does This Include/ Exclude Any Diagnoses? [Fig. 3-3]

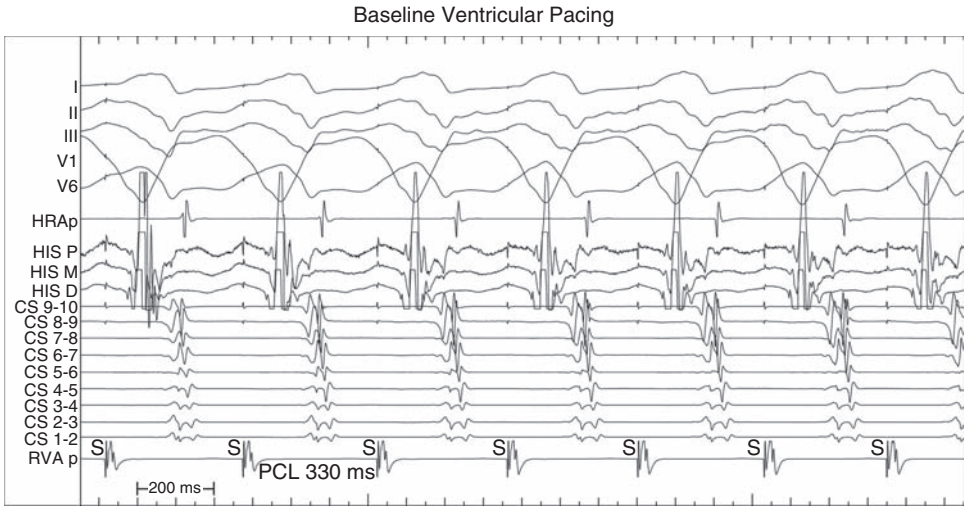


Figure 3-3

A good way to start investigating for causes of SVT is with ventricular pacing. In Fig. 3-3, it appears that retrograde conduction is rather good and midline (suggesting either a fast atrioventricular [AV] nodal pathway or a septal bypass tract). However, none of the potential causes of SVT is excluded by these findings.

Baseline Coronary Sinus Pacing

Does This Include/ Exclude Any Diagnoses? [Fig. 3-4]

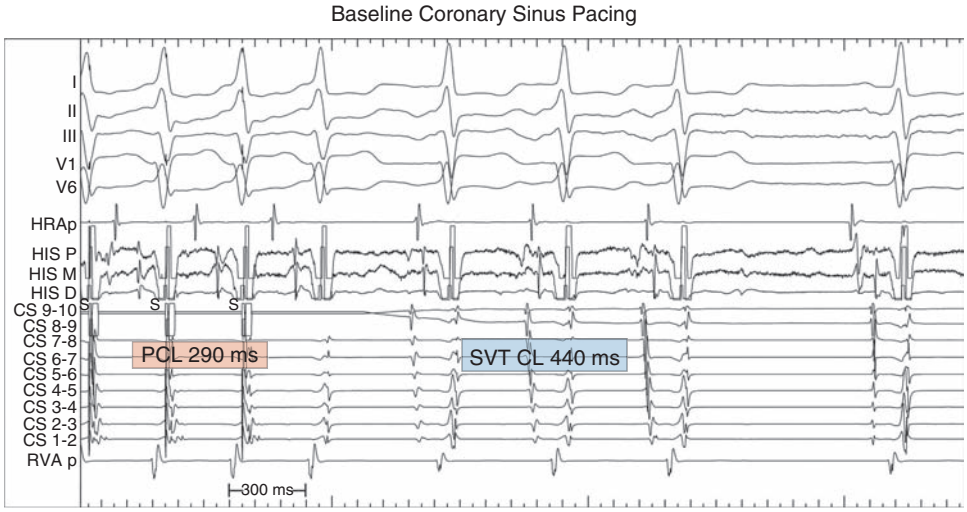


Figure 3-4

Three cycles of a "long-RP" tachycardia are initiated with atrial pacing (Fig. 3-4). The differential diagnosis for this is atrial tachycardia (AT), orthodromic AV reentry using a slowly/decrementally conducting bypass tract as the retrograde limb, or atypical AV nodal reentry (slow pathway retrograde, fast pathway anterograde). Of these diagnoses, a focal AT seems the least good fit because of the prolonged pause between the last stimulated complex and the first tachycardia complex (here, about 550 ms). Nothing in this figure differentiates between the other two possible causes.

SVT Initiation with Ventricular Pacing

What Kinds of SVT Are Initiated With Ventricular Pacing? [Fig. 3-5]

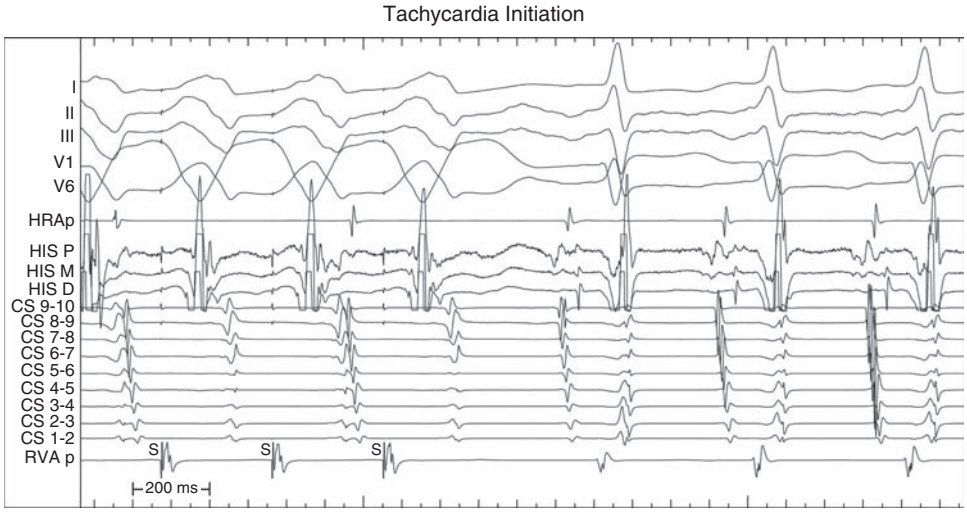


Figure 3-5

In Fig. 3-5, ventricular pacing induces SVT. Several types of SVT can be initiated with ventricular pacing, including orthodromic SVT, atypical AV nodal reentry (AVNRT), and typical AVNRT; even focal ATs (rarely) can be initiated. What information is shown in Fig. 3-5 that could help differentiate among these?

AT initiation with ventricular pacing is rare and likely related to autonomic alterations; it can even occur in the absence of retrograde conduction. The atrial activation sequence is very similar if not the same during ventricular pacing and tachycardia, which would be unusual for AT (not only septal origin—uncommon for AT—but also highly coincidental). Three unlikely events, ventricular pacing induction of AT, tachycardia having the same activation sequence as retrograde conduction, and a septal location, all occurring at once challenge credulity. Thus AT is unlikely. However, there is little here to differentiate

between atypical AVNRT and orthodromic SVT using a slowly conducting bypass tract. The longer VA interval after the last ventricular stimulus, compared with the ongoing rhythm, can be seen with either.

SVT ECG and Intracardiac Recordings

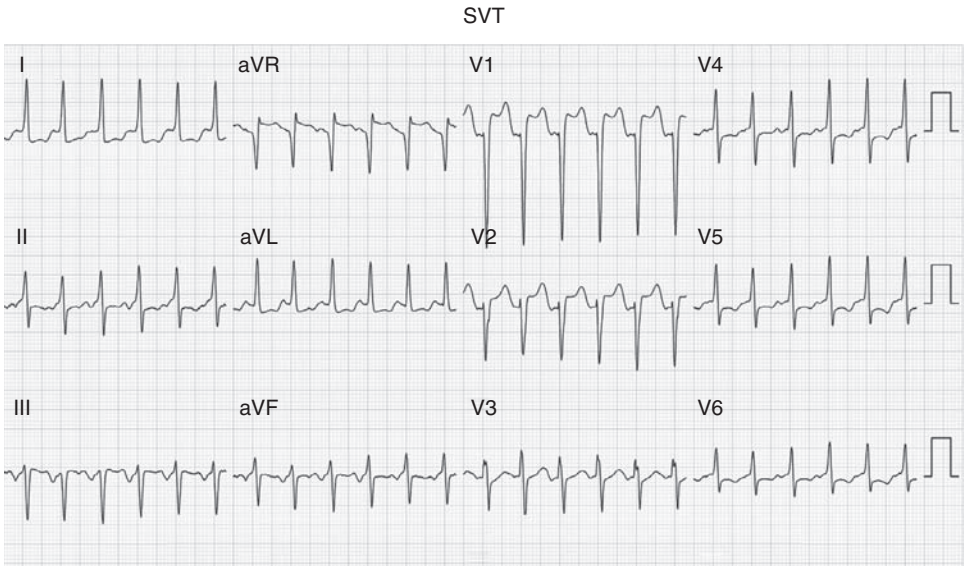


Figure 3-6

Fig. 3-6 shows a 12-lead ECG of SVT, a "long-RP" tachycardia. P-wave morphology suggests a low atrial source of earliest activation.

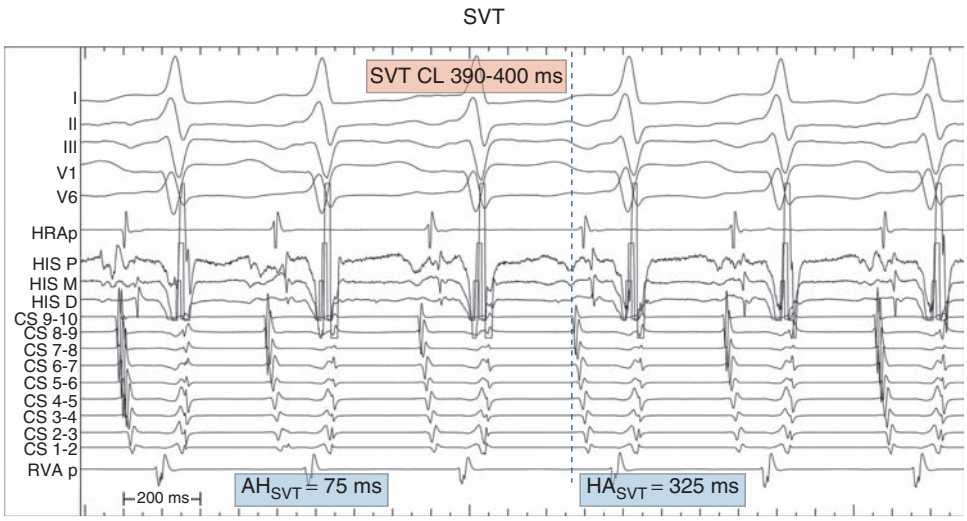


Figure 3-7

Intracardiac recordings during sustained SVT (Fig. 3-7) show an atrial activation pattern with earliest recorded activation near the AV nodal region; measured intervals are as shown for future reference.

Ventricular Extrastimuli and Overdrive Pacing During SVT

Does This Include/ Exclude Any Diagnoses? [Fig. 3-8]

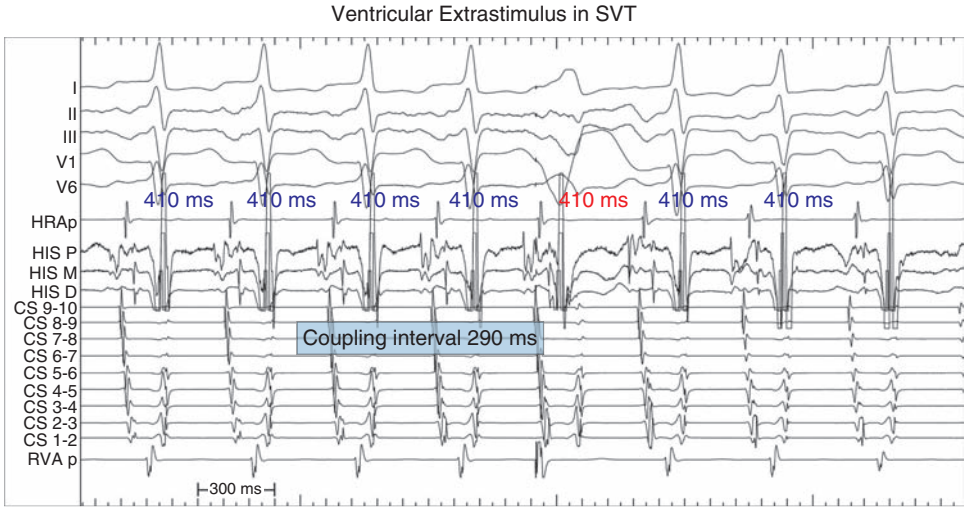


Figure 3-8

A His-refractory has no effect on the timing of subsequent atrial activation; no inference can be made from Fig. 3-8. Closer coupling intervals are needed.

Does This Include/ Exclude Any Diagnoses? [Fig. 3-9]

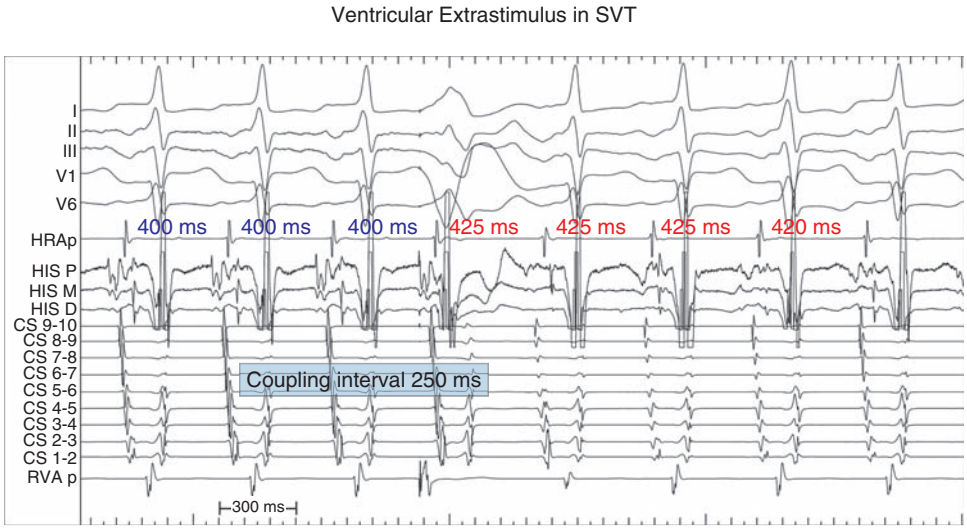
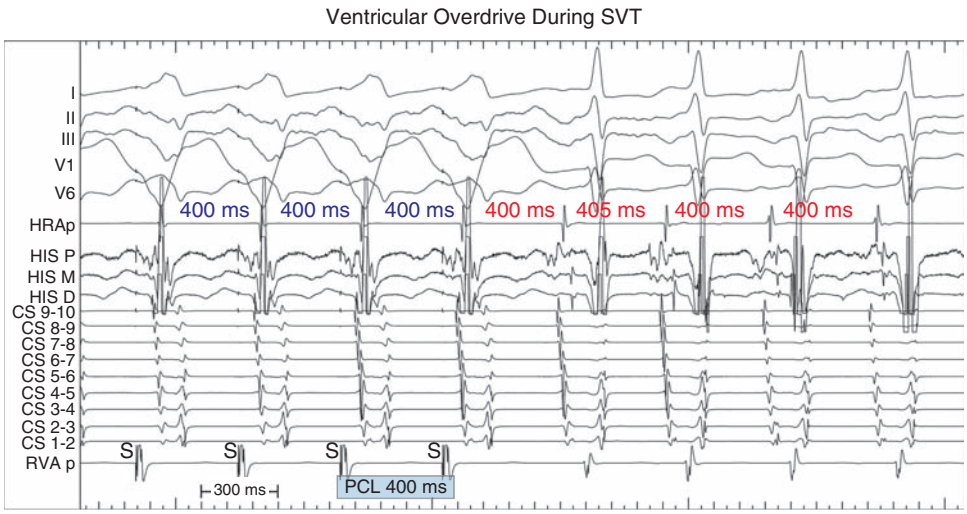


Figure 3-9

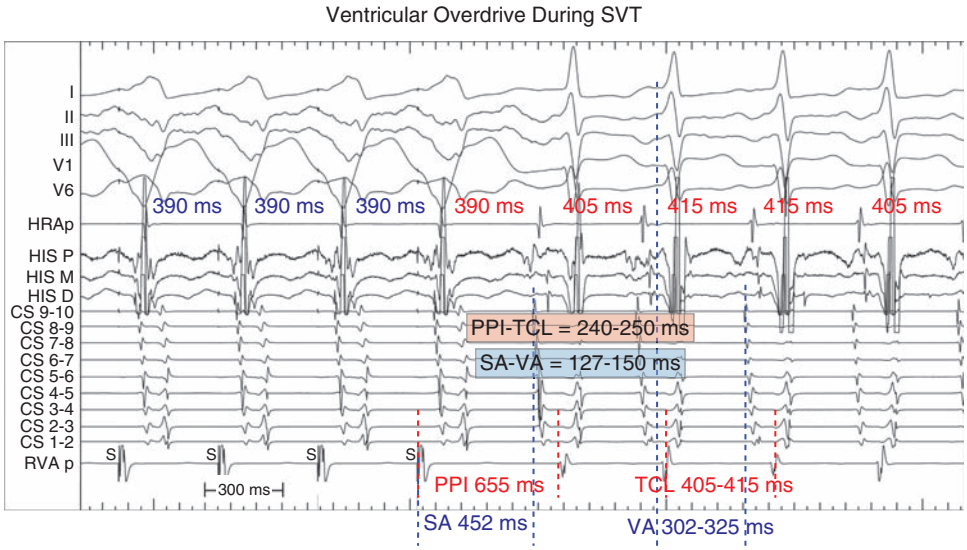
In Fig. 3-9, the A-A interval surrounding the more premature (and still His-refractory) ventricular extrastimulus is longer than baseline; however, tachycardia cycle length (TCL) after this stays at the longer A-A interval. Thus the PVC probably did not actually prolong the VA (hence, A-A) interval but happened to occur at a time when TCL was increasing independently. TCL varied during the procedure from 390 to 440 ms. Because the A-A surrounding the PVC did not differ from others during SVT, no inference can be made from it as to the nature of the tachycardia.



Does This Include/ Exclude Any Diagnoses? [Fig. 3-10]

Figure 3-10

Ventricular overdrive pacing during SVT can often yield important information regarding its diagnosis. The chosen ventricular paced cycle length (400 ms) in Fig. 3-10 is about the same as TCL at this time (400–405 ms); thus no inference should be made as to events after cessation of pacing.



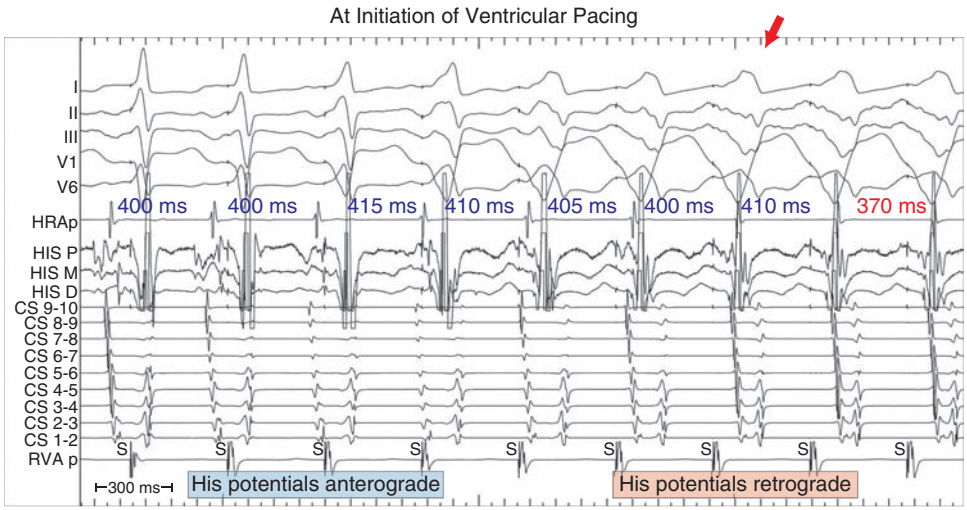
Does This Include/ Exclude Any Diagnoses? [Fig. 3-11]

Figure 3-11

The chosen ventricular paced cycle length in Fig. 3-11 is reasonably faster than TCL; now, conclusions can be made as to events after cessation of pacing. The PPI-TCL (>125 ms) and SA-VA (>85 ms) differences are in a range that suggests AV nodal reentry rather than septal bypass tract-based orthodromic reentry.

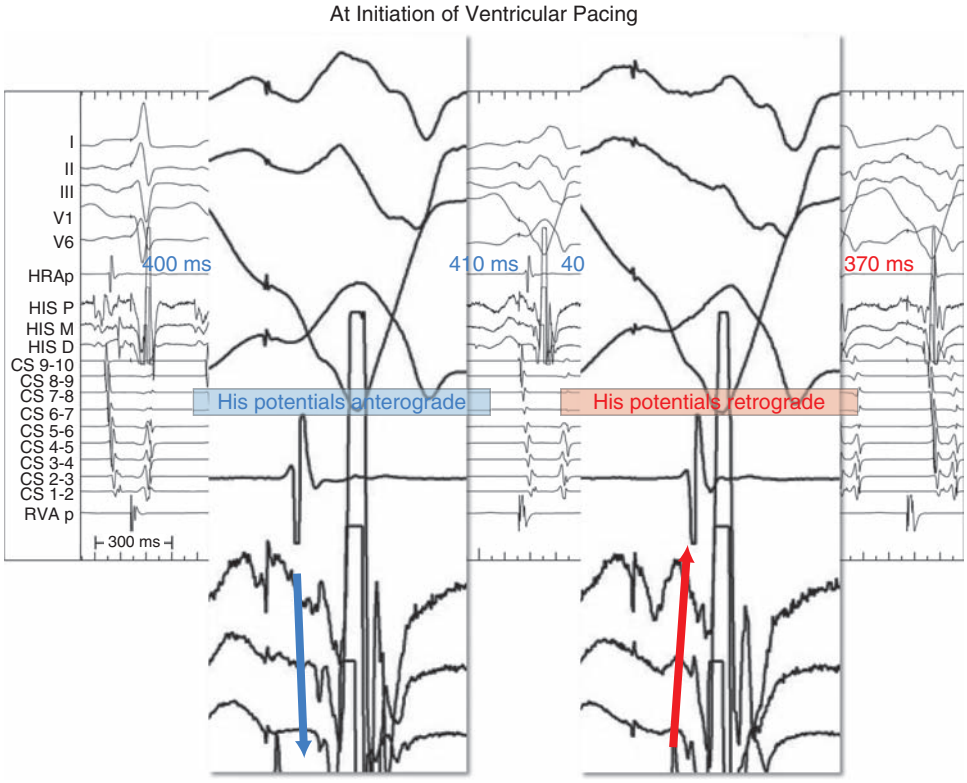
At Initiation of Ventricular Pacing [Fig. 3-12]

Figure 3-12



Fully paced complexes are present for the last 3 cycles in Fig. 3-12 (*arrow*); the A-A interval becomes the same as the ventricular paced CL only on the last cycle.

Figure 3-13



In Fig. 3-13, an enlarged single complex showing anterograde and retrograde His propagation is superimposed on Fig. 3-12.

Initiation of Atrial Fibrillation with Ventricular Pacing

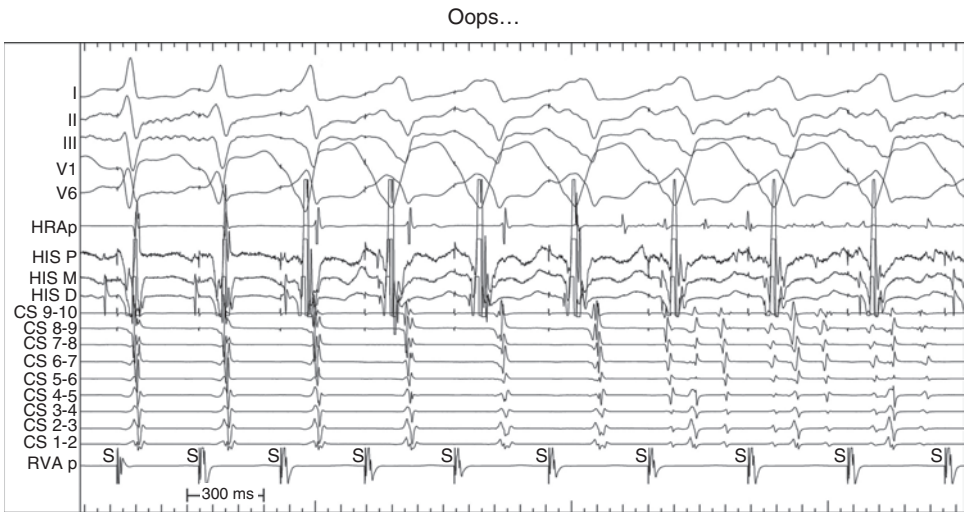
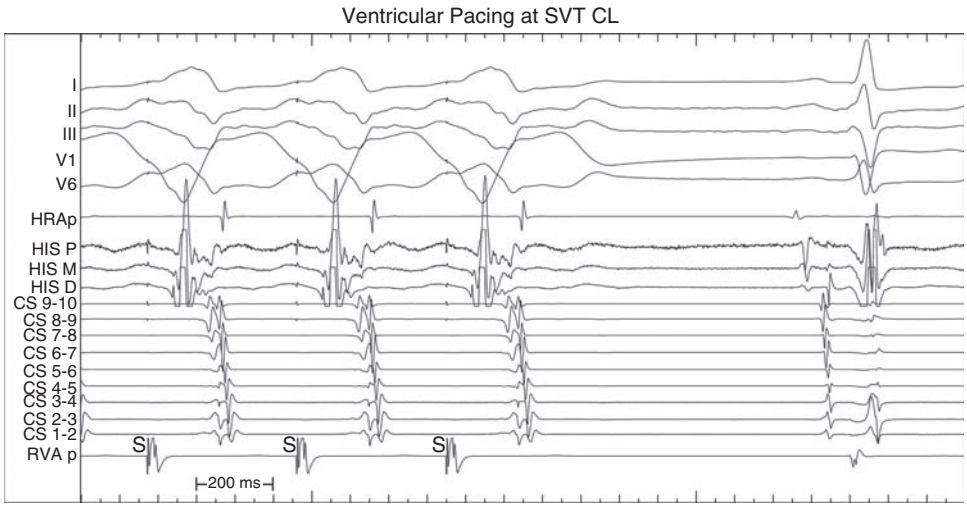


Figure 3-14

As demonstrated in Fig. 3-14, unfortunately, atrial fibrillation (AF) occasionally occurs during ventricular pacing or SVT. This may stop spontaneously or require cardioversion, because it interferes with being able to continue the study. Generally, AF is an artifact of stimulation of the procedure and does not need independent treatment.

Ventricular and Atrial Pacing at TCL During Sinus Rhythm



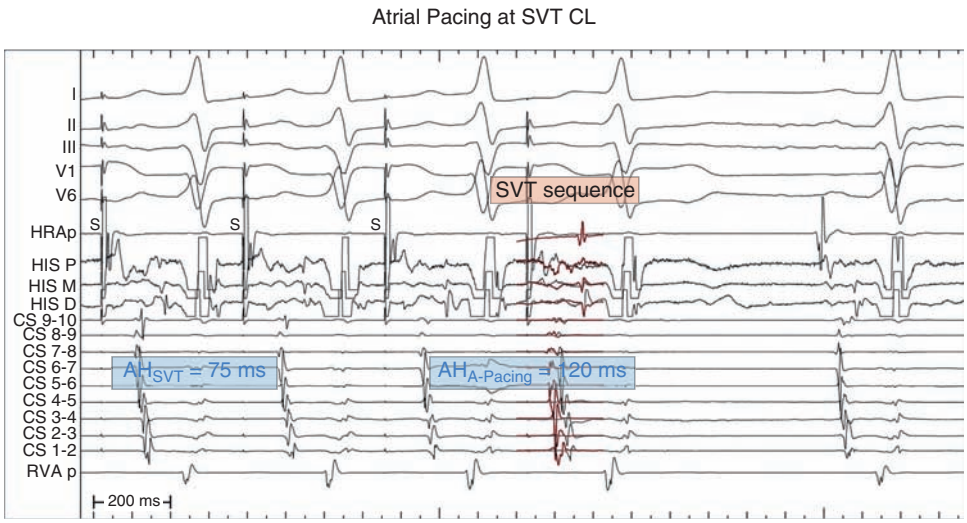
Does This Help In Any Way? [Fig. 3-15]

Figure 3-15

Fig. 3-15 shows HA interval during ventricular pacing at TCL 130 ms; however, this is traveling retrogradely up the fast pathway, not the same pathway as is used during SVT. Thus no comparison of HA intervals (pacing vs SVT) can be made.

Does This Include/ Exclude Any Diagnoses?

Figure 3-16



The AH with atrial pacing at TCL is 120 ms, and during SVT (as measured earlier), 75 ms. Fig. 3-16 is the strongest evidence so far that AV nodal reentry is the diagnosis (AH pacing–SVT difference <20 ms for AT, 20–40 ms for slowly conducting bypass tract, >40 ms for atypical AVNRT). A single complex of SVT is superimposed (*red*) to show that this is not pacing during SVT (different activation sequence with pacing than with SVT).

Parahisian Pacing

Figure 3-17

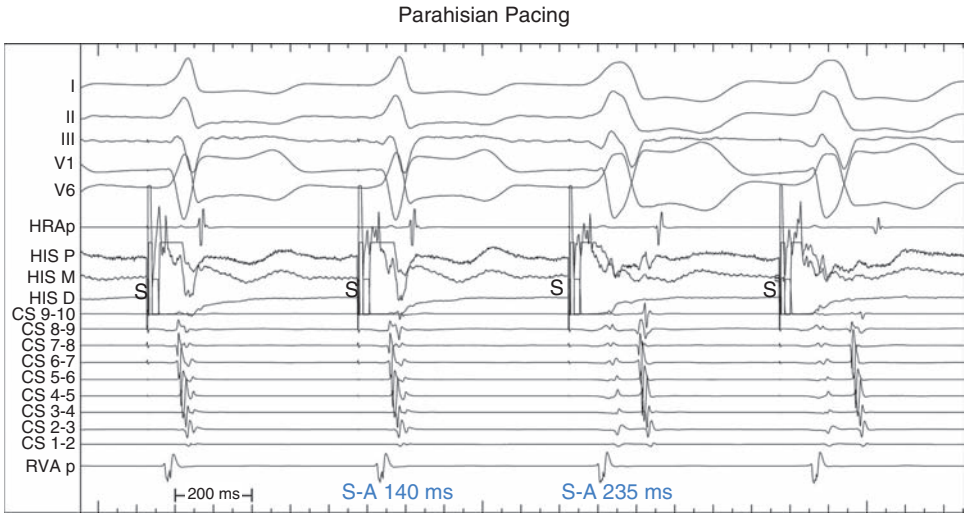


Fig. 3-17 is a nodal pattern (SA in two complexes on the left with a component of His capture shorter than SA with only ventricular capture in two complexes at right) and unfortunately sheds no light for us because any retrograde pathway operative during SVT has a long (rather than short) conduction time and is not evident here, because the retrograde AV nodal fast pathway conducts quite well.

Atrial Extrastimuli in SVT

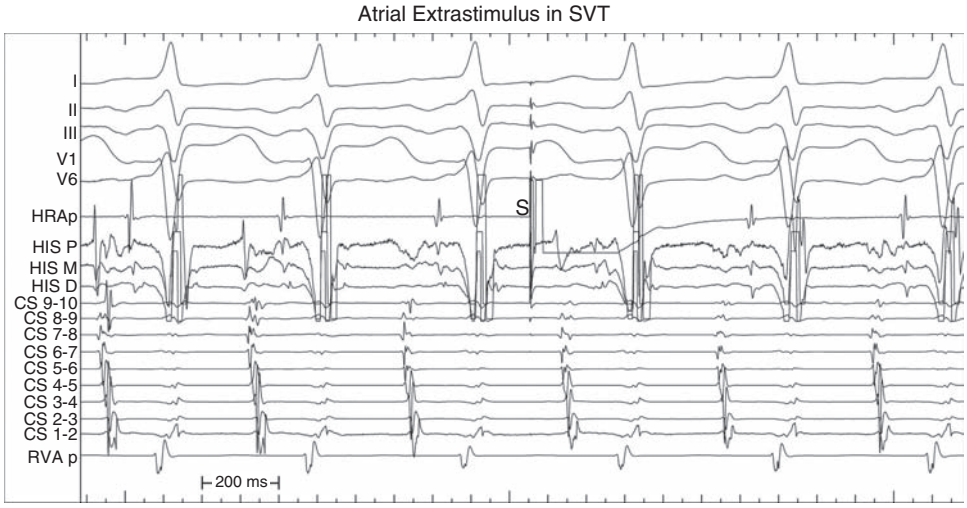


Figure 3-18

Fig. 3-18 is the most premature coupling interval obtainable during SVT (earlier ones met atrial refractoriness). The atrial recording in the His catheter as well as high right atrium are advanced but there is no effect on tachycardia. An AT would not be expected to behave thus.

Ablation Site

Figure 3-19

Having accumulated a substantial amount of data pointing to atypical AV nodal reentry as the tachycardia diagnosis, mapping for an ablation site is begun around the low atrial septum and coronary sinus os. The electrogram at the site shown in Fig. 3-19 begins slightly before all other atrial activations as well as the surface P wave (difficult to discern because of T wave).

Status

At this time, the patient has been diagnosed with atypical (anterograde fast-retrograde slow) AV nodal reentry. An ablation target site below coronary sinus (CS) ostium has been selected, but SVT is now incessant (despite pacing termination, it immediately resumes) and thus ablation cannot be performed during sinus rhythm. How best to proceed? We need to eliminate SVT and not endanger normal AV conduction. Table 3-1 illustrates the advantages and disadvantages of several possible strategies.

TABLE 3-1 Strategies for Ablation During Tachycardia

Ablation Strategy	Advantages	Disadvantages
During tachycardia	Can tell when ablation is successful	Sudden change in heart rate when SVT stops may displace catheter
During sinus rhythm	Can monitor AV conduction	Can't tell when ablation is successful
During ventricular pacing	None	Can't tell when ablation is successful Can't monitor AV conduction
During SVT/ventricular pacing	Can tell when ablation is successful	Can't monitor AV conduction
During SVT/atrial pacing	Can tell when ablation is successful Can monitor AV conduction	Hard to do

Atrial Entrainment During SVT

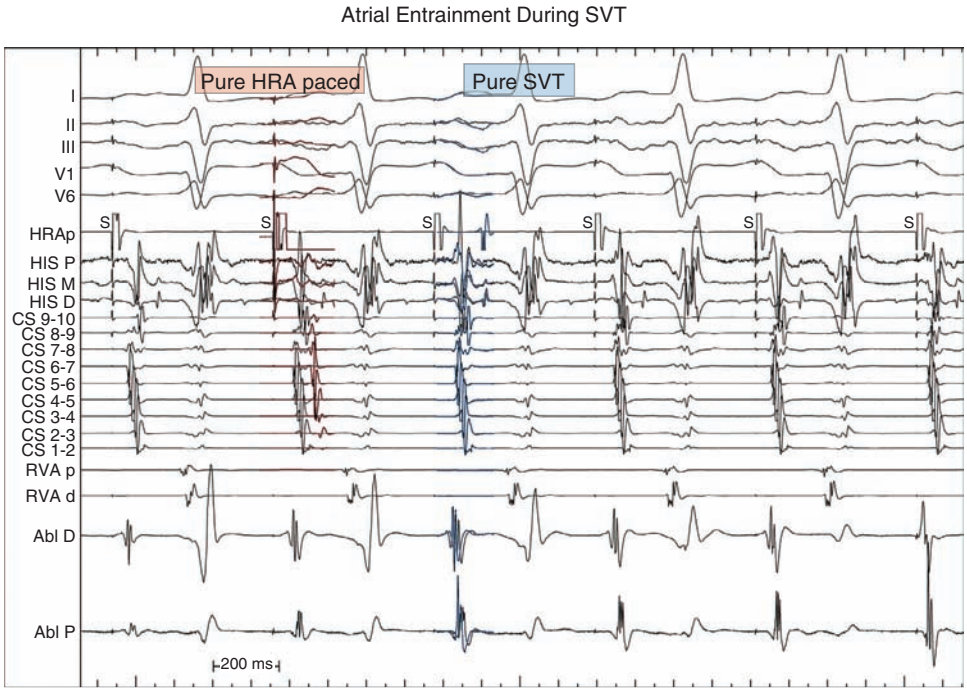


Figure 3-20

The patient had incessant SVT by this time (Fig. 3-20) in the procedure, and so ablation during sinus rhythm was not an option and ablation during SVT was required. If ablation is successful, SVT will terminate and with a sudden heart rate change, the ablation catheter may be displaced from the ablation site, leading to inadequate power delivery at the target. To prevent this, pacing the atrium at the SVT cycle length can help by maintaining the heart rate during successful ablation; the activation sequence will suddenly change when SVT is terminated but there is no sudden change in heart rate that could result in catheter

movement. Pacing has to be performed very carefully to prevent SVT termination by pacing itself. As shown in the figure, the complexes during SVT entrained by right atrial pacing are neither the same as pure atrial pacing (superimposed in *red*) nor SVT (superimposed in *blue*).

Ablation Begins

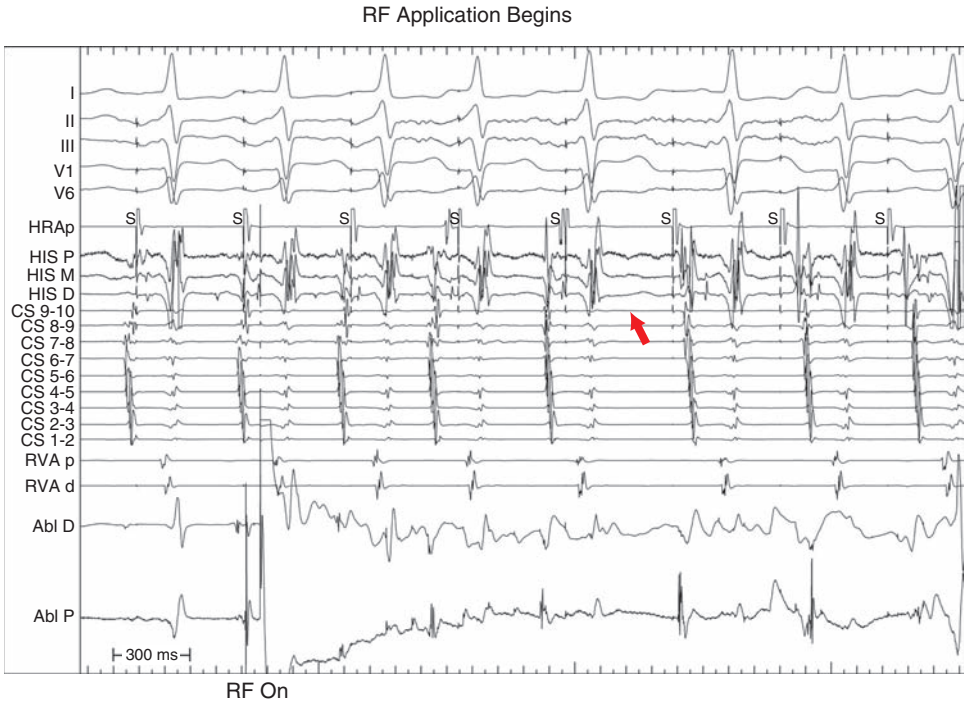
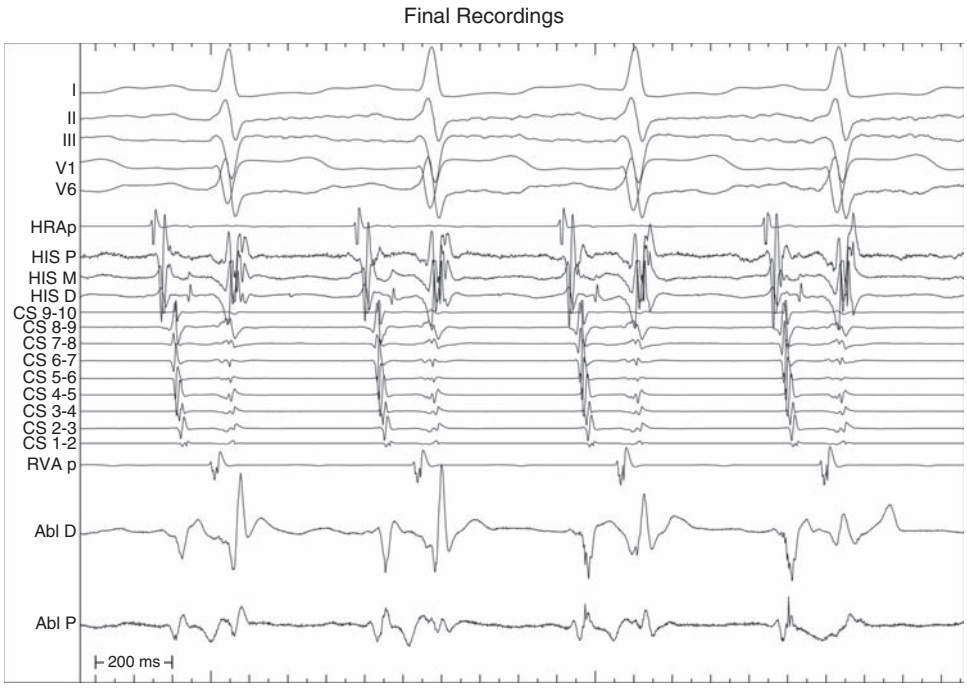


Figure 3-21

SVT terminates (Fig. 3-21, *arrow*) just over 1 second after onset of RF delivery, but the heart rate changes minimally; the ablation catheter position remains stable throughout the time of RF delivery.

Final Recordings

Figure 3-22



As shown in Fig. 3-22, SVT is no longer inducible, and AV conduction is unchanged (normal).

Summary

- Long R-P tachycardias can be challenging to diagnose, but using standard methods the right answer is usually clear:
  - Atrial tachycardia
  - Atypical (fast-slow) AV nodal reentry
  - Orthodromic AV reentry (slowly conducting bypass tract)
  - Rarely, junctional tachycardia with retrograde conduction
- Atypical (fast-slow) AV nodal reentry can occur at any age
- Ablation during incessant tachycardia has several options:
  - *Ablate during tachycardia:* can tell when successful but sudden change in HR with termination may displace ablation catheter
  - *Ablate during SR:* can't tell success but can monitor conduction
  - *Ablate during ventricular pacing:* can't see success during ablation or monitor AV conduction
  - *Ablate during SVT/ventricular pacing:* can tell when successful but AV conduction may suffer
  - *Ablate during SVT/atrial pacing:* can tell when successful as well as monitor AV conduction

Accelerated Junctional Rhythm

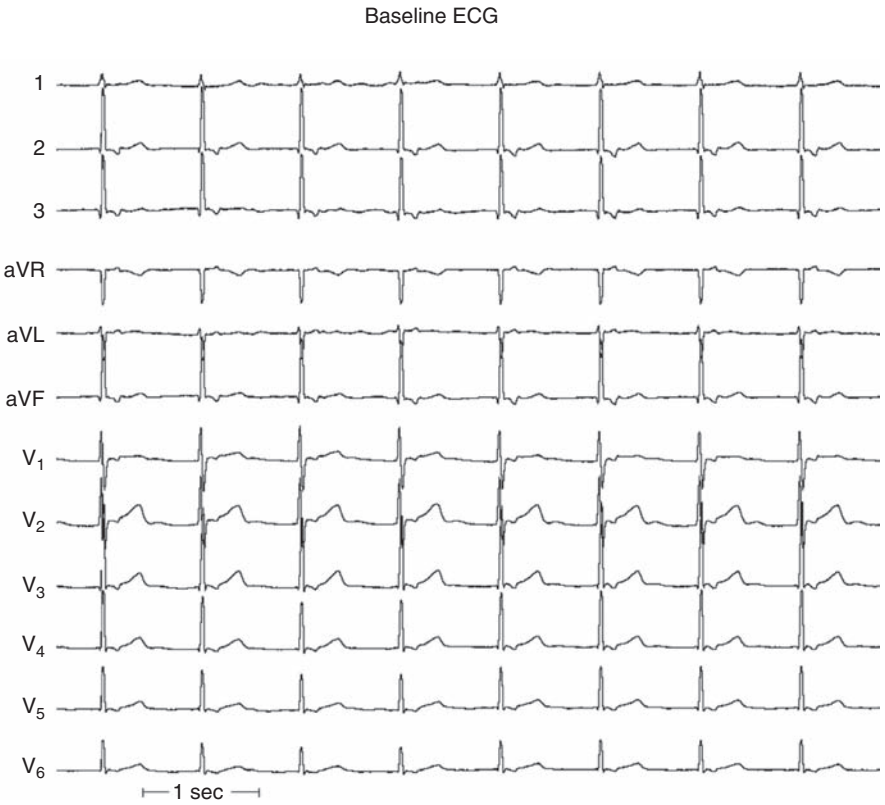
4

Case Presentation

A 29-year-old woman has a history of palpitations and dizziness since age 13. ECGs during episodes showed narrow QRS tachycardia at 190/min. She eventually underwent electrophysiology (EP) study 4 months ago, at which time typical atrioventricular (AV) nodal reentry was initiated and successful slow pathway ablation performed. She had recurrent symptoms within days that became nearly constant. Exam showed heart rate 75/min; large A waves in the jugular veins; soft S1; and was otherwise normal. ECG showed junctional rhythm at 75/min with retrograde P waves. An ambulatory monitor showed junctional rhythm 75 to 90/min most of the time; occasionally, with exertion, sinus tachycardia at 130/min overrode the otherwise constant junctional rhythm. Echocardiogram was otherwise normal. Her symptoms were refractory to beta blockade, propafenone, and flecainide and she was referred for repeat EP study and possible ablation.

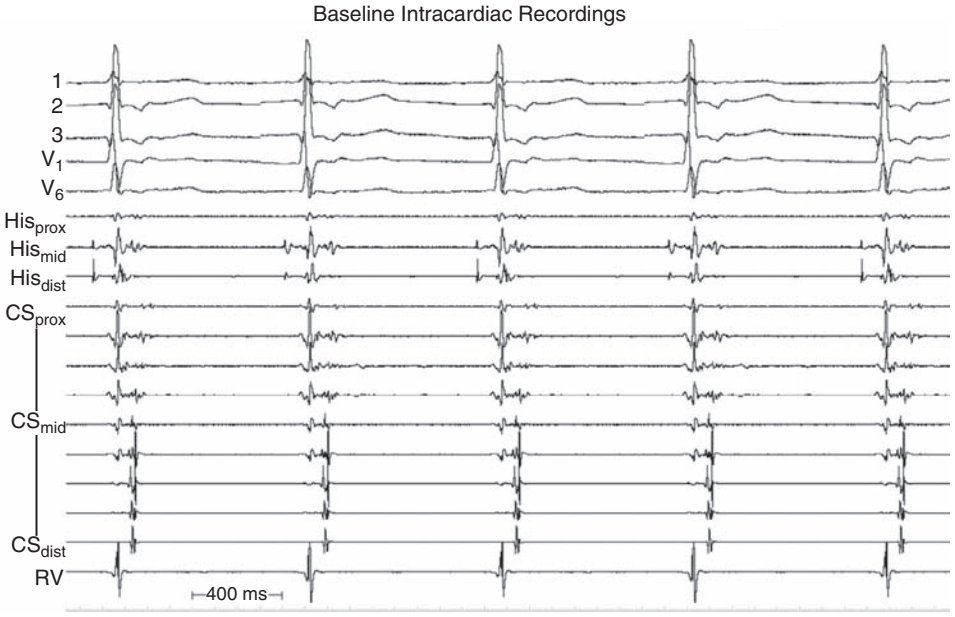
Baseline ECG and Intracardiac Recordings

Figure 4-1



Baseline ECG (Fig. 4-1) appears to show narrow complex junctional rhythm at 75/min with retrograde P waves. This was present nearly constantly and caused a functional pacemaker syndrome (nearly simultaneous atrial and ventricular contraction).

Figure 4-2



Intracardiac recordings during the baseline rhythm (Fig. 4-2) show a His potential before each QRS complex with a normal HV interval (43 ms). Atrial activation is midline and compatible with use of an AV nodal fast pathway. The differential diagnosis for this is automatic accelerated junctional rhythm, AV nodal reentry with a very slow anterograde pathway, or (least likely) atrial rhythm with very slow anterograde AV nodal conduction.

Atrial Extrastimuli in Rhythm

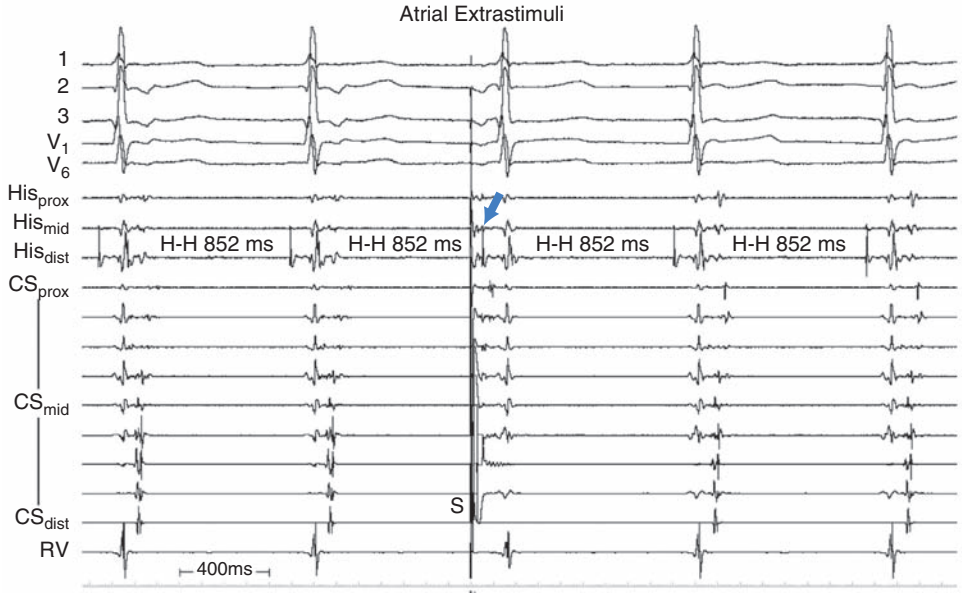


Figure 4-3

To investigate the nature of the rhythm, single atrial extrastimuli are delivered from the coronary sinus. Fig. 4-3 shows that a late-coupled extrastimulus (S), delivered when the His potential has already occurred on time *(arrow)*, captures and advances the timing of atrial activation but does not alter the timing of the next His potential (occurs on schedule at 852 ms). If the rhythm were AV nodal reentry or an atrial rhythm, the timing of the next His potential would have either been advanced or delayed (because in either case its inscription would be dependent on AV nodal conduction). Thus the rhythm is neither AV nodal reentry or atrial in origin.

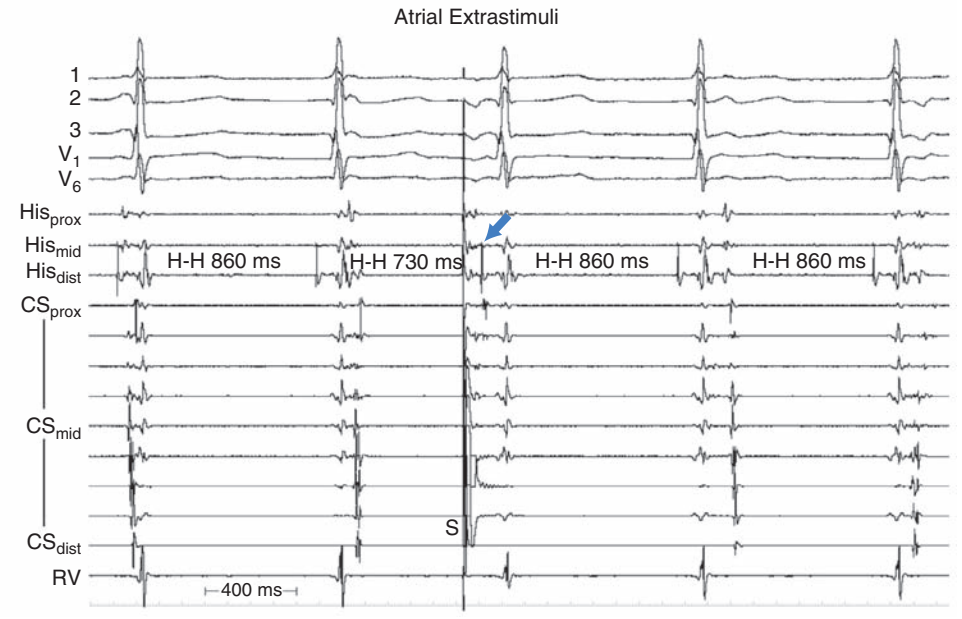


Figure 4-4

In Fig. 4-4, a more premature extrastimulus (S) not only captures and advances the timing of atrial activation, but also conducts over the fast AV nodal pathway to activate the His bundle *(arrow)*. This resets the timing of the rhythm and the next His potential occurs at the same discharge interval (860 ms now) and the rhythm continues on thereafter.

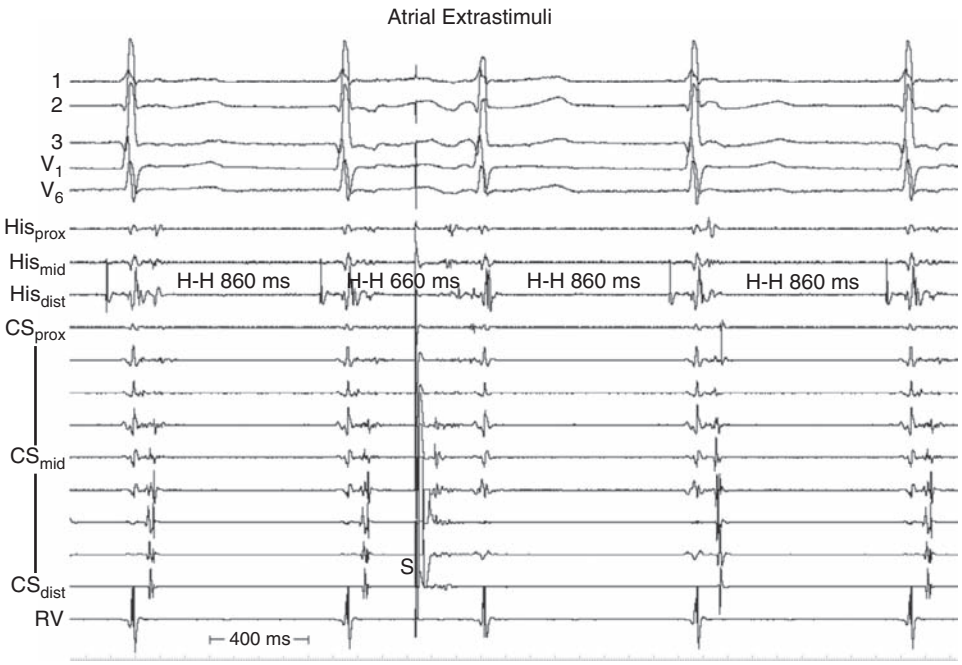


Figure 4-5

A still more premature extrastimulus (S, Fig. 4-5), the earliest one that captured, advances atrial and His activation even more than previously. The next His potential on resumption of the rhythm is at the same discharge interval (860 ms). This is all consistent with accelerated junctional rhythm.

Ventricular Extrastimuli in Rhythm

Where Is the Exact Source of the Abnormal Rhythm? [Fig. 4-6]

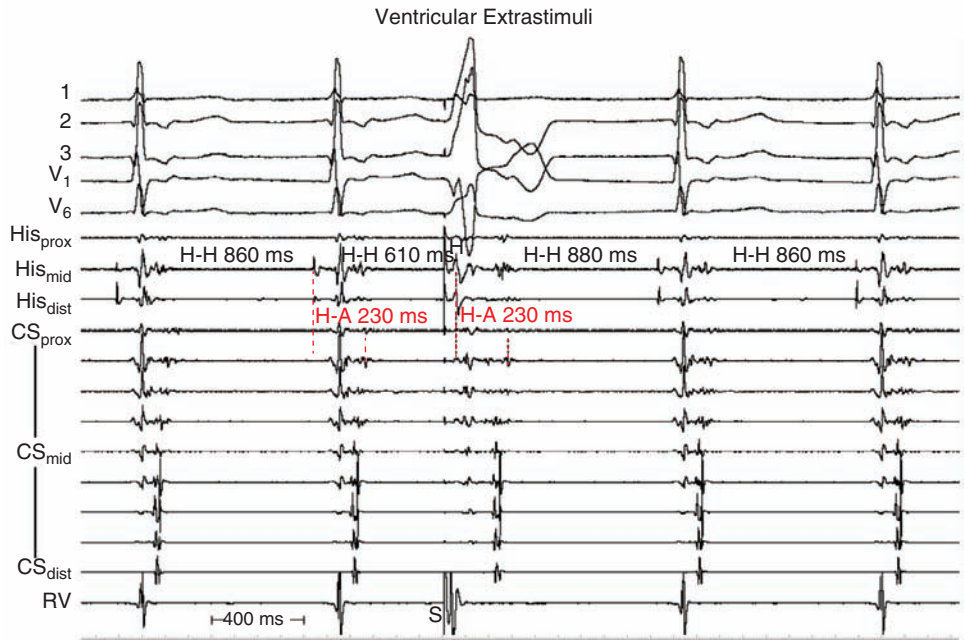


Figure 4-6

From where is the junctional rhythm arising? His propagation is anterograde, indicating somewhere proximal to the His recording site, but where? To investigate this, HA intervals can be analyzed (Fig. 4-6). Here, a ventricular extrastimulus during the baseline rhythm conducts retrogradely to the His (H); the resulting HA interval as shown is the same as during the baseline rhythm, indicating that the site of impulse formation is not far from the

His recording site: if the rhythm originated from a site significantly more proximal in the AV conduction axis, some time would be required to travel from the focus to the His recording site during the rhythm, and thus the "HA" measured would be shorter than the actual time from focus to atrium. Likewise, after ventricular stimulation, the "HA" would be longer than the actual time from the focus to the atrium. A site not far from the proximal His recording can now be sought with the mapping catheter. In this example also, the focus has been prematurely excited to the extent that it shows some overdrive suppression (HH interval after the extrastimulus 880 ms, slightly longer than the baseline interval).

Ablation Site

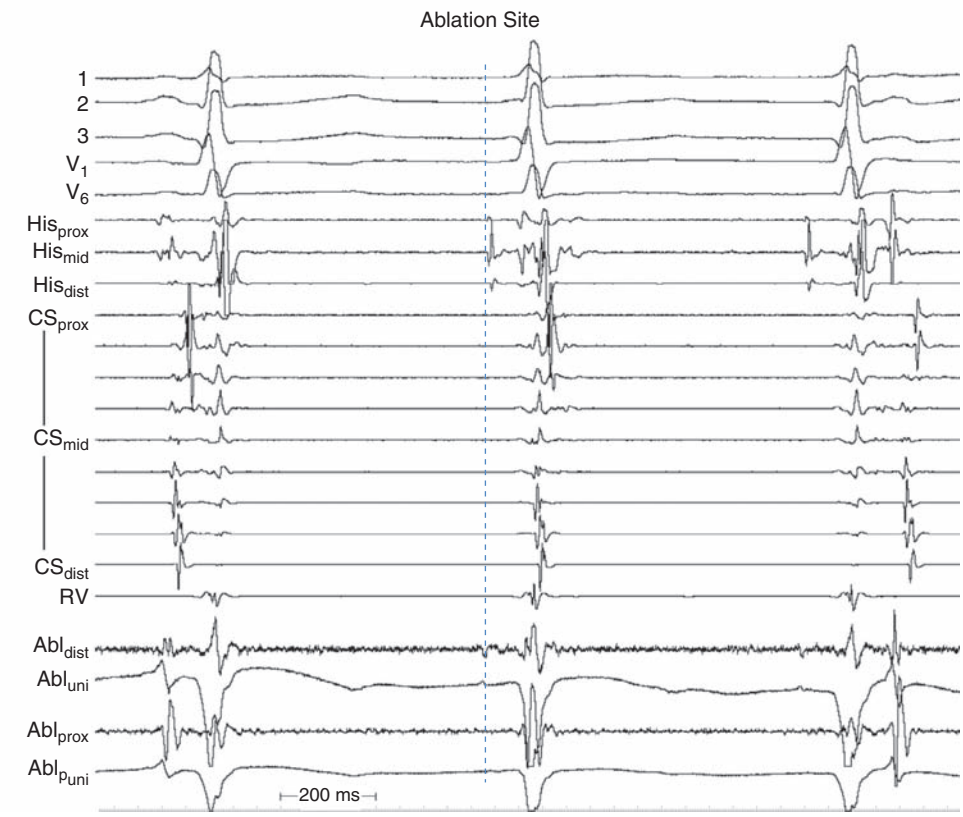


Figure 4-7

The desired ablation target should be the earliest possible His recording, often in the region of the compact AV node. In Fig. 4-7, a potential on the ablation catheter occurs about 10 ms before the earliest activation on the His catheter. At this time in the procedure, the sinus rate had accelerated somewhat accounting for the positive P waves in inferior leads.

RF Ablation Begins

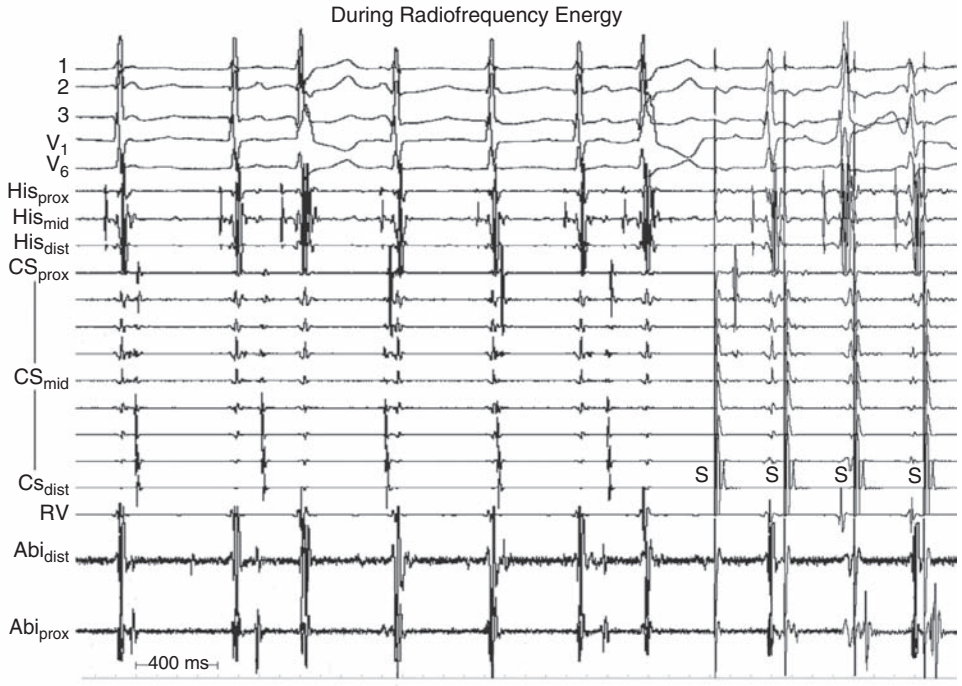


Figure 4-8

RF ablation at this site resulted in acceleration of the junctional discharge rate as well as retrograde conduction block (Fig. 4-8). As is often done during accelerated junctional rhythm with AV nodal reentry slow pathway ablation, atrial pacing (S, on *right* side of figure) is begun to ensure that anterograde AV conduction remains intact during the accelerated junctional rhythm. If the PR lengthens or conduction fails for even one cycle, RF energy delivery can immediately be stopped. Conduction remained intact with a mildly prolonged but stable PR interval throughout a 1 min RF application.

Final Recordings

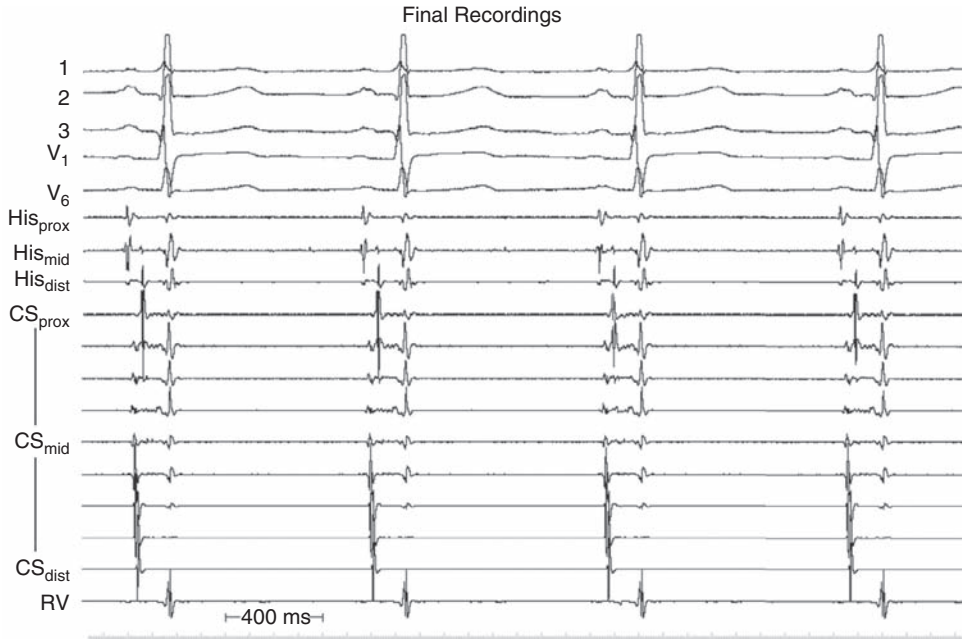


Figure 4-9

As seen in Fig. 4-9, after ablation, sinus rhythm with intact conduction and normal intervals is present, CL 950 to 1000 ms. With isoproterenol, the sinus rate accelerated and AV conduction remained consistent. No accelerated junctional rhythm was observed.

Fluoroscopy of Catheter Positions

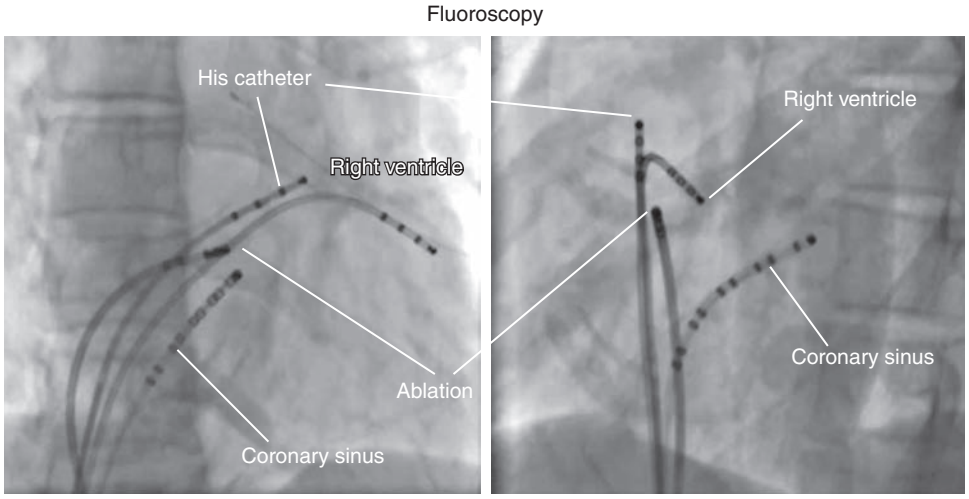


Figure 4-10

Fig. 4-10 displays fluoroscopic images of the ablation catheter at the site of successful ablation, where the compact AV node would be expected to reside.

Summary

- Accelerated junctional rhythm is rare but can be very symptomatic, resulting in functional "pacemaker syndrome"
- It must be distinguished from AV nodal reentry and atrial rhythm with long PR interval
- The site of impulse formation is in the conduction system and must be targeted very carefully to avoid heart block:
  - Site of earliest His potential
  - Often occurs in slow pathway region
  - Further acceleration of junctional rhythm occurs with RF application—a sensitive, but not specific, indicator
  - Atrial pacing to monitor anterograde conduction can help avoid heart block

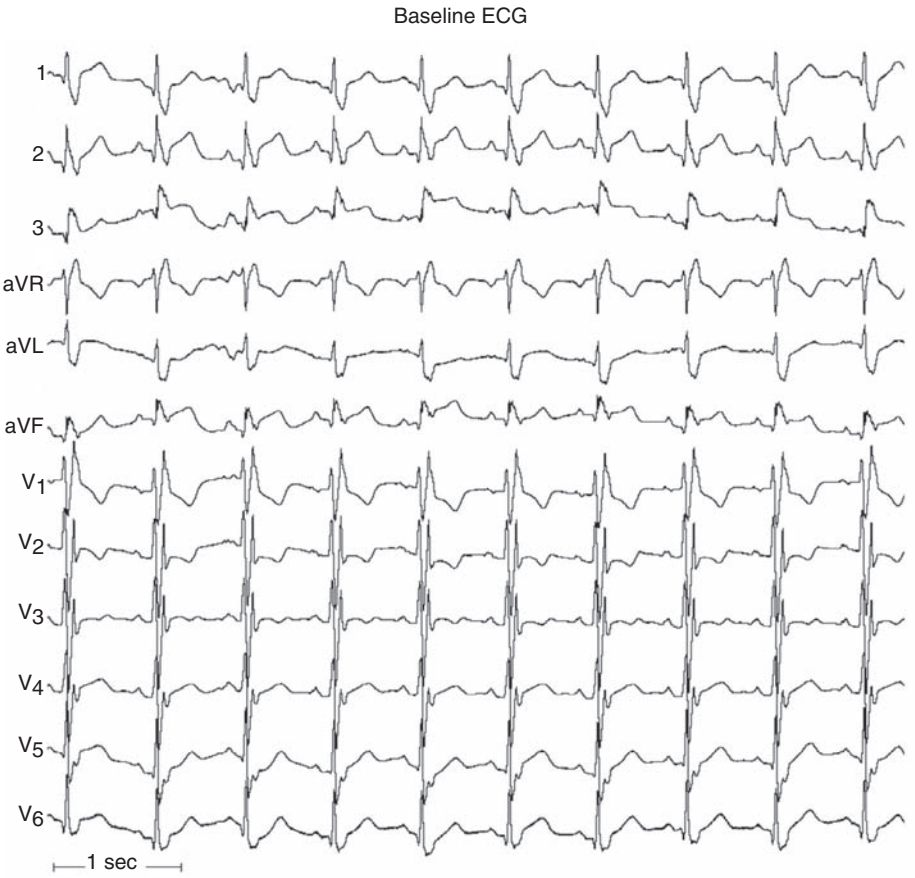
5 Left Lateral Concealed Pathway Supraventricular Tachycardia

Case Presentation

A 21-year-old man with a lifelong history of palpitations and supraventricular tachycardia (SVT) was referred for catheter ablation. He began having episodes as a child, only occasionally at first but more frequently as a teenager. He was diagnosed with SVT at age 10; episodes were characterized as sudden onset with palpitations, lightheadedness, and dyspnea. Medical therapy with beta blockers failed to control episodes and he underwent an attempt at catheter ablation. A concealed left lateral bypass tract was diagnosed but ablation (retrograde aortic approach) failed despite multiple radiofrequency (RF) applications, and the procedure was stopped because of prolonged fluoroscopy time. Three years later another ablation attempt likewise failed (retrograde aortic approach).

He also had a history of cyanosis and a heart murmur at birth and was diagnosed with tetralogy of Fallot. A Blalock-Taussig shunt was constructed at age 2 weeks and he underwent complete intracardiac repair at age 15 months (shunt taken down at that time). He has had progressive pulmonic regurgitation in the ensuing years but a normal physical capacity.

Baseline ECG in Sinus Rhythm: SVT ECG



What Questions Should You Ask About History and Prior Procedures?

Figure 5-1

In Fig. 5-1, right bundle branch block (RBBB) is evident during sinus rhythm, consistent with right ventriculotomy for tetralogy repair.

Figure 5-2

In Fig. 5-2, SVT has the same QRS configuration and no discernible P waves. This could thus be atrioventricular (AV) nodal reentry or atrial tachycardia with P waves hidden in the QRS complex. Orthodromic SVT using a left-sided bypass tract could also appear the same way (P wave inside the widened, RBBB QRS complex). However, the P wave should be visible after the RBBB QRS in orthodromic SVT using a right lateral pathway.

Baseline Intracardiac Recordings in Sinus Rhythm

Figure 5-3

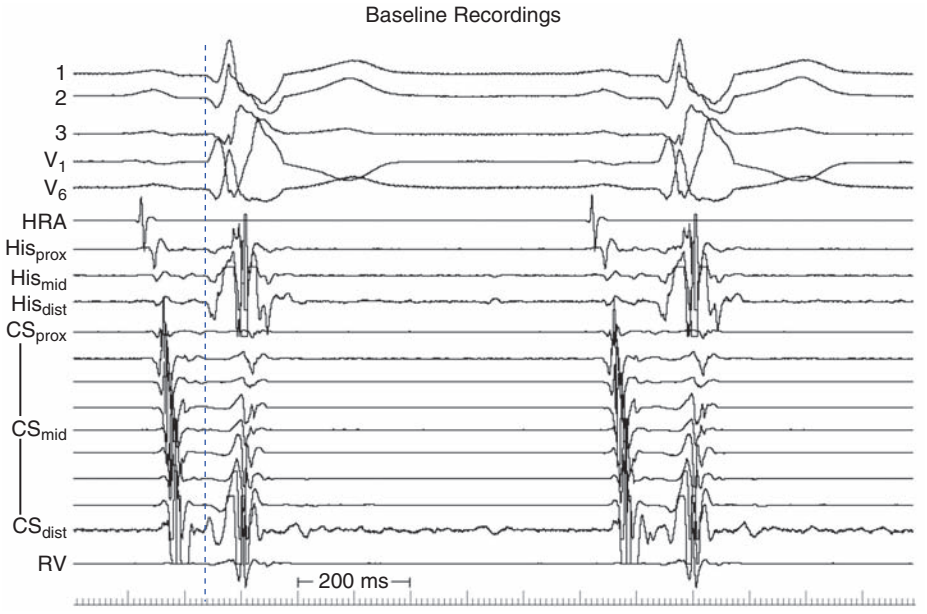


Fig. 5-3 shows no evidence of left lateral (or other location) preexcitation on intracardiac recordings in sinus rhythm; *dashed line* denotes QRS onset.

Ventricular Pacing at Progressively Rapid Rates During Sinus Rhythm

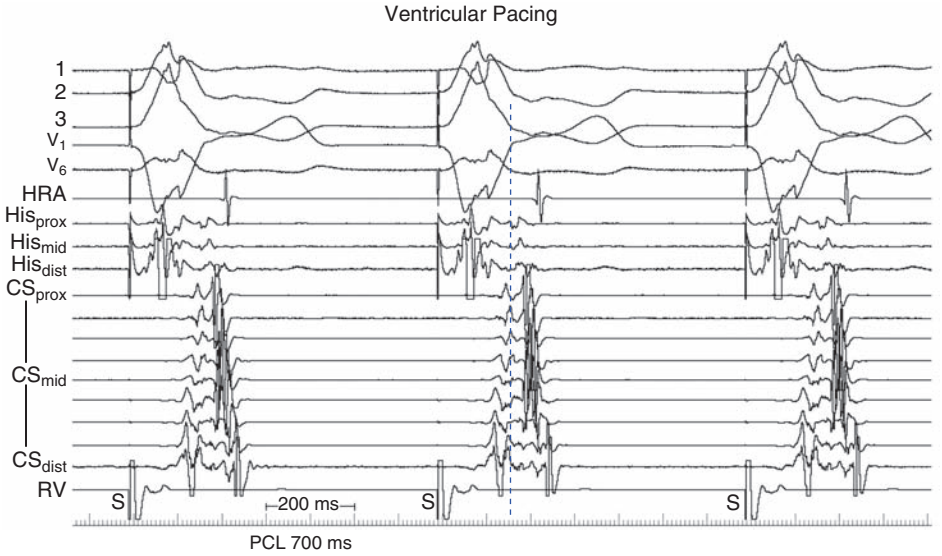


Figure 5-4

With ventricular pacing at 700 ms (Fig. 5-4), it is evident that retrograde conduction is present; the His bundle atrial activation appears earliest *(dashed blue line)*, but the distal coronary sinus (CS) recordings are difficult to interpret (likely because of prior ablation in this area).

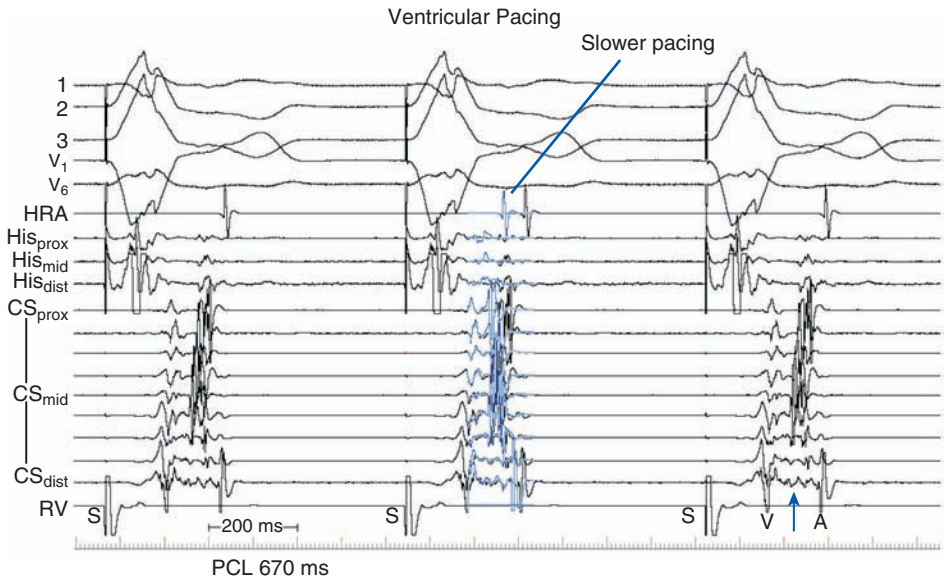


Figure 5-5

With slightly more rapid pacing (670 ms; Fig. 5-5), there is a change in the atrial activation sequence (slower pacing sequence shown superimposed in *blue*). The most obvious change is in the high right atrium (HRA) and His atrial recordings, which are delayed with more rapid pacing, signifying loss of AV nodal conduction, whereas most of the CS recordings are largely unchanged (consistent with conduction over a left lateral bypass tract). A series of complex signals *(blue arrow)* is present in between what is clearly ventricular (V) and what is clearly atrial activation (A); because of prior ablation, these could represent slow conduction in either ventricular or atrial tissue, or recordings from the bypass tract itself.

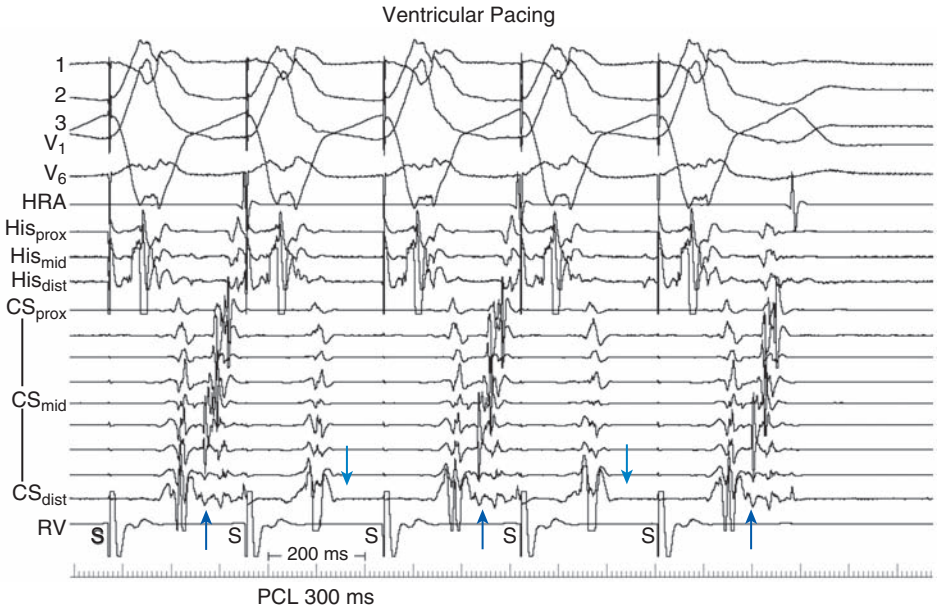


Figure 5-6

To investigate the nature of these signals, some way must be devised to clearly separate atrial from ventricular activation. In Fig. 5-6, rapid ventricular pacing at 300 ms results in 2:1 retrograde conduction. On cycles without atrial recordings *(light blue downward arrows)*, the signals in question are absent *(upward blue arrows)*—signifying that they are not ventricular in origin, because there is a ventricular electrogram on each of the paced complexes.

Ventricular Pacing Initiates SVT

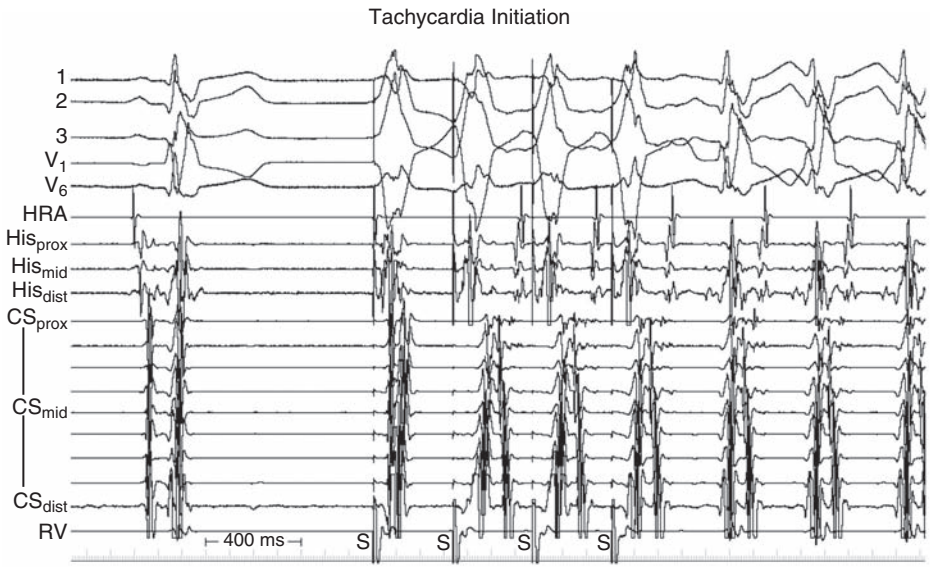


Figure 5-7

Fig. 5-7 shows a burst of rapid ventricular pacing initiating an episode of SVT.

Ventricular Extrastimuli in SVT

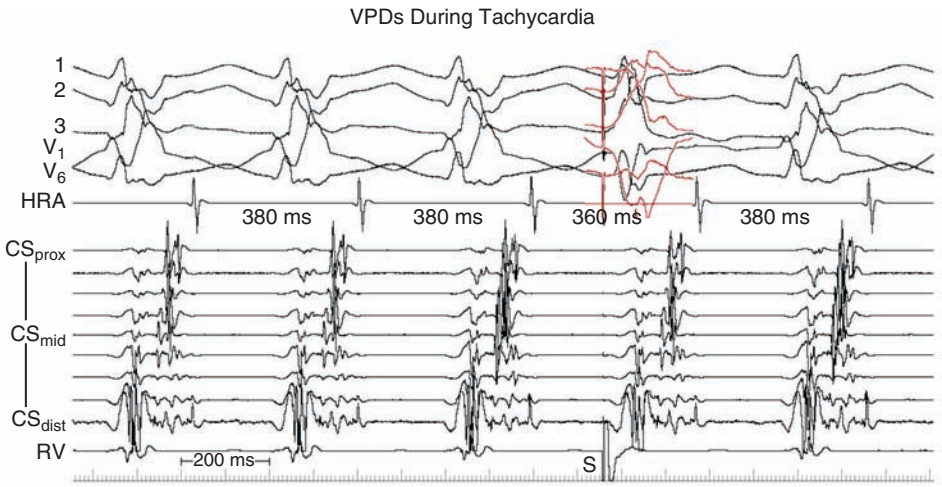


Figure 5-8

In Fig. 5-8, a single extrastimulus (S) is delivered from the right ventricle during SVT. A-A intervals in the HRA recordings are as indicated. The A-A interval surrounding the premature complex is shorter than any other during tachycardia, suggesting bypass tract conduction; however, this is only valid if the His bundle is refractory at the time the extrastimulus is delivered. A complex of pure right ventricular pacing is superimposed in red atop the complex associated with the extrastimulus. It is clear that simulation during tachycardia yields a QRS complex different from both pure pacing and SVT, and is thus a fusion complex between these two. Because the fusion derives from some element of a conducted QRS complex, the His bundle must have already been activated on that complex, and thus by definition the extrastimulus is His-refractory. Thus the fact that the A-A interval surrounding this complex is shorter than all others can be interpreted to indicate that a bypass tract is present, but not necessarily participating in tachycardia.

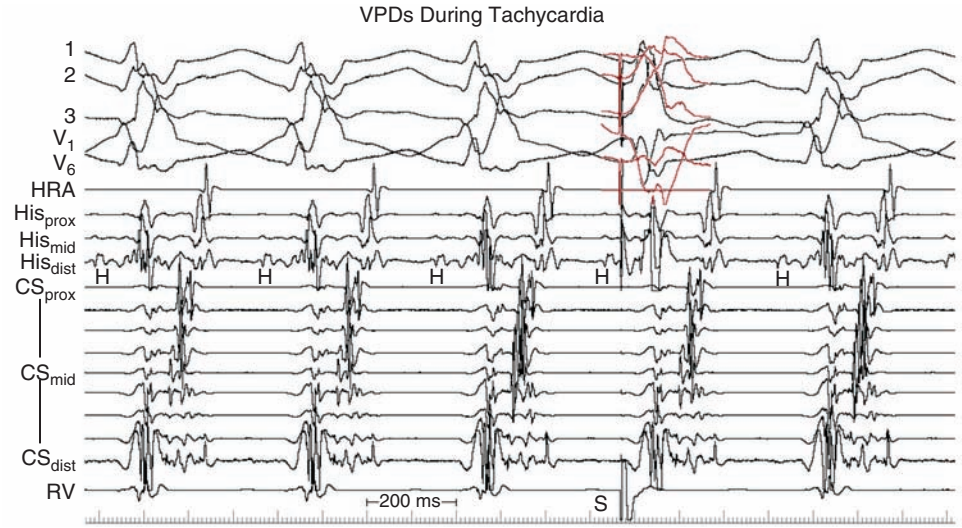
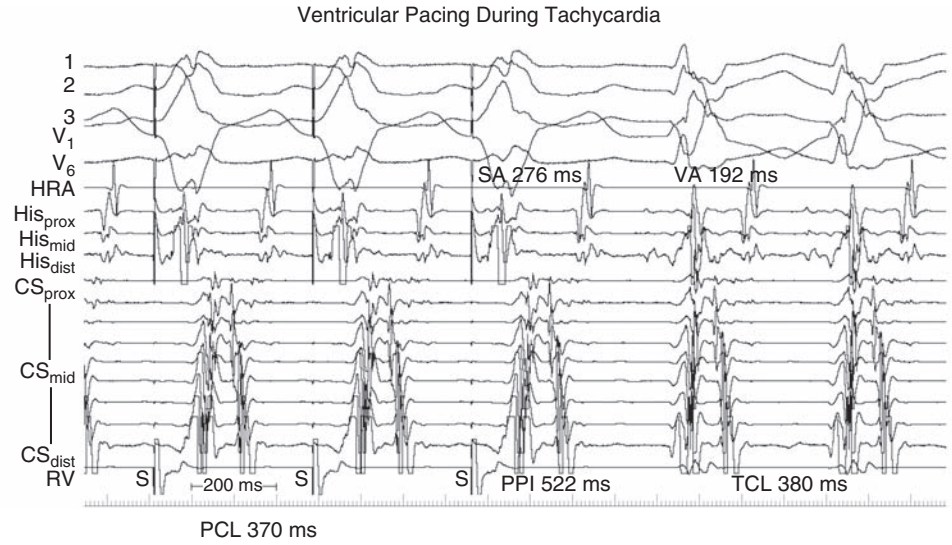


Figure 5-9

The same event is shown in Fig. 5-9, this time including the His recordings where it can be seen that the His bundle (H) had indeed already been activated on the complex in question and was thus refractory.

Ventricular Overdrive Pacing in SVT

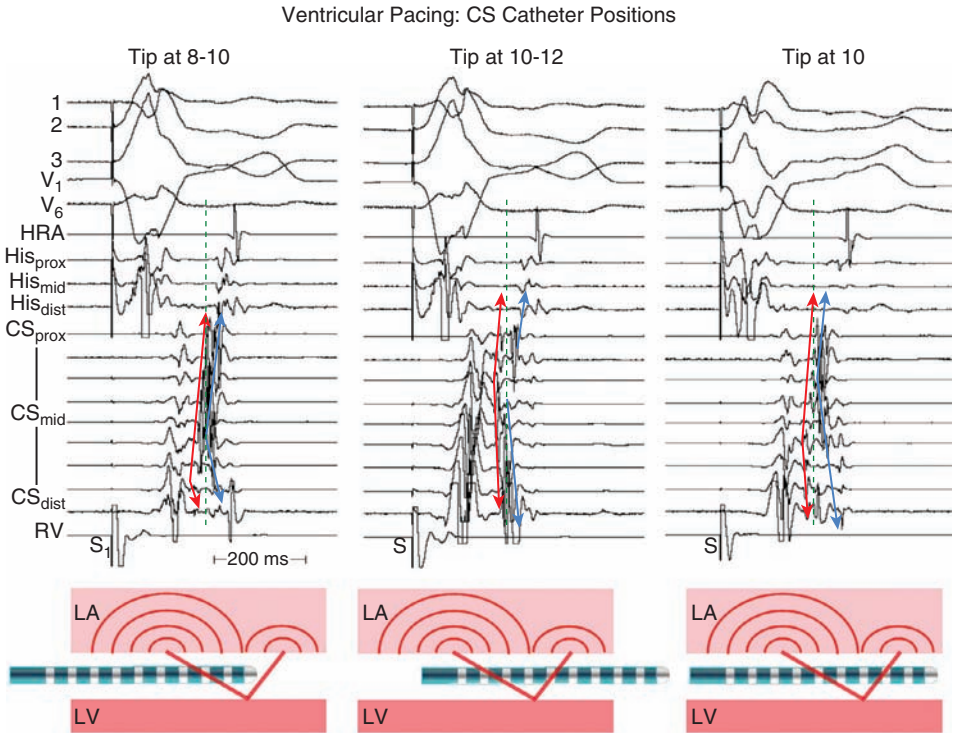
Figure 5-10



The results of ventricular overdrive pacing during SVT are shown in Fig. 5-10; the stimulus-atrial minus ventricular-atrial (SA-VA) difference (84 ms) is just less than 85 ms and suggests orthodromic SVT, whereas the post-pacing interval–tachycardia cycle length (PPI-TCL) difference (158 ms) is more suggestive of AV nodal reentry. Some of the disparity can be accounted for by the longer AH interval after the last paced complex, but the conflicting numbers is one reason that these intervals should be interpreted with caution in situations in which a far left-sided bypass tract is involved. Note also that the CS activations have changed—the catheter has been advanced somewhat (more distally in the CS). Finally, the SA interval during right ventricular pacing—simulating left bundle branch block (LBBB)—is much longer than the VA during SVT, strongly suggesting participation of a left free wall bypass tract during tachycardia.

Ventricular Pacing with Different Coronary Sinus Catheter Positions

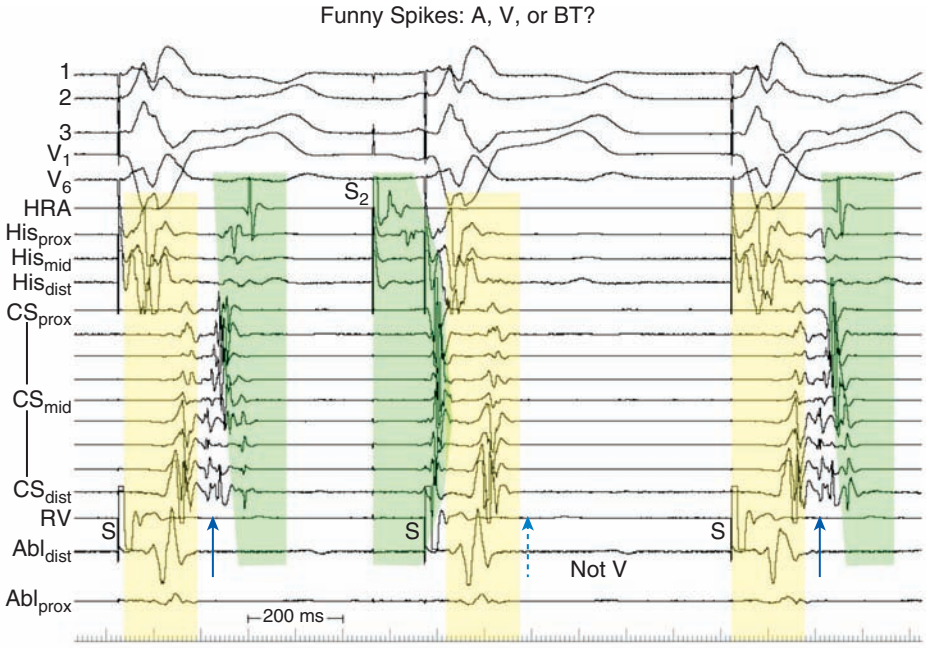
Figure 5-11



It is sometimes useful to "bracket" the site of earliest atrial activation in CS recordings. In Fig. 5-11A, recordings are shown with the catheter tip at site "8-10" (directly lateral on the mitral annulus), site "10-12" (anterolateral mitral annulus), and site "10" (intermediate between these two). A *dashed green line*, placed at the same interval before the HRA recordings in each panel, serves as a reference for comparison of activation sequences (Fig. 5-11B). Two activation sequences are evident within the coronary sinus recordings, indicated by *red arrows* and *blue arrows* (Fig. 5-11C). Whether these represent propagation over a bypass tract or partially insulated strands of atrial muscle within scar from prior ablation is not clear. One possible resolution to the different propagation patterns is shown in the diagram at bottom, where a multipolar electrode catheter is moved along the mitral annulus between the left atrium (LA) and left ventricle (LV). It is possible that there are two atrial insertions of the bypass tract, as indicated.

Nature of "Funny Spikes" Explored

Atrial Extrastimuli During Fixed-Rate Ventricular Pacing



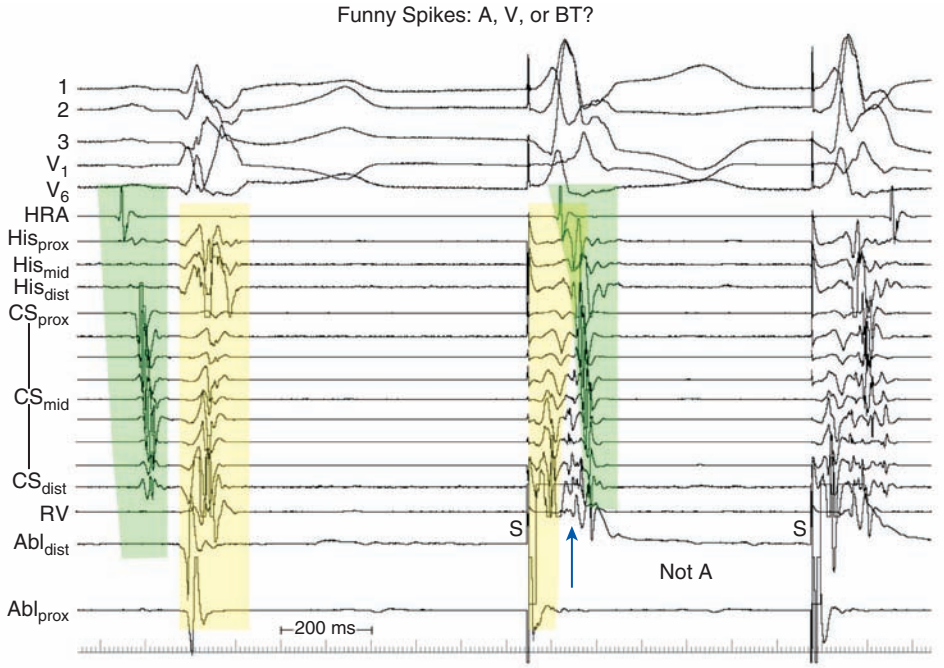
Are the Funny Spikes A, V, or BT? [Fig. 5-12]

Figure 5-12

In Fig. 5-12, to further investigate the nature of the peculiar signals (*blue)* between what is thought to clearly ventricular *(shaded yellow)* and clearly atrial *(shaded green)*, an atrial extrastimulus (S2) is introduced during fixed-rate ventricular pacing (S). This draws the atrial electrograms earlier, whereas the ventricular electrogram is unaffected. Because the complex potentials are no longer seen, they cannot be part of the ventricular recording.

Onset of Ventricular Pacing at Time of Sinus Complex

Figure 5-13



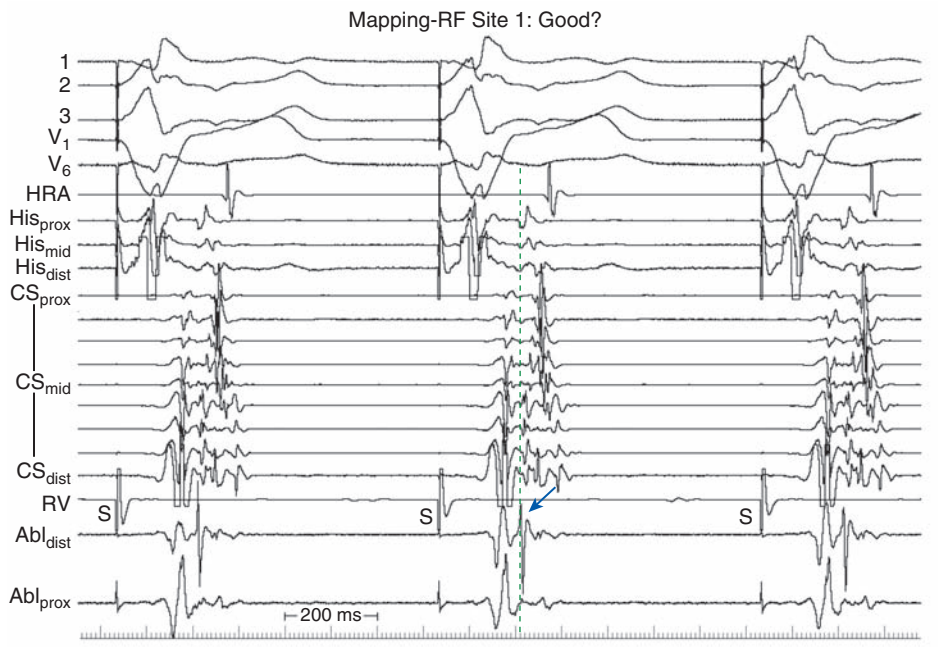
Similarly, a ventricular stimulus introduced during atrial pacing (or, as in Fig. 5-13, sinus rhythm) that causes the potentials in question to appear while the atrial recording is unchanged indicates that the questionable potentials are also not atrial in origin. Because they are neither atrial nor ventricular, they must be bypass tract recordings.

Mapping and Ablation Sites and Results

First Ablation Site

Is This Mapping Site a Good Site to Deliver RF Energy? [Fig. 5-14]

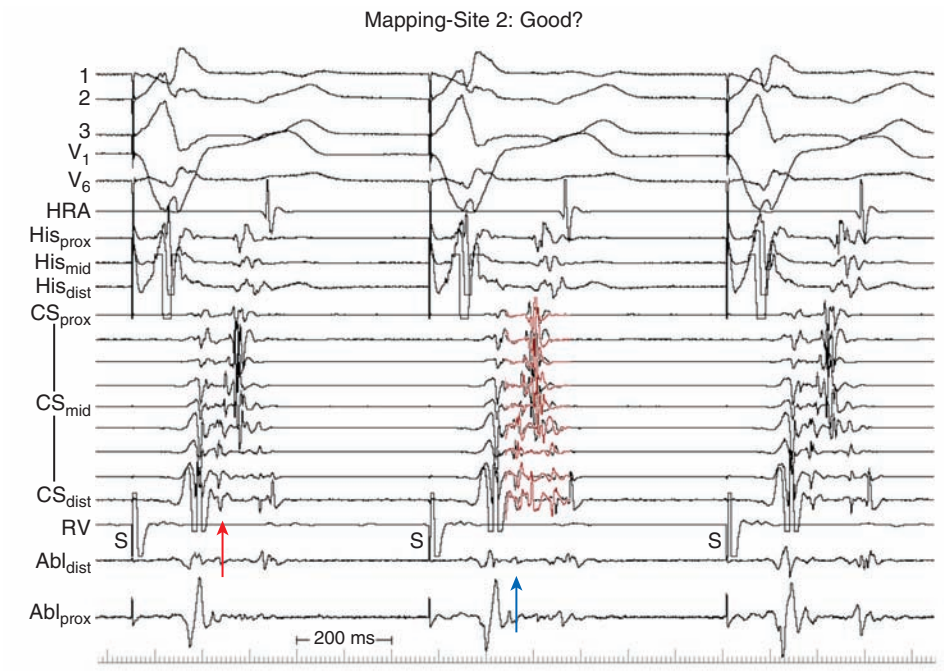
Figure 5-14



Now that the nature of the potentials in the CS recordings is clear, mapping can begin, targeting the bypass tract potentials as the most vulnerable site. Notice in Fig. 5-14, after transseptal catheterization, the ablation catheter records a sharp potential *(arrow)* that

precedes all others in the CS *(dotted green line)*. With a large, stable electrogram, this looks like a good site to deliver RF energy.

Effect of First Ablation, Second Mapping Site



Is This Mapping Site a Good Site to Deliver RF Energy? [Fig. 5-15]

Figure 5-15

After ablation at the first site, retrograde conduction remains; however, the atrial activation sequence has changed (prior sequence superimposed in red on Fig. 5-15). The early bypass tract potentials *(red arrow)* persist, but atrial electrograms in the more distal CS recordings have been delayed. This could be because of ablation of one of two atrial insertions of the pathway, or of a branch of the pathway itself. The mapping site is not particularly attractive because of the small, far-field appearance of the bypass tract potential recording *(blue arrow)*.

Mapping Site No. 4 and Ablation

Is This Mapping Site a Good Site to Deliver RF Energy? [Fig. 5-16]

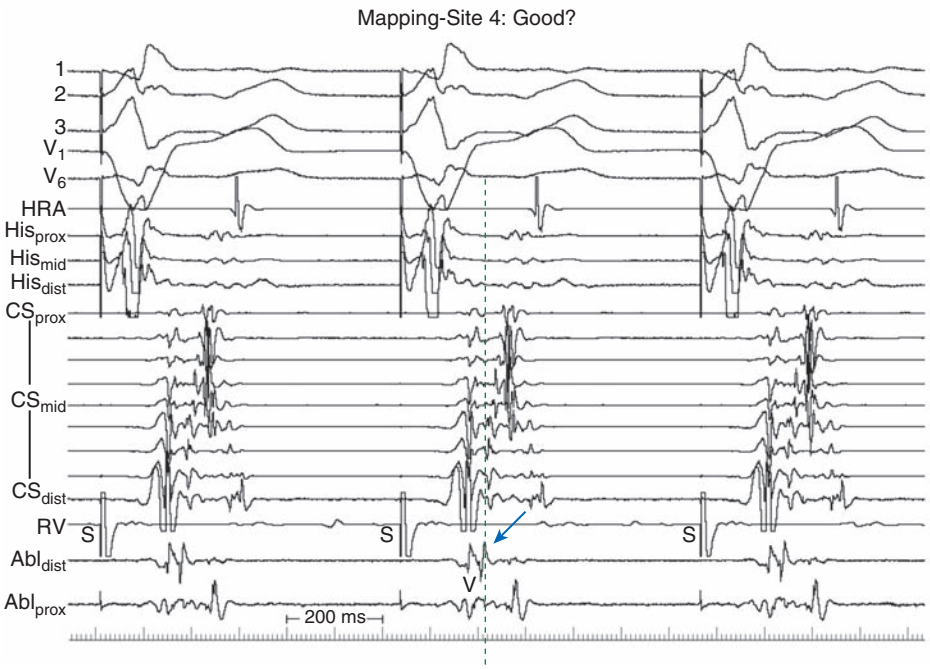


Figure 5-16

Other nearby sites were sampled, this one showing sharp ventricular (V) and bypass tract (*blue arrow*, Fig. 5-16) recordings during ventricular pacing. The *dashed green line* indicates timing of bypass tract potentials recorded in CS electrodes.

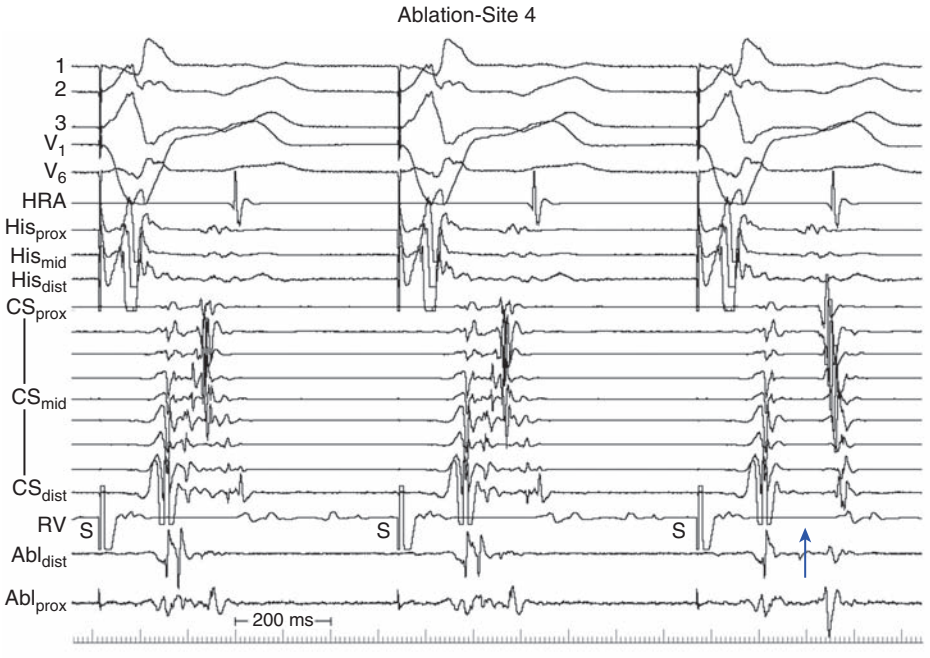


Figure 5-17

During RF energy delivery at this site (Fig. 5-17), retrograde conduction over the bypass tract suddenly fails *(arrow)*, instead now proceeding over the AV node.

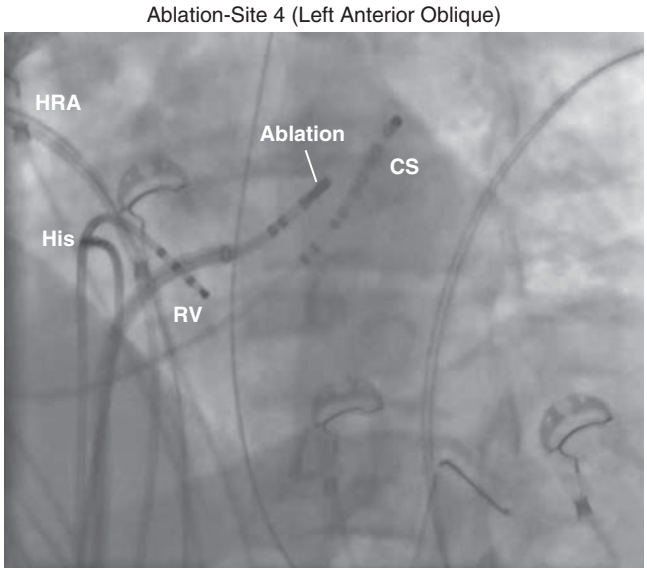


Figure 5-18

A left anterior oblique fluoroscopic image of the ablation site is displayed in Fig. 5-18.

Ventricular Pacing Postablation (AV Nodal Conduction Only)

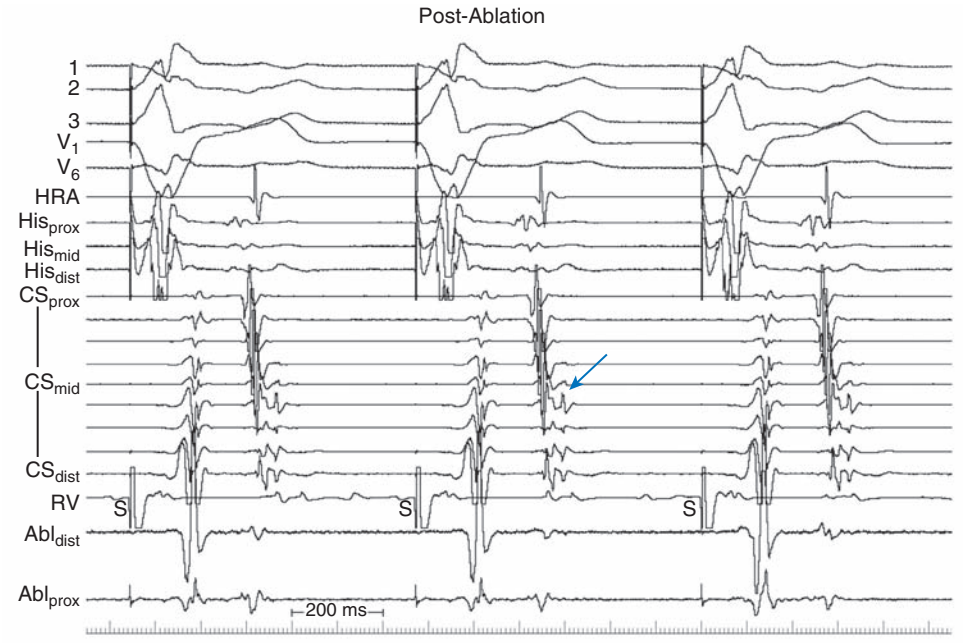


Figure 5-19

After ablation, ventricular pacing in Fig. 5-19 shows retrograde conduction with a midline activation sequence. In addition, small potentials *(arrow)* are now seen after the atrial electrogram in the middle and distal CS, possibly representing activation of the bypass tract after (rather than before) atrial activation. Retrograde conduction over the pathway did not recur during a 45-min waiting period or after isoproterenol provocation. The patient has not had recurrent tachycardia.

Summary

- AV bypass tracts typically cross the AV groove at an angle, with the ventricular insertion more proximal along the coronary sinus than the atrial insertion
- Prior ablation disrupts atrial electrograms, sometimes making interpretation of electrograms difficult
- Searching for and proving the identity of a bypass tract potential may be preferable to looking for earliest atrial activation, especially after prior ablation
- In general, the retrograde and transseptal approaches yield equivalent outcomes, but in any given case, one might be better suited to success than the other

Antidromic Supraventricular Tachycardia

6

Case Presentation

A 52-year-old man developed wide-complex tachycardia (WCT) after coronary artery surgery. He had a history of refractory hypertension and complained of palpitations and chest discomfort. Evaluation ultimately showed an anomalous left coronary artery from the right sinus of Valsalva, coursing between great vessels. He underwent open surgical reconstruction of the left main coronary artery. He reportedly had both severe bradycardia and tachycardia (possibly ventricular fibrillation) coming off the heart-lung machine. He was given amiodarone, and a dual-chamber pacemaker. He had an episode of wide QRS complex tachycardia 5 days postoperatively and was asymptomatic with this; pacemaker interrogation showed a 1:1 A:V relationship in tachycardia. He was treated with metoprolol but continued to have palpitations and tachycardia episodes on pacemaker interrogation. He was referred for electrophsyiology study.

ECG in Sinus Rhythm

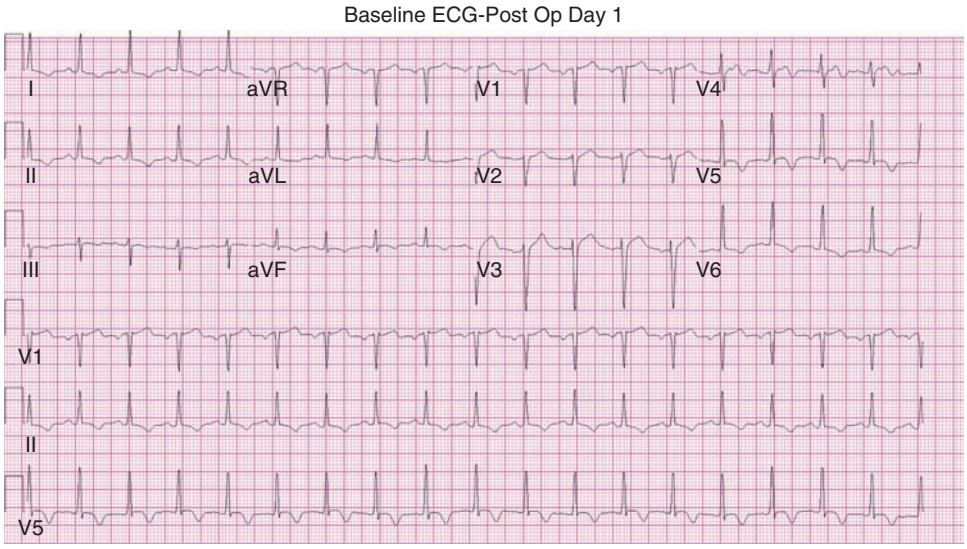


Figure 6-1

The early postoperative sinus rhythm ECG (Fig. 6-1) is relatively normal; there are no normal septal q waves, probably because of longstanding hypertension. Nonspecific ST and T-wave abnormalities may be related to the postoperative state. There is certainly no infarct pattern.

Wide-QRS Tachycardia ECG

Figure 6-2

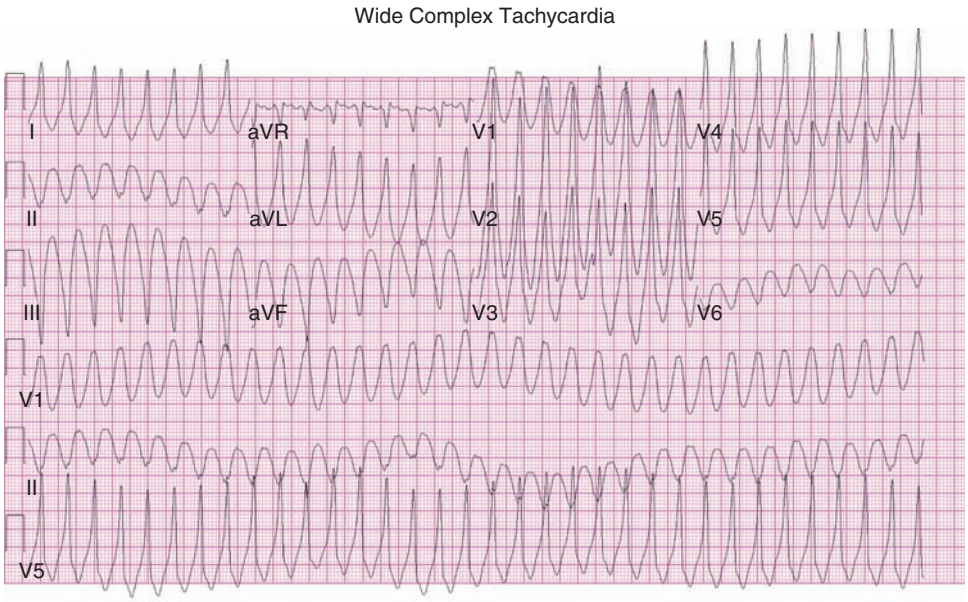


Fig. 6-2 displays the WCT recorded on day 5 postoperatively. It has a right bundle branch block (RBBB), left superior axis morphology, and no clearly discernible P waves. Q waves are evident in the inferior leads as well as V6 (slightly suspect as to its location because of the great disparity between V5 [all positive] and V6 [all negative]; this may be because of postoperative bandaging). The differential diagnosis of this WCT consists of broad categories, including supraventricular tachycardia (SVT) with aberration, a preexcited tachycardia, or ventricular tachycardia. The pattern is not particularly consistent with aberration of any form, and he does not have a reason to have either ventricular tachycardia (no prior scar) or preexcited tachycardia (no delta waves during sinus rhythm). He does have a pacemaker, which can pace the ventricle rapidly in response to atrial flutter or fibrillation, and could account for a wide-QRS tachycardia; however, the pacing lead is in the right ventricle and should yield a left bundle branch block pattern (also, no pacemaker stimulus artifacts are evident).

At this time, additional history from the patient revealed that he had Wolff-Parkinson-White syndrome and had undergone ablation about 12 years earlier that was thought to have been successful. He had nearly forgotten this in all the events surrounding his bypass surgery.

Intracardiac Recordings and Atrial Pacing

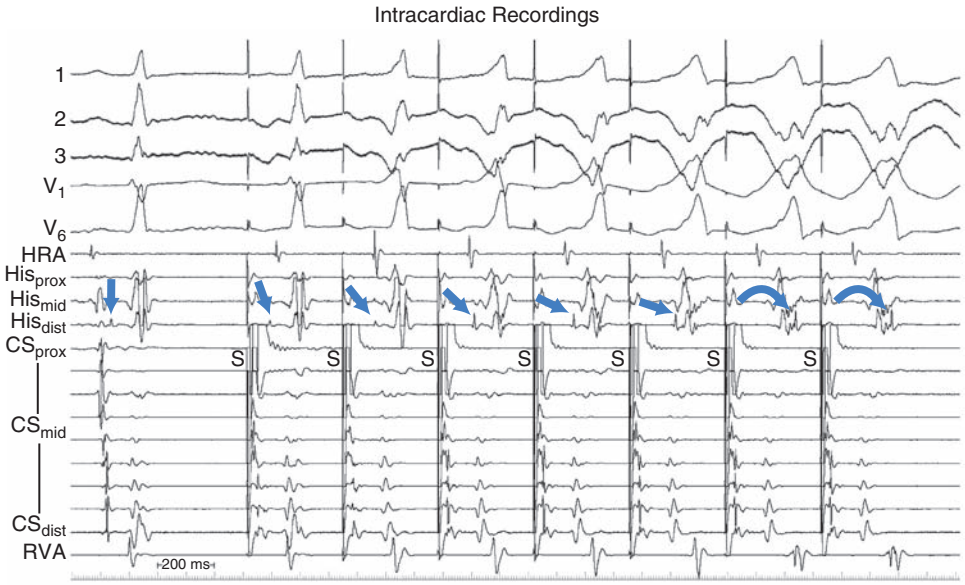


Figure 6-3

At the time of electrophysiologic study 2 months after surgery, catheters were placed in standard intracardiac locations as shown in Fig. 6-3. There is no strong evidence of preexcitation on the surface or intracardiac recordings during the sinus rhythm complex shown at left (*blue arrows* indicate His potential with normal AH and HV intervals on this complex). However, with rapid atrial pacing, the QRS complex shows progressive widening until it assumes a configuration similar to that of the WCT. In addition, the interval from stimulus to the His potential *(blue arrow)* shows progressive delay, with the His potential occurring at or after the QRS onset following the third to last stimulus. Furthermore, the His potential actually becomes retrograde, occurring toward the end of the QRS complex after the last two stimuli *(curved arrows)*. This behavior (progressive widening of the QRS complex with His potential occurring after QRS onset) is seen with ventricular tachycardia or preexcitation. Here, it seems most consistent with preexcitation.

WCT Initiation (Atrial and Ventricular Pacing)

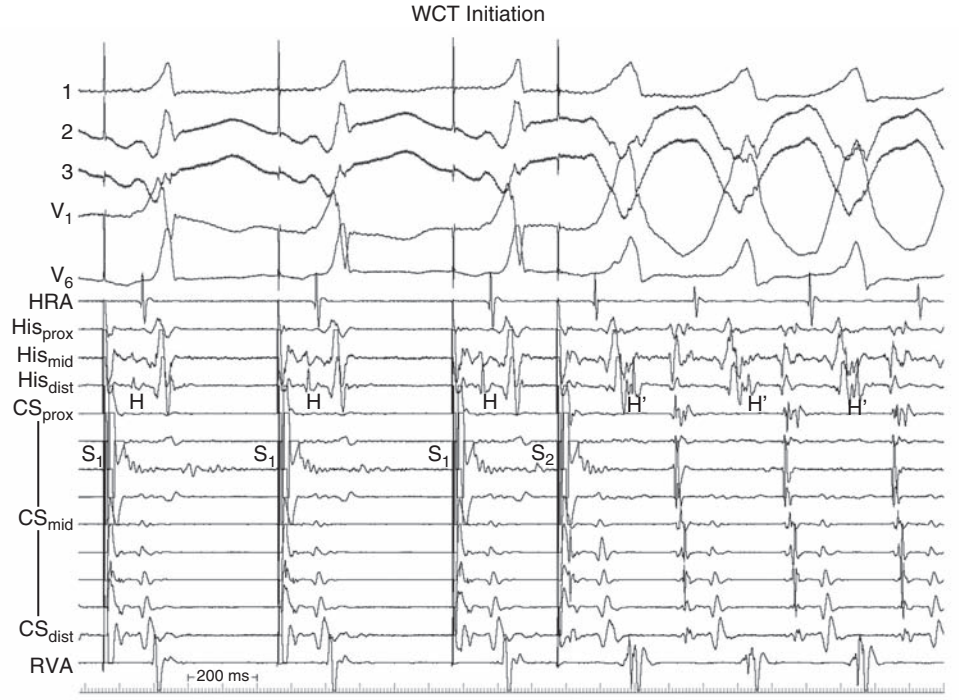


Figure 6-4

With an atrial drivetrain from the proximal coronary sinus, a preexcited QRS complex is evident in Fig. 6-4. An anterograde His potential (H) is still seen. After the extrastimulus (S2), WCT is initiated. A His potential (H′) is seen after the local ventricular electrogram in each complex. This preexcited tachycardia could be true antidromic reentry or the pathway may be a bystander with preexcited AV nodal reentry or atrial tachycardia.

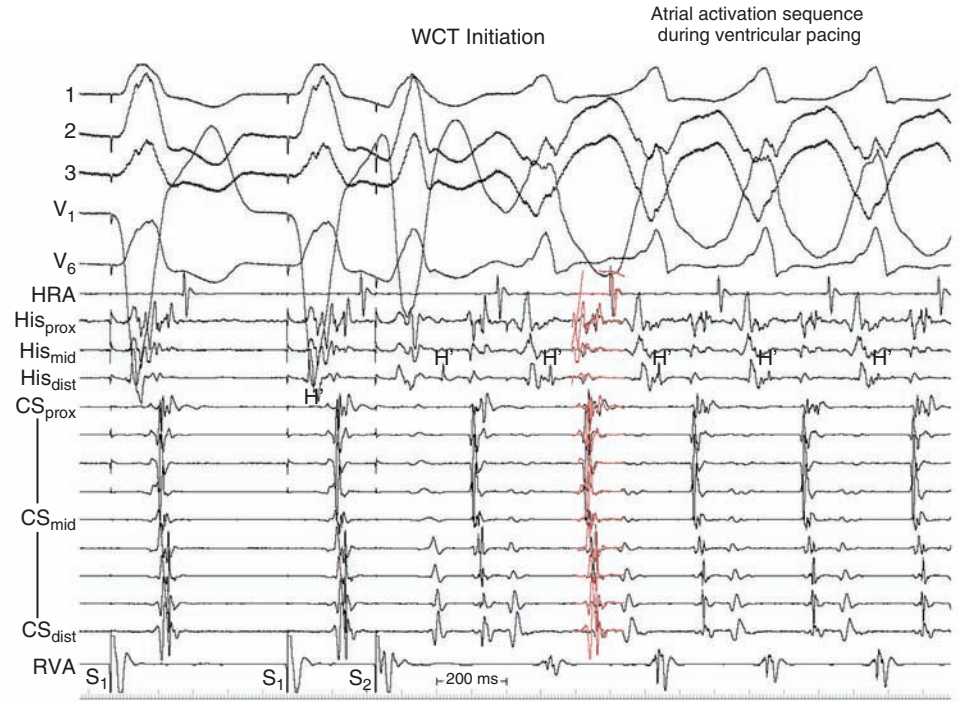


Figure 6-5

The tachycardia was also inducible with ventricular pacing and extrastimuli. In Fig. 6-5, an atrial activation sequence during ventricular pacing is superimposed in red over the atrial activation during tachycardia, showing an identical pattern. Thus it is reasonable to assume that conduction in each instance is over the same pathway, which is compatible with the

AV node (evidenced by His potential [H′] occurs at the same interval before each atrial recording; midline activation sequence; relatively long VA interval).

WCT vs Right Ventricular Pacing at Tachycardia Cycle Length

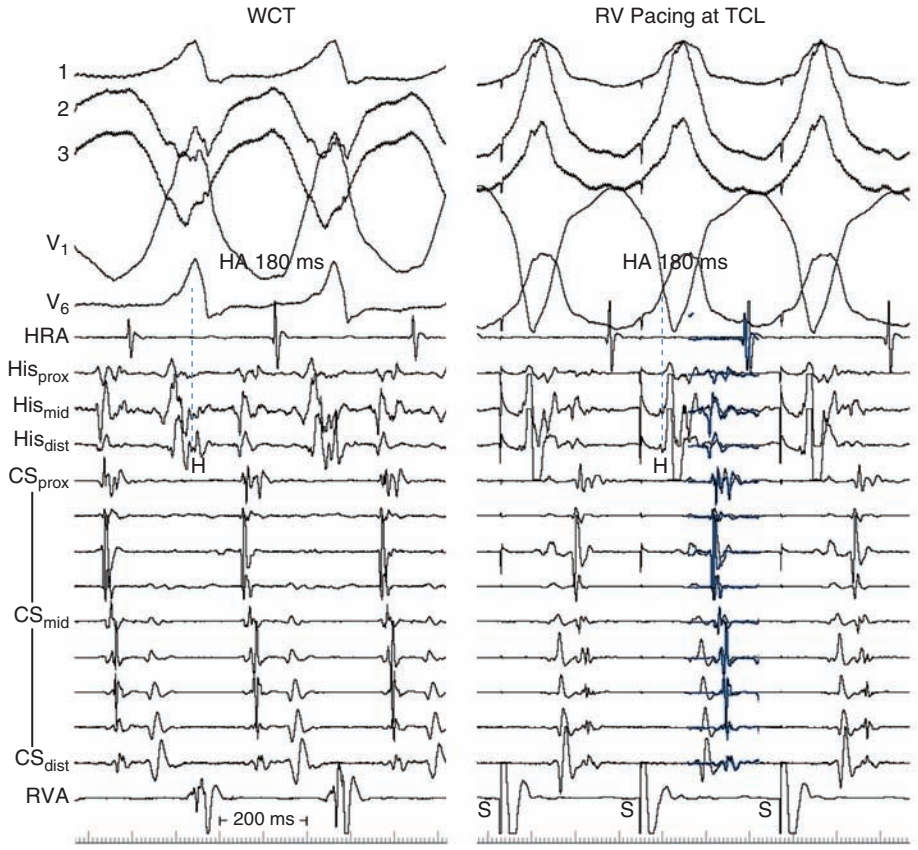


Figure 6-6

In Fig. 6-6, comparison of HA intervals (H denotes His potential) during tachycardia and ventricular pacing at the tachycardia cycle length shows the same atrial activation sequence (WCT activation sequence *superimposed in blue* over that during ventricular pacing at right) and identical HA intervals. If another bypass tract were used in the retrograde direction in either situation, the His and atrium would be activated in parallel during ventricular pacing (in series during tachycardia), leading to an artificially shorter apparent HA interval. Because the HA intervals are identical, conduction is probably proceeding over the same pathway in each situation.

Para-Hisian Pacing

These Findings:

A. Exclude a retrogradely conducting bypass tract (BT)
B. Demonstrate exclusive BT conduction
C. Show AV nodal and BT conduction
D. Show AV nodal conduction
E. Show atrial capture [Fig. 6-7]

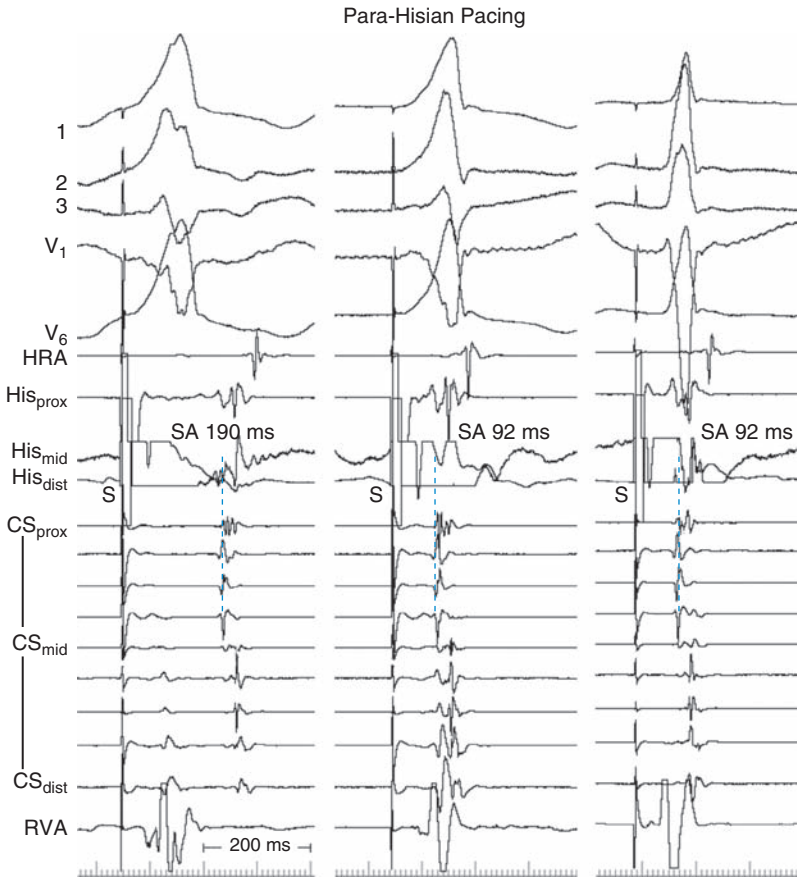


Figure 6-7

Para-Hisian pacing is performed from the His catheter (Fig. 6-7). At left, the widest resulting QRS complex is associated with a stimulus-A (SA) interval 280 ms. The complex at center shows a slightly narrower QRS complex, indicating His + ventricular capture; the SA interval is much shorter (180 ms). At right is an almost totally normal QRS complex, with a long stimulus-QRS interval likely indicating no or minimal ventricular capture ("pure" His capture). Here, the SA interval is also 180 ms. These findings are compatible with retrograde conduction over the AV node, but do not exclude the presence of a bypass tract, especially one with a long conduction time (longer than the retrograde AV nodal conduction time).

Atrial Extrastimuli (Premature Atrial Complex [PAC]) in WCT

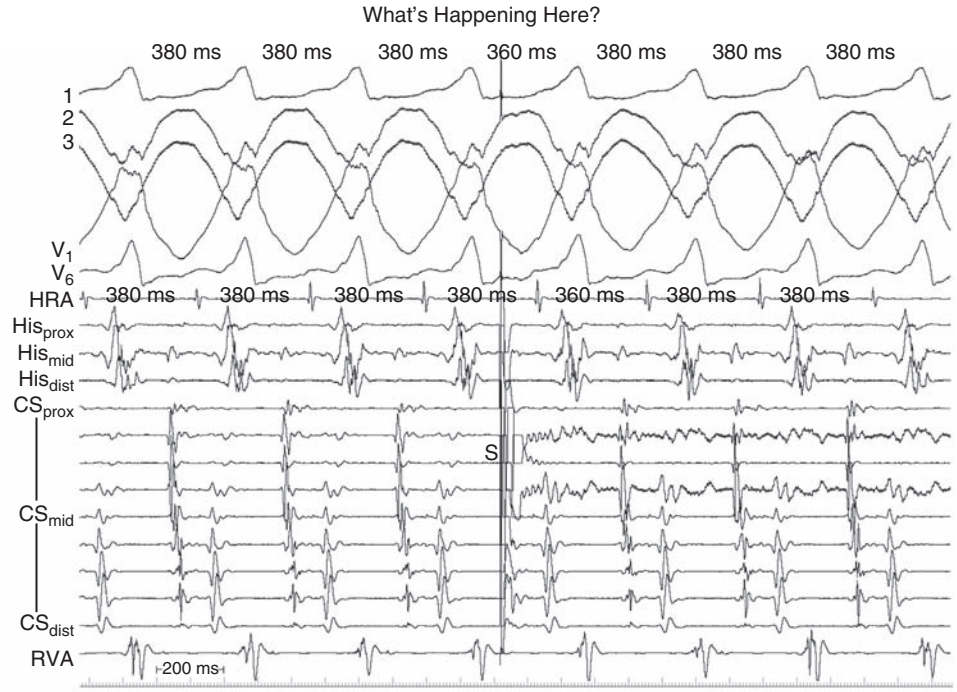


Figure 6-8

During sustained, stable WCT (Fig. 6-8), a single atrial extrastimulus (S) is introduced from the coronary sinus at a time when the atrial electrogram in the His bundle region is being inscribed (and that tissue is thus refractory). Intervals shown at the top are QRS-QRS intervals, showing that the QRS complex immediately after the extrastimulus is advanced by it. This cannot happen with ventricular tachycardia, but can with a preexcited tachycardia. In addition, the intervals shown in the middle are A-A intervals measured in the high right atrium (HRA) recording. These show advancement of the timing of the subsequent atrial electrogram, after the QRS complex that had been advanced. This indicates dependence of atrial activation on the prior QRS complex, and thus an atrial tachycardia is excluded. In addition, the fact that the stimulus occurred while the AV nodal region was refractory shows that this cannot be preexcited AV nodal reentry. Thus true antidromic tachycardia (anterograde bypass tract, retrograde AV node) is favored.

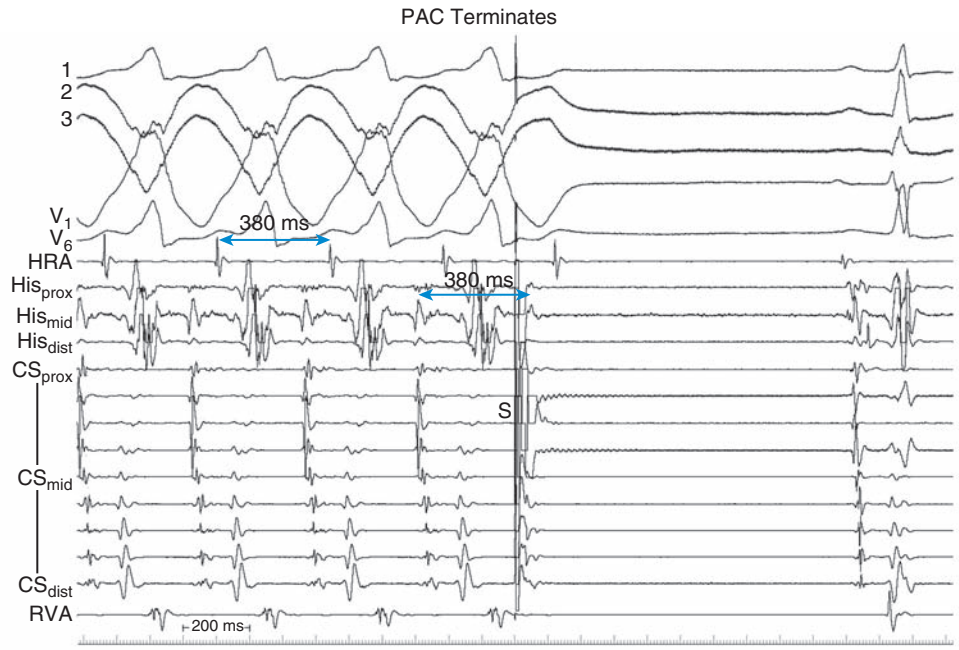


Figure 6-9

As shown in Fig. 6-9, another atrial extrastimulus delivered during stable tachycardia again occurs at a time when the AV nodal region is refractory (*arrows* on atrial recordings). In this case, atrial capture occurs (as indicated by HRA recording), but tachycardia terminates without ventricular activation. This again excludes ventricular tachycardia, as well as forms of SVT in which the bypass tract was a bystander (such as atrial tachycardia or AV nodal reentry), because simply blocking in the bypass tract with the atrial extrastimulus should eliminate preexcitation but the tachycardia should continue with narrow QRS complexes. Thus antidromic tachycardia is the diagnosis.

Investigating Possible Accessory Pathway Potential

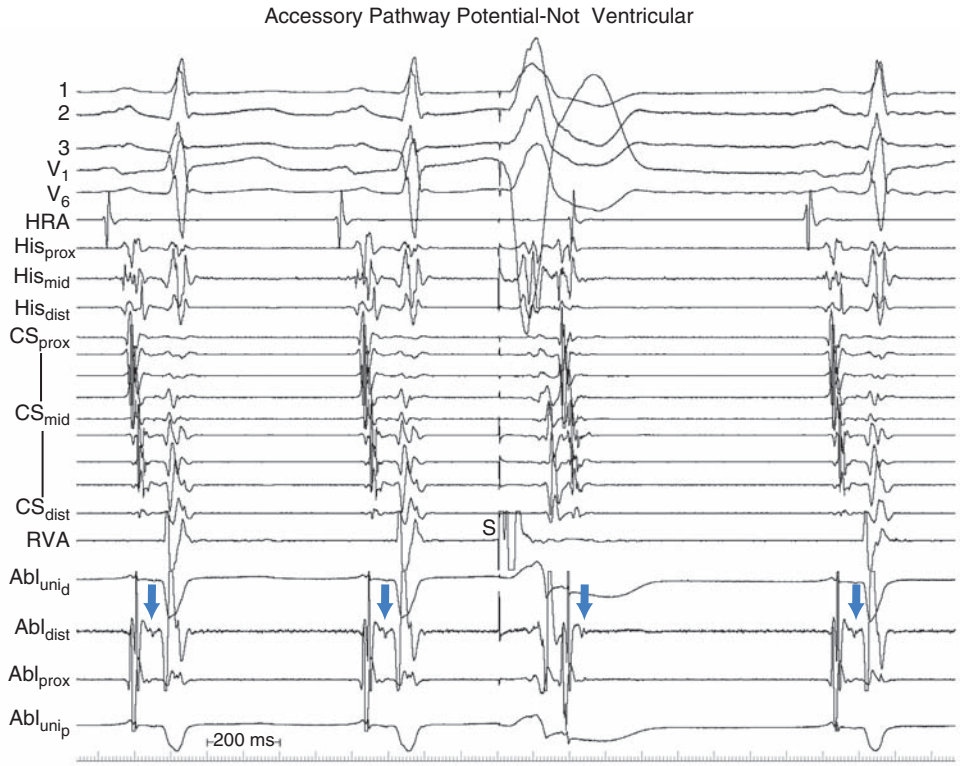


Figure 6-10

Now that a diagnosis has been established, mapping can proceed. At a site around the coronary sinus os, a recording is made that has a large atrial potential, a large ventricular potential, and a small potential between these (*blue arrows*, Fig. 6-10) that may represent the bypass tract. This is tested by introducing a ventricular extrastimulus (S) during sinus rhythm. The small potential remains with a fixed relationship to the atrial recording and is thus not part of the ventricular electrogram.

Preexcited SVT Initiation

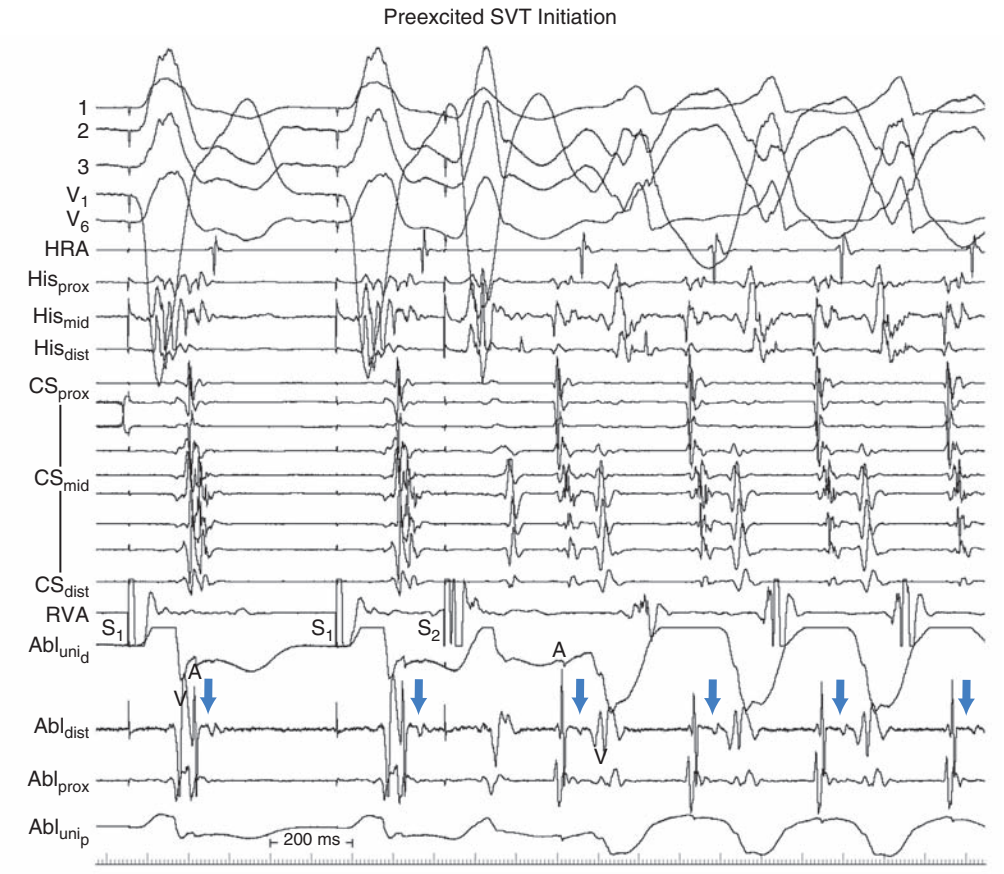


Figure 6-11

During another induction of preexcited tachycardia (Fig. 6-11), the interesting potential *(blue arrow)* remains between atrial (A) and ventricular (V) electrograms during preexcited tachycardia. However, during ventricular pacing, the potential follows the atrial electrogram. This indicates that the pathway has no retrograde conduction (retrograde conduction occurs through the AV node and activates the atrium and the pathway thereafter).

Ablation Site and Ablation Delivery

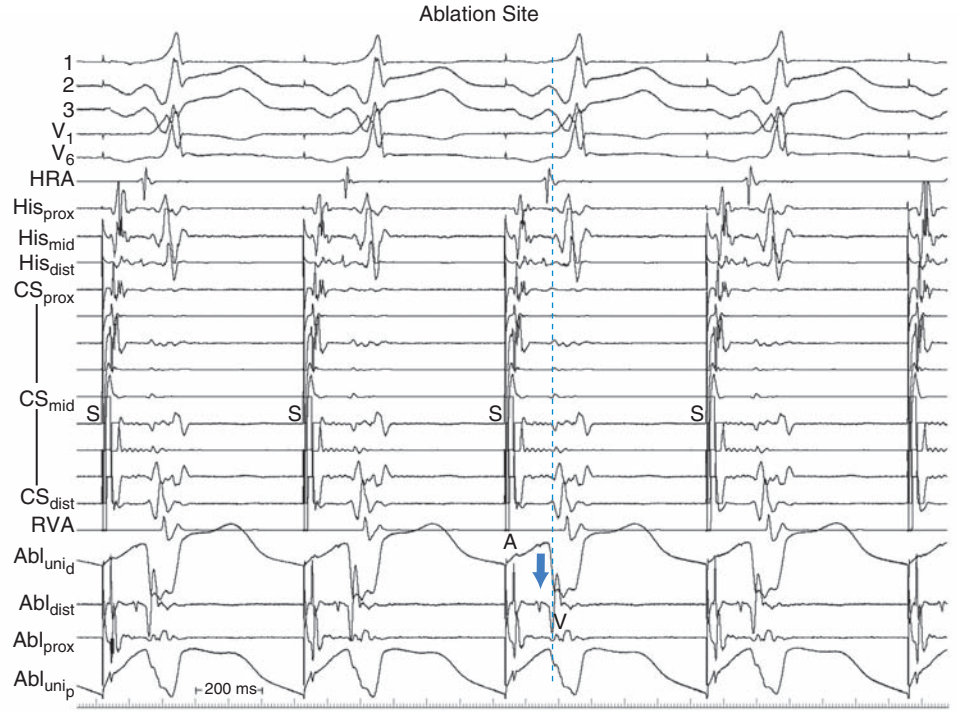


Figure 6-12

A site for possible ablation is chosen as indicated in Fig. 6-12. The surface QRS/delta wave onset is shown by a *dashed blue line*; the recording at this site shows a large atrial potential (A), bypass tract potential *(blue arrow)*, and ventricular electrogram (V). In addition, the unipolar recording shows a "QS" configuration; this and the bipolar ventricular recording precede the onset of the delta wave by about 20 ms.

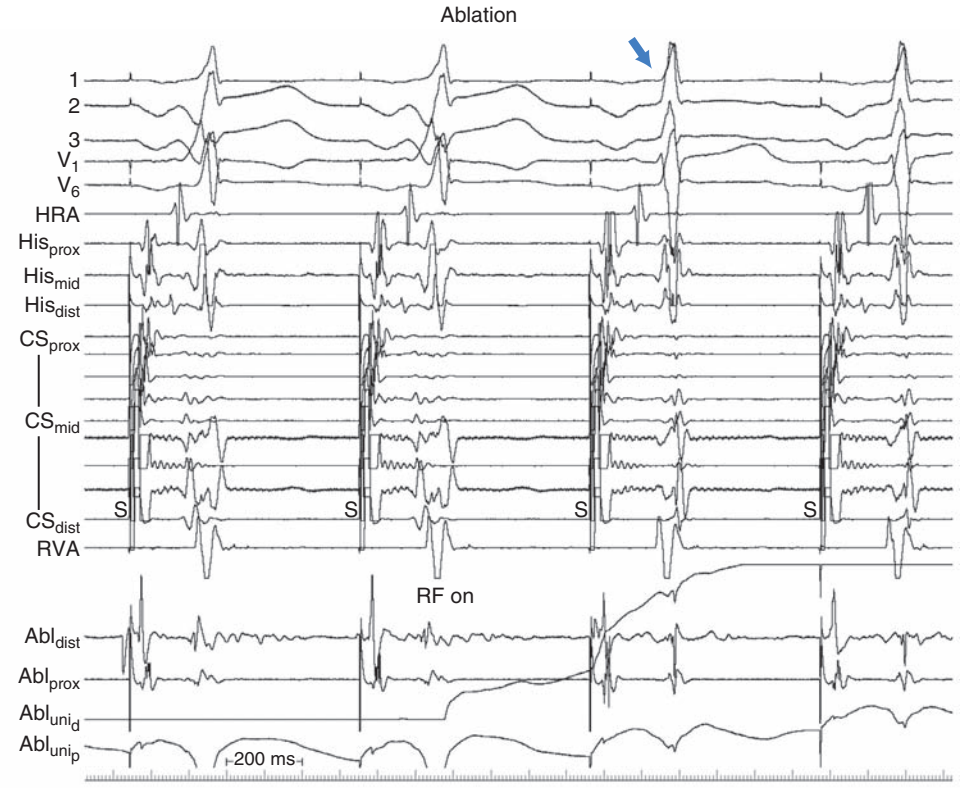


Figure 6-13

Radiofrequency energy application at this site (as indicated in middle of Fig. 6-13) during atrial pacing to maximize the delta wave shows a nearly immediate loss of preexcitation (see surface ECG leads, *arrow*).

Pre- and Postablation ECGs Compared

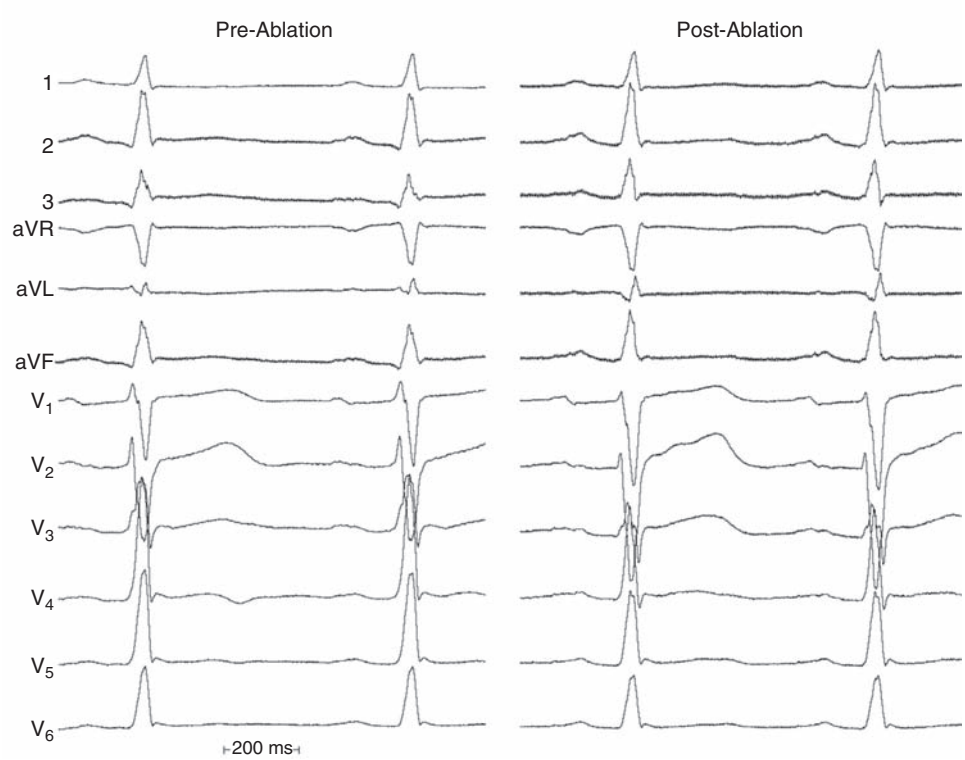


Figure 6-14

In Fig. 6-14, 12-lead ECG recordings before ablation and immediately postablation show subtle differences, suggesting that preexcitation really was present to a very minor degree before ablation (small Q wave in leads 2, 3, and aVF, and larger R wave before ablation in leads V1 and V2).

Bypass tract conduction did not recur during a waiting period, with or without isoproterenol provocation. Electroanatomic mapping was not used during this procedure (only electrogram-based mapping). The patient has done well on long-term follow-up without recurrence of preexcitation or tachycardia for several years.

Summary

- Not all WCTs after coronary artery surgery are ventricular tachycardia
- History is important (remote ablation recalled)
- Usually, partially successful ablation eliminates anterograde pathway conduction; here, it was retrograde conduction that had been ablated successfully at the first procedure. The patient still had the capability of having preexcited tachycardias such as atrial flutter/fibrillation, atrial tachycardia or AV nodal reentry (in which the bypass tract is a bystander), or, as here, antidromic tachycardia
- It is both possible and important to distinguish true antidromic SVT (which will be eliminated by successful pathway ablation) from other preexcited tachycardias (which need additional ablation of the cause of the tachycardia, not just of the pathway, which is a bystander)

7 Atriofascicular Pathway Supraventricular Tachycardia

Case Presentation

A 30-year-old woman had been bothered by sustained palpitations for the last 8 years; there had been a recent (2 years) increase in frequency of episodes. She had several emergency room (ER) visits for palpitations; ECGs consistently showed left bundle branch block (LBBB) tachycardia at ~200/min that terminated reliably with adenosine. Following tachycardia termination, the QRS was normal. She was diagnosed with supraventricular tachycardia (SVT) with LBBB aberration. Physical examination and non-invasive evaluation were completely normal. Because of increased frequency of episodes refractory to beta blockers, an electrophysiology (EP) study and ablation were performed:

EP study 1/11: Atrioventricular (AV) nodal reentrant SVT was diagnosed, leading to extensive slow pathway ablation; the operator noted that the catheter kept falling into a large coronary sinus ostium. A long vascular sheath was used but tachycardia was still inducible at the end of the procedure.

EP study 5/11: AV nodal reentrant SVT was again diagnosed, further ablation in the slow pathway region was performed with "transient success".

In the months following her second ablation, she experienced a "crescendo" in frequency of episodes, resulting in 16 ER visits (each with tachycardia having LBBB pattern, almost all readily terminated with adenosine). She was referred for repeat EP study and possible ablation.

ECG During Tachycardia

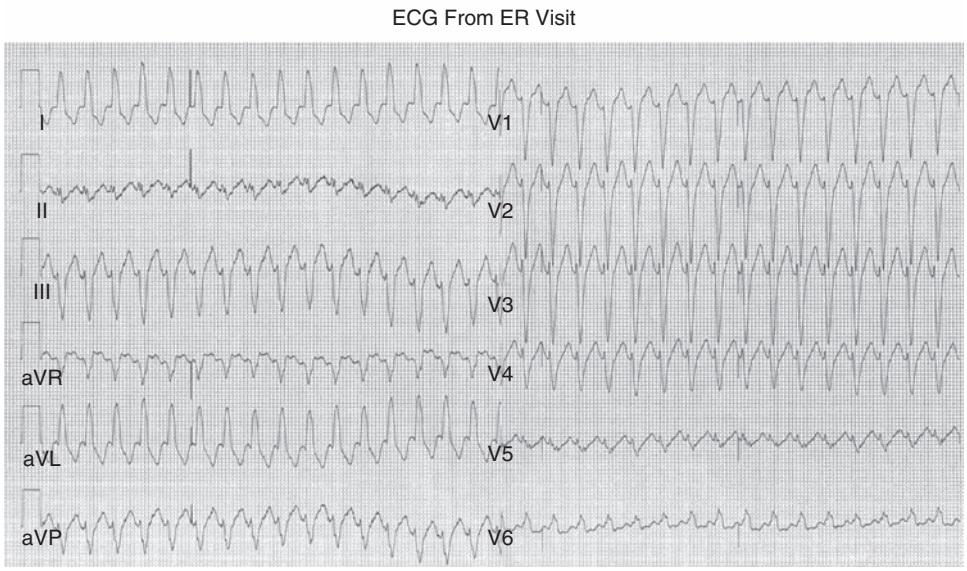


Figure 7-1

The ECG in Fig. 7-1 is representative of those obtained at each of several emergency room visits over the prior months, showing a regular tachycardia with a left bundle branch block pattern. This was reliably terminated with adenosine injection, resulting in a sinus rhythm ECG that showed no abnormalities (narrow QRS complex).

Differential Diagnosis of LBBB-Appearing Tachycardia

What About Left Bundle Branch Block (LBBB) Tachycardias?

Although right bundle branch block (RBBB) aberration is more common in younger individuals, LBBB-type tachycardias can certainly occur, with a certain relatively short list of possibilities as noted below:

- Differential diagnosis of typical LBBB tachycardia in patients with a normal resting ECG and no structural heart disease includes the following:
  - Orthodromic supraventricular tachycardia (SVT) with left lateral concealed bypass tract
  - Any type of SVT with LBBB aberration
  - Antidromic SVT using atriofascicular pathway
  - Right ventricular papillary muscle focal VT
- Typical LBBB tachycardia in patients *with* structural heart disease includes the following:
  - SVT of any type and preexisting LBBB
  - Bundle branch reentry
- *Atypical* LBBB may be seen in the following:
  - Preexcited SVT using an atrioventricular pathway anterogradely
  - VT

Baseline ECG and Intracardiac Recordings

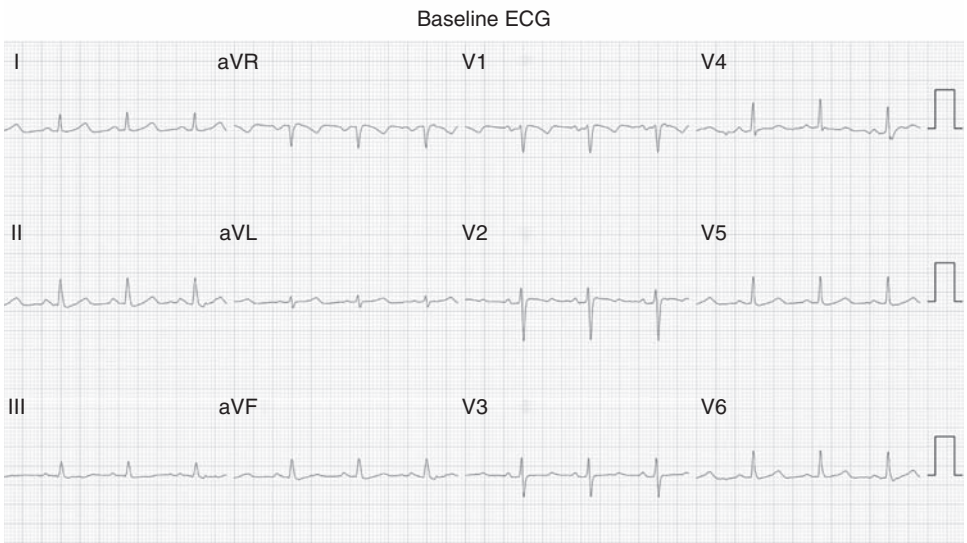
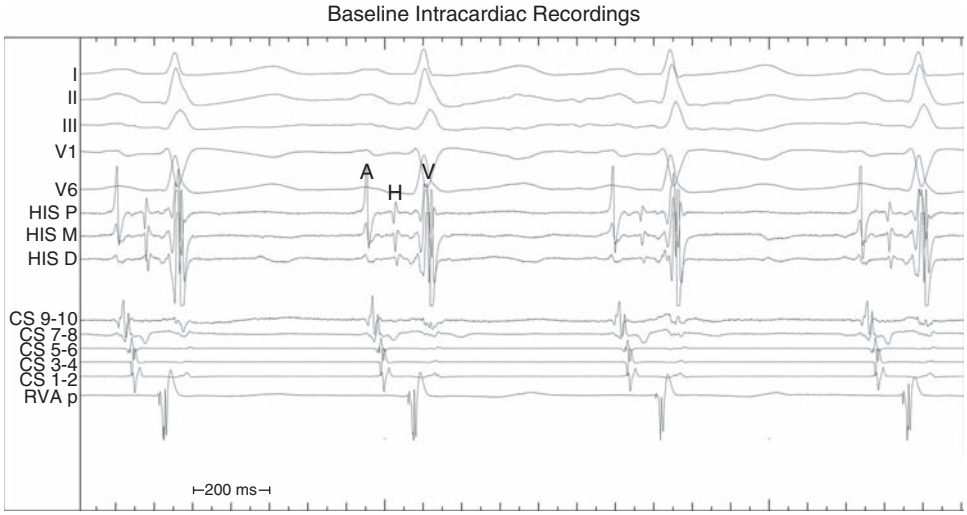


Figure 7-2

The baseline ECG (Fig. 7-2), as indicated previously, was entirely normal without bundle branch block.

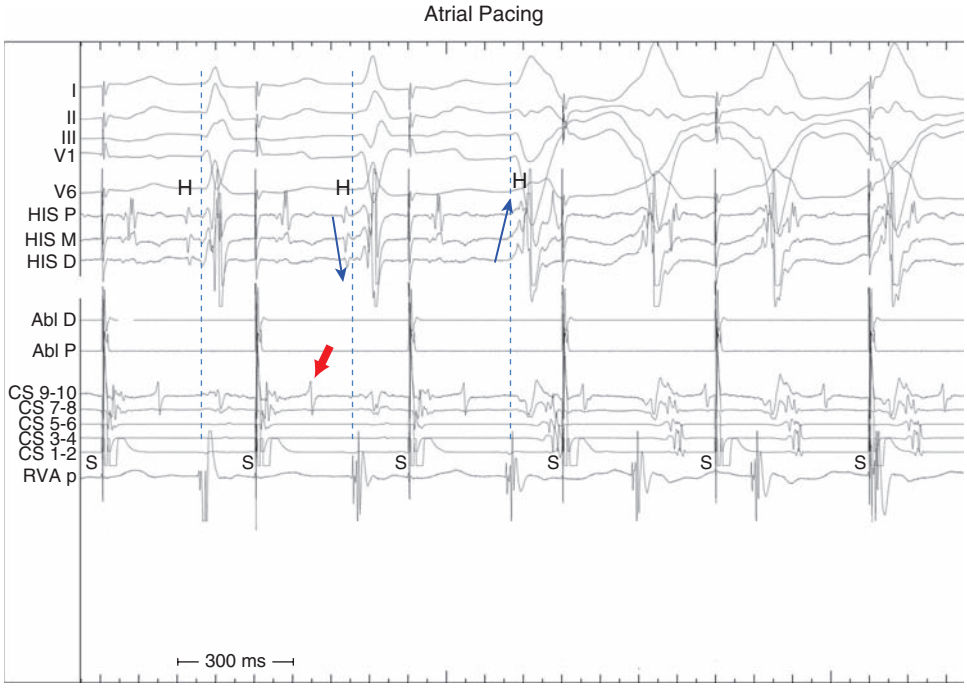
Figure 7-3



Baseline intracardiac recordings (Fig. 7-3) were likewise entirely normal, with AH and HV intervals within the normal range.

Atrial Pacing with Change in QRS and Tachycardia Induction

Figure 7-4



With atrial pacing from the distal coronary sinus, some unusual features are observed in Fig. 7-4. The *red arrow* indicates an odd potential in the region of the coronary sinus ostium; this may have been a "split potential" caused by repeated ablation in this region. Additionally, the surface ECG shows changes with a progressive increase in QRS duration until tachycardia with a left bundle branch block pattern ensues. Before this, while the AH interval changes little, the His potential (H) moves further toward and even into the QRS complex (*dashed line* denotes onset) until its direction of propagation becomes retrograde *(upward blue arrow)*. Note also that the right ventricular recording, which has a right bundle branch potential, precedes the onset of the surface QRS complex as well as the His potential. All of these taken together make a strong case for the presence of an atriofascicular bypass tract (BT); gradual development of left bundle branch block is related to progressive delay in the atrioventricular (AV) node, allowing slow conduction

down the atriofascicular pathway to its insertion in the distal right bundle branch; conduction is then retrograde to the His bundle, recording of which occurs after the onset of the QRS complex. Conduction back to the atrium is typically over the normal AV node, and tachycardia then proceeds with conduction through the atrium to the atriofascicular pathway's atrial portion (which behaves physiologically like an AV node).

Wide QRS Tachycardia

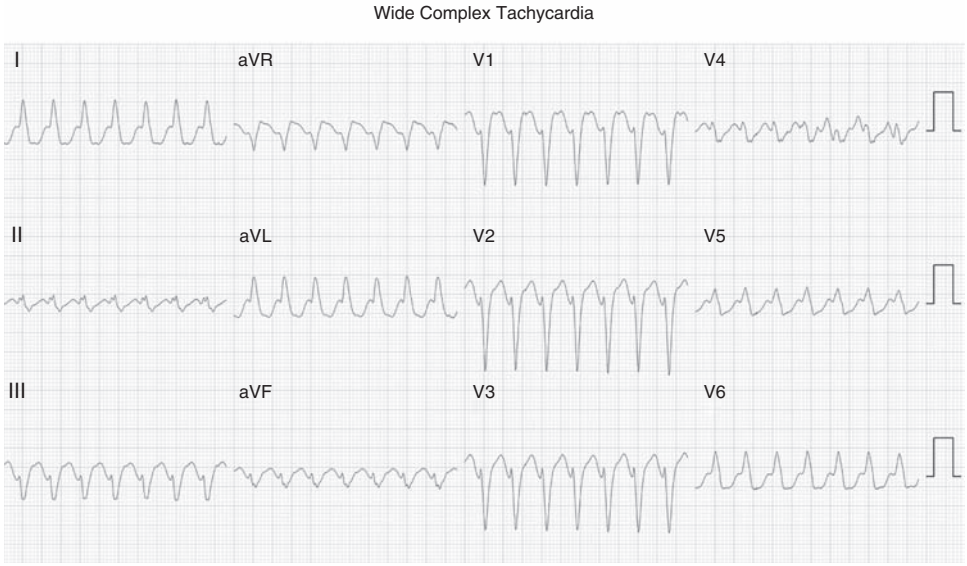


Figure 7-5

A full ECG of the induced tachycardia is shown in Fig. 7-5, matching that of spontaneously occurring episodes with left bundle branch block.

Atrial Extrastimuli During Tachycardia

Is Any Diagnosis Excluded? [Fig. 7-6]

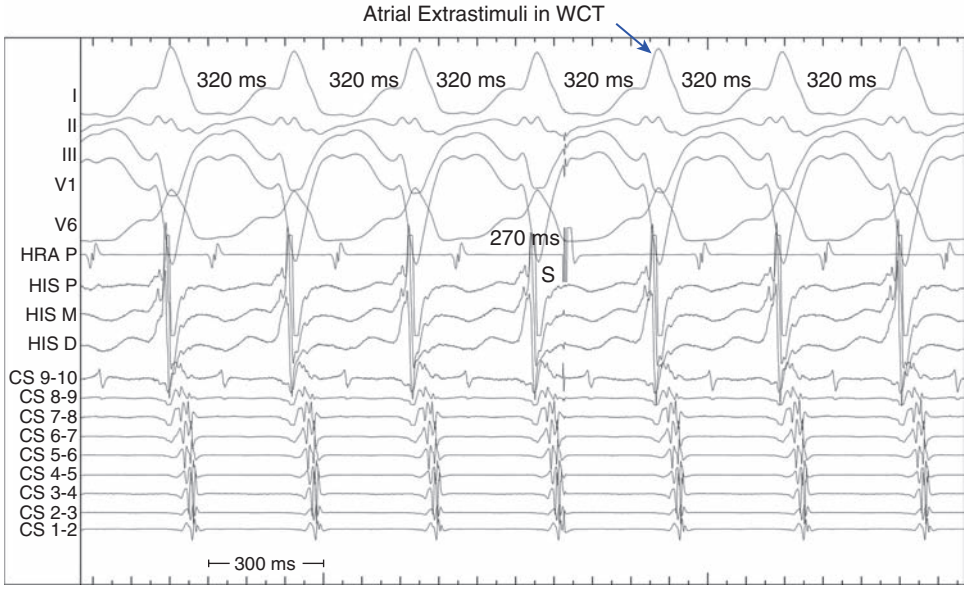


Figure 7-6

To prove that an atriofascicular pathway is present and participating in tachycardia, as well as to exclude other potential causes, atrial extrastimuli are introduced (Fig. 7-6) along the lateral tricuspid annulus at a time when the atrial electrogram in the region of the normal AV node is refractory (such that the AV node cannot be affected by the extrastimulus). The location at which the extrastimuli are delivered is important, because it is desirable to have a relatively small amount of atrium to traverse before arriving at the pathway. In the example shown, numbers of the top indicate intervals between QRS complexes. When the extrastimulus (S) is delivered at 270 ms from the prior atrial recording, the next QRS complex *(arrow)* occurs exactly on time (320 ms). Because there was no effect on the tachycardia, no conclusions can be drawn as to its nature and none of the potential causes is excluded.

Next QRS Advanced While AVJ-A is Refractory: [Fig. 7-7A]

- Excludes ventricular tachycardia
- An accessory pathway present
- Not nodofascicular or nodoventricular

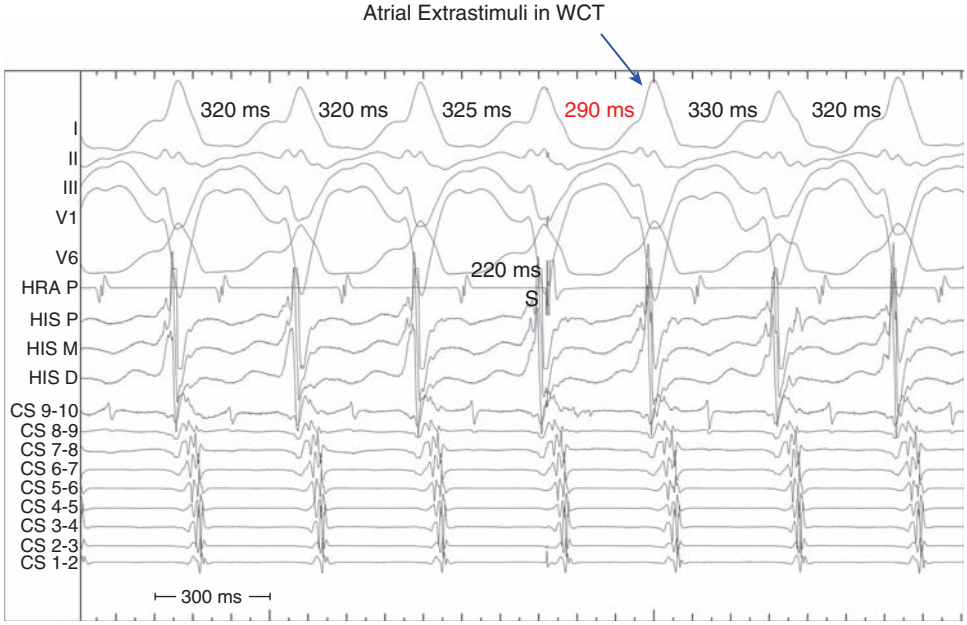
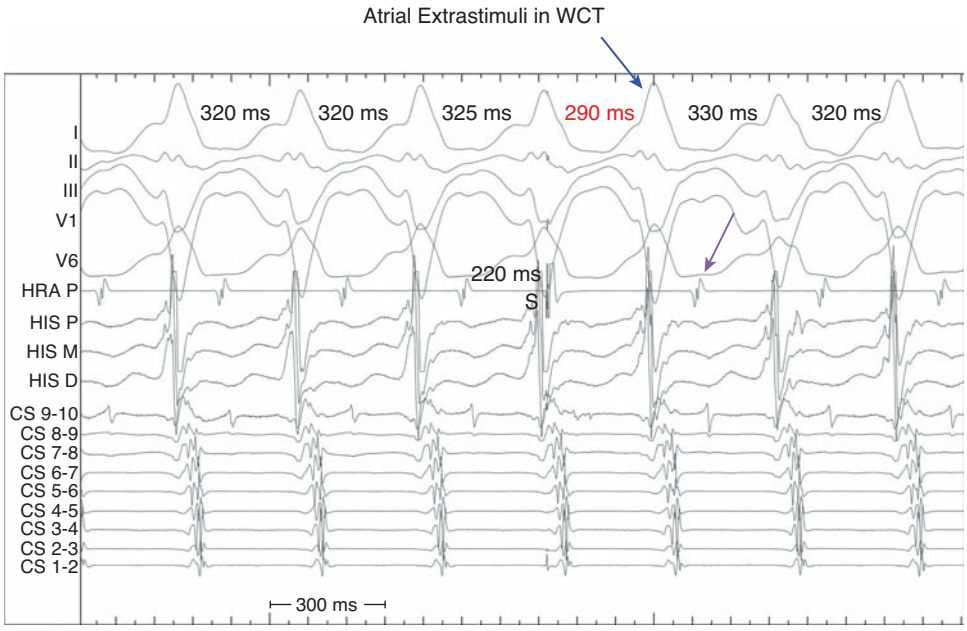


Figure 7-7A

When the atrial extrastimulus (S) is delivered at an interval of 220 ms, the subsequent QRS complex *(blue arrow)* is advanced (290 ms) (see Fig. 7-7A). This excludes ventricular tachycardia, because there is no way an atrial premature event should affect the timing of ventricular activation when the AV node is refractory.

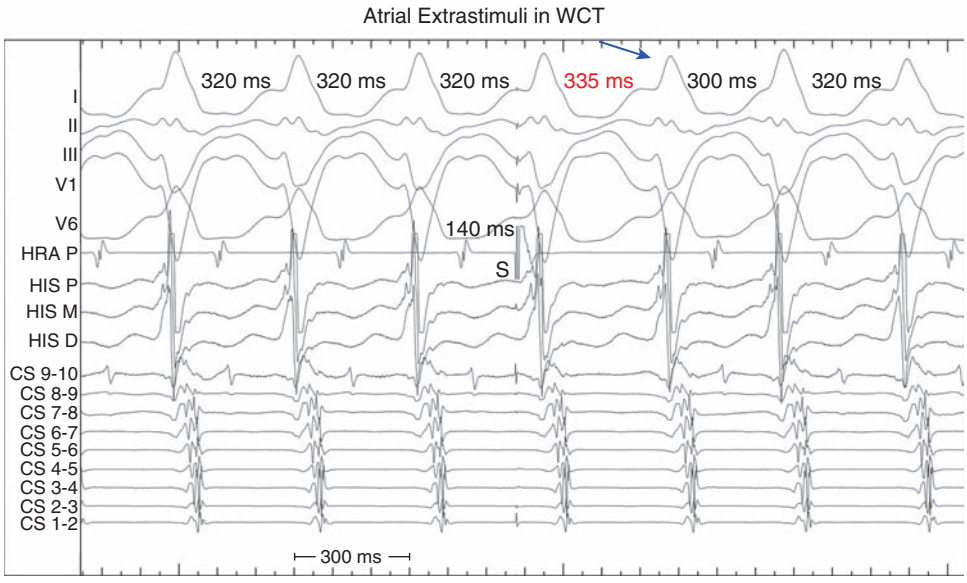


Next A Advanced Only to Same Extent as QRS:

- Not preexcited AVNRT [Fig. 7-7B]
- Not preexcited atrial tachycardia
- Second BT not excluded

Figure 7-7B

In addition, the first atrial event (*purple arrow*, Fig. 7-7B) after the QRS complex that was advanced *(blue arrow)* is likewise earlier than expected. If this tachycardia were AV nodal reentry or an atrial tachycardia, the atrial complex indicated by the *purple arrow* should have occurred exactly on time. However, because its occurrence appears to depend on the timing of the prior QRS complex, this appears to be true antidromic atrioventricular reentry proceeding down the atriofascicular pathway and up the AV node. In addition, a nodofascicular or nodoventricular pathway cannot be involved, because the AV node was refractory when the extrastimulus was delivered.



Next QRS Delayed (Not While AVJ-A is Refractory): [Fig. 7-8A]

- Excludes ventricular tachycardia

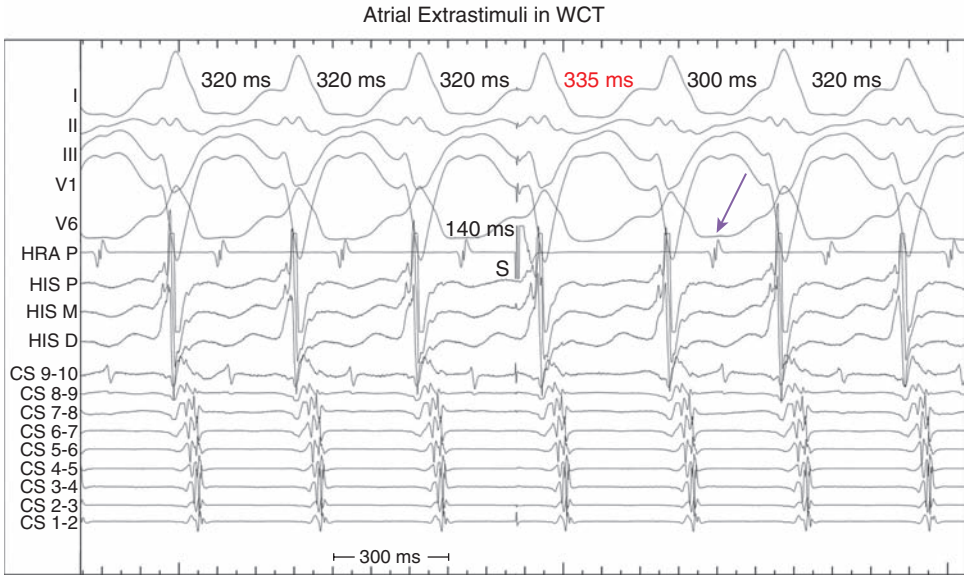
Figure 7-8A

As the atrial extrastimulus (S, Fig. 7-8A) is made to be more premature (140 ms now), the subsequent QRS complex *(blue arrow)* is actually delayed from when it would be expected to occur. This atrial stimulus is so premature that the AV node cannot be considered to be refractory; however, the fact that the next QRS complex is delayed again excludes ventricular tachycardia.

Next A Linked to Next QRS: [Fig. 7-8B]

- Not preexcited AVNRT
- Not preexcited atrial tachycardia
- Second BT not excluded

Figure 7-8B

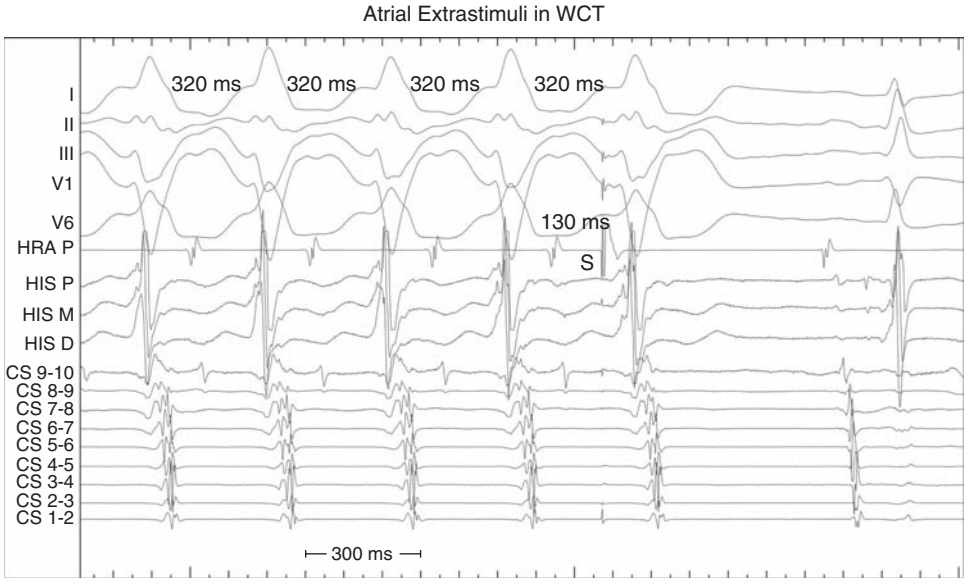


As seen previously, the first atrial complex (*purple arrow*, Fig. 7-8B) that follows the delayed QRS complex *(blue arrow)* occurs at a time later than expected and is linked to the prior QRS complex. This once again excludes atrial tachycardia or a bystander atriofascicular pathway with AV nodal reentry as the main arrhythmia diagnosis. However, retrograde conduction over a second, septal bypass tract is not necessarily excluded thereby.

Next QRS Absent (Not While AVJ-A is Refractory): [Fig. 7-9]

- Excludes ventricular tachycardia

Figure 7-9



Finally, as shown in Fig. 7-9, with an even more premature atrial extrastimulus (S), at 130 ms from the prior atrial complex, the atrium is captured but there is no subsequent QRS complex. Again, this excludes ventricular tachycardia as a potential diagnosis. Because the AV node is not refractory at the time this extrastimulus is delivered, AV nodal-dependent tachycardias could conceivably have been terminated with this and cannot be excluded on the basis of this finding alone.

Atriofascicular Pathways

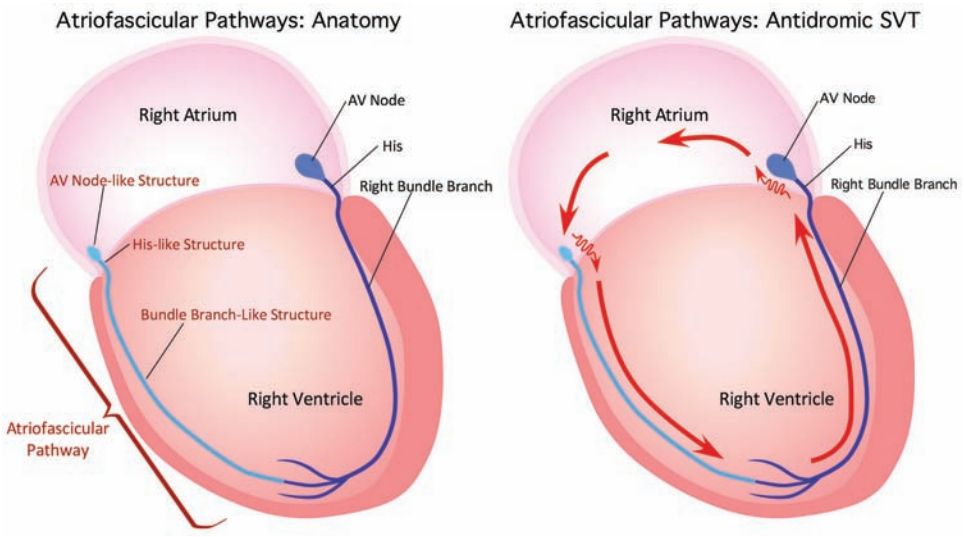
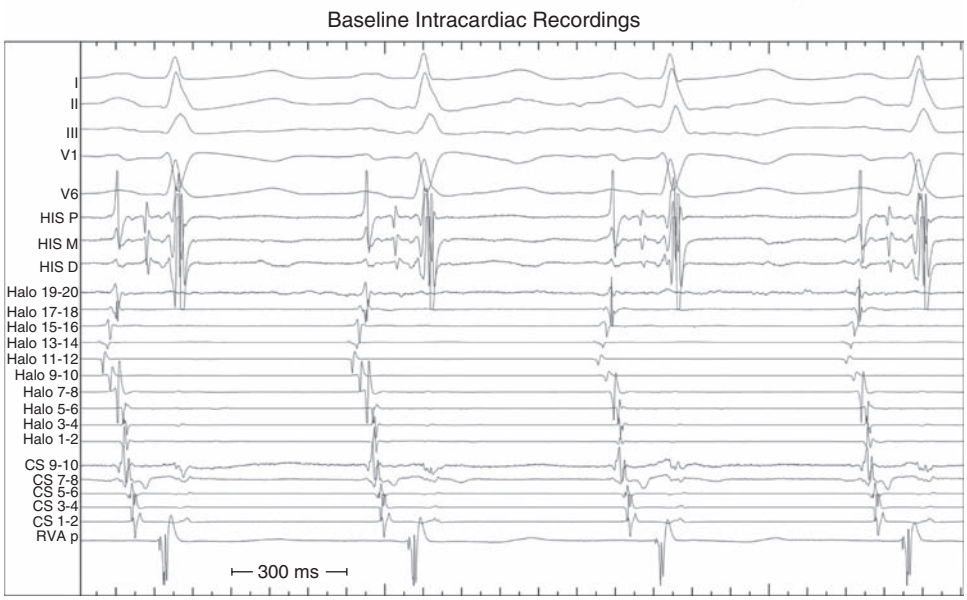


Figure 7-10

The diagram on the left in Fig. 7-10 shows the anatomy of atriofascicular pathways that have several components: an AV node–like structure in the lateral right atrium near the tricuspid annulus, a His bundle–like structure that crosses the annulus, and a long fiber-like right bundle that connects the His-like portion to the true distal right bundle. In this sense, the entire pathway is like a duplication of the normal conduction system. During antidromic tachycardia, as shown at right, the impulse travels down the atriofascicular pathway and up the normal conduction system. Zigzag lines denote slow conduction encountered in the normal AV node and the node-like part of the atriofascicular pathway.

More Baseline Recordings (with Halo Catheter)

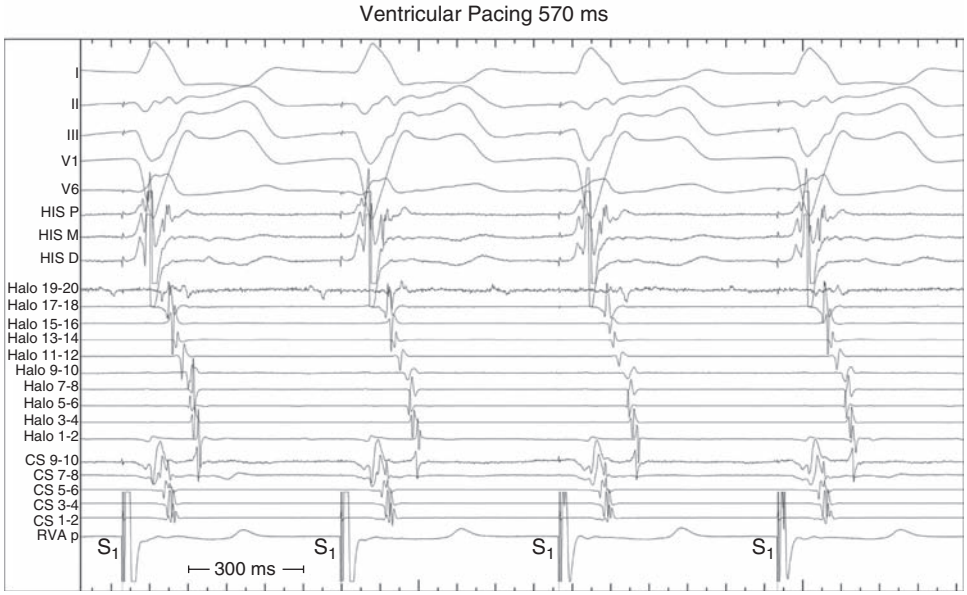
Figure 7-11



Now that a diagnosis of an atriofascicular pathway–mediated atrioventricular reentrant tachycardia has been made, selection of target sites for ablation can begin. At the beginning of the procedure, a multipolar electrode catheter ("Halo") was placed around the tricuspid annulus to facilitate mapping. The recording that had been labeled "HRA" in prior figures was in fact one of the electrodes of this catheter. During sinus rhythm as shown in Fig. 7-11, it is not possible to determine the atriofascicular pathway's location.

Ventricular Pacing

Figure 7-12



Ventricular pacing at a slow rate shows an atrial activation pattern consistent with retrograde conduction over the AV node (Fig. 7-12).

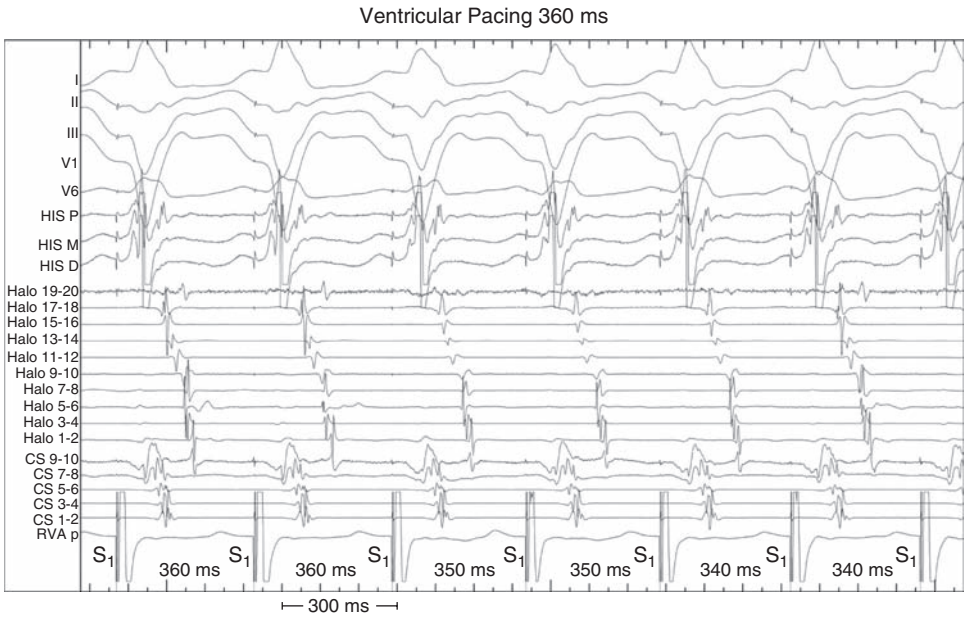


Figure 7-13

The same atrial activation pattern is maintained with ventricular pacing at a more rapid rate in Fig. 7-13.

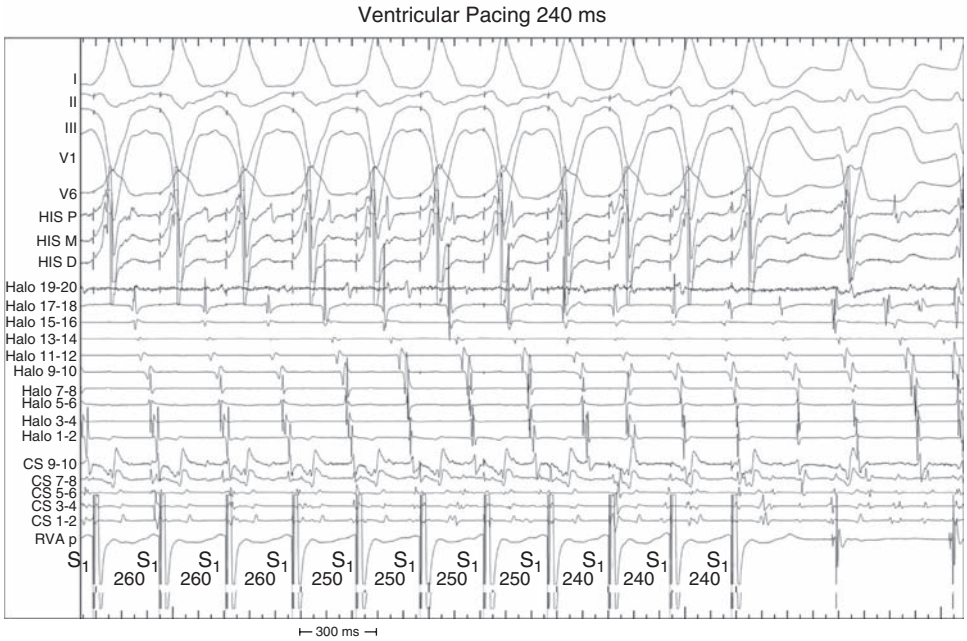
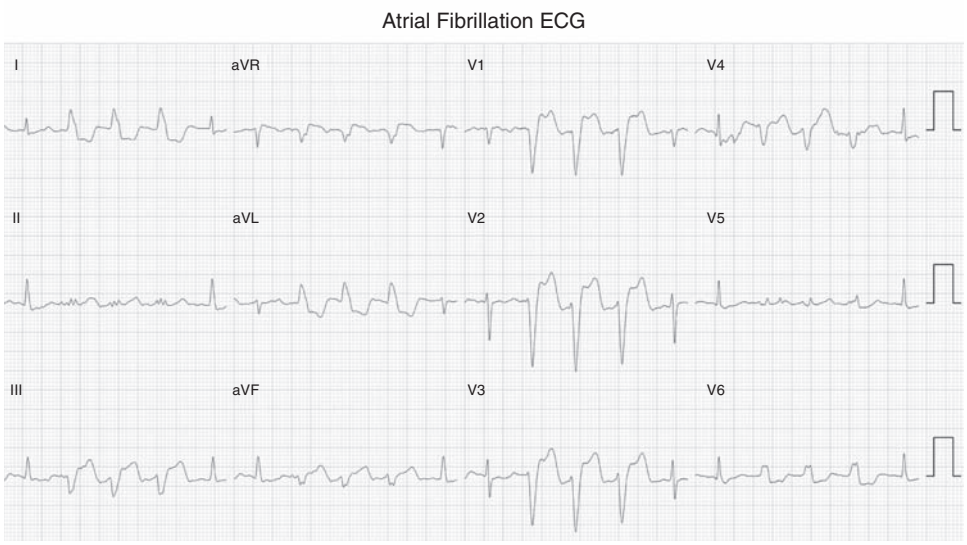


Figure 7-14

With still more rapid ventricular pacing (Fig. 7-14), conduction over the AV node persists. However, atrial fibrillation ensues.

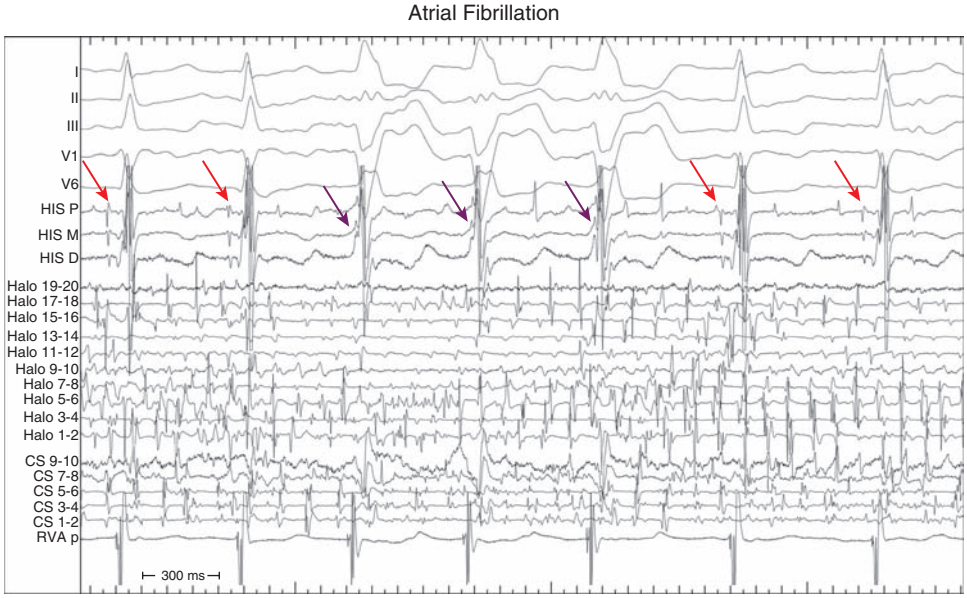
Atrial Fibrillation ECG and Intracardiac Recordings

Figure 7-15A



An ECG of atrial fibrillation, partially conducted over the atriofascicular pathway, is shown in Fig. 7-15A.

Figure 7-15B



In Fig. 7.15B, intracardiac recordings during atrial fibrillation show narrow QRS complexes with an anterogradely activated His potential *(red arrows)*, as well as wide QRS complexes with retrogradely activated His recordings *(purple arrows)*, because of anterograde conduction over the atriofascicular pathway on these complexes rather than the AV node.

Atrial Pacing and Premature Stimulation

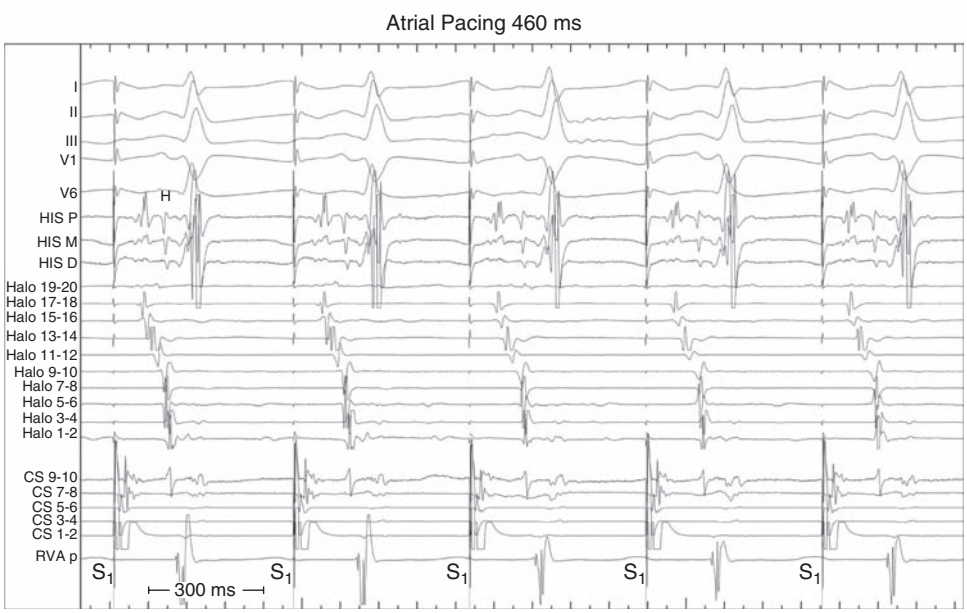


Figure 7-16

Cardioversion was necessary to terminate atrial fibrillation and continue with the procedure. Thereafter, with atrial pacing at 460 ms, ventricular activation is still largely mediated over the normal AV node-His Purkinje system (H), with a relatively narrow QRS complex (Fig. 7-16).

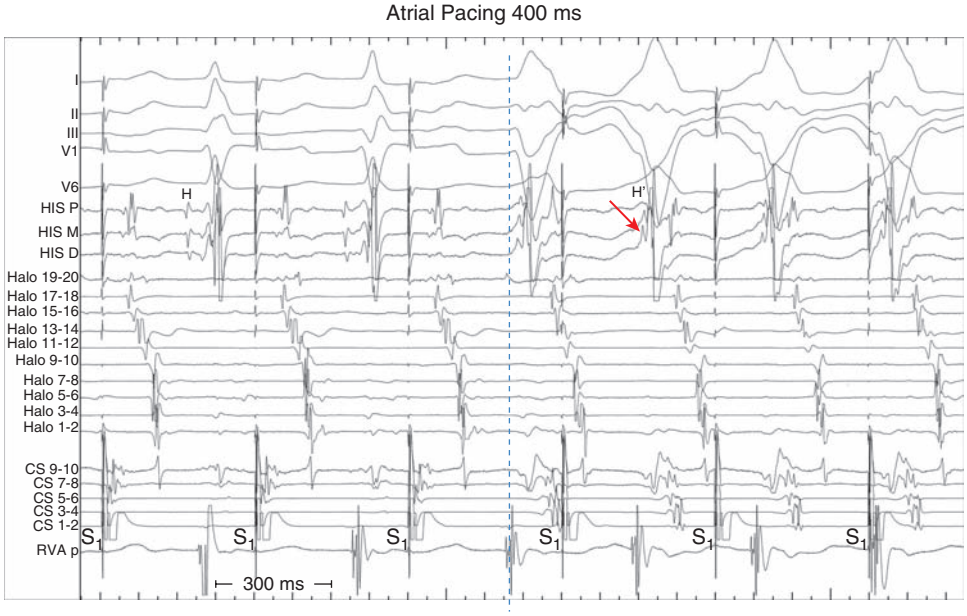
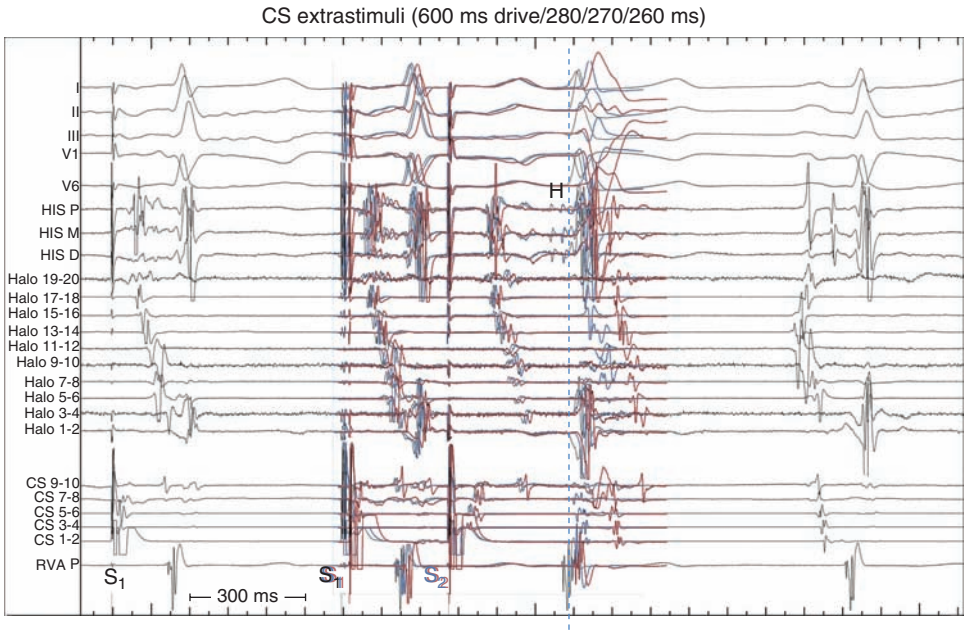


Figure 7-17

As the atrial pacing cycle length is decreased to 400 ms (Fig. 7-17), the AV node fatigues and the atriofascicular pathway becomes the mode of ventricular activation. The His potential (H′, *red arrow*) is activated retrogradely. The onset of the first preexcited QRS is indicated by a *dashed line*; note the RV electrogram and sharp spike (right bundle branch potential) precede the QRS onset.

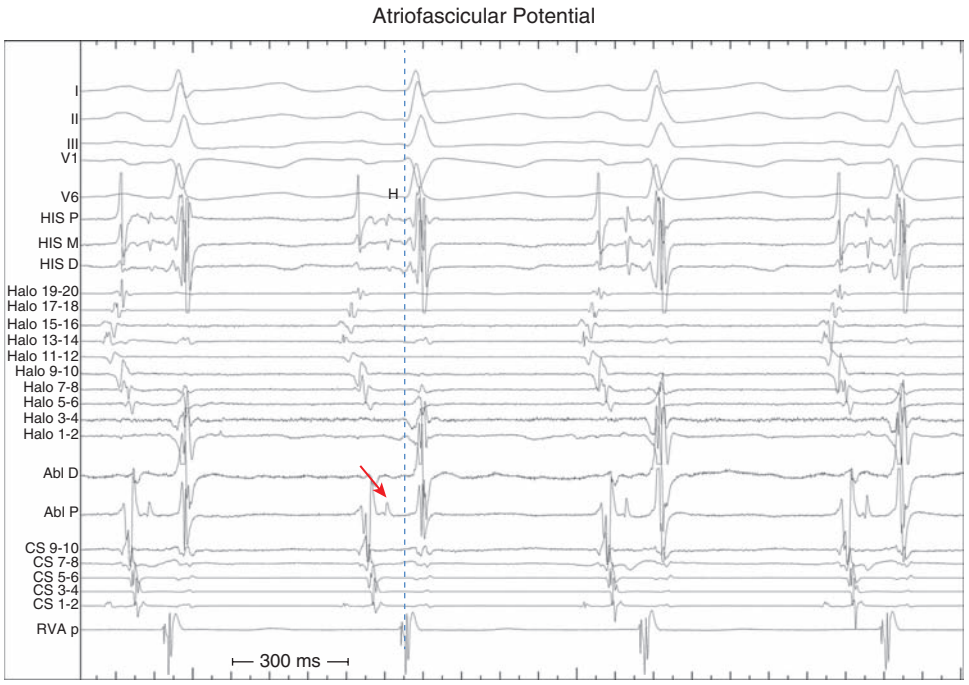
Figure 7-18



The effect of increasing prematurity of atrial stimulation on atrioventricular conduction is illustrated in Fig. 7-18 by superimposing successive coupling intervals (black, 280 ms; blue, 270 ms; red, 260 ms). It can be seen that the His bundle recording (H) is progressively delayed while the timing of the onset of the QRS complex *(dashed line)* does not change significantly, and the QRS duration progressively increases as more of the ventricular muscle is activated over the atriofascicular pathway and less over the AV node.

Mapping Atriofascicular Potential

Figure 7-19



A site along the lateral tricuspid annulus is sampled, at which a recording is obtained (Fig. 7-19) that looks very much like the recording from the His catheter at the septum (atrial electrogram, His-like potential *[red arrow]*, ventricular electrogram). This is compatible with the atriofascicular pathway potential.

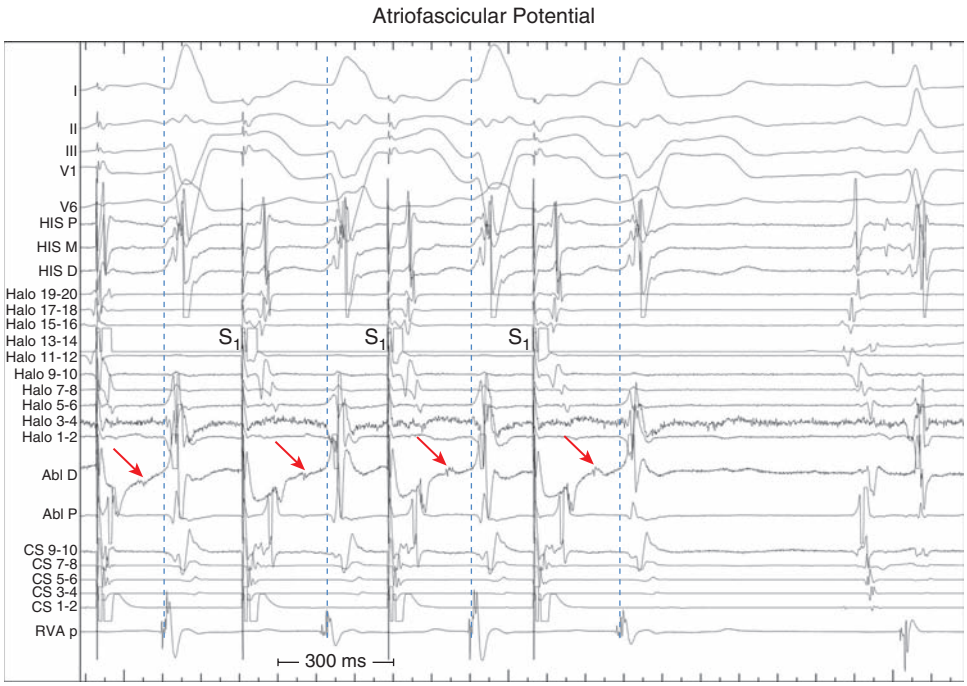
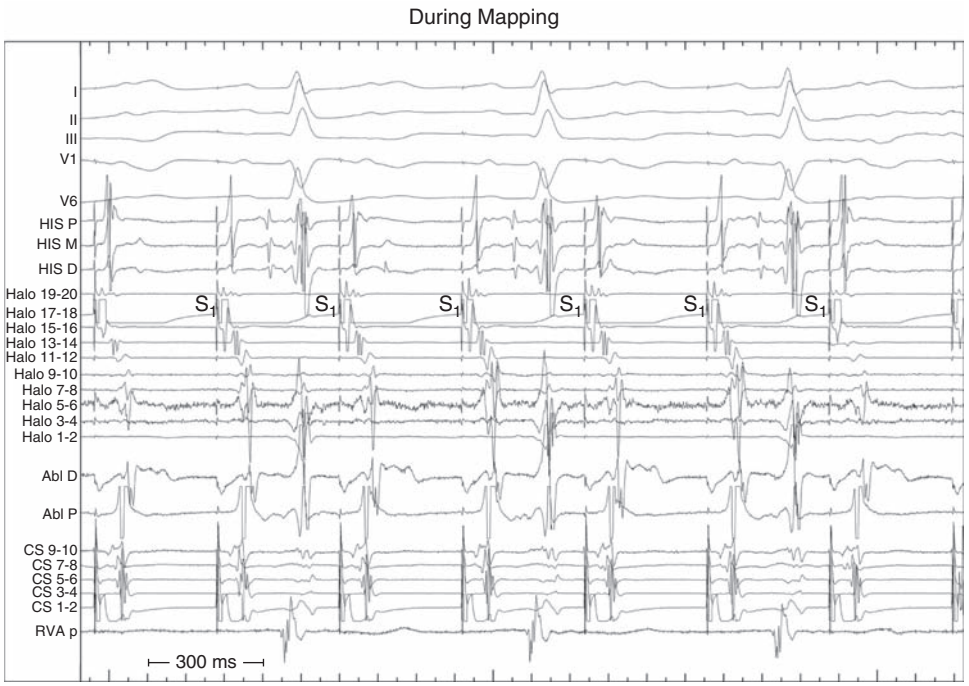


Figure 7-20

To validate the signal at the *red arrows* as a true atriofascicular pathway potential, pacing is performed (Fig. 7-20). If an actual atriofascicular potential, it should always be present during preexcited complexes and at a consistent interval before the QRS onset *(dashed line)*, which it does appear to be.

Figure 7-21



As often occurs in cases of atriofascicular pathways, small movements of the catheter tip in the vicinity of the pathway can "bump" into it and render it unexcitable for extended periods. In Fig. 7-21, under the same conditions as in Fig. 7-20, preexcitation is suddenly lost as is recording of the pathway potential. Although this is further corroboration of being at the correct site, it is not very helpful if pathway conduction does not resume. It is thus important to be very careful and deliberate with movement of the ablation catheter as it nears the anticipated location of the pathway, either to not cause trauma that temporarily eliminates conduction or, if it occurs nonetheless, to be able to ablate at the site where it occurred if the catheter has not moved from that site. Too often, however, the ablation catheter bumps the pathway while brushing past its location, and when the operator observes this and then looks at where the catheter tip is, it is no longer at the location at which mechanical interruption of pathway conduction occurred. Obviously, ablation at this other site will do no good.

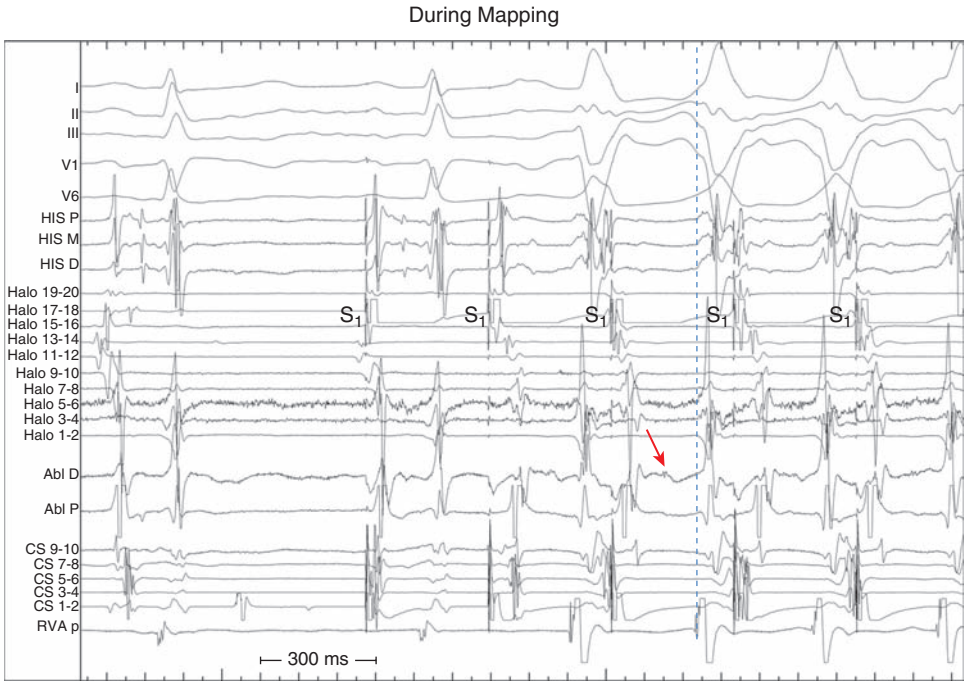


Figure 7-22

Fortunately, pathway conduction did come back a few minutes later, and the catheter was at the same location as shown (Fig. 7-22; *red arrow* shows pathway potential before preexcited QRS with *dashed line* at onset). If it had not resumed, moving the catheter away from there or administering isoproterenol or even adenosine may facilitate resumption of pathway conduction.

Pacing Ablation Site

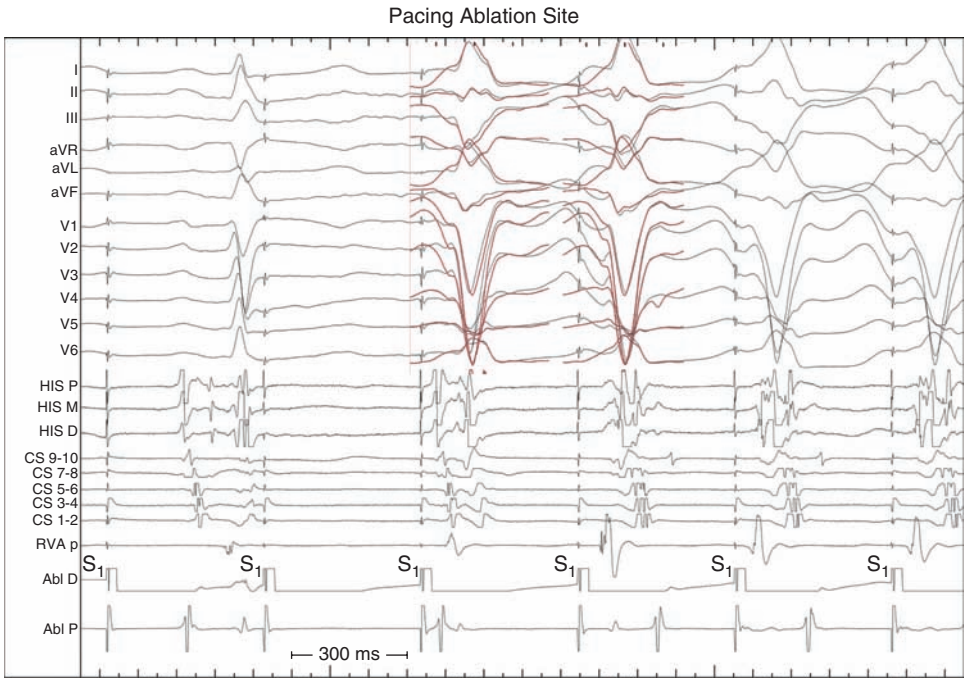


Figure 7-23

As one final corroboration, pacing from the ablation catheter nearly entirely mimicked QRS complexes during SVT (superimposed in red, Fig. 7-23), indicating that the catheter was at the site of the pathway. Importantly, if a significant amount of local ventricular capture had occurred, the QRS complex (pacing from the tricuspid annulus) would be significantly different from SVT complexes (with activation beginning closer to the apex).

Ablation Site and Radiofrequency Delivery

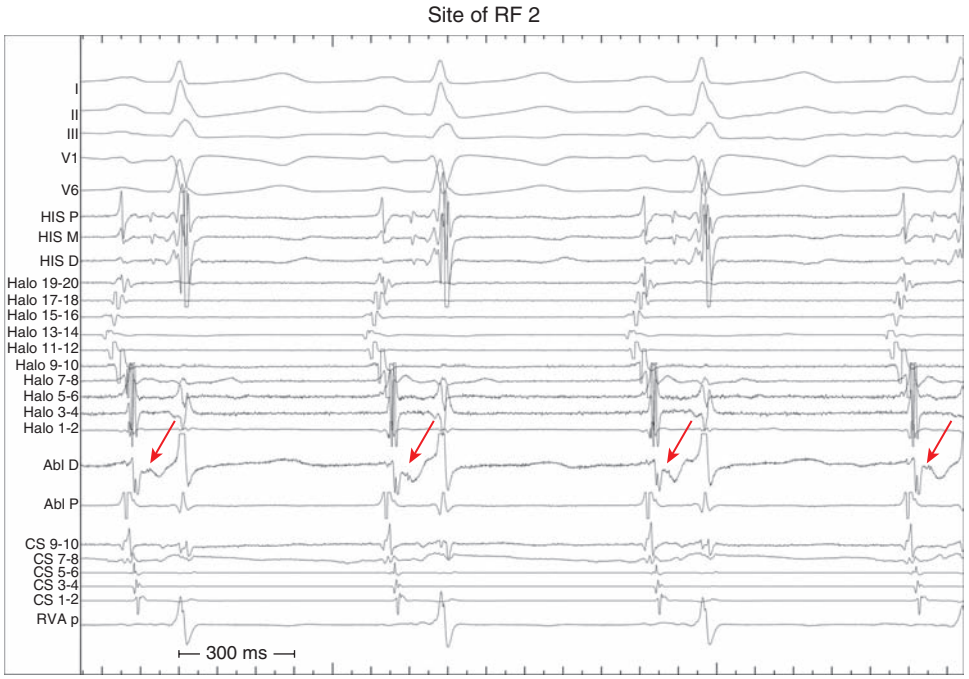


Figure 7-24

The first radiofrequency (RF) application was stopped after a few seconds because of catheter movement. The catheter was repositioned as shown in Fig. 7-24, for a second attempt at RF application. The *arrow* shows a tiny potential, indicating the atriofascicular pathway recording, just after the atrial signal at an annular site (both atrial and ventricular recordings clearly seen).

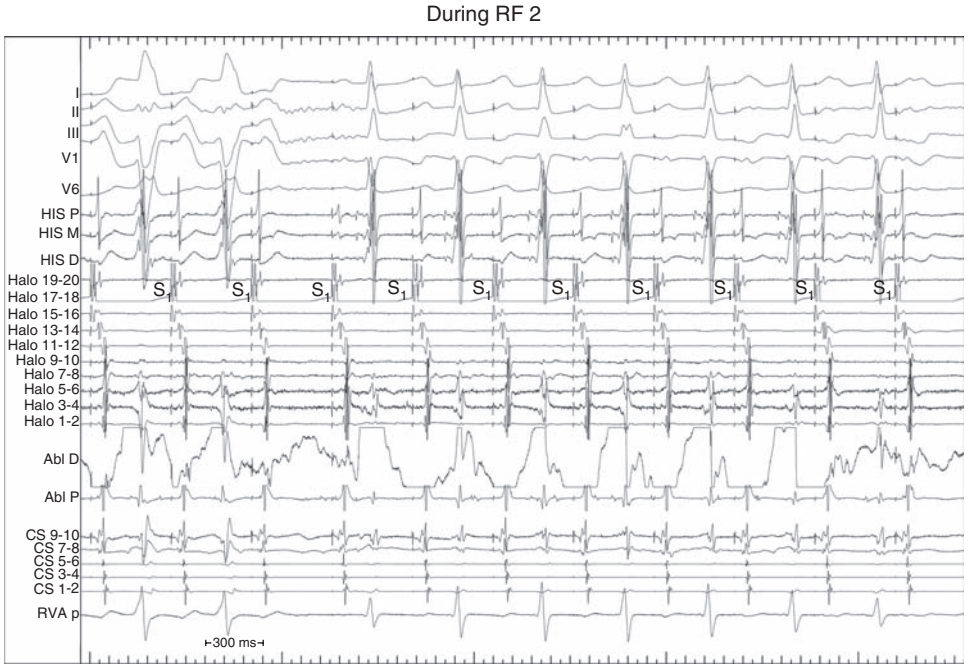


Figure 7-25

Shortly after beginning RF application during atrial pacing, preexcitation suddenly disappears as the pathway has been eliminated (Fig. 7-25).

Atrial Pacing Postablation

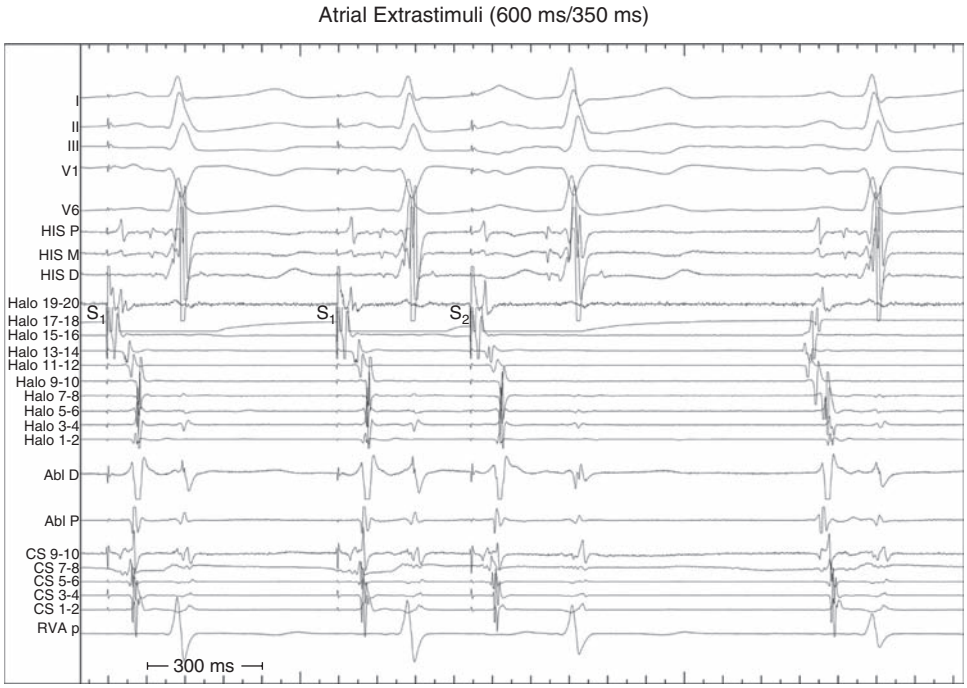


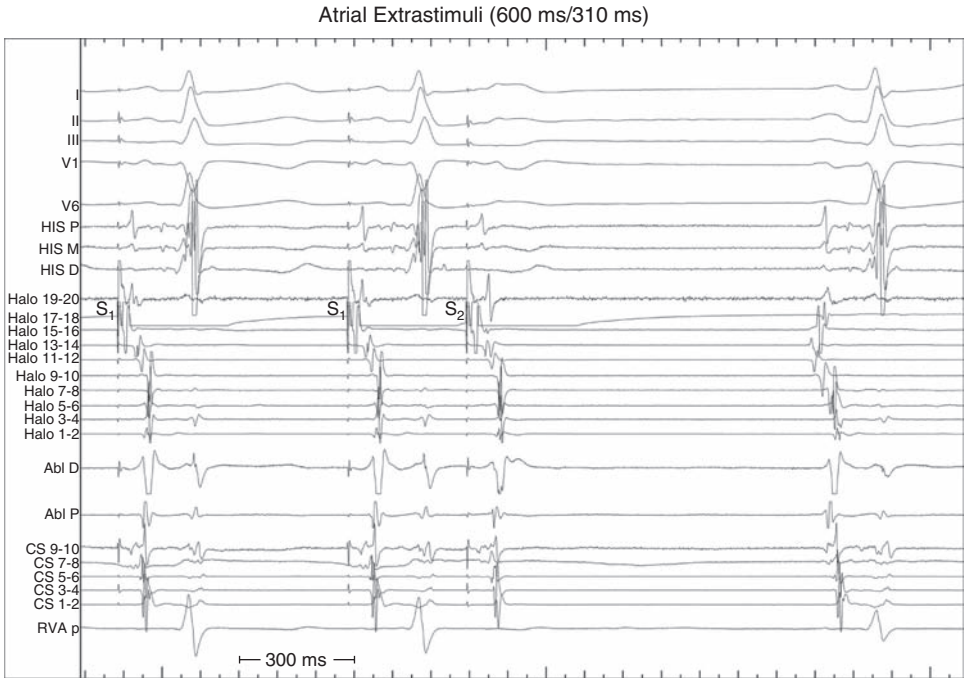
Figure 7-26

In Fig. 7-26, atrial extrastimuli delivered after successful ablation show only conduction over the AV node–His-Purkinje system and no preexcitation.

Figure 7-27

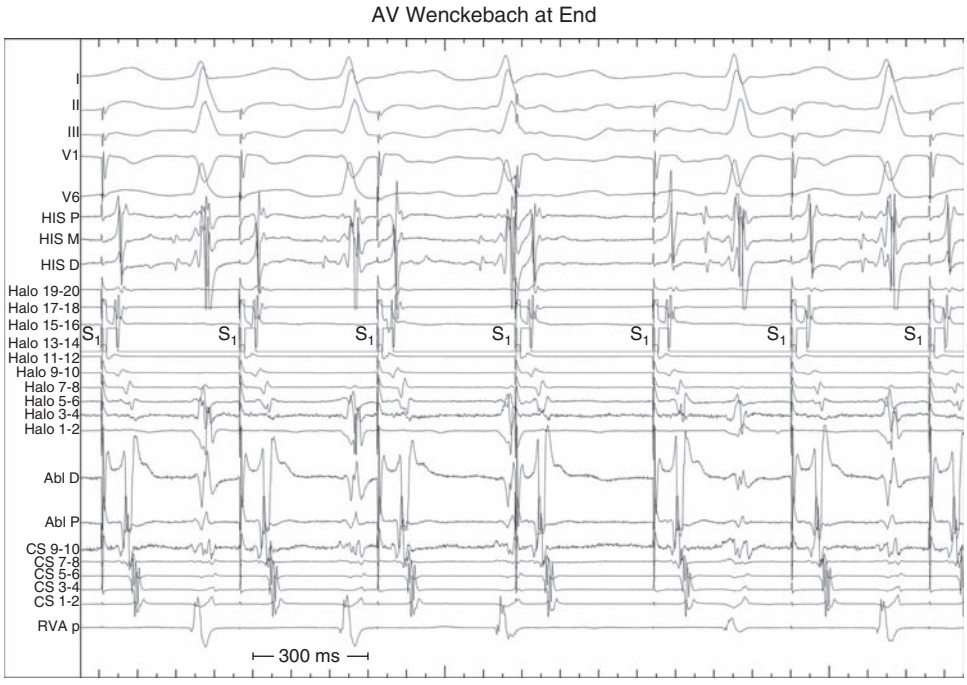
The same coupling intervals as had shown preexcitation before ablation no longer do so, as shown in Fig. 7-27.

Figure 7-28



An atrial extrastimulus results in AV nodal refractoriness; before successful ablation, this would have conducted over the atriofascicular pathway to the ventricle (Fig. 7-28).

Figure 7-29



At the end of the procedure, AV conduction was exclusively over the AV node–His-Purkinje system. Atrioventricular Wenckebach is shown in Fig. 7-29.

Final Fluoroscopy

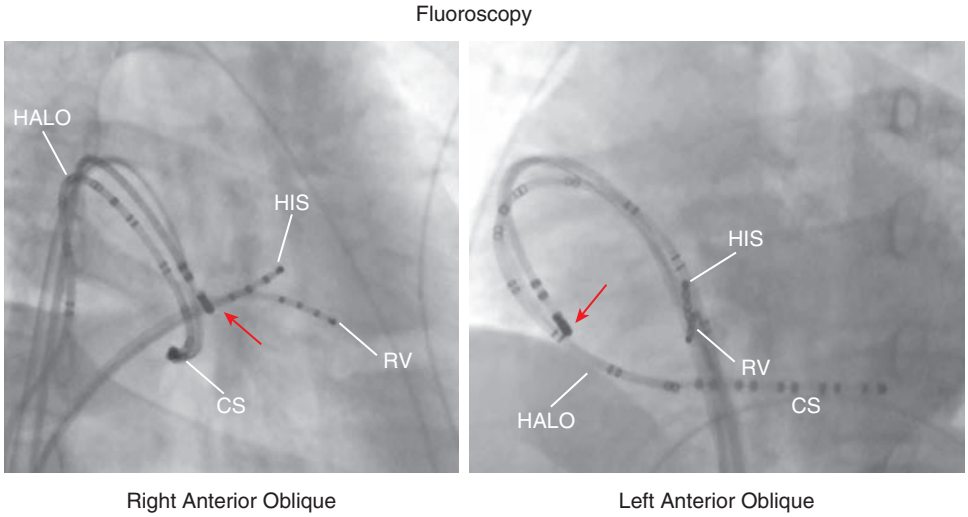


Figure 7-30

Fluoroscopic views of catheter positions at the time of successful ablation are shown in Fig. 7-30. The mapping/ablation catheter (tip indicated by a *red arrow*) is looped around the tricuspid annulus, a technique that is sometimes helpful for maintaining catheter stability. The coronary sinus catheter was also looped around the tricuspid annulus, as was the Halo catheter.

Principles of Mapping Atriofascicular Pathways

Methods for mapping/ablation of atriofascicular pathways include targeting the following:

- Pathway potential
  - At tricuspid annulus
  - In ventricle, be careful (if RBBB occurs this results in longer path length, incessant SVT)
- Site at which longest atrial extrastimulus coupling interval during SVT advances next QRS
- Site at which shortest S-QRS with atrial pacing is seen
- Site at which pace mapping at tricuspid annulus exactly replicates preexcitation pattern
- Site at which catheter manipulation damages pathway
  - Be VERY careful—trauma may somnify pathway for prolonged periods

Summary

- Atriofascicular pathways are rare but full of physiology
- Clues to diagnosis:
  - Multiple episodes of LBBB SVT
  - Delayed R-wave progression in LBBB SVT
- Antidromic reciprocating tachycardia (ART) can mimic AVNRT with LBBB
  - ECG looks like LBBB; His position may be unstable (thus not consistently seen)
  - Earliest retrograde activation is at AVN fast pathway
  - Differentiation:
    - His occurs before (AVNRT) or after (ART) QRS onset
    - ΔHA interval (AVNRT $>$ +10 ms, ART $\approx$ 0 ms)
      - His activation in ART is retrograde (anterograde in AVNRT)
      - Second bypass tract is excluded by ΔHA interval (ART $\approx$ 0 ms, preexcited ORT $<$ −10 ms)

8 Slowly Conducting Bypass Tract Supraventricular Tachycardia

Case Presentation

A 20-year-old woman had been experiencing palpitations and near syncope with increasing frequency over the last 2 years. Beta blockers were used in the past but to no avail. She had several emergency room (ER) visits in the interim where supraventricular tachycardia (SVT) episodes were terminated with intravenous adenosine termination. The electrophysiologist was called at 2 AM one day when the patient was in incessant SVT at an outside hospital ER (despite multiple adenosine doses) and hypotensive. She was also 30 weeks pregnant with her third child. She was transferred to our hospital for further therapy. Options considered: medical therapy (but what medications are effective and safe during pregnancy?) or catheter ablation (but what about fluoroscopic exposure to the unborn child?).

Prior SVT ECG

What Is the Differential Diagnosis? [Fig. 8-1]

Figure 8-1

Figure 8-1 displays a so-called "long-RP" supraventricular tachycardia with inverted P waves in inferior leads. The differential diagnosis for this rhythm includes atrial tachycardia from the low septum/region of the coronary sinus ostium; atypical "fast-slow" AV nodal reentry; automatic junctional tachycardia; and orthodromic SVT using a slowly conducting bypass tract. She clearly needs some treatment not only for her but also for her baby's health.

Her SVT stopped by the time of arrival to our hospital, without recurrence for several hours. She and her family were uncertain about ablation. Medical therapy with sotalol (relatively safe in pregnancy) was recommended. After one dose of sotalol (80 mg), nearly incessant SVT occurred, lasting 20 to 30 min at a time, stopping for a few seconds and resuming; episodes started with either P or QRS. Because of the poor response to medical therapy, catheter ablation was then recommended.

Electroanatomic "Shell" [Fig. 8-2]

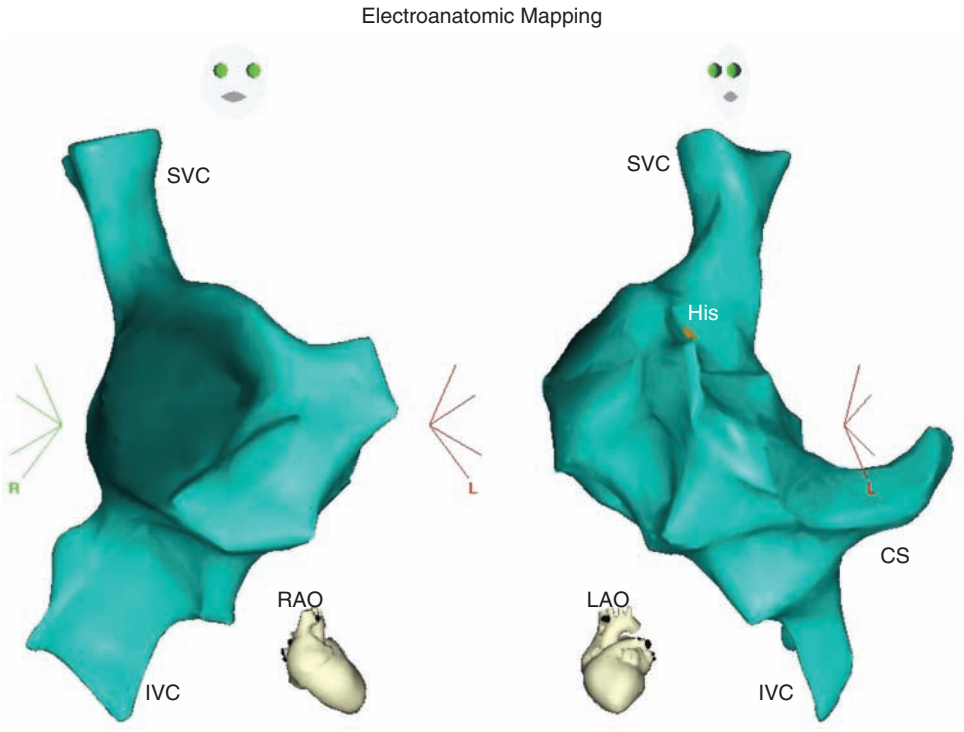


Figure 8-2

At the electrophysiology (EP) study, electroanatomic mapping and stereotactic remote magnetic catheter navigation were used. First, the mapping/ablation catheter was used for delineation and recording of anatomy on an electroanatomic mapping system (navigating to His, coronary sinus (CS), and characterizing the extent of the RA chamber; Fig. 8-2). SVC, superior vena cava; IVC, inferior vena cava; CS, coronary sinus; RAO, right anterior oblique; LAO, left anterior oblique.

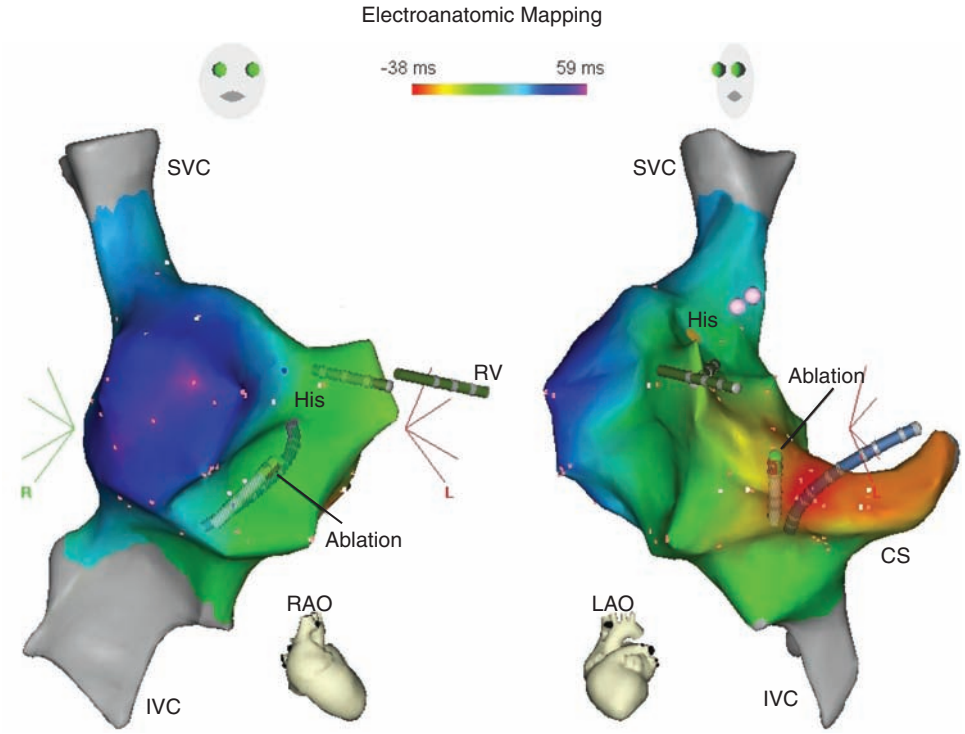


Figure 8-3

Once the anatomy was clear, other electrode catheters were guided into place at previously determined locations (CS, high RA, RV, His) using the electroanatomic map (Fig. 8-3). Representations of the electrode catheters in these locations are as shown. Activation mapping was performed, using a stable CS electrogram as timing reference; all of this was accomplished without use of fluoroscopy. Mapping showed earliest atrial activation at the proximal CS (*red area*). Of note, this is consistent with any of the diagnostic possibilities and does not differentiate among them. Thus EP testing was performed to determine the precise diagnosis. RA, right atrium; RV, right ventricle.

Baseline Intracardiac Recordings During Sinus Rhythm and SVT

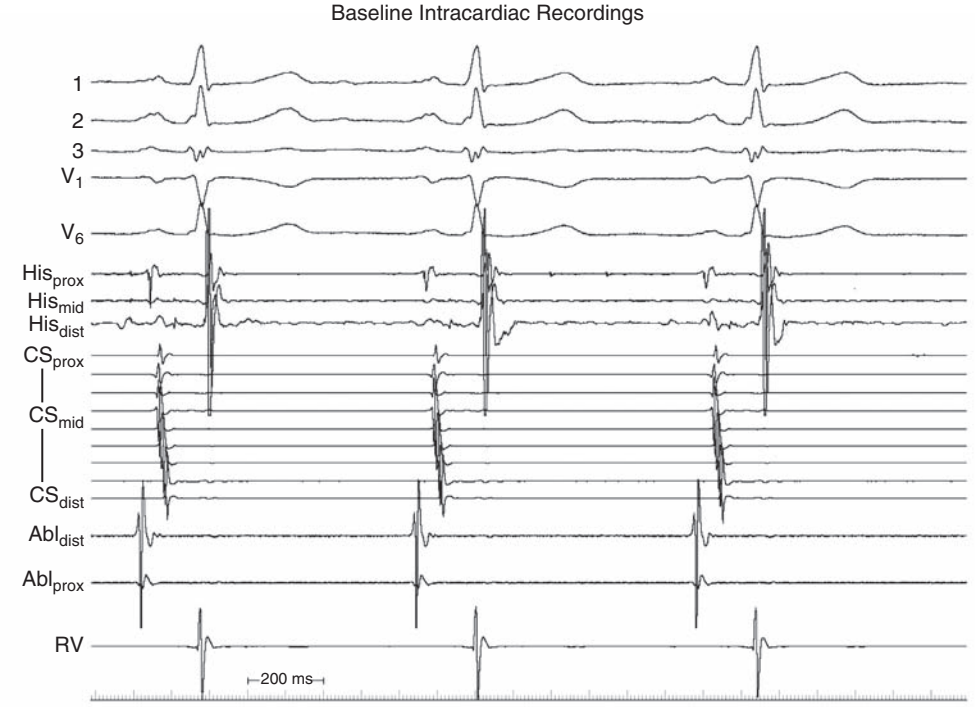
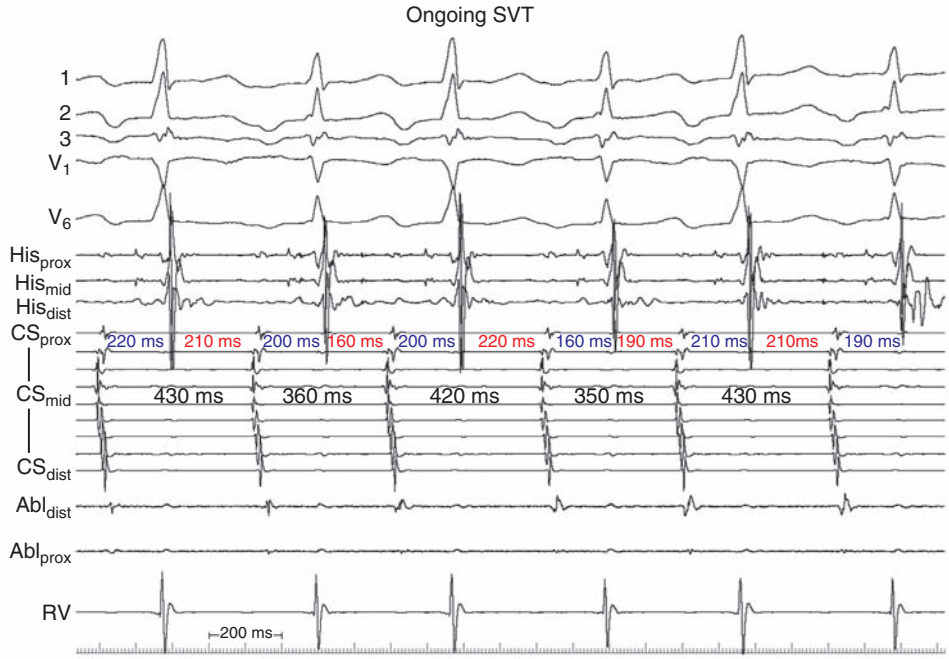


Figure 8-4

Baseline intracardiac recordings are as shown in Fig. 8-4 during sinus rhythm; as anticipated, SVT was readily initialed by a variety of means including spontaneously or following ventricular (VPC) or atrial (APC) premature complexes.



What Can You Diagnose From This, If Anything? [Fig. 8-5]

Figure 8-5

SVT was rather irregular. Whenever this is the case, it is an opportunity to determine which electrograms depend on others and which are "leaders" that other recordings follow. In Fig. 8-5, cycle length (A-A) intervals are shown in *black*, A-V intervals in *blue*, and VA intervals in *red*. There does not seem to be a consistent relationship of one recording definitely leading to another. Irregularity of tachycardia cycle length significantly hampers use of pacing maneuvers, most of which implicitly rely on a regular cycle length to provide a predictable occurrence of the next SVT complex after a pacing-induced perturbation (such as single extrastimuli or trains of pacing). For instance, if the SVT CL is very irregular, it is very difficult to compare the postpacing interval (PPI) to tachycardia CL (TCL) as an indicator of proximity of the pacing site to a tachycardia circuit.

Ventricular Extrastimuli and Overdrive Pacing in SVT

Does This Help? [Fig. 8-6]

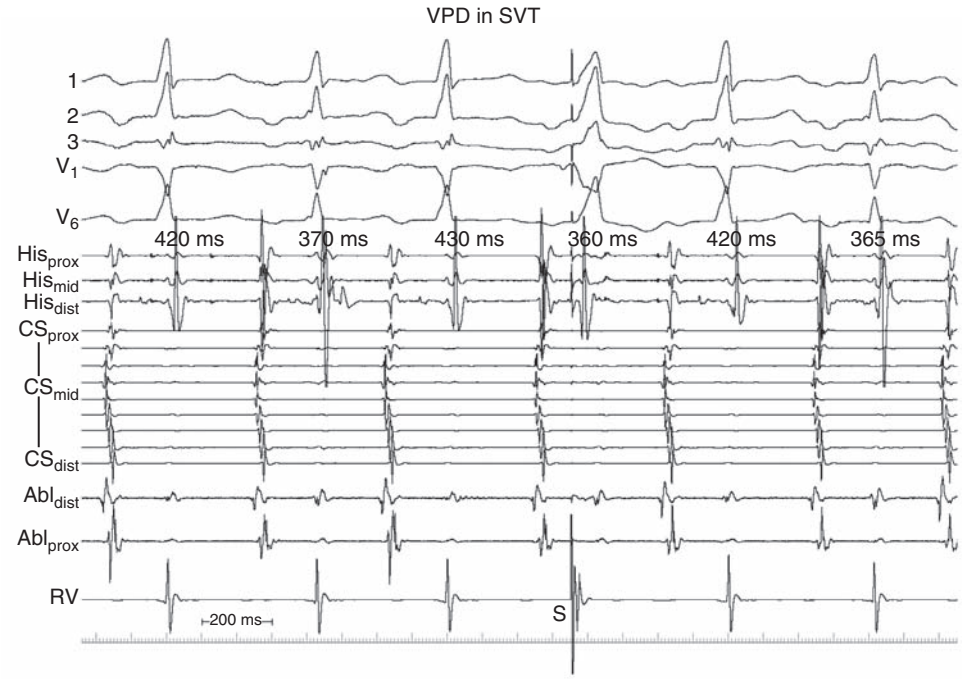


Figure 8-6

In Fig. 8-6, a single ventricular extrastimulus is delivered during SVT. This was difficult to do because the CL was very irregular and timing a ventricular extrastimulus to occur at a time when the His bundle was refractory was a matter of chance. Though one such event is shown here (His-refractory extrastimulus, Fig. 8-6), can anything be inferred from its effect? The atrial recording after the extrastimulus occurs earlier than others and in fact has a slightly shorter A-A interval than any others. The interval surrounding the extrastimulus has to be meaningfully shorter than any other A-A interval in order to use it as evidence for the presence of an atrioventricular bypass tract. The difference between this A-A interval (360 ms) and the shortest spontaneously occurring interval during SVT (365 ms) is very small, and so this should not be the only evidence used to make a diagnosis of a bypass tract.

Does This Help? [Fig. 8-7]

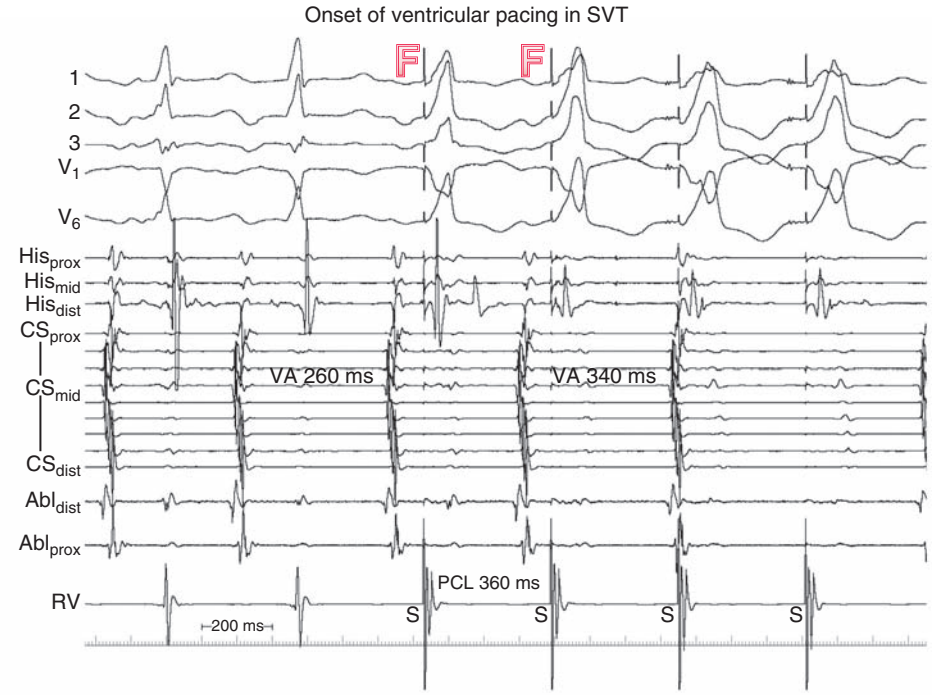
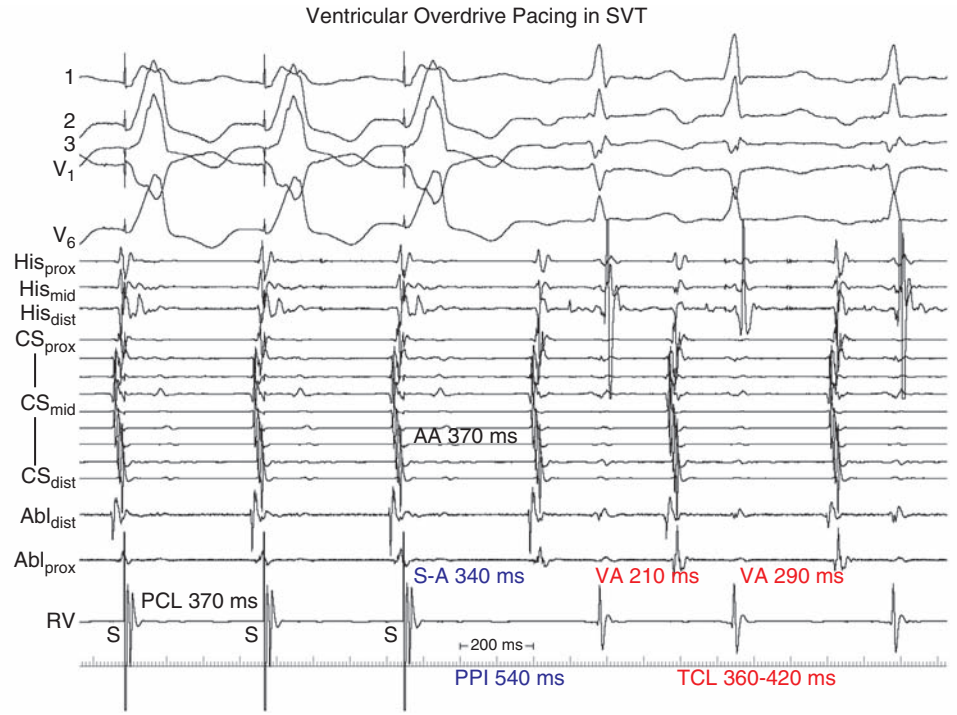


Figure 8-7

Similarly, interpreting the results of overdrive pacing during SVT can be difficult in the presence of significant CL variability. In Fig. 8-7, at the initiation of overdrive ventricular pacing, the second stimulus is followed by an atrial electrogram that occurs much later than anticipated (VA interval 340 ms). This occurred in response to a paced complex that is a fusion (F) between tachycardia and fully paced complexes (the last two). Because the timing of atrial activation was altered at time when the His had been anterogradely activated, this indicates that there is an extranodal pathway over which atrial activation can occur in response to ventricular stimulation. Further, the fact that the atrial activation is delayed from when it would be expected to occur shows that the pathway is not only present but also participates integrally in SVT. Thus a diagnosis of orthodromic SVT is established (stronger if this is a reproducible finding). Note that SVT terminated during continued pacing (no atrial electrogram after the second to last QRS complex).



Does This Help? [Fig. 8-8]

Figure 8-8

At the end of another attempt at ventricular overdrive pacing, SVT resumes. The usual interval measurements are made, with uninterpretable results: the PPI-TCL difference ranges from 120 ms (consistent with bypass tract SVT) to 180 ms (inconsistent with bypass tract SVT) (Fig. 8-8). Similarly, the stimulus-atrial (SA) minus ventriculoatrial (VA) interval difference ranges from 50 ms (consistent with bypass tract SVT) to 130 ms (not consistent with bypass tract SVT). The problem is that the retrograde limb has cycle length–dependent slowing of conduction ("decremental conduction") that invalidates the measurements.

Atrial Pacing at SVT Cycle Length Compared with SVT

Does This Help? [Fig. 8-9]

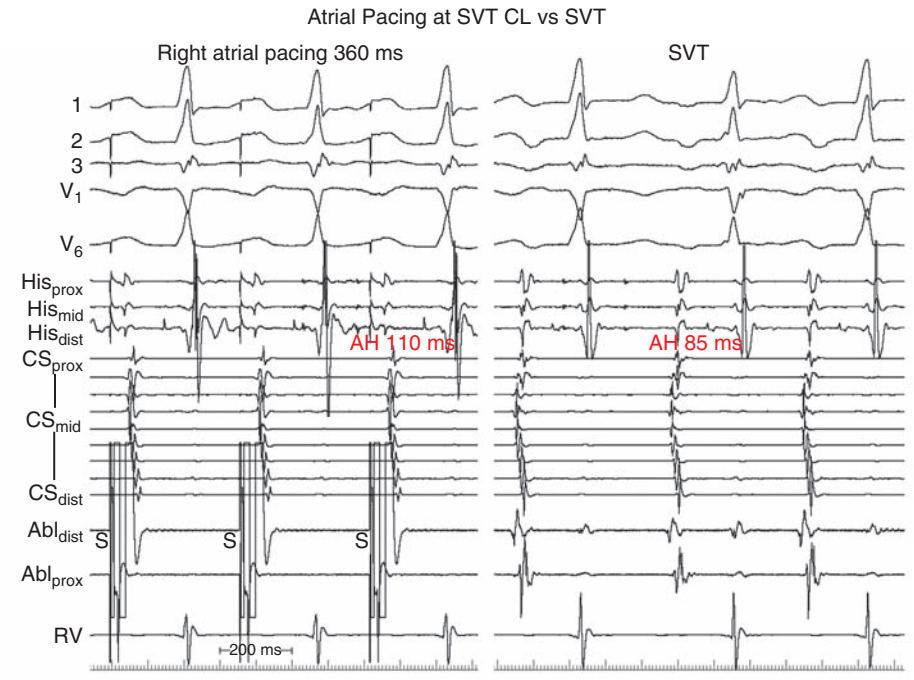


Figure 8-9

To exclude an (unlikely) atrial tachycardia, the atrio-His (AH) interval is compared between that during SVT and during atrial pacing at the SVT CL. If a right atrial tachycardia, the AH intervals should be similar; with orthodromic SVT, the difference between paced and SVT AH intervals is typically 20 to 40 ms, whereas with atypical AV nodal reentry the difference is usually ≥40 ms. Here, the difference of 35 ms is consistent with orthodromic SVT (Fig. 8-9).

Spontaneous SVT Termination

Does This Help? [Fig. 8-10]

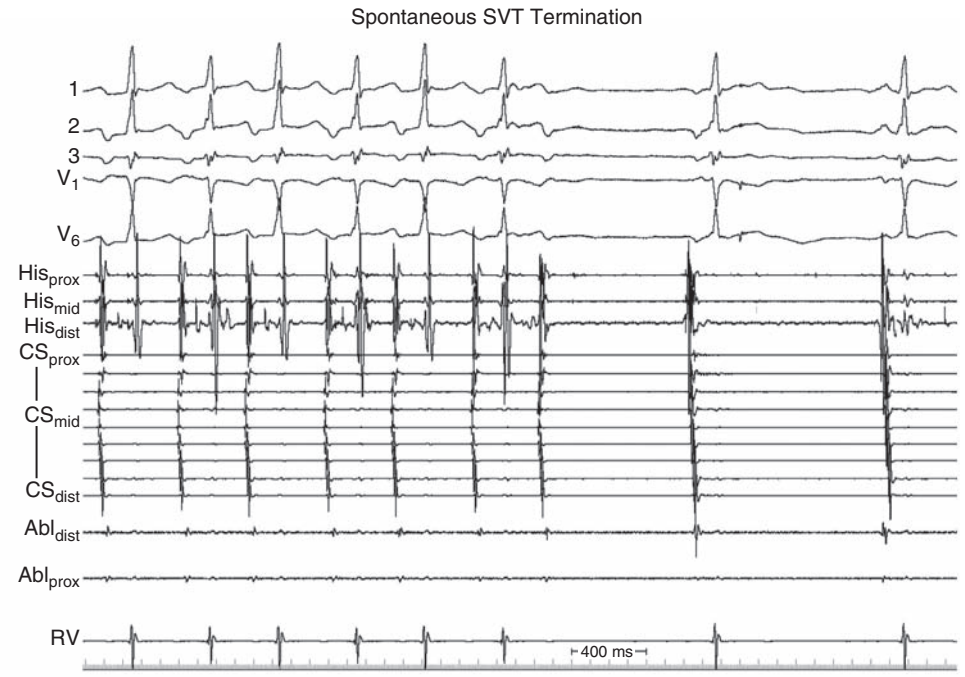


Figure 8-10

Another means of excluding atrial tachycardia as a diagnosis occurred spontaneously here—tachycardia terminates spontaneously with the last event being atrial. An atrial tachycardia with 1:1 AV conduction would not be likely to terminate suddenly at the same instant as AV block occurred (Fig. 8-10).

Comparison of Features and Behavior of Different SVTs

TABLE 8-1 Truth Table

	Atrial Tachycardia	Orthodromic SVT	Atypical (F-S) AVNRT	Junctional Tachycardia
Onset	A first	A or V first	A or V first	V first
Irregularity	A predicts V	V predicts A	V predicts A	V predicts A
His-refract. VPC	No effect	Adv. or delay A	No effect	No effect
Post-V overdrive	No VAC/VAAV	VAV	VAV	VAV
V entrainment	(NA)	SA − VA < 85 ms PPI − TCL < 115 ms	SA − VA > 85 ms PPI − TCL > 115 ms	SA − VA > 85 ms PPI − TCL > 115 ms
Post-A overdrive	AVAV	AVAV	AVAV	AVVA
Delta HA	(NA)	$HA_{SVT} > HA_{Pace}$	$HA_{SVT} < HA_{Pace}$	$HA_{SVT} = HA_{Pace}$
Delta AH	$AH_{SVT} \leq AH_{Pace}$ (10–20 ms)	$AH_{SVT} < AH_{Pace}$ (20–40 ms)	$AH_{SVT} < AH_{Pace}$ (>40 ms)	$AH_{SVT} > AH_{Pace}$
Termination	After V	After A or V	After A or V	After A

A, atrial; AH, atrio-His interval; AHpace, AH during atrial pacing at tachycardia cycle length; AHSVT, AH during SVT; AVAV, sequence of atrial and ventricular events after overdrive pacing; AVNRT, atrioventricular nodal reentrant tachycardia; AVVA, sequence of atrial and ventricular events after overdrive pacing; HA, His-atrial interval; HASVT, HA during SVT; HApace, HA during ventricular pacing at tachycardia cycle length; PPI, post-pacing interval; SA, stimulus-atrial interval; SVT, supraventricular tachycardia; TCL, tachycardia cycle length; V, ventricular; VA, ventriculo-atrial interval; VAV, sequence of atrial and ventricular events after overdrive pacing; VAAV, sequence of atrial and ventricular events after overdrive pacing; VPC, ventricular premature complex.

Table 8-1 is a comparison of features of different types of SVT that are in the differential diagnosis of this SVT. Based on the preponderance of data, orthodromic reentry was diagnosed.

Site of Ablation

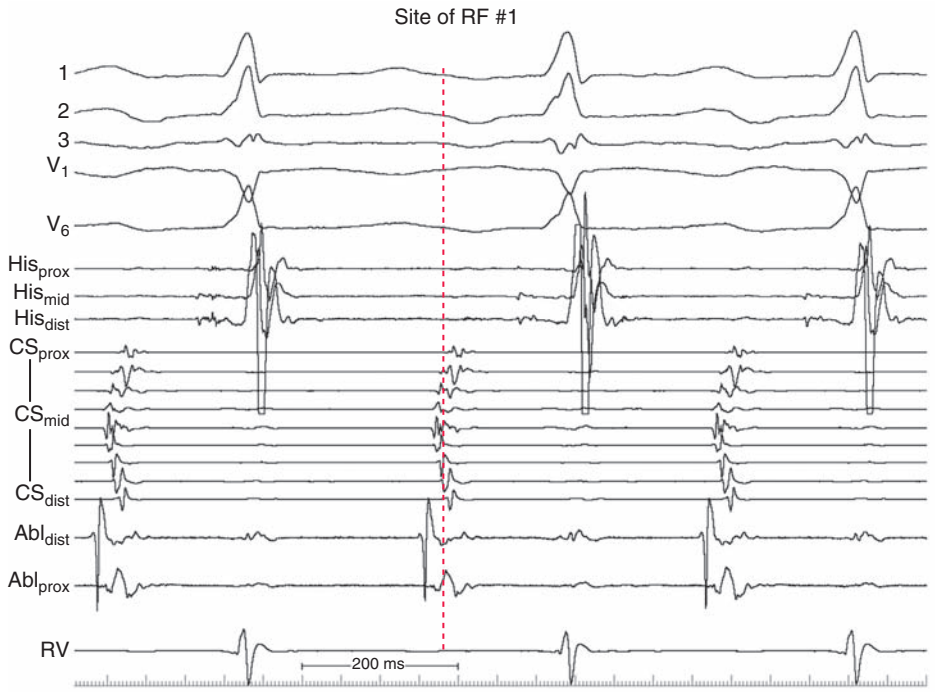


Figure 8-11

With a secure diagnosis, an ablation site may be sought; slowly conducting/decrementally conducting bypass tracts are usually located around the coronary sinus ostium, where more precise mapping began. In Fig. 8-11, a large, sharp potential on the ablation distal recording is seen followed by a more far-field potential. The atrial recording in the proximal electrode suggests that this far-field recording is atrial. The ventricular recording is small and similarly relatively far-field appearing. Because the large potential appears separate from the atrial potential, it is a good candidate for a bypass tract potential. Because of the constraints of cycle length variability, it was not feasible to perform pacing maneuvers to validate this as a true bypass tract potential.

During Ablation SVT Ceases

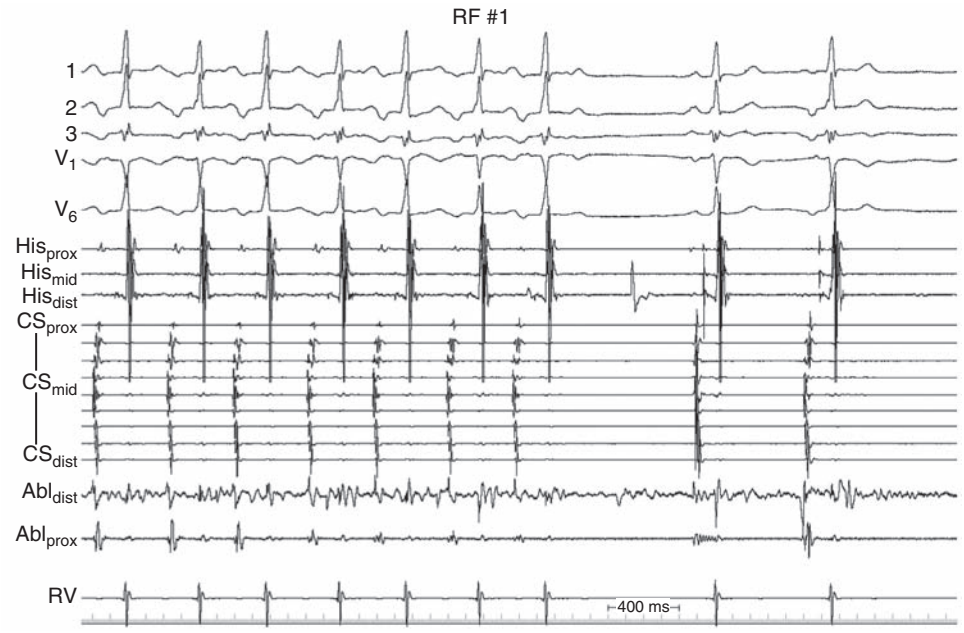


Figure 8-12

RF application at this site terminated SVT within 8 seconds of onset of power delivery (Fig. 8-12). Additional applications were made during sinus rhythm to consolidate the damage.

Ventricular Pacing Postablation

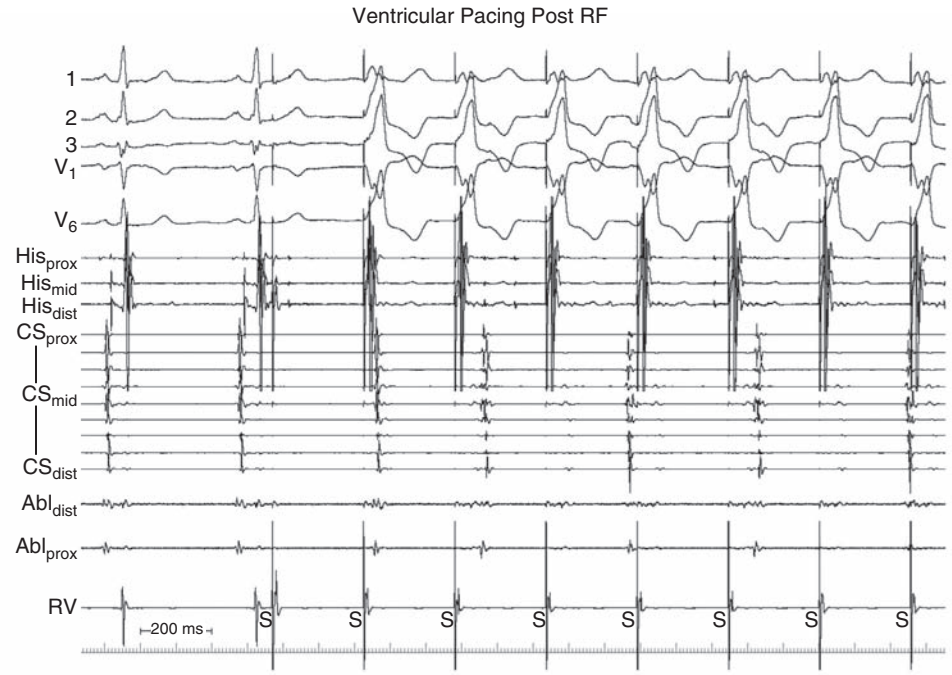


Figure 8-13

After ablation (Fig. 8-13), retrograde conduction was poor and concentric; in contrast to the preablation situation, SVT could not be initiated baseline or after isoproterenol infusion.

Final ECG

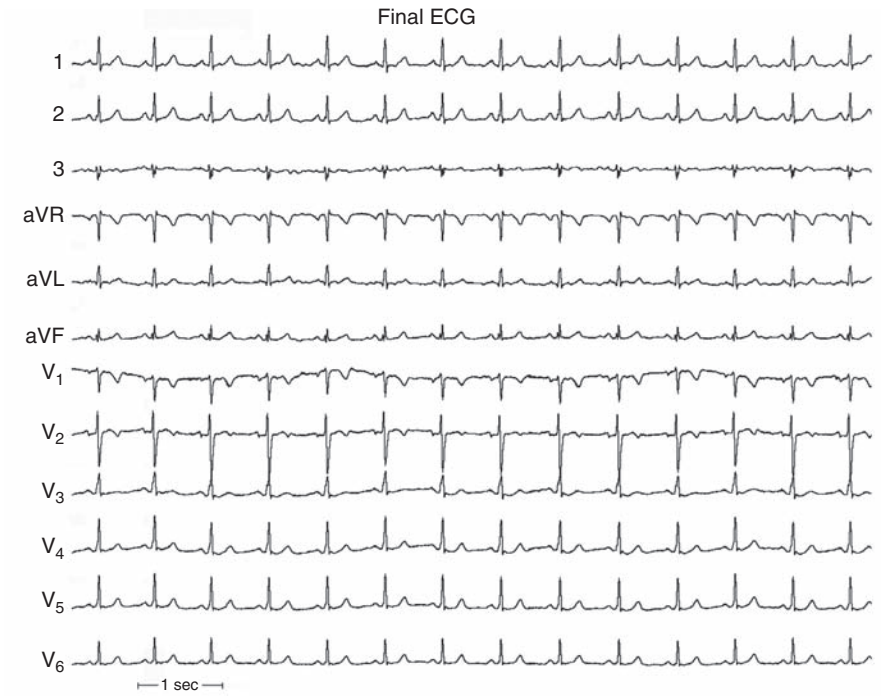


Figure 8-14

Sinus rhythm was present at the end of the procedure and SVT has not recurred (Fig. 8-14). Fetal monitoring throughout the procedure showed no adverse effects on the unborn child (a healthy baby girl, born 8 weeks later).

Electroanatomic Map

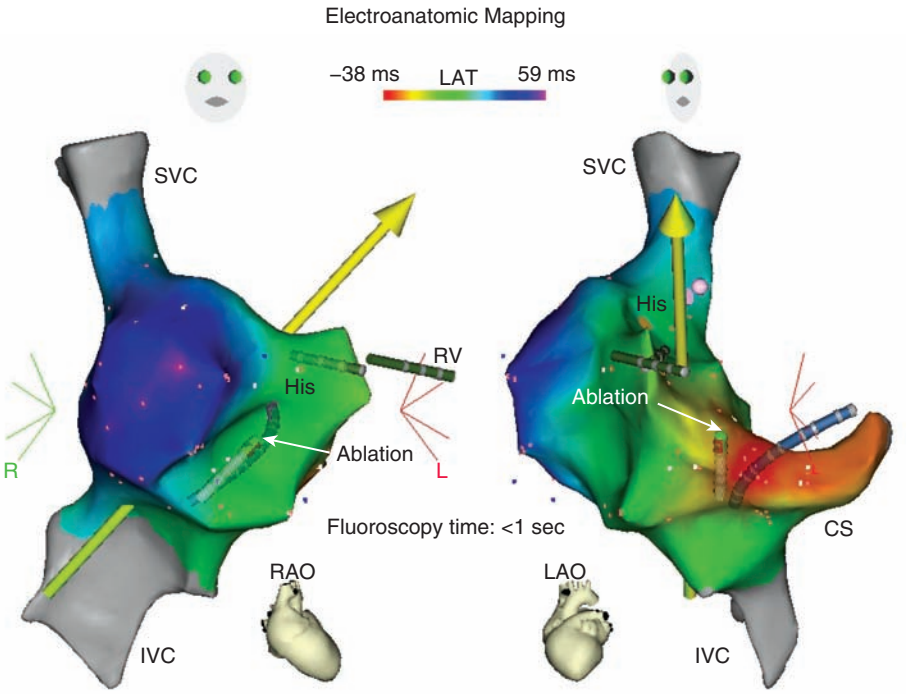


Figure 8-15

The *red area* on the image at the right of the previously shown activation map during SVT (Fig. 8-15) indicates the ablation site. Fluoroscopic exposure was <0.5 seconds (for registration of the patient and electroanatomic system at the beginning of the procedure; no fluoroscopy was used thereafter).

Summary

- A correct diagnosis can almost always be made if the correct tools are used and correct interpretations made
- Significant cycle length variability hampers diagnosis, but can make mapping easier (it is usually clear whether the electrogram of interest leads or follows other recordings)
- Current tools allow drastic limitation in fluoroscopic exposure, including <1 minute in some cases

Fasciculoventricular Pathway 9

Case Presentation

A 13-year-old girl presented with palpitations and lightheadedness for 2 years. She is an orphan, adopted shortly after birth. A muscular ventricular septal defect was detected in early childhood and repaired surgically. She did well until the current syndrome of palpitations developed; these increased in frequency and severity over the 2 years leading up to this evaluation. Physical exam was normal without residual murmur. Her resting ECG showed sinus rhythm with preexcitation. An event monitor was obtained, showing supraventricular tachycardia (SVT) at 250/min. At a prior electrophysiology (EP) study, atrial tachycardia at 250/min was induced, but not mapped or ablated; dual atrioventricular (AV) nodal pathways were observed; preexcitation was noted but not ablated due to proximity to the normal conduction system. Due to continued episodes of palpitations, she was referred for repeat EP study and possible ablation.

Baseline ECG and Intracardiac Recordings

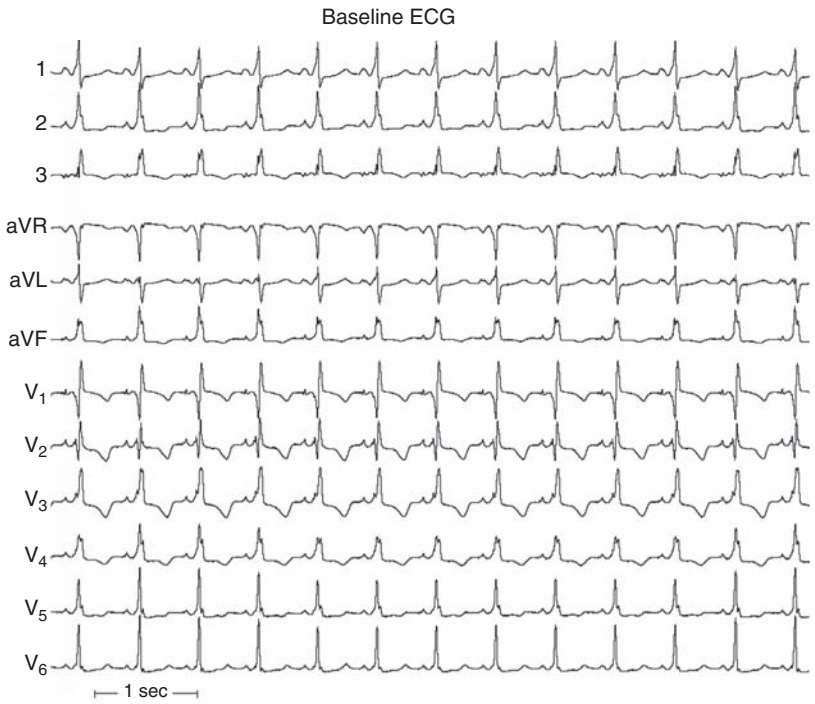


Figure 9-1

The baseline ECG in Fig. 9-1 shows a short PR interval and preexcitation with a pattern suggesting a midseptal pathway insertion. The terminal R′ in V1 and V2 hints that there may be right bundle branch block when preexcitation is absent.

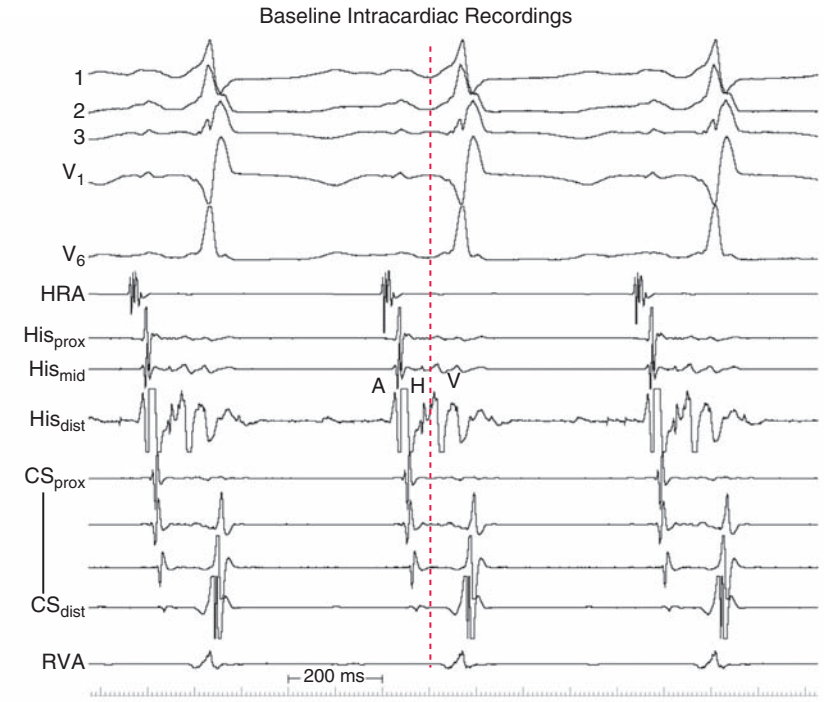


Figure 9-2

Baseline intracardiac recordings confirm preexcitation and show a His potential (H) just before the QRS onset *(dotted line)* with an HV interval 22 ms (Fig. 9-2).

Ventricular Pacing

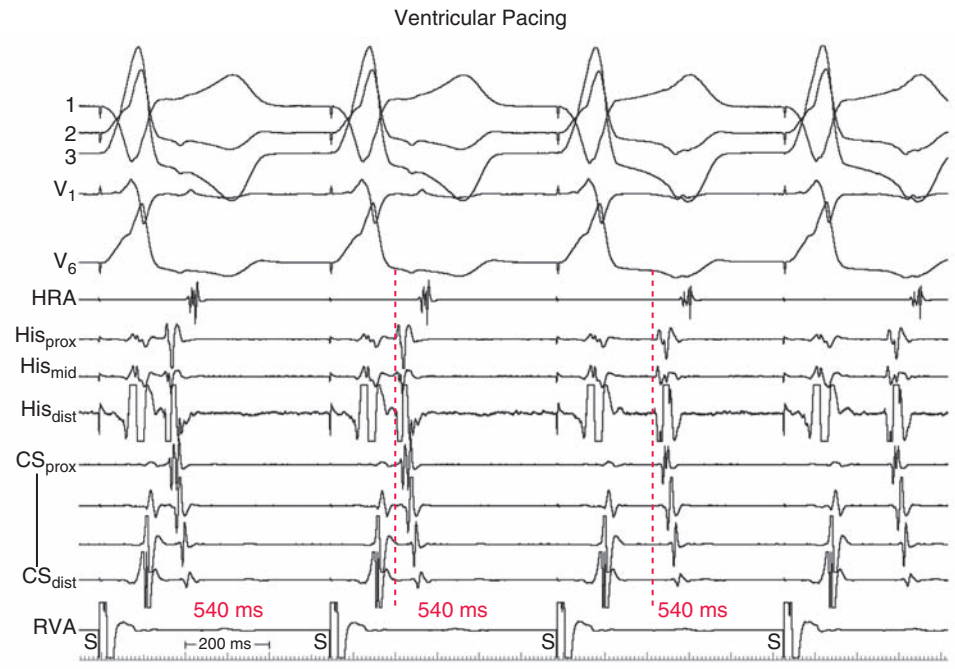


Figure 9-3

Decremental ventricular pacing (Fig. 9-3) shows a concentric activation sequence with a sudden increase in the ventriculo-atrial (VA) interval *(arrows)* without change in pacing rate. Wenckebach VA block occurred at paced cycle length 470 ms. After isoproterenol, VA

Wenckebach block occurred at cycle length 440 ms. Thus because VA conduction characteristics are those of the AV node, the bypass tract either has AV nodal-like properties (very rare) or does not appear to have retrograde conduction.

Atrial Pacing

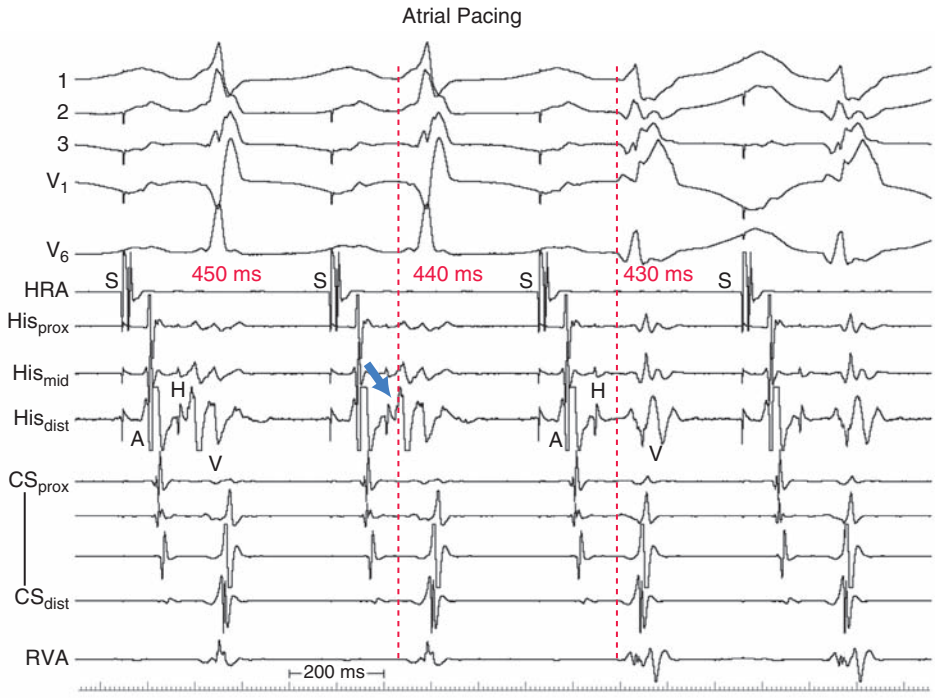


Figure 9-4

With progressively rapid atrial pacing (Fig. 9-4), sudden block in the bypass tract is observed (third and fourth complexes). Coincident with this, the HV interval prolongs from 22 to 50 ms. Of note, right bundle branch block is present in the nonpreexcited beads, as anticipated from the original surface ECG. With the loss of preexcitation, it is evident that early ventricular activation over the pathway had occurred near the His bundle *(arrow)*.

Atrial Extrastimuli

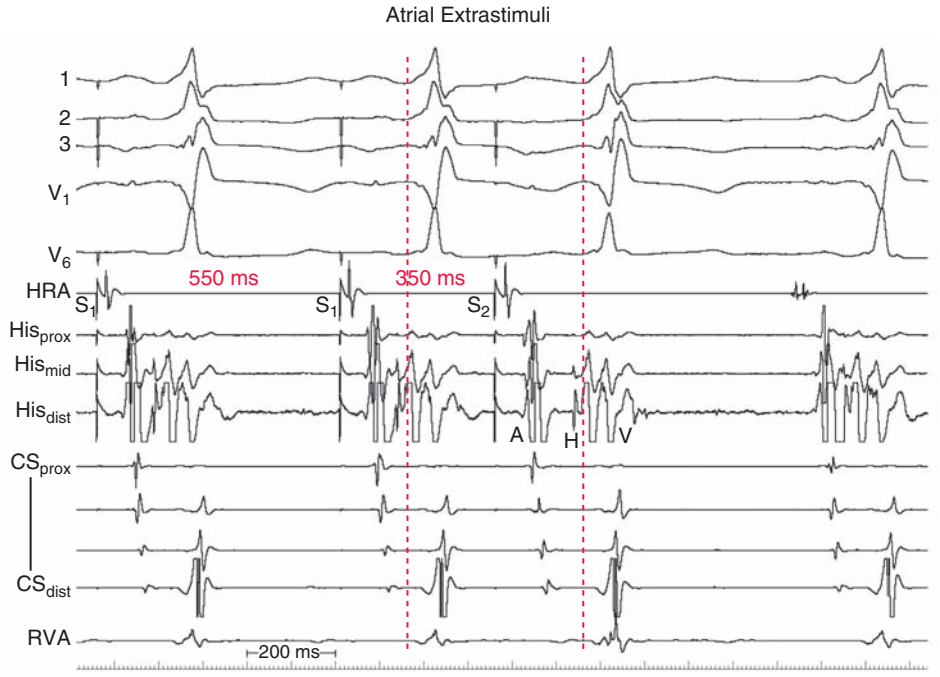


Figure 9-5

In response to atrial premature stimulation, preexcitation persists; the AH interval increases by an anticipated amount consistent with AV nodal behavior (Fig. 9-5). However, the HV interval and preexcitation pattern are unchanged from the drive complexes. *Dashed lines* indicate onset of QRS complexes.

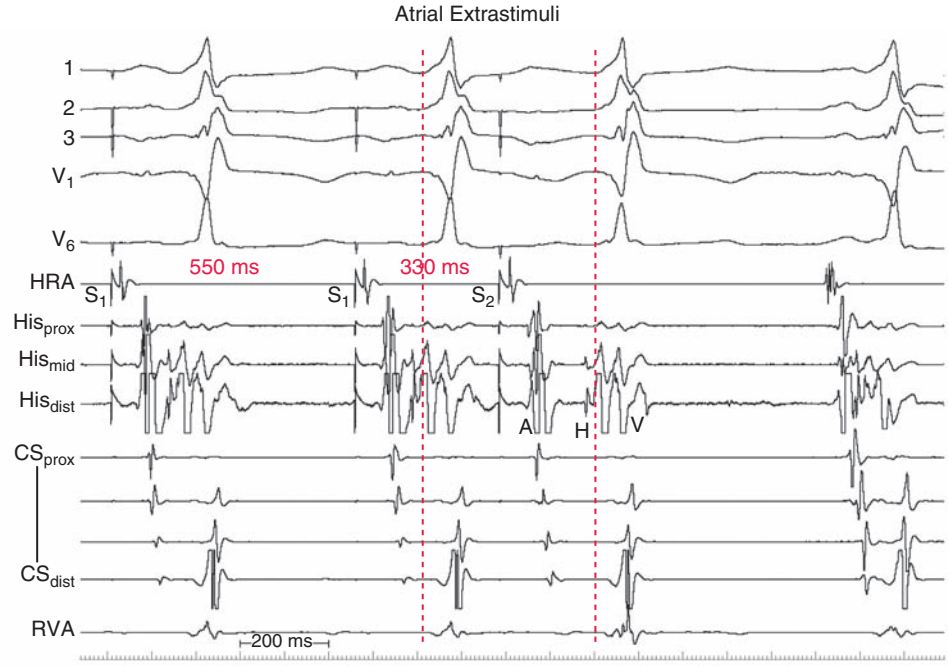


Figure 9-6

With more premature stimulation, preexcitation again persists; the AH interval also increases but the HV interval and preexcitation pattern are unchanged from the drive complexes (Fig. 9-6). This is not typical for the usual atrioventricular pathway, with which the stimulus-delta interval is largely fixed, such that prolongation of the AH interval results in a greater degree of preexcitation and shorter (or even negative) HV interval. Instead, in this case, the HV remains fixed and short, and preexcitation is constant regardless of the AH

interval. These are characteristics of a fasciculoventricular pathway. *Dashed lines* indicate onset of QRS complexes.

Atrial Pacing at Various Rates

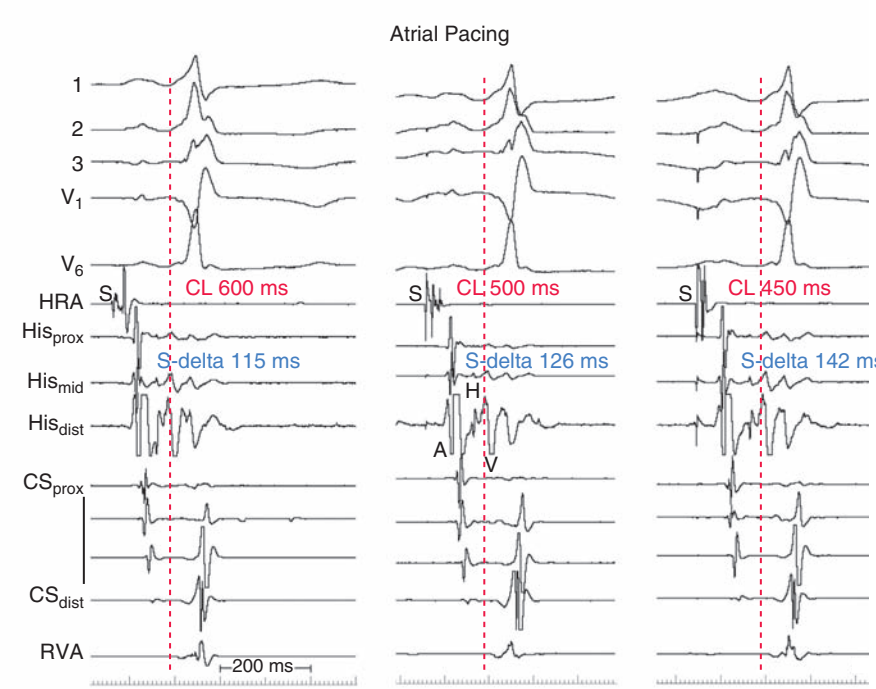


Figure 9-7

In Fig. 9-7 a single complex of atrial pacing at different cycle lengths is shown. It is evident that with progressive shortening of the atrial-paced cycle length, an increase in the S-delta interval occurs. This is because of increase in the AH interval, whereas the HV interval remains fixed at 22 ms and the degree of preexcitation remains unchanged. With standard atrioventricular bypass tracts, there is little if any change in the stimulus-delta interval with faster atrial pacing; because the AH interval lengthens under these conditions, but bypass tract conduction remains rather fixed, a greater proportion of ventricular activation is controlled by bypass tract conduction leading to greater degrees of preexcitation and shortening of the HV interval. The findings in this figure are again most consistent with a fasciculoventricular pathway—one that connects the His bundle with ventricular muscle. With these pathways, the amount of preexcitation does not vary regardless of rate of stimulation or prematurity, and unless there is block in the pathway, whenever the His is activated anterogradely, a preexcited complex ensues.

Junctional Escape Complex

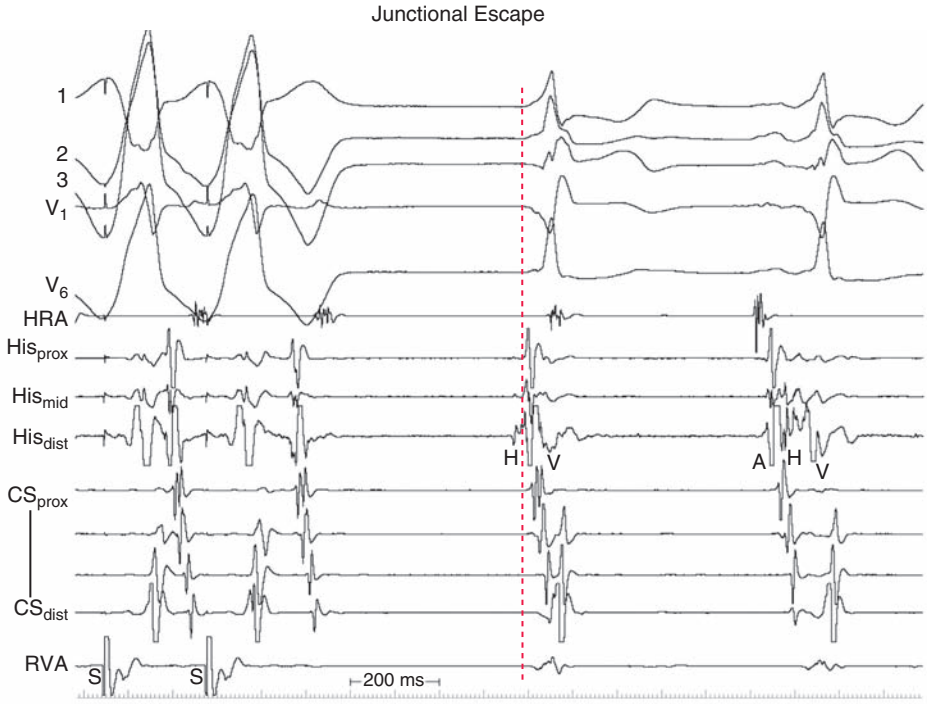


Figure 9-8

One of the strongest lines of evidence for the existence of a fasciculoventricular pathway is shown in Fig. 9-8, with a junctional (His bundle) escape complex after a burst of rapid ventricular pacing. (This technique, when retrograde conduction is present, can suppress the sinus node such that a junctional escape complex may occur.) The junctional escape complex has a pattern of preexcitation identical to that of complexes conducted from the atrium, indicating that the pathway connection is between His bundle and ventricle. With standard atrioventricular bypass tracts, a junctional escape complex will not be preexcited, because preexcited complexes in such cases result from conduction from the atrium to the ventricle over a pathway outside the normal conduction system.

Final ECG

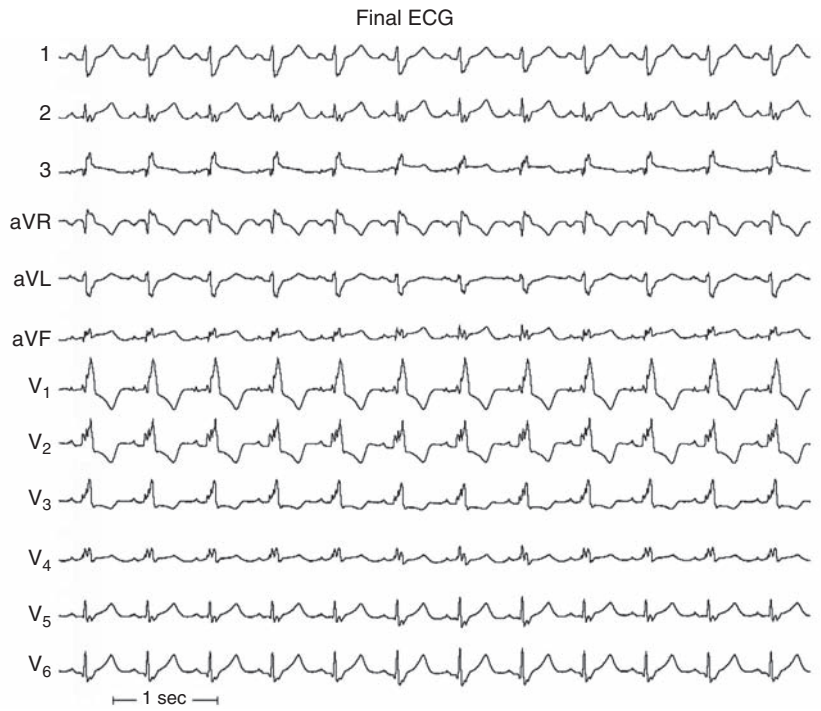


Figure 9-9

Catheter manipulation around the upper septum resulted in "bumping" of the pathway (Fig. 9-9), leading to loss of preexcitation. After the fasciculoventricular pathway was thus traumatized, the QRS complex showed RBBB as anticipated.

The cause of preexcitation in this case was thus a fasciculoventricular pathway; because these do not integrally participate in arrhythmias, this was not targeted for ablation. The patient had inducible typical right atrial cavotricuspid isthmus-dependent atrial flutter at 250 ms cycle length, consistent with the prior findings. Successful ablation was performed for this arrhythmia. At the end of the procedure, after catheter trauma, fasciculoventricular pathway conduction was absent. However, it returned the following day. The patient has done well in follow-up without recurrent arrhythmias.

Summary

- Fasciculoventricular pathways have unique properties:
  - A moderate degree of preexcitation is present
  - Preexcitation does not vary over a range of paced rates
  - The HV interval likewise remains constant
  - Junctional complexes are preexcited
  - These pathways are not integral participants in arrhythmias
- Catheter ablation of bypass tracts is not always necessary, for example:
  - Pathways that do not conduct rapidly enough under any conditions to result in patient risk
  - Pathways with intermittent conduction
  - Pathways that do not participate in arrhythmias (ie, fasciculoventricular pathways)
- This patient had another cause of palpitations unrelated to the bypass tract and consistent with prior data; simple ablation of the bypass tract in this case not only would not have yielded a successful outcome, but could also have risked damage to the normal conduction system

10 Focal Right Atrial Tachycardia

Case Presentation

An 18-year-old woman who was 36 weeks pregnant with her first child presented with dyspnea; she was found to have heart failure (HF), with heart rate 130–170/min, which was believed to be compensatory sinus tachycardia. Echocardiogram showed left ventricular dilation (5.2 cm in diastole), fractional shortening of 0.13, ejection fraction 30%, mild mitral regurgitation, and 4-chamber dilation (or upper-normal size for stage of pregnancy). She was started on standard HF medications (no ACE inhibitor because of pregnancy).

ECG of Tachycardia

What Is the Differential Diagnosis? [Fig. 10-1]

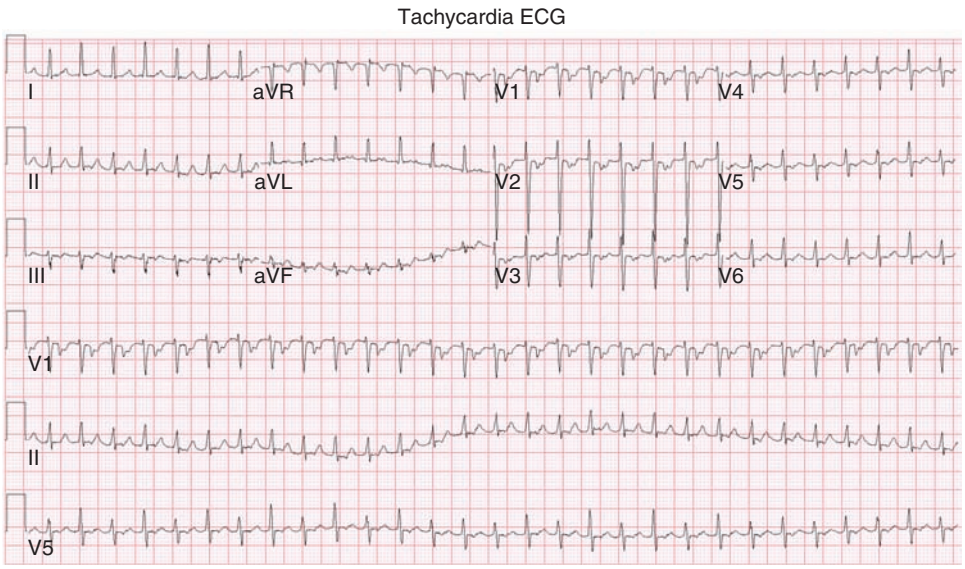


Figure 10-1

The baseline ECG in Fig. 10-1 shows regular supraventricular tachycardia (SVT) about 145/min. The P waves (best seen in lead V1) are very unusual and the PR interval is slightly long for this heart rate, if it were sinus tachycardia. The differential diagnosis includes atrial tachycardia or accessory pathway tachycardia using a right-sided bypass tract for retrograde conduction (from the P-wave vector in the inferior leads and V1). She was given an injection of adenosine that yielded transient 2:1 atrioventricular (AV) block, with continuation of the rapid atrial rhythm. Her child was delivered (cesarean section); tachycardia continued thereafter. She underwent direct-current cardioversion, but reverted to SVT nearly immediately. She was then scheduled for electrophysiology (EP) study and ablation. The response to adenosine excludes orthodromic SVT, in which a 1:1 AV relationship must be maintained, and because the P-wave vector is not consistent with exit from the AV nodal region, AV nodal reentry is excluded; thus, an atrial tachycardia is present.

Subsequent ECG

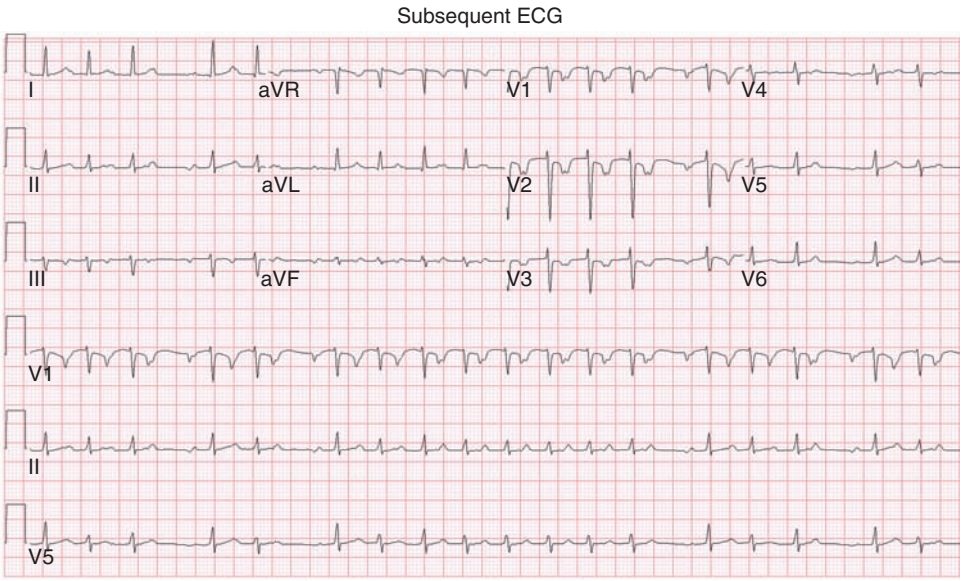


Figure 10-2

An ECG taken after administration of a beta blocker (Fig. 10-2) shows a slightly slower atrial rate along with periods of AV Wenckebach block. This again is indicative of atrial tachycardia and affords a better look at the P-wave morphology (positive in leads 1 and aVL, initially negative in inferior leads and V1–3).

Baseline ECGs and Intracardiac Recordings in SVT

Tachycardia ECGs [Fig. 10-3]

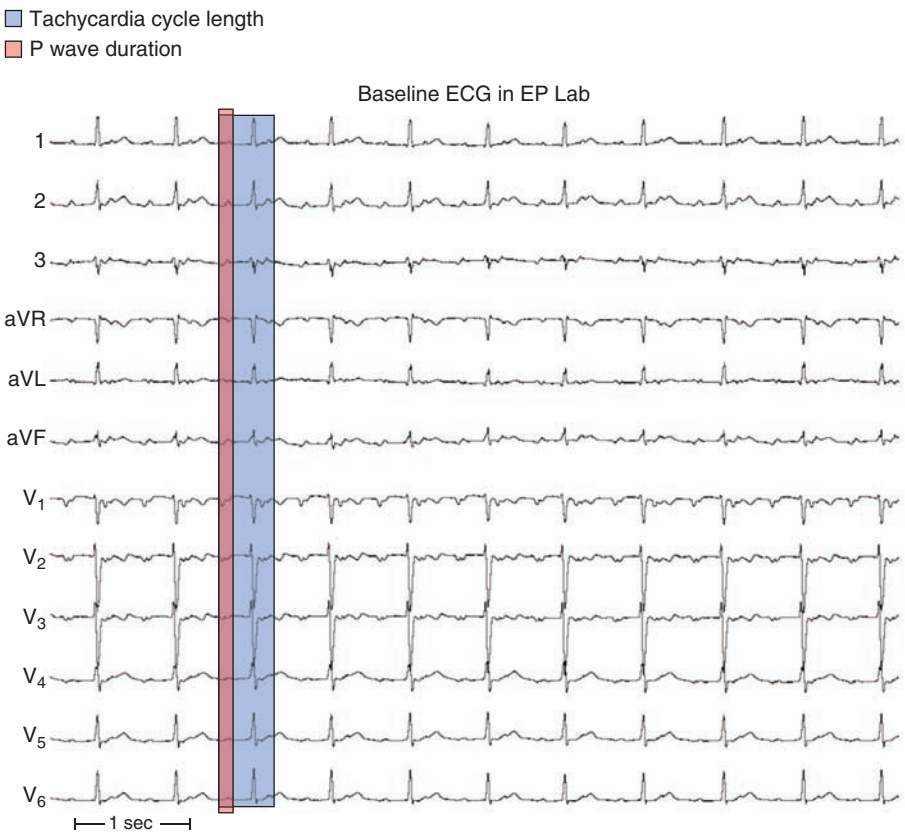


Figure 10-3

The patient was brought to the electrophysiology laboratory for catheter ablation of an atrial tachycardia. The question now is what type of atrial tachycardia: focal or macroreentrant? In most young people with a structurally normal heart, a focal process is present. Macroreentry generally requires some degree of scarring, which is not present in a structurally normal heart. However, because she has HF with early chamber dilatation, perhaps she has scarring in the atrium leading to macroreentry (it is also possible that the arrhythmia has caused a tachycardia-related cardiomyopathy). Because the ablation target is determined by the tachycardia mechanism, it is important to separate focal from macroreentrant causes. In Fig. 10-3, the P-wave duration is shown in *red* and the tachycardia cycle length in *blue* (2:1 AV conduction is present). Generally, the smaller the proportion of the tachycardia cycle length that is occupied by the P wave, the more likely that a focal process is present. In the example here, a focal process seems more likely.

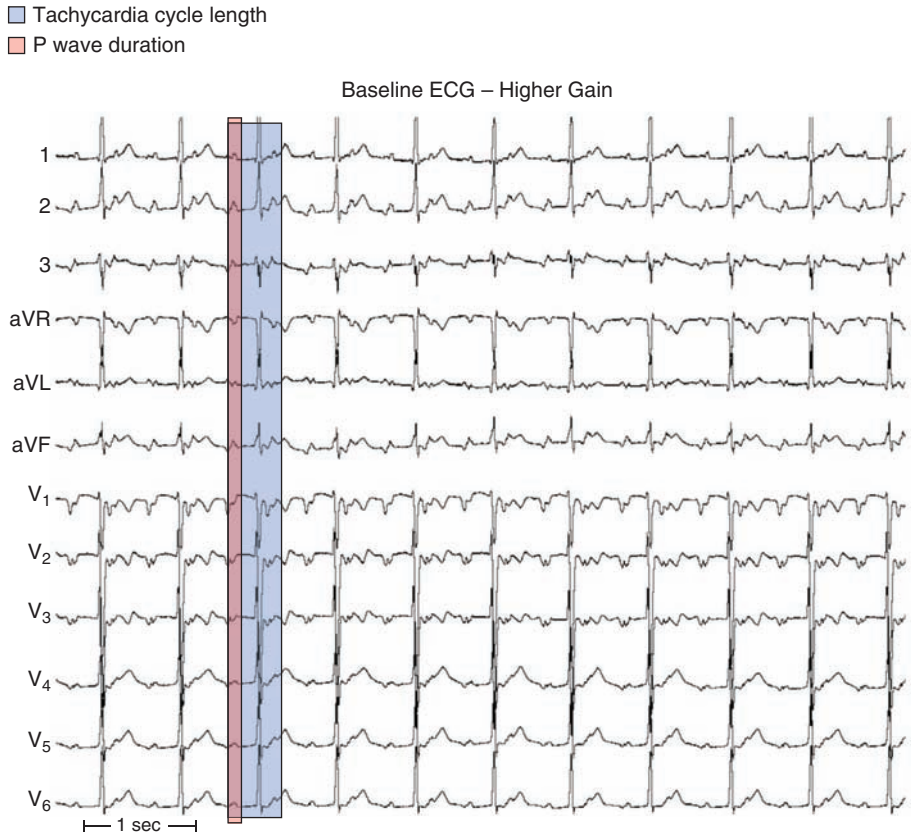


Figure 10-4

Sometimes it is helpful to increase the gain on recordings to be able to see more of the duration of the P wave (Fig. 10-4). In this case the conclusion is the same as before.

Intracardiac Recordings [Fig. 10-5]

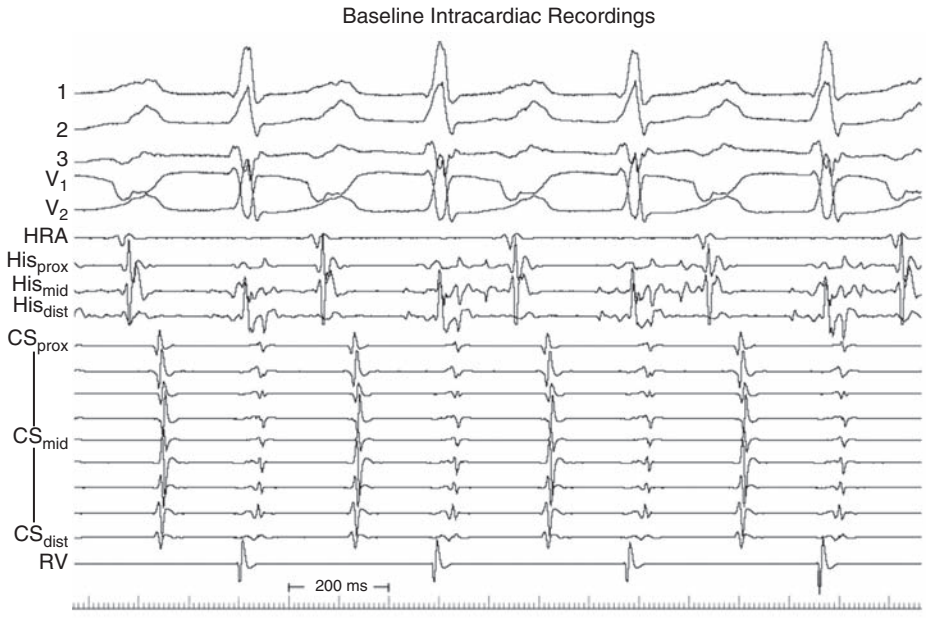


Figure 10-5

Intracardiac recordings during tachycardia are shown in Fig. 10-5. Of the recordings shown, earliest activation appears to occur in the high right atrium (HRA).

TABLE 10-1 Atrial Tachycardias

	Focal			
	Automaticity	**Triggered Activity**	**Microreentry**	**Macroreentry**
Onset	Spontaneous	Induced (burst > PES)	Induced (PES >> burst)	Induced (PES >> burst)
Occurrence	Incessant; bursts	Variable	Sporadic, sustained	Sporadic, sustained
P wave vs TCL	Small fraction	Small fraction	Small fraction	Large portion
Atrial activation	Small fraction	Small fraction	Small fraction	Large portion
Isoproterenol	Facilitates onset; acceleration	Facilitates onset; acceleration	Minimal effect	Minimal effect
Adenosine	Variable effect	Termination	Minimal effect	No affect/ acceleration
Response to single premature extrastimuli	Reset or fusion; flat/ increasing	Reset or fusion; decreasing	Reset or fusion; flat/ increasing	Reset + fusion; flat/ increasing
Overdrive pacing response	Suppression; ↑RC with ↓PCL	Acceleration; ↓RC with ↓PCL	Entrainment; No Δ RC w/↓PCL	Entrainment; No Δ RC w/↓PCL
Ablation target	Late diastolic; unipolar QS	Late diastolic; unipolar QS	Prolonged diastolic	Middiastolic
Response to RF	Accelerate/stop	Accelerate/stop	Slow/stop	Slow/stop

PES, programmed electrical stimulation; TCL, tachycardia cycle length; RC, return cycle of tachycardia; PCL, paced cycle length; QS, completely negative wave in unipolar recording.

Table 10-1 shows differences between three categories of tachycardias with apparent focal propagation from what seems to be a point source (automatic, triggered because of delayed after depolarizations, and microreentry) vs macroreentry.

Overdrive Coronary Sinus Pacing in SVT

Midcoronary Sinus Pacing [Fig. 10-6]

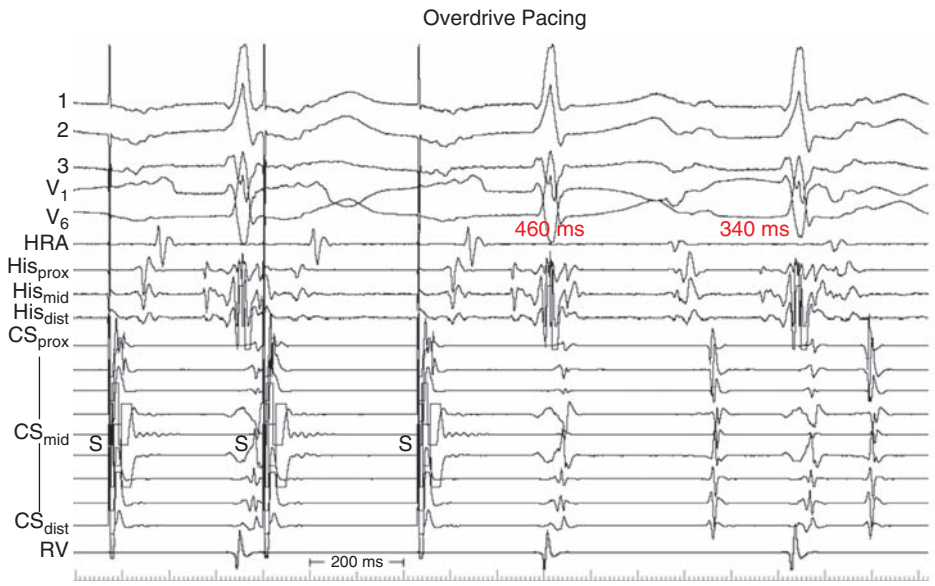


Figure 10-6

The result of overdrive spacing from the midcoronary sinus is shown here, after which the tachycardia resumes. This information, by itself, is not very helpful because both focal tachycardias and macroreentry will have this response. However, the fact that the interval from the last paced complex to the first beat of tachycardia (460 ms) is substantially longer than tachycardia cycle length (340 ms) would be very unusual for macroreentry, in which

the interval consists of propagation time from the pacing site to the circuit, around the circuit once, and back to the pacing site (Fig. 10-6). In most cases of macroreentry, this should ordinarily not be >100 ms or so longer than tachycardia cycle length.

Proximal Coronary Sinus Pacing [Fig. 10-7]

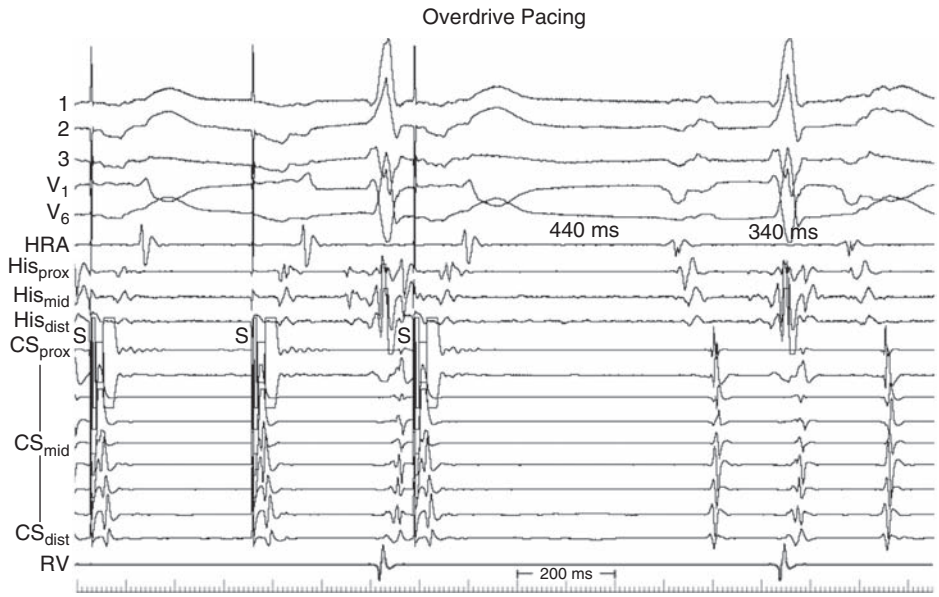


Figure 10-7

Pacing from the proximal coronary sinus yields a slightly shorter interval until the tachycardia resumes, suggesting that this spacing site is slightly closer to the exit from what now appears to be a focus (Fig. 10-7). Ideally, overdrive pacing from several sites could be used looking for fusion (indicating macroreentry), or its absence (suggesting a focal process); however, because the tachycardia is incessant, knowing what pure pacing looks like for comparison to pacing during tachycardia is not possible, making this technique less helpful at this time. Pacing from right atrium and distal coronary sinus yielded similar results. All the evidence taken together suggests a focal process.

Activation Mapping

Various Sites

Activation Mapping [Fig. 10-8]

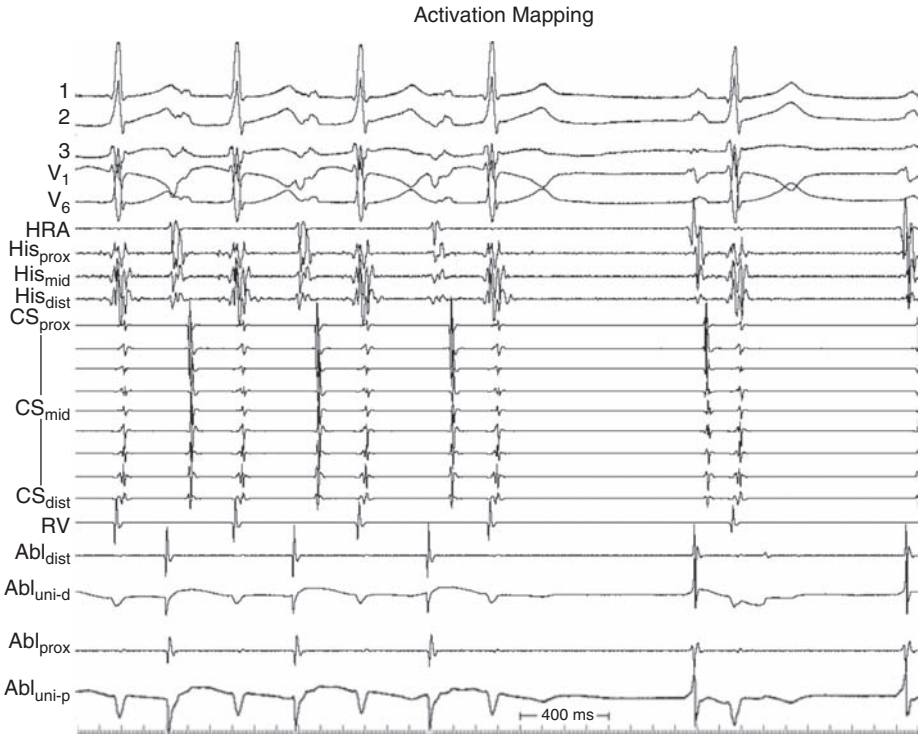


Figure 10-8

Now that a focal process has been identified as the likely cause of the tachycardia, activation mapping can begin. During the process of mapping, the tachycardia suddenly terminated when moving the catheter along the lateral tricuspid annulus (Fig. 10-8). This so-called "bump-mapping" has important implications: it signifies that (1) a critical site for continuation of the tachycardia has been "bumped" by the catheter (thus, where the catheter was at the time of this encounter is important); (2) the amount of tissue necessary for continuation of the tachycardia is quite small, because the effect of trauma with the catheter tip is spatially quite limited; and, finally, (3) the source is on the endocardial surface, because mechanical effects of the catheter on the endocardium would not be expected to affect deep myocardial or epicardial sources. Of note, this phenomenon does not distinguish between a focal process and macroreentry because tachycardias of either type may be terminated by catheter contact.

Activation Mapping [Fig. 10-9]

Figure 10-9

Fortunately, tachycardia resumes in Fig. 10-9, and gradually "warms up" (gradual rate increase after the onset). This is most consistent with a focal, automatic process.

Activation Mapping [Fig. 10-10]

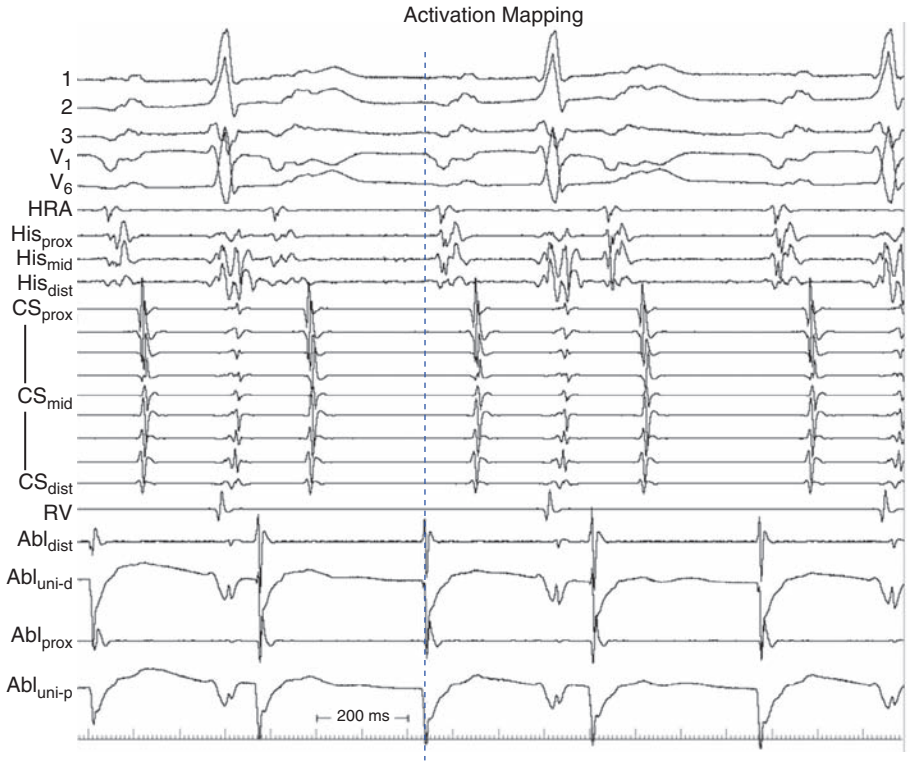


Figure 10-10

A site on the lateral tricuspid annulus is sampled during mapping (Fig. 10-10). The P-wave onset is designated by a *dashed line*; the ablation/mapping electrograms occur slightly (about 5 ms) before the P-wave onset; the distal bipolar electrode and unipolar signal have similar timing, and the unipolar has a "QS" configuration. Although the electrogram parameters are encouraging, the timing is not; ordinarily, propagation from a focus takes 20–40 ms before the onset of the P wave occurs, and so additional mapping is necessary.

Activation Mapping [Fig. 10-11]

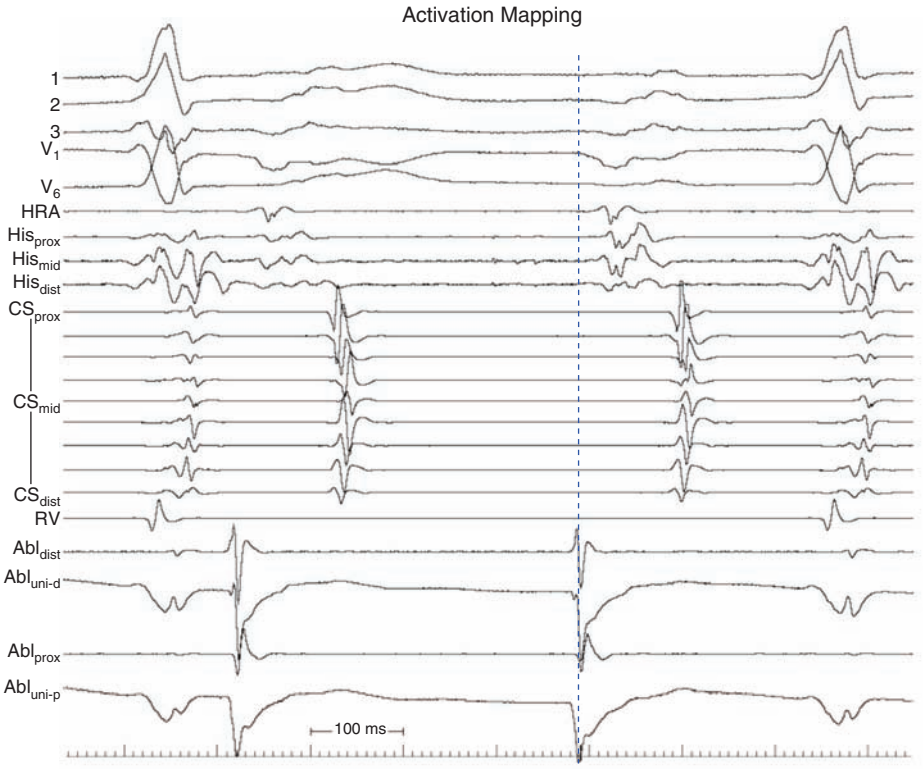


Figure 10-11

At a faster sweep speed (Fig. 10-11), it is clear that this site is not very early before the P-wave onset.

Electroanatomic Map

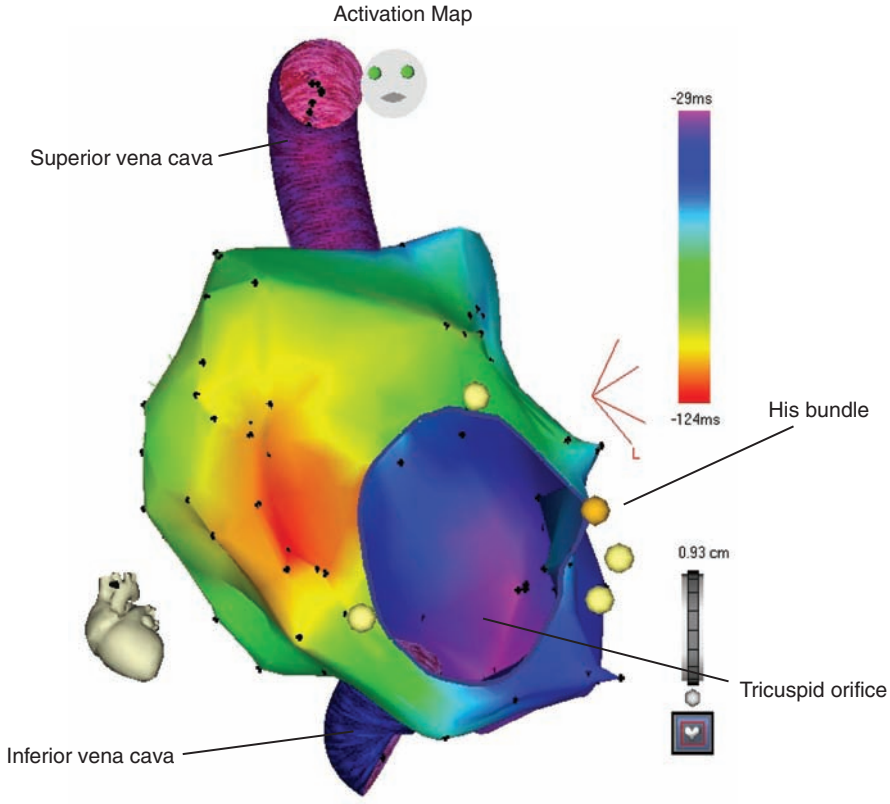


Figure 10-12

An electroanatomic map of right atrial activation during the tachycardia is shown in Fig. 10-12, indicating focal propagation from a site on the lateral tricuspid annulus (red area, surrounded by orange, yellow, etc.).

Additional Sites Sampled and Pace Mapping

Activation Mapping [Fig. 10-13]

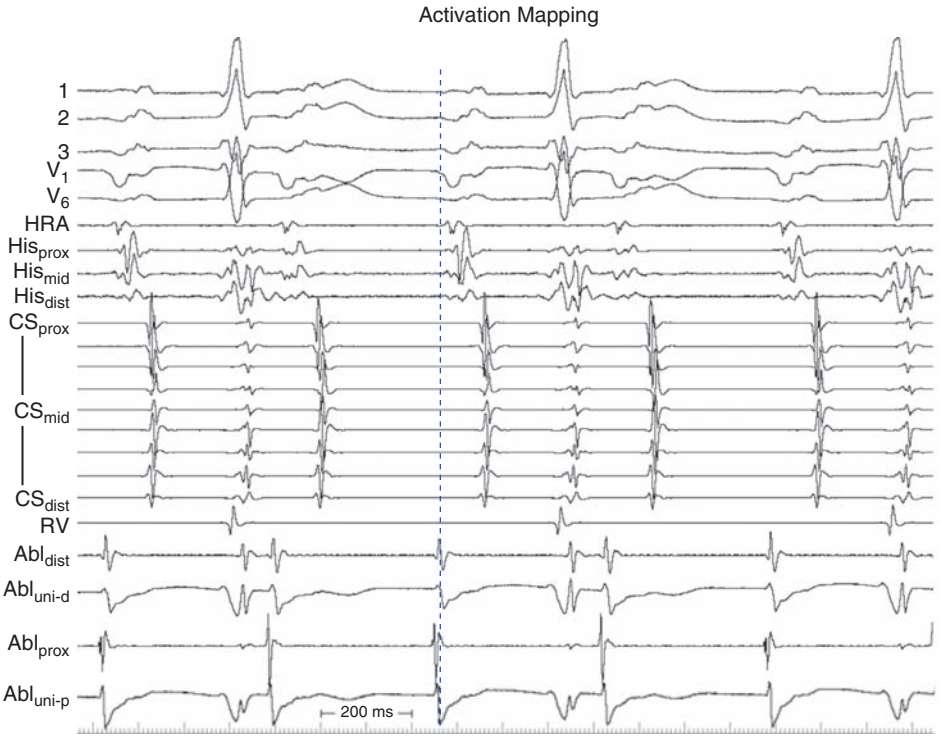


Figure 10-13

Additional mapping is performed; at this site (Fig. 10-13), the proximal bipolar electrogram has a timing before the distal, and is thus not a good site for ablation.

Pace Mapping [Fig. 10-14]

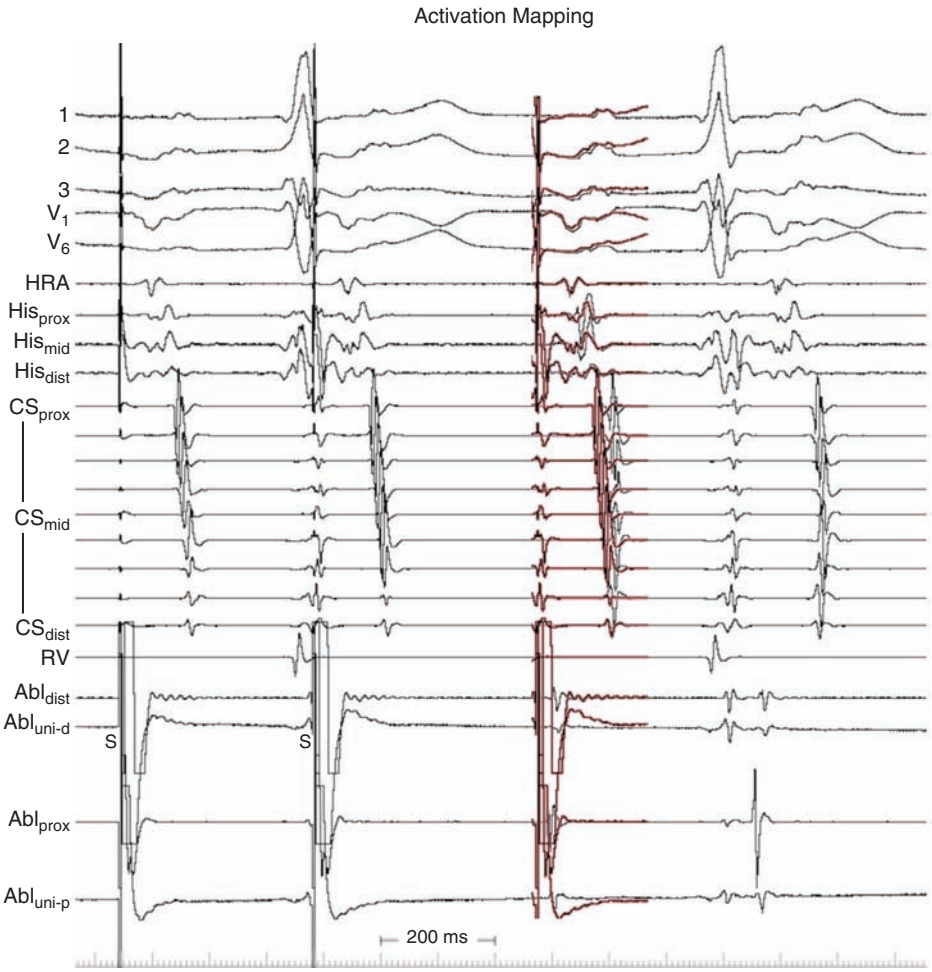


Figure 10-14

Pacing at this site (Fig. 10-14) yields a poor match with tachycardia (paced activation sequence in *red* superimposed on first tachycardia cycle after pacing). When the pacing electrode is at the actual site of impulse formation in a focal tachycardia, pacing should exactly match the activation sequence of the tachycardia.

Activation Mapping [Fig. 10-15]

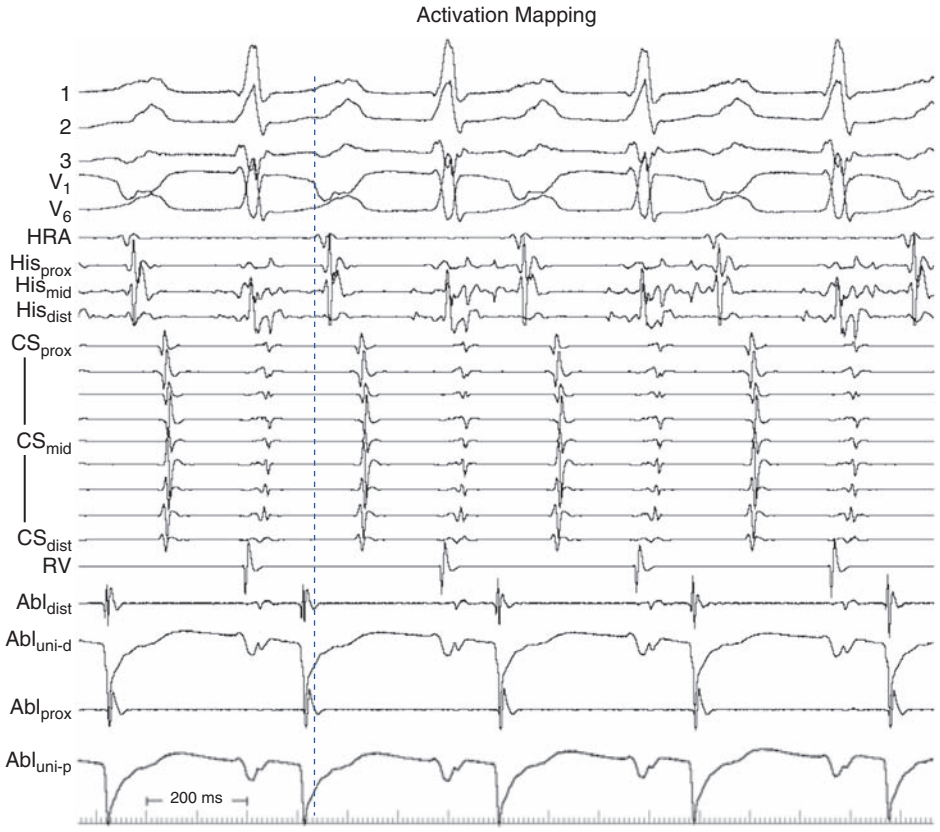
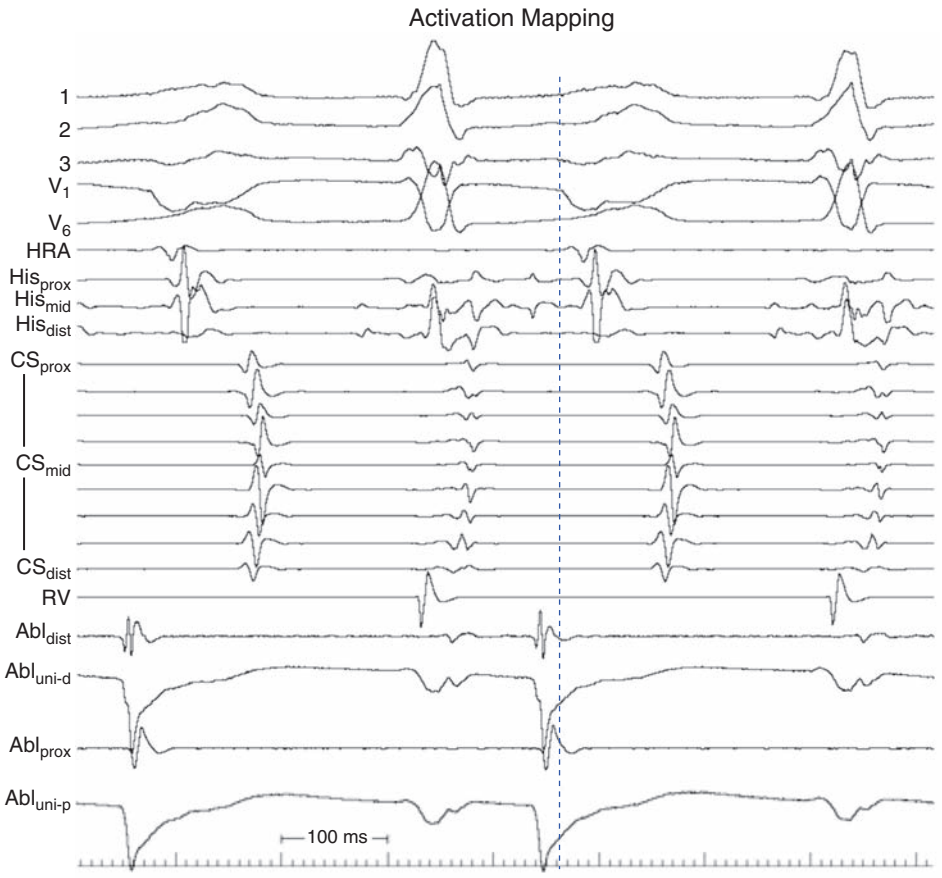


Figure 10-15

Another site is sampled; in Fig. 10-15, local activation in both the bipolar and the unipolar recordings substantially precedes P-wave onset (*dashed line*, inferred from its timing relationship to the HRA recording, because tachycardia now has a 1:1 AV relationship and the onset of the P wave is not as clear). The site is now 40 ms before P-wave onset, with unipolar–bipolar "agreement" and a "QS" unipolar configuration.



Activation Mapping [Fig. 10-16]

Figure 10-16

In Fig. 10-16, the same site is shown at a faster sweep speed, showing the site is 40 ms before P-wave onset.

Pace Mapping [Fig. 10-17]

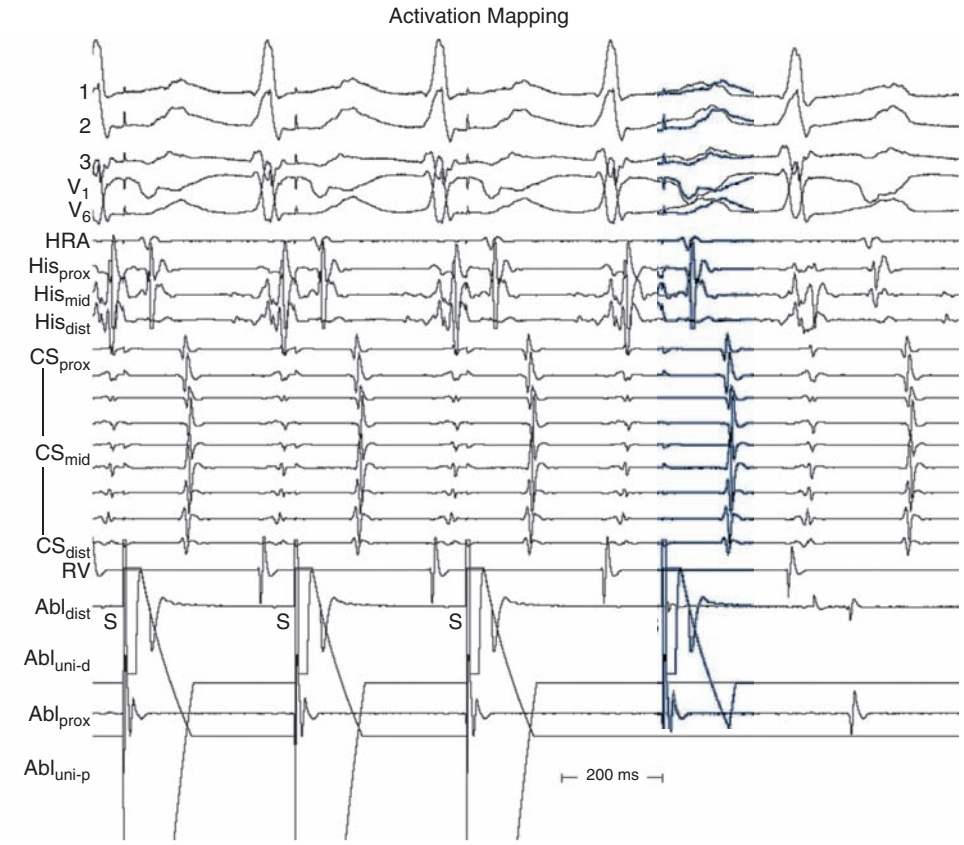


Figure 10-17

Pacing at this site (Fig. 10-17) yields a perfect match with tachycardia (paced complex in blue superimposed on first tachycardia complex after pacing). This corroborates the early local activation time recorded at this site.

Ablation

Figure 10-18

Radiofrequency energy application at this site (Fig. 10-18, starting at the *blue arrow*) results in a rapid acceleration of tachycardia followed by abrupt termination to sinus rhythm.

ECG Postablation

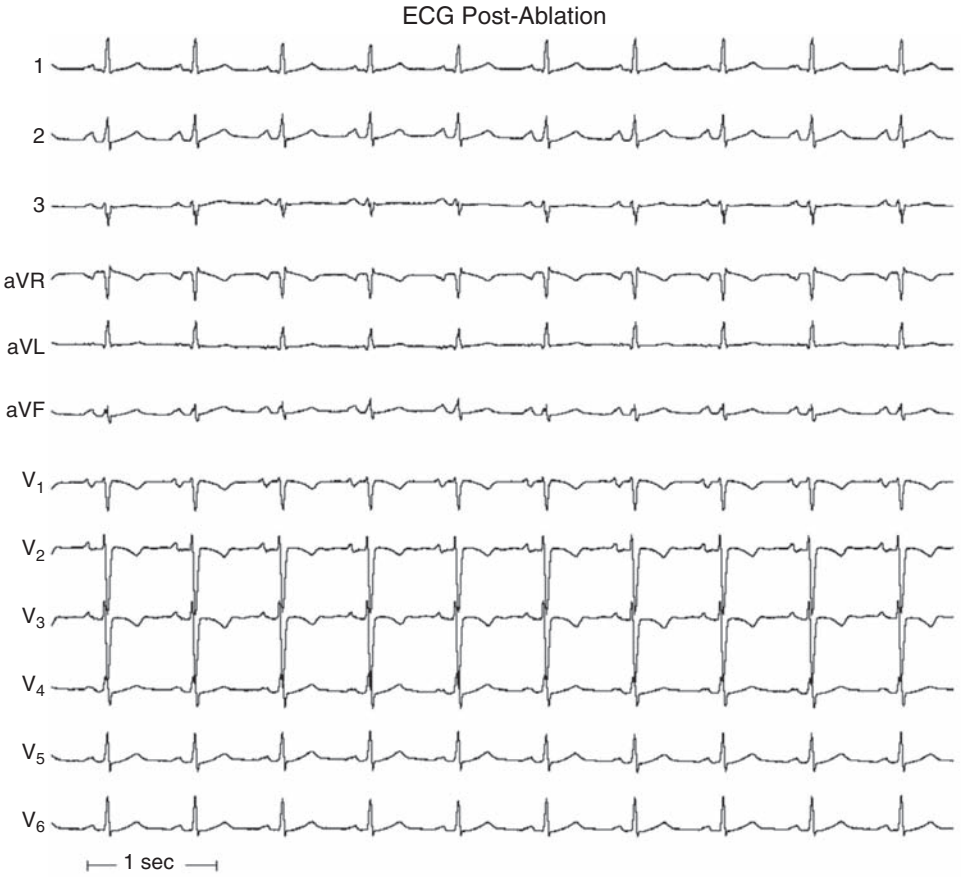


Figure 10-19

Sinus rhythm persisted through the waiting period. The P wave shown in Fig. 10-19 is not particularly abnormal despite the prolonged high rate and mild HF.

Atrial Activation Sequence with Various Sites of Coronary Sinus Pacing vs SVT

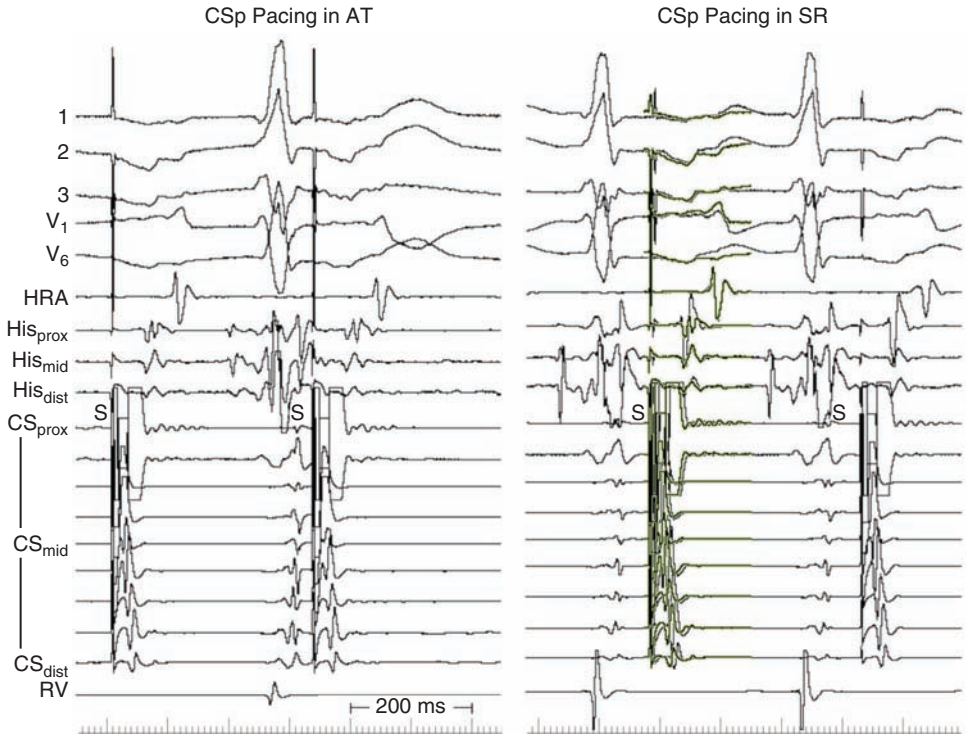


Figure 10-20

After restoration of sinus rhythm, pacing from different sites can be performed to determine what "pure" pacing from these sites looks like, compared with pacing during tachycardia. If there is a difference between these, fusion is present and macroreentry can be diagnosed. If pacing during tachycardia and pure pacing have identical activation sequences, a focal process is more likely. In Fig. 10-20, pacing from the proximal CS (CSp) during SVT at left is compared with pure pacing during sinus rhythm at right. A complex of pacing during SVT *(green)* is superimposed on a pure paced complex; these are identical.

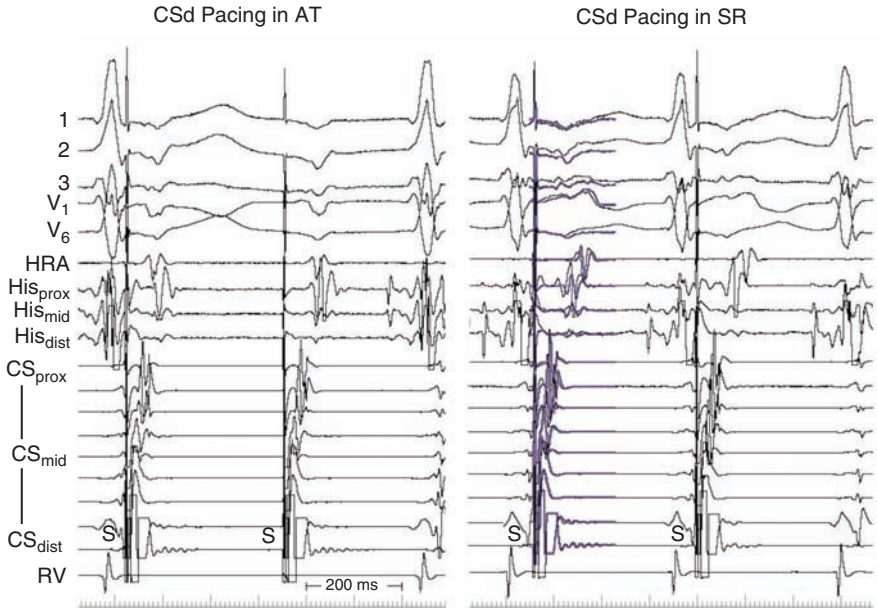


Figure 10-21

Similarly, pacing from the distal CS electrodes is compared when performed during tachycardia vs sinus rhythm. Again, in Fig. 10-21, pacing during tachycardia *(purple)* is superimposed on pure pacing, showing no difference.

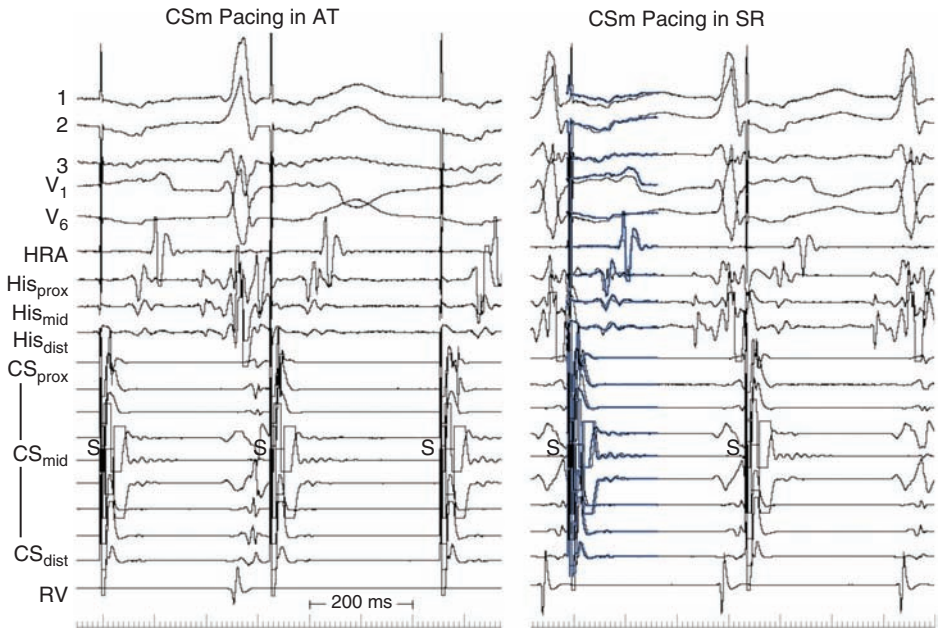


Figure 10-22

Pacing from the middle CS electrodes (Fig. 10-22) again shows no difference in atrial activation whether during tachycardia or sinus rhythm. Again, pacing during tachycardia *(blue)* is superimposed on pure pacing, showing no difference. Had this lack of evidence of fusion despite pacing at several sites been available earlier in the study, it would have helped exclude macroreentry.

Ventricular Pacing During Sinus Rhythm

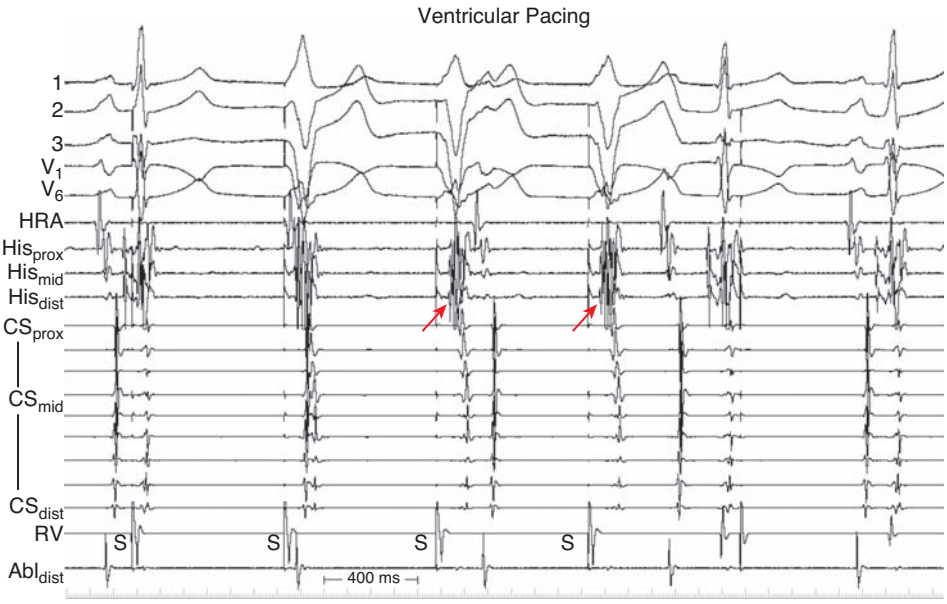
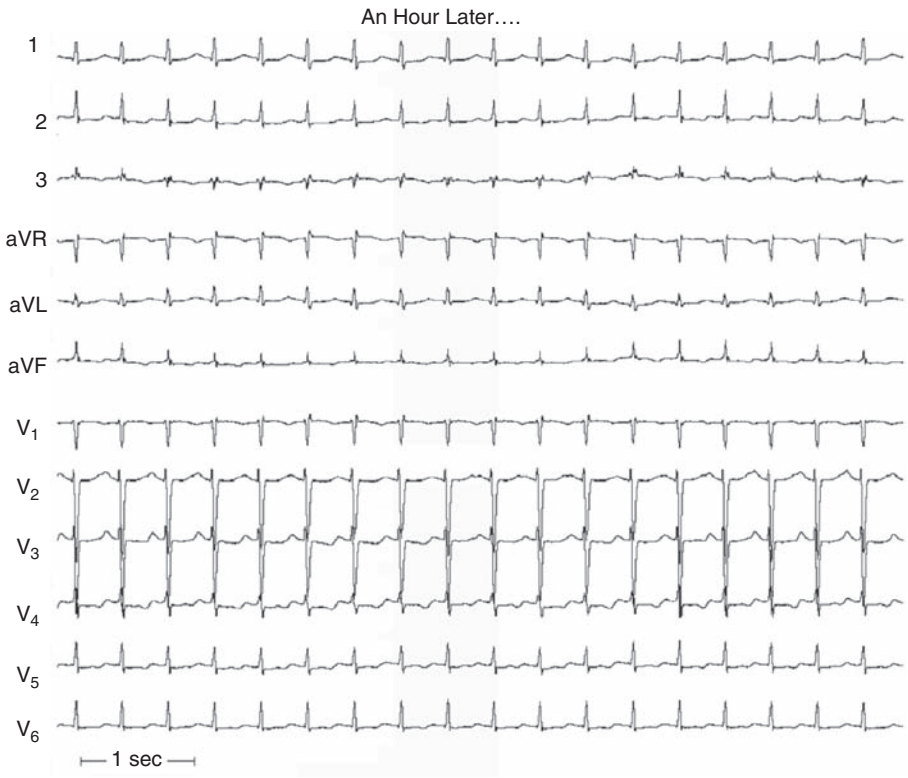


Figure 10-23

In Fig. 10-23, ventricular pacing immediately after ablation shows no retrograde conduction, with block in the AV node (retrograde His seen on third and fourth complexes [*arrow*]).

Tachycardia 1 h After Ablation



Tachycardia [Fig. 10-24]

Figure 10-24

Isoproterenol was administered during the waiting period to try to reinitiate atrial tachycardia, which did not occur; however, this arrhythmia was noted in Fig. 10-24.

Atrial Pacing Induces SVT

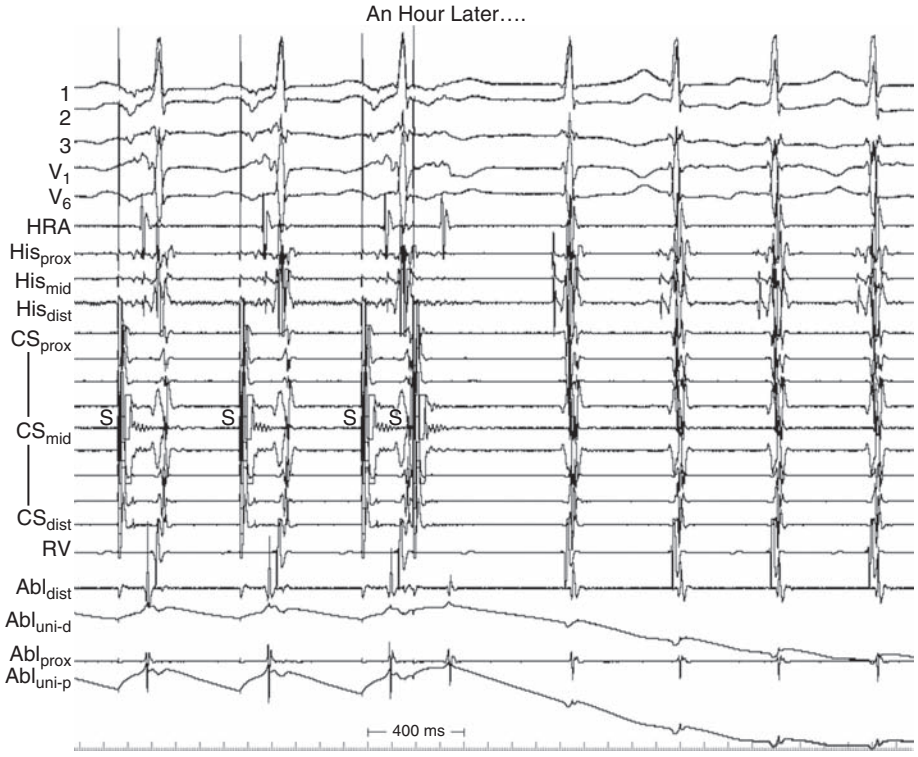


Figure 10-25

Atrial extrastimulus testing, to try to reinitiate atrial tachycardia, instead elicited the arrhythmia seen in Fig. 10-25. The atrial activation is concentric now and is coincident with ventricular activation, and SVT started after a long AH interval. All of these features are consistent with AV nodal reentry as a second tachycardia diagnosis.

Ventricular Extrastimuli and Overdrive Pacing in SVT (Figs. 10.26 and 10.27)

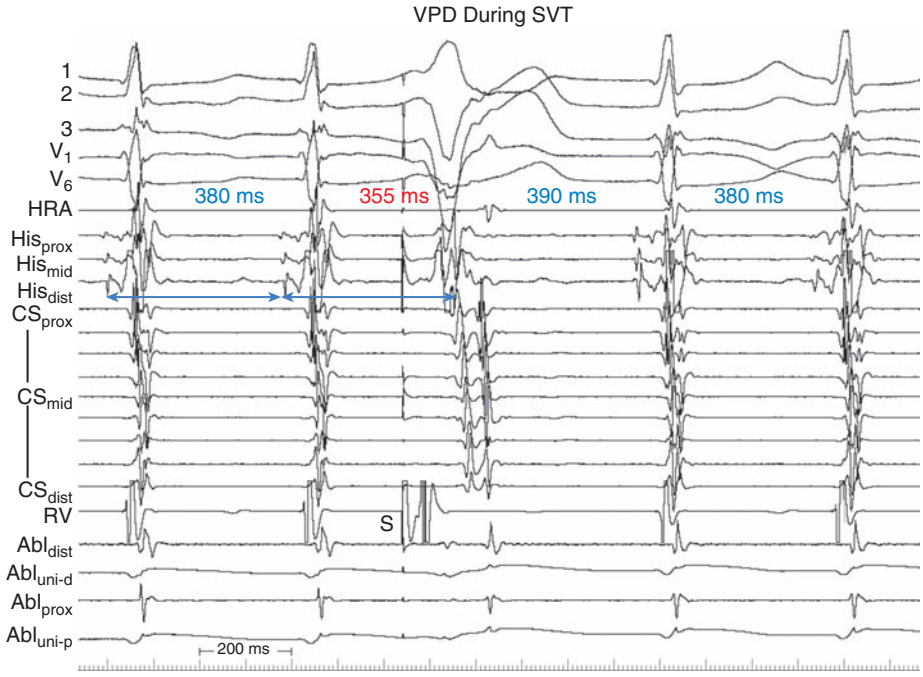


Figure 10-26

A ventricular extrastimulus (S) introduced during tachycardia advances the timing of atrial activation; however, the extrastimulus occurs at a time when the His bundle is not refractory (Fig. 10-26; *arrows* indicate where next expected His would occur). Thus retrograde conduction could easily have gone through the His bundle and AV node to preexcite the atrium. No inference can be made as to whether a bypass tract is present from this (though almost surely not, because atrial activation occurs within the QRS complex).

Ventricular Overdrive Pacing in SVT

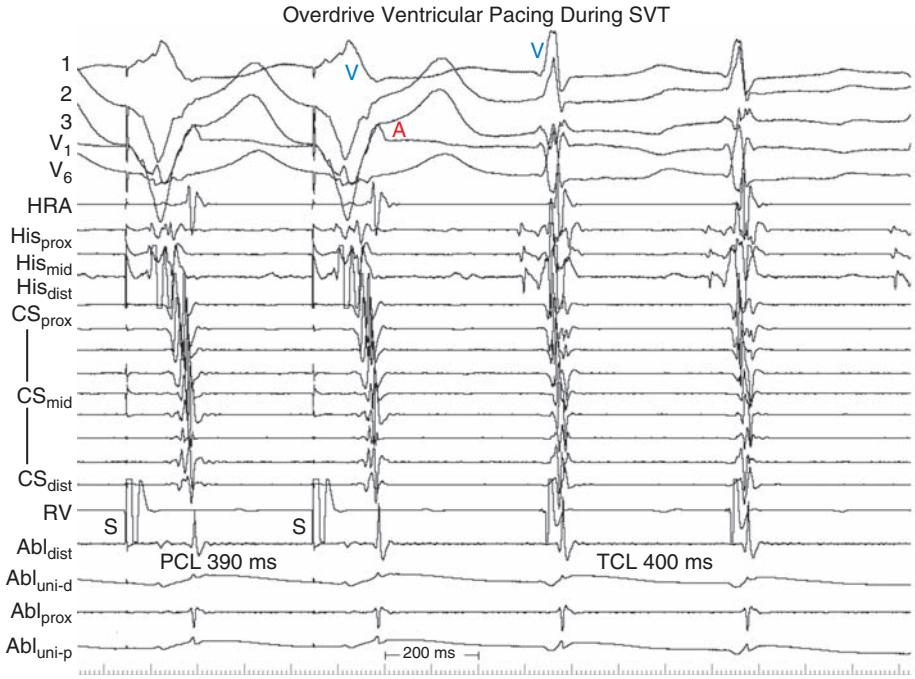


Figure 10-27

A "V-A-V" response seen with ventricular overdrive pacing during SVT excludes atrial tachycardia with a long PR interval and, with all the other data taken together, largely makes a diagnosis of AV nodal reentry (Fig. 10-27). Although this arrhythmia had not been documented clinically, it seemed prudent to undertake ablation at this setting because it was sustained and rather rapid.

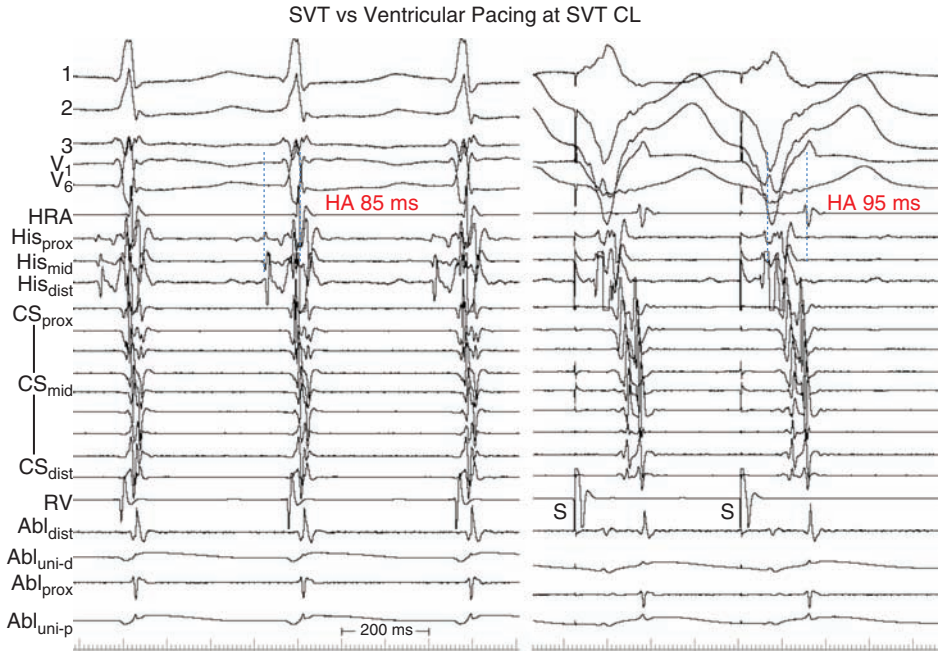


Figure 10-28

Additional evidence for AV nodal reentry, and against atrial or junctional tachycardias, is the HA interval in SVT vs ventricular pacing at the SVT cycle length. In Fig. 10-28, the HA in SVT (from onset of proximal His potential to HRA atrial recording, *dashed lines*) is 85 ms, slightly less than the HA during ventricular pacing at SVT cycle length (measured from end of proximal His deflection to same HRA atrial recording, *dashed lines*). If this were a junctional/His bundle tachycardia, these intervals should be the same; if atrial tachycardia, there is no reason that they should be similar because retrograde conduction with pacing and AH interval during atrial tachycardia are completely independent occurrences.

Catheter Manipulation at Tricuspid Annulus

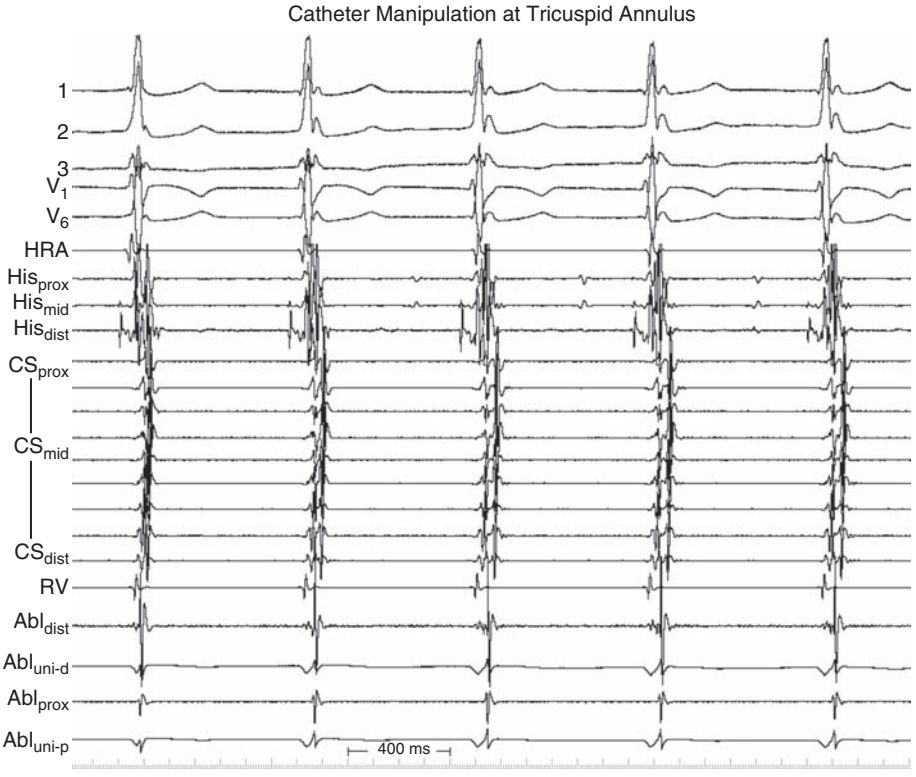


Figure 10-29

While positioning the ablation catheter for AV nodal slow pathway ablation, the rhythm shown in Fig. 10-29 was recorded. This is irritative junctional rhythm from the catheter rubbing on the slow pathway region, indicative of a good site for ablation. Note that, although this appears to be junctional with retrograde conduction, the P waves in the surface ECG are positive, indicating that this is sinus rhythm at almost the same rate.

Successful catheter ablation of the AV nodal slow pathway was accomplished, resulting in accelerated junctional rhythm; inducible AV node reentry was eliminated and atrial tachycardia likewise did not occur, either in the baseline state or after isoproterenol provocation. Normal AV conduction was present at the end of the procedure. After recovery, the patient did well without recurrence of any form of tachycardia and had normalization of left ventricular systolic function 3 months later.

Summary

- Focal AT can cause tachycardia-mediated cardiomyopathy; it is unusual to have the reverse (cardiomyopathy causing AT).
- Features of tachycardia-mediated cardiomyopathy:
  - No symptoms until HF occurs (no palpitations)
  - Ventricular rate 120–140/min (fast enough to cause HF, slow enough to escape detection/not cause palpitations, etc.)
  - HF can be cured when tachycardia is eliminated.
  - HF can recur if rapid rate recurs.
- Lessons:
  - Before ablating, delineate general mechanism: focal vs macroreentry.
  - Focal tachycardia target site features: <40 ms before P wave; QS unipolar
  - Bump mapping: signifies that the target site occupies a small critical area that is very superficial; but because this often occurs with sudden catheter movement, the catheter tip is rarely still at the "bumped" tissue by the time this is noticed.
  - Patients can have more than one type of tachycardia/cause of symptoms.

11 Focal Left Atrial Tachycardia

Case Presentation

A 73-year-old woman with recent onset renal failure complained of palpitations and near syncope for the last few weeks, with increasing frequency during dialysis. ECG showed non-sustained episodes of wide as well as narrow complex tachycardia, CL ~370 ms. She had a history of hypertension; her renal disease was of unclear cause (normal renal function 6 months prior to being on dialysis [via indwelling subclavian catheter]). She is being considered for living related donor transplant. Her last 10 dialysis sessions were stopped prematurely due to tachycardia episodes. Physical examination findings were normal aside from mild hypertension and the dialysis catheter. Her resting ECG showed a possible old anterior scar. An echocardiogram showed left ventricular hypertrophy, stage 2 diastolic dysfunction and mitral annular calcification. She was referred for electrophysiology (EP) study and possible ablation of narrow and wide QRS tachycardias.

Baseline ECG and Intracardiac Recordings

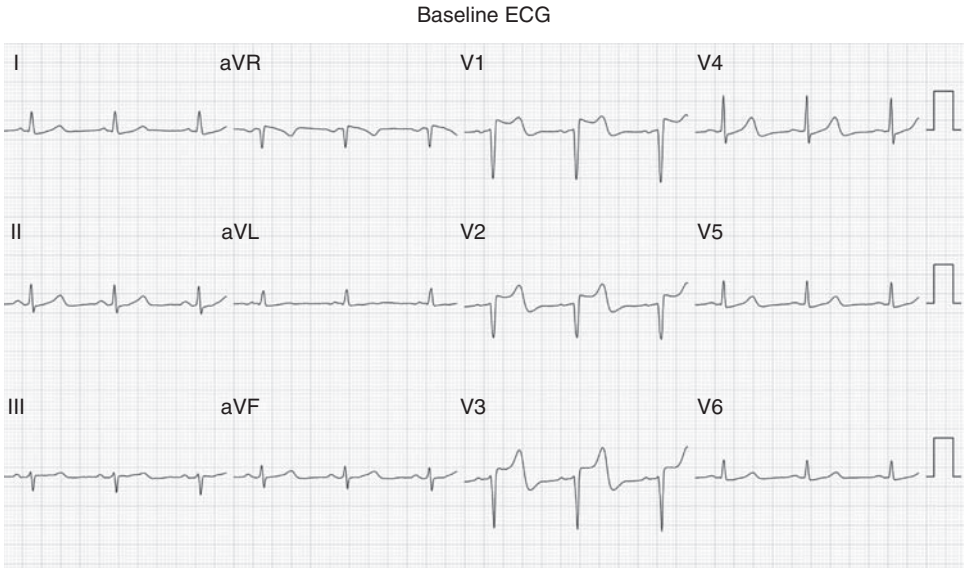


Figure 11-1

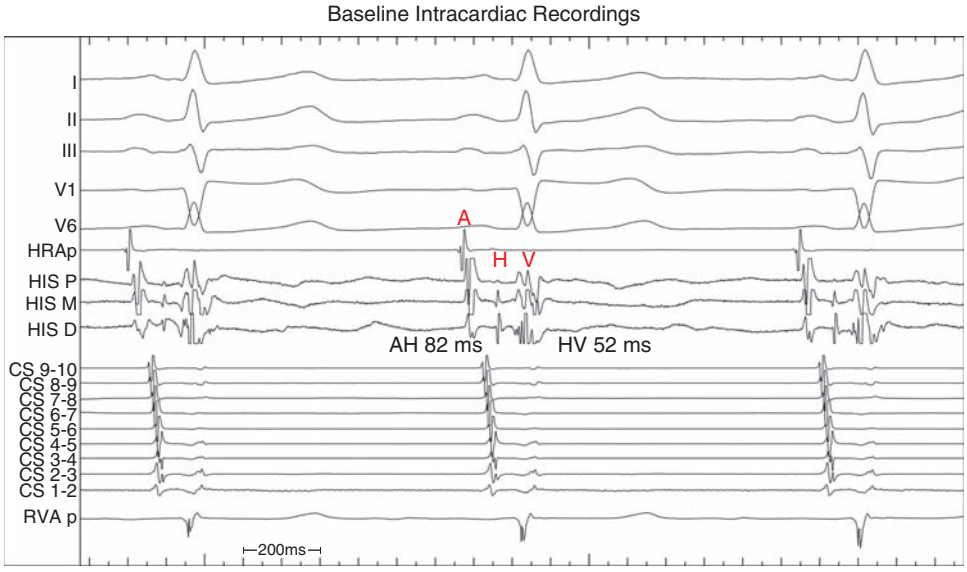


Figure 11-2

In Fig. 11-1 and Fig. 11-2, all intervals are normal. The ST elevation in V1–V3 in Fig. 11-1 is a recording artifact; R-wave progression is delayed but there is no definite infarct pattern. There are no clues from ECG or standard intracardiac recordings as to the nature of the rhythm disturbances.

Ventricular Pacing

What Is the Differential Diagnosis?
Where Is the Block? [Fig. 11-3]

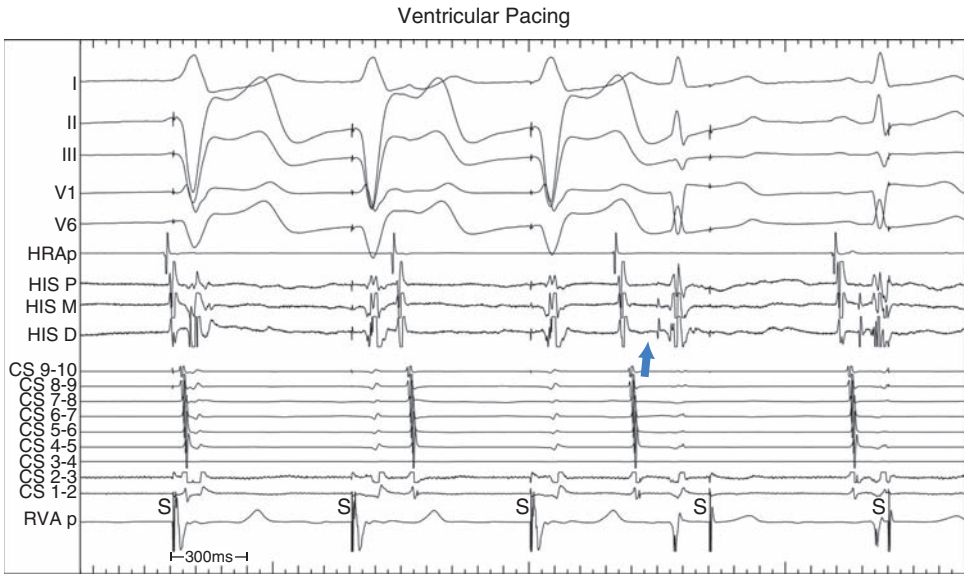


Figure 11-3

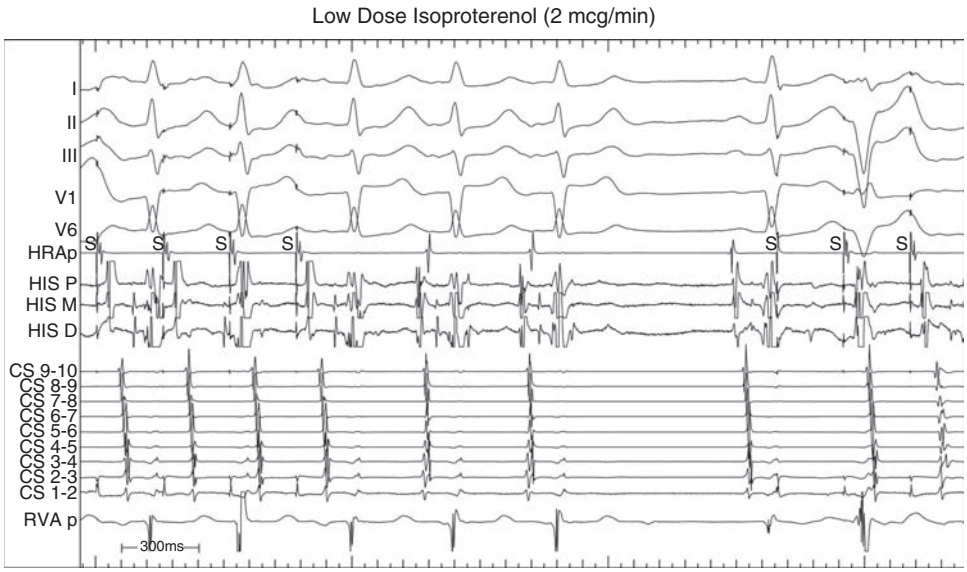
One of the first tests to perform is ventricular pacing to assess retrograde conduction (presence, pattern); in Fig. 11-3, there is no retrograde conduction (sinus complexes continue unaffected by ventricular pacing). This immediately makes orthodromic supraventricular tachycardia (SVT) related to a concealed bypass tract extremely unlikely, and even atrioventricular (AV) nodal reentry usually has retrograde conduction over the fast pathway at rest. In some cases of AV nodal reentry (and rare cases of orthodromic SVT), retrograde conduction may be restored after isoproterenol infusion and SVT can be induced under those conditions. However, the absence of retrograde conduction at this point makes an atrial tachycardia more likely as the cause of the patient's SVT.

The site of retrograde block is identified as the AV node, because the atrio-His interval following a paced complex *(arrow)* is longer than the resting AH (complex at right) because of concealed conduction into the AV node.

What Next?

After some additional testing, we now know that the AH (82 ms) and HV (52 ms) intervals are normal; the AV Wenckebach cycle length is 430 ms; there is no VA conduction; anterograde dual-AV nodal pathways are present, without echoes or inducible tachycardia; and no sustained arrhythmias can be initiated with atrial or ventricular stimulation (bursts, extrastimuli).

Atrial Pacing on Low-Dose Isoproterenol



What Is the Differential Diagnosis? [Fig. 11-4]

Figure 11-4

In the absence of inducible arrhythmias in the baseline state, isoproterenol infusion is begun. In Fig. 11-4, atrial pacing induces two cycles of tachycardia. This is described as a "long RP" rhythm, the differential diagnosis for which is atrial tachycardia, atypical AV nodal reentry (anterograde fast, retrograde slow pathways), and orthodromic reentry related to a slowly conducting bypass tract. The mode of initiation would be quite unusual for AV nodal reentry, because conduction would have to block in the slow pathway with the last atrial stimulus, conduct over the fast pathway, and yet go back up the slow pathway to form the first beat of tachycardia. The other two possibilities (atrial tachycardia or orthodromic reentry) remain.

Higher Dose Isoproterenol

Spontaneous SVT Onset

What Is the Differential Diagnosis [Fig. 11-5]? What Do You Need to Do to Figure It Out?

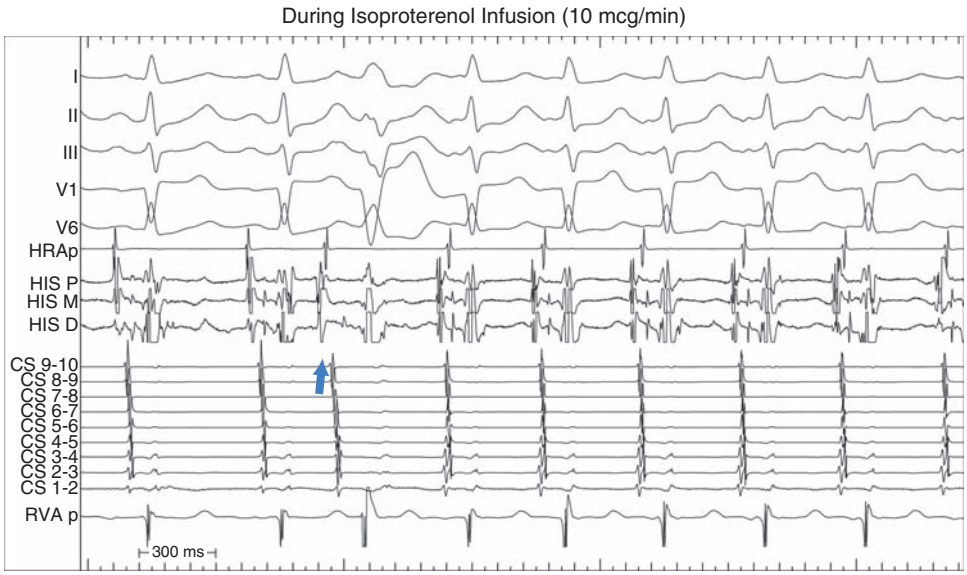


Figure 11-5

With an increase in the dose of isoproterenol, tachycardia occurs spontaneously. A spontaneous atrial premature complex (*arrow*, Fig. 11-5) appears to be conducted with left bundle branch block (LBBB) aberration, after which sustained narrow QRS tachycardia ensues. The atrial activation sequence is the same as in the two cycles of the rhythm seen in the previous figure on a lower dose isoproterenol, and is "concentric." This is consistent with a typical fast pathway exit (less so with slow pathway exit), a septal bypass tract, or a septal (or slightly left-sided) atrial tachycardia. Further testing is needed to distinguish among these possible diagnoses.

ECG and Intracardiac Recordings in SVT

What Is the Differential Diagnosis [Fig. 11-6]?

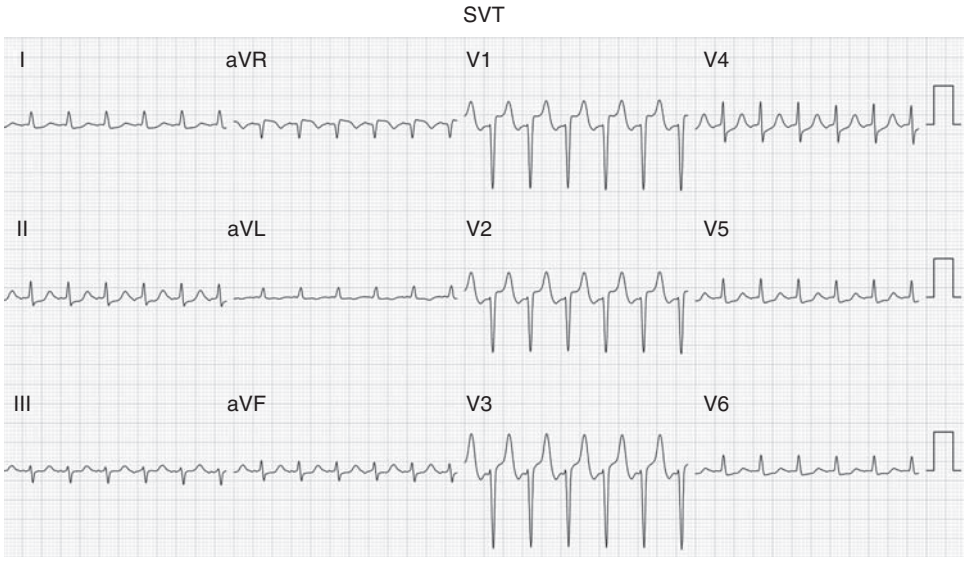


Figure 11-6

A 12-lead ECG of sustained tachycardia is shown in Fig. 11-6. The location and configuration of the P wave is less evident here than on the intracardiac recordings.

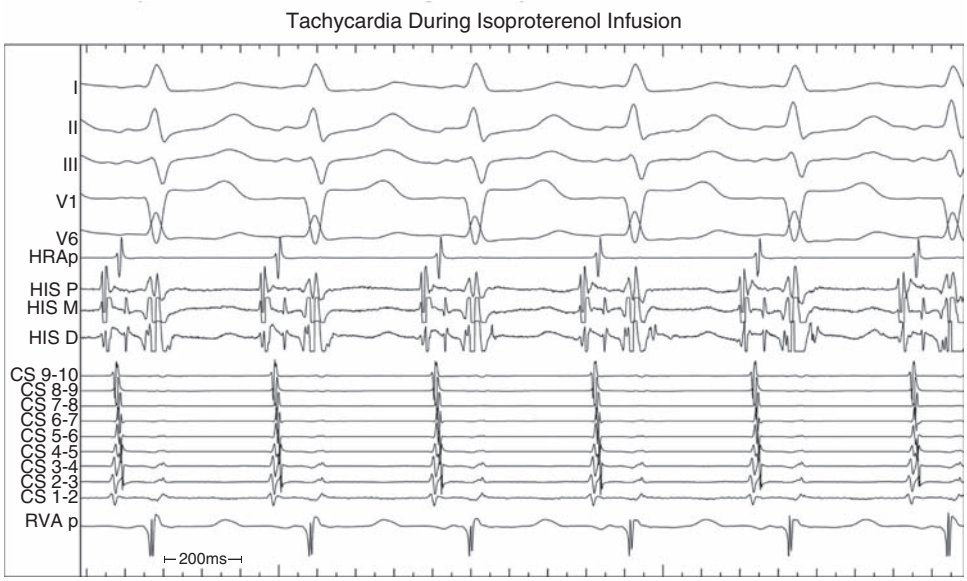
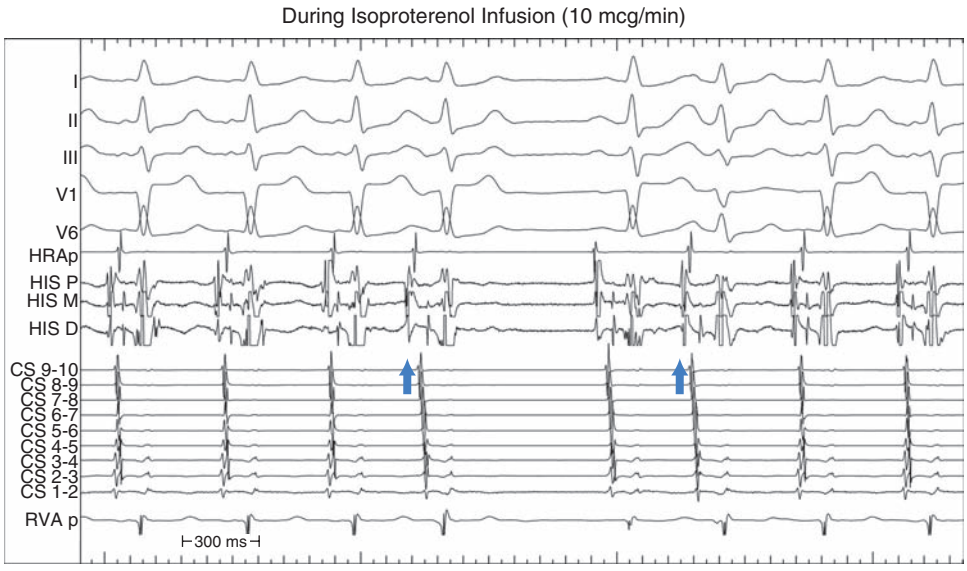


Figure 11-7

Intracardiac recordings of tachycardia are again shown (Fig. 11-7) at a more rapid sweep speed. It is clear that earliest activation among the atrial recordings is at the region of the His bundle.

SVT Termination



What Is the Differential Diagnosis? [Fig. 11-8]

Figure 11-8

In Fig. 11-8, tachycardia suddenly terminates after an atrial premature complex *(arrow)*. A sinus complex follows and then another atrial premature complex *(second arrow)*, and then tachycardia resumes. The fact that sustained tachycardia is terminated as well as initiated by atrial premature complexes that appear to be different from the ongoing tachycardia is suggestive of a reentrant, rather than focal, atrial tachycardia. However, none of the other tachycardia diagnoses have been definitively eliminated as yet.

Ventricular Pacing During Sinus Rhythm

What All Does This Tell? [Fig. 11-9]

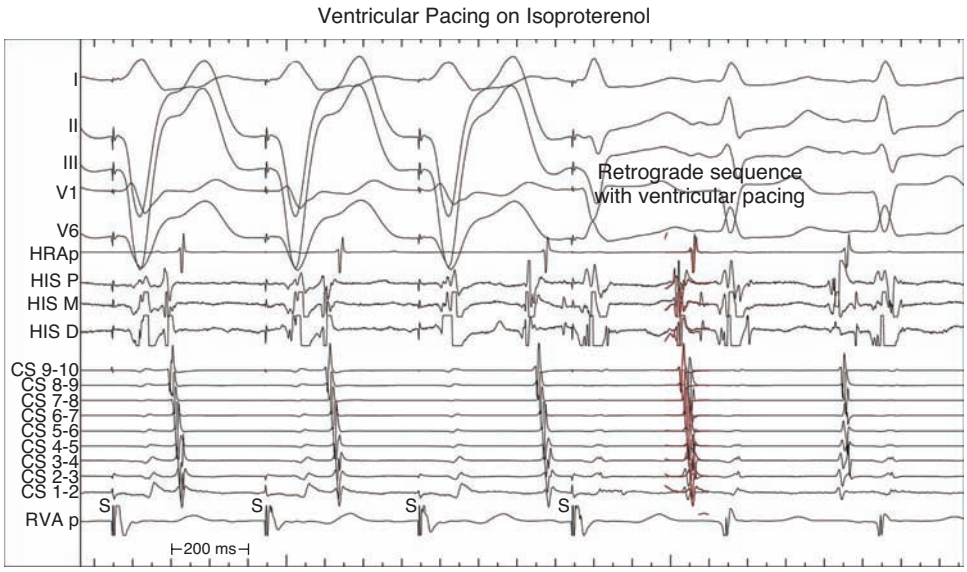


Figure 11-9

Ventricular pacing is now performed during sinus rhythm while on the isoproterenol infusion. As is often the case, retrograde conduction is restored with isoproterenol where it had been absent in the baseline state. On the first two complexes shown in Fig. 11-9, retrograde conduction is concentric with a short retrograde conduction time; on the third complex, a longer retrograde conduction time is seen followed by a His potential and narrow QRS complex despite another stimulus artifact occurring. This is indicative of retrograde dual-AV nodal physiology (retrograde slow pathway, anterograde fast pathway), one of the potential mechanisms of the patient's tachycardia (which starts immediately thereafter). However, the atrial activation sequence of the retrogradely conducted complexes (superimposed in red on an SVT complex) is a little different from that of tachycardia, indicating that the tachycardia diagnosis is probably not, in fact, AV nodal reentry. A slowly conducting bypass tract mediating orthodromic reentry also seems very unlikely because the atrial activation sequence during ventricular pacing is different from tachycardia, but has not been definitively excluded at this point

Wide-QRS Complex Tachycardia ECG and Intracardiac Recordings

What Is the Differential Diagnosis? [Fig. 11-10]

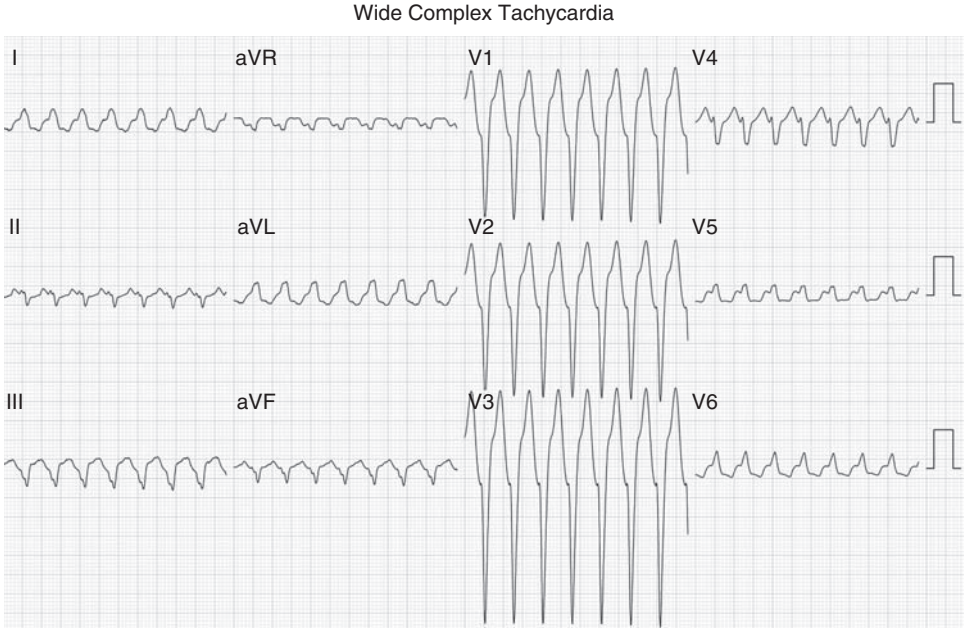


Figure 11-10

A few minutes later, while still on isoproterenol, a wide complex tachycardia occurs (Fig. 11-10). Recall that the patient had both narrow and wide complex tachycardias with similar rates. The tachycardia shown has a rate nearly identical to that of the narrow complex tachycardia encountered minutes earlier, and has a left branch block configuration consistent with SVT with aberration.

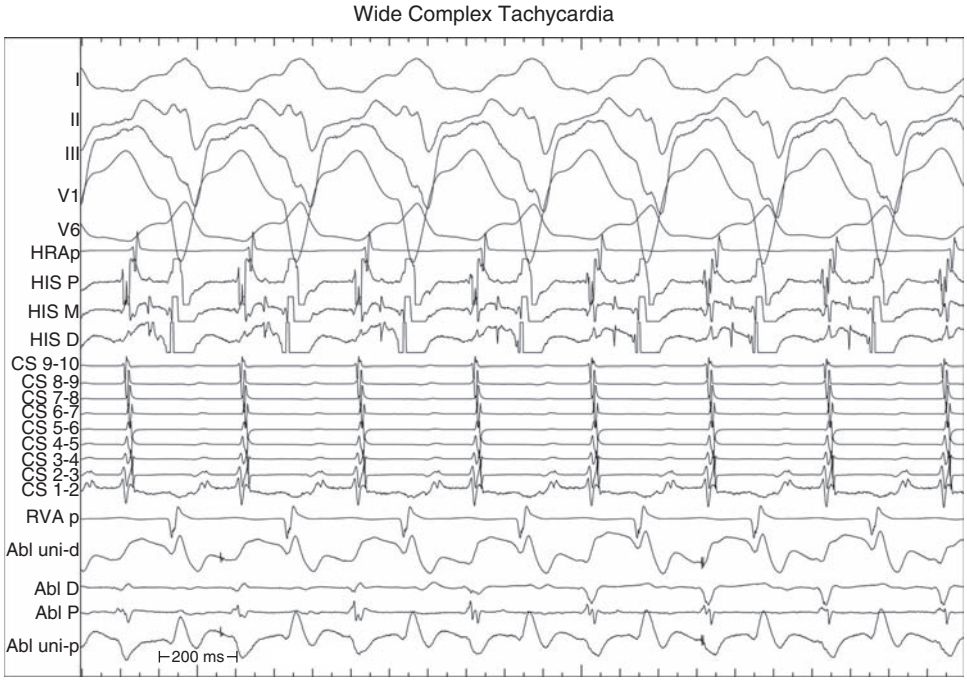


Figure 11-11

Intracardiac recordings from around the same time (Fig. 11-11) show a 1:1 atrioventricular relationship, with an atrial activation sequence identical to that of the narrow complex tachycardia. In addition, a His potential precedes every QRS complex, indicating that the rhythm is supraventricular with aberration.

The coronary sinus catheter has been advanced somewhat, accounting for its change in activation sequence and timing relative to the His bundle atrial activation.

Wide-to-Narrow QRS Tachycardia Transition

Why Did the QRS Narrow? [Fig. 11-12]

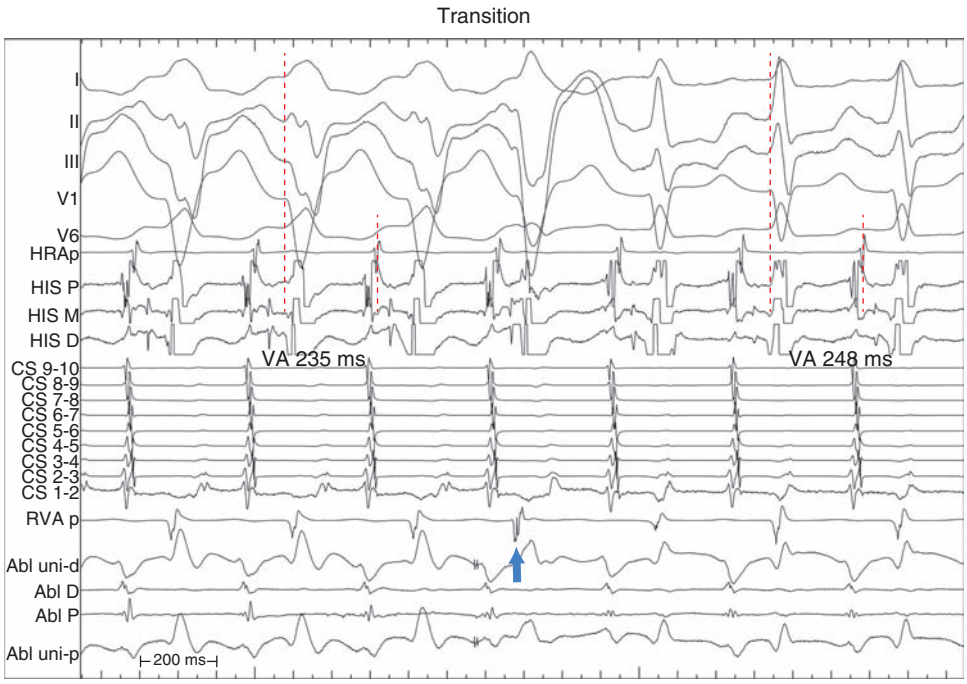


Figure 11-12

Spontaneous transition from wide to narrow QRS complex is seen in Fig. 11-12. An important measurement to make in this situation is the VA interval (onset of QRS to an atrial electrogram *[dashed lines]*). With orthodromic reentry related to a left-sided bypass tract, the VA interval with LBBB will exceed that during narrow QRS tachycardia by >35 ms. In this example, there is no difference in the VA intervals, excluding participation of a left free wall bypass tract.

The QRS complex narrowed because of a spontaneous premature ventricular complex from the right ventricle *(arrow)* that likely prematurely activated the LBBB, allowing it more time to recover for the subsequent complex, that could then conduct normally.

Ventricular Pacing in SVT to Delineate P-Wave Onset

What's Up with This? [Fig. 11-13]

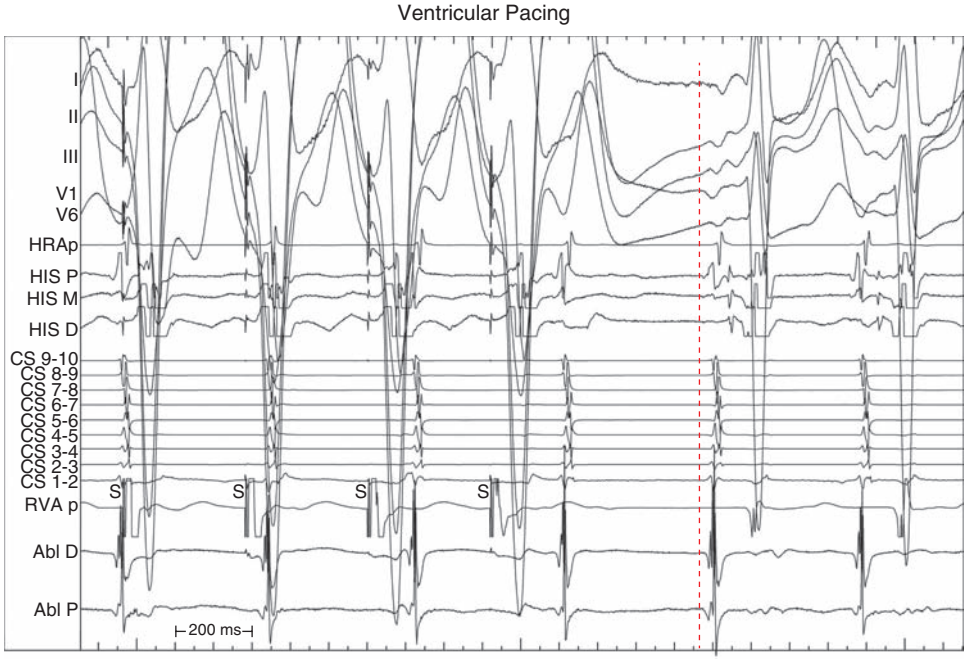


Figure 11-13

In Fig. 11-13, ventricular pacing is performed during tachycardia; surface ECG leads have increased gain to demonstrate P-wave onset for mapping purposes *(dashed red line)*. Of note, atrial activation continues throughout the figure unaffected by ventricular pacing; this excludes orthodromic reentry, in which atrial activation depends on prior ventricular activation. Because this and AV nodal reentry have now been excluded, the diagnosis is atrial tachycardia. Now that the P wave onset has been clarified, it can be indexed to another more readily seen recording (such as HRA, 50 ms after P wave onset) to compare the timing of mapping sites, without having to guess where the P wave starts or repeat ventricular pacing to discern it.

Right Atrial and then Coronary Sinus Pacing During Tachycardia

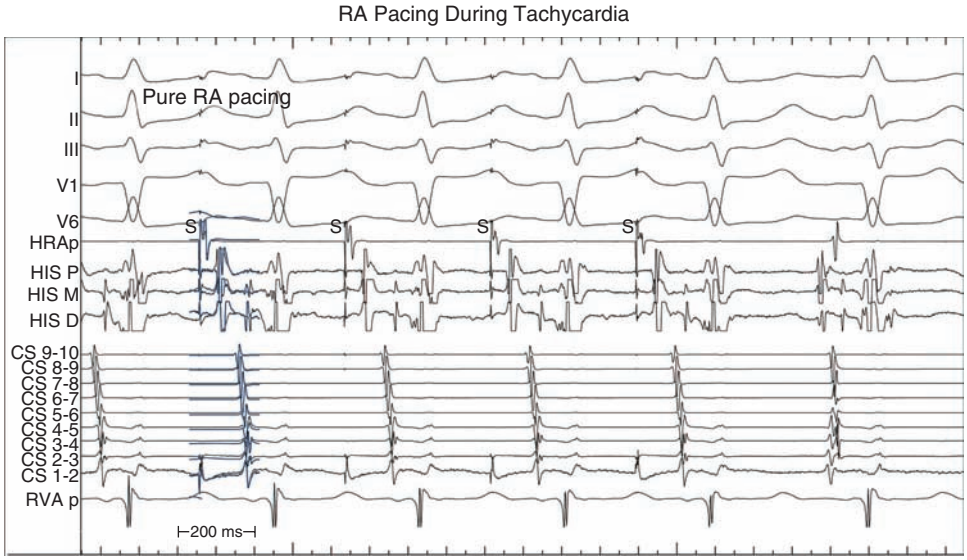


Figure 11-14

Now that a diagnosis of atrial tachycardia has been established, it remains to be determined whether this is because of macroreentry or a focal process. The modes of initiation and termination seen in previous figures are consistent with either. In the example shown in Fig. 11-14, a complex of "pure" right atrial pacing *(blue)* obtained during sinus rhythm is superimposed on a complex of pacing from the same site during tachycardia (a tachycardia beat resumes at right). It is clear that the activation sequence is the same whether pacing during sinus rhythm or tachycardia, indicating absence of fusion. Mere absence of fusion when pacing from one site does not establish a diagnosis of a focal process (however, if macroreentry is present, it is often possible to demonstrate fusion when pacing from a single site).

What Do the Results of Pacing During Tachycardia Tell Us? [Fig. 11-15]

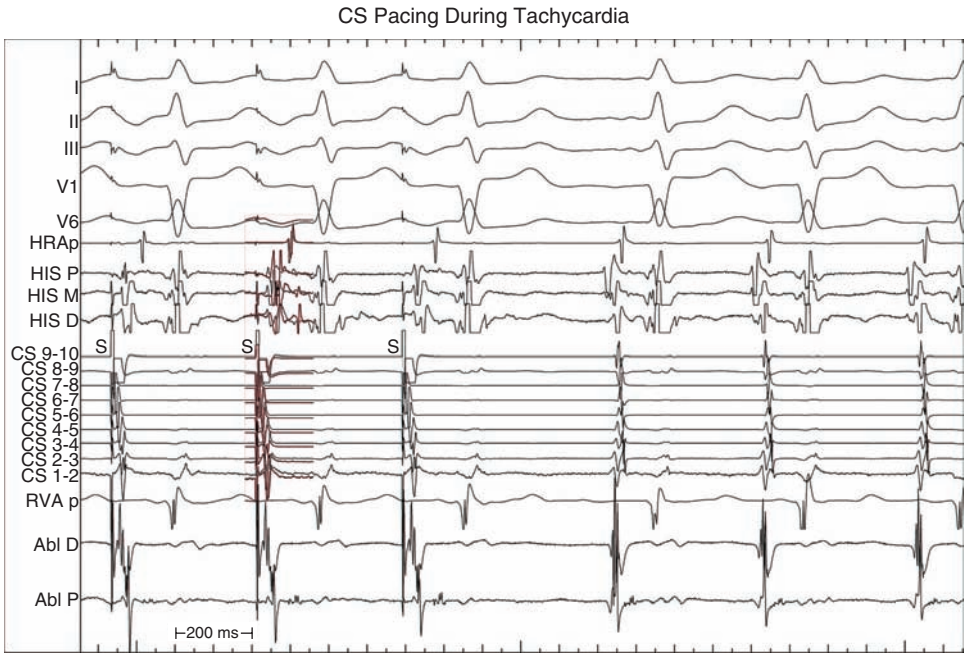


Figure 11-15

In Fig. 11-15, pacing from the proximal coronary sinus (CS) is shown during tachycardia (that resumes at right) as well as a single complex of "pure" CS pacing during sinus rhythm superimposed *(red)*. Again, there is no difference between these, and thus no fusion. Similar results were obtained when pacing from the distal CS (not shown). Thus absence of fusion when pacing from multiple sites, and ideally at multiple cycle lengths, makes a focal process far more likely. This was the diagnosis in this case.

Activation and Pace Mapping in Right Atrium

Is This a Good Site?

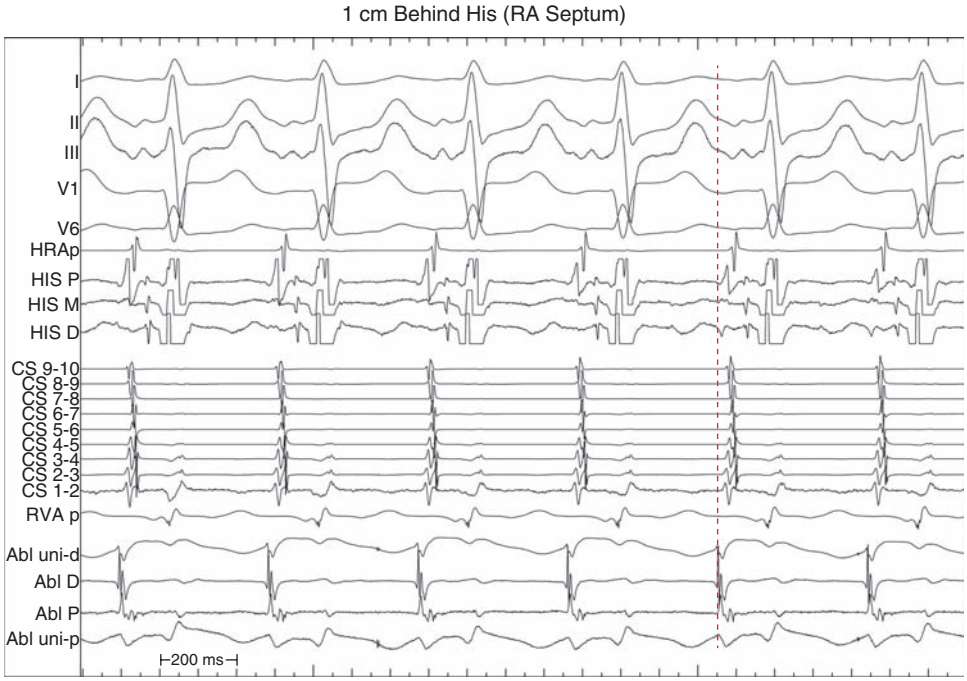
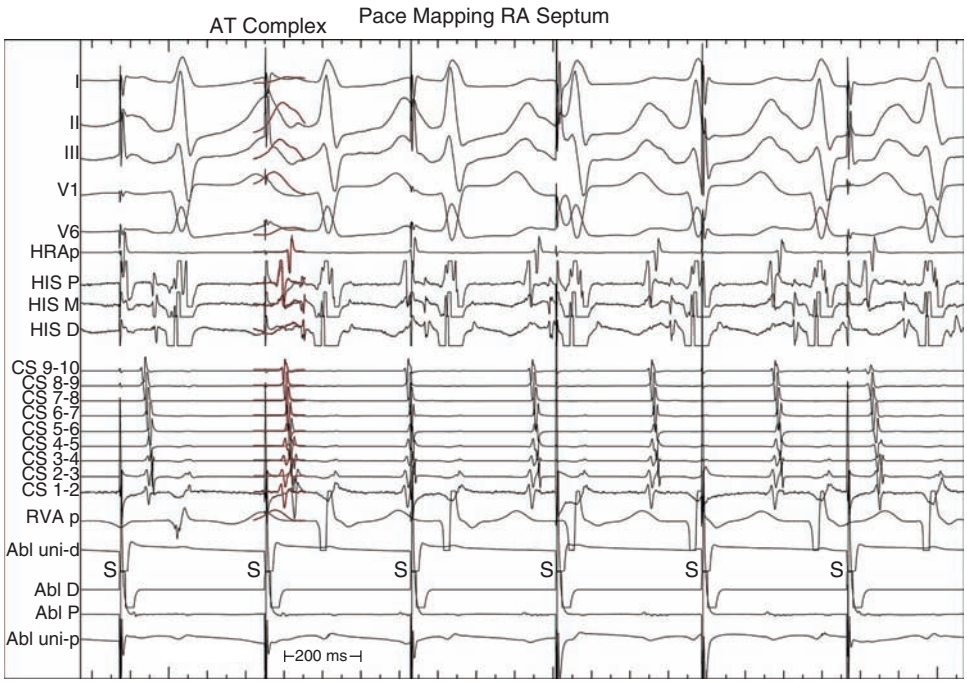


Figure 11-16

Now that a focal atrial tachycardia has been diagnosed, an electrogram that is 30–40 ms before the P-wave onset may be sought for ablation. Mapping on the right side of the interatrial septum (Fig. 11-16), near the His bundle location, discloses a site about 5 ms before P-wave onset (*dashed red line*, 50 ms before HRA recording as demonstrated in figure). The

unipolar recording has a small initial R wave; this, as well as the unimpressive timing of the atrial electrogram, excludes this as a good site for ablation.



Well?

Figure 11-17

Further evidence that this is not a good site for ablation is the fact that pacing from that site yields a very different atrial activation sequence compared with that during tachycardia (Fig. 11-17, in *red*). Pacing from the site of impulse formation of a focal tachycardia should exactly replicate the atrial activation sequence during tachycardia.

Electroanatomic Mapping of Right Atrium

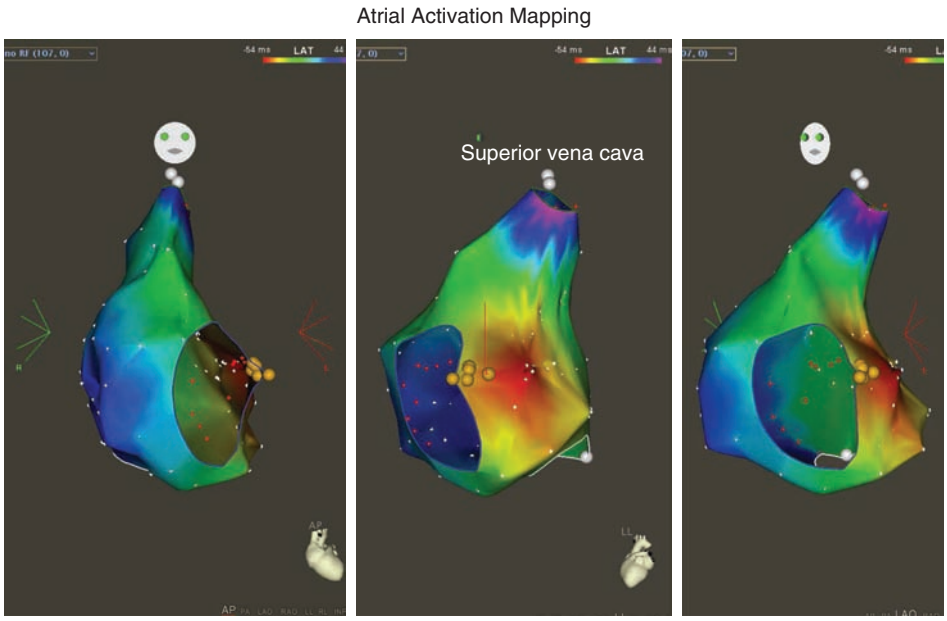


Figure 11-18

What Next?

Electroanatomic activation mapping of the right atrium during tachycardia (Fig. 11-18) shows a pattern of centrifugal spread from a focus just behind the His bundle location *(orange dots)*. At this time in the procedure, we have diagnosed narrow and wide QRS tachycardia that appear to have the same cause (focal atrial tachycardia); the tachycardia has earliest activation at or just behind the His bundle recording site, but is not very early (5 ms before P-wave onset); the earliest site covers a rather broad area; and the pace-match from there is poor. Isoproterenol is still required to sustain tachycardia for mapping but the patient's blood pressure is 200/120 mm Hg.

Activation and Pace Mapping Left Atrial Site

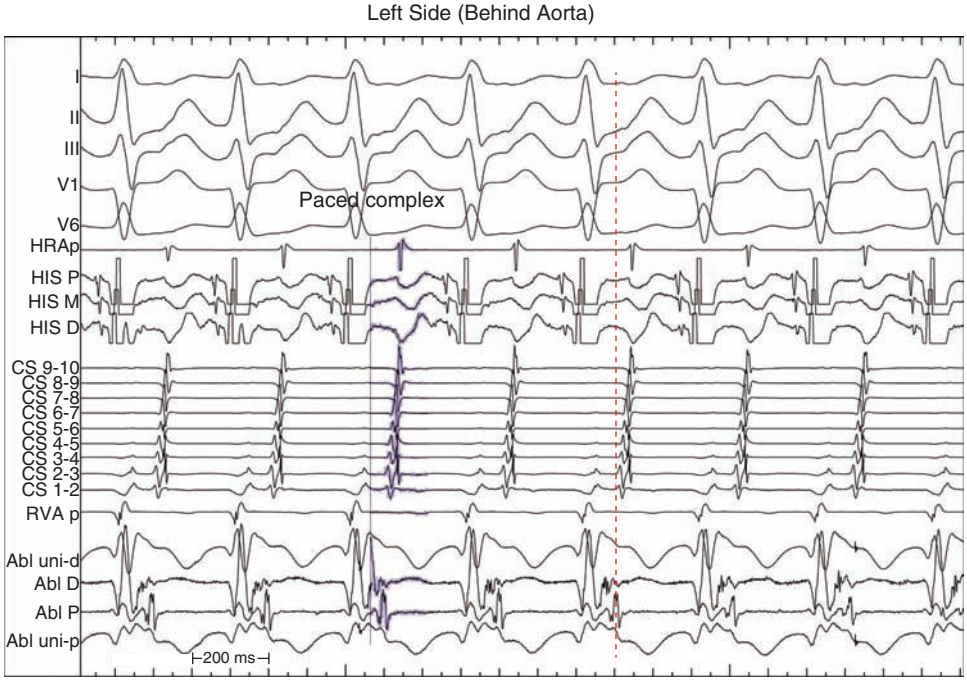


Figure 11-19

Despite the focal activation pattern on the electroanatomic map, no right atrial site showed reasonable activation times; in such cases, the left side of the septum, right superior pulmonary vein, and aortomitral continuity/mitral annulus should be evaluated before ablating behind the His bundle. After transseptal catheterization, mapping of these structures was accomplished; the site shown in Fig. 11-19 is on the mitral annulus at its junction with the aortic root (large ventricular, small and fractionated atrial electrogram). A single complex of pacing from this site is shown *(purple)* superimposed on tachycardia, yielding a perfect match. The unipolar recording is not as helpful in this situation because a large ventricular electrogram obscures the smaller atrial signal. The electrogram at this site is fragmented and considerably before the P wave onset (*dashed red line*, known from relation to HRA recording as in Fig. 11-13).

Radiofrequency Application at Left Atrial Site

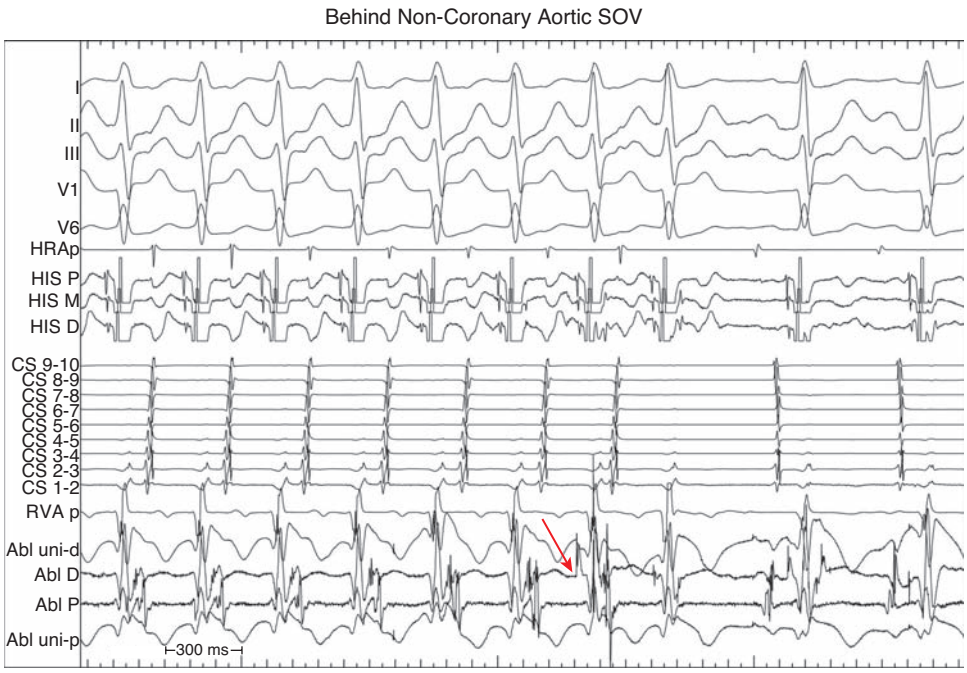


Figure 11-20

Radiofrequency (RF) energy is delivered at the site shown in Fig. 11-20 at the time indicated; tachycardia terminates immediately to sinus rhythm. Additional RF applications were made in this region.

Comparison of Best Right and Left Atrial Sites

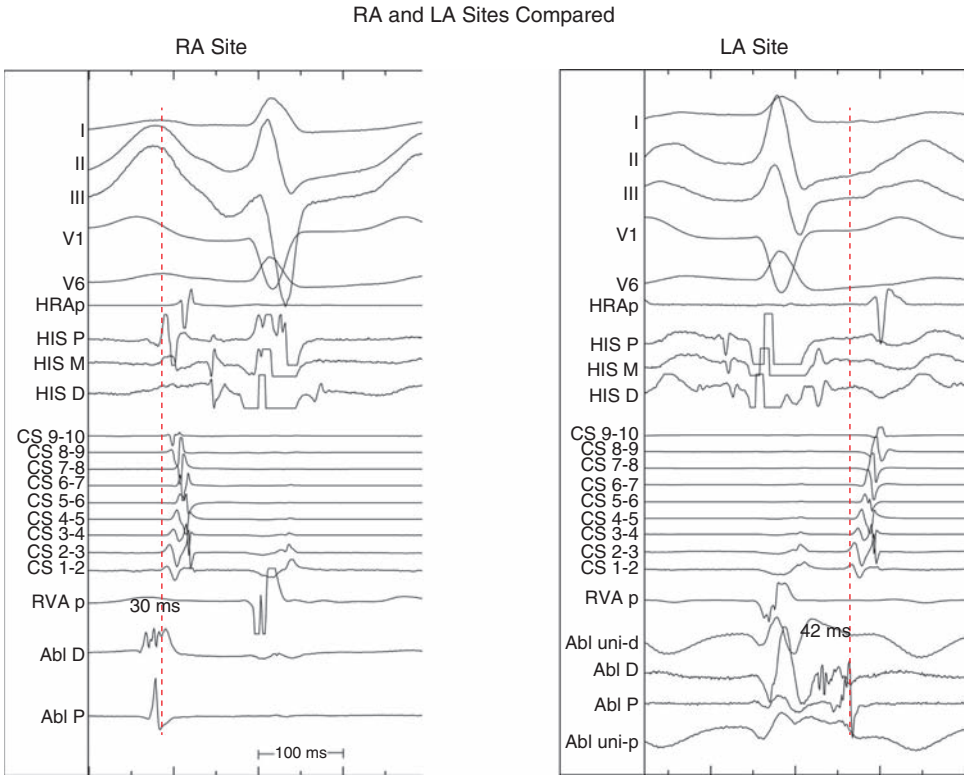


Figure 11-21

A comparison of mapping sites at rapid sweep speed is shown in Fig. 11-21. The best right atrial site is shown at left, preceding the P-wave onset (*dashed red line*, indexed from the timing of the CS atrial recordings) by 30 ms. In contrast, the successful ablation site on the mitral annulus occurs 42 ms before P-wave onset.

Electroanatomic Map of Left Atrium

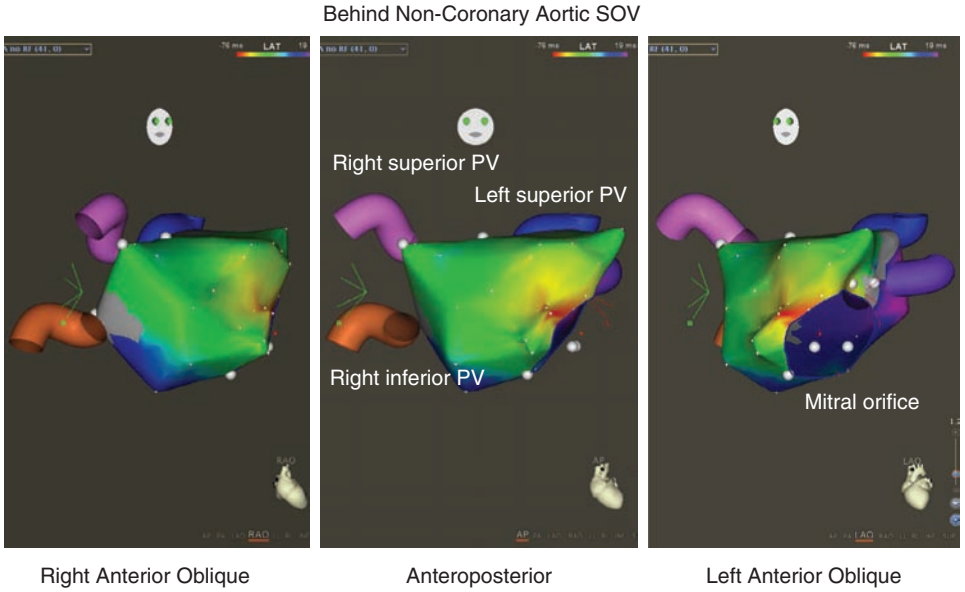


Figure 11-22

Electroanatomic activation map during tachycardia of the left atrium is shown in Fig. 11-22, with a focal propagation pattern from a site *(red spot)* on the anterior medial mitral annulus.

Fluoroscopic Views of Best Right and Left Atrial Sites

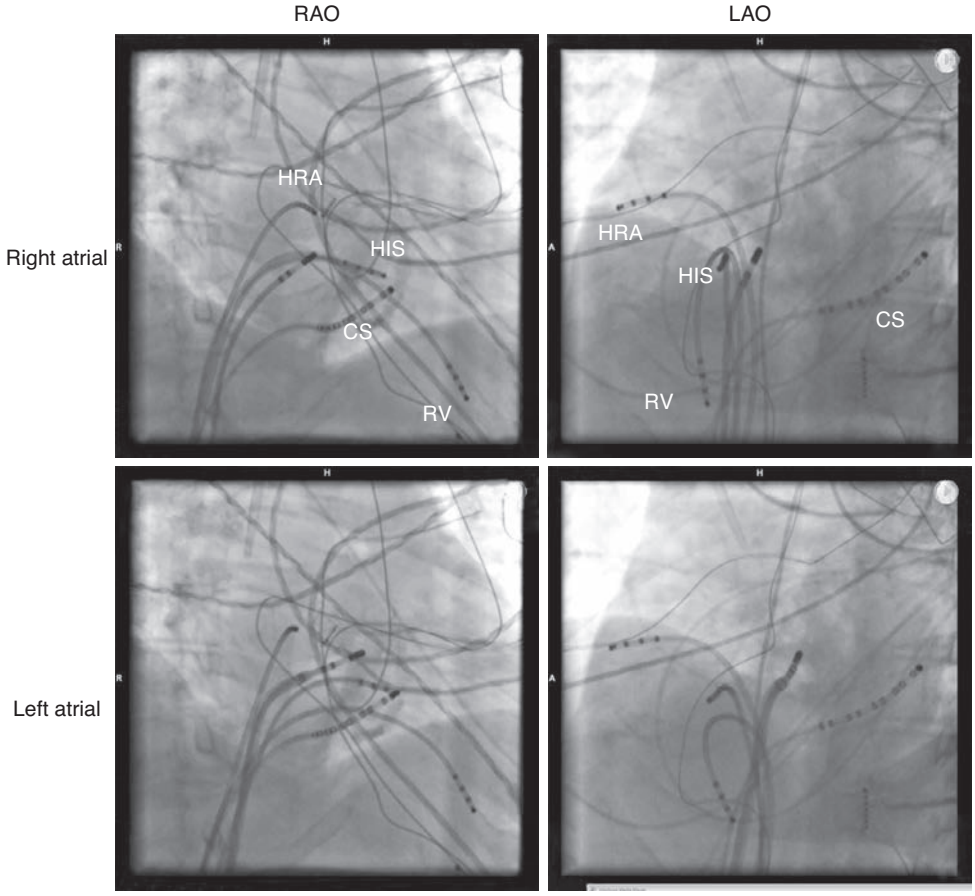


Figure 11-23

Fig. 11-23 displays comparative fluoroscopic views of catheter locations at sites of the earliest right and left atrial activation during SVT (catheter with large electrode at tip). *CS*, coronary sinus; *HRA*, high right atrium; *LAO*, left anterior oblique; *RAO*, right anterior oblique; *RV*, right ventricle.

Cutaway View of Atrioventricular Groove

Figure 11-24

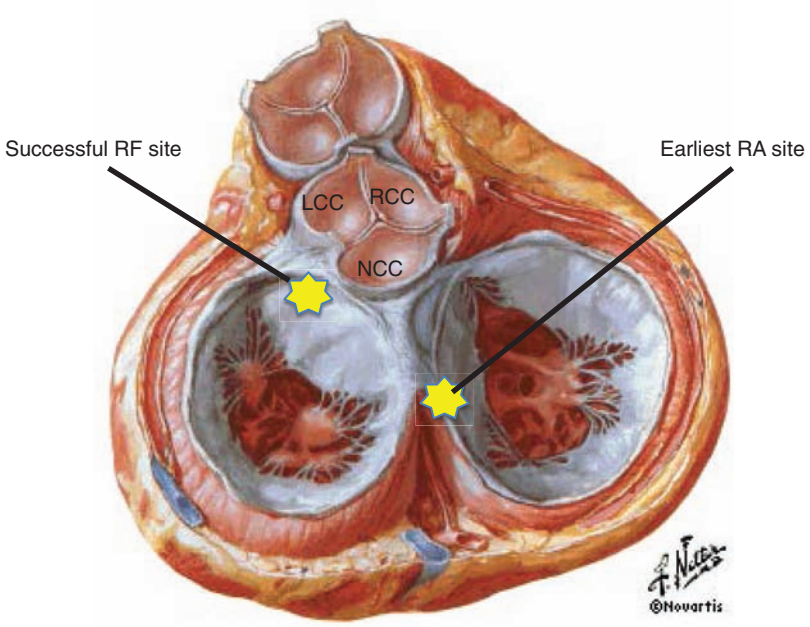


Fig. 11-24 shows atrioventricular valves annuli viewed from above, with both the successful left atrial ablation site and site of the earliest right atrial activation indicated. *LCC*, left coronary cusp; *NCC*, noncoronary cusp; *RCC*, right coronary cusp. (Copyright [2016] Elsevier Inc. All rights reserved. www.netterimages.com.)

Summary

- Atrial tachycardia can strike at any age.
- Know your mechanism (focal vs macroreentry) before mapping (target-site characteristics are determined thereby).
- Focal atrial tachycardia can arise from many places.
- P-wave configuration in SVT provides substantial localization information before and during the procedure.
- "Earliest atrial activation at His" suggests the following:
  - Right superior PV source (His-A after P-wave onset)
  - Left septal source (His-A ~10 ms before P-wave onset)
  - Anterior left atrial source (aortomitral continuity, etc.—His-A ~10 ms before P-wave onset)
  - Para-Hisian source (His-A ~20 ms before P-wave onset)
- Before ablating near the His, check out the left atrium.

12 Typical Atrial Flutter

Case Presentation

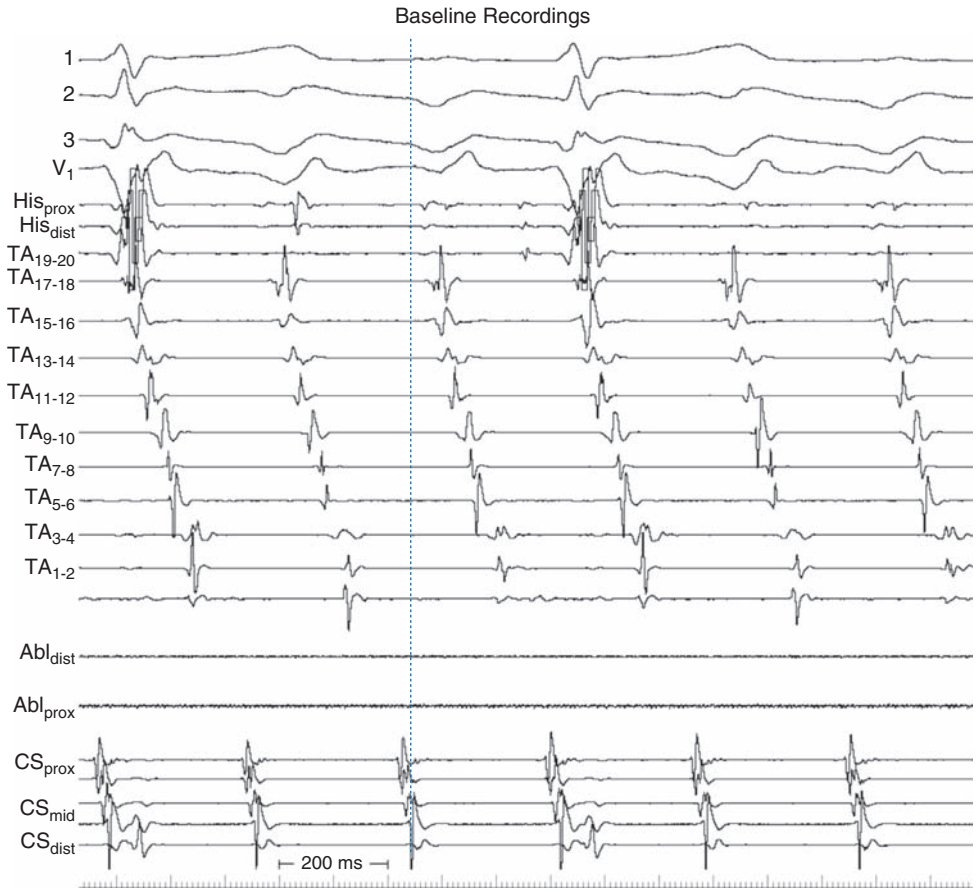
A 58-year-old man with a history of palpitations for several years had a diagnosis of atrial arrhythmias as well as bradycardia, but had no treatment for these. One year before his current presentation, he had an unheralded stroke with aphasia and hemiplegia. He underwent successful thrombolytic therapy with no residual neuorologic impairment. At the time of his stroke, he was diagnosed with atrial flutter and soon after, underwent attempted flutter ablation. At the end of an 8-hour procedure, cavotricuspid isthmus block was achieved but flutter was still present (thought to be either lower loop or intraisthmus reentry). He was chronically anticoagulated; he was also treated with propafenone, but without success. He began having palpitations and was referred for another ablation attempt. Left ventricular function was normal on echocardiography.

Baseline ECG and Intracardiac Recordings

Catheter Choices?
[Fig. 12-1]
Strategy?

Figure 12-1

The baseline ECG in Fig. 12-1 appears to be consistent with typical right atrial cavotricuspid isthmus-dependent flutter, but that was said to have been ablated at the prior procedure. Reasonable choices for catheters are coronary sinus (with some electrodes near the ostium), tricuspid annular catheter ("halo"), and a His bundle catheter, as well as the ablation catheter.



We Begin with the Differential Diagnosis: [Fig. 12-2 and 12-3]

A. Typical CCW flutter
B. Lower loop reentry
C. Intraisthmus reentry
D. Focal AT near CS os
E. AT from left atrium

Figure 12-2

Intracardiac recordings of the baseline rhythm are shown in Fig. 12-2. Again, this appears to be entirely compatible with cavotricuspid isthmus reentry—but there are other possible diagnoses that should be eliminated before choosing an ablation target. A broad differential diagnosis includes typical counterclockwise (CCW) cavotricuspid isthmus flutter; lower loop reentry; intraisthmus reentry; focal atrial tachycardia (AT) near the coronary sinus ostium (CS); or atrial tachycardia from the left atrium.

Diagnostic Maneuvers

CS Distal Pacing

Differential diagnosis:
- typical CCW flutter
- lower loop reentry
- intra-isthmus reentry
- focal AT near CS os
- AT from left atrium

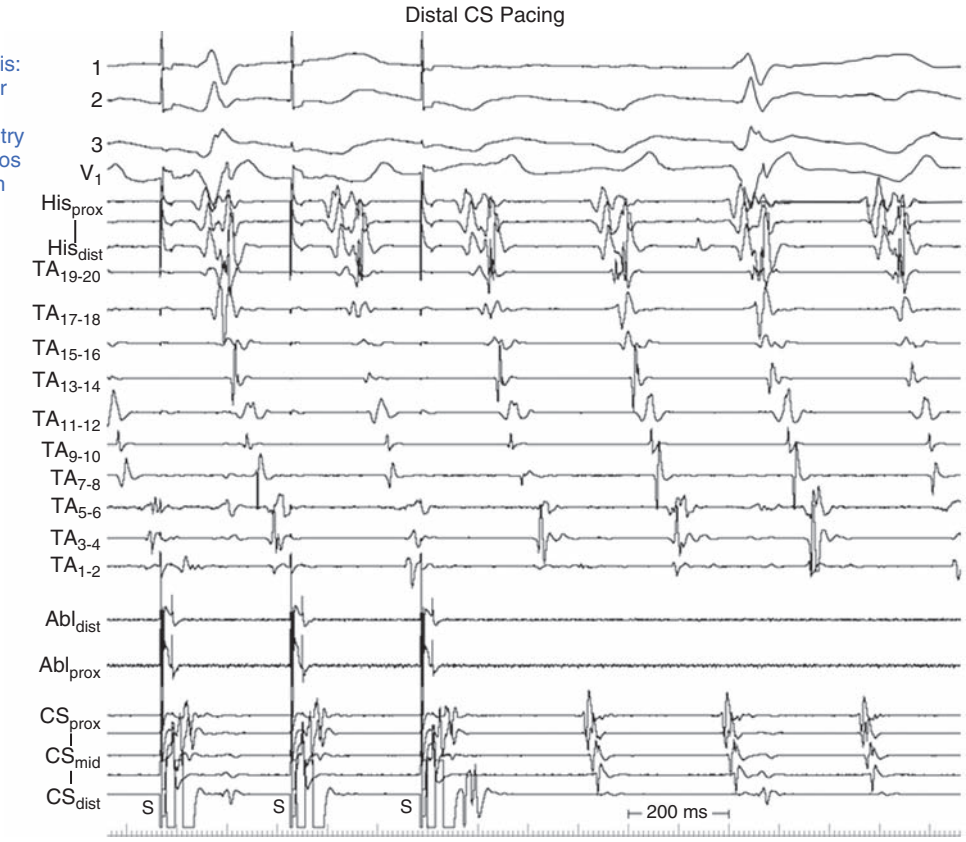
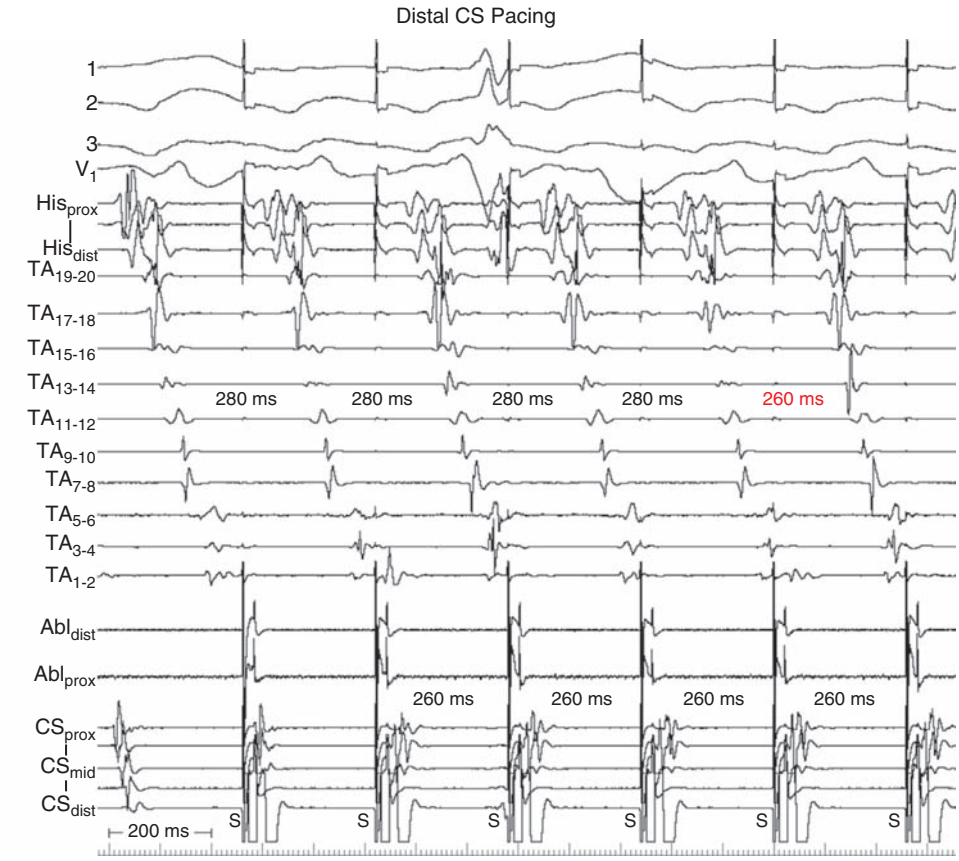


Figure 12-3

Burst pacing from the distal CS, as shown in Fig. 12-3, is a good way to start trying to distinguish among possible diagnoses; in a patient without prior ablation, pacing from this site during sinus rhythm should have a "chevron" appearance to the halo recordings (earlier at TA 1-2 and TA 19-20, latest at lateral right atrium [TA 11-12]). If such a pattern is seen with pacing from the CS during the tachycardia, it is not likely to be typical flutter. The activation pattern in halo recordings shown here looks the same as during tachycardia—suggesting fusion (some contribution from tachycardia, some from pacing). However, it is important to remember that this inference is valid if the patient has not had prior ablation in the right atrium that could disrupt activation patterns. Because this patient has had a previous ablation attempt, we cannot assume what pacing from the distal CS should look like, and thus cannot conclude that entrainment has been demonstrated. Unfortunately, pacing from the distal CS in this case appears to have little diagnostic value, and our differential diagnosis is unchanged.



We Can Eliminate AT from Left Atrium from the Differential Diagnosis: [Fig. 12-4]

A. Typical CCW flutter
B. Lower loop reentry
C. Intraisthmus reentry
D. Focal AT near CS os

Figure 12-4

Although most attention is focused on what happens at the end of a pacing attempt, there is also information at the onset of pacing (Fig. 12-4). Here, with the onset of distal CS pacing, the proximal CS electrodes are controlled by the second stimulus and are accelerated to the paced cycle length (260 ms). The halo recordings, by contrast, are not accelerated until the fifth stimulus. If this tachycardia arose in the left atrium, as soon as that chamber is controlled, all other recordings that are passive should be controlled as well. Here, because the right atrial recordings continue unchanged for a few cycles after full left atrial control, the arrhythmia must arise in the right atrium. Thus one choice in the differential diagnosis (atrial tachycardia from the left atrium) has been eliminated.

Differential diagnosis:
- typical CCW flutter
- lower loop reentry
- intra-isthmus reentry

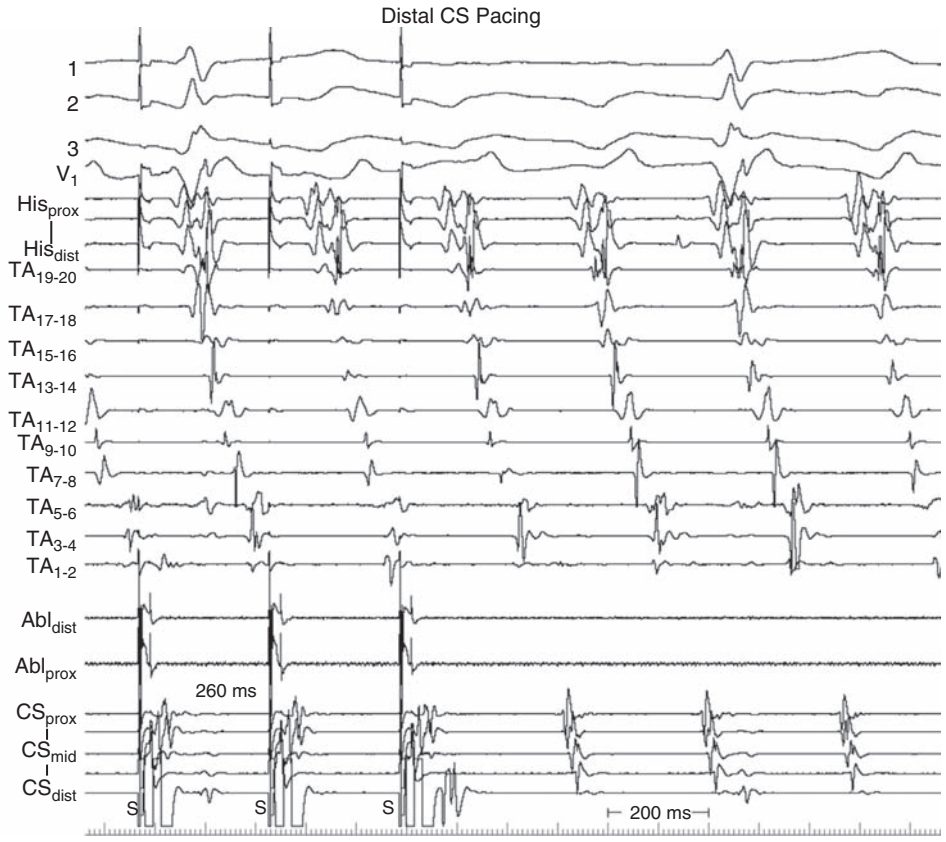


Figure 12-5A

Differential diagnosis:
- typical CCW flutter
- lower loop reentry
- intra-isthmus reentry

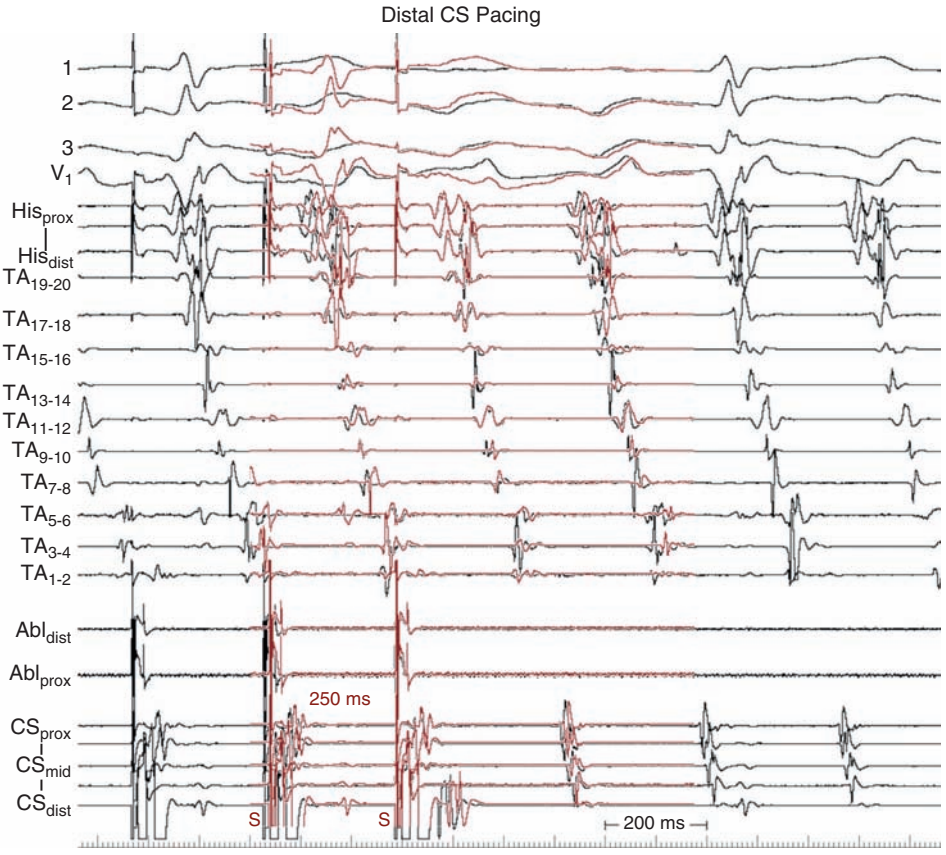


Figure 12-5B

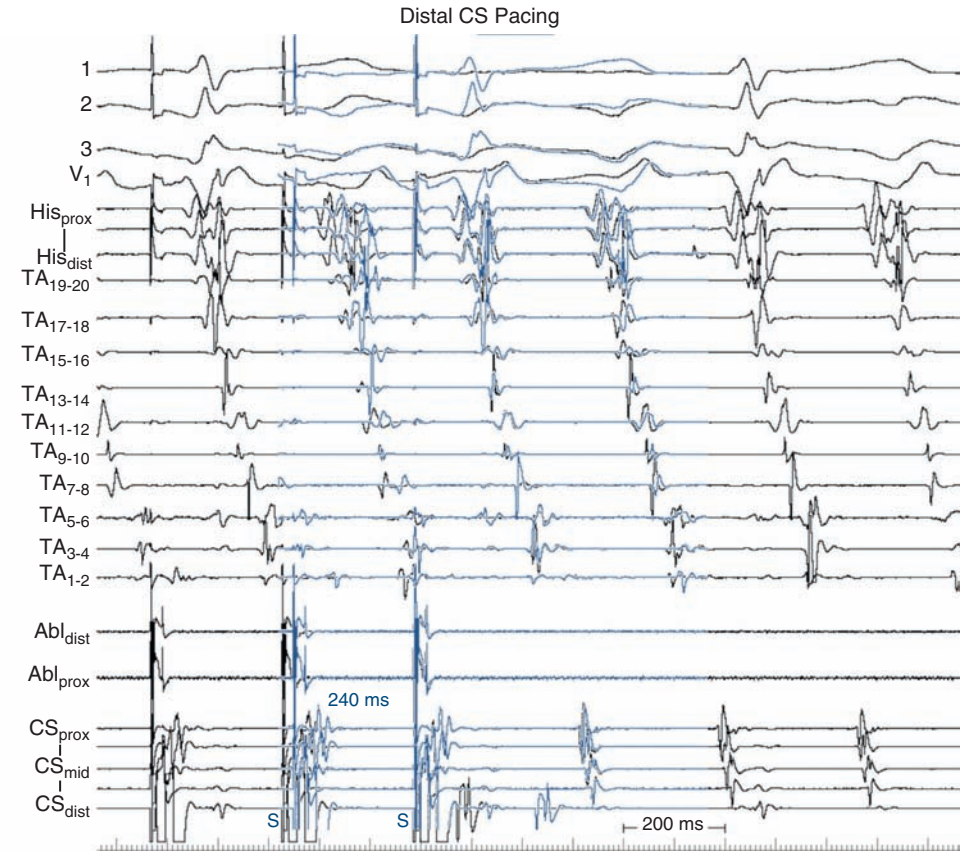


Figure 12-5C

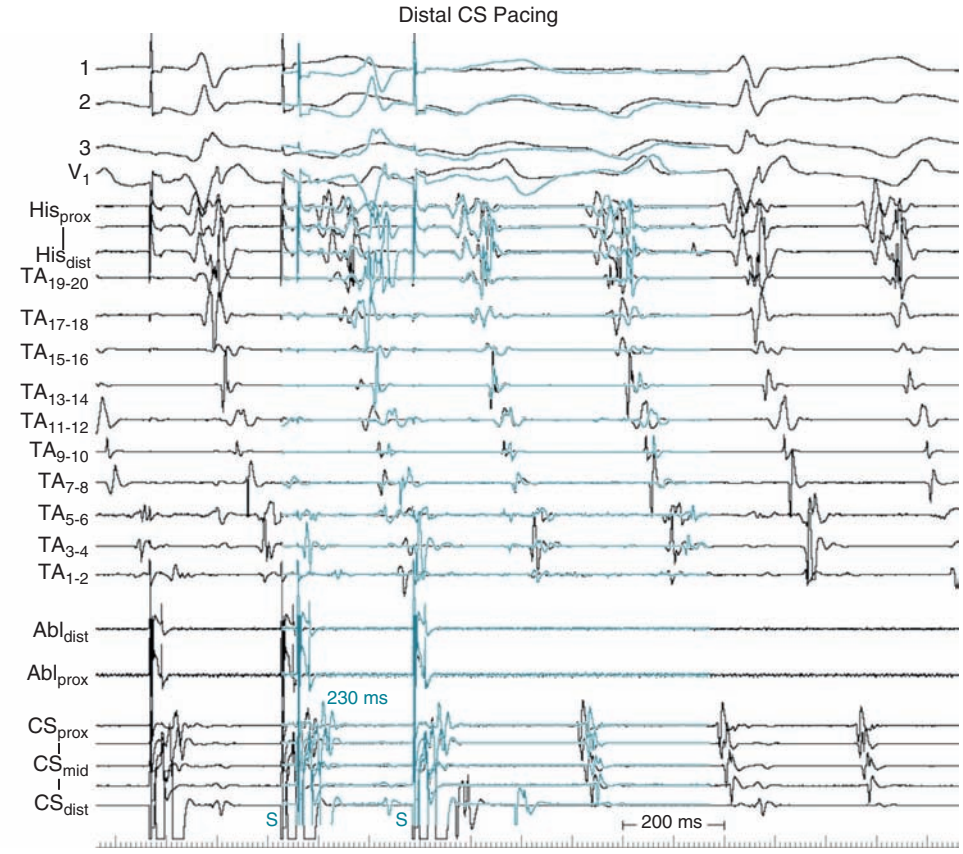


Figure 12-5D

Differential diagnosis:
- typical CCW flutter
- lower loop reentry
- intra-isthmus reentry

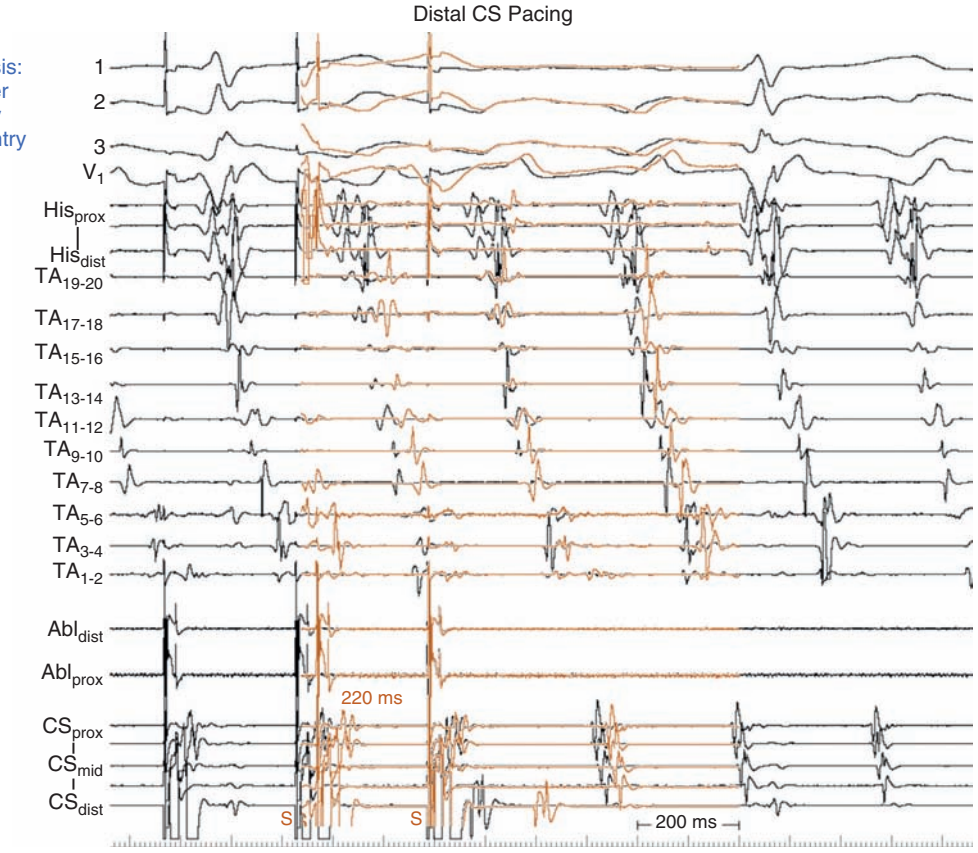
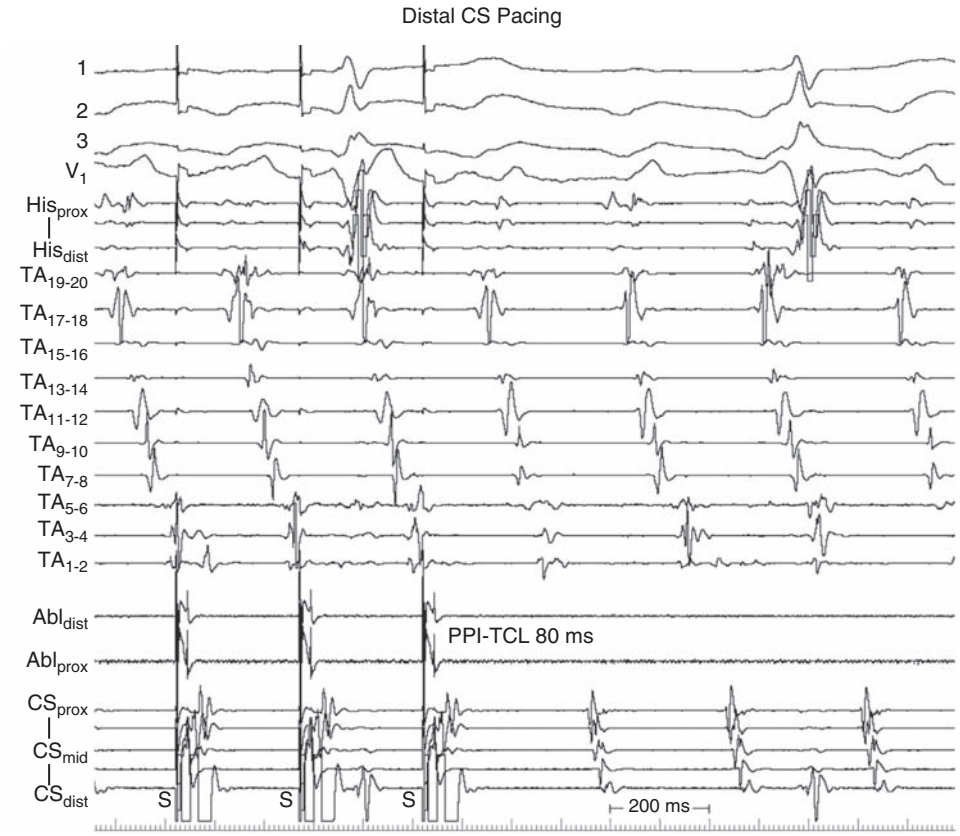


Figure 12-5E

Focal atrial tachycardias often exhibit overdrive suppression; that is, with faster paced rates during tachycardia, the first tachycardia complex after pacing stops will occur after progressively longer delays. In Fig. 12-5 A-E, overdrive pacing at increasingly faster rates (shorter cycle lengths as indicated in different color overlays on Fig. 12-5 B-E) shows no appreciable overdrive suppression. This response is most consistent with a circuit having a fixed path length. Thus a focal tachycardia near the CS ostium (or anywhere else) appears unlikely. Another possible diagnosis has been eliminated.



We Can Eliminate Focal AT Near CS os from Our Differential Diagnosis: [Fig. 12-5E and 12-10B]

A. Typical CCW flutter
B. Lower loop reentry
C. Intraisthmus reentry

Figure 12-6

In Fig. 12-6, pacing is again performed from the distal CS, to evaluate relative distance from the pacing site to a suspected circuit. The post-pacing interval (PPI) minus tachycardia cycle length (TCL) difference, 80 ms, suggests a significant distance from the distal CS pacing location to the circuit.

CS Proximal Pacing

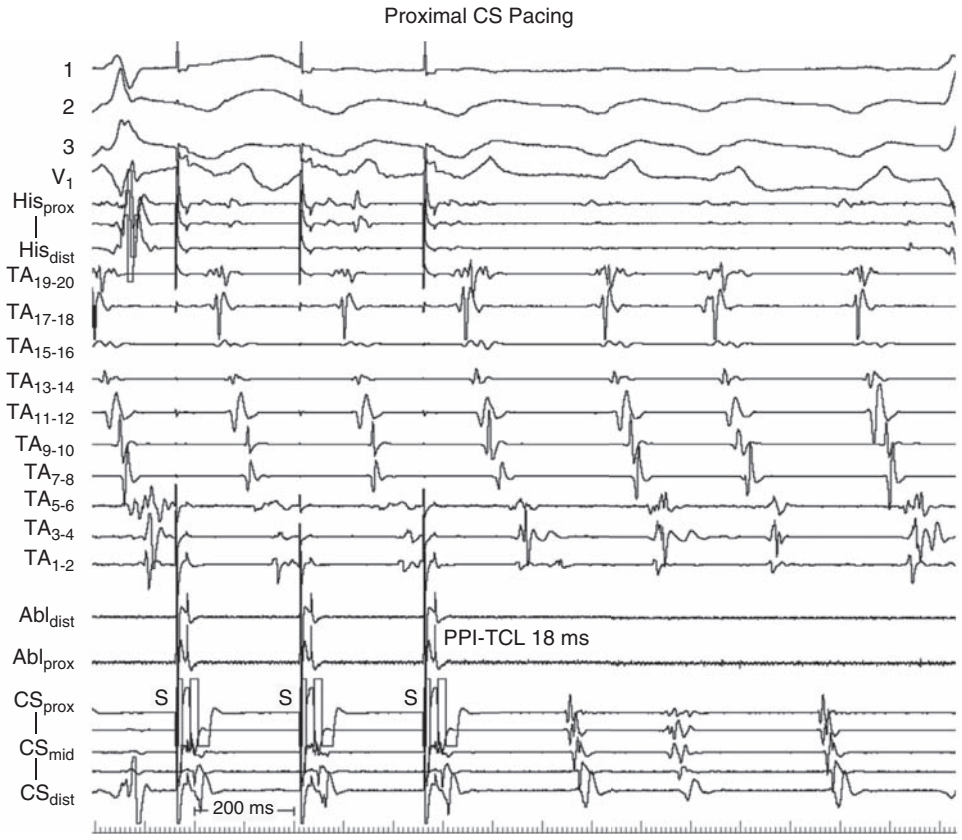
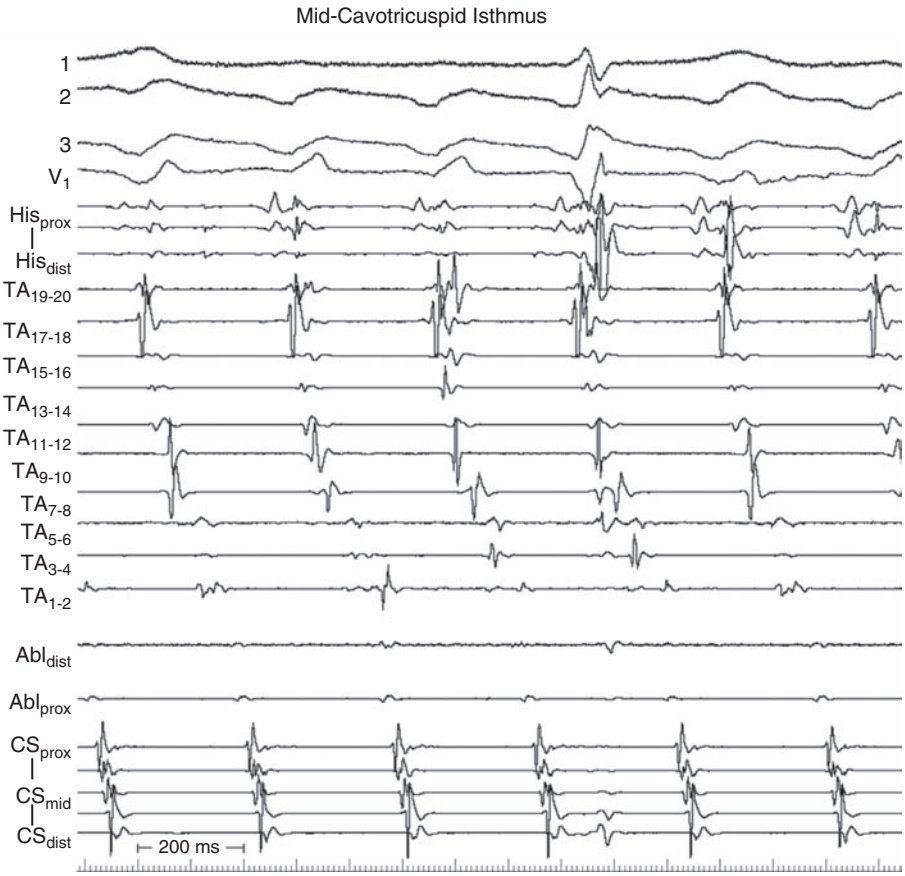


Figure 12-7

Pacing now from the proximal CS electrodes (Fig. 12-7) shows a PPI minus TCL difference of 18 ms, suggesting that it is close to or within the circuit. These electrodes are at the coronary sinus ostium. However, this does not distinguish among the three remaining possibilities—all of which are reentry, and all of which include the region of the CS os in the circuit.

Recording from CTI



Why Is There No Recording at the Abl_{dist} and Abl_{prox} Leads?

Figure 12-8

In the midcavotricuspid isthmus (Fig. 12-8), there are no remaining electrograms at standard recording gain (Abl recordings). This is anticipated because of the prior extensive ablation.

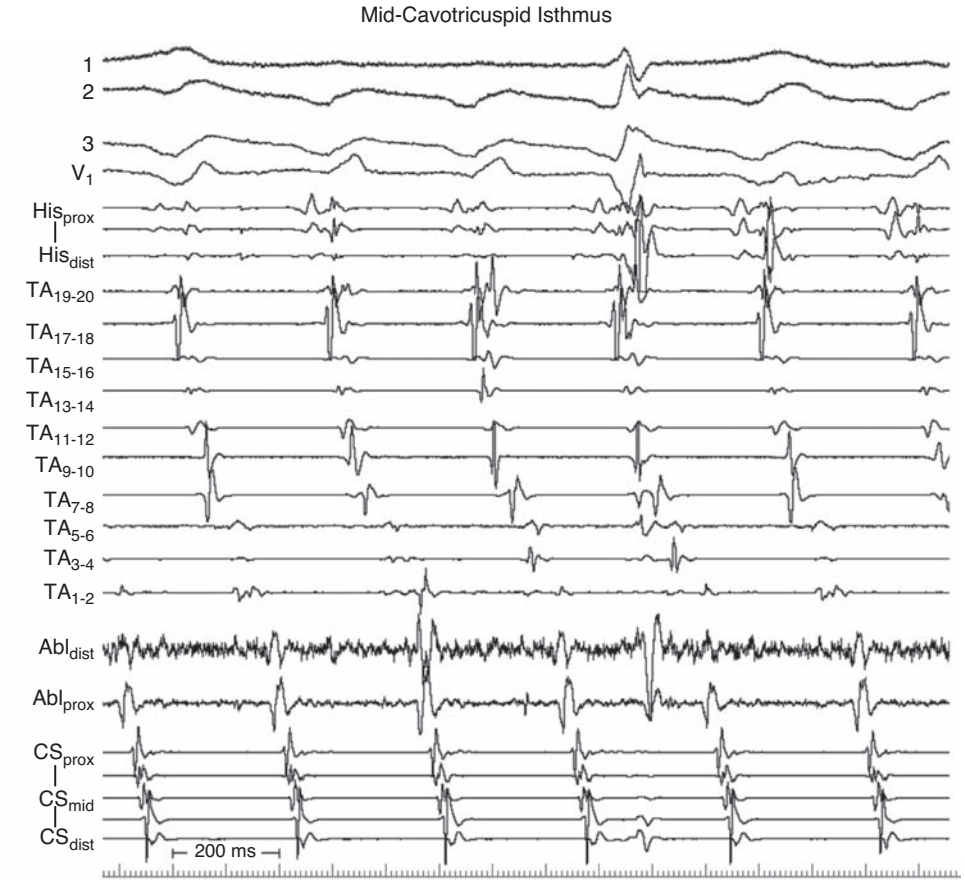


Figure 12-9

However, when the recordings are adequately gained (Fig. 12-9), it is evident that a small but discrete electrogram remains. Two of the three diagnostic possibilities use the cavotricuspid isthmus, but because one does not, it is important to clarify whether this tissue is part of the circuit or not.

Pacing from CTI

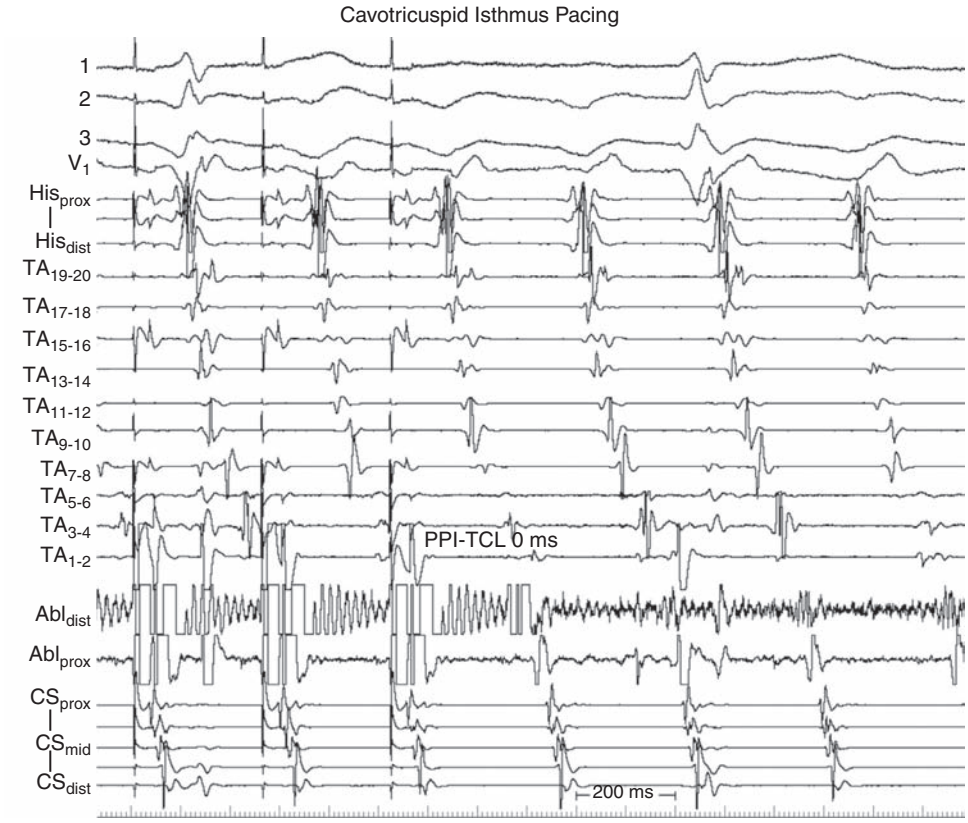


Figure 12-10A

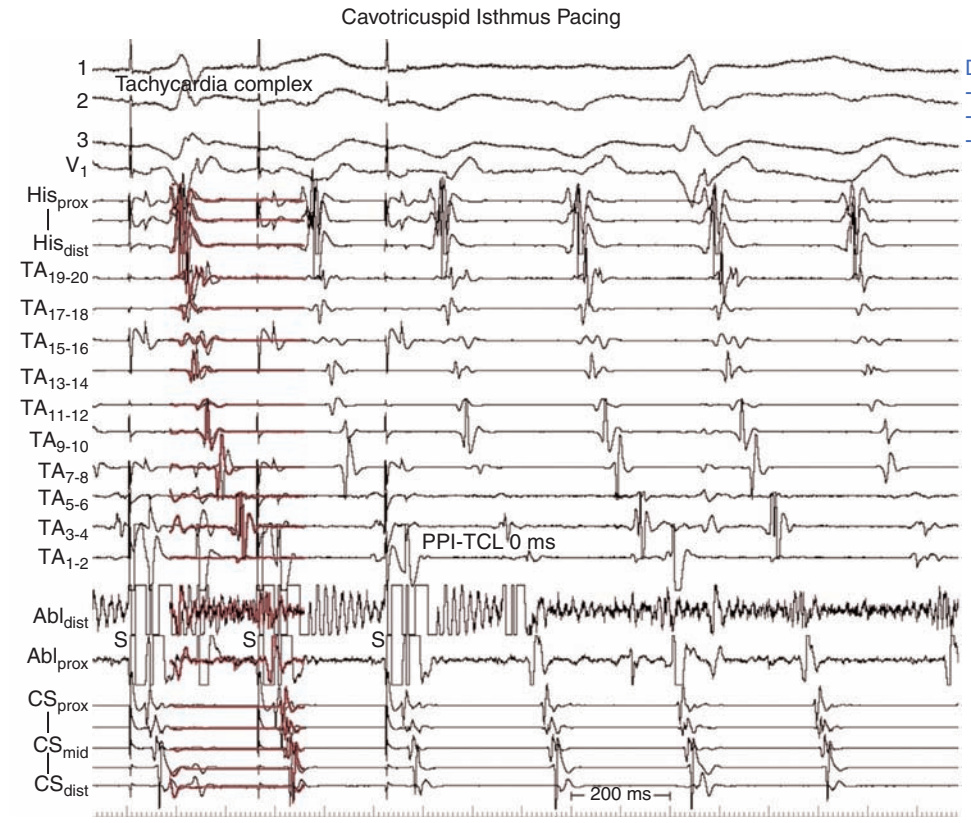


Figure 12-10B

Pacing from the cavotricuspid isthmus (Fig. 12-10A) produces a perfect match with the superimposed tachycardia complex (*red*, Fig. 12-10B) as well as the PPI minus TCL difference of zero, indicating that it is part of the circuit. However, this still does not establish a final diagnosis, because two of the remaining possible diagnoses include this tissue in their circuit.

Pacing from Lateral TA

Differential Diagnosis: [Fig. 12-11]

A. Typical CCW flutter

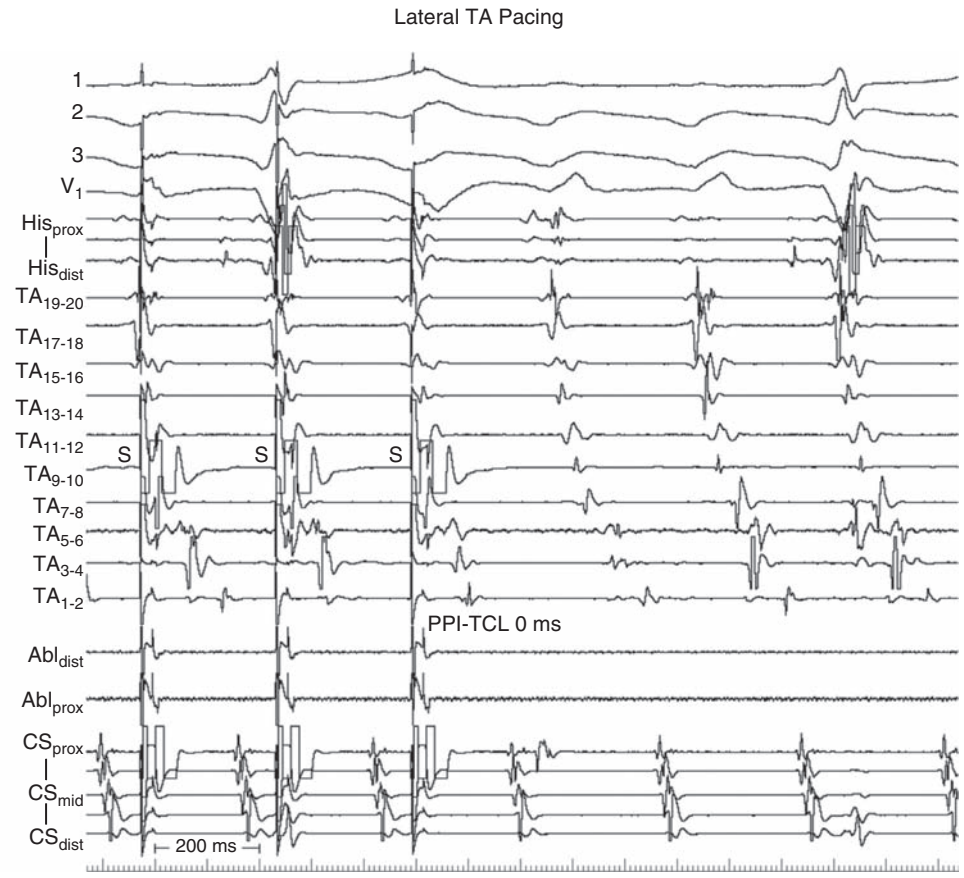


Figure 12-11

Pacing from the lateral tricuspid annulus as shown in Fig. 12-11 produces a PPI minus TCL difference of zero, indicating that it is part of the tachycardia circuit. Of the remaining diagnostic possibilities, only typical counterclockwise flutter incorporates the lateral tricuspid annulus in the circuit. Thus two more diagnostic possibilities have been eliminated and a definitive diagnosis has finally been established. Of note, macroreentry is established with certainty with this pacing maneuver because the stimulus artifact occurs after the onset of an accelerated flutter wave on the surface ECG and the activation pattern with pacing is unlike what would be expected with pure pacing from the lateral tricuspid annulus—signifying fusion, and diagnosing macroreentry. Ablation in the cavotricuspid isthmus at remaining surviving tissue can commence.

Electroanatomic Mapping

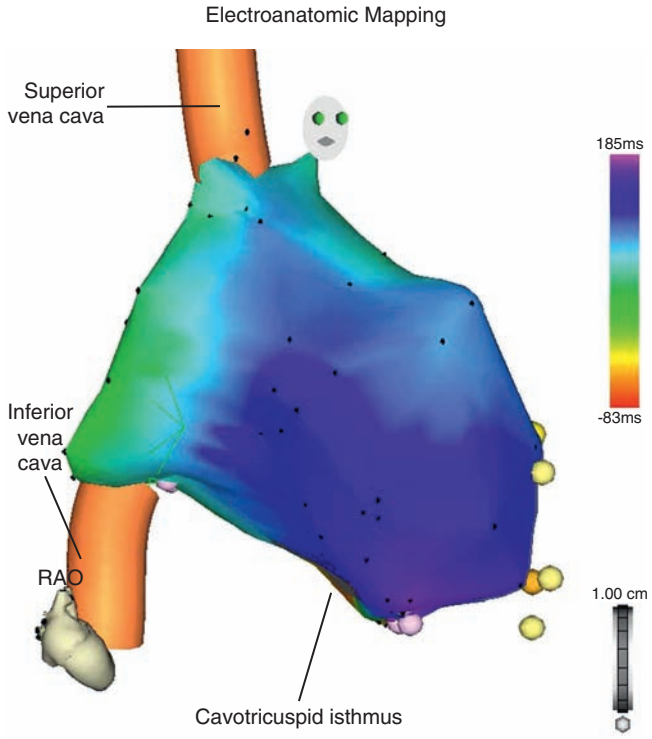


Figure 12-12

In Fig. 12-12, the electroanatomic map of this flutter in the right anterior oblique view is shown; not much useful information can be gathered from this alone.

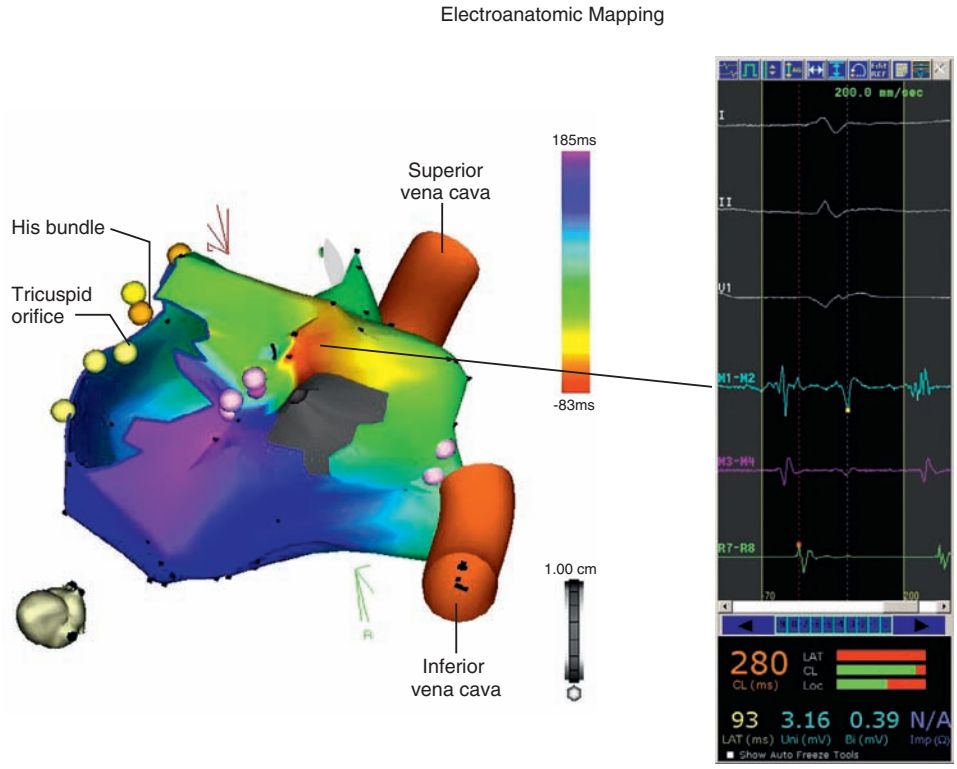


Figure 12-13

In this view from the bottom of the right atrium (Fig. 12-13), the electroanatomic map seems to suggest focal propagation from around the CS os region; the electrogram at the site of earliest activation is shown at right. Unfortunately, the electroanatomic mapping system automatically selected a point on the *ventricular* electrogram as the time of local activation.

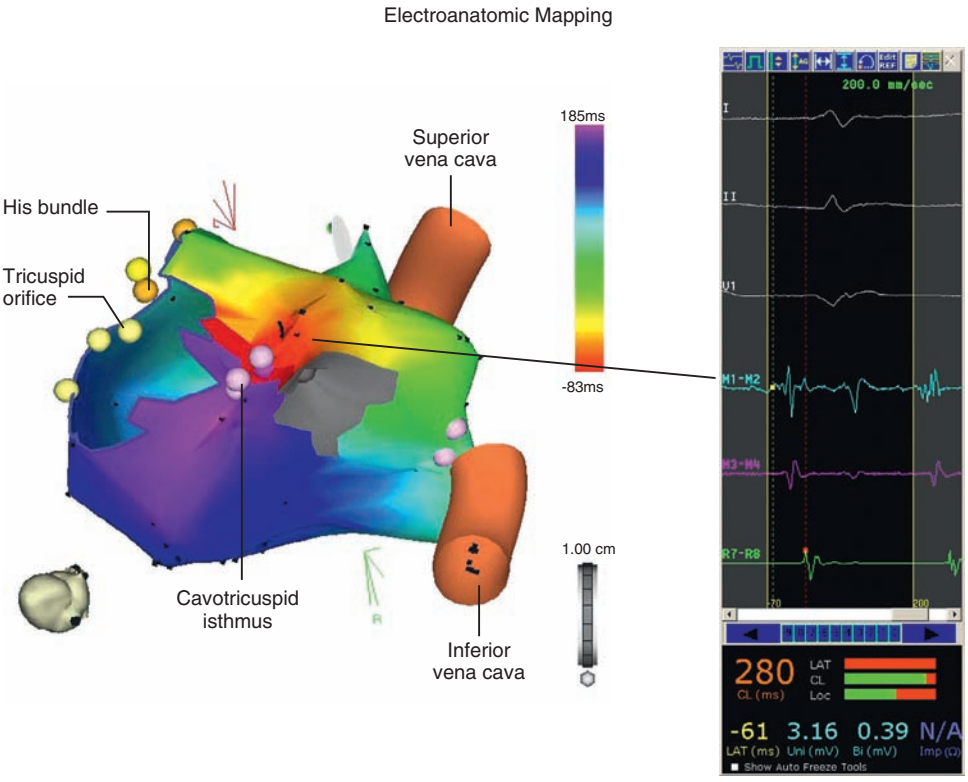


Figure 12-14

In Fig. 12-14, the same map is shown, however with the atrial electrogram correctly annotated to represent local activation. Now, the appearance of a circuit in a counterclockwise fashion around the tricuspid annulus is evident (colors of red-orange-yellow-green-blue-purple).

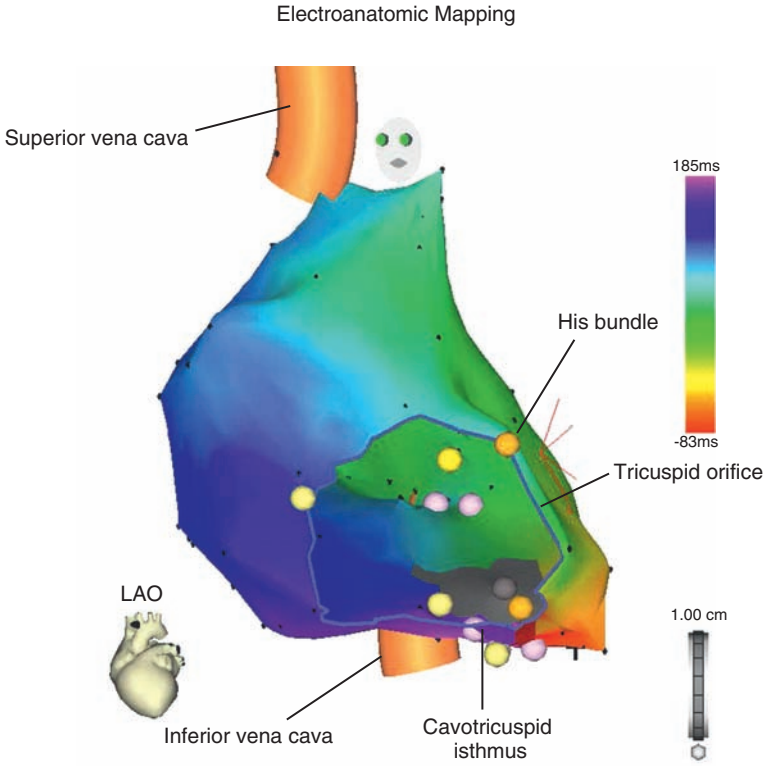


Figure 12-15

A left anterior oblique view (Fig. 12-15), looking at the tricuspid orifice, shows the propagation around the tricuspid annulus in counterclockwise direction.

Ablation

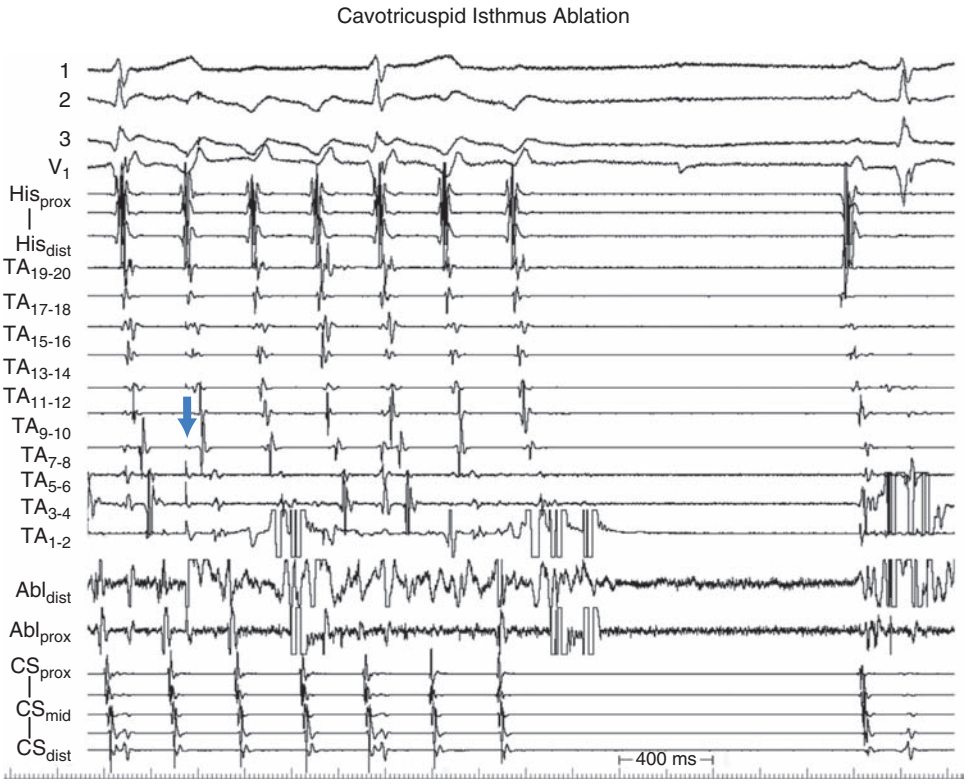


Figure 12-16

The first application of RF energy (onset at *blue arrow*, Fig. 12-16) on the cavotricuspid isthmus at the electrogram shown earlier in Fig. 12-9 results in termination of flutter to sinus rhythm. This corresponded to TA 1-2.

Assessment of Bidirectional Block

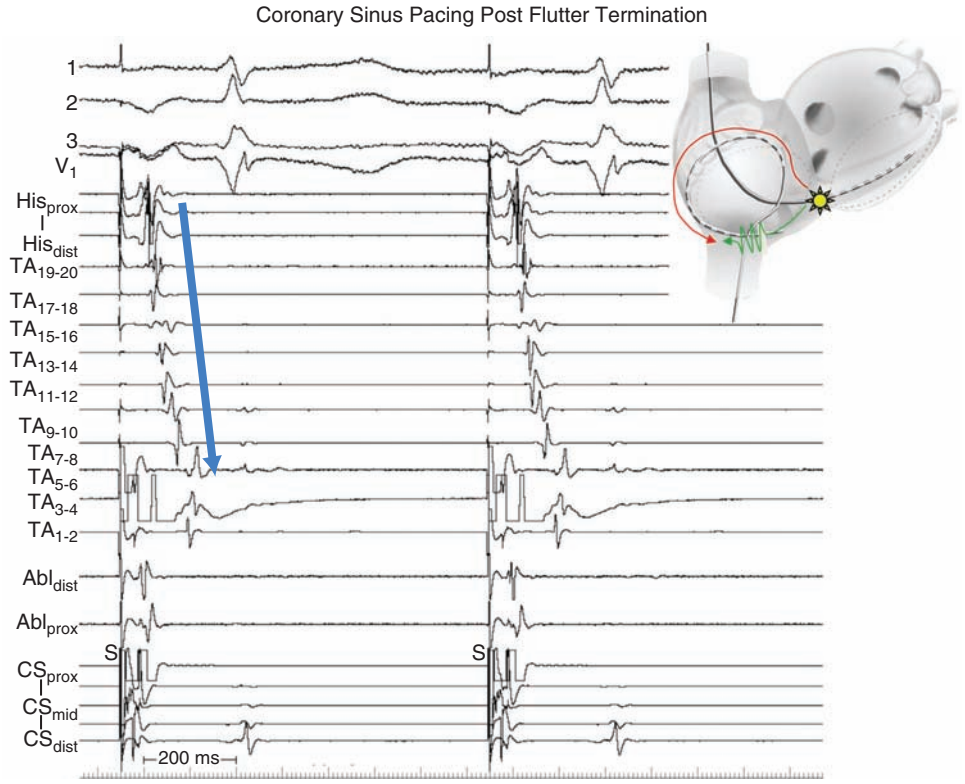


Figure 12-17

In Fig. 12-17, pacing from the CS after flutter termination shows propagation along the tricuspid annulus *(red arrow)* from *top* (TA 19-20) toward the *bottom* (TA 1-2); however, when the wavefront arrives at TA 5-6, it appears to meet a wavefront from the opposite direction (from TA 1-2, *green arrow*). Thus there is still some element of conduction across the isthmus (see diagram at *top*).

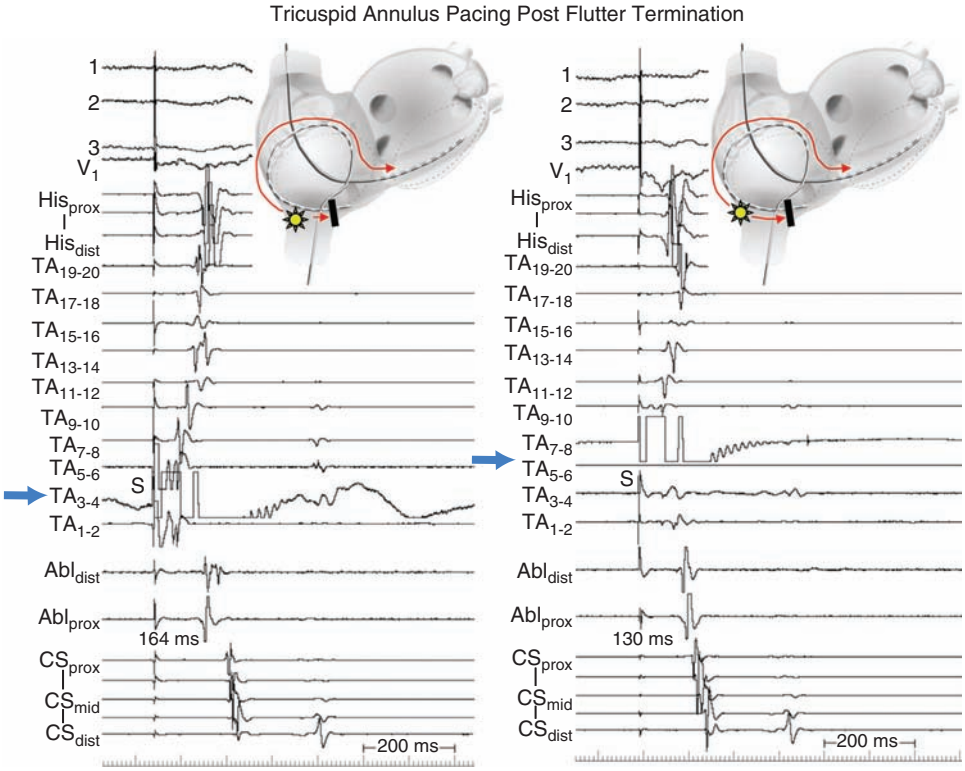


Figure 12-18

Additional ablation was performed at the isthmus (Fig. 12-18). Thereafter, pacing from the indicated electrodes of the halo catheter, lateral to the ablation line, shows a longer interval from stimulus to CS electrodes when pacing from a site closer to the ablation line than when pacing from a site further from the line (see diagrams at top). Though anatomically closer to the CS than TA 5-6 electrodes, the TA 3-4 pacing site is electrically further away. Thus block in the lateral-medial direction is present.

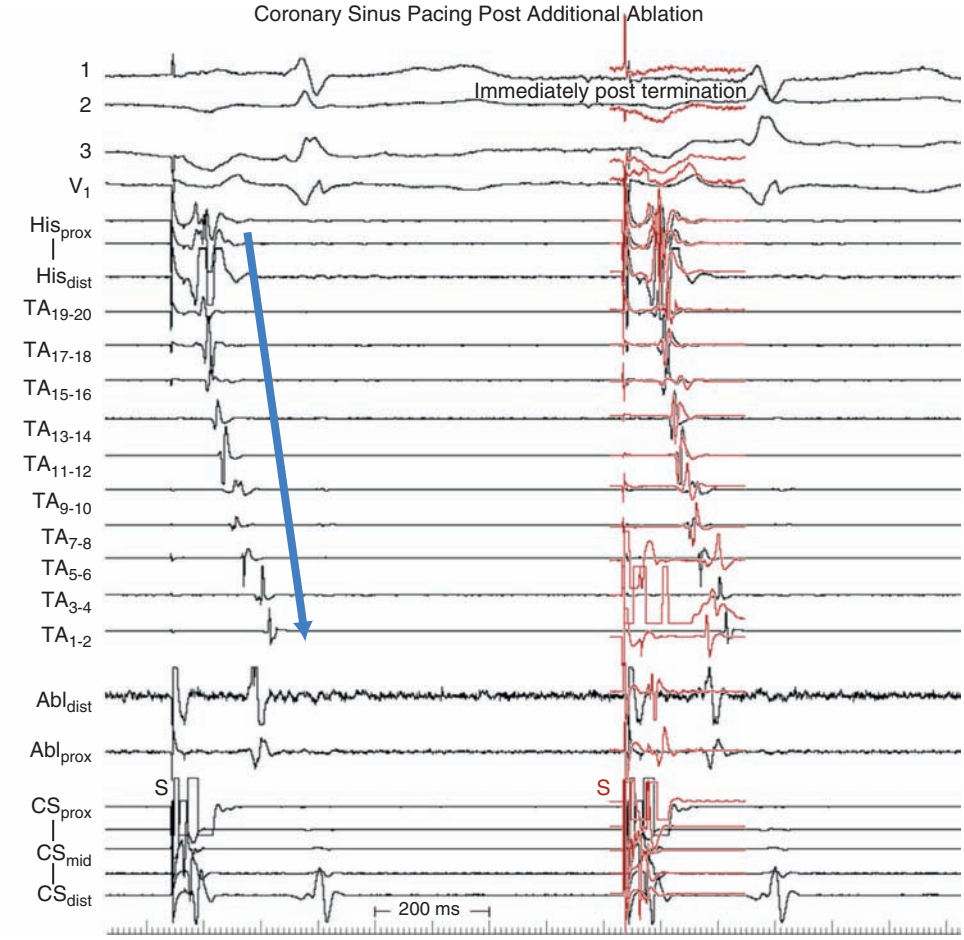


Figure 12-19

After the additional ablation at the isthmus (Fig. 12-19), conduction along the halo catheter is in a straight line (no longer a "chevron"). The activation pattern from immediately after flutter termination is superimposed in *red* (Fig. 12-19) to highlight the difference in activation of atrial electrograms in electrodes TA 1-2 and TA 3-4 in the two settings.

Final ECG

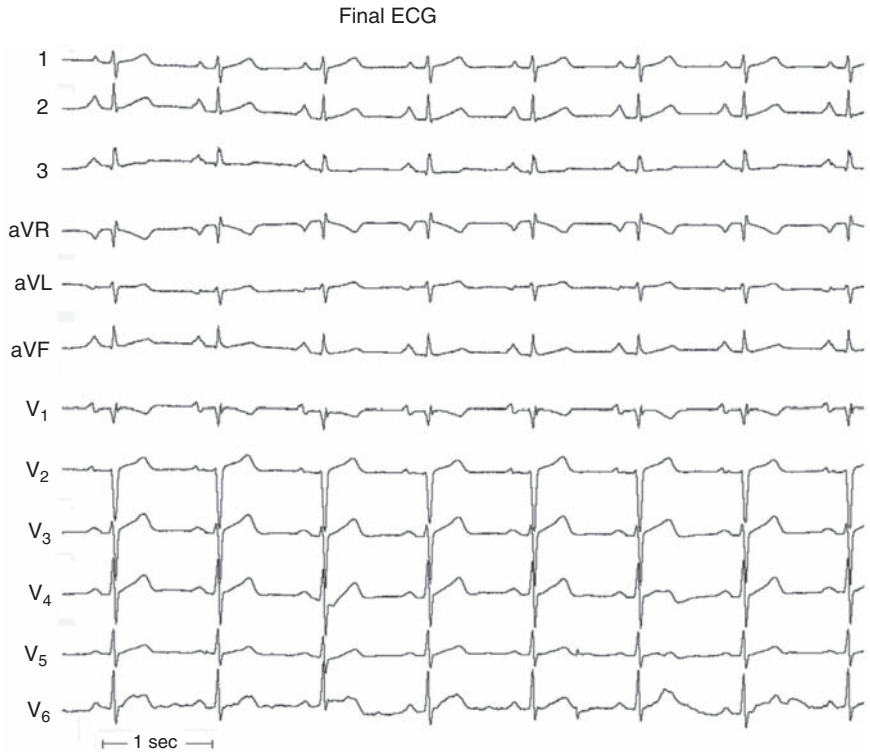


Figure 12-20

At the end of the procedure, sinus rhythm is present (Fig. 12-20), cavotricuspid isthmus block persisted throughout the waiting period and flutter could not be initiated. The procedure took 2 hr, most of which was diagnostic time.

Summary

With recurrent atrial flutter postablation

- Plan for anything (consents, setup, available equipment)
- Prove the nature of the arrhythmia before ablating
- Plan the ablation strategy before ablating (new line, targeting areas of fragmented electrograms, high residual voltage, etc.)
- Terminating flutter during ablation is not an adequate endpoint
- Bidirectional block can be difficult to demonstrate (vs slowing of conduction)
- Electroanatomic mapping is very helpful but
  - Does not make a diagnosis
  - Can be extremely misleading with even one point incorrectly annotated

Atrial Reentry After Valve Surgery

13

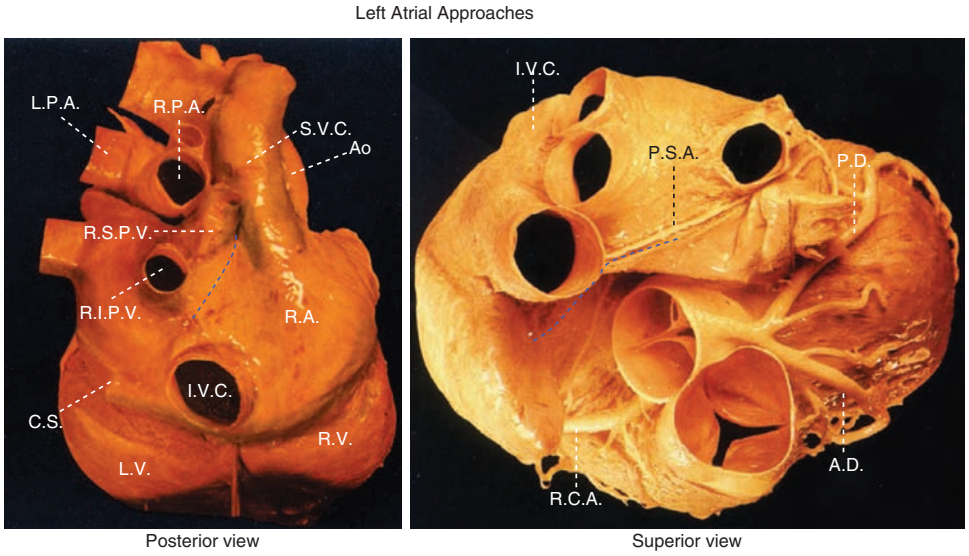
Case Presentation

The patient is a 41-year-old woman with rheumatic mitral valve disease. Mitral valve repair was attempted but required replacement in 3/2010, re-replacement was performed in 4/2010 because of dehiscence of valve, and another re-replacement was done in 6/2010 as a result of perivalvular leak. Then she had perioperative atrial fibrillation, and recurrent regular atrial tachycardias were terminated with adenosine injection. Cavotricuspid isthmus (CTI) ablation was performed in 1/2011; in that procedure, flutter terminated during CTI radiofrequency (RF) delivery; bidirectional conduction block was effected across the CTI, and no other arrhythmias were induced. She was referred for ablation because of recurrent episodes of supraventricular tachycardia (SVT) at 145/min. Echocardiographic findings were as follows: LA 4.1 cm, enlarged RA, moderate TR, and normal LV function; estimated right ventricular systolic pressure 30 mm Hg; and normally functioning mechanical mitral valve. Operative reports were as follows: #1 and #2, Waterston's groove left atrium (LA) access; #3, LA dome incised through top of septum to right atrium (RA). There was no mention of atrial septal patching. EP report was as stated previously, and ECG was recorded during SVT.

Approaches to Mitral Surgery

Figure 13-1

(Adapted from McAlpine, WA. *The Heart and Coronary Arteries,* Springer-Verlag, New York, 1975 with permission of Kalyanam Shivkumar, MD, UCLA.)

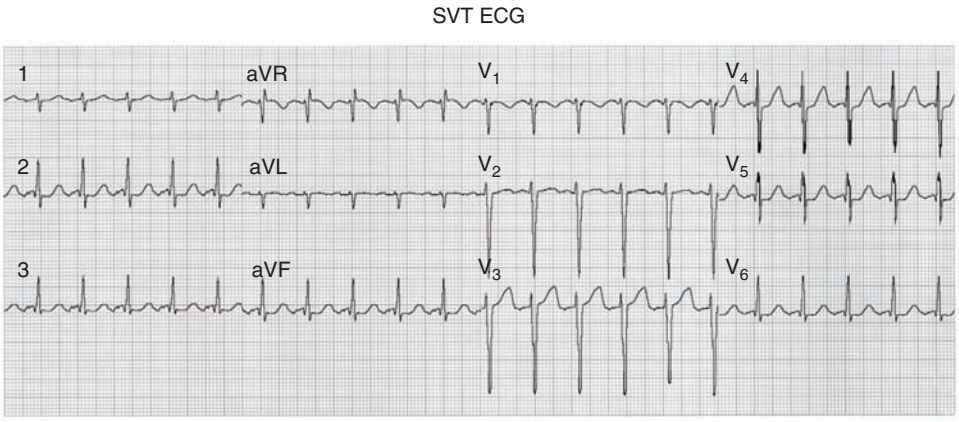


At left of Fig. 13-1, the heart is viewed from behind. A standard mitral approach incision is through Waterston's groove, just on the left atrial side of the interatrial septum *(dashed blue line)*. This rarely results in macroreentrant arrhythmias. At right, another approach (especially for repeat procedures) is through the atrial roofs; the incision *(dashed blue line)* goes through both atria roughly along Bachmann's bundle, anterior to the superior vena cava and pulmonary veins. *AD*, left anterior descending coronary artery; *Ao*, aorta; *CS*, coronary sinus; *IVC*, inferior vena cava; *LPA*, left pulmonary artery; *LV*, left ventricle; *PD*, posterior descending coronary artery; *PSA*, posterior sinus node artery; *RA*, right atrium; *RCA*, right coronary artery; *RIPV*, right inferior pulmonary vein; *RPA*, right pulmonary artery; *RSPV*, right superior pulmonary vein; *RV*, right ventricle; *SVC*, superior vena cava.

Prior SVT ECG

Any Clues as to SVT Diagnosis? [Fig. 13-2]

Figure 13-2



In the "long RP" SVT shown in Fig. 13-2, it looks like there is only 1 P wave per QRS, and that is inverted in the inferior leads and positive in aVL; thus a first approximation would be that this indicates a low right atrial focus or exit from a circuit.

Baseline ECG and Intracardiac Recordings

Any Clues as to SVT Diagnosis? [Fig. 13-3]

Figure 13-3

The sinus rhythm P wave in Fig. 13-3 is remarkably close to normal despite the history of extensive atrial surgery. In scar-based macroreentry, the P wave in sinus rhythm is often very prolonged and fragmented (more so than is seen here).

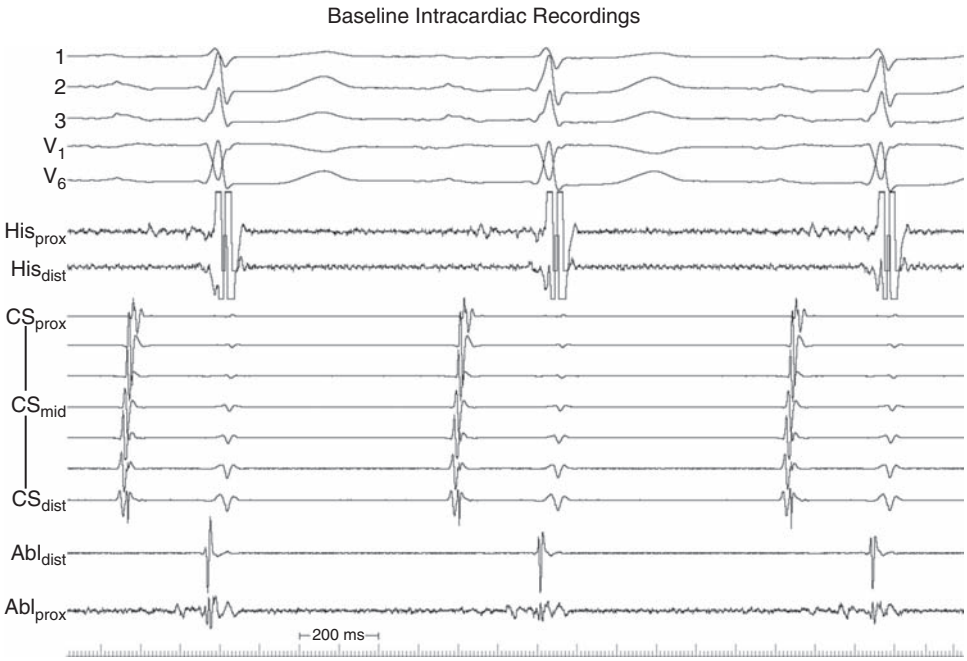


Figure 13-4

Consistent with the relatively normal surface ECG appearance of the P wave, intracardiac activation also appears relatively normal in Fig. 13-4 without much hint of scar that could result in slow conduction, a constituent of macroreentry.

Figure 13-5

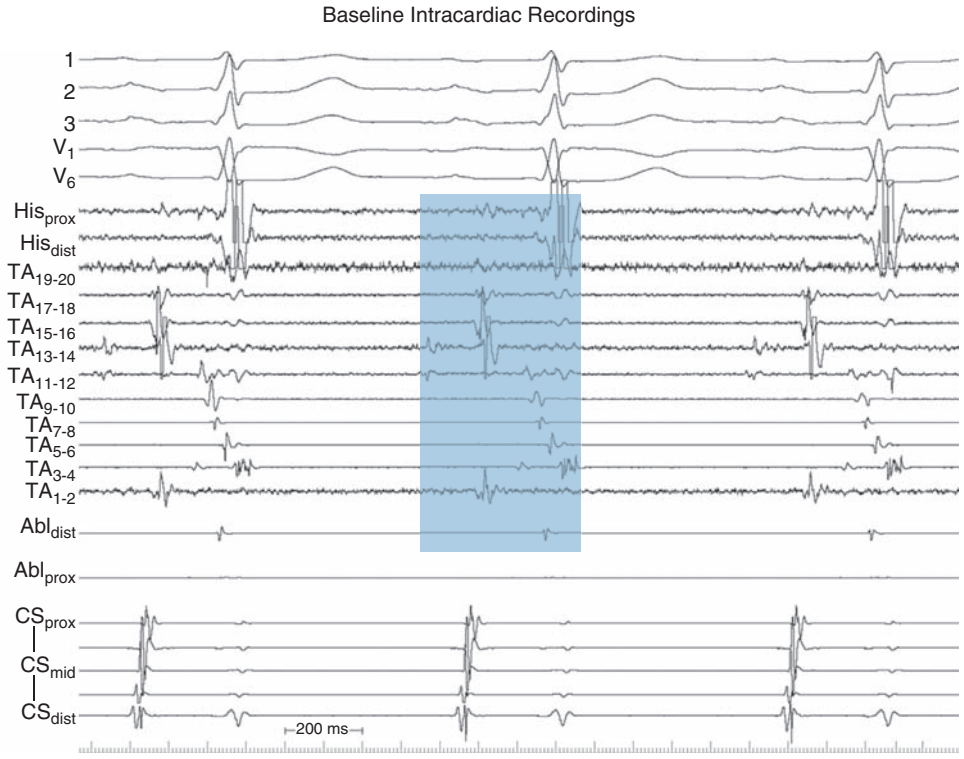


Fig. 13-5 shows the same events as in Fig. 13-4, but with another multielectrode catheter in the right atrium. Now that there are more extensive recordings from the right atrium (RA), dramatically disordered conduction is revealed (duration of RA activation shown in *shaded box* [430 ms]). All of the recordings in the tricuspid annular (TA) catheter are from atrium, despite some of them timing with the QRS complex. With this degree of slow conduction, macroreentry is a real possibility.

Catheter Induction of SVT and ECG and Intracardiac Recordings

Focal or Macroreentry? [Fig. 13-6]

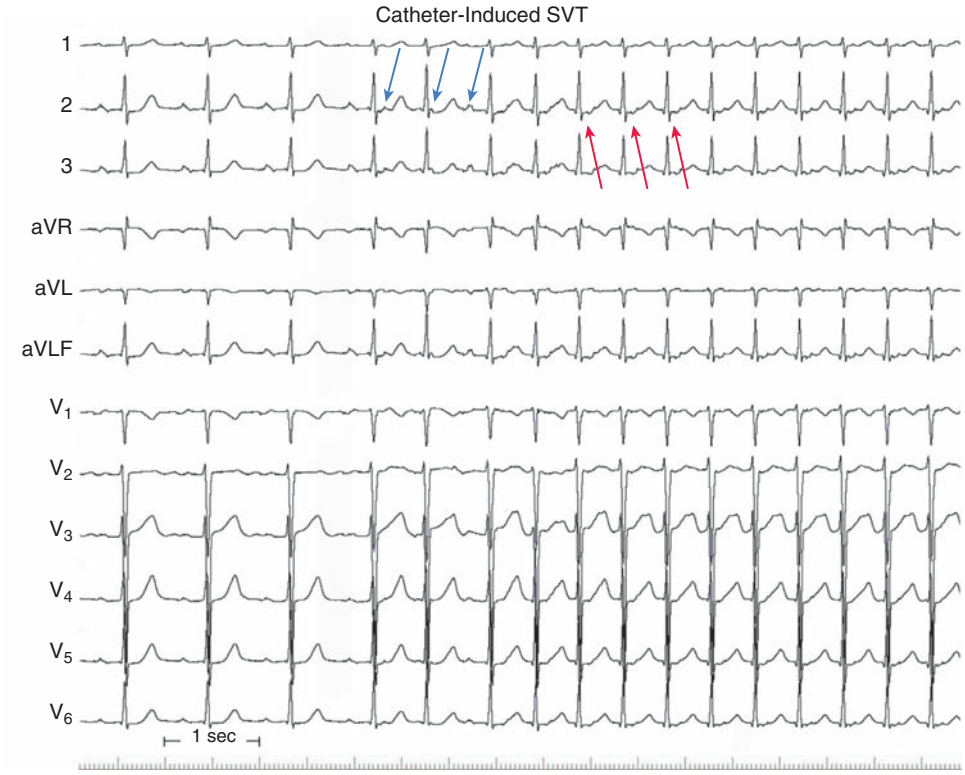


Figure 13-6

Central to achieving a successful ablation outcome is the determination of what the target site of ablation should look like—for focal tachycardias, it is a potential just 30 to 40 ms before the P wave onset, whereas for macroreentry, a middiastolic potential is generally sought. Because the ablation target is very different depending on mechanism, it is important to delineate mechanism (focal vs macroreentry) relatively early in the procedure. A clue to mechanism can sometime be found in how an episode starts (Fig. 13-6); here one or several premature atrial complexes *(blue arrows)*, positive in the inferior leads, seem to start SVT that has inverted P waves in inferior leads *(red arrows)*. A focal tachycardia typically has the same P-wave configuration throughout, whereas in reentrant tachycardias, the initiating P wave is often different from those during tachycardia.

Focal or Macroreentry? [Fig. 13-7]

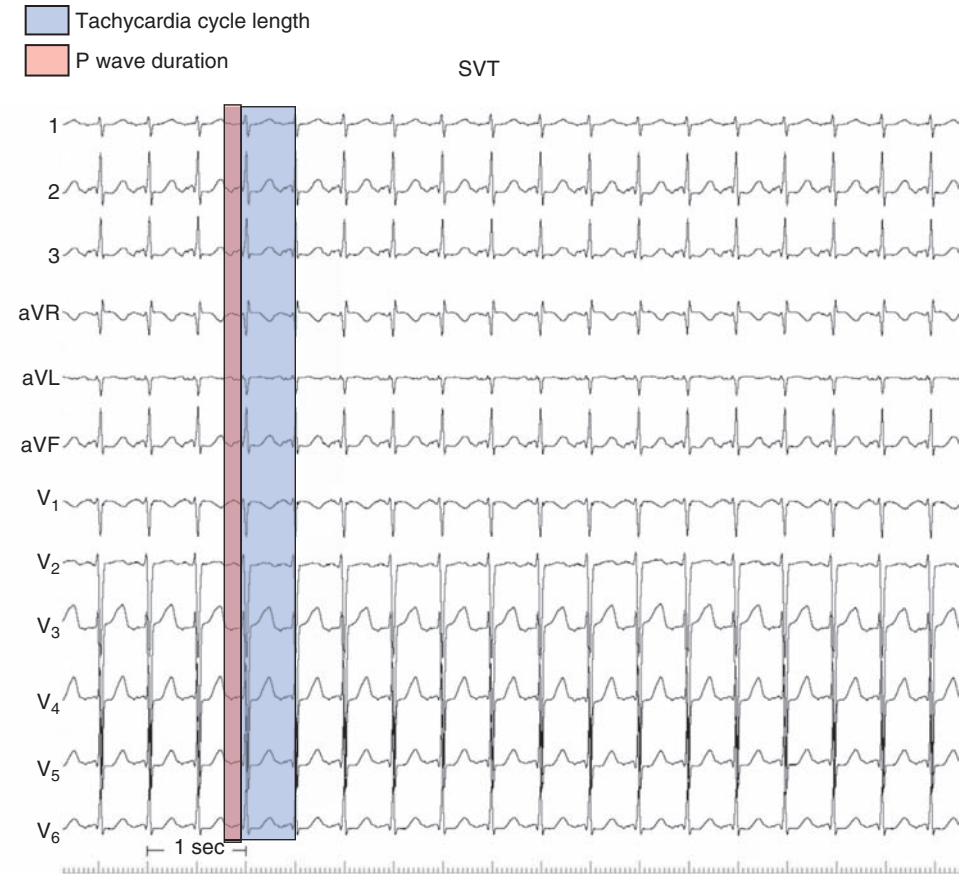


Figure 13-7

A useful principle for distinguishing a focal process from macroreentry is that, in macroreentry, some of the atrium is always being activated throughout the tachycardia cycle length (TCL) and slow conduction is present (required for tachycardia to continue); this leads to a relatively large portion of the cycle length being occupied by P wave. In focal tachycardias, slow conduction is not needed, and once the focus fires, the atria are depolarized relatively quickly, leading to a P wave that takes up a small portion of the tachycardia cycle length. In Fig. 13-7, it appears that the P wave *(red shading)* is pretty narrow compared to cycle length (*blue shading*, that includes *red shading*). This suggests focality.

Focal or Macroreentry?

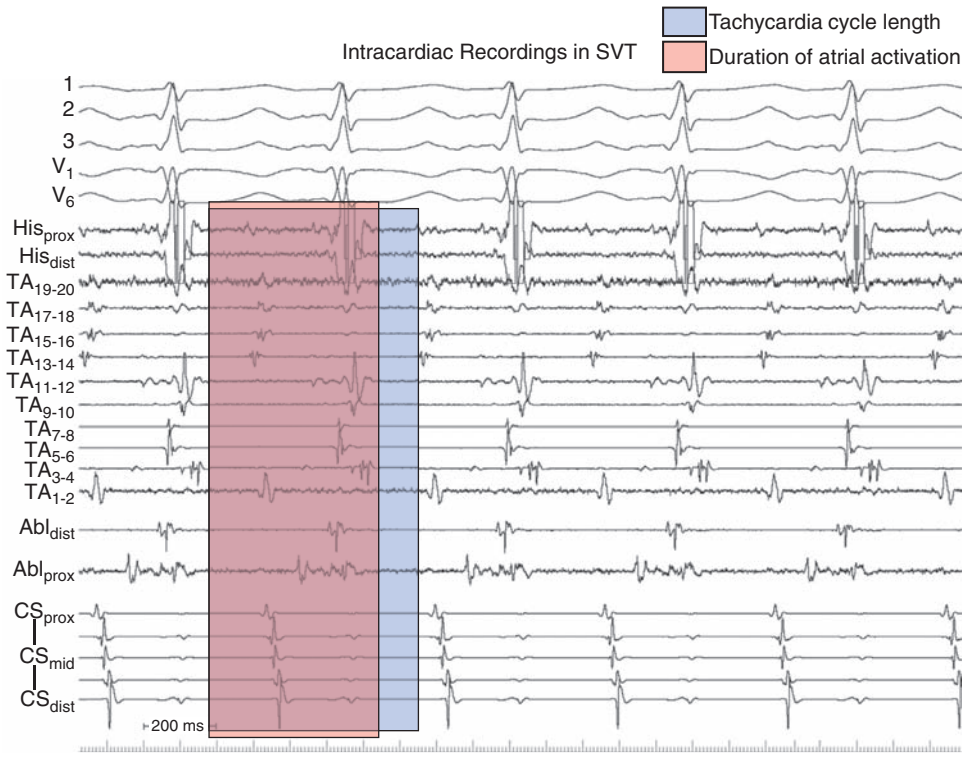


Figure 13-8

With the aid of intracardiac recordings, it becomes clear that atrial activation *(red shading)* takes up much of the TCL (*blue shading*, encompassing *red shading*; Fig. 13-8), now suggesting macroreentry. Specifically, most of the TCL is accounted for in *right atrial* recordings.

Clarifying P-Wave Onset During SVT with Ventricular Pacing

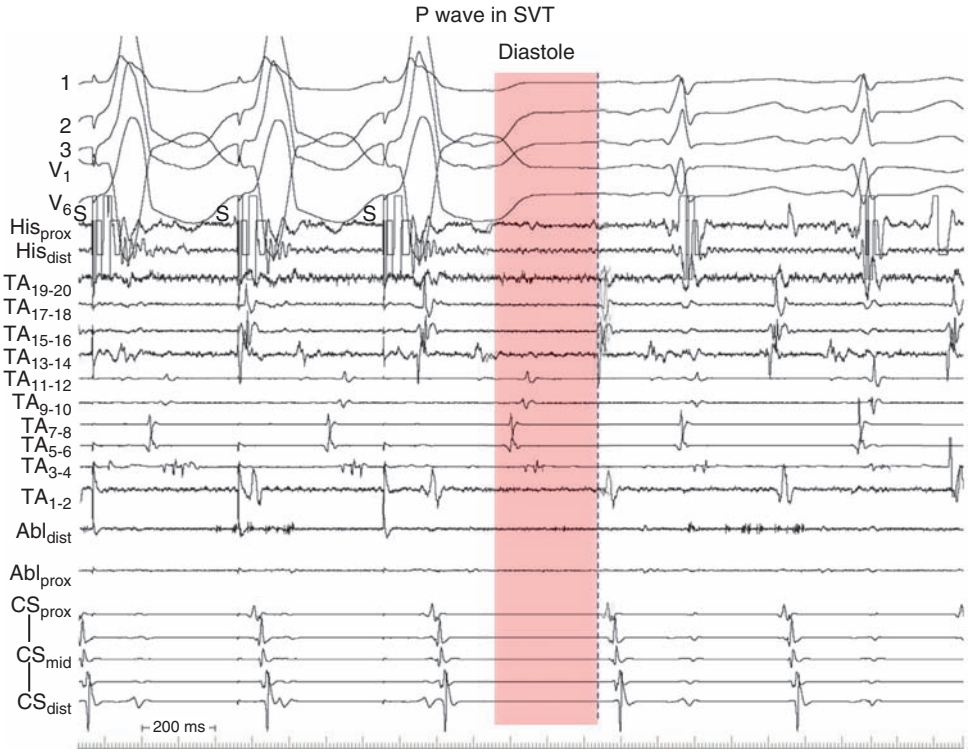


Figure 13-9

Clarifying the limits of the P wave during SVT helps in mapping, so that the onset of the P wave is clear. However, it may not be evident during ongoing SVT and thus some tricks are needed to reveal a partially obscured P-wave onset, such as introduction of premature ventricular complexes (PVCs) or ventricular pacing during tachycardia. The resulting long diastolic period should provide a P wave standing by itself (Fig. 13-9), allowing clear determination of its onset (as well as end of the prior P wave, for designating window of interest with electroanatomic mapping systems). Atrial diastole (end of 1 P wave to beginning of next P wave) is shown in *red shading*.

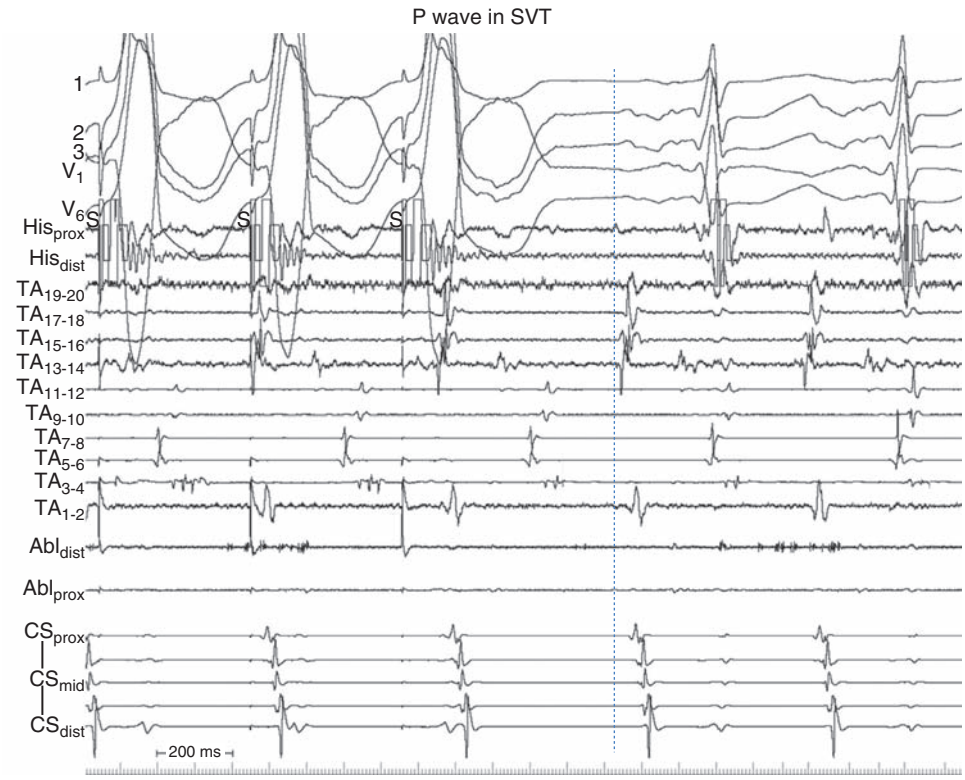


Figure 13-10

Surface ECG leads are shown in Fig. 13-10 with increased gain to better determine P-wave onset *(dashed line)* and morphology. This also shows VA block during SVT, excluding orthodromic SVT as well as almost all cases of AV nodal reentry. The setting (scarred atrium) is perfect for atrial tachycardia.

Overdrive Pacing During SVT

From Distal and Proximal Coronary Sinus

Focal or Macroreentry?

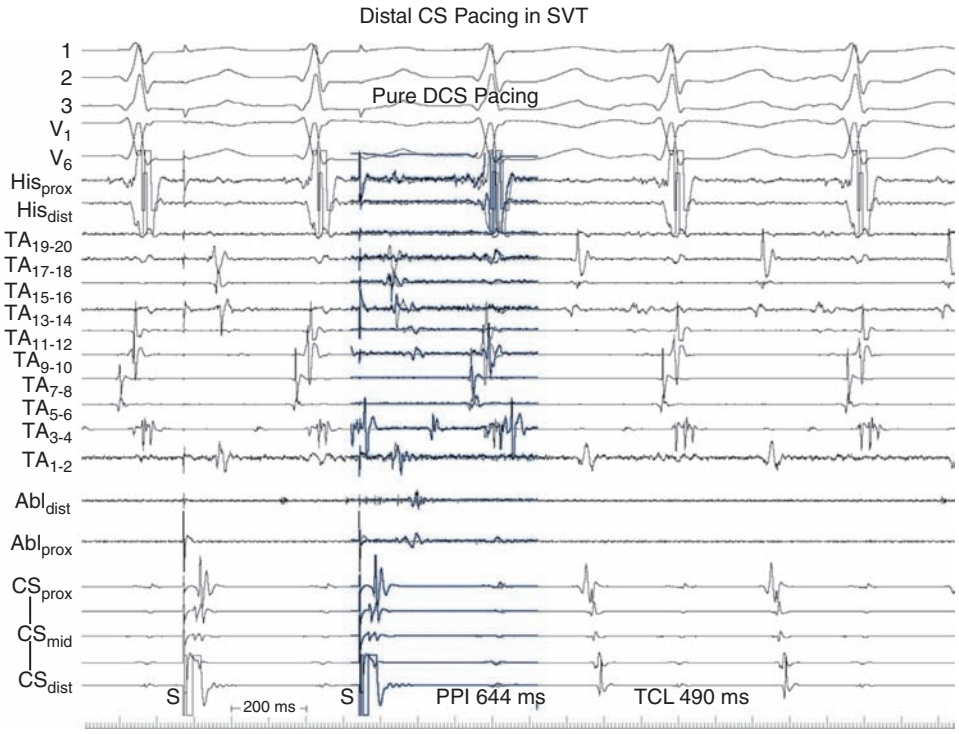


Figure 13-11

To answer the important question of focal versus macroreentry as tachycardia mechanism, overdrive pacing from distal CS—activated late during SVT—is performed, showing a paced sequence during SVT that is a little different from pure CS pacing earlier in the procedure (superimposed in blue) as well as different from SVT (Fig. 13-11). However, the differences are not striking and it is difficult to be definitive that fusion is present. Note also that whatever the mechanism, the distal CS is far from either the focus or exit from a circuit (post-pacing interval [PPI] − TCL = 154).

Focal or Macroreentry?

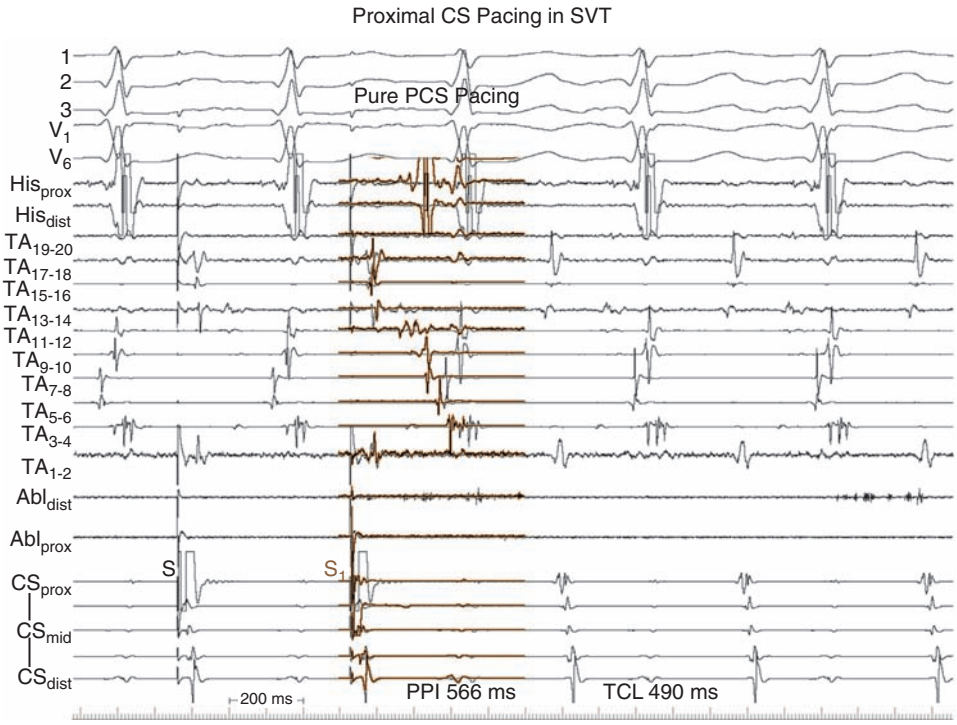
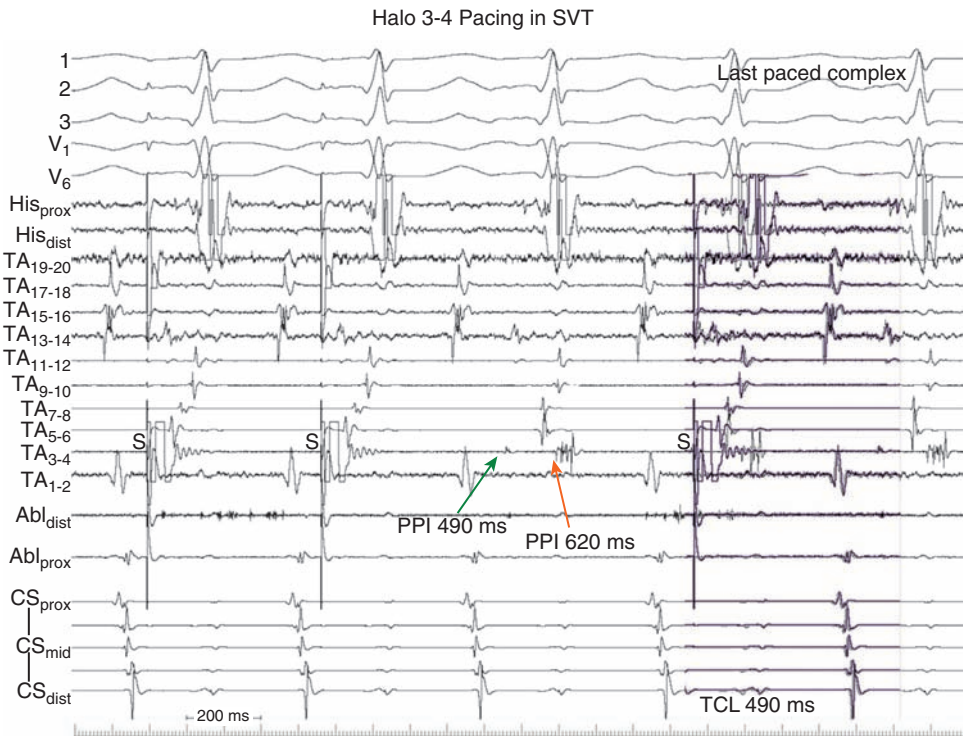


Figure 13-12

Because overdrive pacing from distal CS was equivocal, we should try pacing from a different site, such as the proximal CS. Fig. 13-12 clearly shows a sequence during pacing in SVT that is very different from pure CS pacing earlier in the procedure (superimposed in *orange*), as well as different from SVT. Thus fusion has been demonstrated and macroreentry is diagnosed. The proximal CS pacing site is, like the distal site on the last slide, remote from the circuit but not as far away as the distal CS was (smaller PPI-TCL difference).

From Different Halo Catheter Sites

Figure 13-13



Pacing from a portion of the TA catheter (Fig. 13-13) shows a paced sequence (superimposed in *purple* on a tachycardia complex) that is nearly identical to that during tachycardia (thus almost concealed fusion). The postpacing interval is problematic because the natural place to measure (largest recording) yields a very long PPI (620 ms); however, although that portion is captured, so is the small potential before it, with a PPI identical to TCL. This should be within the circuit; the lack of concealed fusion is likely because of excessive current used in pacing, which captures more than the intended tissue.

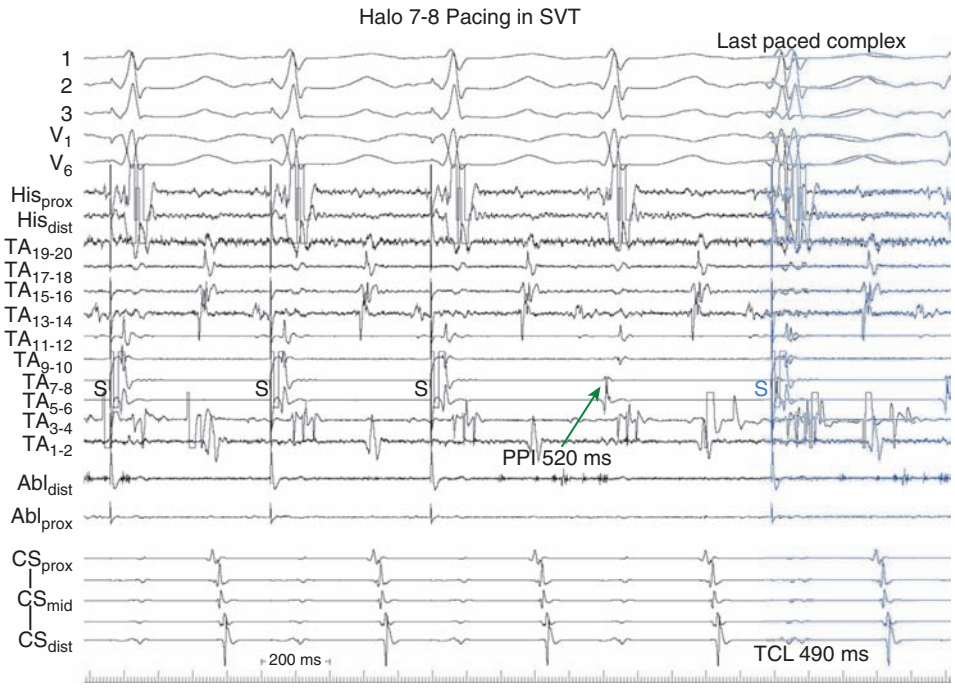


Figure 13-14

Pacing a couple of electrodes away on the TA catheter (Fig. 13-14) shows a less perfect pace match (sequence superimposed on tachycardia complex) and PPI-TCL difference; thus the pacing site is further from the circuit.

From Coronary Sinus Again

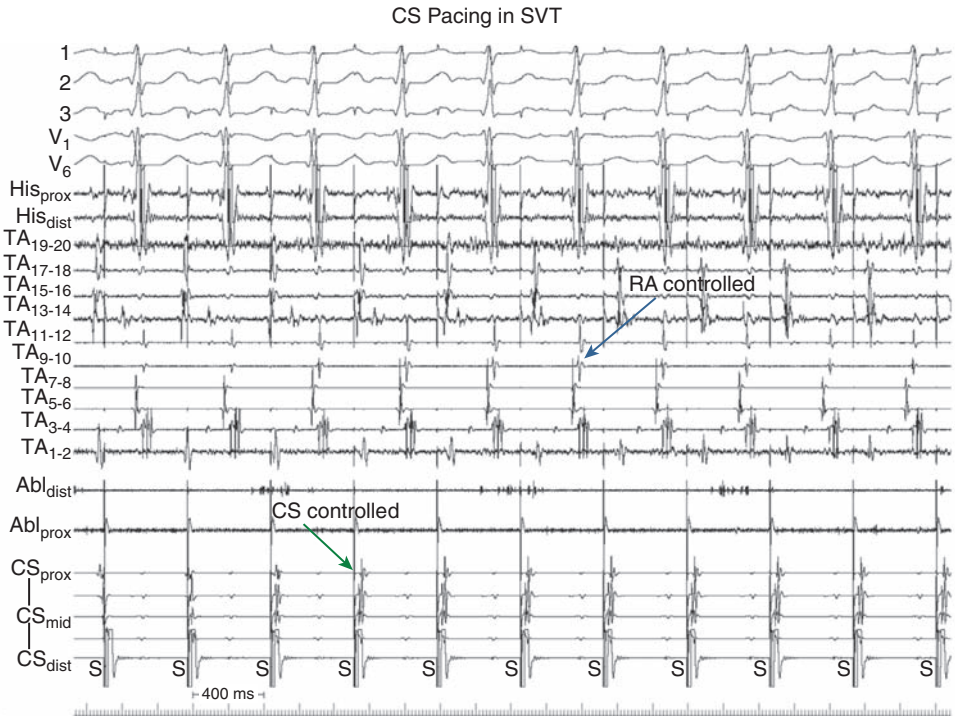


Figure 13-15

In Fig. 13-15, pacing from the distal CS controls all CS recordings long before the TA (RA) is controlled; this signifies that the RA is the chamber of origin (or else it would be controlled coincidently with the control of the LA [CS] if the LA were the chamber of origin).

Spontaneous Change in Atrial Activation Pattern in SVT

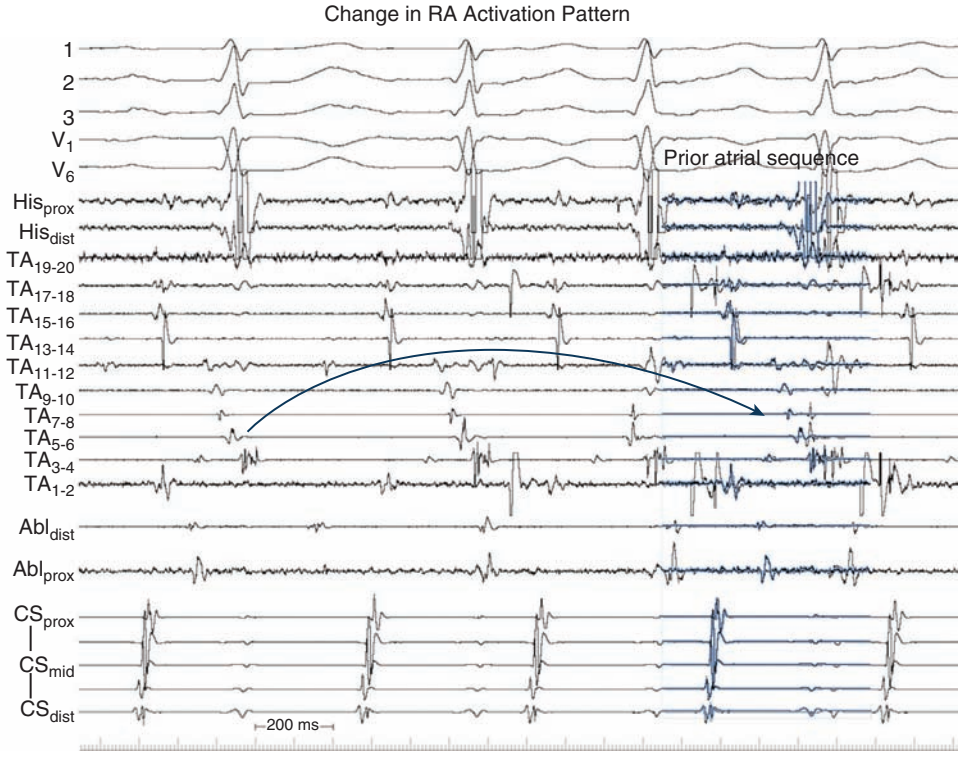


Figure 13-16

Just when we are honing in on the area of interest, the tachycardia changes (Fig. 13-16); the activation sequence on the left half is superimposed in *blue* on the right half to highlight the differences. This may be a change to another circuit, or another path within the same general circuit. It cannot be a sudden reversal of the circuit, as some tissue that had just been activated would have to be activated again too early for its refractory period to have ended (retracing steps during SVT). At some time earlier, another change has occurred: the CS activation was proximal to distal, now reversed.

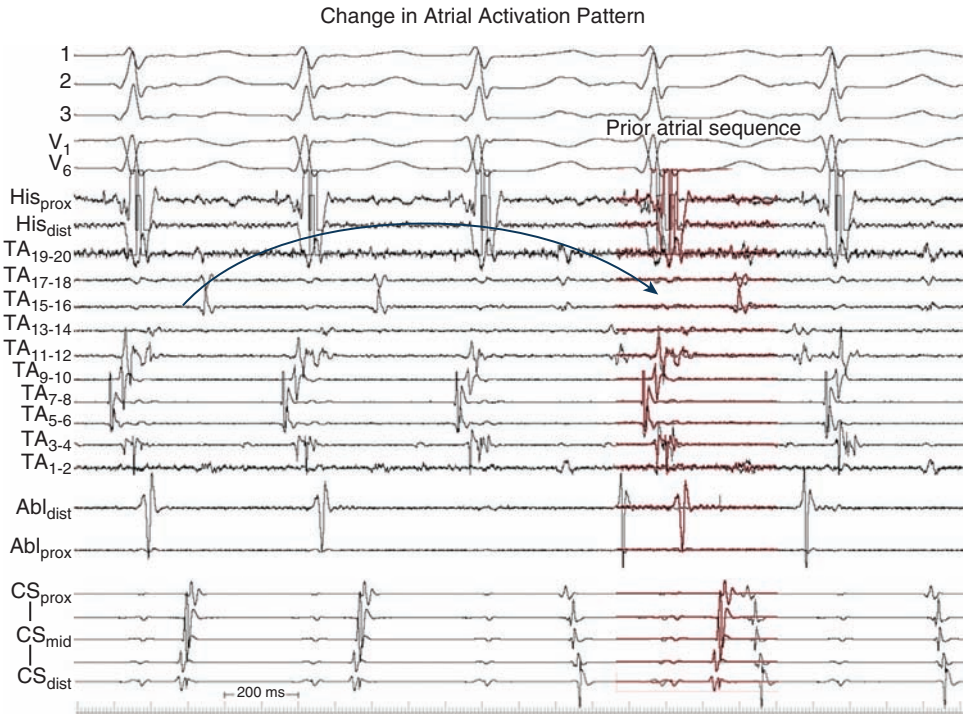


Figure 13-17

A few minutes later, activation changes again (Fig. 13-17). Portions of the TA (RA) are unchanged in both morphology and, largely, cycle length, suggesting that the same basic tachycardia (determined by the diastolic corridor) is continuing, but activation of the rest of the atrium may change (see the CS recordings; although the fundamental tachycardia may not change, the P wave can be altered [not evident here]).

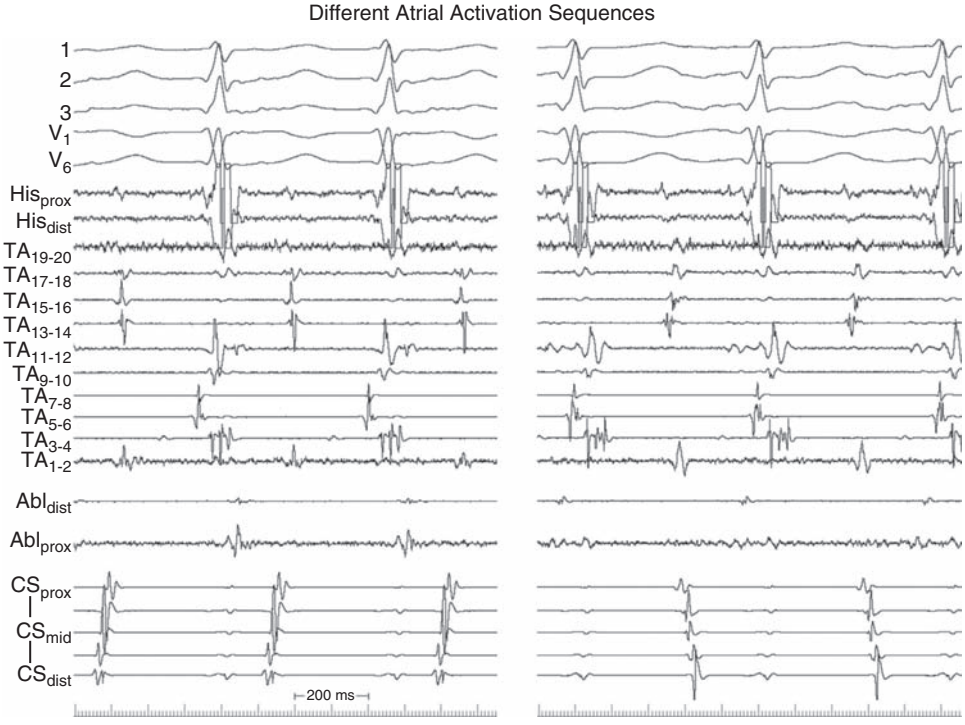
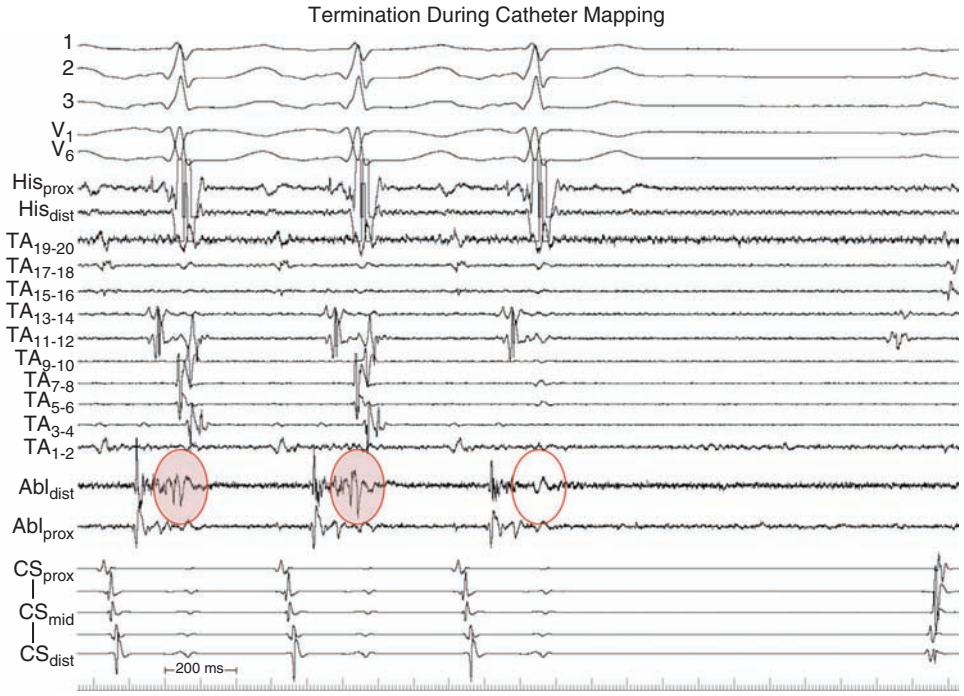


Figure 13-18

Two different atrial activation sequences are compared in Fig. 13-18.

SVT Termination During Catheter Mapping

Figure 13-19



As mapping continues in Fig. 13-19, tachycardia suddenly terminates. Note the change in the electrogram on the ablation distal recording, and the absence of electrograms from TA 9-10 through 1-2 (because of block before they were activated).

Entrainment Mapping: Is It a Good Site?

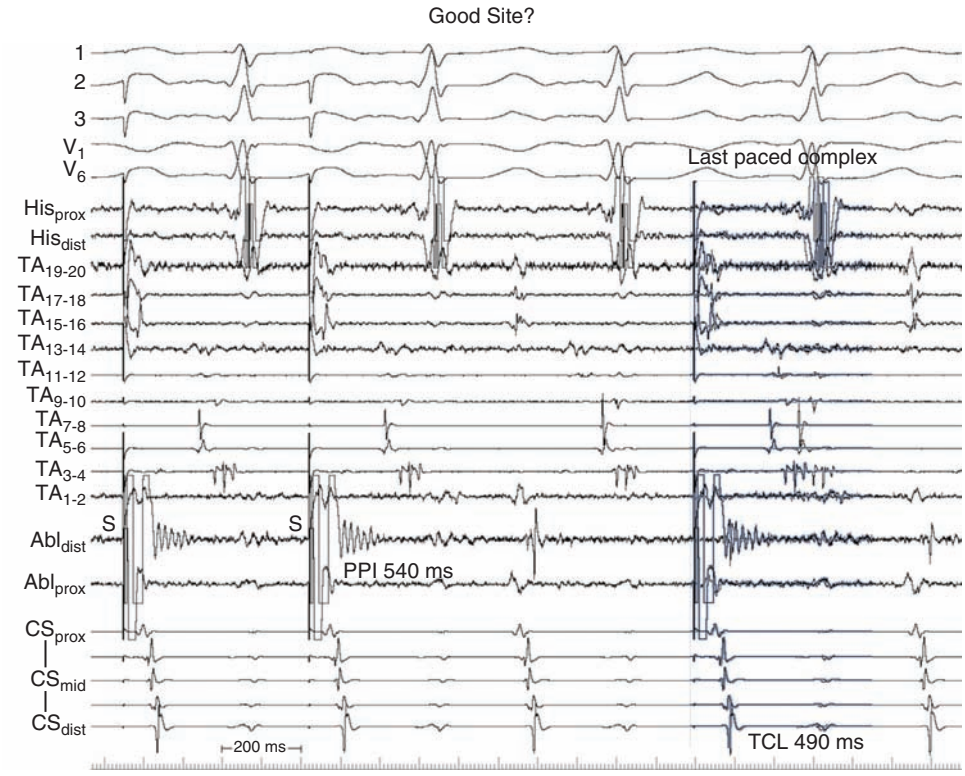


Figure 13-20

Tachycardia was reinitiated and a slightly different site with a diastolic electrogram was chosen for pacing. Fig. 13-20 displays a poor pace match (superimposed on tachycardia) and a long PPI-TCL difference from here—don't ablate at this site.

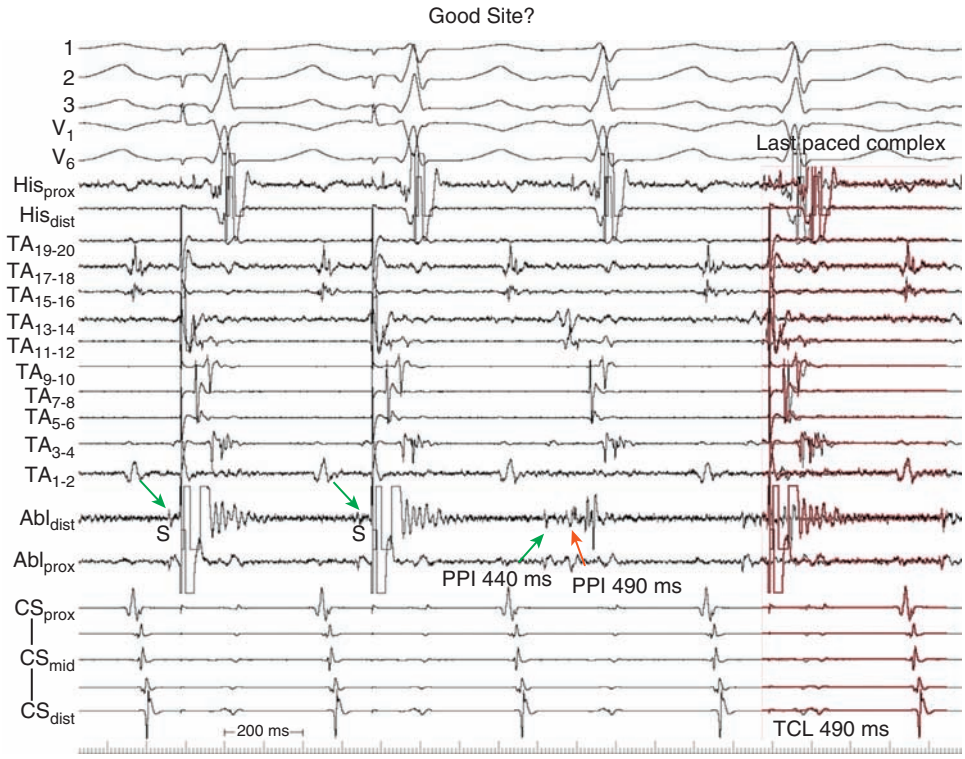


Figure 13-21

Pacing at a slightly different site—close to TA 13-14—produces a nearly perfect pace match but the PPI is again a problem (Fig. 13-21). If measured to the beginning of the complex electrogram *(orange arrow)*, PPI-TCL is perfect; but if measured to the small diastolic potential as before *(upward green arrow)*, the PPI is too short. The problem with the latter is that the small potential is clearly not captured during pacing because it appears before the stimulus artifact *(downward green arrows)*. The conclusion: this site, with a nearly perfect pacematch and perfect PPI-TCL, is a good site for ablation.

Ablation at Site

Are We Done Yet?

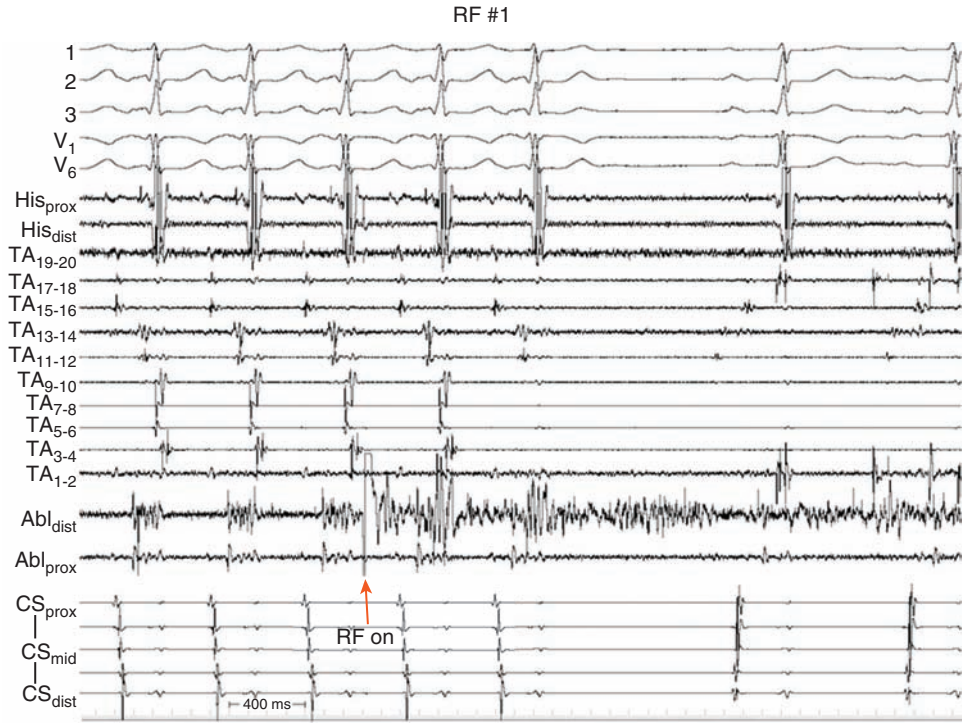


Figure 13-22

RF delivery (as indicated) at the site predicted to be a good ablation site is rewarded by immediate tachycardia termination (Fig. 13-22).

Electroanatomic Maps

Figure 13-23A

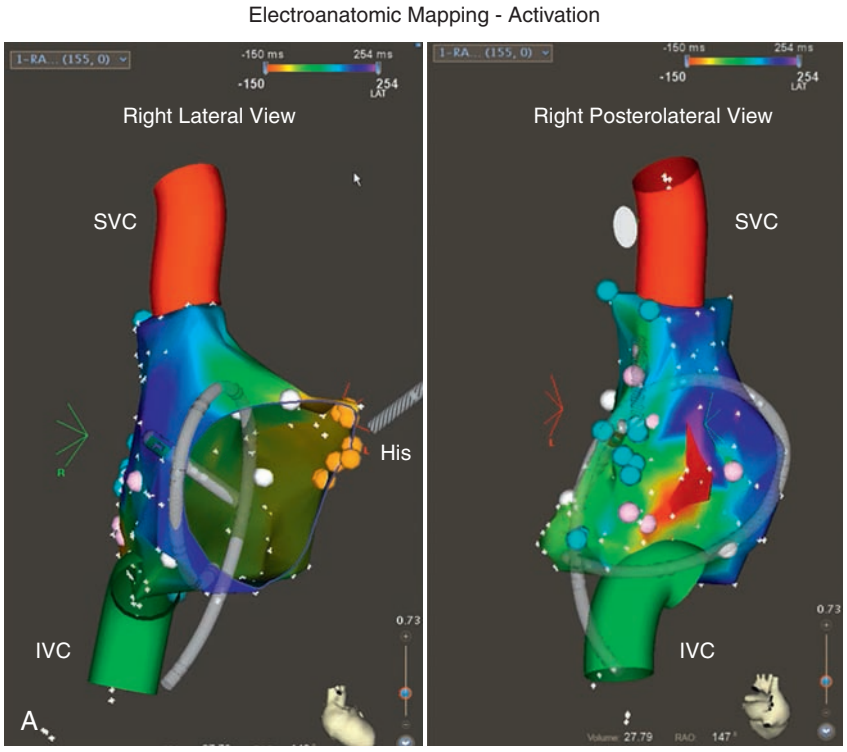
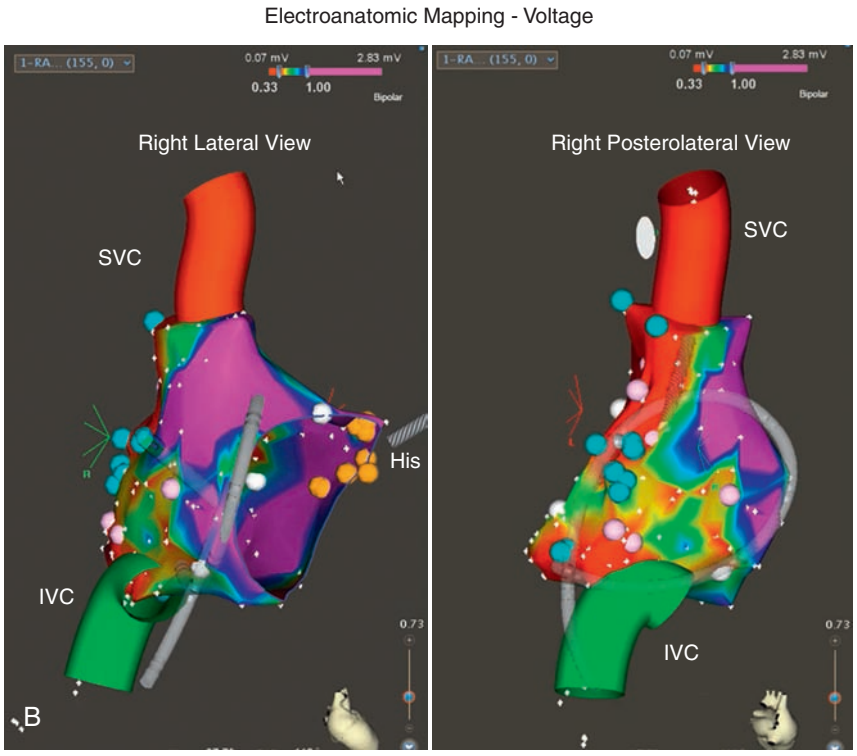


Figure 13-23B



The electroanatomic maps (Fig. 13-23) demonstrate (A) electroanatomic activation mapping of right atrium in tachycardia; (B) electroanatomic voltage map of right atrium; and

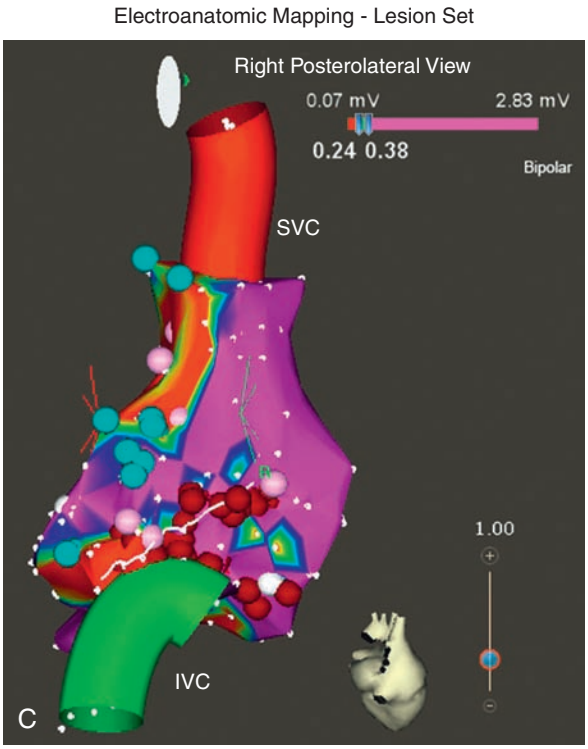


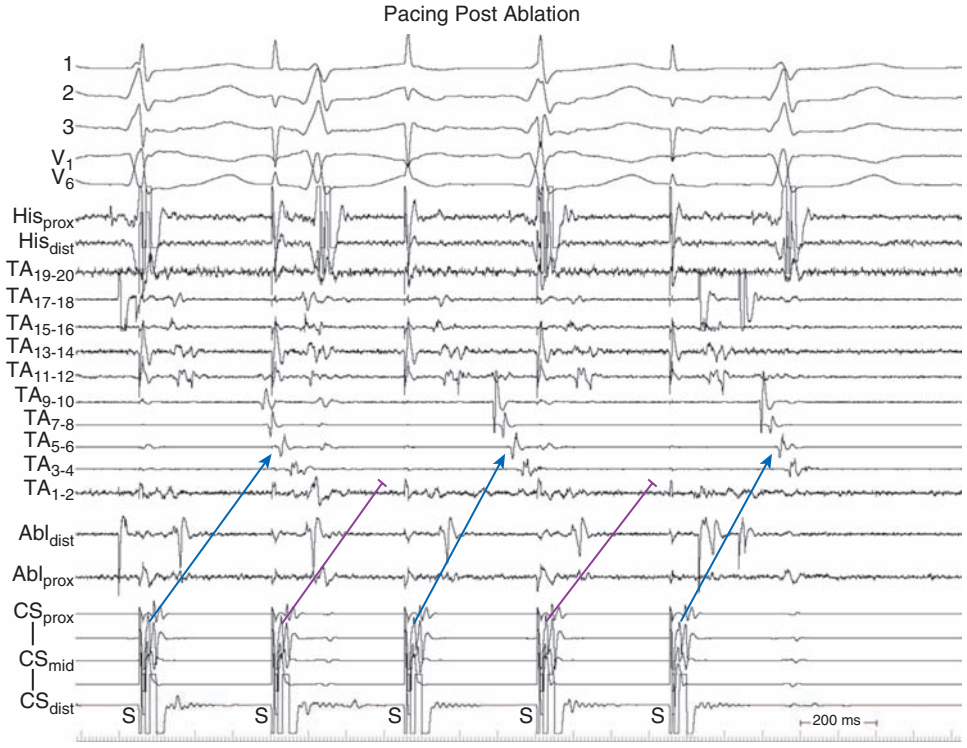
Figure 13-23C

(C) lesion set eventually used to transect the diastolic path and the segment of atrium from this region to the inferior vena cava, to preempt further reentry. In (A), a *red area* corresponding to the diastolic corridor is shown. Representations of the catheters (TA, His, and ablation) are faintly visible.

The prior right atrial cavotricuspid isthmus was evaluated and shown to have persistent bidirectional block from the prior ablation procedure.

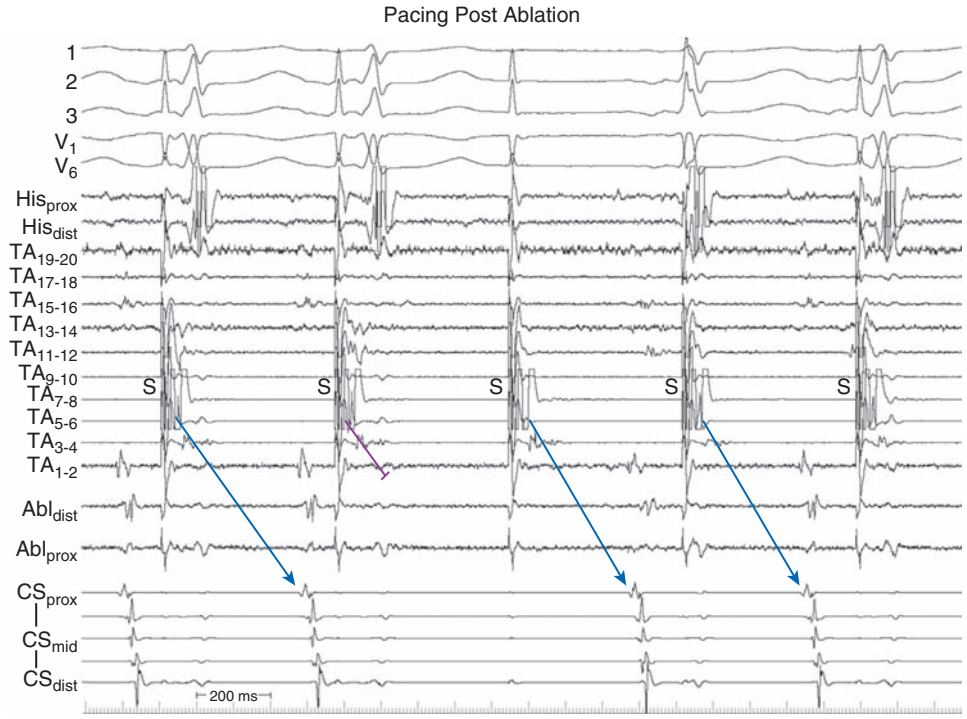
Pacing from Various Sites Postablation

Figure 13-24



Conduction is so disrupted in Fig. 13-24 that pacing from the CS does not get to the RA each time (indicated by *arrows* and *stopped lines*).

Figure 13-25



The same is true for pacing from RA (not conducting each time to CS), in Fig. 13-25.

Final ECG

Figure 13-26

The patient's final ECG is shown in Fig. 13-26. She has been free of tachycardia recurrence for several years since the procedure.

Summary

- Atrial tachycardias after (non-maze) atrial surgery are common:
  - Right atrial macroreentry is much more common than left atrial
  - Atrial flutter is as common as (or more than) free wall macroreentrant circuits
  - Right atrial pathology (and circuits) can be present despite absence of prior extensive right atrial incisions
  - Entrain from multiple sites before concluding a focal mechanism
  - Circuits may be "bump-sensitive"—plan your mapping strategy before starting
- In areas of very slow/disrupted conduction, mapping systems:
  - May not be as helpful for tracking activation during AT as they are in other cases
  - May still be very useful for:
    - Delineation of scar/circuit boundaries
    - Designing strategies for ablation (connecting barriers)

14 Atrial Microreentry After Lung Transplantation

Case Presentation

The patient was a 60-year-old man with palpitations, lightheadedness, and dyspnea and referred for catheter ablation of atrial arrhythmias. He had a history of idiopathic pulmonary fibrosis. He underwent bilateral lung transplant in 2002; he had never shown any rejection. Palpitations began in 2013. ECGs showed supraventricular tachycardia ~190/min, and he was treated with metoprolol (failed); diltiazem (failed); flecainide (failed); and flecainide + metoprolol (partially successful?). Dyspnea continued despite "normal" heart rate (~100/min). He stated that his heart rate was constant all day and night unless he tried to exercise, at which point it sped up to twice as fast (200/min). He was referred for EP study and possible ablation.

Differential Diagnosis and Time Course of ATs After Lung Transplantation

What kinds of tachycardias do patients get after lung transplantation?

- Atrial fibrillation
- Atrial flutter/macroreentrant atrial tachycardia
  - Typical right atrial cavotricuspid isthmus-dependent flutter
  - Perimitral reentry
  - Peripulmonary vein cuff reentry
- Pulmonary vein tachycardias with donor–recipient atrial anastomotic electrical connection
- Other SVTs (which anyone may have)
  - AV nodal reentry
  - AV reentry (accessory pathway—WPW)
  - Focal atrial tachycardia

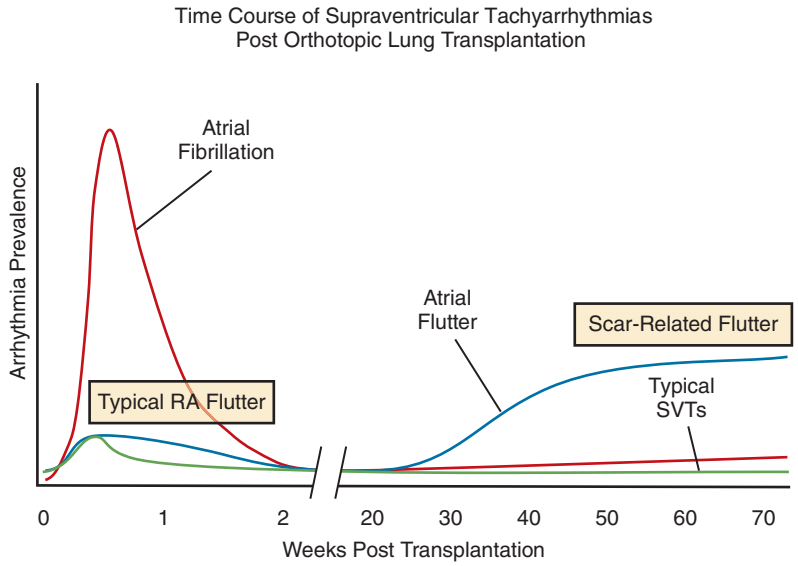


Figure 14-1

Fig. 14-1 demonstrates the time course of supraventricular tachyarrhythmias after lung transplantation. RA, right atrial; SVT, supraventricular tachycardia.

Types of Lung Transplantation Procedures

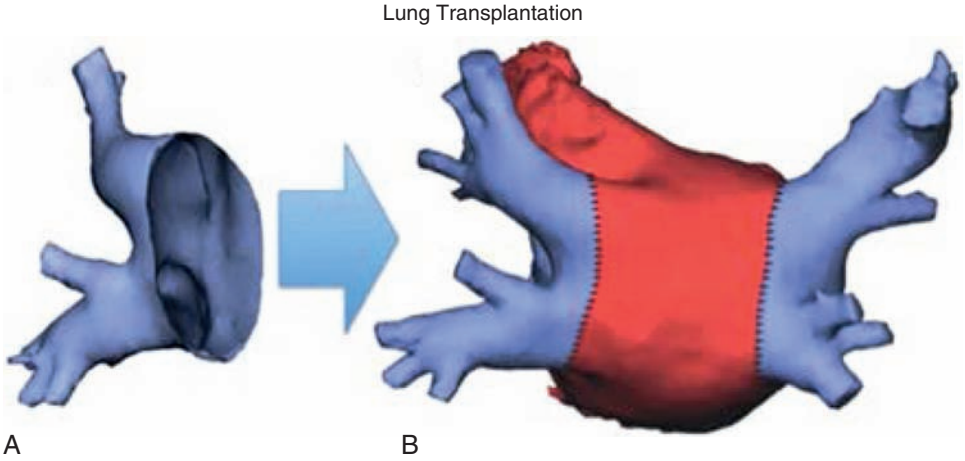


Figure 14-2

(From Lee, G et al. Atrial fibrillation following lung transplantation: double but not single lung transplant is associated with long-term freedom from paroxysmal atrial fibrillation. *Eur Heart J* (2010) 31: 2774-2782.)

A common technique for lung transplantation is to mate the donor lung and pulmonary vein (PV) cuff *(blue)* to the recipient atrium *(red)* (Fig. 14-2).

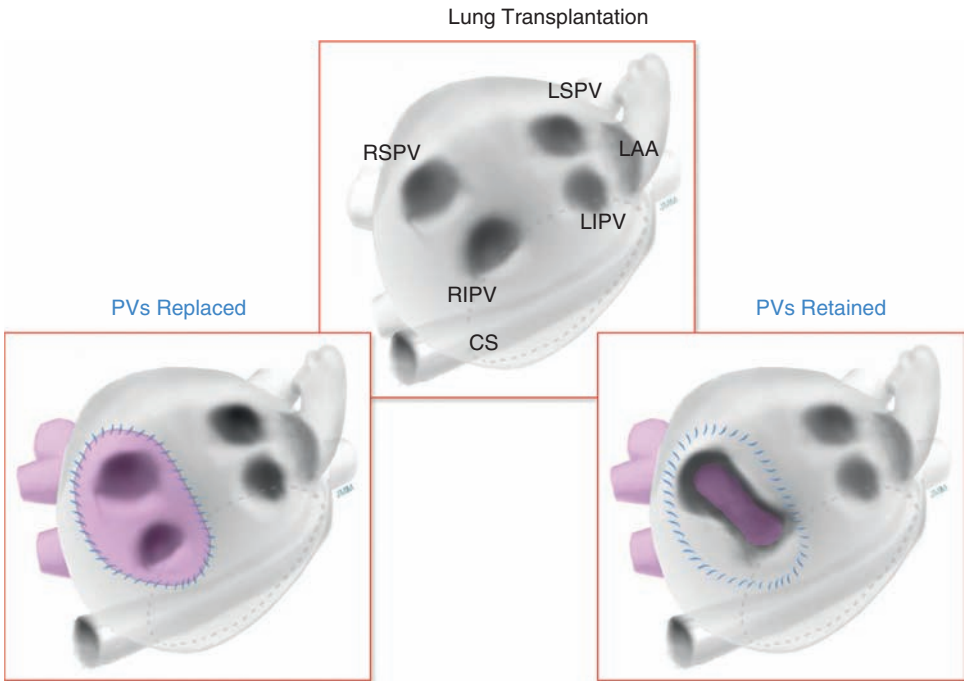


Figure 14-3

Pulmonary veins (PVs) may be replaced as in Fig. 14-2, or retained (with the donor PV cuff sewn around the perimeter of the recipient PVs), as shown in Fig. 14-3. LIPV, left inferior PV; LSPV, left superior PV; RIPV, right inferior PV; RSPV, right superior PV.

Baseline ECG and Intracardiac Recordings

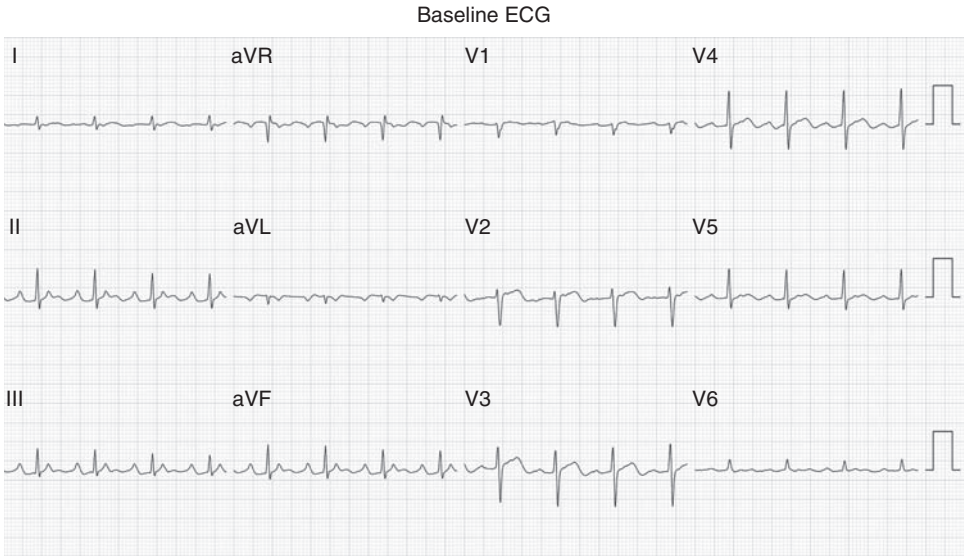


Figure 14-4

Differential diagnosis is only atrial tachycardia; the 2:1 AV relationship excludes orthodromic SVT and the positive P wave excludes AV nodal reentry. What particular kind of atrial tachycardia, however, remains to be diagnosed. The ECG shown in Fig. 14-4 was mistaken as sinus rhythm, which it superficially resembles. However, the rate never varies unless the patient exercises and suddenly conducts 1:1.

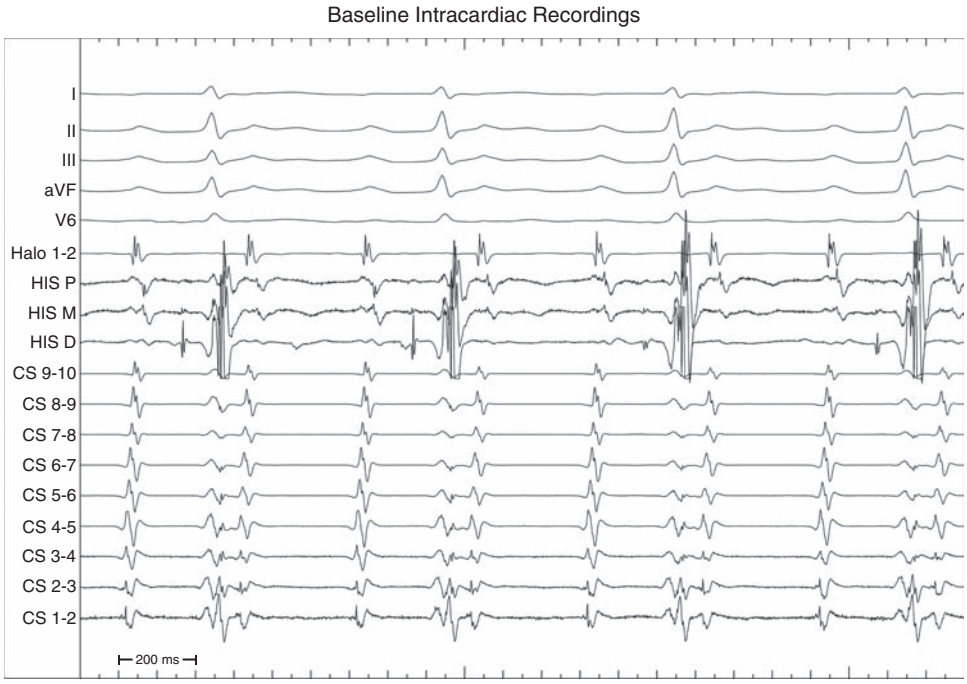


Figure 14-5

In Fig. 14-5, it is hard to tell where the P wave starts because of low-gain ECG channels.

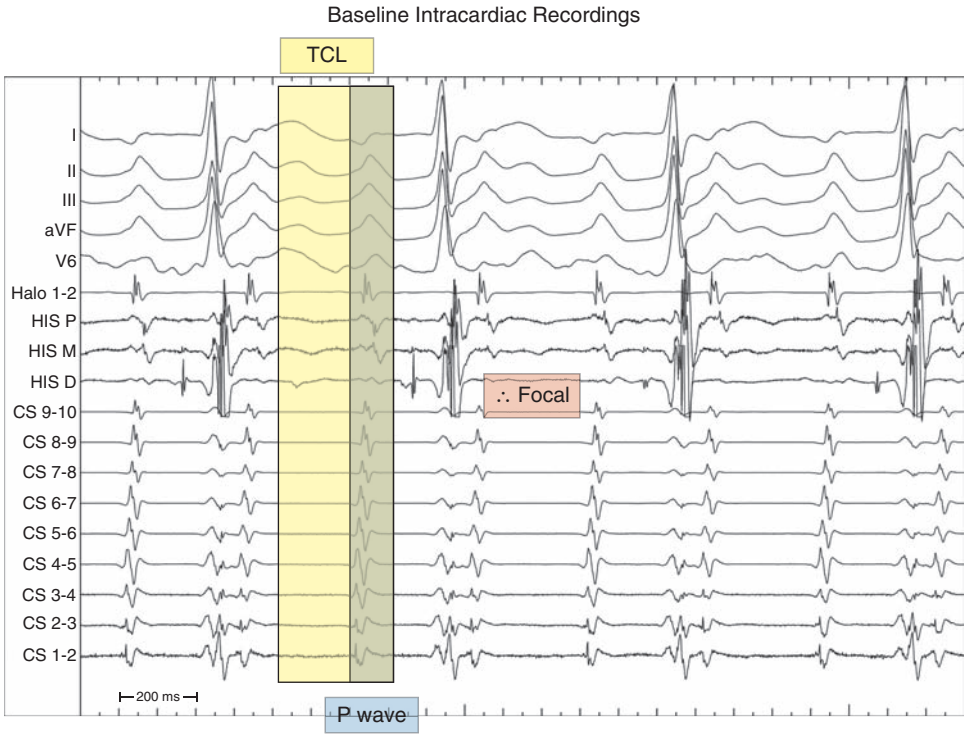


Figure 14-6

One can often infer a mechanism of atrial tachycardia by comparing P-wave duration (and intracardiac electrogram "envelope") to tachycardia cycle length (TCL). The narrower the P wave, especially relative to TCL, the more likely a focal process is involved, but a broader P wave in relation to TCL suggests macroreentry (Fig. 14-6). Specifically, a ratio <0.5 suggests a focal process, because after the focus fires and the atria are activated from that source, there is a pause (diastole) until the next firing of the focus and another P wave begins.

Figure 14-7

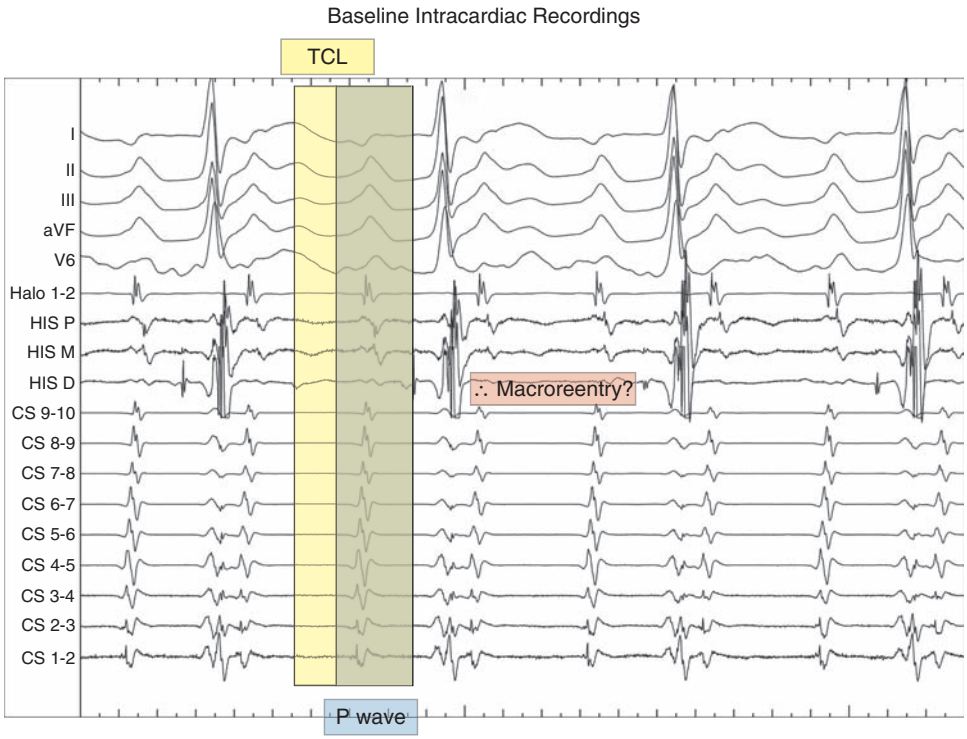
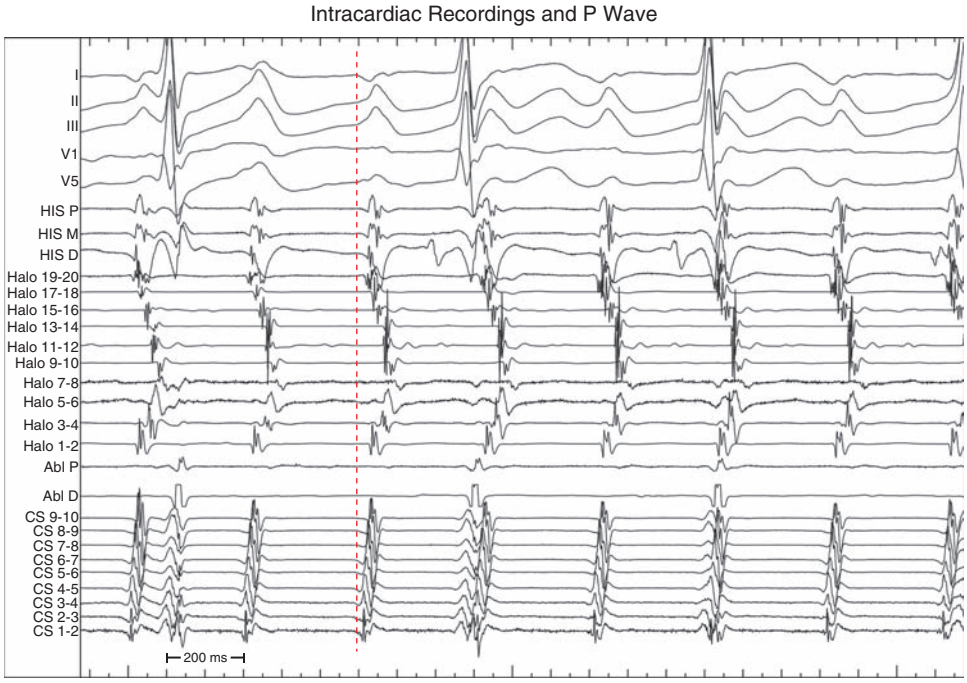


Fig. 14-7 shows a different interpretation of the P-wave duration, while the TCL remains the same. Now, a P-wave duration to TCL ratio >0.7 suggests that atrial activation spreads slowly through large portions of the atrium and thus the mechanism is likely macroreentry. There is considerable overlap with this index (ratio of P duration to TCL) and it is at best suggestive, but not diagnostic, of mechanism.

Figure 14-8



The P-wave morphology (initial negative component) suggests a left atrial origin (Fig. 14-8), as does distal-to-proximal CS activation sequence. None of the recordings show pre–P-wave electrical activity, however (P wave onset denoted by dashed red line).

Status

- Sustained (incessant) SVT is present
- All electrical activity recorded is after P-wave onset
- Recordings suggest left atrial process
  - Initial negative P in lead 1
  - CS activation sequence slightly distal-to-proximal
- Mechanism: unclear
- Choices of strategy at this juncture:
  - Activation mapping
    - Can give idea of where origin/exit is, scar borders
    - Does not designate mechanism
    - Catheter bump-termination can occur
  - Overdrive pacing during tachycardia
    - Can designate mechanism, thus ablation target features
    - Can designate which atrium is involved
    - May terminate tachycardia

Electroanatomic Mapping

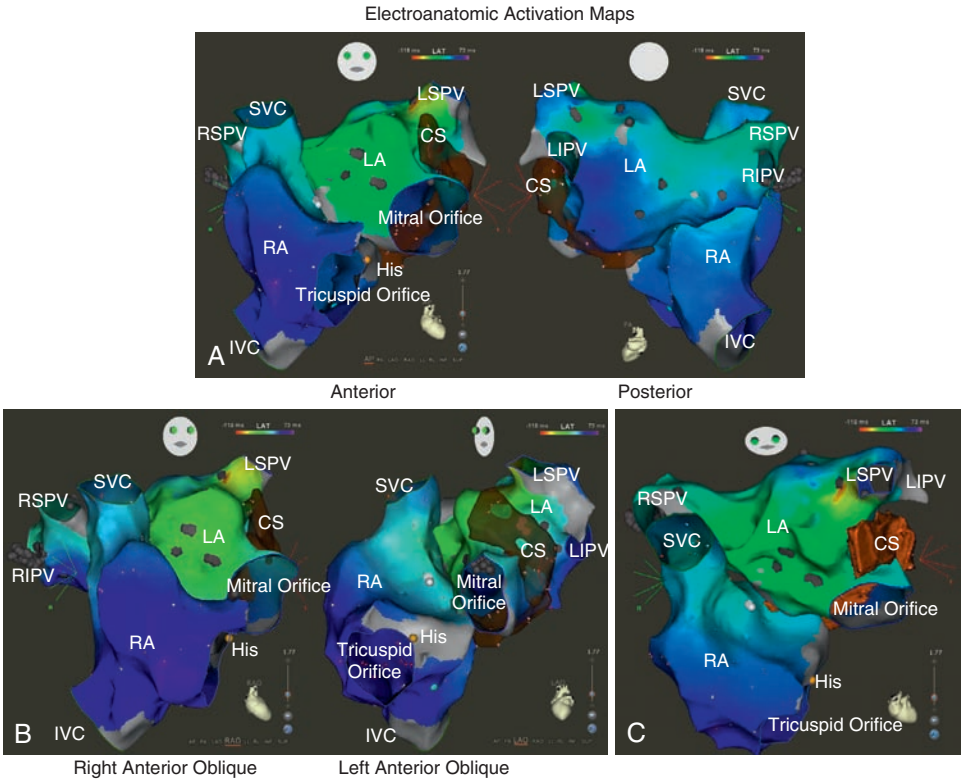


Figure 14-9

We chose activation mapping as the initial strategy, and mapped both atria (Fig. 14-9). The right atrium is clearly activated late in the P wave, but so is everywhere else except for a tiny spot in the top of the left atrium. Note that the span of activation times (−118 to 73 ms, or a total of 291 ms) is almost exactly the TCL (300 ms). This is usually the case with macroreentry but not with focal tachycardias; however, a focus with slow propagation through a scarred atrium can have a total activation time similar to TCL. CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; SVC, superior vena cava.

Mapping

What Does This Mean? [Fig. 14-10]

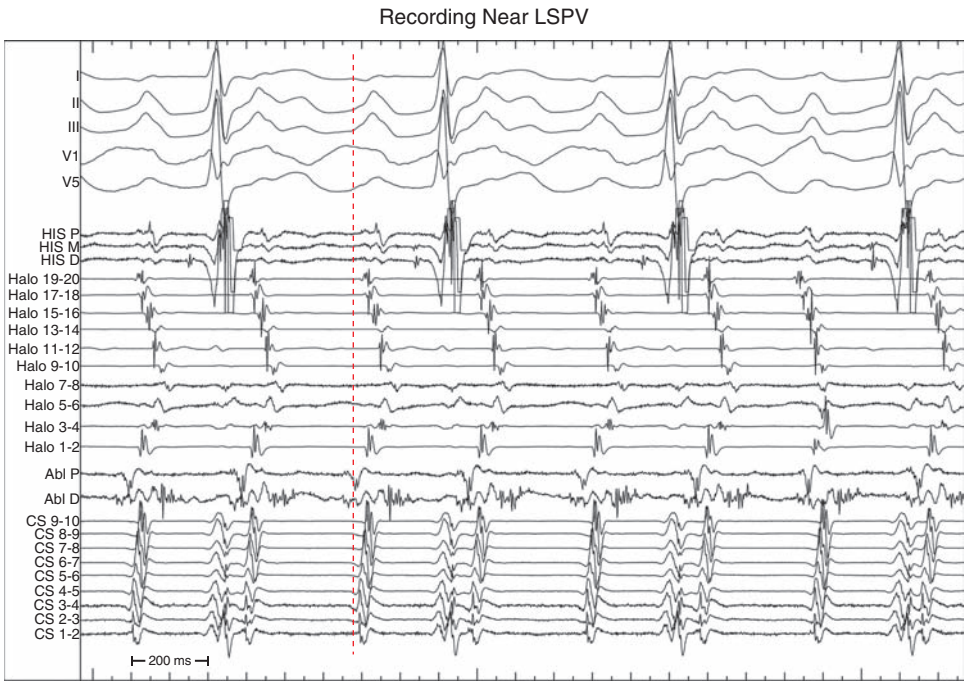


Figure 14-10

A very fractionated electrogram is present near the ostium of the left superior PV, at the site of earliest activation during tachycardia (Fig. 14-10). Although this could still be focal, it raises the question of reentry because the electrogram is so very prolonged and fractionated. At this point, a ring catheter was introduced into the left atrium to interrogate the PVs.

Overdrive Pacing During Tachycardia from Various Sites

Now that we have an idea where the tachycardia exit is (high lateral left atrium), we can clarify the mechanism in order to know what the ideal ablation target site looks like. If a small focus is the cause, a site with minimal pre–P-wave activation (30 to 40 ms) will suffice. If macroreentry, we need a site with middiastolic activation. Responses to overdrive pacing, often from several sites, should provide the answer. In the ablation recording, we already have a middiastolic site near the left superior PV; this could still be a focus there with slow conduction out of it (near a suture line, or conduction from focus in donor PV to recipient LA?), or macroreentry.

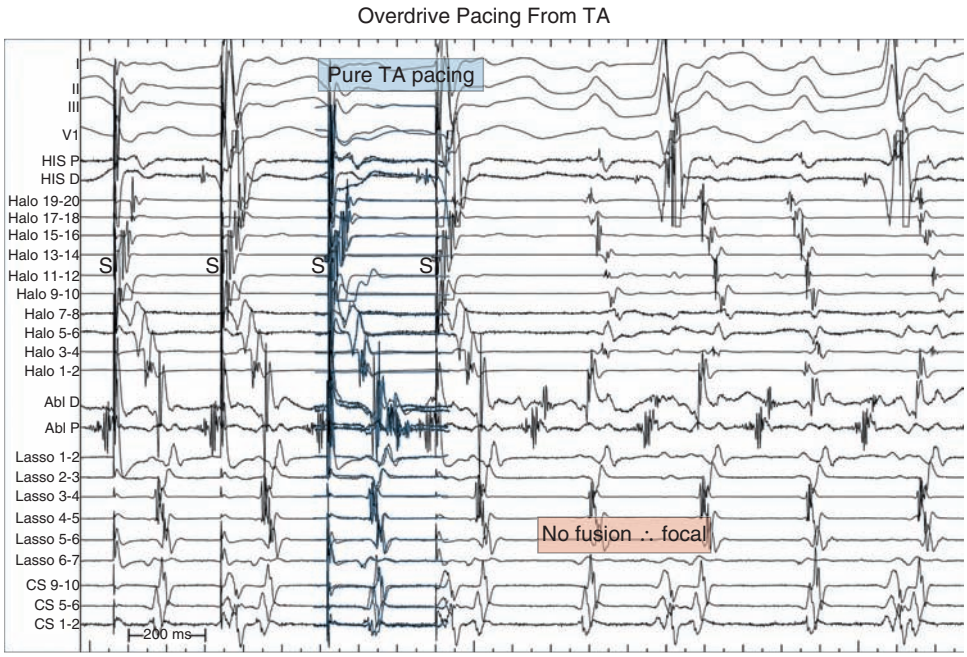


Figure 14-11

In Fig. 14-11, we are overdrive pacing from the lateral right atrium, one of the last places to be activated during tachycardia. Pacing from such a late-activated site makes it easy to see if fusion is present during pacing, because the wavefront caused by pacing and that caused by tachycardia are in theory on opposite sides of the heart. The response to pacing shows that the lateral RA pacing site is indeed among the last to come back on the first beat of resumed tachycardia; superimposition of an example of pure pacing from this site in sinus rhythm shows there to be little, if any, difference between pure pacing and pacing during tachycardia (the ablation catheter position changed between the two recordings and cannot be compared). Thus there is no fusion, further suggesting a focal process.

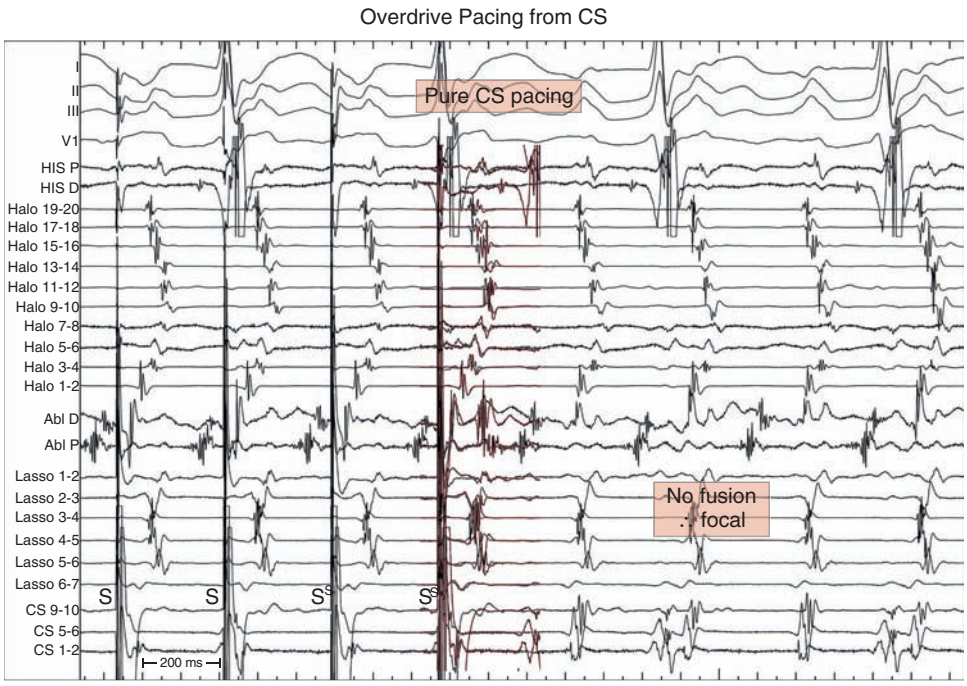


Figure 14-12

Pacing from another site (Fig. 14-12) yields the same findings as before: no fusion, thus likely a focus (as noted before, the position of the ablation catheter had changed between the two recording times and is thus not comparable). However, we had not seen anything but tachycardia to this point in the procedure; the pure pacing examples were obtained only after tachycardia terminated. Thus the comparison of pure pacing versus pacing during tachycardia was not available at the time pacing during tachycardia was performed (it was before ablation, however).

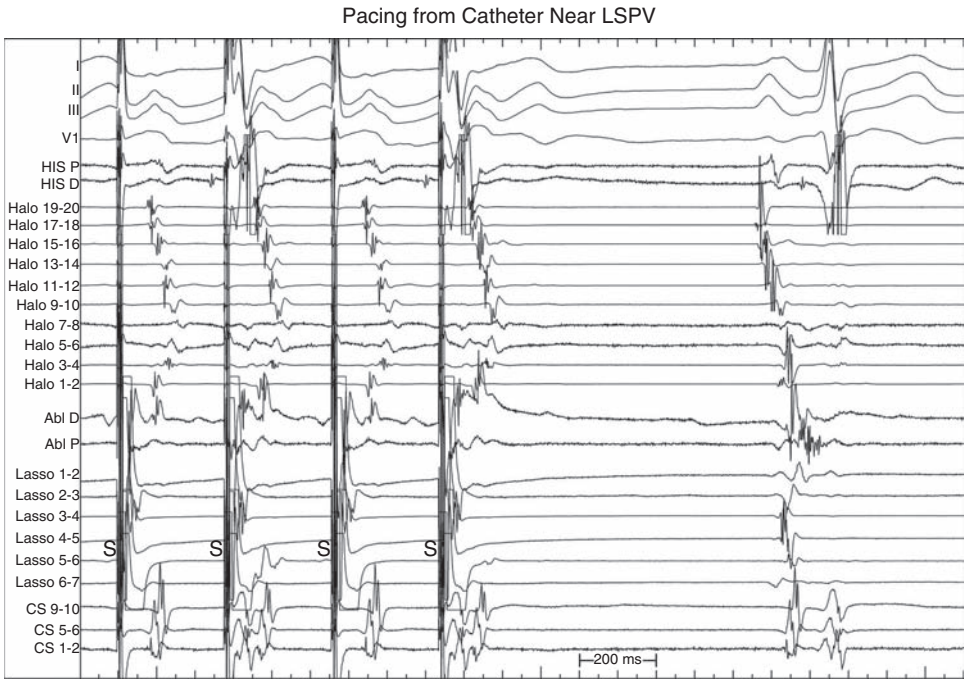


Figure 14-13

Unfortunately, pacing from the ring catheter in the LSPV, near the earliest site of activation during tachycardia, terminated the arrhythmia to sinus rhythm (Fig. 14-13).

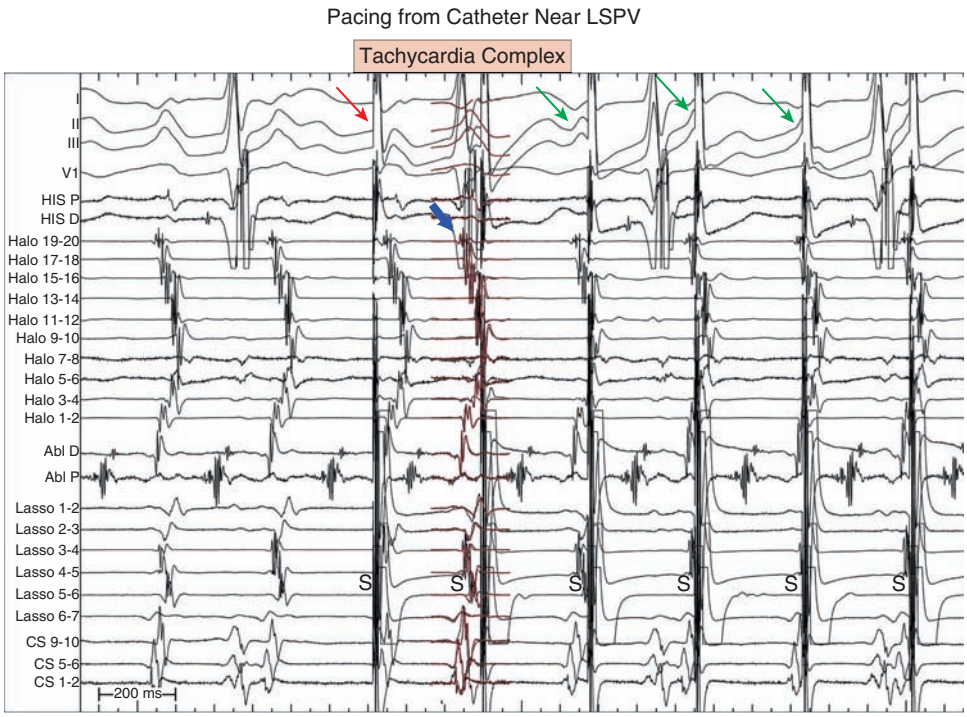
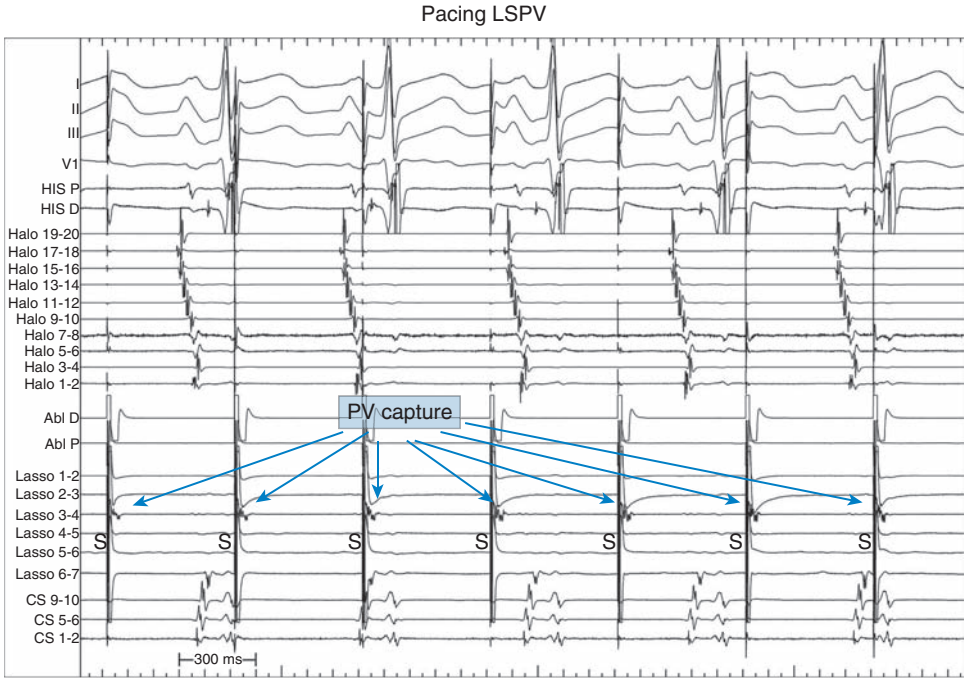


Figure 14-14

All is not lost, however. Looking back at the initiation of pacing at this site in Fig. 14-14 shows some interesting findings. The first complex controlled by pacing, indicated by the *large blue arrow*, appears to have an identical activation sequence to that of tachycardia (superimposed). That in itself is not so unusual; however, the fact that the stimulus artifact occurred at the onset of the P wave that had already been made by the previous tachycardia cycle *(small red arrow)* is suggestive of a circuit with separate entrance and exit locations; this is further exemplified in subsequent complexes, when the stimulus artifact clearly follows the beginning of an accelerated P wave *(green arrows)*. A focus could not do this.

Pacing Donor Left Superior Pulmonary Vein During Sinus Rhythm

Figure 14-15



Now that tachycardia has accidentally been terminated, we take advantage of the situation. Pacing from the right atrial and coronary sinus sites used in pacing during tachycardia can now be used as examples of "pure" pacing from these sites for comparison. Further, to prove that this was not a pulmonary vein (PV) tachycardia from the donor PV that had made an electrical connection to the recipient atrium, pacing from the left superior PV (Fig. 14-15) showed it to be electrically separate from the rest of the atrium (which is in sinus rhythm at this point).

Pacing from Ablation Catheter Near Ablation Site

Approximates Appearance of SVT

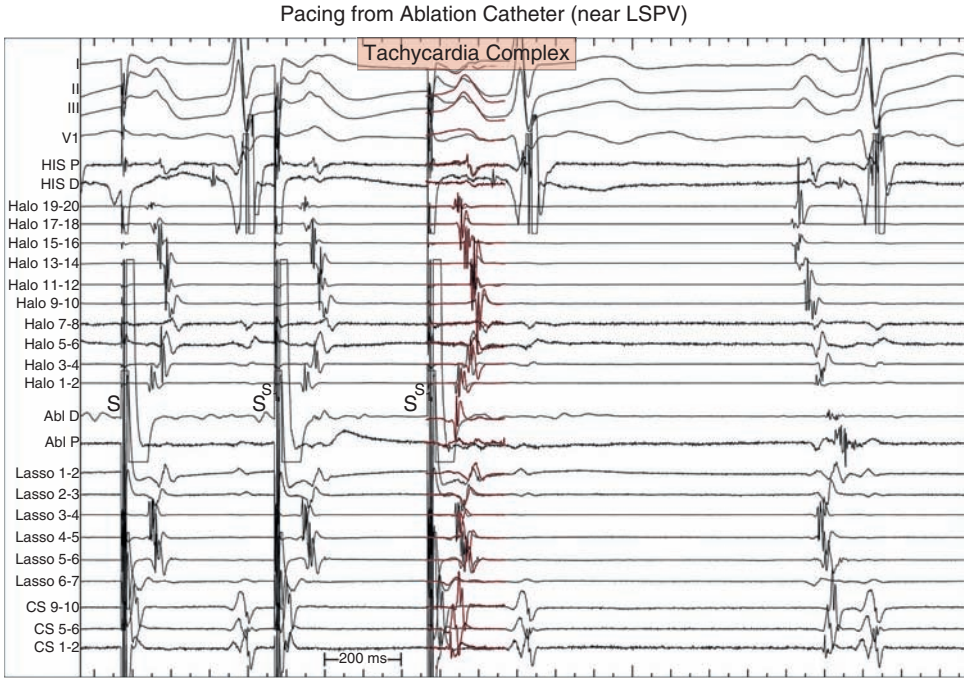


Figure 14-16

In Fig. 14-16, pacing from the ablation catheter (located near the site of the earliest activation during tachycardia) shows an activation sequence almost identical to that of tachycardia—except for the coronary sinus recordings, which are completely different. If this were a focal tachycardia, pacing from the site of the focus should exactly replicate the tachycardia activation sequence and P-wave configuration. The fact is that it does not raise further suspicions about this being a focal firing process.

Initiates SVT

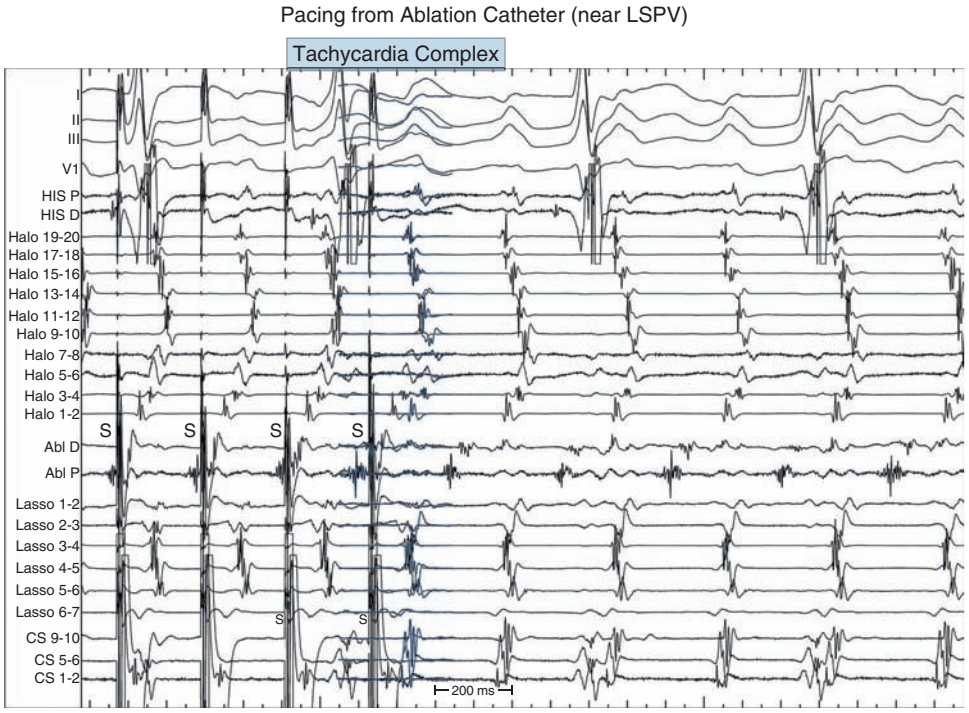


Figure 14-17

Pacing from near the LSPV initiates tachycardia; this would be unusual for a focal firing process (unless it were related to delayed afterdepolarizations). In Fig. 14-17, a complex of tachycardia is again superimposed on the last paced cycle; once again, if this were a focus, pacing here should look very similar to tachycardia. The fact that it does not further calls into question the focal firing hypothesis.

Replicates SVT Appearance

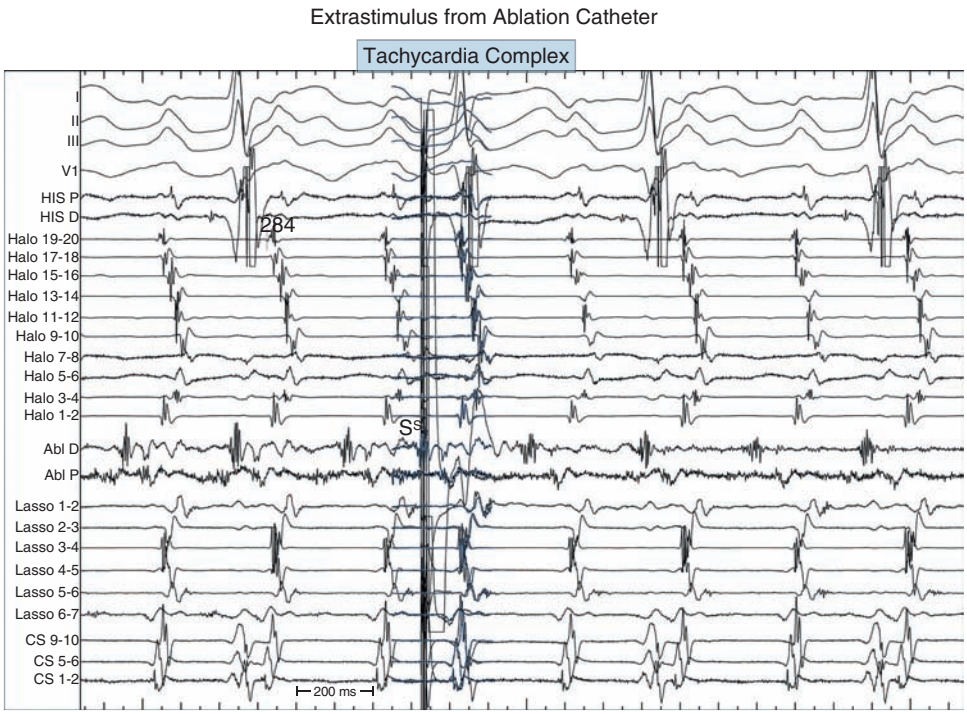


Figure 14-18

An extrastimulus delivered from ablation catheter (recording of a site of middiastolic ablation) captures, resulting in an atrial activation sequence identical to that of tachycardia (Fig. 14-18). This in itself does not differentiate between a focus and reentrant circuit, as one could stimulate from a focus during tachycardia, depolarize the focus, and have a resulting complex that looks identical to tachycardia, and one can certainly stimulate during a reentrant arrhythmia and have the same result.

Terminates SVT Without Propagation

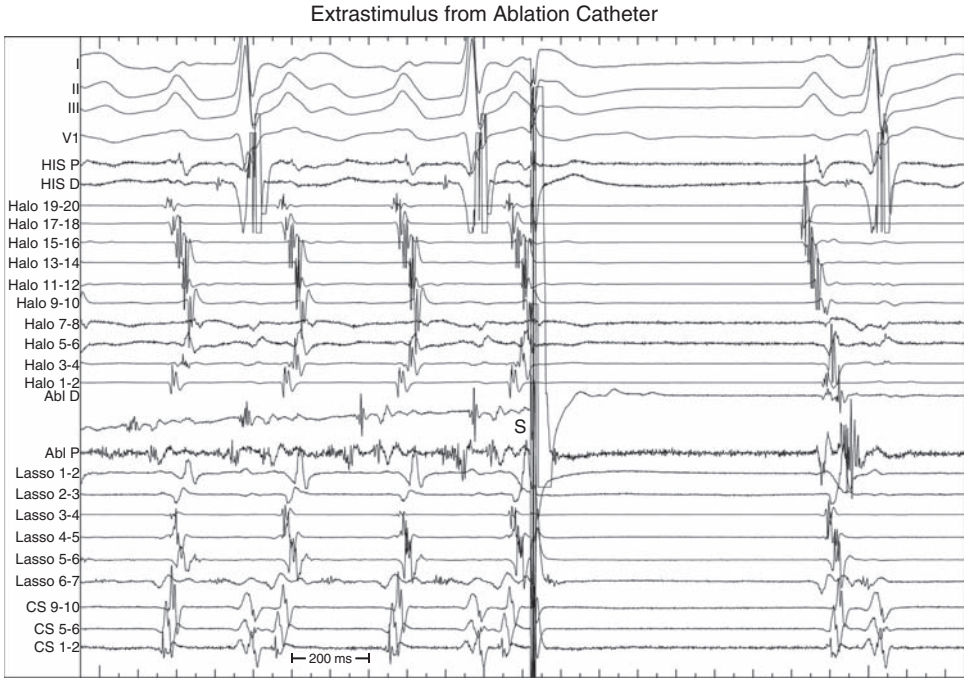
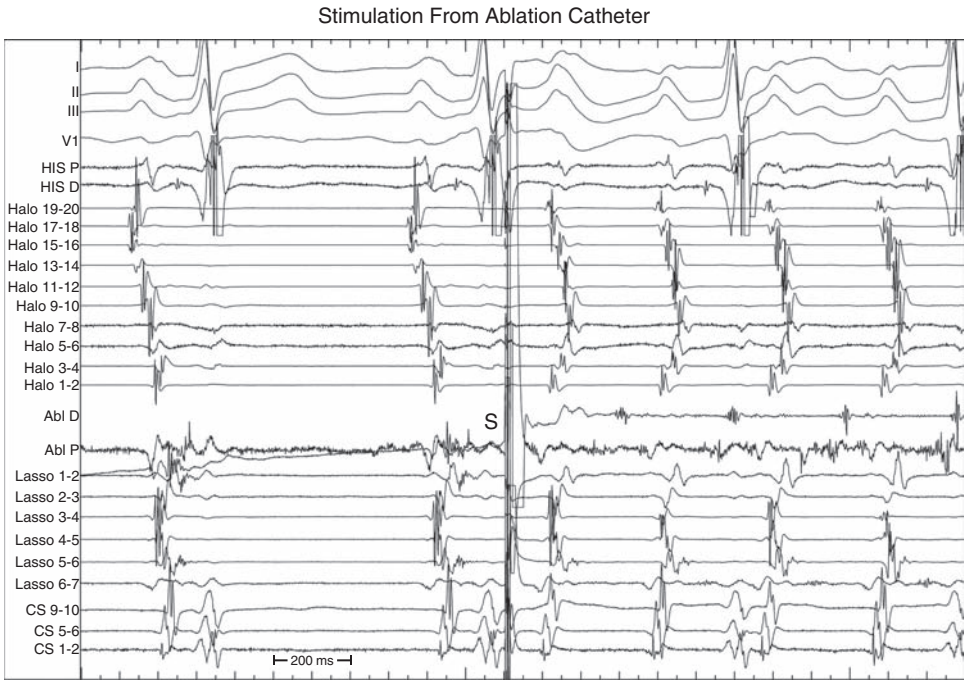


Figure 14-19

As extrastimuli are brought more prematurely (Fig. 14-19), tachycardia terminates, without apparent propagation; this was a reproducible phenomenon during this procedure. This would be extraordinarily unusual behavior for a focus, and strongly suggests reentry (during which this phenomenon is reasonably commonly observed). The very prolonged diastolic electrogram goes along with this. But what kind of reentry? Fusion was never demonstrated, and the activation map did not show an "early-meets-late" juxtaposition of earliest activations to latest activations (in fact, these were on the opposite side of the heart in the right atrium). This could be *micro*reentry, fulfilling all the requirements for reentry (inducible, terminable with pacing, entrainable) but never showing manifest fusion because the circuit is so small. An additional feature of microreentry is an electrogram at the ideal ablation site that nearly spans the tachycardia cycle length. A focus because of delayed afterdepolarizations could conceivably have accounted for most, if not all, of the phenomena encountered before this; however, termination of tachycardia by a nonpropagated stimulus excludes any focal firing process. Instead, this indicates that a reentrant circuit is responsible, and because fusion was not demonstrable from any far-away pacing site, the activation pattern on electroanatomic mapping suggested a small area from which activation emanated simulating a focus, and the electrogram from this site was extremely prolonged, microreentry is the most likely mechanism of tachycardia.

Reinitiates SVT

Figure 14-20



A single extrastimulus (S) delivered from the ablation catheter at the site of the earliest activation during tachycardia easily reinitiates tachycardia (Fig. 14-20). This would again be extremely unusual for a focal-firing process (automaticity), which is typically not inducible.

Recording at Ablation Site

Figure 14-21

In Fig. 14-21, a nearly continuous electrogram is seen in the proximal recording of the ablation catheter, again consistent with microreentry. Note also a small electrogram recorded from the catheter in the LSPV ("Lasso 6-7"), near this site.

Ablation

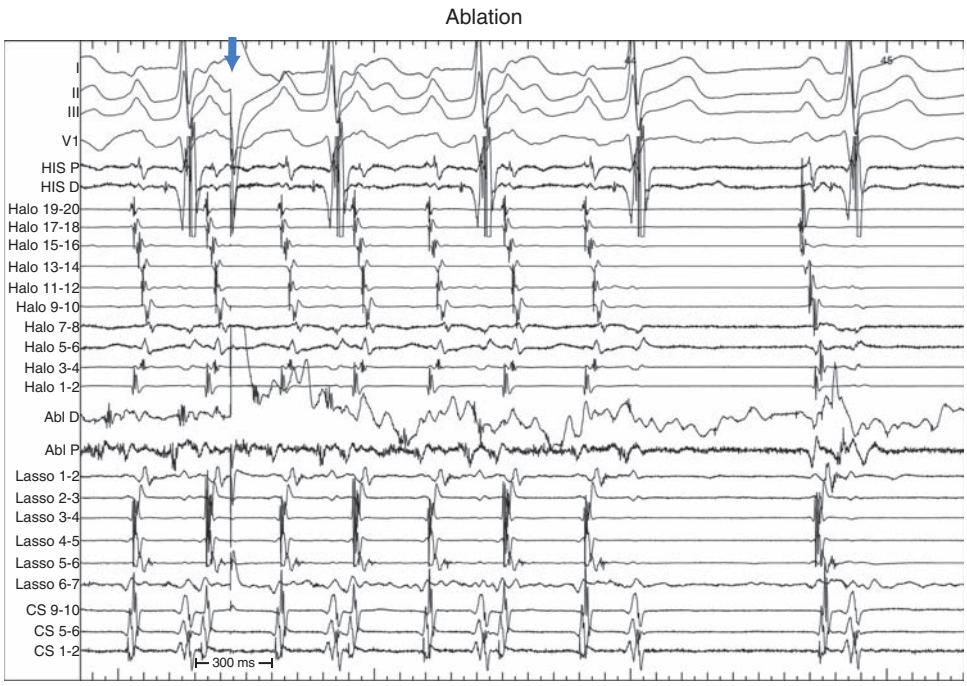


Figure 14-22

After withdrawing the ablation catheter slightly so that the tip was at the site of very prolonged diastolic activation, radiofrequency (RF) energy was applied (Fig. 14-22, *arrow*). Tachycardia terminated in less than 2 seconds. and could not be initiated after this (including with high-dose isoproterenol), whereas it was readily initiated before ablation. A few more RF applications were made in this general area for consolidation of the ablation effect.

Sinus Rhythm at End

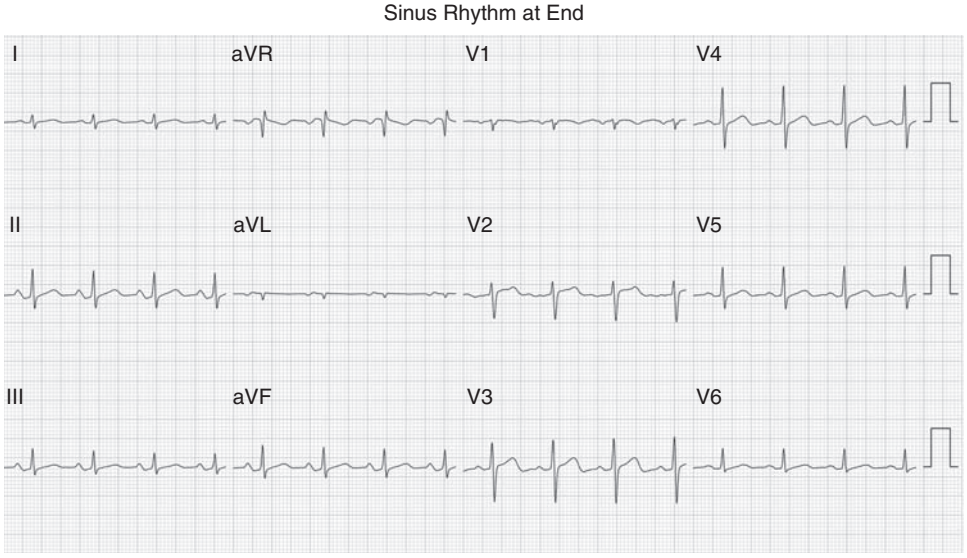


Figure 14-23

The final ECG (sinus rhythm) is shown in Fig. 14-23; the patient has remained free of tachycardia in follow-up and dyspnea is gone.

Summary

- Supraventricular tachyarrhythmias in patients after lung transplantation can have a variety of causes:
  - Atrial fibrillation
  - Atrial flutter/macroreentrant atrial tachycardia
  - Other SVTs (which anyone can have): AV nodal reentry, AV reentry, focal atrial tachycardia
- Successful ablation hinges on correct diagnosis and selection of appropriate target sites
- Microreentry is an unusual but important cause of arrhythmias in patients who have had prior surgery or ablation (practically never occurs in a pristine heart)
  - Overall chamber activation is focal; other features suggest reentry
  - A markedly prolonged diastolic electrogram is a target

Atrial Reentry After Pulmonary Vein Isolation for Atrial Fibrillation

15

Case Presentation

The patient is a 55-year-old man with end-stage renal disease (dialysis, renal allografts + rejection, now on dialysis again), coronary artery disease (CAD) (stents), pericarditis (stripping), pulmonary hypertension, and atrial fibrillation (AF). Longstanding persistent AF was ablated 5 years ago, consisting of pulmonary vein (PV) isolation, left atrial (LA) roof line, mitral isthmus line, complex fragmented atrial electrogram (CFAE) ablation (LA), and cardioverted at the end. He did well initially but then had recurrent atrial tachyarrhythmias despite multiple cardioversions and amiodarone administration. He was very symptomatic despite rate control, and referred for repeat electrophysiologic (EP) study and possible ablation. This is an increasingly common situation, in which ablation either is not completely successful or leads to other arrhythmias.

Baseline ECGs and Intracardiac Recordings

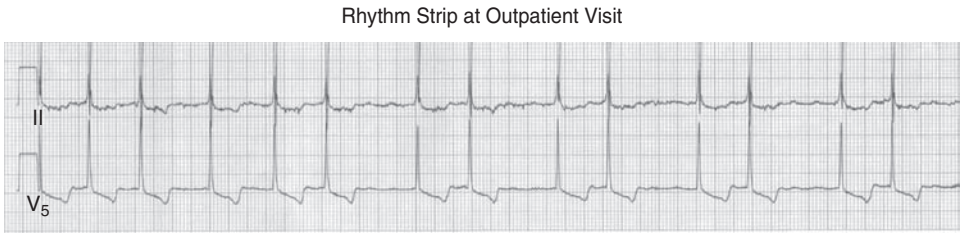


Figure 15-1

The rhythm in Fig. 15-1 appears to be rather irregular (R-R intervals) with no discernible atrial activity and would be appropriately interpreted as atrial fibrillation. However, the last half of the tracing shows QRS complexes that are paired and makes one wonder if there isn't some more organized atrial arrhythmia causing this.

Figure 15-2

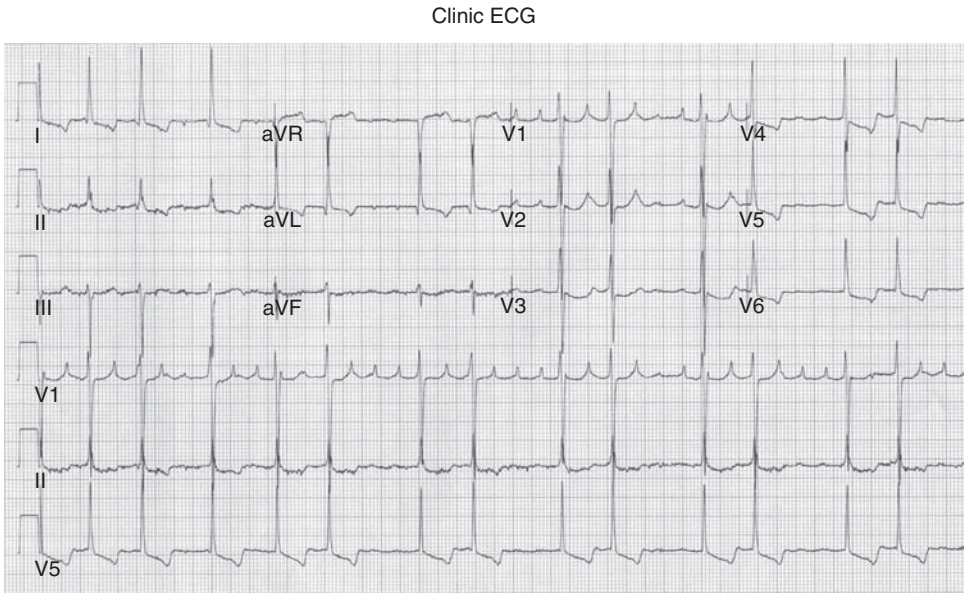


Fig. 15-2 is the rest of that same ECG, showing quite organized activity that is really only evident in lead V1; leads 1 and aVL show very small and narrow P waves.

Figure 15-3

At the beginning of the EP study, the same rhythm was still present. Shown in Fig. 15-3 in 12 simultaneous ECG leads, it is evident that the P wave is quite narrow.

What Is the Likely Mechanism? [Fig. 15-4]

Figure 15-4

Fig. 15-4 is the same ECG, with increased gain on all of the leads. Now, it is evident that there is a very narrow P wave also in lead 1, not readily appreciated on the prior figure. Based on this evidence, the rhythm is clearly not atrial fibrillation, rather an atrial tachycardia (cycle length [CL] 330 ms). But what is the mechanism of the tachycardia? The narrower the P wave relative to tachycardia cycle length, the more likely a focal mechanism is present. If focal, a very late diastolic (ie, just barely presystolic) electrogram will be sought for the ideal ablation target, whereas if it were instead macroreentry, a middiastolic site should be sought. Clearly, it is important to determine whether a focal process or macroreentry is present.

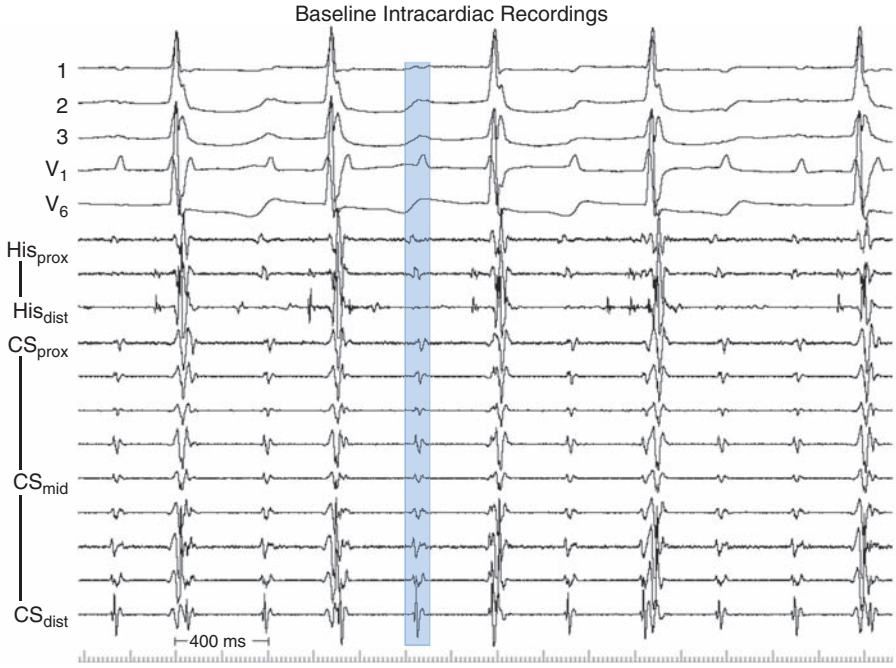


Figure 15-5

After obtaining vascular access and placing electrode catheters in the coronary sinus and His bundle region, the electrograms in Fig. 15-5 are recorded. Again, the "envelope" of atrial activation is very narrow, similar to the P wave during tachycardia.

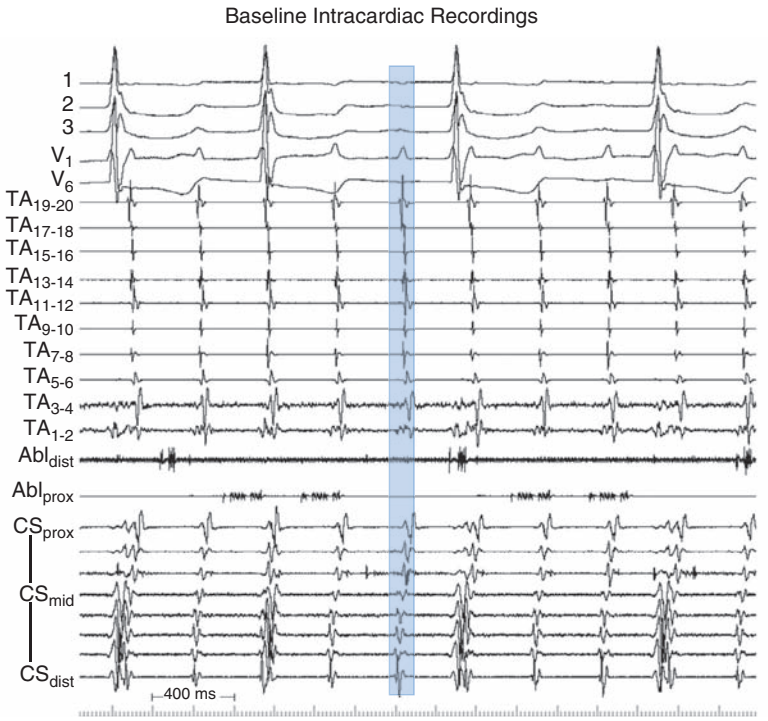


Figure 15-6

Another catheter is placed, this one around the tricuspid annulus (TA), hoping to get more information about atrial activation (Fig. 15-6). All of its electrograms, representing much of right atrial activation, are in the same general "envelope," and all occur within the timing of the surface P wave. This is again suggestive of a focal process. However, this is not certain, and we have to do more to prove or disprove whether it is focal before deciding what our ablation target should look like.

Table 15-1 is a brief comparison of features of different forms of focal propagation from an apparent point source, versus macroreentry.

TABLE 15-1 Atrial Tachycardias

	Focal			
	Automaticity	**Triggered Activity**	**Microreentry**	**Macroreentry**
Onset	Spontaneous	Induced (Burst > PES)	Induced (PES >> Burst)	Induced (PES >> Burst)
Occurrence	Incessant, bursts	Variable	Sporadic, sustained	Sporadic, sustained
P wave vs TCL	Small fraction	Small fraction	Small fraction	Large portion
Atrial envelope vs TCL	Small fraction	Small fraction	Small fraction	Large portion
Isoproterenol effect	Facilitates onset; acceleration	Facilitates onset; acceleration	Minimal effect	Minimal effect
Adenosine effect	Variable effect	Termination	Minimal effect	No affect/acceleration
Response to single premature extrastimuli	Reset or fusion; flat/increasing	Reset or fusion; decreasing	Reset or fusion; flat/increasing	Reset + fusion; flat/increasing
Response to overdrive pacing	Suppression; ↑RC with ↓PCL	Acceleration; ↓RC with ↓PCL	Entrainment; No Δ RC w/↓PCL	Entrainment; No Δ RC w/↓PCL
Ablation target	Late diastolic; unipolar QS	Late diastolic; unipolar QS	Prolonged diastolic	Middiastolic
Response to RF	Accelerate/stop	Accelerate/stop	Slow/stop	Slow/stop

PCL, paced cycle length; PES, programed electrical stimulation; RC, return cycle; TCL, tachycardia cycle length.

Diagnostic Pacing Maneuvers

Pacing from RA at Different Rates

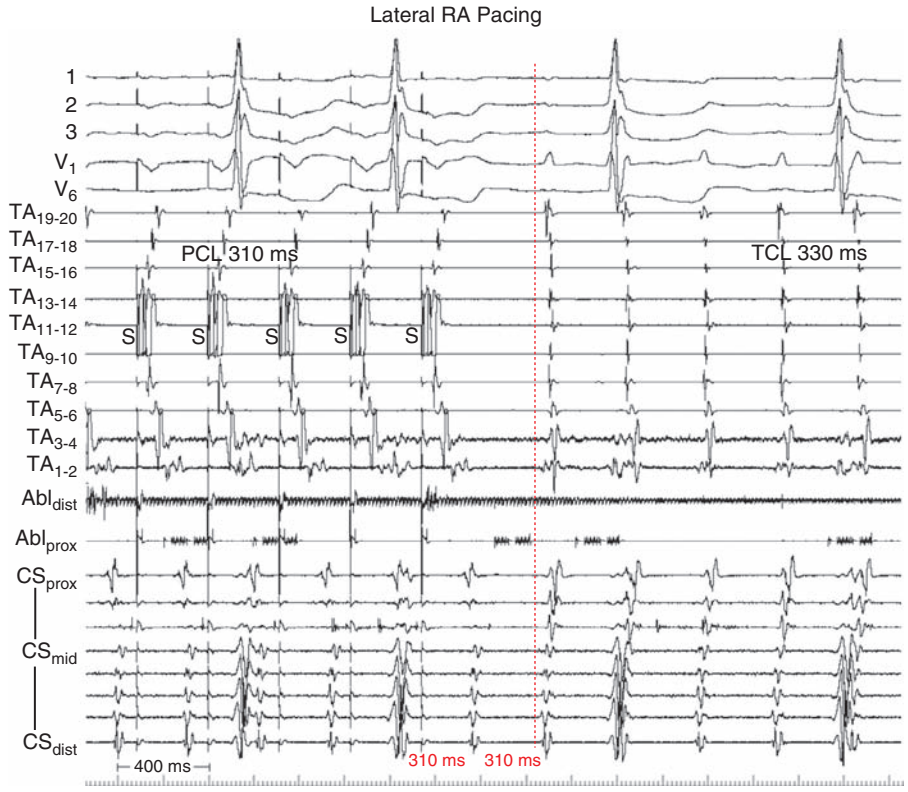


Figure 15-7

In order to try to determine whether a focal process or macroreentry was responsible for the arrhythmia, the first test used was overdrive pacing from the lateral right atrium (RA). We are careful to say "overdrive pacing" rather than "entrainment" at this point, because until we know fusion is present, it is simply "overdrive pacing." In Fig. 15-7, the last five stimuli (S) from the lateral right atrium are shown, after which the same tachycardia resumes. It appears that the right atrium is not part of the process because there is such a long delay until those electrograms are seen again, whereas recordings from the coronary sinus (CS) appear to occur slightly earlier when the tachycardia resumes. However, recordings in the distal half of the coronary sinus catheter are actually controlled by a prior pacing stimulus, because the interval between the first and second CS electrograms after pacing is the same as the paced cycle length. Thus a tremendous amount of slow conduction is present between the stimulation site and the distal coronary sinus, indicating that slow conduction (a necessary constituent of reentry) is certainly present. This in itself does not mean that the arrhythmia is reentrant, however.

Figure 15-8

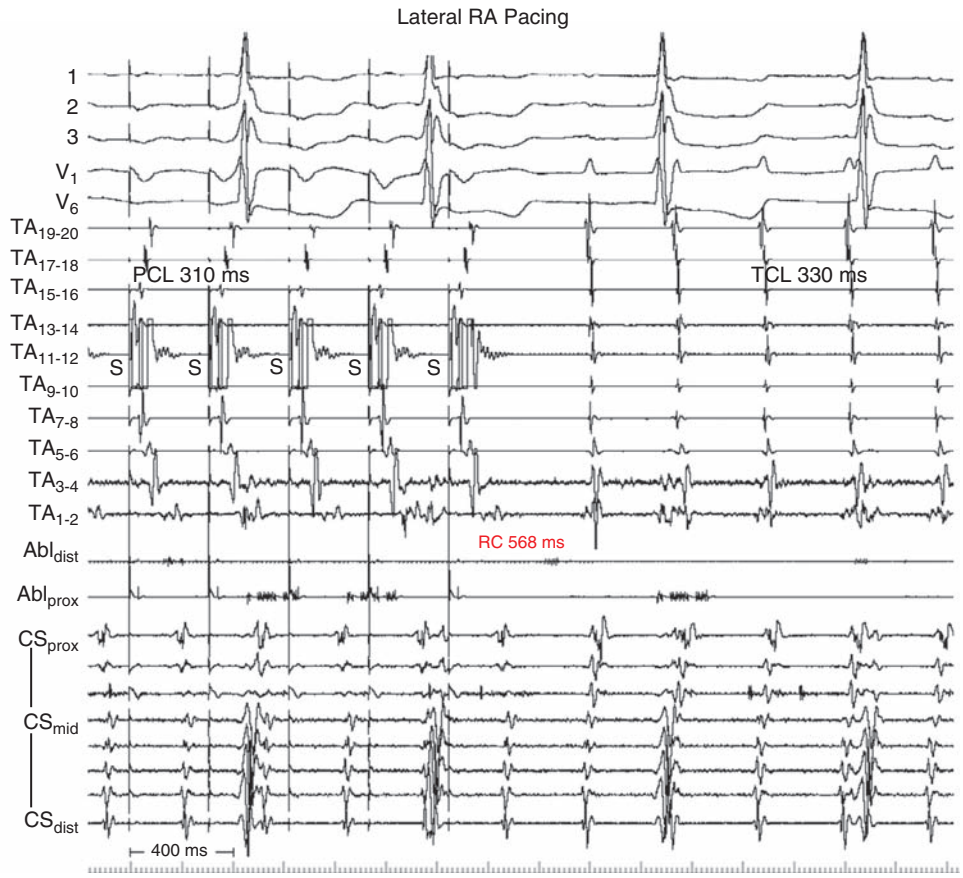


Fig. 15-8 is another burst of pacing at the same cycle length, from the same right atrial site. Here, the "return cycle" (RC) to right atrial recordings is measured at 568 ms, considerably longer than the tachycardia cycle length (TCL). This disparity is not commonly seen in reentry, but may be seen in overdrive suppression of discharge from an automatic focus.

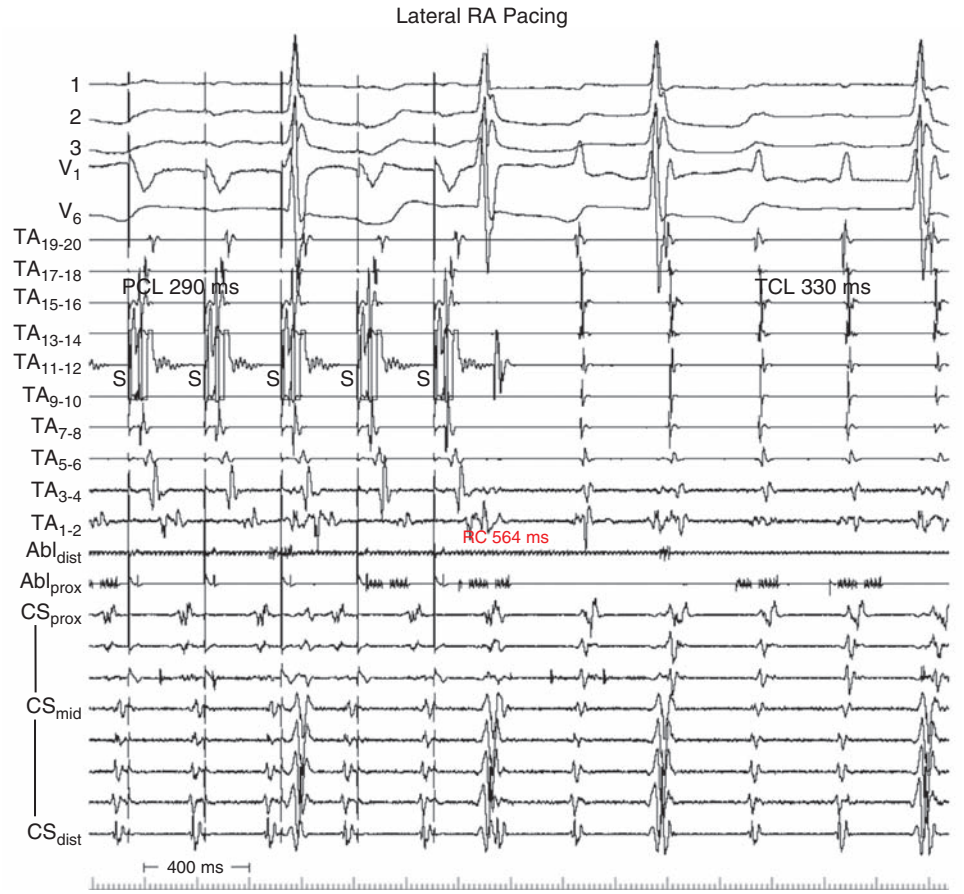


Figure 15-9

In Fig. 15-9, pacing again from the same site, now at a more rapid cycle length, produces a return cycle similar to what was seen earlier. With an automatic focus, more rapid pacing results in more overdrive suppression and a longer return cycle. Thus what is seen here is not entirely keeping an automatic focus.

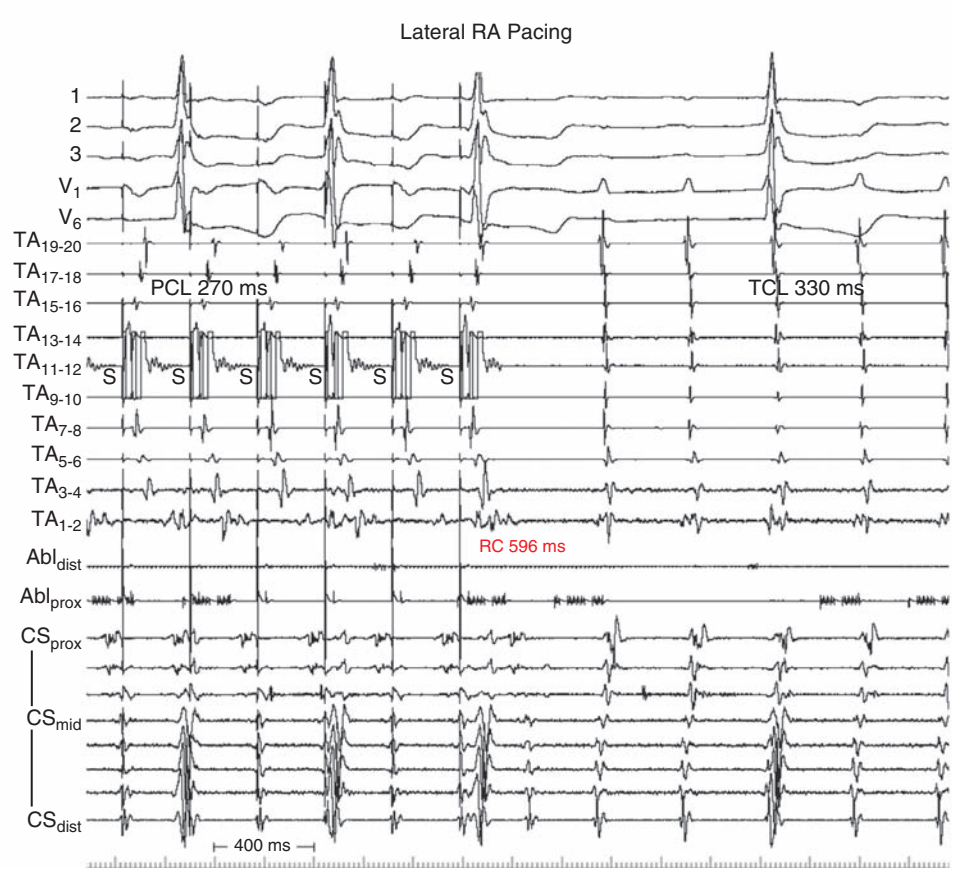


Figure 15-10

However, pacing faster still (270 ms) from the same right atrial site results in a longer return cycle (596 ms), as seen in Fig. 15-10. This *is* consistent with overdrive suppression of an automatic focus.

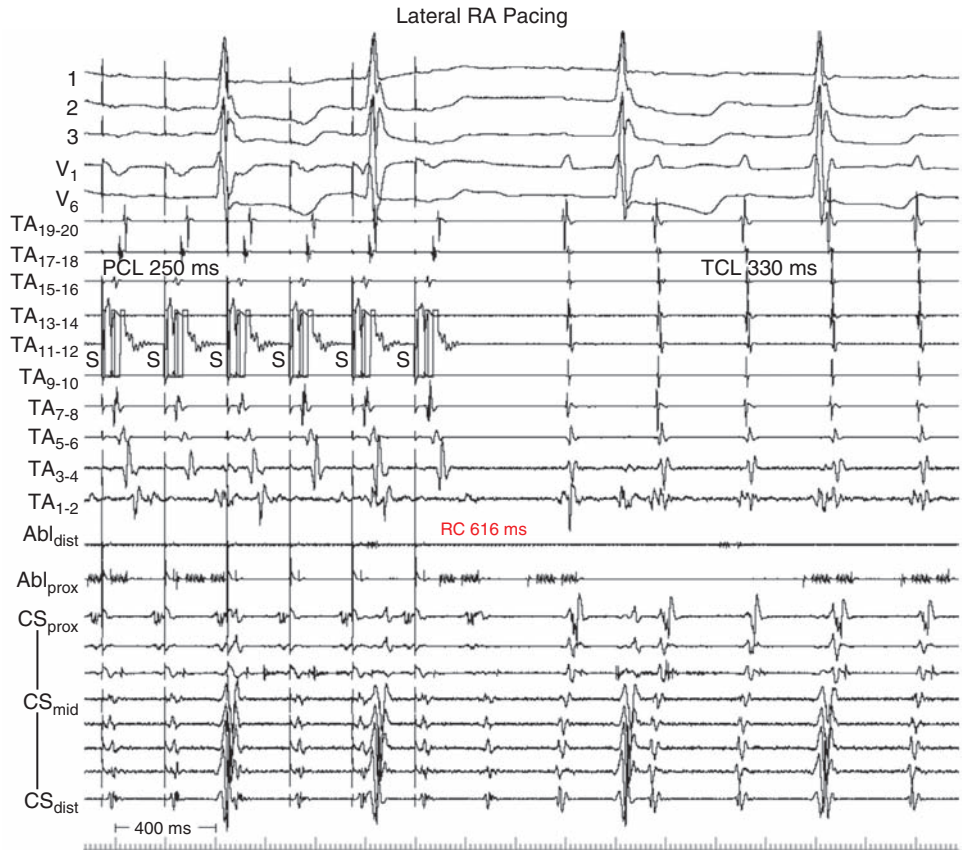


Figure 15-11

Pacing faster still (250 ms), as shown in Fig. 15-11, results in further prolongation of the return cycle to 616 ms, again consistent with overdrive suppression of a focus.

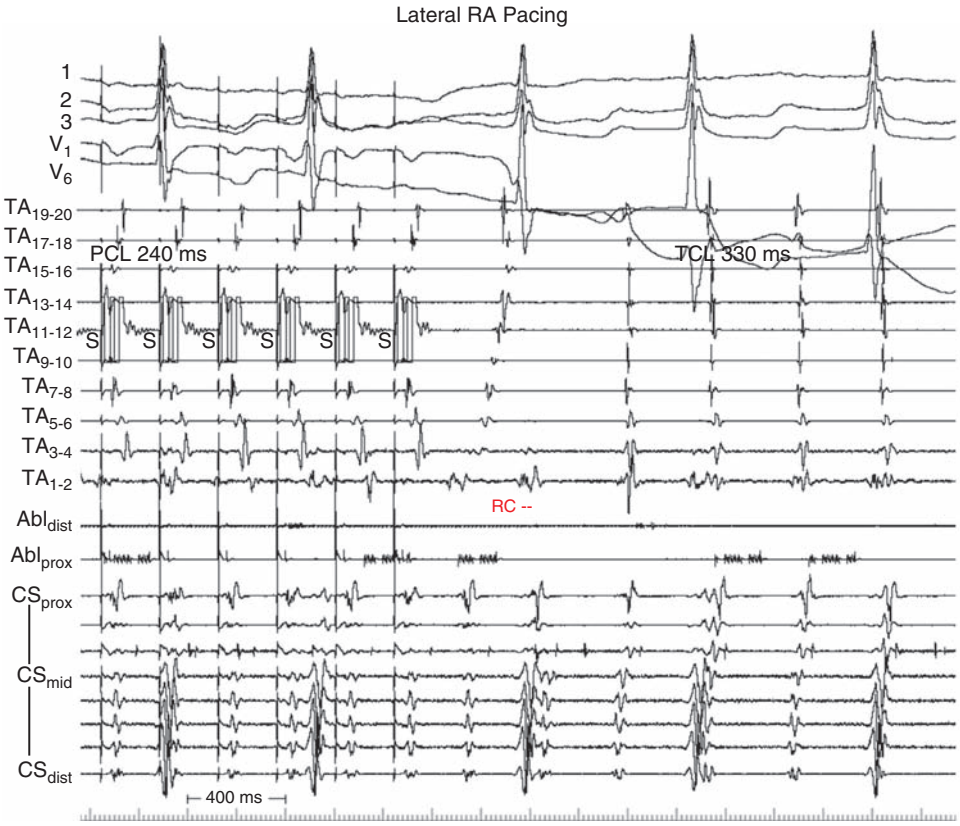


Figure 15-12

Pacing faster still (240 ms) from the same right atrial site (Fig. 15-12) yields uninterpretable results, because the first beat after cessation of pacing is not a tachycardia complex.

Pacing from Different Sites at Same Rate (Figures 15-13 to 15-16)

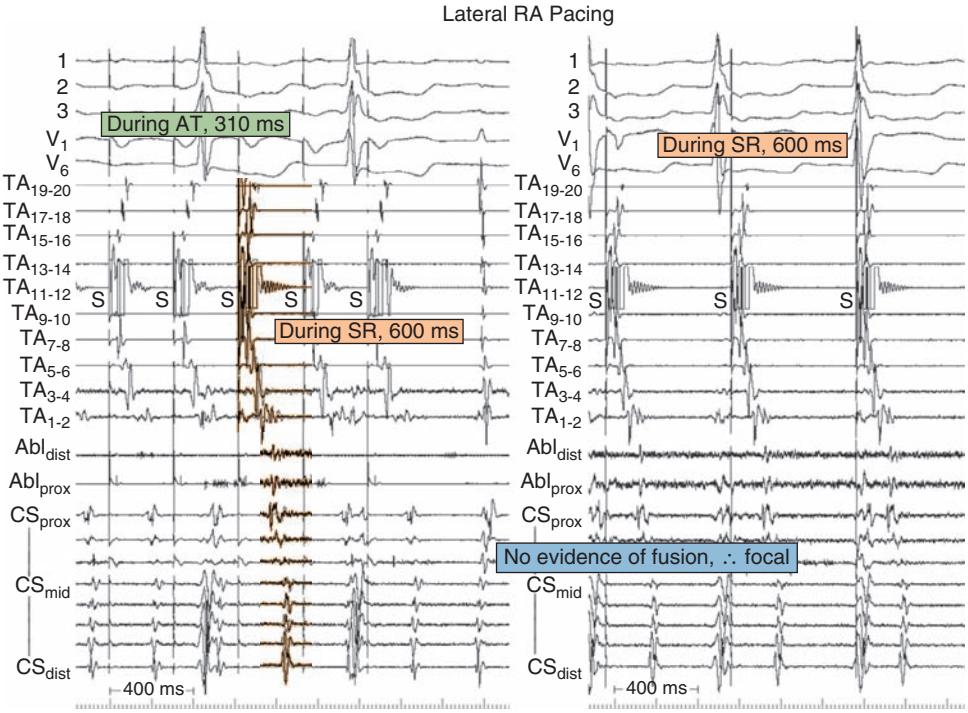
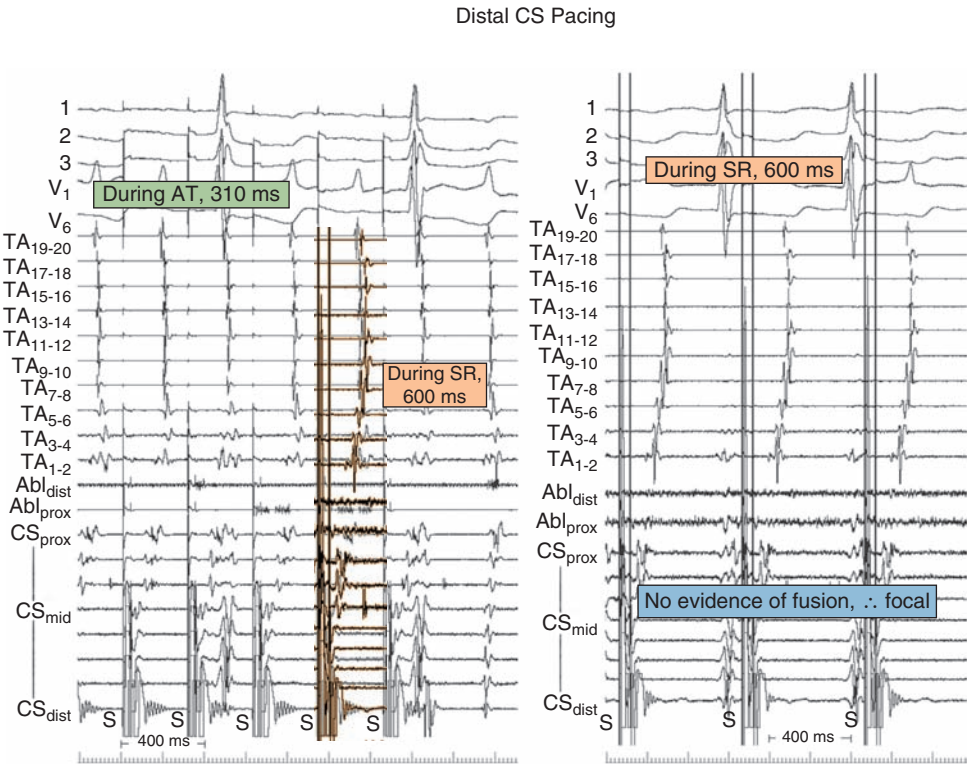


Figure 15-13

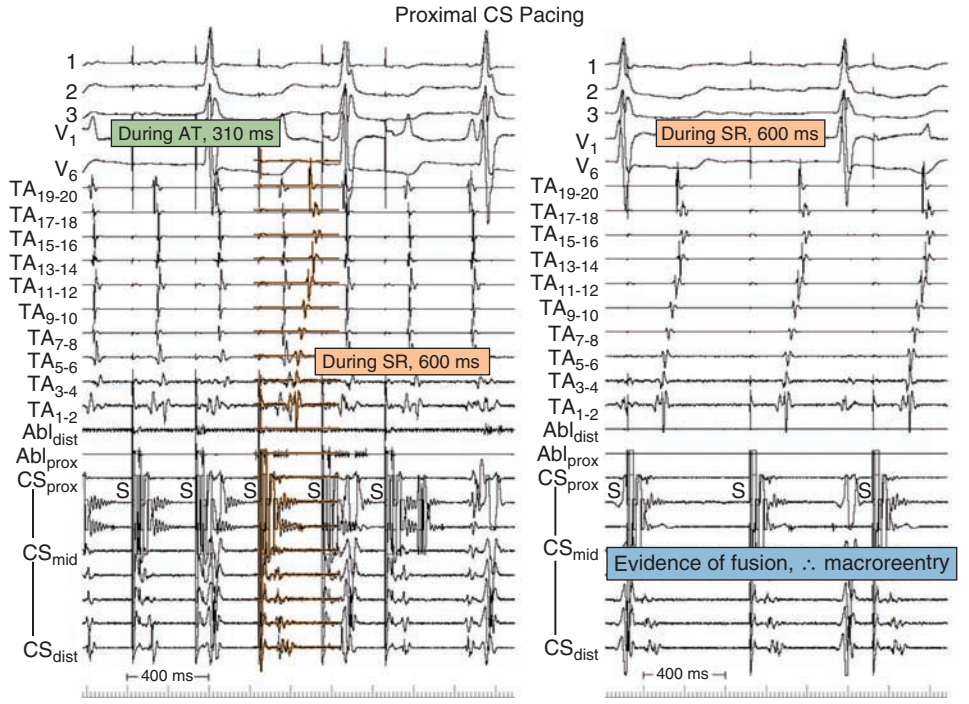
So far, there is evidence for and against the presence of an automatic focus. Further information can be obtained by evaluating activation sequences of pacing from different sites during tachycardia; if pacing during tachycardia does not resemble either tachycardia or "pure" pacing from that site during sinus rhythm, fusion is present, and macroreentry is the diagnosis. On the left of Fig. 15-13, pacing from the lateral right atrium at 310 ms (shown previously) is seen, and on the right, pacing from the same site but later in the procedure after tachycardia has terminated ("pure" pacing). A single complex of "pure" pacing from the site is superimposed on pacing during tachycardia (in *brown*). The activation sequences look identical, and thus there is no fusion. This is consistent with, but not diagnostic of, a focal process. If the same results are obtained when pacing from multiple other sites, a diagnosis of a focal process will be more certain.

Figure 15-14



In Fig. 15-14, pacing from the distal coronary sinus is shown both during tachycardia at left and during sinus rhythm at right ("pure" pacing). Again, a single complex of "pure" pacing is superimposed on a complex of pacing during tachycardia, which it again very closely resembles. Thus there is again no evidence of fusion, and brings us closer to a diagnosis of a focal process.

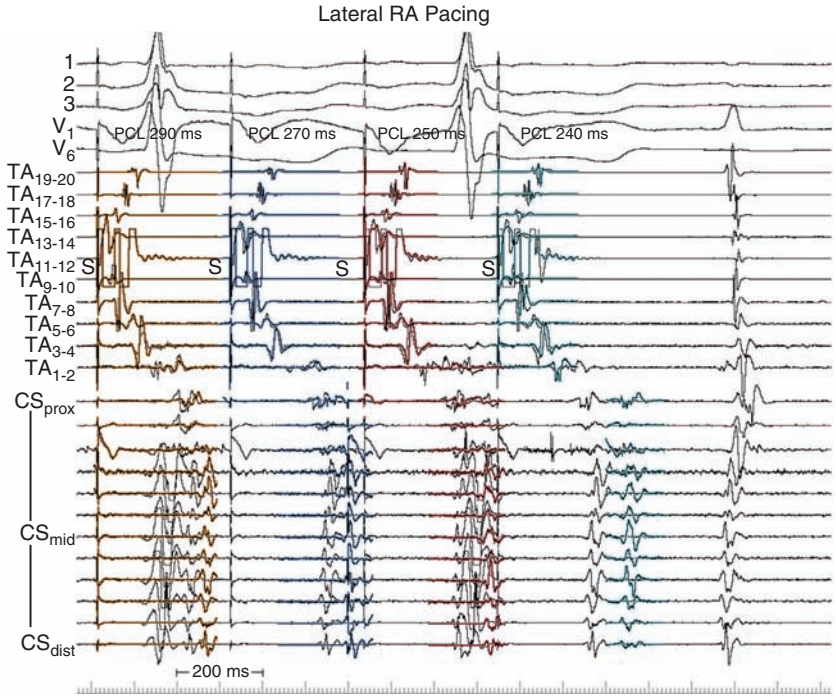
Figure 15-15



Another site is tested, the proximal coronary sinus (Fig. 15-15). As before, pacing during tachycardia is shown at left and pacing during sinus rhythm at right ("pure" pacing). Again, a single complex of "pure" pacing is superimposed on a complex of pacing during tachycardia. In this instance, however, the activation sequences are quite different, indicating the

presence of fusion when pacing during tachycardia. This changes everything, and establishes a diagnosis of macroreentry. It is important to note that a single instance of pacing that shows fusion can diagnose macroreentry, whereas it is much more difficult to prove that fusion is *absent,* requiring pacing from multiple sites sometimes at multiple cycle lengths.

Pacing from RA at Different Rates Superimposed



When Looking for Fusion:

A. Pace far away from presumed exit/focus
B. Evaluate signals far away from pacing site

Figure 15-16

Another way in which macroreentry can be diagnosed is the demonstration of *progressive fusion.* This is performed by pacing at the same site, but different cycle lengths. If macroreentry is present, the faster one paces from the same site, more of the chamber will be governed by the wavefront emanating from the pacing site, and less from the circuit. Thus the faster one paces, the more the resultant activation sequence looks like pure pacing and less like tachycardia. In Fig. 15-16, pacing from the lateral tricuspid annulus is shown over five different cycle lengths. The black recordings are at 310 ms, with a single complex of pacing at progressively shorter cycle lengths superimposed on sequential complexes. It is evident that 1) the faster one paces, as stated previously, the more the resultant activation sequence looks like pacing and less like tachycardia, and 2) when evaluating electrograms near the pacing site, they usually look the same, whereas evaluating electrograms more distant from the pacing site shows greater differences at different cycle lengths. Thus to have the greatest chance of demonstrating fusion, one should choose a pacing site far away from the presumed exit of a focus or circuit, and evaluate recordings far from the pacing site.

Mapping in Left Atrium

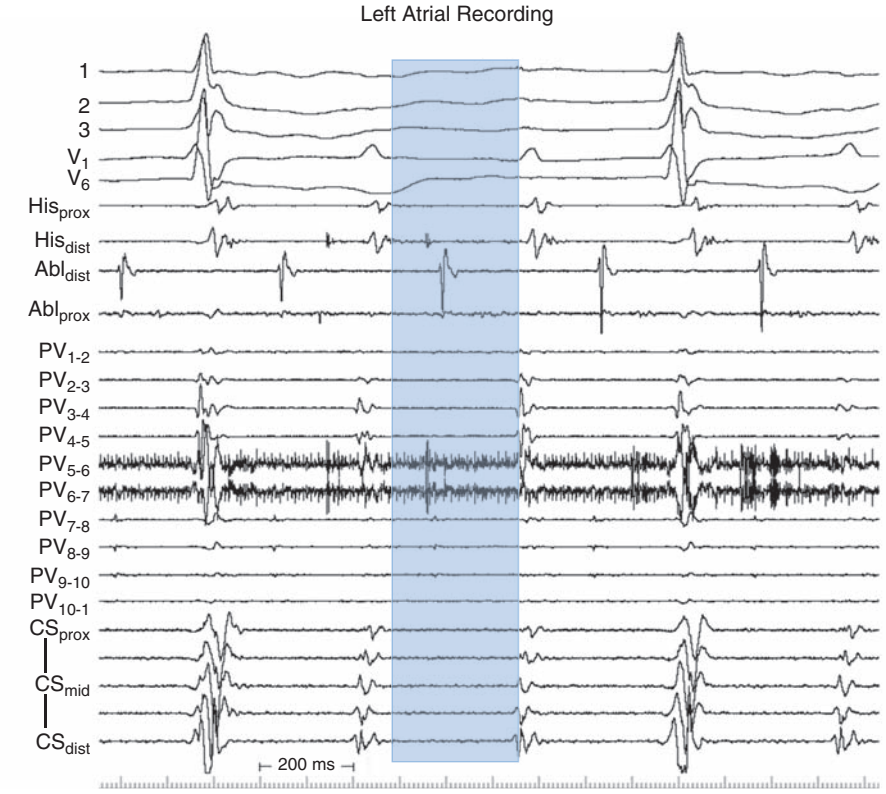


Figure 15-17

Now that a firm diagnosis of macroreentry has been established by a couple of methods, the ablation target becomes a middiastolic potential that can now be sought. Before establishing whether a focal process or macroreentry is present, great caution must be exercised in performing activation mapping because results may be misleading especially in instances in which the focal process is actually present, but substantial slow conduction is also present (such as after a previous ablation procedure). In Fig. 15-17, the ablation catheter records a sharp, isolated potential almost exactly in the middle of diastole (*blue shaded box* from the end of one P wave to the beginning of the next). It appears that we have a good ablation target already.

Electroanatomic Mapping

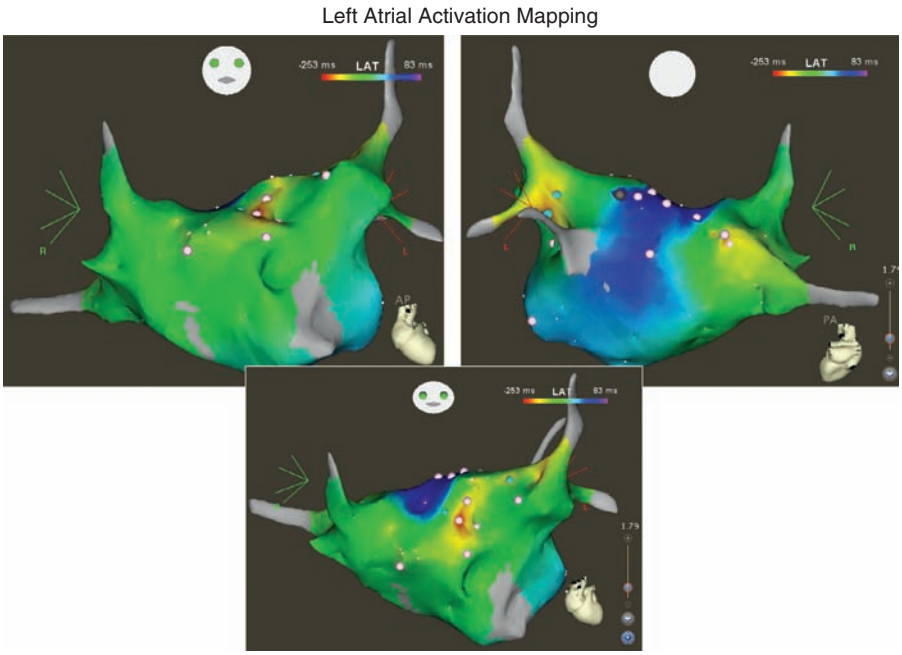


Figure 15-18

Fig. 15-18 is an activation map of the left atrium in several attitudes. This is somewhat disturbing because although a diagnosis of macroreentry has been established, the activation map suggests a focus on the roof of the left atrium *(red area)*, or perhaps a second focus in the region of the left upper pulmonary vein (also *red*). How can this be resolved with the diagnosis of macroreentry?

Mapping and Touch-up Ablation in Pulmonary Veins

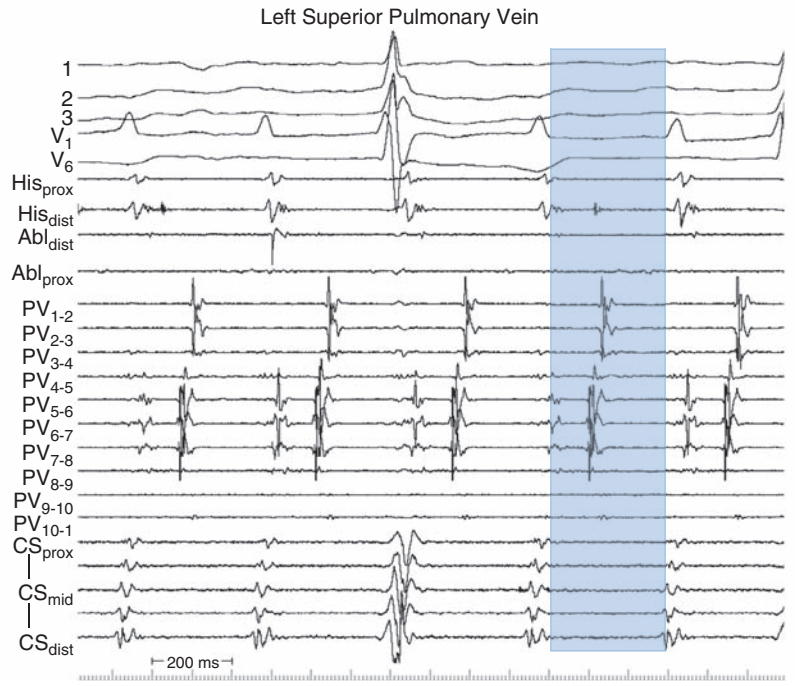


Figure 15-19

The problem with the prior middiastolic potential and the electroanatomic activation map was that pulmonary vein potentials were "contaminating" the activation map, and the middiastolic signal was actually a pulmonary vein recording (Fig. 15-19). Could this be a focus in a pulmonary vein? No, because it has been established as being macroreentry rather than a focus. However, the pulmonary vein potentials are quite large, and it is difficult to know how they should be incorporated into an electroanatomic activation map. One strategy that can be quite useful is to proceed with pulmonary vein isolation at this point; if tachycardia terminates, perhaps pulmonary veins were involved. If tachycardia persists, the PVs were obviously not involved, and the confusing signals they harbored will no longer be problematic.

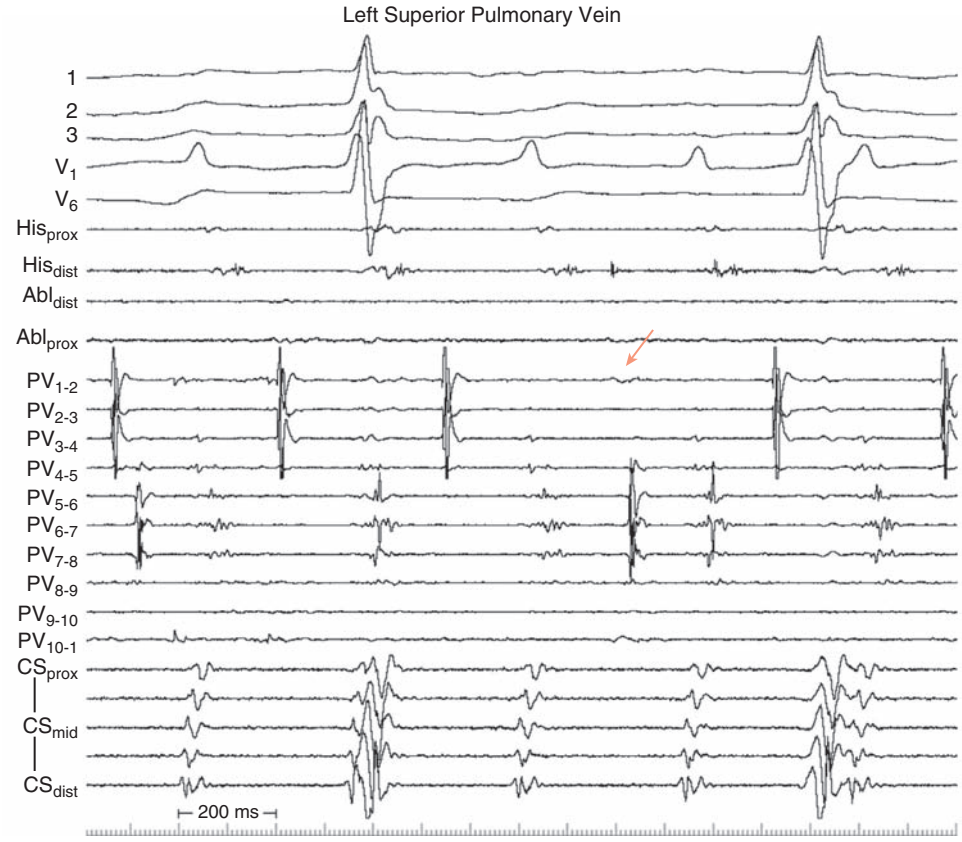


Figure 15-20

Immediately before attempts at isolating the left pulmonary veins, the recordings in Fig. 15-20 were made. Clearly, because the tachycardia persists despite the absence of the signal in PV 1-2 through PV 3-4 on one of the cycles *(orange arrow)*, this pulmonary vein cannot be responsible for the ongoing arrhythmia.

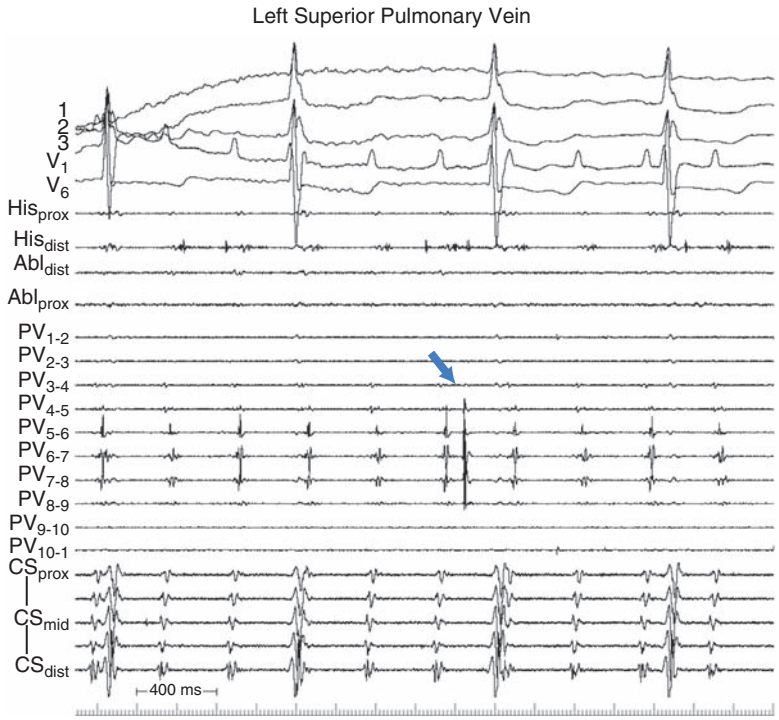


Figure 15-21

After ablation to encircle the left pulmonary veins, they have been isolated (Fig. 15-21). The *blue arrow* points to a random, dissociated potential spontaneously firing from the PV. Other signals noted in PV 5-6 through PV 7-8 were proven to be "far-field" recordings from the adjacent left atrial appendage. Clearly, the left pulmonary veins were not responsible for the ongoing arrhythmia.

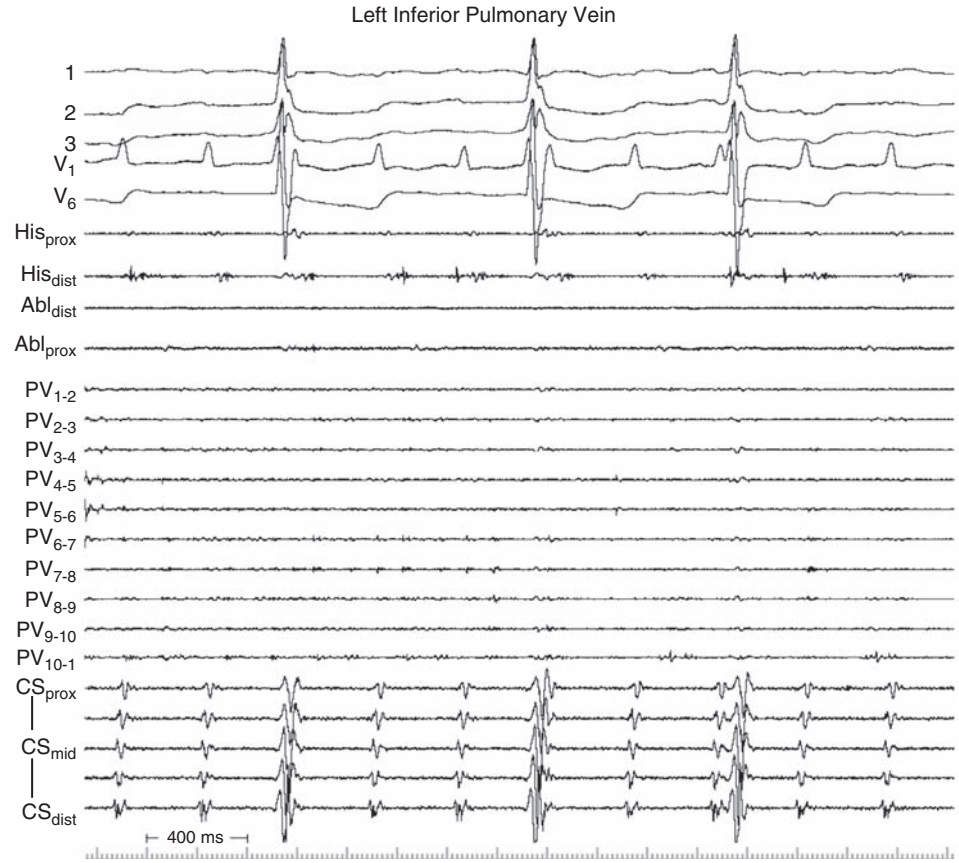


Figure 15-22

Recording from the left inferior pulmonary vein after wide area catheter ablation (Fig. 15-22) reveals no potentials whatsoever.

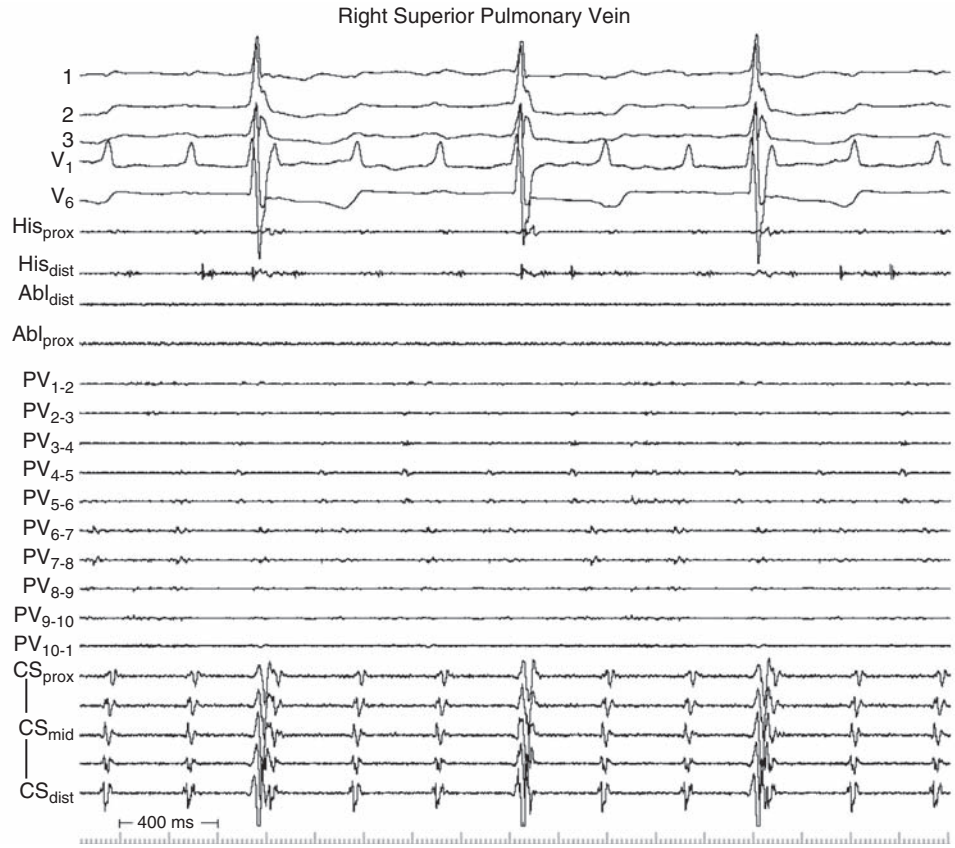


Figure 15-23

Similarly, as shown in Fig. 15-23, the right superior pulmonary vein showed no potentials, having been permanently isolated at the time of the prior procedure.

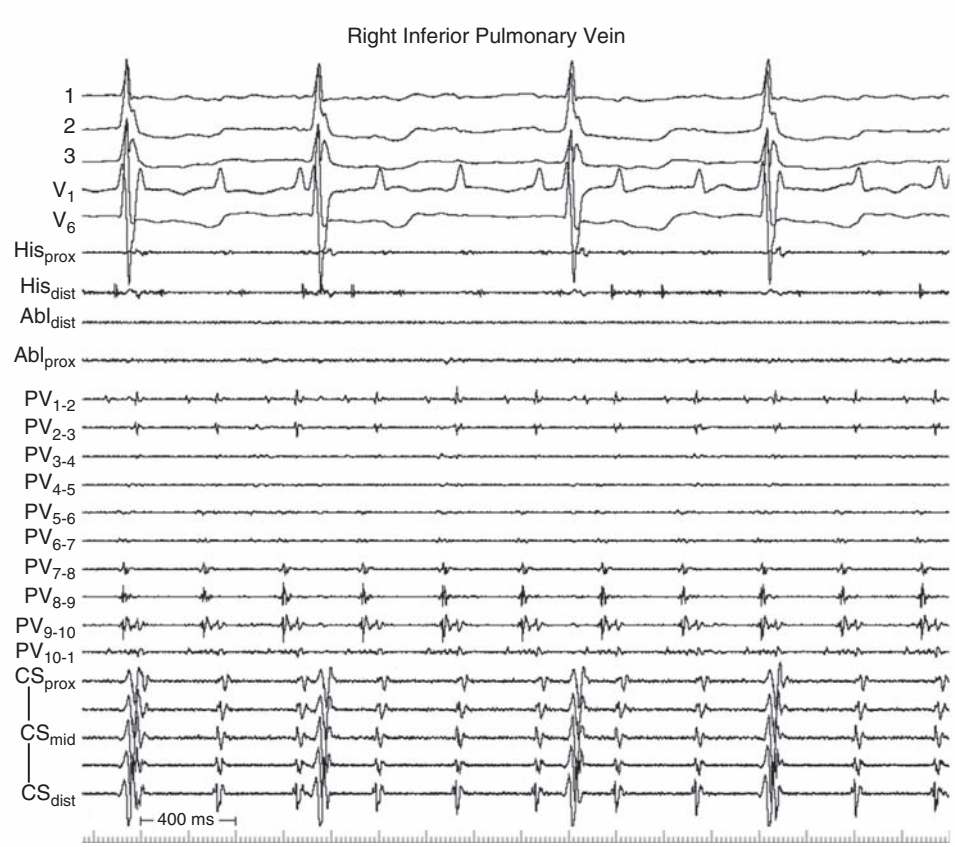


Figure 15-24

The right inferior pulmonary vein showed residual potentials of some interest (Fig. 15-24), because they were quite prolonged.

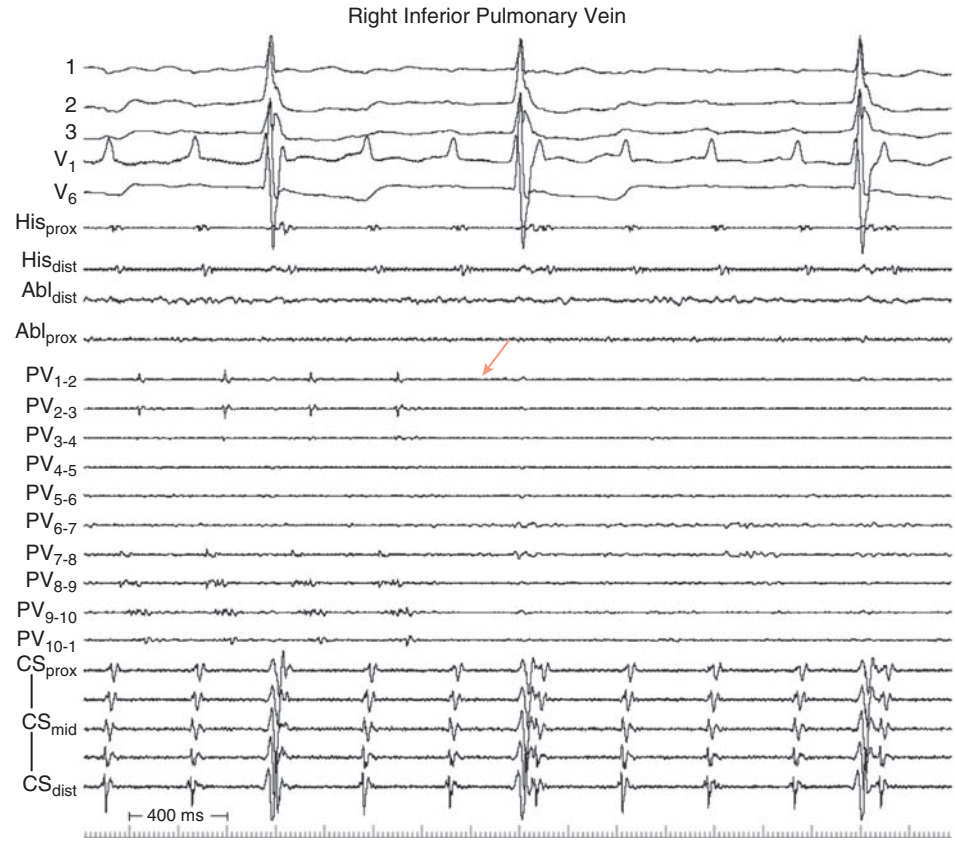


Figure 15-25

Isolation of this pulmonary vein occurs midway through the recordings in Fig. 15-25 *(orange arrow)*, again indicating that it is not responsible for the ongoing arrhythmia.

Electroanatomic Mapping Before and After PV Isolation

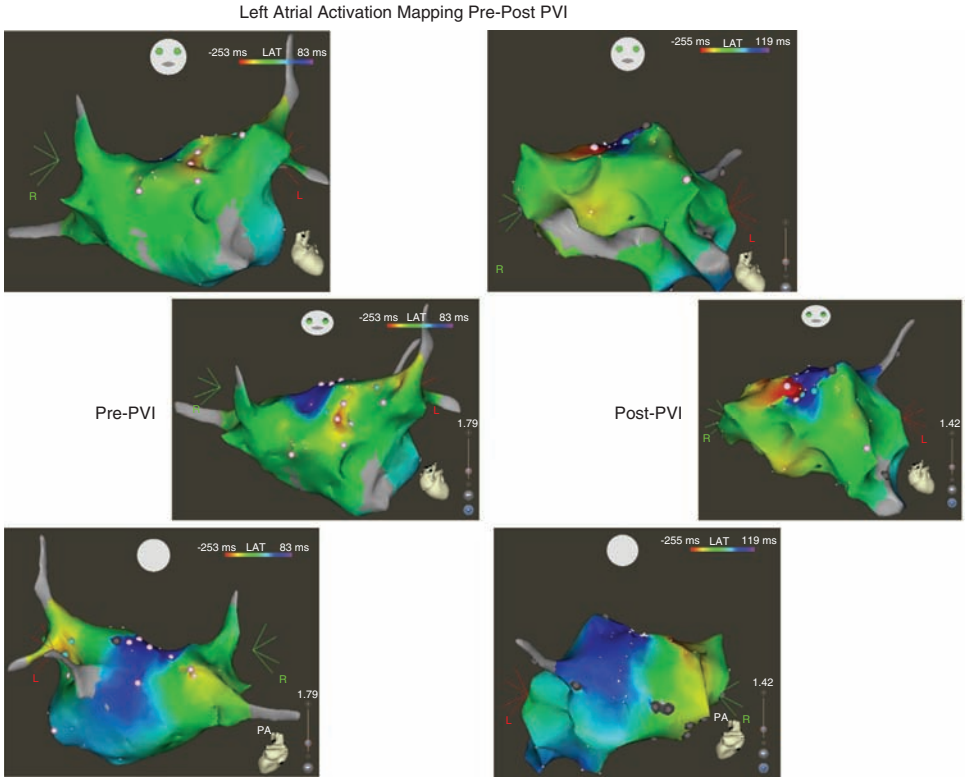


Figure 15-26

The prior electroanatomic map is shown on the left in Fig. 15-26, and on the right when repeated after PV isolation. Now that confusing pulmonary vein potentials have been removed from the activation map, a large reentrant circuit is more readily evident, involving the left atrial roof.

Mapping and Pacing at Left Atrial Roof

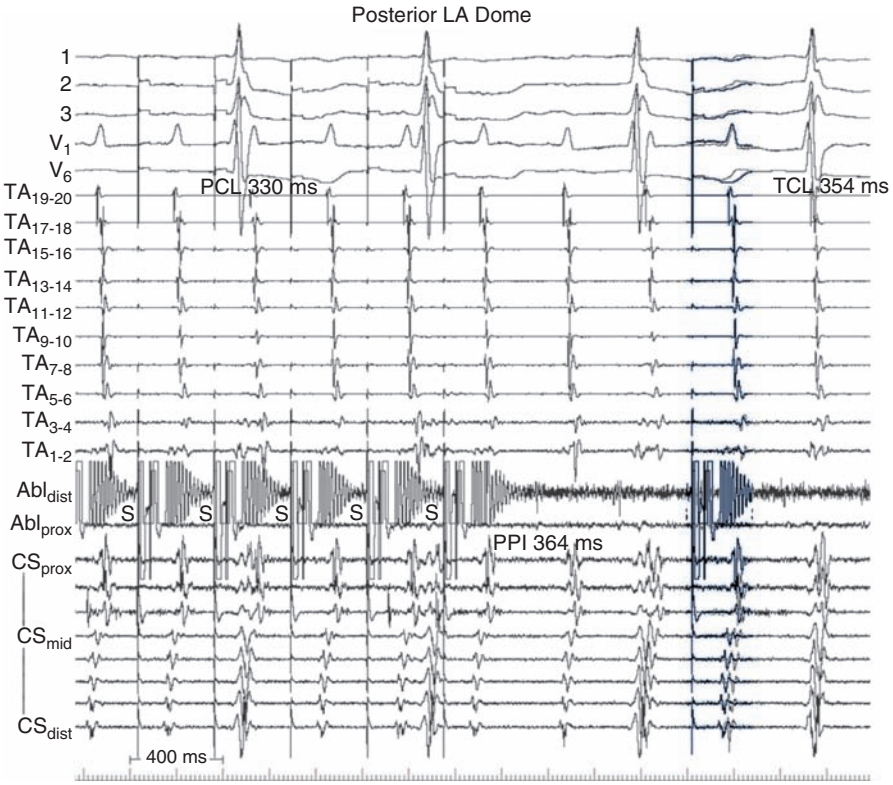


Figure 15-27

Candidate sites for ablation can be tested by overdrive pacing, to ascertain whether they are actually good target sites or not. In Fig. 15-27, pacing from a site on the roof of the left atrium (showing a middiastolic recording during tachycardia, not readily evident here because of distortion after pacing) yields a postpacing interval (PPI) slightly longer than tachycardia cycle length (TCL); a single complex of pacing on the left side has been superimposed on a single beat of tachycardia on the right side, showing strong similarity (though not an exact match). This could be a reasonable site for ablation.

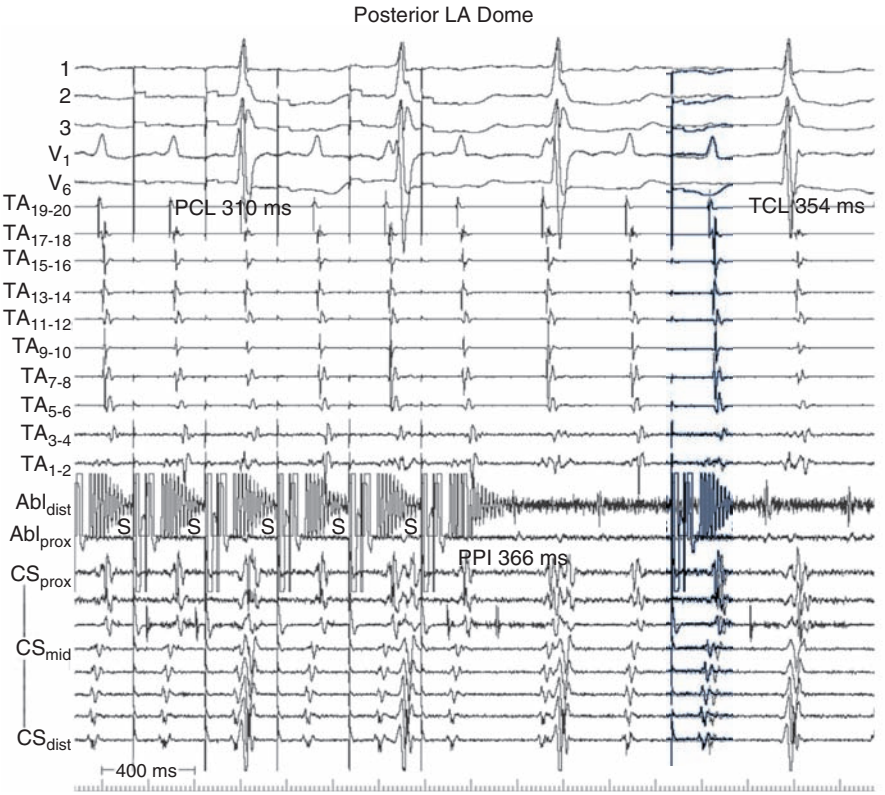


Figure 15-28

Earlier in the procedure, pacing at progressively rapid cycle lengths showed progressive lengthening in the return cycle, leading to suspicion of suppression of an automatic focus. Those data are still valid, and must be explained. In Fig. 15-28, pacing from the same site at a more rapid cycle length yields a similar return cycle to that of the previous figure. This amount of similarity was also seen at relatively slow pacing rates earlier in the procedure.

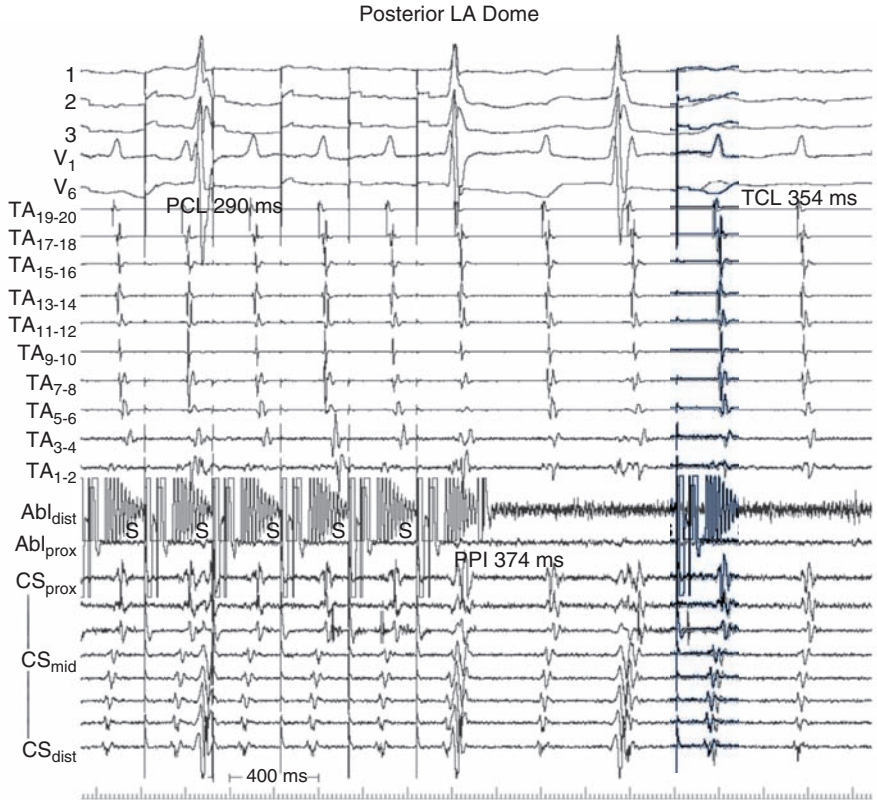


Figure 15-29

Pacing more rapidly from the same site in the left atrium now yields a longer postpacing interval (Fig. 15-29).

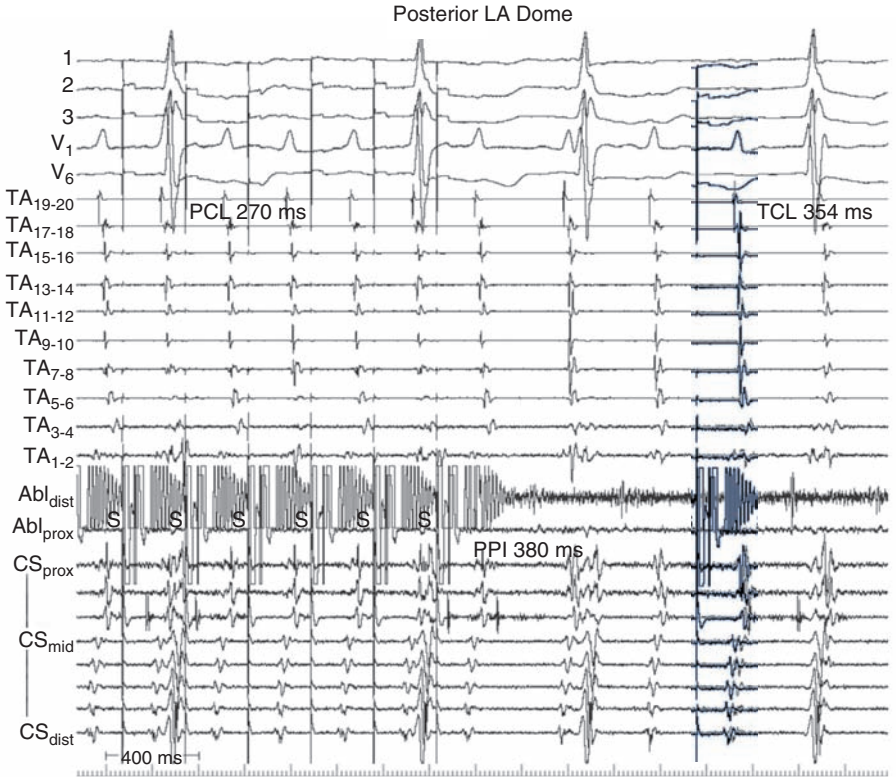


Figure 15-30

Pacing more rapidly still again yields a longer postpacing interval, as shown in Fig. 15-30. This is more than likely because of cycle length–dependent slowing of conduction

("decremental conduction"), not commonly observed in macroreentrant circuits because of their fixed length and conduction properties. However, in the presence of extensive scar, or medications that exhibit use dependence (sodium channel blockers), this phenomenon may be observed. The main significance is that one may never achieve a good "match" between postpacing interval and tachycardia cycle length (the desired result when pacing from the ideal ablation target site), because cycle length–dependent slowing of conduction will always artificially lengthen the postpacing interval.

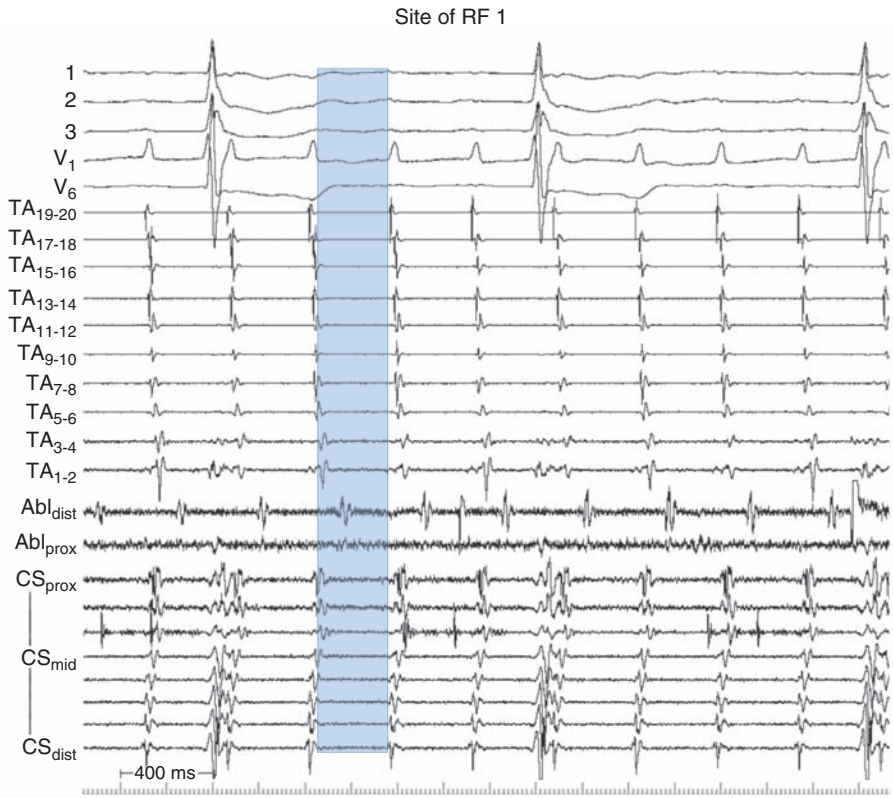


Figure 15-31

A site on the left atrial roof with an early-to-middiastolic recording (Fig. 15-31, diastole shown in *blue shading*) that had good responses to overdrive pacing (PPI similar to TCL, near-perfect pace match with tachycardia activation sequence) was chosen for ablation.

Ablation at Left Atrial Roof

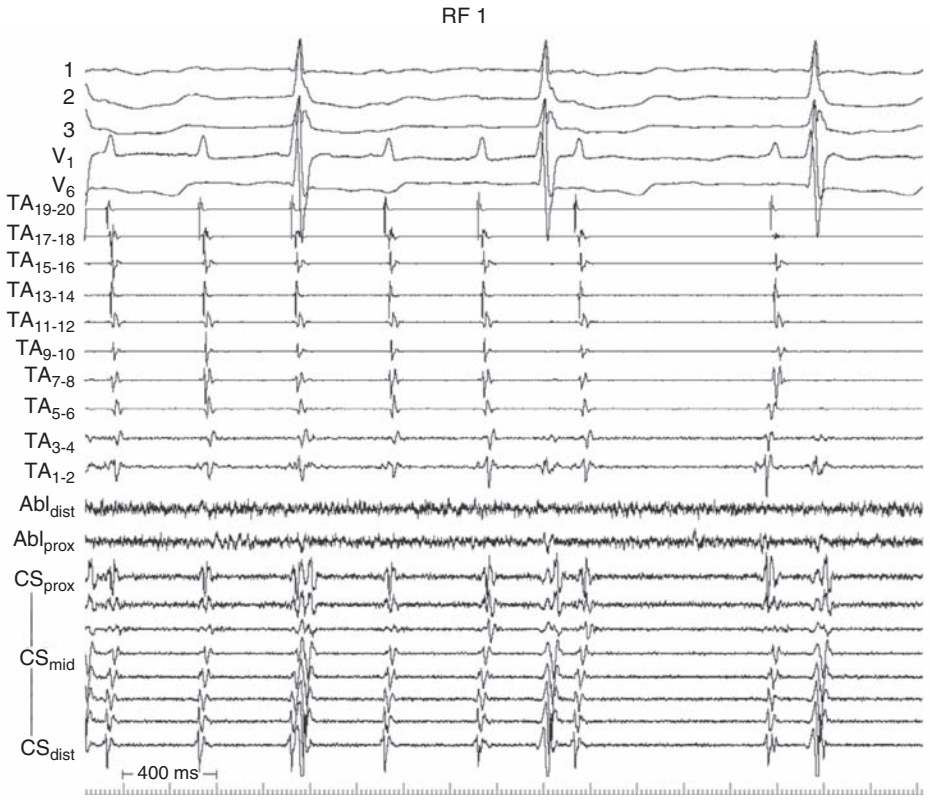


Figure 15-32

After several seconds of the first energy application, tachycardia slows and terminates to sinus rhythm (Fig. 15-32). A line of RF applications on the left atrial roof connecting the two lines encircling the pulmonary veins was made to complete the lesion set. Tachycardia was not inducible thereafter.

Right Atrial Cavotricuspid Isthmus Ablation and Assessment

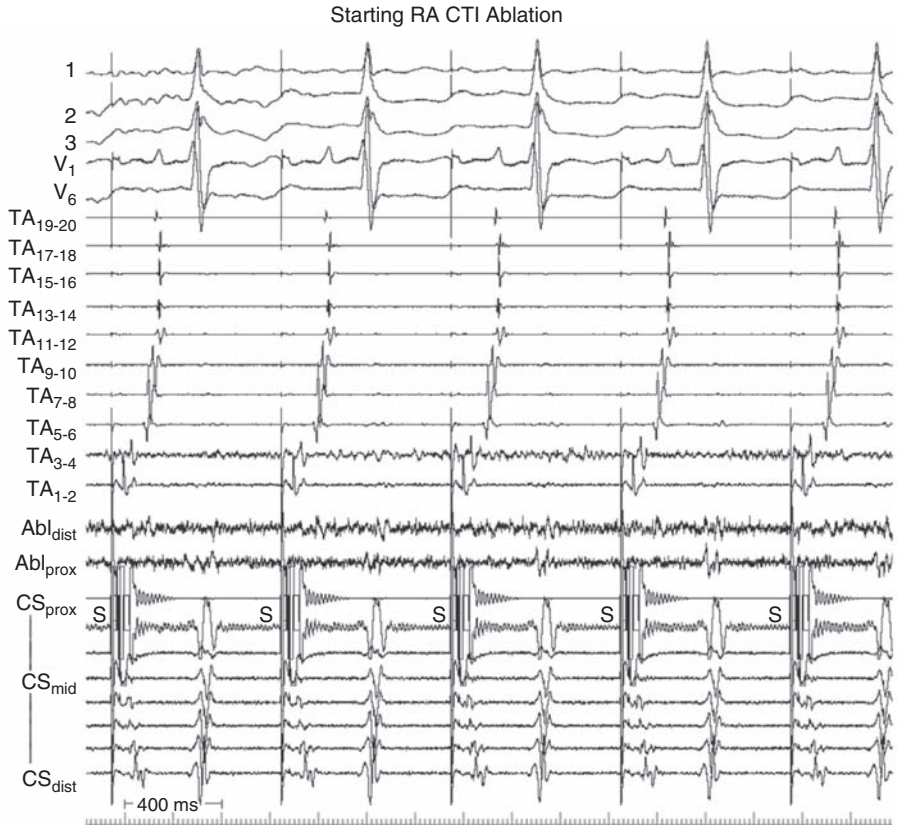


Figure 15-33

Because the patient had some ECGs from 2 yr previously that were compatible with right atrial cavotricuspid isthmus-dependent reentry, this area was also targeted for ablation. In Fig. 15-33, at the beginning of isthmus ablation, pacing from the proximal coronary sinus shows a uniform activation wavefront along the tricuspid annulus (TA).

Figure 15-34

After just one and a half minutes of ablation, electrograms in the cavotricuspid isthmus have already shown substantial delay (Fig. 15-34, *blue arrow*).

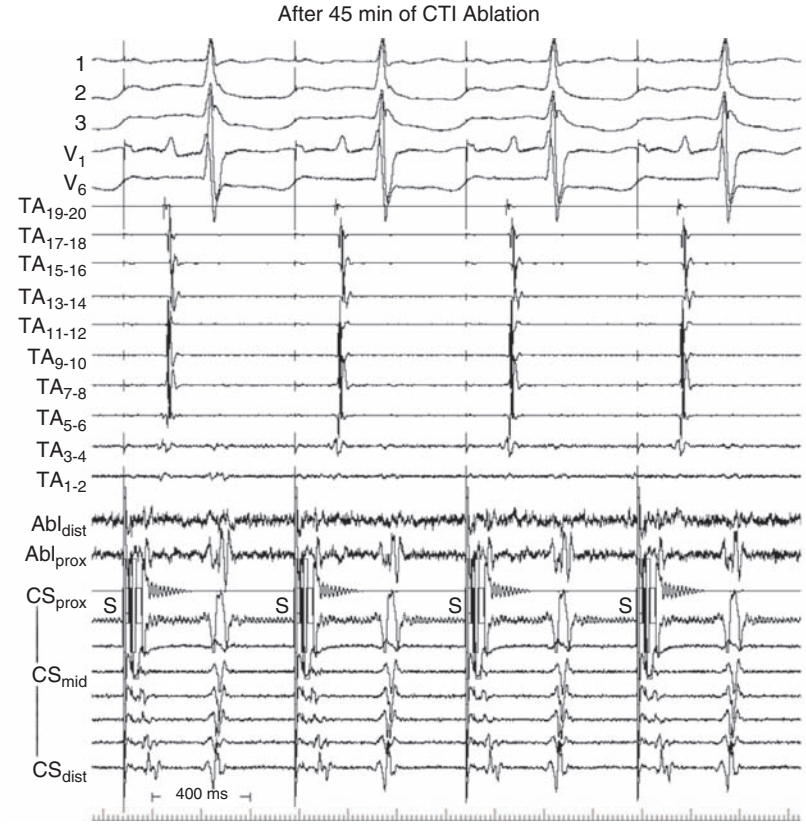


Figure 15-35

Although Fig. 15-35 is actually exactly the same figure as shown previously (Fig. 15-34), it serves to illustrate that after 45 minutes of further ablation in the cavotricuspid isthmus, there has been no substantial change beyond what was seen very early during ablation. This can be because of difficult anatomy ("pouch"), very large bundles of muscle that are difficult to ablate, or incorrect positioning of the tricuspid annulus catheter. Note the absence of any ventricular electrograms on any recording from this catheter, suggesting that it may be too posterior.

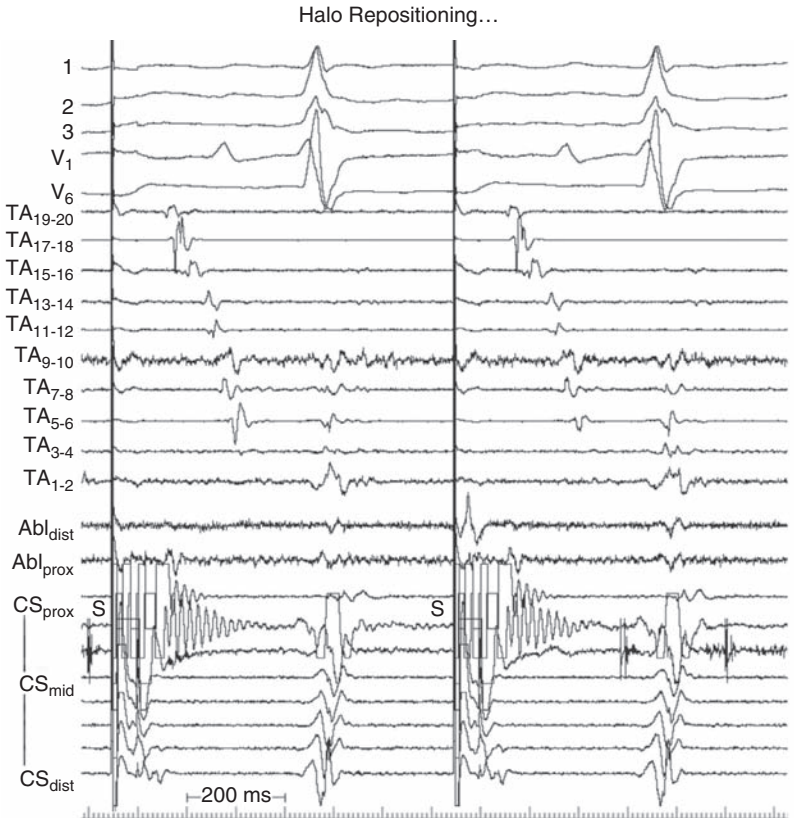


Figure 15-36

After repositioning the tricuspid annulus/"halo" catheter (note at least far-field ventricular signals on electrodes 1 to 10), the paced activation sequence seen in Fig. 15-36 is concordant with what would be expected when block is present in the cavotricuspid isthmus.

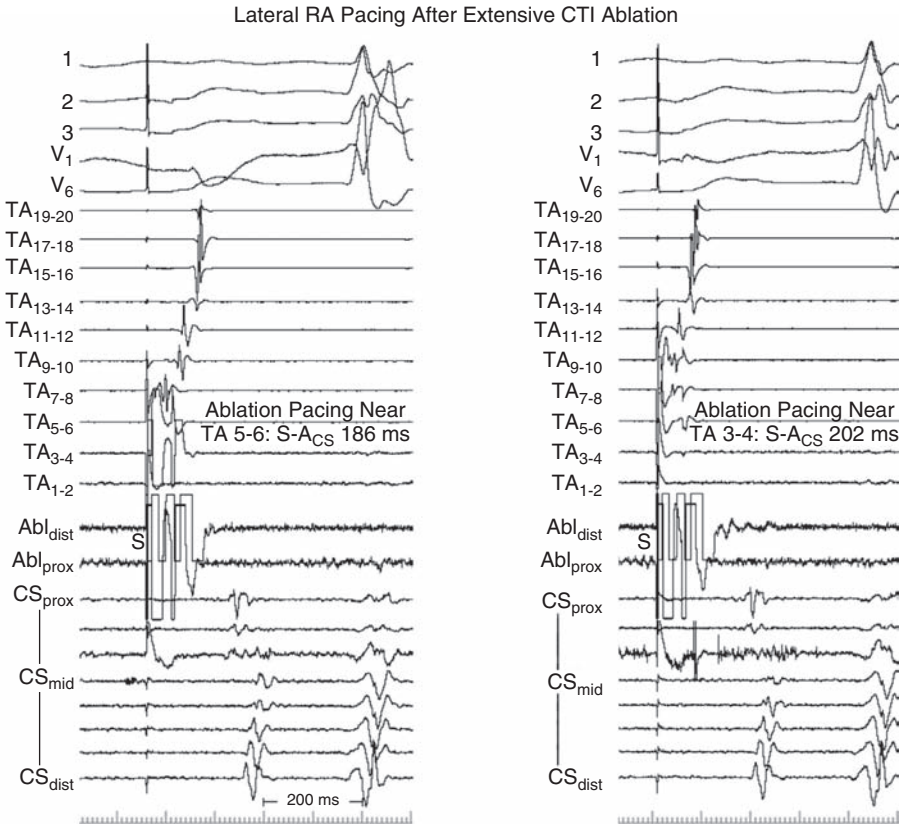


Figure 15-37

Pacing from the tricuspid annulus close to the ablation line (Fig. 15-37) demonstrates block in the lateral-medial direction, because electrodes that are anatomically closer to the ablation line (at right) are electrically further from the opposite side of the ablation line (CS recordings), and sites that are anatomically further away (at left) are electrically closer.

Final ECG

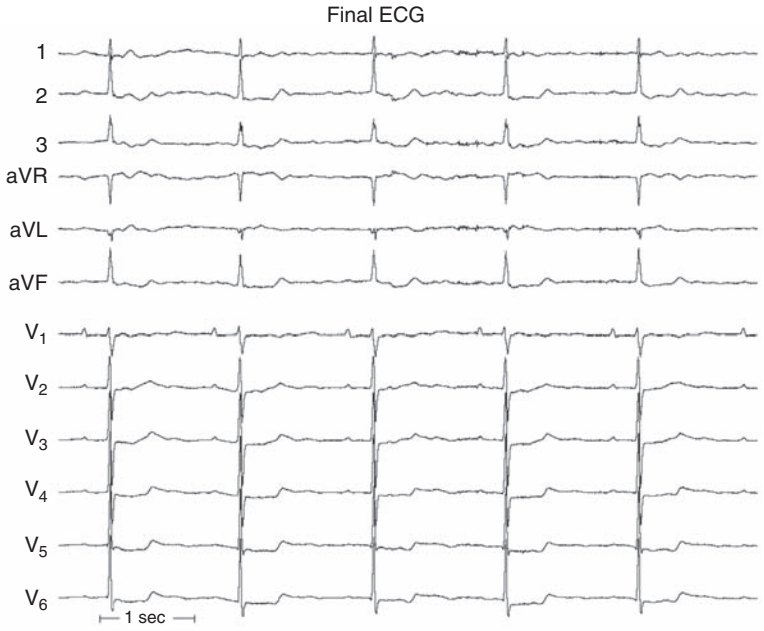


Figure 15-38

At the end of the procedure, sinus rhythm prevailed as shown in Fig. 15-38.

Summary

- Atrial tachycardias in the setting of extensive atrial disease (postsurgical, postablation, postirradiation, etc.) can be focal or reentrant (micro or macro)
- P-wave duration, P-wave duration relative to TCL, and intracardiac activation "envelope" relative to TCL can suggest focality versus macroreentry
- Overdrive pacing techniques are invaluable in diagnosis, revealing:
  - Whether the pattern is focal or macroreentry (and thus the ablation site characteristics)
  - Whether "decremental conduction" is present
- Maintaining correct catheter position (halo) may be critical
- PV potentials can cause confusion during activation mapping

16 Pulmonary Vein Isolation for Atrial Fibrillation

Case Presentation

The patient was a 57-year-old man with paroxysmal atrial fibrillation (AF) present for 3 years. Symptoms were palpitations, lightheadedness, and marked exertional fatigue during episodes 1 to 2 times weekly. His AF was refractory to antiarrhythmic drugs (sotalol, dronedarone), and atrial flutter was observed on some ECGs. Noninvasive evaluation findings were left atrial size 4.1 cm; normal left ventricular systolic function; and no valvular disease. He was referred for electrophysiology (EP) study and possible ablation because of drug-refractory symptomatic AF.

Baseline ECG

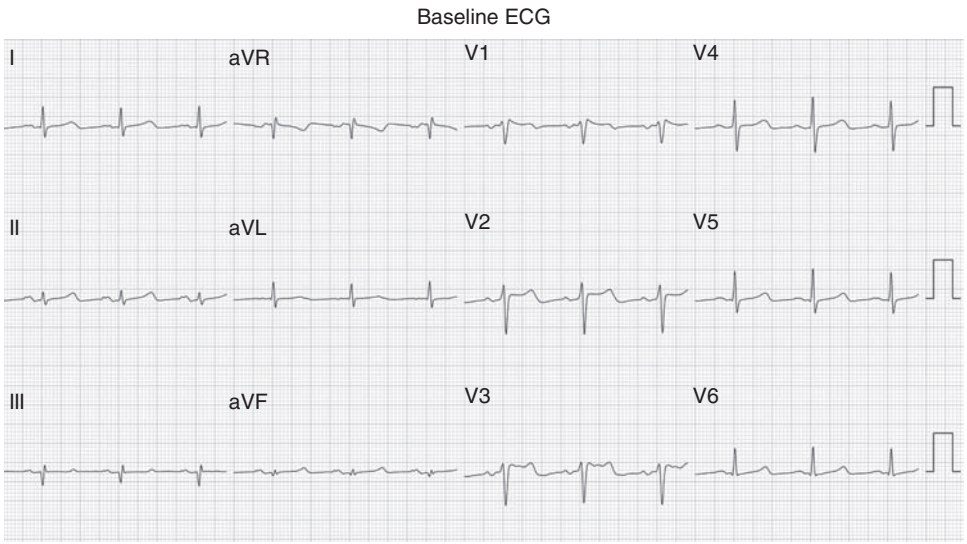


Figure 16-1

Baseline ECG (Fig. 16-1) is pretty normal; the P wave is slightly broad in lead 2.

Recordings from Right Inferior Pulmonary Vein

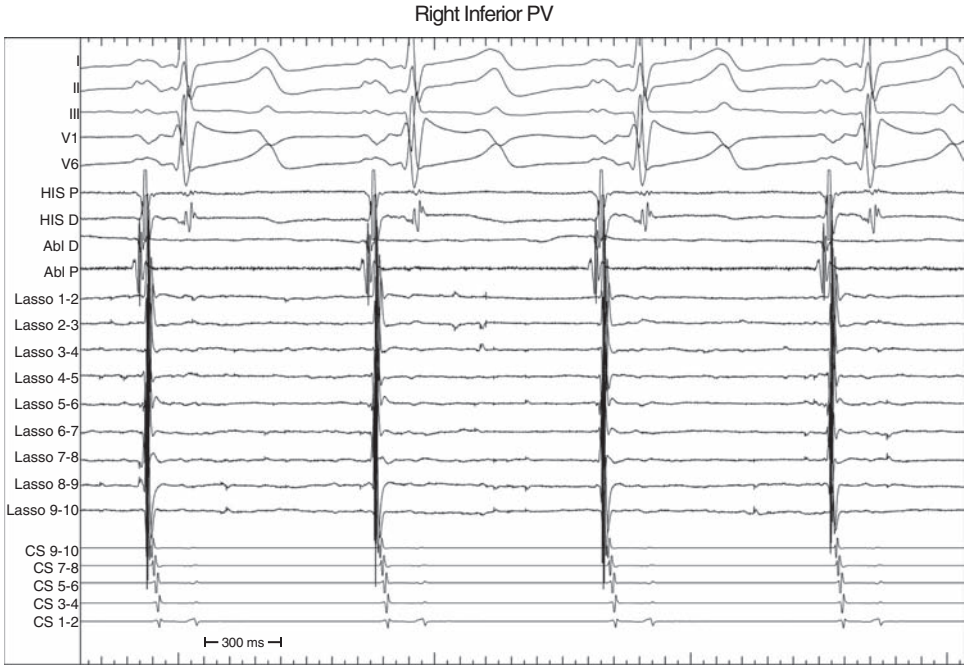


Figure 16-2

After obtaining left atrial access with transseptal catheterization, the left atrial anatomy is delineated by moving a catheter around the chamber. In addition, pulmonary veins (PVs) are interrogated using a ring catheter ("Lasso"). In Fig. 16-2, the catheter is in the right inferior PV and shows very large-amplitude PV recordings. They appear to be atrial recordings, and only by knowing where the catheter was when the recordings were made can we know their nature.

Recording and Pacing from Left Superior PV

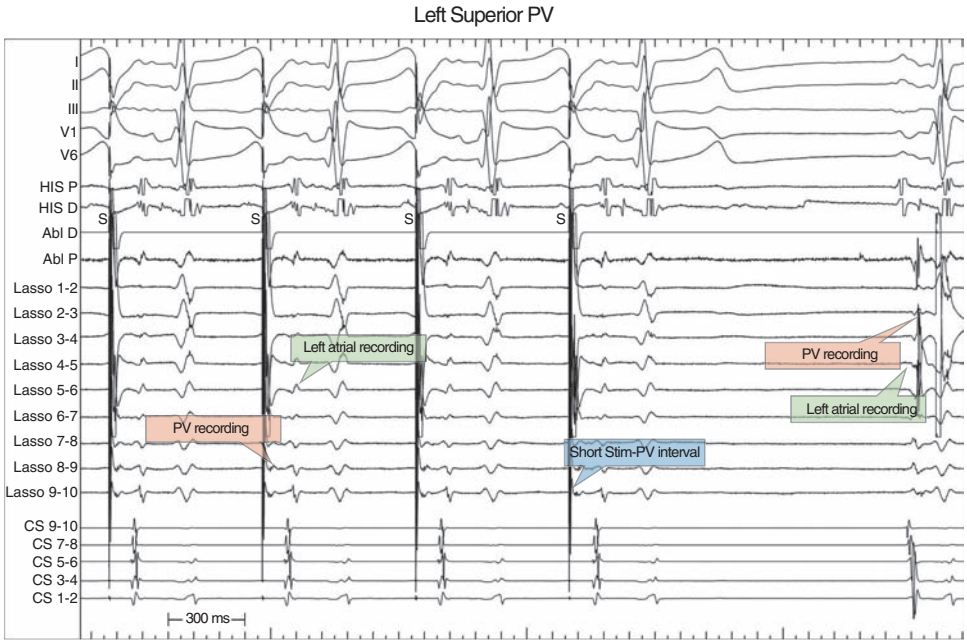


Figure 16-3

With the ring catheter in the left superior PV, pacing from a site more distally in the vein is performed (Fig. 16-3); this location is "tagged" on the electroanatomic mapping system. This will provide a means for checking exit block from the vein after isolation: if pacing from this site captured the PV reliably before isolation, and pacing from the same site does not conduct to the atrium after attempted isolation, one can be assured that exit block is present (even if the ring catheter is no longer recording in the vein). There is a very short interval from stimulus to captured PV potentials, after which conduction to the left atrium occurs (as indicated by *blue arrow*).

Recording from Left Superior PV, Pacing from Left Inferior PV

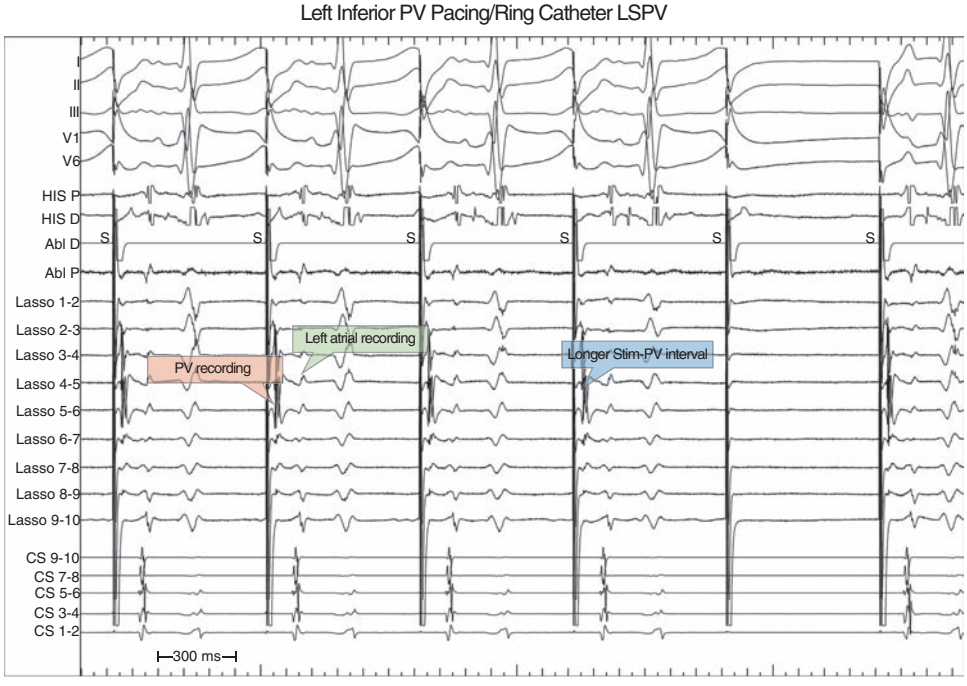


Figure 16-4

In Fig. 16-4, the ring catheter remains in the left superior PV but the ablation catheter has been moved to the inferior vein. Note the slight increase in stimulus-PV potential interval because the impulse must travel from inferior to superior vein before activating these cells.

Recording and Pacing from Right Superior PV

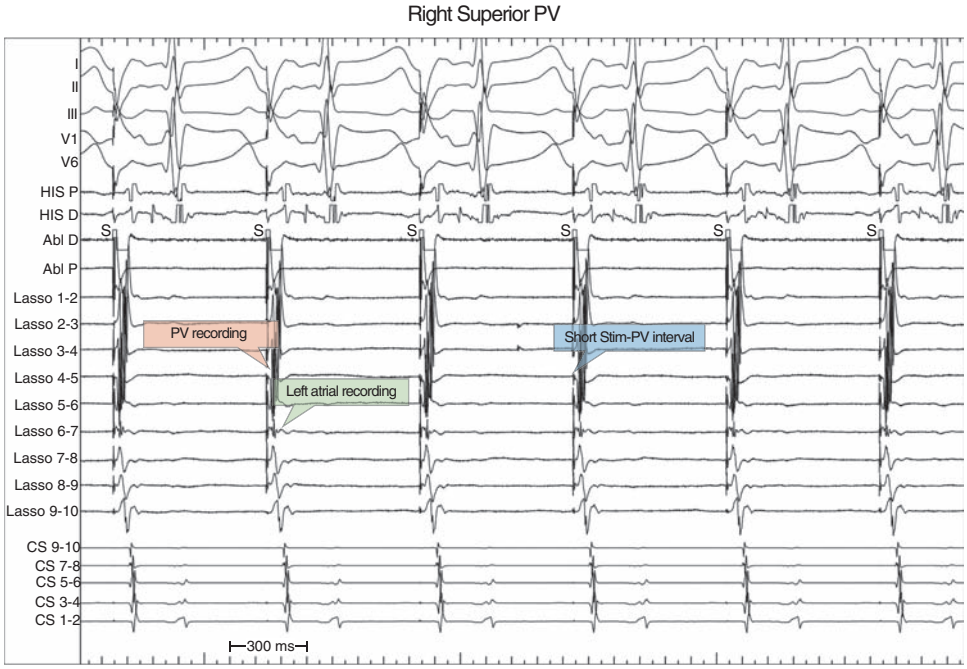


Figure 16-5

Similarly, with the ring catheter in the right superior PV, pacing from a site more distally in the vein is performed (Fig. 16-5); this location is "tagged" on the electroanatomic mapping system. This will provide a means for checking exit block from the vein after isolation.

Recording from Right Superior PV, Pacing from Right Inferior PV

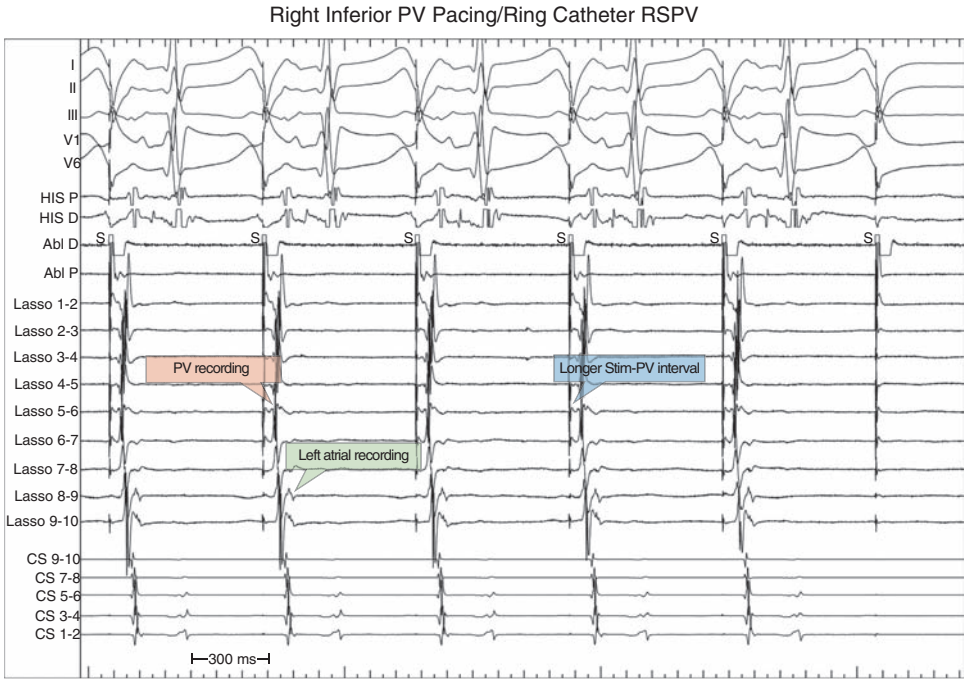
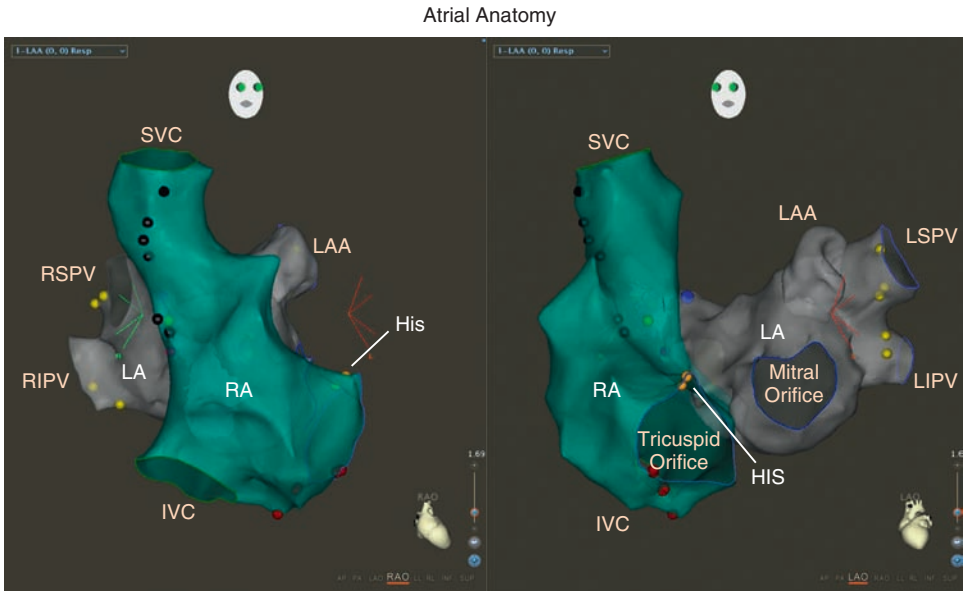


Figure 16-6

In Fig. 16-6, the ring catheter remains in the right superior PV but the ablation catheter has been moved to the inferior vein. Note the slight increase in stimulus-PV potential interval because the impulse must travel from inferior to superior vein before activating these cells.

Atrial Anatomy on Electroanatomic Maps

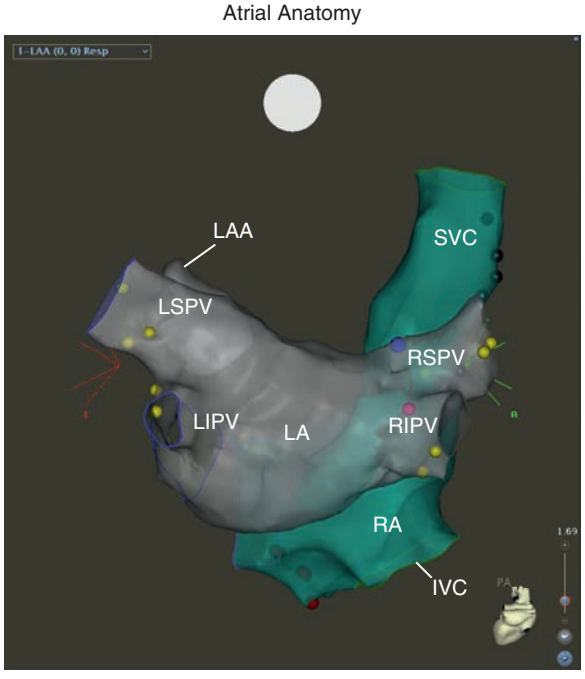
Figure 16-7



Right Anterior Oblique
Black dots: phrenic nerve capture

Left Anterior Oblique
Yellow dots: pulmonary vein capture

Figure 16-8



Figs. 16-7 and 16-8 display the posterior views of fast anatomic map (FAM) generated by manipulating catheters in the atria. *His*, His bundle location; *IVC*, inferior vena cava; *LA*, left atrium; *LAA*, left atrial appendage; *LIPV*, left inferior pulmonary vein; *LSPV*, left superior pulmonary vein; *RA*, right atrium; *RIPV*, right inferior pulmonary vein; *RSPV*, right superior pulmonary vein; *SVC*, superior vena cava. *Black dots* denote locations at which pacing resulted in phrenic nerve capture; *yellow dots* indicate sites at which pacing captured PV sleeves.

Progressive Left PV Isolation

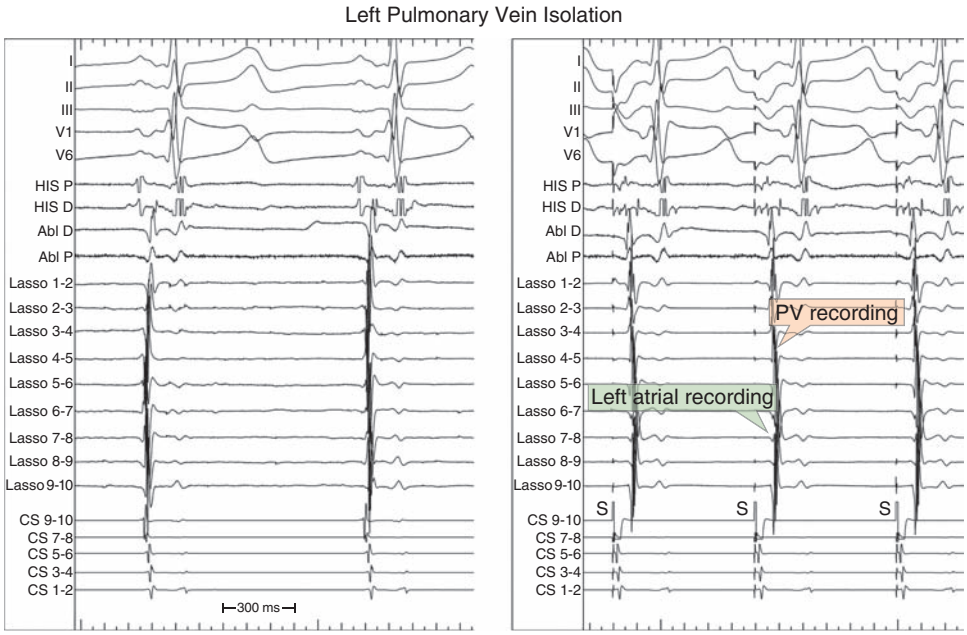


Figure 16-9

The left PVs were isolated as a unit with wide-area catheter ablation (WACA). At left of Fig. 16-9, during sinus rhythm, it is difficult to distinguish PV potentials from nearby left atrial signals; at right, during coronary sinus pacing, high-amplitude, high-frequency PV potentials are slightly more readily distinguished from lower-amplitude, lower-frequency left atrial recordings.

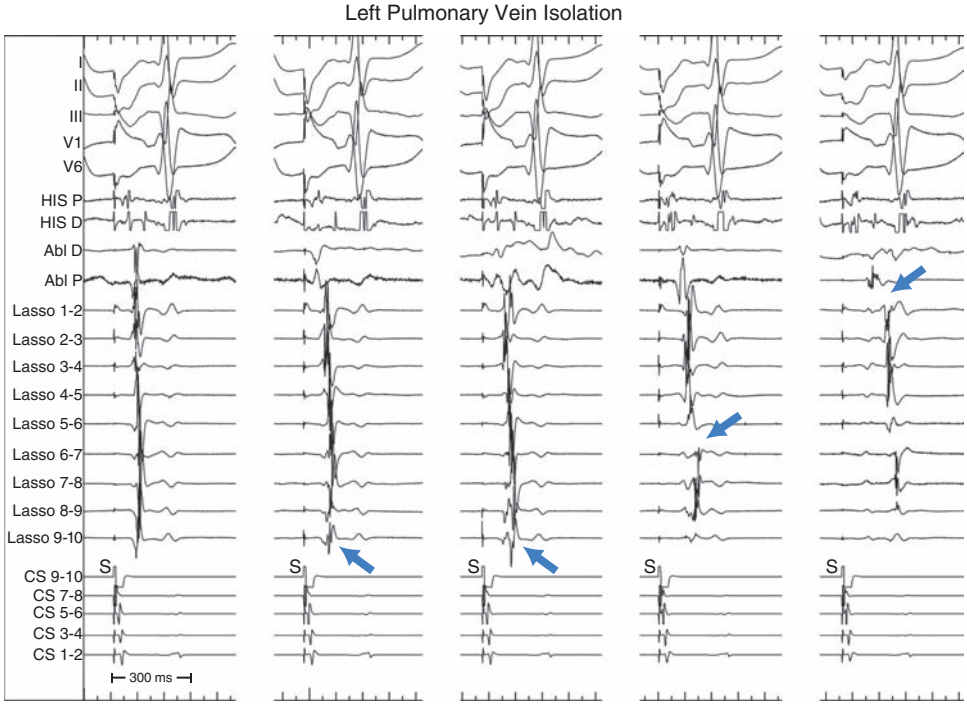
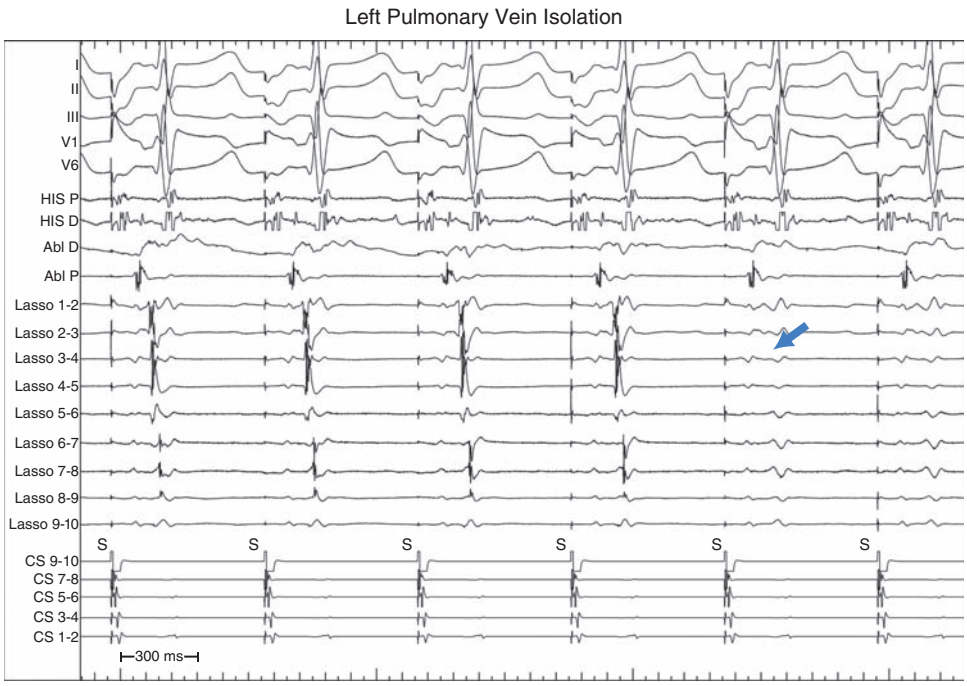


Figure 16-10

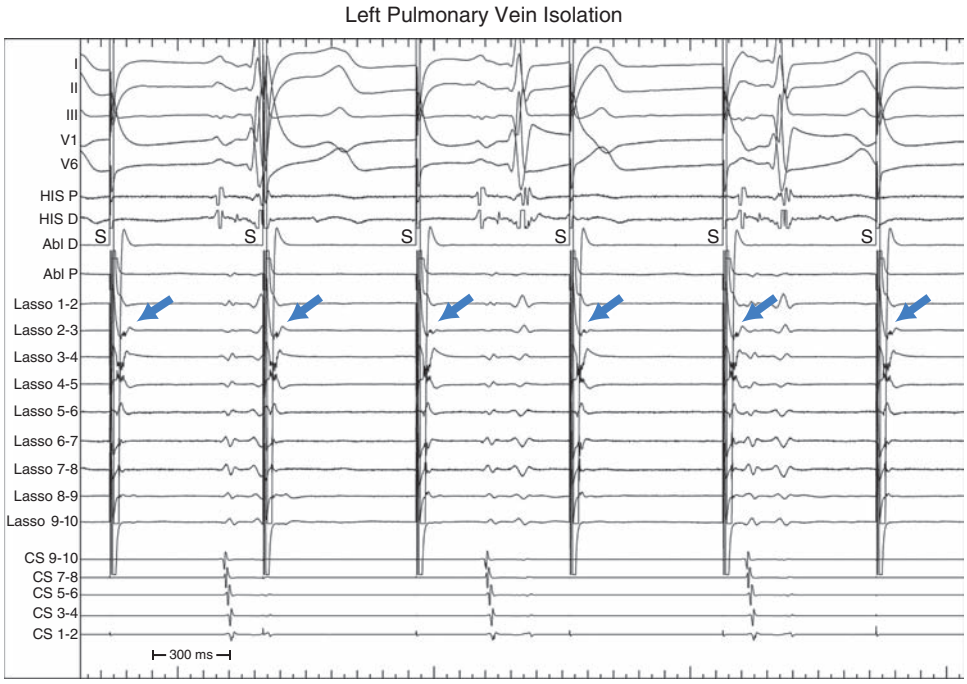
Over the span of several minutes, ablation around the left PV antrum results in progressive delay of PV potentials (Fig. 16-10, *arrows*).

Figure 16-11



Finally, after nearly completely circumscribing the left PV antrum with RF applications, progressive delay of PV potentials is followed by complete loss of PV potentials (Fig. 16-11, *arrow*). Entrance block is now present in the left superior PV.

Figure 16-12



After demonstrating entrance block in the left superior PV, the ablation catheter is moved into the PV to a location tagged before ablation as a site at which pacing captured the PV. Pacing at this site (Fig. 16-12, *arrows*) now shows capture of potentials but no conduction to the adjacent left atrium, which remains in sinus rhythm. Exit block has now been demonstrated in the left superior PV. The same maneuver was performed in the left inferior PV with the same findings.

Progressive Right PV Isolation

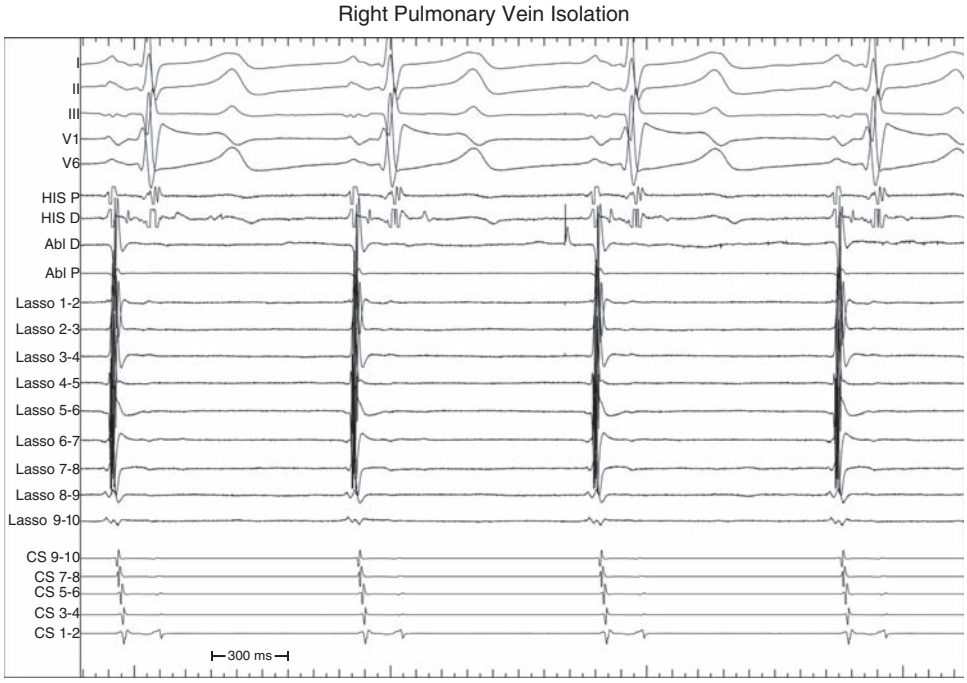


Figure 16-13

Attention is now turned to the right PVs. In Fig. 16-13, the ring catheter is in the right superior PV. Pacing rarely separates PV potentials (large, sharp signals in Lasso recordings) from nearby left atrium, so ablation is performed during sinus rhythm.

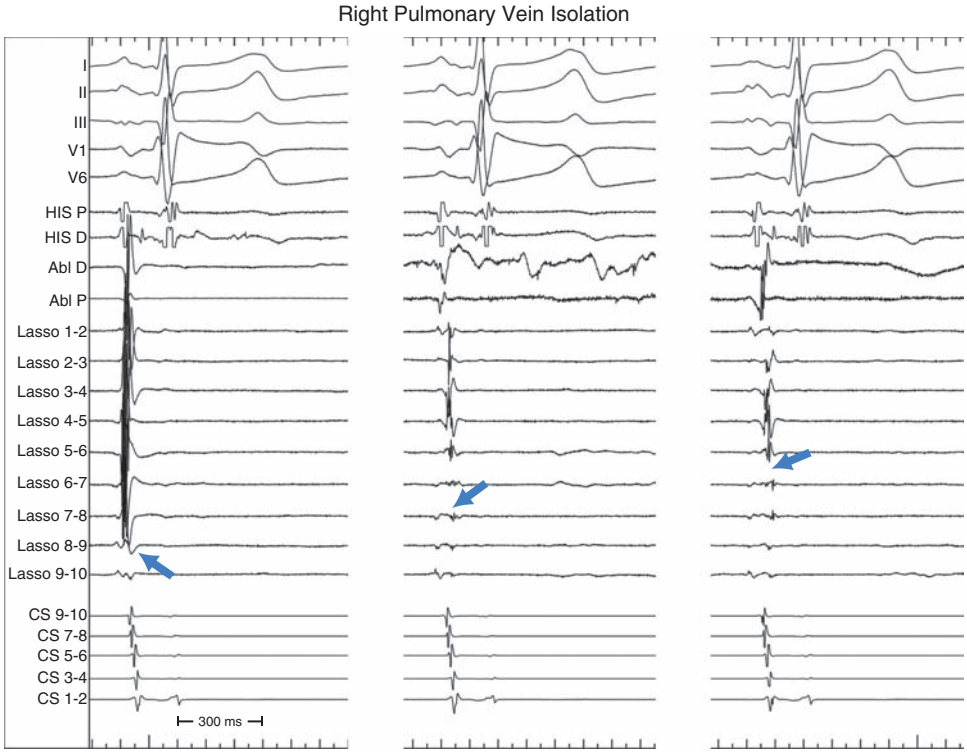
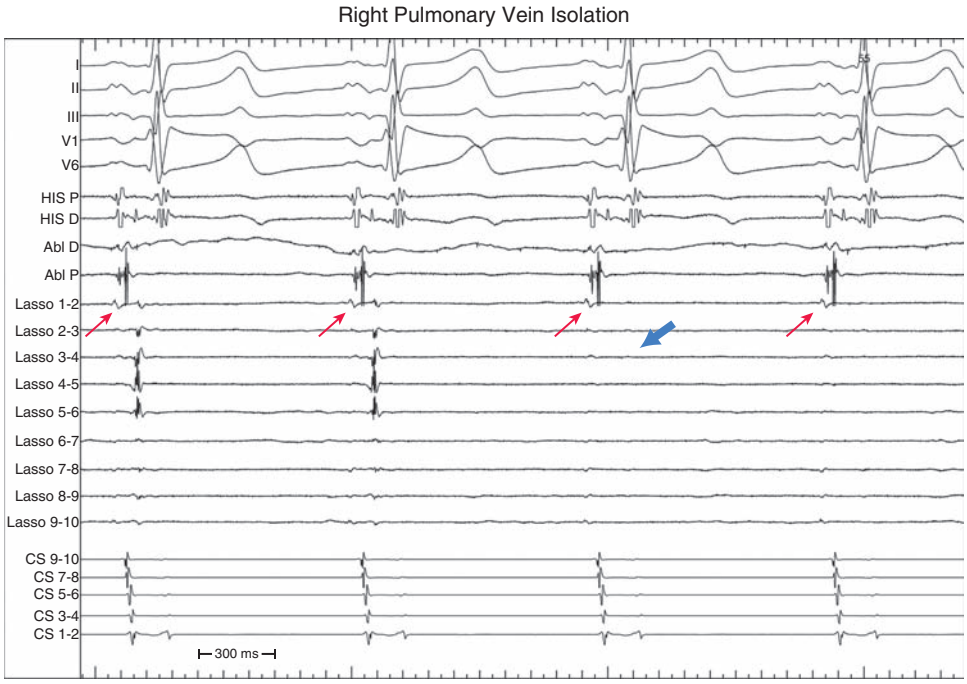


Figure 16-14

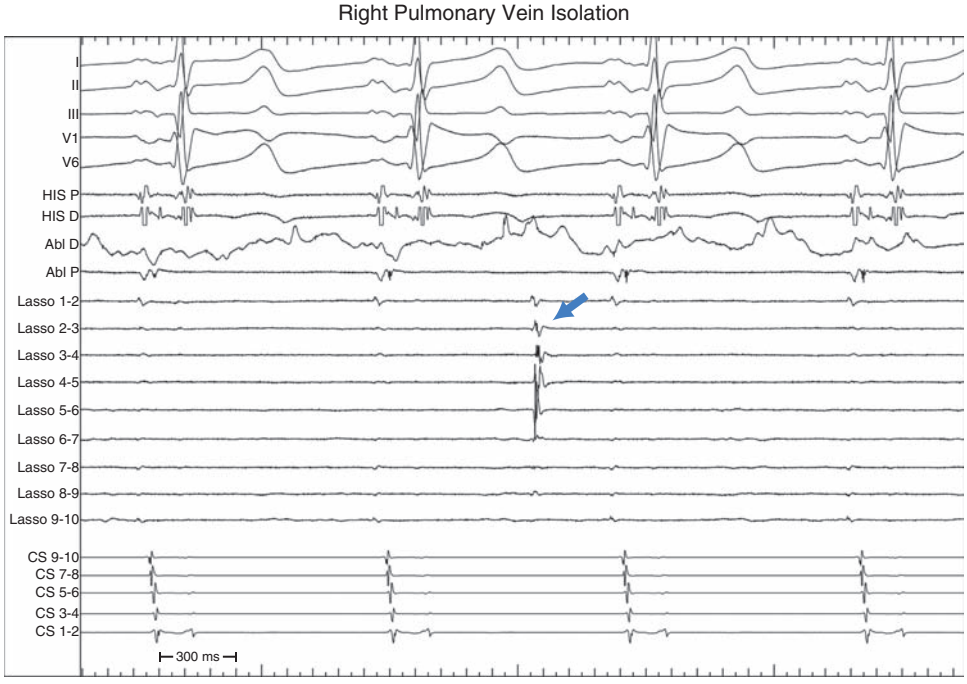
With progressive encirclement around the right PVs, PV potentials become more delayed in Fig. 16-14; the ring catheter has shifted slightly in the PV over the course of ablation, and thus the recordings are not identical in morphology.

Figure 16-15



With still further encirclement around the right PVs, PV potentials cease (Fig. 16-15, *blue arrow*); this could be because the ring catheter had suddenly become displaced deeper in the PV or into the left atrial cavity, but far-field left atrial potentials are unchanged *(red arrows)*; thus the catheter has not moved and the loss of PV potentials means that this PV has entrance block.

Figure 16-16



After encirclement and establishing entrance block into the right superior PV, a dissociated potential is observed in Fig. 16-16 (unaffected by the prevailing atrial rhythm, nor affecting the atrial rhythm).

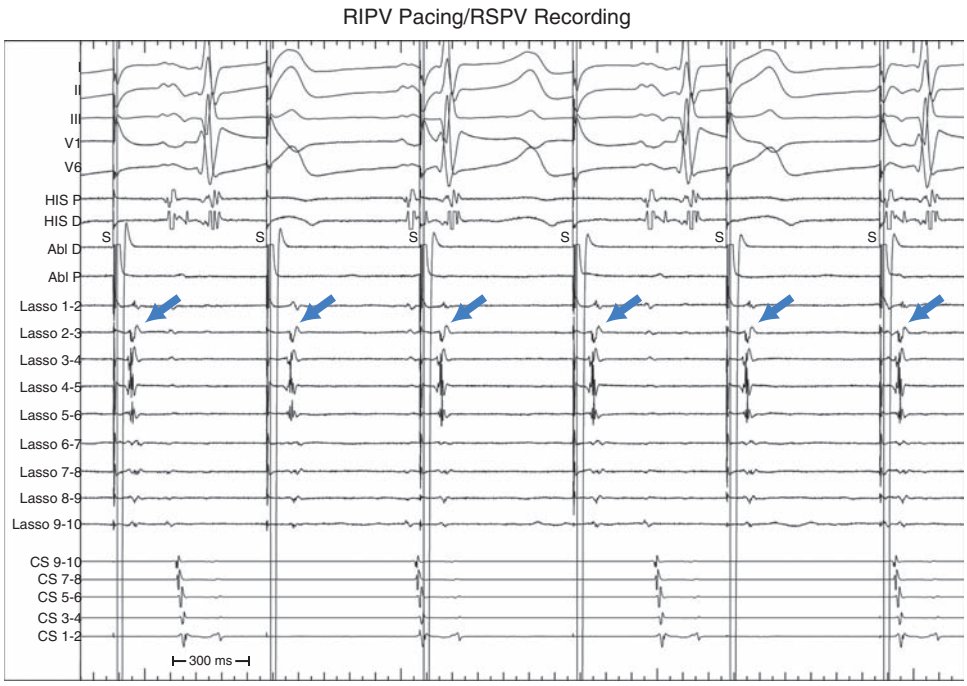


Figure 16-17

Pacing is performed in the right inferior PV with the ring catheter in the right superior PV; this shows PV potentials after each stimulus artifact without conduction to the atrium (Fig. 16-17). Capture of the right inferior PV is inferred, because it conducts to the right superior PV. This shows exit block of *both* PVs.

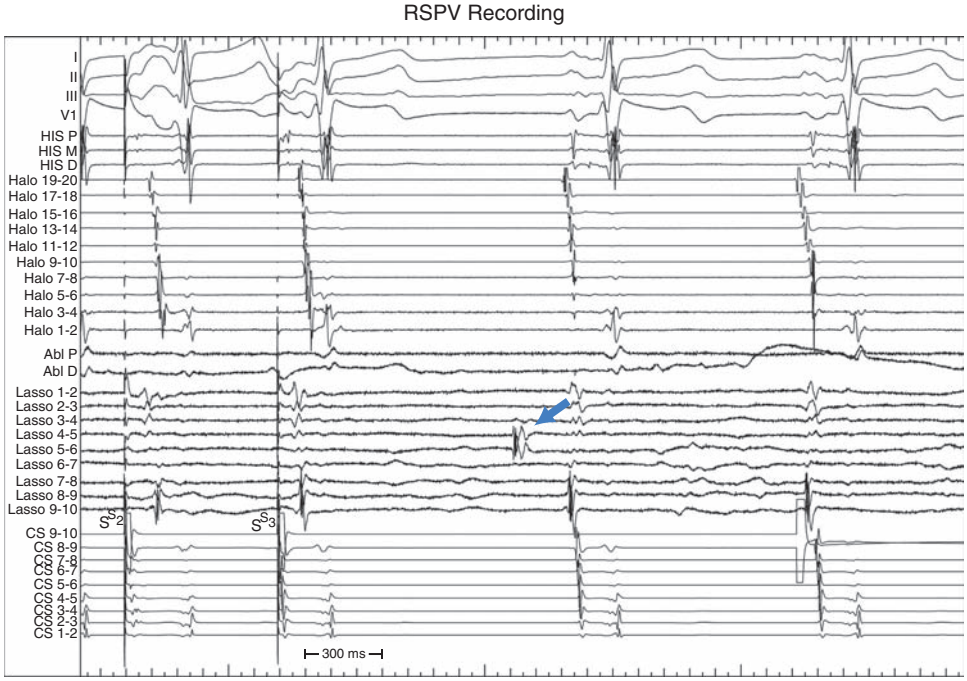
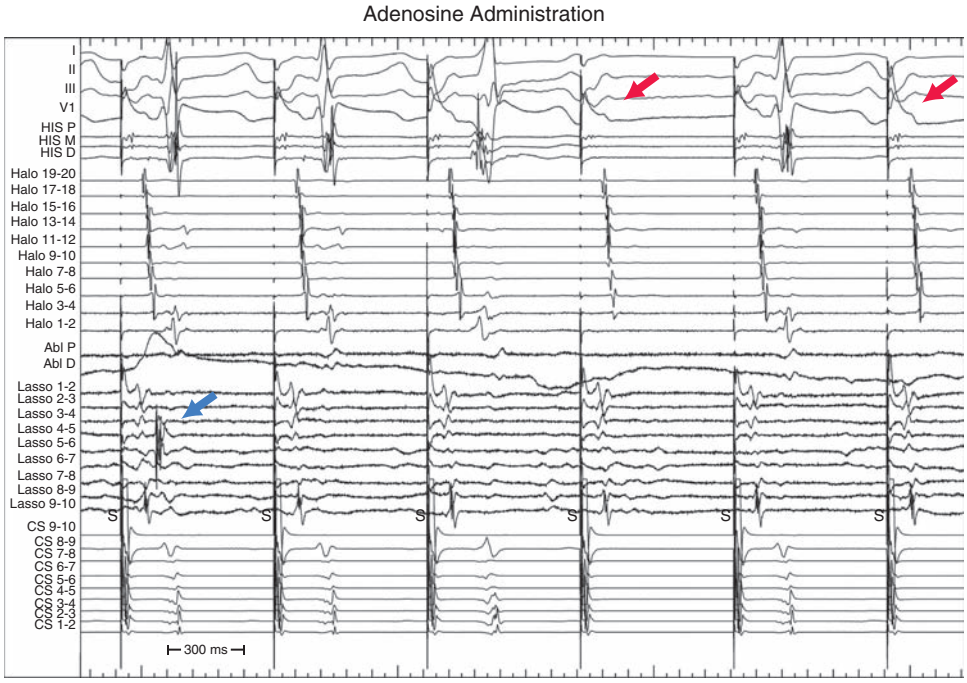


Figure 16-18

A dissociated PV potential is recorded with the ring catheter in the right superior PV (Fig. 16-18, *arrow*). A "halo" catheter has been placed around the tricuspid annulus in preparation for flutter ablation (because of his history of this arrhythmia). Cavotricuspid isthmus ablation was performed resulting in bidirectional conduction block (not shown).

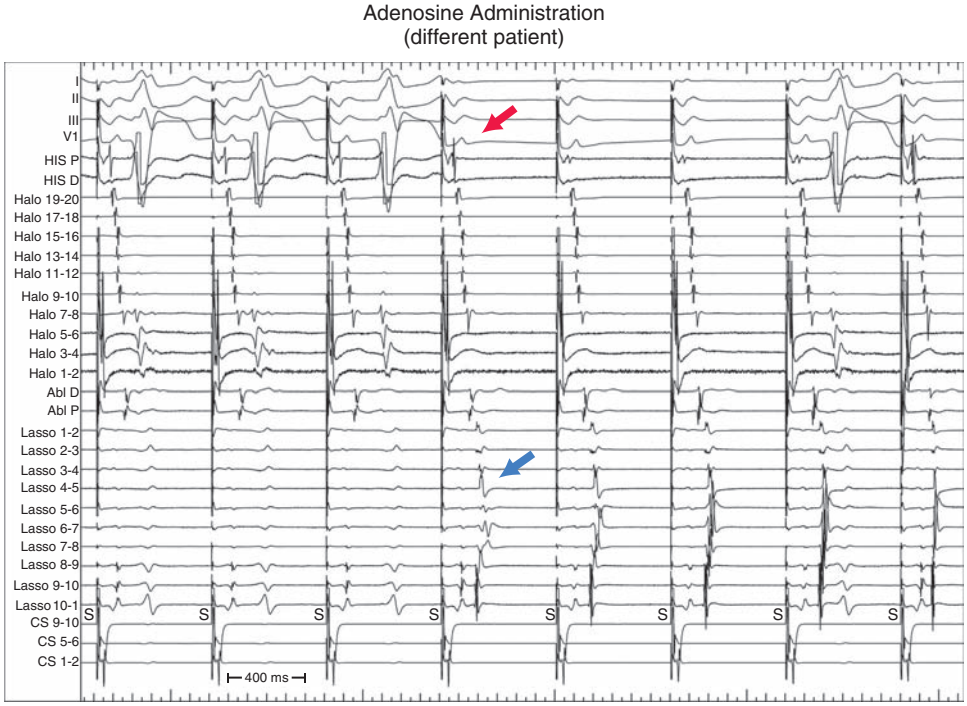
Adenosine Administration

Figure 16-19



After cavotricuspid isthmus ablation, adenosine is administered (12 mg IV bolus). Its effect on the AV node is manifest by heart block (Fig. 16-19, *red arrows*) but cavotricuspid isthmus block persists as does right superior PV isolation; a dissociated PV potential is seen in the ring catheter recordings from this PV *(blue arrow)*.

Figure 16-20



Adenosine administration is a different case (12 mg IV bolus). Its effect on the AV node is again manifest by heart block (Fig. 16-20, *red arrow*), and though cavotricuspid isthmus block persists, potentials are seen again in the left superior PV *(blue arrow)*. Additional ablation around this PV eliminated this response.

Electroanatomic Maps with RF Sites

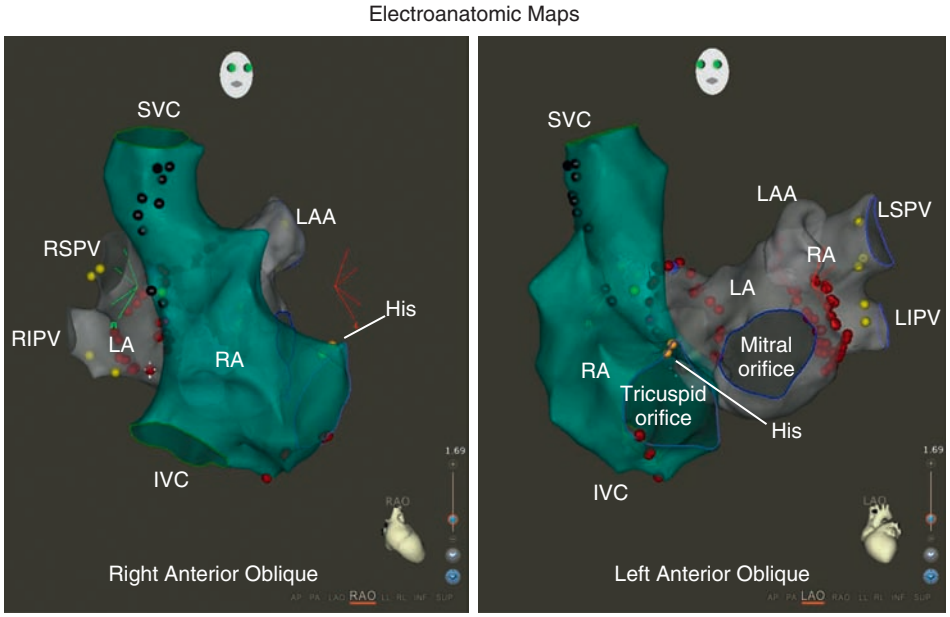


Figure 16-21

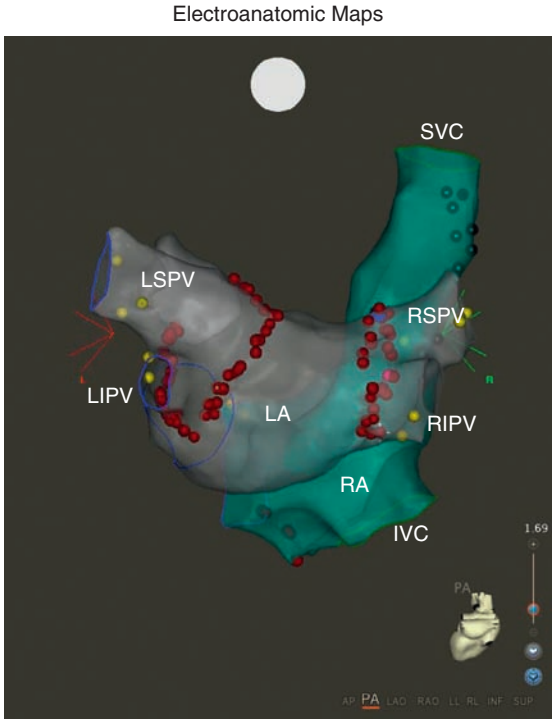


Figure 16-22

In Figs. 16-21 and 16-22, *red dots* show points at which radiofrequency energy was delivered (around PVs).

Summary

- PV isolation remains the standard for catheter-based therapy of atrial fibrillation
- Entrance and exit block should be demonstrated
- Additional means of assuring durable PV isolation may be used, including
  - Voltage mapping (not very sensitive or specific)
  - Adenosine (showing lack of resurgence of conduction)
  - Pacing along ablation line (showing inexcitability)

17 Pulmonary Vein Isolation, Rotor Mapping and Ablation, and Flutter Ablation for AF/Flutter

Case Presentation

The patient was a 67-year-old man with atrial fibrillation (AF) for the past 4 years or more; episodes were paroxysmal but arrhythmia is now persistent. His symptoms included lightheadedness, fatigue, and palpitations. Medical therapy with Metoprolol and then with diltiazem had no effect on his symptoms. Cardioversion without and with amiodarone failed to maintain sinus rhythm. He was referred for electrophysiology (EP) study and possible ablation; amiodarone was discontinued 1 month before the procedure. He was anticoagulated with dabigatran until 1 day before the procedure.

Baseline ECGs and Intracardiac Recordings

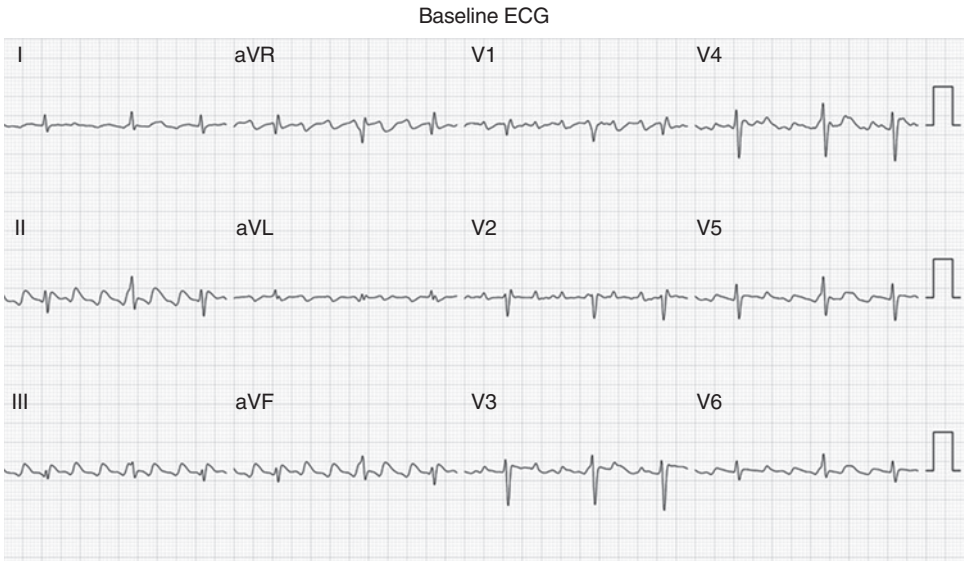
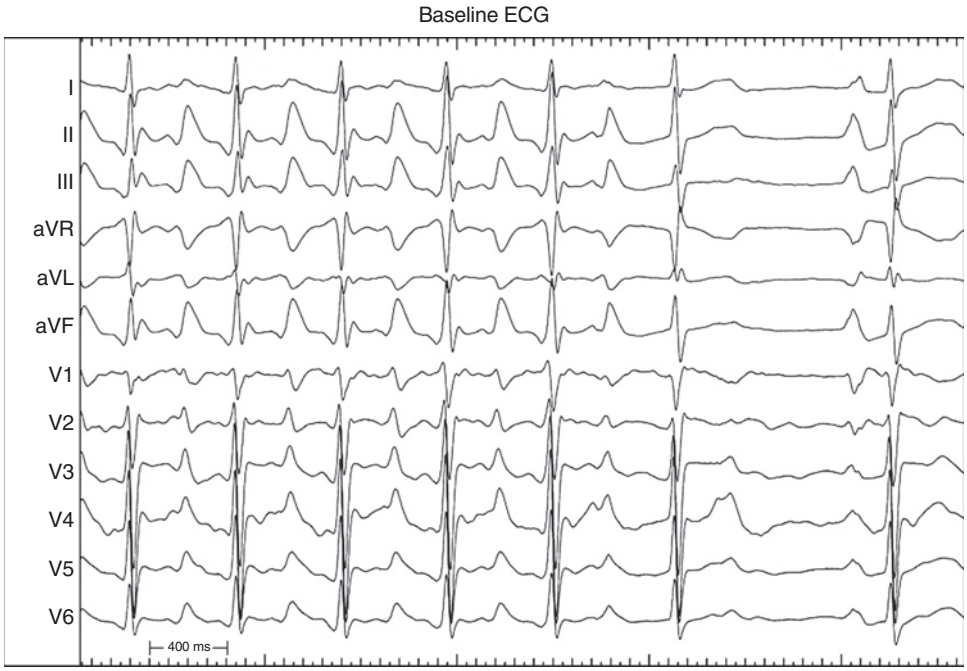


Figure 17-1

Fig. 17-1 was the baseline ECG at the start of the procedure. It is consistent with clockwise right atrial flutter, though slower than usual (300 ms atrial cycle length), and is the first recorded ECG of this arrhythmia (all others had been fibrillation). This may be an effect of residual amiodarone, or just another manifestation of his atrial arrhythmias independent of drug effect.



What Does This Mean? [Fig. 17-2]

Figure 17-2

Shortly after obtaining the baseline ECG, the presenting arrhythmia terminated spontaneously to sinus as shown in Fig. 17-2. This occurred shortly after placement of the coronary sinus catheter and did not appear to result from catheter-mediated trauma or ectopy. This would be very unusual behavior for typical right atrial flutter and is perhaps more suggestive of a focal process. In addition, the morphology of the P wave in the inferior leads is less consistent with typical right atrial flutter.

What Does This Mean? [Fig. 17-3]

Figure 17-3

Fig. 17-3 are surface ECG and intracardiac recordings from the coronary sinus (CS) catheter (the only catheter in the heart then) at the time of termination of the presenting arrhythmia. It is clear that there was no catheter-induced ectopy or cycle length change before termination. It also appears that the CS catheter electrodes are activated before the apparent onset of the surface P wave *(dashed line)*, as well as in a proximal-distal direction.

Figure 17-4

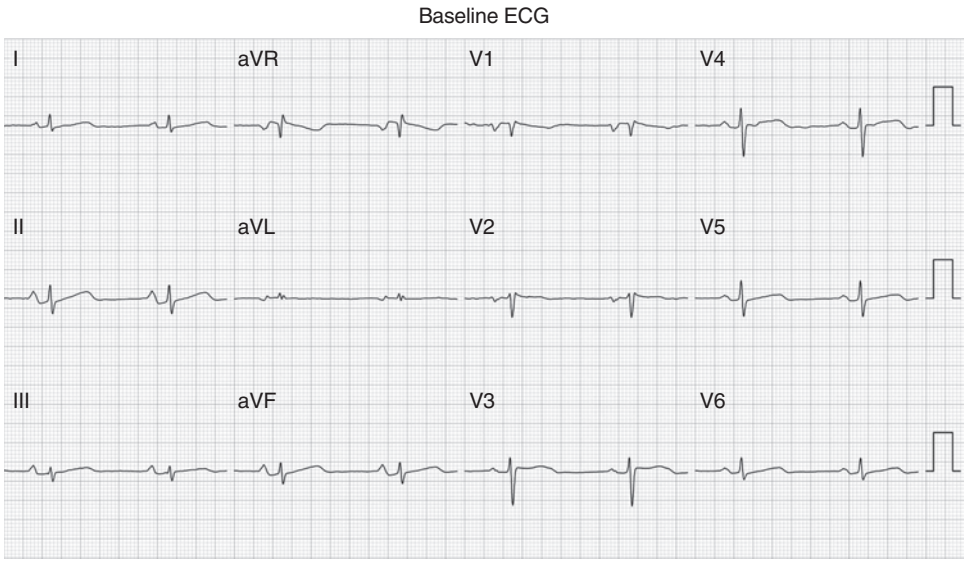
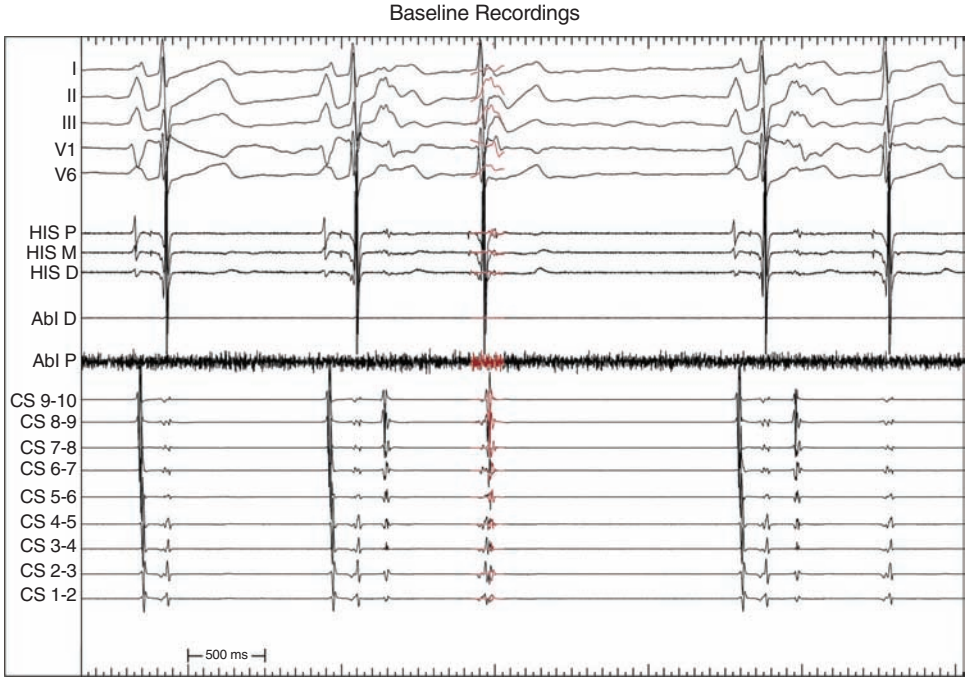


Fig. 17-4 shows sinus rhythm immediately after termination of the presenting arrhythmia. Terminal negativity of the P wave in V1 is consistent with left atrial hypertrophy but there are no other abnormalities.

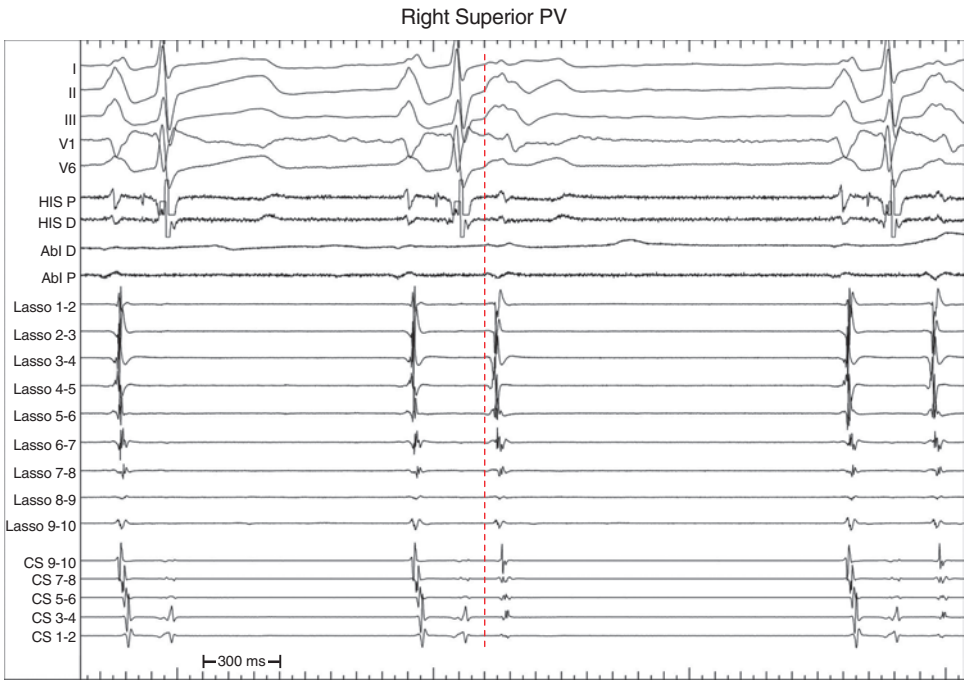
What Does This Mean? [Fig. 17-5]

Figure 17-5



Seen in Fig. 17-5, premature atrial complexes (PACs) can certainly initiate AF episodes; in addition, PACs can emanate from the "culprit pulmonary vein (PV)," the one that is responsible for AF (either as a trigger or driver). Thus targeting consistent, repetitive PACs may be a useful adjunctive strategy in treating AF. The middle QRS complex has an atrial activation associated with it, the timing of which suggests a typical atrioventricular (AV) nodal echo; however, the P wave appears to be positive in the inferior leads (unlike AV nodal echoes) and has a configuration similar to the PAC when that complex is superimposed on it *(red)*.

Right Superior Pulmonary Vein Recordings

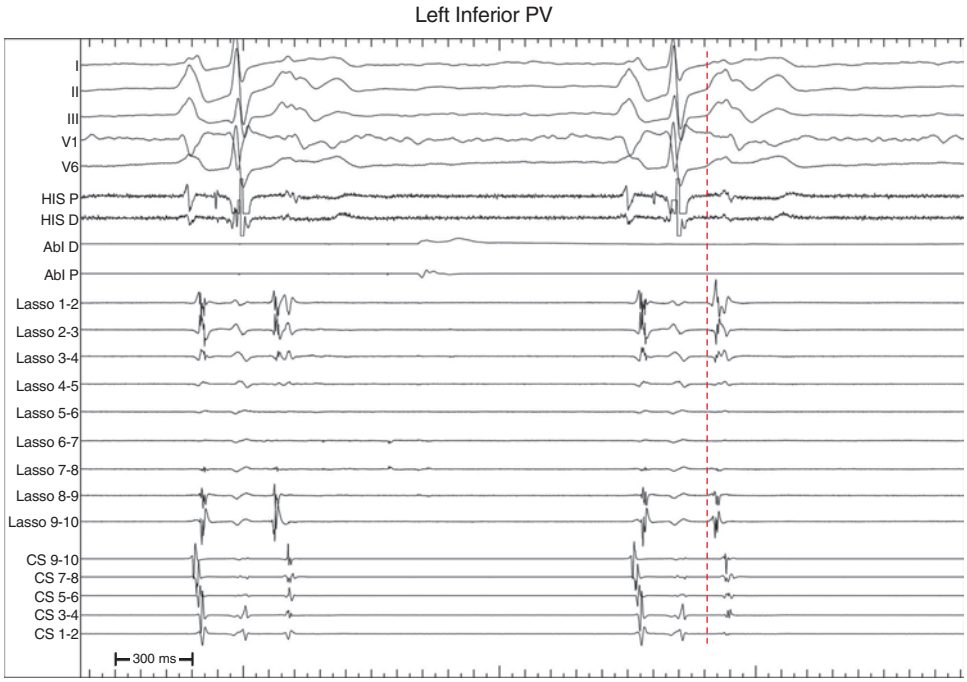


Is the PAC Coming from Here? [Fig. 17-6]

Figure 17-6

Left atrial access was obtained with transseptal catheterization, and a ring catheter ("Lasso") was used to record within PVs. When recording from the PV of origin of PACs (Fig. 17-6), the PV potentials always occur >50 ms before the P-wave origin because of slow conduction when exiting the PV. In this case because the PV potentials in the right superior PV occur after the P-wave onset *(red dotted line)*, the PAC cannot be originating here.

Left Inferior PV Recordings



Is the PAC Coming from Here? [Fig. 17-7]

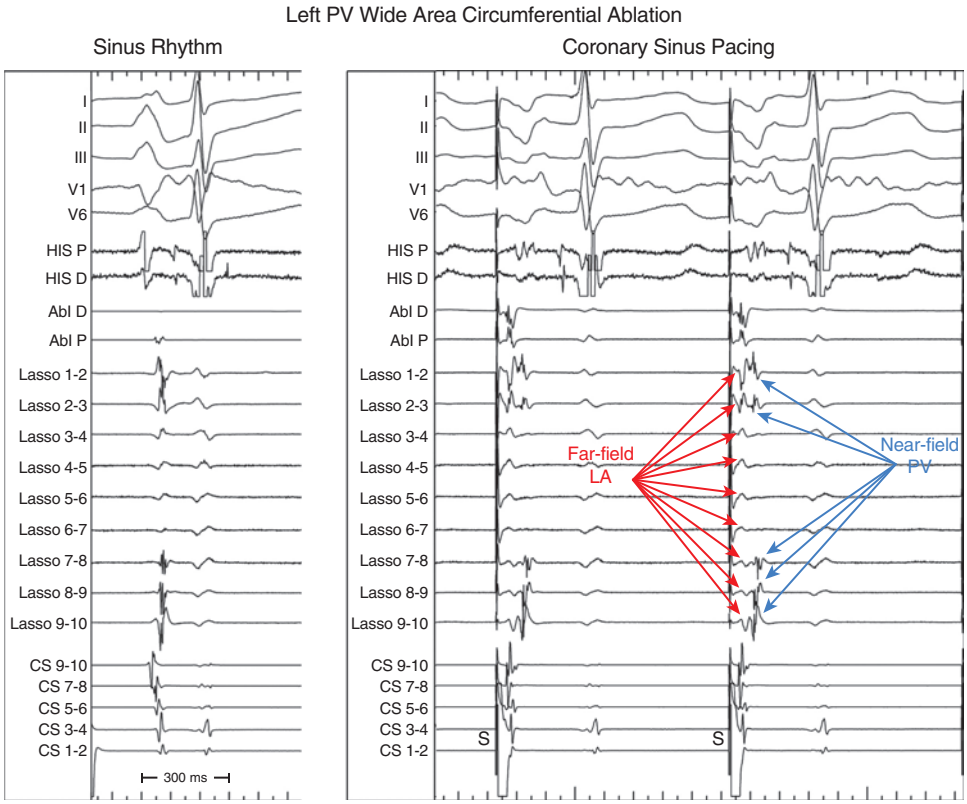
Figure 17-7

Using the same reasoning as in the prior figure, because the P wave of the PAC starts before the electrograms in the left inferior PV occur *(red dotted line)*, the PAC cannot be originating from this PV (Fig. 17-7).

Left Pulmonary Vein Wide-Area Circumferential Ablation

Baseline Pacing

Figure 17-8



In Fig. 17-8, the left superior PV could not be easily engaged with the ring catheter but was the suspected source of the PACs. Circumferential wide-area catheter ablation was begun around the left PVs while the ring catheter was in the left inferior PV. During sinus rhythm, it is not clear which of the recordings represents atrial versus PV potentials; with coronary sinus pacing as shown, PV potentials *(blue arrows)* are clearly separated from far-field left atrial recordings *(red arrows)*.

Start of Ablation

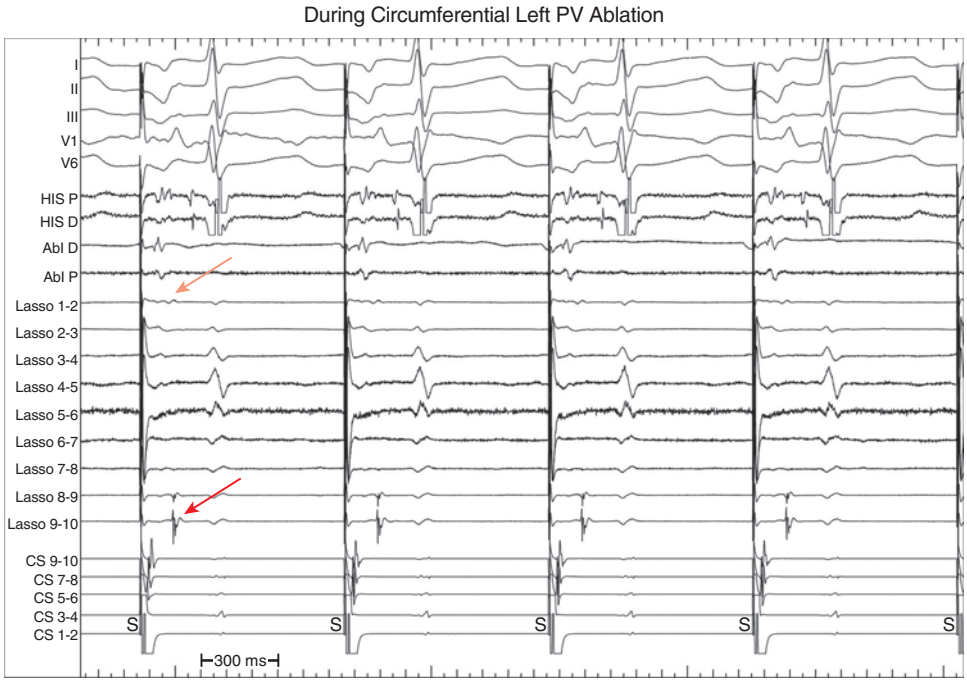
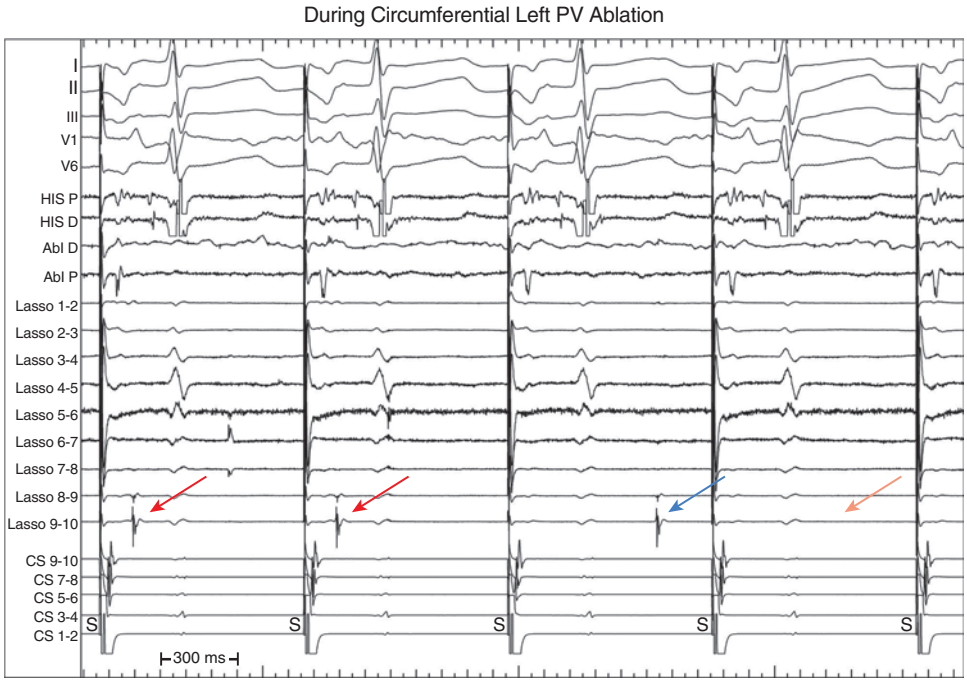


Figure 17-9

In Fig. 17-9, as circumferential ablation around the left PVs continues, some of the PV potentials have been eliminated *(pink arrow)*, whereas others are substantially delayed from their prior timing *(red arrow)*. Of note, the ring catheter has moved slightly within the PV (judging by the appearance of the far-field LA potentials compared with the prior figure), but the fact remains that PV potentials have been dramatically delayed from some, as well as eliminated from other recordings. Additionally, the PACs (which had occurred several per minute before) ceased at this time, signifying that their source was likely along the line of ablation, rather than in a PV; if it had been in a PV, most likely isolated, dissociated firing of PV potentials from the PAC focus would persist (but did not).

Isolation Occurs

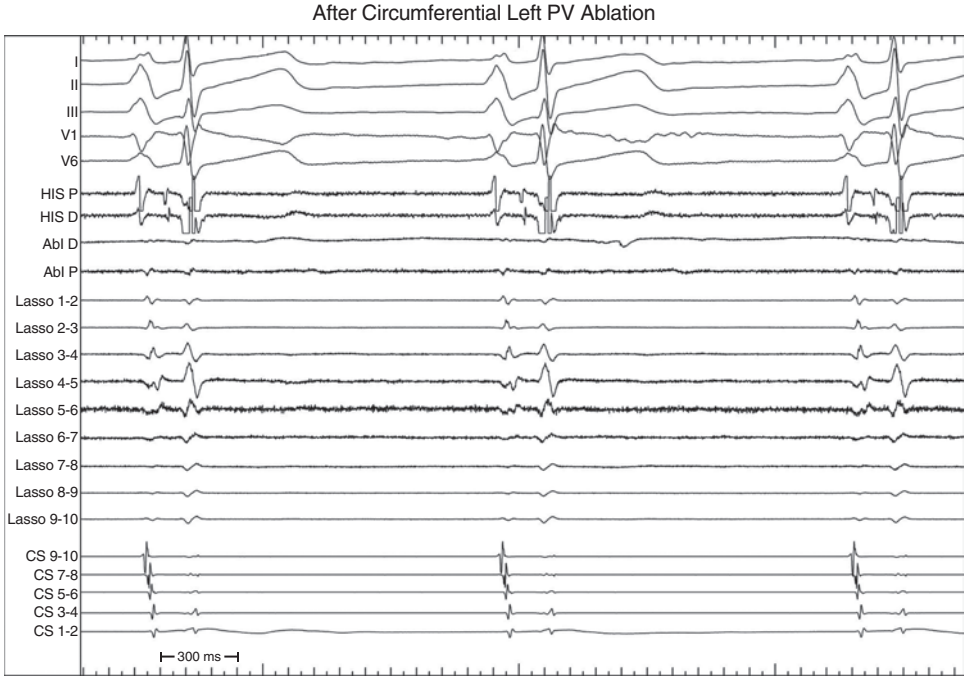
Figure 17-10



As circumferential ablation around the left PVs nears completion in Fig. 17-10, PV potentials *(red arrows)* show further delay after the third stimulus *(blue arrow)*, and then are finally eliminated *(pink arrow)*.

Sinus Rhythm After Isolation

Figure 17-11



After circumferential ablation around the left PVs (Fig. 17-11), no PV potentials are seen during sinus rhythm; PACs are also absent at this time.

Exit Block After Isolation

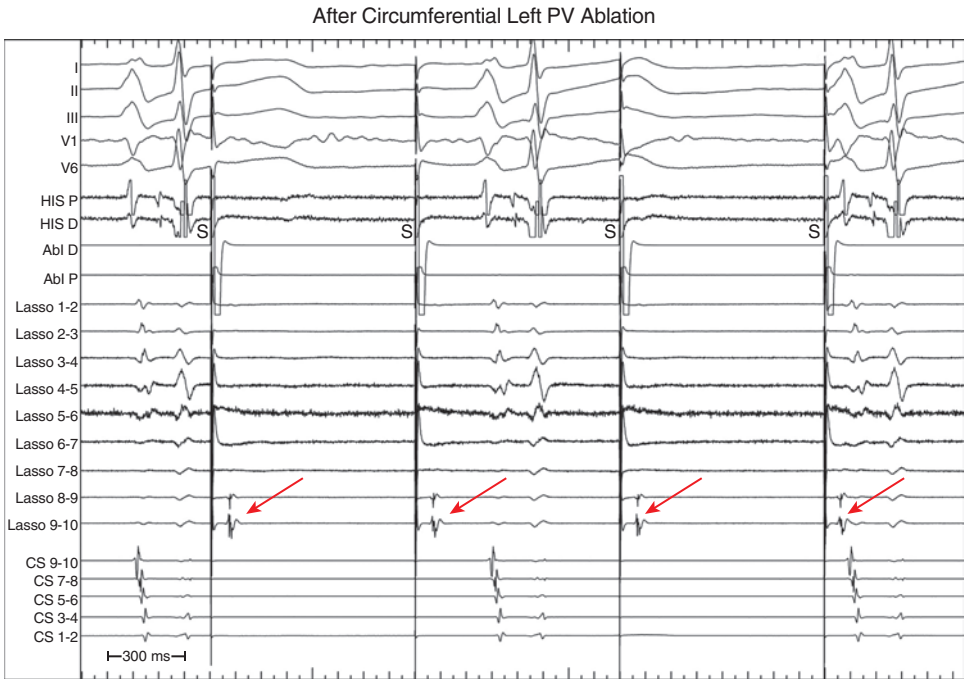


Figure 17-12

Entrance block (propagation into the PV) has been demonstrated, but it is important to show exit block (from PV to atrium) after circumferential ablation around the left PVs. Pacing from the left superior PV, while recording from a ring catheter in the left inferior PV (Fig. 17-12), shows inferred capture of PV potentials in the left superior PV, with conduction to the left inferior PV where potentials are recorded *(red arrows)*, but no conduction to the left atrium (which remains in sinus rhythm, unaffected by PV pacing). Thus both left PVs have been isolated (both entrance and exit block) as a unit.

Right PV Wide-Area Circumferential Ablation

Start of Ablation

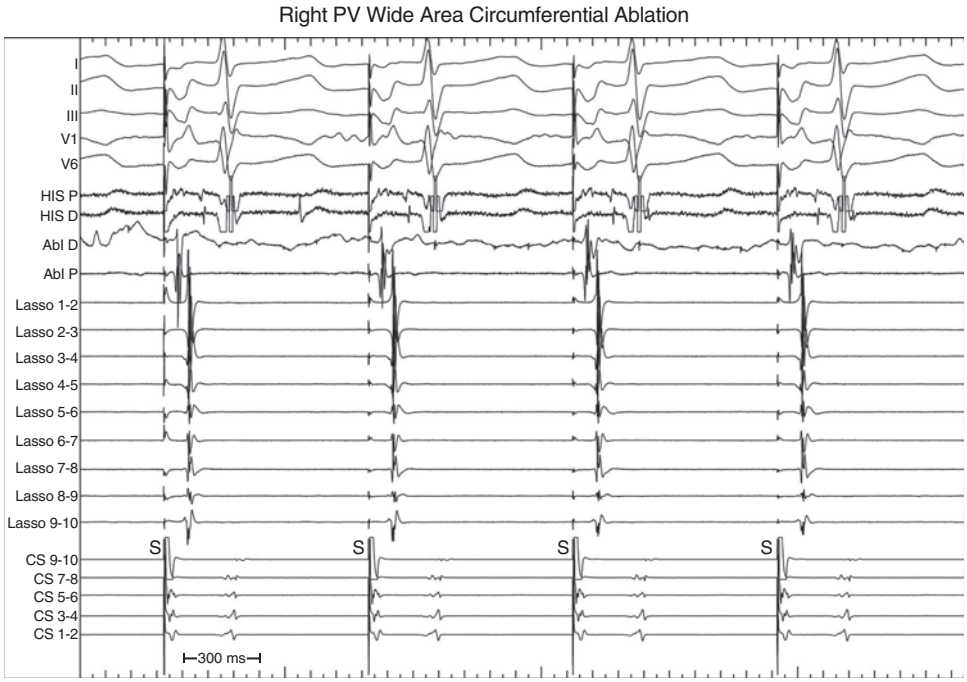


Figure 17-13

After completion of left PV isolation, attention is turned to the right PVs (Fig. 17-13). Here, the ring catheter is in the right superior PV, again during coronary sinus pacing. With right PVs, coronary sinus pacing usually does not separate left atrial and PV potentials nearly as well as it does with left PVs; pacing was done in this instance because of bradycardia.

Flutter Initiates

Figure 17-14

During attempted right PV isolation (Fig. 17-14), a PAC *(blue arrow)* occurs (perhaps due to irritation from the ablation catheter) that initiates what appears to be atrial flutter, with

upright flutter waves in the inferior leads. This is reminiscent of the arrhythmia that was present at the beginning of the procedure when catheters were first being placed.

Flutter Terminates in Right Atrium

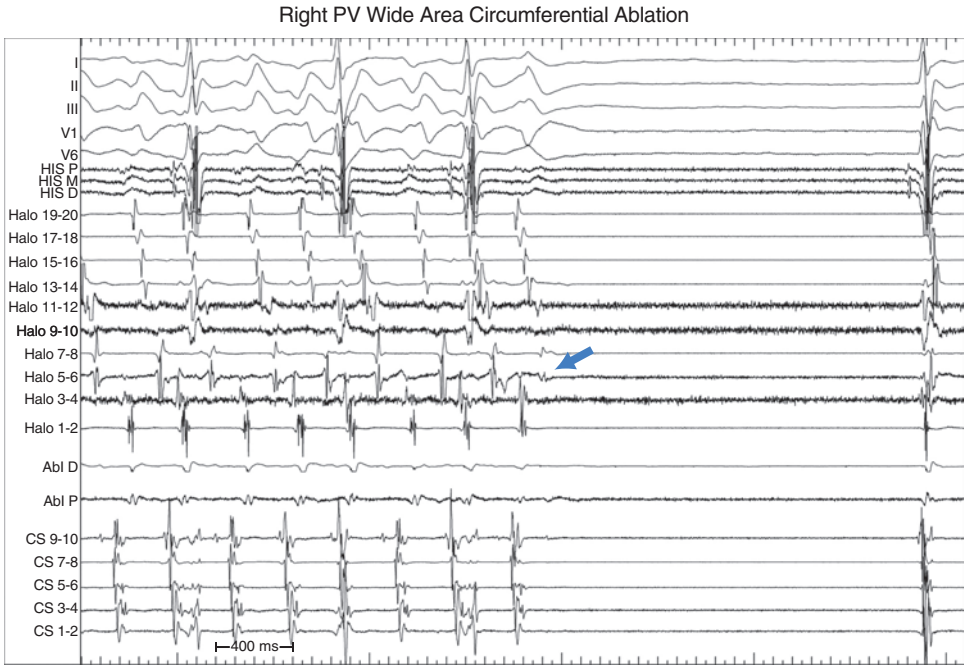


Figure 17-15

Since the last figure, a 20-pole catheter ("Halo") has been placed in the right atrium to record around the tricuspid annulus (Fig. 17-15). Here, a spontaneous termination of the arrhythmia is shown. The last electrograms that are seen are from the tricuspid annulus *(arrow)*, suggesting that the rhythm originates in the left atrium (because, when the arrhythmia ceased, the last cycle was transmitted to the right atrium and no further activity is seen until a junctional escape complex at the far right). It is also possible that the arrhythmia is actual right-atrial, peritricuspid reentry that terminated because of tenuous conduction properties in the tissue between electrodes 5-6 and 3-4 on the tricuspid annular catheter; there is clearly poor conduction in this area, indicated by the prolonged interval between these adjacent electrode pairs compared with others.

Partial Isolation

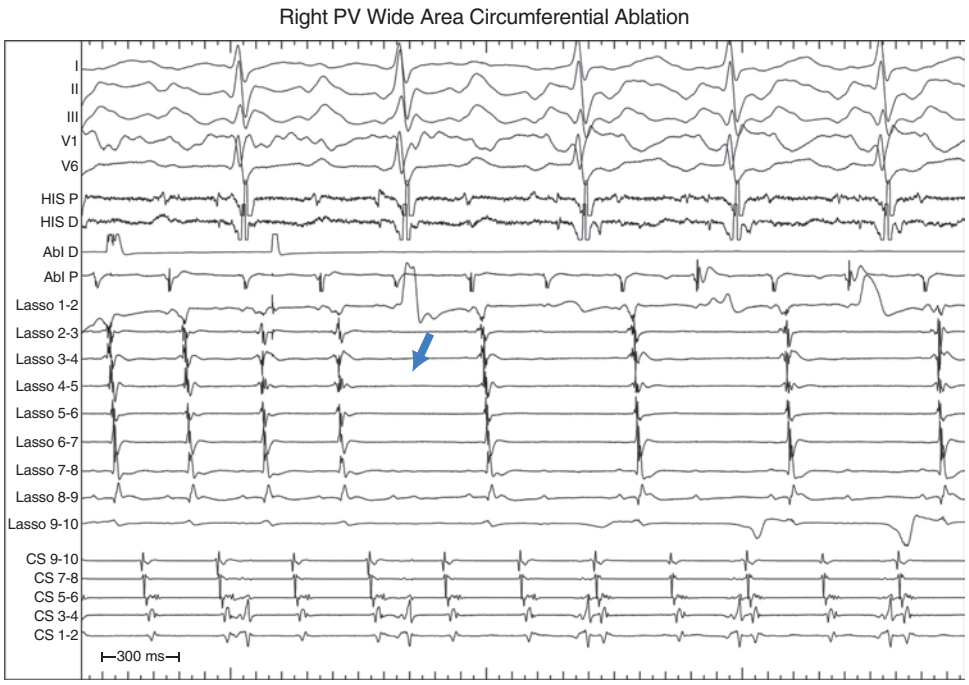


Figure 17-16

In Fig. 17-16, ablation around the right pulmonary veins was continued; in a similar way as previously (PAC; not shown here), the flutter-like arrhythmia began again. Here, PV potentials from the right superior PV go from 1:1 with the arrhythmia to every other cycle *(arrow)*, indicating that this PV is not responsible for the ongoing arrhythmia. PV isolation can be performed during sinus rhythm, atrial pacing, or atrial flutter/fibrillation equally well.

Full Isolation

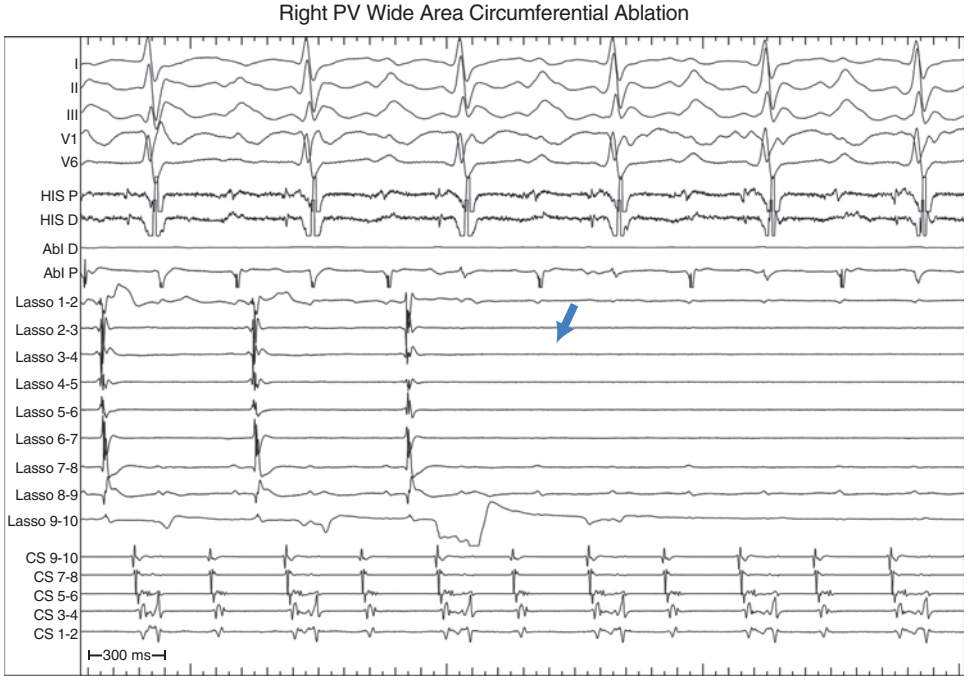
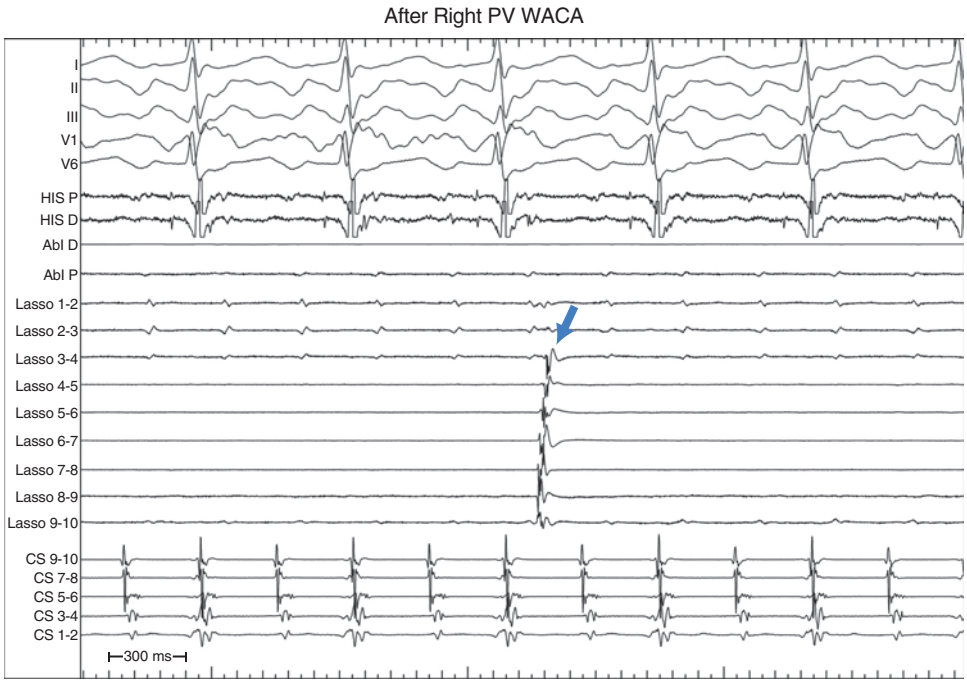


Figure 17-17

Ablation around the right pulmonary veins continues. In Fig. 17-17, PV potentials from the right superior PV are suddenly eliminated *(arrow)*. Obviously, this PV is not responsible for the flutter-like arrhythmia that continues (already known from the prior figure).

Dissociated Potential Seen After Right WACA



What Is Demonstrated? [Fig. 17-18]

A. Entrance block
B. Exit block
C. Both
D. Neither

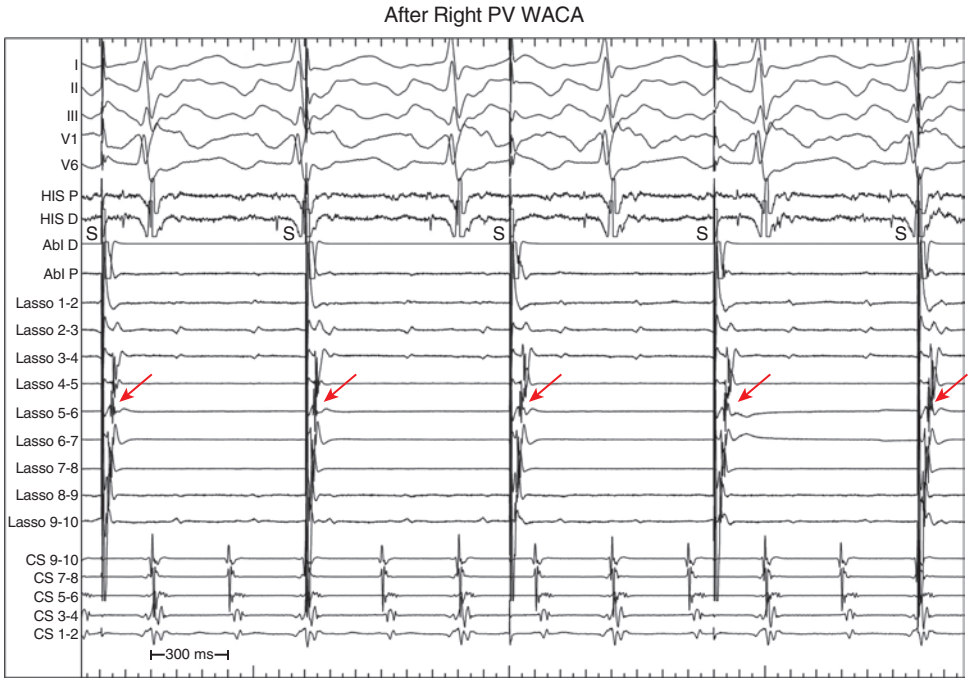
Figure 17-18

The flutter-like arrhythmia continues after the right superior PV has been isolated; a single spontaneous discharge (dissociated potential, *arrow* in Fig. 17-18) occurs during a short waiting period to ensure that the PV does not reconnect to the left atrium. This shows entrance block to the PV, but not exit block (which cannot be demonstrated until the rate in the PV is faster than the rate in the atrium).

Exit Block Can't Be Demonstrated When Pacing in Vein After Right WACA During Flutter. What Is Demonstrated? [Fig. 17-19]

A. Entrance block
B. Exit block
C. Both
D. Neither

Figure 17-19

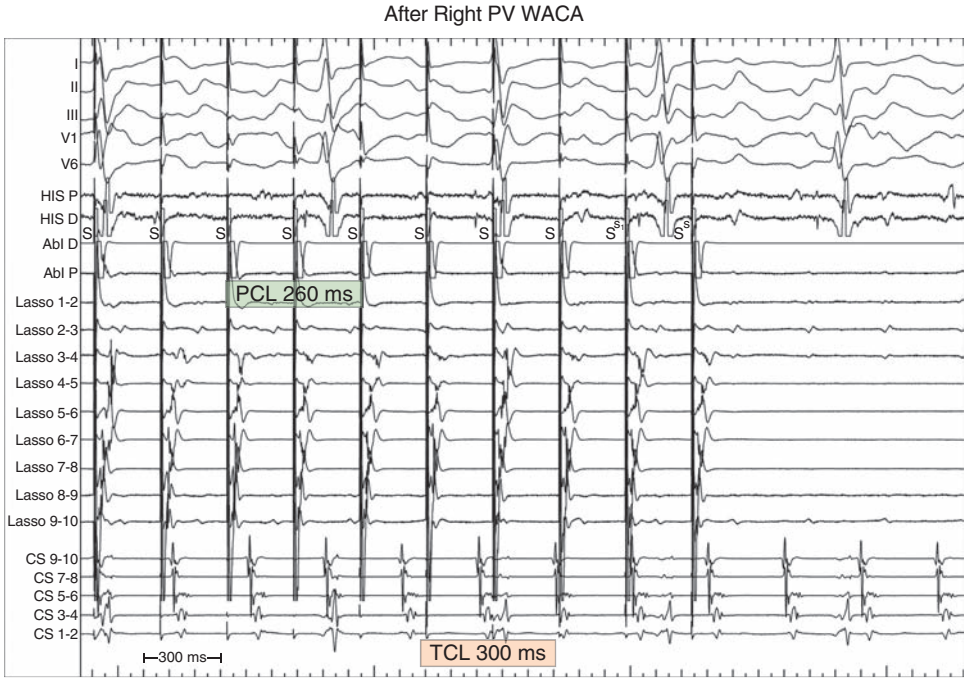


Here, pacing the right *inferior* PV inferentially captures that PV and conducts to the right *superior* PV (where the ring catheter remains; controlled PV potentials are shown by *arrows*) (Fig. 17-19). This again shows entrance block to the PV, because if there were *not* entrance block, the PV potentials would be related to the ongoing flutter-like arrhythmia rather than the stimulus artifacts (as here). This again does not demonstrate *exit* block, which requires dissociation between PV and LA in the presence of a more rapid input from the PV. Although exit block cannot be shown at this time, there is still value in finding a location at which PV capture is possible: after sinus rhythm is restored, the catheter can be maneuvered back to that spot to easily determine whether exit block is present (even without a separate catheter recording from the PV, as here).

Exit Block Testing When Pacing in Vein After Right WACA During Flutter. Which Is Demonstrated? [Fig. 17-20]

A. Entrance block
B. Exit block
C. Both
D. Neither

Figure 17-20



Now, pacing the right inferior PV captures that PV and conducts consistently to the right superior PV at 260 ms, whereas the flutter-like arrhythmia's cycle length is 300 ms and

quite regular (Fig. 17-20). Because there is no influence of the pacing on the ongoing arrhythmia, exit block—from both right PVs, because the inferior PV is paced and the superior PV is recorded—has now been reasonably demonstrated.

Pacing During Flutter

From Midcoronary Sinus

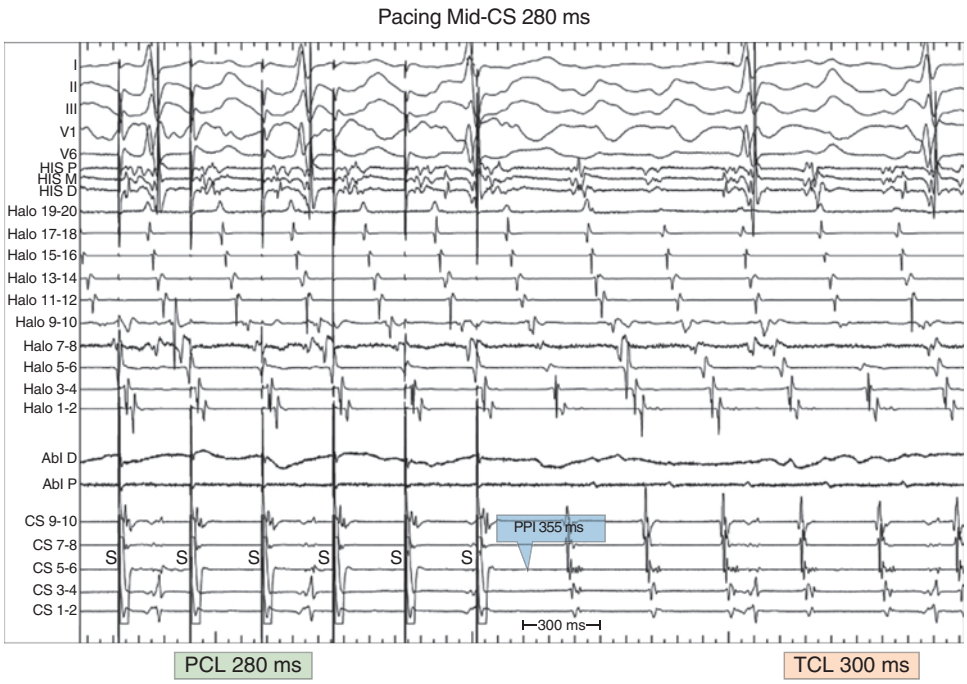
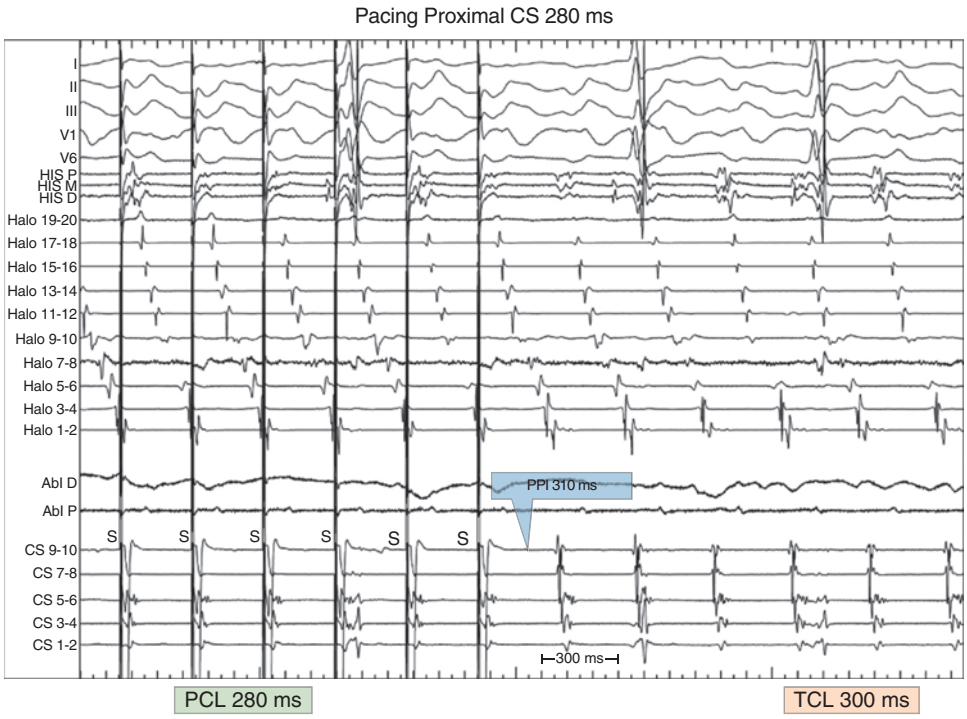


Figure 17-21

Now that all four PVs have been fully isolated with entrance and exit block demonstrated, attention is turned to the flutter-like arrhythmia. In Fig. 17-21, the last several cycles of overdrive pacing from the midcoronary sinus are shown. Because there has been no prior ablation within the right atrium that could alter the expected activation sequence along the tricuspid annulus, the fact that the atrial activation sequence during CS pacing has the configuration shown rather than the expected "chevron" sequence (equivalently early at Halo 1-2 and Halo 19-20, latest at Halo 11-12) is a demonstration of fusion and is diagnostic of macroreentry. Further, the postpacing interval (PPI) at the mid-CS is 355 ms, substantially longer than the tachycardia cycle length (TCL) and suggests that this portion of the CS is not part of the circuit. This is curious, because the prior spontaneous termination event (Fig. 17-15) suggested a left atrial source.

From Proximal Coronary Sinus

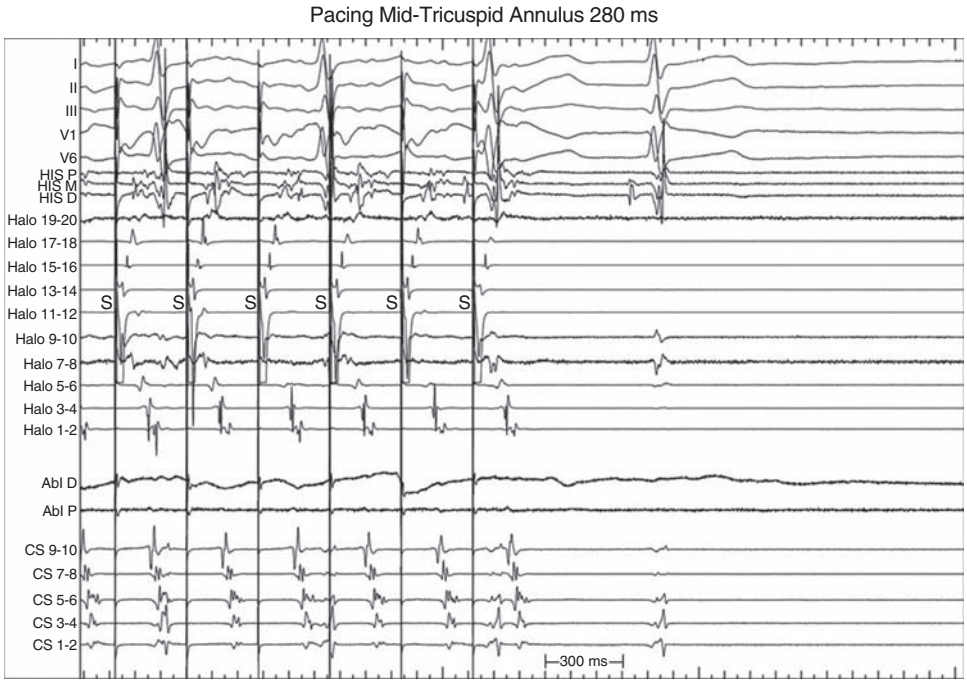
Figure 17-22



In Fig. 17-22, the last several cycles of overdrive pacing from the proximal coronary sinus electrodes (at the ostium) are shown. The atrial activation sequence along the tricuspid annulus is the same as in the prior figure, but the PPI from this site is now 310 ms, nearly the same as the TCL, suggesting that this portion of the CS is very near or part of the circuit.

From Midtricuspid Annulus

Figure 17-23



In Fig. 17-23, the last several cycles of overdrive pacing from the midtricuspid annulus electrodes are shown. Whereas multiple attempts at overdrive pacing from the coronary sinus (some not shown) did not terminate tachycardia, it was nonetheless terminated by

the first attempt at pacing from the tricuspid annulus. When this unexpected result occurs, it is always worth looking back earlier during the episode of stimulation to see if something unusual happened.

Earlier in That Episode of Tricuspid Annulus Pacing

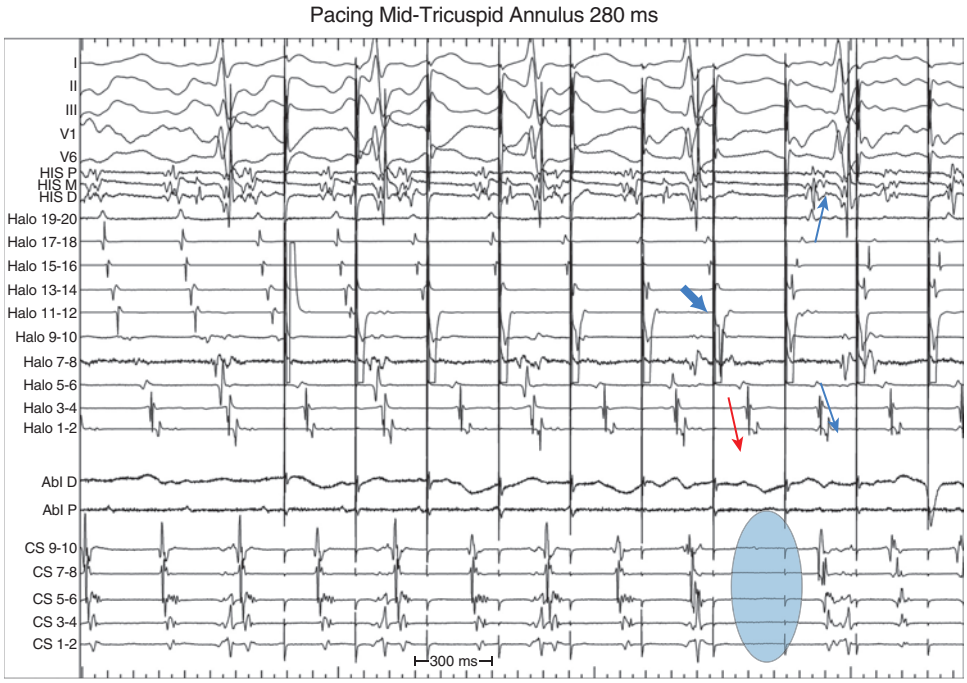


Figure 17-24

In Fig. 17-24, the first several cycles of overdrive pacing from the midtricuspid annulus electrodes are shown. The stimulus indicated by the *large blue arrow* captures the tricuspid annulus tissue and sends the impulse forward *(red arrow)*; however, it does not arrive at the CS *(translucent oval)*. The subsequent stimulus artifact conducts in both directions from the stimulation site *(blue arrows)*, because there is no wavefront from the prior cycle proceeding around the tricuspid annulus. This indicates that tissue close to the proximal CS recordings was essential for perpetuation of the tachycardia (because, in the absence of activation of this site, tachycardia terminates), and that the arrhythmia is most likely right atrial macroreentry (typical, counterclockwise atrial flutter). This is despite the unusual ECG appearance of the flutter waves. Why, then, did a previous figure show this arrhythmia spontaneously terminating in a fashion suggesting a left atrial source (Fig. 17-15)? The answer is in the figure shown here, demonstrating (as noted earlier) that there is a portion of the medial cavotricuspid isthmus where conduction is not robust, and subject to termination when input arrives before full recovery from refractoriness at that site.

Single Extrastimulus from Lateral Tricuspid Annulus

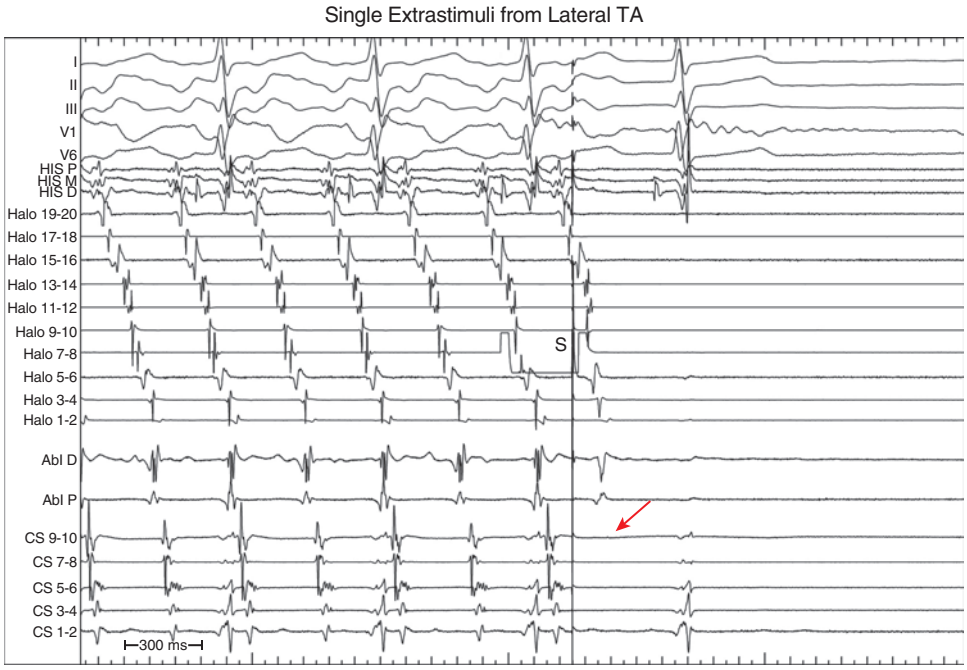


Figure 17-25

To further prove the point, the arrhythmia was reinitiated and a single extrastimulus was given during flutter from another site on the tricuspid annulus (Fig. 17-25); this too propagates distally along the tricuspid annulus toward the CS but fails to reach the CS *(arrow)* because of local refractoriness of that portion of the cavotricuspid isthmus (CTI). This once again shows that the right atrium, not the left, is responsible for this arrhythmia. This phenomenon was reproduced several times after easy reinitiation of flutter. Because of the same phenomenon, overdrive pacing from the CTI (not shown) repeatedly resulted in tachycardia termination rather than entrainment.

Ablation from Cavotricuspid Isthmus

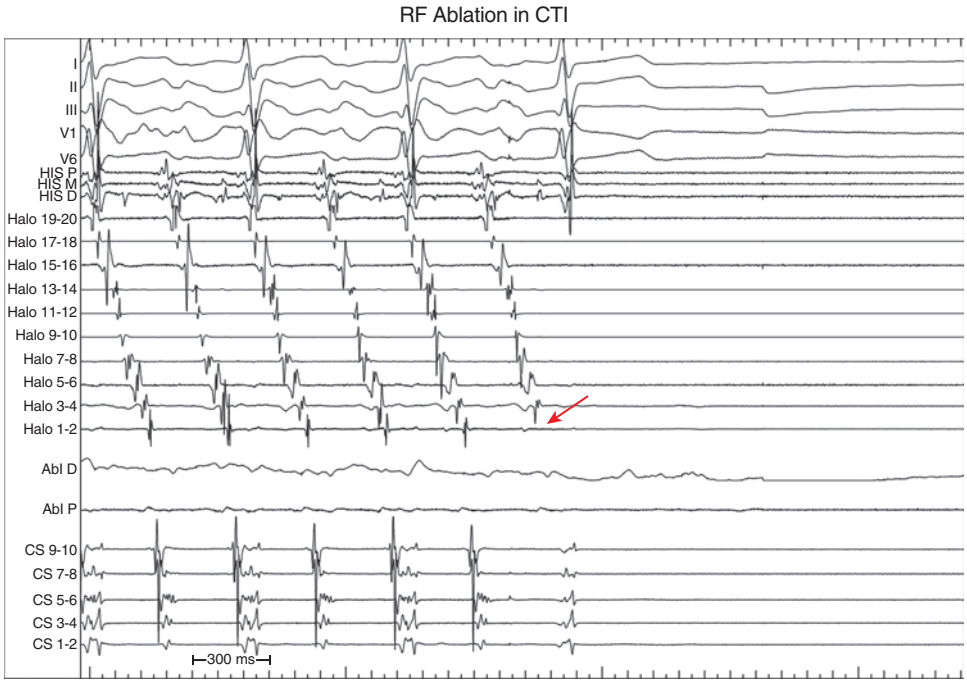


Figure 17-26

Based on the prior findings, ablation in the CTI was begun. This readily terminated flutter, as predicted (Fig. 17-26). Block occurs between electrodes near the tip of the tricuspid annulus catheter (*arrow*, at the medial aspect of the CTI), and proximal CS recordings (at the ostium). This is where spontaneous termination had occurred previously.

Completion of Cavotricuspid Isthmus Ablation

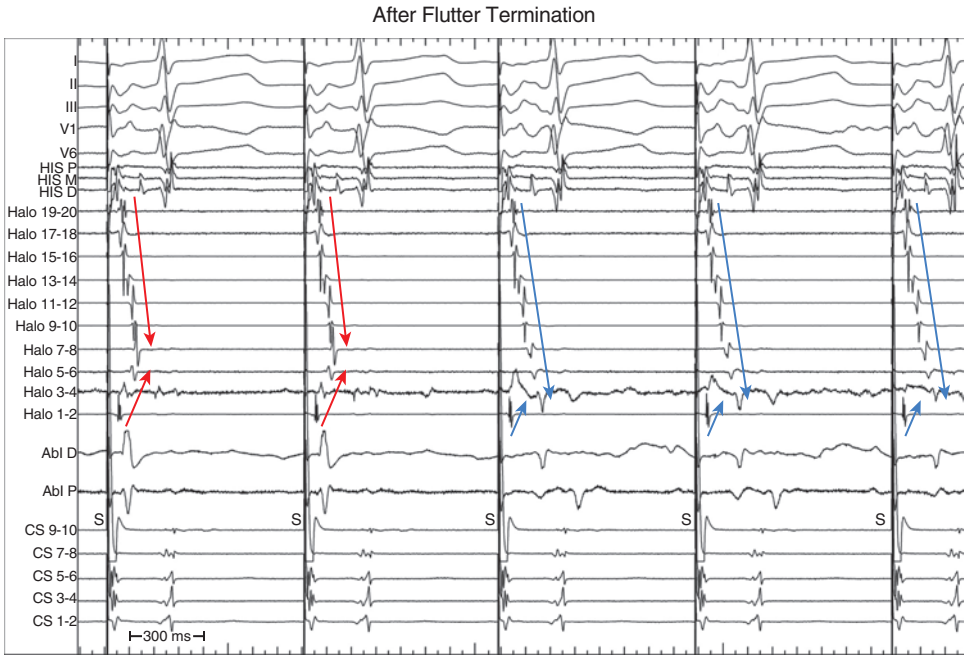


Figure 17-27

As is so often the case, termination of flutter is not equivalent to having bidirectional CTI block. In Fig. 17-27, immediately after termination of flutter, CS pacing shows persistence of conduction in the CTI *(red arrows)*. Additional RF energy is delivered, resulting in medial-lateral block, as shown here *(blue arrows)*. Pacing from the lateral TA (not shown) showed block in the lateral-medial direction as well.

Burst Pacing Initiates Atrial Fibrillation

Figure 17-28

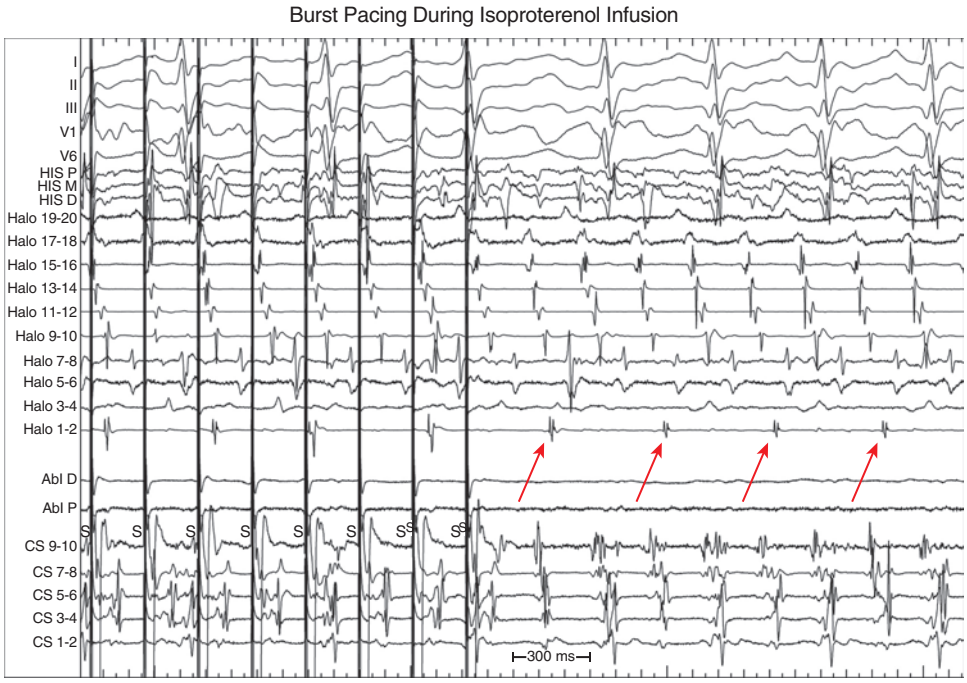
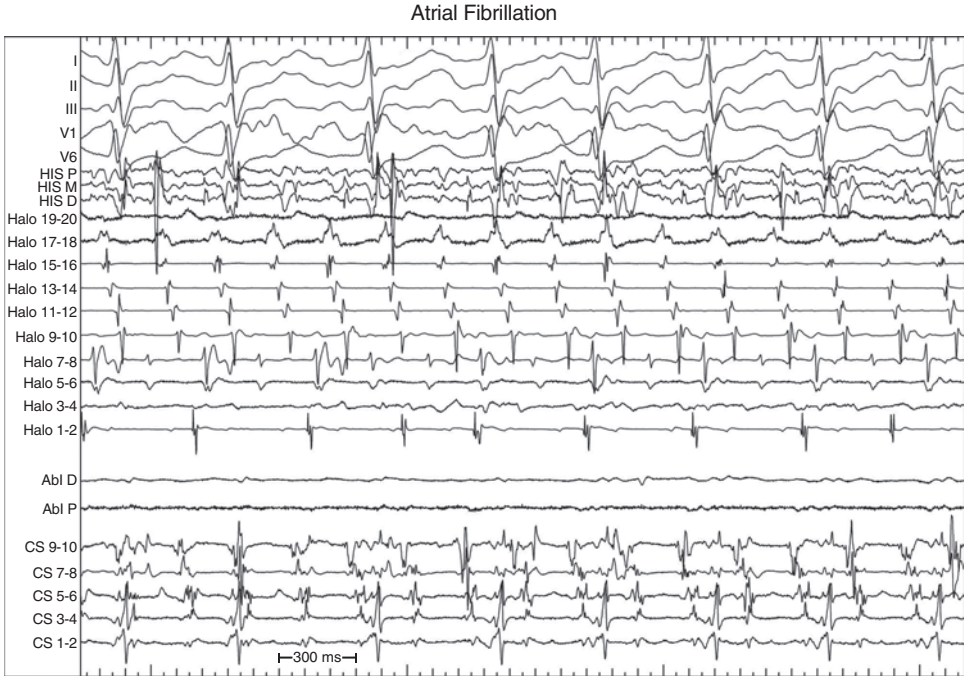


Figure 17-29



Because the patient had a history of only atrial fibrillation by ECG, despite the elimination of atrial flutter, the operators deemed it important to investigate for fibrillation. No arrhythmia was initiated with stimulation in the baseline state, but after isoproterenol infusion at 5 mcg/min, burst pacing initiated the arrhythmia shown in Fig. 17-28. Of note, electrodes at the medial tricuspid annulus (Halo 1-2) are not activated with every atrial cycle *(red arrows)*. At first glance it appears organized, but quickly degenerated to fibrillation (shown in Fig. 17-29), as shown especially in the CS and His recordings.

Standard Intracardiac Recordings and Basket Catheter Recordings in AF

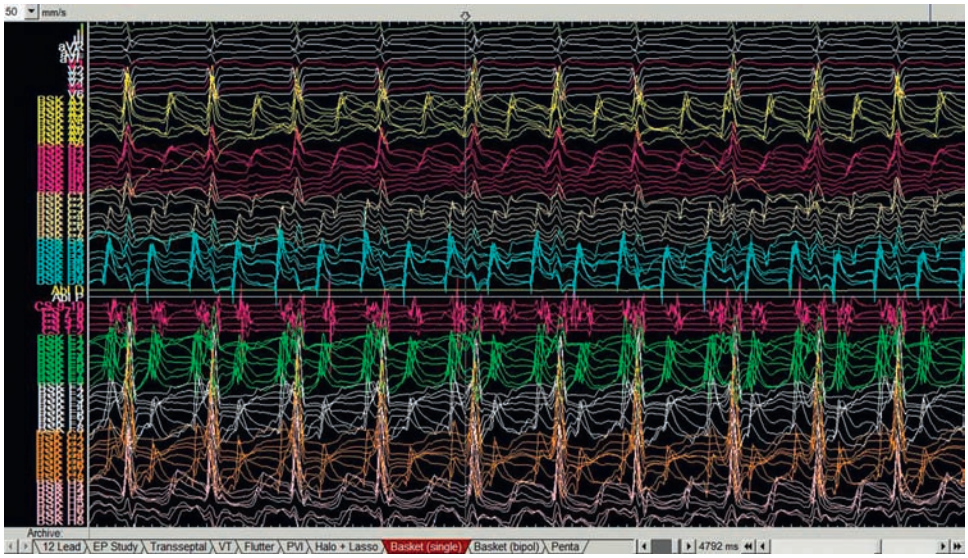


Figure 17-30

Based on the greater degree of disorganization in the CS recordings than those on the tricuspid annulus (right atrium), a 64-pole basket catheter was deployed in the left atrium and recordings were made during fibrillation (Fig. 17-30). Note that, while the CS recordings (*maroon*, at center) are still quite disorganized, the unipolar recordings from the basket catheter appear to be much more uniform from cycle to cycle. One minute of these recordings was acquired and analyzed by a proprietary mapping system looking for rotors or focal sources of atrial fibrillation.

Fluoroscopy of Catheters Including Basket in Left Atrium

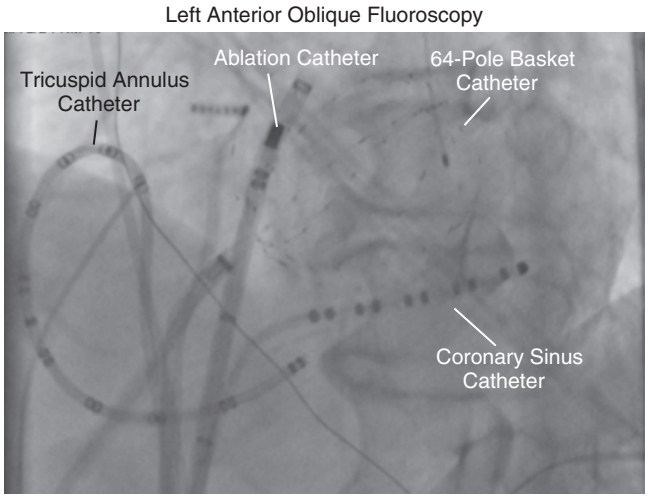
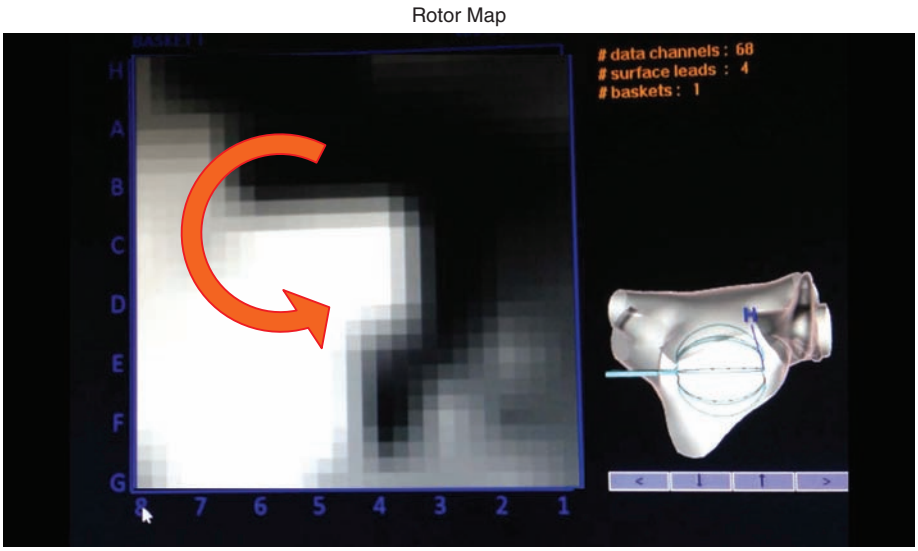


Figure 17-31

Fig. 17-31 shows a fluoroscopic view of catheter locations, including the 64-pole basket catheter in the left atrium; the ablation catheter is still inside a sheath, the tip of which is also in the left atrium. Note the location of the tip of the tricuspid annular catheter in relation to the coronary sinus proximal electrodes (positions the same as during flutter ablation).

Rotor Movie/Still

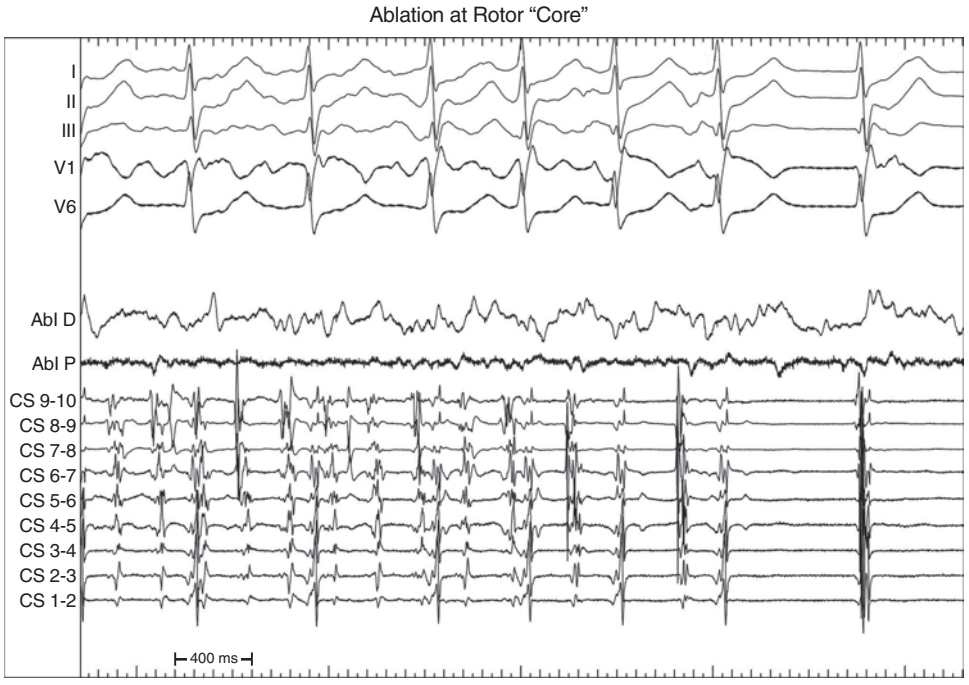
Figure 17-32



In this 4-second movie (Video 17-1 and Fig. 17-32), a counterclockwise left atrial rotor is seen with a center of rotation at about B-6 on the axial coordinates. This area, corresponding to the inferomedial free wall/floor of the left atrium, was targeted for ablation.

Ablation at Rotor "Core" Terminates AF

Figure 17-33



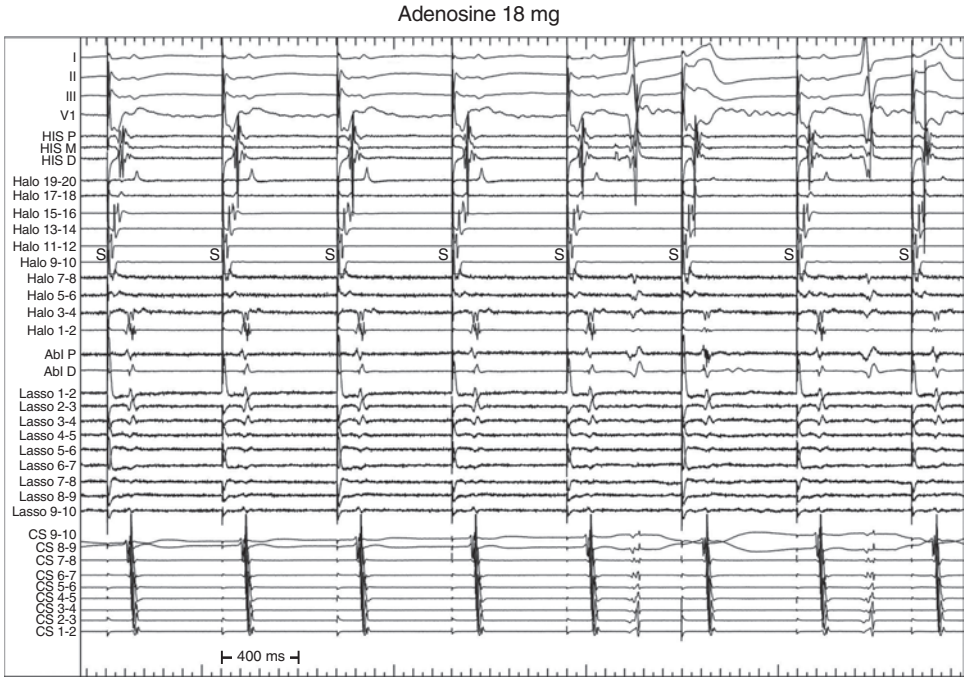
RF ablation near the center of rotation of the previously shown rotor (located on the inferomedial left atrial free wall) resulted in termination of the arrhythmia to junctional rhythm (Fig. 17-33). Fibrillation was reinitiated (with some difficulty) during continued isoproterenol infusion; a second left atrial rotor (located on the inferior portion of the septal aspect of the left atrium) was identified, and during RF ablation at the center of rotation of this rotor, fibrillation terminated to sinus rhythm (not shown). Thereafter, despite higher dose isoproterenol infusion, no arrhythmias could be initiated; the pacing protocol consisted of single- and double-atrial extrastimuli as well as burst pacing for >30 repeated attempts at cycle length 190 ms (shortest cycle length with 1:1 capture at high output).

Adenosine Administration

Figure 17-34

After completion of stimulation and checking for bidirectional block in the CTI as well as four PVs in the resting state before and after discontinuation of isoproterenol, adenosine (18 mg) was administered by intravenous bolus while recording from tricuspid annulus as well as right superior PV ("Lasso") and left superior PV (Abl) (Fig. 17-34). Adenosine-mediated hyperpolarization of atrial cells can transiently restore dormant conduction and show that additional ablation is needed. Here, at the time of atrioventricular block *(center)*, pacing from the proximal CS shows persistence of medial-lateral CTI block; there are no PV potentials recorded from either left or right superior PVs.

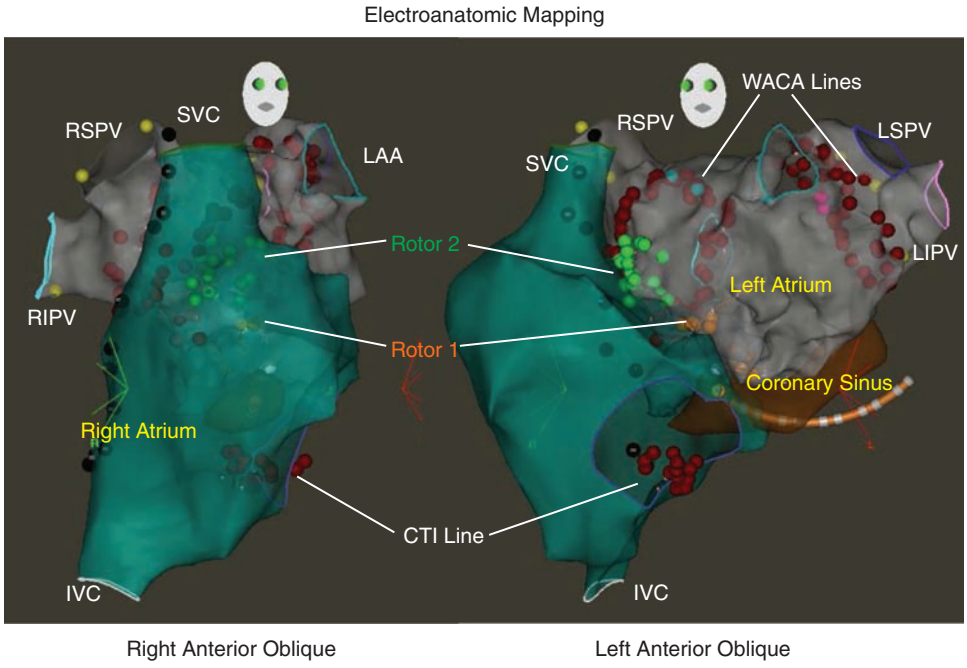
Figure 17-35



Seconds later, the site of simulation is changed to the lateral aspect of the CTI, showing persistence of block in the lateral-medial direction (Fig. 17-35). Again, no PV potentials are recorded from either left or right superior PVs. Not shown is attempted stimulation from the left superior PV, at a site in which capture had been demonstrated previously, without conduction to left atrium. The patient has had no recurrent atrial arrhythmias in long-term follow-up.

Electroanatomic Mapping Showing Ablation Regions

Figure 17-36



In this electroanatomic mapping diagram in Fig. 17-36, the right atrium is *green*, left atrium *gray*, and coronary sinus *brown*. Wide-area circumferential ablation (WACA) lines encircling the PVs are shown as well as sites of rotor mapping (#1 *[orange dots]*, inferomedial left atrial

free wall; #2 *[green dots]*, inferior portion of the septal aspect of the left atrium). It is clear that both of these rotor locations are well outside the standard WACA lines and were "missed" by PV isolation. *CTI,* cavotricuspid isthmus; *IVC,* inferior vena cava; *LAA,* left atrial appendage orifice; *LIPV,* left inferior PV; *LSPV,* left superior PV; *RIPV,* right inferior PV; *RSPV,* right superior PV; *SVC,* superior vena cava.

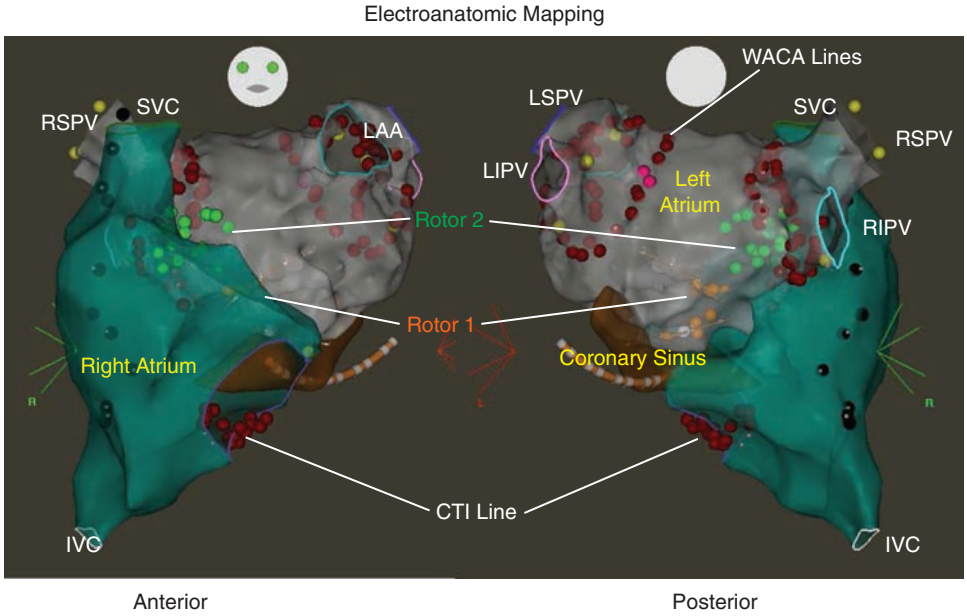


Figure 17-37

The same maps as in the prior figure are displayed in Fig. 17-37 in different orientations. *CTI,* cavotricuspid isthmus; *IVC,* inferior vena cava; *LAA,* left atrial appendage orifice; *LIPV,* left inferior PV; *LSPV,* left superior PV; *RIPV,* right inferior PV; *RSPV,* right superior PV; *SVC,* superior vena cava.

Summary

- Atrial fibrillation can be transformed to atrial flutter by sodium-channel–blocking agents such as amiodarone (which also slows the flutter cycle length)
- Spontaneous termination of atrial flutter is rare but can occur at the narrowest part of the circuit (CTI)
- Careful use of overdrive pacing during tachycardia—analyzing events both at the end and at the beginning of pacing—can be very useful diagnostically
- In patients with predominant atrial fibrillation clinically who are in flutter at the time of the procedure, fibrillation should usually still be treated
- Rotors that maintain fibrillation may reside near typical ablation lines for PV isolation, or outside these zones

Idiopathic Focal Right Ventricular Outflow Tract Ectopy

18

Case Presentation

The patient was a 39-year-old woman referred for management of palpitations for the last 2 years. Episodes began after birth of the eighth child and often worsened when she was upset. Ambulatory recorder showed premature ventricular complexes (PVCs) comprising about 25% of all complexes. Baseline ECG showed sinus rhythm with PVCs having a left bundle branch block (LBBB) and right-inferior axis with a precordial R-wave transition at V3 and smooth R-wave contours in inferior leads. Metoprolol was ineffective at controlling her symptoms (palpitations and fatigue), which were increasingly bothersome. Physical examination finding was normal aside from skipped beats. Echocardiogram showed mild global hypokinesis (ejection fraction 45%). She underwent an EP study elsewhere; the right ventricular outflow tract (RVOT) was thoroughly mapped, and multiple sites were ablated without altering the PVC frequency. She was referred for a repeat EP study and ablation.

Baseline ECGs and Intracardiac Recordings

Where Is the Likely Origin? [Fig. 18-1]

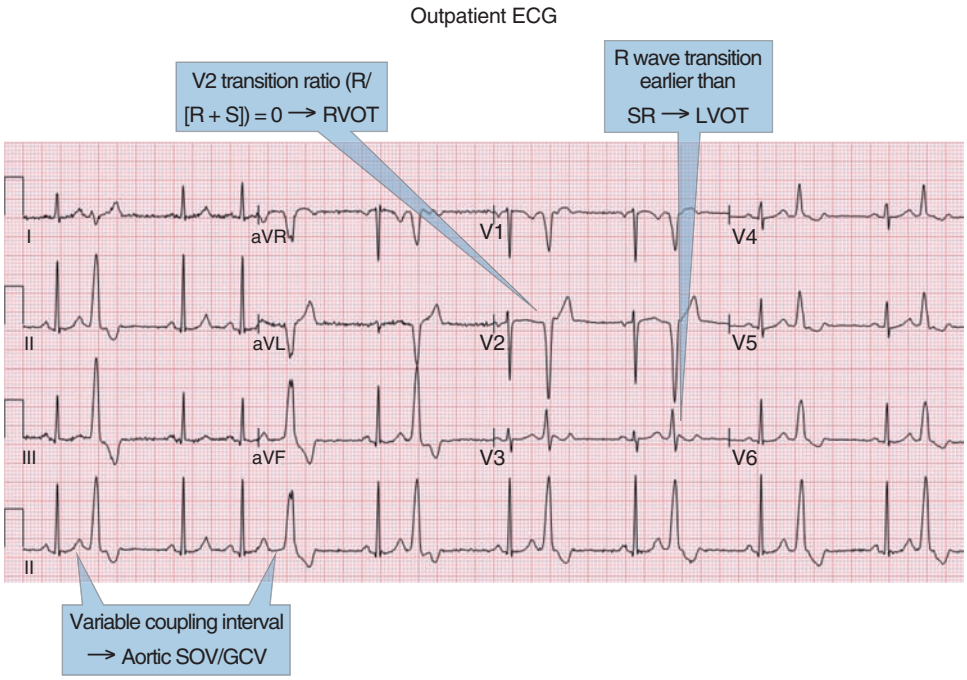


Figure 18-1

A 12-lead ECG of the patient's sinus rhythm with ventricular ectopy is shown in Fig. 18-1. As indicated, several morphologic criteria of the PVCs yield disparate indicators of its origin. For instance, in lead V2, the ratio $R/(R + S)$ of 0 suggests RVOT origin, whereas R-wave transition occurring earlier in the PVC than in sinus rhythm (V3 vs V4) suggests left ventricular outflow origin; finally, the variable coupling interval from the prior sinus complex to the PVC in the rhythm strip suggests aortic sinus of Valsalva (SOV) or great cardiac vein (GCV) origin.

Is This the Same as What We Saw Earlier? [Fig. 18-2]

Figure 18-2

With the patient in the electrophysiology laboratory, PVC coupling intervals appear to be more constant (Fig. 18-2); the V2 ratio still suggests RVOT origin but the precordial transition occurs in V4, the same as in sinus. In many cases, precordial leads positioning in the electrophysiology laboratory is slightly different from that in the clinic because of defibrillation patches and electrode patches for the electroanatomic mapping system, if used.

In general, the ECG leads are the last of these to be applied to the chest, and are placed as close to standard locations as possible, but working around patches that are already in place for other purposes. Thus ECGs taken at this setting may not be identical to those obtained in other settings.

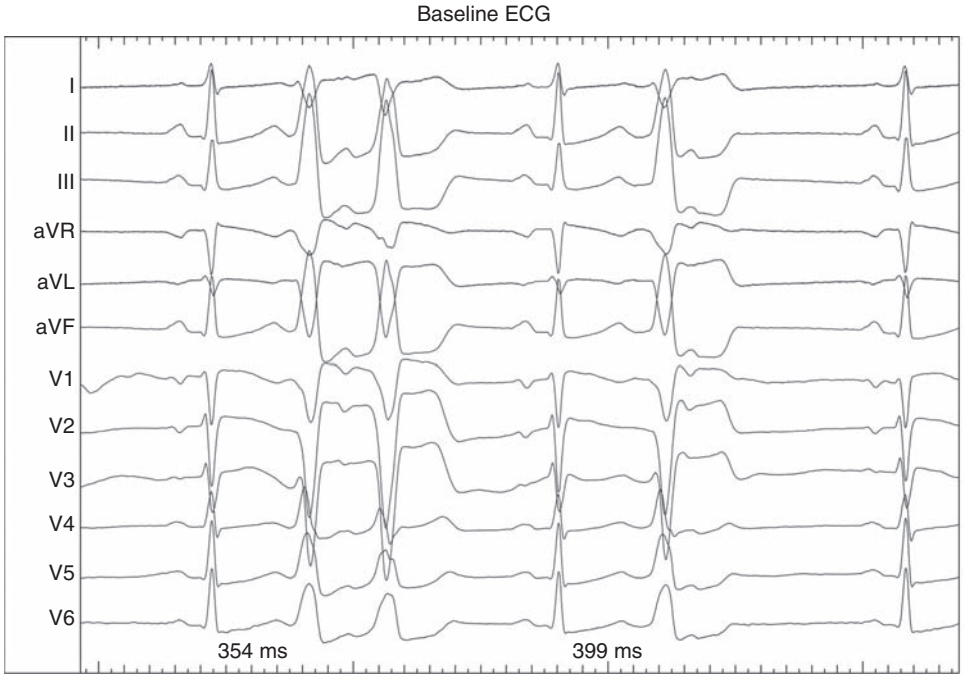
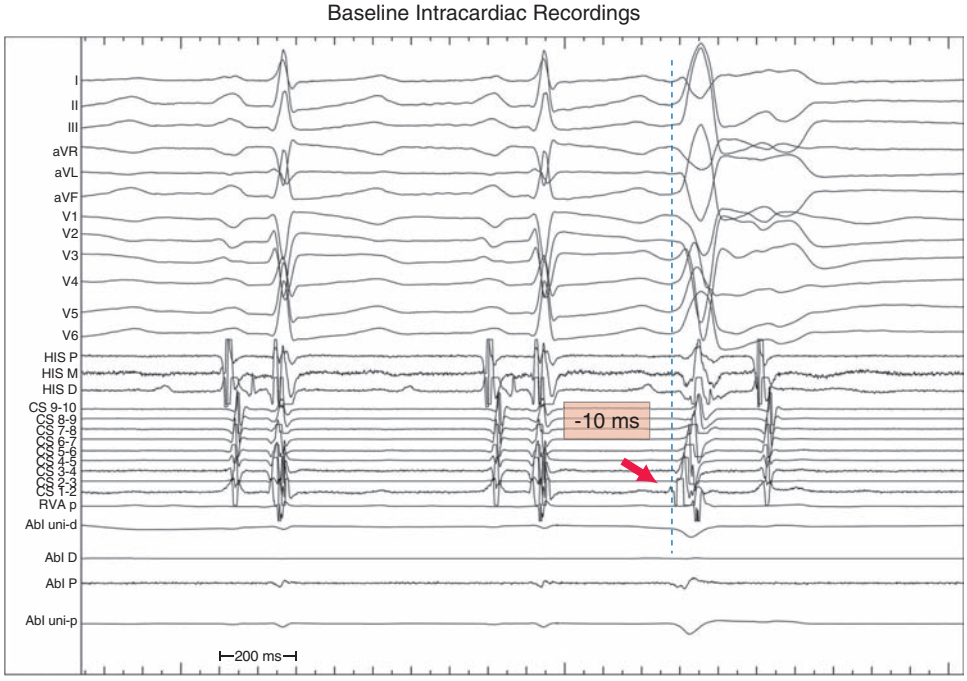


Figure 18-3

A few minutes later in the procedure, PVC coupling intervals in Fig. 18-3 are less constant. It is important to acquire several examples of spontaneously occurring PVCs, as well as noting their coupling intervals, before placement of any endocardial catheters that could cause catheter-induced ectopy and introduce confusion as to morphology and timing of PVCs. Does this indicate anything about target site location?

Figure 18-4

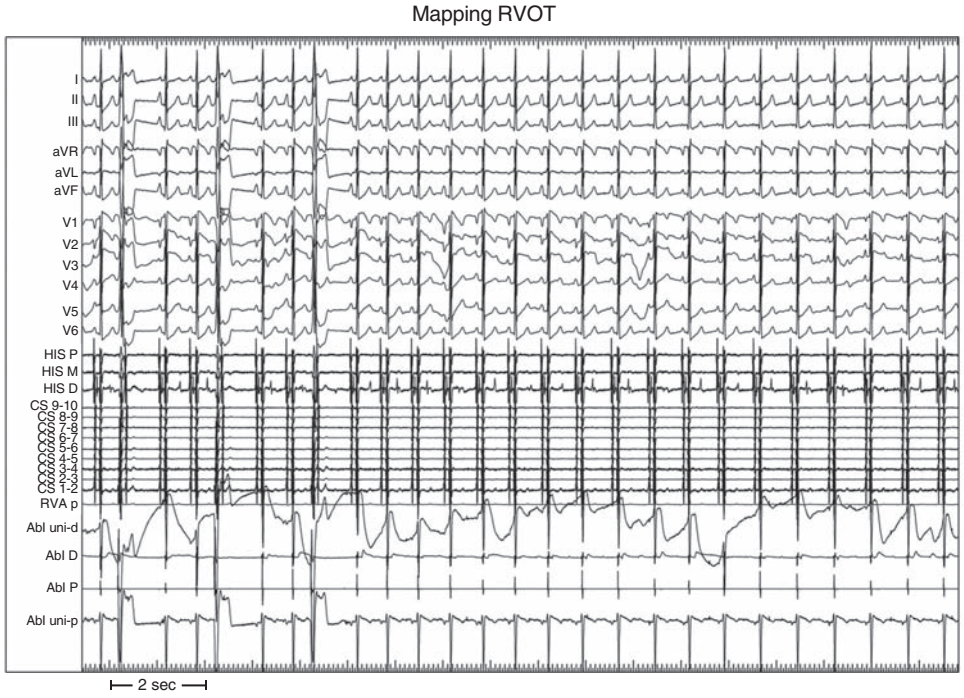


In Fig. 18-4, the coronary sinus (CS) catheter tip has been positioned at the top of the mitral annulus (as distally as possible); the onset of the QRS complex is denoted by a *dashed line*. A far-field component of the distal CS ventricular recording precedes the QRS onset by 10 ms. This suggests that the actual focus is nearby, but probably not exactly at this location (timing at the actual source should be 20 to 40 ms before PVC's QRS onset).

Mapping Different Sites

Does This Mean Anything? [Fig. 18-5]

Figure 18-5



Manipulation of the mapping catheter in the right ventricular outflow tract, where mapping was started, resulted in sudden cessation of ventricular ectopy whereas it previously had occurred every 4 or 5 complexes (seen at left in Fig. 18-5). This probably means that the catheter has "bumped" into the tissue at the source, rendering it transiently depolarized

and unable to discharge again until recovery has occurred. If this is a correct interpretation, it is reasonable evidence that the origin is nearby—endocardial RVOT, and not in the great cardiac vein, left ventricle, epicardial surface, or sinus of Valsalva.

Is This a Good Ablation Site?

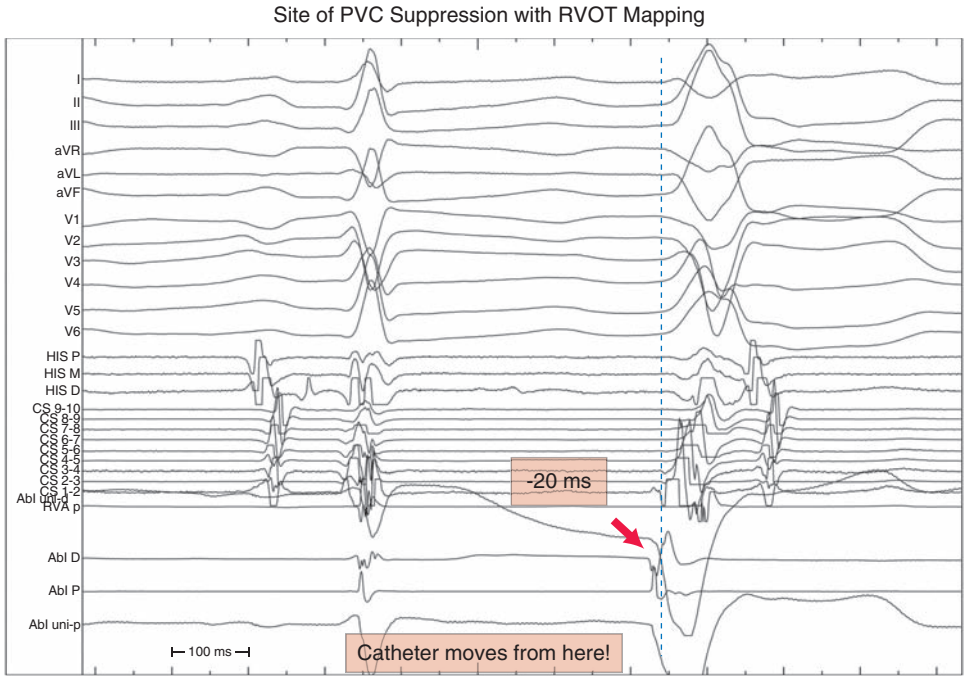


Figure 18-6

Recordings displayed in Fig. 18-6 were made just before inadvertant catheter dislodgement from the site, after which ectopy transiently ceased. Catheter-mediated trauma that eliminates pathway conduction or focal firing suggests proximity to an important site for the arrhythmia. Often, however, trauma has occurred during somewhat vigorous catheter movement (not just gentle "bumping"), so the effect may not be very localizing, and (more important) the catheter tip has often moved on from where the contact actually affected the rhythm—such that the location where it is first observed after the event may not be where the effect occurred. However, the electrogram at this site just before catheter movement had a timing 20 ms before QRS onset and suggests it was, in fact, close to the origin.

Is This a Good Site?

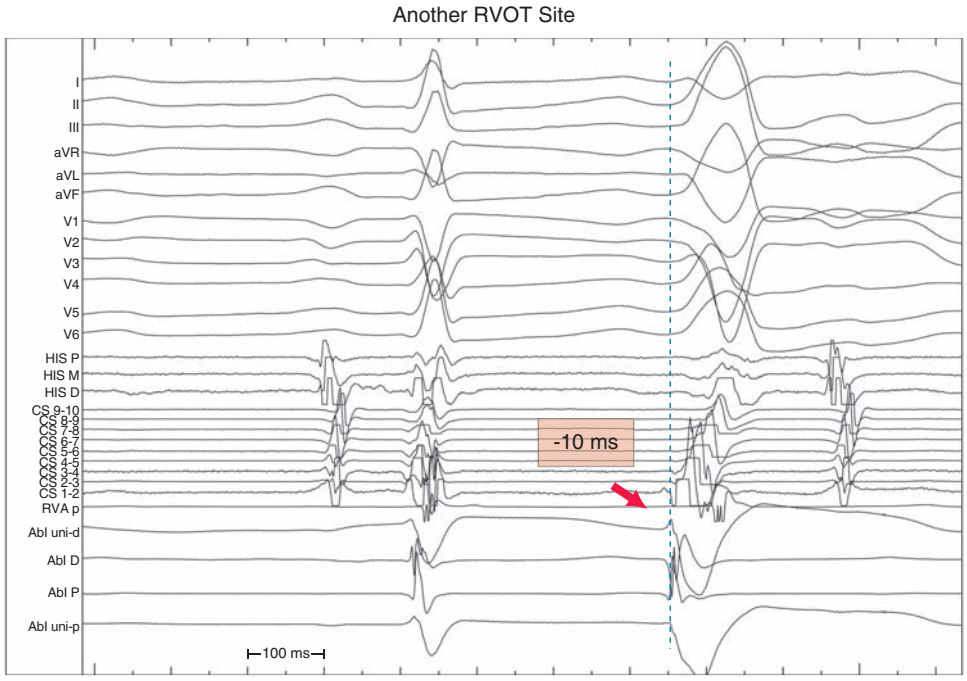


Figure 18-7

Mapping was continued after resumption of PVCs (Fig. 18-7). This is not such a good site; the distal unipolar recording has an R wave, and the proximal bipolar recording is almost as early as the distal, neither of which are as good as the prior site.

Algorithm Says 94% Match. Ablate Here?

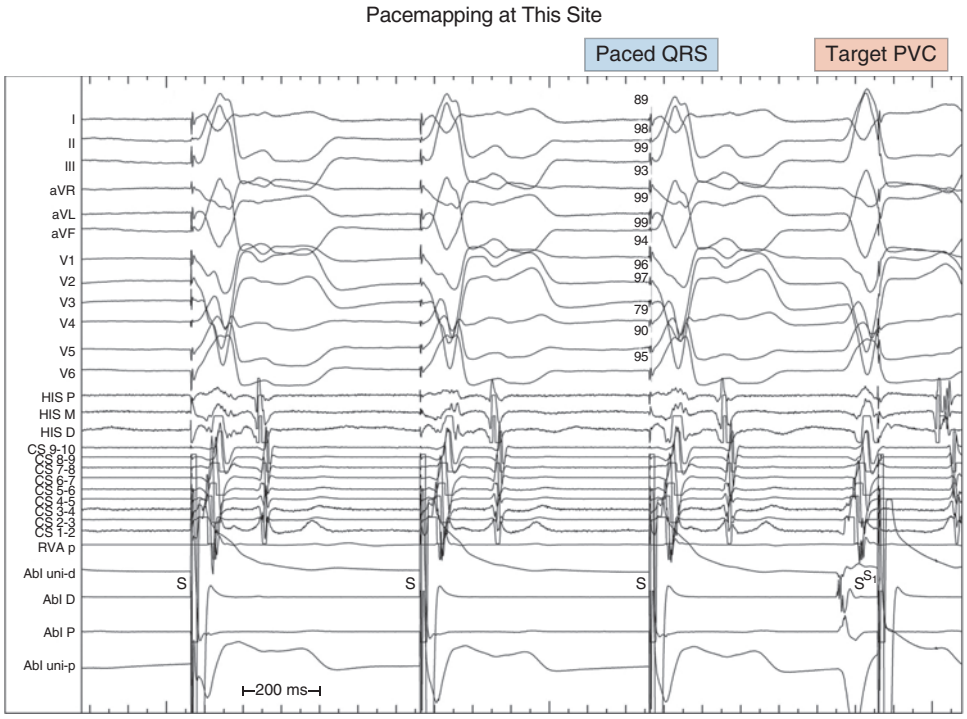


Figure 18-8

Pacing at this site (Fig. 18-8) yields a reasonable, but far from perfect, match. Ablation was not attempted here. Numbers to the left of each QRS complex on the 3rd paced cycle indicate percentage of morphology match (aggregate, 94%), using an algorithm in the recording system.

Algorithm Says 92% Match. Ablate Here?

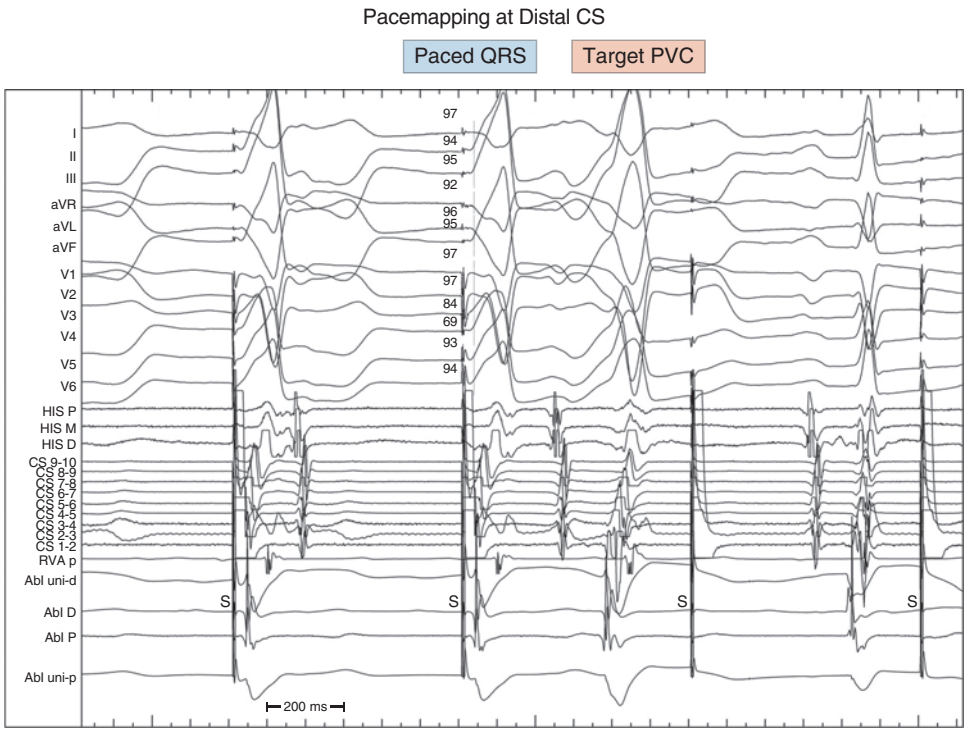


Figure 18-9

Pacing from the distal CS electrode pair yields a reasonable, but inexact, match with the PVC (Fig. 18-9). Ablation was not attempted here.

Is This a Good Site?

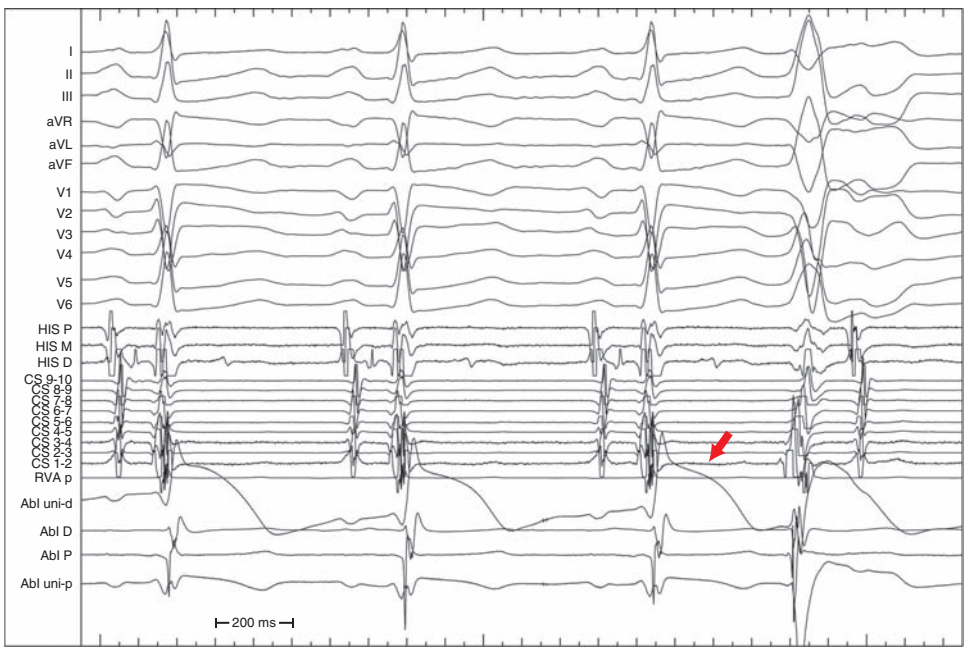
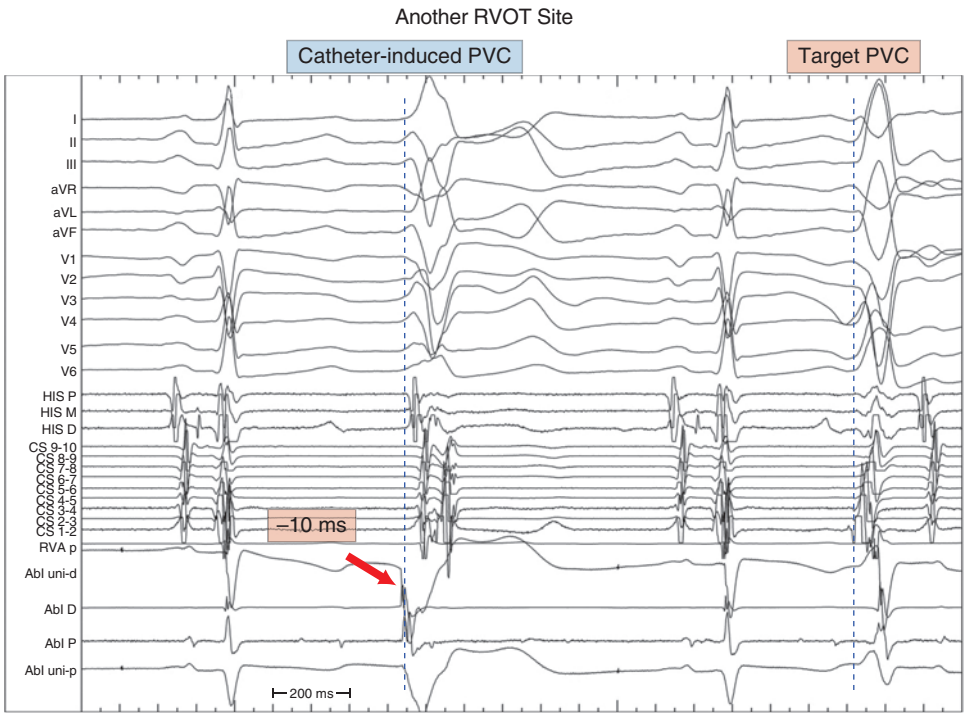


Figure 18-10

Mapping is continued back in the RV outflow tract. ST elevation on the unipolar recording (Fig. 18-10, *red arrow*) indicates too-good contact, threatening perforation. The catheter tip should be withdrawn somewhat from this point.

Is This a Good Site?

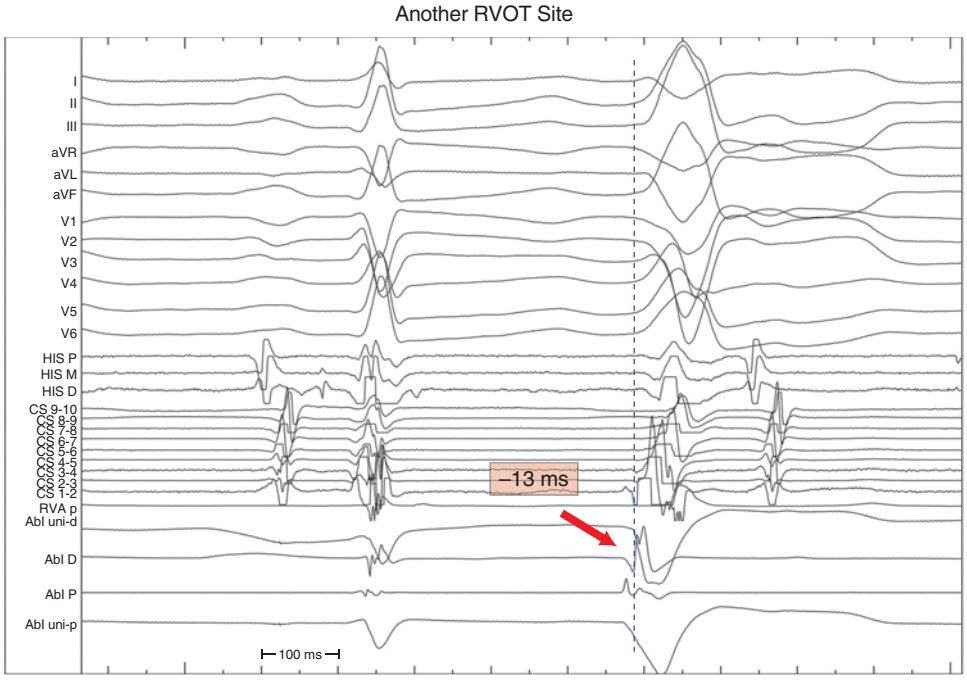
Figure 18-11



Mapping continues; in Fig. 18-11, a reasonably good site is shown; the unipolar recording has no R wave, and it is reasonably early. However, this is a catheter-induced PVC. The beginning of the QRS is difficult to see because of partial obscuration by the P wave. This site is not early during the real PVC (at right).

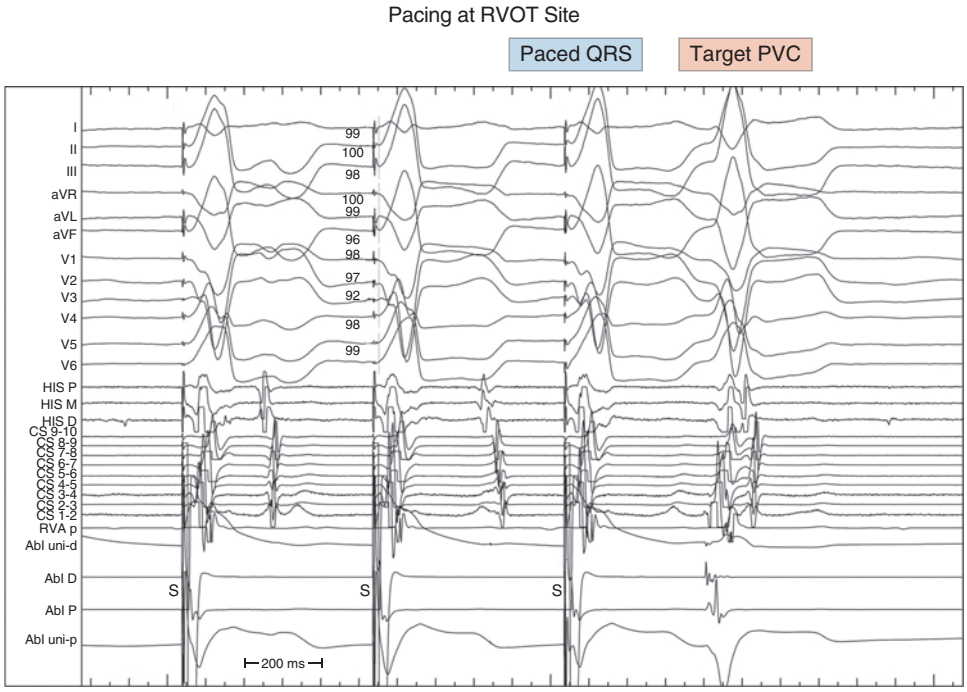
Is This a Good Site?

Figure 18-12



Additional mapping in the RV outflow tract shows another reasonably good site in Fig. 18-12; the unipolar has no R wave, and it is reasonably early. However, the proximal bipolar is almost as early as the distal, and distal unipolar and bipolar do not "agree." This was very near the "bump" site and directly across from the CS tip electrode.

Pacemapping to Corroborate Activation Mapping Data



Algorithm Says 94% Match. Ablate Here?

Figure 18-13

In Fig. 18-13, pacing at the site shown in Fig. 18-12 yields the best match yet, which visually/qualitatively seemed better than the 94% match calculated by machine reading. Ablation was attempted here.

First Ablation Attempted

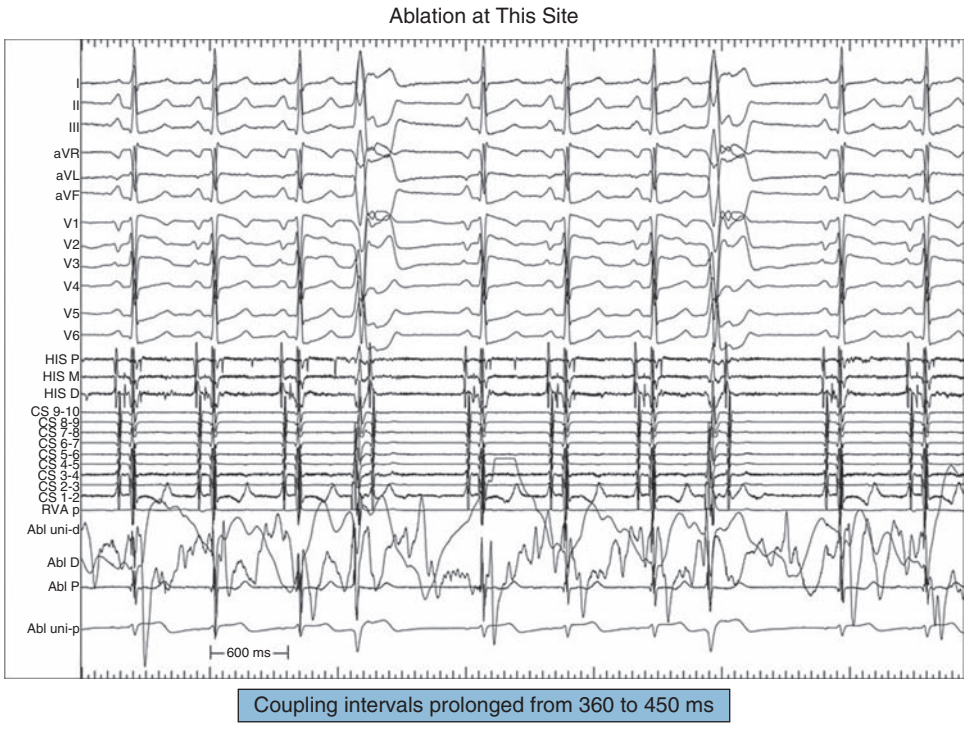


Figure 18-14

As a result of ablation, the coupling intervals of the PVCs from prior complexes increased substantially (Fig. 18-14); nevertheless, PVCs persisted. This probably indicates that the ablation site was near enough to the focus to have an effect on it, but not eliminate it.

Status Update

- RVOT has been thoroughly explored; no better sites were found
- Distal coronary sinus (CS)/great cardiac vein (GCV) has early potential, but we cannot advance the catheter further and cannot get the ablation catheter close to the same site in GCV
- What next?
  - Pericardial access and epicardial mapping?
  - Aortic sinus of Valsalva/left ventricular mapping?
  - Try harder to get the ablation catheter out the CS/GCV?

Mapping Other Sites

Is This a Good Site? [Fig. 18-15]

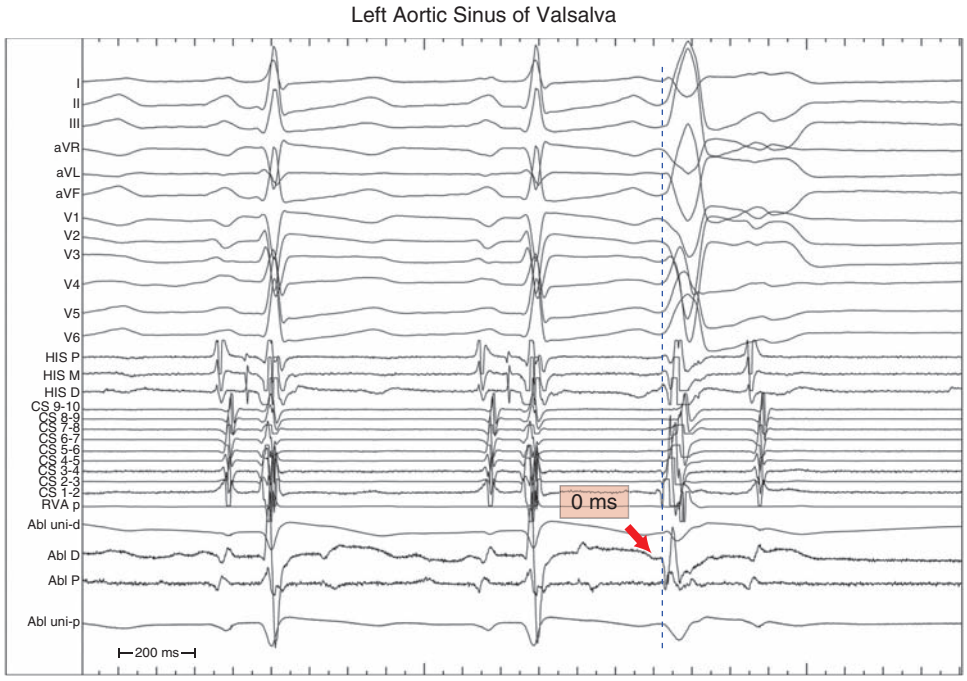


Figure 18-15

Mapping in the left aortic sinus of Valsalva (SOV) shows a site with poor features (Fig. 18-15); timing is not good at all. Because LV myocardium is some distance away, the unipolar signal is less helpful in the left SOV than when in contact with ventricular myocardium.

Algorithm Says 85% Match. Ablate Here?

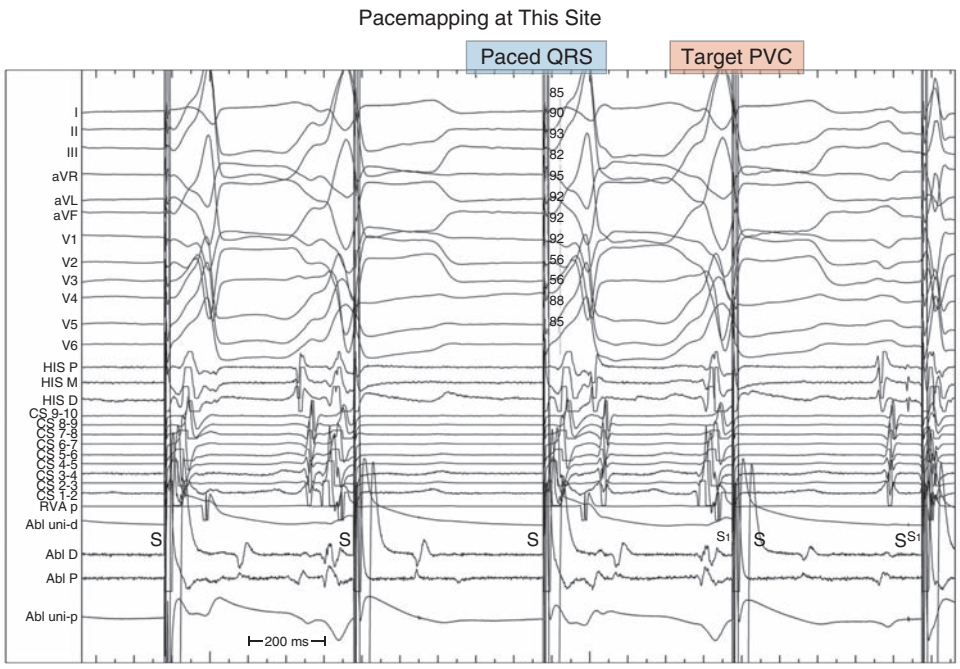


Figure 18-16

Pacing at the site shown in Fig. 18-16 (left aortic SOV) yields the poorest match yet; however, some PVCs can be ablated from this site with poor electrogram and pacemap features. Ablation was attempted here after left coronary arteriography showed >6 mm from this site to the left main ostium. PVCs continued unaffected by a 30-second application of ablation energy.

Is This a Good Site?

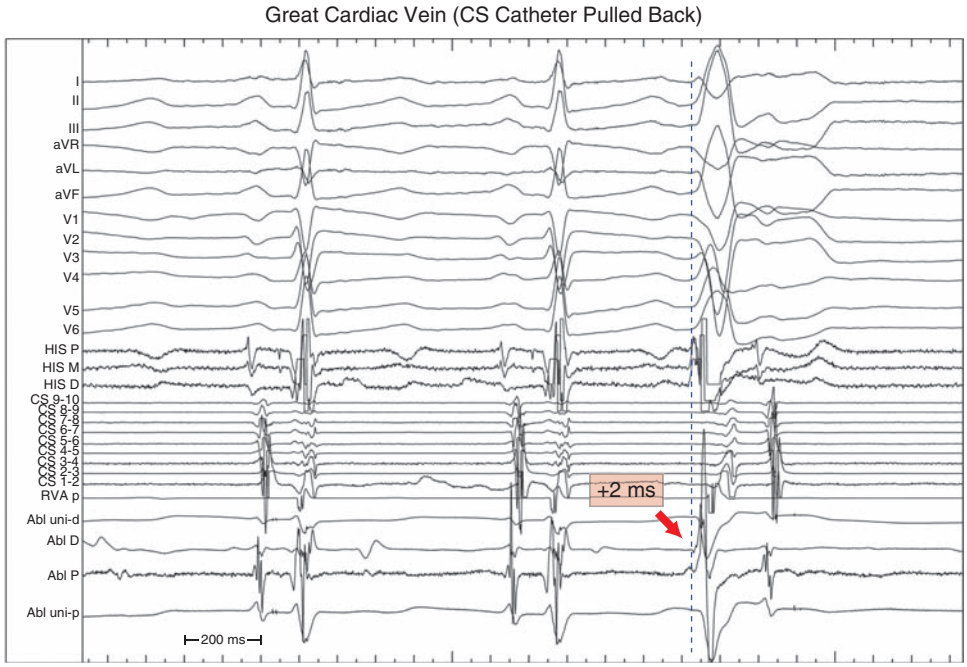


Figure 18-17

Next, the ablation catheter was inserted into the CS and advanced to the great cardiac vein (required partial withdrawal of the CS catheter to fit). Mapping here (Fig. 18-17) showed a poor site; the catheter tip could not be advanced further. The proximal recording has a far-field signal suggesting that something nearby is early (very gained up).

Algorithm Says 79% Match. Ablate Here?

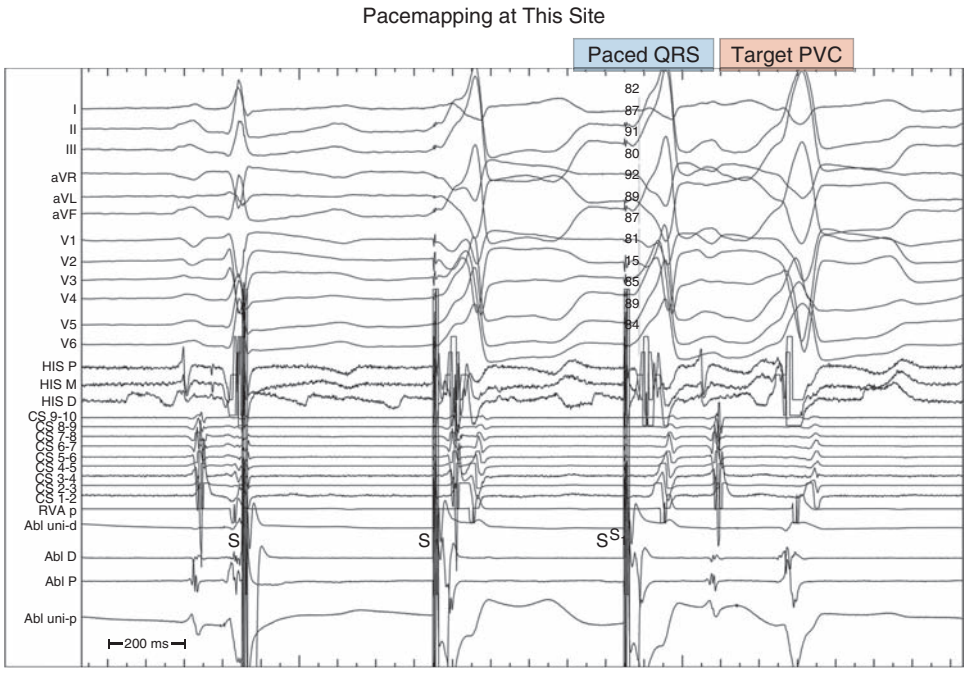


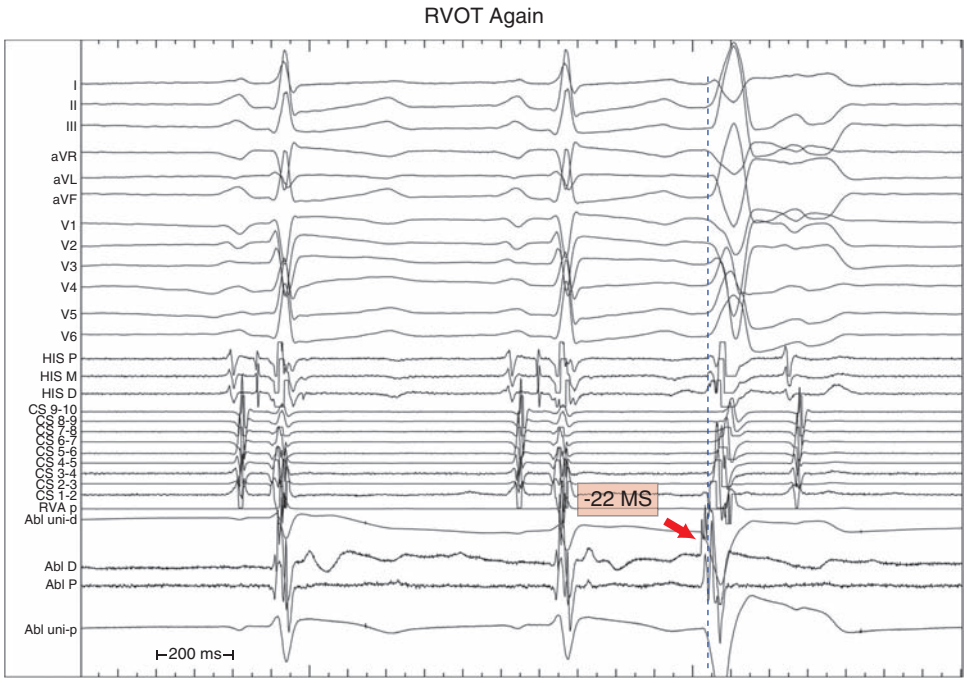
Figure 18-18

Pacing at this site (Fig. 18-18) in the distal CS yields the poorest match of all (aggregate match 79%); there is no point in attempting ablation in this small vessel with such poor mapping features.

Status Update

- RVOT has been thoroughly explored; no better sites were found
- Aortic sinuses of Valsalva showed poor sites
- Distal CS/GCV was even less promising
- What next?
  - Pericardial access and epicardial mapping?
  - Go back to RVOT where best sites were, and where "bump" mapping was observed?

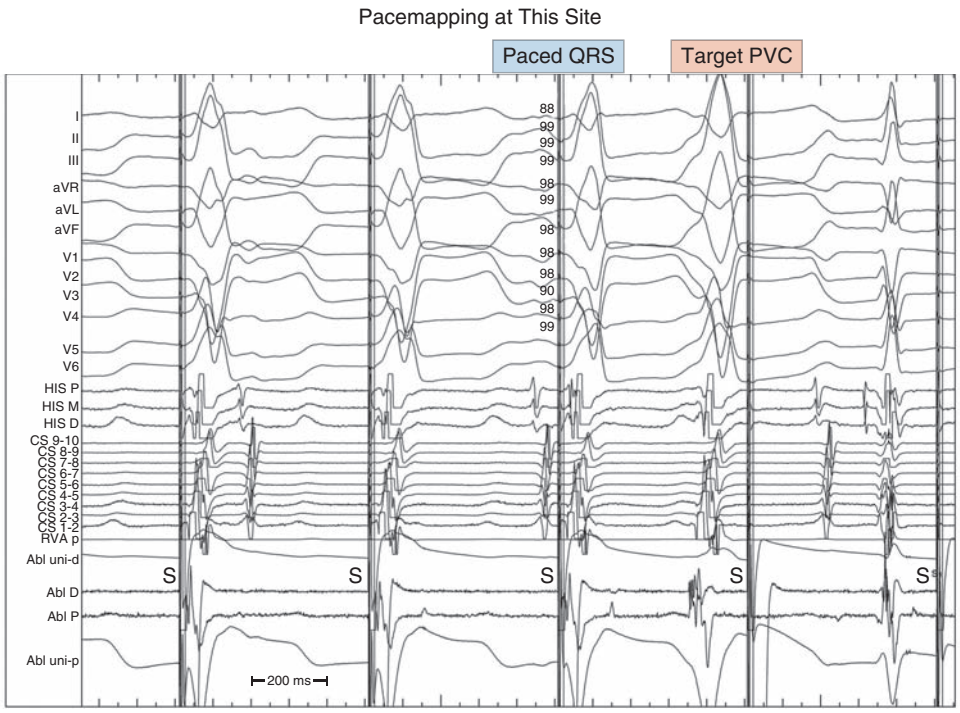
Repeat Right Ventricular Mapping and Ablation



Is This a Good Site?

Figure 18-19

Back in the right ventricular outflow tract again, a very good site is encountered in Fig. 18-19; all good target site features are fulfilled.



Algorithm Says 97% Match. Ablate Here?

Figure 18-20

Pacing at this site (Fig. 18-20) yields a very good pace-match (aggregate, 97%) with the spontaneously occurring PVC. The pacing output is only 2 mA; the lower the output, the more specific this finding is.

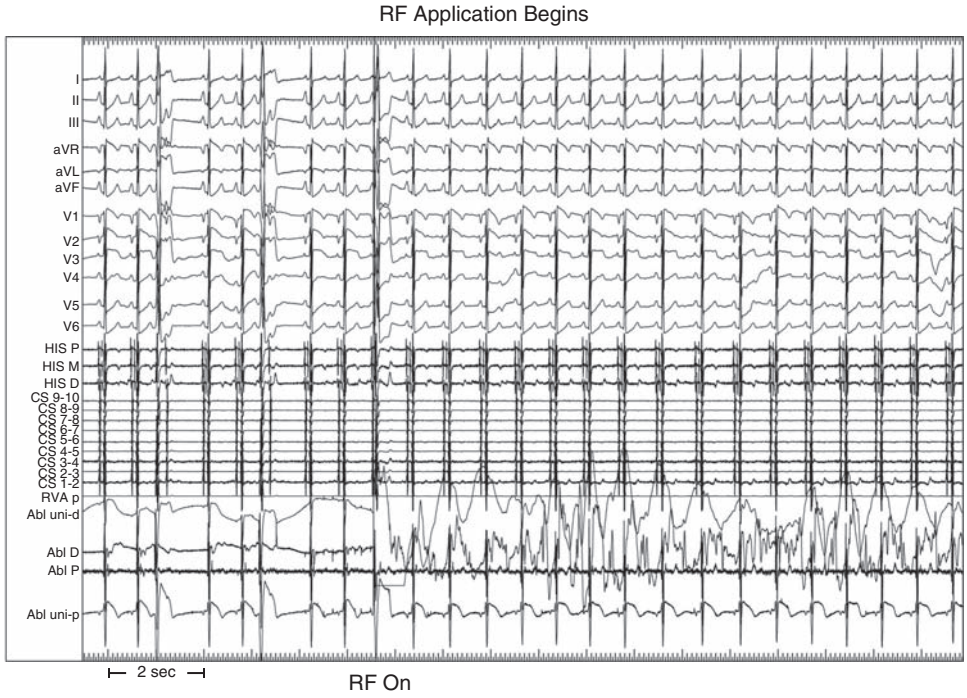


Figure 18-21

Immediately upon beginning radiofrequency (RF) energy delivery at this site in the RVOT, PVCs ceased and did not recur for the remainder of the procedure (Fig. 18-21).

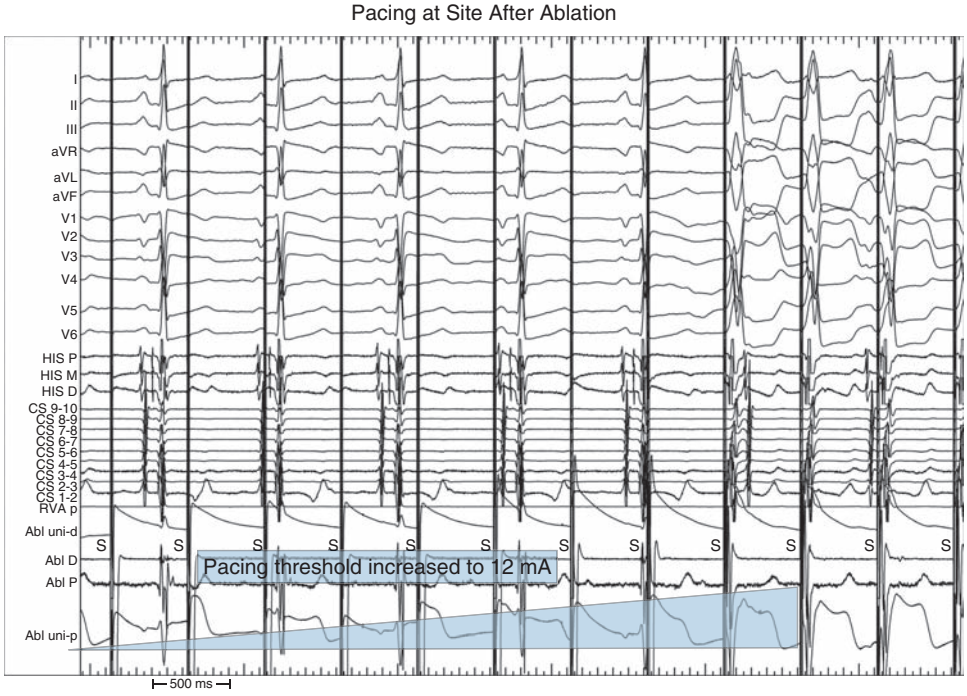


Figure 18-22

After RF application that eliminated ventricular ectopy, pacing at that site has a markedly elevated capture threshold (Fig. 18-22), indicative of substantial damage to the area. In addition, especially evident on the last two complexes on the right, ST elevation in the unipolar recording is seen, corroborating damage.

Images of Catheters and Maps

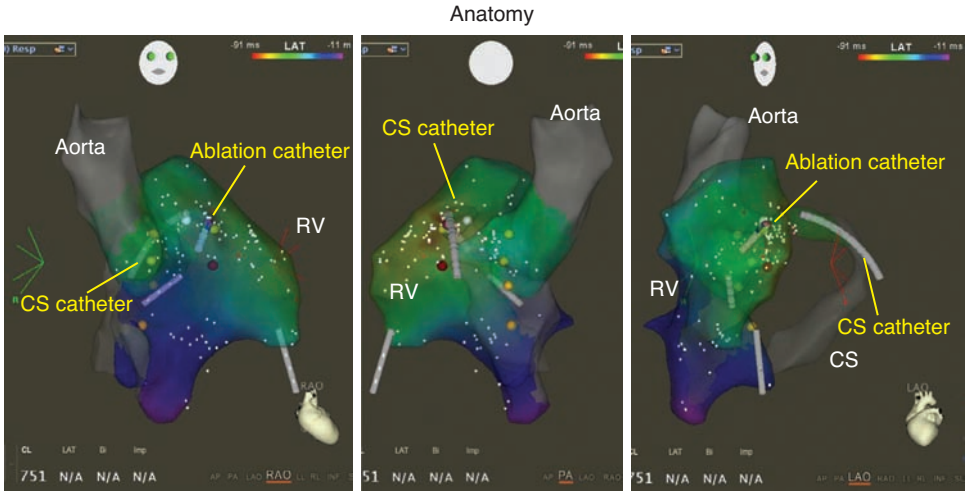


Figure 18-23

Fig. 18-23 displays electroanatomic mapping views of activation timing obtained during PVCs. Different chambers mapped are shown with labels (aorta [root], RV = right ventricle, CS = coronary sinus). In the left anterior oblique view, it is easy to see how the distal CS recordings could have early activation and yet the arrhythmia originates in the leftward aspect of the right ventricular outflow tract, with the two catheters (CS and ablation) nearly touching.

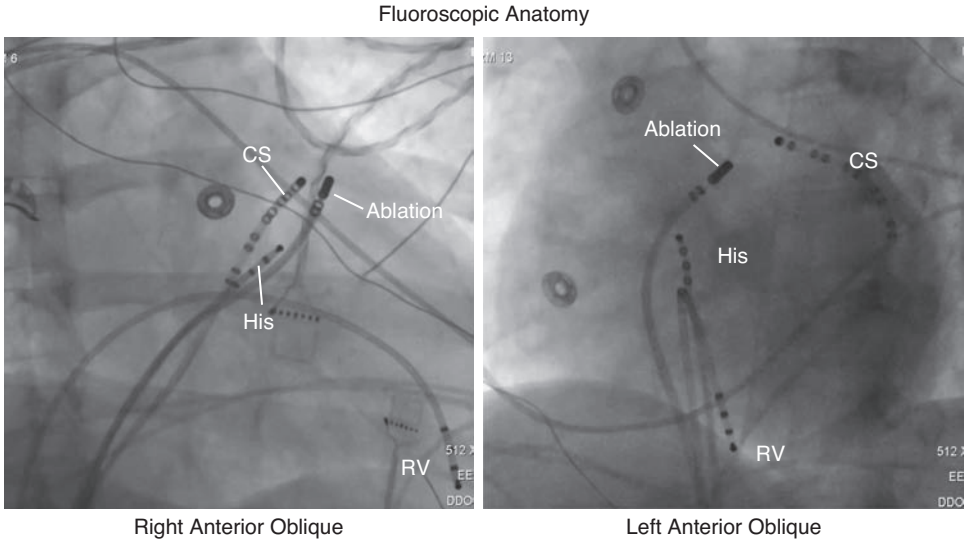


Figure 18-24

Right and left anterior oblique fluoroscopic views of catheter positions, noting especially successful ablation site in the right ventricular outflow tract, are shown in Fig. 18-24.

Final ECG

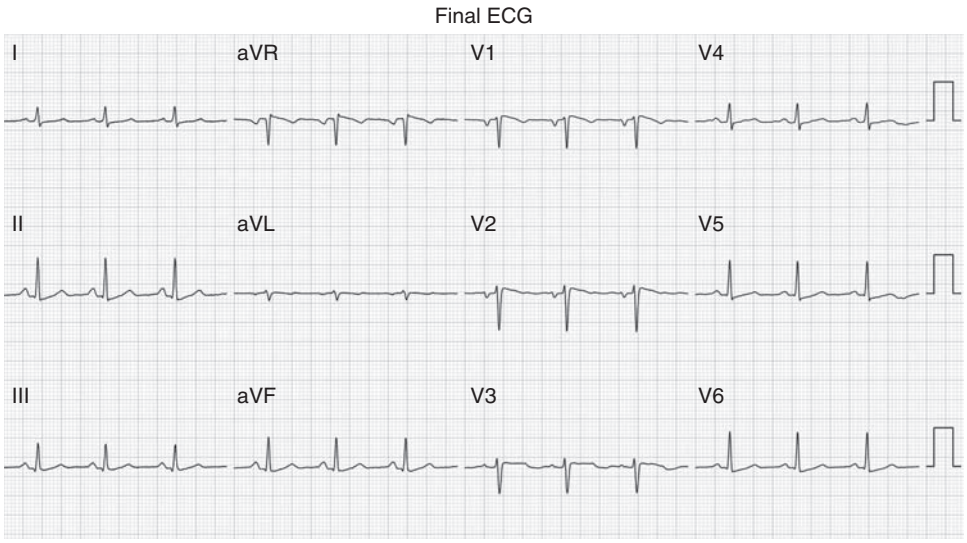


Figure 18-25

The final sinus rhythm ECG (Fig. 18-25) shows no ventricular ectopy. The patient was discharged the next morning, having had no palpitations or ectopy overnight, or on follow-up as an outpatient.

Mapping Sites Compared

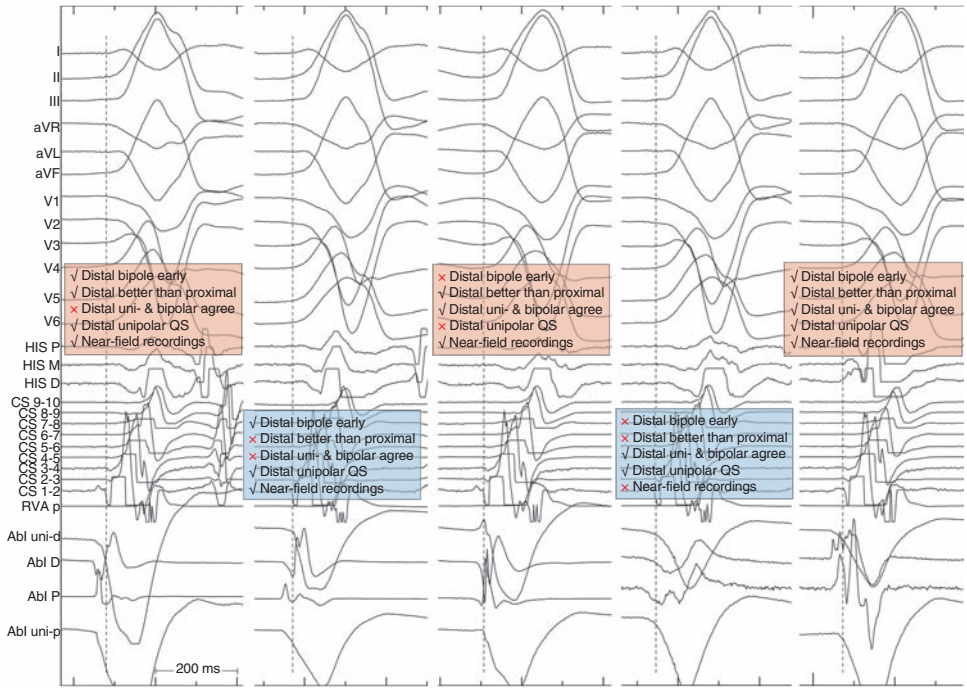


Figure 18-26

Fig. 18-26 provides a summary of electrogram features at different mapping sites, noting good and bad features.

Summary

- LBBB-inferior axis PVCs and VT may arise from:
  - RVOT/pulmonary artery
  - Right aortic sinus of Valsalva
  - LV or RV endocardium
  - LV or RV epicardium
  - Left aortic sinus of Valsalva/great cardiac vein (rare)
- Preprocedure ECG is an indicator of probability of location, but is not entirely specific
- After disappointing mapping and ablation in other areas, it is worth revisiting areas that had reasonable target features earlier
- Electrogram features of successful ablation sites:
  - Pre-QRS timing 15 to 40 ms
  - Unipolar "QS" configuration
  - "Agreement" between unipolar and bipolar recordings
  - Near-field characteristics (high amplitude, high frequency)
  - Consistent appearance from beat to beat (contact)

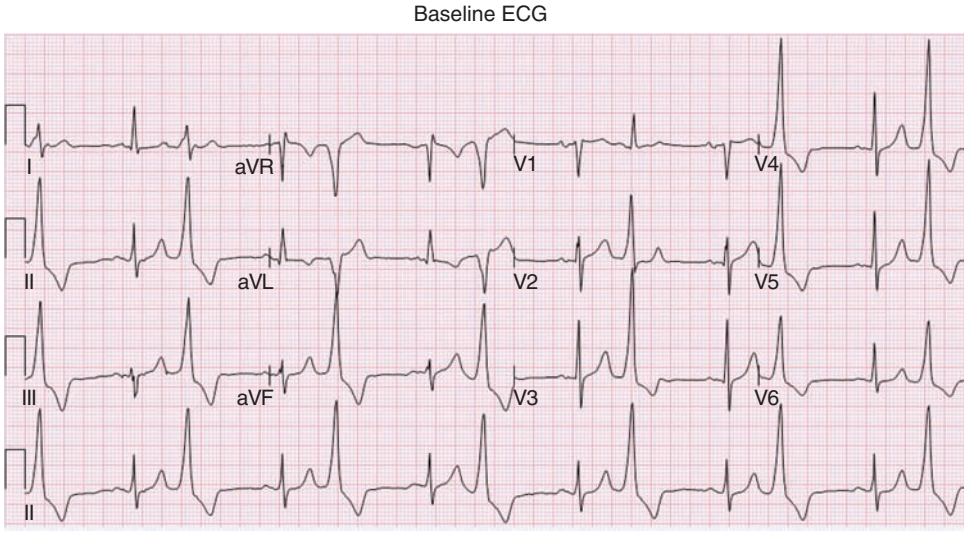
19 Coronary Sinus Ventricular Ectopy

Case Presentation

A 65-year-old man experienced symptomatic premature ventricular complexes (PVCs) for years. He initially sought evaluation 5 years ago because of palpitations: he was found to have an irregular pulse and a soft systolic murmur; ECG showed frequent PVCs; stress test was equivocal for ischemia and had no effect on PVCs; coronary arteriography showed normal epicardial arteries. After all this, he preferred no treatment. However, he developed increasing fatigue in the last few months. Ambulatory ECG showed very frequent PVCs and nonsustained ventricular tachycardia (~57% of complexes were ventricular in origin). Echocardiogram showed ejection fraction of 28% and moderate to severe valvular aortic stenosis. He was referred for consideration of transcutaneous aortic valve replacement (TAVR) and electrophysiologic evaluation and possible ablation.

Baseline ECGs

Figure 19-1



In Fig. 19-1, bigeminal ventricular ectopy is present with fixed coupling to the prior normal QRS.

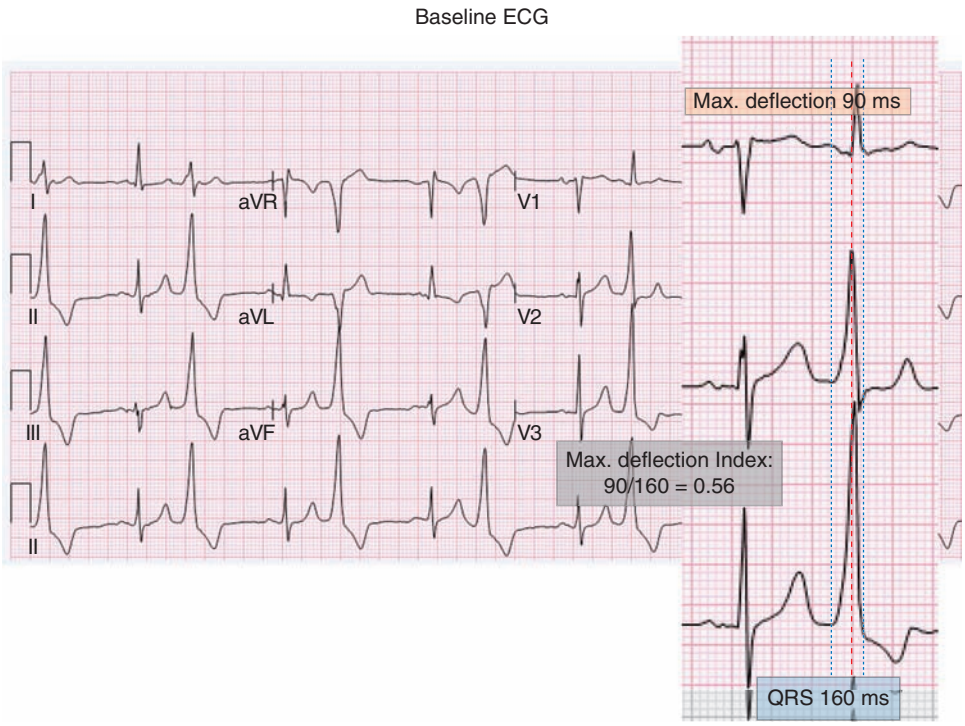


Figure 19-2

The QRS configuration in Fig. 19-2 suggests a possible epicardial source of ventricular ectopy because of the maximum deflection index (0.56). Another potential source, the left aortic sinus of Valsalva, might well become difficult to access (or be completely inaccessible) if he underwent TAVR or surgical valve replacement. Thus EP evaluation and potential ablation before an aortic procedure were reasonable.

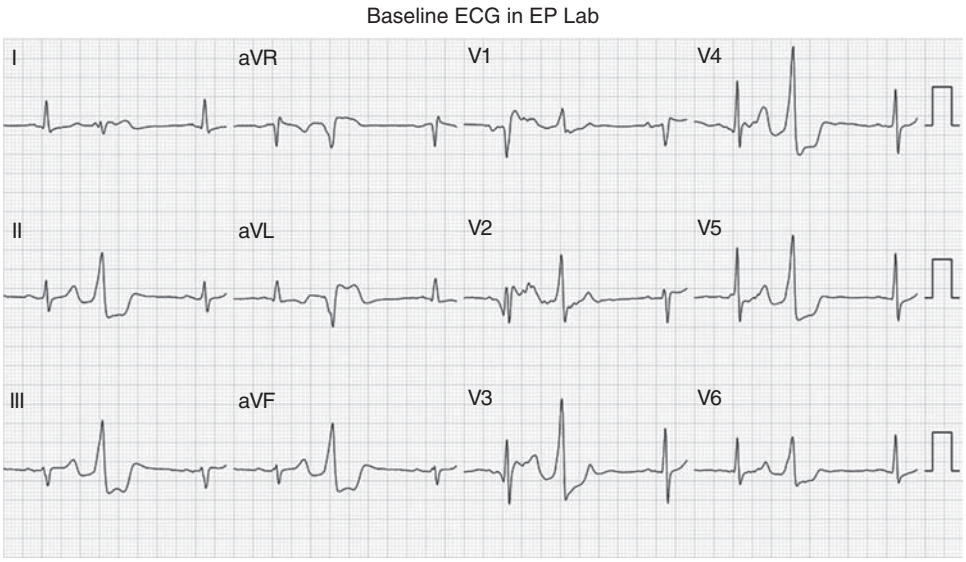
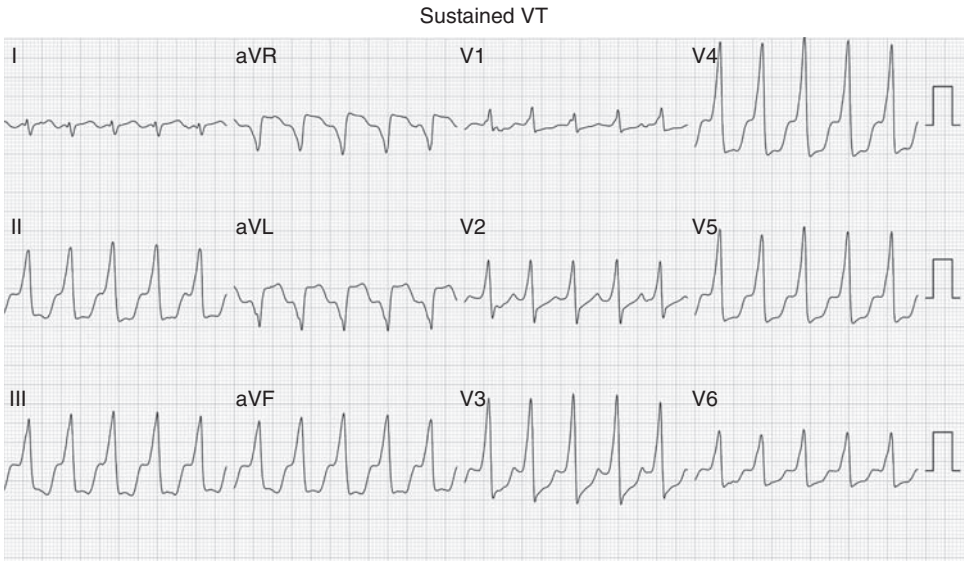


Figure 19-3

PVCs have a slightly different configuration in lead 1 of Fig. 19-3 compared with the office ECG, likely because of lead placement variation. This is a significant limitation of matching ECG morphologies (ventricular tachycardia [VT], Wolff-Parkinson-White syndrome [WPW] of spontaneously recorded episodes with those recorded in the EP laboratory; the ECG leads are typically the last things to go on the patient's chest when they are being prepared for the procedure (defibrillation pads and mapping system surface patches claim their territory first, with whatever skin is left over available for precordial ECG lead placement). It is well-known that differences in limb lead position can influence frontal plane ECG lead appearance.

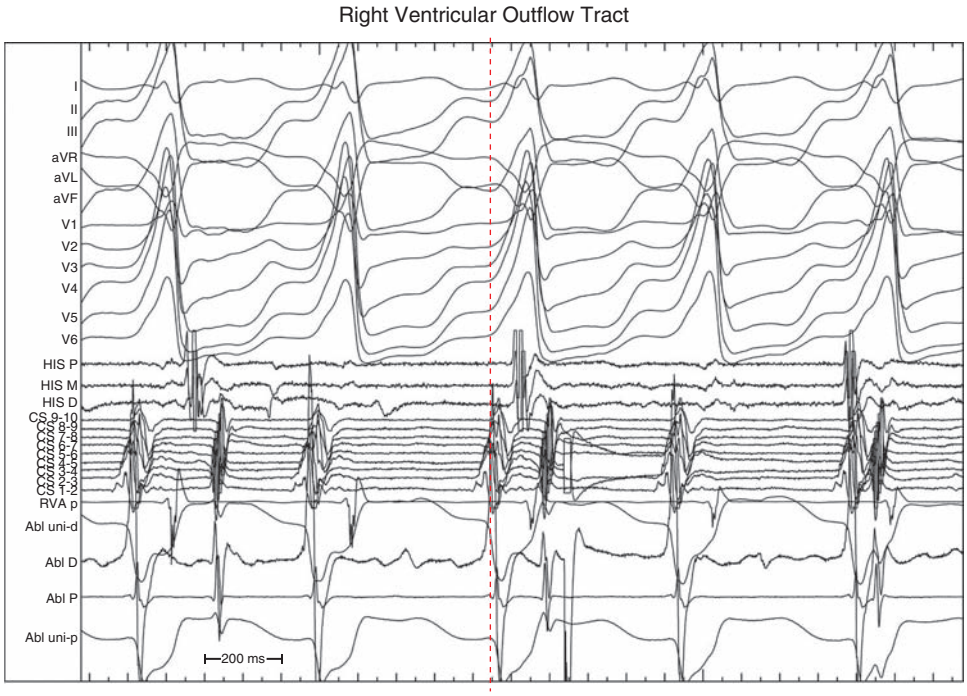
Figure 19-4



Sustained VT developed while operators were getting vascular access (no catheters in the heart at this time). See Fig. 19-4. This was hemodynamically tolerated and came and went during the procedure (went back to sinus with bigeminy, then VT intermittently).

Mapping Various Sites

Figure 19-5



A coronary sinus (CS) catheter, positioned as distally as possible, can often show early activation times and provide clues as to whether the origin is likely to be remote from the recording site (endocardial or aortic sinus of Valsalva, indicated by late activation in the CS), nearby on the epicardial surface (presystolic but far-field appearing), or associated with the coronary venous system (presystolic and near-field). In Fig. 19-5, the distal CS recording occurs well before the QRS onset *(dotted line)* and is relatively sharp, suggesting a nearby source (epicardial, coronary venous, or possibly aortic sinus of Valsalva depending on how close this is to the recording site). Mapping usually starts in the right ventricular outflow tract because, though an unlikely source in this case, it is nonetheless easy to reach. The ablation recording is just at the QRS onset so no ablation was performed.

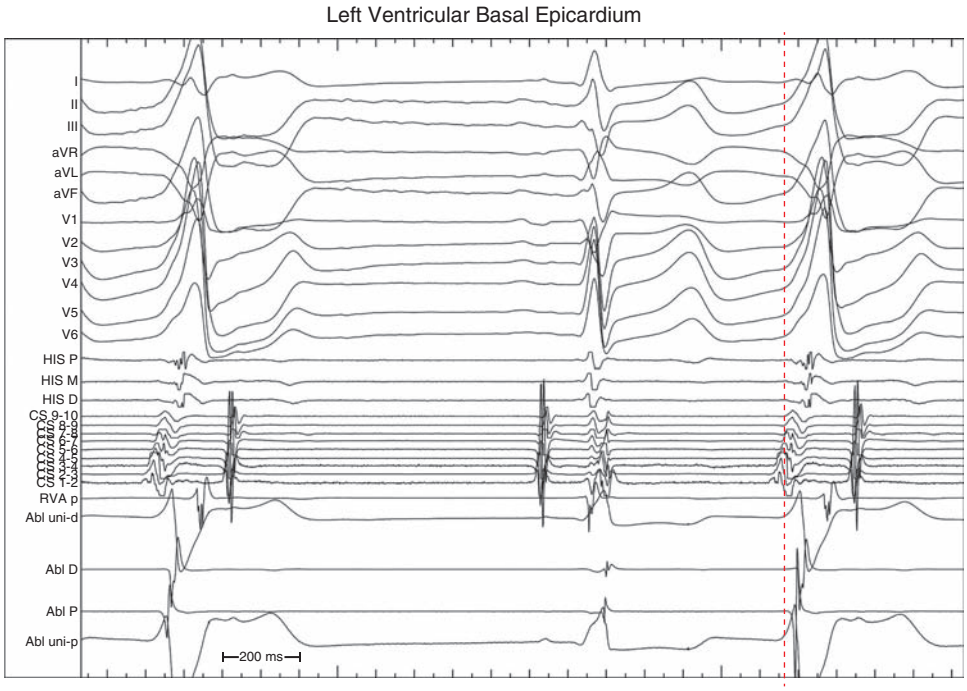


Figure 19-6

Because no attractive ablation sites were found in the right ventricular outflow tract and ECG and electrogram features suggested a possible epicardial source, pericardial access was obtained. In Fig. 19-6, mapping the epicardial surface near the distal CS recording site shows a late activation time, not suitable for ablation. Pacing here (not shown) yielded a poor match with PVCs.

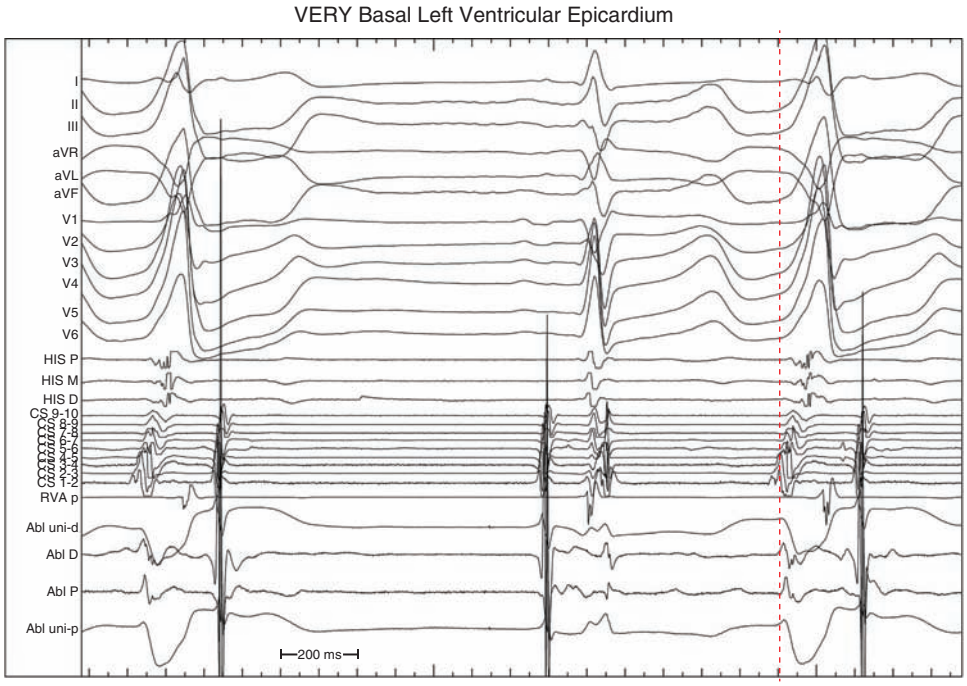


Figure 19-7

A site on the left ventricular epicardial surface even more basal than the prior site (Fig. 19-7, indicated by the large atrial signal) has an electrogram with very minimal presystolic activation with a "QS" in the unipolar recording; the distal bipolar recording precedes the proximal bipolar recording. These features would ordinarily suggest a reasonable ablation site, but earlier recordings remain in the distal CS. Thus this is not an attractive ablation site. Full exploration of areas around this site (that had the best recordings) failed to show any sites more suitable for ablation.

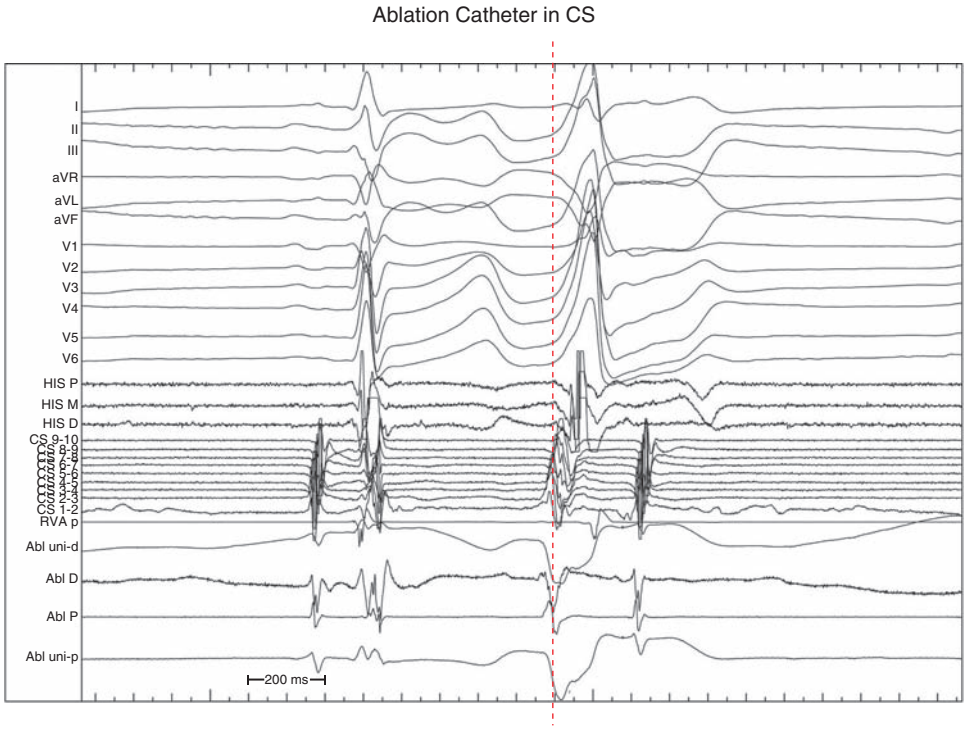


Figure 19-8

The ablation catheter was removed from the pericardial sheath (and replaced with the dilator and guidewire), and mapping of the aortic root and sinuses of Valsalva was performed. No sites with either presystolic activation or reasonable pace-matches were observed (Fig. 19-8). The catheter was then removed from the arterial system and positioned in the CS alongside the CS catheter. Now, the distal bipolar recording has a timing equivalent to the distal CS recording.

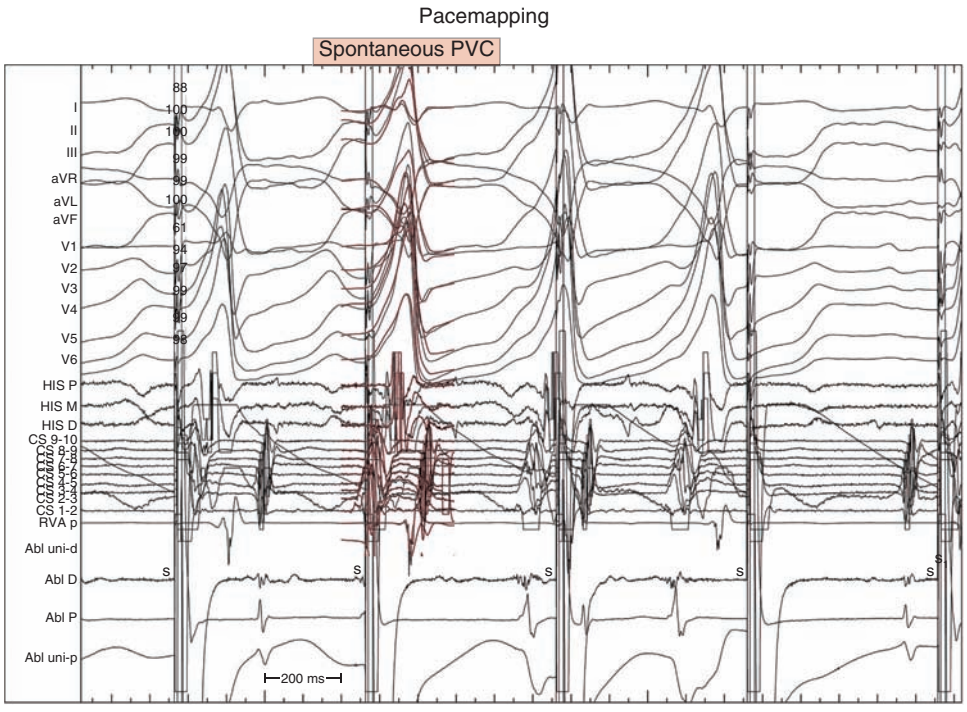


Figure 19-9

Pacing from the ablation catheter at this site yields at 98% electronic pace-match with the spontaneous PVC (Fig. 19-9, superimposed in *red*). This corroborates the early activation in the distal ablation electrode within the distal CS.

Imaging (Fluoroscopy, Electroanatomic Mapping)

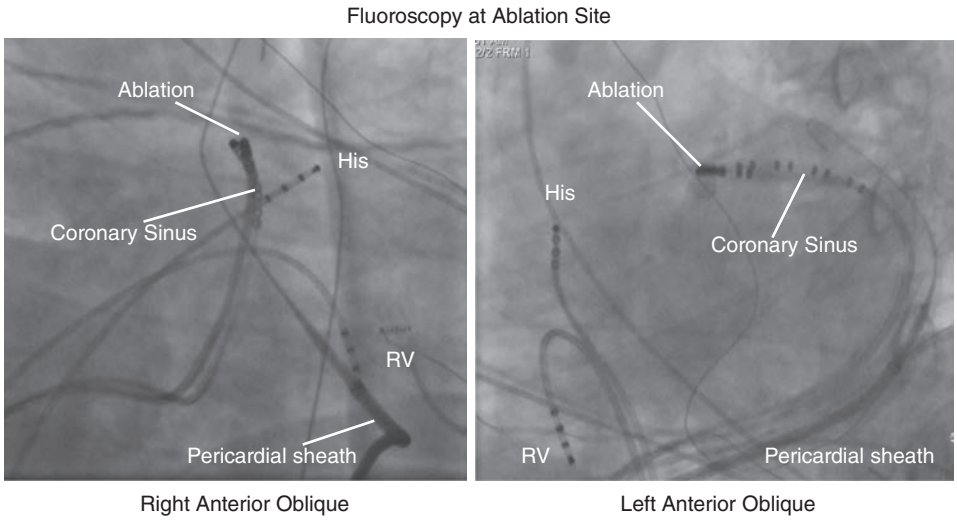


Figure 19-10

Catheter positions during ablation are displayed in Fig. 19-10; note that the ablation catheter tip is slightly distal to the CS catheter (which was pulled back somewhat to allow further advancement of the ablation catheter in the CS). Injection of a diluted solution of radiographic contrast through the irrigation ports of the ablation electrode showed that it was at the junction of the anterior interventricular vein and great cardiac vein. Coronary arteriography showed that the distance to the diagonal artery (closest branch) was about 0.8 cm.

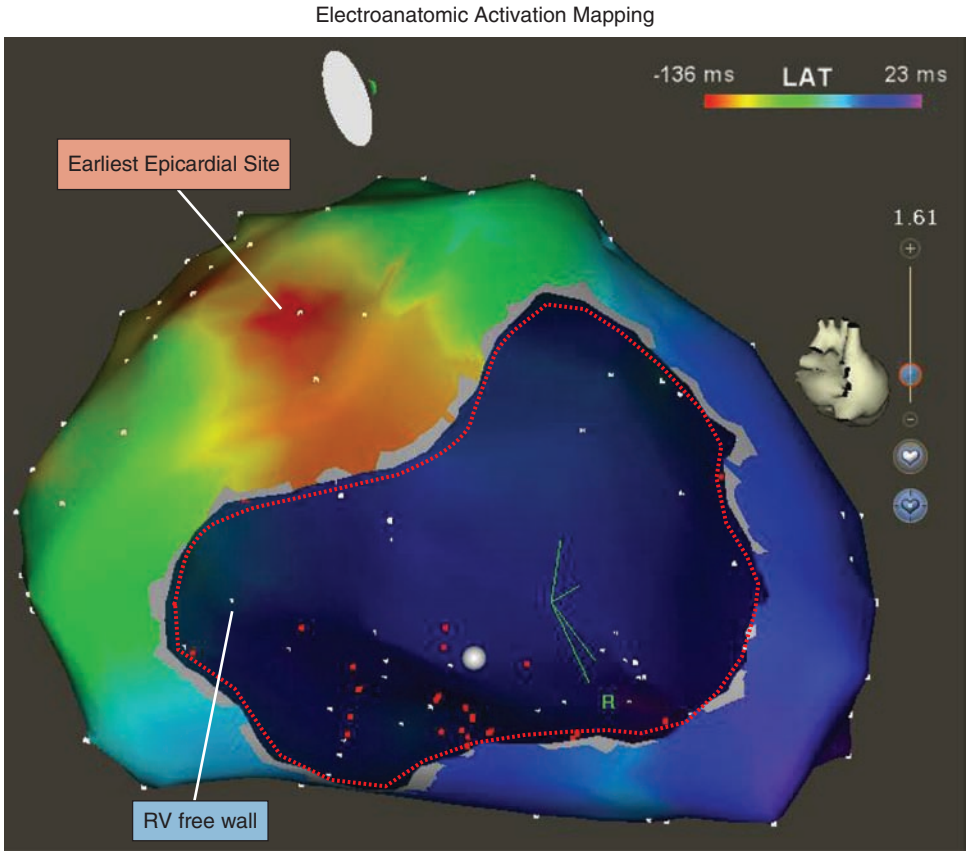
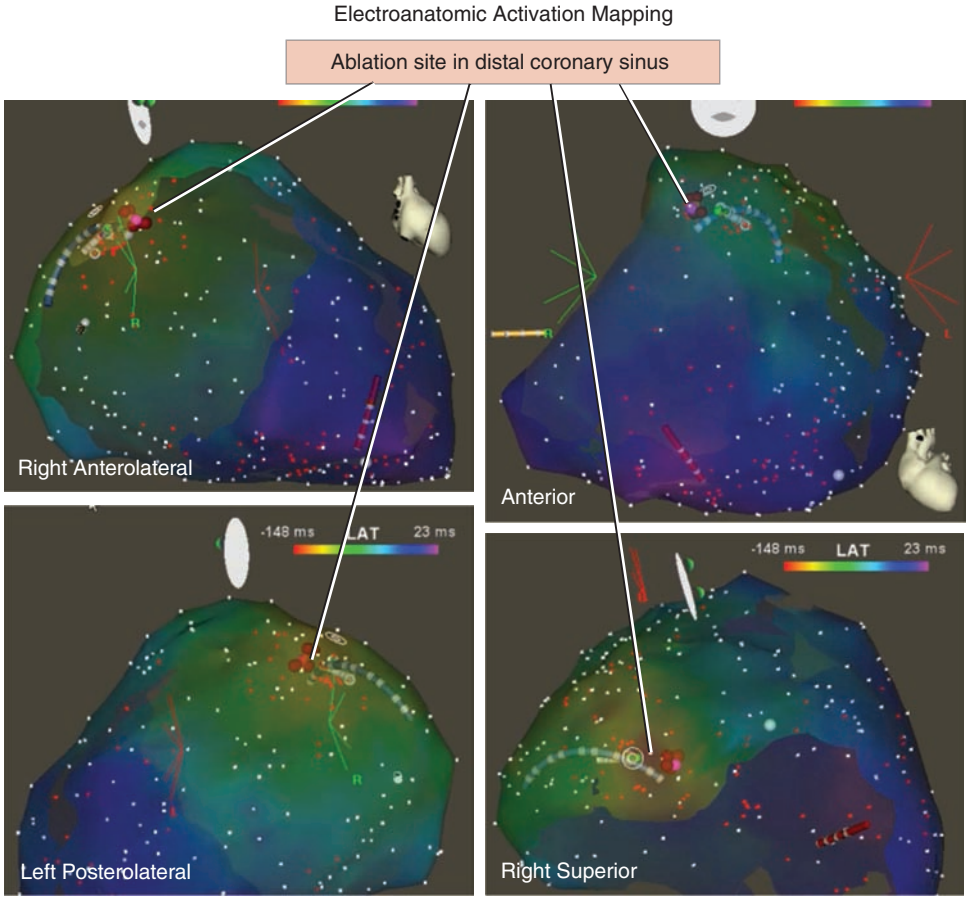


Figure 19-11

Fig. 19-11 provides an activation map of the PVCs on the epicardial surface. The earliest site *(red)* is surrounded by progressively later sites, typical of a focal process. This was at the junction of the great cardiac vein (distal CS) and anterior interventricular vein. Attempts at ablation here would likely have no effect on the ectopy, because of epicardial fat that is always relatively thick in this area.

Figure 19-12



Electroanatomic activation mapping from coronary venous system and epicardium combined is shown in Fig. 19-12. The epicardial map shown previously has been made slightly transparent to allow visualization of the coronary venous mapping sites. *Red dots* indicate ablation sites in the distal portion of the CS, whereas the *purple dot* indicates the site at which ablation eliminated PVCs. It is evident that this site is fundamentally identical to the epicardial site of earliest activation during the PVC.

Ablation

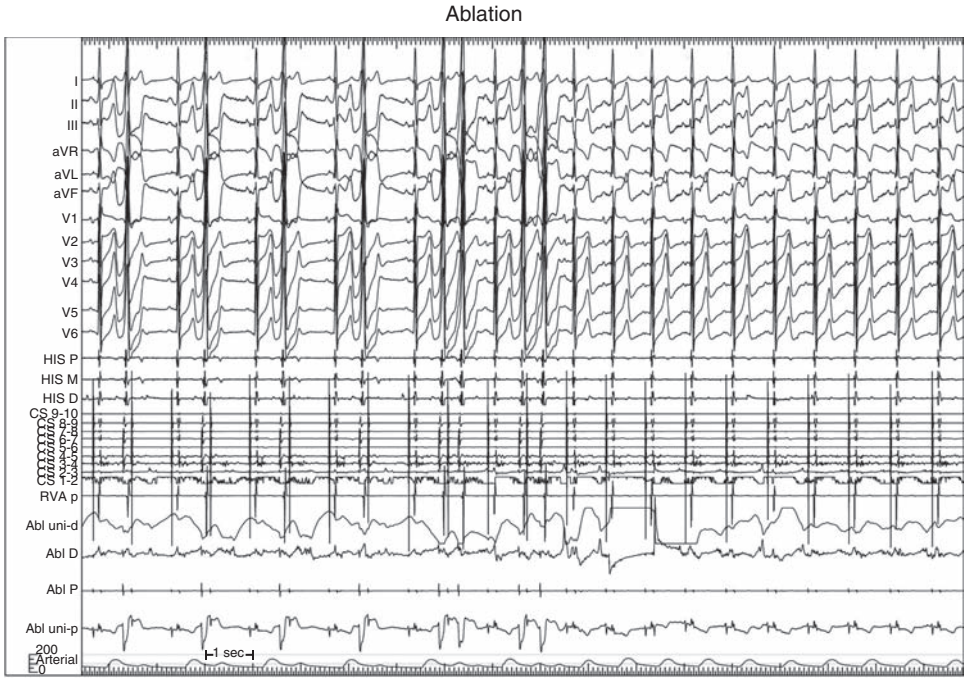


Figure 19-13

Ablation at this site (Fig. 19-13) in the distal CS (15 W) eliminates ventricular ectopy shortly after starting energy delivery. The amount of power delivered in this area should be as little as is needed to achieve the desired effect, because coronary arteries are nearby (left anterior descending, circumflex, or even left main artery). Because the distal CS (actually, great cardiac vein/anterior interventricular vein) is a relatively small vessel, with a relatively small amount of blood to cool an ablation electrode, ablating with a standard (nonirrigated) ablation electrode may not be successful because of rapid heating of the electrode with relatively little power delivery. Using an irrigated electrode overcomes this limitation, allowing greater power delivery without electrode overheating. This does not prevent tissue overheating and steam pops, however. After this RF application, no further ventricular ectopy was observed either spontaneously or after isoproterenol provocation. If this effort had been unsuccessful, ablation in the left aortic sinus of Valsalva would have been attempted.

Hemodynamic Study

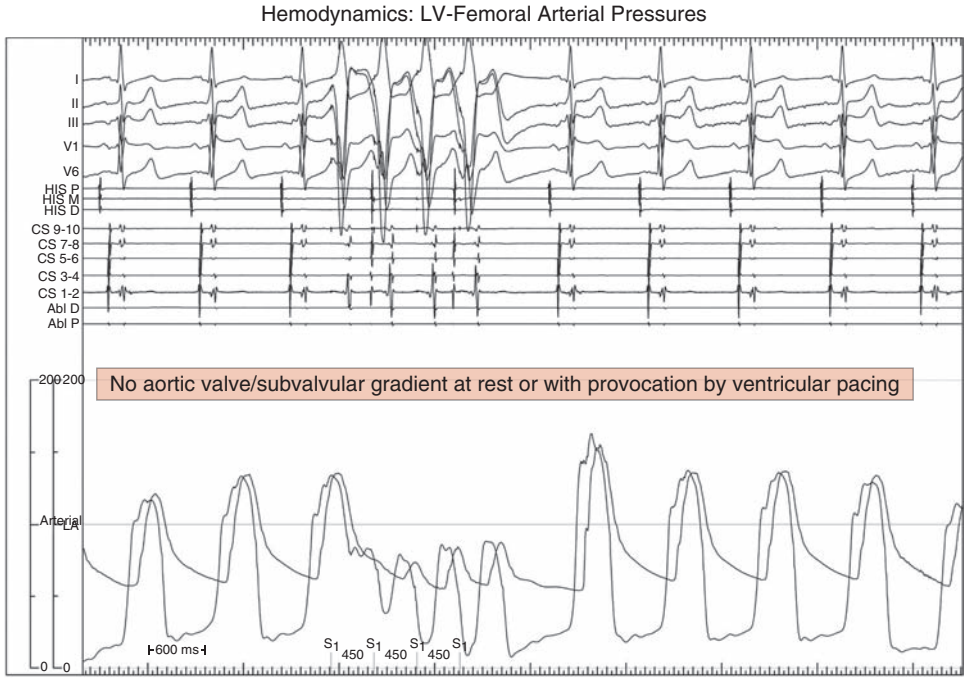


Figure 19-14

A short hemodynamic study after the ablation procedure showed no valvular or subvalvular left ventricular outflow gradient. A burst of ventricular pacing is used to try to provoke a gradient (Fig. 19-14).

Final ECG

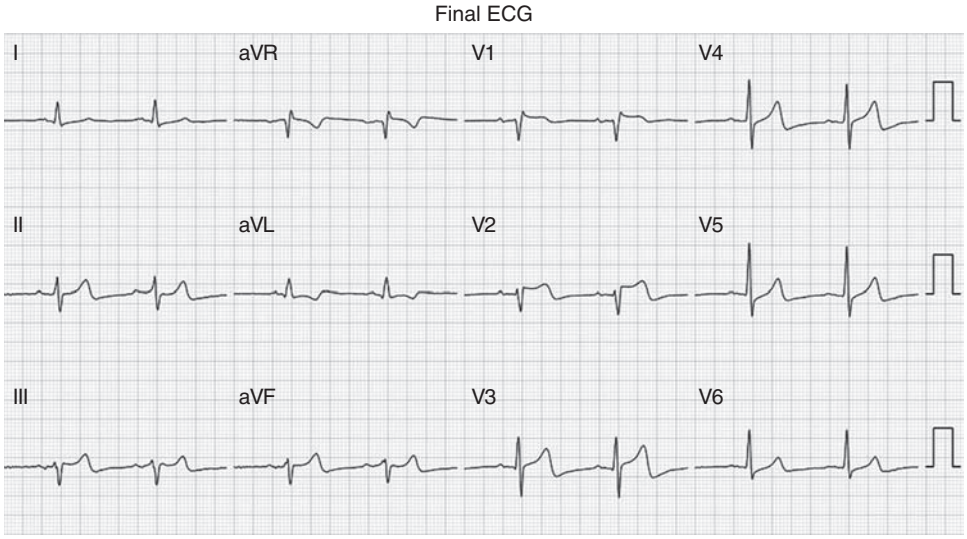


Figure 19-15

The ECG (Fig. 19-15) has entirely normalized, with no residual ectopy. The patient was monitored overnight to ensure no complications related to either pericardial access or ablation in the region of the coronary arteries. Repeat echocardiogram about 10 weeks after the procedure showed ejection fraction 52% and minimal aortic valve gradient.

Summary

- PVCs and ventricular tachycardia that have a configuration that suggests an epicardial source may arise from the actual epicardial surface, or the coronary venous system or aortic sinuses of Valsalva
- Ablation within the coronary venous system is feasible, sometimes necessary, and generally safe, but the veins restrict catheter movement to their lumens; epicardial mapping offers greater versatility, but a layer of epicardial fat interposed between the epicardial surface and catheter in the pericardial space may limit ablation efficacy
- The appearance of abnormal hemodynamics may be related to frequent ventricular ectopy (or other causes of irregular ventricular filling, such as atrial fibrillation)

20 Papillary Muscle Ventricular Ectopy

Case Presentation

A 63-year-old man without prior cardiac history was referred for evaluation of frequent premature ventricular complexes (PVCs). His initial complaint was dizziness and fatigue; finding an irregular pulse led to obtaining an ECG that showed frequent monomorphic PVCs. An ambulatory monitor showed monomorphic PVCs comprising 18% of all complexes. Echocardiogram showed mildly decreased left ventricular ejection fraction (43%). He was referred for electrophysiology study and possible catheter ablation.

Baseline Recordings

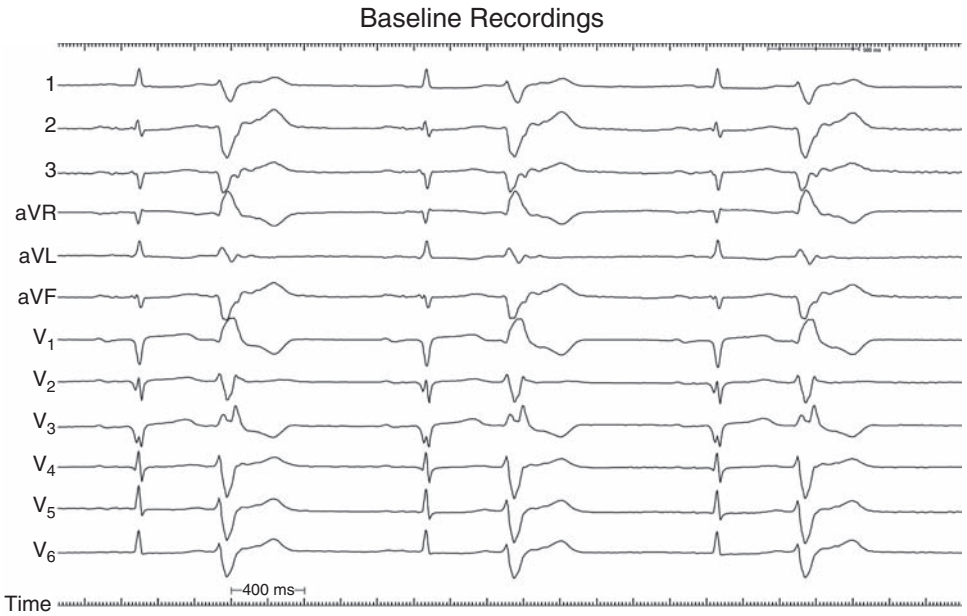


Figure 20-1

Baseline recordings made at the time of EP study (Fig. 20-1) show bigeminal PVCs with a right bundle branch block, rightward superior axis morphology. In a structurally normal heart such as his, the morphology overall suggests an inferolateral, somewhat apical left ventricular (LV) origin (negative in leads 1, 2, and 3 and relatively early R-wave regression in precordial leads). There is a tiny Q wave in lead V1; sometimes this points to a papillary muscle as the origin of the PVC. It is important to make recordings of the spontaneous PVCs before inserting catheters into the heart so that the true target is known, because catheters can themselves cause ectopic complexes that can confuse mapping.

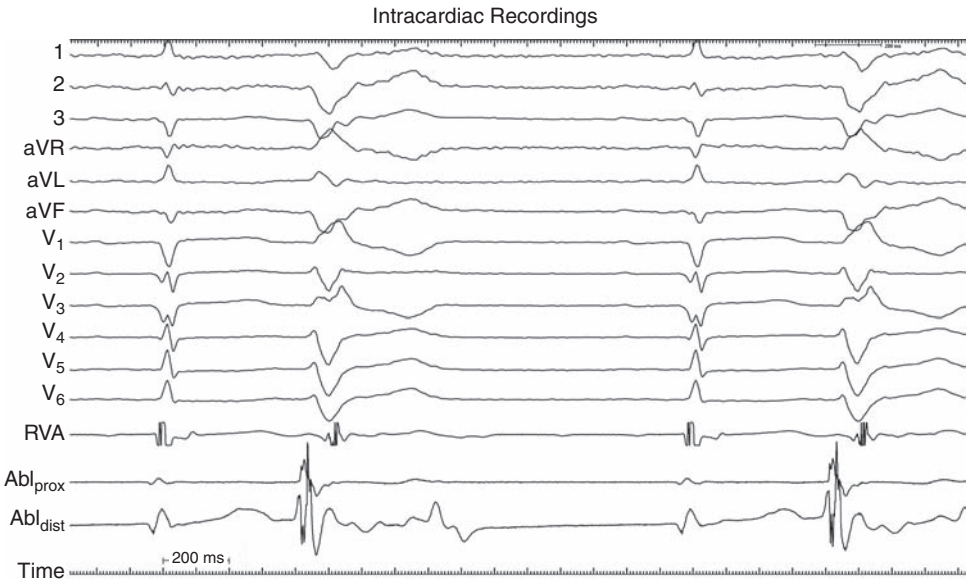


Figure 20-2

Intracardiac recordings from right ventricle and a catheter in the left ventricle (Abl) are shown in Fig. 20-2 during sinus rhythm with ventricular bigeminy.

Mapping

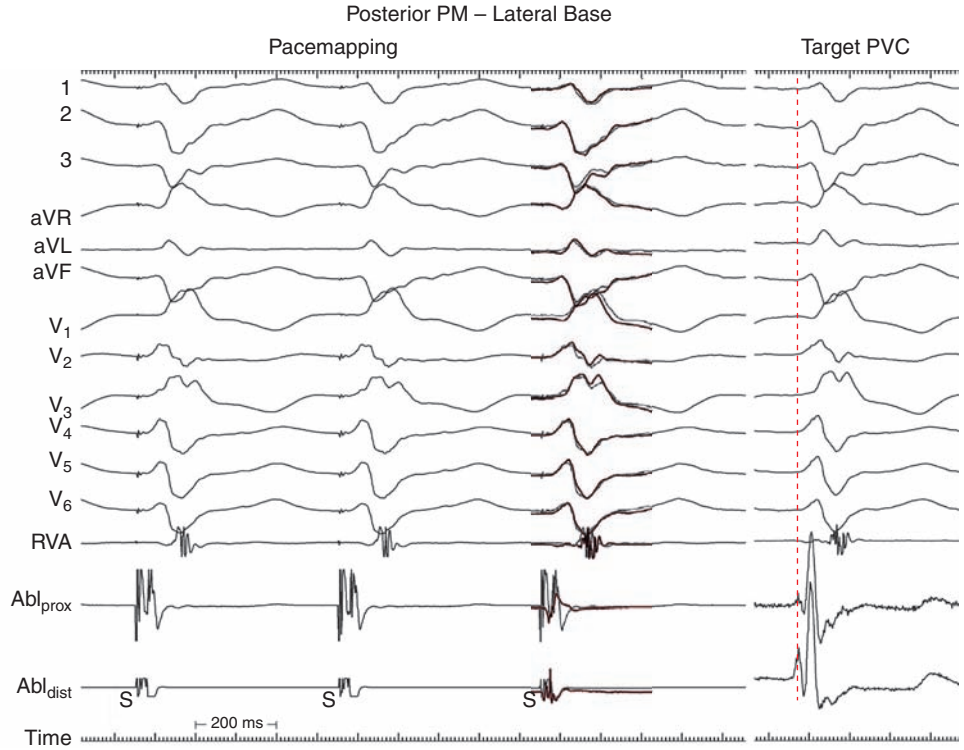


Figure 20-3

The process of mapping in this case consisted of activation mapping (manipulating the ablation catheter to various locations in the heart seeking earliest presystolic activation) corroborated by pacemapping (pacing at candidate sites to see how closely the resulting QRS complex corresponds to the native PVC). For either purpose, it is important to have adequate gain of surface ECG leads to be able to determine (1) the true QRS onset, because this will serve as a point of reference for determining whether a mapping site is early or late, and (2) being able to compare subtle differences in paced versus target PVC complexes. In Fig. 20-3, the activation time at a site on the lateral base of the posterior papillary muscle is shown at right; a *dashed line* indicates the onset of the QRS complex. Pacing at this site for three complexes is also shown. A single beat of the target PVC is superimposed on the last paced complex. The activation time at this site is about −15 ms, with distal electrode earlier than proximal, but the paced morphology is not a very good match. Mapping will continue.

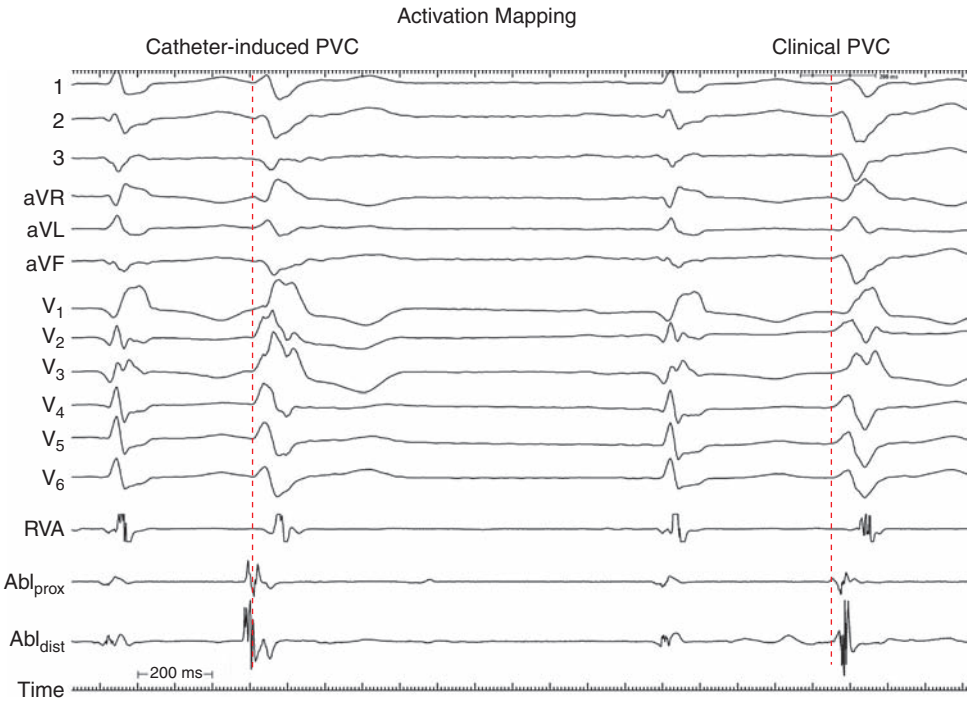


Figure 20-4

At another site, the PVC on the left has an activation time about −33 ms, with the distal electrode earlier than proximal (Fig. 20-4). This looks like a great ablation site, but careful inspection shows that the PVC morphology is different from the target PVC at right (where the activation time is not good at all). The PVC on the left is thus catheter-induced ectopy and illustrates one of the hazards of mapping in such cases. Catheter–tissue contact is important for both mapping and ablation, but can cause PVCs that look like good ablation targets, but are not.

It is no surprise that the activation time is so early, because the catheter tip (where this distal recording is made) caused the ectopy. Of note, catheter-induced right bundle branch block (RBBB) is now present during sinus complexes.

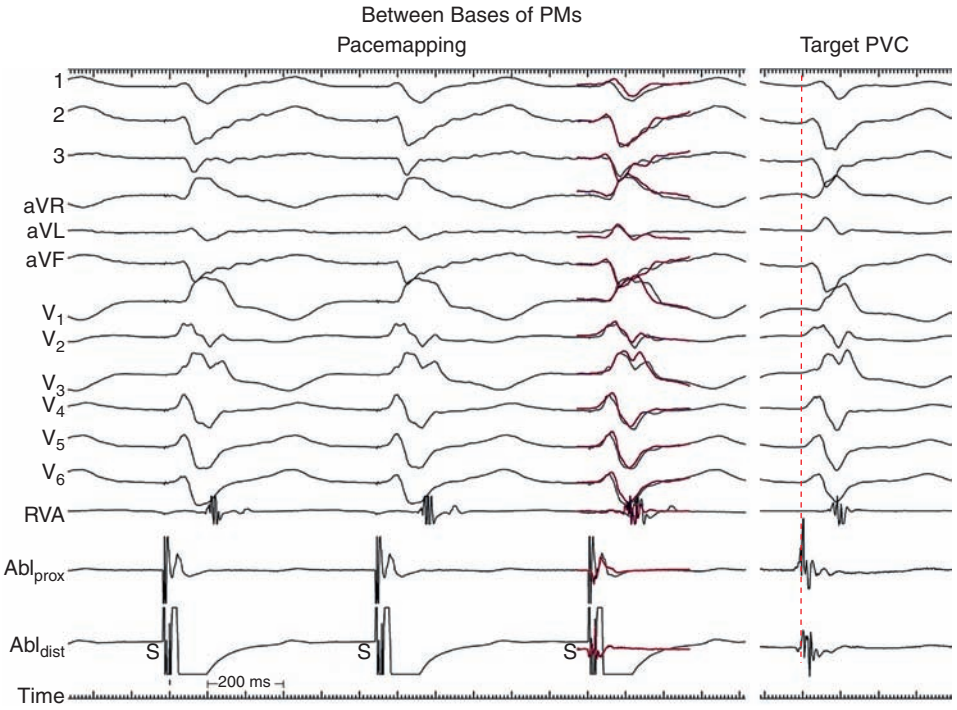


Figure 20-5

At a site between the bases of the anterior and posterior papillary muscles (Fig. 20-5), the activation time is about −15 ms; however, the proximal and distal electrodes have similar timing, and for ablation, the distal should be earlier. Pacing at this site again shows a good, but not exact, match with the target PVC. Mapping will continue.

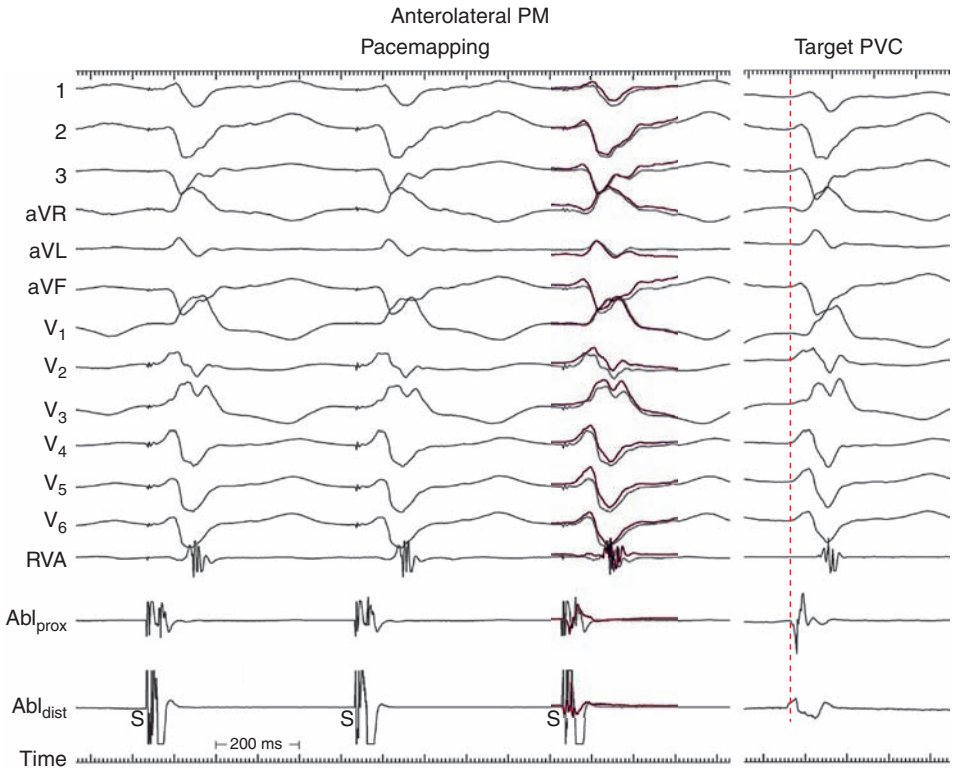


Figure 20-6

A site on the anterolateral papillary muscle (Fig. 20-6) has an activation time at the distal electrode of about −15 ms, but the proximal electrode is even earlier; pacing was performed at the site (even though it would not serve as a good ablation site because of the timing of activation), and again was not a very good match with the target PVC.

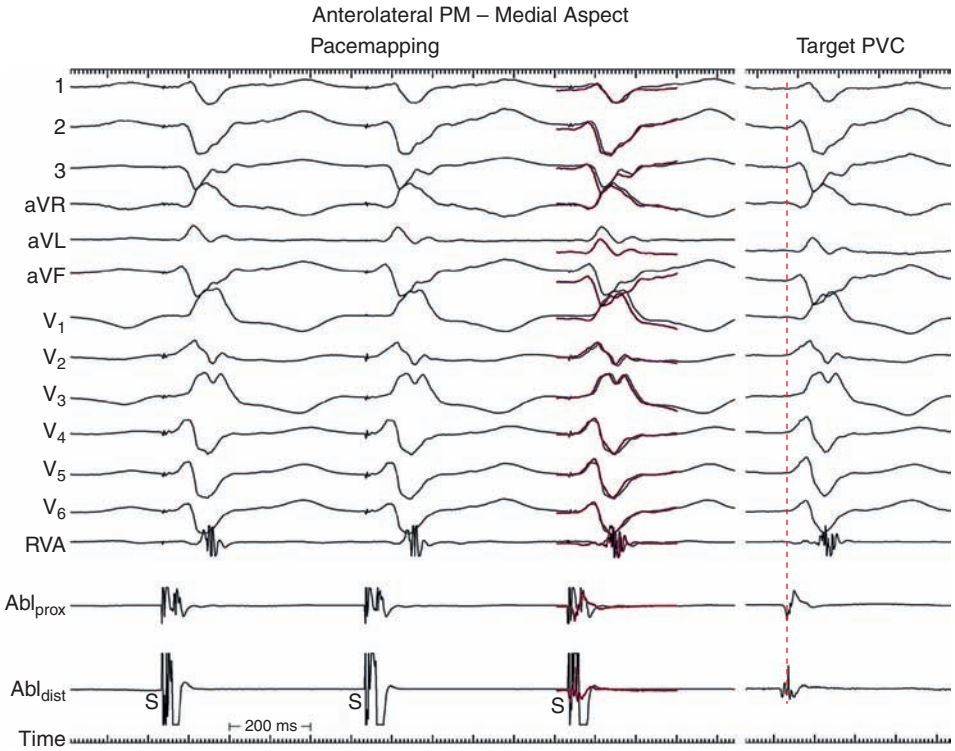


Figure 20-7

In Fig. 20-7, a site on the medial aspect of the anterolateral papillary muscle shows an activation time about −25 ms; this is the earliest that has been found thus far. The location is away from where the Purkinje network should be and the electrogram does not suggest Purkinje tissue (typically a very sharp potential preceding and often separated from a larger ventricular signal by 5 to 10 ms). Thus this seems to be myocardial in origin. Pacing at this site exactly replicates the target PVC. This should hopefully serve as a good ablation site.

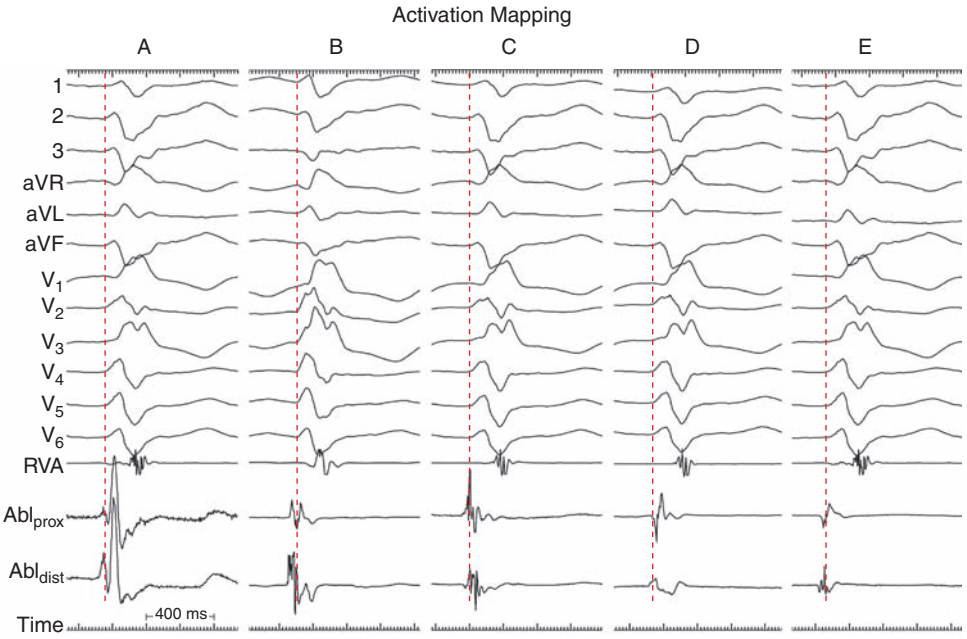


Figure 20-8

Fig. 20-8 is a compilation of activation times from five different LV sites. At site A, the distal electrogram is somewhat early relative to the QRS onset (−15 ms) and precedes the proximal electrogram, but its timing is not particularly early. At site B, the activation time looks great at −33 ms, but the QRS complex is different from the target PVC (our catheter-induced PVC from earlier). Site C has a relatively early electrogram timing (−15 ms), but the proximal electrode is earlier (−20 ms). At site D, the timing of the distal electrogram is about −20 ms, but its shape is rounded rather than sharp, indicating relatively poor contact. None of these candidate sites are suitable for attempting ablation. At site E, a sharp electrogram precedes the QRS complex by about 25 ms and is earlier than the proximal electrode. This is the site at which the perfect pace match was obtained.

Ablation

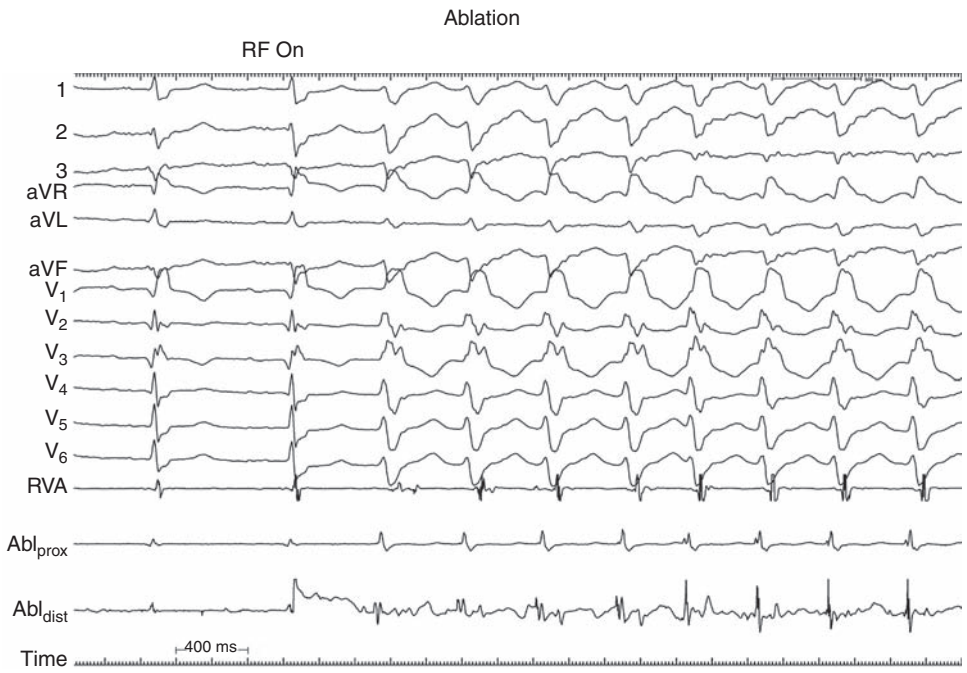


Figure 20-9

In Fig. 20-9, radiofrequency (RF) ablation is begun at the site shown in Fig. 20-7. The first thing to notice is that the first two complexes at left are sinus complexes with RBBB; the

previously bigeminal PVCs have been transiently suppressed by catheter pressure at the site. Almost as soon as RF energy is turned on, a flurry of ventricular tachycardia (VT) with the same morphology as the target PVCs occurs. This is a common finding with focal arrhythmias, so much so that if one does not see RF-induced ectopy during the first few seconds of ablation in such cases, it is worth considering stopping energy delivery and mapping elsewhere or getting better contact on the site.

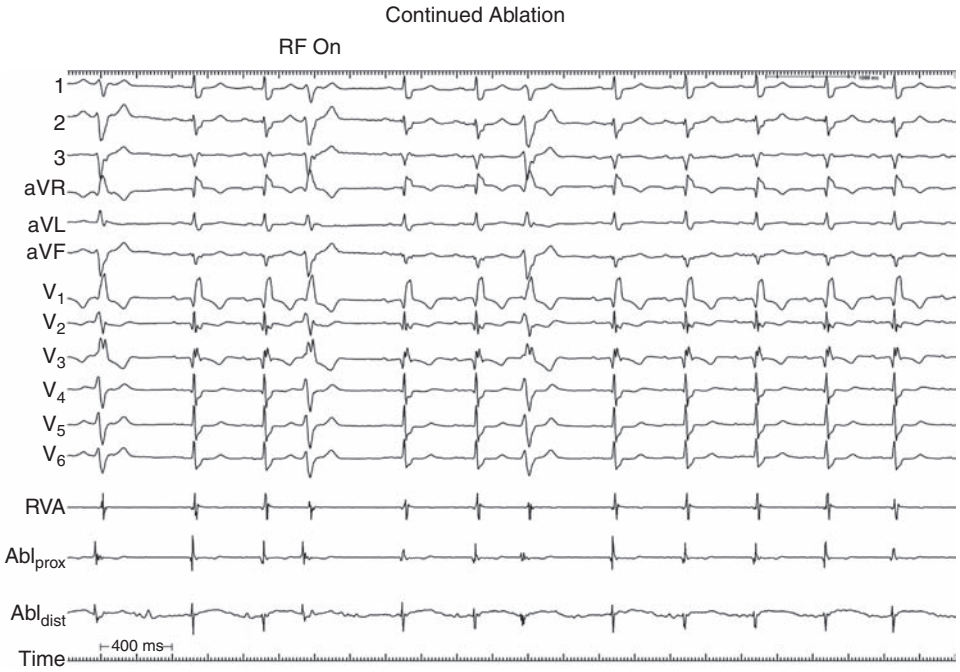


Figure 20-10

After stopping RF delivery at the site, rare PVCs persisted. Here (Fig. 20-10), PVCs have become trigeminal. Additional RF energy is delivered that results in sudden cessation of ectopy. Several more RF applications were delivered in the same general area, because foci of ectopy are sometimes deep and/or diffuse. Despite extensive ablation, papillary muscle dysfunction with mitral regurgitation is rare.

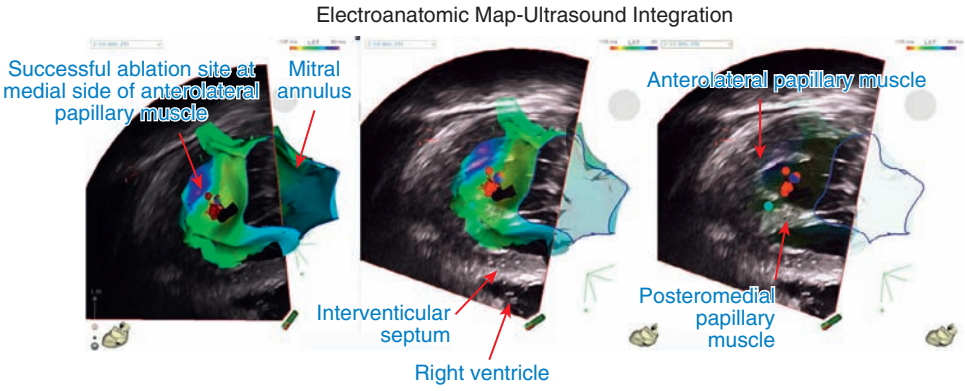


Figure 20-11

Intracardiac echocardiography is often useful for delineation of structures, such as papillary muscles, and stabilization of catheters especially in cases such as this. Stability of catheter contact on papillary muscles is notoriously difficult to achieve. Here (Fig. 20-11), integration of electroanatomic mapping and intracardiac echocardiography shows where ablation was performed (*red dots*, medial aspect of anterolateral papillary muscle).

Summary

- PVCs and VT arising from a papillary muscle are relatively rare and must be distinguished from fascicular ectopy as well as verapamil-sensitive VT
- PVCs more commonly originate from the posterior than anterior papillary muscle, but can arise in a right ventricular papillary muscle as well
- Intracardiac echocardiography may help in localizing the anatomic site of origin of the PVC/VT and aid in stabilization of the ablation catheter, but is not mandatory
- Ectopic foci from papillary muscles may be difficult to ablate because of catheter stability and depth of penetration needed

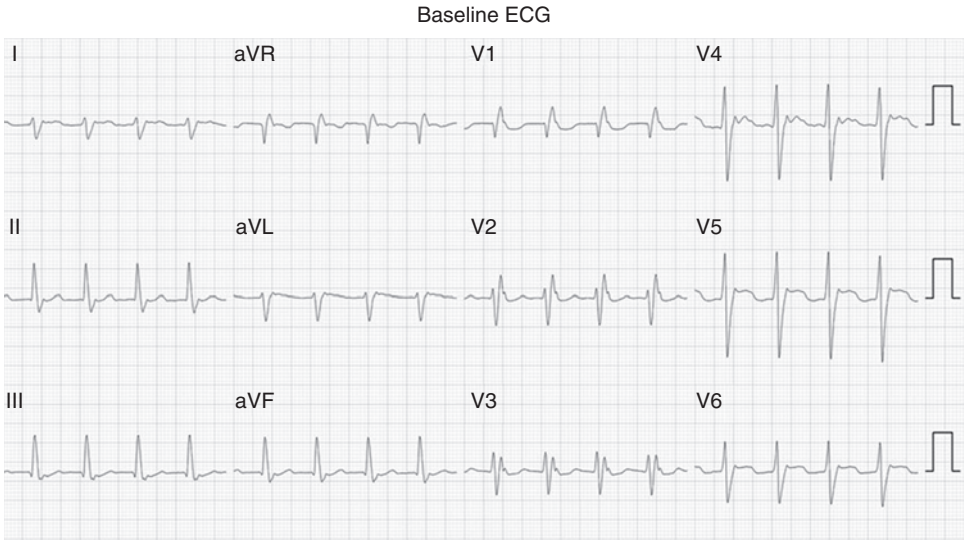
Focal Fascicular Ventricular Tachycardia

21

Case Presentation

The patient was a 37-year-old man with palpitations for many years and had occasional lightheaded episodes. ECG showed right bundle branch block (RBBB) and rightward inferior axis QRS. The rhythm was incessant (present 100% of the time) and atrioventricular (AV) dissociation was evident. Echocardiogram revealed low-normal left ventricle (LV) systolic function (ejection fraction [EF] 40%). He had undergone three catheter ablation attempts in the past, without noteworthy benefit. He was referred for repeat electrophysiology (EP) study and possible ablation, but he expressed skepticism about whether it was worth it to proceed in light of prior failures.

Baseline ECG and Intracardiac Recordings



What Is the Rhythm?

- Ventricular tachycardia (VT)?
- Supraventricular tachycardia (SVT) with aberration?
- Fascicular? [Fig. 21-1]

Figure 21-1

The ECG in Fig. 21-1 shows a wide-complex tachycardia with RBBB-rightward inferior axis. P waves are not clearly seen. Using standard morphologic criteria, most suggest that this is a supraventricular (SVT) QRS complex rather than ventricular in origin (QRS duration, axis, precordial QRS onset to S nadir <100 ms, time to peak in lead 2 <50 ms, sharp Q in aVR). However, an arrhythmia from the infranodal conduction system (junctional with aberration, or fascicular) could look like this and meet the same criteria (suggesting SVT with aberration).

What Does This Say About the Nature of the Arrhythmia? How Can the Mechanism Be Assessed?

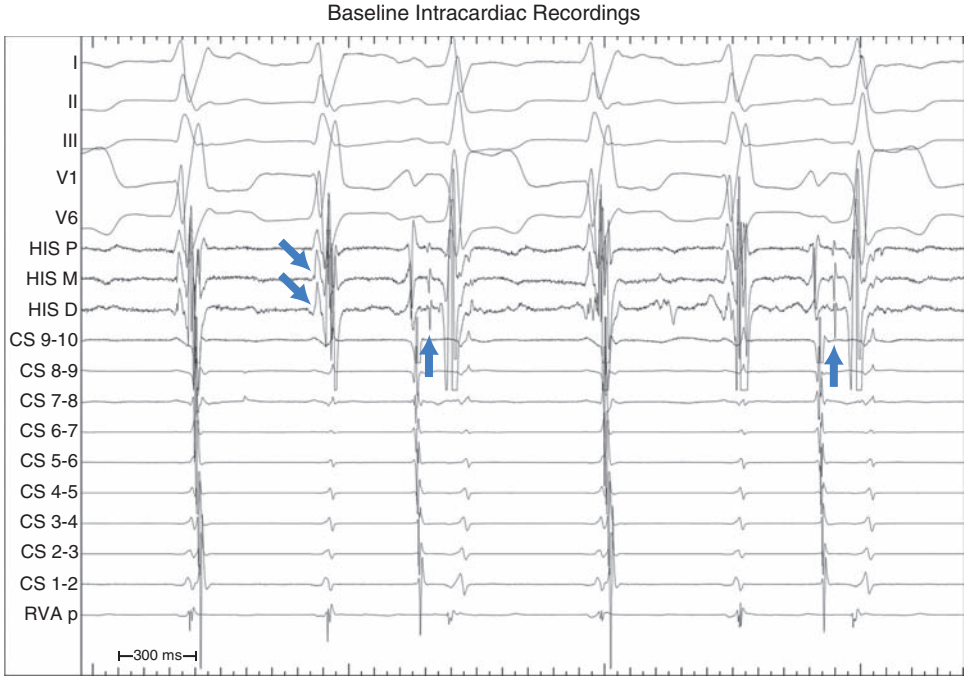


Figure 21-2

Baseline intracardiac recordings (Fig. 21-2) show AV dissociation during the wide-complex tachycardia; the third and sixth QRS complexes are different from the others, being either fusion complexes or complete capture complexes as a result of fortuitous timing of a P wave at such a time that anterograde conduction over the normal conduction system is possible. Both of these QRS complexes have His potentials (inscribed anterogradely; *slanted arrows*) before the QRS complex, identifying them as fusion/capture complexes. The His potential during tachycardia complexes is not as easily seen; *vertical blue arrows* point to possible retrograde His potentials. This also shows that the baseline rhythm is fascicular in origin rather than junctional with RBBB/left posterior fascicular block; in the latter case, conducted complexes should also show RBBB/right axis.

Effects of Right Ventricular Overdrive Pacing

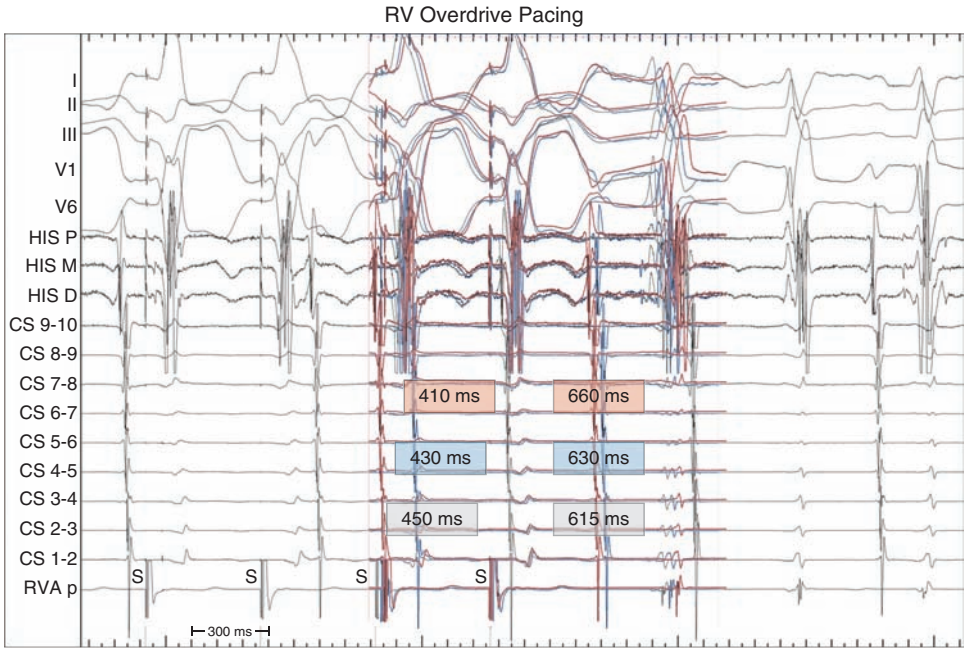
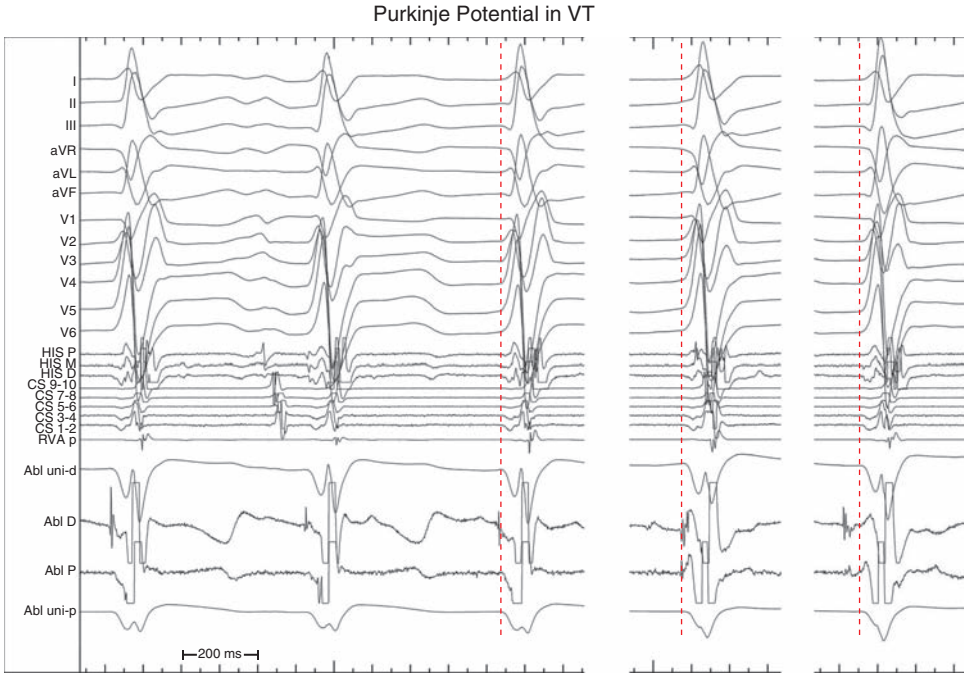


Figure 21-3

To determine whether the tachycardia mechanism was macroreentry or a focus (most likely automatic), overdrive pacing was performed at progressively more rapid rates and the timing of the first return VT cycle measured. In Fig. 21-3, for pacing at cycle length (CL) 450 ms, the first VT complex returns after 615 ms; for pacing at 430 ms (in *blue*), the VT returns at 630 ms; and for pacing at 410 ms (in *red*), the VT returns at 660 ms. This response shows overdrive suppression, a characteristic of automatic foci. In reentrant rhythms, the return cycle is typically relatively constant over a wide range of overdrive paced CLs, whereas in tachycardias due to classical triggered activity related to delayed afterdepolarizations, the first complex of the resumed arrhythmia returns progressively sooner following more rapid paced rates.

Different Mapping Sites ("Purkinje Potential")



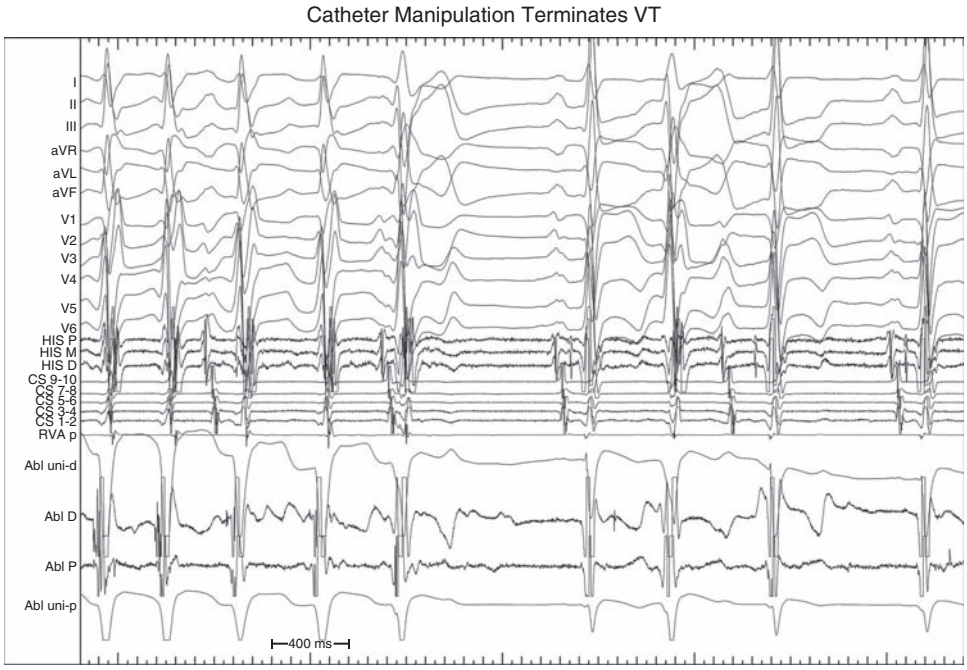
Is There a Good Ablation Site Shown? [Fig. 21-4]

Figure 21-4

Based on the foregoing tests, a diagnosis of a focal, automatic fascicular tachycardia has been made and its origin will be sought. In Fig. 21-4, multiple sites are mapped during the arrhythmia, seeking the earliest Purkinje recording; this should be 15 to 40 ms before QRS onset *(dashed red line)*. Ablation at a site other than that of earliest activation (the focus) will have no effect on the focus but may alter its exit (QRS morphology); see below (Fig. 21-12). Thus it is important to take the time to carefully map and determine the earliest site, from which all other recordings emanate. While each panel shows a Purkinje spike in Abl D recordings, only in the far right panel is it significantly prior to the QRS onset; this was the very earliest site found of about 90 sites sampled during tachycardia.

Catheter Manipulation Terminates VT

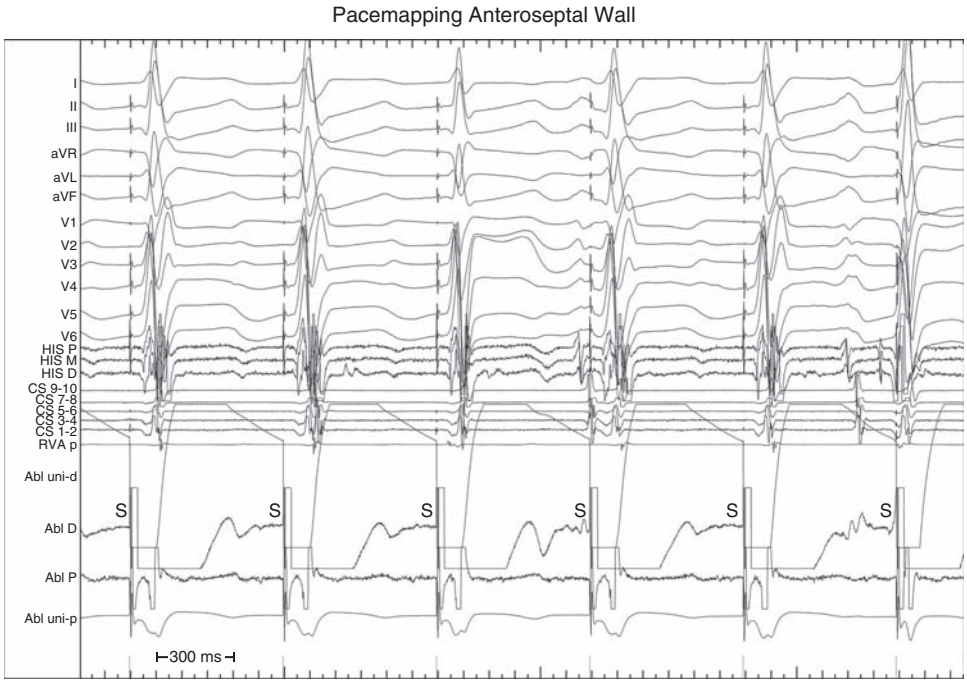
Figure 21-5



The focus is often very superficial on the endocardial surface and thus susceptible to catheter-induced trauma, resulting in arrhythmia termination (as shown in Fig. 21-5) and subsequent quiescence for prolonged periods. In many (but not all) cases, the focus recovers within minutes and mapping can continue. Careful mapping (minute catheter movements) allows logging of the site on an electroanatomic mapping system at the moment of catheter-related arrhythmia termination so that it can still be targeted for ablation even if the arrhythmia remains quiescent. This so-called "bump-mapping" implies a very small discrete target that is superficial (ie, not in deeper layers) and furthermore has been encountered by the catheter (it was "bumped").

Pacemapping Anteroseptal Wall, Superimposed on Baseline VT ECG

Figure 21-6



Pacemapping can corroborate activation mapping data; in Fig. 21-6, pacing at a site with an early Purkinje potential during VT perfectly replicates the arrhythmia on 12-lead ECG with an electrocardiographically quiet, discrete interval from stimulus-QRS that correlates with the interval from the Purkinje potential to QRS onset during VT.

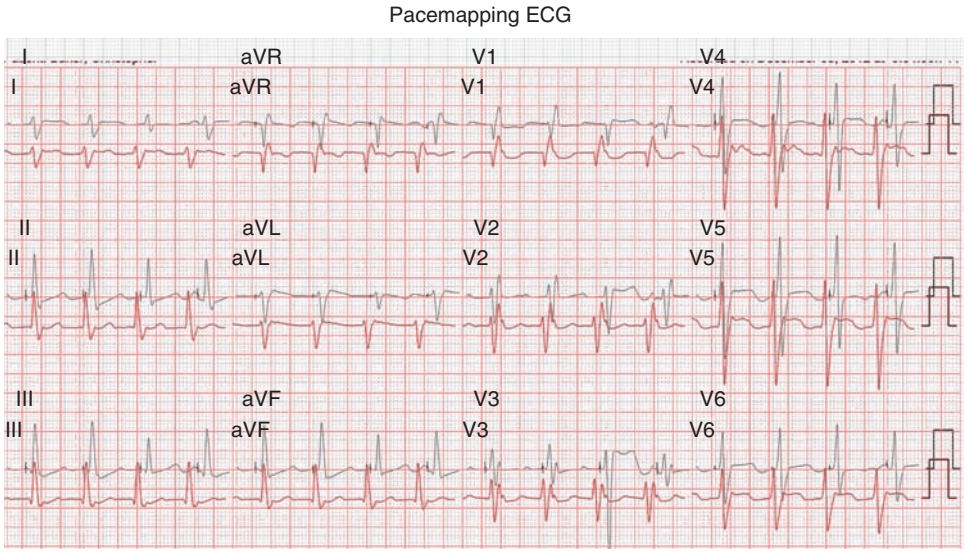


Figure 21-7

Superimposition of the VT ECG atop the pacemapping ECG (in red, aligning the first complex in each panel) shows a perfect match with VT (Fig. 21-7).

RF Energy Delivery

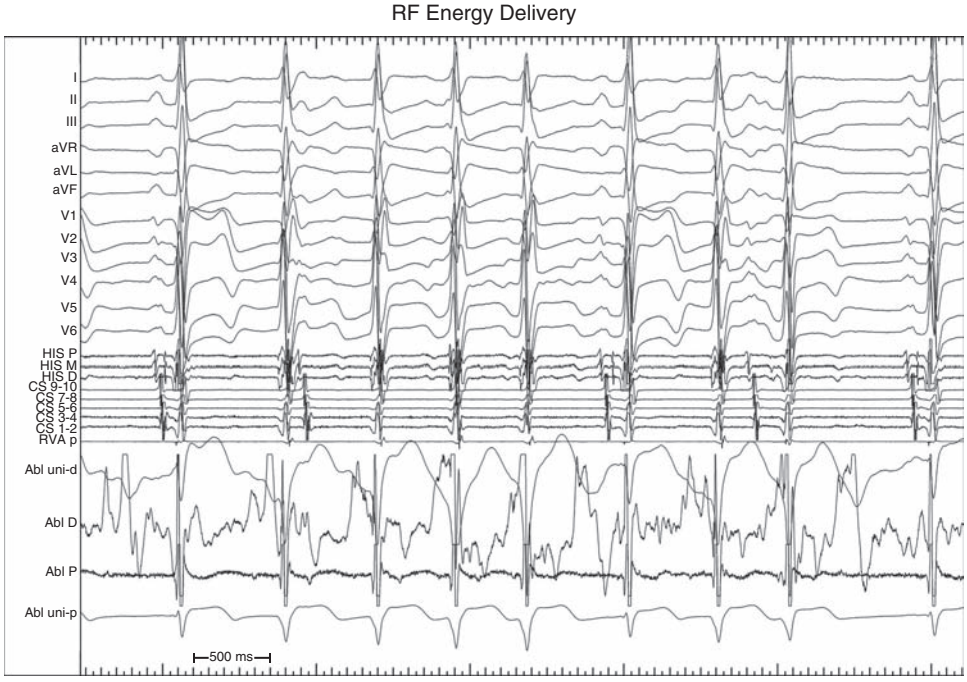
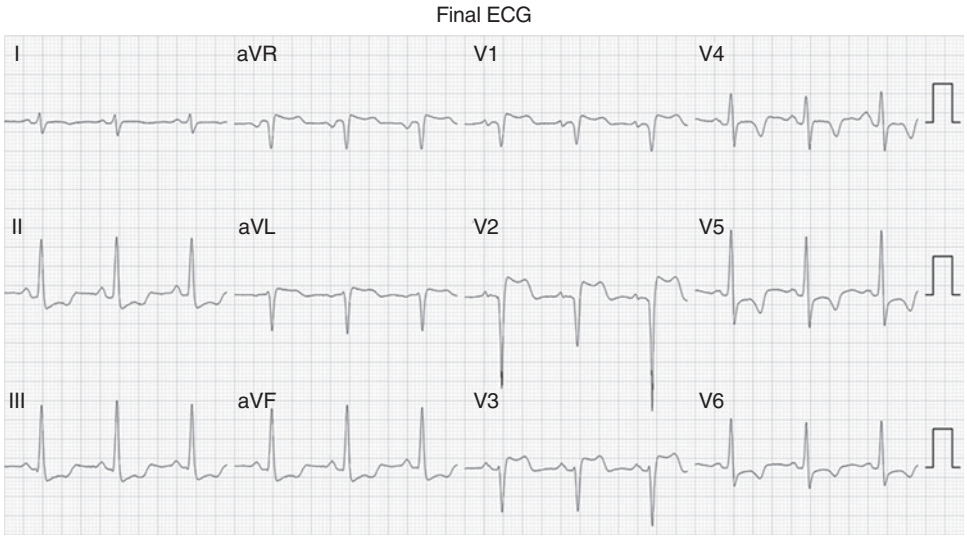


Figure 21-8

During RF delivery at the site of earliest Purkinje activation during VT, a flurry of activity with the same QRS complex occurs followed by termination to sinus rhythm (Fig. 21-8). This effect is characteristic of focal emanation (in contrast, reentrant VTs typically slow before termination).

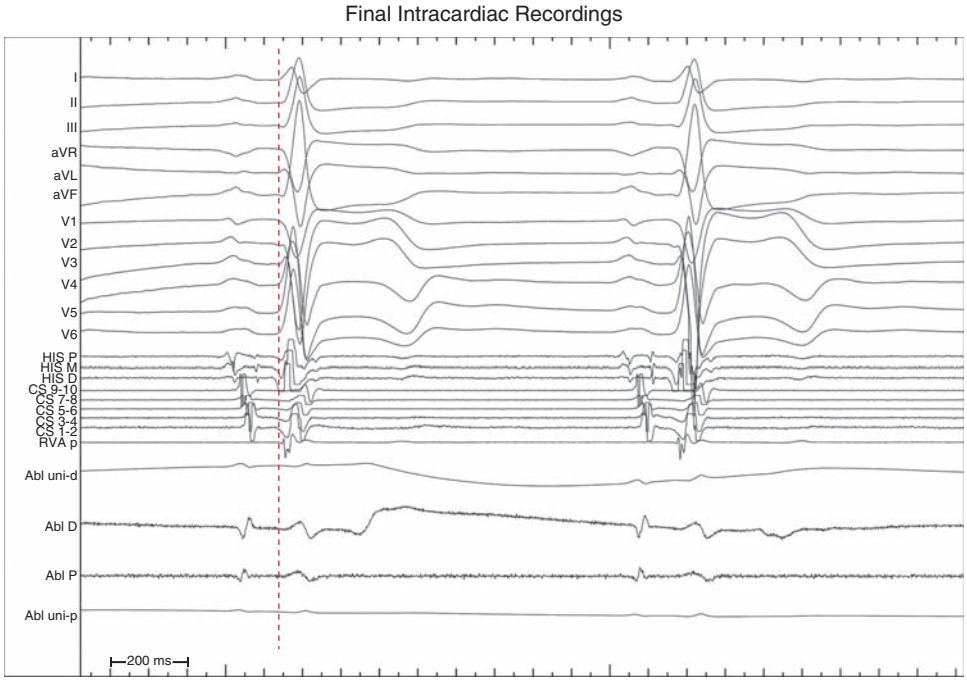
Final ECG and Intracardiac Recordings

Figure 21-9



The final ECG (Fig. 21-9) shows sinus rhythm without bundle branch block or axis deviation; ST-T wave abnormalities are an artifact of the recording system.

Figure 21-10



The final intracardiac recordings (Fig. 21-10) show sinus rhythm without bundle branch block or axis deviation.

Electroanatomic Maps

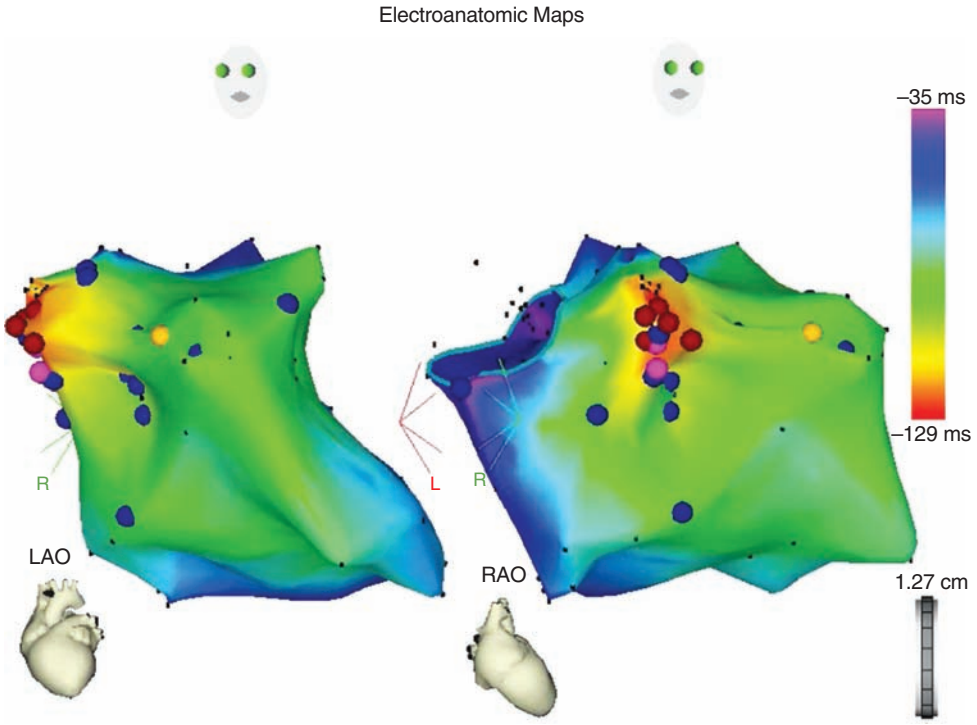


Figure 21-11

Fig. 21-11 displays the right and left anterior oblique views of the left ventricular activation during VT. The *purple dots* signify where perfect pace-matches were obtained as well as ablation sites where tachycardia terminated; *red dots* are consolidation ablation sites; *blue dots* denote where other Purkinje potentials were identified. The activation map shows earliest recordings during VT at the upper basal septal/anterior wall junction, with all other activations proceeding centrifugally from this region (consistent with a focal process).

Points on Mapping Fascicular VTs

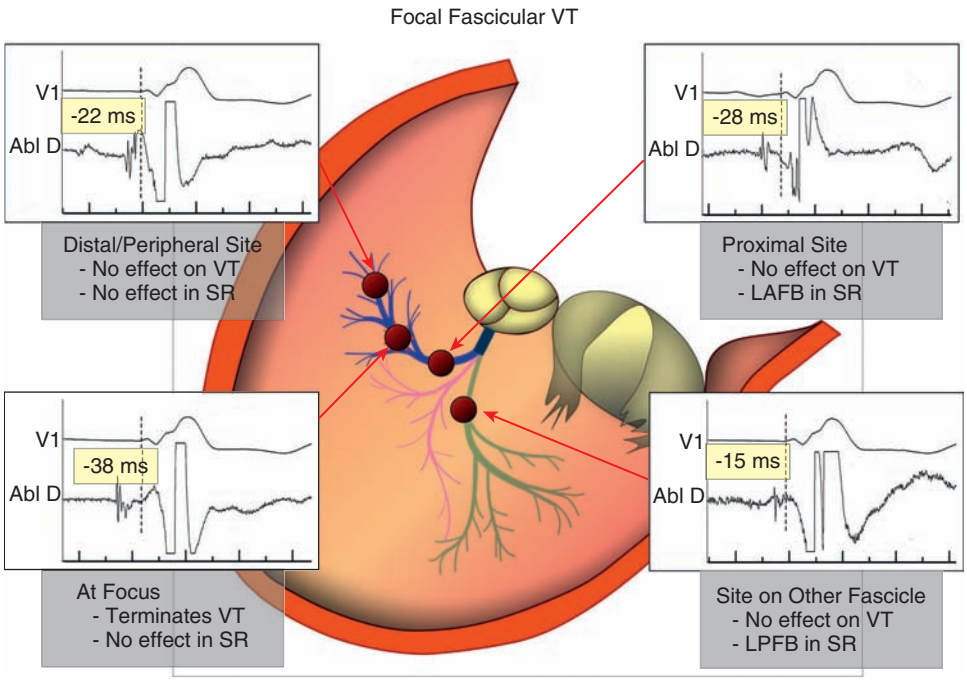


Figure 21-12

Fig. 21-12 shows the importance of ablation at the best site and implications of ablation at incorrect sites. SR, sinus rhythm; LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.

Follow-up

- No further arrhythmias overnight, discharged the following morning
- Seen in follow-up 3 months later:
  - Sinus rhythm, no ectopy
  - Energy significantly improved
  - Very glad now that he had the procedure

Summary

- Fascicular tachycardias can be reentrant or focal (as in this case); overdrive pacing can differentiate these two causes
- It is important to determine whether the arrhythmia is junctional with bundle branch block/fascicular block or fascicular rhythm
- "Bump-mapping" can be useful but has limitations
- Correct targeting of the focus is critical for eliminating it and not causing unwanted "collateral damage" to other areas

Reentrant Fascicular Ventricular Tachycardia

22

Case Presentation

The patient is a 30-year-old man with four episodes of severe palpitations. In the first episode, the patient had palpitations and near-syncope while playing basketball. He was taken to the local ER, and his blood pressure was 110/80 mm Hg and wide complex tachycardia was 200/min. He was given adenosine, metoprolol, and diltiazem, but there was no effect. Arrhythmia was ultimately slowed and terminated. He was hospitalized and underwent an electrophysiology (EP) study; no arrhythmia was initiated. He was diagnosed with probable atrial tachycardia and treated with metoprolol, and subsequently discharged. Subsequent episodes were with and without exertion and stopped spontaneously after 15 to 40 min. He was found to have normal exercise capacity, and findings of physical examination and echocardiogram were normal; baseline ECG was normal too. The EP study found no inducible arrhythmias, and he was referred for a repeat EP study and possible ablation.

Baseline ECGs

What Is the Rhythm? [Fig. 22-1]

- VT?
- SVT with aberration?
- Fascicular?

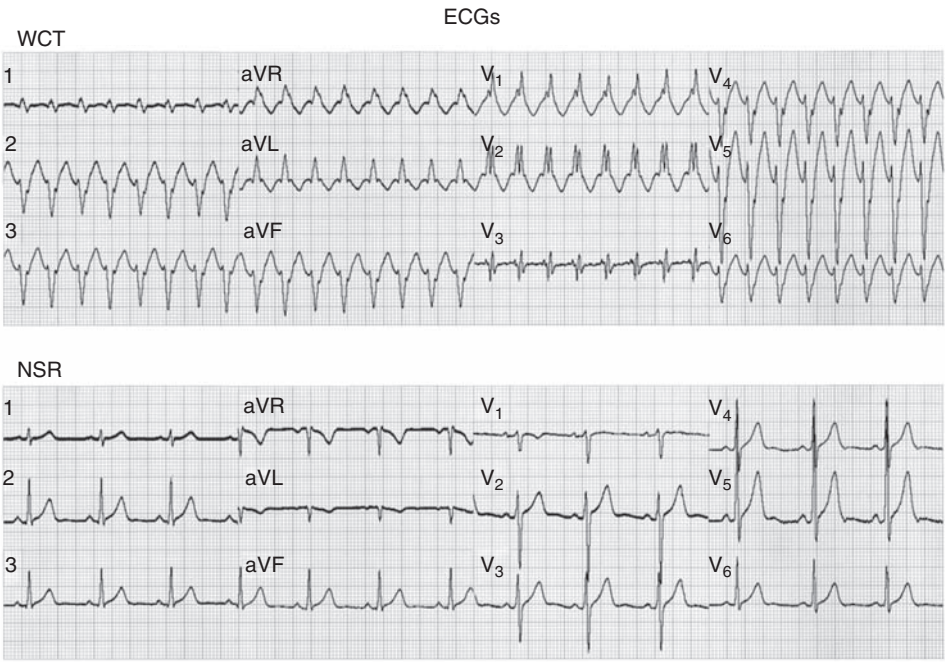


Figure 22-1

As shown in Fig. 22-1, the QRS during the wide complex tachycardia (WCT) is about 130 ms in duration and has RBBB pattern that in V1 and V6 is more consistent with ventricular tachycardia (VT; the rR′ in V1, R/S ratio <1 in V6), but the R-wave peak time in lead 2 (<50 ms), rS interval in a precordial lead <100 ms (Brugada criterion), qR pattern in aVR, and ventricular activation velocity index in V2 and V3 (>1) favor supraventricular tachycardia (SVT). P waves are not clearly evident (thus one cannot determine dissociation of atrial activity). There are no pathologic Q waves during the WCT or sinus rhythm to suggest old infarction. There is no preexcitation or any other abnormality of the QRS or repolarization to suggest a cardiomyopathy. Thus the WCT is either an atypical form of aberration during SVT or it is VT in the absence of structural heart disease. It is notable that no arrhythmias could be initiated at the prior EP study, but some VT in normal hearts as well as some focal atrial tachycardias may be difficult to initiate.

Baseline Atrial Pacing and Arrhythmia Induction

What's Going on Here? [Fig. 22-2]

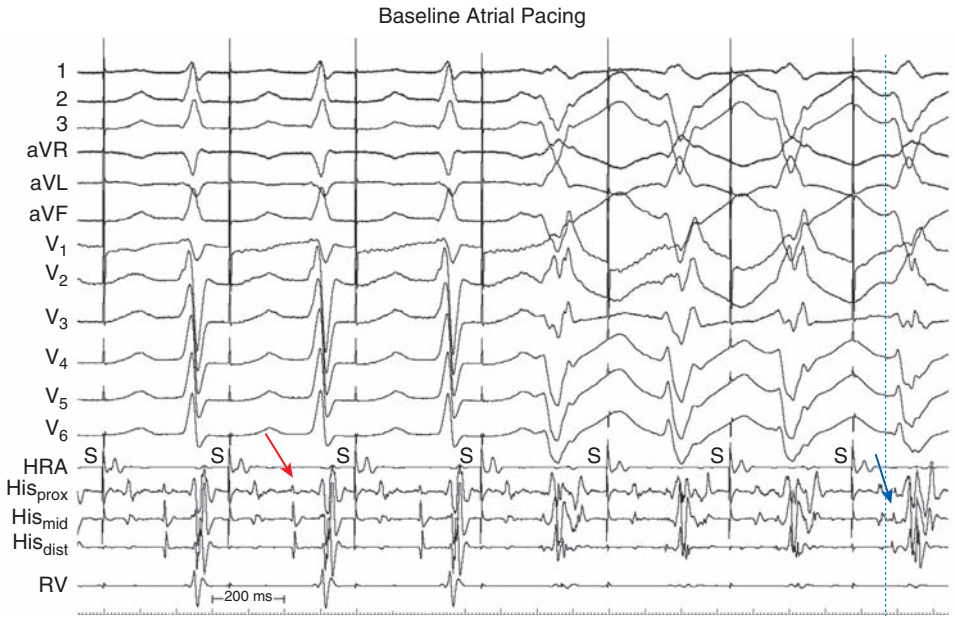


Figure 22-2

During atrial pacing (S) at the beginning of the study (to determine AV Wenckebach cycle length), the WCT occurs (Fig. 22-2). Note the His potential *(red arrow)* with a normal HV interval (45 ms) during atrial pacing on the left half, and the much shorter HV interval during WCT on the right half (in fact, a negative HV interval—the His *[blue arrow]* is after the QRS onset *[dashed line]*). Three situations exist during which the His potential consistently occurs after the QRS onset: 1) ventricular preexcitation, 2) ventricular pacing, and 3) ventricular ectopy/tachycardia. Because this would be an unusual pattern of preexcitation and is definitely not ventricular pacing, VT is favored as the diagnosis. Although many electrophysiologists do not routinely use His recording catheters during EP studies, the simple recording of a consistent His potential can have great diagnostic benefits.

Baseline Arrhythmia

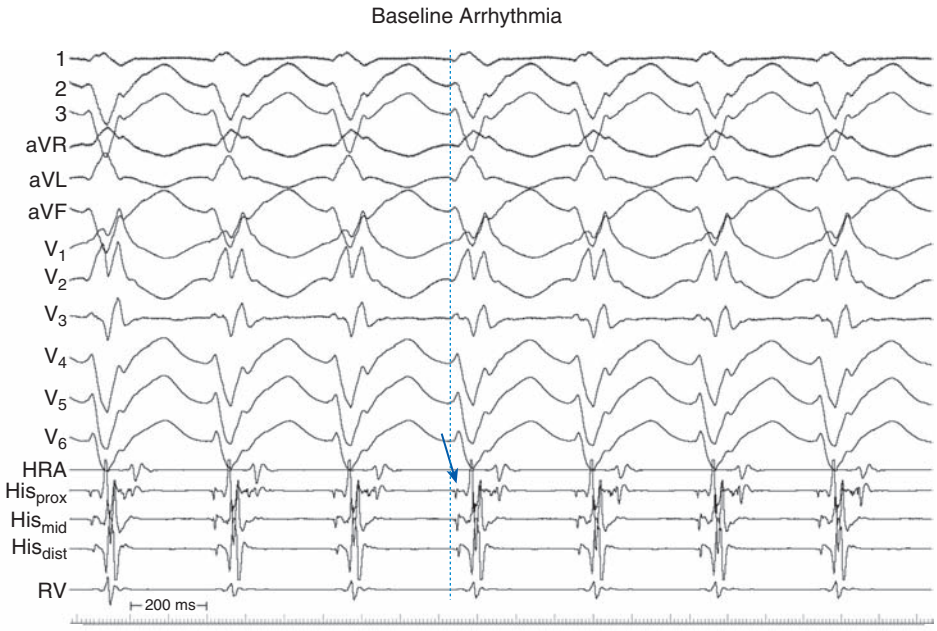


Figure 22-3

After cessation of atrial pacing, VT continues as shown in Fig. 22-3. The *blue arrow* is clearly seen after the QRS onset *(dashed line)*. Note that there is a 1:1 V:A relationship (explaining why dissociation was not evident on the regular ECG). The direction of propagation of the His recordings appears to be proximal to distal; this would be unusual with a retrogradely activated His during VT, but in this case, only the proximal electrodes are actually at the His bundle (with a modest atrial recording in sinus and VT), whereas the middle and distal electrode pairs are probably recording a right bundle potential. The VT spreads from the left ventricle (with RBBB pattern), ascends the left bundle branch, conducts retrogradely through the His bundle, and turns around to activate the right bundle branch anterogradely (whereas the right ventricle may be directly activated across the ventricular septum).

Table of Differential Diagnosis

RBBB WCT in the Absence of Structural Heart Disease:

- Verapamil-sensitive left posterior fascicular (LPF) reentry
- SVT with aberration
- Focal fascicular VT
- Papillary muscle focal VT
- Other myocardial VT

The differential diagnosis of an RBBB WCT includes several possibilities as noted above. Table 22-1 offers some useful distinguishing features. In our case, already determined to be VT, there is a Q wave in lead 1 but not V1, and the rhythm did not terminate with adenosine.

TABLE 22-1 Differential Diagnosis of RBBB WCT

	Verap. Sens. LPF VT	SVT + Aberration	Focal Fascicular VT	Papillary Muscle VT
QRS duration	Rel. narrow	Rel. narrow	Rel. narrow	Wider
Q in lead 1	Yes	Yes	No	No
Q in lead V1	No	No	No	Yes
AV relationship	Variable	1:1	Variable	Variable
Adenosine effect	None	Termination	Termination	None
HV interval	−20 ms	45 ms	−15 ms	−10 ms
Earliest Purkinje	(throughout)	After His	Before His	Before His
Overdrive pacing	Constant return cycle	Variable effects	Overdrive suppress	Overdrive suppress
Pacemapping	Not helpful	Not helpful	Excellent	Excellent

Right Ventricular Pacing in VT

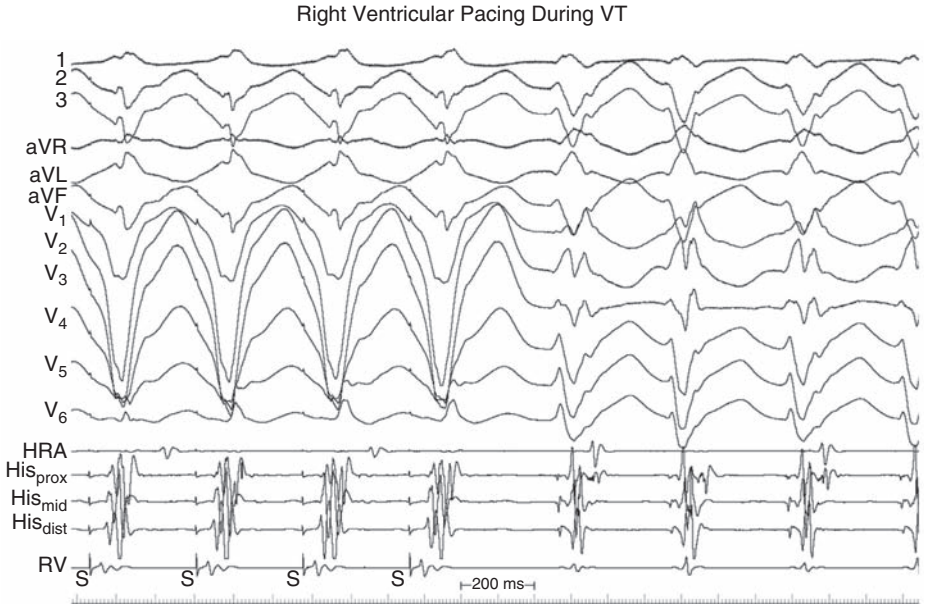


Figure 22-4

As seen in Fig. 22-4, VT had a stable cycle length of 315 ms; the timing of the first beat of VT after the end of right ventricular overdrive pacing during VT did not vary over a range of cycle lengths (310 ms, shown here, to 280 ms); pacing at 270 ms terminated VT. This would not be expected with a focal process, in which overdrive suppression of an automatic focus occurs (faster overdrive pacing results in longer delay until VT resumes); termination of a focal arrhythmia with overdrive pacing is also unusual. A constant return cycle over a range of overdrive paced cycle lengths and eventual termination of VT with more rapid pacing is entirely consistent with reentry, however.

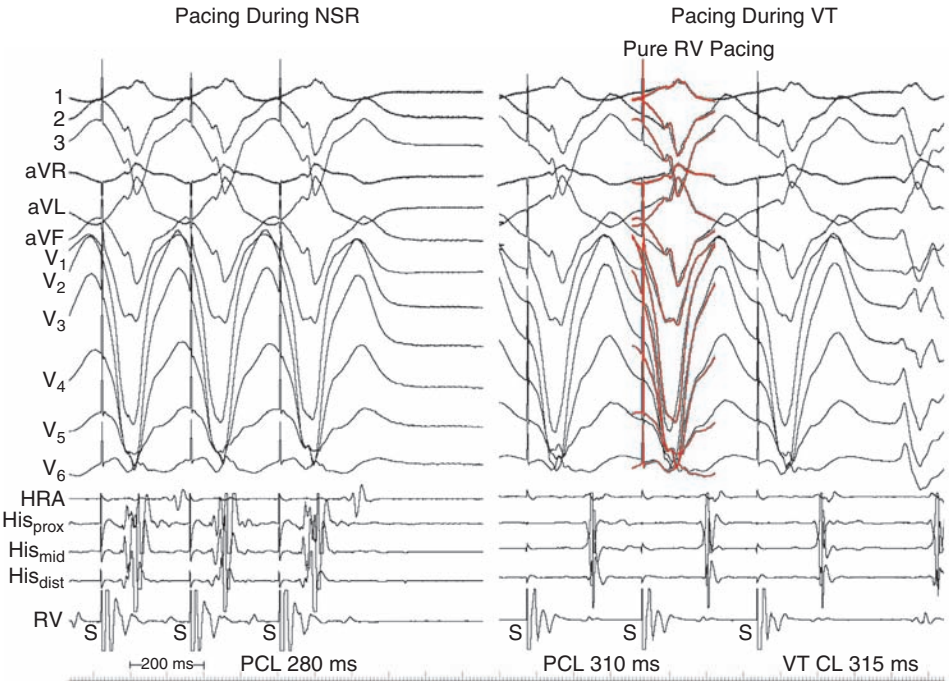
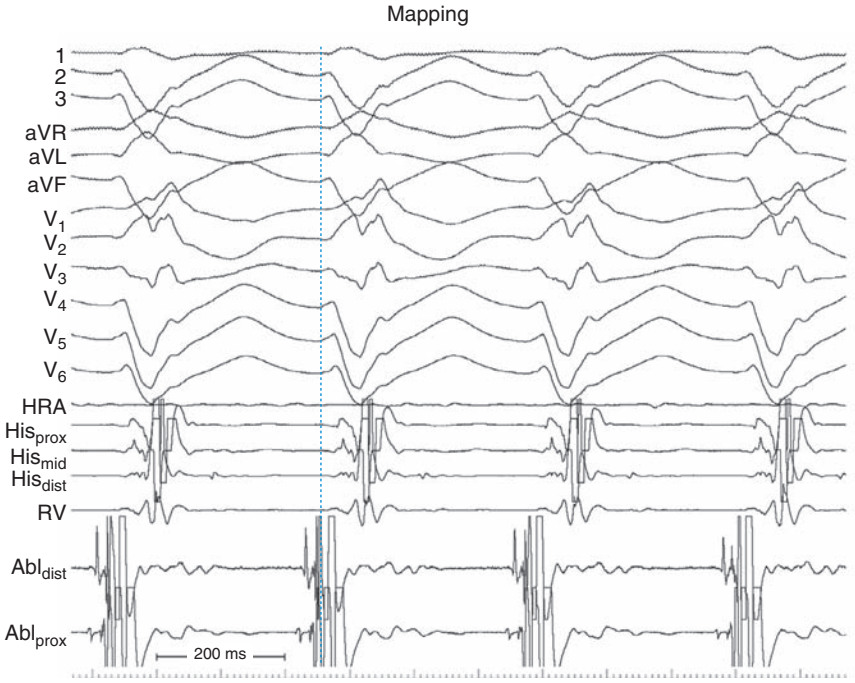


Figure 22-5

Pacing during VT may show fixed fusion (every QRS complex a consistent blend), and if so, is diagnostic of macroreentry. In Fig. 22-5, RV pacing during VT at a rate just slightly faster than VT is shown at *right*, and pure RV pacing (during sinus rhythm) at *left*. A single complex of pure RV pacing superimposed on RV pacing during VT shows little difference; it can be argued that V4 to V6 show some slight differences but these are minimal. Based on this one example, one may be tempted to conclude that because fusion is not evident, the rhythm is not macroreentry. This is an unwise conclusion, because although a single episode of pacing that shows fusion can diagnose macroreentry, it often takes pacing at many cycle lengths and different sites to show fusion. Based on all the information now available, the diagnosis of left posterior fascicular–related reentry ("verapamil-sensitive VT") seems secure at this point. Even though many VTs in the absence of structural heart disease terminate with adenosine injection, this one characteristically does not (although it does respond to verapamil). Before availability of adenosine, many cases of this VT were erroneously diagnosed as SVT because of their occurrence in otherwise healthy people, relatively narrow QRS in tachycardia, and termination with verapamil injection.

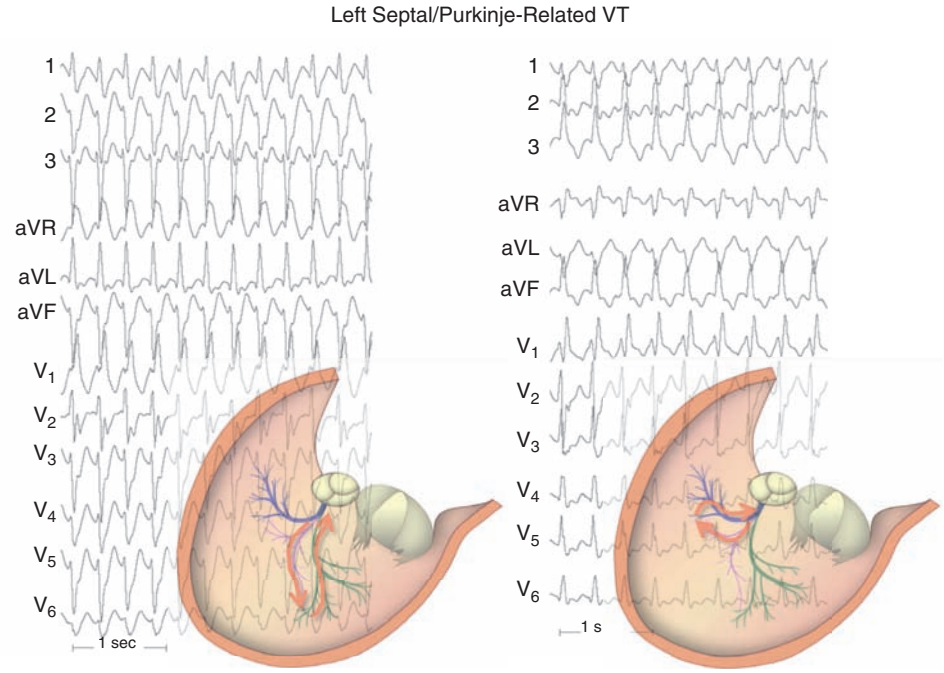
Mapping and Cartoons of Circuits

Figure 22-6



Having established a diagnosis of verapamil-sensitive left posterior fascicular VT, mapping can begin to find an appropriate ablation target. In previous years, finding the most presystolic Purkinje potential (10 to 40 ms, as in Abl_{dist} in the figure) was the goal; more recently, with the understanding that the posterior fascicle is the retrograde limb of tachycardia whereas a diastolic pathway composed of possibly partially depolarized Purkinje cells with calcium channel–dependent activation, or Purkinje cells in a false tendon, the target of ablation has become the lower turnaround site where the anterograde diastolic pathway joins the retrograde posterior fascicle. Recordings from the site in Fig. 22-6 may be >50 ms presystolic and have multiple deflections (as in Abl_{prox}), perhaps signifying activation of the two pathways.

Figure 22-7



The verapamil-sensitive Purkinje-related VTs displayed in Fig. 22-7 usually involve the posterior fascicle, at left, but can also involve the anterior fascicle, as shown at right.

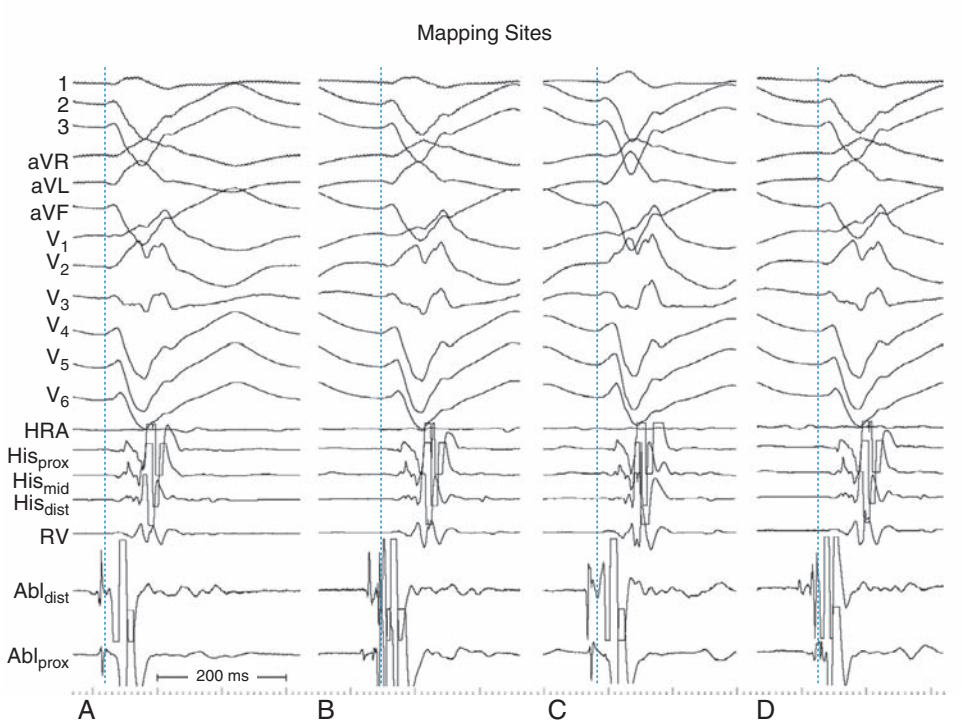
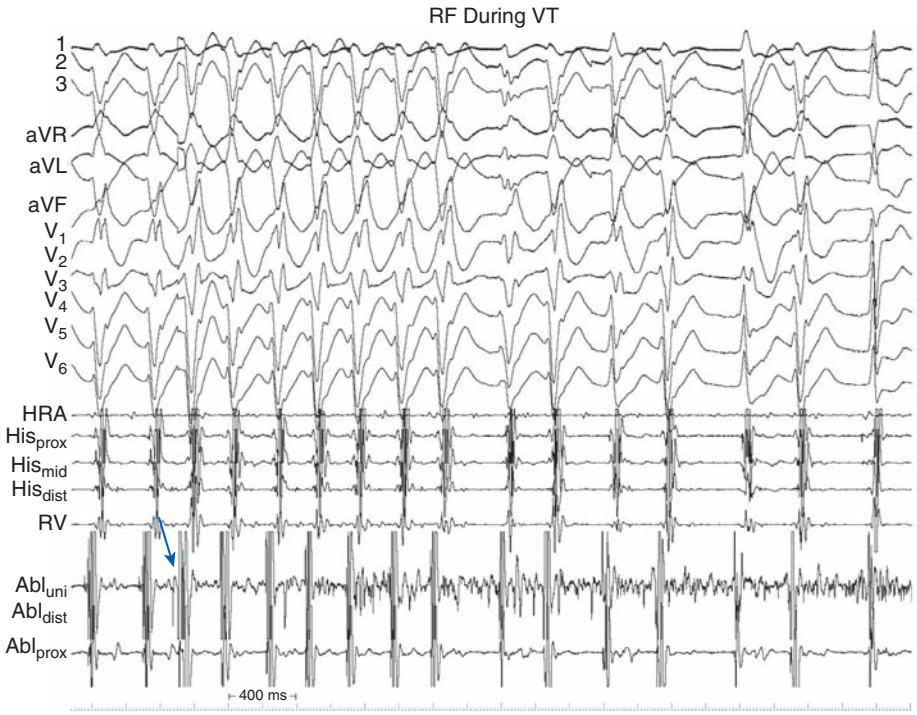


Figure 22-8

Several other mapping sites are shown in Fig. 22-8 (*dashed line* denotes onset of the VT QRS). Though all have presystolic potentials, which is the ideal target site? At site A, the distal electrogram precedes the proximal, but neither is very presystolic. At site B, the distal electrogram is earlier than that in A, but is later than the proximal recording and because ablation can only be done from the distal electrode, this site is not suitable either. At site C, the distal electrogram precedes the proximal, and both are reasonably presystolic, but the deflection is single rather than multiple and suggests posterior fascicle recording only. At site D, the distal electrogram precedes the proximal, is very presystolic, and is very complex (with multiple deflections). This is a very reasonable target site for ablation. Pacemapping during sinus rhythm at this site may or may not replicate the VT (because capture of surrounding myocardium may occur). Thus pacemapping is not a reliable tool for choosing ablation targets in this arrhythmia. Of note, these sites may be very sensitive to even mild catheter trauma, so great care must be taken to move the catheter tip slowly and cautiously; "bump termination" of VT may be followed by noninducibility for the rest of the procedure. Electroanatomic mapping systems that can record a three-dimensional location at which catheter trauma terminates VT can be used to guide ablation even when VT cannot be reinitiated (as long as location of the site was recorded at the actual time of catheter trauma and not seconds later, after the catheter may have moved).

Ablation

Figure 22-9



Radiofrequency energy is delivered at the target site during VT *(blue arrow)*. This causes a nearly immediate acceleration of the arrhythmia (more typical for focal automatic or triggered arrhythmias) and then "stuttering" of cycle length before termination (last complex), as seen in Fig. 22-9. VT could not be reinitiated thereafter, with or without isoproterenol infusion; the sinus rhythm ECG at the end of the procedure was unchanged (ie, no axis shift related to ablation near the His-Purkinje system). Ablation may lead to either acceleration or deceleration in this arrhythmia, whereas most reentrant tachycardias slow before termination during ablation.

Other Mapping Strategies

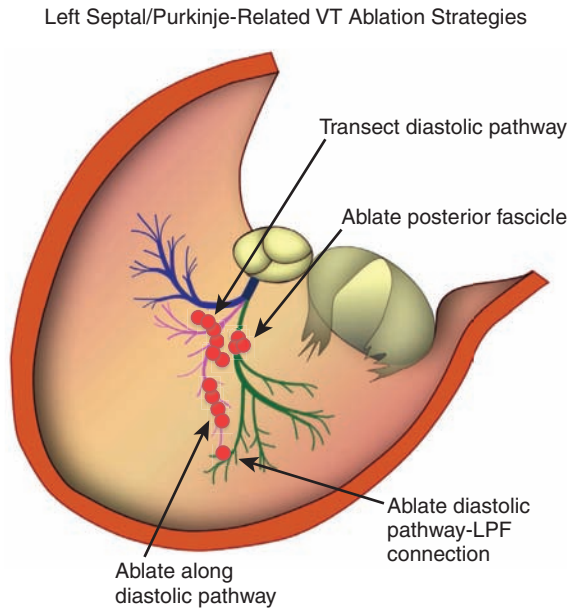
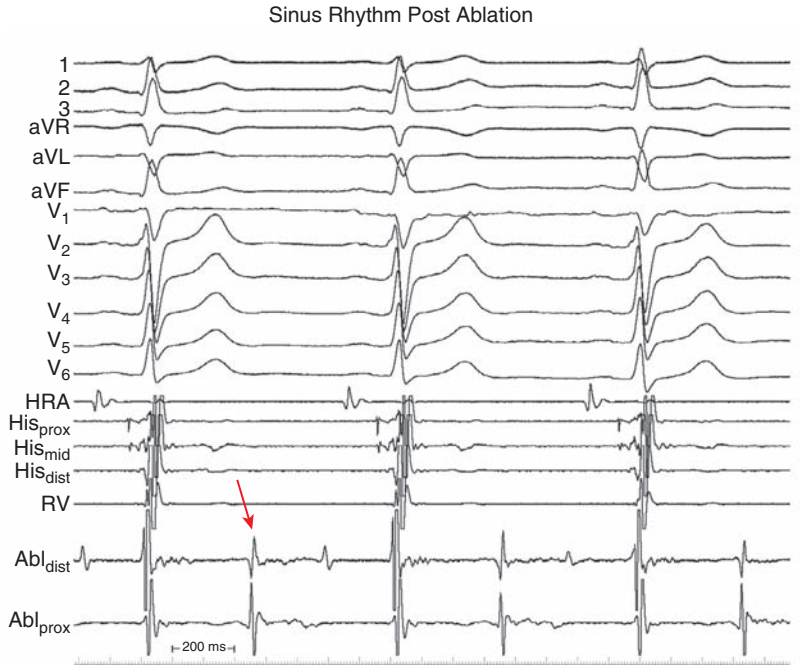


Figure 22-10

In Fig. 22-10, the left ventricle is shown opened along the lateral wall; the anterior fascicle is *blue*, the posterior fascicle is *green*, and the diastolic pathway during VT is shown in *purple*. Ablation strategies in this disorder include ablation at the site of connection of the left posterior fascicle and diastolic pathway (usually on the inferior left ventricular septum, as in our case); ablation along the diastolic pathway indicated by very delayed (and usually very small) potentials during sinus rhythm until these are eliminated; or linear ablation in the basal septum to try to transect the diastolic pathway. The latter may be the only option in cases in which VT cannot be initiated despite a reasonably clear diagnosis from the ECG during a prior spontaneous episode, or when catheter trauma during mapping precludes subsequent VT induction and thus mapping. Ablation of the posterior fascicle is not advised because this is a rather widely distributed structure and its elimination may require very extensive ablation (unwise in a normal heart).

Final Recordings

Figure 22-11



The large deflection indicated by the *red arrow* in Fig. 22-11 may be because of repolarization or recording artifact, or it may be a recording from the diastolic pathway used anterogradely during VT in these cases. Ablation at sites where these potentials are recording, eliminating them, is an effective ablation strategy when VT cannot be induced. Most often, if they can be recorded at all, they are much smaller than those shown here and may show multiple deflections.

Summary

- VT in the absence of structural heart disease often resembles, and is mistaken for, SVT on the ECG
- RBBB VT in the absence of SHD may be
  - Focal fascicular
  - Focal myocardial (including papillary muscle)
  - Verapamil-sensitive left posterior fascicular reentry
- In verapamil-sensitive left posterior fascicular VT, the diastolic pathway is very susceptible to catheter trauma
- Available mapping and ablation strategies include the following:
  - Targeting complex late diastolic potentials in VT
  - Targeting diastolic potentials in sinus rhythm
  - Transecting the presumed location of the diastolic pathway

Focal Cause of Ventricular Fibrillation

23

Case Presentation

The patient was a 45-year-old woman presented with cardiac arrest from polymorphic ventricular tachycardia (VT). Her history included ascending aortic disease with repair of aortic root and mechanical aortic valve replacement two months previously. She recovered well, but suffered unheralded cardiac arrest while shopping. She was hospitalized on cooling protocol, and she recovered well. The ejection fraction was 45%. Unfortunately she suffered recurrent polymorphic ventricular tachycardia/fibrillation. She was treated with amiodarone, beta blockade, and beta agonists, but there was no effect (i.e., she continued to have recurrent episodes of polymorphic VT). She was referred for electrophysiology (EP) study and possible ablation. What is the strategy?

Clinical Rhythm Strips

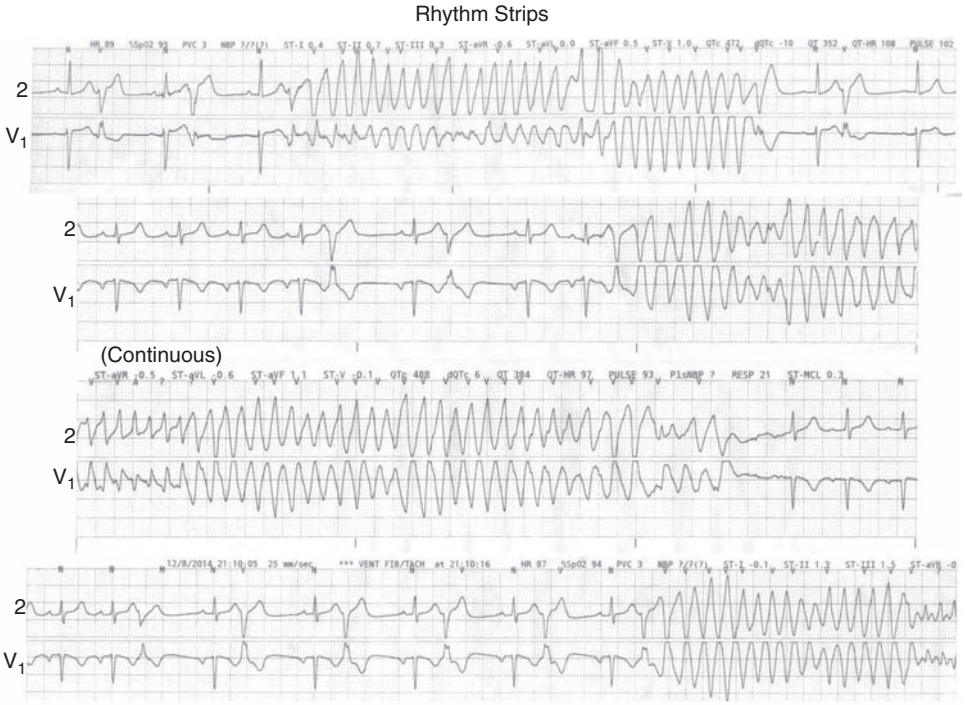


Figure 23-1

Repeated episodes of polymorphic VT (PMVT) are initiated by relatively narrow QRS premature ventricular complexes (PVCs) (Fig. 23-1).

Baseline ECG and Intracardiac Recordings

Figure 23-2

ECG (Fig. 23-2) is otherwise normal (apparent ST elevation in right precordial leads is an artifact of the recording system). The PVC morphology is clearer, having RBBB, leftward superior morphology, and the QRS complex is relatively narrow. Although not clearly fascicular, it is consistent with an origin in or near the Purkinje network.

Figure 23-3

Fig. 23-3 is the typical PVC morphology that led to repeated episodes of PMVT.

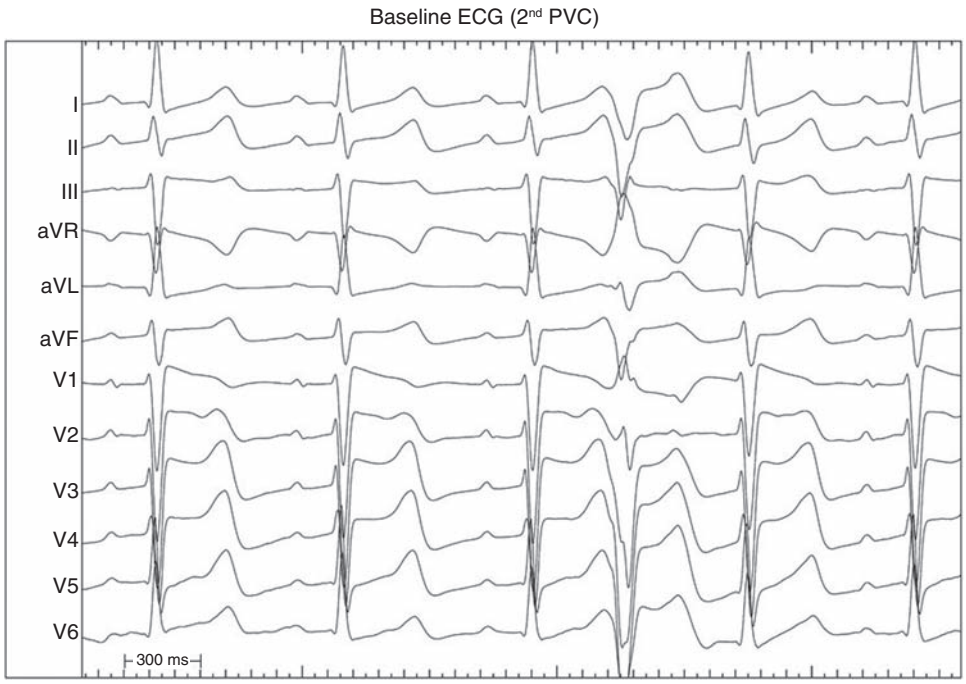


Figure 23-4

Fig. 23-4 is a second PVC morphology that occasionally preceded PMVT episodes (distinct from the main PVC, this has a rightward axis).

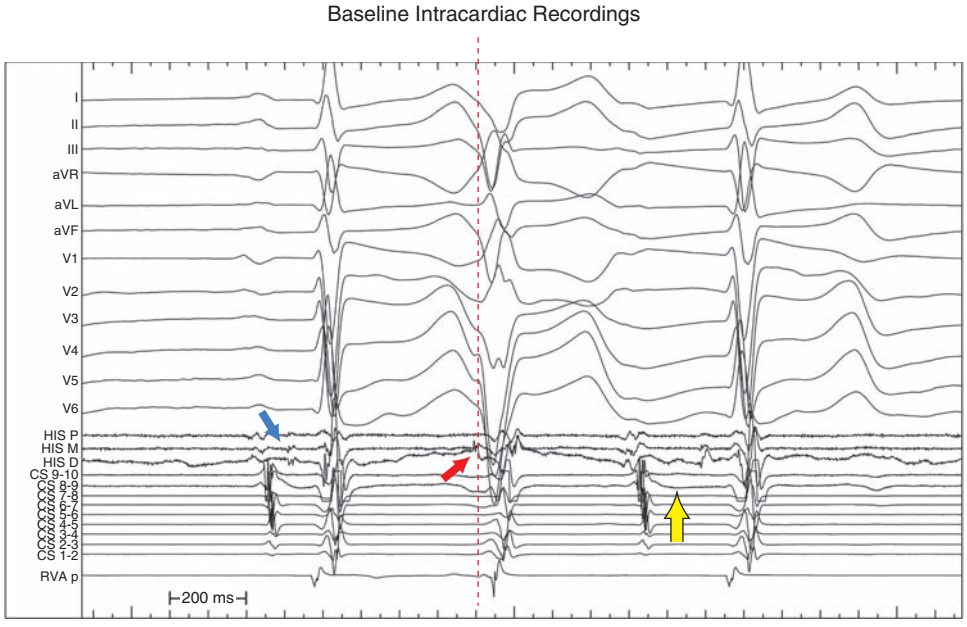
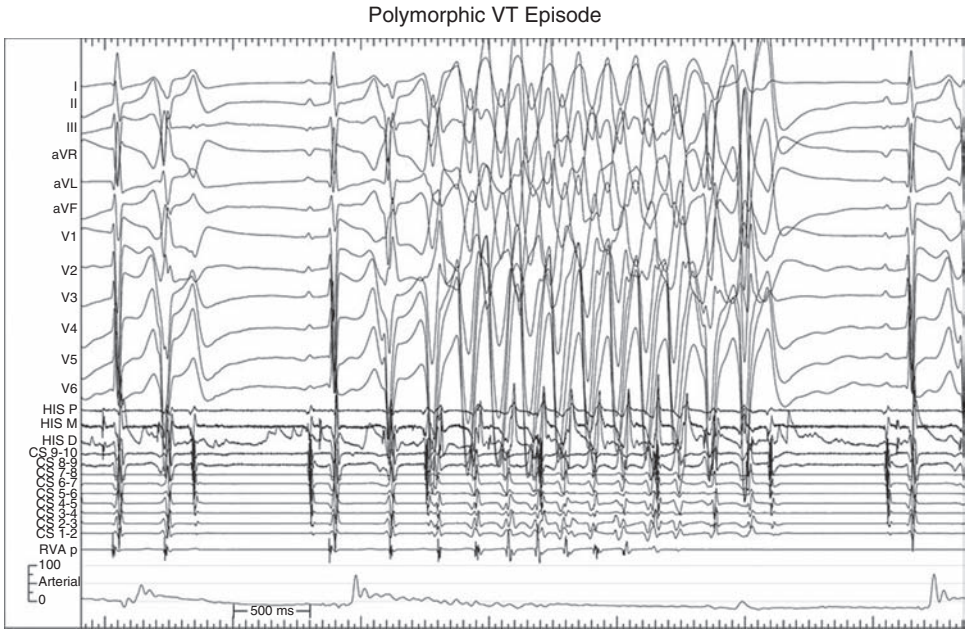


Figure 23-5

Once catheters are in place, an early indicator that the target PVC *(center)* is part of the Purkinje network is the finding that a His potential (Fig. 23-5, *red arrow*) precedes the PVC QRS onset *(dashed line)*. The *blue arrow* shows the same potential in sinus rhythm. The *yellow arrow* shows a longer AH interval on the following sinus complex, indicating retrograde penetration into, but not through, the AV node (concealed conduction).

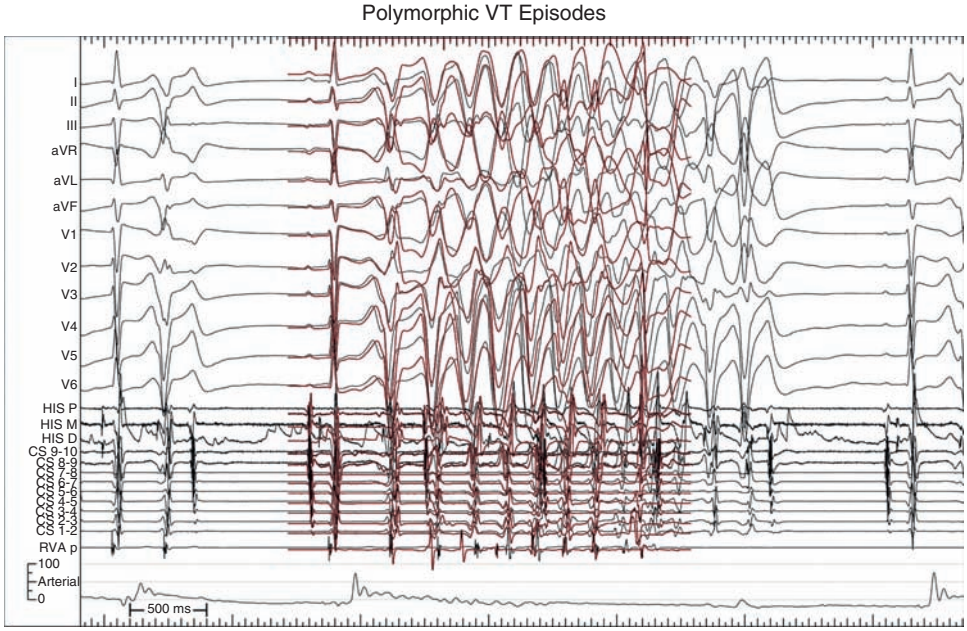
Polymorphic VT Episodes

Figure 23-6



While setting up for transseptal catheterization to access the left ventricle, PVCs initiated several episodes of PMVT (Fig. 23-6). Note that this particular episode was initiated by a relatively narrow QRS PVC with a rightward axis (not the same as the original PVC). Note also that blood pressure *(bottom tracing)* practically disappears for the entirety of the PMVT episode (about 3 seconds).

Figure 23-7



Two episodes of PMVT are shown in Fig. 23-7 with one superimposed on another; this illustrates that the first several cycles of episodes, although polymorphic, may be nearly identical. This suggests a consistent pattern of activation for these cycles until it becomes more disorganized.

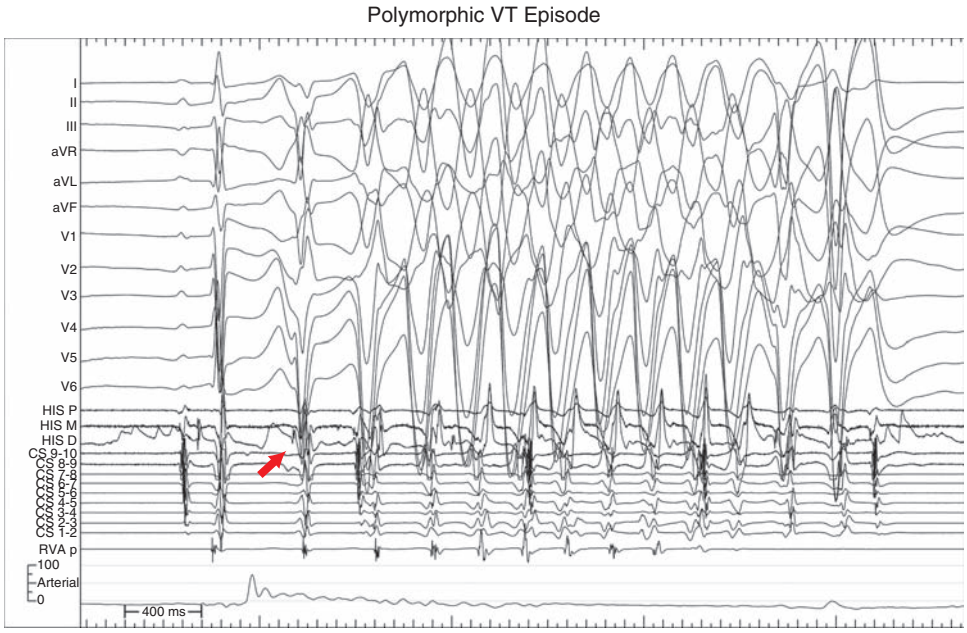


Figure 23-8

Fig. 23-8 is the same episode enlarged, to show the initiating PVC (right axis deviation) and the His potential at its QRS onset *(red arrow)*. This His timing can occur only when the origin is within the His-Purkinje system.

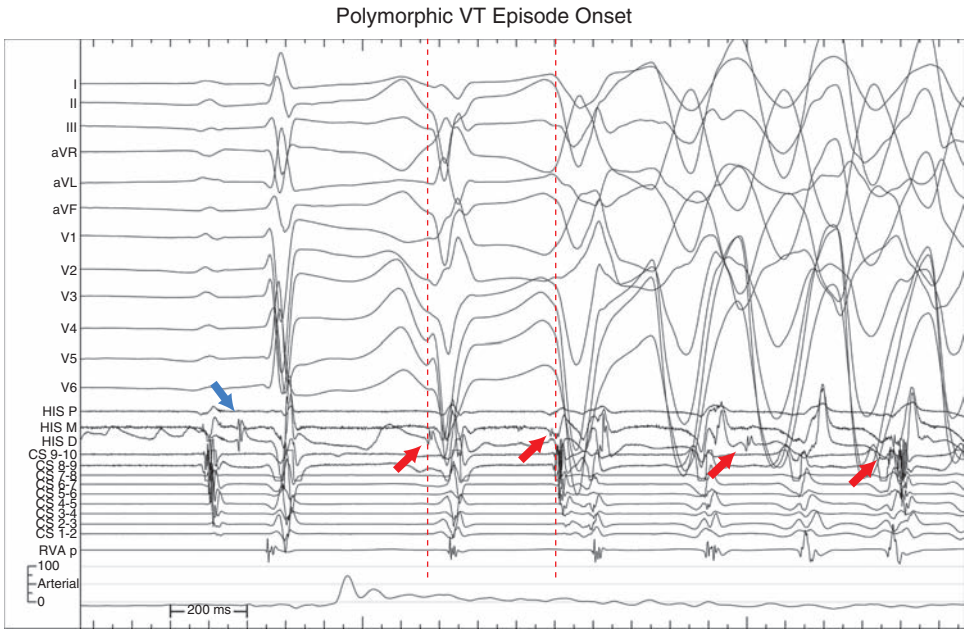


Figure 23-9

Fig. 23-9 shows the same episode enlarged further, to show the initiating PVC (right axis deviation) and the His potential (first *red arrow*) at its QRS onset *(dashed line)*. This sequence repeats, with a nearly identical QRS configuration, on the second complex. His potentials are seen with some, but not all, subsequent complexes. His potential in sinus rhythm is shown with a *blue arrow*.

Mapping Ventricular Ectopy

Is This a Good Ablation Site?

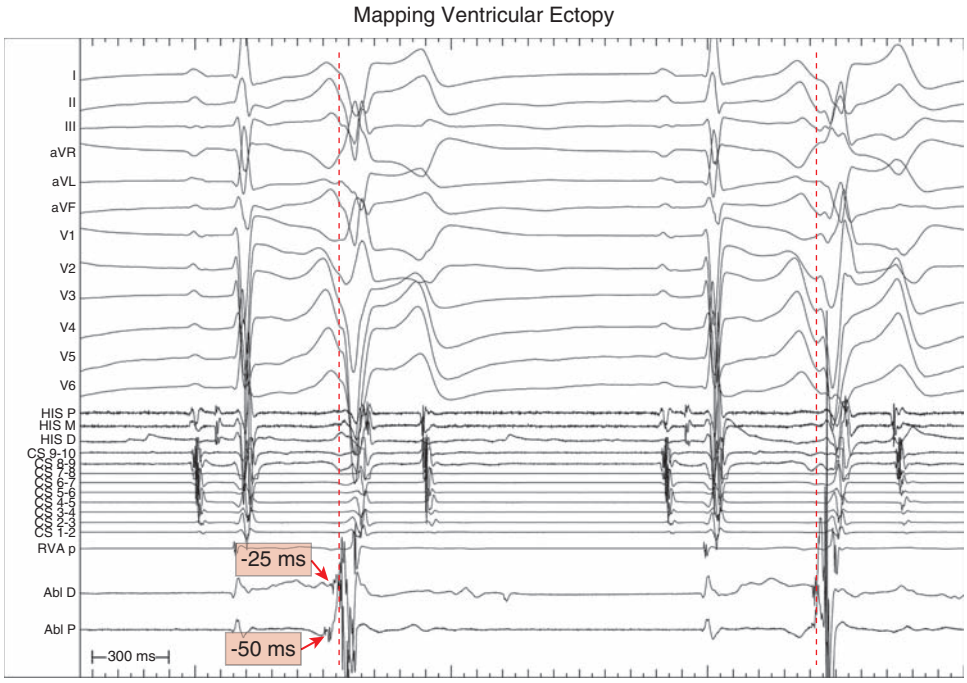


Figure 23-10

In Fig. 23-10, the ablation catheter has been introduced into the left ventricle via transseptal access (mechanical aortic valve). The PVC is of the rightward axis variety (which has caused PMVT episodes); the His potential is not well-seen with the PVC complex in this instance but an origin in or near the Purkinje network is suspected based on the sharp potentials on the ablation recordings. Whereas the distal mapping electrode has a potential 25 ms before QRS onset, which should be adequate for an ablation target, the proximal electrode has an even earlier potential. A Purkinje origin would be more strongly supported if such a potential were present in sinus rhythm (but it is not evident).

Where's the His? [Fig. 23-11] Is This a Good Ablation Site?

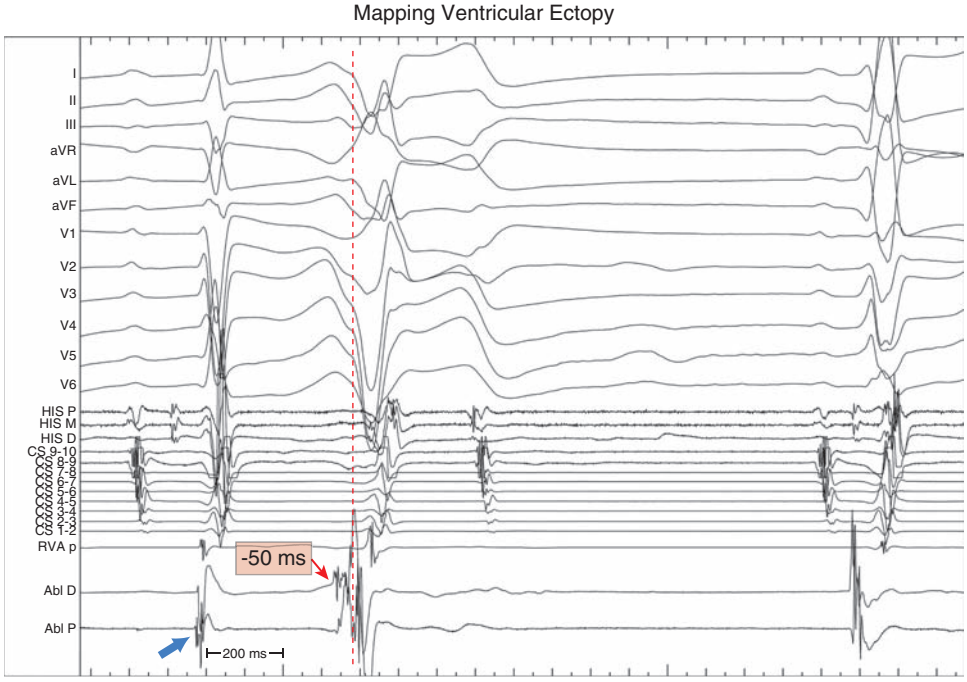


Figure 23-11

Fig. 23-11 shows another mapping site, this time with the distal electrode having a potential 50 ms before PVC onset. The His is again not clearly present during this PVC; the proximal electrode shows a potential consistent with Purkinje origin in sinus rhythm *(blue arrow)*. Attempts at pacemapping at these sites to confirm the same morphology as the PVCs produced inconsistent capture (not shown).

Site of RF and RF Delivery

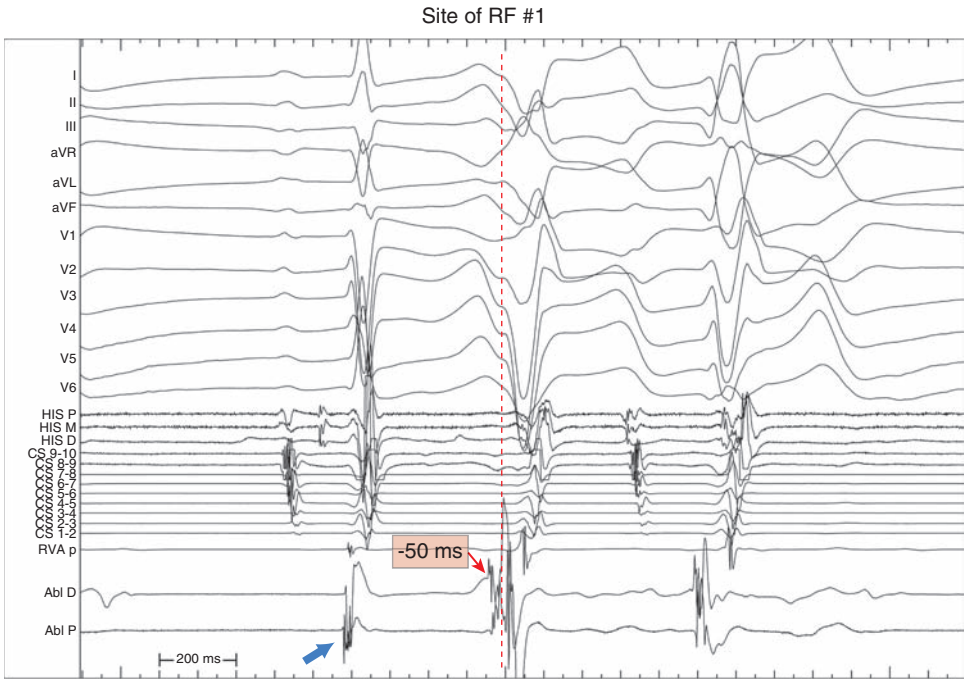
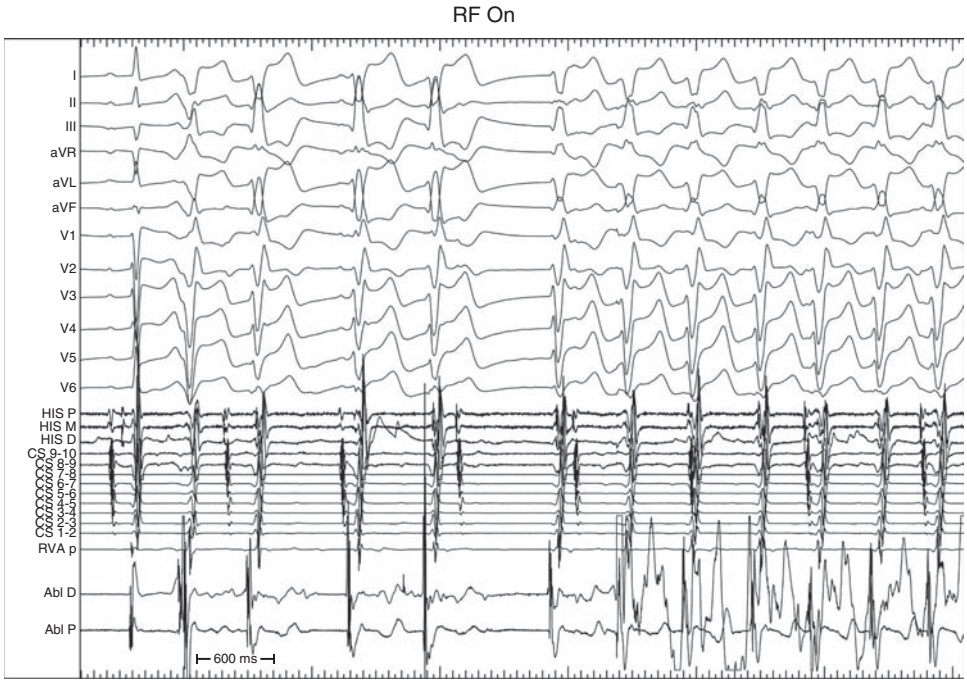


Figure 23-12

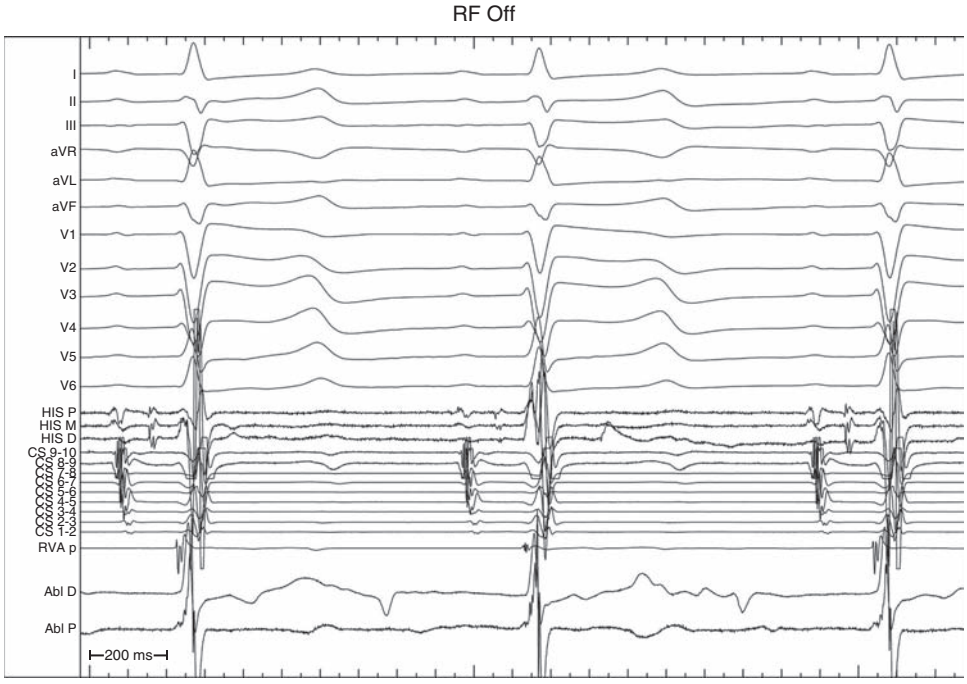
Fig. 23-12 displays the same mapping site, this time with the distal electrode having a potential 50 ms before PVC onset. The His is again not clearly present during this PVC; the proximal electrode shows a potential consistent with Purkinje origin in sinus rhythm *(blue arrow)*.

Figure 23-13



With onset of RF energy delivery *(right of center)*, a run of ventricular tachycardia occurs in Fig. 23-13, suggesting heating of tissue with the property of automaticity. This continued for another 25 seconds, then became nonsustained for 3 to 5 complexes, and then ceased.

Figure 23-14



Purkinje potentials are no longer evident at the ablation site (Fig. 23-14). Note also the presence of left anterior fascicular block (not present until ablation). This was transient.

Additional Findings

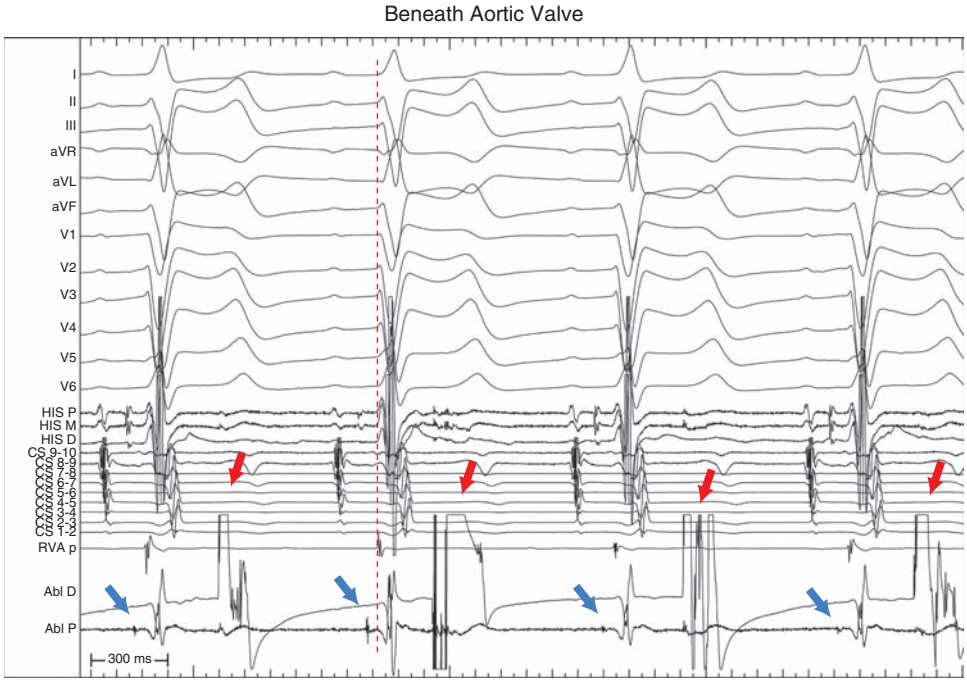
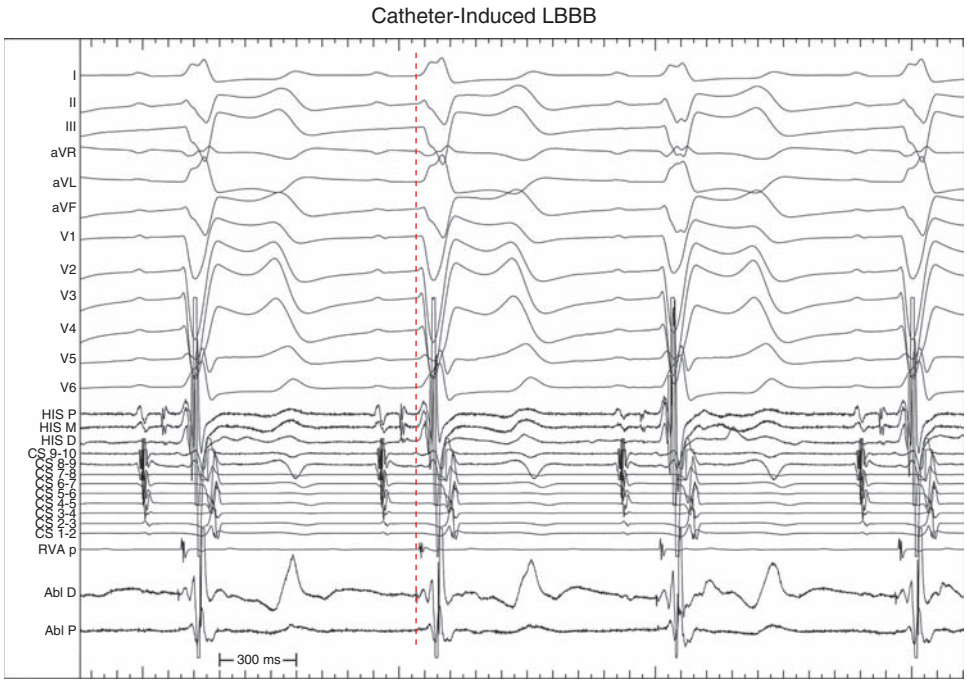


Figure 23-15

In Fig. 23-15, *blue arrows* are Purkinje potentials well before the QRS and without any discernible atrial activity—and recorded beneath the aortic valve. The location and timing are such that these are left bundle branch potentials. Mechanical injury to these can result in transient (or rarely, permanent) LBBB.

Red arrows denote electrical artifact generated by contact of the ablation electrode with the prosthetic valve struts. The signal is unphysiologically large, sharp, multicomponent, and not completely repetitive. It does not occur randomly, but periodically with cardiac motion.

Figure 23-16



In Fig. 23-16, with development of catheter-induced LBBB, the LB potential is no longer before the QRS onset *(dashed line)* but coincident with or even slightly after it. This may not be actual *block,* but possibly significant *delay.*

The patient had no further arrhythmias over a 5-day in-hospital follow-up; LBBB resolved; an ICD was implanted before discharge.

Electroanatomic Mapping

Figure 23-17

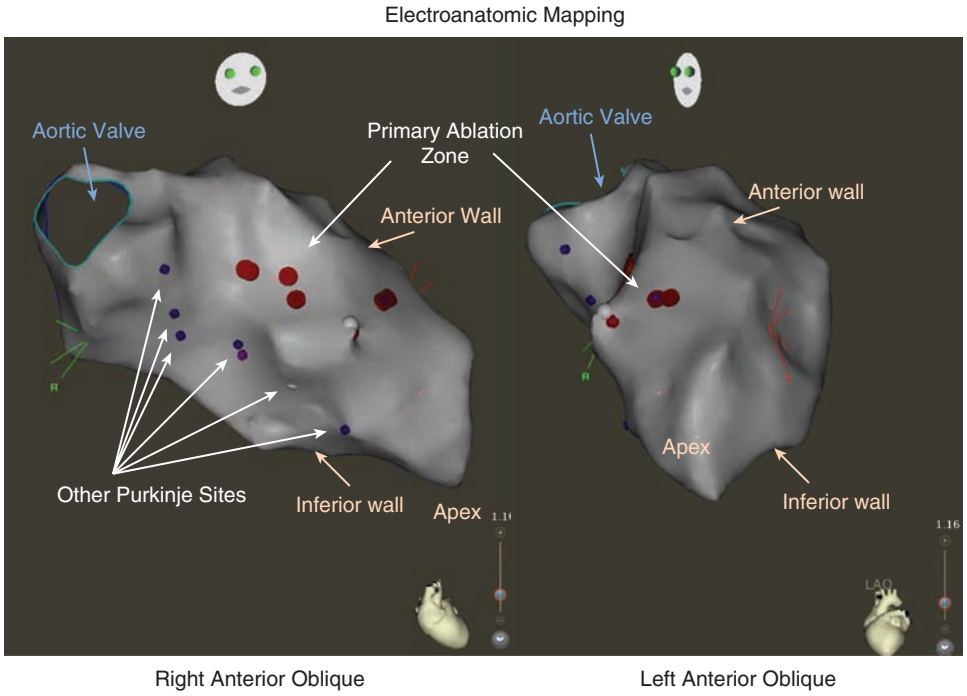


Fig. 23-17 displays an electroanatomic map during sinus rhythm showing sites with purple tags denoting Purkinje potentials as well as red tags denoting ablation sites where PVCs with the morphologies implicated in PMVT initiation were mapped, having Purkinje potentials preceding QRS complexes.

Summary

- Patients with recurrent polymorphic VT/VF should be investigated for severe ischemia, drug/electrolyte derangements, and progressive heart failure as well as the possibility that a focal source of fibrillation is responsible
- Focal-origin PMVT/VF has several features:
  - Episodes start with relatively closely coupled PVCs
  - Initiating PVCs generally have a consistent morphology
  - The first few cycles of PMVT are often identical
  - QRS complexes of initiating PVCs are relatively narrow
- Patients with suspected focal-origin PMVT/VF should have continuous telemetry with multiple leads (ideally full 12 leads) to determine whether initiations are stereotypic as well as defining morphology for potential ablation targets
- Ablation can be life-saving in such patients

24 Ventricular Tachycardia After Remote Infarction

Case Presentation

The patient was a 58-year-old man referred for catheter ablation of incessant ventricular tachycardia (VT). He had a history of inferior wall myocardial infarction (MI) and bypass surgery 5 years earlier. A ventricular fibrillation arrest occurred ~3 months after bypass surgery; he received a secondary prevention implantable cardioverter-defibrillator (ICD). At a routine office visit, his heart rate was 120/min, without symptoms; he was sent to the emergency room, where a tentative diagnosis of supraventricular tachycardia (SVT) was made (no response to adenosine). He was sent home, still in the arrhythmia, knowing that he had a scheduled visit with his electrophysiologist (EP) in several days. During the EP outpatient visit, VT was diagnosed and pace-terminated, and he was scheduled for elective ablation. Episodes recurred, and he was admitted to hospital for ablation more urgently.

Baseline ECG

Figure 24-1

In Fig. 24-1, this appears to be ventricular tachycardia with 1:1 retrograde conduction (*arrows* show P waves). Consistent with his history of inferior infarction, this appears to have a source (focus or exit from circuit) on the inferobasal septal wall, according to published algorithms.

Atrial Pacing Initiates VT

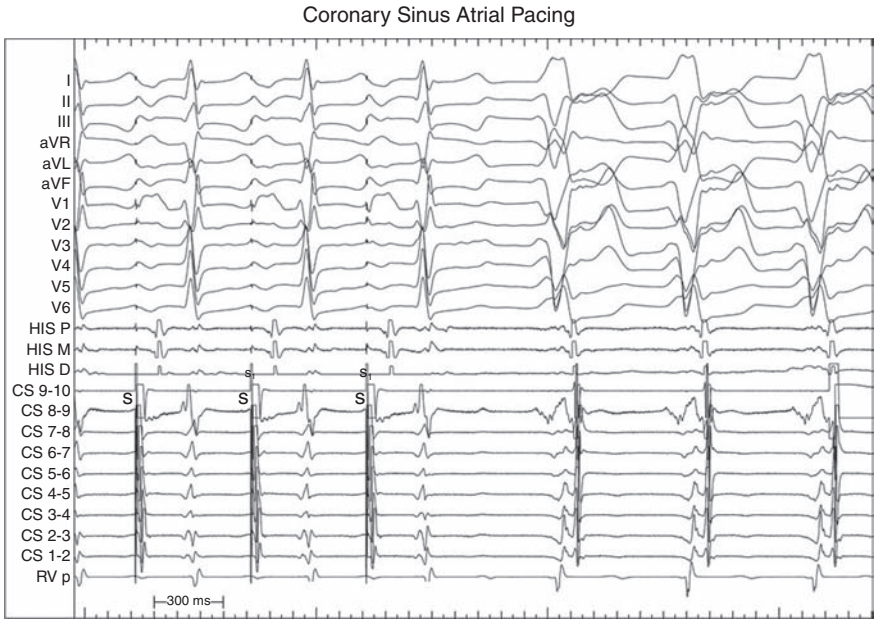


Figure 24-2

VT was accidentally terminated during catheter insertion and manipulation; in Fig. 24-2, during baseline atrial pacing, it is reinitiated. This unanticipated finding is quite unusual with VT at all, but when it occurs, most often a triggered (focal) mechanism is responsible for the VT.

Right Ventricular Overdrive Pacing

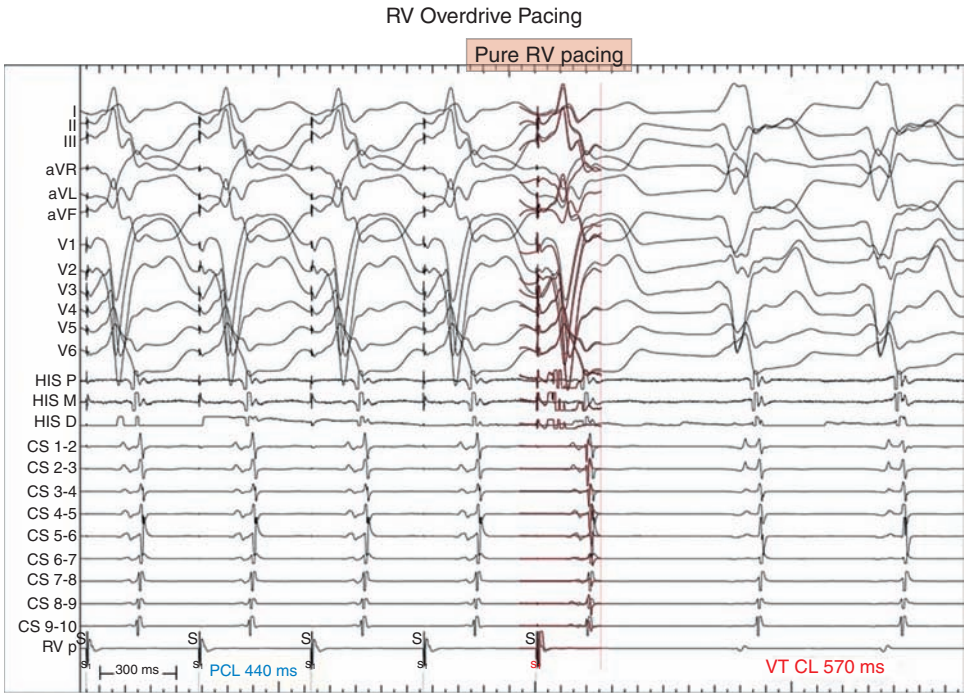


Figure 24-3

Incessant VT may be either focal or reentrant in origin. Because there was a question as to the VT mechanism (focal vs macroreentry) based on how it was initiated with atrial pacing, overdrive ventricular pacing was performed to investigate further. In Fig. 24-3, overdrive pacing at 440 ms is performed from the right ventricular (RV) outflow region, to maximize differences between VT and paced wavefronts. A single complex of pure RV pacing from later in the procedure is superimposed in *red*. This looks very similar to the paced complex during VT with only some minor differences. Because there is no clear fusion, macroreentry cannot be diagnosed; however, the absence of clear fusion on one example of pacing does not allow us to conclude that the VT has a focal origin. As such, this provides no definitive diagnostic information. (PCL, paced cycle length; VT CL, VT cycle length.)

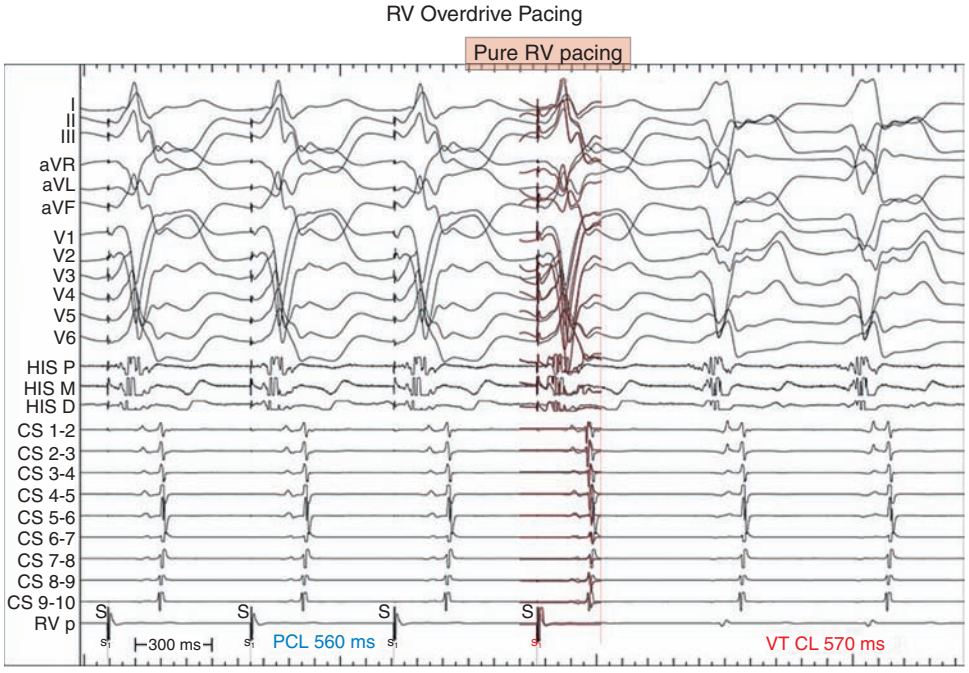


Figure 24-4

In Fig. 24-4, overdrive pacing is performed at a slower rate (560 ms) than before to further amplify differences between VT and paced wavefronts. Again, a single complex of pure RV pacing from later in the procedure is superimposed in *red*. This shows more differences between pure pacing and pacing during VT than were seen in Fig. 24-3: just as the more rapidly one paces during VT, the more all complexes will resemble pure pacing, it is also true that the *slower* one paces during VT (closer to VT cycle length), the contribution of the paced wavefront to the QRS will be less and fusion will be easier to discern. In this example, only minor differences are seen between pure pacing and pacing during VT (lead 1, V1-V2).

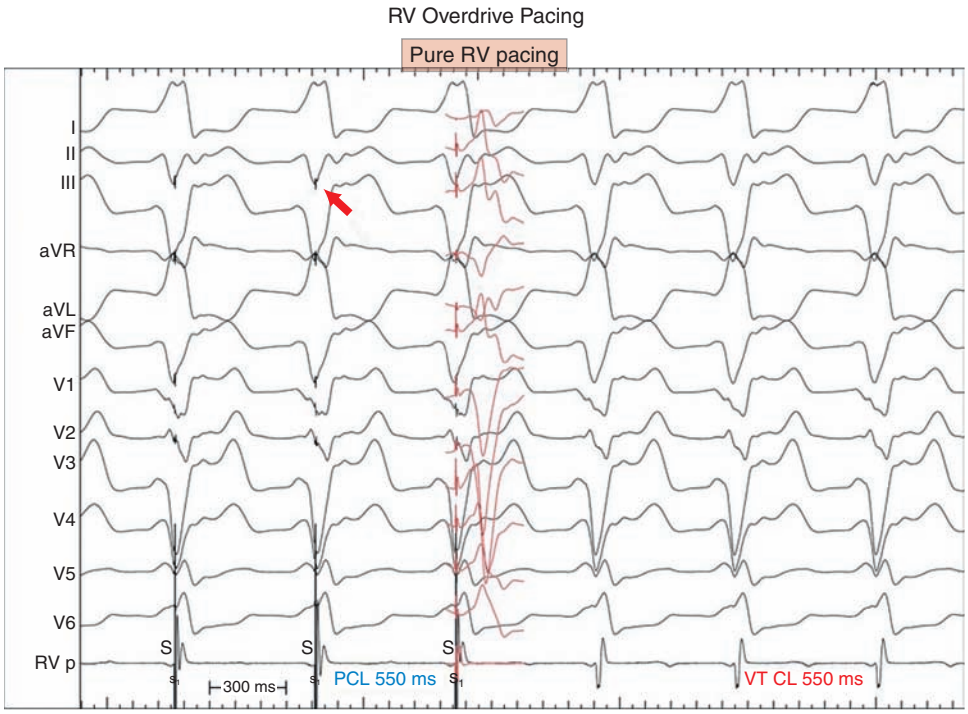


Figure 24-5

Fig. 24-5 shows RV overdrive pacing during VT a few minutes later; again, a single complex of pure RV pacing is superimposed for comparison. Now, it appears that there is a clear difference between pure pacing and pacing during tachycardia—indicating fusion—and thus implicating macroreentry. Note also that the stimulus artifact *(arrow)* occurs after the onset of a paced complex, another hallmark of macroreentry. Why is this so clear now when it was not before, pacing at the same site and rate? Careful inspection of the figure shows that one of the primary requirements for making an assessment has not been met: the VT has accelerated slightly such that its CL and the paced CL are the same. In fact, the RV electrogram starts before the stimulus—so none of it is actually captured (thus explaining why the "paced" QRS complexes are so similar to those of VT). This shows the importance of ensuring that capture is occurring when pacing during VT.

Figure 24-6

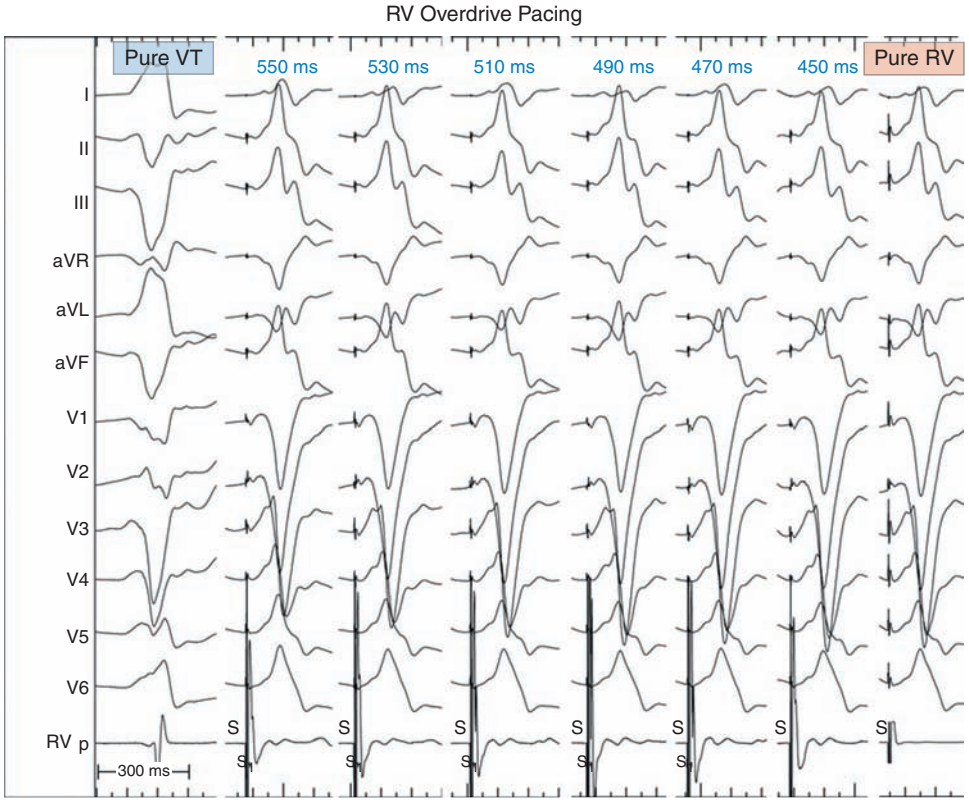
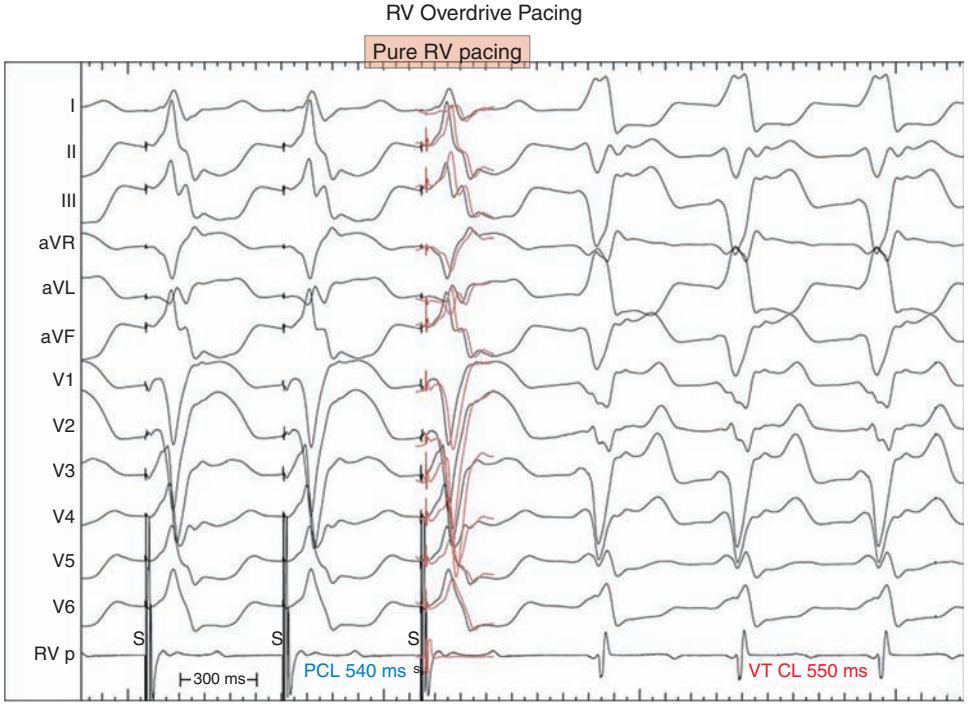


Fig. 24-6 shows a single complex of RV overdrive pacing at several different cycle lengths as indicated. Only minimal changes ("progressive fusion") are evident between pure tachycardia and pure pacing as the paced CL changes, mainly in lead 1. This is suggestive of macroreentry but not nearly as strong evidence as it could be.

Figure 24-7



In Fig. 24-7, we have another attempt at overdrive pacing at 540 ms (when the VT CL is still 550 ms) that now shows clear differences between pacing during VT and pure RV pacing (again, a single complex of pure RV pacing is superimposed). This is clearly evident in lead 1 (also present in leads 3, aVR, aVL) and now makes a strong case for macroreentry.

Left Ventricular Mapping and Pacing

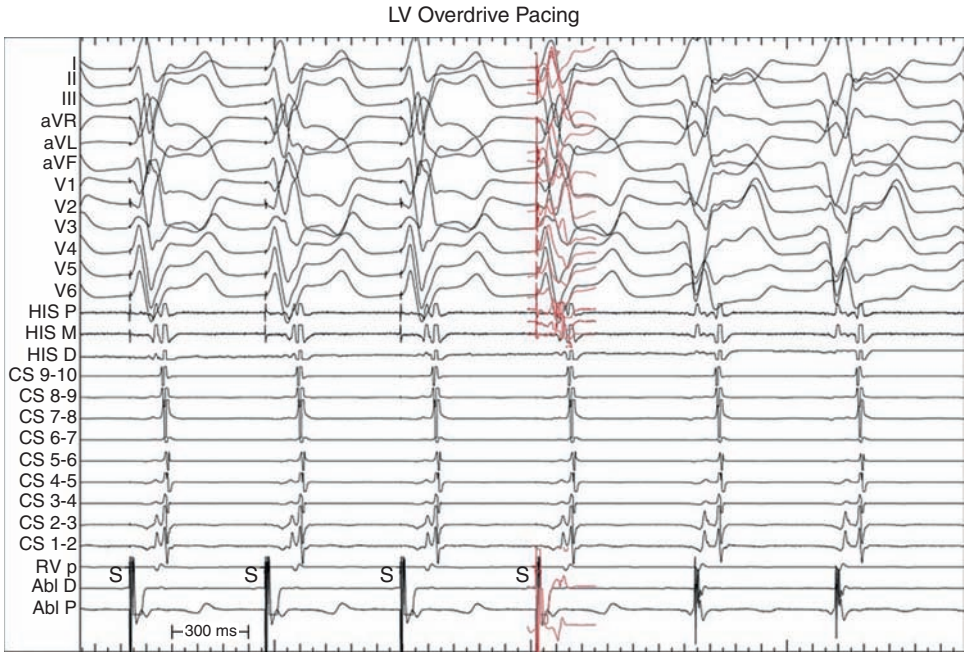
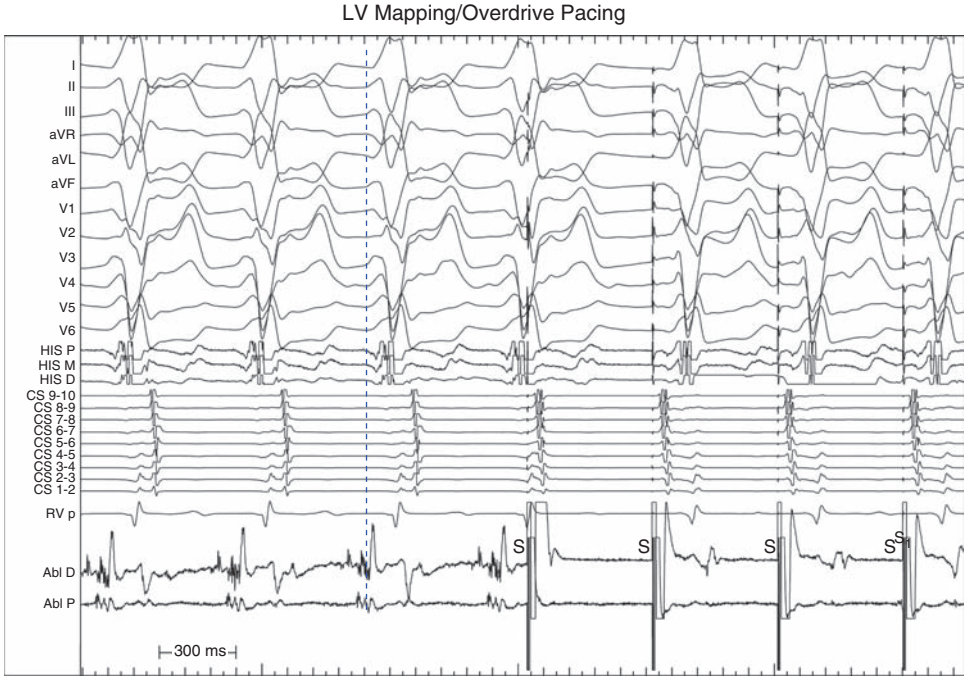


Figure 24-8

Another means of demonstrating fusion, and thus proving macroreentry, is to pace from different sites to accentuate differences between pure pacing and pacing during tachycardia. In Fig. 24-8, a site in the high lateral left ventricle is paced during VT, with a single complex of pacing from this site during sinus rhythm (superimposed in *red*) a few minutes later. Differences between the pure paced complex and those during VT are more marked than were evident with right ventricular pacing. Based on demonstration of fusion with different pacing strategies, macroreentry seems to be a secure diagnosis.

Figure 24-9



Having established a diagnosis of macroreentry, we can now search for a middiastolic electrogram as a reasonable ablation target site. In Fig. 24-9, a site in midlate diastole (*dashed line* denotes QRS onset) with marked fragmentation is shown. When attempting overdrive pacing at this site to determine whether it is a participant in tachycardia, the first stimulus results in termination of tachycardia without propagating to the rest of the heart *(arrow)*. If this is a reproducible phenomenon (ie, not spontaneous termination), it signifies that the site of stimulation is integral to the tachycardia circuit. After this stimulus terminates VT, further stimulation results in capture with a QRS configuration similar to VT, though not identical. Note also that the atrial recordings in the CS are accelerated to the paced CL and occur almost immediately after the stimulus artifact, indicating that there is direct atrial capture with stimulation (thus the catheter is very close to the mitral annulus).

Figure 24-10

In Fig. 24-10, pacing from the same site readily reinitiated the same VT. Of note, the paced QRS complex is similar, but not identical, to that during VT. Part of the difference may be because of atrial capture during stimulation resulting in P-wave distortion of the QRS onset; capture of ventricular tissue outside the diastolic corridor could also contribute to differences between paced and VT QRS complexes.

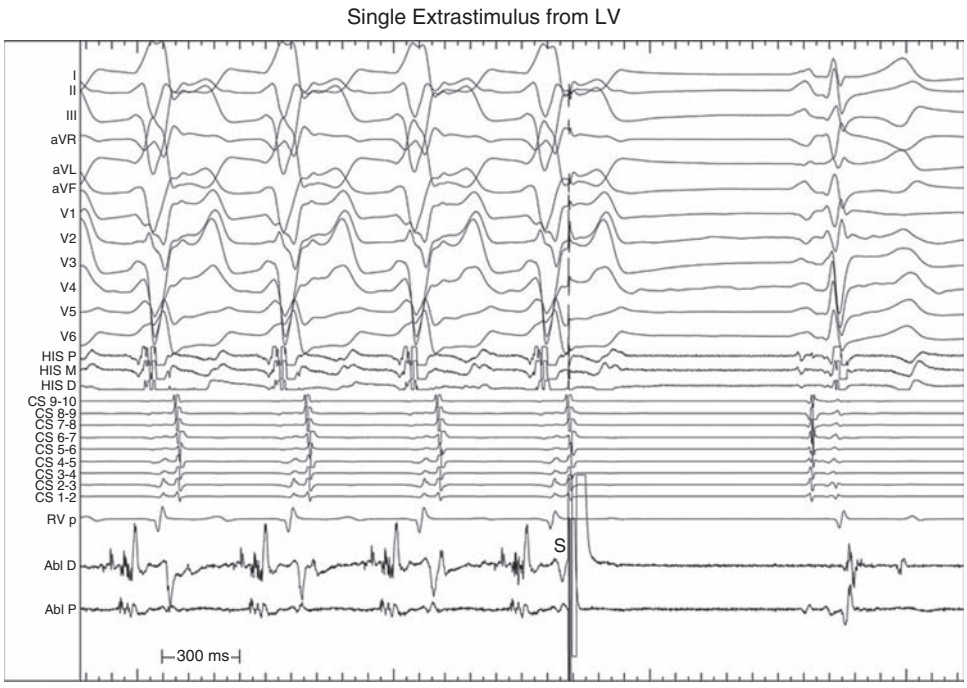
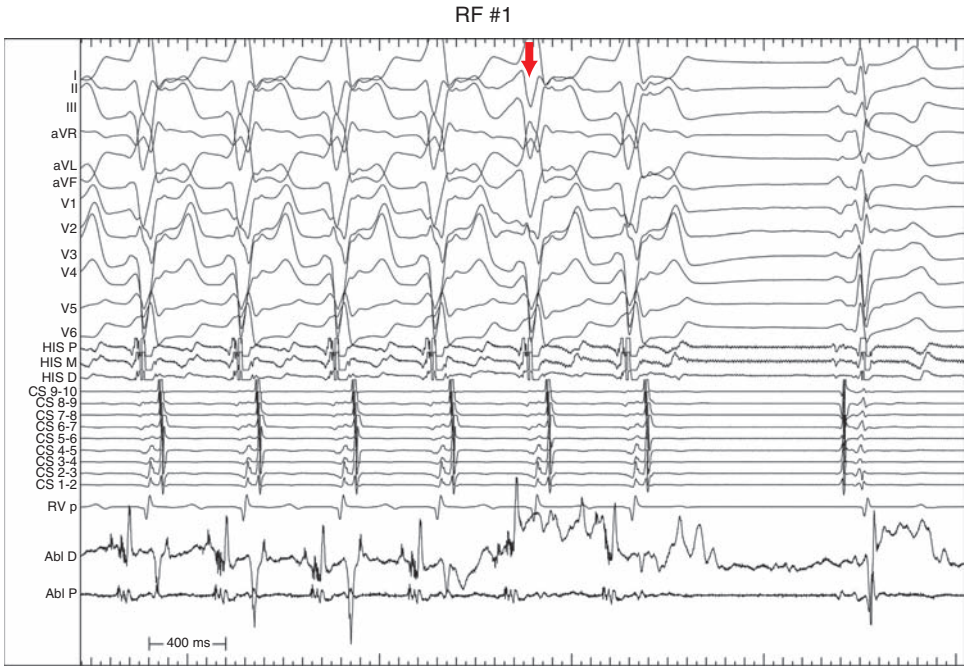


Figure 24-11

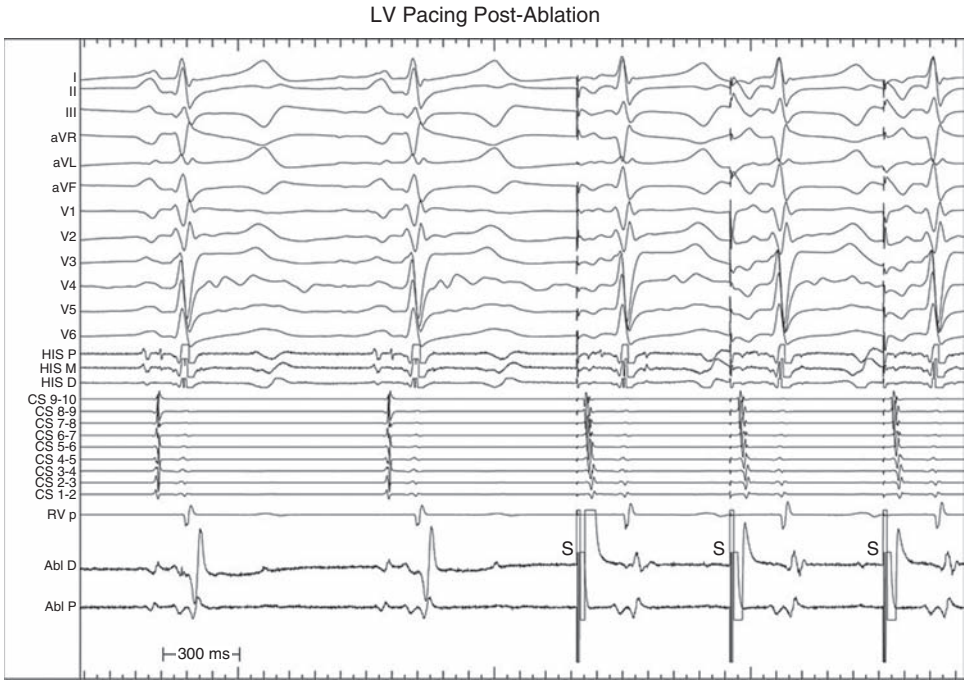
After VT was reinitiated, a single extrastimulus was delivered from the same location as in the prior figure; VT again abruptly terminates without propagation (Fig. 24-11). This sequence was repeated twice more, with the same results. This denotes that the site of stimulation is definitely within a critical isthmus of the VT circuit.

Figure 24-12



Based on the prior information that identified this site as being a critical part of the VT circuit, radiofrequency (RF) energy was delivered (*arrow*; Fig. 24-12). This resulted in termination of VT after <1 second.

Figure 24-13



As had been seen earlier, pacing from this site in the left ventricle can also capture the atrium—but here (Fig. 24-13), after ablation, only atrium is captured. This is despite there being a larger ventricular electrogram at the site in sinus rhythm. Before ablation, it was possible to capture ventricular muscle in this area, but ablation has damaged enough remaining muscle that local ventricular capture is not possible. Subsequently, a full stimulation protocol from the right ventricular site as well as a different left ventricular site (at which capture was feasible) resulted in no inducible VT. The patient has had no VT on follow-up.

Electroanatomic Mapping

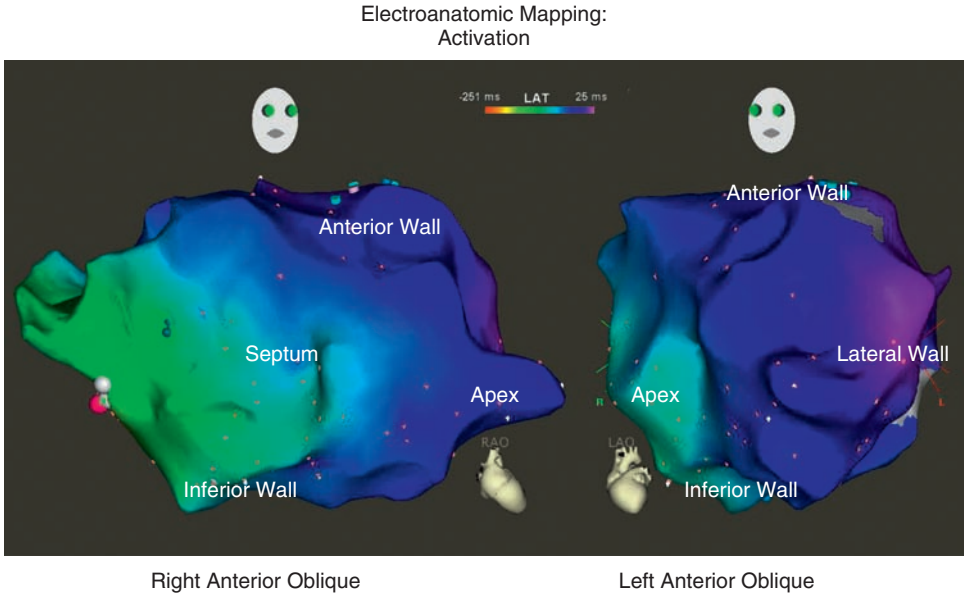


Figure 24-14

Fig. 24-14 (electroanatomic activation mapping) shows relatively late activation from standard right and left anterior oblique views because the pathology is on the inferobasal free wall.

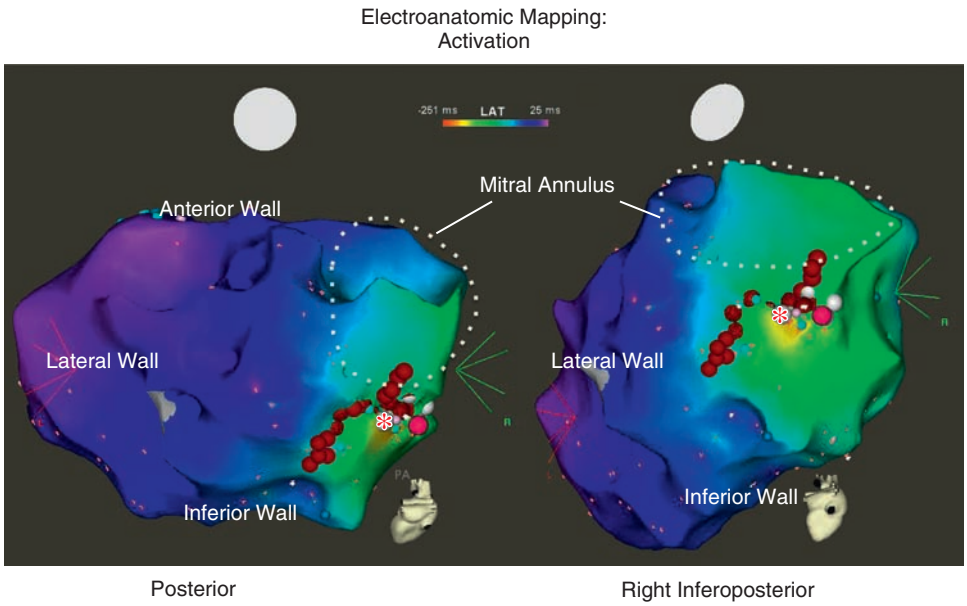
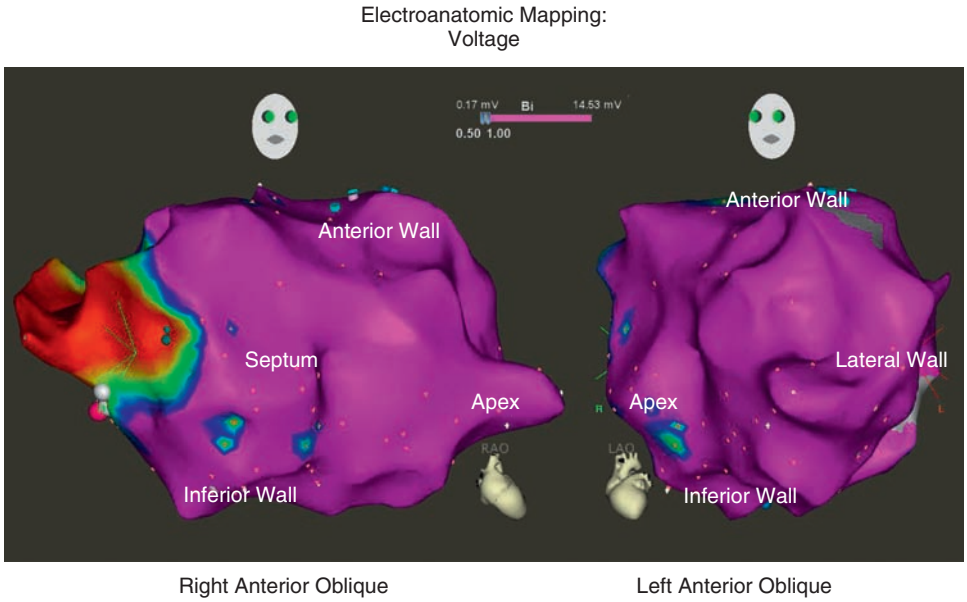


Figure 24-15

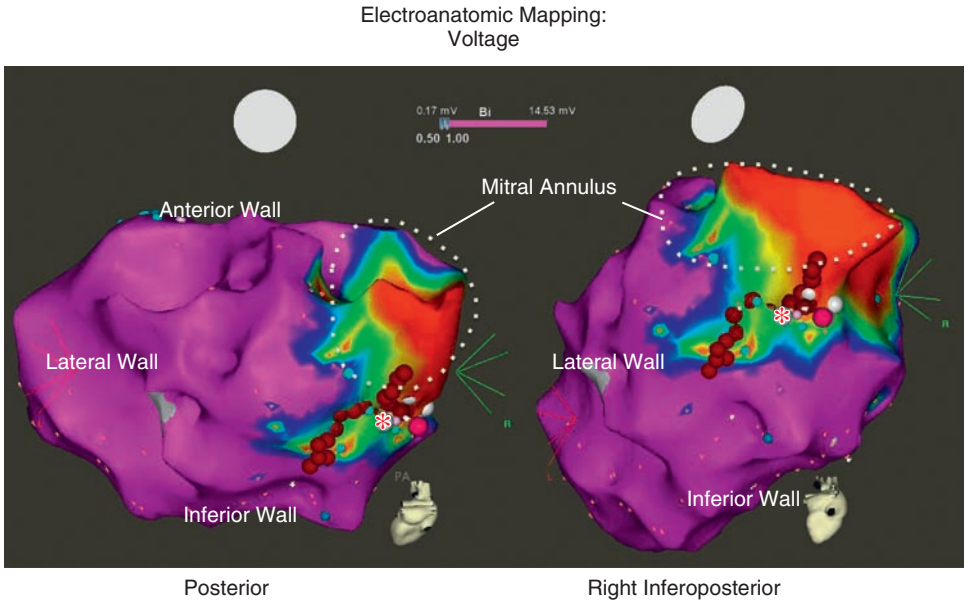
In Fig. 24-15, activation mapping viewed posteriorly shows the site of stimulation at which VT was terminated with a nonpropagated stimulus and where RF energy terminated it, rendering it noninducible thereafter *(asterisk)*. The *pink dot* denotes a site of pacemapping that yielded an excellent match with VT. *Red dots* denote sites at which RF energy was applied to connect the mitral annulus *(dashed line)* to more normal myocardium on the inferior wall (better seen on voltage map in Fig. 24-17).

Figure 24-16



In Fig. 24-16, electroanatomic voltage mapping shows some abnormalities at the basal left ventricle *(red)* in standard right and left anterior oblique.

Figure 24-17



In Fig. 24-17, voltage mapping viewed posteriorly again shows the site of stimulation at which VT was terminated with a nonpropagated stimulus and RF energy delivery *(asterisk)*. *Red dots* again denote sites at which RF energy was applied to connect the mitral annulus *(dashed line)* to more normal myocardium *(purple)* on the inferior wall.

Finally ECG

Interestingly, the final ECG during sinus rhythm (Fig. 24-18) shows no evidence of prior infarction—unusual in cases in which enough damage has occurred to result in relatively slow VT.

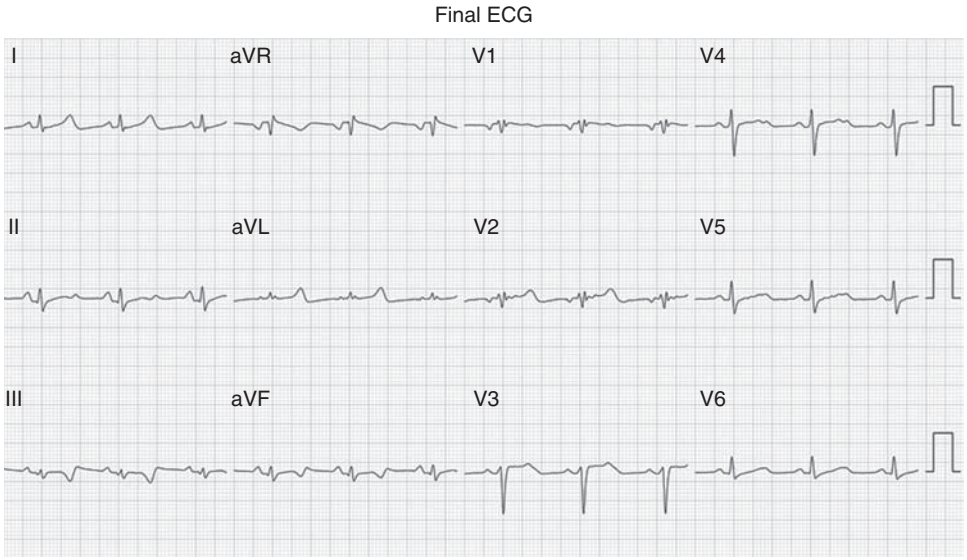


Figure 24-18

Summary

- It is important to determine the mechanism of VT before mapping and ablation in all cases, but especially:
  - In cases of incessant VT (which can be either focal or reentrant)
  - When there are unexpected findings (initiation of VT with atrial pacing or catecholamines)
- Overdrive pacing to determine presence or absence of fusion (and thus macroreentry) may yield data that are equivocal or require careful inspection to make correct conclusions
- Unanticipated diagnostic findings (nonpropagated stimulus terminating arrhythmia) may occur and should not be overlooked, because they have important implications regarding mapping and ablation

25 Focal Ventricular Tachycardia in the Postinfarction Patient

Case Presentation

A 56-year-old man with a history of myocardial infarction (MI) coronary artery bypass surgery had an implantable cardioverter-defibrillator (ICD) placed because of cardiac arrest several months after surgery. He began having episodes of palpitations and was found to have recurrent episodes of slow ventricular tachycardia. Medical therapy (beta blocker, a short course of amiodarone) failed to control episodes. Exercise stress testing 2 months earlier showed no evidence of residual ischemia. Left ventricular function was mildly depressed (ejection fraction 40%) with inferior wall motion abnormality; there was no ventricular thrombus. He was referred for electrophysiologic (EP) study catheter ablation.

Baseline Recordings

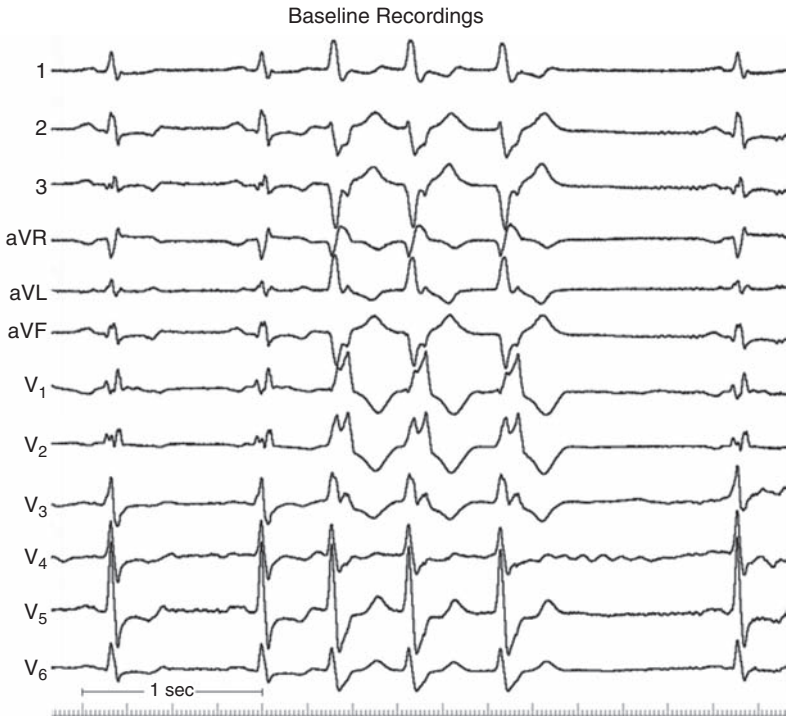


Figure 25-1

A recording of an episode of his typical VT morphology (right bundle branch block [RBBB], left superior axis, Fig. 25-1) was made before the EP procedure. VT starts spontaneously, with the initiating complex identical to all others, and the rhythm is slightly irregular before terminating. Although most VT in patients with prior MI is caused by reentry in the region of scar, the behavior of this VT is unusual for reentry, in which the initiating complex is often different from the rest of the VT complexes, and episodes tend

to be sustained and quite regular. The features of this patient's VT raise the question whether this could be a focal (automatic or triggered) process; this occurs in up to 9% of patients with prior MI. Foci are usually at the periphery of the scarred region. Further investigation is needed to sort out the mechanism of this arrhythmia because ablation-site characteristics (late diastolic signal) are very different from those of the usual macroreentry (middiastolic potential). The VT morphology suggests a left ventricular (LV) source; LV thrombus has already been excluded by echocardiogram (important information before placing a catheter in the LV).

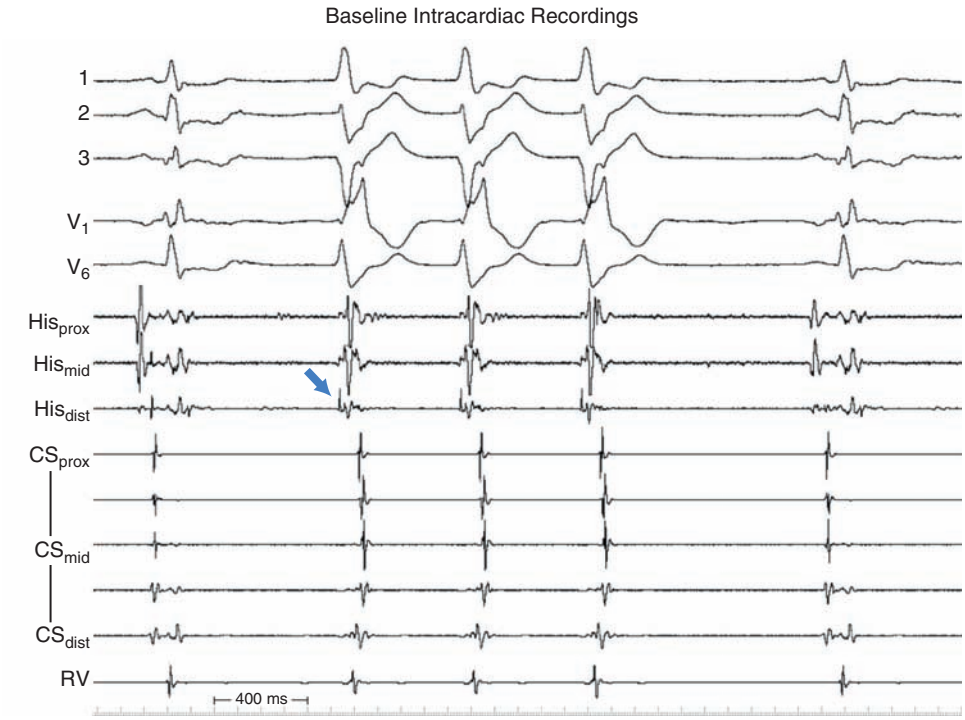


Figure 25-2

At the time of EP study, catheters were placed to be able to record and pace from atrium, His bundle region, and ventricle (Fig. 25-2). An episode of nonsustained VT is seen with corresponding intracardiac recordings. Retrograde conduction is present during VT, which (as seen before) starts spontaneously with the first complex identical to other VT complexes. The *arrow* points to a signal consistent with a His potential (also seen during the sinus rhythm complex at left). This raises the possibility that a focal fascicular tachycardia or reentry within the His-Purkinje system (HPS) could be operative, and the QRS morphology is reasonable for either of these.

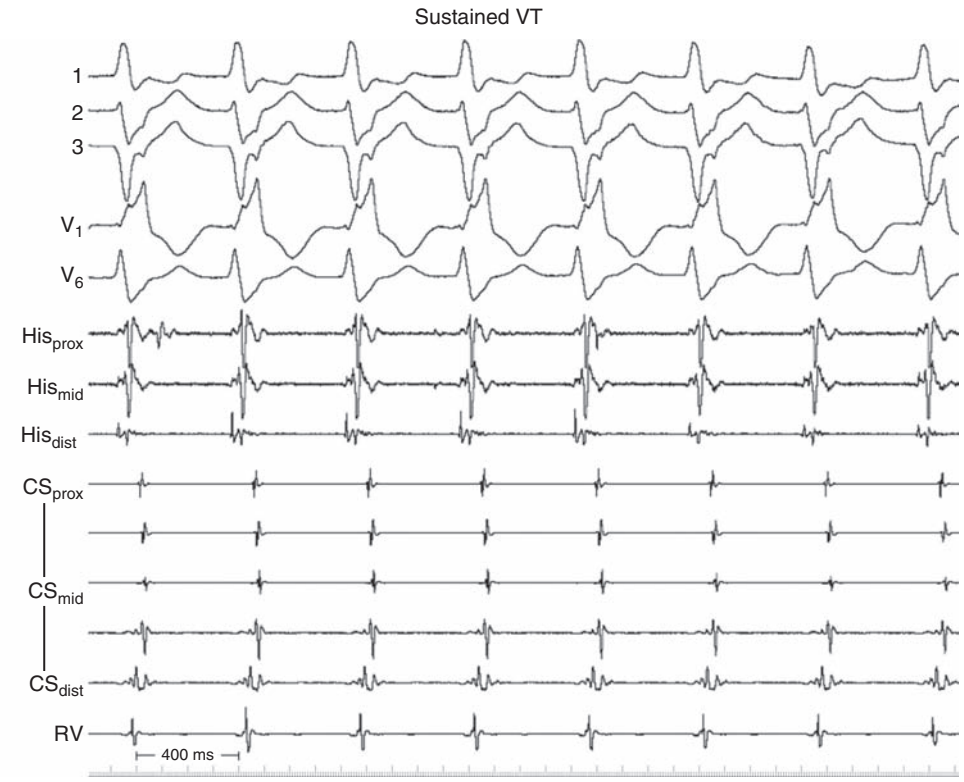


Figure 25-3

With isoproterenol infusion, VT became more sustained and slightly more regular (Fig. 25-3). This is again more consistent with a focal mechanism, but can occur with reentry.

Determining VT Mechanism

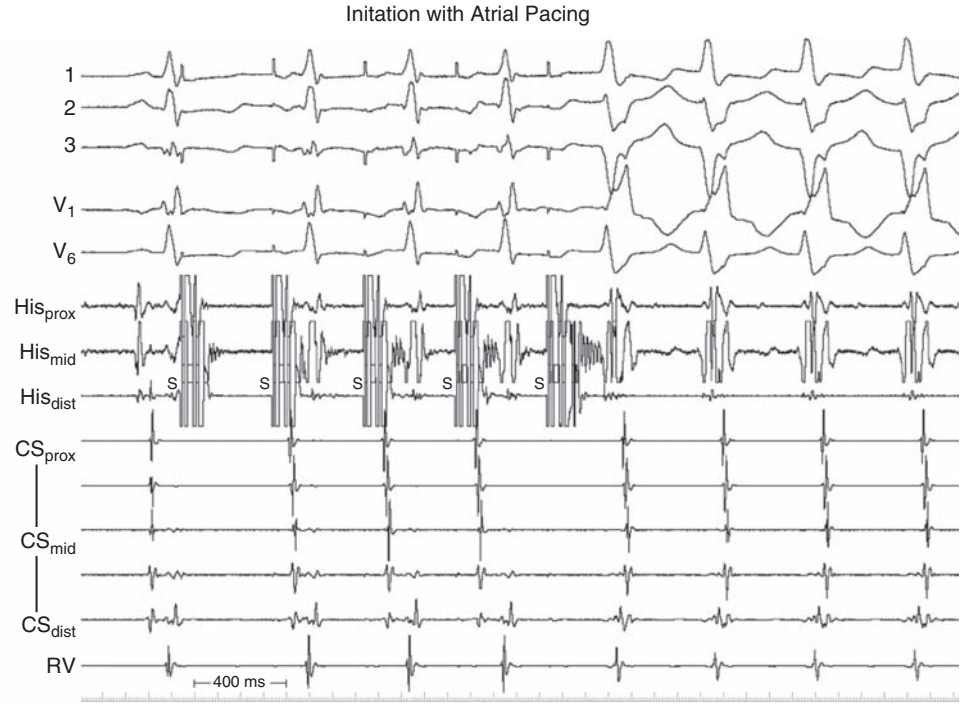


Figure 25-4

VT terminated spontaneously (not shown); in Fig. 25-4, atrial pacing initiates VT again. This was actually an attempt to pace the His bundle region to see if the resulting QRS complex was like that of VT, but instead of His or ventricular capture, only atrial capture

occurred and this initiated VT again (of five stimuli [S], only the middle three capture). This finding again favors a focal source of VT, but nothing is certain yet.

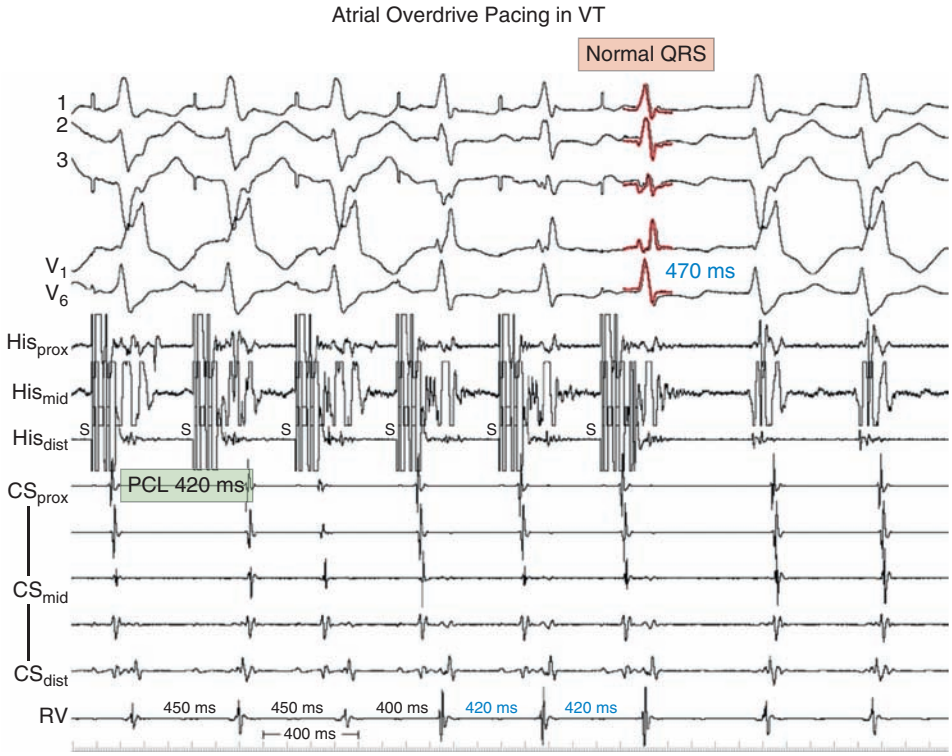
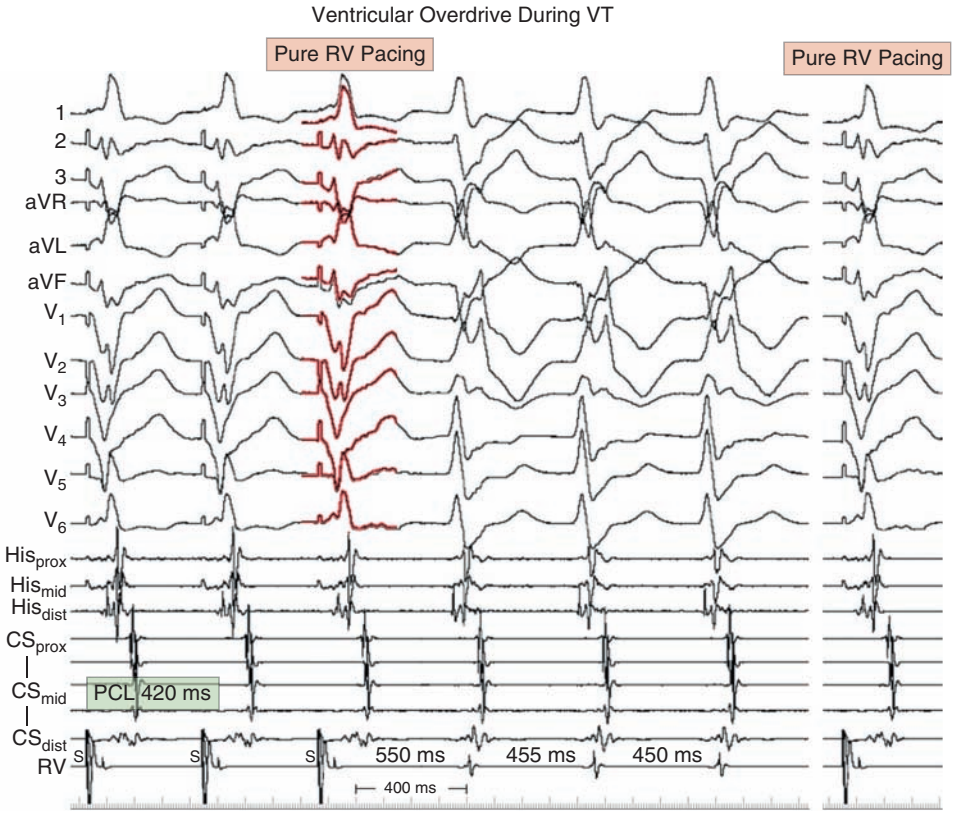


Figure 25-5

Another attempt at pacing from the distal His electrode during VT also results in atrial (not ventricular) capture (Fig. 25-5). Although the last four stimuli capture atrium, the last three affect the QRS complex by having some atrioventricular conduction, and after the last two stimuli, QRS complexes are identical to the sinus complex (superimposed in *red*). This indicates full control of the ventricles (also shown by RR intervals above the RV recording), and should terminate reentry within the HPS; however, the rhythm resumes after the last paced complex. The QRS-QRS interval at the first VT complex is 470 ms, just longer than the tachycardia cycle length (CL). Although HPS reentry is unlikely, a focal mechanism (fascicular or ventricular) is still quite plausible.

Figure 25-6



To try to determine VT mechanism more clearly, overdrive ventricular pacing is performed during VT. In Fig. 25-6, pacing from the RV electrode accelerates all complexes to the paced CL and the same VT returns on cessation of pacing. Although many would call this entrainment of VT, it is not possible to say just yet; fusion is necessary to declare that entrainment is present and thus diagnose macroreentry. Here, a single complex of pure ventricular pacing is shown at right, and is superimposed on a complex of pacing during VT; these appear to be identical. However, the absence of fusion on one attempt at overdrive pacing does not thereby diagnose a focal mechanism; one may have to pace at different CLs and different sites without showing fusion to more certainly diagnose a focal process. One additional feature to evaluate is the interval from last paced complex to first subsequent VT complex (the return cycle, here 550 ms); with reentry, this should stay constant no matter what CL or how many complexes of overdrive pacing are performed at the same site, but may show overdrive suppression with a focal mechanism when pacing faster or longer. Finally, the VT CL after resumption is usually the same as baseline with reentry but may be slower for a few cycles if overdrive suppression of a focus has occurred. Here, the VT CL is a little slower than baseline (450 ms). These again suggest a focal process.

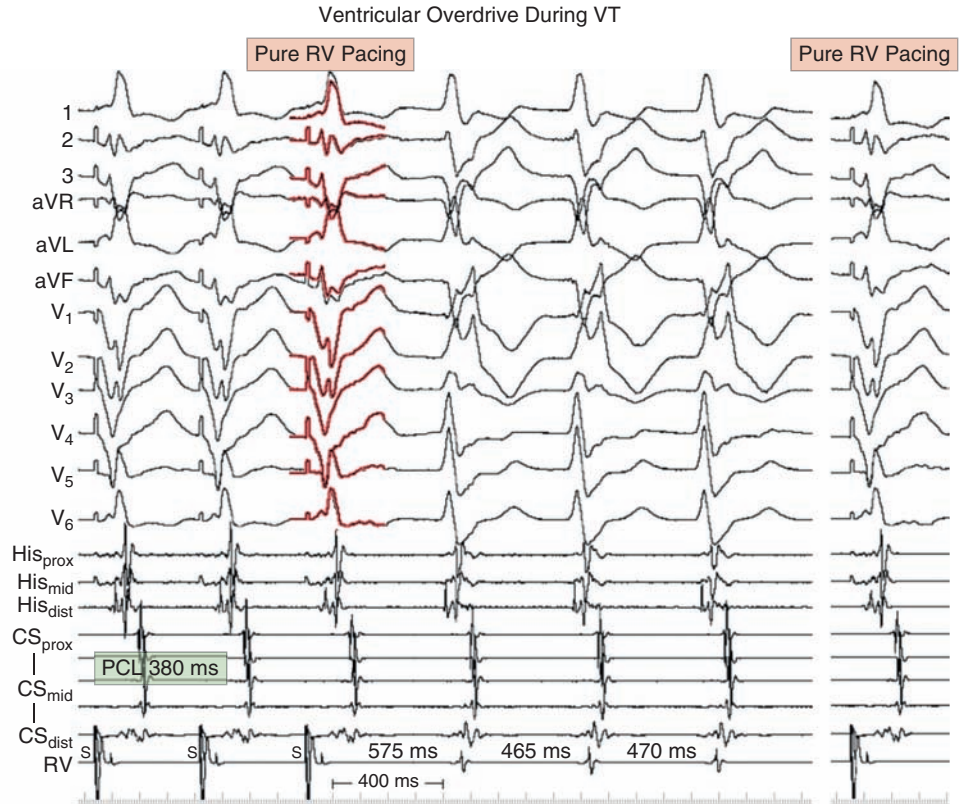
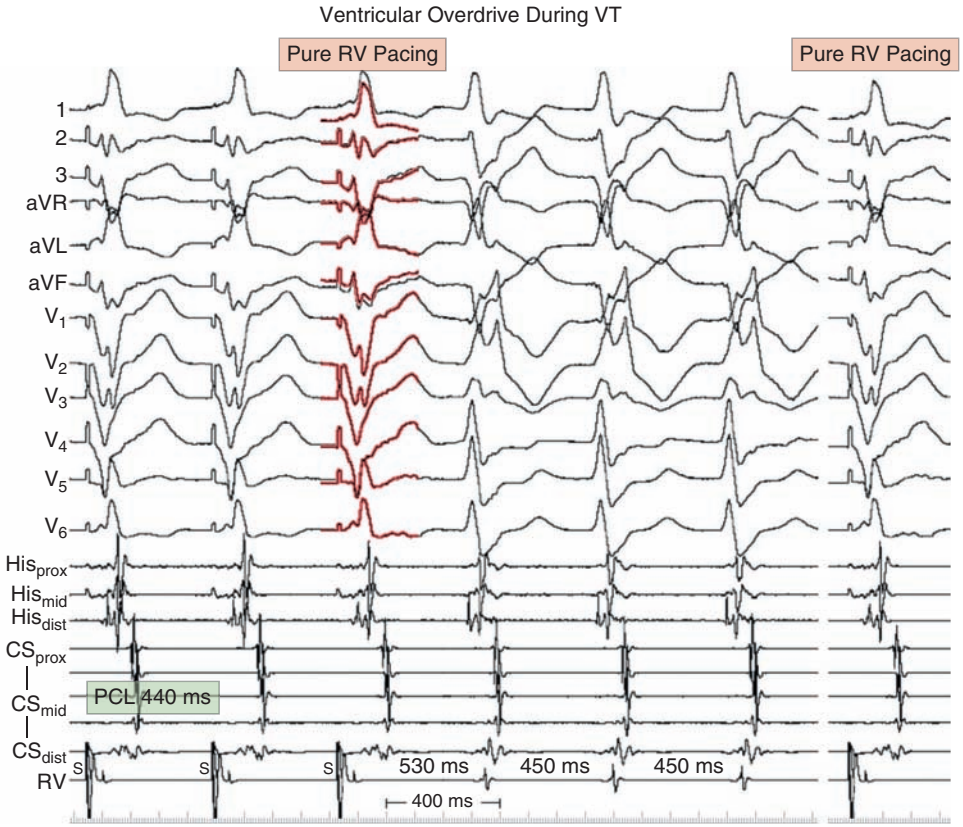


Figure 25-7

In Fig. 25-7, pacing during VT from the same site is performed at a faster CL (380 ms). The return cycle is longer than before (575 ms) and as shown the VT is slower as it resumes. These again suggest a focal process; there is again no fusion on the ECG during pacing, but one would not expect it even if macroreentry were present because if it were not seen at a slower paced CL it will not appear at a faster one. The best chance of showing fusion is to pace well away from where the anticipated exit site (or focus) is, and as close to the VT CL as possible to allow exit from the VT circuit to blend with the paced wavefront.

Figure 25-8



In Fig. 25-8, pacing is performed during VT as slowly as possible and still has capture (440 ms). This again shows no hint of fusion (all complexes look fully paced); the return cycle is shorter and the VT resumes at about the baseline CL. Two other pacing sites were used with the same outcome (not shown). All these data taken together (lack of fusion at multiple CLs and sites of pacing; appearance of overdrive suppression; transient slowing of resumed VT; initiation with atrial pacing) combined with the clinical behavior (irregular bursts of nonsustained VT with the first complex like all others) are very consistent with a focal, automatic process and nothing points to reentry. At this point, we can begin mapping, searching for a site with a late diastolic potential. Scarring around the site may produce some decrease in electrogram amplitude and a longer presystolic interval (50 to 80 ms) than is usually seen in VT in patients without structural heart disease (20 to 40 ms).

Mapping and Ablation

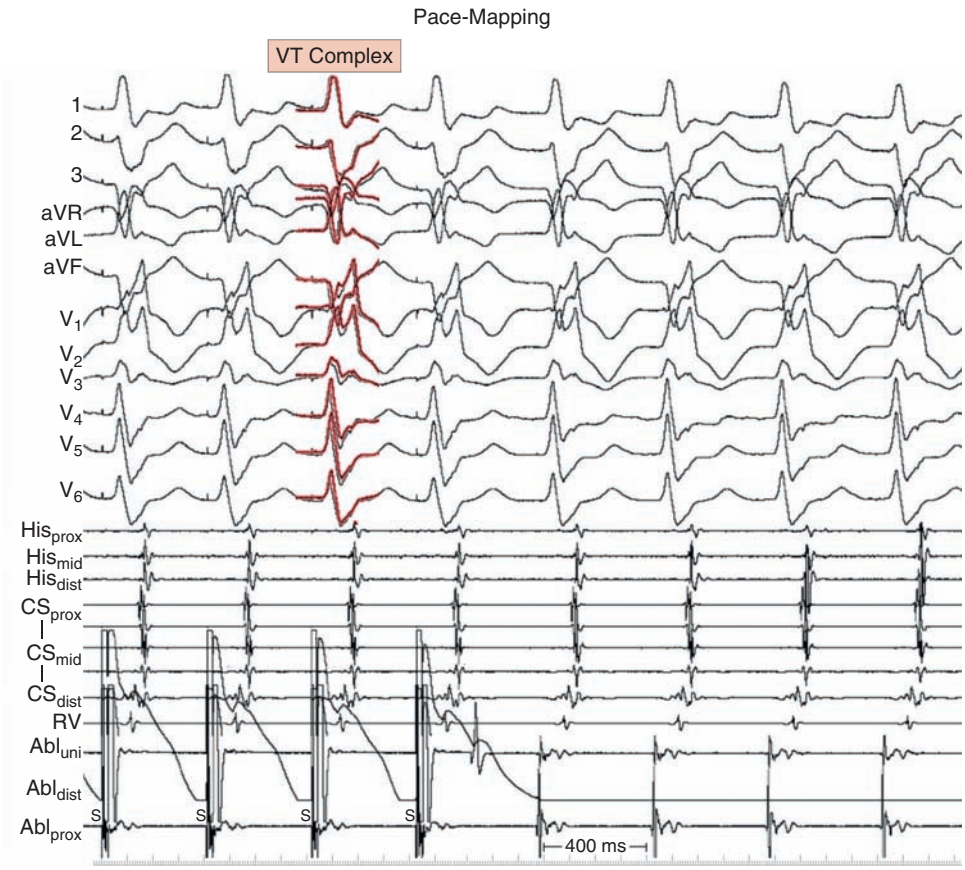


Figure 25-9

In Fig. 25-9, ventricular pacing is performed at a site with a late diastolic electrogram (not shown); a VT complex is shown in *red*, superimposed on a paced complex. Although the overall "match" is quite good, there are some slight differences (leads 2, V2 to V4). If one is pacing from the exact point of emanation from a focal arrhythmia, the resulting paced complex should ideally be identical. Mapping was continued without ablation at this site.

Figure 25-10

In Fig. 25-10, recordings from a site in the inferior LV are shown; the *dashed line* denotes the onset of the surface QRS complex. The distal ablation recording is complex and has a very small component *(blue arrow)* at its onset that is about 60 ms before QRS onset. It is possible that this small component represents a Purkinje potential (and thus the VT would be a focal fascicular tachycardia); VT was incessant at this point; thus it was impossible to know what the site looked like during sinus rhythm (ie, whether a Purkinje potential was present then). Of note, no such potential was evident after restoration of sinus rhythm with ablation, and the lack of an isoelectric interval between the small potential and the main portion of the local electrogram suggests that this is ordinary myocardium rather than fascicular tissue at the source.

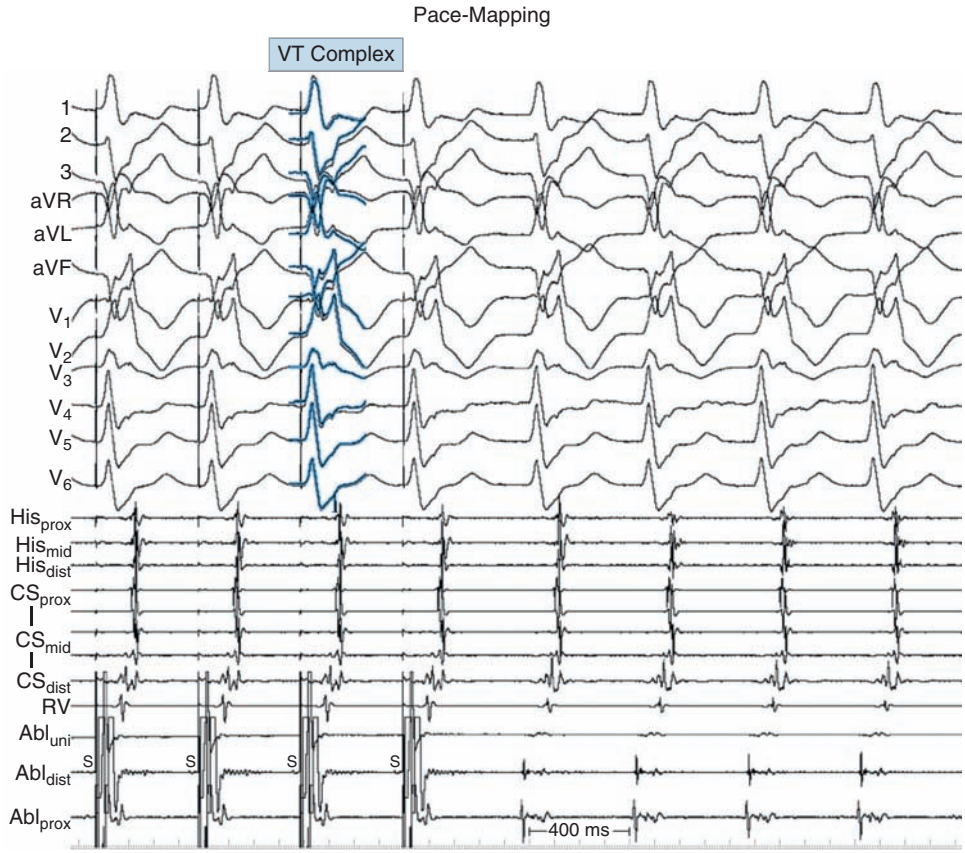


Figure 25-11

In Fig. 25-11, pacemapping is performed from the site shown in Fig. 25-10 to corroborate it as a reasonable site for ablation. As before, a VT complex is superimposed (in *blue*) over a paced complex, showing a perfect "match" with the VT. The stimulus-QRS interval is slightly less than the electrogram-QRS interval during VT, probably signifying the pacing was performed at a slightly excessive output (capturing some tissue beyond the actual focus). Similar to what was observed when pacing at a different site, although VT resumes after stopping pacing, this cannot be considered to be concealed entrainment because to do so, fusion (manifest entrainment) has to be demonstrated at some other time (but could not be in this case because macroreentry is not present).

Figure 25-12

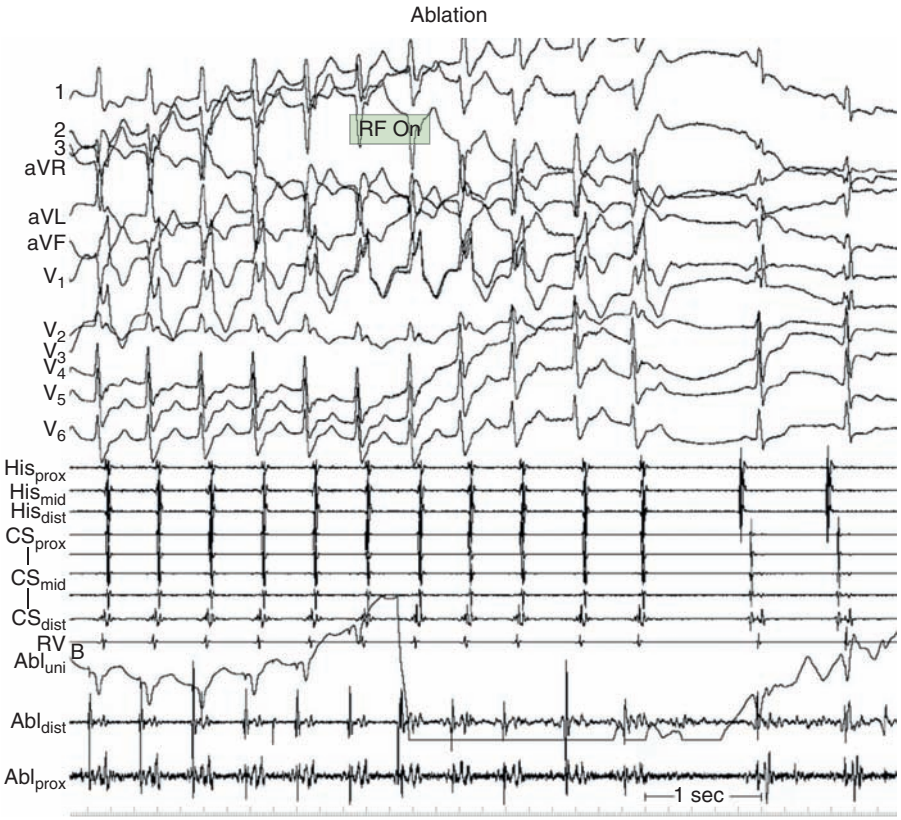
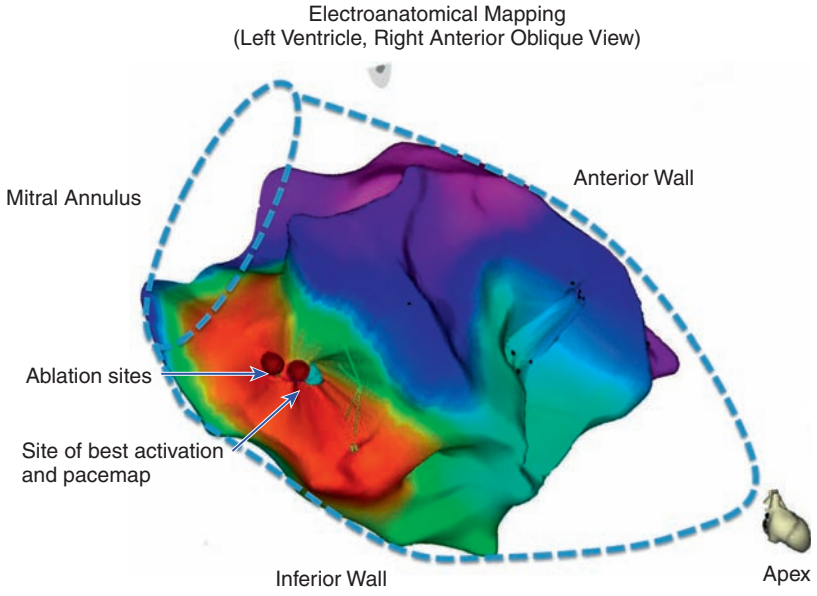


Fig. 25-12 shows the onset of ablation delivered during VT. Less than 3 seconds after the beginning of RF application, VT abruptly ceases after slight acceleration and then slowing. VT could not be initiated thereafter with atrial or ventricular pacing, nor increased isoproterenol infusion.

Figure 25-13



A partial endocardial electroanatomic activation map of the LV made during VT is shown, with an idealized outline of the LV in the left anterior oblique projection (Fig. 25-13). As can be seen, the focus was on the inferior basal portion of the left ventricle.

Summary

- In patients with prior myocardial infarction, a focal mechanism is present in up to 9% of VTs that are induced during electrophysiology study
- Focal VTs often occur in irregular bursts spontaneously or are initiated with atrial pacing, facilitated by catecholamines
- Careful investigation must be performed to ascertain whether a focal process is involved in VT when its behavior is atypical for reentry
- Mechanistic distinction from more typical macroreentrant VT in this population is important because ablation-site characteristics are very different

26 Focal Epicardial Ventricular Tachycardia

Case Presentation

A 38-year-old man was resuscitated from cardiac arrest at home. Ventricular tachycardia (VT) or ventricular fibrillation (VF) was initial rhythm, shocked to sinus, and then "sinus tachycardia with right bundle branch block (RBBB)." His history revealed significant alcohol intake, though none recently. He had been nauseated and bloated for 4 to 6 weeks before the event and had palpitations. Treatment included intravenous (IV) Amiodarone and repeated cardioversions for VT (not "sinus tachycardia with RBBB"); lidocaine was added (with no effect). He was maintained during VT on dopamine and then placed on a cooling protocol. ECG revealed severely dilated left (LV) and right ventricle (RV) with LV ejection fraction 15% to 20%. Catheterization showed a normal left coronary, but could not engage right coronary. VT persisted despite continued amiodarone infusion. Progressive hypotension was refractory to vasopressin, epinephrine and intra-aortic balloon pump.

Baseline VT ECG

The Most Likely Mechanism Is

A. HPS reentry
B. Myocardial reentry
C. Myocardial focus

Figure 26-1

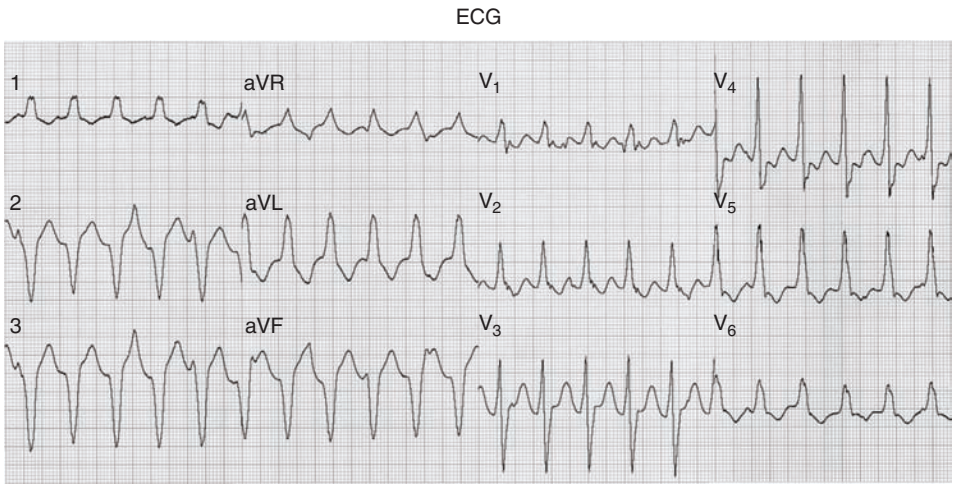
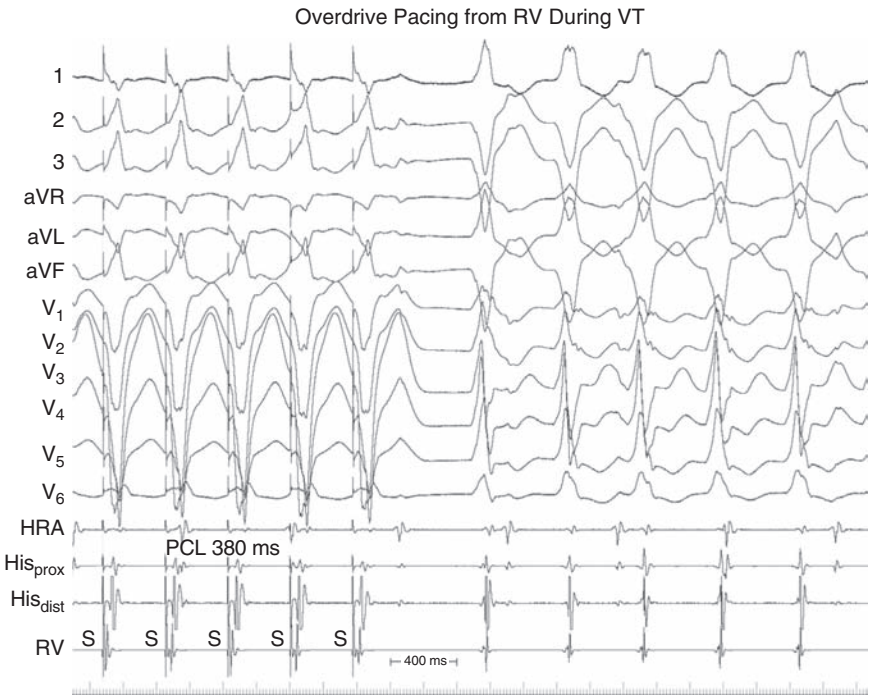


Fig. 26-1 shows a 12-lead ECG of the presenting arrhythmia, diagnosed as VT with AV dissociation (inferior leads) and standard morphologic criteria. The pattern is most consistent with a myocardial source rather than His-Purkinje reentry (which should generally resemble aberrant conduction patterns), but whether this is a focus in the myocardium or exit from a circuit cannot be determined from the ECG.

Overdrive Pacing from RV During VT



The Most Likely Mechanism Is

A. HPS reentry
B. Myocardial reentry
C. Myocardial focus

Figure 26-2

Once electrode catheters had been positioned, overdrive pacing was performed from the right ventricular catheter. Pacing was initiated during tachycardia, all electrograms were accelerated to the paced cycle length, and upon cessation of pacing, the same tachycardia resumed (Fig. 26-2). Although many would call this an example of entrainment, one essential piece is missing: fusion. It is difficult to demonstrate fusion with a single example of overdrive pacing during a tachycardia, and without demonstrating fusion, it is difficult to make a diagnosis of macroreentry. Making this distinction (macroreentry vs a focal process) is critical, because the characteristics of the ablation site are dictated by which mechanism is involved (late diastolic potential for a focal process, mid-diastolic potential for macroreentry).

What Do You Want to Do Now?

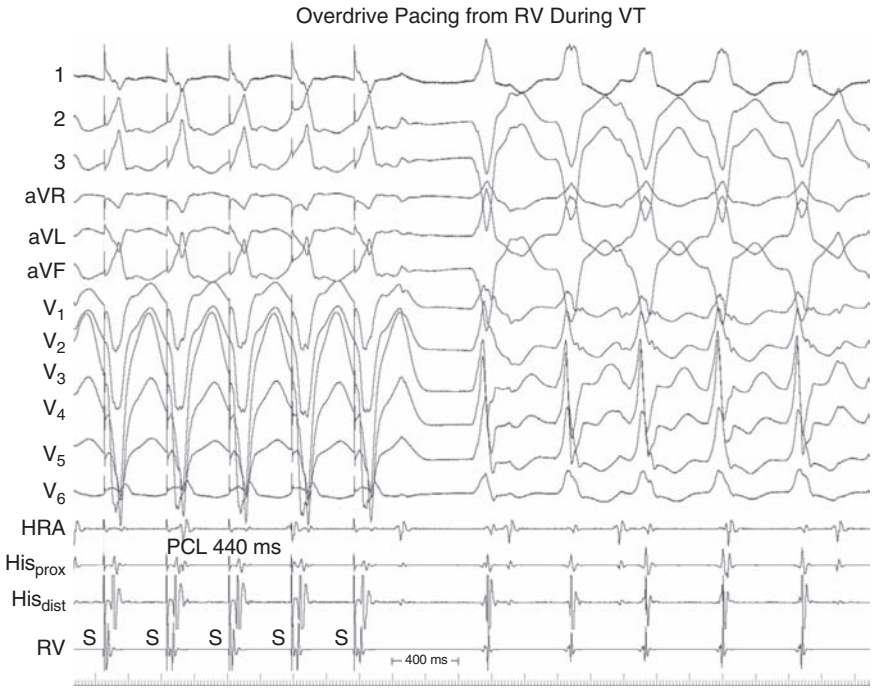


Figure 26-3

One way to ascertain whether fusion is present or not is to pace from the same site at different cycle lengths; the slower the pacing rate (closer to that of tachycardia), the more opportunity there will be to demonstrate fusion, and as the cycle length of pacing changes, the resultant QRS complex (particular blend of pacing vs VT) will change in the presence of macroreentry. In addition, selection of a pacing site can be very helpful: if the pacing site is close to the anticipated exit site of the tachycardia, it will be difficult to demonstrate fusion, whereas if a site is chosen far away from the anticipated exit zone, fusion will be more readily demonstrated. When presented with a RBBB, left superior axis VT, a pacing site was chosen that would produce a LBBB, right inferior axis complex—such that, if fusion were possible, it would certainly be evident when pacing during VT from such a site at a slow cycle length. However, if the VT is because of a focus, there will never be any evidence of fusion, and overdrive pacing from a remote site will always look like pure pacing from that site, no matter what stimulation rate is chosen. In the example shown in Fig. 26-3, pacing is performed at a cycle length (440 ms) just 30 ms shorter than the VT cycle length, yet the complexes during pacing appear to be identical to those when pacing at a more rapid cycle length (380 ms). In addition, the interval from the last paced complex to the first beat of VT that resumes is relatively long compared with the VT cycle length. This would be unusual for macroreentry, but not for an automatic focus that exhibits some degree of overdrive suppression of excitability.

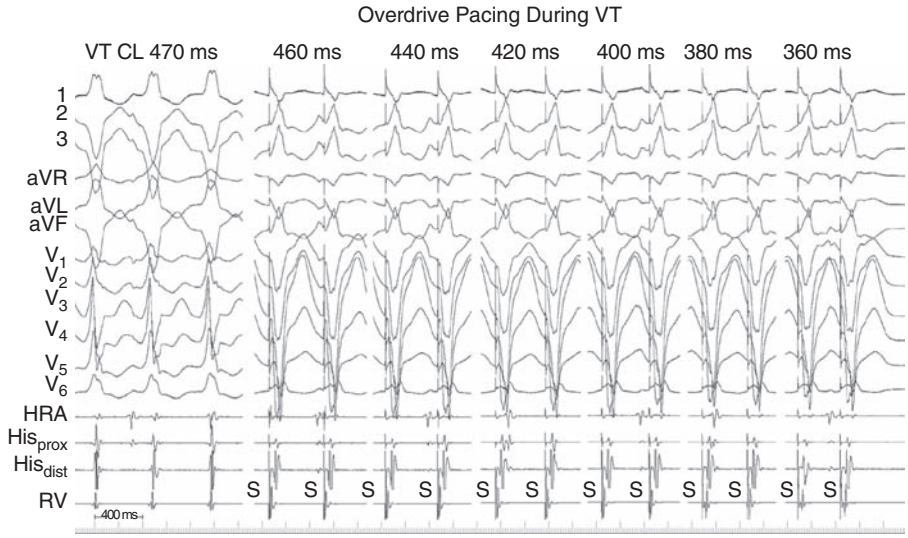


Figure 26-4

In Fig. 26-4, all 12 ECG leads of VT are shown at *left* (470 ms cycle length) as well as 2 complexes of pacing from the right ventricular outflow tract during VT at several different cycle lengths (including 460 ms, just 10 ms faster than the VT). It is evident that, no matter what cycle length of pacing during VT is used, QRS complexes are identical, indicating absence of fusion and strongly suggesting that macroreentry is not present (thus, a focal process). This evidence, taken with the suggestion of overdrive suppression as well as centrifugal pattern of electroanatomic activation mapping (shown later), led to a diagnosis of a focal ventricular tachycardia.

Mapping and Pacemapping

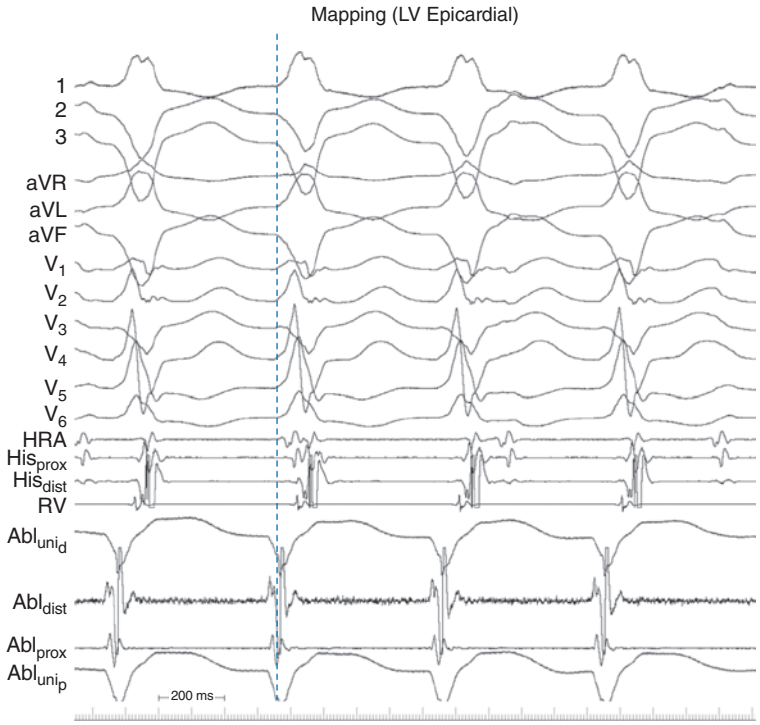


Figure 26-5

Having established a diagnosis of a focal VT, a site is sought with late diastolic activation (20 to 40 ms before the QRS onset), and a "QS" configuration in the unipolar recording. Thorough and extensive mapping of both right and left ventricular endocardial surfaces did not reveal any sites with timing before the QRS onset. With the "QS" configuration in the inferior ECG leads, in the absence of known infarction, pericardial access was obtained for epicardial mapping. The electrogram shown in Fig. 26-5 is from a site on the inferior left ventricular wall, halfway between apex and base, on the epicardial surface. Its features match those of the ideal target site noted previously; the QRS onset is denoted by a *dashed line*.

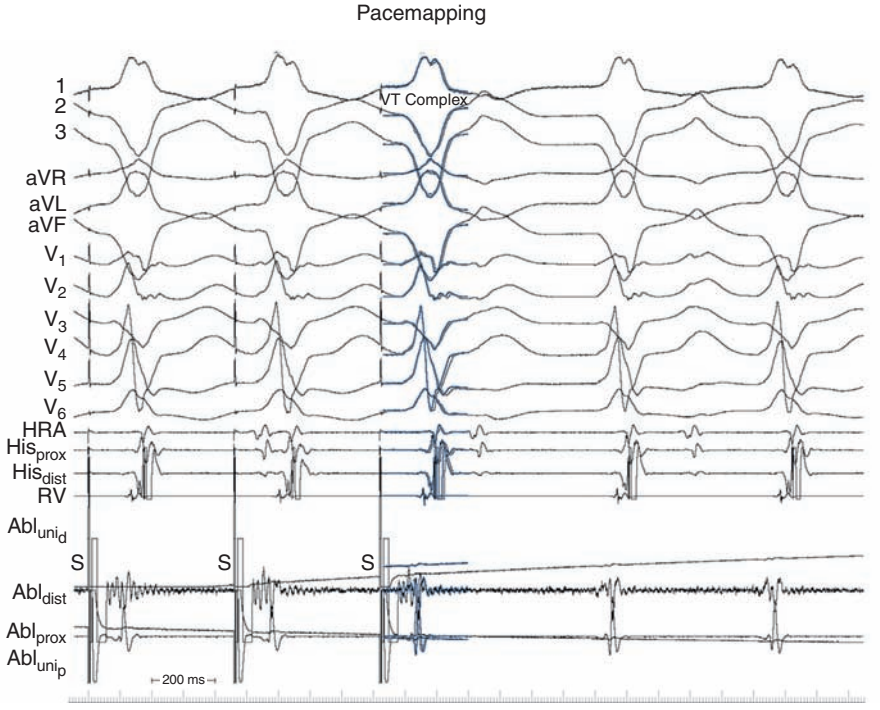


Figure 26-6

Pacing at this epicardial site (Fig. 26-6) produced a perfect 12-lead ECG (and intracardiac) match with a VT complex (superimposed in *blue*). This corroborates the activation mapping information. Note a relatively short stimulus-QRS interval, also consistent with a focal process.

Ablation and Postablation Pacing at Site

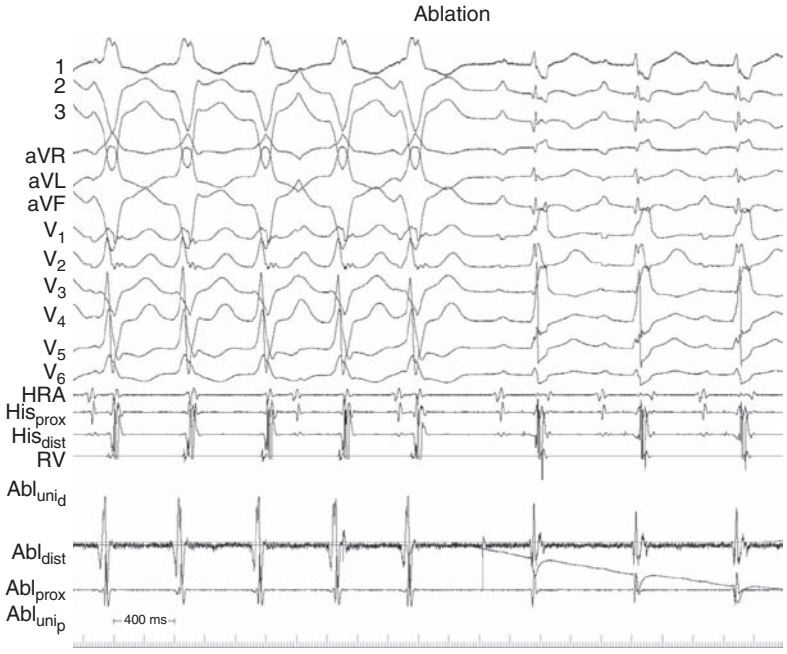
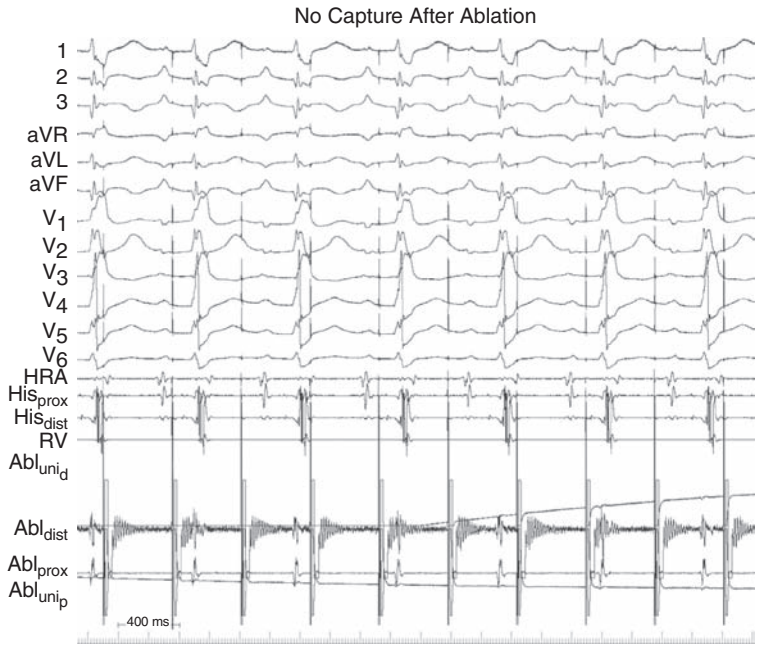


Figure 26-7

During radiofrequency (RF) energy delivery at the site of earliest activation mapping, tachycardia abruptly terminates to sinus rhythm (Fig. 26-7). The arrhythmia did not recur. Several other RF applications were administered in the same area to consolidate the damage.

Figure 26-8



High-output stimulation at the site of ablation shows inability to capture, indicating destruction of excitable tissue in that area (Fig. 26-8). The patient had no further arrhythmias during the course of his hospitalization, during which left ventricular function gradually recovered almost completely (ejection fraction 40% to 45%). He regained full neurologic function and was discharged home.

Before ablation, it is usually important to perform coronary arteriography to avoid injury to a nearby vessel during RF delivery; in this case, because the patient was unlikely to survive unless the VT was controlled, right coronary arteriography was not performed before RF delivery but was done later in the procedure, showing >1 cm from the ablation zone to the posterior descending artery.

Electroanatomic Mapping (Activation and Voltage)

Figure 26-9

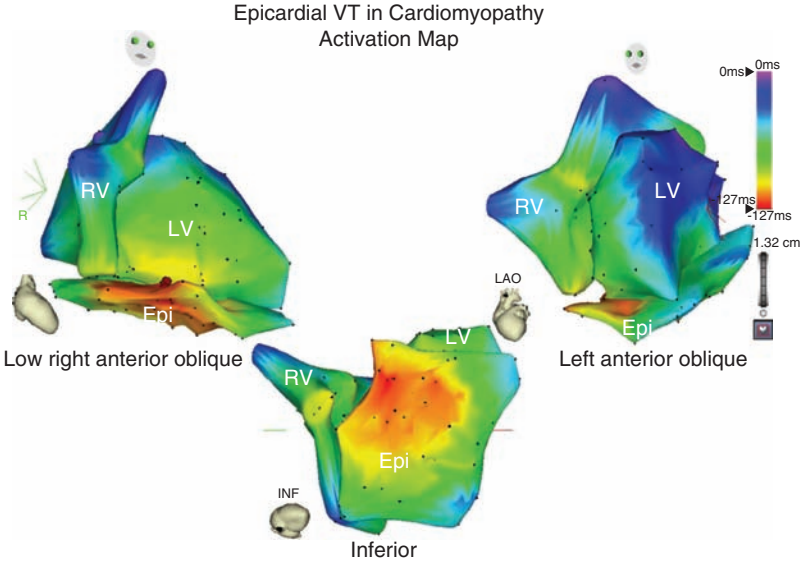


Fig. 26-9 displays electroanatomic activation mapping during ventricular tachycardia of right and left ventricular endocardial surfaces as well as the epicardial surface. *Red coloration* indicates the region of earliest activation, on the inferior wall at the junction of right and left ventricles.

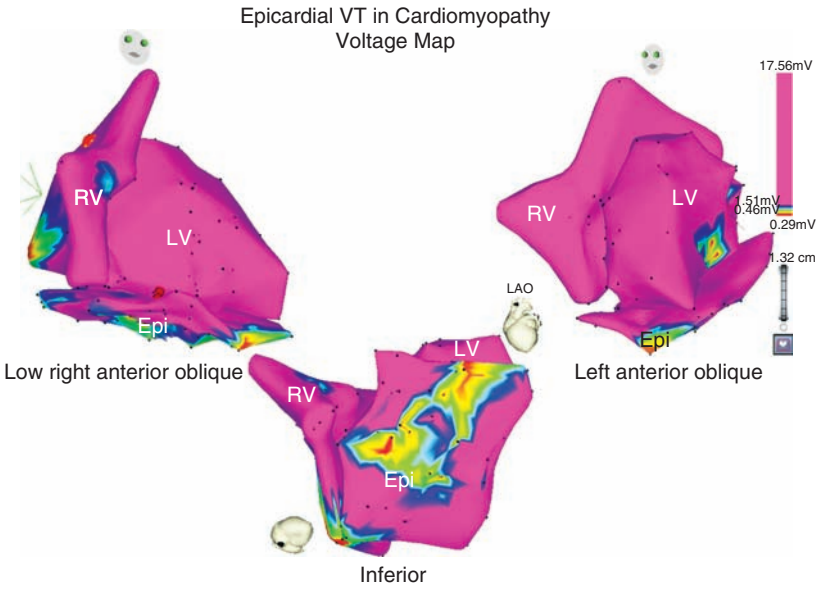


Figure 26-10

Electroanatomic voltage mapping of right and left ventricular endocardium, and epicardial surface of the inferior wall are shown in Fig. 26-10. *Purple color* indicates normal voltage; *red,* very low voltage/scar. The latter was limited to a very small area on the inferior wall of the left ventricle.

Summary

- Patients with nonischemic cardiomyopathy may have different types of VT:
  - Myocardial macroreentry—endocardial versus midwall versus epicardial
  - His-Purkinje reentry (bundle branch reentry [BBR])
  - Focal discharge (myocardial, Purkinje)
- Investigation and mapping attention should be focused:
  - To determine VT mechanism, thus how the ablation target should appear
  - At areas of low voltage/scar (perivalvular)
  - At His-Purkinje system (possibility of BBR)
- Electroanatomic mapping can help:
  - Determining areas of prior damage/scar
  - Delineation of potential channels for ablation
  - Tag sites with abnormal potentials for subsequent targeting
  - Planning and constructing lines of ablation

27 Ventricular Tachycardia in Dilated Cardiomyopathy

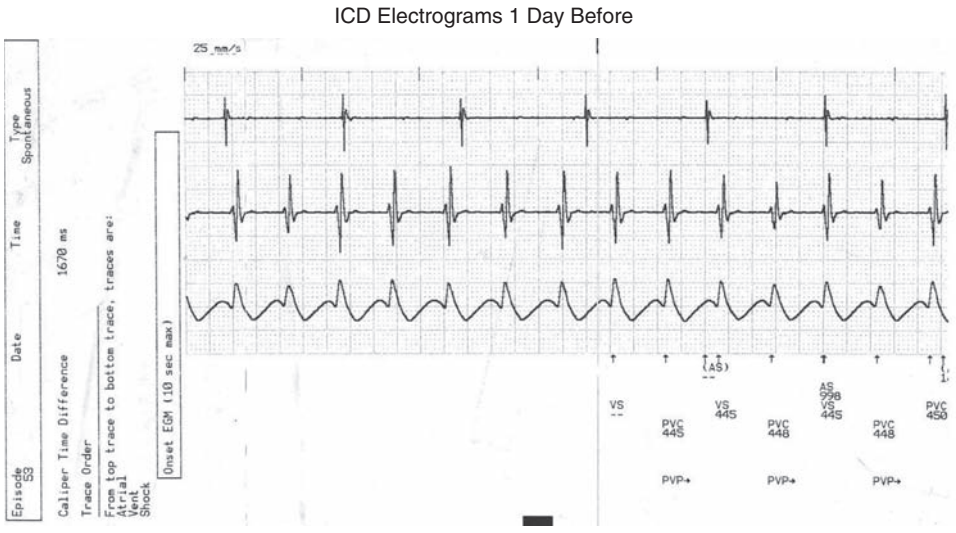
Case Presentation

The patient was a 74-year-old man with increasingly frequent implantable cardioverter-defibrillator (ICD) shocks. In 2009, poor left ventricular (LV) function was noted in the setting of prior (small) myocardial infarction (MI). Single-chamber ICD was implanted (primary prevention). In 2012, there was the first appropriate shock for ventricular tachycardia (VT), and amiodarone was initiated. There were more palpitations and shocks. Antitachycardia pacing (ATP) was modified, and there were more episodes and shocks. Mexiletine was added to amiodarone. There were more palpitations and shocks. In 2014, he was referred for electrophysiology (EP) study and possible ablation. Echocardiogram revealed poor LV systolic function (diffuse); there was no LV thrombus. ICD interrogation: repeated episodes of VT, cycle length (CL) 440 ms, not terminated with ATP (requiring shock).

ICD Stored Electrograms from 1 Day Before Ablation

What Else Do You Need to Know Preprocedure? [Fig. 27-1]
What Will Be the Procedural Strategy?

Figure 27-1

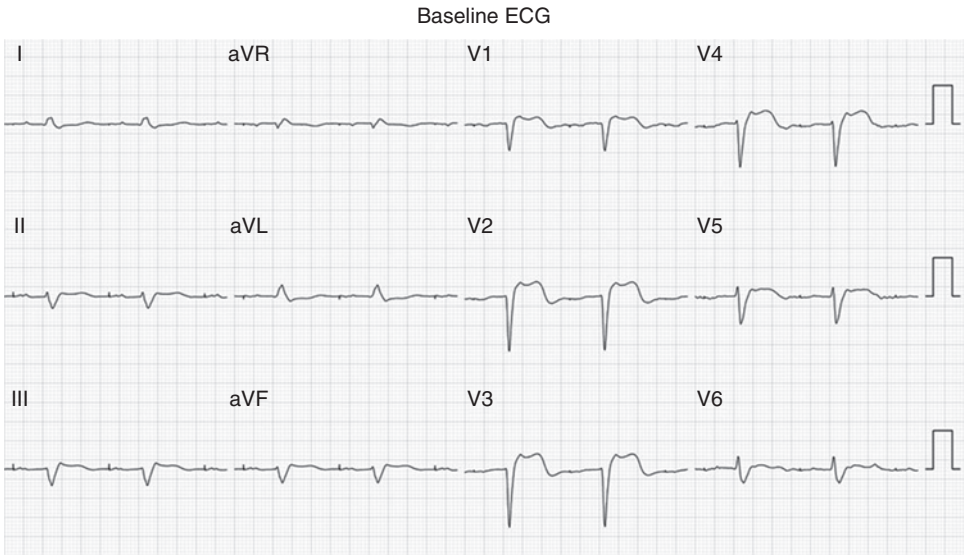


What other studies might be useful? Echocardiogram (exclude LV thrombus, demonstrate regional wall motion abnormalities) or magnetic resonance imaging (identification of scar regions), if your institution will do these in patients with ICDs.

ICD electrograms (Fig. 27-1) can be useful to sort out which of possibly several induced arrhythmias at EP study "match" the spontaneously occurring VT.

Which catheters to use? CS can be helpful for anatomic/fluoroscopic landmark as well as showing interesting electrograms in cases of VT arising from the basal region.

Baseline ECG and Intracardiac Recordings



Can You Interpret as far as Infarction? [Fig. 27-2] Anything to See?

Figure 27-2

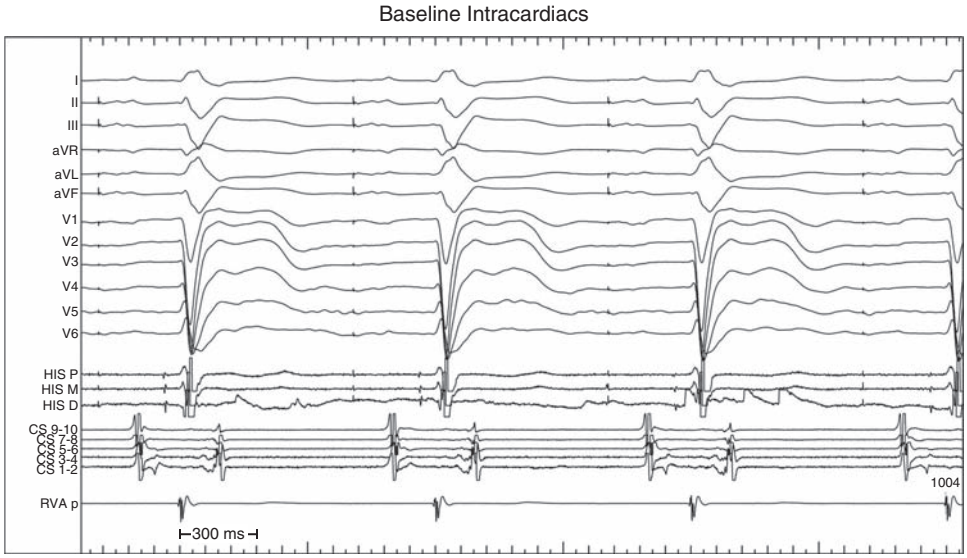


Figure 27-3

ECG during atrial pacing with conduction (Fig. 27-2) shows a wide QRS without clear infarct pattern. Ventricular electrograms (Fig. 27-3) on coronary sinus recordings are very late in the QRS complex—maybe it means something, maybe it doesn't.

Ventricular Pacing Baseline

Is Retrograde Conduction Present? [Fig. 27-4]

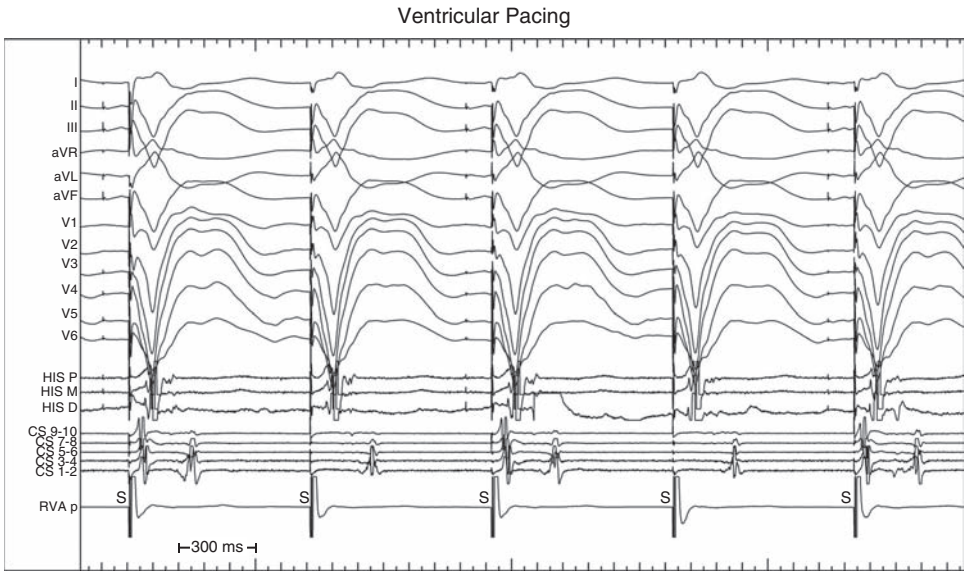


Figure 27-4

Potentials in the coronary sinus recordings that follow each QRS shown in Fig. 27-4 are actually very delayed ventricular signals, not atrial. True atrial signals are driven by atrial pacing from the ICD, and occur immediately after 1st, 3rd, and 5th ventricular stimulus artifact. Thus although retrograde conduction is probably not present, it is difficult to interpret.

VT Initiation and Attempt to Terminate

Is This the VT We're Looking For? [Fig. 27-5]

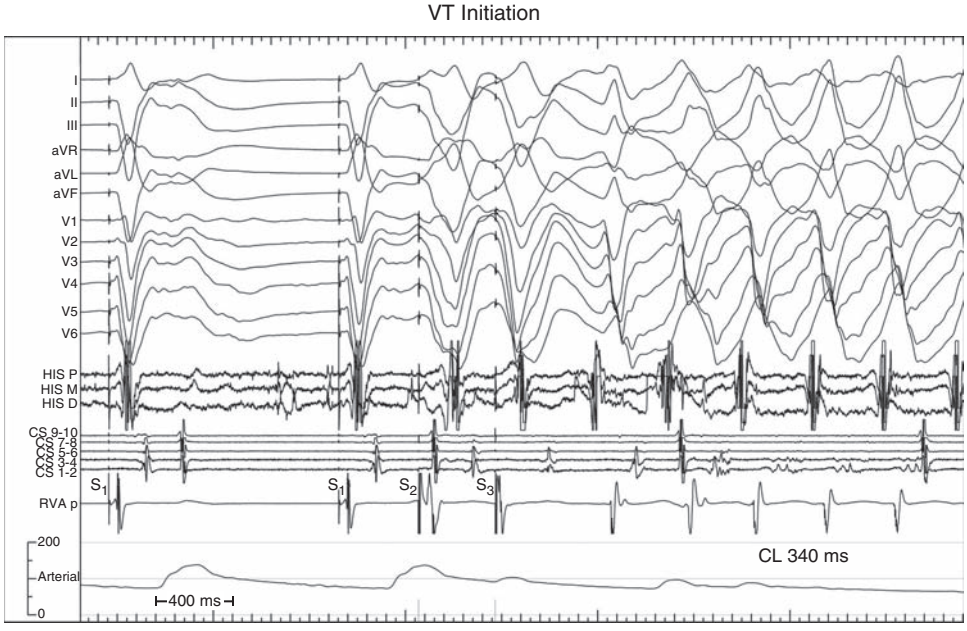


Figure 27-5

VT was initiated with double extrastimuli. The spontaneous tachycardia cycle length was 430 ms; it would be difficult for this one (340 ms) to be the same VT (Fig. 27-5).

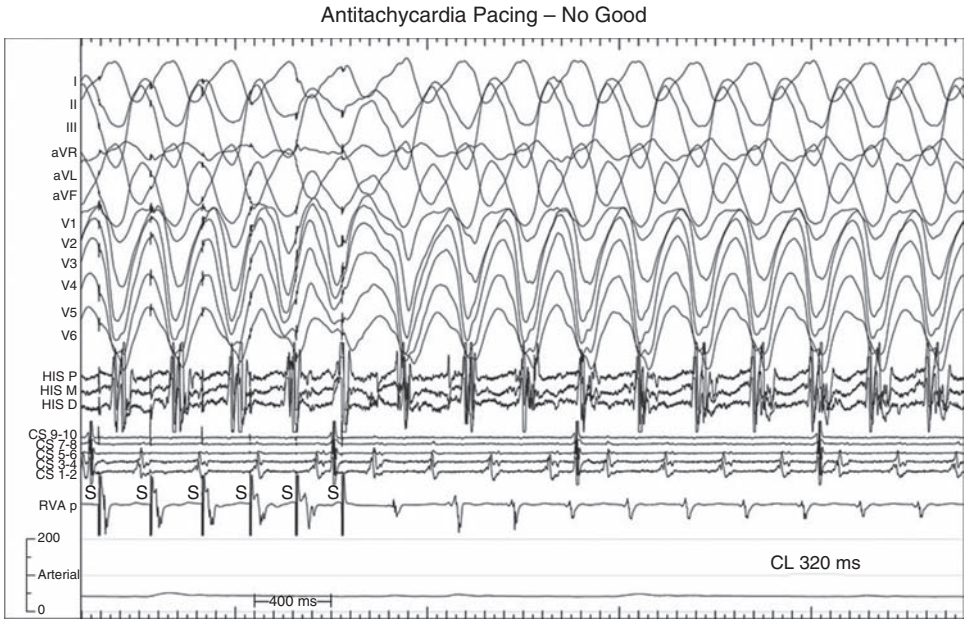


Figure 27-6

Overdrive pacing fails to terminate the rapid VT. At least this phenomenon (Fig. 27-6) is consistent with his clinical behavior—acceleration with antitachycardia pacing.

Why No QRS?

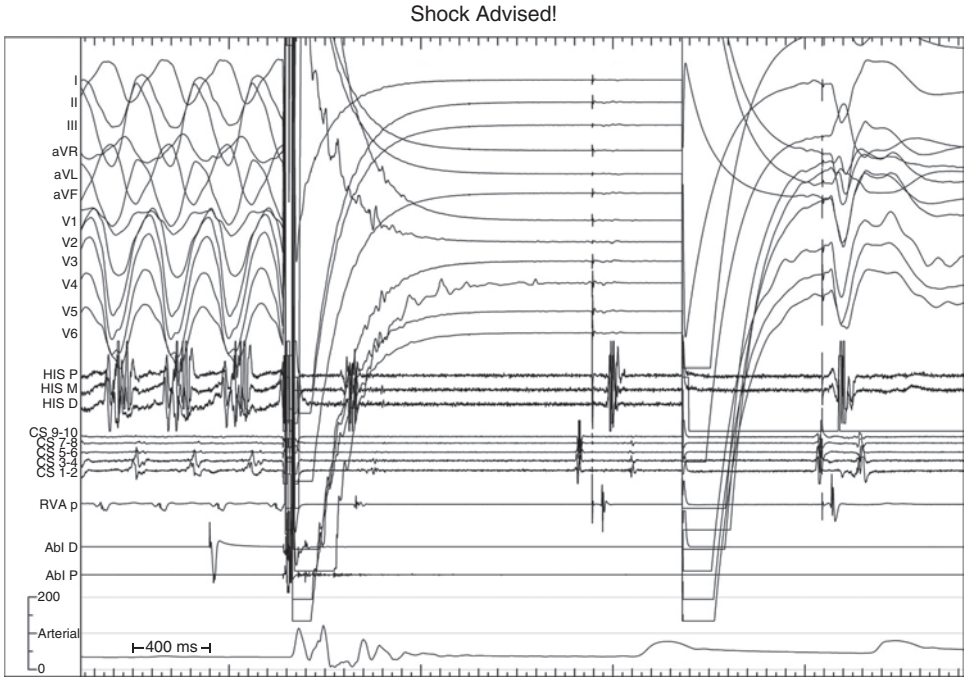


Figure 27-7

In Fig. 27-7, shock terminates rapid VT, but a stimulus from the device after the shock does not seem to capture the ventricle (no QRS complex). There really is one (note ventricular electrogram in RVA signal) and there is a systolic wave in the blood pressure recording, but surface ECG amplifiers have not reset.

VT Reinitiation

Is This the VT We're Looking For?

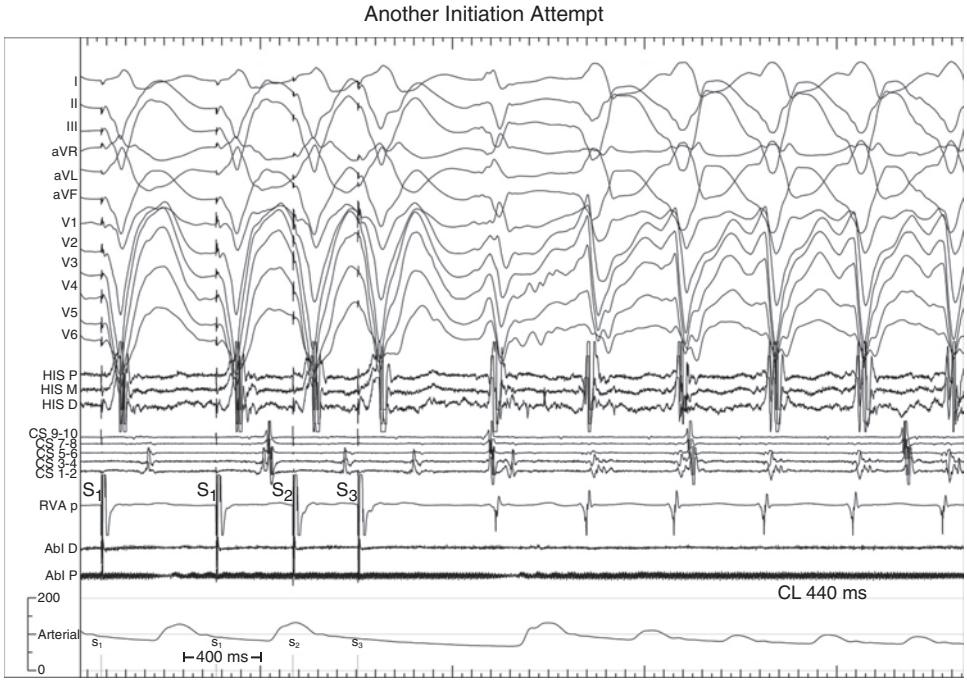


Figure 27-8

Another attempt is made to initiate VT. The VT shown in Fig. 27-8 has a cycle length very similar to the one that occurred spontaneously and is very likely the VT we are seeking.

Comparison of ICD Electrograms from This Episode and Prior Episode

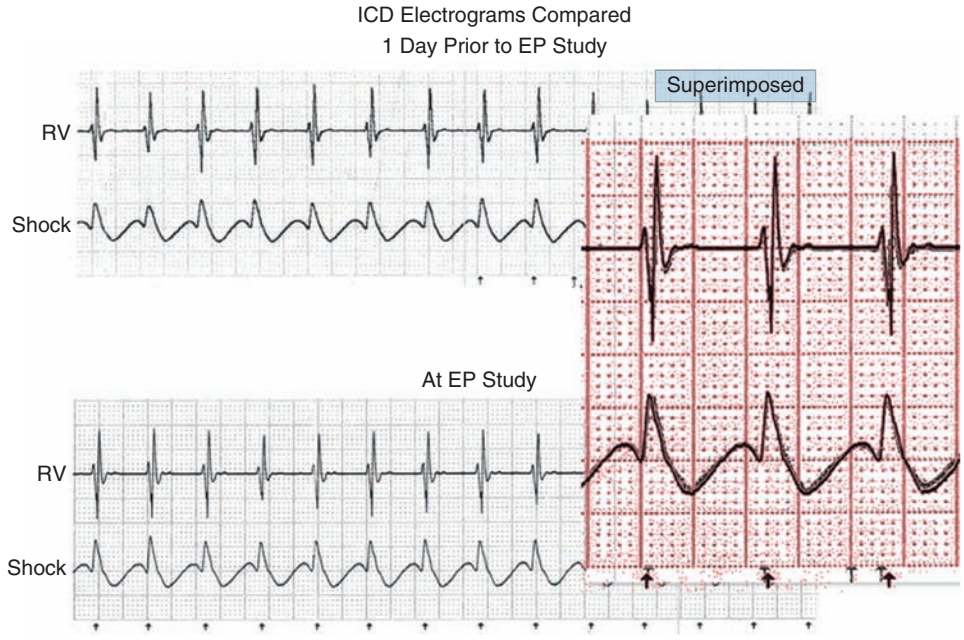


Figure 27-9

In Fig. 27-9, real-time electrograms from EP study (at bottom) are compared with those from the stored episode (at top); they are identical. Thus the induced VT corresponding to these electrograms is the same as the spontaneously occurring VT.

ECG of Target VT

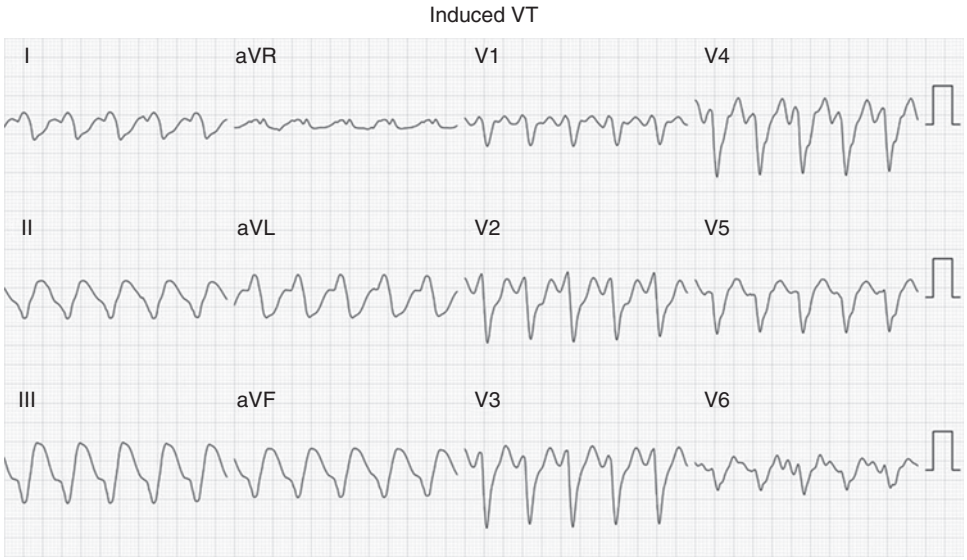


Figure 27-10

In Fig. 27-10, a 12-lead ECG of the induced VT has a left bundle branch block, leftward superior axis. It has findings that suggest a relationship to an inferior scar, though other features (poor R-wave progression) might suggest an apical exit site.

Comparison and Critique of Different Mapping Sites During VT

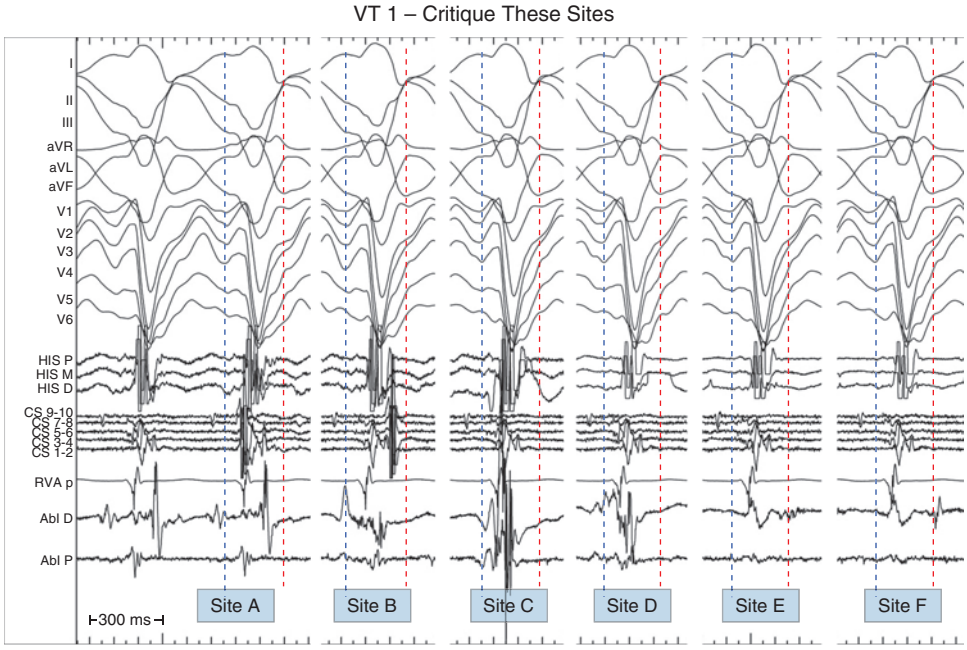


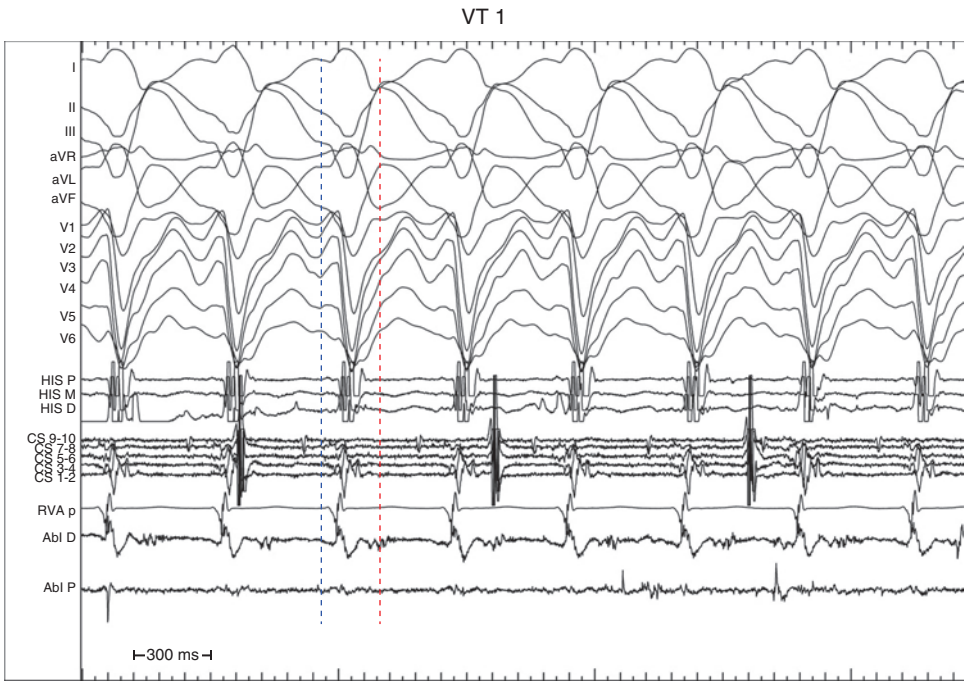
Figure 27-11

Fig. 27-11 displays several mapping sites (*dashed blue line* denotes onset of the QRS complex; *dashed red line,* the end):

A—late diastolic recording looks a little far-field; near-field component occurs during QRS complex
B—fragmented signal during QRS complex, but other portion is barely presystolic
C—high-amplitude, intra-QRS signal, of no interest
D—fragmented signal, with far-field late diastolic component
E—fragmented signal in early diastole—more interesting
F—discrete potential in early diastole—more interesting

Critique This Site . . .

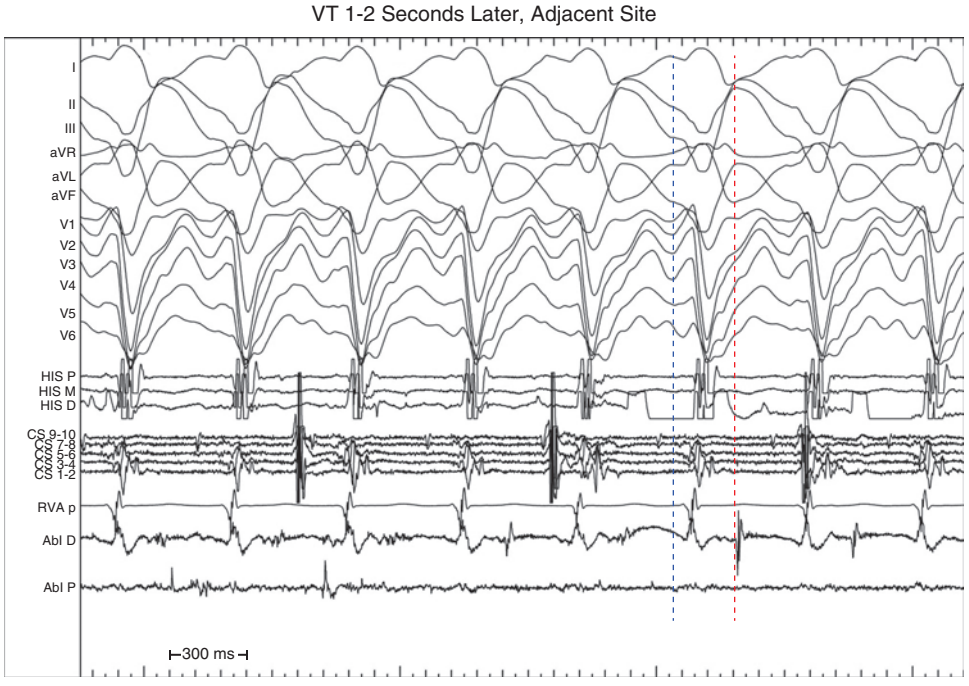
Figure 27-12



The site in Fig. 27-12 is only mildly interesting; though it has a systolic component (inside QRS complex), there is a fragmented portion extending into early diastole.

Critique This Site . . .

Figure 27-13



Recordings from just a few millimeters away have an interesting early diastolic component (Fig. 27-13), showing that potentially important sites may be extremely close to sites that are not very interesting (Fig. 27-12). This underscores the importance of detailed mapping.

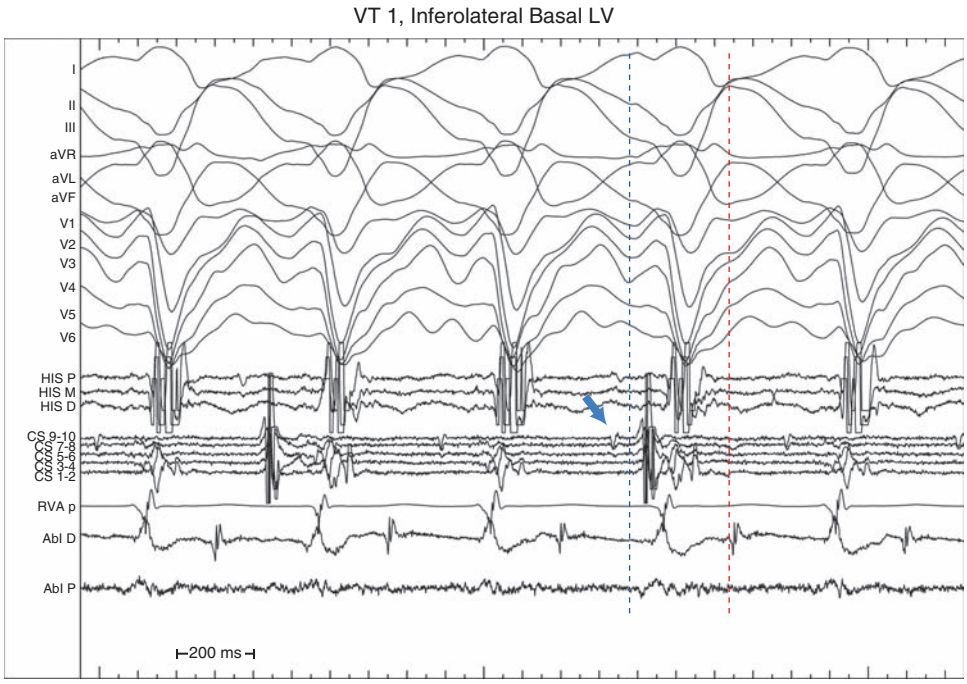


Figure 27-14

All the time we have been mapping, coronary sinus recordings have shown mid-late diastolic potentials (blue arrow) when adequately gained (Fig. 27-14).

What's Going on Here? [Fig. 27-15]

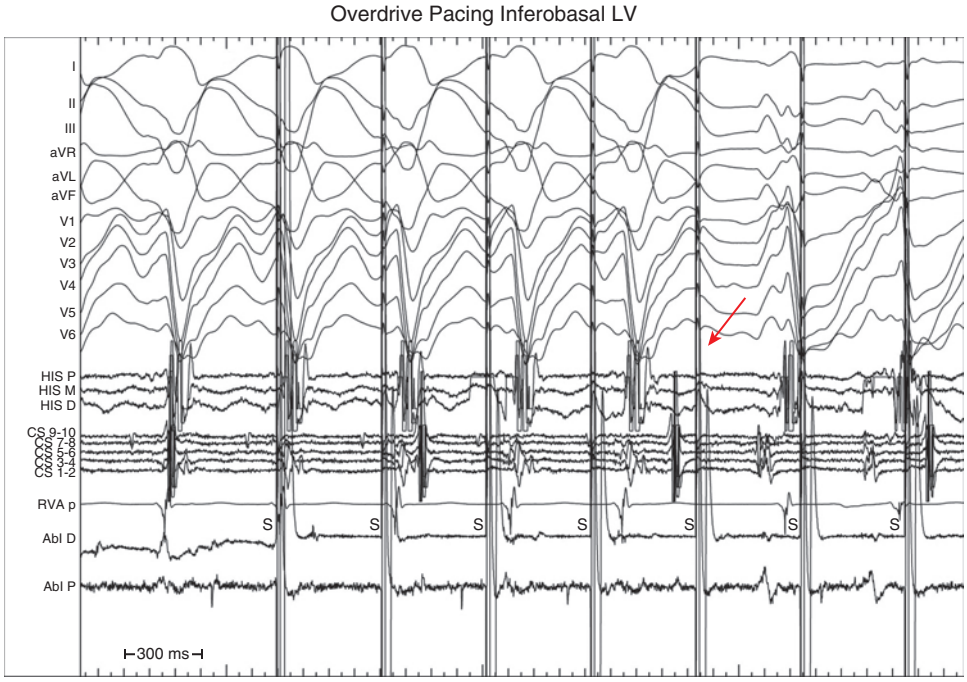


Figure 27-15

An attempt at overdrive pacing during VT results in termination of VT without apparent propagation *(arrow)*; actually, the impulse captures and propagates in the opposite direction as shown by the longer stimulus-QRS and complete change in polarity of the resulting QRS complex (Fig. 27-15). If this is a reproducible phenomenon, it has significant implications regarding the site (within the protected isthmus essential for VT continuation).

Critique This Site . . .
0.15 mV [Fig. 27-16]

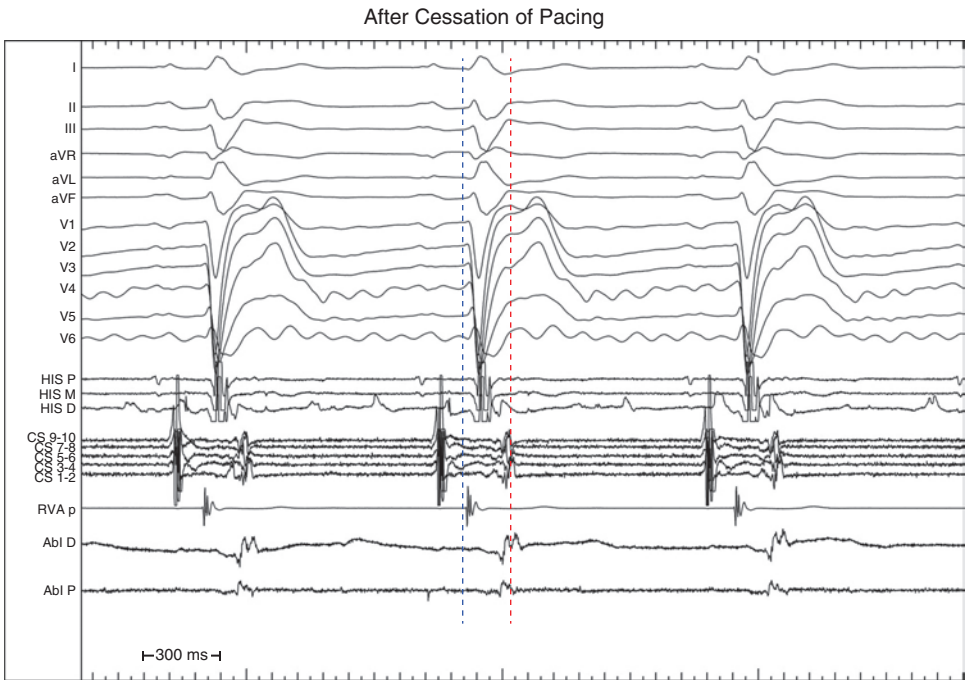


Figure 27-16

The site at which VT terminated with a nonpropagated stimulus is shown in Fig. 27-16 during sinus rhythm—not a very impressive site. This illustrates one of the problems with sinus rhythm/substrate mapping (poor sensitivity).

Comment on Capture at This Site . . . [Fig. 27-17]

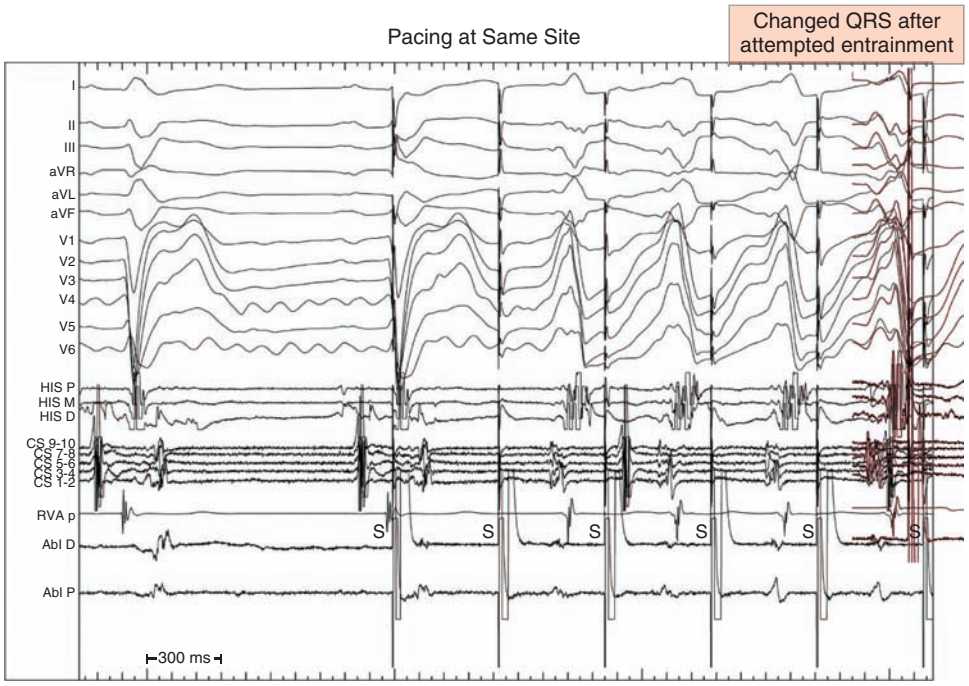
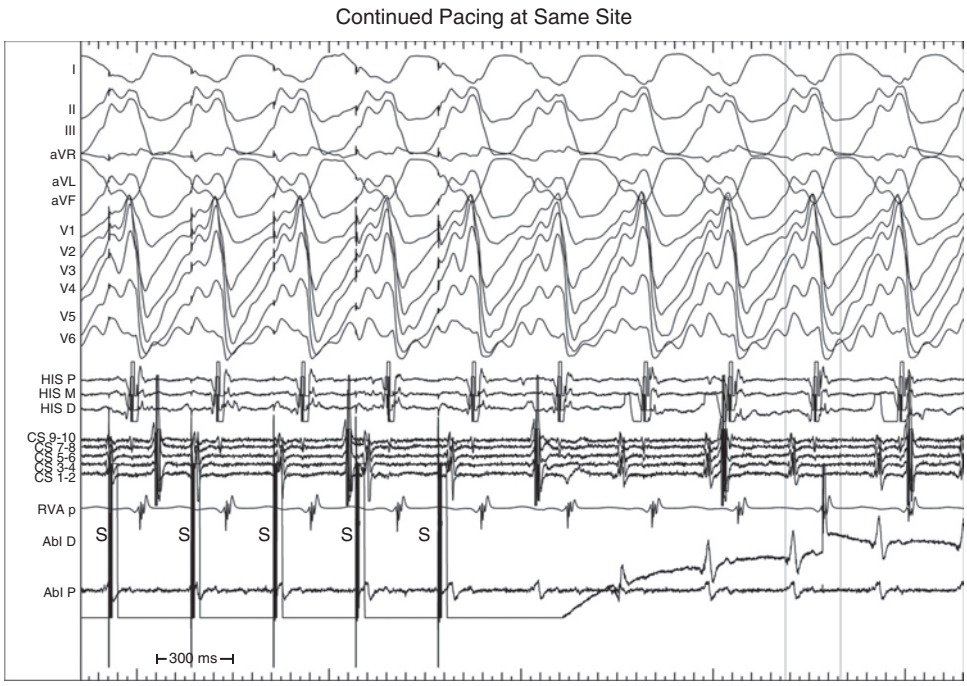


Figure 27-17

Stimulation at this same site (Fig. 27-17) results in a QRS complex very similar to that obtained during overdrive pacing during VT. The interpretation is that it is electrically a shorter distance to propagate in this direction (which would be toward the entrance of the circuit) than toward the exit (that would result in the same morphology as the first VT).

Pacing Induces VT-2



Comment on Capture at This Site . . . [Fig. 27-18]

Figure 27-18

As pacing continues in Fig. 27-18, it is clear that another VT has been initiated (note lack of correlation between stimulus artifacts and QRS complexes on the left of the figure).

ECG of VT-2

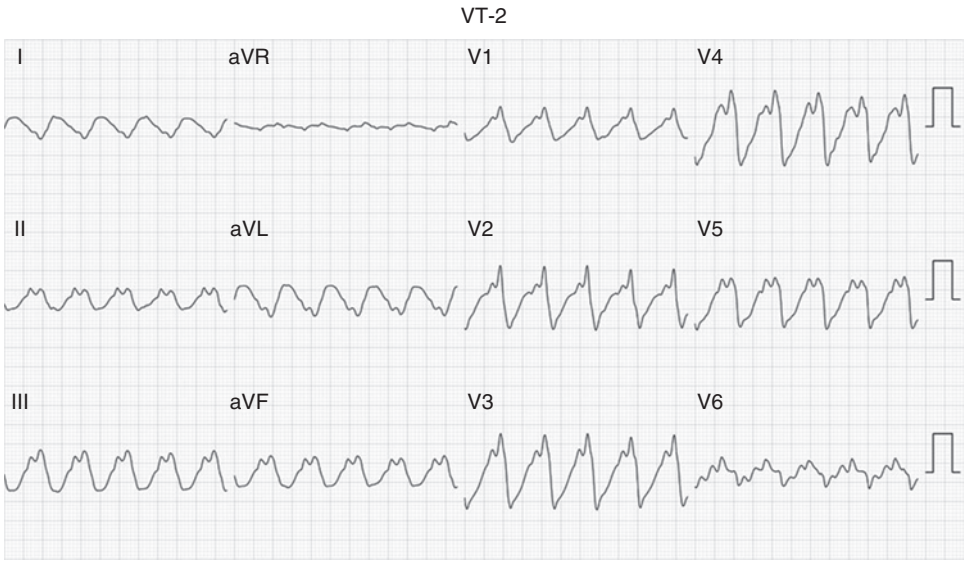


Figure 27-19

Fig. 27-19 shows a 12-lead ECG of the second induced VT.

VT-2, Pacing, and Sinus Rhythm at One Site

Critique This Site . . . and Where Is It? [Fig. 27-20]

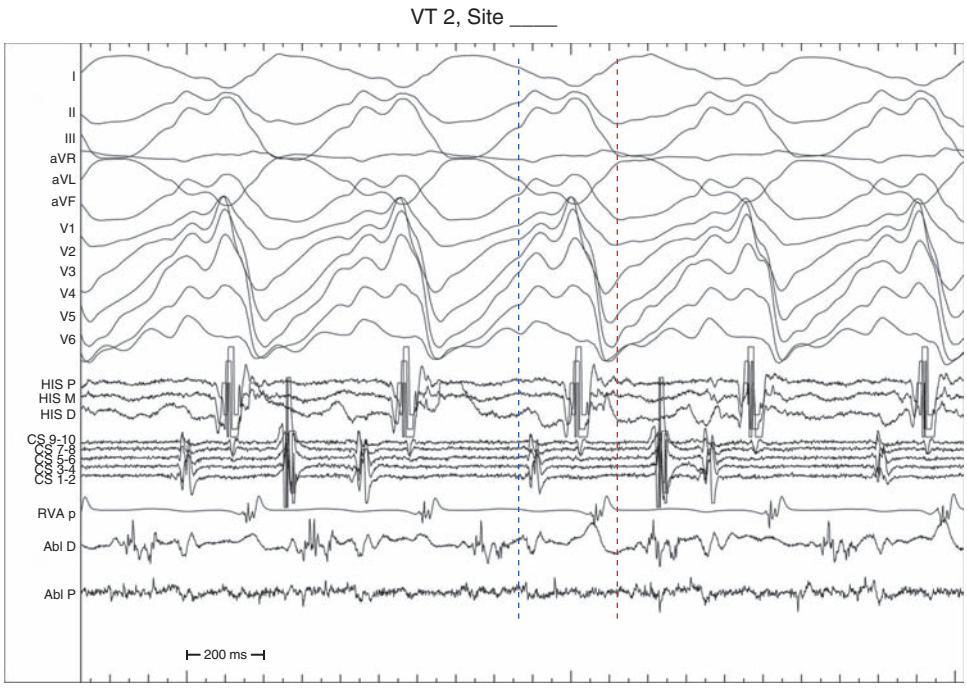


Figure 27-20

Fig. 27-20 shows a mid-diastolic potential, from the basal lateral LV.

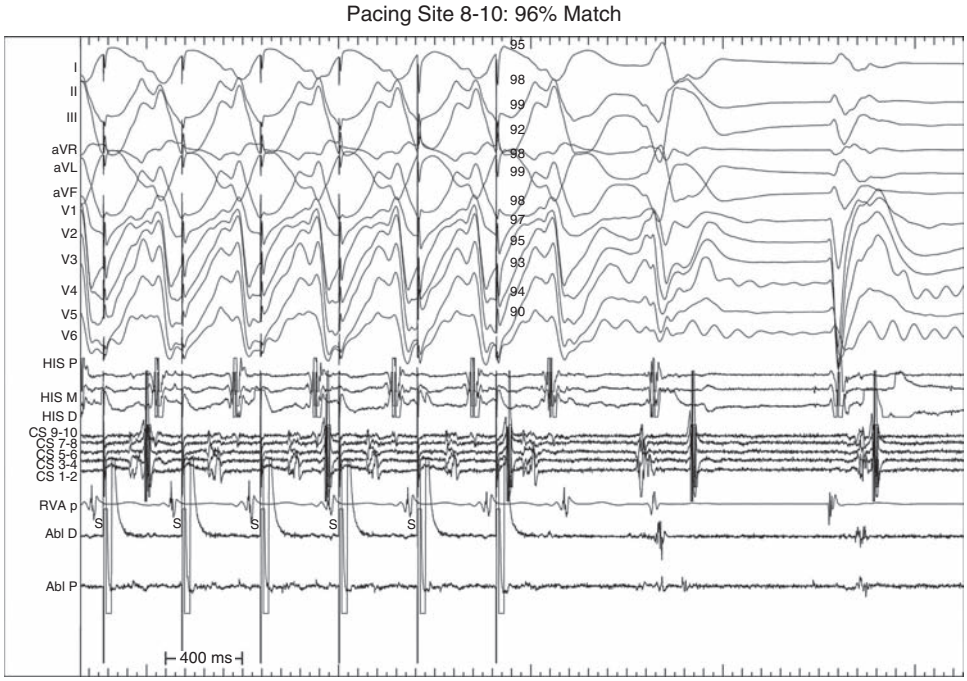
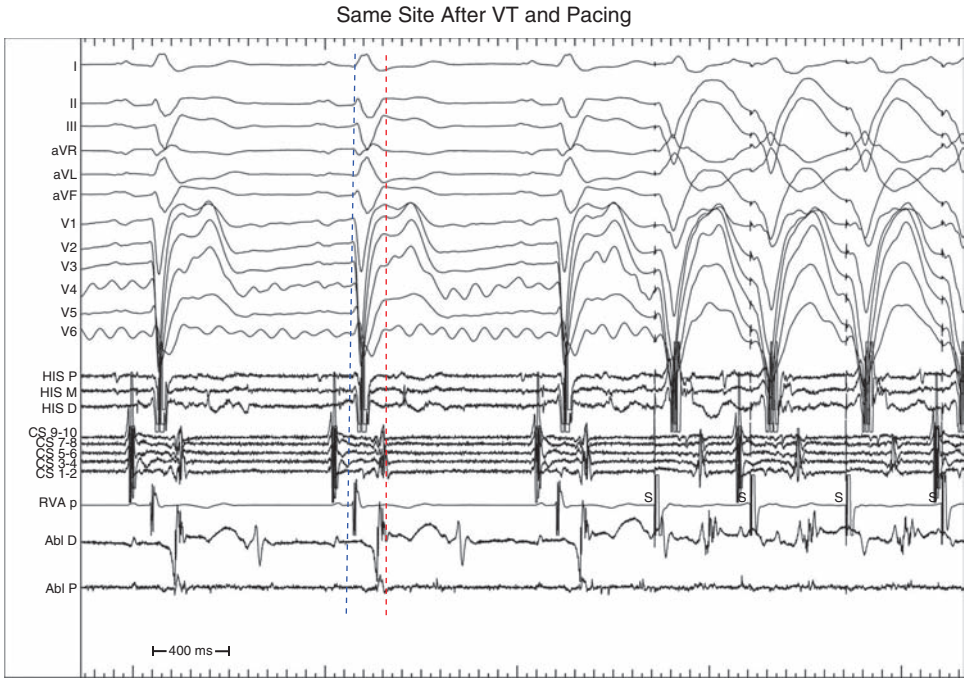


Figure 27-21

Pacing at a basal lateral side produces a 96% computer match of the morphology of VT-2 (Fig. 27-21).



Critique This Site . . . [Fig. 27-22]

Figure 27-22

Fig. 27-22 shows the sinus rhythm recordings from the site of pace match and diastolic signal during VT-2—not very impressive (no fragmentation or late potential). Pacing the right ventricle, however, unveils a highly fragmented and delayed electrogram. This shows the importance of pacing-induced changes in signal characteristics when looking for local abnormal late activities (LAVA).

Reinitiation of VT-1

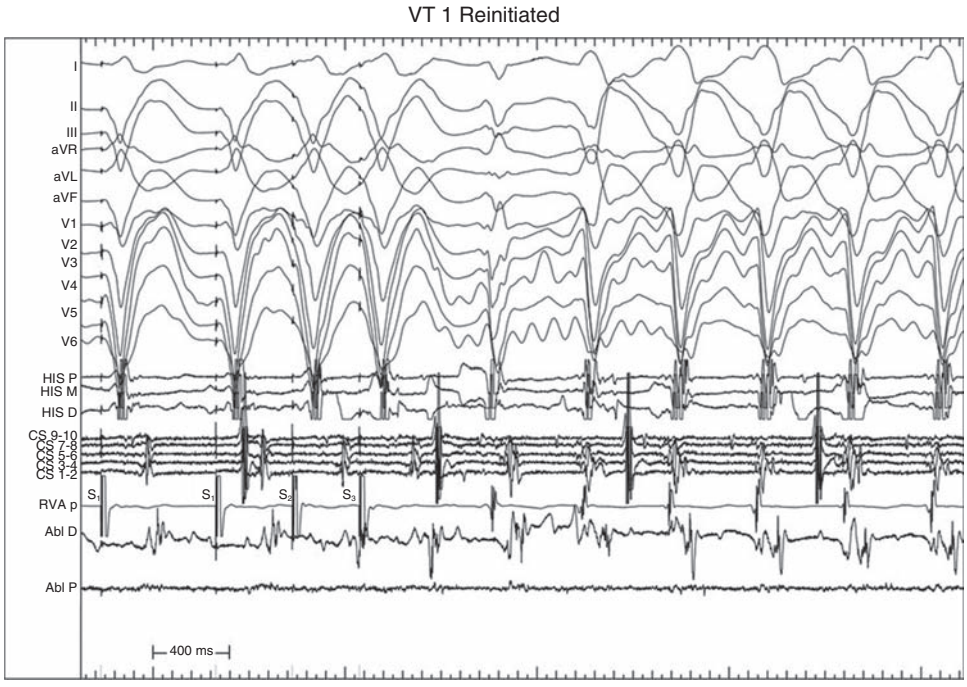


Figure 27-23

In Fig. 27-23, VT was reinitiated to test whether the stimulus that terminated VT without global capture ("nonpropagated termination") was a real phenomenon or chance occurrence (ie, spontaneous change).

Single Extrastimulus Terminates VT-1, Spontaneous Reinitiation, and Further Testing at This Site

What's Going on Here?

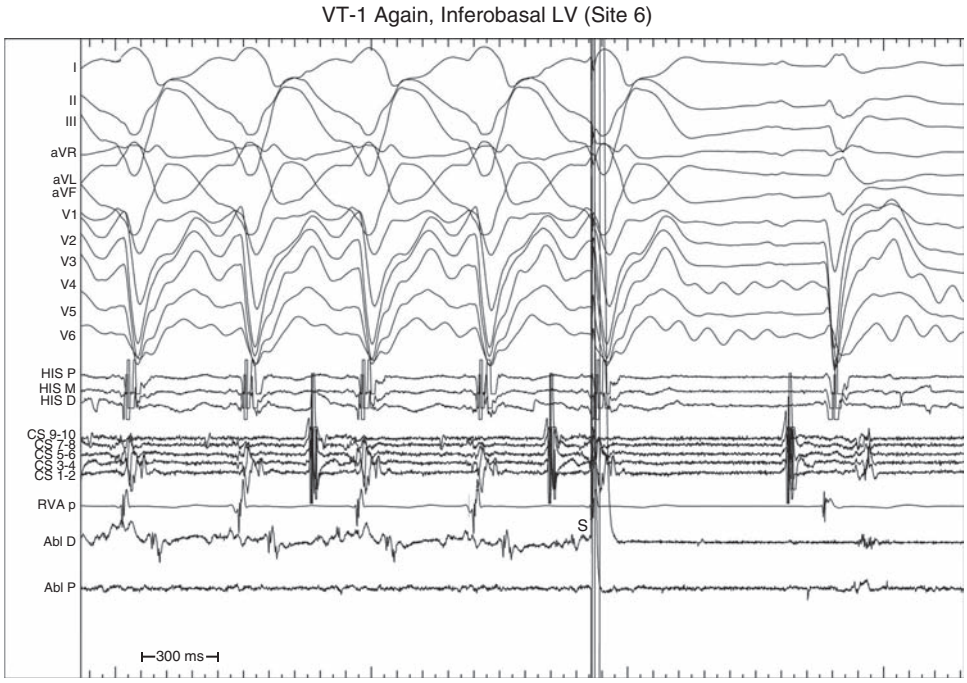


Figure 27-24

At a site very near where an attempt at overdrive pacing terminated VT without propagation, a single extrastimulus terminates VT (Fig. 27-24). This signifies that this is an excellent site for ablation.

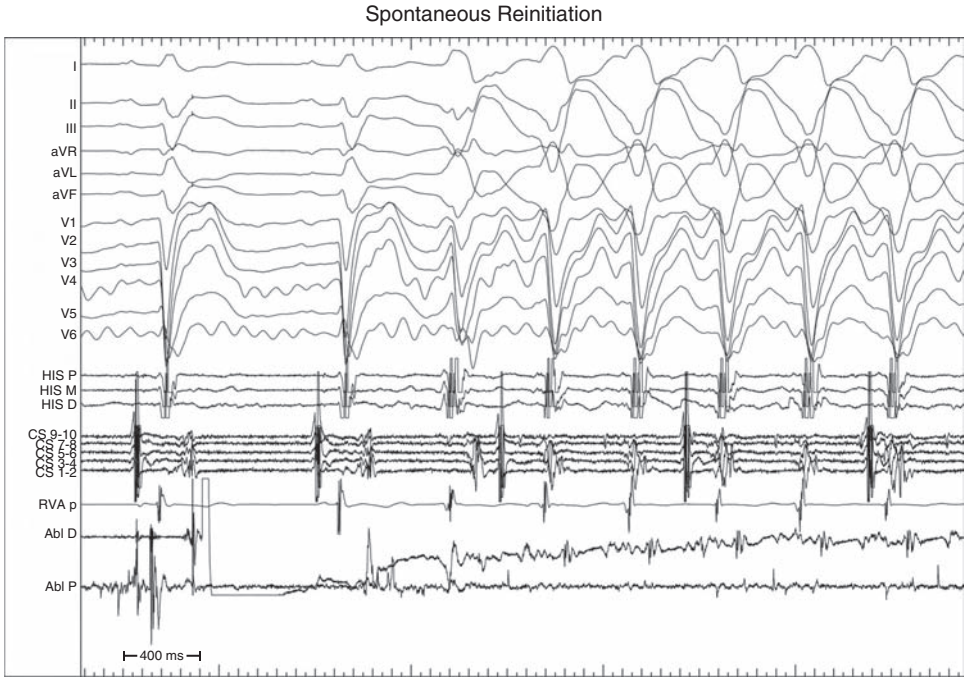


Figure 27-25

Spontaneous initiation of VT occurs when the catheter is at this site, as shown in Fig. 27-25.

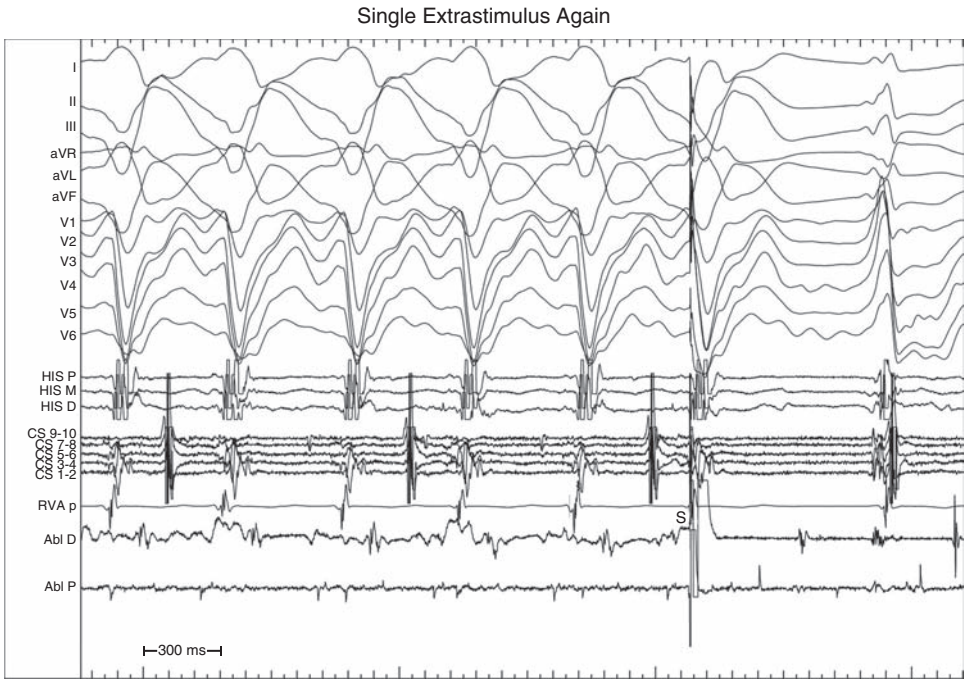


Figure 27-26

Just to prove the point, another single extrastimulus (S) terminates VT without propagation (Fig. 27-26).

Critique This Site . . .

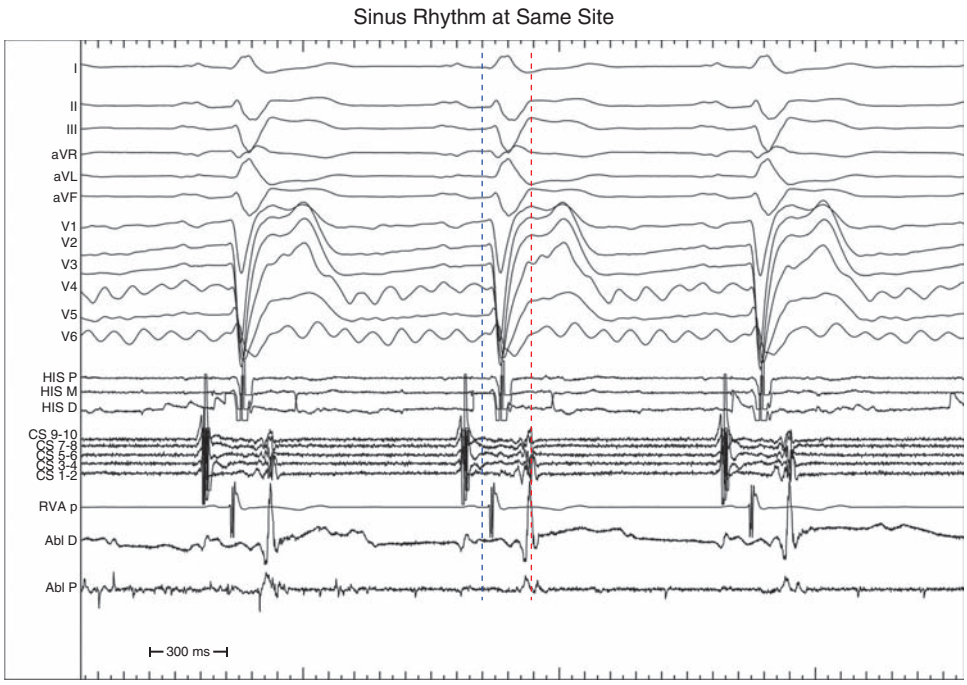
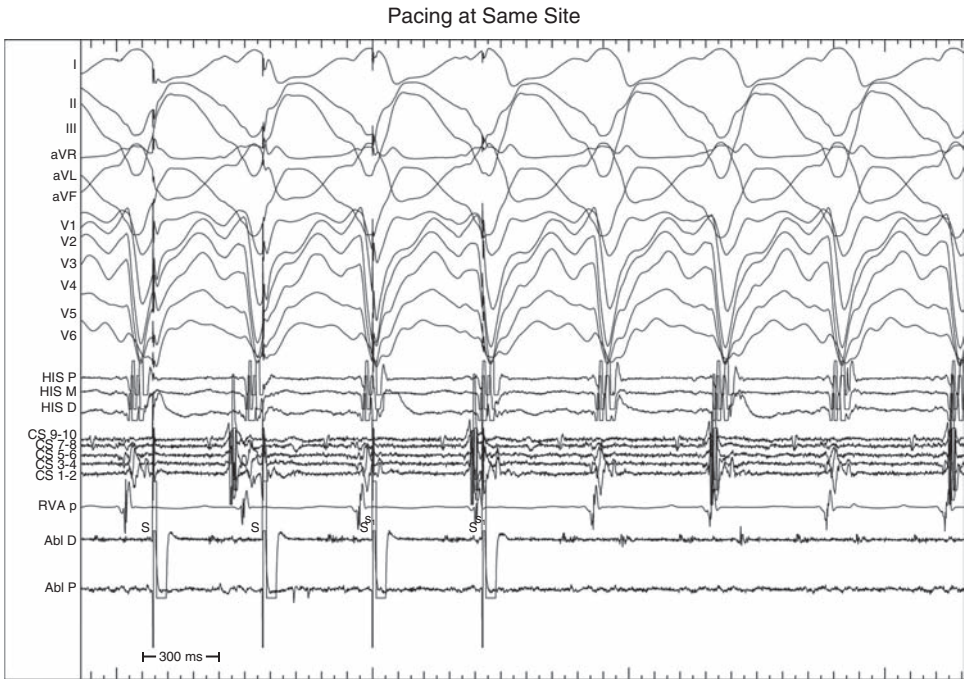


Figure 27-27

A nondescript electrogram is evident during sinus rhythm at the site at which VT was terminated by a single extrastimulus (Fig. 27-27).

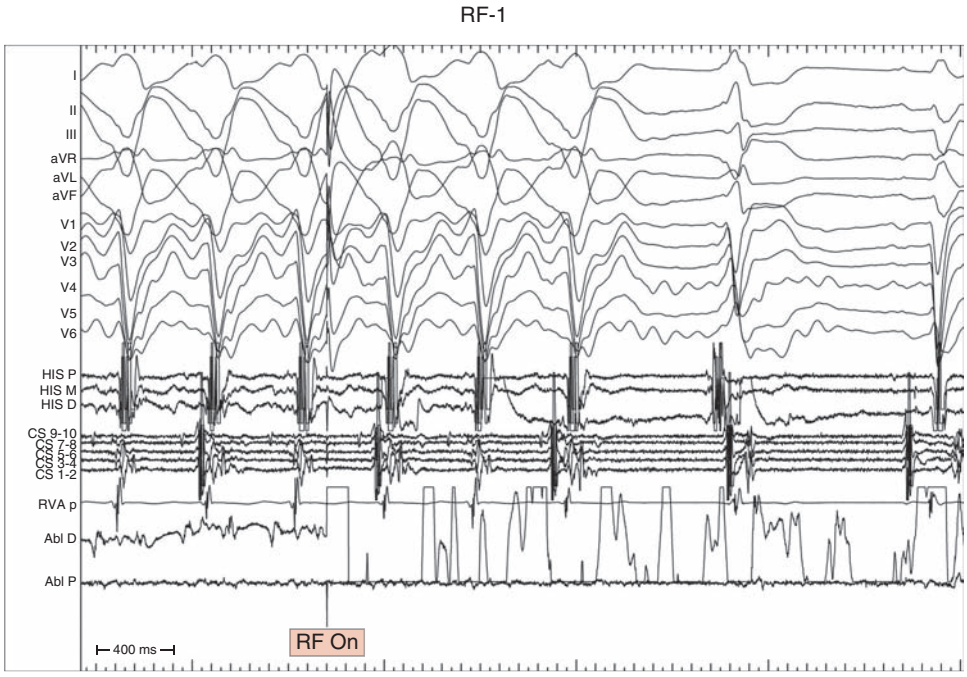
Figure 27-28



As shown in Fig. 27-28, pacing at this same site reinitiates the same VT.

Ablation and Subsequent Pacing at This Site in VT-1

Figure 27-29



Rewarding our hard work is nearly immediate termination of VT with radiofrequency application at this site (Fig. 27-29).

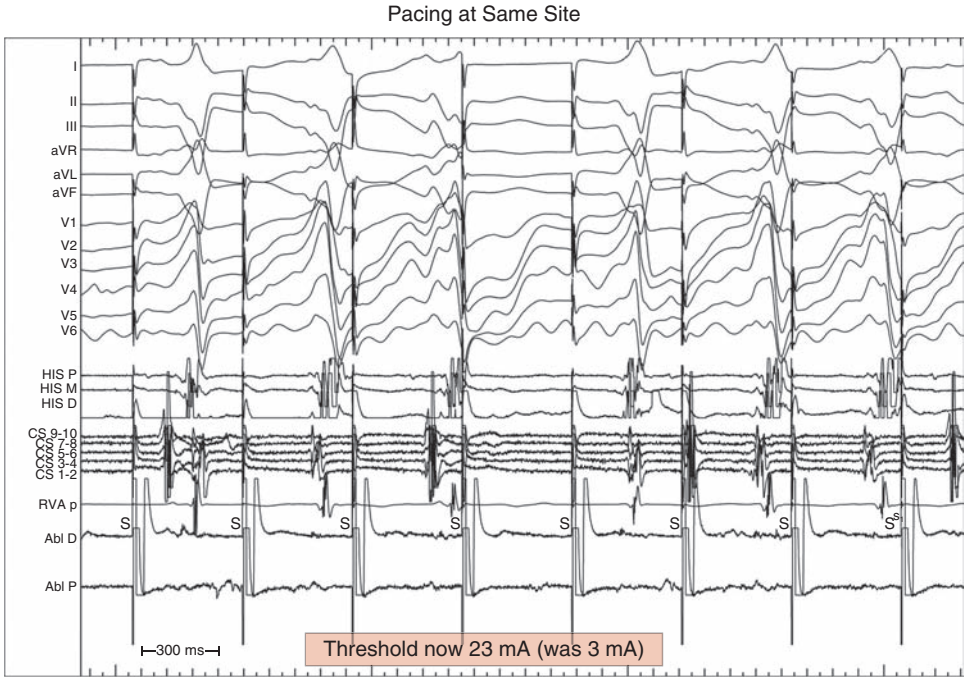
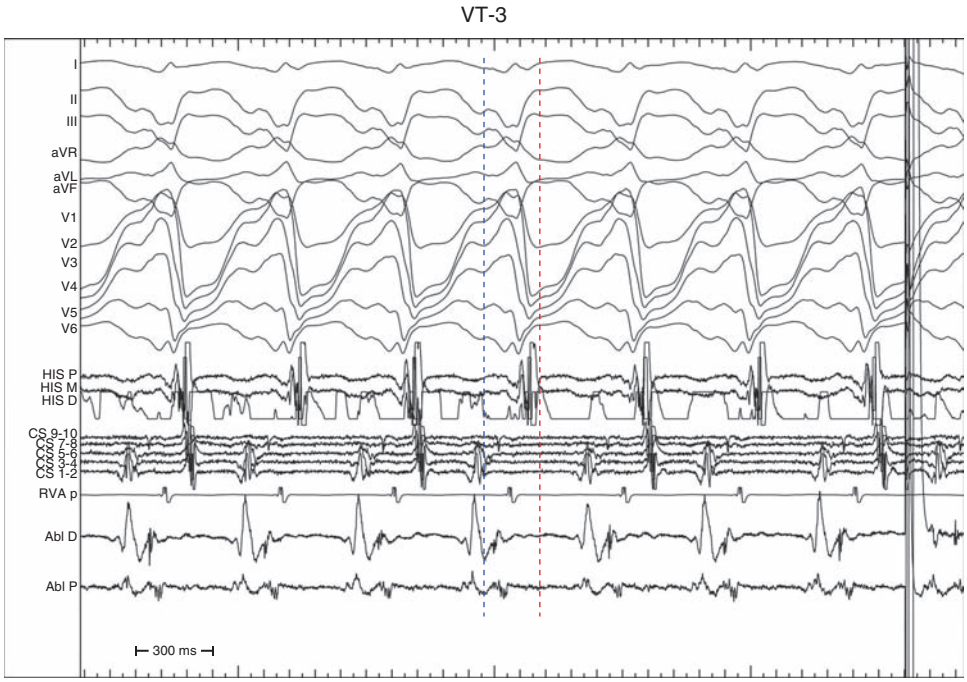


Figure 27-30

VT cannot be reinitiated; a quick check of the pacing threshold at this site after ablation shows it to be markedly elevated (Fig. 27-30).

Initiation and Ablation of VT-3

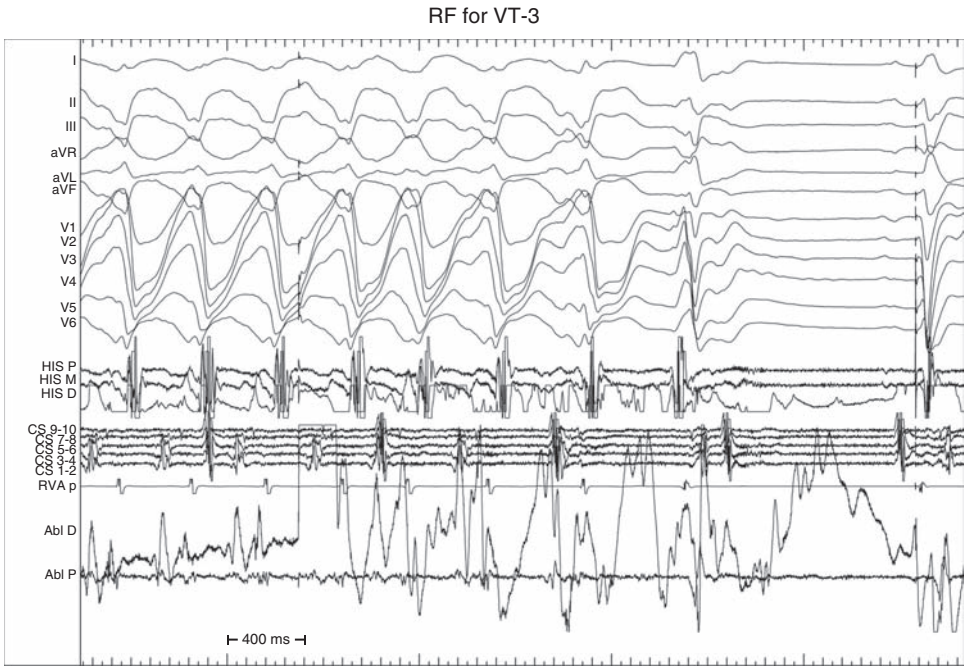


Critique This Site . . . [Fig. 27-31]

Figure 27-31

However, as can be seen in Fig. 27-31, another VT can be initiated.

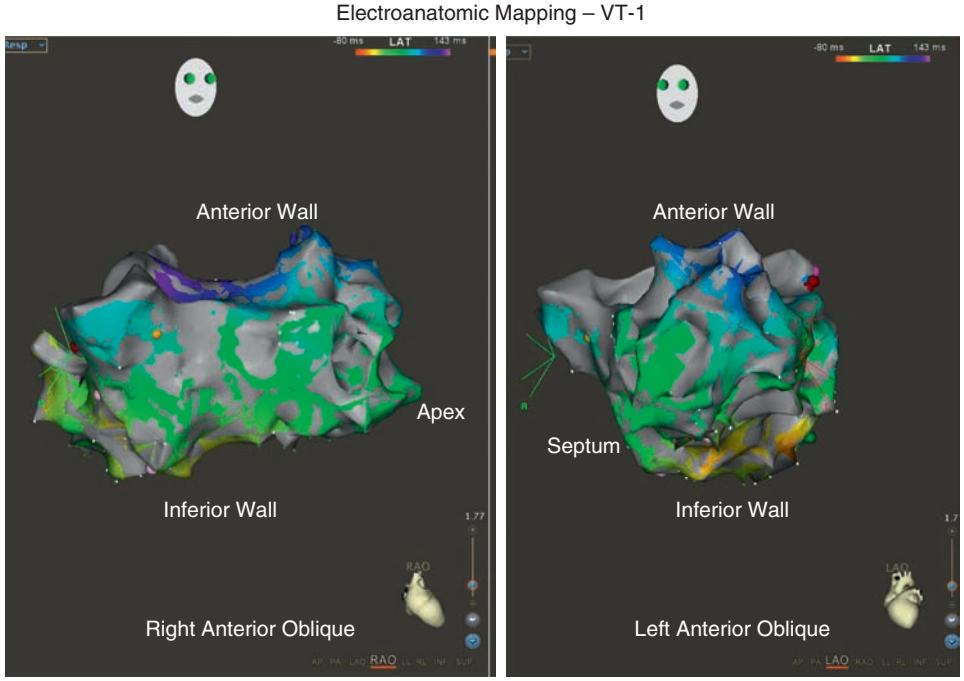
Figure 27-32



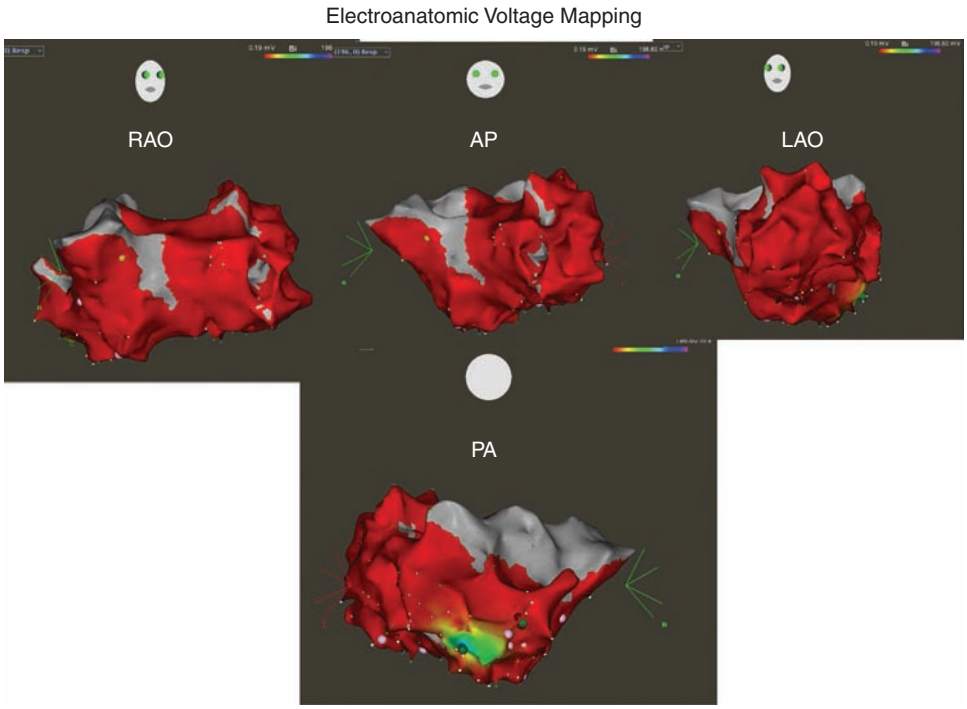
After applying several of the same pacing maneuvers, the VT displayed in Fig. 27-32 is terminated with radiofrequency energy at a site of diastolic activation.

Electroanatomic Mapping Findings

Figure 27-33



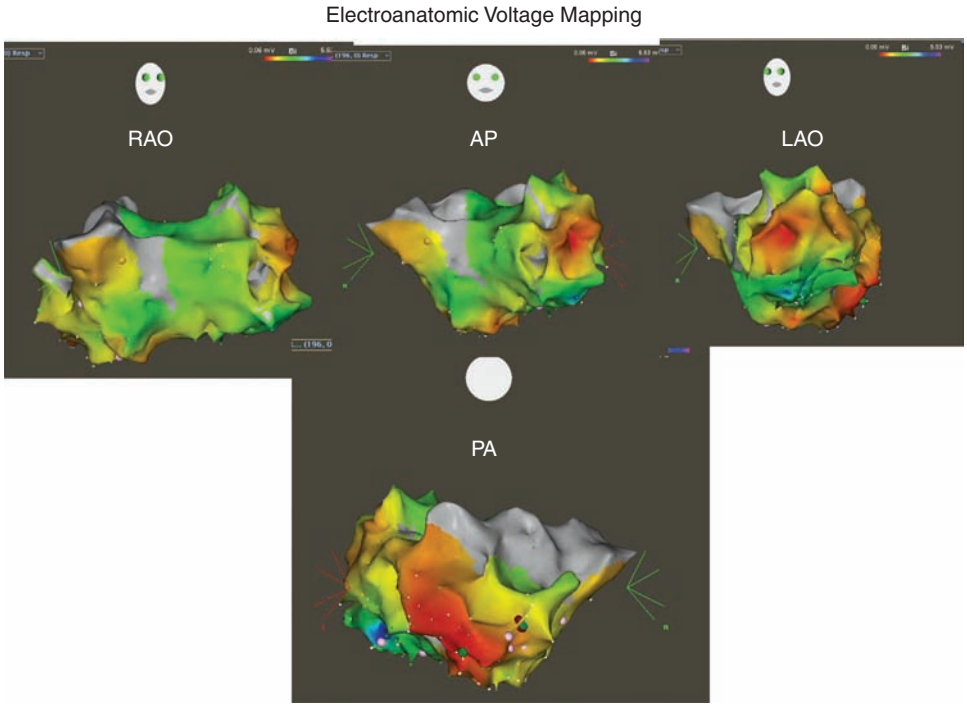
Standard views of the electroanatomic activation map, shown in Fig. 27-33, suggest a region of interest in the inferolateral basal left ventricular free wall (*red* and *orange* areas).



Why So Much Low Voltage? [Fig. 27-34]

Figure 27-34

In Fig. 27-34, it looks like the entire ventricle, except for a small portion (near where we ablated!), has very low voltage. This does not make sense; the ablated area (diseased) should have low voltage (*red*) while other areas should have more normal voltage (*purple*).

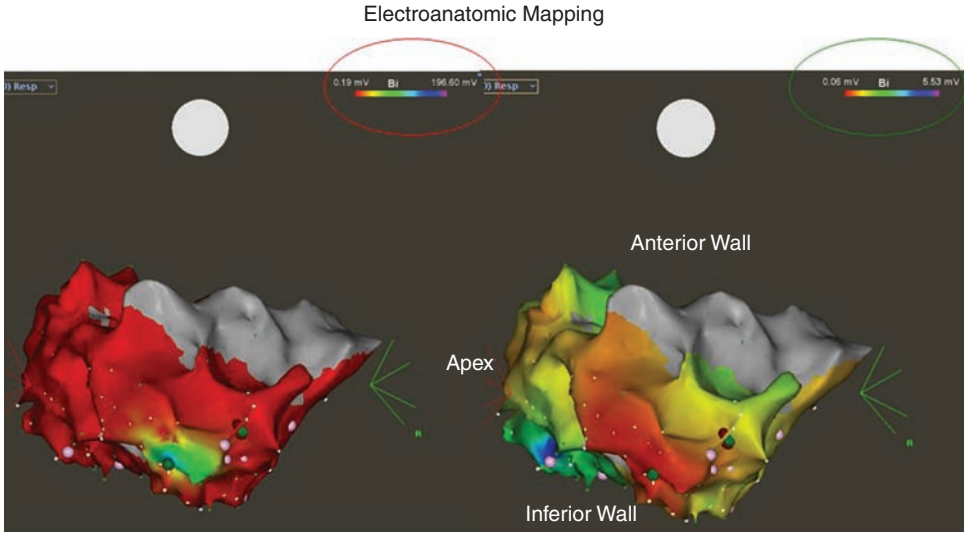


Why Such Different Voltage?

Figure 27-35

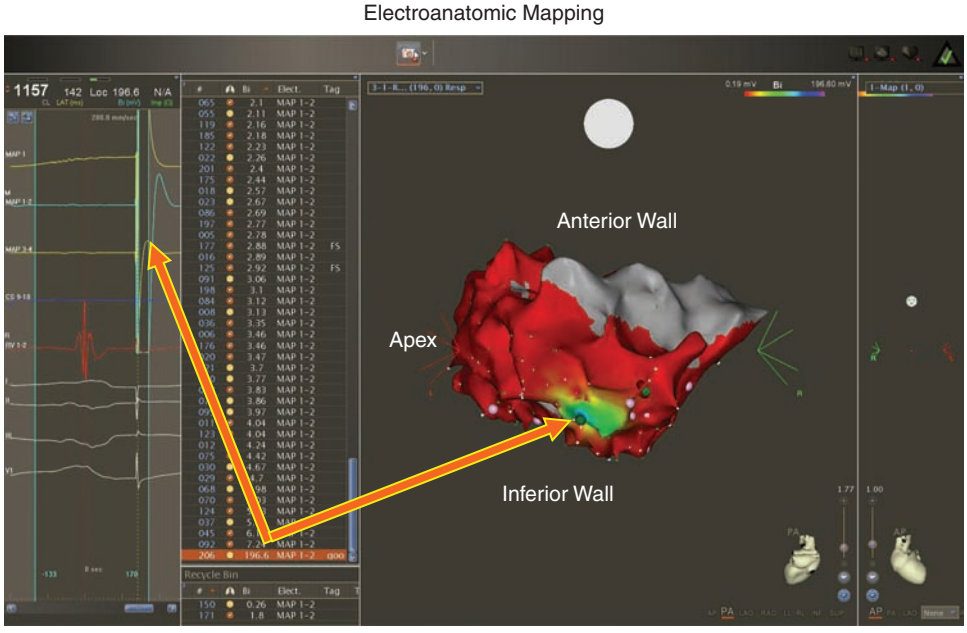
The problem is, a single site of the posterior wall had an extremely high voltage, making everything else seem extremely low (Fig. 27-35).

Figure 27-36



At left of Fig. 27-36 is the original voltage map; at right is the edited voltage map (after adjudicating the computer-designated voltage at one site).

Figure 27-37



In Fig. 27-37, the point with the falsely high voltage was because of a stimulus artifact.

This *single point* in the voltage map threw everything else off (195 other points that were correct).

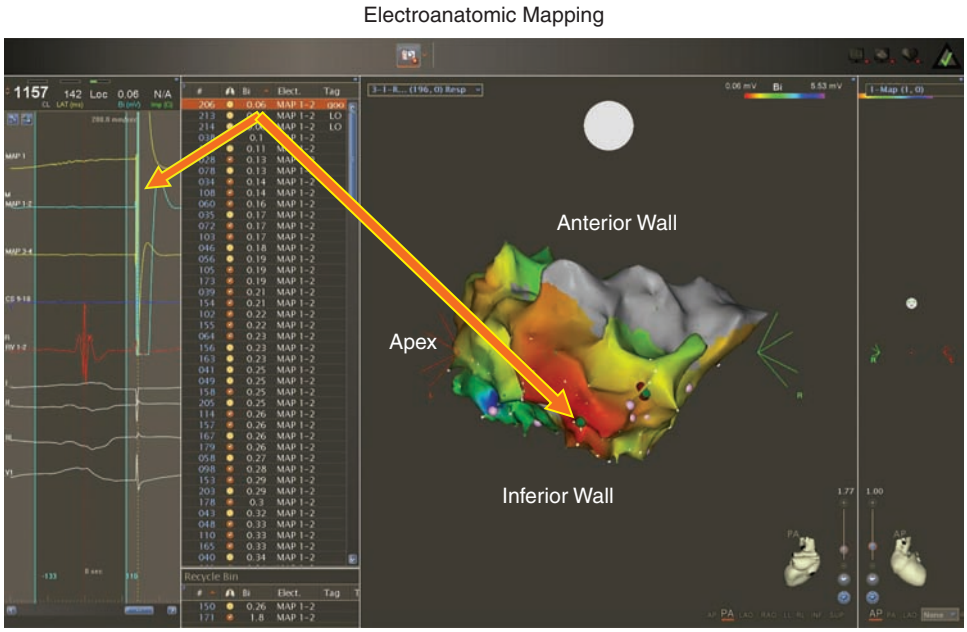


Figure 27-38

In Fig. 27-38 is the correct voltage at that site, obtained by simply sliding the window of interest enough to exclude the stimulus artifact that was causing a problem.

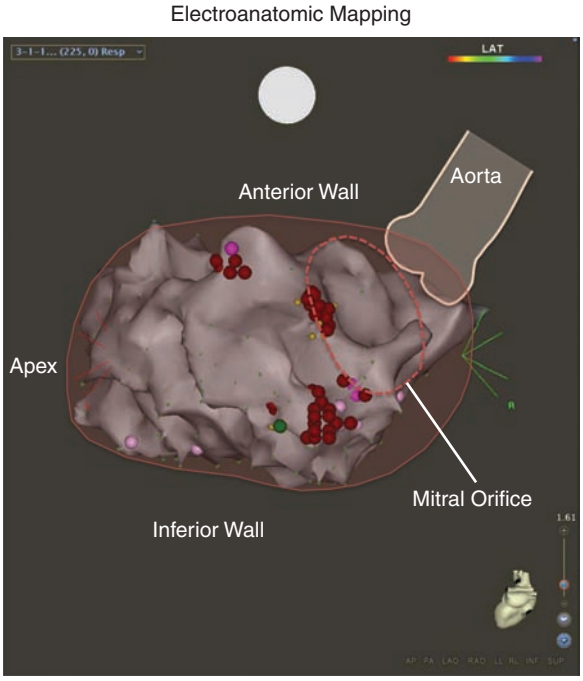


Figure 27-39

In Fig. 27-39, the electroanatomic map as well as ablation sites *(red dots)* are projected on a silhouette of the left ventricle and aorta in a posterior view of the heart.

Summary

- Sometimes it is hard to know what the target area is likely to be (preoperative imaging, ECG in sinus rhythm or VT can help)
- The pathophysiology of VT in dilated cardiomyopathy is fundamentally the same as other scar-based VTs (like post-MI VT); this patient had a small prior MI but LV dysfunction out of proportion to it
- Having *some* information about the spontaneous VT (ICD recordings) can be very useful in deciding what to target
- Serendipitous findings (nonpropagated stimulus terminating VT) are very valuable and should not be ignored
- Voltage mapping can be great but *just one incorrect point* can make interpretation completely wrong

Bundle Branch Reentry Ventricular Tachycardia

28

Case Presentation

A 56-year-old man with inferior wall myocardial infarction (MI) in May 2010 was referred for catheter ablation because of frequent implantable cardioverter-defibrillator (ICD) activity. At the time of his MI, he had percutaneous coronary intervention to the mid-right coronary artery. Left ventricular systolic function was poor at the time and remained so; he underwent biventricular ICD placement for primary prophylaxis of sudden death. Within months, he began experiencing frequent antitachycardia pacing (ATP) and shocks from his ICD because of rapid ventricular tachycardia (VT). Amiodarone was administered; he still received frequent ATP and some shocks, despite additional device reprogramming. He underwent electrophysiology (EP) study and ablation, at which time abnormal electrograms on the left ventricular anterior septum were identified. Only nonsustained VT episodes with multiple left bundle branch block (LBBB) morphologies could be induced. Extensive ablation of anterior septal sites was performed. Unfortunately, even after the procedure, he continued to have episodes of VT requiring ATP or shocks. He was given more amiodarone but still required frequent ATP for treatment of VT. He was referred for repeat ablation.

Baseline ECG (Paced) and Intracardiac Recordings

Figure 28-1

The baseline ECG during atrial and biventricular pacing yields few clues as to where mapping attention should be focused (Fig. 28-1).

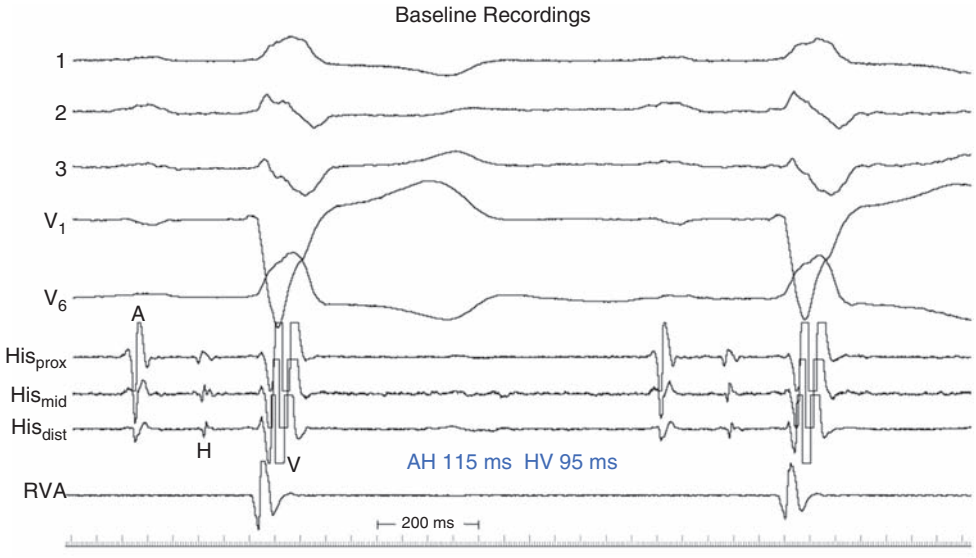


Figure 28-2

When the device was reprogrammed to a backup pacing mode, sinus rhythm with intact AV conduction is revealed. In Fig. 28-2, LBBB is present with intervals as shown.

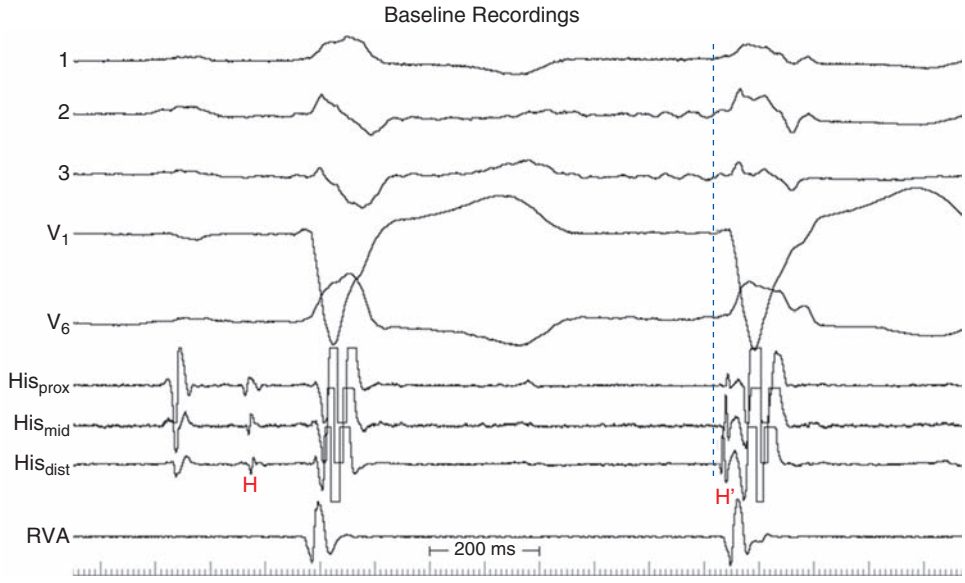


Figure 28-3

In Fig. 28-3, a spontaneous premature ventricular complex occurs that conducts retrogradely over the His bundle (H′, propagated distal to proximal). As early as the retrograde His occurs relative to the QRS onset *(dashed line)*, it must have conducted from the right bundle branch.

Ventricular Stimulation and VT Induction

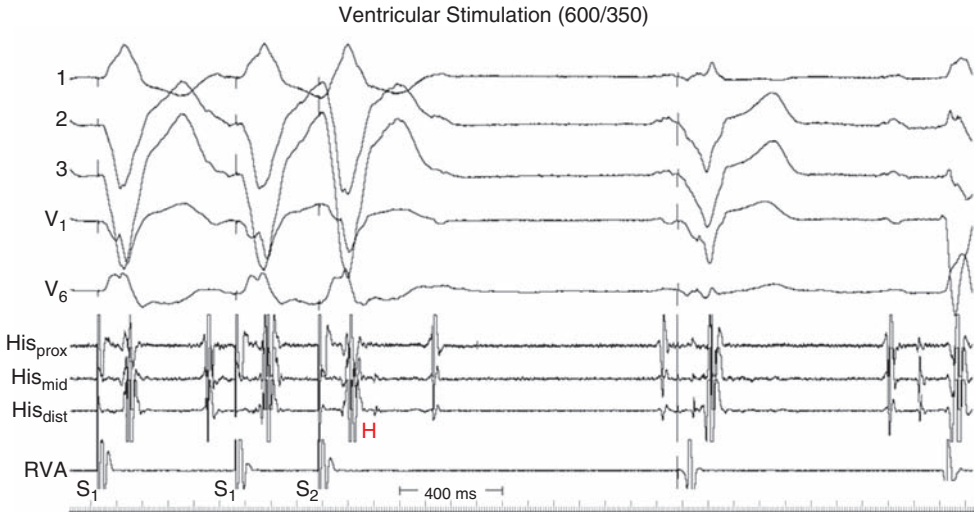


Figure 28-4

With ventricular extrastimulus testing, a His potential (H) is seen "out the back" (retrograde block in RBB with transseptal propagation to the LBB and then to the His bundle) in Fig. 28-4.

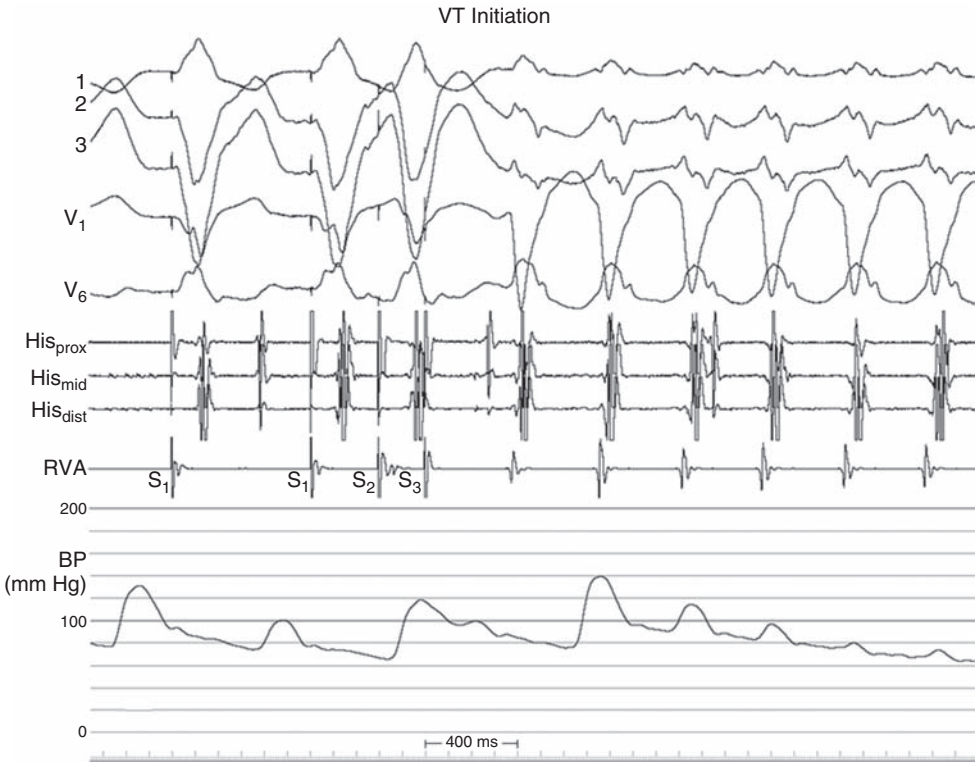


Figure 28-5

With double ventricular extrastimuli, rapid VT is induced; blood pressure is very poor and pacing termination was necessary within a few seconds after this recording (Fig. 28-5) was made.

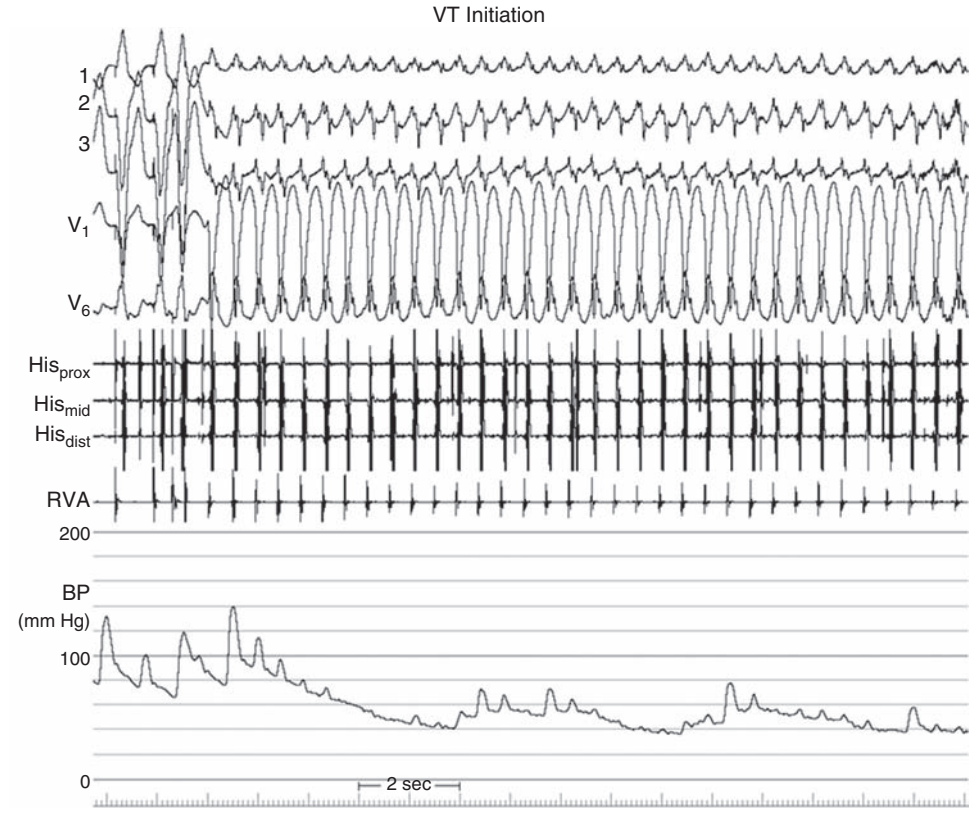


Figure 28-6

Fig. 28-6 presents the same events at a slower sweep speed and clearly shows the poor blood pressure response during induced VT.

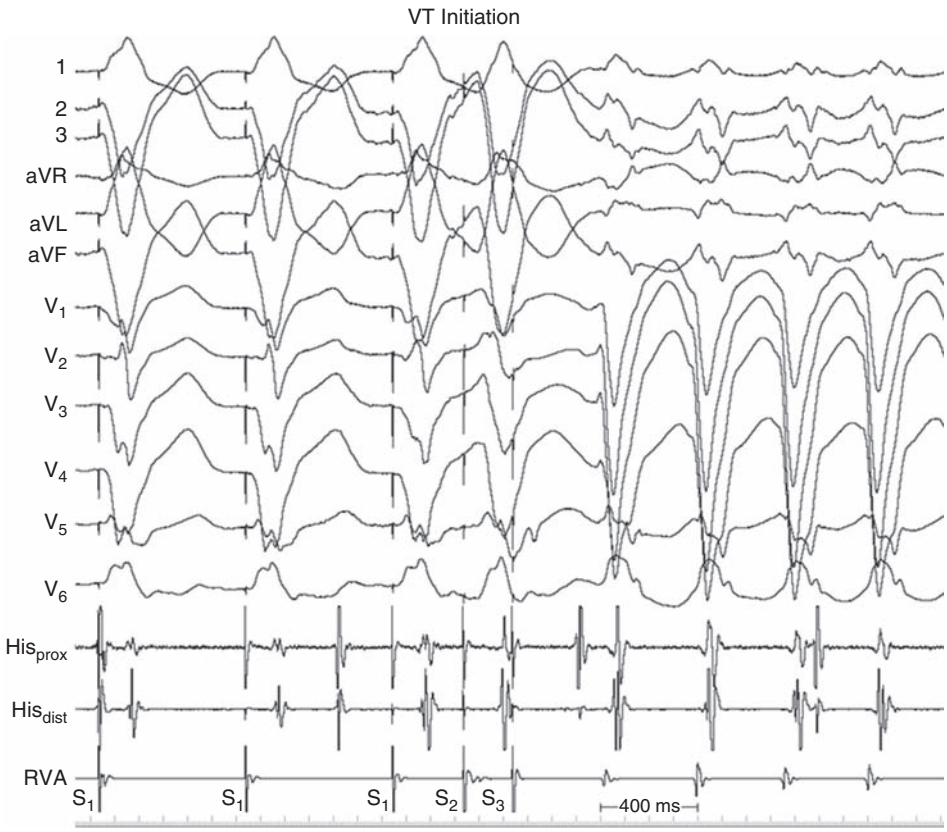


Figure 28-7

In Fig. 28-7, the same events as in the prior figure are shown, but this time displaying all 12 ECG leads. Of note, there is no His potential visible during VT.

VT ECG

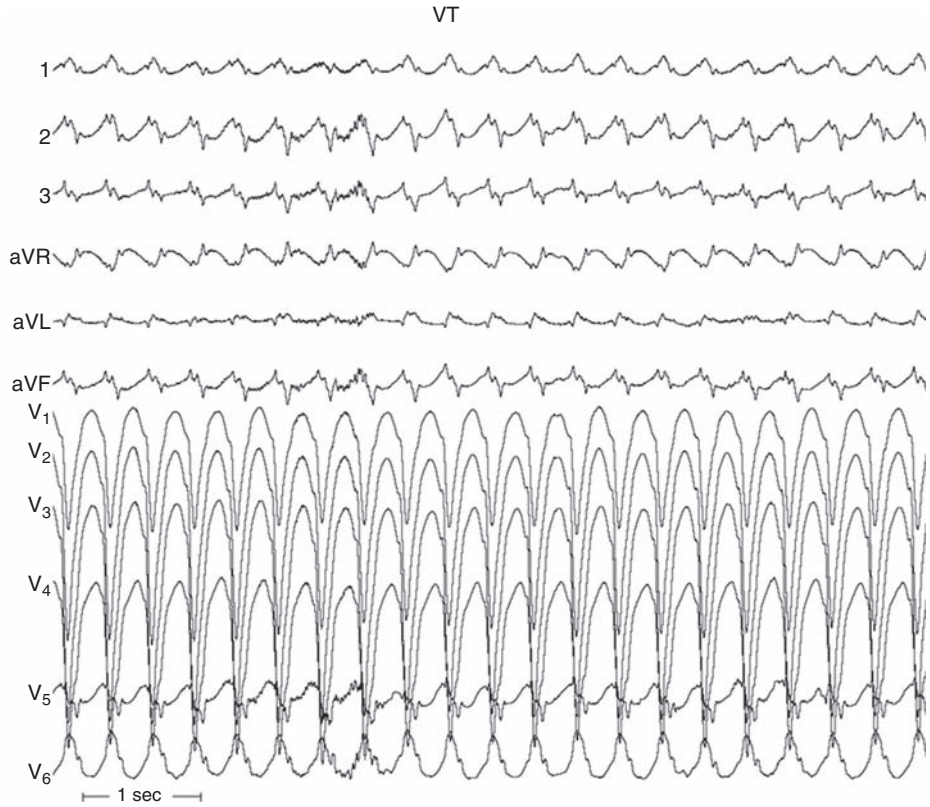


Figure 28-8

The full 12 leads of ECG during this induced VT are shown in Fig. 28-8, having an LBBB morphology (similar to what was described as having been initiated at the previous procedure).

VT Termination

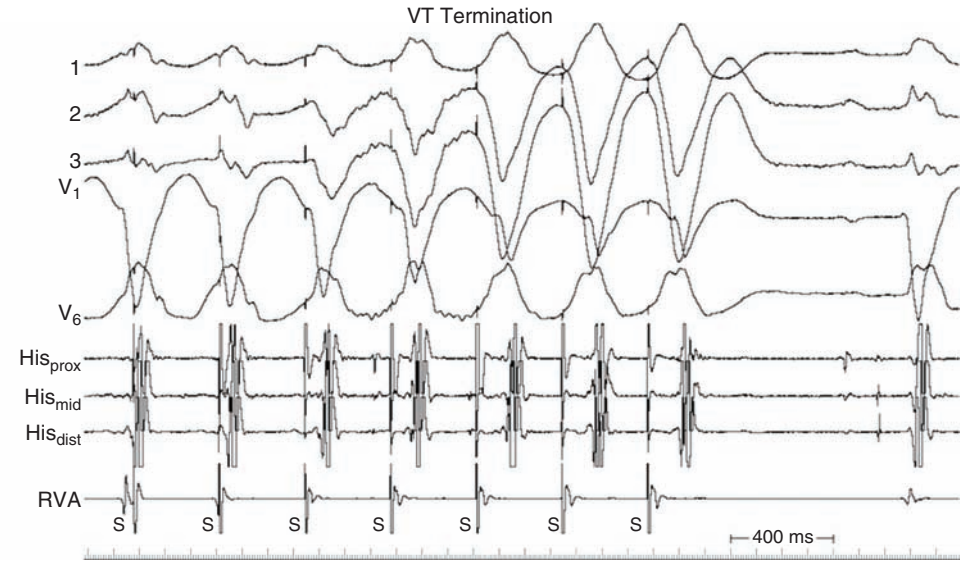


Figure 28-9

Fortunately, a single burst of ventricular pacing was able to terminate VT to sinus rhythm (Fig. 28-9). The situation at this time is as follows: VT is inducible but severe hypotension during VT precludes activation mapping under the current conditions. He had already undergone extensive substrate mapping and ablation, with little beneficial effect. Options at this point include the following: adding an inotropic agent to support blood pressure and

reinitiate VT; add procainamide or amiodarone to slow VT rate, hoping for better hemodynamic stability, and attempt activation mapping if VT is tolerated; use pacemapping to guide ablation; repeat substrate mapping and ablation; perform epicardial mapping and ablation; discontinue procedure and come back another day with mechanical hemodynamic support (percutaneous ventricular assist device, etc.)

Baseline ECG (Nonpaced)

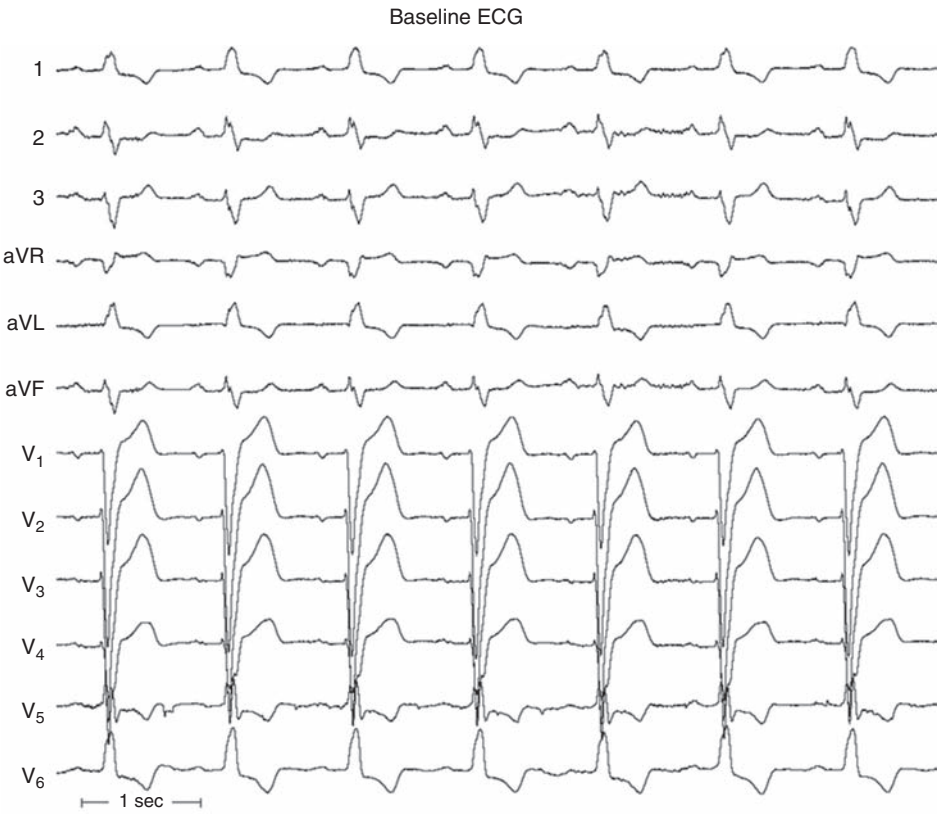


Figure 28-10

Before proceeding, it is worth a look back at what has already been learned in the procedure, starting with the nonpaced ECG at the beginning; this shows a LBBB morphology (Fig. 28-10).

Baseline Intracardiac Recordings Again

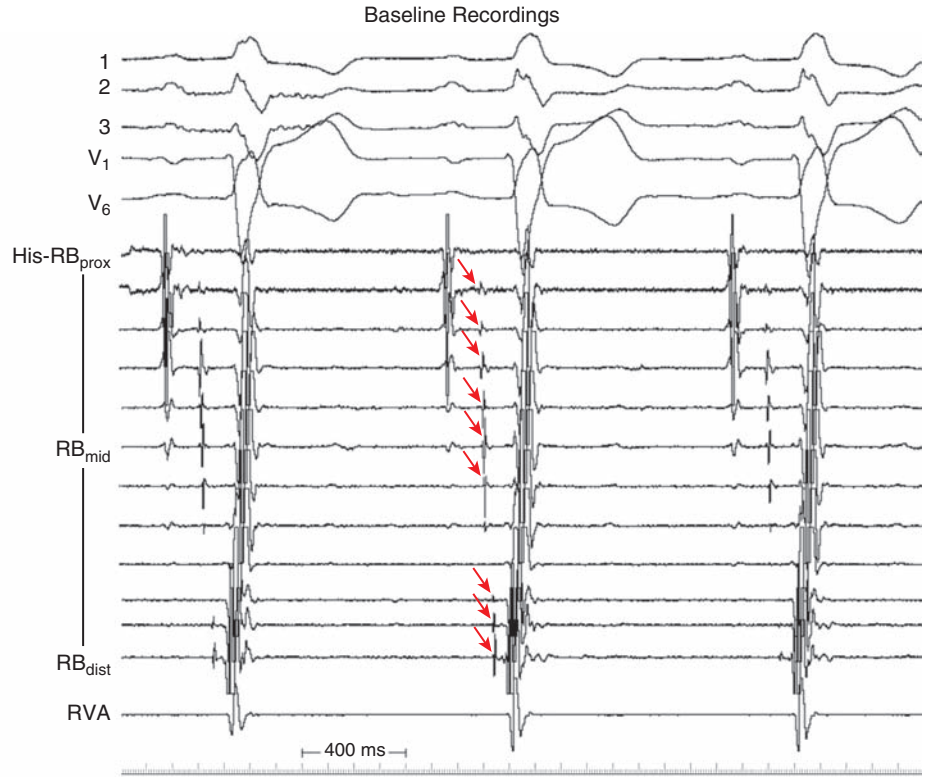


Figure 28-11

Another look back at sinus rhythm before induction of VT shows additional recordings made at the time, but not displayed earlier (Fig. 28-11). A decapolar catheter had been placed roughly in the usual His recording position, extending into the right ventricle along course of the right bundle branch; in addition, the quadripolar catheter usually used for recording the His bundle was placed more distally on the right ventricular aspect of the interventricular septum. Recordings from these two catheters are labeled His-RB_{prox} through RB_{dist}, and show small potentials representing His and RBB recordings *(arrows)*.

VT Initiation Again

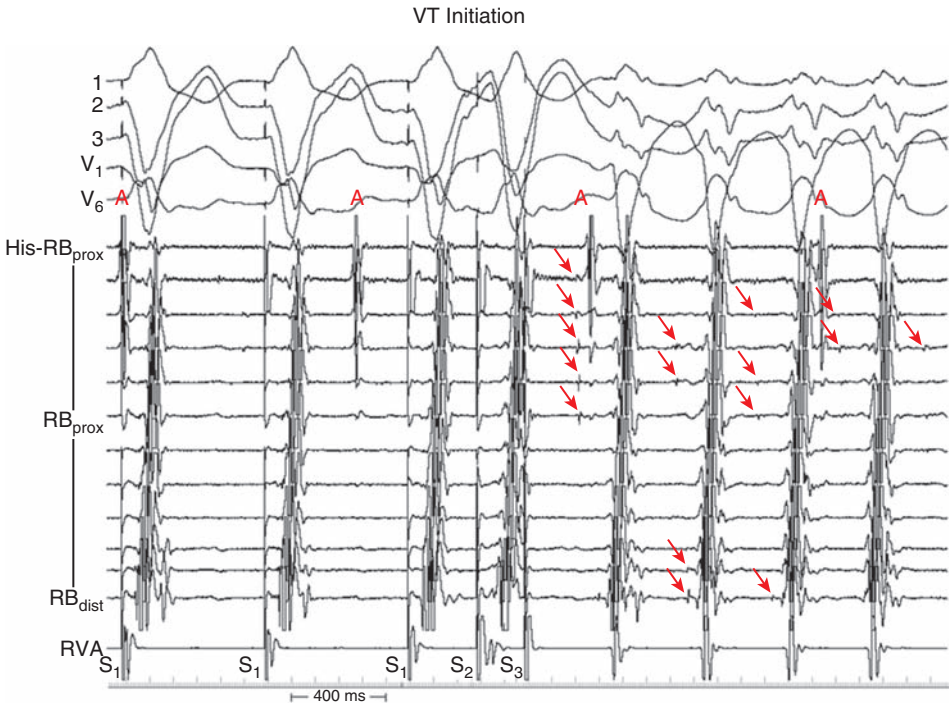


Figure 28-12

Another look back at induction of VT shows the additional recordings described in the prior figure that were made at the time, but not displayed earlier (Fig. 28-12). Recordings from these two catheters show small potentials *(red arrows)* during initiation of VT that are consistent with His and bundle branch potentials; the HV here is about 110 ms (in sinus rhythm, 95 ms). The mere presence of His potentials during VT does not allow a diagnosis of bundle branch reentry (because these are frequently seen in all forms of VT), but is consistent with it. Dissociated atrial electrograms are also seen (*A*).

VT Compared with Sinus Rhythm ECGs

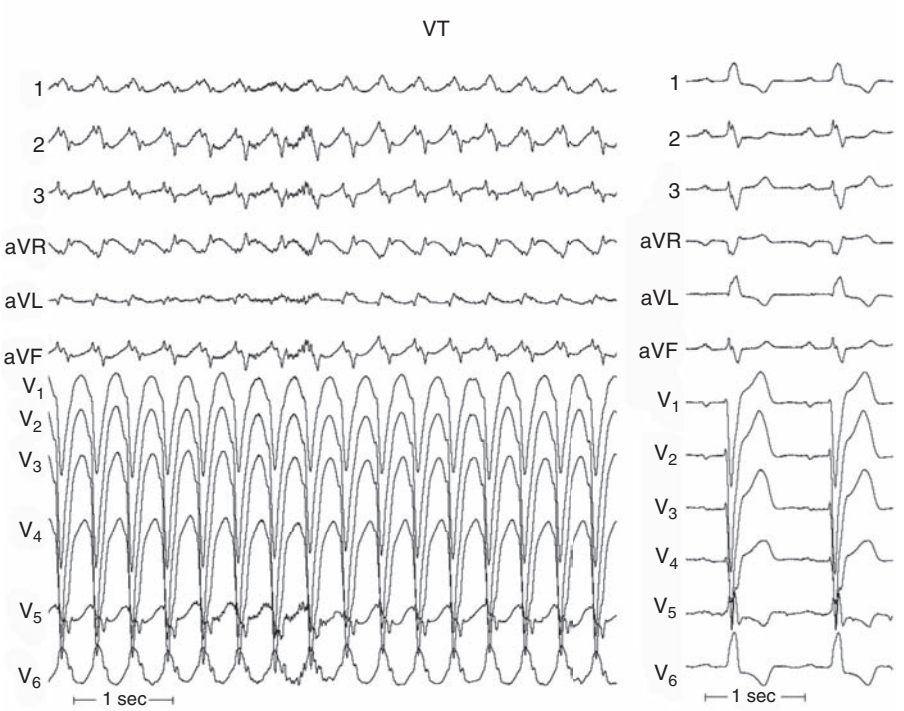


Figure 28-13

Another look at the 12-lead ECG of VT (in Fig. 28-13) shows similarities to the nonpaced QRS (at right) at the beginning of the procedure.

His Recordings During VT

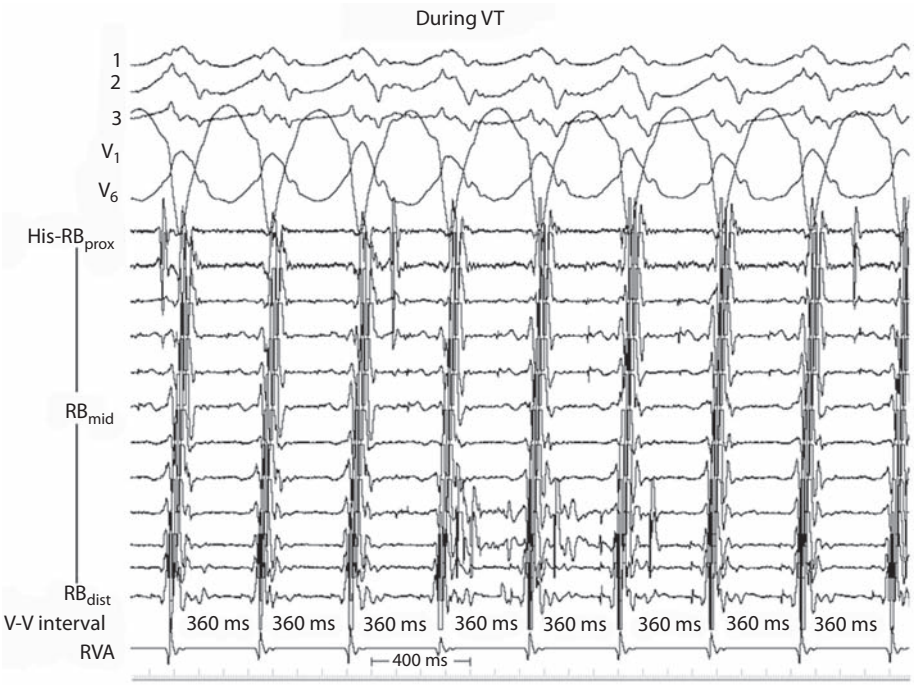


Figure 28-14

A few seconds after initiation of VT, but before pacing termination, the recordings in Fig. 28-14 were made. All intervals appear constant, affording no opportunity to test which signal leads others.

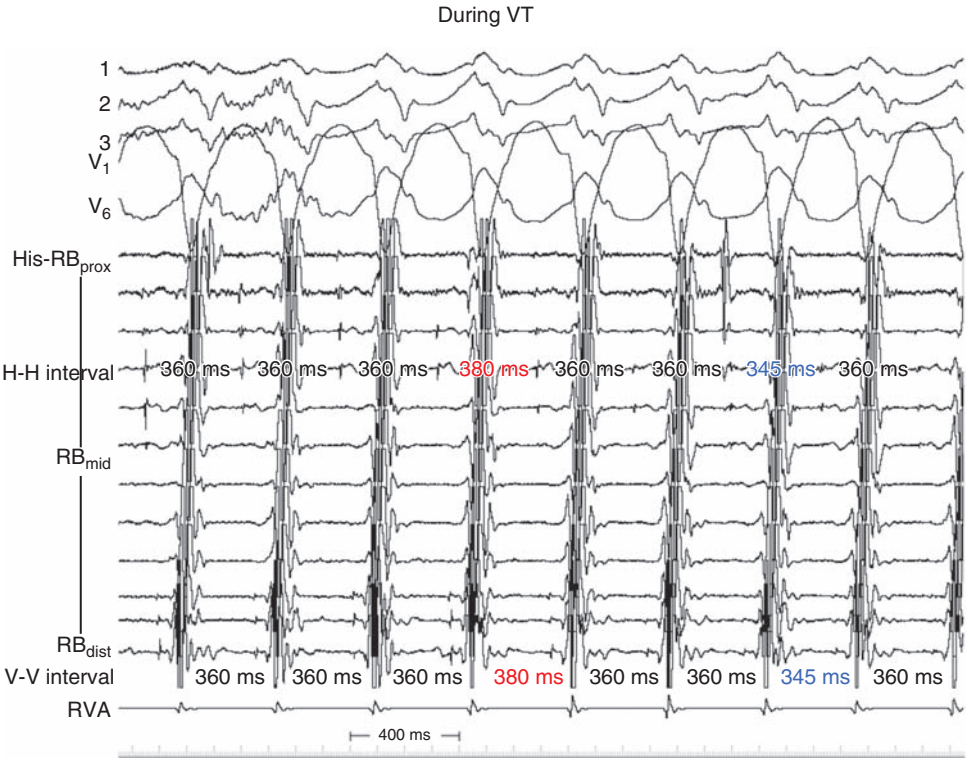


Figure 28-15

A few seconds still later, immediately before pacing termination, some irregularity of VT cycle length is seen (Fig. 28-15); it appears that changes in H-H intervals as shown precede changes in V-V intervals, strongly indicating that His-Purkinje activation drives the VT.

Ablation Site

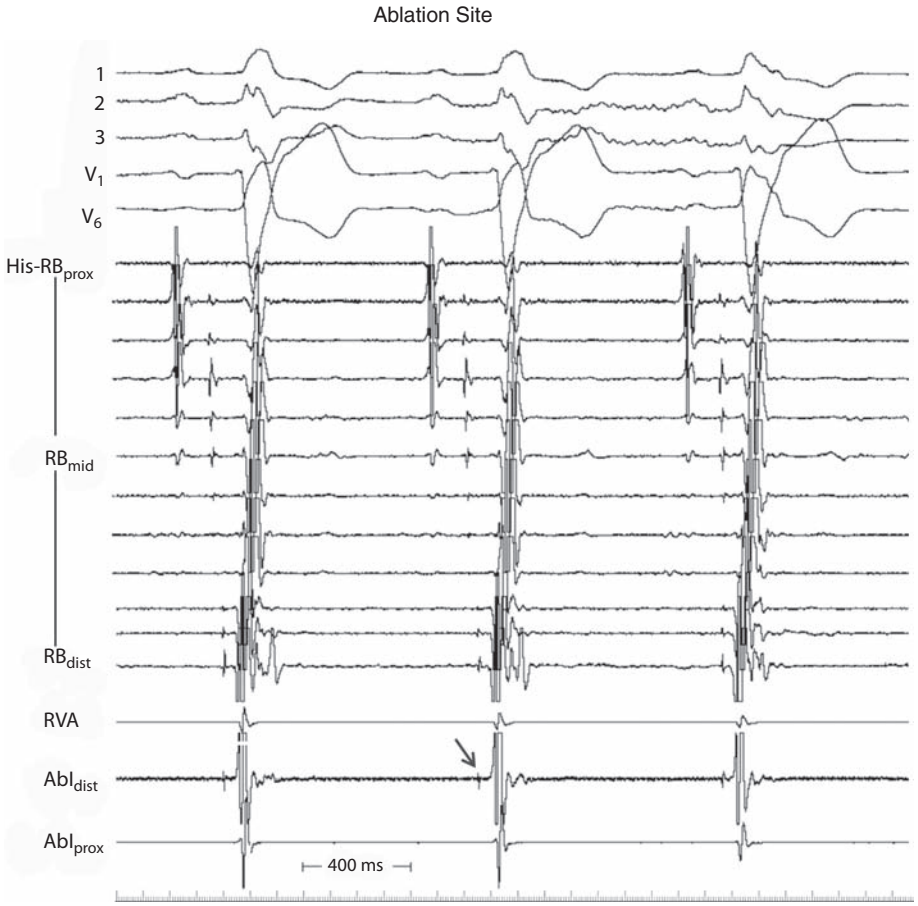


Figure 28-16

With all the data taken together (LBBB in sinus rhythm and similar morphology in VT; long HV baseline and during VT; H-H changes preceding V-V changes during VT; early activation of the RV apex during VT), a diagnosis of bundle branch reentrant VT was made and the RBB was targeted for ablation. Further maneuvers (attempted entrainment from RV) were not attempted because of hemodynamic instability during VT. In Fig. 28-16, a very small, sharp RBB potential *(arrow)* is evident in the ablation recording. These are often of very low amplitude and may be missed if the signal gain is not adequate.

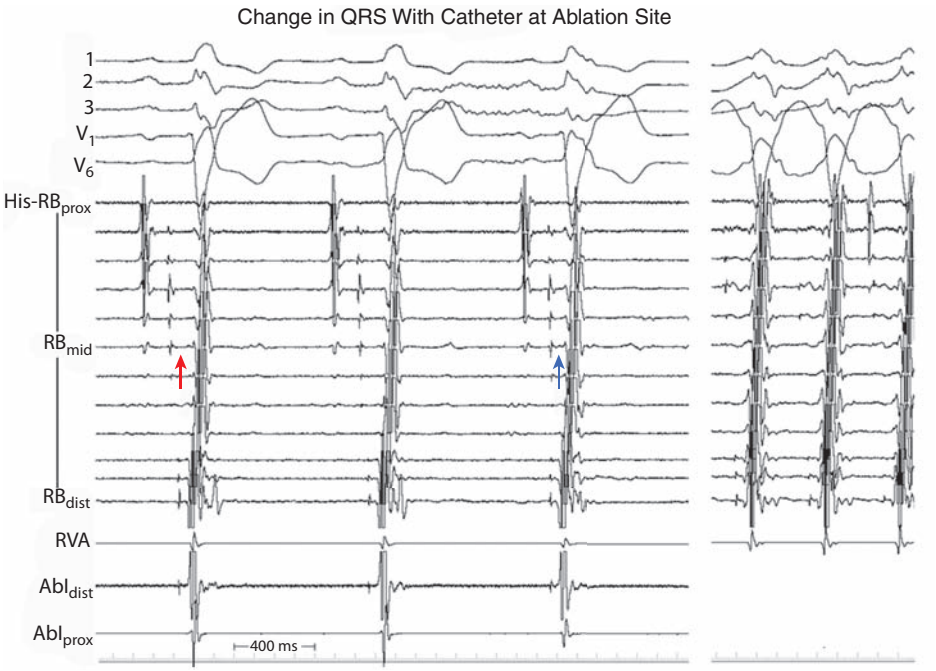


Figure 28-17

Catheter pressure at the ablation site (Fig. 28-17) appeared to cause mild prematurity of the RBB potential (shorter HV interval at *blue arrow* than *red*). Of note, this was accompanied by a slight change in the QRS complex, making it still more like the VT complexes (shown in the right panel). This is likely related to change in the site of breakout from the RBB to initiate ventricular activation.

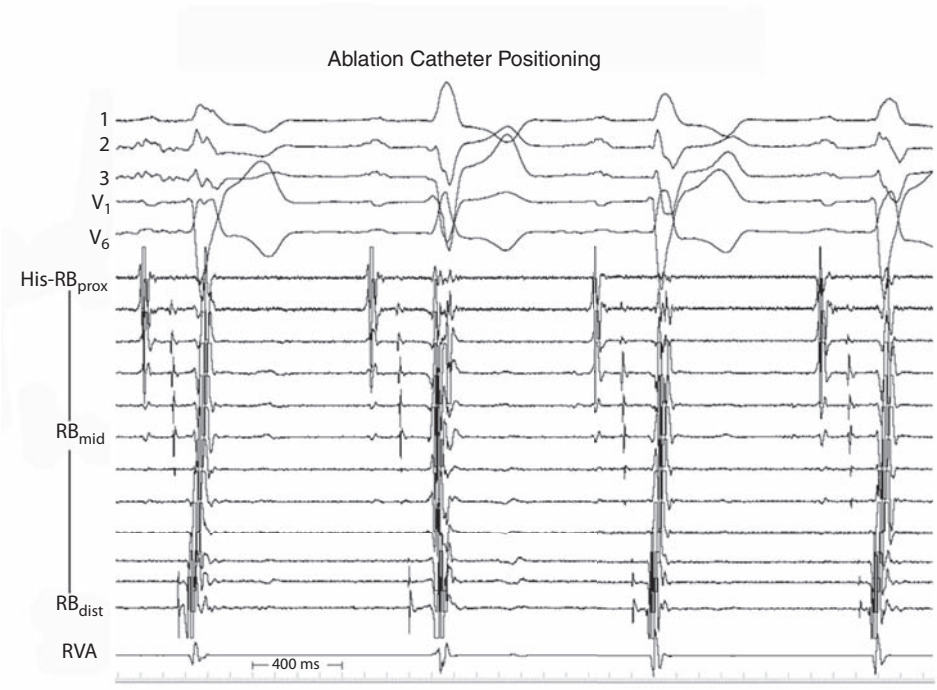


Figure 28-18

Additional catheter manipulation caused further changes in QRS complex and RBB-local ventricular activation times as shown in Fig. 28-18.

RF Ablation

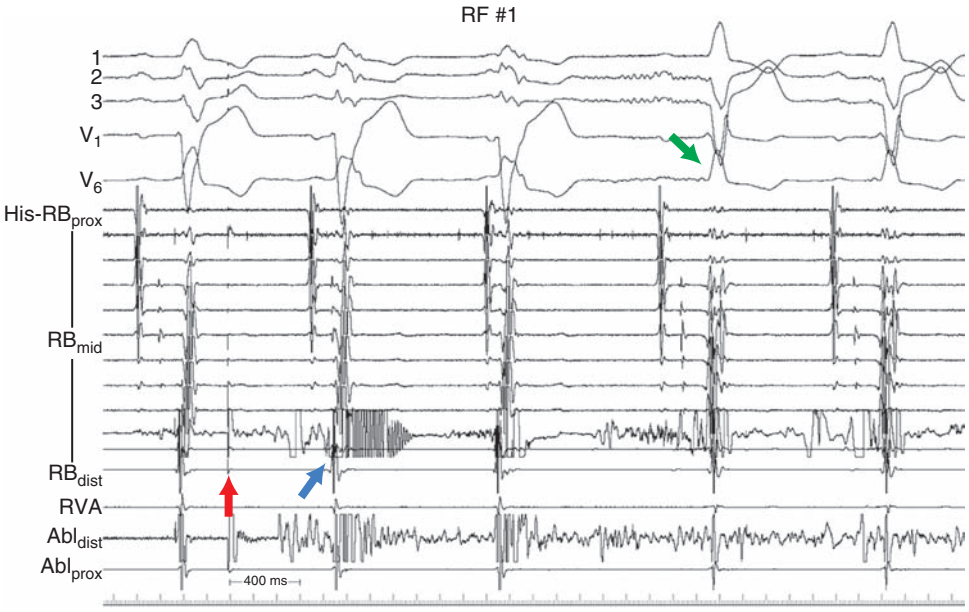


Figure 28-19

Radiofrequency (RF) energy (Fig. 28-19, delivery starting at *red arrow*) results in an accelerated rhythm *(blue arrows)* from the ablation site followed by elimination of conduction over the RBB *(green arrow)*. As is very often the situation in similar cases, RBBB in the presence of preexisting apparent LBBB does not result in complete heart block, but reveals very slow anterograde conduction over the left bundle branch (showing RBBB with a long HV interval).

Final ECG

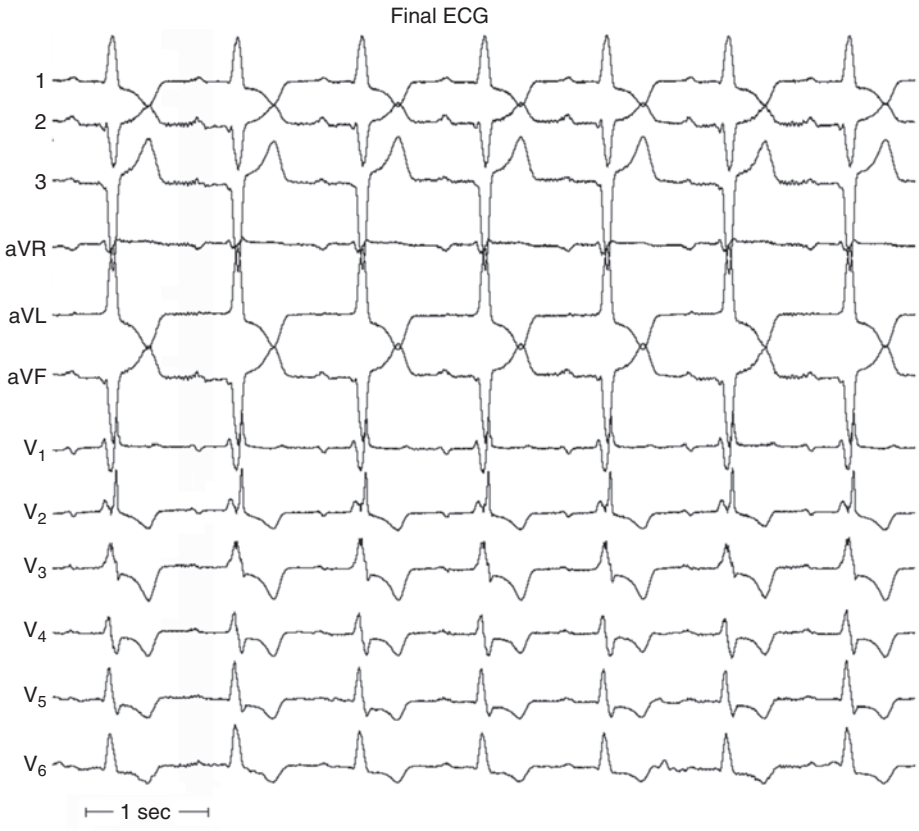


Figure 28-20

The final 12-lead ECG shows RBBB with left axis deviation.

After ablation, repeat ventricular stimulation showed no inducible ventricular arrhythmias; the patient's ICD was reprogrammed to atrial sensed biventricular pacing. After over 2 years of follow-up, no arrhythmias were detected by the ICD (Fig. 28-20).

Other Examples of Bundle Branch Reentry

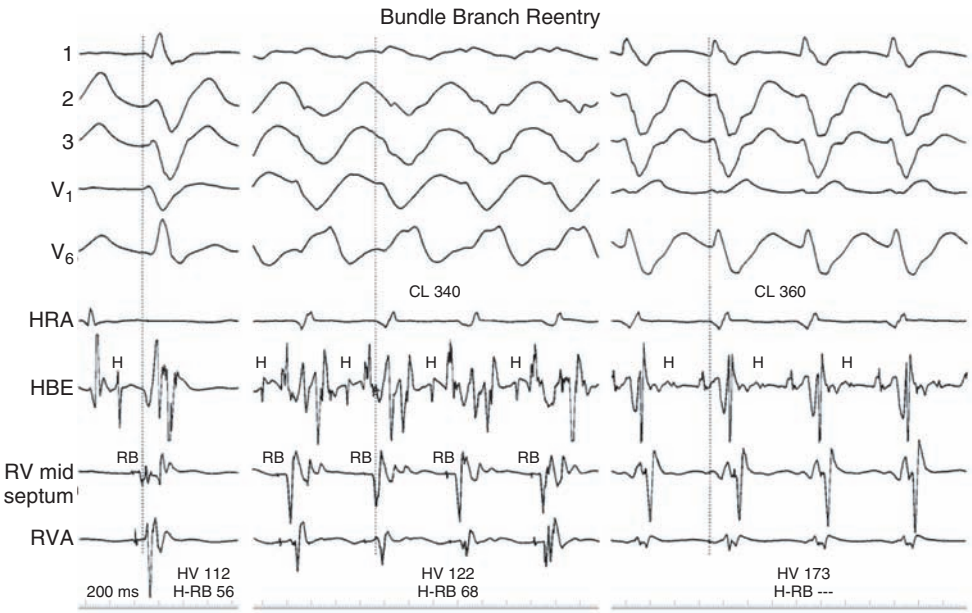


Figure 28-21

In a different patient, two episodes of bundle branch reentry (BBR) with opposite directions of circulation in the His-Purkinje system are illustrated in Fig. 28-21 with sinus rhythm at left, typical LBBB-type BBR in center, and RBBB-type BBR at right. Note relative timing of His and right bundle (RB) branch recordings.

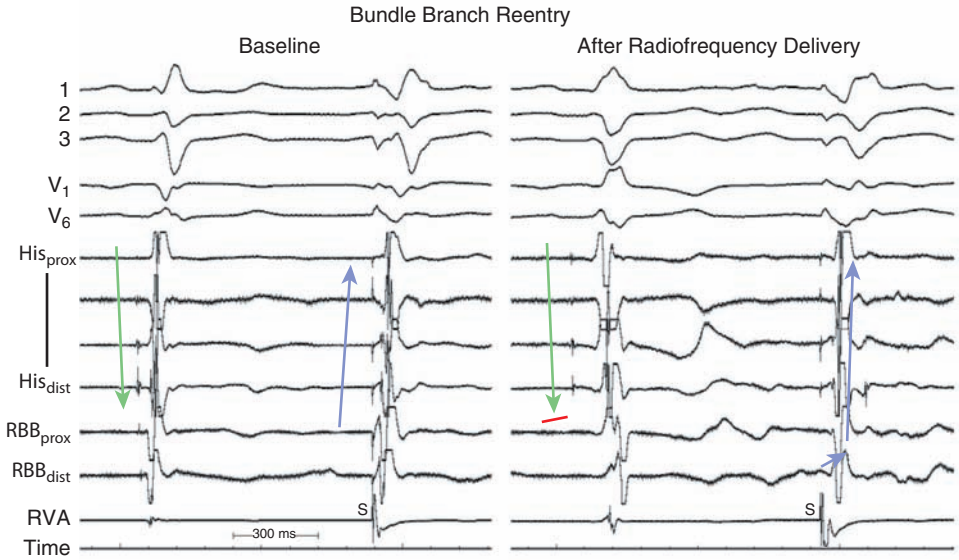


Figure 28-22

In yet another case of BBR, recordings along the RBB are shown in Fig. 28-22 before (baseline) and after RBB ablation, in sinus rhythm (complex at left in each panel) and right ventricular pacing (complex at right in each panel). *Green arrow* indicates anterograde propagation in the RBB during sinus rhythm (blocked after ablation, *red line*), whereas the *blue line* indicates retrograde propagation over the RBB. After ablation, retrograde RBB activation is dramatically delayed (appears after the local ventricular electrogram).

Summary

- Bundle branch reentry is not uncommon in patients with dilated cardiomyopathy
- At least a moderate level of suspicion is necessary for preparing correct recordings to make diagnosis
  - Multiple His + RB recordings are essential (ideally, LB also)
  - Standard catheter setup may easily miss the diagnosis
  - Look for spontaneous variations in VT cycle length (if preceded by H-H changes, BBR is diagnosed)
- Ablation of RB may unmask slow, but present, conduction over the LB with a very long HV interval
- Other myocardial VTs are present in at least 30% of patients, generally necessitating ICD placement (if not already present)

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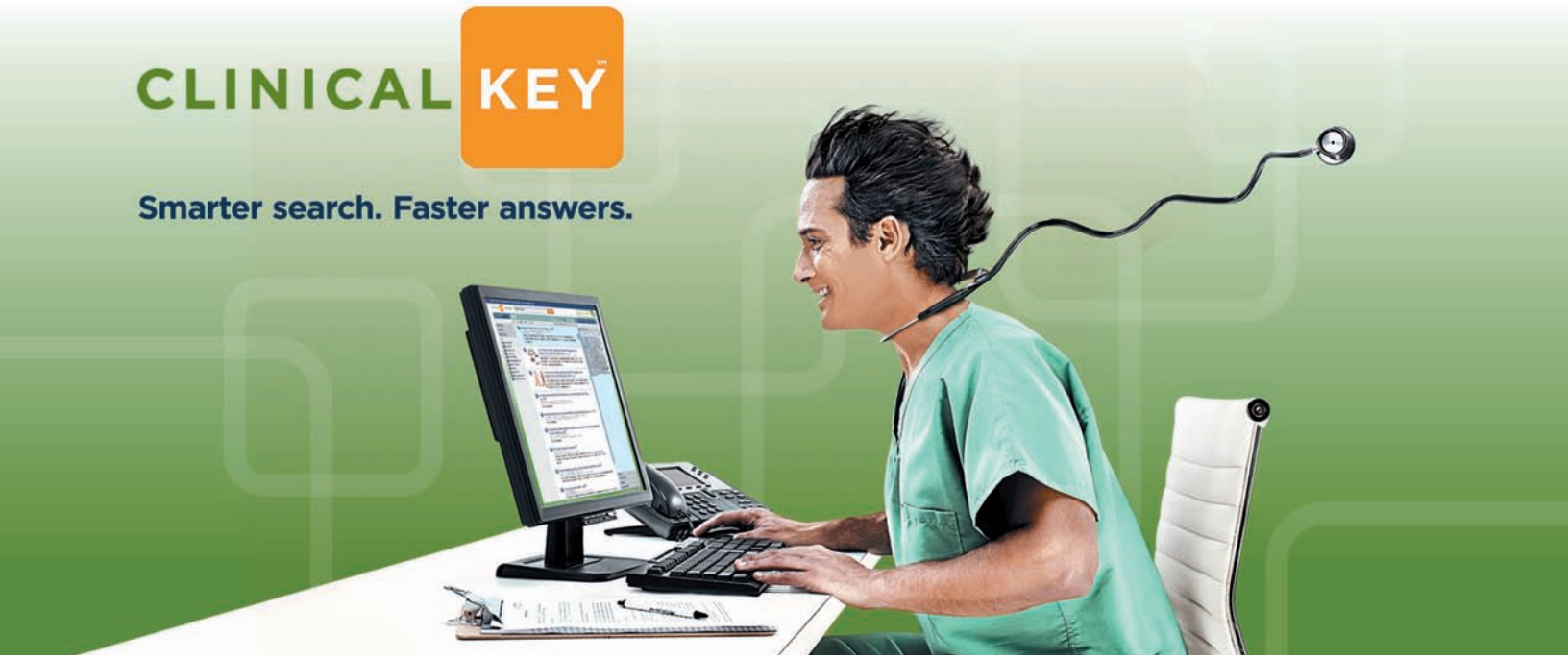

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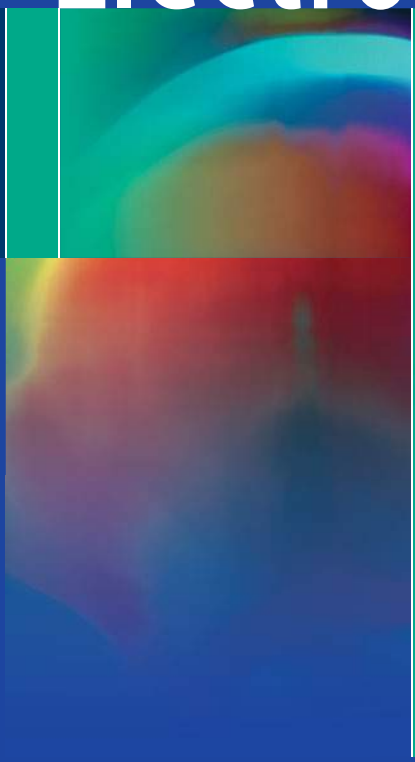

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Clinical Handbook of Cardiac Electrophysiology

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Clinical Handbook of Cardiac Electrophysiology

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ISBN 978-3-319-40816-3 ISBN 978-3-319-40818-7 (eBook)
DOI 10.1007/978-3-319-40818-7

Library of Congress Control Number: 2016948592

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BMG: Pro auxilio sempiterno eorum, toti familiae meae, maxime, uxori, Nualae et filiae, Luciae et filio, Hugo, maximas gratias ago. Cum amore, Benedictus

Foreword

Clinical Handbook of Cardiac Electrophysiology, written and edited by Benedict M. Glover and Pedro Brugada, is a unique book. As the authors acknowledge in the preface, many excellent textbooks have been published on this topic. However, Glover and Brugada make the point that few provide a practical synopsis to bridge the chasm separating basic physiology, anatomy, and pharmacology from its practical application. That is the admirable goal of this book: to serve as the conduit between the basic scientist and beginner, for cardiology fellows, residents, and support personnel. The first three chapters lay a foundation for the rest of the book, including cardiac anatomy and basic electrophysiology (Chap. 1); the electrophysiology study, maneuvers, and ablation (Chap. 2); and electroanatomic mapping (Chap. 3). This book then embarks on a journey discussing the major cardiac arrhythmias including AV nodal reentrant tachycardia (Chap. 4), accessory pathway conduction (Chap. 5), atrial tachycardia (Chap. 6), atrial flutter (Chap. 7), atrial fibrillation (Chap. 8), ventricular tachycardia (Chap. 9), and antiarrhythmic drugs (Chap. 10).

I found this book to be authoritative and to the point with its main strength being the presentation at a level easily comprehended by the early learner. The many figures are very well done in that regard, very helpful and easily comprehended. This book will serve as an excellent stepping-stone for those who wish to delve further into electrophysiology mysteries, or as a final resting place for those contents with a basic understanding. Either way, *Clinical Handbook of Cardiac Electrophysiology* is an important contribution for learners.

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Preface

Cardiac arrhythmia management has evolved as one of the most rapidly expanding fields within medicine. The development of catheter ablation has transformed the treatment of many arrhythmias, providing highly effective treatment options for the majority of tachyarrhythmias. There is also considerable research and development of more effective antiarrhythmic and anticoagulant drugs. Despite these huge technical advances, it is important to understand the basic principles of arrhythmia mechanisms in order to help make a diagnosis and chose an effective treatment strategy.

Although there are many excellent and detailed reference texts in this field, there are few handbooks which provide a practical overview bridging the gap between basic physiology, anatomy, pharmacology and interventional catheter ablations with precise details which should help in the intricate management of the patient.

This book covers all the important aspects of cardiac electrophysiology, presented in an easy-to-use format. For each arrhythmia, the aetiology, classification, clinical presentation, mechanism, electrophysiology set up (including precise set up and ablation parameters) and trouble-shooting are presented and demonstrated using illustrations, fluoroscopy images, ECGs and endocavity electrograms.

The overall aim of this book is to provide a logical and practical approach to cardiac arrhythmia management. We hope that this provides a useful resource and, importantly, helps to promote this wonderful sub-specialty.

This book is aimed at cardiac electrophysiologists, fellows, cardiologists, physicians, family practitioners, cardiology trainees, students, allied professionals and nurses. Given its succinct summary of electrophysiology, this should be available as a reference guide in the electrophysiology laboratory. We hope that this reaches a truly international audience and provides an important guide for those studying for heart rhythm exams.

Kingston, ON, Canada — Benedict M. Glover
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Chapter 1
Cardiac Anatomy and Electrophysiology

Benedict M. Glover, Orla Buckley, Siew Yen Ho, Damian Sanchez-Quintana, and Pedro Brugada

Abstract Cardiac electrophysiology has rapidly moved from the mapping and ablation of accessory atrioventricular connections and ectopic foci to more extensive mapping and substrate modification. Training in cardiac electrophysiology requires a detailed knowledge of the anatomy and physiology of the heart. In order to understand the basis of cardiac electrophysiology it is important to discuss the different phases of the cardiac action potential, variability in morphology and duration throughout the heart and the most important ion channels and electrolyte shifts responsible for depolarization and repolarization of the cardiac cells. Electrophysiology continues to rely heavily on an understanding of these basic principles as well as the relevant anatomy of all cardiac chambers and surrounding structures. It is therefore fundamental to have a thorough understanding of cardiac anatomy as visualized on fluoroscopy, echocardiography, CT, MRI and 3 dimensional cardiac mapping systems.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_1

The Cardiac Action Potential

Spontaneous depolarization of cells within the sinus node (SN) results in propagation of excitation throughout adjacent cells within the right atrium (RA) and left atrium (LA). The electrical impulse spreads through the atrioventricular (AV) junction into the His bundle, through the Purkinje network and then into the ventricular muscle where activation occurs from the septum spreading through the endocardium, mid-myocardium and finally the epicardium.

Each cardiac cell undergoes a process of depolarization and repolarization, which is recorded across the cell membrane as an action potential and occurs as a result of the relative concentration of ions (predominantly potassium, sodium and calcium) and electrostatic forces across the membrane. As shown in Fig. 1.1 this is composed of 5 components in atrial and ventricular myocytes and 3 components in the SN and AV node. The QTc on the surface ECG is an approximation of the mean duration of the ventricular action potential.

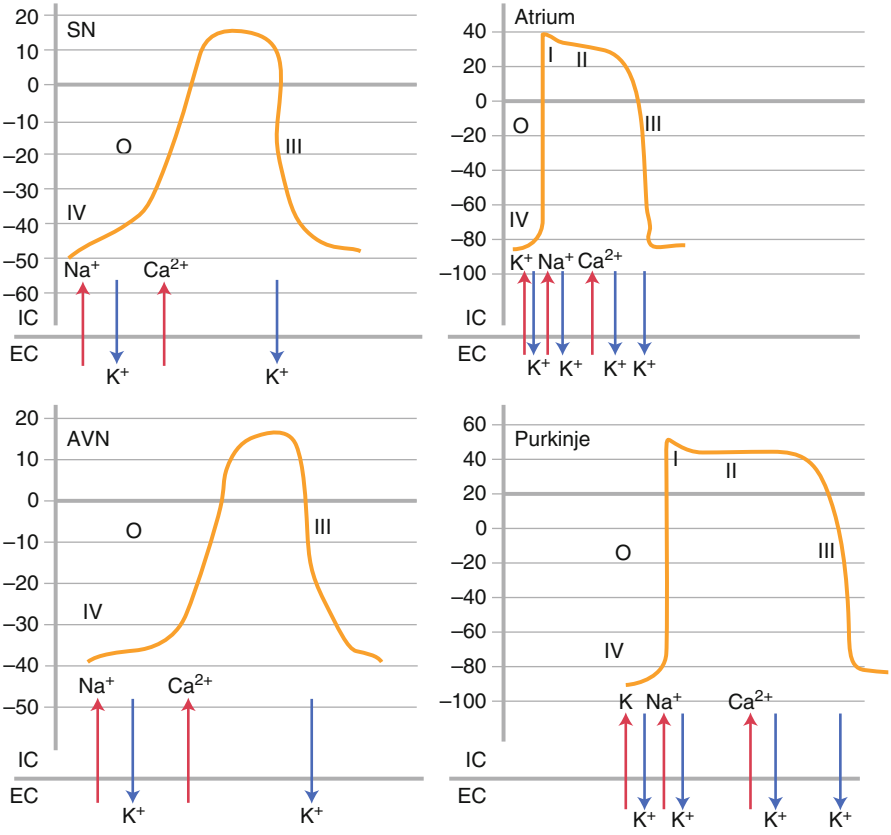


Fig. 1.1 Cardiac action potentials recorded from the SN (*top left*), atrium (*top right*), AV node (AVN) (*bottom left*) and Purkinje network (*bottom right*) and the predominant ionic currents responsible for theses changes in membrane potential (*IC* intracellular, *EC* extracellular, Na^+ sodium, Ca^{2+} calcium, K^+ potassium)

Phase IV is known as the **resting membrane potential**. This is recorded as −80 to −95 mV in atrial, Purkinje and ventricular cells. It is slightly less negative in the atrium than the ventricle. In the SN it is −50 to −60 mV and the AV node −60 to −70 mV. In both the SN and AV nodes there is a slow spontaneous diastolic depolarization which merges with Phase 0 resulting in spontaneous automaticity while Phase IV in other cells is generally more flat.

This is followed by **Phase 0** where the membrane potential becomes positive and is therefore known as **rapid depolarization**.

Phase I, **rapid repolarization** occurs in the atrium and ventricle but not in the SN and AV node. It is much more prominent in the Purkinje and epicardial cells.

Phase II is the **plateau phase** where the action potential becomes relatively flat and does not occur in the SN or AV node. It is followed by **Phase III**, which is known as **rapid repolarization** resulting in restoration of the membrane potential to the resting phase.

Phase IV (Resting Phase)

In the atrium and the ventricle this occurs largely as a result of the balance of potassium (K^+) across the cell membrane and is relatively flat with only a very slight slope.

K^+ is found in much higher concentrations in the intracellular space compared with the extracellular space. As a result of this there is an outward motion of K^+ leaving predominantly negative anions inside the cells at baseline.

This is counteracted during the resting phase by the inward rectifying current, (IK1). In general rectifier currents allow current to pass in a preferential direction. In the case of IK1 the transmembrane channel responsible allows the inward movement of K^+ at more negative potentials than the reversal outward K+ potential with less current movement at more positive membrane potentials [1]. This results in a very slight upward curve as the cell becomes less negative.

The resting phases in the SN and AV node are different from those recorded in the atrium and ventricle. As well as being less negative there is a continual slow spontaneous diastolic depolarization. This occurs as a result of the funny current (If) which plays the predominant role in this phase as opposed to the Ik1 current. This current is activated at voltages in the diastolic range resulting in a slow and steady inward Na^+ current (INa) which would normally occur in the depolarization phase in atrial and ventricular cells. There is also a slow outward movement of K^+ with the overall combined effect of a less negative cell membrane potential.

Phase 0 (Depolarization)

In the atrium and ventricle as a result of electrical stimulation from adjacent myocytes, a rapid inward sodium current (INa^+) results in the abrupt initial upstroke in the action potential known as Phase 0.

There are principally two Na^+ gates responsible for depolarization called the **activation** and **deactivation gates**. At the start of depolarization the activation gates are closed while the deactivation gates are open. As the action potential becomes less negative the activation gates tend to open rapidly allowing the inward movement of Na^+ while the deactivation gates tend to close slowly. This continues beyond zero voltage at which point the rate of Na^+ entry into the cell slows. As the deactivation gates close the fast Na^+ channels become inactive. These remain closed until Phase III of the action potential.

Depolarization in the SN and AV node does not occur as a result of INa^+ but rather as a result of calcium entry through the L-type calcium channels (ICaL) and T-type calcium channels (ICaT).

Phase I (Early Repolarization)

As the vast majority of the inward current deactivates, a rapid transient outward potassium current (Ito) results in early rapid repolarization. Phase I is much more prominent in Purkinje fibers and in epicardial myocytes and does not occur in the SN or the AV node.

Phase II (Plateau Phase)

The plateau phase occurs in the atrium and ventricles as a result of an inward movement of calcium ions (ICaL) combined with an outward movement of potassium (IKs, IKr and IKUr). As the voltage becomes less negative during depolarization the ICaL and ICaT channels become active.

ICaL channels are the predominant type found in cardiac myocytes and are activated when the voltage reaches −30 mV. ICaT channels which are less common in cardiac myocytes are activated at more negative voltages.

Overall ICaL activation begins in late depolarization. Ca^{2+} crosses from outside the cell where the concentration is higher relative to the inside.

K^+ shift is also partially responsible for the plateau phase. The balance of K^+ across the cell membrane is similar to that during the resting phase but the voltage is positive rather than negative which results in an outward movement of K^+ from the cell. The overall balance between the inward movement of calcium and the outward movement of K^+ results in the plateau phase. The transient outward current (Ito) is expressed in the atrium more than the ventricle. As a result of this there is a greater outward movement of K^+ versus the inward movement of calcium resulting in a shorter plateau phase.

Phase II does not occur in the SN or the AV node.

Phase III (Repolarization)

As the outward movement of K^+ exceeds the inward movement of Ca^{2+} the voltage becomes more negative resulting in repolarization. Although the delayed rectifier currents Ikr and Iks are activated during depolarization their action tends to be delayed and gradually increases during the plateau phase. Next to Ito the inwardly rectified K^+ current (Ik1) is also responsible for repolarization although this is more active as the voltage across the cell membrane becomes less negative and is responsible for the small bump seen in the action potential during repolarization.

All these K^+ currents are responsible for restoration of the K^+ balance. The Na^+ which entered the cell during depolarization is removed by the Na^+/K^+ ATPase enzyme while calcium which entered the cell during the plateau phase is removed by the Na^+/Ca^{2+} exchanger.

Repolarization in the SN occurs as a result of the rapid outward movement of K^+ as well as inactivation of the inward Ca^{2+} current making the cell more negative.

Refractoriness

Refractoriness describes the period after phase 0 of the cardiac action potential during which a stimulus does not result in a new depolarization.

There are three different types of refractory periods (RP): relative, absolute and effective.

The **relative RP** is the longest coupling interval resulting in local capture therefore marking the end of refractoriness.

The **absolute RP** is the longest coupling interval which does not result in local capture. The absolute and relative RP's are depicted in Fig. 1.2.

The **effective RP** is the longest coupling interval delivered which fails to propagate through the distal tissue.

In the clinical electrophysiology laboratory the RP is calculated by performing an **extrastimulus test**. In order to perform this the threshold for stimulation is measured in diastole by pacing at a fixed rate and decreasing the intensity of the pacing stimulus until capture fails.

Following a drive of eight beats at a fixed rate (to establish a steady state) a single extrastimulus is introduced at twice the diastolic threshold at shorter intervals until capture no longer occurs. This can be seen in Fig. 1.3 where pacing from the high RA is performed at a cycle length of 600 msec for 8 beats (drivetrain) in order to achieve a steady state followed by a decremental extrastimulus. In this example the first beat on the left is the final beat of the drive train. The extrastimulus occurs at a cycle length of 280 msec and captures the atria but fails to conduct over the AV node. This is considered to be the AV node ERP.

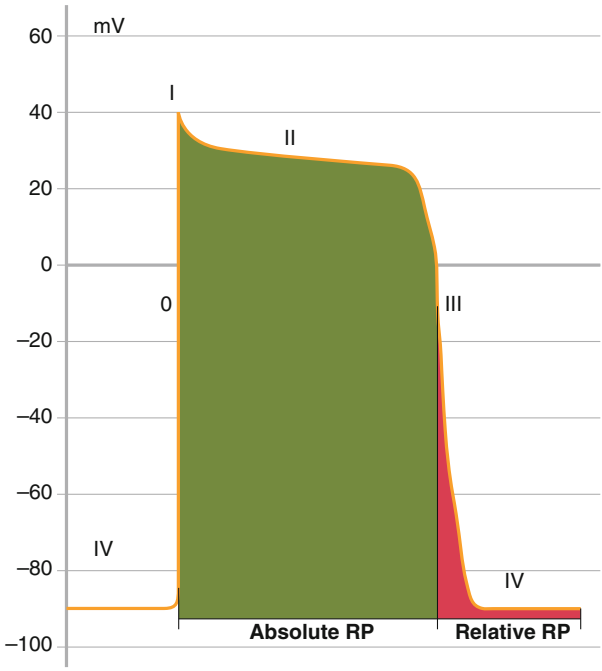


Fig. 1.2 Diagram showing the absolute RP and relative RP during the cardiac action potential. The absolute RP occurs from phase 0 until the transmembrane potential reaches -60 mV during phase III. During this time a stimulus will not result in depolarization. The relative refractory period follows this in which a high voltage stimulus may result in further depolarization

Arrhythmia Mechanisms

Arrhythmias may be classified as either **macro re-entry** or **focal**. Focal arrhythmias may be caused by **micro re-entry**, **enhanced automaticity**, **or triggered activity**.

Re-entry

A very common mechanism of clinical cardiac arrhythmia is re-entry. During re-entry a wave of excitation moves around a circuit which is determined anatomically, functionally or a combination of the two. A macro re-entry circuit which makes understanding of re-entry easy is the circuit during circus movement tachycardia in patients with the Wolf-Parkinson-White (WPW) syndrome (Fig. 1.4).

For re-entry to occur the following conditions have to be fulfilled:

1. There must be two or more pathways for conduction (for example the AV node and accessory pathway in WPW)
2. Unidirectional block in one pathway
3. Alternative conduction over the other pathway with sufficient delay as to retrogradely invade the formerly blocked pathway.

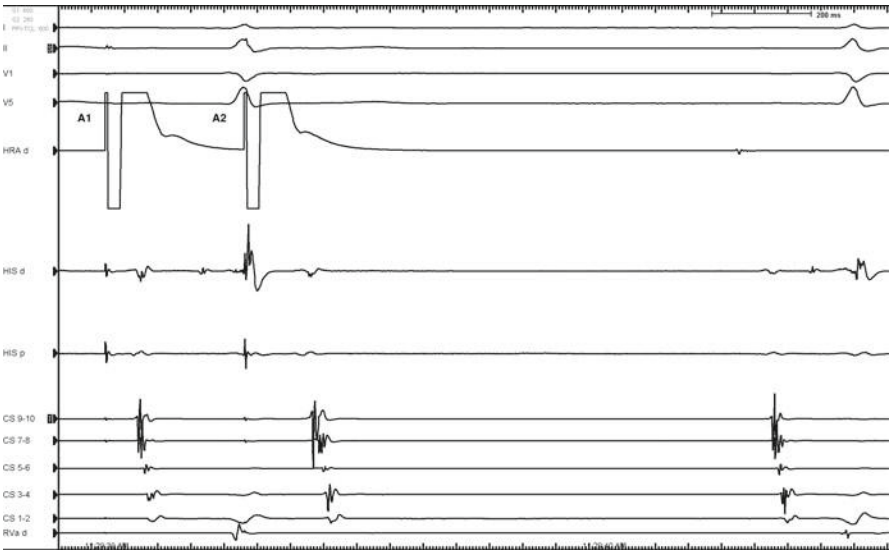


Fig. 1.3 Example of extrastimuli testing by pacing from the high RA (HRA d). The first paced beat on the *left of the image* is the final beat of the drive train where pacing is performed at 600 msec (*A1*). This beat conducts through the His to the ventricle via the AVN. This is followed by an extrastimuli which is performed at a progressively shorter cycle length. In this example this occurs at 280 msec (*A2*). Capture is seen on the high RA (HRA d) and the coronary sinus (*CS*) with lack of conduction through the AV node. This is considered to represent the AV node refractory period. (CS 9–10 is positioned in the proximal CS while CS 1–2 is in the distal CS, His d is positioned along the distal His, His p along the proximal His and RV a d is positioned in the RV apex)

For a re-entry circuit to sustain, the length of the circuit must be greater than or equal to the product of the conduction velocity and the refractory period termed the wavelength of the circuit. The pathways involved in these circuits must therefore have different conduction properties and refractoriness. A slow conduction pathway ensures that the wave of depolarization does not reach tissue which is refractory and thus terminate the arrhythmia.

Another requirement is the existence of a region of conduction block. This may be either anatomical or functional. Anatomical block may be structural such the tissue which exists between the slow and fast pathways in AV nodal re-entry tachycardia (AVNRT) or scar tissue in ischemic VT or functional such as occurs in typical atrial flutter. Functional block occurs as wavelets collide with each other and thus prevents the leading edge of the circuit stimulating refractory tissue resulting in termination of the arrhythmia. Most re-entry circuits involve a combination of structural and functional regions of block. A diagrammatic representation of a re-entry circuit is shown in Fig. 1.5.

The **wavelength of the circuit** is a product of the conduction velocity and the refractory period.

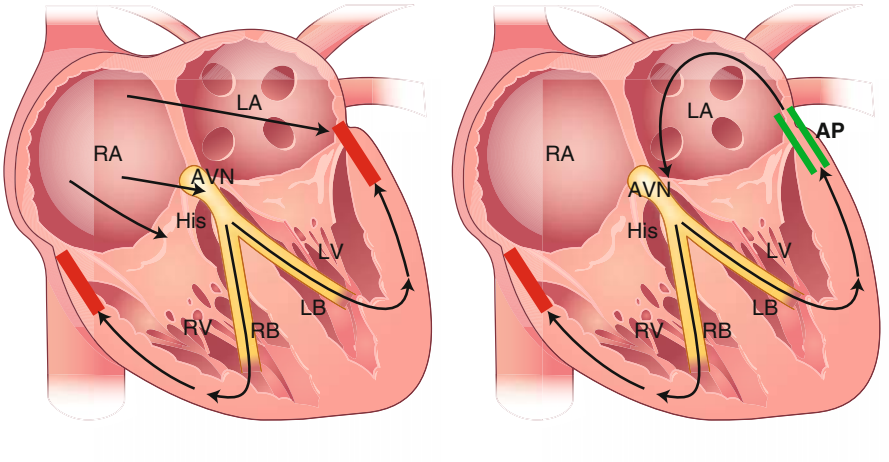


Fig. 1.4 Diagram showing the initiation of circus movement tachycardia (CMT) in a patient with WPW. In the *left image* conduction occurs antegradely through the AV node and is blocked retrogradely as there is no accessory pathway present. In the *right image* a re-entry tachycardia is demonstrated utilizing the AV node as the antegrade limb and the AP as the retrograde limb. *Arrows* indicate the predominant direction of conduction. The *red lines* indicate blocked conduction which prevents a re-entry circuit while the green lines indicate retrograde conduction over an accessory pathway. A denotes atrium, AVN is the AV node, V is ventricle and AP is the accessory pathway

Automaticity

Automaticity results from spontaneous depolarization during phase IV of the AP. Although this is a feature of automatic cells such as the SN, AV node, His bundle and Purkinje cells, if it occurs in other cells then it is considered to be abnormal (ectopic focus).

Spontaneous depolarization does not normally occur in atrial and ventricular myocytes but may occur as a result of various physiological or pathological changes which on a cellular level may result in a reduction in the expression or function of the IK1 channel [2].

Latent automatic cells are normally suppressed by SN activity and only become functional if the sinus rate becomes slower than the rate of spontaneous discharge of these cells. Some regions of increased automaticity are protected from SN discharge and therefore discharge independently of this. These cells which demonstrate evidence of entrance block with exit conduction are called **parasystolic foci** and tend to result in ectopic beats with intervals which are multiples of each other [2]. Incomplete entrance block may also occur resulting in entrainment of the focus at a defined rate resulting in ectopic beats with a fixed coupling interval.

One of the typical features of increased automaticity is the ability to overdrive pace at a rate faster than the tachycardia cycle length. This occurs as a result of an

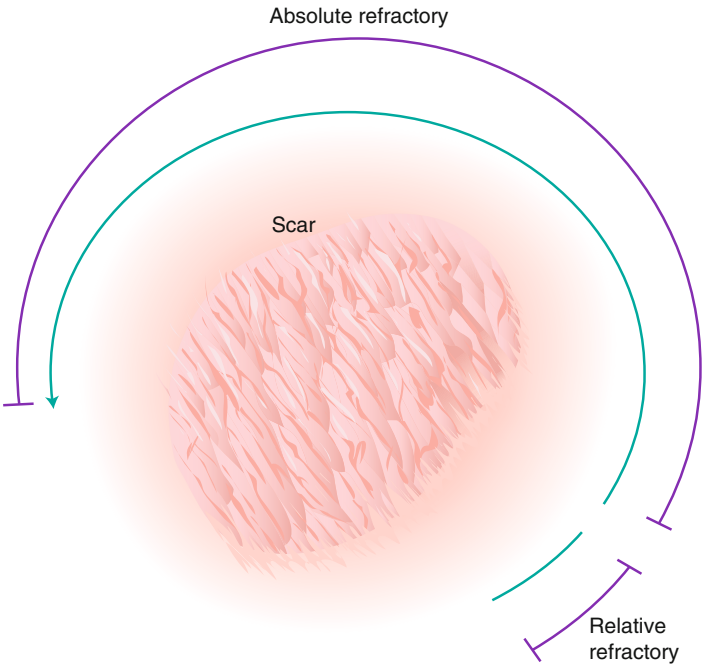


Fig. 1.5 Diagrammatic representation of a re-entry circuit circulating around a conduction barrier in this case scar. The region of tissue where the wavefront is propagating corresponds with tissue during the absolute RP. The tail of the wavefront corresponds with tissue during the relative RP

increase in the activity of the Na^+/K^+ ATPase pump resulting in the generation of a hyperpolarizing current which inhibits phase IV of the action potential [3].

Afterdepolarizations and Triggered Activity

Afterdepolarizations are defined as depolarizations which occur after Phase 0 of the cardiac action potential and may result in a spontaneous action potential known as a triggered response. These are divided into early afterdepolarization (EAD) or delayed afterdepolarization (DAD). These are depicted in Fig. 1.6.

EAD occurs during phase II and phase III while DAD occur after the cardiac action potential is complete. EADs tend to occur when there is an increase in the inward movement of positive ions during the plateau phase of the action potential.

DAD occur as a result of an increase in the inward movement of calcium. This can occur in the setting of digoxin toxicity or in conditions such as catecholamine induced polymorphic ventricular tachycardia (CPVT).

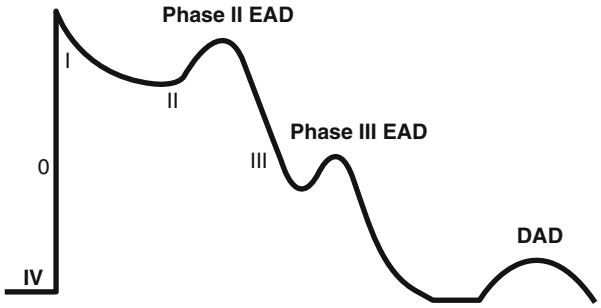


Fig. 1.6 Diagrammatic representation of phase II and phase III early atrial depolarizations (*EADs*) and delayed atrial depolarizations (*DADs*) at the end of the cardiac AP

Anatomy of the Cardiac Chambers

The cardiac chambers may be visualized prior to a complex ablation using computed tomography (CT) or magnetic resonance imaging (MRI) or during the procedure using fluoroscopy, echocardiography and electroanatomic mapping (EAM). The majority of procedures rely on a certain amount of fluoroscopic imaging and often our anatomical understanding is based on the locations of the catheters in various views. The most common views in the electrophysiology laboratory are the right anterior oblique (RAO), left anterior oblique (LAO), posterior – anterior (PA) and left lateral (LL). These views are shown in Fig. 1.7.

The RAO projection helps to demonstrate the postero-anterior (PA) location of a catheter within the cardiac chambers and shows the AV groove more clearly than the PA view. In this view the spine is on the left. Moving the catheter to the right results in a more anterior orientation while moving to the left is more posterior. The left cardiac border is formed by the RV outflow tract (RVOT) superiorly with the RV superior wall inferior to this and the LV apex at the apex. More steep RAO images result in a greater proportion of the RV being visualized with less LV present. The inferior wall of the RV forms the base of the image while the right cardiac border is formed by the posterior wall of the RA and posterior wall of the LA. The AV annular fat strip is best seen in the RAO projection. This 1 cm thick white line is formed as a result of the overlap of the ring of fat in the right anterior, septal and left posterior annulus and either marks the course of, or is slightly ventricular to the coronary sinus (CS). Any catheter posterior to the fat strip is in the atrium and anterior to this is in the ventricle.

In the LAO view the AV rings are viewed parallel to the image. The left cardiac border is formed by the LA superiorly and the lateral wall of the LV inferiorly. Steeper LAO views image more LA and less LV. The right cardiac border is formed by the right atrial appendage superiorly and the RV free wall inferiorly. In this view the spine is on the right side of the image. In the LAO projection anterior is to the left and posterior to the right.

In the PA view the left cardiac border is formed superiorly by the tip of the left atrial appendage (LAA) and the anterior wall of the left ventricle (LV) more inferiorly and the LV apex at the apex. The right heart border is formed by the superior

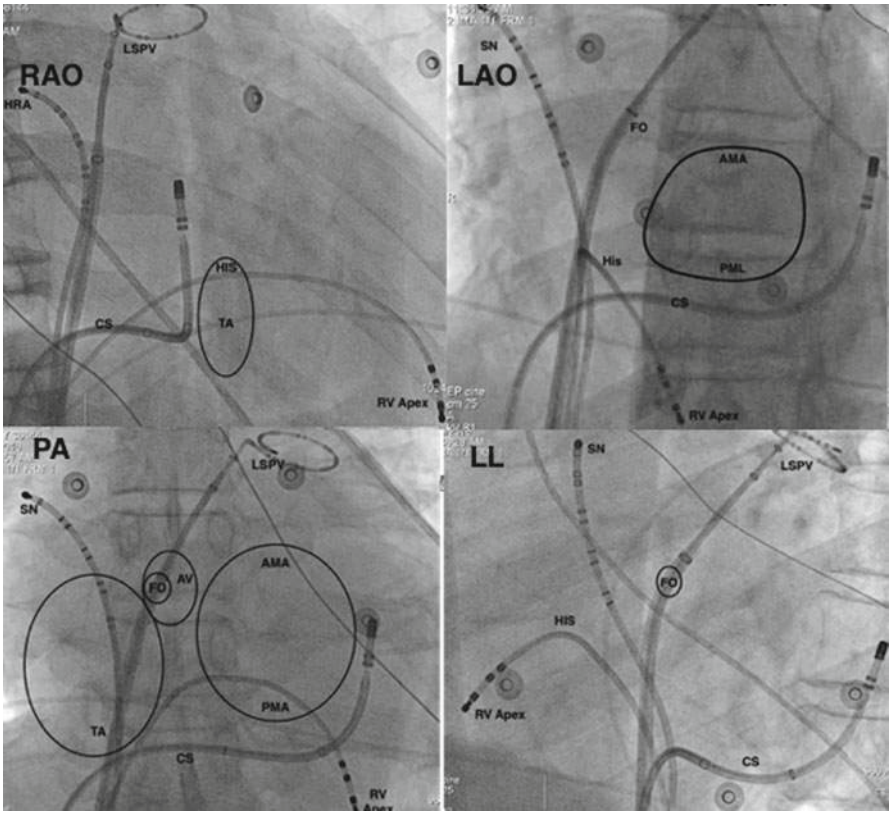


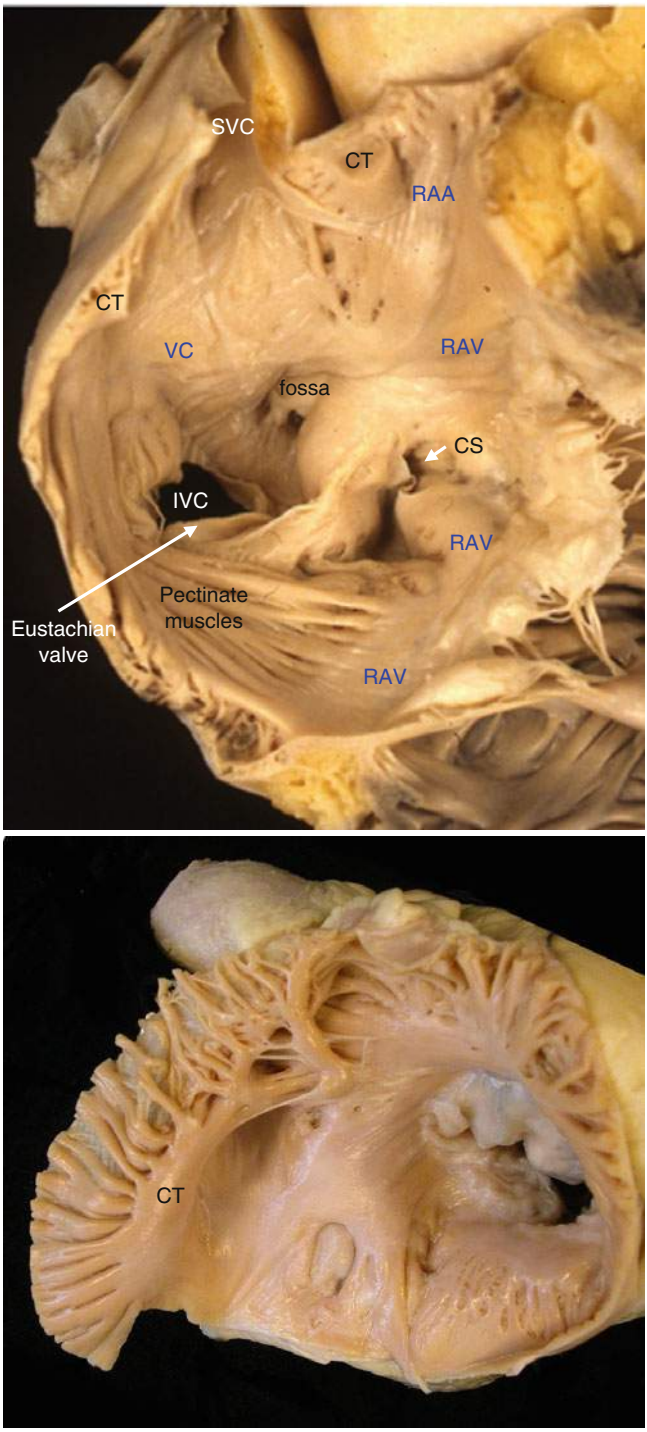
Fig. 1.7 The main fluoroscopic views used in the electrophysiology laboratory. All images have a catheter positioned in the coronary sinus (*CS*), RV apex, high right atrium (*HRA*) close to the sinus node (*SN*) and a catheter positioned across the fossa ovalis (*FO*) into the left superior pulmonary vein (*LSPV*). The location of the His is superimposed on the image. The tricuspid annulus (*TA*), mitral annulus (*MA*, anterior mitral annulus (*AMA*) and posterior mitral annulus (*PMA*)) and aortic valve (*AV*) are superimposed on the four views. The *top left view* shows the RAO projection, *top right* shows an LAO projection, *bottom left* a PA view and the *bottom right* shows a *left lateral view*

vena cava (SVC) to right atrial (RA) junction superiorly and the lateral wall of the RA inferior to this. The base is comprised of the inferolateral wall of the RV.

The LL view is very helpful in determining the anterior – posterior location of the catheter. This is useful for trans-septal access as well as for epicardial access in VT ablation.

The RA

The RA lies anterior, inferior and rightward from the LA and is composed of the venous component, appendage and vestibule. The anatomy of the RA is shown in Fig. 1.8.


SVC
CT
RAA
CT
VC
RAV
fossa
CS
IVC
RAV
Pectinate muscles
Eustachian valve
RAV
CT

The superior and inferior vena cava drain systemic blood into the smooth-walled posterior venous component of the RA. Coronary blood flows through the CS into the RA through the CS os which is located between the inferior vena cava (IVC) and the tricuspid annulus (TA). The CS os is to a variable degree covered by the Thebesian valve which is a thin crescent shaped structure attached at the posterior and inferior boundary of the coronary sinus os. The degree of coverage varies but may practically occlude the CS os in up to 25 % of individuals [4].

The RA appendage is a triangular broad based structure composed of pectinate muscles originating from the **crista terminalis** and is generally where atrial pacemaker leads are positioned for stability. The crista terminalis is one of the most common regions responsible for focal atrial tachycardia's as well as acting as a functional electrical barrier essential for typical atrial flutter. It separates the pectinated appendage from the venous component (or intercaval area) of the atrial body. The latter is posterior whereas the vestibule which surrounds the atrial outlet leading to the tricuspid valve is anterior.

The SN

The SN is a collection of nodal cells within a tough matrix of connective tissue lying just below the epicardium and separated from the endocardium by a layer of atrial myocardium. It is located at the junction between the superior vena cava and the RA, at the antero-lateral quadrant marked by the crista terminalis (CT) (Fig. 1.8) and statistically measures 10–20 mm in length, 3 mm in width and 1 mm in depth but there is an enormous anatomical variation between individuals [5]. Cells in the SN tend to be much smaller than those in the RA measuring approximately 5–10 μm. Typical nodal cells known as P cells are located in the centre of the SN and are generally poorly organized myofilaments. There are fibroblasts and collagen fibers interspersed throughout the SN. There is a gradual transition between the SN and the RA with a disparity in conduction velocity between the cells thus preventing SN depolarization as a result of atrial depolarization [6].

Spontaneous phase IV diastolic depolarization starts at −65 mV until the activation threshold is reached at −40 mV resulting in rapid depolarization. The action potential of the SN differs from that of a Purkinje myocyte with a more gradual upslope and the absence of a plateau phase. Diastolic depolorization occurs as a

Fig. 1.8 Anatomy of the RA (*top image*) and the crista terminalis (*bottom*). The RA is antero-inferior to the LA and is composed of the venous component (*VC*), RA appendage (*RAA*) and RA vestibule (*RAV*). The superior (*SVC*) and inferior vena cava (*IVC*) are seen connected posteriorly into the RAV. The RA appendage is an anterior structure composed of pectinate muscles originating from the crista terminalis (*CT*). The coronary sinus (*CS*) is inferior and posterior. Superior and slightly posterior on the interatrial septum is the fossa ovalis. In the image below the crista terminalis is seen with pectinate muscles radiating out

result of activation of the If current. This operates in a voltage range more negative than normally occurs in the central pacemaker cells (less than −45 mV). It therefore has maximum activity during hyperpolarization and progressively increases opposing repolarization and then initiating diastolic depolarization [7].

The rate of diastolic depolarization in the SN is affected by both sympathetic adrenergic and parasympathetic muscarinic stimulation. This is predominantly affected by the If channel.

Sympathetic adrenergic stimulation results in an increase in the gradient and duration of diastolic depolarization with minimal effects on the overall action potential duration [8]. This occurs as a result of a shift in the activation curve to more positive voltages without a change in the conductance of the If channel as a result of an increase in intracellular cAMP [9].

The reverse occurs with parasympathetic muscarinic stimulation [10]. Slow inward Ca^{2+} channels are involved in the later phase of diastolic depolarization [8] as well as the upslope in the action potential. The transient T type Ca^{2+} channel is activated at more negative voltages and therefore opens first followed by the long lasting L component which opens during the upslope of the action potential [8].

The delayed rectifier Ik channel is the predominant potassium channel in the SN and contributes to repolarization allowing the following depolarization to be initiated.

Respiratory sinus arrhythmia occurs as a result of a reduction in the PP interval with inspiration and a prolongation of the PP interval with expiration. The maximum difference between the longest PP and shortest PP interval should be less than 160 ms. This phenomenon reduces with age.

Ventriculophasic sinus arrhythmia is seen in association with third degree AV block in which the PP interval surrounding a QRS complex is shorter than the PP interval not surrounding a QRS complex.

SN dysfunction encompasses sinus bradycardia, sinus pause, sinoatrial exit block, chronotropic incompetence and inappropriate sinus tachycardia.

Sinus bradycardia is a relatively common finding and in the absence of symptoms is generally of no clinical significance. A sinus pause is defined as the absence of a P wave for greater than or equal to 2 s (although generally not considered clinically significant unless greater than or equal to 3 s while awake or 5 s while asleep). If the duration of the sinus pause is a multiple of the PP interval, then sinoatrial node exit block should be considered. **Chronotropic incompetence** is defined as failure to achieve 70–80 % of maximal predicted heart rate (maximal predicted heart rate = 220-age) during peak exercise.

Inappropriate sinus tachycardia is a persistent elevation in heart rate greater than 100 bpm at rest with no obvious precipitating cause. There is an exaggerated increase in sinus rate with minimal activity and a reduction or normalization of sinus rate during sleep. The p wave morphology and axis are unchanged.

It is important to rule out all potential causes as well as other arrhythmias such as right atrial tachycardia close to the SN or SN re-entry tachycardia. Inappropriate sinus tachycardia is most likely multifactorial with a change in the overall autonomic supply to the SN which may include a reduction in the sensitivity to

anticholinergic effects or an increased sensitivity to adrenergic activity [11]. Pharmacological options for inappropriate sinus tachycardia include beta adrenergic blockers, nondihydropyridine calcium channel blockers and the selective If channel inhibitor ivabradine. Given the selective nature of ivabradine this has been shown to have a useful role in patients with symptomatic inappropriate sinus tachycardia unresponsive to beta adrenergic blockers and calcium channel blockers [12]. Further data is awaited whether this may be considered as first line treatment in this condition.

Catheter ablation for SN modification is an alternative strategy in select cases of inappropriate sinus tachycardia. The SN is often difficult to modify from the RA endocardium as there are multiple connections with sites of early activation between the SN and the RA. Additionally the bulk of the SN is subepicardial, has a significant amount of connective tissue, is often covered by thick muscle of the CT and there is a significant cooling effect from the SN artery. The usual area to target is the superomedial aspect of the CT targeting areas of local activation 15–60 msec ahead of the surface p wave looking for a reduction in the sinus rate to less than 90 bpm and a 20–25 % reduction in the maximum sinus rate with isoprenaline [13]. Although acute results are good long term maintenance is less successful [14]. High output pacing should be performed at sites being considered for ablation to avoid phrenic nerve injury. The need for a permanent pacemaker is unusual but a potential complication of this procedure.

Crista Terminalis (CT)

As shown in Fig. 1.8 this is a C-shaped structure which begins septally at the superior aspect becoming more anterior as it traverses the connection with the SVC and then moves posterior and inferior along the lateral wall of the RA towards the junction with the IVC [15]. The pectinate muscles which form the right atrial appendage span out from the CT. Approximately two thirds of focal atrial arrhythmias occur along this structure [16].

RA Conduction

Following discharge from the SN, conduction occurs through the RA using the muscular architecture of the atrial wall that comprises muscle bundles with well aligned working myocytes that preferentially carry the sinus impulse [17]. The notion of three specific internodal tracts is controversial because histologically specialized tissue tracts akin to the insulated ventricular conduction bundles have never been demonstrated anatomically.

Bachmann's bundle, which is also known as the anterior bundle is responsible for right to left atrial conduction. It is not a discrete bundle nor is it insulated with a

fibrous sheath. Instead, it is a muscle bundle with well aligned myocytes, superficially located across the anterior interatrial groove. Its rightward extension reaches superiorly to the area of the sinus node and inferiorly toward the right atial vestibule. Usually it is the most prominent interatrial bundle [18].

Cavotricuspid Isthmus (CTI)

This is the region of slow conduction in typical atrial flutter bounded anteriorly by the septal component of the TA and posteriorly by the Eustachian valve (EV) and the IVC (Fig. 1.9). Conduction in this region is slow due to the criss-cross arrangement of the myocytes and distal ramifications of the crista terminalis relative to the better aligned and circumferential arrangement of myocytes in the vestibule leading to the tricuspid valve (TV) [19].

In an LAO projection the ablation catheter is generally positioned in the mid isthmus in the 6 o'clock position. In the RAO position the catheter is moved from the right to the left keeping the catheter inferiorly. The EV separates the vestibular

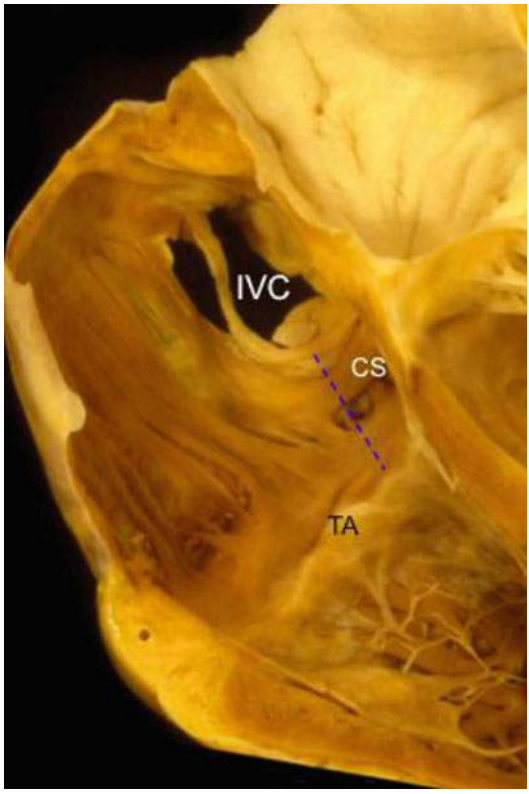


Fig. 1.9 Anatomy of the cavo-tricuspid isthmus (*CTI*). The CTI runs between the tricuspid annulus (*TA*) and the inferior vena cava (*IVC*). The dotted line shows a septal approach close to the coronary sinus (*CS*) which may be used as a line for catheter ablation in order to transect the isthmus

inferior RA from the inferior vena cava (IVC). The Eustachian ridge is an elevated region of tissue between the fossa ovalis and the coronary sinus in continuation with the insertion point of the EV. The Tendon of Todaro (TT) runs in this rim towards the AV node [18].

LA

The LA is posterior, superior and to the left of the RA. The tip of the left atrial appendage (LAA) contributes to the left side of the cardiac silhouette in a PA image. The LA is a smoother structure with the muscular appendage confined to a small tube-like structure arising from the superior and left side of the chamber. As shown in Fig. 1.10 the four pulmonary veins (PV's) drain into the posterior quadrants of the smooth-walled area, which is actually the most posterior region of the heart.

The left sided pulmonary veins are best seen in the LAO projection and are posterior to the left atrial appendage. The right pulmonary veins are best visualized in an RAO projection. The right superior pulmonary vein is posterior to the junction between the right atrium and superior vena cava.

The LA myocardial fibers extend over variable distances into the pulmonary veins. These connections are generally the targets for pulmonary vein isolation.

The LA wall is generally a thin structure and therefore care must be taken when manipulating catheters in this region. The lateral wall is approximately 3.9 ± 0.7 mm in thickness, the posterior wall 4.1 ± 0.7 mm, anterior wall 3.3 ± 1.2 mm and the roof 4.5 ± 0.6 mm when measured on cadaver heart specimens [19].

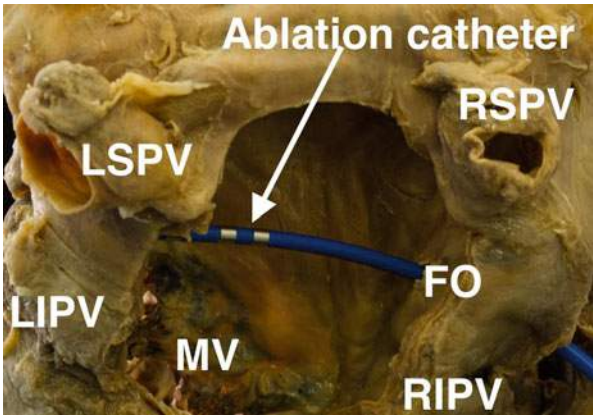


Fig. 1.10 Anatomy of the LA. This is seen from a posterior view. An ablation catheter is positioned via the intra-atrial septum at the location of the fossa ovalis. The left superior pulmonary vein (*LSPV*), left inferior pulmonary vein (*LIPV*), right superior pulmonary vein (*RSPV*) and right inferior pulmonary vein (*RIPV*) are seen as posterior structures in the left atrium. The mitral annulus (*MA*) is seen inferior to the LIPV

The LA is anterior to the esophagus. This is of real importance in terms of posterior wall ablation. The esophagus has a variable course in relation to the LA. There is also a variability in the thickness of the fibrofatty tissue between the LA and the esophagus. In clinical practice this generally results in the application of lower power (25–30 W) and shorter duration lesion in the posterior left atrial wall in order to attempt to minimize the possibility of esophageal injury.

Anterior to the LA is the ascending aorta which is an important consideration when performing trans septal access.

Atrio-Ventricular (AV) Junction

The compact AV node is the atrial component of the specialized AV junctional area and is located between the coronary sinus os and the septal leaflet of the tricuspid valve. It therefore lies inside the **triangle of Koch**.

It measures approximately 5 mm in length and is histologically quite complex. It is not insulated by connective tissue and therefore may potentially be damaged by RF application. The inferior extensions of the compact AV node also run within the triangle of Koch with the rightward extension (fast pathway) parallel to the tricuspid valve and the leftward extension (slow pathway) towards the coronary sinus. These extensions pass either side of the AV nodal artery and also are not protected structures. The histological appearances of these extensions are the same as the compact AV node and are involved in the AVNRT circuit [20]. The boundaries of the triangle of Koch are shown superimposed on an anatomic specimen in Fig. 1.11.

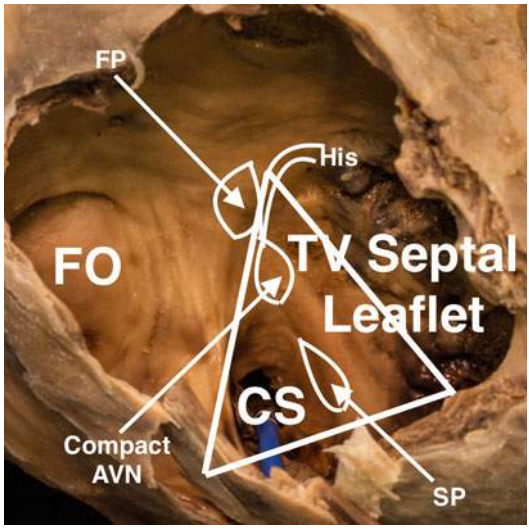


Fig. 1.11 Boundaries of the triangle of Koch superimposed on an anatomic specimen. This is formed by the coronary sinus (*CS*), septal leaflet of the tricuspid valve (*TV*) inferiorly and the tendon of Todaro anterosuperiorly. A catheter is positioned via the inferior vena cava (*IVC*) into the coronary sinus (*CS*). Also shown is the fossa ovalis, approximate location of the slow pathway (*SP*), compact AV node, fast pathway (*FP*) and His

His Bundle

The His bundle is a continuation of the compact AV node and with similar specialized cells although these are more parallel aligned [21]. It is better insulated than the AV node and therefore is not as easily damaged with RF, although this is still possible. The proximal bundle runs from the distal AV node into the fibrous tissue of the central body where it is termed the penetrating portion. Following this it emerges on the ventricular side of the fibrous body, sandwiched between the membranous septum and the muscular ventricular septum, Taking an initial course usually to the left side of the septum, it then bifurcates into the right bundle (RB) and left bundle (LB) branches, still insulated by fibrous tissue sheaths. The RB tends to have a more anterior origin in the membranous septum.

The CS

The CS is a tubular shaped structure which runs from either the Valve of Vieussens or in its absence the entrance of the vein/ligament of Marshall to the CS os where it enters the RA. It is approximately 7 cm in length [22] and 6–16 mm in diameter [23].

As shown in Fig. 1.12 the CS receives blood from the great cardiac vein that channels blood from its tributaries, the anterior interventricular vein, the middle cardiac vein, the left obtuse marginal vein, the right coronary vein and atrial veins of which the most well known is the vein of Marshall. The coronary sinus is generally surrounded by myocardial musculature which extends from the right and left atrial walls [24]. This musculature may extend for a further 2–11 mm along the great cardiac vein [25]. Distal to this the venous wall is not surrounded by musculature and therefore perforation through instrumentation is more likely.

The Valve of Vieussens rarely causes a significant obstruction to the advancement of a catheter but rather the acute bend in the vein beyond this or an advancement into a side branch are more common causes of cannulation problems. It is therefore better to slowly withdraw and rotate the catheter rather than to try to advance further.

The anterior interventricular vein courses from close to the LV apex and then continues into the great cardiac vein that into the left AV groove under the left atrial appendage [26]. Distally the great cardiac vein receives left atrial veins including the Vein of Marshall and more proximally ventricular veins from the anterior RV and LV and the interventricular septum.

The middle cardiac vein joins the CS close to the os. Occasionally it may also enter the RA directly. This vein runs along the diaphragmatic surface between the LV and RV with a close proximity to the right coronary artery and in particular the branch to the AV node. It may be used to map accessory pathways in the pyramidal space.

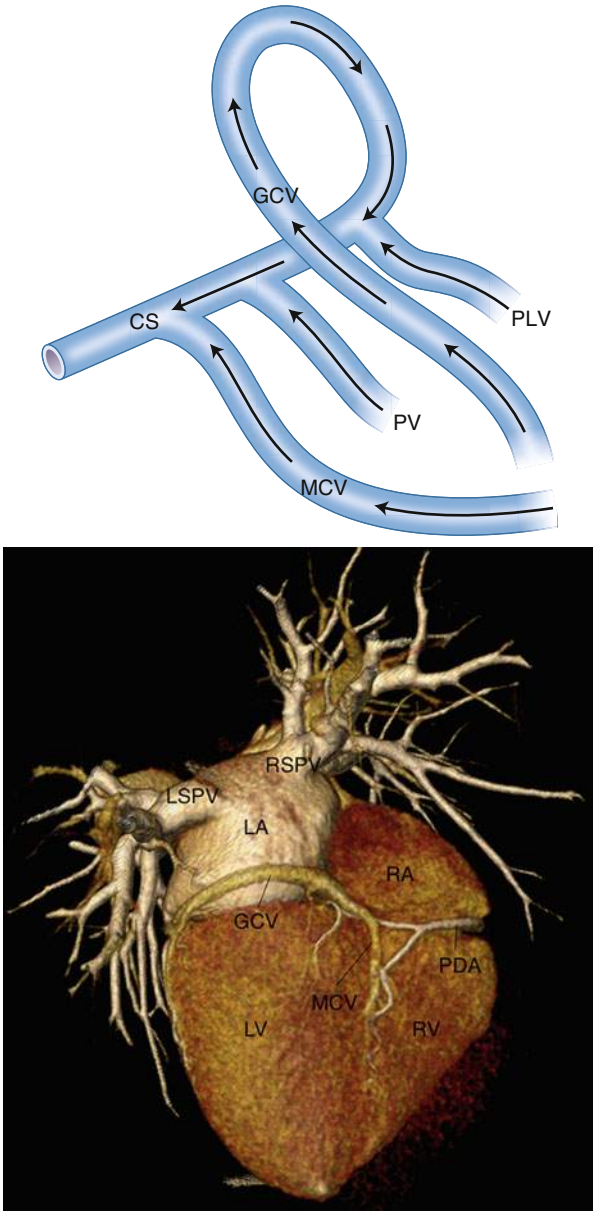


Fig. 1.12 The coronary sinus and its branches. The top image is a diagrammatic representation of the coronary sinus (*CS*) and its main tributaries the great cardiac vein (*GCV*), middle cardiac vein (*MCV*) as well as posterior veins (*PV*) and posterolateral veins (*PLV*) seen in an LAO view. In the image below this the CT shows the coronary sinus running along the inferior left atrium (*LA*) as the great cardiac vein (*GCV*). The middle cardiac vein (*MCV*) runs between the left ventricle (*LV*) and the right ventricle (RV). The posterior descending artery (*PDA*) is seen running between the right atrium (*RA*) and the right ventricle (*RV*). Also seen in this image is the left superior pulmonary vein (*LSPV*) and the rightsuperior pulmonary vein (*RSPV*)

LV Conduction System

The atrioventricular conduction bundle emerges from the central fibrous body to pass below the right and non-coronary cusps and continue into the branching atrioventricular bundle that gives origin to the RB and LB branches. The LB branch courses along the LV septal surface and divides into three fascicles (Fig. 1.13). The **anterior fascicle** which is **superior** runs towards the base of the anterosuperior papillary muscle, the **posterior fascicle** which is **inferior** runs towards the posteroinferior papillary muscle and in 60 % of cases a central or **septal fascicle** which runs to the mid septum. In the remaining 40 % of cases this area is supplied by the anterosuperior and posteroinferior fascicles.

Given that there are often more than two fascicles the term hemiblock is generally not accurate and fascicular block seems more appropriate.

Anterior fascicular block is more common than posterior fascicular block and results in a leftward QRS axis deviation poor R wave progression in V1–V3, with a negative QRS in II, III and aVF and positive QRS in lead I. There is also a tall R wave in aVL and aVR. The QRS is not broad.

Posterior fascicular block is less common due to the short and wide nature of this fascicle. The ECG features are a QRS axis greater than 100° with an rS morphology in leads I and aVL; and a qR pattern in leads II, III, and aVF. The QRS is not broad. Diagrammatic representation of both anterior and posterior fascicular bock are shown in Fig. 1.14.

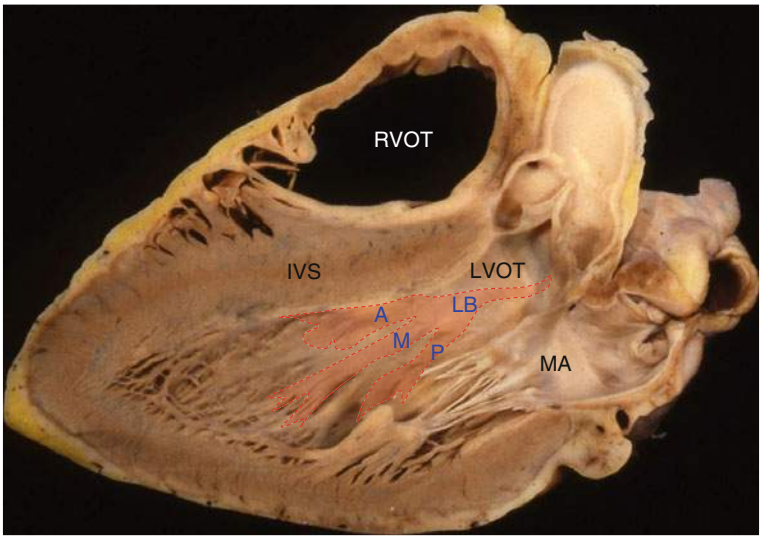


Fig. 1.13 Anatomy of the LV showing the walls of the chamber, interventricular septum (*IVS*), mitral annulus (*MA*) and left ventricular outflow tract (*LVOT*). Superimposed on this image are the approximate locations of the left bundle (*LB*), anterior fascicle (*AF*), posterior fascicle (*PF*) as well as the Purkinje system

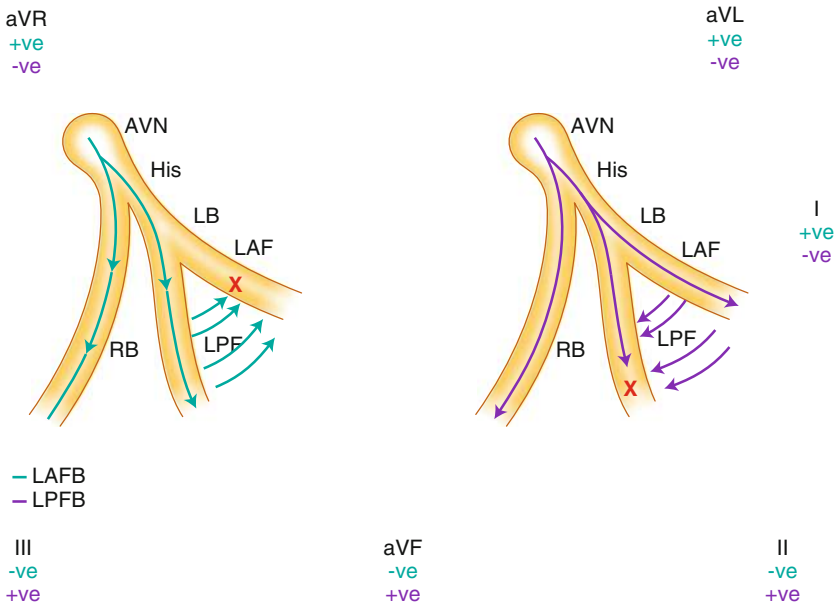


Fig. 1.14 Diagrammatic representation of left anterior fascicular block (*LAFB*) on the *left image* with activation in orange and left posterior fascicular block (*LPFB*) on the *right* with activation in *red* and the effects on the ECG limb leads

Septal fascicular block is the least clinically described of all the fascicular blocks. This may be due to the multiple ventricular connections of this fascicle making complete block of this fascicle less likely [27]. There is a variability in the ECG appearances. In general the changes noted are Q waves in V1 and V2 as a result of anteriorly directly right ventricular depolarization [28].

This may also cause a qrS in V1 and V2. There is also loss of q waves in leads V5, V6 and I due to loss or reversal of left to right ventricular septal activation. The QRS is not significantly broad because activation of the left ventricular free wall and apex occurs via the anterosuperior and posteroinferior fascicles.

Complete bundle branch block occurs as a result of either partial or complete structural or functional block in one of the two bundle branches resulting in a widening of the QRS greater than 120 ms as well as a change in morphology, which generally reflects conduction down the contralateral bundle with secondary repolarisation.

In **left bundle branch block** (**LBBB**) the initial activation is rightward and anterior resulting in small q waves in I, avL, and V6 with an rS in V2. Following this depolarisation spreads from the apex to the base and to the RV free wall and apex. During this process, septal activation is the pre- dominant force and therefore the vector is anterior and to the left, resulting in a wide slurred QRS in I, aVL and V6 (Fig. 1.15). Depolarization then occurs in a leftward and posterior direction through the LV. Finally, the anterior wall of the LV is depolarized.

RV Conduction System

The RV is anterior to the LV as shown in Fig. 1.16. The RB branch is an insulated bundle of specialized myocytes that runs as a direct continuation of the atrioventricular conduction bundle distal to origin of the left bundle branch. It penetrates the

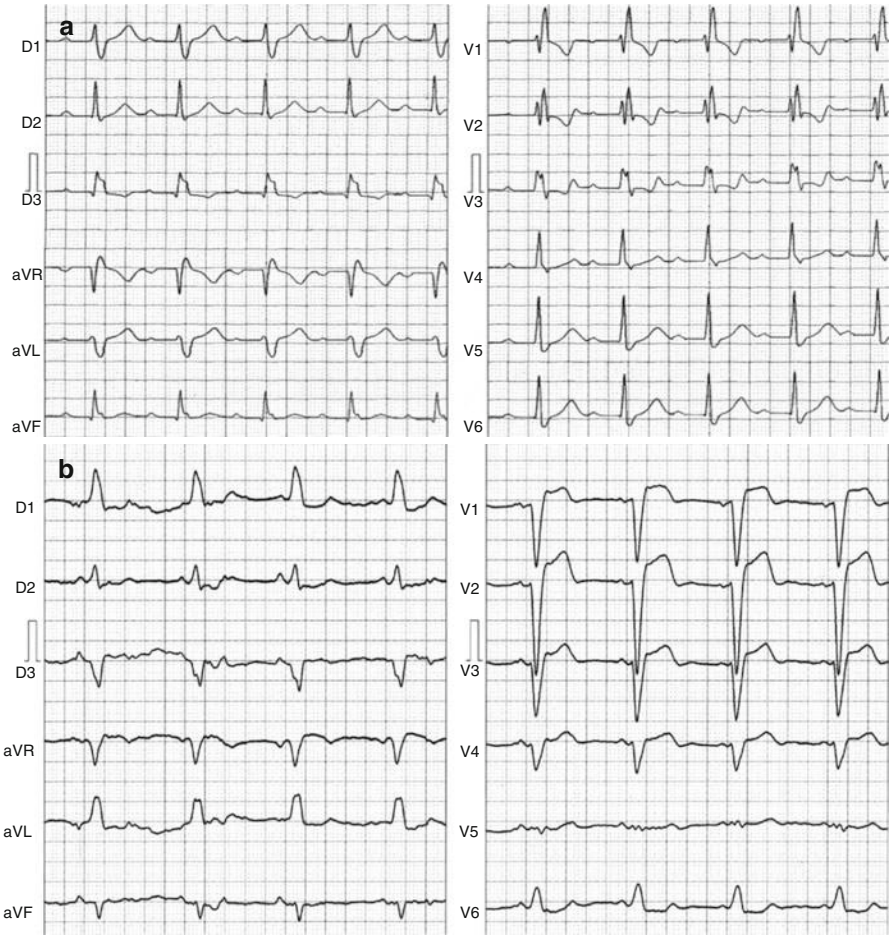


Fig. 1.15 12 lead ECG's showing RBBB (**a**), LBBB (**b**), Left Anterior Fascicular Block (**c**) and Left Posterior Fascicular Block (**d**). The ECG in panel **a** shows RBBB with first degree AV block (PR Interval 280 ms). The QRS duration is 120 ms with an rsR pattern in leads V1 and V2. (**b**) This ECG shows a LBBB with a QRS duration of 165 ms. An rS is seen in leads V1 and V2 and a dominant R wave in leads I, aVL and V6. (**c**) This ECG shows a left anterior fasicular block. The QRS duration is within normal range with a leftward axis. There is poor R wave progression V1–V3. The QRS is negative in leads II, III and aVF and positive in lead I. There is also a tall R wave in lead aVL. (**d**) This shows left posterior fasicular block. The QRS axis is in a rightward direction. There is an rS in lead aVL. There is a small q wave in lead III and a dominant R in leads II, III and aVF with the R wave being greater in amplitude in lead III than lead II

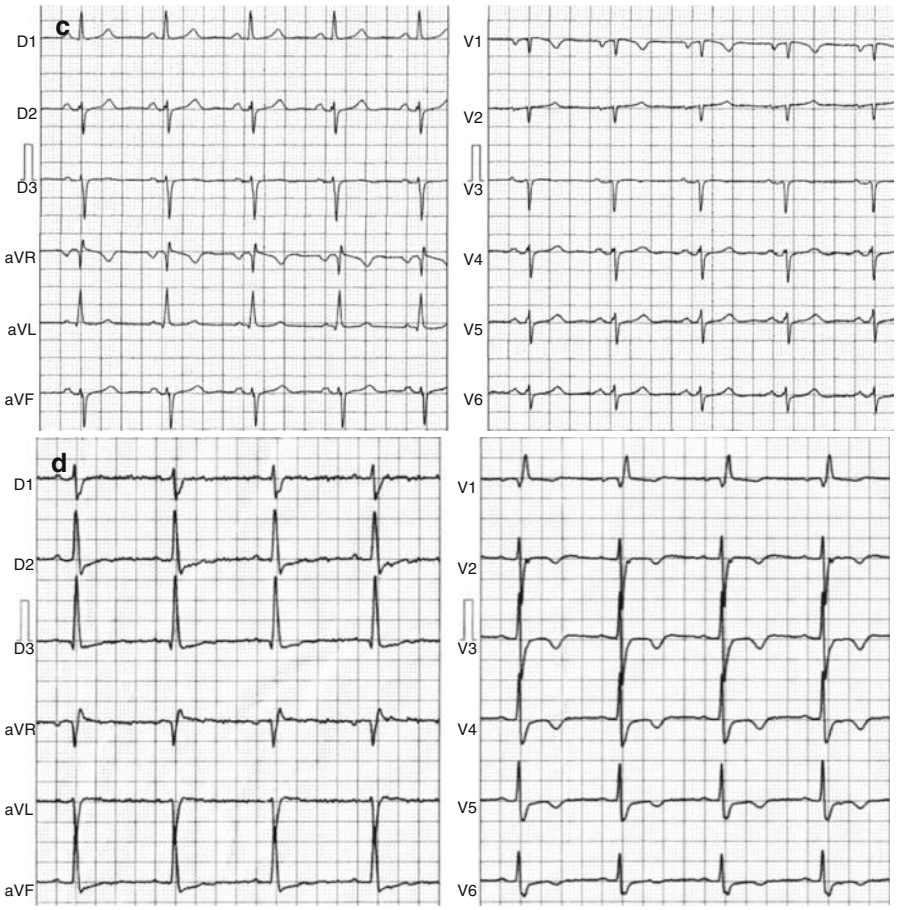


Fig. 1.15 (continued)

musculature of the ventricular septum toward the midseptum where it becomes subendocardial running along the posterior margin of the septal band. Continuing toward the apex, it divides into several branches one of which courses through the moderator band to the base of the anterior papillary muscle, and then the right ventricular free wall. It gives off septal branches which activate the septum almost immediately after left ventricular activation. Septal activation is generally complete within 35 ms and terminates in Purkinje fibres at the apex.

Right bundle branch block (**RBBB**) is more common than LBBB and as shown in Fig. 1.15 the initial septal activation is followed by depolarization of the left ventricle, resulting in R waves in I, aVL and V6. Following this, right ventricular free wall and septal depolarization results in S waves in these leads. Overall, the QRS is ≥120 ms in adults with an rsr, rsR, or rSR in leads V1 or V2. The R or r deflection is usually wider than the initial R wave. ST segment deviation is generally discordant to the QRS vector.

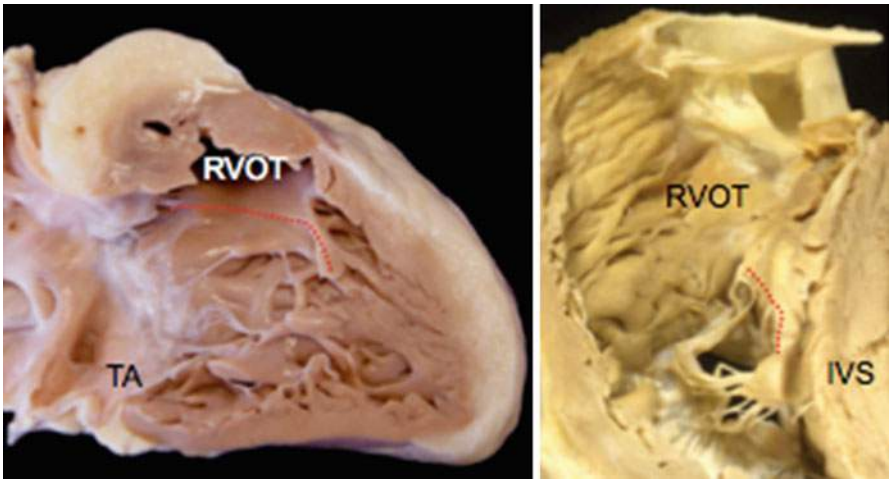


Fig. 1.16 Anatomical image of the Right Ventricle in Right Anterior Oblique (RAO seen on the *left*) and Left Anterior Oblique (LAO seen on the *right*) showing the walls of the chamber, interventricular septum (*IVS*), Tricuspid annulus (*TA*) right ventricular outflow tract (*RVOT*)

Aberrant Ventricular Conduction

This occurs when a supraventricular beat conducts rapidly to the His Purkinje system while one of the bundle branches is refractory and then depolarizes the other bundle branch, resulting in a wide QRS complex.

There are four types of aberrancy:

1. **Phase III dependent** (**Ashman Phenomenon**)
   This occurs when a short RR interval follows a longer RR interval. The longer RR interval results in a prolonged action potential in the His and bundle branches. The right bundle usually has a longer action potential duration than the left bundle and therefore the following beat with the shorter RR interval is blocked in the right bundle, which is still refractory and conducts down the left bundle with a RBBB morphology (Fig. 1.17). This may be seen in AF, where there is a variable cycle length and may be misinterpreted as a PVC.
2. **Acceleration dependent**
   This occurs with very slight acceleration of the heart rate (less than 5 ms) at a critical cycle length which is often within normal heart rate ranges. This tends to occur more commonly in the left bundle resulting in a LBBB morphology (Fig. 1.18). Of note as the rate increases further, the aberrancy often resolves as the action potential duration of the bundles reduces more than that of the AV node. Additionally the action potential duration of the bundle branches often reduces in a time dependent manner known as restitution.
3. **Deceleration dependent**
   This occurs following a long pause during which a premature atrial beat conducts to the ventricle with a resultant bundle branch block pattern (Fig. 1.19). This

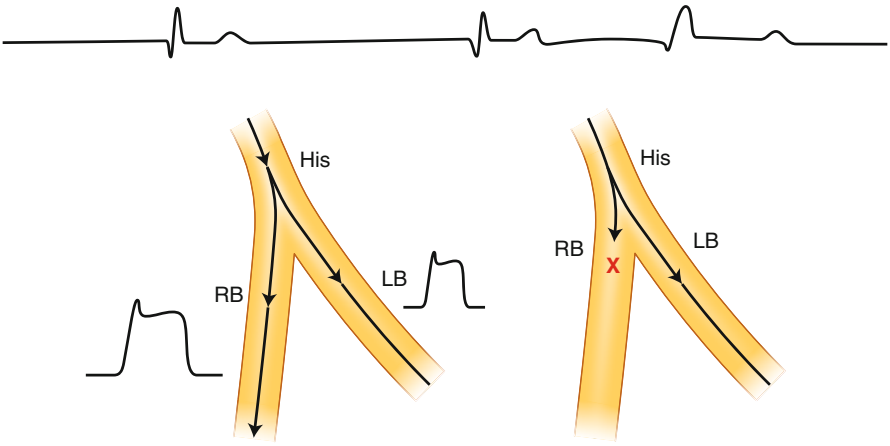


Fig. 1.17 Diagrammatic representation of Phase III dependent aberrant conduction. During AF the longer RR interval on the left results in a prolongation of the action potential in the Right Bundle (*RB*) and to a lesser extent the Left Bundle (*LB*). An early activation occurs during phase III of the action potential in the RB resulting in conduction down the LB with a RBBB morphology

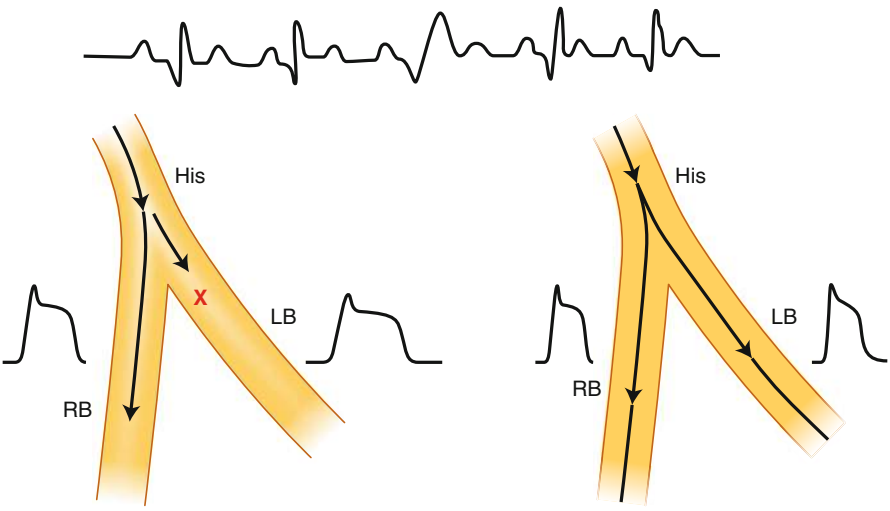


Fig. 1.18 A very slight acceleration in the RR interval results in antegrade block in the left bundle (*LB*). An increase in the rate after this results in a narrowing of the action potential duration with normalization of the surface QRS

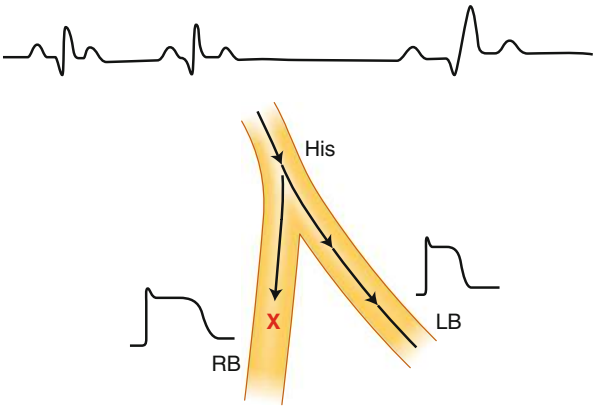


Fig. 1.19 A slow rate with a long pause results in prolongation of the action potential duration in both the right bundle (*RB*) and left bundle. A premature atrial complex (*PAC*) conducts through the His and conducts along the LB with block in the RB

occurs as a result of slow phase IV depolarization of the bundle branches resulting in refractoriness of one of the bundles as the atrial beat results in depolarization. This can be either a RBBB or LBBB pattern,

An example of deceleration dependent right bundle aberrancy is shown in Fig. 1.20. The His catheter is positioned so that the proximal electrogram is recording a His deflection and the distal recording is recording a right bundle potential.. The first beat shows a His potential on the proximal electrogram and a right bundle potential on the distal electrogram followed by ventricular activation. Following this a PAC is introduced by pacing the high RA (arrow). The following beat shows a His potential on the proximal electrogram with no right bundle potential on the distal electrogram and a characteristic RBBB pattern on the surface ECG.

4. **Concealed retrograde conduction**
   This occurs when retrograde conduction in one of the bundle branches from a PVC results in refractoriness for the next antegrade beat. As the bundle recovers the next beat which conducts down the contralateral bundle conducts retrogradely up the bundle again (Fig. 1.21). This continues until a different PVC alters the activation retrograde activation of the bundle. This is a relatively common cause of aberrancy during SVT.

ECG Signal Acquisition

The ECG is used to record the alterations in electrical potentials during the cardiac action potential. Any number of leads can be recorded in order to electrically visualize the heart from different angles.

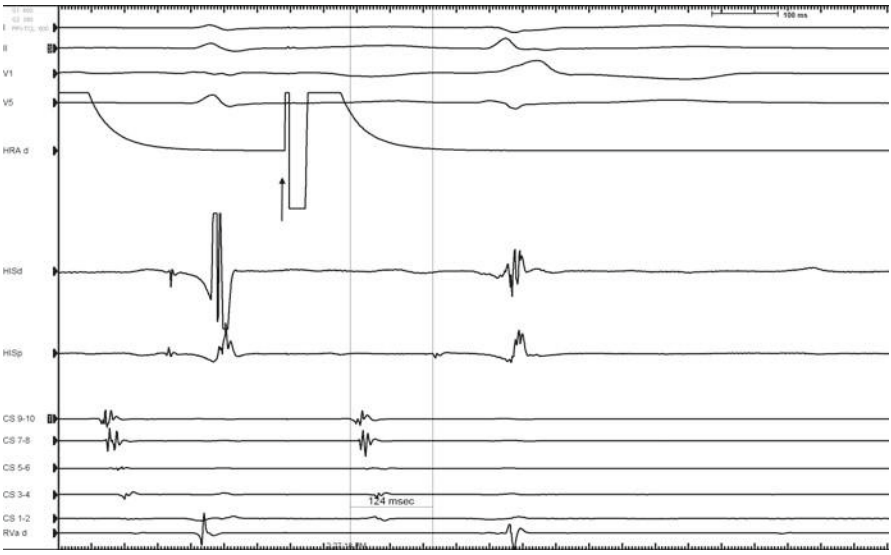


Fig. 1.20 Electrograms showing right bundle abberancy from a PAC (from HRA pacing labeled with an *arrow*). The HIS d is positioned along the proximal right bundle while the HIS p is positioned along the His. The PAC conducts along the His but does not conduct down the right bundle (no RB potential on HIS d on the second beat) with a RBBB morphology QRS. (CS 9–10 is positioned in the proximal CS with CS 1–2 in the distal CS. RV a is positioned in the RV apex)

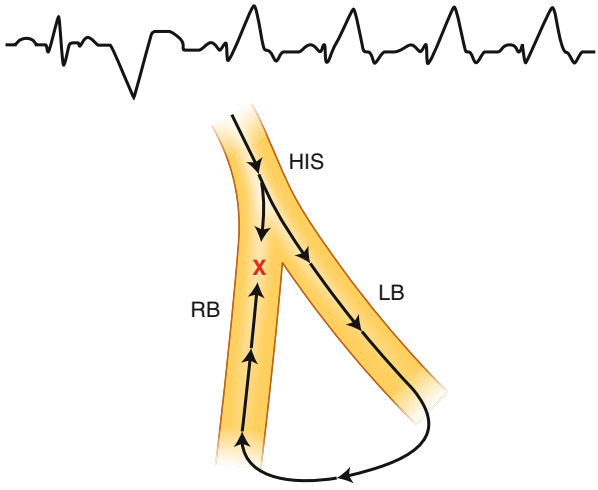


Fig. 1.21 Following the first sinus beat a PVC conducts retrogradely up the right bundle (RB) resulting in antegrade block in the RB with conduction down the left bundle (LB) (from third beat onwards). These beats then conduct retrogradely up the RB which is no longer refractory

The standard 12 lead ECG is composed of six unipolar precordial leads positioned as follows across the anterior chest wall:

V1 4th Intercostal Space Right Parasternal
V2 4th Intercostal Space Left Parasternal

V3 Midway between V2 and V4
V4 5thIntercostal Space Mid Clavicular Line
V5 5th Intercostal Space Anterior Axillary Line
V6 5th Intercostal Space Mid axillary line

The locations of these leads relative to the cardiac chambers can be seen on Fig. 1.22.

Each lead records electrical activation between the precordial electrode and **Wilsons Central Terminal** (WCT). This is a theoretical point close to zero potential created from the electrodes between the right arm, left arm and left leg (Fig. 1.23). These vectors create three bipolar leads I (right arm to left arm), II (right arm to left leg) and III (left arm to left leg) through three large resistors. The electrical activation between these three leads therefore cancels out to come close to a zero potential (WCT). The remaining three leads aVR, aVL and aVF are augmented unipolar leads created from the limb electrodes and referenced to **Goldberger's Central Terminal** (GCT) rather than WCT. GCT is created from two of the three

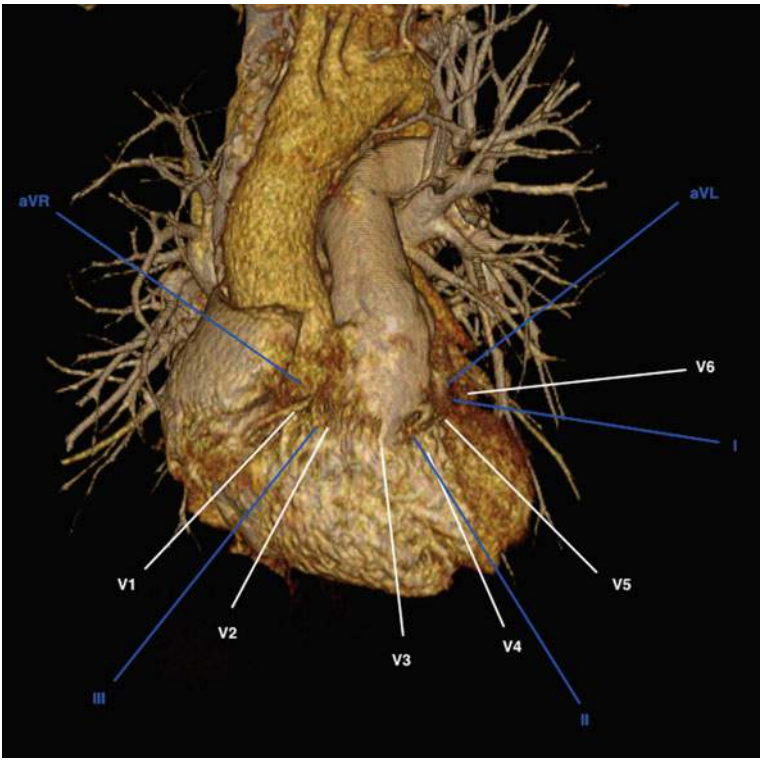


Fig. 1.22 CT Image of the Thorax showing the positions of the surface ECG leads relative to the cardiac chambers. The precordial leads V1–V6 are seen as well as the augmented leads aVR, aVL, II, III and aVF

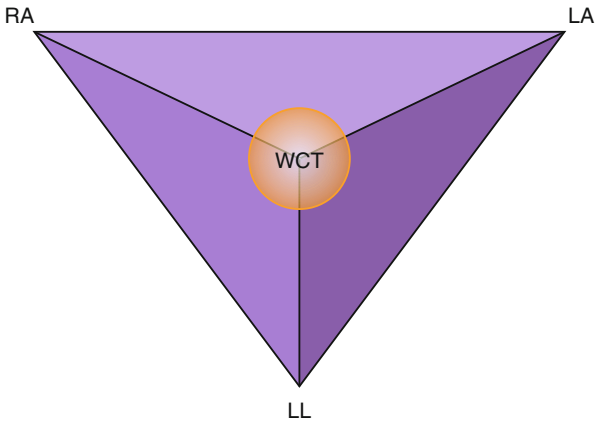


Fig. 1.23 Diagrammatic Representation of an ECG Vector created from the ECG leads from the Right Arm (*RA*), Left Arm (*LA*), Left Leg (*LL*) and Wilsons Central Terminal (*WCT*)

limb leads. When aVR is being recorded the GCT is composed of left arm and left leg, for aVL this is formed by right arm and left leg and for aVF is the right arm and left arm.

The right leg lead is used to introduce a current to the patient in order to maintain a voltage equivalent to that of the amplifier. This feeds back an inverse of potential low frequency interference and which increases if this lead is disconnected.

The QRS axis refers to the mean direction of ventricular activation in the frontal plane. In order to calculate the QRS axis the first step is to identify a limb lead where the QRS complex is isoelectric. In theory, the overall direction of electrical activation should be perpendicular to this. As there are two potential perpendicular directions, the leads either side of the isoelectric lead need to be examined and the axis is in the direction of the more positive lead. For example, if the QRS complex is isoelectric in lead I and positive in lead II, the QRS frontal axis is +90. In general principles the QRS axis shifts for several reasons. If there is chamber hypertrophy the QRS axis will shift in the direction of the hypertrophied ventricle as there is a greater component of electrical activation in that direction. In bundle branch block, activation moves from the opposite side to the side with the bundle branch block and therefore the axis will be in the same direction. In cases of myocardial infarction, the axis tends to move in the opposite direction away from the infarcted tissue.

Autonomic Innervation of the Heart

There is a continual balance between the two main components of the autonomic nervous system; the **sympathetic** (**adrenergic**) and **parasympathetic** (**vagal**) **innervation**.

The sympathetic efferent neurons innervate the SN as well as the atria, AV node and ventricles acting principally on the beta-adrenoceptors. Increased sympathetic

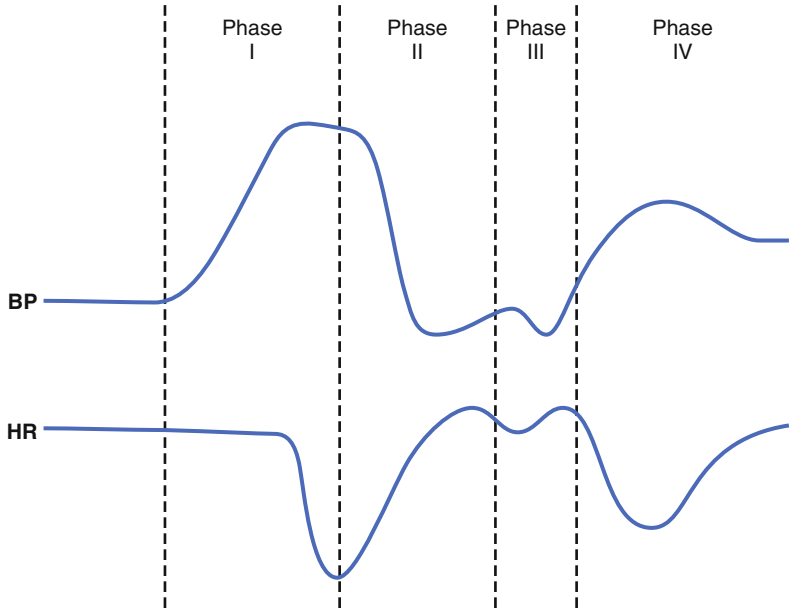


Fig. 1.24 Phases of the valsalva maneuver. The initial rise in intrathoracic pressure results in a elevation in blood pressure (*Phase I*) with a stable and then compensatory drop in heart rate. As well as an elevation in aortic pressure there is a reduction in preload which results in a drop in blood pressure with a rise in heart rate (*Phase II*). As the actual maneuver ends pressure on the aorta is reduced and the blood pressure transiently decreases with a resulting increase in the heart rate (*Phase III*). As the cardiac output increases to normal the blood pressure then increases with a compensatory drop in heart rate (*Phase IV*)

activity results in positive inotropy, positive chronotropy and an increased conduction velocity.

The parasympathetic (vagus) nervous system synapses with ganglia acting on muscarinic receptors in the heart. In general the right vagus innervates the SA node while the left vagus innervates the AV node. The vagus nerve innervates the atria to a lesser extent. There is minimal innervation of the ventricles. Increased vagal stimulation results in negative chronotopy and reduced conduction velocity. Given the lack of vagal innervation in the ventricles there is minimal inotropy.

There are several methods of assessing autonomic activity of the heart including the **valsalva maneuver** and the **tilt table test**.

The valsalva maneuver is performed by exhaling with a closed glottis for a period of 10 s therefore increasing intrathoracic pressure. There are four phases as depicted in Fig. 1.24.

Phase I: Transient increase in blood pressure with no change in heart rate as a result of compression of the ventricles and aorta.

Phase II: A significant reduction or plateau in blood pressure as a result of compression of the intrathoracic vena cava reducing venous return. As a result of this

there is a baroreflex mediated increase in heart rate via the sympathetic nervous system.

Phase III: As the maneuver has now stopped the intrathoracic pressure returns to normal reversing phase I and resulting in a reduction in left ventricular output and an increase in right ventricular output as a result of an increase in venous return.

Phase IV: As the venous return increases further there is an increase in the cardiac output and blood pressure. This results in stimulation of baroreflex which increases parasympathetic activity resulting in a reduction in heart rate.

A tilt table test may be useful in patients with a history of pre-syncope, syncope or postural symptoms such as palpitations when structural heart disease has been excluded. During this test the patient is attached to a specialized table and positioned at a 60–70 degree angle. The ECG and non-invasive blood pressure are continually monitored. Although some laboratories do not gain an intravenous (IV) due to the potential effects on vagal tone, it is reasonable to insert an IV for the administration of pharmacological agents and wait for 15 min prior to commencing the test.

The patient is monitored in the supine position for five minutes and then placed in an upright position at a 60–70 degree angle. The heart rate and blood pressure are monitored and recorded every five minutes for 45 min. If there is an acute drop in blood pressure or loss of consciousness, the table is returned to the supine position. Some centers administer 300–400 microgrammes of sublingual nitrate within the last five minutes of the study while others repeat a negative tilt table test with the administration of isoprenolol at a rate of 1–3 microgrammes per minute in order to increase the heart rate by 25 % above the baseline. It is not uncommon to get a slight drop in blood pressure with isoprenolol and therefore this test is generally only considered positive if syncope occurs. Carotid sinus massage can often be performed either in the supine or erect position, the latter having a slightly higher yield.

Carotid sinus hypersensitivity is defined as a ventricular pause greater than or equal to three seconds with or without a drop in systolic blood pressure by $\geq$50 mmHg. If there is associated syncope then this is defined as carotid sinus syndrome. Carotid sinus hypersensitivity is more common in the elderly and in males, and is extremely uncommon in individuals under the age of 40 years. Carotid sinus massage should not be performed in patients with a prior transient ischemic attack or stroke within the prior three months, or in patients with a carotid artery bruit unless significant carotid artery disease has been excluded on carotid dopplers. Both nitrates and isoprenolol increase the sensitivity but reduce the specificity of the tilt table test.

If syncope occurs in association with bradycardia or reflex hypotension the diagnosis is **neurocardiogenic syncope**. If the major precipitant is bradycardia this is **cardio-inhibitory**, and if the major precipitant is hypotension it is **vasodepressor**.

Postural Orthostatic Tachycardia syndrome (**POTS**) is defined as an increase of heart rate of greater than or equal to 30 bpm or a rate of greater than or equal to 120 bpm within the first 10 min of moving from a supine to erect position with

associated symptoms [29]. Other potential causes such as medications or prolonged bed rest which may alter vascular tone should be excluded prior to making this diagnosis.

POTS can be divided into either partial dysautonomic or hyperadrenergic types.

In **partial dysautonomic POTS** the increase in heart rate is partially due to increased blood pooling in the lower limbs as a result of an alteration in the control of vascular tone.

In **hyperadrenergic POTS** there is often an associated increase in blood pressure associated with the increase in heart rate.

The tilt table results depend on the age of the patient, with younger patients more likely to have cardioinhibitory neuro- cardiogenic syncope, and older patients more likely to have vasodepressor neurocardiogenic syncope.

Important Points to Remember

1. The cardiac action potential is composed of 4 phases.

   Phase IV (resting membrane potential) occurs with a membrane potential of −80 to −95 mV in atrial, purkinje and ventricular cells, −50 to −60 mV in the SN and −60 to −70 mV in the AV node. In both the SN and AV nodes there is a slow spontaneous diastolic depolarization which merges with Phase 0 resulting in spontaneous automaticity while Phase IV in other cells is generally more flat.

   Phase 0 (rapid depolarization) occurs when the membrane potential becomes positive.

   Phase I (rapid repolarization) occurs in the atrium and ventricle but not in the SN and AV node. It is much more prominent in the purkinje and epicardial cells.

   Phase II (plateau phase) occurs when the action potential becomes relatively flat and does not occur in the SN or AV node.

   Phase III (rapid repolarization) occurs when there is restoration of the membrane potential to the resting phase.

2. Refractoriness describes the period during which a stimulus does not result in a new depolarization after phase 0 of the cardiac action potential. There are three different types of refractory periods (RP): relative, absolute and effective.

   The relative RP is the longest coupling interval resulting in local capture therefore marking the end of refractoriness.

   The absolute RP is the longest coupling interval which does not result in local capture.

   The effective RP is the longest coupling interval delivered which fails to propagate through the distal tissue.

3. Re-Entry occurs when a wave of excitation moves around a circuit which is determined anatomically, functionally or a combination of the two. For re-entry to occur the following conditions have to be fulfilled:

   There must be two or more pathways for conduction
   Unidirectional block in one pathway
   Alternative conduction over the other pathway with sufficient delay as to retrogradely invade the formerly blocked pathway

4. Automaticity results from spontaneous depolarization during phase IV of the action potential.
5. Afterdepolarizations are defined as depolarizations which occur after Phase 0 of the cardiac action potential and may result in a spontaneous action potential known as a triggered response. These are divided into early afterdepolarization (EAD) or delayed afterdepolarization (DAD).

   EAD occurs during phase II and phase III while DAD occur after the cardiac action potential is complete. EADs tend to occur when there is an increase in the inward movement of positive ions during the plateau phase of the action potential.

   DADs occur as a result of an increase in the inward movement of calcium. This can occur in the setting of digoxin toxicity or in conditions such as catecholamine induced polymorphic ventricular tachycardia (CPVT).
6. The RAO projection helps to demonstrate the postero-anterior (PA) location of a catheter within the cardiac chambers and shows the AV groove more clearly than the PA view. In this view the spine is on the left.
7. In the LAO view the AV rings are viewed parallel to the image. The left cardiac border is formed by the LA superiorly and the lateral wall of the LV inferiorly.
8. Following discharge from the SN conduction occurs through the RA predominantly utilizing aligned myocytes. Conduction occurs preferentially from the RA to the LA using the Bachmann's bundle.
9. AV conduction occurs through the AV junctional region, the atrial component of which is termed the AV node. This is located between the coronary sinus os and the septal leaflet of the tricuspid valve.
10. The His bundle is a continuation of the compact AV node. Although it has similar cellular components it is better insulated than the AV node and therefore is not as easily damaged with RF. The proximal bundle runs from the distal AV node to the fibrous tissue of the central body where it is termed the penetrating portion. Following this it bifurcates into the right bundle (RB) and left bundle (LB) branches at the level of the septal TV leaflet. The RB tends to have a more anterior origin than the LB.
11. The LB branch originates below the right and non-coronary cusps and then courses along the LV septal surface. It divides into two or three

fascicles. The anterior fascicle which is superior runs towards the base of the anterosuperior papillary muscle, the posterior fascicle which is inferior runs towards the posteroinferior papillary muscle and in 60% of cases a central or septal fascicle which runs to the mid septum. In the remaining 40% of cases this area is supplied by the anterosuperior and posteroinferior fascicles.

12. In LBBB the initial activation is rightward and anterior resulting in small q waves in I, avL, and V6 with an rS in V2. Following this depolarisation spreads from the apex to the base and to the RV free wall and apex. During this process, septal activation is the pre- dominant force and therefore the vector is anterior and to the left, resulting in a wide slurred QRS in I, aVL and V6. Depolarization then occurs in a leftward and posterior direction through the LV. Finally, the anterior wall of the LV is depolarized.
13. Anterior fascicular block results in a leftward QRS axis deviation poor R wave progression in V1-V3, with a negative QRS in II, III and aVF, positive in lead I. There is also a tall R wave in aVL and aVR. The QRS is not broad.
14. Posterior fascicular block results in a QRS axis greater than 100° with an rS morphology in leads I and aVL; and a qR pattern in leads II, III, and aVF. The QRS is not broad.
15. Septal fascicular block has a variable ECG appearances. In general the changes noted are Q waves in V1 and V2 as a result of anteriorly directly right ventricular depolarization. This may also cause a qrS in V1 and V2. There is also loss of q waves in leads V5, V6 and I due to loss or reversal of left to right ventricular septal activation. The QRS is not significantly broad because activation of the left ventricular free wall and apex occurs via the anterosuperior and posteroinferior fascicles.
16. The RB branch is an insulated bundle of fibers as a direct continuation of the penetrating atrioventricular bundle. It runs along the RV septum to the apex where it becomes subendocardial in the mid septum running along the posterior margin of the septal band, courses through the moderator band to the base of the anterior papillary muscle, and then the right ventricular free wall. It gives off septal branches which activate the septum almost immediately after left ventricular activation. Septal activation is generally complete within 35 ms and terminates in Purkinje fibres at the apex.
17. In RBBB the initial septal activation is followed by depolarization of the left ventricle, resulting in R waves in I, aVL and V6. Following this, right ventricular free wall and septal depolarization results in S waves in these leads. Overall, the QRS is ≥120 ms in adults with an rsr, rsR, or rSR in leads V1 or V2. The R or r deflection is usually wider than the initial R wave. ST segment deviation is generally discordant to the QRS vector.

18. Phase III dependent aberrancy also known as Ashman Phenomenon occurs when a short RR interval follows a longer RR interval. The longer RR interval results in a prolonged AP in the His and bundle branches. The right bundle has a longer AP duration than the left bundle and therefore the following beat with the shorter RR interval is blocked in the right bundle which is still refractory and conducts down the left bundle with a RBBB morphology.
19. Acceleration dependent aberrancy occurs with very slight acceleration of the heart rate (less than 5 ms) at a critical cycle length which is often within normal heart rate ranges. This tends to occur more commonly in the left bundle resulting in LBBB.
20. Deceleration dependent aberrancy occurs following a long pause during which a premature atrial beat conducts to the ventricle with a resultant bundle branch block.
21. Aberrancy due to concealed retrograde conduction occurs when retrograde conduction in one of the bundle branches from a PVC results in refractoriness for the next antegrade beat. As the bundle recovers the next beat which conducts down the contralateral bundle conducts retrogradely up the bundle again.

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Chapter 2
Cardiac Electrophysiology Study, Diagnostic Maneuvers and Ablation

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Abstract The overall aim of an invasive electrophysiological (EP) evaluation is to accurately diagnose the mechanism and substrate responsible for a documented or suspected arrhythmia to treat the patient's symptoms or improve his/her prognosis. Significant developments in the understanding of arrhythmias as well as technological advances have allowed electrophysiology studies to be considered as a diagnostic first line option. This chapter discusses the fundamental principles of invasive electrophysiology and provides an essential guide in terms of establishing the correct diagnosis and ablation strategy.

Indications for an EP Study and Ablation

The overall decision on whether to perform an EP study and ablation depends on the balance between the potential benefits, alternative treatment options, risks as well as the individual patient preference. In general for symptomatic supraventricular

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_2

arrhythmias an EP study and ablation should be considered early as the success rates are high and the results of pharmacological treatment are often suboptimal. The decision for the invasive management of AF and VT is often more complex and requires very careful examination of the patients symptoms and potential complications which must be balanced against alternative treatment options. As techniques and technology improve for more complex ablations the threshold for an invasive strategy is already clearly changing.

Supraventricular Arrhythmias (SVT)

Ablation can be considered as first line therapy for the treatment of symptomatic SVT due to AV nodal re-entry tachycardia (AVNRT), atrioventricular re-entry tachycardia (AVRT) or atrial tachycardia (AT) (Class I Indication, Level of Evidence B) [1]. Although it is ideal to have inducible tachycardia at the start of the EP study this is not critical and it is entirely reasonable to perform an ablation if either dual AV nodal anatomy or accessory pathway conduction is present in the setting of electrocardiographic evidence of an SVT.

The issue of ablation in the setting of asymptomatic ventricular pre-excitation is somewhat more complex. Ablation is indicated in patients with high-risk occupations such as pilots, scuba divers and school bus drivers [1]. Inducibility of AVRT in the absence of symptoms may be considered as an indication for ablation although this is not a clear cut decision and may also depend on patient and physician preference as well as the conduction properties of the pathway. Accessory pathways that can lead to rapid ventricular rates during atrial fibrillation should be ablated.

Atrial pacing may be used to calculate the antegrade refractory period of the AP with a measurement greater than 250 ms being considered lower risk. The **Shortest Pre-Excited R-R Interval** (**SPERRI**) may be a more useful measurement with an RR interval greater than 250 ms probably being associated with a lower risk. These measurements may help to guide the decision regarding ablation of an AP.

Typical Atrial Flutter

Typical atrial flutter involving the cavo-tricuspid isthmus (CTI) can be successfully ablated in the majority of cases. An ablation may be considered after a single episode of typical atrial flutter (Class IIa Indication; Level of Evidence B) or following a recurrent episode (Class I Indication; Level of Evidence B) [1]. Ablation can also be considered for atypical atrial flutter (Class IIa Indication; Level of Evidence B) although the overall success may not be as high as for typical atrial flutter [1] (Fig. 2.1).

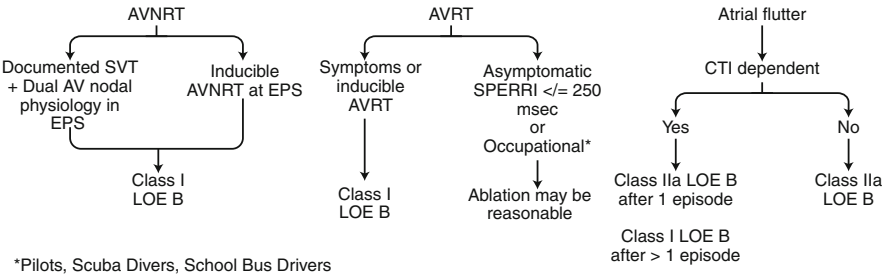


Fig. 2.1 Decision tree for ablation for AV Nodal Re-entry Tachycardia (*AVNRT*), AV Re-entry Tachycardia (*AVRT*) and Atrial Flutter regarding consideration for Catheter Ablation. *SPERRI* shortest pre-excited R-R interval)

Atrial Fibrillation (AF)

In order to consider a catheter ablation for a patient with AF the patient must have symptoms attributed to the arrhythmia. This is extremely important as symptoms may be non-specific and therefore it is often useful to consider an electrical cardioversion and reassess after sinus rhythm has been established. Additionally all patients who are being considered for a catheter ablation must be able to tolerate anticoagulation therapy at least during and after their ablation [2]. There is insufficient data to support routine withdrawal of oral anticoagulation following an AF ablation even if it appears successful and the longer term decision regarding oral anticoagulation should be based on the CHADS2VASC score [2]. This is because patients may continue to have asymptomatic episodes of AF which continue to pose a thrombo-embolic risk.

For patients with symptomatic paroxysmal AF catheter ablation can be considered if at least one Class I/III anti-arrhythmic drug has been tried and is ineffective or poorly tolerated. (Class I Indication, Level of Evidence A) [2]. Catheter ablation may also be considered prior to commencing a Class I/III antiarrhythmic drug in some patients with symptomatic paroxysmal AF. (Class IIa Indication, Level of Evidence B) [2].

Catheter ablation may also be considered in patients with symptomatic persistent AF not controlled effectively with at least one Class I/III antiarrhythmic drug. (Class IIa Indication, Level of Evidence A)

The recommendations and evidence for performing catheter ablation for symptomatic persistent AF prior to commencement of a Class I/III antiarrhythmic drug are not as strong. (Class IIb Indication, Level of Evidence C) [2]. Catheter ablation can also be considered for the management of longstanding persistent symptomatic AF (Class IIb Indication, Level of Evidence B) although the overall success for such a procedure may not be high. If available in the center, a hybrid ablation with thoracoscopic approach and closure of the left atrial appendage offers a better future in these patients [3] (Fig. 2.2).

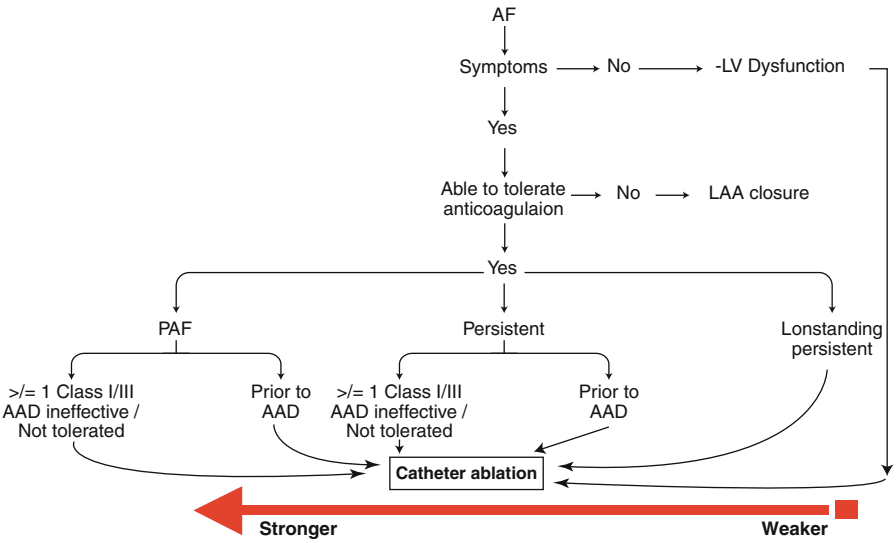


Fig. 2.2 Decision tree for consideration for catheter ablation for atrial fibrillation. *AAD* anti-arrhythmic drug therapy

Ventricular Arrhythmias

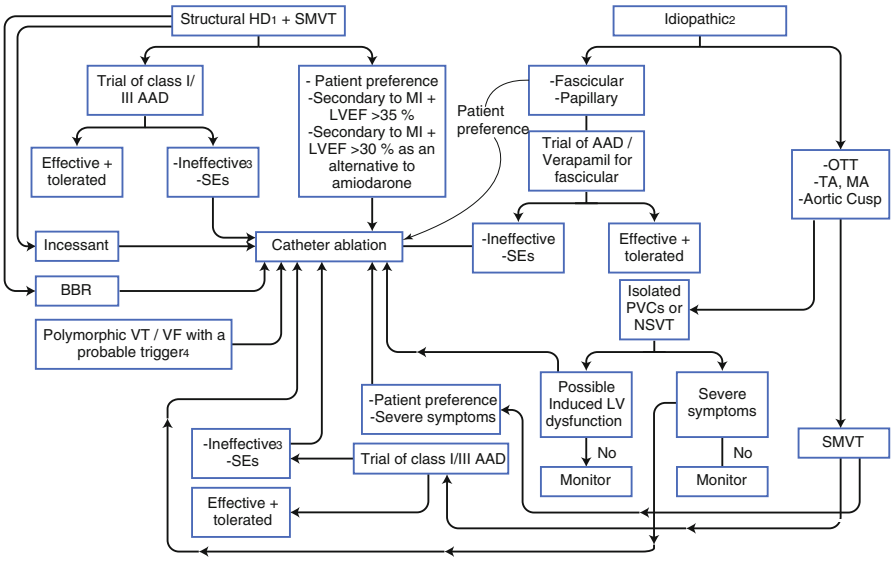
Catheter ablation is recommended for patients with sustained monomorphic VT including VT terminated by an ICD where anti arrhythmic drug therapy is either ineffective or not tolerated as well as the control of incessant VT [4].

It may also be considered when anti-arrhythmic drug therapy has not failed and in particular may be a suitable alternative to amiodarone therapy. Catheter ablation is also recommended for bundle branch re-entry VT and interfascicular VT and for patients with frequent PVC's or non sustained VT resulting in left ventricular dysfunction. It is not recommended for the treatment of asymptomatic PVC's or non-sustained VT not resulting in left ventricular dysfunction (Fig. 2.3).

EP Study and Ablation: Patient Preparation

The most useful test for any patient prior to an EP Study is an ECG or rhythm strip of the arrhythmia as this may guide the entire approach, chamber of access and threshold for potential ablation.

A baseline ECG should be performed as well as electrolytes and urea, full blood count and an international normalized ratio for patients taking warfarin [5].



1 Previous Myocardial Infarction; Dilated cardiomyopathy; ARVC; Congenital Heart Disease

2 Outflow Tract Tachycardia; Annular Tachycardia, Aortic Cusp Tachycardia; Fascicular VT; Papillary Muscle VT

3 ≥ 1 episode of MSVT despite the use of ≥ 1 antiarrhythmic drug

4 For either structural or idiopathic VT

Fig. 2.3 Decision tree for the ablation of ventricular arrhythmias. *HD* heart disease, *SMVT* sustained monomorphic VT, *SE* side effects, *BBR* bundle branch re-entry, *OTT* outflow tract tachycardia, *TA* tricuspid annulus, *MA* mitral annulus

Additionally a pregnancy test in any female of childbearing age should be checked within the 2 weeks prior to the procedure [5].

For potentially high risk procedures a group and crossmatch should be considered.

In general for most diagnostic studies anti-arrhythmic drugs should be stopped for at least 5 half lives. This is not required in patients undergoing catheter ablation unless an EP study or rotor mapping is also being performed.

EP Study and Ablation: Potential Risks

The risks associated with EP studies and ablation vary greatly depending on the procedure being performed. General complications include groin hematoma, vascular injury and pericardial effusion. More specific complications may occur in AF and VT ablations. In general many of these risks can be significantly minimized if care is taken and appropriate action taken. These risks, as well as preventative measures are summarized on Table 2.1.

Table 2.1 Reported incidence, features, prevention and management of potential complications associated with EP procedures

Complication	Features	Prevention and management	Reported incidence (%)	
Groin hematoma Pseudoaneurym AV Fistula	Swelling Tenderness Bruit	Careful palpation of femoral artery Medial approach to the vein Careful post procedure groin management	SVT	0.3 [6] – 0.4 [7]
			AF	1.8 – 2.7 [8]
			VTs	2.0 – 3.6 [9]
			VTsn	0.7 – 0.8 [10]
AV Block	PR prolongation Loss of AV conduction	Map His prior to ablation If close to compact AV node consider lower energy RF or cryoablation Monitor for Accelerated Junctional rhythm, loss of VA conduction, prolongation of AH or PR interval	SVT	0 [7] – 1 [11]
			AF	0.1 [8] – 0.2 [12]
			VTs	0 [6] – 1.6 [13]
			VTsn	0 [6] –0.4 [10]
Coronary Artery Injury	ST elevation Chest pain	Careful use of RF in certain locations of the coronary sinus, LVOT, epicardium. Do not deliver RF if closer than 5 mm	SVT	0 [7] – 0.1 [14]
			AF	0 [7] –0.1 [15]
			VTs	0.6 (epi) [16]
			VTsn	<0.1 [17]
Pericardial Effusion	Hypotension Tachycardia Change in left heart border motion in LAO view Accumulation of pericardial effusion on ICE/TEE	Caution when manipulating catheter, sheaths and wires Cautious use of RF in certain areas considered higher risk such as RVOT, RV apex, RV free wall, LAA, LA roof and LA posterior wall Monitor closely during trans–septal access	SVT	0.4 [18] – 1.0 [7]
			AF	1.8 [7] – 2.5 [8]
			VTs	1.4 [7] – 2.7 [19]
			VTsn	1.3 [20] – 1.7 [7]
Thrombo-embolism	TIA/stroke Systemic embolism	Maintain ACT greater than 350 s for left sided ablations Use of heparinized saline through sheaths on left side Careful use of equipment to ensure no air embolism	SVT	0 [7] – 0.2 [11]
			AF	0.3 [7]–1.0 [5]
			VTs	0.8 [7]–2.7 [18]
			VTsn	0.8 [7]
Phrenic Nerve Injury	Loss of movement of hemidiaphragm, post procedure dyspnea, pleural effusion, consolidation on CXR	Monitor movement of hemidiaphragm Pacing from ablation catheter to monitor for phrenic nerve capture	SVT	<0.1
			AF	0.2 [9]
			VTs	<0.1
			VTsn	<0.1

VTs VT ablation in the setting of structural heart disease; *VTns* VT ablation in structurally normal ventricle; *Epi* Epicardial

Collateral Damage During Ablation

Pericardial Effusion

Pericardial effusion may occur as a direct result of catheter, sheath or wire manipulation as well as during or after trans-septal access or as a direct result of catheter ablation. It is therefore important to be gentle with all of the equipment being used. Some regions within the heart are particularly thin and extra caution should be taken. As demonstrated in Fig. 2.4 these regions include the RV apex, RV free wall, RVOT, LAA, LA posterior wall and LA roof. A pop and/or sudden rise in impedance during ablation may be associated with perforation. The incidence of perforation resulting in either a pericardial effusion or tamponade is 1.3 % for all EP procedures [7]. For SVT ablations this is 0.2 %, 1.8 % for patients undergoing catheter ablation for AF, 1.7 % for VT in a structurally normal heart (predominantly outflow tract tachycardia) and 1.4 % in patients with structural heart disease undergoing VT ablation [7].

Although the pericardial space may accommodate up to 500 cc of fluid accumulated over a long period of time decompensation may occur with 50–100 cc when

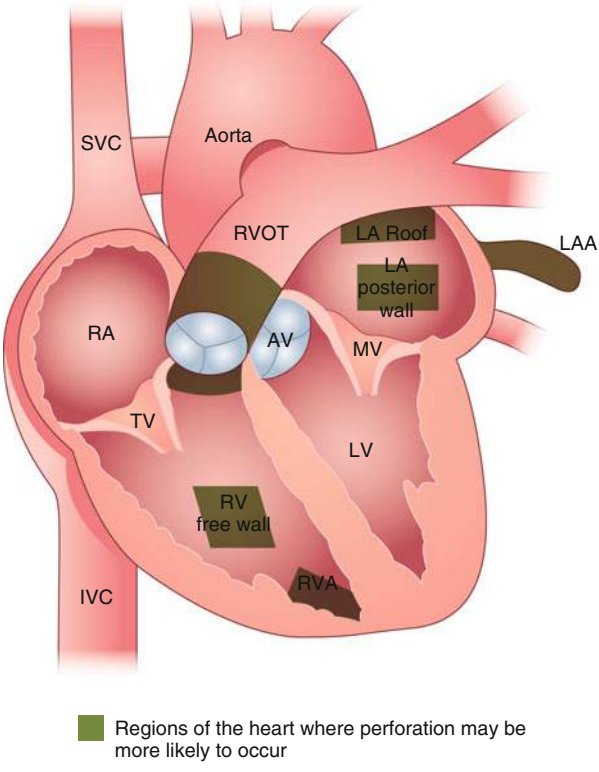


Fig. 2.4 Diagrammatic representation of regions of the heart which are at an increased risk of perforation during instrumentation with catheters and wires; *SVC* superior vena cava, *IVC* inferior vena cava, *RA* right atrium, *TV* tricuspid valve, *RV* right ventricle, *RVOT* right ventricular outflow tract, *LA* left atrium, *LV* left ventricle, *LAA* left atrial appendage

fluid accumulation occurs quickly. This tends to be most evident around chambers with the lowest pressures first; the RA followed by the RV, LA and finally the LV. Accumulation may also be localized and therefore may occur on the left side prior to the right side.

The accumulation of a significant pericardial effusion may be associated with an increase in heart rate with or preceding a drop in blood pressure. It must also be noted, however, that an increase in sympathetic drive may initially result in an increase in the blood pressure. Pericardial stretch may occasionally result in an increase in parasympathetic tone with a transient bradycardia and hypotension. A drop in blood pressure is a relatively late sign of acute pericardial effusion and it is therefore important to monitor for earlier signs.

A reduction in the left lateral wall excursion in the LAO fluoroscopic view has been shown to be associated with pericardial effusion [21]. This occurs as the pericardium is relatively fixed to the spine and the sternum and therefore fluid in the pericardial space is more likely to accumulate posterolaterally followed by anterolaterally. The accumulation of pericardial fluid during ablation can easily be observed using Intracardiac Echo (ICE) or Trans-esophageal echo (TEE). The accumulation of a small pericardial effusion detected on ICE during an AF ablation may indicate an increase in the risk of a late post procedure pericardial effusion while no evidence of effusion on ICE indicates a very low post procedural risk.

All EP laboratories should have equipment for emergency pericardiocentesis including rapid access to echocardiography. In order to keep this as simple as possible the needle used to access the femoral vein and a 0.35 wire can be kept on the table for rapid access. After confirmation that the wire is within the pericardial space by pushing it as far as possible and ensuring that it is not within one or more cardiac chambers a short sheath and a pigtail catheter can be used to rapidly drain the effusion.

Phrenic Nerve Injury

The right phrenic nerve runs alongside the SVC and passes laterally along the RA running anteriorly to the right pulmonary veins passing more closely to the superior than the inferior right pulmonary vein (Fig. 2.5). The left phrenic nerve runs over the fibrous pericardium with a variable course over the LA and LV and terminates in the left hemidiaphragm. The incidence of phrenic nerve palsy following an AF ablation is approximately 0.2% [8] and more commonly affects the right than the left side. This generally occurs with isolation of the right superior pulmonary vein or the superior vena cava. Left phrenic nerve palsy is less common but may occur in left atrial appendage ablation. The incidence of phrenic nerve palsy is much higher with cryoablation and has been reported to occur in approximately 6% of cases although it is usually transient [22].

Various techniques may be used to help map the location of the phrenic nerve before or during catheter ablation. Pacing at high output may be performed in order to assess for phrenic nerve capture. This should be discussed with the anesthesiologist

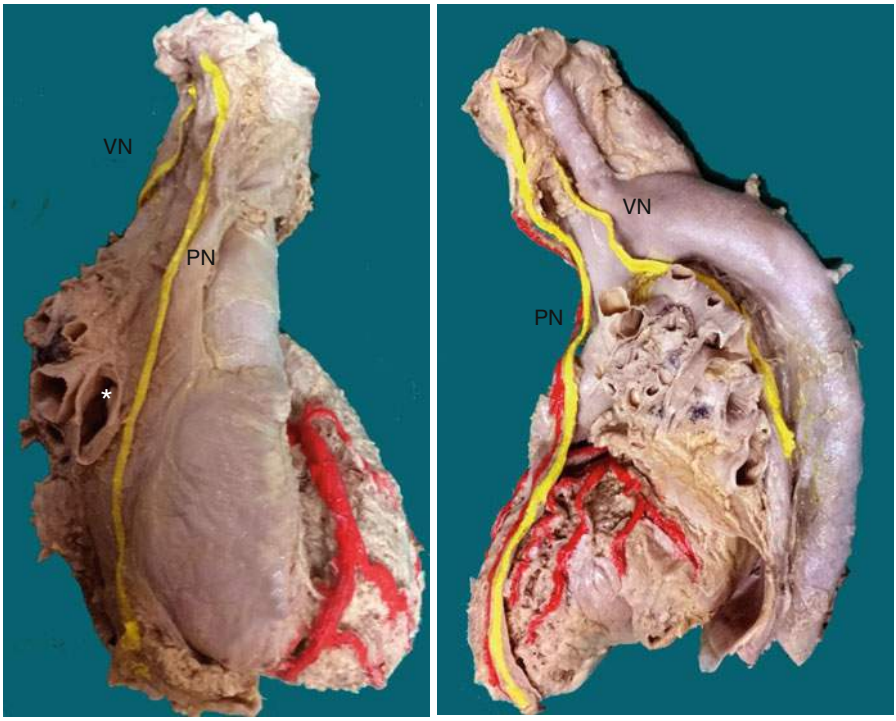


Fig. 2.5 Anatomical images showing the course of the right phrenic nerve (PN) on the *left image* and the left phrenic nerve (PN) on the *right image*. The right lareral view on the *left* shows the close relationship of the right PN to the right inferior pulmonary vein (*). The vagus nerve is also seen in both images

prior to performing this maneuver as muscle relaxants are often administered which will inhibit the effects of pacing on the phrenic nerve. Additionally the diaphragm can be monitored using fluoroscopy during ablation in the absence of nerve paralytic agents. More novel techniques such as recording electromyograms from the diaphragm have been described in which either a catheter is positioned in the hepatic vein or modified surface electrodes are positioned over the diaphragm with pacing performed from either subclavian vein.

Phrenic nerve palsy is generally noted on CXR as an elevated hemidiaphragm and may be associated with dyspnea, a cough or hiccups. The majority of phrenic nerve palsy recovery within 9 months.

Esophageal Injury

As shown on the CT scan in Fig. 2.6 the esophagus is immediately posterior to the LA separated by a thin layer of fibrous pericardium and a layer of fibrofatty tissue containing esophageal arteries as well as the vagus plexus. The distance between the

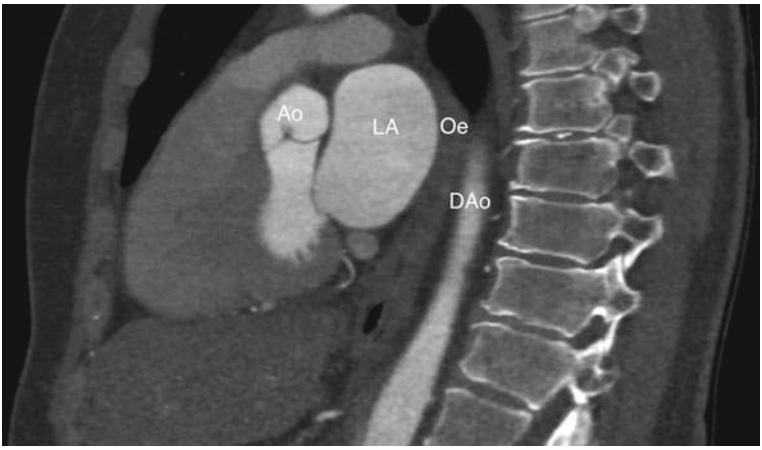


Fig. 2.6 CT showing proximity of esophagus to the posterior wall of the left atrium. In this lateral image the ascending aorta (*Ao*) is anterior to the left atrium (*LA*). The oesophagus (*Oe*) is posterior to the left atrial wall. Also seen in this image is the descending aorta (*DAo*)

posterior wall of the LA and the anterior portion of the esophagus is variable but may be as little as 5 mm [23]. The location of the esophagus may run either central to the posterior wall of the left atrium, towards the left pulmonary veins or towards the right pulmonary veins as is generally closer at the atrial pulmonary vein junction and in more inferior locations. Although the esophagus can be clearly visualized on a pre-ablation CT scan the esophagus is a mobile structure and therefore the location may change during the procedure.

Esophageal injury occurs predominantly as a result of direct thermal injury from catheter ablation along the posterior wall of the LA. Other contributing factors may include damage to the arterial flow to the esophagus as well as to the vagus nerve and plexus. This may result in mucosal erythema, esophagitis or atrioesophageal fistula. Discrete mucosal changes have been noted to be present in approximately half of all patients who undergo catheter ablation for AF with almost one fifth developing esophageal ulceration [24].

The incidence of fistula formation between the left atrium and the esophagus as a result of catheter ablation for AF ranges from 0.03 [25] to 0.2 % [26].

Symptoms relating to atrio-esophageal fistula may occur from 3 days to 6 weeks post ablation and are often non specific. The most common is a pyrexia followed by neurological symptoms relating to thrombo-embolism. Other symptoms include chest pain and dysphagia. The white cell count is generally elevated. Management depends on acute recognition of the condition followed by surgical repair.

Although the esophagus can be visualized pre-procedure this is generally unreliable due to intra-procedural movement. The esophagus can be visualized during ablation using fluoroscopy with a marker such as a naso-gastric tube, a temperature probe or barium paste. This requires fluoroscopy being performed during ablation

along the posterior wall of the left atrium and although it marks the lumen of the esophagus it does not provide an accurate distance from the ablation catheter to the most anterior aspect of the esophagus.

Esophageal temperature monitoring is performed by some operators using a temperature probe. Evidence for the efficacy in preventing esophageal injury is limited and conflicting and overall there is no general consensus as to whether luminal esophageal temperature is a good predictor of mucosal injury.

It is generally considered reasonable to limit maximum power to 25–30 W and to spend no longer than 30 s on one region when ablating along the posterior wall of the left atrium. It is also common to prescrive proton pump inhibitors post ablation in order to reduce the effects of acid reflux on the esophagus.

Coronary Artery Injury

This may occur if ablation is performed in close proximity to a coronary artery such as the aortic cusps. Other regions where ablation may be in close proximity to a coronary artery or one of its branches include the coronary sinus (as shown in Fig. 2.7), great cardiac vein, CTI, mitral annulus, base of the LAA or in the epicardium.

Endocardial ablation of accessory pathways along the mitral and tricuspid annulus carries a low risk of coronary artery stenosis. The risk is increased when ablation is performed in the proximal CS which may be the optimal location for posteroseptal AP's as well as occasionally the slow pathway and focal atrial tachycardia's. The posterolateral branch of the RCA or the circumflex coronary artery often run closely to this location and this may be a closer to the anterior and inferior walls of the

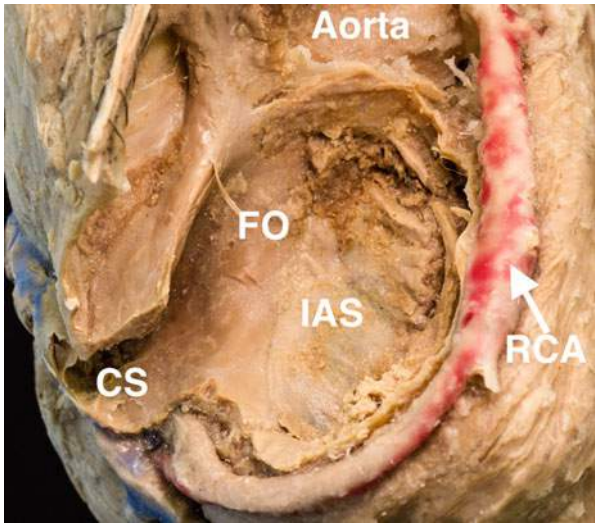


Fig. 2.7 Anatomical images showing proximity of the right coronary artery (*RCA*) to the coronary sinus (*CS*). The RCA originates in the right coronary cusp of the aortic root and courses along the right atrioventricular grove anteriorly and inferiorly where it eventually courses towards the proximal coronary sinus (*CS*). In this region there is close proximity to the CS. Also shown in this image is the right ventricular outflow tract (*RVOT*) and the fossa ovalis (*FO*)

CS. If ablation is being performed in this location a coronary angiogram should be considered and a minimum distance of 5 mm should be maintained between the site of ablation and the coronary artery.

Ablation in the distal cardiac vein for PVC's along the epicardial annulus may also result in coronary artery damage and similar precautions have to be taken in terms of distance.

Epicardial ablation is now increasingly performed particularly for non-ischemic VT and to a lesser degree ischemic VT. Coronary CT or angiography should be performed in these cases prior to ablation.

Important Note on Ionizing Radiation

Ionizing radiation may result in molecular injury to the DNA. In the EP laboratory this is measured in Grays (Gy) or Sieverts (Sv). One gray is defined as the absorption of 1 J of ionizing radiation by 1 Kg of matter. The equivalent dose Sievert is the absorbed dose in Gy multiplied by the radiation weighting factor which varies according to the source of radiation and is 1 for X-rays. This can be further modified in order to calculate the effective dose when the radiation is predominantly exposed to certain regions of the body. It is important to achieve as low as reasonably achievable (ALARA) radiation doses. This can be achieved by reducing the frame rate to as low as possible, minimizing the duration of time performing fluoroscopy and not taking cine images. The development of 3 D mapping systems has had a significant impact on reducing the need for fluoroscopy particularly in complex ablations.

Administration of Sedation and Anesthesia

The requirements for sedation and anesthesia vary according to the precise procedure being performed. For EP studies minimal doses of sedation are given for anxiolytic effects as larger doses may reduce the inducibility of the arrhythmia particularly in adrenaline sensitive focal atrial tachycardia and outflow tract tachycardia. Moderate doses of sedation are often required for ablation and in particular for performing anatomical lesions such as a cavotricuspid isthmus ablation. Ablation for AF and complex VT may be performed with moderate to deep sedation or general anesthesia. There are several potential advantages to the use of general anesthesia in such procedures such as minimizing patient discomfort and movement thus facilitating 3D mapping as well as allowing the use of TEE visualization. Care must be taken in order to minimize the doses of paralytic agents when assessing for phrenic nerve capture.

Benzodiazepines and opioids are used in the EP laboratory for their anxiolytic and partial amnesic effects. If these agents are used it is ideal to administer low

doses before the procedure is performed in order to assess the effect on the individual patient. All patients undergoing any procedure involving the administration of intravenous sedation should have a history and rapid airway assessment prior to starting the procedure. Ideally there should be involvement of an anesthesiologist. It is also advisable to have an individual whose sole purpose is to monitor the patient's respiratory rate, oxygen saturations as well as heart rate and blood pressure throughout the procedure. All patients should be closely monitored post procedure until their vital parameters have returned to normal limits.

The most common benzodiazepines used in the EP laboratory are midazolam and diazepam. Although either of these agents can be used midazolam tends to have a shorter duration of action particularly in the elderly or in those with reduced cardiac output, respiratory depression, hepatic and renal impairment.

Midazolam can be administered at a dose of 0.03–0.07 mg/kg over 2 min for most adults adult with additional doses given after 3 min, if required, at 25 % of the initial dose. Generally no more than 10 mg is needed for the entire procedure.

Midazolam tends to have less effect on suppression of induction of supraventricular tachycardia compared to diazepam. Routine administration of the benzodiazepine antagonist flumazenil should not be performed and this should be reserved only for cases of significant over sedation. A dose of 0.2 mg over 15 s with another dose of 0.2 mg after 45 s and then every 1 min up to a maximum dose of 1 mg should be used. The patient should be monitored closely for 2 h in order to ensure that there are no further sedative effects as the drug effects wear off.

Fentanyl is a useful opioid which can be administered at the start of the case at a dose of 0.5 microgrammes/kg if used with a benzodiazepine or 2 microgrammes/kg if used alone. The effects can be re-assessed after 15 min and a further 25 % of the initial dose administered if required. The overall duration of action is approximately 30–60 min. If used in conjunction with a benzodiazepine fentanyl may result in respiratory depression and therefore monitoring is required. The effects of fentanyl can be partially reversed by naloxone at a dose of 0.1–0.2 mg over 2 min.

Propofol is frequently used in the EP laboratory. The individual responsibility for this depends on the country where the procedure is performed. Propofol is generally administered at a dose of 0.5 mg/kg over a period of 3–5 min. Further doses may be administered in 5 mg boluses if required. It has no significant electrophysiological effects on arrhythmia induction.

Very occasionally propofol infusion syndrome may occur particularly at higher doses and for longer periods of time. This may occur as a result of mitochondrial respiratory chain inhibition or impaired fatty acid metabolism and results in acute refractory bradycardia leading to asystole with either metabolic acidosis, rhabdomyolysis, hyperlipidaemia, and or fatty liver. Coved type ST elevtaion with RBBB occurs in the precordial leads. The only effective treatment for this condition is haemodialysis or haemoperfusion with cardiorespiratory support.

Peri-procedural Anticoagulation

For the majority of right sided ablations anticoagulation is not required although some operators choose to give low dose heparin in order to try to lower the potential risk of deep venous thrombosis and pulmonary embolism. For left sided ablations intravenous heparin is administered aiming for an Activated Clotting Time (ACT) of greater than 350 s. In patients who are already taking oral anticoagulation the decision to continue, discontinue or bridge with heparin depends on the risks of thrombo-embolism compared to the risk of bleeding.

Patients undergoing ablation for AF are at an increased risk of thrombo-embolism due to a combination of pre-existing factors involved in Virchow's triad as well as potential for embolic formation during ablation in the left atrium and possible reversion from AF to normal sinus rhythm. The need for pre-procedural anticoagulation depends on the patients CHADS2VASC score. If this is 0 then anticoagulation is generally not required pre-ablation however in all other cases therapeutic anticoagulation is recommended for a minimum period of 4 weeks [2] (Table 2.2).

Even in patients considered to have a low baseline CHADS2VASC score there is an increased risk of thrombo-embolism post ablation. This occurs as a result of endothelial injury as well as potential mechanical dysfunction of the left atrium post ablation. As shown in Fig. 2.8 manipulation of ablation and mapping catheters and guidewires results in endothelial injury and activation of factor XII which results in intrinsic pathway activation and tissue factor which activates the extrinsic pathway. It is therefore necessary to administer heparin for left sided ablations aiming for an activated clotting time (ACT) of 350 s [2] even in patients who are receiving warfarin. In patients who are allergic to heparin bivalirudin may be considered.

It is recommended that oral anticoagulation is continued for at least 8 weeks post ablation in these patients and long-term in patients with a higher risk of thromboembolism [2].

The choice of whether to continue with oral anticoagulation compared with heparin bridging is largely dependent on individual operator and center experience. Continuation of warfarin during catheter ablation for AF is likely superior to bridging with heparin with reported lower rates of thrombo-embolism, pericardial effusion and major bleeding [27]. Although there is limited data regarding the use of uninterrupted direct oral anticoagulants in AF catheter ablation given the shorter half life of the direct oral anticoagulants minimal interruption can be performed pre-ablation and appears to be effective particularly if a pre-procedure

Table 2.2 Pharmacological properties of Warfarin and direct oral anticoagulants

Drug	Mechanism of action	Time to peak (h)	T1/2 (h)	Renal excretion (%)
Warfarin	Vitamin K antagonist	96–120	40	0
Dabigatran	DTI	1–2	12–17	80
Rivoroxaban	Xa inhibitor	2–3	7–11	33
Apixaban	Xa inhibitor	1–2	12	25

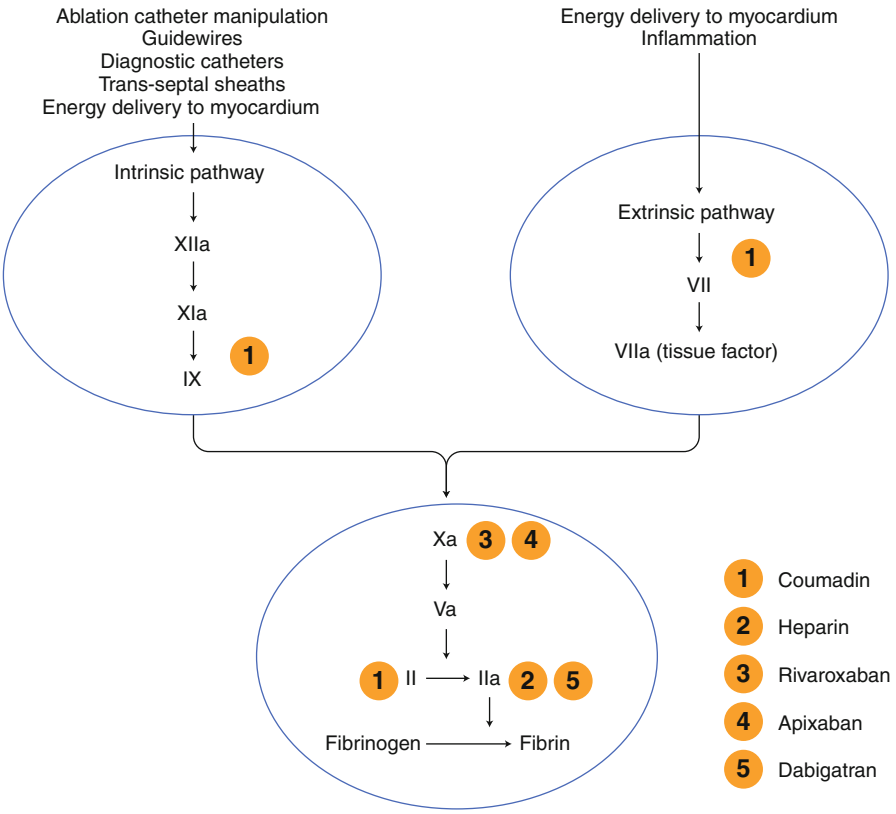


Fig. 2.8 Effect of catheter ablation, sheath and wire manipulation on the coagulation cascade and pharmacological intervention

transesophageal echocardiogram (TEE) is performed. In general provided the patient has normal renal function the last dose of oral anticoagulant can be administered 24 h pre ablation with the first dose post procedure administered 4 h after sheath removal.

EP Laboratory Set-Up

The EP lab is composed of an EP recording system, a stimulator, a RF generator with the potential for irrigation and an electroanatomic mapping (EAM) system as well as a cryoablation system and the cables and interfaces which connect these systems. Additional to this is resuscitation (at least one defibrillator with rapid access to a second and ventilation equipment) and fluoroscopic equipment for image acquisition (Fig. 2.9).

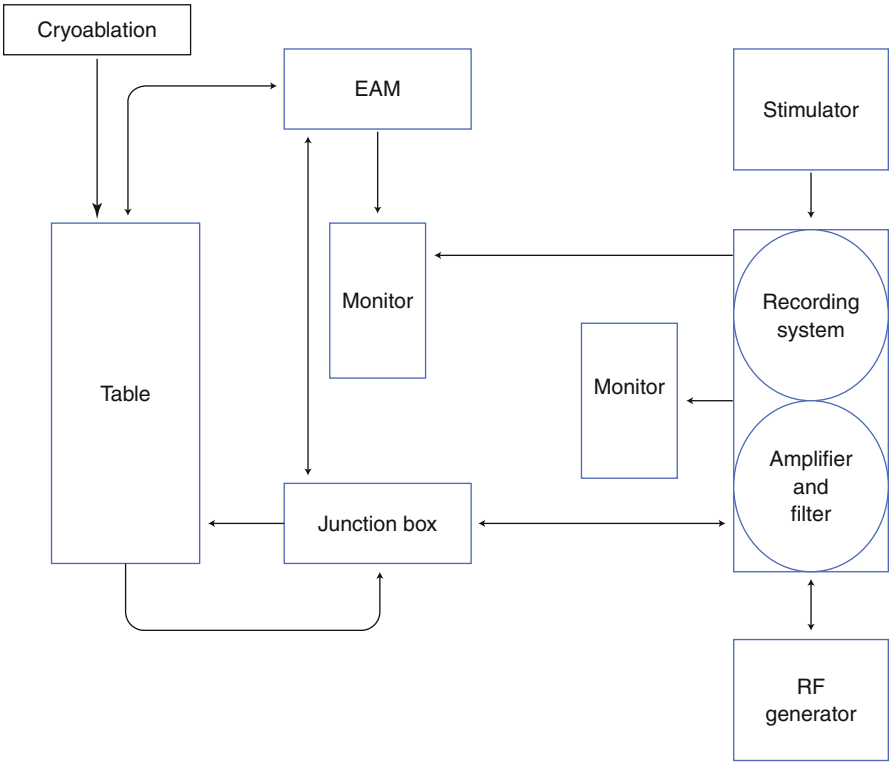


Fig. 2.9 Diagrammatic representation of a typical setup for an EP laboratory. *EAM* electroanatomic mapping system

How Electrograms Are Derived: Amplification and Filtering

Electrograms recorded in the heart are generally less than 5 mV in amplitude and often as small as 0.01 mV in scarred tissue. In order to display these signals they must be amplified and filtered. Signals may be amplified up to 10,000 times prior to being filtered.

The amplified signal then passes through a **high pass filter**. This allows higher frequency signals to pass through while removing signals below a designated frequency. On the **surface ECG** this is set very low at **0.05 Hz** therefore allowing a larger range of low frequencies to pass through. For **bipolar intracardiac signals** this is set higher at **30 Hz** which therefore filters out a larger range of low frequencies that may occur as a result of catheter movement, electrical farfield or respiratory variability.

For **unipolar intracardiac signals** where the morphology of the signal is more relevant the setting is similar to the surface ECG at **0.05 Hz** or else switched off.

This signal then passes through an isolation amplifier which isolates the current from the patient and is subsequently transmitted through a **low pass filter**. This

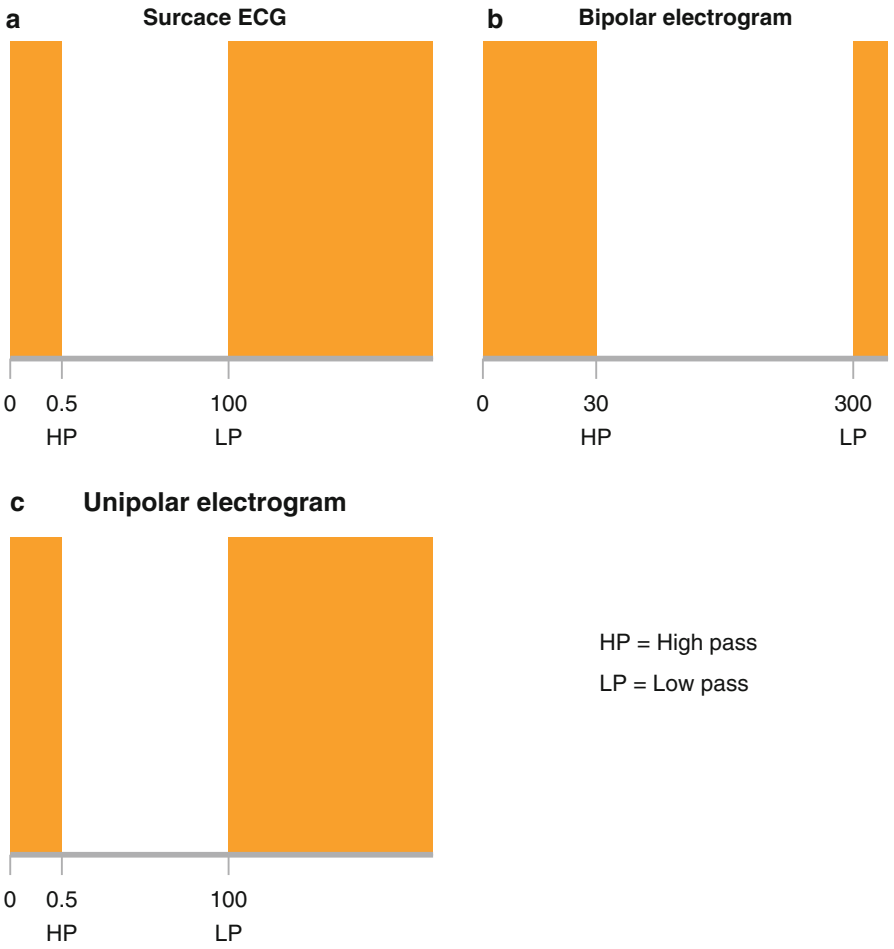


Fig. 2.10 High Pass (*HP*) and Low Pass (*LP*) settings for the surface ECG (**a**), Bipolar intracardiac electrograms (**b**) and Unipolar intracardiac electrograms (**c**)

allows lower frequency signals to be transmitted while filtering out higher frequencies. This is generally set at **300 Hz for bipolar intracardiac electrograms and filtered and unfiltered unipolar electrograms and 100 Hz for surface ECG signals** (Fig. 2.10).

Additionally most EP systems have a **notch filter**, which removes signals at a specific frequency range generally in the range of electrical frequency. This is often set at **50 Hz in Europe and 60 Hz in North America** and is designed to reject interference outside of the range around this. This also has several potential disadvantages including a reduction in the amplitude of certain electrograms such as pulmonary vein potentials as well as the potential to add interference.

Electroanatomic mapping systems have their own high pass and low pass filters programmed and can also be adjusted and are generally set with the range of

30–500 Hz for intracardiac electrograms. For unipolar electrograms the low pass is either minimized or switched off in order to reduce artifact on the signal. If the standard settings are kept on for unipolar signals often an artefactual R wave may appear on the signal.

Despite filtering of signals the best policy is to minimize noise in the first place. This can be due to direct electrical interference from other devices in the lab, leakage current from other devices as well as electrical cables which may be closely coupled with cables transmitting electrograms. It is therefore important when designing the EP laboratory in the first place that electrical cables are not positioned beside cables used for transmitted electrocardiograms. **Leakage current** is the total current from patient connections through the patient to earth and is required to be less than **10 μA** [28]. This cumulative current also may result in considerable electrical interference which must be filtered.

Noise which occurs specifically during ablation may often be due to the fact that the pacing function is enabled at the distal electrode at the same time as the ablation function. This is the result of a slight difference in the current between the distal and proximal poles which exists even when pacing is not being performed.

Other potential causes include problems with the ablation catheter or cable, issues with the grounding pad and inadequate gel on the back patch.

Electrogram Signals: Unipolar and Bipolar

Electrogram signals occur as a result of voltage gradients which occur between myocytes at different phases of the cardiac AP. **Unipolar electrograms** are amplified signals which are recorded between the distal pole of the catheter (+) and Wilsons Central Terminal (−) and are in essence bipolar signals between two regions spaced far apart. This therefore records both near and farfield, the latter of which may distort the local signal.

Bipolar signals are amplified signals recorded from two closely spaced unipoles. In general the distal pole is negative while the proximal pole is positive. Bipolar recordings are affected by the direction of the wave front with respect to the electrode orientation, electrode spacing and configuration and are generally considered more useful in clinical practice.

Both types of signal can be used in cardiac mapping for example in exit site and accessory pathway localization where a deep Q wave with no R wave may indicate proximity to the activation site in unipolar electrograms [29]. This is not perfect for localization of the focus. As shown in Fig. 2.11 during a PVC originating from the LV inferior wall there is a deep Q wave with no R wave in the ABL WCT electrogram. Despite this the electrogram is not significantly earlier than the surface QRS. Although this was the earliest unipolar and bipolar electrogram on the endocardium this focus was found to be located on the epicardial surface.

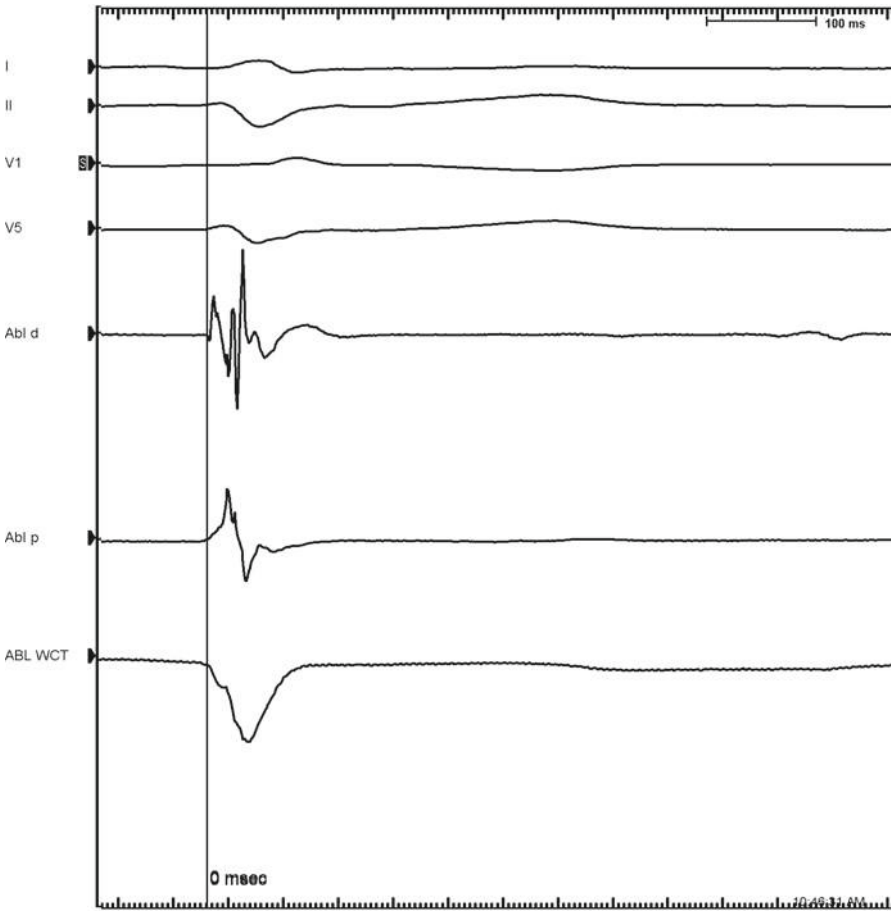


Fig. 2.11 A PVC originating from the inferior LV wall. The bipolar and unipolar electrograms are on time with the onset of the surface QRS. The unipolar electrogram has no R wave and a deep Q wave. Although this indicated activating moving away from the catheter the fact that the signal is not early indicated that this was not the focal site of the PVC. This was mapped to the epicardial surface of the inferior wall of the LV where the local signal was 20 ms ahead. (Abl d is recorded as a bipolar electrogram recorded from the distal electrode on the ablation catheter, Abl p is the bipolar electrogram recorded from the proximal electrode on the ablation catheter, ABL WCT is the unipolar electrogram recorded from the distal electrode on the ablation catheter to Wilson's Central Terminal)

RF Generation and Ablation

Radiofrequency (RF) energy is the most commonly used energy source using for creating an ablation lesion. The generator produces a continuous sinusoidal waveform at a frequency between **500** and **1000 KHz** which is then delivered between

the catheter tip and a patch electrode placed on the skin. As a result of the difference in the surface area between the tip of the ablation catheter and the dispersive electrode pad the maximum zone of resistive heating, which is directly related to current density is generally within 2 mm of the catheter tip. The majority of this is lost in the blood flow as blood has a lower resistance than myocardium.

The rest of the lesion, which is in fact the majority, is formed by conductive heat. This diminishes as a function of $1/r^4$ where r is the distance from the point of maximum resistive heating. The size of the lesion increases as the temperature increases. In general an irreversible lesion occurs at or above 50 °C. If the temperature at the electrode-tissue interface rises to greater than 100 °C the tissue immediately adjacent to the electrode forms a coagulum and a steam pop is heard.

The actual impedance during RF ablation is dependent on the tissue in contact with the catheter, the temperature, body characteristics, catheter properties, cables and reference patch. During the delivery of RF in order to create a lesion there is generally a reduction in the impedance of greater than 10 Ω. A sudden rise in the impedance as shown in Fig. 2.12 is often associated with a steam stop and potential perforation.

A thermocouple incorporated into the tip of the ablation catheter measures the temperature. In temperature guided ablation the temperature of the ablation electrode is set at the start of the ablation and automatically adjusts power output to

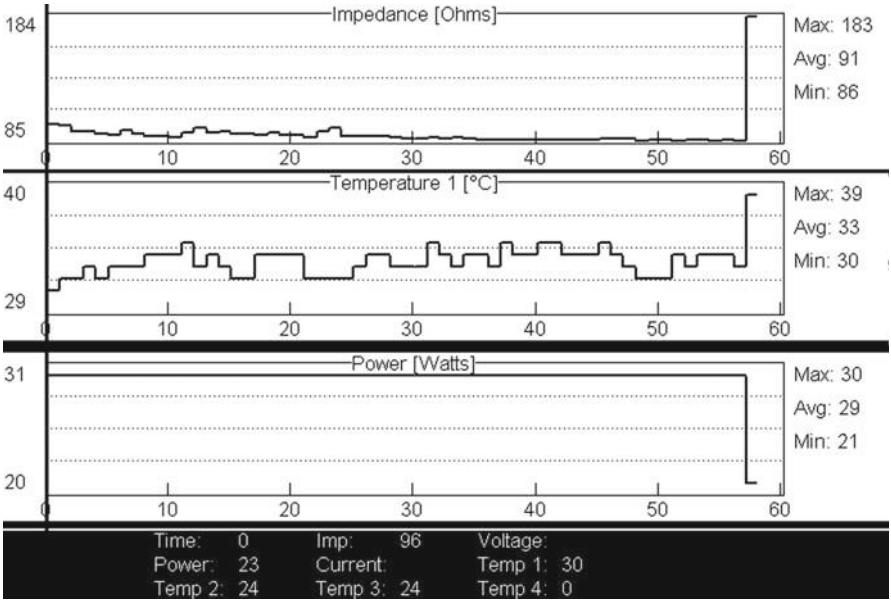


Fig. 2.12 RF ablation in the left atrium using a 4 mm irrigated catheter. There is a sudden rise in impedance and temperature at the interface between the catheter and the endocardium. This results in a steam pop

achieve a targeted electrode temperature of between **55** and **70 °C**. Ablation can also be set at a power limit so that RF is delivered until a certain power is achieved.

Lesion sizes are usually 5 mm in diameter but can be increased by the use of a larger diameter ablation catheter or with the addition of irrigation, which flushes the tip of the catheter.

Cryoablation

Cryoablation has been used in the ablation of slow and accessory pathways anatomically close to the compact AV node as well as in pulmonary vein isolation (PVI). There are several potential benefits in the use of this modality. Following the application of cryoablation there is an initial degree of reversibility in lesion formation, particularly between −10 and −25 C. This confers the potential advantage in the case of ablation of a nodal or accessory pathway that is close to the compact AV node where the risk of AV block is considered to be significant. Permanent tissue damage occurs at temperatures less than −50 C.

During the application of cryoablation the catheter tends to remain stuck to the tissue which results in increased catheter stability.

The concept relies on localised hypothermia at the catheter endocardial surface. There are three biophysical phases to this process.

1. Freezing – thawing phase
   This occurs acutely during delivery of cryoablation. During the first few minutes this may be reversible. Microscopic extracellular ice formation occurs as the temperature drops below −15 °C. Intracellular ice formation then occurs as the temperature drops to less than −40 °C. As a result of this there is an increase in ion concentrations in the extracellular space which becomes hypertonic resulting in a shift of fluid from the intracellular space to the extracellular space. This results in a reduction in intracellular pH causing mitochondrial damage. There is progressive microcirculatory vasoconstriction resulting in further localised damage to the local tissue. Following the completion of localised freezing passive rewarming occurs knowing as thawing. This results in fusion of the ice crystals with further cellular damage as well as resulting in microvascular occlusion as a result of platelet aggregation and microthrombi formation.
2. Hemorrhagic – inflammatory phase
   As thawing continues the changes in the microvasculature result in regional hyperemia and tissue edema with microscopic hemorrhagic changes and inflammation. This tends to occur within 48 h of the thawing process and may continue for up to 1 week.
3. Replacement – fibrosis phase
   Replacement fibrosis and apoptosis of cells near the periphery of the lesion occurs within the first week and up to 3 months after the delivery of the lesion. Neovascularisation and collagen remodelling occurs until finally a fibrotic scar forms.

Ablation Catheters

Ablation catheters in their simplest form delivery energy to the myocardium while providing feedback in terms of tissue temperature and impedance. They vary in the size of the tip electrode as well as ability to delivery irrigation. Some catheters also provide feedback in terms of contact force data. The majority of available catheters tend to have a platinum tip. Other materials such as gold have also been studied and also appear to be efficacious.

Ablation Catheter Size

Larger electrode sizes have a larger percentage of surface area exposed to blood rather than endocardium. As shown in Fig. 2.13 as a result of the cooling effect of the blood flow a smaller lesion is delivered using similar power with a larger diameter catheter [30]. A higher power is therefore required in order to achieve the target temperature which results in a larger lesion. Smaller electrodes have a better electrogram resolution.

Larger tip catheters have been shown to be more effective with a reduced number of RF applications and reduced fluoroscopy time in atrial flutter ablation [31].

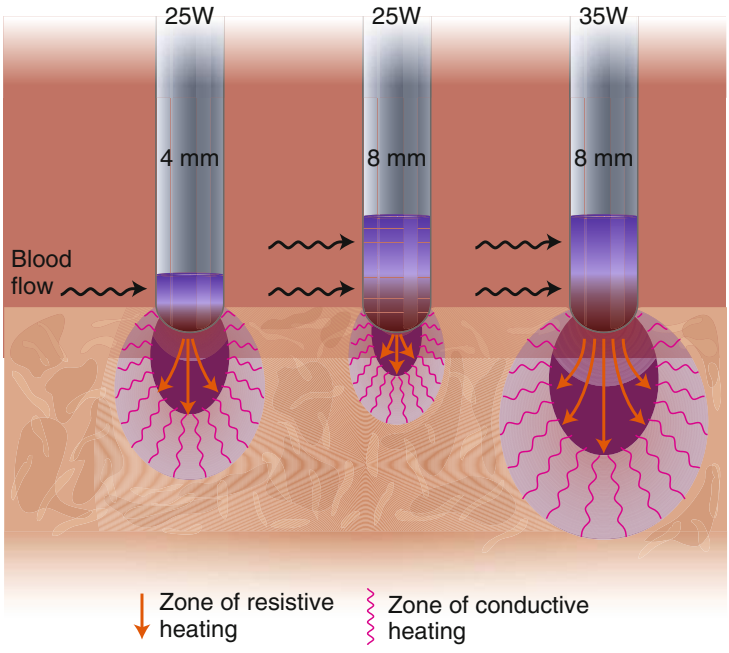


Fig. 2.13 Effect of ablation catheter tip size on the ablation lesion consisting of the zone of resistive heating and the zone of conductive heating. A higher power is required for a lesion to be created by a larger tip electrode due to an increase in loss of energy through an increase in flow across the larger surface area of the catheter

There is a better electrogram resolution with smaller tip catheters and overall smaller tip irrigated catheters have been shown to be very effective in atrial flutter ablation. The temperature measured at the tip of the catheter is not a good estimate of the tissue temperature.

Irrigation

In open loop irrigation saline is flushed through the ablation catheter resulting in cooling of the catheter tip with lowering of the catheter tip temperature resulting in the ability to create deeper lesions, with less focal hot spots and a reduced risk of thrombus formation. As shown in Fig. 2.14 a larger lesion is created over a shorter time period using a catheter with irrigation when compared with no irrigation. Using the same power and electrode size a catheter with irrigation tends to result in a larger lesion (Fig. 2.15). Temperature feedback is not reliable and therefore ablation is limited by power.

Although lesion sizes are larger using irrigation they tend to grow beyond 60 s and therefore a longer application should be considered.

The rate of irrigation should be altered according to the power delivered.

The general recommendations are **2 ml/min during mapping**, **17 ml/min during ablation at a power of less than 30 W** and **30 ml/min at a power of greater than or equal to 30 W**.

Contact Force Catheters

The contact force and orientation between the catheter tip and the endocardial surface provides valuable information regarding whether delivery of RF energy is having a significant impact on the tissue rather than the blood pool. It has been shown

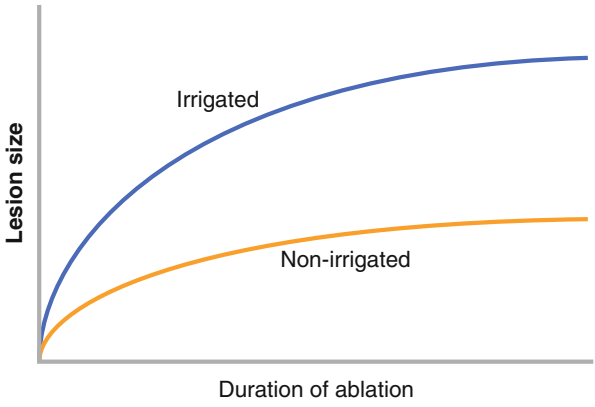


Fig. 2.14 Diagrammatic representation of lesion size developed over time for irrigated and non-irrigated ablation showing a larger lesion created over a shorter time for an irrigated catheter when compared with a non irrigated catheter

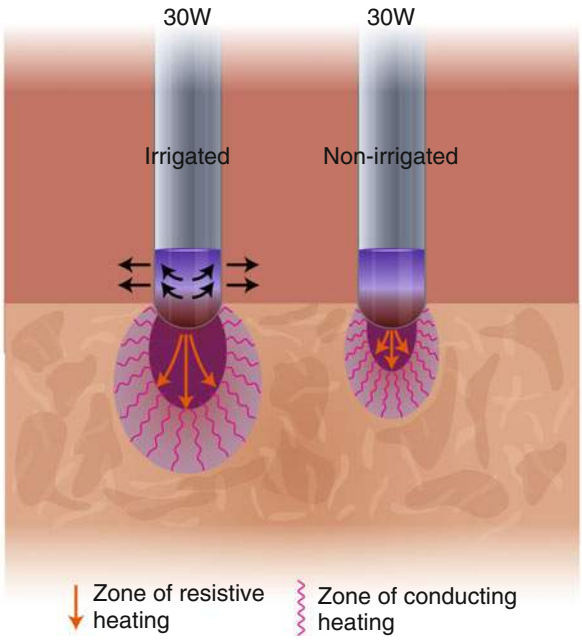


Fig. 2.15 Representation of the effects of irrigation on lesion size using a catheter with the same electrode size and at the same power

that poor tissue contact results in a higher recurrence of AF in patients who underwent a PVI [32, 33]. Excessive contact force may result in perforation. There are two commercially available contact force catheters which employ different technologies.

The SmartTouch catheter (© Biosense Webster, Inc) is shown in Fig. 2.15. This is an irrigated 7.5 Fr catheter with an 3.5 mm electrode in which a magnetic transmitter connected to the main body of the catheter with a spring. This is able to transmit data regarding directionality of the electrode tip relative to the shaft of the catheter to the processing unit. In order to measure the force applied there are an additional 3 sensors within the shaft. Although this records a minimum change of 1 g every 50 ms the mean force is displayed every 1 s [34].

Minimum contact force, duration of force as well as catheter stability, power, impedance and temperature changes can all be programmed on in order to set a minimum criteria for display of a lesion using Visitag software on Carto 3. Given the sensitivity of the electrode tip an introducing tool should be used when advancing the catheter through a sheath. A zero baseline reference should also be obtained after the catheter has been in the blood pool for a minimum of 15 min while the catheter is not in contact with any cardiac structure (Fig. 2.16).

The Tacticath catheter (St. Jude Medical, Cardiology Division, Inc., Plymouth, Minnesota) is an irrigated unidirectional 7 Fr catheter with a 3.5 mm tip electrode with a triaxial fibreoptic sensor shown in Fig. 2.17. Contact force is measured

Fig. 2.16 Image showing the distal component of the SmartTouch Catheter (© Biosense Webster, Inc)

every 100 ms and continually displayed. The force time interval (FTI) can also be displayed and may help to guide ablation. Using the Tacticath a contact force greater than 20 g appears to result in durable pulmonary vein isolation while a contact force less than 10 g tended to be associated with recurrences [32]. A target of 20 g with a minimum greater than 10 g and a minimum force time index greater than 400 g appears to result in a higher likelihood of transmural lesions in the left atrium [33].

Vascular Access

Electrophysiology catheters are positioned in the heart by gaining access via the central veins; generally the femoral veins for most catheters and occasionally the internal jugular or subclavian veins for coronary sinus catheter placement.

Femoral Cannulation

Femoral vein access is the most commonly used for most EP procedures. The femoral artery is palpated and cannulation is performed medial to the femoral artery while maintaining a position inferior to the inguinal ligament. Superior to the

Fig. 2.17 Image showing the TactiCath Catheter and Connector (St. Jude Medical, Cardiology Division, Inc., Plymouth, Minnesota)

inguinal ligament may result in a difficultly with compression and potential bleeding into the retroperitoneal space. In generally up to three standard EP catheters can be positioned into a femoral vein provided separate cannulations are performed although this depends on the overall size of the patient. If there is any concerns regarding the potential for vein occlusion then the left femoral vein can also be cannulated.

The femoral artery may be used to access the left ventricle and in particular LVOT focal tachycardias. It may also be used for LV VT's and left sided accessory pathway ablations. It is important to maximize the distance between the femoral venous and arterial access points in order to minimize the risk of arteriovenous fistula. The relationship of the right femoral vein to the femoral artery is shown on the anatomical images in Fig. 2.18.

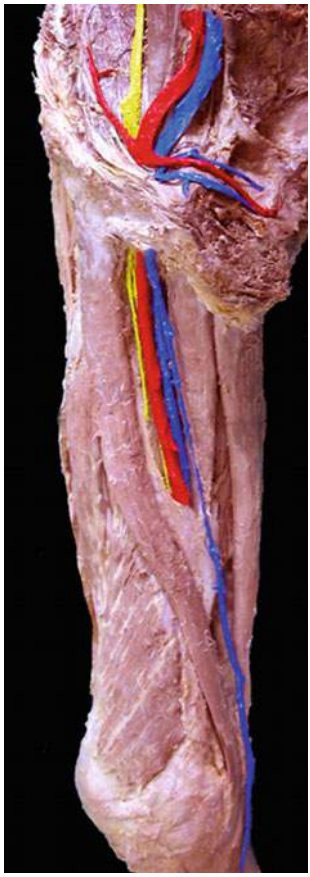


Fig. 2.18 Anatomical images showing the relationship of the femoral vein (*blue*), the femoral artery (*red*) and the femoral nerve (*yellow*)

Subclavian/Axillary Vein

The axillary vein combines with the cephalic vein to become the subclavian vein as it passes superficial to and medial to the anterior portion of the first rib. The course of the left axillary and subclavian vein are shown on the CT scan in Fig. 2.19. Following infiltration with local anesthesia the needle is directed towards and very slightly deep to the junction of the medial one third of the clavicle with the remainder of the clavicle. This should be superficial to the first rib. If fluoroscopy is used this can be achieved. If venous flow is not obtained a slightly deeper approach can be made. Provided the needle does not pass medial to the first rib or deep to the first rib via the second intercostal space then a pneumothorax should not occur. Alternatively a venogram can be performed. The advantage of subclavian access over internal jugular is that the vein does not appear to collapse and remains patent due to soft tissue attachments with the costoclavicular ligament and the clavicular periostium. The Trendelenberg position is therefore not required to

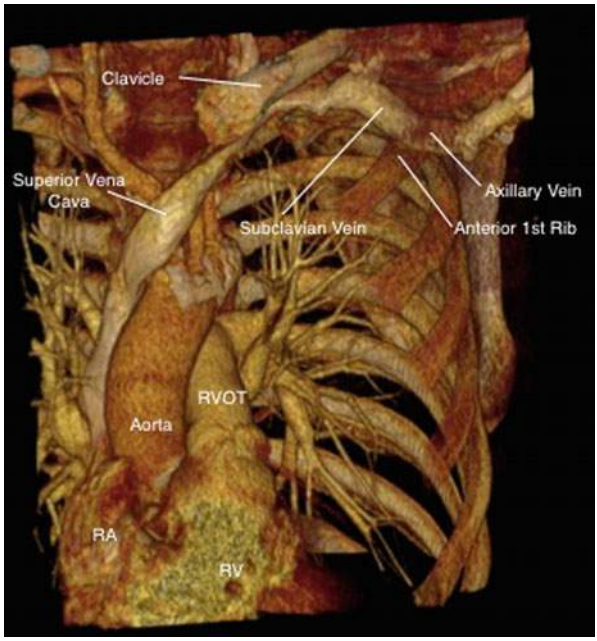


Fig. 2.19 Anatomic course of the left axillary and subclavian vein on a CT scan. The axillary vein runs anterior to the first rib towards the clavicle. Medial to this it becomes the subclavian vein which joins the superior vena cava. Also seen in this image is the ascending aorta. the right ventricular outflow tract (*RVOT*), the right atrium (*RA*) and the right ventricle (*RV*)

increase vein patency although it may reduce the incidence of air embolism. At the subclavian axillary junction the subclavian artery is significantly posterior and slightly superior to the vein. These two structures are separated by the anterior scalene muscle which is 1–1.5 cm thick and reduces the risk of accidental arterial puncture. This muscle is not present laterally however and the risk of arterial puncture increases in more lateral positions. More medial to the juncture of the subclavian and axillary juncture the apical pleura of the lung is posterior to the vein. It is therefore important to keep the needle as horizontal as possible with only slight increases in depth if a more medial approach is being made. More inferior locations are also more likely to puncture the pleura and lung due to the conical shape of the chest.

Internal Jugular Vein

Cannulation of the internal jugular vein may occasionally facilitate positioning of the coronary sinus catheter. Infiltration of local anaesthesia following by Seldinger cannulation should be performed at the apex of the triangle of Sedillot. This triangle is formed medially by the sternal head of the sternocleidomastoid, laterally by the clavicular head of the sternocleidomastoid and inferiorly by the medial one third of the clavicle. Transient flexion of the neck should help to accentuate these landmarks in most patients if they are not clear. If the patient is under general anesthesia

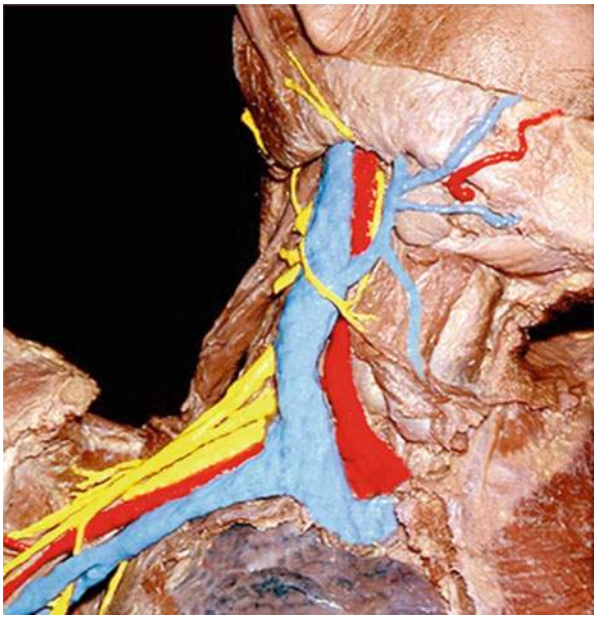


Fig. 2.20 Anatomical image showing the relationship of the right internal jugular vein (*blue*) which lateral to the right common carotid artery (*red*). The right internal jugular passes anterior to the right subclavian artery and joins the right subclavian vein where the two become in innominate vein. The right brachial plexus is shown in *yellow*

palpation of the trachea can be performed while palpating laterally over the sternal head of the sternocleidomastoid into the recess of the triangle. The carotid pulse can also be palpated prior to but not at the same time as cannulation as this often compresses the internal jugular vein. The carotid artery runs medial and posterior to the internal jugular although on occasions may only be posterior. Excessive contralateral rotation of the head beyond a 45 degree angle pushes the carotid artery more lateral and posterior to the internal jugular vein.

The internal jugular vein generally lies 1–2 cm deep in the skin at the apex of the triangle. The needle should be advanced at a 45 degree angle. Advancing the needle greater than 2 cm increases the risk of a pneumothorax. The use of an ultrasound may be helpful to differentiate between vein and artery. The artery is in general more medial, deeper, non compressible and has a visible pulsation. The anatomy of the right internal jugular vein is shown on Fig. 2.20.

Electrophysiology Catheters and Positioning

Electrophysiology catheters are generally made of platinum coated electrodes with polyurethane coated shafts. They are categorized according to the diameter of the shaft, the number of poles used to record and pace through, the spacing between electrodes and the ability to deflect. Ablation catheters are also categorized according to the curve, length of the tip of the catheter, ability for irrigation and ability to measure contact force.

The external diameter of an EP catheter in measured in **French** (**Fr**) where **1 Fr is 1/3 mm**. Therefore to convert the French size to mm it is simply divided by 3. The majority of diagnostic EP catheters are either 5 Fr or 6 Fr. The number of poles recording and pacing can range from 2 up to 20. Commonly quadripolar catheters are positioned in the right atrium, His bundle and right ventricle while a decapolar is positioned in the coronary sinus. A duodecapolar catheter may be used to map right atrial activation during a cavotricuspid isthmus ablation although this is generally not required.

Catheters that are deflectable are easier to position.

The high right atrium (RA) catheter in an EP study is generally positioned in the high posterolateral wall at the junction of the RA with the superior vena cava close to the sinus node. The catheter can also be positioned in the RA appendage. A non deflectable quadripolar catheter is sufficient for this. This can generally be positioned in either the RAO or LAO views.

The RV catheter is generally best placed along the base or septum. It may be positioned close to the His and used to record the His and ventricular signals. This position is achieved in the RAO or LAO projection while withdrawing the catheter from the RV with a clockwise rotation towards the septum.

The coronary sinus catheter is initially positioned in the RA and advanced with a clockwise rotation towards the more posterior CS Os in the LAO projection. Alternatively it can be positioned in the RV and withdrawn with clockwise rotation in the same view. The general locations of EP catheters are shown in Fig. 2.21.

Baseline Measurements

Sinus Node Recovery Time (SNRT)

SNRT is measured using the principle of overdrive suppression in which pacing is performed close to the sinus node at a rate faster than the sinus rate and the time taken from the last paced beat to the first intrinsic sinus beat is measured. This is performed at a cycle length of 600/500/400/300/200 ms for a period of 30 s during each drive train. As shown in Fig. 2.22 the interval from the last paced beat to the first intrinsic beat is then measured. This is longer than the baseline sinus rate and generally takes 5 to 6 beats to return to normal after this maneuver is performed. A prolonged sinus node recovery time **greater than 1500 ms** is abnormal. This may not always occur at faster cycle lengths as entry block may intermittently occur in the perinodal cells and therefore not every beat may depolarize the sinus node. The SNRT is also dependent on the baseline sinus cycle length and is longer for longer baseline cycle lengths and shorter for shorter cycle lengths. In order to correct for this the corrected SNRT can be calculated as:

$$\text{cSNRT} = \text{SNRT} - \text{BCL}$$

A cSNRT of 525 ms or more is considered abnormal.

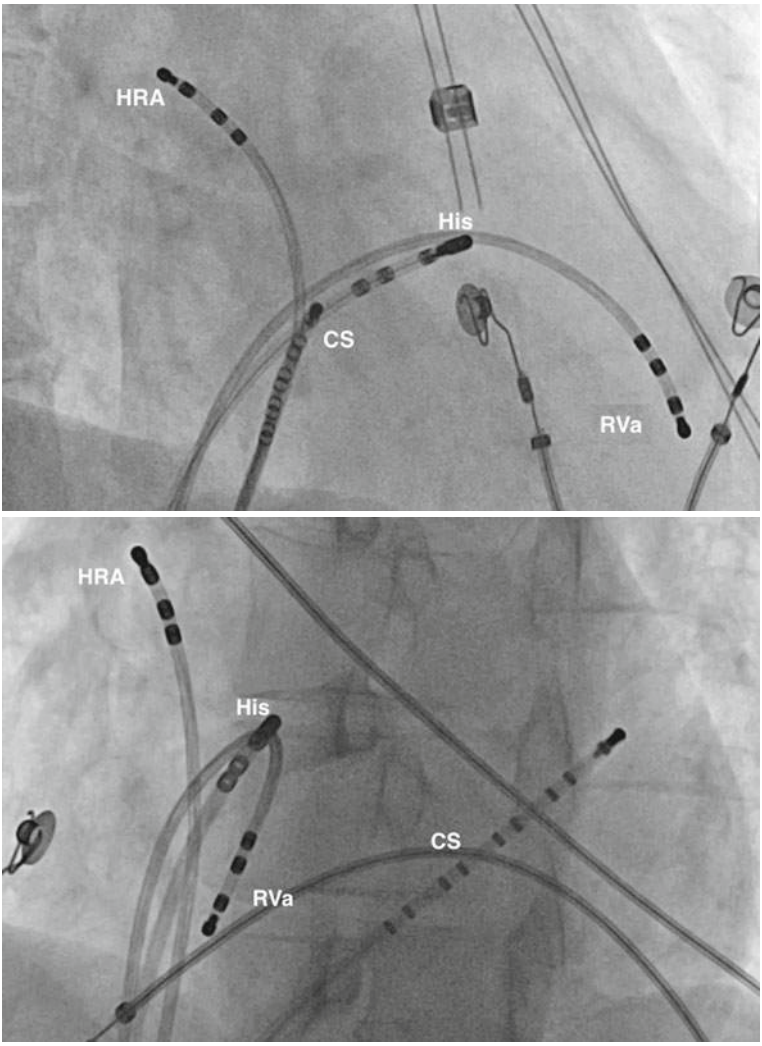


Fig. 2.21 Fluoroscopic image in RAO 30 (*top*) and LAO 30 (*bottom*) showing the locations of EP catheters in the high right atrium (*HRA*), coronary sinus (*CS*), His and right ventricle apex (*RVa*)

Sinoatrial Conduction Time (SACT)

This is the conduction time from the SN to the RA tissue. This is measured by positioning a catheter close to the sinus node and pacing at a rate slightly faster than the baseline cycle length for a single beat only in order to avoid overdrive suppression. As shown in Fig. 2.23 the interval from the last paced beat to the next intrinsic sinus beat is measured and is known as the return cycle length. If the basic cycle length is subtracted from the return cycle the remaining interval is equivalent to the time

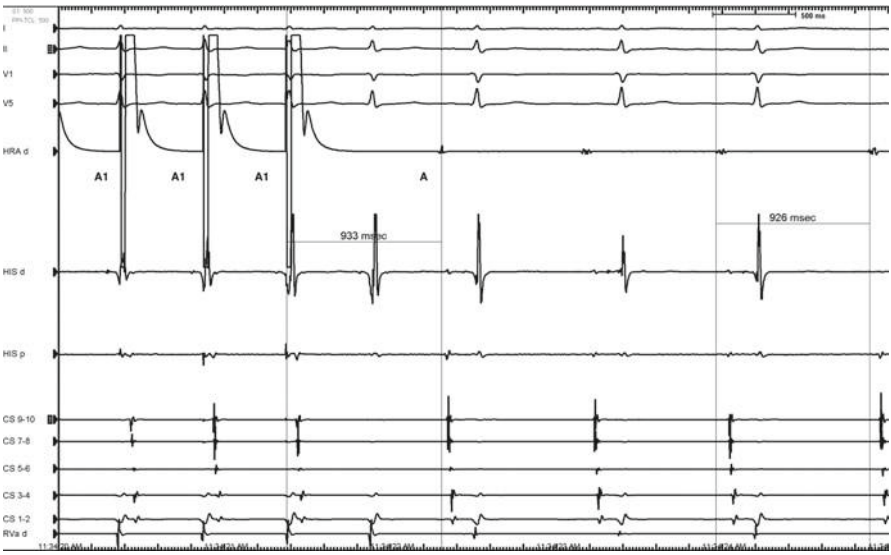


Fig. 2.22 Showing calculation of the sinus node recovery Time (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex) *A1* = paced atrial complexes. *A* = spontaneous sinus beat post pacing

Fig. 2.23 Calculation of sino atrial conduction time (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

taken to conduct into and out of the sinus node. This is therefore divided by two in order to calculate the SACT. **A normal SACT** is considered to be to be **50–125 ms**.

AV Conduction Times (AH and HV Intervals)

The **AH interval** is recorded from the onset of the local atrial electrogram recorded in the His catheter to the onset of the His signal and is considered to represent conduction through the AV node (Fig. 2.24). The normal range is **50–120 ms**. A prolonged AH interval may occur as a result of intrinsic AV nodal dysfunction, as a result of increased vagal tone or a result of antiarrhythmic drugs. A short AH interval can occur spontaneously or under the effect of sympathetic stimulation.

The **HV interval** is measured from the onset of the local His signal to the earliest ventricular signal on the surface ECG (Fig. 2.24). This generally reflects the

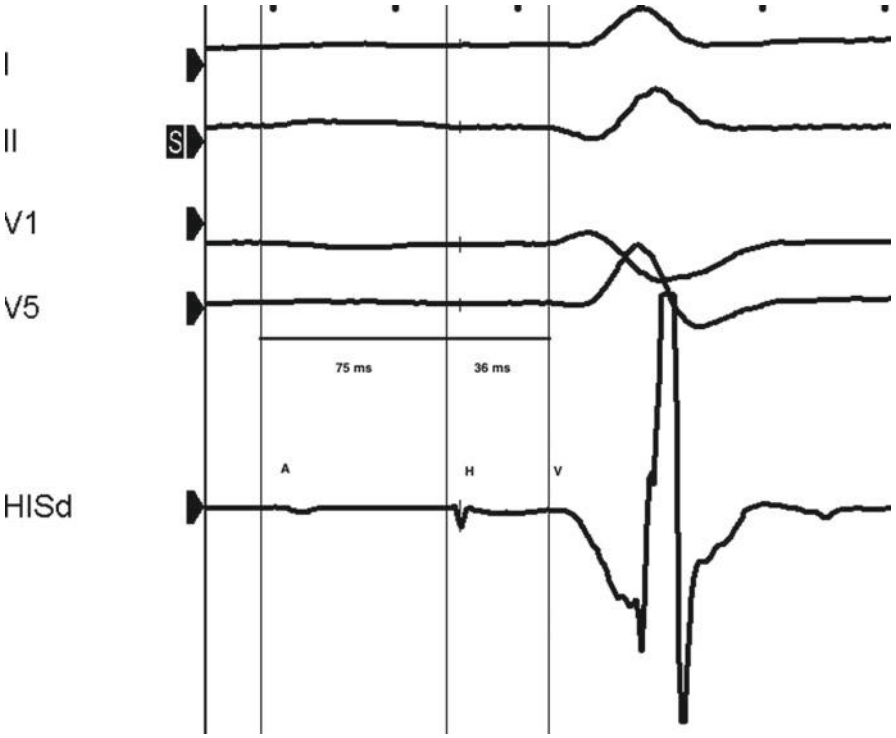


Fig. 2.24 Calculation of the AH interval (75 ms) from the onset of the atrial electrogram on the His recording to the start of the His electrogram and the HV Interval (36 ms) measured from the onset of the His signal to the onset of the ventricular activation on the surface ECG (HIS d is positioned in the distal His)

conduction time through the proximal His, bundle branches and the Purkinje system. The normal range is considered to be between **30** and **55 ms**. Intrinsic His dysfunction or antiarrhythmic drugs may prolong the HV interval. A short HV interval may be seen with accessory pathway conduction which may even be negative. In the presence of accessory pathway conduction the HV does not reflect His-Purkinje conduction but is the result of accessory pathway conduction the true HV interval.

Care must be taken not to confuse the right bundle electrogram as the His electrogram as this may artificially lead to what may seem like a short HV interval.

Refractory Periods (AERP, AVNERP, VERP, VANERP)

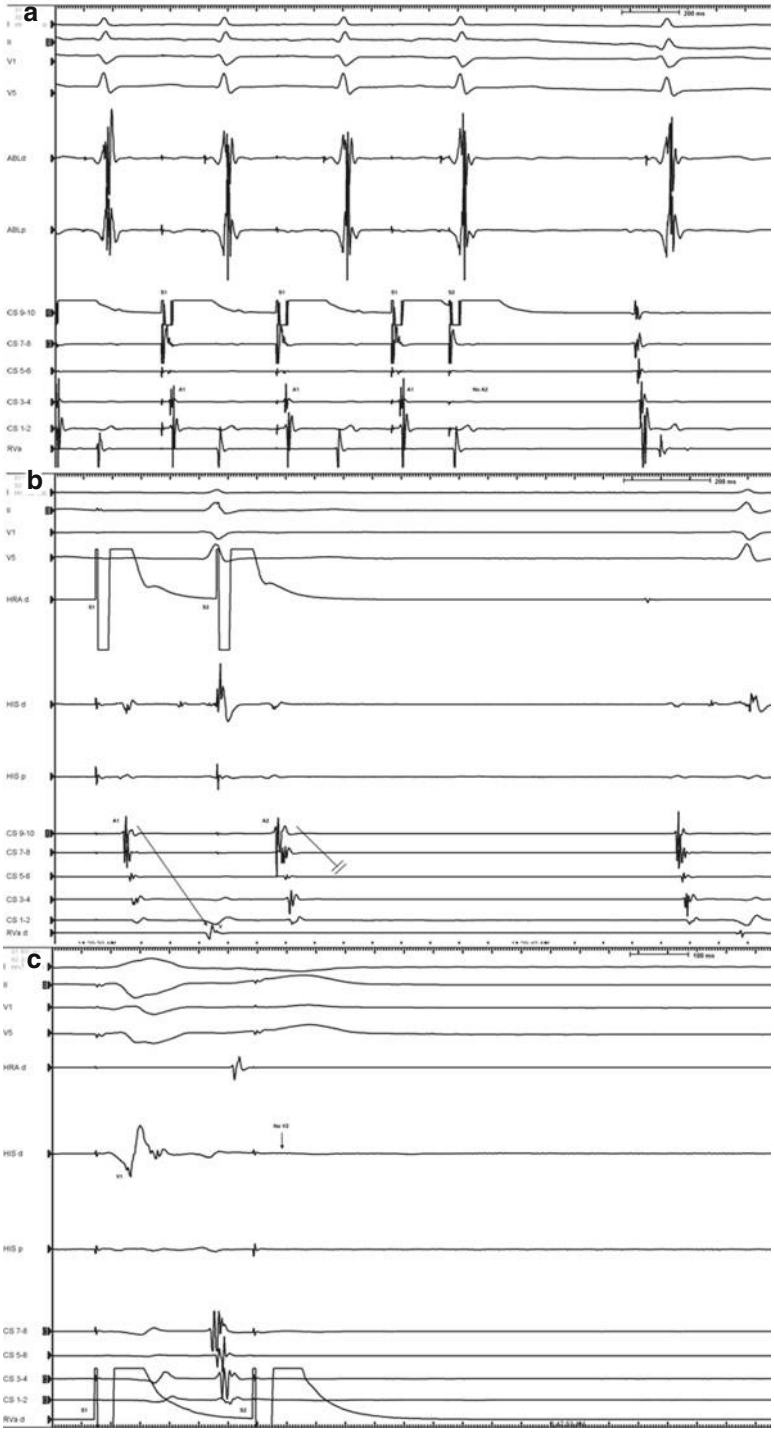
During an EP study the **effective refractory period** (**ERP**) is recorded. This is the longest coupling interval in which the stimulus **fails** to stimulate the myocardium at twice the diastolic threshold.

As shown in Fig. 2.25 to calculate the ERP a drive train of eight beats followed by a progressively shorter extrastimulus is performed. The **normal atrial ERP is 170–300 ms while the ventricular ERP is 170–290 ms** [35]. In order to evaluate the AVNERP the atrium is paced in the same way as when calculating the AERP. During decremental atrial extrastimuli the AH interval gradually prolongs while the HV interval remains the same. The **normal AVNERP is 230–425 ms** [35].

AV Wenckebach Point

As shown in Fig. 2.26 decremental atrial pacing can be performed at progressively shorter cycle lengths until AV block occurs. The AV Wenckeback point is defined as the **longest cycle length which results in AV block**. This provides some data on the functional conduction through the AV node.

Fig. 2.25 Calculation of the atrial RP (**a**), AV node RP (**b**), and ventricular ERP (**c**). In each case a drive train is performed at a cycle length of 600 ms for 8 beats in order to achieve a steady state. This is followed by a progressively shorter extrastimulus until capture fails to occur. In the case of the atrium and ventricle this is seen as lack of local capture. In the case of the AV node local capture of either the atrium or ventricle occurs with failure of the impulse to propagate through the AV node either antegradely (AV Node ERP) or retrogradely (VA ERP). (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)


a
I
II
V1
V5
ABLd
ABLp
CS 9-10
CS 7-8
CS 5-6
CS 3-4
CS 1-2
RVa
b
I
II
V1
V5
HRA d
HIS d
HIS p
CS 9-10
CS 7-8
CS 5-6
CS 3-4
CS 1-2
RVa d
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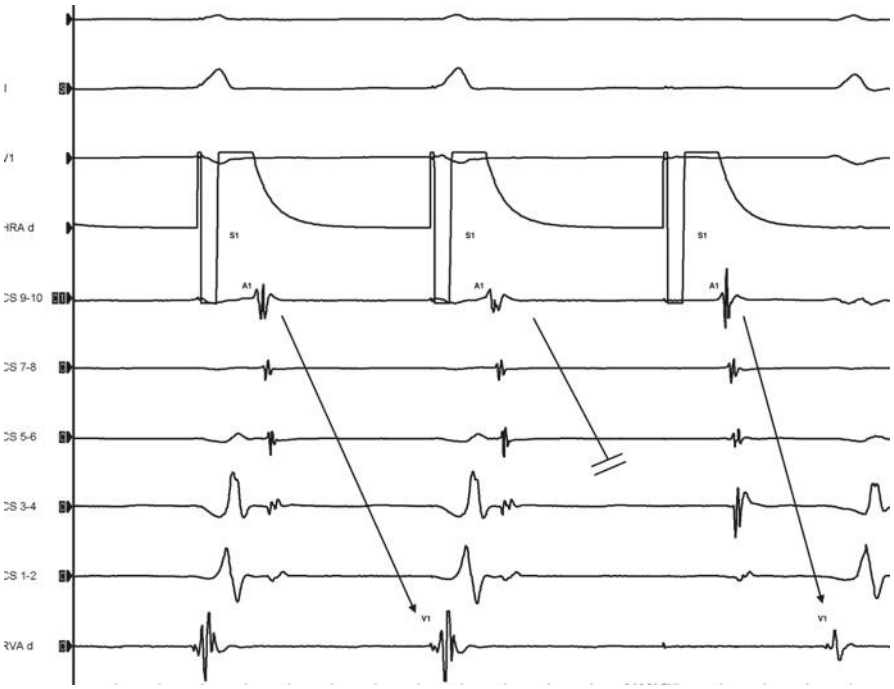

Fig. 2.26 Calculation of AV Wenckeback Point during decremental atrial pacing. (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

Basic EP Study

There is a considerable variability in the number of catheters and positioning of these. In most diagnostic EP studies a quadripolar catheter is positioned in the HRA as well as the RV septum and a decapolar catheter is positioned in the coronary sinus. The RV quadripolar catheter can sometimes be used to record the AH and HV intervals.

Pacing is performed from the RV septal catheter at a constant rate faster than the sinus rate. This is to look for the presence of VA conduction, and if present the atrial activation sequence. As shown in Fig. 2.27 decremental VA conduction is initially anterior and septal. This generally indicates VA nodal conduction. This is not always the case and it is important not to miss an anteroseptal accessory pathway with decremental retrograde conduction. On the converse lack of decrement does not always exclude VA conduction as rapid ventricular pacing from the RV may result in infrahisian block.

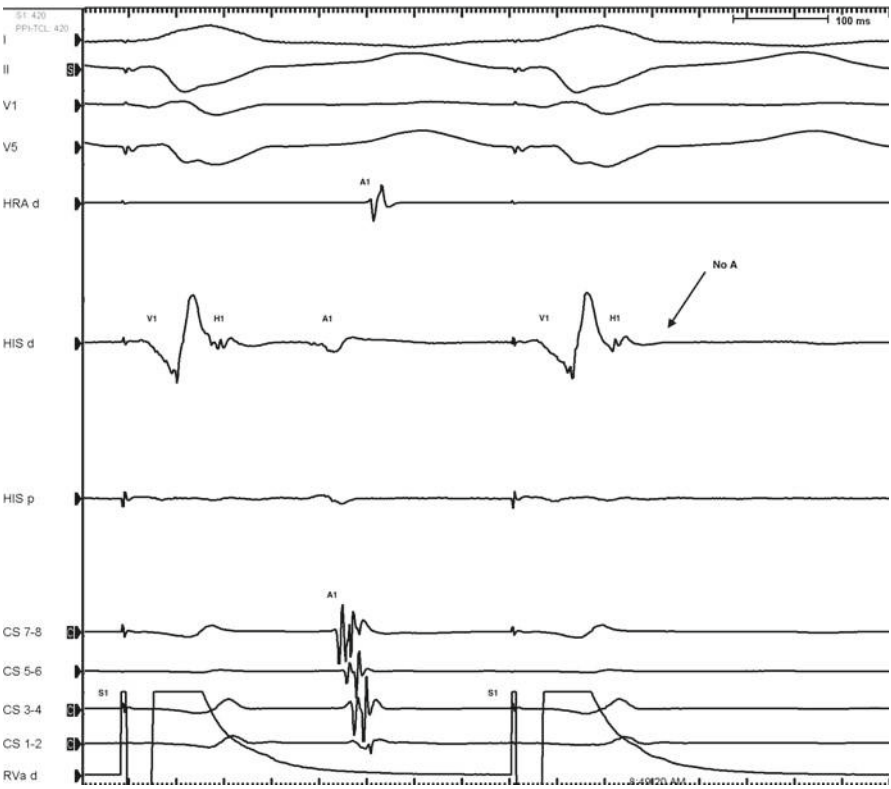

Fig. 2.27 Decremental ventricular pacing (*S1*) from the RV apex (*RVAd*). The first paced beat on the left propagates from the RV apex retrogradely up the right bundle and activates the His. A small His deflection (*H1*) is seen after the ventricular activation (*V1*) on the distal his (*HIS d*) channel. Following this there is atrial activation (*A1*) recorded on the HIS d channel followed shortly thereafter by the proximal his recording (*HIS p*). Atrial activation (*A1*) then occurs from the proximal CS (in this case CS 7–8) and spreads distally. The high RA (*HRAd*) is activated (*A1*) after the proximal CS. This activation is concentric with the His first followed by proximal to distal CS activation and then the HRAd last). In the following beat there is no conduction from the RV activation followed by His activation and no atrial activation

As shown in Fig. 2.28 pacing from the RV does not always result in VA conduction. Although this may infer that AVRT is not possible it is generally better to repeat pacing during infusion of isoprenaline where VA conduction may become evident.

A **ventricular extrastimulus test** is performed by pacing at a contant cycle length and adding in an extrastimulus at a progressively shorter cycle length. This pacing mode is used to calculate the VERP and the retrograde conduction properties.

Pacing from the HRA is performed in order to calculate sinus node function. Atrial extrastimulus testing is then performed looking at the AERP and AVNERP as well as the antegrade conduction properties.

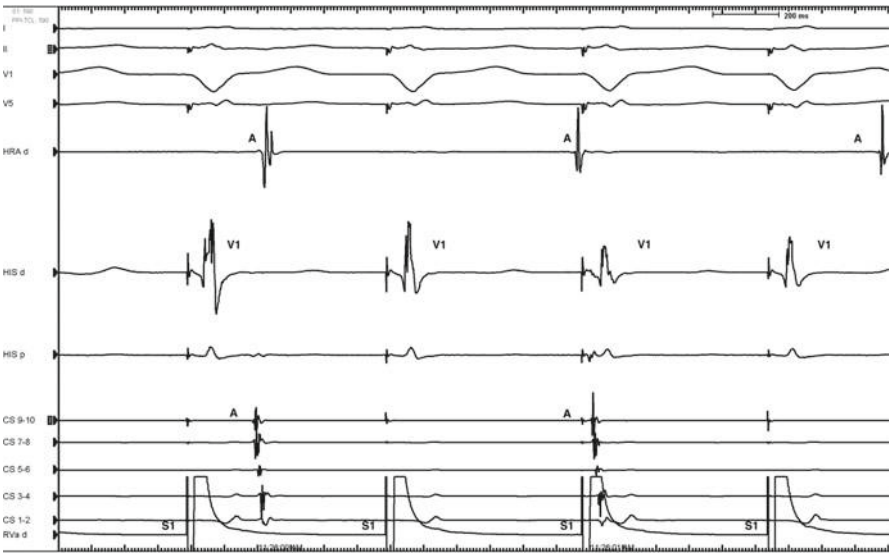

Fig. 2.28 Pacing from the RV (S1) does not penetrate the His and there is no evidence of VA Conduction. (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

An example of an AH jump caused by dual AV nodal pathways is shown in Fig. 2.29. In panel A conduction occurs antegradely over the fast pathway. In panel B a sudden reduction in the atrial extrastimulus by 20 ms results in an increase in the AH interval by more than 50 ms. Antegrade conduction has suddenly shifted from the fast to a slow pathway.

The AV nodal conduction curve in dual AV nodal physiology is shown in Fig. 2.30. A1A2 refers to the interval from the last paced beat of the drive train to the onset of the atrial extrastimulus. A2H2 refers to the interval from the extratimulus (A2) to the his activation A2H2. As the atrial extrastimulus becomes earlier the interval to the His prolongs until there is a sudden increase from 300 to 350 ms which is most likely indicative of a change in antegrade activation from the fast pathway to the slow pathway.

An example of a AH jump and echo beat are shown in Fig. 2.31. In this example there is a jump as antegrade conduction occurs along the slow pathway with ventricular activation and retrograde activation up the fast pathway.

Decremental atrial pacing is used to calculate the AV Wenckebach Point.

Further decremental atrial and sometimes ventricular pacing may be used to initiate tachycardia. If this is ineffective the addition of one or more atrial extrastimuli and the use of incremental doses of atropine or isoprenaline may be required.

In Fig. 2.32 an atrial extrastimulus results in an AH jump in which conduction occurs antegradely along the slow pathway followed by tachycardia in which retrograde conduction occurs along the fast pathway resulted in a short VA interval. This is most likely in keeping with a typical AVNRT

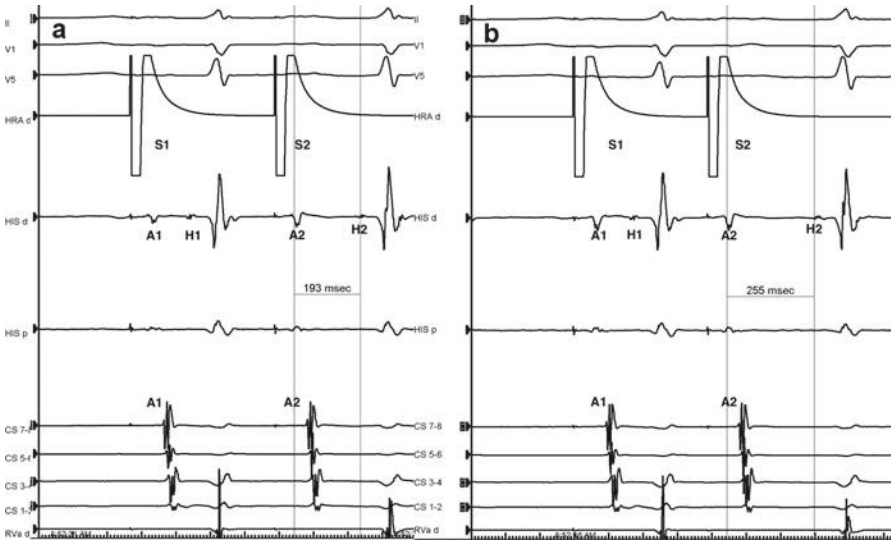

Fig. 2.29 Panel **a**: Atrial extrastimulus testing showing conduction antegradely over the fast pathway. Panel **b**: Antegrade conduction over the slow pathway. Continuous pacing is performed at a cycle length of 600 ms (*S1*). Following this an extrastimulus (*S2*) is given after 400 ms on panel **a** with conduction over the fast pathway. In panel **b** the S2 is shortened to 380 ms. The fast pathway is refractory and conduction shifts to the slow pathway. This is evidenced by a sudden prolongation in the AH interval by more than 50 ms. (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

VT Stimulation Protocol

The general principle of a VT EP study is to assess the potential future risk of VT in a susceptible patient by performing a basic drive train followed by the introduction of extrastimuli at shorter cycle lengths. In general this should be performed at the RV apex and the RV outflow tract with a single quadripolar catheter and another catheter in the right atrial appendage. A basic drive train (S1) of eight beats is introduced at a cycle length of 600 ms followed by an extrastimulus (S2) which is reduced in 10 ms intervals until the ventricular myocardium is refractory. Following this, S2 pacing rate is brought to 20 ms greater than refractoriness and an S3 introduced in the same manner. S3 is then set 20 ms higher than refractoriness and S1 is reduced to 400 ms and the same protocol repeated. If VT is not induced then S1 is brought back to 600 ms and S2 and S3 set at 20 ms above refractoriness and then an S4 is introduced in a similar manner to that describes above.

Following this, S1 is reduced to 400 ms. If no VT is induced then the protocol can be reintroduced with an isoprotenolol infusion. Induction of a monomorphic VT using this protocol is considered a significant finding and if possible this can be compared with the clinical VT. An example of a VT stimulation using a drive train at a cycle length of 400 ms with 3 extrastimuli is shown in Fig. 2.33.

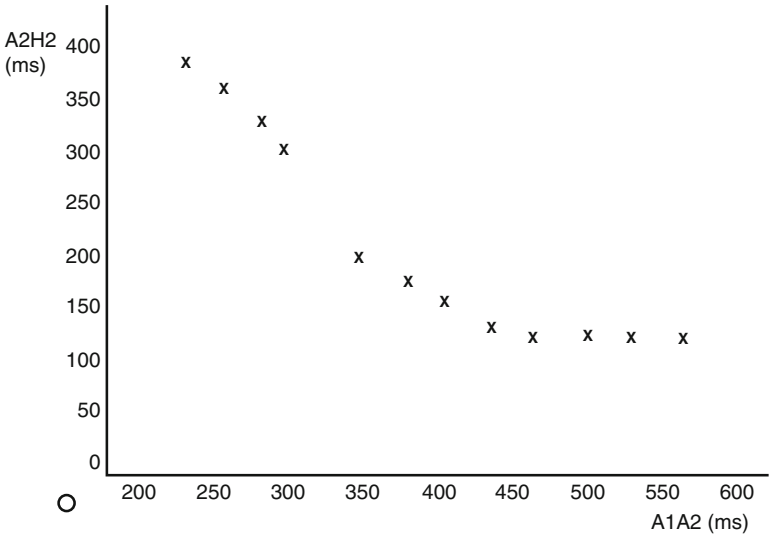

Fig. 2.30 Pacing is performed with a drive train (*A1*) followed by a gradually decmrental atrial extrastmulus (*A2*). As this interval shortens the interval from the atrial extrastimulus (*A2*) to the His (*H2*) prolongs. There is then a sudden increase in this interval by 50 ms which is generally suggestive of antegrade conduction shifting from the fast pathway to the slow pathway

Fig. 2.31 Antegrade conduction occurs along the slow pathway with ventricular activation and retrograde activation up the fast pathway. This is an example of an atrial echo beat

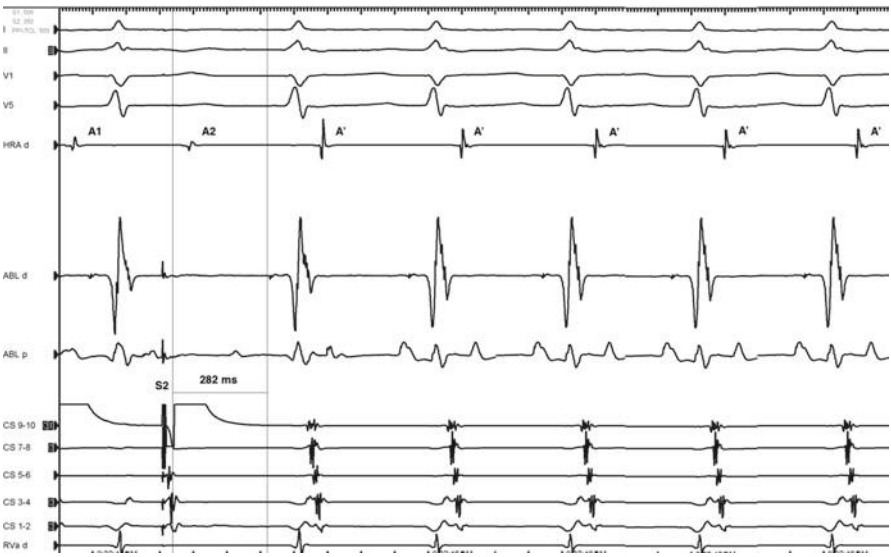

Fig. 2.32 Induction of typical AVNRT. Following a drive train at 500 ms (not shown) an extrastimulus is given after 350 ms from the proximal CS (*S2*). This results in an AH interval of 282 ms (200 ms on prior S2 indicating an AH jump of 82 ms). This is indicative of antegrade conduction shifting from the fast to the slow pathway followed by tachycardia. The ablation distal (*ABL d*) is positioned in the location of the His. Activation is earliest in the proximal CS with a short VA interval. Overall the inititiation and activation sequence is suggestive of a typical AVNRT. (HRA d is positioned in the high right atrium, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

Initiation of polymorphic VT or VF may be non-specific, although this depends on the clinical context. Torsades de pointes in the setting of long QT syndrome is not inducible by ventricular pacing. On the contrary, a polymorphic VT in Brugada syndrome is highly significant.

VT induced during the study can often be terminated by pacing at a rate 20 ms faster than the VT. If this is unsuccessful or the patient is hemodynamically unstable, a DC cardioversion should be performed.

SVT Diagnostic Maneuvers

Although specific maneuvers will be discussed in each chapter this section provides an overview on this topic. Although the diagnosis can frequently be made during basic pacing occasionally it may be difficult to differentiate between AVNRT, AVRT in particular utilizing paraseptal AP's and atrial tachycardia's. In order to help, certain baseline observations can be made which may help followed by pacing maneuvers. In cases where tachycardia cannot be easily initiated parahisian pacing can be

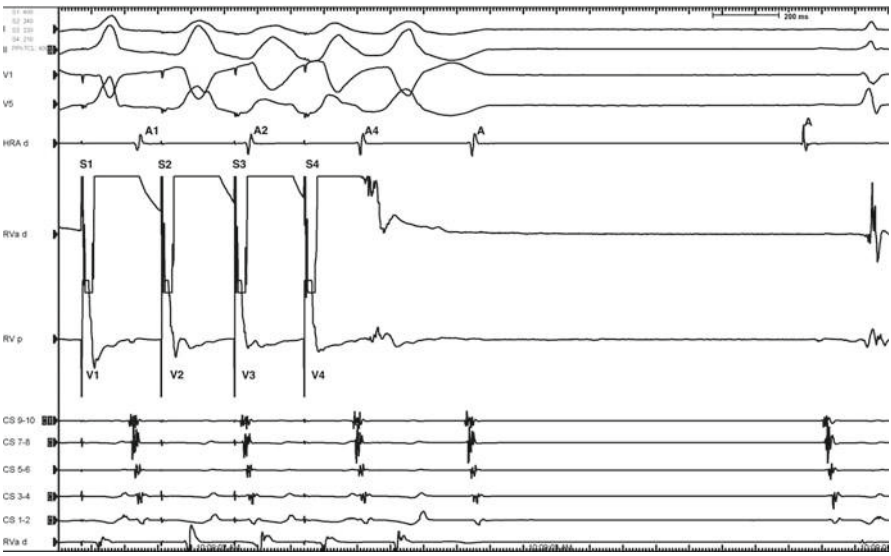

Fig. 2.33 VT stimulation protocol in which a drive train is performed at 400 ms with an S2 of 240, S3 220 and an S4 of 210 from the RV apex. Ventricular activation (*V*) and atrial activation (*A*) can be seen corresponding to each extrastimulus. (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

performed. In those cases where tachycardia can be initiated entrainment, His synchronous PVC's and overdrive pacing can be performed. The choice of maneuver is therefore dependent on the individual case.

Baseline Observations

During baseline testing the presence of dual AV nodal physiology, the onset and termination of tachycardia, presence and effect of tachycardia variability, VA relationship and atrial activation sequence and effect of bundle branch block can all be used to establish the diagnosis.

The presence of functional dual AV nodal physiology may increase the suspicion of AVNRT. This can be demonstrated as an **AH jump** of greater than or equal to **50 ms** in the case of a typical AVNRT or a HA jump of greater than or equal to 50 ms in the case of an atypical AVNRT. The presence of dual AV nodal physiology is reasonably predictive that the mechanism of the tachycardia is AVNRT in a patient with a prior documented SVT and no evident of AP conduction.

Initiation and Termination

Both AVNRT and AVRT can be initiated by a PAC. In the case of a typical AVNRT there is a sudden prolongation of the duration between the PAC and the initial QRS complex as antegrade conduction occurs down the slow pathway (AH jump) (Fig. 2.34).

In orthodromic AVRT the time from the PAC to the initial QRS is shorter as antegrade conduction occurs along the fast pathway. As seen in Fig. 2.35 pacing is performed at a drive train (S1) of 400 ms with an extrastimulus (S2) at 280 ms. This atrial beat conducts antegradely along the fast pathway which shows decrement but no jump. Conduction then occurs retrogradely with a VA interval of 94 ms. This could be in keeping with a paraseptal AP, atypical AVNRT or less likely an AT. In this case the diagnosis was a posteroseptal AP.

Atrial tachycardias tend to warm up and cool down with a gradual shortening of the tachycardia cycle length at the onset. The initial P wave in an atrial tachycardia has a different morphology in general to the preceding sinus beats although occasionally this may be subtle if the focus is close to the sinus node.

PVC's rarely initiate an AVNRT as the His is generally refractory during the timing of retrograde activation. On the other hand PVC's can commonly initiate an AVRT (Fig. 2.36).

Termination of tachycardia with AV block occurring either spontaneously, following a vagal maneuver or following the administration of IV adenosine occurs in arrhythmias in which the AV node plays a vital role in the circuit i.e., AVNRT and AVRT and does not occur in atrial tachycardia. AT's generally but not exclusively terminate with a ventricular complex (Fig. 2.37).

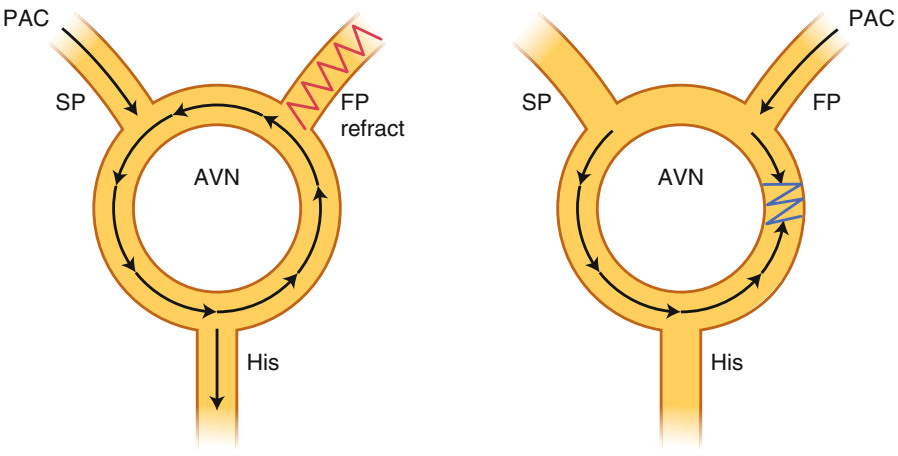

Fig. 2.34 Initiation of a Typical (Slow Fast) AVNRT with a PAC (1) and termination with another PAC (2)

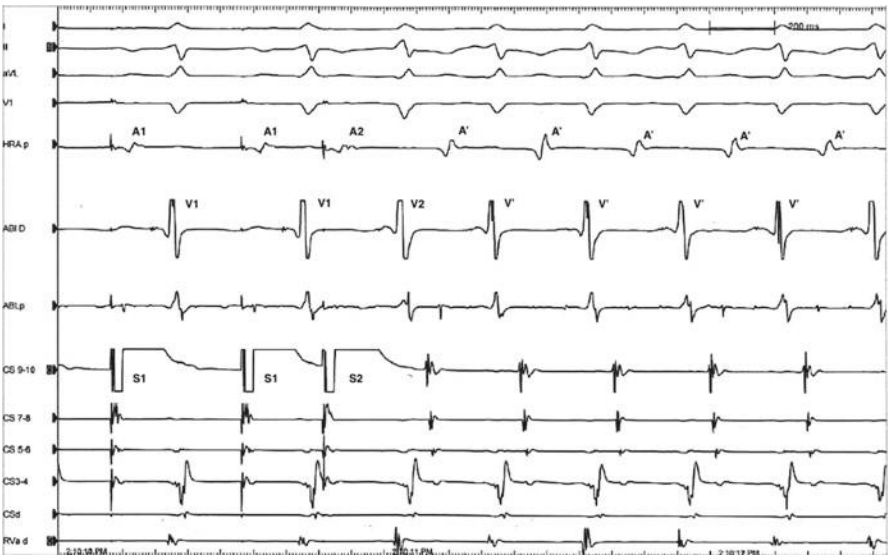

Fig. 2.35 Initiation of an ORT utilizing a retrograde posteroseptal AP. Following a drive train at 400 ms (*S1*) an atrial extrastimulus is given after 280 ms (*S2*). This conducts antegradely over the fast pathway and retrogradely over the AP with a VA interval of 94 ms. The corresponding atrial (*A*) and ventricular (*V*) activations are shown. (HRA p is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS d is in the distal CS and RVa d is located in the RV apex)

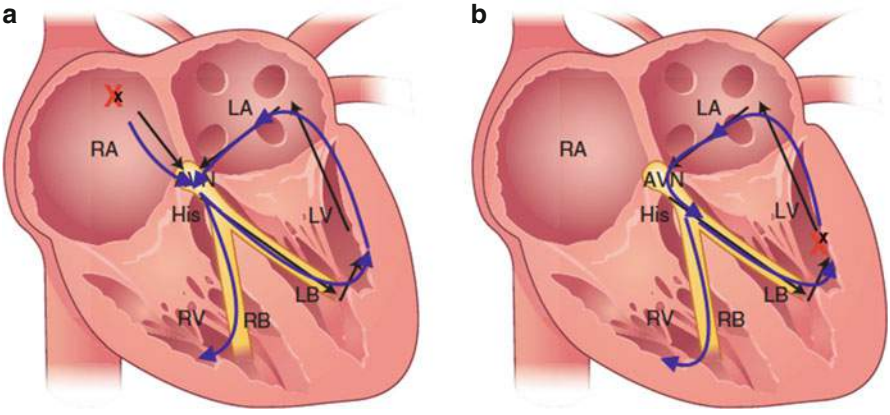

Fig. 2.36 Initiation of AV Re-entry Tachycardia with either a Premature Atrial Complex (PAC) (**a**) or Premature Ventricular Complex (PVC) (**b**)

The continuation of tachycardia despite the presence of AV block however only rules out the possibility of AVRT, but AVNRT and AT may continue to occur in the presence of AV block.

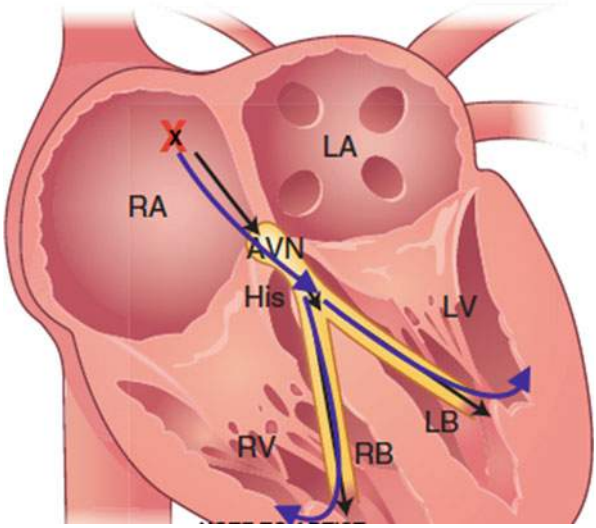

Fig. 2.37 Initiation and termination of Atrial Tachycardia with a long RP Interval

All SVT's can be terminated by varying degrees with either atrial or ventricular premature complexes. In the case of AVNRT the number of atrial beats required depends on the location of the circuit. Generally at least 2 premature ventricular complexes are required to terminate AVNRT. For AVRT termination may occur with either premature atrial complexes or ventricular premature complexes. The number of beats required depends on the distance from the circuit as well as the rate of the tachycardia. In atrial tachycardia the mechanism of the arrhythmia determines the ability for premature atrial complexes to terminate the tachycardia. In general at least 3 PVC's are required for termination of an AT.

VA Relationship and Atrial Activation

The P wave should always be identified in SVT in order to help ascertain the diagnosis. The VA interval corresponds with the RP interval in the surface ECG and is useful in helping to discriminate between various SVT mechanisms. If the septal VA interval is less than 70 ms, this is highly predictive for a typical AVNRT. The VA time is generally longer than 70 ms in cases of orthodromic AVRT, atrial tachycardia and atypical AVNRT. Coumel's tachycardia also known as permanent junctional reciprocating tachycardia (PJRT) results in a long VA time with negative P waves in leads II, III and aVF during tachycardia. This is caused by an orthodromic reciprocating tachycardia using the Av node as the antegrade limb and a slowly conducting accessory pathway as the retrograde limb. The accessory pathway is generally a right sided posteroseptal pathway with an atrial insertion point close to the coronary sinus.

It is useful to compare the P wave morphology during tachycardia with sinus rhythm. This is particular helpful in helping to localize the focus of an atrial tachycardia with narrower P waves more indicative of septal origins.

The atrial activation sequence is very useful in discriminating between the potential causes of SVT. However, central atrial activation may occur with any SVT while eccentric activation more commonly but not exclusively occurs with AVRT or an atrial tachycardia. Eccentric activation may also be seen with AVNRT depending on the atrial insertion point of the retrograde slow pathway. For this reason pacing maneuvers are required to help further differentiation.

Effect of Bundle Branch Block

If the tachycardia cycle length (TCL) prolongs with induction of BBB then this implies that the arrhythmia is AVRT with a VA connection on the same side as the BBB. This principle is known as **Coumel's sign** and is represented on Fig. 2.38 and on the electrogram in Fig. 2.39. As BBB does not affect the AV nodal common pathway this does not affect AVNRT. It also has no effect on AT. Due to the rapid ventricular conduction ventricular aberration is relatively common in the setting of SVT. Bundle branch block on the contralateral bundle has no impact on tachycardia cycle length.

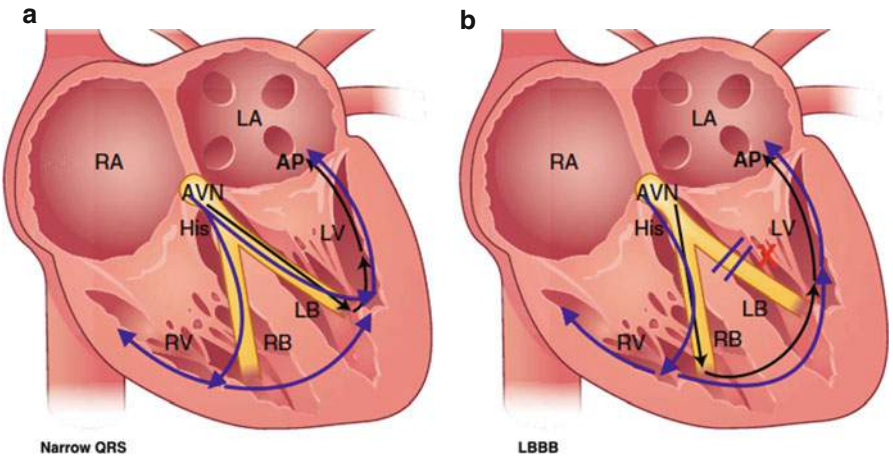

Fig. 2.38 Schematic demonstrating the effect of bundle branch block on the same side as a retrograde accessory pathway. In both images a orthodromic reciprocating tachycardia (ORT) using the AV node as the antegrade pathway is seen. Conduction then occurs through the His and bundle branches. The accessory pathway is located in the left lateral position. In image (**a**) conduction occurs through both the right and the left bundle. Given that this is a left lateral accessory pathway activation along the left bundle will activate the accessory pathway rapidly. In image (**b**) a LBBB occurs thus delaying activation which occurs through the right bundle and then across the interventricular septum. This results in an increase in the VA interval and prolongation of the tachycardia cycle length (TCL)

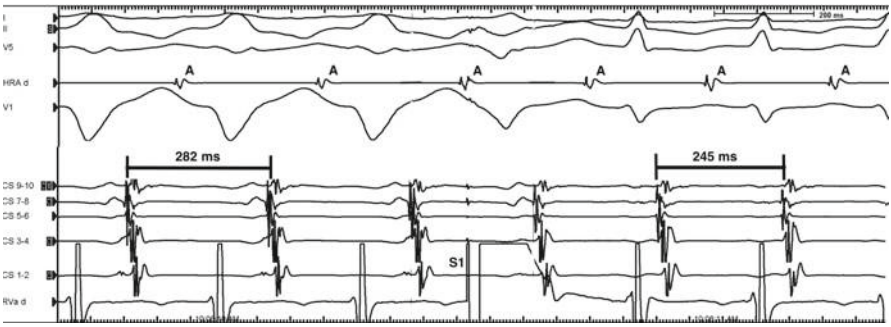

Fig. 2.39 Electrogram showing the effect of bundle branch block on the tachycardia cycle length in a orthodromic reciprocating tachycardia using a left sided accessory pathway as the retrograde limb. On the left of the electrogram the patient is in tachycardia with a wide complex left bundle pattern and a tachycardia cycle length of 282 ms. The atrial activation sequence is earliest in CS 7/8 which is located in the mid coronary sinus and indicates left sided activation. The introduction of a PVC during His refractroriness retrogradely penetrates the left bundle and retrogradely activates the accessory pathway with shortening of the tachycardia cycle length. Following resolution of the left bundle branch block the QRS is narrow and the tachycardia cycle length is shorter. This is indicative of a left sided AP playing a fundamental role in the tachycardia. This electrogram not only demonstrates the effect of a bundle branch block on the tachycardia cycle length but also the effect of a His refractory PVC advancing the next atrial activation. (HRA d is positioned in the high right atrium, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

RV Entrainment

Entrainment is the continual resetting of a re-entry tachycardia by pacing at a site close to or within the circuit at a cycle length slightly shorter that the tachycardia cycle length. The pacing stimulus travels both orthodromically in the same direction as the preceding tachycardia beat and antidromically resulting in a fused beat which is morphologically different to the tachycardia and the paced beats. This continues for all beats during entrainment apart from the final entrained beat where there is no collision of an antidromic beat with the orthodromic waveform.

As the RV apex is closer to the ventricular insertion point of an accessory pathway and further from the AV node entrainment from the RV apex will result in a shorter post pacing interval (PPI) minus tachycardia cycle length for AVRT versus AVNRT. This concept is demonstrated in Fig. 2.40.

This pacing is performed at the RV apex cycle length 20–30 ms shorter than the TCL. This is then examined in order to ensure that capture during pacing has occurred.

If this is confirmed then the PPI – TCL is measured, and the post pacing activation sequence is examined.

As shown in Fig. 2.41 in patients with **AVNRT** (**typical or atypical**) **the PPI – TCL is generally greater than 115 ms** [36]. Figure 2.39 demonstrates a short PPI-TCL of less than 115 ms which is indicative of AVRT.

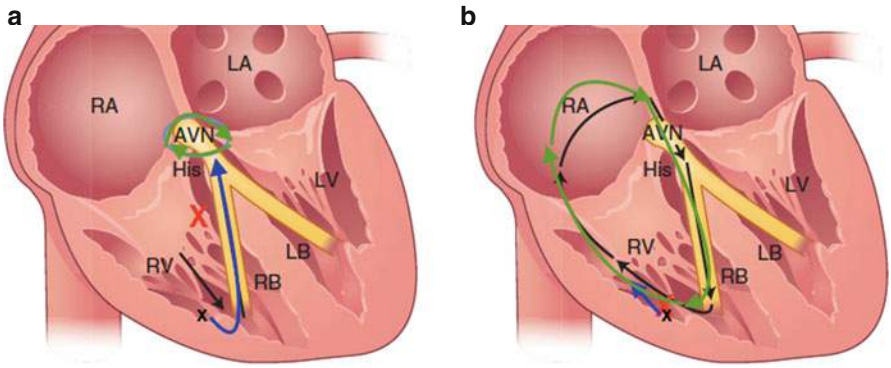

Fig. 2.40 Diagrammatic representation of entrainment from the RV apex. (**a**) On the *left image* the AVNRT circuit is located in the slow and fast pathways in the AV node and pacing from the RV apex is anatomically and electrically distant from the critical circuit resulting in a long PPI – TCL. (**b**) In the image on the *right* the ORT is utilizing the ventricle as part of the circuit and therefore pacing in the RV apex results in a PPI – TCL of less than 115 ms

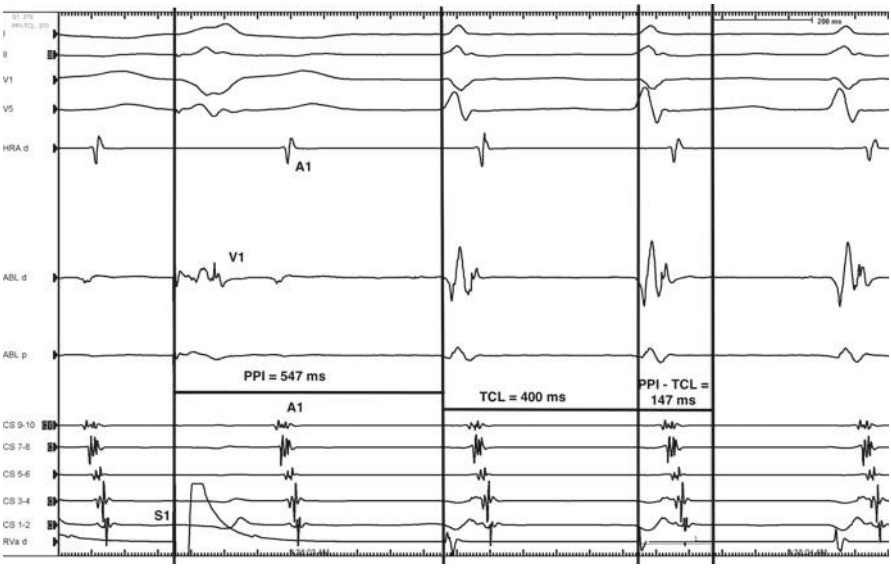

Fig. 2.41 Right ventricular entrainment during SVT. The tachycardia cycle length (*TCL*) of the tachycardia is 400 ms. Pacing is performed at a cycle length of 370 ms from the RV apex. Following confirmation of entrainment (not shown on this tracing) the post pacing interval (*PPI*) is calculated as 547 ms. The post pacing interval (PPI) minus the tachycardia cycle length (*TCL*) is 147 ms which is more indicative of an AVNRT (A refers to atrial activation while *V* is ventricular activation and S is stimulus. The ablation catheter (*ABL d*) is positioned close to the His, HRA d is positioned in the high right atrium, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

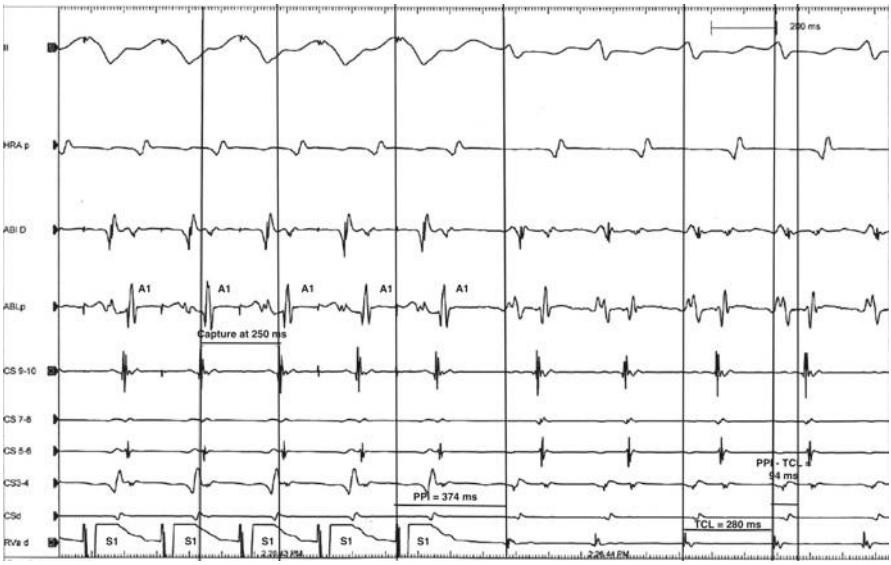

Fig. 2.42 RV entrainment during SVT. The tachycardia cycle length (*TCL*) is 280 ms. Pacing is performed at the RV apex at 250 ms with confirmation of atrial capture at that rate. The PPI – TCL is 94 ms which is suggestive of an ORT. The atrial activation sequence is suggestive of a left sided paraseptal pathway with the earliest retrograde atrial activation at CS 7/8. (The ablation catheter is positioned on the His, HRA d is positioned in the high right atrium, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

It should be noted that rapid ventricular pacing may result in AH prolongation which could artificially prolong the PPI. Therefore this should be corrected by subtracting the baseline AH interval from the PPI. The corrected PPI-TCL should be less than 110 ms for AVRT and greater than 110 ms for an AVNRT.

Examination of the post pacing activation sequence is also important. If the final entrained ventricular beat is followed by an atrial and then ventricular beat this is more likely to be due to an underlying AVNRT or AVRT. If the post pacing sequence is AAV then this is more likely to represent an underlying atrial tachycardia.

An alternative maneuver is to pace from the RV apex and compare the PPI-TCL with pacing from the RV base. A difference of greater than 30 ms between these two locations is suggestive of an AVNRT. This implies that there is a longer PPI-TCL moving further from the septum [37]. A difference less than 30 ms is more indicative of an AP (Fig. 2.42).

PVC During Tachycardia

This is performed in order to differentiate an SVT in which the critical component of the circuit is not dependent on the His such as an AVNRT versus a mechanism which is dependent on the His such as an ORT.

In order to perform this maneuver a PVC is delivered from the RV base earlier and earlier during tachycardia until the His is refractory. The subsequent atrial activation sequence and timing is then compared with that during the tachycardia. If it has no impact on the VA timing then there either is no accessory pathway or it was not penetrated by the PVC. This may occur if the accessory pathway is anatomically distant from the site of pacing such as a left lateral accessory pathway or if it has decremental retrograde conduction properties in which the activation is blocked.

If the next atrial activation is advanced then this implies the presence of an accessory pathway which conducts retrogradely. This does not mean that the accessory pathway is part of the tachycardia circuit. If the atrial activation sequence for this beat is different to that during tachycardia then this is a bystander. If the atrial activation sequence is then the following AH, AA and AV intervals have to be examined in order to assess if the tachycardia has been reset. If the subsequent AH, AA and AV intervals are increased then this implies that the PVC has reset the tachycardia and therefore that the accessory pathway is part of the circuit.

If a PVC delivered during His refractoriness post excites the next atrial activation or terminates the tachycardia then the accessory pathway is part of the circuit. The concept of delivering a PVC during tachycardia is demonstrated in Fig. 2.43.

Para-Hisian Pacing

This can be performed if the tachycardia cannot be induced and is used to differentiate retrograde conduction over the fast or slow pathway in the AV node from that over an accessory pathway. Although it is most commonly used for differentiating septal accessory pathway's from AVNRT it may also be used for left lateral (posterior) and right lateral (anterior) accessory pathway's.

There are two ways to perform this maneuver. The first is to position the mapping catheter towards the RV outflow tract slightly superior to the His recording and pace at 5 mA and 2 ms pulse duration [38]. The catheter is then slowly withdrawn with slight clockwise rotation along the RV anteroseptum until a His signal is recorded on the distal electrodes. The signal is then monitored for evidence of His capture and loss of capture with variability in respiration. With both capture of the His and the local anteroseptum the QRS is less broad than with loss of His capture.

Another method is to position the catheter along the RV basal anteroseptum so that a His signal is recorded on the distal electrodes and pacing is performed during normal sinus rhythm at a high output starting at 10 mA with a pulse width of 2 ms and reducing the output. At high pacing output there is capture of both the His and the local ventricle. As the output is lowered there is loss of His capture with widening of the QRS complex indicating activation of ventricular myocardium further away from the pacing site at the RV basal anteroseptum.

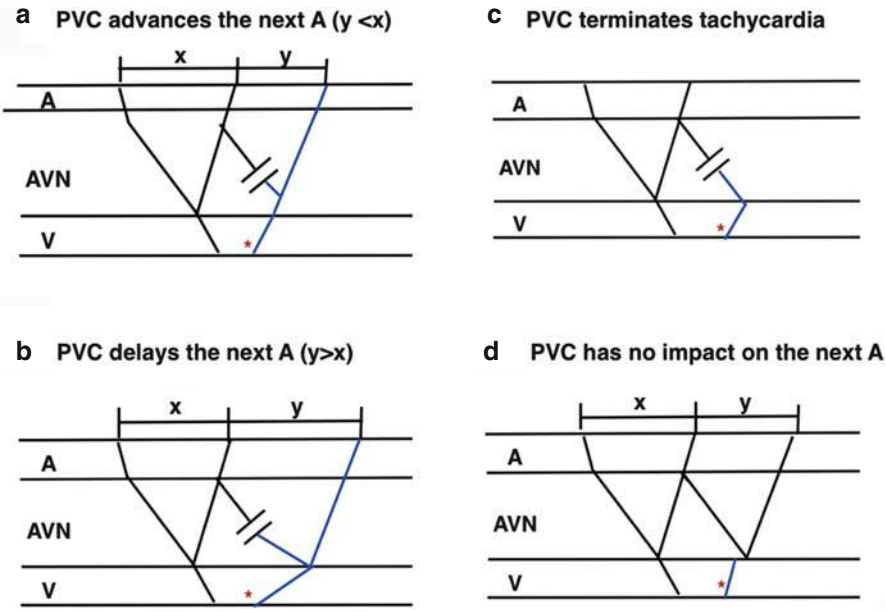

Fig. 2.43 Diagrammatic representation showing the effect of a PVC delivered during His refractoriness during tachycardia. The PVC (*) is delivered in the RV base. In (**a**) the PVC advances the next atrial activation. This indicates the presence of an accessory pathway however does not prove that this is a critical part of the circuit. In image (**b**) the PVC delays the next atrial signal. This indicates the presence of an accessory pathway which is a critical part of the circuit. In image (**c**) the PVC terminates the tachycardia. This also indicates the presence of an accessory pathway which is a critical component of the tachycardia circuit. In image (**d**) the PVC has no effect on the next atrial signal. This may indicate the absence of an accessory pathway. However an accessory pathway may be present but may be anatomically distant from the site of the PVC or may be a decremental pathway which is refractory to the PVC

The following measurements are then compared between a single beat with His and local ventricular capture compared with a single beat with loss of direct His capture:

Stimulus: Atrial Interval (SA)

His: Atrial Interval (HA)

Atrial Activation Sequence (AAS)

The basic principle relies on the anatomic fact that the His is subendocardial and encapsulated in annular tissue meaning that direct capture can only occur when a catheter is positioned along the RV anteroseptum at high pacing outputs. Lowering

the output therefore results in local ventricular capture which activates the RV apex with retrograde conduction up the right bundle to the His resulting in a significant delay to His activation. Although any pacing catheter can be used to perform this maneuver the use of a deflectable catheter with 1 mm spaced electrodes allows easier visualization of the His signal by reducing the width of the recorded local ventricular signal. This principle is demonstrated in Fig. 2.44.

The usual responses to this are shown in Table 2.3. In VA conduction using only the AV node loss of direct His capture results in a prolongation of stimulation to

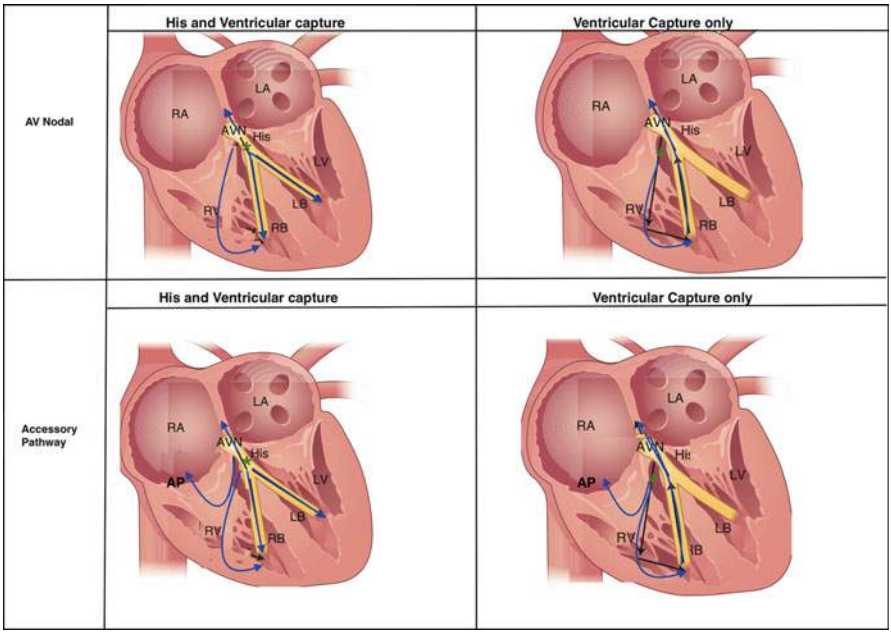

Fig. 2.44 Diagrammatic representation of Parahisian Pacing. In the *top left image* there is capture of both the His and the Ventricle resulting in a relatively short VA time and stimulation to RV apical time. In the *top right* image ventricular capture only conducts via the distal bundle branches via the His and to the atrium resulting in a prolonged VA time. This is indicative of AV nodal conduction. In the bottom left image conduction through the His and ventricle results in the most rapid conduction through an accessory pathway (AP). Conduction through the ventricle only (*bottom left*) results in a similar short VA conduction time through the AP

Table 2.3 Responses to ParaHisian pacing in AV nodal and AP conduction

VA conduction	SA	HA	AAS
AVN	Prolongs	Generally no change but may shorten with dual AVN physiology	Generally no change but may change with dual AVN physiology depending on the atrial insertion point of the slow pathway
AP conduction only	Unchanged or shorter	Shorter	May or may not change

atrial activation interval. In general there is no change in the HA interval although this may shorten in cases of dual AV nodal physiology. This is shown on the electrogram in Fig. 2.45 in which the His and ventricle and the His are both captured at a higher pacing output resulting in a stimulus to atrial interval of 76 ms. When the pacing output is reduced there is only ventricular capture with a prolongation of the stimulus to atrial activation of 136 ms. There is no change in the AAS. This is suggestive of AV nodal conduction only. Generally in AV nodal conduction the atrial activation sequence is generally unchanged, however in certain cases it may change. The slow pathway may have a left atrial insertion point, the CS to atrial connections could be distal or there may be functional block along the Eustachian ridge resulting in activation in the left atrium preceding septal and right atrial activation. Therefore the retrograde AAS is not sufficient to rule out AV nodal conduction only.

In VA conduction using an accessory pathway loss of direct His capture does not prolong the stimulation to atrial activation as the accessory pathway conduction is not dependent on conduction through the His. The HA interval often shortens. The AAS may or may not change depending on the atrial insertion point of the AP and occurs as a result of fusion of retrograde VA nodal and AP conduction.

This maneuver cannot be performed in patients with retrogradely conducting fasciculoventricular accessory pathways as direct His capture will occur at the site

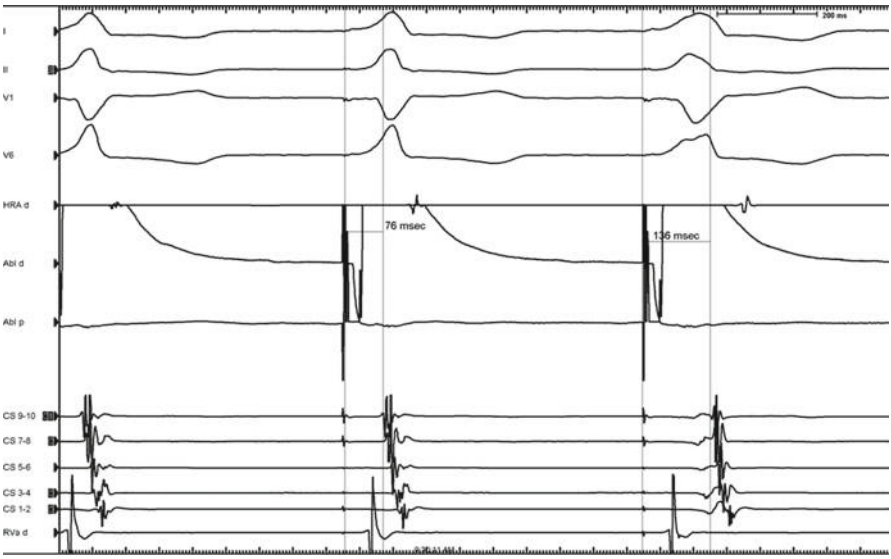

Fig. 2.45 Parahisian pacing in a patient with AV nodal conduction only. Pacing is performed from the ablation catheter which is positioned on the His. The narrower beat indicates capture of both the ventricle and the His with a stimulus to atrial time of 76 ms. When the pacing output is reduced there is only ventricular pacing with loss of His capture. The stimulus to atrial time is longer at 136 ms. This is indicative of AV nodal conduction. (HRA d is positioned in the high right atrium, HIS d in the distal His, HIS p at the proximal component of the His, CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS and RVa d is located in the RV apex)

of the accessory pathway insertion point during both high and low output pacing with no widening of the QRS at lower pacing output. In the reverse situation proximal RBBB may mean that direct pacing of the His via the proximal right bundle is not possible resulting in a wide QRS at high and low pacing output.

High output pacing may result in capture of other closely related structures resulting in an incorrect interpretation. Direct atrial capture at high output may reveal an apparent short stimulus to atrial activation time. High output pacing may also result in capture of the left bundle branch which may result in shortening of VA conduction for left sided pathways with an apparent increase in VA conduction time as the pacing output is reduced.

Transseptal Access

Transseptal access is used in order to gain access to the left atrium and left ventricle for AP mapping and ablation, left sided AT's, AF ablation, VT ablation and left atrial appendage occlusion. This procedure is performed using a combination of fluoroscopic images, pressure monitoring, contrast and often with the assistance of echocardiographic information.

Equipment

Trans-septal Needles

A number of transseptal needles are available for use which vary both in length and angulation. The most commonly used is the Brockenbrough (BRK) which is an 18 Guage needle with an arrow at the proximal end which indicates the direction of the tip of the needle. The BRK needle has a shaft to needle tip angle of 19° while the BRK 1 needle shown in Fig. 2.46 has a shaft to needle tip angle of 55°.

Additionally BRK needles vary in length. For the majority of standard non deflectable sheaths the needle is 71 cm while for a long deflectable sheath this is 98 cm.

The NRG RF transseptal needle shown in Fig. 2.47 (Baylis Medical, Montreal, Canada) is a 21 Guage device which allows delivery of RF at the tip of the needle. This comes in similar lengths to the BRK needle with similar curve option. This needle is useful for aneurysmal septums and has been shown to have a lower incidence of sheering from the inside of a transseptal sheath [39]. The needle is positioned against the fossa ovalis and RF is applied to the tip at 10 W for 2 s. On TEE and ICE entry into the left atrium is seen as bubbles in this chamber.

Fig. 2.46 Showing the main types of BRK Transseptal Needles (St Jude Medical, St Paul, MN, USA). The image on the top shows the 71 cm BRK needle at the top with a shaft to tip angle of 19°, below this is the 71 cm BRK1 needle which has a shaft to tip angle of 55°. Below this is the 56sm BRK needle. On the *bottom right image* the tips of the three needles are shown in closer detail. The image on the *bottom left* shows the *pointer arrow* which in general should be directed at 4–5 o'clock

Fig. 2.47 Showing the Baylis NRG ® Needle (Baylis, Montreal, Canada)

Transseptal Sheaths

There are various sheaths available for trans-septal access. These are either fixed or deflectable. The Swartz Left (SL) range of sheaths (St Jude Medical, St Paul, MN, USA Medical) is most commonly used. These sheaths were principally designed to deflect towards the mitral annulus for accessory pathway mapping and ablation. All of these sheaths have a primary curve of 50° with a secondary curve of 0° in the SLO, 45° in the SL1, 90° in the SL2 and 135° in the SL3. The SL4 has a 35° primary curve and has an angulation of 180°. Other non-deflectable transseptal sheaths include the Channel FX (Boston Scientific Way Marlborough, MA, USA) and the Convoy Advanced (Boston Scientific Way Marlborough, MA, USA).

Several deflectable sheaths also exist. The Agilis sheath (St Jude Medical, St Paul, MN, USA Medical, St Paul, MN, USA) is 91 cm long and requires the 98 cm transeptal needle. This sheath is available in medium and long reach options. Other deflectable sheaths include the Channel steerable (Boston Scientific Way Marlborough, MA, USA), the Direx (Boston Scientific Way Marlborough, MA, USA) and the Mobicath (© Biosense Webster, Inc).

Guidewires

These are generally 0.032 in. in diameter with a J shaped distal end of approximately 3 mm in length at the tip. These wires are placed into the superior vena cava and are used to advance the sheath and dilator over. They may also be advanced through the sheath and dilator into the left superior pulmonary vein in order to confirm position and allow dilatation of the transseptal access point while minimizing the potential risk of the dilator advancing through the lateral left atrial wall. If unsure whether the transseptal needle is in the left atrium an angioplasty wire can also be advanced through the needle prior to advancement of the sheath and dilator.

Fluoroscopic Approach

In order to help with fluoroscopic access a catheter can be positioned in the coronary sinus and the His. The His catheter is at the same level but anterior to the fossa ovalis. The electrode recording the proximal His acts as a surrogate for the aortic root. The coronary sinus catheter shows the direction in which the transseptal needle should pass in an LAO projection. This is parallel and inferior to the direction of the transseptal needle. The distal end of the coronary sinus also marks the lateral wall of the left atrium. The relevant anatomy is demonstrated on the CT in Fig. 2.48.

Fig. 2.48 Relevant anatomy in a trans septal approach. In the top image the fossa ovalis (*FO*) is posterior to the aorta (*Ao*). Also seen in this image is the right atrial appendage (RAA) anteriorly, the coronary sinus (*CS*) posteriorly and the left atrium (*LA*). The mid image shows a trans-septal sheath engaging the fossa ovalis (*FO*) posterior to the aorta). The image at the bottom is a CT showing the right atrium (*RA*) and left atrium (*LA*). The fossa ovalis (*arrow*) is posterior to the ascending aorta (*AAo*). Also seen in this image is the right superior pulmonary vein (*RSPV*), right inferior pulmonary vein (*RIPV*), left superior pulmonary vein (*LSPV*), left inferior pulmonary vein (LIPV), left atrial appendage (*LAA*) as well as the right ventricle (*RV*), left ventricle (*LV* and descending aorta (*DAo*)

Although various fluorosocopic views may be used the most useful are the LAO 30, RAO 30 and the left lateral. The sheath and dilator are flushed with heparinized saline in order to eliminate all air. The trans-setpal needle is flushed and in the case of a BRK the stylet is placed back inside the needle and locked in

place. The needle can be placed inside the sheath and dilator in order to ensure that these are compatible in terms of length. The needle is then removed and the sheath and dilator are introduced over a 0.032 J shaped wire into the superior vena cava. The wire is then removed and the dilator is aspirated and flushed with heparinized saline. The transseptal needle is then introduced into the dilator and sheath with the tip of the needle kept inside the dilator. In the case of a BRK needle it is important that the stylet is kept inside the needle while introducing this into the dilator in order to prevent sheering of plastic from the dilator. This is not required for the NRG RF which has a less sharp tip. Once the needle is close to and still inside the dilator tip the stylet is removed and the needle is aspirated and flushed with heparinized saline. This can then be connected to a three way tap and connected to pressure monitoring and contrast if required. Systemic heparin is then administered to the patient prior to transseptal access being achieved.

The sheath with dilator and needle are positioned between 4 and 6 o clock and withdrawn from the superior vena into the right atrium using an LAO 30 projection. As the apparatus is withdrawn along the superior vena cava the sheath and

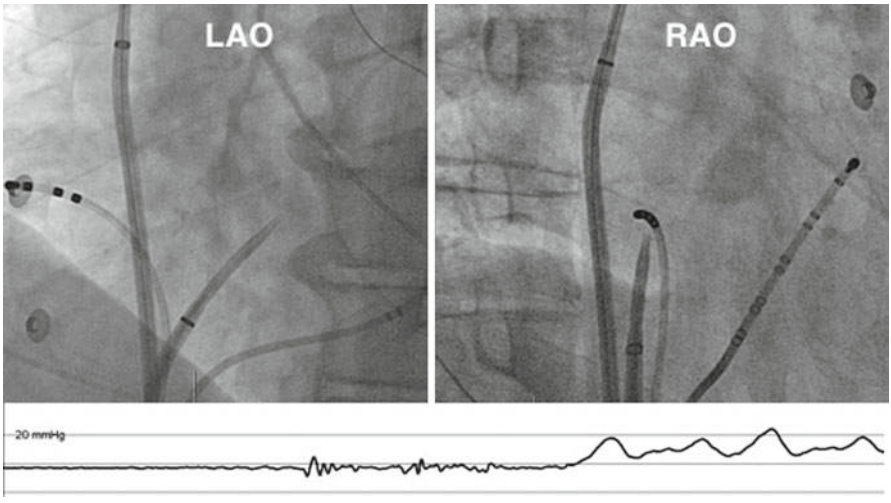

Fig. 2.49 Fluoroscopic guidance of trans-septal access in the *LAO* view (*top left*) and *RAO* view (*top right*). In the LAO projection the tip of the dilator should be superior to and parallel to the coronary sinus which demonstrates the AV groove parallel and posterior to the mitral annulus. The proximal poles of the quadripolar catheter are positioned along the His which acts as an approximate marker of the aortic root. In the RAO image on the *top right* the needle and sheath is clearly posterior to the His catheter. The pressure tracing on the bottom is recorded through the trans septal needle and shows a damped pressure tracing as it is against the septum followed by a left atrial pressure as access is achieved

dilator jumps to the left as it deflects from the descending aorta into the right atrium, Further withdrawal results in a second jump as the apparatus engages the fossa ovalis. In the LAO projection the tip of the dilator should be superior to and parallel to the coronary sinus which demonstrates the AV groove parallel and posterior to the mitral annulus, thus helping to demonstrate the widest portion of the LA. The relevant anatomy for trans septal access is shown in Fig. 2.49. In the RAO projection the anterior and posterior projections can be checked relative to the His catheter. This can also be demonstrated in the left lateral position with the His catheter pointing anterior and the CS posterior. The needle is pointed at 1 o'clock in this view for engagement of the fossa ovalis. The proximal His recording identifies the central fibrous body at the most inferior aspect of the noncoronary aortic cusp. Prior to transseptal access a bolus of heparin should be administered.

The apparatus is then withdrawn very slightly and then advanced with the needle outside of the sheath and dilator with pressure measured from the tip of the needle. There is usually a jump as the needle crosses the septum. Confirmation should be performed by checking the pressure and injecting contrast. As soon as this is confirmed, the dilator and sheath can be advanced over the needle, and the needle and dilator removed so that a long J wire can be gently advanced into the left superior pulmonary vein. Care must be taken at all times to ensure that the sheath and dilator are not advanced too far resulting in a perforation, or that the wire is not advanced into the left atrial appendage. For the second transseptal sheath, some operators withdraw the sheath and leave the J wire in place and then advance the ablation catheter through the puncture site, while others perform a second transseptal puncture using the same puncture.

Echocardiographic Visualization

Although fluoroscopic guidance is fundamental in achieving transseptal access variations in anatomy may result in difficulties crossing the foramen ovale. These include an aneurysmal atrial septum defined as a deviation during the cardiorespiratory cycle of at least 10 mm, prior cardiac surgery, congenital heart disease, dilated atria, multiple prior trans-septal procedures and a dilated aortic root. The interatrial septum cannot be reliably differentiated from the aortic root on trans thoracic echocardiogram and therefore either ICE or TEE can be used. The advantage of both of these imaging modalities is that the fossa can be directly visualized. The disadvantage of ICE is that it often required additional vascular access and is generally quite expensive. TEE is extremely useful but requires the patient to be under general anesthesia and has the potential for esophageal injury. Tenting of the fossa ovalis can be seen on TEE in Fig. 2.50.

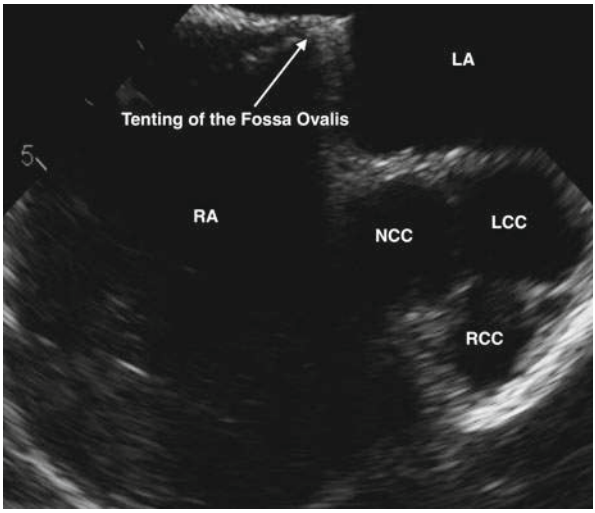

Fig. 2.50 Transesophageal imaging showing tenting of the Fossa Ovalis during trans-septal access. The right atrium (*RA*) and left atrium (*LA*) are seen as well as the non coronary cusp (*NCC*), left coronary cusp (*LCC*) and right coronary cusp (*RCC*) of the aortic valve

Important Points

1. Unipolar electrograms are amplified signals recorded between the distal pole of the catheter (+) and Wilsons Central Terminal (−).
2. Bipolar signals are amplified signals recorded from two closely spaced unipoles. In general the distal pole is negative while the proximal pole is positive.
3. All signals are amplified and filtered. The amplified signal first passes through a high pass filter which allows higher frequency signals to pass through while removing signals below a designated frequency. This then passes through an isolation amplifier which isolates the current from the patient and is subsequently transmitted through a low pass filter. This allows lower frequency signals to be transmitted while filtering out higher frequencies.
4. SNRT is measured using the principle of overdrive suppression in which pacing is performed close to the sinus node at a rate faster than the sinus rate and the time taken from the last paced beat to the first intrinsic sinus beat is measured. A sinus node recovery time, taken as the longest interval after pacing at any cycle length is generally considered abnormal if longer than 1500 ms.
5. SACT is the conduction time from the SN to the RA tissue. A normal SACT is considered to be to be 50–125 ms.

6. The AH interval is measured from the onset of the local atrial electrogram recorded in the His catheter to the onset of the His signal and represents conduction through the AV node. The normal range is anywhere from 50 to 120 ms. A prolonged AH interval may occur as a result of intrinsic AV nodal dysfunction or a result of antiarrhythmic drugs. A short AH interval generally occurs in the presence of catecholamines.
7. The HV interval is measured from the onset of the local His signal to the local ventricular signal on the His catheter (Fig. 2.24). This generally reflects the conduction time through the proximal His, bundle branches and the Purkinje system. The normal range is considered to be between 30 and 55 ms. Intrinsic His dysfunction or antiarrhythmic drugs may prolong the HV interval. A short HV interval may be seen with accessory pathway conduction which may even be negative. Care must be taken not to confuse the right bundle electrogram as the His electrogram may artificially lead to what may seem like a short HV interval.
8. The effective refractory period (ERP) is the longest coupling interval in which the stimulus fails to stimulate the myocardium at twice the diastolic threshold.
9. The AV Wenckebach point is defined as the longest cycle length which results in 2:1 AV block.
10. If the tachycardia cycle length prolongs with induction of BBB then this implies that the arrhythmia is AVRT with a VA connection on the same side as the BBB known as Coumel's sign.
11. Entrainment is the continual resetting of a re-entry tachycardia by pacing at a site close to or within the circuit at a cycle length slightly shorter that the tachycardia cycle length. During an SVT entrainment from the RV results in a shorter PPI-TCL for AVRT versus AVNRT.
12. If a PVC delivered at the same time as the antegrade His signal results in an advancement of the next atrial activation with no change in the AAS this implies the presence of an accessory pathway which participates in the circuit. A change in the AAS implies that the accessory pathway is not participating in the tachycardia. If a His refractory PVC does not affect the following atrial beat then there is either no AP or the PVC has not conducted retrogradely up the AP. This may occur if the AP has decremental retrograde conduction or is anatomically far from the location of delivery of the PVC.
13. If a tachycardia cannot be easily induced parahisian pacing may be helpful to study retrograde conduction properties. In the presence of VA conduction using only the AV node loss of direct His capture results in a prolongation of stimulus to atrial activation interval. In general there is no change in the HA interval although this may shorten in cases of dual AV nodal physiology. In VA conduction using an AP loss of direct His capture does not prolong the stimulation to atrial activation as the AP conduction is not dependent on conduction through the His. The HA interval often

shortens. The AAS may or may not change depending on the atrial insertion point of the AP and occurs as a result of fusion of retrograde VA nodal and AP conduction.

14. Trans septal access may be obtained using a fluoroscopic approach or with the addition of echocardiographic guidance. In the fluoroscopic image the coronary sinus catheter shows the direction in which the transseptal needle should pass in an LAO projection. This is parallel and inferior to the direction of the transseptal needle. The distal end of the coronary sinus also marks the lateral wall of the left atrium.

This can also be demonstrated in the left lateral position with the His catheter pointing anterior and the CS posterior. As shown in Fig. 2.49 pointing the needle at 1 o'clock is reasonable in this view for engagement of the fossa ovalis. The proximal His recording identifies the central fibrous body at the most inferior aspect of the noncoronary aortic cusp.

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Chapter 3
Electroanatomic Mapping

Benedict M. Glover and Pedro Brugada

Abstract Electroanatomic mapping (EAM) involves the rapid acquisition of multiple electrical and anatomical points in order to create a 3 dimensional map encompassing this data. These systems use **magnetic**, **impedance or a combination** of the two for the non-fluoroscopic location of the catheters. Data can be displayed on a recreated anatomic structure. This data includes activation times, voltage recordings and entrainment mapping. One of the original mapping systems the Localisa (© Medtronic plc 2015) has been replaced by three systems which are used most commonly in clinical practice which include CARTO (© Biosense Webster, Inc), NavX (St Jude Medical, St Paul, MN, USA) and Rhythmia (Boston Scientific Way Marlborough, MA, USA). Despite advances in the automation of these systems it is important to examine electrogram quality and annotation otherwise the map may not make any sense.

General Principles of EAM Mapping

Although the current mapping systems differ in the specific technology employed for catheter localization and electrogram acquisition and processing there are several important general principles for all aspects of mapping systems. It is important that useful data are processed. In the electrophysiology laboratory the most common mapping includes activation (isochronal), voltage (isopotential) and entrainment mapping. If respiratory gating is used all points in all systems are generally recorded during the same phase of respiration which is generally end expiration.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_3

Reference Point

A stable reference point is required for activation mapping so that all points can be measured relative to the same electrogram. An ideal reference electrogram should be stable with an obvious positive or negative peak for measurement. The trigger is then set on either the most positive or negative change in voltage over time (dV/dT). In the ventricle a surface QRS can be used for this or the electrogram from the RV apical catheter. In the atrium the surface P wave is not satisfactory and therefore the coronary sinus catheter is generally used given its relative stability. It is important that this is positioned in a stable position with a clear atrial signal.

Window of Interest

It is important to ensure that every point taken for an arrhythmia is related to the same beat. For a **focal arrhythmia** such as PVC's, focal VT and many AT's the window of interest is set relative to the onset of the P wave or QRS. **The earliest component may be set at 80 ms ahead of the surface signal and 30 ms after the offset**.

For a **re-entry tachycardia** such as atrial flutter (both typical cavotricuspid isthmus dependent and atypical), some atrial tachycardia's and scar related VT the window of interest is chosen as **90 % of the tachycardia cycle length** (TCL) to allow for a degree of cycle length variability. The earliest component in the window is half of the value prior to the onset of the P wave or QRS and the latest component is half of the value after the onset of the P wave or QRS. The early and late signals in this method are arbitrary and only used to have an understanding of the mechanism and anatomical regions involved in the circuit. The best location for ablation may therefore not be the earliest recording on this map but a critical isthmus within it.

In order to perform an activation map which helps to locate the isthmus in an atrial re-entry circuit a slightly different technique is used while setting the window of interest. The **earliest component** of the window is set for **mid diastole of the beat of interest and the late component of the window is set for mid diastole for the following beat**. [1] This means that the region where early meets late is the **mid-diastolic region**.

The P wave duration is measured from the surface ECG at 100 mm/s with or without the administration of intravenous adenosine. The early component of the window is calculated by subtracting the P wave duration from the tachycardia cycle length and dividing by two. As the window is being set from the reference signal the distance from the reference to the onset of the P wave is subtracted if the reference occurs before the p wave or added if its occurs after the P wave. This should correspond with mid-diastole. In order to calculate the late component to the window the duration of the early window is subtracted from the tachycardia cycle length and multiplied by 90 % (Fig. 3.1).

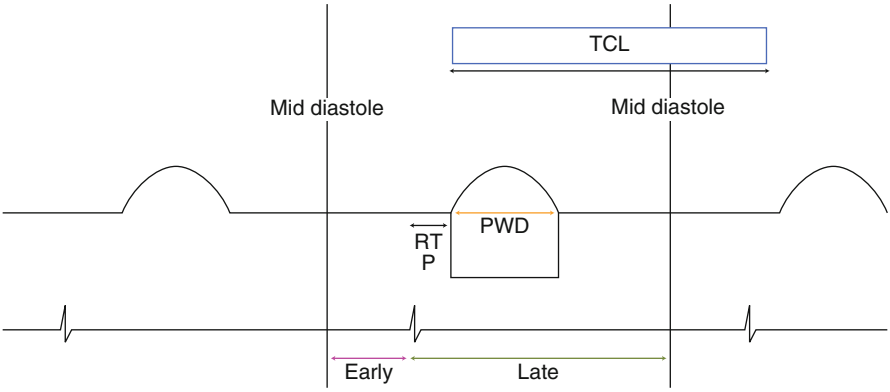

Fig. 3.1 Calculation of window of interest in a re-entry tachycardia. *TCL* tachycardia cycle length, *PWD* P wave duration, *RTP* reference to onset of P wave

Activation Mapping (Isochronal)

One of the many advantages of electroanatomic mapping is the ability to acquire multiple electrogram signals during a tachycardia and color code these so that an activation map can be acquired. Following selection of an appropriate reference signal and window of interest points are acquired and selected relative to the reference signal. Electrograms can be individually viewed and a marker is used to designate the onset of the signal which can then be moved if required. These signals are then color coded so that early is designated as red followed by yellow, green blue, and purple which indicates later activation. In focal arrhythmias regions which are coded red tend to be reasonable areas to explore and consider ablation particularly for the very earliest signal with a QS and no R wave on the unipolar electrogram. In unipolar electrograms the distal pole of the catheter (anode) is connected to a remote electrode known as the indifferent electrode (cathode). Depolarization towards the distal electrode results in a positive deflection while depolarization away from the electrode results in a negative deflection. A QR therefore implies that the wave of depolarization is moving away from the electrode. In cases of poor electrode contact a slurred S wave may also be present which implies that better catheter manipulation is required.

In macro re-entry circuits the earliest site as designated by red is not generally targeted with ablation. Rather the activation sequence should be examined in order to understand the basis of the arrhythmia and further mapping with the catheter should be performed in order to help localize the critical isthmus with mid diastolic signals. As shown in the activation map in Fig. 3.2 a re-entry circuit is seen rotating around a right atrial lateral wall atriotomy scar. Ablation (light and dark red dots) is performed along the lateral wall from the superior vena cava to the inferior vena cava after pacing for phrenic nerve stimulation is performed and marked as a white line. This resulted in termination of the tachycardia.

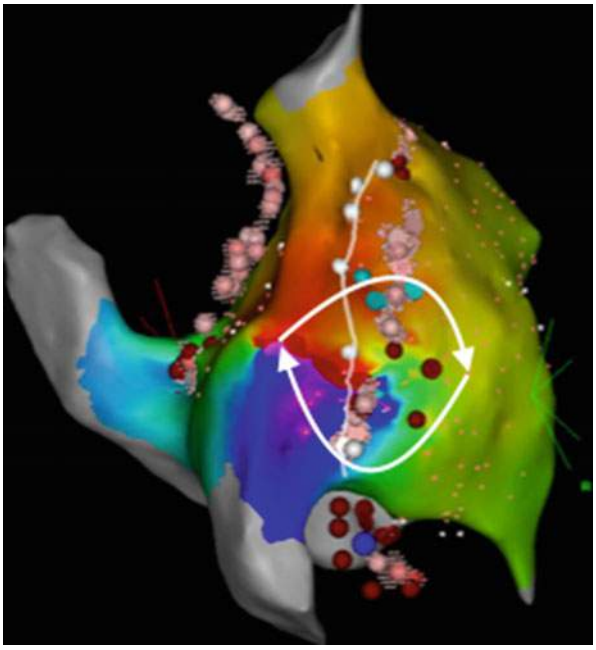

Fig. 3.2 Activation map showing a macro re-entry circuit around an atriotomy scar in a patient who previously underwent mitral valve surgery. The earliest activation is seen as *red* followed by *yellow*, *green*, *blue* and then *purple*. The *white arrow* shows the overall direction of conduction. Prior to ablation high output pacing was performed and the approximate location of the right phrenic nerve was mapped out (shown as a *white line*). Ablation was performed (*light and dark red dots*) from the superior vena cava to the inferior vena cava with termination of the tachycardia. The *light blue* dots indicate fractionated potentials. Also seen on the *left side of the image* in the background is an ablation line along the left interatrial septum which resulted in termination of a second tachycardia and at the inferior aspect of the image a cavotricuspid ablation line which terminated a third tachycardia

Prior to delivery of ablation in this region entrainment can be performed to ensure that the location is within the circuit. If the tachycardia terminates pace mapping may be performed and compared with the clinical arrhythmia. In order to perform pace mapping the minimum output is used from the distal electrodes of the ablation catheter and the paced beats are compared with the clinical arrhythmia. It is possible to have multiple different pace maps by pacing from the same site as the same isthmus may have multiple exit sites. In VT a long stimulation to onset of QRS with an excellent pace map generally indicates close proximity to the isthmus which then conducts to the exit site. Data acquired from an activation map can be used to create a propagation map. This demonstrates a wavefront of activation color coded red with a background blue image. This demonstrates conduction velocity and the overall direction of depolarization for both focal and re-entry circuits.

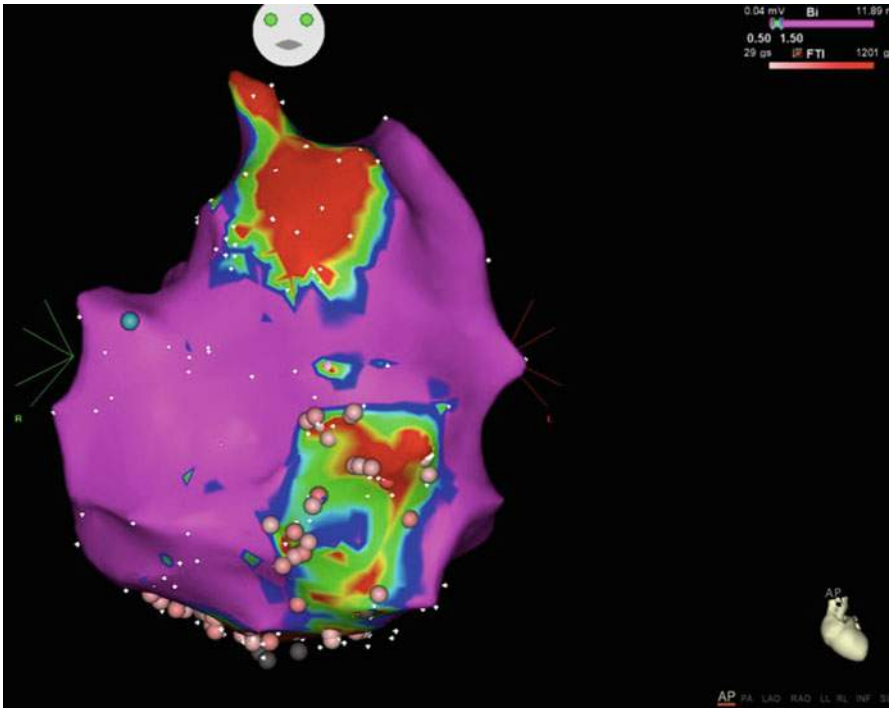

Fig. 3.3 Voltage map of the right ventricle in a patient with a history of tetralogy of fallot. Two regions of dense scar are seen, one in the anterosuperior tricuspid annulus and the other in the anteroapical region. Both of these are surrounded by heterogenous tissue. The inducible VT was found to circulate around the anteroapical scar which terminated with ablation

Voltage Map (Isopotential)

Is used to map local potentials during either sinus rhythm, tachycardia or pacing. The concept is that low amplitude endocardial signals are more indicative of regions of scar while higher amplitudes imply relatively healthy myocytes. As well as the amplitude of the signal the degree of fractionation and duration of the signal are very important as this may imply regions of slow conduction, which are often targeted for ablation.

The amplitude of each signal can be color calibrated so that red implies scar with orange, yellow, green, blue and purple indicating progressively higher amplitudes.

In the right ventricle normal bipolar electrograms have an amplitude of 3.7 ± 1.7 mV and in the left ventricle 4.8 ± 3.1 mV with **1.5 mV or less defined as scar and 0.5 mV or less dense scar**. [2] An example of a voltage map in a patient with tetralogy of Fallot is shown in Fig. 3.3.

In the left atrium normal bipolar amplitudes are considered to be greater than 0.5 mV [3] although in patients with AF this cutoff may be 0.45 mV. [4]

A **late potential** is defined as an isolated potential occurring greater than 10 ms after the end of the surface QRS complex while a **mid diastolic potential** is defined as a high frequency localized potential occurring between two QRS complexes with an isoelectric line either side. **Fractionated potentials** are defined as low amplitude signals with multiple sharp deflections with an overall duration greater than or equal to 70 ms. **Complex fractionated atrial electrograms** (**CFAE's**) are defined as low amplitude fractionated atrial electrograms with a cycle length of less than 120 ms.

Entrainment Mapping

Entrainment mapping can be performed by pacing from the ablation catheter in various locations where the tachycardia circuit location is suspected. By overdrive pacing at a cycle length shorter than the tachycardia cycle length the tachycardia is continuously reset without terminating to the same cycle length with manifest and concealed entrainment. In general the pacing cycle length is 20–30 msec shorter than the tachycardia cycle length although in certain circumstances such as an orthodromic reciprocating tachycardia a rate just slightly less than the tachycardia cycle length is chosen from the RV apex as faster rates may penetrate the AV node and result in termination of the tachycardia.

A short PPI – TCL generally indicated closer proximity to the circuit. This difference can then entered onto the mapping system as a color coded time where red is less than 30 msec followed by yellow, green, blue and finally purple where the difference is greater than 100 msec. This is an effective strategy to help map out the regions of the chamber involved in the re-entry circuit. It does not provide data on where exactly to ablate and this decision must be made based on the location of the isthmus or by joining various anatomic structures. In a diseased atrium where multiple ablations have been performed it may be difficult to capture all areas as well as the potential to terminate the arrhythmia as well as initiation of a different tachycardia.

Specific Mapping Systems

CARTO Mapping System (© Biosense Webster, Inc)

This system uses a combination of magnetic and impedance based technology for catheter localization and data acquisition. A locator pad composed of three coils is positioned under the table and emits very low intensity magnetic fields between 5×10^{-6} to 10^{-5} T. As demonstrated in Fig. 3.4 each coil emits a slightly different field strength which is then detected by a sensor in the proximal tip of the ablation catheter. The relative magnetic field from each coil is then fed back to the system with a three dimensional location in the x,y and z axis and catheter orientation in three

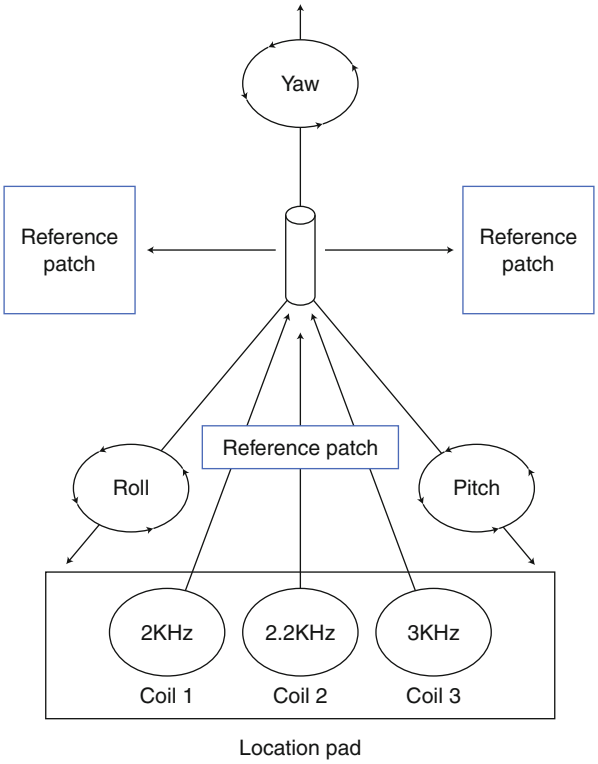

Fig. 3.4 Concept of Electroanatomic mapping using the CARTO system (© Biosense Webster, Inc)

planes termed roll, pitch and yaw. The ablation and diagnostic catheters also emit a low level current which is detected by six reference patches. Although the locations of diagnostic catheters can be visualized the electrogram's can unfortunately only be seen in specific catheters designed by the company such as the Lasso, the Pentarray and the Decanav.

The Lasso is a 10 or 20 pole circular deflectable catheter (Fig. 3.5) which is predominantly used for left atrial mapping and in particular pulmonary vein isolation. The circular component is flexible with a 4.5 Fr diameter and a shaft which fits through an 8 Fr sheath.

The Pentarray catheter consists of 20 electrodes on 5 arms (Fig. 3.6). Each arm is soft with a 3 Fr diameter and a shaft, which can be positioned through a 7 Fr sheath and comes in different curves. Each individual electrode is 1 mm in length with varying electrode spacing; either 4 mm spacing or 2-6-2 mm spacing.

The Decanav catheter is a 10 pole catheter in which each electrode is 2 mm in length and with electrode spacing of 2-8-2 mm (Fig. 3.7). This allows the rapid acquisition of multiple points during mapping and can be useful for both atrial tachycardia and ventricular tachycardia including outflow tract tachycardia. Like

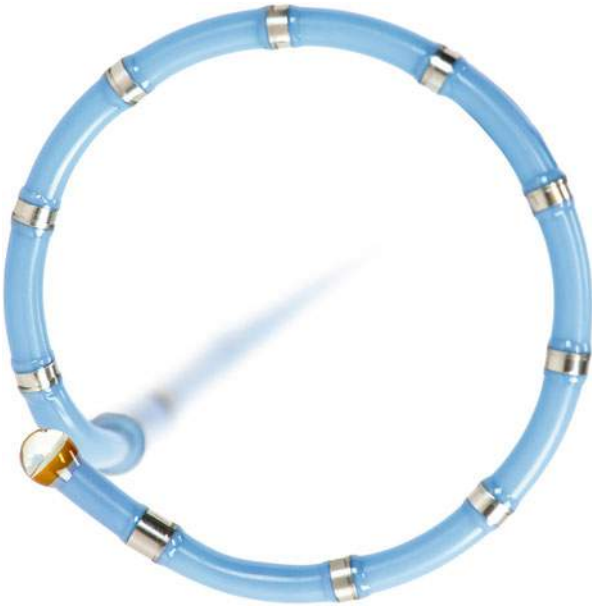

Fig. 3.5 Showing bipolar electrodes on the circular Lasso Catheter with 10 poles on the catheter (© Biosense Webster, Inc)

Fig. 3.6 Image of the Pentarray Mapping Catheter (© Biosense Webster, Inc) showing 20 electrodes on 5 arms with variable spacing

the Pentarray it can be advanced through a 7 Fr sheath and is available in both a D and an F curve.

The location patches also transmit low level current to each other, which helps to record chest impedance allowing for respiratory gating. This is calibrated at the start

of the procedure so that points are taken during end expiration and is particularly useful for accurate fast anatomic mapping. In order to gate the circular mapping catheter should be in contact with the wall of the left atrium. This can easily be achieved by positioning the catheter along the mitral annulus or in one of the pulmonary veins. A threshold for respiratory gating can be set with lower values resulting in more accurate but slightly slower data acquisition.

Merging the Baseline CT/MRI onto the Anatomic Map

Often baseline imaging is useful in order to assess pulmonary vein anatomy and assess for aberrant pulmonary veins. The baseline CT or MRI of the left atrium can also be superimposed on the left atrial shell obtained during fast anatomic mapping in order to create a merge. In order to perform this the baseline CT has to be imported onto the mapping system. This is then segmented so that the chamber of interest is enhanced. Following creation of the map the CT or MRI can be integrated by using a combination of both landmark and surface registration. As shown in Fig. 3.8 select points are chosen on the map and the same points on the CT which are used during the merge process. Inaccuracies may exist between the CT and the map due to changes in time with alterations in either the rhythm or hydration affecting the LA geometry.

Fig. 3.7 Image showing the distal end of the Decanav Mapping Catheter (© Biosense Webster, Inc)

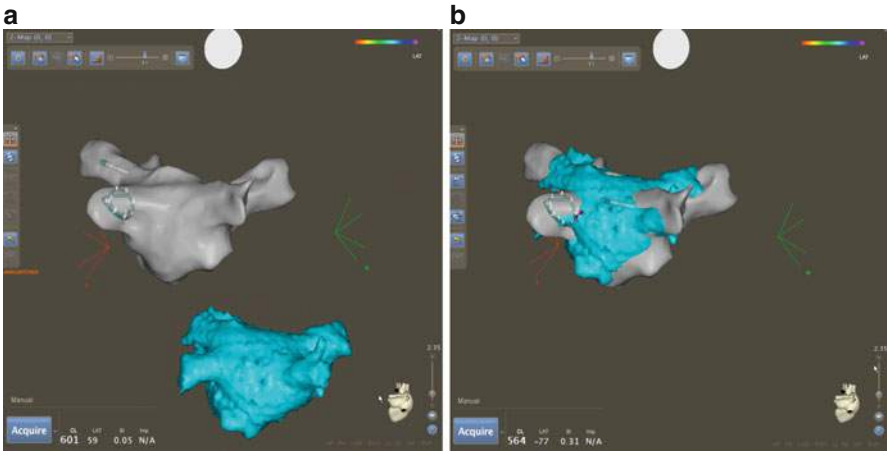

Fig. 3.8 Fast Anatomic Map created using the Lasso Catheter with a CT LA in the *top image*. Landmarks are selected on both the map and the CT and the images are merged as shown in the *bottom image*. (© Biosense Webster, Inc)

Additional Features of Carto

This system has several software features which may be considered to be clinically useful.

Visitag (© Biosense Webster, Inc) uses automation in order to create 4 mm^2 points on the map which fulfill specific pre-programmed parameters. These parameters consist of the minimum time at a particular point, the maximum range of movement of the catheter tip, the minimum force applied as well as the percentage time that the force was obtained for. Impedance and temperature changes can also be tracked. Additionally a grid feature marks 2 mm^2 points along the entire ablation lesion.

Paso (© Biosense Webster, Inc) software has been introduced into the Carto 3 platform in order to help to perform accurate pace mapping. This provides a numerical value for each lead and provides an overall assessment of the accuracy between the clinical arrhythmia and the paced beat. Although the overall efficacy has yet to be studied it appears to have a useful clinical role in particular for focal PVC's as shown in Fig. 3.9 and VT.

CartoUnivu (© Biosense Webster, Inc) allows real time catheter movement to be tracked on a pre-recorded cine angiogram. This is particularly useful for AF ablations where a 3 dimensional rotational angiogram of the left atrium is performed at the start of the procedure following the administration of intravenous adenosine or with rapid ventricular pacing. This image can then be integrated onto the map and viewed in any angle. Coronary angiograms can also be integrated for epicardial ablation as well as LVOT ablations. This may have an overall effect in lowering the total radiation exposure for the entire case, however, data proving this statement are still missing.

Ensite Velocity System (St Jude Medical, Minnesota 55442, USA)

This system emits a 8.136 kHz current between three pairs of surface electrodes in three different planes; cranial to caudal, right to left and posterior to anterior. This is detected by the ablation and diagnostic catheters which use the current degradation to estimate the location of the catheters in the x, y and z axis and allows the processing of up to 128 electrodes on up to four catheters. Impedance variability can lead to an inaccuracy in localising the catheter location and an intracardiac reference is therefore preferred as opposed to the external reference in CARTO. This may be partially compensated for by using field scaling which uses the inter-electrode spacing to attempt to compensate for inconsistencies in the map. Respiratory motion is also compensated for by recording variations in transthoracic impedance during respiration. One of the major advantges of Ensite over CARTO is the ability to acquire data from any catheter rather than a catheter designated by the system. Another attractive feature is the ability of the system to review data while still acquiring further data. An example of a velocity map using the Tacticath is shown on Fig. 3.10.

Fig. 3.9 Paso Software (© Biosense Webster, Inc) Used to compare a paced ventricular beat (*yellow*) with intrinsic ectopic beat (*green*) in the anterior mitral valve annulus

A further incorporation called **Mediguide** (**St Jude Medical**, **Minnesota 55442**, **USA**) now allows visualisation of catheters on a fluoroscopic image acquired at the start of the procedure. This employs a electromagnetic field with a sensor in the catheter and a reference sensor on the patients chest allowing imaging of catheter positions on a pre-acquired cine loop. The electromagnetic transmitter unit is installed in the fluoroscopy detector.

Rhythmia Mapping System (Rhythmia Mapping, Rhythmia Medical, Boston Scientific Inc., Marlborough, MA, USA)

This system uses a combination of magnetic and impedance degradation in order to localize catheters. A magnetic sensor in the tip of the Orion mapping catheter is the predominant guide to location with impedance used for additional clarification of

Fig. 3.10 Velocity Mapping system ((St Jude Medical, Minnesota 55442, USA) with Tacticath contact force catheter showing the left atrium from the mitral annulus on the left and right lateral image showing the left superior and left inferior pulomnary veins posteriorly (*left of the image*) and the left atrial appendage anteriorly (*right of the image*)

Fig. 3.11 Orion Mapping Catheter (Rhythmia Mapping, Rhythmia Medical, Boston Scientific Inc., Marlborough, MA, USA) fully deployed (*left*), intermediate deployment (*middle*) and minimally deployed (*right*)

location on each of the electrodes. As any diagnostic or ablation catheter can be used catheter localization for all other catheters is based on impedance. The Orion catheter requires irrigation at a rate of 1 ml/min.

One of the major advantages to this system appears to be the ability to rapidly acquire a high spatial resolution map using the Orion mapping catheter. This is a 64 electrode small basket catheter mounted on 8 splines in which each electrode is separated by 2 mm. Signals as small as 0.01 mV can be collected. The catheter is deflectable and can be advanced through an 8.5 Fr sheath. As shown in Fig. 3.11 mapping can be performed with the catheter either fully closed (3 mm diameter), fully opened (22 mm diameter) or any range between these two extremes. Anatomic data is only acquired if the electrode is deemed to be within 2 mm of the

Fig. 3.12 Rhythmia (Rhythmia Mapping, Rhythmia Medical, Boston Scientific Inc., Marlborough, MA, USA) screen setup. A surface lead is chosen on the *top left image*. Below this is the CS which is used as a reference electrode. As well as using the electrode timing a change in activation is also recorded in order to minimize the chance of a change in the activation sequence. Both the RAO image on the *left* and LAO in the *right* show the RA during normal sinus rhythm

endocardial surface. Each electrode has a surface area of 0.4 mm^2 with an inter-electrode separation of 2.5 mm. This catheter is irrigated and it is recommended that heparin is administered for all procedures where this catheter is used with an ACT of 300 s.

The setup of Rhythmia is shown in Fig. 3.12. The surface ECG is seen on the top left with reference signals from the CS below this and a combination of electrograms from the Orion catheter below this. Each electrode is code by letter and number. An RAO image of the RA and LAO of the RA are shown during normal sinus rhythm.

Given that multiple signals are acquired simultaneously this system must have the ability to rapidly self annotate signals and in particular activation times. This is achieved by recording the maximum deflection on the bipolar signal or the most negative dV/dT on the unipolar electrogram. There is continuous and automatic electrogram acquisition based on beat acceptance criteria.

In order to set up the system at the start of the case the chamber of interest and type of map is programmed as well as the rhythm (sinus, paced, tachycardia) and the reference. Although the mechanism of the arrhythmia should be programmed at the start i.e. either focal or re-entry this can be changed during or after completion of the map. The system makes recommendations based on analysis of the last 10 s of the intracardiac signals and calculates the tachycardia cycle length and therefore calculates the mapping window as well as suggesting the reference electrograms. An example of mapping across a previous CTI ablation by pacing from the proximal CS during sinus rhythm is seen in Fig. 3.13.

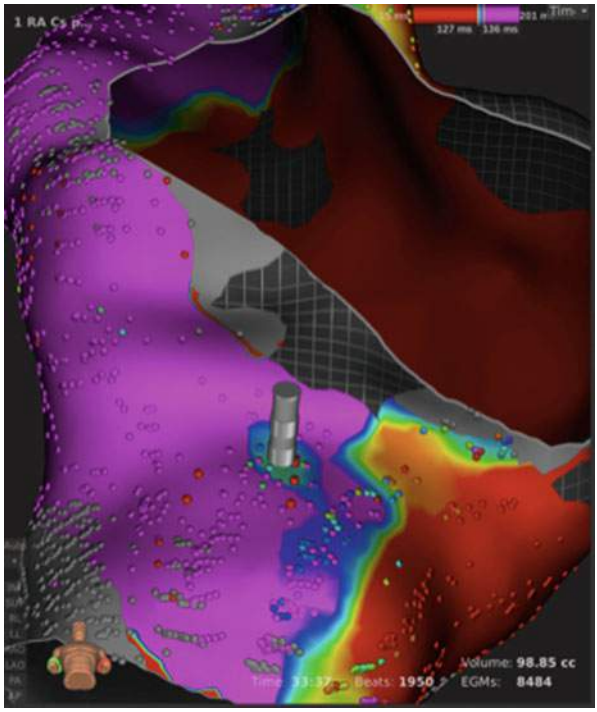

Fig. 3.13 Activation mapping using Rhythmia (Rhythmia Mapping, Rhythmia Medical, Boston Scientific Inc., Marlborough, MA, USA) with pacing from the proximal coronary sinus and mapping the right atrium in a patient with a recurrence of atrial flutter following a previous CTI ablation. The image is taken from an inferior angle with the tricuspid annulus at the *top of the image* and the inferior vena cava at the *bottom*. Although conventional pacing maneouvres suggested clockwise block there is a region of slow conduction in the mid CTI which required further ablation

Important Points

1. A stable reference point is required for activation mapping so that all points can be measured relative to the same electrogram. An ideal reference electrogram should be stable with an obvious positive or negative peak for measurement. The trigger is then set off either the most positive or negative change in voltage over time (dV/dT).
2. The window of interest is set according to whether the arrhythmia mechanism is focal or re-entry. For a focal tachycardia the earliest component may be set at 80 msec ahead of the surface signal and 30 msec after the offset. For a re-entry tachycardia the window of interest is chosen as 90 % of the tachycardia cycle length to allow for a degree of cycle length variability.
3. In activation mapping electrical signals are color coded according to how early or late they are in the window of interest. The earliest is coded as red followed by yellow, green blue, and purple which indicates later activation. In focal arrhythmias early signals are generally targeted. In re-entry ablation is often performed where early meets late.
4. In voltage mapping bipolar signals of 1.5 mV or less defined as scar and 0.5 mV or less dense scar in the ventricle.
5. CFAE's are defined as low amplitude fractionated atrial electrograms with a cycle length of less than 120 msec.

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Chapter 4
AV Nodal Re-entry Tachycardia (AVNRT)

Benedict M. Glover and Pedro Brugada

Abstract AVNRT is the most common paroxysmal supraventricular tachycardia seen in adults. It occurs as a result of dual AV nodal physiology in which an ectopic beat from the atrium or the ventricle conducts along either a slowly conducting or fast pathway and retrogradely along the other pathway which is no longer refractory. In the case of a typical AVNRT this occurs antegradely along the slow pathway and retrogradely along the fast pathway resulting in a short RP tachycardia. In an atypical AVNRT conduction occurs antegradely along the fast pathway and retrogradely along the slow pathway resulting a long RP tachycardia. It is important to carefully map during tachycardia and perform the relevant maneuvers in order to help establish the diagnosis. AVNRT is treatable with catheter ablation and this is highly successful with a low recurrence rate.

Introduction

AVNRT is the most common paroxysmal supraventricular arrhythmia in adults, accounting for approximately 60 % of all SVTs [1]. It generally presents at an age less than 40 years (median age 28 years) and is more common in females than males [2–4]. Presentation tends to occur with intermittent palpitations of acute onset and termination with vagal maneuvers and a normal baseline ECG. During tachycardia the RP interval for typical AVNRT is short and atrial activation is often in or at the terminal end of the QRS complex. The P wave is generally negative and narrow indicating an inferior to super activation from the retrograde fast pathway location.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_4

Anatomy

The relevant anatomy for AVNRT is contained within the triangle of Koch, bounded anteriorly by the septal leaflet of the tricuspid valve, posteriorly by the tendon of Todaro and inferiorly by the superior aspect of the coronary sinus os [5]. The compact AV node is located at the base of the inter atrial septum. Surrounding the compact AV node there is a zone of transitional cells which connect the compact node to the atrial myocytes. This transitional zone is composed of cells which share similar feature to both nodal and atrial myocytes [6]. There are three atrial extensions from the compact AV node to the atria as well as a single common pathway which connects to the ventricular aspect. The ventricle is not part of the circuit involved in AVNRT and helps to distinguish this from AVRT. AVNRT can therefore continue in the presence of AV block.

The superior extension equates to the fast pathway and is located in the anterior portion of the triangle of Koch, the rightward inferior extension which is located anteriorly to the coronary sinus and is often termed the slow pathway and the leftward inferior extension which is directed towards the mitral annulus (Fig. 4.1).

Mechanism

Mechanistically AVNRT involves at least two connections between the atria and the ventricles, often referred to as dual AV nodal conduction. These pathways are classified according to the speed of velocity through the tissue. The **slow pathway** has slower conduction velocity but a shorter refractory period and is located posteriorly along the tricuspid annulus, closer to the coronary sinus os. The **fast pathway** has a faster conduction velocity and is formed by transitional cells crossing the tendon of Todaro superiorly. It has a longer refractory period.

Classification

Slow/Fast AVNRT (Typical AVNRT)

This occurs when a premature atrial complex (PAC) travels antegradely down the slow pathway (right inferior extension) between the CS os and the tricuspid annulus followed by retrograde conduction along the fast pathway. Less commonly in approximately 5 % of cases antegrade conduction may occur along an anatomically different slow/intermediate pathway (left inferior extension). These are generally associated with an AH interval greater than 200 ms. As shown in Fig. 4.2 there is generally a short septal VA interval. The HA interval should be less than 90 ms i.e., AH > HA.

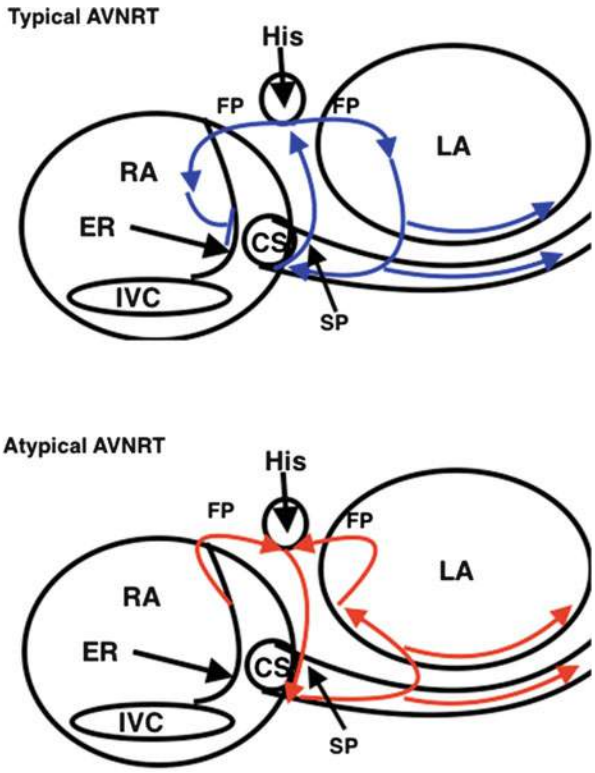

Fig. 4.1 Schematic of the AVNRT circuit in an LAO view showing a typical slow/fast AVNRT utilizing an antegrade slow pathway (*SP*) and retrograde fast pathway (*FP*) (*top image*) and in the *bottom image* an atypical fast/slow AVNRT utilizing the fast pathway antegradely and the slow pathway retrogradely

The earliest atrial activation occurs along the superior septum posterior to the Tendon of Todaro which helps to differentiate this from a Slow/Slow AVNRT. Activation on the left side of the septum continues laterally and inferiorly activating the coronary sinus. Activation on the right side of the septum is blocked by the Eustachian ridge and conducts towards the slow pathway with propagation of the circuit.

Fast/Slow AVNRT (Atypical AVNRT)

As demonstrated in Fig. 4.3 antegrade conduction occurs down the fast pathway and retrograde conduction occurs up the right inferior extension (slow pathway) with earliest atrial activation at the inferior septum. Occasionally retrograde conduction occurs up the left inferior extension (leftward slow pathway). The AH

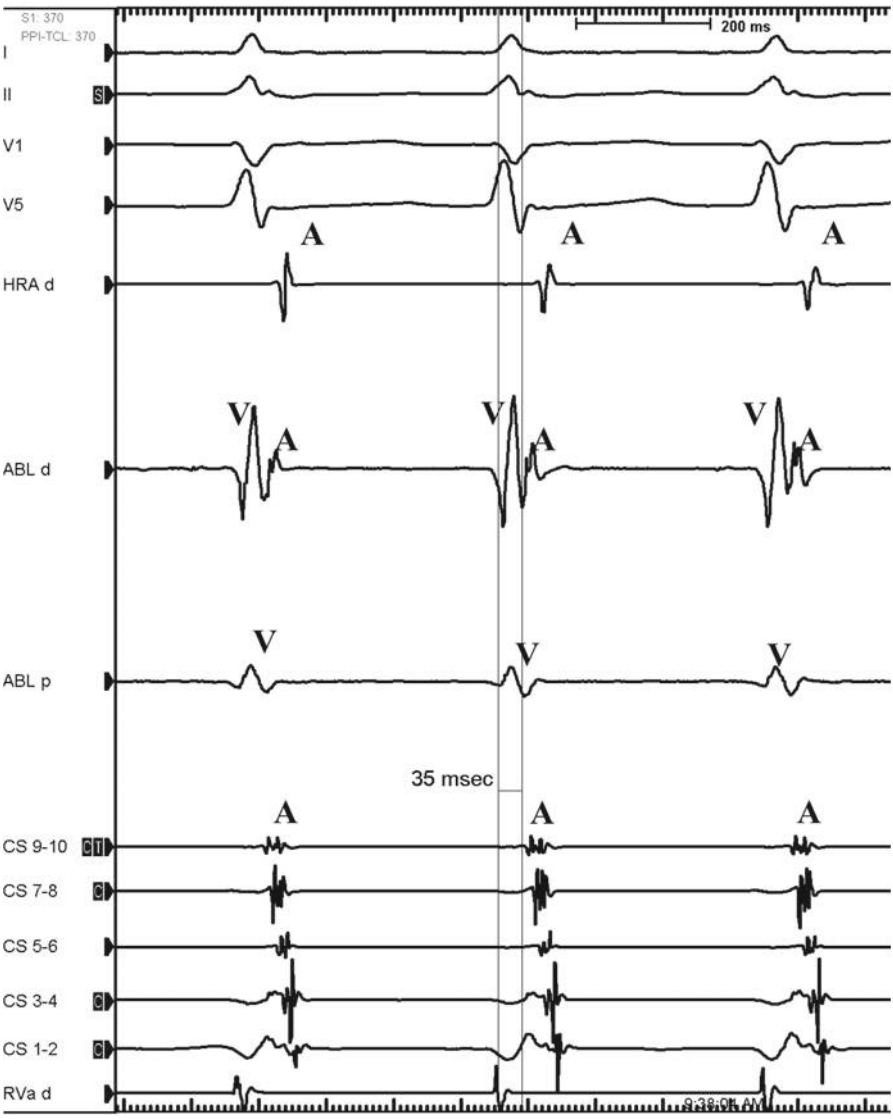

Fig. 4.2 Typical AVNRT. Earliest atrial activation is in the proximal coronary sinus with a short septal VA interval of 35 ms. This could also be a septal AP or an AT and further maneuvers are required to diagnose this. (HRA d is positioned in the high right atrium, Ablation catheter is positioned on the His, CS 9 10 are positioned in the proximal CS with CS 1 2 in the distal CS and RVA d are positioned in the RV apex)

interval is shorter than the HA interval. As the RP interval is long it is straightforward to identify the P wave which is negative in II, III, aVF and V 6 and positive in V1. This should be differentiated from an AT from close to the CS Os or a septal AP.

Fig. 4.3 Initiation of an atypical AVNRT. Decremental pacing from the RV apex results in retrograde conduction along the fast pathway for the first two beats as evidenced by the earliest activation recorded in the His with a septal VA interval of 62 ms. The third beat results in a prolonged VA interval of 306 ms with the earliest atrial activation in the proximal coronary sinus in keeping with a retrograde jump from the fast to the slow pathway. This subsequently conducts antegradely along the fast pathway and back up the slow pathway with a long RP tachycardia. (HRA d is positioned in the high right atrium, ablation catheter is positioned on the His, CS 9 10 is in the proximal CS with CS 1 2 in the distal CS, RVa d is in the RV apex)

Slow/Slow AVNRT

In general in Slow/Slow AVNRT conduction occurs antegradely down the rightward inferior extension and retrogradely up the leftward inferior extension. The earliest retrograde atrial activation is therefore often the roof of the coronary sinus although it may also be between the coronary sinus and the tricuspid annulus if retrograde conduction occurs along the rightward inferior extension. There are often multiple AH jump's reflecting multiple slow pathways. The AH interval is generally greater than 200 ms and is longer than the HA interval.

Electrophysiological Evaluation

Baseline Data

The ECG generally shows a QRS duration less than 120 ms with a short RP interval in the case of a typical AVNRT and a long RP interval in the case of an atypical AVNRT. If aberrancy is present then this more frequently is a RBBB morphology.

A p wave superimposed closely on the QRS is generally suggestive of a typical AVNRT. A negative p wave with a long RP interval in the precordial and inferior leads is more suggestive of an atypical Slow/Slow AVNRT. If the RP interval is longer than the PR interval this is more suggestive of a Fast/Slow AVNRT. RR alternans may occur in AVNRT due to a potential figure of eight type circuit involving the right and left inferior extensions along with the fast pathway.

Risks of EP Study and Ablation

As for all SVT studies the risks of an EP study and ablation include groin haematoma, vascular injury, cardiac tamponade, thrombo-embolism and AV block. The risk of AV block is generally considered to be the most significant complication and has an incidence of less than 0.5 %. AV block is more common if the distance between the slow pathway and fast pathway is less, if a more superior approach is required for successful ablation, if more ablation lesions are required and in patients with retrograde block in association with a junctional rhythm. It is therefore important to monitor these signs during application of RF and stop if necessary. It is generally good practice if the risk of AV block is considered high to stop and discuss further with the patient.

The acute success of a slow pathway ablation is approximately 97 % with a recurrence rate of 0.7–5.2 %.

Procedure

The diagnostic EP evaluation is generally performed with minimal sedation in order to maintain normal physiological parameters of the pathways involved and therefore maximize the chance of arrhythmia induction. Mapping catheters are positioned in the right ventricle, His, coronary sinus and high right atrium. Decremental pacing is first performed from the RV in order to assess retrograde conduction, the atrial activation sequence, and to search for evidence of dual VA nodal conduction. Following this, decremental atrial pacing is performed in order to search for the presence of dual or multiple AV nodal pathways and to try to induce AV nodal re-entry tachycardia. It is extremely uncommon for a ventricular paced beat to initiate AVNRT as the bundle of His is generally refractory to retrograde conduction. This is in contrast with accessory AV pathways, where induction of the re-entry arrhythmia by ventricular pacing is common.

Dual AV nodal physiology is demonstrated by the presence of an AH or HA jump, the presence of an atrial or ventricular echo beat or the induction of AV nodal re-entry tachycardia. An **AH jump** is defined as an increase in the AH interval of **greater than or equal to 50 ms at the moment when the coupling of the atrial extrastimuli is reduced by 10 ms during decremental atrial pacing or**

during single premature stimuli testing [7, 8]. This jump is the result of a change in antegrade conduction from the fast pathway to the slow AV nodal pathway. During ventricular pacing a HA jump of greater than or equal to 50 ms generally represents a retrograde switch from the fast to the slow pathway. Although this may suggest the possibility of AV nodal re-entry tachycardia this finding is common in the general population as the majority of people have superior and inferior atrial extensions into the compact AV node. The administration of intravenous sedation may depress fast pathway conduction thus increasing the incidence of a jump to the slow pathway. Conversely, in some patients with dual AV nodal physiology an AH jump may not be seen particularly if the conduction properties are similar between the two pathways such as an antegrade intermediately conducting left inferior extension pathway [9]. Additionally, the administration of isoproterenol may increase fast pathway conduction which may mask the appearance of an AH jump.

If tachycardia cannot be induced with multiple atrial extrastimuli or decremental atrial pacing then isoprenaline should be administered at a dose of 1–4 microgrammes/min. Isoprenaline should be stopped prior to ablation because it causes hypercontractility of the heart leading to catheter instability.

Differentiation Between AVNRT and AVRT

The fact that the AVRT circuit involves the ventricle as a component can be used to differentiate these arrhythmias from AVNRT in terms of basic observations as well as the maneuvers, that may be performed for the differential diagnosis.

The VA conduction time is generally less than 50 ms in Slow/Fast AVNRT and occasionally Slow/Slow AVNRT and greater than 50 ms in AVRT.

The delivery of ventricular extrastimuli in order to assess the effect on atrial activation is the most straightforward method to help differentiate between the two arrhytnmias. A pacing catheter is positioned in the RV corresponding closely with the location of the earliest atrial activation. If the earliest atrial activation is the inferior aspect of the triangle of Koch the optimal position for introducing ventricular extrastimuli is the inferobasal RV. If the earliest atrial activation is the superior septum close to the apex of the triangle of Koch then this is better positioned close to the His. These positions help to ensure that ventricular activation occurs first with subsequent retrograde His activation via the apex of the RV making much easier to interpret the individual signals.

In order to perform this maneuver a ventricular extrastimulus is delivered 50 ms after the onset of the His electrogram during tachycardia and advanced in 10 ms decrements. Any advance in atrial activation with no advance in the His electrogram implies the presence of an accessory pathway. If the atrial activation sequence of the advanced beat is identical to the tachycardia sequence and the next His electrogram is delayed then this proves that the accessory pathway is part of the arrhythmia mechanism.

As previously described, RV entrainment, delivery of a His synchronous PVC and parahisian pacing should also be performed.

Differentiation of AVNRT from Atrial Tachycardia

In general a typical AVNRT can be distinguished from a septal atrial tachycardia by the short duration of the RP interval. It may be more difficult to distinguish an atypical AVNRT as the RP interval is generally longer and entrainment from the RV apex may be more useful.

As shown in Fig. 4.4 following entrainment of the tachycardia from the RV apex the following sequence is an A followed by V. In the case of an atrial tachycardia this is generally seen as an A-A-V [10]. A pseudo A-A-V response may occur in the setting of a prolonged HV interval where the ventricular electrogram is artificially delayed. If the tachycardia is terminated during ventricular pacing and if the ventricular beat resulting in termination did not conduct to the atrium then atrial tachycardia can be excluded as the critical circuit is outside of both atria.

Several other useful techniques may also be used. If tachycardia can be induced then the AH interval can be recorded during tachycardia and compared with the AH interval during pacing from the high right atrium at the same cycle length. In cases

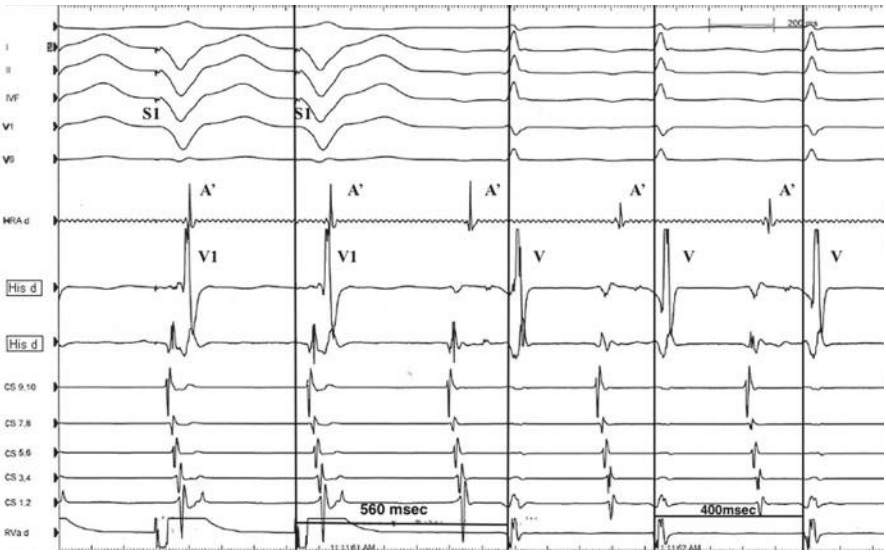

Fig. 4.4 A-V Response to Right Ventricular Entrainment during tachycardia. The tachycardia cycle length (TCL is 400 ms pacing is performed from the RV apex at 370 ms The PPI-TCL is 160 ms which is more suggestive of an AVNRT

of atypical AVNRT the AH interval during atrial pacing is longer by more than 40 ms compared to tachycardia [11].

In cases of either atrial tachycardia or AVRT with a slowly conducting retrograde pathway there is very minimal different in the AH during high right atrial pacing compared with tachycardia.

Additionally pacing from the high right atrium at different rates during tachycardia can be performed and the VA interval recorded. If the VA interval at different rates is unchanged then atrial tachycardia can be excluded.

If ventricular extrastimuli advance the retrograde His without affecting the atrial activation then atrial tachycardia is the most likely diagnosis.

Ablation Techniques

Following confirmation of the diagnosis a 4 mm non-irrigated ablation catheter is positioned in the right ventricle and withdrawn with flexion on the catheter in order to maintain a posterior septal position to the level of the coronary sinus. This is demonstrated on the fluoroscopic images on Fig. 4.5 which shows the ablation catheter position in an RAO and LAO view.

Mapping is then performed between the coronary sinus os and the tricuspid annulus. An A:V ratio of 1:2 to 1:10 should be recorded in which the atrial signal is approximately 20 ms later than the A on the His. As shown in Fig. 4.6 a small discrete slow pathway potential may be recorded in the ablation catheter. If this is seen the latest and highest frequency slow pathway potential should be targeted. Often a degree of clockwise rotation is required while trying not to fall into the coronary sinus. This is required to counteract the counterclockwise force of the Eustachian ridge which tends to rotate the catheter away from the septum during systole.

RF is generally started at 30 W with a maximum temperature set at 55–60 C. This can be increased to 40 W and occasionally 50 W is required.

Junctional beats during ablation are generally considered a indicator of slow pathway modification. These are seen in Fig. 4.7. These beats are likely due to conduction of current injury from the slow pathway to the AV junctional area enhancing diastolic depolarization of the cells in this region [12, 13]. Other potential explanations for junctional beats include an increase in AV junctional automaticity as a result of post ganglionic noradrenaline release exceeding the increase in vagal tone associated with RF application in this region therefore increasing the rate of diastolic depolarization [14] as well as a possible heat sensitive region close to the AV node which may lead to increased junctional activation [15].

Accelerated junctional beats occurring at a cycle length of less than 350 ms or with transient VA are an indicator of potential AV block [16]. It is also useful to monitor the AH interval during ablation. Ablation should stop in the event of any prolongation of the AH interval or if there is a sudden increase or reduction in impedance.

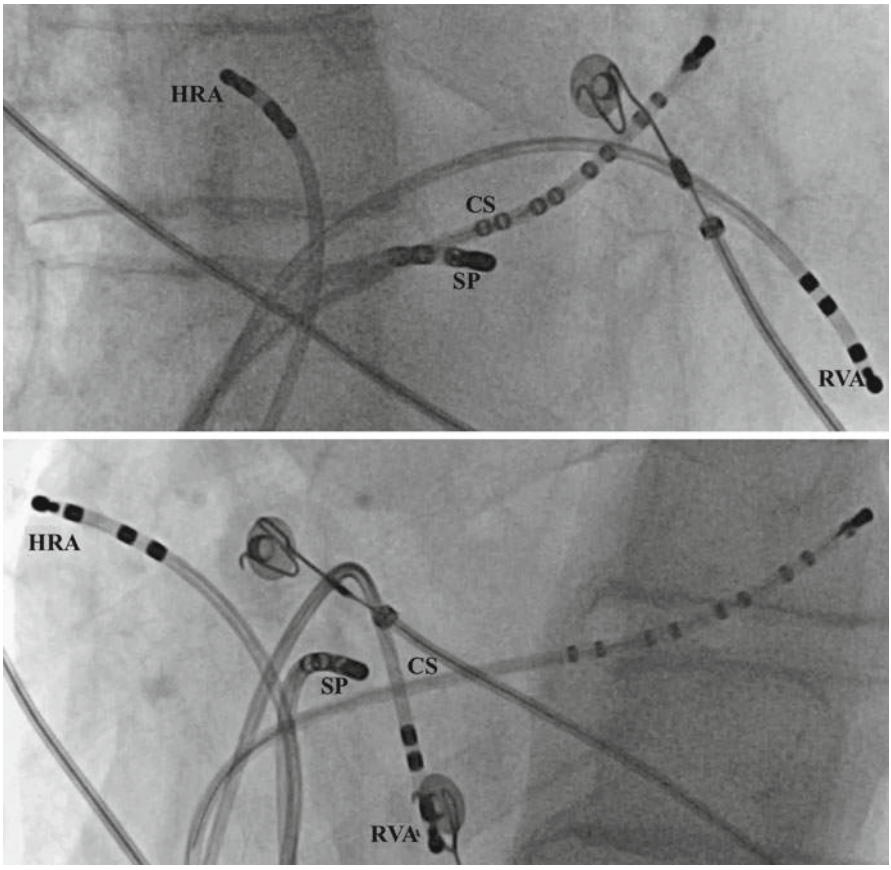

Fig. 4.5 Fluoroscopic location of ablation catheter when mapping the slow pathway. The ablation catheter is recording a A:V ratio with a small slow pathway potential. The *top image* is an RAO view and on the *bottom image* is an LAO view. In both views the ablation catheter is seen anterior to the coronary sinus os. Also seen in the image is a quadripolar catheter in the high RA, RV apex and a decapolar catheter in the coronary sinus

If there are no junctional beats during ablation alternative sites should be chosen. This generally involves a more superior position although this increases the risk of AV block and caution above the level of the roof of the coronary sinus should be taken.

Other potential locations for the slow pathway are the leftward inferior extension which can often be successfully ablated in the proximal coronary sinus.

If AVNRT develops ablation should stop due to catheter instability as well as a difficulty in establishing early signs of AV block.

AV block may be due to ablation injury of the compact AV node or may reflect underlying poor fast pathway conduction. AV block occurring at a more inferior position, including within the coronary sinus os may occur due to a posterior fast pathway variant or as a result of the effects of ablation on the AV nodal artery.

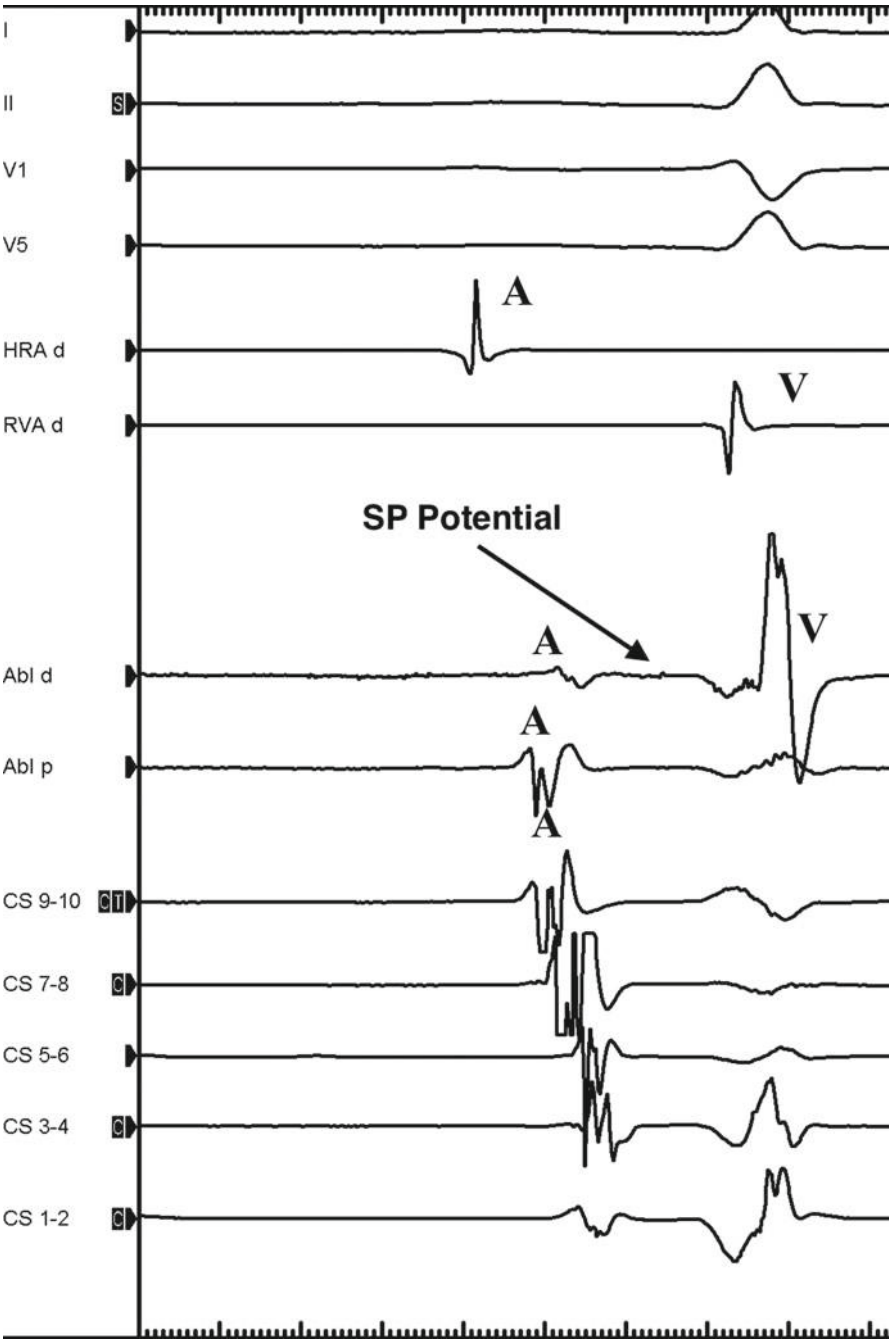

Fig. 4.6 Mapping of the slow pathway. The ablation catheter is positioned anterior to the coronary sinus with an A:V ratio of 1:6. On the first beat there is a small discrete potential recorded on the distal ablation catheter where is in keeping with a slow pathway potential. Ablation at this location was successful in slow pathway modification with no further inducible AVNRT

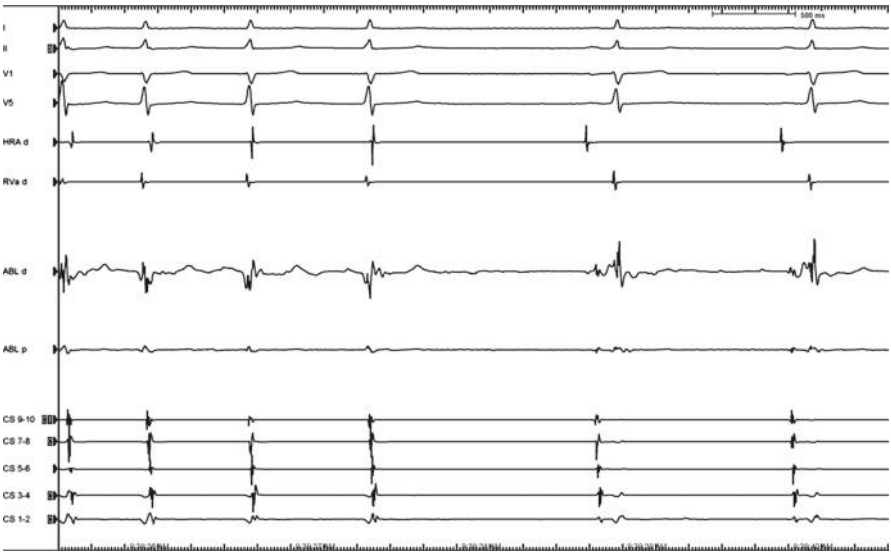

Fig. 4.7 Junctional beats seen during RF ablation at the site of a slow pathway ablation. Following the first 4 beats of junctional rhythm normal sinus rhythm resumes with 1:1 AV conduction. This is generally considered a sign of a good ablation. (HRA d is positioned at the high right atrium, RVa d is positioned at the RV apex, CS 9 10 is positioned at the proximal CS while CS 1 2 is positioned at the distal CS)

Ablation Endpoints

Following application of RF with good target temperatures and junctional beats a repeat EP study should be performed to try to re-induce the tachycardia using the same protocol as pre-ablation. If tachycardia cannot be re-induced this is a good endpoint. The presence of an AH jump or an atrial echo beat can still be considered reasonable as these may often be due to other slow pathways which may be clinically not significant such as a left inferior extension.

Isoprenaline should always be administered at the end of the procedure even if it was not required for induction of the tachycardia at baseline.

Trouble Shooting the Difficult Cases

The main anatomical difficulties which may arise are often related to a large coronary sinus os, difficult to reach slow pathways, close proximity between the slow and fast pathways and variability in the location of the slow pathway.

In general a slight clockwise rotation is required when applying ablation to the slow pathway. In cases where the CS os is large it can be difficult to maintain a

stable position and often a balanced clockwise with counterclockwise rotation is required. In extreme cases a long sheath may be helpful in order to maintain catheter stability.

Occasionally ablation at the conventional slow pathway location results in junctional beats but with still further inducible AVNRT. In these cases a more superior approach is required. This most likely targets the junction of the right and left inferior extensions rather than just the right inferior extension. If a higher position is unsuccessful the roof of the proximal coronary sinus (1–3 cm from the coronary sinus os) may result in a successful ablation.

In some very rare cases the slow pathway has a left sided insertion point and therefore cannot be successfully ablated from any sites on the right side of the interatrial septum. In these cases either transseptal or trans aortic access if required with mapping of the earliest atrial activation during AVNRT along the mitral annulus. This may range from septal to inferolateral mitral annulus.

Important Points

1. The triangle of Koch is bounded anteriorly by the septal leaflet of the tricuspid valve, posteriorly by the tendon of Todaro and inferiorly by the superior aspect of the coronary sinus os.
2. The fast pathway is located in the anterior portion of the triangle of Koch. The slow pathway is generally located anteriorly to the CS although may have a variable course including within the CS.
3. An AH jump is defined as an increase in the AH interval of greater than or equal to 50 ms in association with a reduction in an atrial extrastimuli of 10 ms during decremental atrial pacing.
4. Discontinuous AV conduction curves are not present in all patients with proven AVNRT
5. The presence of two or more AV nodal pathway may be present in patients without AVNRT
6. In Slow/Fast AVNRT (Typical AVNRT) a PAC travels antegradely along the SP with retrograde activation along the FP. This generally results in a short VA tachycardia with the earliest atrial activation along the superior septum posterior to the Tendon of Todaro
7. In Fast/Slow AVNRT (Atypical AVNRT) antegrade conduction occurs down the FP and retrograde conduction occurs up the SP with a long VA time during tachycardia.
8. In Slow/Slow AVNRT antegrade conduction occurs antegradely down the rightward inferior extension and retrogradely up the leftward inferior extension with a long VA time and the earliest activation often anterior to the CS.
9. SP ablation is generally performed using a 4 mm non-irrigated ablation catheter is positioned between the CS os and the tricuspid annulus with

an A:V ratio of 1:2 to 1:10 and ideally a SP potential. RF is generally started at 30 W with a maximum temperature set at 60 C. This can be increased to 40 W and occasionally 50 W is required.

10. Junctional beats during ablation are most likely due to conduction of current injury from the SP to the AV junctional area enhancing diastolic depolarization of the cells in this region and are generally considered a indicator of SP modification.
11. Accelerated Junctional beats occurring at a cycle length of less than 350 msec or with transient VA are an indicator of potential AV block.
12. The most useful endpoint following SP ablation is lack of inducibility of the tachycardia. The presence of an AH jump or an atrial echo beat can still be considered reasonable as these may often be due to other slow pathways which may be clinically not significant such as a left inferior extension.

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Chapter 5
Accessory Pathway (AP) Conduction

Benedict M. Glover and Pedro Brugada

Abstract Ventricular pre-excitation occurs as a result of an extranodal accessory pathway connecting the atrium with the ventricle along the AV groove. Although the baseline ECG may be normal, the common features seen are a short PR interval during normal sinus rhythm, slurring of the initial portion of the QRS complex resulting in a delta wave, a QRS duration greater than 120 ms in adults, and secondary ST and T wave changes, all of which result from a combination of eccentric accessory pathway and midline AV nodal conduction. Ventricular pre-excitation in association with a history of palpitations is named the Wolff–Parkinson–White (WPW) syndrome.

Anatomy

Accessory pathways are muscle fibers which connect the atrium to the ventricle through the fibrofatty and fibrous parietal AV junctional regions. They are generally up to 3 mm in diameter and up to 1 cm in length [1].

They are generally not found in the aortomitral continuity due to the distance between the atrial and ventricular tissues in this region [2]. It has been shown that the majority of accessory pathway's contain ventricular myocytes which function in a similar fashion [3].

Thin extensions of atrial myocardium overlie thicker ventricular myocardium at the right anterior, mid, and posterior septum. The left anterior and left mid septal regions tend to have fibrotic tissue and therefore it is unusual to find AP's in this location.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_5

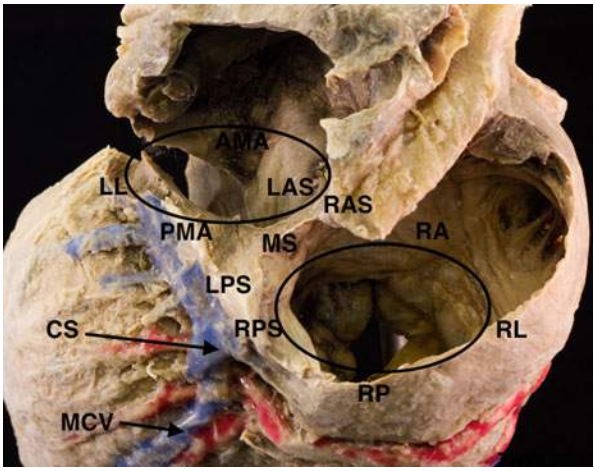

Fig. 5.1 Anatomical specimen with the posterior wall of the right atrium and left atrium removed. *On the left side* AP's may be located in the left lateral (*LL*), anterior mitral annulus (*AMA*), posterior mitral annulus (*PMA*) as well as left anteroseptal (*LAS*) and left posteroseptal (*LPS*). *On the right side* accessory pathways may occur in the right anterior (*RA*), right lateral (*RL*), right posterior (*RP*), right anteroseptal (*RAS*) and right poseroseptal (*RPS*). Mid septal (*MS*) pathways are generally located on the right side but may also be left. Also shown on the image are the coronary sinus (*CS*) and the middle cardiac vein (*MCV*)

The majority of accessory pathways are located within the endocardial atrioventricular fat pad close to the atrioventricular junctions. The anatomy of the tricuspid and the mitral annuli is shown in Fig. 5.1 with the superimposed traditional locations of AP's.

The traditional description of accessory pathway locations has been dependent on a combination of anterior to posterior and left to right in which the coronary sinus is the most posterior landmark and the aortic valve the most anterior. In the LAO view posterior is therefore seen as being at the most inferior location along both the mitral and tricuspid annulus while anterior is located at the most superior aspect. In this view septal is in the centre of the image with lateral being located at the periphery. In reality what is described as anterior is actually superior. As the left atrium is actually posterior to the right atrium what is described as right lateral should in fact be described as right anterior while left lateral is in fact left posterior. This is shown in Fig. 5.2.

Less common accessory pathway locations are shown in Fig. 5.3.

Mechanisms

During normal sinus rhythm, conduction may occur antegradely down the AP as well as through the AV node, resulting in **manifest pre-excitation** on the ECG. Occasionally, this may not be evident as the time taken for conduction through

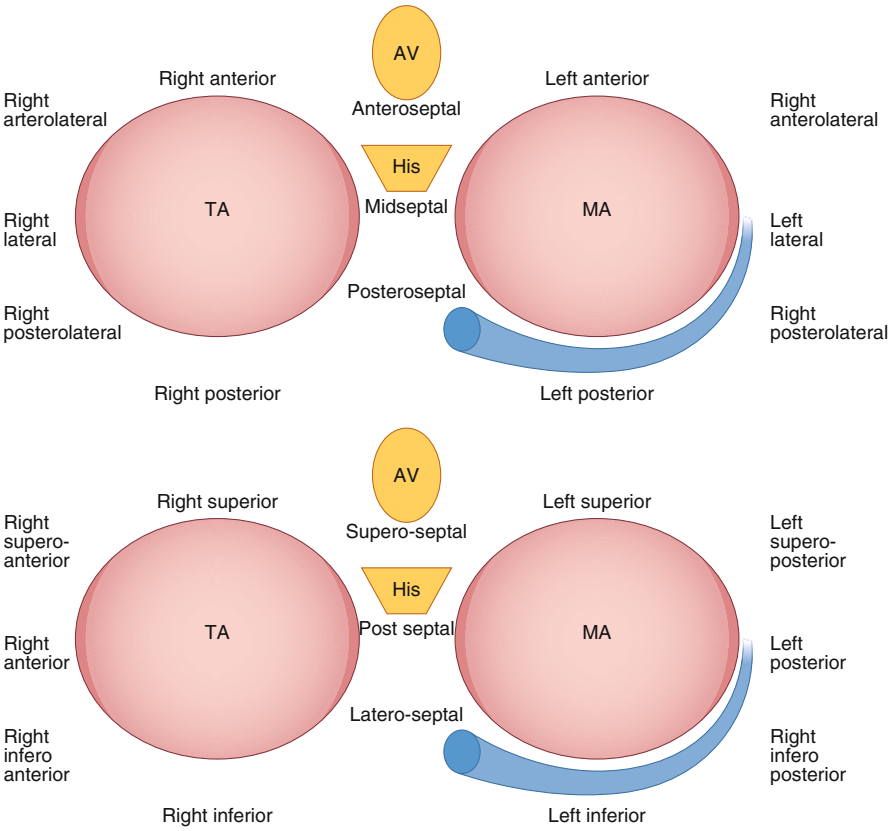

Fig. 5.2 Schematic in LAO view showing Attitudinally Correct (*top*) and historic (*bottom*) locations of Accessory Pathways along the Tricuspid and Mitral Annulus (*TA* tricuspid annulus, *MA* mitral annulus, *AV* atrioventricular)

the accessory pathway is so long that the ventricle has depolarized through the AV node such as in a slowly conducting left lateral accessory pathway. This is called **latent pre-excitation** as the 12-lead ECG during normal sinus rhythm may appear normal. If the AP conducts retrogradely during normal sinus rhythm the ECG will also appear normal and this is called **concealed pre-excitation**. Generally concealed accessory pathways are not capable of conducting AF with pre-excitation. The majority of accessory pathways have antegrade and retrograde properties. Diagrammatic representation of the predominant direction of conduction of accessory pathways is shown in Fig. 5.4.

Orthodromic AVRT occurs when the antegrade accessory pathway is refractory and conduction occurs antegradely through the AV node activating the His and ventricle and retrogradely along the accessory pathway if it is no longer refractory. This is shown in Fig. 5.5. The VA time required for this to occur is generally greater

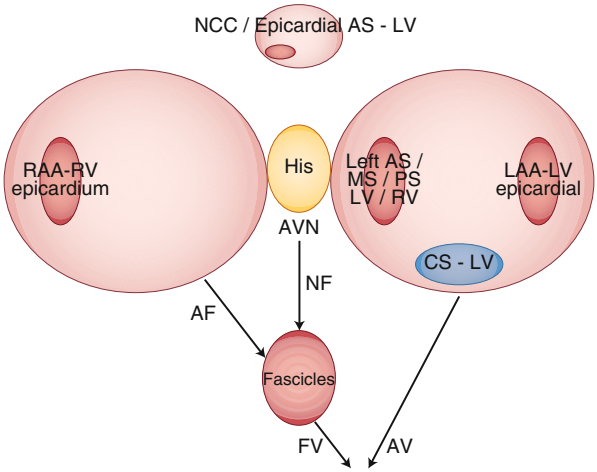

Fig. 5.3 Unusual locations of accessory pathway connections including right atrial appendage (*RAA*) to right ventricular (*RV*) epicardium, the non coronary cusp (*NCC*)/epicardial anteroseptal to left ventricle (*LV*), left sided anteroseptal, midseptal and posteroseptal to left ventricle or right ventricle, left atrial appendage (*LAA*) to left ventricular (*LV*) epicardium, coronary sinus (*CS*) to left ventricle (*LV*) as well as atriofascicular (*AF*), nodofascicular (*NF*), atrioventricular (*AV*) and fasciculoventricular (*FV*) pathways

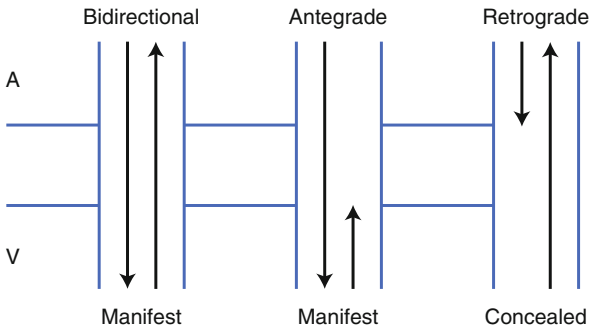

Fig. 5.4 Direction of conduction in accessory pathways. Bidirectional (antegrade and retrograde) resulting in manifest pre-excitation, antegrade only resulting in manifest pre-excitation and retrograde only resulting in concealed conduction

than 70 ms. Despite slight changes in antegrade conduction via the AV node the VA time which represents the time taken to conduction along the accessory pathway is generally stable and does not change.

In antidromic AVRT conduction occurs antegradely via the accessory pathway as the AV node is refractory. This is generally associated with a pre-excitated QRS as conduction is only via the accessory pathway. Ventricular conduction and retrograde His conduction may conduct via the AV node provided it is no longer refractory. HA times are generally greater than 70 ms as conduction is via the VA node. This is more commonly seen in left lateral accessory pathway's as the longer conduction is required to allow the AV node to recover.

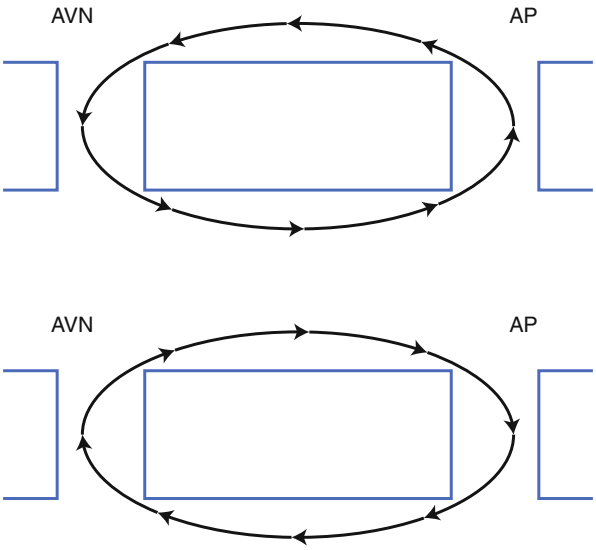

Fig. 5.5 Mode of conduction of circuit in AVRT. Orthodromic reciprocating tachycardia (*Top image*) in which antegrade conduction occurs through the AV node and retrograde through the accessory pathway and Antidromic Reciprocating Tachycardia (*Bottom image*) in which antegrade conduction occurs down the accessory pathway and retrograde through the AV node

Classification

Accessory pathway's are classified according to their anatomical location, direction of conduction, conduction properties and mechanism of action during tachycardia.

Anatomically these are divided into septal (paraseptal) which include posteroseptal, midseptal and anteroseptal, left lateral (left posterior), left posterolateral (left infero-posterior), left posterior (left inferior), left anterolateral (left superoposterior) and left anterior (left superior). The equivalent locations are also possible on the right side using similar nomenclature. Additionally some accessory pathways may be directly connected into the specialized conduction system such as atriofascicular, atrioventricular, nodoventricular and fasciculoventricular pathways. Accessory pathway's may also be located in unusual anatomical locations involving epicardial connections between the coronary sinus and the left ventricle, the non-coronary cusp of the aortic valve to the left ventricle, the right atrial appendage to right ventricle or left atrial appendage to left ventricle.

Accessory pathways can also be described according to the direction of conduction. While most accessory pathway's may conduct in both directions concealed retrograde accessory pathways are more common in the left lateral position. Almost all accessory pathways exhibit rapid and non-decremental conduction but a few paraseptal pathways may have slow decremental conduction somewhat like the AV node.

Finally accessory pathways may be described according to the direction of conduction during tachycardia with orthodromic AVRT much more common than antidromic AVRT.

Electrophysiological Evaluation

Baseline ECG

The location of the accessory pathway can be estimated from the ECG based on the polarity of the delta wave. This is measured 20 ms from the onset from the delta wave. Additionally an exercise stress test and Holter may be used for non invasive monitoring. The presence of intermittent pre-excitation on an ECG or Holter during sinus rhythm suggests that rapid antegrade conduction of atrial fibrillation through the AP is less likely to occur. The shortest pre-excited R-R interval (SPERRI) may be measured on an ECG or Holter although it is more commonly assessed during invasive EP measurements. A measurement less than 220 ms or 220–250 ms may be associated with a higher risk of rapid antegrade conduction during AF and ventricular fibrillation. Abrupt loss of preexcitation on an exercise stress test indicates preferential AV node conduction rather than antegade AP conduction with increasing sympathetic stimulation.

Algorithms

Localization of the accessory pathway on the 12 lead ECG is useful in order to help plan the EP study and ablation. Several algorithms have been developed to help predict the location of the accessory pathway based on the 12 lead ECG during normal sinus rhythm. These generally use the axis of the delta wave, the R wave transition and the QRS morphology which is dependent on the ventricular insertion point of the accessory pathway and the degree of fusion of accessory pathway conduction with AV node conduction. Given the variability in anatomy, as well as differences in underlying ECG patterns, the possibility of more than one accessory pathway and variability in the conduction properties of the AV node as well as the accessory pathway itself no algorithm is 100 % accurate. An example of a useful and practical algorithm for accessory pathway localization is shown in Fig. 5.6.

The polarity of the delta wave is measure 20 ms after the initial onset and is described as either positive, negative or isoelectric.

In general a negative or isoelectric delta wave in certain ECG leads implies that the ventricular activation is originating from that location.

A negative or isoelectric delta wave in leads I, aVL and V6 implies a left lateral accessory pathway or less commonly an anteroseptal accessory pathway. In order to differentiate between these, the QRS morphology should be examined. An atypical

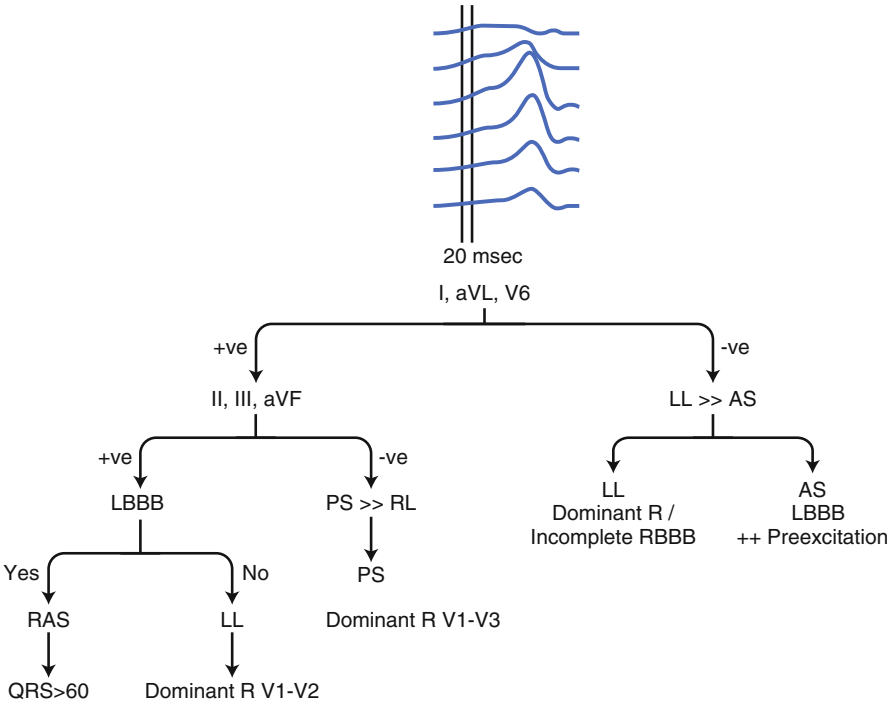

Fig. 5.6 Algorithm to estimate the location of an accessory pathway from the delta wave polarity. The first stage relies on interpretation of the delta wave in leads I, aVL and V6. If this is negative then the accessory pathway is located either in the left lateral (*LL*) location of less likely in an anteroseptal (*AS*) location. A left lateral location is more likely to have either a dominant R wave in V1 or V2 or an incomplete RBBB. An anteroseptal accessory pathway is more likely to have a LBBB pattern and more prominent pre-excitation when compared with a left lateral accessory pathway. If the delta wave is positive in leads I, aVL and V6 then the inferior leads II, III and aVF should be examined. A negative delta wave in these leads indicates either a posteroseptal (*PS*) or right lateral (*RL*) location. A posteroseptal location is more likely than a right lateral and tends to have a dominant R wave in V1–V3. If the delta wave is positive in the inferior leads then the ECG is analyzed for a LBBB pattern. The absence of a LBBB is likely to represent a left lateral location in which there is a dominant R wave in V1–V2. If there is a LBBB this is likely a right anteroseptal (*RAS*) location in which the QRS axis tends to be greater than 60°

LBBB and the presence of more manifest pre-excitation generally points towards a right anteroseptal accessory pathway. The presence of an incomplete RBBB or a dominant R wave in V1 generally points towards a left lateral accessory pathway. More posterior locations tend to have a negative or isoelectric delta wave in the inferior leads as these are more inferior locations while more anterior locations will have a positive delta wave in the inferior leads as these locations are more superior.

If the delta wave is positive in the lateral leads then the inferior leads should be examined. If the delta wave in the inferior leads is negative or isoelectric in the presence of a positive delta wave in the lateral leads then the accessory pathway is most

likely posteroseptal or less commonly right lateral. In order to differentiate a posteroseptal accessory pathway from a right lateral there is more of a tendency for a dominant R wave in V1–V3 in posteroseptal accessory pathway's.

If the delta wave is positive in the lateral leads and positive in the inferior leads then the ECG should be examined for the presence of a LBBB. If there is a LBBB with a QRS axis greater than 60° then the accessory pathway is likely to be located in the right anteroseptal position [4]. The absence of a LBBB with a dominant R wave in V1 or V2 implies that this is likely a left lateral accessory pathway.

ECG Features of Posterospetal Accessory Pathway's

As shown in Fig. 5.7 the delta wave in posteroseptal accessory pathway's is generally negative in III, with a smaller R than S wave in lead II and an R:S ratio in V2 greater than 1. Not all posteroseptal pathways follow this exact pattern.

The majority of posteroseptal accessory pathway's have negative P waves in the inferior leads during tachycardia.

The majority of posteroseptal pathways can be ablated from the right side. It is important to try to differentiate right sided and left sided posteroseptal accessory pathway's. Although this is difficult to conclude from an ECG it has been suggested that a negative delta wave in V1 may favor a right sided AP while a positive delta wave in V1 maybe more suggestive of a left sided AP [5]. An R wave greater than S wave in V1 is suggestive of a left sided accessory pathway as is a narrower QRS in V1. A positive delta wave in II with a negative delta wave in III is also more suggestive of a right sided posteroseptal accessory pathway.

Fig. 5.7 ECG of posteroseptal accessory pathway. There is a negative delta wave in lead III. Although the positive delta in V1 is suggestive of a left sided location the fact that the R wave in V1 is less than the S wave and the positive delta wave in lead II with a negative delta in lead III are more suggestive of a right sided posteroseptal pathway

Coronary Sinus Accessory Pathways

Some posteroseptal accessory pathways are within the coronary sinus. These accessory pathways tend to utilize electrical connections between the ventricle and the coronary sinus and the coronary sinus and the atria. Although the majority of accessory pathways involving coronary sinus connections do not occur in the presence of a coronary sinus diverticulum it is worth checking for this anomaly (Fig. 5.8). These diverticula contain fibres which connect to the coronary sinus myocardial coat and the ventricle. The coronary sinus myocardial coat is generally connected to both atria unless previously disconnected by ablation. There are certain ECG features which may help suggest that a CS connection is involved. The most reliable of them is the presence of a negative delta wave in lead II. As shown in Fig. 5.7 this is not, however, always present. Other features include a steep positive delta wave in lead aVR as well as a deep S wave in V6.

ECG Features of Anteroseptal Accessory Pathway's

Given that anteroseptal accessory pathway's connect from the RA to the RV paraseptal region the delta waves are positive in the inferior leads II, III and aVF as well as the lateral leads I, aVL and V3–V6. An example of an ECG in a patient with an anteroseptal accessory pathway is shown in Fig. 5.9.

ECG Features of Mid-Septal Accessory Pathway's

There is a greater degree of variability in the ECG patterns of mid-septal accessory pathway's reflecting the variability in the atrial and ventricular insertion points and course within this region. In general there are positive delta waves in lead II as well as in the lateral leads with an earlier praecordial transition from V2–V6. Unlike anteroseptal accessory pathways the delta wave is negative in lead III.

ECG Features of Left Lateral Accessory Pathway's

The most important ECG feature of a left lateral accessory pathway is a negative delta wave in leads I, aVL and V6. Additionally, the delta wave in V1 is positive with an R wave greater than S wave in V1. Figure 5.10 shows an example of a left anterolateral accessory pathway. More posterior left lateral accessory pathways are negative in the inferior leads. Anterior accessory pathways are positive in the inferior leads. A negative P wave in lead I during tachycardia is a feature of an ORT involving a left lateral accessory pathway. The first beat shows pre-excitation with a positive delta and R wave in V1 and a positive delta wave in lead II. With the application of RF the next beat shows loss of pre-excitation.

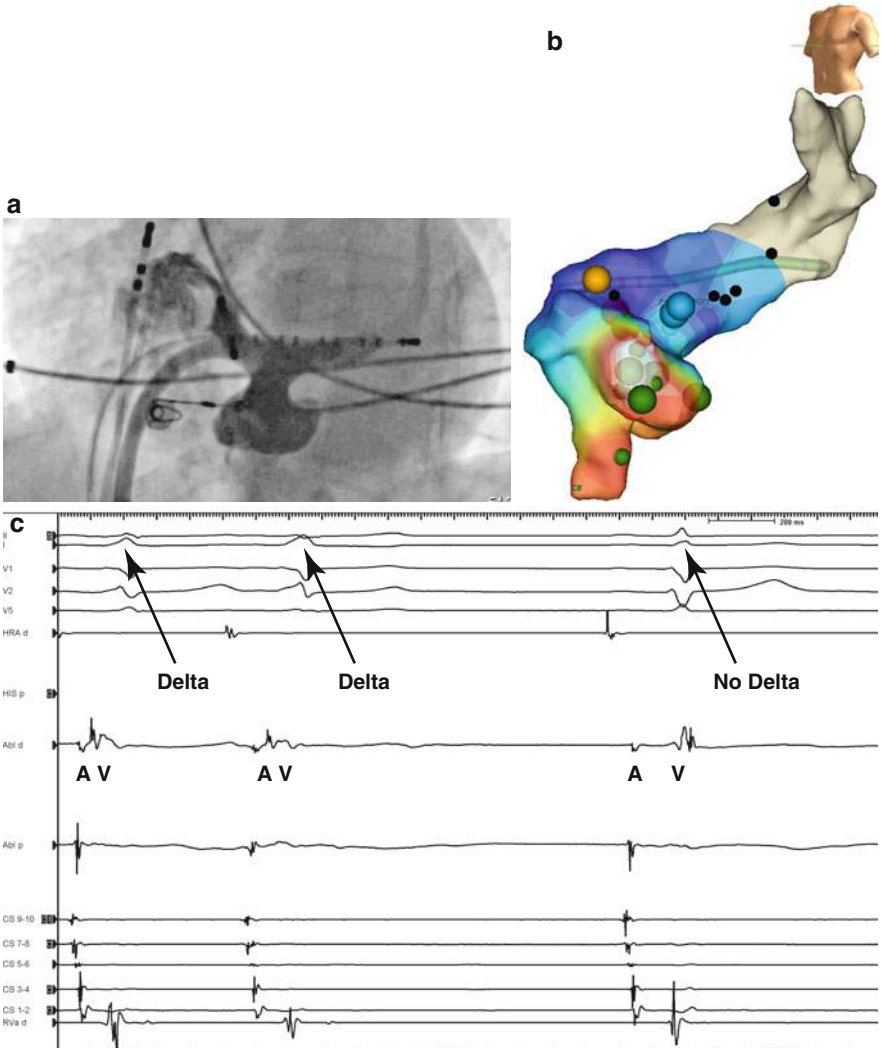

Fig. 5.8 Pre-excitation involving an accessory pathway located on the epicardial surface of a CS diverticulum. Panel **a** shows a venogram of the diverticulum in a PA view which is also shown in the electroanatomic map (Panel **b**). The ECG (Panel **c**) shows clear pre-excitation with a positive delta wave in lead II followed by a slight negative deflection. There is loss of pre-excitation during the third beat with an increase in the AV interval

ECG Features of Right Freewall Accessory Pathways

It can be difficult to differentiate right free wall accessory pathway's from other accessory pathway's. This is because a positive delta wave in V1 may also occur in left lateral accessory pathway's. In order to differentiate these the R wave in V1 should be less than the S wave with a late precordial transition. The delta wave is also positive in the lateral leads I and aVL. The presence of a positive p wave in lead I

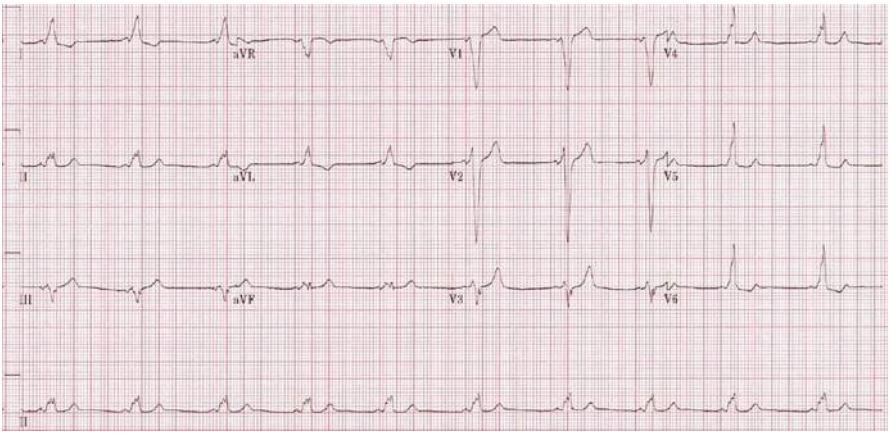

Fig. 5.9 ECG of anteroseptal accessory pathway. There is a LBBB type pattern. The delta wave is positive in lead I and the lateral precordial leads as well as leads II and aVF

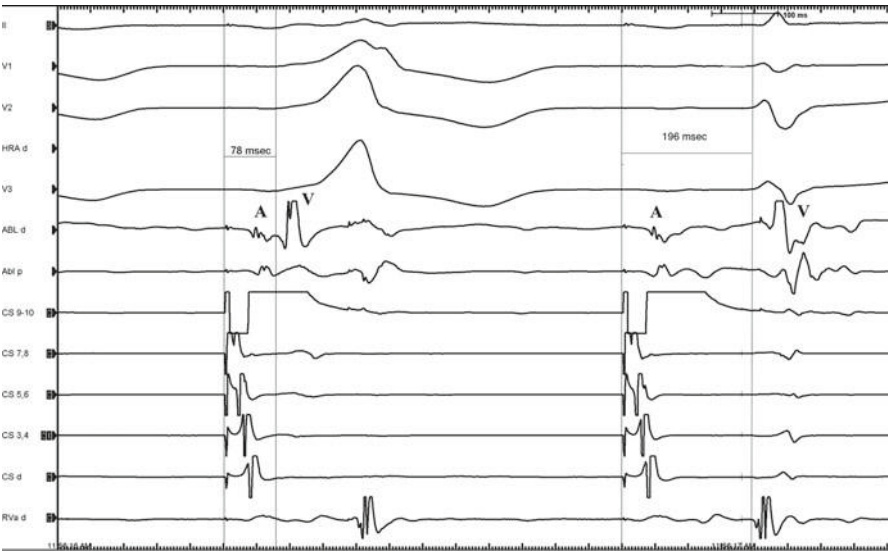

Fig. 5.10 ECG and intracardiac electrograms of ablation being performed for a left anterolateral accessory pathway. The first beat is pre-excited with a positive delta and R wave in lead V1 and a positive delta wave in lead II. Coronary sinus activation is from proximal to distal as a result of atrial pacing with ventricular activation earliest in the distal coronary sinus. There is a short AV interval at the site of the ablation catheter The second beat shows loss of pre-excitation with RF ablation. The surface ECG normalizes with AV prolongation and although the atrial activation in the CS is the same the ventricular activation is proximal to distal implying activation through the AV node. The atrial stimulation to surface QRS is measured and is prolonged from the pre-excited beat at 78–196 ms during normal AV conduction. (CS 9–10 is positioned in the proximal CS while CS 1 2 is located in the distal CS, RVa d is located in the RV apex)

Fig. 5.11 ECG of right lateral accessory pathway. There is a large S wave in lead V1 with a small R wave. Precordial transition occurs in lead V3. There is a positive delta wave in leads I, aVL and the lateral precordial leads

during tachycardiais suggestive of a right freewall accessory pathway. An example of pre-excitation in a patient with a right freewall accessory pathway is seen in Fig. 5.11.

Risks of EP Study and Ablation

The most common complication is that of groin haematoma and vascular injury in approximately 1.4 % [6], particularly if a transaortic retrograde approach is used. The overall risk of thrombo-embolism is 0.6–0.8 % [7], which is generally not of any clinical significance on the right side but on the left side could result in a cardio-embolic stroke or TIA.

The risk of AV block is highest for septal pathways and virtually zero for left lateral accessory pathway's (provided that AV nodal conduction is intact at baseline).

Ablation, particularly if performed within the coronary sinus may result in coronary stenosis or spasm. The incidence of coronary artery injury is 0.06–0.1 % in adults. This generally occurs acutely or shortly after an ablation. Delayed coronary injury as a result of intimal hyperplasia which may increase the risk of coronary thrombosis may present weeks later.

The overall success rate for ablation is approximately 85–95 % and is highest for a left lateral AP and lowest for a posteroseptal accessory pathway.

Diagnostic EP Study

A quadripolar catheter is positioned in the RV septum, a quadripolar in the HRA and a decapolar catheter in the coronary sinus. The RV quadripolar or ablation catheter can be positioned along the His in order to measure the AH and HV intervals. In

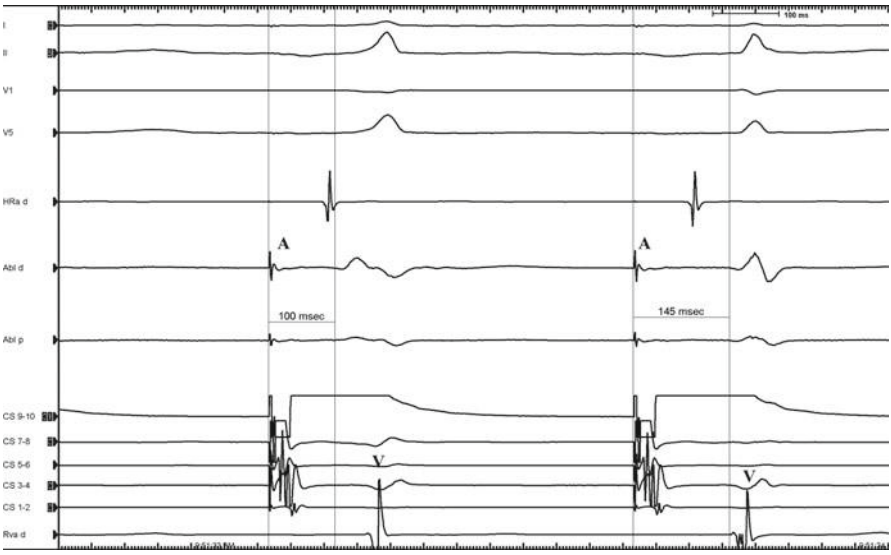

Fig. 5.12 Effective refractory period of the accessory pathway. Decremental pacing from the proximal coronary sinus shows that the first beat is pre-excited with an AV interval of 100 ms. The following beat shows a normal QRS complex with a longer AV interval of 145. At this point antegrade conduction is through the AV node and the accessory pathway is refractory at a cycle length of 480 ms

cases of manifest pre-excitation baseline measurements show a **HV interval that is less than 35 ms** which may even be negative. In order to calculate the accessory pathway ERP an atrial extrastimulus is performed. As the S2 is reduced the AH interval prolongs however the HV interval shortens so that the AV interval is unchanged provided that there is still antegrade accessory pathway conduction. The **antegrade accessory pathway ERP** is defined as the maximum atrial cycle length which results in lack of conduction along the accessory with conduction only along the AVN. This is seen as loss of pre-excitation with normalization of the AH and HV intervals. Figure 5.12 demonstrates loss of pre-excitation with decremental pacing and prolongation of the AV interval as antegrade conduction moves from a combination of AV node and accessory pathway to AV node only. If AV conduction is lost with no normalization of the QRS then the AVN RP is less than or equal to the AP ERP.

Atrial pacing should be performed from both the catheter in the right atrial appendage and the distal coronary sinus as pre-excitation may be more prominent depending on the direction of antegrade atrial pacing. Additionally, there will be a change in the morphology of the QRS or direction of ventricular activation if more than one accessory pathway is present.

Ventricular pacing will reveal the predominant activation sequence of retrograde conduction and may help to localize the accessory pathway as well as calculate the retrograde accessory pathway ERP.

Following this, attempts are made in order to induce AVRT. During decremental atrial pacing antegrade block of the accessory pathway may occur with conduction

antegradely through the AV node. This then activates the ventricle and may conduct retrogradely up the accessory pathway if it is no longer refractory. This may conduct further antegradely through the AV node if it is no longer refractory resulting in an orthrodromic AVRT. Less commonly, with atrial pacing the AV node is refractory and conduction occurs antegradely down the accessory pathway with conduction retrogradely through the AV node resulting in an antidromic AVRT.

Differentiation Between AVNRT and AT

Parahisian pacing may be performed during normal sinus rhythm in order to differentiate between VA nodal conduction and retrograde accessory pathway conduction. Decremental ventricular pacing during sinus rhythm may be useful in order to assess for decrement versus non decremental conduction but is not foolproof as some accessory pathway's have decremental retrograde conduction and also the accessory pathways may not be involved in the tachycardia mechanism. If a tachycardia can be induced a His refractory PVC may be introduced in order to assess if this has any effect on the atrial activation. A His refractory PVC which advances or delays the next atrial depolarization without changing the activation sequence is indicative of an AVRT. Also a His refractory PVC which terminates the tachycardia is indicative of an AVRT. If the PVC advances the next atrial depolarization only by advancing the local His i.e., the His is no longer refractory by an amount slightly greater than the degree of His advancement, then the most likely mechanism is an AVNRT. As shown in Fig. 5.13 in the case of a posteroseptal accessory pathway RV entrainment can be performed during tachycardia with a V-A-V response and a PPI-TCL less than 115 ms.

Mapping the Accessory Pathway

If an accessory pathway is perpendicular to the AV groove then mapping can be performed by localizing the earliest atrial signal during ventricular pacing or mapping the earliest ventricular signal during sinus rhythm or during atrial pacing.

When mapping along the annulus an atrial and ventricular signal are evident. When the catheter is positioned at the location of the accessory pathway then the atrial and the ventricular signals are close together and often merged.

The shortest AV or VA is not always the perfect location for ablation particularly given that a significant percentage of accessory pathway's are oblique and therefore an ideal electrogram also has an accessory pathway potential. This should be recorded between these signals prior to ablation being performed. If this signal disappears with loss of pre-excitation then it is likely an accessory pathway potential.

In order to check whether the potential is an accessory pathway potential ventricular and atrial extrastimuli can be delivered. During mapping of an accessory pathway

Fig. 5.13 Atrial activation is earliest on the proximal coronary sinus followed by the distal ablation (positioned on the His). The tachycardia cycle length is 279 ms Entrainment is performed from the RV apex at 250 ms The post pacing interval is 323 ms The PPI – TCl is therefore 44 ms which is indicative of an AVRT rather than an AVNRT (HRA p is positioned in the high right atrium, the ablation catheter is positioned in the location of the His, CS 9 10 is located at the proximal CS while CS 1 2 is located in the distal CS and RVa d is located in the RV apex)

during antegrade conduction a late ventricular extrastimuli will advance the ventricular electrogram with no effect on the accessory pathway potential. An early ventricular extrastimuli will advance the accessory pathway potential with no effect on the local atrial electrogram. For mapping of the accessory pathway with retrograde conduction a late atrial extrastimuli will advance the atrial electrogram with no effect on the accessory pathway potential while an early atrial extrastimuli will advance the accessory pathway potential with no effect on the atrial electrogram.

An accessory pathway potential may be mapped in 89 % of all cases provided appropriate pacing maneouvres are performed in order to separate out the signals [8]. In order to separate out the local atrial and ventricular signals and expose the accessory pathway potential pacing can be performed from two different locations in either the atrium of the ventricle. A difference in the local AV interval of greater than or equal to 15 ms without moving the mapping catheter when pacing from two different sites implies an oblique accessory pathway. In order to perform this from the atrium pacing can be performed from the right atrial appendage and the distal coronary sinus. The locations of pacing from the ventricular aspect depends on the location of the accessory pathway.

For left lateral, anterolateral, posteroseptal and RV free wall accessory pathway's a counterclockwise activation is achieved from pacing from the inferobasal RV while in anteroseptal and right anterior septal accessory pathway's counterclockwise activation is achieved by pacing from the parahisian location.

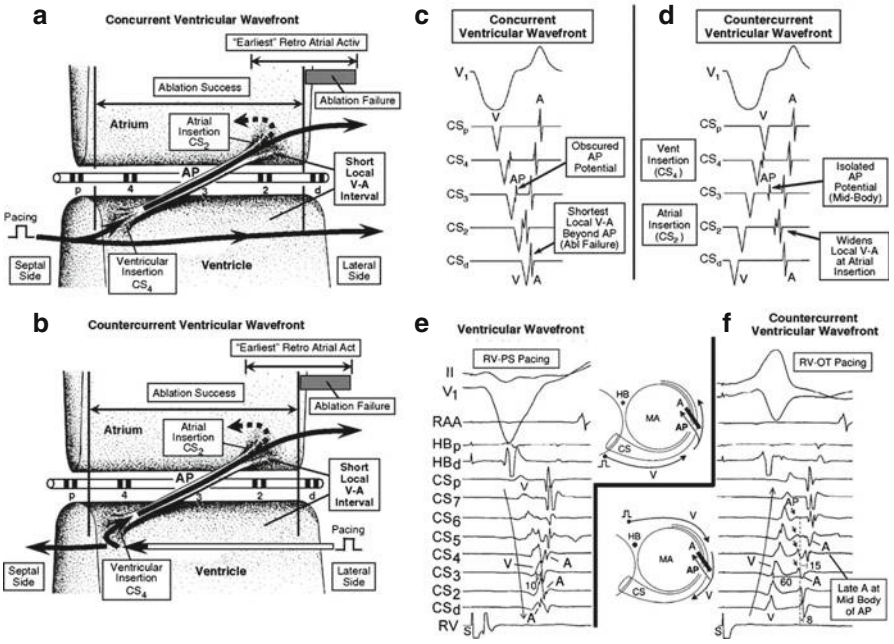

Fig. 5.14 Effects of the oblique course in a left free-wall accessory pathway on the timing of ventricular (*V*), atrial (*A*), and accessory pathway potentials by reversing the direction of the ventricular wave front. (**a**–**d**) Schematic representations. (**e**, **f**) Recordings from a patient with a left lateral accessory pathway. Reversing the ventricular wave front from the concurrent direction (**e**; posteroseptal basal RV pacing [RV-PS]) to the counter current direction (**f**; distal RV outflow tract pacing [RV-OT]) increased the local VA interval at the site in the coronary sinus of earliest atrial activation (electrogram CS3) from 10 to 60 ms and exposed the accessory pathway potential. The ventricular insertion (*left*) was located 15 mm septal to the atrial insertion (*right*). RAA indicates right atrial appendage (**c**–**f**) (Reproduced with permission from Nakagawa and Jackman [9], Wolters Kluwer Health, Inc)

As shown in Fig. 5.14 pacing from lateral to medial in a concurrent direction to the direction of the accessory pathway prolongs the local VA time and therefore exposes the accessory pathway potential. Targeting this region where a potential can be recorded results in a successful ablation of the accessory pathway.

Clockwise activation for left lateral and anterolateral accessory pathway's is achieved by pacing from the RVOT, for posteroseptal accessory pathway's clockwise activation is achieved by pacing from a lateral coronary vein with ventricular capture. For right free wall accessory pathway's clockwise activation is achieved by pacing from the base of the RV septum while for anteroseptal and right anterior septal accessory pathway's clockwise activation is achieved by pacing from the basal anterolateral RV free wall. The optimal ablation location is around the middle of this oblique pathway. In order to separate these potentials pacing can be performed in the opposite direction to course of the accessory pathway [9].

Occasionally mapping has to be performed during tachycardia. This is frequently the case during mapping of an ORT with unreliable VA conduction during RV

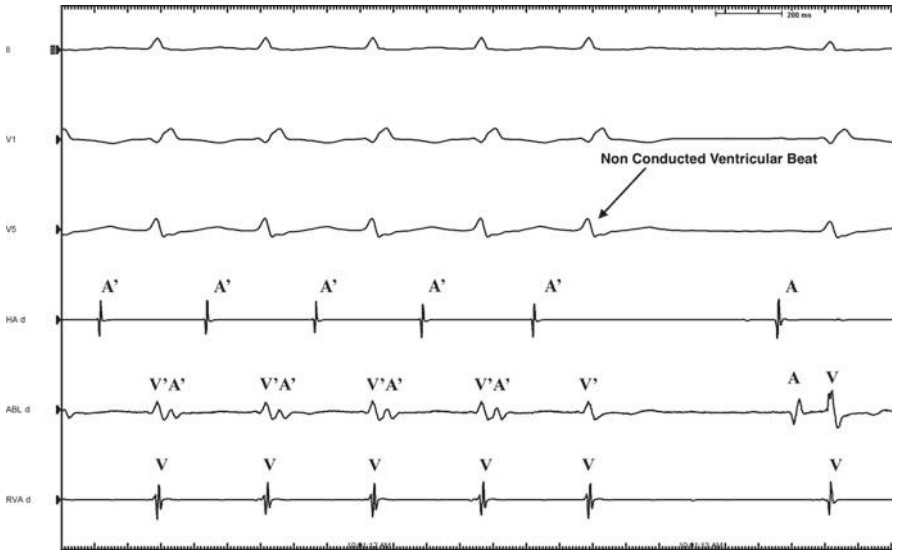

Fig. 5.15 Ablation during orthodromic reciprocating tachycardia in a concealed retrograde left lateral accessory pathway. Mapping is performed during tachycardia looking for the shortest VA interval. Ablation results in block with a non conducted ventricular beat. Thereafter there is sinus rhythm with a normal AV interval is observed. (HRA d is positioned in the high right atrium, ABL d is positioned along the left lateral accessory pathway location and RVa d is located in the RV apex)

pacing. As shown in Fig. 5.15 ablation can be performed during tachycardia looking for the shortest VA interval. If ablation is performed during tachycardia the catheter often falls off the annulus on termination of tachycardia. In order to maintain catheter stability on termination of tachycardia either ventricular pacing can be performed at a faster rate to avoid an abrupt change in the rate and loss of catheter position or further ablation can be performed in the anatomic region during sinus rhythm.

Accessory pathway potentials may be recorded on a unipolar or bipolar electrogram. Both of these can be recorded at the same time but the sharp unipolar signal is more accurate as it reflects the distal pole of the ablation catheter where RF is delivered.

Ablation of Accessory Pathway's

Posteroseptal Accessory Pathway's

These are located between the inferior wall of the right atrium and the superoposterior aspect of the left ventricle [10]. The left border of this region is the left posterior paraseptal region, the right border the right posterior paraseptal region and the anterior and superior border the midseptum.

Local electrograms in this region tend to show a small atrial signal with a large ventricular signal. This occurs as the thin atrial myocardium in this region overlies the thicker ventricular myocardium.

An accessory pathway in this region is posterior to the coronary sinus os and may be either on the tricuspid annular or mitral annular side of the septum. Pacing from the RV catheter and mapping the earliest atrial signal is often unreliable in posteroseptal accessory pathway's. Near simultaneous atrial and ventricular activation in this region results in an AV interval which appears ideal but is not. The optimal approach is targeting of an accessory pathway potential.

As shown in Fig. 5.16 mapping is first performed on the right side of the septum posterior to the coronary sinus and only moved to the left if the accessory pathway cannot be mapped or successfully ablated. Pacing the atrium from either side of the atrial insertion point while mapping for an accessory pathway potential is generally the most accurate method of mapping. Ablation can be performed with 30 W with a target temperature of 60 °C and the power can be titrated up if necessary for a minimum period of 60 s. In general, ablation should be performed during atrial or ventricular pacing during sinus rhythm rather than during AVRT as following cessation of the AVRT the catheter tip can move as sinus rhythm is restored. The patient can be monitored for a period of 30 min with atrial and ventricular pacing to ensure that accessory pathway conduction has not recovered.

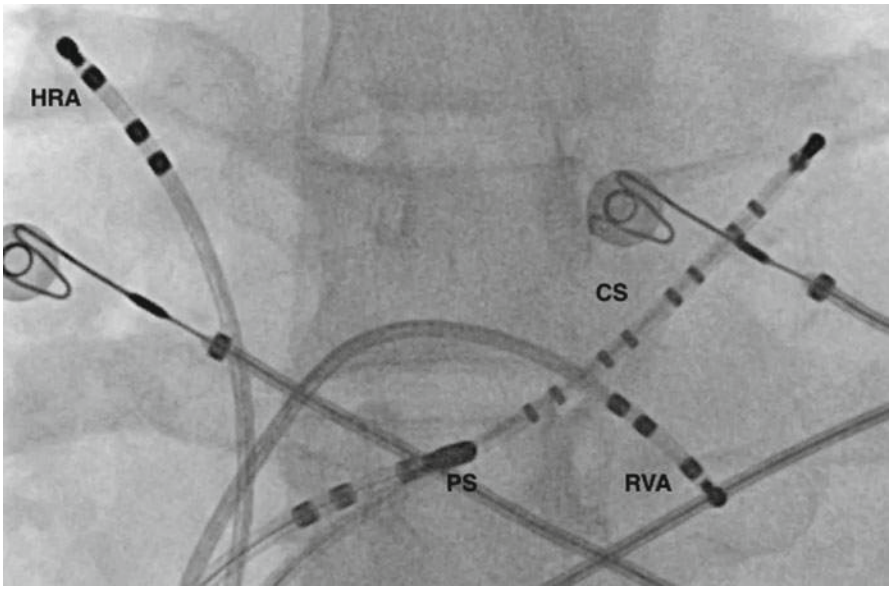

Fig. 5.16 LAO view of a successful site for a right sided posteroseptal accessory pathway. The ablation catheter is posterior to the coronary sinus catheter. A catheter is also positioned in the HRA and the RV Apex

Posteroseptal Accessory Pathway: Difficult Case

Occasionally posterospetal accessory pathways may be subepicardial and involve myocardial connections between the coronary sinus os or within the middle cardiac vein and the epicardium of the left ventricle. In these cases endocardial mapping does not reveal any sites of early activation and the mapping catheter should be advanced into the coronary sinus looking for early ventricular activation during atrial pacing as well as an accessory pathway potential. It is useful to perform a coronary sinus venogram in order to assess for diverticula where accessory pathways may be located. A coronary angiogram should also be performed and ablation should not be attempted if the coronary artery is within 5 mm of the site of ablation. If ablation has to be performed within the coronary sinus at a lower power to 10 W up to a maximum of 25 W irrigated and ablation should be stopped immediately in the event of a rise in the impedance.

Anteroseptal Accessory Pathway

These accessory pathway's are located anteriorly along the central fibrous body close to the His bundle. They are manifest in 80 % of cases in concealed in 20 % and are less common than posteroseptal accessory pathway's.

The difficulty with anteroseptal accessory pathway's is the ability to map them separately from AV nodal conduction and the proximity to the AV node with the potential risk of AV block. The actual His bundle is relatively well insulated and therefore ablation close to the His is generally not high risk. The actual risk is essentially related to potential damage to the compact AV node.

Ablation of an anterospetal accessory pathway can be performed by positioning the ablation catheter in the RV and then curved back on the tricuspid annulus looking for an accessory pathway potential. There is often a small His potential in this region. Mapping can be performed looking for the earliest ventricular signal during sinus rhythm or atrial pacing. The ventricular electrogram should precede the surface delta wave by up to 40 ms.

Midseptal Accessory Pathway

Midseptal Accessory pathway's occur between the His and the CS close to the compact node and therefore carry the highest risk of AV block. In order to minimize this risk the ablation catheter should be positioned with a more dominant ventricular signal. If ablation is unsuccessful despite good contact and a stable position the left side may be mapped.

Mahaim Accessory Pathways

Atriofascicular accessory pathways are the most common of these and account for approximately 80 %. Uncommonly nodofascicular and nodoventricular connections may occur. Fasciuloventricular connections do not seem to present a true clinical issue. Mahaim accessory pathways tend to connect from the lateral tricuspid annulus to or close to the right bundle close to the apex of the right ventricle.

ECG Features

Given that the ventricular insertion point is so close to the right bundle the baseline ECG generally has minimal or no pre-excitation. The degree of pre-excitation increases as the distal insertion point is further from the conduction system. Subtle ECG findings may include a lack of Q waves in the lateral leads V5 and V6. Sometimes a LBBB is present with a normal PR interval. Latent pre-excitation may be seen in Mahaim accessory pathways. Examples of the baseline ECG and the ECG with atrial pacing for atriofascicular and atrioventricular accessory pathways are shown in Fig. 5.17.

EP Study and Mapping of Mahaim

As pre-excitation is often minimal at baseline pacing from the right atrium tends to result in a greater degree of pre-excitation and generally the development of LBBB. Decremental pacing from close to the atrial insertion point tends to result in increasing LBBB as conduction occurs antegradely along the accessory pathway and retrogradely up the right bundle. There is an increase in the AH interval reflecting the decremental conduction and a shortening of the HV interval. If tachycardia is induced the morphology is a LBBB with a superior directed axis.

As these accessory pathways only conduct antegradely the tachycardia is always an antidromic AVRT. The activation sequence is therefore through the pathway into the fascicle followed by retrograde conduction up the right bundle and His followed by the AV node. This activation sequence is useful in order to establish the diagnosis. If an atrial extrastimulus is introduced along the lateral tricuspid annulus whenever the atrial septum is refractory and the extrastimulus advances the tachycardia then there is likely to be a atriofascicular accessory pathway. In order to prove that this accessory pathway participates in the tachycardia a late atrial extrastimulus can be delivered from close to the atrial insertion point of the accessory pathway. If this is advances the ventricular activation and in particular does not advance the His signal during tachycardia then this accessory pathway is participating in the circuit.

Mapping of an atriofascicular accessory pathway may be difficult. Although the right atrium can be paced and the ventricular insertion point can be mapped this does not always prove successful and may cause injury to the right bundle branch with an incessant tachycardia with a longer cycle length conducting retrogradely up the left bundle.

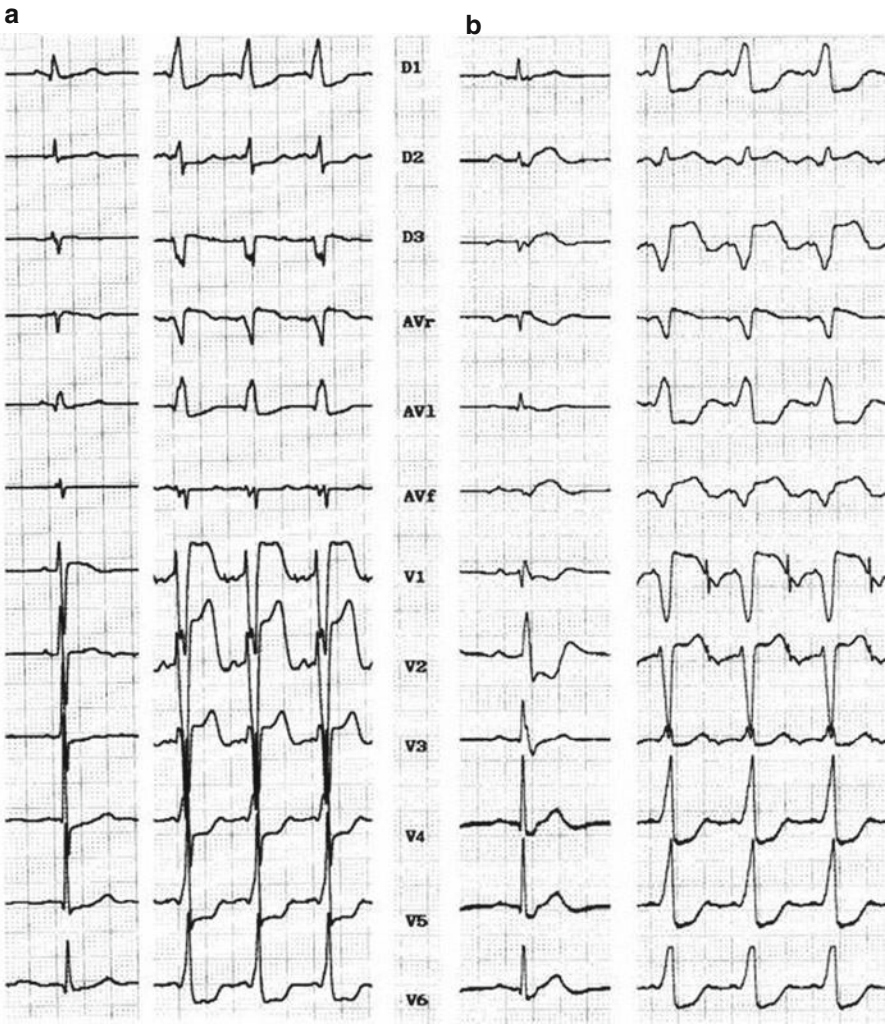

Fig. 5.17 ECG at baseline and with atrial pacing at a faster rate for an atriofascicular pathway in (**a**) and an atrioventricular pathways in (**b**). For an atriofascicular accessory pathway there is minimal preexcitation with a PR interval of 120 ms A LBBB develops with atrial pacing at a faster rate. For an atrioventricular pathway the baseline PR interval is normal with a RBBB. With atrial pacing at a faster rate there is manifest pre-excitation with a LBBB (Courtesy of Sternick [13])

Additionally, given that these pathways do not conduct retrogradely mapping the earliest atrial activation during ventricular activation cannot be performed. The most ideal method is therefore to use a 20 pole catheter along the tricuspid annulus in order to map for a Mahaim potential which is recorded along the length of the accessory pathway.

A Mahaim potential is seen as a sharp deflection between the A and the V which are both widely separated due to the distance between the atrial and ventricular

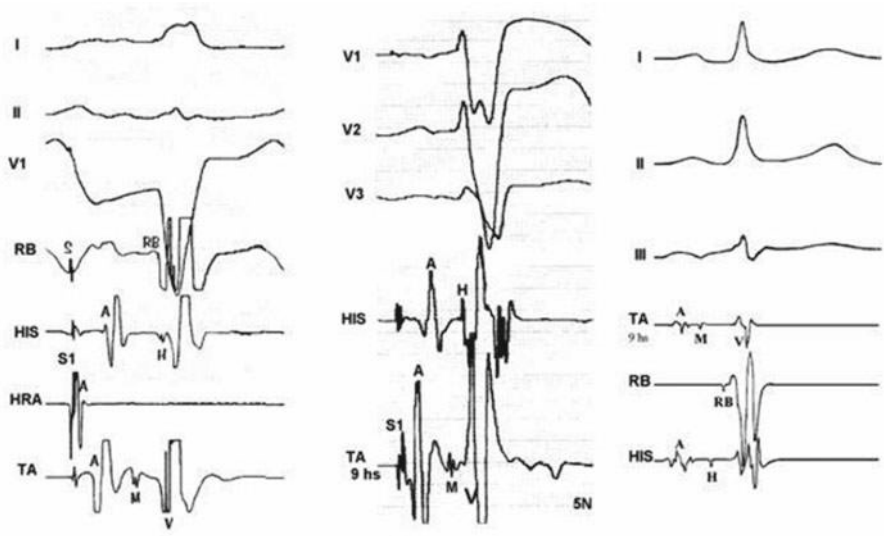

Fig. 5.18 Mahaim (*M*) potentials from left to right: first two cases with His-like potentials and the third with narrow and low amplitude potential. Ablation was successful in each of those sites (*TA* tricuspid annulus electrograms) (Courtesy of Sternick [13])

insertion points. Examples of these are shown in Fig. 5.18. The interval between this potential and the ventricular potential is constant with decremental atrial pacing. Care must be taken when positioning this catheter that the accessory pathway is not bumped and therefore cannot be mapped.

If the Mahaim potential does disappear while bumped with the ablation catheter this is a reasonable location to apply RF. During ablation there is often a slow accelerated rhythm for several seconds known as Mahaim automaticity [11]. This is generally considered a good sign during the application of RF.

Often a sheath is helpful in order to maintain catheter stability along the tricuspid annulus. During ablation transient Mahaim junctional acceleration may occur as shown in Fig. 5.19 which is similar in morphology to the tachycardia. Although a multipolar catheter can be positioned along the tricuspid annulus in order to map the Mahaim potential occasionally electranatomic mapping may also be helpful.

Left Lateral Accessory Pathway

These are the most common accessory pathways with the highest success rate for ablation of 95 % [12]. They may have either minimal pre-excitation given the distance of the ventricular insertion point from the AV nodal conduction. They also have the highest rate of concealed retrograde conduction of all accessory pathway's.

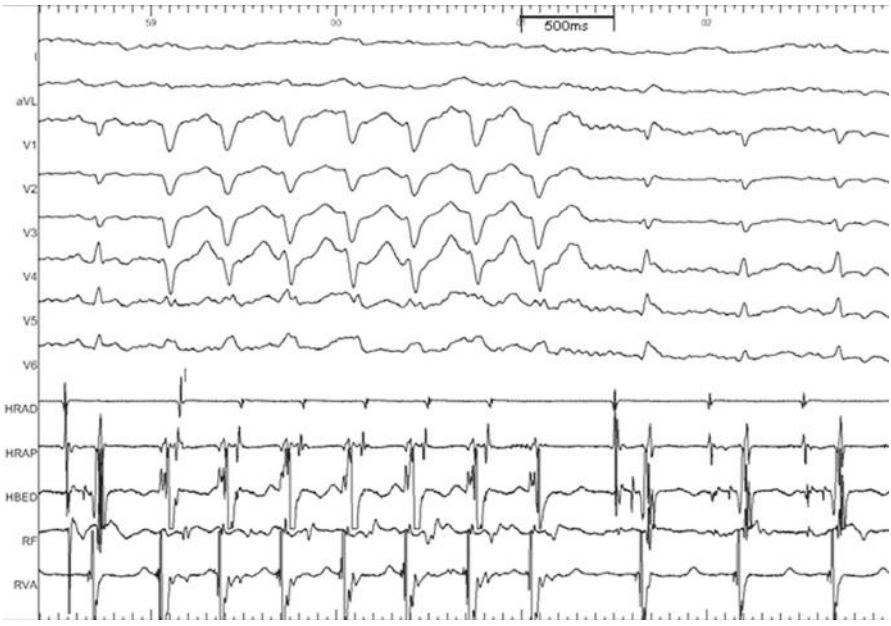

Fig. 5.19 Radiofrequency ablation at the site of Mahaim fibre location resulting transient Mahaim junctional acceleration. The QRS morphology is similar to Mahaim tachycardia. HRAP, high right atrium proximal (Courtesy of Bohora et al. [14]. Oxford Press)

Mapping of the accessory pathway is guided by the coronary sinus catheter which is slightly superior to the mitral annulus but runs along in the same direction as the annulus and therefore gives an approximate idea of where the accessory pathway may be located. Following confirmation of the accessory pathway further mapping can be performed with an ablation catheter either via a transseptal or retrograde approach. The electrodes are parallel to the CS electrodes and the catheter is moved along the catheter with ventricular pacing on order to assess the earliest atrial signal and an A:V ratio of 1:1.

Transseptal access is generally relatively straightforward through the fossa ovalis as the atrial anatomy is normal and can be achieved with a Brockenborough needle and a long non deflectable sheath. For a retrograde approach femoral arterial access is gained and the ablation catheter is prolapsed across the aortic valve in an RAO view with the curve pointing in an anterior direction to the right of the image. After crossing the aortic valve the catheter is then rotated counterclockwise with the curve maintained bringing it in a posterior alignment toward the coronary sinus in the plane of the posterior mitral annulus. The curvature is then slowly released in order to move along the annulus. In order to achieve a greater atrial signal the catheter is withdrawn slightly with an A:V ratio of approximately 1:10 and an atrial electrogram amplitude of 0.4–1.0 mV. Although a retrograde approach may be associated with greater catheter stability it is generally more straightforward to maneuver the catheter via the transseptal access.

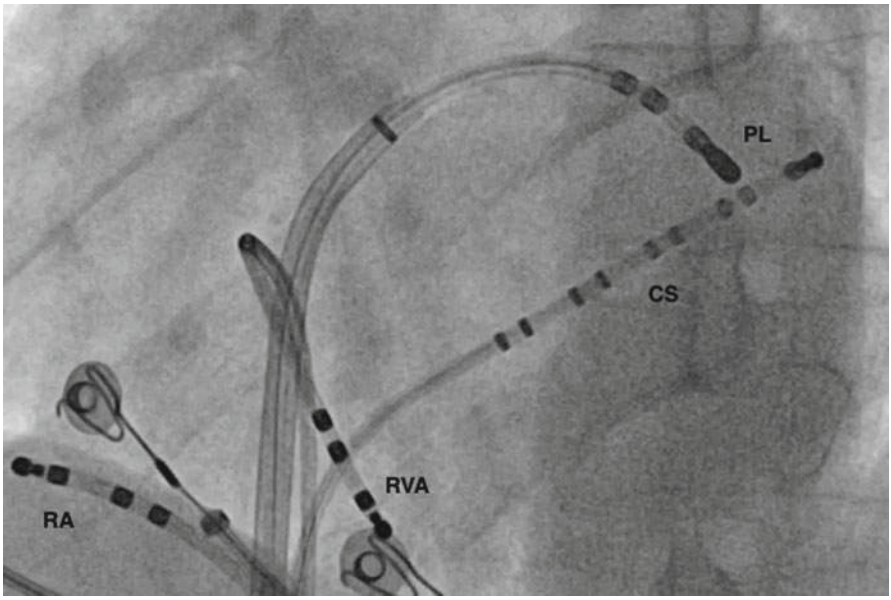

Fig. 5.20 Ablation catheter position on the posterolateral concealed retrograde accessory pathway

As soon as either transseptal access has been obtained or the aortic valve has been crossed heparin should be administered at an initial dose of 100 units/kg aiming for an ACT greater than 300 s. A continual infusion of heparinized saline should be infused through the side arm of the long sheath. Provided there is retrograde conduction along the accessory pathway the most straightforward method of mapping is to pace the ventricle and map for the earliest atrial activation. Pacing from different locations can be used in order to separate out the A and the V so as to record an accessory pathway potential. The ablation catheter can be moved along the mitral annulus. An example of the optimal position for an ablation catheter in a concealed retrograde posterolateral accessory pathway is shown in Fig. 5.20.

Mapping for the earliest ventricular electrogram can also be performed during atrial pacing. For a left lateral accessory pathway the local ventricular electrogram should preceded the surface delta by up to 10 ms. A negative QS in a unipolar electrogram is also a sign of a good position.

It is not ideal to ablate during tachycardia as the catheter can move considerably following termination of the tachycardia although it some cases of incessant tachycardia there is no other option.

Catheter stability may not be as good as a retrograde approach but this method is associated with a lower incidence of vascular complications. Additionally the transseptal approach is better for accessing extreme lateral and anterolateral accessory pathway's.

For a retrograde approach femoral arterial access is achieved with a 7Fr sheath. The ablation catheter is directed up the descending aorta and a curve placed in the catheter as it is advanced around the aortic arch.

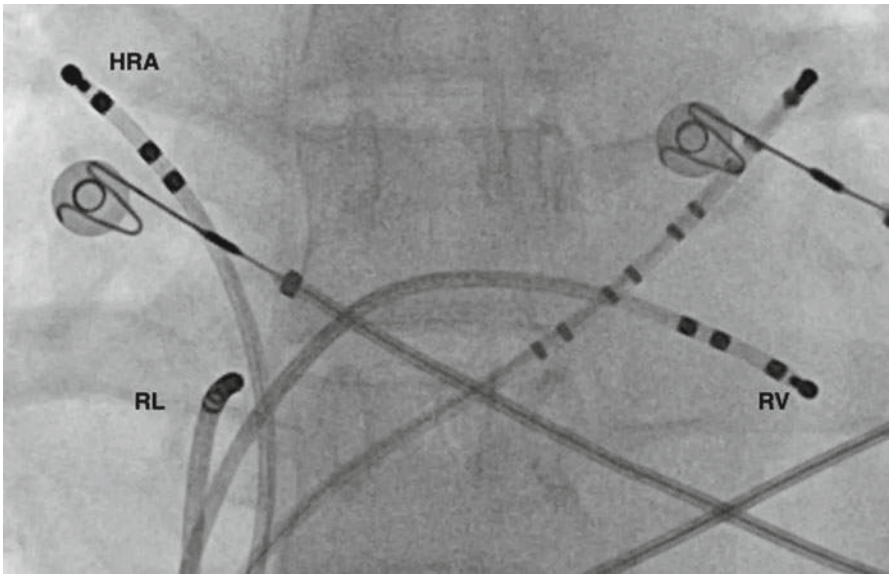

Fig. 5.21 Mapping of an accessory pathway along the tricuspid annulus. The ablation catheter is positioned in the right posterolateral annulus where ablation was successful. Also shown in this image is a catheter in the HRA, RV and CS

Right Free Wall Accessory Pathway

These are considered to be the most difficult accessory pathways to map and successfully ablate. This is due to a combination of catheter instability, the presence of other structural abnormalities such as Ebstein's and the lack of a structure which may assist mapping of the annulus. A 20 pole catheter is often positioned in the RA in order to help map the tricuspid annulus. A deflectable sheath may be helpful for catheter stability and the catheter is moved looking for an early atrial or ventricular signal with an A:V ratio of 1:1 as well as an accessory pathway potential. The local ventricular signal should be compared with the surface delta wave and should be earlier by up to 20 ms [5]. An example of mapping of the tricuspid annulus using an ablation catheter in a right sided accessory pathway is shown in Fig. 5.21.

Accessory Pathway General: Difficult Case

The most common cause for failure to successfully ablate an accessory pathway is the inability to manipulate the ablation catheter to the atrial or ventricular insertion point. For left lateral accessory pathways this may be overcome by switching from retrograde to a transseptal access or vice versa. Changing the curve on the ablation catheter and occasionally the use of a long sheath may also help to maneuver the catheter and provide stability.

The inability to deliver a successful lesion limited by power or temperature may be overcome by repositioning the catheter or changing the angulation of the catheter. If this does not work then switching to an irrigated catheter may help.

If an accessory pathway potential cannot be mapped or is small then the coronary sinus should be mapped. If this is the case then ablation can be performed at lower power from within the coronary sinus.

If the patient is in incessant AVRT ablation can be performed during tachycardia. It is important that ablation is continued after termination of the tachycardia as often the catheter moves during reversion to sinus rhythm.

Important Points

1. Accessory pathway's are muscle fibers which connect the atrium to the ventricle through the fibrofatty and fibrous parietal AV junctional regions. The majority are located within the epicardial atrioventricular fat pad close to the atrioventricular junctions,
2. Anatomically these are divided into septal (paraseptal) which include posteroseptal, midseptal and anteroseptal, left lateral (left posterior), left posterolateral (left infero-posterior), left posterior (left inferior), left anterolateral (left superoposterior) and left anterior (left superior). The equivalent locations are also possible on the right side using similar nomenclature. Additionally some accessory pathways may be directly connected into the specialized conduction system such as atriofascicular, atrioventricular, nodoventricular and fasciculoventricular pathways. Accessory pathway's may also be located in unusual anatomical locations involving epicardial connections between the coronary sinus and the left ventricle, the non-coronary cusp of the aortic valve to the left ventricle, the right atrial appendage to right ventricle or left atrial appendage to left ventricle.
3. Orthodromic AVRT occurs when the antegrade accessory pathway is refractory and conduction occurs antegradely through the AV node activating the His and ventricle and retrogradely along the accessory pathway if it is no longer refractory. The VA time required for this to occur is generally greater than 70 ms.
4. Antidromic AVRT conduction occurs antegradely via the accessory pathway as the AV node is refractory. This is generally associated with a pre-excitated QRS as conduction is only via the AP. VA times are generally greater than 70 ms as conduction is via the VA node.
5. The Shortest Pre-Excited R-R Interval (SPERRI) less than 220 ms or 220–250 ms may be associated with a higher risk of antegrade conduction during AF and may be an indication for catheter ablation.
6. In order to help maximize pre-excitation during an EP study pacing may be performed from different locations on different catheters. This may also help to reveal an accessory pathway potential which should be targeted for ablation.

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Chapter 6
Atrial Tachycardias

Benedict M. Glover and Pedro Brugada

Abstract Atrial tachycardia is a **focal or macro re-entry supraventricular arrhythmia which does not directly involve the AV node**. Overall it accounts for approximately 7 % of all SVT's [1].

Focal atrial tachycardia occurs as a result of either micro re-entry, increased automaticity or triggered activity while macro re-entry occurs over a region of tissue surrounding a region of conduction block. Focal atrial tachycardia due to increased automaticity can usually be initiated with isoprenaline while decremental atrial pacing tends to initiate and terminate micro and macro re-entry.

Although atrial tachycardia's may occur anywhere within the right atrium or left atrium there are more common locations and in particular where anisotropic conduction occurs in which there is rapid linear conduction and slowed transverse conduction. The most common locations are the **crista terminalis**, **coronary sinus os**, **the pulmonary veins and antral regions**, **the tricuspid and mitral annuli**, **the right and left atrial appendages and the interatrial septum**. The location is to an extent dependent on the patient's age, history of structural heart disease, prior ablations or surgery and the presence of other arrhythmias.

Focal Versus Macro Re-entry

It is useful to establish if an atrial tachycardia is either focal or re-entry prior to mapping as this dictates the parameters that are set for mapping as well as interpretation of the mechanism. As shown in Fig. 6.1 a focal atrial tachycardia tends to have a

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_6

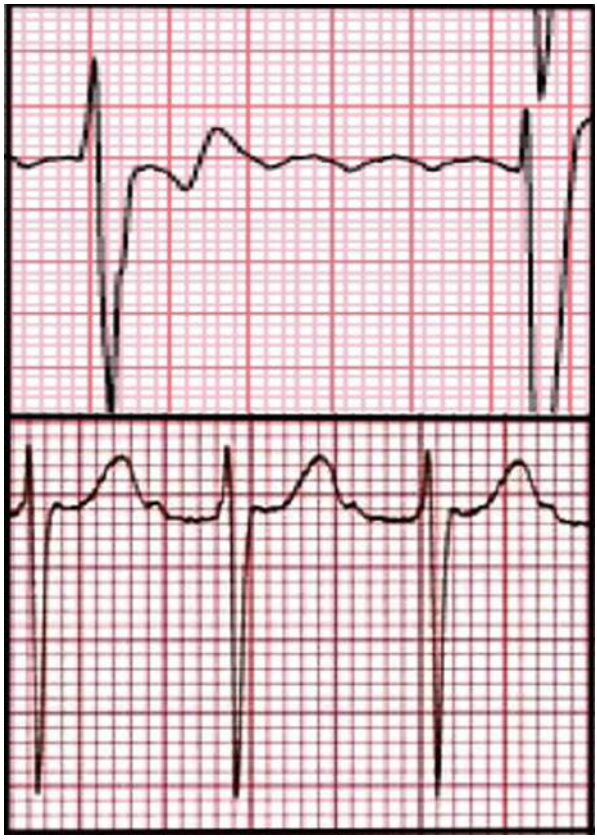


Fig. 6.1 ECG showing macro re-entry tachycardia (*top*) where there is almost continual atrial activation and focal AT (*bottom*) with a clear isoelectric line between atrial activity

very distinct P followed by an isoelectric AV interval while a macro re-entry mechanism tends to have continual atrial electrical activity which may be superimposed on the QRS complex.

If this is unclear vagal maneuvers can be performed or adenosine administered in order to decipher atrial activity more clearly. Of note adenosine may occasionally terminate atrial tachycardia by activation of adenosine sensitive potassium channels [2].

In the electrophysiology laboratory activation mapping can be performed and will easily show whether the entire tachycardia cycle length occupies a region rather than a single focus. Entrainment can also be performed in two anatomically distinct regions to assess if the circuit is macro re-entry, for example the septal and lateral mitral isthmus in mitral annular flutter or anterior and posterior to the roof line in left atrial roof dependent flutter.

For focal atrial tachycardia an early, possibly fractionated signal is often seen as a good target. Fractionation occurs as a result of slow conduction from a region of increased automaticity or micro re-entry connecting into normal atrial tissue [3]. Unipolar electrograms also have a QS pattern [4]. The local signal should be at least 40 ms ahead of the earliest P wave. If the RA is mapped and the earliest signal is no

more than 20 ms ahead of the earliest P wave with septal activation earliest then the left atrium should be mapped because the arrhythmia may originate in the right sided pulmonary veins.

In macro re-entry the critical isthmus is targeted as an area of early meets late during activation mapping. This can easily mapped by performing entrainment in locations likely to contain the isthmus looking for a closely matching PPI-TCL.

Locations of Atrial Tachycardias

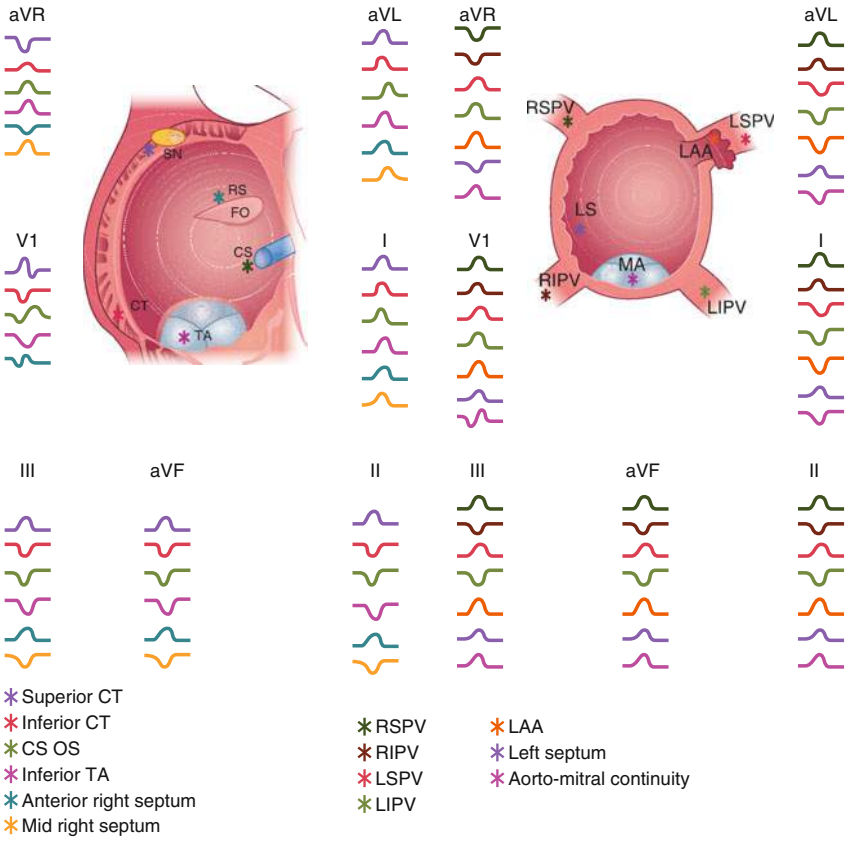
It is useful to use the ECG to predict whether the atrial tachycardia is left or right sided prior to performing an ablation. The most useful leads to examine are V1 and aVL. As the left atrium is more posterior than the right atrium **left sided atrial tachycardia's tend to have a positive P wave in V1. A negative P wave is seen more commonly in V1 in right sided atrial tachycardias. A positive P wave in aVL generally indicates a right sided atrial tachycardia while a negative P wave in aVL generally indicates a left sided atrial tachycardia**. These are general observations and variations exist with anatomy, underlying pathology and previous ablations [5, 6]. The ECG features of atrial tachycardias in the most common anatomic locations are shown in Fig. 6.2.

Crista Terminalis

The crista terminalis runs from the anteromedial high right atrium inferiorly along the lateral RA wall where it ends at the posteroinferior right atrium at the eustachian valve. The majority of right sided atrial tacycardias occur in the region of the crista terminalis. At the superior aspect this may be due to an increase in automaticity as a result of the close proximity of the sinus node. Throughout the structure micro re-entry may occur as a result of anisotropic conduction [7].

Atrial tacycardias originating from this region often have a similar P wave morphology to sinus rhythm and can be confused with sinus tachycardia. Sinus node re-entry tachycardia can also occur at the junction of the sinus node and the crista terminalis. As this is a micro re-entry tachycardia it can be initiated with atrial pacing [8]. As shown in Fig. 6.2 the P wave morphology in atrial tacycardias originating from the crista terminalis depends on the location. Atrial tachycardias from the superior crista terminalis have a similar P wave morphology to sinus rhythm in V1 which is positive and then negative with an inferior directed P wave axis. Atrial tachycardias located in the lower crista terminalis frequently have a negative P wave in V1 with a superior directed P wave axis.

In order to distinguish between atrial tachycardia from the crista terminalis versus sinus tachycardia an abrupt rather than gradual onset and termination with warm up and cool down over several beats favors atrial tachycardia.



Location		V1	II, III, aVF	aVL
CT		Negative if lower down Positive if closer to sinus node	Positive	Positive
Septum	Right	Isoelectric	Positive	Positive
	Left	Negative / Positive	Low amplitude positive	Negative
CS		Negative / Positive or Isoelectric / Positive	Negative	Positive
Annulus	TA	Negative	Negative for Inferoanterior Positive or biphasic for Superior	Positive or isoelectric
	MA	Negative / Positive	Positive	Negative or isoelectric
LSPV	LSPV	Positive	Positive	Negative
	LIPV	Positive	Negative	Negative
	RSPV	Positive	Positive	Positive
	RIPV	Positive	Negative	Positive
LAA		Positive	Positive	Negative

Given the focal nature of these tachycardias activation mapping can be performed looking for a discrete region of early activation. Prior to ablation pacing at high output should be performed in order to ensure that there is no right phrenic nerve capture.

Coronary Sinus os

Atrial tachycardias in this region tend to originate from the superior and posterior regions of the coronary sinus os [9]. The most likely explanation for this is due to anisotropic conduction where coronary sinus fibers connect into the right atrium [10]. This result in either micro re-entry, triggered activity or less commonly increased automaticity [11].

Atrial tachycardias which are located at the os of the coronary sinus have a negative followed by a positive deflection in V1 [9]. The p wave in aVL is positive with a superiorly directed p wave axis.

Given the central activation it is important to distinguish these from atypical AVNRT or AVRT using a septal accessory pathway. Activation mapping should be performed looking for the earliest region of activation. As shown in Fig. 6.2 this is where ablation should be delivered (Fig. 6.3).

Septal Atrial Tachycardias

It is often difficult to ascertain from the ECG as to whether a septal atrial tachycardia is right sided or left sided. Left sided septal atrial tachycardias generally have a positive p wave in V1 while an isoelectric p wave in V1 is more indicative of a right sided focus.

Low septal parahisian atrial tachycardiss are unusual but are associated with a significant risk of AV block. In general the right side is mapped first and if required the left side. Of note the non coronary cusp of the aorta should also be mapped as ablation from this region may reveal an earlier region of activation with a very low risk of AV block.

Fig. 6.2 Common locations of atrial tachycardias along with P wave morphology and ECG features (summarized on table below). In general left sided foci tend to be positive in V1 given the fact that the LA is posterior to the RA. Right sided foci tend to be positive in aVL. Atrial tachycardias originating from closer to the septum tend to be narrower. Superior locations such as the superior CT, anterior septum and superior PV's tend to be positive in the inferior leads while inferior locations such as the CS, inferior TA, inferior MA and inferior pulmonary veins tend to be negative in the inferior leads

Fig. 6.3 ECG of atrial tachycardia originating from the coronary sinus os. At the *top of the image* the surface ECG leads I, II, aVL, V1 and V5 are shown. The activation sequence of the tachycardia shows the earliest coronary sinus activation recorded on the proximal CS (CS 9–10). The ablation catheter is used to map and shows a local atrial electrogram with is 86 ms ahead of the proximal CS. This is recorded at the junction of the CS os with the low right atrium posterior to the CS. Ablation was performed in this region with termination of the tachycardia and no further inducible tachycardia

Tricupid and Mitral Isthmus Atrial Tachycardia

These are not common and on an ECG may mimic typical atrial flutter or mitral isthmus dependent atrial flutter. The majority of atrial tachycardias originating from the tricuspid annulus tend to be inferior and anterior.

The majority of atrial tachycardias from this region tend be caused by micro re-entry around the annulus. Less commonly as a result of increased automaticity which may occur as a result of AV nodal type tissue in this region [11].

In tricuspid annular atrial tachycardias the P wave is generally negative in V1 as the annulus is anterior with activation in a more posterior direction [12, 13].

Atrial tachycradias from the superior tricuspid annulus tend to have an inferiorly directed axis while those in the inferior annulus tend to have a superiorly directed axis. As shown in Fig. 6.4 a long sheath is often useful for catheter stability in the ablation of annular atrial tachycardias. In this case the addition of a long sheath helps to maintain stability for the ablation of a focal atrial tachycardia along the lateral tricuspid annulus.

Atrial tachycardias in the aorta mitral continuity are uncommon. As this is at the superior aspect of the mitral annulus atrial tachycardias originating from this region have an inferior directed axis and a biphasic P wave in V1 [14].

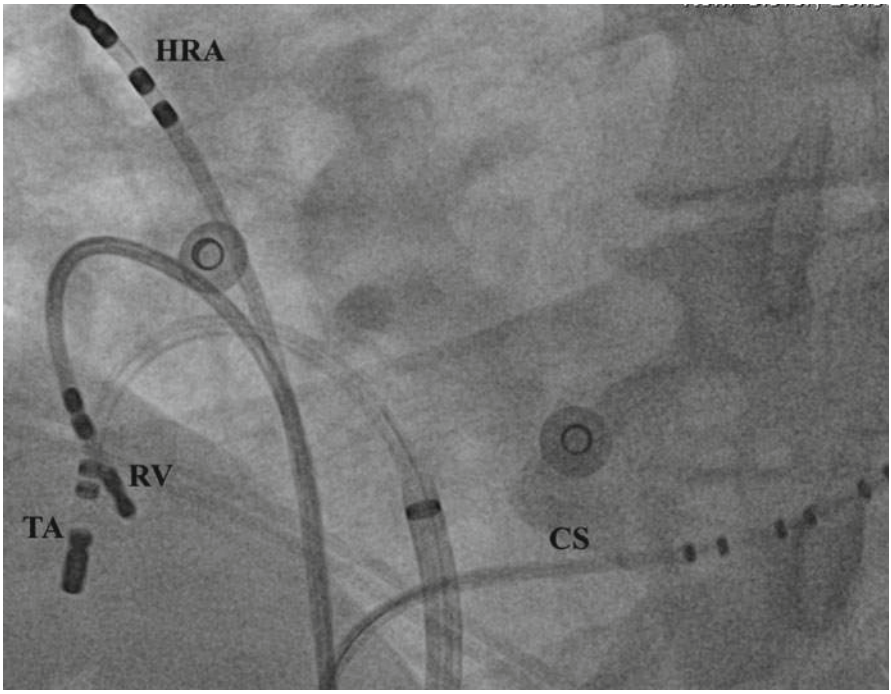


Fig. 6.4 Ablation of a focal atrial tachycardia along the lateral tricuspid annulus using a long sheath in order to maintain catheter stability. This image is taken in an LAO projection with the ablation catheter along the lateral aspect of the tricuspid annulus. Also shown in this image is a catheter in the high right atrium on the *top left of the image*, a catheter in the RV apex shown in the *bottom left of the image* and a catheter in the coronary sinus on the *right of the image*

Pulmonary Vein Atrial Tachycardia

It is generally accepted that ectopic foci from the pulmonary veins may act as initiators for AF in a significant percentage of patients. Atrial tachycardias originating from a single pulmonary vein are relatively common. This tends to occur as a result of increased automaticity but may also result from micro re-entry at the antral areas around the veins. The foci which result in atrial tachycardias tend to be more ostial than those which result in AF [15].

Atrial tachycardias originating from the pulmonary veins are positive in V1 and tend to remain positive across all precordial leads due to the posterior location [15]. Lead I is useful to help differentiate between atrial tachycardias from the right and the left pulmonary veins. The p wave is generally positive in right sided pulmonary veins and negative in left sided pulmonary veins. Atrial tachycardias originating from the left pulmonary veins tend to be broader as septal activation is more delayed when compared with right sided pulmonary veins [16].

It is often difficult to differentiate right superior pulmonary vein from the superior vena cava as the p wave is similar in V1, lead I and both have a similar axis. The p waves in the inferior leads tend to be more positive in atrial tachycardias originating from the superior vena cava.

In order to help differentiate between superior and inferior pulmonary veins the P wave axis should be examined. Atrial tachycardias originating from the superior pulmonary veins have an inferiorly directed P wave axis and those from the inferior pulmonary veins have a superiorly directed P wave axis

Left Atrial Appendage Atrial Tachycardia

Atrial tachycardias originating from the left atrial appendage have a similar morphology in V1 and lead I to those which originate from the left sided pulmonary veins. Given the more anterior position of the left atrial appendage the p waves transition becomes isoelectric in V2 [17].

Clinically atrial tachycardias originating from the LAA tend to be more incessant while those originating from the left superior pulmonary vein may be associated with paroxysmal AF [17]. These may originate from the proximal or distal left atrial appendage. If ablation is performed in the distal left atrial appendage power is usually set at 20–30 W with a target temperature of 45° [18]. This is kept low due to low flow in this region. Prior to ablation high output pacing should be performed in order to ensure that there is no capture of the left phrenic nerve. Access of the distal left atrial appendage may be difficult an a circular catheter may be required in conjunction with the ablation catheter in order to expose the region. Care must be taken to avoid catheter entrapment or perforation of the thin walled appendage.

Important Points

1. Focal atrial tachycardia occurs as a result of either micro re-entry, increased automaticity or triggered activity while macro re-entry occurs over a region of tissue surrounding a region of conduction block.
2. The most common locations are the crista terminalis, coronary sinus os, the pulmonary veins's and antral regions, the tricuspid and mitral annuli, the right and left atrial appendages and the interatrial septum.
3. For focal atrial tachycardia an early, possibly fractionated signal is often seen as a good target.
4. In macro re-entry the critical isthmus is targeted as an area of early meets late during activation mapping. This can easily mapped by performing entrainment in locations likely to contain the isthmus looking for a closely matching PPI-TCL.

5. In order to help decide whether an atrial tachycardia is right sided or left sided the most useful leads to examine are V1 and aVL. As the left atrium is more posterior than the right atrium left sided atrial tachycardias tend to have a positive P wave in V1. A negative P wave is seen more commonly in V1 in right sided atrial tachycardias. A positive P wave in aVL generally indicates a right sided atrial tachycardia while a negative P wave in aVL generally indicated a left sided atrial tachycardia.
6. The majority of right sided atrial tachycardias occur in region of the crista terminalis as a result of anisotropic conduction or changes in automaticity.
7. CS atrial tachycardias tend to originate from the superior and posterior regions of the CS os [9]. The most likely explanation for this is due to anisotropic conduction where CS fibers connect into the right atrial.
8. Tricupid and mitral isthmus atrial tachycardias are relatively uncommon and on an ECG may mimic typical atrial flutter or mitral isthmus dependent atrial flutter. The majority of atrial tachycardias originating from the tricuspid annulus tend to be inferior and anterior.

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Chapter 7
Atrial Flutter

Benedict M. Glover and Pedro Brugada

Abstract Atrial flutter is caused by either macro or micro re-entry circuits within either the right atrium or left atrium. It is broadly divided into either typical or atypical forms. Typical atrial flutter involves the cavotricuspid isthmus as part of the circuit with either a counter-clockwise or clockwise activation. The cavotricuspid isthmus extends from the tricuspid valve to the inferior vena cava, which supports slow conduction.

Atypical atrial flutter involves non-cavotricuspid isthmus dependent circuits in the right atrium, septum or left atrium. Right atrial flutters which are not dependent on the cavotricuspid isthmus include upper loop re-entry, lower loop re-entry, right lateral wall incisional type atrial flutter and circuits around the fossa ovalis. Upper loop re-entry tends to occur around the superior vena cava with slow conduction through the upper component of the crista terminalis. Lower loop re-entry occurs around the inferior vena cava with slow conduction through the lower portion of the crista terminalis.

Left atrial flutters tend to occur around the mitral valve annulus, the ostia of the pulmonary veins or the fossa ovalis on the left side. Mitral annular flutter may propagate either in a clockwise or counterclockwise direction.

ECG analysis of the flutter wave is important in order to help localize the circuit and plan an appropriate ablation strategy for the patient as well as helping to predict the potential success of the procedure.

ECG interpretation does have its own limitations particularly in patients who have undergone prior atrial ablations or in patients with structural heart disease. The most important differentiation is between cavotricuspid isthmus dependent flutter and atypical atrial flutter as well as predict whether the circuit is in the right or left atrium.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_7

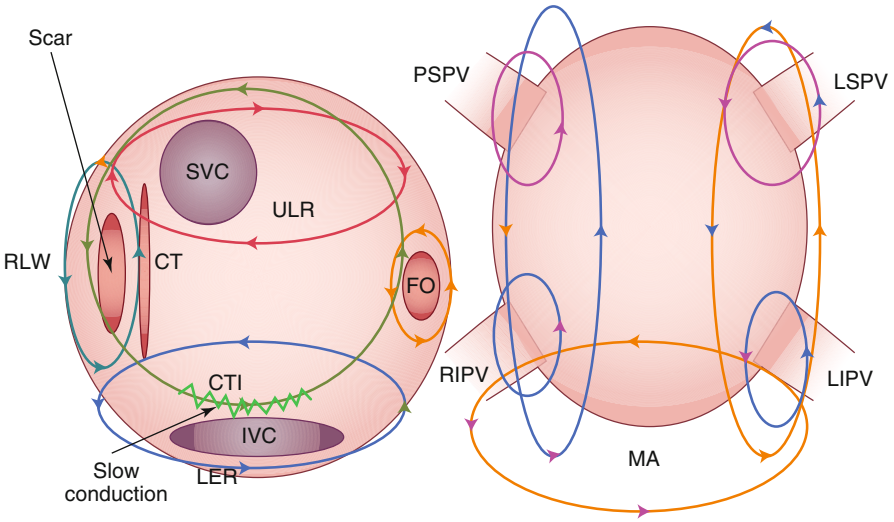

Fig. 7.1 Location of Atrial Flutters in the Right and Left Atrium. Cavotricuspid Isthmus (*CTI*) dependent circulates around the right atrium commonly with counterclockwise propagation (*green arrows*). Upper loop re-entry (*ULR*) rotates around the superior vena cava (*SVC*) with slow conduction through the crista terminalis (*CT*). Lower loop re-entry rotates around the inferior vena cava (*IVC*) also involving the crista terminalis (*CT*). Re-entry may also occur around the right lateral wall (*RLW*) often in post surgical cases where this is related to an incision as well as around the fossa ovalis (*FO*). In the left atrium atrial flutter may occur around the mitral annulus (*MA*) in either a clockwise or counterclockwise direction as well as around the pulmonary veins (*LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein)

Cavotricuspid Isthmus Dependent Atrial Flutter

Overall this is the most common flutter circuit and should always be suspected even in cases of congenital heart disease and post atrial fibrillation ablation, even if the ECG does not look typical (Fig. 7.1).

Anatomy

The cavotricuspid isthmus is an important anatomical structure which acts as an area of slow conduction. As seen in the anatomic image in Fig. 7.2 it is located posteriorly to the tricuspid annulus and anteriorly to the Eustachian valve at the junction of the right atrium and the inferior vena cava. The coronary sinus is superior and medial to the cavotricuspid isthmus. During mapping and ablation of the cavotricuspid isthmus the catheter is generally positioned at 6 o'clock in an LAO projection (Fig. 7.3) which is the mid segment and is considered the thinnest portion where ablation can generally be performed. Moving towards the septum this region is shorter in distance but

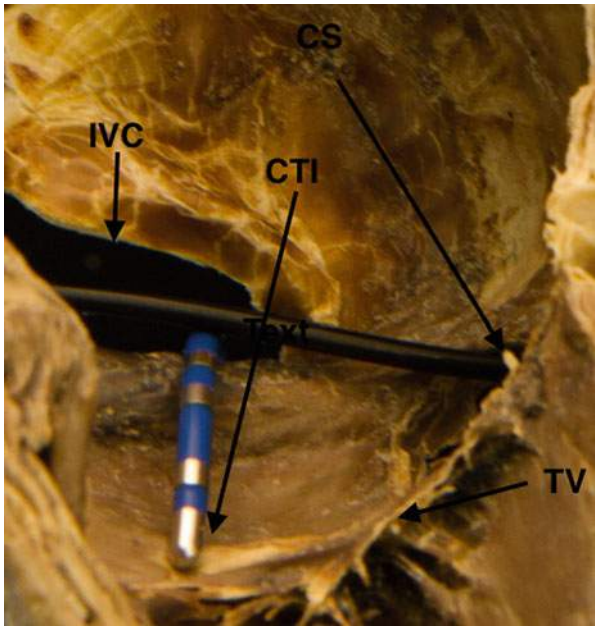

Fig. 7.2 Anatomical image showing the CTI, tricuspid valve (*TV*), inferior vena cava (*IVC*) and coronary sinus (*CS*). Also shown in this image are an ablation catheter in the location of the CTI and a catheter in the coronary sinus

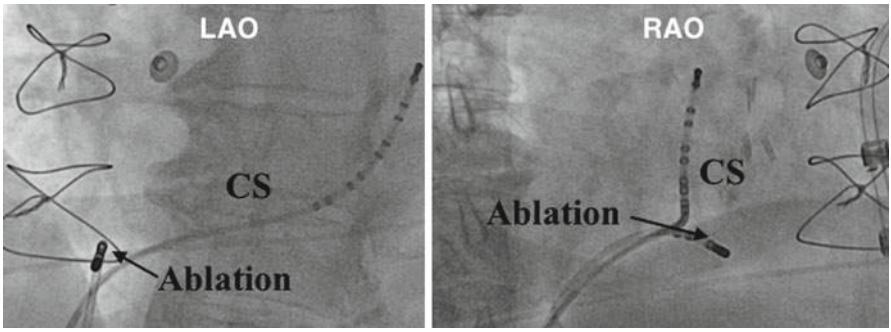

Fig. 7.3 Fluoroscopic image of the catheter location in the mid CTI in an LAO (*left*) and RAO (*right*) projection. The ablation catheter is positioned along the mid CTI. There is a 10 pole catheter positioned in the coronary sinus (CS)

thicker where the fibers merge with the coronary sinus. Inferolaterally it is broader and thicker. The anterior aspect at the tricuspid annulus is muscular while the posterior component at the junction with the inferior vena cava has minimal muscle and is generally fibro-fatty tissue. The cavotricuspid isthmus elevates into the eustachian ridge and this divides it into two components: the sub-eustachian isthmus (between the eustachian ridge and the tricuspid valve) and the crest of the eustachian ridge to the inferior vena cava, separated from the compact AV node by the coronary sinus.

Although the mid cavotricuspid isthmus is the thinnest component and therefore the best target for ablation the anatomy is variable: muscular fibers in this region

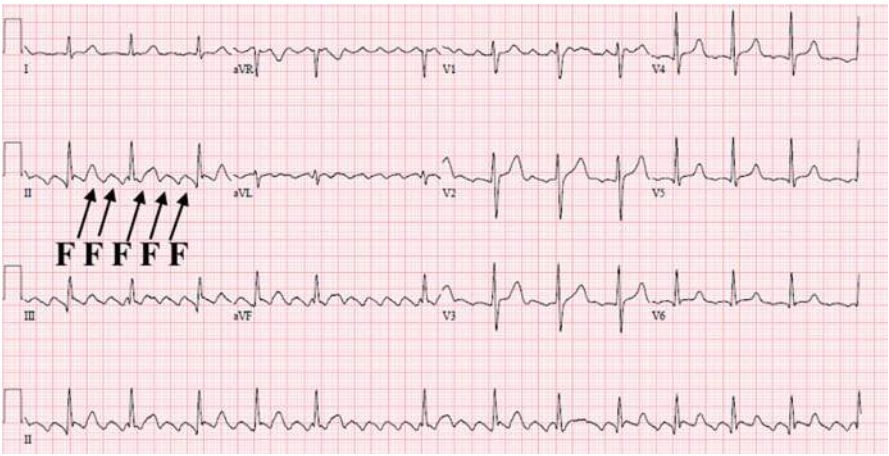

Fig. 7.4 ECG of counterclockwise cavotricuspid isthmus dependent atrial flutter. The flutter waves are negative in the inferior leads II. III and aVF implying activation from inferior to superior in the right atrium

result in irregularities which extend inferiorly and laterally from the coronary sinus wall or medially and superiorly from the crista terminalis. Between the muscular structures are thin membranes. Often these muscular fibres overlap at their superomedial and inferolateral origins and therefore in theory the most parallel segment is the medial cavotricuspid isthmus. The muscular fibers which pass through the cavotricuspid isthmus are of different sizes and therefore have different conduction properties. Narrower fibers in the mid isthmus tend to conduct more slowly than broader fibers in the septal and lateral positions.

ECG Features

Cavotricuspid isthmus dependent atrial flutter tends to have a saw tooth type appearance observed in the inferior leads and V1. The most common direction of conduction is counterclockwise which accounts for approximately 90 % of cases. As shown in Fig. 7.4 this result's in negative flutter waves in the inferior leads with an initial gradual and then steep downslope followed by a steep upslope and then a gradual downslope to baseline. The flutter wave is positive in V1 in counterclockwise activation with a gradual transition from V1 to V6 from positive to isoelectric to negative.

Clockwise (reversed) cavotricuspid isthmus dependent atrial flutter accounts for approximately 10 % of cases of typical atrial flutter. The activation sequence is the reverse of typical counterclockwise atrial flutter. The inferior leads therefore demonstrate a broad positive with a negative flutter wave in V1. There is a transition from V1 to V6 from negative to isoelectric to positive.

Ablation of the CTI for Typical Atrial Flutter

In general this can be performed with two catheters. A quadripolar or decapolar catheter is positioned in the coronary sinus while an ablation catheter can be used for ablation and mapping. Some operators use a multipolar catheter in the right atrium in order to help assess the activation sequence during the atrial flutter as well as to assess for isthmus block at the end of the procedure. This catheter may be positioned in order to map the septum with the proximal electrodes and the lateral wall of the right atrium with the distal electrodes and the mid electrodes spanning across the right atrial roof. The distal electrodes can also be positioned in the proximal coronary sinus with the mid poles spanning the cavotricuspid isthmus and the proximal poles spanning from the high to low right atrium along the crista terminalis in order to assess for bidirectional block at the end of the ablation. This is generally not required and can often lead to diagnostic errors if the catheter is not positioned exactly as described above.

A range of ablation catheters may be considered for ablation of the cavotricuspid isthmus ranging in size from 4 mm to 10 mm as well as the possibility of irrigation versus non-irrigation of the tip. The choice is operator dependent and generally a large curve is used in order to ensure adequate reach of the ventricular side of the isthmus.

It is our practice to use a decapolar catheter in the coronary sinus and a 4 mm irrigated catheter for ablation. A quadripolar catheter may be considered for back up right ventricular pacing in certain cases where the patient is in atrial flutter and there is a suspicion that the patient may develop bradycardia following termination of the arrhythmia.

The ablation catheter is normally positioned at the tricuspid annulus so that the atrial and ventricular electrograms are of equal amplitude. In the LAO projection the ablation catheter is at the 6 o' clock position where the cavotricuspid isthmus is at its narrowest. A more medial position increases the risk of AV block and potential ablation within the middle cardiac vein. A more lateral position generally requires a longer ablation line.

If the patient is in atrial flutter entrainment should be performed from this location at a rate 20 ms faster than the tachycardia cycle length looking for a PPI – TCL of less than 30 ms. An example of this is shown in Fig. 7.5. This patient presented with an atrial flutter following a prior PVI for AF. The tachycardia cycle length was 348 ms. Pacing from the ablation catheter which was positioned along the cavotricuspid isthmus was performed at 320 ms. The PPI was 348 ms which was exactly the same as the tachycardia cycle length indicating that the cavotricuspid isthmus was a part of the circuit.

While pacing from the cavotricuspid isthmus the stimulation to onset of atrial activation is generally quite long due to the slow conduction in the isthmus. This is obviously much shorter on the septal side of the isthmus.

Power settings for a 4 mm irrigated catheter are usually 30–40 W. The temperature limit is generally set at 60 ° C for non-irrigated catheters. Larger 8-mm

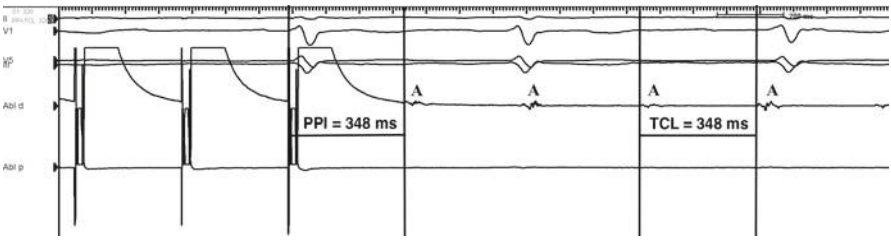

Fig. 7.5 PPI – TCL in Atrial Flutter during and after entrainment from the CTI. This patient presented with atrial flutter following a prior ablation for atrial fibrillation. The tachycardia cycle length was 348 ms. Pacing was performed from the ablation catheter which was positioned along the CTI at 320 ms. The post pacing interval was 348 ms. This was exactly the same as the tachycardia cycle length implying that the CTI was a critical component to the circuit

tip catheters require a higher power often up to 70 W with a maximum temperature of 60 ° C. Following a period of 60–90 s and with significant diminution of the local signal the catheter is moved to a more proximal location. Ablation can be performed either as a point by point technique or a continuous dragging technique from the tricuspid annulus to the junction with the inferior vena cava spending 60–90 s at each position looking for a reduction in local electrogram voltage. Some operators use lack of unipolar pacing to assess whether a lesion has been created prior to moving onto a more proximal location where capture occurs and further ablation is performed in this location. Often atrial flutter terminates prior to the development of bidirectional block across the CTI. If bidirectional block does not occur the same line can be repeated on a more medial or lateral position.

If the patient is in sinus rhythm at the start of the procedure ablation can be performed during proximal coronary sinus pacing assessing for double potentials along the ablation line [1, 2]. The proximal coronary sinus is generally paced at a cycle length of 600 ms and the ablation catheter is moved along the ablation line from the ventricular aspect to the junction with the inferior vena cava. The first potential is recorded from the medial aspect of the line while the second component is lateral to the line. As shown in Fig. 7.6 an interval of greater than 110 ms with minimal variability is generally associated with conduction block across the ablation line [3]. As shown in Fig. 7.7 this can be reversed so that pacing is performed lateral to the ablation line and the interval between this and the proximal coronary sinus can be measured. This is recorded and the ablation catheter is moved further away from the cavotricuspid ablation line and pacing performed. If moving further from the ablation line results in a shorter stimulation to proximal coronary sinus activation then this likely represents counterclockwise block.

When pacing from the proximal CS an interval of less than 90 ms indicates intact conduction across the line.

As shown in Fig. 7.8 the delay from the onset of the first to the second potential is 40 msec. The line between the two potentials is also not isoelectric. This represents intact conduction across the CTI.

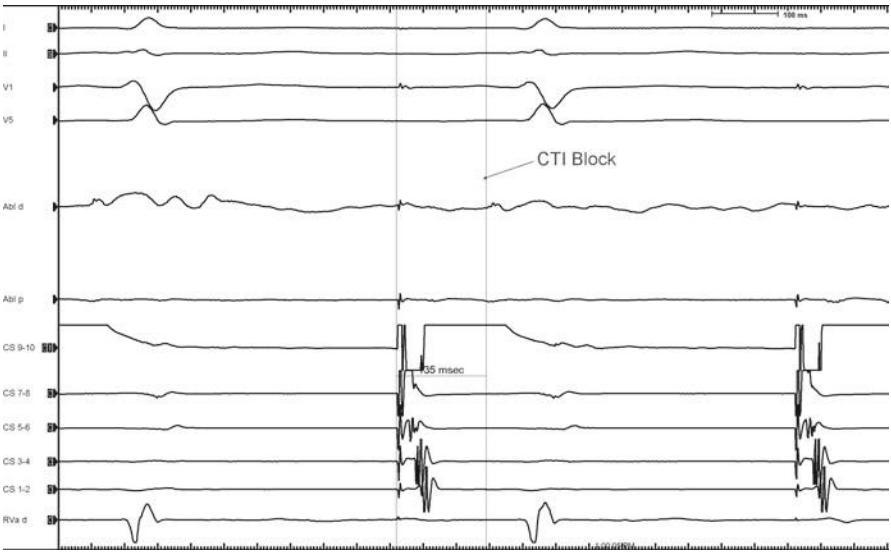

Fig. 7.6 Pacing is performed from the proximal CS (CS 9 10) at a rate of 600 msec. The ablation catheter is positioned along the CTI so that it is recording activation medial to the CTI line seen as the first deflection followed by an isoelectric line and then another atrial activation lateral to the CTI 135 msec later. This represents clockwise block across the CTI. CS 1 2 is located in the distal coronary sinus, RVa d is located in the RV apex

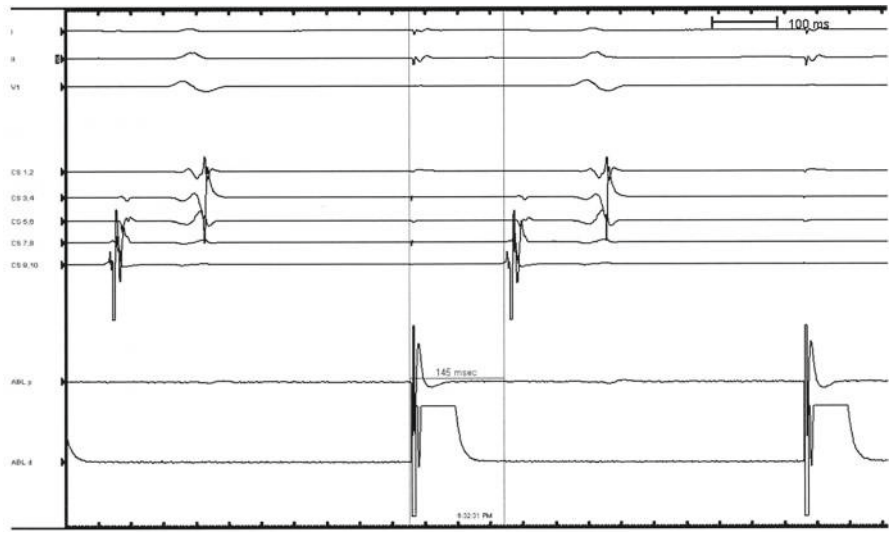

Fig. 7.7 Pacing is performed lateral to the ablation line and the stimulation to proximal CS (CS 9 10) is recorded as 145 msec representing a significant delay. The ablation catheter is moved more superior and lateral to this point and pacing is performed with a delay from stimulation to proximal CS activation of 128 msec (not shown in this image). This is suggestive of counterclockwise block across the CTI. CS 1 2 is positioned in the distal coronary sinus

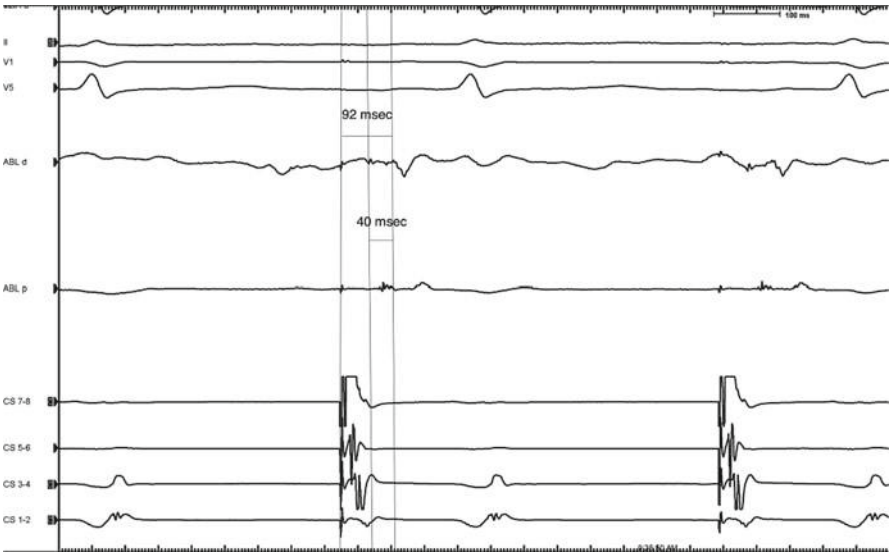

Fig. 7.8 Pacing is performed from the proximal CS (CS 7 8) with the ablation catheter positioned on the CTI. Double potentials are recorded on the ablation catheter. The first potential represents atrial activation medial to the CTI ablation line. The second component represents activation lateral to the CTI ablation line. The time from the proximal CS stimulation to the lateral atrial activation is recorded as 92 msec. The delay from the onset of the first potential to the onset of the second potential is 40 msec. The interval between the two potentials is not isoelectric. This represents intact conduction across the ablation line. CS 1 2 is positioned in the distal coronary sinus

If the interval between the two potentials is between 90 and 110 ms then the electrograms should be examined further. Features indicative of block include an isoelectric line between the first and the second component of the double potential with a negative second potential. The interval between the first and second components of the potentials is generally isoelectric in the presence of block. If this has a fractionated aspect or low amplitude signals there is generally slow conduction across the line.

In the presence of block the second component of the double potential is negative as a result of a change in the polarity of the activation wavefront. The change from positive to negative should be noted on completion of the gap.

The closer to a gap the shorter the distance between the two components. Wider splitting of the double potentials implies a distance further from the gap.

As shown in Fig. 7.9 where the ablation catheter is positioned on the cavotricuspid isthmus while pacing from the proximal CS. The duration from the pacing spike on the proximal CS to the onset of the second potential is 182 ms. The delay from the onset of the first potential to the onset of the second potential is 94 msec. There is a clear isoelectric line between the potentials and the second component is negative. This represents clockwise block across the CTI.

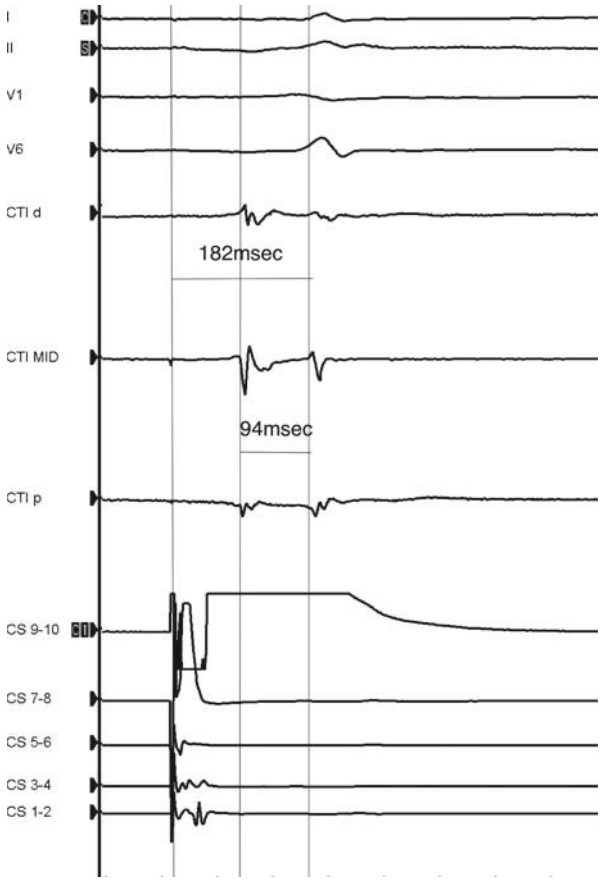

Fig. 7.9 Clockwise block across the CTI. Pacing is performed from the proximal CS (CS 9 10) while the ablation catheter is positioned along the CTI. The duration from the pacing spike to the onset of the second potential is 182 ms. The time from the onset of the first to the onset of the second potential is 94 ms. The line between both potentials recorded on ablation distal (CTId), middle (CTImid) and proximal (CTIp) is isoelectric. The second component of the double potential is negative on the ablation catheter. These features are suggestive of clockwise block across the CTI. CS 1 2 is positioned in the distal coronary sinus

Decremental Pacing

This technique is useful in cases where it is difficult to make a conclusion based on intermediate double potentials [4]. Ablation is performed along the cavotricuspid isthmus until double potentials are noted. Pacing is then performed from the proximal coronary sinus at 600 down to 250 ms while the ablation catheter is used to record double potentials along the ablation line. If the second component of the double potential does not increase by more than 20 ms with decremental pacing then this demonstrates clockwise block. This is then repeated from the lateral right atrial wall in order to prove counterclockwise block. A change in the second component by more than 20 ms with incremental pacing implies conduction through the CTI. A diagrammatic representation of this is shown in Fig. 7.10.

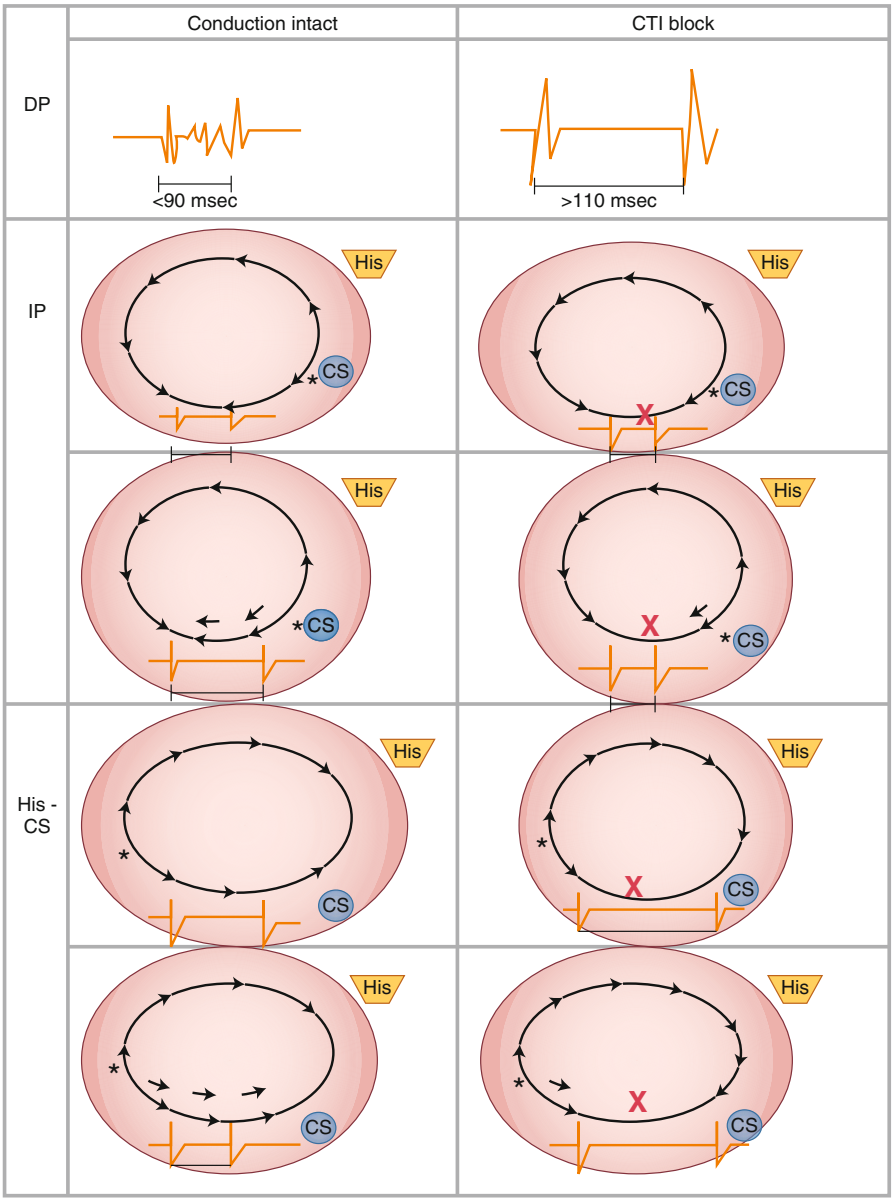

Fig. 7.10 Maneuvers used to prove CTI block. The presence of double potentials with an isoelectric line between potentials of greater than 110 ms is indicative of block across the CTI. Incremental pacing from the CS results in an increase in the separation of the double potentials by greater then 20 msec if CTI conduction is intact. If the CTI line is blocked then there is no significant change with incremental pacing from the CS (*middle images*). Alternatively the atrial signal can be recorded on the His and CS with pacing from the low lateral right atrial wall. If CTI conduction is intact the double potentials narrow with incremental pacing while if the CTI is blocked the potentials separate further but do not decrement with incremental pacing

Decremental His to Coronary Sinus Pacing

This is a modification of differential pacing in which pacing is performed from lateral to the CTI ablation line and activation of the atrial electrogram in the His region is compared with activation of the atrial electrogram in the proximal coronary sinus electrogram [5].

When pacing from the lateral lower right atrium when conduction across the CTI is intact activation occurs in a counterclockwise fashion across the isthmus, via the posteroseptal region followed by activation of the coronary sinus. Activation anterior to the tricuspid annulus results in atrial activation of the His region. Following CTI ablation anterior activation still occurs and the His is still activated which then spreads to coronary sinus which results in an increase in the His – CS timing of >40 ms from baseline. In the presence of CTI block the His to CS timing does not change significantly as activation occurs on the same rather than two pathways.

The advantage of this is that it does not rely on the accurate identification of double potentials which may be difficult to identify. This appears to be an effective strategy in helping to prove block across the CTI

An Alternative Ablation Technique: Maximum Voltage Guided Ablation

Given that different fibers of muscular have different orientations, dimensions and conduction properties there may be discrete regions with high voltage electrograms which can be selectively targeted for ablation [6].

As shown in Fig. 7.11 pacing is performed at 600 ms from the proximal coronary sinus while the ablation catheter is moved from the ventricular of the CTI to the inferior vena cava. The region of highest bipolar voltage is noted and RF delivered in this region for 60 s or shorter if the local potential reduces by more than 50% from baseline [7].

Following this the CTI is remapped looking for the maximum signal and ablated in a similar fashion. This is repeated until bidirectional block is obtained.

This technique appears to be as successful as a conventional line with reduced procedural and fluoroscopy time [8].

Potential Complications of Cavotricuspid Isthmus Ablation

There is a risk of AV block if the ablation performed is septal. This is close to zero if a lateral line is performed. Although the risk of thromboembolism is very low, the patient should be anticoagulated if they are in atrial flutter at the start of the procedure, either with heparin or with continuation of full anticoagulation. Like all catheter ablations there is always a risk of groin hematoma and cardiac perforation.

The risk of coronary artery damage, and in particular the PDA, is very unlikely.

Fig. 7.11 Maximum voltage guided ablation of the CTI. Pacing is performed at 600 msec from proximal CS. A 20 pole catheter (labeled Spi) is positioned in the RA showing earliest activation in the proximal and distal poles and subsequent activation across the RA with no evidence of block across the CTI. The ablation catheter is positioned along the CTI and is recording the region of maximum voltage which in this cases is recorded as 1.81 mV. CS 9 10 is positioned in the proximal coronary sinus with CS 1 2 in the distal CS

Difficult CTI Ablation

Although the majority of cavotricuspid isthmus ablations are relatively straightforward variability in anatomy may result in technical difficulties. The most common of these are difficulty in reaching the ventricular end of the isthmus which is overcome with a long sheath or persistent conduction at the junction between the right atrium and the inferior vena cava which generally requires catheter manipulation.

Additional issues which may not be obvious include prominent pectinate muscles, a prominent Pouch of Keith or prominent Eustachian ridge.

Prominent pectinate muscles in the region of the isthmus may impair the ability to create a line of block. It may be seen on the ablation catheter as large amplitude electrograms. In order to deal with this issue, either a more medial line of ablation can be performed or an irrigated catheter can be considered in order to achieve a deeper lesion.

The Pouch of Keith is located along the isthmus and lateral to the Thebesian valve at the CS orifice. Although this is generally a slight ridge in most patients, occasionally it may be a deep out pouching with poor blood flow, meaning that either the

catheter does not make sufficient contact or, if it does, power delivery is not sufficient to result in a satisfactory ablation line. A prominent Thebesian valve may be a clue to the Pouch of Keith. In order to deal with this problem the isthmus line can be made more laterally.

The Eustachian ridge is a fibrous structure which generally has no impact in an isthmus ablation but if very prominent may actually affect the rotation of the ablation catheter. This means that if the catheter is rotated in a clockwise manner towards the septum, the Eustachian ridge may cause a counter-clockwise rotation away from the septum. In order to counteract this issue a long sheath can be used.

Success of Cavotricuspid Isthmus Ablation

The overall success for an isthmus dependent atrial flutter is approximately 90%, provided bidirectional block has been demonstrated at the end of the ablation. The bigger issue is the occurrence of atrial fibrillation where the reported rate is as high as 82% after 39 months in patients with isolated atrial flutter and no other arrhythmias [9].

Upper and Lower Loop Re-entry

Upper loop re-entry occurs around the superior vena cava with a breakthrough in a gap in the crista terminalis. It often has a similar ECG appearance to clockwise cavotricuspid isthmus dependent flutter with positive flutter waves in the inferior leads. In order to help distinguish upper loop re-entry from clockwise cavotricuspid isthmus dependent flutter lead I can be examined. If the flutter wave in lead I is negative or isoelectric then it is more likely to be upper loop re-entry. If the flutter wave in lead I is positive it may be either. If the flutter wave is less than or equal to 0.07 mV in amplitude then it is more likely to be a result of upper loop re-entry [10]. As the circuit is shorter the tachycardia cycle length is often shorter than typical atrial flutter. It may occur as a result of typical atrial flutter or atrial fibrillation. If entrainment in this region is suggestive for an upper loop re-entry then ablation can be performed at the upper gap along the superior crista terminalis as this may be the narrowest part of the circuit.

Lower loop re-entry uses the cavotricuspid isthmus as part of its circuit but breaks through a gap in the lower portion of the crista terminalis. It is generally counterclockwise and therefore could be confused with typical counterclockwise atrial flutter. As it breaks through at a lower level along the lateral right atrial wall the flutter waves in the inferior leads tend to be less positive and the tachycardia cycle length in general is shorter. Ablation along the cavotricuspid isthmus should result in termination of this tachycardia.

Right Atrial Lateral and Postero-Lateral Wall Flutter

This may occur around areas of scar or low voltage areas such as in patients who have had prior cardiac surgery. It has a variable appearance on ECG depending on the conduction properties in this region, the direction of the circuit and subsequent

activation of the right atrium. Right atrial flutter originating from the lateral wall may often resemble cavotricuspid isthmus dependent flutter. The flutter wave is generally negative in V1. Right atrial flutter involving the septum tends to have an isoelectric or biphasic flutter wave in V1. In general these flutters require detailed mapping looking for regions of scar as well as the activation sequence. Entrainment should help to determine whether the region being mapped is part of the circuit although it may often be difficult to capture due to the presence of scar and low amplitude signals. Certain ablation lines can be performed. For lateral circuits on the lateral wall a line can be made from the region of scar to either the superior or inferior vena cava. If this is performed mapping of the right phrenic nerve should be performed prior to delivery of ablation energy.

Left Atrial Flutter

In order to differentiate a right from a left sided atrial flutter on ECG the most useful lead to examine is V1. If the **initial segment of the flutter wave is negative or isoelectric followed by a positive deflection or the entire flutter wave is negative it is more likely to be right sided while a positive flutter wave is more likely to be left sided**. If the entire flutter wave in V1 is isoelectric it is difficult to localize the flutter to either right or left sided. In left sided atrial flutters as well as these changes noted in V1 the flutter waves in the inferior leads tend to be positive but of low amplitude, generally a reflection of the underlying substrate.

The most simplistic way to distinguish left atrial flutter from atrial tachycardia is to assess the onset and termination of the tachycardia. Re-entry atrial flutter tends to be of acute onset and termination while focal atrial tachycardia tends to accelerate at the onset of the tachycardia and decelerate at the termination of the tachycardia.

Most left atrial flutter circuits either revolve around the mitral annulus in either a clockwise or counterclockwise direction or around the pulmonary veins.

Mitral Isthmus Dependent Atrial Flutter

This circulates around the mitral annulus in either a clockwise or counterclockwise direction and traverses the mitral isthmus. The relevant anatomy is demonstrated in Fig. 7.12. The mitral isthmus is posterior to the mitral annulus and anterior to the left atrial posterior wall. Mitral isthmus dependent flutter may occur following pulmonary vein isolation and in particular as a result of ablation lesions inferior and slightly anterior to the left inferior pulmonary vein.

In order to perform a mitral isthmus line a catheter is positioned in the coronary sinus so that the distal electrodes are slightly posterior to the line. An ablation

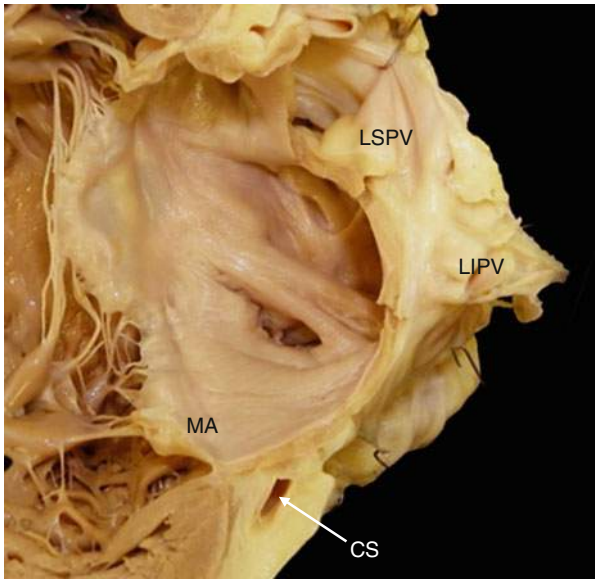

Fig. 7.12 Anatomical image showing the location of the mitral isthmus between the mitral annulus (*MA*) and the left inferior pulmonary vein (*LIPV*). The coronary sinus (*CS*) is also shown in close proximity to the MA

catheter is then positioned along the lateral mitral annulus with an A:V ratio of 1:2 at 4 o'clock in the LAO 30 view. In general a 4 mm irrigated catheter may be used with a power setting of 40 W at the annulus which can then be reduced to 30 W at the inferior pulmonary vein side. In order to move the catheter from the annulus which is anterior to the left inferior pulmonary vein which is posterior, clockwise rotation is applied to the ablation catheter. Following completion of the line pacing can be performed from either the distal coronary sinus or the left atrial appendage to confirm conduction.

If conduction persists then further mapping can be performed looking for early atrial signals during pacing from the left atrial appendage. If conduction persists despite this then ablation can be performed in the coronary sinus in the same location as the endocardial lesions with flexion towards the endocardial mitral isthmus lesions at 25 W. In order to prove block across the mitral isthmus line pacing can be performed from the left atrial appendage which is anterior to the line and the activation sequence examined in the coronary sinus catheter. Clockwise block is demonstrated by an activation from the proximal to the distal coronary sinus indicating counterclockwise activation around the mitral annulus. It is possible to electrically isolate the coronary sinus with resultant proximal to distal activation which may mimic isthmus block. Counterclockwise block is demonstrated by pacing from the distal coronary sinus which is posterior to the mitral isthmus line. Activation therefore occurs from the distal coronary sinus electrodes to proximal prior to activation of the left atrial appendage.

Additionally the ablation catheter can be moved along the mitral line during pacing from either the left atrial appendage or the distal coronary sinus looking for the presence of double potentials.

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Chapter 8
Atrial Fibrillation

Benedict M. Glover and Pedro Brugada

Abstract AF is the most common sustained arrhythmia seen in clinical practice with an overall prevalence of 700–750 per 100,000 of the population in North America (Chugh et al. Circulation 129:837–47, 2014). As well as resulting in considerable adverse sequelae and an increase in hospitalizations there is a 5 fold increase in the risk of stroke associated with non-valvular AF (Wolf et al. Stroke 22:983–8, 1991) and by a factor of 17 in the presence of significant valvular heart disease (Fuster et al. Circulation 123:e269–367, 2011). The risk of AF increases markedly with older age affecting approximately 5 % of people over 65 years and 10 % of people age over 80 years (Miyasaka et al. Circulation 114:119–25, 2006).

Classification of AF

AF is classified as paroxysmal, persistent, longstanding persistent or permanent. **Paroxysmal AF is defined as two or more episodes of AF each of which terminate within seven days and commonly within 24 h. Persistent AF is sustained generally for greater than seven days** (or less if a cardioversion was performed in this time) and requires chemical or electrical cardioversion for termination of the arrhythmia. **Longstanding persistent refers to cases in which AF has been present for more than 1 year and previously may have been designated as being permanent**; **however**, **an electrical cardioversion or ablation strategy is being**

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_8

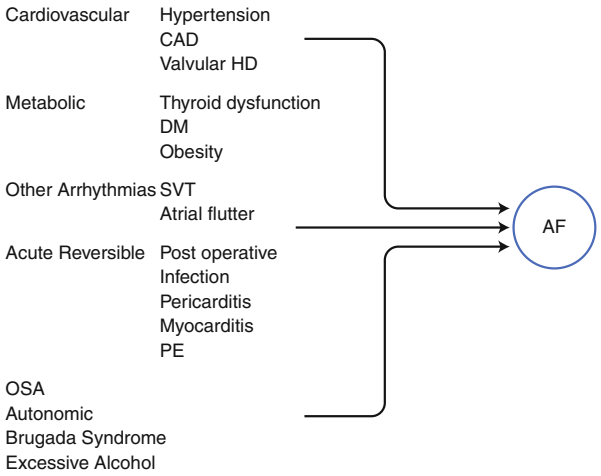

Fig. 8.1 Causes of Atrial Fibrillation. These can be divided into cardiovascular such as hypertension, coronary artery disease (*CAD*) and valvular heart disease (*HD*), metabolic, such as thyroid dysfunction, diabetes mellitus (*DM*) and obesity other arrhythmias such as SVT and atrial flutter and acute reversible causes such as post operative, infections, pericarditis, myocarditis and pulmonary embolism (*PE*). Other causes include OSA, autonomic, Brugada and excess alcohol

pursued and therefore sinus rhythm may be achieved. Permanent AF also continues for more than seven days and cannot be terminated anymore thus a rhythm control strategy has been unsuccessful or not appropriate.

Etiology

The incidence of AF is increased by other cardiovascular and metabolic conditions as well as several lifestyle factors. It may also be secondary to either acute reversible insults or to other arrhythmias.

The main cardiovascular causes of AF are shown on Fig. 8.1 and include hypertension, coronary artery disease and valvular heart disease. Metabolic causes of AF include thyroid dysfunction and diabetes mellitus while lifestyle risk factors include obesity, excessive alcohol and obstructive sleep apnea. AF is frequently seen in the acute setting in post-operative patients as well as those who have infection, or in association with pulmonary embolism, pericarditis and myocarditis. AF may also occur in association with other supraventricular arrhythmias, such as AV nodal re-entry tachycardia, AV re-entry tachycardia and atrial flutter. It is important to perform an EP study in patients who are being considered for an AF ablation and in particular young patients to ensure that there is not an underlying SVT. In patients who have undergone a successful ablation for typical atrial flutter the incidence of AF with 2.5 years post ablation is 50 % [1]. There has been some recent evidence to suggest that triggers from the pulmonary veins may also play a role in the initiation of typical atrial flutter [2]. Other less common causes of AF include autonomic, familial forms (particularly Brugada syndrome) and inflammatory.

Hypertension

The odds ratio for developing AF in association with hypertension is 1.5 for men and 1.4 for women [3]. Although this is not the highest risk for AF in an individual it is the most common cause of AF due to the high incidence of hypertension. Hypertension is often accompanied by left atrial remodeling due to pressure and volume overload as a result of a degree of left ventricular diastolic dysfunction. These changes may result in changes in the electrical properties of the myocytes in the pulmonary veins increasing the potential for them to act as triggers.

Effective treatment of hypertension in patients with AF has been shown to reduce all cause mortality (7.8 %), cardiovascular mortality (4.3 %), nonfatal myocardial infarction (5.3 %) and stroke (2.2 %), independent of blood pressure lowering effects [4]. Additionally effective treatment of hypertension has been shown to reduce the overall risk of developing AF by 28 % [5]. Data supporting this has been inconsistent however which may be a reflection of an the difficulty in optimal blood pressure control.

Coronary Artery Disease

AF is relatively common following an acute myocardial infarction (MI) occurring in approximately 15 % of patients. Early reperfusion as well as the use of beta blockers appears to have had an impact on lowering the incidence of AF post MI. AF may result from occlusion to or proximal to the sinus node artery as well as the hemodynamic changes associated with left ventricular dysfunction. It may also occur as a result of changes in autonomic tone, in particular an increase in adrenergic stimulation or as a result of pericarditis.

Of additional note some patients with AF present with chest pain, an elevated cardiac troponin and no evidence of significant obstructive coronary artery disease. It has been suggested that this may be a result of AT1 receptor mediated oxidative stress accompanied by a reduction in microvascular blood flow [6].

Valvular Heart Disease

The incidence of AF in patients with significant valvular heart disease is approximately 30 % and in patients with mitral stenosis is approximately 50 %. AF tends to be an early manifestation of mitral valve disease and tends to present later in aortic valve disease. Patients with significant mitral and aortic valve disease tend to have elevated left atrial pressure with left atrial dilatation and left atrial fibrosis which increases the possibility of re-entry circuits. The overall reduction in the incidence of rheumatic heart disease in the Western World has lead to a significant reduction in this as an overall contributor to AF.

Diabetes Mellitus

Diabetes mellitus (DM) has been shown to be associated with an increased incidence of AF and this risk increases with diabetes duration and poor glycemic control [7, 8]. DM may result in a disturbance of cardiac autonomic function, in particular an increase in sympathetic tone, which may result in the initiation of AF [9]. The cardiac autonomic dysfunction in patients with DM may also result in coronary microvascular dysfunction and diastolic dysfunction in diabetic subjects [10–12] which may increase the potential for AF. There may also be inflammatory changes responsible for both conditions. CRP and interleukin 6 have been shown to be elevated in atrial biopsies in patients with lone AF which may also be elevated in DM [13, 14].

Obesity and Obstructive Sleep Apnea (OSA)

Obesity is a significant public health concern with increasing prevalence. There is a 2.4 fold increased risk of AF in obese individuals versus those with a normal body mass index (BMI) [15]. Furthermore this risk appears to increase with increasing BMI with a 1.2 fold increase in those with a BMI of 25–30 kg/m^2 and a 2.3 fold increase in those with a BMI greater than 40 kg/m^2 [16].

There are several potential explanations for the increased risk of AF in patients who are overweight or obese. AF may occur as a direct result of obesity or in association with other risk factors, which are more commonly associated with an elevated BMI.

There is a direct association between left atrial dilatation and obesity with a 2.4 fold 10-year risk of left atrial enlargement on echocardiogram [17].

Left atrial pressure may also increase as a result of left ventricular hypertrophy and diastolic dysfunction which may occur in obesity and in particular in association with hypertension. It has also been shown that obese patients have slower left atrial conduction times and shorter effective refractory periods in the left atrium and pulmonary veins even when adjusting for confounding variables including hypertension, DM and OSA [18]. Overall these changes may result in atrial remodeling and atrial arrhythmias.

Atrial remodeling may be summarized as a heterogeneous process characterized by disruption of atrial electrical integrity. Delayed interatrial conduction reflected as a broad and biphasic P wave in the inferior leads has been shown to increase with BMI and waist circumference [19].

Increased pericardial fat occurs frequently with obesity, which may lead to a disturbance in atrial conduction. Variable expression of this adipose tissue may result in heterogeneity of atrial conduction. This has been shown to result in an increased risk of developing AF [20].

OSA may be found in up to 90 % of individuals with obesity [21]. If untreated, this is characterized by significant negative drops in intrathoracic pressure, intermittent hypercapnic hypoxia, and transient repeated wakening at the end of each episode.

These drops in intrathoracic pressure may result in alterations of the left atrial chamber dimensions which may in itself increase the risk of developing AF. Additionally, both hypercapnic hypoxia and frequent changes in sleep patterns may result in an increase in sympathetic tone. Overall these changes may result in an increase in the left atrial volume [22]. Effective treatment with CPAP in patients with OSA and no history of AF has been shown to reduce right and left atrial dimensions [23]. OSA has been shown to be independently associated with failure of catheter ablation for AF [24]. Ablation success rates are higher in patients with OSA who are treated with CPAP versus those not treated [24, 25].

Obesity and its associated conditions are potentially modifiable risk factors for AF. In general, it is currently recommended that individuals with a BMI greater than 25 with 1 associated comorbidity (diabetes, prediabetes, hypertension, dyslipidemia, elevated waist circumference) should be offered advice on dietary and lifestyle modification [25].

Aggressive risk factor modification in patients with a BMI greater than 27 and at least one other risk factor (hypertension, DM, OSA, smoking and excessive alcohol consumption) in patients awaiting catheter ablation has been shown to result in an improvement in patient's symptoms, with 30 % of patients avoiding the need for ablation [26]. In patients undergoing catheter ablation for symptomatic AF there was a significant improvement in symptoms post ablation as measured by the AF severity score [27]. AF-free survival after a single ablation procedure was 62 % for patients with risk-factor-modification and only 26 % for the control arm. After multiple ablations, AF-free survival increased to 87 % in the risk-factor-modification group versus 48 % in the control arm. Structural changes of the heart were also significantly better with left atrial volume and LV diastolic volume reduction.

Autonomic AF

An alteration in sympathetic activity may result in an increase in the potential for the initiation or maintenance of AF. This can occur either by direct effects on the action potential duration and refractory period of the cells in the pulmonary veins or left atrium or by structural changes.

An increase in adrenergic stimulation may result in an enhancement of focal automaticity which may act as a potential trigger for AF. Increased parasympathetic activation increases the action potential duration. However its contribution to AF may result from its ability to shorten the atrial effective refractory period by varying degrees throughout the left atrium, which may contribute to a heterogeneity of conduction properties [28].

Both vagally induced and adrenergic AF tend to occur in younger patients with no other obvious risk factors. Vagally-induced AF is much more common than adrenergic AF and tends to occur after a preceding sinus pause or sinus bradycardia. Vagally induced AF may be partially responsive to flecainide and disopyramide and frequently worsens with beta blockers. Adrenergic AF is often provoked by exercise

or increased emotional stress, and tends to be preceded by an increase in sinus rate. This type of AF responds well to beta-adrenoceptor blockade.

There is a suggestion that ganglionic plexi denervation may have a role in the treatment of AF. Indeed left atrial ablation may have some impact by its effects on the autonomic innervation of the heart. One of the main restrictions in ganglionic plexus denervation using an ablation catheter is the difficulty in optimal access to the nerves which are not easily ablated from the endocardium.

Familial AF

Approximately 5 % of cases of AF may have a genetic component [29]. This may be even higher in patients who develop AF at a younger age and those with no other obvious risk factors for AF. The risk of developing AF in an individual who has a parent with a history of AF is increased by a factor of 1.85 times that of the population [30]. Additionally an increased incidence of AF has been noted in long QT4, short QT and Brugada syndrome.

Several genetic mutations have been implicated in AF. A missense mutation in the KCNQ1 gene has been shown to result in an alteration of the activity of the voltage gated delayed potassium current (IKS) [31]. As well as several other mutations in the KCNQ1 gene upregulation mutations have been detected in the SHOX2, TBX3 and PITX2 genes.

Mutations have also been detected in the KCNN3 gene, which encodes calcium activated potassium channels that predominante in the atria [32].

Oral Anticoagulation

The issue of oral anticoagulation is one of the more complex issues in clinical cardiology. Most risk stratifying scores have been designed to be simple and easy to remember. Currently the most widely used risk scoring system is the CHA2DS2VASc, which is shown in Fig. 8.2. This was based on the CHADS2 score with a greater emphasis on age as well as the addition of vascular disease (prior MI or peripheral vascular disease), female gender and diabetes mellitus. It is generally recommended that oral anticoagulation should be considered in patients with a CHA2DS2VASc of greater than or equal to 2 (Class I Indication, Level of Evidence B) with either Coumadin or a direct oral anticoagulant. In patients with a CHA2DS2VASc score of greater than or equal to 1 oral anticoagulation, aspirin or no antithrombotic therapy can be considered (Class IIb Indication, Level of Evidence C). For patients with a CHA2DS2VASc of 0 no antithrombotic therapy is generally recommended. In general female gender in a patient with no other risk factor for stroke would not result in the institution of oral anticoagulation although this clearly has to be reviewed with increasing age. It should also be

Risk factor	Score	Recommendations
CCF1	1	
Hypertension2	1	0 No OAC
Age 75 years or more	2	
DM3	1	1 Consider OAC / Aspirin / nothing
Ischemic stroke / TIA / TE4	2	
Vascular disease 5	1	2 or greater OAC
Age 65-74 years	1	
Sex6	1	

1 Signs/symptoms of LV/RV/Biventricular dysfunction confirmed with objective testing
2 Resting SBP > 140 mmHg and/or DBP > 90 mmHg on 2 or more measurements or patients receiving antihypertensive medication
3 Fasting plasma glucose greater than or equal to 7.0mmol/L /126 mg/dL or treatment with oral hypoglycemic agent or insulin
4 Ischemic stroke is defined as a sudden focal neurological deficit diagnosed by a neurologist and found to be due to an ischemic orgin lasting greater than 24 hours
TIA is a sudden focal neurological deficit diagnosed by a neurologist and lasting less than 24 hours
5 Vascular disease is considered a prior MI/PVD/aortic plaque
6 Female gender with no other risk factors is not considered sufficient for commencing OAC

Fig. 8.2 Summarizing the CHA2DS2VASc Scoring system for Non-Valvular AF. *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TIA* transient ischemic attack, *TE* thromboembolism, *MI* myocardial infarction, *PVD* peripheral vascular disease

remembered that each individual risk factor does not confer an equal percentage risk for stroke.

Although CHA2DS2VASc is more sensitive for predicting low event rates in low risks patients it is only modestly effective in terms of its positive predictive value with an area under the receiver-operating characteristic curve of approximately 0.6 [33].

Additional factors which have been examined in order to help calculate the risk of stroke include the use of biomarkers as well as LAA morphology. Biomarkers such as NT-pro-BNP, von Willebrand levels, d-dimers and troponin have been studied. Although they appear to have some merit they have yet to be incorporated into the guidelines. LAA morphology appears to correlate to an extent with the risk of thrombo-embolism with a suggestion that an increase in trabeculations, number of bends and narrowness of the LAA orifice may also increase the risk of thrombus formation. Although this can be documented on TEE or CT widespread use is still not recommended for decision making regarding oral anticoagulation.

Vitamin K Antagonist

Warfarin acts by inhibiting the cyclic interconversion of vitamin K and vitamin K epoxide, thereby reducing the vitamin K-dependent clotting factors II, VII, IX and X. When compared with placebo adjusted dose warfarin maintaining an INR or 2.0–2.9 results in an absolute reduction in ischemic and hemorrhagic strokes of 2.7 % per year [34]. Warfarin has also been shown to be superior to aspirin in patients considered to be at an increased risk of stroke.

Several major limitations concerning warfarin exist. The time within the therapeutic range is often less than 75 % exposing patients to the risk of thrombo-embolism for significant periods of time. There are many interactions with other pharmacological agents as well as food and dose adjustments are frequently required. Despite this there is still a role for warfarin in clinical practice particularly in patients with valvular heart disease and AF. The non-vitamin K antagonist agents are contraindicated in the presence of valvular AF and also need to be used with extreme caution in the setting of renal impairment. There is also more clinical experience using warfarin combined with antiplatelet agents and there is also the ability to monitor the effect of the drug which may provide a reasonable indication of patient compliance. Warfarin is also relatively easily, albeit slowly, reversed with vitamin K.

Non-vitamin K Antagonist Oral Anticoagulation Therapy (OAC's)

These agents act by either directly suppressing thrombin or the conversion of prothrombin to thrombin by blocking the activated Xa factor. They have several theoretical advantages over warfarin such as a rapid onset and offset of action, reasonably predictable pharmacokinetics that do not require ongoing monitoring of anticoagulant and fewer interactions. It is important to monitor renal function particularly in patients where the baseline eGFR is below normal limits.

Direct Thrombin Inhibitors

Direct thrombin inhibitors bind to both soluble and fibrin-bound thrombin. The most commonly used in this group is the pro-drug dabigatran etexilate which was compared with warfarin in the RELY study. This prospective, randomized trial compared either 150 mg or 110 mg twice daily with warfarin (INR 2.0–3.0) for the prevention of stroke and systemic embolism in patients with non-valvular AF [35].

Dabigatran at a dose of 150 mg has been shown to be superior to warfarin with no significant difference in the primary safety endpoint of major bleeding. At a dose of 110 mg dabigatran was non-inferior to warfarin, with fewer major bleeds. The

incidence of intracranial haemorrhage and haemorrhagic stroke were lower with both doses of dabigatran.

Based on these results dabigatran etexilate has been approved by the Food and Drug Administration (FDA) at 150 mg twice daily with 75 mg twice daily in renal impairment. The European Medicines Association (EMA) has approved both the 110 mg twice daily and 150 mg twice daily in patients with non-valvular AF.

Factor Xa Inhibitors

The two major clinically available factor Xa inhibitors are rivaroxaban and apixiban.

Rivaroxaban has a plasma half life of 7–11 h with a flat dose response resulting in a once daily administration. Rivaroxaban was compared with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular AF who were at moderate-to-high risk for stroke in the Rocket AF Trial [36]. This double blind trial compared rivaroxaban 20 mg once daily (15 mg daily for those with an estimated creatinine clearance of 30–49 mL/min) with warfarin in 14,264 patients. Rivaroxaban was found to be non-inferior compared with warfarin for the primary endpoint of stroke and systemic embolism with a significant reduction in haemorrhagic stroke and intracranial haemorrhage. Rivaroxaban has a distinct advantage in being a once daily preparation. Additionally the ROCKET AF study enrolled older patients (mean age 73 years), with at least two risk factors (congestive heart failure, hypertension, stroke or TIA), higher mean values of CHADS2 score (3.5) and lower median values for therapeutic INR's compared to other trials which is more compatible with real life conditions.

Approximately one-third of active rivaroxaban is renally excreted and a dose reduction from 20 mg once daily to 15 mg once daily is recommended for patients with moderate to severe renal impairment with period monitoring of renal function. A sub-study of the ROCKET AF study showed this lower dose was safe and effective in patients with a creatinine clearance between 30 and 49 mL min^{-1}. Rivaroxaban has been approved by both the FDA and the EMA for stroke prevention in nonvalvular AF.

Apixaban has been shown to reduce the risk of stroke (predominantly through its effects on a reduction in hemorrhagic stroke) or systemic embolism, major bleeding and mortality in comparison with warfarin [37]. Additionally in patients for whom vitamin K antagonist therapy was considered unsuitable, apixaban compared with aspirin, reduced the risk of stroke or systemic embolism without a significant increase in the risk of major bleeding [38]. Apixaban has gained clinical approval with the FDA and EMA in patients with nonvalvular AF. Although the usual dose is 5 mg BiD this should be reduced to 2.5 mg BiD if 2 out of the following 3 criteria; age greater than or equal to 80 years, weight less than or equal to 60 kg or a serum creatinine greater than or equal to 133 mmol/L. The details associated with the major trials in the NOACs are summarized on Table 8.1.

Table 8.1 Showing a summary of randomized clinical trial data supporting NOAC's

Parameter	Rely	Rocket-AF	Averroes
Drug dose	Dabigatran etexilate 150 mg BID or 110 mg BID versus warfarin (INR 2.0–3.0)	Rivaroxaban 20 mg QD (15 mg QD in patients with creatinine clearance 30–49 ml/min) versus warfarin (INR 2.0–3.0)	Apixaban 5 mg BID versus Aspirin 81–315 mg OD
Study design	Randomized, open label	Randomized double-blind, double Dummy	Randomized, double-blind
Inclusion criteria	AF within 6 mths + 1 risk factor	AF within 6 mths +2 risk factors	AF within 6 mths + 1 risk factor
Number of patients	18,113	14,000	5,600
Mean age	71.5 years	73 years	70 years
Prior stroke/TIA	20 %	55 %	13.5 %
Mean CHADS2 score	2.1	3.5	2.1
Stroke and systemic embolism (percent/year)	1.71 % warfarin 1.54 % dabigatran 110 mg (p = 0.34) 1.11 % dabigatran 150 mg (p < 0.001)	2.42 % warfarin 2.12 % rivaroxaban (p = 0.117)	3.9 % aspirin 1.7 % apixaban (p < 0.001)
Major bleeding	3.57 % warfarin 2.87 % dabigatran 110 mg (p = 0.003) 3.32 % dabigatran 150 mg (p = 0.31)	3.45 % warfarin 3.6 % rivaroxaban (p = 0.576)	1.2 % aspirin 1.4 % apixaban (p = 0.33)
Intracranial haemorrhage rate (percent/year)	0.74 % warfarin 0.23 % dabigatran 110 mg (p < 0.001) 0.3 % dabigatran 150 mg (p < 0.001)	0.74 % warfarin 0.49 % rivaroxaban (p = 0.019)	0.3 % aspirin 0.4 % apixaban (p = 0.83)

HAS-BLED Score

This is a scoring system used to predict the 1 year risk of major bleeding defined as intracranial bleeding, hospitalization, blood transfusion or a drop in hemoglobin of greater than 2 g/L. The components of this scoring system are:

Hypertension: uncontrolled systolic blood pressure >160 mmHg

Abnormal renal or liver function: a serum creatinine greater than 200 mmol/L, need for long term dialysis or history of a renal transplant. Abnormal liver function is defined as an elevation of transaminases greater than 3 times the upper limit of normal or a history of chronic liver disease

Stroke

Bleeding

Labile INR: in the therapeutic range less than 60 % of the time
Elderly
Drugs or alcohol: the use of non-steroidal anti-inflammatory or antiplatelet agents

The maximum score is 9 with a score of greater than or equal to 3 indicative of a high bleeding risk where increased caution and regular review should be performed. It should not be used solely to exclude using oral anticoagulation but should be used to highlight patients at a higher risk of bleeding and should also be used to modify any controllable risk factor.

Catheter Ablation for AF

The concept of catheter ablation for the treatment of AF gained significant momentum when it was discovered that ectopic foci, which originate from sleeves of myocardium extending into the pulmonary veins may initiate AF [39]. This resulted in the concept that isolation of these foci by performing catheter ablation may reduce the likelihood of developing AF. Although the foci themselves were initially targeted this resulted in a high incidence of pulmonary vein stenosis and this has now be largely replaced with wide antral circumferential ablation (WACA). This technique has been shown to be associated with a lower incidence of recurrence of arrhythmias compared with segmental antral ablation [40]. This may be due to isolation of regions of the left atrial PV junction where micro re-entry may occur. Additionally WACA may have a greater effect on elimination of other non PV triggers in the posterior LA wall, debulk the left atrium and have a greater effect on autonomic denervation.

Pulmonary vein isolation (PVI) is currently considered the mainstream catheter approach for paroxysmal AF. It also is a very reasonable approach for the management of persistent AF with additional options to be considered. Some centers perform PVI in all patients with a history of persistent AF followed by an electrical cardioversion for the first ablation procedure. If the patient presents with further AF then either linear lesions, CFAE ablation or rotor ablation can be considered at that stage. Other centers perform more ablation for the first procedure although this may increase the potential for developing AT.

Risks of Catheter Ablation of AF

The risk of a significant complication associated with an AF ablation is approximately 2.9 % [41]. The most common complication is vascular (approximately 1 %) which is largely related to groin hematoma and occasionally femoral pseudoaneurysm formation. The risk of stroke and TIA is 0.6 %, cardiac tamponade (1 %) and clinically evident PV stenosis 0.5 %. The incidence of phrenic nerve palsy is approximately 0.4 % and although esophageal injury is common, atrio-oesophageal fistula is unusual occurring in 0.1 % of cases. The overall mortality is 0.06 %.

How to Perform a PVI

Patient Preparation

A PVI can be performed either with the patient under general anesthesia or with intravenous sedation and analgesia. There are several advantages to either strategy. General anesthesia often results in a quicker procedure with less patient discomfort and less patient movement. It may not always be available and some operators prefer sedation as there is more patient feedback during the procedure.

A TEE is performed in order to rule out a LAA thrombus particularly in patients who are in AF and have not been anticoagulated prior to the procedure. In most cases where the patient is receiving warfarin this can be continued throughout the procedure with an upper INR cut off of 3.5 above which the risk of bleeding is increased by a factor of 6 [42].

If the patient is receiving a non vitamin K antagonists OAC a decision must be made whether to stop the agent or not.

Some data suggests that uninterrupted dabigatran compared with uninterrupted warfarin is associated with an increased rick of bleeding and thrombo-embolic complications [43]. Dabigatran increases the effects of heparin often doubling the effects, an effect not seen to the same degree with rivaroxaban and apixaban [44]. It is therefore current practice to interrupt dabigatran prior to performing an AF ablation. The decision on when to hold dabigatran is dependent on the patient's renal function. In patients with normal renal function the drug may be held either the morning of the procedure or the evening prior but not for more than 24 h pre-procedure [45]. Dabigatran should be stopped earlier if renal function is reduced.

In patients with normal renal clearance, the best option may be drug suspension on the morning of the procedure, or the night before, but always <24 h before the procedure. A target ACT of greater than 350 s should be achieved during the procedure. Dabigatran can then be recommenced 3–4 h following removal of the sheaths [45]. The dosage of dabigatran following this should be based on renal function and the potentially risk of bleeding.

Recent data has shown that uninterrupted rivaroxaban therapy appears to be as efficacious as uninterrupted warfarin in preventing thrombo-embolic and bleeding complications in patients undergoing AF ablation [46]. If the decision if made to hold rivoroxaban for an AF ablation the dose on the morning of the procedure may be held. There is currently limited data regarding the use of apixaban in patients undergoing an AF ablation although it may seem reasonable to hold a dose the morning of or the evening before the procedure.

It is our practice to administer the final dose of the OAC 24 h prior to the ablation and perform a pre-procedure TEE. Heparin is then administered throughout the procedure and the OAC is recommenced 3 h following removal of the venous sheaths which are removed at the end of the case with no reversal of heparin.

If the patient is receiving a general anesthetic the TEE probe can be left in position in order to help facilitate the transseptal access and monitor for pericardial effusion.

Venous access is generally achieved via the femoral vein with two 8Fr sheaths and a 6Fr sheath. A decapolar is positioned in the coronary sinus to help with the transseptal puncture and may also be useful for mapping and pacing particularly if an AT develops during the procedure.

Two transseptal sheaths are then positioned over 0.032 wires into the superior vena cava and flushed with heparinized saline. Heparin is then administered at a dose of 100 iu/kg in order to achieve an ACT of greater than 300 s in patients who are either not on warfarin or have an INR less than 2.0 [47]. For patients who are receiving warfarin and have a therapeutic INR 75 iu/kg of heparin should be administered in order to achieve an ACT of greater than 300 s. ACT should be checked every 20 min and either further boluses or an infusion can be administered.

Transseptal Access

A posterior location in the fossa ovalis is chosen in order to facilitate access to all regions around the pulmonary veins. Although his can be performed under fluoroscopic guidance the addition of echocardiographic data is sometimes helpful particularly if the fossa is difficult to cross or is aneurysmal.

A range of sheaths and transseptal needles are available. A BRK1 needle often results in a good location and is useful in patients who have enlarged atria. If this is tenting the fossa without crossing then the flexion can be slightly reduced or a BRK or a Baylis needle can be considered. Transseptal access can generally be achieved using a combination of a PA, left lateral, RAO and LAO views. In general for PVI standard sheaths are sufficient although deflectable sheaths may help with contact and occasionally with access to superior to the right superior pulmonary vein. Deflectable sheaths may be useful for a linear lesion joining the mitral isthmus to the left inferior pulmonary vein. If a non standard sheath is to be switched to a deflectable sheath a 0.032 wire can be extended out to the left superior pulmonary vein for an over the wire switch.

Whatever choice of sheath it is very important that the side arms are flushed with heparinized saline in a closed circuit and that no air bubbles enter the system.

Anatomic Reconstruction of the Left Atrium

The anatomy of the LA is generally constructed using a multipolar circular catheter. This may merged with a pre-procedure CT. A CT may be helpful in determining the presence of aberrant pulmonary veins as well as the presence of variants such as common ostia. MRI of the LA can also be performed but is more time consuming. Either of these modalities can be merged with the electroanatomic image. CartoMerge (Biosense Webster) uses fiducial points taken from selected anatomical structures such as the pulmonary vein ostia. The image is then rotated in order to

compare the anatomic shells of both structures for comparison. If there is a difference between the two images further points can be taken on the electro anatomic map.

NavX Fusion (St Jude Medical) can also be used to integrate the electroanatomic map onto a baseline CT scan. Following acquisition of the anatomic shell this system utilizes a field scaling algorithm which adjusts for the non-linearity of the geometry taking into account the measured inter-electrode spacing for all the locations within the geometry. Four fiducial points are then taken on the CT and the electroanatomic map and secondary fusion is used to reduce mismatch between the two images [48].

Although these systems may be helpful the LA dimensions vary with rhythm status and are also dependent on the intravascular volume. There is overall no convincing data to suggest that image integration increases success or reduces complications but may reduce fluoroscopy times.

Ablation Technique

Following anatomic reconstruction of the LA a circular mapping catheter is positioned within the ostia in one of the pulmonary veins where is should record nearfield pulmonary vein potentials and farfield left atrial potentials. If a contact force catheter is being used for ablation then this is positioned in the middle of the left atrium where there is no contact and a zero is set on the catheter.

The catheter should then be positioned so that it is on the atrial side of the pulmonary vein ostia. The ostia can be difficult to precisely locate on fluoroscopy or even on an electroanatomic map and there is an overlap between left atrial myocytes extending into the pulmonary veins and venous tissue extending into the left atrium. If the demarcation is unclear the ablation catheter can be placed on the venous side of the ostia while pacing and capturing the pulmonary veins. The point at which pulmonary vein capture no longer occurs is a reasonable estimate of the ostia.

Point by point ablation is generally performed using a 3.5–4.0 mm irrigated catheter. Power is delivered at 30–35 W anterior to the pulmonary veins and 25–30 W along the posterior wall in order to limit delivery of energy to the esophagus and branches of the vagus nerve. A target temperature of less than 40 °C and irrigation at 17 ml/min are set. If contact force is used then a minimum of 10 g of force should be aimed for. The catheter is generally moved every 30–60 s.

Certain regions around the pulmonary veins may be technically more challenging than others and require different catheter manipulations. The Coumadin ridge between the left pulmonary veins and the left atrial appendage is an infolding of the lateral atrial wall is shown in Fig. 8.3. It is at its narrowest at the border of the left superior pulmonary vein measuring 2.2–6.3 mm to its broadest aspect at the boundary of the left inferior pulmonary vein measuring 6.2–12.3 mm [49]. It is at its thickest at the anterosuperior region.

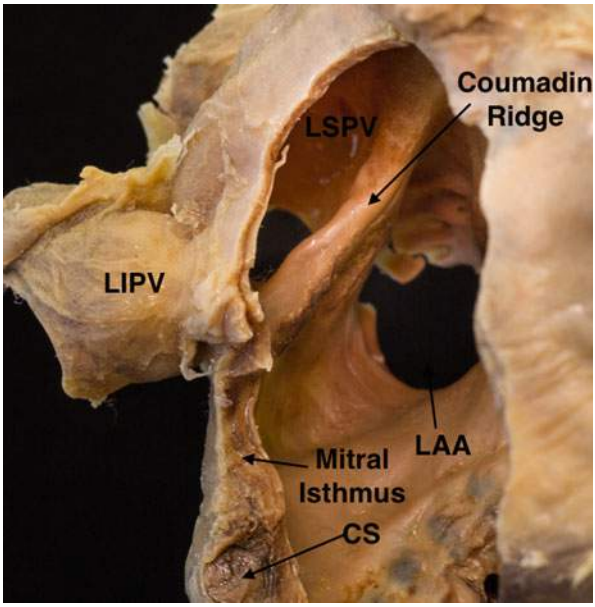

Fig. 8.3 The Coumadin ridge is seen between the left superior pulmonary vein (*LSPV*), the left inferior pulmonary vein (*LIPV*) and the left atrial appendage (*LAA*). Between the LIPV and the mitral annulus (*MA*) is the mitral. Also seen in this image is the coronary sinus (*CS*)

In order to ablate along the Coumadin ridge the ablation catheter can be withdrawn from the left superior pulmonary vein with counterclockwise rotation so that the catheter is moving anterior in the direction of the LAA. This should maximize contact with this region. Excess counterclockwise torque results in the catheter moving into the LAA and this often needs to be counteracted with clockwise rotation. Given the significant autonomic innervation of the Coumadin ridge ablation in this region commonly results in a slowing of the sinus rate.

Flexion and extension of the ablation catheter is required for ablation inferior and superior to the left sided PV's. Ablation starting on the roof superior to the left superior pulmonary vein often results in separation of local pulmonary vein signals and LAA farfield signals.

Ablation superior and inferior to the right sided PV's can be performed often with a combination of rotation with flexion and extension of the catheter. Occasionally a deflectable sheath may be useful in these regions although a bidirectional catheter used through a standard sheath is in general suitable to reach all regions. When ablation is performed inferior to the right inferior pulmonary vein in a small left atrium it is important to flex with an acute angle in order to minimize the risk of losing transseptal access.

Ablation may be required in the carina between the pulmonary veins despite WACA being performed. This may be explained by endocardial to epicardial connections in this region which may result in continued conduction. Additionally con-

nections exist between ipsilateral PV's resulting in several isthmus which may be an important consideration when performing PVI and may in part explain why segmental ablation was previously shown to have limited efficacy [50].

Pulmonary Vein Potentials and Farfield Signals

Electrograms recorded from the ostia of the pulmonary veins show an initial non circumferential lower amplitude atrial signal followed by an isoelectric period followed by sharp pulmonary vein potentials [51]. Depending on the overlap between the left atrium and the surrounding structures as well as the orientation of the mapping catheter there is a variable delay between the farfield electrogram and the pulmonary vein potentials. An example of this is shown in Fig. 8.4 in which the first component is farfield left atrial followed by an isoelectric line followed by a PVP which is a sharp high frequency signal.

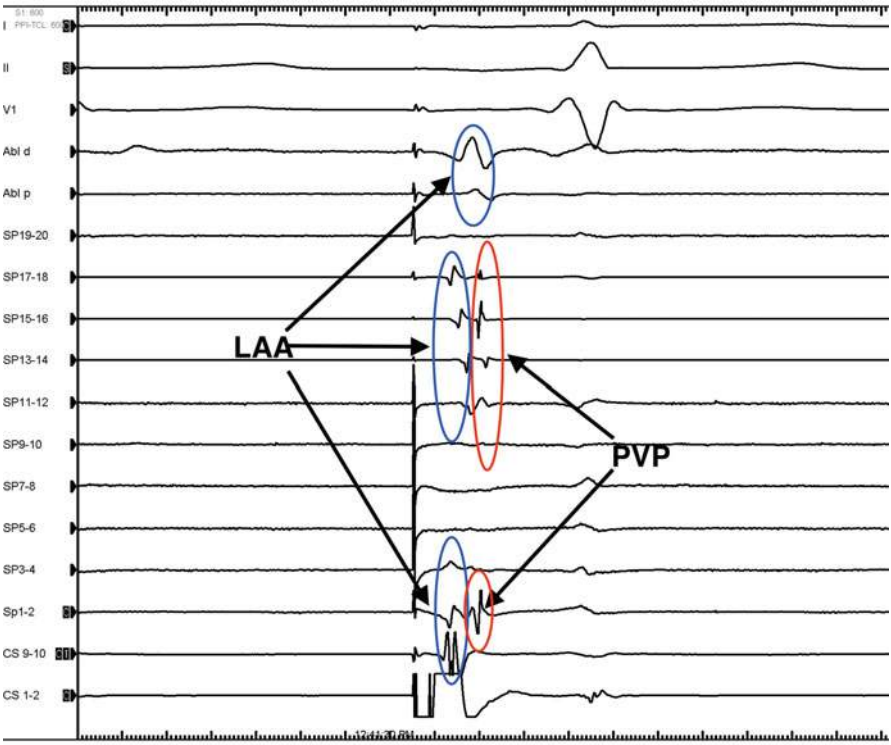

Fig. 8.4 The circular catheter (SP 1–20) is in the left superior pulmonary vein. Pacing is performed from the distal coronary sinus (CS 1–2). The first deflection is farfield from the left atrial appendage (*circled in blue*) followed by an isoelectric line followed by a sharp pulmonary vein potential (*circles in red*)

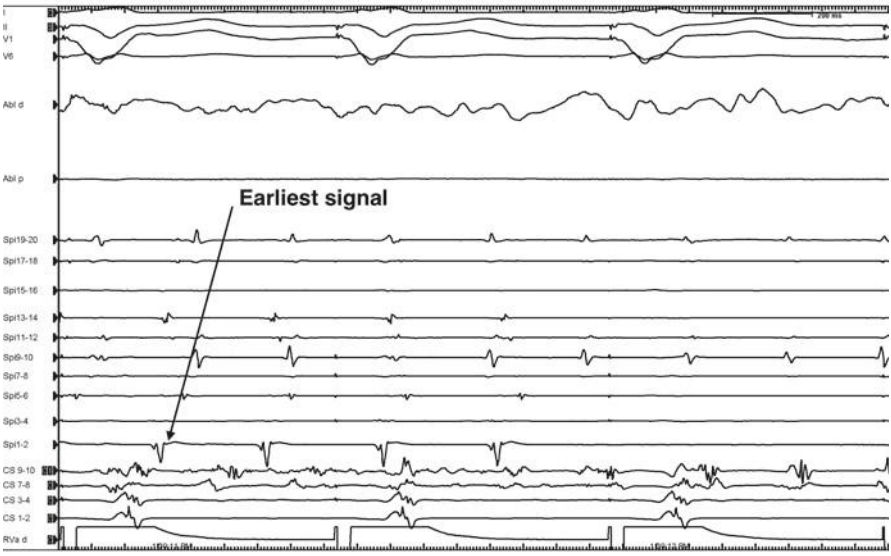

Fig. 8.5 Isolation of the LSPV. The circular catheter is positioned in the LSPV. The earliest nearfield activation is recorded on Spi poles 1–2 followed by 13–14. These poles are almost overlapping and are located along the lower junction between the LSPV and the LAA along the ridge (near to where the ablation catheter is positioned). Ablation in this region results in isolation of the vein with only LAA farfield recorded on the circular catheter. (CS 9 10 is in the proximal coronary sinus and CS 1 2 is in the distal CS). Ventricular pacing from the RV apex is performed as the patient became bradycardic during RF ablation

The LAA is anterior to the left superior pulmonary vein. As a result sharp pulmonary vein potentials can often be merged within LAA signals. In order to help differentiate CS pacing can be used to separate LAA signals from PV potentials as shown in Fig. 8.4. Additionally direct pacing may be performed from the LAA. For the left superior and inferior pulmonary veins pacing from the distal coronary sinus or left atrial appendage can be performed in order to increase the isoelectric line between the farfield and nearfield signals. Although pacing from the distal coronary sinus is reasonably simple it is somewhat dependent on the variable connections between the coronary sinus and the left atrium. Left ventricular farfield may also be recorded in the left inferior pulmonary vein.

This cannot be performed if the patient is in AF and differentiation of farfield LAA signals from local PV potentials can be somewhat more complex. An example of isolation of the LSPV during AF is shown in Fig. 8.5. In this example the circular catheter is positioned in the LSPV during ablation along the ridge between the LAA and the vein. The earliest activation is recorded on poles 13–14 where ablation is performed. This results in isolation of the vein with farfield LAA potentials being recorded on poles 9–10, 11–12 and 19–20 which are all in anterior locations. Another example of isolation of the RSPV is shown in Fig. 8.6. As ablation is performed local PVP's in the vein slow considerably and then disappear with only farfield atrial activation recorded.

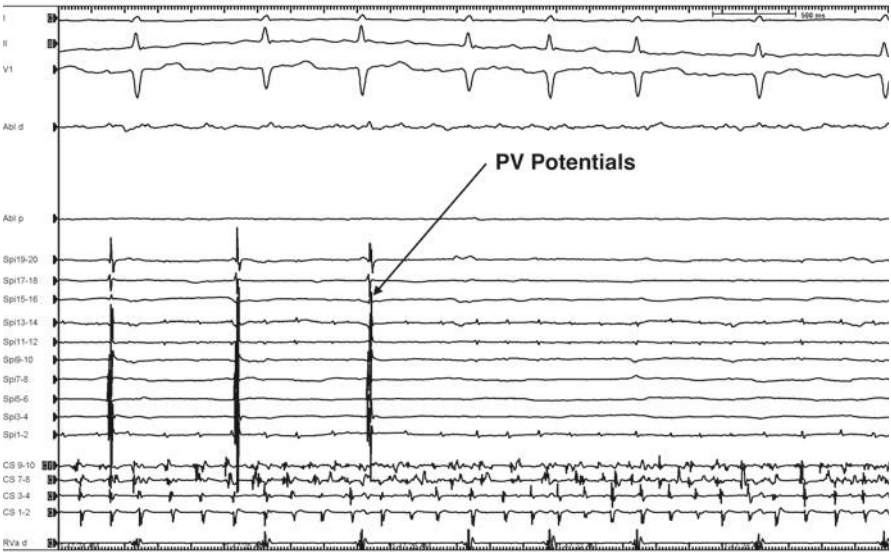

Fig. 8.6 Loss of local PV potentials during isolation of the RSPV. These signals are slowed considerably during ablation and following further ablation only farfield atrial signals are detected. The spiral (Spi) catheter is located in the RSPV (CS 9 10 is positioned in the proximal coronary sinus and CS 1 2 is located in the distal CS)

Fig. 8.7 Anatomic specimen showing a posterior view of the right superior pulmonary vein (*RSPV*) and right inferior pulmonary vein (*RIPV*). The superior vena cava (*SVC*) is anterior and close to both of these structures and farfield electrical activity from the SVC may be detected when mapping these veins

As shown in the anatomic image in Fig. 8.7 the superior vena cava is anterior to the right superior pulmonary vein. In order to differentiate superior vena cava potentials from pulmonary vein potentials the signal can be measured relative to the surface p wave. As the superior vena cava is so close to the sinus node signals will be very early if originating from the superior vena cava. If this is within 30 ms of the onset of the p wave it is likely to reflect superior vena cava activity. There is generally no significant farfield recorded in the right inferior PV. The PV potentials recorded on the circular catheter have slowed considerably during ablation. Further ablation results in loss of PV potentials with only farfield atrial signals.

Fig. 8.8 2:1 conduction from the left atrium to the left superior pulmonary vein. A potential is recorded in the vein after every second atrial electrogram. This signified continued conduction in the posterior region of the LSPV (SP 3–4) which required further ablation for isolation of the vein

Confirming Pulmonary Vein Isolation

PVI may be confirmed by proving bidirectional block with or without the administration of intravenous adenosine as well as pacing along the ablation line around the pulmonary veins. Of note, **entrance block without exit block may occur in up to 40 % of the patients** [52].

Entrance block may be observed either during normal sinus rhythm or with atrial pacing during sinus rhythm. The circular catheter is positioned in the PV antra just distal to the line of ablation. The most important principle is to distinguish between PV potentials and LA or RA signals detected as farfield on the circular catheter. Although PV potentials are sharp and of a much higher frequency than farfield atrial potentials they may be superimposed. Pacing the structure or close to the structure where the atrial signals are originating from should result in these signals becoming earlier if they are originating from that structure. For potentials coming from the LAA either the LAA can be paced directly or the distal CS if the catheter is positioned appropriately. An example of 2:1 conduction from the left atrium to the LSPV seen in Fig. 8.8 in which a potential with the vein is recorded after every second atrial electrogram. This represents slow conduction with conduction through SP 3–4 which was positioned posterior to the LSPV. Ablation in this region resulted in isolation of the vein.

In order to prove exit block the ablation catheter can be positioned in the same pulmonary vein as the circular mapping catheter. Although pacing can be performed from either the ablation catheter alone or the circular catheter alone it is often easier

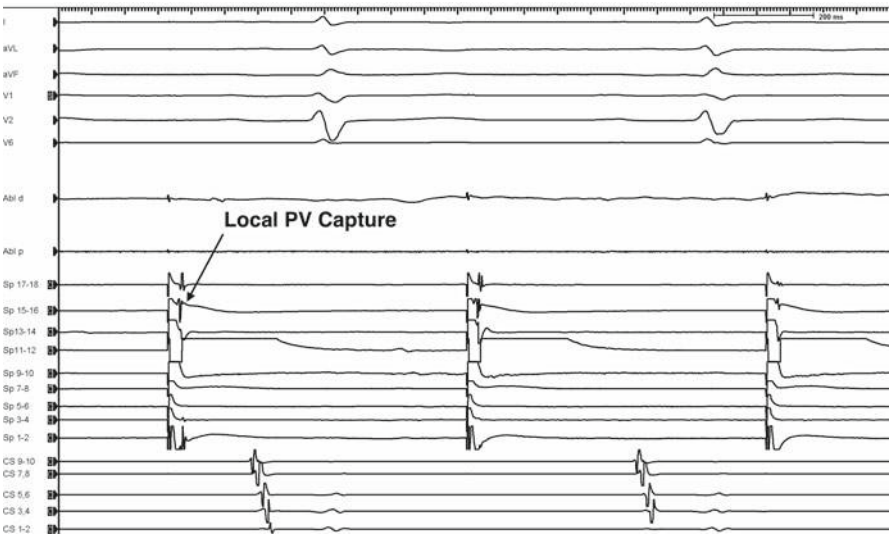

Fig. 8.9 Circular catheter (SP 1–18) in the right superior pulmonary vein with pacing from poles 15–16 showing local capture with sharp local PV potentials which do not capture the left atrium (CS 9 10 is located in the proximal coronary sinus while CS 1 2 is located in the distal coronary sinus)

to discern pulmonary vein potentials from a separate catheter which has closely spaced poles without superimposed pacing arterfact. Pacing can be performed using a decremental output until there is only pulmonary vein capture. This avoids capture of adjacent structures which may mimic intact conduction. Lack of conduction from the pulmonary veins to the left atrium proves that the ablation line is resulting in conduction block. An example of this is shown in Fig. 8.9.

Although the presence of dissociated PV potentials is a useful indicator of exit block conduction may still be present in 10 % of patients who display these [53]. An example of dissociated potentials from the RIPV is shown in Fig. 8.10. Pacing is performed from the high right atrium (HRA). Farfield atrial potentials are seen on the circular catheter with intermittent PV potentials which are not conducted to the atrium.

An additional useful technique to help prove an intact line around the pulmonary veins is to assess for unexcitability to pacing. Following ablation the catheter is positioned along the line during sinus rhythm at an output of 10 mA and a pulse width of 2 ms [54]. If lack of local capture occurs the catheter is moved a further 5 mm along the line and pacing repeated. If local capture occurred then further ablation was performed in this region and pacing performed at the same output.

The administration of intravenous adenosine appears to be of some use in assessing for dormant conduction following isolation of the PV's due to hyperpolarization of myocytes which have been acutely ablated. This can be administered after a period of monitoring post ablation and further ablation performed if there is any evidence of dormant conduction. An example of this is shown in Fig. 8.11.

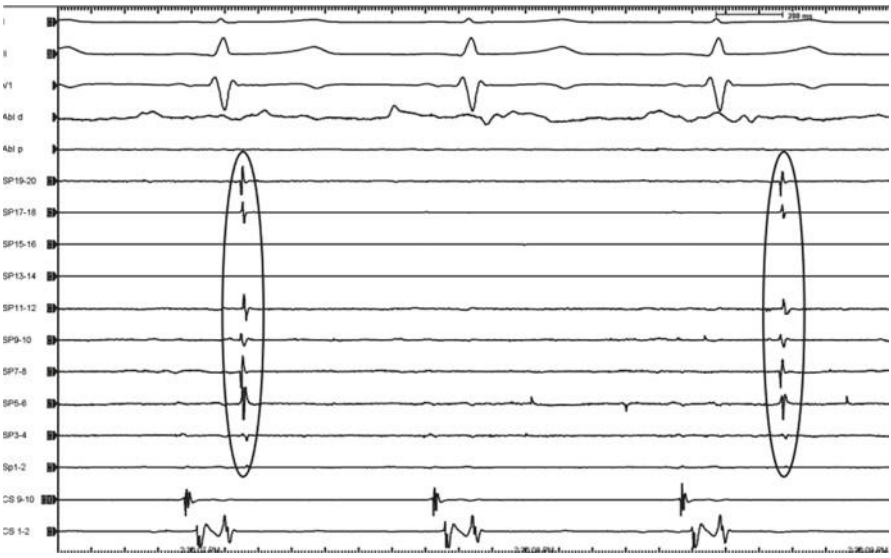

Fig. 8.10 Dissociated PV potentials (*circled*) recorded on a circular catheter (Sp 1–20) positioned in the right superior pulmonary vein (RSPV). Pulmonary vein potentials are seen which do not conduct into the left atrium. The ablation catheter is positioned in the RSPV. CS 9–10 is in the proximal CS while CS 1–2 is in the distal CS

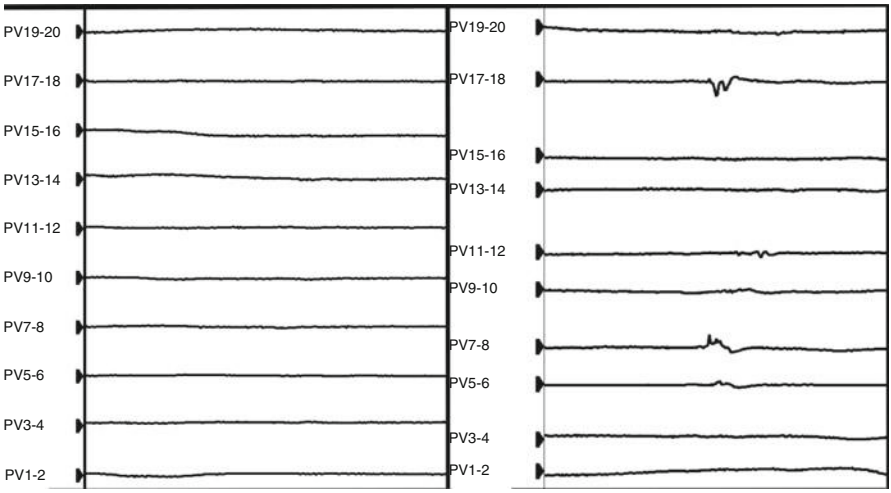

Fig. 8.11 The circular catheter (PV 1–20) is in the right superior pulmonary vein. The image on the right shows the potentials recorded following ablation and before the administration of adenosine. The pulmonary vein appears to be isolated. The image on the right is recorded following the administration of adenosine. This shows early activation in PV 7–8 followed by 5–6, 17–18, 9–10 and 11–12. This region was anterior to the right superior pulmonary vein at the level of the carina. Further ablation was delivered here and the vein was retested with adenosine and found to be isolated

Assessing for Non PV Triggers

Non pulmonary vein triggers may contribute to AF in some cases and are worth looking for particularly in redo ablations where the pulmonary veins have remained isolated. As shown in Fig. 8.12 potential locations include the superior vena cava, coronary sinus, crista terminalis, fossa ovalis, ligament of Marshall and left atrial appendage.

In order to map for non pulmonary vein triggers a multipolar catheter is positioned in the coronary sinus and another along the posterolareral right atrium extending into the superior vena cava. Intravenous isoprenaline is administered in incremental doses from 3 to 20 microgrammes per minute. If AF is not inducible decremental atrial pacing can be performed. Using the earliest sites of activation focal ablation can be performed and further triggers can then be mapped. It may be that given the increasing width of WACA that many triggers may be incorporated into the original lesions.

Cryoablation

Cryoablation utilizes a system (Arctic Front Cardiac CryoAblation, Medtronic, Inc) which pumps the refrigerant N20 into an inflatable balloon as shown in Fig. 8.13. This is positioned at the PV orifice. Contrast is injected into the PV in order to

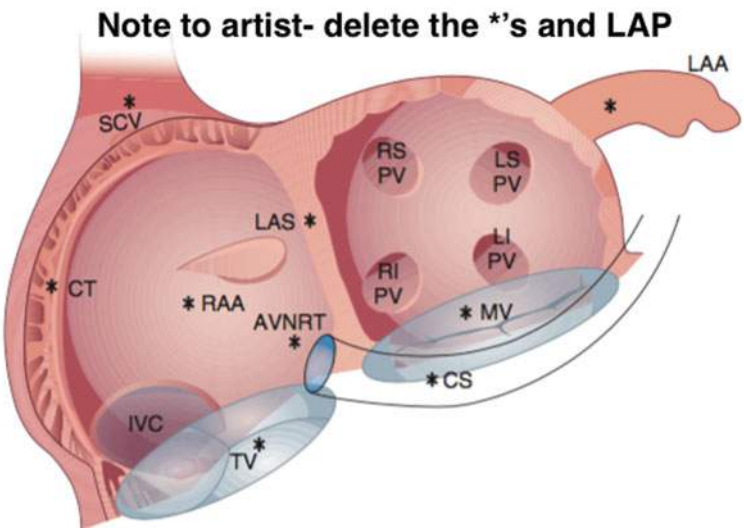

Fig. 8.12 Potential locations of non-pulmonary venous triggers (*RSPV* right superior pulmonary vein, *RIPV* right inferior pulmonary vein, *LSPV* left superior pulmonary vein, *LIPV* left inferior pulmonary vein, *MV* mitral valve, *CS* coronary sinus, *LAA* left atrial appendage, *LAS* left anterior septum, *RAA* right atrial appendage, *AVNRT* AV nodal re-entry tachycardia, *TV* tricuspid valve, *SVC* superior vena cava, *IVC* inferior vena cava)

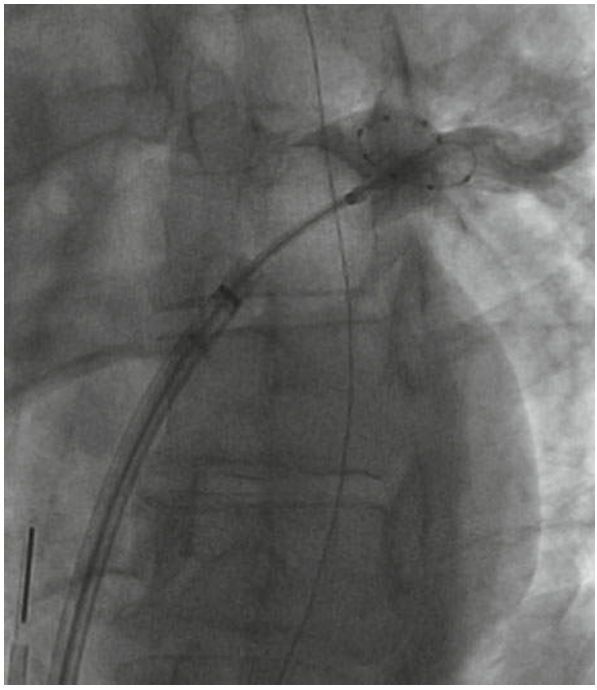

Fig. 8.13 Showing the new generation Cryoballoon used for antral pulmonary vein isolation. On this fluoroscopic image the cryoballoon is positioned in the left superior pulmonary vein (© Medtronic plc 2015)

assess for good contact and applications are generally performed over a period of 4 min. A circular catheter assesses for electrical isolation of the PV's and further applications are performed if required. This procedure generally requires a single trans septal access with a 15 Fr sheath. The balloon is advanced over a guidewire and positioned at the PV ostia. The balloon diameter is available in either 23 or 28 mm. The size can be determined on CT or ICE. Cryoablation has been shown to be non-inferior to point by point RF ablation in terms of freedom from AF and an absence of persistent complications [55]. The second generation cryoballoon has an inner mapping guidewire and an increased number of emission ports.

Hybrid Ablation of AF

Surgical ablation for AF has evolved from the Cox Maze procedure to a minimally invasive epicardial approach. These can be used to deliver RF around the PV antra as well as create a roof and floor line resulting in a posterior box lesion. Although this may be moderately effective in cases of paroxysmal AF freedom from AF for cases of persistent AF is relatively low. As a result of this a hybrid approach has been developed combining endocardial and epicardial ablation. Regions which cannot be easily reached from the epicardial approach can be ablated endocardially such as the CTI and mitral isthmus. Transmural lesions can be created and lines of

block can be assessed and any gaps completed. Although this can be performed at the same time it is often considered reasonable to delay endocardial ablation for several months in order to assess conduction block after a period of time. This may be a useful option in patients with persistent AF and dilated atria.

Ablation of Persistent AF

Ablation strategies in persistent AF are imperfect. Several techniques have been developed for ablation for persistent AF. Linear lesions may be performed until sinus rhythm is restored or until an electrical cardioversion is performed and the lines checked for conduction block. CFAE ablation may be performed in the left and right atria and rotors may be mapped either invasively or non-invasively and selectively targeted.

Linear Lesions

Following isolation of the pulmonary veins linear lesions can be performed. The most common of these involve a linear lesion along the left atrial roof joining the right superior pulmonary vein to the left superior pulmonary vein. A mitral isthmus line may also be performed although it may be difficult to achieve successful and permanent block as the wall may be relatively thick and may require epicardial ablation via the coronary sinus (at a lower power). Rather than performing linear lesions in all cases of AF, these are often performed in cases where the patient develops an atrial flutter either during the ablation or has a documented history of an atrial flutter which is then induced. In such cases the CTI is often mapped first followed by the pulmonary veins. If these are silent then entrainment in certain anatomic locations can then be performed as well as mapping of local signals. The most common locations to map are the mitral annulus and the LA roof as the majority of macro re-entry atrial flutters involve these regions. If there is a significant variability in the tachycardia cycle length (greater than 15 %) then the mechanism is more likely to represent a focal AT. In our experience both a focal AT and a macro re-entry atrial flutter may have a tachycardia cycle length less than 15 % and therefore this is not such as good discriminator.

Roof Dependent Left Atrial Flutter

In order to map roof dependent left atrial flutter the catheter is positioned anterior to the roof and then more inferiorly close to the anterior mitral annulus. This is repeated by positioning the ablation catheter along the roof in the posterior direction and then towards the coronary sinus which generally marks the general direction of the posterior mitral annulus. If the activation is in the reverse direction i.e. earlier inferior

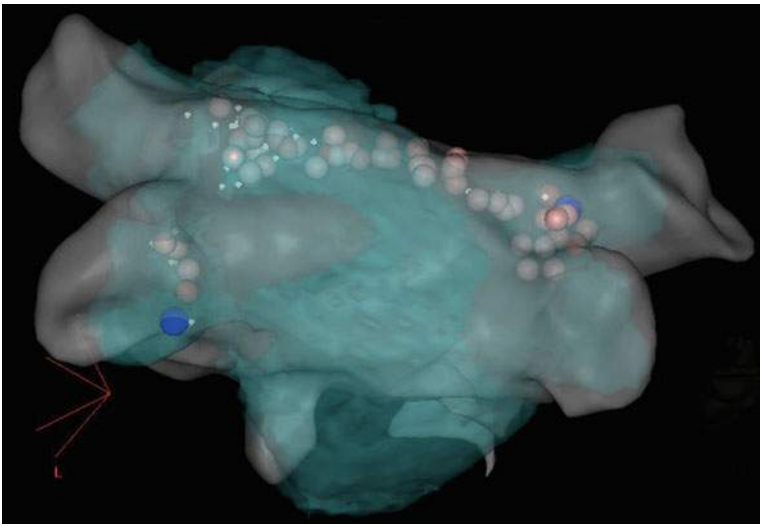

Fig. 8.14 Electroanatomic map showing a linear lesion joining the left superior pulmonary vein to the right superior pulmonary vein. This resulted in termination of the macro re-entrant atrial flutter. Further pacing demonstrated block across this line

than superior on the anterior wall and earlier superior to inferior on the posterior wall or vice versa then this is likely to be a roof dependent atrial flutter. If entrainment is performed in the anterior and posterior regions of the roof then a PPI-TCL of less than 30 ms further helps to confirm roof dependent atrial flutter. In the setting of a prior roof line or PVI with WACA mapping of fractionated potentials in the region of the roof is also helpful.

A roof line connecting the LSPV and the RSPV should be performed in the setting of a macro re-entry atrial tachycardia circulating around the PV's and involving the roof. In order to perform this the sheath is directed towards the right superior pulmonary vein while the catheter is flexed over to the left superior PV (Fig. 8.13). Using 30–35 W the catheter flexion can then be slowly released staying at each point for approximately 30–60 s. A superior and a PA view help to ensure that the line is performed along the roof rather than the posterior wall. In order to evaluate the roof line the LAA is paced during sinus rhythm. Roof line block is demonstrated by the presence of double potentials along the line during pacing as well as caudocranial activation of the posterior wall (Fig. 8.14).

Mitral Isthmus Dependent Atrial Flutter

This is a relatively common cause of post PVI atrial arrhythmias and generally occurs as a result of slow conduction inferior to the LIPV from a prior mitral isthmus ablation or PVI. In this arrhythmia CS activation is either proximal to distal or distal to proximal. It is useful to use the ablation catheter to map the anterior mitral

annulus. If CS activation is proximal to distal then anterior activation should be from lateral to septal. If the CS activation is distal to proximal then the anterior mitral annular activation should be from septal to lateral as shown in Fig. 8.15.

A posterior mitral isthmus line may be performed which connects the LIPV to the posterior mitral annulus close to the coronary sinus. A deflectable sheath is used and the ablation catheter is positioned at the ventricular side of the lateral mitral annulus with an AV ratio of either 1:1 or 2:1 [56].

During proximal CS pacing the catheter and sheath are then rotated clockwise towards the left inferior PV with delivery at 30 W for 90–120 s applied at each location. The catheter is moved whenever there is splitting of the local electrograms. The mitral isthmus varies in thickness along its length being thinner at the annular end and thicker at the medial end.

In order to prove block for a posterior mitral isthmus line pacing is performed from the CS and activation is measured in the LAA. Normally pacing from the distal CS should result in a shorter conduction time to the LAA than pacing from a less distal pole. In the event of posterior mitral isthmus block the more distal location will take longer to travel to the LAA. The presence of double potentials along the entire ablation line with coronary sinus pacing is also a useful endpoint.

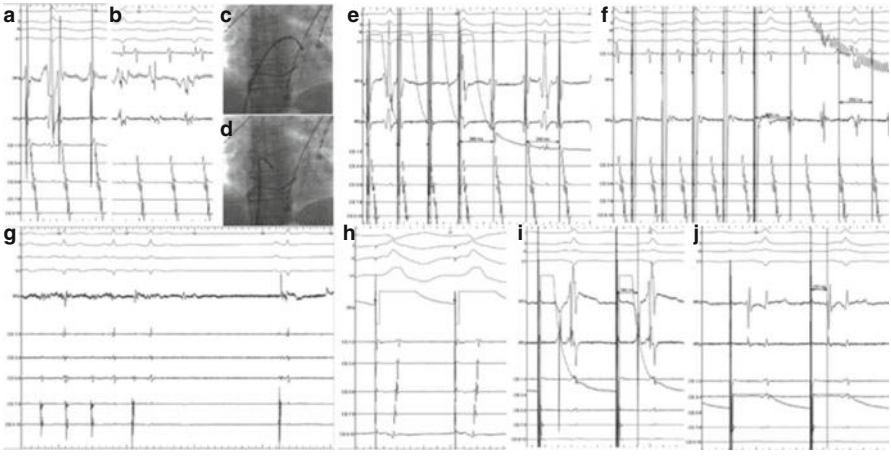

Fig. 8.15 Mitral isthmus dependent atrial flutter in a patient with a prior PVI. In panel **a**, the activation of the coronary sinus can be seen to be distal to proximal. The mapping catheter is anterolateral. As the mapping catheter is moved along the anterior wall to the septum in panel **b**, the direction of activation is clearly septal to lateral. This is compatible with perimitral flutter. Panels (**c**, **d**) demonstrate the catheter positions in panels (**a**, **b**), respectively, in an anteroposterior view. Entrainment maneuvers are performed from the distal CS (panel **e**) and septally, on the mitral annulus (panel **f**), with a return cycle length on both occasions being within 20 ms. A mitral line from the lateral mitral annulus to the left inferior pulmonary vein is performed, resulting in termination of the tachycardia (panel **g**). The completeness of the line is now checked with pacing from the line (panel **h**) demonstrating proximal to distal activation of the coronary sinus and a longer delay from close to the line (panel **i**) than distally to the line (panel **j**), confirming bidirectional block (Courtesy of Weerasooriya et al. [62], Wiley Brothers)

If block is not achieved then the line should be remapped and ablated further. In some cases ablation has to be performed at 20 W from the coronary sinus in order to block epicardial activation. An alternative approach is to perform an anterior mitral isthmus line joining the anterior mitral annulus to the LSPV.

CFAE Mapping and Ablation

CFAE's are defined as local electrograms which are fractionated with at least two components and with cycle lengths less than 120 msec recorded during AF and lasting for at least 10 s [57]. These are frequently recorded during AF within the regions of the LA close to the pulmonary vein antral regions and therefore may be ablated and electrically isolated during a pulmonary vein isolation.

In persistent atrial fibrillation CFAE's may be located anywhere within the left and right atrium with a potential propensity for the septum, inferoposterior wall of the LA and the LAA.

There are various theories as to what CFAE's actually represent with suggestions such as anchor points in rotors, regions of conduction slowing or autonomic activation. The long term results of CFAE ablation are not impressive and certainly this does not appear to represent a very effective strategy for the treatment of persistent AF.

Rotor Mapping

A rotor is defined as an unexcited core termed a phase singularity resulting in reverberations which radiate at very high velocity into the surrounding tissue [58]. Phase singularities are surrounded by different phases of the cardiac action potential and may be considered useful targets for ablation as they may be considered regions of tissue which can support rotors. They may occur on the endocardium, mid myocardium or epicardium or indeed span all layers. The theory is that following initiation of atrial fibrillation from pulmonary vein and non pulmonary vein sources rotors result in maintenance of atrial fibrillation.

Rotors differ from re-entry circuits in several ways. In a rotor the core is the active component with secondary spiral activity. The rotor core is functional and does not appear to be related to a detectable structural obstacle. Rotors are not stationary and may move over a considerable area [59]. Spiral waves also collide with each other altering the overall activation pattern. Additionally there does not appear to be a close correlation between rotors and CFAE's [59].

Some of these features actually make mapping of rotors very complex. Rotor activation is complex, can change during the mapping process and may involve different the endocardium, myocardium and epicardium. There are currently two systems which may be used for mapping rotors. These involve either invasive mapping using a multi-electrode basket catheter called the Focal Impulse and Rotor Modulation system and a non invasive multi electrode vest which is superimposed on a cardiac CT.

Focal Impulse and Rotor Modulation of Atrial Fibrillation

This system uses a 64 electrode basket with eight splines which is positioned in either the right, left or both atria as shown in Fig. 8.16. If the patient is in atrial fibrillation the unipolar electrograms are recorded and exported for analysis. If the patient is in sinus rhythm atrial fibrillation is induced with rapid atrial pacing and the signals are then recorded and analyzed after 10 min of sustained atrial fibrillation. It is extremely important that there is excellent electrode contact. The correct size of basket should be chosen and this can be difficult in large atria. Catheter orientation should be optimized on fluoroscopy and with the aid of a 3 dimensional mapping system in order to record vital areas of the left atrium including the pulmonary veins and the left atrial appendage as well as septal, roof, anterior and posterior activity.

The signals are then processed using RhythmView™ (Topera Inc.). This system is based on restitution monophasic action potential data acquired during rapid atrial pacing and atrial fibrillation. This displays the activation signals on a 2 dimensional image where the operator can then visualize potential rotors or focal sources. The image of each atria is opened so that for the right atrium the tricuspid annulus is inferior with the septal component to the right of the image and the lateral component to the left. For the left atrium the mitral annulus is at the bottom of the image

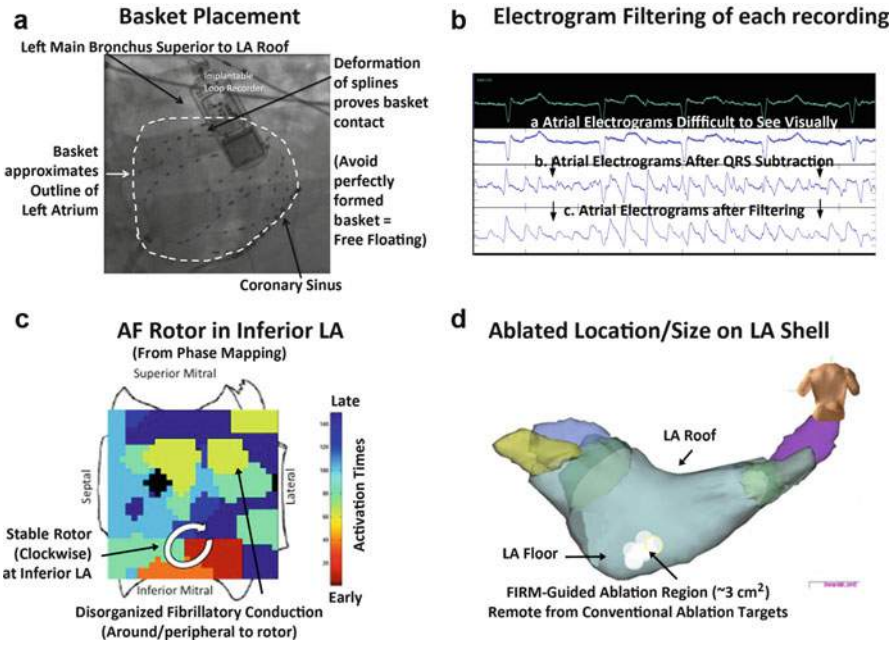

Fig. 8.16 Approach to FIRM (Focal Impulse and Rotor Mapping) guided ablation of atrial fibrillation (Courtesy of Dr Sanjiv Narayen)

and is divided. The electrodes of interest where a rotor core is felt to exist can then be referenced off an electroanatomic system and ablation can then be performed.

It has been shown that focal sources and rotors may be recorded in almost all patients with atrial fibrillation. Approximately one third of these can be recorded in the right atrium [60] and more than one half of all rotors are recorded outside of the regions where a wide area circumferential ablation would be performed [61]. Results suggest that the addition of ablation of rotors using this technique increases the success when compared with pulmonary vein isolation alone.

A. **Baskets placed in left atrium** (**shown**) and also in right atrium to map both chambers sequentially. Good positioning results in deformation of the highly compliant basket, proving electrode contact, and splines that approximate the LA roof and floor. In contrast, a spherical shape when deployed indicates an undersized basket with poor contact.
B. **Electrogram filtering** using well-established methods enables detection of sometimes difficult to visually identify atrial signals.
C. **Rotor during human AF in left atrium**, revealed by spatial phase mapping of filtered atrial electrograms, depicted as clockwise 'snapshot' (isochrone) where early and late activation meet, surrounded by fibrillatory disorganization. Phase mapping is used since activation mapping during of dynamically changing activation in AF is challenging. Intraprocedurally, diagnosis is actually made from animated 'FIRM movies' which better convey rotor precession and their dynamic interaction with the fibrillatory milieu.
D. **FIRM-guided ablation zone**, in inferior left atrium guided by map, typically of $\approx$3 cm^2 areas.

Non-invasive Multi Electrode Mapping

Using this technique a 252 electrode vest (CardioInsight, © Medtronic plc 2015) is applied to the patient during AF. This is used to record unipolar surface potentials. Anatomic data is then acquired by performing a noncontrast cardiac CT with the vest in place so that each electrode position can be calculated relative to the cardiac chambers. The system then performs a calculation in order to calculate and display electrical data on the surface of the heart from the surface unipolar electrograms. Activation sequences are then calculated by looking at the most negative dV/dT. This can then be displayed on a 3 dimensional reconstruction of the right and left atria using colors to animate various phases of depolarization and repolarization as shown in Fig. 8.16. This can be analyzed for focal sources as well as rotors. There are several advantages of this system. Since it simultaneously maps both atria and therefore can help to differentiate between active rotors and passive activation. It also does not rely on contact to record the electrograms. Given that data is acquired prior to an ablation there may be a question of changes in activation or changes related to the ablation itself.

Important Points to Remember

1. AF is classified as paroxysmal, persistent, longstanding persistent or permanent. Paroxysmal AF is defined as two or more episodes of AF each of which terminate within seven days and commonly within 24 h. Persistent AF is sustained generally for greater than seven days (or less if a cardioversion was performed in this time) and requires chemical or electrical cardioversion for termination of the arrhythmia. Longstanding persistent refers to cases in which AF has been present for more than one year and previously may have been designated as being permanent; however, an electrical cardioversion or ablation strategy is being pursued and therefore sinus rhythm may be achieved. Permanent AF also continues for more than seven days and cannot be terminated anymore thus a rhythm control strategy has been unsuccessful or not appropriate.
2. The main cardiovascular causes of AF are hypertension, coronary artery disease and valvular heart disease, metabolic causes of AF include thyroid dysfunction and diabetes mellitus while lifestyle risk factors include obesity, excessive alcohol and obstructive sleep apnea. AF is frequently seen in an acute setting in post operative patients as well as those who have infection, or in association with pulmonary embolism, pericarditis and myocarditis. AF may also occur in association with other supraventricular arrhythmias, such as AV nodal re-entry tachycardia, AV re-entry tachycardia and atrial flutter.
3. PVI is considered to be a reasonable strategy in patients with paroxysmal AF in whom medication has been ineffective, poorly tolerated or in cases of patient preference. This may be performed using a point by point technique or a ‘single shot’ device. PVI may also be useful in patients with persistent AF as a method of isolating the potential triggers.
4. Electrograms recorded from the ostia of the pulmonary veins show an initial non circumferential lower amplitude atrial signal followed by an isoelectric period followed by sharp pulmonary vein potentials. Depending on the overlap between the left atrium and the surrounding structures as well as the orientation of the mapping catheter there is a variable delay between the farfield electrogram and the pulmonary vein potentials. For the LSPV and to a lesser degree the LIPV farfield electrograms from the LAA may be recorded. These can be separated from the PV potentials by pacing from the LAA or the distal CS. For the RSPV farfield electrograms may be recorded from the SVC. If the signal is within 30 msec of the onset of the p wave then these are likely to represent SVC farfield.
5. Entrance block may be observed either during normal sinus rhythm or with atrial pacing during sinus rhythm. The circular catheter is positioned in the PV antra just distal to the line of ablation.
6. In order to prove exit block the ablation catheter can be positioned in the same pulmonary vein as the circular mapping catheter. Although pacing

can be performed from either the ablation catheter alone or the circular catheter alone it is often easier to discern pulmonary vein potentials from a separate catheter which has closely spaced poles without superimposed pacing arterfact.

7. An additional useful technique to help prove an intact line around the pulmonary veins is to assess for unexcitability to pacing. Following ablation the catheter is positioned along the line during sinus rhythm at an output of 10 mA and a pulse width of 2 ms. If lack of local capture occurs the catheter is moved a further 5 mm along the line and pacing repeated. If local capture occurred then further ablation was performed in this region and pacing performed at the same output.
8. In some cases non pulmonary vein triggers may contribute to AF. Potential locations include the superior vena cava, coronary sinus, crista terminalis, fossa ovalis, ligament of Marshall and left atrial appendage.
9. Post PVI atrial arrhythmias may involve the CTI, gaps around the PV's, the mitral annulus or the LA roof. Activation mapping using the ablation catheter relative to a stable CS electrogram may help to distinguish these.
10. Newer mapping techniques including the potential mapping of rotors may help to further understand the mechanism for AF.

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Chapter 9
Ventricular Tachycardia

Benedict M. Glover and Pedro Brugada

Abstract Ventricular tachycardia is defined as an arrhythmia which originates from the ventricles consisting of at least three or more consecutive beats at a rate of greater than 100/min and independent of AV or atrial conduction. If this terminates spontaneously within less than 30 s it is defined as non-sustained. If it lasts greater than 30 s or requires treatment for termination it is defined as sustained. Most commonly VT is associated with structural heart disease such as scar related re-entry in patients who have had a prior MI. Occasionally it may be associated with a structurally normal heart and is termed idiopathic. This is most commonly seen in the right ventricular outflow tract, coronary cusps, coronary veins or around the valve annuli.

ECG Criteria

One of the most important issues is to record an ECG during tachycardia in order to help make a diagnosis as to whether the arrhythmia is ventricular or supraventricular and if ventricular where the exit site may be located. As shown in Fig. 9.1 several criteria exist in order to help make this differentiation.

The Brugada criteria uses a straightforward and stepwise approach. This was developed by examining 348 cases of VT and comparing these with 170 cases of SVT with abberancy [1]. No patients were receiving anti-arrhythmic drugs. The first step looks at the absence of an RS in all of the precordial leads. If this is the case

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_9

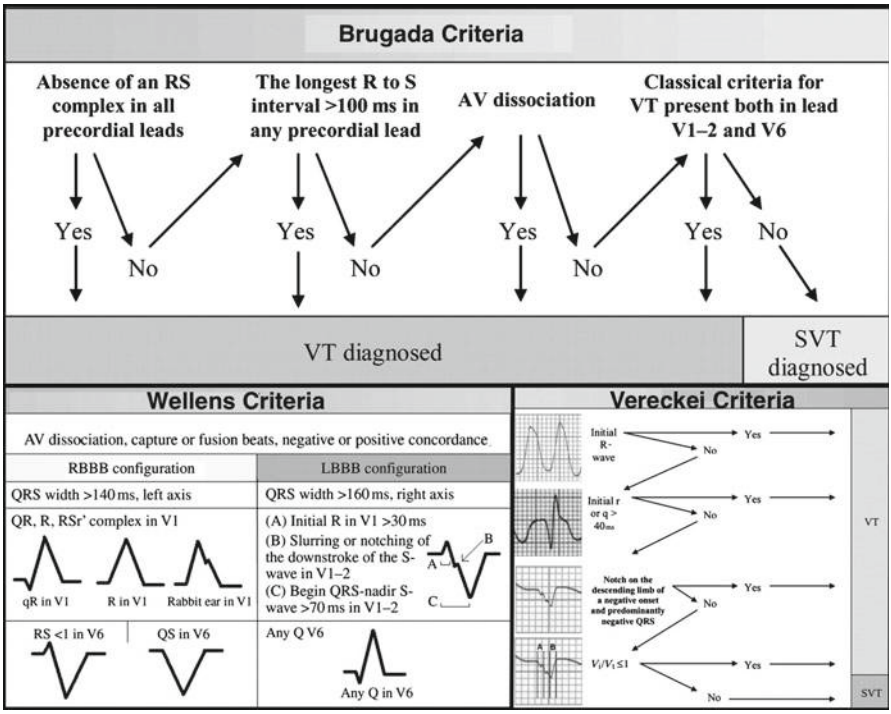

Fig. 9.1 Brugada Criteria, Wellens Criteria and Vereckei Criteria for the diagnosis of VT (Reproduced with permission from Alzand and Crijns [15]. Oxford University Press)

then VT is diagnosed. If not then the longest RS interval is examined and if greater than 100 ms VT is diagnosed. If not the presence of AV dissociation is looked for. As VA conduction may occur in almost half of all cases of VT it is important not to confuse 1:1 VA conduction with a supraventricular arrhythmia with 1:1 A:V conduction or 2:1 VA conduction during VT with AV dissociation.

If this is not seen then the classical Wellens criteria for VT in leads V1 or V2 as well as V6 are looked for [2]. These include a QR, R or RSr' in V1 or V2 with an RS less than 1 in V6 or a QS in V6 in a RBBB morphology or an R in V1 greater than 30 ms with notching of the S wave and an onset of QRS to S wave of greater than 70 ms in V1 or V2 with a Q wave in V6 in a LBBB morphology.

Another interesting algorithm has also been developed in which inly lead aVR is analysed [3]. As shown in Fig. 9.1 the presence of an initial R-wave, the width of an initial r- or q-wave greater than 40 ms, the presence of notching on the initial downstroke of a predominantly negative QRS complex and a V_i/V_t less than or equal to 1 are more indicative of VT.

Scar Related VT

Macro re-entry scar related monomorphic re-entry VT requiring treatment is a common indication for catheter ablation. Although this is most commonly the result of coronary artery disease other potential causes include infiltrative conditions and

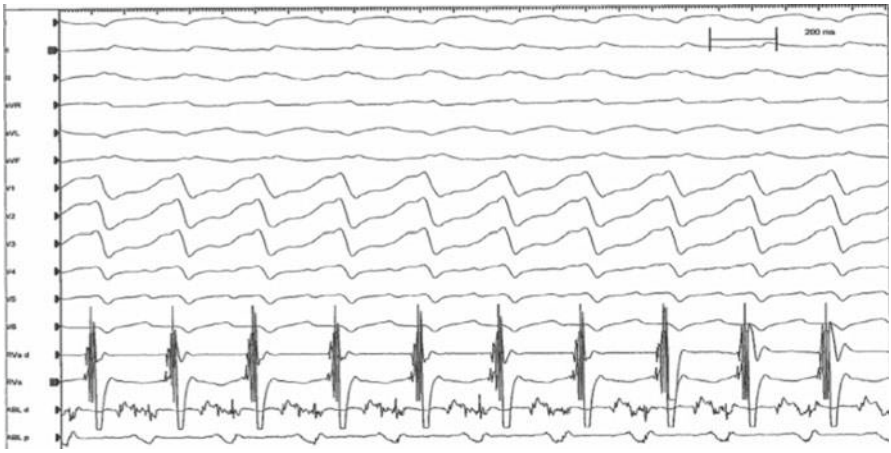

Fig. 9.2 Mapping during scar related re-entry VT showing long fractionated signals on the distal ablation catheter (ABL d) during diastole most likely indicative of a critical isthmus. Ablation in this region resulted in termination of the tachycardia with no further inducible tachycardia

dilated cardiomyopathy. As anti-arrhythmic drugs are often only moderately effective and often have significant side effects catheter ablation represents a reasonable alternative. Of course the potential complications of catheter ablation should also be considered. These include vascular injury, thrombo-embolism, hemodynamic instability and compromise, damage to the conduction system and cardiac tamponade.

Mechanism

Most scar related VT is a macro re-entry circuit. This is composed of an area of slow conduction with functional unidirectional conduction block as well as a structural barrier which is generally scar. Like all re-entry circuits the tachycardia can be entrained and reset if pacing is performed close to the circuit at a cycle length slightly shorter than the tachycardia cycle length with a closely matched post pacing interval minus tachycardia cycle length. There is generally an isthmus which is characterized by electrical activity during diastole. This is often the region which is targeted for catheter ablation. Pacing from this location results in a long stimulation to onset of QRS with a good pace map at the exit site. It is the exit site which determines the QRS morphology. Following this the waveform either propagates around the outer loop of the scar or an inner loop within the scar (Fig. 9.2).

Mapping and Ablation of Scar Related VT

In general it is reasonable to induce VT at the start of the procedure in order to have some procedural endpoint following ablation. Performing activation mapping and

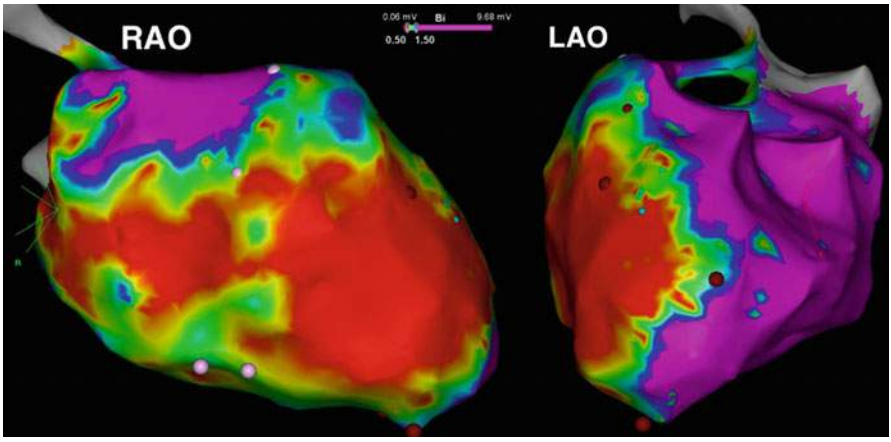

Fig. 9.3 Substrate mapping in a patient with monomorphic ischemic VT. Scar is seen in the LV septum, anterior wall and apex with heterogeneous tissue around this. This is clearly seen in the RAO image on the left and LAO image on the right

ablation of VT can result in significant hemodynamic compromise and may have adverse effects in itself. It is therefore our practice to map the substrate and target fractionated, low amplitude or delayed electrograms. In general **scar is defined as a bipolar voltage less than 1.5 mV and dense scar is a voltage less than 0.5 mV**. As shown in Fig. 9.3 scar is shown as red along the LV septum, anterior wall and apex with a region of heterogeneous tissue around this colored yellow, green and blue and higher voltage areas are seen in pink.

The targeting of **local abnormal ventricular activities** (**LAVA**) which represent poorly coupled fibers surrounded by appears to be an effective strategy [4].

The classical features of LAVA during sinus rhythm are:

- High frequency often double (or more) potentials separated by either a low amplitude baseline
- Separate from and often (but not always) following ventricular far-field
- May require pacing at the site in order to distinguish LAVA from ventricular farfield.

As well as exposing LAVA, which may be within the farfield, ventricular pacing at different outputs may result in different morphologies which means that the pacing substrate is complex. This is shown in Fig. 9.4.

The interesting concept is that although later potentials do tend to be significant and generally should be targeted the timing of these potential relative to the QRS is not just dependent on local conduction but on the anatomic location being earlier closer to the endocardial septum and latest being closer to the posterobasal epicardium which is activated at least 30 ms after [5].

It is therefore a reasonable strategy to perform pacing in order to separate out local fractionated potentials from farfield ventricular activation.

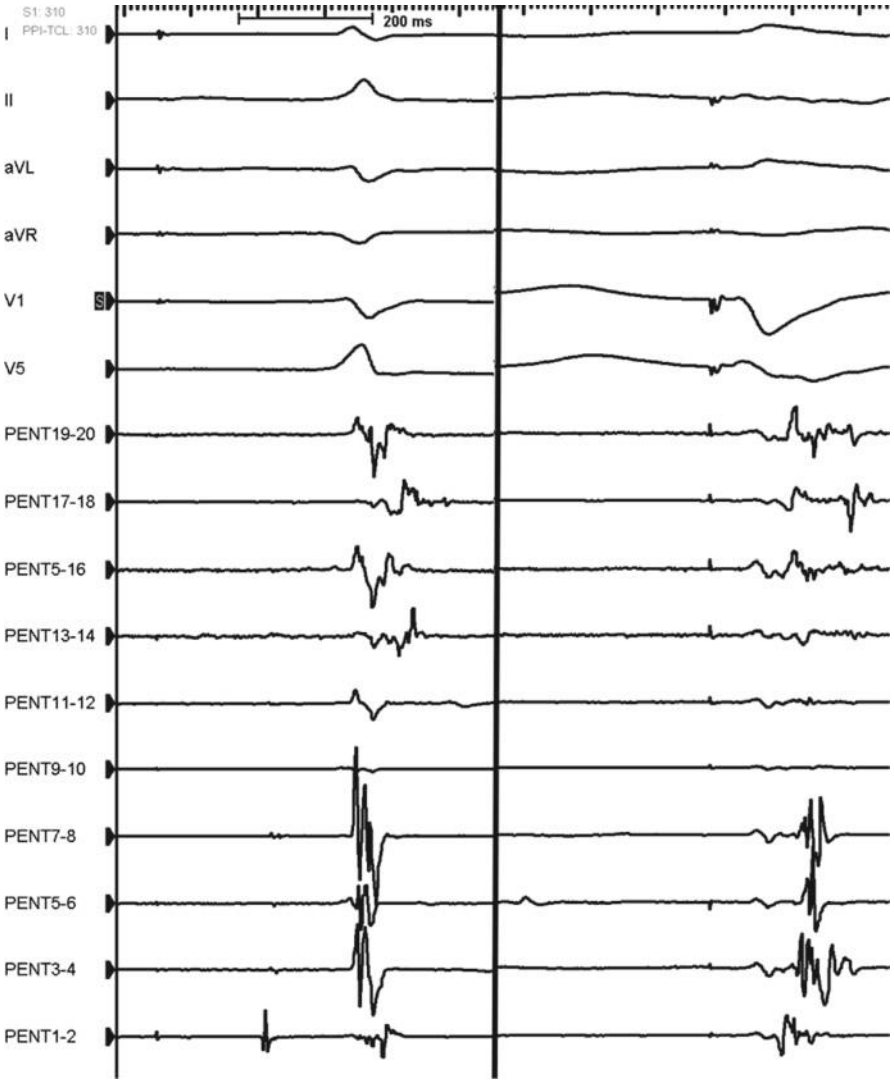

Fig. 9.4 LAVA potentials exposed during pacing from the RV apex (*circled on the right*). The pentarray catheter (PENT 1–20) is positioned in the inferior wall of the left ventricle. The first beat on the left occurs following an atrial paced beat in which fractionation is noted in PENT 13–20. On the right pacing is performed from a catheter in the RV apex which expose higher frequency split potentials in PENT 15–20 and 3–4 which were targeted for ablation

Pace mapping particularly along the critical isthmus is also a very helpful strategy. A long stimulus to QRS with a good pace map is often a reasonable sign of being close to the isthmus. In cases of septal VT we perform this on both the right and left septum. This is shown in Fig. 9.5 in which the patient has extensive scar along the LV septum, anterior wall, inferior wall and apex. A pace map on the RV

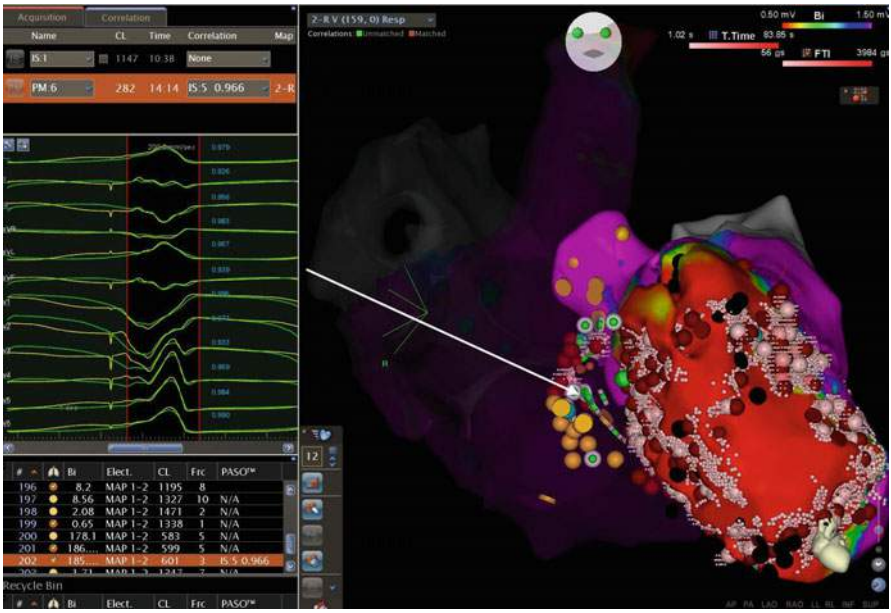

Fig. 9.5 Substrate map showing extensive scarring of the left ventricle involving the septum, anterior wall, inferior wall and apex. VT could be easily induced and terminated with ablation at 50 W along the septum (exact point *green dot*). Despite this VT could be re-initiated and therefore pace mapping was performed on both sides of the septum. The pace map shows a very good match with the clinical VT on the right side of the septum. Despite the appearance of relatively normal signals ablation was performed in this region with no further inducible tachycardia. The *arrow points* to the area with the best pace map and indicates that the exit site was likely on the right side and that ablation was required on both sides of the septum. (*Yellow dots* were regions with less good pace map matches and *black dots* were LAVA potentials which were also targeted)

septum in which the voltages were normal revealed an excellent pace map as shown. Ablation was therefore performed on both sides of the septum which successfully targeted the circuit which was likely deep septal.

If tolerated and a distinct region has been mapped such as the isthmus then VT can be induced and the signals examined during tachycardia or ablation can be performed looking for tachycardia termination. Additionally if the arrhythmia is tolerated entrainment can be performed in order to assess the location of the catheter relative to the circuit.

At the end of the procedure further testing can be performed in order to examine for tachycardia induction.

Epicardial Access and Ablation

Scar related monomorphic VT circuits may involve the endocardium, mid myocardium and epicardium. This is more commonly but not exclusively seen in non-ischemic VT. Certain cases may require epicardial access in order to successfully

target the critical components of the circuit. This may be determined according to the underlying substrate, by using imaging which may help visualize scar distribution, in cases where ablation was unsuccessful from the endocardium and in cases where the ECG may exhibit certain characteristics.

ECG Characteristics Suggestive of Epicardial Involvement

In general the QRS during VT originating from or involving the epicardium results in a significantly wider QRS due to the greater distance from the His Purkinje system. For epicardial VT with a RBBB morphology thought to have an exit site in the region of the left ventricle several parameters can be measured which may suggest epicardial involvement.

These include the following parameters [6]:

1. **The onset of the QRS to a pseudo-delta wave of greater than 34 ms**. A pseudo-delta wave is defined as an early rapid deflection on the upstroke of the QRS complex.
2. **An intrinsicoid deflection time of greater than 85 ms**. The intrinsicoid deflection time is the time from the onset of the QRS to the peak of the R wave measured in V2.
3. **The RS complex duration** defined as the earliest ventricular activation to the nadir of the first S wave in any precordial lead of **greater than or equal to 121 ms**.

For VT originating from the epicardial surface of the RV these parameters do not appear to be helpful [7].

The presence of a Q wave or a QS in the local site of activation provides a more useful indicator. Therefore an inferior origin tends to have a Q or QS in leads II, III and aVF. None of these parameters are useful in determining whether an outflow tract tachycardia is endocardial or epicardial. An example of an ECG in a patient with VT with an epicardial focus involving the LV inferior wall is shown in Fig. 9.6.

Epicardial VT Ablation

Although this procedure can be performed with sedation it is generally uncomfortable for the patient and general anesthesia should be considered. A sterile field is prepared inferior to the sternum and fluoroscopy with or without the addition of echo can be used for imaging.

Epicardial Access

A 17 Guage Tuohy needle is introduced at a 45° angle initially until it has passed through the diaphragm and then a slightly steeper angle. The direction of the needle can be visualized in the RAO view aiming towards the medial one third of the RV

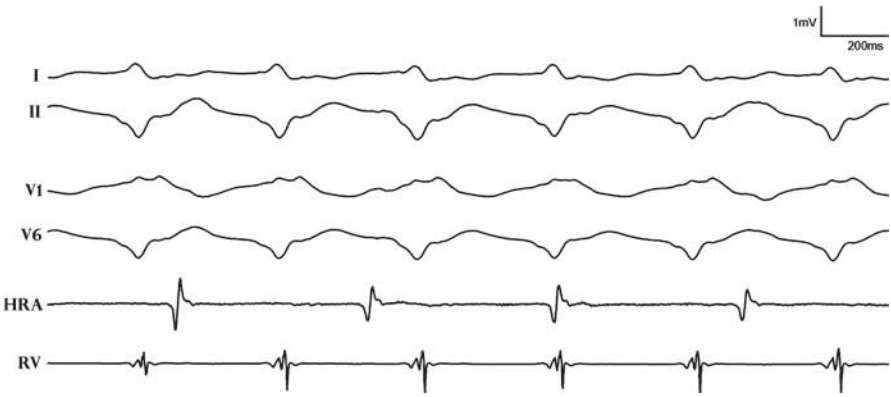

Fig. 9.6 ECG of VT originating located in the epicardial surface of the LV inferior region. V1 and V6 are indicative of a left ventricular origin while lead I and II indicate an inferior origin. The QRS is broad with a pseudodelta wave seen on lead V1. There is clear dissociation seen between the RV and RA activation

(where there are no major coronary vessels) while the depth is most easily seen in a left lateral projection.

As the tip of the needle enters the epicardial space a sensation of a 'give' is felt followed by a cardiac pulsation. Although contrast can be injected this should be minimized as it often then obscures the view. A more straightforward approach is to advance a long wire into the pericardial space. If this is truly in the pericardial space it should not follow the course of any cardiac chamber. If this is in the RV it will tend to pass towards the RVOT and into the pulmonary truck often with significant ectopy. Another option is to record the pressure from the needle which will change from a flat line as the needle is advanced through tissue to a sudden negative pressure as the tip of the needle passes into the pericardial space. Entering the right ventricle will demonstrate an RV pressure waveform. In general as long as only the needle tip and wire enter the ventricle this should not result in a major problem and a fresh attempt can be made with close hemodynamic monitoring.

As soon as it is confirmed that the needle and wire are in the epicardium then a sheath and dilator can be introduced. In general a short deflectable sheath can be used. We also tend to introduce a second wire through the sheath in case access is lost.

It is important that a catheter is left in the sheath and if removed that it is replaced with a wire in order to avoid laceration of the ventricular wall with the tip of the sheath.

The relevant anatomy pertaining to epicardial access is shown on anatomical image and the CT image in Fig. 9.7.

In approximately 10 % of patients epicardial access is not possible. This is particularly common in patients who have had prior cardiac surgery as well as some patients with a prior history of pericarditis. In these cases a surgical window can sometimes be made.

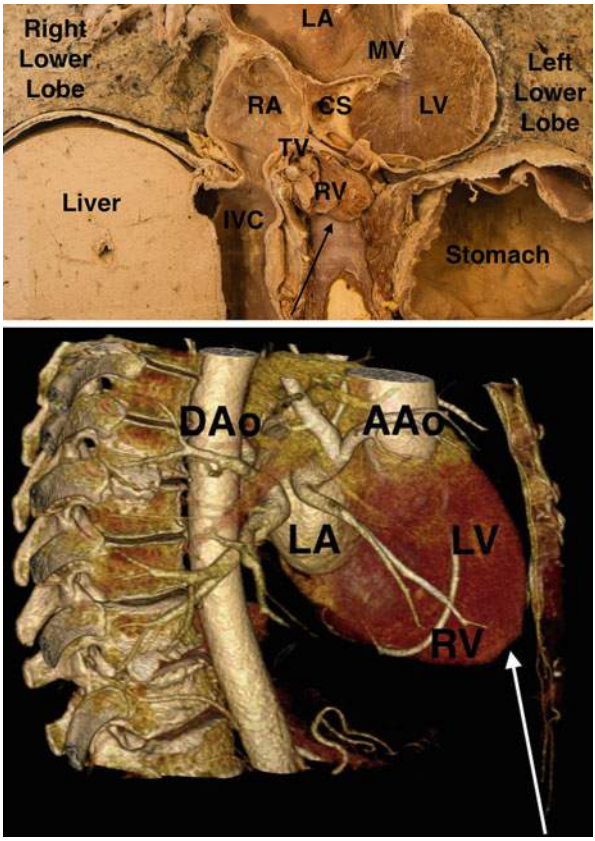

Fig. 9.7 Anatomical image showing the relevant anatomy from an anterior coronal view in epicardial access (*top image*) and a lateral sagittal view shown on a CT (*bottom image*). The *arrow* in the *top image* shows the direction in which the needle should be advanced towards the middle one third of the RV. The angulation of this is seen in the CT image below this in which the arrow shows the course of the needle (*LA* left atrium, *RA* right atrium, *TV* tricuspid valve, *MV* mitral valve, *CS* coronary sinus, *IVC* inferior vena cava, *AAo* ascending aorta, *DAo* descending aorta)

Epicardial Mapping and Ablation

An irrigated catheter is used for mapping and ablation. The general principles of mapping are the same as for endocardial mapping. The main issue which may arise, is the differentiation of scar from epicardial fat. In generally fat greater than 5 mm results in a reduction in the amplitude of the local electrogram. The degree of fractionation is helpful and is generally reasonably specific for local scar rather than fat. If a region of low amplitude signals follows the distribution of a coronary vessel then it is likely to represent epicardial fat. An example of a voltage map recorded on the epicardium and showing scar along the inferior wall of the LV is shown in Fig. 9.8 along with the region of ablation performed.

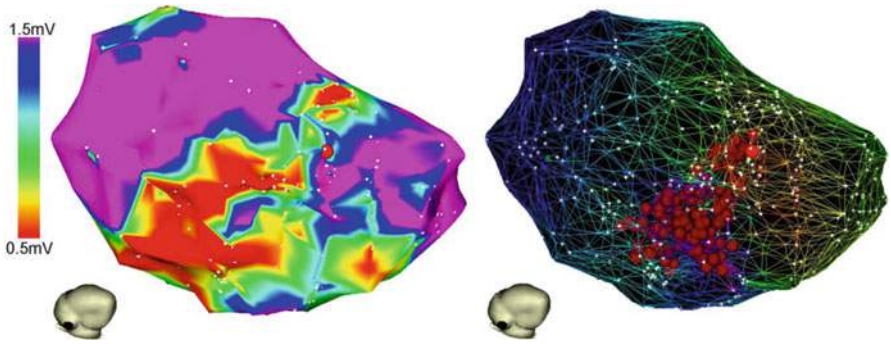

Fig. 9.8 Voltage Map of VT along the epicardial surface of the LV inferior wall. *On the image on the left red* represents dense scar surrounded by heterogeneous zones and normal voltages are shown in *pink*. The *image on the right* shows the points recorded with ablation shown as *red dots* along the critical isthmus

The fact that ablation catheters deliver circumferential radiofrequency energy means that there is always a degree of damage to surrounding structure. This is generally the pericardium and pleura which accommodate this with no major problems. The main structures to be cautious of when delivering RF to the epicardial surface are the coronary arteries and the phrenic nerves. In general either a CT is merged at the start of the procedure with the locations of the coronary arteries or a coronary angiogram is performed prior to ablation. A **minimum distance of 5 mm** should be maintained between the site of ablation and the coronary artery in order to prevent coronary artery spasm or acute thrombosis.

As there is no flow in the pericardium irrigation is used at a rate of 10 ml/min. This should be aspirated from the side arm of the sheath to prevent cardiac tamponade. RF can be delivered at a power ranging from 25 to 50 W.

Epicardial Ablation: The Difficult Case

The difficulties in epicardial mapping and ablation relate to either general issues relating to mapping which are similar to those of endocardial ablations and additional technical issues. One of the first issues is that of gaining access with minimal complications. Maintaining a relatively shallow angle while beneath the diaphragm minimizes the risk of hepatic laceration and subdiaphragmatic injury. Perforation of a subdiaphragmatic vessel should be suspected in a patient with significant hypotension and no evidence of a pericardial effusion.

Another technical issue is that of phrenic nerve proximity to a region where ablation is required. In general the phrenic nerve can be pushed away from the ablation catheter by injecting air through the pericardial sheath. This should be aspirated immediately if defibrillation is required and after ablation has been performed.

Although some centers use local non steroidal drugs in the pericardial space post procedure we tend to manage the majority of cases with simple analgesia.

Idiopathic VT

Bundle Branch Re-entry

Under normal circumstances antegrade conduction through the His Purkinje network is relatively rapid. The fact that the tissue remains refractory for more prolonged periods of time therefore generally prevents re-entry from occurring between the right and the left bundle branches. In cases where conduction is slowed or transiently blocked in either the antegrade or retrograde directions re-entry may occur. As shown in Fig. 9.9 this may result in antegrade conduction down the right bundle with retrograde conduction up the left bundle resulting in a left bundle branch block morphology during VT. The reverse may also occur with antegrade conduction down the left bundle and retrograde conduction up the right bundle resulting in a right bundle branch block morphology during VT.

EP Study and Ablation for Bundle Branch Re-entry VT

In patients with bundle branch re-entry the baseline ECG during normal sinus rhythm often shows first degree AV block with some variant of intraventricular conduction delay or an incomplete bundle branch block.

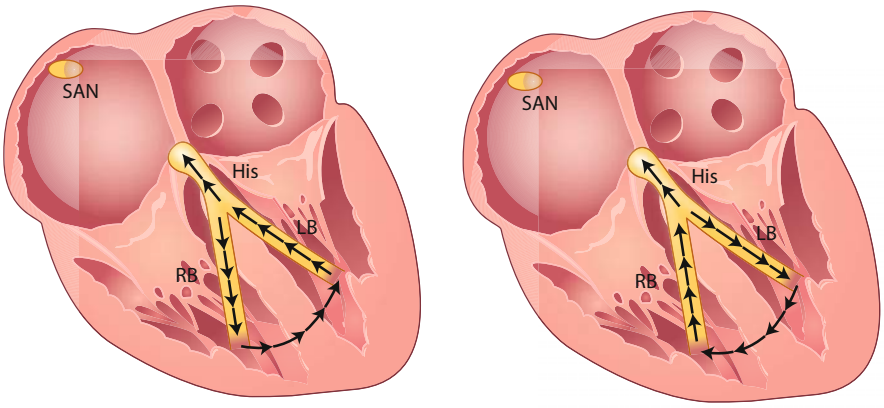

Fig. 9.9 Showing the potential circuits involved in BBR. *Top image* shows the more common scenario where antegrade conduction occurs along the right bundle and retrogradely along the left bundle and below the less common antegrade conduction along the right bundle with retrograde conduction along the right bundle

The baseline EP study demonstrates a **prolonged HV interval during sinus rhythm of greater than 60 ms** [8]. Tachycardia may be induced with either atrial or ventricular pacing. The morphology is more commonly a LBBB than a RBBB. The diagnosis is generally made by the presence of a **His signal before every QRS** with a HV interval slightly shorter than during sinus rhythm. The His signal is generally followed by the right bundle potential or less commonly a left bundle potential depending on the direction of the circuit. As these are all vital components in the circuit a change in either the H-H, RB-RB or LB-LB intervals prolongs the tachycardia cycle length. Entrainment may be possible by pacing from the right ventricular apex. A difference of less than 30 ms is suggestive of bundle branch re-entry [9].

In general ablation of the right bundle branch is performed. In order to map this the His is located and a more distal location with a right bundle electrogram and no atrial signal is chosen along the anterobasal region.

Fascicular Re-entry VT

Fascicular re-entry VT is sometimes referred to as either verapamil sensitive or Belhassen VT. Whereas in Bundle Branch Re-entry VT the His activation occurs before left bundle activation in fascicular re-entry His activation tends to occur after left bundle activation and with a much shorter HV interval during tachycardia. The QRS in fascicular VT although prolonged, is generally less than 140 ms and therefore is not as prolonged as many other types of VT. Upper septal re-entry tends to be narrower and may even be confused with SVT. Three different types of fascicular VT exist.

The most common type is **left posterior fascicular** in which the antegrade component to the circuit involves slowly conducting decremental verapamil sensitive Purkinje fibers extending from the base of the interventricular septum towards the LV apex. The retrograde circuit then propagates along the posterior fascicle with an exit site in the inferoposterior septum resulting in a **RBBB morphology with a superior directed axis**.

Less commonly is **left anterior fascicular** in which the retrograde activation occurs along the anterior fascicle with an exit along the anterolateral wall of the LV resulting in a **RBBB** morphology QRS during tachycardia with an inferior directed axis.

In **upper septal VT** the left posterior and left anterior fascicles both act as the antegrade limbs resulting in a relatively narrow QRS often with a **RBBB** morphology although occasionally there is a LBBB pattern with an inferior or normal axis. Diagrammatic representation of these is shown in Fig. 9.10.

EP Study and Ablation for Fascicular VT

EP evaluation and catheter ablation may be performed successfully in the majority of patients. Given that the circuit is located in the left ventricle access can be achieved either retogradely across the aortic valve or through a transseptal approach.

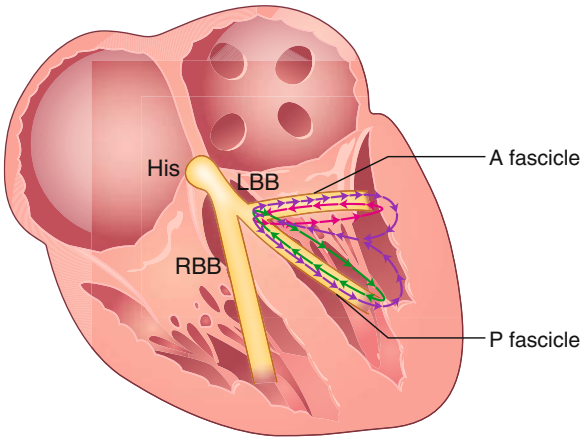

Fig. 9.10 Demonstrating the circuits involved in fascicular VT utilizing the posterior fascicle as the retrograde limb (*green*) and the anterior fascicle as the retrograde limb (*pink*) as well as the uncommon upper septal fascicular re-entry (*purple*)

The risks are therefore similar to those for all left ventricular ablations with the additional potential risk of the development of LBBB and AV block.

One of the interesting and diagnostic features of this type of VT is that it can be induced and entrained by performing atrial pacing. If pacing is insufficient for the induction of VT then isoprenaline can often be helpful.

During normal sinus rhythm and during tachycardia a sharp high frequency Purkinje potential can be recorded prior to the onset of the QRS which represents depolarization of the fascicle. During sinus rhythm a lower frequency potential may be recorded after the QRS which is known as a **pre-purkinje potential**. This term is used for this potential as during tachycardia it represents activation of the verapamil sensitive antegrade limb of the circuit and therefore occurs before the purkinje potential. As the mapping catheter is moved further from the base of the interventricular septum towards the LV apex the pre-purkinje potential becomes later. The area of slow conduction tends to occur at the junction of the fascicle and the antegrade limb where the purkinje potential is at its earliest and the pre-purkinje potential is at its latest.

Ablation is generally performed during tachycardia as termination with ablation with no further initiation is a reasonable endpoint. A region close to the exit site can be targeted approximately one third from the LV apex where the **purkinje potential precedes the QRS by approximately 20 ms**. The pre-purkinje potential tends to occur after the QRS in this region. An alternative approach where the earliest pre-purkinje potential can be targeted until VT is terminated and in which case the potential then becomes late. This appears to be associated with a slightly higher risk of AV block or LBBB.

If VT cannot be induced nor sustained and the suspicion is that of a left posterior fascicular VT then a linear lesion can be made 1 cm proximal to the exit site. The exit site can be identified by careful pace mapping. If the linear lesion is successful the purkinje potential jumps from before to after the QRS complex.

The Difficult Case

Several issues may make ablation of this arrhythmia difficult. In general from a practical perspective the two major issues are difficulty with initiation of the tachycardia and ensuring that the correct diagnosis has been made.

Although atrial and ventricular pacing should initiate the tachycardia if this is not possible the administration of intravenous isoprenaline may be helpful.

In cases where ablation appears to be unsuccessful it is important to review the diagnosis. It is possible to have a focal arrhythmia originating from the purkinje network which also results in a RBBB morphology QRS with either a superior or inferior directed axis. Being focal it tends not to be initiated or entrained from pacing in the atrium or ventricles. In mapping this unusual VT the earliest site of activation should be targeted. Another possibility is that of mitral annular VT which may have a RBBB morphology with a superior axis.

Given the relatively narrow QRS and the fact that initiation may occur with atrial pacing, fascicular VT may also be confused with SVT. This is most easily differentiated by the presence of AV dissociation.

Outflow Tract VT

The most common locations for premature ventricular complex's (PVC's) are within the right and left ventricular outflow tracts. Isolated PVC's in the setting of normal left ventricular function are generally of minimal significance. Indications for ablation include PVC induced left ventricular dysfunction or significant symptoms where pharmacological therapy is ineffective or not tolerated. Non-sustained and sustained focal VT may also originate from the outflow tracts and like PVC's is more commonly found on the right ventricular outflow tract (RVOT) compared with the left ventricular outflow tract (LVOT). Although RVOT extrasystoles are more common in females there is an approximate equal gender distribution in LVOT extrasystoles.

Outflow tract tachycardia generally occur more commonly at rest than with exercise and are often suppressed with an increase in the sinus rate. A proportion of cases are exercise induced occurring either at peak exercise or during the recovery phase.

Anatomy and ECG Features

The RVOT runs from the superior aspect of the tricuspid annulus at the inferior aspect to the pulmonary valve at the superior end. The LVOT includes the coronary cusps superior to the aortic valve and extends inferiorly to the aortomitral continuity and the superior aspect of the mitral annulus. The majority of foci in both outflow tracts tend to be relatively close to the annulus of either valve which may result in anisotropy and arrhythmogenesis.

Given that both the right and left ventricular outflow tracts are superior structures the ventricular activation tends to be from superior to inferior resulting in a positive QRS axis in leads II, III and aVF and negative in aVR and aVL.

The differentiation between tachycardia's originating from the right versus the left ventricular outflow tracts based on the ECG can occasionally be more complex. The majority of outflow tract tachycardia's originate from the superior and anterior septal RVOT making it difficult at times to know if these are originating from the left or the right side. In approximately 15 % of cases the origin is the LVOT. Occasionally the origin may be the right ventricular infundibulum, superior to the pulmonary valve, the aortomitral continuity or with close to the anterior interventricular vein.

As shown on the CT image in Fig. 9.11 the right ventricular outflow tract is anterior to the left ventricular outflow tract and as it becomes more superior moves to the left of the LVOT so that the pulmonary valve is actually left of the aortic valve. As a result of this basic fact, ventricular activation from the RVOT generally spreads from anterior to posterior. This results in a negative QRS in V1 with a LBBB type pattern on the ECG. If the precordial transition occurs at lead V4 or later then the origin is almost certainly RVOT.

The difficulty arises when the precordial transition occurs at or close to V3 and where there may be a predominantly negative QRS in the early precordial leads with an R wave. A small R wave may be present in posterior and superior RVOT foci as

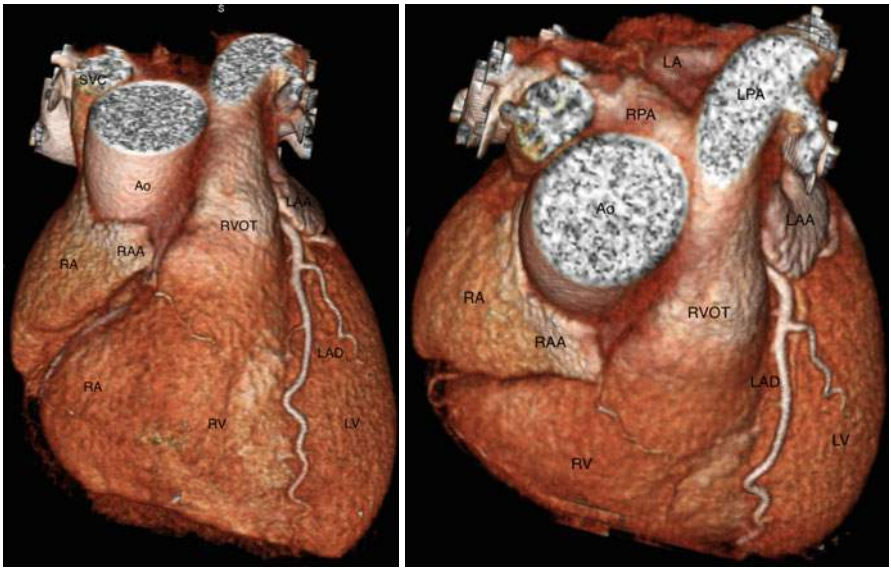

Fig. 9.11 CT Image showing the Relationship of the RVOT and LVOT. The figure on the *top* shows an anterior view in which the RVOT is anterior and to the left of the LVOT. The image at the *bottom* shows a superior view (*Ao* aorta, *RA* right atrium, *RAA* right atrial appendage, *RV* right ventricle, *LAA* left atrial appendage, *SVC* superior vena cava, *LV* left ventricle, *LAD* left anterior descending artery, *LPA* left pulmonary artery, *RPA* right pulmonary artery)

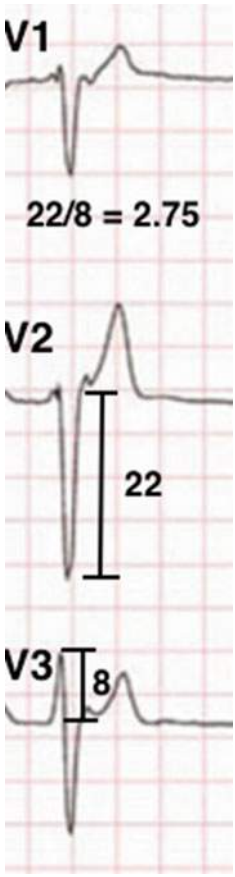

Fig. 9.12 Measurement and calculation of the V2S/V3R ratio for an outflow tract PVC. The S wave in lead V2 is 22, while the R wave is 8 resulting in a V2S/V3R of 2.75 which is indicative of an RVOT origin

well as the anterior LVOT where it tends to be slightly higher in amplitude. In order to help estimate the location several algorithms have been developed.

The V2S/V3R Index is useful in helping to differentiate between a RVOT and LVOT origin in outflow tract PVC's with a LBBB type morphology [10]. As shown in Fig. 9.12 using this simple calculation the amplitude of the S wave in lead V2 is divided by the amplitude of the R wave in lead V3. A value of less than or equal to 1.5 has been shown to be suggestive of a LVOT origin while a value greater than 1.5 represents a likely RVOT origin.

Having ascertained whether the origin is located in either the RVOT or LVOT further ECG analysis can be performed to help estimate the specific location within the specific outflow tract.

As demonstrated in Fig. 9.13 a lateral lead such as Lead I may be useful in further ascertaining the origin of an outflow tract tachycardia. In an RVOT tachycardia a negative QRS in lead I is more indicative of a more superior origin close to or above the pulmonary valve. A positive QRS in lead I indicates a more rightward inferior structure such as the RVOT freewall. Septal and anterior origins often are biphasic in lead I.

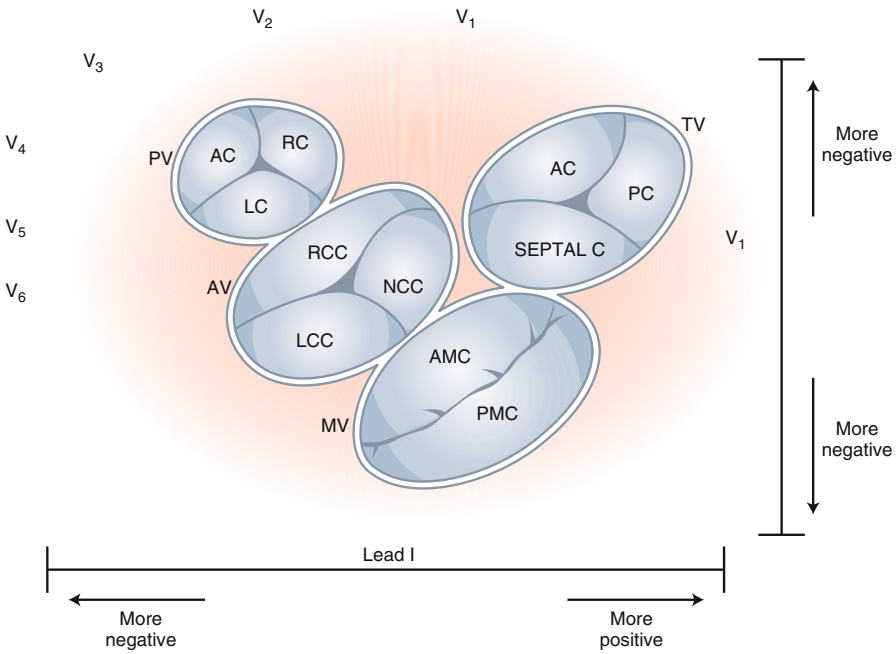

Fig. 9.13 Showing the anatomic relationship of the precordial lead V1 and lead I to the outflow tracts (*PV* pulmonary valve, *AC* anterior cusp, *RC* right cusp, *LC* left cusp, *AV* aortic valve, *RCC* right coronary cusp, *LCC* left coronary cusp, *NCC* non coronary cusp, *MV* mitral valve, *AMC* anterior mitral cusp, *PMC* posterior mitral cusp, *TV* tricuspid valve, *AC* anterior cusp, *PC* posterior cusp, *Septal C* septal cusp)

One further important point to examine on the ECG in more detail is leads aVR and aVL. These are almost always negative for all outflow tract tachycardias. However if aVL is isoelectric or positive the inferior portion of the RVOT close to the Bundle of His and right bundle should be considered.

Outflow Tract Tachycardia: EP Study and Ablation

Indications

The two main indications for the ablation of outflow tract tachycardias are either symptoms which cannot be effectively treated with pharmacological agents or frequent arrhythmias resulting in left ventricular dysfunction. For minimal symptoms often no treatment is required. Pharmacological therapy is often of moderate efficacy if symptoms persist and includes beta blockers, flecainide and calcium channel blockers. Acute termination can be performed with the administration of intravenous adenosine which acts by blocking the beta adrenergic activation of intracellular calcium [11].

Risks

The most common risks of ablation of the outflow tracts are vascular complications in the groin. This is more likely for arrhythmias on the left side which generally require arterial access. For left sided ablations heparin should be administered during the procedure in order to minimize the small risk of thrombo-embolism. Coronary artery damage in the mapping and ablation of aortic cusp tachycardias is a potential risk and therefore it is generally recommended that the coronary arteries are visualized prior to delivering ablation by performing a coronary angiogram. This should also be performed prior to ablation in the cardiac veins which generally run beside the coronary arteries.

On the right side the risks depend on the location of ablation. If the focus is inferior and septal then damage to the His is a possibility. For ablations in the more superior posterior RVOT it must be remembered that the left main coronary artery is often only 5 mm from the site of the ablation catheter [12].

Tamponade is a possibility in either outflow tract however the RVOT is relatively thin in many regions and care must be taken not to use excess power or force.

Procedure

Initiation and Catheter Positioning

In general, if possible all anti arrhythmic drugs should be discontinued for at least 5 half lives prior to the procedure. A single catheter can be used to map and ablate or else a reference catheter can be positioned in either the RV apex or the outflow tract which may help in mapping the level of the focus. For RVOT tachycardia's this is advanced into the right ventricle and then clockwise rotated in order to access the outflow tract. A curl in the tip of the catheter often makes advancement less traumatic with a lower chance of right ventricular outflow tract perforation.

In order to access the LVOT the catheter is generally advanced via the femoral artery with a curve placed on the catheter as it is advanced around the aortic arch. Occasionally trans-septal access can be performed if additional stability is required. The epicardium can often be mapped in this location from the coronary veins.

It is important to try to induce the arrhythmia at the start of the procedure in order to examine the activation sequence of the arrhythmia and map for the earliest and most interesting sites. Activation mapping of outflow tract tachycardias has been shown to result in higher success compared with pace mapping. In general intravenous sedation should be minimized. If there is difficulty with spontaneous initiation of the arrhythmia rapid atrial pacing can be performed provided AV conduction is intact, otherwise ventricular pacing can be carried out. By increasing the ventricular rate this may initiate some outflow tract arrhythmias. If this is unsuccessful isoprenaline or epinephrine can be infused.

Mapping

Activation mapping is superior to pace mapping. It is important to use both the bipolar electrogram looking for early signals relative to the onset of the QRS complex and a unipolar signal which should show only a QS wave with no R wave during ectopy. The earlier the signal the better and success is generally noted when the onset of the local electrogram is at least 10 ms ahead of the onset of the QRS. It is unusual for this to be much earlier than 60 ms ahead of the surface QRS. Following the determination of an early site it is useful to pacemap using the minimal output in order to compare with the morphology of the intrinsic beat. A good pacemap is an additional useful parameter prior to delivery of ablation.

Ablation

Following the mapping of an early region of activation and a good pacemap ablation can be performed in either of the outflow tracts. In general a 4 mm tip catheter is used. For the RVOT if a non irrigated catheter is used then the power is generally set at 40 W with a target temperature of 55 C for a period of 60 s. If an irrigated catheter is used power can be set at 30 W in the RVOT up to a maximum of 35 W.

In the LVOT ablation is typical performed using an irrigated catheter with a power of 25–30 W. Care must be taken in the left and right coronary cusps to ensure that ablation is performed at least 8 mm from the coronary ostia. Of note when mapping the coronary cusps it may be difficult to pacemap and high outputs may be required making this relatively unreliable. Activation mapping in this region is more reliable. During ectopy from this region the electrogram is often biphasic and the earliest component of the first signal should be recorded as the earliest activation. If ablation is performed in the cardiac venous system then power is generally limited to 20–25 W using an irrigated catheter. The issues in these regions may include the possibility of coronary artery damage and a minimum distance of 1 cm should be kept from the coronary artery to the ablation catheter as well as the possibility of impedance rises due to poor flow.

During the delivery of RF in a successful region there is often an episode of non sustained VT or frequent unifocal ventricular ectopy in the first 10–15 s followed by normal rhythm for the remainder of the ablation. The presence of ST segment elevation in the unipolar electrogram is generally a good sign of local tissue injury.

Endpoints and Success

In general it is reasonable to monitor the patient for 30 min following ablation. If there is a recurrence of ectopy with the same morphology then further mapping and ablation should be performed. It is possible that the exit site of an ectopic foci may be shifted by ablation and therefore all the leads on the ECG should be examined in order to ensure this. If pharmacological agents were required fro initiation of the ectopy at baseline then these should be administered following ablation.

The overall acute success for catheter ablation for outflow tract tachycardia is approximately 90 %. Following the procedure ectopy may recur even after 1 year. The two predictors of recurrence are less early local signals targeted for ablation as well as pace mapping being used as the mapping strategy [13].

The Difficult Case

Lack of Spontaneous Ectopy

One of the most common arises from the inability to induce the tachycardia at the start of the case. All anti-arrhythmic agents and beta blockers should be ideally stopped for 5 half lives prior to the procedure. Intravenous sedation should be minimized and if there is no spontaneous ectopy rapid atrial or ventricular pacing can be performed or isoprenaline or epinephrine can be infused at the start of the case. These agents should ideally be stopped during ablation in the RVOT as they may result in hypercontractility of this region which may in theory increase the risk of perforation. If there are very infrequent episodes of ectopy then careful pacemapping can be performed using the minimum output to result in local capture with time spent ensuring that the morphology matches the spontaneous beat very closely.

Lack of Early Sites

If there are no focal regions of early activation but rather a general area either on time with or slightly ahead of the onset of the QRS then the other outflow tract should be mapped. If there are still no particularly early sites then it is useful to map the cardiac venous system.

Continuation of the Arrhythmia Despite Ablation

There are several potential reasons for this. The most likely is that the exact focus has not be accurately mapped and ablated. It is also possible that contact with the catheter is poor and it is useful to flex the catheter in order to alter the angle on the endocardial surface. If the focus is slightly deeper it is possible that the endocardial exit site has shifted with a subtle change in the QRS morphology on the 12 lead ECG. It is also possible that an entirely different PVC is present and a decision must be made as to whether this is significant enough to required further mapping and ablation in another region.

Inability to Deliver Ablation in the Cardiac Venous System

This is not uncommon. The most likely reason for not being able to deliver RF in the cardiac venous system is the proximity to the coronary arteries. It is sometimes possible to perform the ablation in a site which is slightly further from the earliest activation and still achieve success.

Another potential problem with ablation in the cardiac venous system is a significant rise in impedance due to low flow with an inability to deliver sufficient power. This can be overcome by moving the catheter to a slightly different location or different angle as well as increasing the rate of infusion of the irrigation through the ablation catheter.

Mitral Annular VT

This is a less common location for ectopy when compared with the outflow tracts. The ECG typically shows a RBBB pattern with very early precordial transition with in V1 or between V1 and V2 an a positive concordance in the precordial leads due to the relative posterior locations of the mitral annulus relative to the ECG lead positions. For anterolateral origins leads II, III and aVF tend to be positive and leads I and aVL tend to be negative. For posterior or posteroseptal foci leads II, III and aVF tend to be negative and positive in leads I and aVL. More septal origins tend to be narrower than LV free wall locations. Mapping and ablation of a mitral annular PVC is shown in Fig. 9.14.

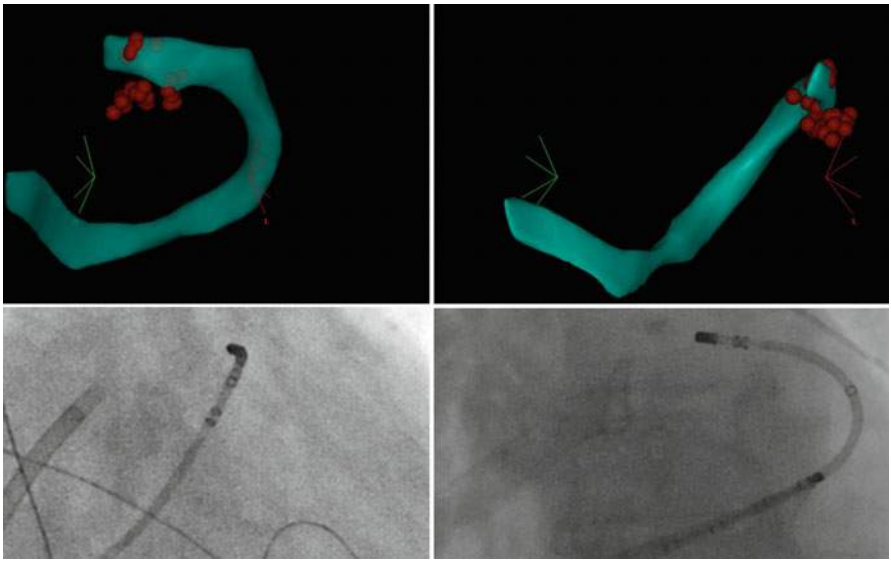

Fig. 9.14 Ablation of a mitral annular PVC resulting in LV dysfunction. This was mapped to the anterior mitral annulus however ablation in this region did not result in termination of ectopy. The ablation catheter was then positioned in the anterior cardiac vein where ablation was successful in terminating ectopy. The successful site of epicardial ablation is shown in the electroanatomic maps on the top of the image (LAO on the *left* and RAO on the *right*) and fluoroscopically (LAO on the *left* and RAO on the *right*). Pace mapping was also used to help confirm the location prior to ablation. These images are shown at the bottom of the figure in which the epicardial map was much closer in morphology to the intrinsic beat when compared with a similar endocardial location

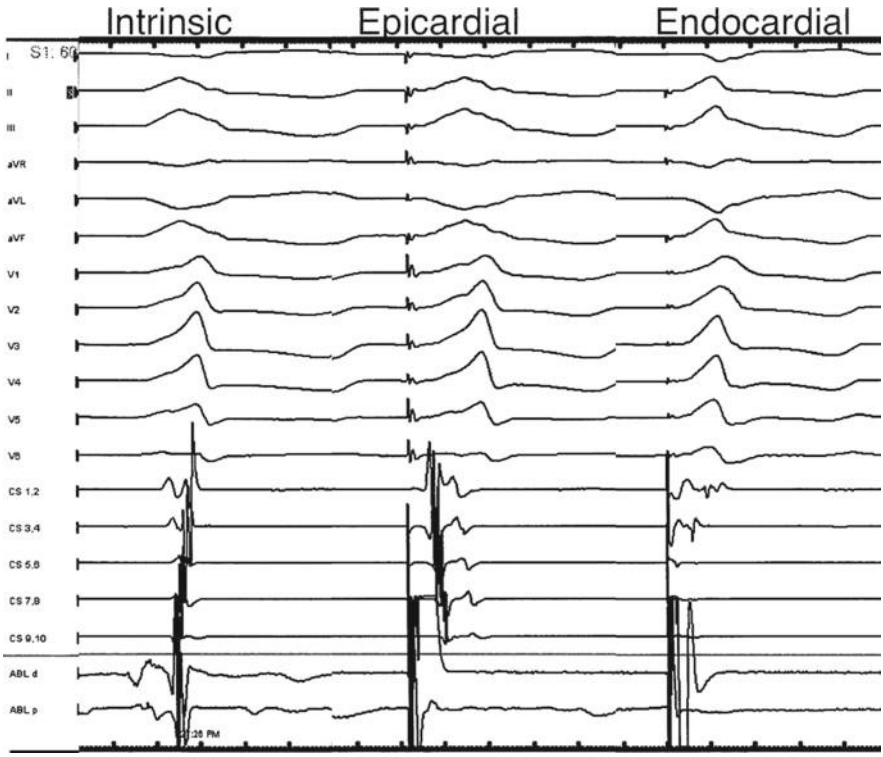

Fig. 9.14 (continued)

Important Points

1. Ventricular tachycardia is defined as an arrhythmia which originates from the ventricles consisting of at least three of more consecutive beats at a rate of greater than 100/min and independent of AV or atrial conduction.
2. The majority of scar related VT is composed of an area of slow conduction with functional unidirectional conduction block as well as a structural barrier which is generally scar.
3. The isthmus is characterized by electrical activity during diastole and is generally the focus for ablation.
4. Scar is defined as a bipolar voltage less than 1.5 mV and dense scar is a voltage less than 0.5 mV.
5. The classical features of LAVA during sinus rhythm are:

   High frequency often double or more potentials separated by either a low amplitude baseline
   Separate from and often but not always after ventricular far-field
   May require pacing at the site in order to distinguish LAVA from ventricular farfield.

6. VT with a RBBB morphology may have an epicardial component if the following features are present:

   The onset of the QRS to a pseudo-delta wave of greater than 34 msec. A pseudo-delta wave is defined as an early rapid deflection on the upstroke of the QRS complex.
   An intrinsicoid deflection time of greater than 85 msec. The intrinsicoid deflection time is the time from the onset of the QRS to the peak of the R wave measured in V2.
   The RS complex duration defined as the earliest ventricular activation to the nadir of the first S wave in any precordial lead of greater than or equal to 121 msec.
   The presence of a Q wave or a QS in the local site of activation provides a more useful indicator. Therefore an inferior origin tends to have a Q or QS in leads II, III and aVF.

7. For VT originating from the epicardial surface of the RV these parameters do not appear to be helpful.
8. Bundle branch re-entry may occur in cases where conduction is slowed or transiently blocked in either the antegrade or retrograde directions re-entry may resulting in a LBBB morphology or less commonly a RBBB morphology.
9. Fascicular re-entry may occur with antegrade or retrograde conduction in the anterior fascicle of the left bundle an conduction in the opposite direction in the posterior fascicle. Either of these activation sequences results in a right bundle branch block type morphology during VT with a superior directed axis.
10. Outflow Tract ectopy is common and may occur in either the RVOT or less commonly the LVOT. Given that both the right and left ventricular outflow tracts are superior structures the ventricular activation tends to be from superior to inferior resulting in a positive QRS axis in leads II, III and aVF and negative in aVR and aVL.
11. Ventricular activation from the RVOT generally spreads from anterior to posterior. This results in a negative QRS in V1 with a LBBB type pattern on the ECG. If the precordial transition occurs at lead V4 or later then the origin is almost certainly RVOT.
12. If the precordial transition occurs at or close to V3 and where there may be a predominantly negative QRS in the early precordial leads with an R wave. A small R wave may be present in posterior and superior RVOT foci as well as the anterior LVOT where it tends to be slightly higher in amplitude. In order to help estimate the location several algorithms have been developed.
13. The V2S/V3R Index is useful in helping to differentiate between a RVOT and LVOT origin in outflow tract PVC's with a LBBB type morphology. A value of less than or equal to 1.5 has been shown to be suggestive of a LVOT origin while a value greater than 1.5 represents a likely RVOT origin.

14. Lead I may be useful in further ascertaining the origin of an outflow tract tachycardia. In an RVOT tachycardia a negative QRS in lead I is more indicative of a more superior origin close to or above the pulmonary valve. A positive QRS in lead I indicates a more rightward inferior structure such as the RVOT freewall. Septal and anterior origins often are biphasic in lead I.
15. If aVL is isoelectric or positive the inferior portion of the RVOT close to the Bundle of His and right bundle should be considered.
16. The mitral annulus This is a less common location for ectopy when compared with the outflow tracts. The ECG typically shows a RBBB pattern with very early precordial transition with in V1 or between V1 and V2 an a positive concordance in the precordial leads due to the relative posterior locations of the mitral annulus relative to the ECG lead positions. For anterolateral origins leads II, III and aVF tend to be positive and leads I and aVL tend to be negative. For posterior or posteroseptal foci leads II, III and aVF tend to be negative and positive in leads I and aVL. More septal origins tend to be narrower than LV free wall locations.

Mitral annular PVC's can be ablated with a success as high as that of outflow tract tachycardia [14]. Mapping can be performed using either a transseptal or retrograde approach. It is also worth mapping within the coronary sinus as the focus may be epicardial.

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Chapter 10
Anti-arrhythmic Drugs

Benedict M. Glover and Paul Dorian

Abstract Anti-arrhythmic drugs (AAD's) alter the electrical properties of the heart principally by either prolonging the cardiac action potential, decreasing conduction velocity, reducing focal automaticity or a combination of these effects. Despite the fact that a large number of AAD's were initially developed for ventricular arrhythmias the most common current indication is actually AF.

Although the majority of these drugs act relatively specifically on certain receptors the overall general distribution of these receptors throughout the ventricular and atrial myocardium may result in unwanted effects such as Torsades de Pointes (TdP) predominantly with class IA and class III drugs, prolongation of AV conduction, QRS widening and monomorphic VT with class IC drugs.

A meta-analysis of 44 trials involving 11,322 patients showed that all AAD's were associated with an increased risk of proarrhythmia with the exception of amiodarone and propafenone (Lafuente-Lafuente et al. Arch Intern Med 166:719–28, 2006). Although amiodarone is a very useful agent in the treatment of both atrial and ventricular arrhythmias its use is often limited as a result of its potential long term non-cardiac side effects which limit its use (Rothenberg et al. Heart Dis Stroke 3:19–23, 1994).

More recently, "atrial selective" AAD's have been developed which may have improved efficacy with better side effect profile. Additionally some drugs (such as renin-angiotensin aldosterone inhibitors and anti-inflammatory agents) may affect the underlying substrate and be indirectly antiarrhythmic.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7_10

Table 10.1 Classification of current anti-arrhythmic drugs as well as inotropic effects on the ventricle and potential pro-arrhythmic effects

Class	Examples	Mechanism	Inotropic effect	Pro-arrhythmia
Ia	Procainamide Quinidine	Inhibition of intermediate Na^+ channel	Negative	QRS widening and VT
Ib	Lidocaine Mexilitine	Inhibition of fast Na^+ channel	Negative	VT
Ic	Flecainide, propafenone	Inhibition of slow Na^+ channel	Negative	1:1 AV conduction
II	B blockers	B Adrenoceptor blockade	Negative	Bradycardia
III	Amiodarone Sotalol	K^+ channel blockade	Neutral	Sotaolol: bradycardia, ↑QT, torsades
IV	Ca channel blockers	Ca^{2+} channel blockade	Negative	Bradycardia

Mechanisms of Action: An Overview

Although the majority of AAD's have multiple effects on either the AP directly or by autonomic modulation, their actions can generally be classified into groups according to the predominant mechanism or resulting electrophysiological effect. This classification is called the Vaughan Williams system which was subsequently modified by Singh and Harrison (Table 10.1). It should be remembered that most AAD's have properties belonging to more than one group.

Drugs with Class I action act by blocking the fast sodium channels that are responsible for phase 0 of the AP thus affecting its slope and amplitude. These drugs are subdivided according to the rate of binding and dissociation from the sodium channel. Class IB mechanism of action is associated with the most rapid onset of action and dissociation, IA has intermediate activities and IC the slowest (Fig. 10.1).

These differences result in clinically relevant differences as a function of heart rate- drugs with slowest rates of binding and unbinding have "rate dependent properties" and the effect increases at high heart rates, not seen with the class 1b mechanism of action. As well as their effects on the slope of rapid depolarization, class I agents also have different effects on the repolarization (and APD) and thus refractory periods. Class IA property is generally associated with an increase, Class IB with a shortening (invitro) and Class IC have no effect on the APD.

Class II mechanism of action is the property of blocking beta adrenergic receptors. The primary consequence is to antagonize the effect of circulating, neurally or locally released catecholamines, with effects on all cardiac tissues and to prolong the phase 2 and 3 (after chronic use) of the AP and thus lengthen the effective refractory period.

Class III agents such as sotalol and amiodarone prolong the APD principally by inhibition of the potassium channels.

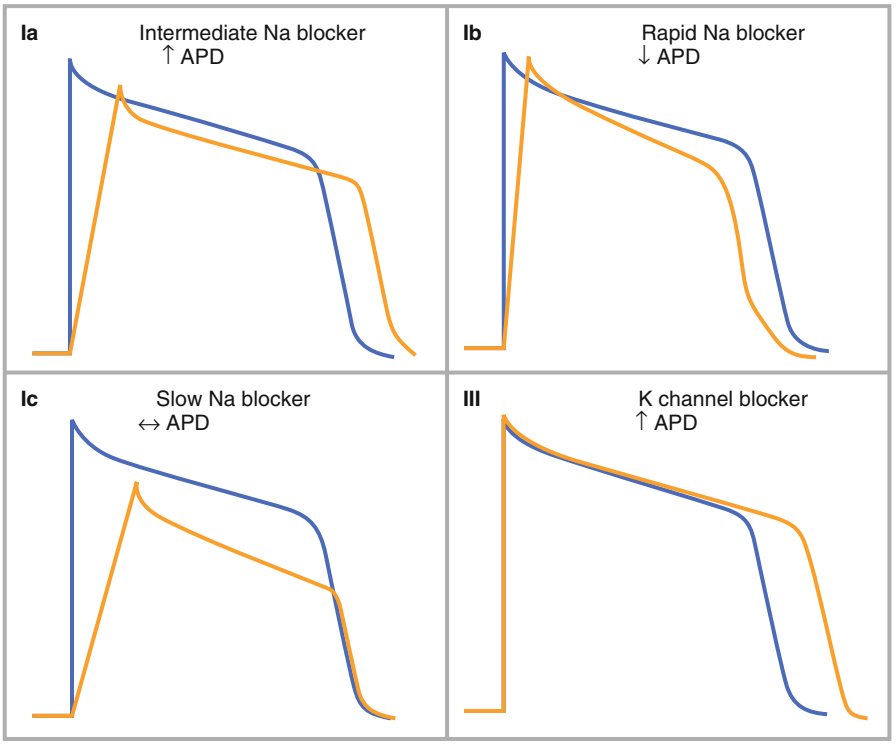

Fig. 10.1 Schematic of the effects of Class Ia, Ib, Ic and Class III AAD's on the cardiac AP

Class IV action inhibits the slow calcium current and therefore depress phase II and III of the AP in certain tissues primarily the SN and AV nodes.

Class IA Antiarrhythmics

Procainamide is conjugated to the active metabolite N-acetylprocainamide at a rate determined by whether the patient is a rapid acetylator [3, 4]. Although it was previously used for the treatment of atrial and ventricular arrhythmias its use is now largely reserved for the treatment of VT. It is also used for the acute management of haemodynamically stable pre-excited AF in the WPW syndrome (Class IIb indication) [5]. Proarrhythmia occurs in up to 9 % of cases [6] and like all class IA drugs its use has been severely restricted due to the associated risk of TdP particularly in patient with bradycardia and left ventricular hypertrophy (LVH) [7]. In general terms the risk of TdP for all class IA and some class III AAD's include a long baseline QT interval, a family history of Td, female gender, bradycardia, renal impairment (for renally excreted drugs) and a low potassium or magnesium [8].

Procainamide can also increase the ventricular rate in patients with uncontrolled AF or flutter (Class IA effect). This occurs as a result of slowing the fibrillation or flutter rate as well as increasing the likelihood that a given impulse will pass through the AV node due to the direct vagolytic action of procainamide. Thus, conduction through the AV node must be slowed and the ventricular response controlled before therapy with procainamide is initiated in these disorders. Nearly all patients will develop a positive antinuclear antibody, with a lupus-like syndrome in approximately one-third of patients taking the drug for more than one year [9]. Severe neutropaenia has been reported with long term use of oral procainamide [10]. There is limited evidence to suggest that procainamide is comparable to or superior to lidocaine in terminating monomorphic VT [11]. It is also commonly used for pharmacological testing in Brugada risk stratification.

Quinidine has similar properties and side effects to procainamide but owing to its additional effect on the the transient outward current there has been a some limited interest in this drug in patients with Brugada syndrome. Although there is some evidence to support a degree of efficacy in maintaining sinus rhythm following an electrical cardioversion for AF [12] it carries significant pro-arrhythmic side effects with an increased associated mortality [13]. The incidence of TdP reported with quinidine use varies from 0.5 to 8 % [14] and like all class IA drugs the QT prolongation tends to occur early and therefore it is recommended that it should be initiated in the hospital under continuous ECG monitoring [15]. Modest QT prolongation is relatively common while excessive prolongation is unusual and generally indicates toxicity. Like all AAD's in this group it is contraindicated in the presence of structural heart disease and LVH and is not a first-line agent for the long-term management of any atrial arrhythmia. One of the more common reasons for discontinuation of the drug is gastrointestinal side effects such as nausea, reduced appetite, an abnormal bitter taste and abdominal discomfort are relatively common occurring in approximately one third of patients.

Although the use of quinidine in cases of asymptomatic Brugada syndrome [16, 17] seems counterintuitive given that other sodium channel blockers are used for provocation; it is thought that the potential beneficial effect may be due to blockade of the transient outward current Ito thus preventing phase II reentry and VF [18]. Discontinuation of quinidine therapy due to predominantly gastrointestinal side effects may occur in approximately one third of patients. A registry of patients with asymptomatic Brugada is currently looking at the effects of quinidine in this population. Overall quinidine is generally not readily available throughout the world except in exceptional circumstances.

Disopyramide has marked anticholinergic effects and thus in theory may prove useful in vagally mediated AF [5]. The evidence for disopyramide in AF however is very weak involving a small study involving 90 patients following a successful electrical cardioversion from AF to sinus rhythm [19]. Following 1 month 70 % of patients receiving disopyramide were in sinus rhythm versus 39 % in the placebo group. It is considered a second or third line agent for suppression of atrial and ventricular arrhythmias and conversion of AF to normal sinus rhythm. Due to its negative inotropic effect it has been used in the treatment of hypertrophic cardiomyopathy

in order to reduce the outflow tract gradient and improve symptoms [20]. Other than the proarrhythmic and negative inotropic effects characteristic to this group the other main adverse effects are related to its anticholinergic effects, including urinary retention, blurred vision, constipation and dry mouth. This drug is therefore rarely used clinically.

Class IB Antiarrhythmics

The two main drugs in IB are lidocaine and mexiletine both of which act predominantly on the ventricular myocardium.

Lidocaine is a short acting intravenous antiarrhythmic which has been used extensively for the management and prophylaxis of ventricular arrhythmias. The initial clinical data for the use of lidocaine was in its ability to suppress PVC's and prevent VF after an acute myocardial infarction [21]. However this practice stopped after data showed an associated increased mortality most likely related to bradyarrhythmias and hypotension [22]. Although one trial has shown an increased prehospital survival with lidocaine [23] other randomised trial comparing lidocaine with amiodarone have shown amiodarone to be superior in terms of return of spontaneous circulation [24] as well as a lower rate of asystole [25]. As a result of this the ALS (UK) guidelines recommend the use of lidocaine only as an alternative if amiodarone is not available.

Mexiletine is structurally similar to lidocaine but has a much higher oral bioavailability and thus is available in an oral preparation. Its main activity occurs in the His Purkinje and ventricular myocardium with minimal effects on the sinus node, atrium and AV node [26, 27]. The most frequent side effects are related to GI disturbances and CNS toxicity. Cardiovascular side effects include hypotension, sinus bradycardia, and worsening of ventricular arrhythmias in 10–15 % of cases [27]. Use of mexiletine has been reported to be associated with an increased mortality [28] but may be used in patients who cannot tolerate amiodarone.

Class IC Action AAD's

The class IC drugs flecainide and propafenone have the slowest onset of action in sodium inhibition and have no effect on action potential duration.

Both flecainide and propafenone have been shown to be relatively similar in terms of efficacy in the management of symptomatic paroxysmal AF in two randomized control trials [29, 30]. Additionally in cases of recent onset AF flecainide has been shown to be effective in termination of the arrhythmia in 90 % of cases [31]. Oral flecainide has been shown to be as effective as the intravenous preparation for acute chemical cardioversion although obviously with a slower onset of action [32].

This fact combined with the large degree of use dependence has lead to the regimen called 'pill in the pocket' in which patients with symptomatic paroxysmal AF self administer a single oral dose of flecainide (generally with a beta blocker) for chemical cardioversion. Although this has been shown to be effective in 94 % of cases with no significant adverse effects, patients in this group were very carefully selected and this strategy is not ideal for many patients with paroxysmal AF [33]. In general if this strategy is to be used patients are usually tested with the identical regimen in hospital to assess for side effects and potential arrhythmias. Despite this 5 % of patients still experience problems such as presyncope, syncope and sinus arrest [34].

Despite the efficacy of class IC drugs their use has been largely limited by safety concerns. They may occasionally convert AF to atrial flutter with 1:1 AV conduction and thus a paradoxical increase in ventricular response rate. This tachycardia occasionally looks like VT particularly when there is QRS widening (also due to the drug) and since they have minimal effects on AV conduction it is recommended that they be used in the presence of an AV nodal blocker such as a beta blocker. However the major concerns regarding these drugs arose from a series of trials showing an increase in cardiovascular mortality in patients with ventricular arrhythmias in the setting of coronary artery disease and other structural heart disease The Cardiac Arrhythmia Suppression Trial (CAST) compared flecainide, encainide, moricine and placebo for the suppression of PVC's in post MI patients [35]. The trial which enrolled 1498 patients was prematurely terminated after showing an increased mortality in patients receiving flecainide and encainide (subsequently withdrawn) primarily due to arrhythmias.

Although propafenone may have a relatively better side effect profile given its additional beta adrenergic blocking effects the Cardiac Arrest Survival in Hamburg (CASH) study, in which 349 survivors of cardiac arrest due to documented VT were randomised to either an ICD, amiodarone, propafenone or metoprolol, showed a significant increase in mortality in patients receiving propafenone [36].

For these reasons, these drugs are contraindicated in the setting of prior myocardial infarction or a history of VT, and relatively contraindicated in the setting of structural heart disease.

Class II Antiarrhythmics

These drugs act by inhibiting sympathetic activity, primarily through beta-adrenergic blockade. This class is subdivided based on the specific adrenergic blockade profile, and associated properties. Propranolol is a first-generation non-selective beta-blocker with equal affinity for the β1 and β2 receptors. At high doses, propranolol may also block sodium channels. Propranolol, although useful in reducing ventricular rate in AF has not been shown to be useful as an atrial anti-arrhythmic' [37].

Metoprolol and bisoprolol are second-generation beta-blockers, which preferentially inhibit β2 receptors and may have more useful atrial antiarrhythmic effects

than propranolol. Bisoprolol has been shown to be similar to sotalol in maintenance of sinus rhythm at 12 months following an electrical cardioversion [38]. Metoprolol, has also been shown to be superior to placebo in maintenance of sinus rhythm as well as a slower ventricular rate during a recurrence [39].

Beta adrenergic blockers have been shown to reduce mortality, likely largely to a reduction in arrhythmic death in most cases, in patients with long QT syndrome [40], survivors of cardiac arrest [41], post myocardial infarction [42] and in patients with impaired LV systolic function [43].

Class III

Class III action AAD's block the potassium channels, thereby prolonging repolarization, the APD, and the refractory period. These changes are manifested on the surface ECG by prolongation of the QT interval. This group includes sotalol, amiodarone, dofetilide, vernakalant and ibutilide.

Sotalol consists of 2 isomers called D and L each of which contribute to the anti-arrhythmic properties. The D isomer blocks the rapid component of the delayed rectifier potassium current (IKr channel) during phase 3 of the AP and thus prolongs the AP duration. The L isomer also prolongs the cardiac AP as well as having a degree of Beta Adrenergic blocking activity. Although a preparation of the D isomer has been developed it has been shown to be associated with an increase in the risk of mortality in patients with impaired LV function and a recent MI or heart failure with a history of prior MI [44]. Therefore that the beta adrenergic blocking effects may also confer an advantage.

Sotalol has been shown to be effective in maintaining sinus rhythm and reducing the incidence of episodes of AF, although not as effectively as amiodarone. The CTAF study randomised patients with a history of AF to sotalol, amiodarone or propafenone [45]. After a mean follow-up of 16 months similar percentages of patients receiving sotalol and propafenone had a recurrence of AF while significantly fewer receiving amiodarone had an AF recurrence.

In clinical practice sotalol is generally used for the control of paroxysmal AF as second or third line agent after flec/propafenone and amiodarone. It has also been shown to reduce the recurrence of sustained ventricular arrhythmias [46, 47] but less than amio (OPTIC study) and can also be considered after amiodarone in terms of reducing ICD discharges.

The most significant risk associated with sotalol is the risk of TdP particularly at slower heart rates. The actual risk of TdP has been reported as approximately 2.5 % at a median follow up of 164 days [48]. This risk is increased in females, patients with a history of heart failure, patients with renal impairment and at high doses of sotalol (greater than 320 mg per day) [48].

Amiodarone was first used as an anti-anginal drug in the 1960s, and its anti-arrhythmic properties were first reported in 1970. The predominant mode of action is class III by blocking the IKr and IKs channels. This results in a reduction in

dispersion of refractoriness, re-entry and proarrhythmia and overall a prolongation of myocardial repolarization homogeneously. Additionally it also blocks sodium channels (Class I effects) and thus reduces conduction velocity, has non selective beta adrenergic blocking effects (Class II) and inhibits the L type calcium channel (Class IV). It causes use dependent potassium channel blockade meaning that as the heart rate increases the refractory period increases incrementally [49].

The onset and mode of action depends on the type of administration. If given intravenously the onset of action is several hours and there is minimal AP prolongation except in the AV node. The oral preparation takes several days and the overall effects are more pronounced after chronic usage.

Amiodarone has been shown to be the most efficacious AAD in the treatment of both AF and VT. The Canadian Trial of AF in which patients with at least one episode of AF were randomized to various antiarrhythmic medications showed that 35 % of patients randomized to amiodarone had a recurrence of AF versus 63 % of patients randomized to either sotalol or propafenone [44]. There was no significant difference in the maintenance of sinus rhythm between those who received either sotalol or propafenone. Given its multichannel effects and minimal negative inotropic effects it is considered relatively safe in patients with impaired LV function and is recommended as first line therapy for the treatment of ventricular arrhythmias unless there is a contraindication [22]. Although amiodarone prolongs the QT interval the risk of torsades de pointes VT is less than 1 % [50].

The most common and significant side effects which limit the longterm use of amiodarone are generally non cardiac and adverse effects have been reported to be as high as 15 % within the first year of treatment and 50 % during long term therapy [50]. It is therefore important that the patient is monitored for side effects as shown in Fig. 10.2.

Amiodarone induced hypothyroidism is more common than thyrotoxicosis. Within the first 3 months of therapy there is an increase in thyroid stimulating hormone (TSH), free T4 and a reduction in free T3. TSH then normalises while T4 and T3 may remain abnormal. The importance of this is that it is generally not useful to check thyroid function within the first 3 months and following this the most useful measure is TSH [50]. Amiodarone induced thyrotoxicosis is less predictable and can occur relatively suddenly at any time during treatment. It can be due either to aggravation of pre-existing thyroid disease or thyroiditis, although often it is difficult to distinguish between these. It is generally recommended that all patients being commenced on long term amiodarone therapy should have baseline TFT's which should be rechecked after 3 months to establish a new baseline and then every 6 months or sooner if clinically indicated [50].

Lung toxicity has been reported as occurring in up to 2 % of patients [50]. Risk factors for pulmonary fibrosis are a prior history of lung disease and a daily dose of amiodarone greater than 400 mg per day [51]. It may present anytime from 1 week following initiation of the drug and is relatively unpredictable and therefore although pulmonary function tests are frequently performed they of limited value.

These and other non cardiac side effects of amiodarone have subsequently lead to the development of the noniodinated benzofuran derivative dronedarone.

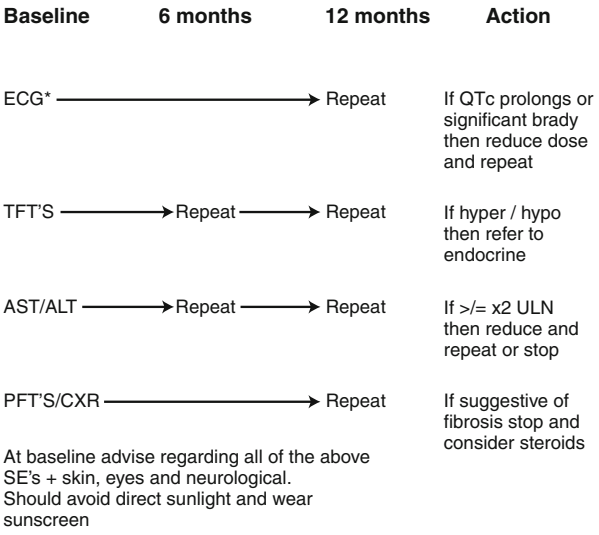

Fig. 10.2 Suggested monitoring for the side effects of long term amiodarone (* Evidence of QTc prolongation, sinus node or AV node conduction abnormalities should prompt close monitoring)

The dose of dronedarone was established in the Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) [52]. Three different doses (800, 1200, or 1600 mg) of dronedarone daily were compared with placebo in patients following a successful electrical cardioversion. 800 mg per day delayed the time to recurrence of AF; 35 % dronedarone versus 10 % placebo at 6 months. Higher doses of dronedarone resulted in better ventricular rate control in patients who converted to atrial fibrillation. Dronedarone was not associated with any thyroid, pulmonary or ocular side effects. Although higher doses of dronedaone were associated with increases in the QT interval, there were no cases of torsades de pointes. The most important side effects associated with the use of dronedarone were gastrointestinal disturbance. Based on these results the dose of 400 mg twice daily was chosen. This dose was studied in patients with either atrial fibrillation or atrial flutter in the twin studies called The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) [53]. These trials randomised patients with a history of paroxysmal atrial fibrillation or atrial flutter to receive either dronedarone or placebo. Dronedarone increased the time to first recurrence of atrial fibrillation from 53 days in the placebo group to 116 days for those patients receiving dronedarone. Additionally in patients who had a recurrence of atrial fibrillation dronedarone significantly reduced the ventricular rate. A post hoc analysis revealed a 27 % reduction of relative risk of hospitalization and death with dronedarone treatment.

The effect of dronedarone in ventricular rate control for patients with permanent AF was studied in the Efficacy and Safety of Dronedarone for Control of Ventricular Rate (ERATO) [54]. The addition of dronedarone (800 mg per day) to standard rate-control therapy reduced the ventricular rate by 11.7 beats per minute after 2 weeks of treatment and by a mean of 24.5 bpm during exercise.

Dronedarone was studied in patient with moderate to severe left ventricular impairment irrespective of the rhythm in the Antiarrhythmic Trial with Dronedarone in Moderate-to- Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) [55]. Patients had a left ventricular ejection fraction less than 35 % and had been hospitalized with new or worsening heart failure. They also had to have had at least one episode of shortness of breath on minimal exertion or at rest (NYHA III or IV) or paroxysmal nocturnal dyspnoea within the month prior to admission. There was no restriction related to renal function.

After a median follow up period of 2 months, a significantly higher mortality rate was reported with dronedarone treatment (8.1 %) as compared with placebo (3.8 %). The worse the left ventricular function the higher the risk of death. This has lead to the avoidance of dronedarone in patients with severe LV dysfunction and heart failure.

To help address some of these issues a further study was carried out looking at patients with stable AF and at least one cardiovascular risk factor. The Assess the Efficacy of Dronedarone for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) [56] had the composite primary end point of all-cause mortality and cardiovascular hospitalization. 4628 patients with a history of paroxysmal or persistent AF/atrial flutter were randomised to dronedarone 400 mg twice a day versus placebo with 12 months of follow-up. The use of dronedarone was associated with a significant 27 % reduction in the primary end point of death or cardiovascular hospitalization. The most frequently reported adverse effect of dronedarone was gastrointestinal, principally nausea and diarrhoea that in several cases led to drug discontinuation. The reduction in hospitalisations was a major reason for dronedarone gaining clinical approval in North America and more recently lead to a second draft guidance by National Institute for Clinical Excellence (NICE) revising its original recommendation that the drug should not be used to treat AF. It is therefore recommended that dronedarone should be considered as a second-line treatment in patients with additional cardiovascular risk factors whose AF has not been controlled by first-line therapy (usually including beta blockers).

Class IV

Verapamil and diltiazem block the L-type calcium channel and principally prolong the atrioventricular nodal refractory period. The VERDICT study showed no benefit in maintenance of sinus rhythm of verapamil over digoxin [57]. Two large trials which examined the use of verapamil in the maintenance of sinus rhythm following an electrical cardioversion both showed verapamil combined with quinidine was similar in efficacy to sotalol with a higher incidence of TdP in the sotalol group [58, 59]. Due to its negative inotropic effects verapamil should be used cautiously in patients with left ventricular dysfunction. As verapamil also suppresses sinus node automaticity it should also be avoided in sick sinus syndrome. Both verapamil and

diltiazem are similar in efficacy and side effects (other than constipation associated with verapamil). Calcium channel blockade may be a reasonable choice of drug for ventricular rate control in patients with preserved LV function and can be considered as an alternative to B blockers.

AAD's Not in the Vaughan Williams Classification

Some drugs such as digoxin, adenosine and ivabradine do not fit into the traditional Vaughan Williams classification.

Digoxin acts directly on the myocardium in order to increase the concentration of intracellular sodium and thus account for its positive inotropic effects. Of interest however this as well as its vagotonic effects actually shortens the atrial effective refractory period and therefore may actually increase the potential to develop AF in patients who are in sinus rhythm [60]. Its role in AF is therefore principally to slow AV conduction (through its vagotonic effects) and thus reduce the ventricular rate. It is not an ideal drug for acute ventricular rate control as the onset of action is 4–6 h and may not be as effective if the rate is partially sympathetically-driven. It continues to have an important role in the management of AF and is particularly effective when combined with a beta adrenergic blocker due to synergistic effects [5]. Recent data suggests that it may have deleterious effects and therefore its use if now relatively limited.

Adenosine is a metabolite of adenosine triphosphate which results in slowing of AV nodal conduction, shortening of the atrial myocardial refractory period and depression of sinus node automaticity [61]. Adenosine is highly effective in terminating supraventricular arrhythmias in which the AV node forms part of the reentrant circuit such as AV nodal reentry and orthodromic reciprocating tachycardia.

Additionally it can be used for diagnostic purposes such as transiently slowing AV conduction in SVT to identify the underlying rhythm and may also be helpful in differentiating SVT from VT (although very rarely adenosine may terminate a specific type of VT). Side effects such as facial flushing (due to cutaneous vasodilation), dyspnoea, and chest pressure have been reported to occur in about 30 % of patients [62]. Given the short half life of adenosine these side effects generally last less than 60 s. The downside to the short duration of action is that in some cases arrhythmias recur after several minutes after termination with adenosine [63].

Ivabradine is a novel selective inhibitor of the If channel in the SA node. It therefore reduces the sinus rate with no effect on either the AV node or intraventricular conduction times [64]. Although its principle clinical use is for symptom relief in patients with chronic stable angina it may also have a role in patients with an inappropriate sinus tachycardia. A recent study examining its use in 18 symptomatic patients with an inappropriate sinus tachycardia (defined as a nonparoxysmal tachyarrhythmia with a P-wave morphology and endocardial activation identical to sinus rhythm and an excessive increase of heart rate in response to minimal physical activity and emotional stress, and nocturnal normalization) showed a significant reduction

in heart rate on Holter and exercise stress tests [65]. Although this was a small study there may be a role for this drug in these patients where other drug therapies can be relatively ineffective and ablation therapy may carry some significant risks.

The Future: Novel AAD's

Given the significant cardiac and non-cardiac side effects associated with current AAD's there has been a huge interest in the development of novel 'atrial selective' drugs for the treatment of AF. These drugs can be broadly divided into amiodarone derivatives such as dronedarone, PM101 and budiodarone, selective Iks blockers such as HMR1556, atrial repolarization-delaying agents such as vernakalant and sodium channel blockers such as ranolazine.

Mention it is approved for angina (US) and being tested for AF (with dronedarone) and ICD shocks (NIH sponsored RAID study).

Atrial Repolarization Delaying Agents: Vernakalent

Vernakalant predominantly targets early-activating K+ channels and frequency-dependent Na+channels in the atria. It has been shown to have an efficacy of 52 % in the acute conversion of recent onset AF compared to a 4 % success rate with placebo [66]. More recently the results of the AVRO trial comparing vernakalant with amiodarone was presented. This randomised double blind multicentre superiority trial in 254 adult patients with AF showed that vernakalant has a higher efficacy for the conversion of AF as well as a greater rate of symptom relief (51.7 % converted with vernakalant versus 5.2 % with amiodarone). Treatment with vernakalant resulted in a rapid conversion to sinus rhythm, with a median conversion time of 11 min. Additionally it is well tolerated and appears to be relatively safe with no cases of ventricular arrhythmias or drug related deaths. This drug is currently under consideration for clinical approval in Europe and North America. The main side effects associated with its use appear to be dysgeusia (30 %), transient sneezing (17 %), hypotension (5 %) and bradycardia (5 %).

Sodium Channel Blockers: Ranolazine

Ranolazine has been shown to be effective as an anti-anginal agent when added to standard medical therapy most likely through various mechanisms but predominantly through its ability to inhibit the inward sodium current. In a similar mechanism it has been postulated that this may have anti-arrhythmic effects in the atria where rapid atrial rates during AF may result in oxidative stress and atrial myocardial

ischaemia. The Metabolic Efficiency with Ranolazine for Less Ischaemia in Non-ST-elevation acute coronary syndrome— Thrombolysis in Myocardial Infarction (MERLINTIMI 36) trial compared ranolazine with placebo in 6560 patients hospitalized with acute coronary syndromes. A significant reduction in tacharrhythmias (SVT and VT) was noted in patients commenced on ranolazine versus placebo on 7 day continuous cardiac monitoring [67]. There was no effect on sustained arrhythmias such as AF and VT and no overall effect on mortality or recurrent ischaemia. Further clinical studies are required to assess the clinical utility of ranolazine as an AAD.

Important Points

1. Anti-arrhythmic drugs alter the electrical properties of the heart principally by either prolonging the cardiac AP, decreasing conduction velocity, reducing focal automaticity or a combination of these effects.
2. The Vaughan Williams classification categorizes anti-arrhythmic drugs into groups according to their main mechanism of action. These are:

   Class I action block the fast sodium channels which are responsible for phase 0 of the action potential thus affecting its slope and amplitude. These drugs are subdivided according to the rate of binding and dissociation from the sodium channel. Class IB mechanism of action is associated with the most rapid onset of action and dissociation, IA has intermediate activities and IC the slowest.

   Class II action block beta adrenergic receptors prolonging the phase 2 and 3 (after chronic use) of the action potential and thus lengthen the effective refractory period.

   Class III agents prolong the action potential duration principally by inhibition of the potassium channels.

   Class IV action inhibits the slow calcium current and therefore depress phase II and III of the AP in certain tissues primarily the SN and AV nodes.

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B.M. Glover, P. Brugada (eds.), *Clinical Handbook of Cardiac Electrophysiology*, DOI 10.1007/978-3-319-40818-7

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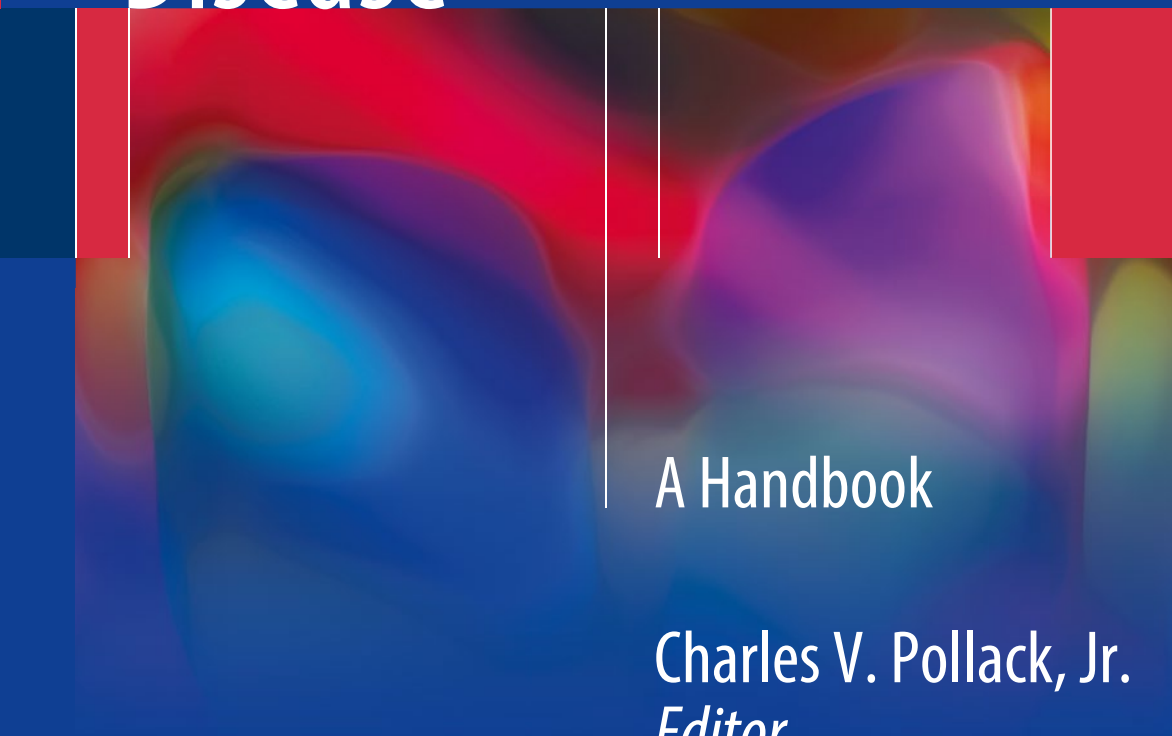

A Handbook

Charles V. Pollack, Jr.
Editor

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Differential Diagnosis of Cardiopulmonary Disease

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Editor

Differential Diagnosis of Cardiopulmonary Disease

A Handbook

Springer

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ISBN 978-3-319-63894-2 ISBN 978-3-319-63895-9 (eBook)
https://doi.org/10.1007/978-3-319-63895-9

Library of Congress Control Number: 2019935819

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Preface

This book is intended to be a ready resource and guide for the evaluation of common symptoms and syndromes that originate in the primary cardiopulmonary system. It should prove particularly useful in the generation of a working differential diagnosis, consideration of diagnostic approach, and initial management decisions. It is not intended to be a comprehensive resource; rather, it follows the classic "emergency medicine approach" of considering first the worst-case scenario, and then exploring other possibilities quickly and efficiently. The image, video, and audio links embedded in the text should help the learner correlate bedside findings with reference material.

It is our hope that this guide will streamline the diagnostic approach to patients with "thoracic" complaints and make the learner more confident in his or her skills. The focus of this book is on differential diagnosis, confirmation of diagnosis, and essential steps towards initiating treatment. Therapeutic modalities change more rapidly that diagnostic approach and may have evolved since a specific chapter was completed. Treatment should always be guided by the latest literature, but is founded upon solid diagnostic acumen.

Philadelphia, PA, USA — Charles V. Pollack, Jr.

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Chapter 1
Achalasia

Christopher J. Rees, Victoria G. Riese, and Charles V. Pollack, Jr.

Name and Synonyms

Achalasia

Incidence/Epidemiology

- Achalasia is a rare disease with an annual incidence of 1–2/100,000 persons.
- It affects men and women with equal frequency.
- It usually presents between the ages of 20 and 40, but may occur at any adult age.
- Onset before adolescence is rare.

Differential Diagnosis

- Achalasia is the most common motility disorder of the esophagus.
- It most often causes dysphagia (difficulty swallowing, as opposed to odynophagia—painful swallowing), so the differential is the differential for dysphagia.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_1

- Other diseases that may present with dysphagia and associated esophageal dilatation (secondary achalasia) include gastric cancer; infiltrative diseases such as amyloidosis, sarcoidosis, eosinophilic gastritis, and neurofibromatosis; and infections such as Chagas disease in South America.

Pathophysiology and Etiology

- Achalasia is a motility disorder of the esophagus; the cause is unknown.
- Histopathologically, achalasia is associated with degeneration of neurons in the myenteric plexus of the esophageal wall near the lower esophageal sphincter (LES). There is also an associated inflammatory response with an influx of inflammatory cells.
- The degeneration is most marked within the inhibitory neurons that allow for relaxation of the LES. This leads to a sustained contraction/increase in tone of the LES, resulting in an increase in LES pressure.
- Degeneration of the inhibitory neurons within the myenteric plexus in the lower two thirds of the esophagus affects the smooth muscle and causes aperistalsis.
- The cause of the degeneration is unknown. It has been ascribed to autoimmune phenomenon and sometimes to chronic viral infections from herpes simplex virus, measles virus, and HSV-1, but there is no conclusive evidence for any of these putative mechanisms.

Presentation

Typical/"Classic"

- Dysphagia (difficulty with swallowing) is the most common presenting symptom of achalasia, occurring in about 90 % of patients. Typically, the dysphagia is to solids and liquids equally.
- Most patients (about 75 %) also report regurgitation of undigested food. The regurgitated food remains in the esophagus, so usually there is no "acid taste" as in reflux. This has been described as a "bland reflux."
- Many patients describe an epigastric or retrosternal fullness after eating that may be severe enough to provoke attempts to induce vomiting, leading to confusion with eating disorders.
- Other commonly reported symptoms include difficulty belching, substernal chest pain associated with reflux, and frequent hiccups.
- Symptoms usually progress gradually. The mean time from symptom onset until diagnosis is about 5 years. This reflects the insidious nature of the symptoms, more than any particular difficulty in diagnosis.

- Some patients are noted to perform mechanical maneuvers (raising the arms above the head, standing erect and hyperextending the back) to help clear the esophagus. These actions may be noticed more by family members.

Atypical

- In retrospect, most patients will have years of somewhat typical symptoms before presentation.
- Most patients will have been treated for gastroesophageal reflux (GERD) before consideration of the diagnosis.
- Patients may present with chest pain, especially with eating. This may have been considered esophageal spasm and not responded to treatment.

Primary Differential Considerations

- Other causes of dysphagia should be considered, including
  - Esophageal tumors
  - Reflux /GERD
  - Connective tissue disorders, such as systemic sclerosis
  - Esophageal perforation
  - Esophageal spasm or stricture
  - Gastric cancer that involves the lower esophagus
  - Much rarer considerations:
    - Chagas disease
    - Plummer–Vinson syndrome

History and Physical Exam

Findings That Confirm Diagnosis

- The history usually is very suggestive of the diagnosis, although there are no absolutely confirmatory findings on history and physical exam. Physical exam usually is normal, although patients may have unintended weight loss.
- Confirmation is with esophageal manometry.

Factors That Suggest Diagnosis

- The historical features as described above suggest the diagnosis.
- An especially suggestive historical feature is dysphagia to solids and liquids equally.

Factors That Exclude Diagnosis

- Early in the course of illness, esophageal manometry may be nondiagnostic, so a high index of suspicion needs to be maintained if the symptoms continue or progress.

Ancillary Studies

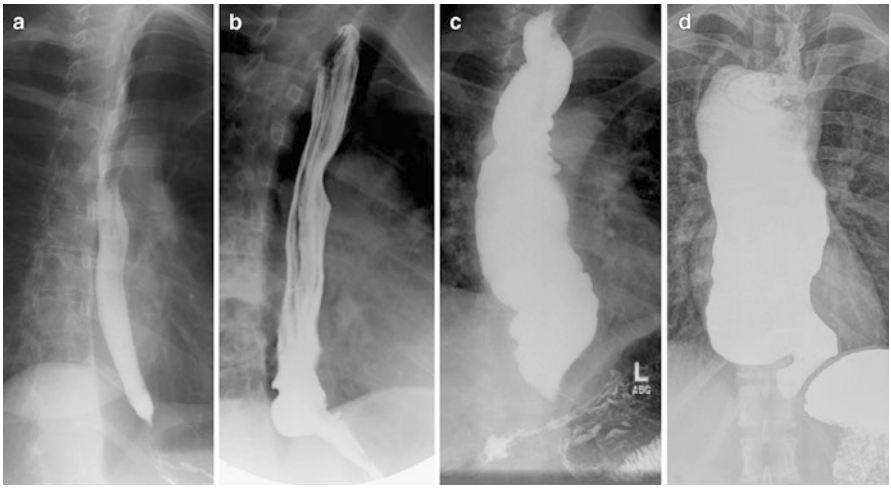
Laboratory

- Lab tests generally are not helpful in the diagnosis.

Imaging

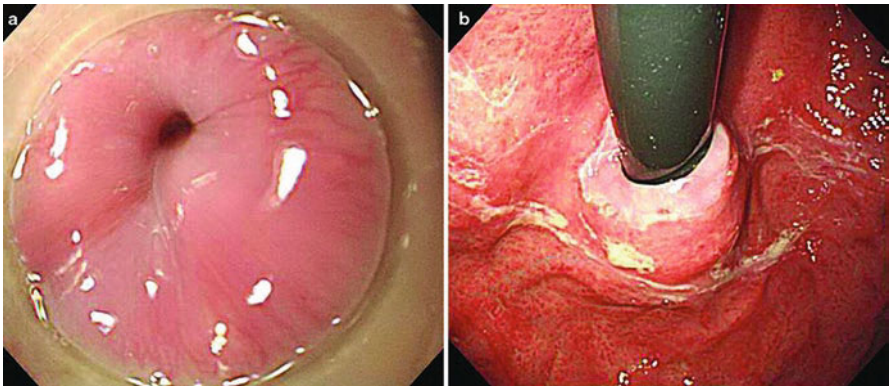
- Chest x-ray may demonstrate widening of the esophagus or mediastinum, but more commonly is normal, especially early in the disease course.
- Barium swallowing studies may be helpful in suggesting the diagnosis, especially later in the course of illness.
- Classically, the barium esophagram demonstrates a proximally dilated esophagus that narrows to a contracted gastroesophageal junction, giving the classic "bird-beak" appearance of the esophagus.

Classic "bird-beak" appearance of the esophagus on barium esophagram in achalasia. [Mittal R. Esophageal motor disorders. In: Orlando RC, editor. Atlas of esophageal diseases. 2nd ed. Philadelphia: Current Medicine; 2002. p 163–78.]



Examples of progressive dilation of the esophagus in different patients with achalasia. a Normal diameter esophagus leading to a bird's beak at the LES. b Minimal esophageal dilation (from 4 to 7 cm). c Progressive esophageal dilation (from 7 to 10 cm) with preserved esophageal axis. d Greater dilation (>10 cm) and initial sigmoidal course of the distal esophagus. [From article: A controversy that has been tough to swallow: is the treatment of achalasia now digested? J Gastrointest Surg. 2010 Feb;14 Suppl 1:S33-45. https://doi.org/10.1007/s11605-009-1013-5, at http://link.springer.com/article/10.1007%2Fs11605-009-1013-5; by Garrett R. Roll, Charlotte Rabl, Ruxandra Ciovica, Sofia Peeva, Guilherme M. Campos, © The Author(s) 2009; licensed under Creative Commons Attribution Noncommercial License https://creativecommons.org/licenses/by-nc/2.0/] *Caption from original*

- Other suggestive findings on barium study include a dilated esophagus, aperistalsis of the esophagus, and poor/delayed emptying of the barium into the stomach.
- Barium studies may be falsely negative in up to one third of cases.
- The diagnosis usually is confirmed by esophageal manometry, which is usually performed at specialized, experienced centers.
- Currently, the procedure of choice is high-resolution manometry (HRM) with or without esophageal pressure topography (HRMEPT).
- The classic finding on manometry is aperistalsis of the distal two thirds of the esophagus with incomplete relaxation of the LES. Increased pressure within the LES is a supportive finding but is not diagnostic.
- HRMEPT allows subtyping of achalasia, which may help in deciding treatment.
- Endoscopy (usually done when considering esophagitis, peptic ulcer disease, or gastritis in the diagnosis) usually is normal, though itmay demonstrate a dilated esophagus with retained products.



Endoscopic appearance of achalasia. (**a**) Sustained contraction of the lower esophageal sphincter as viewed from the proximal esophagus. (**b**) Retroflexed view of the LES from the stomach. [Park JM. Miscellaneous esophageal diseases. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical gastrointestinal endoscopy: a comprehensive atlas. Heidelberg: Springer. 2014. p. 87–98.] *Caption adapted from original*

Special Populations

Age

- Achalasia usually presents between the ages of 20 and 40 but may occur at any adult age.
- May be seen in adolescence, but is rare.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first step.
- It is critical to consider malignancy in the differential diagnosis.

Mimics

- Any disease process that presents predominately with dysphagia can mimic achalasia.

- It is important to consider malignancy and other mechanical causes of dysphagia.
- Gastric cancer close to the gastroesophageal junction is a mimic of achalasia that must be considered.
- Space-occupying lesions (such as cancer) usually present with dysphagia that is greater with solids than liquids, but as they enlarge, they may produce dysphagia to both.
- Another diagnosis that may be confused with achalasia when evaluating a patient for dysphagia is myasthenia gravis. Myasthenia usually produces both dysphagia and dysphonia (decrease in tone/quality of voice).

Time-Dependent Interventions

- There are no particular time-dependent interventions in the evaluation of achalasia other than consideration of and evaluation for malignancy.

Overall Principles of Treatment

- Treatment is aimed at reducing the resting pressure of the LES.
- The first step usually is progressive, endoscopy-guided dilatation of the LES.
- If symptoms persist after three attempts at dilatation, or patients cannot tolerate dilatation, surgical myotomy often is performed.
- Patients who are not surgical candidates, or those who decline surgery, may be offered a trial of endoscopically guided direct injection of botulinum toxin into the LES.
- If all other treatments are unsuccessful, or the patient is not a candidate for surgery or endoscopy, a trial of oral nitrates or calcium channel blockers may be attempted.

Disease Course

- Achalasia is a chronically progressive disease; without treatment, esophageal dilatation will continue.
- Ten to fifteen percent of patients will develop end-stage disease even with treatment.
- Up to 5 % eventually may require complete esophagectomy, especially when the esophageal diameter exceeds 6 cm (megaesophagus).
- Patients with achalasia are at increased risk for squamous cell carcinoma of the esophagus. The absolute risk is low, however, so endoscopic surveillance is not recommended.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Cohort Study

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Esophageal Achalasia"[Mesh] OR "Achalasia"

Chapter 2
Acute Coronary Syndrome: Non–ST-Segment Elevation Myocardial Infarction

Charles V. Pollack, Jr. and Victoria G. Riese

Name and Synonyms

Non–ST-Segment Elevation Myocardial Infarction

- NSTEMI, subendocardial MI, non-Q-wave MI (NQMI), troponin-positive ACS

Incidence/Epidemiology

- In the middle of the continuum of diagnoses collectively called acute coronary syndrome (ACS)—between unstable angina (UA) and ST-segment elevation MI (STEMI).
- More common than STEMI.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_2

	STEMI	NSTEMI/UA
Pathogenesis	Fully occlusive thrombus	Less than fully occlusive thrombus
Incidence		Higher than that of STEMI
Patient profile		Older; higher co-morbidity (diabetes, renal failure) than STEMI patients
Time course	Minutes to hours	Up to a few days
Clinical manifestations		Similar to STEMI
Imaging studies		Similar to STEMI
EKG	ST elevations	No ST elevations[a]
Biomarkers	Elevated	Elevated
Therapy	See Table 2.54	See Table 2.54
Rehabilitation		Similar to STEMI
Complications		Similar to STEMI
Prognosis		Mortality lower in-hospital, higher at 6 months and 4 years than with STEMI

[a]ST elevations may be seen in Prinzmetal's angina

STEMI and NSTEMI/UA: a comparison. [Adelmann GA. Coronary artery disease. In: Adelmann GA, editor. Cardiology essentials in clinical practice. London: Springer; 2011. p. 23–95. Book https://doi.org/10.1007/978-1-84996-305-3] *Caption from original*

- Incidence varies widely by demographics and risk profiles; patients with NSTEMI tend to be older and have more co-morbidities than STEMI patients.
- Of the more than 1.2 million MIs in United States each year; most are NSTEMI, and as troponin assays become increasingly sensitive, there are fewer cases diagnosed as UA and more as NSTEMI.

Differential Diagnosis

- Includes all other causes of chest pain.
- Includes other causes of "anginal equivalents" in susceptible populations, e.g.:
  - Dyspnea
  - Back pain
  - Jaw pain
  - Shoulder pain
  - Epigastric pain
  - Palpitations
  - Dizziness
  - Weakness
  - Nausea
  - Syncope

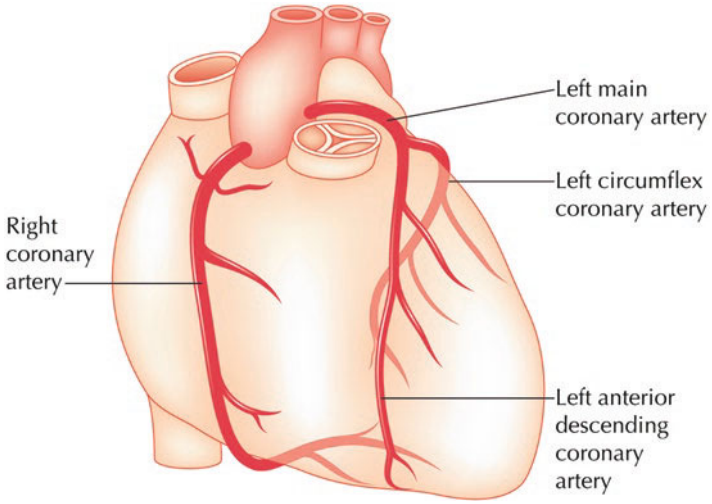
Pathophysiology and Etiology

- ACS is the result of ischemia (diminished blood flow / oxygen delivery) to myocardium.
- If ischemia persists, frank infarction (muscle death) may occur.
- Infarction results in breakdown of cell membranes, allowing release of intracellular proteins (such as myoglobin, troponins, and CPK-MB) into the circulation, where they may be detected in peripheral blood.
- NSTEMI is defined by this protein (enzyme) "leak," and it is that lab finding that differentiates it from UA.
    - Other causes of elevated troponin include:
        - Renal insufficiency
        - Heart failure
        - Pulmonary embolism
        - Septic shock
        - Nonthrombotic causes

Demand ischemia: a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting stenosis (i.e., systemic inflammatory response, hypotension, tachyarrthmias)
Myocardial ischemia in the absence of fixed obstructive coronary disease: an imbalance of the autonomic nervous system and increased catecholamine effect on the myocardial cells (i.e., vasospastic angina, acute stroke or intracranial hemorrhage and subarachnoid hemorrhage)
Direct myocardial damage: cell injury by traumatic or inflammatory process (i.e., pericarditis and myocarditis)
Myocardial strain: volume and pressure overload of both ventricles (i.e., congestive heart failure, pulmonary embolism)

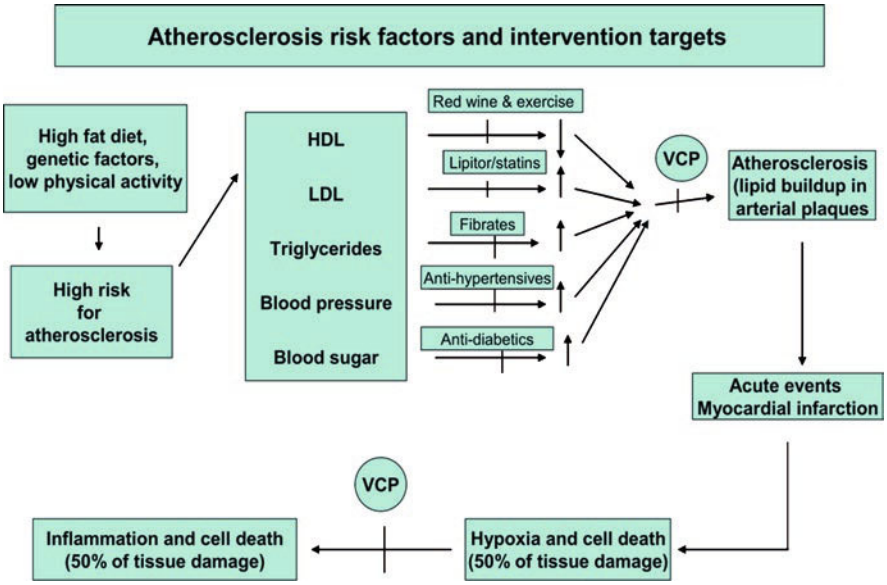
Nonthrombotic mechanisms of troponin elevation in ICU setting. [Lazzeri C, Bonizzoli M, Cianchi G, Gensini GF, Peris A. Troponin I in the intensive care unit setting: from the heart to the heart. Intern Emerg Med. 2008 Mar;3(1):9-16. https://doi.org/10.1007/s11739-008-0089-3] *Caption from original*

- Most NSTEMI occurs as a result of fracture or frank rupture of atherosclerotic plaque in an epicardial artery, but often the artery that is fully occluded is downstream from the plaque and is actually occluded by a platelet aggregate embolism from upstream. It also may occur from incomplete obstruction at the site of plaque and poor collateral circulation upstream.



Normal coronary anatomy. [Achenbach S. Normal coronary anatomy. In: Budoff MJ, Narula J, Achenbach SS, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption from original*

- Atherosclerosis is a product of diverse inherited and acquired conditions, including:
  - Family history
  - Hyperlipidemia
  - Hypertension
  - Diabetes mellitus
  - Tobacco abuse



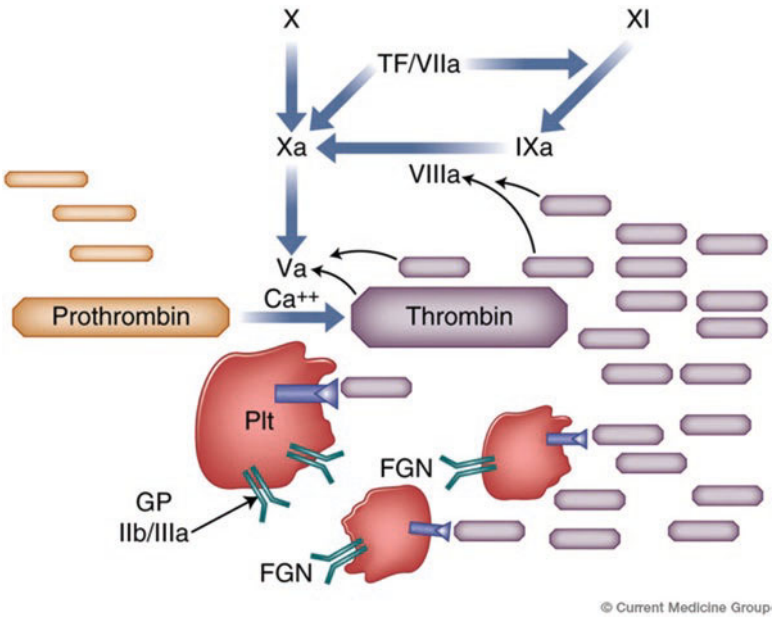
Atherosclerosis risk factors and intervention targets. [Thorbjornsdottir P, Thorgeirsson G, Kotwal GJ, Arason GJ. Control of inflammation with complement control agents to prevent atherosclerosis. In: Suri JS, Kathuria C, Molinari F, editors. Atherosclerosis disease management. New York: Springer; 2011. p. 633-75. Book https://doi.org/10.1007/978-1-4419-7222-4] *Caption adapted from original*

Risk factors	No. of patients
Individual	
Smoking	6
Hypertension	11
Hypercholesterolemia	9
Diabetes mellitus	4
Clusters	
Smoking and hypercholesterolemia	1
Hypertension and hypercholesterolemia[a]	4
Hypertension and diabetes	2
Smoking, hypertension and hypercholesterolemia	1
Smoking, hypertension, hypercholesterolemia and diabetes	2

[a] Hypertension was defined as a diastolic arterial pressure >95 mm Hg and hypercholesterolemia >6 mmol/l

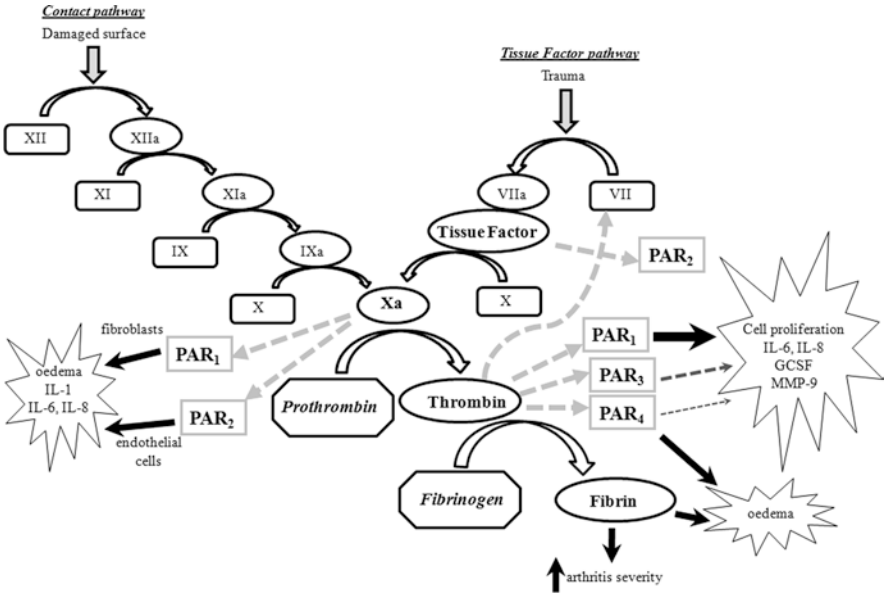
Main known risk factors for atherosclerosis in 16 patients studied. [Watt S, Aesch B, Lanotte P, Tranquart F, Quentin R. Viral and bacterial DNA in carotid atherosclerotic lesions. Eur J Clin Microbiol Infect Dis. 2003 Feb;22(2):99-105. https://doi.org/10.1007/s10096-002-0867-1] *Caption adapted from original*

- Plaque rupture initiates a complex thrombo-inflammatory response locally including activation of:
  - Coagulation



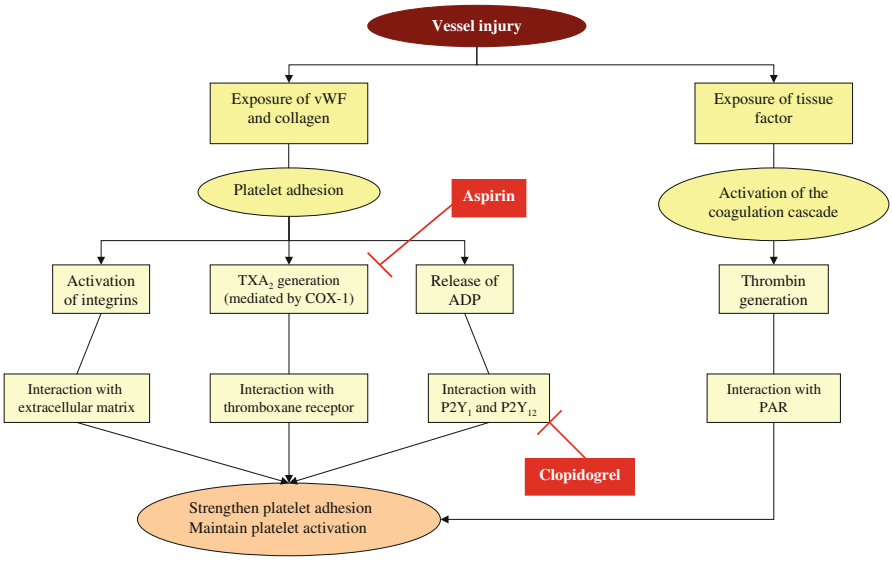
Networking of coagulation cascade and aggregation of platelets (Plt). The extrinsic limb triggers activation of the coagulation cascade when tissue factor (TF) is exposed in a disrupted plaque. Coagulation factor VII is activated (VIIa) and can activate factor X to Xa and promote perpetuation of the coagulation process via the intrinsic limb that results in formation of IXa and VIIIa. The prothrombinase complex of Xa, Va, Ca^{++} forms on a phospholipid surface (*eg*, membrane of a platelet) and converts prothrombin to thrombin. The thrombin that is formed binds to the thrombin receptor on platelets promoting activation and aggregation of platelets, as well as amplifying the coagulation cascade by promoting formation of VIIIa and Va. This diagram depicts the amplification nature of the coagulation process because one molecule of Xa leads to the downstream production of a large number of thrombin molecules (stoichiometric relationship not completely depicted to prevent obscuring the diagram with thrombin molecules). Activated platelets express numerous copies of the active form of the fibrinogen receptor GP IIb/IIIa on their

surface. GP IIb/IIIa recognizes specific amino acid sequences on circulating ligands. One such ligand is fibrinogen (FGN), which has multiple copies of the RGD amino acid sequence and serves to bridge platelets together, promoting formation of aggregates. The more aggregates formed, the greater the surface area for the prothrombinase complex and amplification of the reactions of the coagulation cascade. [Antman E. Acute coronary syndromes. In: Libby P, editor. Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. ISBN: 978-1-57340-309-2] *Caption from original*



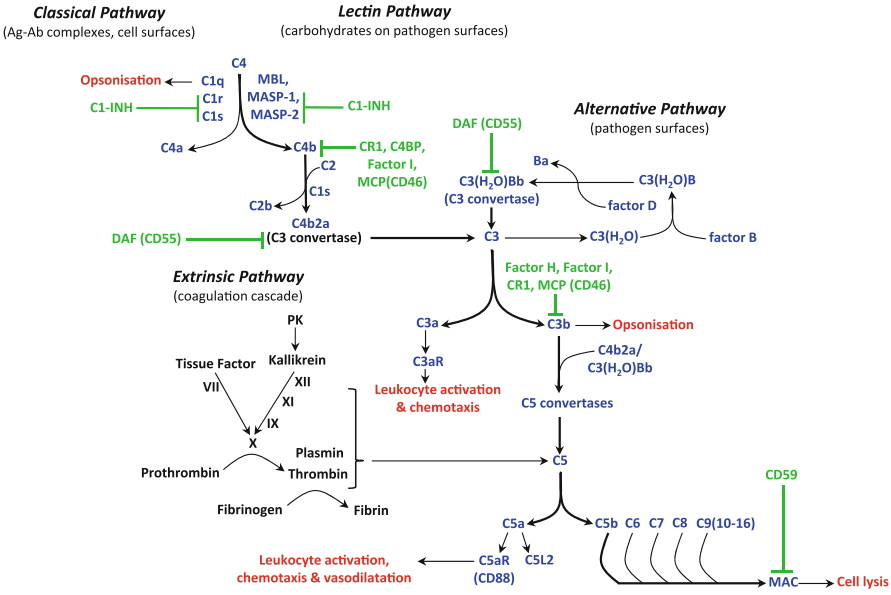
A simplified diagram of the coagulation cascade and its links with PARs and inflammation. Two pathways are involved in coagulation, with the major one being the tissue factor pathway. Most of the coagulation factors are serine proteinases that are present as inactive zymogens (rectangles) that when activated (ovals; lowercase 'a' indicates an active form) can catalyze the next reaction in the cascade. The two pathways converge to activate factor X, thrombin and fibrin. [Russell FA, McDougall JJ. Proteinase-activated receptors and arthritis. In: Vergnolle N, Chignard M, editors. Proteases and their receptors in inflammation. Basel: Springer; 2011. p. 217-42. Book https://doi.org/10.1007/978-3-0348-0157-7] *Caption adapted from original*

- Platelets



Mechanisms of platelet activation. [Ajjan R, Storey RF, Grant PJ. Aspirin resistance and diabetes mellitus. Diabetologia. 2008 Mar;51(3):385-90. https://doi.org/10.1007/s00125-007-0898-3] *Caption adapted from original*

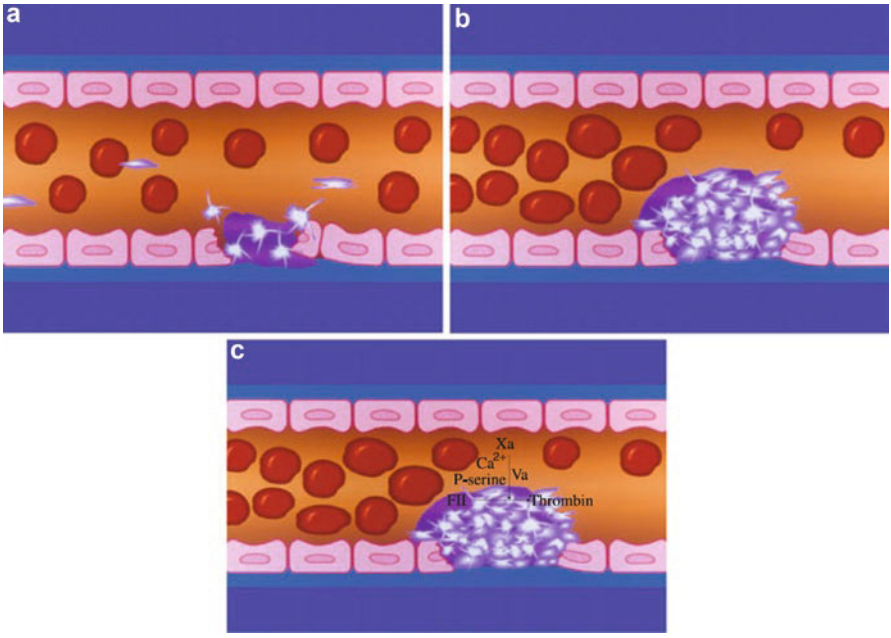
- Complement



Common pathways for complement activation. [From article: Complement activation in the injured central nervous system: another dual-edged sword? J Neuroinflammation. 2012 Jun 21;9:137. https://doi.org/10.1186/1742-2094-9-137

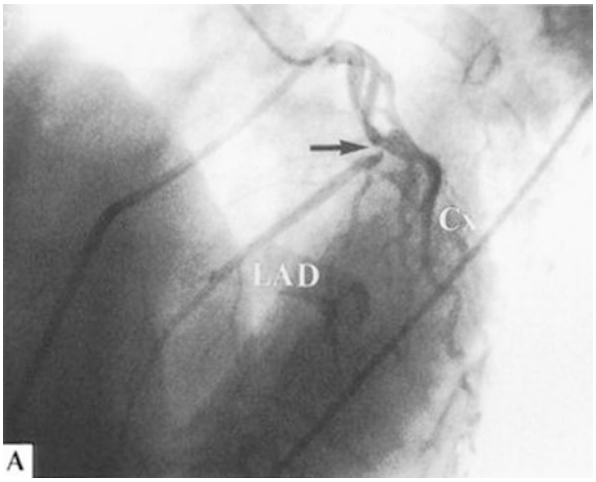
at http://link.springer.com/article/10.1186/1742-2094-9-137 by Faith H Brennan, Aileen J Anderson, Stephen M Taylor, Trent M Woodruff, Marc J Ruitenberg, © 2012 Brennan et al.; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

- This response results in local aggregation of activated platelets that are subsequently linked via strands of fibrinogen connecting the platelets' glycoprotein IIb/IIIa membrane receptors.



Platelet adhesion at the site of injury and aggregation with one another (a). Platelet plug consolidation (b) and platelets expressing procoagulant activity on their surface with subsequent thrombin generation (c). Procoagulant factors are represented by roman numbers. P-serine, phosphatidylserine. [Tripodi A. Haemostasis abnormalities in chronic liver failure. In: Ginès P, Kamath PS, Arroyo V, editors. Chronic liver failure. New York: Springer; 2011. p. 289-303. Book https://doi.org/10.1007/978-1-60761-866-9] *Caption from original*

- Alternative and much rarer etiologic considerations:
  - Pure arterial spasm without plaque rupture
  - Arteritis
  - Lupus



Anteroapical myocardial infarction in a patient with SLE. A, Cranial left anterior oblique view on arteriography showing severe proximal stenosis (arrow) of the left anterior descending (LAD) coronary artery that led into an anteroapical infarction in a 41-year-old woman with flaring SLE. [Roldan CA. Rheumatic and connective tissue diseases and the heart. In: Braunwald E, Crawford MH, editors. Atlas of heart diseases; vol. 6. Philadelphia: Current Medicine; 1996. ISBN: 1-878132-28-8] *Caption adapted from original*

- Takayasu's disease
- Kawasaki's disease

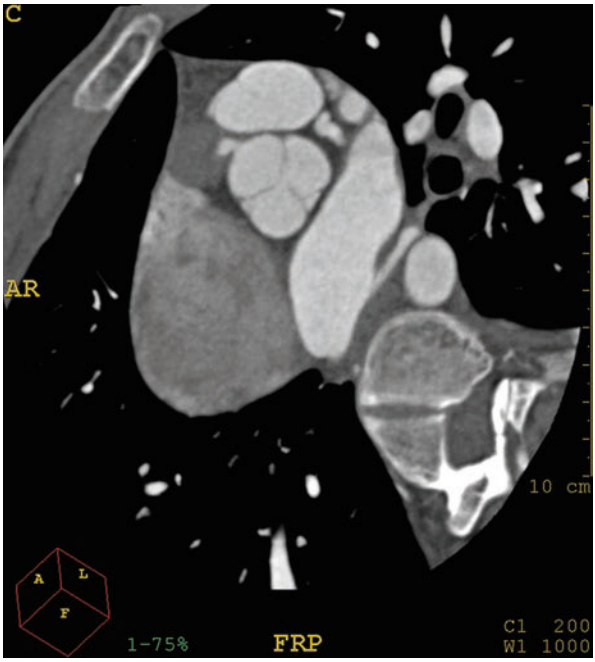


Image obtained from a patient with an acute myocardial infarction caused by thrombosis of a right coronary artery Kawasaki aneurysm (*arrow*). Kawasaki disease results from a mucocutaneous viral infection acquired during childhood. Typically, multiple aneurysms may develop in the coronaries and in other systemic vessels. Thrombosis of these aneurysms may occur later in life. [Garcia MJ. Intracardiac, myocardial and extracardiac abnormalities. In: Budoff MJ, Achenbach S, Narula J, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption from original*

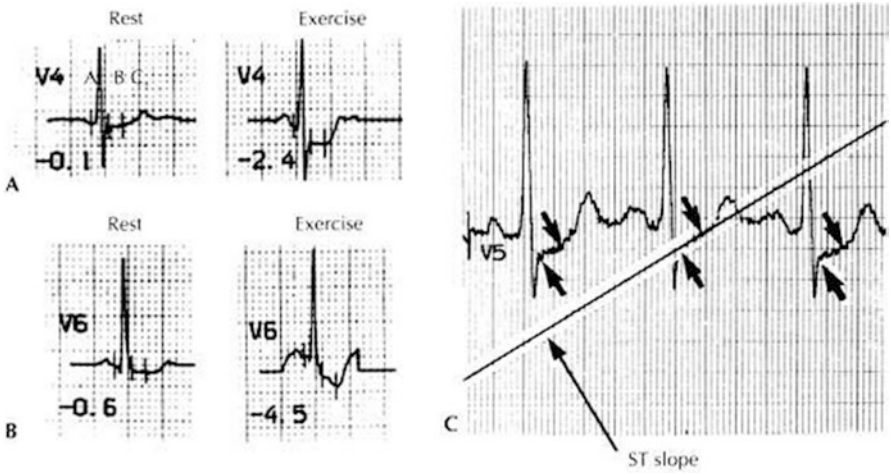
- Cocaine- or methamphetamine-induced vasospasm

Presentation

Typical/"Classic"

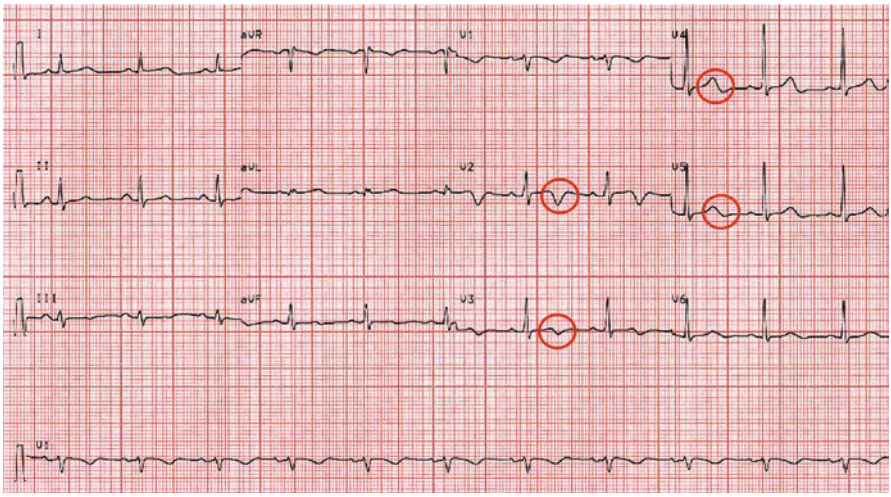
- Pressure-like chest pain starting substernally and radiating toward left shoulder or left jaw.
- Pain is classically associated with diaphoresis, dyspnea, and nausea.
- Pain often accompanied by tachycardia; blood pressure is variable, with very high and very low presenting blood pressures associated with poorer prognosis.

- Pain often starts with exertion; may be improved with rest or with use of nitroglycerin. May also start at rest and often persists >20 minutes before presentation.
- Pain unchanged with movement, positioning, or deep breathing.
- In describing pain, patient may hold clenched fist over chest ("Levine sign").
- Notable for absence of specific, diagnostic ECG findings:
  - Persistent ST-segment elevation is ABSENT
  - ST-segment depression confers higher risk of poor outcomes but IS NOT diagnostic of NSTEMI
    - Particularly high risk when depression is "dynamic"—that is, present when patient is experiencing pain and resolved when that pain is relieved.



A, Example of ischemic horizontal ST-segment depression. The J-point (B) is depressed 0.3 mm relative to the PQ junction (A), and ST-80 (C) is depressed 0.1 mm at rest. During exercise, the J-point and ST-80 are depressed 2.4 mm. The reported net difference in ST-80 depression would be 2.3 mm. B, Example of downsloping ST-segment depression. The second patient reveals 0.6-mm ST-80 depression at rest, which worsens with exercise, resulting in J-point depression of 2.5 mm and ST-80 depression of 4.5 mm during exercise. The reported net difference in ST-80 depression would be 3.9 mm. [Chaitman B. Chapter 2. In: Beller GA. Chronic ischemic heart disease. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 5). ISBN: 1-878132-29-6, 2002-01-23; Chaitman, Bernard; Beller, George; Braunwald, Eugene] *Caption adapted from original*

- T-wave inversion confers higher risk in patients with symptoms of ACS but IS NOT diagnostic of NSTEMI.



Electrocardiogram with T-wave inversions in leads V1 to V4. [From article: Triptans and troponin: a case report. Orphanet J Rare Dis. 2009 Jun 18;4:15. https://doi.org/10.1186/1750-1172-4-15, at http://link.springer.com/article/10.1186/1750-1172-4-15; by Claudia R Weder, Markus Schneemann, © Weder and Schneemann. 2009; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Atypical

- NSTEMI has been discovered in patients with virtually any complaint localized above the umbilicus.
- "Anginal equivalents" listed above include different distributions of pain (e.g. epigastric, jaw, neck, back) and some presentations that are not painful at all (e.g. palpitations, nausea, syncope).
    - Patients with NSTEMI who present without chest pain as their chief complaint frequently experience delays in diagnosis and therefore delays in treatment.
    - Atypical presentations more common in women, in elderly, and in diabetics.
- Elevated troponin levels are the defining and unifying feature of all NSTEMI presentations. Because of the time required for troponin to leak out of dying myocardial cells, the first troponin assay is often not elevated in patients who present soon after onset of symptoms.

Primary Differential Considerations

- Primary differential considerations include pain mimics to NSTEMI and are diverse, including life-threatening and more benign causes:
  - Aortic dissection
  - Pulmonary embolism
  - Peptic and esophageal disease, hiatal hernia
  - Costochondritis
  - Pneumonia
  - Pneumothorax
  - Pleurisy
  - Anxiety and panic disorders
  - Biliary colic
  - Herpes zoster

	Helpful clinical features
Cardiovascular	
Angina	Retrosternal chest pressure, squeezing, heaviness. Associated with exertion or emotional stress, relieved by rest or nitroglycerin. Usually between 2 and 20 min in duration.
Aortic stenosis	Similar features as for angina, but with late-peaking systolic murmur radiating to carotids. May be associated with syncope or signs of left heart failure.
Pericarditis	Sharp, retrosternal, pleuritic chest pain lasting hours to days. May be associated with friction rub and may be alleviated by leaning forward.
Aortic dissection	Sudden onset of tearing, ripping chest pain radiating to back. Associated with underlying hypertension.
Pulmonary embolism	Ipsilateral pleuritic pain associated with dyspnea, tachycardia, possible cor pulmonale. May have irritative cough or hemoptysis or present with syncope. Usually sudden onset.
Pulmonary	
Pneumonia/ pleuritis/pleural effusion	Pleuritic pain, lateralizing to side of infection/ inflammation. May be associated with fevers, dyspnea, cough. Exam with pleural rub, consolidation, or dullness to percussion.
Asthma/COPD exacerbation	Chest "tightness" associated with more prominent findings of dyspnea, tachypnea and diffuse wheezing.
Spontaneous pneumothorax	Sudden onset of pleuritic pain. Unilateral and associated with dyspnea. More common in thin, young males or patients with emphysematous disease. Decreased breath sounds and hyperresonance on side of pneumothorax.
Chest wall	
Muscle spasm/ strain	Associated with prior increased physical activity/ weight lifting. Pain variable in character but usually reproducible with palpation.

	Helpful clinical features
Costochondritis	Sharp, sudden onset pain that is short in duration. May be reproducible with palpation.
Herpes zoster	Sharp, burning, superficial neuropathic pain. May have allodynia, vesicular rash on exam. Unilateral dermatomal distribution.
Rib fracture	Prior trauma or known metastatic disease of bone. Point tenderness over affected rib(s). Pain is usually pleuritic.
Cervical/thoracic nerve root compression	Intermittent neuropathic pain often associated with neck movement or position. Usually unilateral.
Gastrointestinal	
Mediastinitis/ esophageal rupture	Often preceded by esophageal procedure or forceful vomiting. Pt. may have fever, associated septic shock. Symptoms vary from burning chest discomfort to severe dyspnea.
Esophageal reflux	Burning pain, often associated with nausea, belching. Usually worse at night and after large meals. Alleviated by antacids.
Esophageal spasm	Sudden onset, sharp, retrosternal pain. May be relieved by nitroglycerine and exacerbated by cold liquids. Sometimes associated with dysphagia.
Pancreatitis	Sharp epigastric pain, usually constant and prolonged. Exacerbated by food and often associated with nausea/vomiting. Alcohol and gallstones are risk factors.
Peptic ulcer	Sharp or burning epigastric pain. Often relieved by food or antacids. May be associated with occult GI bleeding or massive acute blood loss.
Psychogenic	
Anxiety/panic disorder	May be unable to distinguish from anginal pain, but usually has atypical features such as prolonged duration and no exertional component. Should be a diagnosis of exclusion at initial workup.

Differential diagnosis of acute chest pain. [McClintic BR, Rosenblatt RL. Approach to the patient with chest pain. In: Bisognano JD, Beck R, Connell R, editors. Manual of outpatient cardiology. London: Springer; 2012. p. 349-71. Book https://doi.org/10.1007/978-0-85729-944-4] *Caption from original*

History and Physical Exam

Findings That Confirm Diagnosis

- None

Factors That Suggest Diagnosis

- Nature and history of pain with presence of risk factors

Factors That Exclude Diagnosis

- None

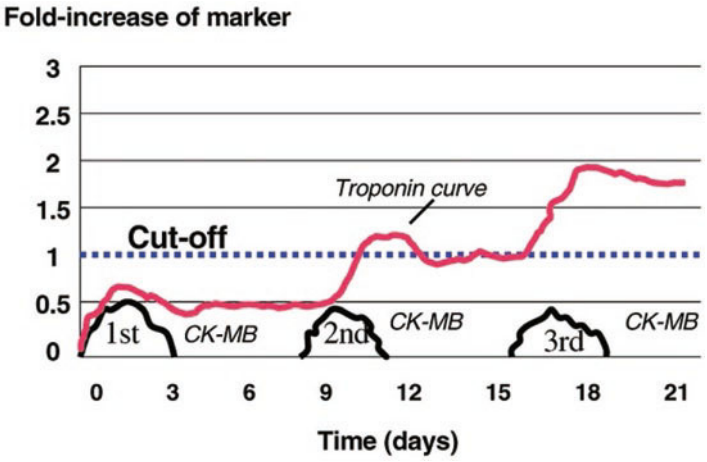
Ancillary Studies

Laboratory

- CBC: no diagnostic findings.
- Electrolytes: no diagnostic findings.
- Renal function: no diagnostic findings, but renal insufficiency/failure is a risk factor for ACS and may complicate treatment.
- Coagulation studies: no diagnostic findings but should be performed before initiation of therapy.
- Cardiac enzymes: Elevation in troponin (I or T) levels is a required part of universal diagnosis of myocardial infarction.
    - Elevated enzyme levels differentiate NSTEMI from UA
    - Time course is critical
        - Depending on specific troponin assay and volume of muscle infarcted, generally takes about 6 hours after onset of symptoms for troponin levels to rise
        - A negative troponin within 6 hours of reliable onset time of symptoms is not particularly helpful
            - If onset time unclear, start at time of presentation
            - Negative troponin does NOT exclude angina

- Positive troponin is *always* helpful, but use caution in interpreting levels in patients with renal insufficiency

- Levels of MB band of CPK enzyme still sometimes used to identify NSTEMI
  - Can sometimes be specifically helpful, e.g., in repeated chest pain presentations within 2-3 days, when troponin levels from first infarct will remain elevated, but CPK-MB may have returned to normal in interim



Summation model. Temporal release of cardiac markers CK-MB and troponins during repetitive episodes of ischaemia causing myocardial necroses in the setting of an acute coronary syndrome. Compared with the release and clearance of CK-MB 48-72 h after each episode (indicated as 1st, 2nd and 3rd), troponin release is cumulative. [From article: Implications of troponin testing in clinical medicine. Curr Control Trials Cardiovasc Med. 2001; 2(2): 75–84. https://doi.org/10.1186/cvm-2-2-075, at http://link.springer.com/article/10.1186/cvm-2-2-075; by Britta U Goldmann, Robert H Christenson, Christian W Hamm, Thomas Meinertz, E Magnus Ohman, © BioMed Central Ltd 2001; Available under Open Access, licensed under Creative Commons Attribution License https://creativecommons.org/licenses/by/2.0/] *Caption from original*

- BNP levels may offer some prognostic significance.

Electrocardiography

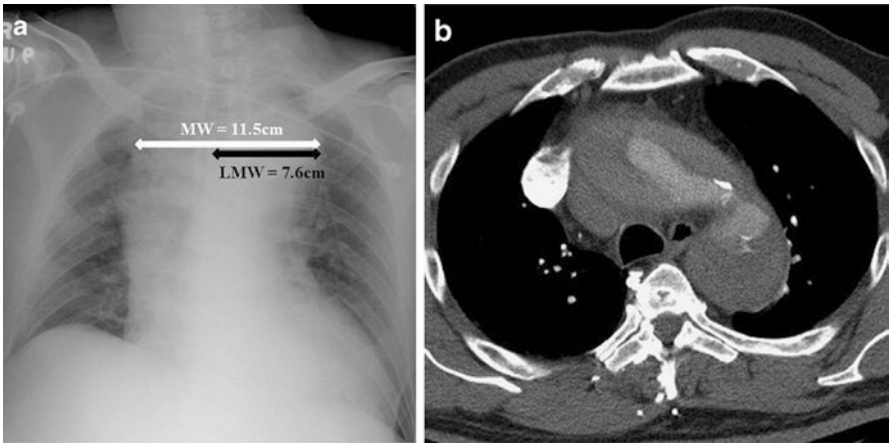
- No diagnostic findings.
- Per national quality standards in the United States, ECG should be obtained within 10 minutes of arrival in an emergency department.

Imaging

- No diagnostic findings for NSTEMI on chest x-ray (CXR).
- Findings of heart failure (cardiomegaly, pulmonary congestion) on CXR portend a poorer prognosis for NSTEMI.

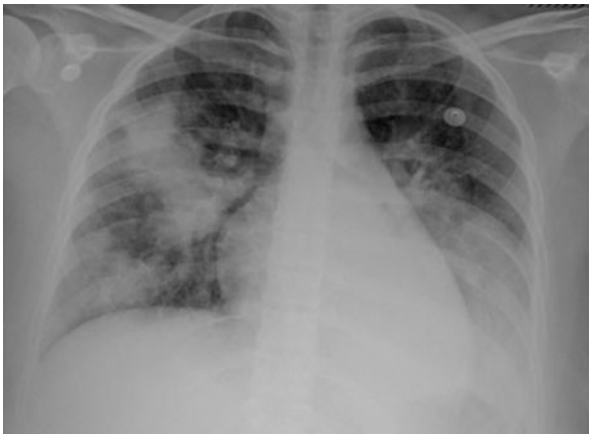
Frontal chest radiograph reveals typical features of pulmonary interstitial edema in a patient with congestive heart failure, manifested by peribronchial cuffing, indistinctness of the pulmonary vessels, and Kerley B lines. Note the cephalization or redistribution of the pulmonary vasculature and mild cardiomegaly. [Boiselle PM, Dass C, Steiner RM. Radiologic imaging in the critically ill patient. In: Criner GF, Barnette RE, D'Alonzo GE, editors. Critical care study guide. 2e, New York: Springer; 2010. p. 181-207. Book https://doi.org/10.1007/978-0-387-77452-7] *Caption from original*

- Findings of a widened mediastinum suggest consideration of aortic dissection but do not exclude NSTEMI. Check differential blood pressures in the upper extremities.



Acute type A aortic dissection in a 46-year-old man. A) AP chest radiograph showing marked widening of the mediastinum with MW and LMW measuring 11.5 and 7.6 cm, respectively. B) Corresponding selected image of CT aortogram confirms type A aortic dissection. [From article: Diagnostic accuracy of mediastinal width measurement on posteroanterior and anteroposterior chest radiographs in the depiction of acute nontraumatic thoracic aortic dissection. Emerg Radiol. 2012 Aug;19(4):309-15. https://doi.org/10.1007/s10140-012-1034-3 at http://link.springer.com/article/10.1007/s10140-012-1034-3 by Vincent Lai, Wai Kan Tsang, Wan Chi Chan, Tsz Wai Yeung, licensed under Creative Commons Attribution License, https://creativecommons.org/licenses/by/2.0/] *Caption from original*

- Findings of pneumonia suggest consideration of that differential but do not exclude NSTEMI. Check for signs of infection. Frank septic shock may result in elevated troponin levels.

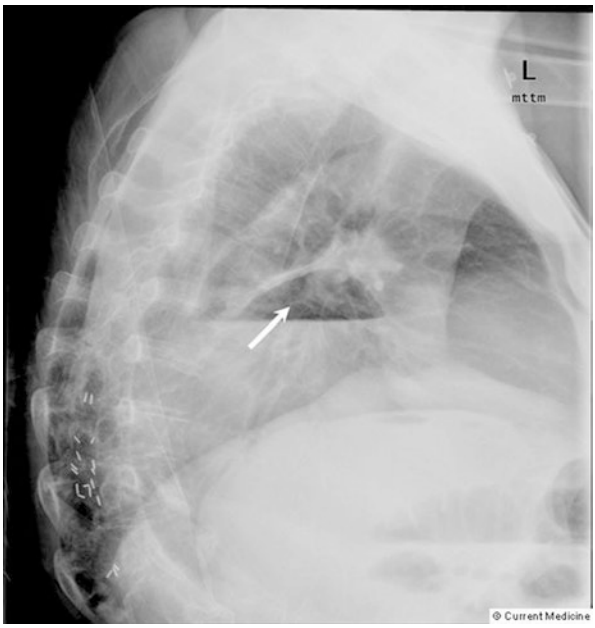


Chest radiograph showing right upper/lower lung field opacities and left lower lung field opacity consistent with pneumonia. [Tsigrelis C, Mohammad M, Fraimow HS, Dellinger RP, Marchesani D, Reboli AC. Secondary bacterial pneumonia due to Staphylococcus aureus complicating 2009 influenza A (H1N1) viral infection. Infection. 2010 Jun;38(3):237-9. https://doi.org/10.1007/s15010-010-0009-0, 2010-06-01] *Caption adapted from original*

- Findings of pneumothorax suggest consideration of that differential but do not exclude NSTEMI. Evaluate oxygenation status.

Posteroanterior upright chest X-ray shows large pneumothorax of the right lung. [Kim SH, Yoo WH. Recurrent pneumothorax associated with pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report and review of the literature. Rheumatol Int. 2011 Jul;31(7):919-22. https://doi.org/10.1007/s00296-009-1240-9] *Caption adapted from original*

- Findings of hiatal hernia suggest consideration of that differential but do not exclude NSTEMI.



Radiograph of large hiatal hernia. [Aurigemma G, Tighe D, Oh J, Espinoza R. Pericardial disease and cardiac masses. In: Solomon S, editor. Atlas of echocardiography. Philadelphia: Current Medicine; 2008. ISBN: 1-57340-217-6] *Caption from original*

Risk Scoring

- TIMI Risk Score may be helpful in establishing short-term prognosis, which helps drive intensity of therapy.

- Age ≥65 years
- History of known CAD (documented prior coronary artery stenosis >50%)
- ≥3 conventional cardiac risk factors (age, male sex, family history, hyperlipidemia, diabetes mellitus, smoking, obesity)
- Use of aspirin in the past 7 days
- ST-segment deviation (persistent depression or transient elevation)
- Increased cardiac biomarkers (troponins)
- ≥2 anginal events in the preceding 24 h

TIMI = Thrombosis in Myocardial Infarction; CAD = coronary artery disease

Score = sum of number of above characteristics

TIMI = Thrombosis in Myocardial Infarction; CAD = coronary artery disease

Score = sum of number of above characteristics

TIMI risk score for unstable angina and NSTEMI. [Stillman AE, Oudkerk M, Ackerman M, Becker CR, Buszman PE, Feyter PJ, Hoffmann U, Keadey MT, Marano R, Lipton MJ, Raff GL, Reddy GP, Rees MR, Rubin GD, Schoepf UJ, Tarulli G, Beek EJR, Wexler L, White CS. Use of multidetector computed tomography for the assessment of acute chest pain: a consensus statement of the North American Society of Cardiac Imaging and the European Society of Cardiac Radiology. Int J Cardiovasc Imaging. 2007 Aug;23(4):415-27. https://doi.org/10.1007/s10554-007-9226-8] *Caption from original*

Value	TIMI risk score[a] (95% CI)	Modified TIMI risk score[b] (95% CI)
Sensitivity	53.7 (44.9–62.3)	58.1 (49.8–66.4)
Specificity	75.2 (72.1–78.2)	82.6 (80.0–85.2)
Negative predictive value	90.6 (88.2–927)	92.2 (90.2–94.1)
Positive predictive value	26.6 (21.5–32.3)	35.9 (29.6–42.2)

[a] Using a cut point of 3 (less than 3 vs. 3 or greater)

[b] Using a cut point of 2 (less than 2 vs. 2 or greater)

A summary of the TIMI risk score and modified TIMI risk scores as predictors of 30-day myocardial infarction/revascularization/death. [Jaffery Z, Hudson MP, Jacobsen G, Nowak R, McCord J. Modified Thrombolysis in Myocardial Infarction (TIMI) risk score to risk stratify patients in the emergency department with possible acute coronary syndrome. J Thromb Thrombolysis. 2007 Oct;24(2):137-44. DOI: https://doi.org/10.1007/s11239-007-0013-0] *Caption from original*

Special Populations

Age

- Risk for NSTEMI increases with age, starting at age 40 in men and at menopause in women.
  - Age is a risk factor for mortality from NSTEMI.
  - Likelihood of atypical presentation with NSTEMI increases with age.

Co-morbidities

- Hypertension, diabetes, and renal failure are important co-morbidities in NSTEMI risk and prognosis.
- Obesity is a weaker predictor of NSTEMI risk.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- ECG must be performed as soon as the diagnosis of ACS is even considered.

Mimics

- All differential considerations listed under Primary Differential Considerations.
  - Of these, only aortic dissection and pulmonary embolism are also life-threatening.

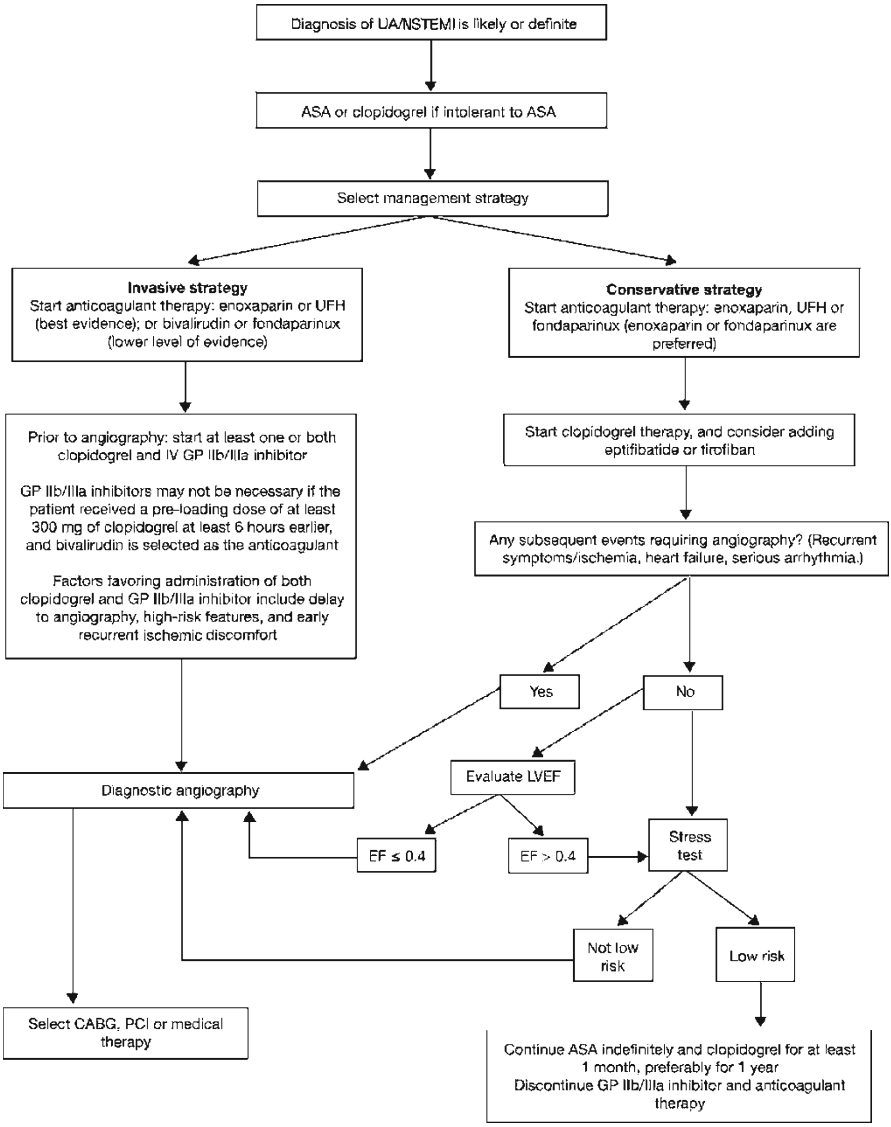
Time-Dependent Interventions

- Stabilization of the NSTEMI patient is time sensitive; unlike in STEMI, restoration of perfusion is not extremely time sensitive.
  - Current guidelines call for diagnostic angiography in 24–48 hours to establish preferred course of management.

- Unless contraindicated (allergy, active bleeding), 324–325 mg aspirin should be administered immediately upon suspicion of an acute coronary syndrome.
- Anticoagulation therapy should be initiated upon confirmation of ACS diagnosis or with high suspicion in high-risk patients.
- Extremes of blood pressure should be promptly treated to avert shock (hypotension) or undue myocardial oxygen demand (hypertension).
- Airway and oxygenation should be monitored and supported as necessary.
- Patients with NSTEMI should be on continuous cardiac monitoring to evaluate for dangerous arrhythmias.
- Consider early initiation of dual antiplatelet therapy (aspirin plus an ADP receptor antagonist—ticagrelor or clopidogrel).

Overall Principles of Treatment

- Immediate stabilization of the patient with control of blood pressure, pulse rate, and pain is critical. The patient may require resuscitation, intubation, and intensive support.
- Medical management with anticoagulation and antiplatelet therapy is important.
  - Bleeding risk should also be assessed so that the risk of treatment-related hemorrhage can be minimized
- The higher the patient's risk, the more disproportionately s/he benefits from aggressive therapy.



Algorithm for the initial management of patients with UA/NSTEMI with an invasive or conservative treatment strategy [1] Abbreviations: ASA, aspirin; CABG, coronary artery-bypass grafting; EF, ejection fraction; GP, glycoprotein; IV, intravenous; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; UFH, unfractionated heparin. [Cohen M. High-risk acute coronary syndrome patients with non-ST-elevation myocardial infarction: definition and treatment. Cardiovasc Drugs Ther. 2008 Oct;22(5):407-18. https://doi.org/10.1007/s10557-008-6120-0] *Caption from original*

Disease Course

- NSTEMI mortality is 6–10 %, depending on the population studied, over 6 months.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"non ST segment elevation myocardial infarction" OR "NSTEMI"

Chapter 3
Acute Coronary Syndrome: ST-Segment Elevation Myocardial Infarction

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

ST-Segment Elevation Myocardial Infarction

- STEMI, ST-elevation MI, acute MI, transmural MI, Q-wave MI

Incidence/Epidemiology

- At the highest-acuity end of the continuum of diagnoses collectively called acute coronary syndrome (ACS)
- Highest pre- and in-hospital 30-day mortality of ACS spectrum
- Incidence varies widely by demographics and risk profiles
- More than 1.2 million MIs in US each year; about 20 % are STEMI

Differential Diagnosis

- Includes all other causes of chest pain

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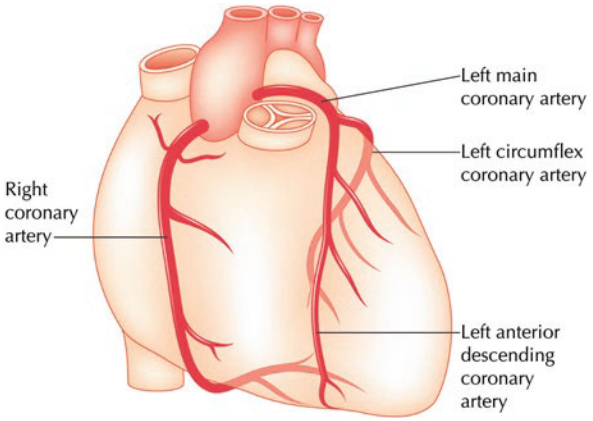
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_3

- Includes other causes of "anginal equivalents" in susceptible populations, e.g.:
- Dyspnea
- Back pain
- Jaw pain
- Shoulder pain
- Epigastric pain
- Palpitations
- Dizziness
- Weakness
- Nausea
- Syncope

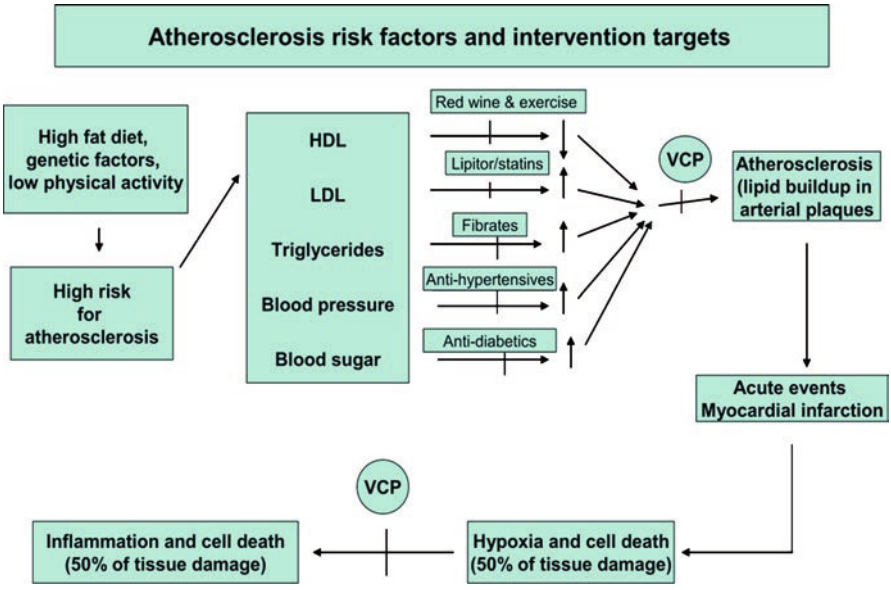
Pathophysiology and Etiology

- ACS is the result of ischemia (diminished blood flow / oxygen delivery) to myocardium
- If ischemia persists, frank infarction (muscle death) may occur
- Infarction results in breakdown of cell membranes, allowing release of intracellular proteins (such as myoglobin, troponins, and CPK-MB) into the circulation, where they may be detected in peripheral blood draw
- STEMI is most extreme and acute form of ACS, with "transmural" ischemia that results in characteristic acute findings on ECG (see below)
- Most STEMI occurs as a result of fracture or frank rupture of atherosclerotic plaque in an epicardial artery



Normal coronary anatomy. [Achenbach S. Normal coronary anatomy. In: Budoff MJ, Achenbach S, Narula J, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007 (Braunwald E, editor. Atlas of heart diseases; vol. 1)] *Caption from original*

- Atherosclerosis is a product of diverse inherited and acquired conditions, including:
  - Family history
  - Hyperlipidemia
  - Hypertension
  - Diabetes mellitus
  - Tobacco abuse



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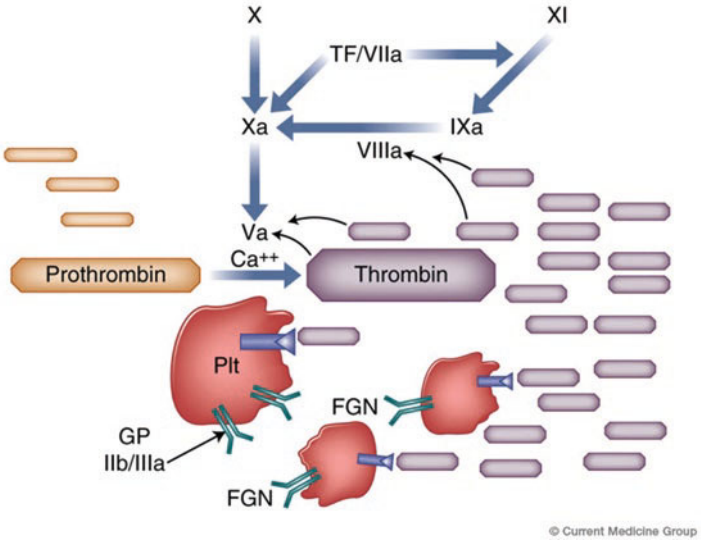
Risk factors	No. of patients
Individual	
Smoking	6
Hypertension	11
Hypercholesterolemia	9
Diabetes mellitus	4
Clusters	
Smoking and hypercholesterolemia	1
Hypertension and hypercholesterolemia[a]	4
Hypertension and diabetes	2
Smoking, hypertension and hypercholesterolemia	1
Smoking, hypertension, hypercholesterolemia and diabetes	2

[a] Hypertension was defined as a diastolic arterial pressure >95 mm Hg and hypercholesterolemia >6 mmol/l

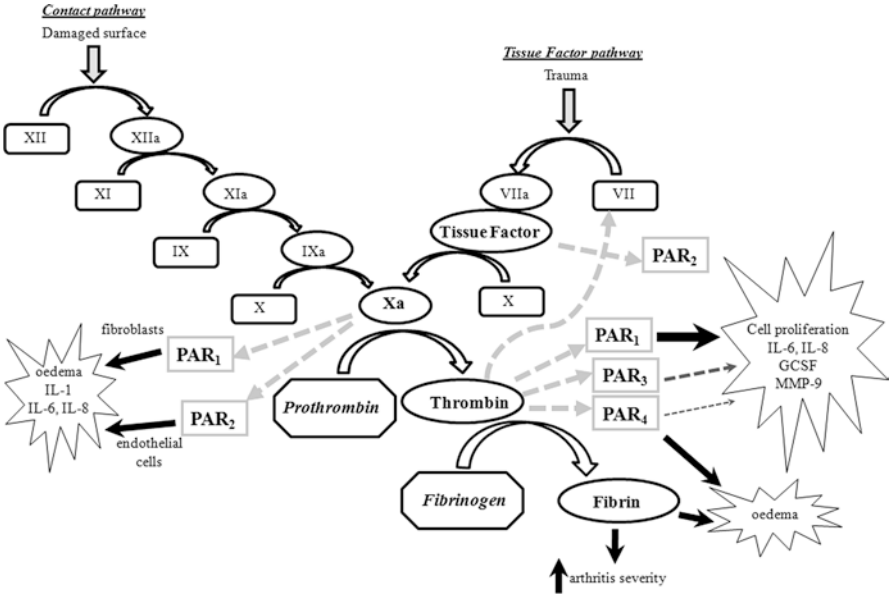
Main known risk factors for atherosclerosis in 16 patients studied. [Watt S, Aesch B, Lanotte P, Tranquart F, Quentin R. Viral and bacterial DNA in carotid atherosclerotic lesions. Eur J Clin Microbiol Infect Dis. 2003 Feb;22(2):99-105. https://doi.org/10.1007/s10096-002-0867-1, 2003-02-01] *Caption adapted from original*

- Plaque rupture initiates a complex thrombo-inflammatory response locally, including activation of:
  - Coagulation



Networking of coagulation cascade and aggregation of platelets (Plt). The extrinsic limb triggers activation of the coagulation cascade when tissue factor (TF) is exposed in a disrupted plaque. Coagulation factor VII is activated (VIIa) and can

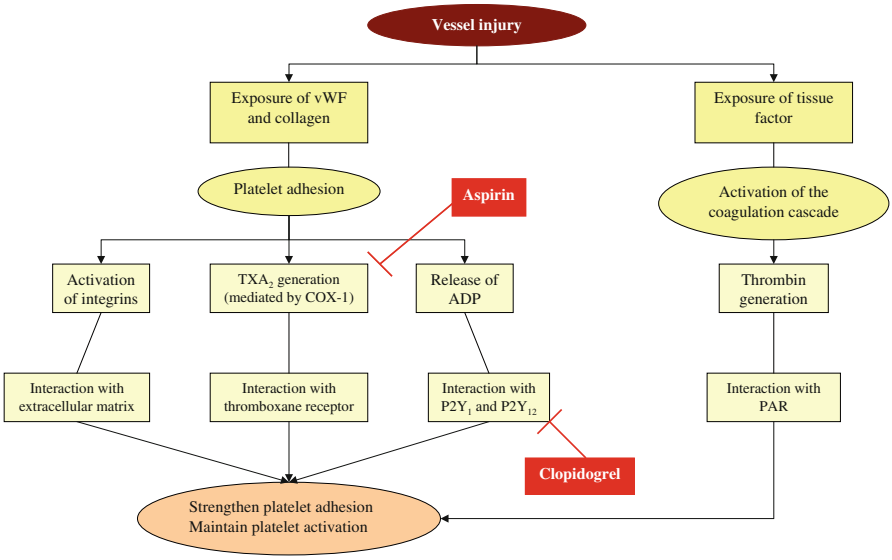
activate factor X to Xa and promote perpetuation of the coagulation process via the intrinsic limb that results in formation of IXa and VIIIa. The prothrombinase complex of Xa, Va, Ca^{++} forms on a phospholipid surface (*eg*, membrane of a platelet) and converts prothrombin to thrombin. The thrombin that is formed binds to the thrombin receptor on platelets promoting activation and aggregation of platelets, as well as amplifying the coagulation cascade by promoting formation of VIIIa and Va. This diagram depicts the amplification nature of the coagulation process because one molecule of Xa leads to the downstream production of a large number of thrombin molecules (stoichiometric relationship not completely depicted to prevent obscuring the diagram with thrombin molecules). Activated platelets express numerous copies of the active form of the fibrinogen receptor GP IIb/IIIa on their surface. GP IIb/IIIa recognizes specific amino acid sequences on circulating ligands. One such ligand is fibrinogen (FGN), which has multiple copies of the RGD amino acid sequence and serves to bridge platelets together, promoting formation of aggregates. The more aggregates formed, the greater the surface area for the prothrombinase complex and amplification of the reactions of the coagulation cascade. [Antman E. Acute coronary syndromes. In: Libby P, editor. Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. ISBN: 978-1-57340-309-2, 2009-05-21; Antman, Elliott] *Caption from original*



A simplified diagram of the coagulation cascade and its links with PARs and inflammation. Two pathways are involved in coagulation, with the major one being the tissue factor pathway. Most of the coagulation factors are serine proteinases that are present as inactive zymogens (rectangles) that when activated (ovals; lowercase 'a' indicates an active form) can catalyze the next reaction in the cascade. The two

pathways converge to activate factor X, thrombin and fibrin. [Russell FA, McDougall JJ. Proteinase-activated receptors and arthritis. In: Vergnolle N, Chignard M, editors. Proteases and their receptors in inflammation. Basel: Springer; 2011. p. 217-42. Book https://doi.org/10.1007/978-3-0348-0157-7; Chapter: 9; Chapter https://doi.org/10.1007/978-3-0348-0157-7_9, 2011-01-01] *Caption adapted from original*

- Platelets



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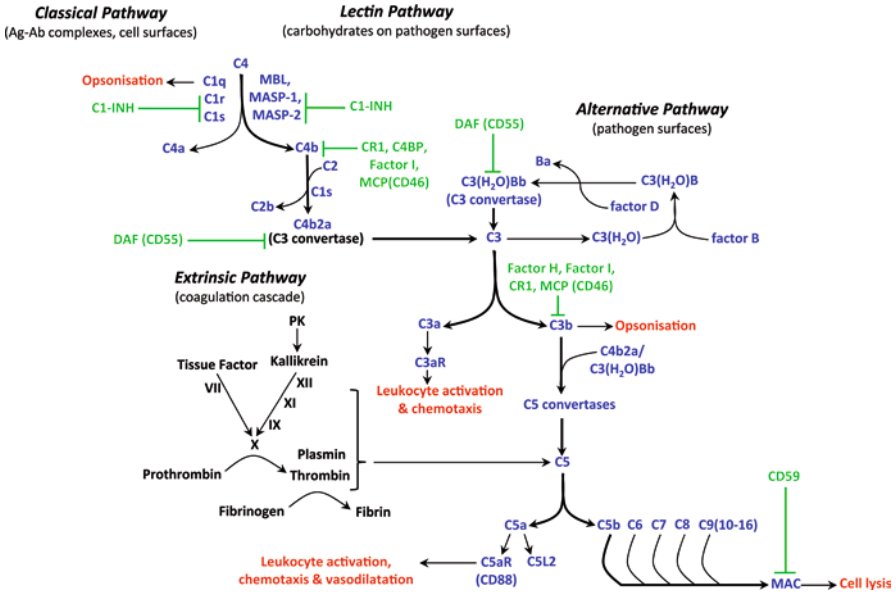
- Complement



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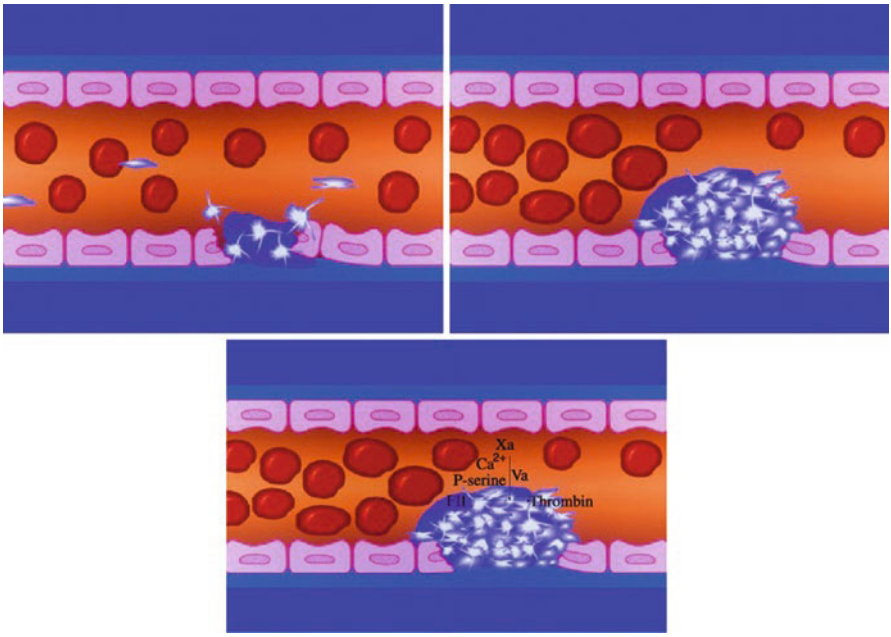
- This response results in local aggregation of activated platelets that decreases and ultimately occludes downstream blood flow, leaving muscle distal to lesion ischemic and subject to infarction unless there is sufficient downstream collateral perfusion.

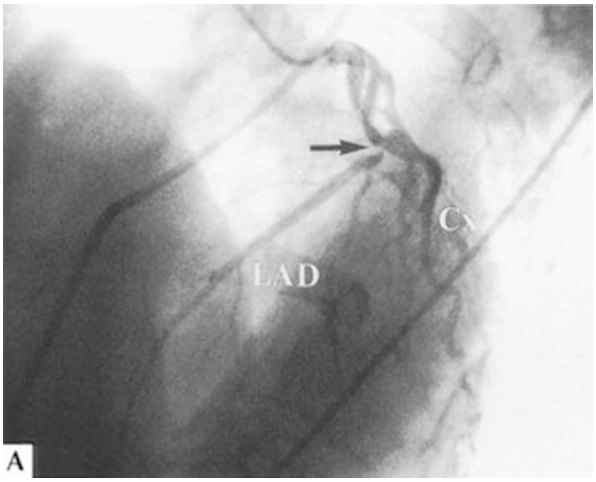


Platelet adhesion at the site of injury and aggregation with one another (a). Platelet plug consolidation (b) and platelets expressing procoagulant activity on their surface with subsequent thrombin generation (c). Procoagulant factors are represented by roman numbers. P-serine, phosphatidylserine. [Tripodi A. Haemostasis abnormalities in chronic liver failure. In: Ginès P, Kamath PS, Arroyo V, editors. Chronic liver failure. New York: Springer; 2011. p. 289-303. Book https://doi.org/10.1007/978-1-60761-866-9; Chapter: 14; Chapter https://doi.org/10.1007/978-1-60761-866-9_14, 2011-01-01] *Caption from original*

- Sudden acute ischemia from complete upstream artery occlusion results in characteristic ECG findings (see below).
- Alternative and much rarer etiologic considerations

- Pure arterial spasm without plaque rupture
- Arteritis

  - Lupus



Anteroapical myocardial infarction in a patient with SLE. A, Cranial left anterior oblique view on arteriography showing severe proximal stenosis (arrow) of the left anterior descending (LAD) coronary artery that led into an anteroapical infarction in a 41-year-old woman with flaring SLE. [Roldan CA. Rheumatic and connective tissue diseases and the heart. In: Crawford MH, editor. Heart disease in the presence of disorders of other organ systems. Philadelphia: Current Medicine; 1996 (Braunwald E, editor. Atlas of heart diseases; vol. 6). ISBN: 1-878132-28-8, 2002-01-23] *Caption adapted from original*

- Takayasu's disease
- Kawasaki's disease

Image obtained from a patient with an acute myocardial infarction caused by thrombosis of a right coronary artery Kawasaki aneurysm (*arrow*). Kawasaki disease results from a mucocutaneous viral infection acquired during childhood. Typically, multiple aneurysms may develop in the coronaries and in other systemic vessels. Thrombosis of these aneurysms may occur later in life. [Garcia MJ. Intracardiac, myocardial and extracardiac abnormalities. In: Budoff MJ, Achenbach S, Narula J, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption from original*

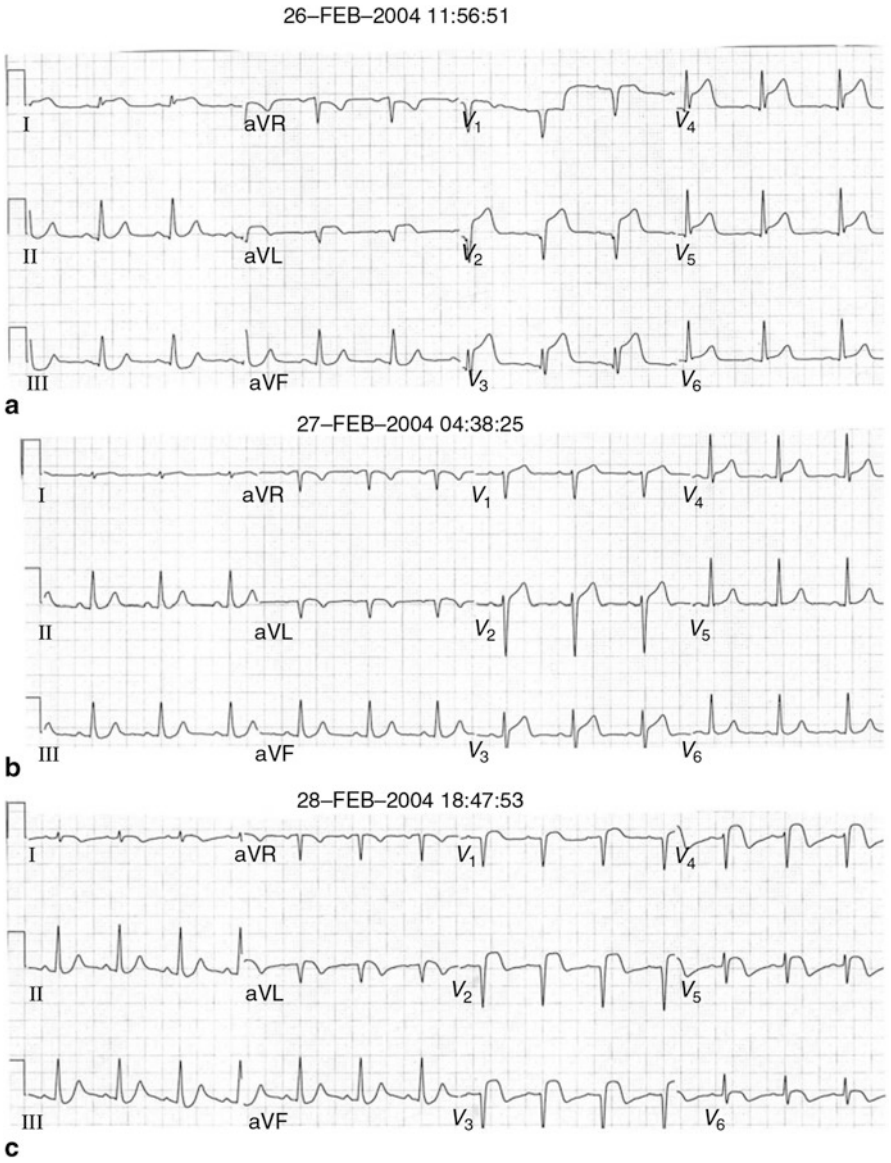
- Cocaine- or methamphetamine-induced vasospasm

Presentation

Typical/"Classic"

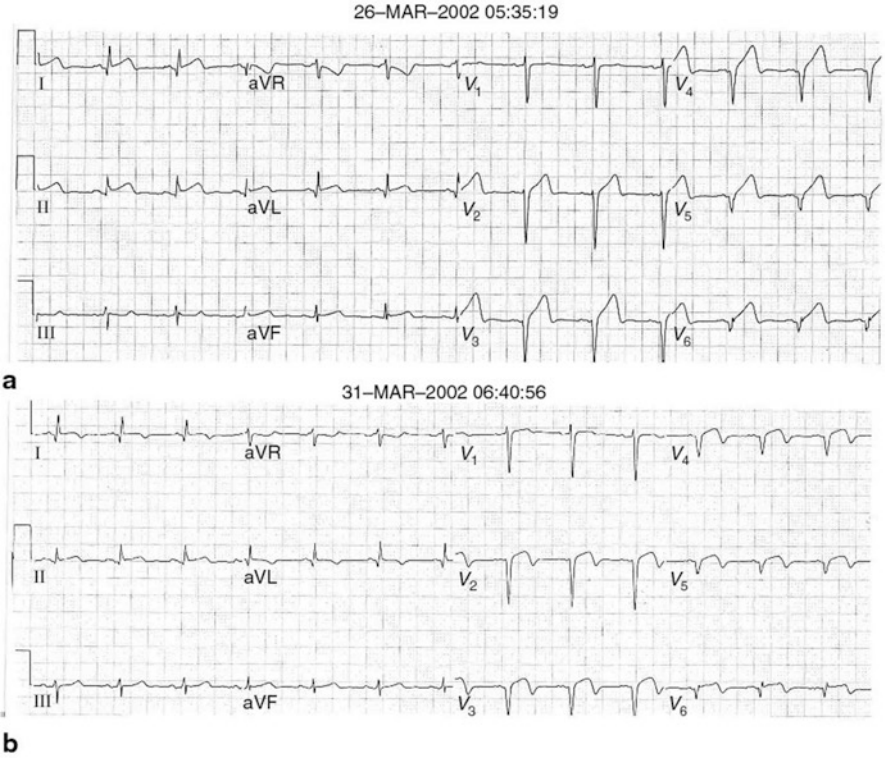
- Pressure-like chest pain starting substernally and radiating toward left shoulder or left jaw
- Pain is classically associated with diaphoresis, dyspnea, and nausea
- Pain often accompanied by tachycardia; blood pressure is variable with very high and very low presenting blood pressures associated with poorer prognosis
- Pain often starts with exertion; may be improved with rest or with use of nitroglycerin. May also start at rest and often persists >20 minutes before presentation
- Pain unchanged with movement, positioning, or deep breathing

- In describing pain, patient may hold clenched fist over chest ("Levine sign")
- Defined (as name implies) by specific ECG findings:
  - ST-segment elevation in two or more contiguous leads OR



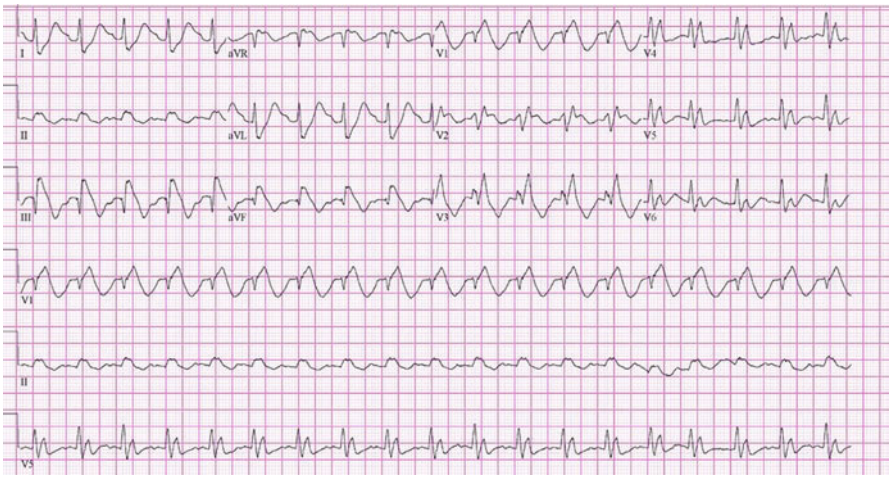
Electrocardiogram of a 51-year-old man with acute anterior-superior myocardial infarction caused by total occlusion of left anterior descending coronary artery proximal to the first septal perforator and the first diagonal branch; there was also

40% occlusion of the first obtuse marginal branch of the left circumflex artery and 70% occlusion of the right coronary artery. Kinesis involved large portion of the anterior wall and the apex. with an estimated left ventricular ejection fraction of 15%. In (a): ST elevation in leads aVL and V1–6, with reciprocal ST depression in leads III and aVR. In (b): one day later "pseudonormalization" with slight ST elevation in the leads V 2–3 and T wave inversion in lead aVL as the only abnormalities. In (c): on the following day when chest pain resolved. ST elevation and T wave inversion in leads I, aVL and V 1–6 with reciprocal ST depression in the leads III, aVF compatible with the evolution of the infarction pattern. Incipient T wave inversion in leads a VL, V 2–6. [Surawicz B. Ventricular repolarization in myocardial ischemia and myocardial infarction: theory and practice. In: Macfarlane PW, van Oosterom A, Pahlm O, Kligfield P, Janse M, Camm J, editors. Comprehensive electrocardiology. London: Springer; 2011. p. 803-31. Book https://doi.org/10.1007/978-1-84882-046-3; Chapter: 18; Chapter https://doi.org/10.1007/978-1-84882-046-3_18, 2010-01-01] *Caption from original*



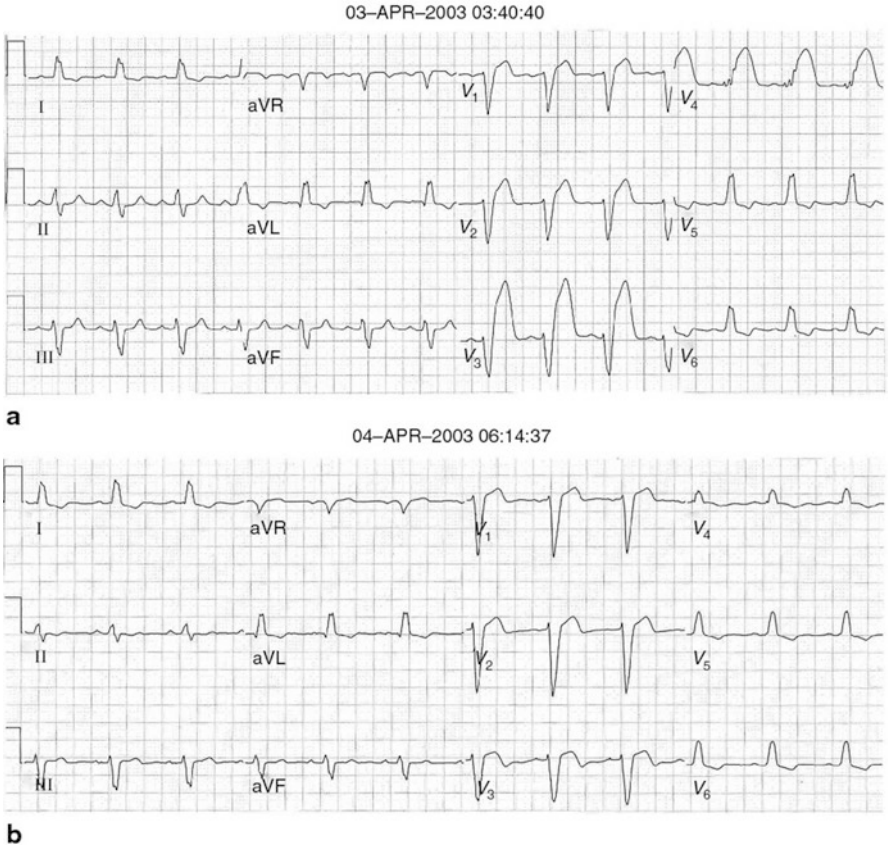
Electrocardiogram of a 47-year-old woman with anterolateral myocardial infarction (MI) caused by total occlusion of left anterior descending coronary artery in midportion associated with 50–70% occlusion of the co-dominant left anterior circumflex artery. Anterior wall and apex were akinetic with an estimated left ventricular

ejection fraction of 30%. In (a): Q waves with ST elevation in leads I, aVL, V 3–6 and reciprocal ST depression in aVR. In (b) 5 days later after an emergent percutaneous intervention evolution of ECG pattern of anterior MI with T wave inversion in leads I, aVL and V 2–6. Residual ST elevation is present in the above leads. [Surawicz B. Ventricular repolarization in myocardial ischemia and myocardial infarction: theory and practice. In: Macfarlane PW, van Oosterom A, Pahlm O, Kligfield P, Janse M, Camm J, editors. Comprehensive electrocardiology. London: Springer; 2011. p. 803-31. Book https://doi.org/10.1007/978-1-84882-046-3; Chapter: 18; Chapter https://doi.org/10.1007/978-1-84882-046-3_18, 2010-01-01] *Caption from original*



Electrocardiogram on presentation showing coved ST-segment elevation in precordial leads with simultaneous ST-segment elevation in leads II, III, and aVF. [Sheikh M, Kanjwal K, Kasmani R, Chutani S, Maloney JD. Simultaneous ST-segment elevation in inferior and precordial leads following ingestion of a lethal dose of desipramine: a novel Brugada-like EKG pattern. J Interv Card Electrophysiol. 2010 Jun;28(1):35-8. https://doi.org/10.1007/s10840-009-9412-9, 2010-04-13] *Caption from original*

- Known-to-be-new left bundle branch block in presence of anginal symptoms



Electrocardiogram of a 58-year-old man with left bundle branch block (LBBB) and acute anterior myocardial infarction (MI). In (a), in addition to secondary ST and T changes of LBBB, there is primary ST elevation in leads $V_{2–4}$-indicative of acute injury pattern. No reciprocal ST depression is discernible. In (b), after percutaneous intervention, primary ST elevation subsided, but primary T-wave inversion in leads $V_{2–3}$ is compatible with evolution of anterior MI pattern. [Surawicz B. Ventricular repolarization in myocardial ischemia and myocardial infarction: theory and practice. In: Macfarlane PW, van Oosterom A, Pahlm O, Kligfield P, Janse M, Camm J, editors. Comprehensive electrocardiology. London: Springer; 2011. p. 803-31. Book https://doi.org/10.1007/978-1-84882-046-3; Chapter: 18; Chapter https://doi.org/10.1007/978-1-84882-046-3_18, 2010-01-01] *Caption from original*

Atypical

- STEMI has been discovered in patients with virtually any complaint localized above the umbilicus.
- "Anginal equivalents" listed above include different distributions of pain (e.g., epigastric, jaw, neck, back) and some presentations that are not painful at all (e.g., palpitations, nausea, syncope).
  - Patients with STEMI who present without chest pain frequently experience delays in diagnosis and therefore delays in treatment.
  - Atypical presentations more common in women, in elderly, and in diabetics.
- Diagnostic ECG findings are the defining and unifying feature of all STEMI presentations.

Primary Differential Considerations

- Primary differential considerations include pain mimics to STEMI and are diverse, including life-threatening and more benign causes:
  - Aortic dissection
  - Pulmonary embolism
  - Peptic and esophageal disease, hiatal hernia
  - Costochondritis
  - Pneumonia
  - Pneumothorax
  - Pleurisy
  - Anxiety and panic disorders
  - Biliary colic
  - Herpes zoster

	Helpful clinical features
Cardiovascular	
Angina	Retrosternal chest pressure, squeezing, heaviness. Associated with exertion or emotional stress, relieved by rest or nitroglycerin. Usually between 2 and 20 min in duration.
Aortic stenosis	Similar features as for angina, but with late-peaking systolic murmur radiating to carotids. May be associated with syncope or signs of left heart failure.
Pericarditis	Sharp, retrosternal, pleuritic chest pain lasting hours to days. May be associated with friction rub and may be alleviated by leaning forward.
Aortic dissection	Sudden onset of tearing, ripping chest pain radiating to back. Associated with underlying hypertension.
Pulmonary embolism	Ipsilateral pleuritic pain associated with dyspnea, tachycardia, possible cor pulmonale. May have irritative cough or hemoptysis or present with syncope. Usually sudden onset.
Pulmonary	
Pneumonia/ pleuritis/pleural effusion	Pleuritic pain, lateralizing to side of infection/ inflammation. May be associated with fevers, dyspnea, cough. Exam with pleural rub, consolidation, or dullness to percussion.
Asthma/COPD exacerbation	Chest "tightness" associated with more prominent findings of dyspnea, tachypnea and diffuse wheezing.
Spontaneous pneumothorax	Sudden onset of pleuritic pain. Unilateral and associated with dyspnea. More common in thin, young males or patients with emphysematous disease. Decreased breath sounds and hyperresonance on side of pneumothorax.
Chest wall	
Muscle spasm/ strain	Associated with prior increased physical activity/ weight lifting. Pain variable in character but usually reproducible with palpation.

	Helpful clinical features
Costochondritis	Sharp, sudden onset pain that is short in duration. May be reproducible with palpation.
Herpes zoster	Sharp, burning, superficial neuropathic pain. May have allodynia, vesicular rash on exam. Unilateral dermatomal distribution.
Rib fracture	Prior trauma or known metastatic disease of bone. Point tenderness over affected rib(s). Pain is usually pleuritic.
Cervical/thoracic nerve root compression	Intermittent neuropathic pain often associated with neck movement or position. Usually unilateral.
Gastrointestinal	
Mediastinitis/ esophageal rupture	Often preceded by esophageal procedure or forceful vomiting. Pt. may have fever, associated septic shock. Symptoms vary from burning chest discomfort to severe dyspnea.
Esophageal reflux	Burning pain, often associated with nausea, belching. Usually worse at night and after large meals. Alleviated by antacids.
Esophageal spasm	Sudden onset, sharp, retrosternal pain. May be relieved by nitroglycerine and exacerbated by cold liquids. Sometimes associated with dysphagia.
Pancreatitis	Sharp epigastric pain, usually constant and prolonged. Exacerbated by food and often associated with nausea/vomiting. Alcohol and gallstones are risk factors.
Peptic ulcer	Sharp or burning epigastric pain. Often relieved by food or antacids. May be associated with occult GI bleeding or massive acute blood loss.
Psychogenic	
Anxiety/panic disorder	May be unable to distinguish from anginal pain, but usually has atypical features such as prolonged duration and no exertional component. Should be a diagnosis of exclusion at initial workup.

Differential diagnosis of acute chest pain. [McClintic BR, Rosenblatt RL. Approach to the patient with chest pain. In: Bisognano JD, Beck R, Connell R, editors. Manual

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History and Physical Exam

Findings That Confirm Diagnosis

- None

Factors That Suggest Diagnosis

- Nature and history of pain with presence of risk factors.

Factors That Exclude Diagnosis

- None

Ancillary Studies

Laboratory

- CBC: no diagnostic findings
- Electrolytes: no diagnostic findings
- Renal function: no diagnostic findings, but renal insufficiency/failure is a risk factor for ACS and may complicate treatment
- Coagulation studies: no diagnostic findings but should be performed before initiation of anticoagulation therapy
- Cardiac enzymes: will be elevated in STEMI, but presentation often precedes abnormal test values. Elevation of enzymes is NOT required for diagnosis of STEMI.
    - Elevation in troponin (I or T) levels is part of universal diagnosis of myocardial infarction

Electrocardiography

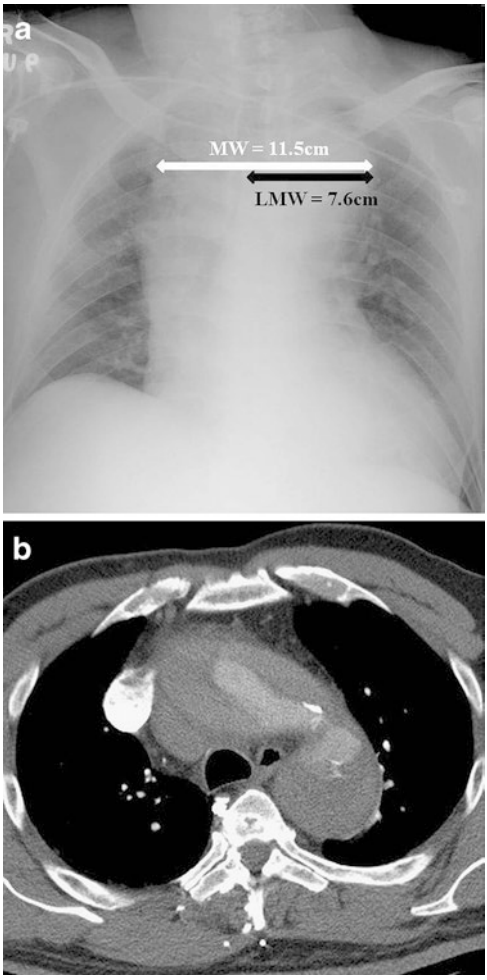
- As above, STEMI is defined by the ECG
- Per national quality standards in the United States, ECG should be obtained within 10 minutes of arrival in an emergency department

Imaging

- No diagnostic findings for STEMI on chest x-ray (CXR)
- Findings of heart failure (cardiomegaly, pulmonary congestion) on CXR portend a poorer prognosis on STEMI

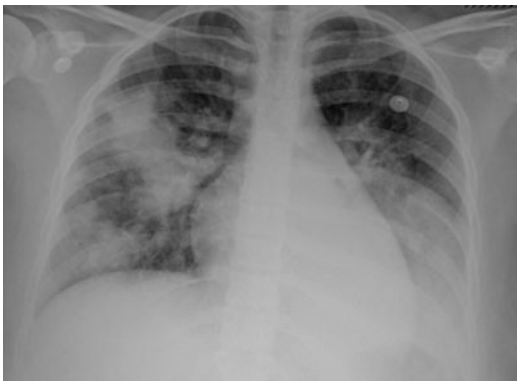
Frontal chest radiograph reveals typical features of pulmonary interstitial edema in a patient with congestive heart failure, manifested by peribronchial cuffing, indistinctness of the pulmonary vessels, and Kerley B lines. Note the cephalization or redistribution of the pulmonary vasculature and mild cardiomegaly. [Boiselle PM, Dass C, Steiner RM. Radiologic imaging in the critically ill patient. In: Criner GJ, Barnette RE, D'Alonzo GE, editors. Critical care study guide. New York: Springer; 2010. p. 181-207. Book https://doi.org/10.1007/978-0-387-77452-7; Chapter: 11; Chapter https://doi.org/10.1007/978-0-387-77452-7_11, 2010-01-01] *Caption from original*

- Findings of a widened mediastinum suggest consideration of aortic dissection but do not exclude STEMI. Check differential blood pressures in the upper extremities.



Acute type A aortic dissection in a 46-year-old man. A) AP chest radiograph showing marked widening of the mediastinum with MW and LMW measuring 11.5 and 7.6 cm, respectively. B) Corresponding selected image of CT aortogram confirms type A aortic dissection. [From article: Diagnostic accuracy of mediastinal width measurement on posteroanterior and anteroposterior chest radiographs in the depiction of acute nontraumatic thoracic aortic dissection. Emerg Radiol. 2012 Aug;19(4):309-15. https://doi.org/10.1007/s10140-012-1034-3, at http://link.springer.com/article/10.1007%2Fs10140-012-1034-3; by Vincent Lai, Wai Kan Tsang, Wan Chi Chan, Tsz Wai Yeung, © The Author(s) 2012; licensed under Creative Commons Attribution License https://creativecommons.org/licenses/by/2.0/] *Caption from original*

- Findings of pneumonia suggest consideration of that differential but do not exclude STEMI. Check for signs of infection.



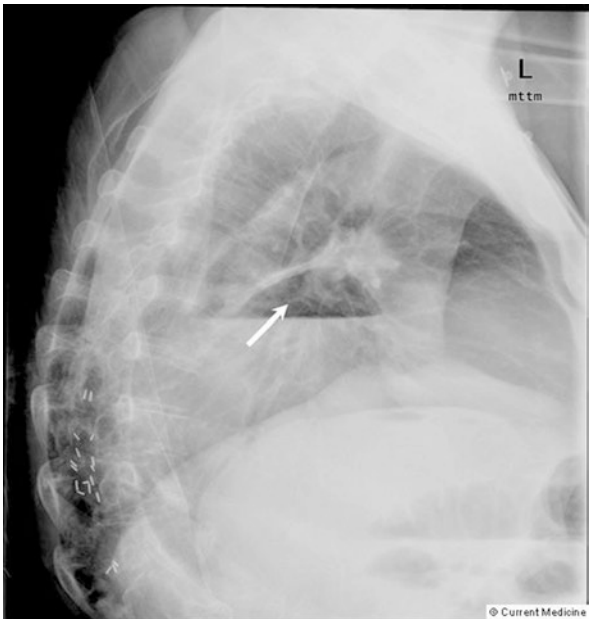
Chest radiograph showing right upper/lower lung field opacities and left lower lung field opacity consistent with pneumonia. [Tsigrelis C, Mohammad M, Fraimow HS, Dellinger RP, Marchesani D, Reboli AC. Secondary bacterial pneumonia due to Staphylococcus aureus complicating 2009 influenza A (H1N1) viral infection. Infection. 2010 Jun;38(3):237-9. https://doi.org/10.1007/s15010-010-0009-0, 2010-06-01] *Caption adapted from original*

- Findings of pneumothorax suggest consideration of that differential but do not exclude STEMI. Evaluate oxygenation status.

Posteroanterior upright chest X-ray shows large pneumothorax of the right lung. [Kim SH, Yoo WH. Recurrent pneumothorax associated with pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report and review of the

literature. Rheumatol Int. 2011 Jul;31(7):919-22. https://doi.org/10.1007/s00296-009-1240-9, 2011-06-21] *Caption adapted from original*

- Findings of hiatal hernia suggest consideration of that differential but do not exclude STEMI



Radiograph of large hiatal hernia. [Aurigemma G, Tighe D, Oh J, Espinoza R. Pericardial disease and cardiac masses. In: Solomon S, editor. Atlas of echocardiography. Philadelphia: Current Medicine; 2008.] *Caption from original*

Special Populations

Age

- Risk for STEMI increases with age, starting at age 40 in men and at menopause in women.
  - Age is a risk factor for mortality from STEMI.
  - Likelihood of atypical presentation with STEMI increases with age.

Pediatric Considerations

- A congenital abnormality of the coronary vasculature, in which there is an anomalous origin of the left coronary artery arising from the pulmonary artery (ALCAPA), may occur in infancy. It presents with various symptoms of cardiac ischemia (diaphoresis when feeding) and if not recognized and corrected surgically, may cause irreversible myocardial damage.

Co-morbidities

- Hypertension, diabetes, and renal failure are important comorbidities in STEMI risk and prognosis.
- Obesity is a weaker predictor of STEMI risk.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- ECG must be performed as soon as the diagnosis of STEMI is even considered.

Mimics

- All differential considerations listed above.
  - Of these, only aortic dissection and pulmonary embolism are also life-threatening.

Time-Dependent Interventions

- Restoration of myocardial perfusion is time sensitive.
  - If possible, STEMI should be managed in the cardiac cath laboratory within 90 minutes of initial evaluation.
  - Outcomes worsen with each 30–60-minute delay in restoration of flow.
  - If interventional management is not possible, evaluation for fibrinolytic therapy should be performed immediately, with a goal of delivering lytic therapy to appropriate STEMI patients within 30 minutes of initial evaluation.

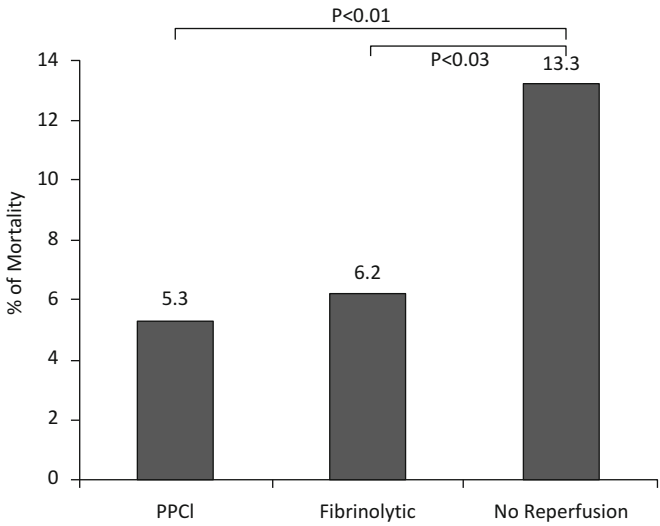
- Unless contraindicated (allergy, active bleeding), 324-325 mg aspirin should be administered immediately upon suspicion of an acute coronary syndrome.
- Extremes of blood pressure should be promptly treated to avert shock (hypotension) or undue myocardial oxygen demand (hypertension).
- Airway and oxygenation should be monitored and supported as necessary.
- Patients with STEMI should be on continuous cardiac monitoring to evaluate for dangerous arrhythmias.

Overall Principles of Treatment

- Immediate stabilization of the patient with control of blood pressure, pulse rate, and pain is critical. The patient may require resuscitation, intubation, and intensive support.
- Measures to reperfuse infarcting myocardium are essential and are time sensitive.

Disease Course

- STEMI mortality is highest in the prehospital setting.
- Once at the emergency department, in-hospital STEMI mortality among patients receiving reperfusion therapy is around 6 %.



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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"ST segment elevation myocardial infarction" OR "STEMI"

Chapter 4
Acute Coronary Syndrome: Unstable Angina

Charles V. Pollack, Jr. and Victoria G. Riese

Name and Synonyms

Unstable angina

- Troponin-negative acute coronary syndrome (ACS)

Incidence/Epidemiology

- Because unstable angina is a clinical diagnosis with inconsistent defining criteria, the true incidence is unknown.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_4

Progressive angina (grade IB)
Characterized by either new-onset angina pectoris or chronic angina with an increase in frequency or severity of episodes
Angina at rest (grades IIB and IIIB)
Recurrent angina with transient ST- or T-wave changes
Early postinfarction angina (grades IIC and IIIC)
Recurrent angina within 30 d following MI; angina either at rest or related to minimal exercise

Classification of unstable angina [Prasad A, Holmes D, Kleiman N. Use of percutaneous coronary intervention in unstable angina and acute myocardial infarction. In: Califf RM, editor. Acute myocardial infarction and other acute ischemic syndromes. 2nd ed. Philadelphia: Current Medicine; 2001. Chapter 7. (Braunwald E, editor. Atlas of heart diseases; vol. 8.)]

- Unstable angina is considered a "non-ST-segment-elevation" (NSTE) ACS. NSTE-ACS (which also includes NSTE myocardial infarction [NSTEMI]) is much more common than STEMI.

	STEMI	NSTEMI/UA
Pathogenesis	Fully occlusive thrombus	Less than fully occlusive thrombus
Incidence		Higher than that of STEMI
Patient profile		Older; higher co-morbidity (diabetes, renal failure) than STEMI patients
Time course	Minutes to hours	Up to a few days
Clinical manifestations		Similar to STEMI
Imaging studies		Similar to STEMI
EKG	ST elevations	No ST elevations[a]
Biomarkers	Elevated	Elevated
Therapy	See Table 2.54	See Table 2.54
Rehabilitation		Similar to STEMI
Complications		Similar to STEMI
Prognosis		Mortality lower in-hospital, higher at 6 months and 4 years than with STEMI

[a]ST elevations may be seen in Prinzmetal's angina

STEMI and NSTEMI/UA: a comparison. [Adelmann GA. Cardiology essentials in clinical practice. London: Springer; 2011. Chapter 2, Coronary artery disease; p. 23-95. Book https://doi.org/10.1007/978-1-84996-305-3; Chapter: 2; Chapter https://doi.org/10.1007/978-1-84996-305-3_2, 2010-01-01] Caption from original

- Incidence varies widely by demographics and risk profiles; patients with NSTE-ACS tend to be older and to have more comorbidities than STEMI patients.

- About 1 million patients are hospitalized with a diagnosis of unstable angina in the US each year, but in the absence of a consistent definition, it is likely that this is an overestimation, with some patients going on to complete MI and others more properly diagnosed as having either stable angina or noncoronary chest pain.

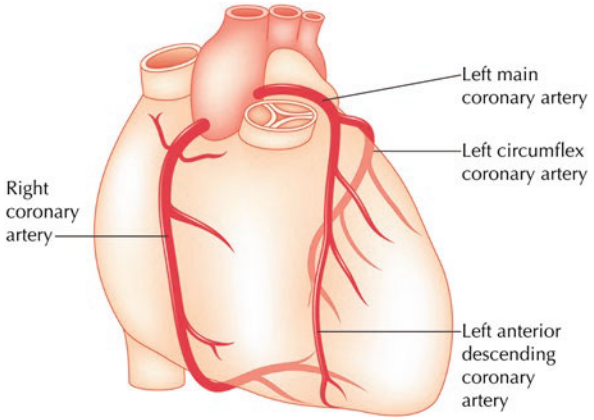
Differential Diagnosis

- Includes all other causes of chest pain
- Includes other causes of "anginal equivalents" in susceptible populations, e.g.:
  - Dyspnea
  - Back pain
  - Jaw pain
  - Shoulder pain
  - Epigastric pain
  - Palpitations
  - Dizziness
  - Weakness
  - Nausea
  - Syncope

Pathophysiology and Etiology

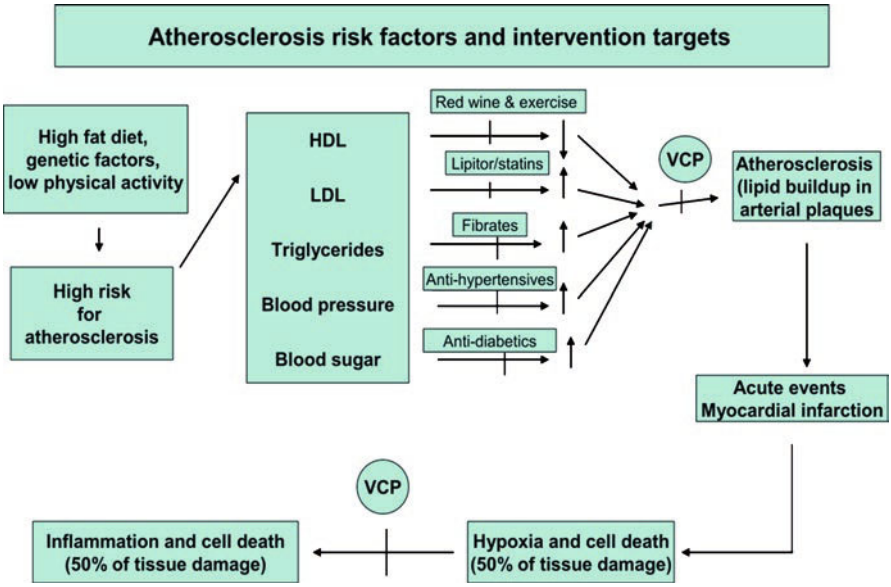
- ACS is the result of ischemia (diminished blood flow / oxygen delivery) to myocardium.
- If ischemia persists, frank infarction (muscle death) may occur.
- Infarction results in breakdown of cell membranes, allowing release of intracellular proteins (such as myoglobin, troponins, and CPK-MB) into the circulation, where they can be detected in peripheral blood draw.
- Unstable angina, as currently defined, is the clinical picture of ACS in the absence of both (1) ST-segment elevation on ECG and (2) elevated biomarker levels. These factors clearly differentiate unstable angina from NSTEMI and STEMI.
- The greatest consensus on the factors that make angina "unstable" include:
  - Anginal onset at rest (especially in patients who previously had only exertional angina)
  - Anginal symptoms do not resolve after

    - rest, if onset was with exertion
    - abortive therapy, such as sublingual nitroglycerin
    - 20 minutes
  - "crescendo" pattern of symptoms or change in usual anginal pattern
  - Multiple episodes within 24 hours
  - Association with signs of heart failure
- Most cases of ACS occur as a result of fracture or frank rupture of atherosclerotic plaque in an epicardial artery, but unstable angina also may result from "demand" ischemia, in which blood flow through a stenotic coronary artery is insufficient to meet increased myocardial oxygen demands (such as in exercise or physiologic stress). In the latter case, the plaque causing the stenosis need not be fractured or ruptured.



Normal coronary anatomy. [Achenbach S. Normal coronary anatomy. In: Budoff MJ, Achenbach S, Narula J, Braunwald E, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007.] *Caption from original*

- Atherosclerosis, which is most often at the foundation of unstable angina, is a product of diverse inherited and acquired conditions, including:
  - Family history
  - Hyperlipidemia
  - Hypertension
  - Diabetes mellitus
  - Tobacco abuse



Atherosclerosis risk factors and intervention targets. [Thorbjornsdottir P, Thorgeirsson G, Kotwal GJ, Arason GJ. Control of inflammation with complement control agents to prevent atherosclerosis. In: Suri JS, Kathuria C, Molinari F, editors. Atherosclerosis disease management. New York: Springer; 2011. p. 633-75. Book https://doi.org/10.1007/978-1-4419-7222-4; Chapter: 20; Chapter https://doi.org/10.1007/978-1-4419-7222-4_20, 2011-01-01] *Caption adapted from original*

Risk factors	No. of patients
Individual	
Smoking	6
Hypertension	11
Hypercholesterolemia	9
Diabetes mellitus	4
Clusters	
Smoking and hypercholesterolemia	1
Hypertension and hypercholesterolemia[a]	4
Hypertension and diabetes	2
Smoking, hypertension and hypercholesterolemia	1
Smoking, hypertension, hypercholesterolemia and diabetes	2

[a] Hypertension was defined as a diastolic arterial pressure >95 mm Hg and hypercholesterolemia >6 mmol/l

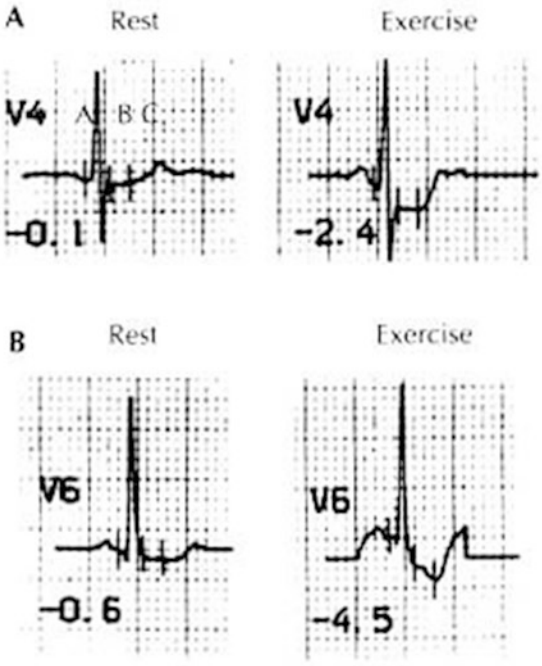
Main known risk factors for atherosclerosis in 16 patients studied. [Watt S, Aesch B, Lanotte P, Tranquart F, Quentin R. Viral and bacterial DNA in carotid atherosclerotic lesions. Eur J Clin Microbiol Infect Dis. 2003 Feb;22(2):99-105. https://doi.org/10.1007/s10096-002-0867-1, 2003-02-01] *Caption adapted from original*

- See pathophysiology discussions under NSTEMI and STEMI for details of the thromboinflammatory processes underlying ACS resulting from a breach of an atherosclerotic plaque.
- Besides atherothrombosis and demand across a critical stenosis, unstable angina may result from a variety of much rarer etiologic considerations, including
    - Pure arterial spasm (which may be precipitated by sympathomimetic agents such as cocaine or methamphetamine)
    - Arteritis
        - Lupus
        - Takayasu disease
        - Kawasaki disease

Presentation

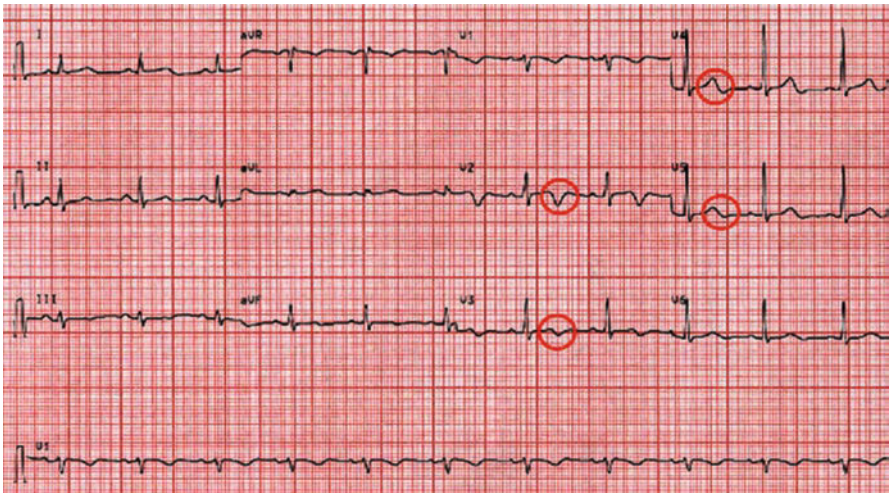
Typical/"Classic"

- Pressure-like chest pain starting substernally and radiating toward the left shoulder or left jaw.
- Pain is classically associated with diaphoresis, dyspnea, and nausea.
- Pain often accompanied by tachycardia; blood pressure is variable, with very high and very low presenting blood pressures associated with poorer prognosis.
- Pain often starts with exertion; may be improved with rest or with use of nitroglycerin. May also start at rest and often persists > 20 minutes prior to presentation.
- Pain unchanged with movement, positioning, or deep breathing.
- In describing pain, patient may hold clenched fist over chest ("Levine sign").
- Notable for absence of specific, diagnostic ECG findings:
    - Persistent ST-segment elevation is ABSENT
    - ST-segment depression confers a higher risk for poor outcomes but IS NOT diagnostic of NSTEMI.
        - Particularly high risk when depression is "dynamic"—that is, present when patient is experiencing pain and resolved when that pain is relieved



A, Example of ischemic horizontal ST-segment depression. The J-point (B) is depressed 0.3 mm relative to the PQ junction (A), and ST-80 (C) is depressed 0.1 mm at rest. During exercise, the J-point and ST-80 are depressed 2.4 mm. The reported net difference in ST-80 depression would be 2.3 mm. B, Example of downsloping ST-segment depression. The second patient reveals 0.6-mm ST-80 depression at rest, which worsens with exercise, resulting in J-point depression of 2.5 mm and ST-80 depression of 4.5 mm during exercise. The reported net difference in ST-80 depression would be 3.9 mm. [Chaitman B. Exercise electrocardiographic stress testing. In: Beller G, editor. Chronic ischemic heart disease. Philadelphia: Current Medicine; 1995. Chapter 2. (Braunwald E, editor. Atlas of heart diseases; vol. 5.) ISBN: 1-878132-29-6, 2002-01-23] *Caption adapted from original*

- T-wave inversion confers a higher risk in patients with symptoms of ACS but IS NOT diagnostic of unstable angina or NSTEMI.



Electrocardiogram with T-wave inversions in leads V1 to V4. [From article: Triptans and troponin: a case report. Orphanet J Rare Dis. 2009 Jun 18;4: 15. https://doi.org/10.1186/1750-1172-4-15, at http://link.springer.com/article/10.1186/1750-1172-4-15; by Claudia R Weder, Markus Schneemann, © Weder and Schneemann. 2009; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Atypical

- Unstable angina has been diagnosed in patients with virtually any complaint localized above the umbilicus.
- "Anginal equivalents" listed above include different distributions of pain (e.g., epigastric, jaw, neck, back) and some presentations that are not painful at all (e.g., palpitations, nausea, syncope).
  - Patients with ACS who present without chest pain as their chief complaint frequently experience delays in diagnosis and therefore delays in treatment.
  - Atypical presentations are more common in women, in elderly people, and in diabetics.
- The absence of an elevated troponin level is required for the diagnosis of unstable angina, by current definitions.

Primary Differential Considerations

- Primary differential considerations include pain mimics to angina and are diverse, including life-threatening and more benign causes:
  - Aortic dissection
  - Pulmonary embolism
  - Peptic and esophageal disease, hiatal hernia
  - Costochondritis
  - Pneumonia
  - Pneumothorax
  - Pleurisy
  - Anxiety and panic disorders
  - Biliary colic
  - Herpes zoster

	Helpful clinical features
Cardiovascular	
Angina	Retrosternal chest pressure, squeezing, heaviness. Associated with exertion or emotional stress, relieved by rest or nitroglycerin. Usually between 2 and 20 min in duration.
Aortic stenosis	Similar features as for angina, but with late-peaking systolic murmur radiating to carotids. May be associated with syncope or signs of left heart failure.
Pericarditis	Sharp, retrosternal, pleuritic chest pain lasting hours to days. May be associated with friction rub and may be alleviated by leaning forward.
Aortic dissection	Sudden onset of tearing, ripping chest pain radiating to back. Associated with underlying hypertension.
Pulmonary embolism	Ipsilateral pleuritic pain associated with dyspnea, tachycardia, possible cor pulmonale. May have irritative cough or hemoptysis or present with syncope. Usually sudden onset.
Pulmonary	
Pneumonia/ pleuritis/pleural effusion	Pleuritic pain, lateralizing to side of infection/ inflammation. May be associated with fevers, dyspnea, cough. Exam with pleural rub, consolidation, or dullness to percussion.
Asthma/COPD exacerbation	Chest "tightness" associated with more prominent findings of dyspnea, tachypnea and diffuse wheezing.
Spontaneous pneumothorax	Sudden onset of pleuritic pain. Unilateral and associated with dyspnea. More common in thin, young males or patients with emphysematous disease. Decreased breath sounds and hyperresonance on side of pneumothorax.
Chest wall	
Muscle spasm/ strain	Associated with prior increased physical activity/ weight lifting. Pain variable in character but usually reproducible with palpation.

	Helpful clinical features
Costochondritis	Sharp, sudden onset pain that is short in duration. May be reproducible with palpation.
Herpes zoster	Sharp, burning, superficial neuropathic pain. May have allodynia, vesicular rash on exam. Unilateral dermatomal distribution.
Rib fracture	Prior trauma or known metastatic disease of bone. Point tenderness over affected rib(s). Pain is usually pleuritic.
Cervical/thoracic nerve root compression	Intermittent neuropathic pain often associated with neck movement or position. Usually unilateral.
Gastrointestinal	
Mediastinitis/ esophageal rupture	Often preceded by esophageal procedure or forceful vomiting. Pt. may have fever, associated septic shock. Symptoms vary from burning chest discomfort to severe dyspnea.
Esophageal reflux	Burning pain, often associated with nausea, belching. Usually worse at night and after large meals. Alleviated by antacids.
Esophageal spasm	Sudden onset, sharp, retrosternal pain. May be relieved by nitroglycerine and exacerbated by cold liquids. Sometimes associated with dysphagia.
Pancreatitis	Sharp epigastric pain, usually constant and prolonged. Exacerbated by food and often associated with nausea/vomiting. Alcohol and gallstones are risk factors.
Peptic ulcer	Sharp or burning epigastric pain. Often relieved by food or antacids. May be associated with occult GI bleeding or massive acute blood loss.
Psychogenic	
Anxiety/panic disorder	May be unable to distinguish from anginal pain, but usually has atypical features such as prolonged duration and no exertional component. Should be a diagnosis of exclusion at initial workup.

Differential diagnosis of acute chest pain. [McClintic BR, Rosenblatt RL. Approach to the patient with chest pain. In: Bisognano JD, Beck R, Connell R, editors. Manual

of outpatient cardiology. London: Springer; 2012. p. 349-71. Book https://doi.org/10.1007/978-0-85729-944-4; Chapter: 13; Chapter https://doi.org/10.1007/978-0-85729-944-4_13, 2012-01-01] *Caption from original*

History and Physical Exam

Findings That Confirm Diagnosis

- None

Factors That Suggest Diagnosis

- Nature and history of symptoms with presence of risk factors

Factors That Exclude Diagnosis

- An elevated troponin level is inconsistent with the diagnosis of unstable angina.

Ancillary Studies

Laboratory

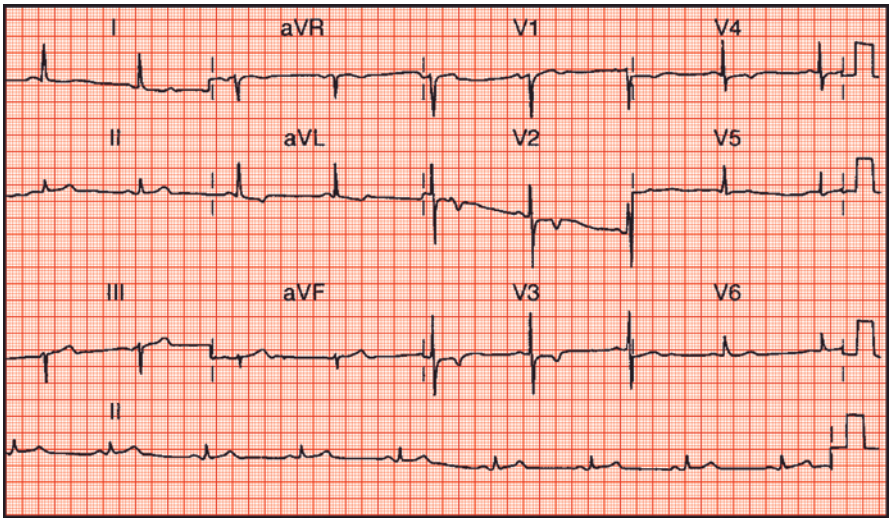
- CBC: no diagnostic findings.
- Electrolytes: no diagnostic findings.
- Renal function: no diagnostic findings, but renal insufficiency/failure is a risk factor for ACS and may complicate treatment.
- Coagulation studies: no diagnostic findings but should be performed before initiation of therapy.
- Cardiac enzymes: lack of elevation in troponin (I or T) levels is required to differentiate unstable angina from myocardial infarction.
    - Time course is critical.
        - Depending on specific troponin assay and volume of muscle infarcted, generally takes about 6 hours after onset of symptoms for troponin levels to rise.

- A negative troponin within 6 hours of reliable onset time of symptoms is not particularly helpful.
  - If onset time unclear, start at time of presentation.
  - Patients may be given the *clinical* diagnosis of unstable angina and then be "upgraded" to NSTEMI if a subsequent troponin assay shows an elevated level.
- Positive troponin is *always* helpful, but use caution in interpreting levels in patients with renal insufficiency.

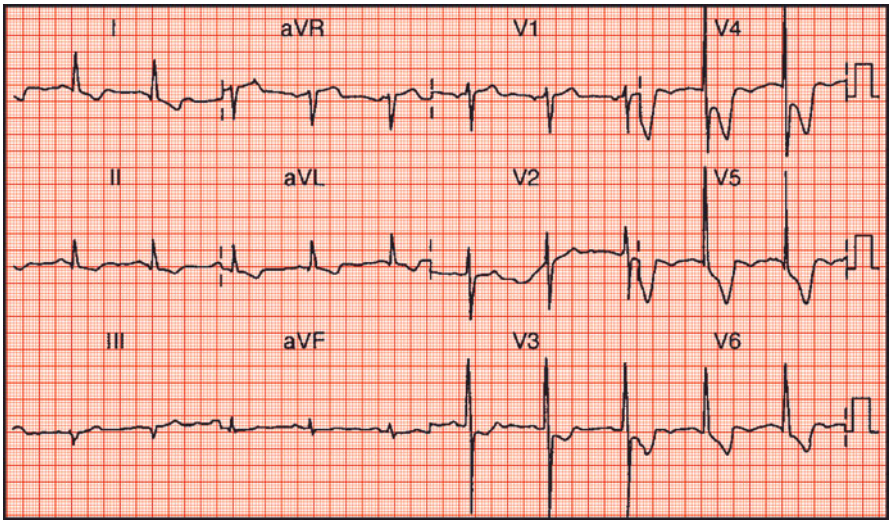
- BNP levels may offer some prognostic significance.

Electrocardiography

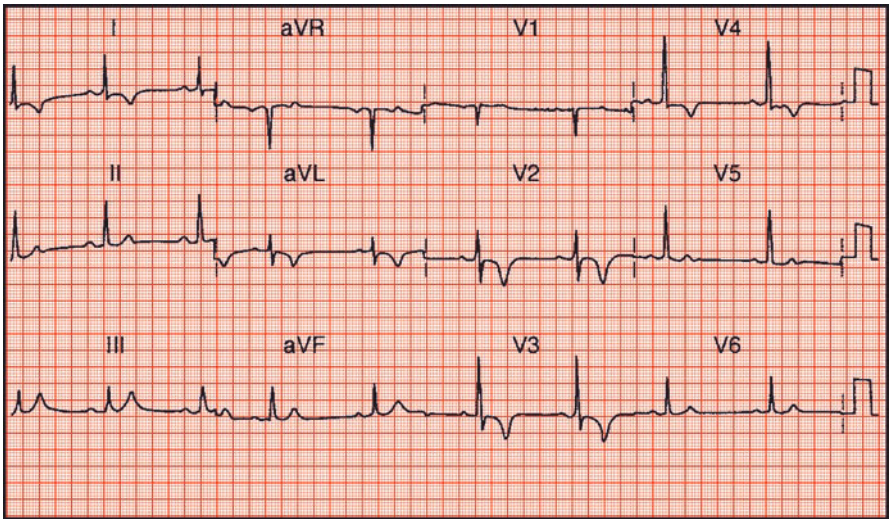
- No diagnostic findings, although both ST-segment depression and T-wave inversion confer a poorer prognosis in the setting of unstable angina.



This 57-year-old patient presented with unstable angina, ischemic changes (T wave inversions) are noted in the anteroseptal leads (aVL, V2, V3, V4) (SM; 13/3/93). [Peters N, Gatzoulis MA, Vecht R. ECG diagnosis in clinical practice. London: Springer; 2009. Chapter 2, Ischaemic (coronary) heart disease; p. 11-66.] *Caption from original*



Unstable angina with marked anterolateral ischemic changes. Cardiac catheterization showed critical mainstem stenosis. The patient underwent surgery on the same day (MK; 5/12/95). [Peters N, Gatzoulis MA, Vecht R. ECG diagnosis in clinical practice. London: Springer; 2009. Chapter 2, Ischaemic (coronary) heart disease; p. 11-66.] *Caption from original*



This 86-year-old man presented with severe unstable angina. His cardiac enzyme levels were not elevated. He was treated medically (PR; 16/4/95) [Peters N, Gatzoulis MA, Vecht R. ECG diagnosis in clinical practice. London: Springer; 2009. Chapter 2, Ischaemic (coronary) heart disease; p. 11-66.] *Caption from original*

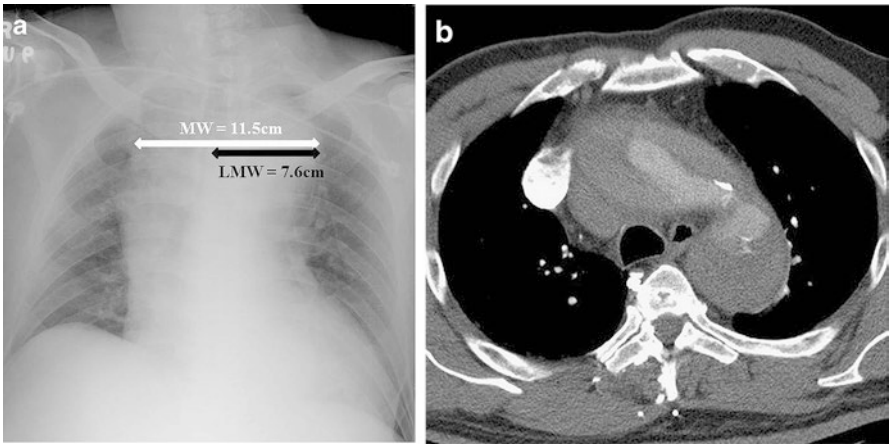
- According to national quality standards in the United States, ECG should be obtained within 10 minutes of arrival at an emergency department.

Imaging

- No diagnostic findings for ACS on chest x-ray (CXR).
- Findings of heart failure (cardiomegaly, pulmonary congestion) on CXR portend a poorer prognosis in unstable angina.

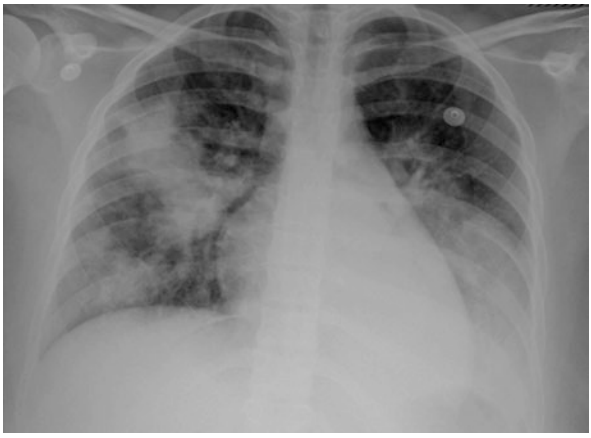
Frontal chest radiograph reveals typical features of pulmonary interstitial edema in a patient with congestive heart failure, manifested by peribronchial cuffing, indistinctness of the pulmonary vessels, and Kerley B lines. Note the cephalization or redistribution of the pulmonary vasculature and mild cardiomegaly. [Boiselle PM, Dass C, Steiner RM. Radiologic imaging in the critically ill patient. In: Criner GJ, Barnette RE, D'Alonzo GE, editors. Critical care study guide. 2nd ed. New York: Springer; 2010. p. 181-207. Book https://doi.org/10.1007/978-0-387-77452-7; Chapter: 11; Chapter https://doi.org/10.1007/978-0-387-77452-7_11, 2010-01-01] *Caption from original*

- Findings of a widened mediastinum suggest consideration of aortic dissection but do not exclude angina. Check differential blood pressures in the upper extremities.



Acute type A aortic dissection in a 46-year-old man. A) AP chest radiograph showing marked widening of the mediastinum with MW and LMW measuring 11.5 and 7.6 cm, respectively. B) Corresponding selected image of CT aortogram confirms type A aortic dissection. [From article: Diagnostic accuracy of mediastinal width measurement on posteroanterior and anteroposterior chest radiographs in the depiction of acute nontraumatic thoracic aortic dissection. Emerg Radiol. 2012 Aug;19(4):309-15. https://doi.org/10.1007/s10140-012-1034-3 at http://link.springer.com/article/10.1007/s10140-012-1034-3 by Vincent Lai, Wai Kan Tsang, Wan Chi Chan, Tsz Wai Yeung, licensed under Creative Commons Attribution License, https://creativecommons.org/licenses/by/2.0/] *Caption from original*

- Findings of pneumonia suggest consideration of that differential but do not exclude angina. Check for signs of infection. Frank septic shock may result in elevated troponin levels.



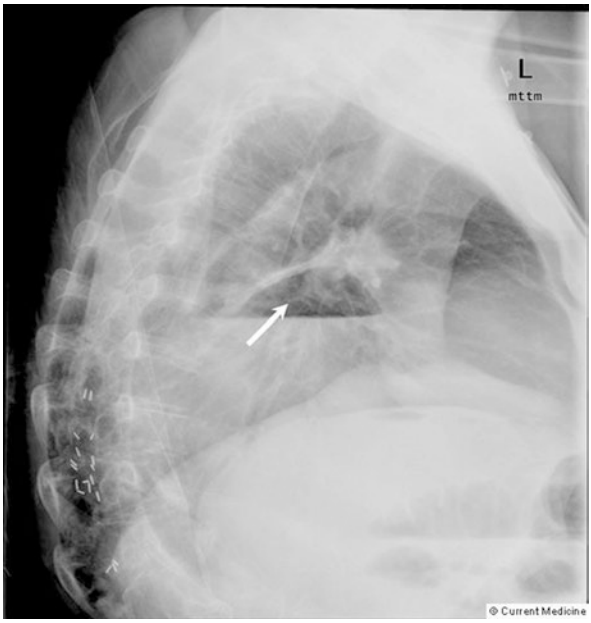
Chest radiograph showing right upper/lower lung field opacities and left lower lung field opacity consistent with pneumonia. [Tsigrelis C, Mohammad M, Fraimow HS,

Dellinger RP, Marchesani D, Reboli AC. Secondary bacterial pneumonia due to Staphylococcus aureus complicating 2009 influenza A (H1N1) viral infection. Infection. 2010 Jun;38(3):237-9. https://doi.org/10.1007/s15010-010-0009-0, 2010-06-01] *Caption adapted from original*

- Findings of pneumothorax suggest consideration of that differential but do not exclude angina. Evaluate oxygenation status.

Posteroanterior upright chest X-ray showing large pneumothorax of the right lung. [Kim SH, Yoo WH. Recurrent pneumothorax associated with pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report and review of the literature. Rheumatol Int. 2011 Jul;31(7):919-22. https://doi.org/10.1007/s00296-009-1240-9, 2011-06-21] *Caption adapted from original*

- Findings of hiatal hernia suggest consideration of that differential but do not exclude angina.



Radiograph of large hiatal hernia. [Aurigemma G, Tighe D, Oh Jae, Espinoza R. Pericardial disease and cardiac masses. In: Solomon SD, Braunwald E, editors. Atlas of echocardiography. 2nd ed. Philadelphia: Current Medicine; 2008. Chapter 16. ISBN: 1-57340-217-6, 2008-10-22;] *Caption from original*

Risk Scoring

TIMI risk score may be helpful in establishing short-term prognosis, which helps drive intensity of therapy.

- Age ≥65 years
- History of known CAD (documented prior coronary artery stenosis >50%)
- ≥3 conventional cardiac risk factors (age, male sex, family history, hyperlipidemia, diabetes mellitus, smoking, obesity)
- Use of aspirin in the past 7 days
- ST-segment deviation (persistent depression or transient elevation)
- Increased cardiac biomarkers (troponins)
- ≥2 anginal events in the preceding 24 h

TIMI = Thrombosis in Myocardial Infarction; CAD = coronary artery disease

Score = sum of number of above characteristics

TIMI = Thrombosis in Myocardial Infarction; CAD = coronary artery disease

Score = sum of number of above characteristics

TIMI risk score for unstable angina and NSTEMI. [Stillman AE, Oudkerk M, Ackerman M, Becker CR, Buszman PE, Feyter PJ, Hoffmann U, Keadey MT, Marano R, Lipton MJ, Raff GL, Reddy GP, Rees MR, Rubin GD, Schoepf UJ, Tarulli G, Beek EJR, Wexler L, White CS. Use of multidetector computed tomography for the assessment of acute chest pain: a consensus statement of the North American Society of Cardiac Imaging and the European Society of Cardiac Radiology. Int J Cardiovasc Imaging. 2007 Aug;23(4):415-27. https://doi.org/10.1007/s10554-007-9226-8, 2007-07-12] *Caption adapted from original*

Value	TIMI risk score[a] (95% CI)	Modified TIMI risk score[b] (95% CI)
Sensitivity	53.7 (44.9–62.3)	58.1 (49.8–66.4)
Specificity	75.2 (72.1–78.2)	82.6 (80.0–85.2)
Negative predictive value	90.6 (88.2–927)	92.2 (90.2–94.1)
Positive predictive value	26.6 (21.5–32.3)	35.9 (29.6–42.2)

[a] Using a cut point of 3 (less than 3 vs. 3 or greater)

[b] Using a cut point of 2 (less than 2 vs. 2 or greater)

A summary of the TIMI risk score and modified TIMI risk scores as predictors of 30-day myocardial infarction/revascularization/death. [Jaffery Z, Hudson MP, Jacobsen G, Nowak R, McCord J. Modified Thrombolysis in Myocardial Infarction (TIMI) risk score to risk stratify patients in the emergency department with possible acute coronary syndrome. J Thromb Thrombolysis. 2007 Oct;24(2):137-44. https://doi.org/10.1007/s11239-007-0013-0, 2007-08-02] *Caption adapted from original*

Special Populations

Age

- Risk for coronary artery disease that causes angina increases with age, starting at age 40 in men and at menopause in women.
  - Age is a risk factor for mortality from all types of ACS.
  - Likelihood of atypical presentation with unstable angina increases with age.

Comorbidities

- Hypertension, diabetes, and renal failure are important comorbidities in ACS risk and prognosis.
- Diabetes is associated with the likelihood of atypical presentation with unstable angina.
- Obesity is a weaker predictor of unstable angina risk.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- ECG must be performed as soon as the diagnosis of ACS is even considered. By definition, in unstable angina, there will not be persistent ST-segment elevation.

Mimics

- All differential considerations are listed under Primary Differential Considerations.
  - Of these, only aortic dissection and pulmonary embolism are also life threatening.

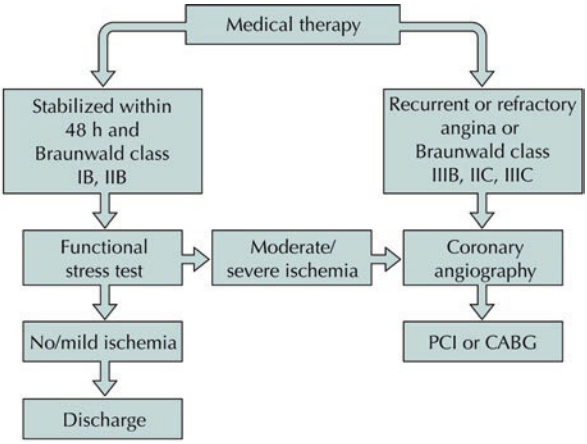
Time-Dependent Interventions

- Stabilization of the unstable angina patient is time-sensitive.
- Derangements in blood pressure should be addressed immediately: hypertension results in increased myocardial oxygen demand, and hypotension reduces blood supply to the myocardium.

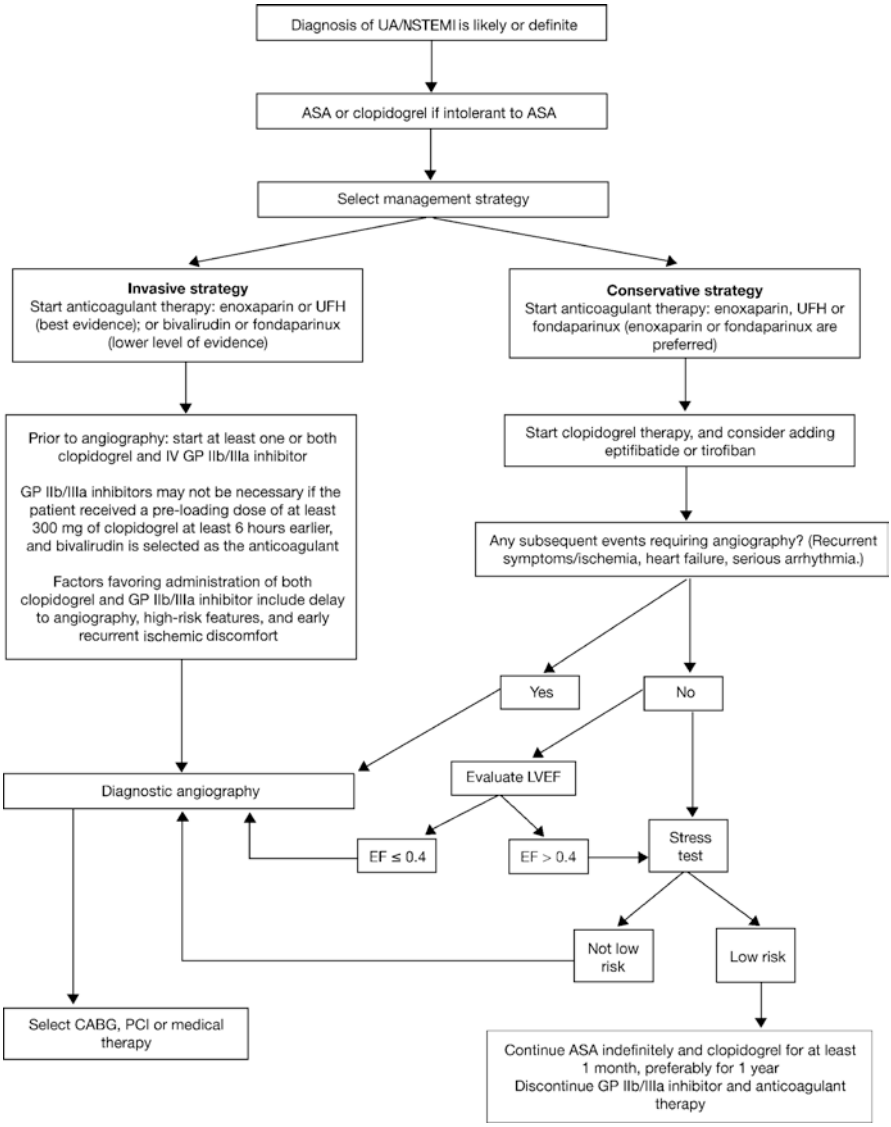
- Current guidelines call for diagnostic angiography in 24–48 hours to establish preferred course of management.
- Unless contraindicated (allergy, active bleeding), 324–325 mg aspirin should be administered immediately upon suspicion of an ACS.
- Anticoagulation therapy should be initiated upon determination of the diagnosis of unstable angina or when there is high suspicion in high-risk patients.
- Airway and oxygenation should be monitored and supported as necessary.
- Patients with a diagnosis of unstable angina should be on continuous cardiac monitoring to evaluate for dangerous arrhythmias.
- Consider early initiation of dual antiplatelet therapy (aspirin plus an ADP receptor antagonist—ticagrelor or clopidogrel).

Overall Principles of Treatment

- Immediate stabilization of the patient with control of blood pressure, pulse rate, and pain is critical. The patient with unstable angina only rarely requires resuscitation, intubation, and intensive support.
- Medical management with anticoagulation and antiplatelet therapy is important.
  - Bleeding risk should also be assessed so that the risk of treatment-related hemorrhage can be minimized.
- The higher the patient's risk, the more disproportionately s/he benefits from aggressive therapy.



Treatment for unstable angina [Prasad A, Holmes D, Kleiman N. Use of percutaneous coronary intervention in unstable angina and acute myocardial infarction. In: Califf RM, editor. Acute myocardial infarction and other acute ischemic syndromes. 2nd ed. Philadelphia: Current Medicine; 2001. Chapter 7. (Braunwald E, editor. Atlas of heart diseases; vol. 8.)]



Algorithm for the initial management of patients with UA/NSTEMI with an invasive or conservative treatment strategy. Abbreviations: ASA, aspirin; CABG, coronary artery-bypass grafting; EF, ejection fraction; GP, glycoprotein; IV, intravenous; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; UFH, unfractionated heparin. [Cohen M. High-risk acute coronary syndrome patients with non-ST-elevation myocardial infarction: definition and treatment. Cardiovasc Drugs Ther. 2008 Oct;22(5):407-18. https://doi.org/10.1007/s10557-008-6120-0, 2008-09-04] *Caption adapted from original*

Disease Course

- The expected mortality rate associated with unstable angina alone is not clear, owing to differences in the definition of the disease. Mortality in NSTEMI—the other component of NSTE-ACS—is 6–10 %, depending on the population studied, over 6 months.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Jneid H, Ettinger SM, Ganiats TG, Lincoff AM, Philippides GJ, Zidar JP; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jun 11;127(23):e663-828. https://doi.org/10.1161/CIR.0b013e31828478ac. Erratum in: Circulation. 2013 Jun 18;127(24):e863-4. PMID: 23630129. http://www.ncbi.nlm.nih.gov/pubmed/23630129 **

Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J. 2007 Jul;28(13):1598-660. PMID: 17569677. http://www.ncbi.nlm.nih.gov/pubmed/17569677 **

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Trost JC, Lange RA. Treatment of acute coronary syndrome: Part 1: Non-ST-segment acute coronary syndrome. Crit Care Med. 2011 Oct;39(10):2346-53. https://doi.org/10.1097/CCM.0b013e31821e855f. PMID: 21602671. http://www.ncbi.nlm.nih.gov/pubmed/21602671 **

Sami S, Willerson JT. Contemporary treatment of unstable angina and non-ST-segment-elevation myocardial infarction (part 1). Tex Heart Inst J. 2010;37(2):141-8. PMID: 20401284. http://www.ncbi.nlm.nih.gov/pubmed/20401284 **

Cohort Study

Antonsen L, Jensen LO, Thayssen P, Christiansen EH, Junker A, Tilsted HH, Terkelsen CJ, Kaltoft A, Maeng M, Hansen KN, Ravkilde J, Lassen JF, Madsen M, Sørensen HT, Thuesen L. Comparison of outcomes of patients ≥ 80 years of age having percutaneous coronary intervention according to presentation (stable vs unstable angina pectoris/non-ST-segment elevation myocardial infarction vs ST-segment elevation myocardial infarction). Am J Cardiol. 2011 Nov 15;108(10):1395-400. https://doi.org/10.1016/j.amjcard.2011.06.062. PMID: 21890087. http://www.ncbi.nlm.nih.gov/pubmed/21890087

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Angina, Unstable"[Mesh] OR "unstable angina"

Chapter 5
Acute Pericarditis

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Acute pericarditis

Incidence/Epidemiology

- Acute pericarditis is the admitting diagnosis in 0.1 % of hospital admissions. Acute pericarditis accounts for 1 % of cases of ST-segment elevation seen in the emergency department.
- Acute pericarditis occurs more commonly in men than in women. There are no known geographic predilections. There is a very rare familial form (Mulibrey nanism)

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_5

Differential Diagnosis

- Acute pericarditis has many causes (see Pathophysiology and Etiology below), and often the differential exploration focuses on determining an etiology for the disease. This involves a search for co-morbidities as diverse as malignancy, renal failure, recent myocardial infarction, adverse effects of certain drugs, and collagen vascular diseases. Because the primary clinical manifestation of acute pericarditis is chest pain, the differential is broad.

Pathophysiology and Etiology

- The pathophysiology of acute pericarditis, regardless of etiology, is inflammation of the pericardium, a double (serous and parietal) membrane separated normally by 15-50 mL of fluid that is an ultrafiltrate of plasma.
- The function of the pericardium is to prevent sudden overdistention of the cardiac chambers and to help maintain the anatomic position of the heart and great vessels. By definition, acute pericarditis is present and symptomatic for less than 6 weeks; pericarditis for 6 weeks to 6 months is termed subacute, and beyond 6 months, chronic.
    - This inflammation may result from a myriad of potential causes:
        - Infectious:
            - Viral (Coxsackie, echovirus, adenovirus, HIV)
            - Tuberculous
            - Pyogenic (pneumococcal, streptococcal, staphylococcal)
            - Fungal (histoplasmosis, coccidioidomycosis, blastomycosis, *Candida*)
        - Noninfectious:
            - Post–myocardial infarction (Dressler's syndrome)
            - Uremia/renal failure
            - Neoplastic (primary or metastatic [lung, breast, lymphoma, Hodgkins])
            - Myxedema
            - Trauma (penetrating or nonpenetrating)
            - Aortic dissection into pericardium
            - Post–radiation therapy
            - Rheumatic fever
            - Collagen vascular disease (lupus, rheumatoid arthritis, scleroderma, Wegener's granulomatosis)
            - Drug-induced (procainamide, hydralazine, INH, phenytoin, doxorubicin, rifampin, methyldopa)
            - Idiopathic (most common)

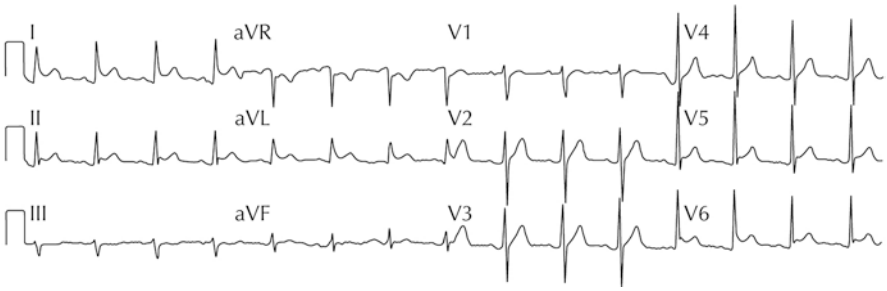
Presentation

Typical/"Classic"

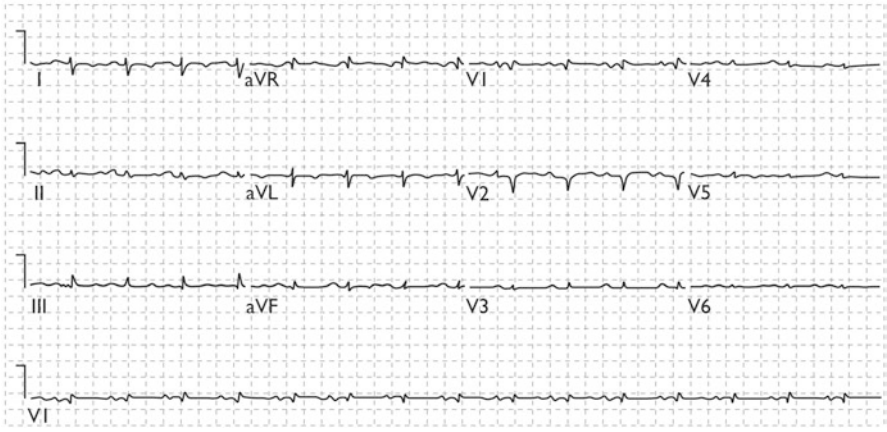
- Chest pain and a pericardial friction rub are most the common findings.

http://www.easyauscultation.com/acute-pericarditis
[Acute Pericarditis Page; Easy Auscultation; copyright 2015, MedEdu LLC]

- On electrocardiography, there are electrical changes suggesting acute pericarditis, and if there is also an effusion there is generalized low voltage.



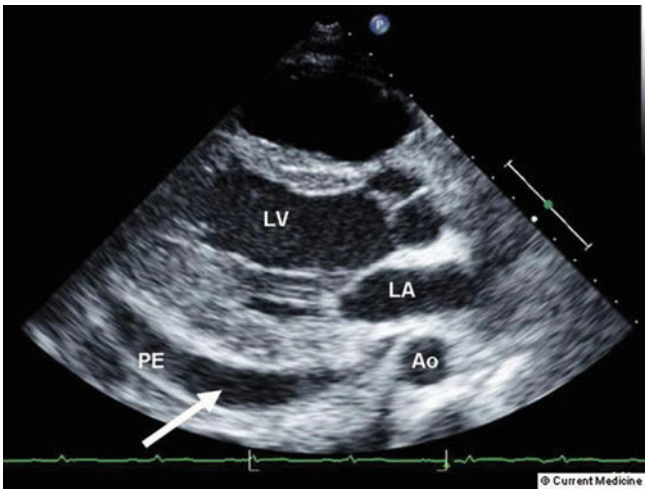
ECG finding in acute pericarditis [Oh J, Espinosa R. Pericardial disease. In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, editors. Atlas of echocardiography. Philadelphia: Current Medicine; 2005 (Braunwald E, editor. Atlas of heart diseases; vol. 16).] *Caption from original*



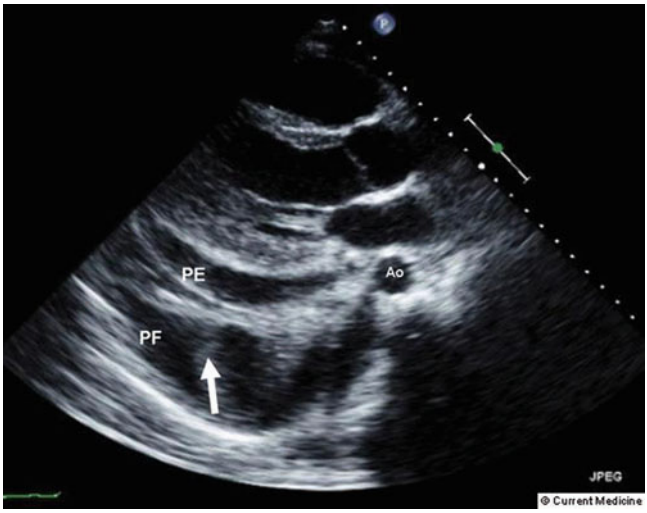
Typical amyloid ECG with diffuse low voltage [Wellens H, Subramaniam K. The electrocardiogram in heart failure. In: Shivkumar K, Weiss JN, Fonarow GC, Narula J, editors. Atlas of electrophysiology in heart failure. Philadelphia: Current

Medicine; 2005 (Braunwald E, editor. Atlas of heart diseases; vol. 15).] *Caption from original*

- On echocardiogram, an effusion may be visible but is not required for a diagnosis of acute pericarditis.



Echocardiogram of pericardial effusion. Arrow indicates descending thoracic aorta. [Aurigemma G, Tighe D, Oh J, Espinoza R. Pericardial disease and cardiac masses. In: Solomon SD, editor. Atlas of echocardiography. 2nd ed. Philadelphia: Current Medicine; 2008.] *Caption adapted from original*



Echocardiogram of pericardial effusion. Arrow indicates lung parenchyma. [Aurigemma G, Tighe D, Oh J, Espinoza R. Pericardial disease and cardiac masses.

In: Solomon SD, editor. Atlas of echocardiography. 2nd ed. Philadelphia: Current Medicine; 2008.] *Caption adapted from original*

- If the effusion is large (>250 mL), the heart takes on a "water bottle" appearance on plain chest x-ray.

Chest X-ray in pericardial effusion: water bottle shaped heart. [Tissot C, Phelps CM, Cruz EM, Miyamoto SD. Pericardial diseases. In: Munoz R, Morell V, Cruz E, Vetterly C, editors. Critical care of children with heart disease. London: Springer; 2010. p. 521-41. https://doi.org/10.1007/978-1-84882-262-7_47; 2009-01-01] *Caption from original*

- Cardiac tamponade may develop, and the patient may have pulsus paradoxus.

http://www.youtube.com/watch?feature=player_embedded&v=jTsjCZ9QxW8
Stanford 25 video on pulsus paradoxus. Provides definition, guidance on testing, sound clip.

- The pain is often severe. It is most often substernal and left-sided. It often radiates to the back and to the trapezius ridge.

Trapezius ridge: the lower border of trapezius, 1; the rhomboids, 2. [Birch R. Surgical disorders of the peripheral nerves. London: Springer; 2010. Chapter 5, Clinical aspects of nerve injury; p. 145-90] *Caption adapted from original*

- The pain is often pleuritic in nature, so it is aggravated by deep inspiration, cough, and lying down as opposed to sitting up.
- The friction rub is the most important physical sign of acute pericarditis. It is often described as "scratching" or "grating," and it may be evanescent. It is best heard with the diaphragm of the stethoscope along the lower left sternal border, with the patient sitting up, during exhalation.
- The classic ECG findings of acute pericarditis are diffuse, mild ST-segment elevation across the precordium. Depression of the PQ segment is common. With large effusions, the overall voltage on the ECG is reduced. Occasionally, atrial fibrillation occurs with acute pericarditis. The ST-segment elevation associated with acute pericarditis can be differentiated from simple early repolarization, and from left ventricular hypertrophy with strain, by considering the ratio of the amplitude of ST segment to the amplitude of the T wave in leads I, V4, V5, and V6.

Atypical

- The most common form of pericarditis is idiopathic, and the diagnosis is one of exclusion. Patients with acute pericarditis and no effusion may present with chest pain and no audible friction rub, with limited to no ECG changes. In this case, acute pericarditis is just one of many differential considerations in the chest pain syndrome presentation. As in other etiologies of chest pain syndrome, the pain may occur in non-substernal locations.

- Pain may be mostly absent in slowly developing pericarditis (neoplastic, uremic, postradiation). Worsening exercise intolerance may be a clue to the diagnosis in these patients.

Primary Differential Considerations

- The initial differential elements to be considered in a patient with a presentation consistent with acute pericarditis are angina, aortic dissection, pulmonary embolism, and distal esophageal pain.

History and Physical Exam

Findings That Confirm Diagnosis

- A full classic presentation (substernal and/or left-sided pleuritic chest pain, a friction rub, and diffuse mild ST-segment elevation on ECG) should be considered confirmatory and should prompt a search for an etiology other than idiopathic.

Factors That Suggest Diagnosis

- Any of the classic findings in isolation should elevate acute pericarditis in the differential diagnosis of the chest pain patient.
- Onset of pain within 2–4 days of acute myocardial infarction (Dressler's syndrome) or after thoracic surgery should elevate acute pericarditis in the differential diagnosis of the chest pain patient.
- A presentation consistent with both acute pericarditis and an apparent cause of pericarditis (such as uremia, myxedema, acute infection, immunocompromise, collagen vascular disease, post chest irradiation) should elevate acute pericarditis in the differential diagnosis of the chest pain patient.
- Uremic pericarditis is most often seen in patients on hemodialysis (HD). A history of HD therefore is suggestive of the diagnosis. It should be noted that chest pain is often minimal or absent in uremic pericarditis, but a friction rub is common.

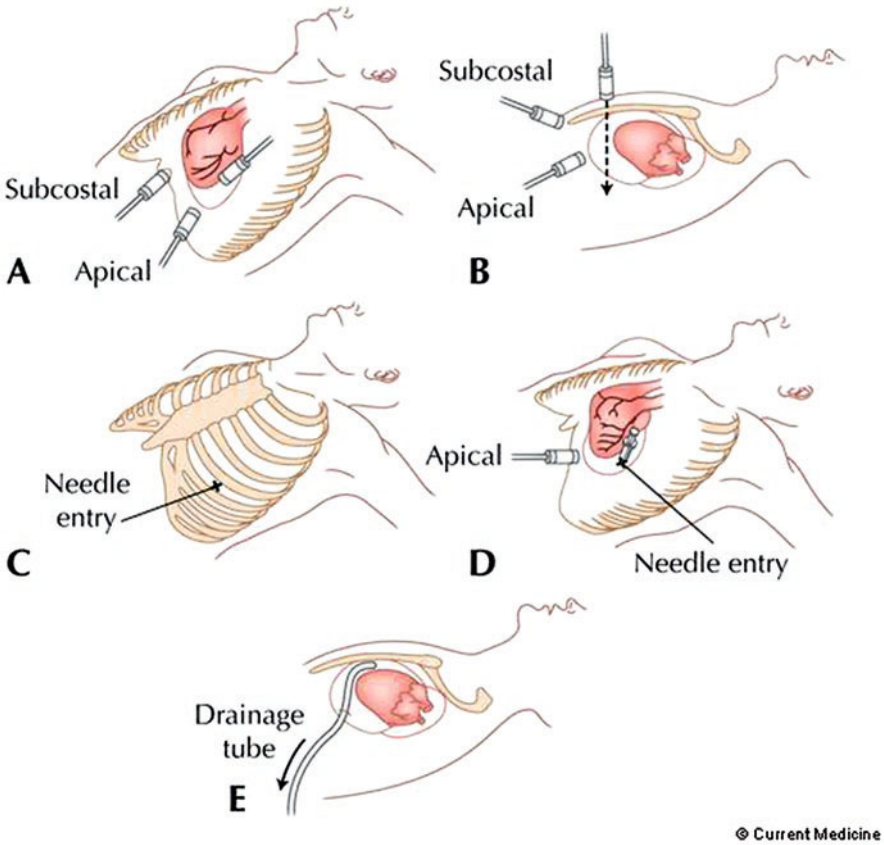
Factors That Exclude Diagnosis

- A normal echocardiogram excludes pericardial effusion and tamponade but not acute pericarditis.

Ancillary Studies

Laboratory

- Lab tests should include CBC; serum electrolyte, blood urea nitrogen (BUN), and creatinine levels; and erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels. In the evaluation of chest pain syndrome, cardiac biomarker measurements are often indicated.
- The ESR and CRP levels are elevated in acute pericarditis, consistent with the underlying inflammation. These tests also are abnormal in patients with collagen vascular diseases, which may be an etiology of acute pericarditis.
- Other laboratory tests may be pertinent to the evaluation of the etiology of the pericarditis:
  - Assessment of renal function in possible uremic pericarditis
  - Assessment of thyroid function in possible myxedema
  - An antistreptolysin O (ASO) titer is indicated if rheumatic fever is suspected.
  - If a pericardial effusion is sampled via pericardiocentesis, the fluid should be tested for cell count, glucose and protein, and culture growth. Other specialized tests may be needed, and fluid should be retained for “unusual” requests by consultants.



Echocardiographically guided pericardiocentesis procedure [Aurigemma G, Tighe D, Oh J, Espinoza R. Pericardial disease and cardiac masses. In: Solomon SD, editor. Atlas of echocardiography. 2nd ed. Philadelphia: Current Medicine; 2008.] *Caption from original*

https://www.youtube.com/watch?feature=player_embedded&v=BQTVqUPimdk

Video from The New England Journal of Medicine on pericardiocentesis. Covers indications, risk factors, contraindications, equipment, preparation, procedure (ultrasound-guided, electrocardiographic monitoring, and blind approaches), aftercare, and complications.

https://www.youtube.com/watch?v=y0-K2RcThi0

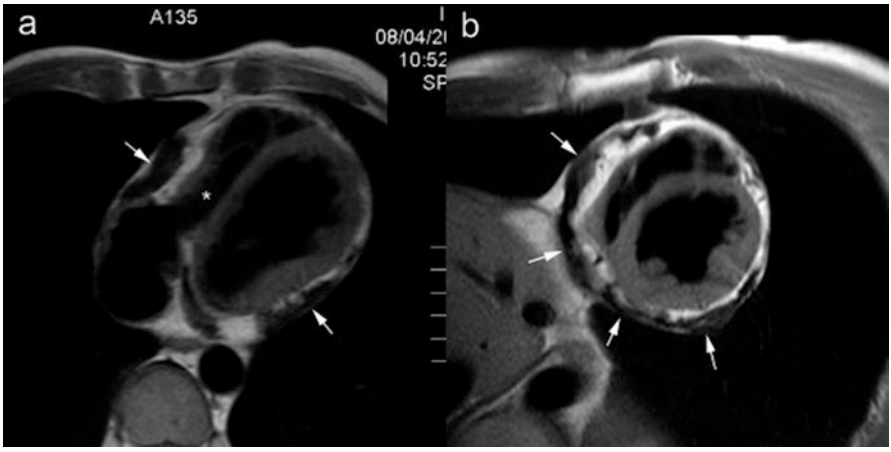
Video from MD Anderson Cancer Center explaining the anterior chest approach to pericardiocentesis.

Imaging

- There are no diagnostic imaging findings of acute pericarditis. When a pericardial effusion is present, transthoracic echocardiography will demonstrate an echo-free space between the visceral and parietal layers of the pericardium.
- Echocardiography should be performed in all cases of pericarditis, because any form of pericardial inflammation may induce pericardial effusion. It is important to note that in the absence of effusion, the pericardium may have a normal appearance in pericarditis.
- With large effusions, a "swinging heart" may be seen on echocardiography, as the heart "floats" in the effusion fluid.

https://www.youtube.com/watch?feature=player_embedded&v=huXuWp_eOKQ
Brief clip of cardiac tamponade with swinging heart echocardiogram.

- Plain chest radiographs are usually normal in acute pericarditis. If there is an effusion of 250 mL or more fluid, the cardiac silhouette will take on an enlarged, "water bottle" appearance.
- Smaller effusions may be detected by MRI, which can also assess the thickness of the pericardium (normal, 4 mm). In acute pericarditis, the pericardium may be globally or locally thickened.



Classic presentation of constrictive pericarditis on T1-weighted fast spin-echo CMR, axial view (a), and short-axis view (b) [From article: Cardiovascular magnetic resonance in pericardial diseases. J Cardiovasc Magn Reson. 2009; 11(1):14. https://doi.org/10.1186/1532-429X-11-14, at http://link.springer.com/article/10.1186%2F1532-429X-11-14; by Jan Bogaert, Marco Francone, © Bogaert and Francone; licensee BioMed Central Ltd. 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Special Populations

Age

- Acute pericarditis is more common in adults than in children, but adolescents are more commonly affected than young adults
- The most common presenting complaint in children with pericarditis is chest pain, accompanied by the typical findings seen in patients of any age.
- In children, the clear majority of cases are viral in etiology, since autoimmune diseases usually present no earlier than late adolescence.

Co-morbidities

- Review of the etiologies of acute pericarditis will indicate co-morbidities of interest. Uremia, malignancy, and immunocompromise are the most worrisome of these.

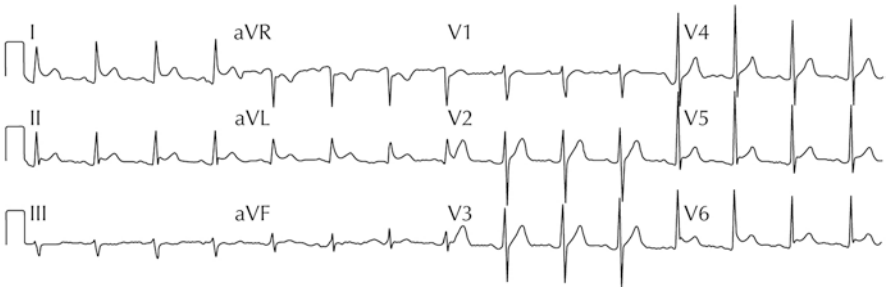
Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. In patients with hemodynamic compromise, an echocardiogram should be performed early to assess for effusion, or even tamponade, and to measure the pumping ability of the heart.
- Acute pericarditis is one of the few diagnoses in which an ESR and CRP are actually very helpful.

Mimics

- The entire constellation of diagnoses that underlies chest pain syndrome can mimic the pain and overall presentation of acute pericarditis.
- Because acute pericarditis is often associated with diffuse ST-segment elevation on ECG, acute coronary syndrome must be always considered as an alternative diagnosis. PR-segment depression usually is also seen in patients with acute pericarditis who have ST-segment elevation.



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Time-Dependent Interventions

- Time-dependent interventions in acute pericarditis are necessary only when cardiac function is compromised, which is usually the case only when there is a large pericardial effusion. In such patients, pericardiocentesis may be a life-saving procedure.

Overall Principles of Treatment

- Because acute pericarditis is an inflammatory disease, the primary treatment in idiopathic pericarditis comprises anti-inflammatory agents (such as corticosteroids [e.g., prednisone] and nonsteroidal anti-inflammatory drugs [NSAIDs]). Resistant cases may require a surgical pericardiectomy, pericardiotomy, or pericardial window.
- Patients with an identified underlying cause of their pericarditis generally benefit from better control/specific treatment of the disease.

Disease Course

- Idiopathic pericarditis generally resolves within 1-2 weeks with anti-inflammatory therapy. The recurrence rate may reach 33 %.
- The course of secondary pericarditis typically follows control of the underlying disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:“acute pericarditis” OR (“acute” AND (“Pericarditis”[Mesh] OR “pericarditis”)

Chapter 6
Anomalous Coronary Arteries

Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

- Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA)
- Also known as Bland-White-Garland Syndrome

Incidence/Epidemiology

- A rare but serious congenital anomaly.
- Usually an isolated cardiac anomaly.
- If unaddressed, mortality rates reach 90 % in the first year of life.

Differential Diagnosis

- Dilated cardiomyopathy
- Myocarditis

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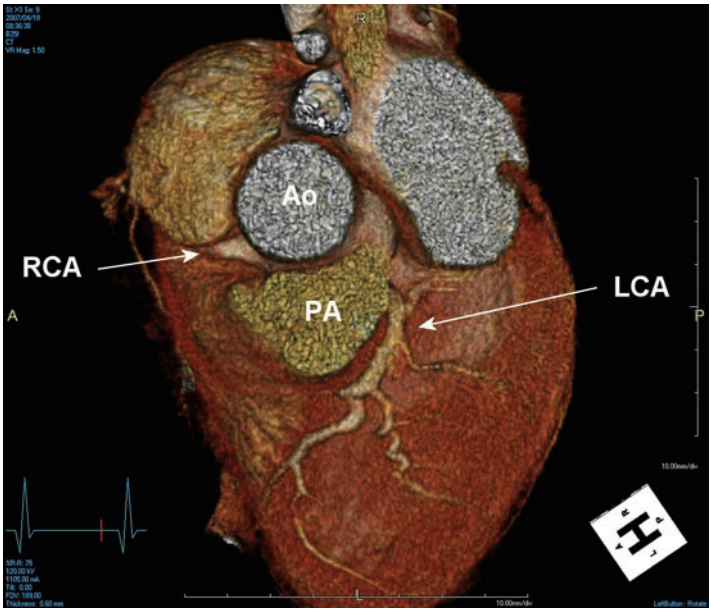
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_6

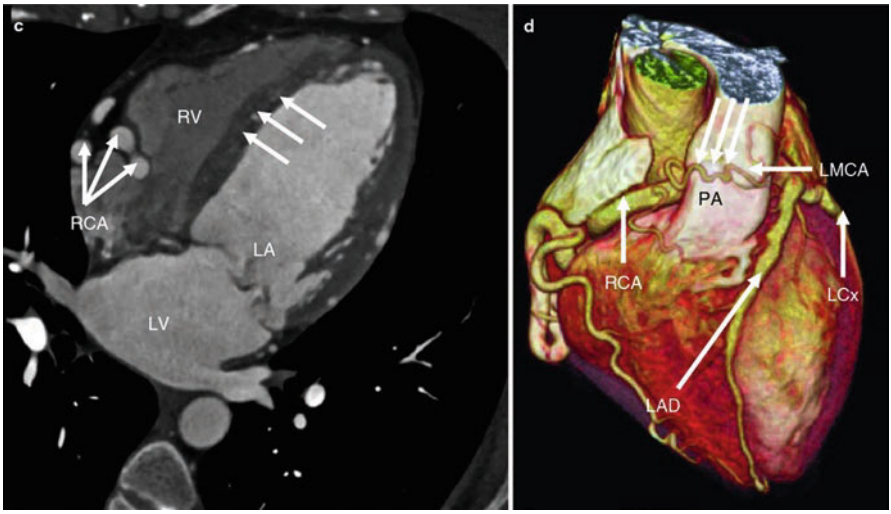
- Coronary artery fistula
- Severe mitral regurgitation

Pathophysiology and Etiology

- After birth, pulmonary pressures decrease, as does pulmonary arterial oxygen content.
- As a result of this, the left ventricular musculature is underperfused and underoxygenated.
- This is often accompanied by varying degrees of mitral insufficiency.



Three-dimensional image of patient. In this cranial view of the heart, the left coronary artery (LCA) can be seen to originate from the pulmonary artery (PA), a condition known as ALCAPA. The right coronary artery (RCA) has a normal origin from the right coronary cusp of the aorta (Ao) [de Jonge GJ, van Ooijen PMA, Piers LH, Dikkers R, Tio RA, Willems TP, van den Heuvel AFM, Zijlstra F, Oudkerk M. Visualization of anomalous coronary arteries on dual-source computed tomography. European Radiology. 2008 Nov;18(11):2425–32.] *Caption adapted from original*



Anomalous pulmonary origin of left main coronary artery (LMCA) from the main pulmonary artery (MPA) also known as ALCAPA or Bland–White–Garland syndrome. Panels (a) and (b) are multiplanar reformats demonstrating the takeoff of the LMCA from the MPA. Panels (c) and (d) illustrate the very large and tortuous right coronary artery (RCA), which provides oxygenated myocardial blood supply for the whole myocardium via an extensive collateral circulation to the branches of the left coronary circulation, and seen best in panel (c and d) and shown by the arrows. Note the flow of blood from the left coronary artery to the MPA. Aoasc ascending aorta, LA left atrium, LAA left atrial appendage, LAD left anterior descending artery, LCx left circumflex artery, LV left ventricle, RA right atrium, RV right ventricle, SVC superior vena cava [Mazur W, Siegel MJ, Miszalski-Jamka T, Pelberg R. Coronary Artery Anomalies. CT Atlas of Adult Congenital Heart Disease [Internet]. London: Springer London; 2013 [cited 2016 May 31]. p. 183–202. Available from: http://link.springer.com/10.1007/978-1-4471-5088-6_16] *Caption from original*

Presentation

Typical/"Classic"

Typical signs and symptoms of ALCAPA appear in the first two months of life and include:

- Abnormal heart rhythm
- Enlarged heart
- Heart murmur (rare)

- Rapid pulse
- Crying or sweating during feeding ("splanchnic steal")
- Pale skin
- Poor feeding, poor weight gain
- Rapid breathing
- Sweating
- Symptoms of pain or distress in the baby (often mistaken for colic)

Atypical

- Poor feeding and fussiness in infant, at first attributed to colic.
- Occasionally ALCAPA does not present until adolescence or early adulthood.

Primary Differential Considerations

- Dilated cardiomyopathy due to other causes, such as myocarditis, should be considered.

History and Physical Exam

Findings That Confirm Diagnosis

- The combination of respiratory distress, diaphoresis, and pallor, accompanied by ECG findings consistent with myocardial ischemia, will point the clinician toward making the diagnosis.
- Auscultation may demonstrate a systolic murmur consistent with mitral valve regurgitation.

http://www.easyauscultation.com/mitral-regurgitation

Mitral regurgitation audio. [Mitral Regurgitation Page; Easy Auscultation; www.easyauscultation.com/mitral-regurgitation; copyright 2015, MedEdu LLC]

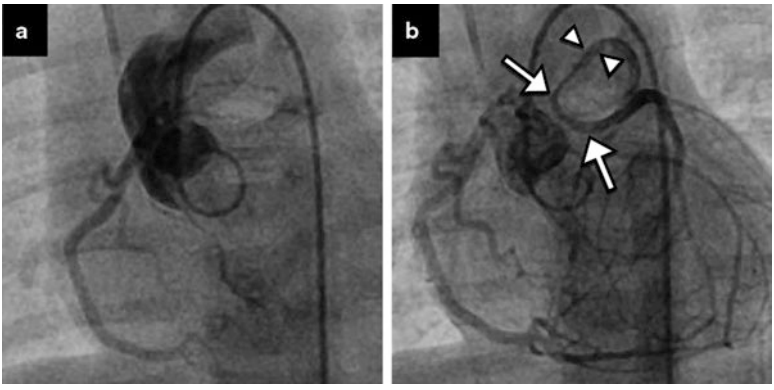
- In severe cases, signs of congestive heart failure (CHF) will be present, including tachycardia, tachypnea, gallop, poor perfusion, and signs of right sided failure (late).

Factors That Suggest Diagnosis

- ANY infant or child who presents with diaphoresis during feedings should be considered a candidate for a full cardiac workup.

Factors That Exclude Diagnosis

- ALCAPA cannot be excluded in symptomatic patients based on history and physical alone. Coronary angiography is required.

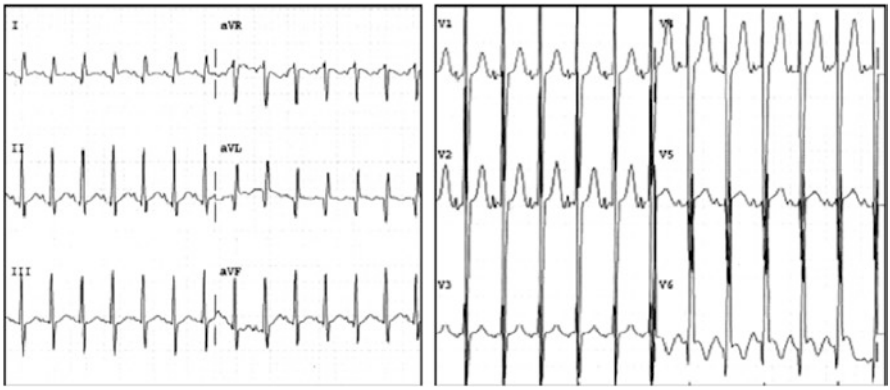


Still images (a, b) from the patient's digital subtraction angiogram (DSA). Injection of the aortic root demonstrates an enlarged and tortuous RCA with several epicardial collateral vessels; no sign of the LCA during early phase of injection (a). There is retrograde filling of the ALCAPA (arrows) (b) via multiple small collaterals from the right coronary system. There is retrograde flow of contrast through the ALCAPA and into the PA (arrowheads) [Day K, Avery R, Oliva I, Jokerst C. Coronary CTA appearance of anomalous left coronary artery arising from the pulmonary artery with Intramural Aortic Route. The International Journal of Cardiovascular Imaging. 2014 Feb;30(2):241–3.] Available from http://springerimages.com/Images/MedicineAndPublicHealth/1-10.1007_s10554-013-0334-3-1. *Caption from original*

Ancillary Studies

Electrocardiography

- In most cases, a pattern consistent with an anterolateral infarct with abnormal deep (>3 mm) and wide (>30 msec) q waves is observed in leads I, aVL, V_5, and V_6.



Typical electrocardiogram in anomalous left coronary artery arising from the pulmonary artery (ALCAPA) syndrome: Q waves in I and avL with prominent Q waves in V6 [Tissot C, da Cruz EM, Miyamoto S. Cardiac Failure. In: Munoz R, Morell V, Cruz E, Vetterly C, editors. Critical Care of Children with Heart Disease [Internet]. London: Springer London; 2009 [cited 2016 Jul 28]. p. 557–72. Available from: http://link.springer.com/10.1007/978-1-84882-262-7_49] *Caption from original*

Cardiac Enzymes

- Unfortunately, laboratory tests are not definitive.

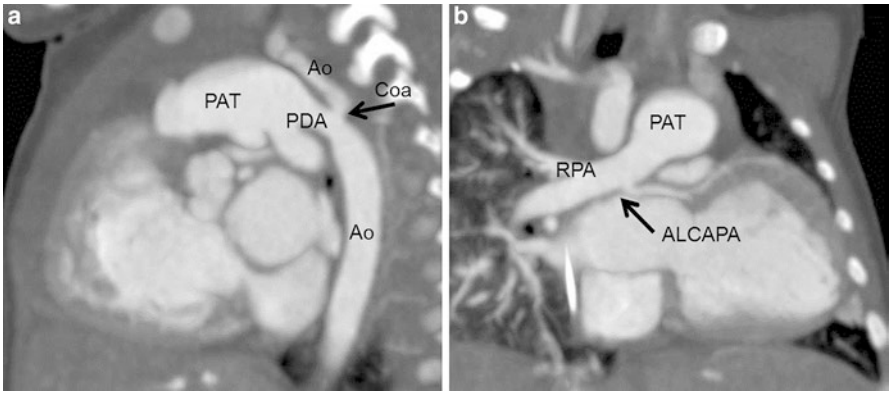
Special Populations

Age

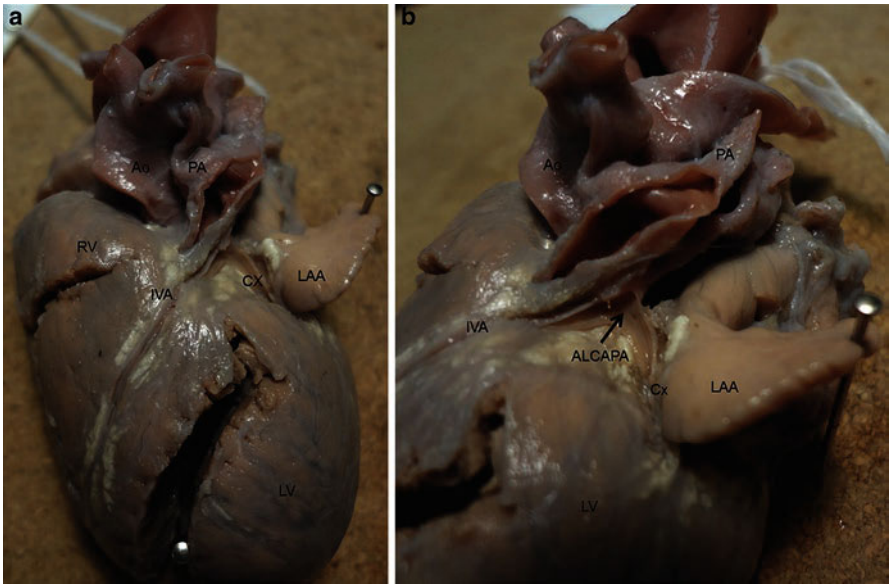
- ALCAPA is almost exclusively a pediatric disease, with only very rare presentations in adolescence or early adulthood.

Co-morbidities

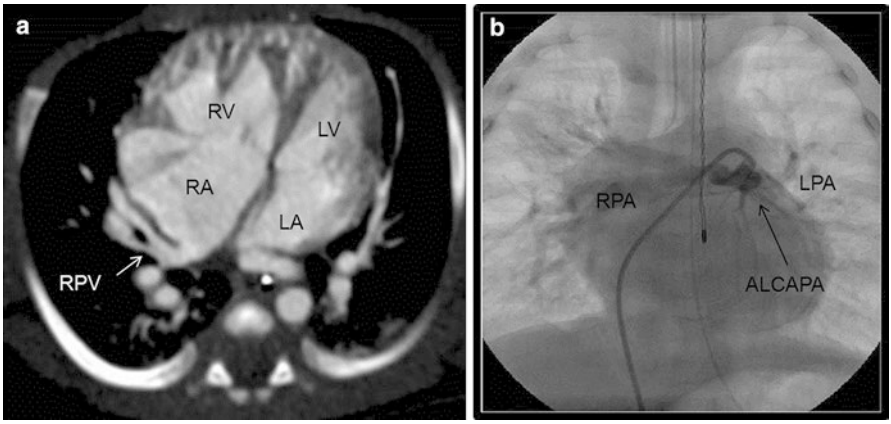
- ALCAPA may occur with other congenital malformations.
- When ALCAPA coexists with other congenital malformations, particularly those associated with pulmonary hypertension, the initial presentation can be quite confusing and is often misinterpreted.



Computer tomographic (CT) images of aortic coarctation and anomalous left coronary artery connected to the pulmonary artery (ALCAPA). a Sagittal CT image showing an aortic coarctation (CoA, black arrow) bypassed by a large persistent arterial duct (PDA). The horizontal aortic arch is hypoplastic. b Coronal CT image with the anomalous left coronary artery (ALCAPA, black arrow) connected to the right pulmonary artery (RPA), a rather rare anatomic variant. PAT pulmonary artery trunk [Laux D, Bertail C, Bajolle F, Houyel L, Boudjemline Y, Bonnet D. Anomalous Left Coronary Artery Connected to the Pulmonary Artery Associated With Other Cardiac Defects: A Difficult Joint Diagnosis. Pediatric Cardiology. 2014 Oct;35(7):1198–205.] Available from http://springerimages.com/Images/MedicineAndPublicHealth/1-10.1007_s00246-014-0916-4-0. *Caption adapted from original*



Macroscopic views of a heart with tetralogy of Fallot and pulmonary atresia associated with anomalous left coronary artery connected to the pulmonary artery (ALCAPA). **a** Frontal view of the heart in anatomic position with the apex to the left: The right (RV) and left (LV) ventricles have been opened, but the interior cannot be seen. The trunk of the pulmonary artery (PA) has been opened to confirm valvular atresia (not shown). The left coronary artery with its division in the infundibular anterior descending artery (IVA) and the circumflex (Cx) artery can be seen connecting to the PA. **b** A lateral, close-up view of the same heart with the opened ALCAPA and its two branches. LAA left atrial appendage, Ao aorta [Laux D, Bertail C, Bajolle F, Houyel L, Boudjemline Y, Bonnet D. Anomalous Left Coronary Artery Connected to the Pulmonary Artery Associated With Other Cardiac Defects: A Difficult Joint Diagnosis. Pediatric Cardiology. 2014 Oct;35(7):1198–205.] Available from http://springerimages.com/Images/MedicineAndPublicHealth/1-10.1007_s00246-014-0916-4-1. *Caption adapted from original*



Computed tomography (CT) scan and cardiac catheter image of patient 9 with divided left atrium, partial anomalous pulmonary venous connection, and anomalous left coronary artery connecting to the pulmonary artery (ALCAPA).**a** Four-chamber view of the patient's heart on an axial CT image: The right pulmonary veins (RPVs) connect to the right atrium (RA). **b** Left coronary artery abnormally connecting to the pulmonary trunk (ALCAPA, black arrow) in the same patient shown by anterograde injection of contrast agent into the pulmonary trunk during cardiac catheterization (frontal view). RV right ventricle, LA left atrium, LV left ventricle, RPA right pulmonary artery, LPA left pulmonary artery [Laux D, Bertail C, Bajolle F, Houyel L, Boudjemline Y, Bonnet D. Anomalous Left Coronary Artery Connected to the Pulmonary Artery Associated With Other Cardiac Defects: A Difficult Joint Diagnosis. Pediatric Cardiology. 2014 Oct;35(7):1198–205.] Available from http://springerimages.com/Images/MedicineAndPublicHealth/1-10.1007_s00246-014-0916-4-2. *Caption from original*

Pitfalls in Diagnosis

Critical Steps Not to Miss

- The most important step in making the diagnosis of ALCAPA is to accept the fact that there is a congenital anomaly that will present *exactly* like the adult form of ischemic heart disease.

Mimics

- As previously mentioned, the feeding difficulties in these infants will often be misinterpreted as colic or some form of dietary intolerance.

Time-Dependent Interventions

- Immediate consultation with a Pediatric Cardiologist is recommended
- Focus is on diagnosis, not treatment; time-dependent interventions are limited.

Overall Principles of Treatment

- In cases that present with CHF, supplemental oxygen is indicated.
- The use of diuretics may be beneficial, but should be applied *only* after consultation with a Pediatric Cardiologist.

Disease Course

- The prognosis is excellent if surgical correction is carried out.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Cohort Study

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Bland White Garland Syndrome"[Mesh] OR "ALCAPA" OR "Bland White Garland"

Chapter 7
Anxiety

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Anxiety, anxiety disorder, panic disorder, panic attacks

Incidence/Epidemiology

- Anxiety disorder is a very common psychiatric condition. It often manifests through physical symptoms; chest pain +/- dyspnea/hyperventilation +/- palpitations is a common presentation of anxiety disorder.
- There is no good estimate of the incidence of anxiety as a cause of chest pain that prompts medical evaluation.
- Around 25 % of individuals are thought to experience at least one panic attack in their lifetimes.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_7

Differential Diagnosis

- Presentation can be quite dramatic. The differential considerations for chest pain due to anxiety therefore include immediate life threats such as pulmonary embolism, acute coronary syndrome, and aortic dissection. Less severe differential considerations include pneumonia and pneumothorax, which can cause pleuritic pain; and chest wall pain.

Pathophysiology and Etiology

- Current thinking is that anxiety and panic result from an imbalance in CNS neurotransmitters.
- The diagnosis of anxiety as an etiology for chest pain that prompts medical evaluation should be made only after more serious causes have been evaluated and reasonably excluded.

Presentation

Typical/"Classic"

- The classic presentation of anxiety- or panic-related chest pain is:
  - Acute onset
  - Associated with dyspnea (the patient may confuse hyperventilation with dyspnea)
  - Associated with diaphoresis
  - Trembling or shaking
  - Fear of dying
  - Sense of loss of control
  - Nausea

Atypical

- Patients with anxiety or panic disorder may present with myriad complaints. Chest pain is common among these, but many other features may be present.

Primary Differential Considerations

- The differential diagnosis of acute anxiety is broad and includes both medical and psychiatric considerations.
- Medical:
  - Because acute anxiety may mimic acute somatic disease, one must consider such immediate life threats as acute myocardial infarction, aortic dissection, arrhythmias, pulmonary embolism, pneumothorax, or stroke.
  - Other concerns include hypo- and hyperglycemia, poisoning and drug abuse, delirium tremens, and encephalopathy.
- Psychiatric:
  - Acute anxiety may be confused with acute psychosis, conversion disorders, dissociative disorders, schizoaffective disorder, and Tourette's syndrome.

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination are not diagnostic for anxiety.

Factors That Suggest Diagnosis

- Symptoms are out of proportion with physical findings.
- Patient-reported dyspnea is found on exam to be hyperventilation.

Video overview of the causes and treatment of hyperventilation
https://www.youtube.com/watch?v=p97HeXx0vN0

- History of anxiety or panic disorder.
- Young age and/or lack of risk factors for more serious conditions.
- Choking sensation accompanying chest pain.
- Current substance abuse.

Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude anxiety as a cause of chest pain.

Ancillary Studies

Laboratory

- There are no diagnostic laboratory studies for anxiety.
- Laboratory tests target suspected underlying disease.

Imaging

- There are no diagnostic imaging studies for anxiety.

Special Populations

Age and Gender

- The epidemiology of anxiety and panic disorder does not indicate any consistent patterns by age or gender. It may begin at a young age.
- Anxiety disorders are the most common psychiatric disturbances in childhood, usually representing negative outcomes of naturally occurring fears associated with childhood development.
- The literature describes multiple forms of anxiety disorders in children, including social anxiety, agoraphobia, panic attacks, separation anxiety, and specific phobias.

Co-morbidities

- It is important to consider and evaluate for the presence of serious underlying disease or psychiatric stress that could prompt situation anxiety, such as:
  - Recent death of a loved one
  - Recent relationship stress
  - Recent diagnosis of serious disease
- Other psychiatric issues may be discovered upon questioning.
- Substance abuse issues may be discovered upon questioning.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Because there are differential considerations that are immediate life threats, evaluation for acute coronary syndrome, pulmonary embolism, and pneumonia should be considered early.

Mimics

- The entire constellation of diagnoses that underlies chest pain syndrome can mimic or cause the pain and overall presentation of anxiety.

Time-Dependent Interventions

- Other than excluding life threats, there are no time-dependent interventions for chest pain deemed due to anxiety or panic disorder.
- Patients who also express suicidal or homicidal ideation should be promptly evaluated in an emergency care setting.

Overall Principles of Treatment

- Treatment of the acute symptoms of chest pain caused by panic or anxiety disorder may include:
  - Reassurance and support
  - Benzodiazepines
  - Monitoring while the effects of acute substance abuse diminish

Disease Course

- The course of patients with anxiety or panic disorder may vary widely, from no further episodes to debilitating psychiatric illness that limits or precludes productive engagement with society.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Anxiety"[Mesh] OR "Anxiety"

Chapter 8
Aortic Regurgitation

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Aortic Regurgitation

- Aortic Insufficiency

Incidence/Epidemiology

- The most common causes of aortic regurgitation (AR) in the developed world are congenital bicuspid aortic valve and aortic root enlargement from diseases such as Marfan's syndrome.
- In the developing world, the most common cause of aortic regurgitation is rheumatic heart disease.
- The prevalence of aortic regurgitation increases with age, with about a 2 % prevalence of moderate to severe AR in men over 70, and about a 2.5 % prevalence of moderate to severe AR in women over 70.

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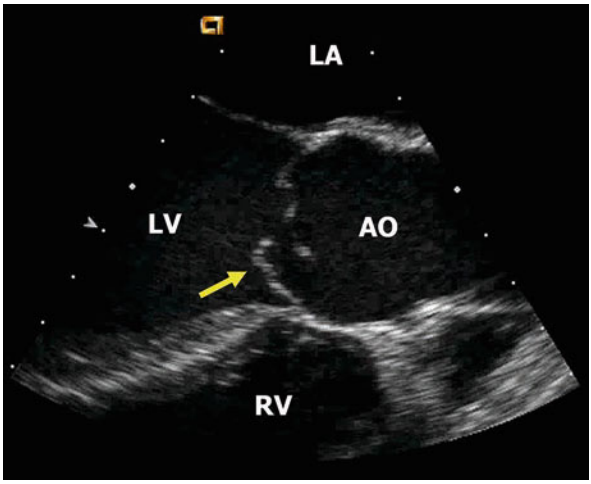
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_8

Differential Diagnosis

- The differential diagnosis of AR is broad, and includes all the pulmonary and cardiac causes of exertional dyspnea, such as myocardial ischemia, pulmonary edema/CHF, pulmonary embolism, and pneumonia.

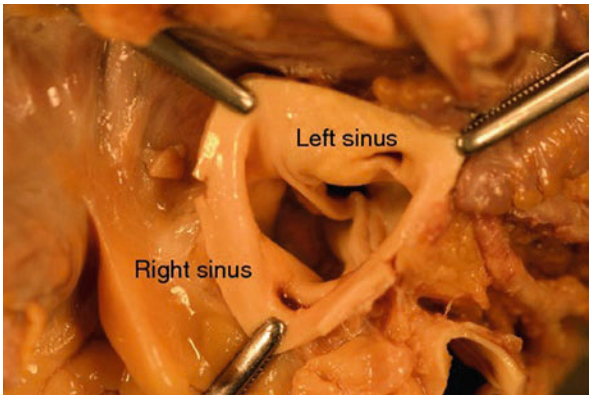
Pathophysiology and Etiology

Aortic valve from a patient with aortic insufficiency. The three-dimensional transesophageal echocardiogram demonstrates a tear in the right cusp (arrow). [Garcia M, Liu Z, Rakowski H. Chapter 4. In: Vannan M, Lang RM, Rakowski H, Tajik AJ. Atlas of echocardiography. Philadelphia: Current Medicine; 2005. (Braunwald E, editor. Atlas of heart diseases; vol. 16). ISBN: 1-57340-217-6, 2005-12-05] *Caption from original*



Aortic valve from a patient with aortic insufficiency. This transesophageal echocardiography image demonstrates a bicuspid valve with severe anterior cusp prolapse (arrow). Ao—aorta; LA—left atrium; LV—left ventricle; RV—right ventricle. [Garcia M, Liu Z, Rakowski H. Chapter 4. In: Vannan M, Lang RM, Rakowski H, Tajik AJ. Atlas of echocardiography. Philadelphia: Current Medicine; 2005. (Braunwald E, editor. Atlas of heart diseases; vol. 16). ISBN: 1-57340-217-6, 2005-12-05] *Caption from original*

- Aortic regurgitation may result from either primary aortic valvular disease or aortic root disease.
- Primary valve disease. There are multiple causes of primary valve disease that may result in aortic regurgitation. The final common pathophysiologic pathway involves some deformity/disease of the valve leaflets that prevents normal systolic opening and/or diastolic closure. Usually these processes cause fibrosis, scarring, and hypertrophy of the valve leaflets. The causes of primary valve disease include:
    - Rheumatic valve disease, which is usually associated with concomitant mitral valve disease.
    - Congenital bicuspid aortic valve, which more commonly results in aortic stenosis, but may also develop into aortic regurgitation.



Bicuspid aortic valve. The origin of the coronary arteries can be appreciated in each of the sinuses. BAV was found during autopsy of a 41-year-old male who died from ischaemic heart disease [Suárez-Mier MP, Morentin B, Cobo M, Castedo E, García-Pavía P. Pathology of the Heart Valves. In: Lucena JS, García-Pavía P, Suarez-Mier MP, Alonso-Pulpon LA, editors. Clinico-Pathological Atlas of Cardiovascular Diseases [Internet]. Cham: Springer International Publishing; 2015 [cited 2016 Apr 4]. p. 171–200. Available from: http://link.springer.com/10.1007/978-3-319-11146-9_7] *Caption from original*

- Membranous, subaortic stenosis
- Infective endocarditis
- Syphilis
- Ankylosing spondylitis
- Ventricular septal defect
- Non-penetrating chest trauma
- Prior use of fenfluramine-phentermine

- Primary aortic root disease. Aortic root disease occurs with any process that causes widening and dilatation of the aortic root. This causes separation of the aortic valve leaflets and prevents normal opening and closing of the valve. Aortic root disease may result from:
  - Marfan's disease
  - Idiopathic
  - Annuloaortic ectasia
  - Osteogenesis imperfecta
  - Severe hypertension
  - Retrograde dissection of the aorta to the aortic root
  - Syphilitic aortitis
  - Ankylosing spondylitis

- Hemodynamic consequences. When the aortic valve does not close completely during diastole, regurgitant blood will flow back from the aorta into the left ventricle. This increases the total stroke volume of the left ventricle because in addition to normal blood flow from the left atrium, regurgitant blood flow from the aorta also fills the left ventricle during diastole. This results in an increased left ventricular end diastolic volume (LVEDV), or increased preload. Initially, the heart compensates for the volume increase with left ventricular (LV) dilatation and subsequent hypertrophy, maintaining a near-normal cardiac output and blood pressure. Eventually, however, the left ventricle can no longer dilate or hypertrophy any further, and the end-diastolic volume continues to increase, leading then to a decrease in stroke volume and forward flow. Initially, these changes manifest as exertional dyspnea and fatigue, as the cardiac output can be maintained during rest but not with exertion. These processes may take many years to develop, and there is generally a long asymptomatic period. It may take 15–20 years for symptoms to develop. This is typical, chronic aortic regurgitation.
- In some cases (especially with endocarditis, dissection, trauma) significant aortic regurgitation may develop acutely. In this situation, the left ventricle cannot handle the massive increase in LVEDV to sufficiently maintain stroke volume, and pulmonary edema or cardiogenic shock develops quickly.

Presentation

Typical/"Classic"

- Aortic regurgitation is generally a chronic, slowly progressive disease and may be asymptomatic for many (typically 15–20) years.
- Early complaints are somewhat nonspecific but may include:
- An unusual awareness of the heart beating, especially when lying down and on the left side. In these positions, the left ventricle becomes closer to the chest wall.
    - Persistent sinus tachycardia.
    - Palpitations with frequent ectopy. Ectopic beats may become even more uncomfortable than usual, as there is even more LV filling during the compensatory pause, so the eventual beat feels even "stronger" than usual.
    - Noticing that the head "bobs" with the heart beat when sitting quietly.
    - Chest pain, either exertional or nocturnal, often accompanied by severe diaphoresis and not significantly alleviated by sublingual nitroglycerin.
- The typical presentation is one of slowly worsening exertional dyspnea, associated with the typical diastolic murmur of aortic regurgitation. Often, the diastolic murmur is the first manifestation appreciated on routine examination, which then leads to the diagnosis.

Atypical

- The atypical presentation of aortic regurgitation is the acute presentation of pulmonary edema or cardiogenic shock.

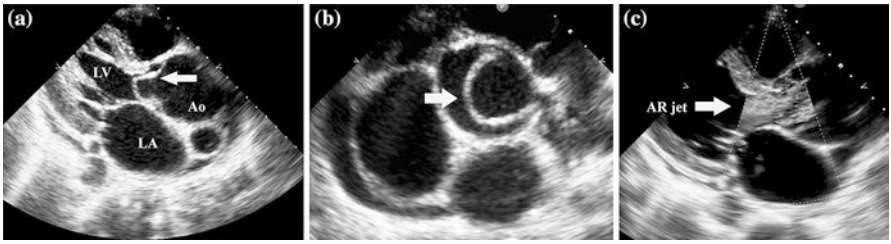
Primary Differential Considerations

- The differential diagnosis of AR is basically limited to other valve disorders, acute coronary syndrome, very proximal aortic dissection, and infective endocarditis.

History and Physical Exam

Findings That Confirm Diagnosis

- A consistent history and physical examination should be confirmed with a transthoracic echocardiogram.

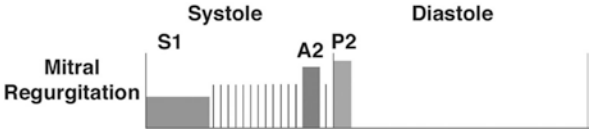


Transthoracic echocardiogram a parasternal long-axis view showing the dissection flap prolapsing into the LVOT (arrow), b parasternal short axis view showing a circular dissection flap (arrow) and c colour Doppler image showing severe aortic regurgitation (arrow). LVOT left ventricular outflow tract, LV left ventricle, LA left atria, Ao aorta, AR aortic regurgitation [Rajesh GN, Sajeer K, Anishkumar N, Sajeev CG, Krishnan MN. Intimo-intimal intussusception–circumferential aortic dissection: a rare mechanism of severe acute aortic regurgitation. Journal of Echocardiography. 2014 Sep;12(3):118–9.] *Caption from original*

Factors That Suggest Diagnosis

- Auscultatory findings.
  - Typical auscultatory findings can strongly suggest the diagnosis of aortic regurgitation.
  - The aortic closure sound (A2) may be soft or absent.
  - The classic murmur of chronic aortic regurgitation is a blowing, high-pitched, decrescendo, diastolic murmur, heard best in the third intercostal space along the left sternal border with the patient sitting up, leaning forward, at end expiration. There is little correlation between the intensity of the murmur and the degree of regurgitation. However, as the degree of regurgitation becomes greater, the duration of the murmur will increase and eventually become holosystolic. The murmur is usually accentuated by maneuvers that increase systemic vascular resistance, such as sustained handgrip, and squatting. The murmur decreases with Valsalva maneuver.

http://www.easyauscultation.com/cases-listing-details?caseID=124
The classic murmur of chronic aortic regurgitation. [Aortic Regurgitation (Decrescendo Diastolic Murmur); Easy Auscultation; www.easyauscultation.com; copyright 2014, MedEdu LLC]



Caused by an insufficiency of the mitral valve, the mitral regurgitation murmur is a systolic murmur best heard over the mitral auscultation area. A2 = aortic valve closure; P2 = pulmonic valve closure; S1 = first heart sound [Bojanov G. Blood Pressure, Heart Tones, and Diagnoses. In: Iaizzo PA, editor. Handbook of Cardiac Anatomy, Physiology, and Devices [Internet]. Totowa, NJ: Humana Press; 2009 [cited 2016 Apr 4]. p. 243–55. Available from: http://link.springer.com/10.1007/978-1-60327-372-5_16] *Caption from original*

- There is often an associated midsystolic ejection murmur, heard best at the base of the heart, that radiates into the carotids.
- The Austin Flint murmur is sometimes heard in severe, chronic AR. It is a soft-pitched, rumbling, mid- to late diastolic murmur, heard best at the apex. It is caused by turbulence from the interaction of the usual antegrade blood flow from the left atrium and the retrograde flow from the aorta. This turbulence may result in displacement of the mitral valve leaflets.

https://www.youtube.com/watch?v=y5CcncRHl38
Video of the Austin Flint murmur.

- Acute AR is associated with a softening of S1 due to the early closure of the mitral valve from the acutely increased LV end-diastolic volume. Often a soft, short, early diastolic murmur also is present.

- Many physical examination findings are associated with chronic, severe AR:
  - Widened pulse pressure. AR is often associated with systolic hypertension and a low diastolic pressure. A clue to disease progression is diastolic blood pressure that seems to increase over time, a result of the worsening regurgitant flow leading to increased end-diastolic volume. As the diastolic pressure approaches the LVEDV, they will eventually become equal and then rise, as the diastolic pressure cannot be below the LVEDV.
  - de Musset's sign: head bobbing with the heartbeat.
  - Corrigan (water hammer) pulse. The pulse is palpated with a forceful, rapid rise, and then quickly dissipates.

https://www.youtube.com/watch?v=OR19BOodAVI
Video demonstrating Corrigan's pulse in aortic regurgitation.

  - Quincke's pulse (capillary pulsations). While holding pressure at the tip of the nail, one can see pulsations of the skin at the nail bed; may also be seen at the lips.

https://www.youtube.com/watch?v=9m_0RAQDFHM
Video demonstrating Quincke's pulse

  - Traube's sign. A "pistol-shot" sound heard over the femoral artery.
  - Duroziez's sign. A back-and-forth bruit heard over the femoral artery after light compression with the head of the stethoscope.

Factors That Exclude Diagnosis

- A normal echocardiogram excludes aortic regurgitation.

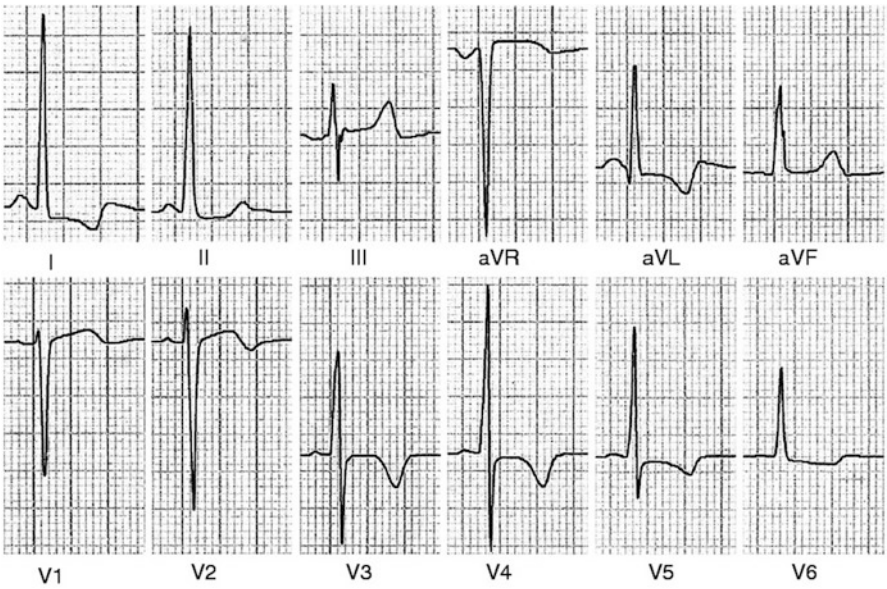
Ancillary Studies

Laboratory

- Lab tests for patients with these nonspecific but questionably cardiac complaints should include a CBC, complete metabolic panel, cardiac biomarkers, and a B-type natriuretic peptide.

Electrocardiography

- The ECG in chronic, severe aortic regurgitation often shows LV hypertrophy with an associated strain pattern. This is usually seen as large-voltage QRS complexes with ST depression and T-wave inversions in the inferolateral leads.

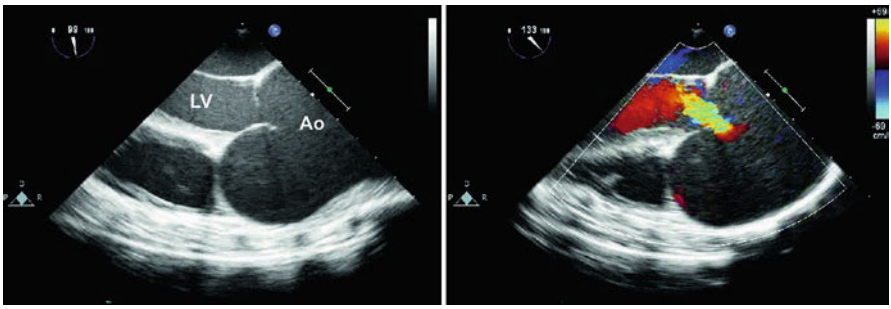


Electrocardiograph (ECG) in a patient with hypertrophic cardiomyopathy (HCM) showing left ventricular (LV) hypertrophy and T-wave inversion [Merlo M, Cocciolo A, Brun F, Sinagra G. Hypertrophic Cardiomyopathy: Clinical Assessment and Differential Diagnosis. In: Pinamonti B, Sinagra G, editors. Clinical Echocardiography and Other Imaging Techniques in Cardiomyopathies [Internet]. Cham: Springer International Publishing; 2014 [cited 2016 Apr 4]. p. 85–94. Available from: http://link.springer.com/10.1007/978-3-319-06019-4_9] *Caption from original*

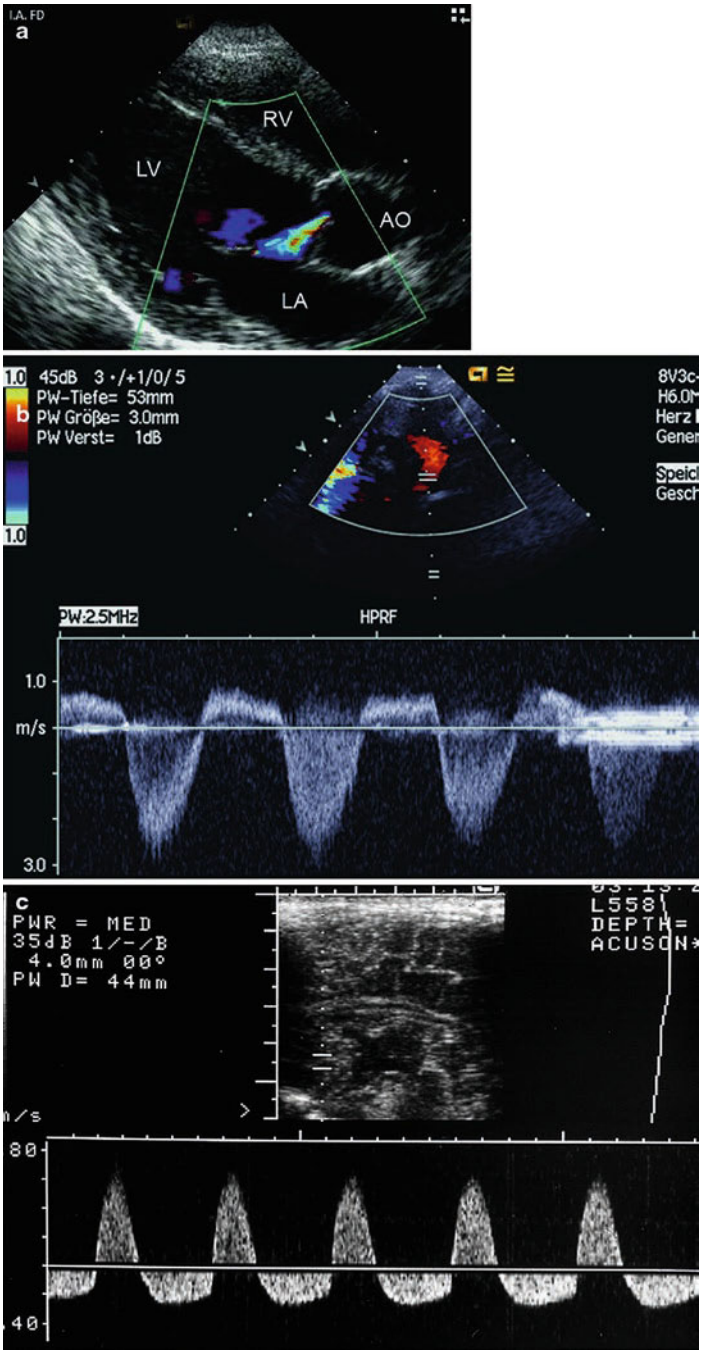
Imaging

- A transthoracic echocardiogram is the diagnostic study of choice in the diagnosis and evaluation of aortic regurgitation. It can document the presence of aortic regurgitation, quantify the regurgitant flow, and define the cause of aortic regurgitation.
- A chest x-ray may be normal, but also may show cardiomegaly associated with LV hypertrophy. In acute aortic regurgitation, the chest x-ray may be consistent with pulmonary edema.

- Cardiac catheterization and angiography may be useful if all other imaging modalities (echo, cardiac MRI) are inconclusive, as well as for preoperative evaluation of aortic regurgitation. Before valve replacement surgery, coronary angiography is often performed to evaluate for concurrent coronary artery disease.



Markedly dilated aortic root as seen from the mid esophageal aortic valve long axis view without color mapping (left panel) and with color mapping, showing central aortic regurgitation (right panel). Ao aorta, LV left ventricle [Lopez L, Ventura R, Choueiter NF. Outflow Tract Anomalies. In: Wong PC, Miller-Hance WC, editors. Transesophageal Echocardiography for Congenital Heart Disease. London: Springer-Verlag London; 2014. p. 283-305. https://doi.org/10.1007/978-1-84800-064-3_11] *Caption from original*



(a) Colour flow imaging of aortic insufficiency. Diastolic flow in the left ventricular outflow tract shown in the parasternal long axis view. The picture shows mild

diastolic backflow from the aorta into the left ventricular outflow tract. AO aorta, LA left atrium, LV left ventricle, RV right ventricle. (b) Flow measurement in the aortic arch in severe aortic regurgitation. Colour Doppler shows retrograde flow in the aortic arch which is displayed red. Pulsed Doppler shows diastolic backflow displayed above the baseline. (c) Flow measurement in the anterior cerebral artery in a patient with severe aortic regurgitation. Diastolic backflow caused by severe aortic regurgitation [Deeg K-H. Cardiovascular Diseases Which Influence the Flow in the Extracardial Arteries. In: Deeg K-H, Rupprecht T, Hofbeck M, authors. Doppler Sonography in Infancy and Childhood [Internet]. Cham: Springer International Publishing; 2015 [cited 2016 Apr 4]. p. 679–730. Available from: http://link.springer.com/10.1007/978-3-319-03506-2_15] *Caption from original*

Special Populations

Age

- Aortic regurgitation is more common in middle-aged and older adults, especially because the latent period before the appearance of symptoms may be two decades.
- Aortic regurgitation may be seen in children, in whom it is usually associated with either severe aortic stenosis or a ventricular septal defect. Most cases in children are mild and asymptomatic, and need only be followed with serial exams and echocardiography.

Co-morbidities

- Aortic regurgitation may be diagnosed in relatively healthy patients but also may present in the setting of numerous other cardiovascular diseases and risks.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. In patients with hemodynamic compromise, an echocardiogram should be performed early to assess all hemodynamic parameters and determine the need for urgent operative intervention.

Mimics

- The entire constellation of diagnoses that underlies dyspnea, chest pain, and other valvular diseases can mimic the presentation of aortic regurgitation.

Time-Dependent Interventions

- Time-dependent interventions in aortic regurgitation are necessary only when acute aortic regurgitation is considered and cardiac and pulmonary function is compromised. In such patients, urgent valve replacement may be a lifesaving procedure.
- For chronic aortic regurgitation, there must be a well-planned and considered approach to operative intervention.

Overall Principles of Treatment

- Acute aortic regurgitation.
  - In acute aortic regurgitation, urgent valve replacement is indicated. Intravenous diuretics and vasodilators (such as sodium nitroprusside) may be helpful as a bridge to surgery.
  - In acute aortic regurgitation, intra-aortic balloon counterpulsation (IABP) is contraindicated, as it may worsen the regurgitation. Intravenous beta-blockers are relatively contraindicated, as they may decrease cardiac output even further.
- Chronic aortic regurgitation.
  - All patients diagnosed with aortic regurgitation, even those who are asymptomatic, must have their systolic blood pressure controlled. Aortic regurgitation is often associated with difficult-to-control systolic hypertension due to increased stroke volume. The goal should be less than 140 mm Hg. Most patients may benefit from vasodilator therapy with ACE inhibitors, dihydropyridine calcium channel blockers, or hydralazine.
  - Patients with early symptoms and mild dyspnea often also benefit from the addition of a diuretic.
  - Surgery with aortic valve replacement is indicated for all symptomatic patients with chronic aortic regurgitation.
  - The optimal time for surgery seems to be after the onset of LV dysfunction but before the development of symptoms. It is important to remember that patients with chronic AR do not become symptomatic until after LV dysfunction develops.

- Appropriately timed surgery often may restore normal LV function. However, surgery delayed for more than 1 year after the onset of LV dysfunction or symptoms often fails to restore normal LV function.
- If there are no indications for surgery, it is generally recommended that the patient be followed up with exams and echocardiograms every 3–6 months.
- Indications for operation in the asymptomatic patient include:
  - An LV ejection fraction <50 %
  - An LV end-systolic dimension < 55 mm or an end-diastolic dimension <75 mm
  - A regurgitant fraction ≥50 %
  - A regurgitant volume ≥ 60 mL

Disease Course

- Patients with AR may remain asymptomatic for decades, but many patients eventually require valve replacement surgery.
- Overall operative mortality is 3 %, but in the presence of prolonged LV dysfunction, mortality approaches 10 % and is then also associated with a late mortality approaching 5 % per year from LV failure.

Related Evidence

Papers of particular interest have been highlighted as:
** *Of key importance*

Practice Guideline

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; ACC/AHA Task Force Members. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 10;129(23):e521-643. https://doi.org/10.1161/CIR.0000000000000031. PMID: 24589853. http://www.ncbi.nlm.nih.gov/pubmed/24589853 **

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Enriquez-Sarano M, Tajik AJ. Clinical practice. Aortic regurgitation. N Engl J Med. 2004 Oct 7;351(15):1539-46. PMID: 15470217. http://www.ncbi.nlm.nih.gov/pubmed/15470217 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Aortic Valve Insufficiency"[Mesh] OR "Aortic Regurgitation"

Chapter 9
Aortic Stenosis

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Aortic stenosis

Incidence/Epidemiology

The frequency of the causes of aortic valve disease varies geographically:

- Worldwide, rheumatic valve disease is the most common cause of aortic stenosis
- In North America, calcified disease is the primary cause of aortic stenosis

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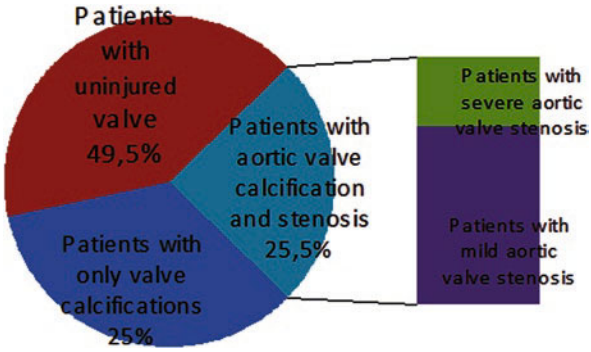
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_9

Differential Diagnosis

- The main issue to recognize is that the symptoms may be attributed to other disease processes, and aortic stenosis can be missed in the acute setting
- Other diagnostic considerations include supravalvular aortic stenosis, congenital subvalvular aortic stenosis, and hypertrophic obstructive cardiomyopathy.

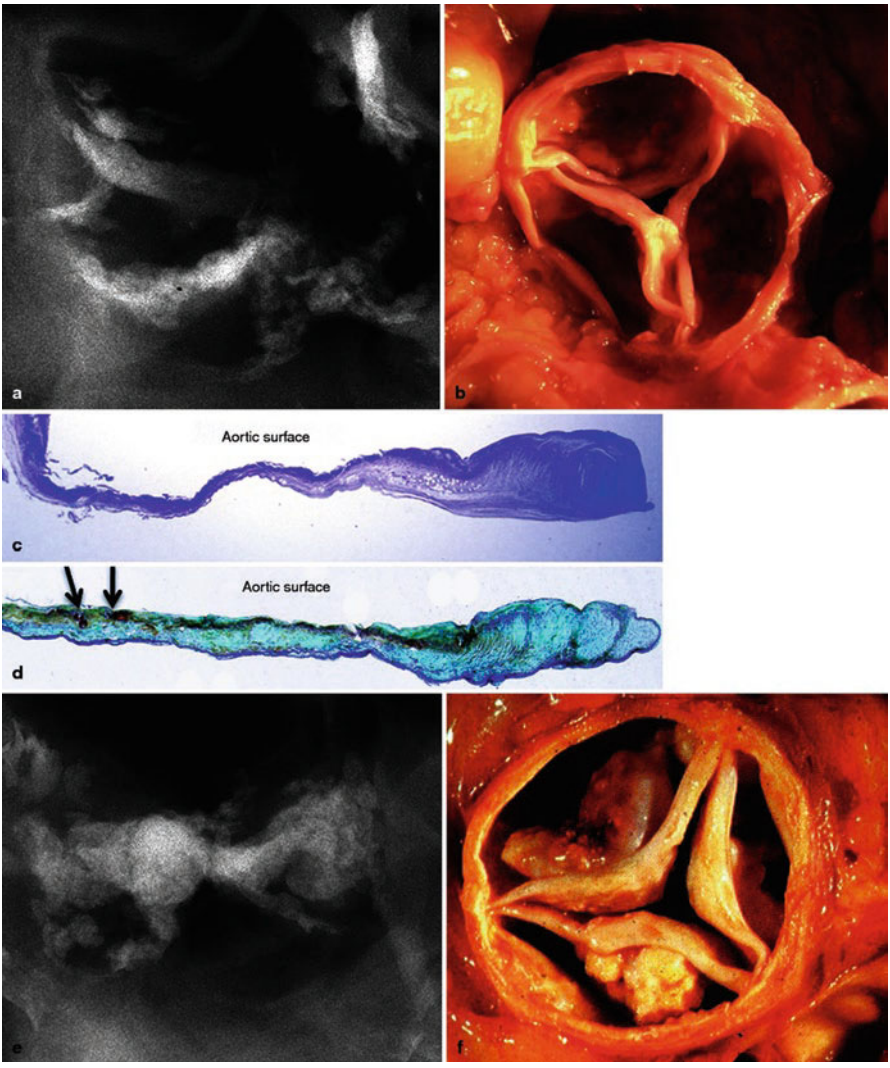
Pathophysiology and Etiology

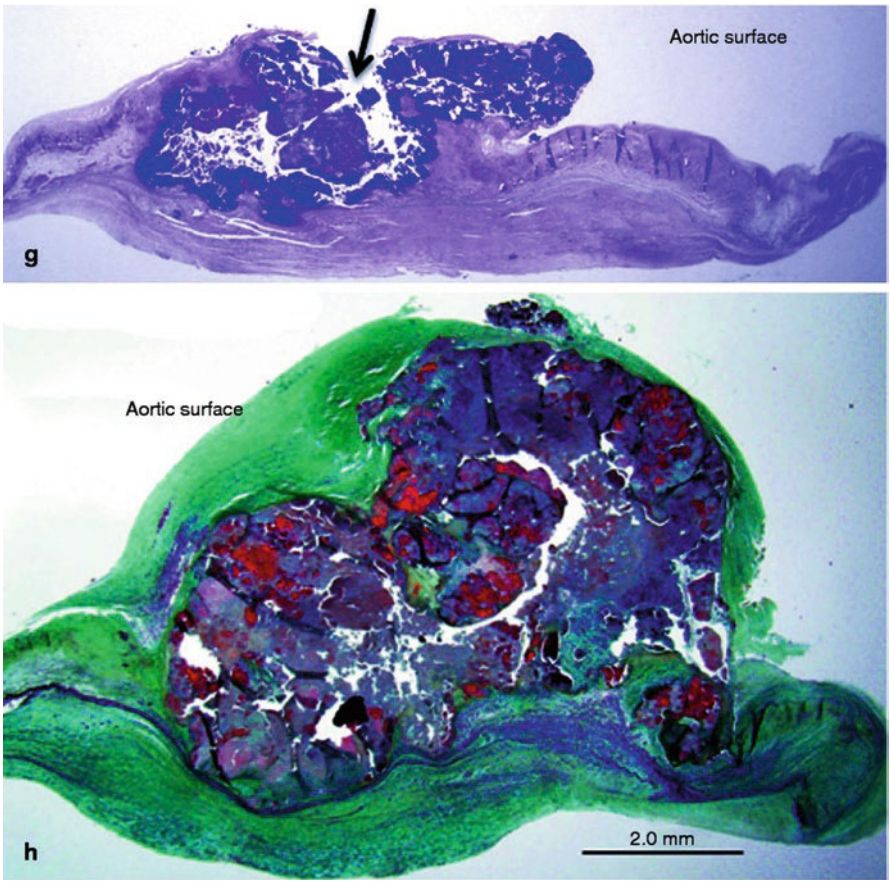
- Three primary causes of aortic stenosis:
  - Congenital (unicuspid/bicuspid valve) with superimposed calcification
  - Calcified disease of a trileaflet aortic valve
  - Rheumatic valve



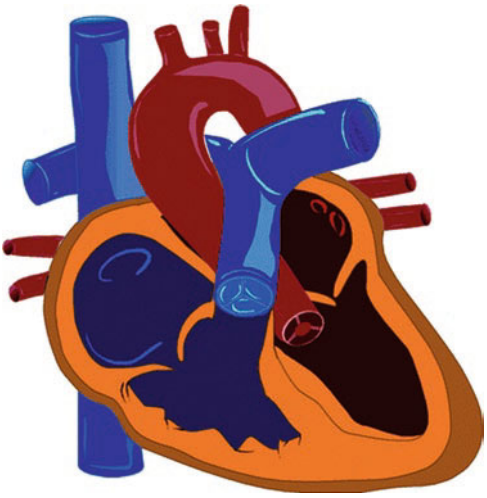
Distribution of population according to aortic valve degeneration. Patients with uninjured valve 49.5 %. Patients with aortic valve calcification and stenosis 25.5 %. Patients with only valve calcifications 25 %. [Fazio G, Caracciolo C, Barone R, D'angelo L, Di Maggio R, Vernuccio F, Siragusa S. An unknown cause of aortic valve stenosis: polycythemia vera. Journal of Thrombosis and Thrombolysis. 2013 Feb;35(2):282–5.] *Caption from original*

- Pathophysiology differs depending on the cause:
  - Calcified disease occurs when lipid accumulation triggers an inflammatory response by various mediators. There is local production of protein that promotes tissue calcification. Aortic stenosis occurs when the antegrade velocity across an abnormal valve is at least 2.6 m/sec.
  - Rheumatic valve disease causes fusion of the commissures between the leaflets leaving a small central opening.

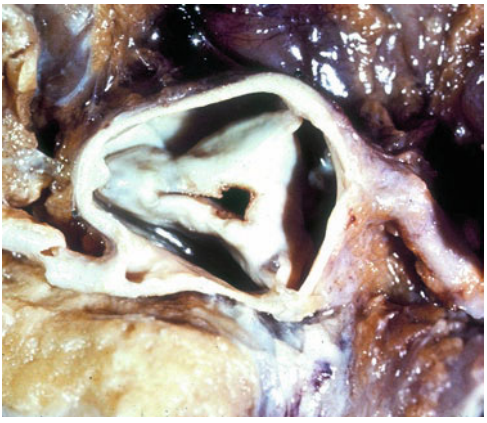




Two aortic valves seen at autopsy showing progression of calcific aortic stenosis. (a, b) Radiograph and gross image of aortic valve from an 83-year-old female. This valve shows mild calcification with small calcific deposits on aortic surface of cusps and sparing of the free edge. (c, d) Histologic sections of cusps showing fibrotic thickening and microscopic calcific deposits in the zona fibrosa (arrows). (e, f). Radiograph and gross image of stenotic aortic valve from an 82-year-old female. There is marked nodular calcification of the cusps with bulky deposits on the aortic surface. (g, h) Histologic sections of the cusps show calcific nodules superimposed on a fibrotic cusp with ulceration of the aortic surface (arrow). Note fibrotic thickening of the ventricular surface [Ladich E, Nakano M, Virmani R. Pathologic Findings in Aortic Stenosis. In: Min JK, Berman DS, Leipsic J, editors. Multimodality Imaging for Transcatheter Aortic Valve Replacement [Internet]. London: Springer London; 2014 [cited 2015 Aug 27]. p. 145–56. Available from: http://link.springer.com/10.1007/978-1-4471-2798-7_11] *Caption from original*



Aortic stenosis (AS). The aortic valve orifice is small; this may be a result of thickening of valve cusps, adhesion of cusp edges rendering separation between cusps during systole limited and/or due to small valve annulus [Holmes KW, McCarville MA. Aortic Stenosis. In: Abdulla R, editor. Heart Diseases in Children [Internet]. Boston, MA: Springer US; 2011 [cited 2015 Aug 27]. p. 149–58. Available from: http://link.springer.com/10.1007/978-1-4419-7994-0_11] *Caption from original*



Rheumatic heart disease: aortic stenosis. In this aortic valve, there is diffuse fibrosis of the three cusps and fusion of the three commissures, producing a narrow central orifice [Buja LM, Cheong B. Cardiovascular Pathology. In: Krueger GRF, Buja LM, editors. Atlas of Anatomic Pathology with Imaging [Internet]. London: Springer London; 2013 [cited 2015 Aug 27]. p. 43–104. Available from: http://link.springer.com/10.1007/978-1-4471-2846-5_2] *Caption from original*

Presentation

Typical/"Classic"

- Typically asymptomatic for a prolonged period of time. There is a wide degree of outflow obstruction that causes symptoms. On average, symptoms develop once the aortic valve area is < 1.0 cm^2. The typical symptoms are heart failure, syncope, and angina, but they reflect late disease.
- In earlier disease dyspnea on exertion, decreased exercise tolerance, dizziness, and exertional angina are more common findings.

Atypical

- Aortic stenosis can manifest as sudden cardiac death, atrial fibrillation, or endocarditis.

Primary Differential Considerations

History and Physical Exam

Findings that Confirm Diagnosis

- There is no single or combination of findings that is sensitive or specific enough to confirm the diagnosis of aortic stenosis.

Factors that Suggest Diagnosis

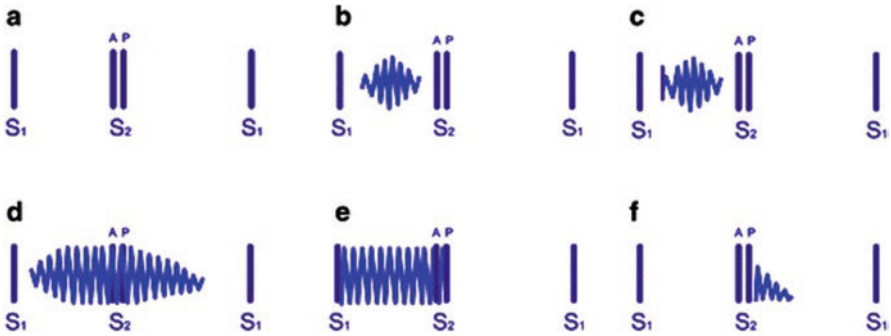
- The quality of the arterial pulse reflects degrees of obstruction. This is often described as "parvus and tardus," meaning the pulse is weak and increases slowly.
- There is a harsh systolic ejection murmur heard best at the second intercostal space on the right. The murmur can be transmitted to the carotid arteries.

http://www.easyauscultation.com/cases?coursecaseorder=11&courseid=31

Aortic Stenosis (Diamond Shaped Systolic Murmur). [Aortic Stenosis (Diamond Shaped Systolic Murmur); Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- The S2 heart sound can be paradoxically split with severe stenosis, and the S2 heart sound is soft.

http://www.easyauscultation.com/cases?coursecaseorder=3&courseid=31
Second Heart Sound – Splitting**.** [Second Heart Sound – Splitting; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]



Heart sounds and murmurs. (a) Normal heart sounds: once the ventricles start to contract at the onset of systole, the tricuspid and mitral valves close. Closure of the atrioventricular valves contributes to the first heart sound which tends to be single. Aortic and pulmonary valves open soon after S1; however, this is usually inaudible in the normal heart. Flow across the aortic and pulmonary valves follows, which is again usually inaudible in the normal heart. The aortic valve closes first, followed by the pulmonary valve; the delay in closure of the pulmonary valve gives the "splitting" character of the second heart sound. Diastole, similar to systole is quiet; during diastole, blood flows through the tricuspid and mitral valves into the right and left ventricles. (b) Systolic flow murmur: increased blood flow across the pulmonary or aortic valve causes turbulence of blood flow which produces a systolic flow murmur heard over the left or right upper sternal border, respectively. In atrial septal defect, increased blood flow across the pulmonary valve causes a systolic ejection murmur along the left upper sternal border. Severe anemia with increase in blood volume to compensate for decreased oxygen-carrying capacity causes turbulence of blood flow and consequently a murmur across both aortic and pulmonary valves. These murmurs are distinguished from those caused by stenosis of the pulmonary or aortic valves by lack of a systolic ejection click heard just before the systolic murmurs. (c) Pulmonary or aortic valve stenosis: flow across the pulmonary and aortic valves occurs during midsystole; therefore, pulmonary or aortic stenosis produces a systolic ejection murmur preceded by a systolic ejection click. These murmurs are loudest over the right upper sternal borders in aortic stenosis and the left upper sternal border in pulmonary stenosis. The systolic ejection click is caused

by the snap sound of opening of abnormal pulmonary or aortic valves. (d) Continuous murmur: a murmur heard over systole and most of diastole reflects abnormal shunting across a vascular structure connecting the systemic to pulmonary circulations, such as with patent ductus arteriosus. Murmur caused by PDA may be restricted to systole in children due to the soft and inaudible flow during diastole. (e) Early diastolic murmur: during early diastole, blood in the proximal portions of the pulmonary artery and aorta eject to the pulmonary and systemic circulations, respectively. Backward flow of blood into the right or left ventricles due to valve regurgitation will cause an early diastolic murmur. Aortic regurgitation is best heard over the mid or left sternal region. Pulmonary regurgitation is typically inaudible due to low pressures in the right heart and if heard may indicate pulmonary hypertension. (f) Mid-diastolic murmur: during mid-diastole blood flows from the atria to the respective ventricles. Excessive blood flow across the tricuspid valve, such as with atrial septal defect, or across the mitral valve such as with patent ductus arteriosus will cause a mid-diastolic murmur heard over the left lower sternal border in patients with atrial septal defect and at the apex in patients with patent ductus arteriosus [Thompson WR, Mehrotra SM. Cardiac History and Physical Examination. In: Abdulla R, editor. Heart Diseases in Children [Internet]. Boston, MA: Springer US; 2011 [cited 2015 Aug 27]. p. 3–16. Available from: http://link.springer.com/10.1007/978-1-4419-7994-0_1] *Caption from original*

	Severity of AS		
	Mild	Moderate	Severe
Arterial pulse	Normal	Slowly rising	Parvus et tardus
Jugular venous pulse	Normal	Normal	Usually normal
Carotid thrill	±	±	±
Cardiac impulse	Normal	Heaving	Heaving, sustained
Precordial thrill	±	±	Palpable *a* wave
			Usually ++
Auscultation			
S_4	–	±	++
ESC	+	±	–
Peak of ESM	Early systole	Mid systole	Late systole
S_2	Normal	Normal or single	Single or paradoxic

Physical examination for aortic stenosis. The findings on physical examination in patients with mild aortic stenosis (AS) are an ejection systolic click (ESC) and ejection systolic murmur (ESM) that peak in early systole. The ESC may be absent if the valve is calcified or is rigid. These patients may have a carotid or precordial

thrill. Patients with severe AS display characteristic physical findings. The arterial pulse, which is best felt over the carotid or the suprasternal notch, shows a slowly rising pulse that takes longer to reach peak (parvus et tardus) (see). The jugular venous pulse is normal and a carotid thrill may be present. The cardiac impulse is left ventricular (LV) in type; it is heaving and sustained. Often a powerful presystolic wave (a wave) is felt. A precordial systolic thrill is often present. On auscultation, there is an S4gallop, the ESC is absent, the ESM peaks in late systole, and the S2 is single. S2 is at times paradoxic, but this usually occurs in the presence of associated left bundle branch block or LV failure. In addition, there is usually a faint diastolic murmur of minimal aortic regurgitation. In the presence of congestive heart failure, the jugular venous pressure is often increased, the LV is dilated, there is an S3, and the ESM may be very soft or absent. Frequently, a holosystolic murmur of mitral regurgitation is present. The findings on physical examination resemble those of heart failure from a variety of causes, eg, a cardiomyopathy, rather than AS. The physical findings in moderate AS are between those seen in mild and severe AS. [Rahimtoola S. Chapter 06. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. ISBN: 1-878132-30-X] *Caption from original*

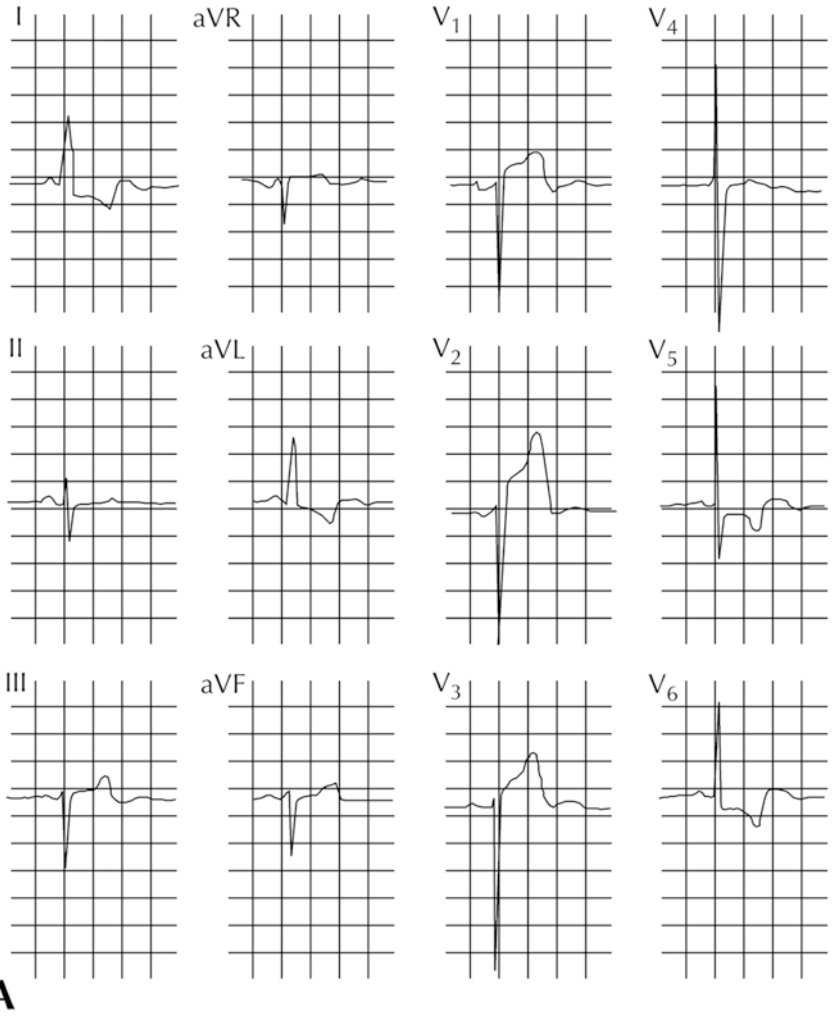
Factors that Exclude Diagnosis

- The presence of a normal split S2 heart sound most reliably excludes **severe** aortic stenosis in adults.

Ancillary Studies

Electrocardiography

- May see left ventricular hypertrophy, increased QRS voltage, ST-T wave changes that reflect subendocardial ischemia and left atrial hypertrophy. Atrial fibrillation is common in adults with aortic stenosis.



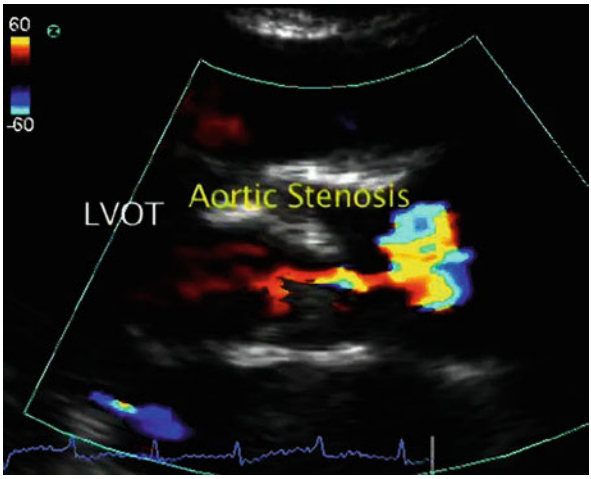
Electrocardiographic data in aortic stenosis. Electrocardiograph (ECG), chest radiographic, left ventricular (LV) and ascending aorta pressure pulses, LV diastolic pulmonary artery wedge (PAW) pressure pulses, and hemodynamic-LV function data. This 61-year-old man had recent onset of symptoms of mild shortness of breath on exertion. A, The ECG shows voltage criteria for LV hypertrophy and ST depression with T-wave inversion in leads I, aVL, V5, and V6. ECG standardization is 1 mV=10 mm. [Rahimtoola S. Chapter 06. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. ISBN: 1-878132-30-X] *Caption adapted from original*

Imaging

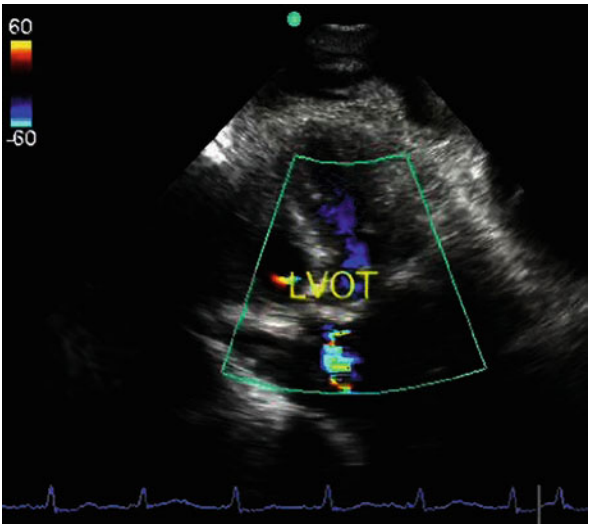
- Chest radiography is usually normal.However, a rounding of the left ventricular apex may be seen, suggesting left ventricular hypertrophy or the calcification of the aortic leaflets and aortic root, but this is a rare finding

Chest radiographic diagnosis of aortic stenosis. Chest radiography (posteroanterior view) shows an increased heart size (cardiothoracic ratio, 0.53) and normal pulmonary vasculature. The cardiac silhouette is typical for LV hypertrophy associated with severe AS. Calcification of the aortic valve would be best appreciated in the lateral view of the chest. [Rahimtoola S. Chapter 06. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. ISBN: 1-878132-30-X] *Caption adapted from original*

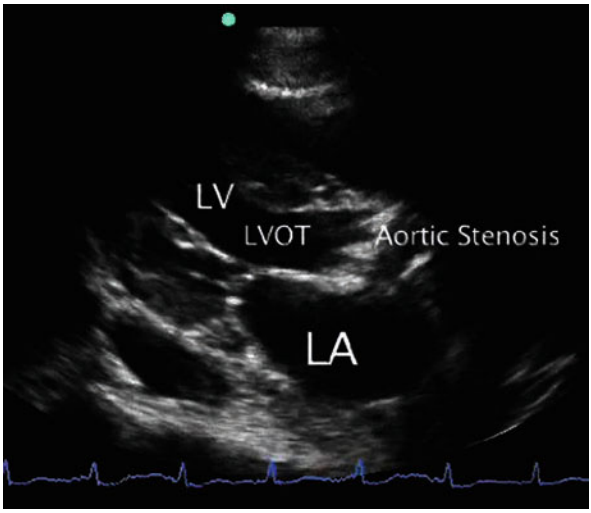
- Echocardiography is the most reliable way to evaluate aortic stenosis.
- Some findings include the finding of a bicuspid valve, thickened and calcified aortic leaflets, possible left ventricular hypertrophy, and probable concurrent aortic regurgitation.
- Echocardiography has reduced the need for cardiac catheterization with hemodynamic measurements.



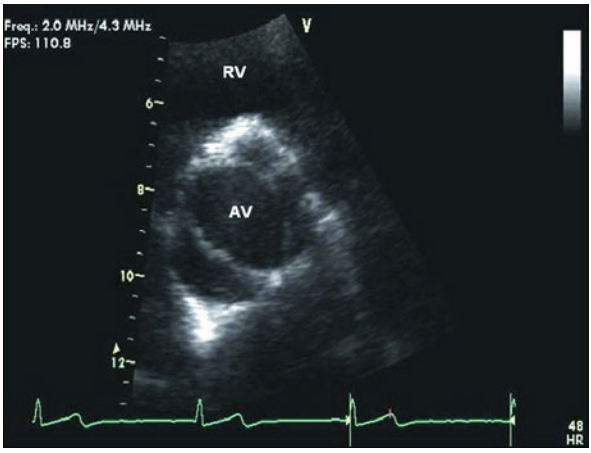
Critical aortic stenosis color Doppler LVOT view [Riley DC, Glassman G, Hodges K. Emergency department diagnosis of critical aortic stenosis using bedside ultrasonography. Critical Ultrasound Journal. 2010 Nov;2(2):87–9.] *Caption from original*



Critical aortic stenosis color Doppler apical 5-chamber view [Riley DC, Glassman G, Hodges K. Emergency department diagnosis of critical aortic stenosis using bedside ultrasonography. Critical Ultrasound Journal. 2010 Nov;2(2):87–9.] *Caption from original*



Critical aortic stenosis parasternal long-axis view [Riley DC, Glassman G, Hodges K. Emergency department diagnosis of critical aortic stenosis using bedside ultrasonography. Critical Ultrasound Journal. 2010 Nov;2(2):87–9.] *Caption from original*



Bicuspid aortic stenosis. Parasternal short-axis view of a bicuspid aortic valve (AV) showing the typical bowing aortic cusps. [Sorajja P, Nishimura RA. Aortic Stenosis. In: Wang A, Bashore TM, editors. Valvular Heart Disease [Internet]. Totowa, NJ: Humana Press; 2009 [cited 2015 Aug 27]. p. 165–86. Available from: http://link.springer.com/10.1007/978-1-59745-411-7_7] *Caption adapted from original*

Special Populations

Age

- Severe isolated aortic stenosis is primarily a disease of older patients
- Aortic stenosis in infancy will often present with signs of CHF, with accompanying growth failure.
- AS in older children is usually asymptomatic.

Co-Morbidities

- Patients with aortic stenosis have an increased risk of bleeding. The increased risk appears to be due to an acquired Von Willebrand syndrome.

Pitfalls in Diagnosis

Critical Steps Not to Miss

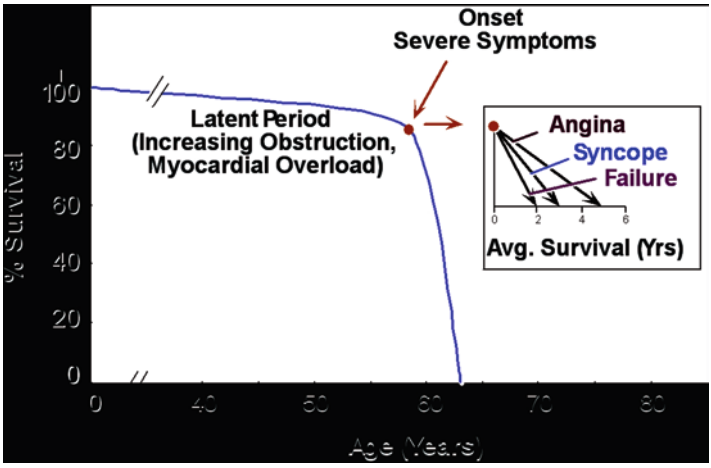
- Once symptoms develop, prompt surgical intervention is needed to increase survival owing to the high risk of sudden death.

Mimics

- Symptoms may be attributed to other diseases, such as coronary artery disease or congestive heart failure, with the diagnosis of aortic stenosis being made only later in the work-up.

Time Dependent Interventions

- Once symptoms develop, even mild symptos, surgery is needed because without a valve replacement the survival rate is only 2 to 3 years.



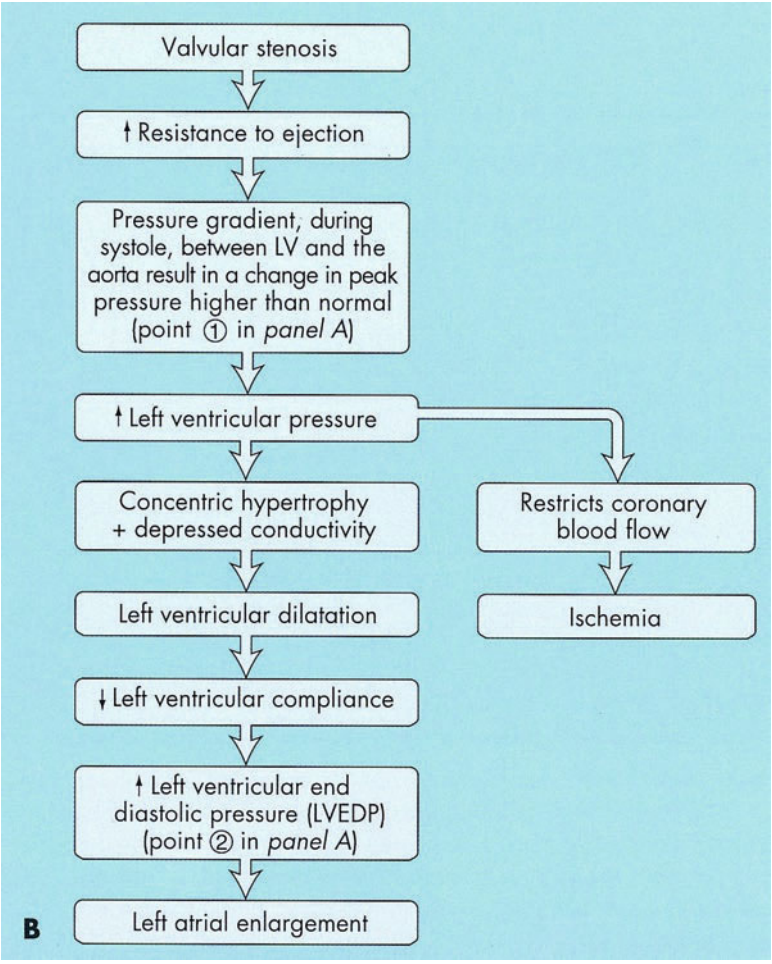
Classic survival curve aortic stenosis. [Ross J, Braunwald E. Aortic Stenosis. Circulation. 1968 Jul 1;38(1S5):V-61-V-67. Reprinted with permission.]

- Symptomatic patients with severe aortic stenosis alone or
  - Undergoing coronary artery bypass surgery
  - Undergoing surgery on the aorta or other heart valves
- Patients with moderate aortic stenosis and
  - Undergoing coronary artery bypass surgery
  - Undergoing surgery on the aorta
  - Undergoing surgery on other heart valves
- Asymptomatic patients with severe aortic stenosis and left ventricular systolic dysfunction typified by
  - Abnormal response to exercise (e.g., hypotension)
  - Ventricular tachycardia
  - Marked or excessive left ventricular hypertrophy (> 15 mm)
  - Valve area $< 0.6\ cm^2$
  - Prevention of sudden death without the findings listed

Aortic valve replacement in aortic stenosis (Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA guidelines for the management of patients with valvular heart disease. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2006;114:e84–231.) [John R, Liao KK. Heart Valve Disease. In: Iaizzo PA, editor. Handbook of Cardiac Anatomy, Physiology, and Devices [Internet]. Totowa, NJ: Humana Press; 2009 [cited 2015 Aug 28]. p. 527–49. Available from: http://link.springer.com/10.1007/978-1-60327-372-5_31] *Caption from original*

Overall Principles of Treatment

- After repair of aortic stenosis, quality of life and survival generally return to those expected for age and comorbidity burden.



Aortic stenosis. The primary hemodynamic abnormality in aortic stenosis is obstruction to left ventricular outflow, which results in a pressure gradient (B) (which can be estimated by Doppler echocardiography) between the left ventricle (LV) and the aorta, leading to left ventricular hypertrophy. Loss of atrial contraction and contribution to ventricular filling may result in clinical deterioration. The increased left ventricular size necessitates an increase in myocardial oxygen demand, and intraventricular wall pressure may exceed coronary artery perfusion pressure, causing myocardial ischemia even in the absence of coronary artery disease. Cardinal signs

are exertional dyspnea (inability to increase cardiac output and elevated pulmonary capillary pressure), angina pectoris, and exertional syncope (caused by decreased arterial pressure associated with vasodilatation in the exercising muscles or arrhythmias). Care must be taken to avoid intravascular volume depletion [Mulligan M, Cousins M. Chapter 4. In: Lichtor JL, editor. Preoperative preparation and intraoperative monitoring. Philadelphia: Current Medicine; 1997. (Miller RD, editor. Atlas of anesthesia; vol. 3)] *Caption adapted from original*

Disease Course

- After the onset of symptoms, patients with severe aortic stenosis have a survival rate as low as 50% at two years and 20% at five years without aortic valve replacement.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Stevenson WG, Yancy CW; American College of Cardiology; American College of Cardiology/American Heart Association; American Heart Association. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132. https://doi.org/10.1016/j.jtcvs.2014.05.014. PMID: 24939033. http://www.ncbi.nlm.nih.gov/pubmed/24939033 **

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Meta-Analysis

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Aortic Valve Stenosis"[Mesh] OR "Aortic Stenosis"

Chapter 10
Aspiration

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Aspiration; Aspiration Pneumonia; Aspiration Pneumonitis; Chemical Pneumonitis

Incidence/Epidemiology

- About half of all healthy adults aspirate to some degree during sleep, but this is usually not clinically significant. Healthy people have physiologic defenses (such as cough and glottic closure) against aspiration that helps to limit the damage that can be caused.
- Aspiration becomes clinically significant when the patient has some underlying condition that compromises the usual defenses.
- Up to 15 % of cases of typical community-acquired pneumonia (CAP) are due to aspiration of pathogenic bacteria from the oro-pharyngeal cavity and the stomach. The incidence increases with age, and up to 20 % of CAP in the elderly is from aspiration.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_10

- It is felt that the majority of hospital- and nursing home-acquired pneumonias are due to aspiration.
- Factors that can increase the risk of aspiration include: decreased level of consciousness; neurologic disorders that affect swallowing; mechanical disruption of the oro-pharynx, epiglottis, trachea, and esophagus, such as endotracheal intubation; nasogastric feeding tubes; tracheostomy, etc.

Differential Diagnosis

- Aspiration, especially aspiration of gastric contents causing aspiration pneumonitis, can present as acute shortness of breath with both tachypnea and hypoxia. As such, the differential is broad, and contains all the usual causes of acute dyspnea and respiratory compromise, such as ACS, pulmonary embolism, and pulmonary edema/CHF, among others.
- Aspiration pneumonia may present as typical CAP or HAP, with fever and cough with purulent sputum, but can also present sub-acutely when caused predominately by anaerobes.

Pathophysiology and Etiology

- Aspiration results in three broad clinical syndromes, often presenting with overlapping features:
  - Aspiration pneumonitis (chemical pneumonitis)
  - Bacterial Infection causing pneumonia, empyema, and/or pulmonary abscess
  - Airway obstruction from larger, solid matter
- The pathophysiology starts similarly in all syndromes. They are caused by the abnormal entry of endogenous secretions, fluids, and/or particulate matter into the lower airway.
- Aspiration/Chemical Pneumonitis. In this syndrome, there is aspiration of materials that have a direct, toxic effect on the lower airways and lung tissue. The best-known and studied substance is gastric acid, and serves as the pathophysiologic model for all other substances.
  - The airways and lungs are relatively resistant to injury. For clinically significant issues to result, there needs to be a large amount of aspirate (generally more than 25 ml in an adult), and the pH must be below 2.5.
  - When this condition is met, rapid physiologic changes occur (within 3 minutes), including atelectasis, peribronchial hemorrhage, pulmonary edema, and rapid death of bronchial epithelial cells.
  - After 4 hours, the alveolar spaces will become filled with an inflammatory exudate composed of inflammatory cells, fibrin, and desquamated tissue.

  - Within 2 days there will be hyaline membrane formation, and the lungs will be edematous and hemorrhagic with consolidation of the alveolar spaces.
  - Lungs that have been injured by acid or other directly toxic materials are more susceptible to subsequent bacterial infection.
- Bacterial Infection/Aspiration Pneumonia. The bacteria that cause aspiration pneumonia generally originate in the upper airways or stomach.
  - Classically, oral anaerobes (*Peptostreptococcus*, *Fusobacterium nucleatum*, *Prevotells*, and *Bacteroides* spp.) and streptococci caused aspiration pneumonia.
  - More recently, hospital- and healthcare-acquired aspiration pneumonia has been associated with more virulent organisms, such as Staphylococcus aureus, Pseudomonas aeruginosa, and gram-negative bacilli.
- Airway obstruction. Airway obstruction may result from either fluids or solid material aspiration.
  - The ingestion of fluids that are not directly toxic to lung tissue (saline, barium, etc.) can initiate a reflex airway closure, such as in drowning.
  - Solid objects cause differing levels of obstruction based upon their size relative to the airways.
  - Most foreign body aspirations occur in children between the ages of one and three.
  - Large objects can obstruct at the larynx, proximal trachea, tracheal bifurcation, or main stem bronchus. They cause nearly immediate respiratory distress, inability to talk, and cyanosis. Unless removed quickly, they can rapidly lead to death.
  - Smaller objects cause local atelectasis, and the patient will have a cough or focal wheezing.

Presentation

Typical/"Classic"

- Aspiration/Chemical Pneumonitis:
  - Acute onset of symptoms with profound dyspnea, and associated hypoxemia.
  - Often seen in the setting of known risk-factors for aspiration.
- Bacterial Infection. Presentation is variable, and depends upon the causative organisms and the overall health status of the affected patient.
  - Most patients present somewhat acutely with the typical symptoms of pneumonia, fever, productive cough, and dyspnea, especially when the infection is due to organisms other than anaerobes (such as Staph, Strep, Pseudomonas, etc.).

- Infections from anaerobic organisms often present more slowly, over days and weeks. There is often necrotic-smelling sputum, and a notable lack of rigors. Most patients with anaerobic aspiration pneumonia will have an easily recognized risk factor for aspiration, and poor dental health.

- Airway Obstruction.
  - Large particle airway obstruction causes acute respiratory compromise and failure, with severe dyspnea, inability to talk, hypoxia/cyanosis, and rapid cardiovascular collapse if not removed.
  - Small particle airway obstruction can present in a more subtle fashion, with an indolent, irritative cough, associated with dyspnea that is sometimes present only with exertion.

Atypical

- There is a wide-spectrum of clinical presentations and syndromes for aspiration. As above, aspiration syndromes typically present acutely, but depending upon many factors, may be sub-acute or indolent. Also, as noted above, atypical presentations occur especially with aspiration pneumonia caused by anaerobic organisms, airway obstruction caused by small particles, or aspiration pneumonitis caused by small volume, higher pH substances.

Primary Differential Considerations

- Differential considerations for aspiration include:
  - Respiratory Distress Syndrome
  - Other respiratory failure
  - Status asthmaticus
  - Circulatory shock
  - RSV infection in children

History and Physical Exam

Findings That Confirm Diagnosis

- A witnessed aspiration event, followed by the typical clinical syndrome of aspiration pneumonitis, confirms the diagnosis.

Factors That Suggest Diagnosis

- A patient who presents with community- or hospital-acquired pneumonia, has risk factors for aspiration, and/or has infiltrates in the dependent lung zones (lower lobes if aspiration occurred in the upright position, or superior segments of the lower lobes and/or posterior segment of the upper lobes if aspiration occurred in the supine position) should be further evaluated for aspiration and swallowing difficulties.

Factors That Exclude Diagnosis

- Finding another cause for the dyspnea/respiratory distress makes aspiration unlikely.

Ancillary Studies

Laboratory

- Laboratory abnormalities in aspiration pneumonitis are usually non-specific. There may be a moderately elevated white blood cell count. Patients may be hypoxic with a respiratory acidosis on blood gas analysis, especially in the acute setting when they are tachypneic.
- Patients with bacterial pneumonia caused by aspiration will usually have laboratory findings of acute infection with a leukocytosis with bandemia and/or a leftward shift. These patients may also be hypoxic.
    - Sputum culture has a limited role in aspiration pneumonia. Most infections are polymicrobial, and many of the causative organisms are difficult to culture. Coughed sputum samples are not useful for culture, as the normal flora of the mouth and upper airway contaminates them.
- Laboratory studies are not helpful in the diagnosis of airway obstruction from particulate matter.

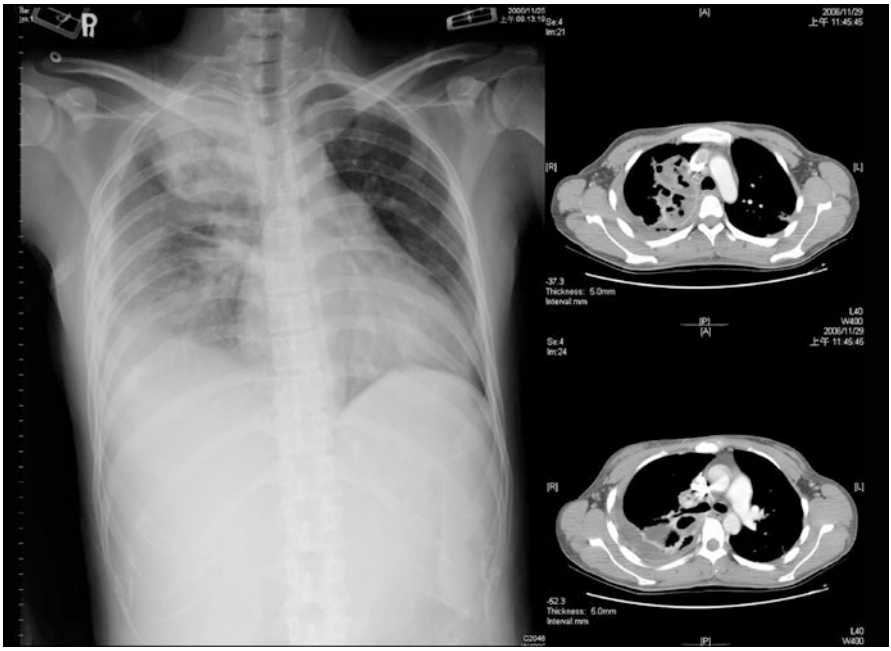
Imaging

- CXR findings in aspiration pneumonitis typically appear about 2 hours after an aspiration event. Typically, there are infiltrates in the dependent lung zones. These are the lower lobes when the patient was in an upright position during the aspiration event, and the superior segments of the lower lobes and posterior segments of the upper lobes if the patient was in the supine position during the aspiration event. Over time, if the disease progresses, the CXR may show evidence of ARDS with diffuse, fluffy infiltrates.

Aspiration pneumonia with infection: image progression. **a** Several hours after aspiration of gastric content, there are patchy infiltrates at both lung bases medially. **b** Three days after aspiration, the consolidation has increased in density and extent. At this phase, aspiration pneumonitis should be improving. This suggests secondary infection. **c** Four days after aspiration, computed tomography reveals dense consolidation in the posterior and lateral basal segments of both lower lobes. This degree of consolidation is more than one usually sees with uncomplicated aspiration pneumonitis. [Goodman LR. Imaging the Intensive Care Patient. In: Hodler J, von Schulthess GK, Zollikofer CL, editors. Diseases of the Heart and Chest, Including Breast 2011–2014 [Internet]. Milano: Springer Milan; 2011 [cited 2015 May 22]. p. 66–9. Available from: http://link.springer.com/10.1007/978-88-470-1938-6_10] *Caption adapted from original*

- The CXR in aspiration pneumonia caused by bacteria will also typically reveal an infiltrate in one or more of the dependent lung zones.
- Patients with pneumonia caused by anaerobic bacteria can have more indolent presentation and may develop either lung abscess or empyema that can be revealed on the CXR.

The chest radiograph and computed tomography scan showed pleural empyema without lung abscess. [From article: Lung abscess predicts the surgical outcome in patients with pleural empyema. Journal of Cardiothoracic Surgery. 2010;5(1):88. https://doi.org/10.1186/1749-8090-5-88, at http://link.springer.com/article/10.1186%2F1749-8090-5-88; by Hung-Che Huang, Heng-Chung Chen, Hsin-Yuan Fang, Yi-Chieh Lin, Chin-Yen Wu, Ching-Yuan Cheng, © Huang et al; licensee BioMed Central Ltd. 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*



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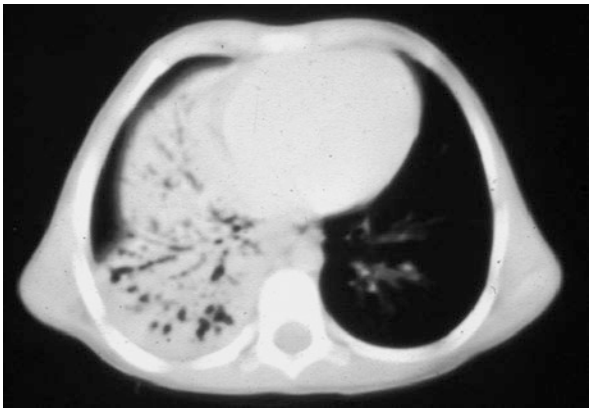
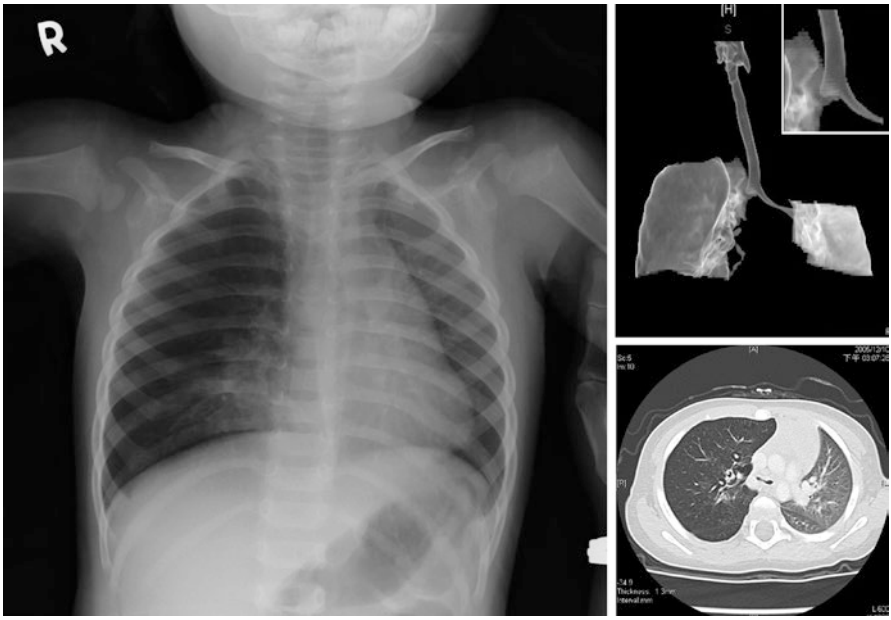
- Airway obstruction from aspirated, large objects must be diagnosed prior to CXR, as the patients are in extremis and need rapid treatment. When the object is smaller, and the presentation not as severe or obvious, a CXR may be helpful. Many objects that are aspirated are biologic and radiolucent (peanuts, vegetables, other food objects), and some are radiodense (teeth, buttons, batteries, etc.). If the object itself is not visualized on the x-ray, there may be atelectasis with an elevated hemidiaphragm, and other signs of lung-volume loss.

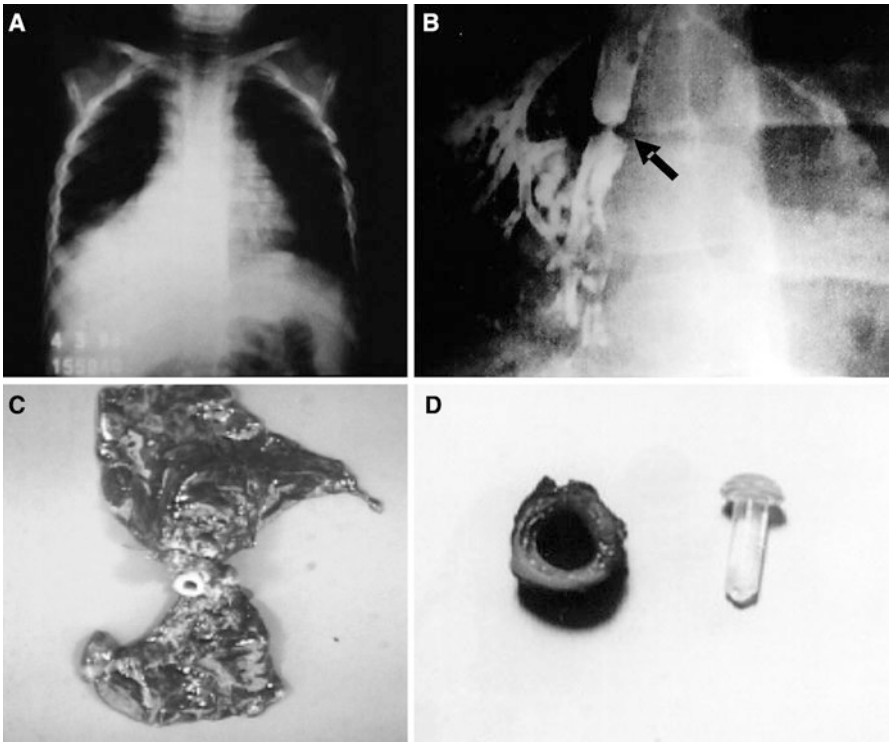
Frontal chest radiograph of a child with foreign body aspiration. The left lung is large and hyperlucent with less vessels due to air trapping caused by partial obstruction of the left main bronchus. Note the mediastinal shift to the right. [Soto G, Moënne K. Classic Chest Radiology Findings, Pearls and Pitfalls. In: Garcia-Peña P, Guillerman RP, editors. Pediatric Chest Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013 [cited 2015 May 22]. p. 13–30. Available from: http://link.springer.com/10.1007/174_2013_905] *Caption from original*



Axial CT of the lower chest in a case of chronic foreign body aspiration into the right intermediate bronchus, causing collapse and bronchiectasis in the right middle lobe and right lower lobe. [Koplewitz BZ, Bar-Ziv J. Foreign Body Aspiration: Imaging Aspects. In: Garcia-Peña P, Guillerman RP, editors. Pediatric Chest Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 22]. p. 305–26. Available from: http://link.springer.com/10.1007/174_2013_952] *Caption from original*



Plain chest radiograph showing a nearly left total opacity with ipsilateral mediastinal shift caused by foreign body aspiration. Three-dimensional chest computed tomography showing a nearly total occlusion in the right main bronchus [Huang H-J, Fang H-Y, Chen H-C, Wu C-Y, Cheng C-Y, Chang C-L. Three-dimensional computed tomography for detection of tracheobronchial foreign body aspiration in children. Pediatric Surgery International. 2008 Feb;24(2):157–60.] *Caption from original*



a Thorax X-ray showing atelectasis of the inferior and middle lobe of the right lung in a child with recurrent pneumonia for 2 years. b Bronchography showing stenosis of the intermediate segment, the foreign body cannot be seen. c Removed inferior and middle destroyed lobes. d Foreign body and blocked bronchus. When saw the foreign body, the mother said that it was part of a toy that had disappeared 2 years earlier [Cataneo AJM, Cataneo DC, Ruiz RL. Management of tracheobronchial foreign body in children. Pediatric Surgery International. 2008 Feb;24(2):151–6.] *Caption from original*

Special Populations

Age

- Aspiration pneumonitis is more common in the elderly, especially those with neurologic and other swallowing difficulties.
- Aspiration of objects is more common among children between the ages of one and three.
- Gastroesophogeal reflux (GER) is common in infancy, resulting in vomiting, albeit without complications.

- The diagnosis of gastroesophogeal reflux disease (GERD) applies when reflux events are associated with pathologic outcomes or debilitating symptoms.
- Concomitant aspiration events are rarely seen in infants with GERD, except in patients with swallowing disorders, e.g., neurological impairment scenarios.

Co-morbidities

- There are multiple co-morbidities that increase the risk of all types of aspiration. These include:
  - Reduced consciousness, which depresses the gag and glottic closure reflexes and can be brought on by causes such as alcohol and drug intoxication, and hepatic failure.
  - Prior stroke or neuromuscular disorder that impairs the ability to swallow.
  - Other neurologic conditions such as stroke, head injury, and dementia.
  - Mechanical instrumentation of the upper airway, such as endotracheal intubation, tracheostomy, nasogastric tube feedings, and upper endoscopy.
  - Periodontal disease.
  - General anesthesia and procedural sedation.
  - Gastroesophageal reflux, esophageal dysmotility.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. Patients presenting with respiratory compromise need all appropriate supportive care until a diagnosis can be established.
- CXR should be performed early, but findings may be delayed by several hours.
- Patients who are felt to have a syndrome-consistent aspiration should have their swallowing function evaluated.

Mimics

- Many conditions can cause acute dyspnea and respiratory compromise, including ACS, pulmonary embolism, pneumothorax, pulmonary edema/CHF, among others.

Time-Dependent Interventions

- Airway obstruction with a large object causing complete airway obstruction is a medical emergency and can be fatal within minutes if not recognized and treated appropriately.
- Aspiration pneumonia from bacterial infection can present with acute respiratory compromise, so the rapid support of ventilatory function and administration of empiric antibiotics for likely pathogens is necessary.
- A witnessed aspiration event should be treated urgently with airway suctioning to remove as much fluid and solid matter as possible, and ventilatory and respiratory function should be supported.

Overall Principles of Treatment

- Aspiration pneumonitis.
  - As noted above, a patient with a witnessed or presumed acute aspiration event should have tracheal suctioning, administration of supplemental oxygen, and all respiratory and ventilator necessary.
  - The use of glucocorticoids is controversial. There are no good data supporting their use in aspiration pneumonitis.
  - Empiric or prophylactic antibiotics are commonly given in aspiration pneumonitis. Chemically injured lungs are at an increased risk for developing bacterial superinfection in the coming days, but there is no good evidence that prophylactic antibiotics administration prevents these infections. It is appropriate to administer antibiotics if the diagnosis is in doubt and bacterial pneumonia remains on the differential.
- Bacterial Aspiration Pneumonia.
  - Antibiotics are necessary in the treatment of aspiration pneumonia due to bacteria.
  - Most of these infections are polymicrobial, and include anaerobes. As such, most patients will be treated (at least initially), with a combination of antibiotics.
  - Clindamycin is the antibiotic of choice to cover anaerobes. Metronidazole should not be used alone, as it has a failure rate of up to 50% when used as monotherapy.
  - Clindamycin can be combined with either amoxicillin or penicillin.
  - When the patient has a hospital- or healthcare-acquired aspiration pneumonia, it is important to consider both gram positive organisms, such as Staph and strep, and the aerobic gram negative bacilli as causes. These patients should be broadly covered with an antibiotic or combination of antibiotics, to cover the gram-positives and negatives. This usually includes vancomycin

with either a carbapenem or piperacillin/tazobactam. These regimens will also cover most pathogenic anaerobes.

- Airway obstruction from large objects needs to be relieved immediately. The preferred method is the Heimlich maneuver. If unsuccessful, a surgical airway may need to be secured.
  - Smaller objects can often be removed by bronchoscopy.

Disease Course

- Aspiration pneumonitis. The course varies considerably based upon the patient's underlying medical condition and the cause of the aspiration. The majority of patients will recover rapidly. A small percentage will go on to develop ARDS and/or bacterial superinfection. There is a significant mortality associated with both of these complications.
- Patients with bacterial aspiration pneumonia often recover fully, but when the predominant pathogens are anaerobic bacteria, a small percentage can go on to develop pulmonary abscess or empyema as complications of the primary infection. The incidence of these complications has been decreasing.
- All patients who suffer from aspiration need to be evaluated for the primary cause of their aspiration, or they remain at risk for further episodes.
- Most patients who have an airway obstruction recover uneventfully if the obstruction is relieved in a timely manner.

Related Evidence

Paper of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Respiratory Aspiration"[Mesh] OR "Pneumonia, Aspiration"[Mesh] OR "Aspiration"

Chapter 11
Asthma

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Name and Synonyms

Asthma

Incidence/Epidemiology

- Approximately 235 million people, worldwide, are affected by asthma.
- Approximately 250,000 people die of asthma each year.
- Rates vary between countries with prevalence between 1 % and 18 %.
- There is some racial predilection (for example, asthma severity and asthma mortality is higher in US blacks than US whites). This may be more socioeconomic than clinical,

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_11

Population (Survey, sample size)	Poor self-rated health %[a] (95 % CI)	Impaired physical health % (95 % CI)	Impaired mental health % (95 % CI)	Limited activity % (95 % CI)
Adults (Behavioral Risk Factor Surveillance System, $N = 1{,}082{,}135$)	16.2 (16.0–16.3)	10.7 (10.6–10.8)	10.2 (10.1–10.3)	4.0 (3.9–4.1)
No asthma[b]	14.8 (14.7–15.0)	9.5 (9.4–9.7)	9.2 (9.1–9.3)	3.3 (3.3–3.4)
Former asthma[c]	15.7 (15.0–16.4)	11.1 (10.5–11.7)	12.3 (11.7–13.0)	4.4 (4.0–4.7)
Current asthma[d]	29.6 (29.0–30.2)	22.2 (21.6–22.7)	18.9 (18.3–19.5)	10.5 (10.1–10.9)
Ever-employed adults with current asthma[e] (Asthma Call-back Survey, $N = 38{,}306$)	26.9 (25.9–27.9)	20.6 (19.7–21.4)	18.2 (17.3–19.1)	10.2 (9.5–10.9)
Non-work-related asthma[f]	21.6 (20.4–22.8)	15.8 (14.8–16.8)	14.3 (13.1–15.4)	6.6 (5.9–7.2)
Possible work-related asthma[g]	31.3 (29.6–33.0)	24.5 (23.0–26.0)	21.9 (20.3–23.5)	13.3 (11.9–14.6)
HCP-diagnosed work-related asthma[h]	40.2 (36.9–43.6)	32.4 (29.2–35.6)	26.2 (23.0–29.4)	19.2 (16.5–21.9)

CI confidence interval, *HCP* health-care professional

[a] Results presented as weighted average annual estimate

[b] Behavioral Risk Factor Surveillance System participants who answered "No" to the question "Were you ever told by a doctor or other health professional that you had asthma?"

[c] Behavioral Risk Factor Surveillance System participants who answered "Yes" to the question "Were you ever told by a doctor or other health professional that you had asthma?" and "No" to the question "Do you still have asthma?"

[d] Behavioral Risk Factor Surveillance System participants who answered "Yes" to the questions "Were you ever told by a doctor or other health professional that you had asthma?" and "Do you still have asthma?"

[e] Asthma Call-back Survey participants who described current employment status as "employed full-time" or "employed part-time" or responded "yes" to the question "Have you ever been employed outside the home?"

[f] "No" to all of the following five questions: "Were you ever told by a doctor or other health professional that your asthma was related to any job you ever had?", "Was your asthma caused by chemicals, smoke, fumes, or dust in your current job?", "Was your asthma caused by chemicals, smoke, fumes, or dust in any previous job you ever had?", "Is your asthma made worse by chemicals, smoke, fumes, or dust in your current job?", and "Was your asthma made worse by chemicals, smoke, fumes, or dust in any previous job you ever had?"

[g] "No" response to the question "Were you ever told by a doctor or other health professional that your asthma was related to any job you ever had?" and "Yes" responses to any of the following four questions: "Was your asthma caused by chemicals, smoke, fumes, or dust in your current job?", "Was your asthma caused by chemicals, smoke, fumes, or dust in any previous job you ever had?", "Is your asthma made worse by chemicals, smoke, fumes, or dust in your current job?", and "Was your asthma made worse by chemicals, smoke, fumes, or dust in any previous job you ever had?"

[h] "Yes" to the question "Were you ever told by a doctor or other health professional that your asthma was related to any job you ever had?"

Estimated proportion of individuals with poor health-related quality of life among select population groups, Behavioral Risk Factor Surveillance System and Asthma Call-back Survey, 38 states and District of Columbia, 2006–2009 [Knoeller GE, Mazurek JM, Moorman JE. Health-related quality of life among adults with work-related asthma in the United States. Quality of Life Research. 2013 May;22(4): 771–80.] *Caption from original*

- Asthma is the most common chronic disease in childhood.
- Asthma occurs more frequently in boys before puberty and in girls after puberty.

Differential Diagnosis

- See chart, but includes:
  - Airway foreign body
  - Bronchitis with bronchospasm
  - Pneumonia with bronchospasm
  - Congestive heart failure
  - Bronchiolitis
  - Chronic obstructive pulmonary disease
  - Cystic fibrosis

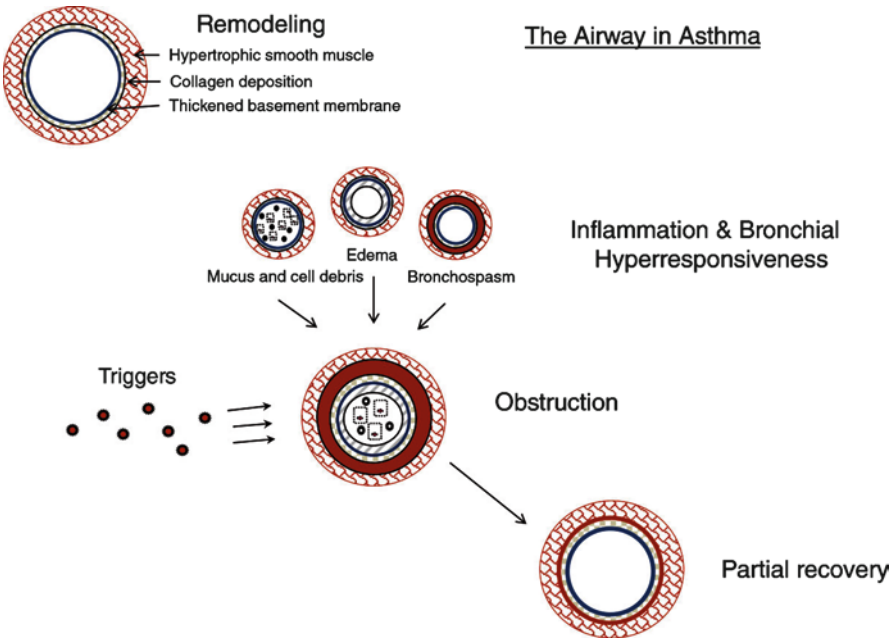
- Pulmonary embolism
- Tracheomalacia
- Vocal cord dysfunction

Chronic bronchitis	Vocal cord dysfunction
Emphysema	Congestive heart failure
Cystic fibrosis	Pulmonary embolism
Viral bronchiolitis	Eosinophilic pneumonia
Bronchial stenosis	Drug-induced cough
Mechanical airway obstruction	β-Blockers
Aspirated foreign body	Angiotensin-converting enzyme inhibitors
Endobronchial tumor	Systemic vasculitis
Superior vena cava syndrome	Carcinoid syndrome
Substernal thyroid	Allergic bronchopulmonary aspergillosis

Differential diagnosis of asthma [Holgate S, Sewell J, Payne KD. Chapter 01. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] *Caption adapted from original*

Pathophysiology and Etiology

- An inflammatory process of the airways that results in periodic, at least partially reversible airflow obstruction.
- Bronchial hyperresponsiveness.
- Family history may be pertinent for asthma diagnosis.
- Many cells and cellular elements contribute to asthma, including:
  - Neutrophils
  - Mast cells
  - Eosinophils
  - Macrophages
  - Activated T lymphocytes
  - Epithelial cells
- Many asthma triggers exist, including:
  - Environmental allergens: dust mites, molds, animal dander, cockroach allergens, fungi, etc.
  - Viral respiratory tract infections
  - Hyperventilation
  - Gastroesophageal reflux disease
  - Environmental pollutants, e.g., tobacco smoke
  - Obesity
  - Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAID)



Pathophysiology of asthma at steady state and during an exacerbation. The airways of asthmatic individuals are characterized by pathological changes, including thickened basement membrane, collagen deposition and hypertrophic smooth muscle, collectively called 'airway remodeling'. Inflammation is triggered by a variety of factors, including allergens and respiratory viruses. These factors also induce hyperreactive responses in the asthmatic airways, associated with mucus and cell debris released into the lumen, oedema and bronchoconstriction, leading to airway obstruction and related acute exacerbations. Although pathophysiological changes related to asthma are generally reversible, recovery may be partial. [From article: Research needs in allergy: an EAACI position paper, in collaboration with EFA. Clinical and Translational Allergy. 2012;2(1):21.; https://doi.org/10.1186/2045-7022-2-21, at http://link.springer.com/article/10.1186%2F2045-7022-2-21/fulltext.html; by Nikolaos G Papadopoulos, Ioana Agache, Sevim Bavbek, et al., © Papadopoulos et al.; licensee BioMed Central Ltd. 2012; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Presentation

Typical/"Classic"

- Wheezing, coughing, shortness of breath, chest tightness, tachypnea, tachycardia, respiratory distress, altered mental status.

Atypical

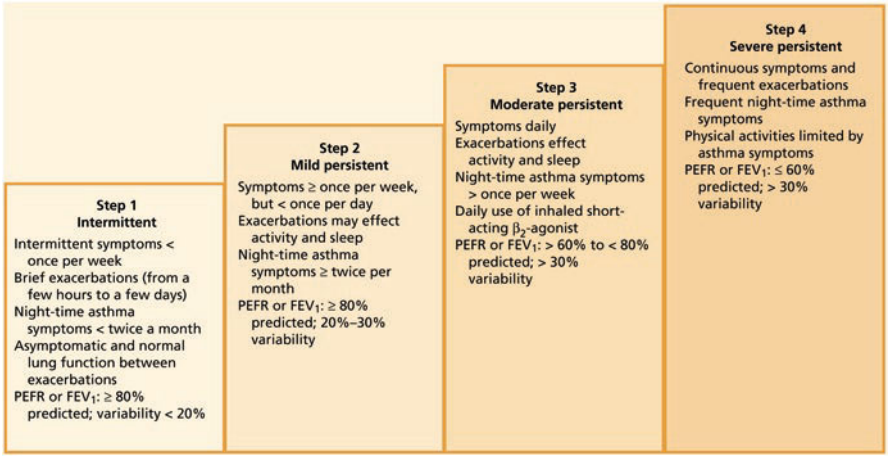
- Cough-variant asthma, nonasthmatic eosinophilic bronchitis, and atopic cough.
  - Approximately 30 % of cough variant asthma that go untreated will result in progression to asthma

Primary Differential Considerations

- Vocal cord dysfunction
- Allergic and environmental asthma
- Tracheal and bronchial lesions
- Foreign bodies
- Pulmonary migraine
- Congestive heart failure
- Diffuse panbronchiolitis
- Aortic arch anomalies
- Sinus disease
- Gastroesophageal reflux
- Pulmonary embolism
- Cystic fibrosis
- Eosinophilia count >8 %, consider allergic bronchoplumonary aspergillosis, Churg-Strauss syndrome, or eosinophilic pneumonia

History and Physical Exam

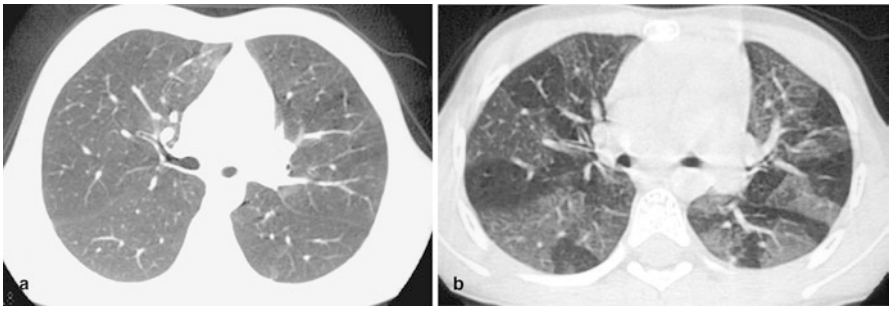
- Categories of asthma severity are determined by the following factors:
  - Reported symptoms over the previous 2 – 4 weeks
  - Current level of lung function: FEV_1, FEV_1 (FVC values)
  - Number of exacerbations requiring oral glucocorticoids per year
- Asthma Severity categories:
  - Intermittent
  - Mild persistent
  - Moderate persistent
  - Severe persistent
- Family history of asthma is often common for diagnoses of asthma, allergies, eczema, and/or nasal polyps.
- Social history is frequently helpful to ascertain for environmental smoke exposure. As mentioned under Incidence/Epidemiology, lower socioeconomic status may be associated with more severe asthma.



Classification of asthma severity. Severity of asthma is classified into four groups according to symptoms and lung function measurements. This method of classification is important because therapy for asthma takes a stepwise approach according to the disease severity. Generally patients have poor perception of the severity of their asthma because they tend to adapt their lifestyle to accommodate their symptoms. This in turn leads to poor control of the disease as well as poor quality of life. Classifying the disease in this stepwise fashion allows the targeting of therapy according to the severity of the disease. FEV1—forced expiratory volume in 1 second; PEFR—peak expiratory flow rate. [Gnanakumaran G, Holgate S. Asthma in Adults. In: Lieberman P, Blaiss M, editors. Atlas of Allergic Diseases, 2e. Philadelphia: Current Medicine; 2005] *Caption from original*

Findings That Confirm Diagnosis

- Arterial blood gases and pulse oximetry for severity and response to treatment.
- Eosinophil counts >4 %, absence is not exclusionary.
- Spirometry before and after short-acting bronchodilator.
- Bronchoprovocation test.
- High-resolution computed tomography (HRCT).



Expiratory HRCT technique. A 9-year-old girl with suspected asthma. a Normal inspiratory HRCT scan. b Expiratory HRCT shows visible differences in lung attenuation (mosaic pattern) due to obstructive small airway disease, which proved to be asthma. Air-trapping is better depicted on expiratory scans [Garcia-Peña P, Lucaya J. HRCT in children: technique and indications. European Radiology Supplements. 2004 Mar 1;14(4):L13–30.] *Caption from original*

Factors That Suggest Diagnosis

- Serum immunoglobulin E levels greater than 100 IU frequently an allergic reaction, may not be asthma but other conditions.
- Elevated blood eosinophils.
- Non-specific IgE >150IU.
- Family history.
- Allergies.

Factors That Exclude Diagnosis

- Laboratory assessments and studies are usually used to exclude other diagnoses.

Evaluation of Exacerbations

- Pulse oximetry: Inability to maintain pulse ox between above 92% suggests impending respiratory failure.
- PEFR or FEV_1 measurement: PEFR is effort-dependent but can be used to compare severity of exacerbation and response to therapy to previous care episodes. FEV_1 is more accurate but is often logistically challenging to obtain in the acute setting

Ancillary Studies

Laboratory

- ABG: progression of severity is typically hyperoxemia → hypoxemia → hypercarbia.
- Pulse oximetry.
- WBC: may be high due to stress release and/or to concomitant infection.

Electrocardiography

- Indicated in patients at risk for cardiac disease, dysrhythmias, myocardial ischemia.
- Transient ST-T wave changes in severe asthma.
- Tachycardia typical.

Imaging

- Chest x-ray is not necessary unless there is suspicion of pneumonia, pneumothorax or pneumomediastinum, foreign body aspiration, comorbid illness, diabetes, AIDS, renal failure, or cancer.

Other Studies

- Peak Flow
- Spirometry
- Lung function study
- Provocative testing
- Diffusing capacity for carbon monoxide (DLco)
- Allergy testing

Special Populations

Age

Pediatrics

- Asthma is not an uncommon cause of chest pain in children.
- Severity classification in children is key.
  - Even children with mild asthma can have severe exacerbations.
  - Controller medications are based on the severity of the symptoms and exacerbation.
- Nonspecific symptoms in infants or young children may have a history of recurrent bronchitis, bronchiolitis, or pneumonia.
- Review for family history or allergy and medical history of early injury to airway.
- Infants are vulnerable to respiratory failure.

Drug name (trade name)	Category	Components (scientific names)	Pediatric indication[a]
Accolate	Leukotriene receptor antagonist	Zafirlukast	5 years and older
Advair Diskus	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 years and older
Advair HFA	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	12 years and older
Albuterol oral syrup	SABA	Albuterol sulfate	2 years and older
Alvesco	Inhaled ICS	Ciclesonide	12 years and older
Asmanex Twisthaler	Inhaled ICS	Mometasone furoate	4 years and older
Atrovent HFA	Anticholinergic	Ipratropium bromide	Not established
Dulera	Combination (ICS + LABA)	Mometasone furoate Formoterol fumarate dihydrate	12 years and older
Foradil	LABA	Formoterol fumarate	5 years and older
Intal inhaler	Anti-inflammatory	Cromolyn	Discontinued in USA, available still in other countries
Intal nebulization solution	Anti-inflammatory	Cromolyn	2 years and older
Pro-Air HFA	SABA	Albuterol sulfate	4 years and older
Proventil HFA	SABA	Albuterol sulfate	4 years and older
Pulmicort Flexhaler	Inhaled ICS	Budesonide	6 years and older
Pulmicort respules	Inhaled (nebulized) ICS	Budesonide	12 months to 8 years
QVAR	Inhaled ICS	Beclomethasone dipropionate	5 years and older
Seretide Accuhaler	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 years and older (Australia)
Seretide MDI	Combination (ICS + LABA)	Fluticasone propionate Salmeterol xinafoate	4 years and older (Australia)
Serevent Accuhaler	LABA	Salmeterol xinafoate	4 years and older (Australia)
Serevent Diskus	LABA	Salmeterol xinafoate	4 years and older (USA)
Serevent Inhaler	LABA	Salmeterol xinafoate	4 years and older (Australia)
Singulair	Leukotriene receptor antagonist	Montelukast	12 months and older (for asthma)
Spiriva HFA	Anticholinergic	Tiotropium bromide	Not indicated in children
Symbicort HFA	Combination (ICS + LABA)	Budesonide Formoterol fumarate dihydrate	12 years and older
Tilade CFC free	Anti-inflammatory	Nedocromil sodium	2 years and older
Ventolin HFA	SABA	Albuterol sulfate	4 years and older
Xolair	Monoclonal anti-IgE	Omalizumab	12 years and older
Xopenex HFA	SABA	Levalbuterol tartrate	4 years and older
Xopenex nebulization solution	SABA	Levalbuterol HCl	6 years and older
Zyflo	Leukotriene receptor antagonist	Zileuton	12 years and older

[a] These are current pediatric age indications by the FDA or corresponding regulatory agency if drug is available elsewhere

Pediatric indications for asthma drugs [Chang C. Asthma in Children and Adolescents: A Comprehensive Approach to Diagnosis and Management. Clinical Reviews in Allergy & Immunology. 2012 Aug;43(1-2):98–137.] *Caption from original*

- The management of an acute asthmatic in a child is not substantially different than that utilized for the adult patient.
- Inhaled anticholinergics in children should be utilized as recue medications. Early administration of steroids is effective and recommended in all cases.
- The use of chest radiographs in pediatric asthma should be reserved for infants or children who present with wheezing for the first time.
- Children are more likely to have cough-variant asthma, in which coughing is a more predominant presenting symptom than wheezing. The cough generally responds to bronchodilator therapy.

Elderly

- The elderly have high prevalence of other obstructive lung disease. The elderly may have increased sensitivity to adverse effects of β_2-agonists and inhaled corticosteroids.

Pregnancy

- Treat asthma aggressively during pregnancy. The National Asthma Education and Prevention Program Working Group Report on Managing Asthma During Pregnancy: Recommendations for Pharmacologic Treatment (2004; U.S. Department of Health and Human Services) can be found at the following link:http://www.nhlbi.nih.gov/health-pro/guidelines/archive/asthma-management-pregnancy-guidelines

Co-morbidities

- Rhinitis and rhinosinusitis management
- Allergic sensitivity and allergen exposure
- Psychological dysfunction
- Paradoxical vocal cord dysfunction
- Asymptomatic gastroesophageal reflux
- Obstructive sleep apnea
- Connective tissue disease
- Dermatologic conditions
- Immunologic and hematologic disease
- Metabolic disorders
- Obesity
- Obstructive lung disease
- Pregnancy
- Respiratory infection

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Altered mental status may signal respiratory failure.
- Correct use of medications such as inhalers and nebulizers.
- Monitor peak flows to assess severity and response to treatment.

Mimics

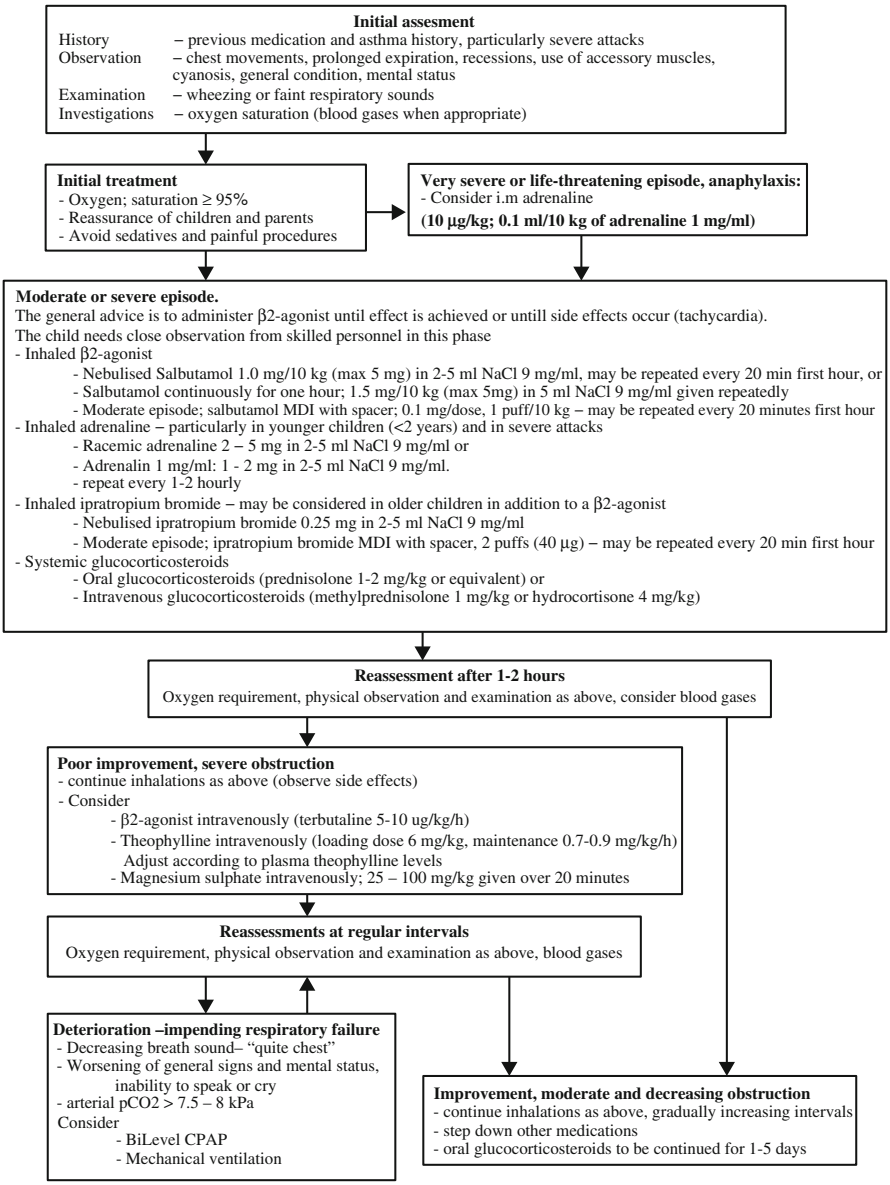
- Sinusitis
- Myocardial ischemia
- Gastrointestinal reflux
- Congestive heart failure
- Not all wheezing in infants and young children is asthma

Time-Dependent Interventions

- Immediate initiation of inhaled β_2- adrenergic agonist.
- Nebulized treatment.
- Supplemental oxygen.
- Administration of subcutaneous epinephrine unless concerned about coronary artery disease or hypertension.
- Intubation in respiratory failure.
- Corticoteroids should be given early, as they require 4–6 hours to show benefit.

Overall Principles of Treatment

- Treatment is based on asthma severity.
- Routine monitoring of symptoms and lung function.
- Patient education is essential.
- Recognize and control trigger factors (environmental factors).
- Controlling comorbid conditions that contribute to asthma severity.
- Pharmacologic therapy.
- Reduction of personal impairment and reduction of risk.
- Preventative approach with regularly scheduled check-ups and family/patient education.
- Awareness, recognition, and treatment of these atypical asthmas is important.
- Many base their management of asthma in children upon the National Asthma Education and Prevention Program (NAEPP) Expert panel guidelines (http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report).



Acute exacerbation treatment: Treatment algorithm for children with moderate or severe asthma exacerbations. [From article: Emergency presentation and management of acute severe asthma in children. Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2009;17(1):40. https://doi.org/10.1186/1757-7241-17-40, at http://link.springer.com/article/10.1186%2F1757-7241-17-40/fulltext.html; by Knut Øymar, Thomas Halvorsen, © Øymar and Halvorsen; licensee BioMed Central Ltd.

2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Disease Course

- By definition, asthma is characterized by *reversible* airflow obstruction, which means the impact of asthma on quality of life varies, from year to year, sometimes from season to season, or even day to day. There is little consensus on factors that determine disease progression versus disease stabilization.
- There is much interindividual variation is the course of asthma, and fatal exacerbations sometimes occur but are clearly unusual.
- With good control, asthmatics lead relatively normal and functional lives and have a normal lifespan. Poorer control is associated with impaired quality of life, more unscheduled healthcare visits, and more common hospitalization.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax. 2014 Nov;69 Suppl 1:1-192. PMID: 25323740. http://www.ncbi.nlm.nih.gov/pubmed/25323740 **

Lougheed MD, Leniere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, FitzGerald M, Leigh R, Watson W, Boulet LP; Canadian Thoracic Society Asthma Clinical Assemby.Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults: executive summary. Can Respir J. 2012 Nov-Dec;19(6):e81-8. No abstract available. Erratum in: Can Respir J. 2013 May-Jun;20(3):185. PMID: 23248807. http://www.ncbi.nlm.nih.gov/pubmed/23248807 **

Kling S, Zar HJ, Levin ME, Green RJ, Jeena PM, Risenga SM, Thula SA, Goussard P, Gie RP; South African Childhood Asthma Working Group (SACAWG). Guideline for the management of acute asthma in children: 2013 update. S Afr Med J. 2013 Feb 5;103(3 Pt 3):199-207. https://doi.org/10.7196/samj.6658. PMID: 23656745. http://www.ncbi.nlm.nih.gov/pubmed/23656745 **

Lalloo UG, Ainslie GM, Abdool-Gaffar MS, Awotedu AA, Feldman C, Greenblatt M, Irusen EM, Mash R, Naidoo SS, O'Brien J, Otto W, Richards GA, Wong ML; South African Thoracic Society. Guideline for the management of acute asthma in adults: 2013 update. S Afr Med J. 2012 Dec 3;103(3 Pt 2):189-98. https://doi.org/10.7196/samj.6526. PMID: 23656743. http://www.ncbi.nlm.nih.gov/pubmed/236567453 **

Review

Murphy VE, Schatz M. Asthma in pregnancy: a hit for two. Eur Respir Rev. 2014 Mar 1;23(131):64-8. https://doi.org/10.1183/09059180.00008313. PMID: 24591663. http://www.ncbi.nlm.nih.gov/pubmed/24591663 **

Patadia MO, Murrill LL, Corey J. Asthma: symptoms and presentation. Otolaryngol Clin North Am. 2014 Feb;47(1):23-32. https://doi.org/10.1016/j.otc.2013.10.001. PMID: 24286676. http://www.ncbi.nlm.nih.gov/pubmed/24286676 **

Maslan J, Mims JW. What is asthma? Pathophysiology, demographics, and health care costs. Otolaryngol Clin North Am. 2014 Feb;47(1):13-22. https://doi.org/10.1016/j.otc.2013.09.010. PMID: 24286675. http://www.ncbi.nlm.nih.gov/pubmed/24286675 **

Reddy AP, Gupta MR. Management of asthma: the current US and European guidelines. Adv Exp Med Biol. 2014;795:81-103. https://doi.org/10.1007/978-1-4614-8603-9_6. PMID: 24162904. http://www.ncbi.nlm.nih.gov/pubmed/24162904 **

Shah S, Sharma G. Current clinical diagnostic tests for asthma. Adv Exp Med Biol. 2014;795:75-80. https://doi.org/10.1007/978-1-4614-8603-9_5. PMID: 24162903. http://www.ncbi.nlm.nih.gov/pubmed/24162903 **

Croisant S. Epidemiology of asthma: prevalence and burden of disease. Adv Exp Med Biol. 2014;795:17-29. https://doi.org/10.1007/978-1-4614-8603-9_2. PMID: 24162900. http://www.ncbi.nlm.nih.gov/pubmed/24162900 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Asthma"[Mesh] OR "Asthma"

Chapter 12
Atrial Fibrillation

Charles V. Pollack, Jr., Melissa Platt, and Victoria G. Riese

Name and Synonyms

Atrial Fibrillation (AF)

Incidence/Epidemiology

- The most common cardiac arrhythmia
  - Affects 4 % of individuals older than 60 years and 8 % of those older than 80 years.
- It is more prevalent in men, and prevalence increases with age.
- In developed countries, hypertension and coronary artery disease are the most common underlying disorders.
- Rheumatic heart disease is associated with a higher incidence of AF, but this is much less common than in the past. Other causes of mitral valve disease also may lead to AF.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_12

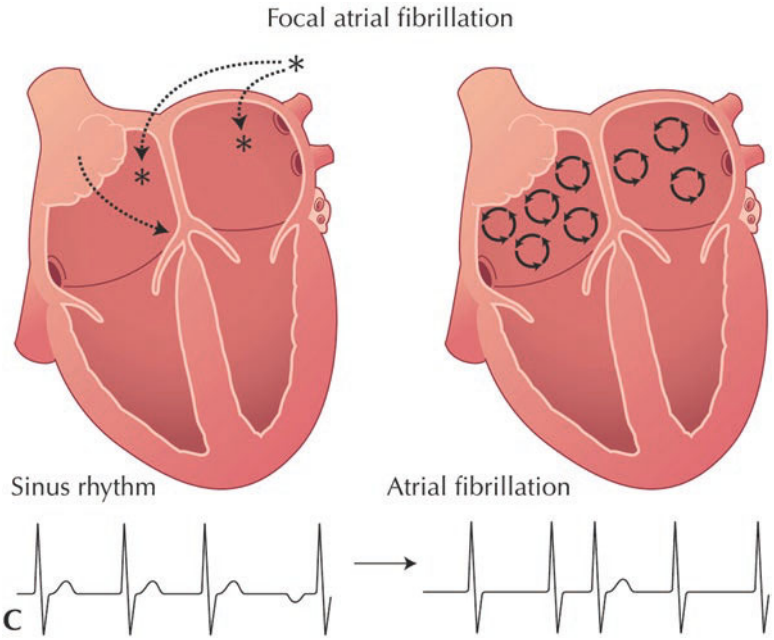
- Classified as follows:
  - Paroxysmal AF: terminates spontaneously or with intervention within 7 days of onset.
  - Persistent AF: does not terminate within 7 days.
  - Permanent AF: persists for a year or longer.
  - "Lone" AF: does not occur with any other clinical or echocardiographic cardiac problems; usually occurs in patients younger than 50.

Differential Diagnosis

- Atrial flutter
- Multifocal atrial tachycardia
- Supraventricular tachycardia

Pathophysiology and Etiology

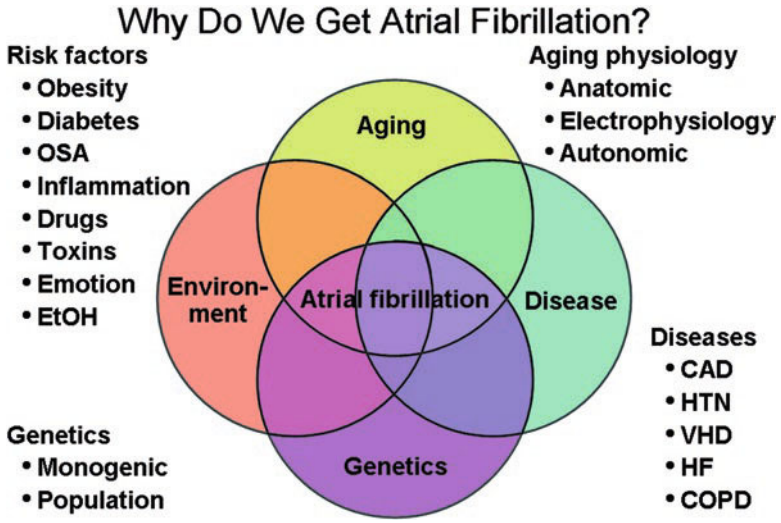
- Instead of being coordinated, atrial contractions are irregular, disorganized, chaotic, and very rapid.
- This electrical malfunction may result in:
  - Tachypalpitations, often described by patients as a "fluttering" or "butterflies" in the chest.
  - Inadequate "topping off" of the ventricular volume prior to ventricular systole, which may result in fatigue, dizziness, or heart failure.
- Because the cardiac cycle of atrial systole followed by ventricular systole is disrupted by the lack of regularity of impulses through the atrioventricular node, the ventricles beat irregularly and often beat faster than normal.
  - This "irregularly irregular" rhythm is classified as showing a "controlled" ventricular response (rate <100 bpm) or "rapid" ventricular response (rate ≥100 bpm).
- The precise mechanism that causes AF is not completely understood, but AF often is seen concomitantly with other heart and metabolic diseases, including:
  - Congestive heart failure
  - Coronary artery disease
  - Valvular heart disease
  - Hypertension
  - Hyperthyroidism
- Acute alcohol abuse, especially in binges, may cause AF ("holiday heart").



Focal atrial premature complexes usually originating from pulmonary veins can initiate AF. Ablation of these arrhythmogenic focal triggers can restore rhythm. This finding opens an exciting era in electrophysiology with the possibility of curing AF by ablation. [Grogin HR. Supraventricular tachycardia. In: Scheinman M, editor. Arrhythmias: electrophysiologic principles. Philadelphia: Current Medicine; 1996. Chapter 5 (Braunwald E, editor. Atlas of heart diseases; vol. 9).] *Caption adapted from original*

Atrial Fibrillation	
Common causes	Heart failure
	Hypertension
	Cardiac ischemia
	Myocardial infarction
	Mitral valve disease
	Pneumonia
	Hyperthyroidism
	Alcohol
	Postoperative AF
Rare causes	Cardiomyopathy
	Constrictive pericarditis
	Sick sinus syndrome
	Bronchial carcinoma
	Atrial myxoma
	Endocarditis
	Haemochromatosis
	Sarcoidosis

Causes of Atrial Fibrillation. [From article: Reversible atrial fibrillation secondary to a mega-oesophagus. BMC Ear Nose Throat Disord. 2006 Dec 13;6(1):15. https://doi.org/10.1186/1472-6815-6-15, at http://link.springer.com/article/10.1186%2F1472-6815-6-15; by Tahwinder Upile, Waseem Jerjes, Mohammed El Maaytah, Sandeep Singh, Colin Hopper, Jaspal Mahil, © Upile et al; licensee BioMed Central Ltd. 2006; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*



Atrial fibrillation is a multifactorial condition resulting from an interaction between cardiovascular disease effects, aging, genetics, and environmental factors. *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, *EtOH* alcohol use, *HF* heart failure, *HTN* hypertension, *OSA* obstructive sleep apnea, *VHD* valvular heart disease [Eleid MF, Cha Y-M, Shen W-K. Atrial fibrillation and heart failure: rate versus rhythm control. In: Bartunek J, Vanderheyden M, editors. Translational approach to heart failure [Internet]. New York: Springer; 2013 [cited 2015 Aug 13]. p. 129–44. Available from: http://link.springer.com/10.1007/978-1-4614-7345-9_6] *Caption from original*

Presentation

Typical/"Classic"

- Not all patients with AF have symptoms, but the risk of thromboembolic complications is the same, regardless.

- Typical symptoms include palpitations, tachycardia, fatigue, weakness, dizziness, lightheadedness, reduced exercise capacity, and dyspnea.

Atypical

- The first presentation of AF may be a thromboembolic complication, such as stroke or mesenteric ischemia.
- AF may present as anginal pain.
- Some patients, particularly those who are elderly, may not notice the palpitations (particularly if the ventricular rate is less than 100 bpm) and may present with completely unrelated complaints.

Primary Differential Considerations

- Atrial flutter
- Multifocal atrial tachycardia
- Supraventricular tachycardia
- Premature atrial contractions
- Premature ventricular contractions

History and Physical Exam

Findings That Confirm Diagnosis

- Although an "irregularly irregular" pulse is suggestive of AF, this also may be associated with other arrhythmias, and an ECG is required to differentiate among them.

Factors That Suggest Diagnosis

- Irregularly irregular pulse on examination
- Palpitations plus dyspnea
- Palpitations plus syncope or near-syncope
- Palpitations and generalized weakness
- Palpitations and hypotension
- Unexplained dyspnea, syncope, generalized weakness, or hypotension
- Acute ischemic stroke

Factors That Exclude Diagnosis

- ECG showing a normal sinus rhythm excludes AF "in the moment," but does not exclude paroxysmal AF.

Ancillary Studies

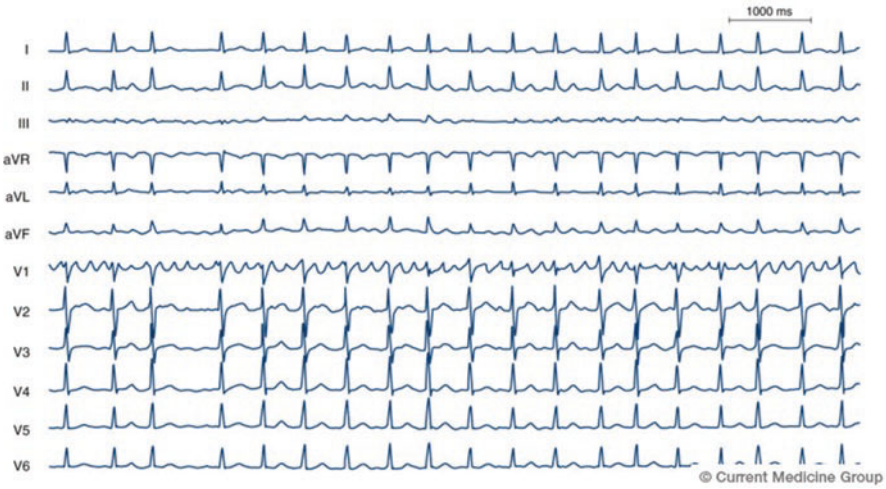
Laboratory

- Often obtained in search for underlying disorders or other associated disorders:
  - B-type natriuretic peptide (BNP)
  - Troponin
  - Electrolytes
  - Blood glucose
  - Thyroid-stimulating hormone (TSH)
  - Toxicology

Electrocardiography

- ECG is necessary to make the diagnosis.
- Irregular rate with an atrial rate greater than 300 bpm
- Ventricular rate may be slow, normal, or fast.
- Absent or erratic P waves are noted.
- PR interval is absent.
- QRS may be normal but may be widened if conduction delay is present.

Atrial fibrillation. Atrial fibrillation is characterized by the absence of P waves, which are replaced by irregular f waves or no sign of atrial activity. The QRS complexes may be normal or irregular and varying in amplitude. The 12-lead ECG shown here demonstrates atrial fibrillation with moderate ventricular response rate. [Leung J. Electrocardiographic monitoring. In: Lichtor JL, editor. Preoperative preparation and intraoperative monitoring. Philadelphia: Current Medicine; 1997. Chapter 7. (Miller RD, editor. Atlas of anesthesia; vol. 3).] *Caption from original*



Atrial fibrillation (AF) 12-lead surface electrocardiogram. AF is the most common sustained arrhythmia and is particularly prevalent in the elderly. Characteristic of AF is an irregular ventricular response and rapid irregular oscillations or fibrillatory waves that vary in shape, amplitude, and timing. [Epstein L, Stevenson W, Steven D, Seiler J, Roberts-Thomson K, See V. Arrhythmias. In: Libby P, editor. Essential atlas of cardiovascular disease. 4th ed. Philadelphia: Current Medicine; 2009. Chapter 7.] *Caption from original*

Imaging

- Transthoracic echocardiography may be performed to evaluate the size of the right and left atria and size and function of the right and left ventricles; this also can detect valvular heart disease.
- Transesophageal echocardiography is used to identify thrombi in the left atrium or left atrial appendage.

Special Populations

Age

- Incidence of AF increases with advancing age.
- "Lone AF" more common below age 50.

Co-morbidities

- As under "Pathophysiology and Etiology," a host of other cardiac and metabolic disorders are frequent co-morbidities in patients with AF.
- Binge alcohol consumption predisposes to "holiday heart."

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Complications such as blood clot formation, strokes, and heart failure may arise, but rhythm conversion reduces the chances that such complications will develop.

Mimics

- Atrial flutter
- Multifocal atrial tachycardia
- Supraventricular tachycardia

Time-Dependent Interventions

- Patients may have potentially life-threatening symptoms that need immediate intervention with electrical cardioversion, including decompensated congestive heart failure, hypotension, angina, or cardiac ischemia.

Overall Principles of Treatment

- The initial focus of AF management is rate control to minimize any perfusion stress on the ventricles.
  - The usual approach is with titrated doses of calcium channel blockers or beta-blockers.
- Once rate is controlled (or if patient presents with a controlled ventricular rate), consideration is given to converting the rhythm out of AF back into a sinus rhythm.
  - This may be approached pharmacologically with a variety of potential drugs, such as ibutilide or procainamide, or electrically via synchronized cardioversion.
- If the patient has been in AF for 24 to 48 hours or longer, anticoagulation therapy should be provided before attempting cardioversion, as clots that may have formed in the fibrillating atria or atrial appendage may dislodge and embolize when normal atrial electrical activity is restored. Therapy may be provided acutely with parenteral agents such as unfractionated or low-molecular weight heparin or with fast-acting non-warfarin oral anticoagulants (dabigatran, rivaroxaban, apixaban, edoxaban)
  - Alternatively, cardioversion may be attempted after transesophageal echocardiography that excludes atrial clots
  - Likelihood of stroke or systemic embolization may be assessed with CHA2DS2-VASc score

Risk factor	Points
Age over 75 years	1
Previous stroke/TIA	2
Hypertension	1
Symptoms or signs of LV dysfunction	1
Diabetes mellitus	1

$CHADS_2VASC$ score points for prediction of stroke in atrial fibrillation. (Data from Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of Clinical Classification Schemes for Predicting Stroke: Results From the National Registry of Atrial Fibrillation. JAMA.2001;285(22):2864-2870. https://doi.org/10.1001/jama.285.22.2864.) [Table from Verheugt FWA. The new oral anticoagulants. Netherlands Heart Journal. 2010 Jun;18(6):314–8.] *Caption adapted from original*

- Patients whose AF is resistant to cardioversion or recurs after initially successful cardioversion may be referred to electrophysiology, where the possibility of catheter ablation of the electrical source of the AF can be addressed definitively and specifically.
  - Success rates usually exceed 65–75 %

Disease Course

- The most feared complication of AF is thromboembolism to a critical vascular bed—especially stroke.
- The palpitations of AF may have a very adverse effect on quality of life. They may be symptomatic even in patients with controlled ventricular response.
- Patients with diminished pump function are particularly sensitive to the absence of consistent ventricular filling (the missing "atrial kick") and may experience persistent easy fatigability and even angina.
- Longstanding AF increases mortality.

Related Evidence

Papers of particular importance have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Atrial Fibrillation"[Mesh] OR "Atrial Fibrillation"

Chapter 13
Bradyarrhythmias

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Bradyarrhythmias

- Bradycardia

Incidence/Epidemiology

- The bradyarrhythmias encompass a broad range of disorders; therefore, their incidence varies widely.
- Sinus bradycardia may be normal in up to 35 % of people younger than 25 years. It also may be normal in well-conditioned athletes at most ages.
- Sick sinus syndrome becomes more common as people age, with more than 50 % of cases occurring in people over 50, but it may occur at any age.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_13

Differential Diagnosis

- Clinically significant bradycardias may cause a wide range of symptoms, the most common of which are syncope, presyncope, chest pain, general fatigue, dyspnea on exertion, and dyspnea at rest. As such, the differential is broad and far ranging.
- Bradycardias also have a broad range of causes; therefore, the differential diagnosis of the bradycardia itself also is extensive.

Pathophysiology and Etiology

- Bradycardia is defined as a heart rate below 60 bpm.
- Bradycardia generally is caused by two different mechanisms:
  - Slowing, blocking, or failure of impulse generation in the sinus node
  - Block in the conduction system from the atrioventricular (AV) node down through the His–Purkinje system.
- Many different processes may lead to these mechanisms, including intrinsic conduction system disease, other heart diseases, other systemic diseases, and drugs, to name a few.
- When these blocks occur, alternative pacemakers within the heart take over the pacemaker function. Other conduction tissue, or even myocytes, may act as alternative pacemakers. In general, the higher within the conduction system the impulse originates, the faster the rate; if the impulse is generated within or above the bundle of His, the rate generally is enough to maintain adequate cardiac output. This association also may be used as a clue to the location of the block based on the escape rate.
- Although slow heart rates can occur with junctional or ventricular pacemakers, the bradyarrhythmias usually are classified according to the location of the block: either sinoatrial (SA) node dysfunction or AV node dysfunction.
- Sinus node dysfunction:
  - Sinus bradycardia: defined as a sinus node rate less than 60 impulses per minute.
    - An ECG will show normal sinus P waves and a fixed P-P interval that is equal to the R-R interval, with 1:1 AV conduction.
    - It may be physiologic and normal in well-conditioned athletes, in young people, and during sleep.
    - It may be secondary to excess vagal stimulation, which may even occur as a result of a necktie that is too tight.
    - Medications are a common cause, especially beta-blockers, calcium channel blockers, digoxin, and opioids.
    - It also (although less commonly) may be pathologic. Sinus bradycardia may be seen in the setting of acute inferior myocardial infarction (MI), increased intracranial pressure, carotid sinus hypersensitivity, and profound hypothyroidism.

Sinus bradycardia. No other abnormalities noted here except for sinus bradycardia at 50 bpm. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption adapted from original*

- Sinus arrhythmia (sinus dysrhythmia): similar to sinus bradycardia except for the presence of a variable P-P interval, leading to a slightly irregular rhythm. This is a normal variant and not pathologic. It is common in children and young adults. In the most common situation, the sinus node rate increases with inspiration and decreases during expiration because of the changes in vagal tone with breathing.

Sinus arrhythmia. Rhythmic variation in the sinus rate is noted across the rhythm strip. P-wave morphology and PR intervals remain essentially unchanged. [Foreman B. Common atrial and ventricular arrhythmias. In: Toth PP, Cannon CP, editors. Comprehensive cardiovascular medicine in the primary care setting [Internet]. Totowa, NJ: Humana Press; 2011 [cited 2015 May 22]. p. 459–96. Available from: http://link.springer.com/10.1007/978-1-60327-963-5_24] *Caption from original*

- Sinus arrest (sinus pause). In sinus arrest, the SA node fails to generate an impulse. It is recognized as a pause in the sinus rhythm. During the pause/arrest, no P waves are seen on the ECG. The P-P interval of the two complexes surrounding the pause will not be a multiple of the usual P-P interval, as would be the case if the pause were from an SA exit block. If the pause lasts long enough, there may be an escape beat from somewhere else along the conduction system or the ventricles. This may be a normal variant, but it also occurs in acute MI, intrinsic SA node disease, digitalis toxicity, stroke, and excessive vagal stimulation. Notably, frequent and prolonged sinus pauses may be seen in up to 30 % of patients with obstructive sleep apnea.

Sinus arrest. Note sudden cessation of sinus impulse for 3 s prior to resumption of normal sinus rhythm. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet].

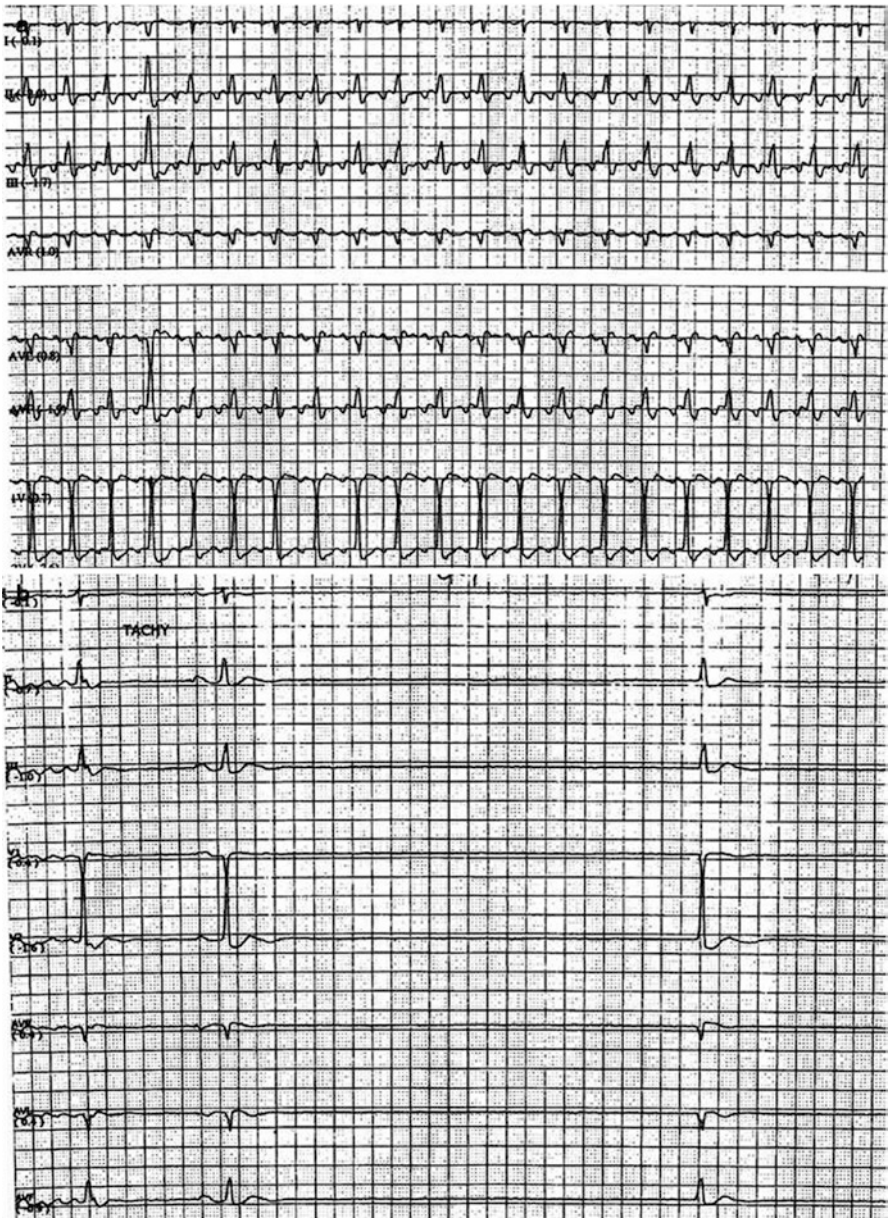
London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption adapted from original*

- SA exit block: recognized as a pause in the usual rhythm resulting from the absence of a normally expected P wave, usually because of blocked or slowed impulse generation within the SA node. The P-P interval of the two complexes surrounding the pause will have a P-P interval that is a multiple of the usual P-P interval. SA exit block may be subclassified as first degree; second degree, types I and II; and third degree. These usually are difficult, if not impossible, to see on a surface ECG and require electrophysiologic mapping of the sinus node discharge. These blocks may be seen following acute MI, acute rheumatic fever, and myocarditis, and secondary to drugs such as beta-blockers, calcium channel blockers, digoxin, quinidine, and salicylates. They also may be seen in well-conditioned athletes or secondary to excessive vagal stimulation. They usually are transient and not clinically significant.

Top panel: Type I second-degree sinoatrial exit block. Note the pause that is less than two times the PP interval. Also note the group beating consistent with Wenckebach periodicity. Bottom panel: Type II second-degree sinoatrial exit block. The pause here is two times the PP interval, with the occurrence of a junctional beat prior to the return of a sinus P wave which is followed by unperturbed sinus mechanism before there is another recurrence. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption from original*

- Sick sinus syndrome (tachycardia–bradycardia syndrome/tachy–brady syndrome): a mixed group of disorders marked by abnormalities of supraventricular impulse formation and conduction that are associated with both tachy- and bradyarrhythmias. It usually is the result of intrinsic disease of the sinus node or the surrounding tissue, sometimes with associated AV nodal disease. The tachyarrhythmias usually are either atrial fibrillation or atrial flutter, and the bradyarrhythmias usually are marked sinus bradycardia, prolonged sinus arrest, and SA block associated with abnormal AV conduction leading to inadequate escape rhythms. On prolonged rhythm monitoring, it is typical to see long periods of tachycardia followed by profound bradycardia upon the spontaneous termination of the tachycardia. It is most

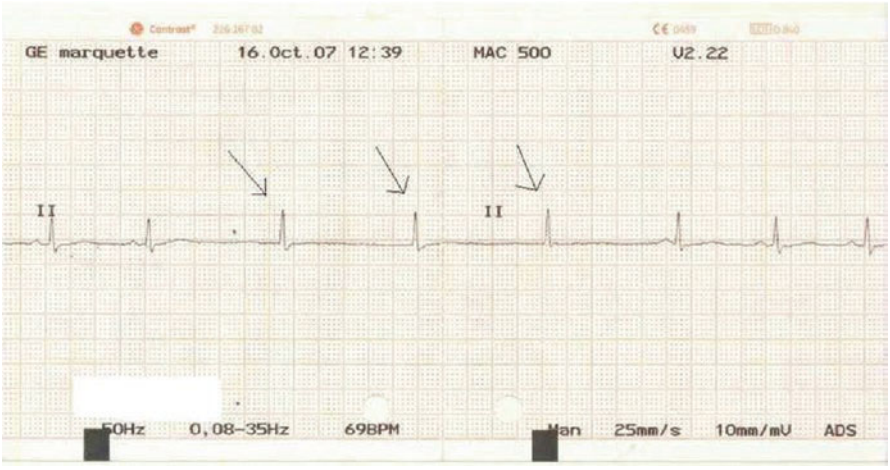
common in the elderly as a result of fibrotic degeneration of conduction tissue. It also may be seen in cardiomyopathies, in connective tissue diseases, and with the use of some medications. It usually is suspected in elderly patients who present with syncope and is an indication for a permanent pacemaker.



(a) Twelve-lead electrocardiogram of an 84-year-old female who presented with altered mental status. Atrial flutter with 2:1 A:V conduction is seen. (b) 12-lead

electrocardiogram showing flutter termination. A 4.9-s period of asystole is noted before ventricular activity resumes. The patient had multiple sinus pauses during sinus rhythm. These rhythms are typical of Tachy–Brady syndrome and are characteristic of sick sinus syndrome [El Hage L, Badhwar N, Goldschlager N. Top ten electrocardiographic (ECG) abnormalities not to miss. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 133–48. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_11] *Caption from original*

- Chronotropic incompetence: failure of the heart rate to increase appropriately with exercise
- Junctional rhythms. Under typical conditions, the sinus node impulses suppress (by nature of being faster) impulse generation distally along the conduction tree. If the sinus impulse is suppressed or blocked, the AV node may take over the pacemaker function. This is termed a junctional or junctional escape rhythm. The AV node naturally discharges at a rate of 40–60 bpm, which usually is enough to maintain cardiac output and blood pressure. As the impulse is generated in the AV node, the QRS complex will be narrow, but because the sinus impulses are blocked, there will be no P waves. Junctional rhythms may be seen after acute inferior MI and in congestive heart failure, myocarditis, hypokalemia, and digoxin toxicity.



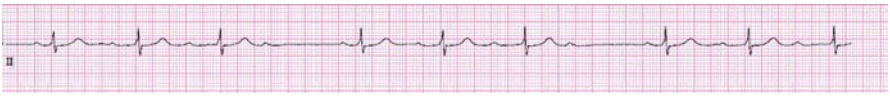
ECG shows transient sinus arrest with escape junctional rhythm. *Arrow* indicates escape junctional rhythm [Bhaskar EM, Moorthy S, Ganeshwala G, Abraham G. Cardiac conduction disturbance due to prallethrin (pyrethroid) poisoning. J Med Toxicol. 2010 Mar;6(1):27–30.] *Caption from original*

- AV node dysfunction
  - AV block is caused by either delayed or blocked conduction of impulses between the atria and the ventricles.

- AV block is classified into first-degree, second-degree (of which there are two types), and third-degree AV block (also referred to as complete heart block).
- First-degree AV block is defined as a P-R interval greater than 0.20 sec on an ECG. This indicates delayed conduction through the AV node, but all impulses are conducted to the ventricles. It may be a normal variant and generally portends no increased risk of further conduction disease or heart disease. It may be associated with increased vagal tone, digoxin toxicity, acute inferior MI, or myocarditis. When there is an underlying cause, the block usually is transient.

First-degree AV block [Mendoza A, Belda S, Salguero R, Granados MA. Congenital complete atrioventricular block associated with QT prolongation: description of a patient with an unusual outcome. Pediatr Cardiol. 2010 Aug;31(6):887–90.] *Caption from original*

- Second-degree AV block is marked by the failure of some sinus impulses to reach the ventricles. On an ECG, some P waves are seen without an associated QRS complex. There are two types: type I (also called Mobitz I or Wenckebach) and type II (Mobitz II).
  - Type I second-degree, Mobitz I AV (Wenckebach) block: There is progressive prolongation of AV conduction (noted as progressive lengthening of the P-R interval) until the atrial impulse is completely blocked and a QRS complex is dropped. The conduction ratio is the ratio of atrial impulses to those that are conducted into the ventricles, i.e., a 4:3 conduction ratio means that three of every four atrial impulses are conducted into the ventricles. In other words, there is a dropped QRS complex after every three sinus beats, so for four P waves, there are only three QRS complexes. This ratio usually is stable for any given patient, but some patients can manifest changing (variable) ratios of block. This block occurs at the level of the AV node. This type of block does not carry an increased risk of progression to third-degree heart block. It usually is transient, reversible, and asymptomatic. It may be seen during acute inferior MI, with myocarditis, with digoxin toxicity, and after cardiothoracic surgery.



Mobitz type I (Wenckebach) Second-Degree AV block. Notice the classic form of Wenckebach in a 4:3 pattern. The PP intervals are fixed, with lengthening of each successive PR interval with progressively decreasing increments and shorter RR intervals prior to the dropped beat. The pause is less than a multiple of the shortest RR interval, the return-cycle PR interval is shorter than the PR interval prior to the dropped beat, and there is obvious group beating periodicity. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption from original*

- Second-degree, Mobitz II AV block: The P-R interval is constant, and there are nonconducted impulses. As with Mobitz I block, there usually is a constant conduction ratio, but it may be variable. When the conduction ratio is 2:1, it is impossible to tell the difference between Mobitz I and Mobitz II heart block, as progressive P-R prolongation cannot be appreciated. This level of block usually occurs below the AV node (infranodal). If the escape pacemaker is high enough in the conduction system, the QRS complexes may still be narrow, but if the pacemaker is lower, the QRS complexes may be wide. This type of heart block almost always indicates some structural damage to the conduction system and usually is permanent. It carries a high risk of progression to third-degree heart block, especially if it occurs in the setting of an acute anterior MI.

Mobitz type II second-degree AV block. Note that there is ongoing sinus rhythm with a fixed PP interval before there is a sudden failure of conduction to the ventricles demonstrated by a dropped QRS. Note that there is no change in the PR interval preceding and following the dropped QRS, and this recurs later in the strip. The resultant pause is exactly twice the PP interval. Note the narrow QRS in this example that may suggest a nodal site of conduction block. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption adapted from original*

- Third-degree heart block (complete heart block): All conduction between the atria and ventricles is blocked. This block is seen on an ECG as the absence of a relationship between the P waves and the QRS complexes; therefore, it also is called *AV dissociation*. The atrial rate must be greater than the escape pacemaker rate for this lack of a relationship to be appreciated. If the rates are similar, it may be difficult to determine that there is no relationship between the P waves and QRS complexes (isorhythmic dissociation). A ventricular rate greater than the atrial rate precludes the diagnosis of third-degree heart block. AV dissociation with a ventricular rate greater than the atrial rate may be seen in some accelerated junctional rhythms, as well as in ventricular tachycardia. If the escape pacemaker is within the AV node (nodal), the escape rate is usually 40 to 60 bpm, with narrow QRS complexes. If the escape pacemaker is infranodal, the escape rate may be less than 40 bpm, in which case the QRS complex usually is widened. Nodal complete heart block may be transient, especially in the setting of an acute inferior MI. Infranodal complete heart block usually is permanent and the result of intrinsic conduction system disease, acute ischemia, drugs, or, rarely, Lyme disease.

Third-degree AV block (Complete heart block). Top panel: Ongoing sinus rhythm at a rate of 75 bpm with complete heart block and a narrow junctional escape at just over 40 bpm. Bottom panel: Sinus tachycardia at a rate of 125 bpm with a wide ventricular escape focus at 24 bpm. The sinus tachycardia indicates that this patient may be in distress and is far more likely to be symptomatic upon presentation. [Almasry IO. Evidenced-based approach to bradyarrhythmias. In: Stergiopoulos K, Brown DL, editors. Evidence-based cardiology consult [Internet]. London: Springer; 2014 [cited 2015 May 22]. p. 105–18. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_9] *Caption adapted from original*

Presentation

Typical/"Classic"

- Bradyarrhythmias often are asymptomatic and sometimes are found on routine evaluation or for evaluation of other complaints. This is especially true for sinus bradycardia, sinus arrhythmia, sinus block, first-degree AV block,

and type I second-degree AV (Wenckebach) block. Sinus bradycardia, sinus arrhythmia, and first-degree AV block may be normal variants. It is a common situation to find one of these abnormalities on an ECG performed for other reasons, such as preoperative clearance in an otherwise healthy person.

- These dysrhythmias also may be associated with other, more serious concerns (e.g., an acute MI or drug overdose or intoxication), and the symptoms of these disorders may predominate in the clinical presentation. In these situations, it often is difficult to discern whether the symptoms are being caused by the primary event or the dysrhythmia. However, these dysrhythmias often are transient and resolve spontaneously or with appropriate treatment of the primary event.
- Patients who have symptoms from their bradyarrhythmias often have vague and nonspecific complaints, such as fatigue, exercise intolerance, shortness of breath (especially on exertion), and feeling generally unwell.
- Most significantly, these dysrhythmias may present acutely with syncope, near-syncope, chest pain, acute dyspnea, and other signs of systemic hypoperfusion (change in mental status, hypotension, cyanosis, i.e., shock state). These presentations are much more likely with heart rates of 40 bpm or less, as well as with greater levels of block.
- Sick sinus syndrome often presents as syncope or near-syncope in elderly patients. Sometimes, however, symptoms from the tachycardia predominate, and the patient will present with palpitations and chest heaviness/pain, followed by syncope, presyncope, or generalized fatigue.

Atypical

- Because there is no "typical" presentation for bradyarrhythmias, almost all presentations are atypical.

Primary Differential Considerations

- Bradycardia is a self-evident diagnosis based on a heart rate less than 50 bpm. The differential diagnosis of *causes* of bradyarrhythmias is broad and includes:
  - Heart blocks or slow atrial fibrillation
  - Primary cardiac causes such as MI with cardiogenic shock
  - Metabolic causes such as hyperkalemia
  - Neurologic causes such as increased intracranial pressure or spinal cord injury
  - Drug toxicity (calcium channel blockers, beta-blockers, digitalis, clonidine)
  - Infections such as myocarditis, rheumatic fever, or Lyme disease
  - Malfunctioning pacemaker

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis is considered by finding a slow pulse rate on physical exam, then confirmed by finding a bradyarrhythmia on a 12-lead ECG and/or continuous cardiac monitoring.

Factors That Suggest Diagnosis

- The diagnosis may be suggested in patients presenting with the symptoms reviewed above (syncope, near-syncope, fatigue, exercise intolerance, chest pain or heaviness, palpitations).
- Patients with any of the aforementioned symptoms should undergo 12-lead ECG and may need further, more prolonged cardiac monitoring if the ECG does not secure the diagnosis.

Factors That Exclude Diagnosis

- Because many of these arrhythmias may be both transient and intermittent, they are all difficult to exclude, and the patient may require reassessments over time for complete exclusion. Patients also may require extended cardiac monitoring and/or electrophysiologic study for any of these abnormalities to be completely excluded.

Ancillary Studies

Laboratory

- In general, there are no specific laboratory tests that are diagnostic for any of these arrhythmias.
- All patients should have their electrolyte levels checked, as hypo- and hyperkalemia may lead to or exacerbate some of these disturbances.
- Thyroid-stimulating hormone levels also should be checked, as hypothyroidism also may cause bradycardia (most commonly sinus bradycardia).
- Patients on digoxin should have their serum levels checked, as digoxin toxicity may cause many of these arrhythmias.

- Patients who present with more acute symptoms, such as chest pain/heaviness or dyspnea, should have their cardiac biomarkers checked, as many of these rhythms may occur in the setting of an acute MI, especially an inferior MI.
- Many times, the laboratory evaluation of these patients is guided by the acuity of the presentation, not the bradyarrhythmia.
- Lyme disease may cause conduction disturbances; therefore, in the correct clinical setting, a Lyme titer may need to be analyzed. Chagas disease also may cause conduction disturbances so in the correct clinical setting, also may need to be evaluated.

Imaging

- Most patients being evaluated for cardiovascular-related complaints will have a chest x-ray, which may indicate contributing issues or show evidence of other heart disease (e.g., heart failure and/or cardiomegaly).
- Echocardiogram (either transthoracic or transesophageal) usually is performed in the workup of patients with symptomatic bradycardias. These studies may help reveal any structural heart disease that may be causative or contributory (e.g., cardiomyopathy, cardiac amyloidosis).

Special Populations

Age

- Most of these arrhythmias increase in incidence as age increases, as they often are associated with underlying heart disease or medication use.
- Exceptions include sinus bradycardia, sinus arrhythmia, and low-level heart blocks, which may be normal variants in the young.
- The most common cause of bradycardia in infancy is hypoxia.
- In adolescents and young adults, the pulse rate may drop normally to 35 to 40 bpm during sleep. This also may be associated with sinus pauses of up to 2 seconds. These findings are normal in this age group and usually do not require further evaluation.
- Complete heart block may be seen in infants and children and is almost always associated with congenital heart disease.
- Children presenting with high-grade heart block and no significant medical history should be evaluated for drug ingestion (digoxin, beta-blockers, calcium channel blockers, other antiarrhythmics, and opiates). It also may be necessary to consider conduction abnormalities from cardiac Lyme disease and, if appropriate (prolonged travel or immigration from endemic areas), Chagas disease.

Co-morbidities

- There are multiple co-morbidities of interest in patients presenting with bradyarrhythmias.
- Many of these disturbances are seen in patients with underlying structural heart disease and in those with coexistent coronary artery disease. Many of these conduction disturbances may be seen with or caused by cardiac medications.
- Increased vagal tone may precipitate many of these abnormalities, so anything that increases vagal tone should be considered (e.g., carotid sinus hypersensitivity, intra-abdominal catastrophe, increased intracranial pressure, drugs).
- As noted, conduction disturbances also may be found in association with many other diseases:
  - Inflammatory: rheumatic heart disease, myocarditis, pericarditis, and collagen vascular diseases such as rheumatoid arthritis and systemic sclerosis
  - Infectious: Lyme disease and Chagas disease
  - Systemic/cardiac amyloidosis
  - Post open heart surgery
  - Post mediastinal radiation therapy
  - Chest trauma
  - Rare genetic and familial diseases, such as myotonic dystrophy

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to consider the entire clinical picture when confronted with a patient who is bradycardic.
- It must be determined whether the patient is symptomatic and, if so, whether the symptoms arise from the bradycardia itself or an underlying/causative disorder.
- It is critical to look for these underlying disorders and not to stop at the diagnosis of bradycardia.
- All patients who are bradycardic should have a 12-lead ECG and, if in an appropriate clinical setting, continuous cardiac and vital sign monitoring.

Mimics

- Because bradycardia usually is defined by an absolute rate, there are no mimics; however, multiple potential etiologies must be considered in patients with bradycardia.

Time-Dependent Interventions

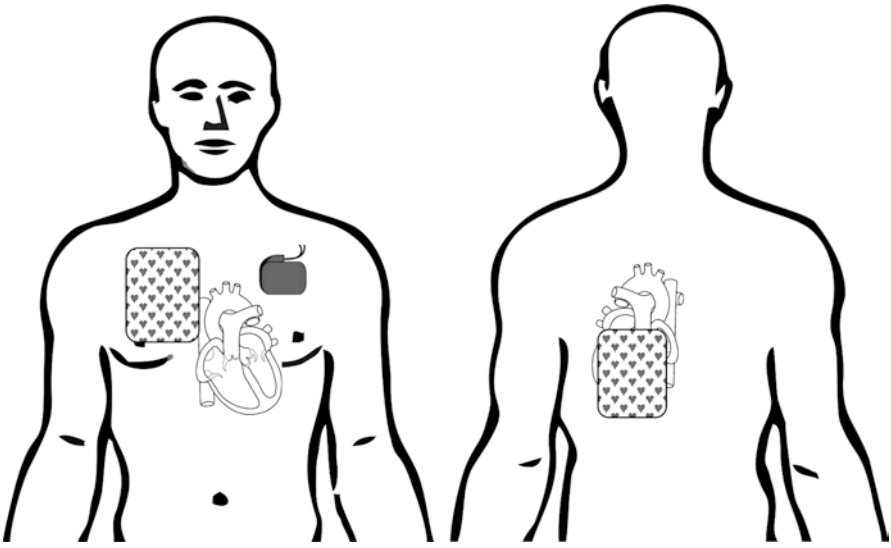
- Time-dependent interventions in bradycardias are necessary only in patients who have symptoms and show signs of reduced cardiac output, such as hypotension, a change in mental status, cyanosis, and syncope.
- In these situations, treatment must begin before obtaining a complete database.
- When a patient demonstrates any of these signs or symptoms, it is critical to act quickly to attempt to return cardiac output to more normal levels.
- Support of airway, breathing, and circulation is of paramount importance. All patients should have supplemental oxygen and adequate intravenous access for administration of medications and fluid. All unstable, or potentially unstable, patients with an arrhythmia should have defibrillator pads placed and attached to the defibrillator/monitor.

Overall Principles of Treatment

- As mentioned earlier, support of airway, breathing, and circulation is the most important management principle.
- All unstable, or potentially unstable, patients should have supplemental oxygen, adequate intravenous access for administration of medications and fluid, and defibrillator pads placed and attached to the defibrillator/monitor.
- In general, emergent treatment of bradycardias is not necessary unless the heart rate is less than 50 bpm and associated with signs of hypoperfusion, or if there is a risk of progression to complete heart block.
- Several urgent/emergent treatments are common and relevant to all the bradycardias:
    - Atropine. Atropine is a class II medication in the treatment of symptomatic bradycardias. It is a naturally occurring antimuscarinic drug that competitively antagonizes the effects of acetylcholine and other antimuscarinic agents. It increases the rate of sinus node firing (automaticity) and enhances AV nodal conduction. Because it blocks vagal activity, it sometimes is described as parasympatholytic or vagolytic. It is administered intravenously as 0.5-mg boluses (in situations other than bradycardia, it may be given as 1-mg boluses). It may be given every 5 minutes until the desired effect is achieved, or until a total of 3 mg (0.04 mg/kg) has been administered (this is the fully vagolytic dosage). If the conduction abnormality is an SA or AV nodal problem, it likely will respond to atropine. If the problem is infranodal or lower, the response rate decreases. Atropine's onset of action is about 2 to 4 minutes, and the effects may last for 5 to 6 hours. However, it is important to remember that the effect is temporary. Atropine must be administered with caution in settings of concurrent myocardial ischemia, as it increases the heart rate, which increases myocardial oxygen

demand, and may worsen ischemia. Atropine is not indicated in asymptomatic bradycardia. Atropine likely will have no effect on a transplanted heart, as heart transplants are denervated. Doses below 0.4 mg may cause a paradoxic bradycardia.

- Transcutaneous pacemaker. Transcutaneous pacing is a class I intervention for unstable patients with symptomatic bradycardia. All unstable patients should undergo transcutaneous pacing. Although atropine may be given as a temporizing measure, it should not replace transcutaneous pacing in unstable patients with high-grade (type II second-degree and complete) heart block. Self-adhesive pads are placed with the left pad over the left anterolateral precordial area and the right pad in the right subscapular region. Most patients have capture (i.e., when the pacing impulse results in a heartbeat) with 100 mA of output. Sometimes, however, it may require up to 200 mA of output for capture to occur. Outputs above 200 mA should not be attempted. Transcutaneous pacing may be uncomfortable and painful; therefore, all patients should receive either pain control or sedation with anxiolytics. If it is impossible to induce capture, it may be necessary to move to transvenous pacing.



Placement of transcutaneous pacemaker pads. [Healey JS, Merchant R, Simpson C, Tang T, Beardsall M, Tung S, Fraser JA, Long L, van Vlymen JM, Manninen P, Ralley F, Venkatraghavan L, Yee R, Prasloski B, Sanatani S, Philippon F. Society position statement: Canadian Cardiovascular Society/Canadian Anesthesiologists' Society/Canadian Heart Rhythm Society joint position statement on the perioperative management of patients with implanted pacemakers, defibrillators, and neurostimulating devices. Can J Anaesth. 2012 Apr;59(4):394–407.] *Caption adapted from original*

The right pad is placed in the alternative, right upper anterior chest and apex positions. [Woodcock B. Hemodynamic emergencies. In: Tremper KK, editor. Principles of anesthetic techniques and anesthetic emergencies. Philadelphia: Current Medicine; 1998. 195 p. (Miller RD, editor. Atlas of anesthesia; vol. 4).]

https://www.youtube.com/watch?v=qkSGaJkNqvg
Video demonstrating transcutaneous pacing.

- Transvenous pacing. Transvenous pacing has the same indication as transcutaneous pacing. It requires central venous access because the leads are passed through the central catheter into the heart. This is an invasive procedure, and although it may be attempted emergently at the bedside, it is best performed in conjunction with expert consultation and guidance. Currently, this technique is performed most often under fluoroscopic guidance in a cardiac catheterization laboratory as a bridge to a permanent pacemaker.
- Epinephrine and dopamine. Epinephrine and dopamine may be considered for blood pressure support if atropine and emergent pacing have been unsuccessful. Administration of these agents is only temporizing measure until the patient can be prepared for definitive therapy.
- Specific drug ingestions that lead to symptomatic and/or unstable bradycardias should be treated with specific antidotes if available, but also may be treated with atropine and pacing as required.

Following is a list of recommendations based on the specific bradycardia:

- Sinus bradycardia: generally requires no treatment unless the rate is less than 50 bpm and associated with symptoms, which may occur with profound vagal stimulation. If necessary, treatment may start with atropine and, if necessary, transcutaneous pacing.
- Sinus arrhythmia: requires no treatment.
- Sinus pauses/sinus arrest: treatment should be aimed at the underlying causes.

- Sick sinus syndrome: this is an indication for a permanent pacemaker.
- Junctional bradycardia: usually does not require treatment and is transient. If the patient is symptomatic or unstable, atropine and/or pacing may be used; however, it also is important to search for the underlying cause.
- SA block: often requires no treatment; however, the underlying cause should be evaluated.
- First-degree AV block: usually requires no treatment.
- Second-degree AV block, Mobitz type I (Wenckebach): usually does not require treatment unless the patient has symptoms. It usually is transient, and when the underlying cause is identified and treated, the block usually resolves. If treatment is necessary, most patients will respond to atropine.
- Second-degree AV block, Mobitz type II: these patients are unstable, with a high risk of progression to complete heart block. They should have pacemaker pads placed and attached for use if necessary. Atropine may be used as a temporizing measure (about 60 % of patients respond), but in most circumstances, pacing will be necessary. Because this type of block usually is associated with permanent damage to the conduction system, most patients will require a permanent pacemaker at some point in their care.
- Third-degree heart block (complete heart block): this is an inherently unstable block and usually is symptomatic and hemodynamically significant. It usually indicates permanent damage to the conduction system and requires either transcutaneous or transvenous pacing as a bridge to a permanent pacemaker. Some patients may respond to atropine if the block is higher within the His–Purkinje system.

Disease Course

- As detailed earlier, many of these rhythms/conduction problems are either normal variants or transient and can be resolved with identification and treatment of the underlying disorders.
- Higher-grade AV blocks almost always indicate some permanent damage to the conducting system and require placement of a permanent pacemaker.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

European Society of Cardiology (ESC); European Heart Rhythm Association (EHRA), Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013 Aug;15(8):1070-118. https://doi.org/10.1093/europace/eut206. PMID: 23801827. http://www.ncbi.nlm.nih.gov/pubmed/23801827 **

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Udo EO, van Hemel NM, Zuithoff NP, Doevendans PA, Moons KG. Prognosis of the bradycardia pacemaker recipient assessed at first implantation: a nationwide cohort study. Heart. 2013 Nov;99(21):1573-8. https://doi.org/10.1136/heartjnl-2013-304445. PMID: 23969476. http://www.ncbi.nlm.nih.gov/pubmed/23969476

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Bradycardia"[Mesh] OR "Sick Sinus Syndrome"[Mesh] OR "Bradycardia" OR "Bradyarrhythmia"

Chapter 14
Bronchiectasis

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Bronchiectasis

Incidence/Epidemiology

- It is estimated that between 100,000 and 125,000 people in the United States have bronchiectasis.
- The prevalence increases with age.
- It is more common in women than in men.
- The incidence of bronchiectasis has been decreasing in developed nations.
- The incidence of bronchiectasis may be up to three times higher in developing nations. This is likely due to a combination of environmental and genetic factors that lead to a higher incidence of recurrent pulmonary infections, especially among children and young adults.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_14

Differential Diagnosis

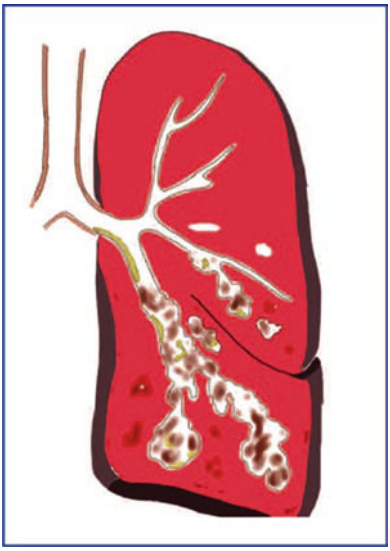
- The differential diagnosis includes all the causes of chronic cough, sputum production, and dyspnea.
- This includes chronic bronchitis, asthma, chronic obstructive pulmonary disease, chronic sinusitis, and idiopathic pulmonary fibrosis, among others.

Pathophysiology and Etiology

- Bronchiectasis refers to lung disease dominated clinically by chronic cough with sputum production. Symptoms are often present for months to years prior to diagnosis.
- The major pathophysiologic change is irreversible airway dilatation with wall thickening and scarring.

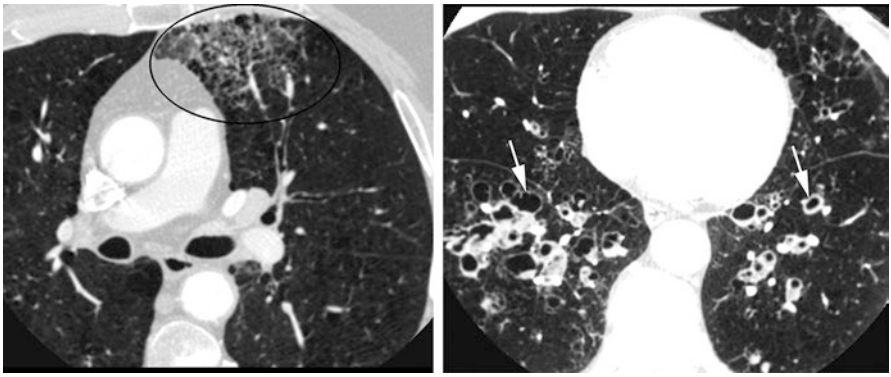
https://www.youtube.com/watch?v=uNeprw1rsgE
Video animation of the pathophysiology of bronchiectasis.

Close inspection of the cut surface of this lung in a case of mild bronchiectasis shows somewhat fibrotic-walled airways, which are dilated and congested. In addition, there is local, patchy emphysema and some cystic change and interstitial scarring. Many cases of lung disease do not show a single, pure format [Suvarna SK. Thorax: Heart, Lungs, Mediastinum, and Pleura. In: Suvarna SK, editor. Atlas of Adult Autopsy [Internet]. Cham: Springer International Publishing; 2016 [cited 2016 Nov 7]. p. 65–160. Available from: http://link.springer.com/10.1007/978-3-319-27022-7_4] *Caption from original*



Bronchiectasis. There is dilatation of the airways with inflammation and increased mucous production [Ruggeri G, Gobbi D, Libri M, Lima M. Pediatric Bronchiectasis. In: Lima M, editor. Pediatric Thoracic Surgery [Internet]. Springer Milan; 2013 [cited 2015 May 11]. p. 351–62. Available from: http://link.springer.com/chapter/10.1007/978-88-470-5202-4_30]

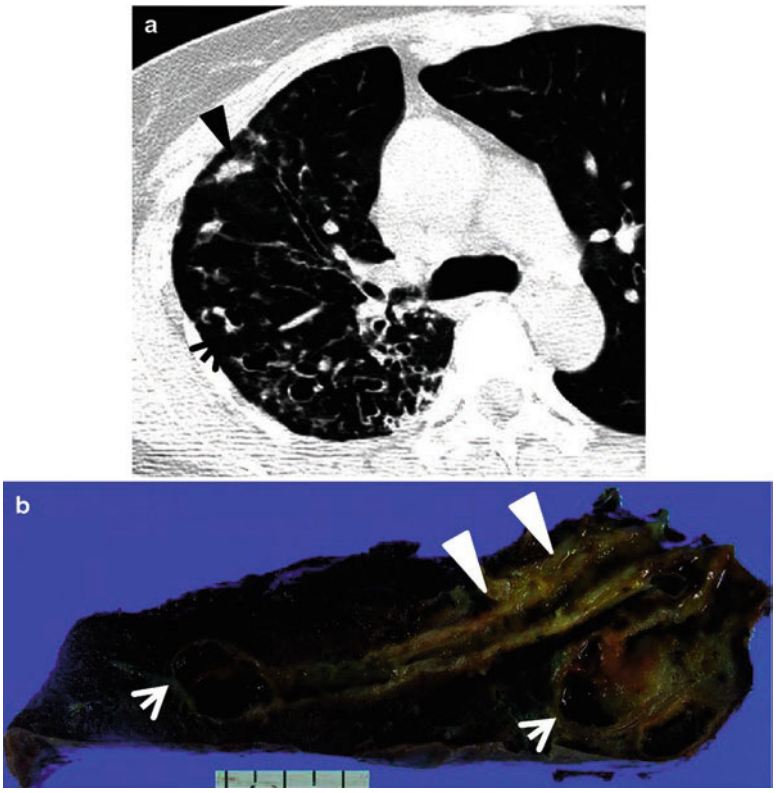
- The lung changes can be focal or diffuse.



Focal bronchiectasis (circled area of upper panel) may be seen in patients with recurrent aspiration or pneumonias. Bilateral and diffuse bronchiectasis (arrows in lower panel) is typically the result of diffuse necrotizing infections in childhood, cystic fibrosis, immotile cilia syndromes, or immunoglobulinopathies, among

others. [Callister T, Budoff M, Braunwald E. Atlas of Cardiovascular Computed Tomography, Volume 01, Chapter 18. In: Budoff M, Narula J, Achenbach SS, editors. Atlas of Cardiovascular Computed Tomography. Philadelphia: Current Medicine; 2007 [cited 2015 May 11]. Book DOI 978-1-57340-267-5] *Caption adapted from original.*

- These changes lead to airways that easily collapse and obstruct airflow.
- The initiation of bronchiectasis requires many factors. It is felt that there needs to be an inciting infectious insult, often in the setting of some impaired host defenses, that leads to airway obstruction that impairs drainage of inflammatory and purulent material and sets up a chronic airway inflammatory response. This leads to chronic inflammation, with permanent scarring, dilatation, and destruction of the airways (both large and small).
- The chronic inflammation leads to recurrent infections, which then lead to continued inflammation, setting up a vicious cycle.
- Many diseases and environmental issues can incite and/or worsen bronchiectasis.
- The pattern of involvement in the lungs may be a helpful clue as to etiology. Focal bronchiectasis points to foreign body aspiration or intrinsic or extrinsic airway compression as the cause.
- Causes/etiologies of bronchiectasis include:
    - Obstruction. Bronchiectasis can result from an aspirated foreign body, intrinsic compression/blockage from an endobronchial lesion or mass, or extrinsic compression from a mass.
- Infection. Can be bacterial pneumonia, atypical pneumonia such as viral or *Mycoplasma*, tuberculous, and non-tuberculous mycobacteria. *Mycobacterium avium*-intracellulare complex (MAC) is the most common non-tuberculous mycobacteria causing bronchiectasis, classically occurring in nonsmoking women over age 50.
- Immunodeficiency. Hypogammaglobulinemias, such as severe, combined immunodeficiency. These patients often have recurrent infections starting in childhood. Immunodeficiency also includes HIV infection and bronchiolitis obliterans after lung transplantation.
- Autoimmune/rheumatologic disorders. Rheumatoid arthritis, Sjogren's syndrome, inflammatory bowel disease.
- Immune-mediated diseases such as allergic bronchopulmonary aspergillosis.
- Genetic causes such as cystic fibrosis, ciliary dyskinesia (by decreasing secretion clearance), alpha-one anti-trypsin deficiency (usually causes early-onset emphysema, but bronchiectatic changes are also common).
- Recurrent aspiration.
- Idiopathic. Often represents from 25 – 50% of cases.
- Cigarette smoking.



Bronchiectasis showing signet ring sign in a 44-year-old man. (a) Lung window image of CT scan (2.5-mm section thickness) obtained at level of the right upper lobar bronchus shows dilated bronchi showing signet ring sign (arrows) in right upper lobe. Also note mucus plugging (arrowhead) in dilated bronchi. (b) Gross pathologic specimen obtained with right upper lobectomy discloses cylindrical bronchiectasis and distal cystic changes (arrows, cystic bronchiectasis). Also note thickened bronchial wall (arrowheads) with active inflammation [Lee KS, Han J, Chung MP, Jeong YJ. Signet Ring Sign. Radiology Illustrated: Chest Radiology [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 Nov 19]. p. 139–42. Available from: http://link.springer.com/10.1007/978-3-642-37096-0_15] *Caption from original.*

Presentation

Typical/"Classic"

- The typical presentation of bronchiectasis is one of prolonged (months) cough that produces thick sputum. Usually there is an absence of acute infectious symptoms such as fever. Patients may also complain of dyspnea, especially on exertion. They may also exhibit wheezing.

Atypical

- Patients may present with symptoms more consistent with chronic obstructive pulmonary disease or asthma, with wheezing and shortness of breath being more prominent.
- Patients may also present with a more acutely infectious appearance with fever, associated with productive cough. This is especially common if they have been undiagnosed and are suffering from an acute infectious exacerbation from their undiagnosed bronchiectasis.

Primary Differential Considerations

- Asthma
- Acute and chronic bronchitis
- Cystic fibrosis
- GERD
- Pneumonia
- Alpha-1-antitrypsin deficiency

History and Physical Exam

Findings That Confirm Diagnosis

- A typical presentation with prolonged cough productive of thick sputum will strongly suggest the diagnosis, but the diagnosis is usually only confirmed by typical findings on CT scan of the chest.

Factors That Suggest Diagnosis

- Again, the typical symptoms should strongly suggest the diagnosis.
- This is especially true if the patient has any of the known predisposing conditions.

Factors That Exclude Diagnosis

- There are no historical or physical examination findings that can reliably exclude the diagnosis.
- Bronchiectasis may coexist with many other diseases, especially COPD.

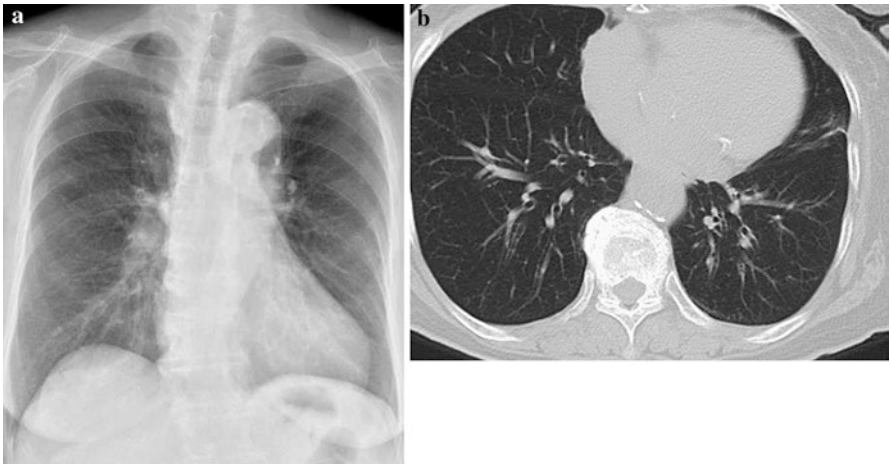
Ancillary Studies

Laboratory

- Although there are no laboratory tests specifically needed for the diagnosis, patients will usually require a CBC with differential and basic chemistries in the evaluation. They may also require tests specific for the disorder if they need to be evaluated for any of the etiologies of bronchiectasis, such as tests for RA, SS, and alpha-one antitrypsin.
- Sputum culture may be necessary when trying to evaluate for MAC or other mycobacterial causes of bronchiectasis. Sputum culture may also be helpful for management of acute infectious exacerbations of bronchiectasis.

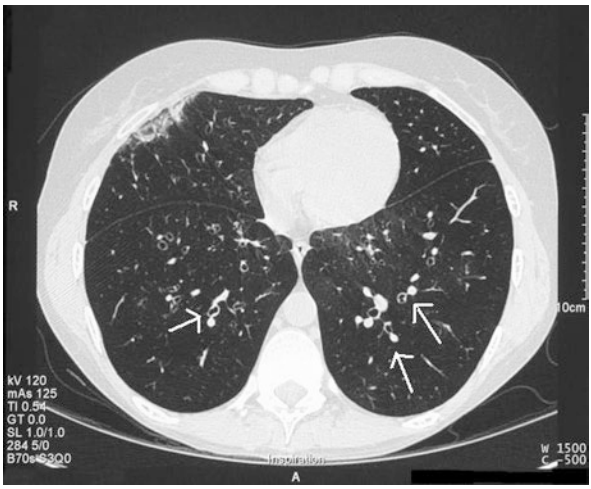
Imaging

- Chest CT is the diagnostic imaging study of choice for confirming the diagnosis of bronchiectasis.
- Plain chest x-ray may show findings consistent with bronchiectasis (such as dilated bronchioles), but CT is necessary to confirm the diagnosis.

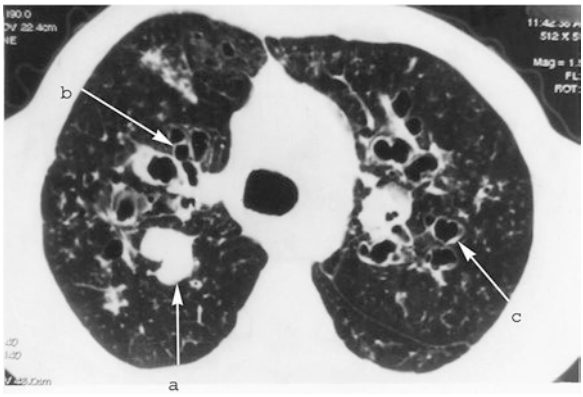


A Chest X-ray revealed clear lung fields. b High-resolution CT image through the lungs at the level of bronchus shows right lower lobe and lingular bronchiectasis. [Toyoda M, Yokomori H, Kaneko F, Yoshida H, Takahashi A, Hoshi K, Takeuchi H, Tahara K, Kondo H, Motoori T. Hepatic granulomas as primary presentation of Mycobacterium avium infection in an HIV-negative, nonimmunosuppressed patient. Clinical Journal of Gastroenterology. 2009 Dec;2(6):431–7.] *Caption adapted from original.*

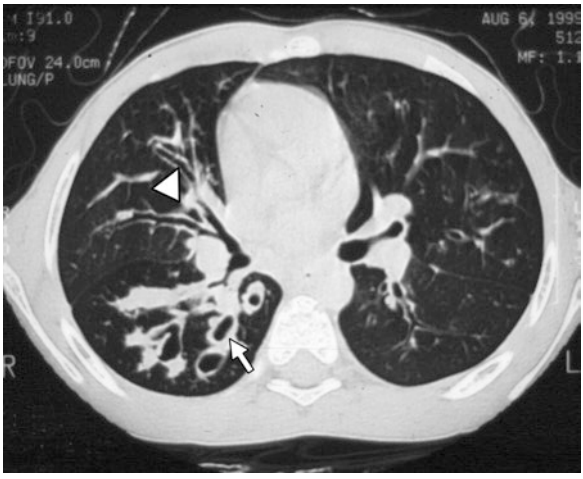
- CT findings in bronchiectasis include airway dilatation, lack of bronchial tapering (usually noticed as tubular structures within 1 cm of the pleural surface), bronchial wall thickening in dilated airways, and a large amount of dried secretions (tree-in-bud pattern).
- The signet-ring sign on CT is when there is a cross-sectional airway with a diameter that is at least 1.5 times larger than an adjacent vessel.



(CT Thorax): Resolution of areas of consolidation and "signet ring sign". The signet ring sign is a finding seen on CT scans of the thorax. It consists of a small circle of soft tissue attenuation that abuts a ring of soft tissue attenuation surrounding a larger low attenuating circle of air and is indicative of bronchiectasis. [From article: Invasive pulmonary aspergillosis 10 years post bone marrow transplantation: a case report. Journal of Medical Case Reports. 2009;3(1):26. https://doi.org/10.1186/1752-1947-3-26, at http://link.springer.com/article/10.1186%2F1752-1947-3-26/fulltext.html; by Rifat Rashid, David W Denning, © Rashid and Denning; licensee BioMed Central Ltd. 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original.*



High resolution chest computed tomography scan (lung window) showing (a) mucus-filled dilated bronchi (arrow) and extensive bilateral central bronchiectasis characterised by (b) "string of pearls" and (c) "signet ring" appearances [Shah A. How to Diagnose Allergic Bronchopulmonary Aspergillosis. In: Comarú Pasqualotto A, editor. Aspergillosis: From Diagnosis to Prevention [Internet]. Dordrecht: Springer Netherlands; 2009 [cited 2015 Nov 19]. p. 725–45. Available from: http://www.springerlink.com/index/10.1007/978-90-481-2408-4_43] *Caption from original.*



Computed tomographic image of bronchiectasis. Chest CT showing diffuse dilated bronchi (bronchiectasis), especially in the right lower lobe. Thick-walled bronchi are seen. Also present is the "signet-ring" sign (arrow), in which the diameter of the airway (lumen) is greater than that of the adjacent vessel. Apparent in the right middle lobe is "tram-tracking" (arrowhead), with absence of tapering of the peripheral bronchi. [MacLusky I, Solomon M, Laxer R, Ford-Jones EL, Friedman J, Gerstle T. Atlas of Pediatrics, Volume IA, Chapter 14. In: Laxer RM, editor. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine Group; 2005. 519 p. ISBN 1-57340-188-9] *Caption from original.*

- Most patients with bronchiectasis will undergo bronchoscopy during evaluation. This is most important in patients with focal bronchiectasis to exclude airway obstruction from a mass or foreign body.
- Pulmonary function testing can help in gauging the functional impairment of the patient.

Special Populations

Age

- The incidence of bronchiectasis increases with age.
- Patients with cystic fibrosis can develop clinically significant bronchiectasis in adolescence or young adulthood.

Co-morbidities

- Co-morbidities of interest include all the etiologies listed above.
- Bronchiectasis may coexist with COPD and other chronic lung diseases.
- Bronchiectasis may also coexist with causes of chronic dyspnea and cough, such as congestive heart failure.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step.
- It is important to perform appropriate imaging in patients in whom the diagnosis is being considered.
- A search for the possible etiology should be performed for all patients being evaluated for bronchiectasis.

Mimics

- Typical mimics of bronchiectasis include COPD/emphysema, asthma, and pulmonary fibrosis.

Time-Dependent Interventions

- Time-dependent interventions in bronchiectasis are rarely necessary. This is a chronic, slowly progressive disease.
- Acute exacerbations often benefit from the timely use of antibiotics, as well as from bronchial hygiene measures (help to enhance secretion clearance) such as chest physiotherapy, mucolytics, hydration, and sometimes bronchodilator therapy.

Overall Principles of Treatment

- The general treatment of bronchiectasis involves:
  - control of any active infection.
  - attempts to improve bronchial hygiene to help minimize the risk of repeated infections.
- Antibiotics are usually administered for acute exacerbations. These are suspected clinically in the presence of a worsened cough, qualitative (and often quantitative) change in the sputum, and sometimes fever. The most commonly isolated causative organisms of acute infectious exacerbations are *Haemophilus influenza*, and *Pseudomonas aeruginosa*. The typical antibiotics used are fluoroquinolones, such as ciprofloxacin and levofloxacin.
- The decision to treat *Mycobacterium avium*-intracellulare complex (MAC) is difficult. This organism can exist as a colonizer as well as a pathogen, and the treatment regimens are prolonged and often poorly tolerated. MAC, however, is the most common non-tuberculous mycobacterial cause of bronchiectasis. The diagnosis of this infection, and the decision to treat, is often guided by expert opinion.
- Multiple approaches are usually taken to try and enhance secretion clearance (bronchial hygiene) in these patients.
  - Maintaining adequate hydration and the use of mucolytics to keep secretions thin.
- Use of bronchodilators.
  - Chest physiotherapy, including chest percussion and newer mechanical devices.
- The use of systemic glucocorticoids is controversial. There has been no compelling evidence demonstrating improvements in pulmonary function or of lower exacerbation rates from their use.
  - Oral or systemic glucocorticoids may be necessary for some patients depending upon the etiology of their bronchiectasis. Patients with allergic bronchopulmonary aspergillosis, Rheumatoid arthritis, and Sjogren's

syndrome may benefit from glucocorticoids for both their bronchiectasis and their underlying disease.

- In severe or refractory cases, surgery (such as resection of involved lung tissue) may be considered. This is especially true of patients with focal bronchiectasis.
- End-stage patients may be considered for lung transplantation.
- All patients with chronic respiratory conditions should be kept up to date on vaccinations, especially influenza and pneumococcal. Appropriate use of these vaccinations can help reduce the rate of recurrent infections.
- Patients who smoke should be counseled about cessation and offered help with quitting.

Disease Course

- Bronchiectasis is a chronic, recurrent, progressive disease.
- Outcomes and course vary widely based upon the underlying etiology.
- The decline in lung function is similar to that seen in patients with COPD.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Bronchiectasis"[Mesh] OR "Bronchiectasis"

Chapter 15
Bronchiolitis

Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Formally known as Respiratory Syncytial Viral (RSV) pneumonia, but many other viruses (such as metapneumovirus, adenovirus, parainfluenza virus) may cause the same clinical disease.

Incidence/Epidemiology

- Typically affects infants under 2 years of age.
- Reported peak incidence between 2 and 6 months.
- Seasonal peaks during fall and winter.
- Bronchiolitis is the leading cause of hospitalization in young children.

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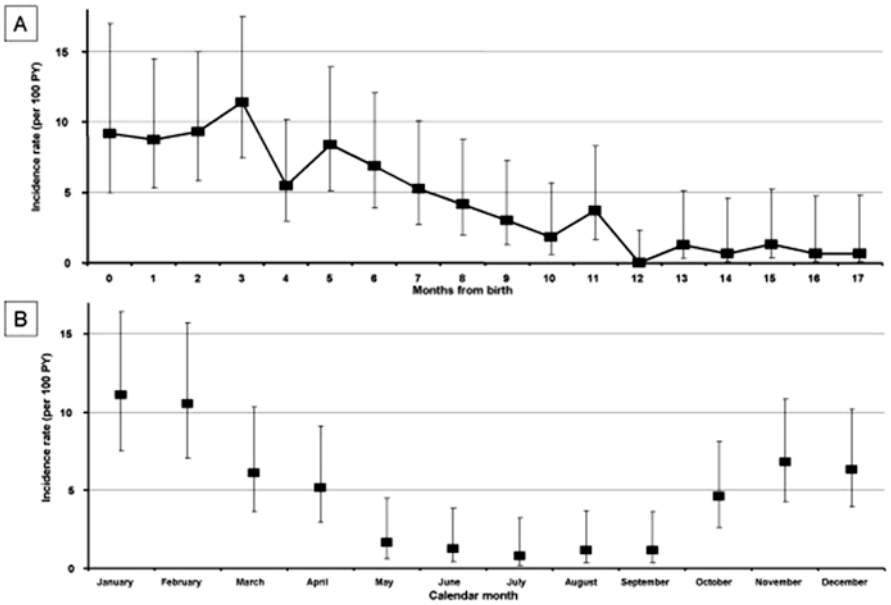
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_15

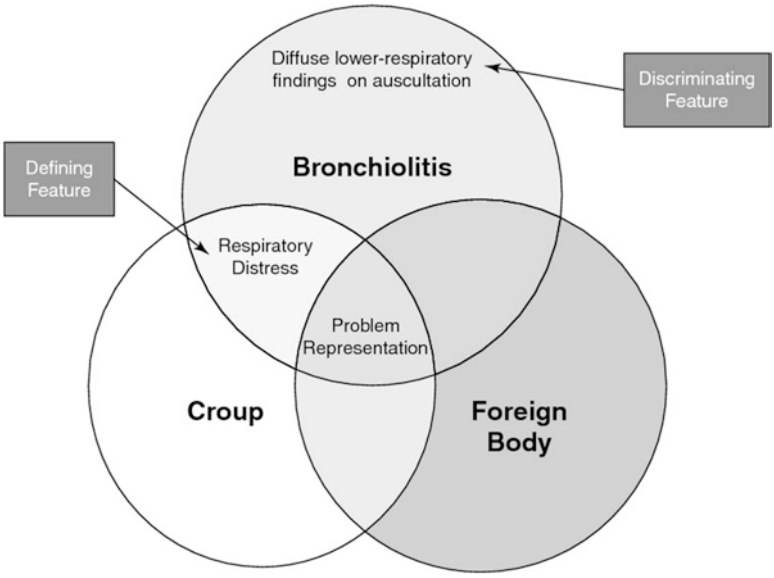


Incidence rates of hospitalizations for bronchiolitis by age (in months) (section A) and by calendar month (section B) in pre-term infants; Rome, Italy 2000-2006. [From article: Incidence and risk factors of hospitalization for bronchiolitis in pre-term children: a retrospective longitudinal study in Italy. BMC Pediatrics. 2009 Sept 10; 9:56; https://doi.org/10.1186/1471-2431-9-56, at http://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-9-56; by Patrizio Pezzotti, Jessica Mantovani, Nicoletta Benincori, Eleonora Mucchino, Domenico Di Lallo, © Pezzotti et al; licensee BioMed Central Ltd. 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Differential Diagnosis

The typical affected infant presents with fever and wheezing, and as such initially prompts these differential considerations:

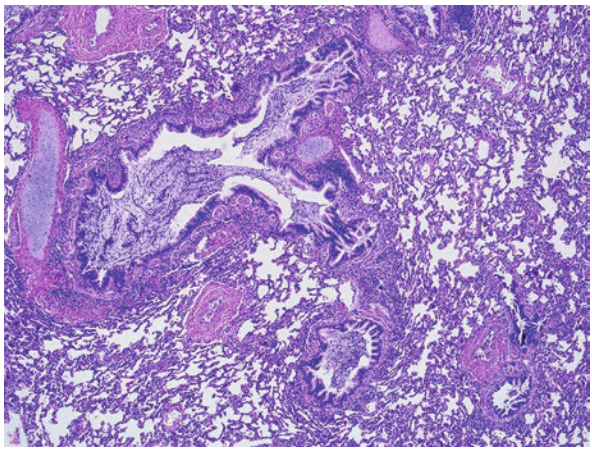
- Bacterial pneumonia
- Chlamydial pneumonia
- Foreign-body aspiration
- Reactive airway disease/asthma
- Aspiration pneumonia
- Congenital heart disease
- Vascular rings



The problem representation allows identification of three illness scripts that fit the defining features of this toddler with respiratory distress case. Diffuse lower respiratory findings on auscultation is the key discriminating feature, which allows a diagnosis of bronchiolitis [Mutnick A, Barone M. Assessing and Remediating Clinical Reasoning. In: Kalet A, Chou CL, editors. Remediation in Medical Education [Internet]. New York, NY: Springer New York; 2014 [cited 2016 Jul 28]. p. 85–101. Available from: http://link.springer.com/10.1007/978-1-4614-9025-8_6] *Caption from original*

Pathophysiology and Etiology

- Viral infiltration of terminal bronchioles results in edema, increased mucous production, and sloughing of respiratory epithelial cells.



Influenza virus infection. Like other forms of respiratory viral infection, influenza may cause a lymphocytic or necrotizing bronchiolitis, in this case associated with mucus stasis in the bronchioles (H&E, 40×). Autopsy examination following fatal influenza viral infection typically shows a necrotizing bronchitis and bronchiolitis with pulmonary edema and diffuse alveolar damage in the background (not shown) [Shah KK, Dishop MK. Infantile Viral Illnesses. In: Fraire AE, Woda BA, Welsh RM, Kradin RL, editors. Viruses and the Lung [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2016 Jul 28]. p. 143–58. Available from: http://link.springer.com/10.1007/978-3-642-40605-8_17] *Caption from original*

- Lymphocytic infiltration causes the typical pattern of peribronchial cuffing seen on plain chest radiographs.
- Known causative viruses include RSV, metapneumovirus, rhinovirus, parainfluenza virus, and adenovirus.

Presentation

Typical/"Classic"

- There is often a 2 to 4-day prodrome consisting of cough and rhinorrhea.
- Infants present after the prodrome with fever, increasing cough, and variable degrees of respiratory distress.
- Patients manifest a wide range of work of breathing, characterized by tachypnea, expiratory prolongation, retractions, and in more severe cases, grunting.

Atypical

- In infants less than 6 weeks of age, apneic episodes may be the first sign of bronchiolitis.

Primary Differential Considerations

- Early diagnostic consideration should also be given to:
  - Asthma
  - Pneumonia
  - Croup

- Congenital heart disease
- Aspiration pneumonitis

History and Physical Exam

- Historically an infant with a mild URI (prodrome, as above) will develop a progressively worsening cough.
- At initial presentation, most infants will have signs of lower respiratory disease.
- Most infants will be febrile, increasing insensible fluid losses.
- Excessive work of breathing may severely impair the ability to feed, resulting in variable degrees of dehydration.
- Cough, retractions, tachypnea, and grunting may be present.
- Auscultation will reveal expiratory prolongation, impairment of air entry, and ronchi/wheezing.

Findings That Confirm Diagnosis

- The typical clinical syndrome, when seasonally encountered (fall and winter) makes the diagnosis obvious.
- Viral testing will further identify the particular etiologic agent.

Factors That Suggest Diagnosis

- As mentioned previously, bronchiolitis is a seasonal epidemic, providing the caregiver with obvious signs.

Factors That Exclude Diagnosis

- The presence of tachycardia with a gallop or cardiomegaly points towards congenital heart disease.
- Toxic appearance, hyperthermia, and lobar infiltrates suggest bacterial pneumonia.

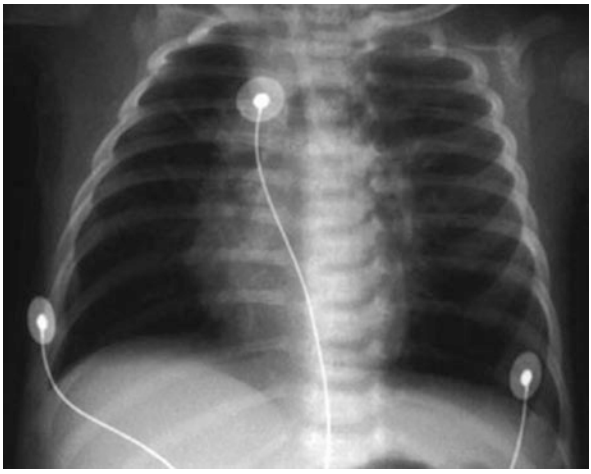
Ancillary Studies

Laboratory Studies

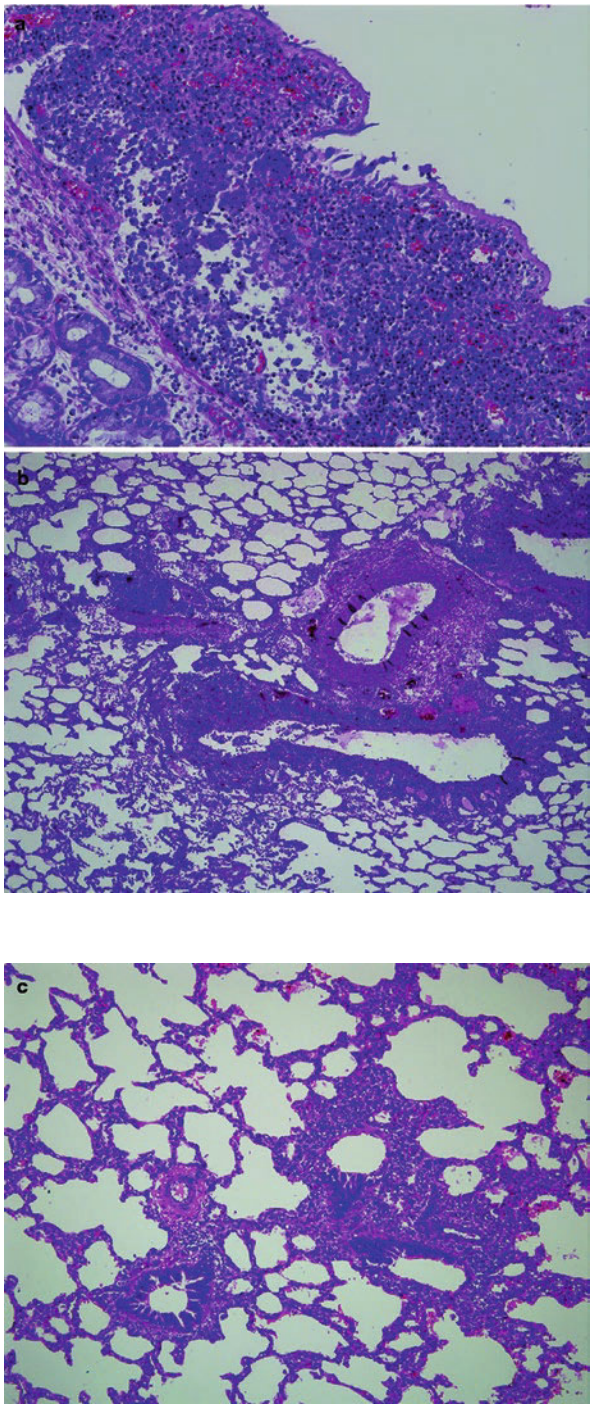
- Viral testing is optional in atypical cases (specifically infants who present only with apnea) and in facilities that have co-bedding of pediatric inpatients.
- Blood work is not indicated.

Imaging

- Chest radiographs will demonstrate hyperinflation, interstitial disease, and peribronchial cuffing; in some instances, variable degrees of atelectasis may be present.



RSV-bronchiolitis. Markedly hyperinflated lungs with flattening of the diaphragm and peribronchial hilar infiltrates are demonstrated on the chest radiograph. [Staatz G. Bronchitis and Bronchiolitis in Childhood. In: Baert AL, editor. Encyclopedia of Diagnostic Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008 [cited 2016 Jul 28]. p. 203–5. Available from: http://www.springerlink.com/index/10.1007/978-3-540-35280-8_337] *Caption from original*


a
b
c

Respiratory syncytial virus infection in an infant. The prototypic infantile respiratory virus, RSV, causes a lymphocytic bronchitis and bronchiolitis. (a) This bronchus demonstrates a cuff of lymphocytes in the submucosa (H&E, 200×). (b) Circumferential lymphocyte infiltrates are also noted in the small airways (H&E, 100×). (c) Bronchiolitis may be accompanied by an interstitial pneumonitis, characterized by interstitial widening by lymphocyte infiltrates. Syncytial-type multinucleate cells are absent or rare in lung tissues from otherwise healthy infants but are characteristic of the viral cytopathic effect seen in culture in the diagnostic virology laboratory (H&E, 100×) [Shah KK, Dishop MK. Infantile Viral Illnesses. In: Fraire AE, Woda BA, Welsh RM, Kradin RL, editors. Viruses and the Lung [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2016 Jul 28]. p. 143–58. Available from: http://link.springer.com/10.1007/978-3-642-40605-8_17] *Caption from original*

Bronchiolitis and pneumomediastinum. Frontal chest radiograph in a patient with RSV infection demonstrates a combination of bilateral perihilar atelectasis and hyperexpanded lungs. Note the presence of pneumomediastinum (arrow) with gas tracking up the neck soft tissues [Krol JJ, von Herrmann PF, Challa HR, Dillon JE. Imaging of Pediatric Emergencies. In: Singh A, editor. Emergency Radiology [Internet]. New York, NY: Springer New York; 2013 [cited 2016 Jul 28]. p. 361–73. Available from: http://link.springer.com/10.1007/978-1-4419-9592-6_26] *Caption from original*

Special Populations

Age

- Children older than 3 may contract viral infections that present identically to bronchiolitis, though RSV titers will be negative.

Co-morbidities

- Risk factors for the development of apnea include:
  - History of prematurity (less than 35 weeks)
  - Age less than 2 months
  - Presence of congenital heart disease
  - Presence of marked atelectasis

Pitfalls in Diagnosis

- Most patients present with typical symptomatology.
- Not considering bronchiolitis in infant apneic spells would be unwise.

Critical Steps Not to Miss

- Obtaining a careful birth history is mandatory.
- There is usually an older child in the home with a simple cold.

Mimics

- As previously mentioned, bacterial pneumonia may present with similar findings.
- New onset CHF will often present with respiratory distress and wheezing.

Time-Dependent Interventions

- Supplemental oxygen is often necessary.
- In dehydrated infants, IV fluids are indicated.

- Nasopharyngeal suctioning may dramatically lessen the work required to breathe.
- The use of albuterol has recently been discouraged in the literature; many practitioners, however, still favor a single albuterol treatment in an attempt to identify the rare patient with reversible bronchospasm.
- Steroids are NOT recommended.
- Severe cases may respond to aerosolized racemic epinephrine.

Overall Principles of Treatment

- Simple correction of hypoxemia and fluid deficits are important first steps.
- Unfortunately, most infants will not respond to bronchodilators.
- Hospital admission is often the only option.

Disease Course

- Studies have demonstrated that this is a 14-to-21-day illness with vacillating degrees of respiratory compromise.
- The cough may take 2 weeks to resolve

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Bronchiolitis"[Mesh] OR "Bronchiolitis"

Chapter 16
Carbon Monoxide Poisoning

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, Victoria G. Riese, and Jaime Friel Blanck

Name and Synonyms

Carbon Monoxide (CO) Poisoning

Incidence/Epidemiology

- CO poisoning is responsible for up to 40,000 emergency department visits and 5000 to 6000 deaths a year.
- CO poisoning is unintentional in about 500 cases annually, whereas the rate of intentional poisoning is 10 times higher.
- The case-fatality rate ranges from 0 % to 31 %.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_16

Differential Diagnosis

- Acute respiratory distress syndrome
- Depression and suicide
- Diabetic ketoacidosis
- Encephalitis
- Gastroenteritis
- Headache, tension
- Hypothyroidism and myxedema coma
- Labyrinthitis
- Lactic acidosis
- Meningitis
- Methemoglobinemia
- Migraine headache
- Pediatrics, hypoglycemia
- Toxicity, alcohols
- Toxicity, narcotics

Pathophysiology and Etiology

- CO is an odorless, tasteless, colorless, nonirritating gas formed by hydrocarbon combustion. It binds to hemoglobin and diminishes the ability to absorb oxygen.
- CO poisoning interferes with oxygen transport to the cells and possibly results in electron transport failure.
- CO combines preferentially with hemoglobin to produce carboxyhemoglobin (COHb), displacing oxygen and reducing systemic arterial oxygen.
- CO poisoning may cause tissue hypoxia and impair tissue perfusion.
- Exogenous sources of CO include the following:
    - Smoke inhalation
    - Poorly functioning heating systems
    - Improperly vented fuel-burning devices
    - Motor vehicles in poorly vented areas
    - Open-air motorboat exhaust
    - Underground electrical cable fires
    - Spray paints and solvents—methylene chloride
    - Wood stoves
    - Tobacco smoke

Presentation

Typical/"Classic"

- Highly variable and nonspecific
- Mild to moderate poisoning: headache, malaise, nausea, dizziness, weakness, vomiting, blurred vision, and shortness of breath
- Severe CO toxicity: seizures, syncope, coma, myocardial ischemia, ventricular arrhythmias, pulmonary edema, and profound lactic acidosis

Atypical

- Unexplained alteration in mental status

Primary Differential Considerations

Consistent with the presentation of CO toxicity, the following differential diagnoses also may apply:

- Sepsis
- Intoxication
- Ketoacidosis
- Hypoglycemia
- Atypical migraine
- Viral syndrome

History and Physical Exam

Findings That Confirm Diagnosis

- There are no physical exam findings that confirm the diagnosis of CO poisoning.

Factors That Suggest Diagnosis

- History and physical exam with headache, nausea, vomiting
- Acute infarction in the globus pallidus bilaterally

- Other forms of pure hypoxia produce similar findings.
- "Cherry red" appearance of lips and skin (a late finding)

The cheeks and neck are red in this patient with carbon monoxide poisoning. [Allen HB. Dermatology terminology [Internet]. London: Springer; 2010. Chapter 8, Miscellaneous disorders; [cited 2015 Sep 9]; p. 171–85. Available from: http://link.springer.com/10.1007/978-1-84882-840-7_8] *Caption from original*

Carboxyhemoglobin saturation (%)	Signs and symptoms
5–10	Visual acuity impairment
11–20	Flushing, headache
21–30	Nausea, impaired dexterity
31–40	Vomiting, dizziness, syncope
41–50	Tachypnea, tachycardia
>50	Coma, death

Signs and symptoms of carbon monoxide poisoning [Knighton J. Nursing management of the burn-injured person. In: Jeschke MG, Kamolz L-P, Shahrokhi S, editors. Burn care and treatment [Internet]. Vienna: Springer; 2013 [cited 2015 Sep 9]. p. 111–47. Available from: http://link.springer.com/10.1007/978-3-7091-1133-8_8] *Caption from original*

COHb concentration	Symptoms
Up to 10 %	No significant symptoms (smoker)
10–15 %	Possible shortness of breath on physical exertion (heavy smoker)
15–25 %	Usually no effects when resting, but shortness of breath on physical exertion
25–35 %	Headache, dizziness, vomiting, impaired judgement, impaired vision
35–45 %	Confusion, signs of paralysis, syncope on mild exertion
45–55 %	Severely impaired consciousness or loss of consciousness, collapse, life-threatening situation after prolonged exposure
55–65 %	Cramps, apnea
From ca. 65 %	Imminent threat of death

Stages of carbon monoxide poisoning [Dettmeyer RB, Verhoff MA, Schütz HF. Forensic medicine [Internet]. Berlin, Heidelberg: Springer; 2014. Chapter 30, Forensic toxicology; [cited 2015 Sep 9]; p. 495–542. Available from: http://link.springer.com/10.1007/978-3-642-38818-7_30] *Caption from original*

Factors That Exclude Diagnosis

The only way to exclude CO toxicity definitively is with an arterial blood gas panel with co-oximetry.

Ancillary Studies

Laboratory

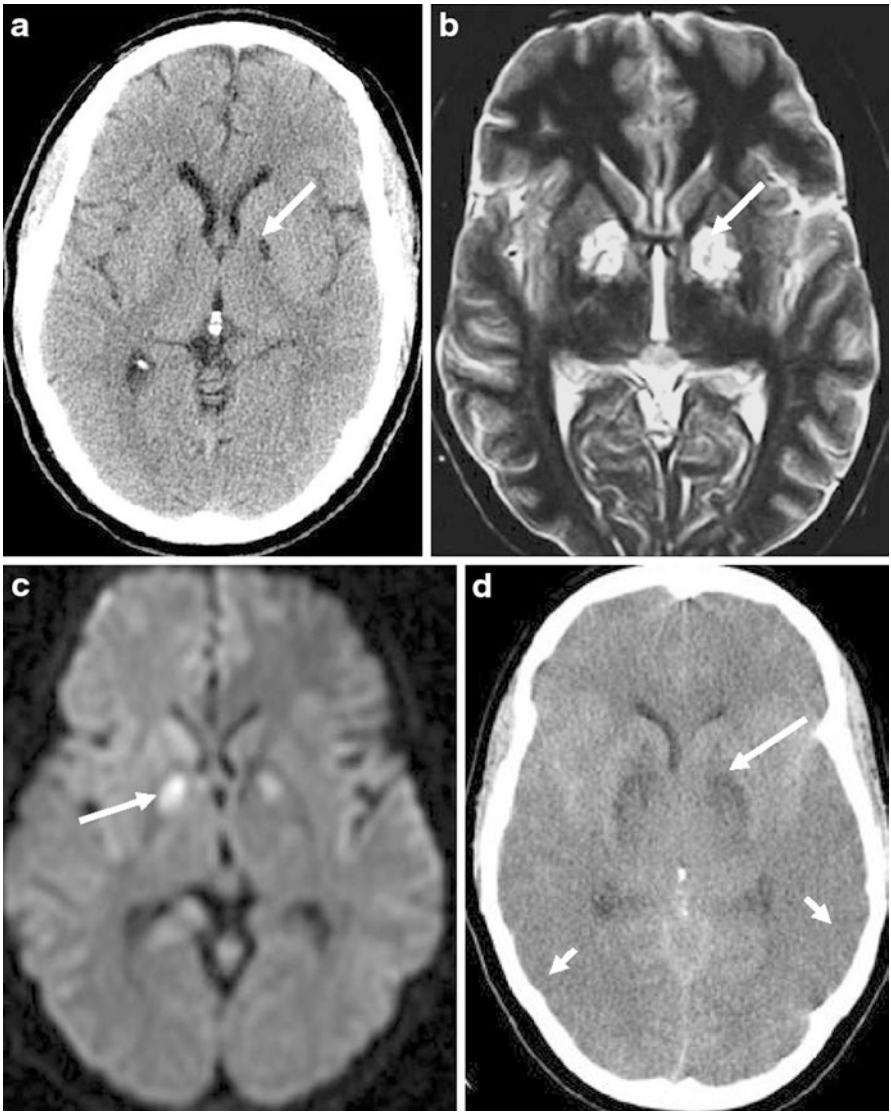
- Elevated COHb level
  - Nonsmokers may have up to 3 %, smokers 10 % to 15 %. Anything above these levels may be considered CO poisoning.
- In CO poisoning as a result of suicide attempt, a drug screen should also be obtained.

Electrocardiography

- Sinus tachycardia/arrhythmias/myocardial injury

Computed Tomography (CT) of the brain

- Hypoattenuation of the globus pallidus and white matter changes



Four different patients with history of carbon monoxide poisoning. a Noncontrast head CT shows focal low density in bilateral globus pallidus (arrows). b Transaxial T2 weighted image shows bilateral symmetric hyperintensity involving globus pallidus (arrows). c DWI shows bilateral pallidal diffusion restriction (arrows). d Noncontrast head CT shows diffuse anoxic injury (short arrows) in addition to the basal ganglia hypodensities (long arrow) [Moore MJ, Vagal AS, Strub WM, Leach JL. Reducing the gray zone: imaging spectrum of hypoperfusion and hypoxic brain injury in adults. Emerg Radiol. 2010 Mar;17(2):123–30.] *Caption from original*

Special Populations

Age

- Older patients with limited cardiopulmonary reserve may develop clinical manifestations at lower CoHb levels.

Co-morbidities

- Pregnancy
  - The fetus is particularly sensitive to hypoxemia, so both mother and child are at significant risk.
- Patients with preexisting lung disease are affected more severely by CO-induced hypoxemia.

Pediatric Considerations

- Signs and symptoms may be subtle and nonspecific.
- Infants and toddlers may have fussiness and difficulty feeding.
- Signs and symptoms in older children are similar to those in adults: headache, nausea, and vomiting.
- Younger children experience problems earlier in exposure because of of higher rates of oxygen utilization and minute ventilation.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Without the patient's history, CO toxicity may be difficult to diagnosis. Standard pulse oximetry cannot screen for CO exposure.

- All individuals at a fire scene and/or with significant thermal injury should be evaluated for CO poisoning.

Mimics

- Most common misdiagnosis is viral syndrome.
- Very high or very low blood glucose levels may present similarly to CO toxicity.

Time-Dependent Interventions

- CO poisoning is associated with high morbidity and mortality. In the absence of exposure history, CO poisoning must be considered in two or more patients who present with similar symptoms simultaneously.
- Oxygen therapy should be started while COHb tests results are pending.
- Hyperbaric oxygen (HBO) therapy, if available, should be considered, especially in cases of severe exposure and in pregnant patients.

Overall Principles of Treatment

- 100 % oxygen therapy is the main treatment for CO poisoning.
- HBO is indicated in anyone who experienced unconsciousness, cardiovascular instability or ischemia, persistent mental and/or neurologic deficits, or a COHb level greater than 25 %.
  - HBO may help the late neurocognitive outcomes.
- HBO should be considered in pregnant patients with elevated COHb levels.

Disease Course

- Outcomes are difficult to predict, even when the CO level is known. Patients with cardiac arrest or coma may recover fully after treatment. The mortality rate in severe CO toxicity is 33 % or higher.

Related Evidence

Papers of particular interest have been highlighted as:
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Kurt F, Bektaş Ö, Kalkan G, Öncel MY, Yakut HI, Kocabaş CN. Does age affect presenting symptoms in children with carbon monoxide poisoning? Pediatr Emerg Care. 2013 Aug;29(8):916-21. https://doi.org/10.1097/PEC.0b013e31829ec22b. PMID: 23903672. http://www.ncbi.nlm.nih.gov/pubmed/23903672

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Carbon Monoxide Poisoning"[Mesh] OR "carbon monoxide poisoning"

Chapter 17
Chest Neoplasms

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Chest Neoplasms

Incidence/Epidemiology

- The incidence of chest neoplasm varies widely by tumor type.
- Chest neoplasms are of much higher incidence in adults.
- Over large populations, chest neoplasia incidence follows tobacco abuse patterns and therefore is more common in older males.
- In women, lung and breast tumors are most common.
- Metastases of colon cancer to the thorax are not uncommon.

Differential Diagnosis

- Many neoplasms may present as chest masses.
- They may be either benign or malignant lesions.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_17

- There are primary chest masses and secondary masses. Secondary masses are metastatic lesions that have primary tumors somewhere other than the chest.
- Primary tumors of the chest include:
  - Breast cancer
  - Lung cancer
  - Esophageal cancer
  - Primary cardiac tumors
  - Primary tumors of the ribs and spine
  - Soft tissue sarcomas
  - Mesothelioma
  - Multiple myeloma
  - Lymphoid tumors
- Many different types of tumors can metastasize to the chest.

Pathophysiology and Etiology

- Pathophysiology varies based on primary vs metastatic etiology, and invasive vs more benign tissue types.
- There are behavioral (e.g., smoking) and genetic (e.g., BRAC1 gene) predispositions to chest tumors.

Presentation

Typical/"Classic"

- Tumors within the chest are often asymptomatic.
- They are most commonly found during diagnostic studies for other reasons.
- Symptoms, if present, are usually the result of direct compression from tumors or direct infiltration into surrounding structures. If the surrounding structures infiltrated are blood vessels, hemoptysis may result.
- Lymphoproliferative tumors often cause constitutional symptoms.
- Bronchogenic carcinoma may present as a postobstructive pneumonia.
- Breast or chest wall tumors may be palpable or painful, prompting presentation.

Atypical

- Fulminant presentations with respiratory insufficiency or massive hemoptysis are unusual.
- Vague constitutional symptoms, such as nagging cough and weight loss, may be presenting symptoms.

Primary Differential Considerations

Prompt consideration also should be given to the possible diagnosis of:

- Pneumonia and other infectious etiologies
- Thymus enlargement
- Pneumoconiosis
- Pulmonary nodule

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis is usually confirmed only through pathologic interpretation of biopsy specimens.

Factors That Suggest Diagnosis

- These are often asymptomatic and found incidentally when performing diagnostic imaging studies for other reasons.

Factors That Exclude Diagnosis

- Advanced imaging studies (CT, MRI) can exclude masses of significance.

Ancillary Studies

Laboratory

- Laboratory studies are sometimes helpful in evaluating chest masses. There may be evidence of lymphoproliferative disorders on a complete blood count. Multiple myeloma is often associated with anemia, renal insufficiency, hypercalcemia, and an anion gap less than 5.

Imaging

- Most chest neoplasms are found incidentally during diagnostic imaging of the chest for other reasons.

- They most often are discovered on either plain chest x-ray or CT scan of the chest.
- Primary cardiac lesions may be found on echocardiogram

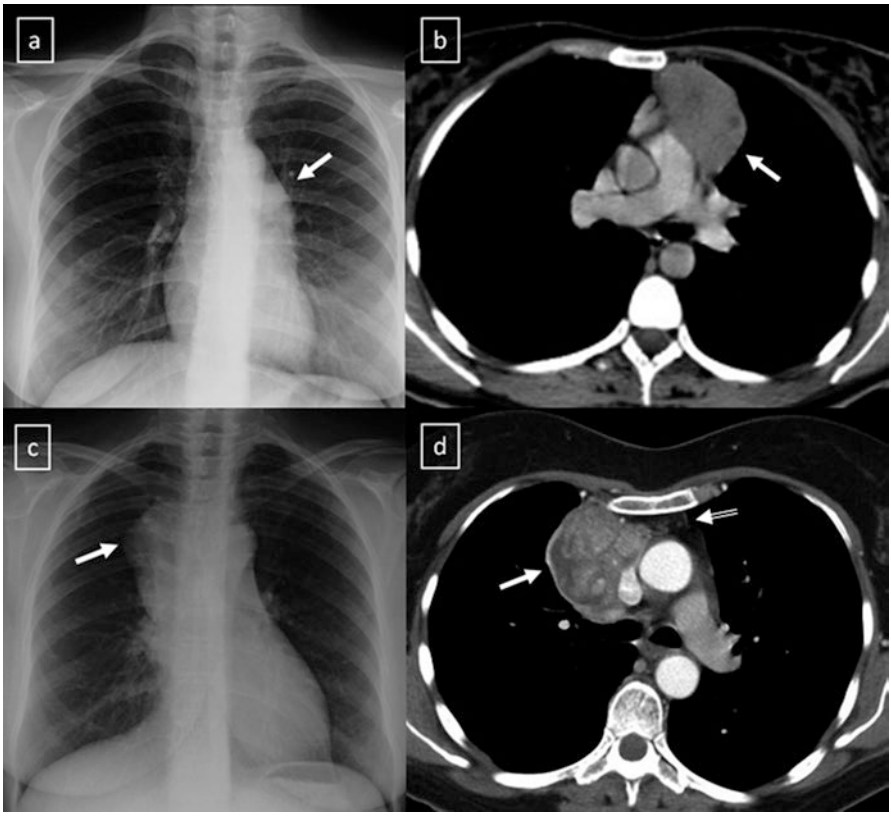
Special Populations

Age

- Chest neoplasms may occur in any age group.

Co-morbidities

- There are many potential co-morbidities to consider depending on the specific type of neoplasm. COPD is often present in patients with bronchogenic carcinoma.
- Thymus mass (thymoma) is associated with myasthenia gravis in about one-half of cases.



a, b Stage II thymoma (WHO type B1) in a 33-year-old woman who presented with myasthenia gravis. Frontal chest radiograph shows a hilum overlay sign (arrow) of a suggestive anterior mediastinal mass. Contrast-enhanced CT scan confirms the presence of a low-heterogeneous anterior mediastinal mass (arrow). Note the indentation of the arterial trunk pulmonary by the mass. c, d Stage III thymoma (WHO type B2) in a 54-year-old woman. Frontal chest radiograph reveals a lobulated mediastinal mass (arrow) on the right side. Contrast-enhanced CT scan demonstrates an enhanced anterior mediastinal mass (arrow) with infiltration of surrounding fat (open arrow) [From article: A diagnostic approach to the mediastinal masses. Insights into Imaging. 2013 Feb;4(1):29–52. https://doi.org/10.1007/s13244-012-0201-0, at http://link.springer.com/article/10.1007%2Fs13244-012-0201-0/fulltext.html; by Sergi Juanpere, Noemí Cañete, Pedro Ortuño, Sandra Martínez, Gloria Sanchez, Lluis Bernado, © The Author(s) 2012; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Pitfalls in Diagnosis

Critical Steps Not to Miss

- A thorough medical history and chest imaging are essential early in the evaluation of a chest tumor

Mimics

- Infection is the primary mimic of neoplasms in the chest

Time-Dependent Interventions

- Ensuring adequate oxygenation
- Imaging to establish likely etiology

Overall Principles of Treatment

- Treatment depends on the type of neoplasm and whether any symptomatic obstruction or compression exists.

Disease Course

- Disease course depends on the specific diagnosis.

Related Evidence

Papers of particular interest have been highlighted as:
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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Thoracic Neoplasms"[Mesh] OR "Breast Neoplasms"[Mesh] OR "Esophageal Neoplasms"[Mesh] OR "Spinal Neoplasms"[Mesh] OR "Sarcoma"[Mesh] OR "Mesothelioma"[Mesh] OR "Multiple Myeloma"[Mesh] OR "Lymphoma"[Mesh]

Chapter 18
Chronic Obstructive Pulmonary Disease

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Chronic Obstructive Pulmonary Disease; COPD; Emphysema

Incidence/Epidemiology

- COPD affects about 5 % of the U.S. population.
- COPD is reported as the third- or fourth-leading cause of death in the U.S, depending upon the survey. COPD is directly responsible for about 120,000 deaths per year in the U.S.
- COPD is associated with a very high rate of medical resource utilization. The majority of these costs are for hospitalization of acute exacerbations of COPD.
- In the U.S., nearly 2 % of all hospital admissions are directly attributable to COPD. It is considered a major contributing factor in another 9 % of hospital admissions. In patients older than 65, the percentage of all hospital admission related to COPD approaches 20 %.
- COPD is the only major cause of death that is increasing in the U.S.

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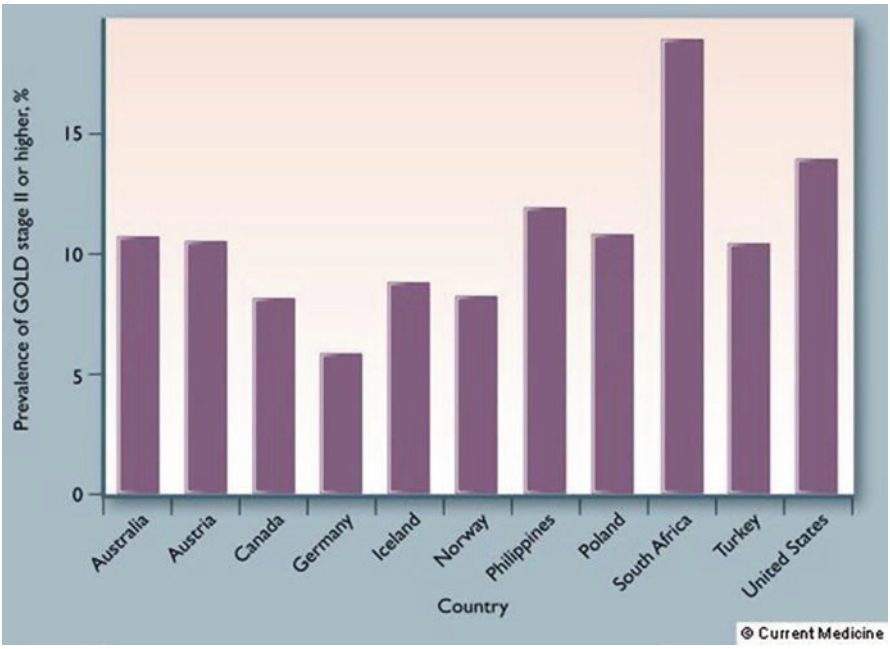
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_18

- The incidence and mortality of COPD in women is increasing worldwide. This is likely related to the increased incidence of smoking among women during the last 50 years.
- Tobacco smoke is the major risk factor for developing COPD, but only 15 % of smokers will develop COPD.
- Alpha-1 antitrypsin deficiency accounts for less than 1 % of COPD cases.



Worldwide prevalence of chronic obstructive pulmonary disease (COPD). The prevalence of COPD (in 2007) in different geographic regions based on the Burden of Obstructive Lung Disease data [Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007; 370:741 -750.] is presented based on results for specific cities within the countries listed. The reasons for these regional differences are not entirely clear and may be due to different environmental exposures (smoking, biomass, occupation), as well as possibly genetic factors. [Cho M, Silverman E. Genetics and Racial, Ethnic, and Gender Characteristics of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption from original*

Differential Diagnosis

- The primary symptoms of COPD are dyspnea (usually exertional early in the disease course), cough, and sputum production.

- The differential diagnosis of these symptoms is broad, and includes many diseases and organ symptoms.
- Patients may present with worsening fatigue, exercise or activity intolerance, and often complain of daily cough for many months.
- In patients without a current diagnosis of COPD, the differential includes:
    - Congestive heart failure
    - Interstitial lung disease
    - Thromboembolic Disease (pulmonary embolism)
    - Asthma
    - Bronchiectasis
    - Tuberculosis
    - Bronchiolitis
    - Airway obstruction from bronchogenic or metastatic cancer, lymphadenopathy (sarcoidosis), and tracheal stenosis/scarring.
- It is important to remember that many of these disorders can occur together.
- In patients with an existing diagnosis of COPD, who present with acute dyspnea (exacerbation of COPD), the cause of the exacerbation needs to be investigated. The differential for acute dyspnea in these patients is also broad, and includes:
    - CHF/pulmonary edema
    - Acute coronary syndrome
    - Pneumonia
    - Viral respiratory infection
    - Pulmonary embolism
    - Pleural effusion
    - Pneumothorax
    - Pericardial effusion
    - Mucous plugging of bronchi
    - Rib fracture from severe coughing
    - Electrolyte imbalance (especially hypokalemia and hypocalcemia)

Pathophysiology and Etiology

- Chronic obstructive pulmonary disease (COPD) is a disease characterized by chronic, progressive airflow obstruction.
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD), sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO), defines COPD as follows: “Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”

Global Initiative for Chronic Obstructive Lung Disease, GOLD [3]: $FEV_1/FVC < 70\%$		
I:	Mild COPD	$FEV_1 \geq 80\%$ predicted
II:	Moderate COPD	FEV_1 50- < 80% predicted
III:	Severe COPD	FEV_1 30- < 50% predicted
IV:	Very severe COPD	$FEV_1 < 30\%$ predicted
British Thoracic Society, BTS [2]: $FEV_1/VC < 70\%$ and $FEV_1 < 80\%$ predicted		
I:	Mild COPD	FEV_1 60- < 80% predicted
II:	Moderate COPD	FEV_1 40-59% predicted
III:	Severe COPD	$FEV_1 < 40\%$ predicted

A group labelled BTS stage 0 was created for subjects with $FEV_1 \geq 80\%$ predicted: i.e. identical with mild COPD according to the GOLD criteria.

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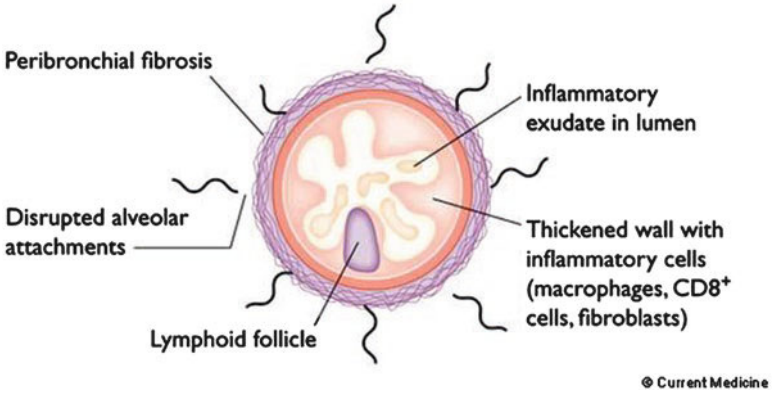
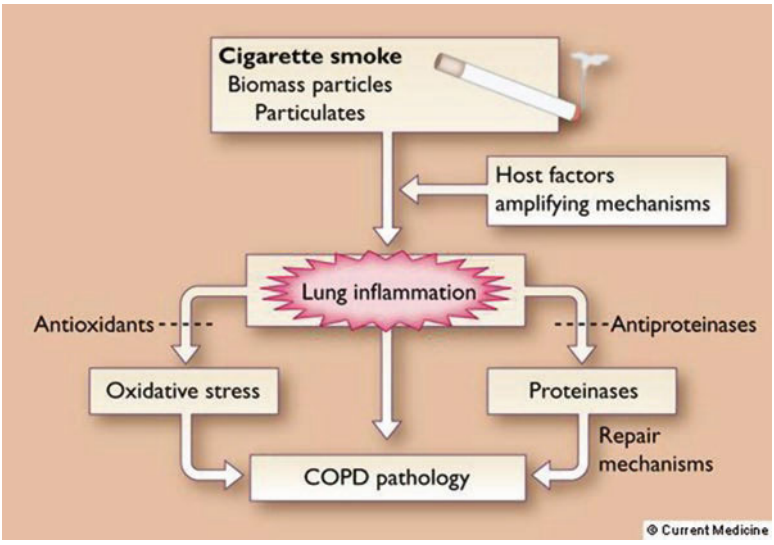
- The pathophysiology of COPD involves the airways, lung parenchyma, and pulmonary vasculature.
  - Airways: The most significant pathologic change in the airways involves chronic inflammation from exposure to cigarette smoke and other pollutants, which leads to several permanent anatomic changes such as:
    - Mucous gland hyperplasia and increased numbers of goblet cells, resulting in increased mucous secretion. Increased mucous secretion and stasis leads to pathogenic bacterial colonization.
    - Increased mucous-secreting and goblet cells replace surfactant-secreting cells, which augments collapse and destruction of the small airways.
    - Increased induction of inflammatory cells with increased local protease production, accelerating tissue damage and breakdown.
    - Fibrosis with loss of elastic recoil, narrowing, collapse, and subsequent destruction and reduction in the number of small airways.
    - There is also squamous metaplasia within the airways resulting in an increased risk for cancer.

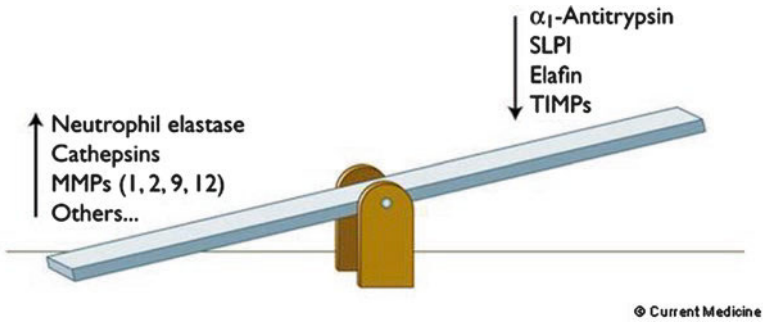


Overview of small airways in COPD: schematic view [Barnes PJ. Pathophysiology of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption adapted from original*

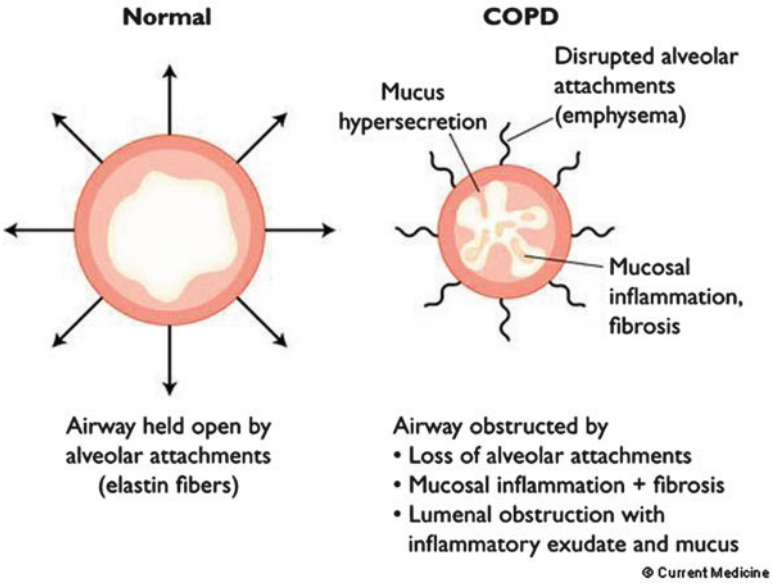


Link between inflammation and airway obstruction in chronic obstructive pulmonary disease (COPD). Chronic exposure to inhaled cigarette smoke and biomass particles (wood smoke) results in chronic inflammation of the lungs. Genetic and other unknown factors are responsible for the increased susceptibility to inhaled irritants. Inflammation generates reactive oxygen species (oxidative stress), which is normally counteracted by endogenous antioxidant mechanisms, but these may be defective in COPD. Inflammation also activates proteinases, which result in connective tissue destruction. This may be countered by antiproteinases and repair mechanisms that may also be defective in COPD.

[Barnes PJ. Pathophysiology of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption from original*



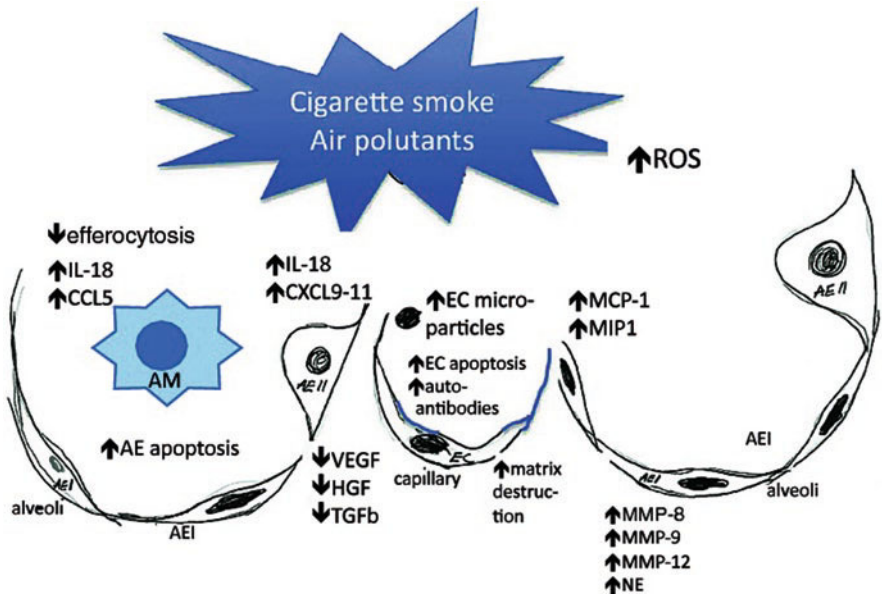
Protease-antiprotease imbalance in COPD: schematic view. Protease–antiprotease imbalance in chronic obstructive pulmonary disease (COPD). In COPD the balance appears to be tipped in favor of increased proteolysis, either because of an increase in proteases, including neutrophil elastase, cathepsins, and matrix metalloproteinases (MMPs), or a deficiency in antiproteases, which may include α_1-antitrypsin, elafin, secretory leukoprotease inhibitor (SLPI), and tissue inhibitors of matrix metalloproteinases (TIMPs). [Barnes PJ. Pathophysiology of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption from original*



Mechanisms of airflow limitation in COPD: schematic view. Mechanisms of airflow limitation in chronic obstructive pulmonary disease (COPD). The airway in normal

subjects is distended by alveolar attachments, which contain elastin fibers during expiration, allowing alveolar emptying and lung deflation. In COPD these attachments are disrupted due to emphysema, thus contributing to airway closure during expiration, trapping gas in the alveoli and resulting in hyperinflation. Peripheral airways are also obstructed and distorted by airway inflammation and peribronchiolar fibrosis (chronic obstructive bronchiolitis), and by occlusion of the airway lumen by inflammatory exudate and mucus secretions that may be trapped in the airways due to poor mucociliary clearance. [Barnes PJ. Pathophysiology of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption from original*

- Lung Parenchyma. The lung parenchymal changes are also called emphysema. The changes mostly affect the acinus, the functional unit distal to the terminal bronchiole that includes the respiratory bronchiole, alveolar ducts, alveolar sacs, and alveoli. There is destruction of this unit leading initially to collapse and then subsequent enlargement as air becomes trapped within the destroyed unit. The loss of elastic recoil prevents the air from escaping. There are three subtypes of emphysema:
  - Centrilobular: This involves the proximal acinus (predominately the respiratory bronchioles.) It is the form most strongly associated with cigarette smoking.
  - Panacinar: This involves all parts of the acinus, and is mostly seen with alpha-1 ant-trypsin deficiency.
  - Distal (paraseptal): Affects predominately the alveolar ducts.
- Pulmonary vasculature. Chronic hypoxia leads to reflex vasoconstriction of the small pulmonary arteries, which results in intimal hyperplasia, smooth muscle hypertrophy and hyperplasia, and ultimately pulmonary hypertension.



Destruction of the lung maintenance program in emphysema. Chronic exposure to cigarette smoke leads to a change in the local milieu: increased release of proinflammatory mediators (IL-8, IL-18, CCL5, IL-8, IFNgama, MIP1) that contribute to paracrine and autocrine signaling, impairment in efferocytosis, decreased levels of growth and survival factors (most notably VEGF and HGF), and extracellular matrix degradation (increased levels of matrix metalloproteases MMP-9 and MMP-12). Increased apoptosis of endothelial and epithelial cells might contribute to autoantibody formation. Reduced levels of TGF might signal delay repair processes and contribute to inflammatory cell activation. AM – alveolar macrophage; AEI – alveoli type I cell; AEII – alveoli type II cell; EC – capillary endothelial cell; ROS – reactive oxygen species [Taraseviciene-Stewart L, Voelkel NF. Immunopathology of COPD. In: Rogers TJ, Criner GJ, Cornwell WD, editors. Smoking and Lung Inflammation [Internet]. Springer New York; 2013 [cited 2016 May 16]. p. 1–27. Available from: http://link.springer.com/chapter/10.1007/978-1-4614-7351-0_1] *Caption from original*

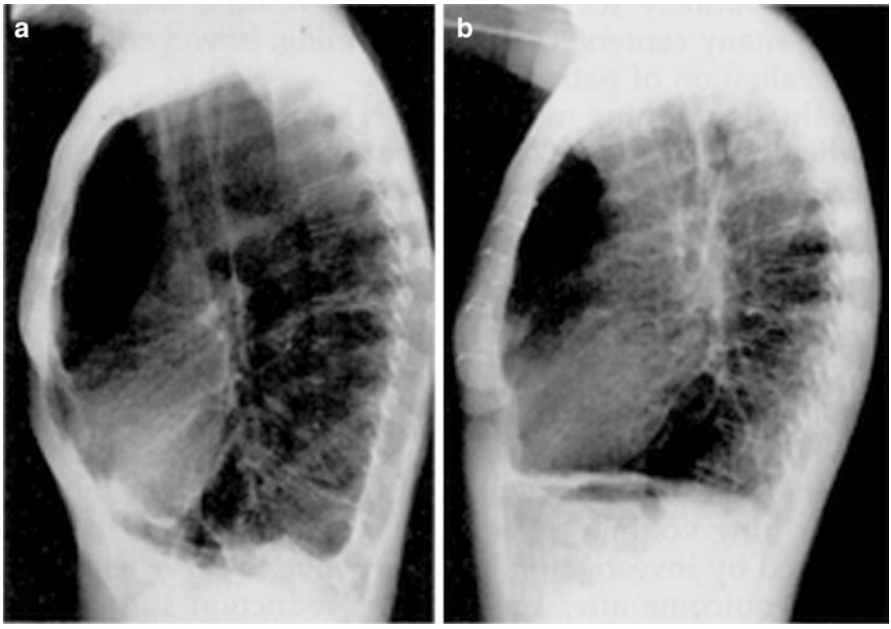
- The single largest risk factor for the development of COPD is cigarette smoking. In the United States, nearly 80 % of patients diagnosed with COPD have history of cigarette smoking. The amount and duration of smoking are the largest predictors of disease severity. The single most reliable predictor for finding airflow obstruction on spirometric testing is a greater than 40 packs-per-year history of cigarette use.
- However, only 15 % of smokers will develop COPD.
- Smoking is the largest risk factor for the development of COPD, but not the only risk factor. Twenty percent of patients with COPD do not have a significant history of cigarette smoking. Other causes of COPD include occupational exposures (such as coal mining, gold mining, and cotton dust). There are also genetic causes, such as alpha-1 anti-trypsin deficiency, although this accounts for less than 1 % of cases of COPD.
- There is currently no strong evidence linking air pollution or second-hand smoke to the development of COPD.

Presentation

Typical/"Classic"

- The most common presenting symptoms of COPD are exertional dyspnea and chronic cough with sputum production.
- COPD is a slowly progressive disease with a prolonged asymptomatic phase. Patients are often unaware of the dyspnea, or just relate it to aging or poor fitness. They will often adjust their activities to limit the symptoms of dyspnea.
- Wheezing is often a later symptom.

- The course is one of slow progression with intermittent exacerbations of dyspnea and cough.
- Early in the course of the disease, the patient may have no physical signs of the disease.
- As the disease progresses, patients may develop the more classic signs of COPD, such as a barrel chest (increased AP diameter from air trapping), prolonged expiration with expiratory wheezing, decreased breath sounds, tachypnea, and pursed lip breathing.



A lateral chest X-ray is shown. (a) Depicts the patient before lung volume reduction surgery (LVRS): the thorax is barrel-shaped with high transparency of the lungs, a large retrosternal air-filled space, and a flattened to concave diaphragm. The chest X-ray of the same subject (b) is shown 3 months after LVRS: the lung fields are less transparent, the air-filled retrosternal space decreased significantly, and the diaphragm exhibits an almost normal, convex shape. [Sullivan EA. Lung Volume Reduction. In: Slinger P, editor. Principles and Practice of Anesthesia for Thoracic Surgery [Internet]. Springer New York; 2011 [cited 2016 May 16]. p. 511–21. Available from: http://link.springer.com/chapter/10.1007/978-1-4419-0184-2_36] *Caption from original*

- Patients will often be noted to need to sit up and lean forward with their hands on their knees (tripod position) as this increases accessory muscle use (sternocleidomastoid, scalene, and intercostal muscles) and diaphragmatic excursion, both of which help to improve lung volumes.

- Patients with advanced disease will often have significant wasting with loss of muscle mass and subcutaneous fat. This is an independent predictor of a very poor prognosis.
- Clubbing of the digits is not a sign of COPD. If a patient with COPD develops clubbing, there is usually another cause, such as the interval development of lung cancer.

Atypical

- COPD less commonly presents initially with wheezing.
- COPD can present with chest tightness as the predominant symptom.

Primary Differential Considerations

- Initial consideration in patients with an acute presentation should be given to these differential diagnoses:
  - Asthma
  - Congestive heart failure
  - Pulmonary hypertension
  - Pulmonary embolism
  - Pneumonia

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical exam findings that can confirm COPD. There is a large overlap with other disease states that cause dyspnea, such as asthma, congestive heart failure, and bronchiectasis.
- The diagnosis can be nearly confirmed when a patient presents with the typical symptoms of dyspnea on exertion with a chronic cough and sputum production associated with findings on spirometry of a forced expiratory volume in one second (FEV_1) less than 80 % of predicted and a ratio of FEV_1 to the forced vital capacity (FVC) of <0.7.

Assess and Monitor Disease: Key Points
Consider a diagnosis of COPD in any patient with a cough, dyspnea, or exposure to risk factors and confirm with spirometry.
Spirometry is the gold standard for the diagnosis and assessment of COPD and a postbronchodilator $FEV_1/FVC < 0.70$ confirms the presence of airflow limitation that is not fully reversible.
Health care workers involved in the diagnosis and management of COPD should have access to spirometry.
Severity of COPD is determined by symptoms, spirometric abnormalities, and complications. Changes in therapy should also be based on these factors.
Blood gas measurements should be made in patients with $FEV_1 < 50\%$ predicted or in those with evidence for right heart failure.
Comorbidities are common in COPD and are often the cause of death. They should be actively identified.

Assessment of COPD. [Dransfield MT. Diagnosis of COPD and the GOLD Guidelines. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption adapted from original*

Factors That Suggest Diagnosis

- A patient who presents with the typical symptoms of dyspnea, cough, and sputum production, and has a greater than 40 pack-per-year history of cigarette smoking, has a high likelihood of having COPD.

Factors That Exclude Diagnosis

- Normal spirometric findings can exclude the diagnosis in a patient with the classic symptoms.

Ancillary Studies

Laboratory

- There are no lab tests that are diagnostic for COPD. However, many lab tests are helpful in the evaluation of the dyspneic patient to evaluate for other causes of the dyspnea.
- A complete blood count can help assess for anemia as the cause of dyspnea. Patients with advanced COPD may demonstrate polycythemia induced by chronic hypoxemia.

- A BNP (brain natriuretic peptide) level may help to distinguish between COPD and congestive heart failure as the cause of dyspnea. It is important to remember, however, that these diseases may often be present in the same patient.
- An alpha-1 anti-trypsin level should be measured in any patient with early-onset (before age 45) COPD, a non-smoker with COPD, or a family history of premature development of COPD.

Imaging

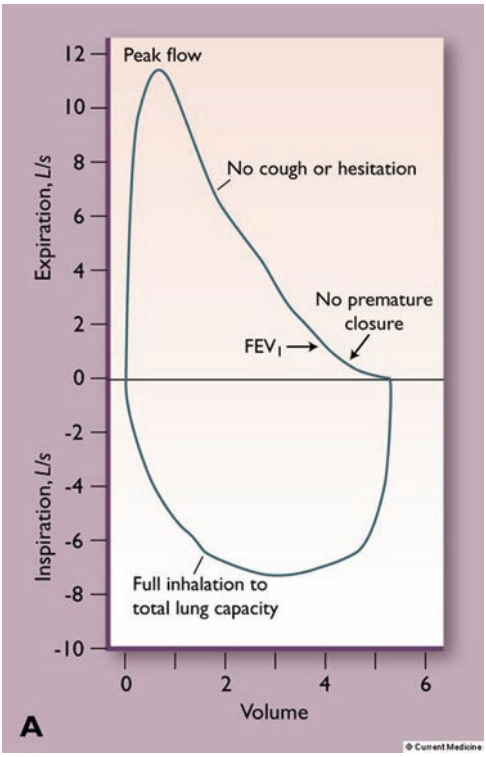
- Plain chest x-rays are unreliable in the diagnosis of COPD. Only about one-half of patients with moderate COPD will have any findings of COPD on a chest x-ray.
- The classic CXR findings of COPD include flattened diaphragms, an increased antero-posterior diameter of the chest, and increased radiolucency of the lungs. These are usually only seen in moderate-to-severe COPD, and are due to hyperinflation and air trapping.
- CXR can also be used to evaluate for alternative diagnoses (such as lung cancer, CHF, bronchiectasis), co-morbidities (the list also includes lung cancer, CHF, and bronchiectasis), and complications (such as pneumonia, pneumothorax) of COPD that are apparent on chest x-ray.
- CT is more sensitive at detecting the pathologic changes of COPD, but is not often needed to make the diagnosis. CT can be very helpful in the evaluation for alternative diagnoses, co-morbidities, and complications of COPD.

Chest X-rays of a 75-year-old patient with a clinical diagnosis of COPD. Posteroanterior (a) and lateral views (b) show radiographic signs consistent with pulmonary emphysema. Thickening of the bronchial wall is also evident in the lung bases. Tracheostomy was previously placed due to respiratory failure [Larici AR, Franchi P, Occhipinti M, Devicienti E, Mereu M, del Ciello A, Bonomo L. Airway Disease. In: Guglielmi G, Peh WCG, Guermazi A, editors. Geriatric Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013 [cited 2016 May 16]. p. 319–52. Available from: http://link.springer.com/10.1007/978-3-642-35579-0_14] *Caption from original*

Pulmonary Function Tests

- PFT's, especially spirometry, are the most helpful studies in diagnosing COPD. They are also useful in assessing the severity of disease, response to treatment, and for following progression.
- Spirometry (the measuring of breathing) is the most useful pulmonary function test in diagnosing and following COPD. Specifically, the forced expiratory volume in one second (FEV1), and the forced vital capacity and their ratio are the most helpful diagnostic tests for COPD.
- Spirometry performed both before and after inhaled bronchodilator use can determine whether airflow limitation is present, and whether it is at all reversible. Airflow limitation that is reversible is characteristic of asthma; airflow that is only partially reversible or is irreversible is consistent with COPD.
- Generally, COPD is felt to be present in a patient with an FEV1 less than 80 % of predicted, and and FEV1/FVC ratio of less than 0.7.

https://www.youtube.com/watch?v=s8pXdtp_Duw
Video demonstrating spirometry procedure, including the patient interview.



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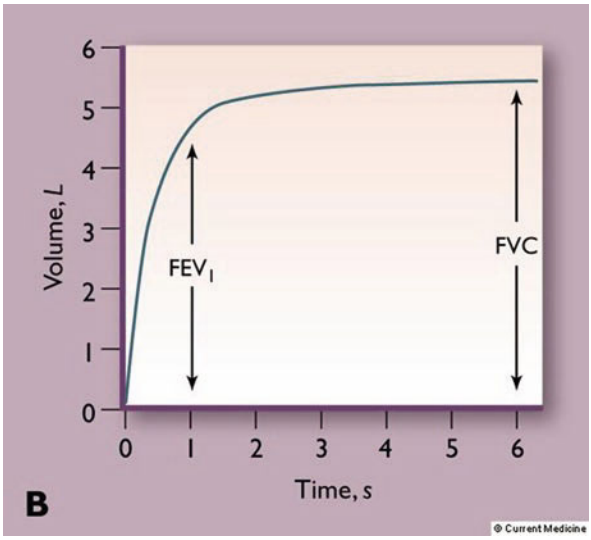


Spirometry in diagnosis of COPD [Hegewald M, Crapo R, Jensen R. Clinical Physiology of COPD. In: Crapo JD, editor. Atlas of Chronic Obstructive Pulmonary Disease. 2009 edition. Philadelphia, PA: Current Medicine Group; 2009. 160 p. ISBN: 978-1-57340-294-1] *Caption adapted from original*

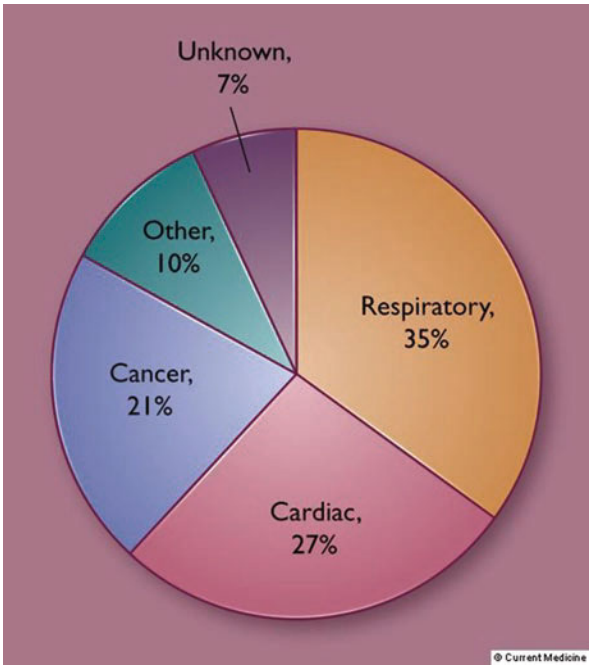
Special Populations

Age

- COPD is a slowly progressive disease that often presents later in life. It is uncommon to diagnose before the sixth decade of life.
- Patients who are diagnosed with COPD before the age of 45 need to be evaluated for alpha-one antitrypsin deficiency.

Co-morbidities

- As a disease of older patients, COPD is often is seen in combination with other diseases, such as coronary artery disease, congestive heart failure, and cancer.



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Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is imperative to consider the diagnosis, especially early in the course of the disease when the symptoms may be non-specific and subtle. Interventions such as smoking cessation can help to slow and stop the progression of disease if instituted early in the course.
- It is imperative to consider to alternative diagnoses, such as lung cancer and congestive heart failure.

Mimics

- Any disease that causes dyspnea can mimic COPD.
- Early COPD can sometimes be confused with atypical angina, as COPD, like angina, can cause chest tightness and dyspnea. Smoking is a significant risk factor for both diseases.
- Early in the course it is easily mimicked by asthma (although asthma has reversible airflow obstruction and COPD has irreversible airflow obstruction).
- Later in the course, COPD can mimic CHF, lung cancer with airway obstruction, bronchiectasis, pulmonary fibrosis, and other disorders causing dyspnea and cough.

Time-Dependent Interventions

- COPD cannot be reversed, so it is important to initiate treatment as early as possible to try and prevent progression of symptoms and pathology.
- Smoking cessation is critically important to these patients. It is also very difficult and may require a multi-modal treatment approach that includes pharmacologic and behavioral interventions.

Overall Principles of Treatment

- Therapy for compensated COPD involves numerous modalities including: oxygen therapy when indicated, bronchodilators, corticosteroids, reducing mucous secretion, smoking cessation, and pulmonary rehabilitation.
- Oxygen therapy in chronically hypoxic patients reduces mortality. The goal is to keep the PaO2 $\leq$60 mmHg of oxygen saturation $\geq$90 % at rest. The generally accepted criteria for oxygen therapy are: PaO2 $\leq$55 mmHg, an oxygen saturation of $\leq$88 % on room air, or a PaO2 of 56–59 mmHg in the presence of pulmonary hypertension, cor pulmonale, and polycythemia.
- Bronchodilator therapy does not affect the progression of the disease, but it can provide symptomatic relief and control and reduce exacerbations. Bronchodilator therapy also can improve quality of life. Patients would typically be maintained on long-acting inhaled beta agonists such as salmeterol and formoterol. Short-acting beta agonists such as albuterol are usually reserved for symptom control and for use during acute exacerbations. Inhaled anticholinergics (ipratropium) also cause bronchodilatation. The use of inhaled beta agonists combined with an inhaled anticholinergic improves FEV1 and symptoms better than either of these alone.

- Systemic corticosteroids can be useful in helping to control acute exacerbations, but most authorities don't recommend their long-term use. Only about 20–30 % of patients will note any improvement with the use of oral steroids. Some patients may improve with the use of inhaled steroids, especially those with an FEV1 <50 % of predicted.
- The only measures shown to help with mucous handling are adequate hydration and room humidification. Antitussives, antihistamines, and decongestants are all drying agents, and their use should be limited. Mucolytics and expectorants are of no clear benefit.
- Smoking cessation is the only intervention proven to reduce the rate of disease progression. Smoking cessation also reduces mortality. A multi-modal approach is often necessary and may include both pharmacologic and behavioral therapies.
- Pulmonary rehabilitation can increase exercise tolerance and improve quality of life, and is indicated for moderate-to-severe COPD.
- It is important that patients with COPD receive a pneumococcal vaccine, and also receive yearly influenza vaccination.

Disease Course

- COPD is a chronic, slowly progressive disease. It is marked by periods of relative stability interrupted by acute exacerbations, and a slow, steady decline in lung function.
- The frequency of exacerbations is a surrogate marker for disease progression.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pulmonary Disease, Chronic Obstructive"[Mesh] OR "COPD" OR "Chronic Obstructive Pulmonary Disease"

Chapter 19
Cor Pulmonale

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Cor Pulmonale; Right Heart Failure; Pulmonary Heart Disease

Incidence/Epidemiology

- The true incidence and prevalence of cor pulmonale are unknown, as there are no standard diagnostic guidelines, and no definitive diagnostic tests for this condition.
- COPD (Chronic Obstructive Pulmonary Disease) causes about half of all cases of cor pulmonale in North America. Up to one-third of patients with COPD will develop cor pulmonale at some point during the course of their illness.
- Up to 20% of patients with obstructive sleep apnea (OSA) will develop cor pulmonale.
- Pulmonary vascular disorders (primary pulmonary hypertension, chronic thromboembolic disease, and scleroderma lung disease) are rare diseases, but cor pulmonale is a common end-stage complication of these diseases.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_19

- Interstitial lung diseases (ILD), especially idiopathic pulmonary fibrosis (IPF), often lead to cor pulmonale.

Differential Diagnosis

- The differential diagnosis of cor pulmonale is broad, and encompasses all diseases that present with dyspnea, fatigue, and exercise intolerance, such as COPD, asthma, PE, CHF, acute and chronic coronary syndromes, interstitial lung disease, and pulmonary vascular diseases, among many others.
- Also, cor pulmonale does not exist in isolation; it occurs as a complication of other disease processes with the common denominator being the presence of significant pulmonary hypertension.
- It is important in the differential diagnosis of these patients to consider worsening of the underlying disease as a cause of worsening dyspnea.
- It is also important to evaluate these patients for left heart failure from cardiac causes.

Pathophysiology and Etiology

- Cor pulmonale is defined as an alteration in the structure and function of the right ventricle in the presence of underlying chronic lung disease.
- Right-sided heart failure that results from left heart failure is not considered cor pulmonale.
- Cor pulmonale is triggered by the development of pulmonary hypertension.
- There are many diseases that can lead to pulmonary hypertension, and subsequently cor pulmonale. These are reviewed in the section on pulmonary hypertension.
- Pulmonary hypertension (either acutely or chronically) causes changes in right ventricular structure (dilatation with or without hypertrophy) and function (decreased contractility). If present chronically, pulmonary hypertension causes the pulmonary vascular bed to undergo vasoconstriction, remodeling, fibrosis, and ultimately destruction. This leads to further increases in pulmonary artery pressure (the normal PA pressure is about 15 mm Hg), increasing the work of the RV to pump against higher pressures (increased RV afterload), leading to decreases in left ventricular filling and cardiac output, but usually with preservation of left ventricular ejection fraction.
- Chronic cor pulmonale is a chronic, slowly progressive condition that leads to worsening pulmonary hypertension, right ventricular hypertrophy, and dilatation.
- Cor pulmonale can also occur acutely, in the absence of right ventricular hypertrophy. A large pulmonary embolism can cause acute increase in right ventricular

and pulmonary artery pressure, leading to right ventricular dilatation and failure.

Presentation

Typical/"Classic"

- Dyspnea is the most common symptom of cor pulmonale. As many of these patients have significant underlying pulmonary disease, they often note a worsening of chronic dyspnea.
- Other symptoms often attributed to cor pulmonale include:
  - dyspnea on exertion
  - fatigue
  - lethargy
  - exertional syncope
  - exertional angina (even in the absence of coronary artery disease)
- Abdominal pain, ascites, and peripheral edema are also frequently seen in patients with cor pulmonale. These are related more to the left heart changes caused by cor pulmonale.
- Patients often present with worsening dyspnea, often with worsening edema and ascites. They will likely exhibit some degree of hypoxia.

Atypical

- Patients with no history of underlying pulmonary disease may present with acute cor pulmonale.
- These patients usually will have profound dyspnea and be hypoxemic and hypotensive. The most common cause for this will be a large, central pulmonary embolism.

Primary Differential Considerations

- The primary differential diagnoses for cor pulmonale are pulmonary hypertension, pulmonary embolism, constrictive pericarditis, and biventricular heart failure.

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that are pathognonomic for cor pulmonale, as many of the symptoms and signs of right heart failure are shared with left heart failure. These symptoms and signs include dyspnea, tachypnea, hypoxia, elevated jugular venous distension, hepatomegaly, and peripheral edema.

Factors That Suggest Diagnosis

- A patient with a history of known, chronic pulmonary disease, and who presents with worsening dyspnea, is a primary candidate for this diagnosis. However, it is important to remember that there are many other causes of worsening dyspnea in these patients (pneumonia, CHF, pulmonary embolism, pneumothorax, profound anemia, and others).
- Physical exam findings that suggest the diagnosis include:
  - A right ventricular third heart sound.
  - Prominent v-waves in the jugular venous pulse. This results from acute tricuspid regurgitation.

https://www.youtube.com/watch?v=ceX3KmZCZhY

An example showing a prominent v-wave in the jugular venous pulse associated with tricuspid regurgitation.

- A right ventricular heave at the left sternal border.
- Carvallo's Sign is an increase in the intensity of the holosystolic murmur of tricuspid regurgitation upon inspiration. This can often be noted with acute cor pulmonale. This finding becomes less apparent as right ventricular failure worsens.
- Central and peripheral cyanosis can be noted, but they are often late signs.
- Patients with end-stage cor pulmonale often have signs of cardiogenic shock such as hypotension, tachycardia, decreased urine output, and peripheral and central cyanosis.

Factors That Exclude Diagnosis

- Cor pulmonale cannot be diagnosed in the presence of left heart failure.

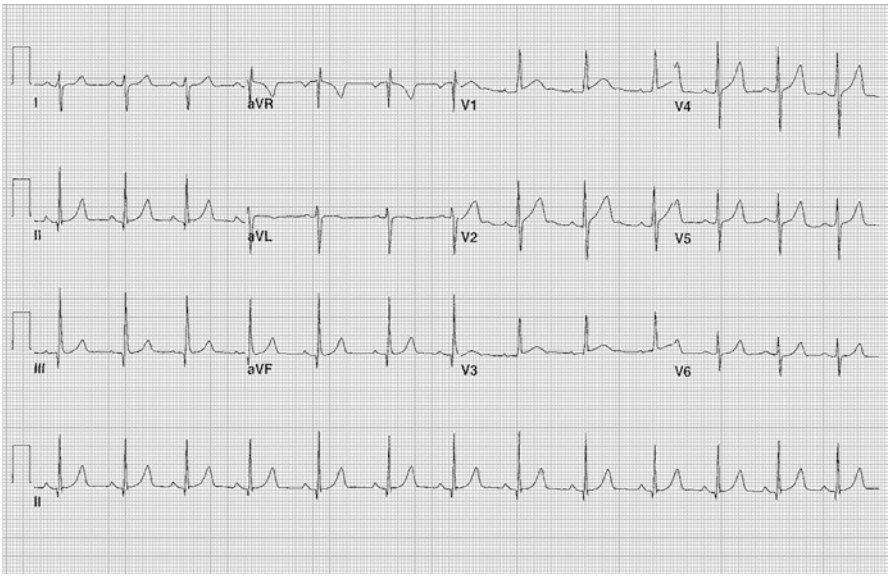
Ancillary Studies

Laboratory

- There are no laboratory studies that are specific for cor pulmonale.
- B-type natriuretic peptide levels should be checked, as they will be elevated. These levels will also be elevated in left heart failure, so they cannot help to distinguish between left heart failure and right heart failure.
- It is helpful to send routine laboratory studies, such as basic chemistries, a complete blood count, thyroid function, and cardiac biomarkers, to evaluate for other causes for the patient's symptoms.

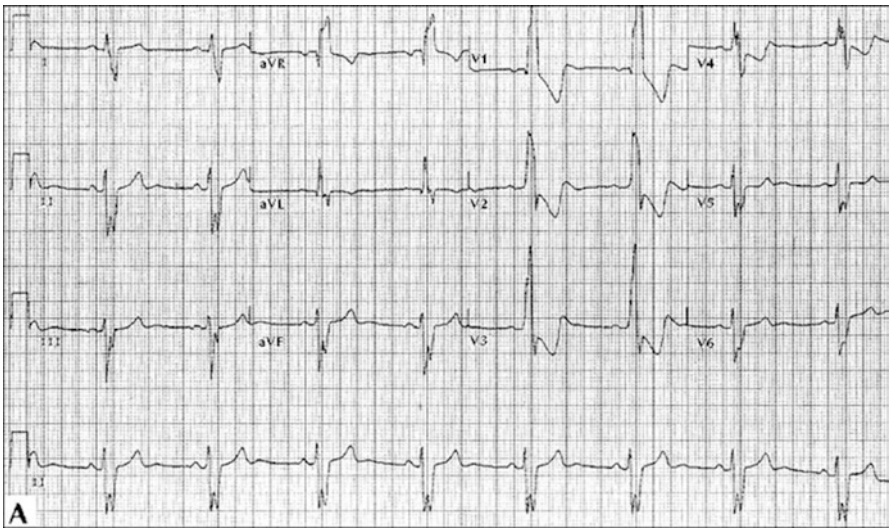
Electrocardiography

- The ECG in cor pulmonale and severe pulmonary hypertension can show a right axis deviation, right ventricular hypertrophy, right atrial enlargement (p pulmonale), and a right bundle branch block. These ECG changes are almost always present in pulmonary hypertension, but can also be present in many other disease states (they are specific but not sensitive).



Electrocardiogram showing the signs of right hypertrophy and right deviation of the cardiac axis in a patient with cor pulmonale [Massimi L, Di Rocco

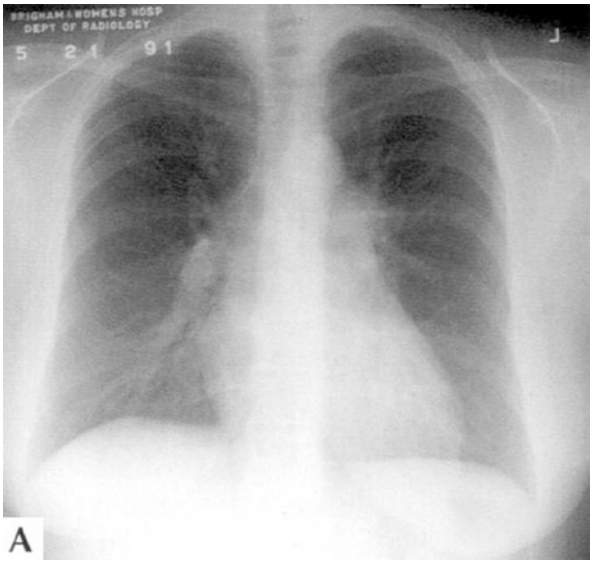
C. Complications Specific to the Type of CSF Shunt: Atrial Shunt. In: Di Rocco C, Turgut M, Jallo G, Martínez-Lage JF, editors. Complications of CSF Shunting in Hydrocephalus [Internet]. Cham: Springer International Publishing; 2015 [cited 2015 Sep 3]. p. 177–85. Available from: http://link.springer.com/10.1007/978-3-319-09961-3_12] *Caption from original*



Electrocardiographic finding with advanced cor pulmonale. Note the complete right bundle branch pattern with an RR′ in lead V1. This tracing demonstrates pressure and volume overload of the right ventricle, consistent with cor pulmonale. [Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption adapted from original*

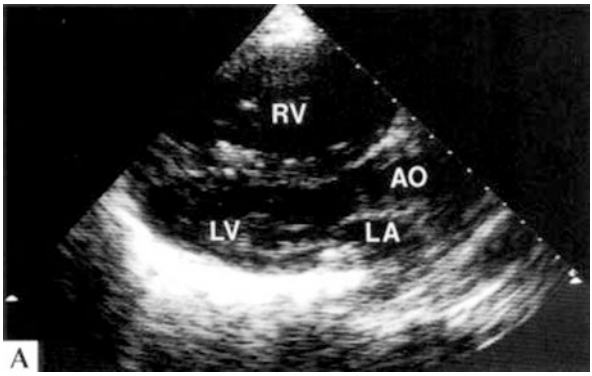
Imaging

- The chest x-ray may be helpful in the evaluation for cor pulmonale. Chronic pulmonary hypertension often leads to enlargement of the main pulmonary artery, hilar vessels, and the descending right pulmonary artery. On the lateral view, there may be loss of the retrosternal air space due to right ventricular enlargement.

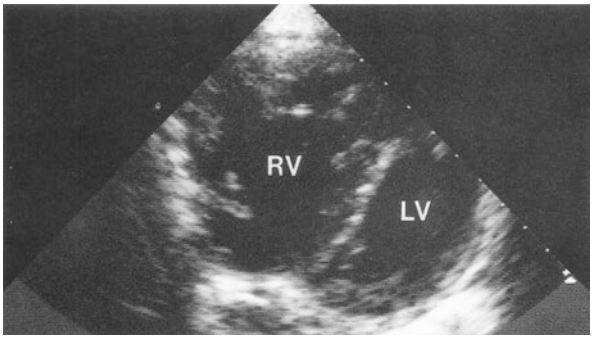


Chest radiograph demonstrating features of advanced cor pulmonale secondary to pulmonary hypertension. Typical radiograph of a patient with primary pulmonary hypertension and cor pulmonale. Note the peripheral oligemia of the pulmonary vessels with mild bilateral enlargement of the main pulmonary arteries.[Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption adapted from original*

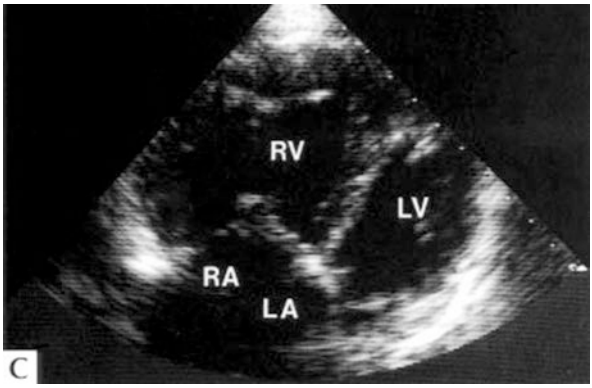
- Transthoracic echocardiography (TTE) can be very helpful in the evaluation for and diagnosis of cor pulmonale and pulmonary hypertension. Pulmonary hypertension alone is associated only with signs of elevated right ventricular pressure. In chronic cor pulmonale there is a thickened (hypertrophied) right ventricular wall and right ventricular dilatation (early in the course of the disease, only hypertrophy may be appreciated). The right ventricular dilatation usually leads to tricuspid regurgitation. Acute cor pulmonale may lead to right ventricular dilatation in the absence of right ventricular hypertrophy. Reduced function of the right ventricle can also often be appreciated on TTE.



Echocardiographic features of the heart in a patient with cor pulmonale. A, Parasternal long-axis view from a patient with advanced primary pulmonary hypertension complicated by cor pulmonale. Note the abnormal flattening of the interventricular septum and its abnormal bulging into the left ventricle (LV), consistent with volume and pressure overload of the right ventricle (RV). [Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption from original*



Short-axis view demonstrating a markedly enlarged RV with RV hypertrophy. Abnormal bowing of the interventricular septum into the LV gives a characteristic D configuration of the LV, consistent with volume and pressure overload of the RV. [Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption from original*



Apical four-chamber view also demonstrating RV hypertrophy and abnormal septal bowing as described in panels A and B. AO—aorta; LA—left atrium; RA—right atrium. [Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption from original*

- Cardiac magnetic resonance imaging (MRI), if available, is superior to transthoracic echocardiography in the evaluation of right ventricular structure and function.
- Right heart catheterization is considered the best diagnostic test for cor pulmonale and pulmonary hypertension. Patients with cor pulmonale will have right ventricular dysfunction as evidenced by an elevated central venous pressure and elevated right ventricular end-diastolic pressure, pulmonary hypertension (PA pressure greater than 25 mmHg), and no evidence of left heart disease, as evidenced by either a normal (less than 15 mmHg) left ventricular end-diastolic pressure. All chamber dimensions and pressures can be directly measured.

Special Populations

Age

- Cor pulmonale is a disease of adults starting in middle-age.
- Most patients with chronic cor pulmonale will have had severe, underlying pulmonary disease for many years prior to the onset of cor pulmonale.
- In the pediatric patient, the vast majority of cases are secondary to cystic fibrosis.
- Neonates with severe bronchopulmonary dysplasia are also susceptible to the development of cor pulmonale.

Co-morbidities

- Many co-morbid conditions can worsen the prognosis, and make the diagnosis of cor pulmonale difficult. These include, but are not limited to, cardiac diseases, other pulmonary diseases, liver disease, and kidney disease.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is imperative that all patients be evaluated for left ventricular dysfunction. The most common cause of right heart failure is left heart failure, and left heart failure precludes a diagnosis of cor pulmonale.
- It is also important to consider all alternative diagnoses that may cause worsening or acute dyspnea in patients with chronic pulmonary and heart disease. This list includes, but is not limited to, pneumonia, CHF, pulmonary embolism, pneumothorax, significant pleural effusion, and acute metabolic issues that can cause dyspnea.

Mimics

- Left heart failure can mimic right heart failure.
- Other diseases that can present in a similar fashion include acute liver failure, acute kidney failure, and others.

Time-Dependent Interventions

- The most important intervention is to decrease the work of breathing by correcting hypoxemia and respiratory acidosis. Correcting these will decrease pulmonary vascular resistance and thereby reduce demands on the right ventricle.

Overall Principles of Treatment

- Optimizing treatment of the underlying lung disease can help improve hemodynamics and lessen the symptoms and progression of cor pulmonale.

- Specific treatment for cor pulmonale consists of managing three physiologic parameters—pulmonary artery pressure; right ventricular pressure; and right ventricular contractility—as follows:
  - Reduce pulmonary artery pressure (reduce right ventricular afterload). This pressure can be reduced by the use of supplemental oxygen to decrease the effect of hypoxia-induced vasoconstriction. This is particularly necessary in hypoxic patients.
  - Reduce right ventricular pressure. Diuretic use has shown some utility in improving hemodynamics in patients with markedly elevated right ventricular pressure. Diuresis must be performed carefully, as over-diuresis can lead to reduced right ventricular filling and a decrease in cardiac output.
  - Improve right ventricular contractility. This therapy is generally reserved for patients with severe cor pulmonale who have resistant hypotension and are in shock. The most common inotropic agents used are dobutamine and milrinone.
- Patients should be evaluated for any underlying or acute issues that, if treated, can help improve the symptoms of cor pulmonale. These include such issues as pulmonary embolism, pneumonia, pneumothorax, and pleural effusions.

Disease Course

- Cor pulmonale is a chronic, progressive disease that occurs only when other underlying pulmonary diseases have progressed and are severe.
- As noted above, acute cor pulmonale is less common but can occur.
- The overall long-term prognosis once cor pulmonale has been diagnosed is poor. Mortality in the first year after the diagnosis of cor pulmonale is around 35%.
- Survival is significantly lessened once cor pulmonale complicates pre-existing lung disease.

Related Evidence

Papers of particular interest have been highlighted as:
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Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

("Pulmonary Heart Disease"[Majr] OR "pulmonary heart disease"[tiab] OR "cor pulmonale"[tiab] OR "right heart failure"[tiab])

Chapter 20
Costochondritis

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Costochondritis; Costosternal Syndrome; Tietze's Syndrome; Chest Wall Pain Syndrome

Incidence/Epidemiology

- Chest pain is a common presenting complaint to both Emergency Departments and primary care offices.
- There are an estimated six million emergency department visits a year for chest pain.
- The evaluation of chest pain utilizes a substantial amount of health care resources, primarily with the goal of excluding life-threatening diagnoses.
- Musculoskeletal causes of chest pain account for up to one-third of all causes in the outpatient evaluation of chest pain.
- The true incidence of costochondritis and other musculoskeletal chest pain syndromes is unknown, as many cases don't present for evaluation.

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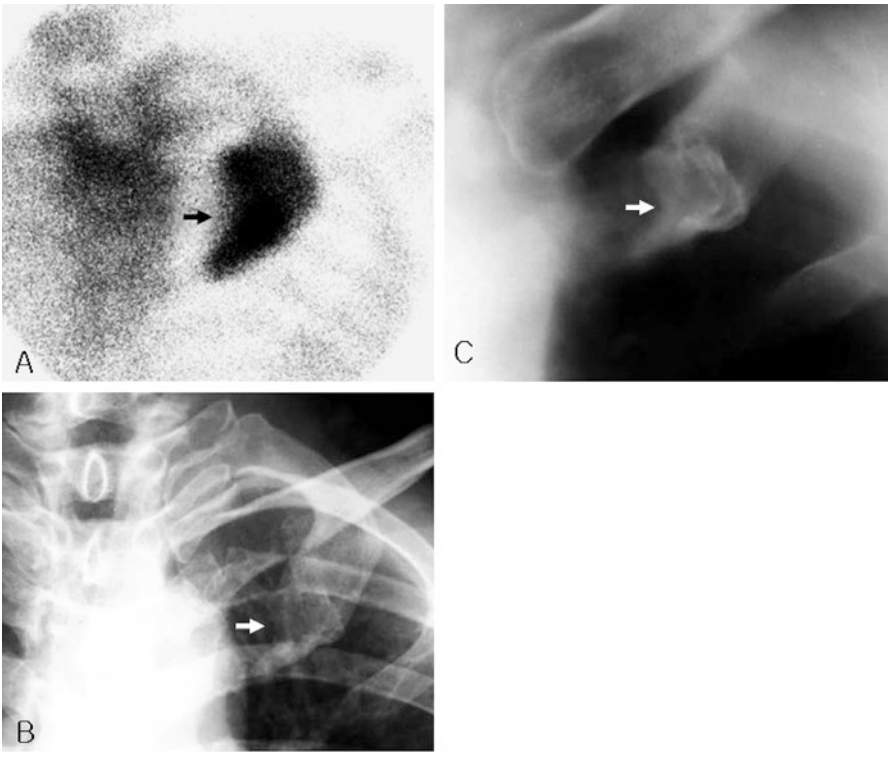
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_20

Differential Diagnosis

- The initial differential diagnosis of chest pain must include all the serious and potentially life-threatening diseases, such as acute coronary syndromes, aortic dissection, pulmonary embolism, and pneumothorax.
- The differential diagnosis of musculoskeletal causes of chest pain is broad. It includes, primarily, inflammatory musculoskeletal pain syndromes such as costochondritis (and others as below), and rheumatic musculoskeletal syndromes such as fibromyalgia, rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.
- Primary (inflammatory) musculoskeletal chest pain syndromes include:
  - Costochondritis. Costochondritis typically affects those over age 40, and usually involves pain to palpation over the costochondral junctions of the third, fourth, and fifth ribs. Costochondritis is diagnosed more often in women.
  - Tietze's Syndrome. In Tietze's syndrome there is painful swelling of usually one (but sometimes several), costochondral joints. It usually involves either the second or third costochondral junctions. There must be obvious physical signs of inflammation, such as erythema, swelling, and warmth over the affected joint, for the diagnosis to be considered. It is a rare disorder of unknown etiology. Tietze's syndrome is more common in those under 40, and affects both sexes equally.



Inverted C-shape tracer uptake in chronic Tietze's disease. **A** Anterior pinhole scan in a 63-year-old man with tender swelling for 2 months in the left first costochondral junction shows inverted C-shape tracer uptake (*arrow*). **B** Posteroanterior radiograph shows nonspecific calcification (*arrow*). **C** Conventional X-ray tomograph shows inverted C-shape ossification in the costochondral junction (*arrow*) [Bahk Y-W. Infective and Infl ammatory Diseases of Bone. In: Combined Scintigraphic and Radiographic Diagnosis of Bone and Joint Diseases [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2013 [cited 2016 Nov 7]. p. 75–106. Available from: http://link.springer.com/10.1007/978-3-642-25144-3_6] *Caption from original*

- Xiphodynia/xiphalgia. Sharp, pleuritic chest pain that is reproduced by light palpation of the xyphoid process.
- Precordial catch syndrome (sometimes called texidor twinge). Fleeting (lasting seconds to minutes), lancinating episodes of chest pain, often precipitated by deep inspiration.
- Slipped rib syndrome. Pain and often a feeling of fullness usually along the inferior margin of the anterior tenth rib. There is often point tenderness and reproduction of the symptoms with pressure. Thought to be secondary to hypermobility of the distal costal cartilage that occurs after lifting or twisting. More commonly diagnosed in women.
- Sternalis syndrome. Localized tenderness over the sternum thought secondary to inflammation of the overlying sternalis muscle. Rare, more common in women, and often causes bilateral pain, especially with palpation.
- Sternoclavicular subluxation. Another rare diagnosis, marked by spontaneous or traumatic subluxation of a sternoclavicular joint. More commonly noted on the side of the dominant hand, and worsens with pulling and lifting motions. Mostly seen in women 40 – 60 years old, and associated with moderately heavy repetitive tasks.

Pathophysiology and Etiology

- The pathophysiology of costochondritis is felt to primarily involve inflammation of the costochondral junctions. The inflammation may be spontaneous and idiopathic, or may be related to injuries cause by trauma or overuse.

Presentation

Typical/"Classic"

- Chest pain that that is highly localized, and consistently reproducible by light palpation over a small area.
- Usually described as sharp and pleuritic, and often worsens when changing positions, coughing, and sneezing.
- Onset can be sudden, but is more often gradual and insidious.

Atypical

- May present as dull, diffuse pain that is poorly localized.

Primary Differential Considerations

- Initial consideration to patients presenting with these symptoms should be given to the following differential diagnoses:
  - Acute coronary syndrome
  - Pulmonary embolism
  - Pericarditis
  - Pleurisy
  - GERD
  - Herpes zoster (shingles)

History and Physical Exam

Findings That Confirm Diagnosis

- It must be stressed that all the life-threatening causes of chest pain must always be considered in patients presenting with a complaint of chest pain.
- It must also be stressed that reproducibility and chest wall tenderness are not sensitive or specific signs, and they can also occur with acute coronary syndromes.
- The diagnosis can usually be confirmed, after more serious causes of have chest pain have been excluded (either by history and physical or testing), when there is a discrete area of tenderness in which the pain is consistently reproduced by light palpation.

Factors That Suggest Diagnosis

- Chest pain that is sharp, localized, and consistently reproducible by light palpation.

Factors That Exclude Diagnosis

- Chest wall pain syndromes can coexist with many other causes of chest pain, and as such can only be excluded when there is no complaint of chest pain.

Ancillary Studies

Laboratory

- Laboratory studies are inly useful in excluding other diagnoses. There are no laboratory studies that help in the diagnosis of costochondritis or other chest wall pain syndromes.

Imaging

- Imaging studies are only helpful in the exclusion of other diagnoses.

Special Populations

Age

- Costochondritis is more common above the age of 40, but can be diagnosed in any adult age group.
- Costochondritis can affect children as well as adults.
- In some studies of musculoskeletal chest pain in children, costochondritis accounted for nearly 15 percent of final diagnoses.

Co-morbidities

- Costrochondritis can coexist with any other diagnosis. There are no co-morbidities of significance.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critically important to first consider the life-threatening causes of chest pain.

Mimics

- Costochondritis can present similarly to other, more serious causes of chest pain, such as pulmonary embolism and acute coronary syndrome.

Time-Dependent Interventions

- There are no time-dependent interventions.

Overall Principles of Treatment

- Costochondritis and the other musculoskeletal chest pain syndromes are usually self-limited conditions.
- Treatment is usually conservative, and starts with reassurance that no more serious condition exists.
- Treatment is usually with simple analgesics such as acetaminophen. If acetaminophen is unsuccessful, a trial of NSAIDs may be appropriate.
- In situations where the precipitating event is felt to be trauma or overuse, a short period of rest may be helpful.
- In situations where the pain is well localized, a trial of capsaicin cream, NSAID creams or patches, or lidocaine patches may be helpful.
- In resistant cases, it may be necessary to refer to a pain center for local injections of a glucocorticoid/local anesthetic mixture.

Disease Course

- The course of costochondritis and the other chest wall pain syndromes is generally benign and self-limited and will resolve spontaneously within 2–3 weeks or a month.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Tietze's Syndrome"[Mesh] OR "Costochondritis"

Chapter 21
Cyanide Poisoning

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Cyanide Poisoning

Incidence/Epidemiology

- Rare occurrence
- Usually in association with smoke inhalation from a residential or industrial fire
- Occasionally seen as suicidal ingestion

Differential Diagnosis

- Myocardial infarction

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_21

- Meningitis and encephalitis
- Hemlock poisoning
- Pulmonary embolism
- Cardiogenic shock
- Ischemic stroke
- Carbon monoxide toxicity
- Hydrogen sulfide toxicity
- Iron toxicity
- Isoniazid toxicity
- Nonsteroidal anti-inflammatory drug toxicity
- Azide toxicity
- Methanol toxicity
- Strychnine toxicity

Pathophysiology and Etiology

- Mitochondrial toxicity by binding cyanide to ferric ion ($Fe3^{+}$). Oxidative phosphorylation ceases, leading to anaerobic metabolism.
- Rapidly absorbed through gastrointestinal tract and skin
- Rapidly lethal
- Exposure may be
  - From smoke inhalation/fire
    - Formed when structures containing both carbon and nitrogen (such as polyurethane) burn
  - Industrial
    - From metal extraction, electroplating
  - Medical
    - Use of some antineoplastic agents (such as amygdalin) and other infusions (such as nitroprusside) may result in accumulation of toxic levels of cyanide.
  - Diet
    - Fruit pits and bitter almond contain cyanogenic glycosides
  - Tobacco abuse
    - At baseline, chronic smokers have significantly higher blood levels of cyanide than nonsmokers

Presentation

Typical/"Classic"

- Symptoms depend on severity and route of poisoning.
- Central nervous system symptoms, including headache, anxiety, confusion, vertigo, coma, and seizures, are most prominent.
- Also prominent are cardiovascular symptoms, including tachycardia, hypertension then bradycardia and hypotension, atrioventricular block, and ventricular dysrhythmias.
- Skin and lip flushing also may be seen.

Atypical

- Lower-level exposure may delay the onset of the aforementioned signs and symptoms.
- Nausea and vomiting
- Muscular twitching

Primary Differential Considerations

- Because of the wide range of signs and symptoms, the differential is quite large and includes exposure to tricyclic antidepressants, organophosphates, methemoglobin, strychnine, carbon monoxide, or arsine.

History and Physical Exam

Findings That Confirm Diagnosis

- There is no clinical confirmation of cyanide toxicity. This is a laboratory diagnosis in a challenging clinical setting in which early testing of arterial blood gas and lactate levels is important.

Factors That Suggest Diagnosis

- Bright red venous blood
  - Despite hypotension, apnea, or bradycardia, cyanosis usually is not present.
- After hydrogen cyanide inhalation:

  - Bitter almond odor
  - Headache, anxiety, nausea, and metallic taste
- After cyanogen chloride inhalation:
  - Eye and mucous membrane irritation, bronchorrhea, cough, and dyspnea
- After dermal exposure/ingestion:
  - Delayed symptoms: minutes to hours
- After parental exposure:
  - Confusion and combativeness initially may be mistaken as intensive care unit (ICU) syndrome
- After ingestion
  - Nausea and vomiting
  - Large quantities of such foods may result in toxicity

The starchy roots of the cassava plant (*Manihot esculenta*) contain cyanide. The roots are a staple in the diet of people living in the tropics, and inadequate processing of the roots can lead to cyanide poisoning [Lottermoser BG. Mine wastes [Internet]. Berlin, Heidelberg: Springer; 2010. Chapter 5, Cyanidation wastes of gold-silver ores; [cited 2015 Aug 13]; p. 243-262. Available from: http://link.springer.com/10.1007/978-3-642-12419-8_5] *Caption from original*

Factors That Exclude Diagnosis

- There is no clinical exclusion for cyanide poisoning when the presentation is suggestive.

Ancillary Studies

Laboratory

- Basic metabolic panel to assess for anion gap metabolic acidosis
- Serum lactate:
  - Closely correlates with severity of cyanide toxicity
  - A normal level casts doubt on true cyanide poisoning.
  - Levels may be used to monitor treatment progress.
- Central venous blood gas to assess venous arterial PO2 gradient
- Carboxyhemoglobin and methemoglobin levels in concomitant carbon monoxide exposure
- Cyanide levels:
  - May be obtained for diagnostic confirmation, but results will not be available in time to be clinically useful and may be unreliable
  - Levels do not correlate directly with survivability.

Special Populations

Age

- Sodium nitrite–induced 20–30 % level of methemoglobinemia may be lethal in children or anemic patients and should not be given to pregnant patients.
- Pediatric patients are thought to be vulnerable to cyanide exposure because of their higher respiratory rates and immature detoxification systems.

Co-morbidities

- Patients with limited cardiopulmonary reserve who are exposed to cyanide have a poorer prognosis.

Pregnancy

- Fetal demise is possible in cyanide poisoning. Aggressive support and antidotal treatment of the mother are essential.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- The presentation of carbon monoxide poisoning from smoke inhalation is similar to that of cyanide poisoning; thus, clinicians often focus on carboxyhemoglobin levels, neglecting coexistent cyanide toxicity.

Mimics

- Mimics of cyanide poisoning include those listed as differential considerations, especially
  - Carbon monoxide poisoning
  - Phosgene exposure
  - Hydrogen sulfide poisoning
  - Arsine exposure
  - Inert gas exposure

Time-Dependent Interventions

- If clinical history and exam suggest cyanide poisoning, antidotal therapy must be given immediately.

Overall Principles of Treatment

- Decontaminate as soon as possible, removing patient from cyanide source.
  - Rescuers should wear protective suits and respirators until proper decontamination is complete.
- Antidotal treatment involves three strategies: binding of cyanide, use of sulfur donors, and induction of methemoglobinemia.
  - Hydroxocobalamin, a precursor of vitamin B_{12}, contains a cobalt moiety that avidly binds to intracellular cyanide, forming cyanocobalamin.

    - Cyanocobalamin is excreted in urine.
- Sodium thiosulfate
    - Sulfur donor excreted renally
- +/− Sodium nitrite
    - Induces methemoglobinemia, with the goal of a 20–30 % methemoglobin level if tolerated
    - It is CONTRAINDICATED in cases of potential carbon monoxide toxicity.
    - May cause hypotension and tachycardia, vasodilation

Disease Course

- Prognosis depends on level of exposure and extent of symptoms at presentation.
- Even in patients with severe symptoms such as seizures at presentation, prompt administration of antidote improves prognosis.
    - The exception is cardiac arrest, in which even early antidote administration is unlikely to reverse the very poor prognosis.
- Patients who survive cyanide poisoning sometimes have long-term central nervous system complications, such as movement disorders and neuropsychiatric problems.
- Suicide attempts with cyanide often are successful because of the deliberately high toxin load.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Cyanide Poisoning" OR "Cyanide Toxicity"

Chapter 22
Cyanotic Congenital Heart Disease

Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Cyanotic Congenital Heart Disease

- Refers to a subset of congenital cardiac malformations that favor the development of variable degrees of cyanosis.
- The vast majority of malformations will present in the newborn period and will be diagnosed in the neonatal setting.
- There are, however, variant forms which will "escape" neonatal diagnosis and have their initial cyanotic presentations in the Emergency Department.
- Late presentations are usually encountered in infants with ductus-dependent lesions necessary for pulmonary blood flow (generally left sided outflow obstructions such as hypoplastic left ventricle or coarctation of the aorta).

Incidence/Epidemiology

- Fifteen to 20 percent of all congenital heart disease cases are of the cyanotic variety.
- Cyanotic forms account for nearly 30 percent of fatal cases.

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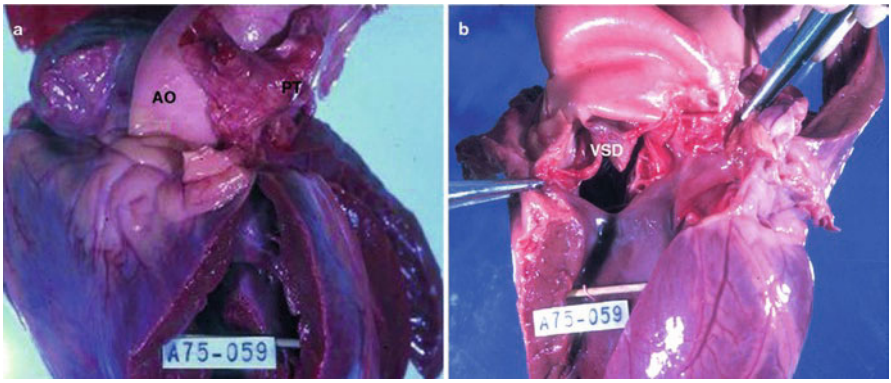
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_22

Differential Diagnosis

- Should be considered in the differential diagnosis of cyanotic congenital heart disease, often represented by the "5 T's":
  - Truncus Arteriosus
  - Transposition of the Great Arteries
  - Tricuspid Atresia
  - Tetralogy of Fallot
  - Total Anomalous Pulmonary Venous Return
- There are other causes of cyanosis in young infants, most traditionally classified into pulmonary insults and hemoglobinopathies (i.e., Methemoglobinemia)

Pathophysiology and Etiology

- The essential common pathway that serves as the basis for all congenital cyanotic cardiac lesions is an inability to deliver oxygen to the general circulation and therefore peripheral target organs.
- The predominant pathophysiology involves variable degrees of right-to-left shunting. Systemic (deoxygenated) blood is unable to access the alveoli, returning to the left side of the heart without being oxygenated. In most cases of cyanotic heart disease, the shunt is intracardiac.



Tetralogy of Fallot. (a, b) Tetralogy of Fallot, the most common cause of cyanotic congenital heart disease, consists of a membranous VSD right ventricular outflow obstruction, rightward displacement of the aorta (AO), and secondary right ventricular hypertrophy. The right ventricular outflow obstruction may take the form of hypoplasia of the pulmonary trunk (PT), pulmonary valvular malformation and stenosis, outflow tract (infundibular) hypoplasia and narrowing, or a combination of all

three components, as seen in this case [Buja LM, Cheong B. Cardiovascular Pathology. In: Krueger GRF, Buja LM, editors. Atlas of Anatomic Pathology with Imaging [Internet]. London: Springer London; 2013 [cited 2016 Jul 29]. p. 43–104. Available from: http://link.springer.com/10.1007/978-1-4471-2846-5_2] *Caption from original*

Presentation

Typical/"Classic"

- Most entities will present within the first few hours of life, with diagnosis made before discharge from the newborn unit.
- Other entities, specifically those with ductal dependency, will only present when the duct closes. The infants will present with varying degrees of shock and/or cyanosis (usually left sided outflow obstructive lesions such as an interrupted aortic arch).

Atypical

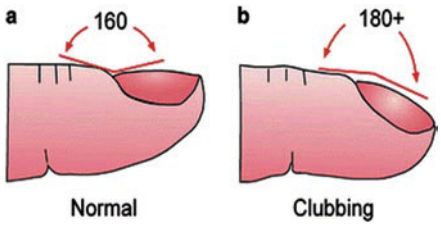
- Infants with Tetrology of Fallot may "escape" diagnosis in the first few days of life, presenting to the ED with what are known as "Tet (hypercyanotic) Spells."
- Management of Hypercyanotic Spells:
  - Provision of supplemental oxygen.
  - Placement in the knee chest position.
    - Sedation with morphine (0.1 mg/kg/dose)
    - Administration of 10-20 cc/kg of normal saline
    - Immediate consultation with a pediatric cardiologist

Primary Differential Considerations

- These specific diagnoses should be considered in patients who present with signs and symptoms of congenital cyanotic heart disease:
  - tricuspid atresia
  - Ebstein's malformation of the tricuspid valve
  - severe pulmonic stenosis with intact ventricular septum
  - complete transposition of the great vessels
  - truncus arteriosus.

History and Physical Exam

- As previously described, the majority of cyanotic congenital lesions will be diagnosed and treated within the first few days of life.
- In some patients, cyanotic presentations may be quite dramatic, unresponsive to any degree of supplemental oxygen (the hyperoxia test).
- Other patients will present with hypoperfusion and frank hypotension. Administration of isotonic volume replacement will often worsen the clinical status, alerting the clinician to the possibility of a cardiogenic etiology as the cause of shock.
- Each particular malformation has a specific set of physical and radiographic findings.
- The presence or absence of a murmur is variable and often not integral in making the diagnosis.



Clubbing. (**a**) The angle at the junction of skin with the nail at the dorsal surface of digits is normally around 160°. (**b**) In children with cyanotic congenital heart diseases this angle becomes wider and may exceed 180°. This is the result of hypoxia in peripheral tissue, which causes the opening of normally collapsed capillaries to better perfuse the hypoxic tissue. Perfusion of these collapsed capillaries will result in expansion of the volume of these peripheral tissues (tips of digits) resulting in clubbing. This phenomenon is seen in other lesions causing hypoxia of peripheral tissue, such as with chronic lung disease and chronic anemia (causing hypoxia through reduction of level of hemoglobin and therefore reduction of oxygen carrying capacity) such as with ulcerative colitis, Crohn's disease, and chronic liver disease [Thompson WR, Mehrotra SM. Cardiac History and Physical Examination. In: Abdulla R, editor. Heart Diseases in Children [Internet]. Boston, MA: Springer US; 2011 [cited 2016 Jul 29]. p. 3–16. Available from: http://link.springer.com/10.1007/978-1-4419-7994-0_1] *Caption from original*

Findings That Confirm Diagnosis

- Echocardiography remains the gold standard.

Factors That Suggest Diagnosis

- The use of the hyperoxia test is traditionally employed to differentiate between pulmonary, cardiac, and hematologic causes of cyanosis in infancy.
- Administer supplemental oxygen.
- If OSAT rises, it is most likely pulmonary disease.
- If OSAT does not rise, consider Cyanotic Heart Disease *or* Methemoglo binemia.
- With the patient on 100% supplemental O_2, and the pO_2 is high and OSAT is low, consider Methemoglobinemia as an etiology,
- With the patient on 100% supplemntalO_2, and the pO_2 is low *and* the OSAT is low, consider cyanotic heart disease as an etiology.

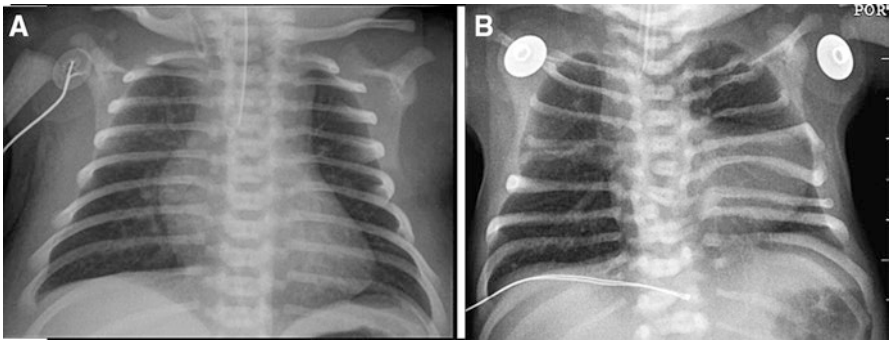
Factors That Exclude Diagnosis

- A normal echocardiogram.

Ancillary Studies

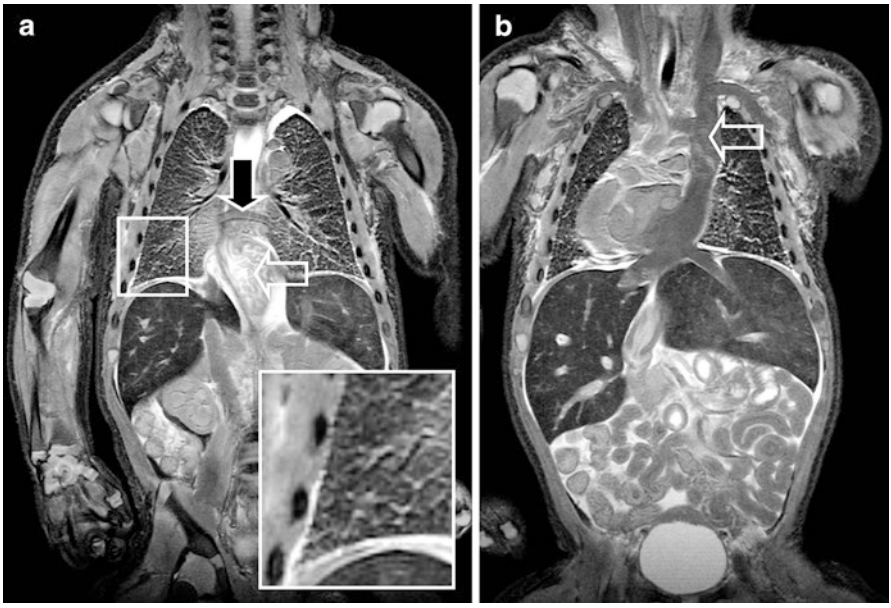
Imaging

- There are certain classic radiographic findings associated with specific forms of cyanotic heart disease in infants:
  - Cardiomegaly is seen with left-sided outflow obstructive lesions.
  - A boot-shaped heart is seen with Tetralogy.
  - An "egg-on-a-string" pattern is seen with Transposition.



Utility of chest radiography in CHD. A: Chest radiograph of a neonate with d-transposition of the great arteries, appearing as an "egg on a string" appearance of the

heart and mediastinum. This pattern-based approach to cardiac morphology is inaccurate and is rarely helpful for clinical management. Cardiac morphology is determined by echocardiography in the neonatal period while the chest radiograph sheds light on physiology. B: Neonate with complex cyanotic congenital heart disease, including mitral atresia, total anomalous pulmonary venous connection to the coronary sinus, double outlet right ventricle, and pulmonary stenosis. The chest radiograph demonstrated decreased pulmonary vascularity, which enabled decision-making regarding initial palliative treatment. The pulmonary blood flow was augmented using a modified Blalock–Taussig shunt. [Krishnamurthy R, Chitkara P. Evidence-Based Approach to Imaging of Congenital Heart Disease. In: Medina LS, Applegate KE, Blackmore CC, editors. Evidence-Based Imaging in Pediatrics [Internet]. New York, NY: Springer New York; 2010 [cited 2016 Jul 29]. p. 339–58. Available from: http://link.springer.com/10.1007/978-1-4419-0922-0_24] *Caption from original*



A neonate with a congenital cyanotic heart disease born at 39 weeks. Maximum support and 100% oxygen did not lead to clinical improvement and the child died. T2-W coronal MRI shows a complete anomalous venous return (arrow) with pulmonary interstitial oedema (insert). A central tendon defect is seen (open arrow) (slice thickness: 2 mm, TR: 5500, TE: 54, FA: 180°). **b** T2-W coronal MRI shows a persistent left superior caval vein (arrow), a dextrocardia and situs intermedius of the liver. Asplenia was also noted [From article: Current techniques in postmortem imaging with specific attention to paediatric applications. Pediatric Radiology. 2010

Feb;40(2):141–52. https://doi.org/10.1007/s00247-009-1486-0, at http://link.springer.com/article/10.1007/s00247-009-1486-0; by Tessa Sieswerda-Hoogendoorn, Rick R. van Rijn, © The Author(s) 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Electrocardiography

ECG finding	Likely CCHD	Remarks
RAD with RVH	TOF	Early & sudden R to S transition from V_1 to V_2
	ccTGA with VSD with PS	CHB, absent septal q in V_{5-6}
	Critical PS with IVS	RV strain (ST- T changes in $V_{1-3,}$ II, III, aVF)
	TGA with IVS	
LAD	AVSD with PS	RVH
	Tricuspid atresia	LVH
Monomorphic QRS in V_{1-6}	Single ventricle with PS	
IRBBB	Ebstein's anomaly	Polyphasic QRS complexes

Typical ECG findings in various cyanotic congenital heart diseases [Gupta SK. Clinical Approach to a Neonate with Cyanosis. The Indian Journal of Pediatrics. 2015 Nov;82(11):1050–60.] *Caption from original*

- Cardiac Enzymes
- Not indicated.

Special Populations

Age

- As discussed, most cases are diagnosed in the first few days of life.

Co-morbidities

- TAPVR is associated with asplenia or polysplenia.

Pitfalls in Diagnosis

- Cyanotic variant
  - Emergency pediatric cardiology consultation is warranted.
- Acyanotic variety
  - Adherence to strict algorhythmic workups of neonatal CHF or respiratory distress will eventually uncover the lesion.

Critical Steps Not to Miss

- Provision of supplemental oxygen
- Early ventilator support
- Immediate PICU or Pediatric Cardiology consultation

Mimics

- Any congenital cardiac lesion causing cyanosis and/or CHF

Time-Dependent Interventions

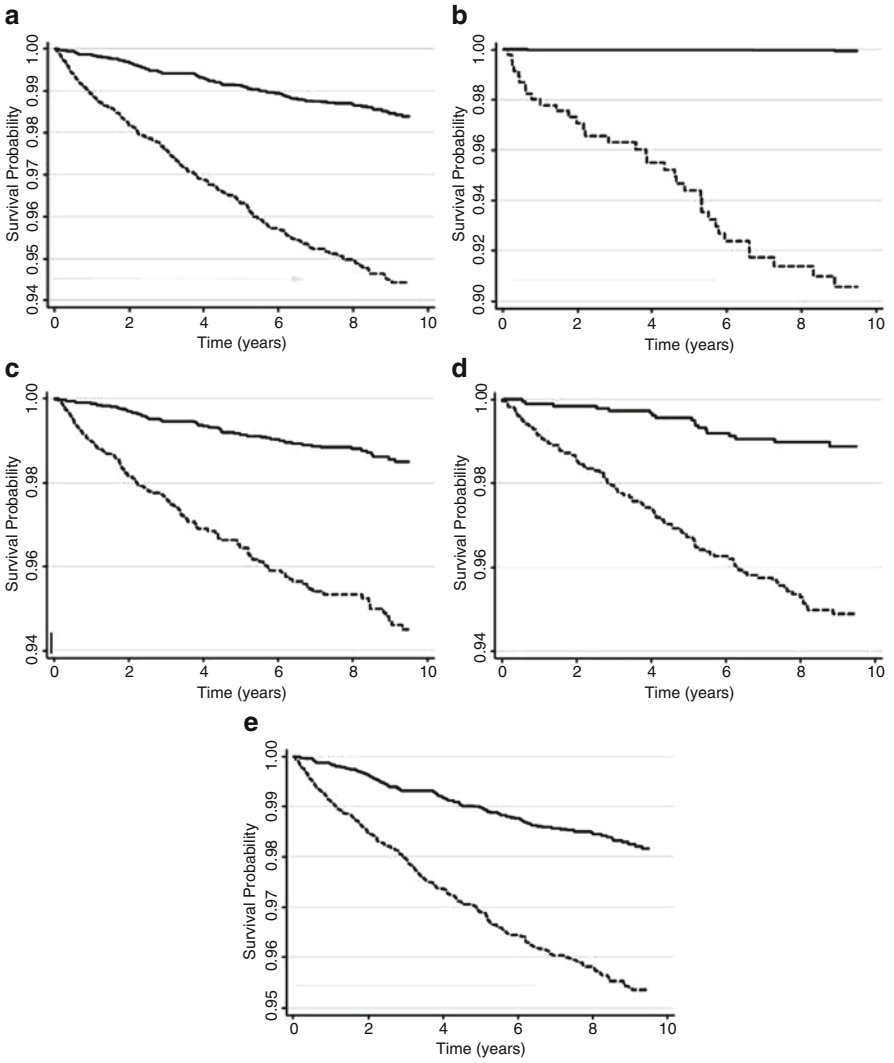
- All interventions are emergent.

Overall Principles of Treatment

- Support oxygenation.
- Urgent echocardiography.
- Arrange specialty consultation to evaluate for surgical management.

Disease Course

- Surgical correction is almost always indicated—the earlier the better.
- Long-term outcomes are dramatically improved after full correction (less than 5%).



Cox survival curves adjusted for age and sex with surgery (solid line) and without surgery (dashed line) of congenital heart diseases patients. Time = 0, time at one and half year of follow-up. (A) Overall congenital heart diseases; (B) Cyanotic congenital heart diseases; (C) Noncyanotic congenital heart diseases; (D) ventricular septal defect; (E)ostium or secundum type atrial septal defect. [From article: Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. BMC Cardiovascular Disorders. 2014 Dec;14:38. https://doi.org/10.1186/1471-2261-14-38, at http://link.springer.com/article/10.1186/1471-2261-14-38; by Yu-Sheng Lin, Pi-Hua Liu, Lung-Sheng Wu, Yu-Ming Chen, Chee-Jen Chang, Pao-Hsien Chu, © Lin et al.; licensee BioMed Central Ltd. 2014; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Mahle WT, Sable CA, Matherne PG, Gaynor JW, Gewitz MH; American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young. Key concepts in the evaluation of screening approaches for heart disease in children and adolescents: a science advisory from the American Heart Association. Circulation. 2012 Jun 5;125(22):2796-801. https://doi.org/10.1161/CIR.0b013e3182579f25. Epub 2012 Apr 30. PubMed PMID: 22547669. http://www.ncbi.nlm.nih.gov/pubmed/?term=22547669 **

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: (“Cyanosis”[Mesh:NoExp] OR “cyanosis” OR “cyanotic”) AND (“Heart Defects, Congenital”[Mesh] OR “congenital heart defect” OR “congenital heart defects” OR “heart abnormalities” OR “congenital heart disease”)

Chapter 23
Cystic Fibrosis

Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Cystic Fibrosis; CF

- The most common autosomal dominant longevity-reducing disorder among Caucasian groups.

Incidence/Epidemiology

- Cystic fibrosis has a reported incidence of 1 in 2,500 live births.
- Although it is most commonly reported in Caucasian children, due to enhanced diagnostic testing, recognition of cases in non-white populations are on the rise.
- The median predicted survival rate is approximate 37 – 38 years.

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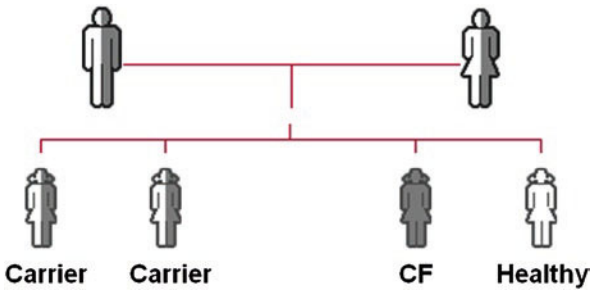
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_23

Differential Diagnosis

- Any immune deficiency disorder may present with pulmonary findings commonly seen in CF.

Pathophysiology and Etiology

- CF is transmitted genetically in an autosomal dominant pattern.



Cystic fibrosis inheritance pattern. This figure shows the inheritance pattern for children born with cystic fibrosis. If both the mother and father are carriers of the gene then they have a one in four chances of having a child with cystic fibrosis [Murphy AJ, Davies PSW. Anthropometry in Children with Cystic Fibrosis. In: Preedy VR, editor. Handbook of Anthropometry [Internet]. New York, NY: Springer New York; 2012 [cited 2015 Sep 14]. p. 1571–83. Available from: http://link.springer.com/10.1007/978-1-4419-1788-1_96] *Caption from original*

- The disorder is secondary to mutations in the cystic fibrosis trans membrane conductance regulator (CFTR) protein.
- The mutation impairs normal transport of chloride and other ions, leading to the production of thick viscous secretions commonly seen in target organs such as the lungs, liver, pancreas, and reproductive tract.

Presentation

Typical/"Classic"

- Most cases are detected by newborn screening and performance of sweat chloride testing in identified infants and children.
- There is a myriad of clinical manifestations of CF, including:

- Respiratory
  - Chronic cough
  - Sinusitis
  - Asthma
  - Bacterial colonization of the respiratory tract
- Clubbing of the digits

Clubbing of the fingers [Karkucak M, Erturk E, Capkin E, Akyazi H, Ozden G, Tosun M. Primary hypertrophic osteoarthropathy (pachydermoperiostosis): a case report. Rheumatology International. 2007 Jan 11;27(4):403–5.] *Caption from original*

- Nasal polyps

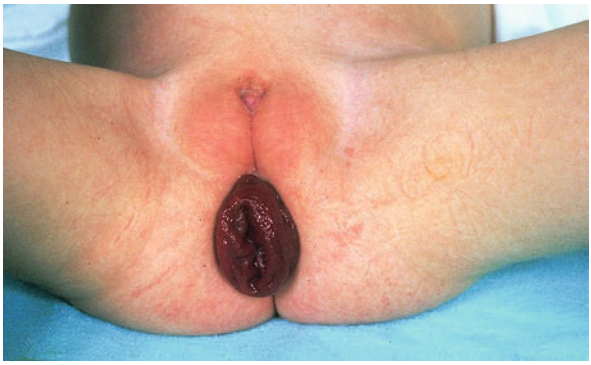
A pedunculated nasal polyp in a patient with cystic fibrosis. The polyp is obstructing the left nostril. Polyps commonly arise from the maxillary antrum. Chronic inflammation results in vasodilatation and edema of the mucosa. This initially

causes mucosal hypertrophy, resulting in irregular folds within the mucosa. As the mucosa enlarges, it may herniate into the nasal cavity, creating a pedunculated polyp that may completely occlude the middle meatus. [MacLusky I, Solomon M, Laxer R, Ford-Jones EL, Friedman J, Gerstle T. Atlas of Pediatrics, Volume IA, Chapter 14. In: Laxer RM, editor. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine Group; 2005. 519 p. ISBN 1-57340-188-9] *Caption from original*

- Gastrointestinal
  - Varying degrees of pancreatic insufficiency
  - Meconium ileus

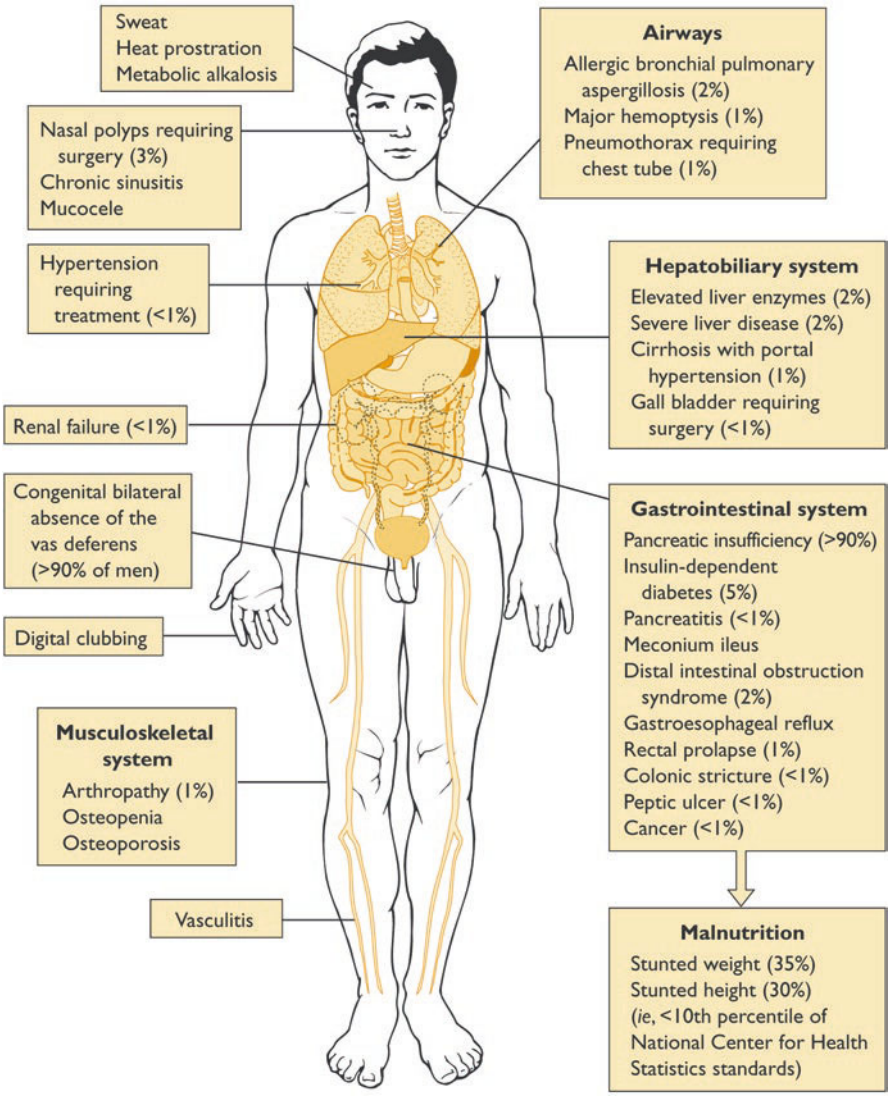
Meconium ileus in cystic fibrosis. The bowel lumen is plugged with meconium [Gilbert-Barness E, Spicer DE, Steffensen TS. Gastrointestinal (GI) System. Handbook of Pediatric Autopsy Pathology [Internet]. New York, NY: Springer New York; 2014 [cited 2015 Sep 14]. p. 355–75. Available from: http://link.springer.com/10.1007/978-1-4614-6711-3_10] *Caption from original*

- Secondary diabetes
- Pancreatitis
- Vitamin deficiencies
- Rectal prolapse



Rectal prolapse, which usually occurs during passage of a large bowel motion, can be a frightening condition for parents of young children. It is hardly ever associated with major medical complications and is easily reduced manually. This condition usually resolves spontaneously by 3 to 4 years of age. Surgical intervention is not advocated, unless the condition is persistent. [Durie P. Chapter 09. In: Hyman P, editor. Gastroenterology and Hepatology, Volume 04. Philadelphia: Current Medicine; 1996 (Feldman M, series editor) ISBN: 0-443-07852-1] *Caption from original*

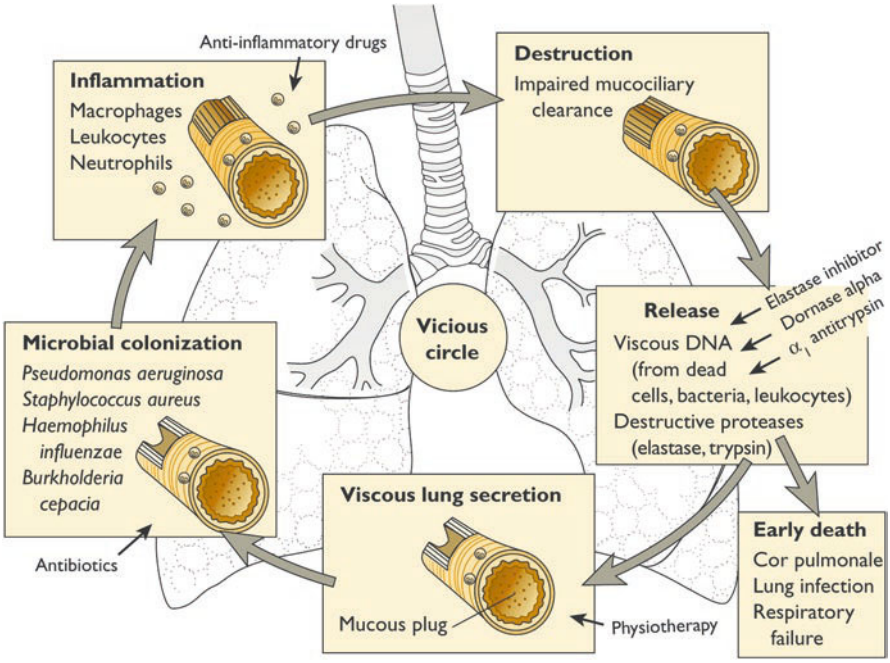
- Genitourinary
  - Male infertility



Clinical manifestations and co-morbidity of cystic fibrosis. Cystic fibrosis is associated with numerous complications and co-morbid conditions. As indicated in the figure, almost every patient with cystic fibrosis who lives long enough will eventually develop pulmonary symptoms. However, the age of onset, the rate at which cystic fibrosis progresses, and the incidence of co-morbid conditions are extremely variable. The 1999 incidence of some of these manifestations and co-morbid conditions, obtained from the Cystic Fibrosis Foundation Registry, are provided in parentheses. It is important to note that the incidence of most of these conditions increases significantly with age and disease progression. Thus, the prevalence of some

conditions (e.g., liver disease and diabetes mellitus) in a clinical setting that includes adolescents and young adults may be significantly higher than these figures suggest. [Coakley R. Boucher R. Fiel S. Schidlow D. Chapter 04. In: Crapo J, editor. Bone's Atlas of Pulmonary and Critical Care Medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] *Caption adapted from original*

- The most common clinical presentations are overwhelmingly pulmonary in nature, including chromic cough with sputum production, dyspnea, and signs of respiratory insufficiency.



The "vicious circle" of lung disease in cystic fibrosis. Cystic fibrosis is a genetic form of chronic bronchitis characterized by a vicious circle of obstruction, infection, and inflammation related to impaired local host-defense mechanisms. This produces progressive bronchiectasis and, ultimately, respiratory failure. Despite the identification of the CFTR gene and characterization of its role as an ion channel, intense efforts are still under way to understand how defective transepithelial electrolyte transport leads to the devastating consequences seen throughout the airways. [Coakley R. Boucher R. Fiel S. Schidlow D. Chapter 04. In: Crapo J, editor. Bone's Atlas of Pulmonary and Critical Care Medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] *Caption from original*

- Most infants and children will have already been diagnosed in the first few months of life.

Atypical

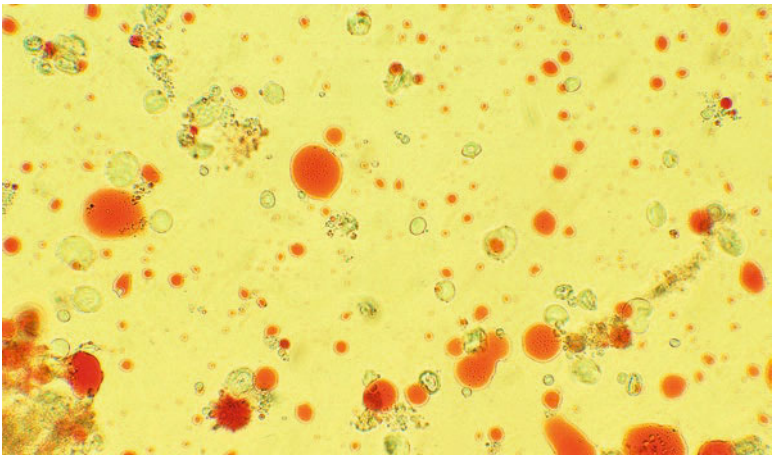
- Any of the aforementioned symptoms and signs may present.

Primary Differential Considerations

- Cystic fibrosis is a distinctive syndrome, but in early stages it may be confused with acute lung or sinus infections. Asthma and metabolic/nutritional disorders may also be differential considerations.

History and Physical Exam

- The history will reveal progressive symptoms and signs of respiratory compromise. The patient will most often have been diagnosed by abnormal screening and confirmatory testing.
- In older children, the cough is productive. In infancy, this finding is masked by the propensity of these children to swallow their secretions.
- Physical examination findings may include:
  - Poor weight gain
  - Clubbing
  - Dyspnea
  - Wheezing
  - Signs of pneumonia
  - Steatorrhea



Steatorrhea by fecal Sudan stain. This photomicrograph stool sample demonstrates the presence of large amounts of fat by Sudan stain. This test is qualitative and

should only be used as a screening tool for gross steatorrhea, but in this particular patient it reveals the presence of a large amount of fat in the stool. [Vanderhoof J. Chapter 06. In: Hyman P, editor. Gastroenterology and Hepatology, Volume 04. Philadelphia: Current Medicine; 1996 (Feldman M, series editor) ISBN: 0-443-07852-1] *Caption from original*

- Increased AP diameter
  - Typical symptoms suggesting the presence of CF include:
    - Meconeum ileus (25% of patients)
    - Respiratory symptoms (50% of patients)
    - Failure to thrive (25% of patients)

Findings That Confirm Diagnosis

- Abnormal sweat chloride and genetic testing

Factors That Suggest Diagnosis

- Any infant or child with failure to thrive and the early development of pulmonary compromise.

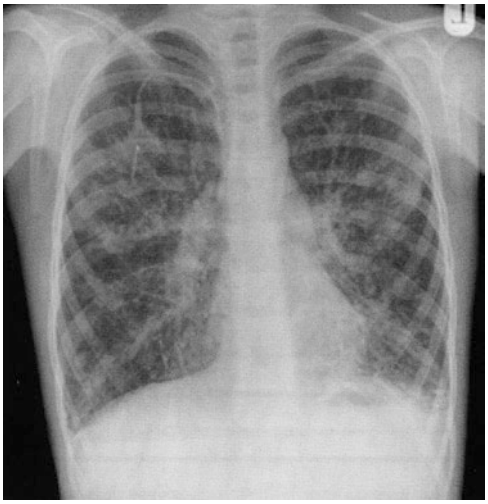
Factors That Exclude Diagnosis

- Normal screening tests

Ancillary Studies

Imaging

- Initial radiographs may be normal, with the eventual development of hyperinflation. Inevitably, the chronic nature of the disease will result in the development of bronchiectasis and cyst formation. In addition, pneumothoraces may develop.



Advanced cystic fibrosis (CF). This is a chest radiograph of a 14-year-old boy with advanced CF. It demonstrates the typical changes of end-stage CF. There is marked generalized hyperinflation. Both lungs demonstrate diffuse bronchial wall thickening, with "tram tracking" (parallel lines due to thickening and absence of tapering of the bronchial walls), most evident in the left lower lobe, indicative of bronchiectasis. There are also scattered peripheral acinar infiltrates, especially in the left apex and in both lung bases, as well as blunting of the left costrophenic sulcus, due to recurrent, long-standing pneumonia. The heart size is within normal limits given the degree of lung hyperinflation. A central line is in place to provide antibiotics. [MacLusky I, Solomon M, Laxer R, Ford-Jones EL, Friedman J, Gerstle T. Atlas of Pediatrics, Volume IA, Chapter 14. In: Laxer RM, editor. The Hospital for Sick Children: Atlas of Pediatrics. Philadelphia, PA: Current Medicine Group; 2005. 519 p. ISBN 1-57340-188-9] *Caption from original*

Electrocardiography

- With the development of chronic lung disease, signs of right-sided strain/hypertrophy will be evident.

Cardiac Enzymes

- Not indicated.

Special Populations

Age

- As discussed under Presentation, most cases are diagnosed in the first few weeks of life.

Co-morbidities

- The gene mutation in CF damages the hepatobiliary system. Diabetes may develop.

Pitfalls in Diagnosis

- Consider CF in all cases of chronic, progressive pulmonary dysfunction.

Critical Steps Not to Miss

- Early administration of bronchodilators
- Radiographic monitoring
- Cultures of expressed sputum
- Consultation with pediatric pulmonology

Mimics

- Any chronic lung disease

Time-Dependent Interventions

- Acute reversal of bronchospasm
- Provision of targeted antibiotics

Overall Principles of Treatment

- The primary goal in CF management is to maintain the patient's lung function to as high a level as possible, for as long as possible. Nutritional support is also important to both quality and quantity of life for patients with CF. Sound and prudent use of antibiotics both treats acute exacerbations and helps protect against antimicrobial resistance.

Organ System	Assessment	Therapy
Pulmonary	Clinical	Daily physiotherapy
	Routine spirometry	Antibiotics: based on sputum culture
	Chest radiography	Daily (inhaled vs oral)
	Routine sputum cultures	For acute exacerbations (oral vs IV)
	Throat swabs in infants or toddlers	Oxygen (if hypoxemic)
		Lung transplant for end - stage disease
Nutrition	Regular growth assessment: height vs weight	Pancreatic enzyme supplementation; high - protein; high-fat diet; caloric supplementation (nasogastric or gastrostomy tube feeds) if persisting malnutrition
	Skin-fold measurement	
	Fecal fat % (dietary intake)	
Gastroenterologic		
Meconium ileus	Clinical: neonate with vomiting, failure to pass meconium	Medical: N-acetylcysteine enema
	Abdominal radiography: gastric and small bowel distention ± “soap bubble” appearance in small bowel	Surgical: decompression - resection of obstructed segment, defunctioning ileostomy
	Contrast enema: meconium obstruction of terminal ileum	
DIOS	Clinical: symptoms or signs of chronic partial distal ileal or cecal obstruction	Exclude surgical complication (appendicitis, intussusception, volvulus)
	Mass in right lower quadrant	Daily mineral oil, balanced intestinal lavage (Golytely, Peglyte®)
	Radiologic: obstructing stool mass in distal ileum or cecum	
Hepatobiliary	Liver function tests	Pancreatic enzymes (increases enterohepatic circulation)
	Abdominal ultrasound (cirrhosis, portal hypertension)	Ursodeoxycholic acid therapy
		Sclerosis of esophageal varices
		Liver transplant for end - stage liver failure
Metabolic		
CF-related diabetes	Glucose tolerance test (ketosis rare unless type 1 diabetes)	Low-dose insulin (potential for hypoglycemia)
		Maintain adequate caloric intake
Sodium chloride depletion	Hyponatremia or metabolic alkalosis: blood electrolytes and gases; urinary electrolytes	Sodium chloride – water repletion
		Prevention: daily electrolyte supplements in hot weather or in high -risk populations (infants and athletes)

Clinical management of cystic fibrosis (CF). [MacLusky I, Solomon M, Laxer R, Ford-Jones EL, Friedman J, Gerstle T. Atlas of Pediatrics, Volume IA, Chapter 14. In: Laxer RM, editor. The Hospital for Sick Children: Atlas of Pediatrics.

Philadelphia, PA: Current Medicine Group; 2005. 519 p. ISBN 1-57340-188-9] *Caption from original*

Disease Course

- Unfortunately, most patients will develop irreversible lung disease in early adulthood.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: (“Cystic Fibrosis”[Majr] OR “cystic fibrosis[tiab]”)

Chapter 24
Diabetic Ketoacidosis

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Name and Synonyms

Diabetic Ketoacidosis; DKA

Incidence/Epidemiology

- Diabetic ketoacidosis (DKA) is classically thought to occur only with type 1 diabetes mellitus, but it can also occur with type 2 diabetes in the setting of severe physiologic stress (infection, trauma, acute MI, or acute CVA).
- It can also occur as a presenting syndrome of type 2 DM, especially in patients of Hispanic or African American origin.
- It is more common in children and young adults than in adults.
- The annual incidence ranges from 4–8 cases per 1,000 patients with diabetes.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_24

- Hospital admissions for DKA have been increasing. There were about 80,000 discharge diagnoses of DKA in 1989, in 2009 there were 140,000 discharge diagnoses of DKA, an increase of 50 %.
- Hospital length of stay for DKA has fallen in the same period from about 6 days to 3.5 days.
- Overall mortality has been declining for the last 20 years and now averages less than 5 % for all patients. This is likely due to improved recognition and care.
- Mortality is still much higher for the extremes of age and illness. Mortality is greater than 20 % in the elderly.

Differential Diagnosis

- The differential diagnosis of DKA includes all the causes of an elevated anion gap metabolic acidosis. The classic mnemonic for the causes of an elevated anion gap acidosis is MUD PILES:
  - **M**ethanol
  - **U**remia (renal failure)
  - **D**KA**,** alcoholic ketoacidosis, and starvation acidosis
  - **P**araldehyde/phenformin ingestion (medications that are no longer available)
  - **I**ron/INH overdose
  - **L**actic acidosis (from multiple causes such as sepsis, metformin overdose)
  - **E**thylene glycol ingestion
  - **S**alicylate overdose
  - Paraldehyde and phenformin are medications that are no longer marketed.
  - Other ingestions/exposures that should be included in this list are: carbon monoxide, cyanide, and toluene.
  - Other diagnoses to consider in the setting of hyperglycemia include: hyperglycemic, hyperosmolar, and nonketotic (HHNK) coma (also referred to as hyperosmolar hyperglycemic state [HHS] or diabetic hyperosmolar state [DHS]). In this disorder the hyperglycemia tends to be more severe (>600 mg/dl), with little or no elevation in the anion gap. It tends to occur in older patients, have a more prolonged onset and course, and is usually associated with more pronounced mental status changes than DKA. The mortality in HHNK is also higher than in DKA.

Finding	Mild DKA	Moderate DKA	Severe DKA	HHS
Plasma glucose (mg/dL)	>250	>250	>250	>600
Arterial pH	7.25–7.30	7.00–7.24	<7.00	>7.30
Serum HCO_3^- (mEq/L)	15–18	10–15	<10	>15
Serum or urine ketones	Positive	Positive	Positive	Small
Beta-hydroxybutyrate	High	High	High	Normal or high
Effective serum osmolality[a] (mOsm/kg)	Variable	Variable	Variable	>320
Anion gap[b]	Upper limits of normal or > normal	>Normal	Significantly > normal	Variable
Sensorium	Alert	Alert or drowsy	Stupor/coma	Stupor/coma

[a]Effective serum osmolality = 2 × measured Na^+ (mEq/L) + BUN (mg/dL)/2.8 + glucose (mg/dL)/18, >320–330 mOsm/kg associated with neurologic deterioration
[b]Anion gap = $(Na^+ + K^+) - (Cl^- + HCO_3^-)$

Diagnostic criteria in DKA and HHS [Shah SJ. Diabetic Ketoacidosis in the Urgent Anesthesia Setting. In: Benumof JL, editor. Clinical Anesthesiology [Internet]. New York, NY: Springer New York; 2014 [cited 2015 Nov 5]. p. 407–14. Available from: http://link.springer.com/10.1007/978-1-4614-8696-1_49] *Caption from original*

- The differential diagnosis prior to the identification of the metabolic abnormalities is much broader and based upon the presenting symptoms. These may include: sepsis/shock/hypovolemic syndromes, abdominal pain associated with nausea and vomiting, change in mental status, and tachypnea.

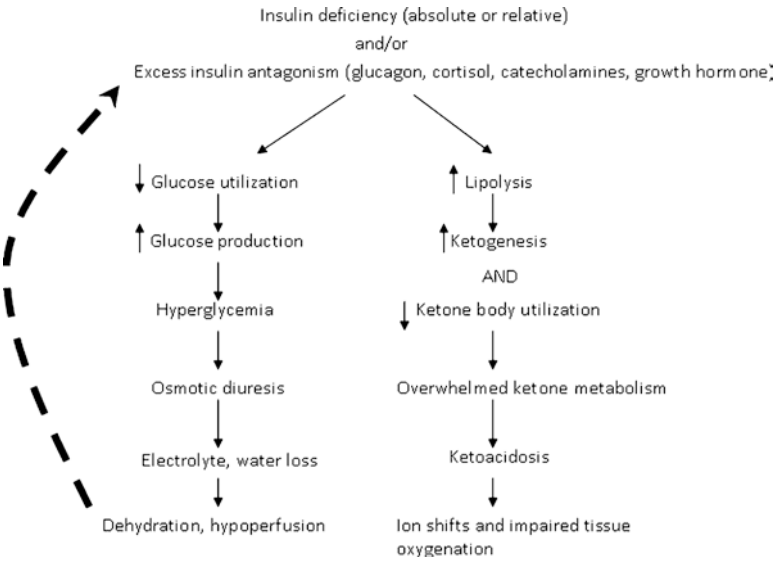
Pathophysiology and Etiology

- The primary pathophysiologic mechanism behind the development of DKA is an insulin deficiency, especially a lack of an appropriate insulin release to hyperglycemia.
- Cells require insulin to utilize glucose as a fuel source. In the absence of insulin, the body will seek alternative fuel sources. Catabolic (counterregulatory) hormones will be released that help break down and utilize protein and fat stores as fuel.
- The primary counterregulatory hormone is glucagon, but other involved counterregulatory hormones include catecholamines, cortisone, and growth hormone.
- The effect of these catabolic hormones is to increase gluconeogenesis and glycogenolysis, which in turn increases production of glucose and worsens hyperglycemia. Increasing both these processes also raises the production of byproducts and precursors such as free fatty acids and glycerol.

- Theses catabolic hormones also increase proteolysis. This boosts the amount of free glucogenic amino acids, which can be used with glycerol to produce glucose and worsen hyperglycemia.
- The free fatty acids that are produced during gluconeogenesis bind to albumin, and then are taken up by the liver, where they are converted to ketone bodies (beta-hydroxybutyrate [βHB], acetoacetic acid [AcAc], and acetone).
- Some body tissues can utilize ketone bodies for energy, but inefficiently. A low insulin level reduces the ability of brain, cardiac, and skeletal muscle to utilize ketones as an energy source, which increases the ketonemia.
- These ketone bodies are responsible for the metabolic acidosis of DKA.
- Under normal physiologic conditions, βHB and AcAc exist in a 1:1 equilibrium. During the increased lipolysis and ketogenesis of DKA, this ratio will approach 10:1. It is important to remember, however, that during insulin therapy, βHB will be metabolized at a faster rate than AcAc. This has important implications for monitoring therapy that will be discussed under the treatment section.
- Hyperglycemia causes an osmotic diuresis, resulting in profound fluid losses and volume depletion, which exacerbates hyperglycemia and ketonemia.
- The volume deficits can be profound and can lead to hypotension and shock.
- The osmotic diuresis also results in profound electrolyte losses (K, Na, Cl, PO2, Ca, Mg, and N).
- The acidosis causes a shift in potassium from intracellular to extracellular exacerbating total body potassium losses.
- In the setting of marked ketonemia, the kidney will exchange chloride for ketones, allowing the ketones to be excreted. The excretion of ketones leads to a decrease in potential bicarbonate, which leads in turn to less buffering capacity and then to worsening of the acidosis, which can lead to a hyperchloremic metabolic acidosis, in addition to the ketoacidosis.
- The breakdown of adipose tissue leads to an inflammatory response with the release of prostaglandins I2 and E2. These cause a peripheral vasodilation that can worsen hypotension and shock.
- Multiple factors and conditions are known to precipitate DKA. Many acute illnesses, as well as physiologic stress, can lead to hyperglycemia, and in the setting of insulin deficiency this leads to DKA.
- It is important to attempt to identify cause when a patient presents with DKA.
- In a significant minority of patients, no precipitating cause can be identified.
- The following list contains some of the common causes of DKA, but any acute illness and/or period of physiologic stress can initiate DKA, so this list is not exhaustive.

    - Reduction of or lack of daily insulin injections
    - Malfunction of insulin pump
    - Any acute infectious process
    - Acute MI
    - Stroke
    - Acute GI bleed

- Pregnancy
- Medications (especially steroids)
- Substance abuse (multifactorial, e.g., cocaine can cause hyperglycemia directly and then these patients forget or have no insulin available)
- Severe, acute illness or trauma



DKA pathophysiology. DKA is shown as unchecked lipolysis occurring alongside progressive water and electrolyte loss. Osmotic diuresis, progressive hypovolemia, and further reductions in glucose and ketone clearance in the absence of insulin creates a feed-forward loop that increases concentrations of antagonistic hormones and perpetuates the cycle [Steenkamp DW, Alexanian SM, McDonnell ME. Adult Hyperglycemic Crisis: A Review and Perspective. Current Diabetes Reports. 2013 Feb;13(1):130–7.] *Caption from original*

Presentation

Typical/"Classic"

- DKA develops acutely over a period of 24–48 hours.
- The early symptoms are often related directly to hyperglycemia with resultant osmotic diuresis and worsening volume loss (polydipsia/polyuria).
- As the metabolic abnormalities worsen and acidosis develops, tachypnea occurs as physiologic compensation to try and decrease the pCO2 to reduce the acidosis. Kussmaul respirations (a profound increase in the rate and depth of breathing) may develop.

- Diffuse, nonspecific abdominal pain associated with nausea and vomiting are common symptoms at presentation (especially in children). They are often related directly to DKA (prostaglandin release is felt to play a role) but can also indicate an underlying cause for the DKA.
- Vomiting contributes to the development of metabolic abnormalities, electrolyte losses, and the development of volume depletion and dehydration.
- As volume depletion worsens, the patient may develop clinical signs of shock with tachycardia, hypotension, and signs of poor perfusion (poor skin turgor, dry mucous membranes, peripheral cyanosis).
- Profound ketonemia (especially acetone) can cause a fruity odor on the breath.
- A change in mental status may occur, but is more common in HHNK. It is felt to be multifactorial and related to volume depletion, metabolic acidosis, hyperosmolarity, and hemodynamic abnormalities.

Atypical

- DKA is associated with multi-organ dysfunction. As such, it is associated with multiple, varying symptoms and presentations as above.
- Fever may be present due to an underlying infection, but it is important to remember that the absence of fever does not exclude underlying infection as a cause for DKA.
- DKA may present with the symptoms of the underlying causative disorder.
- Hypothermia may be present due to peripheral vasodilation from prostaglandin release.
- Abdominal pain with nausea and vomiting are frequent presenting symptoms of DKA as discussed in Typical/"Classic", above. However, abdominal pain and other abdominal symptoms may be due to the underlying cause. Acute pancreatitis can be both a cause and an effect of DKA. Lipase may be elevated in both situations, so it is often difficult to make the distinction.
- An alteration of decrease in the level of consciousness may occur, but is more commonly seen in HHNK. An altered level of consciousness seems to be more associated hyperosmolarity than with acidosis.

Primary Differential Considerations

- DFKA is a rather distinctive clinical entity. It is most likely to be confused with hyperosmolar nonketoic coma and alcoholic ketoacidosis. Other initial differential considerations might include:
    - Lactic academia
    - Septic shock
    - Acute pancreatitis
    - Salicylate toxicity

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that are confirmatory for DKA.
- The diagnosis of DKA requires laboratory confirmation.

Factors That Suggest Diagnosis

- A history of reduced or no insulin use should suggest the diagnosis.
- Any patient with diabetes who presents with an acute illness or severe injury should have the diagnosis of DKA considered.
- Patients being treated for other acute illnesses need to have their metabolic status monitored and controlled to avoid precipitating DKA.

Factors That Exclude Diagnosis

- There are no historical or physical exam findings that can reliably exclude the diagnosis of DKA.
- DKA is only excluded by laboratory analysis documenting the lack of ketonemia.
- It is important to remember that while most patients with DKA will have marked hyperglycemia (400–800 mg/dL), it is possible to have DKA with only modest elevations in glucose (250–500 mg/dL).

Ancillary Studies

Laboratory

- The diagnosis of DKA requires laboratory confirmation.
- Patients with suspected or confirmed DKA need to have a complete laboratory analysis of electrolytes and acid-base status. This includes measurement of glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, renal function, liver function, arterial or venous pH, calculation of the anion gap, and determination of ketonemia. A urine dipstick should also be performed for ketonuria and glucosuria, and for evidence of urinary infection.

- These patients may also need further laboratory evaluation for a precipitating cause for DKA. This may require evaluation of cardiac biomarkers, pancreatic enzymes, and thyroid function.
- The diagnosis is generally confirmed by the presence of all the following findings:
  - a blood glucose >250 mg/dL
  - an anion gap >11 (usually greater than 20)
  - a bicarbonate <15 mEq/L, an arterial or venous pH<7.3
  - at least moderate ketonemia
- All diabetic patients should have a fingerstick glucose determination performed when being evaluated for any acute illness.
- The glucose in DKA is usually between 400 and 800 mg/dL. Higher levels, especially those above 1,000 mg/dL are more common in HHNK. Lower levels (250–500 mg/dL) may be seen, especially in the presence of starvation/inadequate food intake due to nausea or vomiting, alcohol abuse, and other intercurrent illnesses. It may also be lower in the presence of pregnancy, liver disease, and if insulin was given within several hours prior to evaluation.
- In DKA, the anion gap increases due to the presence of the unmeasured anions, beta-hydroxybutyrate (βHB) and acetoacetate (AcAc). When calculating the anion gap, use the measured serum sodium, not the corrected sodium (see sodium below).
- Venous blood gases can be used to assess the serum pH. There is a high degree of correlation between venous and arterial pH in DKA. The venous pH is about 0.03 lower than the arterial pH. Arterial blood gases are painful, and can cause severe complications such as arterial injury and thrombosis, so venous blood gases are currently recommended.
- The degree of acidosis can be assessed by both the serum pH and bicarbonate concentration. The pH and serum bicarbonate are usually both reduced. This is consistent with the metabolic acidosis. Patients with protracted, severe vomiting may also develop a metabolic alkalosis and have normal or slightly elevated bicarbonate levels. In this setting, an elevated anion gap may be the only indication that an underlying acidosis exists.
- Historically, serum and urine ketones were assessed by the use of the nitroprusside reagent. This is mostly a qualitative assay, but the strength of reaction (color change) may give an indication of the amount of ketone present. This reagent only reacts with AcAc, it does not detect βHB. In DKA, βHB is the predominant ketone body. βHB and AcAc exist in an equilibrium that favors βHB in acidic environments. So early in the course, if using the nitroprusside reagent, the level of ketonemia or ketonuria may seem lower than it actually is. As the patient is appropriately treated, and the acidosis improves, the equilibrium will favor the conversion of βHB to AcAc (prior to clearance of the ketone bodies). When using the nitroprusside reagent, there may seem to be a paradoxical increase in ketonemia or ketonuria as the patient improves.

Most hospital laboratories now have a direct, enzymatic assay for βHB that is reliable and quantitative. This is the preferred assay.

- Patients with DKA often have profound total body potassium deficits. Acidosis causes intracellular potassium to shift into the extracellular space. The osmotic diuresis causes the potassium to then be excreted in the urine. However, measured potassium is often normal or even elevated prior to treatment. This is due to the extracellular shift of potassium with acidosis, and the hemoconcentration/increased serum osmolarity associated with hyperglycemia. During the first several hours of treatment, the serum potassium can drop precipitously.
- Osmotic diuresis also leads to renal losses of sodium chloride. Hyperglycemia causes an increase in the measured serum sodium that is factitious. The serum sodium should be corrected for the level of hyperglycemia. The classic correction factor for serum sodium in the presence of hyperglycemia is 1.6. For every elevation of 100 mg of glucose above 100 mg/dL, you add 1.6 to the measured serum sodium for the true sodium concentration. Some authorities believe that the correction factor should be 2.4 when the serum glucose exceeds 400 mg/dL.
- The osmotic diuresis causes increased urinary losses and total body depletion of all electrolytes (including phosphorus, calcium, and magnesium). However, just like potassium, hemoconcentration may cause the initial levels to be elevated. And as with potassium, treatment can cause precipitous drops in these electrolytes.
- Serum creatinine is often elevated due to intravascular volume depletion from the osmotic diuresis.
- Liver functions and lipase are often elevated in DKA even the absence of significant liver or pancreas pathology. These values often improve with treatment. However, they can be associated with an underlying condition that may have precipitated the episode of DKA.
- DKA is often associated with leukocytosis, due to physiologic stress and hemoconcentration. However, significant bandemia (above 10 %) often accompanies an infectious process that may have precipitated DKA.

Electrocardiography

- An ECG should be performed on all patients with suspected or confirmed DKA.
- It can help in the identification of electrolyte abnormalities such as hypo- or hyperkalemia.
- Also, as DKA can be precipitated by an acute myocardial infarction, an ECG should be reviewed for any signs of ischemia or infarction.

Imaging

- Imaging is not helpful in the diagnosis of DKA.
- However, imaging is often necessary in the work-up, evaluation, and treatment of DKA to search for the cause of DKA.
- Most of these patients should have chest x-ray to assess for pneumonia, congestive heart failure, or other issues that can help explain the occurrence of DKA, or help in the safe and appropriate management of DKA.
- Abdominal pain is a difficult complaint to evaluate in DKA. It may be due to the DKA itself, but an abdominal issue may also be the precipitant of DKA. Many patients presenting in DKA with predominant abdominal complaints or with marked abdominal tenderness will require abdominal imaging to evaluate for an intra-abdominal process precipitating DKA. The usual study would be an abdominal/pelvic CT scan. Many of these patients will not tolerate oral contrast due to profound nausea and vomiting, and IV contrast will often be contraindicated due to an elevated creatinine from intravascular volume depletion. A completely non-contrast-enhanced CT scan can be useful in these patients to help exclude an intra-abdominal catastrophe.

Special Populations

Age

Children

- 30–40% of cases of new-onset diabetes in children will present with DKA.
- DKA as a presenting manifestation is more common in younger children (<5), and in those from socioeconomically disadvantaged backgrounds.
- Children are more likely to present initially with diffuse abdominal pain associated with nausea and vomiting.
- DKA in children is defined by the following biochemical abnormalities:
  - Blood glucose greater than 200 mg/dL; AND
  - A venous pH less than 7.3 or plasma bicarbonate less than 15 mEg/L; AND
  - Ketosis (presence of ketones in the urine).
  - Measurements of serum beta-hydroxybutyrate are more sensitive are more accurate indicators of ketosis (levels greater than 3 mmol/L)
- Other clues to the presence of new-onset diabetes in children include polyuria, polydipsia, increased nocturia, and especially daytime enuresis.
- Decreased urine output from dehydration is often not appreciated in children, due to the profound osmotic diuresis associated with DKA.
- DKA is the leading cause of morbidity and mortality in children with type 1 diabetes.

The Elderly

- The elderly are more likely to present with HHS/HHNK than DKA.
- The elderly are also more likely to present with mental status changes.
- Morbidity and mortality are also higher among the elderly.

During Pregnancy

- DKA occurring during pregnancy is associated with a fetal mortality rate approaching 30%.
- DKA can be precipitated by lower sugar levels during pregnancy.
- Several "normal" physiologic changes of pregnancy make pregnant women more likely to develop DKA.
    - Pregnant women have lower fasting plasma glucose levels. This leads to lower baseline insulin levels (a relative insulin deficiency) and increased baseline free fatty acid levels.
    - This is also an associated increase in counter-regulatory hormone levels.
    - There is a decrease in bicarbonate levels from the chronic respiratory alkalosis in pregnancy. This leads to a decreased buffering capacity.
- All the fluid and electrolyte changes that occur in the mother occur in the fetus. Maternal hyperglycemia causes fetal hyperglycemia with resultant osmotic diuresis. Maternal acidosis leads to fetal acidosis. Maternal hyperglycemia, diuresis, volume contraction, and acidosis cause decreased uterine blood flow and decreased fetal oxygenation. Fetal hypokalemia can cause fetal arrhythmias. All these changes lead to the increase in fetal mortality.
- Treatment priorities remain the same: fluids, correction of acidosis and hyperglycemia, and electrolyte repletion.

Co-morbidities

- Any significant medical co-morbidity can increase the morbidity and mortality associated with DKA.
- Significant cardiac, pulmonary, renal, and liver disease can complicate both the diagnosis and treatment of DKA. Any significant disorder of these systems can make fluid therapy challenging.
- Patients with history of severe CHF or end-stage renal disease may need central venous pressure monitoring for appropriate fluid management.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is important to consider the diagnosis in acutely ill patient with a history of diabetes.
- It is also important to consider the diagnosis in patients presenting acutely ill who are found to be academic and hyperglycemic even in the absence of a history of diabetes, as DKA can be the presenting issue with diabetes.
- It is critical to measure the all electrolytes, pH (a venous blood gas is often sufficient), and evaluate for ketosis.
- Appropriate resuscitative measures (especially fluid replacement) may need to be started prior to adequate confirmation of the diagnosis.
- A thorough search for a precipitating cause needs to be performed.

Mimics

- Many processes can mimic the presentation of DKA, as it is a multi-system disorder in which patients are critically ill.
- HHNK (hyperglycemic, hyperosmolar, non-ketosis) is an important mimic of DKA. Patients have ketosis, but usually little or no elevation in the anion gap. The glucose tends to be much higher (usually above 600) than those seen with DKA. These patients are usually older and have more profound mental status changes.
- Other causes of ketosis (such as alcoholic and starvation ketosis) can present similarly, but the glucose is usually normal or low at presentation.
- Patients with SIRS (systemic inflammatory response syndrome) can also present acutely ill with hypotension, acidosis (usually from lactate), and the two processes can co-exist. An acute infection can precipitate DKA.

Time-Dependent Interventions

- It is critically important to initiate fluid resuscitation early in the course of evaluation and treatment. Fluids should usually be started at the time of consideration of the diagnosis rather than after waiting for full laboratory confirmation.
- Immediate interventions on consideration of the diagnosis include aggressive fluid replacement, full monitoring including cardiac monitoring, continuous pulse ox, and frequent vital sign monitoring (blood pressure every 5 minutes

or more frequently). There should be a bedside, finger stick blood glucose check, a urine dipstick for ketones, at least two large-bore IV's, and a 12-lead ECG should be performed.

Overall Principles of Treatment

- Treatment should initially address three issues in the following order:
  - Fluid repletion
  - Potassium repletion
  - Insulin administration
- Fluid.
  - Adult patients with DKA usually have anywhere from a 5–10 liter free water deficit at presentation.
  - The first 2 liters of replacement should be given over the first 30–120 minutes of treatment. Continuing fluids can then be slowed with about 50 % of the total water deficit replaced over the first 12 hours and then subsequent 50 % over the next 12 hours.
  - Normal saline (NS) is the preferred fluid for initial resuscitation. NS helps increase intravascular volume and helps to prevent too rapid a fall in extracellular osmolarity. Too rapid a fall in extracellular osmolarity can lead to rapid transfer of free water into brain cells and cerebral edema.
  - After the initial resuscitation with 2 liters NS, most authorities recommend changing to 0.45 % (half normal) saline, if the corrected serum sodium is normal or elevated.
  - When the blood glucose falls below 250 mg/dl, the fluid should be changed to 5 % dextrose in 0.45 % NS to allow the continuation of insulin therapy.
- Potassium.
  - Patients with DKA almost universally have severe total body potassium deficits. Usually on the order of 3–5 mEq/kg.
  - The development of profound hypokalemia can be a life-threatening complication during the resuscitation and treatment of a patient with DKA.
  - However, the initial measured serum potassium is usually normal or high, due to the shift of intracellular potassium into the extracellular space in the presence of acidosis. Hypokalemia on presentation is urgently life-threatening and requires rapid and careful correction.
  - The primary goals of potassium replacement are to maintain normal extracellular potassium concentration during the acute phases of therapy when the most significant shifts are expected to occur. The intracellular deficit may be corrected over days instead of hours.
  - During initial resuscitation of DKA, the serum potassium may fall quickly due to the resolution of acidosis and insulin therapy, which both cause an

intracellular shift of potassium. This can lead to the precipitous development of profound extracellular hypokalemia with resulting cardiac arrhythmias, rhabdomyolysis, respiratory muscle paralysis, and paralytic ileus.
- The most rapid changes in potassium concentration occurs during the first several hours of therapy, so the potassium concentration needs to be measured frequently during this period (at least every 2 hours.)
- It is recommended that if the initial potassium concentration (prior to any fluids/insulin) is between 3.0 mEq/L and 5.5 mEq/L, then potassium replacement should be initiated at about 10 mEq/hour.
- If the initial potassium is below 3.0 mEq/L, the initial rate of replacement should be about 15 mEq/hour.
- If the initial serum potassium concentration is below 3.3–3.5 mEq/L, it is recommended that potassium replacement occur prior to initiation of insulin therapy, as insulin administration will cause the potassium to shift intracellularly and can precipitate profound, life-threatening extracellular hypokalemia.
- Potassium is usually given as potassium chloride in IV fluid. Potassium phosphate use is discouraged, as it can lead to profound hypocalcemia and the precipitation of calcium phosphate salt in tissues.

- Insulin.
  - There is nearly universal agreement that the administration of low dose (0.1 unit/kg/hour) intravenous short-acting insulin is the safest method for administering insulin in patients with DKA.
  - This method of insulin administration allows for a gradual reduction in plasma glucose of about 50 mg/dL/hour.
  - Multiple studies document that this method of insulin administration is associated with fewer complications (such as profound hypokalemia, hypophosphatemia, and hypoglycemia).
  - In adults, it is acceptable to give a loading dose of insulin at a dose of 1 unit/kg.
  - Children should not have a bolus dose of insulin. An IV-push loading dose has been shown to lead to more complications in children.
  - In general, insulin infusions should not be started until after an initial fluid bolus of 1–2 liters has been given.
  - Insulin therapy should be withheld in the setting of profound hypokalemia (initial serum potassium concentration less than 3.3–3.5 mEq/L) until potassium repletion has commenced. In this setting, insulin can cause profound hypokalemia by causing an intracellular shift of extracellular potassium.
  - In the first hours of treatment, the serum glucose should be measured at least every 2 hours.
  - The insulin infusion should be continued until the anion gap returns to normal and ketonemia resolves.

- Hyperglycemia often resolves before the anion gap normalizes and ketonemia resolves. It is recommended that the IV fluid be switched to fluid containing 5% dextrose when the serum glucose concentration falls below 250 mg/dL.
- Therapy with subcutaneous insulin should be initiated prior to stopping the insulin infusion. Subcutaneous insulin should be administered at least one hour prior to stopping the insulin infusion.

- Other electrolytes.
  - Phosphorus. Phosphorus (like potassium) is primarily intracellular, but shifts to the extracellular compartment in the setting of acidosis. As such, initial phosphorus concentrations are usually elevated in DKA but are not reflective of total body phosphorus. In DKA, total body phosphorus is usually depleted due to increased renal losses from the osmotic diuresis. However, phosphorus levels usually fall more gradually than potassium, and the levels often don't decrease until 24–48 hours into therapy. Intravenous replacement is not recommended unless the serum phosphorus falls below 1.0 mg/dL.
  - Magnesium. Magnesium concentrations may fall from the osmotic diuresis of DKA. Magnesium concentration doesn't usually fall until 24 hours into therapy. Magnesium repletion is recommended when the serum concentration falls below 2.0 mg/dL. Magnesium may be given intravenously as magnesium sulfate 2.0 grams over one hour. If the patient is tolerating orals, it can be given orally as magnesium oxide.
  - Calcium. Calcium homeostasis usually remains intact during DKA, but severe hypomagnesemia can lead to hypocalcemia (due to decreased parathyroid secretion). Patients with severe hypomagnesemia should have calcium levels followed and restored as necessary.
  - Bicarbonate. The administration of supplemental bicarbonate is contraindicated in the vast majority of cases of DKA. The acidosis will resolve spontaneously with resolution of ketogenesis. Bicarbonate therapy can be associated with and cause severe hypokalemia, worsen intracellular acidosis, worsen central nervous system acidosis, shift the oxyhemoglobin dissociation curve to the left, prolong ketogenesis, and precipitate cerebral edema.

Laboratory evaluation
After a brief history and physical examination, initial laboratory evaluation should include determination of complete blood count, blood glucose, serum electrolytes, blood urea nitrogen, creatinine, serum ketones, osmolality, arterial blood gases, and urinalysis. Admission ECG, chest radiograph, and cultures of blood, urine, and sputum may be ordered if clinically indicated. During therapy, capillary blood glucose should be determined every 1–2 hours at the bedside using a glucose oxidase reagent strip; and blood should be drawn every 4 hours for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, phosphorus, and venous pH
Fluids
1000 mL normal saline (0.9% sodium chloride) first hour, then normal or 0.45% saline at 250–500 mL per hour depending on serum sodium concentration and hydration status. When plasma glucose < 250 mg/dL, change to D5%1/2NS saline to allow continued insulin administration until ketonemia is controlled, while avoiding hypoglycemia
Insulin
0.1 U/kg body weight as intravenous bolus followed by 0.1 U/kg/h as a continuous infusion. The goal is to achieve a rate of decline of glucose between 50–100 mg per hour. When plasma glucose is < 250 mg/dL, reduce insulin rate to 0.05 U/kg per hour. Thereafter, adjust insulin rate to maintain glucose levels between 150–200 mg/dL until ketoacidosis is resolved. In patients with mild to moderate diabetic ketoacidosis, subcutaneous regular insulin or rapid-acting insulin analogs may be an alternative to intravenous insulin [037], [038]
Potassium
Serum K^+ > 5.0 mEq/L; no supplementation is required.
Serum K^+ = 4–5 mEq/L; add 20 mEq/L to each L of replacement fluid
Serum K^+ = 3–4 mEq/L; add 40 mEq/L to each L of replacement fluid
Serum K^+ < 3 mEq/L; hold insulin and give 10–20 mEq per hour until K^+ > 3.3, then add 40 mEq/L to each L of replacement fluid
Bicarbonate
Arterial pH < 7.0 or bicarbonate < 5 mEq; 50 mEq/L in 200 ml of H_2O over 1 hour until pH increases to > 7.0. Do not give bicarbonate if pH > 7.0
Phosphate
If indicated (serum levels < 1 mg/dL), 20–30 mmol potassium phosphate over 24 hours. Monitor serum calcium level
Transition to subcutaneous insulin
Insulin infusion should be continued until resolution of ketoacidosis (glucose < 200 mg/dL, bicarbonate > 18 mEq/L, pH > 7.30). When this occurs, start subcutaneous insulin regimen.
To prevent recurrence of diabetic ketoacidosis during the transition period to subcutaneous insulin, intravenous insulin should be continued for 1–2 hours after subcutaneous insulin is given [028]

Summary of management of patients with diabetic ketoacidosis, (028). Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. N Engl J Med. 1977; 297:238 -247. (037). Umpierrez GE, Cuervo R, Karabell A, et al. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Am J Med. 2004; 117:291 -296. (038). Umpierrez GE, Latif K, Stoever J, et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for treatment of diabetic ketoacidosis. Diabetes Care. 2004; 27:1873 -1878. [Kitabchi AE, Murphy MB. Consequences of Insulin Deficiency. In: Skyler J, editor. Atlas of Diabetes. 3rd edition. Philadelphia: Current Medicine Group; 2006. ISBN 1-57340-222-2] *Caption from original*

CO2—carbon dioxide; IV—intravenous; K+—potassium ion; NaCl—sodium chloride; NaHCO3—sodium bicarbonate; SQ—subcutaneous.

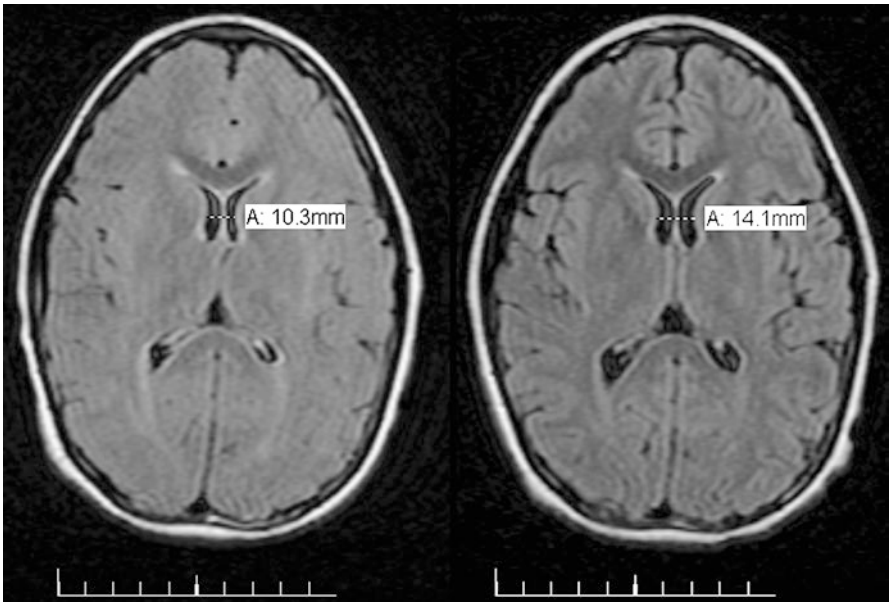
Insulin	Fluid Administration	Potassium repletion	Alkali
1. Give initial IV bolus of 0.2 U/kg actual body weight.	Shock absent: Normal saline (0.9% NaCl) at 7 mL/kg/h for 4 h, and half this rate thereafter	Potassium chloride should be added to the third liter of IV infusion and subsequently if urinary output is at least 30–60 mL/h and plasma [K^+] < 5 mEq/L.	Half-normal saline (0.45% NaCl) plus 1–2 ampules (44–88 mEq) $NaHCO_3$ per liter when blood pH < 7.0 or total CO_2 < 5 mmol/L; in hyperchloremic acidosis, add $NaHCO_3$ when pH < 7.20; discontinue $NaHCO_3$ in IV infusion when total CO_2>8–10 mmol/L.
2. Add 100 U of regular insulin to 1 L of normal saline (0.1 U/mL), and follow with continuous IV drip of 0.1 U/kg actual body weight per h until correction of ketosis.	Shock present: Normal saline and plasma expanders (*ie*, albumin, low molecular weight dextran) at maximal possible rate		
3. Give double rate of infusion if the blood glucose level does not decrease in a 2-h interval (expected decrease is 40–80 mg/dL/h or 10% of the initial value.)	Start a glucose-containing solution (*eg*, 5% dextrose in water) when blood glucose level decreases to 250 mg/dL.	Add K^+ to the initial 2 L of IV fluids if initial plasma [K^+] < 4 mEq/L and adequate diuresis is secured.	
4. Give SQ dose (10–30 U) of regular insulin when ketosis is corrected and the blood glucose level decreases to 300 mg/dL, and continue with SQ insulin injection every 4 h on a sliding scale (*ie*, 5 U if below 150, 10 U if 150–200, 15 U if 200–250, and 20 U if 250–300 mg/dL).			

Diabetic ketoacidosis (DKA) and nonketotic hyperglycemia (NKH) management. Administration of insulin is the cornerstone of management for both DKA and NKH. Replacement of the prevailing water, sodium, and potassium deficits is also required. Alkali are administered only under certain circumstances in DKA and virtually never in NKH, in which ketoacidosis is generally absent. Because the fluid deficit is generally severe in patients with NKH, many of whom have preexisting heart disease and are relatively old, safe fluid replacement may require monitoring of central venous pressure, pulmonary capillary wedge pressure, or both (001), Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. N Engl J Med. 1998; 338:26 -34, 107–111. (017), AdroguÈ HJ. Diabetic ketoacidosis and hyperosmolar nonketotic syndrome. In: Suki WN, Massry SG, eds. Therapy of Renal Diseases and Related Disorders. Boston: Kluwer Academic Publishers; 1997; 233 -251. (018). Adrogué HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. JAMA. 1989; 262:2108 -2113. [Adrogué HJ, Madias NE, Disorders of Acid-Base Balance.

In: Berl T. Bonventre JV, editors. Volume 1: Disorders of Water, Electrolytes, and Acid-Base; Acute Renal Failure. 1 edition. Philadelphia: Current Medicine Group; 1999. (Schrier RW, editor. Atlas of Diseases of the Kidney). ISBN: 0-632-04385-7] *Caption from original*

Disease Course

- With appropriate and aggressive treatment, most cases of DKA resolve over 24–72 hours.
- Advances in knowledge leading to improved and more aggressive treatment has reduced the mortality of DKA to less than 5 %.
- Currently, most mortality is seen in the very young and the very old.
- Overwhelming infection and acute myocardial infarction precipitating DKA are associated with increased mortality.
- In general, the sicker a patient is at presentation, the higher the mortality.
- Some complications related to therapy for DKA have previously been discussed (hypokalemia, hypophosphatemia, and hypoglycemia). Other complications of therapy include the adult respiratory distress syndrome, and cerebral edema.
- Adult respiratory distress syndrome (ARDS): This is a rare complication, generally felt to result in over-aggressive fluid repletion especially in patients with underlying pulmonary or cardiac disease.
- Cerebral edema. Cerebral edema is a feared complication of DKA in children. It tends to occur 4–24 hours after the initiation of therapy, and patients usually appear to be improving prior to its onset. Cerebral edema is associated with high morbidity and mortality. It is thought to result from free water diffusing into brain cells at a fast rate, causing cells to swell. The only known risk factors are young age and DKA being the presenting manifestation of diabetes. There are currently no identified presenting or treatment issues that reliably predict the onset of cerebral edema. Symptoms may include headache, incontinence, change in mental status, seizures, or other changes in autonomic or neurologic function. If the diagnosis of cerebral edema is being considered, therapy with intravenous mannitol (1–2 grams/kg IV) should be started immediately, without awaiting confirmatory studies.



A 12-year-old boy in DKA (left) and following recovery from the DKA episode (right). Axial FLAIR images (1.5 T) demonstrate that the intercaudate distance is smaller during DKA than after recovery, suggesting mild diffuse brain swelling. [Wootton-Gorges SL, Glaser NS. Imaging of the brain in children with type I diabetes mellitus. Pediatric Radiology. 2007 Jul 27;37(9):863–9.] *Caption adapted from original*

Computerized Tomography (CT) head showing diffuse cerebral edema with effacement of basal cisterns and generalized loss of gray-white differentiation [From article: Dialysis Disequilibrium Syndrome: Brain death following hemodialysis for metabolic acidosis and acute renal failure–A case report. BMC Nephrology. 2004 Aug 19;5(1):9. https://doi.org/10.1186/1471-2369-5-9, at http://link.springer.com/article/10.1186%2F1471-2369-5-9/fulltext.html; by Sean M Bagshaw, Adam D Peets, Morad Hameed, Paul JE Boiteau, Kevin B Laupland, Christopher J Doig, © Bagshaw et al; licensee BioMed Central Ltd. 2004; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- Metabolic acidosis that does not respond to usual therapy is often due to lactic acidosis from unrecognized infection.
- Hypotension/shock refractory to fluid administration should prompt a consideration of concurrent gram-negative sepsis or myocardial infarction with cardiogenic shock.
- Venous thromboembolism (VTE) can occur as a late complication.
- Rhinocerebral mucormycosis is a rare, late, complication of DKA. It is an infection of the sinuses, nasal passages, oral cavity, and brain caused by saprophytic, aerobic fungi. It is associated with a very high mortality.

Related Evidence

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*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: “Diabetic ketoacidosis”[mesh] OR “Diabetic ketoacidosis”

Chapter 25
Duchenne Muscular Dystrophy

Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Duchenne Muscular Dystrophy (DMD)

- A member of a group of diseases termed dystrophinopathies (includes Duchenne and Becker Muscular Dystrophy)
- Duchenne's is the most severe form

Incidence/Epidemiology

- Caused by a defective gene on the X chromosome.
- An X linked recessive trait.
- A population-based surveillance study of males 5–24 years old in four states found the overall prevalence of DMD/Becker muscular dystrophy (BMD) to be from 1.3 to 1.8 per 10,000.

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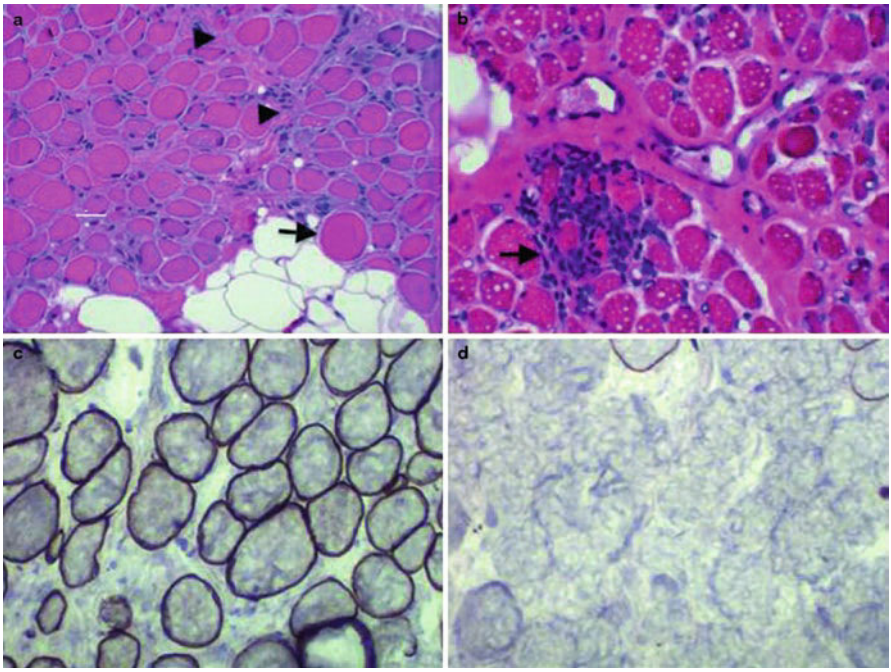
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_25

Differential Diagnosis

- The differential diagnosis of infants and children with muscle weakness is large.
- Some helpful clinical findings include:
  - Cranial nerve deficits are seen in neuromuscular junction dysfunction (myasthenia gravis, botulism, and tick paralysis).
  - Spinal cord dysfunction is heralded by loss of function below the level of the lesion (poor rectal tone, decreased cremasteric reflexes).
- Hyperesthesias are common in peripheral nerve disorders.
- The presence of ataxia and cerebellar signs favors a central anomaly.
- Hyporeflexia is common in Guillain-Barré syndrome, tick paralysis, and botulism.

Pathophysiology and Etiology

- The result of a defective gene located on the X chromosome that is responsible for the production of dystrophin.
- Dystrophin is responsible for stabilization of muscle proteins, protecting them from degradation.
- Damage to these proteins results in muscle fiber degeneration.



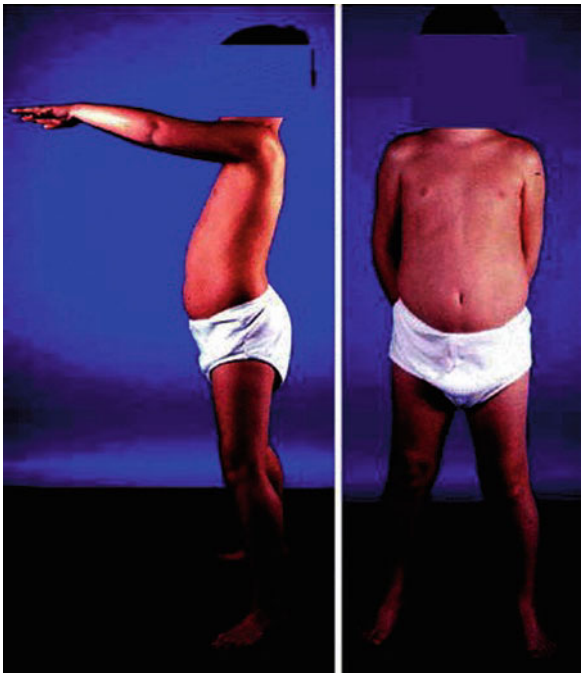
Duchenne muscular dystrophy. (a) On hematoxylin and eosin (H&E) staining, considerable fiber-type variation, including an occasional hypertrophic fiber (arrow) and fibrosis with fatty infiltration (arrow heads), is noted. (b) Also on H&E staining, lymphocytic infiltrates are demonstrated (arrow). (c) Normal dystrophin staining. (d) Loss of dystrophin staining in DMD [Russell JW, Weiss MD, Distad BJ, Castellani RJ. Muscle and Myotonic Diseases. In: Feldman EL, Grisold W, Russell JW, Löscher WN, editors. Atlas of Neuromuscular Diseases [Internet]. Vienna: Springer Vienna; 2014 [cited 2016 Aug 1]. p. 247–81. Available from: http://link.springer.com/10.1007/978-3-7091-1605-0_11] *Caption from original*

Presentation

Typical/"Classic"

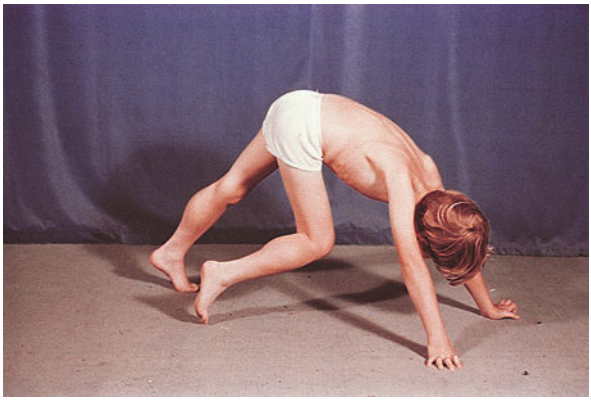
- Neuromuscular presentation is most common.
- Obvious clinical signs of weakness occur between 2 and 3 years of age.
- Lower extremity muscles are initially affected, specifically proximal limb musculature.

Duchenne dystrophy. Duchenne dystrophy is an X-linked progressive myopathy of childhood caused by mutations of the dystrophin gene. A,Lateral photograph of a boy with Duchenne dystrophy. Note the lumbar lordosis and enlarged calves [Pleasure D, Bird S, Scherer S, Sladky J, Schotland D. Neuromuscular Disease. In: Rosenberg RN, editor. Atlas of Clinical Neurology [Internet]. Current Medicine Group; 2003 [cited 2016 Aug 1]. p. 385–401. Available from: http://link.springer.com/chapter/10.1007/978-1-4757-4552-8_11] *Caption from original*.



Duchenne muscular dystrophy. Note the prominent abdomen and lumbar lordosis, calf pseudohypertrophy, and equinus at the ankles [Bleck EE, Robb JE. Hereditary and Developmental Neuromuscular Disorders. In: Benson M, Fixsen J, Macnicol M, Parsch K, editors. Children's Orthopaedics and Fractures [Internet]. London: Springer London; 2010 [cited 2016 Aug 1]. p. 249–64. Available from: http://link.springer.com/10.1007/978-1-84882-611-3_16] *Caption from original*

- There is impairment of running, jumping, and climbing stairs. Fractures from falls are common,
- Look for Gower's Sign—children will have to actively push up with their hands to attain a standing position.

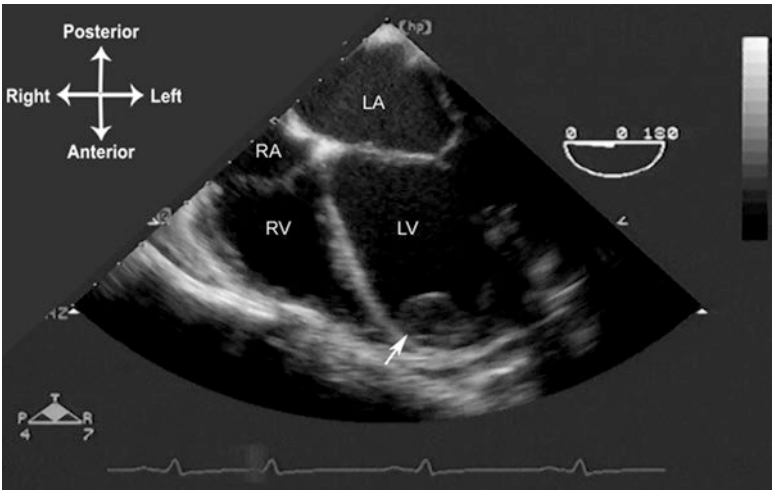


Duchenne's dystrophy, Gower maneuver [MacGregor DL. Neurology. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. Atlas of Pediatrics, Volume IA, Chapter 05;. ISBN: 1-57340-188-9] *Caption from original*

- Most patients are wheelchair-bound by early adolescence.

Atypical

- There may also be variable degrees of global developmental deficits.
- Cardiac presentations are less common than neuromuscular presentations.
- DMD causes a dilated cardiomyopathy.

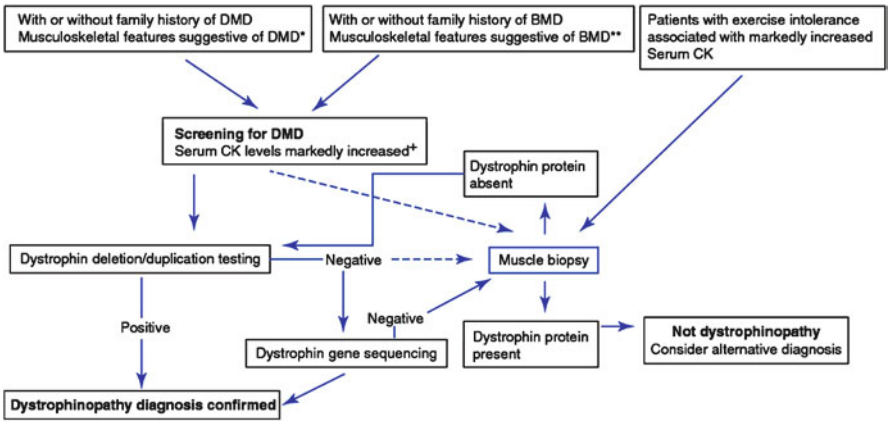


Thrombus (arrow) in the left ventricular apex of a patient with Duchenne muscular dystrophy and dilated cardiomyopathy. Mid-esophageal four-chamber view, multiplane angle 0°. LA left atrium, LV left ventricle, RA right atrium, RV right ventricle [Wong PC. Additional Applications of Transesophageal Echocardiography. In: Wong PC, Miller-Hance WC, editors. Transesophageal Echocardiography for Congenital Heart Disease [Internet]. London: Springer London; 2014 [cited 2016 Aug 1]. p. 399–436. Available from: http://link.springer.com/10.1007/978-1-84800-064-3_16] *Caption from original*

- Conduction abnormalities may be present (resulting in mostly supraventricular disorders).
- The progression of cardiac disease is gradual, with full expression after 18 years of age.
- Most children, by virtue of their lack of strenuous activity, are asymptomatic.
- Most children with DMD develop scoliosis.

Primary Differential Considerations

- Other muscular dystrophies must be considered; the most common is Becker muscular dystrophy. Muscle biopsy can differentiate among these and other diagnoses.



Algorithm to guide diagnostic workup in suspected DMD/BMD patients for confirmation of dystrophinopathy diagnosis. For patients diagnosed by muscle biopsy, dystrophin genetic testing is also necessary. For patients diagnosed by genetic testing, muscle biopsy is not necessary, and if at all possible, defer muscle biopsy until patient participates in a later clinical trial. DMD Duchenne muscular dystrophy, BMD Becker muscular dystrophy, CK creatine kinase [Sahenk Z, Rodino-Klapac LR. Dystrophinopathies. In: Katirji B, Kaminski HJ, Ruff RL, editors. Neuromuscular Disorders in Clinical Practice [Internet]. New York, NY: Springer New York; 2014 [cited 2016 Aug 1]. p. 1207–29. Available from: http://link.springer.com/10.1007/978-1-4614-6567-6_56] *Caption adapted from original*

History and Physical Exam

Findings That Confirm Diagnosis

- Common findings include a wide-based gait, lumbar lordosis, pseudohypertrophy of the calf muscles, shortening of the Achilles tendons, and hyporeflexia or areflexia.
- Depending on the degree of scoliosis, respiratory function may be compromised.

Factors That Suggest Diagnosis

- Most children will have already been diagnosed prior to their first Emergency Department encounter.

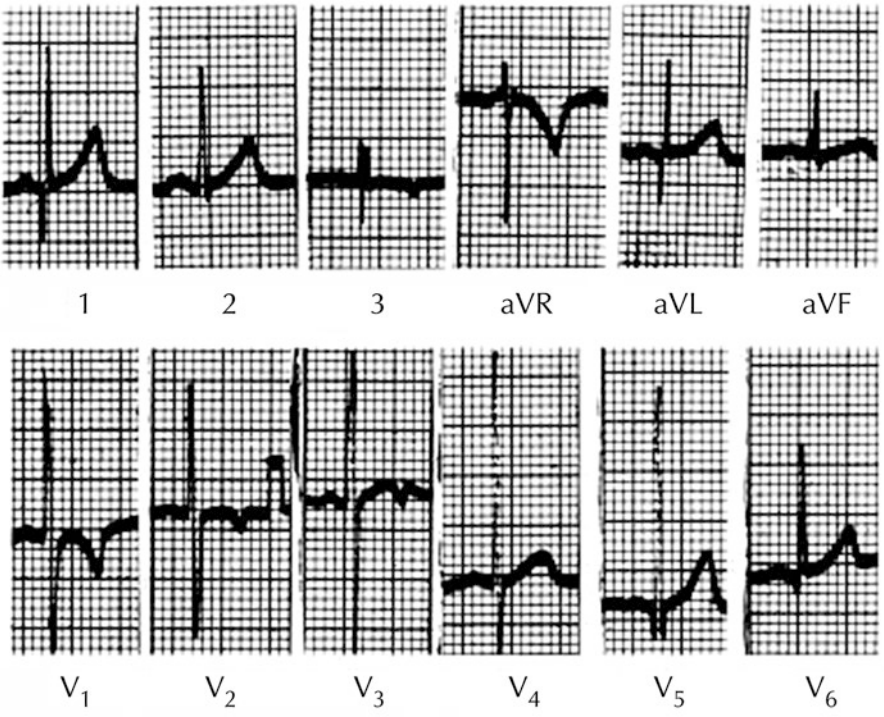
Factors That Exclude Diagnosis

- No clinical findings can exclude DMD in patients with suggestive findings. A muscle biopsy is required.

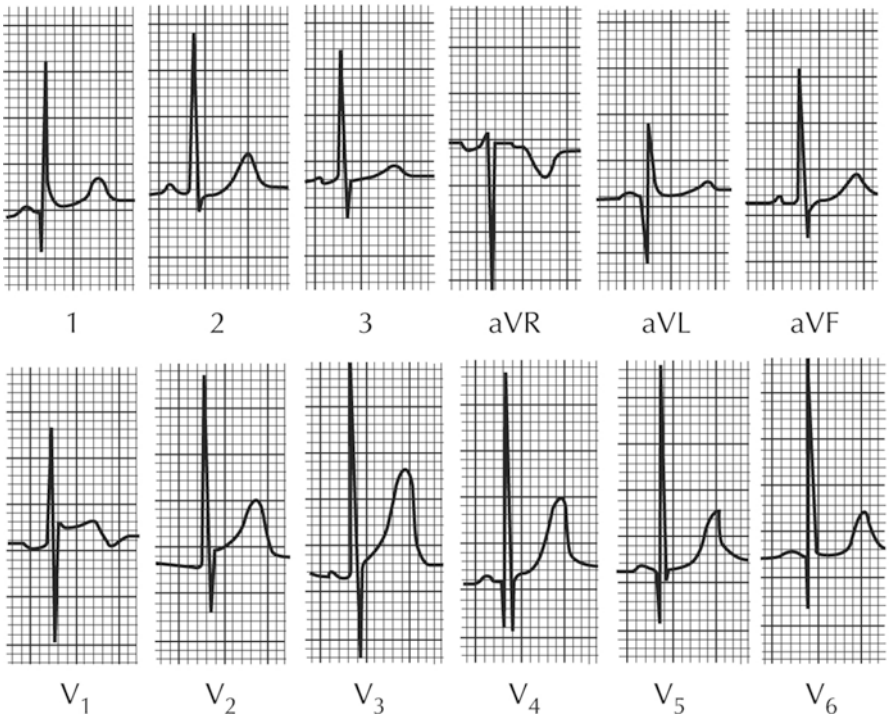
Ancillary studies

Electrocardiography

- As previously mentioned, a variety of arrhythmias may occur, particular supraventricular.



Electrocardiogram of female carrier of Duchenne dystrophy gene [Perloff J, Abelmann W. Chapter 6. In: Lee RT, Braunwald E, editors. Atlas of cardiac imaging. Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption from original*



Electrocardiogram of Duchenne dystrophy in 10-year-old boy [Perloff J, Abelmann W. Chapter 6. In: Lee RT, Braunwald E, editors. Atlas of cardiac imaging. Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption from original*

Laboratory

- Patients with DMD will have elevated levels of serum creatine kinase.
- These elevations may occur prior to the appearance of clinical disease.
- Levels peak in early childhood but may actually normalize as damaged muscle fibers are replaced by fibrotic change.

Special Populations

Age

- DMD is identified in early life. The usual life expectancy of patients with DMD is about 25 years.

Co-morbidities

- None significant

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is most important to anticipate the variable forms of target organ dysfunction that accompany DMD patients.
- Complications of respiratory compromise are the most frequent etiologies of emergency department visits.
- Aspiration pneumonia and cases of primary bacterial pneumonia are commonly encountered.
- Use extreme caution when providing sedation and analgesia to DMD patients.
- DMD patients are susceptible to the development of malignant hyperthermia, specifically associated with administration of succinylcholine and inhalational agents.

Mimics

- In general, these patients are already diagnosed prior to ED presentation.

Time-Dependent Interventions

- Depending on the particular complication, early administration of fluids and broad-spectrum antibiotics are indicated.

Overall Principles of Treatment

- As mentioned, most ED cases necessitate pulmonary support and attention to obvious complications.

Disease Course

- Sadly, most children with DMD are confined to a wheelchair by early adolescence.
- Death usually occurs by early adulthood, and is caused by cardiopulmonary insufficiency.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Muscular Dystrophy, Duchenne"[Mesh] OR "Duchenne muscular dystrophy"

Chapter 26
Epiglottitis

Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

- Epiglottitis (Supraglottitis)

Incidence/Epidemiology

- There has been a marked decrease in cases since the introduction of the Hib vaccine.
- According to current estimates, in the United States 1.6 cases occur per 100,000 adults, and 0.5 cases occur per 100,000 children.
- As a result of immunization practices, the median age of children presenting with epiglottitis has increased from 3 years to 6–12 years of age.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_26

Differential Diagnosis

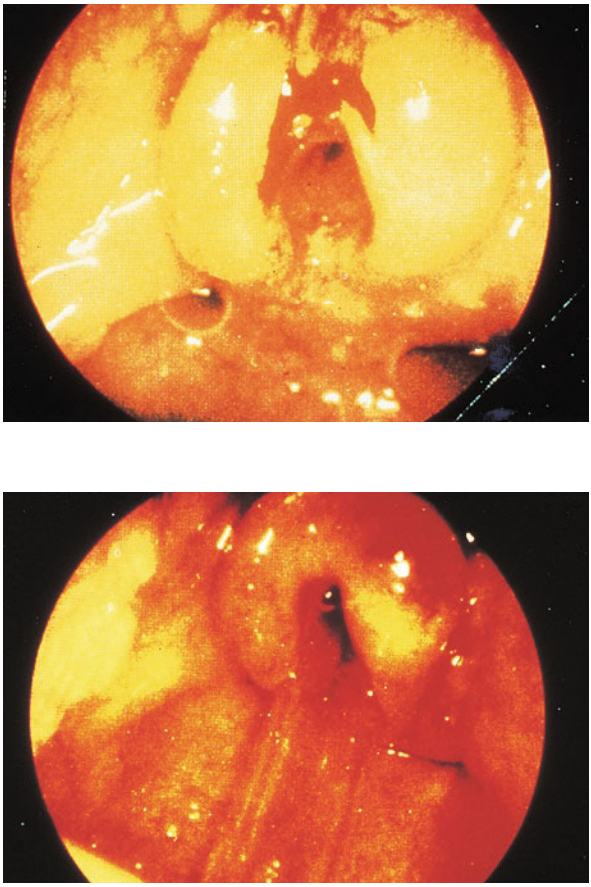
- Other causes of acute upper airway obstruction must be considered:
  - Croup
  - Bacterial tracheitis
  - Peritonsillar abscess
  - Retropharyngeal abscess
  - Upper airway foreign body
  - Congenital upper airway anomalies

	Croup	Epiglottitis
Cause	Viral	Bacterial
Age	6 mo to 3 y	4–6 y
Site of obstruction	Subglottic	Supraglottic
Clinical features		
Onset	Gradual (days)	Sudden (hours)
Fever	With or without low grade fever	High fever (> 102°F)
Dysphagia, drooling		Present
Cough	Barking, dry cough	Not common
Respiratory rate	↑	Normal
Position	Normal	Sitting upright
Appearance	Mild distress	Toxic appearing
Quality of voice	Hoarseness	Muffled
Primary Treatment	Supportive:	Secure airway:
Hydration	Needed	Needed
Antibiotics	Not Needed	Needed to treat *Haemophilus* influenza
Airway support	Not Needed	Always needed
Extubation	Not Needed	When temperature decreases and with leak around the endotracheal tube

Differential diagnosis of croup vs epiglottitis. The two most common infectious causes of upper airway obstruction in children, croup and epiglottitis, differ in etiology, patient demographics, and symptomatology. [Rasmussen G, Deshpande J. Pediatric anesthesia. In: Muravchick S, editor. Subspecialty care. Philadelphia: Current Medicine; 1998. 236 p. (Miller RD editor, Atlas of anesthesia; vol. 5). ISBN: 0-443-07905-6] *Caption from original*

Pathophysiology and Etiology

- Epiglottitis is essentially a cellulitic process secondary to bacteremic spread.
- The onset of edema is rapid and usually does not involve subglottic structures.



Severe epiglottitis. Two patients with severe epiglottitis. A, The characteristic edema of the epiglottis and laryngeal structures and purulent material. B, Extent that advanced edema can become, so that by the time many patients present, they are breathing through an extremely small aperture. [Rasmussen G, Deshpande J. Pediatric anesthesia. In: Muravchick S, editor. Subspecialty care. Philadelphia: Current Medicine; 1998. 236 p. (Miller RD editor, Atlas of anesthesia; vol. 5). ISBN: 0-443-07905-6] *Caption from original*

- Most cases are bacterial in origin, usually from *Haemophilus influenza* type b (Hib).
- Other causes in children include streptococci and *Staphylococcus aureus* (including MRSA strains).

Presentation

Typical/"Classic"

- Look for the "3 D's": distress, drooling, and dysphagia.
- Unlike croup, there is generally no prodromal URI.
- Most children become ill within 24 hours, often with a toxic appearance.
- Younger children will assume a "sniffing posture," in which the chin is thrust forward and the neck hyperextended in order to maximize airway patency.

	Children	Adults
Age at acquisition	3–5 yrs	—
Location of pathology	Supraglottic	Supraglottic
Onset	Rapid	Most have a mild illness with prolonged course, painful dysphagia, and pharyngitis
Fever	High	Variable
Appearance	Toxic	Usually not toxic
Stridor	+++	Not usual
Cough	Not usual	—
Drooling	Often	—

Clinical features of acute epiglottitis [Tristram D. Chapter 07. In: Brook I, editor. Atlas of Upper Respiratory and Head and Neck Infections, 2e. Philadelphia: Current Medicine; 2000. (Mandell GL, editor. Atlas of infectious diseases; vol. 4). ISBN: 1-57340-140-4]

Atypical

- Older children and adults may only complain of a sore throat, and generally do not appear toxic

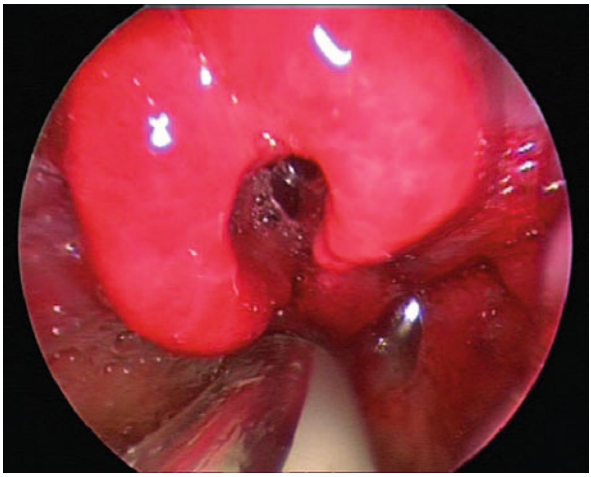
Primary Differential Considerations

- Early consideration in patients with symptoms referable to epiglottitis should also be given to the following differential diagnoses:
  - Peritonsillar or retropharyngeal abscess
  - Angioedema
  - Laryngitis
  - Tonsillitis
  - Laryngeal diphtheria

History and Physical Exam

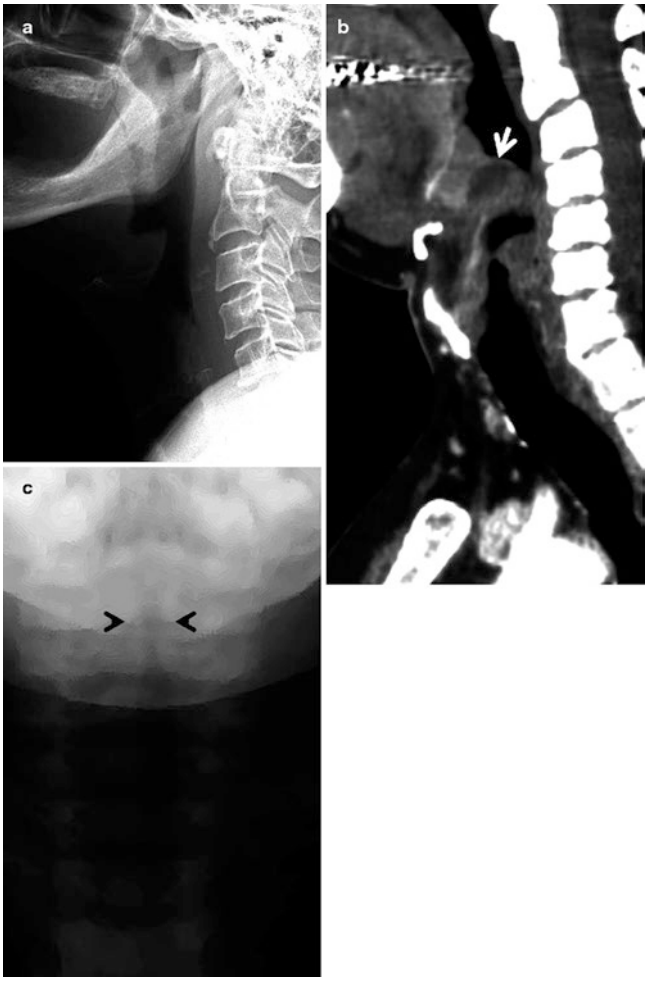
Findings That Confirm Diagnosis

- In the purest sense, the diagnosis is confirmed by direct visualization of the epiglottis in the operating room.



Direct laryngoscopy findings in a 10-year-old presenting with epiglottitis [Hughes AL, Karter N, Swanson DS. Laryngeal Infections. In: Valdez T, Vallejo J, editors. Infectious Diseases in Pediatric Otolaryngology [Internet]. Cham: Springer International Publishing; 2016 [cited 2016 Aug 3]. p. 151–61. Available from: http://link.springer.com/10.1007/978-3-319-21744-4_11] *Caption from original*

- Indirect diagnosis may be obtained by visualization of a swollen epiglottis on lateral neck radiographs (“thumb print sign”).



(a, b) Acute epiglottitis. Note the swollen epiglottis with a thumb-like appearance. Radiography is unnecessary in acute epiglottitis and must not be undertaken lightly but occasionally may be performed to exclude a foreign body. It is best performed with the patient in a sitting position to keep the airway open. Epiglottitis can be life-threatening and resources to secure the airway must be available at all times. The CT image shows an edematous epiglottis containing an abscess (arrow). CT is unnecessary for acute epiglottitis. (c) Croup – "steeple" like narrowing of the subglottic airway (arrowheads) [Raghavan P, Shonka DC, Wintermark M, Mukherjee S. Larynx and Hypopharynx. In: Raghavan P, Mukherjee S, Jameson MJ, Wintermark M. Manual of Head and Neck Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2016 Aug 2]. p. 109–36. Available from: http://link.springer.com/10.1007/978-3-642-40377-4_5] *Caption from original*

Factors That Suggest Diagnosis

- Many studies have highlighted the following findings:
  - Difficulty breathing (80 %)
  - Stridor (80 %)
  - Muffled or hoarse voice (79 %)
  - Pharyngitis (73 %)
  - Fever (57 %)
  - Sore throat (50 %)
  - Difficulty swallowing (26 %)
  - Change in voice (20 %)

Symptom	No. of patients	Percent
Sore throat	272	94
Dysphagia	252	88
Odynophagia	178	62
Fever	118	41
Dyspnea	85	30
Hoarseness	40	14
Foreign body sensation	23	8
Cough	19	7
Muffled voice	18	6
Otalgia	11	4
Stridor	4	1
Drooling	4	1
Heartburn	4	1
Vomiting	2	1
Tripod position	0	0

Patients may have more than one presenting symptom

Presenting symptoms and signs in 288 acute supraglottitis adult patients [Ovnat Tamir S, Marom T, Barbalat I, Spevak S, Goldfarb A, Roth Y. Adult supraglottitis: changing trends. European Archives of Oto-Rhino-Laryngology. 2015 Apr;272(4):929–35.] *Caption from original*

Factors That Exclude Diagnosis

- A normal epiglottitis on direct view in the surgical suite is the only way to exclude the diagnosis fully in patients suspected of having epiglottitis.

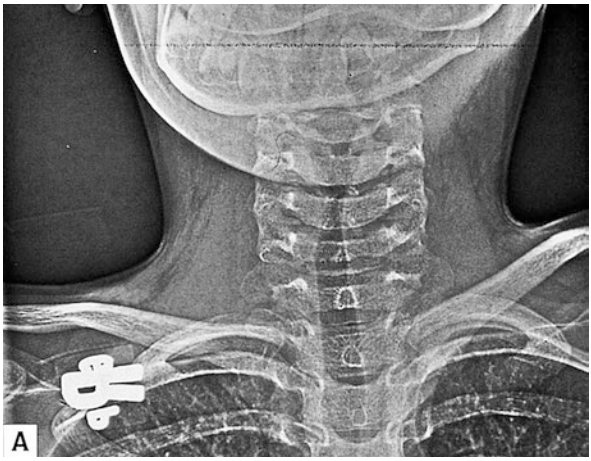
Ancillary Studies

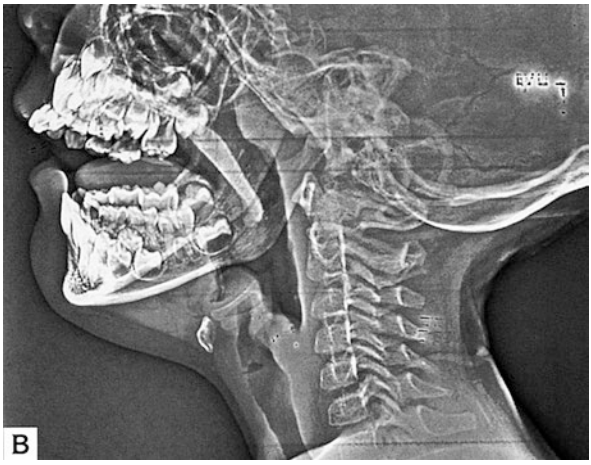
Laboratory

- Note: It is advisable to wait until definitive equipment and personnel are at the bedside (or in the OR) before negatively stimulating the child.
- Although the diagnosis is a clinical one, leukocytosis is common, as are positive blood cultures.

Imaging

- Radiographs should only be obtained at no risk to the child.
- No patient should leave the Emergency Department without adequate airway personnel and equipment.





Epiglottitis as seen by xeroradiography. A, Anteroposterior view of the neck of a child with documented epiglottitis shows narrowing in the diameter of the trachea, which can be confused with acute viral croup. The lateral neck view is preferable because it can demonstrate the enlarged epiglottis, or "thumb sign." B, Xeroradiograph showing a lateral neck view of the same child demonstrates the acute epiglottic and aryepiglottic swelling seen in acute epiglottitis. Direct visualization in the operating room revealed a markedly swollen epiglottis. [Tristram D. Chapter 07. In: Brook I, editor. Atlas of Upper Respiratory and Head and Neck Infections, 2e. Philadelphia: Current Medicine; 2000. (Mandell GL, editor. Atlas of infectious diseases; vol. 4). ISBN: 1-57340-140-4] *Caption from original*

Epiglottitis. Lateral radiograph of the neck demonstrates gross enlargement of the epiglottis (arrowhead) as well as the aryepiglottic fold, resulting in narrowing of the supraglottic laryngeal airway [Singh A. Imaging of Neck Emergencies. In: Singh A, editor. Emergency Radiology [Internet]. New York, NY: Springer New York; 2013 [cited 2016 Aug 2]. p. 183–98. Available from: http://link.springer.com/10.1007/978-1-4419-9592-6_15] *Caption from original*

Special Populations

Age

- Epiglottitis can present at all ages. Adult epiglottitis is generally less acute and is certainly less life-threatening than the pediatric issue.
- Pediatric epiglottitis is much less common in areas where the Hib vaccine is widely given; kids who are not immunized are at higher risk.

Co-morbidities

- Immune-compromised patients are at higher risk of developing epiglottitis. This is particularly true in adult cases.

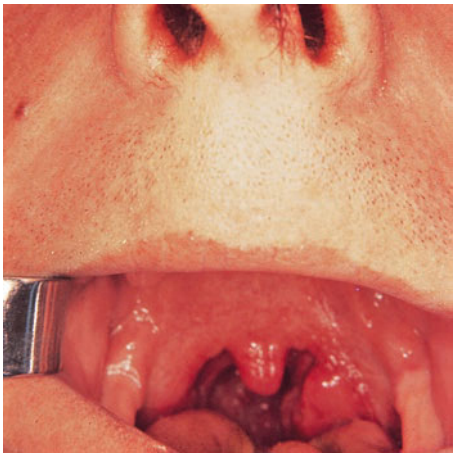
Co-morbidity	Number of patients	Percent
None	108	38
Smoking	121	42
Cardiovascular disease	87	30
Gastroesophageal reflux	37	13
Diabetes mellitus	29	10
Immunosuppression	20	7
Others	124	43

Patients may present with several co-morbidities

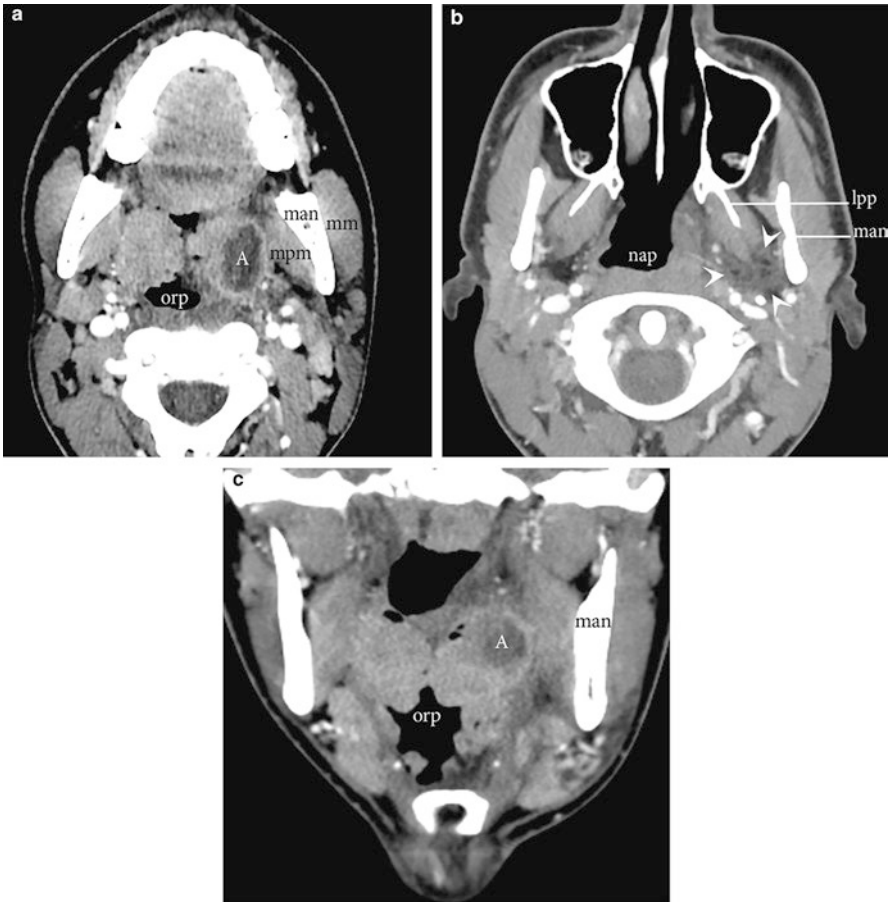
Most common co-morbidities among 288 acute supraglottitis adult patients [Ovnat Tamir S, Marom T, Barbalat I, Spevak S, Goldfarb A, Roth Y. Adult supraglottitis: changing trends. European Archives of Oto-Rhino-Laryngology. 2015 Apr;272(4):929–35.] *Caption from original*

Pitfalls in Diagnosis

- The two most significant pitfalls in diagnosis are:
  - failing to consider the diagnosis altogether
  - being cavalier in the workup and sending a child suspected of epiglottitis to radiology without definitive airway assistance.
- Failing to consider significant differential diagnoses such as peritonsillar abscess is a problem.



Peritonsillar abscess [Endicott J, Seper J. Chapter 10. In: Brook I, editor. Atlas of Upper Respiratory and Head and Neck Infections, 2e. Philadelphia: Current Medicine; 2000. (Mandell GL, editor. Atlas of infectious diseases; vol. 4). ISBN: 1-57340-140-4]



Peritonsillar abscess. Axial (***a***, ***b***) and coronal (***c***) CECT images demonstrate a rim-enhancing left-sided peritonsillar abscess (A) in this child with odynophagia and fever. There is resultant narrowing of pharynx and "kissing" appearance of the enlarged tonsils. There is infiltration of left parapharyngeal fat (white arrows). Medial pterygoid muscle (mpm, ***a***), mandible (man, ***a***, ***b***, ***c***), masseter muscle (mm, ***a***), oropharynx (orp, ***a***, ***c***), lateral pterygoid plate (lpp, ***b***), nasopharynx (nap, ***b***) [Pawha P, Jiang N, Shpilberg K, Luttrull M, Govindaraj S. Gross and Radiographic Anatomy. In: Levine AI, Govindaraj S, DeMaria, S, editors. Anesthesiology and Otolaryngology [Internet]. New York, NY: Springer New York; 2013 [cited 2016 Aug 2]. p. 3–33. Available from: http://link.springer.com/10.1007/978-1-4614-4184-7_2] *Caption from original*

Critical Steps Not to Miss

- If a diagnosis of epiglottitis is suspected, all efforts should be directed toward obtaining the personnel and equipment necessary for intubation.
- Without question, intubation is best carried out in the OR by medical caregivers expert in Pediatric airway management (i.e., ENT or Anesthesia).

Mimics

- Most other causes of upper airway disease in children do not present in a manner similar to that of epiglottitis.

Time-Dependent Interventions

- Early confirmation of the diagnosis and expectant airway management by expert operators is essential to good outcomes in acute epiglottitis.

Overall Principles of Treatment

- The management of epiglottitis has 3 phases:
  - Recognition
  - Intubation
  - Intravenous antibiotics

Disease Course

- The prognosis is excellent if surgical correction is carried out.

Related Evidence:

Papers of particular interest have been highlighted as:
*** Of key importance*

Cohort Study

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Comparative Study

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Epiglottitis"[Mesh] OR "Epiglottitis" OR "Supraglottitis"

Chapter 27
Esophageal Rupture

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Esophageal Rupture

- Esophageal Perforation, Boerhaave's Syndrome

Incidence/Epidemiology

- Esophageal rupture is a rare but life-threatening event.
- Current mortality of 30 %.
- There are many causes of esophageal rupture (described below). Iatrogenic causes are the most common, accounting for about half of all cases. Classic Boerhaave's syndrome accounts for another 15 %, foreign bodies for 14 %, trauma (penetrating, blunt, caustic ingestion) for 10 %, and other miscellaneous causes for the remainder of cases seen.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_27

Differential Diagnosis

- Esophageal rupture usually causes acute onset of chest pain, so all the causes of acute chest pain need to be considered in the differential. These include; acute coronary syndrome, aortic dissection, pulmonary embolism, pneumonia, pneumothorax, other intra-abdominal catastrophes, amongst others.
- Esophageal rupture has many causes. Usually the history will lead to recognition of the cause of the rupture once identified.

Pathophysiology and Etiology

- Rupture of the esophagus allows for the direct contamination/communication of esophageal contents into the mediastinum. The esophagus has no serosal mucosal covering, so there is no anatomic mechanism for containment. The parietal pleura is very thin and weak, so the local inflammatory response allows for easy disruption of the parietal pleura and passage of contents into the pleural space.
- The left, posterior, distal esophagus just above the esophagogastric junction is the weakest point in the esophagus and the most common place for spontaneous rupture and rupture from gastrointestinal endoscopic procedures.
- Complications from tracheal and pharyngeal procedures may lead to rupture of the cervical esophagus at the level of the cricopharyngeal muscle just distal to the esophageal introitus, an anatomic narrowing point of the esophagus. Cervical ruptures often are better localized and not as serious as distal ruptures.
- There are multiple causes of esophageal rupture.
    - Iatrogenic, which is the most common, accounting for about 50 % of cases
        - Esophageal rupture complicates about 0.2–1 % of endoscopies. It is more likely in the setting of pre-existing esophageal disease such as caustic burns, tumors, eosinophilic esophagitis, and other causes of esophageal scarring.
        - Esophageal dilatation.
        - Endotracheal procedures/intubations, and with esophageal obturator airway placement.
    - Spontaneous “Boerhaave’s syndrome”
        - Causes about 15 % of all cases.
        - First described by Boerhaave in the early 1700s.
        - Very high mortality if not recognized early. The forces required to rupture the esophagus also force the spread of esophageal contents throughout the mediastinal space, leading to massive mediastinal contamination.

- The usual site of perforation is the distal esophagus in the left posterior region, just above the gastroesophageal junction.
- Usually occurs after episodes of sudden, forceful vomiting (about 75 % of these cases), but also may occur after severe coughing, straining, seizures, and childbirth (25 % of cases). Therefore, 25 % of cases do not have the typical history of forceful vomiting.
- A history of alcoholism, recent heavy drinking, and/or overindulging in food is found in most of the cases due to forceful vomiting.

- Foreign bodies
  - Cause 10 % of esophageal perforations.
  - Usually from pills, batteries, buttons.
  - Caused by either direct laceration or pressure or chemical necrosis.
  - Usually occurs at either the cervical or lower esophagus.
- Trauma
  - Causes about 10 % of cases.
  - May be from caustic (alkali or acid) burns, penetrating trauma, or blunt trauma.
  - Perforation more likely from alkali burns than acid burns.
  - Penetrating wounds to the neck, chest, and abdomen associated with only about a 0.5 % incidence of esophageal perforation.
  - Often overlooked initially as more obvious injuries are treated.
  - Blunt trauma is a very rare cause.
  - Miscellaneous causes (remaining 15 %)
  - Esophageal tumors, esophageal disease (achalasia, Barrett's esophagus, eosinophilic esophagitis), infectious (rare), aortic pathology (aortic aneurysm, aberrant right subclavian artery).

Presentation

Typical/"Classic"

- Acute onset of severe, constant, sharp, substernal chest pain immediately following an appropriate procedure or an episode of forceful vomiting. Pain is often pleuritic and radiates in an esophageal pattern (neck into chest and upper abdomen). Pain often worsens with swallowing.
- Usually the patient appears ill and uncomfortable. He or she also may complain of shortness of breath and be diaphoretic.
- If the patient presents early in the course, physical exam findings may be normal.
- If presenting 1–2 hours into the course, the patient may appear septic, with fever, tachycardia, hypotension, and hypoxia.

- "Hamman crunch": crunching sound heard on auscultation during systole as the result of air in the mediastinum surrounding the pericardium.
- Classically described subcutaneous emphysema (feeling of crunchiness [crepitus] under skin due to air tracking through subcutaneous tissues) in neck is present in only about 25 % at time of presentation.
- Chest x-ray (CXR) may be normal early in course, but over time pneumomediastinum, left more often than right pleural effusion, pneumothorax, hydropneumothorax, and/or a widened mediastinum may develop. CXR also may demonstrate subcutaneous air.

Atypical

- About one-third of cases will present atypically.
- May present as back pain only.
- Remember that about 25 % of patients with spontaneous esophageal rupture do not give a history of forceful vomiting.
- Many of the classically described physical and radiologic findings may not develop until several hours into the clinical course, so a high index of suspicion must be maintained by the treating physician.
- Pneumomediastinum is demonstrated in only about 40 % on plain CXR, even well into the clinical course.

Primary Differential Considerations

- Patients who present with signs and symptoms consistent with esophageal rupture also should be evaluated for these differential diagnoses:
  - Acute coronary syndrome
  - Aortic dissection
  - Peptic ulcer disease
  - Acute pancreatitis

History and Physical Exam

Findings That Confirm Diagnosis

- Esophageal rupture is a rare disease, and a high index of suspicion must be maintained by the treating physician.
- CT is the most common confirmatory study.

- Contrast esophagoscopy and endoscopy also may be used, but less commonly.
- Endoscopy may be falsely negative.
- The combination of contrast esophagoscopy and endoscopy approaches 100 % sensitivity for diagnosis.

Factors That Suggest Diagnosis

- The development of severe chest or upper abdominal pain after an ENT or GI procedure, after an episode forceful vomiting, after penetrating trauma, or in a patient with known esophageal disease should suggest the diagnosis, and a high index of suspicion should be maintained by the treating physician.
- Finding a pneumomediastinum on CXR in the appropriate clinical setting (s/p procedure, or after forceful vomiting) makes the diagnosis likely enough that appropriate treatment can proceed while confirmation is sought.
- It is important to remember that pneumomediastinum takes 1–2 hours to develop, especially in perforation of the lower esophagus, so its absence does not exclude the diagnosis.
- Pneumomediastinum may be present in only about 40 % of cases.
- Other suggestive findings on CXR include pleural effusions (left-sided more common than right), pneumothorax, hydropneumothorax, subcutaneous emphysema, or pneumoperitoneum.

Factors That Exclude Diagnosis

- The finding of another cause for the acute chest pain (e.g., acute myocardial infarction, aortic dissection) essentially excludes the diagnosis.
- Radiographic studies may all be normal early (first 1-4 hours) in the course of the disease, so in an appropriate clinical setting, suspicion must be maintained even if initial studies are unrevealing.

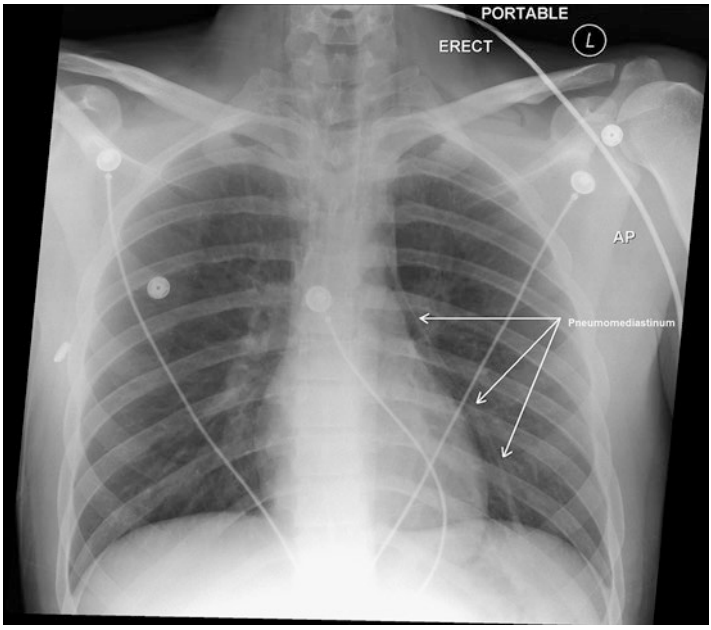
Ancillary Studies

Laboratory

- There are no laboratory tests that are specific to the diagnosis.
- Patients often manifest laboratory values consistent with an acute, severe, infectious, or inflammatory condition, such as leukocytosis, acidosis, or elevated lactate.

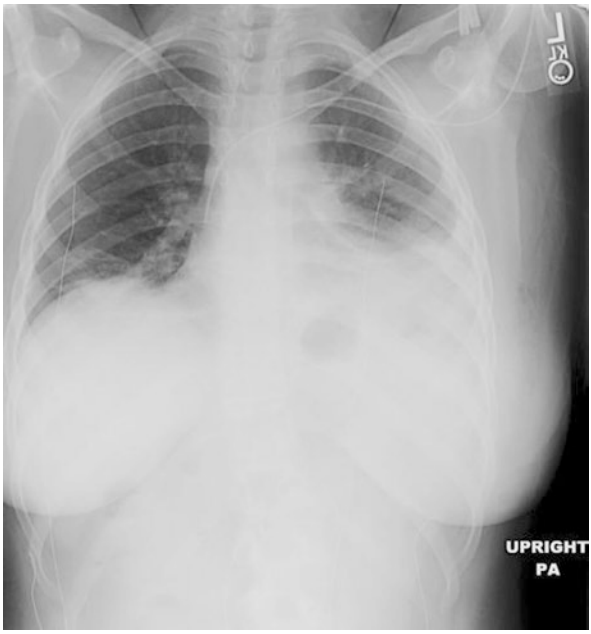
Imaging

- The plain CXR often is normal early in the disease course.
- Classically, the CXR may show multiple findings (alone or in combination):
  - Pneumomediastinum (seen in 40 %) with or without subcutaneous emphysema



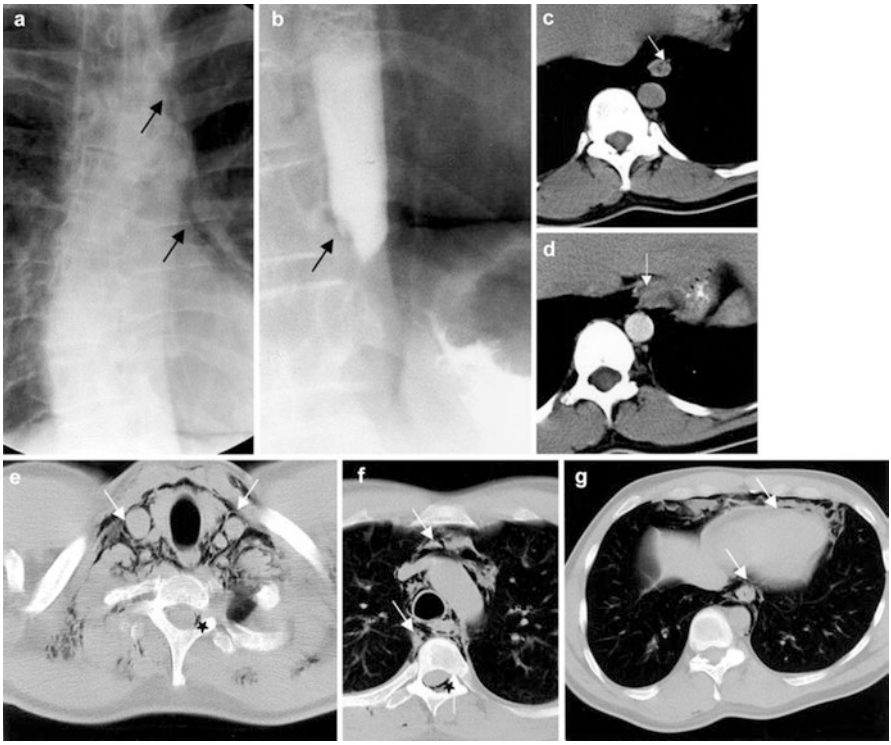
Chest X-ray showing pneumomediastinum. [From article: Pneumomediastinum from nasal insufflation of cocaine. International Journal of Emergency Medicine. 2010 Dec;3(4):435–7. https://doi.org/10.1007/s12245-010-0205-9, at http://link.springer.com/article/10.1007%2Fs12245-010-0205-9; by Brian T. Kloss, Claire E. Broton, Elliot Rodriguez, © Springer-Verlag London Ltd 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

- Left-sided pleural effusion



CXR demonstrating a left-sided pleural effusion. [Kohler JA, Ellis AR. Libman-Sacks Endocarditis in Pediatric Patient With Systemic Lupus Erythematosus. Pediatric Cardiology. 2012 Dec;33(8):1466–8.]

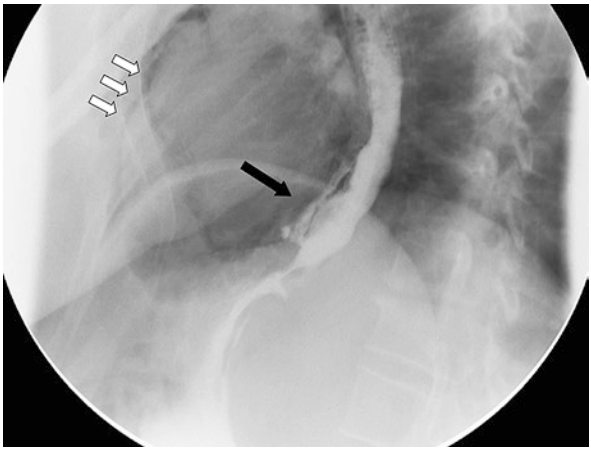
- Pneumothorax or hydropneumothorax
- Widened mediastinum
- CT scan of the chest often demonstrates the esophageal perforation and is more sensitive than CXR for detecting mediastinal air. Chest CT is the diagnostic study of choice.



a Chest radiography demonstrating pneumomediastinum (arrows). There were no infiltrates, atelectasis, or pleural effusion apart from the subcutaneous emphysema. b Esophagography with water-soluble contrast medium depicted a small but visible right-sided submucosal tear representing a contained esophageal perforation (arrow). No contrast medium extravasation through the esophagus was seen. c Nonenhanced CT demonstrated high attenuation of the supradiaphragmatic wall at a typical site, suggesting an intramural hematoma. c, d Nonenhanced and contrast-enhanced CT revealed an esophageal wall thickening which is a nonspecific finding. e–g CT at the level of the thyroid gland showed extensive pneumomediastinum and subcutaneous emphysema. Intraspinal air collections were seen at multiple levels in the spinal canal as visualization of air tracks (*). In addition to a large quantity of air in the anterior and posterior mediastinum, local periesophageal extraluminal air collections were observed indicating extraluminal complications of Boerhaave's syndrome. CT scan depicted air tracks (arrows) extending from the esophagus into the anterior lower mediastinum (g). [Radiological findings in Boerhaave's syndrome - Springer. [cited 2015 May 19]; Available from: http://link.springer.com/article/10.1007%2Fs10140-002-0264-1/fulltext.html] *Caption adapted from original*

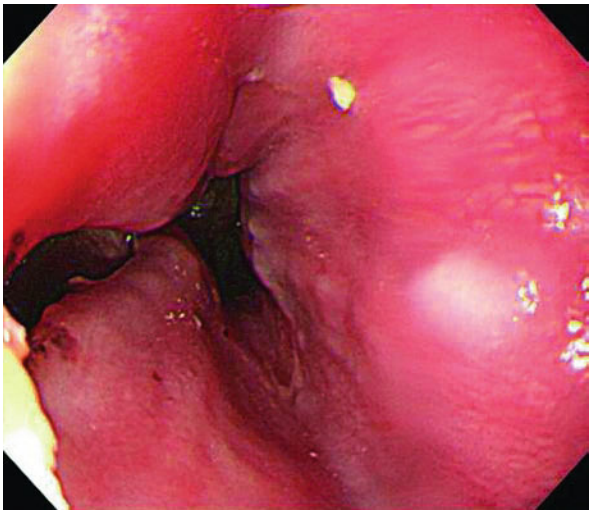
- Contrast esophagoscopy also may demonstrate the esophageal defect. It should be performed initially with a water-soluble contrast agent (Gastrografin), as barium-containing contrast agents, if extruded into the sur-

rounding tissues, may incite an inflammatory response. However, water-soluble contrast has a higher false-negative rate, so a negative water-soluble study should then be confirmed by a barium contrast study if the clinical suspicion remains high.



Water-soluble contrast radiograph of a patient with a distal esophageal perforation. The white arrows indicate free air in the mediastinum; the black arrow indicates extravasation of esophageal contrast. [Sánchez-Pernaute A, Aguirre EP, Talavera P, Valladares LD, de la Serna JP, Mantilla CS, de León AR, Torres A. Laparoscopic approach to esophageal perforation secondary to pneumatic dilation for achalasia. Surgical Endoscopy. 2009 May;23(5):1106–9.] *Caption from original*

- Esophagogastroduodenoscopy (EGD, upper endoscopy) also can directly demonstrate the esophageal defect. However, endoscopy may also miss a small defect. The combination of contrast esophagoscopy and endoscopy approaches 100 % sensitivity for the diagnosis.



Boerhaave syndrome. Perforation site was observed in the left side of the esophagus. [Park JM. Miscellaneous Esophageal Diseases. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 19]. p. 87–98. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_7] *Caption from original*

Special Populations

Age

- Esophageal rupture is slightly more common inmiddle-aged and older populations.

Co-morbidities

- Esophageal rupture is associated with chronic alcohol use and with other esophageal diseases that cause strictures or scarring of the esophagus.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the critical step. It also is critical to continue to consider the diagnosis, as physical and radiographic findings may take several hours to develop after the rupture.

Mimics

- Anything that causes acute chest or upper abdominal pain can mimic esophageal rupture. These include but are not limited to acute myocardial infarction, pulmonary embolism, aortic dissection, spontaneous pneumothorax, perforated peptic ulcer, pancreatitis, acute cholecystitis, and mesenteric thrombosis.

Time-Dependent Interventions

- Early diagnosis is important. Time is critical in decreasing morbidity and mortality. If primary closure of the defect occurs within the first 24 hours, there is 80–90 % survival. If repair occurs greater than 24 hours after rupture, survival falls below 50 % and may reach 30 %.
- Any patient with hemodynamic instability should be resuscitated, as would any patient in shock.

Overall Principles of Treatment

- Rapid resuscitation with intravenous fluids, empiric broad-spectrum antibiotics, and appropriate management of complications such as pneumothorax or hydropneumothorax should begin as appropriate, even if the diagnosis is not certain.
- Early primary surgical repair of the defect is definitive treatment. Some contained cervical esophageal ruptures may be managed conservatively and nonoperatively.

Disease Course

- Esophageal rupture may be rapidly fatal if not identified and treated early.
- Patients often present in extremis or have a rapidly progressive course.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Butler KH, Swencki SA. Chest pain: a clinical assessment. Radiol Clin North Am. 2006 Mar;44(2):165-79, vii. PMID: 16500201. http://www.ncbi.nlm.nih.gov/pubmed/16500201 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Esophageal Perforation"[Mesh] OR "esophageal perforation" OR "esophageal rupture"

Chapter 28
Esophagitis

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Esophagitis

Incidence/Epidemiology

- Esophagitis has been implicated as the cause of chest pain in 20–60 % of patients with chest pain not having an acute myocardial infarction.

Differential Diagnosis

- Esophagitis may cause acute chest pain, so the initial differential diagnostic considerations include all the acute causes of chest pain.
- Once the esophagus is believed to be the source of the chest pain, the differential diagnosis may focus on the causes of acute esophagitis, including inflammatory and infectious esophagitis, each of which has multiple causes.

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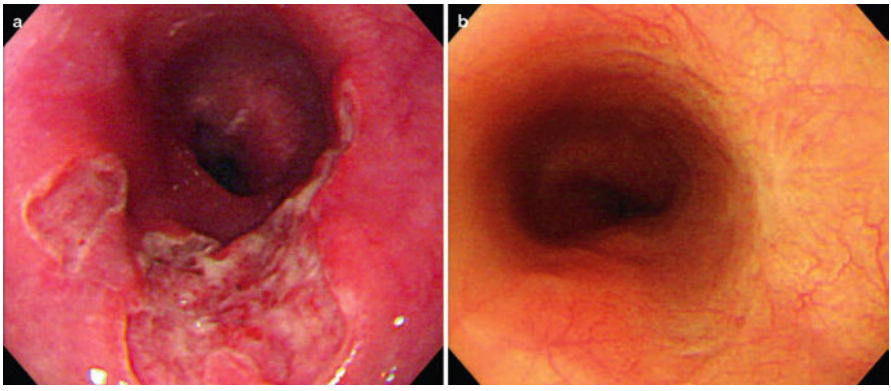
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_28

Pathophysiology and Etiology

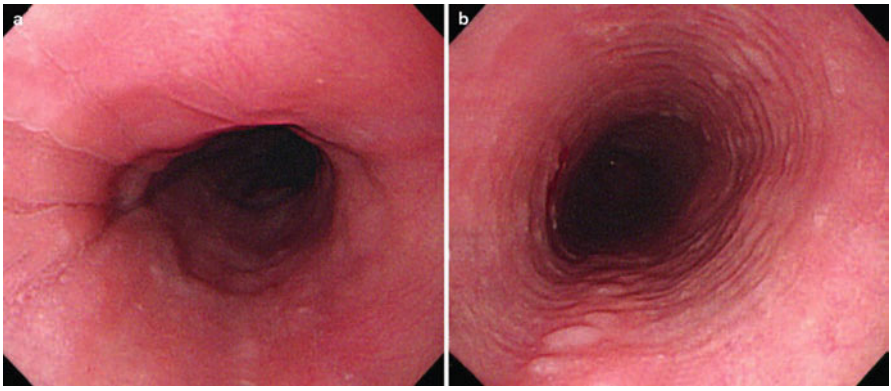
- The final common pathway of pathophysiology is inflammation of the esophageal mucosa. The pathologic changes may progress to include inflammation and ulceration of both the mucosal and muscular layers of the esophagus. Both may lead to permanent scarring with strictures and narrowing of the esophagus.
  - This inflammation may result from multiple insults:
    - Inflammatory:
      - The best example is severe gastroesophageal reflux leading to inflammation, ulceration, scarring, and strictures.
      - "Pill" esophagitis results from pills remaining in contact with the esophageal mucosa. The most common location for pills to get stuck is at the level of the aortic arch, an anatomic narrow point in the esophagus. This may occur with any medication, but the most commonly implicated are nonsteroidal drugs; potassium tablets; antibiotics, such as clindamycin, doxycycline, and tetracycline; and bisphosphonates. Pill esophagitis usually causes dysphagia and odynophagia in addition to chest pain. Risk factors for the development of pill esophagitis include poor pill-taking practices, such as incorrect head position and insufficient water intake with the medication; swallowing of large tablets; and the extremes of age.



Pill-induced esophagitis. (a) Three days after ingestion of an unknown medication, a small and a neighboring, large well-demarcated ulcer with intact surrounding mucosa are noted at mid-esophagus. (b) Scar change of the ulcer after 2 months [Park KS. Infectious and Noninfectious Esophagitis. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg:

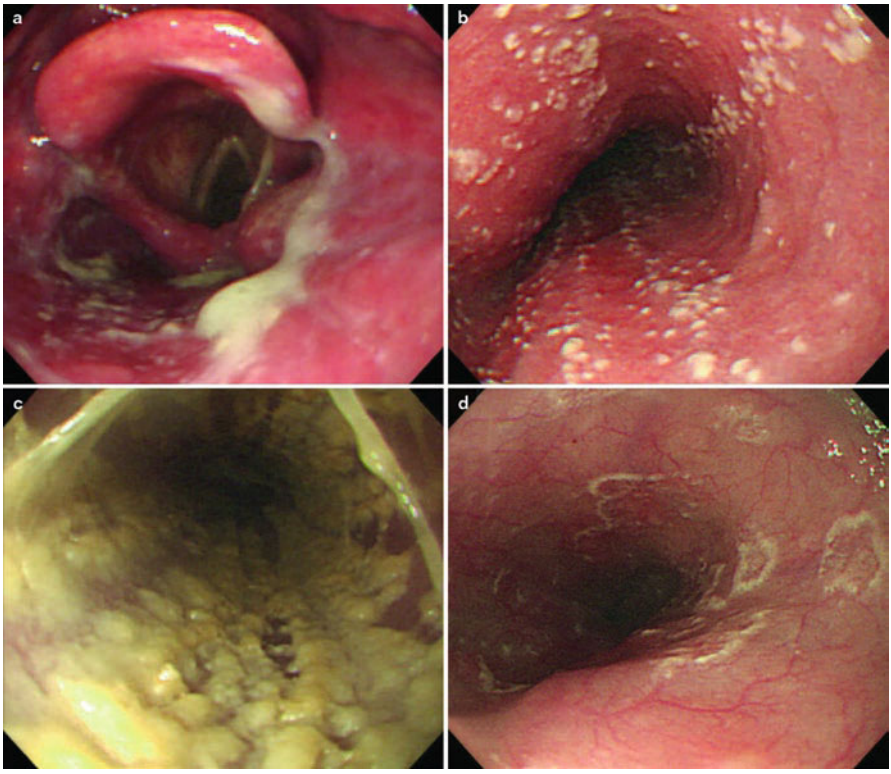
Springer Berlin Heidelberg; 2014 [cited 2015 May 14]. p. 17–30. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_3] *Caption from original*

- Eosinophilic esophagitis. Caused by sequestration and localization of eosinophils within the esophageal mucosa, leading to inflammation and narrowing of the esophageal lumen, with subsequent fibrosis and scarring. Usually causes dysphagia and odynophagia, and is a common cause of esophageal food impaction. Believed to be the result of an allergic response within the esophageal mucosa.



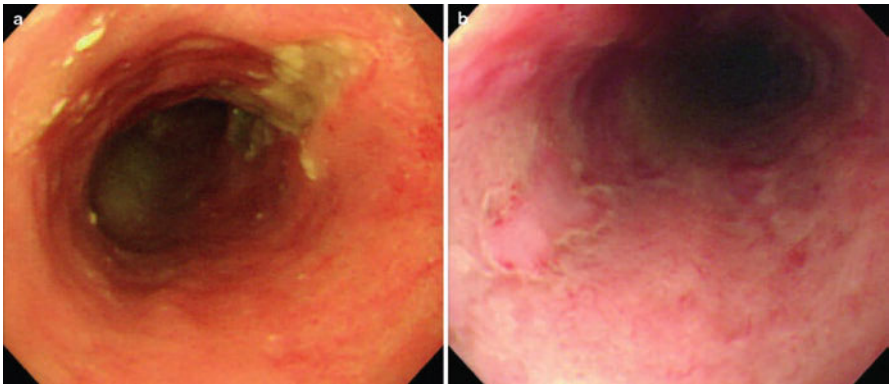
Eosinophilic esophagitis. (a) Linear furrows, (b) multiple rings [Park KS. Infectious and Noninfectious Esophagitis. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 14]. p. 17–30. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_3] *Caption from original*

- Corrosive esophagitis. Occurs after alkali (or less likely, acid) ingestion, with initial inflammation and ulceration and subsequent scarring and stricture formation.
- Radiation esophagitis. A long-term sequela of mantle radiotherapy for cancer.
- Infectious: Infectious esophagitis usually is associated with underlying immunosuppression (such as from HIV, cancer, severe diabetes). Diagnosing infectious esophagitis in an otherwise healthy patient should prompt a search for underlying immunosuppression.
- Candida albicans is the most common cause.

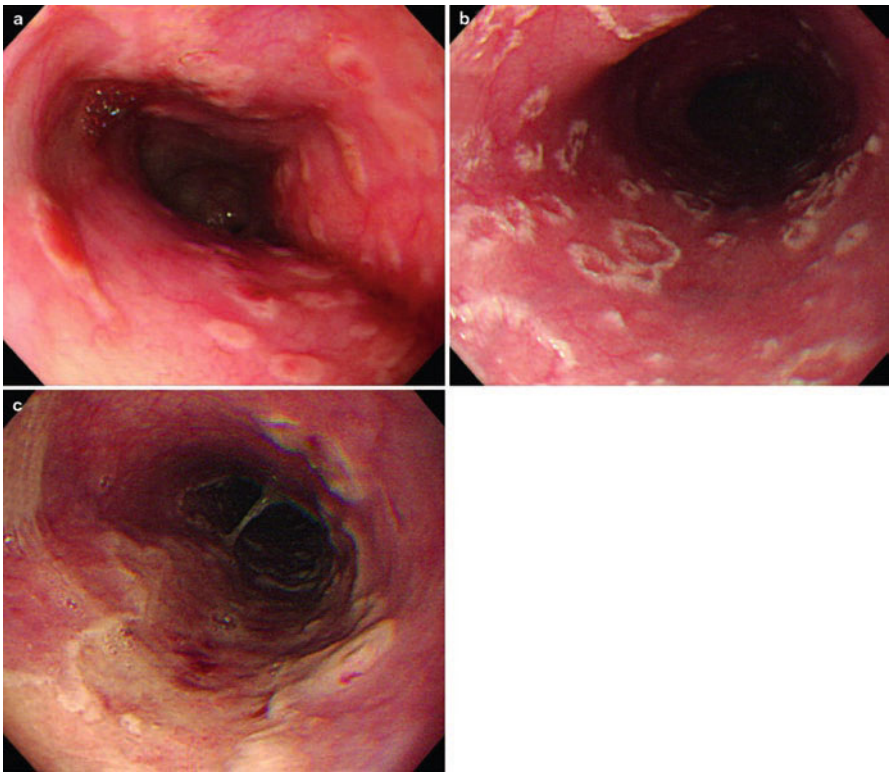


Candida esophagitis. (a) Coexisting pharyngeal lesions help to diagnose Candida esophagitis. (b) Multiple white plaques. (c) Diffuse membranous white material. (d) Atypical lesions which resemble herpetic esophagitis [Park KS. Infectious and Noninfectious Esophagitis. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 14]. p. 17–30. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_3] *Caption from original*

- Viral causes include cytomegalovirus and herpes simplex virus.



CMV esophagitis. (a) Longitudinal deep ulcer, (b) multiple shallow ulcers mimicking herpes esophagitis [Park KS. Infectious and Noninfectious Esophagitis. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 14]. p. 17–30. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_3] *Caption from original*



Herpes esophagitis. (a) Multiple vesicular lesions, (b) shallow ulcers with prominent demarcation, (c) large ulcer formation by confluence of small ulcers [Park KS. Infectious and Noninfectious Esophagitis. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical Gastrointestinal Endoscopy [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 May 14]. p. 17–30. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_3] *Caption from original*

Presentation

Typical/"Classic"

- Chest pain, often described as burning. There is no historical or examination feature sensitive or specific enough to exclude cardiac causes of chest pain; therefore, a cardiac workup should be performed before or during evaluation for esophagitis.

- Certain symptoms may be helpful if present:
  - Odynophagia: pain with swallowing or pain exacerbated by swallowing
  - Dysphagia: difficulty swallowing. It may be described as a sensation of food or liquid getting stuck.

Atypical

- Any complaint of chest pain may be caused by esophagitis, so there is no typical or atypical presentation.

Primary Differential Considerations

Early in the evaluation of patients with symptoms of esophagitis, consider the following important differential diagnoses:

- Acute coronary syndrome
- Aortic dissection
- Acute pericarditis
- Pneumothorax
- Pleurisy
- Pneumonia
- Esophageal rupture
- Peptic ulcer disease

History and Physical Exam

Findings That Confirm Diagnosis

- The only findings that can completely confirm the diagnosis are typical findings on esophagogastroduodenoscopy (EGD/endoscopy).

Factors That Suggest Diagnosis

- Chest pain associated with pain with swallowing (odynophagia) and/or difficulties swallowing (dysphagia) strongly suggest the diagnosis.

Factors That Exclude Diagnosis

- A normal EGD excludes esophagitis.

Ancillary Studies

Laboratory

- No laboratory studies are helpful in suggesting or confirming the diagnosis of esophagitis. Laboratory studies may help exclude the diagnosis, e.g., positive cardiac biomarkers in a patient with chest pain. Remember that esophagitis may coexist with other diagnoses.

Imaging

- Plain chest x-ray usually is unremarkable.
- CT of the chest may demonstrate esophageal wall thickening, but this is often an incidental finding during studies performed for other reasons, such as evaluation for pulmonary embolism. It also may suggest the diagnosis, but it does not confirm the diagnosis.

Special Populations

Age

- Esophagitis may occur at any age. Certain diagnoses within the category may have age predilections, such as eosinophilic esophagitis, which is more likely in children and young adults.
- Clinical manifestations in children include:
  - Emesis
  - Feeding problems
  - Dysphagia
  - Abdominal pain
  - Food impaction
- In the pediatric population, there is a definite association with other forms of allergic disease (asthma, allergic rhinitis, urticaria, eczema)

Co-morbidities

- Common co-morbidities include obesity, diabetes, immunosuppression, alcohol abuse, and cigarette smoking.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is important.
- However, it is more important to make sure the cause of chest pain is not a more immediately life-threatening condition.

Mimics

- The entire constellation of diagnoses underlying chest pain syndrome can mimic the pain and overall presentation of esophagitis.
- Esophagitis is more often considered a "mimic" of cardiac causes of chest pain.

Time-Dependent Interventions

- Check the ECG immediately for signs of acute myocardial ischemia. Remember that a normal ECG does not exclude acute coronary syndrome!
- If the patient has signs of GI bleeding, initiate stabilization and resuscitation immediately.

Overall Principles of Treatment

- Treatment depends on identifying the underlying cause of the esophagitis.
- Inflammatory causes of esophagitis often improve with acid suppression, usually from proton-pump inhibitors.
- Infectious causes need to be treated with the appropriate anti-infective agents.
- Eosinophilic esophagitis may be treated with elimination diets for removal of putative causative agents or with topical or systemic corticosteroids.
- The use of acid suppression with proton-pump inhibitors is prescribed nearly universally for all causes of esophagitis.

- If the esophagus becomes scarred or develops strictures, endoscopically guided esophageal dilatation may be necessary.

Disease Course

- Most cases of esophagitis from almost any cause will improve within several weeks of initiation of appropriate treatment.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Esophagitis"[Mesh] OR "Esophagitis"

Chapter 29
Foreign Body Aspiration

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Foreign Body Aspiration (esophageal/tracheal)

Incidence/Epidemiology

- Swallowed and inhaled foreign bodies both may cause chest pain with or without shortness of breath.
- Both swallowed and inhaled foreign bodies are more common among young children, but esophageal food bolus impaction may occur at any age and is more common in the elderly, often presenting as chest pain.
- Foreign body aspiration may be life threatening at any age; cases in which food is the aspirated agent are referred to as "café coronary."

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_29

Symptoms can include choking, coughing, wheezing, upper airway obstructive breathing, and if severe, cyanosis.
The foreign body can be lodged in the esophagus and compress the trachea, it can lie in the trachea itself, or it can lie in a mainstem bronchus.
The foreign body may be of various materials, including chunks of food, pieces of toys, coins, and—worst of all—a peanut, which may increase in size as it absorbs secretions.
Bronchoscopy usually is performed to remove the foreign body. The anesthetic plan must be tailored to the type of foreign body and the amount of the patient's distress.
Anesthetic induction: An inhalational technique may need to be performed to avoid muscle relaxation and prevent the foreign body from changing position with relaxation. The dilemma is inducing the patient having a full stomach with an inhalational technique. If intravenous access has been obtained, rapid sequence induction may be considered; however, avoid cricoid pressure, which may compress the object and cause tracheal or esophageal lacerations.

Features associated with aspiration of a foreign body. This is a common emergency situation in a child with a foreign body that becomes lodged in either the trachea or the esophagus that can result in airway compromise. The patients undergo bronchoscopy to retrieve the foreign body and are generally kept spontaneously ventilating in order to remove the object. [Rasmussen G, Deshpande J. Pediatric anesthesia. In: Muravchick S, editor. Subspecialty care. Philadelphia: Current Medicine; 1998. 236 p. (Miller RD editor, Atlas of anesthesia; vol. 5). ISBN: 0-443-07905-6] *Caption from original*

	Case	Sex		Percentage (%)
		Male	Female	
Age (years)				
32–39	9	6	3	7.44
40–49	11	7	4	9.09
50–59	49	34	15	40.50
60–69	47	31	16	38.84
Over 70	5	4	1	4.13
Duration of the foreign body impacted in the esophagus				
Within 3 days	17	10	7	14.05
3–5 days	42	31	11	34.71
5–7 days	54	35	19	44.63
7–14 days	8	6	2	6.61
Clinical manifestations				
Dysphagia	121	82	39	100
Odynophagia	121	82	39	100
Polysialia	121	82	39	100
Hematemesis	13	8	5	10.74
Dyspnea	24	11	13	19.83
High fever	45	14	31	37.19
Aerodermectasia	68	39	29	56.20
Cervical abscess	67	43	24	55.37
Cervical and mediastinum abscess	21	16	5	17.36
Mediastinitis	15	10	5	12.40
Mediastinum abscess	17	12	5	14.05
Hemopneumothorax[a]	6	6	0	4.96
Location of the foreign body				
Entrance of the esophagus	67	44	23	55.37
The junction of the cervical esophagus and thoracic esophagus	21	14	7	17.36
The region where the aortic arch is across the esophagus	29	21	8	23.97
The region where the left bronchus is across the anterior wall of the esophagus	4	3	1	3.30
Types of foreign bodies				
Pork bone	6	4	2	4.96[b]
Fishbone	53	34	19	43.80[b]
Chicken bone	21	11	10	17.36[b]
Duck bone	9	6	3	7.44[b]
Dental prosthesis	21	17	4	17.36[b]
Metal articles	7	6	1	5.79[b]
Glass	1	1	0	0.82[b]
Blade	3	3	0	2.48[b]
Total	121	82	39	

[a] Means the patients are with hemopneumothorax and mediastinum abscess simultaneously

[b] Stands for the percentage of one kind of the foreign body

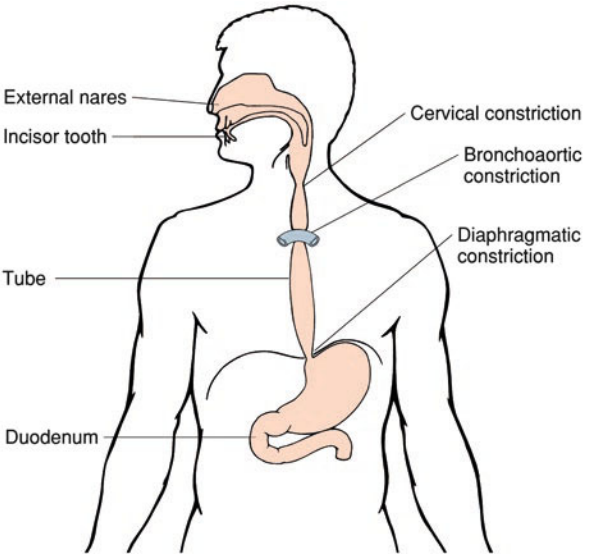
Foreign bodies, sex, age and clinical manifestations of 121 cases with dangerous esophageal foreign bodies. [Peng A, Li Y, Xiao Z, Wu W. Study of clinical treatment of esophageal foreign body-induced esophageal perforation with lethal complications. Eur Arch Otorhinolaryngol. 2012 Sep;269(9):2027–36.] *Caption from original*

Differential Diagnosis

- The differential diagnosis is limited in cases of acute presentation, because the patient usually reports what has happened. Large foreign body aspiration in an unresponsive patient may be identified during direct laryngoscopy for rescue endotracheal intubation. Patients with an esophageal food bolus impaction may present with lower chest pain and retching, suggesting an atypical acute coronary syndrome.

Pathophysiology and Etiology

- Foreign body aspiration in patients above toddler age generally is accidental. Symptoms are driven by the size of the foreign body, which in turn determines the location of "lodging."
- Esophageal food bolus impaction generally is associated with inadequate chewing and often occurs in the setting of concomitant alcohol consumption.



Esophageal foreign bodies. In the last several decades, endoscopy has become the method of choice in the management of esophageal foreign bodies, although a trial of sublingual nitroglycerin and intravenous glucagon is warranted. At times this will allow the offending bolus to pass. The most common location of the impaction is the distal esophagus at the level of the diaphragm; however, compressions at the level of the cricopharyngeus, aortic arch, and left main-stem bronchus may also be the site of impaction. It is also helpful to identify foreign bodies as sharp or dull, pointed or blunt, and toxic or nontoxic (eg, batteries). Also, food-related impactions should be distinguished. If the foreign body is known, in vitro simulation may be helpful in choosing the right accessory for use during the procedure. [Bozymski EM, Kenney CM. Esophageal therapeutics. In: Orlando RC, editor. Atlas of esophageal diseases. 2nd ed. Philadelphia: Current Medicine; 2002. 248 p. ISBN: 1-57340-181-1] *Caption from original*

Type of foreign body	
Coin	553 (84 %)
Penny	317
Nickel	29
Dime	32
Quarter	94
Other/unknown	81
Impacted food	42 (6 %)
Others	60 (9 %)
Unknown	2 (<1 %)
Location of FB	
Proximal 1/3	510 (78 %)
Middle 1/3	64 (10 %)
Distal 1/3	75 (11 %)
Stomach/bowel	8 (1 %)

Type and location of esophageal foreign bodies. [Russell R, Lucas A, Johnson J, Yannam G, Griffin R, Beierle E, Anderson S, Chen M, Harmon C. Extraction of esophageal foreign bodies in children: rigid versus flexible endoscopy. Pediatr Surg Int. 2014 Apr;30(4):417–22.] *Caption from original*

Presentation

Typical/"Classic"

- Aspirated foreign bodies typically present as choking, coughing, and/or shortness of breath

  - Dyspnea
  - Audible wheezes may be present.
  - Large proximal aspirated foreign bodies may present as cardiac arrest.
- Esophageal foreign bodies typically present as lower chest pain and an inability to swallow; the patient often is spitting out saliva.
  - There often is a history of achalasia or previous similar episodes.

Atypical

- Especially in children, no reliable history may be available, making the etiology of typical symptoms more obscure.
- Smaller aspirated foreign bodies may not cause symptoms until days or week later, when secondary inflammation or infection has developed.

Primary Differential Considerations

- For aspirated foreign bodies, consider:
  - Epiglottitis
  - Retropharyngeal or peritonsillar abscess
  - Caustic ingestion
  - Anxiety
- For esophageal foreign bodies, consider:
  - Esophageal injury
  - Anxiety (“globus hystericus”)
  - Caustic ingestion

History and Physical Exam

- Except in toddlers, the history usually is very helpful.
- On physical exam, assessing patency of the airway and adequacy of oxygenation is the priority.

Findings That Confirm Diagnosis

- Visualization of the foreign body
- History of aspiration and subsequent coughing/gagging/choking

- History of swallowing incompletely chewed food and subsequent inability to handle oral secretions

Factors That Suggest Diagnosis

- Suggestive history

Factors That Exclude Diagnosis

- Clinically difficult to exclude, even with few symptoms; passage of time with diminishing symptoms is helpful.

Ancillary Studies

Laboratory

- No diagnostic laboratory findings

Electrocardiography

- Useful only if myocardial ischemia is a diagnostic consideration

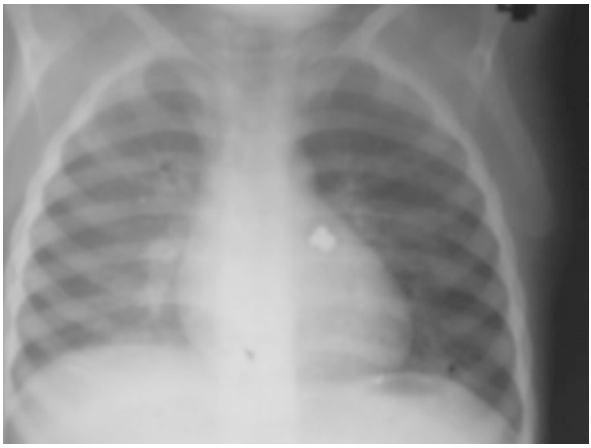
Imaging

- Aspirated foreign bodies:
  - Plain chest radiography may be helpful in patients with bronchial foreign bodies, when asymmetric lung volumes may be appreciated.
  - Chest CT may be helpful in localizing more distal foreign bodies.

Radiological findings	No of cases; *n* (%)
Obstructive emphysema	15 (20.5%)
Collapse	34 (41.65%)
Normal	20 (24.3%)
Pneumonitis	6 (7.3%)
Consolidation	4 (5%)
Foreign body visualised	2 (2.43%)
Abscess	1 (1.25%)

Radiographic findings in patients with airway foreign body. [Jaswal A, Jana U, Maiti PK. Tracheo-bronchial foreign bodies: a retrospective study and review of literature. Indian J Otolaryngol Head Neck Surg. 2014 Jan;66(S1):156–60.] *Caption from original*

Foreign body in right main bronchus. [Tsikoudas A, Sheikh S. An interesting case of a wandering foreign body in the tracheobronchial tree. Eur Arch Otorhinolaryngol. 2005 May;262(5):426–7.] *Caption from original*



Chest radiograph showing foreign body in left main bronchus with obstructive emphysema of left lung. [Jaswal A, Jana U, Maiti PK. Tracheo-bronchial foreign bodies: a retrospective study and review of literature. Indian J Otolaryngol Head Neck Surg. 2014 Jan;66(S1):156–60.] *Caption from original*

- Esophageal foreign bodies:
  - Plain chest radiography is not useful for food bolus impactions.
  - Barium swallow may be challenging for the patient but will be diagnostic.
  - More proximal foreign bodies may be visualized on plain radiography.

Esophageal foreign bodies (FBs). Ingested FBs may become impacted at any level but are typically held up at the three sites of natural narrowing: the cricopharyngeus muscle, the level of the aortic arc, and the gastroesophageal junction. The most common esophageal FBs are coins. They usually lodge at the cricopharyngeus, resulting in marked dysphagia even for liquids. Anteroposterior (from base of skull

to pelvic outlet) and lateral radiographs are recommended if a coin ingestion is suspected because the presence of multiple coins may not be appreciated on a single anteroposterior view. Sharp FBs are particularly treacherous because they may perforate the esophagus, resulting in mediastinitis or major vessel injury and life-threatening hemorrhage. This radiograph shows a metallic foreign body lodged in the midesophagus of a 4-year-old boy who had stopped eating solid foods 2 months previously, precisely at the time his older brother's toy tractor steering wheel disappeared. Removal at esophagoscopy was complicated because the foreign body was deeply embedded in the esophageal wall. [Papsin BC, James A, Friedberg J, Forte V, Crysdale WS. Otolaryngology—head and neck surgery. In: Laxer RM, editor. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. p. 231-250.] *Caption from original*

Other Studies

- Endoscopy often is indicated.

Special Populations

Age

- Aspiration of foreign bodies may occur at any age but is most common in toddlers.

Dysphagia
Sedative or hypnotic drug use
Poor dentition
Altered Sensorium
Chronic aspiration
Parkinson's disease
Primary neurologic disorders with impairment of swallowing or mental status
Trauma with loss of consciousness
Seizure
General anesthesia
Alcohol intoxication
Polypharmacy and difficulty swallowing large pills
Eating while lying supine or just before falling asleep

Risk factors for foreign body aspiration in elderly patients. [Folch E, Majid A. Foreign body aspiration in the elderly patient. Curr Geriatr Rep. 2015 Jun;4(2):192–201.] *Caption from original*

- Esophageal food bolus impaction is more common in older patients.
- Commonly aspirated FBs in children include nuts, seeds, popcorn, food particles, hardware, and fragments of playthings.
- Coins are aspirated more commonly by older children.
- Fatal aspirations usually involve toy balloons or similar items.
- In one study, common anatomic sites in childhood aspiration included the larynx (3 %), trachea/carina (13 %), right hemithorax (60 %), left hemithorax (23 %), and bilateral bronchial tree (2 %).
- In the pediatric patient, the diagnosis often is delayed. Children may present with wheezing, dyspnea, recurrent pneumonia, or chronic cough. Aggressive investigations beyond plain radiography, especially bronchoscopy, are warranted in patients with recurrent or otherwise unexplained symptoms.

Co-morbidities

- Achalasia

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Evaluation for satisfactory airway
- Evaluation for satisfactory oxygenation

Mimics

- Asthma

Time-Dependent Interventions

- Immediate evaluation for adequate airway and gas exchange

Overall Principles of Treatment

- Identify and remove foreign body.
- In cases of esophageal food bolus impaction, consider using glucagon before endoscopy; the use of meat tenderizer, advocated in the past, no longer is recommended.

Disease Course

- The course is determined by the acuity of presentation and underlying etiology, as well as the rapidity with which the foreign body is removed.
- The vast majority of foreign body cases are not life threatening.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Review

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Case Study

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Foreign Bodies"[Mesh] OR "Foreign bodies"

Chapter 30
Gastroesophageal Reflux Disease

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Gastroesophageal Reflux Disease

- GERD, Reflux, Indigestion, Heartburn, Pyrosis

Incidence/Epidemiology

- Six to 7 % of the US population reports daily, persistent heartburn.
- Twenty to 40 % report monthly heartburn.
- GERD is responsible for a significant amount of morbidity and has substantial economic consequences.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_30

Differential Diagnosis

- GERD may present with the acute onset of chest pain similar to acute cardiac pain, so acute myocardial infarction (MI) and the other causes of acute chest pain have to be considered in the differential diagnosis.
- The presentation of GERD also may be similar to that of esophagitis, peptic ulcer disease (PUD), biliary disease, pancreatitis, hepatitis, and gastrointestinal motility disorders.

Pathophysiology and Etiology

- Reflux of gastric contents into the esophagus occurs several times a day in most people as a normal physiologic event. It becomes abnormal, and considered GERD, when it is associated with symptoms or pathologic changes within the gastrointestinal or respiratory tracts. The Montreal Classification defines GERD as "A condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications."
- The lower esophageal sphincter (LES) is the main physiologic barrier to reflux.
- When reflux does occur, both mechanical (gravity) and physiologic (peristalsis, saliva, esophageal secretions) forces can help push gastric contents back into the stomach.
- GERD may be caused or worsened by anything that reduces LES pressure, decreases esophageal motility or gastric emptying time, or directly irritates the esophageal mucosa, as well as by mechanical means.
- Factors that may reduce LES pressure include drugs (anticholinergic agents, benzodiazepines, calcium-channel blockers, progesterone), foods (chocolate, caffeine, high-fat foods, peppermint, nitrates), nicotine, and alcohol.
- Conditions that decrease esophageal motility include achalasia, diabetes, and scleroderma.
- Factors and conditions that may decrease gastric emptying time include anticholinergic medications, diabetic gastroparesis, and gastric outlet obstruction.
- Substances that may act as direct irritants to the gastric mucosa include caffeine, citrus products, and tomato-based products.
- Mechanical factors include stooping, bending forward, the Valsalva maneuver, and the supine position.
- GERD is much more common in obese patients.
- Hiatal hernia (prolapse of a portion of the stomach through the diaphragmatic esophageal hiatus) also is considered a risk factor for GERD.

Presentation

Typical/"Classic"

- The most common complaint is heartburn, a burning sensation from the subxyphoid region radiating into the neck or pharynx.
- Typically, symptoms worsen after large meals or with recumbency.
- Symptoms usually are relieved with antacids; however, this effect is not pathognomonic and does not reliably exclude cardiac causes of pain.
- Other common presenting complaints include regurgitation and nausea, but usually these are associated with heartburn.
- An uncommon but somewhat specific symptom of GERD is water brash, a vagally mediated increase in saliva production often perceived by patients as "foaming at the mouth."
- GERD also may cause extraesophageal symptoms, including asthma (or worsening asthma) from reflux associated with aspiration, chronic cough, hoarse voice, recurrent laryngitis or sore throat, frequent throat clearing, and dental problems.

Atypical

- It is important to remember that GERD symptoms can mimic those of acute MI. Patients may describe the acute onset of chest pressure, dull chest pain, or squeezing. The radiation pattern can mimic that of acute MI and radiate to the back, jaw, or arm.
- Dysphagia (difficulty swallowing) and odynophagia (painful swallowing) are uncommon symptoms for GERD and should prompt further evaluation for other causes.
- Globus is a perception of fullness or a lump in the throat, unrelated to swallowing. It is not a usual symptom of GERD, and its presence should prompt a search for other causes. It often is thought to be related to emotional stress or to have a functional basis.

Primary Differential Considerations

- Prompt consideration also should be given to the possible diagnosis of:
  - Acute coronary syndrome
  - Esophageal spasm
  - Biliary colic
  - Gastritis
  - Hiatal hernia

History and Physical Exam

Findings That Confirm Diagnosis

- Because the diagnosis of GERD can be applied only for symptoms, there are no tests that are confirmatory. A classic history of heartburn, worse after large meals, and recumbency relieved by antacids is enough to make a presumptive diagnosis of GERD.
- The physical exam is often unremarkable and not helpful in making the diagnosis.

Factors That Suggest Diagnosis

- A classic presentation as above suggests the diagnosis.
- The diagnosis of GERD should be kept within the differential when evaluating a patient for new-onset or worsening asthma not explained by other factors, as a cause of chronic cough or laryngitis, and for patients with unexplained hoarseness.

Factors That Exclude Diagnosis

- GERD may exist even in the absence of symptoms; there is no factor that excludes the diagnosis.
- Normal endoscopy does not exclude the diagnosis of GERD.

Ancillary Studies

Laboratory

- Lab tests are unhelpful in the diagnosis of GERD and often are used only to evaluate for other causes of the patient's symptoms.

Imaging

- Imaging usually is not helpful or indicated for the diagnosis of GERD.
- Patients may need imaging or endoscopy to exclude other diagnoses.

- Patients with symptoms such as dysphagia, odynophagia, weight loss, or other constitutional symptoms may need endoscopy to exclude malignancy and other serious causes of their symptoms.

Special Populations

Age

- GERD occurs in all age groups, including infants and children.
- In children, the term *gastroesophogeal reflux disease* applies when the reflux results in untoward complications, such as esophagitis, respiratory events, or growth failure.
  - There is some evidence that severe reflux in infancy predisposes children to GERD later in life.
- GERD and asthma often overlap in children and adolescents, but current data do not suggest that control of one has a significant clinical impact on the other.

Co-morbidities

- GERD may coexist with any other condition.
- Conditions that may make GERD more likely include obesity, diabetes, achalasia, motility disorders, and hiatal hernia.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to consider the more immediately life-threatening causes of chest and abdominal pain.

Mimics

- GERD is a classic mimic of acute MI.
- GERD also can mimic PUD, all the causes of esophagitis, biliary disease, pancreatitis, and esophageal and gastric motility disorders.

Time-Dependent Interventions

- The only time-dependent intervention is to exclude more serious causes of pain.

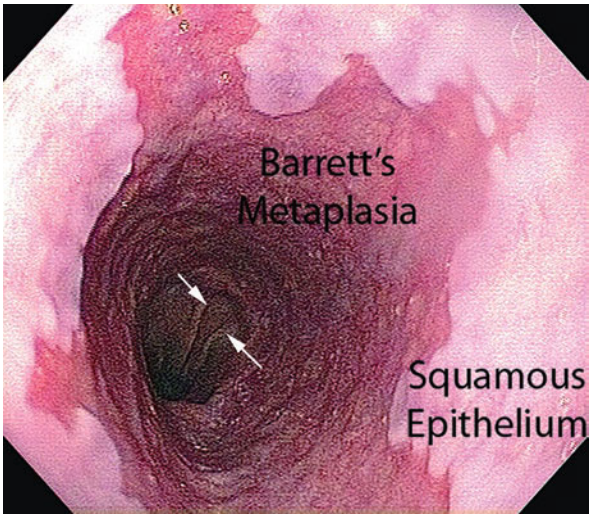
Overall Principles of Treatment

- Patients with a suggestive history, as well as those in whom more serious causes of the symptoms have been excluded, often are treated empirically with acid suppression and lifestyle changes.
- Lifestyle changes include decreasing or stopping known exacerbating substances, weight loss, and elevating the head of the bed.
- Acid suppression usually is attempted with either H2-blockers or proton-pump inhibitors (PPIs). H2-blockers have been shown to promote esophageal healing in mild esophagitis. PPIs suppress acid more effectively than H2-blockers and are more efficacious both in relieving symptoms and in promoting esophageal mucosal healing. However, PPIs are much more expensive than H2-blockers.
- Anywhere from 40–90 % of patients will report symptom improvement from PPIs.
- However, symptom improvement is not a diagnostic criterion for GERD.
- Patients whose symptoms are refractory to treatment may need further evaluation, although this group of patients usually constitutes a small minority. This is especially true for patients with worrisome symptoms such as dysphagia and odynophagia.
- Further evaluation may include esophagogastroduodenoscopy (EGD), esophageal manometry, and ambulatory pH monitoring.
- It is worth remembering that EGD may be normal in GERD, and this study usually is performed to exclude other diagnoses.
- Esophageal manometry and ambulatory pH monitoring are invasive tests; patients should be evaluated by a specialist before undergoing these studies.

Disease Course

- GERD is a chronic condition. It often requires long-term medical therapy for control.
- A minority of patients have long-term relief from lifestyle changes.
- GERD may be associated with several long-term complications, many of them serious.

- GERD may be associated with chronic esophageal mucosal changes, starting with thinning and inflammation and then scarring. These events may lead to esophageal strictures, which may cause dysphagia, odynophagia, food impactions, etc.
- The most serious complication of GERD is damage to the normal esophageal stratified squamous epithelium by acid, leading to replacement with metaplastic columnar epithelium. This condition, known as *Barrett's esophagus*, is associated with a higher incidence of esophageal adenocarcinoma. Currently, it is believed that 1–10 % of people with Barrett's esophagus will develop esophageal adenocarcinoma. Patients with Barrett's esophagus require endoscopic surveillance with biopsies to look for cancerous changes.



Endoscopic photograph of long-segment Barrett's esophagus. The arrows mark the proximal extent of the gastric folds, which is the location of the gastroesophageal junction. Note that Barrett's metaplasia extends well above the GEJ to line the distal esophagus. The reddish-pink (salmon) color and velvet-like texture of Barrett's epithelium contrasts sharply with the pale and glossy appearance of the esophageal squamous epithelium. [Spechler SJ. Barrett's Esophagus. In: Shaker R, Belafsky PC, Postma GN, Easterling C, editors. Principles of Deglutition [Internet]. New York, NY: Springer New York; 2013 [cited 2015 May 14]. p. 723–38. Available from: http://link.springer.com/10.1007/978-1-4614-3794-9_49] *Caption from original*

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Gastroesophageal Reflux"[Mesh] OR "Gastroesophageal Reflex" OR "GERD"

Chapter 31
Goiter

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Goiter

Incidence/Epidemiology

- Dietary deficiency of iodine is the most common cause of goiter worldwide. There are estimated to be about 200 million cases of iodine-deficient goiter worldwide.
- In the United States (where significant dietary deficiency of iodine only occurs in new immigrants), the most common cause of goiter is multinodular goiter.
- The female: male ratio is 4:1.
- Goiter is distributed equally among races.
- The incidence of goiter increases with age.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_31

Differential Diagnosis

- Goiters often present as an anterior neck mass on physical examination. The differential diagnosis of anterior neck masses is broad, but generally falls into several categories:
  - Inflammatory masses (such as lymphadenopathy)
  - Neoplastic masses (both primary and metastatic)
  - Congenital (vascular anomalies, thyroglossal duct cysts)
- Some goiters extend into the thoracic cavity (substernal goiters) and present as mediastinal masses (most often anterior mediastinal masses) found on an imaging study (CXR, CT chest) performed for other reasons. The most common causes of a mediastinal mass (in decreasing order of frequency) are:
  - Substernal goiter
  - Neurogenic tumors
  - Thymoma
  - Pericardial or bronchogenic cysts
  - Lymphoma
  - Teratoma

Pathophysiology and Etiology

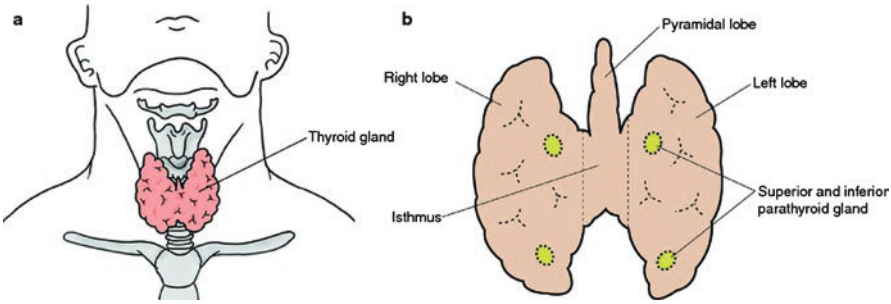
- A goiter refers to an abnormally enlarged thyroid gland.
- Goiters can be classified as diffuse or nodular, toxic or non-toxic, and either benign or malignant. A toxic goiter overproduces thyroid hormone.
- The most common pathophysiologic reason for goiter formation is increased secretion of thyroid stimulating hormone (TSH) by the anterior pituitary gland. This occurs as the thyroid becomes unable to synthesize adequate amounts of T3 and T4. This can have multiple causes, such as iodine deficiency and thyroid cell inflammation and destruction from autoimmune thyroiditis (Hashimoto's Thyroiditis).
- Goiters can also form when TSH secretion is normal. This can result from the action of multiple growth factors acting on thyroid cells over a long period of time, usually in the presence of a genetic predisposition to goiter formation. This leads to nontoxic, multinodular goiters.
- Patients with Graves' disease produce TSH receptor antibodies. These autoantibodies stimulate the TSH receptor and lead to thyroid growth and overproduction of thyroid hormones.
- As stated in the Incidence/Epidemiology section, iodine deficiency is the leading cause of goiter worldwide. However, iodine deficiency is mostly unheard of in the United States and Western Europe. In these areas iodine deficiency is usually only found among recent immigrants.

- In most Western countries, multinodular goiter, Hashimoto's disease (autoimmune thyroiditis), and Graves' disease are the most common causes of goiter.
- Less common causes of goiter include thyroiditis (of any cause), thyroid tumors, and infiltrative diseases of the thyroid.

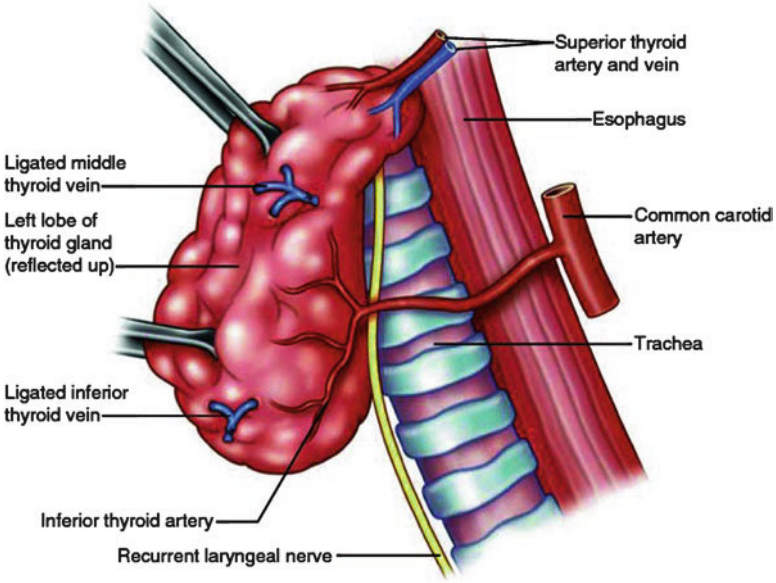
Presentation

Typical/"Classic"

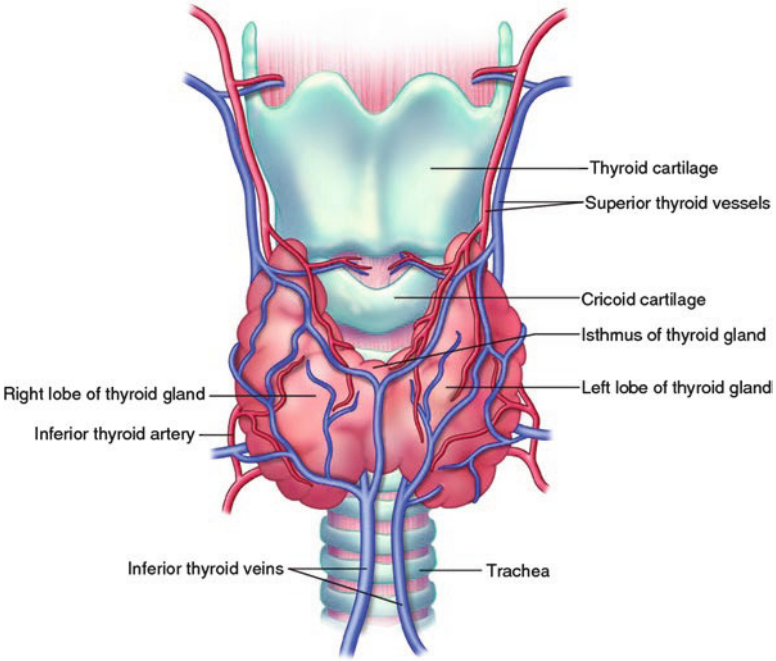
- It is important to review the anatomy of the thyroid gland, as the presenting symptoms of goiter can be related to compression of neighboring structures.
  - The thyroid sits just below the larynx; it has 2 lobes connected by a small bridge of thyroid tissue termed the isthmus. The thyroid partially encircles the anterolateral aspects of the trachea. It is bordered posteriorly by the trachea and esophagus, and laterally by the carotid sheaths. Anteriorly, the thyroid is covered only by the thin strap muscles anterolaterally, and then connective tissue, subcutaneous tissue, and skin. As a result of this minimal anterior anatomic coverage, the thyroid mostly enlarges outward and does not usually compress any lateral or posterior structures.



Position and anatomy of the thyroid gland. (**a**) Normal position of the thyroid gland, (**b**) anatomy of the thyroid gland. [Youn Y-K, Lee KE, Choi JY. Surgical Anatomy of the Thyroid Gland. Color Atlas of Thyroid Surgery [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 Dec 4]. p. 1–10. Available from: http://link.springer.com/10.1007/978-3-642-37262-9_1] *Caption from original*



Surgical anatomy during thyroidectomy: trachea, esophagus, common carotid artery, superior thyroid artery, superior thyroid vein, middle thyroid vein, inferior thyroid artery, inferior thyroid vein, and recurrent laryngeal nerve [Sarpel U. Thyroidectomy. Surgery [Internet]. New York, NY: Springer New York; 2014 [cited 2015 Dec 4]. p. 195–205. Available from: http://link.springer.com/10.1007/978-1-4939-0903-2_18] *Caption from original*



Thyroid gland anatomy and blood supply [Porter S, Schwartz A, DeMaria S, Genden EM. Thyroid, Parathyroid, and Parotid Surgery. In: Levine AI, Govindaraj S, DeMaria, S, editors. Anesthesiology and Otolaryngology [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Dec 4]. p. 217–40. Available from: http://link.springer.com/10.1007/978-1-4614-4184-7_14] *Caption from original*

- In goiters that grow asymmetrically, however, enlargement of one lobe is predominant. Asymmetrical goiters can also enlarge circumferentially around the trachea, which can cause compression of the jugular veins, tracheal narrowing, and/or impingement of the esophagus.
- Goiters can also extend caudally into the thoracic inlet. The thoracic inlet is an oval-shaped area about 5 cm (anteroposteriorly) by 10 cm (laterally). It is bordered anteriorly by the sternum, laterally by the first ribs, and posteriorly by the first thoracic vertebra. Structures within the thoracic include the trachea, esophagus, and major vascular structures. As the borders of the thoracic inlet are all bony, there is no room for expansion. If a goiter extends caudad through the thoracic inlet, the goiter is referred to as substernal (or retrosternal). Substernal goiters are more likely to cause compression than purely cervical goiters. Substernal goiters are thought to account for anywhere from 2–20 % of all goiters.
- Most goiters grow very slowly, do not cause thyroid dysfunction, and are asymptomatic. They are usually found on routine physical examination, and on imaging studies being performed for other reasons.
- Most goiters are painless.
- Once a goiter is detected, an evaluation should be performed with three major goals:
  - Identify the underlying cause.
  - Evaluate for the presence of obstructive symptoms.
  - Evaluate for the presence of features suspicious for malignancy.

Atypical

- As most goiters are asymptomatic, any symptomatic goiter can be considered the "atypical" presentation of goiter.
- However, goiters may be associated with either hypo- or hyperthyroidism, and patients can present with symptoms of those disorders.
  - Hypothyroidism. A goiter due to long-standing, burned-out Hashimoto's (autoimmune) thyroiditis, and severe iodine deficiency, can be associated with hypothyroidism. Those symptoms are protean and can include profound fatigue, unintentional weight gain, constipation, and cold intolerance.
  - Hyperthyroidism. Some causes of goiter can be associated with hyperfunctioning thyroid tissue (multinodular goiter with autonomously functioning nodules), and Graves' disease. Patients with goiter from these conditions may present with symptoms of hyperthyroidism, such as unexplained weight loss, palpitations, and dyspnea on exertion.

- Goiters may present with symptoms of obstruction or compression of neighboring structures. This occurs most commonly from substernal goiters, but can also occur from large cervical goiters. It can also happen acutely, if there is acute enlargement of the thyroid. This can happen from acute thyroiditis, and also, rarely, from hemorrhage into a thyroid nodule (these situations are also associated with pain in the thyroid.)
    - Exertional dyspnea is the most common compressive symptom from goiters, present in 30–60 % that have compressive symptoms. The development of exertional dyspnea usually indicates that the tracheal diameter has been reduced to less than 8 mm. When the tracheal diameter is reduced below 5 mm, patients will typically have wheezing or stridor.
        - In the early stages, the dyspnea may be intermittent and positional, occurring when lying down, or when reaching or bending (reaching and bending force the thyroid further into the thoracic inlet.)
    - Cough is also a common symptom of obstruction, present in 10–30 % of patients with compressive symptoms.
    - Other, less common obstructive/compressive symptoms include:
        - Dysphagia from extrinsic narrowing of the esophagus.
        - Hoarseness from compression of the recurrent laryngeal nerve with vocal cord paralysis (can be transient or permanent).
        - Venous engorgement of the face, neck, and upper anterior chest from jugular vein compression. This can also lead to thrombosis of the jugular vein.

Photograph of a woman who has a large retrosternal goiter with signs of compression of the venous system. She has engorged superficial veins on her anterior neck

and chest. [Medeiros-Neto G. Chapter 3. In: Surks MI, editor. Volume 1: Thyroid Diseases. 1 edition. Philadelphia: Current Medicine Group; 1999. (Korenman SG, editor. Atlas of Clinical Endocrinology). ISBN: 0-632-04397-0]

- Horner's syndrome. Horner's syndrome results when the goiter causes compression of the cervical sympathetic nerve supply to the eye. Horner's syndrome is rare, and it is especially rarely caused by goiter. The classic triad of Horner's consists of (all on the affected side);
  - Miosis (constricted pupil).
  - Partial ptosis, drooping eyelid from partial paralysis of the superior tarsal muscle.
  - Hemifacial anhidrosis, loss of sweating on the affected half of the face.

Photograph of the eyes showing the left ptosis and miosis of Horner's syndrome. [Mutalib M, Vandervelde C, Varghese A, Sallomi DF, Silva P de, Casey JMH, Howlett DC. Horner's syndrome secondary to asymptomatic pneumothorax in an adolescent. Eur J Pediatr. 2006 Sep 19;166(5):507–8.] *Caption from original*

Primary Differential Considerations

- Patients who present with an exam consistent with goiter should be also be evaluated for other possible diagnoses, including:
  - Other thyroid pathology, such as nodules, thyroiditis, or malignancy
  - Parathyroid cyst or malignancy
  - Lipoma or fibroma
  - Branchial cleft cyst or cystic hygroma

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis can be confirmed by the direct palpation of the goiter. A goiter can usually be distinguished from other anterior neck masses (such as fatty tissue, redundant skin, etc.) as the thyroid will go up and down with swallowing. It is often helpful to ask the patient to swallow a sip of water and just observe the anterior neck for this up and down motion.

Diffuse goiter: Hashimoto's thyroiditis [Gharib H. Chapter 4. In: Surks MI, editor. Volume 1: Thyroid Diseases. 1 edition. Philadelphia: Current Medicine Group; 1999. (Korenman SG, editor. Atlas of Clinical Endocrinology). ISBN: 0-632-04397-0] *Caption adapted from original*

Large goiter in a 57-year-old man. [Giovanella L. Nontoxic Multinodular Goiter. In: Giovanella L, Treglia G, Valcavi R, editors. Atlas of Head and Neck Endocrine Disorders [Internet]. Cham: Springer International Publishing; 2016 [cited 2015 Dec 17]. p. 67–72. Available from: http://link.springer.com/10.1007/978-3-319-22276-9_10] *Caption adapted from original*

- In patients with short and thick necks it can be difficult to adequately palpate the thyroid. These patients may require some form of imaging to be certain a goiter is present.

Factors That Suggest Diagnosis

- Patients with a family history of thyroid disease, recent immigrants from areas of the world considered iodine-deficient, those with a history of head and neck irradiation, or other radiation exposure, should be considered to be at higher risk for goiter.
- All patients in whom the diagnosis is being considered should be directly questioned about the presence of hyper- or hypothyroid symptoms, and for the presence or absence of obstructive symptoms.
- The presence of a substernal thyroid can be suggested by:
  - The inability to directly palpate the inferior thyroid margin on either side.
  - Pemberton's maneuver. In this provocative physical exam test, the examiner holds the patient's arms directly above the head for about one minute. This maneuver forces the thyroid into the thoracic inlet and can exacerbate obstructive symptoms and signs. These include dyspnea, distension of the neck veins, facial flushing or cyanosis, or the inability to swallow.

Pemberton's sign. The presence of a retrosternal goiter causes facial flushing and distended superficial veins. Mild flushing is noted with the arms by the side indicating some baseline obstruction at rest. [Sharma N, Watkinson JC. Retrosternal Goiter.

In: Watkinson JC, Scott-Coombes DM, editors. Tips and Tricks in Endocrine Surgery [Internet]. London: Springer London; 2014 [cited 2015 Dec 17]. p. 161–6. Available from: http://link.springer.com/10.1007/978-1-4471-2146-6_20] *Caption from original*

- Kocher's test. This is a physical examination maneuver that can be used to test for the presence of tracheal compression. In a positive test, compression of the lateral lobes of the thyroid will produce stridor from tracheal compression.

Factors That Exclude Diagnosis

- No historical or physical examination factors can adequately exclude the diagnosis.
- In patients with short and thick necks it can be difficult to adequately palpate the thyroid. These patients may require some form of imaging to be certain a goiter is either present or absent.

Ancillary Studies

Laboratory

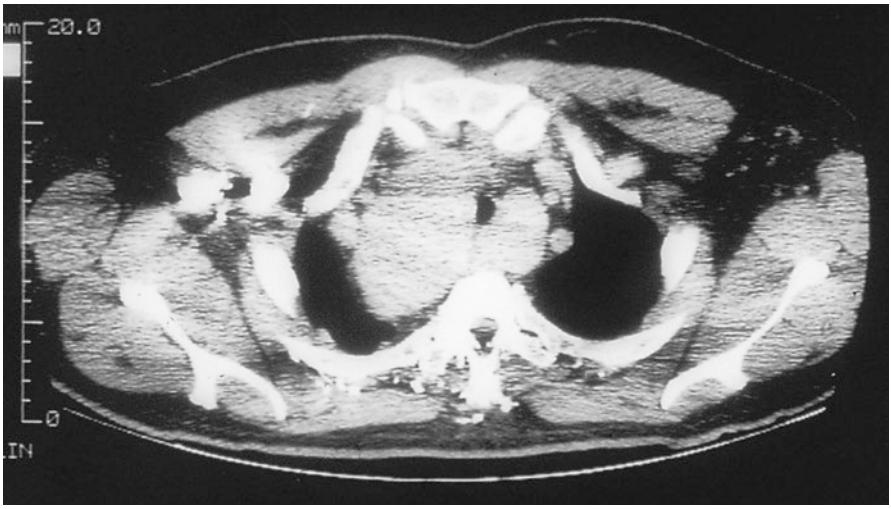
- Thyroid stimulating hormone (TSH). All patients with goiter should have their thyroid function evaluated by measurement of their serum TSH. Serum TSH is often normal (euthyroid), but can also be low (suppressed) with hyperthyroidism, and high with hypothyroidism.
  - If the TSH is low, the serum-free thyroxine (T4) and total triiodothyronine (T3) should also be measured to assess for an autonomously functioning multinodular goiter or Graves' disease.
  - If the TSH is high, free T4 should be measured as part of the evaluation for likely Hashimoto's disease.
- Thyroid peroxidase antibodies (TPO). Patients with Hashimoto's (autoimmune) thyroiditis almost always have elevated TPO. Patients with goiter and hypothyroidism in the United States will most likely have Hashimoto's thyroiditis as the cause of their goiter. This can be confirmed by elevated TPO.
- TSH receptor antibodies. These should be measured when Graves' disease is being considered in the differential diagnosis of the goiter. This is mostly in the setting of a goiter associated with hyperthyroidism.

Imaging

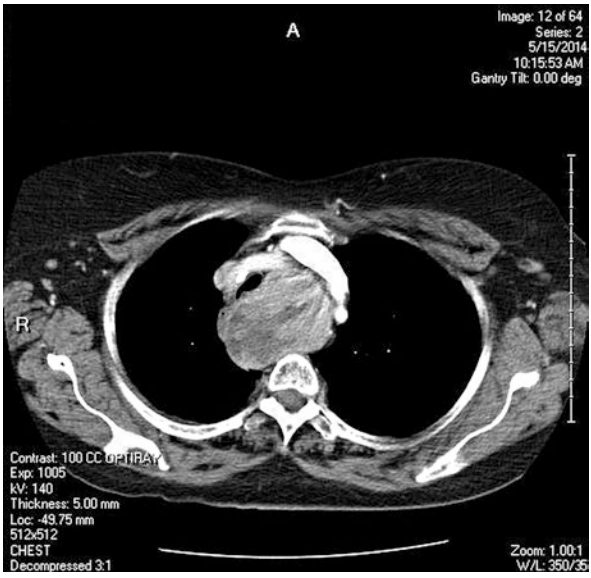
- Thyroid ultrasound should be obtained in most patients with goiter. Thyroid ultrasound can be used to evaluated thyroid size and volume; it can also help assess thyroid function. Thyroid ultrasound can also help in the evaluation of a goiter with features that may be consistent with thyroid cancer. These "worrisome" features include a rapidly growing goiter, asymmetric thyroid enlargement, firm consistency to focal areas of the thyroid, and tenderness to palpation.
- Chest x-ray. Substernal goiters are often found incidentally on a CXR being performed for other reasons. They can appear as a mass that causes tracheal deviation or narrowing, or as superior mediastinal widening, or a mediastinal mass.

Chest radiograph in substernal goiter. There is an anterior mediastinal mass, which was thought to be compatible with a substernal goiter. Note the deviation of the trachea to the left and the presence of a mass in the upper anterior mediastinum. [Singer P. Chapter 12. In: Surks MI, editor. Volume 1: Thyroid Diseases. 1 edition. Philadelphia: Current Medicine Group; 1999. (Korenman SG, editor. Atlas of Clinical Endocrinology). ISBN: 0-632-04397-0] *Caption adapted from original*

- CT scan. Goiters may be incidentally noted on CT scans of the neck and chest being performed for other reasons, but a CT chest can also be an important test in the evaluation of large cervical goiters and suspected substernal goiters. CT can help delineate the extent of the goiter. To fully evaluate the goiter, a CT of the neck and chest may be necessary.



Computed tomography in substernal goiter. Note the predominantly right-sided mass with tissue to the left of the trachea as well. The trachea is not significantly narrowed. [Singer P. Chapter 12. In: Surks MI, editor. Volume 1: Thyroid Diseases. 1 edition. Philadelphia: Current Medicine Group; 1999. (Korenman SG, editor. Atlas of Clinical Endocrinology). ISBN: 0-632-04397-0] *Caption adapted from original*



Substernal goiter Substernal goiter (SG) leading to significant tracheal deviation and compression with symptomatic dyspnea on exertion[Wilhelm SM. Multinodular Goiter. In: Pasieka JL, Lee JA, editors. Surgical Endocrinopathies [Internet]. Cham:

Springer International Publishing; 2015 [cited 2015 Dec 17]. p. 57–63. Available from: http://link.springer.com/10.1007/978-3-319-13662-2_11] *Caption from original*

Image from a computed tomography of a patient with a massive intrathoracic goiter. The goiter is clearly below the aortic arch[Rolighed L, Rønning H, Christiansen P. Sternotomy for substernal goiter: retrospective study of 52 operations. Langenbeck's Archives of Surgery. 2015 Apr;400(3):301–6.] *Caption from original*

- Thyroid radionuclide imaging may be necessary to identify any nodules or areas of autonomous functioning within the thyroid.

Other

- Flow-Volume Loop. Any patient with symptoms or signs consistent with an obstructive goiter should have pulmonary function tests with a flow-volume loop. If another imaging study reports a tracheal diameter less than 10 mm, the patient should also have a flow-volume loop performed. A fixed, mechanical obstruction in the trachea will show a blunted or "notched" flow-volume loop. A positive flow-volume loop may influence treatment and suggest the need for surgery.
- Fine needle aspiration (FNA) biopsy. FNA biopsy may be necessary to evaluate suspicious areas of goiter, or suspicious nodules for cancer. Suspicious findings include:
  - Rapid growth of the goiter
  - Pain or tenderness
  - Asymmetry in the consistency of the thyroid on examination

Special Populations

Age

- Goiter is most common in the middle-aged to older adult population. The incidence of goiter rises with age.
- Although rare, goiters can occur in infants and children. They can be congenital or acquired.
    - Congenital Goiter. Goiters can occur in infants from congenital causes. Congenital goiters may not be evident at birth, but will usually develop over the first several months of life. The causes of congenital goiter include:
        - Inborn errors of thyroid hormone production
        - Mother's with Hashimoto's or Graves' can have transplacental transfer of maternal antibody leading to goiter
        - Maternal ingestion of antithyroid drugs
        - Inborn mutations of thyroid hormones and receptors
        - Thyroid tumors
    - Acquired Goiter. Acquired goiters in children follow a similar distribution as adults. In iodine-deficient parts of the world, iodine-deficient goiters are the most common cause. In areas of the world where iodine-deficiency is uncommon, common causes of goiter include:
        - Hashimoto's Thyroiditis
        - Graves' Disease
- Colloid Goiter. This is a unique form of goiter that occurs in adolescent girls. The cause is unknown. Thyroid function is usually normal. It usually improves over time with no treatment.

Co-morbidities

- Goiters can occur in patients with multiple other co-morbid illnesses. Significant cardiac and pulmonary disease can complicate the management of goiters. As one of the primary treatments for goiter may be surgical, patients with multiple co-morbid conditions may not be good candidates for surgery.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to take a complete history, including a family history and exposure to radiation history, to help determine the cause for a goiter and to guide the appropriate work-up and treatment.
- It is critical to assess for a substernal goiter, by asking about obstructive symptoms, performing a thorough examination, and ordering appropriate imaging studies.

Mimics

- There are no significant mimics of goiter.
- There are other causes of anterior neck masses, but thorough physical examination, and/or an appropriate imaging study, can determine the etiology of the mass.

Time-Dependent Interventions

- Goiters are usually very slow-growing and can be dealt with over time.
- Substernal goiters may cause acute symptoms from tracheal compression. This can be due to continued growth of the thyroid, acute hemorrhage into a large nodule, or from acute swelling from thyroiditis. These symptoms usually include dyspnea, associated with wheezing or stridor.
- In these situations, an adequate airway must be obtained. Temporary measures can include humidified oxygen, positive pressure ventilation such as continuous positive airway pressure (CPAP), and use of heliox (a helium/oxygen mixture). All of these are temporizing measures however, and a secure airway will need to be obtained. This usually requires the involvement of a surgeon with experience in these matters.

Overall Principles of Treatment

- The treatment goals for goiters differ based upon the cause of the goiter, whether the goiter is symptomatic or asymptomatic, and whether the goiter is cervical or substernal.

- Goiters that are not associated with hyperthyroidism and are non-obstructive (such as Hashimoto's): The primary goals are to treat any underlying hypothyroidism, decrease the size of the goiter, and prevent further growth. If there is significant hypothyroidism, treatment with thyroid replacement hormone can decrease the size of the goiter. If the patient is asymptomatic, the goiter can be followed. If the goiter is large, surgery or radioiodine ablation (RIA) may be appropriate. Surgery is indicated for large goiters, especially those that are continuing to grow over time. RIA can be an alternative to surgery for those patients that are not good surgical candidates.
- Substernal (or cervical) Goiter with obstructive symptoms:
    - Once obstructive symptoms occur, the patient requires treatment. There is a small incidence of spontaneous hemorrhage into an enlarged thyroid. This can cause an acute increase in thyroid size leading to acute compression that can be fatal.
    - The usual treatment is surgical resection of the thyroid gland.
    - If the patient is unable or unwilling to have surgery, RIA can be considered.
- Asymptomatic Substernal Goiter:
    - These patients can be observed over time for the development of obstructive symptoms.
    - These patients can also be offered definitive surgical treatment.
    - Early, definitive surgical treatment should be considered, for the following reasons:
        - Most goiters will continue to enlarge.
        - Surgery will become more technically difficult as the goiter enlarges.
        - A significant minority (up to 40%) of patients with asymptomatic substernal goiter have abnormal flow-volume loops.
        - There is a small risk of cancer developing in the goiter. The risk of cancer developing in a goiter is about the same as the risk of cancer developing in any thyroid nodule.
        - There is a small risk of acute hemorrhage into the thyroid with potentially fatal acute airway obstruction.
    - Patients are considered safe to observe, rather than to undergo surgery, when any of the following conditions is met:
        - They have a normal flow-volume loop.
        - The substernal component ends at or above the brachiocephalic vein.
        - The patient is a poor surgical candidate.
    - Patients being observed should be followed closely for the development of obstructive symptoms, and should have a CT scan every year until stability is documented.

- Goiters with associated hyperthyroidism: These are usually associated with Graves' disease. These patients need to have their primary disease process treated. Goiters associated with Graves' will often become smaller owing to treatment of the Graves'.

- Any goiter or thyroid nodule that has features or findings concerning for malignancy should have a fine needle aspiration (FNA) biopsy performed.
- Radioiodine ablation works best in large, hyperfunctioning (hyperthyroid), multinodular goiters. In this setting there can be a 30–40% reduction in the size of the goiter.

Disease Course

- Goiters usually grow slowly.
- Most will continue to increase in size over time, but a minority may remain stable in size.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: “Goiter”[Mh] OR “goiter”[tiab] OR “goiters”[tiab]

Chapter 32
Heart Failure

Charles V. Pollack, Jr. and Victoria G. Riese

Name and Synonyms

Heart Failure; Congestive Heart Failure

Incidence/Epidemiology

- Heart failure is a clinical state in which perfusion of tissues and/or venous return to the heart is impaired because of inadequate pumping functionality of the cardiac muscle, or when perfusion can only be maintained from an abnormally high diastolic volume.
- There are multiple ways to characterize heart failure:
  - Systolic vs diastolic
    - In systolic failure, the ventricles are unable to contract normally.
    - In diastolic failure, the ventricles fail to relax and fill properly.
    - Patients who have both dilated and hypertrophic ventricles may have both systolic and diastolic failure
  - Right-sided vs left-sided
    - Left-sided heart failure leaves blood in the lungs and therefore usually presents as pulmonary edema.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_32

- Right-sided heart failure leaves blood in the periphery and therefore usually presents with edema and liver congestion.
- Long-standing heart failure usually manifests findings of both left- and right-sided failure

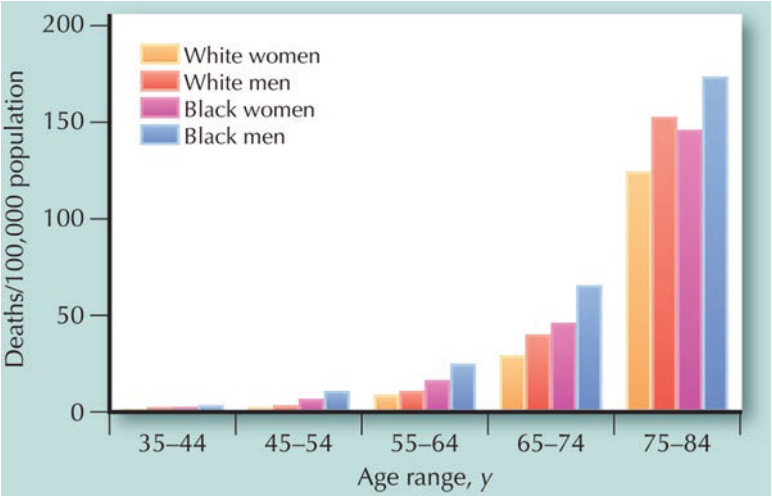
- Acute vs chronic
  - Acute heart failure usually develops immediately after a large myocardial infarction or rupture of a heart valve.
  - Chronic heart failure develops more slowly and is often due to systemic hypertension, dilated cardiomyopathy, or multivalvular disease.

Chronic heart failure	Chronic heart failure is a clinical syndrome characterized by complex and variable symptoms and signs. The cardinal manifestations of heart failure are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Chronic heart failure is often punctuated by acute decompensation.
Acute heart failure	New onset of decompensated heart failure or decompensation of chronic, established heart failure with symptoms sufficient to warrant hospitalization. Cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and after-load mismatch.
Heart failure with reduced LVEF (also referred to as systolic heart failure or heart failure with reduced systolic function)	A clinical syndrome characterized by signs and symptoms of heart failure and reduced LVEF. Most commonly associated with left ventricular chamber dilation.
Heart failure with preserved LVEF (also referred to as diastolic heart failure or heart failure with preserved systolic function)	A clinical syndrome characterized by signs and symptoms of heart failure with preserved LVEF. Most commonly associated with a nondilated left ventricle. May be the result of valvular disease or other causes.

Classification of the heart failure syndrome. Heart failure is often classified as heart failure with abnormal systolic function versus heart failure with preserved systolic function. These classifications often consider normal systolic function and normal ejection fraction to be the same. Heart failure with preserved left ventricular ejection fraction (LVEF) is variably defined as an LVEF greater than 40%, greater than 45%, or greater than 50%. Heart failure with preserved LVEF is not a distinct condition, but rather a syndrome with numerous possible causative or comorbid conditions, including hypertension, diabetes mellitus, vascular stiffness, renal impairment, and atrial fibrillation. There is no current consensus about nomenclature for heart failure with preserved systolic function. The clinical classification of patients with acute decompensated heart failure continues to evolve and reflects ongoing changes in the understanding of the pathophysiology of this syndrome. Worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function all seem to play a role. Decompensation also commonly occurs without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications or an inadequate medical regimen may

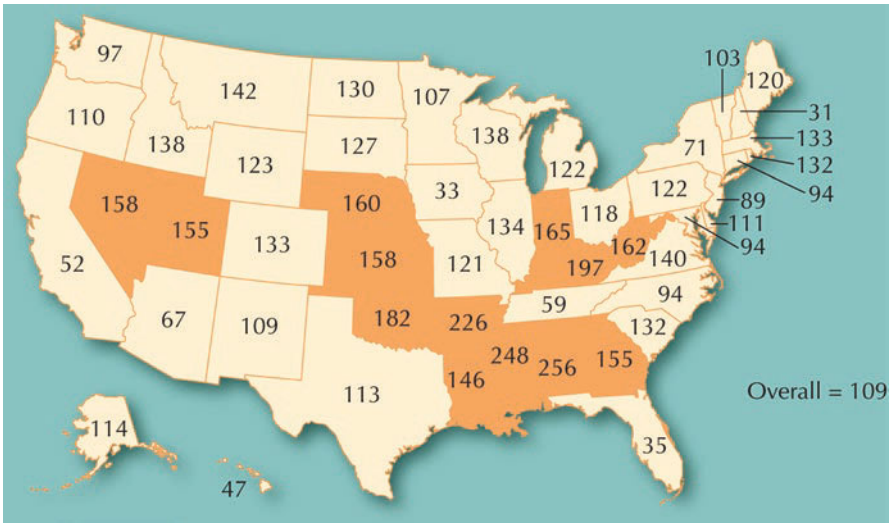
lead to hospitalization without a worsening of underlying circulatory function. Other descriptive terms used for heart failure include right- and left-sided heart failure referring to syndromes presenting predominately with congestion of the systemic or pulmonary vascular beds. Mild, moderate, and severe heart failure are used as clinical symptomatic descriptions instead of or in addition to New York Heart Association functional classification. [Kittleson MM, Fonarow GC. Clinical Syndromes of Acute and Chronic Heart Failure. In: Colucci WS, editor. Atlas of heart failure, 5th ed. Philadelphia: Current Medicine Group; 2008. 344 p. ISBN: 1-57340-261-3] *Caption adapted from original*

- Black males have the highest incidence of heart failure per capita.



US heart failure deaths by age, sex, and race. Among all age groups, black men experienced the highest rates of heart failure death. In all age groups except ages 75 to 84 years, black women experienced the next highest rates of heart failure death followed by white men. In the age group of 75 to 84 years, white men had higher rates of heart failure–-related death than black women. In all age groups, white women experienced the least heart failure–related mortality (American Heart Association: Heart Disease and Stroke Statistics —2007 Update.. Dallas: American Heart Association; 2007). [Parikh NI, Vasan RS. The Epidemiology of Heart Failure. In: Colucci WS, editor. Atlas of heart failure, 5th ed. Philadelphia: Current Medicine Group; 2008. 344 p. ISBN: 1-57340-261-3] *Caption from original*

- There is a “heart failure belt” across middle America



Geographic heterogeneity in US heart failure death rates. Numbers reflect state-specific, age-adjusted death rates per 100,000 persons for men and women > 65 years of age for the period from 1990 to 1996. The 13 highlighted states have the highest heart failure death rates. Possible explanations for the apparent "heart failure belt" across middle-America are 1) higher prevalence of hypertension and myocardial infarction in the belt, 2) varying access to early diagnosis, 3) regional differences in congestive heart failure treatment, or 4) differing practices of diagnostic coding for heart failure in death certificates (Changes in mortality from heart failure: United States, 1980-1995. MMWR Morb Mortal Wkly Rep. 1998; 47:633 -637). [Parikh NI, Vasan RS. The Epidemiology of Heart Failure. In: Colucci WS, editor. Atlas of heart failure, 5th ed. Philadelphia: Current Medicine Group; 2008. 344 p. ISBN: 1-57340-261-3] *Caption from original*

- Heart failure is classified by multiple scales, but the most commonly used is from the New York Heart Association (NHYA) and is symptom-driven.

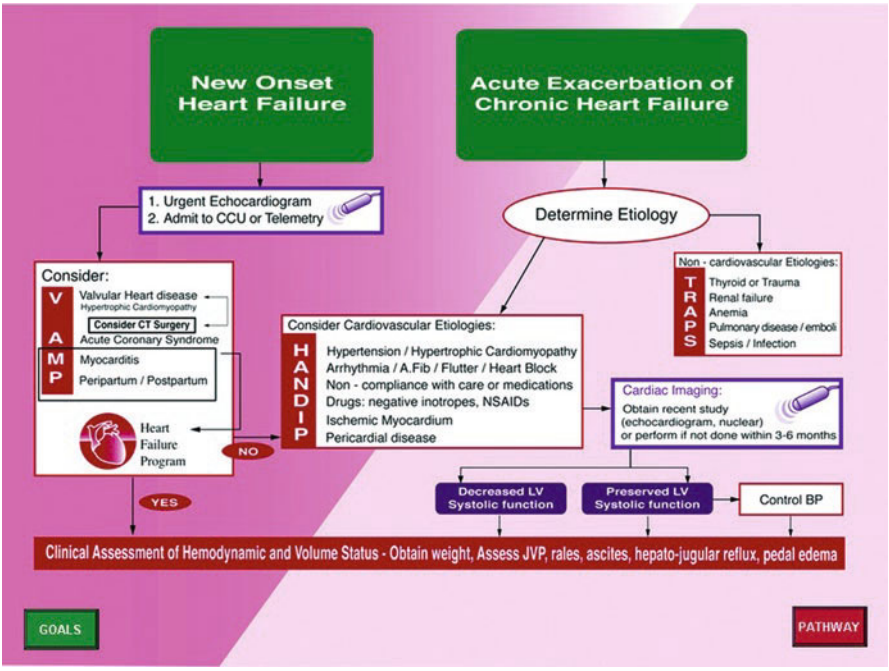
Class I	No limitation of daily physical activity.
Class II	Slight limitation of activity. Comfortable at rest but ordinary physical activity produces fatigue and dyspnea.
Class III	Marked limitation of physical activity. Fatigue and dyspnea results from minimal physical activity.
Class IV	Severe physical limitation. Dyspnea at rest and unable to carry on physical activity without severe symptoms.

New York Heart Association classification of heart failure. The functional classification of patients with congestive heart failure developed by the New York Heart Association is based on the amount of activity tolerated by patients before the onset of symptoms. Despite the limitations of this subjective classification, it is a useful

descriptive system and remains the standard by which patients with heart failure are compared (Boston: Little, Brown; 1964; 114). [O'Connor C, Tuman K. Chapter 7. In: Miller RD, Reves JG, editors. Atlas of Anesthesia: Cardiothoracic Anesthesia, Volume 8, 1e. Philadelphia: Current Medicine Group; 1999. 256 p. ISBN: 0-443-07974-9] *Caption from original*

Differential Diagnosis

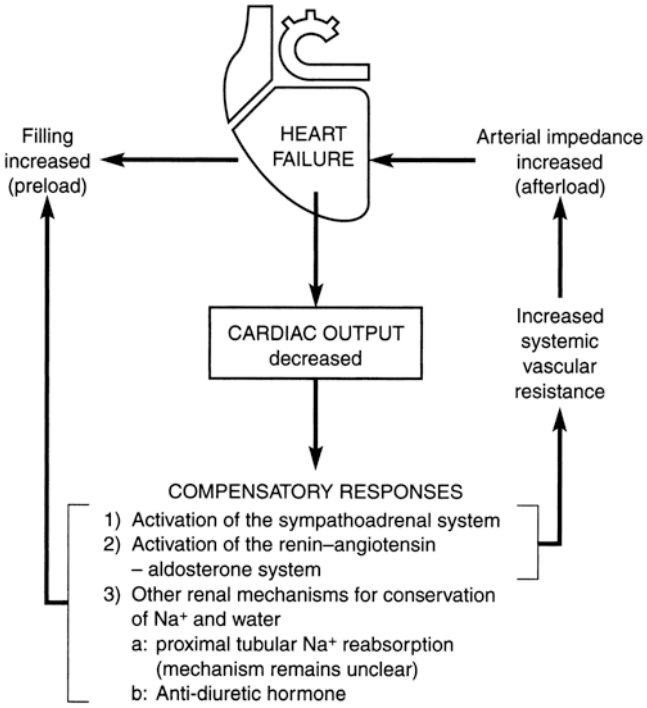
- The differential diagnosis of heart failure is to some extent dependent upon the type of failure being manifest. In general, the differential includes:
  - Acute exacerbation of COPD



Differential diagnosis between new onset heart failure and acute exacerbation of chronic heart failure with timing of imaging and consideration of precipitating pathophysiology. [Wild D, Herzog E, Aziz E, Kukin M. Pathway for the Management of Heart Failure Complicating Acute Coronary Syndrome. In: Herzog E, Chaudhry F, editors. Echocardiography in Acute Coronary Syndrome [Internet]. London: Springer London; 2009 [cited 2015 Jun 4]. p. 365–76. Available from: http://link.springer.com/10.1007/978-1-84882-027-2_25] *Caption from original*

- Pulmonary embolism
- Pneumonia
- Acute renal failure
- Noncardiogenic pulmonary edema
- Myocardial infarction
- Respiratory failure

Pathophysiology and Etiology



Pathophysiology of heart failure. [Khan MG. Heart Failure. Cardiac Drug Therapy, 8e [Internet]. Totowa, NJ: Humana Press; 2015 [cited 2015 Jun 4]. p. 369–421. Available from: http://link.springer.com/10.1007/978-1-61779-962-4_12] *Caption from original*

Common
Coronary heart disease
Hypertension
Idiopathic
Diabetes mellitus
Valvular disease
Less common
Anemia
Connective tissue disease
Viral myocarditis
Hemochromatosis
Human immunodeficiency virus infection
Hyperthyroidism, hypothyroidism
Hypertrophic cardiomyopathy
Infiltrative disease (including amyloidosis and sarcoidosis)
Mediastinal radiation
Peripartum cardiomyopathy
Restrictive pericardial disease
Tachyarrhythmia
Toxins (including drugs and alcohol)
Trypanosomiasis (Chagas' disease)

Etiologies of heart failure. [Marín-García J. Diagnosis of Heart Failure: Evidence-Based Perspective. Heart Failure [Internet]. Totowa, NJ: Humana Press; 2010 [cited 2015 Jun 4]. p. 353–63. Available from: http://link.springer.com/10.1007/978-1-60761-147-9_18] *Caption from original*

- There are many contributing factors to the development of heart failure, including:
  - Increased metabolic demand on the heart, such as:
    - Infection
    - Anemia
  - Other demand for increased cardiac output, such as:
    - Pregnancy
    - Thyrotoxicosis
    - Sepsis
    - Hypovolemia
  - Physical demand on the heart, such as:
    - Hypertension
    - Endocarditis
    - Pulmonary embolism
    - Salt and volume retention

- Injury to heart muscle, such as:
  - Myocardial infarction
  - Myocarditis
- Arrhythmia
- Toxic exposures
- Chagas' disease

Presentation

Typical/"Classic"

- Most patients with acute heart failure present with shortness of breath.
- Dyspnea on exertion and orthopnea are common.
- Chest pain and palpitations are not uncommon.
- Patients with right-sided failure only will complain of dependent edema, weight gain, and swelling of the abdomen.

Atypical

- Patients may present only with weight gain or nocturia.
- Chest pain or palpitations without dyspnea would be unusual.

Primary Differential Considerations

- Patients who present with signs and symptoms of heart failure should also be evaluated for these potential diagnoses:
  - Acute coronary syndrome
  - Pulmonary embolism
  - COPD exacerbation
  - Pneumonia

History and Physical Exam

- In the history, focus on symptoms of fluid overload and pump failure, such as:
  - Dyspnea (specifically asking about dyspnea at rest vs only with exertion, and about nocturnal dyspnea/orthopnea)

- Peripheral edema and ascites (socks leaving indentations, having to loosen belt)
- Nocturia and insomnia
- Fatigue
- Generalized weakness
- Abdominal pain (which may result from hepatic congestion)

- On physical examination, there are a number of findings associated with heart failure that should be sought:
  - Pulmonary rales

http://www.easyauscultation.com/rales

Rales. [Rales Lung Sounds; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Peripheral edema
- Hepatomegaly
- Orthopnea
- Third heart sound (S3 gallop)

https://www.youtube.com/watch?v=xbLMC0kPQ-E

Audio of the third heart sound.

- Fourth heart sound

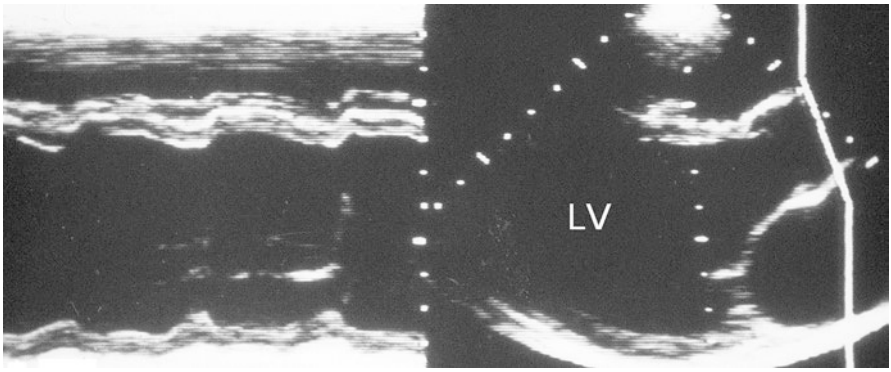
https://www.youtube.com/watch?v=r-HqK7NRL8I

Audio of the fourth heart sound with animated diagram.

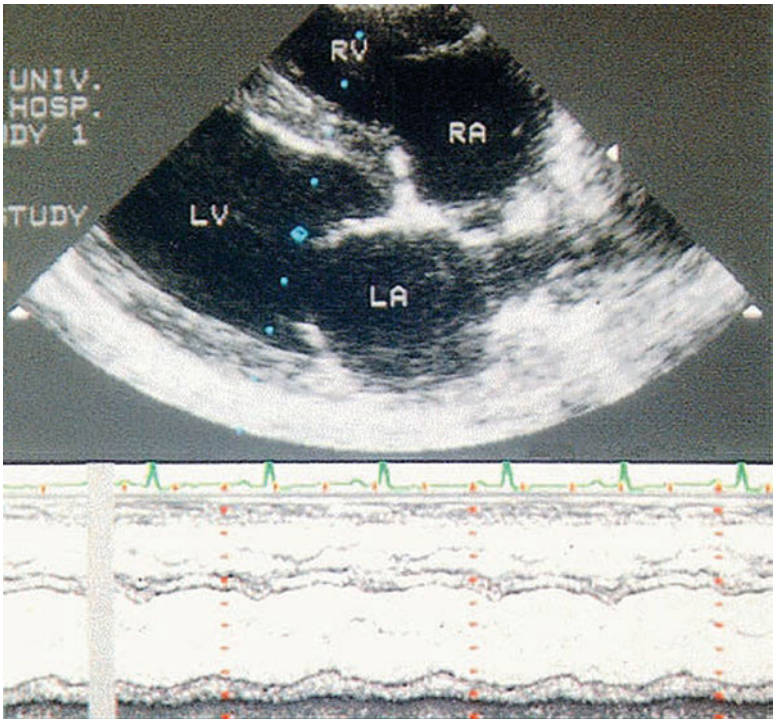
- Neck vein distention

Findings that Confirm Diagnosis

- More than two or three of the signs and symptoms are strongly suggestive of heart failure. Confirmation of the diagnosis (and important prognostic information) is obtained by echocardiography.



M-mode echocardiogram (left) and parasternal long-axis view from a patient with marked alcohol consumption and heart failure. The echocardiographic pattern is that of dilated cardiomyopathy with reduced contraction. [Nihoyannopoulos P. Cardiomyopathies. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography [Internet]. London: Springer London; 2009 [cited 2015 Jun 4]. p. 399–434. Available from: http://link.springer.com/10.1007/978-1-84882-293-1_20] *Caption from original*



Two-dimensional M-mode echocardiogram of a dog with congestive heart failure induced by rapid pacing. Note the generalized cardiac dilatation and decreased left

ventricular shortening fraction. LA—left atrium; LV—left ventricle; RA—right atrium; RV—right ventricle. [Gwathmey J, Abelmann W. Chapter 11. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging, 1e. Philadelphia: Current Medicine; 1998. 248 p. ISBN: 0-443-07567-0] *Caption from original*

Factors that Suggest Diagnosis

- More than two of the signs and symptoms listed above are suggestive and warrant specific evaluation

Factors that Exclude Diagnosis

- A normal echocardiogram and a normal brain-type natriuretic peptide (BNP level) exclude heart failure. It may not be possible to exclude the diagnosis fully on clinical grounds alone.

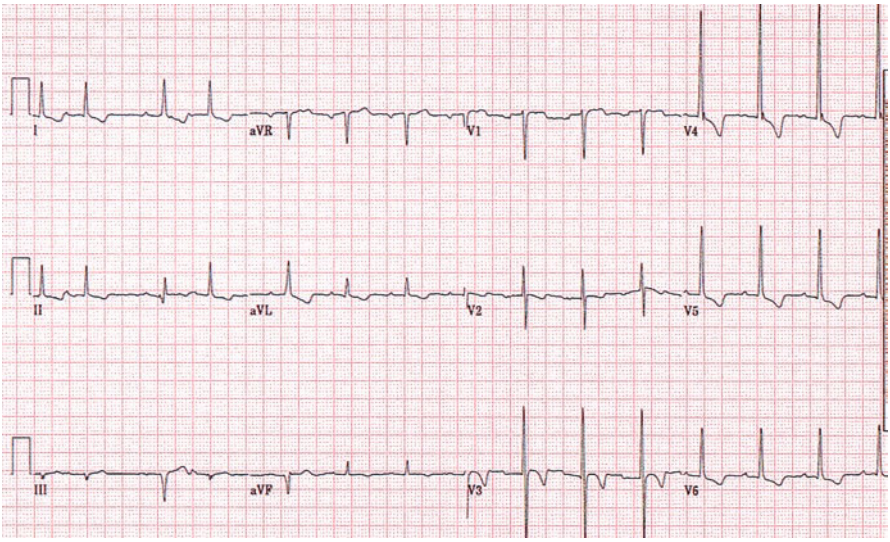
Ancillary Studies

Laboratory

- Baseline CBC (to exclude anemia) and renal function should be evaluated
- Urine should be checked for protein, blood, and glucose
- Serum electrolytes (especially potassium) should be checked
- A BNP level should be checked

Electrocardiography

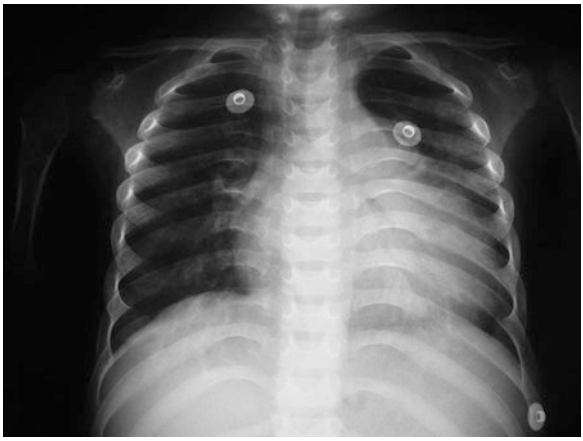
- Electrocardiogram should be obtained to evaluate rhythm and to look for left ventricular hypertrophy or Q-waves. There are no pathognomonic findings for heart failure on ECG.



A 12-lead electrocardiogram demonstrating left ventricular hypertrophy with a "strain" pattern. [Fleisher L. Chapter 3. In: Miller RD, Lichtor JL, editors. Atlas of Anesthesia: Preoperative Preparation and Intraoperative Monitoring, Volume 3, 1e. Philadelphia: Current Medicine; 1997. 251 p. ISBN: 0-443-07902-1] *Caption adapted from original*

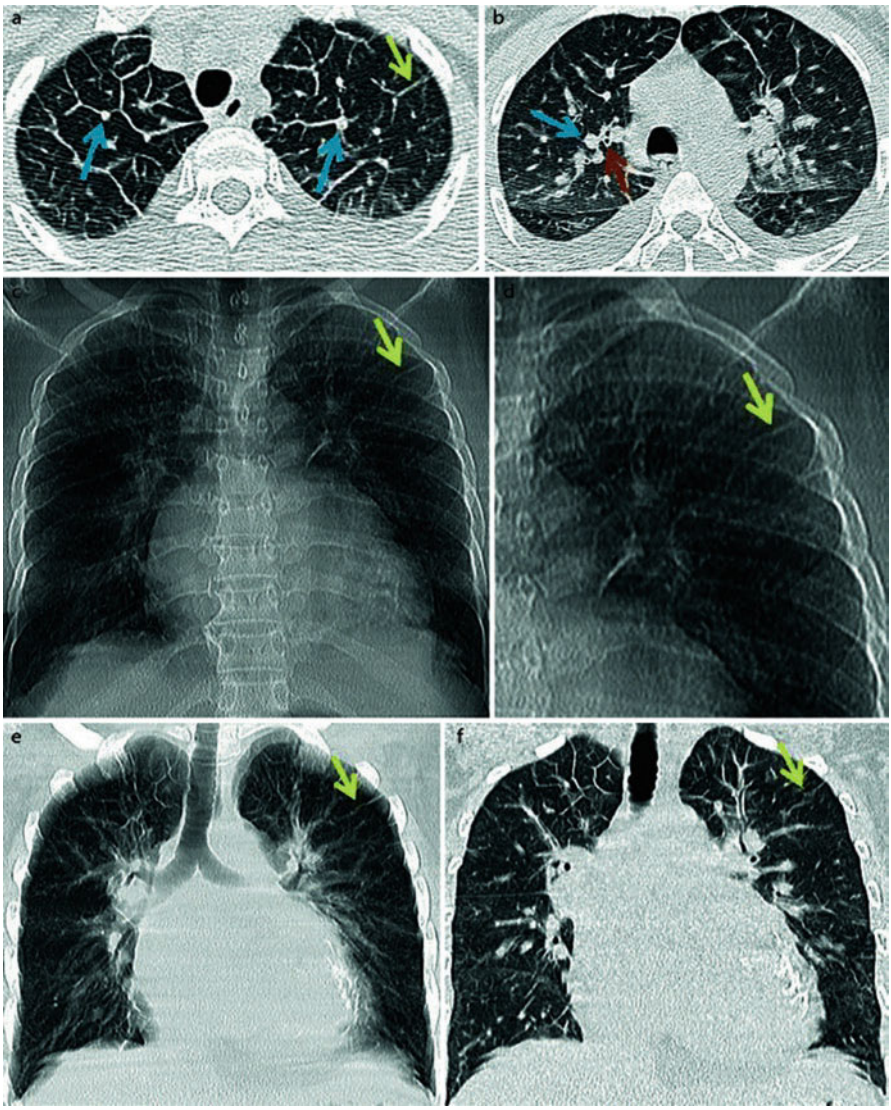
Imaging

- Chest x-ray should be obtained to look for cardiac enlargement, pleural effusion, signs of pulmonary edema, COPD, or pneumonia.



Cardiomegaly on chest X-ray. [Yıldırım SV, Durmaz C, Pourbagher MA, Erkan AN. A case of achondroplasia with severe pulmonary hypertension due to

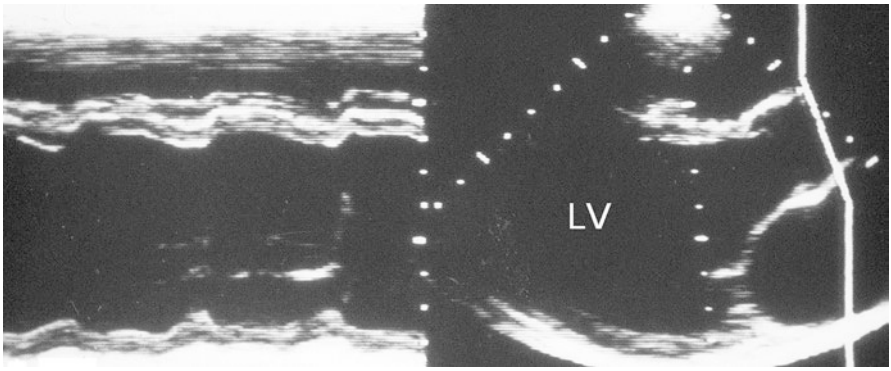
obstructive sleep apnea. European Archives of Oto-Rhino-Laryngology. 2006 Aug;263(8):775–7.] *Caption from original*



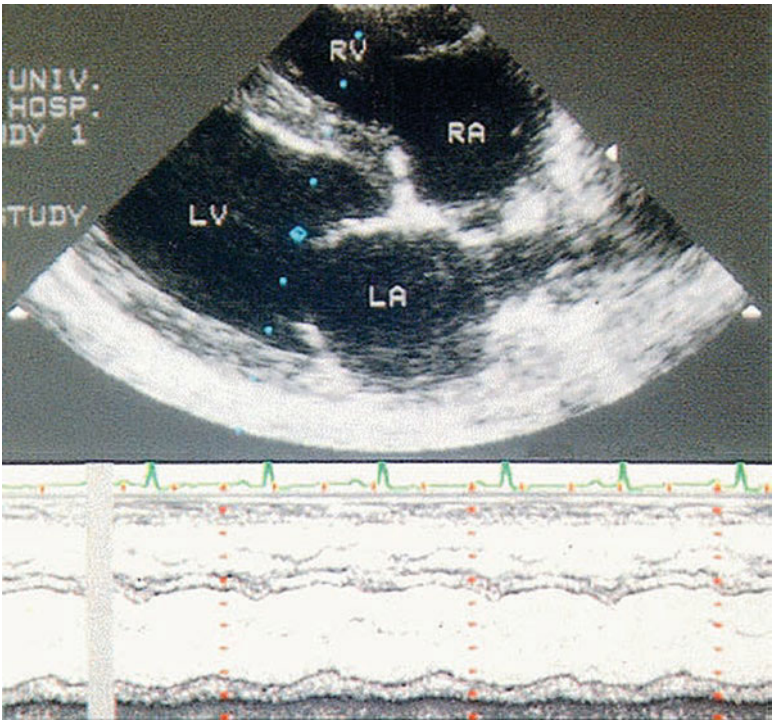
Hydrostatic pulmonary edema in a patient with congestive heart failure. Two successive axial computed tomography slices (a and b) demonstrate a nodular thickening of the interlobular septa reflecting the enlarged pulmonary veins (blue arrows) with bilateral pleural effusion. Note the peribronchial cuffing on (b; orange arrow). The chest radiograph equivalent (c) and the focused view on the left upper lobe (d) show a loss of definition of vascular markings throughout both lungs associated

with Kerley lines (yellow arrows), reminiscent of interstitial edema. Note the enlargement of the cardiac silhouette. By viewing average coronal slabs (c–f) of decreasing slice thickness, Kerley A lines seen on (f) corresponding to septal thickening are perfectly understood. [Ilsen B, Gosselin R, Delrue L, Duyck P, de Mey J, Beigelman-Aubry C. Interstitial Lung Disease. In: Coche EE, Ghaye B, de Mey J, Duyck P, editors. Comparative Interpretation of CT and Standard Radiography of the Chest [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011 [cited 2015 Jun 4]. p. 195–220. Available from: http://link.springer.com/10.1007/978-3-540-79942-9_8] *Caption from original*

- Echocardiography is helpful in diagnosing, staging, and following heart failure.



M-mode echocardiogram (left) and parasternal long-axis view from a patient with marked alcohol consumption and heart failure. The echocardiographic pattern is that of dilated cardiomyopathy with reduced contraction. [Nihoyannopoulos P. Cardiomyopathies. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography [Internet]. London: Springer London; 2009 [cited 2015 Jun 4]. p. 399–434. Available from: http://link.springer.com/10.1007/978-1-84882-293-1_20] *Caption from original*



Two-dimensional M-mode echocardiogram of a dog with congestive heart failure induced by rapid pacing. Note the generalized cardiac dilatation and decreased left ventricular shortening fraction. LA—left atrium; LV—left ventricle; RA—right atrium; RV—right ventricle. [Gwathmey J, Abelmann W. Chapter 11. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging, 1e. Philadelphia: Current Medicine; 1998. 248 p. ISBN: 0-443-07567-0] *Caption from original*

Other Studies

- None indicated in initial evaluation.

Special Populations

Age

- With rare exception, heart failure is a disease of older patients, with the incidence increasing with increasing age.

Co-morbidities

- Co-morbidities may include:
  - Hypertension
  - Renal disease
  - Cardio- and cerebrovascular disease
  - Drug and alcohol abuse

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Recognition of acute heart failure that may precipitate circulatory collapse or severe pulmonary

Mimics

- Potential mimics include:
  - Pneumonia
  - COPD
  - Acute coronary syndrome
  - Pulmonary embolism

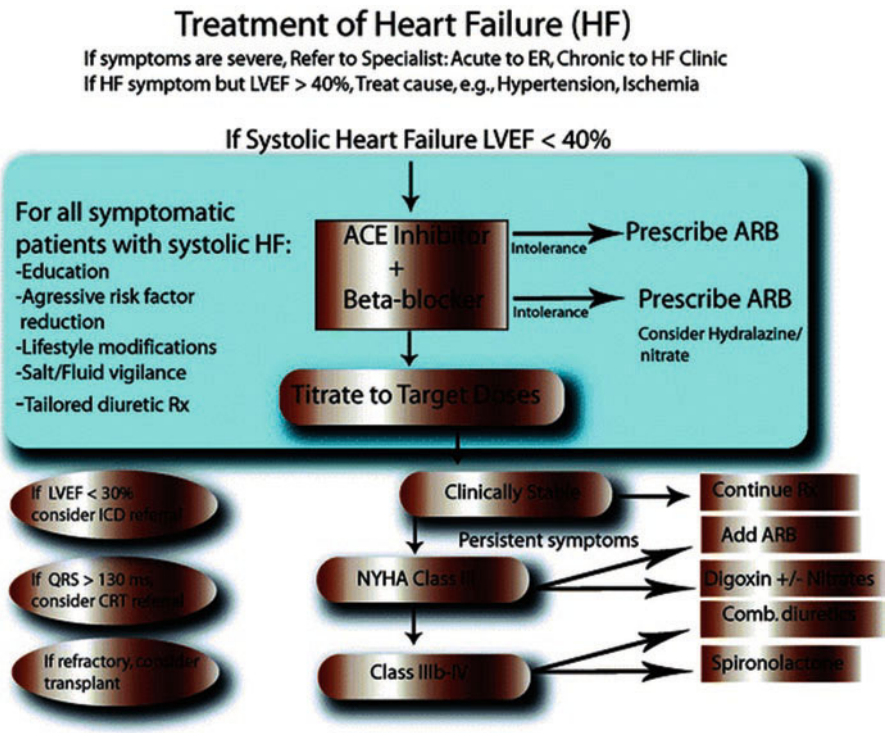
Time-Dependent Interventions

- Provide ventilatory and circulatory support as needed.
- Noninvasive ventilation should be attempted before intubation and mechanical ventilation unless the patient is already in ventilatory failure.
- Initiation of diuresis.

Overall Principles of Treatment

- Relief of fluid overload and improvement in ventilatory and circulatory status are paramount.
- Diuresis with attention to electrolyte levels will improve symptoms.

- ACE inhibitors and beta-blockers will improve long-term management.
- Diet and exercise counseling will help patients manage their symptoms better.



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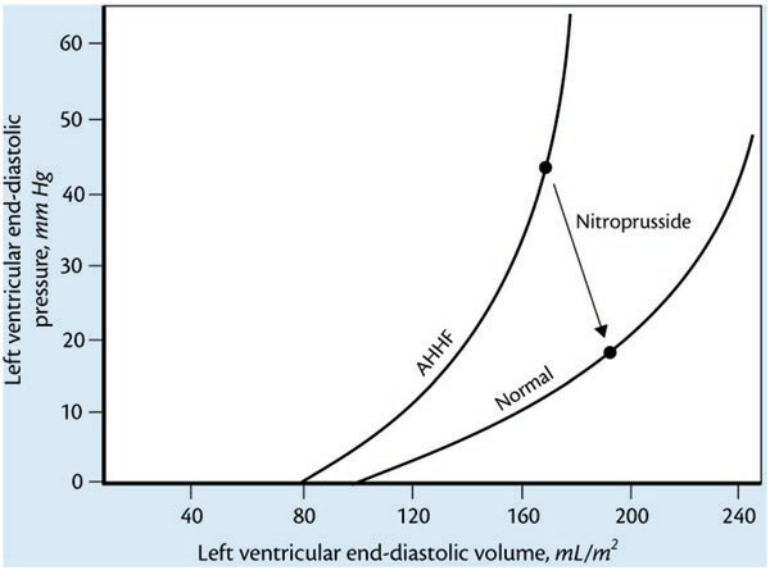

Treatment of acute hypertensive heart failure. The left ventricular (LV) end-diastolic pressure-volume relationships (compliance curves) in acute hypertensive heart failure (AHHF) before and after treatment with sodium nitroprusside are represented schematically. In AHHF, the pressure-volume curve is shifted up and to the left, reflecting an acute decrease in LV compliance caused by severe systemic hypertension. In this setting, a higher than normal LV end-diastolic pressure (LVEDP) is required to achieve any given level of LV end-diastolic volume (LVEDV). Normal LV systolic function (ejection fraction and cardiac output) is maintained but at the expense of a very high wedge pressure that results in acute pulmonary edema. Treatment with sodium nitroprusside causes a reduction in the elevated systemic vascular resistance, with a concomitant decrease in impedance to LV ejection. As a result, LV compliance improves. Pulmonary edema resolves owing to a reduction in LVEDP, despite the fact that LVEDV actually increases during treatment. Sodium nitroprusside is the preferred drug for treatment of AHHF. There is no absolute blood pressure goal. The infusion should be titrated until signs and symptoms of pulmonary edema resolve or the blood pressure decreases to hypotensive levels. Rarely is it necessary to lower the blood pressure to this extent, however, because reduction to levels still within the hypertensive range is usually associated with dramatic clinical improvement. Although hemodynamic monitoring is not always required, it is essential in patients in whom concomitant myocardial ischemia or compromised cardiac output is suspected. After the hypertensive crisis has been controlled and pulmonary edema has resolved, oral antihypertensive therapy can be substituted as the patient is weaned from the nitroprusside

infusion. As in the treatment of hypertensive patients with chronic congestive heart failure symptoms owing to isolated diastolic dysfunction, agents such as β-blockers, angiotension-converting enzyme inhibitors, or calcium channel blockers may represent logical first-line therapy. These agents directly improve diastolic function in addition to reducing systemic blood pressure. In patients with malignant hypertension or resistant hypertension, however, adequate control of blood pressure may require therapy with more than one drug. Potent direct-acting vasodilators such as hydralazine or minoxidil may be used in conjunction with a β-blocker to control reflex tachycardia and a diuretic to prevent reflex salt and water retention. [Nolan CR. Hypertensive Crises. In: Schrier RW, Wilcox CS. Atlas of Diseases of the Kidney, Volume 3: Hypertension and the Kidney. Philadelphia: Current Medicine Group; 1999. 182 p.] *Caption from original*

Goals of Treatment in Decompensated Heart Failure

Clinical goals	Hemodynamic goals
Resolution of dyspnea and orthopnea	Systolic blood pressure ≥ 80 mm Hg
Resolution of ascites and peripheral edema	Right atrial pressure ≤ 8 mm Hg
Jugular venous pressure ≤ 8 cm H_20	Pulmonary capillary wedge pressure ≤ 16 mm Hg
Control of hypertension	Systemic vascular resistance ≤ 1200 dynes/s/cm-5
Minimize adverse effects of treatment, reduce duration and cost of stay	
Initiate treatments that improve long-term outcome	

Goals of treatment in decompensated heart failure. Goals of in-patient therapy. The early goal of treatment is to improve symptoms while maintaining or improving the hemodynamic status. Progress may be tracked by following body weights and fluid intake and output while monitoring vital signs, electrolytes, and renal function. Consideration also should be given to identifying precipitating factors and etiology, and patients who may benefit from coronary revascularization. [Givertz MM, Colucci WS. Heart Failure. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p.] Caption adapted from original

Drug	Dosing	Potential Advantage	Potential Disadvantages
Nitroglycerin	Sublingual: 1 tablet (or 1–2 sprays) three or four times at 5-minute intervals; IV: 0.4 μg/kg/min initially (increase as needed)	Favorable effect on coronary vasculature and in myocardial ischemia/infarction; preload reduction > afterload	Tolerance during prolonged infusion; inadequate afterload reduction in catastrophic cardiovascular disorders (*eg*, acute valvular insufficiency, ventricular rupture)
Nitroprusside	IV: 0.1 μg/kg/min initially; increase as needed	Relatively powerful preload and afterload reduction	Less favorable effects on coronary vasculature and myocardial ischemia; administration must be closely monitored to avoid marked hypotension; thiocyanate or cyanide toxicity during high-dose or prolonged infusions, particularly in patients with renal or hepatic dysfunction
Nesiritide	0.005–0.01 μg/kg/min initially, ± bolus; increase as needed	Preload and afterload reduction; possible facilitative effect on diuresis	Hypotension; meta-analysis of clinical trials suggests adverse effects on mortality and renal function

Principal preload- and afterload-reducing drugs for acute or severe heart failure. Nesiritide, nitroglycerin, and nitroprusside are the primary vasodilators used to reduce excessive preload and afterload in acute or severe heart failure. Nitroglycerin is used most often, particularly in conditions caused by occlusive atherosclerotic coronary artery disease. Nitroprusside is the drug of choice when more aggressive afterload and preload reduction are needed; examples include catastrophic cardiovascular events (eg, acute, severe mitral, or aortic regurgitation), hypertensive emergencies (eg, aortic dissection, pulmonary edema), and inadequate response to nesiritide or nitroglycerin. [Ooi H, Colucci WS. Management of the Hospitalized Patient. In: Colucci WS, editor. Atlas of heart failure, 5th ed. Philadelphia: Current Medicine Group; 2008. 344 p. ISBN: 1-57340-261-3] *Caption adapted from original*

Disease Course

- Prognosis depends on type and severity of failure.
- With aggressive medical therapy, ventricular assist devices, and even cardiac transplant, even severe heart disease is no longer a short-term mortality diagnosis.
- Patient compliance with management is an important predictor of both outcomes and quality of life.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Heart Failure"[Mesh] OR "Heart Failure"

Chapter 33
Hemoptysis

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Hemoptysis

Incidence/Epidemiology

- Hemoptysis is the expectoration of blood from the respiratory tract with cough. Because coughing sometimes leads to vomiting (tussive emesis), it is important to distinguish between hemoptysis and hematemesis.
- Hemoptysis may range in severity from scant blood-streaked mucous that is self-limited to life-threatening airway obstruction from blood clots or diminished gas exchange in blood-filled alveoli.
- Because there are so many varied causes of hemoptysis, epidemiologic data are not meaningful. Smokers and those with chronic lung or sinus disease are more likely to have hemoptysis.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_33

Hemoptysis	Massive	Exsanguinating
One expectoration (mL)		>300
mL by hour	>25	>150
mL by 24 h	>600	>1,000

Definition of hemoptysis. [Bussières JS. Massive hemoptysis. In: Slinger P, editor. Principles and practice of anesthesia for thoracic surgery [Internet]. New York: Springer; 2011 [cited 2015 May 28]. p. 485–96. Available from: http://link.springer.com/10.1007/978-1-4419-0184-2_34] *Caption from original*

Differential Diagnosis

- The important first differential issue to address is whether the bleeding is a result of a respiratory or gastrointestinal (GI) cause. The possibility of epistaxis as a cause should also be evaluated. Beyond that, the differential concerns regard the *cause* of hemoptysis, which generally may be divided into these categories:
  - Infectious
  - Vascular
  - Iatrogenic
  - Coagulopathic
  - Traumatic
  - Neoplastic
  - Pulmonary miscellaneous

Infections • Mycobacteria, particularly tuberculosis • Fungal infections (mycetoma) • Lung abscess • Necrotising pneumonia (Klebsiella, Staphylococcus, Legionella)	Vascular • Pulmonary embolism and infarction • Mitral stenosis • Arteriobronchial fistula • Arteriovenous malformations • Bronchial telangiectasia • Left ventricular failure
Iatrogenic • Bronchoscopy • Swan–Ganz catheterization • Transbronchial biopsy • Transtracheal aspirate	Coagulopathy • Von Willebrand's disease • Hemophilia • Anticoagulant therapy • Thrombocytopenia • Platelet dysfunction • Disseminated intravascular coagulation • Vasculitis • Behcet's disease • Wegener's granulomatosis
Parasitic • Hydatid cyst • Paragonimiasis	
Trauma • Blunt/penetrating injury • Suction ulcers • Tracheoarterial fistula	
Neoplasm • Bronchogenic carcinoma • Bronchial adenoma • Pulmonary metastases • Sarcoma	Pulmonary • Bronchiectasis (including cystic fibrosis) • Chronic bronchitis • Emphysematous bullae
Hemoptysis in children • Foreign body aspiration • Bronchial adenoma • Vascular anomalies	Miscellaneous • Lymphangioleiomyometosis • Catamenial (endometriosis) • Pneumoconiosis • Broncholith • Idiopathic
	Spurious • Epistaxis • Hematemesis

Causes of hemoptysis. [Subramanian S, Kate AH, Chhajed PN. Role of bronchoscopy in hemoptysis. In: Mehta A, Jain P, editors. Interventional bronchoscopy [Internet]. Totowa, NJ: Humana Press; 2013 [cited 2015 May 28]. p. 245–56. Available from: http://link.springer.com/10.1007/978-1-62703-395-4_14] *Caption from original*

Pathophysiology and Etiology

- Hemoptysis may result from several different processes.
- The two most common causes are bronchitis and other lung infections and endobronchial carcinoma with erosion into a bronchial vessel.
- Many patients may never have a definitive cause identified.
- Hemoptysis may result from inflammation/infection or from physical injury to a bronchial vessel.

- Hemoptysis may also result from the high pulmonary venous pressure that results from severe mitral valve stenosis
- The mnemonic "BATTLE CAMP" may be helpful in remembering common etiologies of hemoptysis:

B	Bronchitis, bronchiectasis
A	Aspergillosis, alveolar hemorrhage
T	Tumor, trauma
T	Tuberculosis
L	Lung abscess
E	Emboli
C	Coagulopathy
A	Autoimmune, AVM
M	Mitral stenosis
P	Pneumonia
Others	Tracheostomy related, foreign bodies, aortopulmonary collaterals

Causes of hemoptysis—"Battlecamp." [Hogan MJ. Bronchial artery interventions in children. In: Temple M, Marshalleck FE, editors. Pediatric interventional radiology [Internet]. New York: Springer; 2014 [cited 2015 May 28]. p. 71–83. Available from: http://link.springer.com/10.1007/978-1-4419-5856-3_6] Caption from original

Presentation

Typical/"Classic"

- Patients who present "coughing up blood" usually are hemodynamically stable (massive hemoptysis that causes shock is a medical emergency).
- Patients may not be able to distinguish among cough with expectoration of blood caused by pulmonary sources, posterior epistaxis, and GI bleeding with hematemesis.
- The amount of blood loss should be quickly assessed, and that will drive the pace of evaluation and management.

Atypical

- "Rusty"-colored sputum may not be recognized as hemoptysis.

Primary Differential Considerations

- Primary differential considerations for hemoptysis are limited to:
- Epistaxis
- Hematemesis
  - To help differentiate, remember that blood from the GI tract likely has been exposed to the acidic pH of the stomach and will be darker, whereas blood from the respiratory tract tends to be a brighter red, although chronic infection/tumor may result in expectoration of "older" blood that is darker in color.
- Airway foreign bodies

History and Physical Exam

- Expectoration of even small amounts of blood may provoke significant anxiety in patients, and their quantification of the amount of blood loss may be exaggerated.
- The first historical factors to be established include:
  - Timeframe—how long has hemoptysis been occurring?
  - Course—is it getting worse or better?
  - Character of hemoptysis—is it blood-streaked sputum or is it frank blood?
  - Associated issues—fever and chills? Night sweats? Weight loss? Using an anticoagulant or antiplatelet drug? Any chronic lung disease?
  - Is there pleuritic chest pain with or without dyspnea, suggesting a pulmonary embolism? Are there any signs of deep venous thrombosis?
  - Is the patient a smoker?
- On physical examination, the lungs should be auscultated for evidence of bronchospasm, consolidation, or pleural friction.
- Check the heart sounds for a murmur of mitral stenosis.

Mitral stenosis murmur. [Mitral stenosis (diastolic murmur); Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]
http://www.easyauscultation.com/cases?coursecaseorder=14&courseid=31

Bronchiectasis	Pulmonary tuberculosis
Fungal infections in cavities—aspergilloma	Bronchogenic carcinoma
Severe mitral stenosis	Coagulopathies
Foreign bodies	Trauma
Vasculitis	Pulmonary embolism

Causes of severe hemoptysis. [Bansal A, Kantroo V. Massive hemoptysis. In: Chawla R, Todi S, editors. ICU protocols [Internet]. India: Springer India; 2012 [cited 2015 May 28]. p. 65–70. Available from: http://www.springerlink.com/index/10.1007/978-81-322-0535-7_8] *Caption from original*

Findings That Confirm Diagnosis

- Witnessed expectoration of blood confirms the diagnosis; without firsthand evidence, it is difficult to know with certainty that there is a respiratory tract source.

Factors That Suggest Diagnosis

- A reported history of hemoptysis in a patient at risk for one or more common etiologies of hemoptysis (acute or chronic lung infection, chronic obstructive pulmonary disease [COPD], mitral stenosis, coagulopathy, or pulmonary embolism) should prompt diagnostic evaluation for one of these causes.

Factors That Exclude Diagnosis

- Clinically, hemoptysis cannot be excluded. The history of blood expectoration should be evaluated thoroughly on the supposition that the patient's history is accurate.

Ancillary Studies

Laboratory

- Patients with active hemoptysis and those with a history of repeated or chronic episodes should be evaluated with a complete blood count (CBC).
- Patients on warfarin anticoagulation should be checked for international normalized ratio (INR); patients on unfractionated heparin should be evalu-

ated for activated partial thromboplastin time (aPTT); patients taking an injectable low-molecular-weight heparin should be checked for renal function, and the time of last dose should be noted.
- D-dimer testing may be helpful in determining possible pulmonary embolism.
- Sputum evaluation may be helpful.

Electrocardiography

- In general, ECG should be performed in ill patients but is unlikely to be particularly helpful in the evaluation of hemoptysis.

Imaging

- Chest x-ray is an essential first step in evaluating hemoptysis. Look for mass lesions, infection, signs of chronic lung disease, or evidence of a foreign body.
- A computed tomographic pulmonary angiogram is indicated if pulmonary embolism is suspected.

Other Studies

- Bronchoscopy may be indicated.

Special Populations

Age

- Older patients have a higher risk of lung cancer, COPD, pulmonary embolism, and pneumonia.
- Hemoptysis in children is less common than in adults and has a different differential diagnosis. Infection of the lungs is less likely to manifest as hemoptysis in children. Instead, consider foreign body aspiration or
  - bronchial adenoma
  - congenital vascular anomalies

Co-morbidities

- COPD
- Lung cancer
- Bronchitis
- Pneumonia
- Therapeutic anticoagulation
- Tobacco abuse

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Evaluation for satisfactory oxygenation
- Evaluation for hemodynamic stability
- Evaluation for correctable coagulopathy
- Altered mental status may signal respiratory failure.
- Chest x-ray should be done early.

Mimics

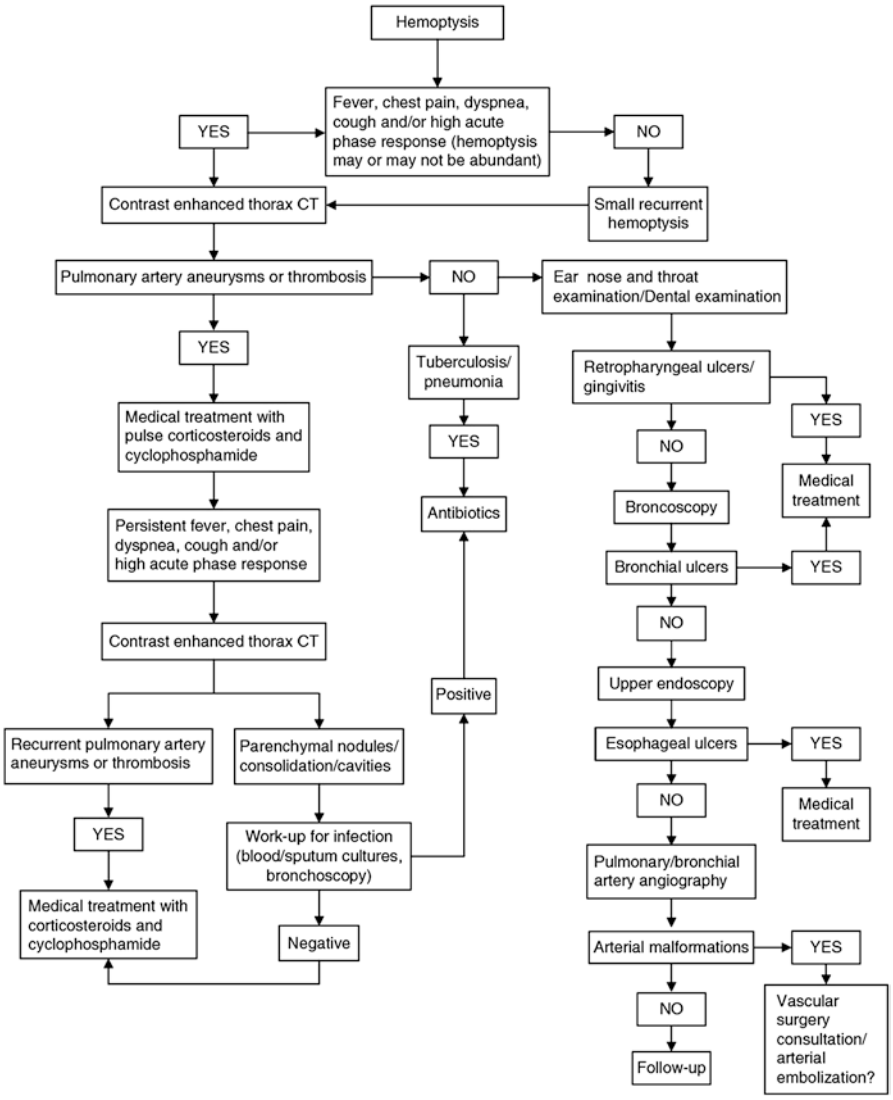
- Upper GI bleed
- Posterior epistaxis

Time-Dependent Interventions

- Immediate evaluation for adequate gas exchange and hemodynamic stability
- Chest x-ray early

Overall Principles of Treatment

- Stabilize hemodynamic and ventilatory status.
- Evaluate for etiology.
- Treat accordingly with antibiotics, bronchoscopic intervention, reversal of anticoagulation, etc.



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Disease Course

- Course is determined by acuity of presentation and underlying etiology.
- The vast majority of hemoptysis cases are not life threatening, although the underlying etiology may be significant.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Review

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Hemoptysis"[Mesh] OR "Hemoptysis"

Chapter 34
Herpes Zoster

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Herpes Zoster; Shingles

Incidence/Epidemiology

- The Centers for Disease Control and Prevention (CDC) estimates that up to one-third of the adult population in the United States will be diagnosed with shingles at some point in their lives.
- There are about 1 million to 1.2 million cases annually in the United States.
- It may occur in all adult age groups, but the incidence increases dramatically after age 50.
- It is unusual in children.
- Shingles has a very low mortality and is rarely life threatening but has substantial morbidity, mostly as the result of postherpetic neuralgia (PHN).
- Most cases occur in healthy individuals, but the incidence increases among the immunocompromised.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_34

Differential Diagnosis

- Coxsackievirus and herpes simplex virus also may cause a vesicular rash in a dermatomal distribution.

Pathophysiology and Etiology

- The varicella-zoster virus (VZV) causes shingles.
- Primary infection with VZV causes chickenpox.
- After primary infection, the virus may become dormant in the dorsal root ganglia of the spinal cord. It may lie dormant for decades, but in response to immunosuppression, or the waning of innate immunity due to aging, the virus may reactivate. The virus travels down the corresponding sensory nerve of the involved dorsal root ganglion to cause the rash along those sensory dermatomes. Reactivation usually involves just one dermatome, but may involve several or many dermatomes, especially if there is an underlying immunosuppression.
- The exact mechanisms and causes of reactivation are unknown.

Presentation

Typical/"Classic"

- Symptoms usually start with pain in one sensory dermatome. Patients also often note paresthesias or itching in the area of pain. The dermatomal distribution of the pain sometimes is not recognized by either the patient or the physician.
- In retrospect, most patients also describe a prodrome of malaise with a mild headache.
- The rash classically erupts within 1-10 days (most typically 3) of symptom onset.
- The skin lesions often start as an erythematous maculopapular rash. Vesicles then erupt. The vesicles are generally small and closely grouped into clusters of lesions. The grouped vesicles remain on an erythematous base. The vesicles initially contain clear fluid, but the fluid becomes cloudy and appears more purulent over the next several days. Ultimately the lesions dry, ulcerate, and crust over. It may be 2 weeks until the lesions crust, and then another 2 weeks for the scabs to fall off.
- The lesions do not cross the midline.
- The vesicles may be of differing sizes, and they may be of differing stages in the same areasimialr to primary chicken pox.
- The thorax and face are the most commonly affected areas, but shingles may occur anywhere on the body.

Vesicles in a dermatomal distribution represent herpes zoster. [Allen HB. Vesiculobullous Disorders (Including Dermatitis/Eczema). In: Dermatology Terminology [Internet]. London: Springer London; 2010 [cited 2016 Aug 22]. p. 15–32. Available from: http://link.springer.com/10.1007/978-1-84882-840-7_2] *Caption from original*

Early stage of shingles with clear vesicles on an erythematous base. [Gilsdorf J, Shope T. Viral exanthems of childhood. In: Fekety R, editor. External manifestations

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More developed stage of shingles with crusting. [Gilsdorf J, Shope T. Viral exanthems of childhood. In: Fekety R, editor. External manifestations of systemic infections. Philadelphia: Current Medicine; 1996. 237 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 6.) ISBN: 0-443-07760-6]

Atypical

- Shingles may occur less commonly in more than one dermatome, or be generalized.
- There is some thought and evidence that zoster may cause a syndrome of dermatomal pain without a rash: zoster sine herpetica.

Primary Differential Considerations

- Pain from shingles may precede the appearance of the rash, making early diagnosis more challenging. Differential diagnoses that should be considered include:
  - Acute coronary syndrome
  - Pulmonary embolism
  - Pleurisy

History and Physical Exam

Findings That Confirm Diagnosis

- Shingles is a clinical diagnosis. A full classic presentation of prodromal pain with development of the classic rash confirms the diagnosis.

Factors That Suggest Diagnosis

- Any rash or pain in a dermatomal distribution should suggest the diagnosis.

Factors That Exclude Diagnosis

- There are no historical or physical exam findings that can exclude the diagnosis.

Ancillary Studies

Laboratory

- Laboratory studies often are not required to make the diagnosis.
- Confirmatory testing may include antigen testing, viral culture, and polymerase chain reaction (PCR) on vesicular fluid. Culture and PCR generally are not available clinically; they usually are research techniques.
- The diagnosis may be suggested by performing a Tzanck smear. A fresh vesicle is unroofed, the bottom of the lesion is superficially scraped, and a slide is made of the scraped material. The presence of multinucleated giant cells may confirm the diagnosis; however, the false negative rate is high.

Imaging

- There are no diagnostic imaging findings that are helpful in the diagnosis of shingles.

Special Populations

Age

- It may occur in all adult age groups, but the incidence increases dramatically after age 50.
- It is unusual in children.

Co-morbidities

- Co-morbidities of importance are any type of immune compromise, including:
  - iatrogenic, from immune suppressive therapy for organ transplants, and long-term glucocorticoid therapy
  - lymphoproliferative disorders (especially leukemia and Hodgkin's lymphoma) and HIV
- The incidence of shingles increases with immune suppression, as does the risk for complications.
- Patients who have undergone hematopoietic stem cell transplantation are at particularly increased risk for shingles and its complications.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Always consider this diagnosis.

Mimics

- Coxsackievirus and herpes simplex virus also may cause a vesicular rash in a dermatomal distribution.
- Shingles may cause severe pain and can mimic many other causes of acute, severe pain if the patient presents before the rash develops.

Time-Dependent Interventions

- The only time-dependent intervention in shingles is to start treatment with antivirals within 3 days of the eruption of the rash.
- Treatment within this timeframe has been shown to reduce the incidence of developing PHN, especially in those over 50.

Overall Principles of Treatment

- The primary goal of treatment is to reduce the incidence and severity of PHN.
- This is accomplished by starting antivirals (typically valacyclovir) within 72 hours of the onset of the rash.
- Immunocompromised patients should be treated regardless of the timing from the onset of rash.
- Adjunctive corticosteroids may be considered for severe pain or for older patients with no contraindications to their use.
- Administering the shingles vaccine in those over 65 may help reduce the incidence and severity of shingles, and also reduces the incidence of PHN by up to two-thirds.
- Admission for intravenous antivirals is often indicated for disseminated shingles, central nervous system (CNS) shingles, and severely immunocompromised patients.

Disease Course

- The rash usually dries and crusts within 2 weeks. Crusts fall off over the next 2 weeks.
- Recurrence occurs in only 1–4 %. Recurrence should make one consider underlying immunocompromise.
- Complications may be serious and debilitating, and they account for most of the morbidity associated with shingles.
- PHN is the continuation of pain (often severe) for more than 30 days after the rash resolves. PHN is the most common complication of shingles. It is more common in older and immunocompromised patients. The incidence rises from 5 % in those under 60 to greater than 20 % in those over 80. The pain from PHN may be debilitating and may last for months to years. At least 50 % of affected patients over age 50 report some pain in the involved dermatome even months after resolution of rash. Many patients with PHN also describe sensory changes over the affected dermatome. The incidence may be reduced by the appropriate use of the shingles vaccine.
- Multidermatomal (disseminated zoster) is much more common in the immunocompromised. If shingles disseminates, the risk for other complications rises by 5–10 %. If an otherwise young, healthy person presents with shingles in three or more dermatomes, it is important to consider underlying immunosuppression (such as HIV).
- Shingles occurring along the ophthalmic division of the trigeminal nerve may cause zoster ophthalmicus. Shingles involving the eye may lead to severe retinitis and blindness. Patients with zoster in this distribution should be evaluated and followed up by an ophthalmologist. Vesicles present on the tip of the nose should increase suspicion of zoster ophthalmicus.

Zoster ophthalmicus. Note lesions on tip of nose. [Wassilew SW, Wutzler P. Schutz vor zoster: impfung blockiert virusreaktivierung. Präv Gesundheitsf. 2010 Jun;5(S1):23–7.]

- Ramsay-Hunt syndrome (zoster oticus) may occur when shingles involves the sensory branch of the facial nerve. The classic triad of Ramsay-Hunt is pain and vesicles in the external auditory canal, loss of taste on the anterior two-thirds of the tongue, and ipsilateral facial palsy. The facial palsy may be prolonged and severe. The presence of Ramsay-Hunt is a risk factor for CNS zoster.

Zoster oticus. Note lesions in the external auditory canal. [Weisshaar E, Kallen U, Klintworth N, Zenk J. Pruritus, erytheme & co: das ohr aus dermatologischer sicht. HNO. 2011 Mar;59(3):301–10.]

- Shingles rarely may involve the CNS. CNS involvement can manifest as meningoencephalitis, transverse myelitis (with or without motor involvement), or, very rarely, granulomatous angiitis.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Herpes Zoster"[Mesh] OR "Shingles"

Chapter 35
Hiatal Hernia

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Hiatal Hernia

- Hiatus Hernia

Incidence/Epidemiology

- Hiatal hernias commonly are found incidentally when patients undergo imaging for other reasons, or during endoscopy.
- Most hiatal hernias are asymptomatic.
- The true incidence is unknown, as they often are asymptomatic and only incidentally found.
- The incidence increases with age, obesity, and pregnancy.
- Hiatal hernias (especially type 1) significantly increase the risk for gastroesophageal reflux disease (GERD).

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_35

Differential Diagnosis

- Because hiatal hernias usually are found incidentally during either chest or abdominal imaging to evaluate another issue, there is no specific differential diagnosis. However, it is important to determine the type of hiatal hernia that exists.
- If the patient has symptoms, they usually are the symptoms of GERD; therefore, the differential is that of GERD, including:
    - Esophagitis
    - Gastritis
    - Peptic ulcer disease
    - Esophageal motility disorders
    - Functional dyspepsia

Pathophysiology and Etiology

- A hiatal hernia is a structural disorder of the esophagus marked by the herniation of intra-abdominal contents (most often the cardia of the stomach) through the esophageal hiatus of the diaphragm.
- The esophagus is anchored to the diaphragm by the phrenoesophageal membrane (PEM) or ligament. The PEM is composed mostly of elastic connective tissue and inserts circumferentially into the esophageal musculature at the diaphragmatic hiatus. A defect or laxity of the PEM allows for the herniation of abdominal contents.
- It most commonly is thought to be caused by age-related degeneration of the PEM.
- Longstanding acid reflux also may lead to tonic contracture of the longitudinal muscle layer of the esophagus, resulting in increased stress on and degeneration of the PEM.
- Types II through IV are recognized complications of surgery involving the hiatus.
- There are four distinct anatomic types of hiatal hernia.
- Type I, or sliding hiatal hernia:
    - These account for about 95 % of all hiatal hernias.
    - Laxity of the PEM allows the gastric cardia to “slide” through the diaphragmatic hiatus. It is not a true hernia; there is no defect in the PEM and no true hernia sac.
    - The likelihood of symptomatic GERD increases with the size of the hernia.
    - It is felt that a hiatal hernia impairs the function of the gastroesophageal (GE) junction and prolongs clearance of esophageal contents, leading to symptoms of GERD.

- However, many asymptomatic patients are found to have a type I hiatal hernia.

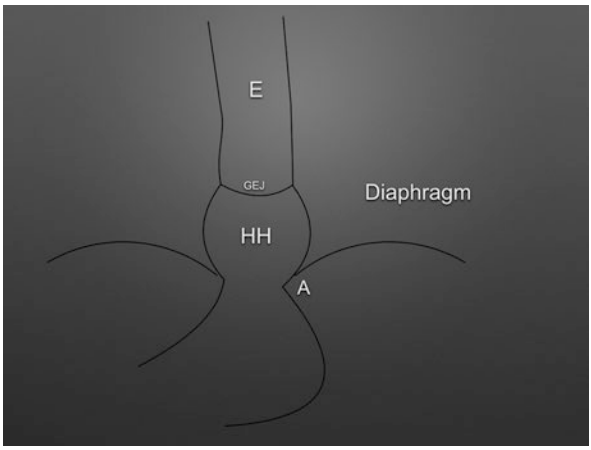

Diagram of a type I (sliding) hiatal hernia (HH). The gastroesophageal junction (GEJ) has migrated above the diaphragm into the chest. The Angle of HIS (A) is blunted, reducing its ability to protect against gastroesophageal reflux [Belafsky PC, Kuhn MA. The clinician's guide to swallowing fluoroscopy [Internet]. New York: Springer; 2014. Chapter 11, Abnormal esophageal fluoroscopy; [cited 2015 Aug 14]; p. 95–123. Available from: http://link.springer.com/10.1007/978-1-4939-1109-7_11] *Caption from original*

- Type II through IV:
  - Types II through IV are all paraesophageal hernias. They are true hernias with defects in the PEM and true hernia sacs, and include viscera other than the gastric cardia.
  - In a type II hernia, the gastric fundus also herniates, but the GE junction remains fixed at the hiatus.
  - Type III hernia is a combination of types I and II: it is both a sliding and a paraesophageal hernia.
  - Types II and III may lead to gastric volvulus and ischemia. As the defect enlarges, more of the stomach may herniate through. Because the stomach remains fixed at the GE junction, it may invert, leading to an upside down, intrathoracic stomach. This may interrupt the blood supply and cause ischemia, resulting in a mechanical gastric volvulus.
  - Type IV hiatal hernias are associated with the largest defects in the PEM, and they involve herniation of abdominal contents other than the stomach, most commonly the colon.
  - Type III is the most common type of paraesophageal hiatal hernia, accounting for about 90 % of paraesophageal hernias. Type II is the least common.

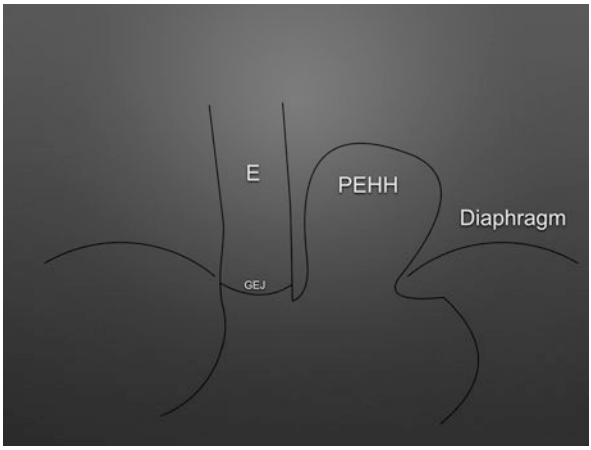

Diagram of a type II hiatal hernia. A type II hernia is a pure paraesophageal hiatal hernia (PEHH) and the gastroesophageal junction (GEJ) remains at or below the level of the diaphragm [Belafsky PC, Kuhn MA. The clinician's guide to swallowing fluoroscopy [Internet]. New York: Springer; 2014. Chapter 11, Abnormal esophageal fluoroscopy; [cited 2015 Aug 14]; p. 95–123. Available from: http://link.springer.com/10.1007/978-1-4939-1109-7_11] *Caption from original*

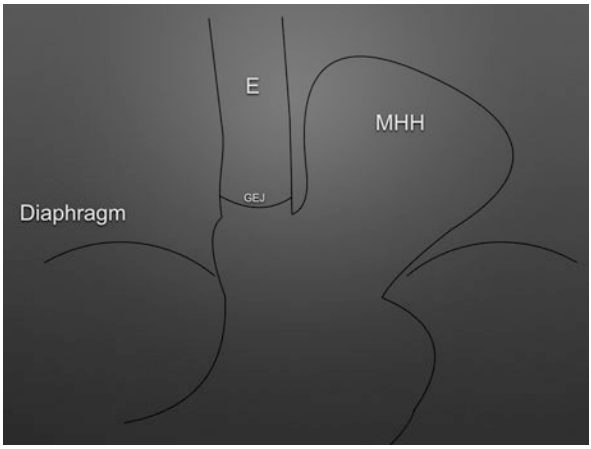

Diagram of a type III (mixed) hiatal hernia (MHH). A type III hiatal hernia is a mixed hernia in which the fundus and gastroesophageal junction (GEJ) have herniated alongside each other above the diaphragm into the chest. The majority of paraesophageal hiatal hernias are type III [Belafsky PC, Kuhn MA. The clinician's guide to swallowing fluoroscopy [Internet]. New York: Springer; 2014. Chapter 11, Abnormal esophageal fluoroscopy; [cited 2015 Aug 14]; p. 95–123. Available from: http://link.springer.com/10.1007/978-1-4939-1109-7_11] *Caption from original*

Sagittal CT scan images of a patient with a large Type IV hiatal hernia; note the retrocardiac herniation of small bowel [Sarpel U. Surgery: an introductory guide [Internet]. New York: Springer; 2014. Chapter 4, Fundoplication; [cited 2015 Aug 14]; p. 27–35. Available from: http://link.springer.com/10.1007/978-1-4939-0903-2_4] *Caption from original*

Presentation

Typical/"Classic"

- Most are asymptomatic.
- Type I (sliding) hiatal hernias often are associated with symptomatic GERD.
- Type II through IV (paraesophageal) hernias often have ambiguous symptoms. They may be asymptomatic, or patients may describe epigastric or chest pain, early satiety, excessive fullness after eating, nausea, or retching. GERD is a less common complaint for these types.

Atypical

- Because most hiatal hernias are asymptomatic, there are no typical or atypical features.

Primary Differential Considerations

- Chest pain resulting from hiatal hernia often is nonspecific. Other diagnoses that should be considered early in the evaluation of patients with similar symptoms include:
  - Acute coronary syndrome
  - GERD
  - Peptic ulcer disease
  - Pneumonia
  - Gastric outlet obstruction
  - Esophageal food bolus impaction or other foreign body

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis can be confirmed only by imaging, most likely by CT scan but also by barium study of the upper gastrointestinal tract.
- There are no confirmatory historical or physical examination findings.

Factors That Suggest Diagnosis

- Sliding hiatal hernias are suggested in patients with symptoms of GERD and increasing age.
- Paraesophageal hernias are suggested in patients who have vagus upper abdominal symptoms have had a previous surgical procedure involving the diaphragmatic hiatus.

Factors That Exclude Diagnosis

- Paraesophageal hernias can be excluded by a normal CT scan.
- Small sliding hiatal hernias may be missed on endoscopy and imaging and therefore cannot be excluded, but their clinical significance remains in question.

Ancillary Studies

Laboratory

- Laboratory studies are not helpful in the diagnosis of hiatal hernia.

Imaging

- Sliding hiatal hernias often are diagnosed incidentally on imaging studies (chest x-ray, chest and abdominal CT). They also may be found on other imaging studies, such as endoscopy, barium swallow or upper gastrointestinal series, or esophageal manometry. However, sliding hiatal hernias less than 2 cm long may be missed by all the aforementioned studies.
- Paraesophageal hernias usually are diagnosed by CT of the chest and abdomen. Although barium swallow is performed less frequently, it is more sensitive in detecting paraesophageal hernias.

Special Populations

Age

- The incidence of sliding hiatal hernias increases with age.

Co-morbidities

- Sliding hiatal hernia may coexist with any other diagnosis.
- Paraesophageal hernias are found mostly in patients who have had prior thoracic or abdominal surgery involving manipulation of the diaphragmatic hiatus.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- A critical mistake would be attributing a patient's symptoms (especially chest pain, epigastric pain, nausea and/or vomiting, and shortness of breath) to a sliding hiatal hernia and not continuing diagnostic evaluation for other causes.

Mimics

- Because hiatal hernias usually are asymptomatic, no significant mimics exist, and they typically do not mimic any other diseases.
- The appearance on imaging studies, especially plain radiographs, may sometimes mimic that of an elevated hemidiaphragm or a cavitary lung lesion.

Time-Dependent Interventions

- There are no time-dependent interventions.

Overall Principles of Treatment

- There is no specific treatment for a sliding hiatal hernia; treatment often is aimed at symptomatic treatment of GERD.
- It is important to stress that atypical symptoms, such as chest pain, abdominal pain, and shortness of breath, should not be attributed to a sliding hiatal hernia.
- Asymptomatic paraesophageal hernias often are treated conservatively with only follow-up.
- Symptomatic or very large paraesophageal hernias may need to be repaired surgically.

Disease Course

- Sliding hiatal hernias often grow and worsen in radiologic appearance as the patient ages, which may increase the likelihood of symptomatic GERD, although the true clinical significance is unknown.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Hernia, Hiatal"[Mesh] OR "Hiatal Hernia" OR "Hiatus Hernia"

Chapter 36
Hypertension

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Hypertension

- High blood pressure, "high blood"

Incidence/Epidemiology

- Hypertension is the most prevalent disease state in the world.
- There are many definitions and staging systems for hypertension, but in general, a diastolic blood pressure greater than 90 mm Hg and/or a systolic blood pressure greater than 150 mm Hg are associated with the incidence of cardiovascular and cerebrovascular disease, and with benefit from chronic pressure-lowering therapy.
- Most cases of hypertension are "primary" (also called "essential"), but there are secondary causes, such as renal disease, pheochromocytoma, hyperaldosteronism, and Cushing's syndrome. Pregnancy is also often associated with hypertension.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_36

- Many adjectives frequently are associated with hypertension, such as *controlled* or *uncontrolled*, *resistant* for hard-to-treat hypertension, and *accelerated* or *malignant* for hypertension that is severe and acute.
- Prevalence is higher among African American populations than white populations.

Hypertension is highly prevalent
Hypertension is associated with an increased risk of heart disease, stroke, renal failure, and death
The treatment of moderate and severe hypertension reduces the risk of hypertensive complications
The treatment of mild hypertension decreases the incidence of strokes and probably reduces the incidence of CHD
The treatment of hypertension is widespread, and approximately $10 billion/y is spent on therapy

The epidemiology and rationale for cost-effectiveness analysis of the treatment of hypertension. CHD—coronary heart disease. [Heidenreich P, Krumholz H. Cost-effectiveness of risk factors. In: Grundy SM, editor. Atlas of atherosclerosis. 4th ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-224-9] *Caption from original*

Blood pressure, mmHg	NICE 2011 [3]	ESH/ESC 2013 [4]	AHA/ACC/CDC 2013 [6]	ASH/ISH 2013 [5]	JSH 2014 [7]	JNC 8 [2]
Definition of hypertension	≥140/90 and daytime ABPM (or home BP) ≥135/85	≥140/90	≥140/90	≥140/90	≥140/90 and home BP ≥135/85	Not addressed
In mild hypertension at low to moderate risk, lifestyle management without drugs can be considered	Not addressed	Not addressed	3 months	Some months	3 months	Not addressed
Initiate drug therapy in low-risk patients	≥160/100 or daytime ABPM ≥150/95	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90 for <60 years ≥150/90 for ≥60 years
Blood pressure targets						
Diabetes	Not addressed	<140/85	<140/90 Lower targets may be appropriate	<140/90	<130/80	<140/90
CKD with proteinuria	Not addressed	SBP <130 may be considered	<140/90 Lower targets may be appropriate	<130/80	<130/80	<140/90
Elderly	<150/90 for ≥80 years	SBP 140–150 for ≥80 years	<140/90 Lower targets may be appropriate	<150/90 for ≥80 years	<150/90 for >75 years, <140/90, if tolerated	<150/90 for ≥60 years

NICE the National Institute for Health and Clinical Excellence, *ESH/ESC* the European Society of Hypertension and the European Society of Cardiology, *AHA/ACC/CDC* the American Heart Association, the American College of Cardiology, and the Centers for Disease Control and Prevention, *ASH/ISH* the American Society of Hypertension and the Internal Society of Hypertension, *JSH* the Japanese Society of Hypertension, *JNC-8* the Eighth Joint National Committee, *ABPM* ambulatory blood pressure monitoring, *BP* blood pressure, *CKD* chronic kidney disease, *SBP* systolic blood pressure

Comparison of hypertension guidelines regarding definition of hypertension and blood pressure targets 2011–2014. [Kokubo Y, Iwashima Y, Kamide K. Hypertension: introduction, types, causes, and complications. In: Jagadeesh G, Balakumar P, Maung-U K, editors. Pathophysiology and pharmacotherapy of cardiovascular disease [Internet]. Cham, Switzerland: Springer; 2015 [cited 2015 Jun 22]. p. 635–53. Available from: http://link.springer.com/10.1007/978-3-319-15961-4_30] *Caption from original*

Differential Diagnosis

- Hypertension is a quantitatively defined disease. Consideration of differentials is more limited to possible causes of secondary disease. Hypertension may also be a cardinal aspect of the presentation of acute coronary syndrome, acute heart failure, acute renal failure, and acute stroke. Acute presentations also may be prompted by anxiety, stimulant use, or steroid use.

Primary care	Cause of resistant hypertension	Tertiary center
Problems with BP measurement		
20–30%	White-coat hypertension	10–20%
Medication-related causes		
~5%	Suboptimal medication regimen	30–60%
~10%	Drug-drug interaction	<5
<2%	Objective medication intolerance[a]	<2%
Interfering substances		
1–5%	Excessive dietary sodium	1–10%
1–7%	Ethanol or illicit substances	1–12%
Secondary hypertension		
<5%	Sleep apnea/aldosterone excess	1–83%
<5%	Traditional secondary causes[b]	5–28%
Psychological causes		
1–2%	Anxiety/panic disorder/depression	1–2%
1–2%	Subjective medication intolerance[a]	1–5%

[a] Objective and subjective medication intolerance are distinguished based on whether or not, respectively, the patient's reported adverse effect is mentioned in the prescribing information approved by the US Food and Drug Administration.

[b] Traditional secondary causes include renovascular hypertension, primary hyperaldosteronism, pheochromocytoma, Cushing's syndrome, etc.

BP blood pressure.

Differential diagnosis of resistant hypertension, with relative proportion of each, depending on the population studied. [Elliott WJ. Management of resistant hypertension. Curr Cardiovasc Risk Rep. 2011 Oct;5(5):373–82.] *Caption from original*

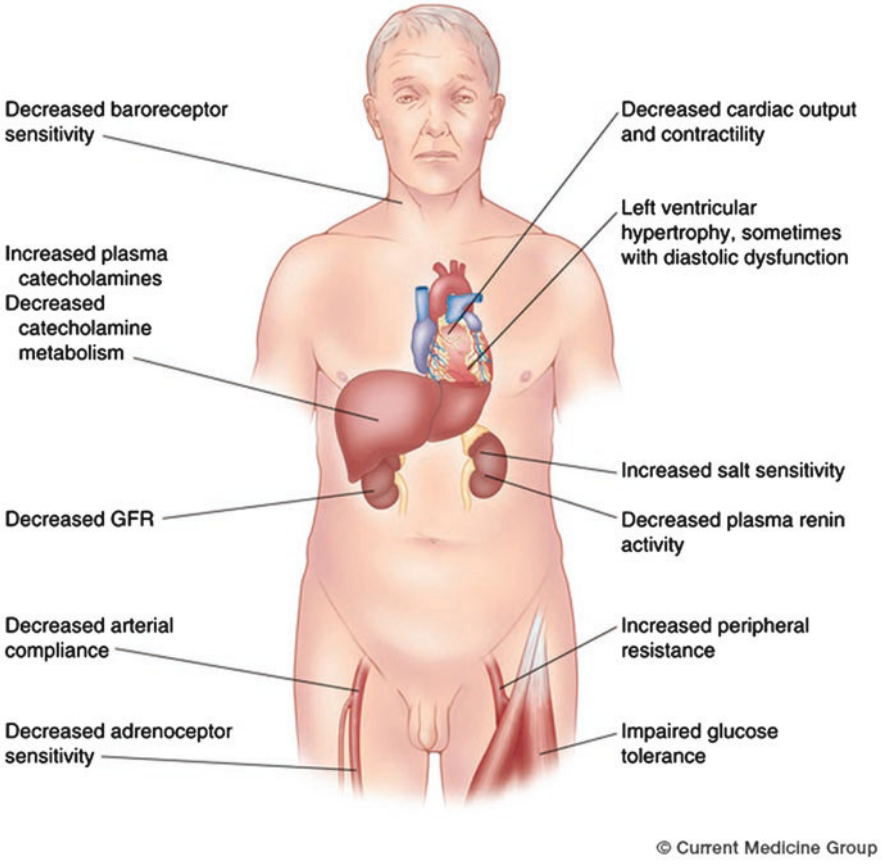
Pathophysiology and Etiology

- Hypertension is a pleomorphic disease, the etiology of which may be inapparent (although even in these cases, a genetic contribution is likely)
- Other defined causes include
  - Renal (renal artery stenosis, chronic pyelonephritis, polycystic kidney disease)
  - Endocrine (adrenocortical hyperfunction, pheochromocytoma)
  - Neurogenic (dysautonomia)
  - Vascular (such as coarctation of the aorta or polyarteritis nodosa)
- Factors contributing to hypertension are varied and include
  - Obesity
  - Salt intake
  - Alcohol intake
  - Medication use
  - Drug abuse
  - Tobacco use

Age Group	Etiology
Newborn	Renal artery or venous thrombosis
	Renal artery stenosis
	Congenital renal abnormalities
	Coarctation of the aorta
	Bronchopulmonary dysplasia
	History of Prematurity
First Year	Renovascular disease
	Renal parenchymal disease
	Coarctation of the aorta
	Iatrogenic (medication, volume)
	Tumor
	History of Prematurity
1 to 6 years	Renal parenchymal disease
	Renovascular disease
	Coarctation of the aorta
	Tumor
	History of Prematurity
	Endocrine causes*
	Iatrogenic
	Essential hypertension
Age 6 to 10 years	Renal parenchymal disease
	Essential hypertension
	Renovascular disease
	Coarctation of the aorta
	Endocrine causes
	Tumor
	Iatrogenic
Adolescence, Age 12 to 18 years	Essential hypertension
	Iatrogenic
	Renal parenchymal disease
	Endocrine causes
	Coarctation of the aorta

Shaded areas are uncommon for category

Most Common Causes of Secondary Hypertension: By Age. [Samuel JP, Swinford RD, Portman RJ. Evaluation of hypertension in pediatric patients. In: Flynn JT, Ingelfinger JR, Portman RJ, editors. Pediatric hypertension [Internet]. Totowa, NJ: Humana Press; 2013 [cited 2015 Jun 22]. p. 491–504. Available from: http://link.springer.com/10.1007/978-1-62703-490-6_32] *Caption from original*



Some of the pathophysiologic features of hypertension in the elderly. Although some features are common in many elderly patients with elevated blood pressure, it is unusual for all of these features to be present in any one patient. GFR—glomerular filtration rate. [Elliott WJ, Black HR. Special situations in the management of hypertension. In: Hollenberg NK, editor. Atlas of hypertension. 6th ed. Philadelphia, PA: Springer; 2009. 334 p. ISBN: 978-1-57340-308-5] *Caption from original*

Presentation

Typical/"Classic"

- Most patients with hypertension are asymptomatic, and their elevated blood pressure is discovered incidentally.
- Moderate to severe hypertension may prompt presentation with headache, dizziness, epistaxis, or hematuria. Anxiety also is common.

- Severe hypertension may present as headache, dizziness, epistaxis, chest pain, dyspnea and heart failure, syncope, or stroke.
- There may be a history of stimulant use/abuse.

Atypical

- Health care providers often are surprised that patients with (chronically) very high blood pressures are asymptomatic.

Primary Differential Considerations

- As above, differential considerations usually apply to the symptoms that manifest with hypertension, not the elevated blood pressure itself.

History and Physical Exam

- In the history, focus on family history, age of onset, medication use (especially steroids and oral contraceptives), alcohol and drug abuse, history of renal disease, and signs and symptoms of other cardiovascular disease.
- On physical examination, note the patient's general appearance and overall health. Blood pressure should be checked in both upper extremities. Note height and weight. A thorough funduscopic exam should be performed to look for hypertensive changes. Check for neck and abdominal bruits. Listen for a fourth heart sound.

Fourth heart sound. [Fourth Heart Sound; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]
http://www.easyauscultation.com/cases-listing-details?caseID=42

Findings that Confirm Diagnosis

- Elevated blood pressure in both upper extremities should be documented in confirmation of the diagnosis. To make a new diagnosis of hypertension, the blood pressure should be elevated on at least two separate evaluations.

Factors that Suggest Diagnosis

- A history of elevated blood pressure and suggestive symptoms as above.

Factors that Exclude Diagnosis

- Repeatedly normal blood pressure excludes acute hypertension but may not fully exclude chronic disease.

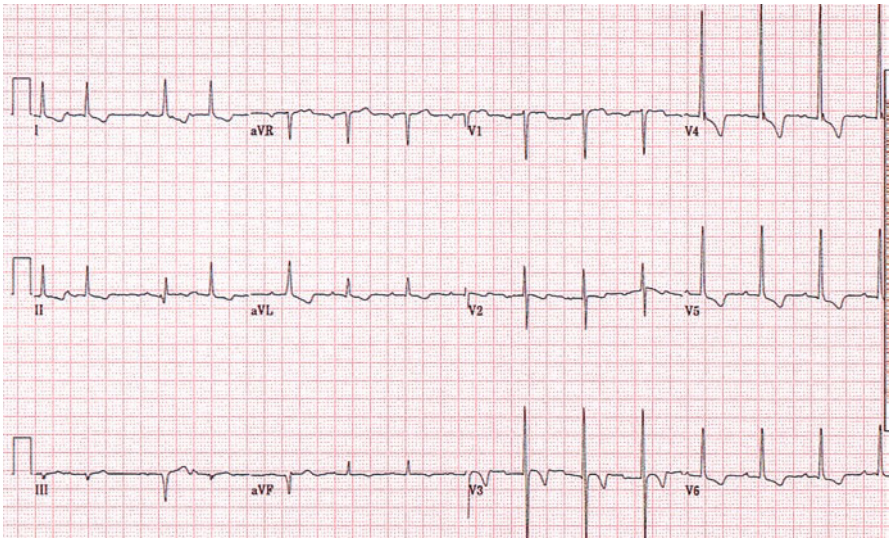
Ancillary Studies

Laboratory

- Baseline CBC (to exclude anemia) and renal function should be evaluated.
- Urine should be checked for protein, blood, and glucose.
- Serum electrolytes (especially potassium) should be checked.
- Lipid profile may be helpful.
- Serum calcium, phosphate, and uric acid should be checked.

Electrocardiography

- Should be obtained to evaluate rhythm and to look for left ventricular hypertrophy or Q waves.

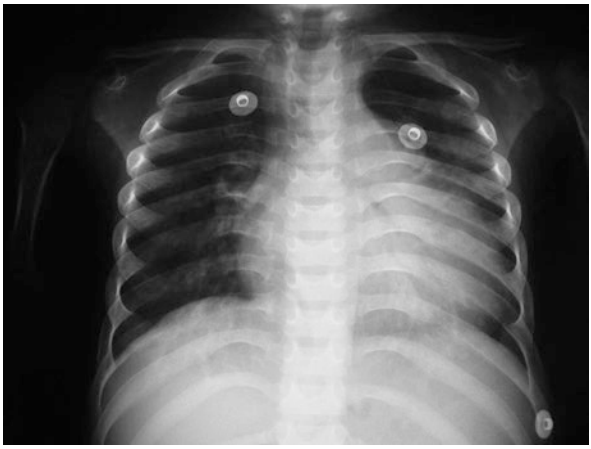


A 12-lead electrocardiogram demonstrating left ventricular hypertrophy with a "strain" pattern. [Fleisher L. Chapter 3. In: Lichtor JL, editor. Preoperative preparation and intraoperative monitoring. Philadelphia: Current Medicine; 1997. 251 p.

(Miller RD, editor. Atlas of anesthesia; vol. 3.) ISBN: 0-443-07902-1] *Caption adapted from original*

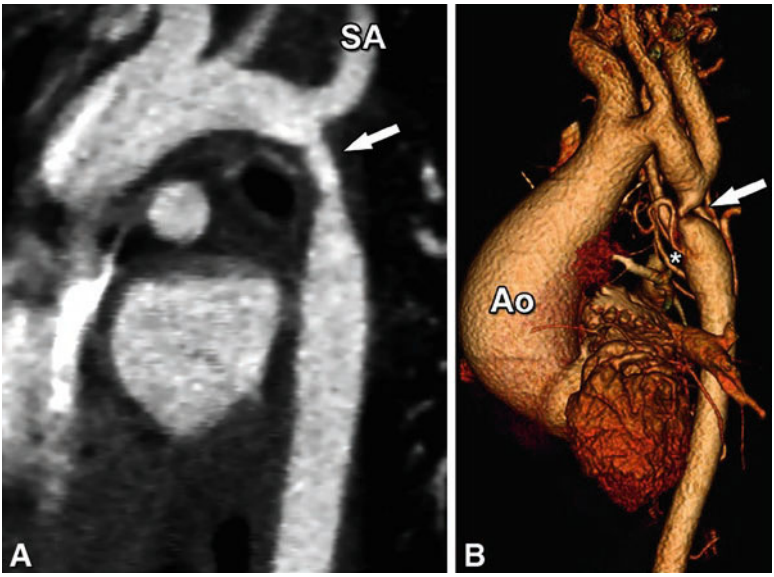
Imaging

- Chest x-ray should be obtained to look for cardiac enlargement, aortic dilation, rib notching from aortic coarctation, or signs of pulmonary edema.



Cardiomegaly on chest X-ray. [Yıldırım SV, Durmaz C, Pourbagher MA, Erkan AN. A case of achondroplasia with severe pulmonary hypertension due to obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2006 Aug;263(8):775–7.] *Caption from original*

- Concern for aortic disease should prompt more sophisticated imaging.



Aortic coarctation in two patients. Panel A is a double-oblique image from a prospectively ECG-triggered CT scan showing coarctation in a 2-year-old patient (arrow) just distal to the takeoff of the left subclavian artery (SA). The high-pitch CT scan was performed during free breathing with an acquisition time of 0.25 s and a dose-length product of 6 Gy.cm. The patient underwent subsequent repair of coarctation with an end-to-end anastomosis. Panel B shows a three-dimensional reconstruction of a CT scan performed for evaluation of severe aortic coarctation (arrow) in an 11-year-old patient who presented for evaluation of a murmur. His ascending aorta (Ao) was dilated and the murmur was secondary to aortic insufficiency. He was noted to be hypertensive with a blood pressure gradient of 30 mmHg between the right arm and leg. Note the collateral vessels supplying the descending aorta (asterisk). He underwent surgical repair of aortic coarctation and has since been followed clinically for aortic insufficiency and aortic root dilation [Ley S, Han BK, Arnold R, Lesser JR. Congenital and acquired heart disease. In: Dewey M, editor. Cardiac CT [Internet]. Berlin, Heidelberg: Springer; 2014 [cited 2015 Jun 22]. p. 393–414. Available from: http://link.springer.com/10.1007/978-3-642-41883-9_26] *Caption from original*

Other Studies

- Echocardiography or renal ultrasound imaging may be indicated

Special Populations

Age

- Essential hypertension rarely occurs in children. Younger patients with hypertension should be evaluated for secondary causes.
- The most common causes of hypertensive emergencies by age are listed in the table below:

Infancy	Childhood	Adolescence
Renal vascular disease	Renal disease	Primary hypertension
Congenital renal anomaly	Renal vascular disease	Nonadherence to meds
Coarctation	Pheochromocytoma	Renal disease
Volume overload	Increased intracranial pressure	Toxemia
Renal disease	Drug induced	Pheochromocytoma
Renal vein thrombosis		Illicit drug use
Congenital adrenal hyperplasia		

Co-morbidities

- May include:
  - Renal disease
  - Cardio- and cerebrovascular disease
  - Drug and alcohol abuse
  - Endocrine disorders such as diabetes, metabolic syndrome, Cushing's syndrome, or primary hyperaldosteronism

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Recognition of "hypertensive emergency," as this requires parenteral treatment. Hypertensive emergency is defined as acute hypertension plus end-organ damage, such as acute heart failure, acute coronary syndrome, acute aortic dissection, or acute stroke.

Definitions of Hypertensive Emergencies and Urgencies

Hypertensive emergency
Severe elevation in blood pressure with signs or symptoms of acute, severe target organ damage, which must be reduced within minutes (typically using parenteral therapy)
Hypertensive urgency
Severe elevation in blood pressure with mild or no acute target organ damage, which must be reduced within hours (typically with oral therapy)

Definitions of hypertensive emergencies and hypertensive urgencies (Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA. 2003;289:2560–72; Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. National High Blood Pressure Education Program Coordinating Committee. Hypertension. 2003;42:1206–52). Note that the older terms *accelerated hypertension* and *malignant hypertension* have been eliminated (with the exception of the terminology used by hospital administrators, as mandated by the Federal Diagnosis-Related Groups Handbook). Severe hypertension without acute target organ damage is never an emergency and does not require parenteral therapy. [Elliott WJ, Black HR. Special situations in the management of hypertension. In: Hollenberg NK, editor. Atlas of hypertension. 6th ed. Philadelphia, PA: Current Medicine Group; 2009. 334 p. ISBN: 978-1-57340-308-5] *Caption from original*

Essential or accelerated hypertension
Acute aortic dissection
Preeclampsia and eclampsia
Acute myocardial infarction or ischemia
Endocrine disorders
  Pheochromocytoma (excess catecholamines)
  Aldosteronism
  Renin-secreting tumors
  Glucocorticoid excess
Renal diseases
  Chronic pylonephritis
  Renal parenchymal disease (glomerulonephritis)
  Renovascular disease
Drugs
  Cocaine
  Amphetamines
  Clonidine and methyldopa withdrawal
  Monoamine oxidase inhibitor interactions
Central nervous system injury/trauma

Causes of hypertensive emergencies. [Brennan KJ, Goldman J, D'Alonzo GE. Hypertensive crisis. In: Criner GJ, Barnette RE, D'Alonzo GE, editors. Critical care study guide 2e [Internet]. New York, NY: Springer; 2010 [cited 2015 Jun 22].

p. 1060–75. Available from: http://link.springer.com/10.1007/978-0-387-77452-7_53] *Caption from original*

Mimics

- Anxiety
- Intoxication

Time-Dependent Interventions

- In true hypertensive emergency, rapid reduction of the blood pressure (by no more than 20 %), with accompanying treatment as needed for reflex tachycardia, is required

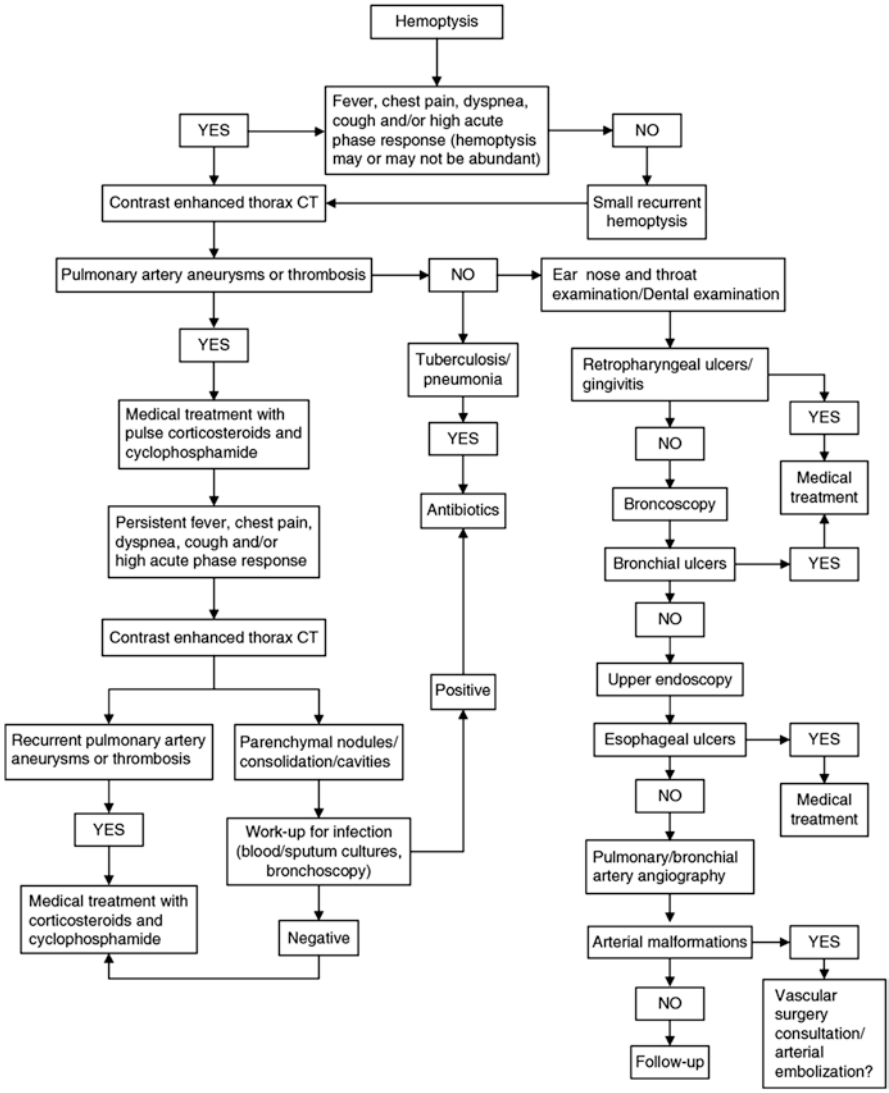
*These doses may vary from those in the Physicians Desk Reference, 51st edition.†Hypotension may occur with all agents.‡Requires special delivery system.

DRUG	DOSE	ONSET OF ACTION	DURATION OF ACTION	ADVERSE EFFECTS†	SPECIAL INDICATIONS
Vasodilators					
Sodium nitroprusside	0.25–10 μg/kg/min as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies, except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 μg/kg/min IV infusion	< 5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100μg/min as IV infusion	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 h IV	15–30 min	6–12 h	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV	10–20 min IV	1–4 h IV	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
	10–40 mg IM	20–30 min IM	4–6 h IM		
Adrenergic inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min	5–10 min	3–6 h	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies, except acute heart failure
	0.5–2.0 mg/min IV infusion				
Esmolol hydrochloride	250–500μg/kg/min IV bolus	1–2 min	10–30 min	Hypotension, nausea, asthma, first-degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

Parenteral drugs for treatment of hypertensive emergencies. IM—intramuscular; IV—intravenous. [Hollenberg NK. Recommendations of the JNC 7 report. In: Hollenberg NK, editor. Atlas of hypertension. 5th ed. Philadelphia, PA: Current Medicine Group; 2005. 383 p. ISBN: 1-57340-220-6] *Caption from original*

Overall Principles of Treatment

- Do not treat chronic hypertension aggressively; it may have taken years for the patient to develop hypertension; there is no physiologic reason to try to correct it in days, much less hours.
- Be alert for signs of end-organ damage in patients with acute hypertension.



Algorithm for diagnosis and management of hemoptysis due to Behçet's syndrome [Seyahi E, Tascilar K, Yazici H. Behçet's syndrome: clinical presentations affecting prognosis and survival. In: Khamashta MA, Ramos-Casals M, editors. Autoimmune

diseases [Internet]. London: Springer; 2011 [cited 2015 Jun 22]. p. 163–84. Available from: http://link.springer.com/10.1007/978-0-85729-358-9_11] *Caption from original*

Situations	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)
Uncomplicated hypertension	140	90
Elderly	140–150	90
Diabetes mellitus	140	85
Stroke	140	90
Coronary artery disease	140	90
Chronic kidney disease		
Without albuminuria[a]	140	90
With albuminuria	130	80

[a]Microalbuminuria or macroalbuminuria.

Target blood pressures in hypertension treatment. [From article: 2013 Korean Society of Hypertension guidelines for the management of hypertension. Part II—treatments of hypertension. Clin Hypertens. 2015 Dec;21(1). https://doi.org/10.1186/s40885-014-0013-2, at http://link.springer.com/article/10.1186%2Fs40885-014-0013-2; by Jinho Shin, Jeong Bae Park, Kwang-il Kim, Ju Han Kim, Dong Heon Yang, Wook Bum Pyun, Young Gweon Kim, Gheun-Ho Kim, Shung Chull Chae, The Guideline Committee of the Korean Society of Hypertension, © Shin et al.; licensee BioMed Central. 2015; licensed under Creative Commons Attribution License BY 4.0 http://creativecommons.org/licenses/by/4.0] *Caption from original*

Risk factor	Blood pressure (mm Hg)		
	Stage 2 prehypertension (130–139/85–89)	Stage 1 hypertension (140–159/90–99)	Stage 2 hypertension (≥160/100)
Risk factors 0	Lifestyle modification	Lifestyle modification[a] or drug therapy	Lifestyle modification or drug therapy[†]
Risk factors 1–2 other than DM	Lifestyle modification	Lifestyle modification[a] or drug therapy	Lifestyle modification and drug therapy
Risk factors ≥3, subclinical organ damage	Lifestyle modification	Lifestyle modification and drug therapy	Lifestyle modification and drug therapy
DM, cardiovascular disease, chronic kidney disease	Lifestyle modification or drug therapy[b]	Lifestyle modification and drug therapy	Lifestyle modification and drug therapy

DM diabetic mellitus.
[a]Lifestyle modification is carried within several weeks to 3 months. [†]Drug therapy may be begun immediately according to the height of BPs.
[b]Drug therapy may be begun as target blood pressure determined.

Treatment for hypertension according to the risk. [From article: 2013 Korean Society of Hypertension guidelines for the management of hypertension. Part II—treatments of hypertension. Clin Hypertens. 2015 Dec;21(1). https://doi.org/10.1186/s40885-014-0013-2, at http://link.springer.com/article/10.1186%2Fs40885-014-0013-2; by Jinho Shin, Jeong Bae Park, Kwang-il Kim, Ju Han Kim, Dong Heon Yang, Wook Bum Pyun, Young Gweon Kim, Gheun-Ho Kim, Shung Chull Chae, The Guideline

Committee of the Korean Society of Hypertension, © Shin et al.; licensee BioMed Central. 2015; licensed under Creative Commons Attribution License BY 4.0 http://creativecommons.org/licenses/by/4.0] *Caption from original*

Disease Course

- Patients with hypertension die prematurely, most often of heart disease, stroke, or renal failure
- Treatment is positively correlated with outcomes.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guidelines

Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, Gottdiener J, Haluska B, Ofili E, Segers P, Senior R, Tapp RJ, Zamorano JL. Recommendations on the use of echocardiography in adult hypertension: a report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE)†. Eur Heart J Cardiovasc Imaging. 2015 Jun;16(6):577-605. PMID: 25995329. http://www.ncbi.nlm.nih.gov/pubmed/25995329 **

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Hypertension"[Mesh] OR "hypertension" OR "high blood pressure"

Chapter 37
Hypertrophic Cardiomyopathy

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Hypertrophic cardiomyopathy (HCM)

- Obstructive cardiomyopathy, idiopathic hypertrophic subaortic stenosis (IHSS)

Incidence/Epidemiology

- HCM is defined by hypertrophy of the left ventricle, usually in the absence of dilation of the chamber itself.
- At least half the cases of HCM are hereditary.
- It occurs in well under 1 % of the US population.

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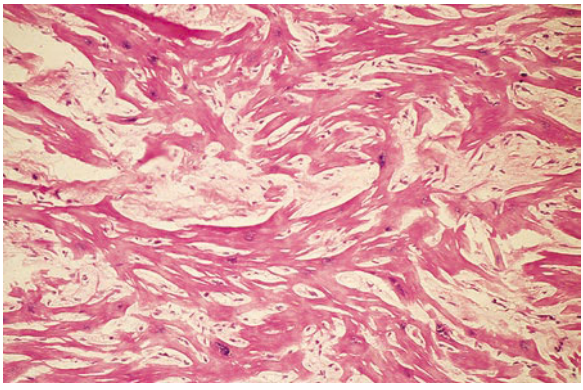
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_37

Differential Diagnosis

- The primary differential considerations for chest pain due to HCM include valvular aortic stenosis and other types of obstructive or restrictive cardiomyopathy.
- Simple left ventricular hypertrophy (LVH) may be identified on electrocardiogram or chest radiography, and is much more common than HCM. LVH is usually the result of systemic hypertension.
- The entire constellation of differential considerations for unstable angina, aortic dissection, and pulmonary embolism should be considered, and may coexist with HCM.
- HCM may also present as syncope or near-syncope, which has broad differentials, including cardiac, neurologic, metabolic, psychiatric, and toxicologic etiologies.

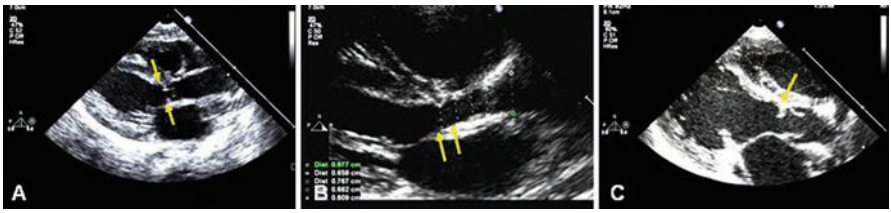
Pathophysiology and Etiology

- The hallmark of HCM is that it occurs in the absence of typical inciting factors for LVH.



Hypertrophic cardiomyopathy. Typical histologic appearance in hypertrophic cardiomyopathy. Histologically, the left ventricle in hypertrophic cardiomyopathy exhibits disarray of myofibers and often extensive interstitial fibrosis. [Saffitz J, Zimmerman F, Lindsay B. Pathology of cardiac arrhythmias. In: McManus B, Braunwald E, editors. Atlas of cardiovascular pathology for the clinician. Philadelphia: Current Medicine; 2000. Chapter 16. ISBN: 1-57340-160-9; 2002-01-21] *Caption adapted from original*

- It is often hereditary.
- Abnormal calcium metabolism in the myocardium may lie at the root of HCM. As intracellular calcium concentrations rise, the muscle hypertrophies.
- The hypertrophy is often asymmetric. As the interventricular septum hypertrophies, there is often narrowing of the LV outflow tract, resulting in "stenosis" below the aortic valve itself (hence the term *hypertrophic subaortic stenosis*). Reduction in flow may result in anginal chest pain.



Subaortic stenosis diagnosed by echocardiography. (**a)** Parasternal left ventricular long-axis sectional view showing circumferential membranous subaortic stenosis. (**b)** Parasternal left ventricular long-axis sectional view showing tunnel-type subaortic narrowing. (**c)** Parasternal left ventricular long-axis sectional view showing an asymmetric obstructive fibrous ridge at the interventricular septum side of the left ventricular outflow tract below the aortic valve. [Ma X, Huang G, Liang X, Liu X, Jia B. Atypical Shone's complex diagnosed by echocardiography. Pediatr Cardiol. 2011 Apr;32(4):442-8. https://doi.org/10.1007/s00246-011-9886-y; 2011-03-19] *Caption from original*

Presentation

Typical/"Classic"

- Many patients with HCM are asymptomatic, and the diagnosis is discovered incidentally on imaging studies.
- Symptomatic patients may present with:
  - Dyspnea, the most common presentation of symptomatic HCM, probably occurs because stiffness of the LV walls limits LV filling.
  - Anginal chest pain, thought to be due to inadequate cardiac output for the level of the patient's exertion.
  - Sudden cardiac death, usually due to ventricular fibrillation.
  - Syncope ("black-outs") and near-syncope ("gray-outs"), due to inadequate cardiac output for the level of the patient's exertion.
  - Palpitations, due to both ventricular and atrial ectopic beats.

Atypical

- Anginal chest pain (especially with dyspnea) and sudden cardiac death often present without known antecedent. These presentations may distract the clinician from the potential diagnosis of HCM.
- Syncope and near-syncope, especially in younger patients, have a broad differential and may often have a component of anxiety. This should not distract the clinician from completing a thorough cardiovascular examination.

Primary Differential Considerations

- In the patient presenting with signs and symptoms of HCM, early consideration should also be given to the following differential diagnoses:
  - Valvular aortic stenosis
  - Restrictive cardiomyopathy

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination are not diagnostic for HCM.

Factors That Suggest Diagnosis

- A family history of known HCM is helpful.
- Confirming that symptoms are related to exertion (especially chest pain, palpitations, dyspnea, and syncope/near-syncope) is helpful.
- A fourth heart sound (S4) is often present.

https://www.youtube.com/watch?v=r-HqK7NRL8I
Video about the fourth heart sound

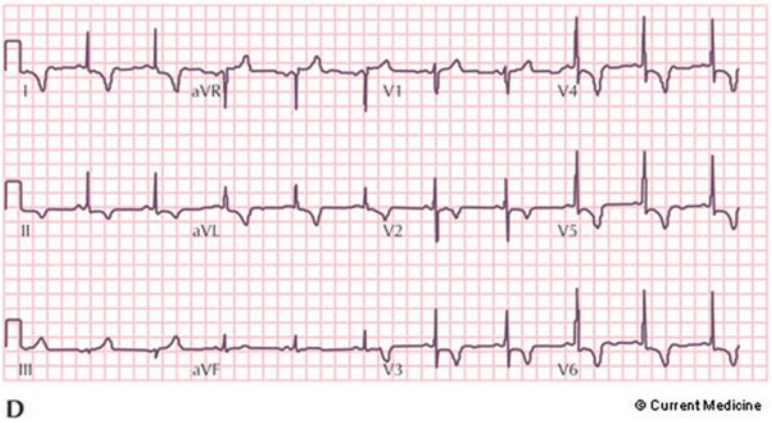
- A harsh, crescendo-decrescendo systolic murmur, heard best at the apex and lower left sternal border.

https://www.youtube.com/watch?v=2OK4-vWRlWo
Systolic Murmur video with color flow Doppler

- Mitral regurgitation is common in HCM, so the murmur may sound more blowing in nature.

https://www.youtube.com/watch?v=k3ubxo-JATU
Mitral regurgitation video providing sound and depiction of anatomy

- A double carotid pulse (pulsus bisferiens) is common.
- The 12-lead ECG shows LVH.



Echocardiogram of apical hypertrophic cardiomyopathy. Apical HCM is often associated with giant negative T waves on ECG, present in the lateral precordial leads (D). [Ho C, Maron B. Hypertrophic cardiomyopathy. In: Solomon SD, Braunwald E, editors. Atlas of echocardiography. Philadelphia: Current Medicine; 2008. Chapter 13. ISBN: 1-57340-217-6; 2008-10-22;] *Caption adapted from original*

Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude HCM.

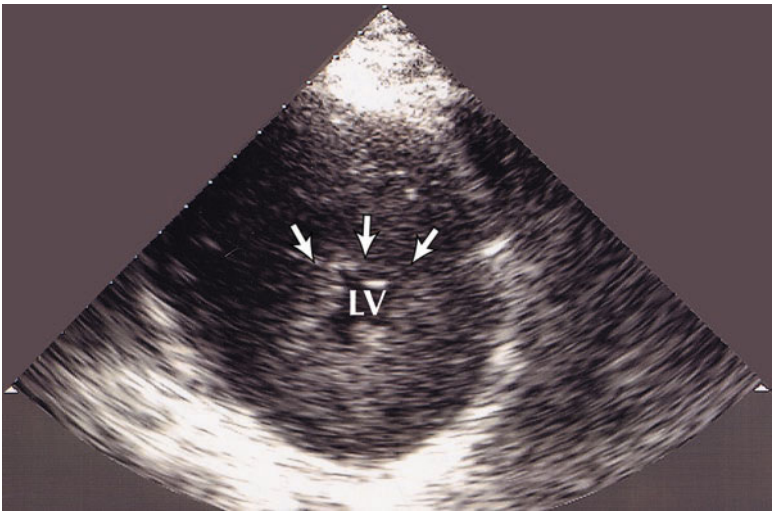
Ancillary Studies

Laboratory

- There are no diagnostic laboratory studies for HCM.

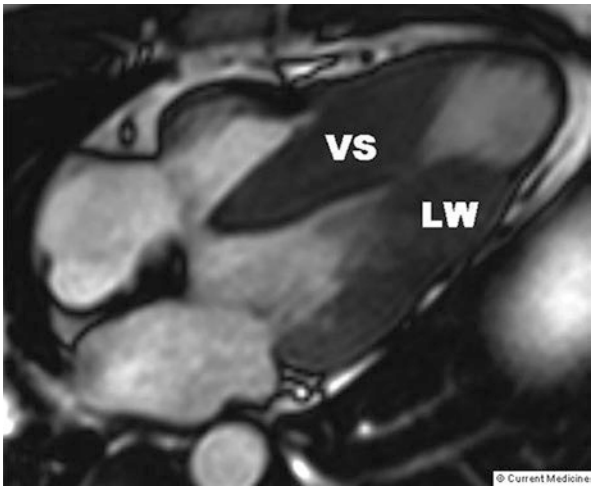
Imaging

- The diagnosis of HCM is confirmed on 2D echocardiography.



Hypertrophic cardiomyopathy. [Reimold S, Lee R. Echocardiography in acquired heart disease. In: Lee R, Braunwald E, editors. Atlas of cardiac imaging. Philadelphia: Current Medicine; 1998. Chapter 1. ISBN: 0-443-07567-0; 2002-01-23; Braunwald, Eugene]

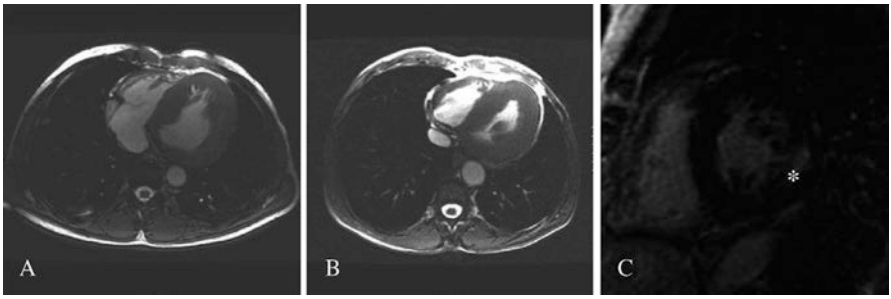
- Cardiac MRI also demonstrates HCM.



Cardiac MRI: hypertrophic cardiomyopathy with left ventricular aneurysm. Hypertrophic cardiomyopathy (HCM) patients with left ventricular (LV) apical

aneurysm represent an important but fairly uncommon subgroup of the HCM disease spectrum. HCM patients with apical aneurysms also commonly demonstrate midventricular obstruction because of midsystolic apposition of the hypertrophied ventricular septum (VS) and LV free wall. It was proposed that long-standing increased LV systolic pressures created by midventricular obstruction may contribute to apical aneurysmal formation in select susceptible HCM patients in the absence of coronary artery disease. A, HCM patient with an LV apical aneurysm and characteristic midventricular hypertrophy with apposition to the septum and LV free wall in midsystole, creating midventricular obstruction. [Maron M. Dilated cardiomyopathy. In: Manning WJ, Braunwald E, editors. Atlas of cardiovascular magnetic resonance. Philadelphia: Current Medicine; 2009. Chapter 13. ISBN: 978-1-57340-299-6; 2009-01-16] *Caption from original*

- If cardiac catheterization is performed (perhaps in the evaluation of anginal chest pain), HCM may be detected as an elevated LV diastolic pressure.



Cardiac MRI for the assessment of left ventricular hypertrophy and fibrosis: A: Left ventricular hypertrophy in a 51-year-old male patient with cerebrovascular involvement and end stage renal disease (dialysis). B: Hypertrophic cardiomyopathy in a 56-year-old male patient with arrythmya, leukoareiosis and kidney transplant. C: Late enhancement after gadolinium in a 63-year-old female patient with end stage renal disease (dialysis). [From article: Fabry disease. Orphanet J Rare Dis. 2010 Nov;5(1):30. https://doi.org/10.1186/1750-1172-5-30, at http://link.springer.com/article/10.1186/1750-1172-5-30; by Dominique P Germain, © Germain; licensee BioMed Central Ltd. 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Special Populations

Age and Gender

- HCM occurs slightly more often in males than in females.
- In females, HCM often presents at a younger age and tends to be more symptomatic.

- HCM is most commonly diagnosed in either the first or the third decade of life.
- HCM may present in infancy, but most pediatric cases present during the growth spurt associated with the onset of puberty.
- When it occurs in younger patients, it is most common for LVH to develop during the pubertal growth spurt.
- Wall thickness measurements generally do not change once adulthood is reached.

Co-morbidities

- A hereditary pattern is seen in about half the cases of HCM, but there are no typical co-morbidities.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. Echocardiography is required to confirm the diagnosis.

Mimics

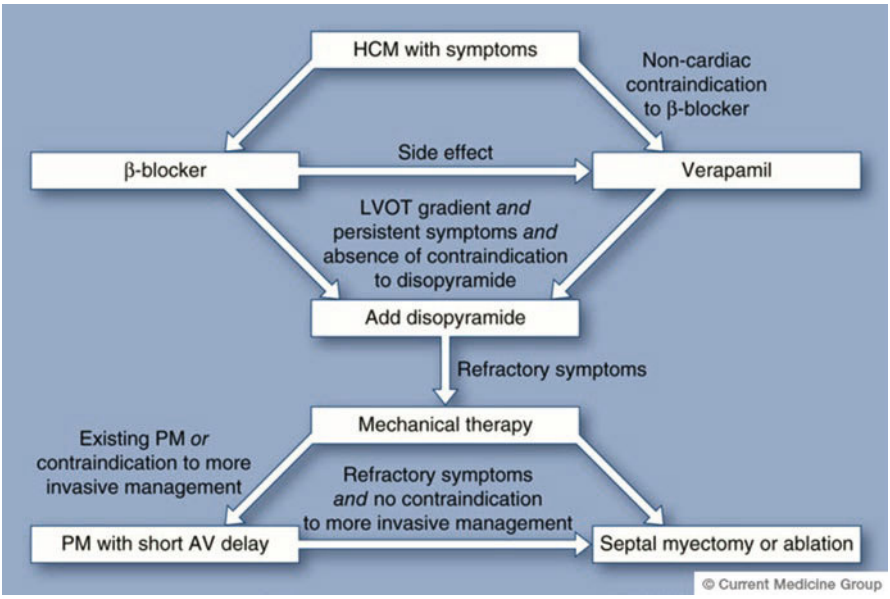
- The entire constellation of diagnoses that underlies chest pain syndrome, especially those often accompanied by dyspnea, can mimic the pain and overall presentation of HCM.
- Sudden cardiac death may mimic or be a presentation of HCM.
- Syncope or near-syncope may mimic or be a presentation of HCM.

Time-Dependent Interventions

- There are usually no time-dependent interventions in the management of HCM, unless the presentation is dramatic (angina, heart failure, arrhythmia/sudden death).

Overall Principles of Treatment

- Treatment of HCM is multimodal, with abstention from strenuous activities, beta-blockers, and calcium blockers often being used in maintenance care.



Treatment algorithm for hypertrophic cardiomyopathy. Proposed algorithm for the medical, mechanical, and surgical/interventional ablative treatment of patients with hypertrophic cardiomyopathy. Only 20% to 30% of patients with hypertrophic cardiomyopathy have outflow obstruction and would be candidates for the addition of disopyramide pacemaker therapy, or septal ablation [15]. AV—atrial ventricular; HCM—hypertrophic cardiomyopathy; LVOT—left ventricular outflow tract; PM—pacemaker. [Baughman K. Cardiomyopathy, myocarditis, and pericardial disease. In Libby P, editor. Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. Chapter 6. ISBN: 978-1-57340-309-2; 2009-05-21;] *Caption from original*

Disease Course

- HCM may improve or stabilize over time.
- The risk of sudden cardiac death is always present and, even in less symptomatic patients, is justification for limited strenuous/athletic activities.
- There are limited surgical options for severe cases.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman CE, Towbin JA, Udelson JE, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011 Dec 13;58(25):e212–60. https://doi.org/10.1016/j.jacc.2011.06.011. PMID: 22075469. http://www.ncbi.nlm.nih.gov/pubmed/22075469 **

Nagueh SF, Bierig SM, Budoff MJ, Desai M, Dilsizian V, Eidem B, Goldstein SA, Hung J, Maron MS, Ommen SR, Woo A; American Society of Echocardiography; American Society of Nuclear Cardiology; Society for Cardiovascular Magnetic Resonance; Society of Cardiovascular Computed Tomography; American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with hypertrophic cardiomyopathy: Endorsed by the American Society of Nuclear Cardiology, Society for Cardiovascular Magnetic Resonance, and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2011 May;24(5):473–98. https://doi.org/10.1016/j.echo.2011.03.006. PMID: 21514501. http://www.ncbi.nlm.nih.gov/pubmed/21514501 **

Review

Efthimiadis GK, Pagourelias ED, Gossios T, Zegkos T. Hypertrophic cardiomyopathy in 2013: Current speculations and future perspectives. World J Cardiol. 2014 Feb 26;6(2):26–37. https://doi.org/10.4330/wjc.v6.i2.26. PMID: 24575171. http://www.ncbi.nlm.nih.gov/pubmed/24575171

Jacoby DL, DePasquale EC, McKenna WJ. Hypertrophic cardiomyopathy: diagnosis, risk stratification and treatment. CMAJ. 2013 Feb 5;185(2):127–34. https://

doi.org/10.1503/cmaj.120138. PMID: 23109605. http://www.ncbi.nlm.nih.gov/pubmed/23109605 **

Sen-Chowdhry S, Tomé Esteban MT, McKenna WJ. Insights and challenges in hypertrophic cardiomyopathy, 2012. Herzschrittmacherther Elektrophysiol. 2012 Sep;23(3):174–85. https://doi.org/10.1007/s00399-012-0227-5. PMID: 23008086. http://www.ncbi.nlm.nih.gov/pubmed/23008086

Review. Moak JP, Kaski JP. Hypertrophic cardiomyopathy in children. Heart. 2012 Jul;98(14):1044–54. https://doi.org/10.1136/heartjnl-2011-300531. PMID: 22591735. http://www.ncbi.nlm.nih.gov/pubmed/22591735

Yetman AT, McCrindle BW. Management of pediatric hypertrophic cardiomyopathy. Curr Opin Cardiol. 2005 Mar;20(2):80–3. PMID: 15711191. http://www.ncbi.nlm.nih.gov/pubmed/15711191

Cohort Study

Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. JAMA. 1999 Feb 17;281(7):650–5. Erratum in: JAMA 1999 Jun 23–30;281(24):2288. PubMed PMID: 10029128. http://www.ncbi.nlm.nih.gov/pubmed/10029128

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

("Cardiomyopathy, Hypertrophic"[Mesh] OR "hypertrophic cardiomyopathy")

Chapter 38
Idiopathic Pulmonary Fibrosis

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Idiopathic Pulmonary Fibrosis (IPF)

- Cryptogenic Fibrosing Alveolitis

Incidence/Epidemiology

- IPF is the most common interstitial lung disease (ILD). It accounts for 25–35 % of all diagnoses of ILD.
- The diagnosis usually is not considered in those under 40.
- It is typically seen in those over 55 years of age.

Differential Diagnosis

- The differential diagnosis of IPF is broad and includes all the diagnoses encompassing the ILDs, of which there are more than 200.

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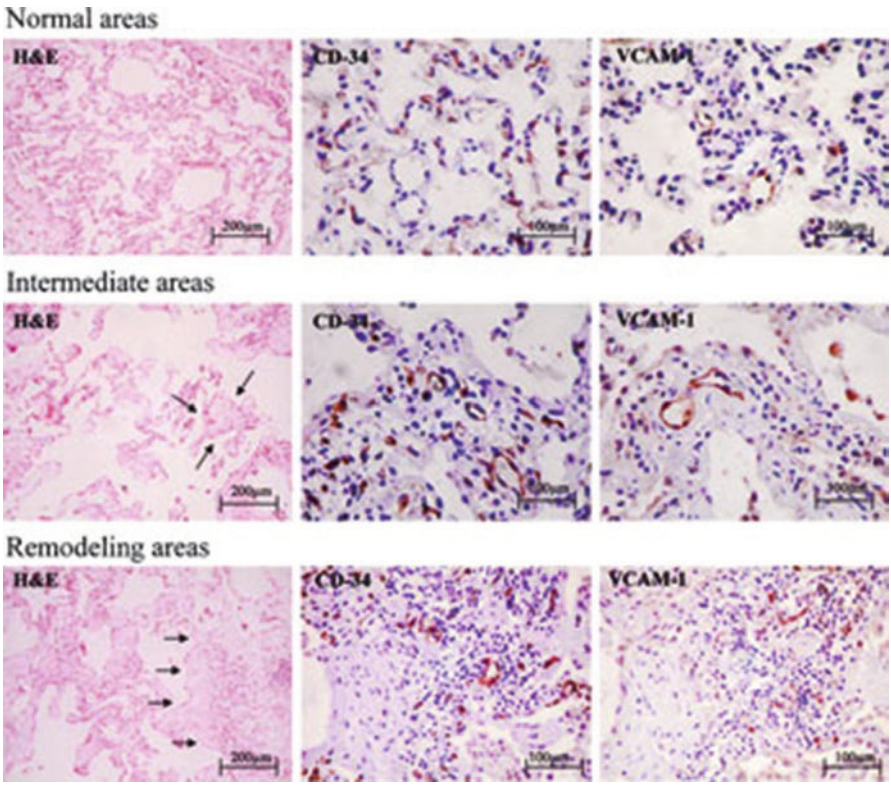
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_38

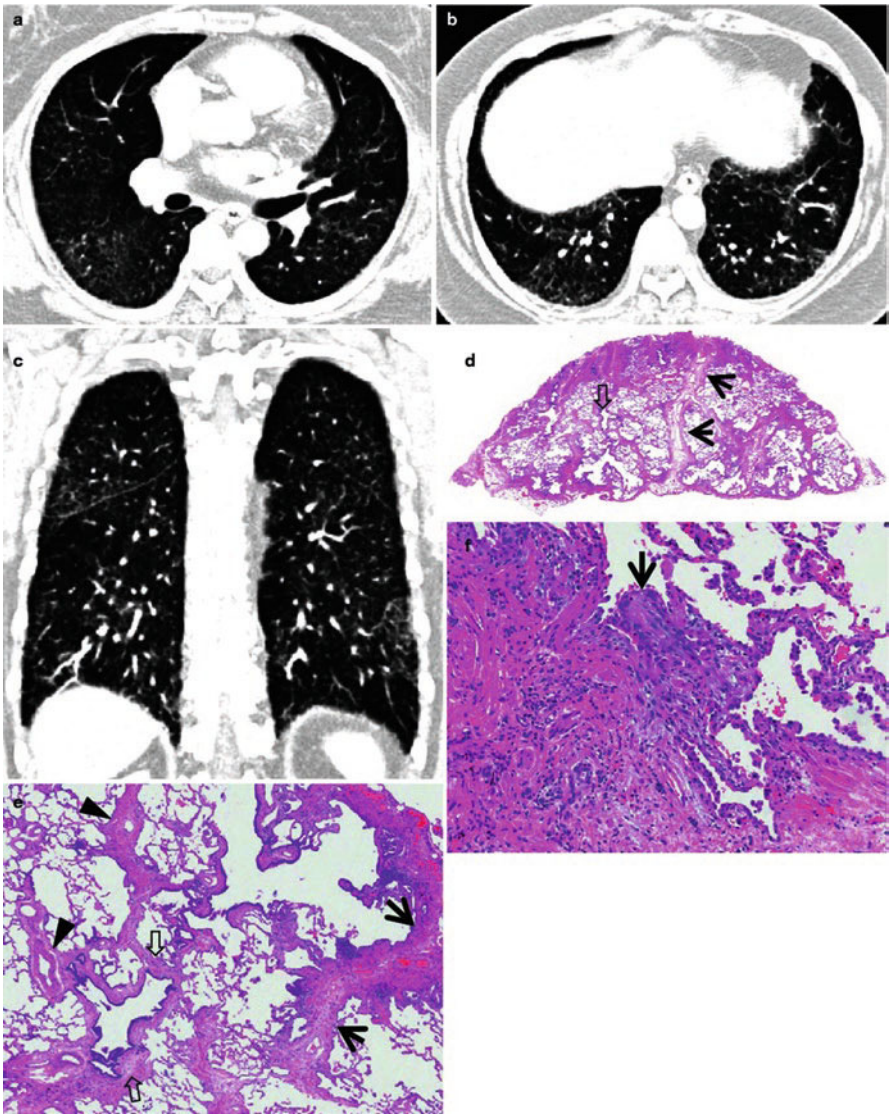
- The differential also includes all the causes of chronic dyspnea and cough, especially chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF).

Pathophysiology and Etiology

- IPF is a chronic, progressive disease of the lower respiratory tract; so far, no precipitating cause has been identified.
- It is predominately a fibrotic disease, with abnormal fibroblast proliferation and abnormal collagen metabolism.
- Chronic inflammation, once thought to play a role in the pathogenesis, is now known to be less important than fibrosis in the pathophysiology of IPF. When biopsies are performed for diagnosis, there often is little inflammation present.
- The classic histologic pattern is termed *usual interstitial pneumonia* (UIP). Although UIP is not pathognomonic to IPF, it may be seen in other lung diseases marked by fibrosis, such as diseases associated with connective tissue disorders, chronic hypersensitivity pneumonitis, and asbestosis.
- UIP is characterized by the presence of "honeycomb cysts." These are subpleural, cystic airspaces in which there are an abnormal proliferation of mesenchymal cells, varying degrees of fibrosis, and overproduction and disorganized deposition of collagen and extracellular matrix.
- Another characteristic feature of UIP is the presence of fibroblast foci, clusters of fibroblasts and myofibroblasts found next to areas of established fibrosis. The presence and number of fibroblastic foci correlate with disease severity and mortality.



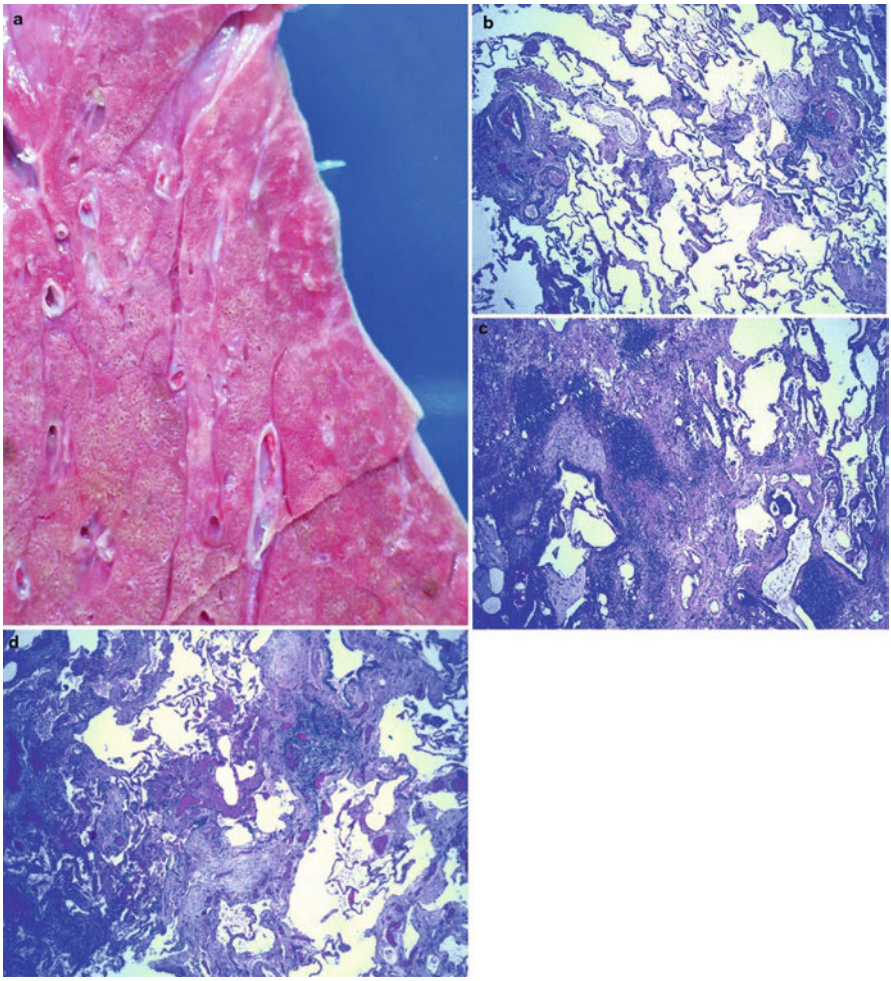
UIP (usual interstitial pneumonia) lungs showing nonhomogeneous CD34-positive and VCAM-1-positive immunostaining in alveolar capillaries. In normal parenchyma areas (H&E) (×100), a diffuse decrease of CD34 immunolocalization and endothelial cells of increased capillaries strongly immunoreactive with VCAM-1 can be appreciated (×200). Collapsed and mural organizing fibrosis areas present in UIP are shown at H&E staining (×100). In a high magnification of the area with arrows, CD34 decreases gradually toward more severe mural fibrosis. In contrast, increased VCAM-1 is shown in inflammatory septal thickening (nonorganizing fibrosis) and mural organizing fibrosis areas (200). [Parra ER, da Costa LRS, Ab'Saber A, de Carvalho CRR, Kairalla RA, Fernezlian SM, Teixeira LR, Capelozzi VL. Nonhomogeneous density of CD34 and VCAM-1 alveolar capillaries in major types of idiopathic interstitial pneumonia. Lung. 2005 Oct;183(5):363–73.] *Caption from original*

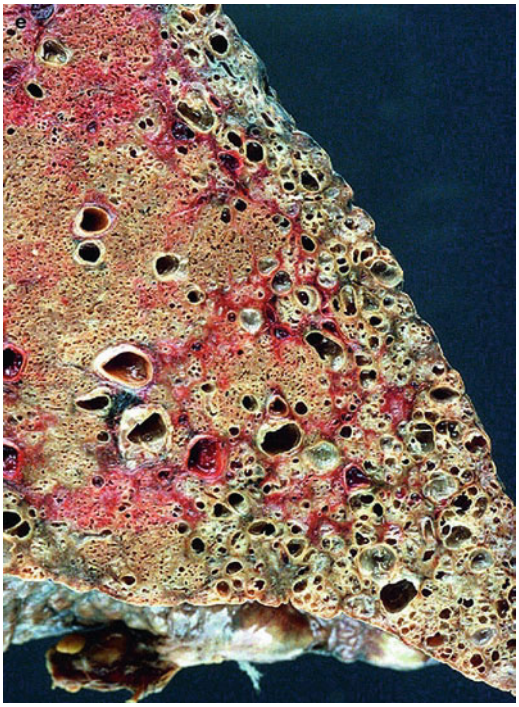


Interstitial fibrosis of usual interstitial pneumonia pattern in a 59-year-old woman with progressive systemic sclerosis. (a, b) Lung window of CT scans (3.0-mm section thickness) obtained at levels of bronchus intermedius (a) and liver dome (b), respectively, show patchy and extensive areas of reticulation and ground-glass opacity in both lungs. (c) Coronal reformatted image (3.0-mm section thickness) demonstrate similar pattern of reticulation and ground-glass opacity extensively in both lungs. (d) Low-magnification (×4) photomicrograph of surgical lung biopsy specimen obtained from right lower lobe exhibits dense fibrosis along interlobular septum

(arrows) and around bronchiole (open arrow). (e) High-magnification (×100) photomicrograph depicts dense fibrosis in interlobular septum (arrows) and around bronchiole (open arrows). Also note thick fibrotic vessel wall (arrowheads). (f) High-magnification (×200) photomicrograph discloses area of focal active fibrosis (arrow) [Lee KS, Han J, Chung MP, Jeong YJ. *Radiology illustrated: chest radiology [Internet]. Berlin, Heidelberg: Springer; 2014. Chapter 28,* Interstitial *lung disease in collagen vascular disease;* [cited 2015 Aug 21]*;* p. 275–83. Available from: http://link.springer.com/10.1007/978-3-642-37096-0_28] *Caption from original*

- The end result is an abnormal fibrotic response within the lung that distorts and destroys lung tissue from the pleura into the lung parenchyma.





Idiopathic pulmonary fibrosis (interstitial lung disease, idiopathic interstitial pneumonias) with varying alveolar and interstitial inflammatory infiltrates, progressive interstitial fibrosis, secondary hypertensive vascular disease, and a final stage with honeycombing of the lungs. Note the fleshy gross appearance of the lungs in earlier stages (a), with various microscopic interstitial infiltrates (b–d) and gross honeycombing at the end stage (e). [Krueger GRF, Wagner M, Oldham SAA. Pathology of the respiratory tract. In: Krueger GRF, Buja LM, Chandrasekhar C, editors. Atlas of anatomic pathology with imaging [Internet]. London: Springer; 2013 [cited 2015 May 28]. p. 105–89. Available from: http://link.springer.com/10.1007/978-1-4471-2846-5_3] *Caption adapted from original*

- Causative factors currently are unknown.
- There are, however, some known risk factors, including:
    - Cigarette smoking
    - Viral infection
    - Environmental pollutants
    - Chronic aspiration
    - Genetic predisposition
    - Drugs
- None of these risk factors can explain the pathogenesis of IPF. It is felt that these risks precipitate the process in those who are susceptible.

- Several mutations have been found that may increase the risk. These mutations have been identified in both sporadic cases and in familial clusters. They include mutations of surfactant proteins, gel-forming mucin, and telomerase.

Presentation

Typical/"Classic"

- The typical presentation is chronic cough with progressive dyspnea associated with decreased lung function, as measured by a decrease in the forced vital capacity in one second (FVC1) and a decrease in the diffusing capacity to carbon monoxide (DLCO).
- High-resolution CT scan (HRCT) of the lungs will reveal typical findings of UIP, including:
  - Reticular opacities in a peripheral and basal lung distribution
  - Traction bronchiectasis
  - Honeycombing (clustered, abnormal, enlarged airspaces 3 to 10 mm in diameter) in subpleural distribution
  - Ground-glass opacities may be present but usually are less extensive than reticular opacities.
- A thorough search must be undertaken for other contributing factors that may lead to an alternative diagnosis. This includes a search for asbestos exposure, hypersensitivity pneumonitis, systemic sclerosis, and rheumatoid arthritis.

Atypical

- Some patients may present with a typical clinical syndrome of chronic cough, dyspnea, and decreased lung function but have atypical findings on HRCT. In this situation, it may be necessary to proceed to lung biopsy for a confirmation of the diagnosis.
- Patients may present with more focus on either the cough or dyspnea, but both usually are present.

Primary Differential Considerations

- In patients presenting with signs and symptoms suggesting IPF, other diagnoses warranting early consideration include:

- Acute and chronic pneumonias
- "Exposure" lung disease such as asbestosis, farmer's lung, coal worker's lung, and tobacco worker's lung
- Fungal disease such as histoplasmosis

History and Physical Exam

Findings That Confirm Diagnosis

- A full classic presentation with chronic cough, chronic progressive dyspnea, and decreased lung function, with the usual findings of UIP on HRCT, usually confirms the diagnosis.
- However, no historical or physical exam findings are pathognomonic for IPF. For example, digital clubbing is present in only 30 % of patients with IPF.

An example of digital clubbing. [Siddiqui M, Melia MT. Clinical image: clubbed with a reminder to test for HIV. J Gen Intern Med. 2014 Sep;29(9):1308–1308.] *Caption adapted from original.*

Factors That Suggest Diagnosis

- The diagnosis should be considered in any person with chronic cough and dyspnea, especially if he or she is over 55 years of age and no other causes for the cough and dyspnea are easily identified.
- On lung exam, patients often have bilateral basilar (sometimes diffuse) "dry" crackles, although this finding is not specific to IPF.

  http://en.wikipedia.org/wiki/File:IPF_Lung_Sound.ogg

Dry or "Velcro" crackles in a patient with IPF. [File:IPF Lung Sound.ogg [Internet]. Wikipedia, the free encyclopedia. [cited 2015 Jun 11]. Available from: http://en.wikipedia.org/wiki/File:IPF_Lung_Sound.ogg; licensed under the Creative Commons Attribution-Share Alike 3.0 Unported license.]

Factors That Exclude Diagnosis

- It is difficult to completely exclude the diagnosis with either historical or physical exam findings. However, if another easily identified cause for the symptoms is found, the diagnosis becomes less likely.

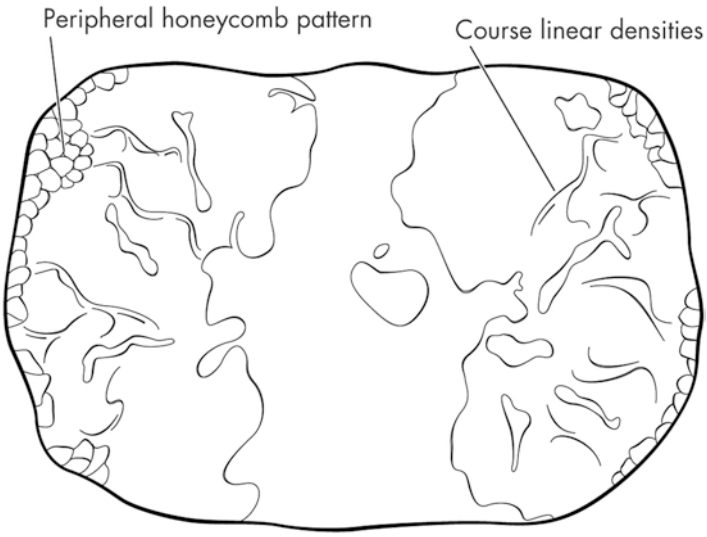
Ancillary Studies

Laboratory

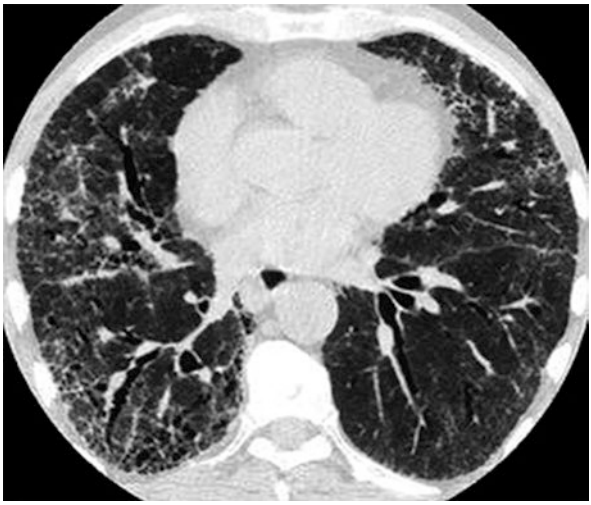
- Laboratory studies are not useful in the diagnosis and confirmation of IPF, but they are helpful in seeking alternative and complicating diagnoses.
- It is useful to check laboratory studies to evaluate for abnormalities such as significant anemia, infectious issues (leukocytosis, eosinophilia, etc.), rheumatologic disorders (rheumatoid arthritis, systemic sclerosis), cardiac issues (such as brain natriuretic peptide for CHF), and other alternative and complicating diagnoses.

Imaging

- Imaging is a necessary part of the evaluation of patients with suspected IPF, indeed for any suspected ILD.
- Nearly all patients with unexplained chronic cough and dyspnea will require HRCT of the lungs as part of their diagnostic evaluation.
- HRCT showing the typical changes of UIP (peripheral and basal reticular opacities, traction bronchiectasis, honeycombing) in a patient with chronic cough and dyspnea associated with decreased lung function is nearly diagnostic of IPF, as long as alternative diagnoses (e.g., asbestos exposure, hypersensitivity pneumonitis, systemic sclerosis, and rheumatoid arthritis) have been considered and excluded.



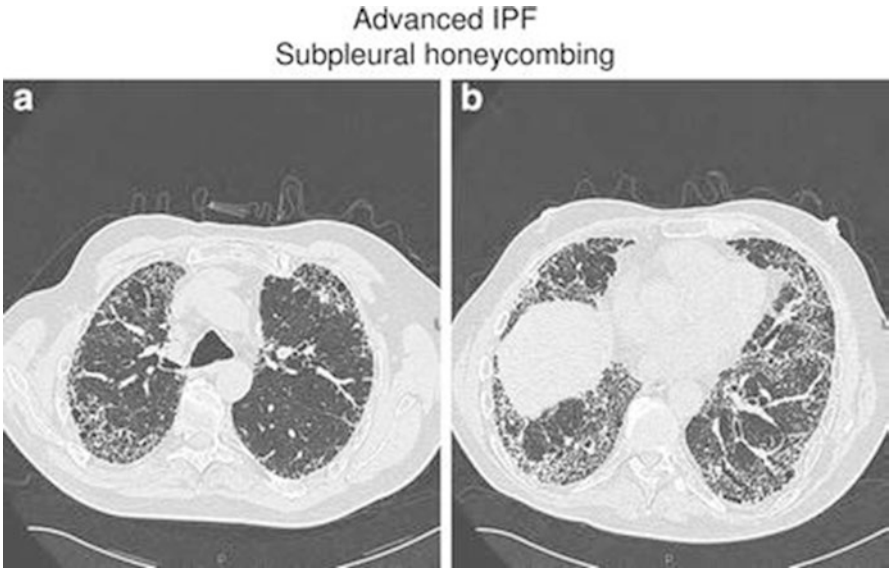
Schematic representation of chest computed tomography in IPF, showing coarse linear densities and a peripheral honeycomb pattern. [Smith M, Grichnik K. Anesthetic considerations for lung transplant and thoracic aortic surgery. In: Reves JG, editor. Cardiothoracic anesthesia. Philadelphia: Current Medicine; 1999. (Miller RD, editor. Atlas of anesthesia; vol. 8) ISBN: 0-443-07974-9] *Caption adapted from original*



Idiopathic pulmonary fibrosis. HRCT at the level of the lower lobes shows a subpleural "reticular pattern" characterized by thickened interlobular septae, thickened intralobular interstitium, traction bronchiolectasis and bronchiectasis and

minimal honeycombing. [From article: Mimics in chest disease: interstitial opacities. Insights into Imaging. 2013 Feb;4(1):9–27; https://doi.org/10.1007/s13244-012-0207-7, at http://link.springer.com/article/10.1007%2Fs13244-012-0207-7/fulltext.html; by Anastasia Oikonomou, Panos Prassopoulos, © The Author(s) 2012; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- HRCT also is helpful in staging the severity of the disease.
- HRCT and chest x-ray also are helpful during periods of acute exacerbation to help identify and exclude complicating and alternative diagnoses and causes for the worsening dyspnea, as well as to evaluate new and advancing changes of UIP.



Patient with idiopathic pulmonary fibrosis. Subpleural honeycombing is identified. Disease is more extensive at the base of the lung (b) than in mid lung (a). [Baughman R, Pirozynski M. Health effects of nanoparticles (inhalation) from medical point of view/type of diseases. In: Marijnissen JC, Gradon L, editors. Nanoparticles in medicine and environment [Internet]. Dordrecht: Springer; 2010 [cited 2015 Jun 11]. p. 187–202. Available from: http://www.springerlink.com/index/10.1007/978-90-481-2632-3_10] *Caption from original*

Lung Biopsy

- Lung biopsy may be necessary when the findings on HRCT are equivocal. Transbronchial biopsy is not recommended, as the specimen usually is too small for examination. The usual approach is video-assisted thoracoscopic or open surgical biopsy.

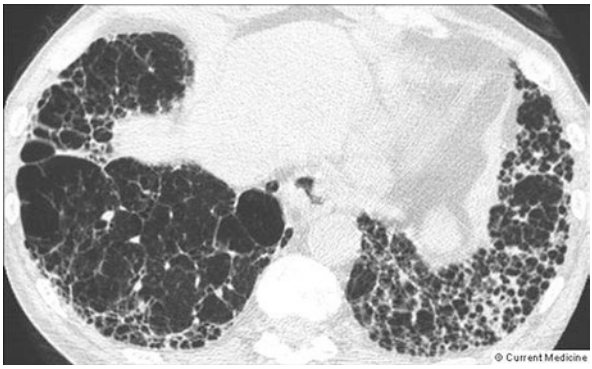
Special Populations

Age

- IPF is a disease of middle-aged and older adults. It is typically diagnosed after age 55 and usually is not even considered a diagnostic possibility before age 40.

Co-morbidities

- Important co-morbid conditions to consider include all diseases and conditions that may worsen dyspnea and accelerate the course of IPF. Most importantly, given the population most at risk for IPF (older than 50), both COPD and CHF are important diseases to consider. However, any condition that may worsen dyspnea (e.g., anemia, coronary vascular disease, pneumonia, lung cancer, pulmonary embolism (PE), pneumothorax) must be considered in the evaluation of both newly diagnosed IPF and IPF exacerbations.
- Gastroesophageal reflux disease (GERD) is an important co-morbid condition to consider in patients diagnosed with IPF. Up to 90 % of patients with IPF also have GERD. Treatment of GERD in those with IPF has been associated with a decrease in the radiographic findings of IPF and may even be associated with improved survival.
- Pulmonary hypertension. Development of pulmonary hypertension is relatively common in patients with IPF, especially as the disease advances, and is a poor prognostic sign.



Emphysema associated with idiopathic pulmonary fibrosis in a heavy smoker. Axial thin slices of the chest, showing advanced emphysema predominantly distributed in the upper lobes. Honeycombing, as typically present in usual interstitial pneumonia-idiopathic pulmonary fibrosis, involves the subpleural regions of the lung bases. It is identified as clustered, cystic airspaces usually measuring 2 mm to 10 mm in diameter and having well-defined walls. The cysts appear to share walls and occur in several layers. [Grenier P, Beigelman-Aubry C. Radiologic phenotypes of COPD. In: Crapo JD, editor. Atlas of chronic obstructive pulmonary disease. Philadelphia: Current Medicine; 2009. ISBN: 978-1-57340-294-1] *Caption adapted from original*

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step, next is establishing the diagnosis.
- More than 200 diseases encompass the diagnosis of ILD. Many of them have more and better treatment options than currently exist for IPF, so an accurate diagnosis is important for the patient to obtain the best available information about treatment and prognosis.

Mimics

- The diagnosis category of ILD includes more than 200 different diseases, many of which present similarly to IPF, with chronic cough, dyspnea, and decreased lung function.

- In addition, several other diseases may have a similar clinical syndrome and show signs of UIP on HRCT, including asbestosis, hypersensitivity pneumonitis, and lung disease associated with systemic sclerosis and rheumatoid arthritis.

Time-Dependent Interventions

- There are no time-dependent interventions in most cases of IPF. The disease is chronic and progressive.
- As with all diseases that cause dyspnea, hypoxemia must be promptly and aggressively treated and avoided.
- In the setting of an acute exacerbation of IPF, it is important and somewhat time sensitive to evaluate and rule out the presence of an emergent complication such as acute coronary syndrome, CHF, PE, pneumothorax, or infection.

Overall Principles of Treatment

- The treatment of IPF has been changing dramatically during the past several years. In 2014, the US Food and Drug Administration approved two new agents: pirfenidone and nintedanib. In clinical trials, both drugs slowed the progression of disease, and they may even confer a mortality benefit.
- In the past, many different anti-inflammatory treatments were attempted, most without success. This is not surprising considering the pathophysiology of IPF, in which biopsy samples show progressive fibrosis with little to no inflammation.
- Treatment has been mostly supportive, including:
  - Patient education
  - Oxygen therapy if hypoxemia is present
  - Pulmonary rehabilitation
  - Appropriate vaccination
  - Identification and treatment of all co-morbidities
  - Prevention and treatment of GERD
  - Lung transplantation as the disease progresses
- Pirfenidone is an antifibrotic agent that inhibits transforming growth factor-β (TGF-β). TGF-β stimulates collagen synthesis as well as fibroblast proliferation; therefore, blocking this protein decreases the extracellular matrix and fibroblast proliferation, two of the major pathophysiologic mechanisms of IPF. Side effects may include rash, photosensitivity, nausea, diarrhea, abdominal discomfort, anorexia, fatigue, and elevation in liver function tests (LFTs). It is recommended that LFTs be checked before and during treatment.

- Nintedanib is a monoclonal antibody that blocks multiple tyrosine kinase receptors. Tyrosine kinases are known to stimulate production of multiple fibrogenic growth factors. As with pirfenidone, this agent may cause LFT elevations; therefore, liver tests should be performed before and during treatment. Nintedanib also may increase the risk of bleeding from anticoagulation. Other common adverse effects include diarrhea, nausea, and vomiting.
- In severe cases complicated by pulmonary hypertension, some authorities add phosphodiesterase inhibitors (or other vasodilators) to the treatment regimen. These agents, however, are used primarily to treat pulmonary hypertension; their use in IPF is under study.
- Currently, IPF is the second most frequent diagnosis for which lung transplantation is performed. Because IPF is a chronically progressive disease associated with numerous co-morbidities, it generally is believed that lung transplantation is better and more safely performed earlier in the course of the illness.

Disease Course

- IPF is a relentlessly progressive disease. All patients have progression; no spontaneous remissions have been reported.
- The overall prognosis is poor, with a 5-year mortality rate of about 75 %.
- Multiple factors are associated with more rapidly progressive disease and shortened survival:
    - Older age at diagnosis
    - History of prolonged tobacco use
    - Lower weight
    - More severe disease at diagnosis
    - The presence of a co-morbid condition that may worsen and complicate the clinical course of IPF, such as COPD, CHF, pulmonary hypertension, coronary artery disease, or lung cancer.
- At the time of diagnosis, it is important to try to pinpoint the severity of the disease.
- Currently no validated staging system exists for IPF; its classification is based mainly on clinical grounds, including symptoms, pulmonary function test (PFT) findings, and results of HRCT.
- A typical assessment of severity is based on the following guidelines:
    - Mild or early disease
        - Patient may be asymptomatic or have only a mild cough.
        - Patient may have dyspnea on exertion (DOE), but it may be mild and unnoticed or thought to be related to some other cause.
        - Radiographic changes (reticular opacities and honeycombing) typically involve less than 10 % of the lungs.

    - PFTs may be normal or demonstrate only mild decreases in FVC1 and DLCO.
  - Moderate disease
    - Cough and DOE are more pronounced and noticeable.
    - Radiographic changes involve 20–30 % of the lungs.
    - On PFTs, the FVC1 is 50–70 % predicted and DLCO is about 50 % predicted.
  - Severe/advanced disease
    - DOE is severe; patient cannot climb one flight of stairs without stopping to rest.
    - Patient usually requires supplemental oxygen.
    - Extensive honeycombing is seen on HRCT.
    - FVC1 and DLCO are less than 50 % predicted.
- Acute exacerbations of IPF. The clinical course of IPF may be complicated by acute exacerbations in up to 60 % of patients. The term *exacerbation* is somewhat misleading, as patients often do not return to their "pre-exacerbation" level of functioning. These acute exacerbations also are known as *accelerated phases of rapid clinical deterioration*. They are associated with a poor prognosis, with in-hospital mortality approaching 80 %. Recurrences are common.
  - Accepted definition of an acute exacerbation of IPF includes:
    - Known diagnosis of IPF
    - An unexplained worsening of dyspnea within the past 30 days
    - HRCT demonstrating new bilateral ground-glass opacities and/or consolidation on a background of UIP (honeycombing and reticular opacities)
    - No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage
    - The exclusion of alternative causes of worsened dyspnea, especially pneumonia, heart failure, PE, and pneumothorax
  - Treatment usually involves the administration of antibiotics for presumed superinfection and glucocorticoids for acute inflammation; however, there is no evidence that either of these agents is helpful.

Related Evidence

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*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Idiopathic Pulmonary Fibrosis"[Mesh] OR "idiopathic pulmonary fibrosis" OR "cryptogenic fibrosing alveolitis"

Chapter 39
Infective Endocarditis

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Infective Endocarditis

Incidence/Epidemiology

- Infective endocarditis (IE) has an estimated annual incidence of between 3 to 9 cases per 100,000 people per year in developed nations. Incidence rates can vary widely based upon predisposing conditions, risk factors, and geographic area.
- Predisposing conditions include the presence of a prosthetic heart valve, the presence of an intracardiac device, unrepaired cyanotic congenital heart disease, a prior history of infective endocarditis, chronic rheumatic heart disease, age-related degenerative valvular lesions, hemodialysis, diabetes, HIV infections, and intravenous drug use, dental infections, and poor dental hygiene. Age greater than 65 and male sex are also risk factors for IE.
- Rheumatic heart disease is now an uncommon cause of IE in developed nations, but remains a significant cause of IE in developing nations.
- Incidence has been increasing among and shifting toward those greater than 65 years old.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_39

- Increasing proportions (up to one-third) of cases of IE are now health-care associated.
- The male-to-female ratio is about 2:1.
- About 10,000–15,000 cases per year are diagnosed in the United States.

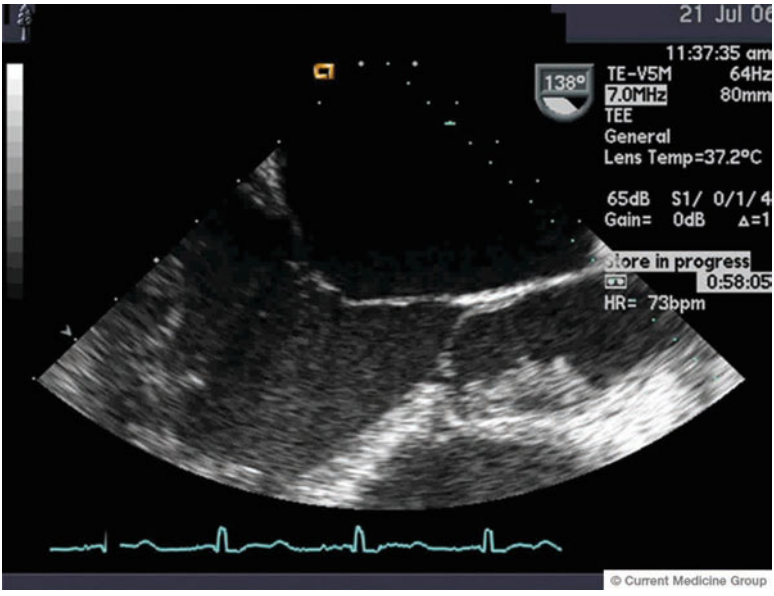
Differential Diagnosis

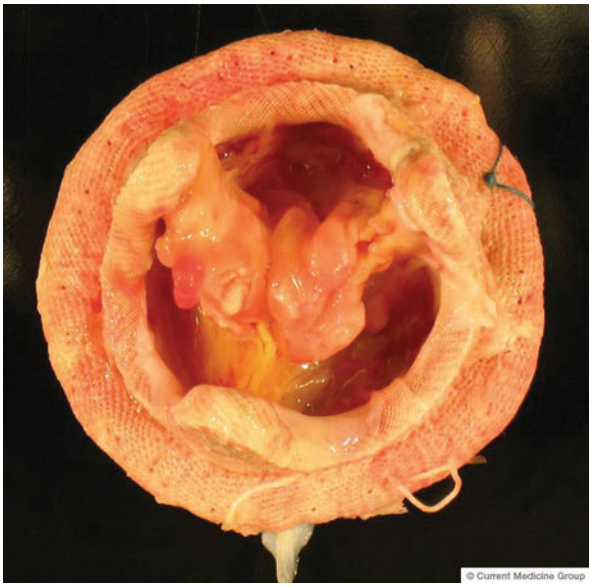
- The differential diagnosis for IE is exceptionally broad, and a high index of suspicion needs to be maintained.
  - Many diseases can present with fever and diffuse/multi-organ symptoms, including many infections, vasculitides, connective tissue diseases, and malignant diseases.
  - Many diseases can be associated with bacteremia, such as skin and soft tissue infections, osteomyelitis, pneumonia, meningitis, and others. All patients with bacteremia, even if there is an associated cause as above, should have an evaluation for valvular vegetations with echocardiography, as all causes of bacteremia can coexist with IE, and many are known predisposing factors for IE or complications of IE.

Pathophysiology and Etiology

- The majority of cases of endocarditis (80 %) are caused by Streptococci and Staphylococci.
- Staphylococci are the most frequent cause of health-care associated IE.
- Ten percent of cases of IE are blood culture negative. This generally results from either exposure to antibiotics prior to the diagnosis of IE, or when IE is due to slow-growing, fastidious organisms.
  - These slow-growing, fastidious organisms include bartonella species, brucella species, Coxiella burnetii, Tropheryma whippelii, and bacteria in the HACEK group. The HACEK group of organisms includes haemophilus species, Aggregatibacter actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae.
- The classic model of the pathogenesis of native-valve infectious endocarditis involves valvular endothelial damage that allows colonization by bacteria.
  - Endothelial damage may result from turbulent blood flow around the valve, direct trauma from the repeated injection of particulate contaminants in those who inject intravenous drugs, or by direct trauma from electrodes or catheters used during cardiac procedures.

- The bacteria that are most likely to cause IE often have specific adherence factors that facilitate their adherence and formation of vegetations.
- Vegetations are the characteristic pathologic lesions of IE. They are a mass of platelets, fibrin, organisms, and inflammatory cells that adhere to damaged endothelium or myocardium. Vegetations are most commonly found on heart valves, but can also attach to any area of myocardial damage or scarring, such as an atrial septal defect, ventricular septal defect, or endocardium damaged by foreign bodies (pacemakers, automatic implantable cardiac defibrillators [AICD]).





Infective endocarditis. **A**, Large, multilobulated vegetation on the anterior leaflet of the mitral valve from a patient with *Staphylococcus lugdunensis* endocarditis who died of a rupture mycotic cerebral aneurysm. **B**, Transesophageal echocardiographic image showing a cluster of vegetative material adherent to and above the anterior leaflet of the aortic valve. TEE is more sensitive than transthoracic echocardiogram (TTE) for the detection and characterization of vegetation and abscess in patients with suspected infective endocarditis. **C**, Gross operative specimen from a patient with prosthetic valve endocarditis affecting the valve leaflets, but sparing the sewing ring. [O'Gara P. Chapter 9. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p.] *Caption adapted from original*

- Chronic inflammation of valvular tissue can also lead to endothelial damage and bacterial colonization. This is the case in rheumatic heart disease and degenerative valve disease.
- Several microorganisms are felt to cause endocarditis from a maladaptive host immune response. C. burnetii, bartonella species, and T. Whippelii are all intracellular pathogens, and when they infect valvular tissue they can cause a host immune response that can damage valvular tissue.

Presentation

Typical/"Classic"

- The classic presentation is a patient with a known predisposing factor with a fever and a new or worsened murmur.
- Fever is the most common symptom. It is present in up to 80 % of patients.
- The majority of patients will have one of the predisposing conditions noted in the etiology section.
- About half of all patients will have new murmur; about a quarter will have worsening of a known prior murmur.
- There is usually no other obvious source for the fever.

Atypical

- Infective endocarditis frequently presents atypically, especially early in the course of the disease.
- Symptoms may be non-specific, and the diagnosis may not be considered until there is fever or a complication secondary to IE.
- Patients may initially present with a complication of IE, especially from embolic infected vegetations. These complications include:
  - Pulmonary embolism, pneumonia, or pulmonary abscess from septic pulmonary emboli.
  - Stroke (both ischemic and hemorrhagic), TIA, brain abscess, and meningitis.
  - Renal failure.
  - Peripheral arterial occlusion.
  - Sepsis.
- IE caused by S. aureus, especially involving the mitral valve, is the most common cause of systemic embolic complications.
- It is important to know that embolic complications (for example, septic pulmonary emboli, cerebrovascular emboli) can occur before the diagnosis of IE is made, and may be a clue to the diagnosis.
- IE associated with injection drug use is limited to the tricuspid valve about half the time, and as such usually has no murmur that can be appreciated by auscultation, and will have no peripheral manifestations of IE. There is a higher incidence of septic pulmonary emboli in IE among injection drug users, so the diagnosis of pulmonary abscess should lead one to suspect and evaluate for the diagnosis of IE.

Primary Differential Considerations

Other diagnoses to consider in patients with signs and symptoms suggestive of IE include:

- Fever of unknown origin
- Septic pulmonary emboli
- Vasculitis
- Connective tissue diseases

History and Physical Exam

Findings That Confirm Diagnosis

- There are no completely confirmatory historical or physical examination findings for IE.
- The Duke Criteria is the current reference standard for the diagnosis of IE. They are a series of clinical, microbiologic, and echocardiographic findings that together have a sensitivity and specificity of greater than 80% for the diagnosis of IE.

Definite IE any of (1) or (2)	(1) Pathologic criteria: Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen, or pathologic lesions – vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
	(2) Clinical criteria: Any of two major criteria, or one major criterion and three minor criteria, or five minor criteria
Possible IE	One major criterion and one minor criterion or three minor criteria
Rejected	Firm alternative diagnosis explaining evidence of IE, or resolution of IE syndrome with antibiotic treatment for 4 or less days, or no pathologic evidence of IE at surgery or autopsy with antibiotic therapy for 4 or less days, or does not meet criteria for possible IE
Major criteria:	(1) Positive blood culture for IE: (a) Typical microorganisms consistent with IE from two separate blood cultures: Viridans streptococci, *Streptococcus bovis*, HACEK group; *Staphylococcus aureus* or community-acquired enterococci in the absence of a primary focus (b) Microorganisms consistent with IE from persistently positive blood cultures defined as: At least two positive blood cultures drawn more than 12 h apart, or all of three, or a majority of four or more blood cultures with first and last sample drawn at least 1 h apart (c) Single positive blood culture for *Coxiella burnetii* or antiphase I IgG antibody titer >1:800
	(2) Evidence of endocardial involvement: (a) Positive echocardiogram for IE: Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or abscess, or new partial dehiscence of prosthetic valve, or new valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
Minor criteria:	(1) Predisposition – predisposing heart condition or injection drug use
	(2) Fever – temperature of 38 °C or more
	(3) Vascular phenomena – major arterial embolism, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
	(4) Immunological phenomena – glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
	(5) Microbiological evidence – positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

Modified Duke Criteria for the Diagnosis of Infective Endocarditis (IE) [Rodriguez ER, Tan CD. Cardiovascular Pathology. In: Cheng L, Bostwick DG, editors. Essentials of Anatomic Pathology [Internet]. Cham: Springer International Publishing; 2016 [cited 2016 Aug 8]. p. 1295–351. Available from: http://link.springer.com/10.1007/978-3-319-23380-2_27]

- The Duke criteria require microbiologic and echocardiographic results and as such are not particularly helpful early in the course of evaluation. A high index of suspicion is necessary for the early diagnosis of IE.

Factors That Suggest Diagnosis

- The presence of a fever with no obvious source, with any of the predisposing factors discussed in the etiology section, or with a new or worsened murmur suggests the diagnosis.
- The classic physical examination findings associated with IE have become uncommon, but their presence should suggest the diagnosis.
  - Splinter hemorrhages (linear petechiae in the center of the nail bed, as opposed to traumatic petechiae which are usually in the distal nail bed) are found in only about 5 –8% of patients.

Splinter hemorrhages in a fingernail. Splinter hemorrhages may be due to simple trauma, but when multiple nails are involved in a patient with infective endocarditis, they represent a vasculitic component of the infection. [Miró J, Wilson W, Chapter 01. In: Korzeniowski O, editor. Cardiovascular Infections, 1e. Philadelphia: Current Medicine; 1998. (Mandell GL, editor. Atlas of infectious diseases; vol. 10). ISBN: 0-443-07750-9] *Caption adapted from original*

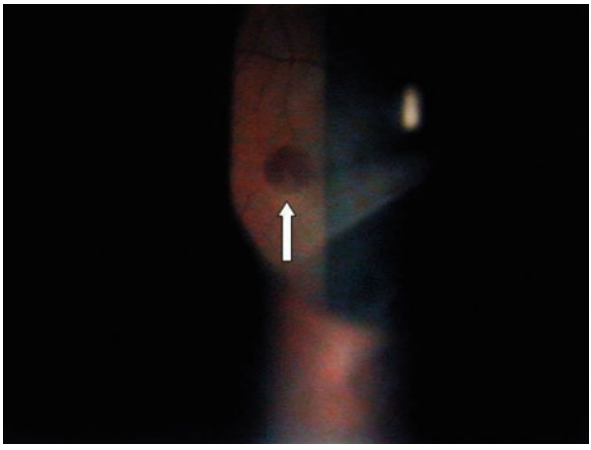
- Janeway lesions (non-tender, palpable hemorrhages on the palms and soles) in about 5%.

Janeway lesions in *Staphylococcus aureus* left-sided endocarditis [Miró J, Wilson W, Chapter 01. In: Korzeniowski O, editor. Cardiovascular Infections, 1e. Philadelphia: Current Medicine; 1998. (Mandell GL, editor. Atlas of infectious diseases; vol. 10). ISBN: 0-443-07750-9] *Caption from original*

- Osler's nodes are painful, purple nodules found on fingerpads and toepads, and are very rarely seen.

A and **B**, Osler's nodes in patients with infective endocarditis. These lesions usually occur in the tufts of the fingers or toes and are painful and evanescent. They likely are mediated by immunopathologic factors. [Scheld MW. Chapter 02. In: Fekety R, editor. External manifestations of systemic infections. Philadelphia: Current Medicine; 1997. 237 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 8.) ISBN: 0-443-07760-6] *Caption from original*

- Roth's spots (white centered retinal hemorrhages) in 5%.



Roth's spot on the retina of the left eye. [From article: Case report: Infective endocarditis caused by *Brevundimonas vesicularis*. BMC Infectious Diseases. 2006 Dec;6(1). https://doi.org/10.1186/1471-2334-6-179, at http://link.springer.com/article/10.1186%2F1471-2334-6-179/fulltext.html; by Mei-Li Yang, Yen-Hsu Chen, Tun-Chieh Chen, Wei-Ru Lin, Chun-Yu Lin, Po-Liang Lu, © Yang et al; licensee BioMed Central Ltd. 2006; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- Conjunctival hemorrhages in 5%.

Conjunctival hemorrhages in a patient with *Staphylococcus aureus*endocarditis. [Scheld MW. Chapter 02. In: Fekety R, editor. External manifestations of systemic infections. Philadelphia: Current Medicine; 1997. 237 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 8.) ISBN: 0-443-07760-6] *Caption from original*

- Patients with prosthetic heart valves are at increased risk for IE, and the diagnosis should always be considered when these patients have unexplained fever or other constitutional symptoms (such as unexplained weight loss, night sweats, loss of appetite).
- Hospitalization, especially prolonged hospitalization with indwelling venous access or recent intravascular procedures, also increases the risk for IE.

Factors That Exclude Diagnosis

- There are historical or physical examination findings that can reliably exclude the diagnosis.
- Negative blood cultures also do not reliably exclude the diagnosis, as 10% of cases of IE will have negative blood cultures (see pathophysiology and etiology section).
- The diagnosis can be rejected as per the Duke Criteria.

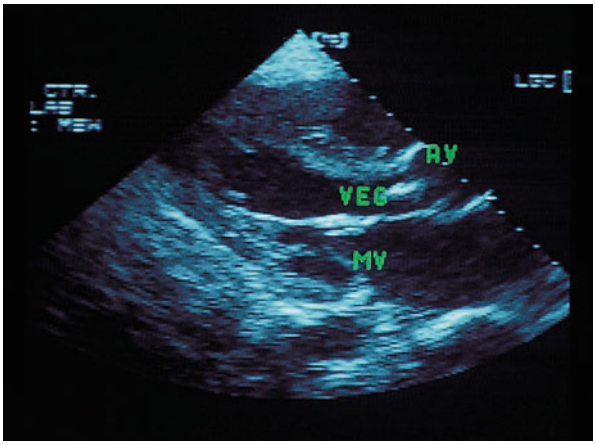
Ancillary Studies

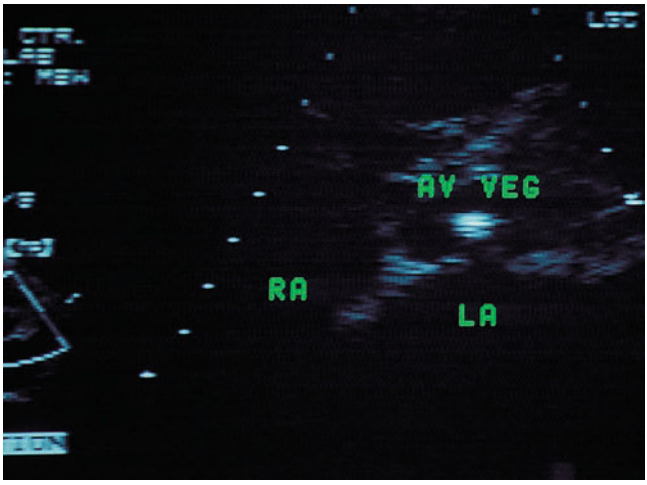
Laboratory

- Blood cultures are imperative for the diagnosis of IE. All patients with suspected IE should have three sets of blood cultures drawn. Each individual blood culture should be from a separate venipuncture site (not from a vascular catheter), and include at least 10 ml of blood for adults (5 ml for each bottle), 0.5 ml for infants, and 5 ml for children. If the patient is acutely ill, the cultures should be obtained over a one-hour period. All cultures should be obtained prior to the initiation of antibiotic therapy.
    - When three sets of appropriately drawn blood cultures are performed, the causative microorganism is identified in about 90 % of cases of IE.
- Multiple other laboratory studies are often abnormal in the setting of IE, but they are also very nonspecific.
- Patients with either acute Streptococcal or Staphylococcal IE often have elevated white blood cell counts and a thrombocytopenia.
    - In sub-acute presentations, the WBC count may be normal.
- Other laboratory markers of inflammation and infection may be elevated, such as the erythrocyte sedimentation rate (ESR), and the c-reactive protein (CRP).
- IE can cause interference with and abnormal results on multiple serologic and immune tests. In fact, an elevated rheumatoid factor in a patient without a known prior history of a rheumatologic disorder is a minor criterion for the diagnosis of IE in the Duke criteria.
- The majority of patients with IE will have an abnormal urinalysis. There may be proteinuria, pyuria, and either microscopic or gross hematuria. All of these findings are nonspecific. However, glomerulonephritis, often manifested with red blood cell casts on a microscopic urinalysis, is a minor criterion for the diagnosis of IE in the Duke criteria.

Echocardiography

- Echocardiography is indispensible in the diagnosis of IE, and should be performed as soon as reasonably possible when the diagnosis of IE is considered. Echocardiography can show valvular vegetations, valve dysfunction, and para-valvular abscesses.
- In general, trans-thoracic echocardiography (TTE) should be performed first. It is less sensitive and less specific than trans-esophageal echocardiography (TEE), but it is also less invasive and doesn't require sedation to perform.

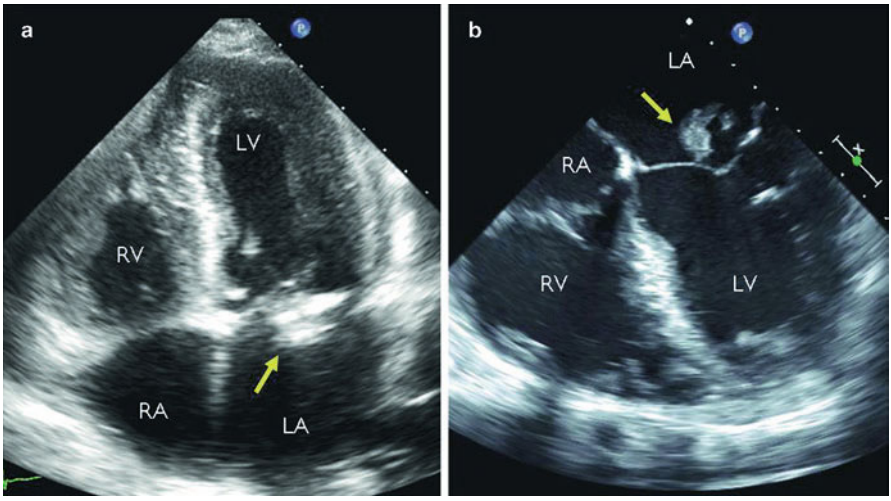




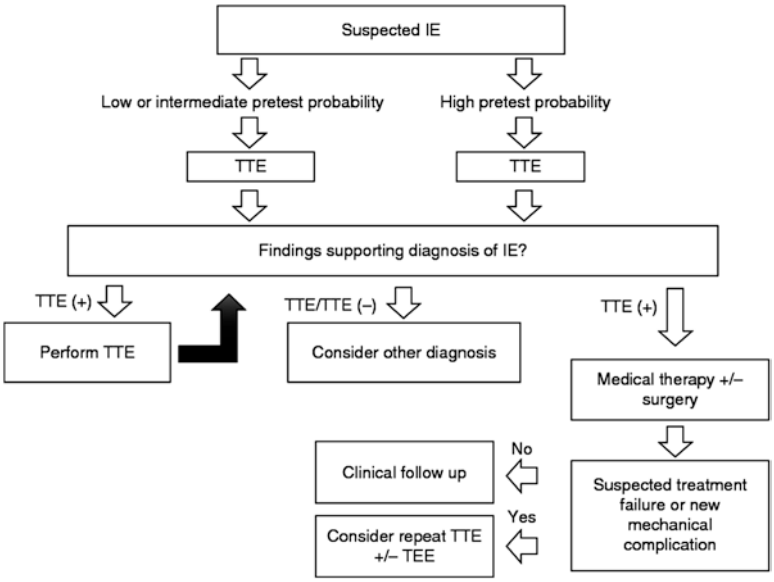
Transthoracic echocardiographic views of aortic valve endocarditis. **A**, Parasternal long-axis view shows an aortic valve vegetation prolapsing into the left ventricular outflow tract. **B**, Short axis view of the aortic valve shows a prominent vegetation in the same patient.[Scheld MW. Chapter 02. In: Fekety R, editor. External manifestations of systemic infections. Philadelphia: Current Medicine; 1997. 237 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 8.) ISBN: 0-443-07760-6] *Caption from original*

- TEE is more sensitive and specific for the diagnosis of IE and should be performed in multiple situations:

- After a negative or technically difficult TTE when the clinical concern for IE is moderate-to-high.
- After a positive TTE (demonstrating a valvular vegetation) when there is also a concern for an intracardiac complication such as para-valvular abscess, significant valvular regurgitation, and in the assessment for the need for surgery.
- In patients with a prosthetic valve.
- In patients with a known history of valvular disorder (including a prior history of IE).



Representative images acquired by transthoracic echocardiography (TTE,**a**) and transesophageal echocardiography (TEE, **b**) in the same patient with mitral valve endocarditis (arrowhead points to bacterial vegetation adherent to the anterior leaflet). The proximity of the mitral valve to the esophagus and superior acoustic window results in improved spatial resolution of TEE over TTE. RA right atrium, RV right ventricle, LA left atrium, LV left ventricle [Michelis KC, Choi BG. Cardiovascular Imaging in Global Health Radiology. In: Mollura DJ, Lungren MP, editors. Radiology in Global Health [Internet]. New York, NY: Springer New York; 2014 [cited 2016 Aug 8]. p. 189–203. Available from: http://link.springer.com/10.1007/978-1-4614-0604-4_18] *Caption from original*



Algorithm for the use of echocardiography in the diagnosis and management of infective endocarditis [Kiefer TL, Wang A. Infective Endocarditis. In: Stergiopoulos K, Brown DL, editors. Evidence-Based Cardiology Consult [Internet]. London: Springer London; 2014 [cited 2016 Aug 8]. p. 71–8. Available from: http://link.springer.com/10.1007/978-1-4471-4441-0_6] *Caption from original*

- The combination of TTE and TEE demonstrates valvular vegetations in 90% of cases of IE.
- Echocardiography may need to be repeated if the initial study was unrevealing but the clinical suspicion remains high (for example, known risk factor in setting of positive blood cultures.)
- Echocardiography also may need to be repeated if there is a new or suspected complication of IE, clinical worsening, and at the end of therapy.

Imaging

- Chest X-ray. There are no specific findings of IE on CXR. CXR may, however, reveal complications of OE such as infiltrates or pulmonary abscess from septic pulmonary emboli.
- Other imaging studies, such as CT scan or MRI, have no specific findings for IE, but may also demonstrate, or be used to search for, complications of IE such as vertebral osteomyelitis with MRI of the spine, solid organ or other intraperitoneal collection with CT scan of the abdomen and pelvis, and any intracranial complication with either CT scan or MRI of the brain.

Special Populations

Age

- Greater than 50% of cases of IE occur in patients above the age of 65.
- IE is uncommon in children, but the incidence has been reported to be increasing over the last several decades due to the increased rate of successful surgery for congenital heart disease, and the increased use of central venous catheters. Correspondingly, these are the two biggest risk factors for IE in children.
    - As in adults, Streptococci and Staphylococci are the most common causative organisms.
    - The presentation, diagnosis, and treatment are similar in children and adults.
    - Duke's criteria are applicable to the pediatric population.
    - There is about a 5% mortality rate for children with IE.

Co-morbidities

- Important pre-disposing and co-morbid conditions that increase the incidence and complications are detailed as per the incidence and epidemiology section, and include the presence of a prosthetic heart valve, the presence of an intracardiac device, unrepaired cyanotic congenital heart disease, a prior history of infective endocarditis, chronic rheumatic heart disease, age-related degenerative valvular lesions, hemodialysis, diabetes, HIV infections, intravenous drug use, age greater than 65, poor dental hygiene, and dental infection.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- All patients in whom IE is being considered need three sets of correctly drawn blood cultures prior to the administration of antibiotics.
- All patients in whom IE is being considered need to have echocardiography as soon as possible.
- It is important to know that embolic complications (for example, septic pulmonary emboli, cerebrovascular emboli) can occur before the diagnosis of IE is made, and may be a clue to the diagnosis.
- IE associated with injection drug use is limited to the tricuspid valve about half the time, and as such usually has no murmur that can be appreciated by auscultation, and will have no peripheral manifestations of IE. There is a

higher incidence of septic pulmonary emboli in IE among injection drug users, so the diagnosis of pulmonary abscess should lead one to suspect and evaluate for the diagnosis of IE.

Mimics

- Many diseases can present with fever and diffuse/multi-organ symptoms, including many infections, vasculitides, connective tissue diseases, and malignant diseases.
- Many diseases can be associated with bacteremia, such as skin and soft tissue infections, osteomyelitis, pneumonia, meningitis, and others.

Time-Dependent Interventions

- It is important to obtain three sets of appropriately drawn blood cultures prior to the initiation of antibiotics.
- An echocardiogram needs to be performed as soon as possible in any patient in whom the diagnosis of IE is being seriously considered.
- Patients that present acutely with fever and other constitutional symptoms should have empiric antibiotics initiated only after blood cultures are drawn.
- Patients may present with acute complications of IE, such as brain abscess, cerebrovascular accident from emboli/infarct, pulmonary embolism, pulmonary abscess, splenic abscess/infarct, renal abscess/infarct, and vertebral osteomyelitis. These patients need to have the complication treated.
- Patients who develop acute heart failure, or who have significant embolic complications, may require urgent surgical valve replacement or repair.

Overall Principles of Treatment

- The goal of treatment is the eradication of the causative agent of IE, with sterilization of the valve, blood, and all involved organs.
- This usually requires prolonged courses of bactericidal antibiotics.
- Multiple professional societies and organizations have published guidelines for the administration of antibiotics in IE. All are available both in printed and online formats.
- Surgery may be required to aid in removing infected material and draining associated abscesses.
- Patients who present acutely with fever and have a high clinical concern for endocarditis (i.e., a known risk factor or predisposing factor) should have

empiric therapy initiated after three sets of blood cultures are obtained. Empiric therapy should generally cover the most likely etiologic organisms. In developed countries that would be staphylococci, streptococci, and enterococci. For this reason, most empiric regimens should include vancomycin (15-20 mg/kg/dose, every 12 hours, not to exceed 2 grams per dose.).
- Subsequent therapy should be guided by culture results and sensitivity results.
- Therapy usually continues for at least 6-weeks.
- Surgical therapy, either valve repair or replacement, will be necessary in up to 50% of cases. The need for early valve surgery (surgery occurring during the initial course of antibiotics) is indicated by: acutely decompensated heart failure; inability to control infection marked by persistent bacteremia; and the prevention of embolic events.

Disease Course

- In-hospital mortality can range from 10–20%, based upon the predisposing factors (10% for native valve lesions to 40% for prosthetic valve lesions).
- The six-month mortality ranges from 25–30%, and the 5-year mortality approaches 40%.
- Complications of IE can include multiple organ systems (such as cardiovascular, central nervous system, renal, and musculoskeletal), and can occur from multiple pathologic mechanisms (direct extension (abscess), embolization of infected and thrombotic material, and damage and scarring of infected structures (mycotic aneurysm).
- Multiple complications can occur in the same patient.
- Cardiovascular complications include:
    - Heart failure (can be acute or chronic). Heart failure is the most common indication for valve surgery. Heart failure is also the leading cause of death among patients with IE.
    - Abscess around the affected valve.
    - Pericarditis.
    - Intracardiac fistula.
    - Mycotic aneurysm. These can develop in any vessel, including intracerebral vessels, and are most common at areas of weakness such as bifurcations.
- Central Nervous system complications include:
    - Stroke
    - Brain abscess
    - Meningitis

- Renal complications include:
  - Kidney abscess
  - Kidney infarction
  - Immune-mediated glomerulonephritis
- Musculoskeletal complications include:
  - Vertebral osteomyelitis
  - Septic arthritis
- Prolonged antibiotic therapy can also be associated with complications (especially allergic and renal complications).

Related Evidence

Papers of particular importance have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

("infective endocarditis" OR "Endocarditis"[Majr:NoExp] OR "Endocarditis, Bacterial"[Mesh] OR "bacterial endocarditis")

Chapter 40
Interstitial Lung Disease

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Interstitial Lung Disease (ILD); Diffuse Parenchymal Lung Disease (DPLD); Diffuse Infiltrative Lung Disease (DILD)

Incidence/Epidemiology

- The interstitial lung diseases encompass more than 200 individual diseases, all with unique incidences and epidemiology.
- The incidence of specific disorders depends upon many factors, including age, sex, smoking status, environmental and occupational exposures, medications used, exposure to radiation, and medical history.
- Most are rare diseases.
- The most common of these disorders, idiopathic pulmonary fibrosis (IPF), accounts for about 55 % of all ILD diagnoses. It has an incidence that ranges from 10–25/100,000 in the population between 40 and 50 years old, to >175/100,000 in those over age 75.
- All of these disorders are associated with considerable morbidity and mortality.

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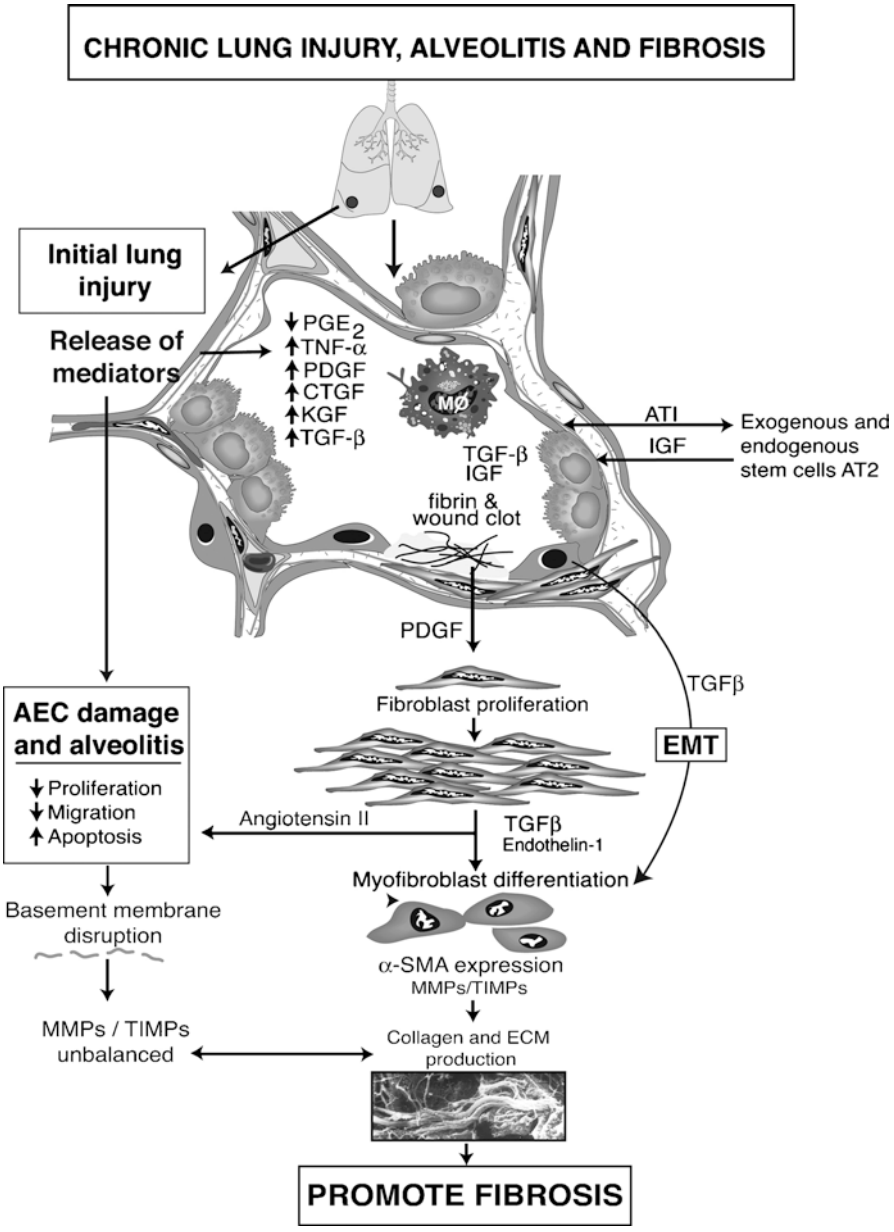
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_40

Differential Diagnosis

- The differential diagnosis is broad and encompasses all diseases that can present primarily with dyspnea and cough, such as asthma, COPD, CHF, and bronchiectasis, among others.
- The differential diagnosis within this class of disorders is also very broad, with over 200 individual diseases to consider.

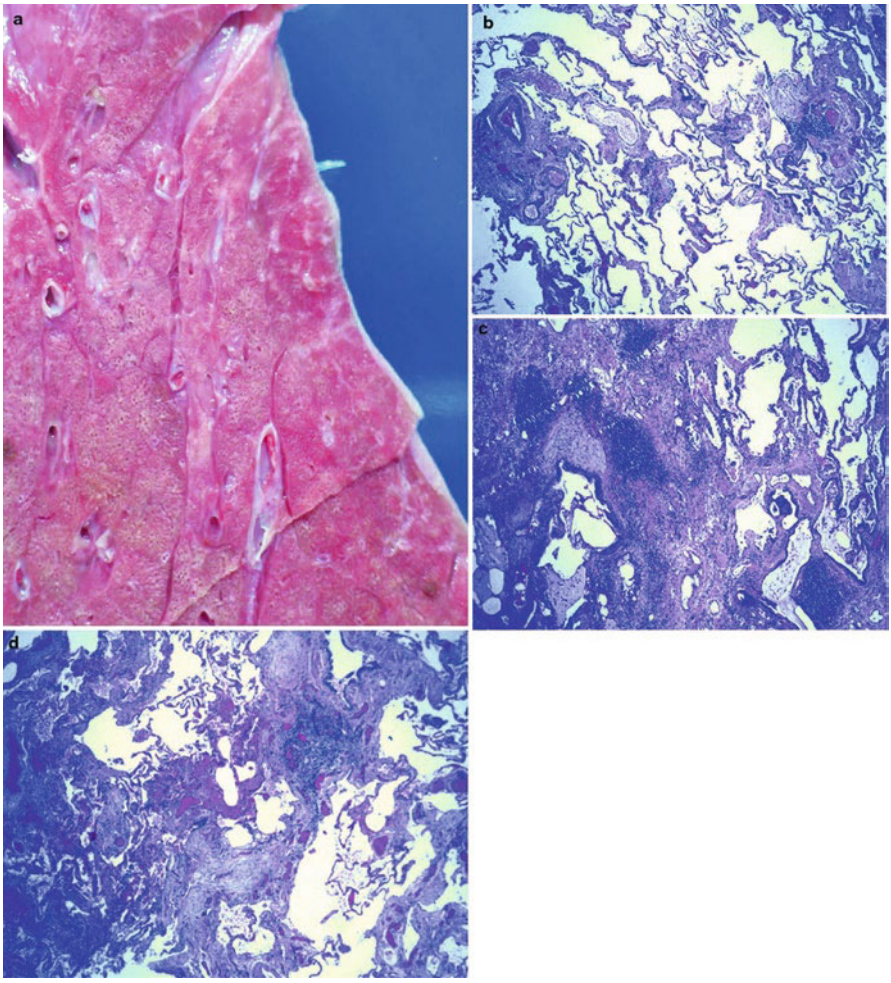
Pathophysiology and Etiology

- ILD is a broad category of diseases that share pathologic involvement of the lung parenchyma and common clinical, radiologic, and physiologic manifestations.
- These are all non-malignant and non-infectious diseases.
- There are several different classification schemes for these diseases. Some schemes classify based upon whether there is a known cause. Some classify based upon primary underlying histopathology (inflammation with fibrosis versus granulomatous.) Some systems classify based upon a combination of both known cause and underlying histopathology.
- Inflammation and fibrosis. This pathophysiologic process starts with some injury or insult to the epithelial surface of the lung that leads to a diffuse inflammatory response in the air spaces and alveoli. This may remit or become chronic. If the inflammatory becomes chronic, the inflammation spreads to the lung interstitium and vasculature, which can lead to permanent interstitial fibrosis and scarring. This then leads to progressive and permanent impairment in physiologic parameters such as gas exchange and ventilation. Most of these disorders are difficult to treat and resistant to treatment.



A schematic drawing of pathogenetic mechanism of alveolar epithelial cells (AEC) in lung injury alveolitis and fibrosis. An initial injury of known or unknown etiology provokes an unresolved inflammation or AEC damage and alveolitis. Alveolitis is an initial event in the pathogenesis of lung fibrosis. A fibrin clot forms early and serves as a provisional matrix for the migration and proliferation of endogenous

AEC stem cells. Bone marrow-derived stem cells, HSCs, can also contribute to the populations of AECs. Activated epithelial cells secrete numerous mediators that create a strong profibrotic microenvironment in lung fibrosis inducing AEC injury, alveolitis and apoptosis. Also injured AEC exhibit a defect in the release of some antifibrotic mediators such as prostaglandinE-2 (PGE2). Epithelial cell damage and cell death during alveolitis induce the formation of gaps in the epithelial basement membrane. Progression from the acute phase of lung injury is accompanied by abnormal alveolar reepitalization, tissue repair and remodeling, which may result in progressive fibrosis. AEC produce MMPs that increase basement membrane disruption and allow fibroblast migration, proliferation and differentiation to myofibroblasts. Myofibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between MMPs and TIMPs provokes the progressive deposit of the extracellular matrix (ECM) and abnormal collagen accumulation and promotes fibrosis. Alveolar macrophages and AEC secrete TGF-β1, which induces epithelial mesenchymal transition (EMT), and this may contribute to fibroblast/myoflbroblast accumulation in the processes of fibrosis. [Gharaee-Kermani M, Gyetko MR, Hu B, Phan SH. New Insights into the Pathogenesis and Treatment of Idiopathic Pulmonary Fibrosis: A Potential Role for Stem Cells in the Lung Parenchyma and Implications for Therapy. Pharmaceutical Research. 2007 Apr 12;24(5):819–41.] *Caption from original*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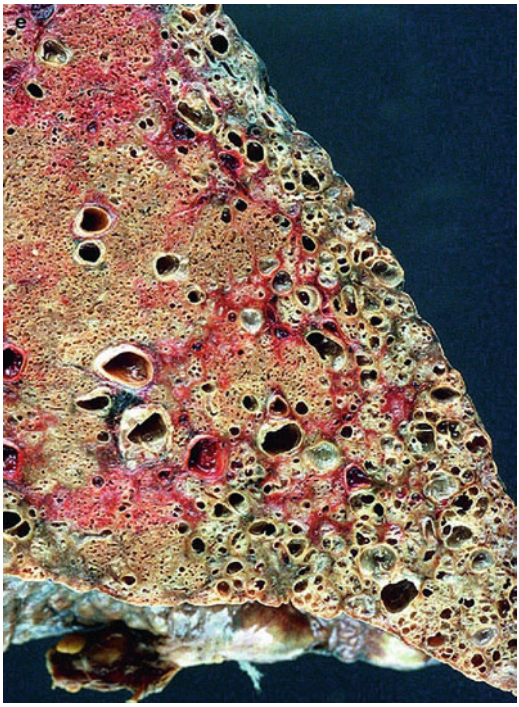


Idiopathic pulmonary fibrosis (interstitial lung disease, idiopathic interstitial pneumonias) with varying alveolar and interstitial inflammatory infiltrates, progressive interstitial fibrosis, secondary hypertensive vascular disease, and a final stage with honeycombing of the lungs. Note the fleshy gross appearance of the lungs in earlier stages (a), with various microscopic interstitial infiltrates (b–d) and gross honeycombing at the end stage (e). The etiology of these diseases is inhomogeneous, as demonstrated by the large variety of terms in use. In many cases, these diseases appear to be autoimmune, either primary or secondary in the course of other systemic autoimmune disorders, but frequently the etiology remains obscure. These disorders are grouped together because of similar clinical manifestations, including severe shortness of breath, diffuse abnormalities of lung mechanics and gas exchange, and diffuse abnormalities in chest radiographs and CT scans, as well as similar clinical outcomes [Krueger GRF, Wagner M, Oldham SAA. Pathology of the Respiratory Tract. In: Krueger GRF, Buja LM, editors. Atlas of Anatomic Pathology with Imaging [Internet]. London: Springer London; 2013 [cited 2015 May 28]. p. 105–89. Available from: http://link.springer.com/10.1007/978-1-4471-2846-5_3] *Caption adapted from original*

- The granulomatous disorders are marked by the pathologic accumulation of inflammatory cells and epithelial cells into granulomas within lung tissue. Many of these patients can remain with mild-to-moderate symptoms, and many may improve with treatment.

- A helpful schema clinically is to group these disorders as to whether the cause is known or unknown.
- Known causes: Inflammatory pathology unless otherwise labeled.
  - Associated with connective-tissue diseases (most commonly rheumatoid arthritis, scleroderma, and polymyositis).
  - Hypersensitivity pneumonitis (e.g., farmer's lung and bird fancier's lung). Granulomatous.
  - Pneumonoconioses (asbestosis, silicosis, coal miner's lung).
  - Drug-induced (chemotherapeutic agents, amiodarone, methotrexate).
  - Smoking-related.
  - Pulmonary Langerhans cell histiocytosis.
  - Respiratory bronchiolitis ILD.
  - Desquamative interstitial pneumonia.
  - Acute eosinophilic pneumonia.
  - Radiation-induced.
  - Toxic-inhalation induced (e.g., cocaine, ammonia, etc.).
- Unknown Causes: Inflammatory pathology unless labeled otherwise.
  - Idiopathic pulmonary fibrosis.
  - Sarcoidosis. Granulomatous.
  - Other idiopathic interstitial pneumonias.
  - Cryptogenic organizing pneumonia (bronchiolitis obliterans organizing pneumonia).
  - Nonspecific interstitial pneumonia.
  - Lymphocytic interstitial pneumonia.
  - Acute interstitial pneumonia.
  - Eosinophilic pneumonias.
  - Pulmonary vasculitides. Mostly granulomatous.
  - Pulmonary lymphangioleiomyomatosis.
  - Pulmonary alveolar proteinosis.
  - Many other rare disorders.

Presentation

Typical/"Classic"

- Dyspnea is the most common and prominent complaint in ILD.
- Classically, patients will have dyspnea with a persistent, non-productive cough associated with diffuse, interstitial infiltrates on chest x-ray.
- Often, patients will have been treated with one or several courses of antibiotics for typical and atypical pneumonia. This non-response to antibiotics should raise suspicion for an ILD.

- The most common time course of presentation is chronic, with symptoms ongoing over months-to-years. A sub-acute presentation over weeks-to-months is also common.
- A detailed history is very important in the evaluation of a patient with a suspected ILD. It can help to narrow the differential to a manageable number of conditions. The history should include detailed questioning as to the pattern and timing of symptoms, smoking history, a detailed environmental and occupational history, and a family history.
- Patients with inflammatory/fibrotic disorders will often have bibasilar "dry" crackles on physical exam. These are often also called "Velcro" crackles as they sound like Velcro being pulled apart.
- Cyanosis and clubbing can occur with advanced disease, and are noted in up to 30% of patients with advanced idiopathic pulmonary fibrosis.

Clubbing of the fingers [Karkucak M, Erturk E, Capkin E, Akyazi H, Ozden G, Tosun M. Primary hypertrophic osteoarthropathy (pachydermoperiostosis): a case report. Rheumatology International. 2007 Jan 11;27(4):403–5.] *Caption from original*

https://www.youtube.com/watch?v=9C5RFb1qWT8
Audio recording of crackles, including late inspiratory crackles.

Atypical

- An acute presentation is unusual, happening mostly in disorders with an allergic basis.
- Some disorders will present in an episodic fashion with acute exacerbations that improve with treatment (sarcoidosis).
- Wheezing and chest pain are not common presenting complaints/findings, except in sarcoidosis.
- Hemoptysis is uncommon, but may be seen in the alveolar hemorrhage syndromes.

Primary Differential Considerations

- Early consideration should be given to
  - ARDS
  - Sarcoidosis
  - Pneumoconiosis
  - Hypersensitivity or drug-induced pneumonitis
  - Pulmonary edema
  - Pneumonia

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical exam findings that can confirm the diagnosis.
- The diagnosis is confirmed with appropriate findings on high-resolution CT of the lungs, or by specific pathologic findings on lung biopsy.

Factors That Suggest Diagnosis

- A classic presentation as described, with slowly progressive dyspnea, a chronic non-productive cough, and diffuse infiltrates on chest x-ray, with symptoms that don't improve with antibiotic treatment, should clearly raise suspicion for an ILD.
- A careful physical examination can help to identify related systemic processes such as any evidence of a connective-tissue disease.

Factors That Exclude Diagnosis

- There are no historical or physical exam findings that can exclude the diagnosis.
- A normal high-resolution CT scan of the lungs would essentially rule out the diagnosis.

Ancillary Studies

Laboratory

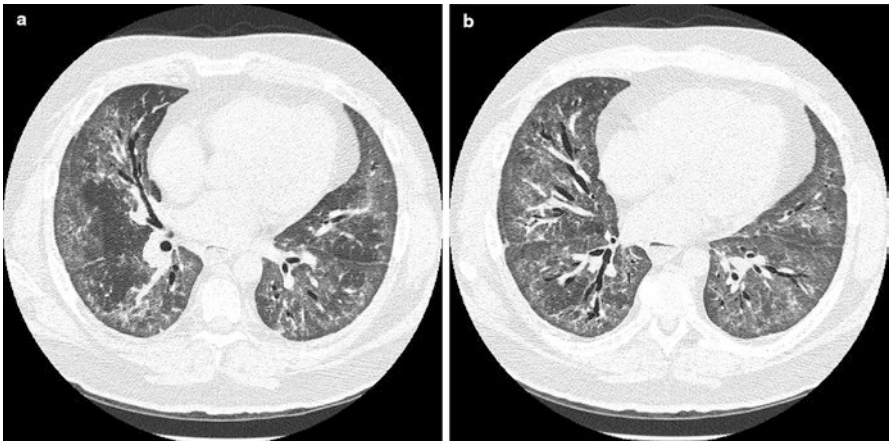
- Most patients will have had routine laboratory studies (CBC, basic chemistries) checked, but they are unlikely to be helpful.
- Specific laboratory evaluation for specific disorders being considered should be performed.
- A raised lactate dehydrogenase (LDH) level is a common, non-specific finding in many ILDs.
- The serum level of angiotensin-converting enzyme (ACE) is commonly elevated in sarcoidosis.
- Anti-nuclear Ab and anti-immunoglobulin Ab (rheumatoid factor) can be found even in patients without an obvious connective-tissue disease.
- If a vasculitis is suspected, it may be helpful to check for the presence of anti-neutrophil cytoplasmic Ab's and anti-basement membrane Ab.

Imaging

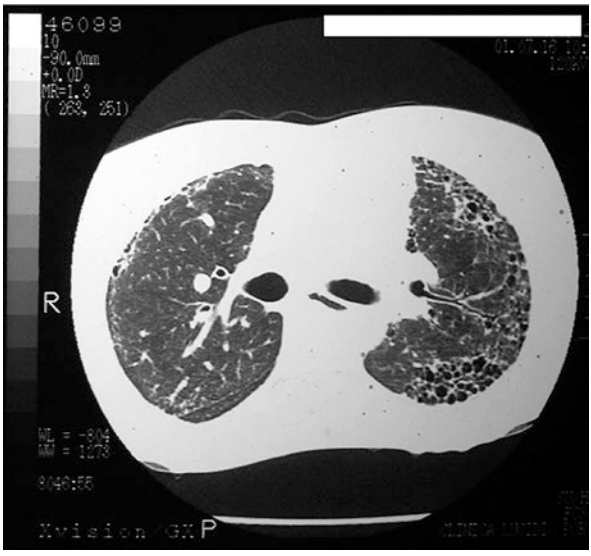
- Most evaluations for ILD are initiated and suspected based upon an abnormal chest x-ray But plain CXRs are neither sensitive nor specific for a diagnosis of ILD. In fact, up to 20% of patients with ILD can have a CXR that is read as normal. CXR findings correlate poorly with clinical findings, and also with the histopathologic stage of the disease.
- High-resolution CT (HRCT) of the chest is the imaging study of choice for the diagnosis of any diffuse interstitial process. The classic "honeycombing" of lung tissue is an end-stage finding.
- HRCT can narrow the differential diagnosis, and in some cases can confirm the diagnosis.
- The pattern of abnormalities, distribution of abnormalities, and associated findings (pleural effusions, lymphadenopathy) found on HRCT, used in conjunction with the clinical context, can sometimes confirm the diagnosis. This can obviate the need for a lung biopsy.

Interstitial lung disease in polymyositis. Magnification lateral-view chest radiograph showing lower zonal reticular interstitial lung disease. [Berney S, Heldmann M. Chapter 14. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] *Caption from original*

High-resolution computed tomography images from a patient with respiratory bronchiolitis interstitial lung disease demonstrating areas of faint, patchy ground glass opacification and reticular thickening. [Coley CJ, Tolle LB, Hasvold J, Schmidt LA, Flaherty KR. Non-specific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia. In: Cottin V, Cordier J-F, Richeldi L, editors. Orphan Lung Diseases [Internet]. London: Springer London; 2015 [cited 2015 May 28]. p. 349–62. Available from: http://link.springer.com/10.1007/978-1-4471-2401-6_23] *Caption from original*



High-resolution computed tomography from the mid (panel a) and lower (panel b) lung fields of patient with nonspecific interstitial pneumonia. The images demonstrate patchy areas of ground glass opacification, reticular thickening and traction bronchiectasis. Some subpleural sparing of disease can be appreciated. Honeycombing is absent. [Coley CJ, Tolle LB, Hasvold J, Schmidt LA, Flaherty KR. Non-specific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia. In: Cottin V, Cordier J-F, Richeldi L, editors. Orphan Lung Diseases [Internet]. London: Springer London; 2015 [cited 2015 May 28]. p. 349–62. Available from: http://link.springer.com/10.1007/978-1-4471-2401-6_23] *Caption from original*



CT diffuse interstitial lung disease with honeycombing. [Teixeira Moreira Almeida M do S, Dias LT, Fernandes SJS, Almeida JVM. Spontaneous pneumomediastinum and subcutaneous emphysema in systemic sclerosis. Rheumatology International. 2007 Apr 10;27(7):675–7.] *Caption from original*

Pulmonary Function Tests

- Spirometry is helpful in evaluating the extent of disease.
- Most forms of ILD will produce a restrictive pattern of PFTs (COPD gives an obstructive pattern). This includes a reduced total lung capacity (TLC), functional residual capacity (FRC), and residual volume (RV).
- Forced expiratory volume in one second (FEV1) and functional vital capacity (FVC) are often reduced, but their ratio is usually normal or increased, as opposed to COPD, where there is a reduced ratio.
- Lung volumes continue to decrease as the disease progresses and lung compliance worsens (the lungs become "stiff").
- The rate of decline of PFTs can have prognostic significance.
- The diffusing capacity to carbon monoxide (DLCO) is reduced in most ILDs, but this is a nonspecific finding and does not correlate with disease stage.
- Arterial blood gases can be normal, but may also show hypoxia from ventilation perfusion mismatch. Ventilation perfusion mismatch occurs because as the fibrosis worsens, lung compliance reduces (the lungs become more stiff). This reduces ventilation in these areas of the lung, but perfusion in these areas remains the same. This leads to blood that has not been adequately oxygenated returning to the heart, which allows this "venous" blood to mix with oxygenated blood in the left heart.
- Carbon dioxide retention is uncommon in ILD (it is more common in COPD), but if present it indicates severe, end-stage disease.
- Exercise pulmonary testing can be used to follow disease progression.

Lung Biopsy

- Lung biopsy may be necessary if the diagnosis is in question after work-up, including HRCT.
- Lung biopsy is the most effective method for diagnosis and assessment of disease severity.
- If possible, a biopsy should be performed prior to the initiation of treatment.
- Bronchoscopy with transbronchial biopsy is usually the first approach to obtaining lung tissue for biopsy. However, this approach gives small tissue samples, and often cannot lead to a definitive diagnosis.
- In these cases it may be necessary to perform a surgical lung biopsy. Surgical lung biopsy has a diagnostic yield of nearly 90%.
- Surgical lung biopsy is usually performed under video-assisted thorascopic surgery (VATS). However, this approach can have a mortality of 2% and a complication rate of 5–10%.

- Bronchoalveolar lavage during bronchoscopy is not useful in the diagnosis of ILD, but may help offer alternative diagnoses (cancer or infections), or assess for complications of ILD (also cancer and infections).

Special Populations

Age

Infants and Children

- Interstitial lung disease does occur in infants and children. It is marked by pulmonary symptoms with diffuse pulmonary infiltrates on lung imaging.
- It is very rare in this age group, with a reported incidence between 1.5–3.6 cases per 1 million in those under the age of 16.
- Many of the causes of ILD in children are similar to the causes in adults, but there are syndromes unique to infants and neonates. These include:
  - Diffuse developmental disorders. This includes alveolar capillary dysplasia with misalignment of the pulmonary veins (ACD-MPV), and acinar dysplasia.
  - Disorders of lung growth and development. This group includes pulmonary hypoplasia and chronic neonatal lung disease with bronchopulmonary dysplasia.
  - Neuroendocrine cell hyperplasia of infancy (NEHI). This is a very rare disorder with an unknown etiology.
  - Pulmonary interstitial glycogenolysis (PIG).
  - Genetic disorders of surfactant production and metabolism.
- In neonates and infants, ILD often presents with unexplained respiratory failure.
- In older infants and children the presentation can be non-specific and includes persistent and unexplained tachypnea, chronic cough, hypoxemia, exercise intolerance, and clubbing of the digits. ILD can also present as failure to thrive and unexplained feeding difficulties. Children above age 2 are more likely to present with exercise intolerance and clubbing.
- The work-up should begin with a complete history and physical examination. The evaluation should initially focus on assessing and excluding the more common causes of respiratory symptoms with diffuse infiltrates. These include: infectious causes, congenital heart disease, and cystic fibrosis. Other rare causes can include immunodeficiencies and structural lung and airway abnormalities.
- The evaluation can then follow as described above for adults.
- An important addition to the evaluation of ILD in children, especially in neonates with respiratory failure and children with suspected ILD and another

affected sibling, is genetic testing for mutations of surfactant production and metabolism. Finding one of these mutations can be diagnostic and obviate the need for lung biopsy.
- Treatment is often supportive (avoiding respiratory irritants, nutritional support, oxygen for hypoxemia, appropriate vaccinations, and appropriate treatment of intercurrent infections), and should be guided by the specific syndrome.
- The prognosis greatly depends upon the specific disorder. Some will spontaneously remit.
- The prognosis is generally poor with ACD-MPV, surfactant mutations, and if pulmonary hypertension complicates ILD.
- Lung transplantation can be considered for end-stage disease not responding to therapy.

Adults

- ILD can present across the spectrum of age groups. The age at presentation can be a significant help in narrowing the differential.

Co-morbidities

- The presence of other or multiple co-morbidities can make the diagnosis and management of ILD more challenging. Of particular concern would be the presence of cancer, heart disease, congestive heart failure, diabetes mellitus, and renal failure.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. Strong consideration of the diagnosis should be given when a patient has not responded to several courses of antibiotics for presumed infectious pneumonia when there are diffuse infiltrates on the CXR.
- When considering the diagnosis, it is critical to take an exhaustive history that should include a complete occupational, travel, and hobby/leisure activity history.
- HRCT is a critical test in the evaluation of suspected ILD.

Mimics

- With several hundred different forms of ILD, any of these may mimic another.
- Other diseases that can present with a cough, dyspnea, and diffuse infiltrates include: primary or metastatic cancer, atypical pneumonias, congestive heart failure, and bronchiectasis.

Time-Dependent Interventions

- Most ILDs are insidious and progress slowly.
- Diagnosis often requires months, and symptoms may have been ongoing and worsening for months to years.
- Some of these diseases may present in an acute fashion, developing over days to weeks. These can include allergy, vasculitides, acute interstitial pneumonia, eosinophilic pneumonia, and hypersensitivity pneumonitis.
- In patients with known ILD, acute respiratory worsening, especially if over 4 weeks or less, is usually due to either acute infection or pulmonary edema.

Overall Principles of Treatment

- Treatment should be tailored to the specific disorder if possible.
- The course can be highly variable, but most ILDs are chronic and progressive.
- There is no therapy to reverse fibrosis once present, so the goal of therapy is usually to reduce inflammation to limit any further damage.
- Oxygen should be used if the patient is hypoxemic (resting PaO2 <55 mmHg)
- Pulmonary rehabilitation has been shown to improve quality of life.
- Glucocorticoids are the most commonly used pharmacologic agents in the majority of ILDs. They are commonly started at high doses, up to 1 mg/kg/day, and continued for 1–3 months. If there has been a response, they are slowly tapered over 3–12 months. Too rapid tapering can lead to recurrence. Many patients will require a maintenance dose of steroids. However, the overall response rate is low.
- If patients on glucocorticoids don't improve, or if their condition worsens, second-line agents include cyclophosphamide and azathioprine. These agents can be used alone or in combination with glucocorticoids.

Disease Course

- Most cases are chronic, slowly progressive, and resistant to most treatments.
- Lung transplant can be considered for end-stage disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Lung Diseases, Interstitial"[Mesh] OR "Interstitial Lung Disease"

Chapter 41
Ischemic Cardiomyopathy

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Jaime Friel Blanck

Name and Synonyms

Ischemic cardiomyopathy

- Heart failure; there is some overlap with Dilated Cardiomyopathy (the term *ischemic cardiomyopathy* refers to severe coronary artery disease PLUS global left ventricular dysfunction)

Incidence/Epidemiology

- It is the most common cause of heart failure in developed countries.
- It effects approximately one out of 100 people.
  - Occurs most often middle-aged-to-elderly men.

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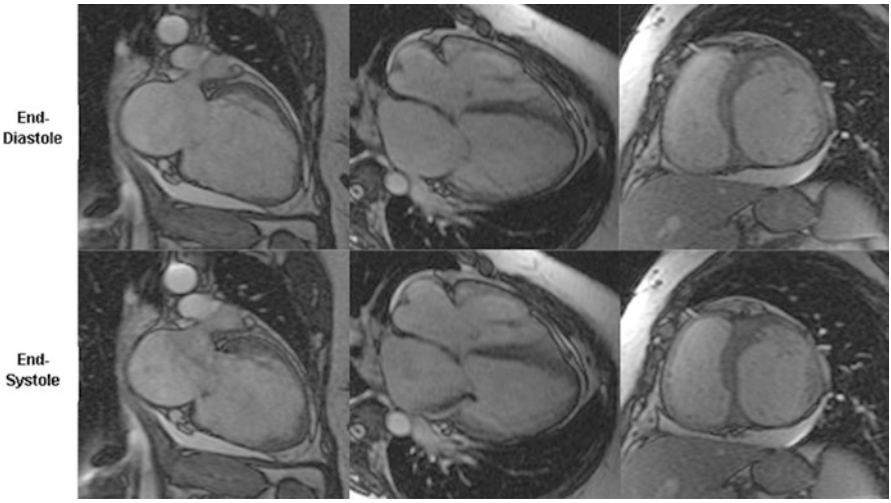
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_41

Differential Diagnosis

- Nonischemic cardiomyopathy
- Dilated cardiomyopathy
- Restrictive cardiomyopathy
- Hypertrophic cardiomyopathy
- Peripartum cardiomyopathy
- Infectious cardiomyopathy

Pathophysiology and Etiology

- Impaired left ventricular function (less than 35–40 %) that results from coronary artery disease
  - may result from irreversible loss of myocardial cells from infarction.
  - may result from contractility deficit that is variable in the setting of ischemic but not frankly infarcted myocardial cells.
  - Ejection fraction less than 35–40 %.



Ischemic cardiomyopathy demonstrating inferior wall thinning and akinesis in the two chamber image (far left). In the four chamber image (middle) there is lateral wall akinesis with RV dilatation and markedly reduced RV free wall shortening and minimal tricuspid annular movement from end-diastole to end-systole. In the short axis images there is RV dilatation with reduced free wall thickening and severe LV systolic dysfunction. The LV inferior wall akinesis is also present in the inferior portion of the interventricular septum [Dell'Italia LJ. The Right Ventricle in Left Heart Failure. In: Voelkel NF, Schranz D, editors. The Right Ventricle in Health and Disease [Internet]. New York, NY: Springer New York; 2015 [cited 2015 Oct 22]. p. 361–90. Available from: http://link.springer.com/10.1007/978-1-4939-1065-6_17] *Caption from original*

Presentation

Typical/"Classic"

- Patients usually have a clear clinical history of coronary heart disease.
- Shortness of breath, with or without chest pain.
- Edema which may cause weight gain.
- Easy fatigability.
- Palpitations.
- Dizziness, lightheadedness, or syncope.

Atypical

- An atypical presentation would manifest as unexplained easy fatigability without the other symptoms noted above.

Primary Differential Considerations

- Consider acute heart failure of other etiologies, acute coronary syndrome, pulmonary embolism, and primary ventricular arrhythmia.

History and Physical Exam

Findings That Confirm Diagnosis

- There are no clinical findings that irrefutably confirm the diagnosis of ischemic cardiomyopathy.

Factors that Suggest Diagnosis

- Fatigue.
- Dyspnea on exertion, shortness of breath.
- Orthopnea, paroxysmal nocturnal dyspnea.
- Increasing edema, weight, or abdominal girth.
- Physical exam may note:
  - Tachypnea
  - Tachycardia
  - Hypertension
  - Hypoxia
  - Jugular venous distension (JVD)
  - Pulmonary crackles and/or wheezes
  - S_3 gallop
  - Peripheral edema
- The level of cardiac compensation determines which signs are present.

Factors That Exclude Diagnosis

- While there are no clinical factors that can exclude ischemic cardiomyopathy in the patient with heart failure symptoms, the finding (on imaging) of no significant coronary artery disease essentially removes the diagnosis from consideration.

Ancillary Studies

Laboratory

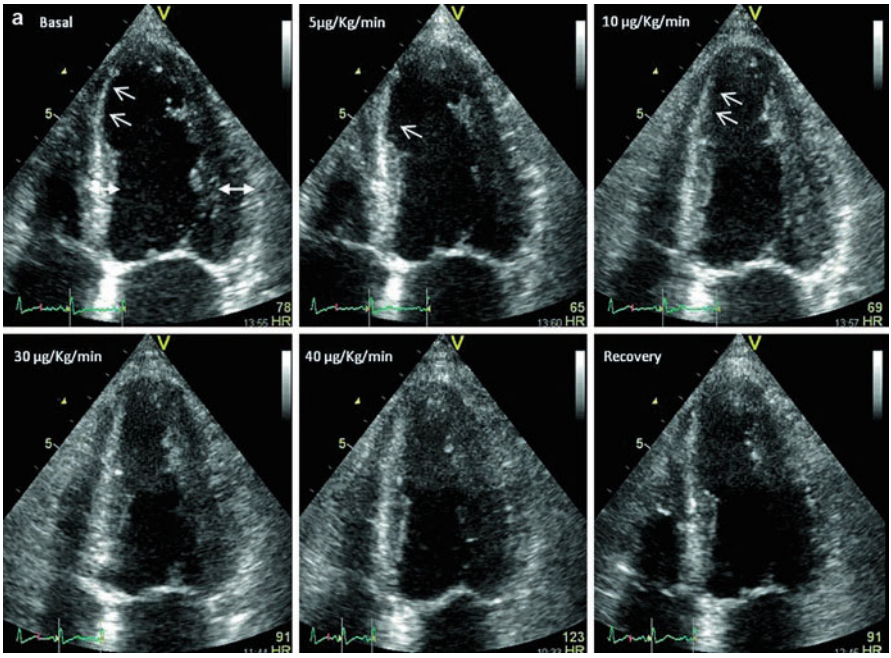
- Cardiac biochemical markers
- Brain-type natriuretic peptide (BNP) or NT-pro-BNP
- Coronary risk profile including lipid profile

Electrocardiography

- Left ventricular hypertrophy.
- Left bundle branch block is not uncommon.
- Nonspecific ST-T wave changes and Q waves are common and may reflect past infarction or current ischemia as much as the cardiomyopathy.

Imaging

- Chest x-ray:
  - Cardiomegaly is uniformly present.
  - There may be signs of heart failure, with pulmonary vascular congestion and Kerley B lines.
- Echocardiography is commonly performed to assess pump function.
- Needs evaluation for coronary artery disease, usually including exercise stress testing with myocardial imaging.



Example of a patient with ischemic cardiomyopathy (left ventricular ejection fraction 35%). At baseline, the resting echocardiography shows areas of thinning (<1 cm markers) in the mid and apical segments of the septal wall (arrows) whereas the lateral wall and the basal segment of the septum show preserved thickness (double arrows). During low-dose and peak-dose dobutamine stress echocardiography, the mid and apical segments of the septal wall show improved thickening (arrows) consistent with myocardial viability. [Delgado V, Schinkel AFL, Yiu K-H, Bax JJ. Nuclear Imaging to Assess Infarction, Reperfusion, No-Reflow, and Viability. In: Kaski JC, Hausenloy DJ, Gersh BJ, Yellon DM, editors. Management of Myocardial Reperfusion Injury [Internet]. London: Springer London; 2012 [cited 2015 Sep 15]. p. 161–89. Available from: http://link.springer.com/10.1007/978-1-84996-019-9_8] *Caption adapted from original*

- Cardiac catheterization with coronary angiography is reasonable for a patient with new-onset heart failure of uncertain cause, who would be eligible for revascularization.
- Noninvasive coronary arteriography including CT or cardiovascular magnetic resonance imaging is also available if the patient does not have angina or is not a candidate for revascularization.

Special Populations

Age

- Most patients with ischemic cardiomyopathy have experienced a transmural myocardial infarction. That means most of these patients are at least 50 years of age.

Co-morbidities

- Coronary artery disease with risk factor:
  - A family history of heart disease
  - Hypertension
  - Smoking
  - Hypercholesterolemia
  - Obesity
  - Diabetes
  - End-stage kidney disease

Pediatric Considerations

- Ischemic cardiomyopathy is generally not a pediatric disease.

Pitfalls in Diagnosis

Critical Steps not to Miss

- Diagnosis consists of 2 steps:
  - 1) The detection of significant coronary artery disease
  - 2) The detection of potentially reversible myocardial function

Mimics

- Chest pain alone is insufficient to make the diagnosis.
  - Nonischemic cardiomyopathy may have chest pain that resembles angina.

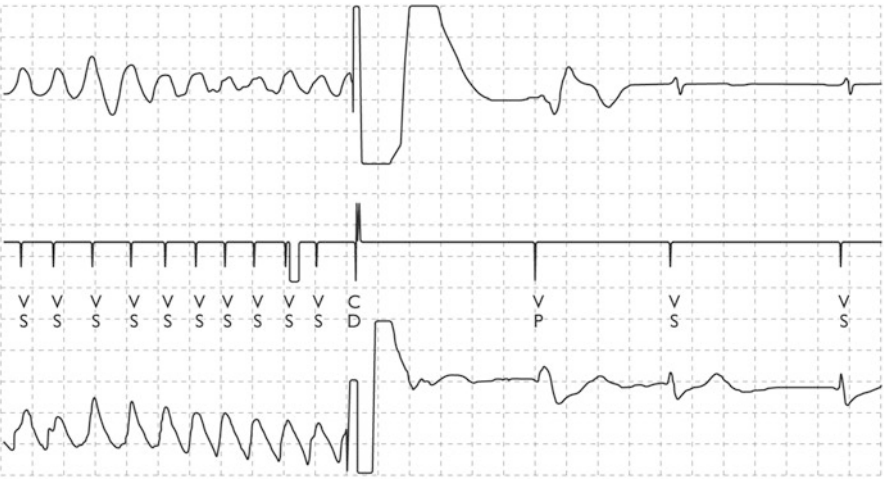
Time Dependent Interventions

- The most time-sensitive issue to address is any current ischemia.

Overall Principles of Treatment

- Medical therapy of heart failure:
  - ACE inhibitors.
  - Beta-blockers.
  - Statin as part of secondary prevention of established coronary heart disease.
  - Loop diuretic and dietary salt restriction in patients with fluid volume overload.
  - Removal of drugs that adversely affect systolic dysfunction like nonsteroidal anti-inflammatory drugs, antiarrhythmic drugs, certain calcium channel blockers.

- Device therapy:
  - Implantable cardioverter-defibrillator for prevention of sudden cardiac death.



Intracardiac electrogram of implantable cardioverter-defibrillator (ICD) shock terminating ventricular fibrillation in patient with ischemic cardiomyopathy. The ICD is the most effective therapy for prevention of sudden death in patients with heart failure. The use of the ICD for primary prevention of sudden cardiac death has provided the impetus for identification of individuals at highest risk of sudden death. In this example, the ICD accurately recognized ventricular fibrillation and terminated the rhythm with a shock. [Sauer W, Nayak H, Marchlinski F. Chapter 08. In: Shivkumar K, Weiss J, Fonarow G, Narula J, editors. Atlas of electrophysiology in heart failure. Philadelphia: Current Medicine; 2005. (Braunwald E, editor. Atlas of heart diseases; vol. 15); ISBN: 1-57340-225-7] *Caption from original*

- Biventricular pacing for patients in sinus rhythm, LVEF <35 %, prolonged QRS duration and symptoms despite medical therapy.
- Coronary artery bypass graft surgery or angioplasty may improve cardiac blood flow.
- Heart transplant may be tried if other treatments have failed.
- Risk reduction measures for secondary prevention is indicated in patient with ischemic cardiomyopathy includes aspirin, control of hypertension and diabetes, and cessation of smoking.

- Decision to proceed with medical therapy and/or surgical revascularization in patients with ischemic cardiomyopathy should be individualized.

Disease Course

- Ischemic cardiomyopathy is an independent predictor of mortality.
- Prognosis is related primarily to the degree of ventricular dysfunction and the extent of coronary artery disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Myocardial Ischemia"[Mesh] OR "Ischemic cardiomyopathy"

Chapter 42
Kawasaki Disease

Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Kawasaki Disease

- Also known as mucocutaneous lymph node syndrome.

Incidence/Epidemiology

- One of the most common vasculitides of infancy and childhood.
- Its highest incidence is in East Asian children. One in 100 Japanese children will develop KD by age 5.
- Within the US, there is a winter-spring predominance of cases. Incidence estimates vary between ethnic groups in the US, with lowest rates reported amongst Caucasian children.
- Peak incidences occur before the age of one year. Eighty to 90% of cases affect children less than 5 years of age.
- The etiology of KD remains unknown. See legend.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_42

Single etiologic agent
Uncommon agent that immunologically cross-reacts with, common agent
Common agent with unusual host response
Multiple etiologic agents with final common pathway
Common agents with unusual host response

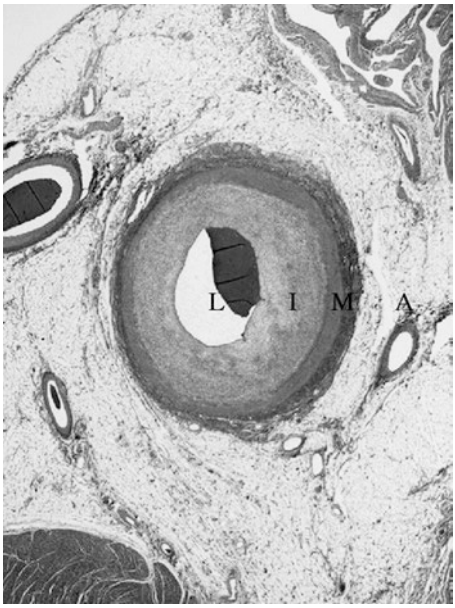
Paradigms for the cause of Kawasaki disease or syndrome. Debate continues as to whether Kawasaki disease is caused by a single etiologic agent ("disease") or by multiple different agents that result in a stereotyped host response ("syndrome"). [Burns J, Glodé M. Chapter 10. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption from original*

Differential Diagnosis

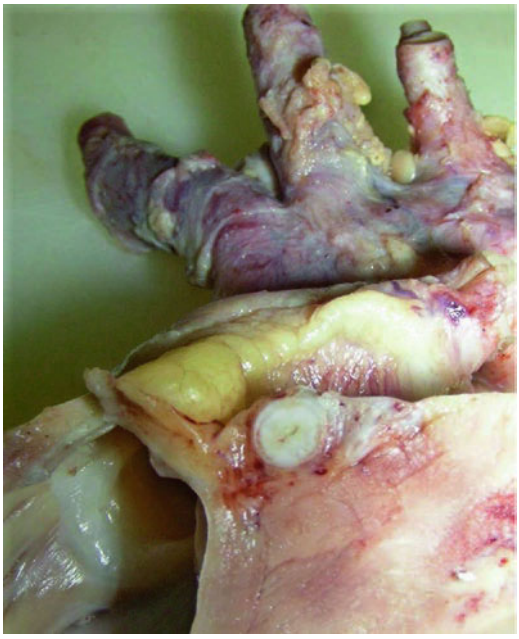
- Kawasaki Disease is accompanied by fever, an exanthema, profound mucous membrane involvement, and lymphadenitis. As such the differential diagnosis includes, but is not limited to:
  - Measles
  - Adenoviral infections
  - Scarlet fever
  - Echoviral infections
  - EBV infections
  - Rocky Mountain Spotted Fever
  - Systemic juvenile rheumatoid arthritis

Pathophysiology and Etiology

- The etiology of KD remains unknown.
- The basic pathology involves a widespread vasculitis, with particular involvement of medium-sized arteries (i.e., the coronaries).
- Coronary involvement will result in the development of aneurysms and generalized dilatation. See legend.



Coronary artery of a patient who died of pachymeningitis 9 months after contracting Kawasaki disease [Takahashi K, Oharaseki T, Yokouchi Y, Naoe S, Saji T. Kawasaki disease: basic and pathological findings. Clinical and Experimental Nephrology. 2013 Oct;17(5):690–3.] *Caption adapted from original*



Coronary artery vasculitis in a child with treatment-resistant Kawasaki disease and ischemic cardiomyopathy [Markelj G, Avčin T. Systemic Corticosteroids in Childhood Vasculitides. In: Cimaz R, editor. Systemic Corticosteroids for Inflammatory Disorders in Pediatrics [Internet]. Cham: Springer International Publishing; 2015 [cited 2015 Aug 28]. p. 77–94. Available from: http://link.springer.com/10.1007/978-3-319-16056-6_7] *Caption from original*

Presentation

Typical/"Classic"

- **Fever** is the most common presenting sign. It is usually present for more than 4 days, and generally unresponsive to antipyretic therapy. It is most often greater than 38.5° C.
- **Mucositis** involves the development of red, cracked lips and a strawberry tongue. See figure.

Strawberry tongue, mucosal redness, and cracked lips in a 3-year-old boy [Falcini F. Kawasaki Disease. In: Matucci-Cerinic M, Furst D, Fiorentino D, editors. Skin Manifestations in Rheumatic Disease [Internet]. New York, NY: Springer New York; 2014 [cited 2015 Sep 4]. p. 283–8. Available from: http://link.springer.com/10.1007/978-1-4614-7849-2_34, courtesy of Fernanda Falcini, MD] *Caption from original*

- **Conjunctival** involvement occurs in more than 85 % of patients. Though generally a superficial disease, some cases will go on to develop uveitis. See

Hemorrhagic conjunctivitis. A, In this case of conjunctivitis, the lids are not thickened and crusted but diffusely swollen. [Wald ER. Eye and Orbit Infections. In: Brook I, editor. Atlas of Upper Respiratory and Head and Neck Infections, 2e. Philadelphia: Current Medicine; 2000. (Mandell GL, editor. Atlas of infectious diseases; vol. 4). ISBN: 1-57340-140-4] *Caption from original*

- The **rash** is polymorphous. It usually involves the development of erythematous papules with variable distribution.
- One of the later findings is **induration** of the hands and feet. During the convalescent phase, distal **desquamation** occurs in 80 % of cases. See figure.

Kawasaki disease. Peeling of the top of the toes [Schneider R, Laxer R. Rheumatology. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-188-9] *Caption adapted from original*

Periungual desquamation during the convalescent phase of Kawasaki disease. The peeling is usually noted after the acute signs and symptoms of inflammation have subsided in the 2nd to 3rd week of the illness. [Burns J, Glodé M. Chapter 10. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption from original*

Desquamating rash in child with Kawasaki disease. [Watts RA, Scott DGI. Kawasaki Disease. In: Watts RA, Scott DGI, editors. Vasculitis in Clinical Practice [Internet]. Cham: Springer International Publishing; 2015 [cited 2015 Aug 28]. p. 117–26. Available from: http://link.springer.com/10.1007/978-3-319-14871-7_11] *Caption from original*

- The presence of **lymphadenopathy** is the least consistent finding of KD.

Atypical

- There is a subcategory of KD, namely incomplete, or atypical KD. It is important for the clinician to recognize this entity, since early treatment of KD will prove cardioprotective.

- Studies of children with incomplete KD demonstrate the following variances from the typical findings:
  - Cervical adenopathy was absent in 90 % of infants.
  - Fifty percent have no rash.
  - Peripheral extremity changes were absent in 40 % of patients.
- Consistent findings seen in both typical and atypical KD include fever and mucous membrane involvement.

Primary Differential Considerations

- The most common differential considerations for KD are acute focal infections such as:
  - Orbital cellulitis
  - Lymphangitis
  - Retropharyngeal or peritonsillar abscess
- The rash of KD may look similar to:
  - Measles

Typical erythematous maculopapular rash of measles. Measles is an acute febrile infection caused by the rubeola virus and characterized by a prodrome of fever and upper respiratory symptoms followed by the characteristic measles exanthem. The rash, which is erythematous and maculopapular, usually begins on the head and spreads

downward to involve the trunk and upper and lower extremities. [Gilsdorf J, Shope T. Viral exanthems of childhood. In: Fekety R, editor. External manifestations of systemic infections. Philadelphia: Current Medicine; 1996. 237 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 6.) ISBN: 0-443-07760-6] *Caption from original*

- Rocky Mountain Spotted Fever

Petechial lesions in Rocky Mountain spotted fever. [Woodward T, Sexton D, Walker D, Bleck T. Chapter 09. In: Stevens DL, editor. Skin, Soft Tissue, Bone and Joint Infections. Philadelphia: Current Medicine; 1995. 250 p. (Mandell GL, editor. Atlas of Infectious Diseases; vol. 2.) ISBN: 1-878132-44-X] *Caption adapted from original*

- Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome. A faint macular erythema is present on the trunk and arms of a febrile 4-year-old girl. The redness is accentuated in the skinfolds of the upper arms and the antecubital area. This disease occurs from the effects of epidermolytic toxins produced by some strains of *S. aureus*, most commonly group II phage types. The patients are usually children less than 5 years of age, in whom the staphylococci commonly colonize the mucous membranes of the nasopharynx, vagina, or conjunctivae, from which the toxin is readily absorbed. This disorder is rare in adults, apparently because they can inactivate or eliminate the

toxins by immunologic mechanisms or urinary excretion. Affected adults usually have had suppurative infections, rather than just mucosal colonization, and severely compromised renal or immune function. [Hirschmann J, Bleck T. Chapter 02. In: Stevens DL, editor. Skin, Soft Tissue, Bone and Joint Infections. Philadelphia: Current Medicine; 1995. 250 p. (Mandell GL, editor. Atlas of Infectious Diseases; vol. 2.) ISBN: 1-878132-44-X] *Caption from original*

- Toxic Epidermal Necrolysis

Toxic epidermal necrolysis in a female patient covering more than 30% of the total body surface area. A special critical care infrastructure such as that provided in burn centers with positive pressure units providing a constant environmental temperature of more than 30° C and an adjustable atmospheric humidity of 70% should be considered in the early course of the disease [Struck MF, Hilbert P, Mockenhaupt M, Reichelt B, Steen M. Severe cutaneous adverse reactions: emergency approach to non-burn epidermolytic syndromes. Intensive Care Medicine. 2010 Jan;36(1):22–32.] *Caption from original*

History and Physical Exam

- Most children will seek medical care due to the presence of high fevers. They will be irritable, paradoxically (i.e., not wanting to be touched). There will be a history of a rash, red eyes, and cracked lips. The rash, if present, will often be a chief complaint.

Findings That Confirm Diagnosis

- Commonly accepted diagnostic criteria for Kawasaki disease include the presence of fever for at least 5 days AND at least 4 of the 5 following criteria:
  - Conjunctival injection
  - Oral mucous membrane changes (fissured lips, strawberry tongue)
  - Peripheral extremity changes (erythema of palms/soles, edema of hands and feet, periungual desquamation)
  - Polymorphous rash
  - Cervical lymphadenopathy
- Laboratory findings consistent with a diagnosis of KD include:
  - Elevated ESR or CRP
  - Elevated WBC
  - Anemia (normochromic/normocytic)
  - Thrombocytosis (< 450,000 after 5 days)
  - Pyuria
  - Elevated liver enzymes
- Decreased serum albumin

Factors That Suggest Diagnosis

- In all published reports, the presence of fever for more than 5 days, in any pediatric age group, should raise suspicion for atypical forms of KD.

Factors that Exclude Diagnosis

- The absence of fever essentially rules out KD.

Ancillary studies

Laboratory

- The use of the laboratory is mandatory when evaluating all cases of suspected KD.

- Recommended tests include:
  - ESR or CRP
  - CBC with differential
  - Urinalysis
  - Liver function tests
  - Serum albumin

Electrocardiography

- ECG findings are not helpful.

Cardiac Enzymes

- Not indicated.

Special Populations

Age

- There have been reported cases of KD in adolescents.

Co-morbidities

- Case reports have described associated arthritis in older patients with KD.

Pitfalls in Diagnosis

- One must consider KD (in any form) when evaluating infants and children with prolonged febrile illnesses.
- Early consultation with Pediatric Cardiology is mandatory in suspected cases.

Critical Steps Not to Miss

- When presented with a patient with irritability, fever, and rash, always consider KD in your differential.

Mimics

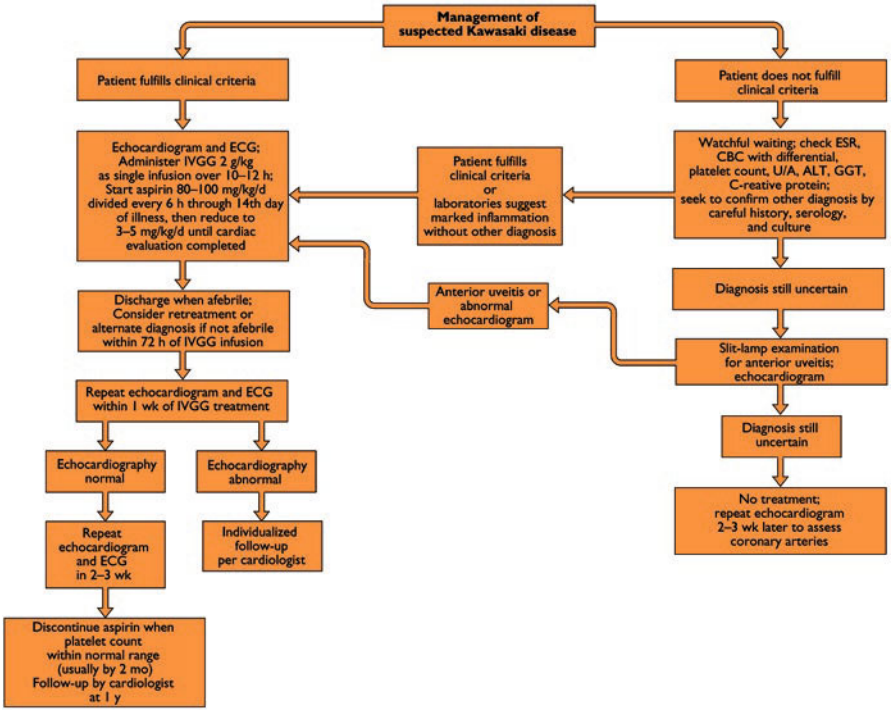
- Measles
- Adenoviral infections
- Scarlet fever
- Echoviral infections
- EBV infections
- Rocky Mountain Spotted Fever
- Systemic juvenile rheumatoid arthritis

Time-Dependent Interventions

- Obtaining a Pediatric Cardiology consult is always indicated.
- Recommended pharmacologic treatments include:
  - Administration of a single dose of IV immunoglobulin (IVIG) (2 mg/kg) over 8 to 12 hours.
  - Administration of aspirin. The recommended initial dose is 80 to 100 mg/kg/day in 4 divided doses.

Overall Principles of Treatment

- The primary goals of KD management are to prevent the development of coronary lesions and to relieve symptoms.



Algorithm for management of patients with suspected Kawasaki disease. The current recommended therapy for patients with Kawasaki disease who present within the first 10 days of illness is intravenous gamma globulin (IVGG), 2 g/kg as a single infusion over 10 to 12 hours, in conjunction with aspirin (80 to 100 mg/kg/d divided into four doses through illness day 14, then 3 to 5 mg/kg/d until cardiac evaluation is completed). The mechanism of action of IVGG has not been elucidated, although downregulation of the inflammatory response after treatment has clearly been demonstrated. ALT—alanine aminotransferase; CBC—complete blood count; ECG—electrocardiogram; ESR—erythrocyte sedimentation rate; GGT—γ-glutamyl transferase; U/A—urinalysis.[Burns J, Glodé M. Chapter 10. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption adapted from original*

TARGETS OF THERAPY IN KAWASAKI DISEASE

LIFESTYLE MODIFICATIONS	PHARMACOLOGIC THERAPY	SURGICAL INTERVENTION
Implementation of heart-healthy diet, with specific recommendations guided by serum liqid profile	Goals	CABG
Prevention or cessation of smoking	Decrease overall prevalence and size of coronary artery aneurysms	PTCA
Physical activity guided by status of coronary arteries and use of antithrombolytic therapy (see Figs. 9-29–9-34 for stratified recommendations)	Prevent coronary artery thrombosis in patients with aneurysms	Stents
Maintenance of healthy weight	Treat ischemic heart disease in patients with coronary aneurysms	Cardiac transplantation

Targets of therapy for Kawasaki disease (KD). Children with KD and their parents should receive lifestyle modification counseling. This is especially important because various follow-up studies in children with coronary aneurysms in the acute phase have indicated that even when these aneurysms regress, there is persisting vascular dysfunction. This may put these children at risk for accelerated atherosclerosis in adulthood. [Taubert K, Newburger J. Kawasaki Disease. In: Creager MA, editor. Atlas of Vascular Disease. 2e, Philadelphia: Current Medicine; 2003. (Braunwald E, series editor, vol 07). ISBN: 1-57340-191-9] *Caption adapted from original*

Disease Course

- Long-term outcomes for children treated early with IVIG and salicylates are very favorable.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Research Committee of the Japanese Society of Pediatric Cardiology; Cardiac Surgery Committee for Development of Guidelines for Medical Treatment of Acute Kawasaki Disease. Guidelines for medical treatment of acute Kawasaki disease: report of the Research Committee of the Japanese Society of Pediatric Cardiology and Cardiac Surgery (2012 revised version). Pediatr Int. 2014 Apr;56(2):135-58. https://doi.org/10.1111/ped.12317. PubMed PMID: 24730626. http://www.ncbi.nlm.nih.gov/pubmed/24730626 **

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Meta-Analysis

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:"http://www.ncbi.nlm.nih.gov/pubmed/22634168"

"Mucocutaneous Lymph Node Syndrome"[Mesh] OR "Mucocutaneous Lymph Node Syndrome"[tiab] OR "kawasaki"[tiab]

Chapter 43
Laryngospasm

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Laryngospasm

Incidence/Epidemiology

- Incidence is 8.6/1000 in adults.
- Higher incidence of 27.6/1000 was noted in children perioperatively.
- Overall incidence is just under 1 % in both adult and pediatric anesthesia.
- Increased in infants

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_43

Differential Diagnosis

- Epiglottitis
- Croup
- Tracheitis
- Retropharyngeal abscess
- Infectious mononucleosis
- Aspirated foreign body
- Laryngeal trauma
- Anaphylaxis
- Angioedema
- Vocal cord dysfunction
- Congenital anomalies

Pathophysiology and Etiology

- Acute manifestation of vocal cord dysfunction beyond the normal airway protective reflex
- Usually precipitated by irritation of the vocal cords
- May be incomplete or complete
- May occur as a complication of anesthesia, especially with ketamine
- May occur during intubation procedures or post extubation

Partial laryngospasm is not uncommon during and at the end of a bronchoscopic procedure [Goudra BG, Singh PM, Borle A, Farid N, Harris K. Anesthesia for

Advanced Bronchoscopic Procedures: State-of-the-Art Review. Lung. 2015 Aug;193(4):453–65.] *Caption from original*

Presentation

Typical/"Classic"

- Patient will describe a choking sensation and be unable to breathe or speak.
- Patient may have stridor.
- Episode may last only minutes.

Atypical

- If prolonged, may lead to hypoxia and hypercapnea
- Vocal cord dysfunction usually is chronic, and worsening of stridor may be a clue to a progressive anatomic problem.

Primary Differential Considerations

- Angioedema
- Asthma
- Epiglottitis
- Croup
- Laryngomalacia
- Tracheal foreign body
- Vocal cord paralysis or tumor

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis is made clinically (as below), then attention is turned to the underlying cause.

Factors That Suggest Diagnosis

- Lack of upper airway patency
- Inspiratory stridor if partial obstruction
- Decreased chest wall movement
- Fever suggests an infectious etiology
- Sensation of choking and inability to breathe or speak
- Increased respiratory effort
- Tracheal tug
- Paradoxic respiratory effort
- Oxygen desaturation with or without bradycardia

Factors That Exclude Diagnosis

- A patent trachea with no increased breathing effort excludes significant laryngospasm, but stridor, even in the presence of normal respiratory effort, warrants further evaluation for a fluid or evolving clinical scenario.

Ancillary Studies

Imaging

- Imaging should never interfere with stabilization of a critical obstruction.
- Soft tissue radiographs of the neck may help diagnose epiglottitis/croup/foreign body.

Special Populations

Age

Co-morbidities

- Those with reactive airway disease are more prone to laryngospasm during intubation.

Pediatric Considerations

- Seen mainly in children, especially in infants 1–3 months of age.
- Has been reported in association with ketamine use; however, this is thought to be idiosyncratic in etiology.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Triggering factors:
  - Painful stimulation
  - Primary vagal hypertonicity
  - Insufficient depth of anesthesia on endotracheal intubation
  - Irritants:
  - Blood
  - Mucus
  - Laryngoscope blade
  - Suction catheter
  - Surgical debris or other foreign body

Mimics

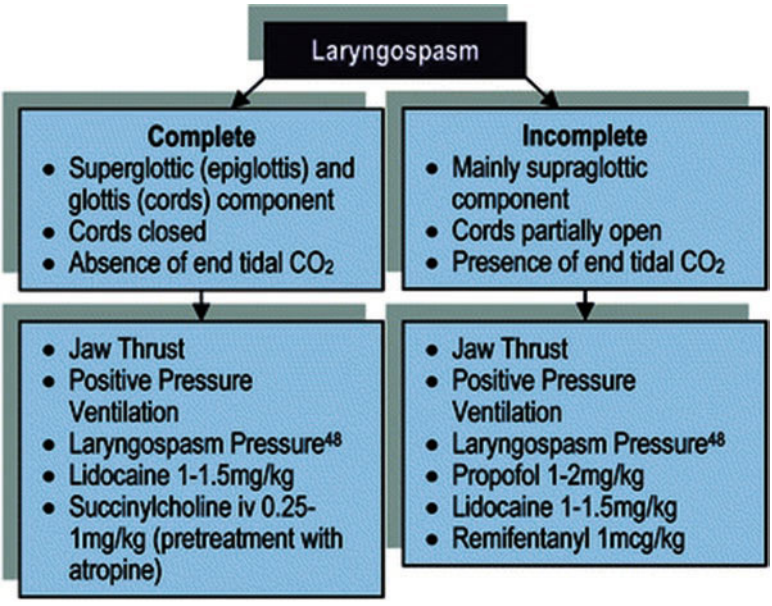
- Other causes of upper airway obstruction, such as a foreign body, may cause a clinical picture similar to that of laryngospasm, but with normal vocal cord action.

Time-Dependent Interventions

- Acute upper airway compromise/obstruction may be a life-threatening emergency.
- Prompt recognition is needed.

Overall Principles of Treatment

- Factors influencing the choice of treatment:
  - Degree of airway compromise
  - Etiology of laryngospasm
  - Presence of fever
  - Acuteness of symptom onset
  - History of injury
  - Age
- Treatment options:
  - Suctioning of foreign material from the oropharynx
  - Removal or avoidance of painful stimuli
  - "Jaw thrust" at the angle of the mandible while applying positive pressure ventilation with oxygen by bag and mask
  - Laryngospasm pressure
  - Lidocaine: 1 to 1.5 mg/kg intravenously (IV)
  - Topical lidocaine: direct administration to vocal cords
  - Succinylcholine: recommended dose varying from 0.25 to 1 mg/kg IV or 4 mg/kg intramuscularly; must be followed by definitive airway and ventilation management



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2010. Chapter 10, Pediatric airway management; [cited 2015 Aug 13]; p. 415–513. Available from: http://link.springer.com/10.1007/978-0-387-09558-5_10] *Caption from original*

1.	Identification and removal of the noxious stimulus (blood, secretions)
2.	Chin lift and jaw thrust
3.	Positive airway pressure with 100 % oxygen
4.	Intravenous succinylcholine (0.5–1 mg/kg) or intramuscular (1–4 mg/kg) if no IV access
5.	Deepen anesthesia with propofol or inhalational agent
6.	Endotracheal intubation if required

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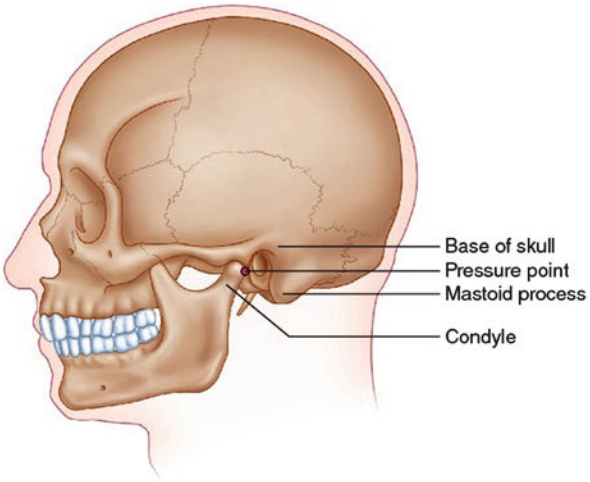

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Disease Course

- People experiencing laryngospasm describe a sensation of choking and cannot breathe or speak.
- As the airways slowly open, the person may have stridor.
- The episode may last only a minute or two before breathing returns to normal.
- Some people lose consciousness during these episodes.
- Underlying pathology will determine extended course and risk of recurrence.

Related Evidence

Papers of particular interest have been highlighted as:
** *Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Laryngismus"[Mesh] OR "Laryngospasm"

Chapter 44
Mallory-Weiss Syndrome

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Mallory-Weiss Syndrome

- Mallory-Weiss Tear

Incidence/Epidemiology

- Mallory-Weiss tears are the fourth most common cause of upper gastrointestinal bleeding in adults.
- They account for 5 % of all upper gastrointestinal (UGI) bleeding cases.
- Three percent of deaths from UGI bleeding are the result of Mallory-Weiss tears.
- It is much less common in children.
- Mortality may be up to 3 %, but most mortality is associated with significant co-morbidities, such as portal hypertension, known coagulopathy, or older age.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_44

Differential Diagnosis

- Chest pain typically occurs with Mallory-Weiss tears, but is usually overshadowed in the presentation by the complaint of hematemesis. Mallory-Weiss tears cause UGI bleeding.
- All the causes of acute UGI bleeding need to be considered, including:
  - peptic ulcer disease (gastric and duodenal ulcers and erosions)
  - esophageal varices
  - esophagitis
  - duodenitis
- Older patients who may have coronary artery disease may develop angina from the exertion of vomiting or from the anemia that results from blood loss.
- Esophageal rupture, which only rarely causes UGI bleeding, may present with chest pain.

Pathophysiology and Etiology

- A Mallory-Weiss tear is a 1- to 4-cm longitudinal tear through the mucosa and submucosa of the esophagus or cardiac region of the stomach. The tear causes pain that may radiate into the chest.
- Bleeding results from extension of the tear into the submucosal arterial or venous plexus.
- It is usually associated with sudden increases in intra-abdominal pressure, especially from forceful vomiting.
- It also may be seen after other events that result in large increases in intra-abdominal pressure, such as straining, coughing, and seizures. It also has been noted after colonoscopy preps containing PEG (polyethylene glycol).
- Most will stop spontaneously and heal within 24–48 hours.

Presentation

Typical/"Classic"

- Acute onset of bright red hematemesis, typically following several episodes of forceful vomiting.
- May be associated with chest pain, epigastric pain, and/or back pain.
- Patient often has a history of recent, heavy alcohol use (40–80 %) or a known history of a hiatal hernia.
- Most often, patients are hemodynamically stable. A minority of cases present with bleeding significant enough to cause hemodynamic instability.

Atypical

- May be found incidentally on endoscopy performed for other reasons.

Primary Differential Considerations

- Upon initial presentation of bright red hematemesis, more serious diagnoses should be considered before attributing the findings to a Mallory-Weiss tear, such as:
  - Esophageal rupture
  - Gastric or peptic ulcer bleeding
  - Consideration should also be given to posterior epistaxis.

History and Physical Exam

Findings That Confirm Diagnosis

- There are no pathognomonic findings on history and physical exam that confirm the diagnosis.
- The diagnosis can be confirmed by upper endoscopy.

Factors That Suggest Diagnosis

- The acute onset of bright red hematemesis after prolonged, forceful vomiting associated with hemodynamic stability will strongly suggest the diagnosis.

Factors That Exclude Diagnosis

- The finding on endoscopy of another cause for UGI bleeding.

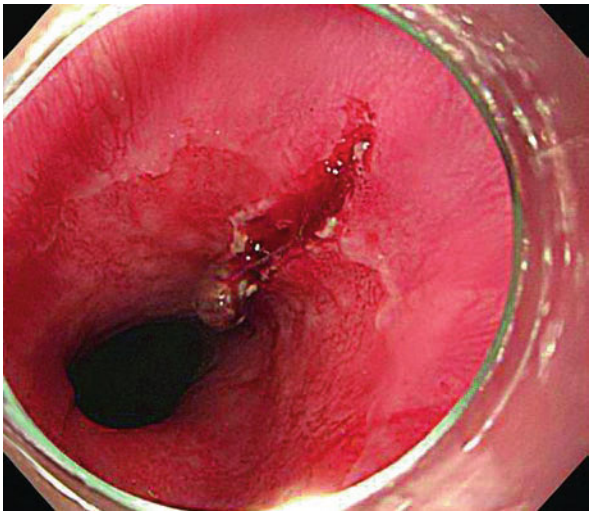
Ancillary Studies

Laboratory

- There are no laboratory tests that are specific to the diagnosis.
- Blood loss is often minimal, so the hemoglobin may be mildly reduced.

Imaging

- No specific imaging study helps in making the diagnosis, but imaging may help exclude other causes.
- Upper endoscopy is the study of choice to confirm the diagnosis and also for therapeutic intervention if indicated.



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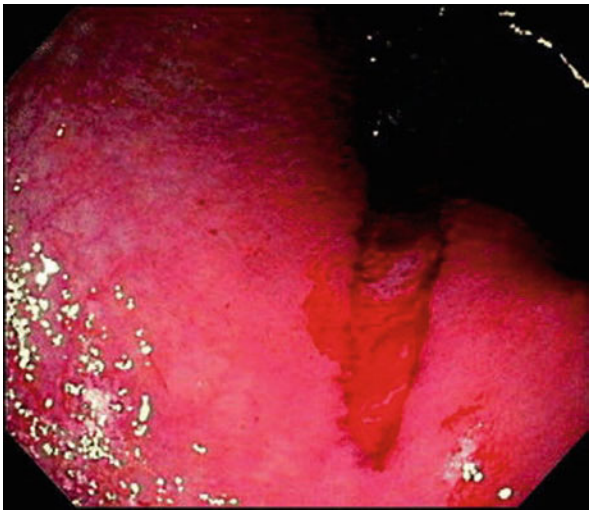

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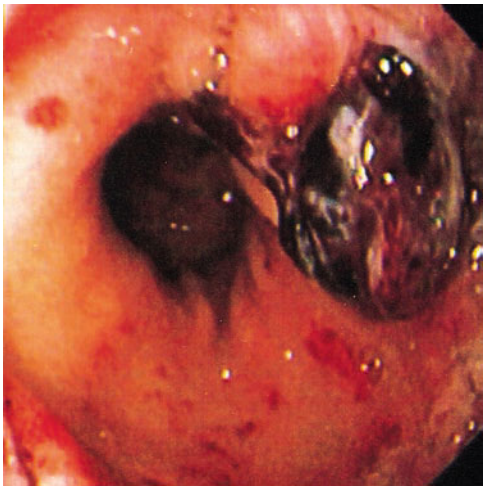

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Special Populations

Age

- Slightly more common in older individuals.
- Uncommon in children, except perhaps in patients with cyclic vomiting disorders.

Co-morbidities

- Up to 80 % of cases are associated with alcoholism.
- Also associated with hiatal hernia.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is important to initially consider the more serious causes of UGI bleeding.

Mimics

- Mallory-Weiss tears can mimic other causes of UGI bleeding, such as peptic ulcers and esophageal variceal bleeding.

Time-Dependent Interventions

- Any patient with hemodynamic instability should be resuscitated, as would any patient in shock.
- Most patients are stable, and there are no time-dependent interventions.

Overall Principles of Treatment

- Most Mallory-Weiss tears stop spontaneously and do not cause physiologically significant bleeding.
- Ninety percent heal spontaneously within 24–48 hours.
- It is most important to distinguish Mallory-Weiss tears from more severe causes of UGI bleeding.
- Treatment is usually supportive, and most patients will be started on acid suppressive therapy.
- Less than 10 % of patients will have significant bleeding. These patients are given treatment similar to that of patients with other causes of UGI bleeding, with resuscitation and stabilization, and transfusions as needed.
- Endoscopic-guided therapies are usually the treatment of choice in patients with more significant bleeding. Endoscopic therapies include thermal coagulation, local injection of epinephrine or vasopressin, or balloon tamponade. In very rare cases, interventional radiologic embolization may be indicated, and even more rarely, surgical management may be indicated.
- Most patients should be admitted or observed for at least 24 hours to document stability and to allow time for endoscopy to confirm the diagnosis.

Disease Course

- The course is usually mild and self-limited.
- Ninety percent will heal spontaneously within 24–48 hours.
- Up to 7 % may re-bleed. Risk factors for re-bleeding include portal hypertension and coagulopathy.

Related Evidence

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
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Chapter 45
Mediastinal Masses

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Mediastinal masses

- Mediastinal tumors

Incidence/Epidemiology

- Mediastinal masses often are incidental findings of chest imaging performed for other reasons.

Differential Diagnosis

- Many neoplasms may present as mediastinal masses.
- They may be either benign or malignant lesions.
- The differential diagnosis is guided by location (anterior, middle, posterior) within the mediastinum.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_45

Pathophysiology and Etiology

- The anterior mediastinum is the anatomic space that extends from the posterior aspect of the sternum to the anterior aspect of the great vessels and pericardium. Contained within the anterior mediastinum are the thymus, lymph nodes, and internal mammary arteries and veins. It is the most common location for mediastinal masses in adults. The most common masses found within the anterior mediastinum (in decreasing order of prevalence) are thymomas, teratomas (germ-cell tumors), lymphoma, and thyroid masses that extend into the anterior mediastinum.
- The middle mediastinum extends from the anterior pericardium to the posterior pericardium. It contains the heart, great vessels, airway, lymph nodes, and phrenic nerve. The most common cause of a mass within the middle mediastinum is lymphadenopathy from lymphoma, sarcoidosis or other granulomatous diseases, infectious processes, and metastatic lung cancer.
- The posterior mediastinum extends from the posterior aspect of the pericardium and trachea to the spine. It contains the descending thoracic aorta, esophagus, thoracic duct, azygous veins, posterior lymph nodes, spinal ganglia, and sympathetic chain. Neurogenic tumors are the most common posterior mediastinal tumors, especially in children.

Presentation

Typical/"Classic"

- Masses within the mediastinum are often asymptomatic.
- They commonly are found while undergoing diagnostic studies for other reasons.
- Symptoms, if present, usually result from direct compression from tumors or direct infiltration into surrounding structures.
- Compression, obstruction, or infiltration of airway structures may lead to cough, stridor, hemoptysis, shortness of breath, or pain. Hoarseness may result from phrenic nerve compression. Dysphagia may result from compression (either intrinsic or extrinsic) of the esophagus.
- Superior vena cava syndrome is a symptom complex due to compression or infiltration of the superior vena cava by a pathologic process in a contiguous structure. The most common causes are malignancies (either primary or metastatic) within the mediastinum. Dyspnea is the most common symptom, but facial swelling and "fullness" and arm swelling usually are present. The most characteristic exam finding is distension of the veins in the arm and neck.
- Malignant masses are more likely to be symptomatic.
- Many tumors, especially the lymphoproliferative tumors, may cause constitutional symptoms such as fevers, night sweats, and weight loss.

Atypical

- Mediastinal masses are often asymptomatic. More dramatic presentations, such as acute dyspnea, pneumonia with hemoptysis, or severe pain, are less common.

Primary Differential Considerations

- When evaluating a patient suspected of having a mediastinal mass, one also should consider these differential diagnoses:
  - Cysts
  - Enlarged thyroid
  - Aneurysm (aortic arch or proximal great vessels)
  - Loculated pleural effusion
  - Pneumonia

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical exam findings that can confirm the diagnosis.
- The diagnosis usually is confirmed by imaging studies, most commonly CT scan of the chest. Biopsies may also be needed to confirm specific pathology.

Factors That Suggest Diagnosis

- These are often asymptomatic and found incidentally when performing diagnostic imaging studies for other reasons.
- Symptoms are nonspecific, but any of the symptoms reviewed in the classic presentation section above should suggest the diagnosis. Often, persistence of nonspecific symptoms results in the diagnostic study that leads to the diagnosis.

Factors That Exclude Diagnosis

- If a mediastinal mass is suspected, imaging (CT or magnetic resonance [MR]) with or without biopsy is required to exclude it or establish an alternative diagnosis.

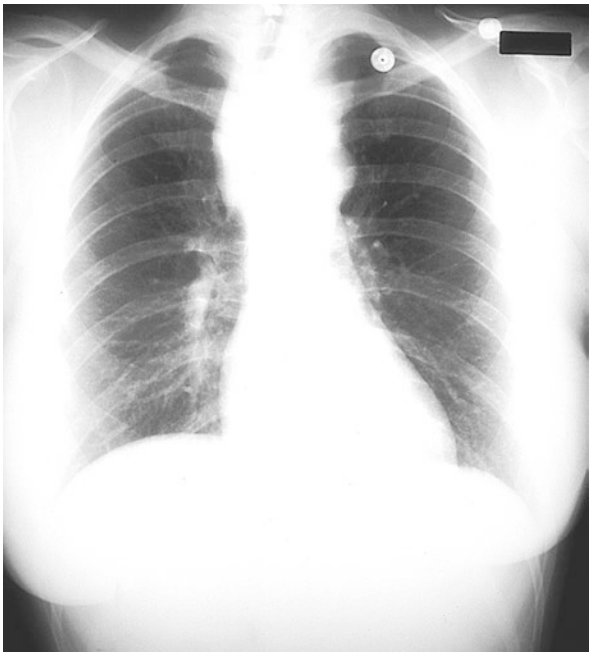
Ancillary Studies

Laboratory

- Laboratory studies are often nonspecific.
- Lymphoproliferative tumors may be associated with anemia and other hematopoietic cell line abnormalities.
- Some specific tumors will have biologic tumor marker abnormalities.

Imaging

- Most mediastinal masses are found incidentally while performing diagnostic imaging of the chest for other reasons.
- They most often are discovered on either plain chest x-ray or CT scan of the chest.
- The diagnostic study of choice is usually a contrast-enhanced CT scan of the chest.



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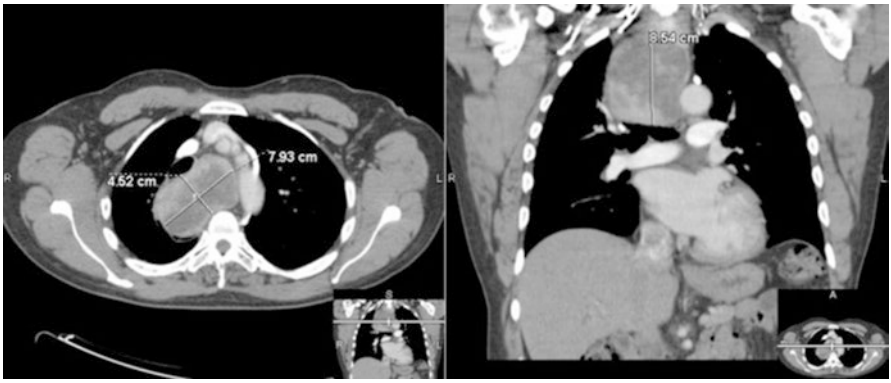

CT of the chest revealing a posterior mediastinal mass that extends all the way down to the aortic arch with tracheal compression and deviation. [From article: Novel thoracoscopic approach to posterior mediastinal goiters: report of two cases. Journal of Cardiothoracic Surgery. 2008;3(1):55. https://doi.org/10.1186/1749-8090-3-55, at http://link.springer.com/article/10.1186%2F1749-8090-3-55/fulltext.html; by Faisal Al-Mufarrej, Marc Margolis, Barbara Tempesta, Eric Strother, Farid Gharagozloo, © Al-Mufarrej et al; licensee BioMed Central Ltd. 2008; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Special Populations

Age

- The etiologies of mediastinal masses differ in children and adults as per the etiology section above.
- Most mediastinal masses in children are discovered on routine chest radiographs.
- Warning signs in pediatric mediastinal masses are similar to those seen in adults, such as weight loss, cough, shortness of breath, or localized wheezing. Inexperienced readers are often concerned about the normal mediastinal silhouette of the thymus in young patients.

Co-morbidities

- Expected co-morbidities depend on the cell type of the mass.
- The clearest associations are between thymoma and myasthenia gravis and between chronic lung disease and pulmonary tumors.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Advanced imaging (CT/MR) will guide the diagnostic evaluation.

Mimics

- Thyroid enlargement and pulmonary infections are the diagnoses most likely to initially be confused with a mediastinal mass.

Time-Dependent Interventions

- Patients with respiratory or cardiovascular insufficiency (uncommon at presentation) must be stabilized.

Overall Principles of Treatment

- Treatment depends on the type of neoplasm and whether any symptomatic obstruction or compression exists.
- As with most neoplasms, a tissue diagnosis must be confirmed to guide appropriate treatment. This commonly can be achieved by percutaneous biopsy guided by imaging of the appropriate anatomic area, such as CT scan, endoscopy (both endobronchial and esophageal), and echocardiography. In rare cases, video-assisted mediastinoscopy or thoracoscopy will need to be performed.

Disease Course

- The disease course depends on the specific diagnosis.

Related Evidence

Papers of particular interest have been highlighted as:
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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: (“Mediastinal Neoplasms”[Mesh] OR mediastinal mass*)

Chapter 46
Mediastinitis

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Mediastinitis

Incidence/Epidemiology

- Acute necrotizing mediastinitis is a life-threatening infection of the mediastinum.
- Historically, it was an uncommon but deadly complication of retropharyngeal space infections that tracked downward from the prevertebral fascia into the posterior mediastinum. Currently, acute mediastinitis occurs most often after cardiovascular or thoracic surgery.
- It also may result from esophageal perforation/rupture.
- The incidence postoperatively ranges from 0.5–5 %, but most large, experienced centers have rates lower than 2 %.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_46

- The incidence is higher for heart transplant patients and those with cardiac assist devices in place.
- The mortality approaches 25 %, even with appropriate treatment.

Differential Diagnosis

- The differential diagnosis is broad and includes any cause of sepsis syndrome, especially during the postoperative period.

Pathophysiology and Etiology

- The pathophysiology of postoperative mediastinitis is complex, but the final common pathway appears to be intraoperative wound contamination. It may occur even in the presence of meticulous surgical technique and sterile preparation. It seems to be related more to host factors than surgical technique.
- Recognized risk factors for postoperative mediastinitis include:
  - Diabetes or perioperative hyperglycemia
  - Obesity
  - Peripheral vascular disease
  - Tobacco use
  - Prior cardiac surgery
  - Dissection of the internal mammary artery
  - Procedure longer than 5 hours
  - The need to return to the operating room within 4 days
  - Prolonged postoperative ICU stay
- A single organism causes most cases.
- Virtually any organism can cause mediastinitis, but the most commonly reported are:
  - Methacillin-sensitive *Staphylococcus aureus* (MSSA), 45 %
  - Methacillin-resistant *S. aureus* (MRSA), 16 %
  - Gram-negative rods, 17 %
  - Coagulase-negative staphylococci, 13 %
  - Streptococci, 5 %
- Mediastinitis also may result from esophageal rupture, with direct spread of esophageal contents into the mediastinum.
- Other (uncommon) causes include:
  - complication of retropharyngeal space infection
  - rupture of a mediastinal abscess
  - direct extension of empyema into the mediastinum
- Bacteremia is present in more than 50 % of cases.

Presentation

Typical/"Classic"

- Classically, patients with postoperative mediastinitis will have fever, tachycardia, chest pain, sternal instability from a sternal wound infection, and/or purulent wound drainage from the sternal area. Patients with nonoperatively related mediastinitis also often present with a sepsis-like syndrome or frank sepsis.

Atypical

- Patients may present with postoperative fever alone.
- Patients may be found to have asymptomatic postoperative bacteremia.
- Patients may show signs only of superficial wound infection.
- The infection may take a more indolent course, with vague symptoms.

Primary Differential Considerations

- Early in the evaluation of patients with symptoms of mediastinitis, consider the following important differential diagnoses:
  - Acute coronary syndrome
  - Aortic dissection
  - Pulmonary embolism
  - Acute pericarditis
  - Pneumothorax
  - Deep neck infection
  - Pneumonia
  - Esophageal rupture

History and Physical Exam

Findings That Confirm Diagnosis

- Intraoperative findings of purulent discharge with necrotizing infection can confirm the diagnosis.
- Patients who present within two weeks of cardiovascular or thoracic surgery with fever, tachycardia, chest pain, sternal wound instability, and sternal wound infection may be considered to have mediastinitis, and treatment should be initiated immediately.

Factors That Suggest Diagnosis

- Patients presenting postoperatively with sepsis or a sepsis-like syndrome with no other obvious source, especially if there is bacteremia.

Factors That Exclude Diagnosis

- A normal, uncomplicated postoperative course excludes the diagnosis.

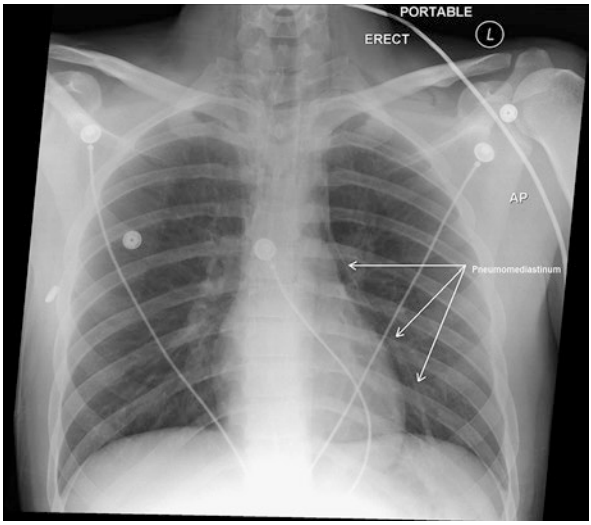
Ancillary Studies

Laboratory

- Patients often manifest the laboratory abnormalities associated with sepsis or an acute infectious process, such as leukocytosis with bandemia or leftward shift, acidosis, and an elevated lactate level.
- Bacteremia is present in more than 50 % of cases.

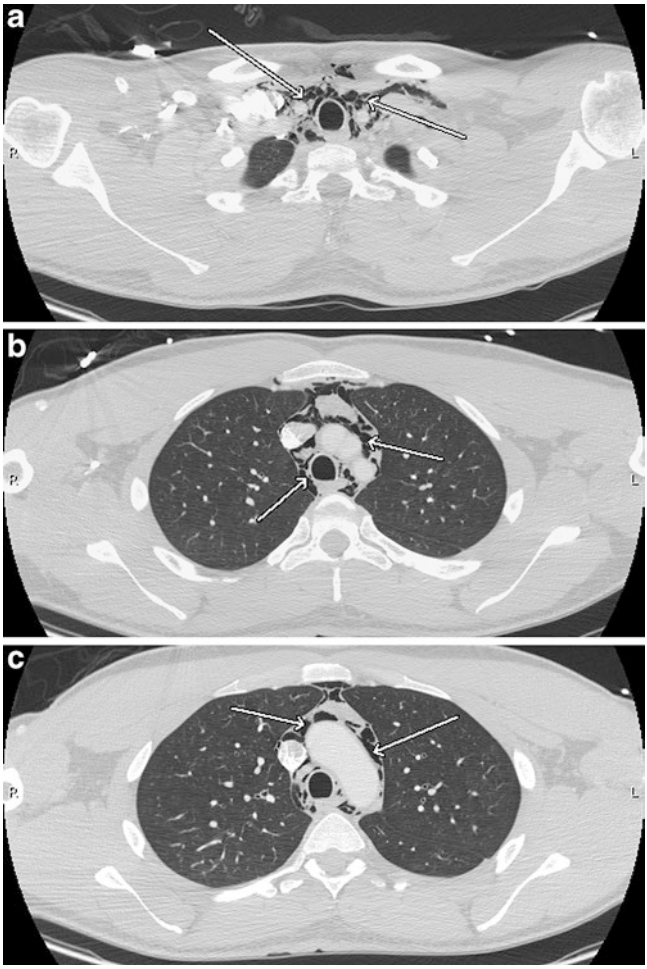
Imaging

- Plain chest radiography is sometimes helpful in suggesting alternative causes for the fever, such as pneumonia or atelectasis. The x-ray also may reveal findings that increase suspicion for mediastinitis in the correct clinical setting, such as pleural or pericardial effusion, empyema, and pneumomediastinum, all of which may result from mediastinitis.



Chest X-ray showing pneumomediastinum. [From article: Pneumomediastinum from nasal insufflation of cocaine. International Journal of Emergency Medicine. 2010 Dec;3(4):435–7. https://doi.org/10.1007/s12245-010-0205-9, at http://link.springer.com/article/10.1007%2Fs12245-010-0205-9; by Brian T. Kloss, Claire E. Broton, Elliot Rodriguez, © Springer-Verlag London Ltd 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

- CT of the chest with intravenous contrast is the study of choice if the diagnosis is in question. CT is most helpful in the following situations:
  - In patients with systemic signs and symptoms (fever, tachycardia, hypotension, chest pain), with or without bacteremia, when there are no signs of a sternal wound infection or instability
  - When there is clinical evidence of a sternal wound infection but no systemic signs or symptoms
  - In the evaluation of asymptomatic, postoperative bacteremia



Contrast-enhanced CT with arrows showing pneumomediastinum [From article: Pneumomediastinum from nasal insufflation of cocaine. International Journal of Emergency Medicine. 2010 Dec;3(4):435–7. https://doi.org/10.1007/s12245-010-0205-9, at http://link.springer.com/article/10.1007%2Fs12245-010-0205-9; by Brian T. Kloss, Claire E. Broton, Elliot Rodriguez, © Springer-Verlag London Ltd 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

Contrast-enhanced CT scan of descending necrotizing mediastinitis at the lower neck shows brachiocephalic vein thrombosis (arrow), increased density of the middle mediastinal space (white asterisk), and bilateral pleural effusion. In addition, swelling of the left soft tissues of the thorax is evident (black asterisk) [Scaglione M, Pinto A, Romano S, Giovine S, Sparano A, Romano L. Determining optimum management of descending necrotizing mediastinitis with CT; experience with 32 cases. Emerg Radiol. 2005 Jul;11(5):275–80.] *Caption adapted from original*

Special Populations

Age

- Mediastinitis may occur at any age but is most common in older patients after cardiac or thoracic surgery.
- Mediastinitis also may occur in the pediatric population as a complication of cardiovascular or thoracic surgery, or as a complication of retropharyngeal abscess.
- Soft tissue neck infections in children (parapharyngeal abscess, peritonsillar abscess, retropharyngeal abscess, dental abscess, etc.) also contribute to the development of mediastinitis.

Co-morbidities

- Review of the etiologies of acute mediastinitis will indicate co-morbidities of interest. Diabetes, obesity, tobacco use, peripheral arterial disease, and prior cardiac/thoracic surgery are the most concerning.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. Patients who present with sepsis or sepsis-like syndrome postoperatively or those with evidence of a sternal wound infection need urgent resuscitation and institution of broad-spectrum antibiotic coverage while a more definitive diagnosis is pursued.

Mimics

- Many other infectious processes can mimic mediastinitis. Pneumonia and empyema may occur in isolation but also may coexist or be a complication of mediastinitis.
- Superficial sternal wound infection may mimic mediastinitis.

Time-Dependent Interventions

- Consideration of the diagnosis and adequate resuscitation and antibiotic coverage are critical.
- Mortality increases as the infection and necrosis progress.

Overall Principles of Treatment

- Adequate resuscitation and antibiotic coverage are critical.
- Definitive treatment usually involves surgical debridement and continued antibiotics.

Disease Course

- The mortality of postoperative mediastinitis may approach 50 %, even with adequate treatment.
- The occurrence of postoperative mediastinitis is associated with an increased mortality rate that continues for 10 years postoperatively.

Related Evidence

Papers of particular interest have been highlighted as:
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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Mediastinitis"[Mesh] OR "Mediastinitis"

Chapter 47
Mitral Valve Prolapse

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Mitral Valve Prolapse (MVP); systolic click-murmur syndrome; Barlow's syndrome

Incidence/Epidemiology

- MVP is the most common heart valve abnormality, found in about 3–5% of the US population.
- The clinical syndrome associated with MVP is quite variable, but it is usually benign.

Differential Diagnosis

- The primary differential considerations for chest pain associated with MVP are mitral regurgitation and anxiety/panic attacks.
- Older patients with chest pain and palpitations should be evaluated for possible ACS.

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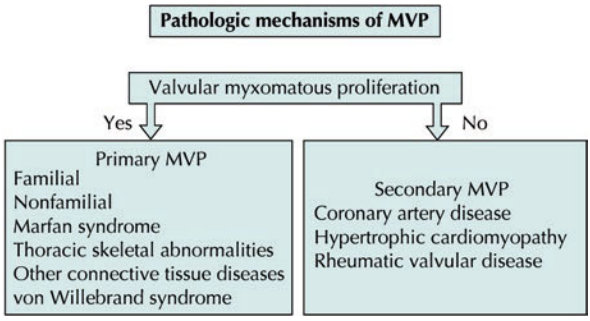
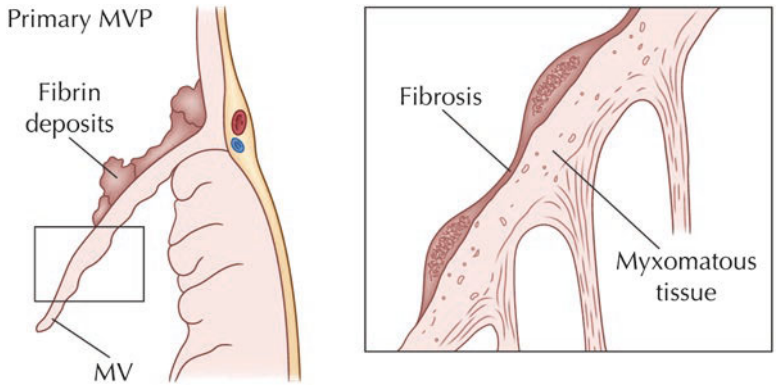
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_47

Pathophysiology and Etiology

- Mitral valve prolapse is a ballooning of a competent (or minimally incompetent) mitral valve into the left atrium during left ventricular systole. This anatomic defect may result from:
  - Redundant mitral leaflet tissue (myxomatous degeneration)
  - Elongated or redundant chordae tendineae
  - Inherited connective tissue disorders such as Marfan's and Ehler-Danlos syndromes



Causes of mitral valve prolapse. A variety of pathologic mechanisms involving any of the functional components of the mitral valve apparatus can result in MVP. Prominent among these is valvular collagen disruption and myxomatous infiltration, termed primary MVP. In most cases, primary MVP is an inherited disorder; it can also occur in a nonfamilial, isolated form. Less commonly, primary MVP is associated with connective tissue diseases. The most important of these is Marfan syndrome, where it can be detected echocardiographically in greater than 90% of affected patients. Thoracic skeletal abnormalities (pectus excavatum, pectus carinatum, straight back syndrome, scoliosis) are also associated with primary MVP. Primary MVP may be a manifestation of a generalized disorder of connective tissue, with a variable range of phenotypic expression within and outside of the cardiovascular system. For example, it can also be associated with myxomatous changes and prolapse of the tricuspid (40%), pulmonic (10%), and aortic valves (2%). The histologic changes are similar to those seen in the mitral valve. Other associated conditions include ostium secundum atrial septal defect and Wolff-Parkinson-White syndrome. Secondary MVP occurs in the absence of myxomatous valvular proliferation and can occur in patients with hypertrophic cardiomyopathy and occasionally as a result of coronary artery disease. Prior rheumatic fever may result in secondary MVP, especially of the anterior leaflet. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*



Primary mitral valve prolapse. Histopathology of primary mitral valve prolapse (MVP). A, The normal mitral valve (MV) is composed of three layers: 1) the atrialis, a thin layer of collagen and elastic tissue along the atrial aspect of the leaflet; 2) the fibrosa (ventricularis), a denser layer of collagen along the ventricular aspect; and 3) the spongiosa, the fine myxomatous connective tissue layer between the two. B, In primary MVP, dissolution of collagen bundles occurs primarily with secondary myxomatous proliferation of the spongiosa and interruption of the fibrosa and fibrosis of the atrial and ventricular surfaces of the valve. These secondary effects appear to occur as a response to repeated stress on the valve apparatus. Focal endothelial disruption occurs commonly and may provide a site for thrombus formation. Fibrin deposits often form at the MV–left atrial angle. Similar histologic changes can occur in the chordae tendineae and result in chordal thinning and rupture. Myxomatous degeneration of the annulus can occur as well, especially in patients with connective tissue disorders, resulting in annular dilation and calcification and worsening of mitral regurgitation. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

- The ballooning often causes a click that is audible on cardiac auscultation. If there is any incompetence to the overlapping leaflets, a murmur will also result.
- The chest pain associated with MVP, which is typically described as sharp or stabbing, is *not* anginal in origin. MVP is not associated with coronary artery disease nor does it have any other direct relation to myocardial ischemia.
- Chest pain in MVP is often associated with anxiety or panic disorder.
- Besides chest pain and anxiety, MVP is also associated with a variety of symptoms that can prompt acute presentation, including:
    - Autonomic dysfunction
    - Palpitations from both supraventricular and ventricular premature beats
    - Lightheadedness
    - Syncope

- Very rarely, the redundant valve leaflets in MVP can be a nidus for vegetations of endocarditis. This is (relatively) much more common in the frankly regurgitant mitral valve.

Presentation

Typical/"Classic"

- Many patients with MVP are asymptomatic. Chest pain due to MVP is most often described as sharp and stabbing, associated with anxiety, and is occasionally accompanied by palpitations.

Palpitations
Chest pain
Dyspnea
Fatigue
Syncope and lightheadedness
Focal neurologic events
Anxiety

Symptoms in mitral valve prolapse. The most common symptom is palpitations, which often correlates poorly with arrhythmias on ambulatory electrocardiographic monitoring. Chest pain is usually atypical and does not resemble angina pectoris. The etiology is unknown. It has been suggested that the prolapsing mitral valve places undue tension on the papillary muscles and results in subendocardial ischemia. Dyspnea and fatigue may occur without mitral regurgitation or objective impairment of exercise tolerance. Syncope and presyncope may occur in association with postural hypotension and arrhythmias but often are present without any clinical correlates. Transient neurologic events occur with greater frequency in patients with MVP, although the overall incidence is quite low. These may be the result of platelet and fibrin emboli occurring at sites of endothelial disruption and at the mitral valve–left atrial junction. The true association of MVP and neuropsychiatric syndromes remains controversial. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

- Patients may or may not report a previously detected click or murmur.

Atypical

- Typical anginal features (pressure-like pain, midsternum perhaps radiating to jaw or left upper extremity, related to exertion) would be very unusual in describing pain caused by MVP.

Primary Differential Considerations

- When evaluating a patient suspected of having MVP, one should also consider the following differential diagnoses:
  - Mitral regurgitation
  - Anxiety

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis of MVP is typically made upon cardiac auscultation. There is usually a mid-systolic ejection click thought to be caused either by the tensing of the elongated chordae or by the snapping of the redundant valve leaflet tissue at the peak of systole.

https://www.youtube.com/watch?v=PsmGx2XMxF8
Audio of mid-systolic click

- The murmur, which is less consistently identified than the click, is usually high-pitched, crescendo-decrescendo, and heard best at the apex.

https://www.youtube.com/watch?v=MMJBSd5Z_Uc&list=PL85424CD4340A8D55
Audio of mitral regurgitation murmur

- The click and murmur occur earlier and louder with standing and with Valsalva, and occur later and more quietly (and indeed may disappear) with squatting and isometric exercise.

https://www.youtube.com/watch?v=AHBzu5zhFuA
Video on mitral valve prolapse and mitral regurgitation. Offers animation of blood flow and muscle movement.

Factors That Suggest Diagnosis

- The click and murmur are suggestive of MVP even without chest pain.
- Other body habitus characteristics of connective tissue disease may be helpful.

Thoracic skeletal abnormalities
Arachnodactyly
High-arched palate
Low body weight (< 90% ideal)
Low blood pressure (< 120 mm Hg systolic)
Orthostatic hypotension and tachycardia

Physical findings in mitral valve prolapse. General physical findings in MVP. Thoracic skeletal abnormalities can be seen in association with MVP. Arachnodactyly may be seen without other evidence for Marfan syndrome and these cases may represent formes frustes of this disorder. Patients with MVP tend to have low body weight, low systolic blood pressure, and postural hypotension and tachycardia. These signs may be related to a combination of autonomic dysfunction and reduced intravascular volume in these patients. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

Factors That Exclude Diagnosis

- No history or physical findings can definitively exclude MVP; an echocardiogram is required.

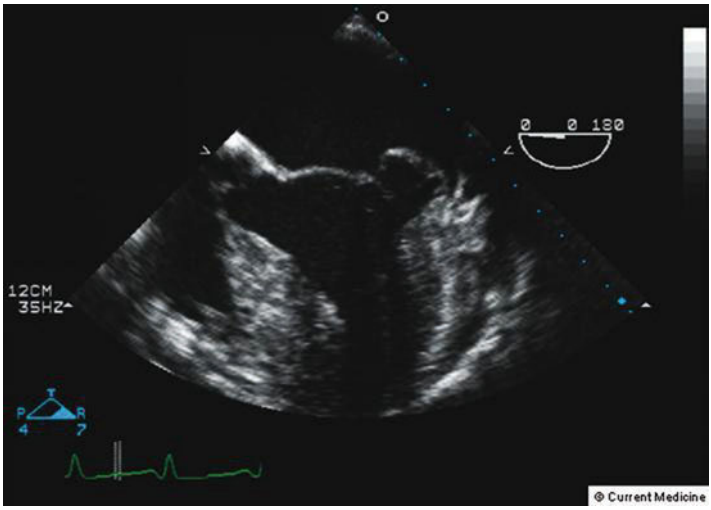
Ancillary Studies

Laboratory

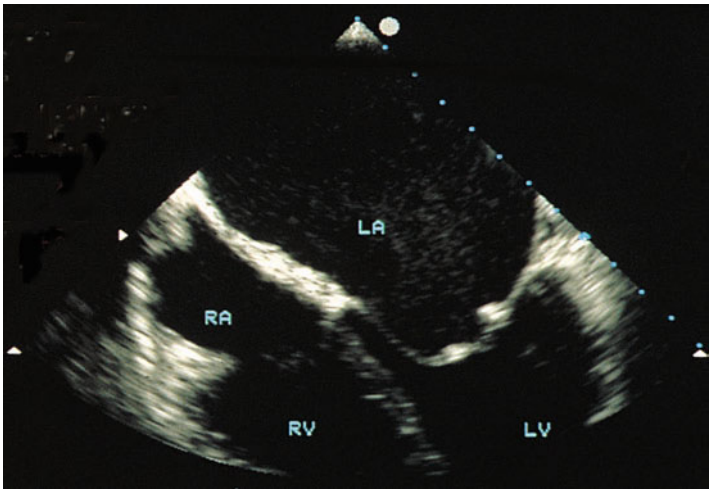
- There are no diagnostic laboratory studies for MVP.

Imaging

- Echocardiography can confirm or refute the diagnosis of MVP and can differentiate it from mitral regurgitation.



Mitral valve prolapse: transesophageal echocardiogram. Transesophageal echocardiogram showing prolapse of the mitral valve. [Greer DM, Kamalian S, Silverman SB, Mitha AP, Kinnecom CE, Sanborn DY, Greenberg SM, Ogilvy CS, Lev MH, Kistler JP, Furie KL, Camargo ECS de. Cerebrovascular Disease. In: Rosenberg RN, editor. Atlas of Clinical Neurology [Internet]. Current Medicine Group; 2009 [cited 2015 May 20]. p. 133–214. Available from: http://link.springer.com/chapter/10.1007/978-1-57340-359-7_5] *Caption adapted from original*

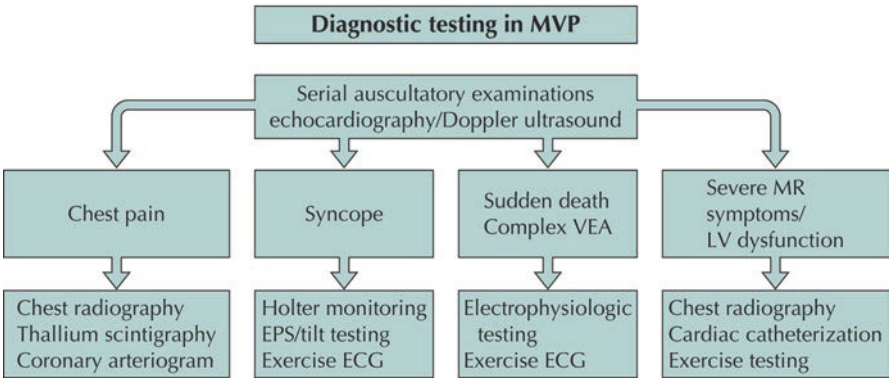


Mitral valve prolapse. Two-dimensional image transesophageal echocardiographic image of mitral valve with severe prolapse of the posterior leaflet due to chordal rupture. B, Doppler color flow image of the same valve with a large regurgitant jet (arrow) directed away from the prolapsed leaflet. LA—left atrium; LV—left ventricle; RA—right atrium; RV—right ventricle. [Clements F, de Bruijn N,

Bennett-Guerrero E, Newman M, Reves JG. Chapter 1. In: Miller RD, Muravchick S, editors. Atlas of Anesthesia: Subspecialty Care, Volume 5, 1e. Philadelphia: Current Medicine; 1998. 236 p. ISBN: 0-443-07905-6] *Caption from original*

https://www.youtube.com/watch?v=h6aJSuUTVb0
Video depicting echocardiography of mitral valve prolapse.

- It has been thought in the past that echocardiographic studies "overdiagnosed" MVP. This concern can be alleviated at least in part by relying on the parasternal long-axis view.
- Other imaging or tests are sometimes helpful.



Diagnostic testing in mitral valve prolapse (MVP). The diagnosis of MVP is based on the presence of typical auscultatory findings detected during carefully performed serial examinations. Echocardiography (M-mode, two-dimensional, and Doppler) is the single most useful test in the definition of MVP. It is used to assess natural history and prognosis, the presence of associated conditions (e.g., atrial septal defect, hypertrophic cardiomyopathy), the need for antibiotic prophylaxis, and the degree of mitral regurgitation (MR). Echocardiography should not supplant the physical examination in the diagnosis of MVP; up to 10% of patients diagnosed with MVP by typical auscultatory findings will have a non-diagnostic two-dimensional echocardiogram. Electrocardiography (ECG) is routinely performed to assess for ventricular preexcitation and resting ST- and T-wave abnormalities. The tests listed in the lowest level of the flow diagram are not required for the diagnosis of MVP, but they are useful in assessing certain symptoms and complications that can occur in this disorder. EPS—electrophysiology; LV—left ventricular; MR—mitral regurgitation; VEA—ventricular ectopic arrhythmia. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption from original*

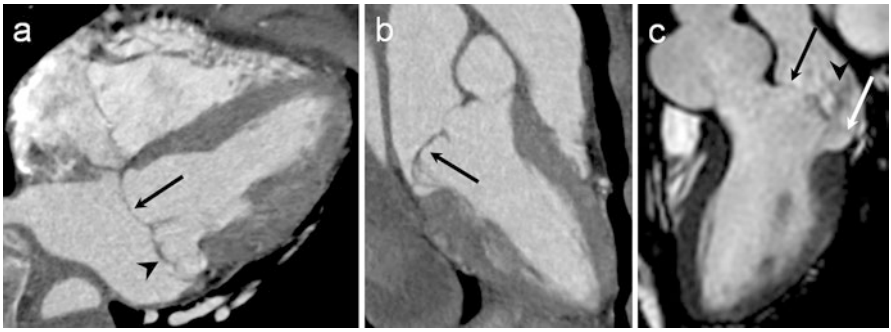
Special Populations

Age and Gender

- MVP is more common in females than males.
- It is most commonly diagnosed in the second or third decade of life.
- MVP in children most often presents with palpitations.
- Children will often describe a "butterfly" in their chest.

Co-morbidities

- Connective tissue diseases such as Marfan's are often associated with MVP.



A 33-year-old woman with Marfan syndrome and mitral valve prolapse. a, b Four- (a) and two-chamber (b) CT images in systole show entire anterior mitral leaflet prolapse (arrows) and P2 prolapse in the posterior mitral leaflet (arrowheads). c Three-chamber balanced-steady state precession cine cardiac MRI in systole demonstrates bileaflet mitral prolapse (arrows) and a dephasing jet from mitral regurgitation (arrowhead) [Ko SM, Song MG, Hwang HK. Evaluation of the aortic and mitral valves with cardiac computed tomography and cardiac magnetic resonance imaging. Int J Cardiovasc Imaging. 2012 Nov 9;28(2):109–27.] *Caption from original*

Pitfalls in Diagnosis

Critical Steps Not to Miss

- There are no critical steps in diagnosing MVP. The clinical situation is more important if mitral regurgitation has developed. Either way, an echocardiogram is diagnostic.

Mimics

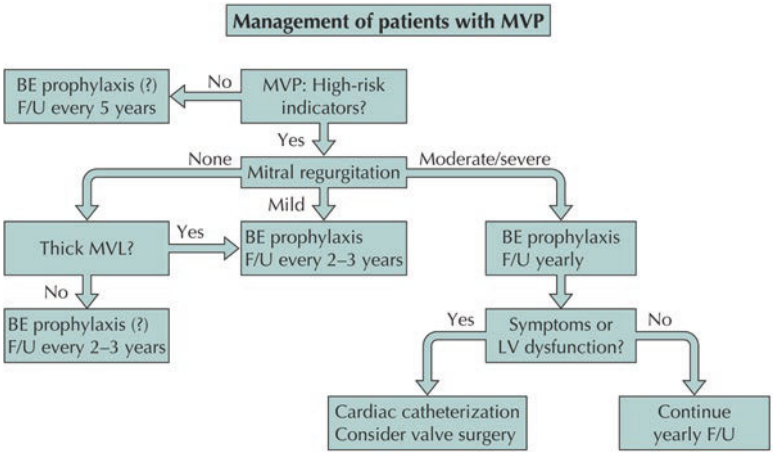
- Acute anxiety or panic disorder can mimic MVP, especially if there is a coincident heart murmur or history thereof.
- It is unlikely that chest pain associated with MVP will be confused with anginal pain.

Time-Dependent Interventions

- There are no time-dependent interventions in the diagnosis and management of MVP.

Overall Principles of Treatment

- For most cases of MVP, reassurance of the benign nature of the valve abnormality is sufficient.

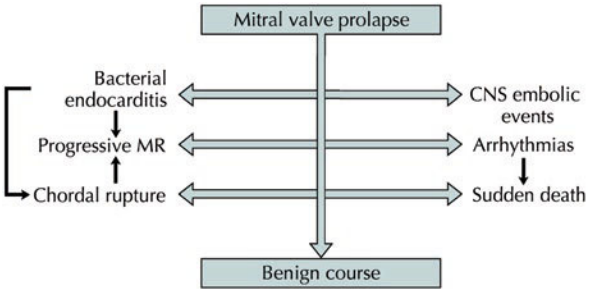


Management of mitral valve prolapse. Management of patients with mitral valve prolapse (MVP). High-risk characteristics in MVP patients are additive, that is, the more indicators present, the greater the total risk. The majority of patients with MVP are asymptomatic and have no or minimal high-risk indicators. They are treated with reassurance and can lead a normal life. Clinical and echocardiographic assessment every 5 years is reasonable to determine passage into a higher risk group. If any high-risk indicators are present, patients can be further stratified based on the presence of mitral regurgitation (MR). Some authorities advocate prophylaxis for bacterial endocarditis (BE) only if MVP is associated with MR or thickened mitral valve leaflets (MVL). However, given the variability of physical findings and the dynamic nature of MR in MVP, prophylaxis may be reasonable in all patients with MVP. Patients with MVP and severe MR should be managed in the same manner as patients with severe MR due to other causes. The decision to proceed with valve surgery is based on the presence of symptoms or impairment of left ventricular (LV) systolic function. Mitral valve reconstructive surgery can often be used in lieu of valve replacement to correct regurgitant floppy valves. Compared with valve replacement, valve repair is associated with a lower operative and late mortality, lower long-term thromboembolic risk, and lower BE risk. F/U—follow-up. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

- For patients with frequent chest pain, palpitations, or other autonomic manifestations, beta-adrenergic blockage may provide symptomatic relief.
- An echocardiogram will provide a basis for deciding whether or not patients with MVP should receive antibiotic prophylaxis prior to dental procedures or other procedures that could result in transient bacteremia.
- Patients with mitral regurgitation should be managed by a cardiologist.

Disease Course

- MVP generally runs a benign course.



Clinical course in mitral valve prolapse. Overview of the clinical course in MVP. The majority of patients with MVP follow a benign course and their age-adjusted survival is similar to persons without MVP. However, serious complications can occur in 10% to 20% of patients. These include infective endocarditis, chordal rupture, progressive mitral regurgitation (MR), life-threatening arrhythmias, neurologic and embolic events, and sudden death. The risk of infective endocarditis is five to eight times greater in patients with MVP than in the general population and MVP is the leading underlying diagnosis in patients with endocarditis. Progressive MR is often accelerated by infective endocarditis or chordal rupture. The overall incidence of ophthalmologic and central nervous system (CNS) embolic events is generally low. An increase in risk for CNS events associated with MVP is detectable in patients who do not have other cerebrovascular risk factors, especially young women. Sudden death is the least common complication of MVP and occurs mainly in patients with significant MR, reduced ventricular function, and malignant ventricular arrhythmias. [Prabhu S, O'Rourke R, Rahimtoola S. Chapter 10. In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

- Patients should be evaluated intermittently to assess for progression to mitral regurgitation.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schäfers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J. 2012 Oct;33(19):2451-96. https://doi.org/10.1093/eurheartj/ehs109. PMID: 22922415. http://www.ncbi.nlm.nih.gov/pubmed/22922415 **

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Review

Benenstein R, Saric M. Mitral valve prolapse: role of 3D echocardiography in diagnosis. Curr Opin Cardiol. 2012 Sep;27(5):465-76. https://doi.org/10.1097/HCO.0b013e328356afe9. PMID: 22874124. http://www.ncbi.nlm.nih.gov/pubmed/22874124

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Cohort Study

Guven B, Eroglu AG, Babaoglu K, Demir T, Güzeltas A, Oztunc F, Saltik L. QT dispersion and diastolic functions in differential diagnosis of primary mitral valve prolapse and rheumatic mitral valve prolapse. Pediatr Cardiol. 2008 Mar;29(2):352-8. PMID: 17917767. http://www.ncbi.nlm.nih.gov/pubmed/17917767 **

Case Study

Tagarakis GI, Karantzis I, Tsolaki F, Stylianakis GE, Daskalopoulos ME, Tsilimingas NB. Classic and non-classic forms of mitral valve prolapse. Anadolu Kardiyol Derg. 2012 Feb;12(1):2-4. https://doi.org/10.5152/akd.2012.001. PMID: 22214735. http://www.ncbi.nlm.nih.gov/pubmed/22214735 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
"Mitral Valve Prolapse"[Mesh] OR "mitral valve prolapse"

Chapter 48
Mitral Valve Regurgitation

Charles V. Pollack, Jr. and Jaime Friel Blanck

Name and Synonyms

Mitral valve regurgitation
Mitral valve incompetence
Mitral valve insufficiency

Incidence/Epidemiology

- Mitral valve disorders are the second-most common valvulopathies (aortic valve is most common).
- Mitral regurgitation (MR) may be acute or chronic. The chronic form is most often related to prior rheumatic fever, the incidence of which is decreasing in the industrialized world. The acute form is most often a complication of acute inferior wall myocardial infarction, and is rare but potentially catastrophic.
- MR is more common in females.

Differential Diagnosis

- The differential diagnosis of MR includes
  - Endocarditis
  - Aortic regurgitation/insufficiency
  - Ventricular septal defect

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Welch Medical Library, Johns Hopkins University, Baltimore, MD, USA

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_48

Pathophysiology and Etiology

- The explicit pathophysiology of MR is reduced resistance to emptying of the left ventricle (LV), with regurgitant return of LV blood to the left atrium (LA).

Primary mitral regurgitation:
Mitral valve prolapse: the most common cause of mitral regurgitation in developed countries
Rheumatic disease: more common in underdeveloped countries. Usually manifests as mitral stenosis or double mitral lesion
Annular calcification: associated with aging. Does not cause severe mitral regurgitation
Infective or marantic endocarditis (associated with connective tissue disease)
Trauma that may produce rupture of the *chordae tendinae* and acute mitral regurgitation
Congenital anomalies, principally mitral cleft
Secondary to drugs: anorexigens, carbergoline, pergolide or ergotamine
Secondary mitral regurgitation:
Dilation and dysfunction of the left ventricle that causes stretching and distortion on the mitral valve annulus leading to centrally directed mitral regurgitation
Ischaemic heart disease, usually as a result of ischaemia or necrosis of the posterior papillary muscle, which can lead to acute mitral regurgitation
Hypertrophic obstructive cardiomyopathy, caused by the movement of the mitral valve anterior leaflet due to the "Venturi effect" caused by outflow tract obstruction

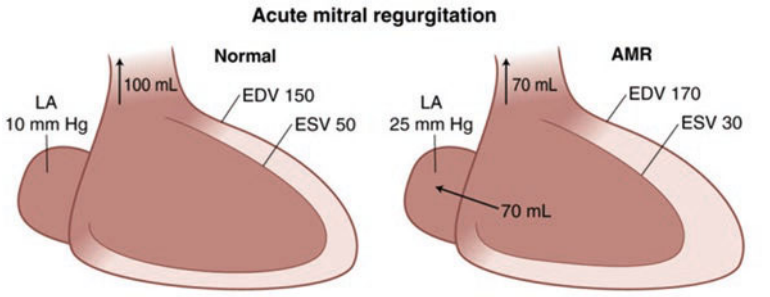
Causes of mitral regurgitation. [Suárez-Mier MP, Morentin B, Cobo M, Castedo E, García-Pavía P. Pathology of the Heart Valves. In: Lucena JS, García-Pavía P, Suarez-Mier MP, Alonso-Pulpon LA, editors. Clinico-Pathological Atlas of Cardiovascular Diseases [Internet]. Cham: Springer International Publishing; 2015 [cited 2016 Apr 4]. p. 171–200. Available from: http://link.springer.com/10.1007/978-3-319-11146-9_7] *Caption from original*

- In acute MR, this typically results from rupture of the papillary muscles that connect the chordae tendinae to the cardiac wall. Loss of papillary muscle function leads to incompetence of one or more of the valve leaflets. When the LV contracts, its contents flow both ante- and retrograde, significantly reducing forward cardiac output and disrupting LA function.

	Primary ("Organic")	Secondary ("Functional")
Acute	Papillary muscle ischemia	Acute ischemic LV dilatation
	Ruptured papillary muscle (trauma, infarction)	
	Flail mitral valve leaflet	
	Ruptured chordae tendinae	
	Endocarditis (leaflet perforation)	
Chronic	Flail mitral valve leaflet	Chronic ischemic mitral regurgitation (CIMR)
	Mitral valve prolapse	Non-ischemic LV dilatation (failure of leaflets to coapt)
	Ruptured chordae tendinae	Non-ischemic LV systolic dysfunction
	Degeneration (myxomatous, endocarditis, calcification)	Hypertrophic cardiomyopathy
	Rheumatic	Right ventricular pacing
	Congenital	Aortic insufficiency [1]

Classification of mitral regurgitation by mechanism and acuity [From article: Echocardiographic assessment of ischemic mitral regurgitation. Cardiovasc Ultrasound. 2014 Dec 1;12(1):46. https://doi.org/10.1186/1476-7120-12-46, at https://link.springer.com/article/10.1186%2F1476-7120-12-46; by David M Dudzinski, Judy Hung, © Dudzinski and Hung 2014; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 4.0 http://creativecommons.org/licenses/by/4.0] *Caption from original*

- In chronic MR, damage to the valve apparatus (as in rheumatic heart disease) leads gradually to LA and LV enlargement and the patient remains largely asymptomatic until LV systolic dysfunction develops. Fatigue, dyspnea, and diminished exercise tolerance ensue. Frank heart failure may follow over time. With LV dilatation, the risk of atrial fibrillation and its attendant risk of thromboembolic complications rises.



	Preload SL, μ	Afterload ESS, *Kdyne/cm²*	CF	EF	RF	FSV, *mL*
N	2.07	90	N	0.67	0.0	100
AMR	2.25	60	N	0.82	0.50	70

A

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Pathophysiology of acute mitral regurgitation (AMR). A, AMR. Left ventricular (LV) sarcomere length (SL) is increased, but afterload (as estimated by end-systolic stress [ESS]) is initially reduced, as the LV ejects into the low impedance left atrium (LA). Contractile function (CF) is unchanged, but ejection fraction (EF) increases. The regurgitant fraction (RF) in this example is 50%. Forward stroke volume (FSV) is reduced from 100 to 70 mL. Pressure in the unprepared and relatively noncompliant LA rises abruptly to 25 mm Hg. [O'Gara P. Chapter 9. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009.] *Caption adapted from original*

- Chronic MR can also be caused by a host of other diseases, especially connective tissue disorders such as lupus and scleroderma.
- MR is distinct from mitral valve prolapse (MVP), in which there is ballooning of the mitral valve leaflets during LV systole, but there is no valve incompetence

Presentation

Typical/"Classic"

- The presentation of MR depends on whether it is acute or chronic. Acute MR, which often occurs proximal to an inferior wall myocardial infarction (MI) or as a complication of infective endocarditis, classically presents with
  - Shortness of breath
  - Chest pain
  - Orthopnea
  - Pulmonary edema
- Chronic MR may be asymptomatic for years, prior to presenting with decreased exercise tolerance and orthopnea.

Atypical

- Patients with acute MR may present hemodynamically unstable, requiring immediate intervention including use of a balloon pump.
- The damaged valve leaflets in MR are at risk for bacterial vegetations and endocarditis.
- MR may present with thromboembolism, from thrombi that form as a result of concomitant atrial fibrillation.

Primary Differential Considerations

- Consider the following diagnoses:
  - Aortic stenosis
  - Aortic insufficiency
  - Ventricular septal defect

History and Physical Examination

- Check for a thrill at the cardiac apex.
- Check for a brisk carotid upstroke.
- On cardiac auscultation, check for
  - Wide splitting of S2
  - Presence of an S3
  - Holosystolic, high-pitch, blowing murmur best heard over the apex

https://www.med.ucla.edu/wilkes/MRmain.htm

Mitral Regurgitation. [Systolic Murmurs - Mitral Regurgitation; The Auscultation Assistant; Christopher Cable, MD, https://www.med.ucla.edu/wilkes/]
Listen for rales in the lower lung fields

http://www.easyauscultation.com/rales

Rales. [Rales Lung Sounds; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Peripheral findings of heart failure, including a hypoperfused state, may be apparent in acute MR.

Findings That Confirm Diagnosis

- The echocardiogram confirms the diagnosis. The MR murmur in the context of MR symptoms (starting with exertional dyspnea), should prompt the imaging study.

Factors That Suggest Diagnosis

- Prior to diagnostic confirmation with echo, presence of two or more of the symptoms cited above suggests MR.
- The lack of a history of rheumatic fever does not exclude the diagnosis.
- Signs of pulmonary hypertension or right heart failure in the presence of a holosystolic murmur are suggestive of MR.

Factors That Exclude Diagnosis

- MR is definitively excluded only by an echocardiogram showing competence of the mitral valve.

Ancillary Studies

Laboratory

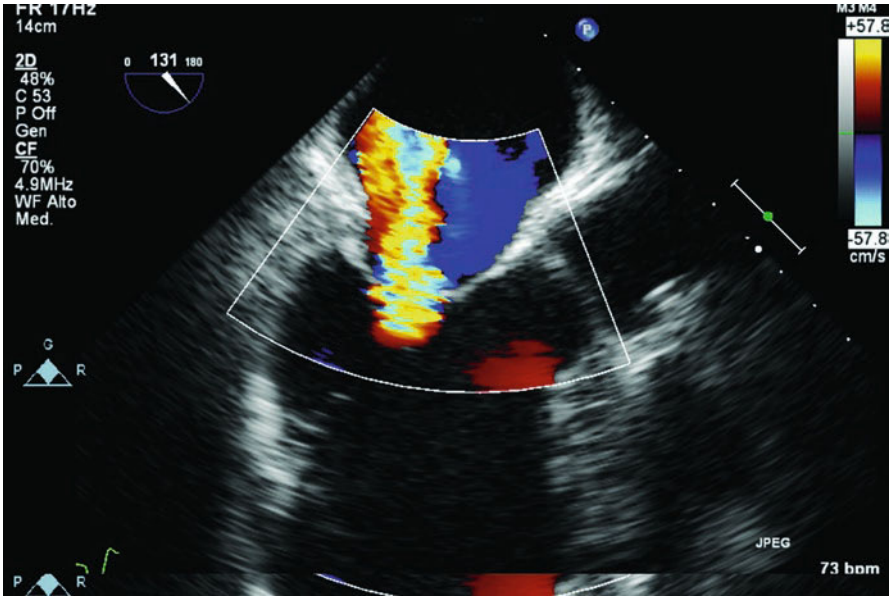
- It is helpful to send routine laboratory studies such as basic chemistries and a complete blood count to evaluate for other causes of the patient's symptoms.
- There may be value to checking a brain-type natriuretic peptide (BNP) level, especially if the patient has heart failure symptoms.

Electrocardiography

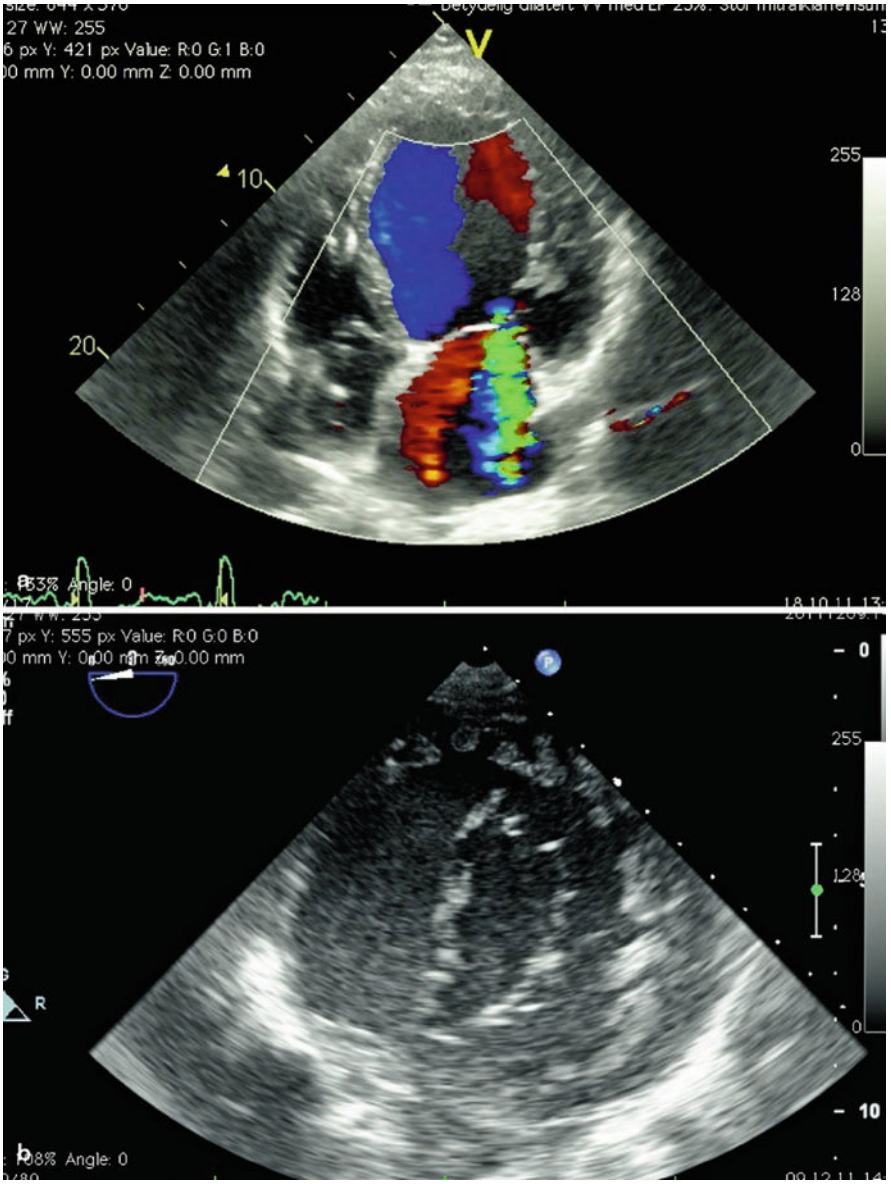
- The ECG should be obtained and interpreted promptly. Findings on electrocardiography may include the following:
  - Ischemic changes or new Q-waves in the inferior leads.
  - Left ventricular hypertrophy.
  - Left atrial enlargement as manifest by wide P-waves in II, III, and aVF.

Imaging

- The chest x-ray may be helpful in the evaluation of possible MR. Look for straightening of the left border of the cardiac silhouette or a double shadow in the right cardiac silhouette. Frank cardiomegaly and signs of pulmonary edema may be evident in acute MR or in late stages of chromic MR, but usually does not occur until fairly late in the disease progression.
- Echocardiography is the most sensitive and specific noninvasive test for MR. Transthoracic 2-D echo can usually confirm the diagnosis, and with Doppler echo and color jet imaging the degree of incompetence can be clearly delineated.



Transesophageal echocardiography (TEE) long-axis view. The picture shows severe ischemic mitral regurgitation (vena contracta 0.67 cm) [Colombo A, Godino C, Agricola E. The Degree and Type of Mitral Regurgitation Present at the Baseline Is Not Always a Good Predictor of the Procedural Technical Needs or of the Final Result. In: Feldman T, Franzen O, Low R, Rogers J, Yeo KK, editors. Atlas of Percutaneous Edge-to-Edge Mitral Valve Repair [Internet]. Springer London; 2013 [cited 2017 May 3]. p. 521–3. Available from: http://link.springer.com/chapter/10.1007/978-1-4471-4294-2_41] *Caption from original*



Transesophageal echo demonstrated very extensive mitral regurgitation located centrally between A2 and P2, dilated mitral annulus (4.4 × 4.8 cm) with malcoaptation of leaflets due to tenting of the leaflets. Coaptation depth 13 mm, coaptation length 2 mm. Four-chamber view (a) showing a very large, central mitral regurgitation reaching the roof of the left atrium. In the transgastric, short axis view (b) we measured the opening area of the mitral orifice to be more than 4 cm2. [Dahle G, Andersen KA, Brekke M, Rein KA. Functional Mitral Regurgitation with a Wide Extension of the Central Regurgitant Jet. In: Feldman T, Franzen O, Low R, Rogers

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Special Populations

Age

- Acute onset MR follows the age distribution for myocardial infarction, although infective endocarditis may cause MR at younger ages.
- Chronic MR usually becomes symptomatic later in life.

Co-morbidities

- The most important co-morbidities are underlying cardiopulmonary disease, including coronary artery disease and heart failure. Atrial fibrillation increases the risk of thromboembolic complications in MS.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- An echocardiogram should be obtained early in the evaluation of patients with signs and symptoms suggestive of MR.
- Stabilize patients who present with hemodynamic compromise and poor oxygenation.

Mimics

- The echocardiogram will resolve differential considerations.

Time-Dependent Interventions

- The most important intervention is to stabilize patients with hemodynamic instability.
- Recognition of acute MR and heart failure may require life-saving intervention, including resuscitation and placement of a balloon pump.

Overall Principles of Treatment

- Afterload reduction is key in acute resuscitation.
- Biventricular pacing and an aortic balloon pump may be required.

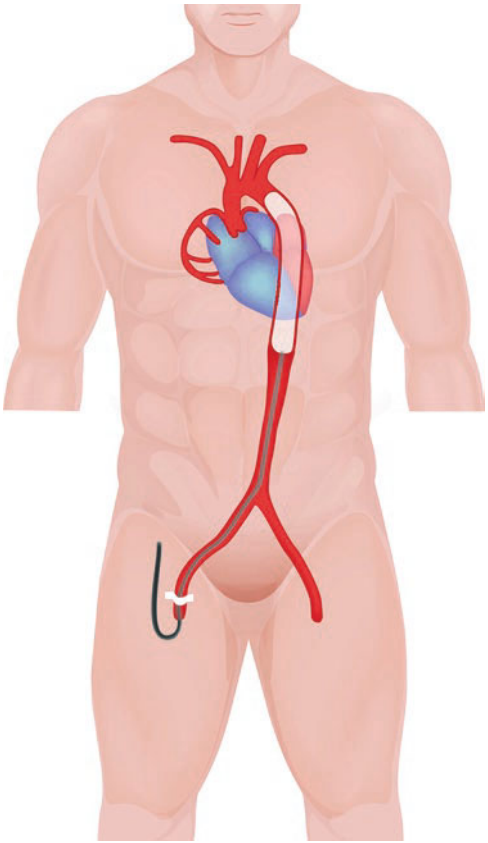

Illustration of an intra-aortic balloon pump [Baker ZP, Keenan JB, Khalpey Z. Difficult Decisions in Cardiothoracic Surgery: Acute Cardiogenic Shock. In: Surgical Decision Making [Internet]. Springer International Publishing; 2016 [cited

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- In chromic MR, nitrates, diuretics, and beta-blockers may be helpful in controlling MR symptoms.
- Sodium restriction with or without diuretic therapy can help ease symptoms of pulmonary vascular congestion.
- Rate control and thromboembolic protection should be provided to MS patients with atrial fibrillation.
- Surgical repair or mitral valve replacement may be required in severe cases.

Disease Course

- Prognosis is dependent on the severity of the MR and underlying co-morbidities.
- Co-morbid heart failure or atrial fibrillation worsens the course.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Mitral Valve Insufficiency"[Mesh] OR "Mitral Valve Regurgitation"[tiab] OR "Mitral Regurgitation"[tiab] OR "Mitral Valve Incompetence"[tiab] OR "Mitral Incompetence"[tiab] OR "Mitral Insufficiency"[tiab] OR "Mitral Valve Insufficiency"[tiab]

Chapter 49
Mitral Valve Stenosis

Charles V. Pollack, Jr. and Jaime Friel Blanck

Name and Synonyms

Mitral valve stenosis

Incidence/Epidemiology

- Mitral stenosis (MS), a narrowing of the channel between the left atrium and left ventricle, is most often a late sequela of acute rheumatic fever; it is occasionally congenital.
- The incidence of rheumatic fever is steadily diminishing in the US and the developed world.
- About two-thirds of patients with rheumatic MS are female.
- Symptoms usually manifest during the third or fourth decade of life and most patients are unaware that they ever had rheumatic fever.

Differential Diagnosis

- MS can be diagnosed definitively with echocardiography, so it can therefore be confirmed expeditiously if suspected. The symptoms associated with MS can overlap with those of a handful of other syndromes, such as:
  - Endocarditis
  - Left atrial myxoma
  - Atrial septal defect

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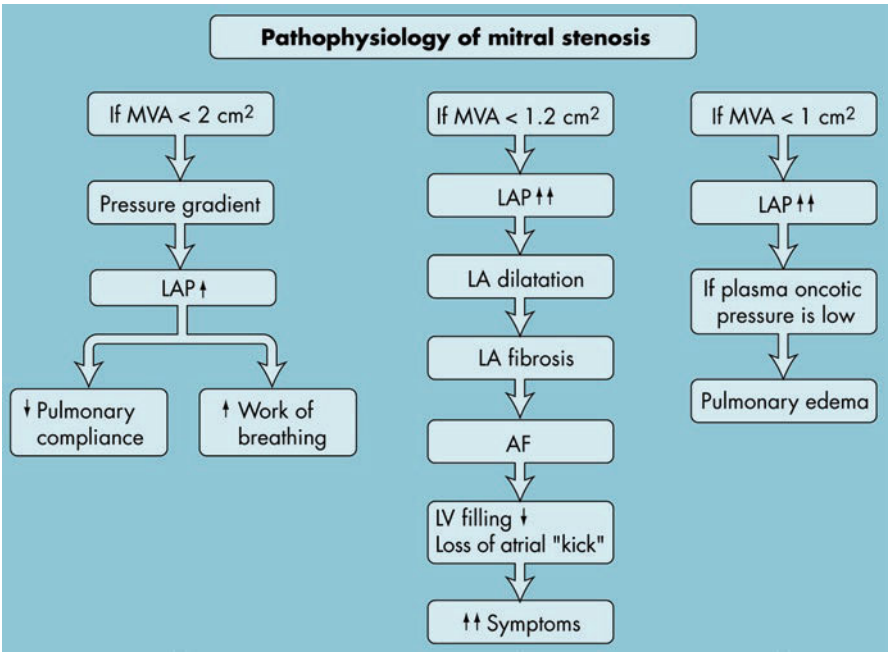
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_49

Pathophysiology and Etiology

- In MS, the valve leaflets are thickened and coarsened by fibrous tissue and/or calcific deposits. The mitral commissures eventually fuse and the valve cusps become rigid. The chordae tendineae also fuse and shorten, and eventually the aperture of the funnel-shaped valve narrows.



Pathophysiology of mitral valve stenosis. AF—atrial fibrillation; LA—left atrial; LAP—left atrial pressure; MVA—mitral valve area. [Clements F, de Bruijn N, Bennett-Guerrero E, Newman M, Reves JG. Chapter 1. In: Miller RD, Muravchick S, editors. Atlas of Anesthesia: Subspecialty Care, Volume 5, 1e. Philadelphia: Current Medicine; 1998. 236 p. ISBN: 0-443-07905-6] *Caption from original*

- The damage to the valve caused by the initial rheumatic insult is exacerbated over years by inflammatory and traumatic changes that occur because of altered flow patterns across the leaflets.
- MS eventually becomes symptomatic as the left atrium must generate higher and higher pressures to empty into the left ventricle across the narrower and narrower valve. In adults, the normal valve diameter is 4–6 cm^2. Symptoms usually are not apparent until the diameter is 2–2.5 cm^2. The left atrial pressure required to pump blood across that opening begins to increase dramatically at

that point, and patients may experience dyspnea and/or tachycardia on exertion. With severe MS, marked by a valve diameter of 1 cm^2 or less, a left atrial pressure of 25 mm Hg or more is required to maintain a normal cardiac output. This level of pressure in turn increases pulmonary venous and capillary pressures and further reduces pulmonary compliance, resulting in worsening dyspnea. Symptoms are worse with physical stress or exertion that increases heart rate because in tachycardia, diastole is shortened disproportionately compared to systole, leaving less time available for flow across the mitral valve.

- As left atrial, pulmonary capillary, and pulmonary arterial pressures rise, it becomes more difficult for the right ventricle to empty its full volume into the lungs for oxygenation, ultimately reducing cardiac output.
- When severe, pulmonary hypertension results in tricuspid and pulmonic valve incompetence and right-sided heart failure, or "cor pulmonale." With pulmonary hypertension there is also an increased risk of atrial fibrillation and its attendant thromboembolic complications.

Presentation

Typical/"Classic"

- The presentation of MS varies along a continuum, determined by the extent of valve narrowing and presence of pulmonary hypertension. Patients are usually asymptomatic for decades, but then symptoms typically progress continuously over a period of 2–3 years once dyspnea or cough with exertion begins to occur. The symptoms that suggest MS include:
  - Shortness of breath
  - Chest pain
  - Palpitations
  - Hemoptysis
  - Decreased exercise tolerance

Atypical

- Patients with advanced MS may have signs of right heart failure, such as severe dependent edema, liver congestion, and ascites.
- Hoarseness may develop from compression of the left recurrent laryngeal nerve by the enlarged left atrium as it hypertrophies to overcome the pressure gradient in the stenotic mitral valve.

- The damaged valve leaflets in MS are at risk for bacterial vegetations and endocarditis.
- MS may present with thromboembolism, from thrombi that form in the enlarged atrial appendages of patients with advanced MS.

Primary Differential Considerations

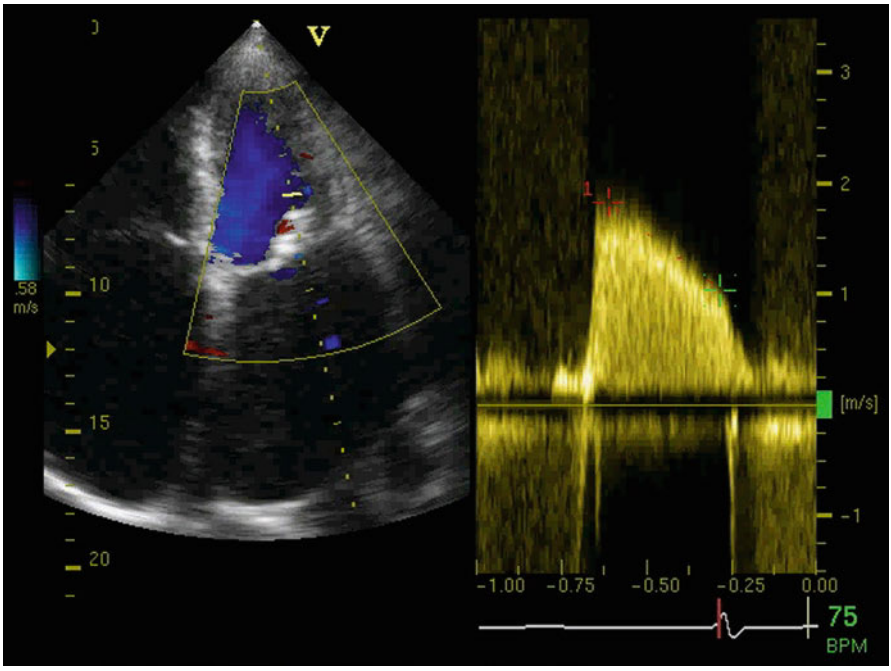
- Mitral stenosis, once symptomatic, may prompt searches for primary pulmonary causes of dyspnea, such as bronchitis, pneumonia, pulmonary edema, or pulmonary hypertension of other etiology.
- Other cardiac diagnoses to be considered are limited to atrial myxoma, atrial septal defect, heart failure, and arrhythmia. Early echocardiography can establish the culprit.

History and Physical Examination

- "Mitral facies"—purplish patches on the cheeks—has been described as being commonly seen in these patients.
- Ask about dyspnea, chest pain, or palpitations with exertion; ask about previous echocardiograms or a history of heart murmur.
- Ask about hemoptysis.
- Inquire about a history of rheumatic fever.
- Listen carefully over the heart for a low-pitched, rumbling, diastolic murmur, accentuated by exercise and diminished by Valsalva. Other suggestive findings on cardiac auscultation include:
  - Loud, snapping first heart sound.
  - Opening snap of the mitral valve, heard best in exhalation at or just medial to the cardiac apex.
- A diastolic thrill may be palpable at the cardiac apex. Check with the patient in the left lateral recumbent position.
- Look for pedal edema, jugular venous distension, or ascites as indications of right heart involvement.

Findings That Confirm Diagnosis

- The echocardiogram confirms the diagnosis. The MS murmur, opening snap, and diastolic thrill noted above, particularly in the context of MS symptoms (starting with exertional dyspnea), should prompt the imaging study.



Rheumatic mitral stenosis. Continuous-wave Doppler flow recording demonstrates a pressure half-time of 220 μsec yielding an estimated orifice area of 1 cm^2. [Garcia M, Liu Z. Chapter; In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, Braunwald E, editors. Atlas of Echocardiography. 1e. Philadelphia, PA: Current Medicine Group; 2005. 312 p. ISBN: 1-57340-217-6] *Caption from original*

https://www.easyauscultation.com/cases?coursecaseorder=14&courseid=31
Mitral stenosis murmur. [Mitral Stenosis (Diastolic Murmur); Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Factors That Suggest Diagnosis

- Prior to diagnostic confirmation with echo, presence of two or more of the symptoms cited above suggests MS.
- The lack of a history of rheumatic fever does not exclude the diagnosis.
- Signs of pulmonary hypertension or right heart failure in the presence of a diastolic murmur are suggestive of MS.

Factors That Exclude Diagnosis

- MS is definitively excluded only by an echocardiogram showing unimpeded flow across the mitral valve.

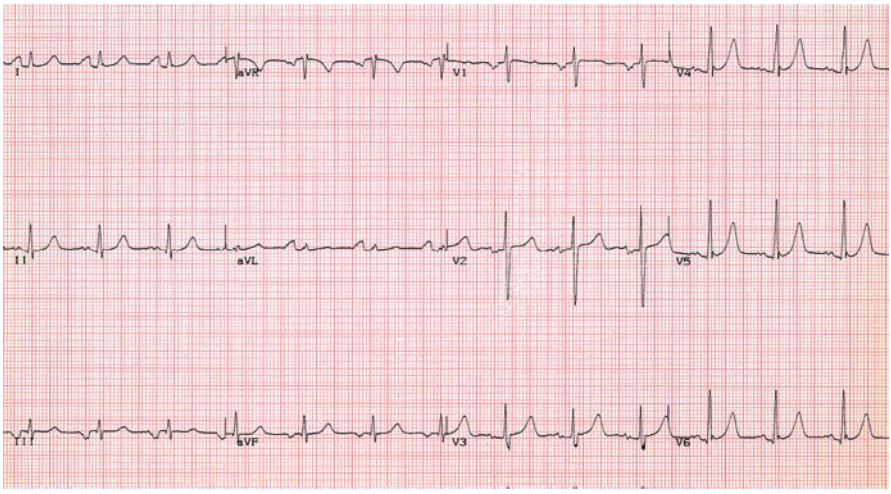
Ancillary Studies

Laboratory

- It is helpful to send routine laboratory studies, such as basic chemistries and a complete blood count, to evaluate for other causes for the patient's symptoms.
- There may be value to checking a brain-type natriuretic peptide (BNP) level, especially if the patient has heart failure symptoms.
- Liver and renal function should be evaluated.

Electrocardiography

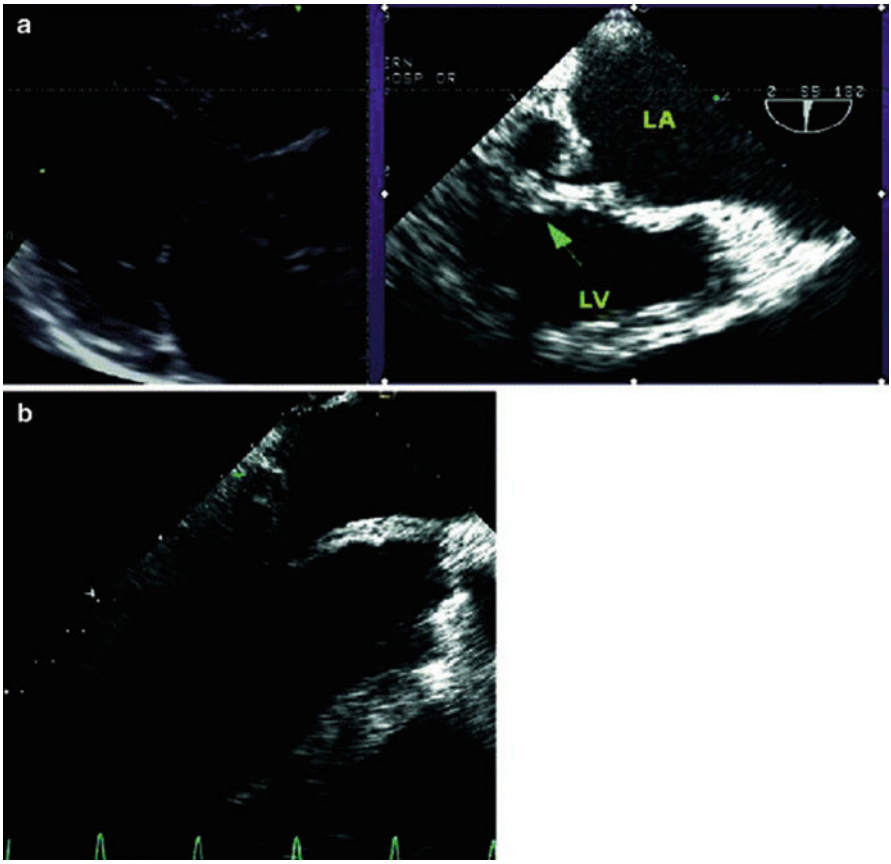
- The ECG should be obtained and interpreted promptly. If MS is suspected, look for a tall and peaked P-wave in lead II and an upright P-wave in lead V_1. These findings are more prominent with more advanced MS.



Electrocardiographic (ECG) signs in MS. A, The ECG findings from a patient with MS and regular sinus rhythm is normal except for signs of left atrial (LA) enlargement, that is, a P wave widened to 0.12 second or more. In lead II, the P wave has a double peak often characterized by an M-shaped configuration. In lead V1, the late negative portion of the P wave is characteristically increased in both width and depth. The P-wave changes are also called "P mitrale." [Kawanishi D, Rahimtoola S. Chapter; In: Braunwald E, editor. Atlas of Heart Disease: Valvular Heart Disease, Volume 11, 1e. St. Louis, Mo.: Current Medicine; 1997. 200 p. ISBN: 1-878132-30-X] *Caption adapted from original*

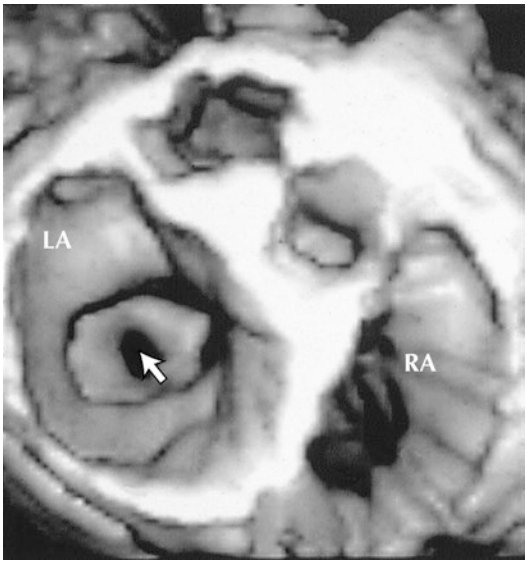
Imaging

- The chest x-ray may be helpful in the evaluation of possible MS. Look for straightening of the left border of the cardiac silhouette and prominence of the main pulmonary arteries. Prominence of the upper lobe pulmonary vasculature may be seen. In rare cases, a calcified mitral valve may be seen. Frank cardiomegaly usually does not occur until fairly late in the disease progression.
- Echocardiography is the most sensitive and specific noninvasive test for MS. Transthoracic 2-D echo can usually confirm the diagnosis, and with Doppler echo and color flow imaging the actual size and function of the valve can be assessed. In the past, cardiac catheterization was used to determine a therapeutic plan—i.e., whether surgery is required—but latest-generation echo now usually suffices.



Echocardiographic features of mitral stenosis. (a) Rheumatic mitral stenosis. This figure demonstrates typical findings of rheumatic mitral stenosis (MS). The left panel shows hockey stick deformity of the anterior leaflet of the mitral valve

in diastole. This appearance is a manifestation of the preferential involvement of the tips of the leaflets with the inflammatory/fibrosis process. This leads to relatively preserved mobility of the body with restricted mobility of the tip and the typical appearance. The right panel is a TEE from a different patient. The green arrow shows severe thickening and shortening of the chordae tendinae. Another common feature of rheumatic mitral stenosis is commissural fusion. The presence of commissural fusion may be a good predictor of who will respond to balloon valvuloplasty. (b) Other etiologies of mitral stenosis. Other etiologies of mitral stenosis include radiation and connective tissue disorders. Systemic lupus erythematosus causes diffuse thickening of the body of the valve leaflet as opposed to the tips in rheumatic heart disease [Akhter N, Mikati IA. Mitral Prolapse Regurgitation and Mitral Stenosis. In: Abraham T, editor. Case Based Echocardiography [Internet]. Springer London; 2010 [cited 2017 May 4]. p. 195–218. Available from: http://link.springer.com/chapter/10.1007/978-1-84996-151-6_17] *Caption adapted from original*



Three-dimensional echocardiographic (3DE) images of mitral valve (MV) from a patient with mitral stenosis. A, The MV as seen from above the left atrium (LA). The right atrium (RA) is seen to the right of LA and aorta anteriorly adjoining both atria. This type of 3DE sections displays MV and the narrowed MV orifice (arrow) in a view that stimulates intraoperative visualization [Hsu T, Yao J, De Castro S, Pandian N. Chapter; In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging. Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption adapted from original*

Special Populations

Age

- Onset of MS symptoms is usually in the third or fourth decades of life.

Co-morbidities

- The most important co-morbidities are underlying cardiopulmonary disease, including heart failure and pulmonary hypertension. Atrial fibrillation increases the risk of thromboembolic complications in MS.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- An echocardiogram should be obtained early in the evaluation of patients with signs and symptoms suggestive of MS.
- Stabilize patients who present with hemodynamic compromise and poor oxygenation.

Mimics

- The echocardiogram will resolve differential considerations.

Time-Dependent Interventions

- The most important intervention is to stabilize patients with hemodynamic instability.
- Recognition of pulmonary hypertension and right heart failure will prompt immediate therapy.

Overall Principles of Treatment

- The goals of medical treatment for MS are to:
  - Protect against recurrent rheumatic fever.
  - Protect against infective endocarditis.
  - Provide symptomatic relief.

- Sodium restriction with or without diuretic therapy can help ease symptoms of pulmonary vascular congestion.
- Beta-blockers may also provide some symptomatic relief for patients in sinus rhythm by prolonging diastolic filling time.
- Rate control and thromboembolic protection should be provided to MS patients with atrial fibrillation.
- Rheumatic fever prophylaxis with antibiotics providing Group A beta-hemolytic strep protection should be considered, as should antibiotic prophylaxis for infective endocarditis in association with interventions that may seed the bloodstream with bacteria, such as some dental procedures.
- Percutaneous balloon commissurotomy is the procedure of choice when medical therapy is insufficient to provide symptom relief.
- Surgical repair or mitral valve replacement may be required in severe cases or those in which commissurotomy does not provide relief.

Disease Course

- Prognosis is dependent on the severity of the MS.
- Co-morbid heart failure or atrial fibrillation worsens the course.
- The availability of percutaneous commissurotomy has improved the course of symptomatic MS.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jun 10;63(22):e57-185. https://doi.org/10.1016/j.jacc.2014.02.536. Epub 2014 Mar 3. Erratum in: J Am Coll Cardiol. 2014 Jun 10;63(22):2489. Dosage error in article text. PubMed PMID: 24603191. https://www.ncbi.nlm.nih.gov/pubmed/24603191

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: (“Mitral Valve Stenosis”[Mesh] OR “mitral valve stenosis”[tiab] OR “mitral stenosis”[tiab] OR “mitral stenoses”[tiab] OR “mitral valve stenoses”[tiab])

Chapter 50
Myocarditis

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Myocarditis

- Carditis, cardiac inflammation

Incidence/Epidemiology

- There are many diverse causes of myocarditis, and disease severity varies widely; therefore, the overall incidence of the disease is unknown.
- It is estimated that as many as 1–3 % of patients with acute viral infections may develop at least subclinical viral myocarditis.
- Overall, myocarditis is an unusual cause of acute chest pain. Although usually benign and self-limited, severe myocardial injury may occur.

Differential Diagnosis

- The differential considerations for myocarditis include all other causes of acute chest pain. These include, in particular, the potentially life-threatening diagnoses of acute coronary syndrome (ACS; unstable angina, NSTEMI, STEMI), pulmonary embolism, and aortic dissection.

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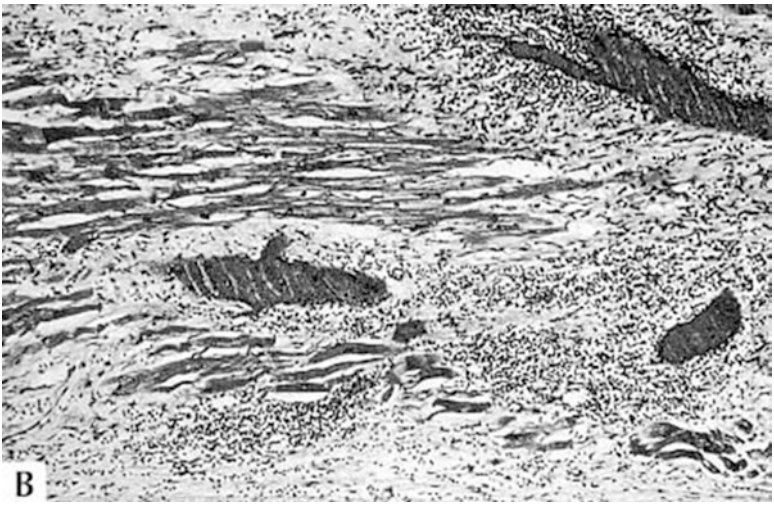
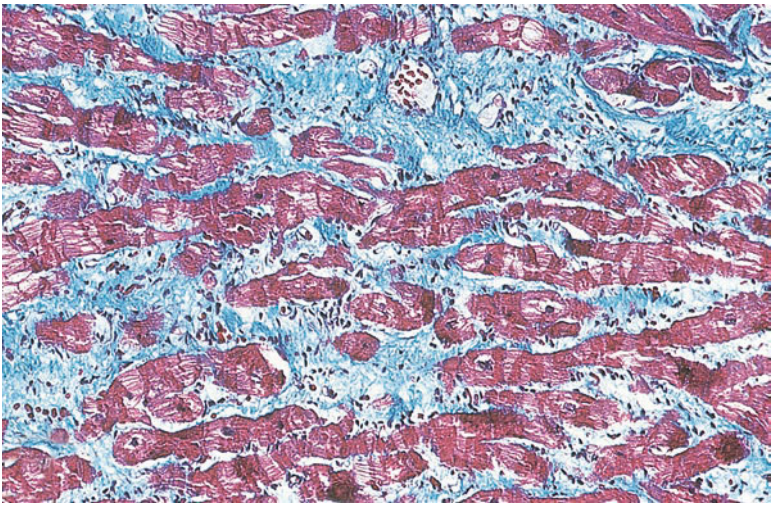
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_50

- Pneumonia, pleurisy, and pneumothorax should also be considered.
- Some patients with myocarditis have transient (or persistent) myocardial dysfunction, which brings heart failure, arrhythmias, and pericarditis into the differential.

Pathophysiology and Etiology

- Myocarditis is inflammation of the cardiac muscle. It may result from infection, secondary reaction, autoimmune problems, or exposures as follows:





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Gross autopsy specimen and photomicrographs of myocarditis. A, Gross autopsy specimen of a heart with fulminant myocarditis. The right ventricle is cut along the long axis to demonstrate an apical mural thrombus. B, Low-power photomicrograph of the myocardium revealing extensive mononuclear inflammation, which has replaced large clusters of myocytes that have undergone necrosis. Fulminant myocarditis is characterized by a nonspecific, severe influenza-like illness and the distinct onset of cardiac involvement. The patient's condition deteriorates rapidly, and the disorder frequently results in profound hemodynamic compromise and multisystem failure. Endomyocardial biopsies from fulminant myocarditis patients demonstrate unequivocal active myocarditis and are particularly notable for very extensive inflammatory infiltrates and numerous foci of myocyte necrosis. Within 1 month, the patients usually recover left ventricular function completely or die [045]. In contrast, acute myocarditis describes the clinical spectrum of the largest group of patients with active or borderline myocarditis. These patients have minimally dilated, hypokinetic left ventricles on presentation. The onset of cardiac symptoms is frequently indistinct, and some patients provide a vague history consistent with (but not diagnostic of) an antecedent viral illness. Active or borderline myocarditis is present on initial (but not subsequent) endomyocardial biopsies. Some patients in this group appear to respond to immunosuppressive therapy [046], while others experience either partial recovery of ventricular function or continue to deteriorate to end-stage dilated cardiomyopathy. (045. Rockman HA, Adamson RM, Dembitsky WP, et al. Acute fulminant myocarditis: long-term follow-up after circulatory support with left ventricular assist device. Am Heart J. 1991; 121:922 -926.) (046. Jones SR, Herskowitz A, Hutchins GM, et al. Effects of immunosuppressive therapy in biopsy-proved myocarditis and borderline myocarditis on left ventricular function. Am J Cardiol. 1991; 68:370 -376). C, Masson's trichrome (which stains collagen blue) of an endomyocardial biopsy of a patient with

chronic active myocarditis. Note the extensive collagen deposition characteristically seen in end-stage dilated cardiomyopathy. Patients with chronic active myocarditis usually have a vague clinical presentation. Such patients have a slowly progressive course that inevitably deteriorates but may be punctuated by brief, often-dramatic but unsustained responses to immunosuppressive therapy. Serial endomyocardial biopsies demonstrate ongoing myocarditis with the development of extensive interstitial fibrosis. Inflammatory infiltrates in this subgroup of myocarditis patients may contain multinucleated giant cells. [Herskowitz A, Ansari A, Abelmann W. Myocarditis. In: Lee RT, Braunwald E, editors. Atlas of cardiac imaging. Philadelphia: Current Medicine; 1998. Chapter 9. (Braunwald E, editor. Atlas of heart diseases; vol. 2). ISBN: 0-443-07567-0; 2002-01-23] *Caption from original*

Etiologies of Human Myocarditis: Infectious

Viral	Protozoal and metazoal
Coxsackievirus (A and B)	Trypanosomiasis
Parvovirus	Toxoplasmosis
Echovirus	Malaria
Influenza	Schistosomiasis
Cytomegalovirus	Trichinosis
Hepatitis	Bacterial
Mumps	Diphtheria
Herpes simplex	Tuberculosis
Rabies	Legionella
EBV	Brucella
HIV	Clostridium
Rickettsial	Salmonella/shigella
Q fever	Meningococcus
Rocky Mountain spotted fever	Yersinia
Scrub typhus	Spirochetal
Fungal	Borrelia (Lyme)
Cryptococcus	
Candidiasis	
Histoplasmosis	
Aspergillus	

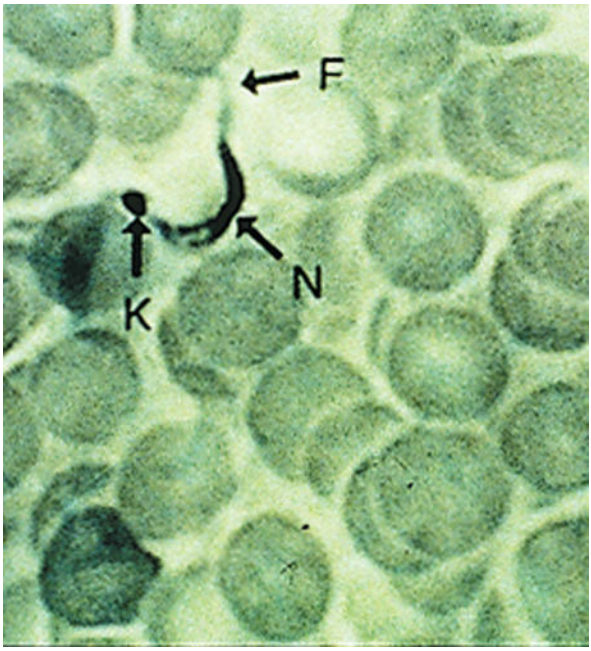
Infectious causes of human myocarditis. Most cases of myocarditis are clinically idiopathic and likely represent the largest subgroup of cases of human myocarditis (Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation. 2001; 104:1076 -1082.). EBV—Epstein-Barr virus. [Baughman K. Etiologies of human myocarditis: infectious, viral, protozoal, and metazoal. In: Libby P, editor.

Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. Chapter 6. ISBN: 978-1-57340-309-2; 2009-05-21;] *Caption adapted from original*

Infectious	Immune-mediated	Toxic	Other/unknown
All types of microorganisms	Post-infectious	Drugs	Sarcoidosis
1. Virus	Systemic disorders	Toxins	Giant cell myocarditis
2. Fungus	Drug hypersensitivity		
3. Bacteria	Transplant rejection		
4. Protozoa			
5. Parasite			

How myocarditis can be sub-typed/grouped [Baandrup U. Myocarditis/inflammatory cardiomyopathy. In: Suvarna SK, editor. Cardiac pathology. London: Springer; 2013. p. 133-46. Book https://doi.org/10.1007/978-1-4471-2407-8; Chapter: 8; Chapter https://doi.org/10.1007/978-1-4471-2407-8_8; 2013-01-01] *Caption from original*

- Viral infection, including but not limited to
  - Coxsackie B virus (most common)
  - Enterovirus
  - Adenovirus
  - Influenza
  - HIV
  - Mumps
  - Rubeola
- Bacterial infection, including but not limited to
  - Diphtheria
  - *Streptococcus*
  - *Mycoplasma*
  - Tuberculosis
- Acute rheumatic fever
- Protozoal infection, including but not limited to
  - Chagas disease

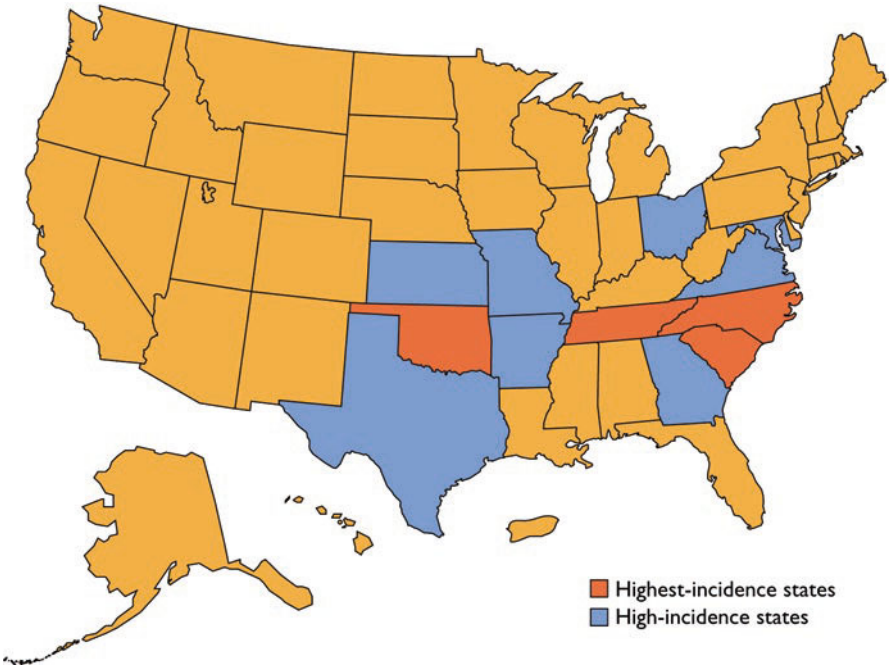


American trypanosomiasis (Chagas' disease): myocarditis. The most common infection of the heart worldwide is Chagas' disease, caused by the protozoan parasite Trypanosoma cruzi, which is spread by reduviid insects (Kirchhoff LV. American trypanosomiasis (Chagas' disease): a tropical disease now in the United States. N Engl J Med. 1993; 329:639 -644.). Infection with T. cruzi is endemic in Latin America and is now increasingly observed in the United States. Acute Chagas' disease is characterized by the systemic spread of the parasites to muscle, including myocardium. A, T. cruzi isolated from the blood of a patient with Chagas' disease. The trypomastigote is shown in mouse blood (Giemsa stain, × 2000). B, Histopathology of acute Chagas' myocarditis with a mononuclear infiltration. The arrows denote myocytes containing amastigote forms of the parasites (hematoxylin and eosin, × 360). C, High magnification of an infected myocyte (hematoxylin and eosin, × 900). F—flagellum; K—kinetoplast of amastigotes; N—nucleus. American trypanosomiasis (Chagas' disease): myocarditis [Hare J. Pathologic etiologies of heart failure. In: Colucci WS, editor. Atlas of heart failure. 5th ed. Philadelphia: Current Medicine; 2008. Chapter 3. (Braunwald E, editor. Atlas of heart diseases; vol. 4). ISBN: 1-57340-261-3; 2008-04-23] *Caption from original*

- toxoplasmosis
- Spirochetal infection, including but not limited to
    - Syphilis
    - Lyme disease

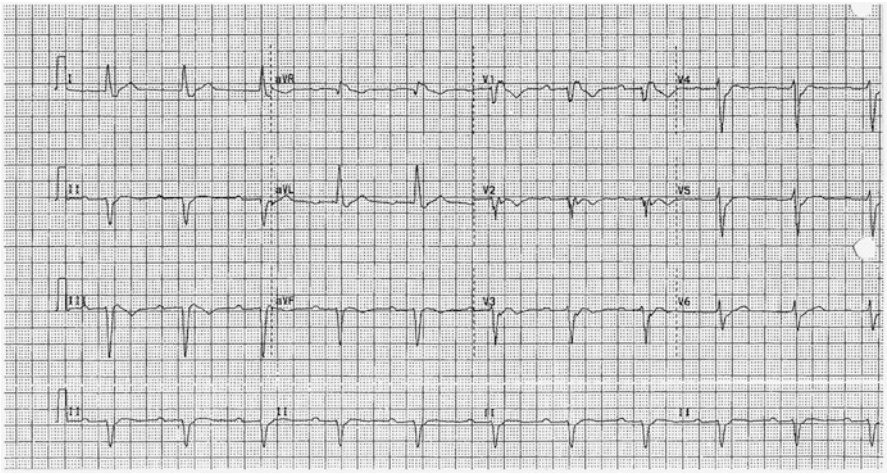
Borrelia burgdorferi in human myocardium: Lyme myocarditis. Detection of the spirochete Borrelia burgdorferi (arrow) in human myocardium (modified Steiner's silver stain). Lyme disease, a multisystem disorder caused by infection with B. burgdorferi, produces cardiac disease, notably arrhythmias and myocarditis, as a tertiary manifestation [045]. Here the spirochete is demonstrated in myocardium from a patient with a 4-year history of dilated cardiomyopathy and a serologic profile consistent with chronic Lyme disease. [Hare J. Pathologic etiologies of heart failure. In: Colucci WS, editor. Atlas of heart failure. 5th ed. Philadelphia: Current Medicine; 2008. Chapter 3. (Braunwald E, editor. Atlas of heart diseases; vol. 4). ISBN: 1-57340-261-3; 2008-04-23] *Caption from original*

- Rickettsial infection, including but not limited to
  - Rocky Mountain spotted fever



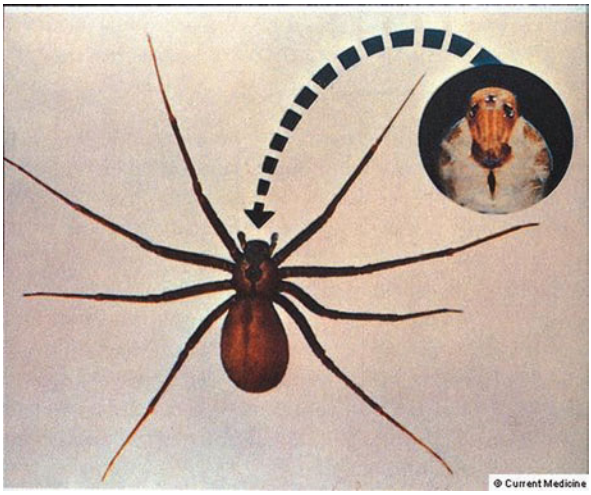
Incidence of Rocky Mountain spotted fever in the United States. High and medium incidence rates of Rocky Mountain spotted fever (RMSF) in the United States. Although RMSF has now been reported in almost every state, four states (North Carolina, South Carolina, Tennessee, and Oklahoma) have reported the highest number of cases in recent years. Other high incidence states in recent years include Maryland, Virginia, Georgia, Tennessee, Ohio, Missouri, Arkansas, Texas, and Kansas. Certain focal regions, such as Cowan and Rowan counties in North Carolina, are considered hyperendemic. [Spach D. Chapter 14. In: Wilfert S, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1998. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8; 2002-01-23] *Caption from original*

- Fungal infection, including but not limited to
  - Candidiasis
  - Histoplasmosis
- Systemic inflammatory disease, including but not limited to
  - Giant cell myocarditis
  - Sarcoidosis



Sarcoidosis of the heart. Resting ECG in a patient with advanced sarcoidosis. The tracing shows evidence of first-degree atrioventricular block as well as a right bundle branch block pattern. Echocardiography showed no evidence of regional wall motion abnormality and an estimated left ventricular ejection fraction of 40%. The patient underwent cardiac catheterization, which demonstrated no evidence of coronary artery disease. Based on the prior history of pulmonary sarcoidosis and the presence of conduction system abnormalities and cardiomyopathy in the absence of coronary artery disease, the patient was felt to have cardiac sarcoidosis. The patient underwent electrophysiologic study, which demonstrated inducible sustained ventricular tachycardia. An implantable cardio-defibrillator device was placed. [Tanoue L, Elias J. Sarcoidosis. In: Crapo J, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. Chapter 12; ISBN: 1-57340-211-7; 2005-01-14] *Caption adapted from original*

- Kawasaki's disease
- Crohn's disease
- Radiation exposure
- Chemical or drug toxicity, including but not limited to
  - Chemotherapeutic agents such as doxorubicin and anthracyclines
  - Antiseizure drugs such as phenytoin and carbamazepine
  - Antibiotics such as penicillin and chloramphenicol
- Envenomations, including but not limited to
  - Black widow spider bites



Neurotoxic black widow spider. The black widow spider (Latrodectus mactans) elaborates a venom that can cause severe neurologic dysfunction. The female (shown here) contains a red hourglass mark on the abdomen and is one of the most aggressive and most dangerous of the American spiders. (From US Government Printing Office [9].) 009. Venomous Arthropod Handbook. USAF School of Aerospace Medicine, Brooks Air Force Base, Texas 78235. Stock no. 008-070-00397-0, catalog no. D 301-35:161/43. Washington, DC: US Government Printing Office; 1977 [Prockop L, Brock C, Spencer P. Neurotoxic disorders. In: Rosenberg RN, editor. Atlas of clinical neurology. 3rd ed. Philadelphia: Current Medicine; 2009. p. 543-64. ISBN: 978-1-57340-283-5; 2009-01-28;] *Caption adapted from original*

- Scorpion stings

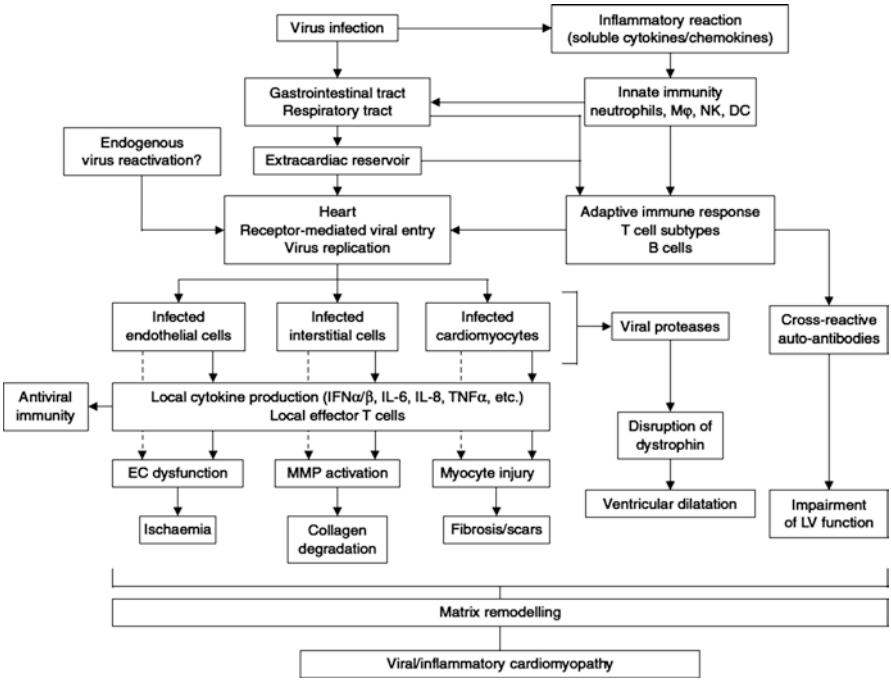
Scorpion envenomation. Scorpions secrete a complex mixture of substances, including an array of proteins with neuropharmacologic and enzymatic activity. The venom is delivered from a tail stinger. (From Anon [008].) 008. Anon: Venomous

Arthropod Handbook. USAF School of Aerospace Medicine, Brooks Air Force Base, Texas 78235. Stock No. 008–070–00397–0, catalog no. D 301.35: 161/43. Washington, DC: US Government Printing Office; 1977 [Gold B, Schnell J, Spencer P. Neurotoxic disorders. In: Rosenberg RN, editor. Atlas of clinical neurology. 2nd ed. Philadelphia: Current Medicine; 2003. Chapter 14. ISBN: 1-57340-175-7; 2002-01-24] *Caption adapted from original*

- Snake venom

Rattlesnake (*Crotalus durissus*). [From article: The use of zootherapeutics in folk veterinary medicine in the district of Cubati, Paraíba State, Brazil. J Ethnobiol Ethnomed. 2007 Sep;3(1):32. https://doi.org/10.1186/1746-4269-3-32, at http://link.springer.com/article/10.1186%2F1746-4269-3-32/fulltext.html; by Raynner RD Barboza, Wedson de MS Souto, José da S Mourão, © Barboza et al; licensee BioMed Central Ltd. 2007; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- Postpartum
- Idiopathic
- The common denominator of all these diverse causes is inflammation and potential dysfunction of myocardial cells, the consequences of which may range from subclinical to life threatening. Damage to the adjacent cardiac conduction system is common, with arrhythmias the potential result. Exploration of possible underlying causes is important to determine specific treatments beyond basic support of heart function.



Causes of myocardial injury in viral and post-infectious heart disease. Myocardial tissue injury emerges during different phases of infectious myocarditis from direct virus-associated and/or immune-mediated tissue injury. DC = dendritic cells; EC = endothelial cells; IFN = interferon; IL = interleukin; LV = left ventricular; Mφ = monocytes; MMP = matrix metalloproteinase; NK = natural killer cells; TNFα = tumour necrosis factor-α. [Kühl U, Schultheiss HP. Viral myocarditis. Drugs. 2009 Jul;69(10):1287-302. https://doi.org/10.2165/00003495-200969100-00001; Published: 2009-07-01] *Caption from original*

Presentation

Typical/"Classic"

- Because of the broad range of etiologies, there is no "classic" presentation of myocarditis. Common features that may prompt presentation for care include:
  - Acute or chronic heart failure
  - Chest pain
  - Arrhythmias
  - Exercise intolerance
  - Fever, chills, and other signs and symptoms of systemic illness
- Signs and symptoms range from quite mild to life threatening.

Aspecific	1. Gastrointestinal: nausea and vomiting, cramp, diarrhea, appetite loss, abdominal and epigastric pain 2. Respiratory: cough, pharyngeal pain 3. General: increased fever, general fatigue, arthralgia and myalgia, headache, and back pain
Cardiac	1. Chest pain or discomfort (particularly common in young patients with coronary vasospasm), concomitant pericarditis, syncope, palpitations, dyspnea 2. Heart failure: generalized fatigue, intolerance to exercise and dyspnea. Subsequently acute or fulminant cardiogenic shock 3. Sinus tachycardia (most common, especially out of proportion with concomitant fever), premature atrial and ventricular contraction, atrial fibrillation, and ventricular tachycardia. I and II degree, up to complete AV block (more common with infiltrative and GCM), RBBB, and LBBB

Clinical presentation of myocarditis. [Cortinovis B, Scanziani M, Celotti S. ECMO in myocarditis and rare cardiomyopathies. In: Sangalli F, Patroniti N, Pesenti A, editors. ECMO-extracorporeal life support in adults. Milan: Springer; 2014. p. 137-49; Book https://doi.org/10.1007/978-88-470-5427-1; Chapter: 12; Chapter https://doi.org/10.1007/978-88-470-5427-1_12; Published: 2014-01-01] *Caption from original*

Atypical

- Because of the broad range of etiologies and co-morbidities, atypical or distracting presentations of myocarditis are common.

Primary Differential Considerations

- Prompt consideration also should be given to the possible diagnosis of ACS, pulmonary edema, cardiac tamponade, and cardiomyopathy.

History and Physical Exam

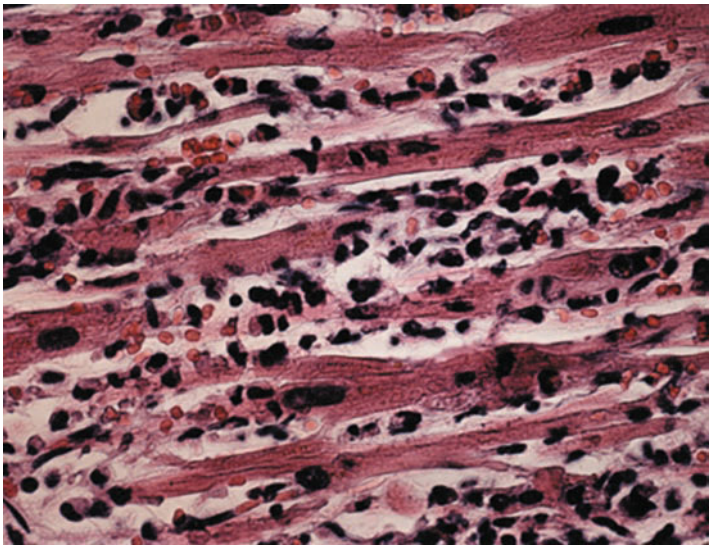
Findings That Confirm Diagnosis

- The diagnosis of myocarditis is usually presumptive, based on recognition of the combination of suggestive symptoms, a potential exposure, and clinical suspicion.

Diagnostic test	Common features
Chest radiography	Cardiomegaly, pulmonary vascular congestion, and/or pleural effusion (depending on right ventricular and tricuspid valve dysfunction). No specific abnormalities
ECG	Completely normal or with minor, aspecific abnormalities to markedly abnormal Brady- and tachyarrhythmias, conduction abnormalities, ST and T wave alterations, abnormal Q wave, low voltage, and poor R wave progression. Patterns of infarction or pericarditis. Presence of Q wave associated with a severe course, higher early cardiac enzymes, worse LV function, and higher incidence of cardiogenic shock, but not necessarily with a worse long-term outcome (31)
Cardiac enzymes	CPK MB, TnT, and TnI may be elevated (reflecting the extent of myocardial injury). TnI probably superior to CPK MB early in the disease, TnT levels correlating with more extensive damage
Echocardiography	Highly variable, from a completely normal to a markedly abnormal Various degrees of hypokinesis most commonly (mild hypokinesis limited to areas of focal infiltration, segmental wall motion abnormalities or diffuse involvement, with severe hypokinesis) LVEF or FS reduced, not necessarily with LV dilatation
Magnetic resonance imaging	Areas of inflammation and infiltration, mostly focal within the first 2 weeks, more diffuse within 4 weeks. Extent of the lesion correlates with LV dysfunction
Endomyocardial biopsy	5–10 samples from RV septum. Submit 4–5 to light microscopic examination. Transmission electron microscopy may be useful but reserved to infiltrative disorders Routine viral genome testing only for referral centers Several patterns of infiltration (histiocytic and mononuclear), varying in severity and structural abnormalities of myocardium

Diagnostic test results in myocarditis. [Cortinovis B, Scanziani M, Celotti S. ECMO in myocarditis and rare cardiomyopathies. In: Sangalli F, Patroniti N, Pesenti A, editors. ECMO-extracorporeal life support in adults. Milan: Springer; 2014. p. 137-49; Book https://doi.org/10.1007/978-88-470-5427-1; Chapter: 12; Chapter https://doi.org/10.1007/978-88-470-5427-1_12; Published: 2014-01-01] *Caption adapted from original*

- The diagnosis cannot be fully confirmed without endomyocardial biopsy.



Severe myocarditis. Infiltrative disorders. A, Histologic section of myocardium showing severe myocarditis (hematoxylin-eosin stain ×50). Panel A shows the histology of the heart of a college student who came home for the winter holidays and died suddenly during Christmas dinner with her family. She was apparently asymptomatic in spite of the presence of severe myocarditis. B, Endomyocardial biopsy of a young woman who was successfully resuscitated from an episode of sudden death. At the time of electrophysiologic studies, an endomyocardial biopsy was obtained that showed non-necrotizing granulomas (arrow), leading to the diagnosis of isolated cardiac sarcoidosis. [Fishbein M, Chen PS. Structural substrates for arrhythmias in heart failure. In: Shivkumar K, Weiss J, Fonarow G, Narula J, editors. Atlas of electrophysiology in heart failure. Philadelphia: Current Medicine; 2005. Chapter 2. (Braunwald E, editor. Atlas of heart diseases; vol. 15); ISBN: 1-57340-225-7; Published: 2005-07-18; Braunwald, Eugene] *Caption adapted from original*

Factors That Suggest Diagnosis

- Systemic illness, chest pain, and exposure to an etiologic concern are suggestive and should prompt consideration of the diagnosis. Detection of arrhythmia in this setting is more suggestive.
- Associated pericarditis may result in an audible friction rub.

http://www.easyauscultation.com/myocarditis

Myocarditis heart sounds. [Myocarditis Page; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Patients with more significant or advanced disease may have an audible S3 heart sound.
- One might arrive at the diagnosis by first recognizing the underlying cause (such as toxic drug exposure, viral infection, or systemic inflammatory disease) and then attributing cardiac symptoms to the myocarditis.

Factors That Exclude Diagnosis

- No history or physical findings can definitively exclude myocarditis.

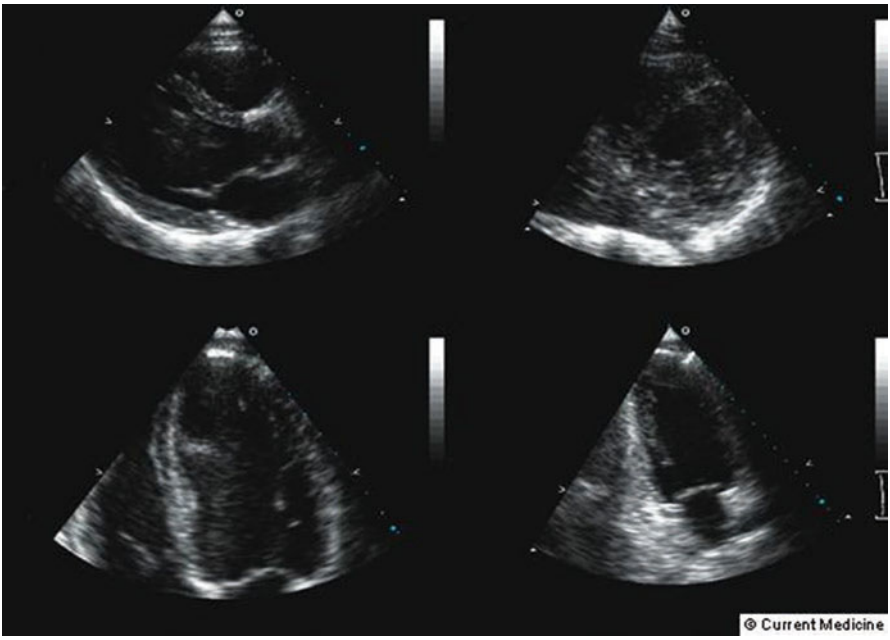
Ancillary Studies

Laboratory

- There are no diagnostic laboratory studies for myocarditis other than endomyocardial biopsy, which demonstrates inflammation of the myocardial cells.
- Some laboratory studies may be helpful in raising suspicion of myocarditis, evaluating causative/co-morbid conditions, or both. These may include:
  - Complete blood count
  - Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)
  - Cardiac enzymes (CPK-MB and/or troponin)
  - Viral antibody titers
  - Rheumatologic studies

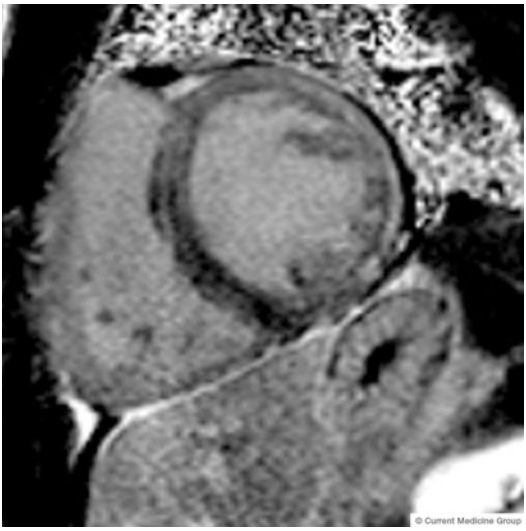
Imaging

- Echocardiography may be used to evaluate the extent of heart failure.



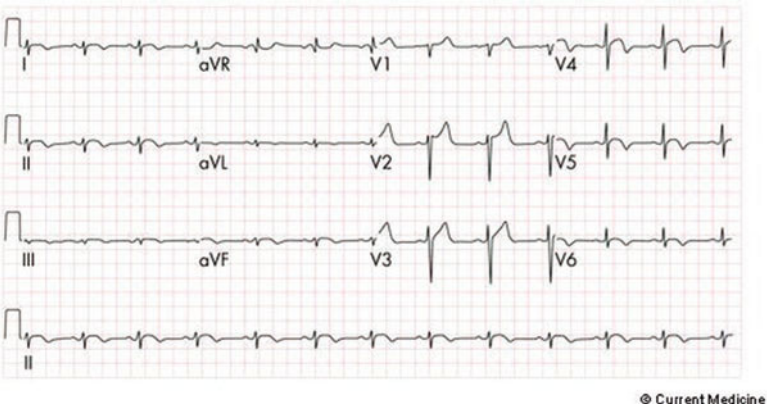
Transthoracic echocardiography in suspected acute myocarditis. Transthoracic echocardiography: Three long axis views (upper left and lower panels) and one short axis view (upper right panel) are shown. Severely reduced ejection fraction with preserved left ventricular size is demonstrated; valvular function was normal, as was the right ventricular size and function. [Strohm O, Friedrich M. Chapter 12. In: Manning WJ, editor. Atlas of cardiovascular magnetic resonance. Philadelphia: Current Medicine; 2009; ISBN: 978-1-57340-299-6; Published: 2009-01-16] *Caption from original*

- Magnetic resonance scanning with gadolinium may identify areas of myocardial inflammation.



Acute myocarditis. A 20-year-old male student who was previously healthy developed an influenza-like illness while visiting Mexico. He developed worsened dyspnea and was found to have severe depression of left ventricular (LV) global systolic function and moderate LV dilatation. At hospital admission, he had frequent nonsustained ventricular tachycardia, physical findings consistent with cardiogenic shock, with an LV ejection fraction (LVEF) quantified by volumetric cine cardiac magnetic resonance (CMR) to be 25% (A). Serial blood and urine cultures revealed no bacterial pathogens. Endomyocardial biopsy revealed moderate interstitial fibrosis only. Contrast-enhanced late gadolinium enhancement (LGE) imaging demonstrated diffuse and patchy enhancement of the anterolateral and inferolateral wall (B). These CMR findings are consistent with diffuse acute myocardial inflammation and edema presumably from acute viral myocarditis. The patient fortunately followed a stable and then progressively improving clinical course in the months following initial presentation. [Kwong R. Cardiac magnetic resonance imaging. In: Libby P, editor. Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. Chapter 16. ISBN: 978-1-57340-309-2; Published: 2009-05-21;] *Caption from original*

- Electrocardiographic findings are usually nonspecific but may suggest ACS.



ECG in suspected acute myocarditis. 12-Lead electrocardiogram at presentation, demonstrating nonischemic changes in the ST and T segments. Physical examination revealed severe chest pain and shortness of breath (New York Heart Association III), blood pressure 98/58 mm Hg, and heart rate 97 bpm. aVF—augmented voltage, unipolar left leg lead; aVL—augmented voltage, unipolar left arm lead; aVR—augmented voltage, unipolar right arm lead. [Strohm O, Friedrich M. Chapter 12. In: Manning WJ, editor. Atlas of cardiovascular magnetic resonance. Philadelphia: Current Medicine; 2009; ISBN: 978-1-57340-299-6; Published: 2009-01-16] *Caption from original*

Special Populations

Age and Gender

- Perhaps owing to the diverse etiologies of the disease, there is no age or gender predilection for myocarditis in general. Obviously, some causes affect specific groups, such as postpartum myocarditis in women and viral myocarditis in younger patients.
- In the pediatric population, viral etiologies predominate, specifically enteroviral (Coxsackie B), parvovirus B19, adenovirus, and human herpes 6.
- In children, the mean age at diagnosis is 9 years, with bimodal peaks at 9 months of age and 16 years.
- Affected infants will manifest signs of congestive heart failure, including tachypnea, tachycardia, and increased work of breathing and diaphoresis when feeding.

Co-morbidities

- The list of etiologies provided above signifies the major co-morbidities of interest.
- Of particular note are HIV disease—in which myocarditis may be caused by direct viral infection; associated opportunistic infections, such as toxoplasmosis; or related disorders, such as Kaposi's sarcoma—and malignancies treated with doxorubicin or anthracyclines, which are particularly cardiotoxic.
- Lyme disease is complicated by myocarditis in about 10 % of cases.
- Chagas' disease bears mention because it is one of the most common forms of heart disease in Central and South America. Most patients with this infection (cased by the protozoan *Trypanosoma cruzi*) develop chronic cardiomyopathy and heart failure without an acute phase of myocarditis, but it should still be considered in migrants from or visitors to endemic areas.
- Because viral etiologies of myocarditis are common, it should be remembered that patients may give a history of a recent febrile illness, either upper respiratory or gastrointestinal.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Failing to consider the diagnosis of myocarditis, especially in patients with more severe presentations, may be costly. The disease may be mistaken for ACS, viral syndrome, pneumonia, and fatigue associated with co-morbid conditions.

Mimics

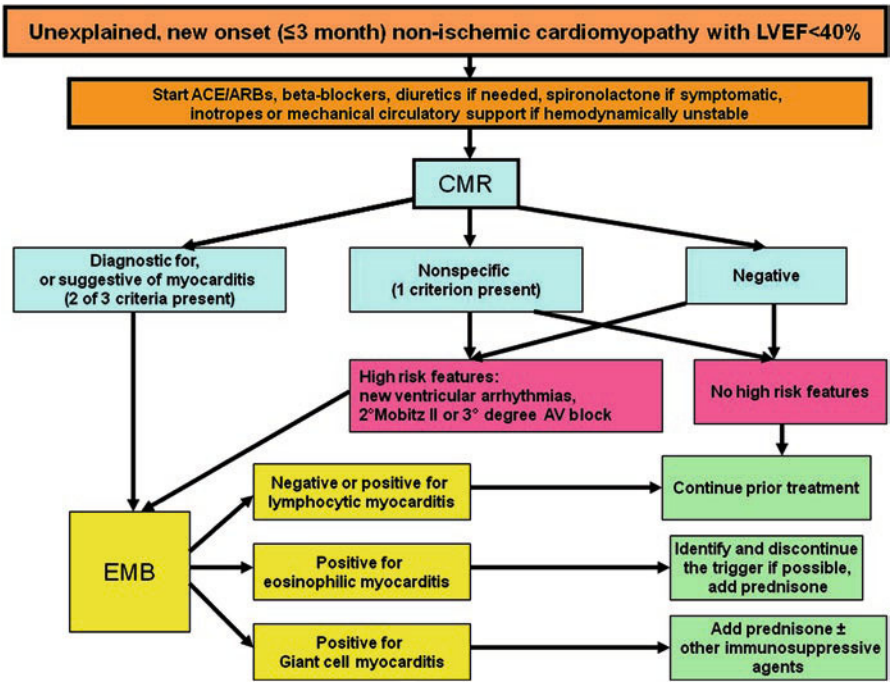
- Many of the mimics and causes of myocarditis are themselves treatable. Preoccupation with such management may lead the clinician to overlook the specific myocardial involvement.

Time-Dependent Interventions

- Patients who present with fulminant heart failure, symptoms consistent with ACS, a pneumonia-like syndrome, or significant arrhythmias must be quickly evaluated and stabilized as the work-up proceeds.

Overall Principles of Treatment

- Treatment of myocarditis is in large part dependent on the cause. Usually—but not always—treating the etiology improves the patient's myocardial function.
- Treat infections if possible (with viral myocarditis, only supportive therapy may be feasible)
- Remove the offending agent/drug if it can be identified
- Treat heart failure, if present, with diuretics, nitrates, and inotropes as needed.

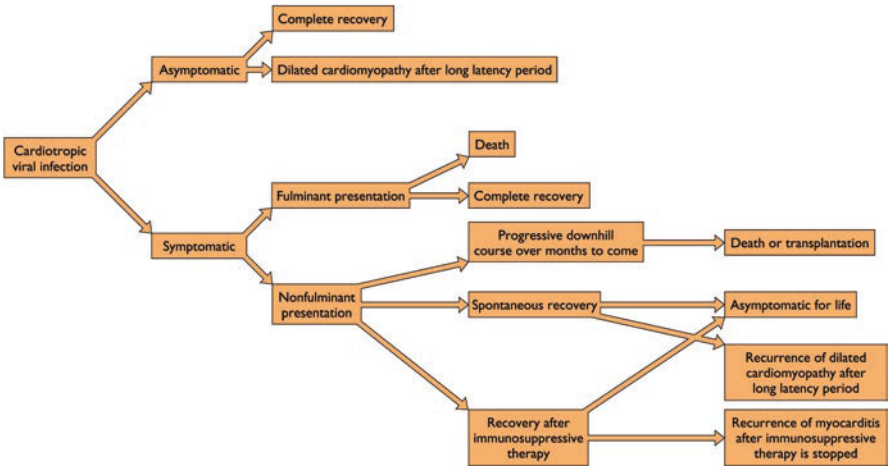


Algorithm for diagnostic work-up and treatment of myocarditis. CMR cardiac magnetic resonance, LVEF left ventricular ejection fraction, EMB endomyocardial biopsy. [Guglin M, Nallamshetty L. Myocarditis: diagnosis and treatment. Curr Treat Options Cardiovasc Med. 2012 Dec;14(6): 637-51; https://doi.org/10.1007/s11936-012-0204-7; Published: 2012-12-01] *Caption adapted from original*

- Specific antiarrhythmic therapy is usually not helpful, but if arrhythmias persist after correction of any oxygenation and electrolyte derangements, antiarrhythmics may be used. Digoxin is not recommended in the treatment of myocarditis.

Disease Course

- Myocarditis is a self-limited disease in most cases.



Natural history of human myocarditis [Herskowitz A, Ansari A. Myocarditis. In: Abelmann WH, editor. Cardiomyopathies, myocarditis, and pericardial disease. Philadelphia: Current Medicine; 1996. (Braunwald E, editor. Atlas of heart diseases; vol. 2).] *Caption from original*

- Dilated cardiomyopathy and chronic heart failure may result from severe cases of acute myocarditis.
- Arrhythmias associated with myocarditis can rarely be fatal.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guidelines

CS Joint Working Group. Guidelines for diagnosis and treatment of myocarditis (JCS 2009): digest version. Circ J. 2011;75(3):734-43. PMID: 21304213. http://www.ncbi.nlm.nih.gov/pubmed/21304213 **

Review

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Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis. 2010 Jan-Feb;52(4):274-88. https://doi.org/10.1016/j.pcad.2009.11.006. PMID: 20109598. http://www.ncbi.nlm.nih.gov/pubmed/20109598 **

Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. Circulation. 2006 Feb 14;113(6):876-90. PMID: 16476862. http://www.ncbi.nlm.nih.gov/pubmed/16476862 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Myocarditis"[Mesh] OR "myocarditis"

Chapter 51
Neuromuscular Disease: Myasthenia Gravis, Guillain-Barré, Amyotrophic Lateral Sclerosis

Charles V. Pollack, Jr. and Jaime Friel Blanck

Name and Synonyms

Neuromuscular Disease, inclusive of:

- myasthenia gravis (MG)
- Guillain-Barre syndrome (GBS)
- amyotrophic lateral sclerosis (ALS) or Lou Gehrig's Disease

This diverse group of neurologic diseases can, through different mechanisms, cause disordered breathing. MG is a disease of the neuromuscular junction, GBS is a demyelinating neuropathy, and ALS is a motor-neuron degenerative disorder.

Incidence/Epidemiology

- MG has an incidence of around 20/100,000 patients. Women are affected more commonly than men, with the typical MG patients being females in their 20s and 30s and males in their 50s and 60s.
- GBS is rare, with an incidence of about 1/100,000 patients. Males are more commonly affected than females, and the incidence increases with age. There have also been occasional transient increases in incidence attributable to the use of specific influenza vaccines.
- ALS is rare, with an incidence of fewer than 3/100,000 patients. Males are somewhat more frequently affected than females.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_51

Differential Diagnosis

- The differential diagnosis for MG includes
  - Botulism
  - Multiple sclerosis (MS)
  - Lambert-Eaton Syndrome

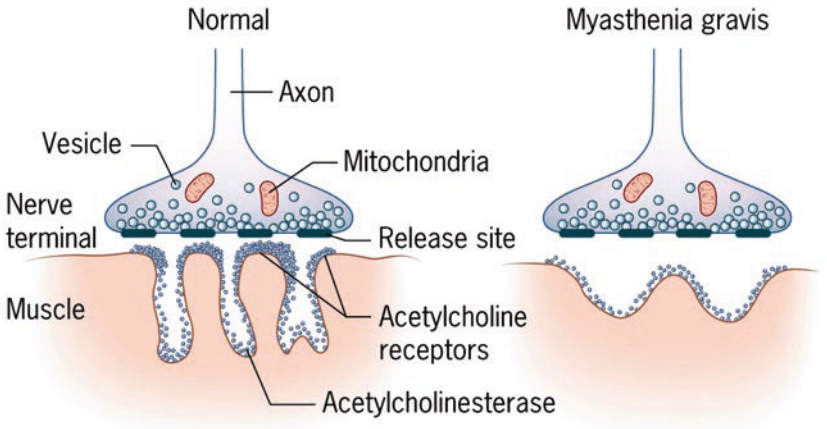
Feature	Myasthenia gravis	Eaton–Lambert syndrome
Most commonly associated malignancy	Thymoma (40%)	Small cell lung cancer (1–3%)
Antibody target	Acetylcholine receptor	Voltage-gated calcium channel
Area of NMJ affected	Postsynaptic membrane	Presynaptic membrane
Common presenting feature	Ocular and bulbar weakness	Limb weakness, oculomotor sparing
Ocular and bulbar muscle involvement	Common	Rare
Autonomic dysfunction	None	Common
Deep tendon reflexes	Normal	Reduced
Strength improved by	Rest, sleep	Exercise

Myasthenia gravis vs. Lambert–Eaton syndrome. [Chelico L, McRae K. Thymic Surgery and Paraendocrine Syndromes. In: Slinger, MD, FRCPC P, editor. Principles and Practice of Anesthesia for Thoracic Surgery [Internet]. New York, NY: Springer New York; 2011 [cited 2016 Mar 29]. p. 211–23. Available from: http://link.springer.com/10.1007/978-1-4419-0184-2_15] *Caption from original*

- The differential diagnosis for GBS includes
  - Botulism
  - MG
  - MS
  - Spinal cord tumor
  - Lyme disease
- The differential diagnosis for ALS includes
  - Spinal cord disease/tumor/compression
  - Myopathy
  - Lead or mercury poisoning

Pathophysiology and Etiology

- MG is characterized by weakness and rapid fatigability of skeletal muscle. It is a result of ineffective nerve firing activity at the neuromuscular junction (NMJ), which in turn is caused by a decrease in the number of available acetylcholine (ACh) receptors. ACh is the neurotransmitter at the NMJ, and the receptors are decreased in number because of an antibody-mediated autoimmune disorder.



Myasthenia gravis. Myasthenia gravis affects approximately 25,000 patients or 50 to 125 cases per million. Features of myasthenia gravis are weakness (focal or generalized) and skeletal and muscle fatigability, which generally increases with repeated activity and improves with rest. An example is ptosis, which is improved with 3 minutes of eye closure (rest). Approximately three quarters of patients with myasthenia gravis have abnormalities of the thymus (thymic lymphoid hyperplasia [85%] or thymoma [15%]). A thymectomy frequently improves the symptoms of myasthenia gravis, but this has been more common in patients with hyperplasia than with thymoma. [Loehrer Sr, P. Henley, J. Johnson, D. Chapter 30. In: Markman, M, editor: Volume 3: Atlas of Cancer. 1 edition. Philadelphia: Current Medicine Group; 2002. ISBN: 0-7817-4280-3] *Caption adapted from original*

- GBS is a demyelinating neuropathy. Myelin is a protein that covers nerve sheaths and greatly increases nerve conduction velocities. GBS is a "polyneuropathy," meaning that many peripheral nerves in the body are affected. The muscles at the periphery—in the hands and feet—are affected first, because the nerve sheaths supplying them are the longest, and therefore the problems with "insulation" are more pronounced there. This is probably an autoimmune process, but the specific etiology remains obscure.
- ALS is the most common form of progressive and likely the most devastating of the motor neuron diseases. ALS gradually affects both upper motor neurons (motor cortex and corticospinal cells) and lower motor neurons (anterior

horn cells in the spinal cord and brainstem motor cells that innervate the bulbar muscles). As these nerve cells die, the innervated muscle fibers atrophy and lose function.

Presentation

Typical/"Classic"

- MG typically presents with:
  - Extraocular muscle weakness leading to ptosis.

Left-sided ptosis in a patient with myasthenia gravis before initiation of therapy with cholinergic drugs and immunosuppressants. [Finsterer J. Ptosis: Causes, Presentation, and Management. Aesthetic Plastic Surgery. 2003 Jun 1;27(3):193–204.] *Caption from original*

- Bulbar and facial muscle weakness.
- Inability to hold head up.
- Easy fatigability of routine and repetitive tasks.
- Exacerbations of this chronic disease may be prompted by such diverse stimuli as:
  - Acute illness
  - Medications
  - Emotional stress
  - Menstruation
  - Immunization
- GBS typically presents with the following characteristics:
  - "Ascending weakness"; that is, feet before hands, and then extremities toward trunk. The cranial nerves are usually affected later in the course, leading to double vision and difficulties speaking and swallowing.

- Ultimately, in severe cases, patients are quadriplegic and have ventilatory failure.
- Most patients complain of numbness or burning paresthesias prior to the onset of weakness.
- More than half of patients with GBS complain of severe pain, especially in proximal muscle groups.
- Autonomic nerves are often involved as GBS progresses, leading to orthostatic hypotension, tachy- or bradycardia, and facial flushing.
- Cardiac arrhythmias may develop.
- There is usually a benign viral prodrome 2–4 weeks before the onset of weakness.

- ALS typically presents with:
  - Progressive loss of strength and function.
  - Limb involvement first, then with bulbar involvement (the latter manifests as difficulty swallowing and voice changes).
  - "Pseudobulbar" manifestations—exaggerated emotions, sometimes inappropriate emotional responses.

Atypical Presentations

- MG may sometimes present with:
  - Isolated muscle weakness and no extraocular or bulbar involvement.
  - Acute respiratory failure without preceding ocular or bulbar worsening.
- GBS may sometimes present with:
  - Weakness in the cranial nerves *prior to* the extremities. This is called the Miller-Fisher variant of GBS.
  - Asymmetric or incomplete weakness, which may delay consideration of the diagnosis.
  - No history of viral prodrome or influenza vaccination.
- ALS may sometimes present with:
  - Bulbar involvement preceding limb involvement.
  - Numbness and paresthesias (sensory function is ordinarily preserved in ALS).

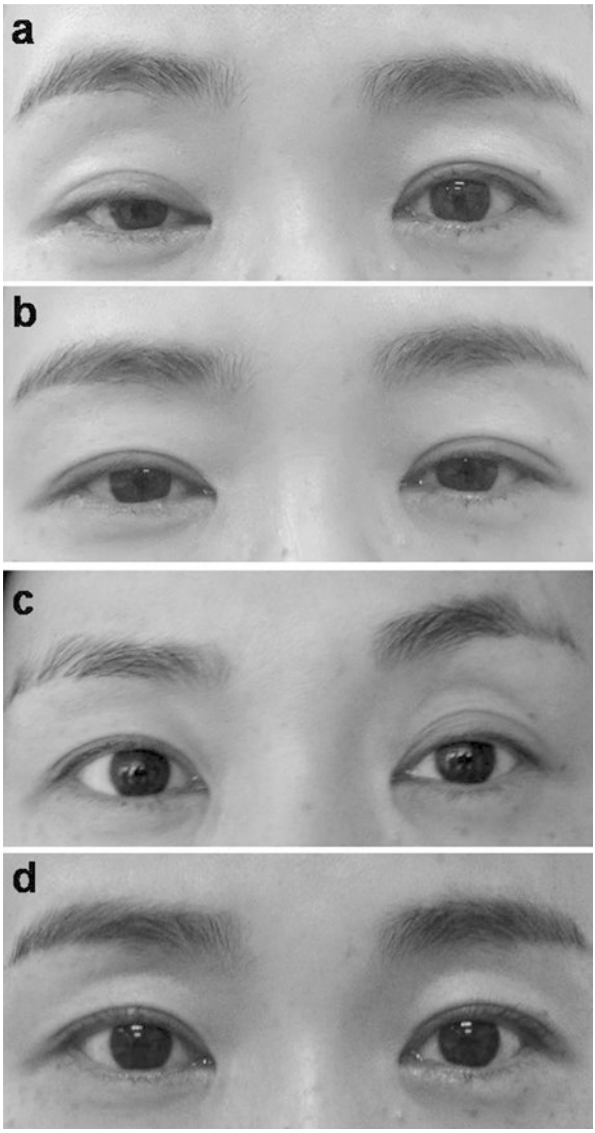
Primary Differential Considerations

- These are unusual diseases. The differential diagnosis for each is usually limited to other neural or neuromuscular diseases as described above. These patients do not ordinarily present with primary cardiorespiratory symptoms.

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis of MG is confirmed with laboratory demonstration of antibodies to acetylcholine receptors. Electromyography (EMG) and nerve conduction studies (NCS) are also used to confirm the diagnosis.
- The edrophonium test can be performed at the bedside and has reasonably high sensitivity.



Ptosis in a patient with ocular myasthenia gravis. The patient showed right ptosis when referred to our hospital (a). Edrophonium injection improved right ptosis and induced minor left ptosis (b). After intravenous methylprednisolone therapy, right ptosis was satisfactorily relieved, however, left ptosis got appeared (c). Left ptosis was resolved after 1-month observation without additional immunosuppressive therapy (d)[Nishijima H, Ueno T, Suzuki C, Baba M, Tomiyama M. Eyelid ptosis enhanced after steroid pulse therapy in ocular myasthenia gravis: a case report. Neurological Sciences. 2015 Jun;36(6):1055–6.] *Caption from original*

- On physical exam the disease is characterized by weakness in repetitive activities that improves with rest.
- The "ice bag test" for ptosis may be used to evaluate for MG.
- The diagnosis of GBS cannot be confirmed at the bedside. EMG and NCS are helpful, as is evaluation of the cerebrospinal fluid.
- The diagnosis of ALS is often challenging. EMG and NCS are useful. There are no confirmatory bedside tests.

Factors That Suggest Diagnosis

- MG:
  - Positive edrophonium test
  - Positive ice-bag test
  - Ptosis in the absence of thyroid disease
  - Ventilator capacity can be assessed by testing negative inspiratory force (NIF)
- GBS:
  - Symmetric ascending weakness
  - Viral-like prodrome or immunization 2-4 weeks prior to onset of weakness

Viral infections
Cytomegalovirus
Influenza
Parainfluenza
Epstein-Barr virus
Cocksackie
Echo
Measles
Mumps
Rubella
Herpes simplex virus
Herpes Zoster virus
Hepatitis A and B virus
Human immunodeficiency virus
Bacterial and other infections
Campylobacter jejuni
Mycoplasma pneumoniae
Typhoid
Shigella
Legionella pneumonia
Cyclospora
Systemic illnesses
Hodgkin's lymphoma
Thyroid disease
Addison's disease
Leukemia
Paraproteinemia
Solid tumors (lung cancer)
Sarcoidosis
Systemic lupus erythematosus
Surgery
Trauma
Vaccination
Pregnancy

Antecedent illnesses associated with Guillain-Barré syndrome. [Piccione EA, Salame K, Katirji B. Guillain-Barré Syndrome and Related Disorders. In: Katirji B, Kaminski HJ, Ruff RL, editors. Neuromuscular Disorders in Clinical Practice [Internet]. New York, NY: Springer New York; 2014 [cited 2016 Mar 29]. p. 573–603. Available from: http://link.springer.com/10.1007/978-1-4614-6567-6_28] *Caption from original*

- ALS:
  - "slapping gait"
  - Involuntary emotional exaggerations

	Tongue strength				*p*
	Abnormal ($n = 20$) median (range)/ n (%)		Normal ($n = 34$) median (range)/ n (%)		
Sex (male)	7	(35)	18	(51)	0.26*
Onset site (bulbar)	13	(65)	6	(18)	<0.00*
Bulbar symptoms (presence)	17	(85)	9	(32)	<0.00*
Bulbar signs (presence)	15	(75)	5	(15)	<0.00*
Gastrostomy (presence)	12	(60)	14	(41)	0.09*
MPT (<10 sec)[a]	6	(35)	5	(17)	0.28*
Age at diagnosis (year)	66.0	(20.0–80.0)	63.5	(40.0–79.0)	0.52**
Time from symptoms to diagnosis (month)	12.0	(6.0–60.0)	10.0	(4.0–60.0)	0.70**

Clinical and demographic characteristics of the 54 patients with amyotrophic lateral sclerosis [From article: Prognostic value of decreased tongue strength on survival time in patients with amyotrophic lateral sclerosis. Journal of Neurology. 2012 Nov;259(11):2360–5. https://doi.org/10.1007/s00415-012-6503-9, at http://link.springer.com/article/10.1007%2Fs00415-012-6503-9; by J. G. Weikamp, H. J. Schelhaas, J. C. M. Hendriks, B. J. M. de Swart, A. C. H. Geurts, © The Author(s) 2012; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Factors That Exclude Diagnosis

- In patients with weakness, no historical or physical examination factors can completely exclude these diagnoses at all stages.

Ancillary Studies

Laboratory

- For MG:
  - Ordinary baseline lab studies are not helpful.
  - Serologic testing for antibodies to ACh receptors should be performed.

- For GBS:
  - Ordinary baseline lab studies are not helpful.
  - Evaluate cerebrospinal fluid (from lumbar puncture) for protein levels, which are ordinarily high (unless patient has HIV) in GBS.
  - Liver function tests are abnormal in one-third to one-half of GBS patients.
- For ALS:
  - Ordinary baseline lab studies are not helpful.

Imaging

- MG:
  - Chest radiography or CT chest may show a thymoma. A normal chest radiograph does not exclude MG.
- GBS:
  - MRI with gadolinium contrast may show enhancement at the nerve root, but this is not a consistent finding in patients diagnosed with GBS.
- ALS:
  - Imaging studies are needed only to exclude other etiologies of weakness.

Other

- MG:
  - As above, the following tests are potentially useful:
  - Ice-pack test
  - EMG
  - NCS
  - serology
- GBS:
  - Serology
  - Lumbar puncture
  - EMG
  - NCS
- ALS:
  - Genetic testing (familial in a small number of cases)
  - EMG
  - NCS

Special Populations

Age

- MG:
  - MG can occur at any age.
  - It typically occurs earlier in females than males.
- GBS:
  - Incidence increases with increasing age
- ALS:
  - Slightly more common in men than in women.

Co-morbidities

- MG:
  - The most common co-morbidities are thyroid disease, lupus, and rheumatoid arthritis.
- GBS:
  - The most common co-morbidities are COPD, diabetes, and obesity.
- ALS:
  - The most common co-morbidity is cardiovascular disease.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- These are unusual diseases. Early consideration to the diagnosis should be given or it may be missed on multiple presentations.

Mimics

- Other neuropathies
- Other neuromuscular disorders
- Botulism

Time-Dependent Interventions

- Time-dependent interventions are present only in the rare case of presentation with ventilator failure.

C	Conduction block, bradycardia, asystole
R	Rapid progression of motor weakness
I	Infection
T	Tachyarrhythmias
I	Intensive care monitoring of respiratory and autonomic dysfunction
C	Complications of critical illness: pulmonary embolism, myocardial infarction
A	Airway: ventilatory failure, bulbar weakness
L	Labile blood pressure: hypertension/hypotension

The word "critical" is used as a mnemonic for the different indications

Clinical Indications for admission to the ICU in patients with Guillain-Barré Syndrome [Cordova FC, Lim MRC, Criner GJ. Neuromyopathies in the Critically Ill. In: Criner GJ, Barnette RE, D'Alonzo GE, editors. Critical Care Study Guide [Internet]. New York, NY: Springer New York; 2010 [cited 2016 Mar 29]. p. 541–70. Available from: http://link.springer.com/10.1007/978-0-387-77452-7_29] *Caption from original*

Overall Principles of Treatment

- MG:
  - MG is a chronic disease.
  - Symptoms can be generally managed with anticholinesterase medications and immunosuppressants.
  - Plasmapherseis can be used in severe or recurrent exacerbations.
  - Thymectomy may be considered.
  - Intravenous immunoglobulin is generally beneficial
- GBS:
  - GBS is generally managed with support only, although this may entail prolonged mechanical ventilation.
- ALS:
  - Treatment of ALS is supportive.

Disease Course

- MG:
  - With close medical management, MG can generally be well tolerated by patients.
- GBS:
  - The course of GBS may be prolonged, but patients usually substantially recover.
- ALS:
  - ALS is an inexorably fatal disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: “Neuromuscular Diseases”[tiab] OR “neuromuscular disease”[tiab] “Myasthenia Gravis”[Mesh] OR “Amyotrophic Lateral Sclerosis”[Mesh] OR “Guillain-Barre Syndrome”[Mesh] OR “Myasthenia Gravis” OR “Amyotrophic Lateral Sclerosis” OR “Guillain-Barre Syndrome”

Chapter 52
Noncardiogenic Pulmonary Edema

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Noncardiogenic Pulmonary Edema (NCPE)

- Acute respiratory distress syndrome (ARDS), high-altitude pulmonary edema, neurogenic pulmonary edema, reperfusion pulmonary edema, re-expansion pulmonary edema

Incidence/Epidemiology

- Less common than cardiogenic pulmonary edema
- ARDS incidence is uncertain but has been on the decline.
- Overall mortality is 50–75 % and prognosis varies with the patient's age, the cause of ARDS, and the number of organs involved.
- No single variable has been found to predict patient outcome.
- Even the degree of hypoxemia has not been valuable in this regard.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_52

Differential Diagnosis

- Cardiogenic pulmonary edema
- High-altitude pulmonary edema
- Neurogenic pulmonary edema
- Reperfusion pulmonary edema
- Re-expansion pulmonary edema
- Opioid overdose
- Salicylate toxicity
- Pulmonary embolism
- Viral infections
- Pulmonary veno-occlusive disease
- Eclampsia
- Inhaled toxins
- Aspiration
- Disseminated intravascular coagulation
- Acute hemorrhagic pancreatitis
- Sepsis
- Smoke inhalation
- Oxygen toxicity

Pathophysiology and Etiology

- The clinical coincidence of bilateral alveolar infiltrates causing hypoxemia in the absence of pneumonia or congestive heart failure
- It is caused by various disorders responsible for protein and fluid accumulation in the alveoli.
- Unlike cardiogenic pulmonary edema, it is not caused by high pulmonary capillary pressure.
- Most common mechanism is an increase in pulmonary capillary permeability and elevated intravascular pressure.
- The major cause of NCPE is ARDS, followed by high-altitude and neurogenic pulmonary edema.
- A subset of NCPE, neurogenic pulmonary edema, may occur after seizure or stroke and is thought to be centrally mediated.

Presentation

Typical/"Classic"

- Patients classically present with profound dyspnea and diaphoresis.
- Onset often is sudden.

- Anxiety due to hypoxemia.
- Cough is common.
- Tachypnea and tachycardia.

Atypical

- Gradual onset (over 24 hours) is less common.
- Patients may complain only of paroxysmal nocturnal dyspnea or orthopnea.
- Chest pain more predominant than dyspnea would be atypical but has been reported.

Primary Differential Considerations

- Myocardial ischemia
- Pneumothorax
- Pulmonary edema of other causes (cardiogenic, neurogenic)
- Pulmonary embolism
- ARDS

History and Physical Exam

Findings That Confirm Diagnosis

- There are no clinical findings that confirm NCPE specifically; it is a combined clinical and radiographic diagnosis.

Factors That Suggest Diagnosis

- Earliest sign is increased respiratory rate.
- Shortness of breath is the most common symptom.
- A pulmonary artery wedge pressure less than 18 mm Hg favors NCPE over cardiogenic pulmonary edema.
- NCPE usually has bounding pulses, no gallop, and no jugular venous distention.
- Fine inspiratory rales are noted.
- Cough with frothy sputum may be present.

Factors That Exclude Diagnosis

- No clinical findings can exclude NCPE, but clear lung fields on auscultation make it unlikely.

Ancillary Studies

Laboratory

- B-type natriuretic peptide (BNP) has been used to distinguish heart failure from lung disease.
  - Intermediate values are not helpful.
  - Role of biomarker in pulmonary edema has limited utility.
- In NCPE, the ratio of pulmonary edema fluid protein to plasma protein concentration is 0.7 or greater.

Electrocardiography

- Usually does not show signs of ischemia

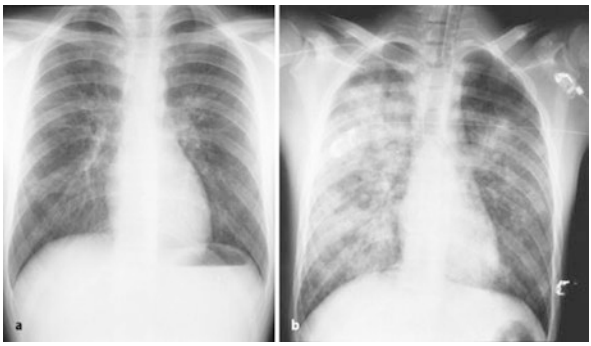
Imaging

- Chest x-ray:
  - Usually a normal cardiac silhouette.
  - Bilateral pulmonary edema, frequently in a "butterfly" pattern, is a consistent finding.
  - Air bronchograms often are seen, but Kerley lines are not.

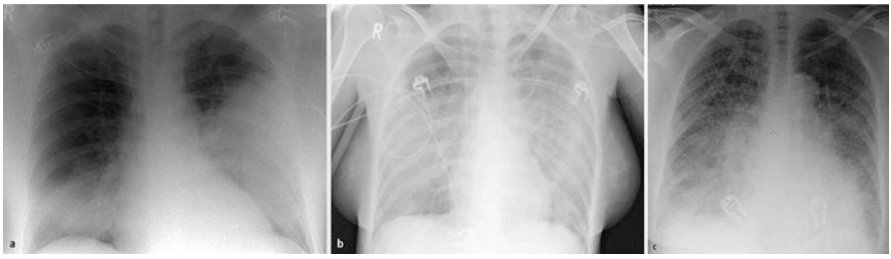
Cardiogenic	Noncardiogenic
Lower lobes	Peripheral
Perihilar	Patchy
No air bronchograms	Air bronchograms
Large heart and vascular pedicle	No cardiovascular enlargement
May be asymmetric in COPD	May be asymmetric in COPD*

*chronic obstructive pulmonary disease

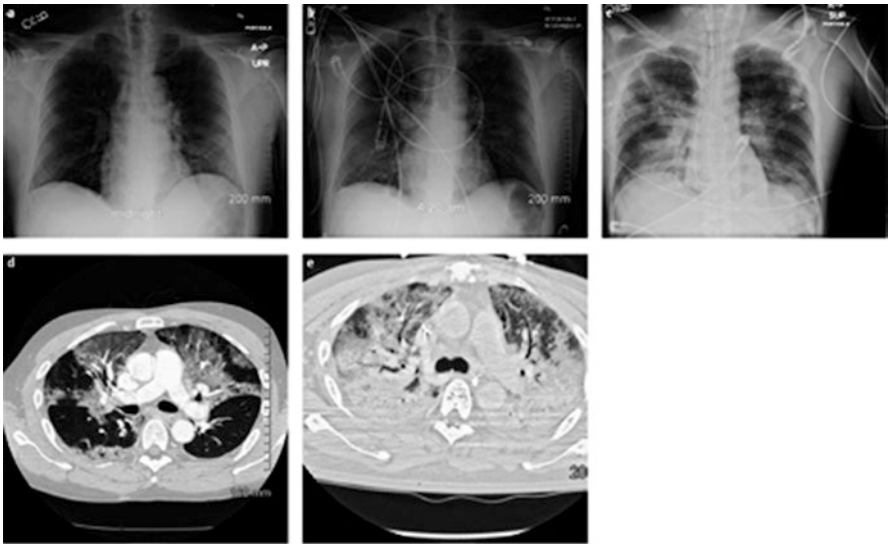
Chest radiograph in cardiogenic versus noncardiogenic pulmonary edema. [Vilar J, Andreu J. The lung parenchyma: radiological presentation of alveolar pattern. In: Coche EE, Ghaye B, de Mey J, Duyck P, editors. Comparative interpretation of CT and standard radiography of the chest [Internet]. Berlin Heidelberg: Springer; 2011 [cited 2015 Aug 13]. p. 221–45. Available from: http://link.springer.com/10.1007/978-3-540-79942-9_9] *Caption from original*



a. ARDS stage I. b. ARDS stage II. [Häuser H, Wohlgemuth WA. Bildgebende diagnostik des thorax bei intensivpatienten. Der Anaesthesist. 2005 Aug;54(8):827–48.]



The most common causes of hypoxemic ARI: a severe, community-acquired pneumonia; b ARDS during sepsis; c cardiogenic pulmonary edema [Westhoff M, Rosseau S. Nichtinvasive beatmung bei akuter respiratorischer insuffizienz: indikationen und grenzen. Der Pneumologe. 2010 Mar;7(2):89–99.] *Caption translated from original*



Acute respiratory distress syndrome (ARDS) following abdominal infection: imaging progression. a Relatively normal chest X-ray 12 h after abdominal surgery for sepsis. The patient was starting to experience dyspnea and some hypoxia. A normal chest X-ray is frequent in the early symptomatic stages of ARDS. b Four hours later, there is mild but definite interstitial thickening. c Thirty hours later, there is a dense bat's-wing consolidation in the perihilar areas. A Swan-Ganz catheter was inserted to rule out heart failure as a cause of the edema. d A computed tomography scan on day 3 shows the antigravity distribution of the ground-glass opacification that appeared to be perihilar on the chest X-ray. e In a different patient, 5 days after onset of ARDS, the edema is visible ventrally, whereas there is atelectasis, dorsally, in the gravity-dependent areas [Goodman LR. Imaging the intensive care patient. In: Hodler J, von Schulthess GK, Zollikofer CL, editors. Diseases of the heart, chest and breast 2011–2014 [Internet]. Milan: Springer; 2011 [cited 2015 Aug 13]. p. 66–9. Available from: http://link.springer.com/10.1007/978-88-470-1938-6_10] *Caption from original*

- CT:
  - CT scan is not required to make the diagnosis of NCPE.
  - When CT is performed, the scan looks similar to that of ARDS.

Special Populations

Age

- Because NCPE is a secondary event, it may occur across the age spectrum, but in general, it is more likely in elderly patients.

- In the pediatric patient, NCPE has been associated with any form of upper airway disease, including croup and epiglottitis, and choking episodes.

Co-morbidities

- Eclampsia in pregnancy may cause pulmonary edema.

Pitfalls in Diagnosis

- At times, both cardiogenic and NCPE may occur simultaneously.

Critical Steps Not to Miss

- Although pulmonary edema is the most prominent feature of ARDS, the two terms should not be used interchangeably.
- Hypoalbuminemia alone is not a cause of pulmonary edema.

Mimics

- The primary mimic of NCPE is cardiogenic pulmonary edema. Initial management of the two illnesses is similar and focuses on supporting oxygenation and reducing preload.

Time-Dependent Interventions

- Try to maintain a $Pa0_2$ of 60 mm Hg through use of oxygen and mechanical ventilation.

Overall Principles of Treatment

- Treatment varies depending on the underlying pathophysiology.
  - For example, descent to a lower altitude is the mainstay of treatment for high-altitude pulmonary edema.

- Currently, no known measures exist to correct the permeability abnormality in ARDS.
- Treatment is largely supportive and aimed at ensuring adequate ventilation and oxygenation.
  - Goal of treatment is to keep the $Pa0_2$ >60 mm Hg without injuring lungs with excessive O_2 or volutrauma/barotrauma.
- Lowering the pulmonary artery wedge pressure with diuretics and fluid restriction may improve pulmonary function in ARDS.
- Positive pressure ventilation is useful in severe NCPE.

Disease Course

- NCPE commonly develops within 24 hours of onset of the initial insult.
  - Presentation may be delayed 5 days.
- Begins with mild signs and symptoms that may progress rapidly to hypoxic respiratory failure
- Most patients require a high FiO_2 and will require mechanical ventilation.
- Ventilator-associated pneumonia is a frequent complication of ARDS.
- In severe cases, pulmonary scarring and diffuse alveolar damage may occur, especially if mechanical ventilation is used.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Noncardiogenic pulmonary edema" OR "NCPE" OR "Non cardiogenic pulmonary edema"

Chapter 53
Peptic Ulcer Disease

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Peptic Ulcer Disease (PUD)

- Gastric or Duodenal Ulcers

Incidence/Epidemiology

- Peptic ulcer disease (PUD) affects about 4 million adults in the United States, with an incidence of 0.09–0.3 % per patient year.
- Estimated annual cost to the health care system is around $15 billion, with an overall economic effect on the economy for health care, lost work, etc. of $50 billion.
- People who are infected with *Helicobacter pylori* have a lifetime prevalence of up to 20 %. Those who are uninfected have a lifetime prevalence of 5–10 %.
- The incidence of PUD has been falling steadily in the United States and all other developed nations.
- At one time, there was a decided male predominance; now, the rate is about equal in both genders.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_53

Differential Diagnosis

- The differential diagnosis of PUD is broad and includes all causes of chest and upper abdominal pain. All the causes of acute chest and abdominal pain, especially those that are immediately life threatening (e.g., acute myocardial infarction, pulmonary embolism, aortic dissection, perforated ulcer, perforated esophagus, acute cholecystitis, acute pancreatitis) must be considered first.
- In addition, there is a syndrome called non-ulcer dyspepsia that presents very similarly to PUD, but in which no ulcer or gastritis is found. The official criteria for diagnosis of non-ulcer dyspepsia is a chronic, recurrent upper abdominal pain or discomfort for at least 1 month that is present at least 25 % of the time and in which there is no evidence of organic disease. It is thought this condition may result from ulcers that are too small to be seen, acid hypersecretion, bile reflux, malabsorption, motility disorders, or sphincter of Oddi dysfunction, or that it may be functional.
- Gastritis (gastric mucosal inflammation without ulcer formation) also may have a presentation identical to that of PUD.
- *Peptic ulcer disease* refers to ulcers that develop within either the stomach (gastric) or duodenum. Although there may be subtle differences in presentation, risk factors, and natural history, the treatment remains very similar for both. Therefore, it often is not immediately necessary to refine the diagnosis to one or the other before beginning empiric treatment.

Pathophysiology and Etiology

- The upper gastrointestinal (GI) tract is regularly bathed in acid. Injury to the mucosal lining allows damage to underlying cells, which may result in ulceration and bleeding. There are a limited number of causes of PUD, including:
  - Infection with *H. pylori*, a bacterium whose growth disrupts the acid-protective barrier of the gastric mucosa:
    - *H. pylori* is more common in lower socioeconomic strata.
    - It is spread by the fecal–oral route.
    - It increases the risk of gastric carcinoma.
  - Use and abuse of nonsteroidal anti-inflammatory drugs (NSAIDs), which reduces mucosal protection from acid via interference with prostaglandin production in the upper GI mucosa.
  - Toxins such as cigarette smoke exposure and regular alcohol ingestion.
  - Hyperacidic states such as chronic anxiety.
  - Gastrin-producing tumor (Zollinger–Ellison syndrome) is a rare cause.

Presentation

Typical/"Classic"

- Chest or upper abdominal pain is typical, with the pain often described as burning or gnawing.
  - Pain may radiate to the back.
  - Pain usually occurs 2 to 3 hours after eating, at bedtime, or in the early morning hours, when gastric acid production levels are high.
  - Pain usually is relieved by eating.
  - Antacids often relieve the pain, but neither relief nor the absence of relief is pathognomonic.

Atypical

- Patients may describe only back pain; some duodenal ulcers may present with right scapular or shoulder pain.
- Patients may describe increased belching, but this is more typical of biliary tract disease.
- Vomiting is an atypical symptom of PUD. The presence of vomiting should raise concern for another diagnosis.
- Other symptoms that occasionally may be attributed to PUD but that should raise concerns for other conditions, especially malignancy, include weight loss, early satiety, dysphagia, unexplained anemia, and occult GI bleeding. Patients with any of these symptoms and those older than 55 years at first diagnosis should undergo endoscopy to exclude malignancy as the cause.

Primary Differential Considerations

- Patients with signs and symptoms of PUD may warrant an evaluation for:
  - Acute coronary syndrome
  - Esophagitis
  - Cholelithiasis and cholecystitis

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination features that confirm the diagnosis.
- The diagnosis can be confirmed only by direct visualization through endoscopy.

Factors That Suggest Diagnosis

- A history as discussed in the presentation section may suggest the diagnosis.
- The absence of another cause of chest or abdominal pain may suggest the diagnosis.
- The initial diagnosis usually is clinical and treatment is started empirically, unless any of the "red flag" symptoms discussed under the atypical presentation section are present.

Factors That Exclude Diagnosis

- There are no historical or physical examination factors that exclude the diagnosis.
- Patients diagnosed with another cause of the initial symptoms may be acutely ill, which in and of itself is a risk factor for PUD.
- PUD may coexist with any other diagnosis.
- The only factor that excludes the diagnosis is a normal endoscopy that fully visualizes the stomach and duodenum.

Ancillary Studies

Laboratory

- Lab tests should include a complete blood count to look for anemia; measurement of serum electrolyte, blood urea nitrogen, and creatinine levels; liver function tests; and lipase testing to help evaluate for other diagnoses. In patients presenting with chest pain, cardiac biomarker testing may be indicated.
- Patients with a presumptive diagnosis of PUD should be tested for *H. pylori* infection.
    - The method for *H. pylori* testing depends on whether empiric treatment is to be initiated or the patient is proceeding to endoscopy.
    - Noninvasive tests for *H. pylori* include serologic testing for IgG. These tests have a low sensitivity and specificity; therefore, the positive predictive value of a positive test in a low-prevalence population (e.g., most of the United States) is low, limiting the usefulness of these tests. Urea breath tests have sensitivity and specificity above 95 %, so they are used frequently.

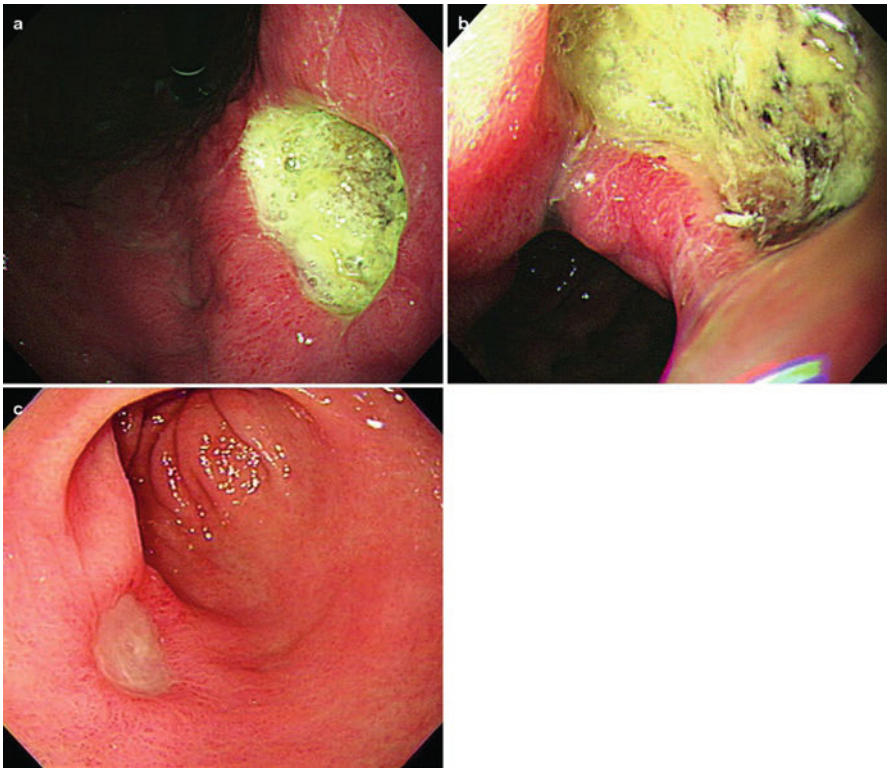
Stool antigen (Ag) tests to look for *H. pylori* have sensitivity and specificity above 90 %; these tests commonly are used to confirm cure 4 weeks after treatment completion.

- Invasive, endoscopically based tests include the rapid urease test, direct histologic examination, polymerase chain reaction tests, and culture. The only one of these tests routinely used in clinical practice is the rapid urease test. The others are expensive, as well as time and resource intensive; therefore they usually are used only used in research settings.
- If the clinical suspicion for infection is high, one positive test confirms infection. However, one negative test does not exclude infection, and a second test should be performed.
- In cases of acute bleeding, the biopsy rapid urease and stool Ag tests lack specificity; therefore, if testing must be done in this setting, the urea breath test should be used.

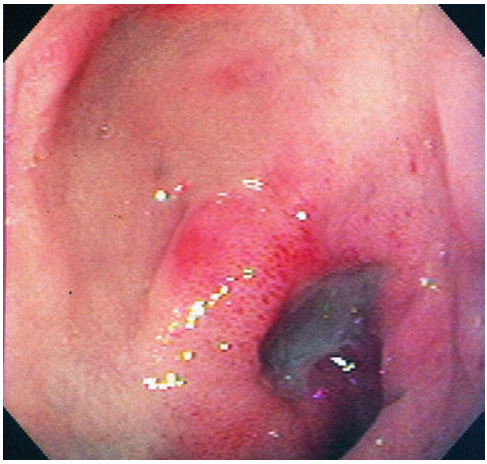
Imaging

- There are no diagnostic imaging findings of PUD
- Upper GI endoscopy is the diagnostic study of choice.

Gastric ulcer with greenish adherent exudate. [Graham D, Genta R. Helicobacter pylori. In: Lorber B, editor. Intra-abdominal infections, hepatitis and gastroenteritis. Philadelphia: Current Medicine; 1996. (Mandell GL, editor. Atlas of infectious diseases; vol. 7). ISBN 0-443-07730-4]



Endoscopic features of active gastric ulcers. (a) well-circumscribed and deeply penetrating active ulcer (b) Black pigmented area shown on close observation (c) clean ulcer base and a regular shape ulceration without exudate. [Lee SK. Gastritis and gastric ulcers. In: Chun HJ, Yang S-K, Choi M-G, editors. Clinical gastrointestinal endoscopy [Internet]. Berlin, Heidelberg: Springer; 2014 [cited 2015 Aug 28]. p. 99–122. Available from: http://link.springer.com/10.1007/978-3-642-35626-1_8] *Caption from original*



Duodenal ulcer. A deep duodenal ulcer is seen. There is surrounding inflammation with hyperemia of the mucosa. [Wilcox MC. Helicobacter pylori. In Feldman M, editor. Stomach and duodenum. Philadelphia: Current Medicine; 1996. Chapter 7. (Feldman M, editor. Gastroenterology and hepatology; vol. 3). ISBN: 0-443-07843-2]

Special Populations

Age

- The incidence of PUD increases with age.
- The incidence of upper GI bleeding from PUD increases with age.
- PUD rarely is encountered in the pediatric population.
- Younger children often present with emesis, hemorrhage, and perforation.
- *H. pylori* rarely is seen in pediatric patients; in this age range, most PUD is idiopathic.

Co-morbidities

- Patients who are acutely ill, such as those in intensive care units, have higher rates of PUD.
- Patients who smoke, abuse alcohol, use NSAIDs daily, or are maintained on glucocorticoids also are at higher risk for PUD.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is important not to ascribe symptoms to PUD prematurely, before evaluating for the more immediately life-threatening conditions that may present similarly.

Mimics

- The pain from PUD may mimic the pain of cardiac ischemia.
- Non-ulcer dyspepsia
- Gastritis
- Esophageal disorders

Time-Dependent Interventions

- If patients present with upper GI bleeding, they must be resuscitated and stabilized urgently.

Overall Principles of Treatment

- Most patients can be started empirically on a trial of acid suppression based on the history and normal physical examination findings. Most patients will be started on proton-pump inhibitors (PPIs), as these provide much greater acid suppression than H2-blockers.
- Patients with any of the red-flag symptoms discussed in the atypical presentation section, as well as those over 55 years old, should be referred to a gastroenterologist for endoscopy to confirm the diagnosis and rule out malignancy.
- Patients who test positive for *H. pylori* must be given appropriate antibiotic treatment to eradicate the infection. The recurrence rate of *H. pylori*–associated ulcers is 65–95 % if the infection is not eradicated and <10 % if it is. Generally, patients are started on a combination of antibiotics (most commonly, clarithromycin and amoxicillin) with a PPI. The antibiotics are given for 2 weeks; there is controversy over whether to discontinue the PPI at 2 weeks as well.
- All patients should be counseled on lifestyle modifications as appropriate. Patients who smoke cigarettes should try to quit, alcohol intake should be limited, and NSAIDs, including aspirin, should be avoided.

Disease Course

- Ulcers that are not treated, those that are poorly treated, and, rarely, even those that are adequately treated may develop many complications. Some may be life threatening.
- In order of prevalence, the most common complications of PUD are:
  - Bleeding, typically from inflamed mucosa, but sometimes from ulcer erosion into a submucosal vessel.
    - Hemorrhage is more common in older patients.
  - Perforation of the ulcer through the gastric or duodenal wall, most often posteriorly and causing severe back pain from leakage of gastric contents.
  - Gastric outlet obstruction from chronic inflammation and swelling around an ulcer in or near the gastroduodenal junction.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Koletzko S, Jones NL, Goodman KJ, Gold B, Rowland M, Cadranel S, Chong S, Colletti RB, Casswall T, Elitsur Y, Guarner J, Kalach N, Madrazo A, Megraud F, Oderda G; H pylori Working Groups of ESPGHAN and NASPGHAN. Evidence-based guidelines from ESPGHAN and NASPGHAN for Helicobacter pylori infection in children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):230-43. https://doi.org/10.1097/MPG.0b013e3182227e90. PMID: 21558964. http://www.ncbi.nlm.nih.gov/pubmed/21558964 **

ASGE Standards of Practice Committee, Banerjee S, Cash BD, Dominitz JA, Baron TH, Anderson MA, Ben-Menachem T, Fisher L, Fukami N, Harrison ME, Ikenberry SO, Khan K, Krinsky ML, Maple J, Fanelli RD, Strohmeyer L. The role of endoscopy in the management of patients with peptic ulcer disease. Gastrointest Endosc. 2010 Apr;71(4):663-8. https://doi.org/10.1016/j.gie.2009.11.026. PMID: 20363407. http://www.ncbi.nlm.nih.gov/pubmed/20363407 **

Meta-Analysis

Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007 Mar;82(3):286-96. PMID: 17352364. http://www.ncbi.nlm.nih.gov/pubmed/17352364

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Holle GE. Pathophysiology and modern treatment of ulcer disease. Int J Mol Med. 2010 Apr;25(4):483-91. PMID: 20198295. http://www.ncbi.nlm.nih.gov/pubmed/20198295

Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet. 2009 Oct 24;374(9699):1449-61. https://doi.org/10.1016/S0140-6736(09)60938-7. PMID 19683340. http://www.ncbi.nlm.nih.gov/pubmed/19683340 **

Ramakrishnan K, Salinas RC. Peptic ulcer disease. Am Fam Physician. 2007 Oct 1;76(7):1005-12. Review. PMID: 17956071. http://www.ncbi.nlm.nih.gov/pubmed/17956071 **

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Chelimsky G, Czinn S. Peptic ulcer disease in children. Pediatr Rev. 2001 Oct;22(10):349-55. PMID: 11581488. http://www.ncbi.nlm.nih.gov/pubmed/11581488 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Peptic Ulcer"[Mesh] OR "Peptic ulcer"

Chapter 54
Pericardial Effusion

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Jaime Friel

Name and Synonyms

Pericardial effusion; tamponade

Incidence/Epidemiology

- 60 % of cases are related to a known or suspected underlying process.
- Malignancies with the highest prevalence of pericardial effusion include lung, breast, and leukemia/lymphoma.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_54

Differential Diagnosis

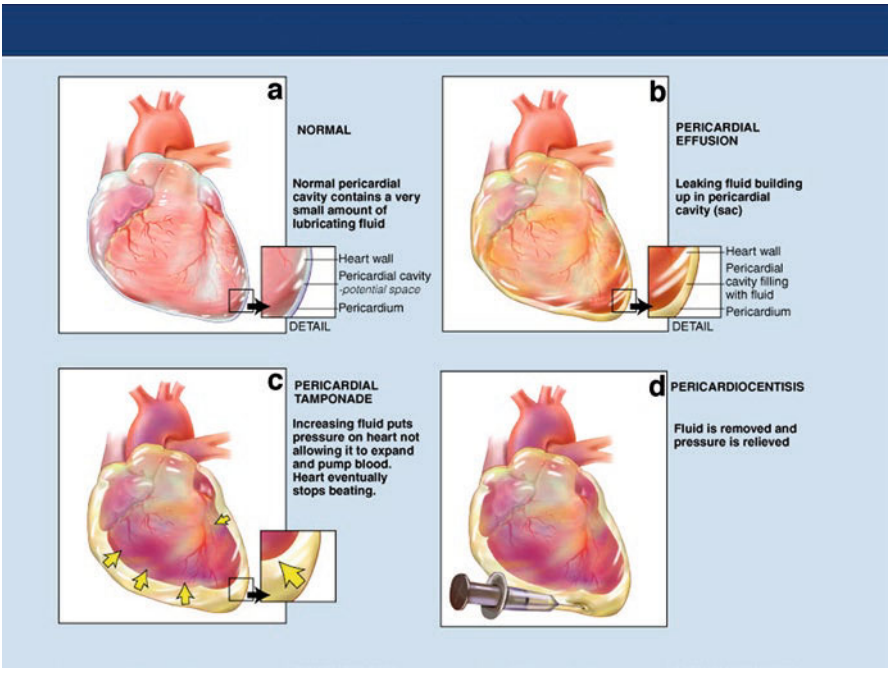
- Acute pericarditis
- Autoimmune disease
- Postmyocardial infarction or cardiac surgery
- Sharp or blunt chest trauma
- Malignancy
- Mediastinal radiation
- Renal failure with uremia
- Myxedema
- Aortic dissection extending into pericardium
- Dilated cardiomyopathy
- Pulmonary edema
- Pulmonary embolism
- Myocarditis

Pathophysiology and Etiology

- Accumulated fluid within the pericardial sac exceeds the small amount that is normally present.
  - 25–50 ml may be physiologic
- May develop rapidly or slowly.
- Accumulation of pericardial fluid into a closed space increases intrapericardial pressure.
- Cardiac tamponade is present when intrapericardial pressure becomes high enough to impede cardiac filling and function.
  - May occur with small amounts of fluid (~80 cc) when the pericardial cavity fills quickly; effusions may accumulate slowly to much higher volumes (up to 2 L) without symptoms.
  - Occurs when diastolic filling pressures equalize and prohibit effective pump function

Malignancy
Postoperative (postpericardiotomy)
Cardiac puncture from invasive procedures (electrophysiology studies, cardiac catheterization, pacemaker/ICD implantation)
Ischemic heart disease related (postinfarct as in Dressler's Syndrome; myocardial rupture)
Infectious
Immune/connective tissue diseases (lupus; rheumatoid arthritis; vasculitides)
Idiopathic
Renal failure
Drug-related and anticoagulants
Postradiation
Chest trauma
Hypothyroidism
Amyloidosis

Etiologies of pericardial effusion [Tsang TSM, Sinak LJ, Oh JK. Pericardial Effusion, Tamponade, and Constriction. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography [Internet]. London: Springer London; 2009 [cited 2015 Sep 2]. p. 297–310. Available from: http://link.springer.com/10.1007/978-1-84882-293-1_14] *Caption from original*



Illustrations demonstrate the progressive effects of a large pericardial effusion on the heart (a–c). If the effusion is large enough to compress the cardiac chambers it

will ultimately limit cardiac output. In this setting, an emergency pericardiocentesis is necessary (d) [Towbin R. The bowed catheter sign: a risk for pericardial tamponade. Pediatric Radiology. 2008 Mar;38(3):331–5.] *Caption from original*

Presentation

Typical/"Classic"

- Many patients with pericardial effusion have no symptoms.
- Signs and symptoms may not occur until a large amount of fluid has collected over time.
- Beck triad of pericardial **tamponade**: Hypotension, muffled heart sounds, jugular venous distention.

Atypical

- Atypical presentations might include primary complaints of syncope, shortness of breath (especially on exertion), and chest pain.

Primary Differential Considerations

- Diagnostic approach consists of 3 steps:

  1. Confirm the presences of a pericardial effusion
  2. Assess its hemodynamic impact
  3. Establish the cause of the effusion

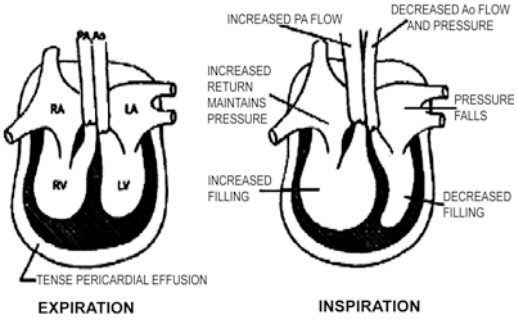
History and Physical Exam

Findings That Confirm Diagnosis

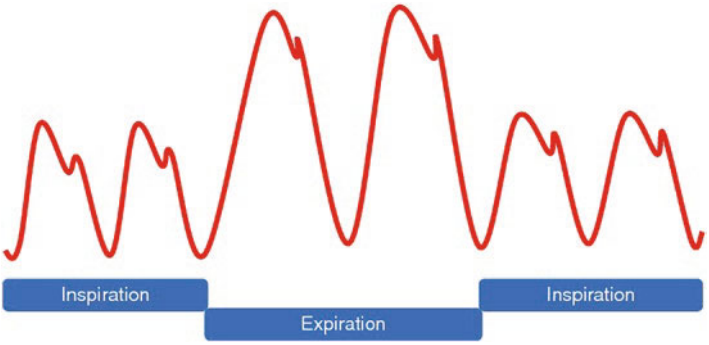
- The diagnosis is strongly suggested by the finding of concomitant hypotension, muffled heart sounds, and jugular venous distention. Confirmation requires imaging, typically with an echocardiogram.

Factors That Suggest Diagnosis

- Chest pain
- Syncope
- Cough
- Ewart's sign (triangular area of dullness at the tip of the left scapula along with tubular breath sounds and egophony at the same location)
- May have fever in the setting of pericarditis
- Elevated jugular venous pressure
- Edema
- Pulsus paradoxus
- Pericardial friction rub
- Tachycardia
- Hepatojugular reflux
- Tachypnea
- Hepatosplenomegaly



Pulsus paradoxus expiration and inspiration. [Reprinted from Curr Probl Cardiol., Vol. 29, Iss. 9, Goldstein JA. Cardiac tamponade, constrictive pericarditis, and restrictive cardiomyopathy. Pages 503-567, Copyright 2004, with permission from Elsevier].



Pulsus paradoxus demonstrating an exaggerated decline in systolic blood pressure during inspiration, resulting from an increase in negative intrathoracic pressure [Patel S, Kronzon I. History and Physical Examination of a Patient with Pericardial Disease. In: Herzog E, editor. Management of Pericardial Disease [Internet]. Cham: Springer International Publishing; 2014 [cited 2015 Sep 2]. p. 27–35. Available from: http://link.springer.com/10.1007/978-3-319-06124-5_3] *Caption from original*

Factors That Exclude Diagnosis

- The absence of a pericardial effusion on echocardiogram is the only way to exclude the diagnosis with certainty.

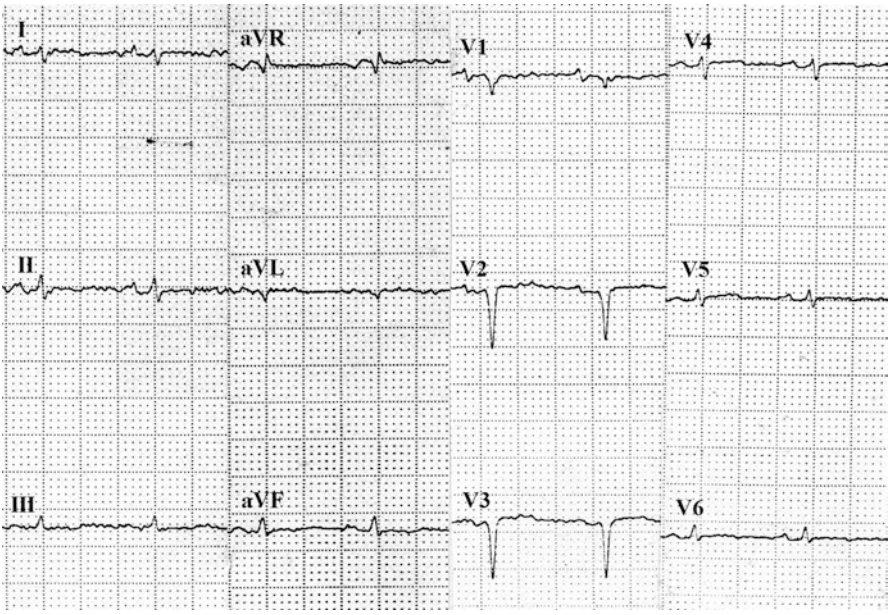
Ancillary Studies

Laboratory

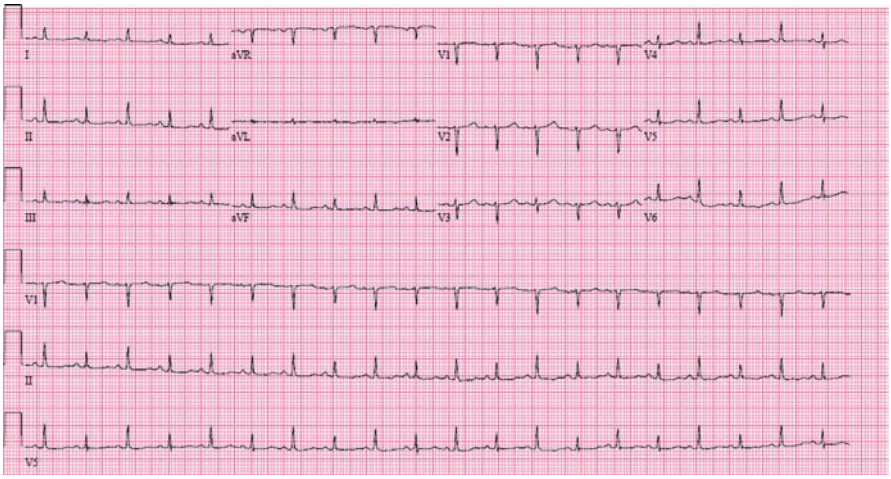
- Cardiac biomarkers may be elevated with acute myopericarditis or myocardial infarction.
- Moderate or large effusions etiology may be established with fluid and/or pericardial tissue analysis.
  - Fluid analysis may be obtained if clinical suspicion of purulent, tuberculous, or neoplastic pericarditis.
- CBC.
- Chemistry profile with renal function.
- Thyroid function.
- ANA testing.

ECG

- Sinus tachycardia.
- Low QRS voltage.
- Electrical Alternans.
- The combination of low voltage with sinus tachycardia should raise concern about pericardial effusion with tamponade.
- Electrical alternans with sinus tachycardia is highly specific of pericardial effusion.
    - Its absence does not exclude cardiac tamponade.



ECG in a patient with massive pericardial effusion causing pericardial tamponade. The key feature is a significant decrease in the QRS voltage in all leads [Romanò M. The Electrocardiogram in Diseases of the Pericardium and Myocardium. Text Atlas of Practical Electrocardiography [Internet]. Milano: Springer Milan; 2015 [cited 2015 Sep 2]. p. 209–12. Available from: http://link.springer.com/10.1007/978-88-470-5741-8_13] *Caption from original*



EKG demonstrating electrical alternans [Aksoy O, Rodriguez L. Tamponade. In: Anwaruddin S, Martin JM, Stephens JC, Askari AT, editors. Cardiovascular Hemodynamics [Internet]. Totowa, NJ: Humana Press; 2013 [cited 2015 Sep 2]. p. 181–96. Available from: http://link.springer.com/10.1007/978-1-60761-195-0_9] *Caption from original*

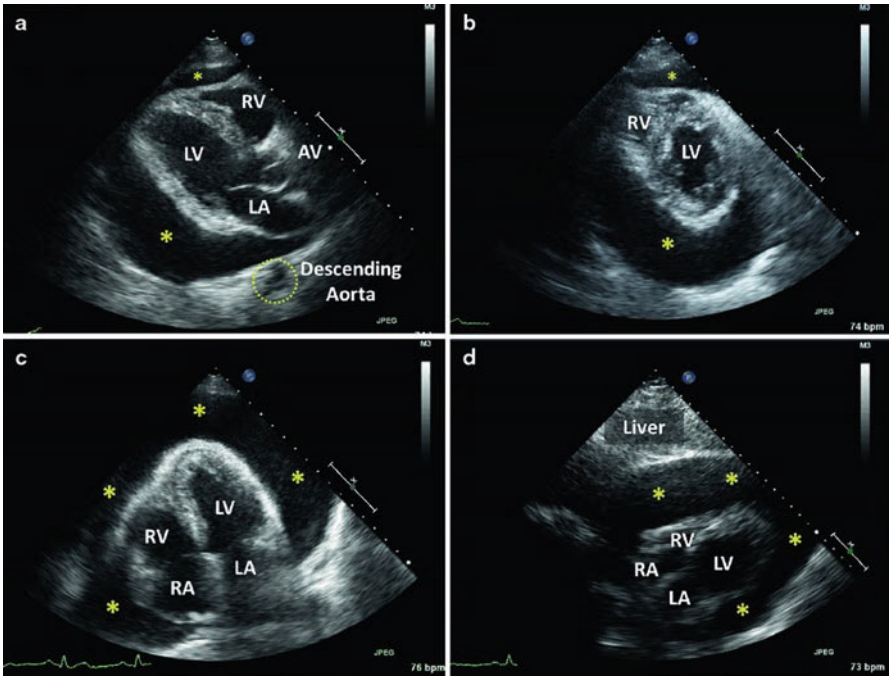
Imaging

- Chest x-ray
  - Variable.
  - Depends on etiology and size of effusion.
    - Small-to-moderate effusions (less than 200–300 ml) may not be apparent on CXR.
  - Enlarged cardiac silhouette "water bottle heart" is not specific and cannot be considered diagnostic.

Chest radiograph of a large pericardial effusion. The cardiac diameter is markedly enlarged and the cardiac silhouette has a characteristic globular shape. This picture is seen in slowly developing chronic effusions when there is time for the pericardium to stretch. In an acute cardiac tamponade caused by bleeding into the pericardium the chest radiograph may show little or no cardiac enlargement. [Woodcock B. Hemodynamic Emergencies. In: Miller RD, Tremper KK, editors. Atlas of Anesthesia: Principles of Anesthetic Techniques and Anesthetic Emergencies, Volume 4, 1e. Vol. IV. Philadelphia: Current Medicine; 1998. 195 p.] *Caption from original*

Echocardiography

- Sensitive and specific for pericardial effusion.
- Can provide information regarding the hemodynamic significance of the effusion.
- Small effusions (50–100 mL) can be seen posterior to the left ventricle.
- Most sensitive and specific view is the accumulation of pericardial fluid above the right atrium in the apical four chamber view with the patient in the left lateral decubitus.
- Plays important role in diagnosis of cardiac tamponade.
    - Collapse of the right atrium at end diastole and the right ventricle in early diastole.
    - Reciprocal changes in left and right ventricular volumes with respiration.
    - Dilation of IVC and less than a 50 % reduction in its diameter during inspiration.

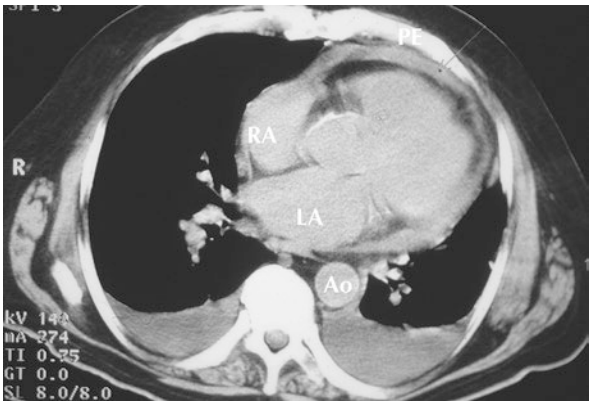


Pericardial effusion. Transthoracic echocardiogram demonstrates a large pericardial effusion (asterisks) in a 47-year-old woman with breast cancer. Panel a: Parasternal long axis view demonstrates typical interposition of the pericardial effusion (asterisks) between the heart and the descending thoracic aorta. This finding differentiates a pericardial effusion from a left pleural effusion in which there is no such interposition between the heart and the descending thoracic aorta. Panel b: Parasternal short axis at the level of the papillary muscles demonstrates that the pericardial effusion (asterisks) is larger posterior to the left ventricle that anterior to the right ventricle. This is due to gravity in this supine patient. Panel c: In the apical 4-chamber view, note that the pericardial effusion (asterisks) surrounds the cardiac apex. This feature helps distinguish a pericardial effusion from a pleural effusion. Panel d: Subcostal view demonstrates a large pericardial effusion (asterisks). Abbreviations: AV aortic valve, LA left atrium, LV left ventricle, RA right atrium, RV right ventricle [Saric M. Echocardiography in Pericardial Disease. In: Herzog E, editor. Management of Pericardial Disease [Internet]. Cham: Springer International Publishing; 2014 [cited 2015 Sep 2]. p. 49–70. Available from: http://link.springer.com/10.1007/978-3-319-06124-5_5] *Caption from original*

CT and MRI

- May be used after non-diagnostic echocardiography.

- May be useful when quantification and localization of pericardial fluid is important, when complex effusions are present, or when epicardial fat and pleural effusions need to be excluded.



Pericardial effusion (PE). PEs are usually well shown by echocardiography. However, they are often a finding on conventional computed tomography (CT) scan or ultrafast CT (UFCT; Imatron, South San Francisco, CA). CT may show loculated pericardial fluid that cannot be shown by echocardiography. A, On unenhanced scans, a PE often has attenuation similar to soft tissue and therefore has the same density as do myocardium and blood pool. PE is usually visible as a layer of abnormal thickening separated from the heart by a line of low-attenuation epicardial fat, as shown in this example. Sometimes the epicardial fat is very thin; however, it still should be visible. Ao—aorta; LA—left atrium; RA—right atrium. [Hartnell G. Chapter 7. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging. Atlas of Heart Diseases, Volume 01, Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption adapted from original*

B, If there is doubt whether there is a PE or if there is no epicardial fat, intravenous contrast medium will enhance the myocardium but not the pericardial fluid. The attenuation of the myocardium will increase, as shown in this patient with

lymphoma invading the pericardium, whereas the attenuation of the pericardial fluid (here mostly loculated posteriorly) is unchanged, enhancing the difference between the two. Although CT is not recommended as the first line method for detecting PEs, it frequently shows underlying conditions such as tumor, which may lead to pericardial effusion. In addition, in patients who are poor subjects for echocardiography, CT will show PEs, including effusions loculated in areas difficult to examine by echocardiography. [Hartnell G. Chapter 7. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging. Atlas of Heart Diseases, Volume 01, Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption adapted from original*

Special Populations

- Populations at particular risk for development of a pericardial effusion include patients with
  - Malignancy
  - Renal failure
  - Autoimmune diseases, such as lupus
  - Certain unusual systemic infections, such as tuberculosis
  - Some viral infections, incluing HIV
  - Very recent myocardial infarction
  - Very recent heart surgery

Age

- Most common in the fourth and fifth decades of life.
- Within the pediatric population, reported cases of pericardial effusion are most likely due to enteroviral infections, specifically Coxsackie viral infections. Other pediatric specific etiologies include malignancies, specifically the leukemias.
- In addition, cases of pediatric myocarditis may involve the pericardium as well.

Co-morbidities

- Patients with heart disease, renal failure, or malignancy are at risk of developing pericardial effusion.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Rapid diagnosis of cardiac tamponade is needed for urgent treatment.
- No positive-pressure ventilation because of its adverse effects on venous return and cardiac output.

Mimics

- Cardiomyopathy, which also causes diminished cardiac output and an enlarged cardiac silhouette on chest radograph.

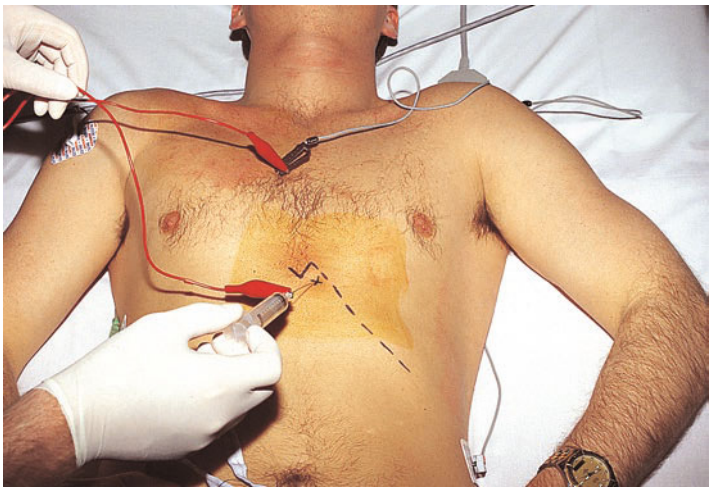
Time-Dependent Interventions

- Drainage of a pericardial effusion is often performed for therapeutic benefit, as in cardiac tamponade.
- Patients with a pericardial effusion and evidence of hemodynamic compromise should undergo urgent drainage.
- Cardiac tamponade is initially treated with expansion of intravascular volume and urgent pericardial drainage.

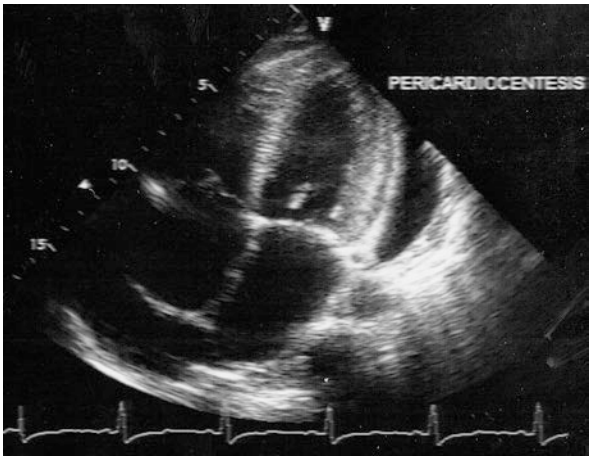
Overall Principles of Treatment

- Development of pericardial effusion may have implications for prognosis and diagnosis.
- Patient with effusion who are hemodynamically stable do not require immediate drainage.
- Manage underlying cause:
    - NSAIDs or prednisone for inflammatory effusions
    - Diuretics for heart failure-associated effusions
    - Antibiotic if infection is suspected
    - Malignant effusions may respond as the underlying cancer is treated with chemotherapy or radiation
- The choice between pericardiocentesis and open surgical drainage is multifactorial and institution specific:
    - Both techniques allow for rapid relief of cardiac tamponade
    - Both allow for fluid analysis if needed

- A percutaneous continuous catheter drain may be placed for intermittent or continuous removal until the rate of fluid return is negligible.

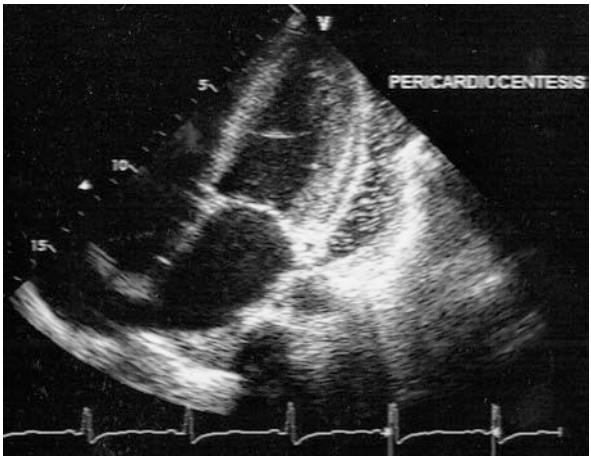


Pericardiocentesis [Woodcock B. Hemodynamic Emergencies. In: Miller RD, Tremper KK, editors. Atlas of Anesthesia: Principles of Anesthetic Techniques and Anesthetic Emergencies, Volume 4, 1e. Vol. IV. Philadelphia: Current Medicine; 1998. 195 p.]



Echocardiographically guided pericardiocentesis. In addition to confirming the presence, location, and distribution of pericardial effusion, two-dimensional echocardiography can enhance the safety of percutaneous pericardiocentesis by identifying the optimal entry site (the point at which the distance from skin to prominent

fluid accumulation is minimized, with no intervening vital organ). Once the needle has entered the pericardial space and a sheath or catheter is inserted, confirmation and documentation of intrapericardial location can be achieved by injecting a small amount of agitated saline. A moderate-to-large size pericardial effusion is present as shown in the modified apical four-chamber view (A). [Goldstein S, Pita F. Chapter 9. In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, Braunwald E, editors. Atlas of Echocardiography. 1e. Philadelphia, PA: Current Medicine Group; 2005. 312 p. ISBN: 1-57340-217-6] *Caption adapted from original*



Proper catheter location is confirmed by the echogenic microbubbles observed within the pericardial space (B). This technique should be used routinely to minimize complications. [Goldstein S, Pita F. Chapter 9. In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, Braunwald E, editors. Atlas of Echocardiography. 1e. Philadelphia, PA: Current Medicine Group; 2005. 312 p. ISBN: 1-57340-217-6] *Caption adapted from original*

Disease Course

- Often self-limited or responsive to NSAIDs or corticosteroids.
- Many secondary cases are responsive to better management of underlying disease.
- Perform follow-up echocardiography to rule out accumulation and constrictive physiology.

Related Evidence

Papers of particular interest have been highlighted as:
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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Pericardial Effusion"[Mesh] OR "Cardiac Tamponade"[Mesh] OR "pericardial effusion" OR "Pericardial effusions" OR "cardiac tamponade" OR "pericardial tamponade"

Chapter 55
Pleural Effusion

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Pleural Effusion

- Hydrothorax, chylothorax, malignant effusion, parapneumonic effusion

Incidence/Epidemiology

- Pleural effusions may develop as a result of more than 50 different disorders.
  - The most common causes are congestive heart failure, malignancy, severe pneumonia, and thromboembolism.
  - A particularly worrisome, potentially infectious cause is tuberculosis.
  - In pediatrics, the incidence of parapneumonic effusions is increasing.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_55

Differential Diagnosis

- The differential diagnosis of pleural effusion is quite broad and includes the following:
  - Congestive heart failure
  - Hepatic hydrothorax
  - Nephrotic syndrome
  - Hypoproteinemia
  - Glomerulonephritis
  - Superior vena cava obstruction
  - Malignancy
  - Pneumonia
  - Tuberculosis
  - Pulmonary embolism
  - Fungal infection
  - Pancreatic pseudocyst
  - Intra-abdominal abscess
  - Post coronary artery bypass graft surgery
  - Post–cardiac injury syndrome
  - Pericardial disease
  - Meigs syndrome
  - Ovarian hyperstimulation syndrome
  - Rheumatoid pleuritis
  - Lupus
  - Drug-induced pleural disease
  - Asbestos pleural effusion
  - Uremia
  - Chylothorax
  - Acute respiratory distress syndrome
  - Chronic pleural thickening
  - Malignant mesothelioma

Pathophysiology and Etiology

- The pleural space (which lies between the parietal pleura and visceral pleura) is a potential anatomic space which normally holds only a small amount of sterile fluid. Fluid is filtered by the parietal pleura and absorbed by the visceral pleura. Governed by Starling's equation, blood and pleural fluid are in hydrostatic and oncotic balance. When an imbalance exists between the blood and pleural hydrostatic and oncotic pressure, fluid accumulates in the pleural space. Pleural effusions develop whenever influx of fluid into the pleural space exceeds lymphatic efflux.

- There are two types of pleural effusions: transudative and exudative.
  - The fluid in a transudative effusion contains very little protein but is otherwise similar to plasma.
    - Most transudates result from heart failure, but sometimes they are seen in advanced liver disease, nephrotic syndrome, and hypoalbuminemia.
  - The fluid in an exudative effusion is protein rich and is generally associated with pneumonia ("parapneumonic effusion") or cancer ("malignant effusion").

Presentation

Typical/"Classic"

- Small pleural effusions may be entirely asymptomatic.
- Large pleural effusions may present with significant respiratory distress that usually is insidious in onset.
- In pediatrics, the most common presenting symptoms are fever, cough, malaise, anorexia, chest pain, and dyspnea.

Atypical

- Chest pain in isolation is unusual; a viral-type prodrome with low-grade fever preceding chest pain is more common.

Primary Differential Considerations

- The underlying disease process may dominate or obscure the signs and symptoms of the pleural effusion.

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis cannot be confirmed without imaging.

Factors That Suggest Diagnosis

- Localized reduced breath sounds on auscultation and dullness to percussion in the same area suggest pleural fluid collection.
- A history of typical predisposing diagnoses, such as heart failure, pneumonia, nephrotic syndrome, liver disease, or malignancy, in a patient with the aforementioned physical findings should prompt imaging. Pleural friction rub is sometimes appreciated and may suggest the diagnosis.

http://www.easyauscultation.com/cases?coursecaseorder=7&courseid=201

Pleural friction rub. [Pleural Rubs; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Factors That Exclude Diagnosis

- The absence of effusion on radiographic study is the only way to exclude the diagnosis with certainty.
- Symmetric breath sounds on auscultation and the absence of dullness to percussion in the lower lung fields make the diagnosis of pleural effusion unlikely. Small loculated effusions may still be present, however, and must be excluded by imaging.

Ancillary Studies

Laboratory

- Usual laboratory studies for evaluating co-morbidities should be obtained.
- If pleural tap is performed, fluid should be sent for Gram stain, cytology, cell count, cultures, protein, lactate dehydrogenase (LDH), and glucose.
    - As menti.oned earlier, transudative fluid has little protein (pleural protein to serum protein < 0.5).

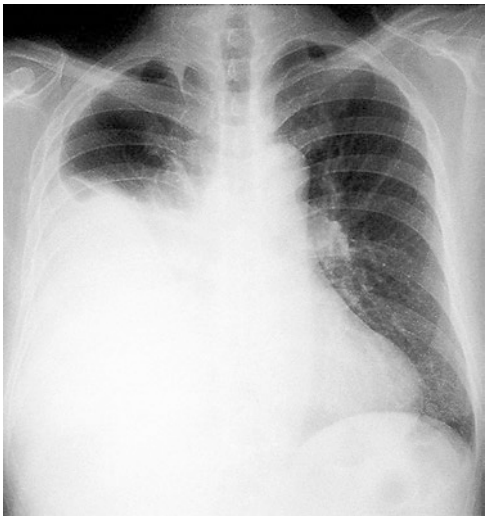
Infection
Bacterial
Mycobacterial
Fungal
Parasitic
Mixed
Gastrointestinal disease
Esophageal perforation
Mediastinitis
Subdiaphragmatic infection
Other
Collagen-vascular disease
Malignancy
Uremia
Drug-induced disease
Pulmonary embolism
Abestosis
Sarcoidosis
Radiation injury
Trauma
Hemothorax
Chylothorax

Differential diagnosis of exudative pleural effusion. Once an effusion is classified as exudative, diagnostic considerations include many infectious and noninfectious diseases. [Salmon C, Bryant R. Pleural effusion and empyema. In: Simberkoff MS, editor. Pleuropulmonary and bronchial infections. Philadelphia: Current Medicine; 1996. Chapter 10. (Mandell GL, editor. Atlas of infectious diseases; vol. 6). ISBN: 0-443-07740-1] *Caption from original*

- The measurement of pleural cholesterol, triglycerides, and amylase also may provide useful information in selected patients.
    - Blood cultures should be performed in all children with parapneumonic effusions. Blood cultures are positive in 10–22 % of children with complicated parapneumonic effusions.
    - In certain instances, tuberculosis testing may be warranted.

Imaging

- Chest radiography (posteroanterior [PA] or anteroposterior upright and lateral decubitus radiographs) confirms the following:
  - Blunting or obliteration of the costophrenic angle on an upright chest radiograph
  - A "meniscus sign" (rim of fluid ascending the lateral chest wall) may be seen.
  - On a PA view, opacification of more than half the thorax suggests a large effusion.
  - On a PA view, opacification of more than one quarter but less than half of the thorax suggests a moderate-sized effusion.
  - A decubitus permits free fluid to layer out on the dependent chest wall and may help distinguish the meniscus from pleural thickening.



Pleural effusion. Pleural effusion is present in about 6% of patients with ascites, and more often it is on the right side. This is the result of a defect in the diaphragm that allows the ascitic fluid to pass up into the pleural cavity. In contrast, a left-sided pleural effusion in an ascitic patient may indicate pulmonary pathology. Occasionally, a pleural effusion can be seen in the absence of ascites caused by the negative intrathoracic pressure drawing up the ascitic fluid through the diaphragmatic defect into the pleural cavity. Thoracocentesis is followed by rapid refilling of the pleural cavity because of the negative intrathoracic pressure. Control of the pleural effusion can only be achieved with the control of ascites. Insertion of a permanent chest tube can lead to the development of a fistula and is not recommended. [Wong F. Cirrhosis: ascites and spontaneous bacterial peritonitis. In: Maddrey WC, series editor. Atlas

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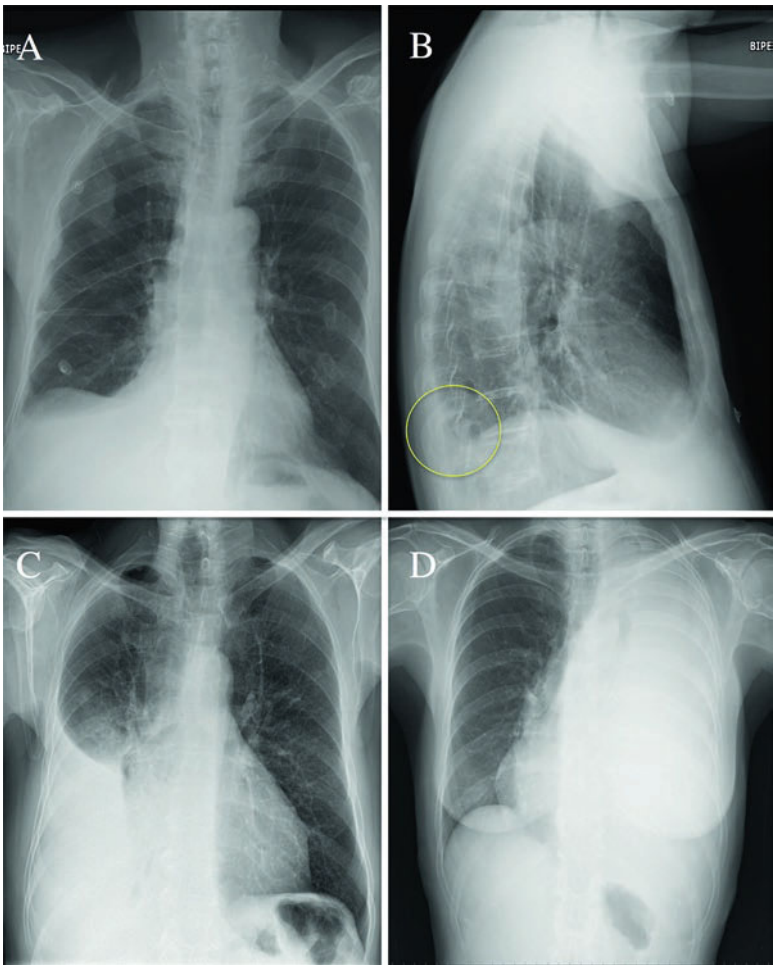
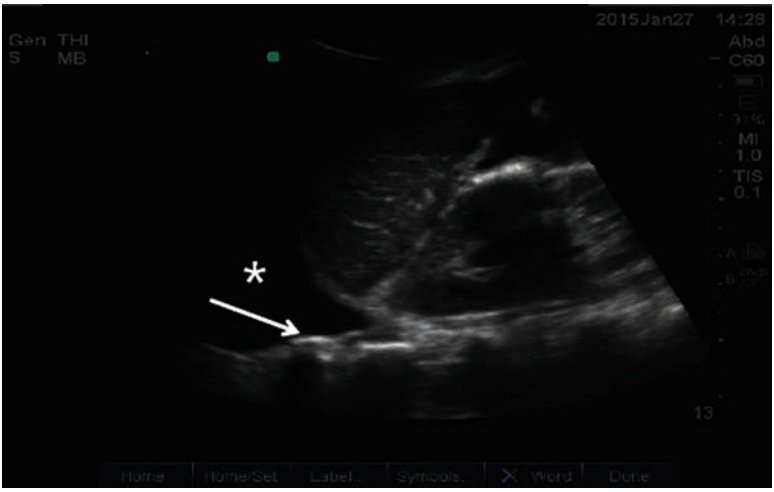


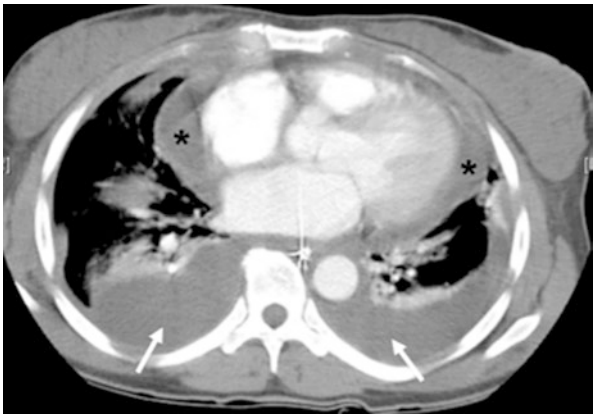
Different chest x-ray images in patients with pleural effusion. (a) Postero-anterior (PA) chest x-ray of a patient with minimal pleural effusion impossible to be detected in this projection. (b) Lateral chest x-ray of the same patient. The circle shows a detectable posterior costo-phrenic angle blunting confirming the presence of minimal pleural effusion. (c) PA chest x-ray of a patient with a moderate right pleural effusion. (d) PA chest x-ray of a patient with a massive left pleural effusion with contralateral mediastinal shift *[*Call S, Sánchez D, Rami-Porta R. Diagnosis and treatment of malignant pleural effusion. In: Kiselevsky MV, editor. Malignant effusions [Internet]. Dordrecht, Netherlands: Springer; 2012 [cited 2015 Aug 28]. p. 23–55. Available from: http://link.springer.com/10.1007/978-94-007-4783-8_3*]* *Caption from original*

- Ultrasound is particularly helpful in guiding thoracentesis.
  - Preferred modality in pediatrics
  - Superior to CT because of better accuracy in detecting early loculations and septations



Pleural effusion. Pleural effusion (*asterisk*) permits the ultrasound beam to penetrate deeply to reveal the vertebral stripe (*arrow*). The vertebral stripe will not be visible above the diaphragm if the lung is aerated [From article: Clinically integrated multi-organ point-of-care ultrasound for undifferentiated respiratory difficulty, chest pain, or shock: a critical analytic review. J Intensive Care. 2016 Aug 15;4(1):54. https://doi.org/10.1186/s40560-016-0172-1, at http://link.springer.com/article/10.1186%2Fs40560-016-0172-1/fulltext.html; by Young-Rock Ha, Hong-Chuen Toh, © The Author(s). 2016; licensed under Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/] *Caption from original*

- Chest CT
  - Can identify small effusions and determine whether larger effusions are loculated, and may identify underlying disease



Pleural effusion in systemic lupus erythematosus. Enhanced CT scan at systemic lupus erythematosus (SLE) presentation. Bilateral pleural (arrows) and pericardial (asterisk) effusions resolved promptly with therapy. [Berney S, Heldmann M. Chapter 14. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] *Caption adapted from original*

Special Populations

Age

- Pleural effusion may occur at any age, although owing to the greater number of underlying disease processes (heart failure, cirrhosis, uremia, malignancy), the incidence increases with age.
- The most common cause of pleural effusion in the pediatric population is lung infection (parapneumonic effusion).
    - Within the pediatric population, reported cases of pleural effusion are on the rise, usually as a result of resistant organisms causing the primary infectious process.
    - Many emergency departments are using ultrasound to accurately diagnose pleural effusions in infants and children.

Co-morbidities

- Because pleural effusion likely is the result of an underlying disease process, those with a history of congestive heart failure, cirrhosis, nephrotic syndrome, mesothelioma, esophageal rupture, certain rheumatologic diseases, or drug-induced lupus, to name a few, also are at risk for pleural effusions.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Any child who remains febrile or unwell 48 hours after initiation of antibiotic therapy for pneumonia should be reevaluated for possible pleural effusion.
- Always consider pulmonary embolism as a potential underlying cause of effusion.

Time-Dependent Interventions

- Emergency thoracentesis may be warranted for severe respiratory distress.

Overall Principles of Treatment

- Empyema mandates chest tube insertion.
- If effusion does not have a clear etiology, pleural fluid analysis is required.
- Heart failure–associated effusions usually improve with diuresis for the underlying disease.
- Many small effusions are not clinically important and resolve spontaneously.

Disease Course

- Malignant pleural effusions seldom resolve spontaneously.
- Effusions that do not clear with management of underlying disease are more worrisome.
- Effusions may recur, especially in patients with chronic underlying disease, such as heart failure, cirrhosis, or nephrotic syndrome.
- Effusions associated with acute disease, such as pneumonia, usually do not recur.

Related Evidence

Papers of particular interest have been highlighted as:
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Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pleural Effusion"[Mesh] OR "Pleural Effusion" OR "Pleural Effusions"

Chapter 56
Pleurisy

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Pleurisy

- Pleuritic, pleuritic pain

Incidence/Epidemiology

- Pleurisy or pleuritic pain is common and nonspecific.
- There are no clear incidence data, as many patients with pleurisy do not seek medical attention. Others may have significant chest pain as a result of pleurisy.

Differential Diagnosis

- The differential considerations for chest pain due to pleurisy include immediate life threats such as pulmonary embolism, acute coronary syndrome, and aortic dissection.

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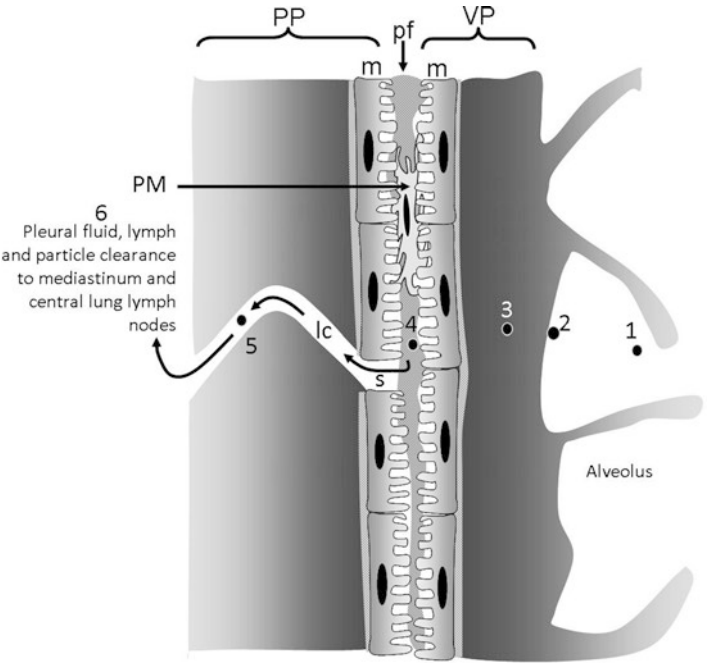
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_56

- Less severe differential considerations include pneumonia and pneumothorax, which may cause pleuritic pain, as well as chest wall pain and anxiety.
- Pericarditis may present similarly.
- Acute chest syndrome in sickle cell disease is a differential consideration in at-risk patients.

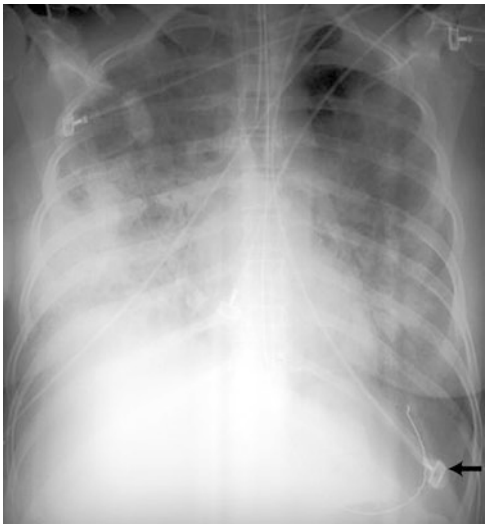
Pathophysiology and Etiology

- The pleura is a two-layer membrane in the thorax. The outer, or parietal, layer lines the chest cavity, whereas the inner, or visceral, layer adheres tightly to the lungs. Between these layers is a tiny space that normally contains a small amount of lubricating fluid. In pneumothorax, this space contains air, and in pleural effusion, this space contains larger amounts of fluid.

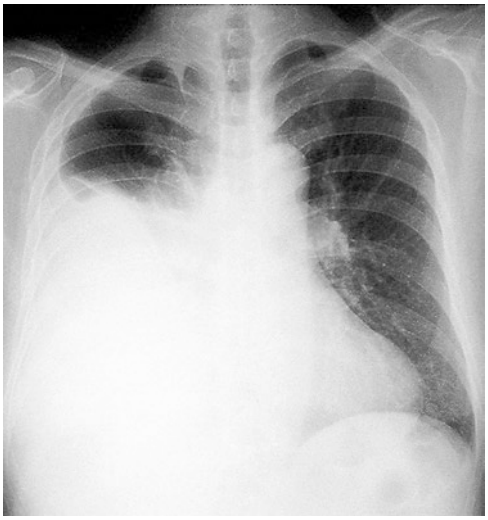


Diagrammatic representation of the relationship between the visceral and parietal pleurae. The visceral pleura (VP) and the parietal pleura (PP) are seen in close apposition separated by a pleural space that contains a small volume of pleural fluid (pf). Contact between the 2 pleurae is made via the mesothelial cell layers (m) on the surface of the parietal and visceral pleurae. Pleural macrophages (PM) are present

in the pleural space. The rigid chest wall is tightly locked to the lungs by the adherence of the visceral pleura to the parietal pleura allowing movements of the chest wall caused by the action of the diaphragmatic muscle and intercostal muscle (IM) to expand and relax the lungs, allowing pulmonary inspiration and expiration. The pathway for particles to reach the pleural space is unknown but the path for an airborne particle (1) that deposits in the distal alveoli (2) is shown as it passes into the interstitium (3) enters the pleural space (4) and exits through a stoma in the parietal pleura (s) into a lymphatic capillary (lc, 5) to enter the lymph flow to the lymph nodes in the mediastinum and central lung. [From article: Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Part Fibre Toxicol. 2010 Mar;7:5. https://doi.org/10.1186/1743-8977-7-5, at http://link.springer.com/article/10.1186/1743-8977-7-5; by Ken Donaldson, Fiona A Murphy, Rodger Duffin, Craig A Poland, © Donaldson et al; licensee BioMed Central Ltd. 2010; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*



Pneumothorax . A, Chest radiograph of a critically ill patient with a deep sulcus sign on the left (arrow), consistent with the diagnosis of a pneumothorax. B. Chest radiograph of a critically ill patient on mechanical ventilation with the presence of a right loculated tension pneumothorax (arrow). Note the increase in volume of the right hemithorax, depression of the right hemidiaphragm, and contralateral mediastinal shift. [Huggins J, Sahn S. Pleural disease. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Current Medicine; 2005. Chapter 25. ISBN: 1-57340-211-7; 2005-01-14] *Caption from original*



Pleural effusion in ascites. Pleural effusion. [Wong W. Cirrhosis: ascitis and spontaneous bacterial peritonitis. In: Maddrey W, editor. Atlas of the liver. 4th ed. Philadelphia: Current Medicine; 2006. Chapter 10 (Feldman M, editor. Gastroenterology and hepatology; vol. 1; ISBN: 1-57340-241-9; 2006-06-27] *Caption adapted from original*

- Inflammation of the pleura causes the two layers to rub together and results in pain and dyspnea. Although the underlying problem may be the actual cause of dyspnea (pneumonia, pneumothorax), pleurisy itself does not actually *cause* shortness of breath or ventilatory compromise. Instead, the patient perceives dyspnea because of pain on inspiration, which may involuntarily limit inspiratory effort.

Presentation

Typical/"Classic"

- The classic presentation of pleuritic pain is:
  - Acute or relatively acute onset
  - One-sided
  - Exacerbated by inspiration, cough, sneeze, or sudden movement
  - Worse when lying down than when sitting up
  - May extend to shoulder (raising concern of acute coronary syndrome) or abdomen

- A pleural friction rub may be heard.

https://www.youtube.com/watch?v=t2QE0O_exAQ
Audio of pleural friction rub.

http://www.easyauscultation.com/cases?coursecaseorder=7&courseid=201
Pleural Friction Rub [Pleural Rubs; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Atypical

- Because of underlying pathology, pleurisy may present with dyspnea that is more concerning to the patient than the chest pain.
- With pneumonia, fever may be a dominant symptom.

Primary Differential Considerations

- Keeping in mind that pleurisy may be either an independent diagnosis or a symptom of many other thoracic illnesses, the differential diagnosis is broad.
- The most worrisome primary differential considerations are pulmonary embolism and pneumonia.
- Myocardial ischemia and pleural effusion with pleuritis also should be considered early on.

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination are not diagnostic for pleurisy.

Factors That Suggest Diagnosis

- Typical pain description (see earlier) with exacerbations from deep breathing or coughing. A change in position is suggestive.
- A pleural friction rub in patients with chest pain indicates pleural involvement.

https://www.youtube.com/watch?v=t2QE0O_exAQ
Audio of pleural friction rub.

Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude pleurisy.

Ancillary Studies

Laboratory

- There are no diagnostic laboratory studies for pleurisy.
- Laboratory tests target suspected underlying disease.
- If measured, erythrocyte sedimentation rate and C-reactive protein may be elevated in patients with pleurisy, but these tests are not essential for the diagnosis or treatment.

Imaging

- Chest radiography does not reveal pleurisy itself, but may reveal the underlying cause.
- Chest radiography or CT scanning may exclude pneumothorax and pulmonary embolism as causes of pleurisy.

Special Populations

Age and Gender

- The epidemiology of pleurisy follows that of the underlying cause. Therefore, it may occur at any age from childhood to old age. Some diseases (e.g., lung cancer) have a gender predilection, and secondary pleurisy therefore will follow that.
- Pleurisy in children is synonymous with any atraumatic cause of chest pain.
- Texidor's twinge, or precordial catch, is a benign cause of musculoskeletal chest pain in children. It is associated with brief, sharp, painful episodes near the left sternal border.
- Pleurodynia, or Bornholm disease, is an infrequent complication of Coxsackie B infections
    - It is characterized by sudden, severe episodes of unilateral chest pain, restricting air entry (hence the name "devil's grip").
    - It resolves spontaneously.

Co-morbidities

- Typical co-morbidities (and underlying causes) of pleurisy include:
  - Viral and bacterial lower respiratory tract infections
  - Chest wall trauma
  - Recent thoracic surgery
  - Sickle cell disease
  - Pulmonary embolism
  - Autoimmune disease (lupus, rheumatoid arthritis)
  - Pneumothorax
  - Pericarditis
  - Tuberculosis

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Pleurisy is a symptom, not a disease. Therefore, there are no critical steps in the evaluation of pleurisy.
- Because there are underlying causes of pleurisy that are immediate life threats, evaluation for acute coronary syndrome, pulmonary embolism, and pneumonia should be considered early.

Mimics

- The entire constellation of diagnoses underlying chest pain syndrome, especially those often accompanied by dyspnea, can mimic the pain and overall presentation of pleurisy.
- Pericarditis may mimic pleurisy in presentation. Listen for a pericardial friction rub.

http://www.easyauscultation.com/acute-pericarditis

Acute Pericarditis Audio Recordings. [Acute Pericarditis; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Time-Dependent Interventions

- Underlying disease may be rapidly fatal, but therapy is targeted at the cause of the pleurisy not the pleurisy itself.

Overall Principles of Treatment

- Treatment of the symptoms of pleurisy usually is successful with nonsteroidal anti-inflammatory drugs.
- Treatment of the underlying disease usually will diminish pleurisy symptoms.

Disease Course

- Pleurisy will resolve as the underlying condition clears. There typically is no anatomic damage to the pleura, with the possible exception of tube thoracostomy for pneumothorax. Rarely, patients develop chronic pleuritic pain after chest tube placement.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Review

Jeon D. Tuberculous pleurisy: an update. Tuberc Respir Dis (Seoul). 2014 Apr;76(4):153-9. https://doi.org/10.4046/trd.2014.76.4.153. PMID: 24851127. http://www.ncbi.nlm.nih.gov/pubmed/24851127 **

Cagle PT, Allen TC. Pathology of the pleura: what the pulmonologists need to know. Respirology. 2011 Apr;16(3):430-8. https://doi.org/10.1111/j.1440-1843.2011.01957.x. PMID: 21362105. http://www.ncbi.nlm.nih.gov/pubmed/21362105 **

Kass SM, Williams PM, Reamy BV. Pleurisy. Am Fam Physician. 2007 May 1;75(9):1357-64. PMID: 17508531. http://www.ncbi.nlm.nih.gov/pubmed/17508531 **

English JC, Leslie KO. Pathology of the pleura. Clin Chest Med. 2006 Jun;27(2):157-80. PMID: 16716811. http://www.ncbi.nlm.nih.gov/pubmed/16716811 **

Segura RM. Useful clinical biological markers in diagnosis of pleural effusions in children. Paediatr Respir Rev. 2004;5 Suppl A:S205-12. PMID: 14980272. http://www.ncbi.nlm.nih.gov/pubmed/14980272 **

Cohort Study

Valdés L, Alvarez D, San José E, Penela P, Valle JM, García-Pazos JM, Suárez J, Pose A. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med. 1998 Oct 12;158(18):2017-21. PMID: 9778201. http://www.ncbi.nlm.nih.gov/pubmed/9778201

Comparative Study

Bösner S, Haasenritter J, Hani MA, Keller H, Sönnichsen AC, Karatolios K, Schaefer JR, Baum E, Donner-Banzhoff N. Gender differences in presentation and diagnosis of chest pain in primary care. BMC Fam Pract. 2009 Dec 14;10:79. https://doi.org/10.1186/1471-2296-10-79. PMID: 20003406. http://www.ncbi.nlm.nih.gov/pubmed/20003406

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:
("Pleurisy"[Mesh] OR "Pleurisy")

Chapter 57
Pneumoconiosis

Christopher J. Rees, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Pneumoconiosis
Black Lung Disease (Coal Worker's Pneumoconiosis)
Asbestosis
Silicosis

Incidence/Epidemiology

- The incidence of pneumoconiosis in Western nations has been declining for the past 20 years. However, in developing nations, where regulatory oversight is not as consistent, the incidence of these disorders continues to increase.
- From 1968 through 1992 in the United States, there were 100,800 death certificates listing pneumoconiosis as a contributing or primary cause of death.
- In 2013, there reportedly were about 250,000 deaths worldwide from pneumoconiosis.
- The most common pneumoconioses are the result of exposure to coal dust, silica, and asbestos.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_57

Differential Diagnosis

- The differential diagnosis of pneumoconiosis is broad and includes the entire spectrum of diseases that may present with cough and dyspnea, such as asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), pneumonia, lung cancer, and all the other interstitial lung diseases (ILDs).

Pathophysiology and Etiology

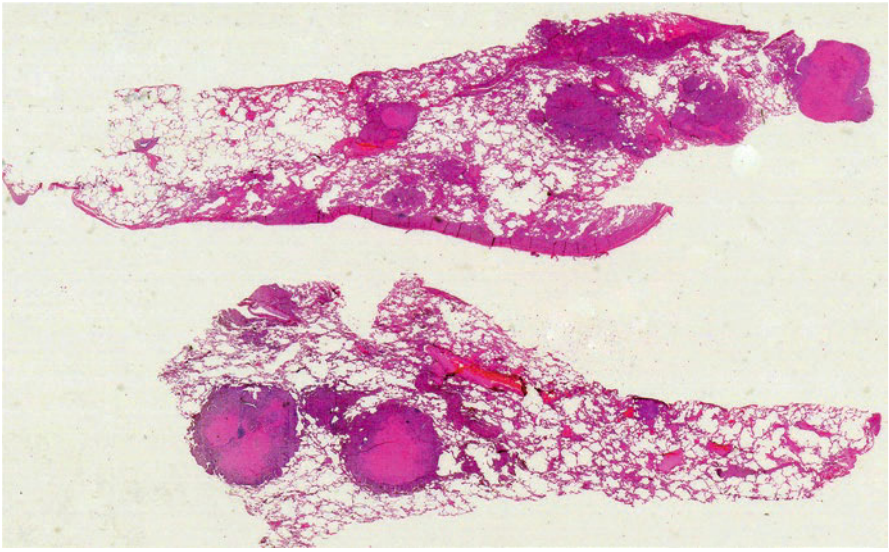
- Pneumoconioses are a group of ILDs caused by the chronic inhalation of inorganic dusts.
- *Pneumoconiosis* classically refers only to dusts that cause a fibrotic, restrictive pattern of lung disease.
- Exposure to organic dusts tends to cause reactive airway disease that may mimic asthma or, more chronically, obstructive diseases such as COPD.

Table Some types of pneumoconiosis according to dust and lung reaction

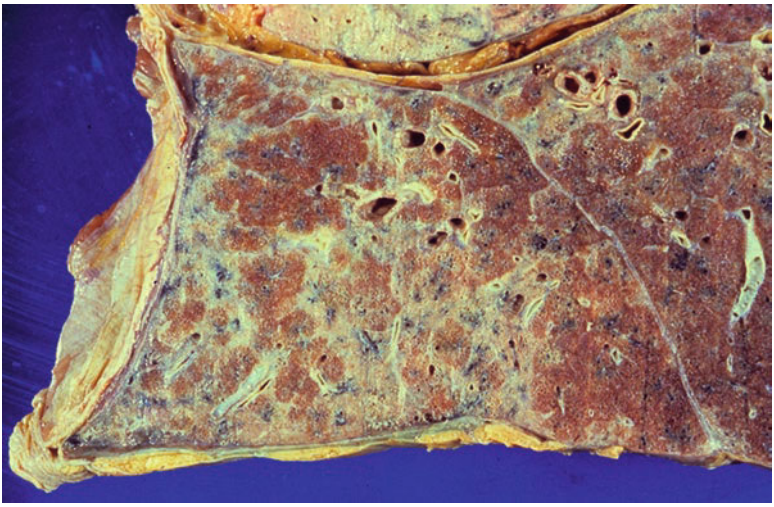
Inorganic Dust	**Type of Disease**	**Lung Reaction**
Asbestos	Asbestosis	Fibrosis
Silica (Quartz)	Silicosis	Fibrosis
Coal	Coal Pneumoconiosis	Fibrosis
Beryllium	Beryllium Disease	Fibrosis
Tungsten Carbide	Hard Metal Disease	Fibrosis
Iron	Siderosis	No Fibrosis
Tin	Stannosis	No Fibrosis
Barium	Baritosis	No Fibrosis
Organic Dust		
Mouldy hay, straw and grain	Farmer's lung	Fibrosis
Droppings and feathers	Bird fancier's lung	Fibrosis
Mouldy sugar cane	Bagassosis	Fibrosis
Compost dust	Mushroom worker's lung	No Fibrosis
Dust or mist	Humidifier fever	No Fibrosis
Dust of heat-treated sludge	Sewage sludge disease	No Fibrosis
Mould dust	Cheese washers' lung	No Fibrosis
Dust of dander, hair particles, and dried urine of rats	Animal handlers' lung	No Fibrosis

Some types of pneumoconiosis according to dust and lung reaction [*What are the Effects of Dust on the Lungs?, http://www.ccohs.ca/oshanswers/chemicals/lungs_dust.html, OSH Answers Fact Sheets,* Canadian Centre for Occupational Health and Safety (CCOHS)*, October 1, 2012.* Reproduced with the permission of CCOHS*, 2016.*]

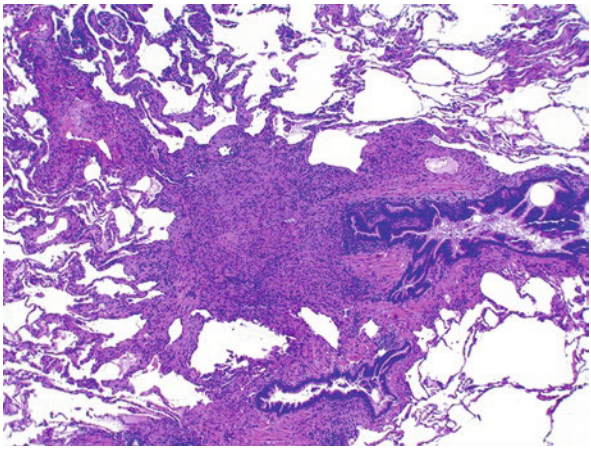
- Exposure to organic dusts also may cause a distinct syndrome: hypersensitivity pneumonitis.
- This discussion is limited to the classic pneumoconioses.
- The etiology of these diseases usually is multifactorial, with occupational and environmental factors (such as exposure to cigarette smoke) interacting with genetic risk to produce a spectrum of disease activity in affected individuals.
- Many different industries and metals may be associated with the development of pneumoconiosis. This discussion centers on the three most common: coal dust, silica, and asbestos.
- The exact pathophysiologic mechanisms by which these substances produce fibrosis are not well elucidated. In general, it involves chronic immune activation due to direct exposure, phagocytosis of the inorganic particles by macrophages, and the generation of reactive oxygen species with subsequent oxidative injury to the lung tissue.



Silicosis. “Dirty” macrophages in a subpleural perilymphatic and peribronchovascular distribution associated with bronchiolocentric fibrotic nodules (haematoxylin–eosin, ×20. Courtesy Dr Alberto Cavazza Reggio Emilia, Italy). [Spagnolo P, Sverzellati N, Wells AU, Hansell DM. Imaging aspects of the diagnosis of sarcoidosis. Eur Radiol. 2014 Apr;24(4):807-16.] *Caption from original*

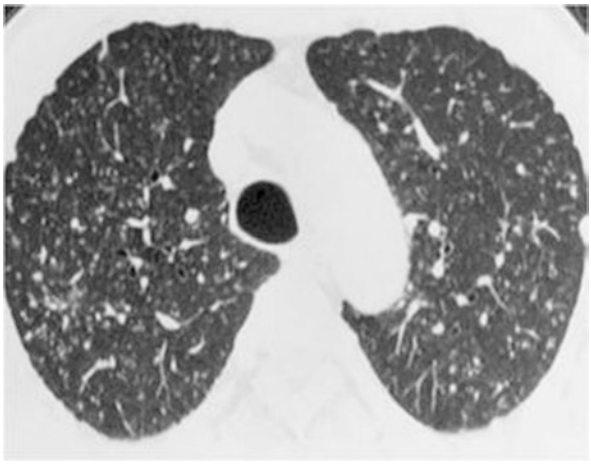


Coronal section of the lower lobe in an insulator with asbestosis. There is coarse linear interstitial fibrosis, but changes of advanced fibrosis or honeycombing are not present. Note accompanying visceral pleural fibrosis [Sporn TA, Roggli VL. Asbestosis. In: Oury TD, Sporn TA, Roggli VL, editors. Pathology of asbestos-associated diseases [Internet]. Berlin, Heidelberg: Springer; 2014 [cited 2015 Dec 22]. p. 53-80. Available from: http://link.springer.com/10.1007/978-3-642-41193-9_4] *Caption from original*



Silicosis. There is a cuff of dust-filled histiocytes around a small bronchiole [Colby TV, Leslie KO. Pathology of diffuse lung disease. In: Baughman RP, du Bois RM, editors. Diffuse lung disease [Internet]. New York: Springer; 2012 [cited 2016 Jan 14]. p. 49-70. Available from: http://link.springer.com/10.1007/978-1-4419-9771-5_4] *Caption from original*

- Coal dust: Coal is a combustible rock formed over eons by the biologic and geologic processing of dead plant matter. Coal is considered a fossil fuel, and the burning of coal is the largest source of energy for electricity generation worldwide. Long-term exposure (>10–20 years) to coal dust in coal mines may cause coal worker's pneumoconiosis (CWP). Inhaled coal dust appears to become phagocytized by macrophages, which tend to group together and develop into "coal macules" within the lung tissue. CWP may be classified radiographically and clinically into simple or complicated CWP. Cigarette smoking does not appear to increase the incidence of CWP.
  - Simple CWP is diagnosed when coal macules grow to about 2–5 mm and become visible on plain chest x-ray (CXR; within upper lung zones). These patients usually are asymptomatic. Simple CWP may be seen in about 10–15 % of coal miners who have worked in the mines for 20 years or more.

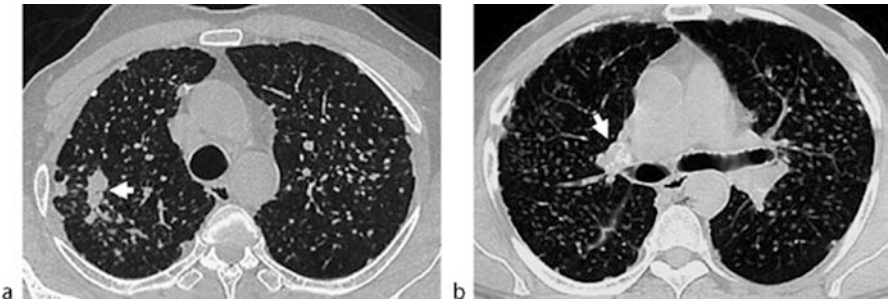


Coal workers pneumoconiosis. HRCT at the level of the upper lobes exhibits a "nodular without tree-in-bud pattern" characterized by ill-defined centrilobular nodules of slightly variable size that have an upper lobe and posterior predominance. A distinctive characteristic occasionally observed is that the micronodules of CWP tend to be less sharply defined and of more granular density than those of silicosis. [From article: Mimics in chest disease: interstitial opacities. Insights Imaging. 2013 Feb;4(1):9-27. https://doi.org/10.1007/s13244-012-0207-7, at http://link.springer.com/article/10.1007%2Fs13244-012-0207-7; by Anastasia Oikonomou, Panos Prassopoulos, © The Author(s) 2012; licensed under Creative Commons Attribution License http://creativecommons.org/licenses/by/2.0] *Caption and text from original*

- Complicated CWP is diagnosed when these macules coalesce into nodules 1 cm or larger. These nodules may take up an entire lobe. These patients usually have symptoms of dyspnea and chronic cough with a restrictive physiology. When the macules become very large and associated with fibrosis, the term *progressive massive fibrosis* (PMF) may be applied. This also is often referred to as "black lung". These patients have severe symptoms associated with hypoxia and a high mortality rate.

Coal worker's pneumoconiosis. PA chest film: This study demonstrates progressive massive fibrosis, which is usually seen in the upper lobes and posterior to midline on lateral view. Peripheral to the masses is lucency, also very characteristic as the masses "migrate" toward the hila [Goodman PC. Radiography and CT of occupational and environmental lung diseases. In: Huang Y-CT, Ghio AJ, Maier LA, editors. A clinical guide to occupational and environmental lung diseases [Internet]. Totowa, NJ: Humana Press; 2012 [cited 2015 Dec 22]. p. 59-92. Available from: http://link.springer.com/10.1007/978-1-62703-149-3_4] *Caption from original*

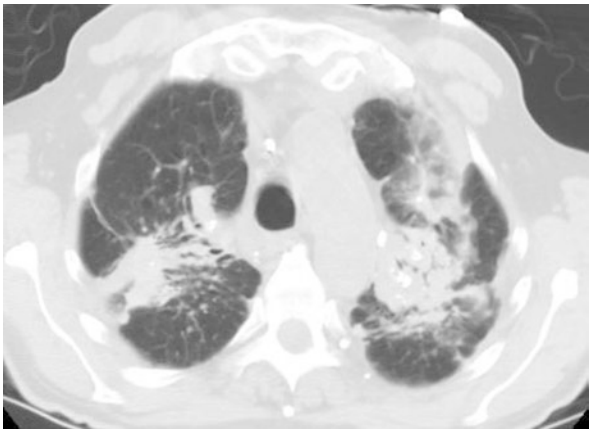
- Silica: Free silica (silicon dioxide, SiO2, crystalline quartz) is commonly encountered by employees in the mining, stonecutting, cement manufacturing, and other stone-related industries. In general, many years of exposure are required to develop pulmonary fibrosis. Silicosis also may be classified as simple or complicated. There also is a much less common syndrome from acute, high-intensity exposure: acute silicosis. Silica is taken up by alveolar macrophages, to which it is toxic. Patients with silicosis therefore have an increased risk for atypical lung infections associated with decreased macrophage function, such as tuberculosis, atypical mycobacteria, and fungi.
    - Simple silicosis, like simple CWP, is marked by the appearance on CXR of small (0.3–5-mm) round opacities in the upper lobes. These patients are mostly asymptomatic. About 20 % of patients will have associated calcification of their hilar lymph nodes, which gives a characteristic "eggshell" appearance on CXR and high-resolution CT (HRCT).



Silicotic nodules. (a) Centrilobular and randomly distributed pleural nodules and large opacity (arrow) due to complicated silicosis (progressive massive fibrosis). (b) Egg-shell calcification (arrow) in lymph nodes. [Hering KG. Pneumoconioses. In: Baert AL, editor. Encyclopedia of diagnostic imaging [Internet]. Berlin, Heidelberg: Springer; 2008 [cited 2015 Dec 22]. p. 1509-12. Available from: http://www.springerlink.com/index/10.1007/978-3-540-35280-8_1976] *Caption from original*

Silicosis. PA chest film demonstrates bilateral small nodules seen best over the lingual. [Goodman PC. Radiography and CT of occupational and environmental lung diseases. In: Huang Y-CT, Ghio AJ, Maier LA, editors. A clinical guide to occupational and environmental lung diseases [Internet]. Totowa, NJ: Humana Press; 2012 [cited 2015 Dec 22]. p. 59-92. Available from: http://link.springer.com/10.1007/978-1-62703-149-3_4] *Caption from original*

- Complicated silicosis occurs when the nodules grow or coalesce to greater than 1 cm in diameter. This usually is associated with significant fibrosis and usually leads to symptoms. As in CWP, these fibrotic nodules may become quite large and also lead to PMF and significant functional impairment and mortality. Once the process of fibrosis starts, it may continue even in the absence of continued exposure.



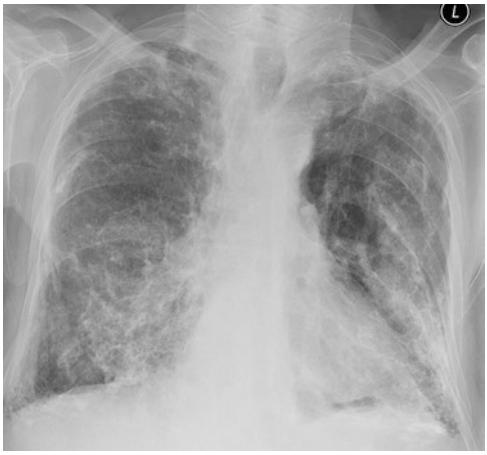
Silicosis. Single slice from a CT scan in lung windows demonstrates the typical upper posterior location of conglomerate opacities or progressive massive fibrosis in a patient with silicosis. Note the small clustered nodules posterior to the right-sided PMF as well as the bilateral hilar and mediastinal calcified lymph nodes. Also note that some calcified parenchymal nodules are incorporated in the PMF. [Goodman PC. Radiography and CT of occupational and environmental lung diseases. In: Huang Y-CT, Ghio AJ, Maier LA, editors. A clinical guide to occupational and environmental lung diseases [Internet]. Totowa, NJ: Humana Press; 2012 [cited 2015 Dec 22]. p. 59-92. Available from: http://link.springer.com/10.1007/978-1-62703-149-3_4] *Caption from original*

  - Acute silicosis is an uncommon syndrome that occurs after short-term exposure (about 1 year) to high concentrations of silica in confined spaces (e.g., from sandblasting or tunneling through rock with a high quartz content). It is manifest with progressive dyspnea and a chronic, usually nonproductive cough, although the patient occasionally may have gelatinous sputum, with low-grade fever and constitutional symptoms. CXR usually reveals a diffuse miliary pattern but may show diffuse alveolar opacities. HRCT shows a characteristic "crazy paving" pattern.

- Asbestos: *Asbestos* is a general term that refers to several mineral silicates. Silicate minerals are the predominant minerals in rock and make up 90 % of the earth's crust. These silicates differ from silica, which is silicon dioxide; rather, silicates have many different ratios of silicon to oxygen. Asbestos is characterized by being made up of long, thin, fiber-like crystals. Each visible fiber is composed of millions of microscopic "fibrils" that may be released by abrasion and other processes. Asbestos has been mined and used for millennia. It has excellent thermal, electrical, and acoustic insulating properties and is markedly fire resistant. Although synthetic materials largely have replaced asbestos use in developed nations, asbestos continues to be mined and used widely in developing countries. Asbestos predominantly affects the respiratory tract and causes pleural fibrosis, pulmonary fibrosis, cancers of the respiratory tract, and pleural and pulmonary mesothelioma. The development of asbestos-related diseases is

directly related to the extent and duration of exposure. In general, more than 10 years of exposure is necessary for any of these diseases to develop.

- *Asbestosis* is the term given to the pneumoconiosis associated with asbestos exposure. It is a diffuse, nodular, interstitial fibrosing disease of the lung. CXR usually shows the typical progression of disease, usually with pleural plaques as the initial finding. These plaques are observed as thickening or calcification of the parietal pleura, usually along the diaphragmatic border. Pleural plaques are a clue to significant asbestos exposure; they generally are asymptomatic and in isolation do not signify underlying pulmonary disease. Benign pleural effusions also may occur. As the disease progresses, CXR will show linear opacities in the lung bases that may become irregularly shaped and spread into the middle and upper lung zones. Severe disease may be associated with a diffuse ground-glass appearance and/or honeycombing on CXR. Once patients become symptomatic, they demonstrate restrictive pulmonary disease with decreased lung volumes and decreased diffusing capacity.



Asbestosis and asbestos-related pleural plaques. PA chest film demonstrates bibasilar heterogeneous irregular lung opacities (look at lung overlying both costophrenic angles) as well as calcified bilateral pleural plaques, many seen en face, which makes assessment of underlying lung disease difficult [Goodman PC. Radiography and CT of occupational and environmental lung diseases. In: Huang Y-CT, Ghio AJ, Maier LA, editors. A clinical guide to occupational and environmental lung diseases [Internet]. Totowa, NJ: Humana Press; 2012 [cited 2015 Dec 22]. p. 59-92. Available from: http://link.springer.com/10.1007/978-1-62703-149-3_4] *Caption from original*

- Other asbestos-related pulmonary disease:
  - Lung cancer is the most common cancer associated with asbestos exposure. It is directly related to the extent and duration of the exposure.

Smoking dramatically increases the risk of lung cancer in those exposed to asbestos. The risk is beyond what would be expected from just adding each risk (asbestos exposure and smoking) individually.

- Mesothelioma. Pleural and peritoneal mesothelioma is associated with asbestos exposure. It may occur with much less exposure and with prolonged latent periods (up to 40 years). Smoking does not appear to increase the risk of mesothelioma. Mesothelioma is much less common than lung cancer.

Presentation

Typical/"Classic"

- Pneumoconiosis may range from asymptomatic findings on imaging to severe, life-threatening restrictive pulmonary disease.
- Patients who develop symptoms usually will have slowly progressive shortness of breath and a dry cough.
- It usually is possible to obtain a history of occupational exposure to a known cause of pneumoconiosis.
- On examination, symptomatic patients usually have fine, inspiratory crackles.
- CXR and/or HRCT of the lungs usually show the typical changes of the inciting pneumoconiosis (see "Imaging").

Atypical

- Silicosis rarely may present more acutely, in patients who have been exposed to large amounts of silica dust in a small space (such as in tunneling and sandblasting). Acute silicosis may occur with short-term exposure (1 year or less). The presentation of acute silicosis is unlike that of usual silicosis (or other pneumoconioses), as it is not a restrictive disease. Although patients with acute silicosis have shortness of breath and cough, the cough may produce a copious amount of thick, white sputum. CXR may show diffuse, miliary nodules that subsequently develop into lobar consolidations. HRCT reveals the characteristic crazy-paving appearance of the lung parenchyma.

Primary Differential Considerations

- Pneumonia
- Acute exacerbation of COPD
- Pulmonary edema
- Acute exacerbation of asthma
- Lung cancer

History and Physical Exam

Findings That Confirm Diagnosis

- The diagnosis often may be nearly confirmed by a history of prolonged occupational exposure to a known inciting agent.
- There are no pathognomic physical examination findings for pneumoconiosis. Patients often demonstrate the signs of restrictive lung disease, such as diffuse, fine inspiratory crackles. Later findings with more advanced disease may include digital clubbing and hypoxia.
- The aforementioned findings together with a confirmatory imaging study confirm the diagnosis.

Factors That Suggest Diagnosis

- A history of occupational exposure to a known inciting agent should suggest the diagnosis.
- Symptoms that occur, or worsen, only while the patient is at work strongly suggest an occupational cause.

Factors That Exclude Diagnosis

- The complete lack of any occupational/environmental/hobby exposure to any of the known inciting agents for pneumoconiosis should lead to evaluation for an alternative diagnosis.

Ancillary Studies

Pulmonary Function Studies

- Pulmonary function tests (PFTs) may be very helpful in the diagnosis of pneumoconiosis. PFTs should show a restrictive pattern, with diffusely decreased lung volumes (total lung capacity [TLC], functional residual capacity [FRC], residual volume [RV], and forced vital capacity [FVC]) and a decreased diffusing capacity for carbon monoxide (DLCO). As opposed to obstructive lung disease (asthma, COPD), airway resistance in restrictive lung disease is normal.

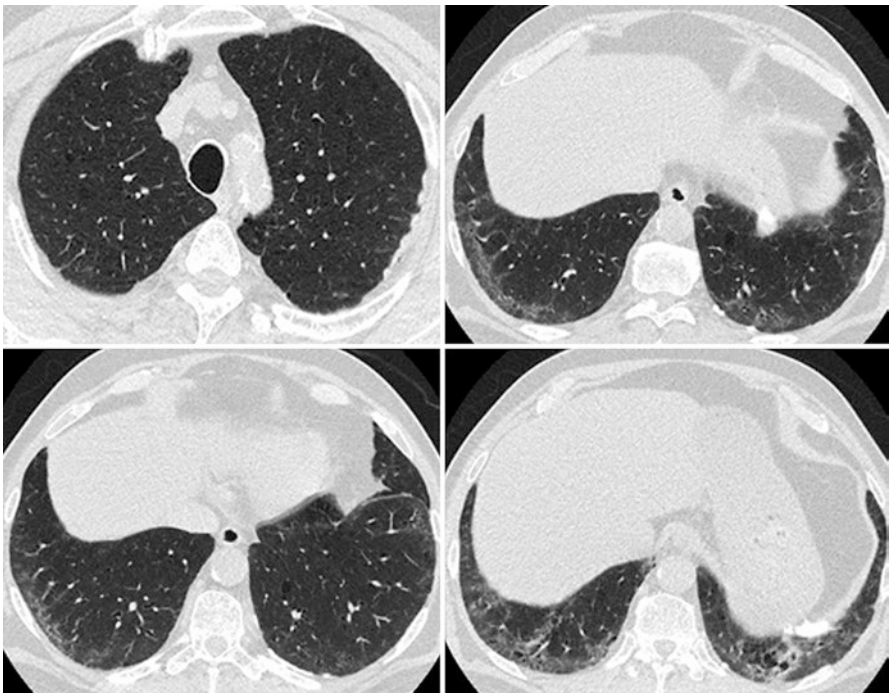
Laboratory

- There are no laboratory studies particularly helpful for the diagnosis or management of pneumoconiosis.

Imaging

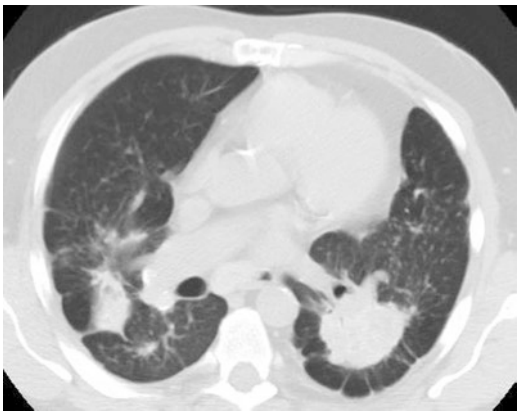
- CXR:
  - The plain CXR may be extremely useful in the diagnosis of pneumoconiosis.
  - In general, small round opacities in the upper lung zones are characteristic of both simple silicosis and simple CWP.
  - In both silicosis and CWP, the nodules may coalesce and grow to 1 cm or greater. Both diseases also progress to significant pulmonary fibrosis with larger areas of opacity as well as lung volume loss, usually noted in the upper lung zones. Sometimes these changes involve an entire lobe or even multiple lobes; this situation is termed progressive massive fibrosis.
  - About 20 % of patients with silicosis will develop calcification of the hilar lymph nodes, as seen on CXR; this is termed eggshell calcification and is characteristic of silicosis.
  - Asbestosis is characterized by pleural plaques (usually diaphragmatic) and small linear opacities in the lung bases. These opacities may spread to include all lung fields.
- HRCT of the lungs:

- HRCT is very helpful in the diagnosis and evaluation of all the ILDs.
- The changes associated with these diseases may be appreciated earlier and be more characteristic on HRCT as compared with CXR.
- HCRT has been shown to improve the detection and diagnosis of asbestosis compared with plain CXR.



HRCT scan of a 62 year old plumber with asbestosis showing linear opacities and subpleural nodular opacities (upper left), ground-glass attenuation, subpleural honeycombing, and calcified plaques [Müller-Quernheim J, Zissel G, Kayser G, Prasse A. Chronic beryllium disease and other interstitial lung diseases of occupational origin. In: Cottin V, Cordier J-F, Richeldi L, editors. Orphan lung diseases [Internet]. London: Springer; 2015 [cited 2015 Dec 22]. p. 473-91. Available from: http://link.springer.com/10.1007/978-1-4471-2401-6_30] *Caption from original*

- HRCT may lead to consideration of alternative ILDs in the differential diagnosis.
- HRCT may demonstrate the crazy-paving pattern typical of acute silicosis.



Coal worker's pneumoconiosis. Single slice of a CT scan demonstrates progressive massive fibrosis as represented by the larger opacities posterior to midline in the upper lobes. Just adjacent to the masses are very small nodular opacities which represent the earlier changes of coal worker's pneumoconiosis. As these small nodules coalesce, the large opacities are formed. As the masses migrate centrally, areas of emphysema are formed in the lung periphery as seen here bilaterally [Goodman PC. Radiography and CT of occupational and environmental lung diseases. In: Huang Y-CT, Ghio AJ, Maier LA, editors. A clinical guide to occupational and environmental lung diseases [Internet]. Totowa, NJ: Humana Press; 2012 [cited 2015 Dec 22]. p. 59-92. Available from: http://link.springer.com/10.1007/978-1-62703-149-3_4] *Caption adapted from original*

Special Populations

Age

- Given the decades-long latency between exposure and disease, these are diseases of middle-aged to older adults.

Co-morbidities

- There are multiple comorbidities of importance. Many of these patients also have risk factors for other pulmonary diseases, such as COPD, from other exposures and smoking, making the diagnosis and management more difficult.

- In many patients, the etiology of their pulmonary disease is multifactorial and includes occupational, environmental (smoking, air pollution), and genetic factors.
- Any cause of chronic dyspnea and cough (COPD, CHF, another ILD) may coexist with a pneumoconiosis.
- Patients with silicosis have decreased alveolar macrophage numbers and function, because silica is cytotoxic to these macrophages. These patients then have an increased risk and incidence of pulmonary infections associated with decreased macrophage function, primarily tuberculosis, atypical mycobacterial pneumonia, and fungal pneumonia.
- Silicosis (and to a lesser extent, CWP) also is associated with an increased incidence of autoimmune connective tissue diseases, such as rheumatoid arthritis (both silicosis and CWP) and scleroderma (silicosis only). Seropositive rheumatoid arthritis associated with findings of simple silicosis or simple CWP on CXR has been called Caplan's syndrome.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to obtain a complete occupational, environmental, and hobby history to be able to ascertain any significant exposures the patient may have sustained.
- If supported by the history, and the diagnosis is being considered, it is critical to perform appropriate imaging (CXR, HRCT) and PFTs to secure the diagnosis.

Mimics

- Many different diseases may present similarly to pneumoconiosis (with dyspnea and cough), including all the ILDs, COPD, asthma, and CHF.
- With an appropriate history, examination, imaging, and PFTs, the mimics include other restrictive lung diseases, such as other ILDs.

Time-Dependent Interventions

- These disorders tend to be chronic and slowly progressive, so there are no significant time-dependent interventions.

- If a patient presents with hypoxia, oxygen should be administered.
- If a patient is having ventilatory difficulty, ventilation should be supported. Patients with ventilatory difficulty generally have advanced disease, and the approach to managing ventilatory emergencies would ideally have been discussed with the patient and family and decisions made before the acute event.

Overall Principles of Treatment

- There is no specific treatment for any pneumoconiosis.
- Treatment tends to be supportive and should proceed as for most restrictive lung diseases.
- Patients with hypoxia require oxygen.
- Patients with silicosis should be monitored for atypical lung infections, such as tuberculosis.
- All patients should receive routine care as appropriate for any patient with chronic lung disease, including appropriate vaccinations (influenza, pneumococcus).
- Patients who smoke tobacco should be offered all assistance needed to stop.
- Patients still working in an occupation with risk for continued exposure should stop or be moved to a position with no exposure risk.
- These patients may be at increased risk for lung cancer and may need periodic monitoring.

Disease Course

- These diseases are slowly progressive.
- The diseases may continue to progress even after the exposure has stopped.
- There is a large individual variation in the severity of disease. Although development of a pneumoconiosis is related to the extent and duration of exposure, severity of disease is less so.
- Many patients will remain asymptomatic, with only CXR findings, throughout their lives. Some patients may develop only minor symptoms; others may progress to life-altering and -shortening disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Review

Prazakova S, Thomas PS, Sandrini A, Yates DH. Asbestos and the lung in the 21st century: an update. Clin Respir J. 2014 Jan;8(1):1-10. https://doi.org/10.1111/crj.12028. PMID: 23711077. http://www.ncbi.nlm.nih.gov/pubmed/23711077 **

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Karkhanis VS, Joshi JM. Pneumoconioses. Indian J Chest Dis Allied Sci. 2013 Jan-Mar;55(1):25-34. PMID: 23798087. http://www.ncbi.nlm.nih.gov/pubmed/23798087 **

Laney AS, Weissman DN. The classic pneumoconioses: new epidemiological and laboratory observations. Clin Chest Med. 2012 Dec;33(4):745-58. https://doi.org/10.1016/j.ccm.2012.08.005. PMID: 23153613. http://www.ncbi.nlm.nih.gov/pubmed/23153613 **

Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012 May 26;379(9830):2008-18. https://doi.org/10.1016/S0140-6736(12)60235-9. PMID: 22534002. http://www.ncbi.nlm.nih.gov/pubmed/22534002 **

Review. Yucesoy B, Luster MI. Genetic susceptibility in pneumoconiosis. Toxicol Lett. 2007 Feb 5;168(3):249-54. PMID: 17161563. http://www.ncbi.nlm.nih.gov/pubmed/17161563 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pneumoconiosis"[Mesh] OR "Pneumoconiosis"

Chapter 58
Pneumonia

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Pneumonia

Incidence/Epidemiology

- Pneumonia is an infection of the lung parenchyma.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_58

Pneumococcal pneumonia, Chest radiograph of a black African man aged 19 years who presented with a 1-week history of cough, fever, and chest pain. Radiograph shows dense consolidation of the right upper lobe. Differential diagnosis included Klebsiella pneumonia. Sputum Gram stain and blood culture confirmed Streptococcus pneumoniae. The patient also had marked weight loss and oropharyngeal candidiasis. [Lalloo UG, Ambaram A, Vawda F. Pulmonary Complications. In: Mildvan D, editor. International Atlas of AIDS. 4e.: Current Medicine; 2008. 366 p. ISBN: 1-57340-270-2] *Caption adapted from original*

- Chest pain due to pneumonia tends to be pleuritic in nature.
- Pneumonia may be caused by any of a broad variety of infectious agents, including viruses, bacteria, fungi, rickettsiae, and parasites.
- Pneumonia is typically classed as community-acquired (community-acquired pneumonia or "CAP"), healthcare- (or hospital-) associated (HCAP or HAP), or ventilator-associated (VAP). Each of these classifications carries a largely predictable etiologic profile. Classification does not usually affect the chest pain presentation of pneumonia, although pneumococcal pneumonia and infections that cause pleural effusions or lung abscesses typically present with more severe pain.
- The bacterial pathogens that cause pneumonia may be "typical" (such as pneumococcal, *Hemophilus*, or staphylococcal) or "atypical" (such as *Mycoplasma* or *Chlamydophila*). Pathogen does not usually affect the chest pain presentation of pneumonia.

Pathogen	CAP	HAP/HCAP	Adults	Children
Bacteria				
S. pneumoniae	+++	+++	+++	+++
H. influenzae	++	++	++	++
M. pneumoniae	+++	+	++	+++
Chlamydia spp.	+		(+)	++
Klebsiella spp.	+	++		
Legionella spp.	++	+++		
S. aureus	++	+++	+++	+
P. aerugenosa	+	+++	+	
Acinetobacter spp.		++		
Viruses				
RSV	++		+	+++
Rhinovirus	++		(+)	++
Influenza virus	++	+	+	++
Parainfluenza virus	++		+	++
Fungi				
Candida spp.		++1		
Aspergillus spp.		++1		
P. jirovecii		+2		

+ indicates the relative importance of the pathogen and the frequency of isolation in adults or children. 1 of importance in immunocompromised hosts. 2 important opportunistic pathogen in HIV/AIDS patients. CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; HCAP, health-care associated pneumonia. Based on collective data [2,5,6,15-18,23,252,253].

Important pathogens causing pneumonia. (See article for data sources.) [From article: Lung epithelium as a sentinel and effector system in pneumonia – molecular mechanisms of pathogen recognition and signal transduction. Respiratory Research. 2006 Jul 8;7(1):97. https://doi.org/10.1186/1465-9921-7-97, at http://link.springer.com/article/10.1186/1465-9921-7-97; by Stefan Hippenstiel, Bastian Opitz, Bernd Schmeck, Norbert Suttorp, © Hippenstiel et al. 2006; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

Differential Diagnosis

- The differential considerations for chest pain due to pneumonia are for the most part other primary lung diagnoses such as pulmonary embolism and pleurisy.
- As in all chest pain presentations, immediate life threats such as acute coronary syndrome and aortic dissection should always be considered.
- Less severe differential considerations include pneumothorax, which can cause pleuritic pain, as well as chest wall pain/costochondritis, and anxiety.
- Pericarditis may present similarly to pneumonia and may also be accompanied by fever.
- Acute chest syndrome in sickle cell disease is a differential consideration in at-risk patients.

Pathophysiology and Etiology

- The clinical manifestations of pneumonia result from a variable combination of actual infection, as well as the host's inflammatory response to the infection.
- The actual etiologic agents behind pneumonia would require an exceedingly long list. For purposes of considering pneumonia in the differential diagnosis of chest pain syndrome, pain is typically caused by inflammation of the pleura. Chest pain in pneumonia can also result from lung abscess, pleural effusion or empyema, myalgias associated with a more systemic infection, or chest wall pain from coughing.

Presentation

Typical/"Classic"

- The classic presentation of pneumonia includes:
  - Cough, which may or may not be productive.
  - Fever, which may be mild or high.
  - Shortness of breath, typically more evident with exertion.
  - Chills.

Atypical

- Especially with "atypical" etiologies, pneumonia may present with more prominent extrapulmonary symptoms, such as headache, myalgias, sore throat, gastroenteritis-type symptoms, or fatigue. Chest pain may or may not be a prominent feature at presentation.
- Elderly patients with pneumonia may present with altered mental status. Chest pain may or may not be a prominent feature at presentation.

Extra-pulmonary symptoms	Chills, nausea, vomiting, altered sensorium, diarrhea, delirium, worsening of a chronic confusion, fall to the ground
Pulmonary symptoms	Dyspnea, pleuritic chest pain
Signs of pneumonia	Fever, crackles, cough
Clinical features suggestive of aspiration pneumonia	Evident macroaspiration
	Reduced level of consciousness
	Dysphagia
	Mechanical or neurological dysfunction of the high gastrointestinal tract

Signs and symptoms most commonly associated with pneumonia in elderly patients. [Falcone M, Blasi F, Menichetti F, Pea F, Violi F. Pneumonia in frail older patients: an up to date. Internal and Emergency Medicine. 2012 Oct;7(5):415–24.] *Caption from original*

- *Mycoplasma* pneumonia may present with ear pain (from bullous myringitis) or with rashes (such as erythema multiforme). Chest pain may or may not be a prominent feature at presentation.

Characteristics	*M. pneumoniae*	*S. pneumoniae*	*p* value
Number	64	68	
Mean age (range), years	36.6 (18–69)	61.8 (19–86)	<0.0001
Male: Female	34: 30	42: 26	0.3791
Co-morbid illness	15 (23)	33 (48)	<0.0001
PSI risk classes**			
I – III	41 (64)	29 (43)	0.0154
IV	23 (36)	39 (57)	
V	0	0	
WBC mean (/μL)	7,400	13,800	<0.0001

*Data represent the numbers of patients, and numbers in parentheses are percentages.
**PSI, pneumonia severity index.

Clinical characteristics in patients with *Mycoplasma pneumoniae* pneumonia and *Streptococcus pneumoniae* pneumonia on admission* [From article: Radiographic features of *Mycoplasma pneumoniae* pneumonia: differential diagnosis and performance timing. BMC Medical Imaging. 2009;9(1):7. https://doi.org/10.1186/1471-2342-9-7, at http://link.springer.com/article/10.1186/1471-2342-9-7; by Naoyuki Miyashita, Tadaaki Sugiu, Yasuhiro Kawai, Keiko Oda, Tetsuya Yamaguchi, Kazunobu Ouchi, Yoshihiro Kobashi, Mikio Oka, © Miyashita et al; licensee BioMed Central Ltd. 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- *Chlamydophila* pneumonia may present with bronchospasm and wheezing even in nonasthmatics, but it should be noted that patients with underlying asthma or COPD who present with pneumonia are likely to be wheezing. Chest pain may or may not be a prominent feature at presentation.
- Patients with pneumonia may present with overwhelming sepsis, but chest pain is typically not the most prominent feature.

Primary Differential Considerations

- Early consideration should be given to bronchitis, acute exacerbation of COPD, foreign body aspiration, asthma, and ARDS.

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination cannot confirm the presence of pneumonia.

Factors That Suggest Diagnosis

- A history of fever, chills, and/or sputum production—especially hemoptysis—is suggestive of pneumonia in the patient with chest pain.
- Findings of consolidation of pulmonary exam—such as egophony and percussion dullness—are suggestive of pneumonia.

http://www.easyauscultation.com/egophony
Egophony. [Egophony Page; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

https://www.youtube.com/watch?v=48nzLXnEHvg
Percussion of the Chest (Stanford Medicine 25 video): Demonstrates percussion technique and surface anatomy

- Tachycardia and reduced pulse oximetry readings are suggestive of pneumonia in the patient with chest pain.
- Wheezing, rales, and pleural friction rub may all suggest pneumonia in the patient with chest pain.

http://www.easyauscultation.com/wheezing
Wheezing. [Wheezing; *Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]*

http://www.easyauscultation.com/rales
Rales. [Rales Lung Sounds; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

https://www.youtube.com/watch?v=t2QE0O_exAQ
Pleural Friction Rub

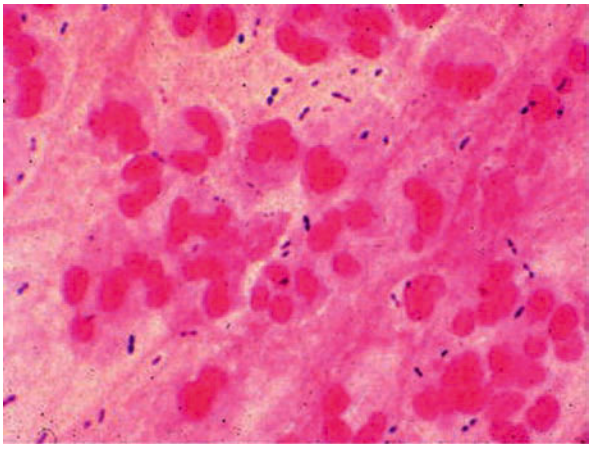
Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude pneumonia in the patient with chest pain.

Ancillary Studies

Laboratory

- Bacterial pneumonia is confirmed, not in real time, by the presence of a positive bacterial culture from sputum or blood.
- Various diagnostic tests performed on sputum, blood, or urine can provide confirmation of the etiology of a clinical pneumonia.
- Sputum Gram stain is a notoriously unreliable test for evaluating possible pneumonia.



Gram stain of sputum sample from patient with pneumococcal pneumonia. Note diploid organisms surrounded by polymorphonuclear cell infiltrate [Shelburne S, Musher DM. Management of Gram-Positive Bacterial Disease: Staphylococcus aureus, Streptococcal, Pneumococcal and Enterococcal Infections. In: Safdar A, editor. Principles and Practice of Cancer Infectious Diseases [Internet]. Totowa, NJ: Humana Press; 2011 [cited 2015 Jun 2]. p. 409–21. Available from: http://link.springer.com/10.1007/978-1-60761-644-3_35] *Caption from original*

- A CBC in pneumonia will typically show an elevated WBC count except in severely immunocompromised patients. This is also less likely in viral pneumonias.
- *Legionella* pneumonia is often associated with hyponatremia.

	Patients with Legionella that met IDSA/ATS criteria for Legionella testing	Patients with Legionella that did not meet IDSA/ATS criteria for Legionella testing	All patients with Legionella pneumonia
Male	15	9	24 (65%)
Recent travel	1	0	1 (3%)
History of alcohol abuse	6	0	6 (16%)
Anti-TNF therapy	1	1	2 (5%)
Daily steroid use	0	1	1 (3%)
Cancer	4	4	8 (22%)
Diabetes	5	6	11 (29%)
COPD	5	4	9 (24%)
Solid-organ transplant recipient	0	1	1 (3%)
HIV infection	1	0	1 (3%)
Receipt of antibiotics prior to hospitalization	4	0	4 (11%)
Pleural effusion present at hospital admission	7	0	7 (19%)
ICU admission	14	0	14 (38%)
Abnormal liver function tests	15	5	20 (54%)
Hyponatremia (Sodium < 130 mEq/L)	9	4	13 (35%)
Crude mortality	6	0	6 (16%)

SD, standard deviation; TNF, tumor necrosis factor; COPD, chronic obstructive pulmonary disease; abnormal liver function test defined as above reference range; Crude mortality defined as in-hospital death or discharge to hospice care with impending death.

Characteristics of Adult Patients with *Legionella* Pneumonia, 2005-2009 [From article: How often is a work-up for *Legionella* pursued in patients with pneumonia? A retrospective study. BMC Infectious Diseases. 2011; 11(1):237. https://doi.org/10.1186/1471-2334-11-237, at http://link.springer.com/article/10.1186/1471-2334-11-237; by Brian Hollenbeck, Irene Dupont, Leonard A Mermel, © Hollenbeck et al; licensee BioMed Central Ltd. 2011; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

- Normal laboratory studies do not exclude pneumonia as a cause of chest pain.

Imaging

- Chest radiography can confirm the presence and location of pneumonia.

Hospital-acquired pneumonia. Chest radiograph of a patient with hospital-acquired pneumonia. This patient developed bilateral infiltrates after aspirating postoperatively. [Rumbak MJ. Nosocomial infections including pneumonia. In: Crapo JD, editor. Bone's Atlas of Pulmonary Medicine. 3rd edition. Philadelphia, PA: Current Medicine Group; 2005. 338 p. ISBN: 1-57340-211-7] *Caption adapted from original*

- Chest radiography can identify abscesses, cavities, and pleural involvement.

Chest radiograph of a patient with complicated lung abscess. [Ayed AK, Al-Rowayeh A. Lung resection in children for infectious pulmonary diseases. Pediatric Surgery International. 2005 Aug;21(8):604–8.] *Caption from original*

- Chest radiography can be used to follow the treatment success (or lack thereof) of pneumonia management.
- A normal chest radiograph does not exclude pneumonia, as patients who are immunocompromised, dehydrated, or very early in the disease process may not show an infiltrate. Chest CT may be helpful in patients suspected of having pneumonia but lacking diagnostic certainty on plain chest radiography.

Computed tomography (CT) findings of organizing pneumonia on admission. Multiple consolidations with sub-pleural distribution were detected in both lungs by CT scan. The lesions were accompanied by ground glass opacities. [Nakamura H, Kita J, Kawakami A, Yamasaki S, Ida H, Sakamoto N, Furusu A, Eguchi K. Multiple bone fracture due to Fanconi's syndrome in primary Sjögren's syndrome complicated with organizing pneumonia. Rheumatology International. 2009 Dec;30(2):265–7.] *Caption from original*

Special Populations

Age and Gender

- Pneumonia occurs in all age, ethnic, and socioeconomic groups. It occurs in both males and females.
- Pneumonia often has poorer outcomes at the extremes of age.
- In children, atypical pathogens predominate.
- In newborns and infants, viruses (including RSV), pneumococcus, and aspiration are important etiologic ocnsiderations.

- Current recommendations for the management of community-acquired pneumonia in children include:
  - Viral testing for infants less than 1 year.
  - Avoidance of routine chest radiographs.
  - Omission of blood work, including CBC's and blood cultures.
  - Use of amoxicillin in pre-school children.
  - Use of a macrolide in school-age children.

Co-morbidities

- Co-morbidities associated with the various types of pneumonia include but are not limited to:
  - congestive heart failure
  - cancer
  - chronic renal failure
  - COPD and chronic respiratory failure
  - chronic hepatic disease
  - alcoholism
  - diabetes mellitus
  - neurologic disease
  - immunosuppression, including HIV infection

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Except in significantly compromised patients, pneumonia is most often not a life-threatening diagnosis. Still, it is a cause of significant morbidity, loss of productivity, and cost. Even in immunocompetent patients, pneumonia can cause sepsis and death. It is therefore critical to at least consider the diagnosis in the patient with chest pain, and a chest radiograph often gives useful information.

Mimics

- The entire constellation of diagnoses that underlies chest pain syndrome, especially those often accompanied by dyspnea, can mimic the pain and overall presentation of pneumonia. Be especially cognizant of pulmonary embolism as a mimic, as PE has a higher case-mortality rate than pneumonia.
- Pericarditis may mimic pneumonia in presentation. Listen for a pericardial friction rub.

http://www.easyauscultation.com/acute-pericarditis

Acute Pericarditis Audio Recordings. [Acute Pericarditis; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Time-Dependent Interventions

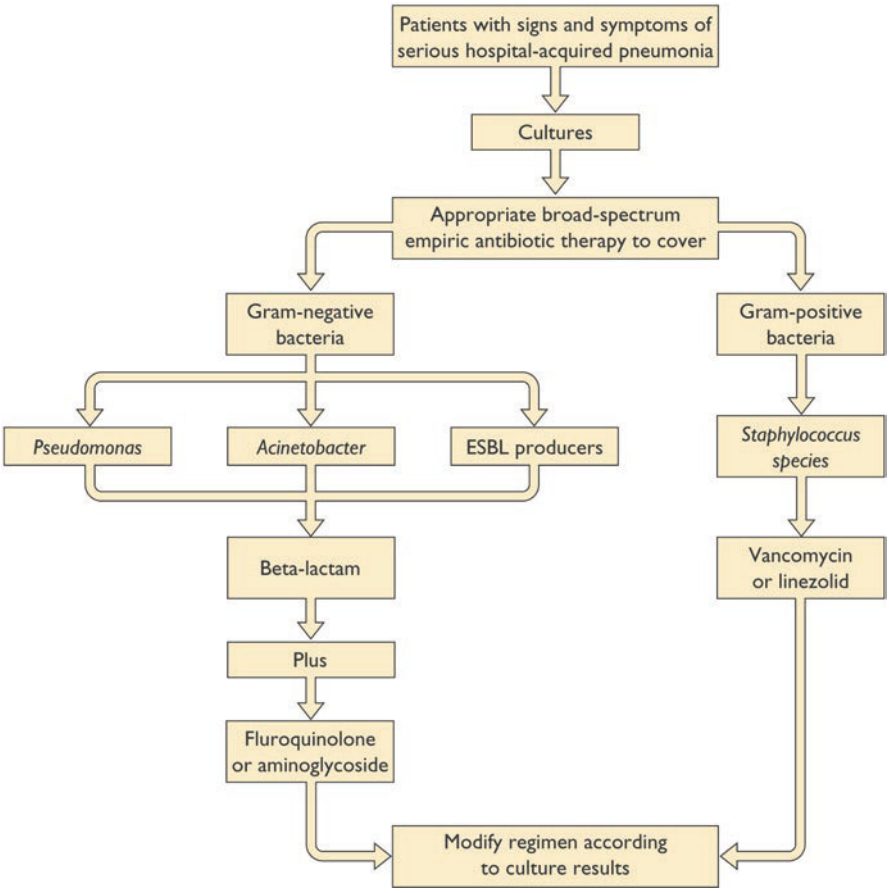
- Anti-infective therapy, usually at first with empiric antibiotic therapy, should be initiated when the diagnosis of pneumonia is strongly considered or confirmed. Consult your local antibiogram for guidance on choosing a specific agent.
- Choice of antimicrobial is also driven by the classification of the pneumonia (CAP vs HAP vs VAP).

Overall Principles of Treatment

- Anti-infective therapy is the mainstay of pneumonia treatment. Unfortunately, treatment is not always guided by positive microbiologic or virologic results.

Patient status	Treatment
Outpatient (previously healthy without history of antimicrobials in the last 3 months)	Macrolide or Doxycycline
Outpatient (comorbidities such as chronic heart, lung, liver or renal disease, diabetes, alcoholism, malignancy, asplenia, immunosuppressed, or history of antimicrobials in the last 3 months)	Respiratory fluoroquinolone or Beta lactam plus macrolide
Inpatient (non-ICU)	Respiratory fluoroquinolone or Beta lactam plus macrolide
Inpatient (ICU)	Beta lactam plus Either azithromycin or respiratory fluoroquinolone
Inpatient (with concern of *Pseudomonas*)	Antipneumococcal, antipseudomonal beta lactam (piperacillin–tazobactam, cefepime, imipenem, or meropenem) plus ciprofloxacin or levofloxacin or Above beta lactam plus either aminoglycoside or azithromycin or Above beta lactam plus azithromycin and aminoglycoside
Inpatient (with concern of methicillin-resistant *Staphylococcus aureus*)	Add vancomycin or linezolid to regimen

Recommendations for empiric treatment of community-acquired pneumonia. [Nguyen HH. Pneumonia. In: Mainous III AG, Pomeroy C, editors. Management of Antimicrobials in Infectious Diseases [Internet]. Totowa, NJ: Humana Press; 2010 [cited 2015 Jun 3]. p. 169–82. Available from: http://link.springer.com/10.1007/978-1-60327-239-1_9] *Caption from original*



Treatment of patients with ventilator-associated pneumonia (VAP). This algorithm suggests initial broad-spectrum antibiotics to cover gram- negative and gram-positive bacteria. Once the cultures are back from the laboratory, the antibiotics are tailored to the bacteria. "Beta-lactams" here include carbapenems and monolactems. ESBLS and *Acinetobacter* may respond best to carbapenems. ESBL—extended-spectrum β-lactams [Rumbak MJ.Nosocomial infections including pneumonia. In: Crapo JD, editor. Bone's Atlas of Pulmonary Medicine. 3rd edition. Philadelphia, PA: Current Medicine Group; 2005. 338 p. ISBN: 1-57340-211-7] *Caption from original*

- Chest pain associated with pneumonia usually improves quickly as the infection resolves. Non-steroidal anti-inflammatory drugs or narcotics can be given to patients with persistent or severe pain.

Disease Course

- The course pneumonia varies widely with mortality rates as high as 50% in some severely compromised patients, and as low as less than 1% in immunocompetent, nonsmoking adults with CAP.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, Kaplan SL, Mace SE, McCracken GH Jr, Moore MR, St Peter SD, Stockwell JA, Swanson JT, Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011 Oct;53(7):e25-76. https://doi.org/10.1093/cid/cir531. PMID: 21880587. http://www.ncbi.nlm.nih.gov/pubmed/21880587 **

Levy ML, Le Jeune I, Woodhead MA, Macfarlaned JT, Lim WS; British Thoracic Society Community Acquired Pneumonia in Adults Guideline Group. Primary care summary of the British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: 2009 update. Endorsed by the Royal College of General Practitioners and the Primary Care Respiratory Society UK. Prim Care Respir J. 2010 Mar;19(1):21-7. https://doi.org/10.4104/pcrj.2010.00014. Erratum in: Prim Care Respir J. 2010 Jun;19(2):108. PMID: 20157684. http://www.ncbi.nlm.nih.gov/pubmed/20157684 **

Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55. https://doi.org/10.1136/thx.2009.121434. PMID: 19783532. http://www.ncbi.nlm.nih.gov/pubmed/19783532 **

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Review

Song JY, Eun BW, Nahm MH. Diagnosis of pneumococcal pneumonia: current pitfalls and the way forward. Infect Chemother. 2013 Dec;45(4):351-66. https://doi.org/10.3947/ic.2013.45.4.351. PMID: 24475349. http://www.ncbi.nlm.nih.gov/pubmed/24475349 **

Asrar Khan W, Woodhead M. Major advances in managing community-acquired pneumonia. F1000Prime Rep. 2013 Oct 1;5:43. https://doi.org/10.12703/P5-43. PMID: 24167724. http://www.ncbi.nlm.nih.gov/pubmed/24167724

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Lippi G, Meschi T, Cervellin G. Inflammatory biomarkers for the diagnosis, monitoring and follow-up of community-acquired pneumonia: clinical evidence and perspectives. Eur J Intern Med. 2011 Oct;22(5):460-5. https://doi.org/10.1016/j.ejim.2011.02.023. PMID: 21925053. http://www.ncbi.nlm.nih.gov/pubmed/21925053

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Cohort Study

Medford AR, Husain SA, Turki HM, Millar AB. Diagnosis of ventilator-associated pneumonia. J Crit Care. 2009 Sep;24(3):473.e1-6. https://doi.org/10.1016/j.jcrc.2008.06.012. PMID: 19327300. http://www.ncbi.nlm.nih.gov/pubmed/19327300

Comparative Study

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pneumonia"[Mesh] OR "Pneumonia"

Chapter 59
Pneumothorax (Simple)

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Simple pneumothorax; dropped lung; ruptured lung; ruptured bleb

Incidence/Epidemiology

- Because simple pneumothorax may be largely or completely asymptomatic, the incidence is clearly underestimated. It ranges from 2–60 per 100,000 people per year, depending on gender and associated lung disease.
- Primary spontaneous pneumothorax is more common in men than in women, and is more common in smokers than in nonsmokers.
- Primary spontaneous pneumothorax occurs most commonly in the third decade of life and is rare after the fifth decade.
- Secondary spontaneous pneumothorax tends to occur in older patients because of the prevalence of underlying lung disease in those patients.
- Traumatic pneumothorax can occur at any age and may result from accidental or iatrogenic trauma.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_59

Differential Diagnosis

- The differential considerations for pneumothorax are primarily driven by the size of the pneumothorax and the extent of any underlying lung disease. Exacerbations of asthma and COPD may both precipitate and present similarly to simple pneumothorax. Other causes of dyspnea and pleuritic chest pain, alone or together, should also be considered, including pulmonary embolism, pneumonia, pleurisy, mediastinal disorders, and anxiety.

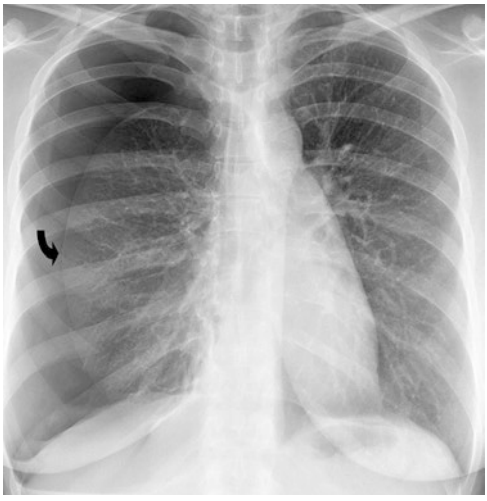
Pathophysiology and Etiology

- Pneumothorax is defined by the presence of air in the pleural space, which is the ordinarily tiny space between the visceral and parietal layers of the pleura.

Primary spontaneous (simple) pneumothorax
Secondary spontaneous (complicated) pneumothorax
Catamenial pneumothorax
Pneumothorax associated with drug abuse
Iatrogenic pneumothorax
Pneumothorax associated with mechanical ventilation
Traumatic pneumothorax
Tension pneumothorax

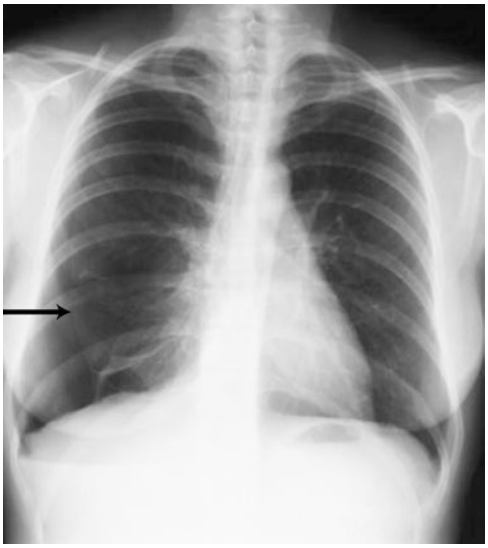
Types of pneumothorax. Primary spontaneous pneumothorax occurs in patients without underlying lung disease. It usually occurs in young, tall, slender male patients. Secondary pneumothoraces occur in those patients with underlying lung disease. Pneumothorax has also been associated with drug abuse and is believed to be related to the inhalational route of drug abuse, in which the abuser performs a Valsalva maneuver with generation of pressures greater than 200 cm H2O. Iatrogenic pneumothorax occurs most commonly during attempted central line placement, with the risk between 3% and 6% for subclavian placement and about 1% to 2% with internal jugular catheterization. Traumatic pneumothorax may be caused by blunt or penetrating trauma and may have associated hemopneumothorax and other vascular injuries. [Szokol J, Vender J. Respiratory emergencies (pulmonary aspiration of gastric contents, acute epiglottis, anterior mediastinal mass). In: Tremper KK, editor. Principles of anesthetic techniques and anesthetic emergencies. Philadelphia: Current Medicine; 1998. 195 p. (Miller RD, editor. Atlas of anesthesia; vol. 4). ISBN: 0-443-07903-X] *Caption from original*

- Simple pneumothorax may be small and asymptomatic or larger, resulting in dyspnea. Depending on the size of the pneumothorax, the adjacent lung may be deformed or compressed, or totally collapsed. Simple pneumothorax is differentiated from the more obvious, more symptomatic, and life-threatening "tension pneumothorax" by the fact that in the latter, the pressure in the pleural space is positive throughout the respiratory cycle, resulting in forced deviation of the mediastinum to the contralateral side.



Tension pneumothorax. Portable chest radiograph demonstrates large right-sided tension pneumothorax (curved arrow) with mediastinal shift to the left side [Carter BW, Muse VV. Imaging of Nontraumatic Mediastinal and Pulmonary Processes. In: Singh A, editor. Emergency Radiology [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Aug 31]. p. 321–32. Available from: http://link.springer.com/10.1007/978-1-4419-9592-6_23] *Caption from original*

- Simple pneumothorax may be spontaneous (primary or secondary) or traumatic:
  - Primary spontaneous pneumothorax is usually the result of rupture of an apical pleural bleb or bulla, a small cystic space lying just under the visceral pleura. The designation "primary" is meant to imply the absence of underlying lung disease, but primary spontaneous pneumothorax occurs more commonly in smokers than in nonsmokers, indicating the likely presence of subclinical lung pathology. The "primary" also signifies the absence of a known inciting event, such as trauma. A special case is so-called "catamenial" pneumothorax, which typically occurs in women age 30–40, presents within 48 hours of menses onset, and may be recurrent.



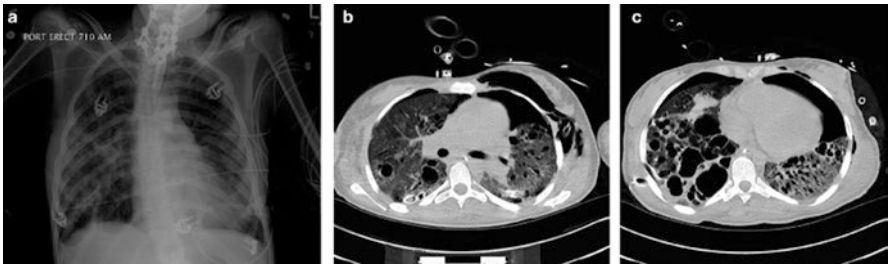
Catamenial pneumothorax. Chest radiograph of a 31-year-old nonsmoking woman with multiple spontaneous right-sided pneumothoraces who presented with acute onset of pleuritic chest pain and dyspnea. There is a large right-sided pneumothorax; the arrow signifies the 1 mm visceral pleural line. [Huggins J, Sahn S. Pleural disease. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Current Medicine; 2005. Chapter 25. ISBN: 1-57340-211-7] *Caption adapted from original*

  - Secondary spontaneous pneumothorax has been reported with virtually all lung diseases, but is most common with COPD. Air enters the pleural space through distended or damaged alveoli.
  - Traumatic pneumothorax occurs as a result of physical disruption of the pleura, either from blunt force pressure or from puncture. Puncture may be accidental, as in blunt trauma with rib fracture, or iatrogenic, as in puncture of the pleura during placement of a central venous catheter.

- Primary spontaneous pneumothorax is more likely to occur in tall, thin individuals. There is an association with Marfan's syndrome. It is much more common in smokers than in nonsmokers. There seems to be a familial tendency to develop primary spontaneous pneumothorax. It is also more common during pregnancy.

Clinical features. Many of the typical features of Marfan's syndrome are seen in this patient, including arm length greater than height, increased lower to upper extremity ratio, pectus excavatum, and pes planus. [Maricic M, Ko M. Diseases of bone and connective tissue. In: Hunder G, editor. Atlas of rheumatology. Philadelphia: Current Medicine; 2005. Chapter 6. ISBN: 1-57340-210-9] *Caption adapted from original*

- Secondary spontaneous pneumothorax is most common in patients with obstructive lung disease, such as COPD or asthma, in which intrathoracic pressures are higher. It is also more common in pneumonia (including necrotizing pneumonia, *Pneumocystis* pneumonia in AIDS, and tuberculosis), sarcoidosis and other connective tissue diseases, and lung neoplasms.
- Accidental traumatic pneumothorax may result from penetrating or nonpenetrating (blunt) injury. Iatrogenic traumatic pneumothorax has been reported with:
    - Central venous catheter insertion (subclavian or internal jugular)
    - Lung, pleural, or mediastinal biopsy
    - Intercostal nerve block
    - Chest compressions for CPR
    - Positive-end-expiratory pressure (PEEP) ventilation



AP chest radiograph (a) axial CT (b, c) confirms the presence of subcutaneous emphysema and bilateral pneumothorax in this ICU patient who developed barotrauma secondary to high levels of PEEP. There is evidence of acute respiratory distress syndrome (ARDS). [Boiselle PM, Dass C, Steiner RM. Radiologic Imaging in the Critically Ill Patient. In: Criner GJ, Barnette RE, D'Alonzo GE, editors. Critical Care Study Guide [Internet]. New York, NY: Springer New York; 2010 [cited 2015 Aug 31]. p. 181–207. Available from: http://link.springer.com/10.1007/978-0-387-77452-7_11] *Caption from original*

Presentation

Typical/"Classic"

- Pleuritic chest pain and shortness of breath are the most common findings in simple pneumothorax at presentation. Pain is often of sudden onset. With larger pneumothorax volumes, patients may manifest hypoxemia and have hemodynamic instability or mental status changes.
- The diagnosis of simple pneumothorax is made on chest radiography—typically a plain CSR, sometimes computed tomography. Ultrasound is occasionally used.
- Patients with traumatic pneumothorax usually offer a pertinent history.
- Patients with primary spontaneous pneumothorax are typically tall and thin and are often smokers.
- Patients presenting with secondary spontaneous pneumothorax often manifest signs and symptoms of their underlying lung disease.

Atypical

- Patients with pneumothorax of sufficient size to be diagnosed will have some dyspnea. Chest pain may not be the presenting complaint.
- There may be distractions to the presentation, as in catamenial pneumothorax, which occurs within 48 hours on onset of menses.

Primary Differential Considerations

- When evaluating a patient suspected of having a pneumothorax, early consideration should be given to these differential diagnoses:
  - Acute coronary syndrome
  - Asthma
  - Pneumonia
  - Pulmonary embolism
  - Rib fracture

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination are key to diagnosing simple pneumothorax, but the magnitude of those findings is dependent almost wholly on the side of the pneumothorax. With larger lesions, patients are quite dyspneic. With smaller lesions, the diagnosis may prove elusive. Chest radiography is diagnostic.

Factors That Suggest Diagnosis

- Pleuritic chest pain and dyspnea on history are suggestive but not confirmatory.
- Those same findings in smokers, asthmatics, Marfanoid body habitus, women within 48 hours of menses onset, recent sharp procedure above the diaphragm, or recent thoracic trauma should be suspected of having pneumothorax.
- Patients with larger pneumothoraces are likely to show signs of frank respiratory distress, including tachycardia, tachypnea, diaphoresis, and pallor or cyanosis. These patients are also more likely to manifest asymmetric breath sounds upon careful lung auscultation.
- The larger the pneumothorax, the more likely it is that the patient will have tracheal shift (classic for tension pneumothorax), hyperresonance upon percussion of the affected lung, or jugular venous distention.

Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude simple pneumothorax.

Ancillary Studies

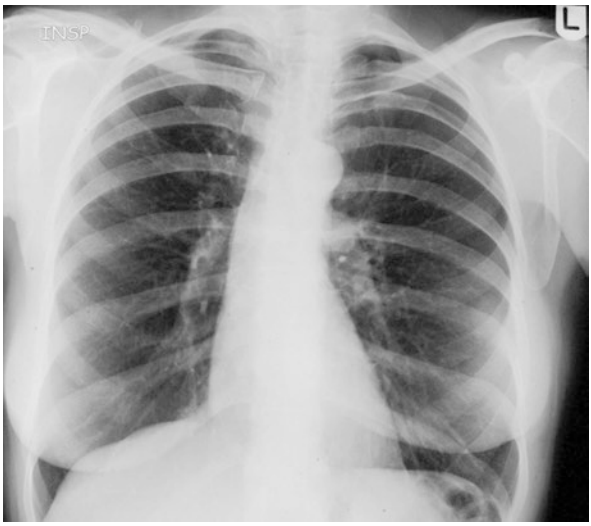
Laboratory

- There are no diagnostic laboratory studies for pneumothorax. Patients with secondary spontaneous pneumothorax should undergo laboratory screening pertinent to their underlying diagnosis.

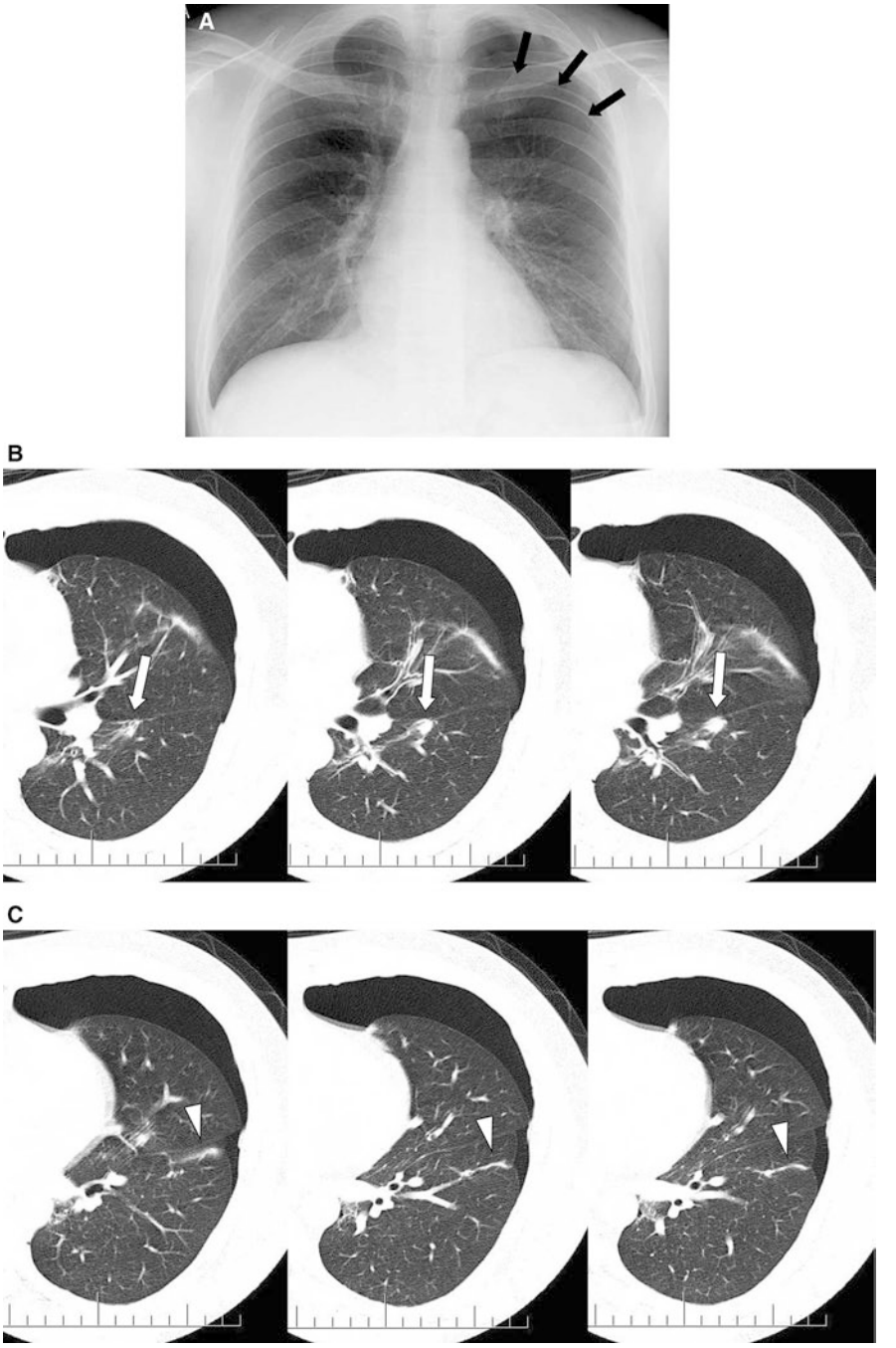
Imaging

- The diagnosis of simple pneumothorax is confirmed on chest radiography. Small pneumothoraces may only be visible on computed tomography of the chest. Look for a thin line representing the pleura separate from the chest wall. The upright, inspiratory posteroanterior film offers the best opportunity of demonstrating a simple pneumothorax.

Poteroanterior upright chest X-ray shows large pneumothorax of the right lung [Kim S-H, Yoo W-H. Recurrent pneumothorax associated with pulmonary nodules after leflunomide therapy in rheumatoid arthritis: a case report and review of the literature. Rheumatology International. 2011 Jul;31(7):919–22.] *Caption from original*



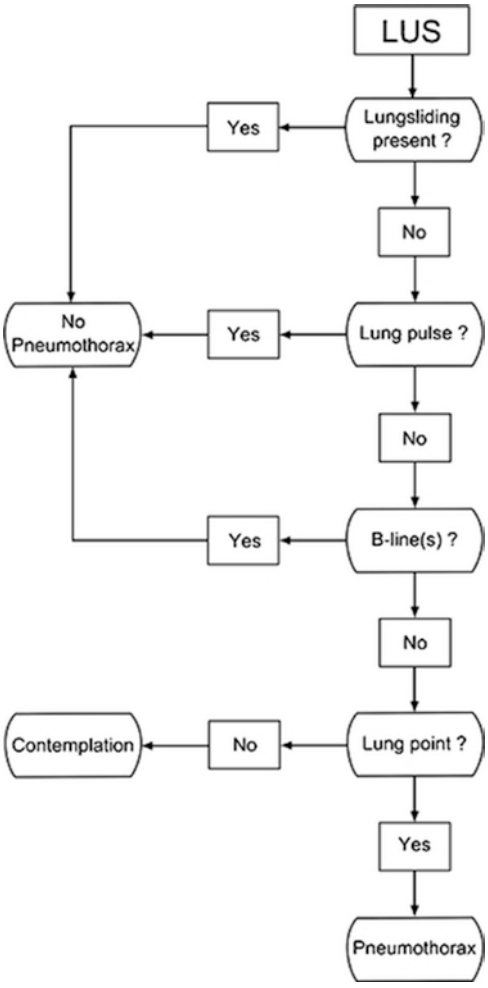
CXR in inspiration showing left sided small pneumothorax [From article: Pneumothorax after a clinical breast fine-needle aspiration of a lump in a patient with Poland syndrome. International Seminars in Surgical Oncology. 2005 Aug 19;2(1):14. https://doi.org/10.1186/1477-7800-2-14, at http://link.springer.com/article/10.1186/1477-7800-2-14; by M Salhab, W Al Sarakbi, N Perry, K Mokbel, © Salhab et al; licensee BioMed Central Ltd. 2005; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*


A
B
C

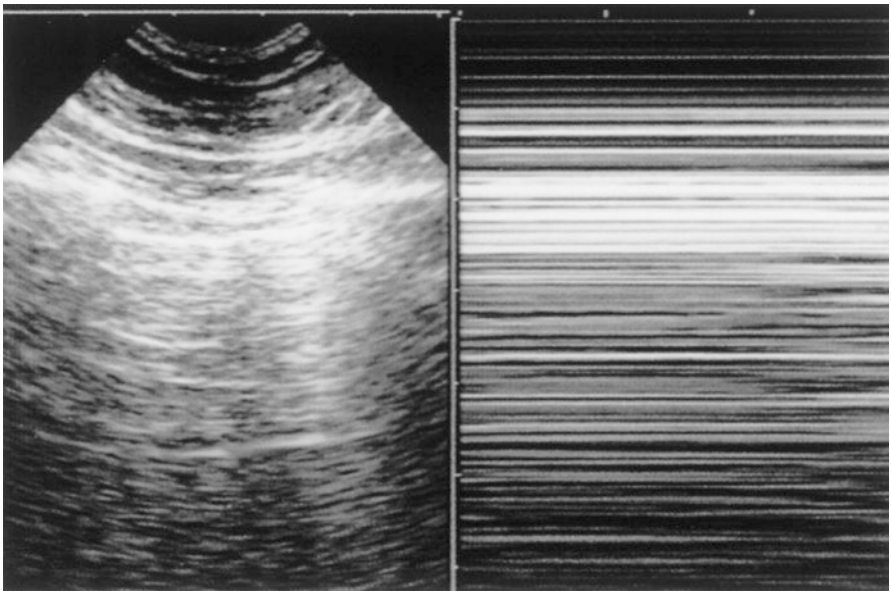
a A radiograph demonstrating pneumothorax of the left lung. The arrow indicates the line of the lung apex. b A computed tomography (CT) scan showing the pneumothorax and an irregular dense nodular shadow (white arrows) beneath the interlobular surface. c A CT scan showing linear-reticular shadows (white arrowheads) in the lung parenchyma within the left lower lobe [Kato T, Ishikawa K, Kadoya M, Okamoto K, Kaji M. Spontaneous pneumothorax in a patient with dendriform pulmonary ossification: report of a case. Surgery Today. 2012 Sep;42(9):903–8.] *Caption from original*

- The lateral film may be especially helpful.
- The lateral decubitus film (affected side up) may better demonstrate a simple pneumothorax.

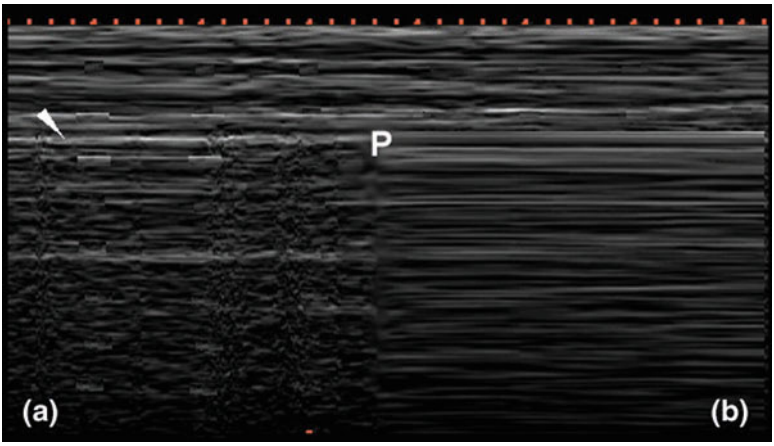
- Ultrasound may be useful in some cases. Look for the "sliding lung sign."



Algorithm for the diagnosis and exclusion of pneumothorax using LUS. Initially one should look for signs which rule out the presence of pneumothorax [lung sliding, lung pulse, B-line(s)] at the anterior surface of the chest. If none of these are present, then one should gradually move the transducer laterally and posterior on the surface of the chest and look for lung point in order to establish the diagnosis of pneumothorax. If neither sign is present, contemplation is needed since pneumothorax can neither be ruled in nor out. In young, previously healthy patients, such as most trauma patients, the absence of lung sliding alone is sufficient to diagnose pneumothorax. In such patients the absence of all signs will be consistent with pneumothorax. In comparison, patients with known lung diseases or previous chest surgery may have a variety of causes for the absence of lung sliding. In such patients the absence of all signs can neither be used to rule in nor to rule out a pneumothorax and further imaging should be performed in order to establish whether pneumothorax is present or absent [From article: Ultrasonography for clinical decision-making and intervention in airway management: from the mouth to the lungs and pleurae. Insights into Imaging. 2014 Apr;5(2):253–79. https://doi.org/10.1007/s13244-014-0309-5, at http://link.springer.com/article/10.1007/s13244-014-0309-5; by Michael S. Kristensen, Wendy H. Teoh, Ole Graumann, Christian B. Laursen, © The Author(s) 2014; licensed under Creative Commons Attribution License https://creativecommons.org/licenses/by/2.0/] *Caption from original*



Pneumothorax. *Left* Real-time. Lung sliding or pathological comet-tail artifacts are absent. In real time the pleural line appears completely motionless. *Right* Time motion. This mode objectifies the complete disappearance of lung sliding, without any visible “lung pulse” [Lichtenstein DA, Lascols N, Prin S, Mezière G. The”lung pulse”: an early ultrasound sign of complete atelectasis. Intensive Care Medicine. 2003 Dec 1;29(12):2187–92.] *Caption from original*



Time-motion mode lung ultrasound. (a) Normal lung and (b) pneumothorax patterns using time-motion mode lung ultrasound. In time motion mode, one must first locate the pleural line (white arrow) and, above it, the motionless parietal structures. Below the pleural line, lung sliding appears as a homogenous granular pattern (a). In the case of pneumothorax and absent lung sliding, horizontal lines only are visualised (b). In a patient examined in the supine position with partial pneumothorax, normal lung sliding and absence of lung sliding may coexist in lateral regions of the chest wall. In this boundary region, called the 'lung point' (P), lung sliding appears (granular pattern) and disappears (strictly horizontal lines) with inspiration when using the time-motion mode. [From article: Clinical review: Bedside lung ultrasound in critical care practice. Crit Care. 2007 Feb 16;11(1):1–9. https://doi.org/10.1186/cc5668, at http://link.springer.com/article/10.1186/cc5668; by Bélaïd Bouhemad, Mao Zhang, Qin Lu, Jean-Jacques Rouby, © BioMed Central Ltd 2007; licensed under Creative Commons Attribution License https://creativecommons.org/licenses/by/2.0/] *Caption from original*

Special Populations

Age and Gender

- Primary spontaneous simple pneumothorax occurs most often in tall, thin adults between the ages of 18 and 40 and is more common in smokers. It is more common in men than in women.
- Secondary spontaneous simple pneumothorax occurs in older patients, often with COPD. It is more common in men than in women.
- Catemenial pneumothorax occurs in menstruating females, most often in the fourth decade of life.
- In the pediatric population, the highest incidence of simple pneumothoraces occurs in the newborn period. In some studies, the incidence approaches 2 in 10,000 live births.

- In adolescents, the development of both pneumothorax and pneumomediastinum has been associated with smoking marijuana and crack cocaine.

Co-morbidities

- Asthma and COPD are common comorbidities.
- Marfan's syndrome and other connective tissue disorders predispose to simple pneumothorax.
- Tobacco use increases the incidence of simple pneumothorax.

Pitfalls in Diagnosis

Critical Steps Not to Miss

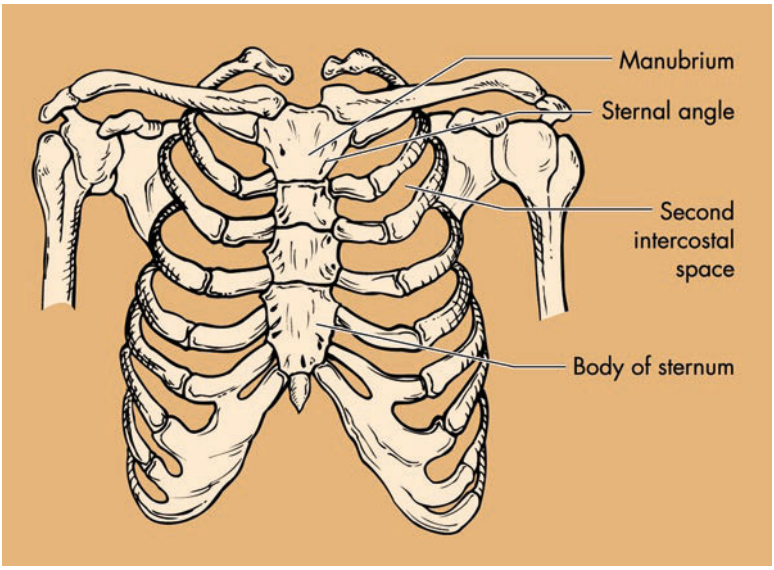
- Consideration of the diagnosis is the first critical step. Chest radiography is required to confirm the diagnosis.

Mimics

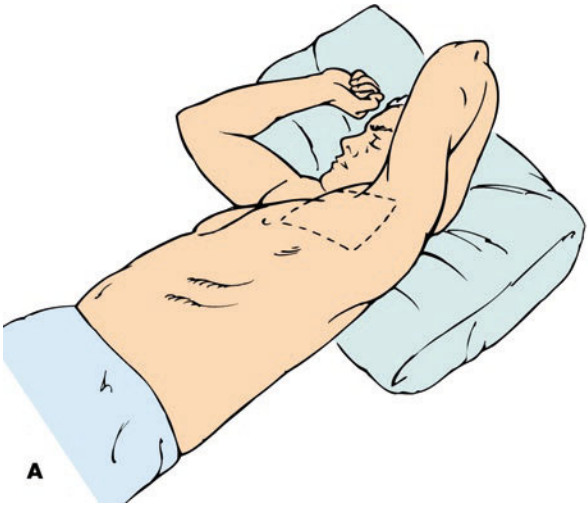
- The entire constellation of diagnoses that underlies chest pain syndrome, especially those often accompanied by dyspnea, can mimic the pain and overall presentation of simple pneumothorax.

Time-Dependent Interventions

- There are usually no time-dependent interventions in the management of simple pneumothorax. In this way the diagnosis differs sharply from tension pneumothorax, which is immediately life-threatening.
- Patients with significant underlying pulmonary disease may be intolerant of the hypoxemia that may result from simple pneumothorax, even without tension. For those patients, decompression of the pneumothorax (with needle, catheter, or tube thoracostomy) should be performed immediately.



Needle thoracostomy. The occurrence of a pneumothorax in the patient receiving positive pressure ventilation necessitates the placement of a chest tube. If the patient has evidence of a tension pneumothorax and exhibits hemodynamic or respiratory instability, a needle thoracostomy should be undertaken immediately. The procedure involves using a 14-gauge angiocatheter and inserting it into the second intercostal space in the midclavicular line of the side of the pneumothorax. The needle is "walked off" the superior portion of the third rib into the second intercostal space. This is done to prevent laceration of the intercostal vessels. If the tension is not released then a tube thoracostomy should be done in the same location. Once a tension pneumothorax is decompressed, a chest tube must be inserted to prevent reaccumulation of air. The angiocatheter, once it has released the tension in the chest, should not be removed until a chest tube is in place.[Szokol J, Vender J. Respiratory emergencies (pulmonary aspiration of gastric contents, acute epiglottis, anterior mediastinal mass). In: Tremper KK, editor. Principles of anesthetic techniques and anesthetic emergencies. Philadelphia: Current Medicine; 1998. 195 p. (Miller RD, editor. Atlas of anesthesia; vol. 4). ISBN: 0-443-07903-X] *Caption from original*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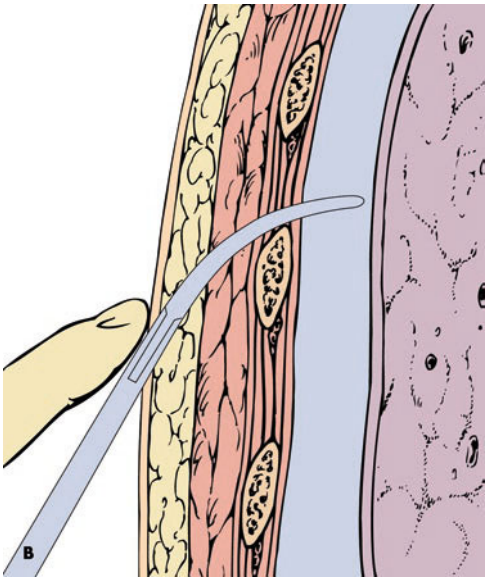
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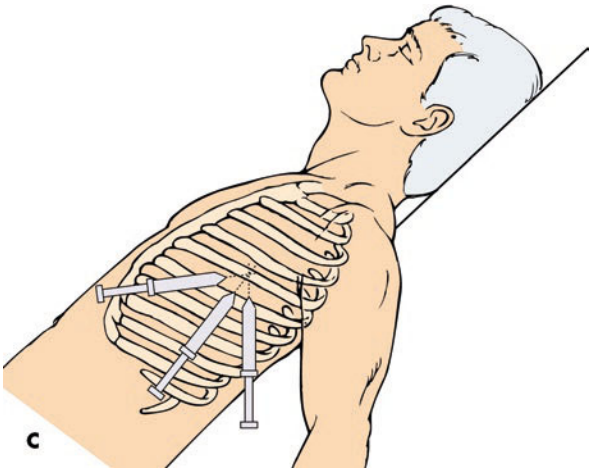
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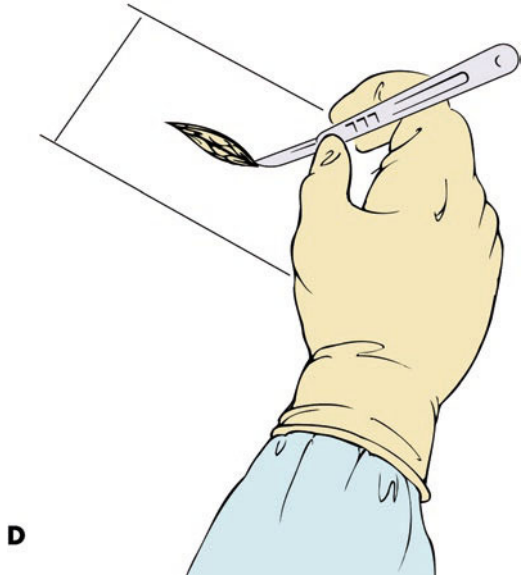
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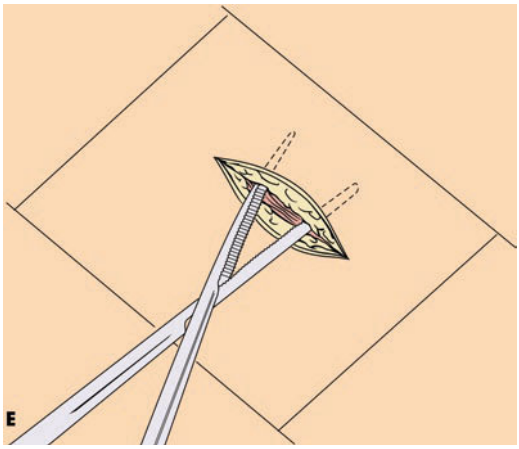
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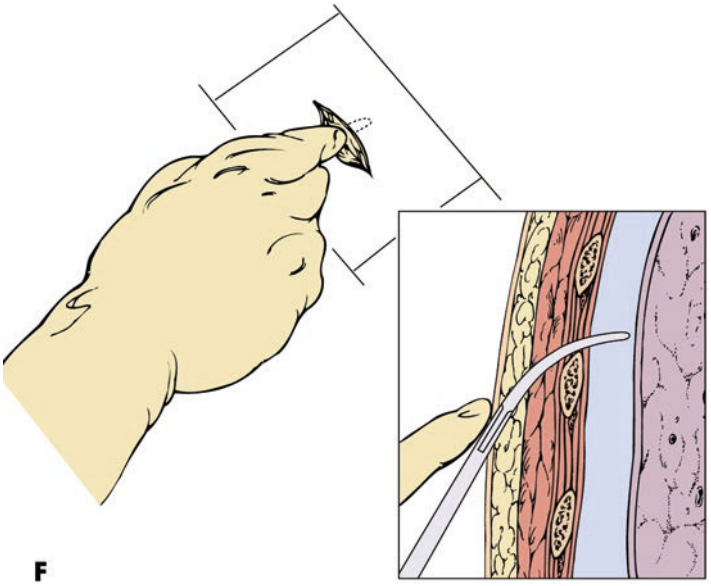
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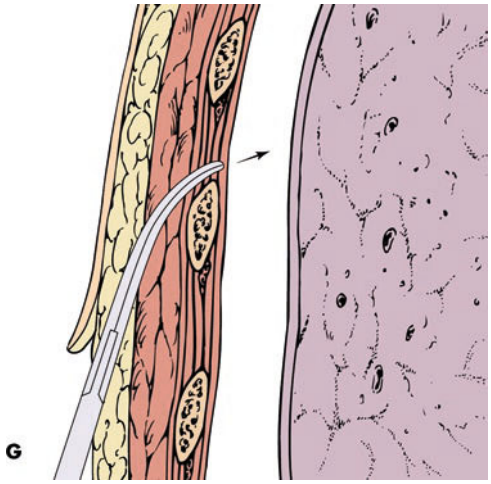
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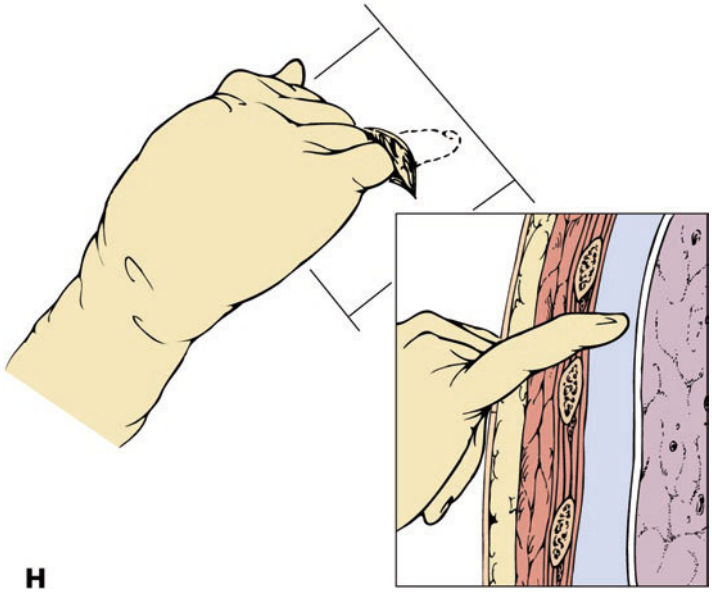
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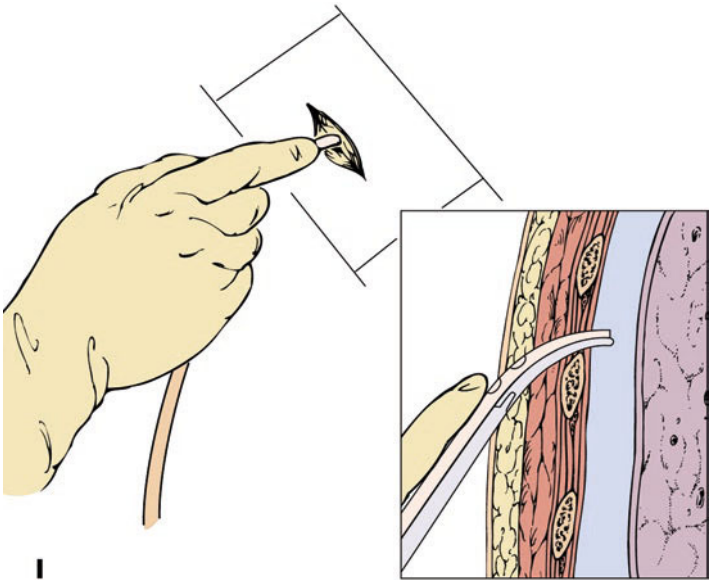

Tube thoracostomy. Tube thoracostomy is indicated to remove air or fluid (including blood) from the pleural space. Preferred sites are the fourth or fifth intercostal space in the anterior axillary line (A) or the second interspace in the midclavicular line (pneumothorax alone) (B). Local anesthetic is infiltrated into the skin, subcutaneous tissue, intercostal muscles, periosteum, and pleura (C). A 2-cm incision is made below the selected rib (D) and a subcutaneous tunnel formed with a Kelly clamp (E). The clamp is then inserted into the pleural space over the superior margin of the upper rib (F and G), followed by insertion of a gloved finger to confirm thoracic penetration (H). The tip of the thoracostomy tube is grasped by the Kelly clamp and inserted posteriorly and superiorly into the pleural space (I). The tube is then connected to a collection-suction apparatus with high-volume flow, adjustable suction, and underwater seal and is sutured to the skin. [Yeston N. Chapter 12. In: Kirby R, editor. Critical Care. Philadelphia: Current Medicine; 1997. (Miller RD, editor. Atlas of anesthesia; vol. 1). ISBN: 0-443-07906-4] *Caption from original*

Overall Principles of Treatment

- Treatment of simple pneumothorax involves evacuation of the air collection between the pleural layers. This should be done for all cases of simple pneumothorax except those that are shown to be very small on chest radiograph and are not causing symptoms; such lesions may be treated with supplemental oxygen and observation. Percutaneous management options include simple aspiration, chest tube placement, one-way valve insertion, and tube thoracostomy with continuous suction.

- Intensity of treatment is driven by size of the pneumothorax, degree of respiratory distress, severity of underlying lung disease, and risk of recurrence. Sometimes pharmacologic agents are instilled into the pleural space in an effort to prevent recurrence.

Disease Course

- It typically takes about 10 days for a simple pneumothorax to completely resolve, although symptoms typically improve much more quickly. Recurrence rates are 25–35 % for primary spontaneous simple pneumothorax and 40–50 % for patients with severe underlying lung disease.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

MacDuff A, Arnold A, Harvey J, BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. Thorax. 2010 Aug;65(Suppl 2):ii18-31. PMID: 20696690. http://www.ncbi.nlm.nih.gov/pubmed/20696690 **

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Kaneda H, Nakano T, Taniguchi Y, Saito T, Konobu T, Saito Y. Three-step management of pneumothorax: time for a re-think on initial management. Interact Cardiovasc Thorac Surg. 2013 Feb;16(2):186-92. https://doi.org/10.1093/icvts/ivs445. PMID: 23117233. http://www.ncbi.nlm.nih.gov/pubmed/23117233

Ding W, Shen Y, Yang J, He X, Zhang M. Diagnosis of pneumothorax by radiography and ultrasonography: a meta-analysis. Chest. 2011 Oct;140(4):859-66. https://doi.org/10.1378/chest.10-2946. PMID: 21546439. http://www.ncbi.nlm.nih.gov/pubmed/21546439

Wakai AP. Spontaneous pneumothorax. Clin Evid (Online). 2011 Jan 17;2011. pii: 1505. PMID: 21477390. http://www.ncbi.nlm.nih.gov/pubmed/21477390 **

Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. Eur Respir Rev. 2010 Sep;19(117):217-9. https://doi.org/10.1183/09059180.00005310. PMID: 20956196. http://www.ncbi.nlm.nih.gov/pubmed/20956196

Tschopp JM, Rami-Porta R, Noppen M, Astoul P. Management of spontaneous pneumothorax: state of the art. Eur Respir J. 2006 Sep;28(3):637-50. PMID: 16946095. http://www.ncbi.nlm.nih.gov/pubmed/16946095 **

Ryan B. Pneumothorax: assessment and diagnostic testing. J Cardiovasc Nurs. 2005 Jul-Aug;20(4):251-3. PMID:16000911. http://www.ncbi.nlm.nih.gov/pubmed/16000911

Cohort Study

Belchis DA, Shekitka K, Gocke CD. Multi-institutional retrospective cohort study of spontaneous pneumothorax. Pathol Res Pract. 2013 Aug;209(8):486-9. https://doi.org/10.1016/j.prp.2013.05.002. PMID: 23778154. http://www.ncbi.nlm.nih.gov/pubmed/23778154

Jalli R, Sefidbakht S, Jafari SH. Value of ultrasound in diagnosis of pneumothorax: a prospective study. Emerg Radiol. 2013 Apr;20(2):131-4. https://doi.org/10.1007/s10140-012-1091-7. PMID: 23179505. http://www.ncbi.nlm.nih.gov/pubmed/23179505

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Pneumothorax"[Mesh] OR "Pneumothorax"

Chapter 60
Pneumothorax (Tension)

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Tension Pneumothorax, Dropped Lung

Incidence/Epidemiology

- The incidence of tension pneumothorax is clearly underestimated. Because it results in such dramatic ventilatory and hemodynamic compromise, it often is treated rapidly, before the diagnosis is confirmed. Needle thoracostomy, for example, may relieve tension pneumothorax, but if the presumed diagnosis is incorrect, it creates a simple pneumothorax.
- Tension pneumothorax is a rare complication of primary spontaneous pneumothorax. In the 1800s, the most common underlying cause of tension pneumothorax was pulmonary tuberculosis.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_60

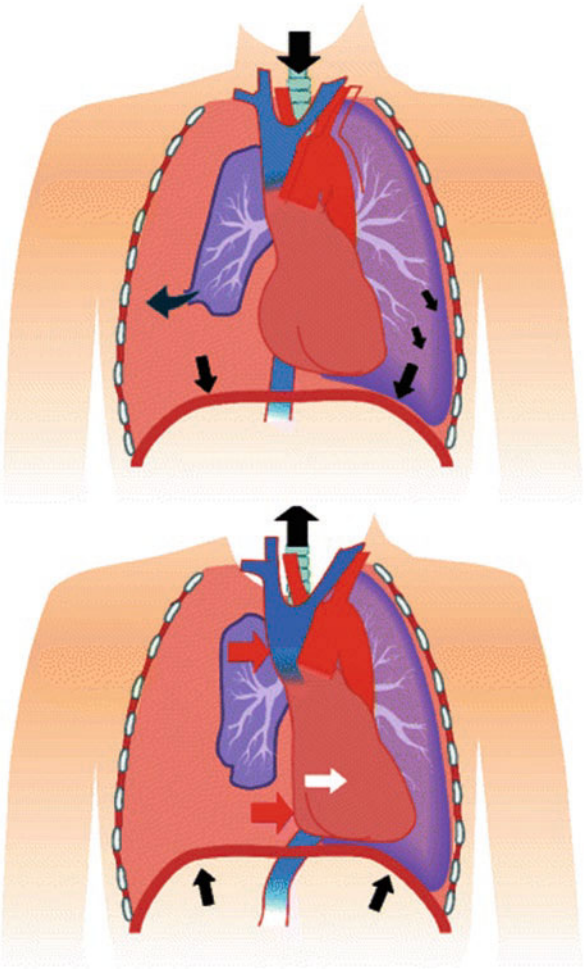
- Probably the most common cause of tension pneumothorax in the community is blunt chest trauma. It may occur in the hospital as a complication of mechanical ventilation with positive end-expiratory pressure (PEEP), which may or may not be associated with a sharp procedure (such as central line placement). Rupture of blebs during PEEP ventilation is an important cause of significant pneumothorax.

Differential Diagnosis

- The differential considerations for tension pneumothorax are quite limited. Given the dramatic presentation with tracheal shift and extraordinary hemodynamic and ventilatory compromise, the diagnosis is usually straightforward. This is important because emergency treatment is required.
- If the tracheal deviation and unilateral hyperresonance described below are not readily apparent, other dramatic diagnoses, such as overwhelming pulmonary embolism or cardiac rupture, may be considered.

Pathophysiology and Etiology

- Pneumothorax is defined by the presence of air in the pleural space, which is the usually tiny space between the visceral and parietal layers of the pleura.
- Tension pneumothorax occurs when the abnormal gas-filled space become so large that the ipsilateral lung completely collapses and the pressure in the pleural space is positive throughout the respiratory cycle. The expanding gas eventually extends across the mediastinum and affects the volume and function of the contralateral lung.



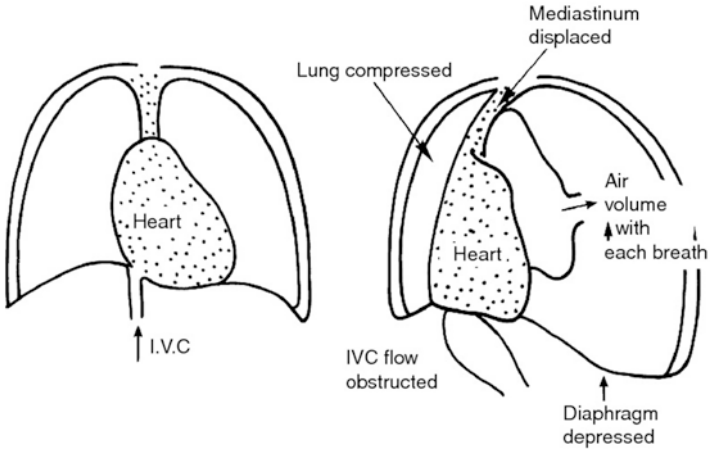
Tension pneumothorax, a feared and immediately life-threatening complication of pneumothorax. At the site of the lung injury, a valve mechanism occurs so that air leaks out but not back in. In a closed pneumothorax (intact chest wall) this leads to an increase of intrapleural pressure. The mediastinum is pushed toward the unaffected side, leading to ventilatory insufficiency on that side. The most threatening consequence of this condition is the pressure on the large chest veins with impairment of the refilling of the heart, which can lead to a rapidly progressing circulatory collapse. Immediate normalization of the pressure with needle thoracotomy is a prerequisite for survival [Lennquist S. Medical response to major incidents and disasters. Berlin Heidelberg: Springer; 2012. Chapter 7, Incidents caused by physical trauma; p. 111–96. Book https://doi.org/10.1007/978-3-642-21895-8; Chapter: 7; Chapter https://doi.org/10.1007/978-3-642-21895-8_7; Published: 2012-01-01] *Caption from original*

- The ventilatory compromise associated with tension pneumothorax results from the burden of trying to overcome consistent positive intrathoracic pressure combined with the loss of functional lung volume.
- The circulatory compromise associated with tension pneumothorax results in part from the impact of continuous positive pressure on the mediastinum, which reduces both venous return to the heart and cardiac output.
- Tension pneumothorax may be diagnosed as a complication in patients in whom simple pneumothorax has already been recognized, or it may present *de novo*.
- Tension pneumothorax in the outpatient setting is often the result of trauma, which is more commonly blunt (nonpenetrating) than penetrating. In the hospital, iatrogenic trauma may result from sharp procedures that violate the pleura (central line placement, lymph node or lung biopsy, etc.) or from positive-pressure ventilation, especially in patients with blebs.
- Tension pneumothorax in nontraumatic settings is most often the result of a severe infection process, such as necrotizing pneumonia. Pneumothorax is more common in smokers than nonsmokers, and is more common in patients with Marfan's syndrome and other connective tissue disorders associated with a tall, thin body type.

Presentation

Typical/"Classic"

- Tension pneumothorax presents dramatically—with a hypotensive patient who cannot ventilate effectively.
- Classically, the trachea is deviated out of the midline away from the collapsed lung.
- The ipsilateral hemithorax is hyperresonant (because it is filled with gas and the lung is collapsed) and may be visibly distended. Breath sounds are absent on that side.
- If the patient is on mechanical ventilation, airway pressure alarms will sound.
- The patient is hypotensive and tachycardic.



The effect of tension pneumothorax on ventilation and venous return [Hutson JM, Beasley SW. The Surgical Examination of Children, 2e. Berlin Heidelberg: Springer; 2013. Chapter 12, Trauma; p. 151–83. Book https://doi.org/10.1007/978-3-642-29814-1] *Caption from original*

- Jugular venous distension is present.
- Although chest radiography is diagnostic, it is often said that tension pneumothorax should never be diagnosed by x-ray, because delays in obtaining imaging may lead to further deterioration and death of the patient. If the diagnosis is suspected, treatment with decompressive needle thoracostomy should begin immediately.

Atypical

- Given the underlying pathophysiology of tension pneuomothorax, presentation is almost always "typical" (see above). The presentation may be slightly less dramatic very early and slightly obscured in the ICU when the patient is on a ventilator.
- Bilateral pneumothoraces with tension may present without tracheal deviation, but other cardinal features, especially hemodynamic collapse, will be present.

Primary Differential Considerations

- Because the clinical presentation of tension pneumothorax is so dramatic, there are few immediate differential considerations. In fact, pausing to consider other possibilities is dangerous to the patient. The only other immediate considerations might be severe shock or acute respiratory distress syndrome.

History and Physical Exam

Findings That Confirm Diagnosis

- Tension pneumothorax is a clinical diagnosis. Whether or not the patient has been injured, whether in the hospital or in the community, the findings of severe cardiopulmonary distress and volume/pressure shift in the chest are suggestive enough of the diagnosis that treatment should be empirically undertaken.

Factors That Suggest Diagnosis

- Each of the cardinal findings—respiratory distress, cardiovascular compromise, tracheal shift, asymmetry of sound and appearance in the two sides of the chest—points to the diagnosis.
- Appreciation of trauma or the presence and extent of underlying pulmonary disease may be helpful.

Factors That Exclude Diagnosis

- Tension pneumothorax results from the impact of persistently positive intrapleural pressure. Even finding a concomitant diagnosis (pulmonary embolism, pneumonia) not associated with this pressure shift does not exclude tension pneumothorax.

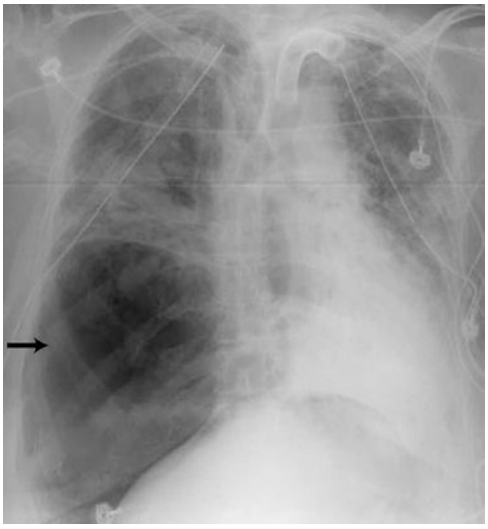
Ancillary Studies

Laboratory

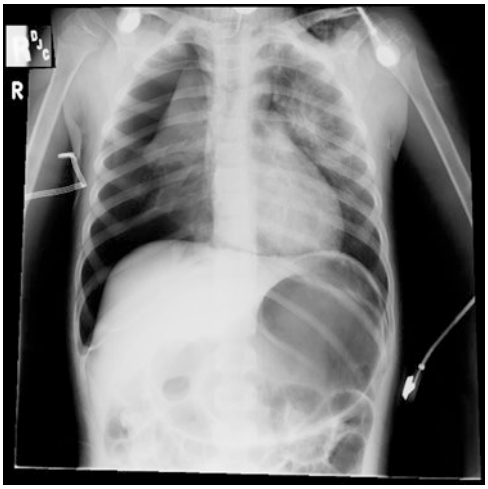
- There are no diagnostic laboratory studies for tension pneumothorax. Obtaining "resuscitation labs" is appropriate but must not delay treatment with decompressive needle thoracostomy.

Imaging

- Tension pneumothorax is readily identified on chest radiograph. However, it is often said that tension pneumothorax should never be diagnosed by x-ray, because delays in obtaining imaging may lead to further deterioration and death of the patient. If the diagnosis is suspected, treatment with decompressive needle thoracostomy should begin immediately.



Tension pneumothorax. A, Chest radiograph of a critically ill patient with a deep sulcus sign on the left (arrow), consistent with the diagnosis of a pneumothorax. B. Chest radiograph of a critically ill patient on mechanical ventilation with the presence of a right loculated tension pneumothorax (arrow). Note the increase in volume of the right hemithorax, depression of the right hemidiaphragm, and contralateral mediastinal shift. [Huggins J, Sahn S. Pleural disease. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Current Medicine; 2005. Chapter 25. ISBN: 1-57340-211-7; Published: 2005-01-14] *Caption from original*



Chest radiograph of the chest showing tension pneumothorax on the right side [Parray T, Siddiqui SM, Hughes M, Shah S. Tension pneumothorax and subcutaneous emphysema during retrieval of an ingested lithium button battery. J Anesth. 2010 Jun;24(3):469–71. https://doi.org/10.1007/s00540-010-0908-3; Published: 2010-06-10] *Caption from original*

- There is no role for CT or ultrasound imaging in patients with tension pneumothorax.

Special Populations

Age and Gender

- Because the potential etiologies of tension pneumothorax are so varied, there are limited age and gender predilections. Patients with chronic obstructive pulmonary disease (COPD; who are more likely older males) have more blebs, the rupture of which may eventually lead to tension pneumothorax, especially in the setting of positive pressure ventilation.
- Because tension pneumothorax may be a complication of untreated or extensive simple pneumothorax, the age and gender considerations discussed for the former may be applicable.
- It cannot be stressed enough that consideration of differential diagnoses, special populations, etc. must not result in delay in recognition and immediate treatment of tension pneumothorax.
- Within the pediatric population, both simple and tension pneumothoraces are rarely encountered.

- There are, however, well recognized associated pediatric conditions that may present with pneumothoraces, such as cystic fibrosis, reactive airway disease, Marfan's syndrome, and Ehlers-Danlos syndrome.

Co-morbidities

- Asthma and COPD are common comorbidities. Pneumonia may be associated with either simple or tension pneumothorax.
- Marfan's syndrome and other connective tissue disorders predispose to pneumothorax.

Clinical features of Marfan syndrome. Clinical features. Many of the typical features of Marfan's syndrome are seen in this patient, including arm length greater than height, increased lower to upper extremity ratio, pectus excavatum, and pes planus. Marfan's syndrome is characterized by autosomal dominant inheritance and has a prevalence of one in 20,000. A disorder of fibrillin, a glycoprotein abundant in the aortic media, skin, and ciliary zones, has recently been implicated as the most likely cause of this disorder. Musculoskeletal features include limbs disproportionately long for trunk size (dolichostenomelia), arachnodactyly, pectus excavatum or

carinatum, scoliosis, pes planus, and joint hypermobility. Serious extraskeletal features include dilation of the aortic root (leading to aortic dissection) and upward subluxation of the lens. [Maricic M, Ko M. Diseases of bone and connective tissue. In: Hunder G, editor. Atlas of rheumatology. Philadelphia: Current Medicine; 2005. Chapter 6. ISBN: 1-57340-210-9; Published: 2005-01-18] *Caption from original*

- Tobacco use increases the incidence of pneumothorax.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis in the acutely compromised patient is the first critical step.

Mimics

- There are no real mimics of the dramatic presentation of tension pneumothorax. In the absence of tracheal deviation, one might consider large pulmonary embolism, cardiac rupture, or other intrathoracic catastrophe.

Time-Dependent Interventions

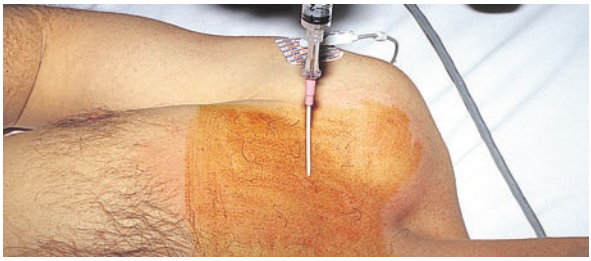
- Immediate release of the positive intrapleural pressure is required. Needle thoracostomy is the fastest means of relieving the tension.

Overall Principles of Treatment

- Treatment of tension pneumothorax is best provided by simple needle thoracostomy. The needle is usually inserted into the second or third intercostal space, in the midclavicular line, of the ipsilateral side. A rush of air through the needle confirms the diagnosis. The patient should then undergo formal tube thoracostomy while other hemodynamic support measures, as needed, are taken.

Video that describes the pathophysiology, diagnosis, and technique for decompressing a tension pneumothorax.
https://www.youtube.com/watch?v=ZZO5EEILnAA

Video covering the indications, instruments, and approach for performing a needle decompression of the chest
https://www.youtube.com/watch?v=UvHJ4pjNh2Q



Needling the chest for tension pneumothorax. This procedure is performed with readily available equipment and can be accomplished rapidly before a chest tube is obtained and inserted. A, A 12- or 14-gauge intravenous cannula is inserted in the second intercostal space in the midclavicular line. The cannula is inserted on the side of the pneumothorax, if known, or it can be inserted bilaterally, if the side is not evident clinically or if bilateral pneumothoraxes are suspected. [Woodcock B. Hemodynamic emergencies. In: Tremper K, Miller R, editors. Atlas of anesthesia. Philadelphia: Current Medicine; 1998. Chapter 11. ISBN: 0-443-07903-X; Published: 2002-01-22] *Caption from original*

B, Entry into a tension pneumothorax is confirmed by air rushing rapidly through the needle. There is risk of causing pulmonary damage with needle insertion if a pneumothorax is not present, and this technique should be reserved for the patient who is rapidly deteriorating and cannot tolerate any delay for chest radiography. [Woodcock B. Hemodynamic emergencies. In: Tremper K, Miller R, editors. Atlas of anesthesia. Philadelphia: Current Medicine; 1998. Chapter 11. ISBN: 0-443-07903-X; Published: 2002-01-22] *Caption from original*

Video that demonstrates how to insert a chest tube for trauma.
https://www.youtube.com/watch?v=qyJkh-ghl70

Chest radiograph obtained after decompression showing resolution of tension pneumothorax with a small apical crescent of residual right pneumothorax. [Wachsman AM, Hoffer EK, Forauer AR, Silas AM, Gemery JM. Tension pneumothorax after placement of a tunneled pleural drainage catheter in a patient with recurrent malignant pleural effusions. Cardiovasc Intervent Radiol. 2007 May;30(3):531–3. https://doi.org/10.1007/s00270-006-0073-0; Published: 2007-06-01] *Caption from original*

Disease Course

- Tension pneumothorax is fatal if untreated. Ultimate recovery after initial treatment depends on a variety of factors, including comorbidity burden and extent of other injuries.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

MacDuff A, Arnold A, Harvey J, BTS Pleural Disease Guideline Group. Management of spontaneous pneumothorax: British Thoracic Society pleural disease guideline 2010. Thorax. 2010 Aug;65(Suppl 2):ii18-31. PMID: 20696690. http://www.ncbi.nlm.nih.gov/pubmed/20696690 **

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Leigh-Smith S, Harris T. Tension pneumothorax–time for a re-think? Emerg Med J. 2005 Jan;22(1):8-16. PMID: 15611534. http://www.ncbi.nlm.nih.gov/pubmed/15611534 **

Barton ED. Tension pneumothorax. Curr Opin Pulm Med. 1999 Jul;5(4):269-74. PMID: 10407699. http://www.ncbi.nlm.nih.gov/pubmed/10407699 **

Clinical Trial

Notrica DM, Garcia-Filion P, Moore FO, Goslar PW, Coimbra R, Velmahos G, Stevens LR, Petersen SR, Brown CV, Foulkrod KH, Coopwood TB Jr, Lottenberg L, Phelan HA, Bruns B, Sherck JP, Norwood SH, Barnes SL, Matthews MR, Hoff WS, Demoya MA, Bansal V, Hu CK, Karmy-Jones RC, Vinces F, Hill J, Pembaur K, Haan JM. Management of pediatric occult pneumothorax in blunt trauma: a subgroup analysis of the American Association for the Surgery of Trauma multicenter prospective observational study. J Pediatr Surg. 2012 Mar;47(3):467-72. https://doi.org/10.1016/j.jpedsurg.2011.09.037. PMID: 22424339. http://www.ncbi.nlm.nih.gov/pubmed/22424339 **

Cohort Study

Yoon JS, Choi SY, Suh JH, Jeong JY, Lee BY, Park YG, Kim CK, Park CB. Tension pneumothorax, is it a really life-threatening condition? J Cardiothorac Surg. 2013 Oct 15;8:197. https://doi.org/10.1186/1749-8090-8-197. PMID: 24128176. http://www.ncbi.nlm.nih.gov/pubmed/24128176

Case Study

Mayordomo-Colunga J, Rey C, Medina A, Concha A. Iatrogenic tension pneumothorax in children: two case reports. J Med Case Rep. 2009 Jun 30;3:7390. https://doi.org/10.4076/1752-1947-3-7390. PMID: 19830199. http://www.ncbi.nlm.nih.gov/pubmed/19830199 **

Watts BL, Howell MA. Tension pneumothorax: a difficult diagnosis. Emerg Med J. 2001 Jul;18(4):319-20. PMID: 11435384. http://www.ncbi.nlm.nih.gov/pubmed/11435384

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Tension Pneumothorax"

Chapter 61
Pulmonary Embolism

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Pulmonary embolism (PE); venous thromboembolism

Incidence/Epidemiology

- Pulmonary embolism is relatively common and is clearly underreported, as it is the most common cause of in-hospital death, and autopsies are not always performed on these patients.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_61

Autopsy specimen demonstrating pulmonary embolism. The patient subsequently suffered a cardiac arrest and died 3 days later despite maximal resuscitative efforts. At autopsy, the right main pulmonary artery, seen in cross-section, was filled with thrombus of varying age. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption adapted from original*

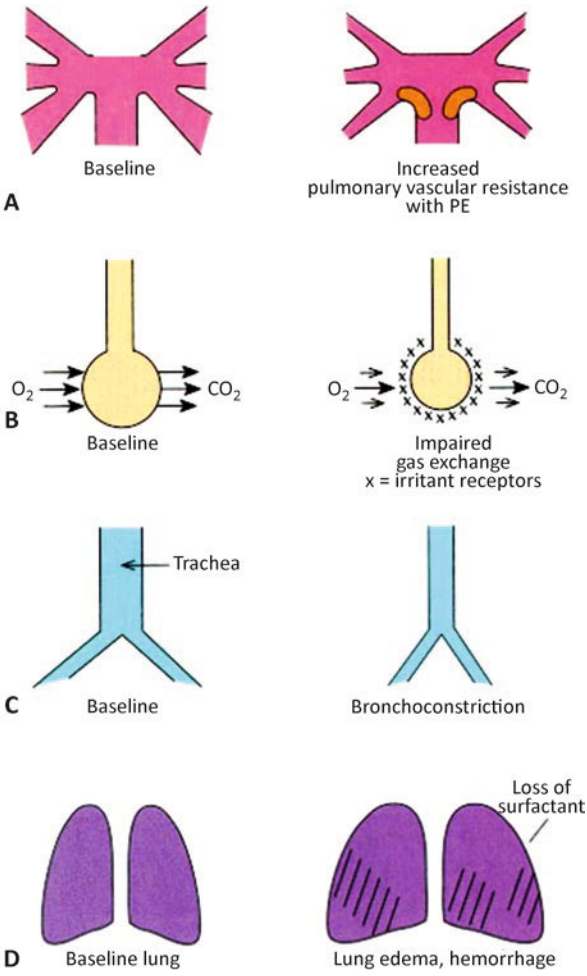
- On the other hand, PE is likely diagnosed now more than in previous times because of the ubiquitous availability of computed tomographic (CT) pulmonary angiography.
- The estimated incidence of PE in the US is about 1 case per 1,000 persons per year.
- The incidence of venous thromboembolism (PE plus deep venous thrombosis, or DVT) is increasing as the population ages and as obesity, cancer, and longer lifespans with debilitating disease all become more common.

Differential Diagnosis

- The differential considerations for chest pain due to PE includes acute coronary syndrome and aortic dissection, both of which—like PE—are potentially life-threatening.
- Less severe differential considerations include pleurisy, pneumonia, pneumothorax, chest wall pain, and anxiety.
- With significant hypoxemia patients may present with syncope, near-syncope, or seizure, so the differential considerations for those entities also must be entertained.
- Acute chest syndrome in sickle cell disease is a differential consideration in at-risk patients.

Pathophysiology and Etiology

- As the name implies, PE is an embolic phenomenon. The usual embolus is a thrombus that originates in a deep vein, typically in the lower extremities or pelvis, or occasionally from the upper extremities or other sources.



Pathophysiology of pulmonary embolism (PE). A, Increased pulmonary vascular resistance due to vascular obstruction, vasoconstriction by neurohumoral agents, vasoconstriction because of baroreceptors in the pulmonary arteries (which sense pressure exerted against the wall of the pulmonary artery by blood flowing past an obstructing blood clot), or increased pulmonary artery pressure. Baroreceptors may induce reflex pulmonary vasoconstriction. B, Impaired gas exchange due to irritant

receptors, increased alveolar dead space (from vascular obstruction), hypoxemia (from alveolar hypoventilation), and right-to-left shunting; impaired carbon monoxide transfer due to loss of gas exchange surface also occurs. C, Increased airway resistance due to bronchoconstriction. D, Decreased pulmonary compliance due to lung edema and hemorrhage as well as loss of surfactant. [Chapter 3 in: Braunwald E, Goldhaber S, editors. Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. 1st edition. Philadelphia: Current Medicine; 1995. ISBN: 1-878132-23-7.] *Caption from original*

- The thrombus fragments and detaches (or may detach in its entirety), passes through the right atrium, tricuspid valve, and right ventricle, and into the pulmonary vasculature. It lodges in a vessel either proximally or distally, depending on its size and pulmonary flow dynamics. Infarction of pulmonary tissue occurs when obstruction is complete and there is no collateral blood flow to that tissue.
- The result of pulmonary infarction is pain and hypoxemia (the extent of which relates to the volume of tissue infarcted). In some cases, the infarction will cause bleeding or sloughing of bloody tissue into the alveolar space, and hemoptysis may ensue.
- Even in the absence of frank infarction, PE results in pain, dyspnea, increased alveolar dead space and ventilation : perfusion (V:Q) mismatch.

Presentation

Typical/"Classic"

- The classic PE presentation is characterized by the combination of dyspnea, pleuritic chest pain, hypoxemia, and hemoptysis. Of these, hemoptysis is the least consistent.
- An even more "classic" presentation would include a known history of, or evidence of, DVT. Recall, however, that pelvic vein DVTs do not always cause significant findings on physical examination, and also that DVT from any source may *completely* embolize, leaving no clinical or ultrasonographic evidence behind.

Atypical

- The classic presentation is not typical. The most consistent finding in acute PE is dyspnea. The presentation of dyspnea and tachycardia together should always prompt consideration of PE.
- Patients with PE may present with syncope, seizure, or with sudden death.
- Patients with massive PE may present with hemodynamic collapse.

- Depending on the area of lung involved, presenting pain in PE may be in the flank or abdomen.
- Patients with PE may present with wheezing and may be confused with asthma or COPD.
- The coincidence of fever and chest pain in PE may mimic pneumonia.

Primary Differential Considerations

- Pulmonary embolism carries an immediate life threat and as such should be considered at the top of the list of differential considerations that present with the signs and symptoms described above. Other diagnostic considerations that are potentially immediately life-threatening include:
  - acute coronary syndrome
  - aortic dissection
  - tension pneumothorax
  - shock
- Other less acute but important differential diagnoses to consider include:
  - simple pneumothorax
  - pneumonia
  - pleurisy

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination are not diagnostic for PE.

Factors That Suggest Diagnosis

- History and physical findings are dependent upon the size of the PE. PE is typically classed as:
  - Massive, implying hemodynamic compromise, or
  - Submassive, implying clear symptoms but with intact hemodynamics
- Known DVT, risk for DVT, or swollen extremity suggestive of DVT is suggestive. A prior history of PE puts the patient at increased life-long risk for another episode.

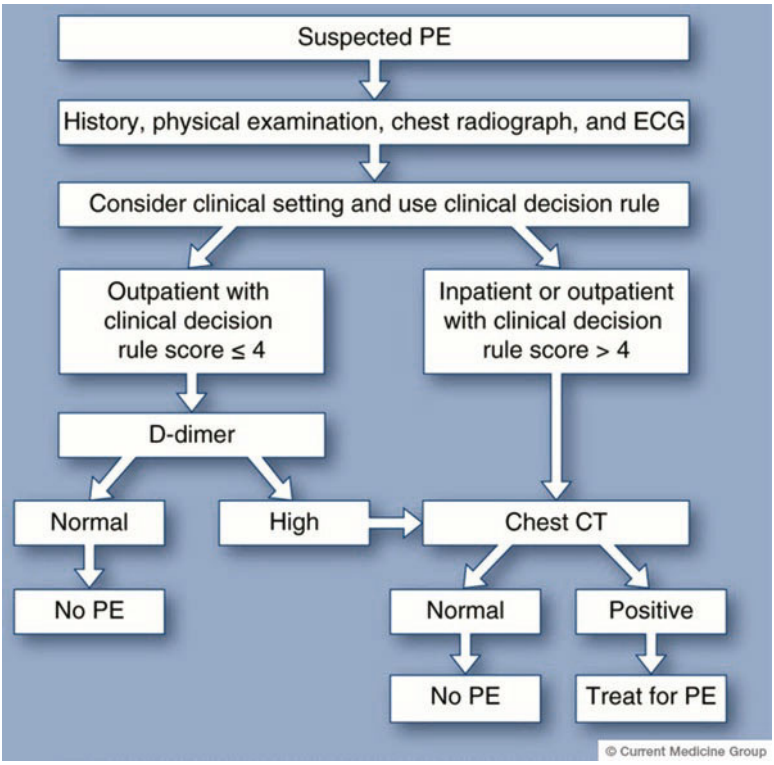
  - Findings of two or more of the cardinal symptoms (dyspnea, pleuritic chest pain, hypoxemia, and hemoptysis) should prompt serious consideration of PE.
  - Local wheezes in the affected area are commonly heard.
- There are predictive scores, such as that published by Wells, which may be useful.

Criteria	Points
1. Suspected PE	3.0
2. An alternative diagnosis is less likely than PE	3.0
3. Heart rate > 100 beats/min	1.5
4. Immobilization or surgery in previous 4 weeks	1.5
5. Previous DVT/PE	1.5
6. Hemoptysis	1.0
7. Malignancy (on treatment or treated within past 6 months)	1.0

Score	Mean probability of PE	% of Patients with this score	Risk
<2	3.6	40	low
2–6	20.5%	53	medium
>6	66.7%	7	high

Wells criteria for assessment of pre-test probability of pulmonary embolism (Data from Wells et al., 2000)[McIntyre LK, Langdale LA. Pulmonary Embolism. In: Bland, KI, Sarr, MG, Büchler, MW, Csendes, A, Garden, OJ, Wong, J (Eds.), editors. General Surgery [Internet]. Springer London; 2009 [cited 2016 May 27]. p. 263–72. Available from: http://link.springer.com/referenceworkentry/10.1007/978-1-84628-833-3_25] *Caption from original*

  - The Geneva Score is another such predictive tool. Many authorities hold, however, that clinical gestalt (that is, the evaluator's clinical impression) is superior—or at least noninferior—to any validated scoring systems.



Algorithm for diagnosis of pulmonary embolism. An integrated approach. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption adapted from original*

Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude PE.

Ancillary Studies

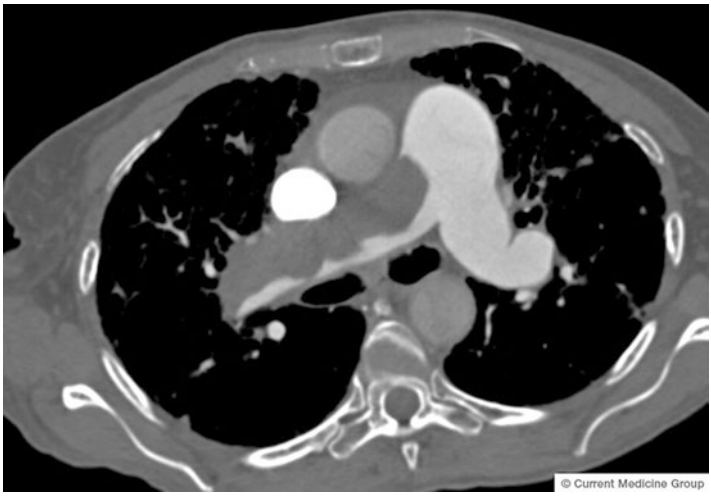
Laboratory

- There are no diagnostic laboratory studies for PE.
- Arterial blood gases may be used to calculate an arterial-alveolar oxygen gradient or to quantify hypoxemia, although in most cases transcutaneous pulse oximetry is sufficient.

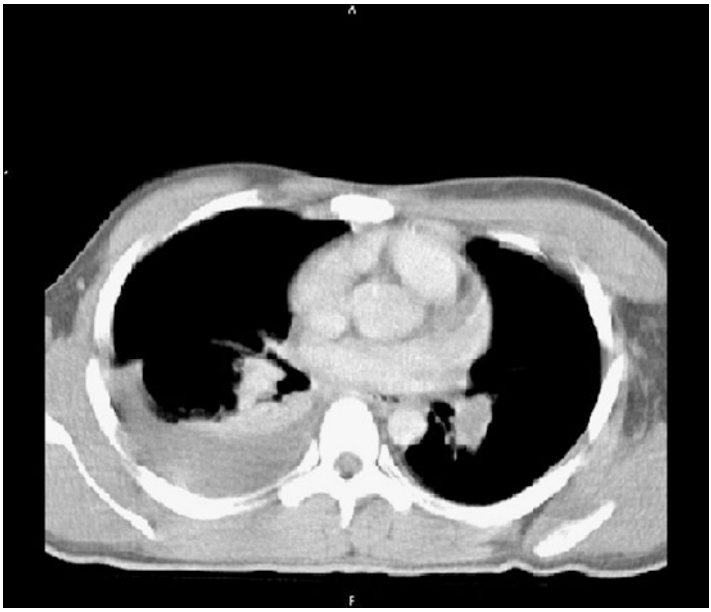
- A D-dimer assay (D-dimer is a byproduct of fibrin degradation, and can be found in the body when there is active or chronic clotting) is very sensitive for VTE but is not particularly specific. It should therefore be used to reassure providers that there is *not* a PE. In the setting of low clinical probability, a negative D-dimer is very helpful. If the D-dimer is positive, it should not be assumed that PE (or underlying DVT) is present, but further evaluation (usually by imaging) should ordinarily then be performed.

Imaging

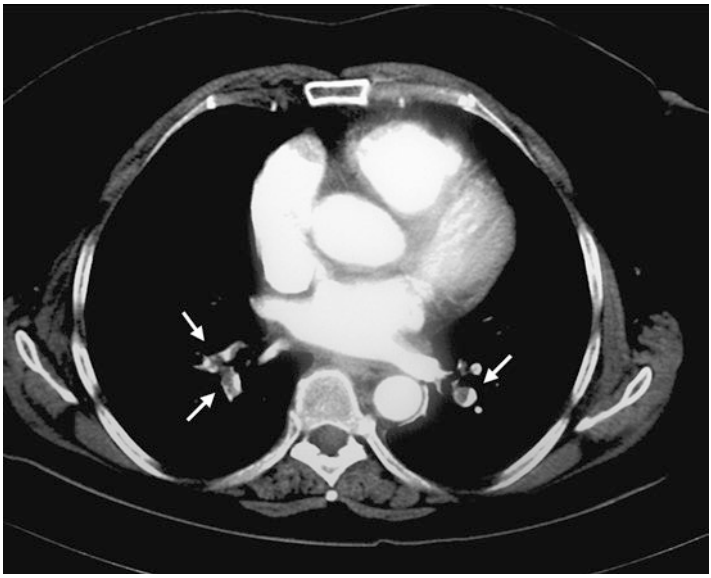
- The usual means of confirming the diagnosis of PE is with contrast-enhanced computed tomography of the thorax (called a computed tomographic pulmonary angiogram, or CTPA). This test is very sensitive for detecting PE down to the subsegmental pulmonary artery level.



Chest computed tomography in pulmonary embolism. Diagnosis of acute pulmonary embolism (PE) by CT of the chest. This image is from a 59-year-old woman with advanced sarcoidosis who underwent chest CT as part of an evaluation before lung transplantation. The CT demonstrated a previously unsuspected PE indicated by the large filling defect in the right main pulmonary artery. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption from original*

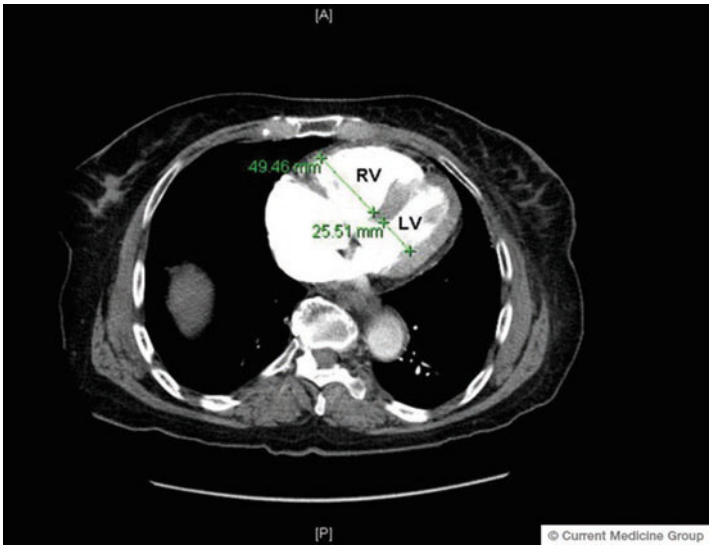


Acute pulmonary embolism. CECT chest showing thrombus in left pulmonary artery with right pleural effusion. [Vikram S, Jacob P, Nair CG, Vaidyanathan S. Gastric Carcinoma—A Rare Presentation. Indian Journal of Surgical Oncology. 2010 Dec;1(4):346–8.] *Caption from original*



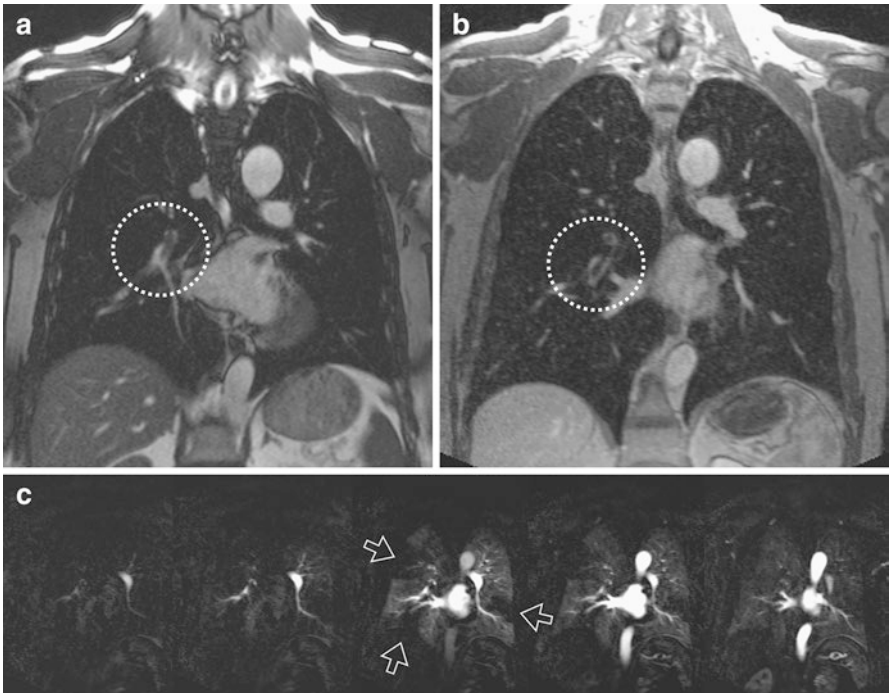
Visualization of a filling defect in the lumen of a vessel. *Arrows* indicate multiple filling defects in segmental branches of both pulmonary arteries diagnostic of bilateral pulmonary embolism. [Garcia-Bolado A, Del Cura JL. CT venography vs ultrasound in the diagnosis of thromboembolic disease in patients with clinical suspicion of pulmonary embolism. Emergency Radiology. 2007 Nov;14(6):403–9.] *Caption adapted from original*

- Because contrast material is required, CTPA may not be feasible in patients with renal insufficiency and should not be performed in pregnant patients.
- CT may also reveal suggestive right ventricular enlargement in PE.



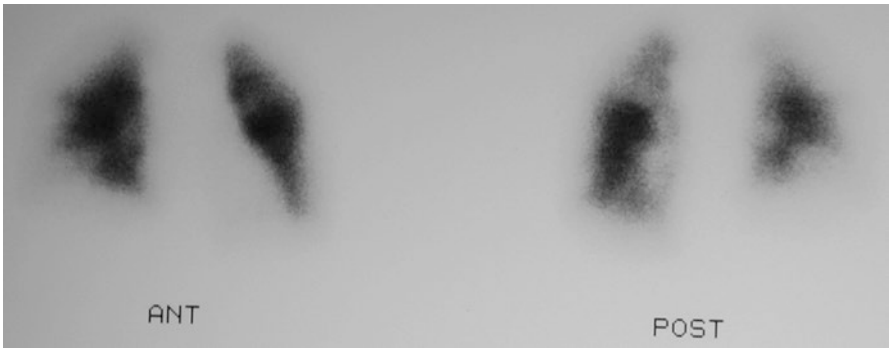
Chest computed tomography (CT) demonstrating right ventricular (RV) enlargement. This chest CT image demonstrates RV enlargement with a ratio of RV dimension to left ventricular (LV) dimension of 1.9. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption adapted from original*

- MRI of the chest can be used to evaluate for PE in patients who cannot undergo CT imaging.



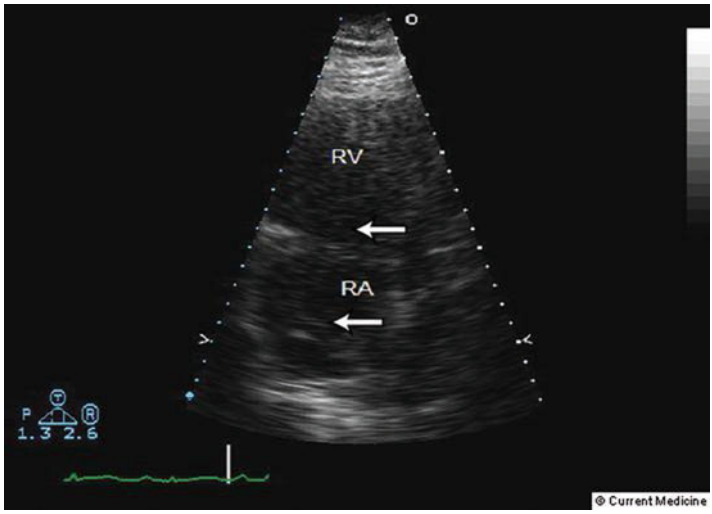
MRI of acute pulmonary embolism. A 55-year-old patient with acute pulmonary embolism. Coronal steady-state free precession images acquired during free breathing (a) and contrast-enhanced coronal 3d flash angiogram acquired in breathhold (b; embolus inside the right lower lobe artery circled); c series of subtracted images from the first pass perfusion study, perfusion deficits marked with open arrows at the image obtained at peak lung enhancement; 1.5-T MRI scanner [Biederer J, Mirsadraee S, Beer M, Molinari F, Hintze C, Bauman G, Both M, Van Beek EJR, Wild J, Puderbach M. MRI of the lung (3/3)—current applications and future perspectives. Insights into Imaging. 2012 Aug;3(4):373–86.] *Caption adapted from original*

- Ventilation-perfusion imaging (V/Q scan) is a nuclear medicine study that can demonstrate mismatches between ventilation and perfusion of the lungs and therefore indirectly identify PE. The test is more difficult to interpret than CT or MRI and is notably compromised in patients with existing lung disease such as COPD. It is still sometimes used when patients cannot receive contrast for CTPA.



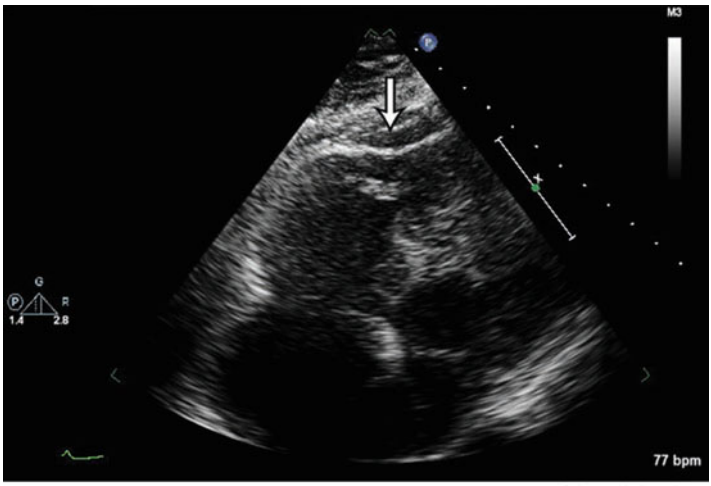
Ventilation-perfusion scan was interpreted as a high probability for pulmonary embolism involving the right lung and left upper lung. Patient was diagnosed as having deep venous thrombosis and pulmonary embolism. [Kawaguchi Y, Mine T, Kawana I, Umemura S. Protein-losing enteropathy, deep venous thrombosis and pulmonary embolism in a patient with generalized inflammatory polyposis in remission stage of ulcerative colitis. Clinical Journal of Gastroenterology. 2009 Jun;2(3):156–60.] *Caption adapted from original*

- An echocardiogram will typically demonstrate right ventricular strain with larger PEs and may occasionally show the thrombus.

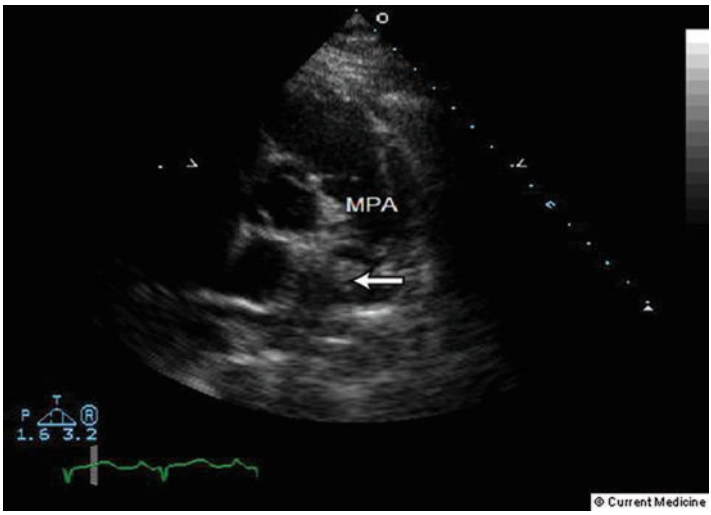


Echocardiogram of pulmonary embolism with thrombus in transit. Pulmonary embolism, thrombus in transit. Apical four-chamber view, demonstrating large mobile thrombi (arrows) within a dilated and hypokinetic RA and RV, which is consistent with acute pulmonary emboli. The appearance of thrombus in transit has been described as similar to "sausage links." Because most pulmonary emboli originate from the deep veins in the legs, it is hypothesized that the valves within the

deep veins create indentations in the thrombus, which contribute to the "sausage link" appearance. [Mangion J, Solomon S. Chapter 15. In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, Braunwald E, editors. Atlas of Echocardiography. 1e. Philadelphia, PA: Current Medicine Group; 2005. 312 p. ISBN: 1-57340-217-6] *Caption from original*

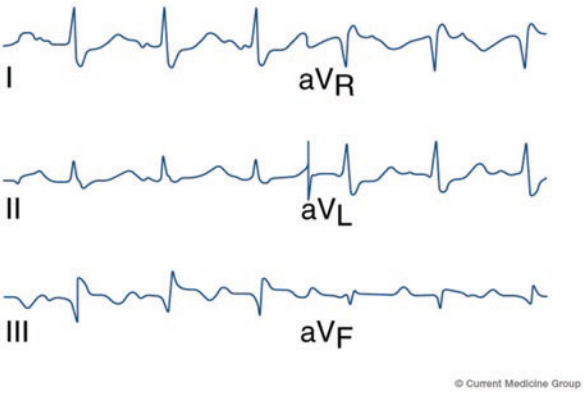


Echocardiographic assessment of pulmonary embolism. Pulmonary embolism. Apical four-chamber view, demonstrating right ventricular (RV) dilatation, hypokinesis, as well as McConnell's sign (arrow), which are markers of acute pulmonary embolism. [Mangion J, Solomon S. Echocardiography. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption adapted from original*



Echocardiogram of pulmonary embolism with right pulmonary artery thrombus Pulmonary embolism, thrombus within the right pulmonary artery (*arrow*). Main pulmonary artery and bifurcation view. Although echocardiography is often used in the setting of pulmonary embolism, it is not recommended as a routine imaging test for the diagnosis of pulmonary embolism because most patients with pulmonary embolism will have a "normal" echo. In patients with known pulmonary emboli, or with strong clinical suspicion for pulmonary emboli, it is important to visualize the pulmonary artery and branches, as in this case example. MPA—main pulmonary artery. [Mangion J, Solomon S. Echocardiography. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption from original*

- Ultrasound of the extremities can identify DVT as a potential source of PE. Keep in mind that an entire DVT focus can embolize, creating PE and leaving behind no clot to be detected in the extremities.
- Electrocardiographic manifestations of PE are inconsistent, but the "classic" S1Q3T3 pattern is occasionally seen. Tachycardia is the most common finding on ECG in PE patients.



Electrocardiogram in pulmonary embolism. Electrocardiogram of a 64-year-old woman who was hospitalized with "atypical chest pain" and subsequently diagnosed with pulmonary embolism (PE). This patient's electrocardiogram shows sinus tachycardia, incomplete right bundle branch block, an S wave in lead I, Q wave in lead III, and T-wave inversion in lead III. This so-called S1Q3T3 pattern along with the new incomplete right bundle branch block is indicative of right ventricular strain in the setting of pressure overload from PE. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption adapted from original*

Special Populations

Age and Gender

- The risk of PE increases with age.
- In general, the risk of PE is higher in men (perhaps owing to higher rates of cigarette smoking, cancer, and obesity), but women have higher risk when pregnant, in the post-partum period, and when taking hormone therapy (both oral contraceptives and replacement therapy).
- Blacks have higher rates of PE than whites in the US, and also have higher mortality with PE.
- The incidence of PE in children has risen sharply during the past decade, as a result of either more sensitive testing methods or greater survival from serious diseases (e.g., malignancies).
- The vast majority of PE in children is associated with the presence of central venous catheters, usually for the provision of chemotherapy or total parenteral nutrition (TPN).
- Within the adolescent population, adult risk factors apply.

Co-morbidities

- Hereditary thrombophilia (such as Protein C deficiency, antithrombin deficiency, Factor V Leiden) increases the risk of thromboembolism.
- Any state associated with increased levels of female hormones (including both pregnancy and prescribed therapy) increases the risk of thromboembolism.
- COPD is associated with PE, but that may derive from tobacco exposure more than from structural lung disease.
- Post-operative DVT and PE are common, owing primarily to post-op immobility, especially without prophylaxis such as low-molecular weight heparins.
- Prior VTE is a life-long risk factor for recurrent disease.
- Both malignancy and most forms of cancer treatment (surgery, chemotherapy, hormonal therapy) increase the risk of thromboembolism.
- Obesity increases the risk of thromboembolism.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step. Therapeutic anticoagulation may be initiated while awaiting formal confirmation of the diagnosis.

Mimics

- The entire constellation of diagnoses that underlies chest pain syndrome, especially those often accompanied by dyspnea, can mimic the pain and overall presentation of PE.
- Sudden cardiac death may mimic or be a presentation of PE.
- Syncope or near-syncope may mimic or be a presentation of PE.

Time-Dependent Interventions

- Pulmonary embolism can be rapidly fatal.
- Parenteral anticoagulation therapy should be initiated upon high suspicion or confirmation of PE.
- Patients with PE and hemodynamic compromise (inability to support blood pressure or oxygenation) should be immediately evaluated for suitability for thrombolytic therapy.

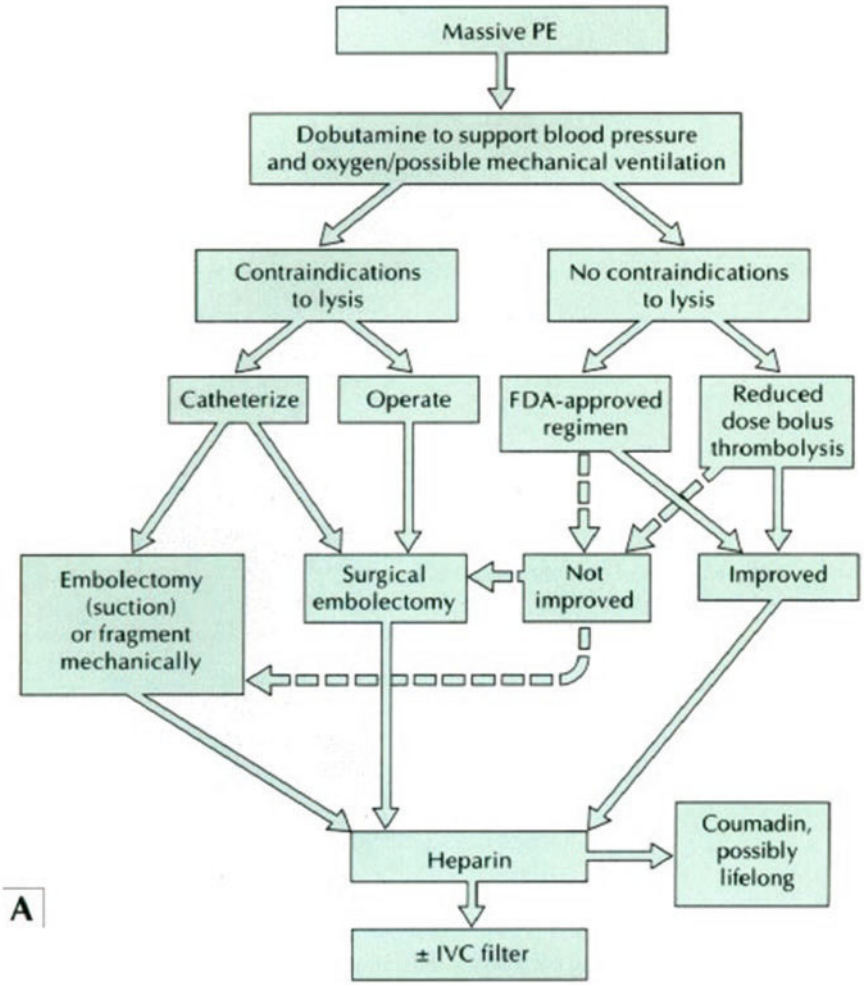
PRINCIPAL INCLUSION CRITERIA	MAJOR EXCLUSION CRITERIA
Massive pulmonary embolism	Intracranial disease
Anatomically small or moderate size pulmonary embolism with hemodynamic instability (*eg*, prior cardiopulmonary disease)	Recent major trauma or surgery
Hemodynamically stable, but right ventricular dysfunction detected on baseline echocardiogram	Active bleeding, known bleeding diathesis, or unexplained anemia
Normal echocardiogram and moderate size pulmonary embolism associated with massive pelvic or leg vein thrombosis	Uncontrolled hypertension

Inclusion and exclusion criteria for thrombolysis. The greatest challenge of thrombolysis for pulmonary embolism is gaining a thorough familiarity of when it should be utilized and, conversely, when it should be withheld. [Chapter 3 in: Braunwald E, Goldhaber S, editors. Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. 1st edition. Philadelphia: Current Medicine; 1995. ISBN: 1-878132-23-7.] *Caption from original*

Overall Principles of Treatment

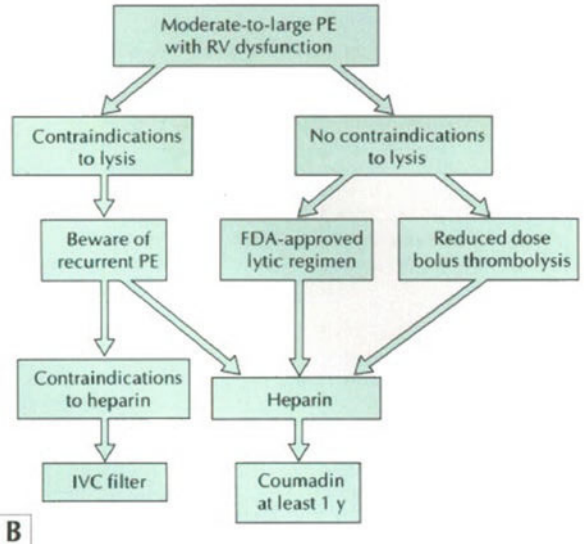
- Treatment of PE is with anticoagulation. Anticoagulants prevent clot progression while the body's native thrombolytic defenses gradually break down the clot and while collateral perfusion channels develop around the occluded vessel.

- Anticoagulation is recommended for at least 3 months after PE, but may be extended to 6 or 12 months or even longer based on the patient's thrombotic risk and the bleeding risk while on anticoagulants.

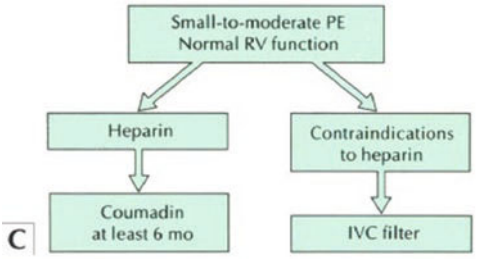


Protocols for treating different types of pulmonary embolism (PE). The optimal duration of Coumadin has not been studied in patients with pulmonary embolism. A, The patient who is hemodynamically compromised can receive an array of pharmacologic or mechanical interventions designed to lyse, remove, and dissipate the embolism while maintaining adequate right ventricular function. Consideration should be given to placement of a filter in the inferior vena cava (IVC) to prevent

recurrent embolism that may be fatal in a patient with persistently compromised cardiopulmonary status. [Chapter 3 in: Braunwald E, Goldhaber S, editors. Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. 1st edition. Philadelphia: Current Medicine; 1995. ISBN: 1-878132-23-7.] *Caption from original*



B, Moderate to large pulmonary embolism with associated right ventricular dysfunction. Although they are normotensive, these patients may benefit from thrombolytic therapy or suction catheter embolectomy not only to reverse right ventricular dysfunction rapidly and hasten pulmonary reperfusion but also to reduce the frequency of such adverse clinical events as recurrent embolism [Chapter 3 in: Braunwald E, Goldhaber S, editors. Cardiopulmonary Diseases and Cardiac Tumors. Atlas of Heart Diseases. 1st edition. Philadelphia: Current Medicine; 1995. ISBN: 1-878132-23-7.] *Caption adapted from original*



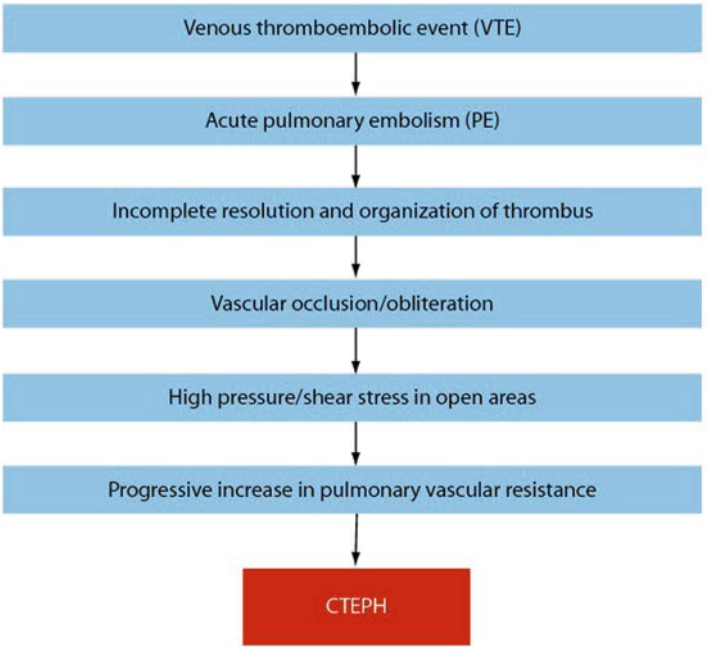
C, Small to moderate pulmonary embolism with normal right ventricular function. The prognosis of these patients is usually good with anticoagulation therapy alone. [Chapter 3 in: Braunwald E, Goldhaber S, editors. Cardiopulmonary Diseases and

Cardiac Tumors. Atlas of Heart Diseases. 1st edition. Philadelphia: Current Medicine; 1995. ISBN: 1-878132-23-7.] *Caption from original*

- Hemodynamically unstable PE is likely to benefit from thrombolytic therapy if contraindications do not exist.
- Remove or ameliorate risk as possible (e.g., stop smoking, lose weight if obese, discontinue birth control pills, etc).

Disease Course

- PE can be fatal. The true case mortality rate is not known owing to minor PEs that may not even be diagnosed on one end of the disease spectrum, and lack of autopsy data on the other end.
- Repeated PE may result in a serious disease called chronic thromboembolic pulmonary hypertension, or CTEPH.



Embolic hypothesis of CTEPH. [Humbert M, Lang IM, Mayer E. Chronic thromboembolic pulmonary hypertension (CTEPH): specific disease characteristics and similarities to idiopathic pulmonary arterial hypertension. Clinical Research in Cardiology Supplements. 2010 Sep;5(S2):12–5.] *Caption from original*

- Most patients with first submassive PE, treated with early anticoagulation, have full recovery.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2 Suppl):e419S-94S. https://doi.org/10.1378/chest.11-2301. PMID: 22315268. http://www.ncbi.nlm.nih.gov/pubmed/22315268 **

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Review

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pulmonary Embolism"[Mesh] OR "pulmonary embolism"

Chapter 62
Pulmonary Fibrosis

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, Victoria G. Riese, and Jaime Friel Blanck

Name and Synonyms

Pulmonary Fibrosis

- Synonyms:
  - Chronic interstitial pneumonitis
  - Hamman–Rich syndrome
  - Diffuse fibrosing alveolitis

Incidence/Epidemiology

- Idiopathic pulmonary fibrosis affects about 128,100 people in the United States
  - 48,000 new cases diagnosed annually
  - 40,000 people die each year

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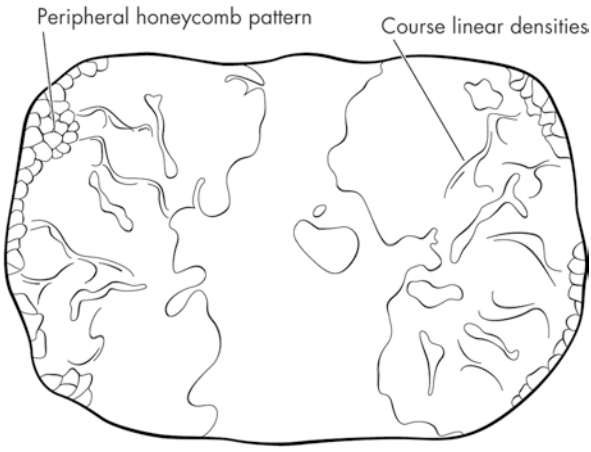
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_62

Differential Diagnosis

- The differential diagnosis is broad and includes acute and chronic lung infections, pneumoconioses, collagen vascular diseases, and hypersensitivity syndromes.
  - Usually a diagnosis of exclusion
  - Sarcoidosis
  - Histiocytosis X
  - Collagen vascular disease
  - Drug-induced pulmonary toxicity
  - Eosinophilic pneumonia
  - Farmer's lung
  - Histoplasmosis
  - Pneumonia (aspiration, bacterial, fungal, viral)
  - Pneumonitis (interstitial)
  - Pulmonary edema
  - Restrictive lung disease
  - Silicosis
  - Tobacco worker's lung

Pathophysiology and Etiology

- Scarring throughout the lungs results in impaired gas exchange.



Pathophysiology of idiopathic pulmonary fibrosis. Schematic representation of chest computed tomography in IPF, showing coarse linear densities and a peripheral honeycomb pattern. [Smith M, Grichnik K. Anesthetic considerations for lung transplant and thoracic aortic surgery. In: Reves JG, editor. Cardiothoracic

anesthesia. Philadelphia: Current Medicine; 1999. (Miller RD, editor. Atlas of anesthesia; vol. 8). ISBN: 0-443-07974-9] *Caption adapted from original*

- Associated with many conditions, including:
  - Infection
  - Pneumoconiosis (asbestos, silica)
  - Radiation exposure
  - Lupus, rheumatoid arthritis
  - Certain medications, including amiodarone
  - Granulomatous processes such as pulmonary sarcoidosis and Wegener's granulomatosis
  - Idiopathic: fibrosis develops without an identifiable cause
    - Most common form

Presentation

Typical/"Classic"

- Onset usually is gradual as symptoms worsen from a dry cough through dyspnea on exertion to dyspnea at rest.

Shortness of breath, exercise limitation
Cough
Age > 50 years
Crackles on physical examination (>80%)
Clubbing on physical examination (>20–50%)
Restrictive defect (reduced lung volumes) on pulmonary function tests
Hypoxemia (at rest or with exercise)
Characteristic HRCT scan

Clinical features of idiopathic pulmonary fibrosis [Lynch JP, Belperio JA. Idiopathic pulmonary fibrosis. In: Baughman RP, du Bois RM, editors. Diffuse lung disease [Internet]. New York, NY: Springer; 2012 [cited 2015 Sep 9]. p. 171–94. Available from: http://link.springer.com/10.1007/978-1-4419-9771-5_10] Caption from original

Atypical

- Occasionally seen as Hamman–Rich syndrome, in which symptoms and deterioration progress rapidly.

Primary Differential Considerations

Patients with signs and symptoms consistent with pulmonary fibrosis also may need to be evaluated for other lung and cardiopulmonary diseases, including:

- Pneumoconiosis
- Pneumonia
- Congestive heart failure
- Drug-induced lung toxicity
- Radiation pneumonitis
- Sarcoidosis
- Restrictive lung disease

History and Physical Exam

Findings That Confirm Diagnosis

Imaging (and often lung biopsy) is required to confirm the diagnosis of pulmonary fibrosis

Factors That Suggest Diagnosis

- History of occupational exposure
- History of connective tissue disease, inflammatory bowel disease, or malignancy
- Medication history
- Smoking history
- Prior irradiation
- Physical exam findings are nonspecific
  - Crackles may be present
  - Clubbing of the digits may occur

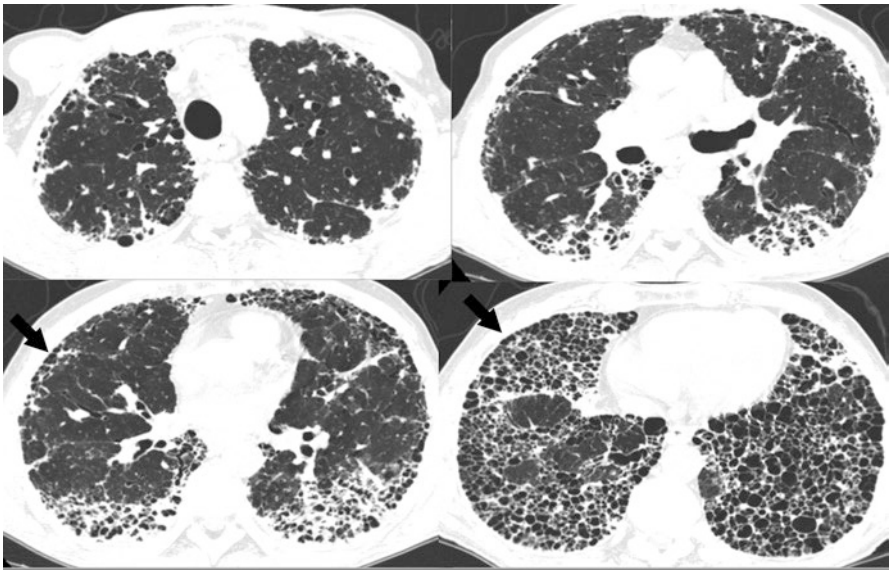
Factors That Exclude Diagnosis

- A productive cough is unusual.
- Wheezing and chest pain are uncommon signs.

Ancillary Studies

Imaging

- Plain chest radiography typically shows reticulonodular opacities and sometimes a "ground glass" appearance of the lung fields.
  - This is nonspecific, and advanced imaging is required in the evaluation.
- Chest CT reveals "honeycomb lung" with cysts that grow larger as the disease advances.



Multiple axial HRCT images show basilar- and peripheral-predominant pulmonary fibrosis characterized by reticulation, traction bronchiolectasis, and subpleural honeycombing (arrows), diagnostic of UIP [Chung JH, Kanne JP. Imaging of idiopathic pulmonary fibrosis. In: Meyer KC, Nathan SD, editors. Idiopathic pulmonary fibrosis [Internet]. Totowa, NJ: Humana Press; 2014 [cited 2015 Sep 9]. p. 55–75. Available from: http://link.springer.com/10.1007/978-1-62703-682-5_4] *Caption from original*

Special Populations

- Those with certain occupational, medication, or tobacco exposure are at increased risk.

Pediatric Considerations

- Pulmonary fibrosis generally is not a pediatric disease.
- As in the adult, it may be associated with certain medications, if taken by the child.
- At the extremes of chronicity (i.e. bronchopulmonary dysplasia, bronchiolitis, cystic fibrosis), it may develop.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Diagnosis needs a complete, thorough history and physical including occupation, drug exposures, and family history to exclude other diagnoses.

Mimics

- Many symptoms may be shared with a variety of pulmonary and cardiac diseases.

Time-Dependent Interventions

- Fibrosis is a chronic disease; unless the patient presents with acute ventilatory failure, there are no time-critical interventions.

Overall Principles of Treatment

- The course typically is inexorably downhill, with no consistently effective pharmacotherapy.
  - In some cases, corticosteroid therapy may be beneficial.
- Lung transplantation is reserved for very advanced cases.

Disease Course

- Scarring is permanent once it has developed.
- As the disease progresses, it may lead to pulmonary hypertension, cor pulmonale, respiratory failure, and increased risk of lung cancer.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Pulmonary Fibrosis"[Mesh] OR "Pulmonary Fibrosis"

Chapter 63
Pulmonary Hypertension

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Pulmonary Hypertension; Idiopathic Pulmonary Hypertension; Pulmonary Arterial Hypertension; Primary Pulmonary Hypertension

Incidence/Epidemiology

- The incidence and prevalence of pulmonary hypertension is difficult to ascertain, as the disease has 5 general classes as defined by The World Health Organization (see Pathophysiology and Etiology section below), all with multiple etiologies.
- Pulmonary hypertension affects all age groups, races, and both sexes.
- The incidence varies among the different groups and etiologies.
- Group 1 (pulmonary arterial hypertension) is rare, with an estimated incidence of about 10 cases per one million adults. Group 1 affects adults younger than those in the other groups.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_63

Differential Diagnosis

- The differential diagnosis of pulmonary hypertension is broad, as the presenting symptoms of pulmonary hypertension are nonspecific.
- The most common initial symptom is dyspnea on exertion, and the differential diagnosis of this complaint is broad and includes a large spectrum of pulmonary, cardiac, and metabolic diseases.
- Initial symptoms often include dyspnea on exertion (the most common initial symptom), atypical chest pain, and exertional syncope. These symptoms are slowly progressive and often long-standing when the patient presents for care.
- It is important to consider pulmonary hypertension in the differential of patients being evaluated for any of these complaints.
- As the presenting symptoms are nonspecific, the diagnosis of pulmonary hypertension is often delayed for months to years after symptoms begin.

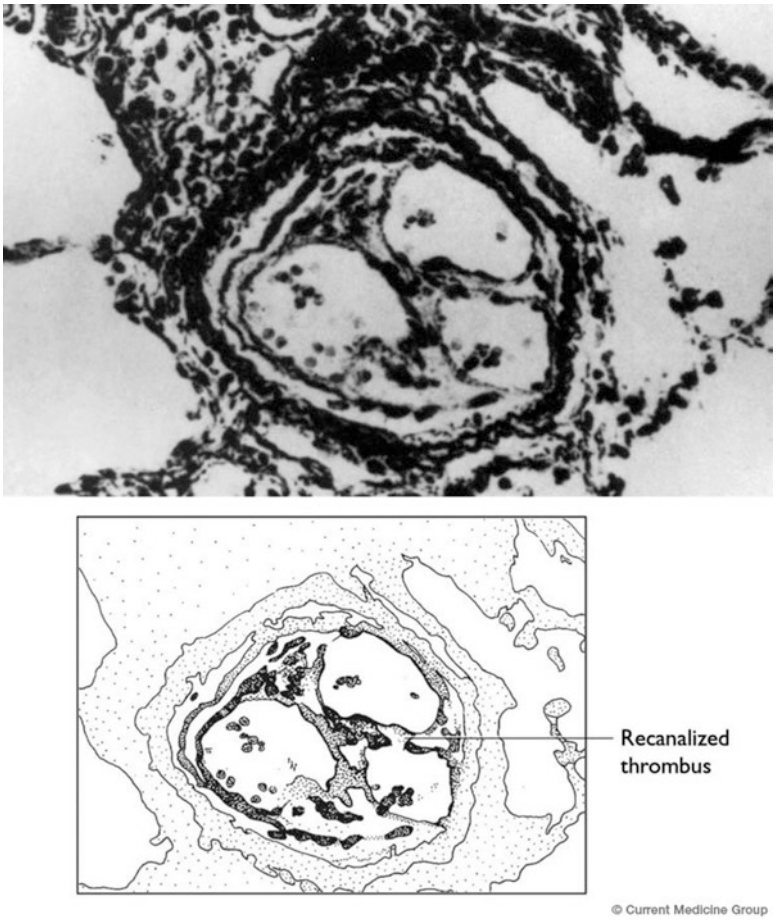
Pathophysiology and Etiology

- Pulmonary hypertension refers to elevated pulmonary arterial pressure. It is defined as a mean pulmonary arterial pressure of greater than or equal to 25 mm Hg at rest, usually measured during right heart catheterization.
- It can occur as a primary condition, with hypertension only within the pulmonary system; or, it can occur has a secondary condition in the context of pressure elevation within the pulmonary venous system. Primary pulmonary hypertension (outdated term) is now referred to as idiopathic pulmonary arterial hypertension (IPAH), and secondary pulmonary hypertension is referred to as pulmonary hypertension (PH). When referring to the group of disorders collectively, pulmonary hypertension is the appropriate term.
- IPAH has no identifiable cause, whereas PH generally has an identifiable cause, such as heart disease, thromboembolic pulmonary disease, and chronic lung disease.
- The World Health Organization has recently re-classified pulmonary hypertension into five broad groups based upon etiology.
    - Group 1: Pulmonary arterial hypertension (PAH). This group includes idiopathic PH (IPAH), familial (heritable) PAH, and PAH due to diseases that share the common pathologic basis of involvement of the small pulmonary muscular arterioles. This includes PAH caused by drugs and toxins, PAH secondary to connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, and schistosomiasis.
    - Group 2: This is PH due to left heart disease.
    - Group 3: PH secondary to chronic lung disease and/or hypoxemia.
    - Group 4: PH secondary to chronic thromboembolic pulmonary disease. Often referred to as chronic thromboembolic pulmonary hypertension (CTEPH).

- Group 5: PH due to unclear multifactorial mechanisms.

- Group 1. Patients with idiopathic and familial PAH are pathologically and clinically nearly identical. The distinction can only be made when and if a patient with PAH is found to have a genetic defect known to cause PAH. It is estimated that up to 10 % of patients in Group 1 have familial PAH. The mutation BMPR2 is the most common mutation to cause familial PAH. It may account for up to 80 % of all cases of familial PAH. Other causes of Group 1 PAH include:
  - Drugs and toxins. Several drugs are known to induce PAH. These include appetite suppressants (fenfluramine, dexfenfluramine, aminorex, and diethylpropion), toxic rapeseed oil, and benfluorex. Other drugs that are considered to be possible causes of PAH include: amphetamines, L-tryptophan, methamphetamines, cocaine, phenylpropolamine, St. John's Wort, dasatinib, and interferon.
  - Connective tissue diseases. Systemic sclerosis (scleroderma), Rheumatoid arthritis, and systemic lupus erythematous (SLE) can cause PAH. The mechanism is unknown.
  - HIV. PAH occurs in about 0.5 % of patients with HIV. The cause is unknown.
  - Portal hypertension associated with chronic liver disease can lead to PAH. When portal hypertension and pulmonary hypertension are present together it is called portopulmonary hypertension.
  - Congenital heart disease. PAH can develop in patients with large left-to-right intracardiac shunts due to congenital heart disease such as atrial septal defects and ventricular septal defects. PAH can also develop in patients with left-to-right shunts from great artery defects. PAH develops due to increased pulmonary blood volume and subsequent pressure overload.
  - Schistosomiasis. Schistosomiasis is rare in the United States and other developed nations, but it is the most prevalent cause of PAH worldwide.

- Group 2. Pulmonary hypertension from left heart disease. Characterized by elevated left atrial and pulmonary venous pressures. Left atrial hypertension is most commonly caused by left ventricular systolic or diastolic dysfunction and mitral or aortic valvular disease. Other, less common, causes include: restrictive cardiomyopathies, constrictive pericarditis, left atrial myxoma, and congenital cardiomyopathies.
- Group 3. Group 3 PH is PH caused by underlying lung diseases and/or hypoxemia. This includes: chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILD), and obstructive sleep apnea (OSA), especially in the presence of obesity hypoventilation syndrome and hypoxemia.
- Group 4. Group 4 PH is PH caused by thromboembolic disease. Chronic thromboembolic pulmonary hypertension (CTEPH) occurs from chronic, small pulmonary emboli with occlusion of the pulmonary vasculature. This leads to pulmonary hypertension and vascular remodeling.
- Group 5. Pulmonary hypertension from unclear and multifactorial mechanisms. Examples include PH due to sickle cell anemia and other hemolytic anemias.



Vascular pathology in idiopathic pulmonary arterial hypertension. Thrombotic arteriopathy in a pathologic specimen from a patient with idiopathic pulmonary arterial hypertension. Evidence of thrombosis with recanalization can be observed in pathologic specimens from patients with idiopathic pulmonary arterial hypertension. [Goldhaber SZ, Piazza G. Interventional cardiology. In: Libby P, editor. Essential Atlas of Cardiovascular Disease. 4th ed. Philadelphia: Current Medicine Group; 2009. 432 p. ISBN: 978-1-57340-309-2] *Caption from original*

Presentation

Typical/"Classic"

- The symptoms of pulmonary hypertension are non-specific. In retrospect, patients are often found to have complained of dyspnea on exertion and fatigue. These are not uncommonly attributed to other causes, such as age, deconditioning, or a coexisting and/or alternative medical condition.

- These early symptoms are caused by the inability to adequately increase cardiac output to match demand during exertion.
- Because the initial symptoms of PH can be very vague and nonspecific, patients are often not correctly diagnosed for several years after the development of symptoms.
- As PH is a chronic and progressive disease, the diagnosis is often not considered until the patient develops severe symptoms. These include exertional chest pain, exertional syncope, and signs of right heart failure such as peripheral edema.
- PH is frequently only considered and identified during the evaluation and work-up for an alternative diagnostic consideration.

Atypical

- It is difficult to define an atypical presentation of a process with such vague symptoms and signs.
- Ortner's Syndrome is one such defined atypical presentation of PH. It is marked by cough, hoarseness, and hemoptysis secondary to compression of the recurrent laryngeal nerve by a dilated main pulmonary artery.

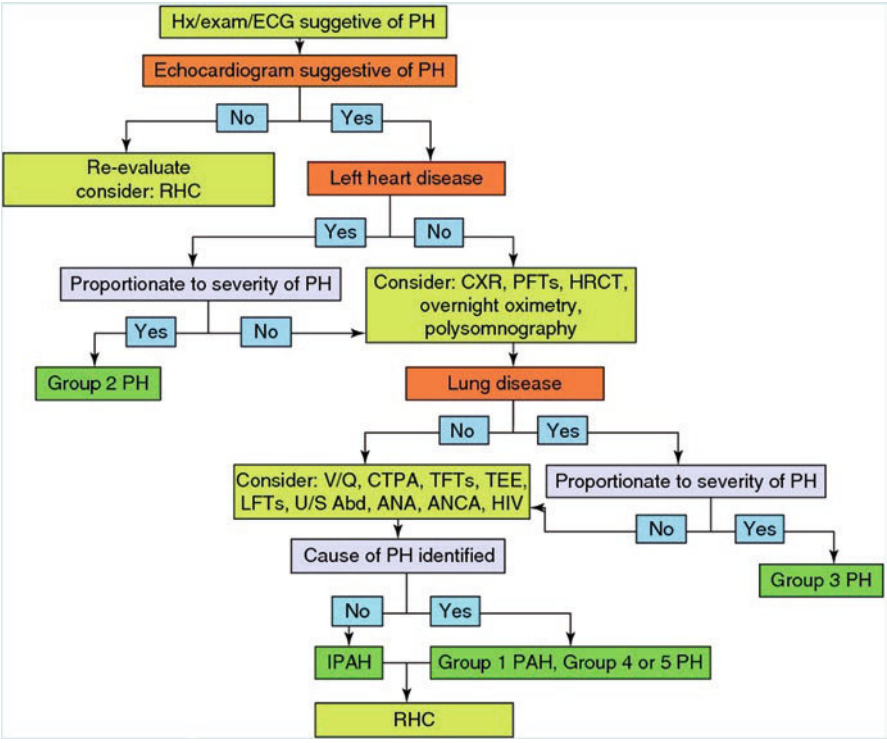
Primary Differential Considerations

- Patients with signs and symptoms referable to pulmonary hypertension should also be evaluated early on for other potentially accurate diagnoses, such as:
  - dilated cardiomyopathy
  - pulmonic valve stenosis
  - mitral valve stenosis

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that are pathognomic for pulmonary hypertension.
- The diagnosis is only confirmed by diagnostic testing. Right heart catheterization is currently the standard test for confirmation of the diagnosis.



Suggested algorithm for evaluation of suspected pulmonary hypertension. Hx clinical history, Exam clinical examination, ECG electrocardiogram, PH pulmonary hypertension, CXR chest radiograph, PFTs pulmonary function tests, V/Q ventilation/perfusion scintigraphy, CTPA computed tomography pulmonary angiography, TFTs thyroid function tests, TEE transesophageal echocardiogram, LFTs liver function tests, U/S abd ultrasound of the abdomen, ANA antinuclear antibody, ANCA anti-neutrophil cytoplasmic antibody, HIV human immunodeficiency virus serology, IPAH idiopathic pulmonary arterial hypertension, RHC right heart catheterization [Judge EP, O'Callaghan D, Gaine SP. Pulmonary Vascular Disease. In: Rosendorff C, editor. Essential Cardiology [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Sep 29]. p. 603–25. Available from: http://link.springer.com/10.1007/978-1-4614-6705-2_35] *Caption from original*

Factors That Suggest Diagnosis

- The diagnosis should be considered in any patient (especially a patient with any of the associated diseases and exposures as detailed in the Etiology section) with complaints of progressive dyspnea on exertion.

- The work-up and evaluation of a patient with dyspnea on exertion is broad, and should include studies (such as a chest x-ray, echocardiogram, or CT chest) that may give clues to the presence of PH.
- Physical exam findings in PH are also nonspecific, especially early in the disease course.
- Early in the course of PH, before right heart failure develops, patients may have a loud pulmonic component to the second heart sound, and the second heart sound may be narrowly split or single.
- As right heart failure develops, patients may develop the physical signs as described in the section on cor pulmonale.

Findings	Patients, %
Increase in P_2	93
Tricuspid regurgitation murmur	40
Right-sided S_4	38
Peripheral edema	32
Right-sided S_3	23
Cyanosis	20
Pulmonic insufficiency murmur	13

Physical findings in patients with idiopathic pulmonary arterial hypertension. The physical examination is nonspecific, revealing signs of pulmonary hypertension and right ventricular failure. In the NIH study, the presence of an S3 gallop and tricuspid regurgitation were associated with an increase in right atrial pressure and a decrease in cardiac index; the finding of pulmonic valve insufficiency was associated with a higher mean pulmonary artery pressure. The physical examination helps exclude secondary causes of pulmonary hypertension by an absence of crackles, wheezes, and clubbing. (Data from Rich S, Dantzker DR, Ayres SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med. 1987; 107:216 -223.) [Singh J, Tapson V, Markewitz B, Elliott GC, Michael J. Chapter 18. In: Crapo J, editor. Bone's atlas of pulmonary and critical care medicine. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7] Caption adapted from original

Factors That Exclude Diagnosis

- There are no reliable historical or physical findings that exclude PH from the differential.

Ancillary Studies

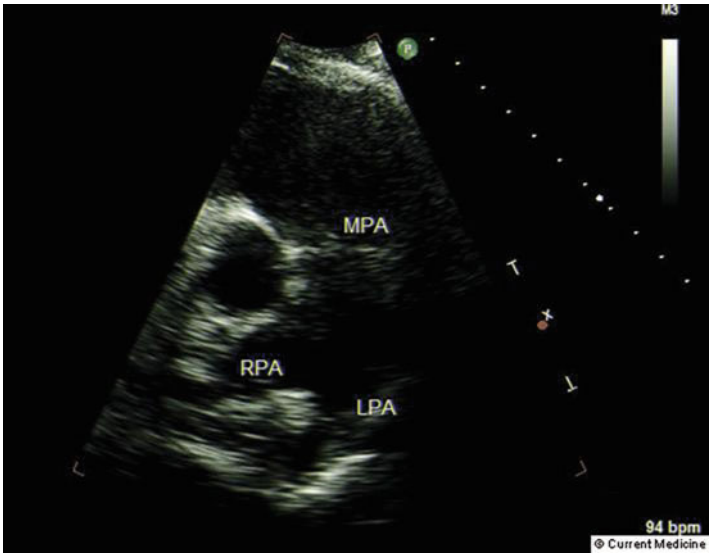
- Extensive diagnostic testing is usually performed on patients thought to have PH, with three common goals:
  - to confirm the diagnosis
  - to attempt to identify an underlying cause
  - to evaluate the severity of the physiologic derangement
- Evaluation often begins with an echocardiogram, and includes multiple other tests as determined by the clinical scenario and symptoms. The diagnosis is usually confirmed by right heart catheterization.

Echocardiography

- Transthoracic echocardiography (TTE) is often the first step in the evaluation and diagnosis of pulmonary hypertension. TTE is used to estimate the pulmonary artery pressure, right ventricular size thickness and function, and right atrial size and function.
- TTE can also be used to assess left heart function, valve function, and any congenital heart anomalies, all three of which are necessary steps in the evaluation of PH.
- As PH progresses, patients will develop findings of right ventricular pressure overload, such as:
  - Paradoxical bulging of the septum into the left ventricle during systole
  - Hypertrophy of the right ventricle
- Echocardiographic findings of right ventricular failure/cor pulmonale are described in the chapter on cor pulmonale.

https://www.youtube.com/watch?v=jpEXFf2tRL4
Video demonstrating Echocardiogram in PH.

https://www.youtube.com/watch?v=3yOdNyTH07g
Video of Echocardiographic findings in PH.



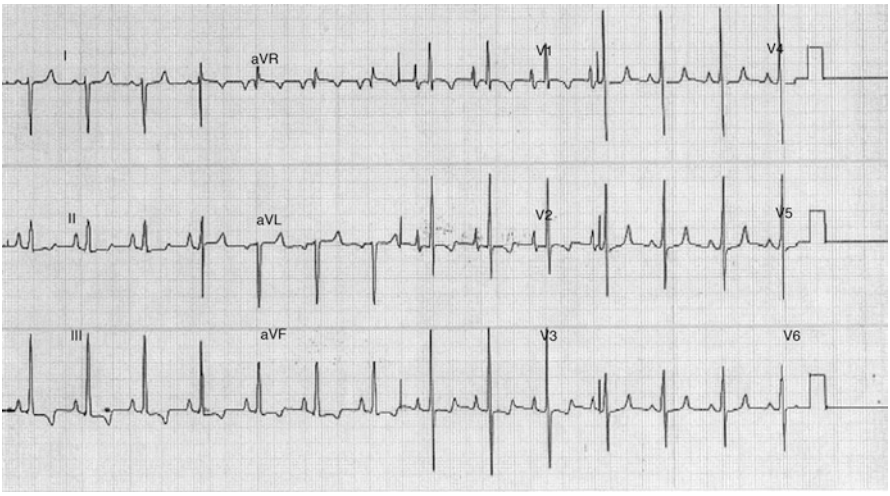
Echocardiogram of severely dilated main pulmonary artery in pulmonary hypertension. Main pulmonary artery (MPA) and bifurcation view, demonstrating severely dilated MPA and branches in a patient with severe pulmonary hypertension. LPA: left pulmonary artery; RPA: right pulmonary artery. [Mangion J, Solomon S. Chapter 15. In: Vannan MA, Lang RM, Rakowski H, Tajik AJ, Braunwald E, editors. Atlas of Echocardiography. 1e. Philadelphia, PA: Current Medicine Group; 2005. 312 p. ISBN: 1-57340-217-6] *Caption from original*

Laboratory

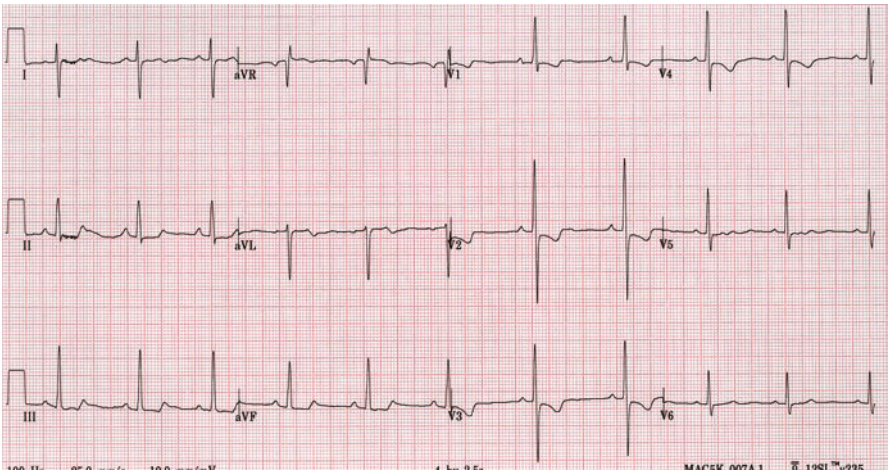
- Typical laboratory tests performed in the evaluation include evaluation for anemia with a complete blood count, and a complete metabolic panel to evaluate electrolytes, renal function, and liver function.
- In the appropriate clinical setting, HIV serology should be checked to screen for HIV-associated PH.
- An antinuclear antibody (ANA) should be sent to evaluate for connective tissue as the cause for PH. Further, more specific connective tissue disease testing can be performed as indicated.
- In areas of increased prevalence, screening for hemolytic anemia such as sickle cell anemia, and screening for Schistosomiasis should be considered.
- Brain natriuretic peptide (BNP) and its precursor, N-terminal pro-brain natriuretic peptide (NT-proBNP), are peptides that are released by myocardial cells when stretched. They are elevated in both right and left heart failure, and are not helpful in distinguishing between the two. Patients with known PH who have elevated levels of either have a worse prognosis than those with normal levels.

Electrocardiography

- The ECG in PH can show a right axis deviation, right ventricular hypertrophy (an R wave/S wave ratio greater than one in lead V1), right atrial enlargement (p pulmonale, an increase P wave amplitude in lead II), and an incomplete or complete right bundle branch block. These ECG changes are almost always present in pulmonary hypertension especially as the disease progresses, but can also be present in many other disease states (they are specific but not sensitive).



A 12-lead ECG strip of a 31-year-old male patient with pulmonary hypertension (p-pulmonale, right-axis deviation, and right ventricular hypertophy) [Stübgen J-P. Rigid Spine Syndrome: A Noninvasive Cardiac Evaluation. Pediatric Cardiology. 2008 Jan;29(1):45–9.] *Caption from original*



An ECG taken in a patient with idiopathic pulmonary arterial hypertension. Note the signs of right ventricular hypertrophy with a rightward mean frontal QRS axis. [Simon J, Gibbs R, Stefanidis A, Li W. Pulmonary Hypertension Clinical Echocardiography. In: Nihoyannopoulos P, Kisslo J, editors. Echocardiography [Internet]. London: Springer London; 2009 [cited 2015 Sep 3]. p. 229–49. Available from: http://link.springer.com/10.1007/978-1-84882-293-1_10] *Caption from original*

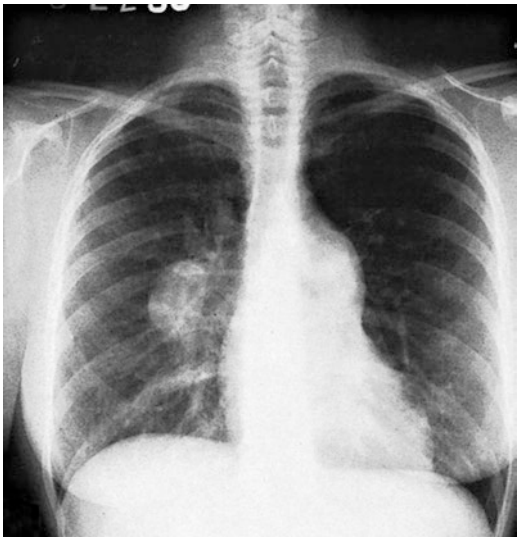
Pulmonary hypertension with severe right atrial and ventricular overload in a young woman. The ECG shows signs of right atrial and ventricular enlargement, the latter manifested by qR complexes in V1-V3 and ST-segment depression. The electrical axis is also deviated to the right. [Romanò M. The Electrocardiogram in Disorders of the Pulmonary Circulation. Text Atlas of Practical Electrocardiography [Internet]. Milano: Springer Milan; 2015 [cited 2015 Sep 3]. p. 213–5. Available from: http://link.springer.com/10.1007/978-88-470-5741-8_14] *Caption from original*

Imaging

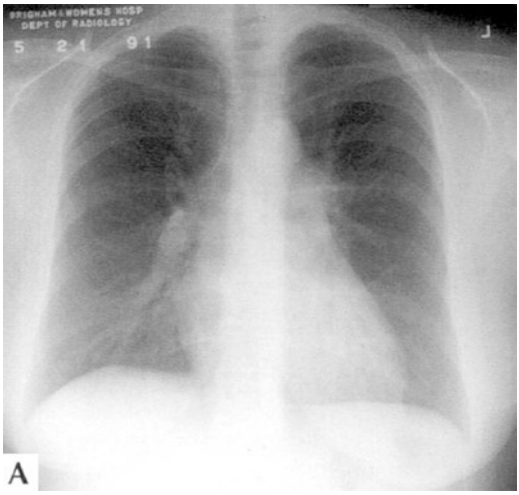
Chest X-ray

- Pulmonary hypertension often leads to enlargement of the central pulmonary arteries, i.e., the main pulmonary artery, the hilar vessels, and the descending right pulmonary artery, associated with gradual diminution in the peripheral vessels, leading to hyperlucent peripheral lung fields (oligemia). Other findings on CXR can include:
  - right ventricular enlargement (noted as loss of the retrosternal airspace on a lateral view)
  - right atrial dilatation (noted as a prominent right heart border)
- The chest x-ray can also occasionally help in giving clues to any underlying diseases that may be complicating PA, such as COPD, interstitial lung disease, and congestive heart failure.

https://www.youtube.com/watch?v=9y-PDoJoL2M
Video explaining radiographic findings in PH.



Pulmonary hypertension. A, An injection drug user aged 32 years presented with progressive shortness of breath. Marked dilatation of both pulmonary arteries is shown. For unknown reasons, the incidence of primary pulmonary hypertension is increased in patients with HIV infection. [Lalloo UG, Ambaram A, Vawda F. Pulmonary Complications. In: Mildvan D, editor. International Atlas of AIDS. 4e.: Current Medicine; 2008. 366 p. ISBN: 1-57340-270-2] *Caption adapted from original*

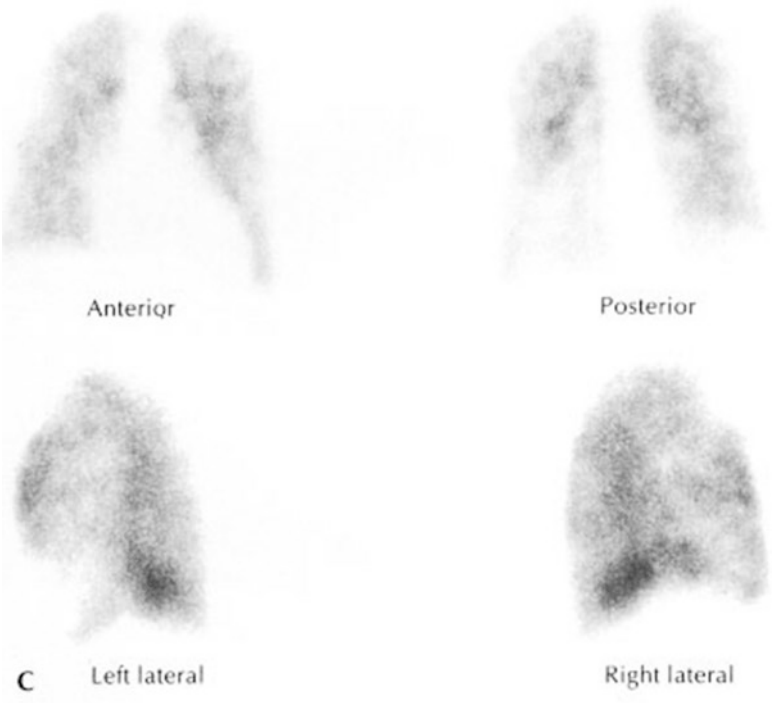


Typical radiograph of a patient with primary pulmonary hypertension and cor pulmonale. Note the peripheral oligemia of the pulmonary vessels with mild bilateral enlargement of the main pulmonary arteries. [Loh E. Chapter 01. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption adapted from original*

Ventilation/Perfusion Scanning (V/Q scan)

- V/Q scan is the imaging of choice in the evaluation of patients for CTEPH (Group 4 PH).
- A normal V/Q scan can nearly exclude chronic thromboembolic disease as the cause for PAH.
- If the V/Q suggests the presence of chronic thromboembolic disease, an angiogram or a CT angiogram should be performed to confirm the diagnosis.

Perfusion lung scan in chronic thromboembolic pulmonary hypertension. B, Perfusion lung scan in a patient with CTEPH. Ventilation scan was normal. [Fedullo P, Auger W, Channick R, Jamieson S, Moser K. Chapter 07. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption adapted from original*



C, Perfusion lung scan in primary pulmonary hypertension. Ventilation-perfusion lung scanning provides an excellent, low-risk, noninvasive means of distinguishing between pulmonary hypertension due to potentially operable CTEPH and obliterative, small-vessel pulmonary hypertension. In chronic thromboembolic disease, at least one (and, more commonly, several) segmental or larger mismatched defect is present. In primary pulmonary hypertension, the perfusion scan is either normal or has a mottled appearance consisting of patchy, subsegmental abnormalities. Although the ventilation-perfusion lung scan can suggest the diagnosis of CTEPH, it is incapable of confirming the diagnosis or establishing surgical feasibility. Any process that occludes major pulmonary arteries, either through external compression (fibrosing mediastinitis, mediastinal tumors) or intraluminal obstruction (thrombus, tumor), will result in similar defects. [Fedullo P, Auger W, Channick R, Jamieson S, Moser K. Chapter 07. In: Goldhaber S, editor. Cardiopulmonary Diseases and Cardiac Tumors. Philadelphia: Current Medicine; 1995 (Braunwald E, editor. Atlas of heart diseases; vol. 3.)] *Caption adapted from original*

CT Scan/MRI

- CT scans of the lungs can be helpful in the evaluation and diagnosis of causes of PH, such as ILD, COPD, CTEPH.

- Cardiac magnetic resonance imaging (MRI), if available, is superior to transthoracic echocardiography in the evaluation of right ventricular structure and function.

Other

- Right heart catheterization is considered the best diagnostic test for confirming the diagnosis of pulmonary hypertension and evaluating the severity of the disease. Pulmonary hypertension is defined as a pulmonary artery (PA) pressure greater than 25 mmHg, and no evidence of left heart disease, as evidenced by either a normal (less than 15 mmHg) left ventricular end-diastolic pressure. All chamber dimensions and pressures can be directly measured.
  - Measuring *only* the pulmonary capillary wedge pressure (PCWP) is insufficient to distinguish PH alone from PH due to left heart disease, as the PCWP may be falsely elevated in all cases of PH due to dilatation of the main pulmonary artery, which prevents accurate measurement of the PCWP.
- Vasoreactivity test. Patients with Group 1 PAH should have a vasoreactivity performed prior to the initiation of any PAH-specific therapy. A small subset of patients with IPAH, hereditable PAH, and drug-induced PAH will have significant hemodynamic and symptomatic improvement with the use of calcium channel blockers. Vasoreactivity testing involves administering a short-acting vasodilator (such as inhaled nitric oxide, or infusions of adenosine or epoprostenol) during right heart catheterization and then measuring the response of the mean pulmonary artery pressure. Patients with a positive vasoreactivity test (decrease in mean PA pressure of at least 10 mm Hg to at least 40 mmHg, an increased or unchanged cardiac output, and insignificant change in systemic blood pressure) should have therapy with a calcium channel blocker started.
- Pulmonary function tests are used to evaluate for underlying lung disease such as interstitial lung disease (ILD) and chronic obstructive pulmonary disease (COPD) as the underlying causes for PH.
- Sleep studies (polysomnography) are used to diagnose obstructive sleep apnea as the underlying cause for PH when the clinical suspicion is high.
- Exercise testing (most commonly the 6-minute walk test) is often performed during the evaluation of or after the diagnosis of PH is established. Exercise testing helps to establish a clinical baseline to guide therapy and measure the response to therapy.

Special Populations

Age

- Pulmonary hypertension is mostly a disease of middle-aged to older adults.
- Group one PAH typically affects younger adults, and is slightly more common in women.
- There is a subset of Group 1 PH (Group 1″) known as persistent pulmonary hypertension of the newborn (PPHN). This is a rare disease of late preterm or term infants with abnormal development of the pulmonary vasculature.
- PH may complicate and be caused by diseases of childhood, congenital heart disease, sickle cell anemia, and cystic fibrosis. However, the development of PH in patients with these disorders is usually a late complication, developing in young adulthood.

Co-morbidities

- Many co-morbid conditions can worsen the prognosis and make the diagnosis of PH difficult. These include but are not limited to, cardiac diseases, other pulmonary diseases, liver disease, and kidney disease.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is important to keep PH on your differential diagnosis in the evaluation of patients with exertional dyspnea and fatigue, as the symptoms and exam findings are nonspecific. It is important to diagnose this disorder as early into the clinical course as possible, as this improves the ability to treat the disease and improves the overall prognosis.
- It is important to perform a detailed and specific evaluation for alternative diagnoses and causative factors for PH.
- It is also important to consider all alternative diagnoses that may cause worsening or acute dyspnea in patients with chronic pulmonary and heart disease. This list includes, but is not limited to, pneumonia, CHF, pulmonary embolism, pneumothorax, significant pleural effusion, and acute metabolic issues that can cause dyspnea.

Mimics

- Many diseases can present with exertional dyspnea and fatigue. This includes, but is not limited to, lung diseases such as COPD and ILD, coronary artery disease, valvular heart disease, congenital heart disease, chronic anemia, metabolic diseases, neuromuscular diseases, etc.

Time-Dependent Interventions

- It is important to make the diagnosis as early as possible into the disease course to improve treatments and outcomes.

Overall Principles of Treatment

- Early diagnosis and treatment is important, as less advanced disease responds better to treatment, and outcomes are better.
- Treatment is generally classified as primary therapy, which is treatment directed at the underlying cause of the PH, and advanced therapy, which is therapy directed at PH.
- Certain treatments need to be considered in all patients with PH. These include:
    - Anticoagulation. PH increases the risk for pulmonary thromboembolism through multiple mechanisms. As such, chronic anticoagulation is indicated in all patients with PH, but especially those with Groups 1 (especially IPAH, hereditary PAH, and drug-induced PAH) and 4 PH.
    - Diuretics. Diuretics are useful to reduce fluid retention and associated edema.
    - Oxygen. All patients with hypoxemia should be given oxygen.
    - Pulmonary rehab/exercise therapy. Pulmonary rehabilitation improves patients' exercise tolerance, daily function, and quality of life.
    - Digoxin. Digoxin is positively inotropic, meaning that it can increase the mechanical contractile strength of the heart. Digoxin's therapeutic window is narrow, however, and it has significant toxicities associated with its use. Patients receiving digoxin need to be closely monitored.
- Primary therapy.
    - Group 1 PAH. There are limited therapeutic options for Group 1 PAH patients. Management of the primary disease should be maximized for patients with an identified underlying cause (such as HIV, congenital heart disease, Schistosomiasis). However, this often does not improve symptoms of PAH once they develop and these patients often require advanced therapy for PAH.
    - Group 2. Therapy for the underlying heart disease must be maximized for patients with Group 2 PH.

- Group 3. These patients need to have their underlying lung disease treated, and they require oxygen therapy if hypoxemic.
- Group 4. Anticoagulation is the most important treatment for patients with group 4 PH. Some selected patients may benefit from surgical thromboendarterectomy.
- Group 5. Patients with group 5 PH should have their underlying diseases treated.

- Advanced Therapy. Patients requiring advanced therapy for PH should be referred to and managed by a center with significant experience managing these disorders. All patients should have a complete diagnostic evaluation (which includes right heart catheterization and vasoreactivity test) and functional class staging WHO functional class) prior to initiating advanced therapies.
- WHO Functional Classes for PH.
  - Group 1. Advanced therapy for PH by a specialized center is the treatment of choice for most patients with Group 1 PAH. Patients with a positive vasoreactivitiy test should have a trial of treatment with a either a dihydropyridine calcium channel blocker (e.g., amlodipine and others that end in *–ipine*) or diltiazem. If patients have a negative vasoreactivity test or are non-responders they need to have an alternative advanced therapy agent started. The choice of agent is complex and multifactorial, and best managed by a specialized center.
- Treatment with advanced agents is often guided by WHO functional class, and includes:
  - WHO functional class II or III (oral therapy preferred):
    - Oral endothelin receptor antagonists (ambrisentan, bosentan, macitentan)
    - Oral phosphodiesterase inhibitors (sildenafil, tadalafil)
    - Oral guanylate cyclase stimulants (riociguat)
  - Some patients with WHO functional class III disease may benefit from other parenteral agents such as intravenous epoprostenol, inhaled iloprost, or intravenous trepostinil.
  - WHO functional class IV. Intravenous epoprostenol.
- Patients with refractory disease may be considered for combination drug therapy or surgical therapy.
  - Surgical therapy includes: creation of a right-to-left intracardiac shunt (atrial septostomy, or a Potts shunt, a shunt between the left pulmonary artery and the descending aorta); and bilateral lung or bilateral lung and heart-lung transplantation. These therapies are reserved for refractory cases and should be considered only at highly specialized centers.

Disease Course

- Patients on therapy should be seen at least every three months. Patients on no therapy should also be followed at least every three-to-six months for reevaluation.
- PH is a chronic, progressive, and frequently fatal disease, especially if untreated.
- The course of disease progression and mortality is highly variable and dependent upon the type of PH and the disease severity at diagnosis.
- In general, Group 1 PAH tends to have a more rapid course and worse survival than the other types of PH. Recently reported data from the REVEAL registry (Registry to Evaluate Early and Long-term PAH Disease Management) shows survival rates one, three, five, and seven years from the time of right heart catheterization of 85, 68, 57, and 49 percent, respectively, for Group 1 PAH.
- There is early data that advanced therapy can improve survival in Group 1 PAH.
- The following factors are associated with a poorer prognosis in Group 1 PAH.
    - Age > 45
    - Male
    - WHO functional class III or IV
    - Failure to improve clinically with advanced therapy
    - Evidence of right heart failure on echocardiogram (large right atrial size, elevated right atrial pressure, septal shift during diastole, presence of a pericardial effusion, low right ventricular ejection fraction)
    - Increased NT-pro-BNP or BNP levels
    - Prolonged QRS duration
    - Hypocapnia
    - Certain comorbid conditions (especially interstitial lung disease, COPD, diabetes)
    - Persistent supraventricular arrhythmias (atrial fibrillation or flutter)
    - Long-term use of selective serotonin reuptake inhibitors
- The overall course and prognosis in other types of PH varies greatly and is mostly related to the course of the underlying disease.
- Patients with PH (especially those with PAH) are at increased risk for complications and death from any surgical procedure, use of general anesthesia, or mechanical ventilation.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Chapter 64
Radiation Pneumonitis

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Radiation Pneumonitis; Radiation-induced Lung Injury (RILI); Radiation Fibrosis

Incidence/Epidemiology

- The incidence of radiation pneumonitis varies widely depending upon the regimen/modality of radiation used, and the size/volume of tissue treated.
- Radiographic changes of pneumonitis are much more common than symptomatic disease.
- Across all cancers, about 50% of patients who receive radiation therapy to the chest, lungs, or mediastinum will develop some radiographic findings of pneumonitis, but only about 10–15 % will develop symptoms.
- About 65 % of all patients with cancer will undergo therapeutic radiation therapy at some point during their cancer treatment. This leads to a large number of people being "at risk" for the development of radiation pneumonitis.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_64

Differential Diagnosis

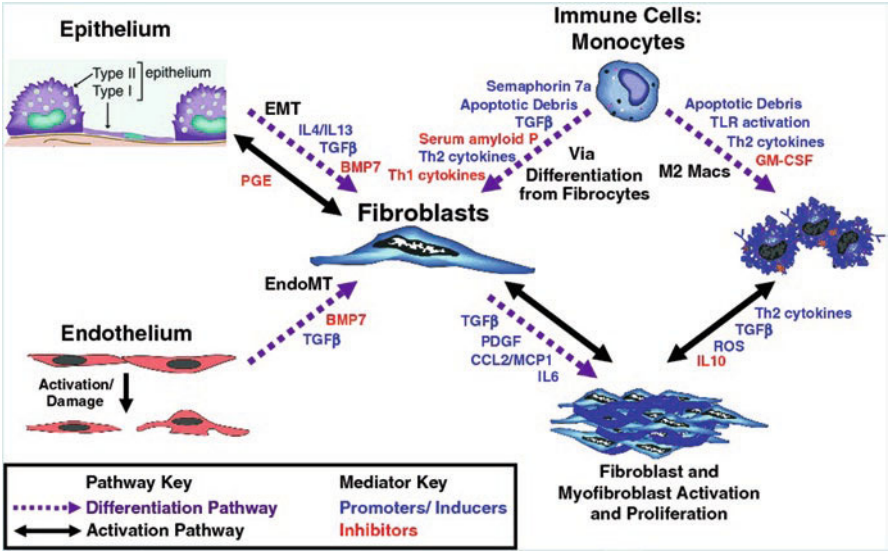
- The differential diagnosis can be broad, and includes all causes of dyspnea and cough, especially in a cancer patient.
- The differential can often be focused to include those processes that have a similar radiographic appearance to radiation pneumonitis. These include:
  - Infection, such as pneumonia, tracheobronchitis, and empyema. Infections can be bacterial, viral, atypical, or fungal.
  - Lymphangitic spread of tumor.
  - Pulmonary embolism (especially if dyspnea is the prominent complaint).
  - Drug reaction.
  - Congestive heart failure (especially in patients who have received chemotherapeutic agents such as doxorubicin).
  - Hypersensitivity pneumonitis-like reaction. This is a less common reaction to radiation that is distinguished from radiation pneumonitis by including areas of the lung outside those that received radiation. It is often bilateral, even if the radiation was only delivered to one lung. It follows a similar time course to early radiation pneumonitis.

Pathophysiology and Etiology

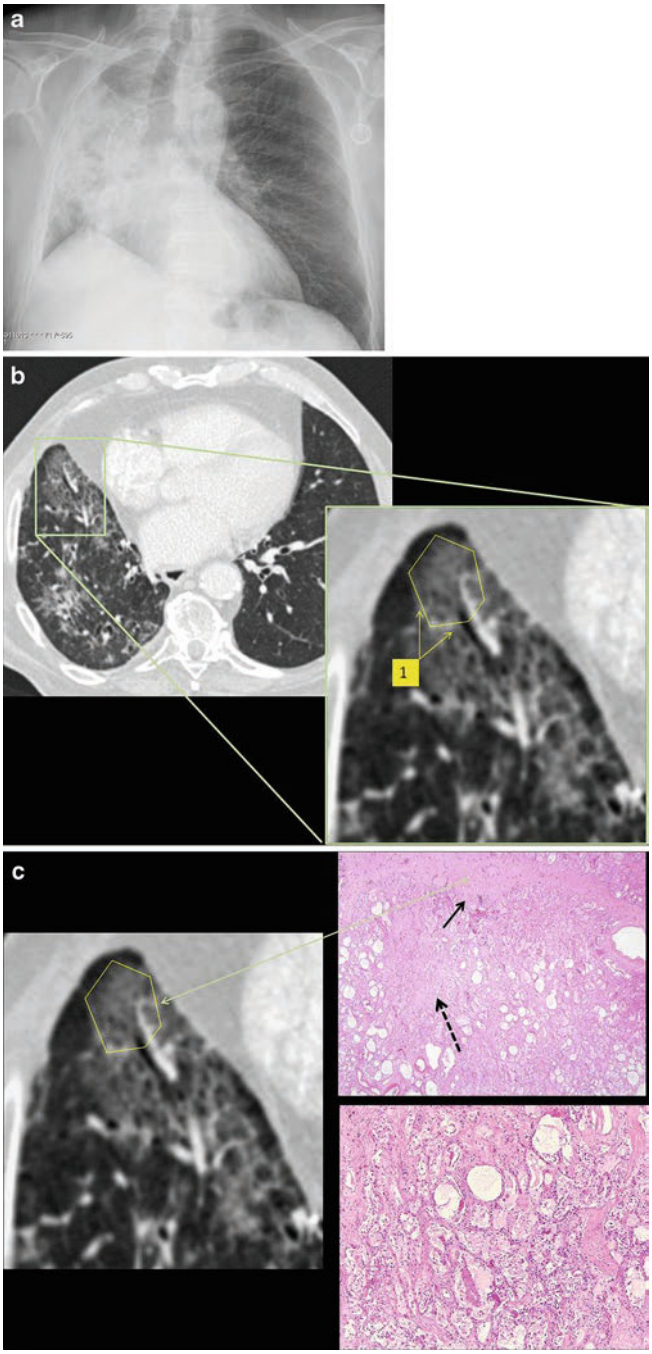
- Ionizing radiation passing through tissue causes the release of large amounts of energy, which can lead to the production of reactive free radicals in the tissue. As water is plentiful, the majority of free radicals include reactive oxygen and hydrogen ions. Other important free radical species include reactive nitrogen species. These free radicals react with and damage other cellular molecules such as DNA, RNA, peptides, and lipids. This can lead to direct cytotoxicity and death to normal lung cells and tissue, especially high turnover cells such as surfactant-producing cells.
- Radiation energy, cell damage, and cell death lead to the activation of inflammatory pathways and the release of a large number of cytokines that can cause inflammatory reactions in lung tissue. Pro-inflammatory cytokines up-regulated after exposure to radiation include, transforming growth factor beta, tumor necrosis factor alpha, interleukin 1-alpha, interleukin-6, platelet-derived growth factor, and basic fibroblast growth factor.
- There are several factors that affect the incidence and risk of the development of radiation pneumonitis.
  - Genetics. In patients with small cell and non-small cell lung cancer, the presence of a mutation in the methylene tetrahydrofolate reductase gene has been shown to be associated with an increased risk for the development

of radiation pneumonitis. There are other, less well-defined, genetic associations in both breast and lung cancer.
- The risk of developing radiation pneumonitis is directly related to the volume of lung tissue exposed to radiation.
- Using the modality of radiation delivery that most limits the dose to the affected tissue helps to prevent the development of radiation-induced lung injury.
- The risk also increases directly with increasing doses of radiation.
- Some chemotherapeutic agents are known to increase tissue sensitivity to radiation. These include doxorubicin, gemcitabine, taxanes, dactinomycin, bleomycin, cyclophosphamide, vincristine, mitomicin, recombinant interferon-alpha, and bevacizumab.
- Concurrent chemotherapy and radiotherapy also appears to increase the risk of radiation pneumonitis, especially in the treatment of breast cancer.
- Current tobacco-smoking and chronic obstructive pulmonary disease have been associated with a lowered risk of developing radiation pneumonitis in some studies.

- The pathologic changes within the lung after exposure to radiation can be divided into five phases.
    - Immediate phase. These changes occur within hours to days after radiation exposure. It consists of mucosal inflammation, increased capillary permeability, mucous hypersecretion, with subsequent sloughing of alveolar epithelial cells. This is usually asymptomatic.
    - Latent phase. During this phase, goblet cells start to proliferate, leading to an increase in secretions. Radiation has also induced ciliary dysfunction, leading to an inability to clear these increased secretions, which then pool in alveoli.
    - Acute exudative phase. This phase occurs anywhere from 3 to 12 weeks after exposure to radiation. It is during this phase that the clinical syndrome of radiation pneumonitis usually occurs. It is characterized by increased sloughing of epithelial and endothelial cells, microvascular thrombosis, alveolar exudate, with subsequent hyaline membrane formation with narrowing of small airways and pulmonary capillaries.
    - Intermediate phase. During this phase, many patients will have resolution of all changes. Some patients, however, will continue to progress with increased collagen deposition by fibroblasts, resulting in thickening and distortion of the interstitial tissues.
    - Fibrosis. In some cases, fibroblasts can continue to migrate into lung tissue and continue to produce collagen, which leads to disruption of alveolar and vascular tissue. These changes can become clinically apparent in anywhere from 6 months to several years after radiation exposure.



Key cell types associated with fibrosis and the differentiation pathways and mediators that promote and inhibit these pathways. Fibrosis is characterized by excess extracellular matrix deposition from collagen-producing cells including fibroblasts and myofibroblasts. These cells are resident within tissues, generating matrix to support tissue function and homeostasis. However, during fibrosis, fibroblasts become activated, proliferate at greater rates than unactivated cells and are resistant to apoptosis. There is also an increased number of myofibroblasts, which are normally at low levels in non-fibrotic tissue. Monocytes activate fibroblasts through either differentiating to fibrocytes or alternatively activated M2 macrophages. Both of these monocyte-derived cells are found at elevated numbers in the circulation of patients with chronic lung fibrosis and at sites of tissue remodeling. Both epithelial cell and endothelial cell injury is observed at sites of fibrotic tissue remodeling. Moreover, the transition of epithelial cells to mesenchymal cells and endothelial cells to mesenchymal cells has been hypothesized as sources for increased mesenchymal cell numbers in fibrosis. Multiple mediators, especially radiation exposure, have been shown to promote fibrosis and to direct cells to a pro-fibrotic or anti-fibrotic phenotype, with the cellular environment also helping to direct cell phenotype. Many of the mediators shown to induce pro-fibrotic responses are pleiotropic, directing more than cellular response on multiple cell types [Murray LA, Sleeman MA. Fibrosis. In: Sonis ST, Keefe DM, editors. Pathobiology of Cancer Regimen-Related Toxicities [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Dec 22]. p. 167–86. Available from: http://link.springer.com/10.1007/978-1-4614-5438-0_9] *Caption adapted from original*



Radiation pneumonitis. **a** Chest radiograph showed an area of consolidation in the right lung with an air bronchogram. There was also loss of volume of the right lung. **b** CT showed the therapy response of the tumor. There was patchy distribution of a

crazy-paving pattern with increased lung attenuation (ground-glass opacity) and thickening of the interlobular septa in the right lung (1). **c** Radiological-histopathological correlation. Histological examination after autopsy showed air-space filling with an exudate in combination with thickening of the interlobular septa (arrow), thickening of the interstitium surrounding the airspaces and also the presence of irregular fibrosis (dotted arrow). Alveolar spaces filled with an exudate of proteinaceous material were responsible for the ground-glass opacities on CT. The reticular pattern was due to congestion of capillaries and oedema of the interstitium [De Wever W, Meersschaert J, Coolen J, Verbeken E, Verschakelen JA. The crazy-paving pattern: a radiological-pathological correlation. Insights into Imaging. 2011 Apr;2(2):117–32.] *Caption from original*

Presentation

Typical/"Classic"

- There are two distinct clinical syndromes associated with radiation damage to the lungs: an acute clinical syndrome due to pneumonitis, and a later syndrome caused by fibrosis.
    - Acute radiation pneumonitis. This develops anywhere from 2 weeks to 3 months after exposure to radiation.
        - Most patients remain asymptomatic throughout this period.
        - Most patients will develop radiographic evidence of pneumonitis (patchy opacities within irradiated areas), but only about 50 % have symptoms.
        - As noted in the Pathophysiology section, the pathologic changes during this period include mucosal inflammation with increased and thickened secretions. These pathologic changes lead to the classic symptoms.
        - The classic symptoms include:
            - Dry cough
            - Shortness of breath
            - Fever
        - Physical examination may be normal, but crackles in the area of consolidation may be noted. Patients may also be tachypneic. In about 10 % of cases a small pleural effusion may be present and decreased breath sounds and dullness to percussion over the effusion may be noted. Pleural inflammation may be noted with a pleural rub.
        - The majority of patients who develop symptoms improve spontaneously over 2 – 4 weeks.

- Late radiation pneumonitis/radiation fibrosis. Although the pathologic process leading to fibrosis can start within 2 weeks of radiation exposure, symptoms (if present) don't usually start until 6 months to even years later.
  - Up to 50 % of patients with radiographic abnormalities will remain asymptomatic.
  - The most common symptoms are dry cough and shortness of breath. Fever can occur but is less common than in acute radiation pneumonitis.
  - In advanced cases of radiation fibrosis, patients may develop signs of pulmonary hypertension and cor pulmonale.

Atypical

- Atypically, patients may present with chest pain. The pain is often pleuritic, and often due to pleural inflammation.
- Chest pain may also occur secondary to esophageal irritation or inflammation. Chest pain in this setting in often worsened by swallowing.

Primary Differential Considerations

- Patients with radiation pneumonitis may present with symptoms that prompt consideration of:
  - Other causes of pulmonary fibrosis
  - Acute pneumonia
  - Pulmonary embolism

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that can completely confirm the diagnosis.

Factors That Suggest Diagnosis

- The diagnosis is suggested when a patient presents with the typical symptoms or radiographic changes in the appropriate time frame after receiving radiation, especially when the radiographic changes are confined to the areas irradiated.

Factors That Exclude Diagnosis

- There are no historical or physical examination findings that can completely exclude the diagnosis, except for an absence of exposure to radiation.

Ancillary Studies

Laboratory

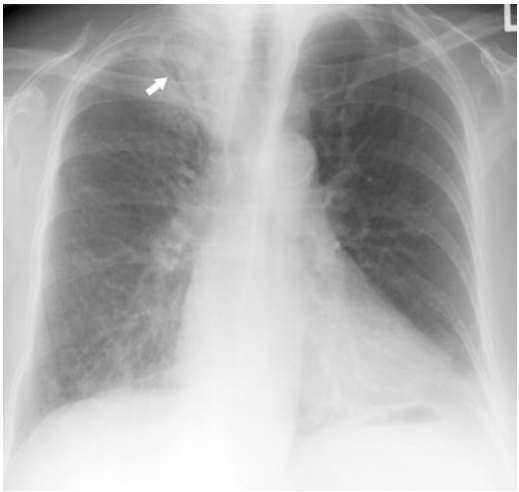
- There are no laboratory studies specific to the diagnosis of radiation pneumonitis.
- Routine laboratory studies are often performed in the evaluation to seek other possible causes of symptoms and radiographic changes.
  - For example, a complete blood count (CBC) showing a leukocytosis with a bandemia or leftward shift may help increase the suspicion for an infectious cause. Patients with radiation pneumonitis may have a slight leukocytosis, but without a bandemia or left shift.
  - An elevated brain natriuretic peptide (BNP) may suggest a diagnosis of congestive heart failure.

Imaging

- Chest x-ray. The classic CXR pattern is one of patchy alveolar densities in the areas treated with radiation. Patients who progress to radiation fibrosis may exhibit lung-volume loss with dense opacities. Again, these are within the areas that received radiation. Some patients may have small pleural effusions.
  - Historically, the CXR in radiation pneumonitis would often show a "straight-line" effect. This straight line of radiographic changes did not conform to anatomic boundaries but to the area that was irradiated. Modern methods of radiation administration allow mostly three-dimensional therapy that can closely conform to the tissue needing treatment, so the straight-line effect is no longer a common finding.

Features of alveolar pattern
Lesions in radiation field
Airspace 1–3 months
Fibrosis 6–12 months
Organizing pneumonia may appear

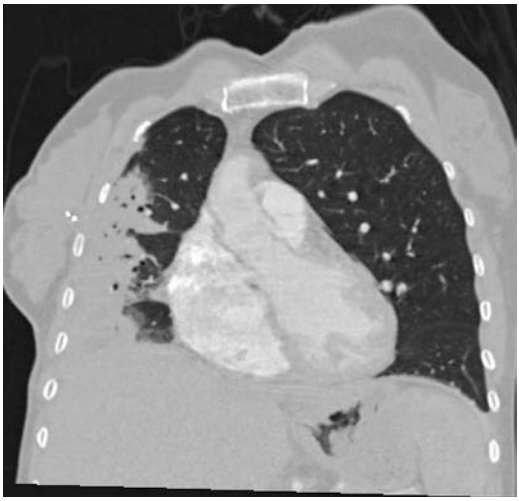
Imaging findings in radiation pneumonitis. The diagnosis of radiation pneumonitis should be made when focal pulmonary disease coincides with the areas of the radiation field [Vilar J, Andreu J. The Lung Parenchyma: Radiological Presentation of Alveolar Pattern. In: Coche EE, Ghaye B, de Mey J, Duyck P, editors. Comparative Interpretation of CT and Standard Radiography of the Chest [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011 [cited 2015 Dec 21]. p. 221–45. Available from: http://link.springer.com/10.1007/978-3-540-79942-9_9] *Caption and text from original*



Radiation pneumonitis. PA radiograph shows consolidation (arrow) in the right upper lobe. [Kanne JP, Godwin JD. Imaging the Chest Following Radiation Therapy. In: Ravenel JG, editor. Lung Cancer Imaging [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Dec 21]. p. 153–68. Available from: http://link.springer.com/10.1007/978-1-60761-620-7_13] *Caption from original*

- Computed tomography (CT) of the chest. A CT scan of the chest is frequently performed during the evaluation of these patients. CT is more sensitive than CXR for the diagnosis of radiation pneumonitis. However, a CT scan is more frequently performed to help exclude other causes of the patient's symptoms (as per the Differential Diagnosis section). As with the CXR, lung involvement should follow the irradiated areas.

Early radiation pneumonitis changes with ground-glass attenuation in the radiation field 6 weeks after radiotherapy for a localized right side breast cancer.[Murchison JT, van Beek EJR. Complications and Toxicity of Radiotherapy for the Breast, Lung and Heart. In: Kauczor H-U, Bäuerle T, editors. Imaging of Complications and Toxicity following Tumor Therapy [Internet]. Cham: Springer International Publishing; 2015 [cited 2015 Dec 21]. p. 115–28. Available from: http://link.springer.com/10.1007/174_2015_1083] *Caption from original*



Subacute radiation pneumonitis in a patient treated with radiotherapy for breast cancer 10 weeks earlier. There is consolidation with air bronchograms which is largely limited by the radiation field and is not bounded by fissures [Murchison JT, van Beek EJR. Complications and Toxicity of Radiotherapy for the Breast, Lung

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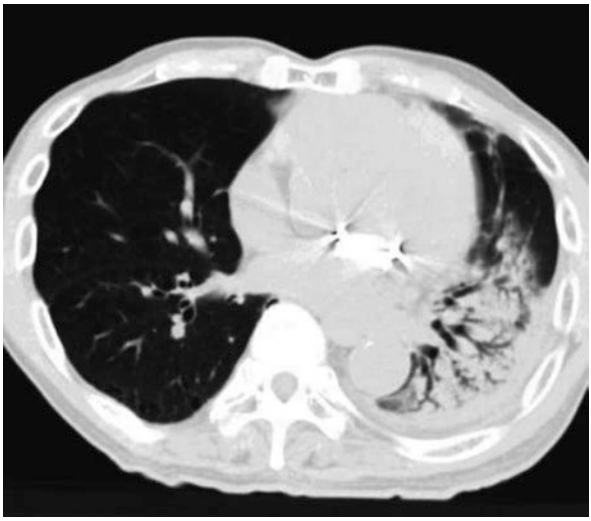

Computed tomography (CT) image of radiation pneumonitis (RP). [From article: Exceptionally high incidence of symptomatic grade 2–5 radiation pneumonitis after stereotactic radiation therapy for lung tumors. Radiation Oncology. 2007;2(1):21. https://doi.org/10.1186/1748-717X-2-21, at http://link.springer.com/article/10.1186/1748-717X-2-21/fulltext.html; by Hideomi Yamashita, Keiichi Nakagawa, Naoki Nakamura, Hiroki Koyanagi, Masao Tago, Hiroshi Igaki, Kenshiro Shiraishi, Nakashi Sasano, Kuni Ohtomo, © Yamashita et al; licensee BioMed Central Ltd. 2007; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

Other

- Pulmonary Function Tests (PFTs). If performed, PFTs will often show diffusely reduced lung volumes, a decreased diffusing capacity for carbon monoxide (DLCO), and an increased alveolar-arterial oxygen gradient. In advanced fibrosis, patients may be hypoxic.
- Bronchoscopy. Bronchoscopy is useful to exclude other diagnoses (as per the differential diagnosis section).

Special Populations

Age

- Age is not a factor in developing radiation pneumonitis. It can occur in any patient who has received radiation to the chest.

Co-morbidities

- Patients with radiation pneumonitis often have multiple co-morbid conditions that can make the diagnosis and management of radiation pneumonitis challenging. Such conditions include chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), cardiomyopathies, and interstitial lung diseases (ILD).

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to carefully consider and evaluate for all diagnoses in the differential.

Mimics

- As the symptoms of radiation pneumonitis are non-specific and also occur with many other conditions, many diseases can present identically to radiation pneumonitis (as per the differential diagnosis section).

Time-Dependent Interventions

- Patients with a known cancer, and who present with shortness of breath, cough, and fever, need to be urgently evaluated for either an infectious or thrombotic (pulmonary embolism) etiology as cause of their symptoms. It may be necessary to treat for infection empirically until this can be adequately ruled out. A CT scan of the chest (or suitable alternative) may be necessary to exclude pulmonary embolism.
- Any patient with hypoxia should receive supplemental oxygen.

Overall Principles of Treatment

- Asymptomatic (or minimally symptomatic) patients who are found to have radiographic abnormalities consistent with radiation pneumonitis can be followed without treatment, as many (up to 50 %) will have a spontaneous recovery.
- All symptomatic patients should be offered supportive, symptomatic treatments such as oxygen for hypoxia, anti-tussives for cough, and anti-pyretics for fever.
- Patients who are symptomatic and have had or are in the process of having alternative diagnoses evaluated can be started on glucocorticoids, specifically prednisone starting at 0.5–1 mg/kg/day in divided doses. This treatment recommendation is based upon consensus, expert opinion, as there are no randomized, controlled trials of glucocorticoids in the treatment or radiation pneumonitis.
- When initiated, steroids should be tapered gradually (over 1–3 months) to prevent a recurrence of symptoms.
- Patients who fail to respond to steroids often have rapid disease progression.
- There is no indication for the treatment of radiation fibrosis with steroids.
- Prophylactic administration of glucocorticoids has not been shown to prevent the development of radiation pneumonitis.

Disease Course

- Many patients with radiation pneumonitis (especially if asymptomatic or minimally symptomatic) will improve spontaneously.
- Patients who progress to fibrosis have less likelihood of spontaneous improvement.
- Fibrosis can continue to progress, but many patients will have both clinical and pathologic stabilization after about 18 months.

Related Evidence

Papers of particular interest have been highlighted as:
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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Radiation Pneumonitis"[Mesh] OR "radiation induced lung injury" OR "radiation fibrosis"

Chapter 65
Retropharyngeal Abscess

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Retropharyngeal Abscess; Retropharyngeal Cellulitis

Incidence/Epidemiology

- The incidence of retropharyngeal abscess has decreased as the use of antibiotics for pharyngeal and dental infections has increased.
- In children, it is most prevalent between the ages of 2 and 4 years.
- Retropharyngeal abscesses are among the most serious of the cervical deep space infections, as they may spread directly into the mediastinum.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_65

Differential Diagnosis

- The differential diagnosis of retropharyngeal abscess includes all the other deep neck space infections, pharyngitis, epiglottitis, cervical osteomyelitis, meningitis, angioedema, tumors, and other space-occupying lesions.

Pathophysiology and Etiology

- About half of pediatric cases are preceded by an upper respiratory tract infection. Another quarter are the result of penetrating trauma (e.g., from swallowing chicken bones, iatrogenic trauma after procedures); the remainder are secondary to pharyngitis, dental infections, and, rarely, vertebral osteomyelitis.
- In adults, it now is seen most commonly as an iatrogenic complication of oropharyngeal procedures, a direct extension from other contiguous infectious foci, or a result of penetrating trauma (swallowing of chicken bones, stab wounds, gunshot wounds).
- The retropharyngeal space is a potential space between the posterior prevertebral fascia and the alar fascia. It extends from the base of the skull to the posterior mediastinum at the tracheal bifurcation. It is fused in the midline (so infections usually stay localized to one side) and contains two chains of lymph nodes that drain the nasopharynx, adenoids, and posterior nasal sinuses.
- Children usually have an antecedent infection that is drained by one of the lymph node chains in the retropharyngeal space. The lymph nodes become infected, suppurate, and develop into an abscess. Adults tend to develop infection in the space by direct contamination from penetrating trauma or by contiguous spread from other infections.
- The retropharyngeal space communicates directly with the mediastinum and the lateral pharyngeal space, both of which communicate with the carotid sheath. Infection may spread within all these spaces.
- The infections typically are polymicrobial and include normal flora of the oropharynx.
- The infection often includes oral anaerobes.
- The most commonly found organisms include *Streptococcus viridans*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter*, *Peptostreptococcus*, and *Fusobacterium*.

Presentation

Typical/"Classic"

- Children more commonly present classically than do adults.
- Commonly presents with fever (65 %), sore throat (76 %), pain or difficulty with swallowing (35 %), and neck spasms with the patient's unwillingness or inability to move (especially extend) the neck (37 %)
- Neck swelling or a discreet neck mass may be present.
- Cervical lymphadenopathy often is present.
- Children often drool and cannot handle oral secretions appropriately.
- Vocal quality may change, with hoarseness or a muted quality to the voice.
- The patient may have respiratory distress and stridor.
- Trismus (difficulty or inability to open the jaw) is present in 20 %.
- Affected patients usually appear ill and toxic, and the onset generally is acute.
- The nonconstitutional symptoms manifested by the patient usually are related to whatever structures are being obstructed or compressed by the abscess cavity.

Atypical

- Onset may be more insidious and less dramatic, especially if the patient has been on antibiotics.
- Early in the course of illness, the symptoms may be identical to those of pharyngitis.

Primary Differential Considerations

- When evaluating a patient in whom retropharyngeal abscess is suspected, early consideration also should be given to the following differential diagnoses:
  - Angioedema
  - Epiglottitis
  - Meningitis
  - Pharyngitis
  - Peritonsillar abscess
  - Caustic ingestion

History and Physical Exam

Findings That Confirm Diagnosis

- There are no confirmatory findings on history and physical examination. The other diagnoses in the differential may present with remarkable similarity.

Factors That Suggest Diagnosis

- The index of suspicion should be high for any child who presents febrile with any combination of the symptoms reviewed in the classic presentation.
- Adults may give a history of a recent procedure or trauma, leading to consideration of the diagnosis.

Factors That Exclude Diagnosis

- There are no historical or physical findings that exclude the diagnosis.
- The diagnosis is excluded only by the absence of an abscess on advanced imaging.

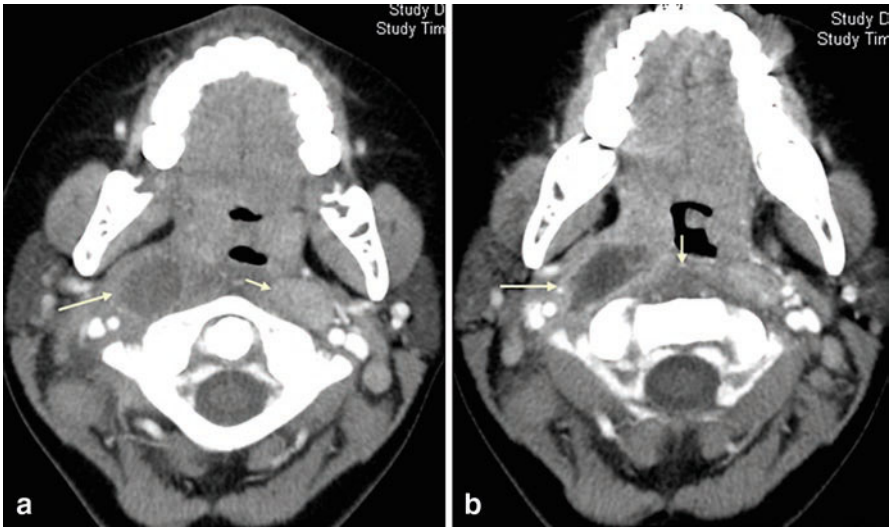
Ancillary Studies

Laboratory

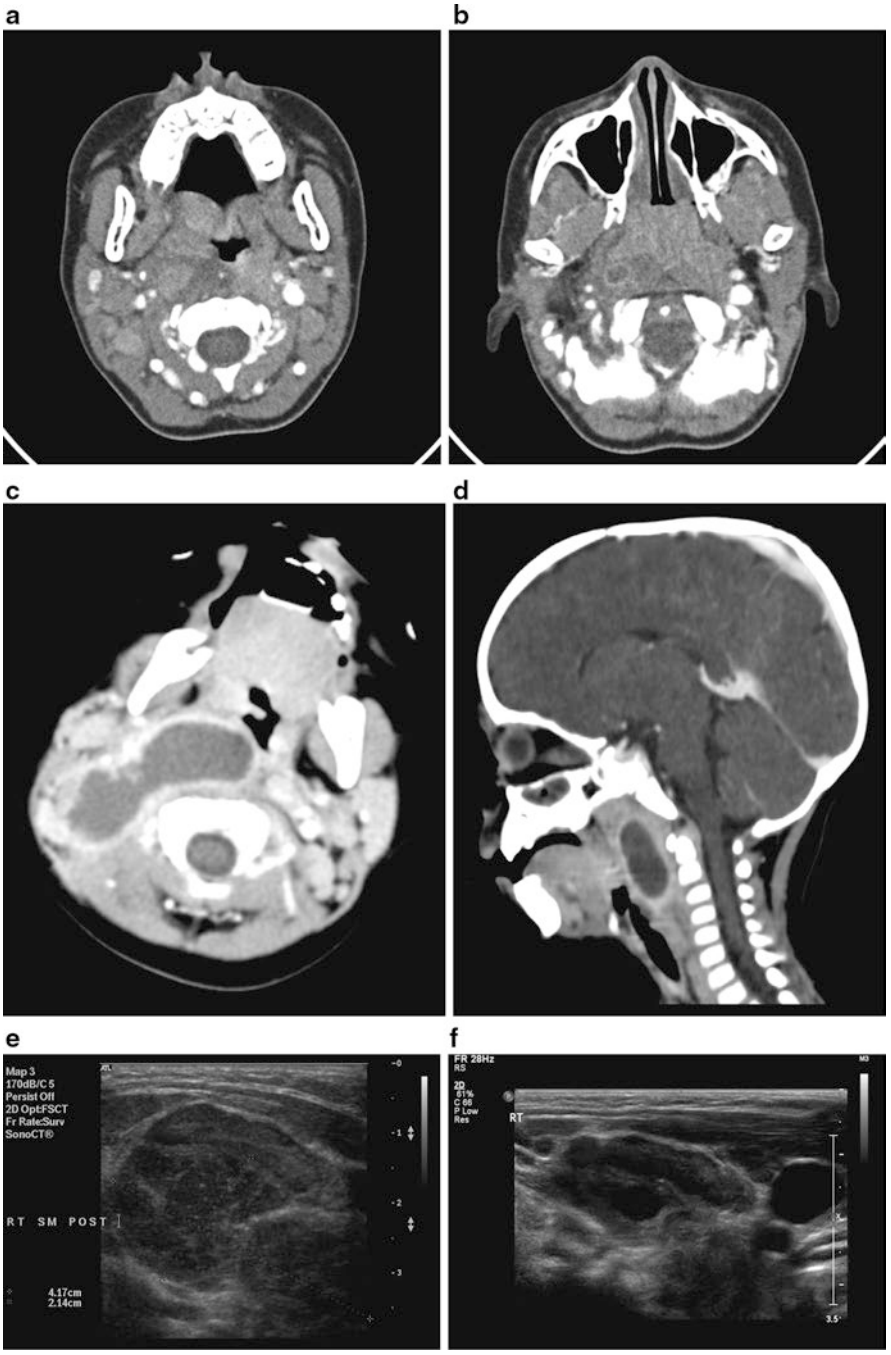
- Lab studies should include the typical tests for any patient who presents febrile with an acute illness. These include (but are not limited to) a complete blood count with differential, electrolyte and renal function tests, serum lactate measurement, blood cultures, and pharynx culture if possible.

Imaging

- Contrast-enhanced CT of the neck is the diagnostic test of choice. A CT scan can differentiate among the different cervical deep space infections, epiglottitis, and other diseases in the differential. CT also may help the otolaryngologist plan appropriate operative intervention.
- Contrast-enhanced MRI also may be performed, but it takes longer and is more difficult for children.



Retropharyngeal abscess. CT scans of the neck of a child at early and later stages of suppurative adenitis evolving into a retropharyngeal abscess. a At an earlier stage, CT image shows right parapharyngeal adenopathy with central necrosis (long arrow). Note the prominent hyperdense adenopathy on the contralateral side (short arrow). b There was no clinical improvement after antibiotic administration. A repeat examination at the same level shows abscess formation on the right (long arrow) causing a mass effect upon the airway and improvement of the adenopathy on the left. The hypodense area in the prevertebral space indicates edema/exudate (short arrow). [Restrepo R, Oneto J, Lopez K, Kukreja K. Head and neck lymph nodes in children: the spectrum from normal to abnormal. Pediatr Radiol. 2009 Aug;39(8):836–46.] *Caption from original*



Retropharyngeal infection in two different patients. First patient is an infant with acute pharyngitis and tonsillitis. Axial image of contrast-enhanced CT at the level of the tonsils (a) demonstrates enlarged enhancing retropharyngeal lymph nodes with

associated inflammatory phlegmon displacing the right tonsil anteriorly; in the same patient, an axial image at the level of the nasopharynx demonstrates a right-sided suppurated retropharyngeal lymph node (b). Second patient is a 1-year-old girl with complicated ear infection, and axial (c) and sagittal reformat (d) images from contrast-enhanced neck CT demonstrate a large retropharyngeal fluid density rim-enhancing collection consistent with an abscess, which involves the posterior triangle of the neck. An US study before (e) and after (f) surgical drainage of the abscess demonstrated a more complex appearance of the abscess content with thick pus as opposed to the relative simple fluid-like appearance on the CT; the US allows follow-up after drainage and demonstrates collapse of the abscess cavity. [Shiran SI. Imaging of pediatric neck and airway. In: Kountakis SE, editor. Encyclopedia of otolaryngology, head and neck surgery [Internet]. Berlin, Heidelberg: Springer; 2013 [cited 2015 Aug 24]. p. 1277–307. Available from: http://link.springer.com/10.1007/978-3-642-23499-6_414] *Caption from original*

Special Populations

Age

- Retropharyngeal abscess is more common in children, especially those between the ages of 2 and 4 years.
- The child appears ill, sometimes toxic, and febrile.
- Associated signs and symptoms include dysphagia, drooling, neck stiffness, torticollis, change in vocal tone, and trismus.
- In the young child or infant, CT scanning may be necessary to define the extent of the problem.

Co-morbidities

- There are no specific co-morbidities associated with retropharyngeal abscess.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step.
- Ensuring that the patient has a secure airway, especially if undergoing diagnostic testing, is critically important.

Mimics

- Retropharyngeal abscess can mimic and be mimicked by all the other cervical deep space infections, pharyngitis and pharyngeal cellulitis, epiglottitis, and the other diagnoses in the differential.

Time-Dependent Interventions

- Retropharyngeal abscesses may progress rapidly. Appropriate resuscitation, cultures, antibiotic treatment, and confirmatory imaging should proceed as quickly as possibly once the diagnosis is considered.

Overall Principles of Treatment

- When the diagnosis of retropharyngeal abscess is seriously considered, patients should undergo rapid resuscitation and receive antibiotic therapy even before confirmatory imaging.
- It is critical to ensure that the patient has a secure airway, especially when going "off unit" for any diagnostic testing.
- Broad-spectrum antibiotic coverage should be initiated to cover the usual oropharyngeal pathogens, including anaerobes.
- Urgent otolaryngologic consultation should be obtained.
- Definitive care often is guided by imaging. If the patient presents early in the course and there is no discrete collection, antibiotic therapy without surgery may arrest further abscess development and be curative. If collection is present, definitive treatment is operative drainage along with continued antibiotic therapy.

Disease Course

- With early and appropriate treatment, most patients will recover fully with few sequela.
- Delays in presentation and treatment may lead to serious complications, including death. Airway compromise may occur; the abscess may rupture spontaneously, with direct spread to contiguous structures, most ominously the mediastinum and carotid sheath.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Retropharyngeal Abscess"[Mesh] OR "Retropharyngeal Abscess"

Chapter 66
Sarcoidosis

Christopher J. Rees, Richard M. Cantor, Charles V. Pollack, Jr., and Victoria G. Riese

Name and Synonyms

Sarcoidosis; Sarcoid

Incidence/Epidemiology

- Sarcoidosis occurs throughout the world, but its prevalence and racial mix varies from country to country. For example, in the United States sarcoidosis is 3–4 times more common in blacks than whites, but in Ireland and Northern Europe (especially the Nordic countries), it is more prevalent among whites.
- The estimated worldwide prevalence of sarcoidosis is 20–60 cases per 100,000 people per year.
- The disease is usually diagnosed in young, otherwise healthy adults between the ages of 20 and 40, but there is also a second peak at about age 60. There is a slight female predominance. It is rare in children.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_66

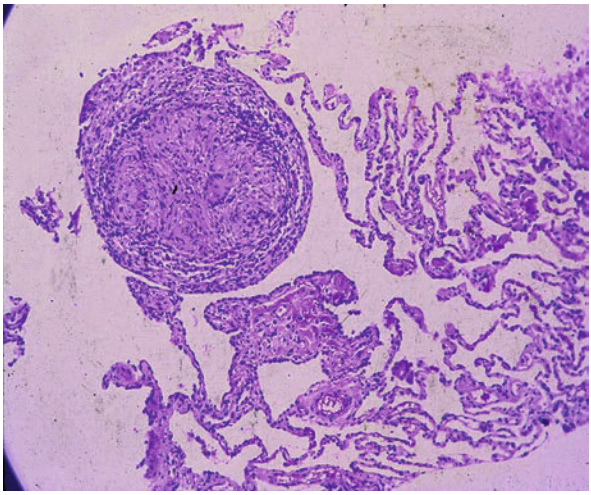
- In the United Stavtes, the lifetime risk among the black population is about 2.5 %. The lifetime risk in the white population is only about 0.85 %.
- Blacks are more likely to present younger and with more acute and severe disease.
- In Ireland, and among African Americans in the United States, there can be a familial predisposition to the disease. This is thought to be due to linkage to the major histocompability complex (MHC). Increased susceptibility to the disease is noted in the presence of certain human leukocyte antigen (HLA) alleles (DRB1, 11, 12, 14, 15, and 17).

Differential Diagnosis

- The differential diagnosis of sarcoidosis is broad, and includes all the diseases that can cause shortness of breath and cough, such as asthma, COPD, interstitial lung disease, pneumonia, and congestive heart failure.
- Sarcoidosis can also present with hilar adenopathy on chest x-ray, so the differential must also include all the diseases associated with mediastinal and hilar adenopathy. This includes tuberculosis (both tuberculosis and atypical mycobacterial infections), fungal infections (such as histoplasmosis, blastomycosis, and Pneumocystis), and cancer (especially lymphoma).
- Other granulomatous diseases of the lungs that need to be considered include: hypersensitivitiy pneumonitis, pneumoconioses (beryllium), drug-induced hypersensitivity (causative agents include methotrexate, etanercept, infliximab, adalimumab, amoxicillin, sirolimus, and fluoxetine, among others), Pulmonary Langerhans cell histiocytosis, foreign body granulomatosis, vasculitides (Wegener's, Churg-Strauss, primary lymphomatoid granulomatosis), and primary immunodeficiencies.
- It is important in the evaluation of someone for presumed sarcoidosis that all these diseases be considered.

Pathophysiology and Etiology

- Sarcoidosis is a multi-system, inflammatory, granulomatous disease of unknown cause.
- The characteristic pathologic finding of sarcoidosis is the presence of noncaseating granulomas in affected tissues. The granulomas contain a mixture of multiple different inflammatory cells, epithelial cells, multi-nucleated giant cells, and fibroblasts. The majority of these granulomas gradually resolve without scarring or fibrosis. Large amounts of scarring, fibrosis, or necrosis should make one consider an alternative diagnosis.



Sarcoidosis: a non-caseating granuloma. [Mahmoudi M, Sharma OP. Sarcoidosis. In: Mahmoudi M, editor. Challenging Cases in Pulmonology [Internet]. New York, NY: Springer New York; 2012 [cited 2015 Jun 9]. p. 253–74. Available from: http://link.springer.com/10.1007/978-1-4419-7098-5_15] *Caption from original*

- Sarcoidosis is thought to result from an exaggerated cell-mediated immune response to an as yet unidentified antigen.
- The etiology remains unknown, despite extensive investigations. An NIH-funded case-control study, Access, that included 700 patients with known sarcoidosis, and nearly 30,000 relatives, could not identify a single etiologic agent.
- Population studies have identified two possible associations: exposure to beryllium and beryllium salts, which can produce granulomas very similar to sarcoidosis. There has also been an increased incidence of sarcoid-like granulomatous disease in people exposed to the dust from the collapse of the World Trade Centers.

Presentation

Typical/"Classic"

- The most common presenting symptoms of sarcoidosis are cough, dyspnea, and chest pain. They are often associated with more constitutional symptoms such as fatigue, fever, and weight loss.
- Nearly one-third of patients are asymptomatic on presentation, and only present with an abnormal CXR.
- Sarcoidosis can affect virtually all organs of the body, but the lung, impacted in over 95 % of cases, is the most frequently affected. The next most fre-

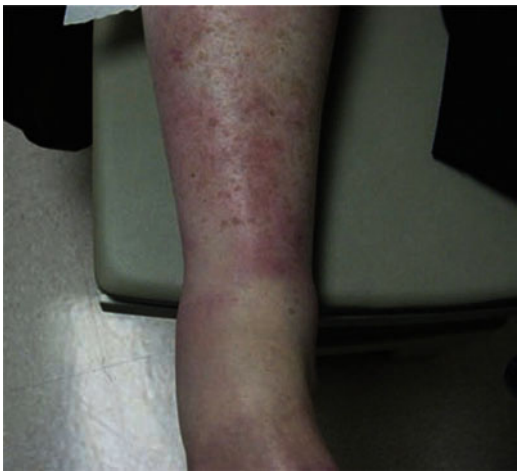
quently involved organ is the skin, which is affected in about 25 % of cases at presentation, but will be involved in nearly one-third of all cases throughout the course of the disease.
- Ninety-five percent of patients eventually diagnosed with sarcoidosis will have pulmonary involvement at presentation. This may manifest as pulmonary symptoms or chest x-ray findings.
- The classic CXR findings of sarcoidosis are hilar adenopathy with associated reticular opacities.
- Patient will often also note eye problems (uveitis) and skin and/or joint lesions on presentation.

Atypical

- Thirty percent of patients will present with predominantly extra-thoracic manifestations of sarcoidosis.
- Löfgren Syndrome is an uncommon, acute, systemic presentation of sarcoidosis. Patients will have fever, erythema nodosum, polyarthralgia, uveitis, and bilateral hilar adenopathy on the CXR.
- Sarcoidosis can affect virtually any organ system in the body. Most of the pathologic and clinical manifestations are due to granulomatous infiltration of the relevant tissues. Some of the more common extra-pulmonary manifestations of sarcoidosis are reviewed below.
    - Skin. Overall, about one-third of patients will develop skin involvement. There are many different skin lesions associated with sarcoidosis, including:
        - Erythema nodosum

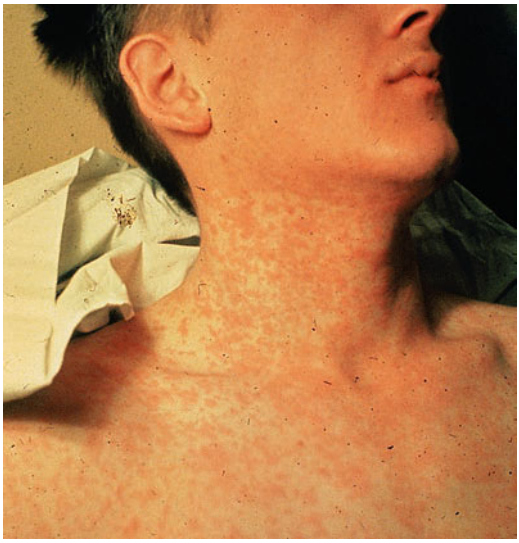
Erythema nodosum. Red nodules of erythema nodosum in the pretibial area. Lesions are usually tender, poorly circumscribed, and located deep within the subcutaneous

fat. Their appearance is usually accompanied by an exacerbation in the underlying inflammatory bowel disease. Erythema nodosum occurs in about 4% of patients with ulcerative colitis and in 2% of patients with Crohn's disease. Treatment includes bed rest, systemic or intralesional steroids, nonsteroidal anti-inflammatory agents, potassium iodide, colchicine, and dapsone. [Pandya A. Chapter 12. In Feldman, M, editor. Gastroenterology and Hepatology, Volume 03. Philadelphia: Current Medicine; 1996. ISBN: 0-443-07843-2] *Caption from original*



Erythema nodosum on the leg of a sarcoidosis patient [Baughman RP, Lower EE. Sarcoidosis. In: Stone JH, editor. A Clinician's Pearls and Myths in Rheumatology [Internet]. London: Springer London; 2009 [cited 2015 Jun 17]. p. 409–20. Available from: http://link.springer.com/10.1007/978-1-84800-934-9_42] *Caption from original*

- Maculopapular lesions. These are the most common form of skin involvement, and the most common form of chronic disease. They are often asymptomatic and overlooked by patients.



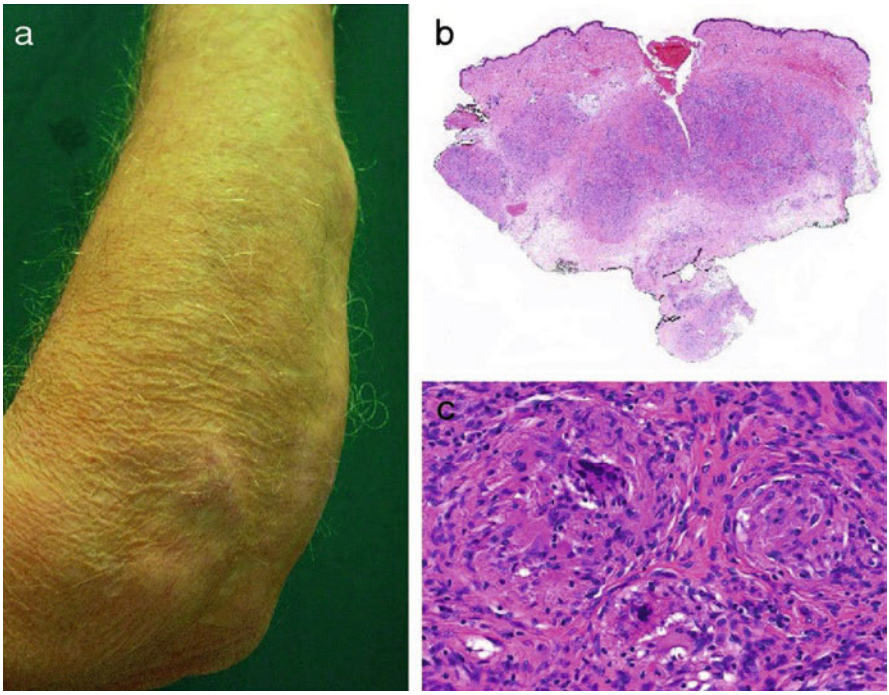
Rash of acquired rubella. The rash of acquired rubella is usually maculopapular, which may eventually coalesce. The rash is usually mild. [Maldonado Y. Chapter 01. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption from original*

- Hyper and hypo-pigmentation.

Sarcoidosis on the arm of an African American female demonstrating hypopigmentation. [Goldman S, Pandya AG. Post-inflammatory Hypopigmentation. In: Jackson-Richards D, Pandya AG, editors. Dermatology Atlas for Skin of Color [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2015 Jun 17]. p. 9–12.

Available from: http://link.springer.com/10.1007/978-3-642-54446-0_2] *Caption adapted from original*

- Keloid formation.
- Subcutaneous nodules (these are actual granulomas).



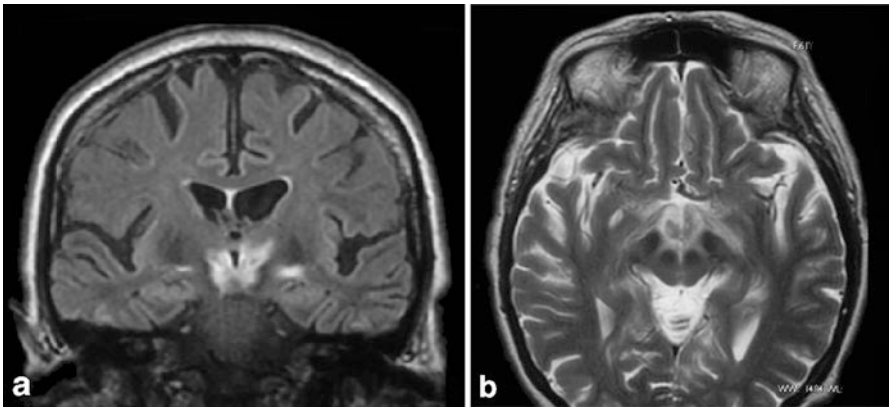
Subcutaneous nodules covered by normal-looking skin on the right forearm (a). Histology confirmed the presence of subcutaneous nodular infiltrates (×4, haematoxylin and eosin) (b), showing the typical features of sarcoid granuloma (×200, haematoxylin and eosin) (c). [Dalle Vedove C, Colato C, Girolomoni G. Subcutaneous sarcoidosis: report of two cases and review of the literature. Clinical Rheumatology. 2011 Aug;30(8):1123–8.] *Caption adapted from original*

- Lupus pernio is a specific complex of skin findings that involves the bridge of the nose, the area beneath the eyes, and the cheeks. This is more common in African Americans and it predicts a progression to chronic disease.

Lupus pernio in an African American female, left face [Jackson-Richards D. Sarcoidosis. In: Jackson-Richards D, Pandya AG, editors. Dermatology Atlas for Skin of Color [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2014 [cited 2016 Mar 24]. p. 141–5. Available from: http://link.springer.com/10.1007/978-3-642-54446-0_26] *Caption from original*

- Eyes. Anterior uveitis is the most common ophthalmologic manifestation of sarcoidosis. Patients can note tearing, pain, and sometimes changes in visual acuity. In the U.S., only about 10–20 % of sarcoid patients will have eye involvement, but it is more common in African Americans. In Japan, greater than 70% may have eye involvement.

- Liver. Liver involvement can be found in about 50% of patients, but only 10–15 % have elevated liver function tests and clinically significant liver disease.
- Bone Marrow. Bone marrow involvement is often noted by the presence of lymphopenia and anemia. There is infiltration of the bone marrow with granulomas and also sequestration of blood cells in lymphoid tissue (splenomegaly).
- Renal. Seen in less than 5 % of patients. Direct granulomatous infiltration may cause nephritis. Most of the renal complications are secondary to hypercalcemia and hypercalciuria.
- Neurologic. Seen in about 5–10 % of patients. Sarcoidosis can affect any part of the central or peripheral nervous system. Neurosarcoid can cause cranial nerve abnormalities, seizures, and cognitive changes. Involvement of the optic nerve can cause an optic neuritis that is difficult to distinguish from multiple sclerosis.



Presumed intracranial sarcoidosis. a The coronal FLAIR and b axial T2-weighted MRI scan show a hyperintense lesion involving the optic chiasm and hypothalamus with posterior extension along both optic tracts which appear hyperintense. [Jäger HR. Loss of vision: imaging the visual pathways. European Radiology. 2005 Mar;15(3):501–10.] *Caption from original*

- Cardiac. Cardiac manifestations are seen in about 2–5 % of patients in the U.S. and Europe, but in up to 25 % of patients in Japan. The most common cardiac manifestations are cardiomyopathy and CHF from diffuse myocardial infiltration, and conduction system abnormalities due to granulomatous infiltration of conduction tissue.
- Bone/joint/muscle. The patient can present with bone cysts that cause myalgias and arthralgias.

Primary Differential Considerations

- When patients present with signs and symptoms such as those that suggest pulmonary sarcoidosis, other diagnoses warranting early consideration include:
  - infection, especially with fungi and tuberculosis.
  - reactions to minerals and metals such as beryllium and aluminum.
  - Wegener granulomatosis.

History and Physical Exam

Findings That Confirm Diagnosis

- There are no pathognomonic historical or physical findings of sarcoidosis.
- Lung exam is often normal. Wheezing is present only when there is endobronchial involvement that causes airway obstruction.
- The diagnosis is confirmed only when typical noncaseating granulomas are found on biopsy of an involved organ in the presence of the usual clinical and radiographic findings and the exclusion of other causes. It is important to remember that there are causes of noncaseating granulomas other than sarcoidosis.
- The identification of classic Löfgren's Syndrome can usually confirm the diagnosis without a need for biopsy.

Factors That Suggest Diagnosis

- The diagnosis can be suggested by the presence of typical symptoms and bilateral hilar adenopathy on the CXR.
- Typical CXR findings can be found in asymptomatic patients who are having a CXR for other reasons.

Factors That Exclude Diagnosis

- The confirmation of an alternative diagnosis that can explain the patient's symptoms and findings can essentially exclude the diagnosis.

Ancillary Studies

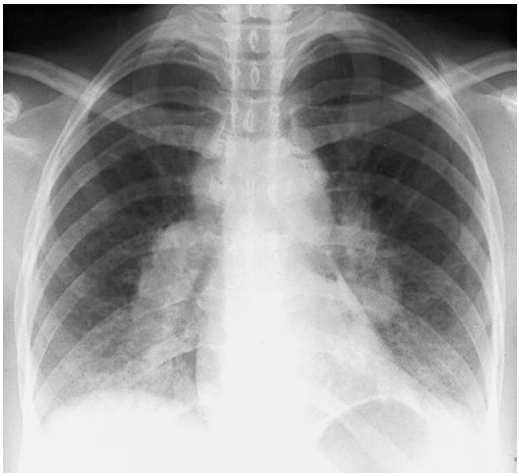
Laboratory

- All patients being evaluated for sarcoidosis should have a complete laboratory evaluation that includes a CBC with differential, complete metabolic panel, liver function tests, and a urinalysis. These may not be helpful in diagnosing sarcoidosis, but may lead to a consideration of an alternative diagnosis.
- Testing for HIV should be considered.
- Patients should also have testing for tuberculosis with either a TB skin test, or an interferon gamma release assay.
- Angiotensin converting enzyme (ACE) levels are elevated in about three-quarters of patients with acute, untreated sarcoidosis, but this test is neither sensitive nor specific for the diagnosis of sarcoidosis, with about a 10 % false positive rate. Many diseases can cause a small elevation (about 10% above upper limit of normal) in the ACE level (such as diabetes), while fewer disease are associated with an ACE level that is greater than 1.5 times the upper limit of normal. These include: sarcoidosis, leprosy, Gaucher's disease, hyperthyroidism, miliary tuberculosis.
- Common laboratory abnormalities found in patients with sarcoidosis include:
  - Anemia, usually secondary to anemia of chronic disease (AOCD).
  - Leukopenia, seen in 5–10 % of patients.
  - Hypercalcemia/hypercalciuria are seen in about 10% of patients, and are more common in Caucasians. Sarcoid granulomas can produce 1,25-dihydroxyvitamin D, which leads to increased intestinal absorption of calcium with resultant hypercalcemia and hypercalciuria.
  - While sarcoid granulomas can produce 1,25-dihydroxyvitamin D, nearly all patients with sarcoidosis will have a deficiency of 25-hydroxyvitamin D. The pathologic basis of this has not been elucidated.
  - Elevated alkaline phosphatase (suggests liver involvement).

Imaging

- Imaging is necessary in the evaluation and diagnosis of sarcoidosis.
- The classic finding on plain chest x-ray is bilateral hilar adenopathy. The lung parenchyma may be normal (especially in early disease), or may show diffuse reticular or ground glass opacities.
- The chest x-ray findings have been classified into stages. These stages are only a reflection of the anatomic extent of pulmonary disease, and may not correspond to symptoms and disease activity. They may, however, offer some prognostic information.

- Stage I. Bilateral hilar adenopathy (with or without right paratracheal lymph node enlargement) with no parenchymal changes in the lung. Up to half of all patients will have this as their initial finding of sarcoidosis. Up to 75 % of patients with Stage 1 disease on presentation will have spontaneous regression of adenopathy within 1–3 years. Fewer than 10% will develop chronic enlargement.



Chest radiograph of a patient with stage I sarcoidosis. [Tanoue L, Elias J. Sarcoidosis. In: Crapo J, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7; 2005-01-14] *Caption adapted from original*

- Stage II. Bilateral hilar adenopathy with associated parenchymal changes, usually reticular opacities (upper lobes predominantly). These changes are found in about 25 % of patients at diagnosis. About two-thirds of patients with stage II findings on CXR at diagnosis will have spontaneous regression, and one-third will go on to have chronic changes. Patients with stage II disease at diagnosis are generally symptomatic.

Stage II sarcoidosis. [Tanoue L, Elias J. Sarcoidosis. In: Crapo J, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7; 2005-01-14] *Caption adapted from original*

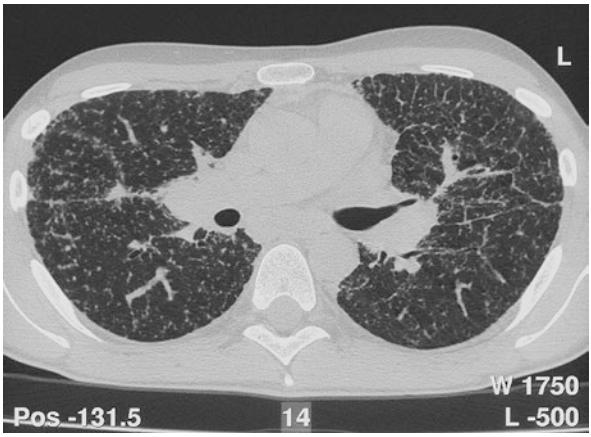
- Stage III. Marked reticular opacities (again upper lungs >> lower lungs) with regression of hilar nodes.

Stage III sarcoidosis. [Tanoue L, Elias J. Sarcoidosis. In: Crapo J, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7; 2005-01-4] *Caption adapted from original*

- Stage IV. Reticular opacities with evidence of volume loss (upper lungs). Consolidated masses of granulomas causing traction bronchiectasis may be seen. Lung tissue calcification, cavitation, and cyst formation may be seen.

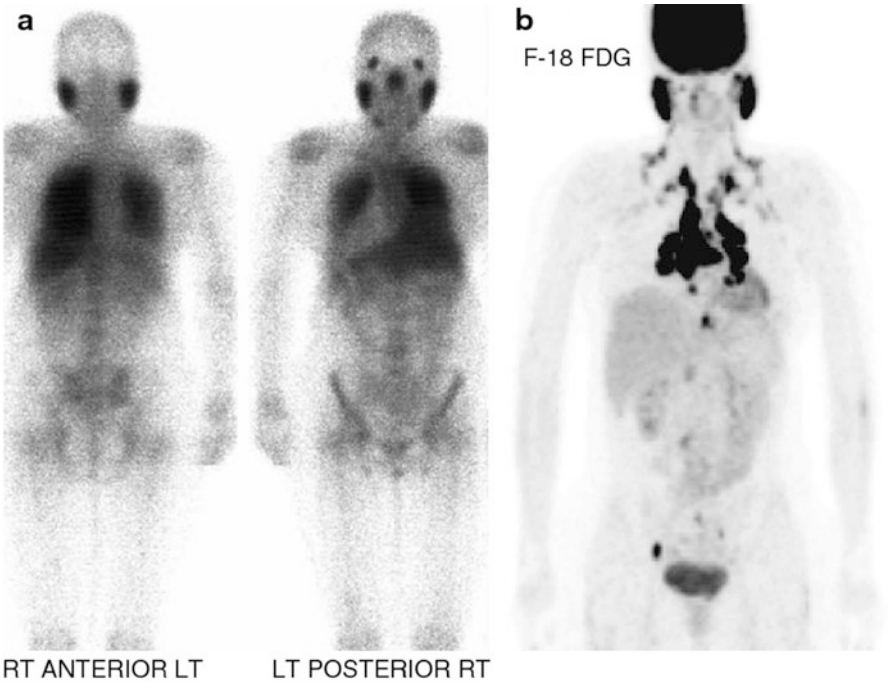
Stage IV sarcoidosis. With extensive fibrosis. [Tanoue L, Elias J. Sarcoidosis. In: Crapo J, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-211-7; 2005-01-4] *Caption adapted from original*

- Other radiologic studies (such as high resolution CT scan [HRCT], PET scanning, gallium scanning), are not necessary in the evaluation of suspected sarcoidosis, but may be obtained for other reasons. They may be helpful in evaluating for alternative diagnoses, and for further supporting the diagnosis of sarcoidosis.
  - HRCT may be performed for the evaluation of dyspnea and cough in a patient with an unremarkable CXR. Many patients will have a HRCT, as it is standard of care in the evaluation of suspected interstitial lung disease. Findings on HRCT in that situation may lead to earlier consideration of the diagnosis. Findings on HRCT that are highly suggestive of sarcoidosis include:
    - Hilar and mediastinal adenopathy
    - Beading or intermittent thickening of the bronchovascular bundles



HRCT with the classical perilymphatic distribution of nodules in a patient with sarcoidosis. Note the occurrence of small nodules along subpleural surface and fissures, along interlobular septa and the peribronchovascular bundles giving these structures a "beaded" appearance. This is thought to be pathognomic for sarcoidosis. [Veltkamp M, Grutters JC. The Pulmonary Manifestations of Sarcoidosis. In: Judson MA, editor. Pulmonary Sarcoidosis [Internet]. New York, NY: Springer New York; 2014 [cited 2015 Jun 17]. p. 19–39. Available from: http://link.springer.com/10.1007/978-1-4614-8927-6_2] *Caption from original*

- The use of gallium scanning for the diagnosis of sarcoidosis is currently of only historic interest, as the sensitivity and specificity are low. Gallium scanning may be useful in the unlikely event that there are no easily amenable areas for biopsy. The presence of a panda sign (increased uptake in the parotid and lacrimal glands), and/or a lambda sign (increased activity in the right paratracheal and left hilar lymph nodes), is considered very suggestive of sarcoidosis.



(a) Gallium-67 images for a patient with sarcoidosis illustrating diffuse lung uptake in addition to uptake in salivary glands, lacrimal glands, and inguinal lymph nodes. (b) 18 F-FDG image of a 35-year-old female with proven sarcoidosis. The study shows uptake in the areas of active inflammation in mediastinum, pulmonary hilus, salivary glands, cervical, supraclavicular, axillary, para-aortic, iliac, and inguinal lymph nodes. [Elgazzar AH. Respiratory System. Synopsis of Pathophysiology in Nuclear Medicine [Internet]. Cham: Springer International Publishing; 2014 [cited 2015 Aug 26]. p. 253–72. Available from: http://link.springer.com/10.1007/978-3-319-03458-4_11] *Caption from original*

- Cardiac MRI may be useful in the diagnosis of cardiac sarcoid.

Other

- All patients should have an ECG to screen for conduction abnormalities
- Pulmonary Function Testing. PFT's are not helpful in the diagnosis of sarcoidosis, but they are used to assess the severity of respiratory disease and to monitor the course of the disease. Most patients with early (stage I or II) disease will have normal PFT's. As symptoms worsen patients will usually demonstrate a restrictive pattern on PFT's with a reduced diffusing capacity for

carbon monoxide. If the patient has significant and lumen-narrowing endobronchial lesions, an obstructive pattern may be present on PFT's.

- Biopsies. The majority of patients with suspected sarcoidosis will need to have a biopsy to confirm the diagnosis. In general, biopsies should be obtained from the most accessible of the sites that are affected. This can include skin lesions (except for erythema nodosum), conjunctival lesions, and palpable lymph nodes, among others.
  - Patients who may not need a biopsy include asymptomatic patients with stage I disease on CXR, as the majority of these patients will have spontaneous resolution without progression, and those with classic Löfgren's syndrome.
- Fiber optic bronchoscopy (FOB). Flexible, fiber optic bronchoscopy can be a useful, minimally invasive procedure for the diagnosis of sarcoidosis. During FOB, Bronchoalveolar lavage (BAL), endobronchial biopsy, or transbronchial biopsy can be performed.
  - BAL via flexible bronchoscopy can be a useful and minimally invasive method to help diagnose sarcoidosis. BAL fluid can be evaluated for numbers of CD 4 and 8 cells. Sarcoid is usually associated with a reduced number of CD8 cells, with a ratio of CD4 to CD8 cells greater than 3.5–4:1. BAL is also useful to help exclude malignancy or infections as alternative diagnoses.
  - Endobronchial and transbronchial biopsies have a high yield for the diagnosis of sarcoidosis.

Special Populations

Age

- Sarcoidosis is unusual in children.
- It is, however, well described in patients less than 4 years of age, who most often present with skin, joint, and eye involvement without "typical" pulmonary disease.
- U.S. demographics indicate that southeastern and south central states contain more than 65% of reported cases (Virginia, North and South Carolina, and Arkansas)
- Sarcoidosis is most commonly diagnosed in young to middle-aged adults.

Co-morbidities

- The presence of HIV can make the diagnosis more challenging, as these patients may present atypically, and they are at risk for atypical presentations of many of the alternative diagnoses that need to be considered.
- All the diseases that can present with dyspnea and cough (such as asthma, COPD, CHF, other interstitial lung diseases) can make the diagnosis and management of sarcoidosis more challenging if they exist concurrently.
- However, many of the patients diagnosed with sarcoidosis are young adults and have few if any co-morbid conditions.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step.
- Consideration of all alternative diagnoses.
- Recognizing that a gold-standard diagnostic test does not exist, and that the diagnosis generally requires three elements: 1) consistent clinical and radiographic abnormalities; 2) detection of noncaseating granulomas on biopsy; and 3) the exclusion of alternative diagnoses.

Mimics

- As per the differential diagnosis section, many diseases can present with either symptoms consistent with sarcoid (dyspnea, cough, fever, fatigue), granulomas, or hilar adenopathy.

Time-Dependent Interventions

- Sarcoidosis is generally not an acute disease. Löfgren's syndrome (fever, erythema nodosum, arthralgias, and bilateral hilar adenopathy) may present acutely, but often will resolve spontaneously with no specific treatment.
- Symptoms that may indicate involvement of some extra-pulmonary organ systems, especially cardiac, central nervous system, or renal involvement, may require urgent diagnosis and treatment.

Overall Principles of Treatment

- When the diagnosis of sarcoidosis is considered likely, a thorough search should be undertaken to find the presence and extent of involvement of other organ systems.
- All patients should have a complete history that includes an occupational and hobby history.
- All patients should have a thorough skin examination.
- All patients should have an ophthalmologic examination to assess for ocular involvement.
- All patients should have an ECG to screen for conduction abnormalities.
- Laboratory testing as detailed above should be performed.
- Treatment is based upon symptoms. If the patient is asymptomatic and only has CXR findings, it is appropriate to just monitor for the development of symptoms.
- It also is appropriate to monitor patients with only mild symptoms, as about 50 % of cases will resolve spontaneously within 2–5 years.
- If there is mild-to-moderate skin or ocular involvement, it is reasonable to attempt a trial of topical treatment with topical steroids. This treatment should be guided and monitored by an experienced dermatologist/ophthalmologist.
- Systemic glucocorticoids (prednisone, methylprednisolone) are the treatment of choice if systemic treatment is warranted.
- Patients on long-term glucocorticoids, or with intolerable side effects from glucocorticoids, may be candidates for steroid-sparing therapy.
    - Hydroxychloroquine and minocycline may be useful for patients with predominant skin involvement.
    - Cytotoxic therapy may be necessary for patients with significant extrapulmonary sarcoidosis. Methotrexate is the cytotoxic agent with the most clinical experience. It is effective in managing symptoms in up to 65–70 % of those with extrapulmonary sarcoidosis. Other agents include, azathioprine, chlorambucil, and cyclophosphamide.
    - Infliximab, a monoclonal antibody against tumor necrosis factor, has recently been shown to improve lung function in those with chronic sarcoidosis already on glucocorticoids and cytotoxic agents. This agent is a potent immune suppressor, and has been associated with an increased risk for infections, especially reactivation tuberculosis.

Disease Course

- Fifty percent of cases will resolve within 2–5 years.
- About 20 % will go on to develop chronic sarcoidosis.

- The disease is generally non-life-threatening, but organ-threatening disease can occur, especially when there is ocular, cardiac, neurologic, and renal disease.
- Death due to sarcoidosis occurs in less than 5 % of cases, and mostly occurs due to progressive lung, cardiac, neurologic, or renal disease.
- The following factors have been found to be markers for progressive disease:
    - Fibrosis on CXR
    - Lupus pernio
    - Bone cysts
    - Cardiac or neurologic disease
    - Renal calculi due to hypercalciuria
    - Disease requiring systemic glucocorticoid treatment within the first six months of diagnosis

Related Evidence

Papers of particular interest have been highlighted as:
** Of key importance

Review

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Müller-Quernheim J, Prasse A, Zissel G. Pathogenesis of sarcoidosis. Presse Med. 2012 Jun;41(6 Pt 2):e275-87. https://doi.org/10.1016/j.lpm.2012.03.018. PMID: 22595775. http://www.ncbi.nlm.nih.gov/pubmed/22595775 **

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Sarcoidosis"[Mesh] OR "Sarcoidosis"

Chapter 67
Sepsis

Charles V. Pollack, Jr., Melissa Platt, Richard M. Cantor, and Jaime Friel Blanck

Name and Synonyms

Sepsis; Severe Sepsis; Septic Shock; Systemic Inflammatory Response Syndrome (SIRS)

Incidence/Epidemiology

- Tenth leading cause of death in the United States.
- 750,000 patients will be hospitalized annually for sepsis in the United States.
  - Males have a higher incidence of sepsis than females.
- Two percent of all hospitalized patients in developed countries suffer from sepsis.
- More than 50 % of severe sepsis patients will require intensive care.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_67

- Mortality rate of septic shock is nearly 50 %.
- In developing countries sepsis is more common in younger people.
  - Gram negative and atypical pathogens are usually the cause (e.g., malaria)
- Improvement in treatments has decreased the fatality rate, but due to the increase of incidence the number of deaths has increased.
- Most cases of septic shock are hospital-acquired Gram-negative bacilli or Gram-positive cocci.
  - Immunocompromised and chronic illness are risk factors for sepsis.
- Candida or other fungi are rare causes of sepsis.

Differential Diagnosis

- Trauma
- Pancreatitis
- Adrenal insufficiency
- Toxic Shock Syndrome
- Cardiogenic shock
- Hemorrhage
- DIC-Disseminated Intravascular Coagulation
- Heatstroke
- MI
- Myocardial rupture
- Shock

Pathophysiology and Etiology

- Sepsis is a complex, multimediated state that is generally considered to be inflammatory in response to infection. Mediators of inflammation generally cause peripheral vasodilation which, if not reversed, causes blood pressure to drop (“septic shock”) and tissues to be hypoperfused.
  - This can be identified by an increase in serum lactate.
  - If severe, this can result in multi-organ system failure.

Mediator	Potential role in intra-abdominal sepsis or injury	Reference(s)
CRP	A serum marker of sepsis that increases in concentration in plasma following abdominal surgery	[20-22]
Haptoglobulin	Elevated expression in blood leukocytes following severe blunt trauma	[23]
IL-1ra	Elevated in plasma following trauma; elevated expression in blood leukocytes following severe blunt trauma	[23,24]
IL-6	Potent inflammatory mediator and marker of sepsis; elevated levels correlate with length of hospital stay, complications, and mortality among patients with intra-abdominal sepsis; elevated levels in peritoneal fluid in a porcine model of intra-abdominal sepsis; elevated plasma/serum levels following abdominal surgery; elevated plasma levels following severe trauma associate with injury severity, development of organ dysfunction, and poor outcomes, including mortality	[21-23,25-28,44-50]
IL-8	Potent neutrophil chemoattractant; elevated expression in blood leukocytes following severe blunt trauma	[23,29]
IL-10	Elevated serum levels during intra-abdominal sepsis; blocks pro-inflammatory cytokine release; elevated after abdominal surgery	[30-32]
IL-15	Elevated levels in serum correlate with organ dysfunction and poor patient prognosis	[33]
IL-17	Potent pro-inflammatory mediator; promotes neutrophil recruitment to the peritoneal cavity and enhanced bacterial clearance in a mouse model of intra-abdominal sepsis; elevated plasma levels in select patients following severe trauma	[28,34,35]
IL-22	Elevated serum levels during intra-abdominal sepsis	[30]
IL-33	Mediates neutrophil recruitment to peritoneum; promotes bacterial clearance and reduces mortality in a mouse model of intra-abdominal sepsis	[36]
MCP-1 (CCL2)	Potent monocyte chemoattractant; serum levels elevated in a rat model of intra-abdominal sepsis; elevated expression in blood leukocytes following severe blunt trauma	[23,37]
M-CSF	Elevated in plasma following trauma	[24]
MIF	Present early in sepsis and remains elevated for a prolonged time period; significantly higher levels in non-survivors of sepsis compared to survivors; MIF neutralization reduces mortality in a mouse model of intra-abdominal sepsis	[38,39]
PDGF	Elevated in plasma following trauma	[24]
Procalcitonin	Marker of infectious complications following abdominal surgery and negatively associated with survival; elevated after abdominal surgery	[32,40]
TNF-α	Serum levels elevated in a rat model of intra-abdominal sepsis	[37]
tPA	Enhances bacterial clearance, reduces cellular influx, increases plasma and peritoneal IL-12 and IL-10 levels, and reduces lung and liver damage in a mouse model of intra-abdominal sepsis	[16]
TRAIL	Promotes inflammatory cell recruitment to the peritoneum, enhances bacterial clearance, and reduces mortality in a mouse model of intra-abdominal sepsis; modulates apoptosis	[41,42]

CCL2, Chemokine (C-C motif) ligand 2; CRP, C-reactive protein; IL-1ra, Interleukin-1 receptor antagonist; IL-6, Interleukin-6; IL-8, Interleukin-8; IL-10, Interleukin-10; IL-15, Interleukin-15; IL-17, Interleukin-17; IL-22, Interleukin-22; IL-33, Interleukin-33; MCP-1, Monocyte chemoattractant protein-1; M-CSF, Macrophage colony-stimulating factor; MIF, Macrophage migration inhibitory factor; PDGF, Platelet-derived growth factor; TNF-α, Tumor necrosis factor-alpha; tPA, Tissue plasminogen activator; TRAIL, Tumor necrosis factor-related apoptosis-inducing ligand.

Inflammatory mediators associated with intra-abdominal sepsis or injury, including abdominal surgery, among studies of animals or humans [From article: Efficacy and safety of active negative pressure peritoneal therapy for reducing the systemic inflammatory response after damage control laparotomy (the Intra-peritoneal Vacuum Trial): study protocol for a randomized controlled trial. Trials. 2013;14(1):141. https://doi.org/10.1186/1745-6215-14-141, at http://link.springer.com/article/10.1186%2F1745-6215-14-141; by Derek J Roberts, Craig N Jenne, Chad G Ball, Corina Tiruta, Caroline Léger, Zhengwen Xiao, Peter D Faris, Paul B McBeth, Christopher J Doig, Christine R Skinner, Stacy G Ruddell, Paul Kubes, Andrew W Kirkpatrick, © Roberts et al.; licensee BioMed Central Ltd. 2013; licensed under Creative Commons Attribution License BY 2.0 http://www.creativecommons.org/licenses/by/2.0] *Caption from original; See http://link.springer.com/10.1186/1745-6215-14-141 for references*

- Sepsis can result from any infectious etiology, bacterial, viral, or fungal. Nonbacterial causes are more common in immunocompromised patients.

Presentation

Typical/"Classic"

- Fever, dyspnea, altered mental status, nausea and vomiting, cough, SOA, abdominal pain, diarrhea and dysuria.
  - **SIRS**-4 criteria, **Sepsis = infection with ≥ 2 SIRS criteria**
    - Temperature > 38°C or < 36°C
    - HR > 90 bpm
    - RR > 20/min or $PaCO_2$ < 32 mm Hg
    - WBC > 12,000/mm^3, or > 10 % band forms

Stage	Clinical symptoms	Value
SIRS (≥2 symptoms)	Temperature	<36 °C or >38 °C
	Heart rate	>90 beats/minute
	Respiratory rate	>20 breaths/minute or $PaCO_2$<32 mmHg
	White blood cell count	>12,000 cells/mm^3 or < than 4,000 cells/mm^3
Sepsis	SIRS with proven infection	
Severe sepsis	Sepsis with organ dysfunction hypoperfusion and/or hypotension	
Septic shock	Severe sepsis, hypoperfusion and/or hypotension despite adequate fluid resuscitation	

Systemic Inflammatory Response Syndrome (SIRS) and sepsis stages [Loonen AJM, Wolffs PFG, Bruggeman CA, van den Brule AJC. Developments for improved diagnosis of bacterial bloodstream infections. European Journal of Clinical Microbiology & Infectious Diseases. 2014 Oct;33(10):1687–702.] *Caption from original*

- **Severe Sepsis** is indicated if the patient presents with an additional sign or symptom, such as those in the following list, that indicates an organ may be failing:
  - Decrease urine output
  - Confusion
  - Difficulty breathing
  - Decreased platelet count
- **Septic Shock:** The patient must present signs and symptoms of severe shock and decreased blood pressure that is not responding to fluid replacement treatments.

Atypical

- Older patients, immunocompromised patients, and patients on beta blockers may present without overt signs of shock. Younger patients with normal physiologic reserve may maintain normal vital signs and mentation for a relatively long period of time before suddenly manifesting shock.

Primary Differential Considerations

- Consider the following alternative diagnoses:
  - ARDS
  - Cardiogenic shock
  - DKA
  - Myocardial rupture
  - Toxic shock syndrome

History and Physical Exam

- **History and risk factors:**
  - Immunosuppressive states
  - Underlying terminal illnesses
  - Recent chemotherapy
  - Malignancy
  - Splenectomy
  - HIV
  - Diabetes
  - Nursing home
  - Source of infections: abdominal exam, rectal exam, chest exam, any rashes, decubitus ulcers, indwelling catheters, CNS infections.

Findings That Confirm Diagnosis

- Dyspnea
- Fever
- Nausea/vomiting
- Blood Pressure <90 mmHg, mean arterial pressure <70 mmHg, decrease in SBP>40 mmHg.
- Poor organ perfusion with early sign of flushed skin or later signs with cool skin due to redirection of blood flow to organs.
- Tachycardia >90 bpm
- Confusion/depressed consciousness-may be caused by encephalopathy
- Components of the "SIRS" (Systemic Inflammatory Response Syndrome) score are helpful in establishing the diagnosis of sepsis. A calculator and guidance for interpreting a SIRS score can be found at http://www.mdcalc.com/sirs-sepsis-and-septic-shock-criteria/.

Factors That Suggest Diagnosis

- Hyperthermia/hypothermia
- Tachypnea
- Tachycardia
- Prolonged capillary refill time

Factors That Exclude Diagnosis

- Negative blood cultures

Ancillary Studies

Laboratory

- CBC
- Lactate: Elevated lactate can be a manifestation of organ hypoperfusion.
- Blood cultures prior to antibiotics
- Platelet count
- Hematocrit
- Electrolytes
- BUN
- Creatinine
- Bilirubin
- Ca, Mg, pH
- C-reactive protein
- Cortisol level
- INR/prothrombin time/partial thromboplastin time
- LFT's
- Urine analysis and culture
- Pro calcitonin

Screening tests	Prothrombin time
	APTT
	Platelets
	Fibrinogen INR
Confirmatory tests	Soluble fibrin monomer complex
	Fibrinogen degradation products
	D-dimer
	Prothrombin fragments 1 and 2
	Antithrombin III

Screening and coagulopathy tests in the diagnosis of consumption coagulopathy (DIC) [Gullo A, Celestre CM, Paratore AL, Silvestri L, van Saene HK. Sepsis and Organ(s) Dysfunction. In: Gullo A, editor. Anaesthesia, Pharmacology, Intensive Care and Emergency APICE [Internet]. Milano: Springer Milan; 2014 [cited 2015 Aug 31]. p. 157–91. Available from: http://link.springer.com/10.1007/978-88-470-5516-2_14] *Caption from original*

Imaging

- Chest X-ray
- Soft tissue plain films
- Imaging to locate source of infections
  - CT of abdomen and pelvis
  - Ultrasound for gallbladder, etc.

Other

- Lumbar puncture
- Central Venous pressure measurement
- $Sv0_2$ measurement

Special Populations

Age

Pediatric

- Reports of pediatric sepsis are increasing nationwide, accounting for nearly 8 percent of patients treated in Pediatric ICUs.
- Primary sources of sepsis are primary bacteremia and respiratory infection.
- Organisms to consider are:
  - Staphylococcus aureus, including MRSA
  - S pneumonia
  - S pyogenes
  - Group B streptococcus in neonates
  - Coagulase negative Staphylococcus in children with indwelling catheters
- Viral infections may mimic bacterial sepsis, particularly respiratory pathogens.
- It is not unusual to have co-infections with viral etiologies and bacterial superinfection.
- Hallmarks of treatment remain early recognition, culture acquisition, volume replacement, and the administration of broad spectrum antibiotics.
- When treating children for sepsis, check labs frequently, as it is important to avoid hyponatremia and hypoglycemia.
- Dexamethasone should be given early for streptococcal bacterial meningitis.

Neonate

- Septic shock often manifests with:
  - Hypoglycemia
  - Seizures
  - Disseminated intravascular coagulation (DIC)
  - Cardiovascular collapse and death if untreated

Antibiotic class	Oral bioavailability	Protein binding	CNS penetration	Metabolism	Excretion	$t_{½}$
Aminoglycosides						
Gentamicin	Poorly absorbed	<25 %	Extracellular fluids and vascularized tissues; poor CSF penetration	None	Renal	<1 week PGA: 5–14 h; ≥1 week PGA: 3–5 h[a]
Aminopenicillins						
Ampicillin	50 %	10 %	Penetrates most tissues; poor CSF penetration	Hepatic (10 %)	Renal (25–40 %)	2–7 days PNA: 4 h; 8–14 days PNA: 2.8 h; 15–30 days PNA: 1–1.8 h
Cephalosporins						
Cefotaxime	Not administered orally	30–50 %	Penetrates most tissues; adequate CSF penetration when meninges are inflamed	Hepatic	Renal (60 %)	BW ≤1.5 kg: 4.6 h BW >1.5 kg: 3.4 h
Glycopeptides						
Vancomycin	Poorly absorbed	30 %	Penetrates most tissues; erratic CSF penetration	None	Renal; minimal biliary	4–11 h (dependent upon renal maturation)

Comparative pharmacokinetic data are derived from DiCenzo et al., Yoshioka et al., Rodvold et al. [132–134]

[a] For neonates <1 week PGA, the $t_{½}$ of aminoglycoside agents is inversely associated with BW

BW birthweight, *CNS* central nervous system, *CSF* cerebrospinal fluid, *PGA* post-gestational age, *PNA* postnatal age, $t_{½}$ elimination half-life

Comparative pharmacokinetics, bioavailability, protein binding, central nervous system penetration, metabolism, and excretion of antibiotics used in the empiric treatment of neonatal sepsis [Stockmann C, Spigarelli MG, Campbell SC, Constance JE, Courter JD, Thorell EA, Olson J, Sherwin CMT. Considerations in the Pharmacologic Treatment and Prevention of Neonatal Sepsis. Pediatric Drugs. 2014 Feb;16(1):67–81.] *Caption from original*; *See http://link.springer.com/10.1007/s40272-013-0057-x for references*

Antifungal class	Oral bioavailability	Protein binding	CNS penetration	Metabolism	Excretion	$t_{½}$
Polyenes						
Amphotericin B	Poorly absorbed[a]	90 %[a]	Poor CSF penetration (<5 % of plasma concentration)[a]	Minimal hepatic[a]	Renal[a]	50 h
Liposomal amphotericin B	Poorly absorbed[a]	Unknown	Poor CSF penetration (<1 % of plasma concentration)[a]	Unknown	Unknown	100–153 h[a]
Cytosine analogs						
5-Fluorocytosine	80 %[a]	3–4 %[a]	Good CSF penetration (74 % of plasma concentration)[a]	Minimal hepatic[a]	Renal (90 %); feces (10 %)	3–6 h
Azoles						
Fluconazole	>90 %[a]	11–12 %[a]	Good CSF penetration (75 % of plasma concentration)[a]	Minimal[a]	Renal[a]	Pre-term: 74 h; 1 week PNA: 53 h; 2 weeks PNA: 47 h
Echinocandins						
Caspofungin	Poorly absorbed	97 %[a]	Poor CSF penetration (0 % of plasma concentration)[a]	Hepatic[a]	Renal (42 %); feces (35 %)	40 h
Micafungin	Poorly absorbed	>99 %	Poor CSF penetration (0 % of plasma concentration)[a]	Hepatic	Feces (71 %)	7 h

Comparative pharmacokinetic data are derived from Baley et al., Walsh et al., Smith et al., Wurthwein et al., Piper et al., Wade et al., and Doby et al. [69, 72, 74, 135–138]

CNS central nervous system, *CSF* cerebrospinal fluid, *PNA* postnatal age, $t_{½}$ elimination half-life

[a] Data obtained from adults (applicability to neonates is unclear)

Comparative pharmacokinetics, bioavailability, protein binding, central nervous system penetration, metabolism, and excretion of antifungals used in the empiric treatment of neonatal sepsis [Stockmann C, Spigarelli MG, Campbell SC, Constance JE, Courter JD, Thorell EA, Olson J, Sherwin CMT. Considerations in the Pharmacologic Treatment and Prevention of Neonatal Sepsis. Pediatric Drugs. 2014 Feb;16(1):67–81.] *Caption from original; See http://link.springer.com/10.1007/s40272-013-0057-x for references*

Co-morbidities

- Cancer
- Chronic-obstructive pulmonary Disease
- Immunosuppressed
- Congestive Heart Failure (CHF)
- Diabetes
- HIV/AIDS
- Renal Disease

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Misdiagnosing septic arthritis
- In elderly and nursing home patients, watch for bedsores, UTI's, etc.
- Always consider the risk of sepsis in immunocompromised patients (diabetes, HIV, cancer on chemotherapy, etc.)
- Serum lactate should be done early and blood cultures prior to antibiotics. Placement of central line and broad spectrum of tests to identify source or infection.

Mimics

- Inflammatory colitis
- Hypovolemia
- Medication effects
- Adrenal insufficiency
- Acute myocardial infarction
- Acute pulmonary embolus

Time-Dependent Interventions

- Airway and breathing stabilization are a priority. Utilize supplemental oxygen with pulse oximetry. Intubation may be required.
- Assess perfusion. Utilize aggressive fluid resuscitation for hypotension (excluding patients with heart failure).
- Central line.
- Saline boluses until CVP > 8 cm H_2O
- Initiate pressors—Norepinephrine or dopamine.
- Administer antibiotics early, based on most likely organism.
- Additional therapies (conflicting evidence) include inotropic therapy or red blood cell transfusions

Sepsis resuscitation bundle—(to be started immediately and completed within 6 h)
• Serum lactate measured
• Blood cultures obtained prior to antibiotic administration
• Broad-spectrum antibiotics administered within 3 h for ED admissions and 1 h for non-ED ICU admissions
• In the event of hypotension and/or lactate >4 mmol/L:
– Deliver a minimum of 20 ml/kg of crystalloid (or colloid equivalent)
– Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mmHg
• In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate >4 mmol/L (36 mg/dl):
– Achieve central venous pressure (CVP) of ≥8 mmHg
– Achieve central venous oxygen saturation ($ScvO_2$) of ≥70%[a]
Sepsis management bundle—(to be started immediately and completed within 24 h)
• Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
• Glucose control maintained ≥lower limit of normal, but <150 mg/dl (8.3 mmol/L)
• For mechanically ventilated patients inspiratory plateau pressures maintained <30 cmH_2O

[a]Achieving a mixed venous oxygen saturation of 65% is an acceptable alternative

Sepsis Bundles: The goal is to perform all indicated tasks 100% of the time within the first 6 h (Sepsis Resuscitation Bundle) or first 24 h (Sepsis Management Bundle) of the diagnosis of severe sepsis [Kreiner LA, Moore LJ. Early Management of Sepsis, Severe Sepsis, and Septic Shock in the Surgical Patient. In: Moore LJ, Turner KL, Todd SR, editors. Common Problems in Acute Care Surgery [Internet].

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Overall Principles of Treatment

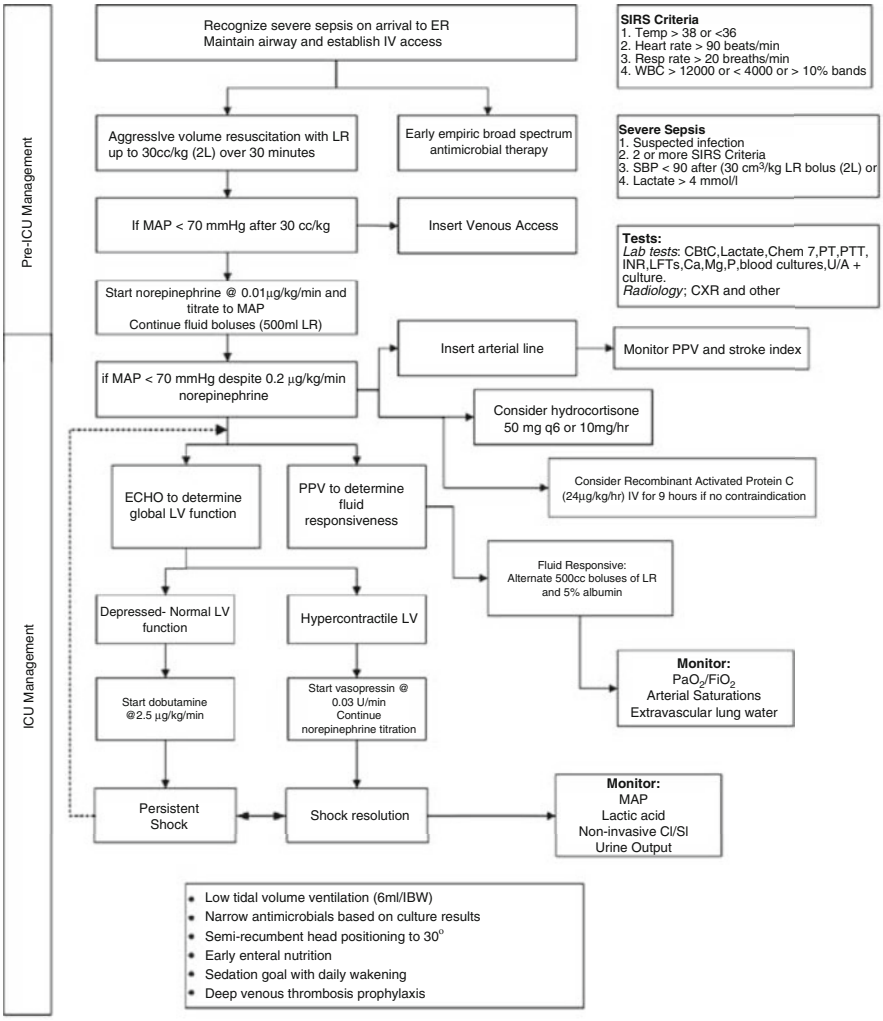
- The primary goal of managing sepsis is to address inflammation by restoring perfusion and treating the infection.
- Early goal-directed therapy (EGDT) targets to be measured:
  - Mean arterial pressure (MAP) ≥65 mmHg
  - Urine output ≥0.5 mL/kg/hr
  - Predictors of fluid responsiveness
  - Central venous oxyhemoglobin saturation ($Scv0_2$) ≥65 percent
  - Lactate clearance should be followed
- Protocol-directed therapies assist in management of septic patients.
- Early antimicrobial therapy is important and should be targeted at the likely primary site. Broad-spectrum coverage with at least two agents is usually indicated.
- Additional therapies:
  - Glucocorticoids: pathogenesis of sepsis involves host inflammatory response.
  - Nutrition: nutritional support improves nutritional outcomes.
  - Intensive insulin therapy: hyperglycemia and insulin resistance.
  - External cooling: controlling fever.
  - Investigational therapies: cytokine and toxin inactivation.

Prevention and Treatment Summary

Author (year)	Subject #	Method	Outcome
Primary Prevention			
Murugan (2012)	1,836	Prospective cohort	Statin use in patients with pneumonia not associated with reduction in acute kidney injury
Rothberg (2012)	121,254	Retrospective review	Modest reduction in non-ICU pneumonia mortality
Novack (2012)	17,802	Placebo controlled	No reduction in sepsis incidence. Modest reduction in pneumonia incidence
Nseir (2012)	342	Retrospective review	Mortality reduction in patients with bacteremia Statin use more than 12 weeks prior to bacteremia increased benefit
Leung (2012)	2,139	Retrospective cohort	Statin use not associated with improved survival in patients with bloodstream infection
Yende (2011)	1,895	Multicenter inception	No reduction in severe sepsis or 90-cohort day mortality
O'Neal (2011)	575	Prospective cohort	Reduction in risk of developing severe sepsis and acute lung injury
Al Harbi (2011)	763	Nested cohort	Reduction in severe sepsis related hospital mortality
Williams (2011)	2,642	Prospective cohort	No reduction in infection related 30-day mortality
Goodin (2011)	568	Retrospective cohort	No reduction of vasopressor duration, ICU length or stay, or hospital mortality
Secondary Prevention			
Kruger (2011)	150	Placebo-controlled	Continuation of statin in patients with infection did not reduce risk of developing sepsis
Novack (2009)	83	Placebo-controlled	Patients with infection randomized to statin therapy had reduced TNF-α and IL-6 levels
Treatment			
Patel (2011)	100	Placebo controlled	Atorvastatin reduced risk of sepsis progression
Dessap (2011)	76	Retrospective cohort	Continuation of statin in patients with severe sepsis and septic shock was not associated with reduction in severity of organ failure or mortality

Recent clinical reports on the prevention and treatment of sepsis [Mermis JD, Simpson SQ. HMG-CoA Reductase Inhibitors for Prevention and Treatment of Severe Sepsis. Current Infectious Disease Reports. 2012 Oct;14(5):484–92.] *Caption from original*

Severe Sepsis and Septic Shock Protocols



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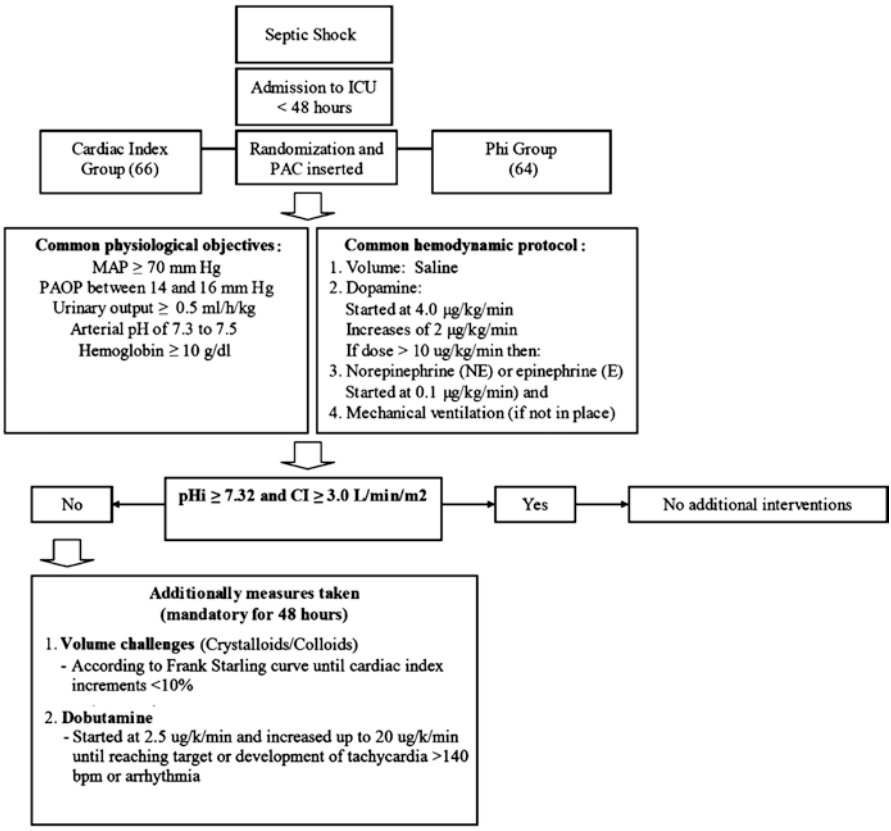

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Disease Course

- Sepsis is a high-risk syndrome that is sometimes fatal even with aggressive treatment. Current literature suggests that early recognition and early, aggressive, goal-directed treatment are associated with better outcomes.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

("Shock, Septic"[Mesh] OR "Systemic Inflammatory Response Syndrome"[Mesh] OR "Sepsis"[Mesh] OR "sepsis" OR "septic shock" OR "SIRS" OR "Systemic inflammatory response syndrome")

Chapter 68
Tachyarrhythmias

Charles V. Pollack, Jr., Richard M. Cantor, and Jaime Friel Blanck

Name and Synonyms

Tachyarrhythmias

Incidence/Epidemiology

- "Tachyarrhythmias" include several distinct syndromes of varying incidence and epidemiology.
- A tachycardia (fast heart rate) is defined as a ventricular rate of 100 beats per minute or more, and may be regular or irregular in rhythm.
- The diagnoses addressed in this discussion include:
  - Sinus tachycardia, which is not a primary tachycardia (i.e., it is not caused by an abnormality of the cardiac conducting system).
  - Multifocal atrial tachycardia (MAT), which is most often seen in patients with lung disease such as COPD.
  - Atrial fibrillation (AFib), the most common arrhythmia, in which the atria do not beat in a coordinated fashion, and which may present with a "controlled" (less than 100 bpm) or "rapid" (greater than 100) ventricular rate.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_68

An American who lives until age 75 without atrial fibrillation has a one-in-four chance of developing AFib during the rest of his or her life.
  - Atrial flutter (AFlutt), a less stable rhythm than AFib, where the atria beat regularly, but not every beat is transmitted to the ventricles.
  - Paroxy mal supraventricular tachycardia (PSVT), which may be seen more often in younger patients than AFib or AFlutt.
  - Wolff-Parkinson-White syndrome, in which an alternate transmission route for the electrical impulses through the heart is present.
  - Ventricular tachycardia (VT), the most lethal of the tachyarrhythmias, is usually the result of myocardial ischemia.
- There are much rarer types of tachyarrhythmias that are beyond the scope of this review.

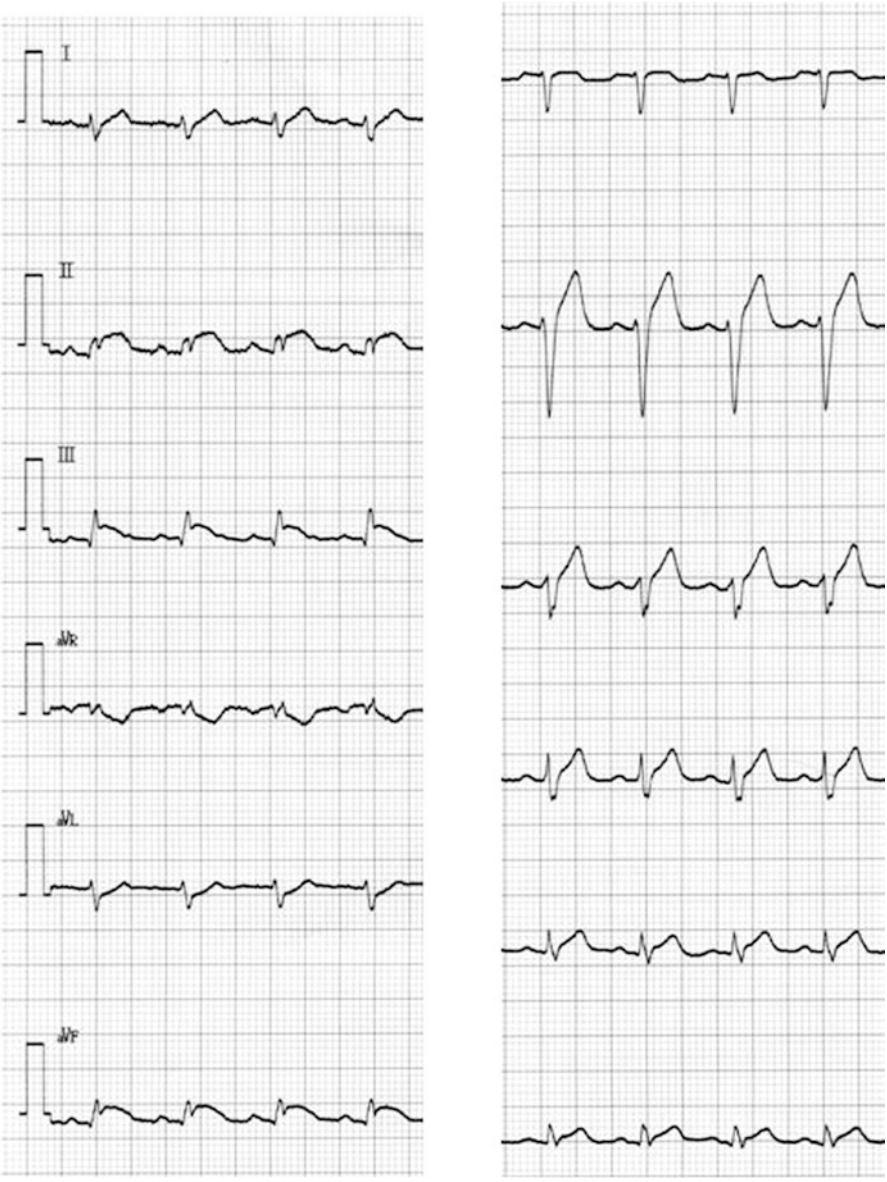
Differential Diagnosis

- Tachycardia is a straightforward diagnosis, confirmed with an ECG or even a manual pulse check. The important diagnostic inquiries related to tachycardia are centered on the actual rhythm (e.g., supraventricular vs ventricular) and underlying etiology of the rapid heart rate. Diagnostic considerations include but are not limited to:
  - Acute myocardial infarction
  - Acute heart failure
  - Pulmonary embolism
  - Sepsis
  - Myocarditis
  - Hypoxemia
  - Hypovolemia
  - Anemia
  - Hyperthyroidism
  - Poisoning or withdrawal syndrome

Pathophysiology and Etiology

- Tachyarrhythmias may be primary (i.e., the result of a defective cardiac electrical conduction system or cardiac injury) or secondary (e.g., tachycardia as a result of withdrawal syndromes, thyroid storm, or sepsis).
- Tachyarrhythmias may be associated with chest pain and dyspnea because they derive from a primary ischemic etiology such as acute myocardial ischemia, or they may cause ischemic pain because the rate does not allow sufficient time for perfusion of stressed myocardium.

- Sinus tachycardia is a normal physiologic response to stress, such as fever, anemia, exercise, anxiety, or hypotension. The patient's normal QRS morphology is present.

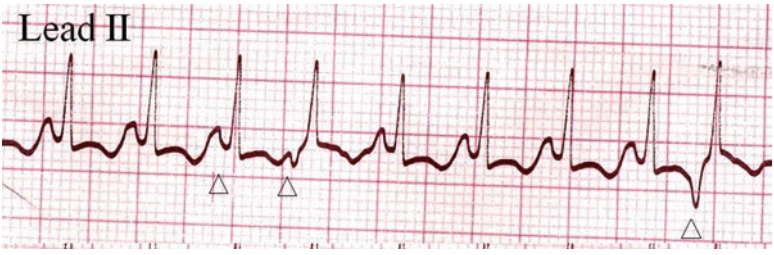


Electrocardiogram on admission showing sinus tachycardia with significant ST elevation in leads II, III, aVF, and V2–V4 [Okai I, Inoue K, Maruyama M, Maruyama S, Komatsu K, Nishizawa H, Okazaki S, Fujiwara Y, Sumiyoshi M, Daida H. Transbrachial intra-aortic balloon pumping for a patient with fulminant myocarditis. Heart Vessels. 2012 Nov 1;27(6):639–42.] *Caption from original*

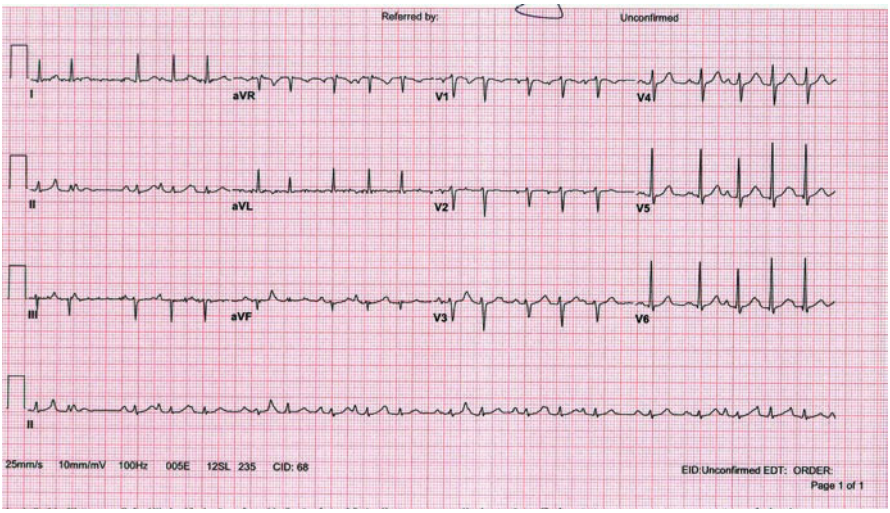
Medical conditions	Physiological	Drugs, substances
Hyperthyroidism	Exercise	Caffeine
Cushing's disease	Emotion	Alcohol
Pheochromocytoma	Pain	Tobacco
Anemia	Fever	Catecholamines
Infection	Pregnancy	Vasodilators
Dehydration	Volume depletion	Atropinic substances
Cardiomyopathy		Theophylline
Panic attack		Illicit drugs: cocaine
Pericarditis		Decongestants
Aortic or mitral regurgitation		Sympathomimetics
Myocardial infarction		Thyroid hormones
Postural hypotension		

Explainable causes of sinus tachycardia that should be ruled out before making the diagnosis of inappropriate sinus tachycardia. [Peyrol M, Lévy S. Clinical presentation of inappropriate sinus tachycardia and differential diagnosis. J Interv Card Electrophysiol. 2016 Jun 1;46(1):33–41.] *Caption from original*

- Multifocal atrial tachycardia is caused by multiple sites of competing atrial electrical activity. The atrial rate by definition exceeds 100 bpm, and there are multiple morphologically identifiable p-waves. Conduction to the ventricles is 1:1, but the P-P intervals are variable. It is characterized by an irregular atrial rate greater than 100 beats per minute (bpm).

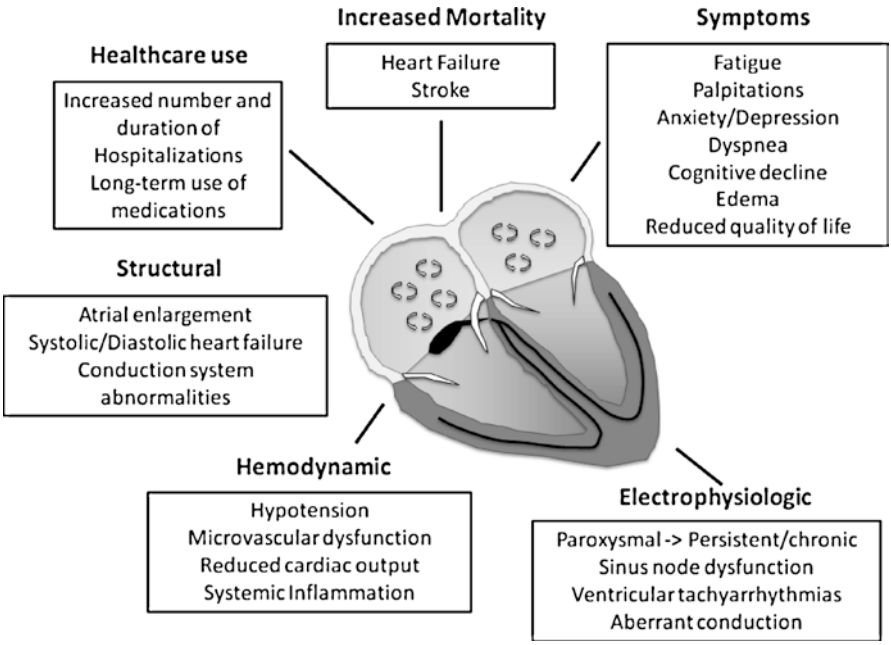


Three different morphologies of P-wave complexes (arrowheads) suggesting multifocal atrial tachycardia [Shabanian R, Kiani A, Rad EM, Eslamiyeh H. Lown-Ganong-Levine Syndrome in a 3-Month-Old Infant with Isolated Left Ventricular Noncompaction. Pediatr Cardiol. 2010 Feb 1;31(2):274–6.] *Caption from original*

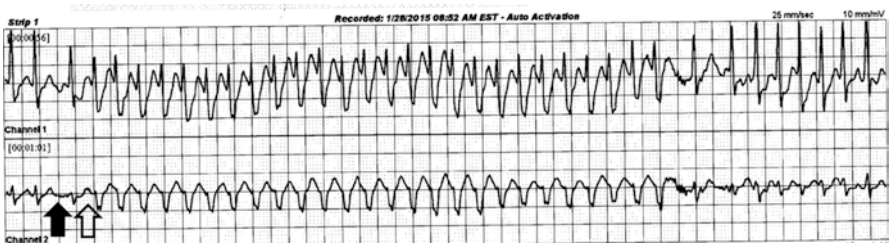


Multifocal atrial tachycardia (MAT). The diagnosis is made by three or more ectopic (i.e., not all sinus) P-waves. The heart rate (approximately 100–140 bpm) may be variable due to the site of ectopy or non-conduction of certain P-waves. MAT is commonly observed in patients with chronic obstructive pulmonary disease. [Chung EH, Martin DT. Management of Postoperative Arrhythmias. In: O'Donnell JM, Nácul FE, editors. Surgical Intensive Care Medicine [Internet]. Springer US; 2010 [cited 2017 May 24]. p. 209–27. Available from: http://link.springer.com/chapter/10.1007/978-0-387-77893-8_21] *Caption from original*

- Atrial fibrillation may be isolated, paroxysmal, or persistent. The first two are often prompted by an episode of emotional stress, hormonal stress, trauma, surgery, or intoxication. Persistent AFib usually is a manifestation of structural heart disease or chronic lung disease. It is manifest on the ECG and by manual pulse check as an "irregularly irregular" rhythm, reflecting uncoordinated, chaotic atrial activity that does not send the ventricles a clear and regular signal to contract. The ECG typically shows an erratic electrical baseline between QRS complexes.



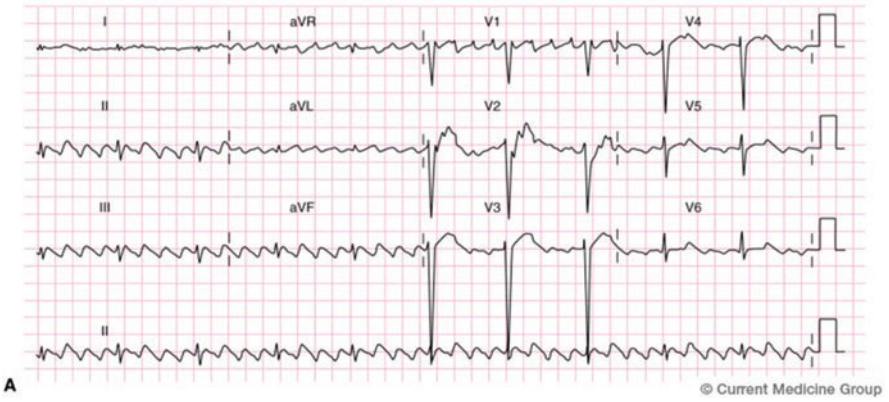
Broad consequences of atrial fibrillation. [Bunch TJ, Gersh BJ. Rhythm Control Strategies and the Role of Antiarrhythmic Drugs in the Management of Atrial Fibrillation: Focus on Clinical Outcomes. J GEN INTERN MED. 2011 May 1;26(5):531–7.] *Caption from original*



Ambulatory event monitor tracing showing long-short initiation of aberrant ventricular conduction during atrial fibrillation. The preceding long R-to-R interval is indicated by the *black-filled arrow* and the short R-to-R interval is indicated by the *unfilled arrow* [Winchester DE, Kaufmann MR, McKillop MS, Miles WM. Pitfalls in the Acute Management of Atrial Fibrillation. In: Peacock WF, Clark CL, editors. Short Stay Management of Atrial Fibrillation [Internet]. Springer International Publishing; 2016 [cited 2017 Jun 2]. p. 145–73. (Contemporary Cardiology). Available from: http://link.springer.com/chapter/10.1007/978-3-319-31386-3_14] *Caption from original*

- Atrial flutter is usually transient and is characterized by a regular atrial rate between 250 and 350 bpm, with a regular ventricular response to every third (3:1 conduction) or fourth (4:1 conduction) atrial beat. The ECG will typically show "sawtooth" p-waves in the inferior leads.

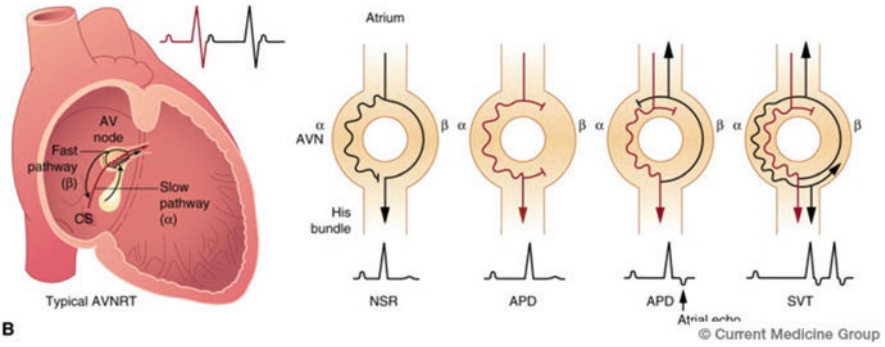
Six-lead ECG immediately after admission revealing the typical signs of atrial flutter [Haas NA, Wegendt C, Schäffler R, Kirchner G, Welisch E, Kind K, Blanz U, Kececioglu D. ECMO for cardiac rescue in a neonate with accidental amiodarone overdose. Clin Res Cardiol. 2008 Dec 1;97(12):878–81.] *Caption from original*



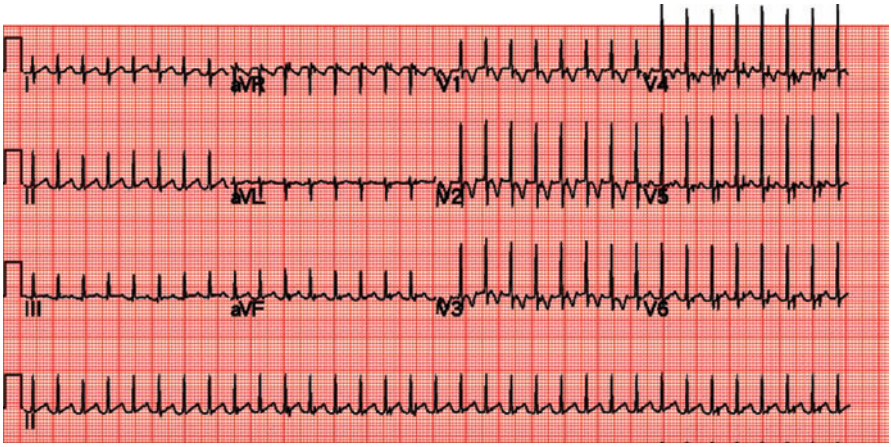
Macroreentrant atrial tachycardias. A, 12-Lead electrocardiogram (ECG) of common counterclockwise atrial flutter. Note the typical sawtooth P-waves in leads II, III, and aVF. [Epstein L, Stevenson W, Steven D, Seiler J, Roberts-Thomson K, See

V. Chapter 7 Arrhythmias. In: Libby P, editor. Essential atlas of cardiovascular disease. 4th ed. Philadelphia: Current Medicine Group; 2009.] *Caption adapted from original*

- PSVT is caused by functional differences in conduction and refractoriness in the AV node, or by the existence of an "accessory" or "bypass" tract involving the SA and AV nodes. The atrial rate is typically 120–180 bpm and conduction to the ventricles is usually 1:1 with a normal QRS morphology.

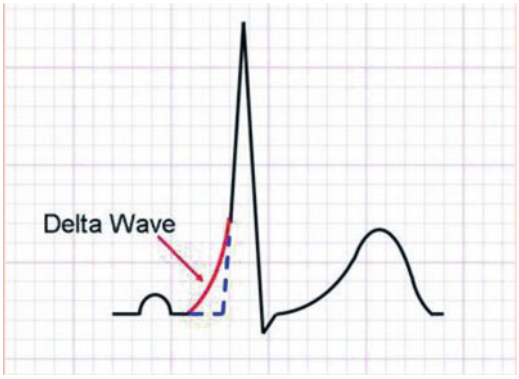


The mechanism of the common form of AVNRT. A lobe of the AV node extends inferiorly along the tricuspid annulus, anterior to the coronary sinus os, which functions as a slowly conducting pathway. During AVNRT-conduction occurs from inferior to superior through the slow pathway, then through the compact portion of the AV node to the His bundle and retrograde through this superior portion of the AV node to the atrium. The path from the compact AV node back down to the slow pathway may involve musculature around the coronary sinus, within the atrium, or may be largely confined to the AV node. Initiation of AV nodal reentry is shown in schematics on the right in which α is the slow AV nodal pathway and β is the fast pathway. During normal sinus rhythm (NSR), an impulse from the atrium enters the AV node and travels down both the slow and fast pathways with the impulse from the fast pathway reaching the His bundle first and activating the ventricles with a short PR interval. Collision of fast pathway and slow pathway impulses in the distal portion of the AV node prevents reentry. An atrial premature depolarization (APD) that blocks in the fast pathway (β) allows conduction of the impulse down the slow pathway to the ventricles, thus a longer PR interval. If this impulse blocks in the distal fast pathway, no reentry occurs. However, an APD can produce an atrial echo beat if the fast pathway has recovered allowing the impulse to continue retrogradely in the fast pathway back to the atrium. If the slow pathway has recovered to allow conduction, the impulse may continue circulating as supraventricular tachycardia (SVT). [Epstein L, Stevenson W, Steven D, Seiler J, Roberts-Thomson K, See V. Chapter 7 Arrhythmias. In: Libby P, editor. Essential atlas of cardiovascular disease. 4th ed. Philadelphia: Current Medicine Group; 2009.] *Caption adapted from original*



Electrocardiogram. Initial ECG with paroxysmal supraventricular tachycardia [From article: A male infant had subdural effusion and paroxysmal supraventricular tachycardia during the febrile episode of Kawasaki disease: a case report and literature review. BMC Pediatr. 2016 Dec 1;16(1):71. https://doi.org/10.1186/s12887-016-0606-x at https://link.springer.com/article/10.1186/s12887-016-0606-x by Chia-Pei Chou, I-Chun Lin, Kuang-Che Kuo, © Chou et al. 2016; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution 4.0 International License http://creativecommons.org/licenses/by/4.0/] *Caption from original*

- WPW is a specific type of tachycardia that results from firing along an accessory electrical conduction tract. It is also called "pre-excitation syndrome" and often shows a particular upsloping of the QRS complex ("delta wave"). It can be associated with congenital cardiac anomalies such as Ebstein's anomaly. The QRS complex in WPW is often wide and the p-wave appears normal.



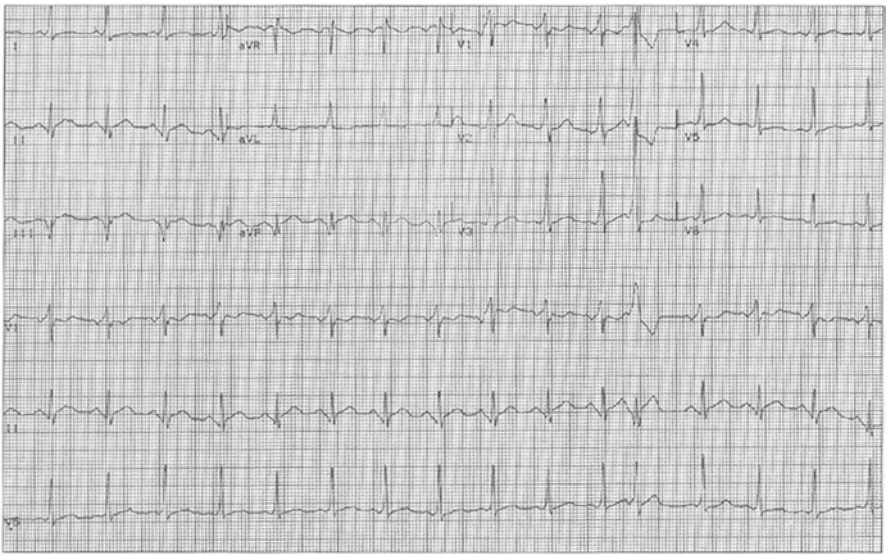
Delta wave, seen in WPW syndrome [Gnanaprakasam R, David S. Acute Cardiac Arrhythmias. In: David SS, editor. Clinical Pathways in Emergency Medicine

[Internet]. Springer India; 2016 [cited 2017 May 24]. p. 101–15. Available from: http://link.springer.com/chapter/10.1007/978-81-322-2710-6_8] *Caption from original*

Morphologic features of Ebstein anomaly	% of patients	Reference(s)
1. Adhesion of the posterior and septal leaflets to the underlying myocardium with displacement of the hinge point of the septal leaflet into the ventricular cavity, and atrialization of the right ventricle. [a]	100 %	[10]
[By echocardiography, exaggerated displacement of the septal leaflet into the ventricular cavity in the apical four-chamber view.]		
2. Dilatation of the tricuspid valve annulus[a]	100 %	[9]
3. Redundancy ± fenestrations of the anterior tricuspid valve leaflet [a]	100 %	[9]
4. Right ventricular dilatation	66 %	[7]
Associated echocardiographic abnormalities		
1. Varying degrees of tricuspid regurgitation	100 %	[11]
2. Atrial communication (patent foramen ovale or atrial septal defect)	50 % 89 %	[9, 11, 40••]
3. Ventricular septal defect	2 %	[40••]
4. Tricuspid stenosis		
5. Right ventricular outflow tract obstruction (functional or anatomic pulmonary atresia)	6 %	[40••]
6. Mitral valve prolapse	13 %	[9]
7. Bicuspid aortic valve	5 %	[9]
8. Left ventricular abnormalities (noncompaction, systolic and diastolic dysfunction)		
9. Partially anomalous pulmonary venous drainage	2 %	[40••]
Associated electrocardiographic abnormalities		
1. Right bundle branch block	58 % 68 %	[9, 11]
2. First degree heart block	31 %	[9]
3. Pre-excitation	18 % 44 %	[9, 11, 40••]
4. Nonspecific intraventricular conduction delay/block	15 %	[9]

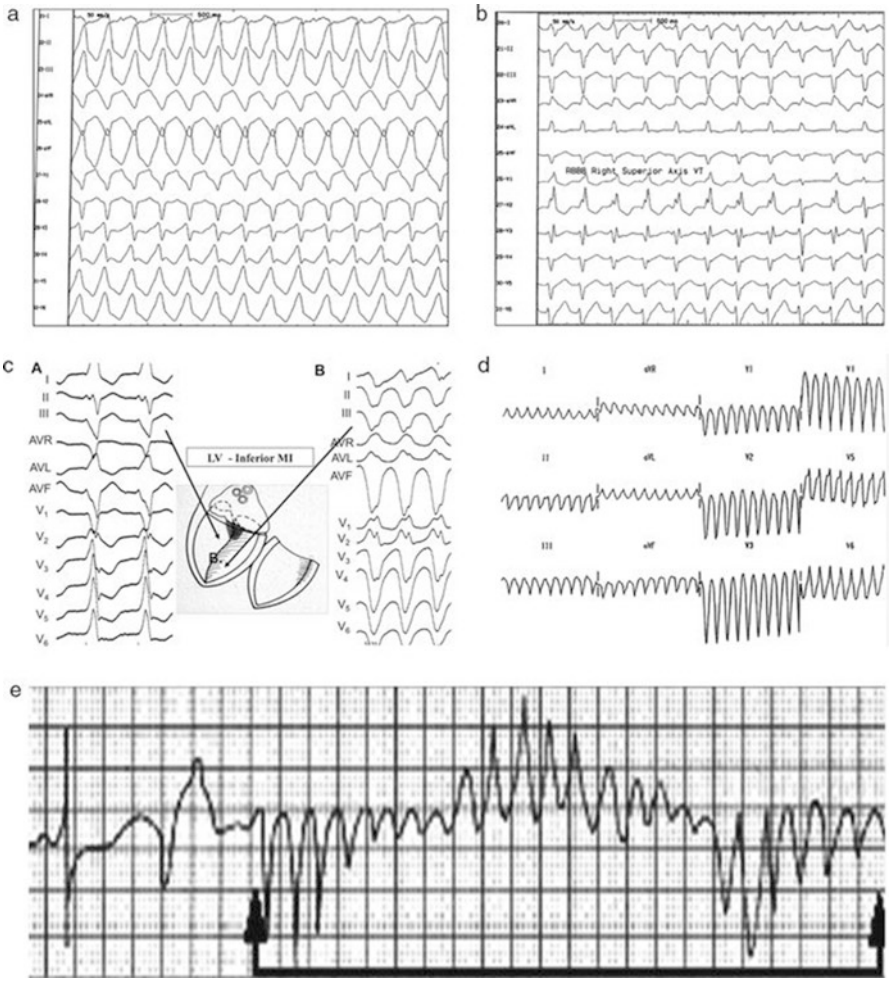
[a] Required for diagnosis.

Morphologic features of Ebstein anomaly and associated abnormalities. References available at https://link.springer.com/article/10.1007/s11936-014-0338-x [Arya P, Beroukhim R. Ebstein Anomaly: Assessment, Management, and Timing of Intervention. Curr Treat Options Cardio Med. 2014 Oct 1;16(10):338.] *Caption adapted from original*



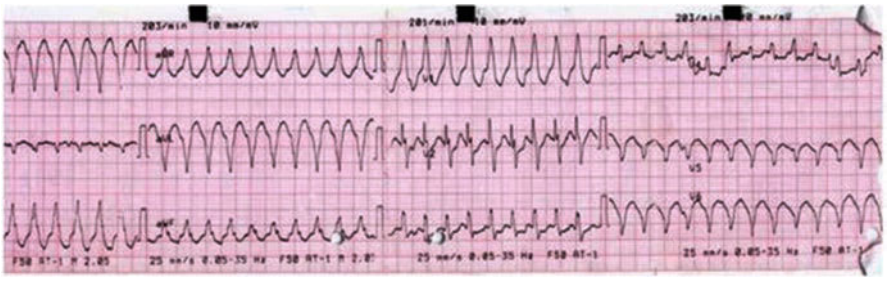
An electrocardiogram (ECG) from a 34-year-old asymptomatic aircrew member showing typical features of the Wolff-Parkinson-White (WPW) syndrome—ie, a short P-R interval and delta waves in multiple leads. [Ferry D, Anholm J, Blomqvist GC, Levine B, Lane L, Buckey J, Wachholz C. Chapter. In: Crawford C, editor. Heart Disease In Presence of Disorders of Other Organ Systems. 1st ed. Philadelphia: Current Medicine; 1996 (Braunwald E, editor. Atlas of heart diseases; vol. 6.)] *Caption adapted from original*

- Ventricular tachycardia is a potentially lethal tachyarrhythmia that is usually associated with structural heart disease, including ischemia. Occasionally it is seen in patients with intoxications, with metabolic derangements, with long QT syndrome, and, rarely, without identifiable precipitant. VT that persists more than 30 seconds is called sustained VT. Because it is driven by a ventricular pacemaker, the QRS complex is wide. VT may or may not generate a palpable pulse.



ECG types of VT and most common causes are shown with characteristic ECG features of selected VTs. LBBB indicates left bundle branch block; RBBB, right bundle branch block; L, left; and R, right. (a) Sustained monomorphic ventricular tachycardia with LBBB and inferior axis suggesting origin from RVOT. This tachycardia is idiopathic in origin. (b) Sustained monomorphic ventricular tachycardia with RBBB and right superior axis, suggesting origin in the left ventricular septum. This type of tachycardia is commonly idiopathic in origin. (c) Two different ventricular tachycardias originating in the left ventricle long after an inferior wall myocardial infarct. This type of VT is related to scars that form after myocardial infarct. (d) Fast ventricular tachycardia with LBBB and left superior axis. Morphology and rate are suggestive of bundle branch reentry ventricular tachycardia. This type of VT is related to nonischemic cardiomyopathy. (e) Polymorphic ventricular tachycardia. This type of tachycardia is frequently related to electrolyte abnormalities,

ischemia, or drug toxicity. [Kocovic D. Ablation for Ventricular Tachycardia. In: Yan G-X, Kowey PR, editors. Management of Cardiac Arrhythmias [Internet]. Humana Press; 2011 [cited 2017 May 24]. p. 257–82. (Contemporary Cardiology). Available from: http://link.springer.com/chapter/10.1007/978-1-60761-161-5_12] *Caption from original*



Electrocardiogram showing monomorphic ventricular tachycardia. [From article: Ventricular tachycardia – an atypical initial presentation of sarcoidosis: a case report. J Med Case Reports. 2013 Dec 1;7(1):196. https://doi.org/10.1186/1752-1947-7-196 at https://link.springer.com/article/10.1186/1752-1947-7-196 by Meera Ekka, Sanjeev Sinha, Raghunandan Purushothaman, Nitish Naik, Rajiv Narang, Lavleen Singh, © Ekka et al. 2013; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

Presentation

Typical/"Classic"

- Patients with tachyarrhythmias typically present with:
  - Palpitations
  - Chest pain
  - Dizziness
  - Weakness

Atypical

- Patients with tachyarrhythmias, especially atrial fibrillation, may be largely asymptomatic.
- Sometimes the cardinal symptoms of underlying illness (e.g. sepsis, hyperthyroidism, withdrawal syndrome) may overwhelm the patient's perception of tachycardia

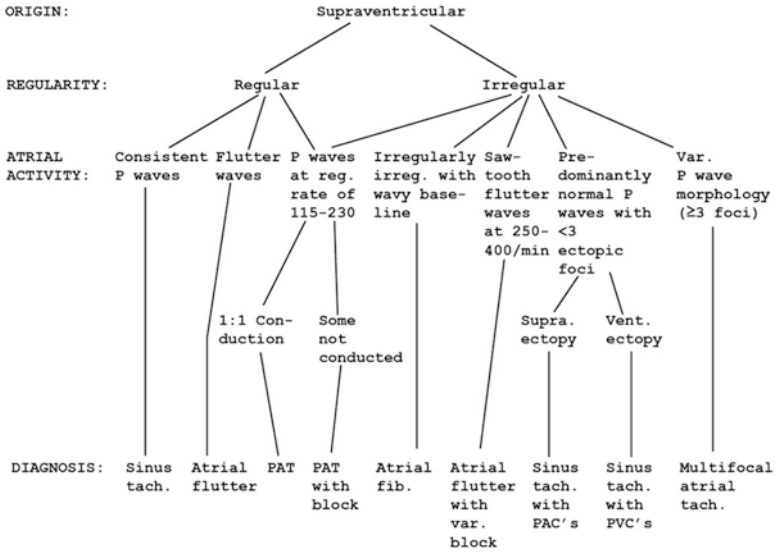
Primary Differential Considerations

- Patients with tachyarrhythmias should be evaluated for type of rhythm abnormality and for underlying cause. Among the important early considerations are:
  - Acute myocardial ischemia/infarction
  - Pulmonary embolism
  - Sepsis
  - Shock
  - Ventricular tachycardia
  - Sustained supraventricular tachycardia

History and Physical Exam

Findings That Confirm Diagnosis

- The ECG confirms the type of arrhythmia and may give clues of myocardial ischemia if present. The clinician should assess the patient's hemodynamic stability while the ECG is being performed. On first review of the ECG, focus on identifying the rhythm and on whether the QRS is narrow or wide.



Flow sheet for supraventricular tachycardia [Petty BG. Arrhythmias. In: Basic Electrocardiography [Internet]. Springer New York; 2016 [cited 2017 May 24]. p. 101–35. Available from: http://link.springer.com/chapter/10.1007/978-1-4939-2413-4_7] *Caption from original*

Factors That Suggest Diagnosis

- Tachypalpitations, weakness, with or without chest pain or shortness of breath.
- ECG should be obtained immediately and will guide the diagnostic process.

Factors That Exclude Diagnosis

- A heart rate (on ECG, monitor, or manual pulse count) of < 100 bpm excludes tachyarrhythmia. A patient with suggestive symptoms, however, should be maintained on a monitor, because the abnormal rhythm may be paroxysmal.

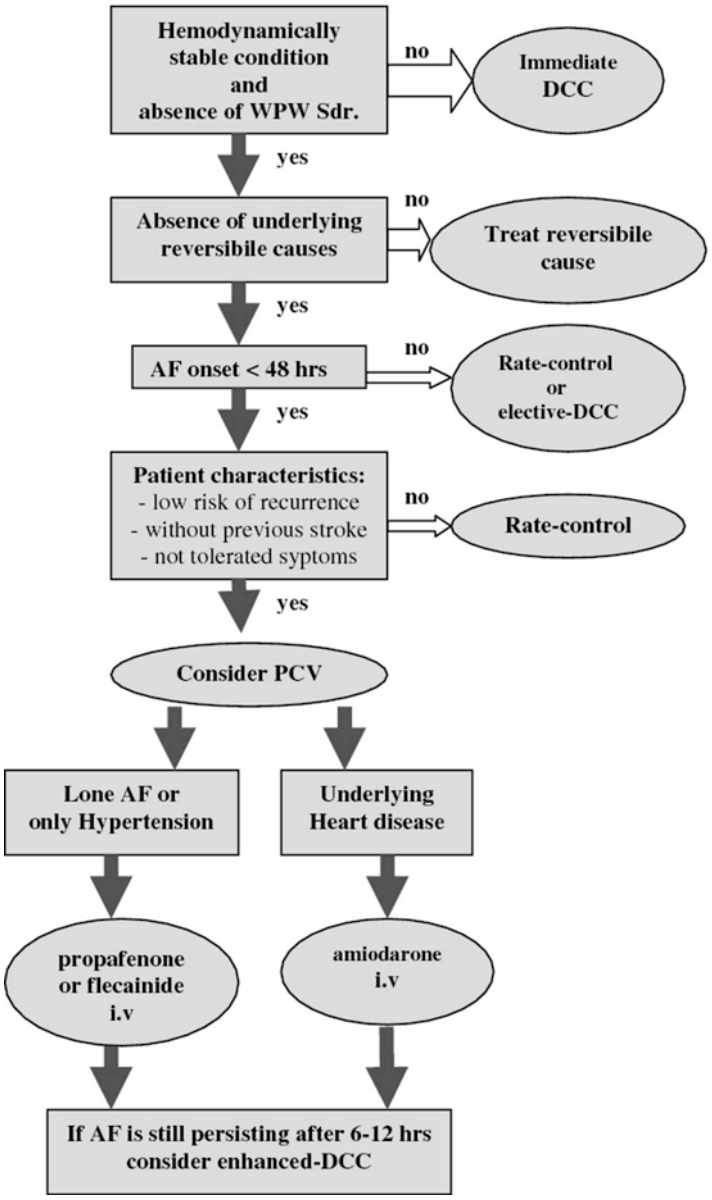
Ancillary Studies

Laboratory

- It is helpful to send routine laboratory studies such as basic chemistries, a complete blood count, and cardiac biomarkers to evaluate for other causes for the patient's symptoms.
- Specialized studies should be ordered as pertinent to the presentation, such as thyroid studies, blood cultures, etc.
- If the patient is taking digoxin or theophylline, check drug levels.

Electrocardiography

- The ECG should be obtained and interpreted promptly.
  - Look first for signs of acute ischemia (in particular, ST-segment elevation).
  - Then look to see if QRS rhythm is regular or irregular.
  - Then evaluate the width of the QRS complex: narrow (normal conduction) or wide (abnormal conduction from above, or ventricular origin).



Key findings of common arrhythmias [Winchester DE, Kaufmann MR, McKillop MS, Miles WM. Pitfalls in the Acute Management of Atrial Fibrillation. In: Peacock WF, Clark CL, editors. Short Stay Management of Atrial Fibrillation [Internet]. Springer International Publishing; 2016 [cited 2017 May 24]. p. 145–73. (Contemporary Cardiology). Available from: http://link.springer.com/chapter/10.1007/978-3-319-31386-3_14] *Caption from original*

Imaging

- The chest x-ray may be helpful in the evaluation of tachyarrhthmias. Other imaging is typically not needed except in specific diagnostic evaluations for underlying problems, such as CT pulmonary angiogram for suspected pulmonary embolism.

Special Populations

Age

- Atrial fibrillation, atrial flutter, MAT, and VT are more likely to occur in older patients.
- PSVT and sinus tachycardia can occur at any age.
- Tachycardia is common in the pediatric age group; etiologies are often benign.
- Parental diagnosis is often accomplished by observing the neck veins or sensing a bounding pulse while holding the child.
- SVT is the most common symptomatic dysrhythmia of infancy and childhood.
- Symptoms of SVT in infancy range from minor to cardiogenic shock.
- In infants, lethargy, feeding problems, or irritability may be manifested.
- In newborns or infants with SVT, the heart rate is often > 220 bpm.

Co-morbidities

- The most important co-morbidities are underlying cardiopulmonary disease, including coronary artery disease, heart failure, structural heart abnormalities, and COPD.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is imperative that all patients be monitored in an ongoing fashion for hemodynamic stability.
- Recognition of ventricular arrhythmia is critical, as VT is an unstable and potentially lethal rhythm.

- Patients with supraventricular arrhythmia (AFib, AFlut, PSVT) often present in relatively stable condition but may not tolerate the ongoing high myocardial oxygen demand for long, so early stabilization and rate control are warranted.

Mimics

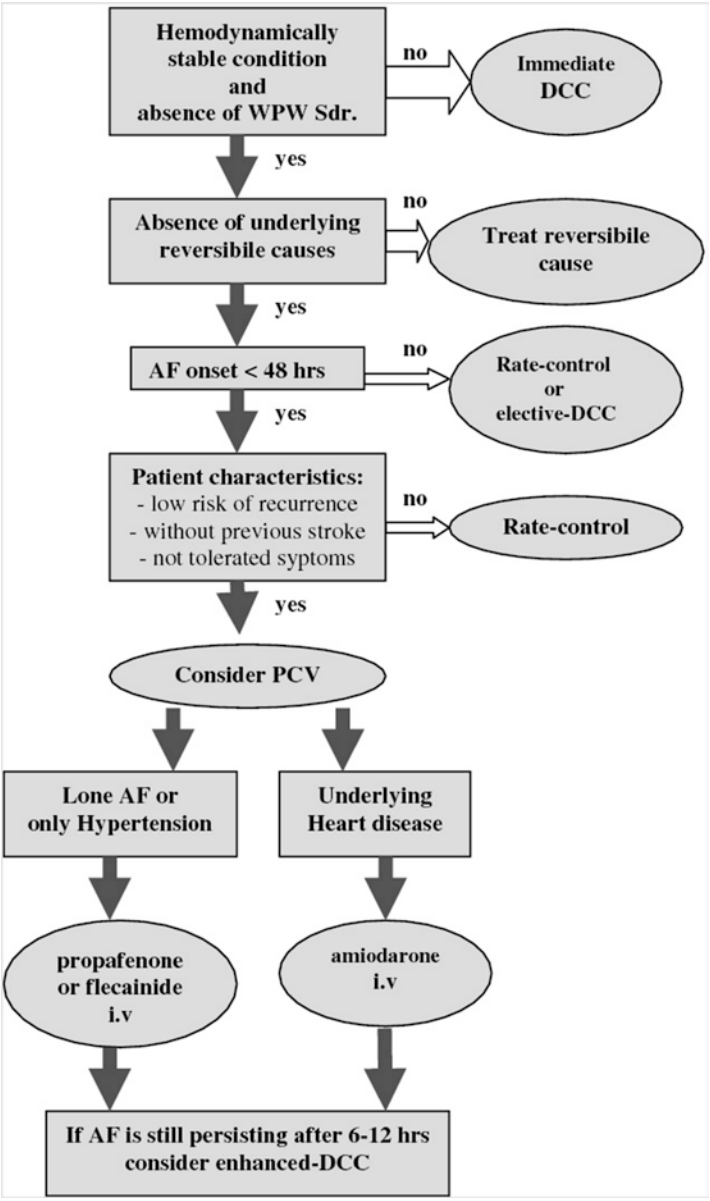
- Palpitations can be caused by anxiety, but sometimes this is not a clear diagnosis, and a prompt ECG should still be obtained.

Time-Dependent Interventions

- The most important intervention is to stabilize patients with hemodynamic instability.
- Recognition of potentially lethal arrhythmias is important.
- Identification and management of underlying illness are important steps and may be life-saving (e.g., PE, sepsis).
- Rate control should be established as soon as possible in order to spare the myocardium ongoing high oxygen consumption that may lead to ischemia.

Overall Principles of Treatment

- Treatment approach is specific to the tachyarrhythmia diagnosis and/or underlying disease. Treatment may be very complex, but first-line actions typically are as follows:
  - Sinus tachycardia: identify and treat underlying cause.
  - MAT: focus on treating underlying pulmonary disease.
  - AFib: consider rate control with diltiazem (if hemodynamically stable) or with cardioversion (if unstable)



Proposed approach to the management of patients with recent-onset AF. Stratify thromboembolic risk and initiate appropriate prophylaxis in all patients. When elective DCC is considered in patients with AF >48 h or after a failed attempt at cardioversion, OAC treatment is required for at least 3 weeks before and 4 weeks after cardioversion [Tampieri A, Rusconi AM, Lenzi T. Cardioversion in atrial fibrillation. Focus on recent-onset atrial fibrillation. Intern Emerg Med. 2012 Oct 1;7(3):241–50.] *Caption from original*

  - AFlutt: consider rate control with diltiazem (if hemodynamically stable) or with cardioversion (if unstable).
  - PSVT: consider rate control with adenosine or diltiazem (if hemodynamically stable) or with cardioversion (if unstable).
  - WPW: if narrow complex QRS, can use adenosine or diltiazem; if wide-complex, treat as VT and avoid these drugs.
  - VT: synchronized cardioversion.
- Patients should be evaluated for any underlying or acute issues that, if treated, can help improve the cardiac function.

Disease Course

- Prognosis is dependent on the specific type of arrhythmia and underlying co-morbidities.
- The mortality of VT is highest within this group of diagnoses.
- Patients with AFib should be evaluated for chronic oral anticoagulation once stabilized.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, Estes NA 3rd, Field ME, Goldberger ZD, Hammill SC, Indik JH, Lindsay BD, Olshansky B, Russo AM, Shen WK, Tracy CM, Al-Khatib SM; Evidence Review Committee Chair‡. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016 Apr 5;133(14):e506-74.https://doi.org/10.1161/CIR.0000000000000311. Erratum in: Circulation. 2016 Sep 13;134(11):e234-5. PubMed PMID: 26399663. https://www.ncbi.nlm.nih.gov/pubmed/26399663 **

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With Supraventricular Tachycardia: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2016 Apr 5;133(14):e471-505. https://doi.org/10.1161/CIR.0000000000000310. Erratum in: Circulation. 2016 Sep 13;134(11):e232-3. PubMed PMID: 26399662. https://www.ncbi.nlm.nih.gov/pubmed/?term=26399662 **

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Review

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: "Tachycardia"[Mesh] OR "tachycardia" OR "tachycardias" OR "tachyarrhythmia" OR "tachyarrythmias"

Chapter 69
Tetralogy of Fallot

Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Tetralogy of Fallot (TOF): A constellation of four anatomic cardiac anomalies.

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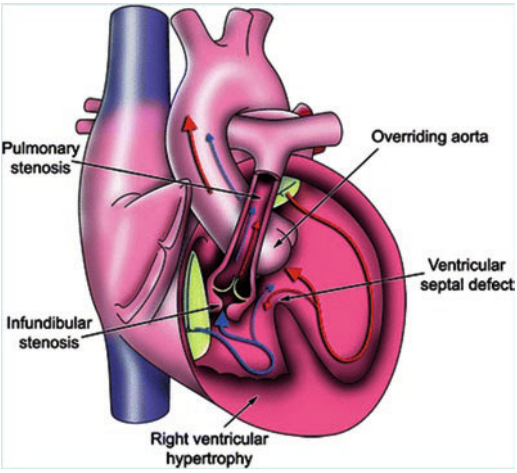
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_69



Schematic drawing of tetralogy of Fallot [Sridharan S, Price G, Tann O, Hughes M, Muthurangu V, Taylor AM. Tetralogy of Fallot. Cardiovascular MRI in Congenital Heart Disease [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010 [cited 2015 Sep 1]. p. 74–7. Available from: http://link.springer.com/10.1007/978-3-540-69837-1_31] *Caption from original*

Incidence/Epidemiology

- Tetralogy of Fallot is seen in 4 per 10,000 live births.
- It accounts for 7–10 % of reported cases of congenital heart disease.
- Repair is usually necessary within the first year of life.

Differential Diagnosis

- Should be considered in the differential diagnosis of cyanotic congenital heart disease, often represented by the "5 T's":
  - Truncus Arteriosus
  - Transposition of the Great Arteries
  - Tricuspid Atresia
  - Tetralogy of Fallot
  - Total Anomalous Pulmonary Venous Return

Pathophysiology and Etiology

- In patients with TOF, the degree of compromise is directly dependent on the severity of the right ventricular outflow obstruction. In most cases, the size of the VSD is generous enough to permit bidirectional blood flow. If left-sided pressures are high enough, the shunting will be "left-to-right," and the patient will be acyanotic. In the converse situation, shunting away from the pulmonary bed will present with cyanosis.
- In the most severe obstructive scenarios, episodes of profound cyanosis may occur (so-called "tet spells" or "hypercyanotic" spells). The etiology of these episodes is unclear.

Presentation

Typical/"Classic"

- As previously mentioned, in situations with severe right-sided outflow obstruction, infants will present with severe cyanosis. This most often occurs during the newborn period.
- In situations where pulmonary and systemic blood flows are equivocal, the infant will often present with a murmur, prompting further investigation.

Atypical

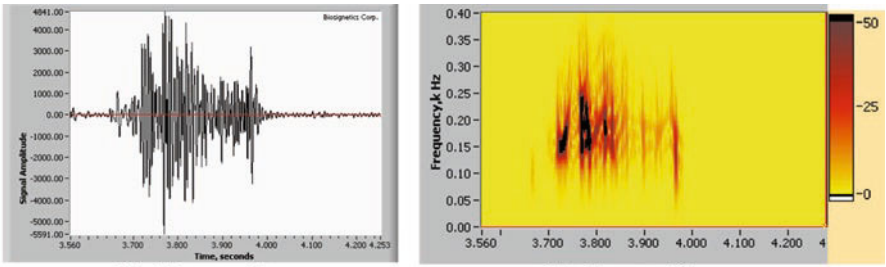
- In cases of minimal right-sided outflow obstruction, shunting across the large VSD will promote the development of congestive heart failure from pulmonary overperfusion.

Primary Differential Considerations

- The other components of the 5 T's (see above) are the most important differential diagnoses to consider.

History and Physical Exam

- Most infants will present with cyanosis in the first few days of life.
- In others, the diagnosis will often be difficult, since most patients with TOF will appear comfortable and in no distress.
- The development of a hypercyanotic (tet) spell will be heralded by the development of cyanosis, hyperpnea, and marked agitation.
- A prominent right ventricular impulse may be palpable.
- The murmur in TOF is secondary to right ventricular outflow obstruction (not from the VSD). As obstruction increases, the murmur will often diminish in intensity, as blood will preferentially be shunted across the VSD.



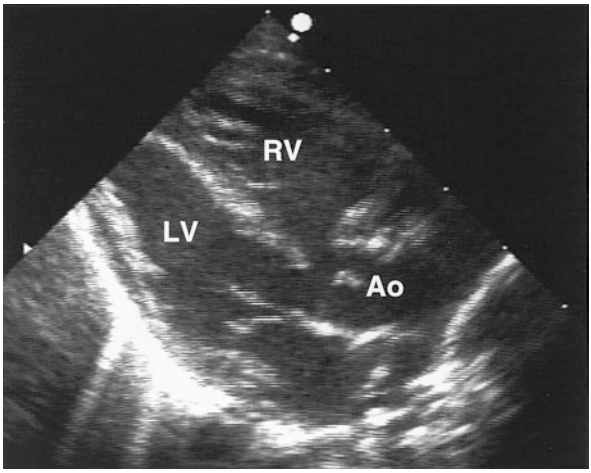
(A, B). Abnormal heart sound of Severe Tetralogy of Fallot (acyanotic). A) PCG (single heart beat). B) HES (single heart beat). [From article: Heart energy signature spectrogram for cardiovascular diagnosis. BioMed Eng OnLine. 2007 May 4;6(1):1–22. DOI: 10.1186/1475-925X-6-16, at http://link.springer.com/article/10.1186/1475-925X-6-16; by Vladimir Kudriavtsev, Vladimir Polyshchuk, Douglas L Roy, © Kudriavtsev et al; licensee BioMed Central Ltd. 2007; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original*

http://www.easyauscultation.com/cases?coursecaseorder=5&courseid=29

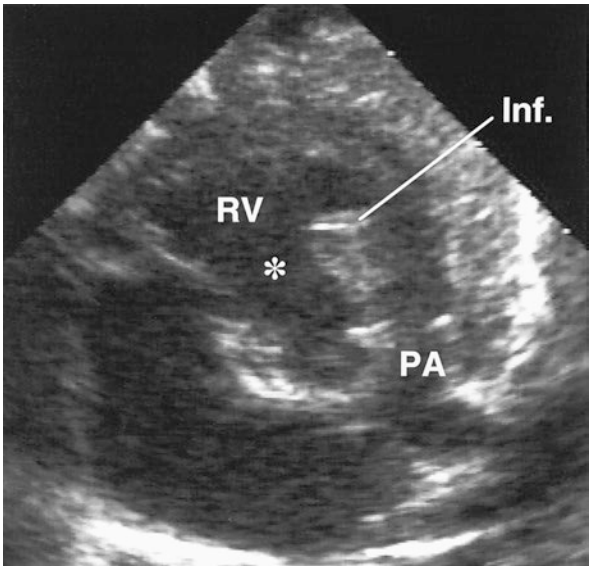
Tetralogy of Fallot murmur. [Congenital Abnormalities: Tetralogy of Fallot; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

Findings That Confirm Diagnosis

- Echocardiography is the gold standard for establishing the diagnosis of TOF.



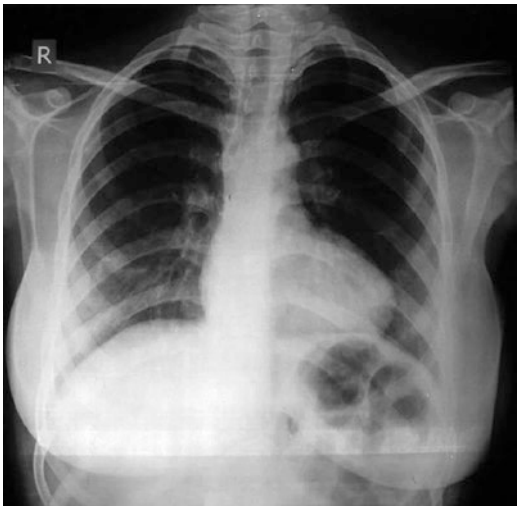
Tetralogy of Fallot. Both subxiphoid and parasternal long- and short-axis images demonstrate the most important aspects of tetralogy of Fallot. A,Parasternal long-axis view demonstrating the large anterior malalignment ventricular septal defect (VSD) with aortic overriding of the crest of the ventricular septum. Ao—aorta; LV—left ventricle; RV—right ventricle. [Hornberger L, Schwartz M. Chapter 2. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging. Atlas of Heart Diseases, Volume 01, Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption adapted from original*



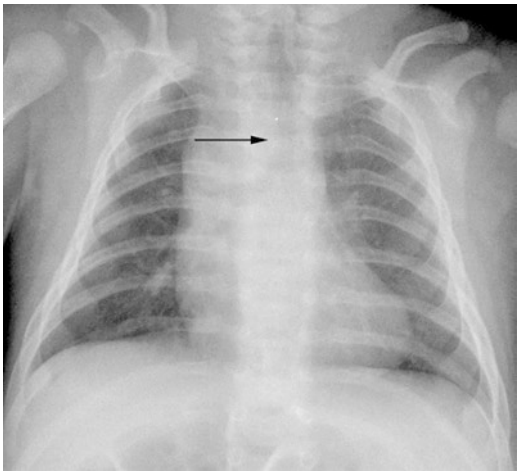
B, Parasternal short-axis view of the right ventricular outflow tract (RVOT) demonstrating anterior malalignment of infundibular septum (Inf). The large subaortic,

malalignment VSD can be seen (asterisk). Other lesions to be excluded in tetralogy of Fallot include additional VSDs, branch pulmonary artery (PA) stenoses, mitral valve abnormalities, and coronary abnormalities, particularly the left anterior descending from the right coronary artery (which crosses over the RVOT) or a single right coronary artery. A prominent conal branch from the right coronary that partially crosses the infundibulum is common in tetralogy of Fallot. RV—right ventricle. [Hornberger L, Schwartz M. Chapter 2. In: Lee RT, Braunwald E, editors. Atlas of Cardiac Imaging. Atlas of Heart Diseases, Volume 01, Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption adapted from original*

- In more typical scenarios, the presence of cyanosis unresponsive to supplemental oxygen, combined with typical X-ray findings (boot-shaped heart), will point to the diagnosis.

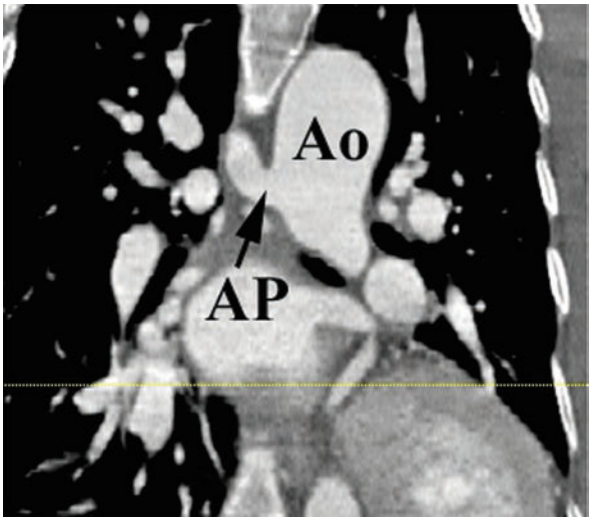


Boot-shaped heart, concave main pulmonary artery segment, and decreased pulmonary vasculature in a tetralogy of Fallot patient [Sadeghpour A, Alizadehasl A, Mahdavi M. Tetralogy of Fallot. In: Sadeghpour A, Kyavar M, Alizadehasl A, editors. Comprehensive Approach to Adult Congenital Heart Disease [Internet]. London: Springer London; 2014 [cited 2015 Sep 1]. p. 237–44. Available from: http://link.springer.com/10.1007/978-1-4471-6383-1_28] *Caption from original*



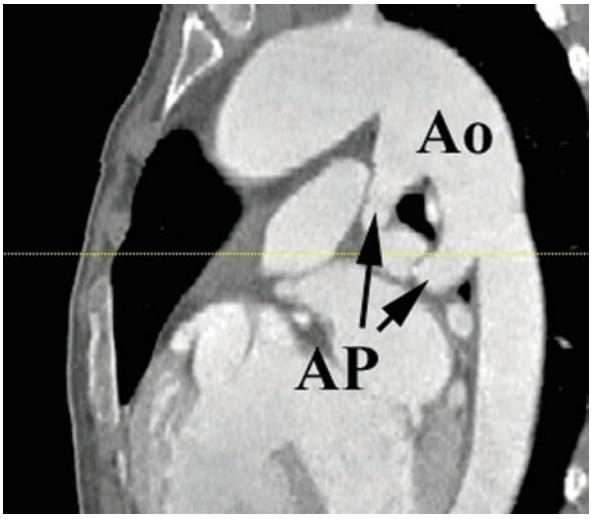
Tetralogy of Fallot. The "boot-shaped" heart is a result of upward tilting of the apex and attenuation of the main pulmonary artery segment. Note the leftward deviation of the trachea (black arrow) indicative of a right aortic arch, which is a common association. [Golding IF, Yoo S, Hamilton R. Cardiology. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. ISBN: 1-57340-188-9] *Caption adapted from original*

- CT scanning may also be helpful.

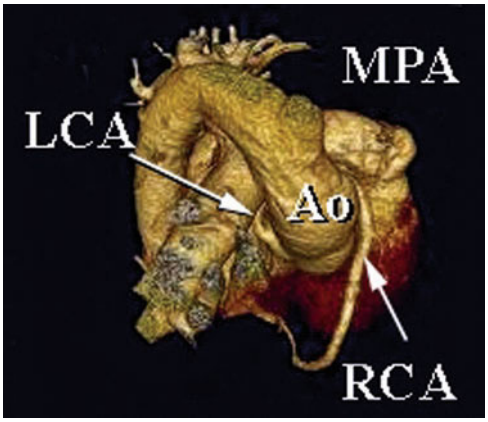


Unrepaired tetralogy of Fallot and pulmonary atresia: CT angiography. Electron beam angiogram of a cyanotic adult with unrepaired tetralogy of Fallot with pulmonary atresia and multiple aortopulmonary (AP) collaterals. A, Coronal slice

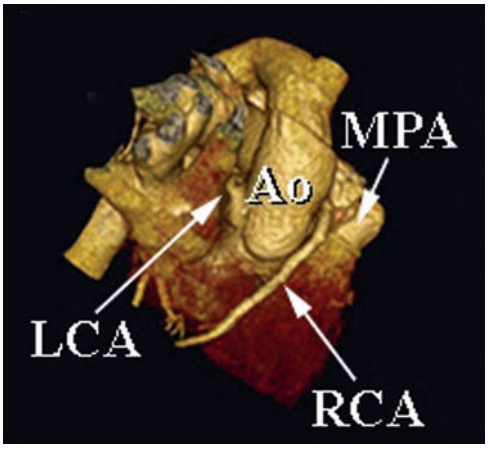
demonstrating large AP collateral emerging rightward from the descending thoracic aorta (Ao). [Aboulhosn J. Chapter 11. In: Budoff MJ, Achenbach S, Narula J, Braunwald E, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption adapted from original*



B, Sagittal slice demonstrating two AP collaterals emerging anteriorly from the descending thoracic aorta (Ao). Delineating the origin, course, and patency of these AP collaterals is challenging and time consuming but imperative to the management of these patients. Depending on anatomic findings patients may be candidates for complete surgical repair, unifocalization, or transcatheter interventions. [Aboulhosn J. Chapter 11. In: Budoff MJ, Achenbach S, Narula J, Braunwald E, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption adapted from original*



Repaired tetralogy of Fallot: CT angiography. Sixteenslice CT angiography with threedimensional volume rendering of a 21-year-old woman with repaired tetralogy of Fallot. A, Right anterior oblique and cranial projection, the right coronary artery (RCA) emerges from the anterior and left facing cusp and courses between the aortic root (Ao) and main pulmonary artery (MPA). The left coronary artery (LCA) emerges from the posterior facing cusp and courses leftward behind the Ao and below the MPA. [Aboulhosn J. Chapter 11. In: Budoff MJ, Achenbach S, Narula J, Braunwald E, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption adapted from original*



B, Right anterior oblique caudal projection. [Aboulhosn J. Chapter 11. In: Budoff MJ, Achenbach S, Narula J, Braunwald E, editors. Atlas of cardiovascular computed tomography. Philadelphia: Current Medicine; 2007] *Caption adapted from original*

Factors That Suggest Diagnosis

- A history of repeated cyanotic episodes, which may resolve spontaneously, should alert the clinician to the possibility of TOF.

Factors that Exclude Diagnosis

- The absence of cyanosis essentially rules out TOF except during periods of normal intracardiac shunting (the "pink" tet).

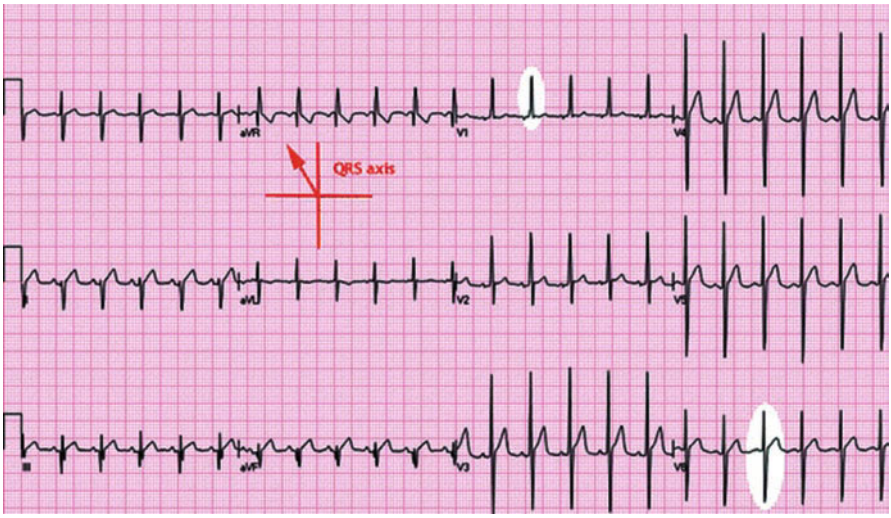
Ancillary Studies

Laboratory

- Basic laboratory tests are rarely indicated.
- As mentioned, arterial blood gas measurements will demonstrate low values for both partial pressures of oxygen and oxygen saturation.

Electrocardiography

- The ECG in TOF will show right ventricular hypertrophy. There will also be right axis deviation, along with varying degrees of R and T wave disruption.



ECG in tetralogy of Fallot. Right ventricular hypertrophy is the dominant feature of ECG in patients with tetralogy of Fallot. RVH may manifest itself in different ways such as tall R in V1 and deep S in V6, rsR′, pure R-wave or qR pattern of QRS complex in right chest leads. In this ECG, RVH is manifested as a pure R in V1, deep S in V6, and right axis deviation [Luxenberg DM, Torchen L. Tetralogy of Fallot. In: Abdulla R, editor. Heart Diseases in Children [Internet]. Boston, MA: Springer US; 2011 [cited 2015 Sep 1]. p. 167–76. Available from: http://link.springer.com/10.1007/978-1-4419-7994-0_13] *Caption from original*

Cardiac Enzymes

- Not indicated,

Special Populations

Age

- The vast majority of patients will present in the neonatal period or early infancy.

Co-morbidities

- About 15–20 % of patients with TOF will present with other syndromes, including Trisomy 21, DiGeorge Syndrome, and velocardiofacial syndrome.

Pitfalls in Diagnosis

- The majority of cyanotic congenital heart defects will present within the first few days of life and be diagnosed during the first few days of life.
- The most common clinical error made when confronted with a cyanotic infant or child is distinguishing between cardiac, pulmonary, and hemoglobin derangements.

Critical Steps Not To Miss

- Clinical paths to follow include:
  - Recognition of central cyanosis.
  - Provision of hyperoxia.
    - If no clinical response is seen, consider cardiac etiologies.
    - If there is measured improvement in oxygenation, pulmonary causes are most likely.

Mimics

- Other causes of cyanosis.

Time-Dependent Interventions

- Immediate consultation with a Pediatric Cardiologist is recommended.
  - Focus is on diagnosis, not treatment, so this is limited.

Overall Principles of Treatment

- Provision of supplemental oxygen.
- In cases of hypercyanotic spells:
  - Placement in the knee-chest position.
  - Sedation with morphine (0.1 mg/kg/dose).
  - Administration of 10–20 cc/kg of normal saline.
  - Immediate consultation with a pediatric cardiologist.

Disease Course

- Short term is excellent after neonatal surgical repair; greater than 90% survival 25 years after neonatal repair.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: “Tetralogy of Fallot”[Mesh] OR “tetralogy of fallot”

Chapter 70
Thoracic Aortic Dissection

Charles V. Pollack, Jr., Richard M. Cantor, and Victoria G. Riese

Name and Synonyms

Thoracic Aortic Dissection (TAD)

- Occasionally referred to as "aortic syndrome" or "aortic disaster"

Incidence/Epidemiology

- TAD is the admitting diagnosis in 1 per 10,000 hospital admissions. Because TAD may be a rapidly fatal disease and autopsies are performed in very few deaths in the US, the true incidence remains unknown but likely is higher. A 2004 autopsy study found evidence of TAD in 1–3% of cadavers.
- TAD occurs more commonly in men than in women, roughly mirroring the prevalence of hypertension. It is more common in blacks than whites and more common in whites than in Asians.
- Peak age for TAD is 50–65 years. It may occur earlier in patients with Marfan's syndrome, in patients undergoing aortic and mitral valve replacements, in patients undergoing percutaneous coronary intervention, in patients with syphilis, and in those who abuse cocaine.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_70

- The dissection typically occurs either along the right lateral wall of the ascending aorta, where the shear stress of blood flow is highest, or in the ascending aorta just below the ligamentum arteriosum.

Differential Diagnosis

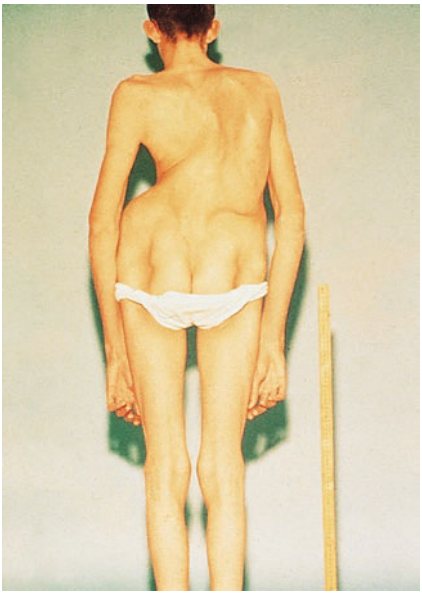
- Because the primary clinical manifestation of TAD is chest pain, the differential is broad. The other life-threatening etiologies of chest pain syndrome—acute myocardial infarction and pulmonary embolism—may present similarly, but because TAD is more often associated with back pain, the differential for this diagnosis may be broader.

Pathophysiology and Etiology

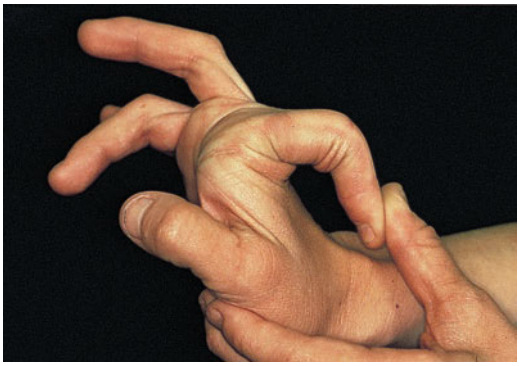
- The pathophysiology of TAD stems from the development of a split in the media of the aortic wall. The innermost layer of the aortic wall, the intima, is torn or interrupted, and blood dissects into the next layer (media) and with the aortic flow pressure behind it, may progress forward, creating a "false lumen." The outermost layer of the aortic wall, the adventitia, prevents the free flow of misdirected blood into the thoracic cavity. The split is usually a circumferential tear that leaves an "intimal flap," but also might result from an aortic ulcer.

Intimal flap seen in the aortic arc. [Niino T, Unosawa S, Shimura K. Stanford type A aortic dissection with intimal intussusception. Gen Thorac Cardiovasc Surg. 2012 Sep;60(9):578-80. https://doi.org/10.1007/s11748-012-0051-1, 2012-09-04] *Caption adapted from original*

- This tearing down the middle of the aortic wall causes pain that is characteristically (but not universally) described by the patient as "ripping." As the false lumen develops and extends, driven by the hydrostatic pressure of continued pulsatile blood flow, it may prevent blood flow through the remaining true lumen into aortic branches that perfuse vital organs, including the heart itself, brain, lung, and kidneys (see Presentation).
- Several problems may predispose the thoracic aorta to dissection. The most important, by far, is hypertension. Problems with the aortic valve (aortic stenosis, bicuspid valve) and the aorta itself (coarctation) are associated with TAD. In addition, several connective tissue diseases are known to increase the risk of TAD, including Marfan's syndrome and Ehlers-Danlos syndrome.

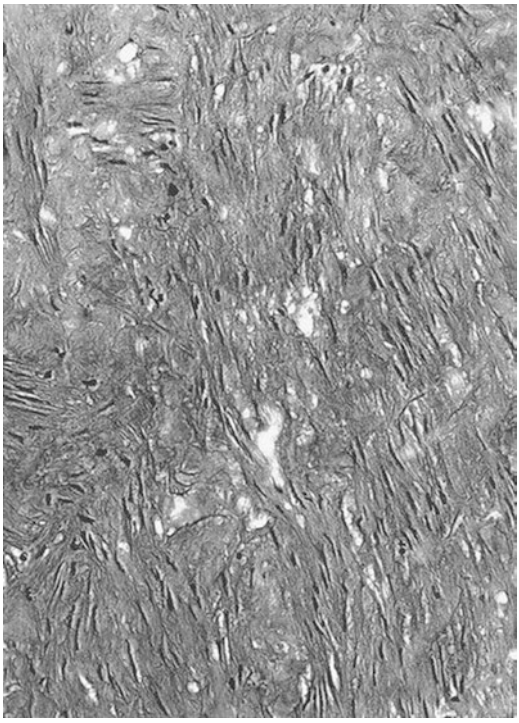


Marfan's syndrome. [Radio S, Godfrey M, Baxter T. Diseases of the aorta. In: McManus B, Braunwald E, editors. Atlas of cardiovascular pathology for the clinician. Philadelphia: Current Medicine; 2000. Chapter 17. ISBN: 1-57340-160-9; 2002-01-21]



Joint hypermobility in Ehlers-Danlos syndrome. [Maricic M, Ko M. Diseases of bone and connective tissue. In Hunder G, editor. Atlas of rheumatology. 4th ed. Philadelphia: Current Medicine; 2005. Chapter 6. ISBN: 1-57340-210-9; 2002-03-07] *Caption adapted from original*

- Hypertension, connective tissue diseases, and the aging process itself may result in cystic medial necrosis, in which degenerative changes occur in the middle layer of the aortic wall. Elastin, collagen, and smooth muscle all start to break down, potentially predisposing to the development of TAD.



Cystic medial necrosis. [Elefteriades JA. Thoracic aortic aneurysm: reading the enemy's playbook. World J Surg. 2008 Mar;32(3):366-74. https://doi.org/10.1007/s00268-007-9398-3, 2008-02-20]

- Other diagnoses associated with TAD are:
  - Congenital
    - Polycystic kidney disease

Evidence of cysts in autosomal recessive polycystic kidney disease. [Marks S, Geary DF. Nephrology. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. Chapter 17. ISBN: 1-57340-188-9, 2006-01-20] *Caption adapted from original*

- Turner syndrome

Turner syndrome. [Teebi A, Kennedy S, Chitayat D, Teshima I, Unger S, Babul-Hirji R, Shuman C, Weksberg R. Clinical genetics. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. Chapter 1. ISBN: 1-57340-188-9, 2006-01-20] *Caption adapted from original*

- Noonan syndrome

Noonan syndrome. Webbed neck and double structural curve with rib deformity evident. [From article: Rare causes of scoliosis and spine deformity: experience and particular features. Scoliosis. 2007 Oct;2(1):15. https://doi.org/10.1186/1748-7161-2-15, at http://link.springer.com/article/10.1186/1748-7161-2-15; by Konstantinos C Soultanis, Alexandros H Payatakes, Vasilios T Chouliaras, Georgios C Mandellos, Nikolaos E Pyrovolou, Fani M Pliarchopoulou, Panayotis N Soucacos, © Soultanis et al; licensee BioMed Central Ltd. 2007; licensed under Creative Commons Attribution License http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

- Osteogenesis imperfecta

Blue sclera characteristic of osteogenesis imperfecta. [Teebi A, Kennedy S, Chitayat D, Teshima I, Unger S, Babul-Hirji R, Shuman C, Weksberg R. Clinical genetics. In: Laxer R, Ford-Jones EL, Friedman J, Gerstle T, editors. The Hospital for Sick Children: atlas of pediatrics. Philadelphia: Current Medicine; 2005. Chapter 1. ISBN: 1-57340-188-9, 2006-01-20]

    - Familial aortic dissections
- Infectious:
    - syphilis

Papular lesions on the tongue in secondary syphilis. [Fiumara N. Primary and secondary syphilis. In: Rein M, editor. Sexually transmitted diseases. Philadelphia: Current Medicine; 1996. Chapter 9. (Mandell G, editor. Atlas of infectious diseases; vol. 5). ISBN: 0-443077-20-7, 2002-01-23] *Caption from original*

- Trauma:
    - Sudden deceleration injury
- Toxicologic:
    - Cocaine use
- Iatrogenic:
    - Catheter- or surgery-related aortic injury, especially near the aortic valve

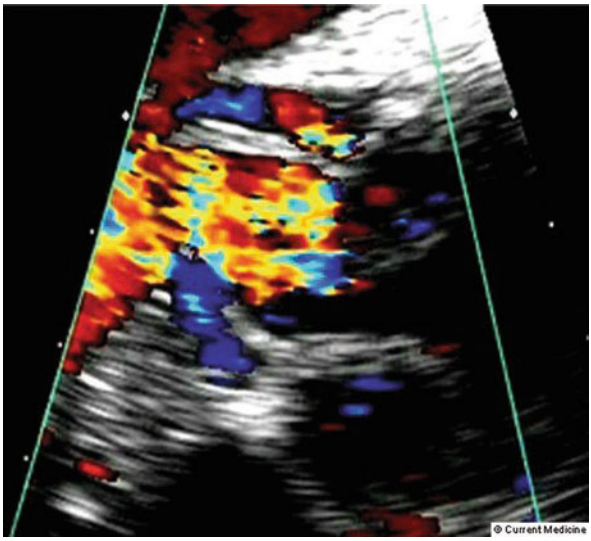
Presentation

Typical/"Classic"

- Chest pain that is often described as "ripping" or "tearing" in nature is the classic presenting symptom in TAD. Less classically, but probably more commonly, the pain is described simply as "sharp." This pain may be felt in the front and/or back of the chest; when the latter, it is classically localized between the scapulae. The pain is usually noted to move with the extension of the dissection. Patients can often identify the exact time the pain started. Other symptoms may result from occlusion of branch arteries and compression of adjacent tissues and therefore are variable. Patients are usually

hypertensive at presentation, although shock may also occur. Related signs and symptoms include:

- Syncope or stroke, when the dissection occludes the carotid arteries
  - Hemiplegia or hemianesthesia may result if just one carotid root is obstructed
- Dyspnea and a clinical picture of heart failure, when the dissection disrupts the aortic root, preventing valve closure and resulting in acute aortic regurgitation

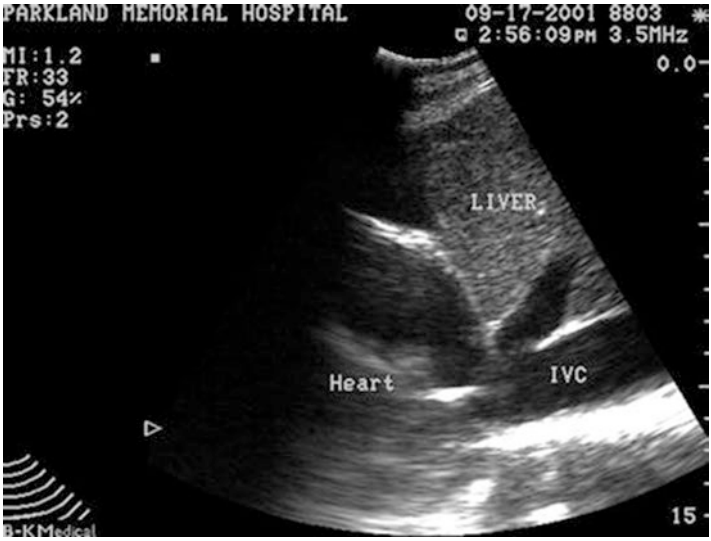


Severe aortic regurgitation from Stanford type A dissection. [Michelena H, Mankad S, Enriquez-Sarano M. Echocardiography in valvular heart disease: aortic valve disease. In: Solomon SD, Braunwald E, editors. Atlas of echocardiography. 2nd ed. Philadelphia: Current Medicine; 2008. Chapter 9. ISBN: 1-57340-217-6, 2008-10-22] *Caption from original*

- Classic signs of aortic regurgitation include a wide pulse pressure, bounding pulses, and a diastolic murmur heard best over the right sternal border.

http://www.easyauscultation.com/cases?coursecaseorder=1&courseid=27
Diastolic murmur. [Aortic Regurgitation – Mild; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Hypotension, when the dissection spills false lumen blood into the pericardial sac, resulting in pericardial effusion and tamponade



Ultrasound of acute pericardial effusion causing cardiac tamponade. [Tchorz KM. Ultrasound-guided drainage procedures for the intensivist. In: Frankel HL, deBoisblanc BP, editors. Bedside procedures for the intensivist. New York: Springer; 2010. p. 113-37. Book https://doi.org/10.1007/978-0-387-79830-1; Chapter: 6; Chapter https://doi.org/10.1007/978-0-387-79830-1_6, 2010-01-01] *Caption adapted from original*

- Check for jugular venous distension and muffled heart sounds.

- Abdominal pain, from obstruction of mesenteric arteries
- Paraplegia, from obstruction of aortic branches perfusing the spinal cord (such as the great artery of Adamkiewicz)
- Hoarseness, difficulty swallowing, or dyspnea (perhaps with stridor) from pressure on the larynx, trachea, and esophagus caused by the expanding aortic hematoma

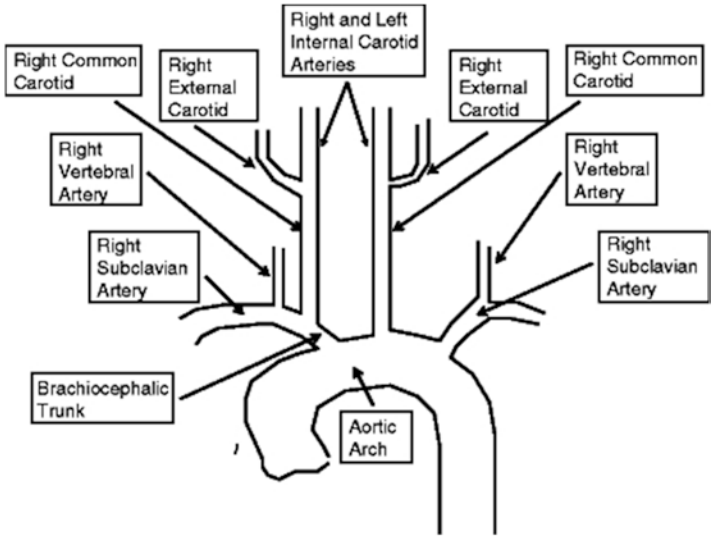
http://www.easyauscultation.com/cases.aspx?coursecaseorder=13&courseid=202
Stridor. [Stridor; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Horner's syndrome, from compression of the superior cervical ganglia caused by the expanding aortic hematoma

Left ptosis and miosis of Horner's syndrome. [Mutalib M, Vandervelde C, Varghese A, Sallomi DF, Silva P, Hickman CJM, Howlett DC. Horner's syndrome secondary to asymptomatic pneumothorax in an adolescent. Eur J Pediatr. 2007 May;166(5):507–8. https://doi.org/10.1007/s00431-006-0271-4, 2007-03-19] *Caption adapted from original*

- Horner's syndrome manifests as ipsilateral ptosis, miosis, and anhydrosis.

- Physical findings in TAD are highly variable because the location of the dissection and the direction (antegrade or retrograde) in which it extends will determine side branch involvement. If the dissection involves the aortic arch, there may be a difference in the blood pressure measured in each arm. A difference of 20 mm Hg is significant and suggestive of the diagnosis in the right clinical setting.



Anatomy of the aortic arch. [Pelberg RA, Mazur W. Vascular CT angiography manual. London: Springer; 2011. Chapter 5, Carotid and upper extremity CT

angiography; p. 47-90. Book https://doi.org/10.1007/978-1-84996-260-5; Chapter https://doi.org/10.1007/978-1-84996-260-5_5, 2010-01-01]

Atypical

- The most vexing atypical presentation of TAD is a painless presentation. This may occur in elderly people who present with syncope or stroke only. In other cases, the TAD symptoms may simply be overwhelmed by other symptoms or findings, such as stroke, shock, or myocardial infarction (if the dissection extends to the ostium of a coronary artery and causes ST-segment elevation).

Primary Differential Considerations

- Primary differential considerations include pain mimics to TAD and other significant diagnoses (such as stroke) that distract the examiner. The most concerning pain mimics that may share other symptoms associated with TAD include myocardial infarction, pulmonary embolus, aortic aneurysm, and aortic regurgitation without dissection.

History and Physical Exam

Findings That Confirm Diagnosis

- Because there are so many mimics and related multisystem complications of TAD, the diagnosis cannot be confirmed without a definitive imaging study of the thoracic aorta.

Factors That Suggest Diagnosis

- Immediate onset of sharp, ripping, or tearing pain in the presence of ST-segment elevation, syncope, stroke, dyspnea, or weakness should raise suspicion for TAD and prompt consideration of an emergent diagnostic imaging study.
- Suggestive pain with a known diagnosis (or suggestive physiognomy) of Marfan's syndrome, Ehlers-Danlos syndrome, or syphilis should raise suspicion for TAD and prompt consideration of an emergent diagnostic imaging study.

- Suggestive pain and a difference in blood pressure readings between the two arms or between the arms and the legs should raise suspicion for TAD and prompt consideration of an urgent or emergent diagnostic imaging study.
- Any of the related symptoms or findings above *in the absence of suggestive pain in elderly patients with a history of hypertension* should raise suspicion for TAD and prompt consideration of an urgent or emergent diagnostic imaging study.

Factors That Exclude Diagnosis

- A normal imaging study (via CT scan, MRI, or transesophageal echocardiogram) of the thoracic aorta excludes the diagnosis of TAD.

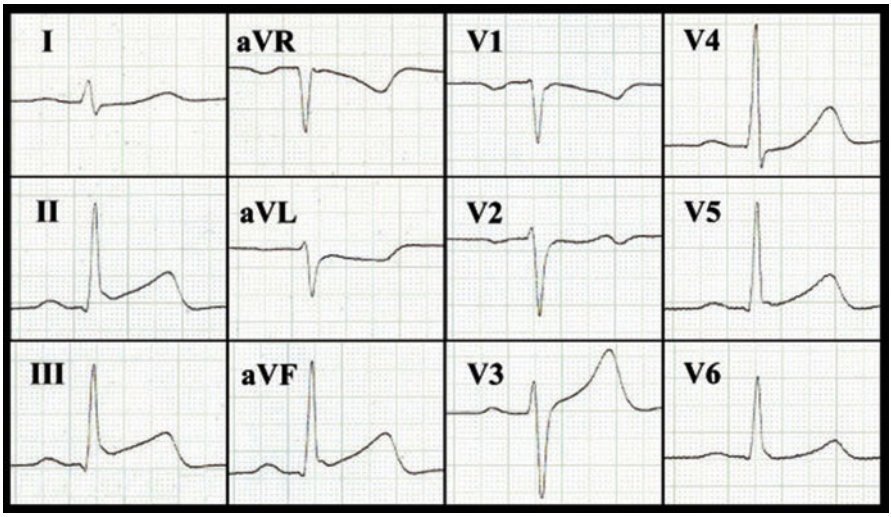
Ancillary Studies

Laboratory

- Lab tests should include CBC; serum electrolyte, blood urea nitrogen (BUN), and creatinine levels; and coagulation studies. Generally, cardiac biomarker measurements are indicated because of the differential consideration of ACS and the possibility of a retrograde dissection that occludes a coronary artery and causes myocardial ischemia.
- If TAD is the presumed or confirmed diagnosis and surgical intervention is anticipated, a type and cross-match specimen should be sent.

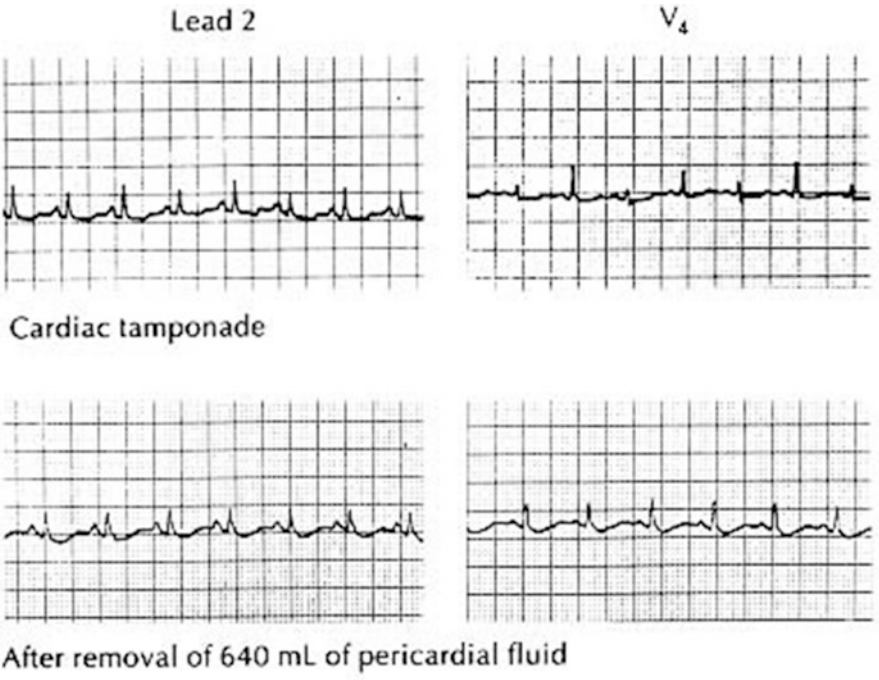
Electrocardiography

- The ECG in most patients with TAD either is normal or shows only nonspecific ST-T changes. Because many patients with TAD have a longstanding history of hypertension, the ECG may show evidence of left ventricular hypertrophy with strain.
- A small minority of patients with TAD will have evidence of STEMI (usually inferior) due to occlusion of the right coronary artery as a complication of TAD.



Twelve-lead ECG demonstrating inferiorly located STEMI with ST-segment elevation in the inferior leads (II, III, aVF) and ST-segment depression in leads I and aVL. [From article: Cardiovascular magnetic resonance of myocardial infarction after blunt chest trauma: a heartbreaking soccer-shot. J Cardiovasc Magn Reson. 2009 Oct;11(1):39. https://doi.org/10.1186/1532-429X-11-39, at http://link.springer.com/article/10.1186/1532-429X-11-39/fulltext.html; by Hannibal Baccouche, Torsten Beck, Martin Maunz, Peter Fogarassy, Martin Beyer, © Baccouche et al; licensee BioMed Central Ltd. 2009; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*

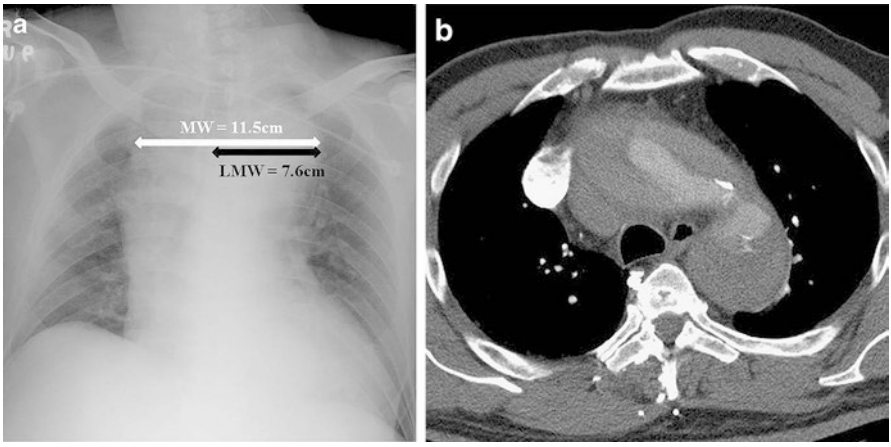
- An even smaller cohort will have ECG changes suggesting pericardial tamponade, such as low voltage or electrical alternans.



Electrical alternans of the QRS complex in a patient with cardiac tamponade. [Fowler N, Abelmann W. Chapter 13. In: Lee RT, Braunwald E, editors. Atlas of cardiac imaging. Philadelphia: Current Medicine; 1998. ISBN: 0-443-07567-0] *Caption from original*

Imaging

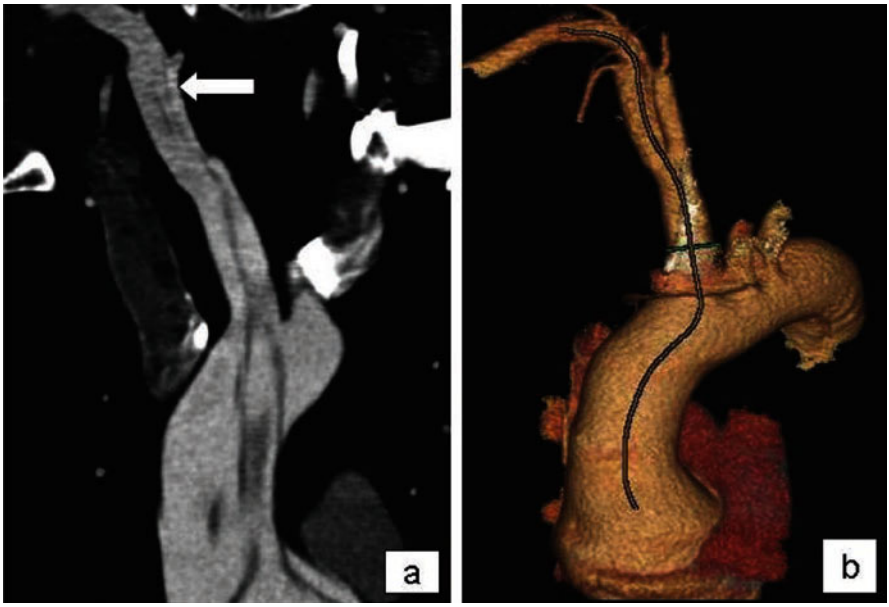
- Imaging studies are used definitively to confirm or refute the diagnosis of TAD.
- The plain chest radiograph (CXR) may suggest TAD but cannot be used to confirm or refute the diagnosis.
    - The most important finding on CXR is a widened mediastinum, which is seen in more than half the patients with TAD. Often these films are recorded with patients in the supine position because of their clinical status; this makes the mediastinum appear wider than on an erect film even in the absence of TAD.



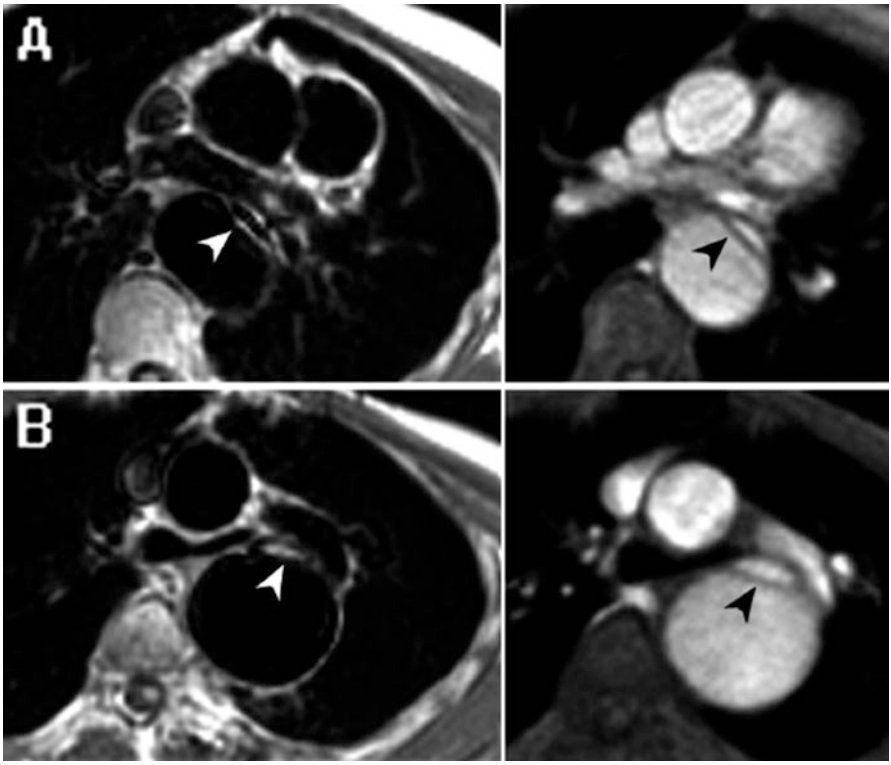
Acute type A aortic dissection in a 46-year-old man. A) AP chest radiograph showing marked widening of the mediastinum with MW and LMW measuring 11.5 and 7.6 cm, respectively. B) Corresponding selected image of CT aortogram confirms type A aortic dissection. [From article: Diagnostic accuracy of mediastinal width measurement on posteroanterior and anteroposterior chest radiographs in the depiction of acute nontraumatic thoracic aortic dissection. Emerg Radiol. 2012 Aug;19(4):309–15. https://doi.org/10.1007/s10140-012-1034-3, at http://link.springer.com/article/10.1007/s10140-012-1034-3/fulltext.html; by Vincent Lai, Wai Kan Tsang, Wan Chi Chan, Tsz Wai Yeung, © The Author(s) 2012; licensed under Creative Commons Attribution License http://creativecommons.org/licenses/by/2.0] *Caption from original*

  - Other findings suggestive of TAD that may appear on CXR include pleural effusion, inward displacement of aortic intimal calcifications, and a double aortic shadow.
  - The CXR is normal in more than 10% of cases of TAD.

- The choice of which definitive imaging study to use in suspected TAD is based on both the efficiency/availability of the test and the clinical stability of the patient. In the past, the diagnosis was made by invasive imaging (aortography). Less invasive modalities (CT, MRI, TEE) are more commonly used today. Of these, CT is the quickest and for the hemodynamically unstable or tenuous patient, is probably the safest approach. It does require iodinated contrast. CT has the additional benefit of potentially identifying another etiology of the patient's pain (such as pulmonary embolism). All three of these modalities allow classification of the TAD (Stanford or DeBakey models; See Overall Principles of Treatment), which directs the choice of medical vs surgical treatment.



A, Contrast-enhanced CT scan showing the intimal flap due to dissection from the aortic root to the ascending aorta, innominate artery and subclavian artery. B, Enhanced reconstructed CT scan image showing the path of dissection. [From article: Postoperative peri-axillary seroma following axillary artery cannulation for surgical treatment of acute type A aortic dissection. J Cardiothorac Surg. 2010 May;5(1):43. https://doi.org/10.1186/1749-8090-5-43, at http://link.springer.com/article/10.1186/1749-8090-5-43; by Efstratios E Apostolakis, Nikolaos G Baikoussis, Konstantinos Katsanos, Menelaos Karanikolas, © Apostolakis et al; licensee BioMed Central Ltd.; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption adapted from original*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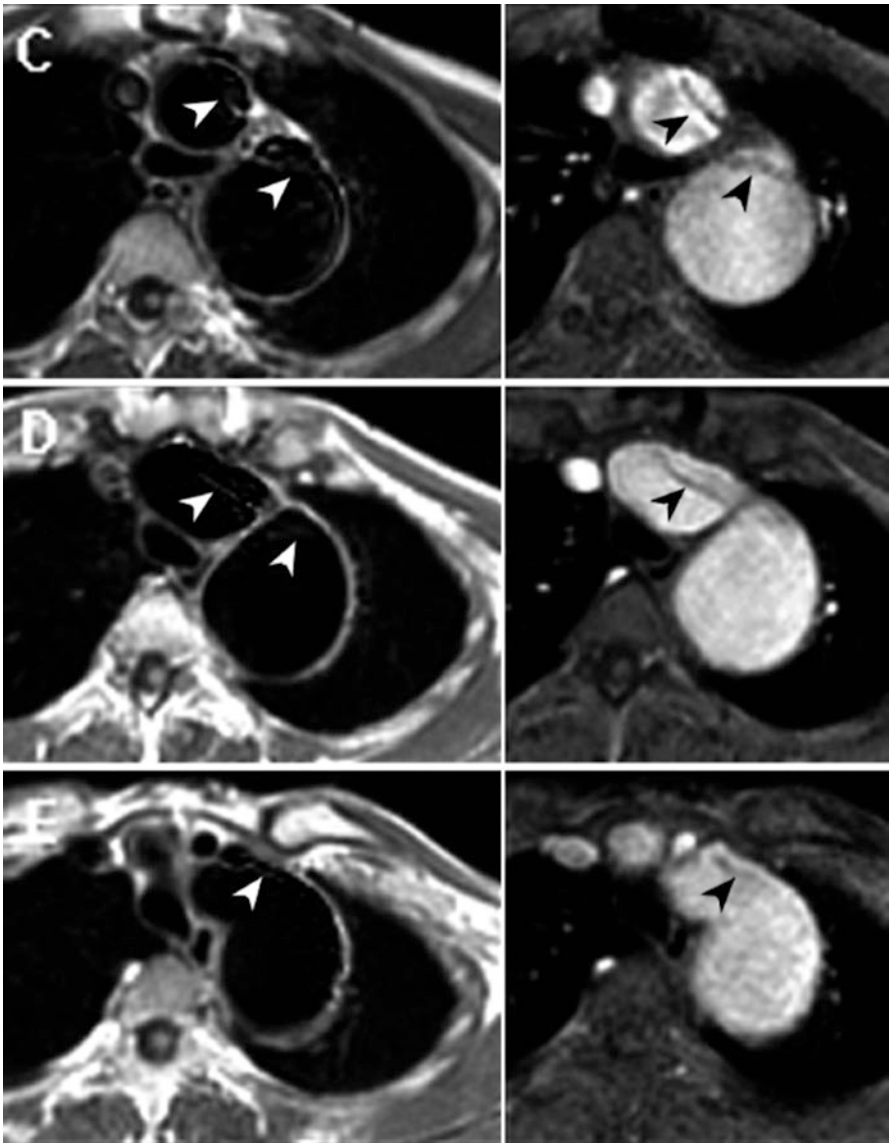
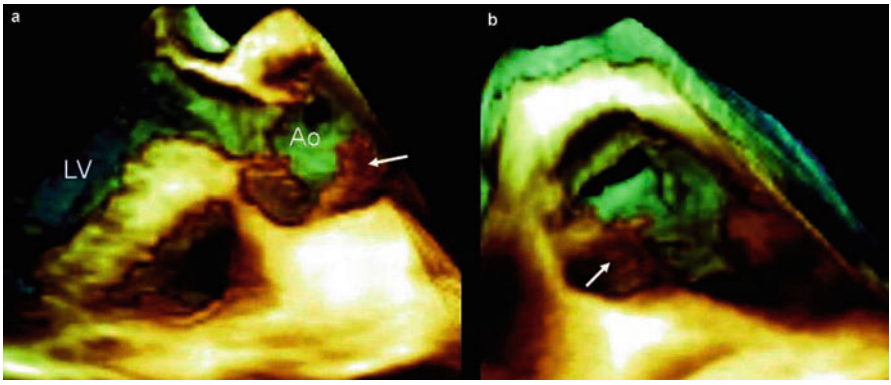


Type A aortic dissection in Marfan syndrome: the intimal flap (arrowhead) and the two channels are visible on sequential black blood (left) and bright blood cine-MRI (right) images. [Kastler B. MRI of cardiovascular malformations. Berlin Heidelberg: Springer; 2011. Chapter 6, Other aortic malformations; p. 147–75. https://doi.org/10.1007/978-3-540-30702-0] *Caption from original*



(a) RT 3D TEE image showing the dissection of the aortic wall (arrow) in longitudinal view and (b) from the aortic perspective. Ao aorta; LV left ventricle. [Faletra FF, de Castro S, Pandian NG, Kronzon I, Nesser H-J, Ho SY. The Aortic Valve and the Aorta. Atlas of Real Time 3D Transesophageal Echocardiography [Internet]. London: Springer London; 2010 [cited 2016 May 27]. p. 47–62. Available from: http://link.springer.com/10.1007/978-1-84996-083-0_4] *Caption from original*

Special Populations

Age

- TAD most commonly occurs between 50 and 65 years of age. Older patients may have less perception of the pain and more often present with stroke or syncope.
- Within the pediatric population, TAD is associated with Marfan syndrome, Turner syndrome, Ehler-Danlos syndrome, and homocystinuria.

Co-morbidities

- The most important comorbidities in TAD are hypertension and connective tissue disease.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Attributing chest pain to another, potentially less serious etiology may result in loss of valuable treatment time for TAD.
- Focusing on the sequelae of TAD—such as syncope, stroke, weakness, or dyspnea—without considering TAD as the source, may result in loss of valuable treatment time for TAD and further complications from ongoing extension of the false lumen.

Mimics

- The entire constellation of diagnoses that underlies chest pain syndrome can mimic the pain and overall presentation of TAD.

Time-Dependent Interventions

- Control of blood pressure and heart rate (the "pulse-pressure product" that creates shear stress on the aortic wall and may extend the dissection) is critical in stabilizing patients with TAD. Both alpha- and beta-adrenergic blockade is required, as reducing blood pressure alone with a potent agent such as nitroprusside will result in a reflex tachycardia that may be just as harmful as continued hypertension in promoting extension of the dissection.
- Adequate pain control (with attention to iatrogenic hypotension) is also important for reducing shear stress.

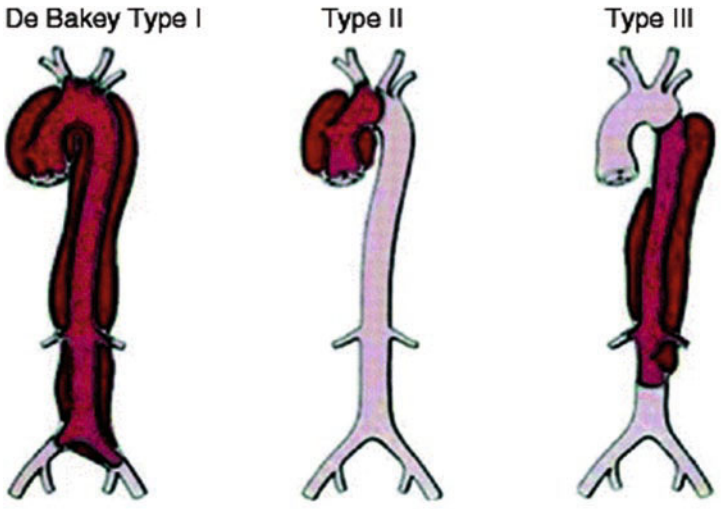
Overall Principles of Treatment

- Stabilization of the patient with control of blood pressure, pulse rate, and pain is critical. The patient may require resuscitation, intubation, and intensive support.
- Definitive treatment approaches for TAD are driven by the anatomic location of the dissection. There are two classification systems for TAD: DeBakey and Stanford. The Stanford system is simpler and more widely used: type A involves the ascending aorta, and type B does not involve the ascending aorta. In the DeBakey classification, there is involvement of the ascending aorta in types I and II but not in type III. Surgical management ordinarily is

indicated for type A (DeBakey I and II) lesions, whereas type B (DeBakey III) dissections may be managed medically or with (percutaneous) endovascular repair.

Steps in the Early Medical Management of a Patient Presenting With Suspected Acute Aortic Dissection
1. Immediate monitoring and stabilization of vital signs
2. Quick assessment: directed history, physical examination, chest radiograph, ECG, lab work
3. Reduce dP/dT with intravenous β-blockers: propranolol, labetalol, metoprolol, or esmolol
4. Treat hypertension to reduce dP/dT: intravenous nitroprusside (use in the presence of a β-blocker, because alone it may increase dP/dT); goal is to reduce systolic blood pressure to 100–120 mm Hg or the lowest level possible while still maintaining cerebral and vital organ perfusion
5. If β-blockers are absolutely contraindicated, consider using intravenous calcium channel blockers or enalaprilat
6. Pain control with morphine as needed
7. Select and proceed promptly to a diagnostic study
8. Decide on medical vs surgical therapy (and determine surgical candidacy as well)

Steps in the early medical management of a patient presenting with suspected aortic dissection. [Creager M. Vascular disease. In Libby P, editor. Essential atlas of cardiovascular disease. Philadelphia: Current Medicine; 2009. Chapter 4. ISBN: 978-1-57340-309-2, 2009-05-21] *Caption adapted from original*



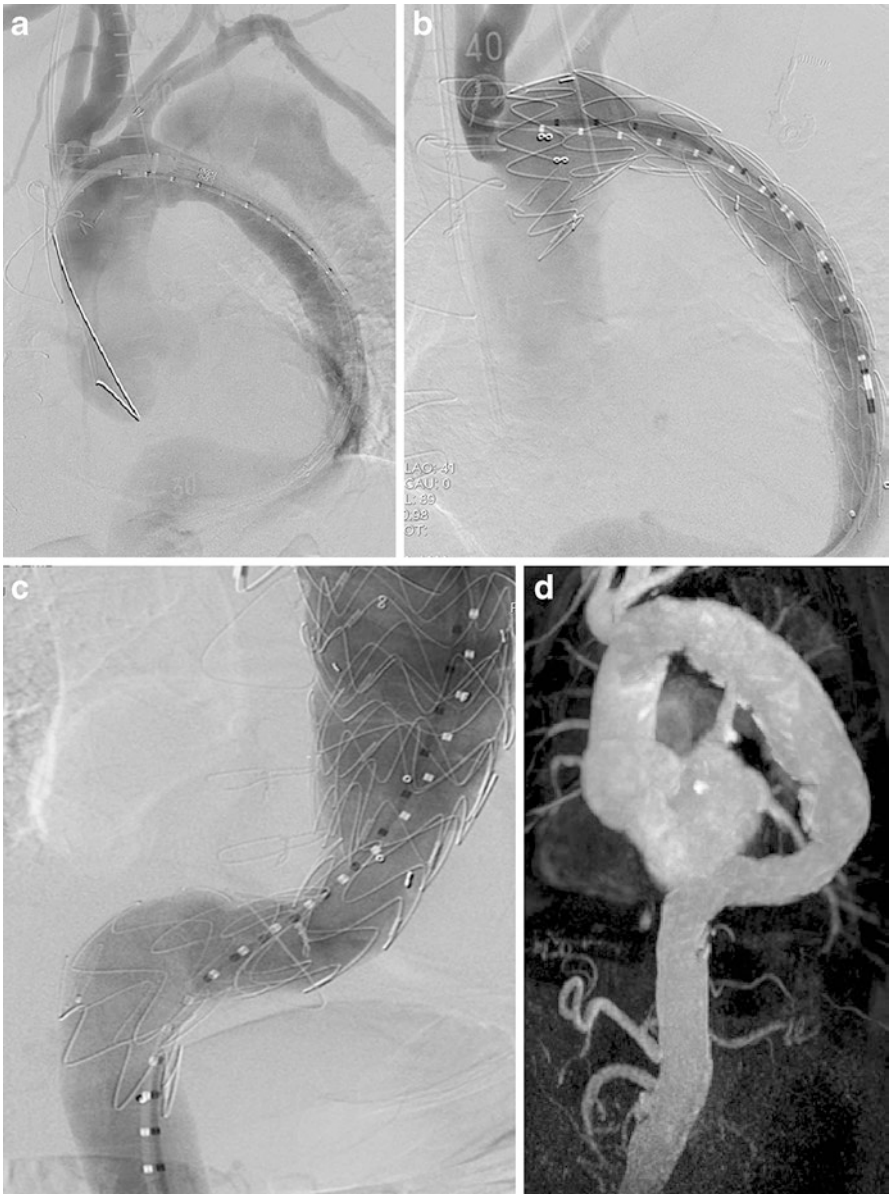
Acuity:	
Acute	<2 weeks after onset
Subacute:	2–8 weeks after onset
Chronic:	>8 weeks after onset

Anatomic location:	
Ascending aorta:	Stanford Type A, DeBakey Type II
Ascending and descending aorta:	Stanford Type A, DeBakey Type I
Descending aorta:	Stanford Type B, DeBakey Type III

Pathophysiology:

Class 1: Classical aortic dissection with initimal flap between true and false lumen
Class 2: Aortic intramural he matoma without identifiable intimal flap
Class 3: Intimal tear without hematoma (limited dissection)
Class 4: Atherosclerothic plaque rupture with aortic penetrating ulcer
Class 5: Iatrogenic or traumatic aortic dissection
(intra-aortic catherterization, high-speed deceleration injury, blunt chest trauma)

Classification of thoracic aortic dissection. [Akin I, Rehders TC, Kische S, Ince H, Nienaber CA. Endovascular treatment of thoracic aorta. In: Lanzer P, editor. Catheter-based cardiovascular interventions. Berlin Heidelberg: Springer; 2013. p. 957-70. Book https://doi.org/10.1007/978-3-642-27676-7; Chapter https://doi.org/10.1007/978-3-642-27676-7_59, 2013-01-01] *Caption from original*



Thoracic endovascular aortic repair (TEVAR) of a type B aortic dissection extending from the arch to the abdominal aorta. (A) Pre- and (B, C) post-implantation angiograms showing two stent-grafts placed from the arch, covering the left subclavian artery (LSA), to the distal descending aorta in order to treat different entry tears and the true lumen compression. (D) MRA at 1 year from the implantation: the true lumen is well expanded at the proximal and middle descending aorta,

while a smaller diameter is observed at the distal part of the vessel. [Midulla M, Moreno R, Baali A, Chau M, Negre-Salvayre A, Nicoud F, Pruvo JP, Haulon S, Rousseau H. Haemodynamic imaging of thoracic stent-grafts by computational fluid dynamics (CFD): presentation of a patient-specific method combining magnetic resonance imaging and numerical simulations. Eur Radiol. 2012 Oct;22(10):2094–102. https://doi.org/10.1007/s00330-012-2465-7, 2012-08-30] *Caption adapted from original*

Disease Course

- TAD carries a high mortality rate. Type A dissections have a 30% mortality even with surgical treatment, and twice that with medical treatment. Thrombotic complications of dissection carry their own risks of morbidity and mortality.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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PubMed Clinical Queries can provide the most recent evidence. Use this search strategy: ((“Aortic Aneurysm, Thoracic”[Mesh]) AND (“Aneurysm, Dissecting”[Mesh])) OR “thoracic aortic dissection”

Chapter 71
Total Anomalous Pulmonary Venous Connection

Richard M. Cantor, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Total anomalous pulmonary venous connection (TAPVC) is also commonly referred to as Total Anomalous Pulmonary Venous Return (TAPVR).

The basic anomaly involves a failure of all four pulmonary arteries to normally connect to the left atrium.

Electronic supplementary material The online version of this chapter (https://doi.org/10.1007/978-3-319-63895-9_71) contains supplementary material, which is available to authorized users.

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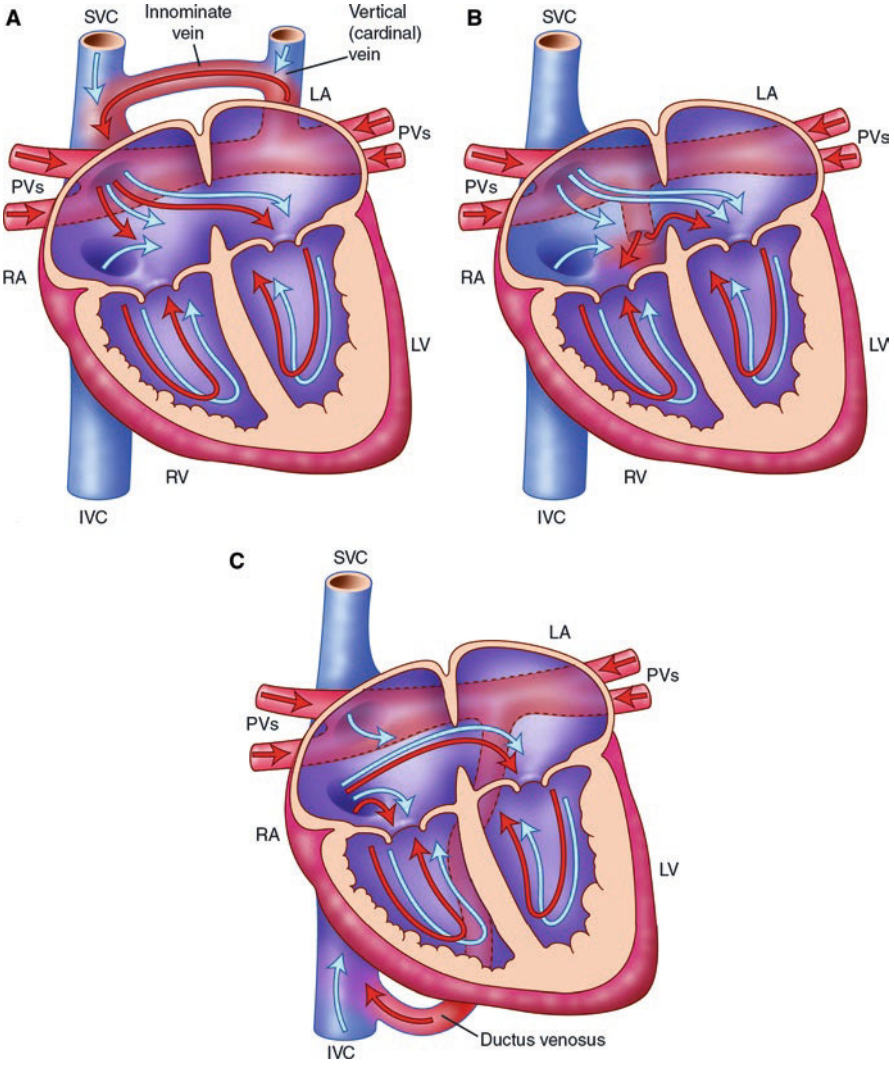
C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_71



Graphic representation of total anomalous pulmonary venous return. Panel a, supracardiac drainage. In this lesion the path of pulmonary venous drainage is from a vertical vein to the innominate vein into the right atrium (RA). In most defects an associated atrial septal defect is present. Panel b, cardiac drainage. In this pathology, the pulmonary veins (PVs) typically empty into the coronary sinus, draining into the RA. Panel c, infracardiac drainage. In this setting, PVs drain through the ductus venosus to the RA. Frequently this anomaly is associated with pulmonary venous obstruction. IVC inferior vena cava, LA left atrium, LV left ventricle, RV right ventricle, SVC superior vena cava [Miller-Hance WC, Gottlieb EA, Motta P. Anesthesia for Cardiac Surgery in Neonates. In: Lerman J, editor. Neonatal

Anesthesia [Internet]. New York, NY: Springer New York; 2015 [cited 2015 Aug 31]. p. 291–357. Available from: http://link.springer.com/10.1007/978-1-4419-6041-2_12] *Caption from original*

Incidence/Epidemiology

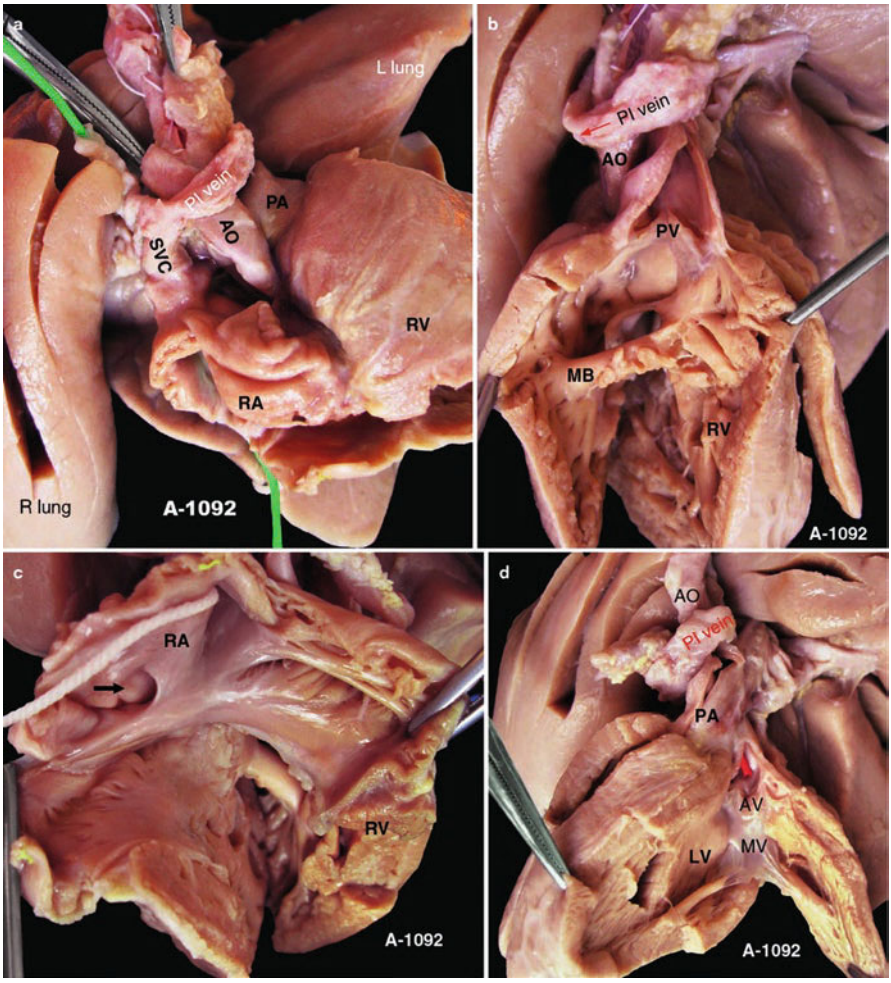
- Within the population of infants with congenital heart disease, TAPVR accounts for approximately 1 percent of newborns.
- It is the fifth-most common cause of cyanotic heart disease.

Differential Diagnosis

- Should be considered in the differential diagnosis of cyanotic congenital heart disease, often represented by the "5 T's":
  - Truncus Arteriosus
  - Transposition of the Great Arteries
  - Tricuspid Atresia
  - Tetralogy of Fallot
  - Total Anomalous Pulmonary Venous Return

Pathophysiology and Etiology

- There are four variants of this defect:
  - Supracardiac (nearly 50 %): All blood returns form the pulmonary bed to the right atrium.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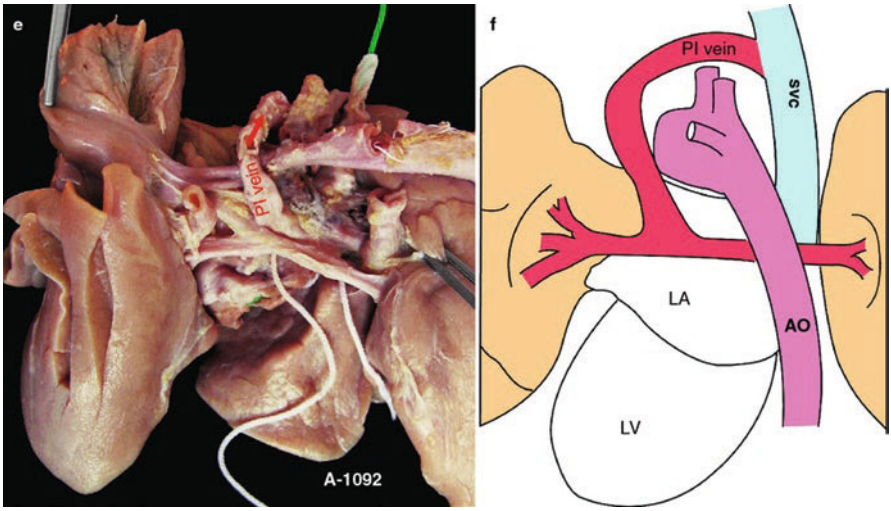
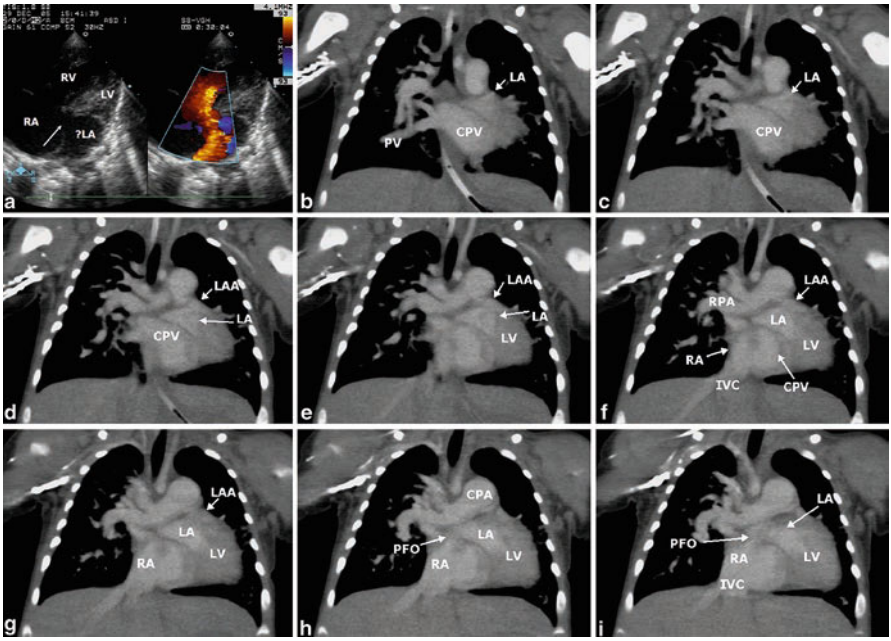


(**a**) Total anomalous pulmonary venous drainage, supracardiac type. Front view of the heart shows RA and RV cut open. At the root of the great vessels, the pulmonary vein is connected to anonymous veins and then to the SVC in front of the ascending aorta. The green probe is placed in the SVC. PI vein means that blood from the pulmonary vein flows through the anonymous vein. Ao aorta, RA right atrium, RV right ventricle, PA pulmonary artery, L lung left lung, R lung right lung. (**b**) View from the left to observe the pulmonary vein. PI vein: The pulmonary vein common trunk is connected to the anonymous vein in front of the aorta. This is the normal great artery relationship. The RV has a coarse moderator band. MB moderate band, PV pulmonary valve, RV right ventricle, AO ascending aorta. (**c**) View from right atrium and right ventricle. The arrow indicates the foramen ovale, RA right atrium, RV right ventricle. (**d**) View from left ventricle outlet tract. The left heart is normal. Red probe is in the aorta (Ao). The pulmonary vein (PI vein) originates from the left and right lungs, then passes by the aorta and returns to the SVC. LV left ventricle, MV mitral valve, PA main pulmonary vein, AV aortic valve. (**e**) Dorsal view of the heart and lung. The left and right pulmonary veins converge, then go forward and return to the SVC. The red arrow indicates the pulmonary artery blood flow. (**f**) Schematic diagram (dorsal view). PI vein means that blood from the pulmonary vein flows through the anonymous vein. LA left atrium, LV left ventricle, AO ascending aorta, SVC superior vena cava and PI vein[Zhu X. Anomalous Pulmonary Venous Drainage. In: Zhu X, editor. Surgical Atlas of Cardiac Anatomy [Internet]. Dordrecht: Springer Netherlands; 2015 [cited 2015 Aug 31]. p. 215–24. Available from: http://link.springer.com/10.1007/978-94-017-9409-1_14] *Caption from original*

- Cardiac (20 %): Pulmonary venous return connects to the coronary sinus.



A 26-day-old boy with cardiac type total anomalous pulmonary venous return (TAPVR) who presented to our hospital for evaluation of progressive dyspnoea. aEchocardiography shows a large septal defect (long arrow) between the right atrium and suspected left atrium. The initial impression was a primum-type atrial septal defect. The paediatric cardiologist also noted the unusually early heart failure and dilated right atrium and right ventricle. MDCT was undertaken for further evaluation. b–i Sequential coronal MIP images from posterior to anterior clearly demonstrate cardiac type TAPVR. The pulmonary veins drain into a large common pulmonary vein and then into the right atrium. The common pulmonary vein and left atrium are separated by a septum. The patent foramen ovale, which is necessary for survival, is also visualized (h, i). After discussion, the paediatric cardiologist believed the misdiagnosis was probably related to the limited spatial resolution of echocardiography. Even on retrospective review, the anatomical detail shown by echocardiography was not as clear as identified on MDCT (?LAechocardiography-proposed LA, but is actually a common pulmonary vein; CPA central pulmonary artery; CPV common pulmonary vein; IVC inferior vena cava; LA left atrium;LAA left atrial appendage; LV left ventricle; PFO patent foramen ovale; PV pulmonary vein; RA right atrium; RPA right pulmonary artery; RV right ventricle) [Lee T, Tsai I-C, Fu Y-C, Jan S-L, Wang C-C, Chang Y, Chen M-C. Using multidetector-row CT in neonates with complex congenital heart disease to replace diagnostic cardiac catheterization for anatomical investigation: initial experiences in technical and clinical feasibility. Pediatric Radiology. 2006 Nov 10;36(12):1273–82.] *Caption adapted from original*

- Infracardiac (30 %): Pulmonary blood return connects to parts of the portal system.
- Mixed (10 %): Return at multilevels.

- Regardless of the anatomic derangement, there is admixing of oxygenated blood with deoxygenated blood, resulting in varying degrees of cyanosis.
- Eventually, right-sided cardiac enlargement will develop in response to volume overload on a chronic basis.

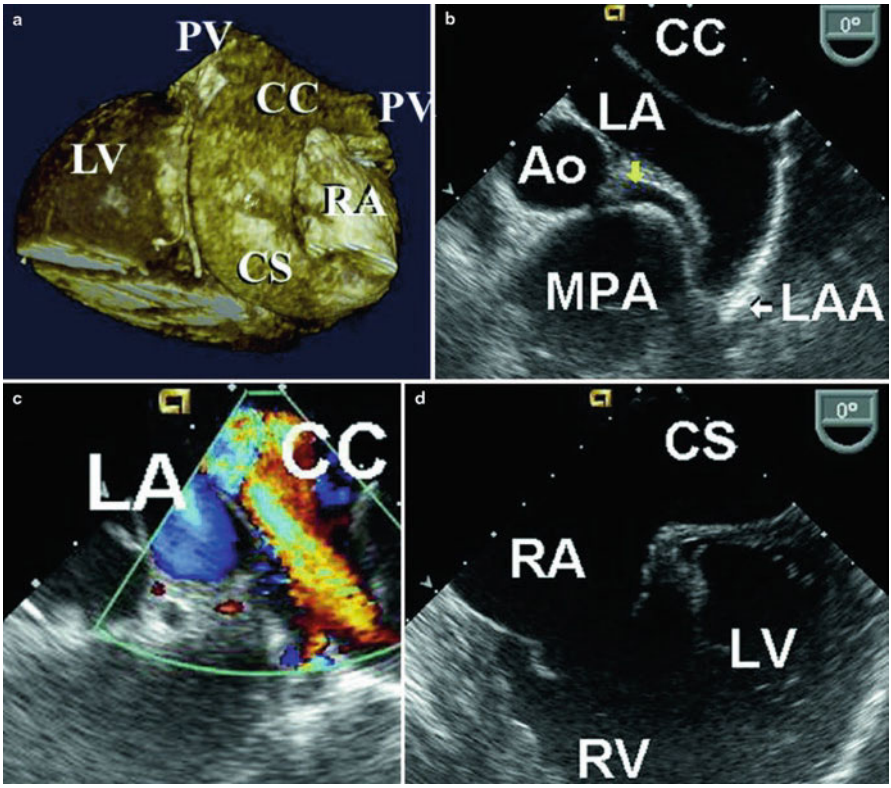
Presentation

Typical/"Classic"

- Presentations vary, depending on the degree of pulmonary venous obstruction.
- Severely obstructed infants present in the early hours after birth, with cyanosis and poor perfusion. Many of these newborns are difficult to diagnose, since premature lung disease is often considered at first.
- In infants with no or mild obstruction, presentations mimic clinical situations encountered in any patient with large volume left-to-right shunts (such as a VSD or ASD). Findings may include poor weight gain, tachycardia, and tachypnea. Oxygen saturations vary, from normal to slightly diminished.

Atypical

- As mentioned, mild cases may not present for months, until right-sided volume overload dominates.
- Older patients may present with TAPVR.



(a) Three-dimensional reconstruction of ECG gated CT angiogram in a 27-year-old cyanotic patient with uncorrected total anomalous pulmonary venous return. Two pulmonary veins (PV) connect to a posterior confluence chamber (CC) that courses inferiorly behind the left atrium (LA) into a dilated coronary sinus (CS) that in turn connects to the right atrium (RA). (b) TEE in the same patient, in the mid esophageal aortic valve short axis view with leftward probe position. Note the posterior CC closely apposing but not connected to the LA. The left main coronary artery (yellow arrow) is seen emerging from the aortic root (Ao) and coursing anterior to the left atrial appendage (LAA) and posterior to a dilated main pulmonary artery (MPA). (c) Color flow Doppler imaging demonstrating low velocity flow towards the transducer from the left sided pulmonary veins to the CC. Note the absence of flow between the CC and LA. (d) Mid esophageal four chamber view with the transducer in a more inferior position at the level of entry of the dilated CS into an enlarged RA. The right ventricle (RV) is also dilated, in comparison to the left ventricle (LV) [Aboulhosn JA, Child JS. Transesophageal Echocardiography in Adults with Congenital Heart Disease. In: Wong PC, Miller-Hance WC, editors. Transesophageal Echocardiography for Congenital Heart Disease [Internet]. London: Springer London; 2014 [cited 2015 Aug 31]. p. 455–73. Available from: http://link.springer.com/10.1007/978-1-84800-064-3_18] *Caption from original*

Primary Differential Considerations

- The other components of the 5 T's (see above) are the most important differential diagnoses to consider.

History and Physical Exam

- Assuming an uneventful neonatal course (i.e., no serious obstruction), these infants will demonstrate the signs and symptoms of progressive heart failure, including, but not limited to, poor weight gain, diaphoresis while feeding, and signs of respiratory distress.
- Heart sounds vary widely. Hepatomegaly will eventually develop.

Findings That Confirm Diagnosis

- Echocardiography remains the gold standard.

The video represents a representative sweep in an infant with total anomalous pulmonary venous connection to the left innominate vein. The exam is initiated at the midesophageal four chamber view. From this window, modified views at the level of the mid esophagus display the right upper and lower pulmonary veins (RUPV, RLPV) and left pulmonary veins (LPVs) are seen returning to a large horizontal confluence. A large vertical vein (VV) arises from the left side of the confluence and travels anteriorly and superiorly, coursing over the left pulmonary artery (LPA) to insert into the left innominate vein (Inn V). The length of the vertical vein is best seen in a sagittal plane, with the midesophageal ascending aortic and upper esophageal aortic arch short axis views, and leftward rotation of the probe. There is no obstruction at any point to pulmonary venous return. A catheter placed in the left internal jugular vein is seen in the vertical vein by two-dimensional imaging. On this video, prominent electrocautery and Doppler mirror image artifacts are seen (MPG 38454 kb) [Tacy TA. Systemic and Pulmonary Venous Anomalies. In: Wong PC, Miller-Hance WC, editors. Transesophageal Echocardiography for Congenital Heart Disease [Internet]. London: Springer London; 2014 [cited 2015 Aug 31]. p. 145–69. Available from: http://link.springer.com/10.1007/978-1-84800-064-3_6] *Caption from original*

- TAPVR should be considered in any infant who presents with cyanosis associated with pulmonary over-circulation.

Factors That Suggest Diagnosis

- TAPVR remains a difficult diagnosis.
- Since eventual echocardiography is often considered in the workup of neonatal cyanosis or CHF, the diagnosis will reveal itself.

Factors That Exclude Diagnosis

- A normal echocardiogram rules out TAPVR diagnosis.

Ancillary Studies

Laboratory

- Laboratory results will demonstrate hypoxia, acidosis, and hypercarbia in severe cases (nonspecific findings).

Electrocardiography

- ECG findings, unfortunately, are nonspecific and cannot be utilized in making the diagnosis of TAPVR.

Cardiac Enzymes

- Not indicated.

Special Populations

Age

- As discussed, most cases are diagnosed in the first few days of life.

Co-morbidities

- TAPVR is associated with asplenia or polysplenia.

Pitfalls in Diagnosis

- Cyanotic variant:
  - Pediatric cardiology consultation is emergently warranted.
- Acyanotic variety:
  - Adherence to strict algorhythmic workups of neonatal CHF or respiratory distress will eventually uncover the lesion.

Critical Steps Not to Miss

- Provision of supplemental oxygen
- Early ventilator support
- Immediate PICU or Pediatric Cardiology consultation

Mimics

- Any congenital cardiac lesion causing cyanosis and/or CHF.

Time-Dependent Interventions

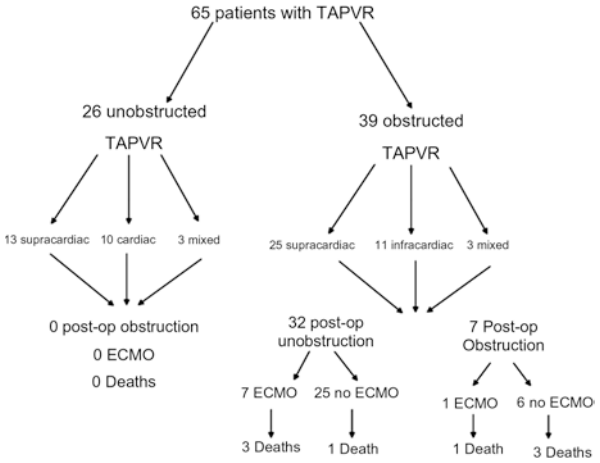
- All interventions are emergent.

Overall Principles of Treatment

- Surgical repair of TAPVR is required; catheter-based treatments have not been shown to be effective. The timing of surgery varies by case.

Disease Course

- Surgical correction is almost always indicated – the earlier the better.



Surgical outcome. The flow chart summarizes the outcome of the cohort presenting for surgical repair of total anomalous pulmonary venous return (TAPVR) at Children's Hospital of Wisconsin from 1991 to 2007 [Frommelt PC, Sheridan DC, Deatsman S, Yan K, Simpson P, Frommelt MA, Litwin SB, Tweddell JS. Unobstructive Total Anomalous Pulmonary Venous Return: Impact of Early Elective Repair on the Need for Prolonged Mechanical Ventilatory Support. Pediatric Cardiology. 2010 Nov;31(8):1191–7.] *Caption from original*

- Long-term outcomes are dramatically improved after full correction (less than 5 %).

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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"Scimitar Syndrome"[Majr] OR "pulmonary venous return anomaly"[tiab] OR "TAPVR"[tiab] OR "anomalous pulmonary venous return"[tiab] OR "anomalous pulmonary venous connection"[tiab] OR "scimitar syndrome"[tiab] OR "scimitar anomaly"[tiab]

Chapter 72
Tracheal Tumors

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Tracheal Tumors

Incidence/Epidemiology

- Tracheal tumors are very rare. They account for only 2 % of all tumors of the respiratory tract.
- Tracheal tumors account for less than one-half of one percent of all malignant tumors.
- Tumors found in the tracheae are more commonly seen from direct extension of primary lung cancer.
- Metastatic lesions in the trachea arising from non-pulmonary cancers are rare.
- Tracheal tumors have an estimated annual incidence of 0.1/100,000 people per year.
- Tracheal tumors are exceptionally rare in children. Most tracheal tumors in children are benign.
- The majority of tracheal tumors in adults are malignant (80–90 %).

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_72

- Squamous cell carcinoma (SCC) accounts for up to two-thirds of all tracheal malignancies.
  - SCC is more common in older adults (>60), has a significant male predominance, and is almost always associated with cigarette smoking (90 %).
- Adenoid cystic carcinoma (ACC/cylindroma) accounts for 10–15 % of all tracheal malignancies.
  - ACC is more common in younger age groups (40 and up), and has equal distribution between genders.

Differential Diagnosis

- Tracheal tumors are frequently misdiagnosed as adult-onset asthma. Pulmonary function tests (PFTs) in both may show a similar obstruction pattern. The diagnosis of tracheal tumor should be considered in any patient diagnosed with adult-onset asthma who doesn't respond or worsens despite usual treatment with steroids and bronchodilators.
- The most common symptoms of tracheal tumors are cough and dyspnea, so the differential can be very broad, and includes all the causes of cough and dyspnea such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), pneumonitis, interstitial lung disease (ILD), congestive heart failure (CHF).
- Tracheal tumors can also be initially misdiagnosed as invasive thyroid cancers.

Pathophysiology and Etiology

- Tumors of the trachea can be primary (arising from tracheal tissue), secondary (metastatic from other tissues), or from direct invasion from tumors arising in other contiguous structures.
- The majority (about 80 %) of primary tracheal tumors in adults are malignant.
- Malignant tumors of the trachea include the following cell types.
  - Squamous Cell Carcinoma (SCC). Squamous cell carcinomas account for up to two-thirds of all malignant tracheal tumors. They are pathologically identical to SCC of the lung. They are predominately related to cigarette smoking. There is a male predominance, and most cases occur in those over age 60.

    - SCC are rapid-growing tumors. About half are not amenable to surgical removal when diagnosed.
  - Adenoid Cystic Carcinoma (ACC) has also been called cylindroma. These account for about 10–15 % of malignant tracheal tumors. They arise from bronchial/salivary glandular tissue. These occur about a decade earlier than SCC (in 40's and up), are not associated with cigarette smoking, and occur equally in men and women.
    - ACC grow more slowly than SCC and are usually more amenable to surgical removal.
  - Others. Mucoepidermoid carcinoma, non-small cell bronchogenic cancer, sarcomas, and carcinoid tumors can occur primarily in the trachea, but all are very rare.
- Benign tumors of the trachea also occur. These include chondromas, hemangiomas, hamartomas, neurogenic tumors, granular cell tumors, and squamous papillomas.
  - Chondromas are the most common (but still very rare) non-malignant tracheal tumors. They arise from the tracheal rings. These do have metastatic potential.
  - Papillomas. These are usually associated with infection from human papilloma virus (HPV) types 6 and 11. They commonly arise in areas of prior tracheal injury (tracheotomy sites). They have a tendency to extend down into the lungs, instead of out into the tracheal lumen, making them difficult to diagnose until they are large. Malignant transformation is possible.

Presentation

Typical/"Classic"

- As noted above, tracheal tumors are very uncommon, so there is no "classic" presentation.
- The two most common symptoms of tracheal tumors are cough and dyspnea.
- Other symptoms that can be seen include wheezing, stridor (when the mass is large and nearly obstructing), hoarseness (when the recurrent laryngeal nerve is involved), hemoptysis (more common with SCC) and dysphagia (from external compression of the esophagus).
- As these symptoms are non-specific and frequently seen with much more common diagnoses (asthma, chronic bronchitis, COPD, CHF, etc.), the diagnosis of a tracheal tumor may not have even been considered in the initial differential diagnosis.

- It is important to consider the diagnosis in a patient diagnosed with adult-onset asthma, especially when they are not responding appropriately to usual treatment.
- These tumors are usually large at diagnosis. They don't usually cause symptoms until the tracheal lumen is narrowed by at least 75 %.

Atypical

- As tracheal tumors are uncommon, all presentations could be considered atypical.
- Many patients will have the diagnosis considered only when an imaging study performed for other reasons shows a tracheal mass.

Primary Differential Considerations

- Patients with tracheal tumors may present with symptoms suggestive of other diagnostic considerations, including but not limited to:
  - Tuberculosis and other infectious masses
  - Inflammation
  - Scar tissue

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that can confirm the diagnosis.
- The diagnosis is generally confirmed by imaging or direct visualization by bronchoscopy.

Factors That Suggest Diagnosis

- It is important to consider the diagnosis in a patient diagnosed with adult-onset asthma.
- The diagnosis should also be considered in a patient with a significant smoking history and with cough and dyspnea.
- Inspiratory stridor that worsens with recumbency can be a clue to an obstructing lesion of the trachea.

Factors That Exclude Diagnosis

- There are no historical or physical examination findings that can exclude the diagnosis.
- The diagnosis can only be excluded by a normal bronchoscopic examination.

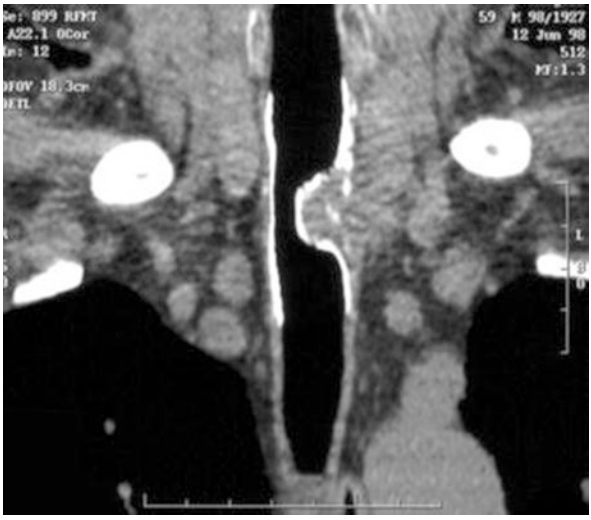
Ancillary Studies

Laboratory

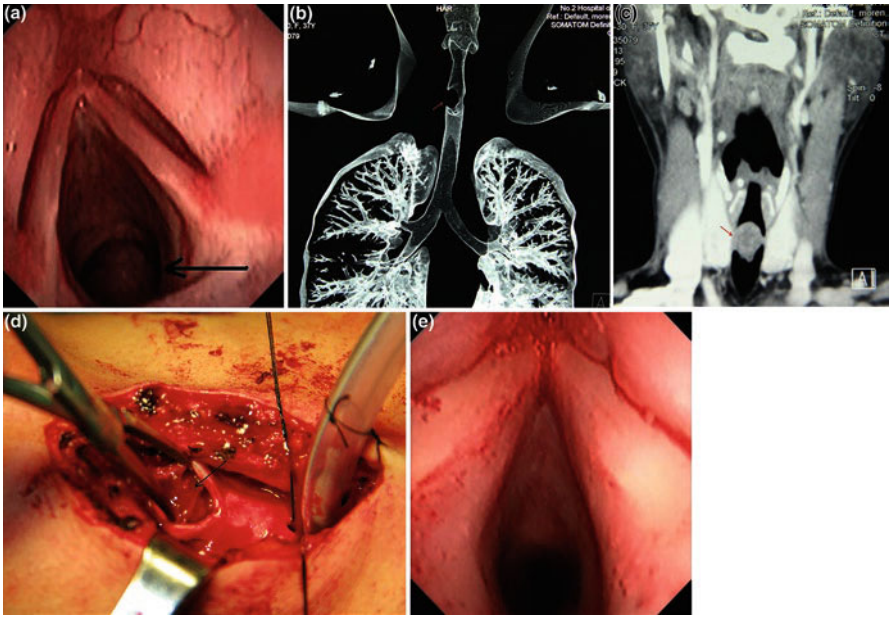
- Laboratory studies are not helpful in the diagnosis of tracheal tumors.

Imaging

- Plain chest x-ray (PA and lateral) will show an abnormality in only about 25 % of cases.
- Computed tomography (CT) of the chest and trachea is the imaging study of choice for the diagnosis of tracheal tumors. Appearance on CT may be able to help distinguish benign from malignant lesions.



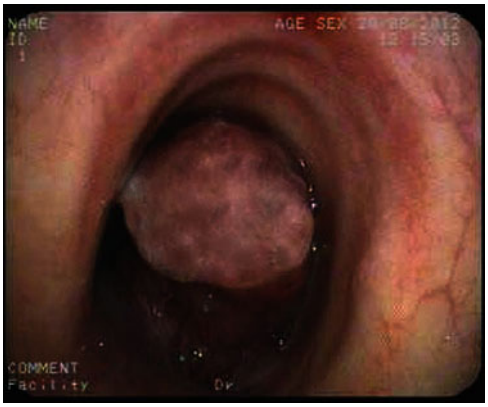
A 59-year-old man with upper tracheal squamous cell carcinoma. [Ferretti GR, Kocier M, Calaque O, Arbib F, Righini C, Coulomb M, Pison C. Follow-up after stent insertion in the tracheobronchial tree: role of helical computed tomography in comparison with fiberoptic bronchoscopy. Eur Radiol. 2003 Feb 7;13(5):1172–8.] *Caption adapted from original.*



a Female, 37 years old, with tracheal adenocystic carcinoma which is located beneath the annular cartilage under tracheobronchoscope (the black arrow). b 3-D CT scan frontal image reconstruction shows there is a tracheal tumor presenting an

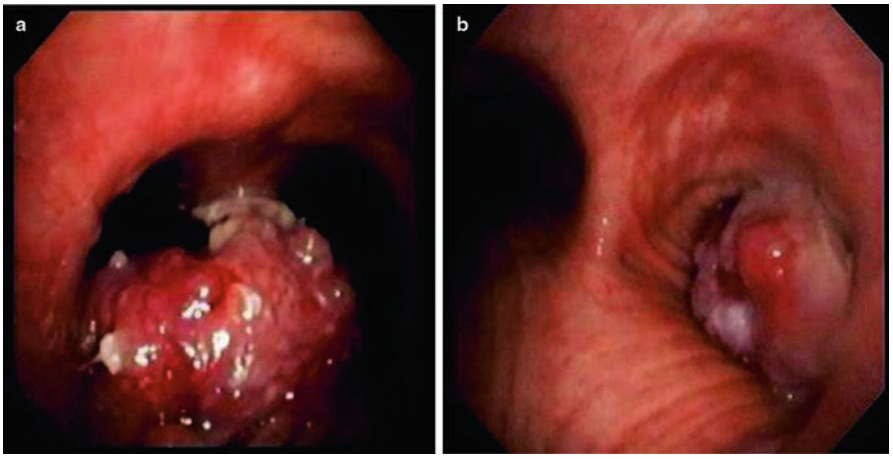
irregular filling defect inside the trachea cavity (the red arrow). c 3-D CT scan image reconstruction shows the tracheal tumor is a nodular round tumor protruding inside the tracheal cavity with an even density and a smooth border. Its narrow base is connected to the tracheal wall. There is no increase in the thickness of the tracheal wall (the red arrow). d After the first tracheal rings were incised, there is a tumor protruding into the tracheal cavity from the tracheal wall on the right, and there is no increase in the thickness of the wall (the black arrow). e Electronic fiberoptic bronchoscopy shows that the tracheal wall is smooth and there is no stenosis of the first tracheal rings after postoperative radiotherapy [Li Y, Peng A, Yang X, Xiao Z, Wu W, Wang Q. Clinical manifestation and management of primary malignant tumors of the cervical trachea. European Archives of Oto-Rhino-Laryngology. 2014 Feb;271(2):225–35.] *Caption from original.*

- Bronchoscopy (either flexible or rigid) is currently considered the gold standard test for the diagnosis and evaluation of tracheal tumors. Not only can the tumor be directly visualized, tissue biopsy can be done to allow for pathologic examination and cell typing.

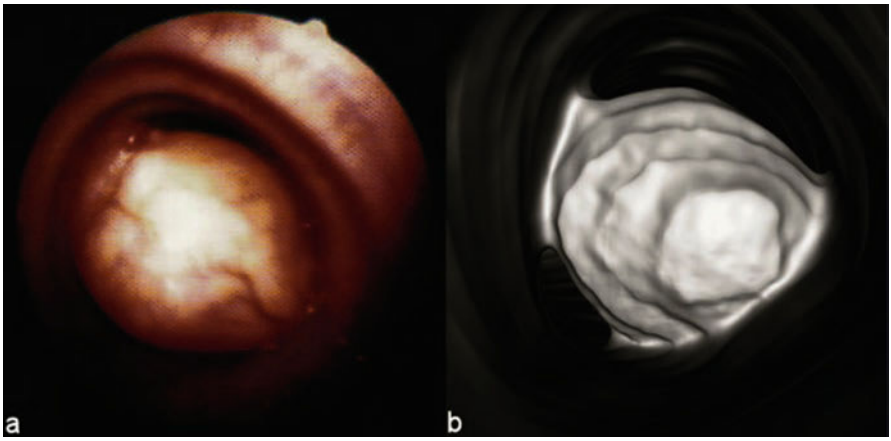


Bronchoscopy showing broad based pedunculated intraluminal tracheal mass which markedly narrow the lumen [Sukumaran R, Nair RA, Jacob PM, Koshy SM, Mathew AP. Extramedullary Plasmacytoma of the Trachea. Head and Neck Pathology. 2014 Jun;8(2):220–4.] *Caption from original.*

Fiberoptic bronchoscopy showed a submucosal tracheal tumor (arrow). [From article: About a submucosal tracheal tumor. World Journal of Surgical Oncology. 2013;11(1):229. https://doi.org/10.1186/1477-7819-11-229, at http://link.springer.com/article/10.1186/1477-7819-11-229; by Mounia Serraj, Marouane Lakranbi, Jamal Ghalimi, Yassine Ouadnouni, Siham Tizniti, Mohamed Smahi, © Serraj et al.; licensee BioMed Central Ltd. 2013; licensed under Creative Commons Attribution License BY 2.0 http://creativecommons.org/licenses/by/2.0] *Caption from original.*



(a) Tracheal tumor obstructing left mainstem bronchus. (b) Right upper lobe tumor obstructing the right mainstem bronchus [Gorden JA. Rigid Bronchoscopy. In: Ernst A, Herth FJ, editors. Principles and Practice of Interventional Pulmonology [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Dec 4]. p. 285–95. Available from: http://link.springer.com/10.1007/978-1-4614-4292-9_27] *Caption adapted from original.*



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- Positron emission tomography (PET/CT). This is often done to help "stage" the disease and to help make treatment decisions.

Special Populations

Age

- Tracheal tumors are very rare in children. When found they are almost universally benign. They can include papillomas, hemangiomas, and granular cell tumors.

Co-morbidities

- A large majority of the patients with SCC of the trachea are smokers, so they often have co-morbidities (COPD, coronary disease, CHF) that can make the diagnosis more difficult. Many of these patients will have the diagnosis considered when an imaging study performed for other reasons shows a tracheal mass.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- It is critical to consider the diagnosis in any patient diagnosed with adult-onset asthma.
- Patients diagnosed with adult-onset asthma should probably have a chest CT as part of their evaluation to exclude competing diagnoses.
- It is important to remember that "all that wheezes is not asthma."

Mimics

- Adult-onset asthma is the most significant mimic of tracheal tumors.
- Chronic bronchitis can also mimic tracheal mass lesions.

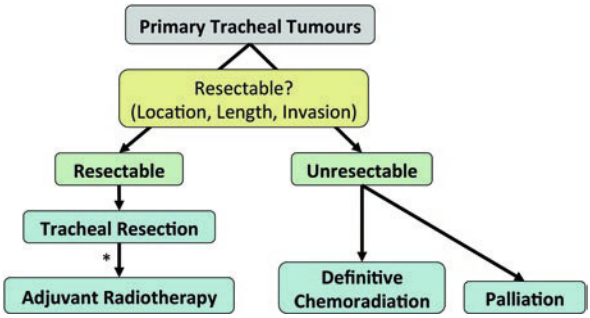
Time-Dependent Interventions

- In patients who present with respiratory distress, it is helpful to start humidified oxygen and avoid the recumbent position. It may be helpful to also use heliox (a mixture of helium and oxygen) to aid with ventilation. Some patients may benefit from tracheal stents or bronchoscopic laser ablation as bridges to surgery or for palliation of symptoms.

Overall Principles of Treatment

- The primary treatment for tracheal tumors is surgical resection.
  - Resectability is decided based upon the physical characteristics of the tumor (such as how much of the trachea is involved, how large the tumor is, and whether there is evidence of spread/metastases.
  - SCC's are usually rapidly growing tumors that metastasize early in their course. Only about one-half of SCC's are amenable to surgical removal when diagnosed.
- As these are rare tumors, there are few clinical trials to help guide treatment; most treatments are guided by expert opinion.
- Because they are so uncommon, there is no validated staging system for any of these tumors.

- Radiation therapy (RT) is often used after surgical resection, especially if the surgical margins were positive, or if the tumor could only be incompletely resected.
- Chemotherapy is often used (usually combined with RT) in unresectable tumors, but there are no good clinical trials documenting benefit.



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- Bronchoscopy with laser ablation may be helpful in alleviating symptoms in tumors not amenable to resection, and to control symptoms prior to surgery.
- Non-malignant tumors are also usually treated primarily surgically. Papillomas may respond to bronchoscopic laser ablation, but the treatment may need to be repeated several times. Some papillomas may respond to intralesional injection of cidofovir.

Disease Course

- The five-year survival rate for resectable SCC is about 39 %.
- The five-year survival rate for unresectable SCC is 7 %.
- The five-year survival rate for ACC is about 50 %.
- Benign tumors of the trachea that can be surgically repaired should not recur.
- The only non-malignant tumor associated with long-term complications is the papilloma associated with HPV. It may require numerous endoscopic-guided procedures and treatments and can lead to an increased incidence of tracheal stenosis and tracheomalacia from recurrent "injury" to the trachea. It is important to start treatment only for symptomatic lesions to avoid all unnecessary tracheal injury.

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Chapter 73
Tracheomalacia

Christopher J. Rees, Charles V. Pollack, Jr., and Jaime Friel Blanck

Name and Synonyms

Tracheomalacia/Tracheobronchomalacia

Incidence/Epidemiology

- The incidence and prevalence are unknown.
- Acquired tracheomalacia (TM) seems to be more common in men over the age of 40.
- The estimated incidence of primary TM in children is one in 2,100 births.

Differential Diagnosis

- The predominant symptoms and signs of TM in adults are dyspnea and cough, so the differential includes all diseases associated these complaints.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_73

- This includes asthma, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), cigarette smoking, chronic aspiration, gastroesophageal reflux disease (GERD), interstitial lung disease (ILD), and others.

Pathophysiology and Etiology

- Tracheomalacia (TM) is the term used to describe tracheal weakness. This weakness can be focal/segmental (confined to small lengths of the trachea) or diffuse (involving long portions of the trachea.) When the weakness extends into one or both mainstem bronchi, the term tracheobronchomalacia (TBM) is often used. The disorders are similar and share symptoms, pathophysiology, and treatment, so the following discussion will relate to both, and will be referred to as TM.
- The physiologic result of the tracheal cartilage and surrounding connective tissue weakening is exaggerated luminal narrowing during expiration, and excessive widening during inspiration.
- The trachea can completely collapse during periods of increased expiratory flow, such as coughing and crying (in infants and children).
- The severity appears to be related to the length of the involved segment and the degree of narrowing.
    - TM is generally classified as primary or acquired. Acquired TM is much more common in adults.
        - Congenital TM usually presents in childhood.
            - TM in children more commonly involves the distal third of the trachea and is associated a congenital abnormality.
            - These congenital abnormalities include:
                - Cardiovascular abnormalities (vascular rings, anomalous innominate artery)
                - Developmental delay
                - Severe GERD
                - Tracheoesophageal fistula
                - Esophageal atresia
        - Idiopathic giant trachea is a type of congenital TM that presents in adulthood. It is due to atrophy of the longitudinal elastic fibers and thinning of the muscularis mucosa of the trachea. There is diffuse tracheomegaly. When the process extends into the central bronchi, it is called, Mounier-Kuhn Syndrome. These are exceedingly rare conditions.

- Acquired TM. Acquired TM is more common in adults. There are many causes.
  - Prolonged endotracheal intubation and tracheostomy can lead to tracheal cartilage destruction and usually segmental tracheomalacia.
  - Other causes of direct tracheal injury that can lead to cartilage destruction include direct chest trauma and surgery such as lung transplantation.
  - Chronic compression from extrinsic masses can also lead to cartilage destruction. This can result from vascular compression from aortic aneurysms, vascular rings, malignancies, goiter, and other mediastinal mass lesions.
  - Recurrent cartilaginous inflammation from relapsing polychondritis can cause cartilage injury and destruction leading to tracheomalacia.
  - Recurrent tracheobronchial infections (especially associated with cystic fibrosis and COPD) can lead to tracheomalacia.
  - Prolonged exposure to known airway irritants (tobacco smoke, chronic GERD with aspiration) can also be associated with tracheomalacia.

- Appearance of the trachea: Some patients have predominantly posterior tracheal wall weakness and this results in a crescent-shaped trachea. Other patients have lateral wall tracheal weakness, resulting in a fissure-shaped trachea.
- Distribution: Segmental vs. diffuse distribution of weakness. This classification is important for guiding treatment.

Presentation

Typical/"Classic"

- The predominant symptoms and signs of TM in adults are dyspnea, cough, and sputum retention.
- The disease tends to be slowly progressive and goes through a prolonged asymptomatic period.
- As the disease progresses and symptoms develop, they may only be noticed first during periods of physiologic stress such as infections and while undergoing general anesthesia.
- Dyspnea tends to be less associated with exertion and more with maneuvers that force expiration, such as coughing, valsalva, and a recumbent position.

- Coughing can occur in severe paroxysms and be associated with expiratory wheezing or stridor. The wheezing with asthma and COPD tends to be inspiratory or both inspiratory and expiratory, and the presence of purely expiratory wheezing may be a subtle clue to the diagnosis.
- The symptoms and signs of TM are very nonspecific and can be seen with multiple other diseases, such as asthma, COPD, and CHF.
- Infants with TM are often noted to have expiratory stridor (sometimes called laryngeal crow) within the first few weeks of life. The stridor tends to be worsened and exacerbated by crying, supine position, and feeding.
- Infants may also be noted to have feeding difficulties, e.g., coughing and choking while feeding.

https://www.youtube.com/watch?v=X7xgW5-AFUw
Audio of infant with tracheomalacia.

https://www.youtube.com/watch?v=DFqL3bFQpTE&list=PLRr91eakaLBZvq7dUGWiXlhLRME0SDr3Y
Audio of stridor associated with laryngomalacia, tracheomalacia, and bronchomalacia.

Atypical

- As noted above, the symptoms and signs of TM can be very nonspecific.
- Initial symptoms may be thought to be caused by many other conditions.
- Patients may be noted to have recurrent pulmonary infections due to the inability to clear their sputum.
- When TM develops in the presence of other conditions, the symptoms of dyspnea and cough may seem to be worse than what would be predicted by the severity of the underlying condition.
- Some patients may present with cough syncope.

Primary Differential Considerations

- Patients with tracheomalacia may present with signs and symptoms of other diagnostic considerations, including but not limited to:
  - Laryngomalacia
  - Laryngeal cysts
  - Vocal cord paralysis

History and Physical Exam

Findings That Confirm Diagnosis

- There are no historical or physical examination findings that can confirm the diagnosis.
- The diagnosis can only be confirmed by appropriate findings (airway collapse upon forced expiration) on bronchoscopy.

Factors That Suggest Diagnosis

- The diagnosis can be suspected when a patient presents with a chronic cough or dyspnea that can be related historically or on exam to forced expiratory maneuvers such as coughing and valsalva.
- Predominantly expiratory wheezing should suggest the diagnosis.
- Early symptoms may only be noted during periods of physiologic stress, such as infections, and while undergoing general anesthesia.

Factors That Exclude Diagnosis

- There are no historical or physical examination findings that can completely exclude the diagnosis.

Ancillary Studies

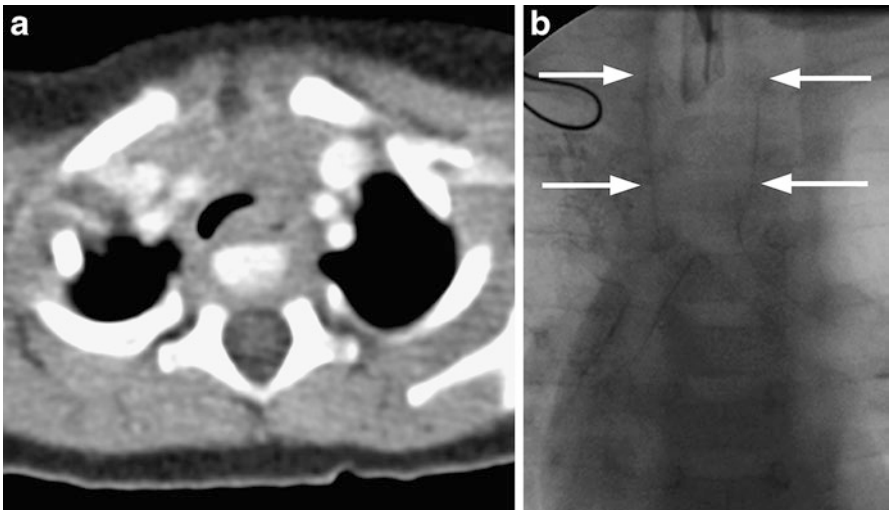
Laboratory

- Laboratory studies are generally not helpful in the diagnosis of TM.

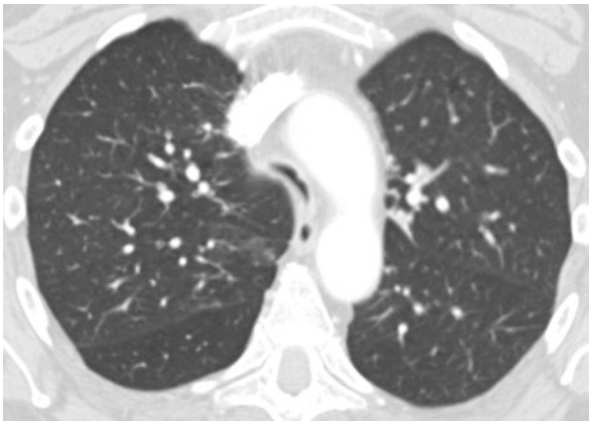
Imaging

- Chest x-ray. Plain chest x-ray is generally not helpful in the diagnosis of TM. The CXR may help if TM is caused by compression from other processes (goiter, mass, aneurysm, etc.).

- Chest CT. Chest CT can be helpful in the diagnosis and evaluation of TM. Ultrafast, multidetector CT performed both normally, and then under forced expiration or cough can document airway collapse. Airway collapse can even be quantified and used to help guide treatment decisions. Chest CT can also help diagnose the cause of acquired TM.

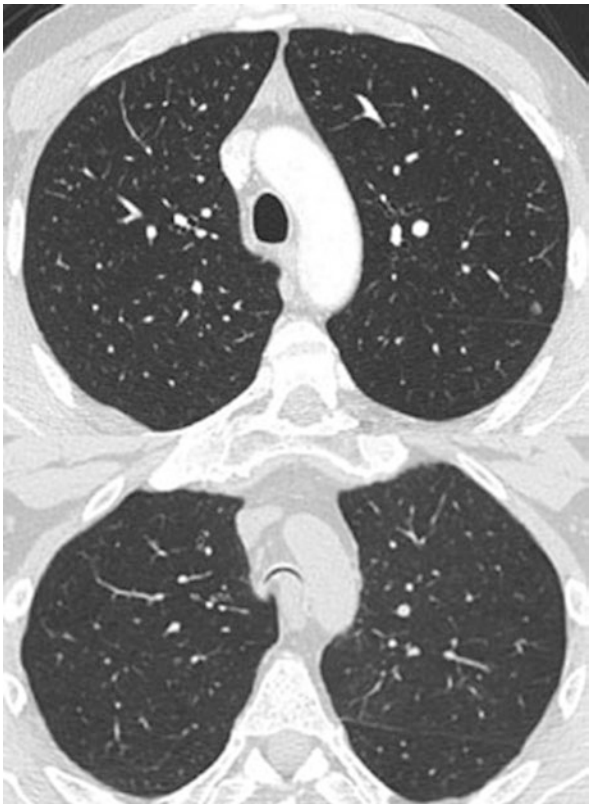


a. Axial CT shows anteroposterior narrowing of the upper trachea suggesting tracheomalacia (W 412, L 55). b. Massive tracheal dilatation is seen at bronchography with only 5 cmH2O CPAP (arrows) [McHugh K, Afaq A, Broderick N, Gabra HO, Roebuck DJ, Elliott MJ. Tracheomegaly: a complication of fetal endoscopic tracheal occlusion in the treatment of congenital diaphragmatic hernia. Pediatric Radiology. 2010 May;40(5):674–80.] *Caption from original.*



CT scan of the chest of a 57-year-old man with severe tracheomalacia demonstrating the "frown sign" [Maldonado F, Tomassetti S, Ryu JH. Orphan Tracheopathies.

In: Cottin V, Cordier J-F, Richeldi L, editors. Orphan Lung Diseases [Internet]. London: Springer London; 2015 [cited 2015 Dec 4]. p. 73–89. Available from: http://link.springer.com/10.1007/978-1-4471-2401-6_6] *Caption from original.*



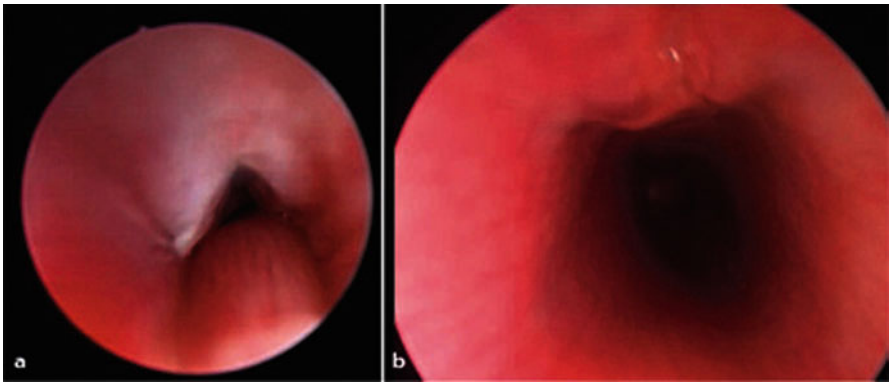
Tracheomalacia. The tracheal lumen has a normal appearance on the inspiratory transverse CT scan (top). This lumen collapses on the expiratory transverse scan (bottom). The posterior tracheal wall bows anteriorly tremendously reducing the airway lumen. [Grenier PA. Airway Disease. In: Baert AL, editor. Encyclopedia of Diagnostic Imaging [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2008 [cited 2015 Dec 4]. p. 57–60. Available from: http://www.springerlink.com/index/10.1007/978-3-540-35280-8_85] *Caption from original.*

Other

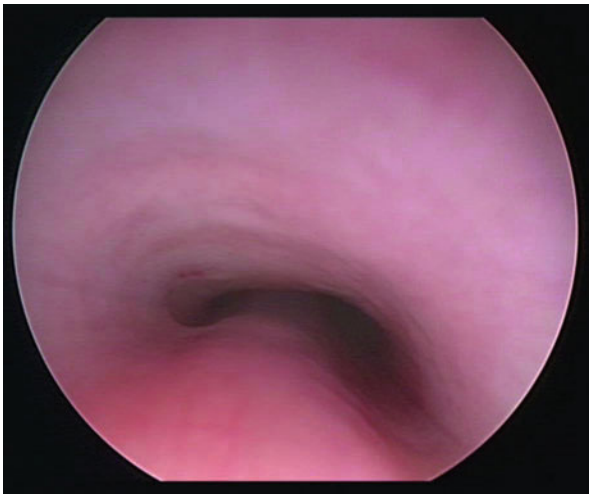
- Bronchoscopy. Currently, the diagnostic gold standard for the diagnosis of TM is direct visualization of dynamic airway collapse during bronchoscopy. Bronchoscopy allows the direct visualization and measurement for grading

the severity of TM. Mild TM is defined as luminal narrowing of less than 50 % during expiration. Moderate TM is defined as narrowing of 25–50 %, and severe TM is diagnosed if the anterior and posterior tracheal walls touch during expiration.

https://www.youtube.com/watch?v=rNADYJySIl4
Video of focal tracheomalacia.



Tracheomalacia. Severe tracheomalacia (a) and after aortopexy (b) [Masciopinto F, Gentili A, Bianchini A, Baroncini S. Airway Endoscopy. In: Lima M, editor. Pediatric Thoracic Surgery [Internet]. Milano: Springer Milan; 2013 [cited 2015 Dec 4]. p. 181–91. Available from: http://link.springer.com/10.1007/978-88-470-5202-4_15] *Caption from original.*



Primary tracheomalacia with soft, collapsible cartilaginous support proximal to the carina [Berg EE, McClay J. Tracheobronchomalacia. In: Lioy J, Sobol SE, editors. Disorders of the Neonatal Airway [Internet]. New York, NY: Springer New York;

2015 [cited 2015 Dec 4]. p. 87–95. Available from: http://link.springer.com/10.1007/978-1-4939-1610-8_11] *Caption from original*.

- Pulmonary Function Tests (PFTs). PFTs can help support a diagnosis of TM, but they cannot make or confirm the diagnosis. PFTs will often show reduction in the expiratory flow rate on a flow volume curve and the expiratory curve will have a "notched" appearance.

Special Populations

Age

- Acquired TM is more common in adults over age 40.
- Congenital TM is more common in children.
- TM in children more commonly involves the distal third of the trachea and is associated a congenital abnormality.
    - These congenital abnormalities include:
        - Cardiovascular abnormalities (vascular rings, anomalous innominate artery)
        - Developmental delay
        - Severe GERD
        - Tracheoesophageal fistula
        - Esophageal atresia
- TM in infants generally disappears spontaneously by the age 0f 18–24 months.
- Infants with TM are often noted to have expiratory stridor (sometimes called laryngeal crow) within the first few weeks of life. The stridor tends to be worsened and exacerbated by crying, supine position, and feeding.
- Infants may also be noted to have feeding difficulties with coughing and choking with feeding.
- Treatment in children is more guided by the pattern (focal or diffuse) of disease.
- Infants and children with mild-to-moderate symptoms can often be managed with conservative measures until the disease spontaneously remits. Conservative treatment includes:
    - Humidified air
    - Chest physiotherapy
    - Slow feedings
    - Meticulous control of secretions
    - Appropriate treatment of infections
- Surgery may be indicated for infants/children with severe disease who do not respond to conservative treatments.
- Infants with reflex apnea should be managed surgically.

Co-morbidities

- Patients with tracheomalacia will frequently have other medical issues that can complicate and worsen TM.
- TM can occur in patients with long-standing asthma and COPD.
- Gastroesophageal reflux disease (GERD) can both cause and worsen TM. Aggressively treating (when present) may prevent worsening.

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Consideration of the diagnosis is the first critical step.
- TM can coexist with other cardio-pulmonary and laryngeal diseases, so it is important to consider even if a competing/alternative diagnosis has been confirmed.
- TM should be considered if the patients' cough and dyspnea seem out of proportion to the severity of the current diagnosis.

Mimics

- Asthma and COPD can both mimic TM.
- Severe GERD can also cause similar symptoms to TM.

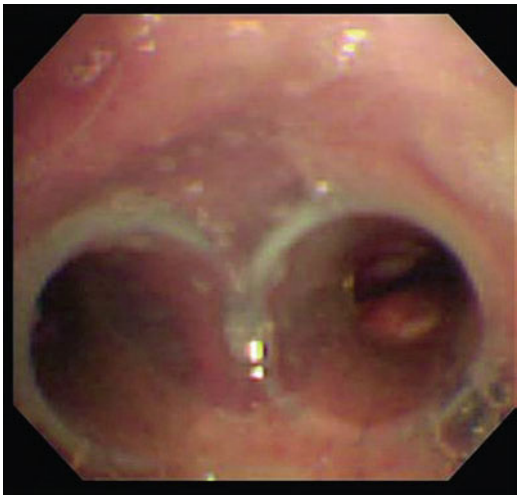
Time-Dependent Interventions

- TM is generally a slowly progressive disease, and as such there are usually no immediately time-sensitive interventions.
- Patients with TM who are admitted to the hospital with another acute illness may benefit from the use of continuous positive airway pressure (CPAP). This can help maintain an open airway and secretion mobilization.

Overall Principles of Treatment

- Treatment is guided by the symptoms and graded severity of TM.
- There is no indication for treatment of asymptomatic patients.

- All patients with suspected TM should have both bronchoscopy and CT chest to help gauge severity and guide therapy.
- The underlying cause of TM should be sought and treated.
- The treatment of contributing, comorbid diseases (COPD, asthma, GERD, CHF) should be maximized.
- If patients remain symptomatic after treatment of all contributing factors, primary therapy for TM should be considered.
- Prior to starting primary therapy, patients should have functional respiratory testing with PFTs, six-minute walk test, and a quality-of-life assessment. This assessment will be used to guide and assess the success of therapy.
- In general, primary therapy for TM can involve stenting and primary surgical repair.
- Many experienced centers will start with stenting and assess response to guide long-term treatment.
    - If patients are not surgical candidates, but they improve with stent insertion, they may be managed with long-term silicone stents. Stents tend to be most helpful in focal, proximal disease.



Silicone Y-stent inserted in a patient with tracheomalacia [Anantham D. Management Principles of Nonmalignant Airway Obstruction. In: Ernst A, Herth FJ, editors. Principles and Practice of Interventional Pulmonology [Internet]. New York, NY: Springer New York; 2013 [cited 2015 Dec 4]. p. 269–83. Available from: http://link.springer.com/10.1007/978-1-4614-4292-9_26] *Caption from original*.

- Patients who are surgical candidates and improve with stenting should be offered definitive surgical repair. Definitive surgical repair generally involves tracheobronchoplasty (the application of a mesh to the posterior tracheal wall, which increases the rigidity of the wall).

- Patients who do not improve with stenting should have the stent removed and be managed with positive airway pressure when needed.

- Future treatments:
  - There is ongoing research on biogenic stents and tracheal replacement.

Disease Course

- In infants, TM usually resolves spontaneously by 18 – 24 months of age
- TM is a slowly progressive disease in adults.
- Almost all patients will worsen over time.
- There have been no reports of spontaneous remission or improvement in adults.

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

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Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy: “Tracheomalacia”[Mesh] OR “tracheomalacia” OR “tracheomalacias” OR “tracheobronchomalacia”

Chapter 74
Tuberculosis

Charles V. Pollack, Jr. and Victoria G. Riese

Name and Synonyms

Tuberculosis, TB

Incidence/Epidemiology

- Tuberculosis is a multisystem disease with many varied presentations, all of which evolve from infection with the atypical pathogen *Mycobacterium tuberculosis*, an acid-fast bacterium that is endemic in some parts of the world, especially underdeveloped regions where living conditions and access to health care are poor.
- Chest pain due to tuberculosis tends to be pleuritic in nature, and may result from lung infection and/or pleural or pericardial involvement.
- In the United States, the current incidence of TB is 3–4/100,000 persons, with the highest incidence in states with the most immigrants—California, Texas, Florida, and New York. The prevalence of HIV disease in those states also may be a contributing factor.
- Globally, the highest incidence of TB is found in India, China, South Africa, Indonesia, and Pakistan.

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C. V. Pollack, Jr. (ed.), *Differential Diagnosis of Cardiopulmonary Disease*,
https://doi.org/10.1007/978-3-319-63895-9_74

Differential Diagnosis

- The differential considerations for chest pain due to TB are primarily other pleuritic pain processes, such as pulmonary embolism, pericarditis, pneumonia, pneumothorax, and pleurisy.
- As in all chest pain presentations, immediate life threats such as acute coronary syndrome and aortic dissection should always be considered.
- Acute chest syndrome in sickle cell disease is a differential consideration in at-risk patients.

Pathophysiology and Etiology

- The clinical manifestations of TB result from a variable combination of actual infection and the host's inflammatory response to the infection.
- Chest pain syndrome in patients with TB typically arises from actual pneumonia or from involvement of the pleura or pericardium.
- There may also be chest wall pain from coughing.

Presentation

Typical/"Classic"

- The classic presentation of pulmonary or extrapulmonary thoracic TB that causes chest pain is marked by most or all of the following:
  - Cough
  - Weight loss/anorexia
  - Fever
  - Night sweats
  - Hemoptysis
  - Fatigue
  - Lymphadenopathy
- TB is a more likely presentation in patients with such symptoms if they have risk factors for exposure, such as:
  - Recent travel to an endemic area
  - Recent imprisonment, homelessness, or living in a shelter
  - HIV infection

- Prior TB exposure or infection
- Known positive prior PPD (purified protein derivative) test

Atypical

- TB may affect multiple organ systems, including the spine and other bones, the gastrointestinal and genitourinary (GU) tracts, and the meninges. These types of tuberculous infections are less likely to present with chest pain.

Primary Differential Considerations

Pulmonary TB has protean manifestations. In patients with a history concerning for TB exposure, other diagnoses must still be considered, including:

- Necrotizing bacterial pneumonia
- Fungal pneumonia
- Lung abscess
- Lung cancer
- Bronchiectasis

History and Physical Exam

Findings That Confirm Diagnosis

- History and physical examination cannot confirm the presence of tuberculosis.

Factors That Suggest Diagnosis

- A history of fever, chills, weight loss, and hemoptysis is suggestive of TB in the patient with chest pain.
- Findings of consolidation on pulmonary exam—such as egophony and percussion dullness, especially in the upper lung fields—are suggestive of TB in the patient with chest pain.

http://www.easyauscultation.com/egophony
Egophony. [Egophony Page; Easy Auscultation; www.easyauscultation.com; copyright 2015, MedEdu LLC]

- Evidence of malnutrition or chronic illness on physical exam should raise suspicion for TB in the patient with chest pain.

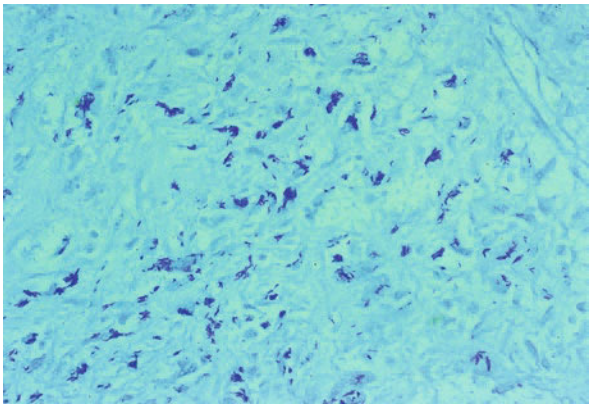
Factors That Exclude Diagnosis

- There are no history or physical findings that conclusively exclude TB in the patient with chest pain.

Ancillary Studies

Laboratory

- Confirmation of TB infection is provided by the finding of acid-fast bacilli (AFB) on smear and/or culture of a bodily fluid, such as sputum



Granulomatous area with acid-fast bacilli in a lung biopsy specimen. Lung biopsy specimen showing a granulomatous area with numerous acid-fast bacilli. Diagnostic fiberoptic bronchoscopy with transbronchial biopsy and bronchial washings is an effective way to obtain diagnostic materials when sputum examination is unrevealing, in the early diagnosis of miliary disease, and in lower lobe tuberculosis when the number of bacilli may be small. (Kinyoun stain.) [Maslow M. Tuberculosis and nontuberculosis mycobacterial infections of the lungs. In: Simberkoff MS, editor. Pleuropulmonary and bronchial infections. Philadelphia: Current Medicine; 1996.

283 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 6). ISBN: 0-443-07740-1] *Caption from original*

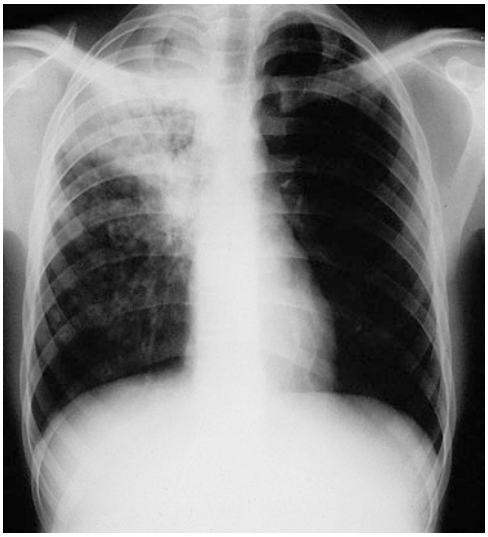
- An HIV test should be obtained in patients with TB and unknown HIV status.
- Basic laboratory tests are of limited clinical value in assessing the patient with chest pain for TB, but they may be appropriate in the evaluation of potential differential considerations.
- Patients suspected of having pulmonary TB should undergo urinalysis; sterile pyuria is a common manifestation of GU TB.

Imaging

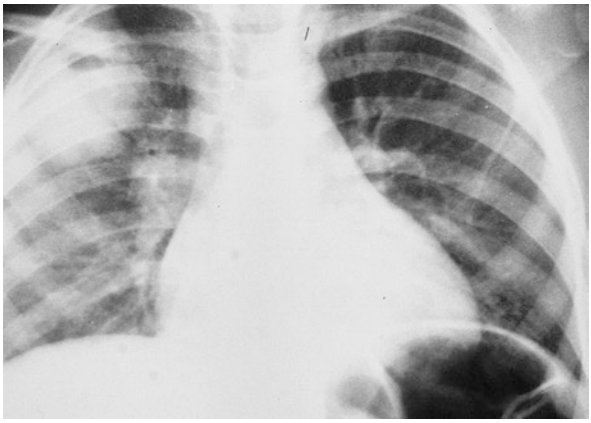
- Chest radiography and CT may strongly suggest pulmonary TB.

Multidrug-resistant tuberculosis (MDR TB). Chest radiograph of a black African man aged 31 years with a CD4 count of 79 cells/mm3 showing bilateral patchy confluent consolidation with cavitatory changes in the left upper lobe. Left apical pleural thickening and features of volume loss suggest previous TB. Tubular lucencies in the left upper lobe suggest underlying bronchiectasis. [Lalloo UG, Ambaram A, Vawda F. Pulmonary complications. In: Mildvan D, editor. International atlas of AIDS. 4th ed. Philadelphia: Current Medicine; 2008. 366 p. ISBN: 1-57340-270-2] *Caption adapted from original*

- The classic findings on x-ray are apical infiltrate(s), often with a cavitary lesion.



Pulmonary tuberculosis (TB) presenting as a right upper lobe infiltrate. [Jacobs R. Tuberculosis. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. 283 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption adapted from original*



Pulmonary tuberculosis (TB) presenting as a lung abscess. [Jacobs R. Tuberculosis. In: Wilfert CM, editor. Pediatric infectious diseases. Philadelphia: Current Medicine; 1999. 283 p. (Mandell GL, editor. Atlas of infectious diseases; vol. 11). ISBN: 0-443-06526-8] *Caption adapted from original*

- A normal chest radiograph *does not* exclude TB, but casts doubt on the diagnosis if chest pain features prominently in the patient's presentation.

Special Populations

Age and Gender

- TB occurs in all age, ethnic, and socioeconomic groups. It occurs in both males and females.
- Pulmonary TB often has poorer outcomes at the extremes of age.
- In the United States, foreign-born patients with TB most often are Hispanic or Asian.

Comorbidities

- Comorbidities associated with pulmonary TB include but are not limited to:
  - HIV

TB—Tuberculosis

Transmission
1 of 3 TB cases in HIV patients is recently acquired
Immunity is not conferred by previous exposure to TB organisms
Lack of cavitary disease with HIV may render patients less contagious
Spread of TB facilitated by grouping HIV patients together in health care facilities, homeless shelters, and prisons
Clinical manifestations
Positive purified protein derivative with early stages of HIV only
Usual symptoms (fever, sweats, cough, and weight loss) are usually more exaggerated
Rapid progression from exposure to active disease (from loss of cell-mediated immunity)
Higher rate (40%–89%) of extrapulmonary manifestations
Lymphadenitis with fistula formation and abscesses
Radiographic features
Nonapical distribution
Infiltrates in any lung zone
Cavitation rare late in the disease
Intrathoracic adenopathy in 1 of 3 cases
Miliary infiltrates and pleural effusions
Normal chest radiograph in early stages of pulmonary

Tuberculosis and HIV. All patients with tuberculosis should be screened for HIV, and conversely, all HIV positive patients should have a purified protein derivative (PPD) skin test. The sensitivity of the test is inversely proportional to the degree of immunosuppression. Anergy is common, so a negative PPD should be interpreted

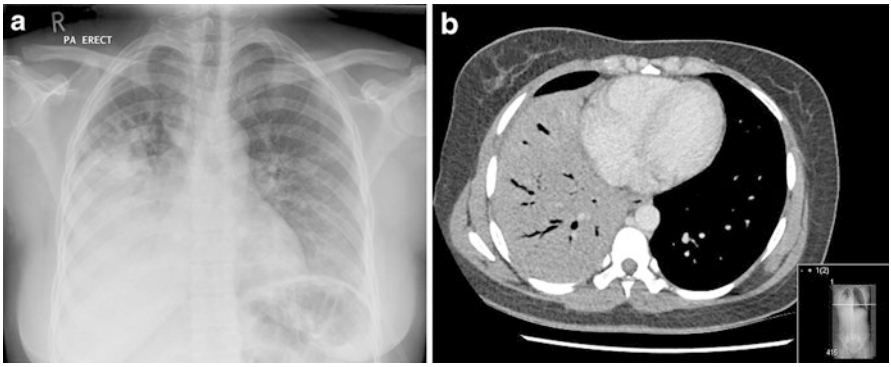
with caution. Prophylactic regimens should be continued for 9 months. Tuberculosis should be considered in any HIV-positive patient with unexplained fevers, cough, infiltrate, adenopathy, meningitis, brain abscess, pericarditis, pleural effusion, or an abscess anywhere in the body. The diagnosis is difficult because the symptoms are nonspecific, the PPD is often negative despite active disease, atypical radiographs are the rule, and extrapulmonary manifestations are common (American Thoracic Society: Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep. 2000; 49(RR-6):1 -43.) [Bates JH, Huitt GA. Infections. In: Crapo JD, editor. Bone's atlas of pulmonary medicine. 3rd ed. Philadelphia: Current Medicine; 2005. 338 p. ISBN: 1-57340-211-7] *Caption from original*

- Other immunocompromise
- Cancer
- COPD and chronic respiratory failure
- Chronic hepatic disease
- Alcoholism
- Neurologic disease

Pitfalls in Diagnosis

Critical Steps Not to Miss

- Early consideration of the diagnosis of TB in the patient with chest pain is essential in order to protect other people—family members as well as health-care providers—from possible exposure to the disease.



Case example: a 39-year-old Zambian woman presented with a 4-day history of pleuritic chest pain, cough and breathlessness, and a 6-week history of weight loss and night sweats. She was initially treated with amoxicillin and clavulanic acid, which resulted in symptomatic improvement. Tests on admission demonstrated

HIV-1 infection, with a CD4 count of 192 cells/μL. a Chest radiograph demonstrates right-sided middle and lower zone consolidation. b CT image of the thorax demonstrates nodular shadowing in both upper lobes, with dense consolidation of the right middle and lower lobes. Sputum microscopy was 3+ positive for acid-fast bacilli and culture confirmed Mycobacterium tuberculosis. This emphasizes the importance of testing for HIV and mycobacterial disease in patients with community-acquired pneumonia [Brown J, Lipman M. Community-acquired pneumonia in HIV-infected individuals. Curr Infect Dis Rep [Internet]. 2014 Mar [cited 2015 May 29];16(3)397. Available from: http://link.springer.com/10.1007/s11908-014-0397-x] *Caption from original*

- Accessible, pertinent body fluids (especially sputum in patients with chest pain) should be sent for AFB smear and culture as soon as possible.

Mimics

- The entire constellation of diagnoses underlying pleuritic chest pain, especially those often accompanied by dyspnea and/or fever, can mimic the pain and overall presentation of TB.
- Pericarditis may mimic pleuritic chest pain from TB in presentation. Listen for a pericardial friction rub.

Time-Dependent Interventions

- Anti-infective therapy, usually with empiric antibiotic therapy initially, should be initiated when the diagnosis of pneumonia is strongly considered or confirmed. Consult your local antibiogram for guidance in choosing a specific agent.
- Choice of antimicrobial also is driven by the classification of the pneumonia (community-acquired vs hospital-acquired vs ventilator-associated pneumonia).

Overall Principles of Treatment

- Respiratory isolation should be implemented immediately upon serious consideration of the presence of TB.
- There are several drugs used to treat TB, often in combination. Resistance patterns evolve; therefore, treatment is guided by microbiologic studies.

Categories	Patients	Treatment
Category I	New smear-positive pulmonary TB, smear-negative pulmonary TB with parenchymal involvement, seriously ill pulmonary TB, extrapulmonary TB, severe concomitant HIV disease	2HRZE + 4HR
Category II	Previously treated sputum/smear-positive pulmonary TB relapse, treatment after interruption, treatment failure	2HRZES/1HRZE + 5HRE
Category III	New smear-negative pulmonary TB, less severe form of extrapulmonary TB	2HRZE + 4HR
Category IV	Chronic and MDR-TB	Specially designed/individualized regimens

The number before the letters refers to the number of months of treatment

H isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin

Categories of tuberculosis and their treatment regimens as recommended by WHO (Toman K [2004] Toman's tuberculosis case detection, monitoring, treatment, 2nd edn. WHO, Geneva) [Rajasekaran S, Khandelwal G. Drug therapy in spinal tuberculosis. Eur Spine J. 2013 Jun;22(S4):587–93.] *Caption from original*

- Chest pain associated with TB usually improves quickly as the infection resolves. Nonsteroidal anti-inflammatory drugs or narcotics may be given to patients with persistent or severe pain.

Disease Course

- The course of TB is determined by multiple factors, most important of which are:
  - The overall health and immune status of the individual host
  - The number of organ systems involved
  - The extent of infection prior to initiation of treatment
  - Age (older patients have poorer prognoses)
  - Patient adherence to the treatment regimen

Related Evidence

Papers of particular interest have been highlighted as:
*** Of key importance*

Practice Guideline

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Fair E, Hopewell PC, Pai M. International Standards for Tuberculosis Care: revisiting the cornerstones of tuberculosis care and control. Expert Rev Anti Infect Ther. 2007 Feb;5(1):61-5. PMID: 17266454. http://www.ncbi.nlm.nih.gov/pubmed/17266454

Use PubMed Clinical Queries to find the most recent evidence. Use this search strategy:

"Tuberculosis"[Mesh] OR "Tuberculosis"

ESC Congress 2018 In Review

Official peer-reviewed highlights

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Main Edition

In This Issue

Highlights of the 2018 ESC Clinical Practice Guidelines

The European Society of Cardiology revealed 4 new guideline updates developed by expert task forces covering the topics of syncope, cardiovascular diseases during pregnancy, arterial hypertension, and myocardial revascularization, and a consensus document on the fourth universal definition of myocardial infarction. The evidence base supporting the guidelines are summarised, and valuable clinical decision-making tools for practicing clinicians are provided.

Also

- Strategies for Secondary Prevention
- Clinical Trial Highlights
- Antithrombotic Therapy in Patients with AF + ACS

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ESC
European Society of Cardiology

Dear Colleagues,

In this issue of *ESC Congress 2018 in Review*, we are delighted to share with you peer-reviewed highlights of the European Society of Cardiology Congress 2018 held in Munich, Germany. Over the five days of the congress – in addition to a rich educational programme - 12 Basic & Translational Science Hot Line presentations, 35 Late Breaking Clinical Trial presentations, 15 Clinical Trial Updates, 30 Late-Breaking Registry Results, 4 new ESC Clinical Practice Guidelines, and 4,461 abstracts were presented. The congress spotlight was 'Valvular Heart Disease' to place a special emphasis on the substantial growth in this area over the past decade. Some new features added to the Congress this year included a track called 'Cardiology in 4 Days', which covered the entire field of cardiology with focused lectures given by leading experts; the expansion of the successful 'Expert Advice' sessions; and a dedicated lecture hall, the 'Library Room', which provided a unique forum for discussions.

The articles selected for this issue of *ESC Congress 2018 in Review*, the official highlights report for ESC Congress 2018, will summarise the most newsworthy, cutting-edge, and clinically relevant topics presented in Munich. A typical example would be the ATTR-ACT study, in which tafamidis reduced hospitalisations and improved both survival and quality of life in patients with transthyretin amyloid cardiomyopathy. The results of ATTR-ACT, COMMANDER HF, MITRA-fr, and the numerous other trials presented at ESC Congress 2018 will influence cardiovascular care and allow us to better understand diseases and manage patients.

New ESC Clinical Practice Guidelines were presented on the diagnosis and management of syncope, the management of cardiovascular diseases during pregnancy, myocardial revascularisation (in conjunction with European Association for Cardio-Thoracic Surgery), and management of arterial hypertension (in conjunction with European Society of Hypertension); with dedicated sessions to help attendees understand the underlying science that support the recommendations and the impact of the new guidelines on their own clinical practice.

We are confident that the articles in this edition of *ESC Congress 2018 in Review* will be useful for your clinical practice. Please also be reminded that ESC 365, presenting all congress resources in one online library, provides access to all abstracts, slides and presentations, along with ESC TV interviews and other material from ESC Congress 2018. To access this unique source of up-to-date information, visit us online at www.escardio.org/365.

We hope you will enjoy this issue of *ESC Congress 2018 in Review* and look forward to seeing you in Paris for ESC Congress 2019. For more information, please visit www.escardio.org/ESC2019.

Professor Stephan Achenbach, FESC
Chairman, ESC Congress Programme Committee 2016-2018

Dear Practitioner,

We are pleased to share with you highlights from the European Society of Cardiology (ESC) Congress 2018 held in Munich, Germany.

The featured article provides a topline summary of the 4 new ESC Clinical Practice Guideline updates released during the congress covering myocardial revascularisation, cardiovascular diseases during pregnancy, arterial hypertension, and syncope, as well as the 4th universal definition of MI.

Several highly anticipated clinical trials were presented at ESC Congress 2018. The ATTR-ACT study investigated tafamidis as a treatment for wild-type transthyretin amyloid cardiomyopathy and found that it improved both survival and quality of life, and reduced hospitalisations in these patients for whom the average survival is 3-5 years after diagnosis and there are no currently approved therapies. The CAMELLIA-TIMI 61 study examined the safety and efficacy of a weight-loss drug (lorcaserin) in overweight or obese patients. Results showed that adding lorcaserin to diet and exercise resulted in sustained weight loss compared with placebo without increasing the risk for MACE. Two highly anticipated trials of aspirin for primary CV prevention (ARRIVE and ASCEND) suggest that aspirin may be of benefit in patients with diabetes, but is accompanied by increased gastrointestinal bleeding and its role in moderate risk non-diabetics is uncertain. Results from two studies of rivaroxaban failed to show significant clinical benefits. In MARINER, rivaroxaban 10 mg daily post discharge did not significantly reduce symptomatic venous thromboembolism (VTE) or VTE-related death versus placebo in medically-ill patients, although unexpectedly low event rates reduced the ability to demonstrate a statistical difference given the observed 24% relative risk reduction. In COMMANDER HF, rivaroxaban 2.5 mg twice daily did not significantly reduce the composite of death, MI, or stroke compared with placebo in patients with ischaemic cardiomyopathy in sinus rhythm.

In addition to guideline updates and the results from Hot Line sessions, you will also find information on selected areas of cardiovascular medicine including innovative strategies for secondary prevention and antithrombotic therapy in patients with AF + ACS.

We hope that you find the articles and practical perspectives that are contained in the pages of this issue of *ESC Congress 2018 in Review* helpful in integrating this new information into your clinical practice.

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Address
Content Ed Net Medicom
Faas Eliaslaan 5, 3742 AR, Baarn
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ISSN
ISSN 2468-8762 18:15

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Main Session

4 Highlights of the 2018 ESC Clinical Practice Guidelines

Late-Breaking Science

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ESC European Society of Cardiology

Highlights of the 2018 ESC Clinical Practice Guidelines

Written by **Lisa Buttle**

The European Society of Cardiology (ESC) revealed 4 new guideline updates developed by expert task forces covering the topics of syncope, cardiovascular diseases (CVD) during pregnancy, arterial hypertension, and myocardial revascularisation, and a consensus document on the fourth universal definition of myocardial infarction (MI). The guidelines summarise the evidence base on these topics, and provide a valuable clinical decision-making tool for practicing clinicians. All guidelines can be accessed from the ESC website (www.escardio.org/guidelines) and the ESC Pocket Guidelines App.

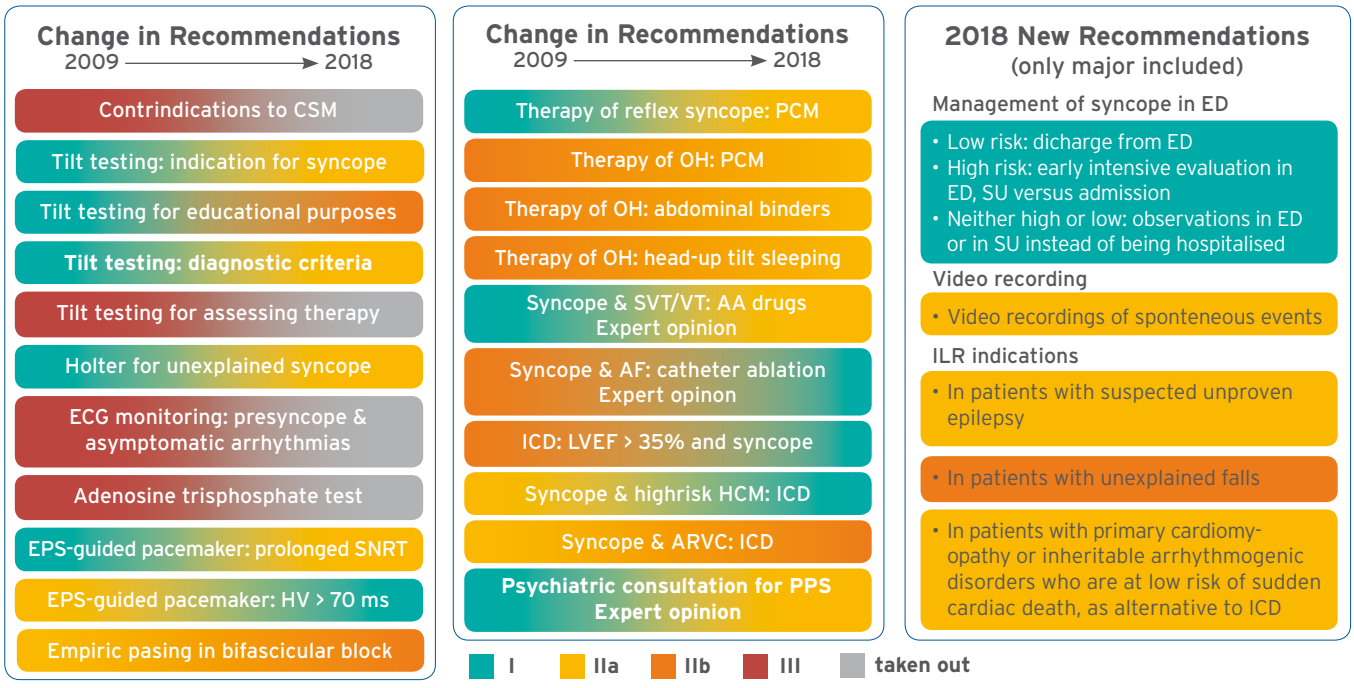
Syncope

The 2018 ESC Guidelines for the Diagnosis and Management of Syncope [Brignole M et al. *Eur Heart J*. 2018] were developed with the special contribution of the European Heart Rhythm Association (EHRA) and presented by Javier Moreno, MD, PhD, Hospital Universitario Ramón y Cajal, Madrid, Spain.

The 2018 guidelines contain a number of updated recommendations and important new and revised concepts, which are summarised in Figure 1, notably with the downgrade of Tilt testing, and the upgrade to class I recommendation for catheter ablation when syncope occurs with atrial fibrillation (AF).

Risk stratification in the emergency department at the initial presentation of syncope is essential to determine whether admission and subsequent investigations are needed, and the revised recommendations for management based upon risk are shown in Figure 2. Examples of high-risk features include new onset of chest discomfort, shortness of breath, headache, abdominal pain, sudden onset of palpitations followed by syncope, or a history of structural or coronary artery disease.

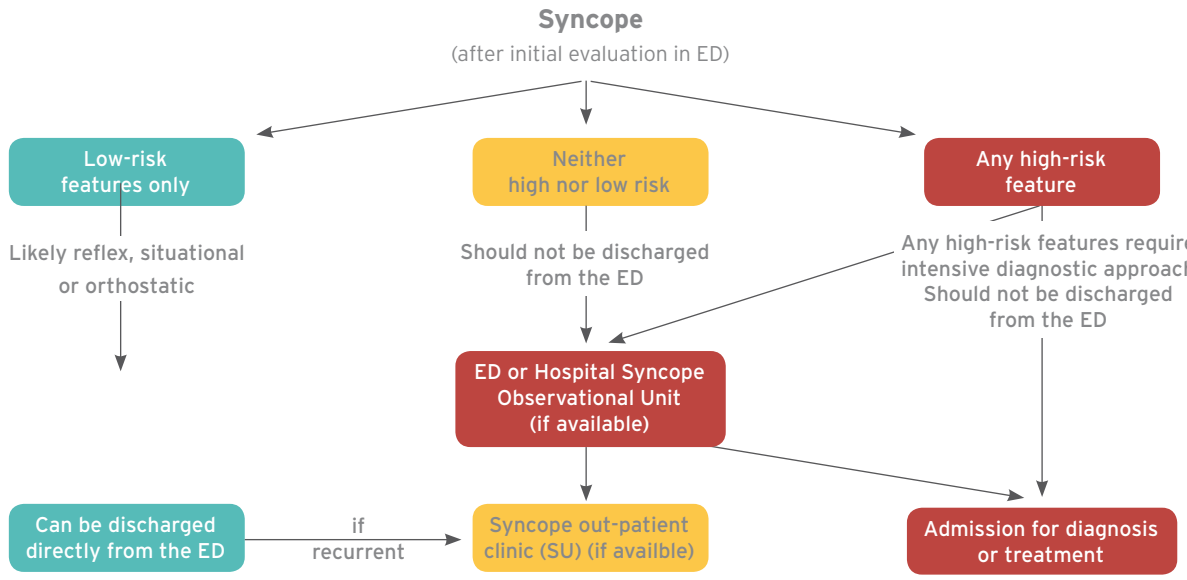
Figure 1. What Is New in the 2018 Syncope Guidelines



AA, antiarrhythmic; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; CSM, carotid sinus massage; ECG, electrocardiogram; ED, emergency department; LVEF, left ventricular ejection fraction; EPS, electrophysiological study; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; OH, orthostatic hypotension; PCM, physical counter-pressure manoeuvres; POTS, postural orthostatic tachycardia syndrome; PPS, psychogenic pseudosyncope; SNRT, sinus node recovery time; SU, syncope unit; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

Reprinted from Brignole M et al. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy037. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Figure 2. Emergency Department Risk Stratification Flow Chart



ED, emergency department; SU, syncope unit.

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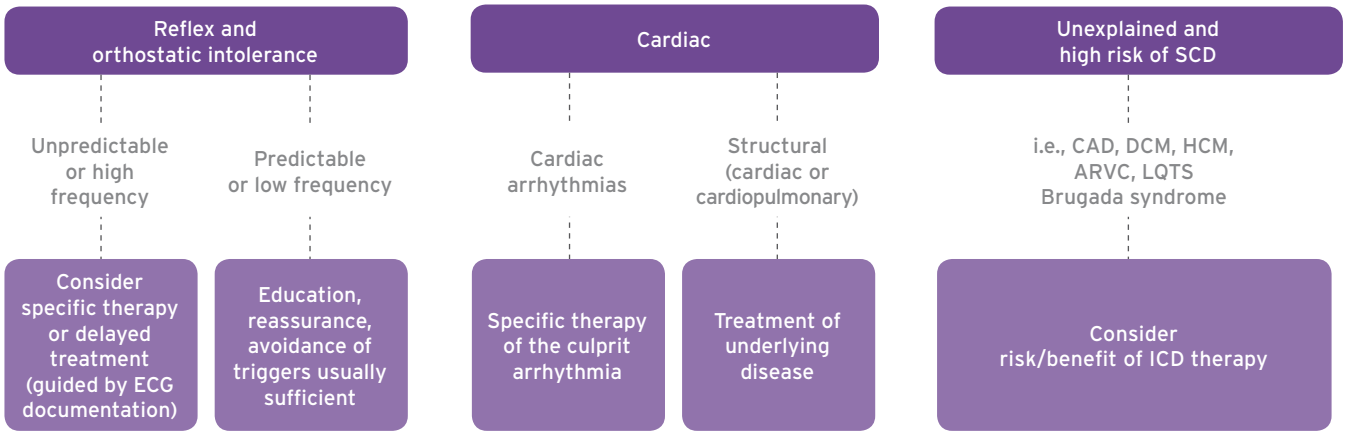
Subsequent investigations of syncope may include prolonged electrocardiographic monitoring, electrophysiology studies, and exercise testing; indications for use of these investigative techniques are included in the full guidelines. A new recommendation suggests the use of video recording of spontaneous events either at home or in hospital; video recording offers pathophysiological insights into syncope and may allow complex events to be diagnosed. Treatment recommendations are based on the identification of specific causes of syncope, wherever possible, and treatment principles are outlined in Figure 3. A new addition to the 2018 guidelines is a chapter focusing on organisational aspects of care, and outlining key drivers for efficient operation of the Syncope Unit.

Cardiovascular Diseases During Pregnancy

The 2018 ESC Guidelines for the Management of Cardiovascular Diseases during Pregnancy [Regitz-Zagrosek V et al. *Eur Heart J*. 2018] were presented by Christi Deaton, PhD, RN, University of Cambridge School of Clinical Medicine, United Kingdom. Since the 2012 guidelines were published, new evidence has accumulated on diagnostic techniques, risk assessment, and the use of CV drugs; full details of these topics are provided in the 2018 update along with new user-friendly summaries in each section highlighting recommendations and remaining 'gaps in the evidence'. New concepts introduced in the 2018 update are listed in Table 1.

Figure 3. General Framework for Treatment of Syncope and the Identification of Specific Mechanisms



ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; ECG, electrocardiographic; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; SCD, sudden cardiac death.

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Table 1. New Concepts in the 2018 ESC Guidelines on Cardiovascular Diseases in Pregnancy

New concepts
Enforcing mWHO classification of maternal risk.
Introduction of the pregnancy heart team.
More attention for assisted reproductive therapy.
Discussion of the use of bromocriptine in peripartum cardiomyopathy.
Introduction of specific levels of surveillance based on low/medium/high risk for arrhythmia with haemodynamic compromise at delivery.
New information on pharmacokinetics in pregnancy, more detailed information on pharmacodynamics in animal experiments on all drugs.
Perimortem caesarean section is discussed.
Advice on contraception and the termination of pregnancy in woman with cardiac disease is now provided.

mWHO, modified World Health Organization.

Reprinted from Regitz-Zagrosek V et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy340. By permission of Oxford University Press on behalf of the European Society of Cardiology.

All women with known cardiac or aortic disease who wish to become pregnant should receive prepregnancy counseling to facilitate informed maternal decision making. To assess maternal risk of cardiac complications during pregnancy, the ESC Task Force recommends the modified World Health Organization (mWHO) disease-specific risk classification tool. The general principles of the mWHO classification, and follow-up and management during pregnancy are presented in Table 2. Prepregnancy counseling as well as management during pregnancy and around delivery should be conducted in an expert centre by a multidisciplinary team – the pregnancy heart team – including a cardiologist, obstetrician, anaesthetist, and other specialists.

Peripartum cardiomyopathy (PPCM) is a rare condition that may cause severe complications in pregnancy. PPCM presents with HF secondary to left ventricular (LV)

Table 2. Modified World Health Organization Classification of Maternal Cardiovascular Risk

	mWHO I	mWHO II	mWHO II–III	mWHO III	mWHO IV
Diagnosis (if otherwise well and uncomplicated)	Small or mild – pulmonary stenosis – patent ductus arteriosus – mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation	Mild LV impairment (EF > 45%) Hypertrophic cardiomyopathy Native or tissue valve disease not considered WHO I or IV (mild mitral stenosis, moderate aortic stenosis) Marfan or other HTAD syndrome without aortic dilatation Aorta < 45 mm in bicuspid aortic valve pathology Repaired coarctation Atrioventricular septal defect	Moderate LV impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual LV impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation. If otherwise the patient is well and the cardiac condition uncomplicated Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m^2, tetralogy of Fallot < 50 mm) Ventricular tachycardia	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF < 30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual LV impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (> 45 mm in Marfan syndrome or other HTAD, > 50 mm in bicuspid aortic valve, Turner syndrome ASI > 25 mm/m^2, tetralogy of Fallot > 50 mm) Vascular Ehlers–Danlos Severe (re)coarctation Fontan with any complication
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity	Small increased risk of maternal mortality or moderate increase in morbidity	Intermediate increased risk of maternal mortality or moderate to severe increase in morbidity	Significantly increased risk of maternal mortality or severe morbidity	Extremely high risk of maternal mortality or severe morbidity
Maternal cardiac event rate	2.5–5%	5.7–10.5%	10–19%	19–27%	40–100%
Counselling	Yes	Yes	Yes	Yes: expert counselling required	Yes: pregnancy contraindicated: if pregnancy occurs, termination should be discussed
Care during pregnancy	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease
Minimal follow-up visits during pregnancy	Once or twice	Once per trimester	Bimonthly	Monthly or bimonthly	Monthly
Location of delivery	Local hospital	Local hospital	Referral hospital	Expert centre for pregnancy and cardiac disease	Expert centre for pregnancy and cardiac disease

ASI, aortic size index; EF, ejection fraction; HTAD, heritable thoracic aortic disease; LV, left ventricular; mWHO, modified World Health Organization; NYHA, New York Heart Association.

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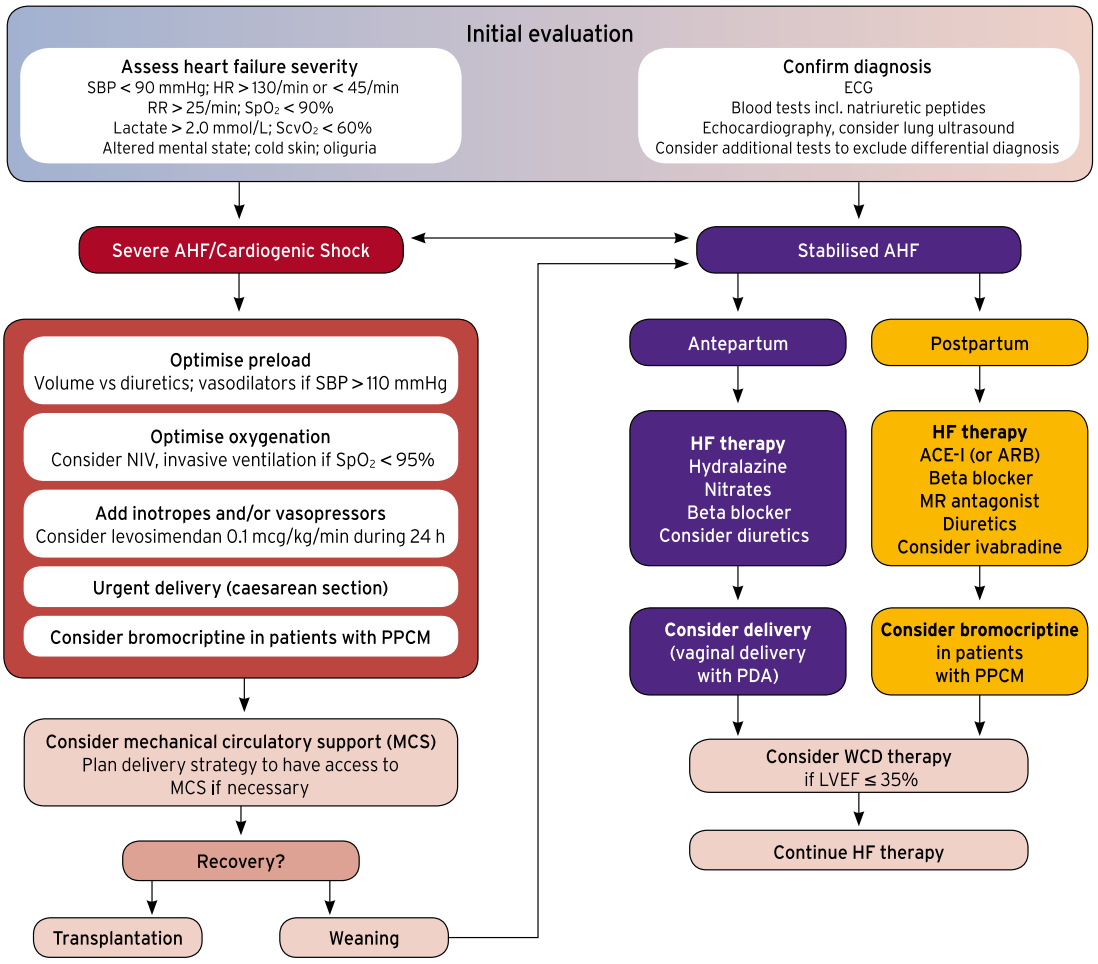
Figure 4. Management of Acute Heart Failure During/After Pregnancy



ACE-I, angiotensin-converting enzyme inhibitor; AHF, acute heart failure; ARB, angiotensin receptor blocker; ECG, electrocardiogram; HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; MR, mineralocorticoid receptor; NIV, non-invasive ventilation; PDA, peridural analgesia; PPCM, peripartum cardiomyopathy; RR, respiratory rate; SBP, systolic blood pressure; $ScvO_2$, central venous oxygen saturation; SpO_2, peripheral oxygen saturation; WCD, wearable cardioverter-defibrillator.

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systolic dysfunction towards the end of pregnancy and in the months following delivery. The use of bromocriptine has emerged as a new concept for the management of PPCM and HF in pregnancy in the 2018 guidelines. The addition of bromocriptine to standard HF therapy may be considered to stop lactation and improve LV recovery and clinical outcome in women with acute severe PPCM, and should be accompanied by anticoagulation therapy. Patients with symptoms and signs of acute heart failure (AHF) should be evaluated according to AHF guidelines, and the management goals are similar to non-pregnant HF while avoiding fetotoxic drugs during pregnancy (Figure 4).

For all CV drugs used in pregnancy, new and extensive safety data are included in the full 2018 guidelines update. The principles of drug treatment of CV diseases during pregnancy are outlined in Table 3.

Table 3. Recommendations for Drug Use in Pregnancy

Recommendations	Class[a]	Level[b]
Before pharmacological treatment in pregnancy is started, it is recommended to check full guidelines for clinical safety data.	I	C
In the absence of clinical safety data, it is recommended to check the electronic drug table (www.safefetus.com) for pre-clinical safety data.	I	C
In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profiles, and the available animal data, and the decision must be made together with the patient.	IIa	C
Decision-making based on former FDA categories alone is no longer recommended.	III	C

[a]Class of recommendation; [b]Level of evidence. FDA, US Food and Drug Administration.

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Figure 5. Classification of Hypertension Stage According to Blood Pressure, Presence of Cardiovascular Risk Factors, Hypertension-mediated Organ Damage, or Comorbidities

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High normal SBP 130-139 DBP 85-89	Grade 1 SBP 140-159 DBP 90-99	Grade 2 SBP 160-179 DBP 100-109	Grade 3 SBP ≥ 180 or DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to Moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High risk to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; DBP, diastolic blood pressure; HMOD, hypertension-mediated organ damage; SBP, systolic blood pressure; SCORE, Systematic Coronary Risk Evaluation.

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Management of Arterial Hypertension

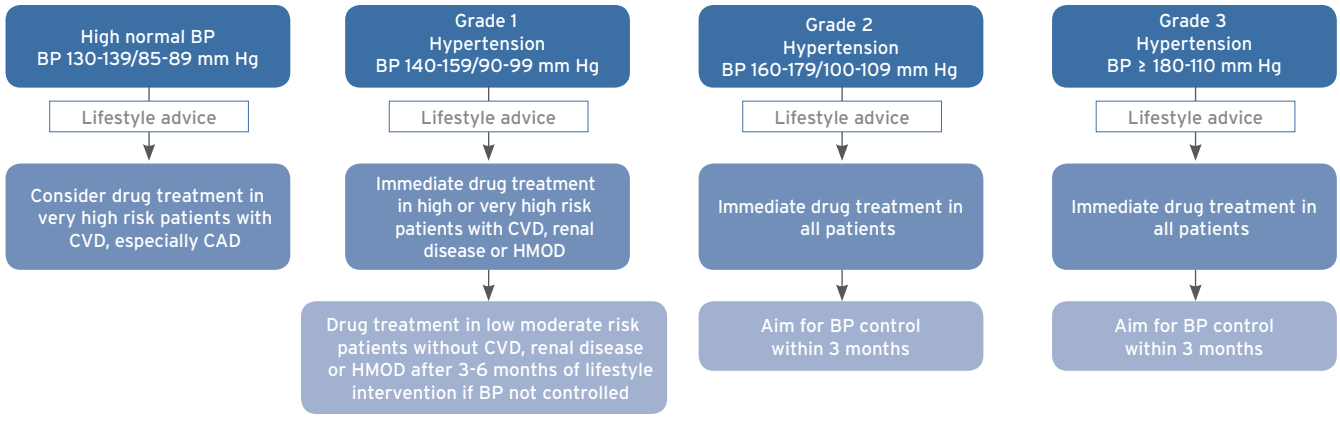
The 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension [Williams B et al. *Eur Heart J*. 2018] were developed in collaboration with the European Society of Hypertension (ESH) and presented by Guy De Backer, MD, PhD, University of Ghent, Belgium. An important shift in the 2018 guidelines is a move away from the sole use of repeat office blood pressure (BP) measurements for diagnosis, with promotion of the use of out-of-office ambulatory or home BP measurements for diagnosis, to detect white coat and masked hypertension, and to monitor BP control.

Global risk stratification is a key message of the 2018 guidelines. The management of hypertension requires formal CV risk assessment, which is recommended with the SCORE model. CV risk can be modified by other risk qualifiers, in particular by the presence of hypertension-mediated organ damage (previously termed 'target organ damage') which should be screened for in hypertensive patients (Figure 5).

For hypertension management, lifestyle adaptations are strongly recommended in all patients and drug treatment is based upon risk assessment and hypertension grade. The 2018 guidelines recommend a more aggressive drug-therapy regimen than the previous guidelines, particularly in the elderly where the biological rather than the chronological age should be considered. The treatment strategy should also take into account fitness, drug tolerance, and total CV risk (Figure 6).

The 2018 Task Force recommends a first treatment target to BP < 140/90 mm Hg in all patients, and if well-tolerated, treated BP should be targeted to ≤ 130/80 mm Hg in most patients, depending on a patient's age and comorbidities, although in some groups the evidence is less compelling. Regarding treatment selection, the 2018 guidelines make two new recommendations: to start treatment in most patients with 2 drugs not 1 (excluding an ACE + ARB combination), and the preferred use of single pill combination therapy to improve adherence to treatment. Detecting poor adherence is

Figure 6. Initiation of Blood Pressure-Lowering Treatment at Different Initial Office Blood Pressure Levels



BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; HMOD, hypertension-mediated organ damage.

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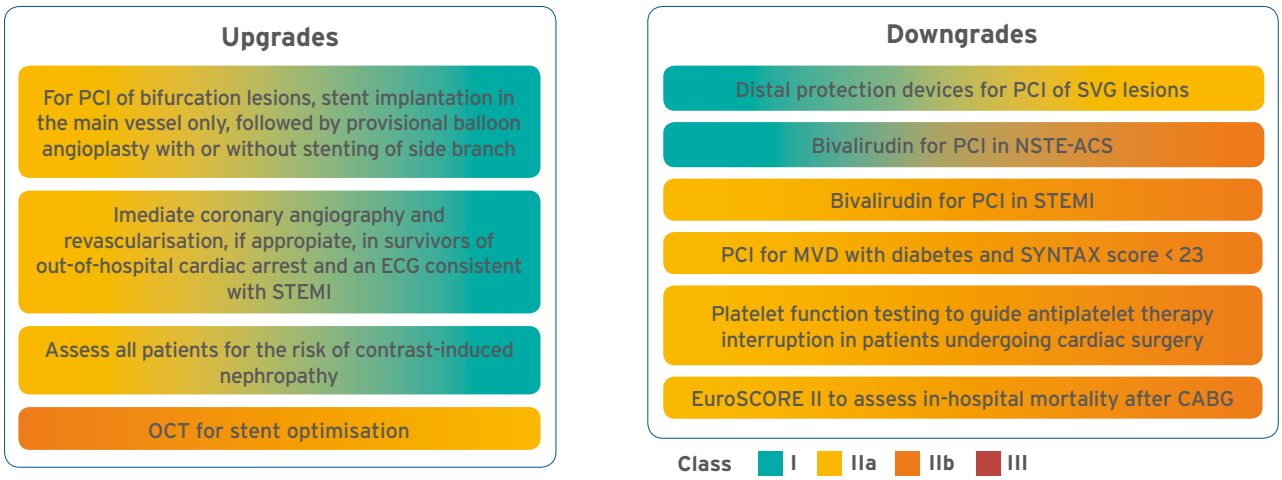
Figure 7. New Recommendations in the 2018 ESC/EACTS Guidelines on Myocardial Revascularization



CABG, coronary artery bypass grafting; ECG, electrocardiogram; MVD, multivessel coronary artery disease; NSTE-ACS, non-ST elevation-acute coronary syndrome; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SVG, saphenous vein grafts.

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strongly emphasised in the new guidelines; nurses and pharmacists should play a key role in patient education and support, which will facilitate adherence. More details on treatment and a new chapter on hypertension in specific circumstances can be found in the full 2018 guidelines.

Myocardial Revascularisation

The 2018 ESC/EACTS Guidelines on Myocardial Revascularization [Neumann F-J et al. *Eur Heart J*. 2018] were developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI). New recommendations included in the 2018 guidelines are listed in Figure 7.

The guidelines overview was presented by William Wijns, MD, PhD, National University of Ireland, Galway, Ireland, who identified four essential take home messages of the 2018 guidelines:

1) Decision making for stented percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be based on combined evaluation of anatomy and physiology (non-invasive or invasive testing; Table 4).
2) Evaluation of the extent of coronary artery disease (CAD) by SYNTAX score (www.syntaxscore.com) is essential when choosing between revascularisation modalities (CABG or PCI).
3) The presence of diabetes is an important decision modifier by itself.
4) The probability of achieving complete revascularisation is of extreme prognostic importance.

Table 4. Aspects to be Considered by the Heart Team for Decision Making Between PCI and CABG Among Patients With Stable Multivessel and/or Left Main Coronary Artery Disease

	Favours PCI	Favours CABG
Clinical characteristics	- Presence of severe co-morbidity (not adequately reflected by scores) - Advanced age/frailty/ reduced life expectancy - Restricted mobility and conditions that affect the rehabilitation process	- Diabetes - Reduced LV function (EF ≤ 35%) - Contraindication to DAPT - Recurrent diffuse in-stent restenosis
Anatomical and technical aspects	- MVD with SYNTAX score 0–22 - Anatomy likely resulting in incomplete revascularisation with CABG due to poor quality or missing conduits - Severe chest deformation or scoliosis - Sequelae of chest radiation Porcelain aorta[a]	- MVD with SYNTAX score ≥ 23 - Anatomy likely resulting in incomplete revascularisation with PCI - Severely calcified coronary artery lesions limiting lesion expansion
Need for concomitant interventions		- Ascending aortic pathology with indication for surgery - Concomitant cardiac surgery

[a]Consider no-touch off-pump CABG in case of porcelain aorta.
CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; EF, ejection fraction; LV, left ventricular; MVD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

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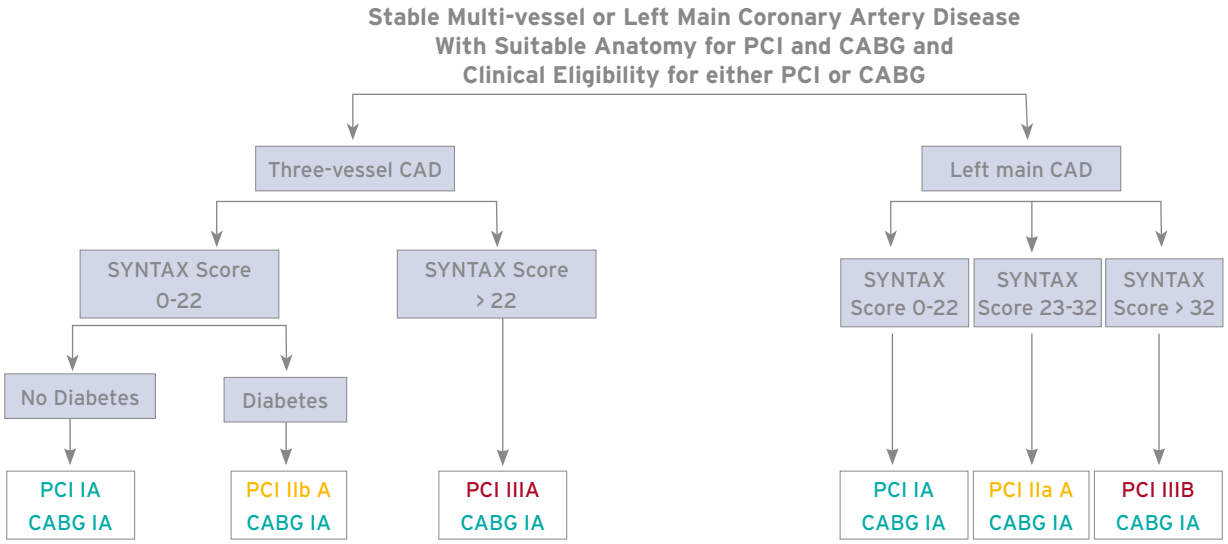
Figure 8. Algorithm to Guide the Choice of Revascularisation Procedure Across Major Categories in Patients With Multivessel or Left Main Coronary Artery Disease



Class recommendations correspond to the 2018 ESC/EACTS Guidelines on Myocardial Revascularization.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; PCI, percutaneous coronary intervention; SYNTAX, Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

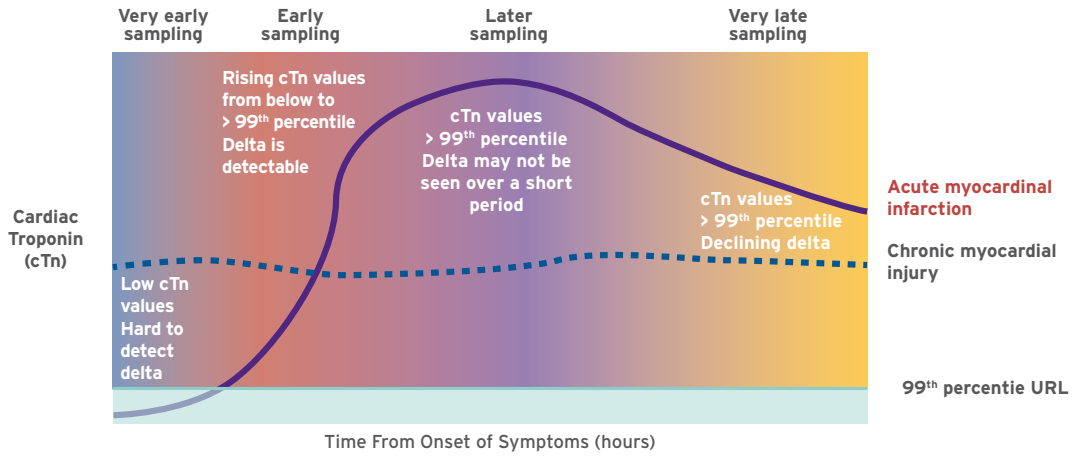
Reprinted from Windecker S et al. Considerations for the choice between CABG and PCI as revascularisation strategies in major categories of patients with stable multivessel coronary artery disease. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy532. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Considerations for the choice between CABG and PCI as revascularization strategies are further discussed by Windecker et al. in an article accompanying the 2018 guidelines [Windecker S et al. *Eur Heart J*. 2018]. This article expands upon the guidelines chapter on revascularisation in stable CAD and presents an algorithm to guide choice of revascularisation (Figure 8).

Universal Definition of Myocardial Infarction

The Fourth Universal Definition of MI (2018) [Thygesen K et al. *Eur Heart J*. 2018] was developed by a joint Task Force of the ESC, American College of Cardiology (ACC), American Heart Association (AHA), and World Heart Federation (WHF), and was presented by David Hasdai, MD, Rabin Medical Center, Tel Aviv, Israel. One of the key reasons for the Fourth Universal Definition of MI document is the introduction and adoption of high-sensitivity troponin assays to define MI. A chapter identifies strict technical criteria on the use of troponin assays, highlights caveats and advantages of their use, and discusses troponin level kinetics and the influence of timing on assay measurement (Figure 9).

Figure 9. Early Cardiac Troponin Kinetics in Patients After Acute Myocardial Injury Including Acute Myocardial Infarction



cTn, cardiac troponin; URL, upper reference limit.

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An important new concept in the Fourth Universal Definition of MI is the differentiation between myocardial injury and MI, which is defined in Table 5. There are many conditions that lead to increased troponin level denoting myocardial injury (e.g., HF, CM). Only when there is clinical evidence of myocardial ischaemia and myocardial injury can MI be diagnosed. Figure 10 provides a model for interpretation of myocardial injury versus MI in clinical scenarios. The Fourth Universal Definition of MI includes further details on the differentiation between type 1 MI and type 2 MI, which is a cause of some confusion in clinical practice. A framework is provided for determining type 2 MI considering the clinical context and mechanisms attributable to acute MI.

The Fourth Universal Definition of MI includes a chapter on the use of imaging techniques that can be employed to diagnose and characterise myocardial injury and MI. For example, magnetic resonance imaging can detect evidence of scarring which is apparent in MI, but can also be used to rule out a diagnosis of MI and identify other causes of myocardial injury (e.g., Takotsubo syndrome, AF); these other scenarios are discussed in new sections in the Fourth Universal Definition of MI.

Table 5. Universal Definitions of Myocardial Injury and Myocardial Infarction

Criteria for Myocardial Injury
The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.
Criteria for Acute Myocardial Infarction (types 1, 2 and 3 MI)
The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: • Symptoms of myocardial ischaemia; • New ischaemic electrocardiogram (ECG) changes; • Development of pathological Q waves; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; • Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs). Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.
Criteria for Coronary Procedure-related Myocardial Infarction (types 4 and 5 MI)
Percutaneous coronary intervention (PCI) related MI is termed type 4a MI. Coronary artery bypass grafting (CABG) related MI is termed type 5 MI. Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following: • New ischaemic ECG changes (this criterion is related to type 4a MI only); • Development of new pathological Q waves; • Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology; • Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolisation. Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularisation procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG. Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria. Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.
Criteria for Prior or Silent/Unrecognised Myocardial Infarction
Any one of the following criteria meets the diagnosis for prior or silent/unrecognised MI: • Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes. • Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology. • Patho-anatomical findings of a prior MI.

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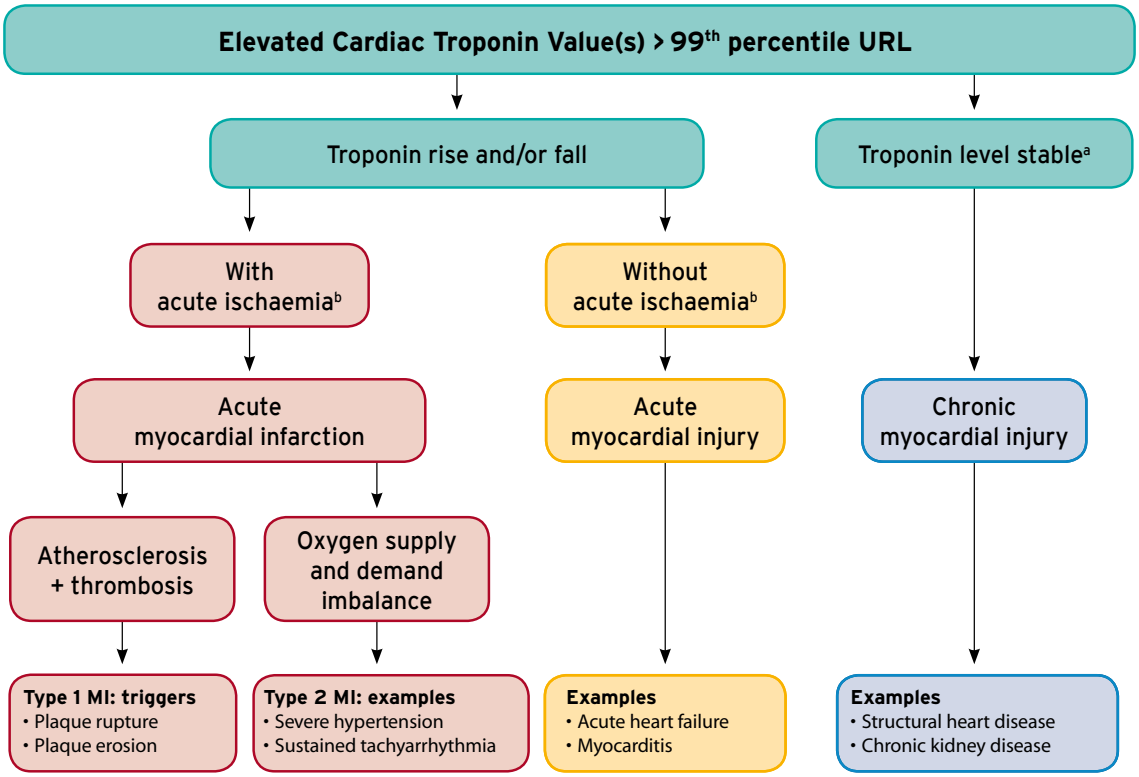
Figure 10. A Model for Interpreting Myocardial Injury



[a]Stable denotes ≤ 20% variation of troponin values; [b]Ischaemia denotes signs and/or symptoms of clinical myocardial ischaemia.
MI, myocardial infarction; URL, upper reference limit.

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Content Ed Net
MEDICOM

The Editors would like to thank the many Members of the ESC Congress 2018 presenting faculty, who generously gave their time to ensure the accuracy and quality of the articles in this publication

No Advantage of Early Invasive Strategy in NSTE-ACS

Written by **Michiel Tent**

Very early invasive coronary evaluation, within 12 hours, does not improve overall long-term clinical outcomes compared with an invasive strategy conducted within 2-3 days in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). In patients with the highest risk, however, very early invasive therapy improves long-term outcomes.

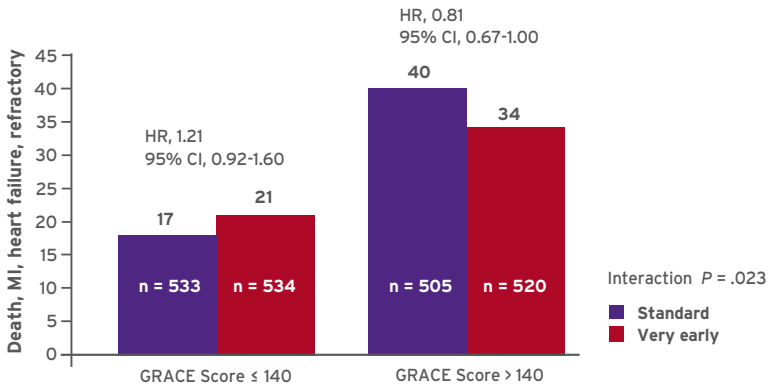
Current guidelines recommend invasive angiography within 24 hours in high-risk patients with NSTE ACS. European Society of Cardiology guidelines define high-risk as a GRACE score > 140, a rise in troponin, or ECG with ischaemia. However, the ideal timing of invasive angiography and revascularisation is unclear. The Very EaRly vs Deferred Invasive evaluation using Computerized Tomography [VERDICT; Kofoed KF et al. *Circulation*. 2018] trial was designed to test the hypothesis that very early invasive coronary angiography (ICA) and possible revascularisation within 12 hours of diagnosis is superior, in terms of clinical outcomes, to an invasive strategy performed within 48-72 hours in patients with NSTE-ACS.

Eligible for inclusion were patients with clinical suspicion of NSTE ACS, electrocardiogram changes indicating new ischaemia, and/or elevated troponin. Excluded were patients with ST-segment elevation myocardial infarction (STEMI) or very high-risk non-STEMI ACS. Participants were randomised 1:1 to coronary angiography within 12 hours of diagnosis (the very early group) or 48-72 hours after diagnosis (the deferred group). Percutaneous coronary intervention (PCI) was the preferred revascularisation strategy; patients not feasible for PCI were allowed coronary artery bypass graft (CABG) surgery. The primary endpoint was a composite of all-cause death, non-fatal recurrent myocardial infarction (MI), hospital admission for refractory myocardial ischaemia, or hospital admission for heart failure.

Thomas Engstrøm, DMSci, PhD, Rigshospitalet, University of Copenhagen, Denmark, presented the results for the 2,147 patients who were randomised. Thirty-two percent had no significant coronary artery disease (CAD). A quarter of patients presented with at least one occluded artery. In the very early group, time to angiography was a median of 4.7 hours compared with 61.6 hours after randomisation in the deferred group. Among patients with significant CAD identified by ICA, revascularisation was performed slightly more often in the very early group (88.4% vs 83.1%).

After a median follow-up of 4.3 years, the composite primary endpoint occurred in 296 patients (27.5%) in the very early group and in 316 (29.5%) in the deferred group (HR, 0.92; 95% CI, 0.78 to 1.08; *P* = .29). Prof. Engstrøm added that in high-risk patients (GRACE score > 140; n = 1,025) a very early invasive treatment strategy lowered the risk of reaching the primary outcome (HR, 0.81; 95% CI, 0.67 to 1.00; *P* for interaction = .023; Figure 1). Risk of nonfatal MI, one of the secondary outcomes, was also significantly lower in the very early group (8.4% vs 11.2%; HR, 0.73; 95% CI, 0.56 to 0.96; *P* = .025); these findings, however, were only hypothesis-generating.

Figure 1. Primary Endpoint Results According to GRACE Risk Score



Reproduced with permission from T Engstrøm, DMSci, PhD.

Prof. Engstrøm observed that very early invasive angiography is feasible, but logistically challenging and possibly not cost effective. It should, however, be performed in patients that present with symptoms of ACS, elevated troponin, and a high GRACE risk score.

Higher Mortality With FFR-Guided Treatment Choice of Multivessel Disease

Written by **Michiel Tent**

Final results of the FUTURE [FUnctional Testing Underlying Revascularization; NCT0188155] trial showed that the use of fractional flow reserve (FFR) to guide treatment choice in all-comer patients with multivessel disease was associated with more than double the risk of mortality after one year despite decreasing the rate of revascularisation.

Gilles Rioufol, MD, PhD, Hospital Louis Pradel, Bron, France, presented the results and noted that the use of FFR is recommended in the current guidelines for guiding percutaneous coronary intervention (PCI) in patients with multivessel disease who are eligible for PCI [Windecker S et al. *Eur Heart J*. 2014]. The trial was conducted to verify whether FFR may aid in the decision between different treatment strategies – PCI, coronary artery bypass grafting (CABG), or optimal medical treatment (OMT) only – and thereby improve clinical prognosis compared with traditional management.

FUTURE was a multicentre, randomised, prospective, open-label, controlled study in 31 French centres. The primary composite endpoint was all-cause mortality, myocardial infarction (MI), repeat revascularisation, or stroke at one year. Patients with either stable angina or stabilised acute coronary syndrome (ACS) and multivessel disease (> 50% stenosis) were eligible for the study. Eligible patients were randomised to either FFR or angiography. A total of 1,728 patients were to be enrolled, but the trial was prematurely halted after 938 patients had been randomised because of higher rates of all-cause mortality in the FFR group.

Of 938 randomised participants, 31% presented with diabetes, 20% with a history of MI, and 46% with ACS, while 52% had three significant lesions. The average SYNTAX score was 19 in the FFR-guided group and 18 in the angiography-guided group. Overall, 470 of 1,090 lesions (43%) evaluated by FFR had a reading above 0.80.

Prof. Rioufol said global results showed that use of FFR resulted in a lower rate of PCI than did angiography (71% vs 79%; *P* = .002) and in a higher rate of OMT alone (17% vs 9%). The rate of ad hoc PCI was 91% and 90%, respectively. CABG was used in only 12% of patients in both arms.

At 1 year, there was no significant difference in the primary composite endpoint of all-cause mortality, MI, repeat revascularisation, or stroke at 1 year between the FFR- and the angiography-guided group (HR, 0.97; 95% CI, 0.69 to 1.36; *P* = .85) or 2 years (HR, 0.99; 95% CI, 0.75 to 1.30; *P* = .93). In a subgroup analysis, the risk of the primary endpoint was higher in patients randomised to FFR-guided strategy who had a Syntax Score > 32 (HR, 3.32; 95% CI, 0.66 to 16.84) or stable angina (HR, 2.31; 95% CI, 1.02 to 5.22). A safety analysis revealed the risk of all-cause mortality at 1 year was significantly higher in the FFR group (HR, 2.39; 95% CI, 1.05 to 5.43; *P* = .038), after which the trial was prematurely halted; notably, this was not procedure-related.

Prof. Rioufol hypothesised that three factors may explain the excess mortality in the FFR-guided group, including the lower-than-expected rate of CABG in a population of multivessel disease patients; the high rate of PCI in severe patients with a SYNTAX score > 32; and the high rate of ad hoc PCI.

Gastrointestinal and Genitourinary Bleeding May Predict Underlying Cancer

Written by **Phil Vinall**

New data from the COMPASS trial indicates that increased gastrointestinal (GI) and genitourinary (GU) bleeding in patients treated with antithrombotic drugs is associated with GI and GU cancer diagnoses.

GI and GU bleeding may be the first sign of an underlying cancer [Jones R et al. *BMC*. 2007; Ford AC et al. *Gut*. 2008]. In the COMPASS trial, treatment with rivaroxaban compared with aspirin was associated with increased GI, but not GU bleeding [Eikelboom JW et al. *N Engl J Med*. 2017]. Using data from COMPASS, John W. Eikelboom, MD, McMaster University, Hamilton, Ontario, Canada, sought to determine whether GI and GU bleeding were associated with increased rates of new cancer diagnoses in patients treated with rivaroxaban.

The COMPASS trial included 27,395 patients with stable coronary or peripheral arterial disease who were randomised to treatment with rivaroxaban 2.5 mg twice daily plus aspirin, 5 mg rivaroxaban, or 100 mg once daily aspirin. Bleeding was defined according to the International Society of Thrombosis and Haemostasis (ISTH) criteria. A new cancer diagnosis was defined as first-ever, or recurrent cancer from a previous diagnosis in patients whose cancer had been thought to have

been eradicated. The proportion of new cancers before and after bleeding, the association between bleeding and new cancer diagnosis, and rates of cancer diagnosis according to randomised treatment were analysed.

In all, 1,082 new cancers were diagnosed during the trial; 257 (23.8%) of these were diagnosed after bleeding (70 were GI cancers and 62 were GU cancers). There was a significant association between GI bleeding and new GI cancers (HR, 12.9; 95% CI, 9.77 to 17.0; *P* < .0001). There was also a significant, but much weaker, association between non-GI bleeding and new GI cancers (HR, 1.77; 95% CI, 1.20 to 2.61; *P* = .004). A highly significant association was also noted between GU bleeding and new GU cancers (HR, 83.4; 95% CI, 58.6 to 118.6; *P* < .0001). The association between non-GU bleeding and new GU cancers was not significant.

The majority of new GI (77.1%) and GU (88.7%) cancers diagnosed after bleeding occurred within 6 months of the bleed. Rivaroxaban-based treatments compared with aspirin increased GI bleeding within the first year, but not in the second or third year, and this was accompanied by an increase in the number of GI cancers diagnosed after bleeding in the first year, but not in the second or third (Table 1).

Table 1. Frequency of GI Cancer After GI Bleeding in Year 1, 2, and 3+

Year	Rivaroxaban 2.5 mg bid + ASA 100 mg od n (%)	Rivaroxaban 5 mg bid n (%)	Aspirin 100 mg bid n (%)
1	22/268 (8.2%)	18/216 (8.3%)	8/114 (7.0%)
2	6/72 (8.3%)	6/81 (7.4%)	5/58 (8.6%)
3+	1/34 (2.9%)	2/29 (6.9%)	2/29 (6.9%)

GI, gastrointestinal.

Among COMPASS patients with vascular disease on long-term antithrombotic therapy, more than 1 in 5 new diagnoses of all cancers were preceded by bleeding and more than 75% of these cancers were diagnosed within 6 months of the bleed. This suggests that GI and GU bleeding are powerful predictors GI and GU cancer diagnosis. An early increase in GI bleeding with antithrombotic treatments appears to be associated with earlier diagnosis of GI cancer.

Prof. Eikelboom suggests that physicians detecting the occurrence of GI or GU bleeding in patients receiving antithrombotic drugs should lead to expedient evaluation for cancer in the same organ. Extended follow-up of COMPASS trial participants may help to determine whether earlier diagnosis of GI cancer in patients with GI bleeding improves cancer outcomes.

Coronary CT Angiography Reduces 5-Year Risk of Myocardial Infarction

Written by **Michiel Tent**

In patients with stable chest pain, coronary computed tomographic angiography (CTA)-guided management reduced 5-year coronary heart disease (CHD) death or non-fatal myocardial infarction (MI) compared with standard care alone in the Scottish Computed Tomography of the Heart trial [SCOT-HEART trial; Newby DE et al. *N Engl J Med*. 2018]. The final clinical outcomes were presented by David E Newby, MD, PhD, University of Edinburgh, United Kingdom.

Coronary CTA improves diagnostic certainty in the assessment of patients with stable chest pain, but its effect on 5-year clinical outcomes was unknown. The SCOT-HEART trial was designed to determine the longer-term effect of CTA on investigations, treatments, and clinical outcomes. The trial had an open-label, multicentre, parallel-group design. Eligible for inclusion were patients aged 18 to 75 years with stable chest pain who had been referred by a primary care physician to an outpatient cardiology clinic. A total of 4,146 patients from 12 Scottish cardiology centres were included. Following routine clinical evaluation, they were randomly assigned to either standard care plus CTA (n = 2,073) or standard care alone (n = 2,073). Clinical endpoints included death (cardiovascular [CV] death, non-CV death, death from CHD, and death from any cause), MI, and stroke. The primary endpoint was death from CHD or nonfatal MI at 5 years.

The median duration of follow-up was 4.8 years, comprising a total of 20,254 patient-years. The rate of the primary long-term endpoint was significantly lower in the CTA group than in the standard-care group (2.3% [n = 48] vs 3.9% [n = 81]; HR, 0.59; 95% CI, 0.41 to 0.84; *P* = .004). This difference was driven primarily by a lower rate of nonfatal MI in the CTA group (HR, 0.60; 95% CI, 0.41 to 0.87). There were no significant differences in non-CV death or deaths from any cause.

The rates of invasive coronary angiography (ICA) and coronary revascularisation were higher in the CTA group than in the standard-care group in the first few months of follow-up. At 5 years however, overall rates were similar. ICA was performed in 491 patients in the CTA group and in 502 patients in the standard-care group (HR, 1.00; 95% CI, 0.88 to 1.13). Coronary revascularisation was performed in 279 patients in the CTA group and in 267 in the standard-care group (HR, 1.07; 95% CI, 0.91 to 1.27). Beyond the first year analysis, patients assigned to CTA had lower rates of ICA (HR, 0.70; 95% CI, 0.52 to 0.95), and of coronary

revascularisation (HR, 0.59; 95% CI, 0.38 to 0.90). In the CTA group, more preventive therapies were initiated (OR, 1.40; 95% CI, 1.19 to 1.65), as well as more antianginal therapies (OR, 1.27; 95% CI, 1.05 to 1.54).

Prof. Newby concluded that, in this trial, CTA in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from CHD or nonfatal MI at 5 years than standard care alone, without resulting in a significantly higher rate of coronary angiography or coronary revascularisation. Early increases in ICA and coronary revascularisation were offset by lower rates beyond 1 year. Benefits seem to be attributable to better targeted preventive therapies and coronary revascularisation.

Ticagrelor Monotherapy Beyond 1 Month No Better Than Standard Dual Antiplatelet Therapy After Stenting

Written by **Constance de Koning**

Discontinuing aspirin after 1 month continuing monotherapy with ticagrelor is no better than standard dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS) or stable coronary artery disease (CAD), according to the results of the GLOBAL LEADERS study [Vranckx P et al. *Lancet*. 2018] presented by Patrick W. Serruys, MD, PhD, Erasmus Medical Center, Rotterdam, the Netherlands.

In this multicentre, open-label, superiority trial, a total of 15,968 patients who underwent PCI with a biolimus A9-eluting stent for stable CAD or ACS were randomised to either 75-100 mg aspirin daily plus 90 mg ticagrelor twice daily for 1 month, followed by 23 months of ticagrelor monotherapy (n = 7,988), or standard DAPT with 75-100 mg aspirin daily plus either 75 mg clopidogrel daily (in patients with stable CAD) or 90 mg ticagrelor twice daily (in patients with ACS) for 12 months, followed by aspirin monotherapy for 12 months (n = 7,980). The composite primary endpoint was the cumulative incidence of all-cause death or new Q-wave myocardial infarction (MI) within 2 years; the secondary endpoint was the rate of moderate or severe bleeding (BARC criteria 3 or 5) over the 2-year period.

At 12 months, all-cause mortality or new Q-wave MI was 1.95% in the ticagrelor group versus 2.47% in the standard DAPT group (risk ratio [RR], 0.79; 95% CI, 0.64 to 0.98; *P* = .028; Table 1).

Table 1. Primary and Secondary Outcomes at 12 Months (ITT)

	Experimental group	Reference group	Risk Ratio (95% CI)	*P*-value
Number of patients	n = 7,980	n = 7,988		
All-cause mortality or new Q-wave MI	1.95% (156)	2.47% (197)	0.79 (0.64-0.98)	.028
All-cause mortality	1.35% (108)	1.64% (131)	0.82 (0.64-1.06)	.138
New Q-wave MI	0.60% (48)	0.86% (69)	0.70 (0.48-1.00)	.052

ITT, intent-to-treat; MI, myocardial infarction.

At 24 months, all-cause mortality or new Q-wave MI was 3.81% for ticagrelor versus 4.37% for standard DAPT (RR, 0.87; 95% CI; 0.75 to 1.01; *P* = .073; Table 2).

Table 2. Primary and Secondary Outcomes at 24 Months (ITT)

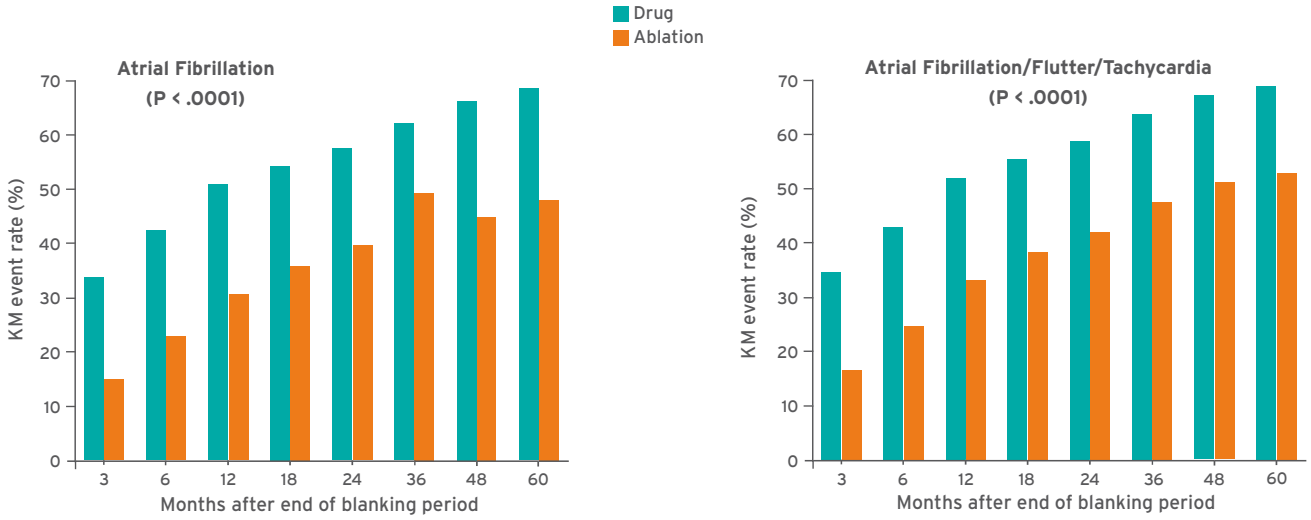
	Experimental group	Reference group	Risk Ratio (95% CI)	*P*-value
Number of patients	n = 7,980	n = 7,988		
All-cause mortality or new Q-wave MI	3.81% (304)	4.37% (349)	0.87 (0.75-1.01)	.073
All-cause mortality	2.81% (224)	3.17% (253)	0.88 (0.74-1.06)	.18
New Q-wave MI	1.04% (83)	1.29% (103)	0.80 (0.60-1.07)	.14

ITT, intent-to-treat; MI, myocardial infarction.

Major bleeding (BARC 3 or 5) was observed in 2.04% of patients who received aspirin for 1 month and extended ticagrelor and in 2.12% of patients treated with conventional DAPT (RR, 0.97; 95% CI, 0.78 to 1.20; *P* = .767).

Although the rate of serious adverse events did not differ significantly between the two groups, according to Prof. Serruys, adherence may have compromised the assessment of superiority, as in the second year of treatment 78% of ticagrelor patients were adherent versus 93% in the reference group. Investigator reporting was used without central adjudication on the secondary outcomes, so it is possible that bias or misclassification could have occurred. Additionally, the unexpected lower rate of all-cause mortality and the composite primary endpoint limits the predictive power of the study. In conclusion, ticagrelor plus low-dose aspirin for 1 month followed by 23 months of ticagrelor monotherapy was not superior in reducing the 2-year rates of all-cause mortality and non-fatal, new Q-wave MI compared with 12 months of standard DAPT followed by aspirin monotherapy in patients who underwent PCI.

Figure 1. Cumulative First Recurrence Event Rates After 90 Days of Blanking



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Ablation Reduced Recurrent Arrhythmias Compared With Drug Therapy in AF Patients

Written by **Michiel Tent**

In the CABANA trial, catheter ablation was associated with a significant relative risk reduction of around 50% in recurrence of atrial arrhythmias in patients with atrial fibrillation (AF) compared with drug therapy. AF was the dominant first recurrent rhythm after the 90-day blanking period during the 5 years of follow-up.

The results of this secondary analysis of the CABANA trial focusing on the recurrence of atrial arrhythmias were presented by Jeanne Poole, MD, University of Washington Medical Center, Seattle, Washington, USA. The single-blind CABANA trial randomised 2,204 symptomatic patients with paroxysmal or persistent AF 1:1 to percutaneous left atrial catheter ablation or medical therapy. Patients aged ≥ 65 years or < 65 years with > 1 risk factor for stroke who were eligible for both ablation and ≥ 2 rhythm or rate controlling drugs were followed for a median of 4 years [Packer DL et al. *Am Heart J*. 2018]. The primary composite endpoint of death, disabling stroke, serious bleeding, or cardiac arrest was not significantly reduced with ablation (HR, 0.86; 95% CI, 0.65 to 1.15; *P* = .30) [Packer DL. HRS 2018 Scientific Sessions].

The current analysis reported rates of recurrent atrial arrhythmias using electrocardiographic monitoring every 3 months (monitoring duration alternated between 24 hours and 96 hours each 3-month period). In CABANA, a 2-channel recording system was used for electrocardiogram monitoring by 86% of enrolling sites, while the remaining centres employed other heart rhythm monitoring systems. Endpoint-determining rhythms (EDR) were defined as: AF, atrial flutter (AFL), or atrial tachycardia (AT) lasting ≥ 30 seconds.

The hazard ratios of a first episode after 90 days of blanking in 1,240 patients with a CABANA recorder in patients randomised to AF ablation versus drug therapy were 0.52 (95% CI, 0.45 to 0.60; *P* < .001) for recurrent AF and 0.53 (95% CI, 0.46 to 0.62; *P* < .001) for the combined outcome of AF, AFL, and AT. In 803 patients without a CABANA recorder, the results similarly favoured the ablation group (HR 0.50 and 0.56, respectively). Ablation was associated with a significant reduction across the 5 years of therapy in cumulative first recurrence event rate, again after 90 days of blanking (Figure 1). There were no reductions in the rates of AFL and AT by treatment strategy (HR, 1.08; 95% CI, 0.83 to 1.39; *P* = .58); only the outcome of recurrent AF was reduced by ablation (HR, 0.53; 95% CI, 0.46 to 0.62; *P* < .001). The average AF burden as assessed by biannual 96-hour Holter monitoring was also found to be significantly lower in the ablation group across all 5 years of treatment (*P* < .0001). These findings were significant regardless of the baseline pattern of AF, paroxysmal or persistent/long-standing persistent AF.

Looking to the future, Prof. Poole noted that this large base of rhythm data provides a foundation for addressing many other important questions with respect to recurrent arrhythmias and treatment of patients with AF.

CAMELLIA-TIMI 61 Established Cardiovascular Safety of Lorcaserin

Written by **Constance de Koning**

Adding lorcaserin to diet and exercise resulted in sustained weight loss compared with placebo without increasing the risk for major adverse cardiovascular events (MACE) in the CAMELLIA-TIMI 61 study [Bohula EA et al. *N Engl J Med*. 2018], presented by Erin A. Bohula, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA.

Weight loss is an important factor when improving cardiovascular (CV) risk factors, but thus far there have been no agents with proven CV safety. In clinical trials, lorcaserin, a selective agonist of the 5HT-2C receptor, has shown efficacy for weight loss, but its CV safety had not been tested.

Twelve-thousand overweight and obese patients were included in this is multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Patients who had established CV disease or CV risk factors, such as type 2 diabetes, and a median baseline body mass index of 35 mg/kg^2 were randomised 1:1 to receive lorcaserin 10 mg twice daily or placebo. Median follow-up was 3.3 years. The primary CV efficacy endpoint was MACE+ (i.e., MACE, hospitalisation for heart failure, unstable angina, or coronary revascularisation). The primary CV safety endpoint was MACE (i.e., CV death, myocardial infarction, or cerebrovascular accident).

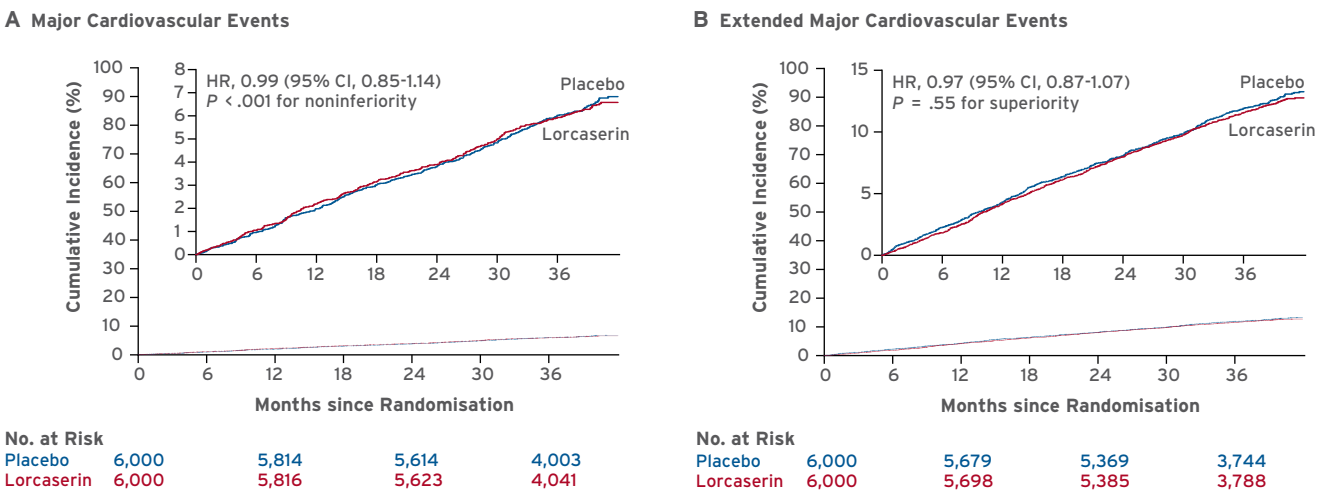
A total of 98% of patients in the lorcaserin group and 97% in the placebo group completed the study. Weight loss achieved with lorcaserin was on average 4.2 kg after 1 year versus 1.4 kg for placebo; a between group difference of 2.8 kg (P < .001). At 1 year, 38.7% of patients on lorcaserin had ≥ 5% weight loss compared with 17.4% of those on placebo (OR, 3.01; 95% CI, 2.74 to 3.30; P < .001). Ten percent weight loss or more was achieved by 14.6% and 4.8% of patients, respectively (OR, 3.40; 95% CI, 2.92 to 3.95; P < .001). Weight loss with lorcaserin was sustained over time and remained significant up to 3.3 years.

At 3.3. years, MACE occurred in 6.1% of the lorcaserin-treated patients and 6.2% of patients treated with placebo (HR, 0.99; 95% CI, 0.85 to 1.14; P < .001 for non-inferiority ; Figure 1A). The composite of MACE+ occurred in 707 patients (12.8%, or 4.1% per year) in the lorcaserin group and in 727 (13.3% or 4.2% per year) in the placebo group (HR, 0.97; 95% CI, 0.87 to 1.07; P =.55; Figure 1B).

Adverse events considered to be possibly related to the study drug lead to discontinuation in 7.2% of lorcaserin patients versus 3.7% of placebo patients. The most commonly reported adverse events leading to discontinuation in the lorcaserin group were dizziness, fatigue, headache, diarrhea, and nausea. Lorcaserin seemed to have a favourable effect on glycaemia although it was suggested this may be due to the achieved weight loss.

These findings support using lorcaserin as an adjunct to lifestyle modification for long-term weight management, even in high-risk CV patients. However, whether this new therapy is a cost-effective and sustainable approach to achieving a modest degree of weight loss without additional CV benefit compared with lifestyle changes or bariatric surgery remains to be seen.

Figure 1. Major Adverse Cardiac Outcomes



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Percutaneous Mitral Valve Repair Is Safe in Patients With Secondary Mitral Regurgitation but Does Not Improve Outcomes

Written by **Phil Vinall**

Results from the MITRA.fr study show that percutaneous mitral valve repair is as safe as optimal medical treatment (OMT) but does not reduce death or unplanned hospitalisation for heart failure (HF) in patients with secondary mitral regurgitation (MR). The data were presented by Jean-Francois Obadia, MD, PhD, Civils Hospices of Lyon, France [Obadia JF et al. *N Engl J Med*. 2018]

The MITRA.fr study was a national, multicentre, investigator-initiated, open-label, randomised trial. The objective was to evaluate the clinical efficacy and safety of percutaneous mitral valve repair using the MitraClip system plus OMT versus OMT alone in patients with severe symptomatic secondary MR contraindicated for surgical repair. Patients were randomly assigned to receive the MitraClip plus OMT (n = 152) or OMT alone (n = 152). The primary endpoint was a composite of all-cause mortality or unplanned hospitalisations for HF at 12 months after randomisation.

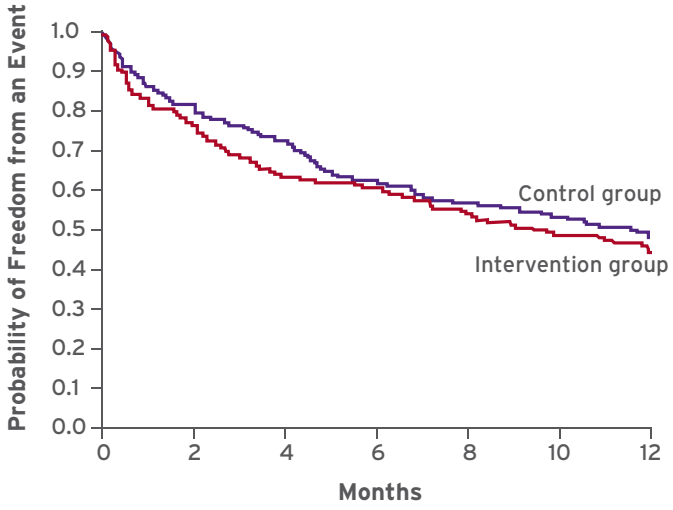
Eligibility requirements included: age > 18 years; NYHA class ≥ II; ≥ 1 hospitalisation for HF within 12 months preceding randomisation; severe secondary MR with an effective regurgitant orifice > 20 mm^2 or regurgitant volume > 30 mL/beat and left ventricular ejection fraction between 15% and 40%. Patients considered eligible for mitral surgery intervention according to the Heart Team and those having a Corelab assessment outside of the predefined parameters were excluded.

The per-protocol analysis includes 109 patients in the MitraClip group and 137 in the OMT group. Participants were a mean age of 70 years (> 75% male). Sixty percent had ischaemic cardiomyopathy and 2/3 were either NYHA Class III or IV. Mean ejection fraction was 33%; mean effective regurgitation orifice area was 31 mm^2; and mean systolic blood pressure was 108.5 mm Hg. The majority of participants were being treated with diuretics, beta blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and/or a mineralocorticoid receptor antagonist.

The rate of the primary outcome of all-cause death or unplanned rehospitalisation for HF did not differ significantly between the two groups (54.6% for patients who received the MitraClip plus OMT vs 51.3% for those who received OMT only). There were also no differences in the components or within the intention-to-treat or per-protocol analysis (OR, 1.16; 95% CI, 0.73 to 1.84; *P* = .53; Figure 1).

Implantation was successful in 96% of patients. The mortality rate at 1-year was similar for the two groups (24.3% and 22.4%, in the intervention and control groups, respectively). There were no periprocedural incidents of urgent conversion to heart surgery or periprocedural mortality at 3 days. Vascular complications requiring surgery or haemorrhage resulting in transfusion occurred in 3.5% of patients; 1.4% had a cardiac embolism or tamponade. MR grade improved in the

Figure 1. Primary Composite Endpoint



No. at Risk							
Control group	152	123	109	94	86	80	73
Intervention group	151	114	95	91	81	73	67

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MitraClip group at discharge and was maintained at 12 months. NYHA class improved significantly in both groups for the majority of patients (from Class II and III at baseline to Class I and II at discharge; $P < .001$).

Percutaneous correction of secondary MR with the MitraClip system is safe but does not improve patient outcomes when compared with OMT. The effectiveness of earlier intervention in a more selected sub-group of patients remains to be explored.

Rivaroxaban Does not Reduce the Composite of Death, MI or Stroke in Heart Failure Patients

Written by **Constance de Koning**

Patients with heart failure are at heightened risk of adverse cardiovascular (CV) events including thromboembolic complications such as stroke [Cleland JGF et al. *Am Heart J*. 2004; Massie BM et al. *Circulation*. 2009; Homma S et al. *N Engl J* Med. 2012; Zannad F et al. *Eur J Heart Fail*. 2015]. Low-dose rivaroxaban (2.5 mg) has been shown to reduce CV death, myocardial infarction (MI), and stroke in patients with acute coronary syndromes (ACS) and in selected high-risk patients with stable coronary artery disease (CAD) when added to antiplatelet agents, according to Faiez Zannad, MD, Université de Lorraine, Nancy, France.

It was hypothesised that the addition of rivaroxaban 2.5 mg twice daily to background antiplatelet therapy would reduce risk of major adverse CV events in patients with recent worsening of congestive heart failure (CHF) and underlying CAD compared with placebo.

The Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease trial [COMMANDER HF; Zannad F et al. *N Eng J Med*. 2018] was a randomised, double-blind, parallel-group, event-driven, multicentre study. The primary efficacy outcome was the composite of all-cause mortality, MI or stroke following a HF event. The principal safety outcome was the composite of fatal bleeding or bleeding into a critical space, which could potentially lead to permanent disability. Eligible patients (n = 5,022) were assigned to rivaroxaban 2.5 mg twice daily or placebo added to standard care. Participants had at least a 3-month history of CHF with reduced left ventricular ejection fraction ≤ 40%, CAD, and elevated plasma BNP or NT-proBNP during the index event. Exclusion criteria were a high risk of bleeding, atrial fibrillation (AF), or another condition that required long-term anticoagulation.

The primary endpoint was not significantly different between groups and occurred in 13.4% of rivaroxaban patients and in 14.3% of placebo patients (HR, 0.94; 95% CI, 0.84 to 1.05; $P = .27$). There was also no difference in all-cause mortality between the groups (11.4% and 11.6%, respectively; HR, 0.98; 95% CI, 0.87 to 1.10). There was a nominally significant reduction in stroke with rivaroxaban compared with placebo (1.08% vs 1.62%: HR, 0.66; 95% CI, 0.47 to 0.95) and a trend for MI (HR, 0.83; 95% CI, 0.63 to 1.08). The principal safety outcome occurred in 0.7% of rivaroxaban patients and 0.9% of placebo patients (HR, 0.80; 95% CI, 0.43 to 1.49; $P = .48$).

Low-dose rivaroxaban as an addition to guideline-based treatment does not improve the composite of all-cause mortality, MI, or stroke in patients with recent worsening of CHF and reduced ejection fraction, and CAD without AF. Prof. Zannad noted that as this study included HF patients who were at high risk after recent HF hospitalisation, it opened the possibility that HF deaths made up a substantial proportion of all deaths in this population instead of deaths due to atherothrombotic events. Trends for reduction in MI and stroke support the hypothesis that more potent antithrombotic strategies may reduce thrombotic risk in patients with HF. However, rates of death are high and may occur from predominantly non-thrombotic causes attenuating benefit for the primary composite endpoint of this trial. Future studies focused on outcomes modifiable with antithrombotic therapies may demonstrate efficacy.

FRANCE-TAVI Registry Results

Written by **Michiel Tent**

Male gender, renal failure, and atrial fibrillation (AF) predicted mortality at 3 years of follow-up in patients who underwent successful transcatheter aortic valve replacement (TAVR). Primarily for AF, anticoagulation was associated with a lower risk of bioprosthetic valve dysfunction (BVD) after TAVR but a higher risk of long-term mortality.

The results from FRANCE-TAVI, a prospective, multicentre, nation-wide French registry were, presented by Jean-Philippe Collet, MD, Sorbonne University and Pitie Salpetriere Hospital, Paris, France [Overtchouk P et al. *J Am Coll Cardiol*. 2018]. Prof. Collet explained that the optimal antithrombotic treatment after TAVR is still unknown. Dual antiplatelet therapy (DAPT) is used most frequently but single antiplatelet therapy or oral anticoagulation (OAC) are also used. The objectives of the French research group were two-fold: to investigate whether antithrombotic treatment influences long-term mortality and early BVD, and to explore independent correlates of long-term mortality and early BVD after TAVR. BVD was defined as increased prosthetic gradient ≥ 10 mm Hg or new gradient ≥ 20 mm Hg, and was identified by multislice computed tomography (MSCT).

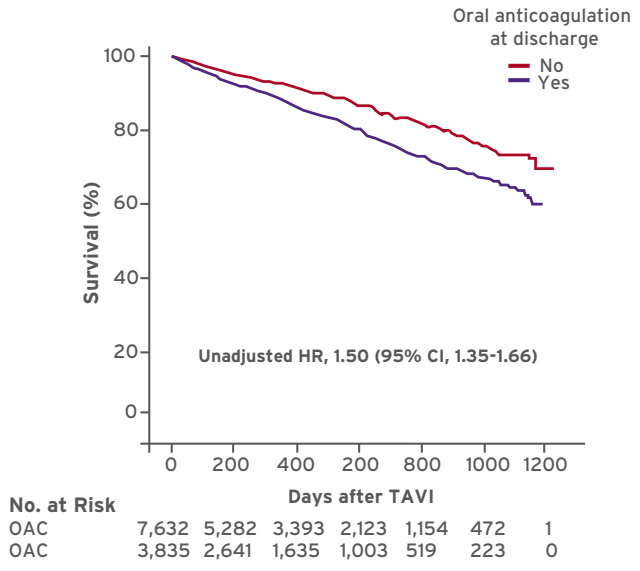
Between 1 January 2013 and 31 December 2015, 12,804 patients were included. Of these, 11,469 were alive at discharge with known antithrombotic treatment and were analysed for mortality. Mean age was 82.8 years, mean logistic Euroscore was 17.8, and mean follow-up was 495 days. A total of 2,555 patients had at least two echocardiographic evaluations and were eligible for BVD assessment. The prevalence of BVD post-TAVR in the registry was 5.5% (n = 140). One third of patients had a history of AF; the same proportion had OAC at discharge (n = 3,836), primarily for the prevention of cardioembolic stroke. The results showed that neither aspirin nor clopidogrel were independently associated with mortality (Table 1).

Table 1. Independent Correlates of Mortality

	Adjusted HR (95% CI)	*P*-value
Male gender	1.63 (1.44-1.84)	.001
History of AF	1.41 (1.23-1.62)	.001
Chronic renal failure	1.37 (1.23-1.53)	.001

Prof. Collet noted that anticoagulation at discharge remained a correlate of mortality (unadjusted HR, 1.50; 95% CI, 1.35 to 1.66; Figure 1) independent of AF, despite the strong correlation between AF and mortality.

Figure 1. Kaplan-Meier Survival Curves According to Anticoagulation at Discharge



OAC, oral anticoagulation.

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Anticoagulation at discharge was also independently associated with lower rates of BVD (adjusted OR, 0.54; 95% CI, 0.35 to 0.82; *P* = .005). The same was true for a non-femoral approach (adjusted OR, 0.53; 95% CI, 0.28 to 1.02; *P* = .049). A higher risk of BVD was yielded by chronic renal failure (adjusted OR, 1.46; 95% CI, 1.03 to 2.08; *P* = .034); and by a prosthesis size of ≤ 23 mm (adjusted OR, 3.43; 95% CI, 2.41 to 4.89; *P* < .001). Prof. Collet noted that antithrombotic treatment is driven not by the procedure but by patient characteristics. Of the patients in this study, 70% used OAC therapy to manage their AF and use of OAC was associated with lower risk of BVD.

Limitations of the study include its non-randomised, observational nature, which means unknown confounders cannot be excluded; the declarative clinical outcome reporting; treatment cross-over, which could not be assessed; and the identification of BVD with MSCT, which may have led to different correlates.

Primary Results From the MARINER Trial

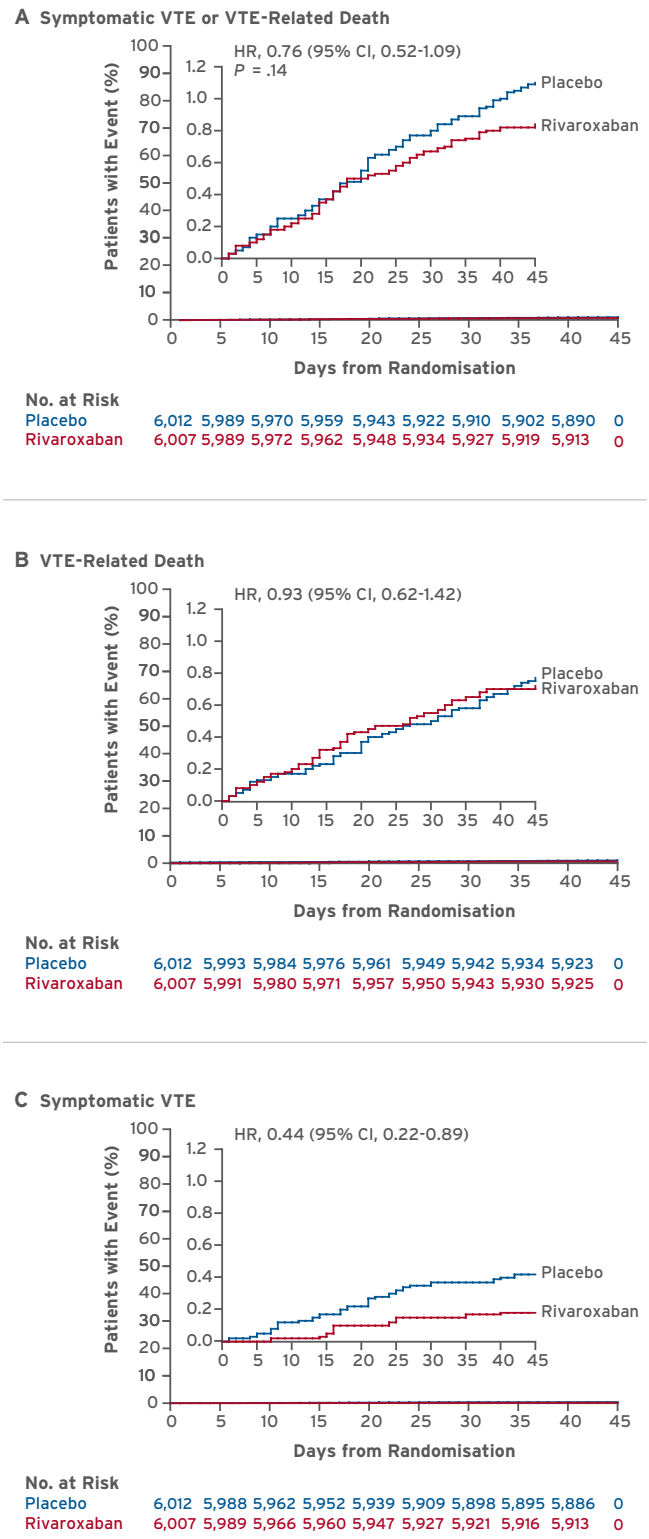
Written by **Constance de Koning**

Primary results from the MARINER trial [Spyropoulos AC et al. *N Engl J Med*. 2018] showed that treatment with rivaroxaban did not significantly reduce the risk of symptomatic venous thromboembolism (VTE) and VTE-related death in medically ill patients after hospital discharge.

Hospitalised patients run a substantial risk of developing VTE after discharge. According to Alex C. Spyropoulos, MD, Lennox Hill Hospital, New York, USA, the role of extended thromboprophylaxis has been investigated but has either shown excess bleeding or beneficial effects from reducing mostly asymptomatic deep vein thrombosis (DVT). MARINER was designed to compare rivaroxaban with placebo for the prevention of symptomatic VTE and VTE-related death in medically ill patients at heightened risk of VTE after discharge from the hospital. The principal safety objective was major bleeding.

The trial was a randomised, double-blind, placebo-controlled, event-driven study that included a total of 12,024 patients aged ≥ 40 years who had been hospitalised with an acute medical illness for 3-10 consecutive days and had an elevated VTE risk, defined as a modified IMPROVE score ≥ 4 or a score of 2 or 3 plus a plasma D-dimer level more than twice the upper limit of normal. The rivaroxaban regimen consisted of 10 mg once daily or 7.5 mg for patients with a creatinine clearance of 30 to < 50 ml/min. The first dose was given on the day of discharge and the last dose at Day 45. Patients were followed up for an additional 30 days. Baseline characteristics were similar between groups.

Figure 1. Primary Efficacy Outcome up to Day 45



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The results showed that symptomatic VTE and VTE-related death up to Day 45 occurred in 66 patients receiving placebo versus 50 patients receiving rivaroxaban. This represented a 24% relative risk reduction or a 0.27% absolute risk reduction (HR, 0.76; 95% CI, 0.52 to 1.09; *P* = .136 ; Figure 1A).

There was a slight benefit in the patients who received the full 10 mg rivaroxaban dose (0.65% vs 0.98%; *P* = .075), with no such signal in the patients with moderate renal insufficiency who received the lower 7.5 mg dose. Exploratory, prespecified secondary outcomes showed a nominally significant 56% reduction in symptomatic VTE (*P* = .023) and a 27% reduction in the composite of symptomatic VTE and all-cause mortality (*P* = .033) with rivaroxaban. Major bleeding was low in both groups (0.28% for rivaroxaban and 0.15% for placebo; HR, 1.88; 95% CI, 0.84 to 4.23; *P* = .124).

Rivaroxaban in this trial did not significantly reduce the composite of symptomatic VTE and VTE-related death in at-risk patients post-discharge (Figure 1B). The number of major bleeding events with rivaroxaban was low, with no significant increase in major, critical or fatal bleeding. These differences in risk suggest that the number needed-to-treat (NTT) to prevent one symptomatic VTE is 430 while the NTT to cause one major bleed is 856.

The event rate for the primary endpoint in the population selected was low (1.1% over 45 days in the placebo group) relative to that estimated in the design (2.5%) and even lower for the endpoint of symptomatic VTE (0.42%, 25 of 6,012 randomised to placebo). The trial was powered estimating a 40% relative risk reduction requiring 161 primary endpoint events. However, the observed relative risk reduction was 24% with only 116 events, raising the question of whether the trial was adequately powered. That no effect was observed with rivaroxaban on VTE-related death raises the question whether the definition used in the trial, which included sudden and unexplained death, was specific enough to capture true thrombotic related causes of death.

It should be noted that the observed event rate in the placebo group was 1.1% – less than half the estimate in the original protocol (2.5%). Although a protocol amendment increased the enrolment from 8,000 to 12,000 patients to allow more primary endpoint events to accrue, the final number was fewer than anticipated (116 vs 161 events). These results indicate that either a higher risk population and/or larger trial with a greater number of events would be needed to determine whether low-dose oral anticoagulation may significantly reduce recurrent VTE events in medically ill patients.

Primary Prevention With Aspirin: Effective in Patients with Diabetes, but Role in Moderate-Risk Patients Less Clear

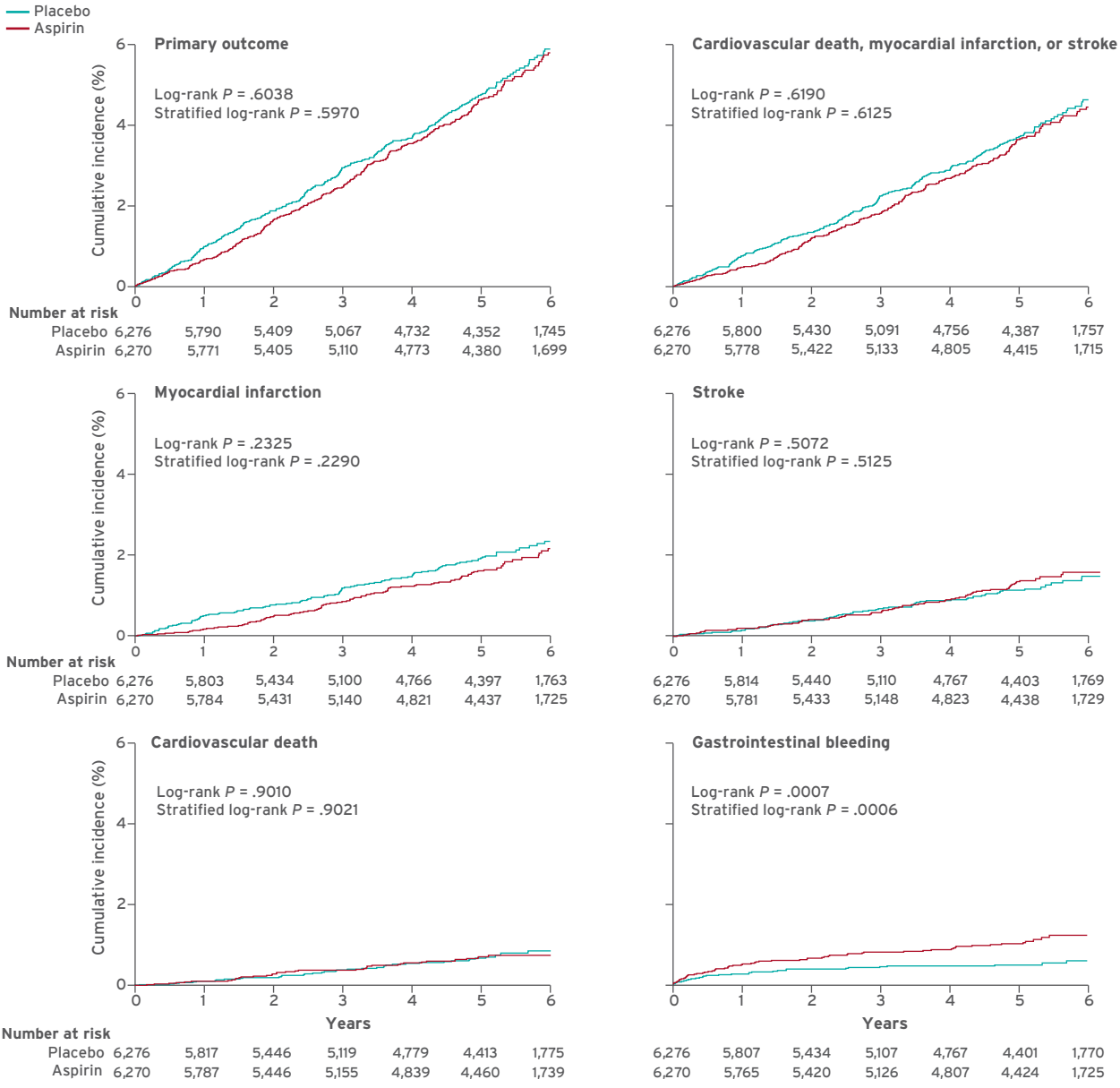
Written by **Constance de Koning**

Prevention of cardiovascular (CV) events plays a key role in achieving optimal patient outcomes, especially in high-risk groups. Although aspirin did not reduce CV risk in moderate-risk patients, it did prevent serious vascular events (SVE) in diabetic patients without CV disease (CVD), although major bleeding was increased.

No Clear Role for Aspirin in CV Risk Reduction in Moderate-Risk Patients

Findings from the Aspirin to Reduce Risk of Initial Vascular Events trial [ARRIVE; Gaziano JM et al. *Lancet*. 2018] showed that aspirin does not reduce the long-term risk of CV events in patients at moderate risk. This randomised, double-blind, placebo-controlled, multicentre trial assessed the efficacy and safety of aspirin in patients at moderate estimated risk of a CV event (men age ≥ 55 years with ≥ 2 CV risk factors and women age ≥ 60 years with ≥ 3 CV risk factors). Patients had no known history of CVD or diabetes plus an estimated 10-year risk of major coronary heart

Figure 1. Key outcomes



Reprinted from *Lancet*. Gaziano JM et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial; http://dx.doi.org/10.1016/S0140-6736(18)31924-X. Copyright 2018. With permission from Elsevier.

disease events of 10-20% corresponding to a 10-year 20-30% CVD risk were randomised to 100 mg enteric-coated aspirin daily (n = 6,270) or placebo (n = 6,276). Statins were used by 43% of patients in this study. The primary efficacy endpoint was time of first occurrence of composite endpoint (CVD death, myocardial infarction [MI], stroke, unstable angina, transient ischaemic attack [TIA]). Researchers found that 4.3% of patients taking aspirin and 4.5% of patients taking placebo experienced the primary endpoint over a mean of 5 years (HR, 0.96; 95% CI, 0.81 to 1.13; *P* = .60). The primary safety endpoints were haemorrhagic events and incidence of other adverse events; gastrointestinal bleeding (GI) events occurred in 0.97% of patients taking aspirin and in 0.46% of patients on placebo (HR, 2.11; 95% CI, 1.36 to 3.28; *P* = .0007). Rates of severe GI bleeding were extremely low (0.06% for aspirin and 0.03% for placebo) The mortality rates were 2.55% in the aspirin group and 2.57% in the placebo group (HR, 0.99; 95% CI, 0.80 to 1.24; *P* = .95). Other findings included a lower risk of fatal or non-fatal MI for patients on aspirin if they were at least 60% compliant with treatment: 1.52% versus 1.78% in the placebo group (HR, 0.85; 95% CI, 0.64 to 1.11; *P* = 0.23; Figure 1) but not reduction in stroke (1.2% vs 1.07%; HR, 1.12; 95% CI, 0.80 to 1.55; *P* = .507).

J. Michael Gaziano, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, added that despite a lack of overall reduction in CV events, these results emphasised the ability of aspirin to reduce the risk of a first non-fatal MI without affecting the risk of total stroke, while providing more insights into the efficacy and safety of aspirin in the primary prevention of CVD in older individuals and women.

Aspirin Prevented SVE in Diabetic Patients Without CVD but Caused Major Bleeding

The risks and benefits of aspirin to prevent a first CV event in patients with diabetes was evaluated in the Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus trial [ASCEND; ASCEND Study Collaborative Group. *N Engl J Med*. 2018]. A total of 15,480 patients with diabetes (94% type 2, median duration 7 years) and no prior CVD were randomised to aspirin 100 mg daily or placebo, with a mean follow-up of 7.4 years. The primary efficacy outcome was the first SVE (i.e., MI, stroke or TIA, or vascular death, excluding any confirmed intracranial haemorrhage). The primary safety outcome was the first major bleeding event. Secondary outcomes included GI cancer. Statins were used by approximately 75% of participants. Aspirin significantly reduced the risk of a SVE (non-fatal MI, stroke or TIA, or vascular death; 8.5% vs 9.6%; rate ratio, 0.88; 95% CI, 0.79 to 0.97; *P* = .01). A breakdown of the outcomes per separate SVE is shown in Table 1.

Table 1. Components of Primary Efficacy Outcome Plus Revascularisation

Type of event	Aspirin (n = 7,740)	Placebo (n = 7,740)
	no. of participants with events (%)	
Any SVE	658 (8.5)	743 (9.6)
Any arterial revascularisation	340 (4.4)	384 (5.0)
Any SVE or revascularisation	833 (10.8)	936 (12.1)

SVE, serious vascular event.

However, these outcomes came with an increased risk of major bleeding (4.1% vs 3.2%; HR, 1.29; 95% CI, 1.09 to 1.52; *P* = .003), of which 41% were GI, 21% were sight-threatening events, 17% were intracerebral haemorrhage (ICH), and 20% were bleeding events at other sites. No significant effect of the use of aspirin on mortality from all vascular causes combined (representing ~30% of all deaths) was observed when compared with placebo. There were no between-group differences in the rates for any type of cancer after more than 7 years (11.6% in the aspirin group vs 11.5% in the placebo group; RR, 1.01; 95% CI, 0.92 to 1.11), but longer-term follow-up is ongoing.

These trials of aspirin for primary prevention suggest that aspirin may be of benefit in high-risk, compliant patients, although GI bleeding is increased.

Tafamidis Safe and Effective for Patients With Transthyretin Amyloidosis

Written by **Phil Vinall**

Transthyretin amyloidosis (ATTR) is an underdiagnosed life-threatening disease that causes restrictive cardiomyopathy (CM) and progressive heart failure. Median survival is 2.5 to 3.6 years after diagnosis and the only treatment currently available is supportive care. Tafamidis is a novel non-NSAID benzoxazole derivative that binds to the thyroxine-binding sites of both variant and wild-type transthyretin (TTR). It then inhibits dissociation of tetramers into monomers, the rate limiting step in the formation of TTR amyloid leading to CM.

Claudio Rapezzi, MD, University of Bologna, Italy, presented the results of the Transthyretin Amyloid Cardiomyopathy Clinical Trial [ATTR-ACT], a multicentre, international, double-blind, placebo-controlled, Phase 3 trial [Maurer MS et al. *Circ Heart Fail*. 2017; Maurer MS et al. *N Engl J Med*. 2018].

The primary objective of ATTR-ACT was to compare the efficacy, safety, and tolerability of 80 or 20 mg tafamidis meglumine oral daily dose with placebo plus standard of care in patients with hereditary or wild-type

ATTR-CM. After screening, patients (n = 441) were randomly assigned (2:1:2) to tafamidis 80 mg, tafamidis 20 mg, or placebo for the 30-month treatment phase. Patients were stratified for genotype (wild-type or variant) and disease severity (NYHA class).

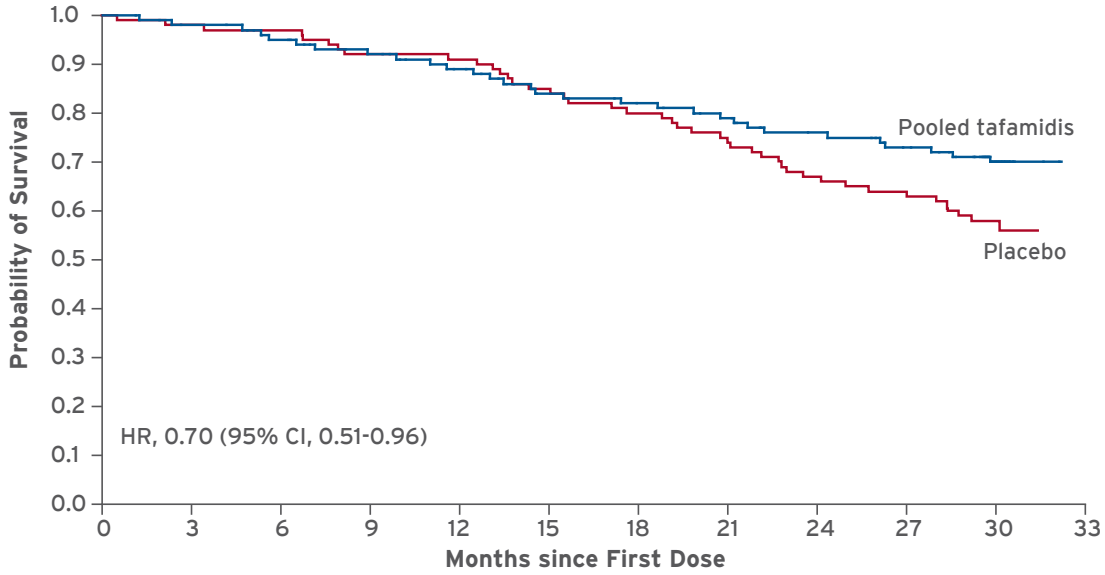
The primary efficacy analysis was the hierarchical combination of all-cause mortality and frequency of cardiovascular (CV)-related hospitalisations. Secondary endpoints included change in the 6-minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire-Overall

Figure 1. Primary Analysis and Components

A Primary Analysis, with Finkelstein-Schoenfeld Method

	No. of Patients	*P* Value from Finkelstein-Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Month 30 *no. (%)*	Average Cardiovascular-Related Hospitalisations during 30 Months among Those Alive at Month 30 *per patient per year*
Pooled Tafamidis	264			186 (70.5)	0.30
		< .001	1.70 (1.26-2.29)		
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality



No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalisations

	No. of Patients	No. of Patients with Cardiovascular-Related Hospitalisations *total no. (%)*	Cardiovascular-Related Hospitalisations *no. per yr*	Pooled Tafamidis vs Placebo Treatment Difference *relative risk ratio (95% CI)*
Pooled Tafamidis	264	138 (52.3)	0.48	
				0.68 (0.56-0.81)
Placebo	177	107 (60.5)	0.70	

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Summary (KCCQ-OS) score. Data were pooled from the two tafamidis treatment groups.

Patients were a mean age of 74 years (90% male; about 80% white); 76% had the wild-type genotype. Disease severity was mostly NYHA class II and III. N-terminal pro b-type natriuretic peptide (NT-proBNP) were ~3,000. In the primary analysis, the combined endpoint of all-cause mortality and rates of CV-related hospitalisations were less frequent among the 264 patients who received tafamidis than among the 177 patients who received placebo (Win Ratio, 1.70; 95% CI, 1.26 to 2.29; $P < .001$; Figure 1A). Tafamidis was associated with lower all-cause mortality than placebo (78 of 264 [29.5%] vs 76 of 177 [42.9%]; HR, 0.70; 95% CI, 0.51 to 0.96; Figure 1B) and a lower rate of CV-related hospitalisations, with a relative risk ratio of 0.68 (0.48 per year vs 0.70 per year; 95% CI, 0.56 to 0.81; Figure 1C). At Month 30, tafamidis was also associated with a lower rate of decline in distance for the 6MWT ($P < .001$) and a lower rate of decline in KCCQ-OS score ($P < .001$). Using the more traditional Cox model, the reduction in the risk of all-cause mortality with tafamidis compared with placebo was 30% ($P = .0259$) with divergence of the event curves noted at 18 months of treatment.

Across prespecified subgroups including etiology wild-type (ATTR vs hereditary ATTR), NYHA class (I/II vs III), and tafamidis dose (80 vs 20 mg), the reduction in all-cause mortality and frequency of CV-related hospitalisations favoured tafamidis over placebo, except for patients in NYHA class III at baseline in whom CV-related hospitalisations were higher in tafamidis-treated patients, which may be a consequence of longer survival during a more severe period of disease.

Tafamidis was well tolerated with a safety profile comparable to placebo. In particular, permanent discontinuation due to adverse events, dose reductions, diarrhoea, and urinary tract infections were less common with tafamidis than with placebo.

These findings provide strong evidence that tafamidis is an effective therapy for patients with ATTR-CM and underscore the importance of early diagnosis and treatment in this disease.

Lowering the Threshold for Diagnosing MI Does Not Improve Patient Outcomes

Written by **Phil Vinall**

Improvements in assay sensitivity have allowed for highly precise quantification of very low levels of troponin, a critical factor when diagnosing myocardial infarction (MI). The 4th Universal Definition of MI now recommends use of high-sensitivity cardiac troponin (hs-cTnI) and a sex-specific 99th centile upper reference limit as the diagnostic threshold. Nicholas L. Mills, MD, PhD, Edinburgh University, United Kingdom, presented the results from the High-Sensitivity Troponin in the Evaluation of Patients With Acute Coronary Syndrome trial showing that such strict classification does not improve outcomes [High-STEACS; Shah ASV et al. *Lancet*. 2018].

High-STEACS was a stepped-wedge, cluster-randomised, controlled trial designed to test the hypothesis that the new definition would reduce subsequent MI or cardiovascular (CV) death at one year in patients who had been hospitalised with suspected acute coronary syndrome.

Both the contemporary and high-sensitivity assays were measured in all patients throughout the trial. During the 6 to 12-month validation portion of the trial, care was guided by the contemporary assay and the results of the high-sensitivity assay were suppressed. After validation, sites were randomised to either early or late implementation during which time the high-sensitivity assay was used to guide care and the results of the contemporary testing was suppressed. Using the assay results, patients likely to benefit from high-sensitivity troponin were stratified into 3 groups: those without myocardial injury (hs-cTnI concentrations within the reference range); those with myocardial injury that had already been identified for some time by the contemporary assay (any cTnI concentration greater the diagnostic threshold of this assay); and patients reclassified by the high-sensitivity cardiac troponin assay (increased hs-cTnI concentration, > 16 ng/L for women, > 34 ng/L for men, cTnI concentrations below the diagnostic threshold on the contemporary assay). The primary endpoint was a composite of MI or CV death at one year.

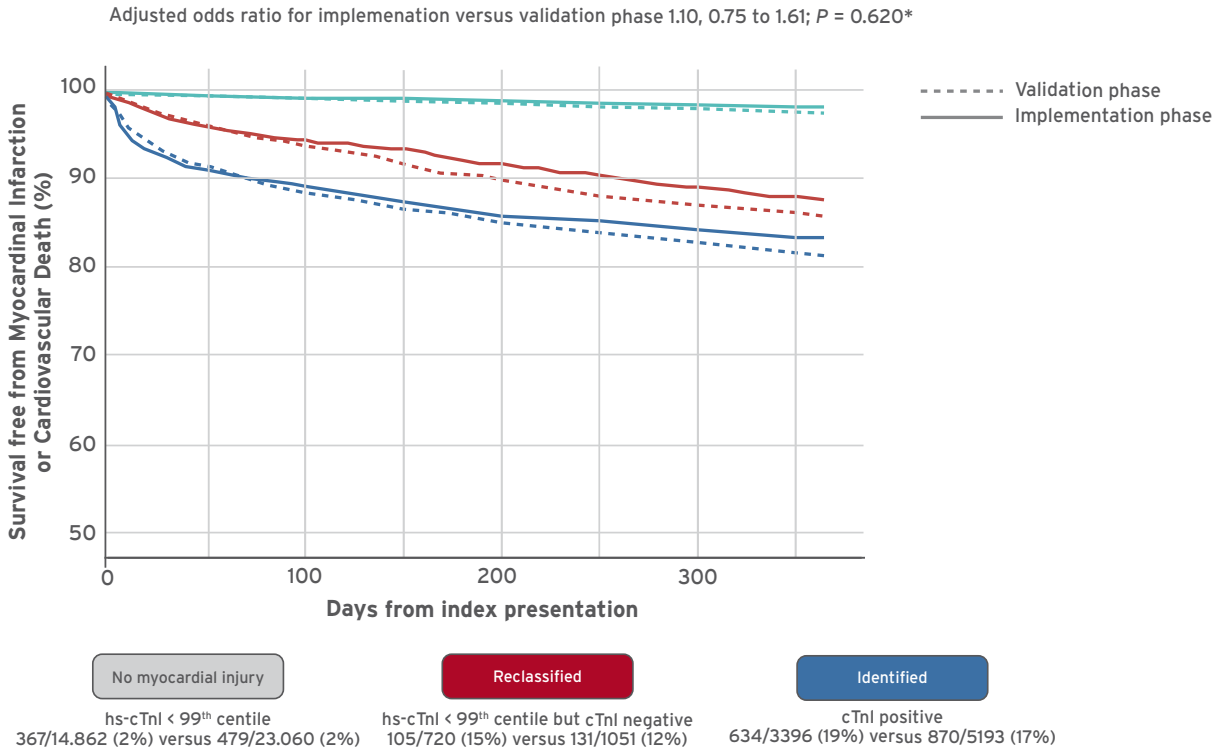
In all, 48,282 consecutive patients were enrolled (mean age 61 years; 47% female) of whom 10,360 had myocardial injury (8,589 identified by contemporary assay and 1,771 reclassified by high sensitivity assay). Patients with myocardial injury were similar except that reclassified patients were older (mean age 75 years) and more likely to be female (83%).

The primary outcome of MI or death from CV causes occurred in 2,586 patients. Patients with no myocardial injury had excellent outcomes with only 2% experiencing the primary outcome in both phases of the trial. Patients identified by contemporary assay had worse outcomes with 19% experiencing an event in the validation phase and 17% in the implementation phase. Reclassified patients, those with evidence of injury not disclosed by contemporary assay, had intermediate outcomes that did not improve with the implementation of

high sensitivity assay (15% of patients in the validation phase and 12% in the implementation phase; Figure 1).

Implementation of hs-cTnI and the 99th percentile threshold reclassified 1 in 6 patients, but only one-third had a diagnosis of type 1 MI, and the rate of subsequent MI or CV death at one year was unaffected. The results of this trial led Prof. Mills to question the recommendations by the Global Task Force for the Universal Definition of MI to base the diagnostic threshold for MI on the 99th percentile from a normal reference population.

Figure 1. Probability of Freedom From Recurrent Acute Coronary Syndrome



* linear mixed effects model adjusted for patients covariates, site, season, and time

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Dual Antithrombotic Therapy Safer and as Efficacious as Triple Therapy in AF patients Undergoing PCI

Written by **Michiel Tent**

In patients with atrial fibrillation (AF) and presenting with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI), presenters agreed that dual antithrombotic therapy (DAT: oral anticoagulant + clopidogrel) is equally effective as, and safer than triple antithrombotic therapy (TAT: oral anticoagulant [OAC] + dual antiplatelet therapy).

Kurt Huber, MD, Sigmund Freud University Medical School, Vienna, Austria, provided an update on the use of DAT and TAT for AF patients undergoing PCI. He argued that choosing DAT or TAT should be done on an individual basis. Positive outcome studies have shown safety benefits for DAT in patients with AF and PCI in cases of increased bleeding risk [Hansen ML et al. *Arch Intern Med*. 2010; Dewilde WJ et al. *Lancet*. 2013].

The current European Society of Cardiology guidelines [Valgimigli M et al. *Eur Heart J*. 2018] state that in patients with ACS treated with coronary stent implantation, dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months (class I, level A), unless there are contraindications such as excessive risk of bleeding (e.g., PRECISE-DAPT score ≥ 25). In patients with an indication for oral anticoagulation undergoing PCI, TAT should be considered for 1, 3, or 6 months (class IIa, level B) followed by up to 6 months of DAT (class IIa, level A) if concerns about ischaemic risks are prevailing. If concerns for bleeding risk are prevailing, TAT may be considered for 1 month (class IIa, level B), followed by DAT for up to 12 months (class IIa, level A); and if bleeding risk is very elevated, up to 12 months of DAT may be appropriate, in the form of clopidogrel and a non-vitamin K antagonist oral anticoagulant (NOAC; class IIa, level A).

Prof. Huber argued that drug-eluting stents (DES) with a low stent thrombosis rate may make the choice for DAT or for the duration of TAT easier. The Biofreedom™ drug-coated stent almost halved the risk of clinically driven target lesion revascularisation at 2 years compared with a bare-metal stent (BMS; HR, 0.54; 95% CI, 0.41 to 0.72; $P < .0001$) [Garot P et al. *J Am Coll Cardiol*. 2017]. The Synergy™ DES also significantly lowered the incidence of major adverse cardiac and cerebrovascular events at 1 year (12% in the DES group vs 16% in the BMS group; RR, 0.71; 95% CI, 0.52 to 0.94; $P = .02$) [Varenne O et al. *Lancet*. 2018].

Observational Trials of AF in ACS or Stenting

Andrea Rubboli, MD, Cardiology Division, Ospedale Maggiore, Bologna, Italy, discussed lessons from observational studies of AF in ACS or stenting. These studies show a high variability in the choice of antithrombotic therapy; an increased risk of bleeding with newer $P2Y_{12}$ inhibitors in TAT; and an efficacy of DAT at least equal to TAT, with a superior safety profile.

Over 170,000 patients were included in observational studies. According to Prof. Rubboli the results are difficult to compare and analyse because of overall differences in design and other aspects. There is a high variability in use of antithrombotic regimens, which is largely irrespective of the patient's risk profile: TAT ranged from 8.5 to 85%; DAT from 5 to 81%; and DAPT from 10 to 22%.

Temporal trends in Italy (2001 to 2014) in non-ST elevation (NSTE) ACS patients show a significant and progressive decrease in the use of single therapy with either antiplatelets or oral anticoagulants [De Luca L et al. *Int J Cardiol*. 2017]. The use of DAPT and of DAT was stable, while the use of TAT increased. Compared with clopidogrel, the newer $P2Y_{12}$ inhibitor prasugrel as part of TAT more than doubled the bleeding risk in NSTEMI/STEMI patients undergoing PCI (adjusted incidence rate ratio, 2.37; 95% CI, 1.36 to 4.15; $P = .003$) [Jackson LR 2nd et al. *JACC Cardiovasc Interv*. 2015]. However, the same may not be true for DAT. In registration trials of AF patients, the absolute incidence rate of major bleeding averages 4-5% for up to 12 months of TAT, which favourably compares with approximately 3.5% observed for OAC monotherapy in registration trials of non-vitamin K antagonist OACs in AF patients.

Observational studies also suggest DAT to be at least as effective as TAT, with a superior safety profile. According to Prof. Rubboli, there is no room for DAPT, except in AF patients undergoing PCI with a CHA_2DS_2-VASC score of 1, in whom adding an OAC does not decrease stroke risk, while increasing the bleeding risk, as opposed to patients with a score of ≥ 2.

Additional variables can play a role in establishing a reduced risk of bleeding, notably a high quality of OAC (reflected by being a long time in therapeutic range) when vitamin K antagonists (VKAs) are used in TAT; and use of chronic anticoagulation at the time of PCI; while a shorter (> 1 month) duration of TAT does not worsen net clinical outcomes and thus may be optimal.

TAT Versus DAT in Clinical Trials

Jean-Philippe Collet, MD, PhD, Pitié-Salpêtrière Hospital, Paris, France, weighed the benefits of triple versus dual therapy in major clinical trials in AF with ACS or stenting. He concluded that DAT is safer than TAT; patients who use TAT have a high risk of bleeding; and the most appropriate combination for DAT remains unknown.

In the open-label WOEST trial, DAT (with a VKA + clopidogrel) was associated with significantly lower rates of bleeding (19.4% vs 44.4%; HR, 0.36; 95% CI, 0.26 to 0.50; $P < .0001$) and overall mortality than TAT (VKA + clopidogrel + ASA), with similar rates of thrombotic events [Dewilde WJ. *Lancet*. 2013]. There were 573 participants, 69% of whom had AF. First generation DES and a femoral approach were the most common procedural aspects, and left main disease was an exclusion criterion. Ischaemic and bleeding risk should be weighed when choosing the duration of antiplatelet therapy, as there were significantly fewer BARC type 2 – 5 bleedings in DAT versus TAT (HR, 0.68; 95% CI, 0.47 to 0.98) in the landmark analysis at Week 6.

In the PIONEER AF-PCI trial [Gibson CM et al. *N Engl J Med*. 2016] 2,124 AF patients undergoing PCI with stent placement were randomised to one of three groups after PCI: Group 1: DAT, comprised of low-dose rivaroxaban (15 mg once dialy) plus a $P2Y_{12}$ inhibitor for 12 months; Group 2: very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months; Group 3: standard TAT therapy with a VKA (INR 2.0 to 3.0) plus DAPT for 1, 6, or 12 months. DAPT duration was prespecified and no power calculation was made. The rates of clinically significant bleeding were lower in the groups who received rivaroxaban than in the group who received standard TAT therapy with VKA + DAPT (6.8% in Group 1, 18.0% in Group 2, and 26.7% in Group 3; HR for Group 1 vs Group 3, 0.59; 95% CI, 0.47 to 0.76; $P < .001$; HR for Group 2 vs Group 3, 0.63; 95% CI, 0.50 to 0.80; $P < .001$; Figure 1). The three groups had similar efficacy rates.

In the REDUAL-PCI multicentre trial [Cannon CP et al. *N Engl J Med*. 2017], 2,725 AF patients who had undergone PCI were randomly assigned to TAT with warfarin plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) plus aspirin (for 1 to 3 months; triple-therapy group), or DAT with dabigatran (110 mg or 150 mg twice daily) plus a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and no aspirin (110-mg and 150-mg dual-therapy groups). The risk of bleeding was lower among those who received DAT (HR, 0.52; 95% CI, 0.42 to 0.63; $P < .001$ for noninferiority; $P < .001$ for superiority for 110 mg dabigatran; HR, 0.72; 95% CI, 0.58 to 0.88; $P < .001$ for noninferiority for 150 mg dabigatran) than among those who received TAT. DAT was noninferior to TAT with respect to the risk of thromboembolic events.

The most favourable duration of DAPT has yet to be determined, and is the subject of ongoing trials, such as the AUGUSTUS trial. The new ESC/EACTS Guidelines on Myocardial Revascularization [Neumann FJ et al. *Eur Heart J*. 2018.] present a list of strategies to avoid bleeding complications in patients with oral anticoagulants (Table 1), as well as a practical table with information on high-risk features for ischaemic events.

Table 1. Strategies to Avoid Bleeding Complications of OAC in Myocardial Revascularisation Patients

Assess ischaemic and bleeding risks using **validated risk predictors** (e.g., CHA_2DS_2-VASC, ABC, and HAS-BLED) with a focus on modifiable risk factors.
Keep **triple therapy duration as a short as possible**; dual therapy after PCI (OAC and clopidogrel) to be considered instead of triple therapy.
One should consider the **use of a NOAC instead of a VKA** when NOACs are not contraindicated.
Consider a **target INR in the lower part of the recommended target** range and maximise time in the therapeutic range (i.e., > 65%) when a VKA is used.
Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
Use **low-dose (≤ 100 mg daily) aspirin**.
Routine use of **PPIs**.

Reprinted from Neumann F-J et al. 2018 ESC/EACTS Guidelines on Myocardial Revascularization. *Eur Heart J*. 2018. doi:10.1093/eurheartj/ehy394. By permission of Oxford University Press on behalf of the European Society of Cardiology.

Innovative Strategies for Secondary Prevention

Written by **Constance de Koning**

Secondary cardiovascular (CV) prevention remains a highly dynamic field, in which new strategies are continuously being developed and tested in contemporary trials. Novel approaches include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition, anti-cytokine therapy, $P2Y_{12}$ inhibition, and targeting residual inflammatory, lipid, and thrombotic risk.

Residual Inflammatory, Lipid, and Thrombotic Risk in CAD

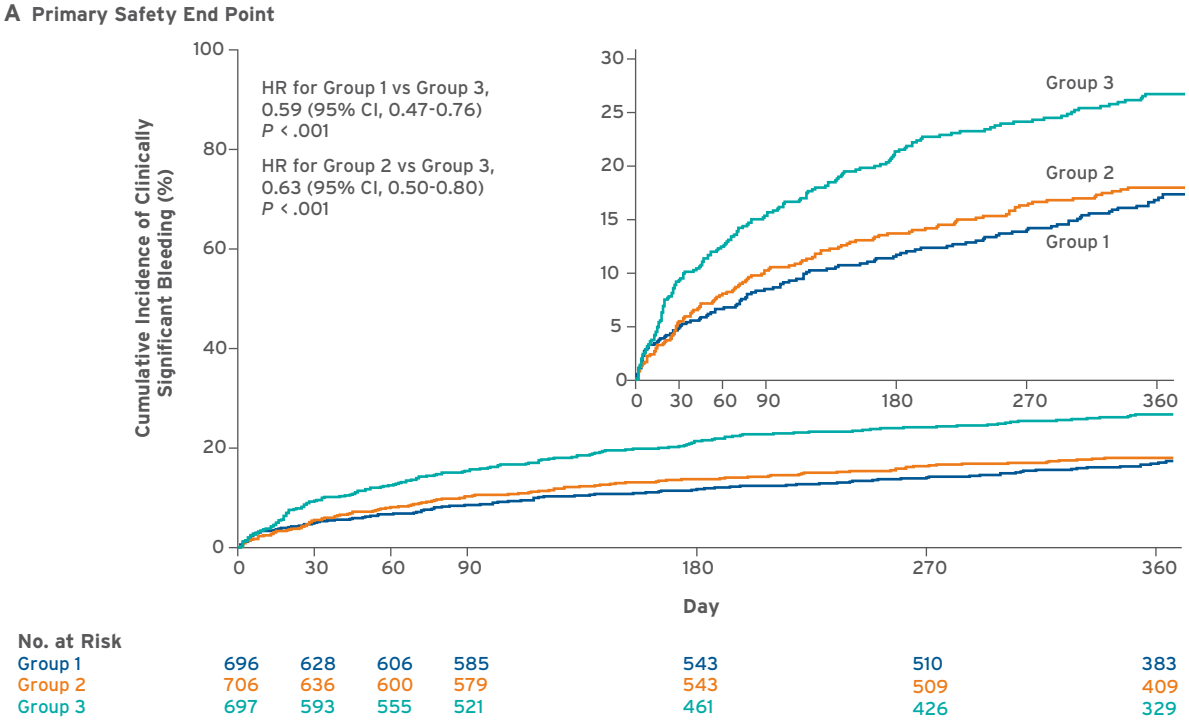
Despite optimum medical therapy, the recurrent event rate in post-acute coronary syndrome (ACS) in trials remains high (about 10% in the first year). This is even higher in clinical practice, with up to one-third of elderly, high-risk patients having a recurrent event in the first year post-ACS. The protective role of high density lipoproteins (HDL) has been questioned based on human genetic studies and negative clinical trial results of various HDL raising therapies. In contrast, recent genetic analyses support the causality of triglyceride-rich lipoproteins in CV risk. According to Peter Libby, MD, Brigham & Women's Hospital, Boston, Massachusetts, USA, the dependent and independent variable in adjusting the CV risk of triglycerides for HDL may have been confused [Libby P et al. *Eur Heart J*. 2014]; it may be the case that HDL is in fact a marker for triglycerides. These findings may aid in achieving biomarker-guided personalisation of the management of risk in secondary prevention by targeting residual low-density lipoprotein (LDL) risk, residual inflammatory risk, and residual risk due to triglyceride-rich lipoproteins.

Role of PCSK9 Inhibition Still Evolving

Inhibition of PCSK9 is effective in reducing LDL, in patients with familial hypercholesterolemia and in very high-risk patients. PCSK9 monoclonal antibodies may also be useful in managing ACS, as ACS induces increased PCSK9 levels, which in turn may influence plaque vulnerability of the coronary vessels [Navarese EP et al. *Ann Int Med*. 2016]. The FOURIER study [Sabatine MS et al. *N Engl J Med*. 2017] showed a 1.5% absolute risk reduction (RR) with evolocumab on time to CV death, myocardial infarction (MI), stroke, hospitalisation for unstable angina, or coronary revascularisation in very high-risk patients who used the highest tolerated dose of statins (HR, 0.85; 95% CI, 0.79 to 0.92; $P < .001$). The ODYSSEY trial [Steg PG et al. ACC Conference 2018], which assessed alirocumab, also showed a reduction in LDL-cholesterol (LDL-C) and CV endpoints. The study included an even higher-risk group of patients and longer follow-up than the FOURIER study, demonstrating a 15% RR in major adverse cardiovascular events (MACE; HR, 0.85; 95% CI, 0.78 to 0.93; $P = .0003$) and a 1.6% absolute risk reduction. The EVOlocumab study for early reduction of LDL-C levels in patients with ACSs [EVOPACS; NCT03287609] is currently investigating the safety and efficacy of evolocumab in ACS patients.

Other methods to reduce LDL-C are being investigated, including inclisiran, a RNA interference therapeutic inhibiting the synthesis of PCSK9, which was found to lower PCSK9 and LDL-C levels in patients at high CV risk with elevated LDL cholesterol levels [Ray KK et

Figure 1. Clinically Significant Bleeding in PIONEER AF-PCI



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al. *N Engl J Med*. 2017]. However, there are still some unanswered questions, according to François Mach, MD, Geneva University Hospital, Switzerland. These include the need for more data regarding inclisiran and other silencing drugs, whether PCSK9i could be of use in patients with chronic kidney disease, and the clinical effect of PCSK9i on Lp(a) reduction. The benefits of PCSK9 inhibitors are clear, Prof. Mach stated, they offer the possibility of treating patients 1 or 2 times a month, with most patients (95%) reaching target levels with minimal side effects. However, long-term follow-up data is still needed and cost is an issue. Nevertheless, PCSK9 inhibition is a promising therapy.

Preventing CV Events by Targeting Residual Inflammatory Risk

Paul M. Ridker, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA, presented data from the CANTOS trial, which included more than 10,000 patients. First presented at the European Society of Cardiology Congress 2017, CANTOS demonstrated large dose-dependent reductions in C-reactive protein (CRP) with no change in LDL-C and high-density lipoprotein cholesterol [Ridker PM et al. *N Engl J Med*. 2017]. In the secondary endpoint analysis, it was found that those with greater high-sensitivity (hs)CRP reduction had a greater risk reduction of MACE [Ridker PM et al. *Lancet*. 2018]. Interestingly, the reduction of MACE in patients with moderate chronic kidney disease (n = 1,875) was also significant (HR, 0.82; 95% CI, 0.68 to 1.00; *P* = .05) [Ridker PM et al. *J Am Coll Cardiol*. 2018]. New data suggest that residual inflammatory risk is still present irrespective of on-treatment LDL-C (including patients with LDL-C < 20 mg/dL) and is associated with increased rates of adverse events (Figure 1) [Bohula EA et al. *Circulation*. 2018].

Figure 1. Presence of Residual Inflammatory Risk in Patients with hsCRP < 1, 1-3, and > 3

		LDL-C at 1 month (mg/dL)				
		< 20	20-49	50-69	70-99	≥ 100
Incidence rate at 3 years	hsCRP < 1 mg/L	9.0%	9.8%	10.4%	10.9%	12.3%
	hsCRP 1-3 mg/L	10.8%	12.0%	12.6%	13.2%	14.9%
	hsCRP > 3 mg/L	13.1%	14.7%	15.4%	16.4%	18.2%

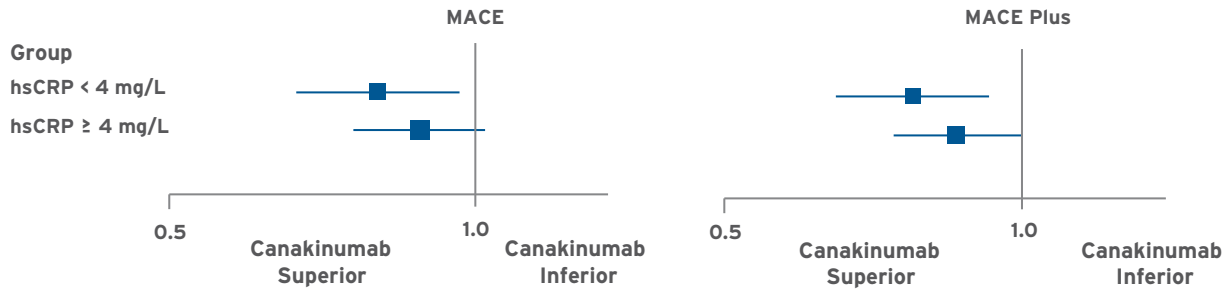
LDL-C, low-density lipoprotein cholesterol

Profound LDL reduction without inflammation effects is very effective, as is profound inflammation effects without LDL reduction, Dr Ridker stated. There are two important questions to answer for evidence-based guidelines: is there consistent evidence that the biomarker independently predicts risk, and is there randomised trial proof that lowering the biomarker lowers the risk? The confirming answer to the first question concerns many biomarkers, whereas the second answer only applies to LDL-C/ApoB and hsCRP/IL-6 [Ridker PM et al. *J Am Coll Cardiol*. 2018; in press].

Optimised Antithrombotic Strategy Post-ACS: Which Option?

When optimising antithrombotic strategy in high-risk, post-ACS patients, two periods can be distinguished: the time between discharge and 1 year post-ACS, and the time beyond 1 year post-ACS. For the early post-ACS period, dual antiplatelet therapy (DAPT; aspirin plus clopidogrel) is the gold standard. Optimisation may be achieved by using stronger $P2Y_{12}$ inhibition; providing an ischaemic benefit, but also a higher bleeding risk [Wiviott SD et al. *N Engl J Med*. 2007; Wallentin L et al. *N Engl J Med*. 2009]. A second option is to add Factor Xa inhibition to standard of care [Mega JL et al. *N Engl J Med*. 2012]. As Thomas Cuisset, MD, CHU TIMONE,

Figure 1. CANTOS: Consistency of Effect



Adapted from Ridker PM et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391:319-28.

Marseille, France, pointed out, the gold standard as of August 2018 is to use more potent $P2Y_{12}$ inhibitors (e.g., prasugrel, ticagrelor). Current guidelines state that triple therapy with aspirin plus clopidogrel and low-dose rivaroxaban is possible in patients with low bleeding risk.

Beyond the first year post-ACS, the gold standard has been lifelong single antiplatelet therapy after discontinuation of DAPT. Clinicians now have two options to add to aspirin; the PEGASUS trial [Bonaca MP et al. *N Engl J Med*. 2015] investigated ticagrelor and the COMPASS trial [Eikelboom J et al. *N Engl J Med*. 2017] assessed rivaroxaban in patients with stable coronary artery disease or peripheral arterial disease.

The first option to optimise antithrombotic strategy is prolonged $P2Y_{12}$ inhibition, which in itself consists of various options. The second option is to add Factor Xa inhibition to aspirin. Prof. Cuisset explained that a 2-step approach is required, although this can be challenging. Firstly, candidates for an optimised strategy would need to be identified (i.e., high/low bleeding risk), and secondly, the best strategy should be selected for each patient based on individual patient characteristics. Still, a number of issues may arise, such as the risk of nonadherence in case of multiple treatment changes, the duration of the chosen optimised strategy (30 months, 3 years or lifetime?), the choice of long-term DAPT and whether monotherapy with new $P2Y_{12}$ blockers is feasible.

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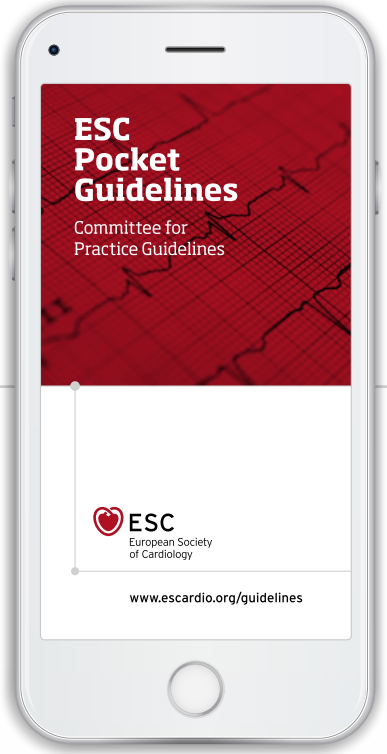

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Introduction

There is considerable overlap of the current document with other guidelines, specifically with those on "Stable Coronary Artery Disease", "Non-ST-Elevation Myocardial Infarction", "ST-Elevation Myocardial Infarction", "Heart Failure" and "Valvular Heart Disease" and the "Focused Update on Dual Antiplatelet Therapy".

Unless supported by new evidence, the recommendations of the current guidelines follow these guidelines.

A summary of the key changes in comparison with the previous guideline is provided in Figure 1 and Figure 2.

Figure 1 New recommendations

Calculation of the Syntax Score, if left main or multivessel revascularization is considered	Completeness of revascularization prioritized, when considering CABG vs PCI
Radial access as standard approach for coronary angiography and PCI	NOAC preferred over VKA in patients with non-valvular AF requiring anticoagulation and antiplatelet treatment
DES for any PCI	No-touch vein technique, if open vein harvesting for CABG
Systematic re-evaluation of patients after myocardial revascularization	Annual operator volume for left main PCI of at least 25 cases per year
Stabilised NSTE-ACS patients: revascularization strategy according to principles for SCAD	Pre- and post-hydration with isotonic saline in patients with moderate or severe CKD, if expected contrast volume is >100 mL
Use of the radial artery grafts over saphenous vein grafts in patients with high-degree stenosis	
Myocardial revascularization in patients with CAD, heart failure, and LVEF ≤35% CABG preferred PCI as alternative to CABG	
Routine non-invasive imaging surveillance in high-risk patients 6 months after revascularization	Dabigatran 150-mg dose preferred over 110-mg dose when combined with single antiplatelet therapy after PCI
Double-kissing crush technique preferred over provisional T-stenting in true left main bifurcations.	De-escalation of $P2Y_{12}$-inhibitor guided by platelet function testing in ACS patients
Cangrelor in $P2Y_{12}$-inhibitor naïve patients undergoing PCI	Routine revascularization of non-IRA lesions in myocardial infarction with cardiogenic shock
GP IIb/IIIa inhibitors for PCI in $P2Y_{12}$-inhibitor naïve patients with ACS undergoing PCI	Current generation BRS for clinical use outside clinical studies

	Class I		Class IIa
	Class IIb		Class III

The figure does not show changes compared with the 2014 version of the Myocardial Revascularization Guidelines that were due to updates for consistency with other ESC Guidelines published since 2014.

ACS = acute coronary syndromes; AF = atrial fibrillation; BRS = bioresorbable scaffolds; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; DES = drug-eluting stents; GP = glycoprotein; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K oral anticoagulants; NSTE = non-ST-elevation; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; VKA = vitamin K antagonists.

= chronic kidney disease; DES = drug-eluting stents; GP = glycoprotein; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; NOAC = non-vitamin K oral anticoagulants; NSTE = non-ST-elevation; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; VKA = vitamin K antagonists.

Figure 2 Changes in Class of Recommendations

UPGRADES
For PCI of bifurcation lesions, stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch
Immediate coronary angiography and revascularization, if appropriate, in survivors of out-of-hospital cardiac arrest and an ECG consistent with STEMI
Assess all patients for the risk of contrast-induced nephropathy
OCT for stent optimization

DOWNGRADES
Distal protection devices for PCI of SVG lesions
Bivalirudin for PCI in NSTE-ACS
Bivalirudin for PCI in STEMI
PCI for MVD with diabetes and SYNTAX score <23
Platelet function testing to guide antiplatelet therapy interruption in patients undergoing cardiac surgery
EuroSCORE II to assess in-hospital mortality after CABG

The figure does not show changes compared with the 2014 version of the Myocardial Revascularization Guidelines that were due to updates for consistency with other ESC Guidelines published since 2014.

	Class I		Class IIa
	Class IIb		Class III

CABG = coronary artery bypass grafting; MVD = multivessel coronary artery disease; NSTE-ACS = non-ST-elevation acute coronary syndromes; OCT = optical coherence tomography; PCI = percutaneous coronary interventions; STEMI = ST-elevation myocardial infarction, SVG = saphenous vein grafts.

Objective evidence of myocardial ischaemia by non-invasive stress imaging and intravascular assessment of the functional relevance of coronary artery stenoses are key to clinical decision making for myocardial revascularization. Because of the low sensitivity of stress ECG and its inability to gauge the extent and distribution of ischaemia, non-invasive stress imaging is recommended as the first line test.

Recommendation for non-invasive imaging in patients with coronary artery disease and heart failure with reduced ejection fraction

Recommendation	Class[a]	Level[b]
Non-invasive stress imaging (CMR, stress echocardiography, SPECT, or PET) may be considered for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization) before the decision on revascularization.	IIb	B

CAD = coronary artery disease; CMR = cardiac magnetic resonance; HF = heart failure; PET = positron emission tomography; SPECT = single photon emission computed tomography.

[a] Class of recommendation.

[b] Level of evidence.

Recommendations on functional testing and intravascular imaging for lesion assessment

Recommendations	Class[a]	Level[b]
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis.	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI.	IIa	B
IVUS should be considered to assess the severity of unprotected left main lesions.	IIa	B

FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention.

[a] Class of recommendation.

[b] Level of evidence.

Decision making and patient information

The Heart Team should provide a balanced, multidisciplinary decision-making process. For common case scenarios, interdisciplinary institutional protocols should be developed. However, complex cases—defined by the protocols—should be discussed individually. Ad hoc meetings of the Heart Team should facilitate efficient clinical workflows.

Active patient participation in the decision-making process should be encouraged.

Patient information needs to be unbiased and evidence-based. Short-term, procedure-related and long-term risks and benefits should be thoroughly discussed. The patient's right to decline the treatment option recommended by the Heart Team has to be respected. Patient refusal of a recommended treatment should be acknowledged in a written document after the patient has received the necessary information by the Heart Team members. In this case, the patient may be offered an alternative treatment option by the Heart Team.

Table 3 Multidisciplinary decision pathways, patient informed consent, and timing of revascularization

	ACS	
	Shock	**STEMI**
Multidisciplinary decision making	Not mandatory during the acute phase. Mechanical circulatory support according to Heart Team protocol.	Not mandatory during the acute phase.
Informed consent	Witnessed verbal informed consent or family consent if possible without delay.	Witnessed verbal informed consent may be sufficient unless written consent is legally required.
Time to revascularization	Emergency: no delay.	Emergency: no delay.
Procedure	Proceed with intervention based on best evidence/ availability. Ad-hoc treatment of culprit lesion, staged treatment of non-culprit lesions according to institutional protocol or Heart Team decision.	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol or Heart Team decision.

Table 3 Multidisciplinary decision pathways, patient informed consent, and timing of revascularization (continued)

	ACS
	NSTE-ACS
Multidisciplinary decision making	Not mandatory during the acute phase. After stabilization, recommended as in SCAD.
Informed consent	Written informed consent[a]. In emergency cases witnessed verbal informed consent may be sufficient.
Time to revascularization	Urgency: within 2 hours to within 72 hours depending on the risk criteria.
Procedure	Proceed with intervention based on best evidence/ availability. Non-culprit lesions treated according to institutional protocol or Heart Team decision.

Decision making and patient information

Table 3 Multidisciplinary decision pathways, patient informed consent, and timing of revascularization (continued)

	SCAD without ad-hoc PCI indication according to Heart Team protocol	SCAD with ad-hoc PCI indication according to Heart Team protocol
Multidisciplinary decision making	Required.	Not required.
Informed consent	Written informed consent[a].	Written informed consent[a].
Time to revascularization	Within 2 weeks for high-risk patients[b] and within 6 weeks for all other patients	Ad hoc.
Procedure	Allow for enough time from diagnostic catheterization to decide on the appropriate intervention.	Proceed with intervention according to institutional protocol defined by Heart Team.

[a] This may not apply to countries that are not legally required to ask for written informed consent. ESC and EACTS advocate documentation of patient consent for all revascularization procedures.

[b] Severe symptoms (CCS class 3), anatomy (left main disease or equivalent, three-vessel disease or proximal left anterior descending artery), or depressed ventricular function.

ACS = acute coronary syndromes; CCS = Canadian Cardiovascular Society; ESC = European Society of Cardiology; EACTS = European Association for Cardio-Thoracic Surgery; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; STEMI = ST-segment elevation myocardial infarction.

Recommendations for decision-making and patient information in the elective setting

Recommendations	Class[a]	Level[b]
It is recommended that patients undergoing coronary angiography are informed about benefits and risks as well as potential therapeutic consequences ahead of the procedure.	I	C
It is recommended that patients are adequately informed about short- and long-term benefits and risks of the revascularization procedure with information about local experience and allowed enough time for informed decision making.	I	C
It is recommended that institutional protocols are developed by the Heart Team to implement the appropriate revascularization strategy in accordance with current Guidelines.	I	C
In PCI centres without on-site surgery, it is recommended that institutional protocols are established with partner institutions providing cardiac surgery.	I	C

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

[a] Class of recommendation.

[b] Level of evidence.

Myocardial revascularization is performed for relief of symptoms of myocardial ischaemia and improvement of prognosis. In stable coronary artery disease, the prognostic benefit is dependent on the extent of myocardium subject to ischaemia. With the exception of subtotal stenoses in a major coronary vessel, angiography alone does not suffice to establish the indication for PCI, but documentation of ischaemia or haemodynamic relevance is required. Indications for revascularization in patients with stable angina or silent ischaemia are shown in the Table here.

Whether conservative therapy, PCI or CABG is preferred should depend on the risk– benefit ratios of these treatment strategies, weighting the risks of peri-procedural complications against improvements in health-related quality of life, as well as long-term freedom from death, MI or repeat revascularization. Predicted surgical mortality, anatomical complexity of CAD, and the anticipated completeness of revascularization are important criteria for decision making with respect to the type of revascularization (see Table here).

Individualized treatment decisions should respect the range of predicted surgical risks in the major RCTs which inform the choice of revascularization modality (Table 5). Apart from these issues of individual operative risk and technical feasibility, diabetes mellitus (see Chapter) and anatomical complexity of CAD, as assessed by the SYNTAX score (calculator at http://www.syntaxscore.com), determine the relative benefits of PCI and CABG. Moreover, the ability to achieve complete revascularization is a key issue when choosing the appropriate treatment strategy. The prognostic and symptomatic benefit of myocardial revascularization critically depends on the completeness of revascularization.

Indications for revascularization in patients with stable angina or silent ischaemia		
Recommendations	**Class[a]**	**Level[b]**
For prognosis		
Left main disease with stenosis >50%[c].	I	A
Proximal LAD stenosis >50%[c].	I	A
Two- or three-vessel disease with stenosis >50%[c] with impaired LV function (LVEF ≤35%).	I	A
Large area of ischaemia detected by functional testing (>10% LV) or abnormal invasive FFR[d].	I	B
Single remaining patent coronary artery with stenosis >50%[c].	I	C
For symptoms		
Haemodynamically significant coronary stenosis[c]in the presence of limiting angina or angina equivalent, with insufficient response to optimized medical therapye.	I	A

CAD = coronary artery disease; FFR = fractional flow reserve; iwFR = instantaneous wave-free ratio; LAD = left anterior descending coronary artery; LV = left ventricular; LVEF = left ventricular ejection fraction. [a] Class of recommendation - [b] Level of evidence - [c] With documented ischaemia or haemodynamically relevant lesion defined by FFR ≤0.80 or iwFR ≤0.89 or >90% stenosis in a major coronary vessel - [d] Based on FFR <0.75 indicating a prognostically relevant lesion - [e] In consideration of patient compliance and wishes in relation to intensity of antianginal therapy.

Recommendations on criteria for the choice between coronary artery bypass grafting and percutaneous coronary intervention		
Recommendations	**Class[a]**	**Level[b]**
Assessment of surgical risk[c]		
It is recommended that the STS score is calculated to assess in- hospital or 30-day mortality, and in-hospital morbidity after CABG.	I	B
Calculation of the EuroSCORE II may be considered to assess in- hospital mortality after CABG.	IIb	B
Assessment of CAD complexity		
In patients with LM or multivessel disease, it is recommended that the SYNTAX score is calculated to assess the anatomical complexity of CAD and the long-term risk of mortality and morbidity after PCI.	I	B
When considering the decision between CABG and PCI, completeness of revascularization should be prioritized.	IIa	B

CABG = coronary artery bypass grafting; CAD = coronary artery disease; LM = left main; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

[a] Class of recommendation - [b] Level of evidence

[c] Level of evidence refers to prediction of outcomes.

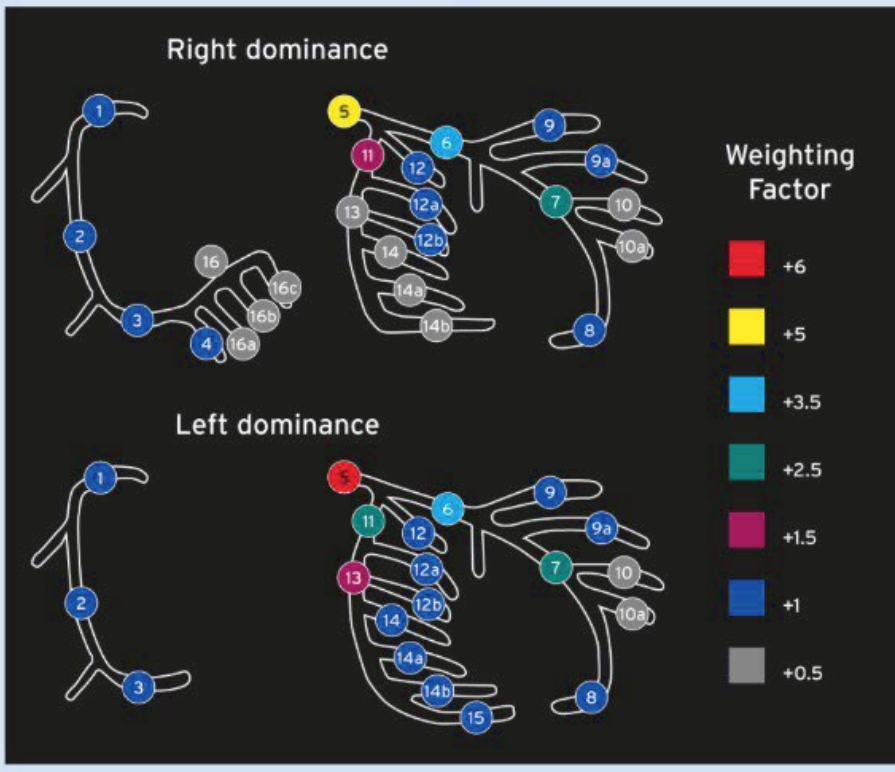
Table 5 Logistic EuroSCOREs[a] in major randomized trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG)

Trial	EuroSCORE PCI	EuroSCORE CABG
SYNTAX	3.8 ± 2.6	3.8 ± 2.7
BEST	2.9 ± 2.0	3.0 ± 2.1
FREEDOM	2.7 ± 2.4	2.8 ± 2.5
PRECOMBAT	2.7 ± 1.8	2.8 ± 1.9
EXCEL	not reported	not reported
NOBLE	2 [2-4]	2 [2-4]

Numbers are presented as mean ± standard deviation or median [interquartile range].

[a] Compared with the contemporary EuroSCORE II, the logistic EuroSCORE has similar discrimination, but poorer calibration and, thus, overestimates surgical mortality by roughly two-fold.

Table 6 Guide to calculate the SYNTAX score[a]

Steps	Variable assessed	Description
Step 1	Dominance	The weight of individual coronary segments varies according to coronary artery dominance (right or left). Co-dominance does not exist as an option in the SYNTAX score.
Step 2	Coronary segment	The diseased coronary segment directly affects the score as each coronary segment is assigned a weight depending on its location, ranging from 0.5 (i.e. posterolateral branch) to 6 (i.e. left main in case of left dominance). 
Step 3	Diameter stenosis	The score of each diseased coronary segment is multiplied by x2 in case of a stenosis 50–99% and by x5 in case of total occlusion. In case of total occlusion, additional points will be added as follows: – Age >3 months or unknown: +1 – Blunt stump: +1 – Bridging: +1 – First segment visible distally: +1 per non visible segment – Side branch at the occlusion: +1 if <1.5 mm diameter; + 1 if both <1.5 mm and ≥1.5 mm diameter; +0 if ≥1.5 mm diameter (i.e. bifurcation lesion)
Step 4	Trifurcation lesion	The presence of a trifurcation lesion adds additional points based on the number of diseased segments: – 1 segment: +3 – 2 segments: +4 – 3 segments: +5 – 4 segments: +6

	Bifurcation lesion	The presence of a bifurcation lesion adds additional points based on the type of bifurcation according to the Medina classification:[126] – Medina 1,0,0–0,1,0–1,1,0 +1 – Medina 1,1,1–0,0,1–1,0,1–0,1,1 +2 Moreover, the presence of a bifurcation angle <70° adds 1 additional point
	Aorto-ostial lesion	The presence of aorto-ostial lesion segments adds 1 additional point
	Severe tortuosity	The presence of severe tortuosity proximal of the diseased segment adds 2 additional points
	Lesion length	Lesion length >20 mm adds 1 additional point
	Calcification	The presence of heavy calcification adds 2 additional points
	Thrombus	The presence of thrombus adds 1 additional point
	Diffuse disease/small vessels	The presence of diffusely diseased and narrowed segments distal to the lesion (i.e. when at least 75% of the length of the segment distal to the lesion has a vessel diameter <2 mm) adds 1 point per segment number

X score calculation http://www.syntaxscore.com

Recommendations for selection of the type of myocardial revascularization (CABG or PCI) in patients with stable CAD, with suitable coronary anatomy for both procedures and low predicted surgical mortality, are provided in the table below.

Recommendation for the type of revascularization in patients with stable coronary artery disease with suitable coronary anatomy for both procedures and low predicted surgical mortality[d]

Recommendations according to extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.	I	A	I	A
Two-vessel CAD				
Without proximal LAD stenosis.	IIb	C	I	C
With proximal LAD stenosis.	I	B	I	C
Left main CAD				
Left main disease with low SYNTAX score (0–22).	I	A	I	A
Left main disease with intermediate SYNTAX score (23–32).	I	A	IIa	A
Left main disease with high SYNTAX score (≥33).[c]	I	A	III	B
Three-vessel CAD without diabetes mellitus				
Three-vessel disease with low SYNTAX score (0–22).	I	A	I	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c]	I	A	III	A
Three-vessel CAD with diabetes mellitus				
Three-vessel disease with low SYNTAX score (0–22).	I	A	IIb	A
Three-vessel disease with intermediate or high SYNTAX score (>22).[c]	I	A	III	A

CABG = coronary artery bypass grafting; CAD = coronary artery disease; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

SYNTAX score calculation http://www.syntaxscore.com

[a] Class of recommendation - [b] Level of evidence.

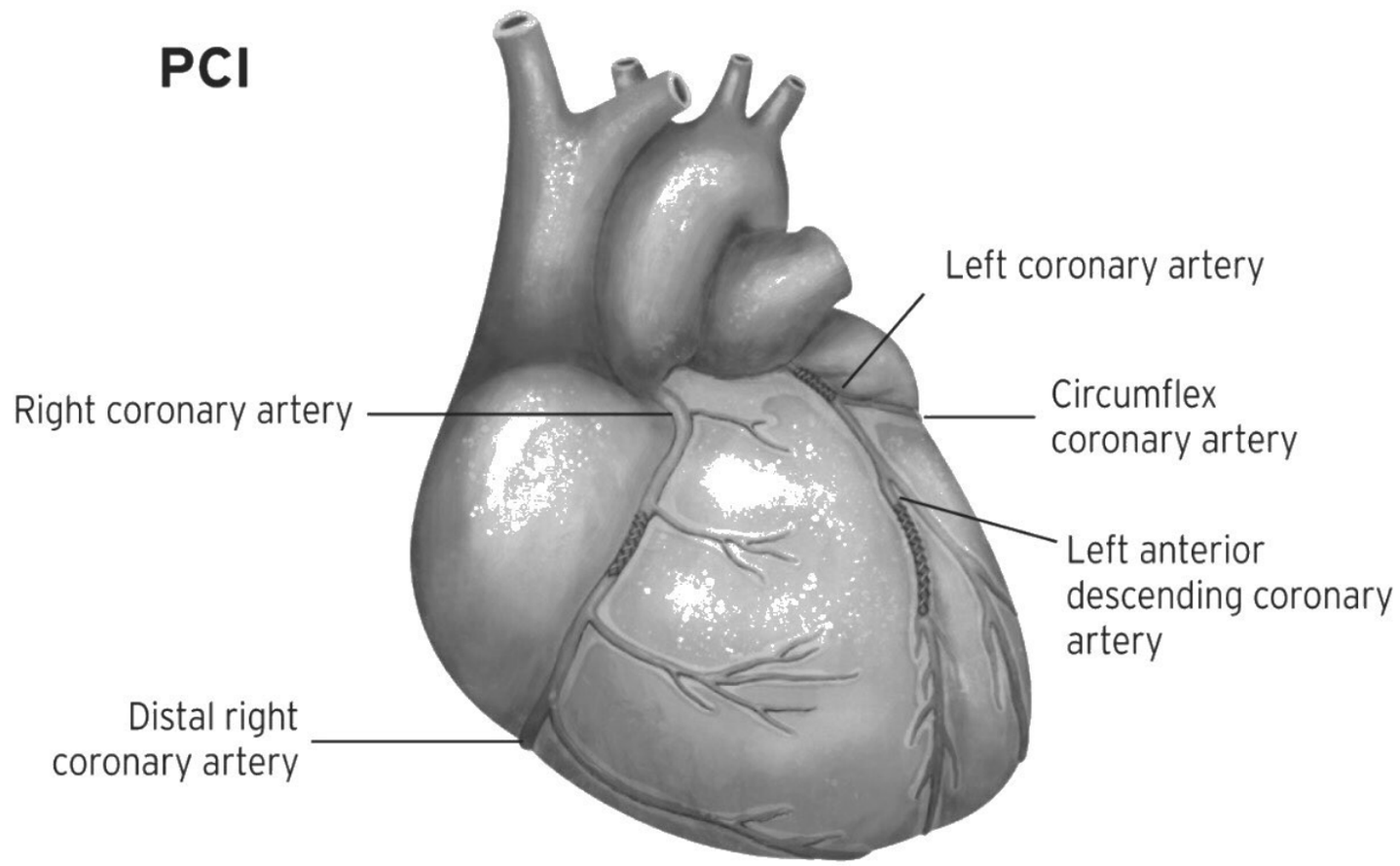
[c] PCI should be considered, if the Heart Team is concerned about the surgical risk or if the patient refuses CABG after adequate counselling by the Heart Team.

[d] For example, absence of previous cardiac surgery, severe morbidities, frailty, immobility, precluding CABG (also see Table 5).

Individualized treatments concepts with respect for the preferences of the patient informed about early and late outcomes call for the Heart Team to be consulted.

Figure 3 summarizes aspects to be considered by the Heart Team.

Figure 3 Aspects to be considered by the Heart Team for the decision making between percutaneous coronary intervention and coronary artery bypass grafting among patients with stable multivessel and/or left main coronary artery disease



FAVOURS PCI

Clinical characteristics

Presence of severe co-morbidity (not adequately reflected by scores)

Advanced age/frailty/reduced life expectancy

Restricted mobility and conditions that affect the rehabilitation process

Anatomical and technical aspects

MVD with SYNTAX score 0–22

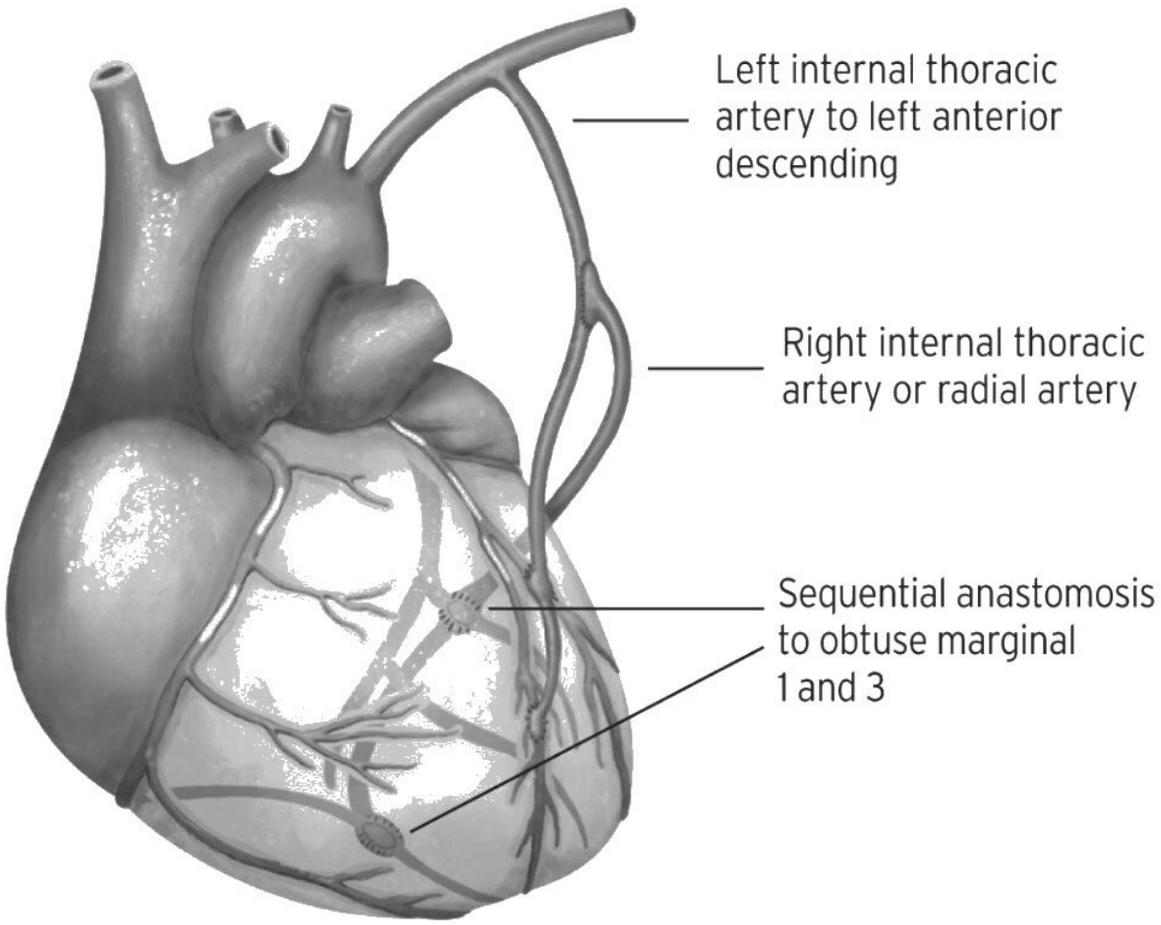
Anatomy likely resulting in incomplete revascularization with CABG due to poor quality or missing conduits

Severe chest deformation or scoliosis

Sequelae of chest radiation

Porcelain aorta[a]

CABG



FAVOURS CABG

Clinical characteristics

- Diabetes.
- Reduced LV function (EF ≤35%).
- Contraindication to DAPT.
- Recurrent diffuse in-stent restenosis.

Anatomical and technical aspects

- MVD with SYNTAX score ≥23
- Anatomy likely resulting in incomplete revascularization with PCI
- Severely calcified coronary artery lesions limiting lesion expansion

Need for concomitant interventions

- Ascending aortic pathology with indication for surgery
- Concomitant cardiac surgery

CABG = coronary artery bypass grafting; Cx = circumflex; DAPT = dual antiplatelet therapy; EF = ejection fraction; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; LV= left ventricular; MVD = multivessel coronary artery disease; PCI = percutaneous coronary intervention; PDA = posterior descending artery; RA = radial artery; RIMA = right internal mammary artery; SYNTAX = Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

[a]Consider no-touch off-pump CABG in case of porcelain aorta.

Recommendations for timing of invasive evaluation and myocardial revascularization in patients with NSTE-ACS are provided in the table below and in Figure 4.

Recommendations for invasive evaluation and revascularization in non-ST-elevation acute coronary syndrome

Recommendations	Class[a]	Level[b]
Urgent coronary angiography (<2 hours) is recommended in patients at very high ischaemic risk (Figure 4).	I	C
An early invasive strategy (<24 hours) is recommended in patients with at least one high-risk criterion (Figure 4).	I	A
An invasive strategy (<72 hours after first presentation) is indicated in patients with at least one intermediate-risk criterion (Figure 4) or recurrent symptoms.	I	A
It is recommended to base the revascularization strategy (ad hoc culprit-lesion PCI/multivessel PCI/CABG) on the clinical status and comorbidities as well as the disease severity, [i.e. the distribution and angiographic lesion characteristics (e.g. SYNTAX score)], according to the principles for SCAD.[c]	I	B
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI.	III	B

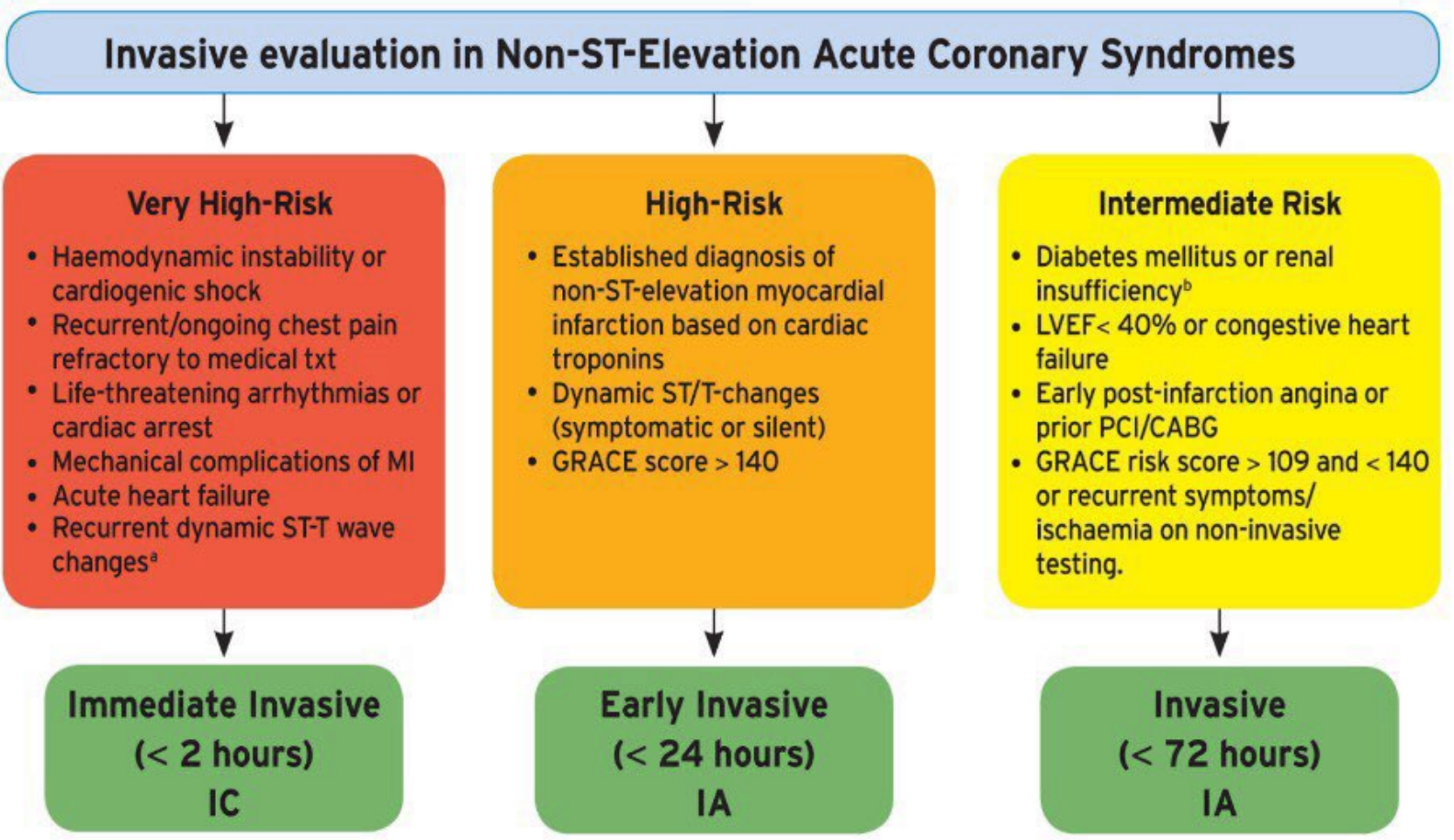
CABG = coronary artery bypass grafting; IRA = infarct-related artery; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease; SYNTAX = Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery.

[a] Class of recommendation.

[b] Level of evidence.

[c] May apply to stabilized NSTE-ACS patients.

Figure 4 Selection of non-ST-elevation acute coronary syndrome (NSTE-ACS) treatment strategy and timing according to initial risk stratification.

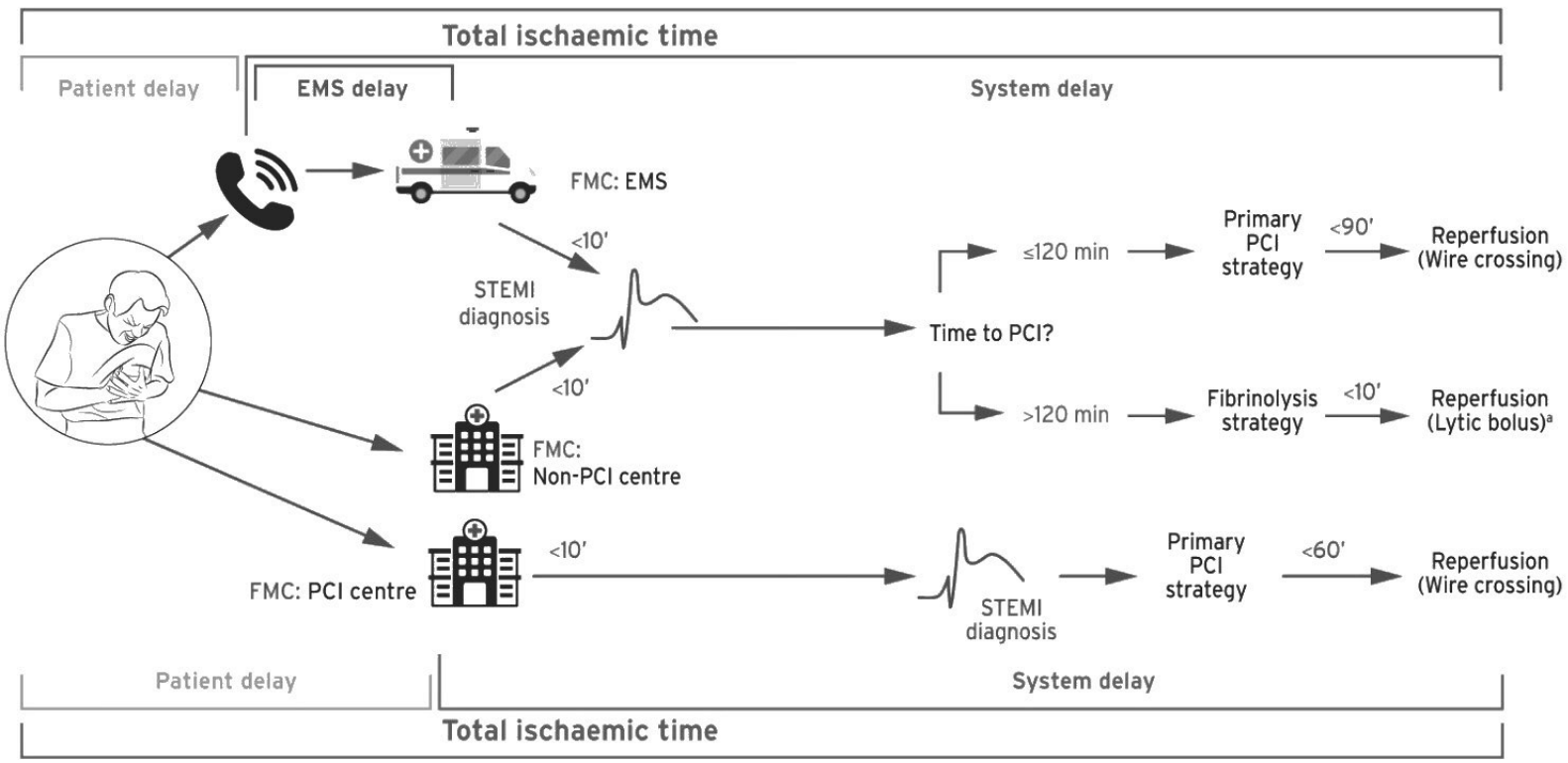


CABG = coronary artery bypass grafting; GRACE = Global Registry of Acute Coronary Events; LVEF = left ventricular ejection fraction; MI =myocardial infarction; PCI = percutaneous coronary intervention.

[a] Particularly intermittent ST-elevation; [b] Estimated glomerular filtration rate <60mL/min/1.73m^2

Delays in the timely implementation of reperfusion therapy are key issues in the management of STEMI as the greatest benefit gained from reperfusion therapy occurs within the first 2–3 hours of symptom onset. Optimal treatment of STEMI should be based on the implementation of regional networks between hospitals with various levels of technology, connected by an efficient ambulance service. The goal of these networks is to provide optimal care while minimizing delays–as summarized in Figure 5–in order to improve clinical outcomes.

Figure 5 Modes of patient's medical contact, components of ischaemia time and flowchart for reperfusion strategy selection



The recommended mode of patient presentation is by alerting the EMS (call national emergency number: 112 or similar number according to region). When STEMI diagnosis is made in the out-of-hospital setting (via EMS) or in a non-PCI centre, the choice of reperfusion strategy is based on the estimated time from STEMI diagnosis to PCI-mediated reperfusion (wire crossing). System delay for patients alerting the EMS starts at the time of phone alert, although FMC occurs when the EMS arrives at the scene.

EMS = emergency medical service; FMC = first medical contact; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

'denotes minutes.

[a] Patients receiving fibrinolysis should be transferred to a PCI centre immediately after administration of the lytic bolus.

Recommendations for myocardial reperfusion with primary PCI in the setting of STEMI are provided in the table below.

Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: indications and logistics

Recommendations	Class[a]	Level[b]
Indication		
Reperfusion therapy is indicated in all patients with time from symptom onset <12 hours' duration and persistent ST-segment elevation.	I	A
In the absence of ST-segment elevation, a primary PCI strategy is indicated in patients with suspected ongoing ischaemic symptoms suggestive of MI and at least one of the following criteria present: • haemodynamic instability or cardiogenic shock • recurrent or ongoing chest pain refractory to medical treatment • life-threatening arrhythmias or cardiac arrest • mechanical complications of MI • acute heart failure • recurrent dynamic ST-segment or T-wave changes, particularly with intermittent ST-segment elevation.	I	C
A primary PCI strategy is recommended over fibrinolysis within the indicated timeframes.	I	A
In patients with time from symptom onset >12 hours, a primary PCI strategy is indicated in the presence of ongoing symptoms or signs suggestive of ischaemia, haemodynamic instability, or life- threatening arrhythmias.	I	C
A routine primary PCI strategy should be considered in patients presenting late (12–48 hours) after symptom onset.	IIa	B
Logistics		
It is recommended that the prehospital management of STEMI patients be based on regional networks designed to deliver reperfusion therapy effectively in a timely fashion, and to offer primary PCI to as many patients as possible.	I	B
It is recommended that all EMS, emergency departments, coronary care units, and catheterization laboratories have a written updated STEMI management protocol, preferably shared within geographic networks.	I	C
It is recommended that primary PCI-capable centres deliver a 24-hour/7-day service and ensure that primary PCI is performed as fast as possible.	I	B
It is recommended that patients transferred to a PCI-capable centre for primary PCI bypass the emergency department and CCU/ICCU and are transferred directly to the catheterization laboratory.	I	B

CCU = coronary care unit; EMS = emergency medical services; ICCU = intensive coronary care unit; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

[a] Class of recommendation - [b] Level of evidence.

Recommendations regarding procedural aspects of primary PCI are listed in the table below.

Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: procedural aspects (strategy and technique)

Recommendations	Class[a]	Level[b]
Strategy		
Routine revascularization of non-IRA lesions should be considered in patients with multivessel disease before hospital discharge.	IIa	A
CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.	IIa	C
In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI.	III	B
Technique		
Routine use of thrombus aspiration is not recommended.	III	A

CABG = coronary artery bypass grafting; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

[a] Class of recommendation

[b] Level of evidence.

Recommendations for myocardial revascularization in patients with chronic heart failure and systolic LV dysfunction are listed in the table below.

Recommendations on revascularizations in patients with chronic heart failure and systolic left ventricular dysfunction (ejection fraction ≤35%)

Recommendations	Class[a]	Level[b]
In patients with severe LV systolic dysfunction and coronary artery disease suitable for intervention, myocardial revascularization is recommended.	I	B
CABG is recommended as the first revascularization strategy choice in patients with multivessel disease and acceptable surgical risk.	I	B
In patients with one or two-vessel disease, PCI should be considered as an alternative to CABG when complete revascularization can be achieved.	IIa	C
In patients with three-vessel disease, PCI should be considered based on the evaluation by the Heart Team of the patient's coronary anatomy, the expected completeness of revascularization, diabetes status, and comorbidities.	IIa	C
LV aneurysmectomy during CABG should be considered in patients with NYHA class III/IV, large LV aneurysm, large thrombus formation, or if the aneurysm is the origin of arrhythmias.	IIa	C
Surgical ventricular restoration during CABG may be considered in selected patients treated in centres with expertise.	IIb	B

CABG = coronary artery bypass grafting; LV = left ventricular; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

[a] Class of recommendation.

[b] Level of evidence.

Myocardial revascularization is the cornerstone of treatment in patients with cardiogenic shock complicating ACS. Therefore, emergency coronary angiography is indicated in this setting. The general triage and treatment of patients with cardiogenic shock is displayed in Figure 6.

Figure 6 Algorithm for management of patients with cardiogenic shock

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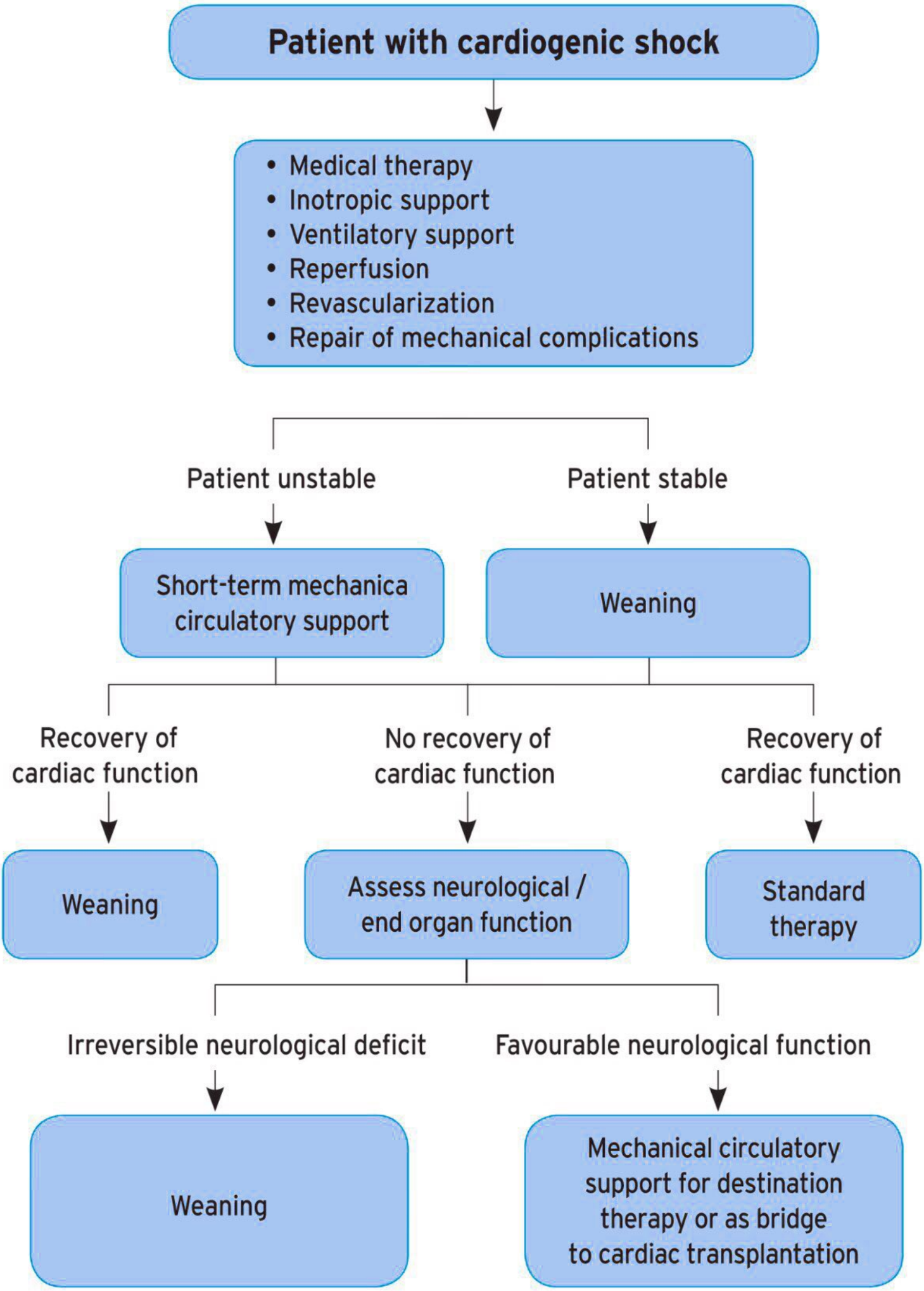
Figure 6 Algorithm for management of patients with cardiogenic shock



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Recommendations for the management of patients with cardiogenic shock		
Recommendations	**Class[a]**	**Level[b]**
Emergency coronary angiography is indicated in patients with acute heart failure or cardiogenic shock complicating ACS.	I	B
Emergency PCI of the culprit lesion is indicated for patients with cardiogenic shock due to STEMI or NSTE-ACS, independent of time delay of symptom onset, if coronary anatomy is amenable to PCI.	I	B
Emergency CABG is recommended for patients with cardiogenic shock if the coronary anatomy is not amenable to PCI.	I	B
In cases of haemodynamic instability, emergency surgical or catheter-based repair of mechanical complications of ACS is indicated, as decided by the Heart Team.	I	C
In selected patients with ACS and cardiogenic shock, short-term mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life.	IIb	C
Routine use of IABPs in patients with cardiogenic shock due to ACS is not recommended.	III	B

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; IABP = intra-aortic balloon pump; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

[a] Class of recommendation - [b] Level of evidence.

In general the indications for revascularization in diabetic patients with SCAD and ACS are similar to those in patients without diabetes (see Chapter 5). In the selection of the optimal myocardial revascularization strategy for patients with multivessel CAD, diabetes mellitus is an important criterion favouring CABG. Specific recommendations for myocardial revascularization in patients with diabetes are provided in the Table on page 15 (see Chapter 5).

Recommendation for patients on metformin

Recommendation	Class[a]	Level[b]
It is recommended to check renal function if patients have taken metformin immediately before angiography and withhold metformin if renal function deteriorates.	I	C

[a] Class of recommendation - [b] Level of evidence.

Recommendations for prevention of contrast-induced nephropathy in patients undergoing coronary angiography and myocardial revascularization are provided in the table below.

Recommendations for the prevention of contrast-induced nephropathy

Recommendations	Dose	Class[a]	Level[b]
Patients undergoing coronary angiography or MSCT			
It is recommended that all patients are assessed for the risk of contrast-induced nephropathy.		I	C
Adequate hydration is recommended.		I	C
Patients with moderate or severe CKD (National Kidney Foundation stages 3b and 4)			
Use of low-osmolar or iso-osmolar contrast media is recommended.		I	A
It is recommended that the volume of contrast media be minimized.	Total contrast volume/GFR <3.7.[c]	I	B
In statin-naïve patients, pretreatment with high-dose statins should be considered.	Rosuvastatin 40/20 mg or atorvastatin 80 mg.	IIa	A
Pre- and post-hydration with isotonic saline should be considered if the expected contrast volume is >100 mL.	1 mL/kg/h 12 hours before and continued for 24 hours after the procedure (0.5 mL/kg/h if LVEF ≤35% or NYHA >2).	IIa	C
As an alternative to the pre- and post- hydration regimen, tailored hydration regimens[d] may be considered.		IIb	B
Patients with severe CKD (National Kidney Foundation stage 4)			
Prophylactic haemofiltration 6 hours before complex PCI may be considered.	Fluid replacement rate 1000 mL/h without negative loss and saline hydration continued for 24 hours after the procedure.	IIb	B
Haemodialysis is not recommended as a preventive measure.		III	B

CKD = chronic kidney disease; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MSCT = multi-slice computed tomography; NYHA = New York Heart Association; PCI = percutaneous coronary angiography. [a] Class of recommendation - [b] Level of evidence. [c] Example: 370 mL of contrast medium in a patient with a GFR of 100 mL/min will yield a ratio of 3.7. [d] Options are: infusion of normal saline adjusted to central venous pressure; furosemide with matched infusion of normal saline (for details see web addenda).

The table below provides a list of recommendations for combined valvular interventions and myocardial revascularization according to primary diagnosis and type of valvular disease.

Recommendations for combined valvular and coronary interventions		
Recommendations	**Class[a]**	**Level[b]**
Primary valve intervention and coronary revascularization		
CABG is recommended in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis >70%.	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis of 50–70%.	IIa	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa	C
PCI should be considered in patients with a primary indication to undergo transcatheter mitral valve interventions and coronary artery diameter stenosis >70% in proximal segments.	IIa	C
Primary myocardial revascularization and valve intervention		
SAVR is indicated in patients with severe AS undergoing CABG, or surgery of the ascending aorta or another valve.	I	C
Mitral valve surgery is indicated in patients with severe[c] secondary MR undergoing CABG and LVEF >30%.	I	C
Mitral valve surgery should be considered in symptomatic patients with severe[c] secondary MR, LVEF <30%, but with evidence of myocardial viability and an option for surgical revascularization.	IIa	C

AS = aortic stenosis; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation. [a] Class of recommendation - [b] Level of evidence. [c] Severe secondary MR was defined as an effective regurgitant orifice area (EROA) >0.40 cm^2.

Recommendations for carotid artery revascularization in patients scheduled for CABG are provided in the table below.

Recommendations on the management of carotid stenosis in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
In patients scheduled for CABG it is recommended that the indication (and if so the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with recent (<6 months) history of TIA/stroke:		
– Carotid revascularization should be considered in patients with 50–99% carotid stenosis.	IIa	B
– Carotid revascularization with CEA should be considered as first choice in patients with 50–99% carotid stenosis.	IIa	B
– Carotid revascularization is not recommended in patients with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG:		
– Carotid revascularization may be considered in patients with bilateral 70–99% carotid stenosis or 70–99% carotid stenosis and contralateral occlusion.	IIb	C
– Carotid revascularization may be considered in patients with a 70–99% carotid stenosis, in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke[c], in order to reduce stroke risk beyond the perioperative period.	IIb	C
– Routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.	III	C

CABG = coronary artery bypass grafting; CEA= carotid endarterectomy; TIA = transient ischaemic attack.

[a] Class of recommendation - [b] Level of evidence.

[c] Contralateral TIA/stroke, ipsilateral silent infarction on cerebral imaging, intraplaque haemorrhage or lipid- rich necrotic core on magnetic resonance angiography, or any of the following ultrasound imaging findings: stenosis progression (>20%), spontaneous embolization on transcranial Doppler, impaired cerebral vascular reserve, large plaques, echolucent plaques, increased juxta-luminal hypoechogenic area.

Recommendations for pre-operative strategies to reduce the incidence of stroke in patients undergoing CABG are provided in the table below.

Pre-operative strategies to reduce the incidence of stroke in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, carotid DUS is recommended in patients with recent (<6 months) history of stroke/TIA.	I	B
In patients with no recent (<6 months) history of TIA/stroke, carotid DUS may be considered before CABG in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit.	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C

CABG = coronary artery bypass grafting; DUS = duplex ultrasound; LEAD = lower extremity artery disease; TIA = transient ischaemic attack. [a] Class of recommendation - [b] Level of evidence.

Repeat revascularization procedures

Recommendations on repeat revascularization strategies after CABG and PCI are provided in the tables below.

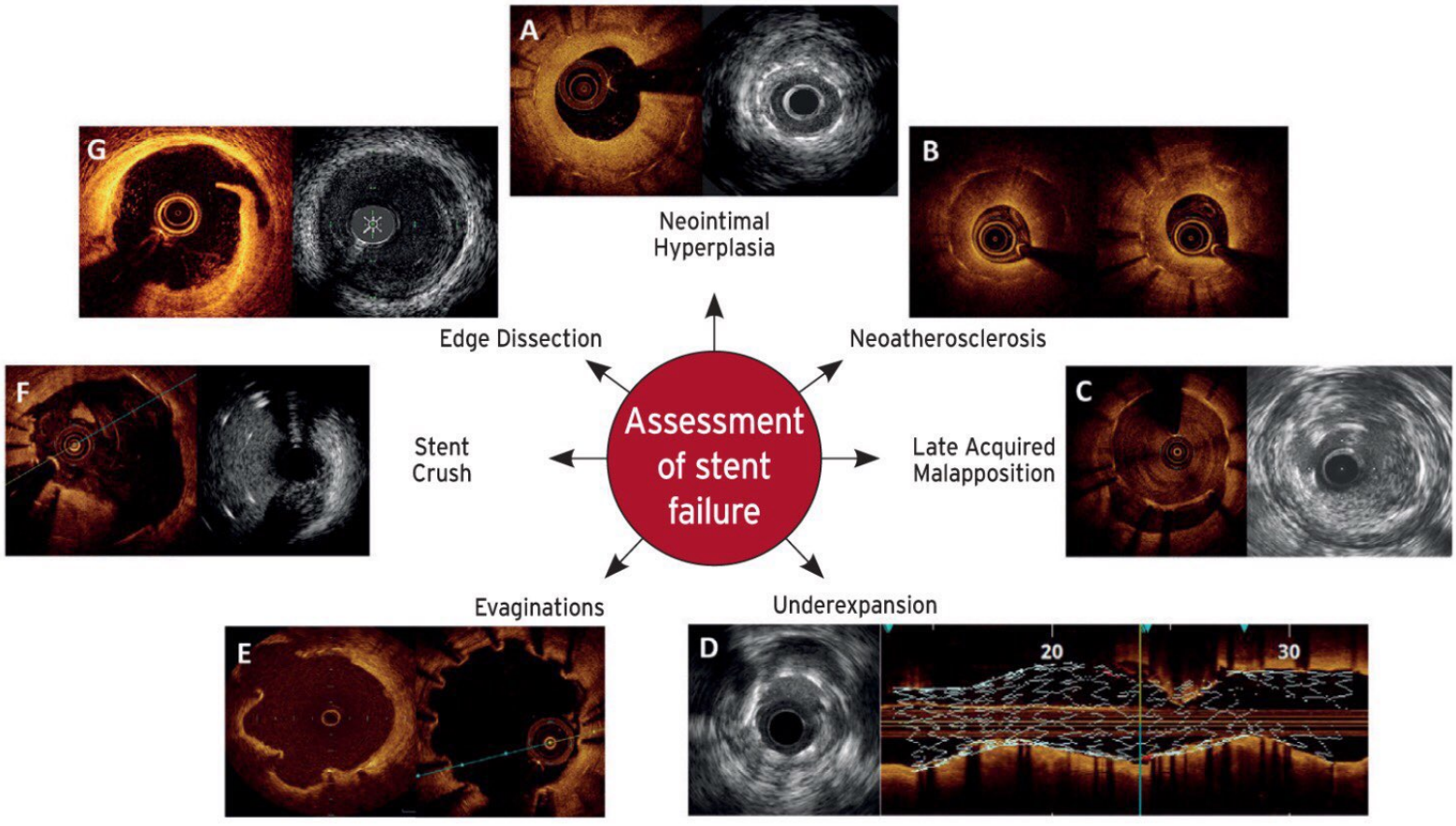
Recommendations on repeat revascularization		
Recommendations	**Class[a]**	**Level[b]**
Early post-operative ischaemia and graft failure		
Coronary angiography post-CABG is recommended for patients with: • symptoms of ischaemia and/or abnormal biomarkers suggestive of peri-operative MI • ischaemic ECG changes indicating large area of risk • new significant wall motion abnormalities • haemodynamic instability.	I	C
It is recommended that either emergency reoperation or PCI is decided upon by ad hoc consultation in the Heart Team, based on the feasibility of revascularization, area at risk, comorbidities, and clinical status.	I	C
Disease progression and late graft failure		
Repeat revascularization is indicated in patients with a large area of ischaemia or severe symptoms despite medical therapy.	I	B
If considered safe, PCI should be considered as first choice over CABG.	IIa	C
Procedural aspects of the revascularization modalities		
CABG		
IMA is the conduit of choice for redo CABG in patients in whom the IMA was not used previously.	I	B
Redo CABG should be considered for patients without a patent IMA graft to the LAD.	IIa	B
PCI		
Distal protection devices should be considered for PCI of SVG lesions.	IIa	B
PCI of the bypassed native artery should be considered over PCI of the bypass graft.	IIa	C
Restenosis		
DES are recommended for the treatment of in-stent restenosis of BMS or DES.	I	A
Drug-coated balloons are recommended for the treatment of in-stent restenosis of BMS or DES.	I	A
In patients with recurrent episodes of diffuse in-stent restenosis, CABG should be considered by the Heart Team over a new PCI attempt.	IIa	C
IVUS and/or OCT should be considered to detect stent-related mechanical problems leading to restenosis.	IIa	C

BMS = bare-metal stent; CABG = coronary artery bypass grafting; DES = drug-eluting stent; ECG = electrocardiogram; IMA = internal mammary artery; IVUS = intravascular ultrasound; LAD = left anterior descending artery; MI = myocardial infarction; OCT = optical coherence tomography; PCI = percutaneous coronary intervention; SVG = saphenous vein graft.

[a] Class of recommendation - [b] Level of evidence.

Figure 7 summarizes the contribution of intracoronary imaging to the management of stent failure.

Figure 7 Intracoronary imaging for the assessment of stent failure



Examples of intravascular imaging findings (IVUS or OCT) in patients with stent failure. Panel A displays OCT (left) and IVUS (right) examples of in-stent restenosis due to excessive neointimal hyperplasia. Panel B displays two OCT examples of in-stent restenosis due to neoatherosclerosis. Panel C displays OCT (left) and IVUS (right) examples of late acquired malapposition. Panel D displays IVUS (left) and longitudinal OCT reconstruction (right) images of stent underexpansion. Panel E displays two OCT examples of in-stent evaginations, a typical finding of delayed arterial healing. Panel F displays OCT (left and IVUS (right) examples of stent crush. Panel G displays an OCT (left) and IVUS (right) case of coronary dissection at the stent edge. IVUS = intravascular ultrasound; OCT = optical coherence tomography.

Intracoronary images for this figure were kindly provided by Drs Nicolas Amabile, Fernando Alfonso, and Gennaro Sardella.

Recommendations for the prevention of ventricular arrhythmias by myocardial revascularization are provided in the table below.

Recommendations for the prevention of ventricular arrhythmias by revascularization

Recommendations	Class[a]	Level[b]
A primary PCI strategy is recommended in patients with resuscitated cardiac arrest and an ECG consistent with STEMI.	I	B
Urgent angiography (and PCI if indicated) should be considered in patients with resuscitated cardiac arrest without diagnostic ST-segment elevation but with a high suspicion of ongoing myocardial ischaemia.	IIa	C
In patients with electrical storm, urgent coronary angiography and revascularization (as required) should be considered.	IIa	C

ECG = electrocardiogram; STEMI = ST-elevation myocardial infarction; PCI = percutaneous coronary intervention.
[a] Class of recommendation - [b] Level of evidence.

Recommendations for prevention and treatment of atrial fibrillation in the setting of myocardial revascularization

Recommendations	Class[a]	Level[b]
Peri-operative oral β-blocker therapy is recommended for the prevention of post-operative AF after CABG surgery.	I	B
Restoration of sinus rhythm by electrical cardioversion or antiarrhythmic drugs is recommended in post-operative AF with haemodynamic instability.	I	C
Peri-operative amiodarone should be considered as prophylactic therapy to prevent AF after CABG surgery.	IIa	A
Long-term anticoagulation should be considered in patients with AF after CABG or PCI, at risk for stroke, considering the individual stroke and bleeding risk.	IIa	B
Rate control and anticoagulation should be considered as the initial management of asymptomatic post-operative AF.	IIa	B
Antiarrhythmic drugs should be considered for symptomatic post- operative AF after CABG or PCI in an attempt to restore sinus rhythm.	IIa	C
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing CABG surgery.	IIb	B

AF = atrial fibrillation; CABG = coronary artery bypass grafting; LAA = left atrial appendage; PCI = percutaneous coronary intervention. [a] Class of recommendation - [b] Level of evidence.

Procedural aspects of CABG

Recommendations on procedural aspects of CABG are listed in the table below and in Figure 8.

Recommendations on procedural aspects of coronary artery bypass grafting		
Recommendations	**Class[a]**	**Level[b]**
General considerations		
Complete myocardial revascularization is recommended.[c]	I	B
Minimization of aortic manipulation is recommended.	I	B
CT scans of the ascending aorta should be considered in patients over 70 years of age and/or with signs of extensive generalized atherosclerosis.	IIa	C
Routine intraoperative graft flow measurement should be considered.	IIa	B
Prior to aortic manipulation, epiaortic ultrasound should be considered to identify atheromatous plaques and select the optimal surgical strategy.	IIa	C
Conduit selection		
Arterial grafting with IMA to the LAD system is recommended.	I	B
An additional arterial graft should be considered in appropriate patients.	IIa	B
The use of the radial artery is recommended over the saphenous vein in patients with high grade coronary artery stenosis.[d]	I	B
BIMA grafting should be considered in patients who do not have a high risk of sternal wound infection.[e]	IIa	B
Vessel harvesting		
Skeletonized IMA dissection is recommended in patients with a high risk of sternal wound infection[d].	I	B
Endoscopic vein harvesting, if performed by experienced surgeons, should be considered to reduce the incidence of wound complications.	IIa	A
No-touch vein harvesting should be considered, when an open technique is used.	IIa	B
Minimally invasive techniques		
Off-pump CABG and preferably no-touch techniques on the ascending aorta, by experienced operators, are recommended in patients with significant atherosclerotic aortic disease.	I	B
Off-pump CABG should be considered for subgroups of high-risk patients by experienced off-pump teams.	IIa	B
Where expertise exists, minimally invasive CABG through limited thoracic access should be considered in patients with isolated LAD lesions or in the context of hybrid revascularization.	IIa	B
Hybrid procedures, defined as consecutive or combined surgical and percutaneous revascularization, may be considered in specific patient subsets at experienced centres.	IIb	B

BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; CT = computed tomography; IMA = internal mammary artery; LAD = left anterior descending coronary artery. [a] Class of recommendation - [b] Level of evidence.

[c] Definitions of complete revascularization are provided in Section 5.3.1.3. of the Full Text.

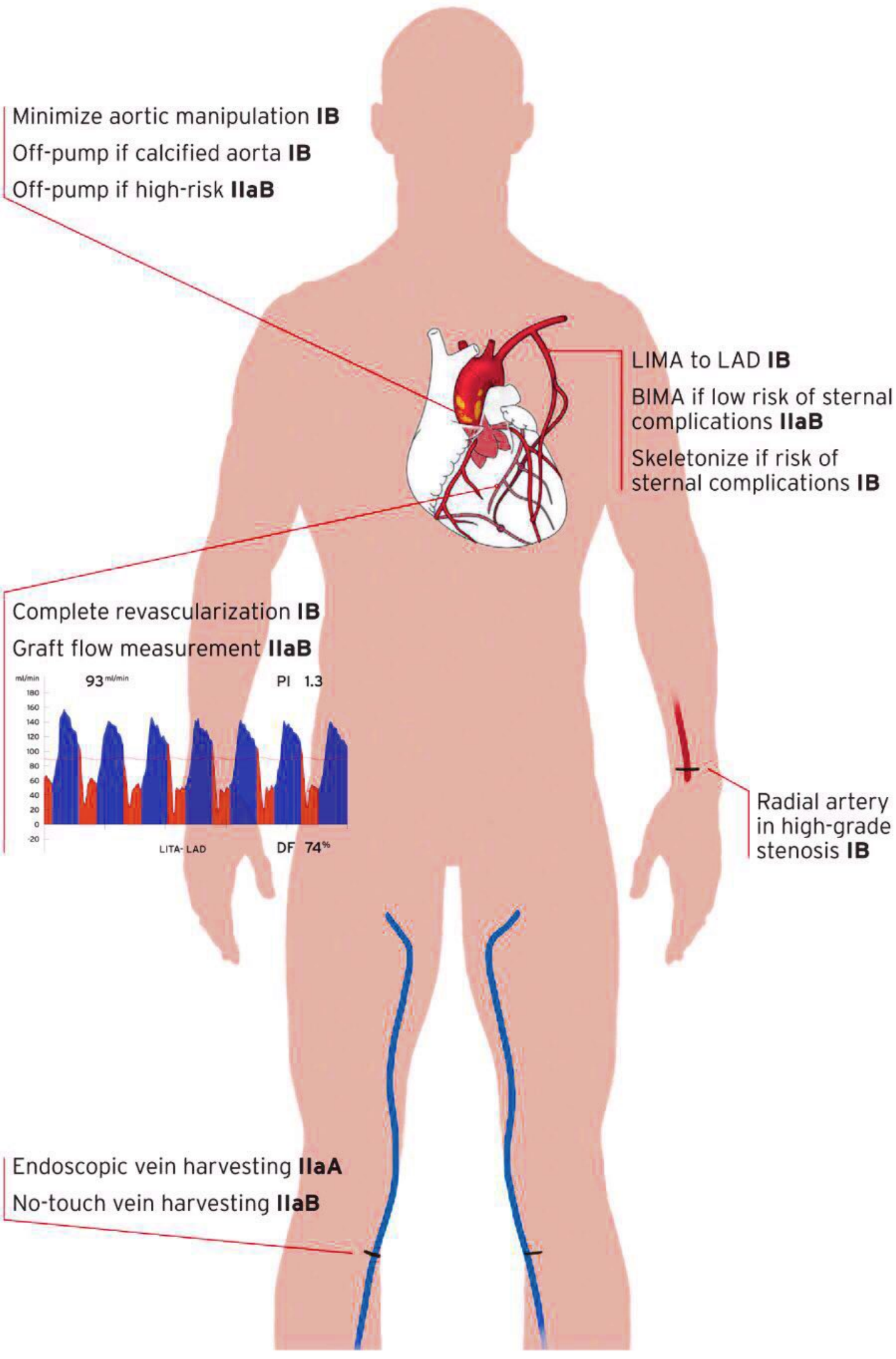
BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; CT = computed tomography; IMA = internal mammary artery; LAD = left anterior descending coronary artery. [a] Class of recommendation - [b] Level of evidence.

[c] Definitions of complete revascularization are provided in Section 5.3.1.3. of the Full Text.

[d] Specially in patients with poor vein grafts. The radial artery should not be used if previously catheterized, if the Allen test is positive or if calcific degeneration is present.

[e] Patients with diabetes mellitus, chronic pulmonary obstructive disease, previous mediastinal radiation, and obesity, particularly when multiples of these are present.

Figure 8 Technical aspects of CABG



BIMA = bilateral internal mammary artery; CABG = coronary artery bypass grafting; IMA = internal mammary artery; LAD = left anterior descending coronary artery.

Recommendations on the choice of stent type and access site are provided in the table below.

Recommendations on choice of stent and access site		
Recommendations	**Class[a]**	**Level[b]**
DES are recommended over BMS for any PCI irrespective of: • clinical presentation • lesion type • planned non-cardiac surgery • anticipated duration of DAPT • concomitant anticoagulant therapy.	I	A
Radial access is recommended as the standard approach, unless there are overriding procedural considerations.	I	A
BRS are currently not recommended for clinical use outside of clinical studies.	III	C

BMS = bare-metal stents; BRS = bioresorbable scaffolds; DAPT = dual antiplatelet therapy; DES = drug- eluting stents; PCI = percutaneous coronary intervention.
[a] Class of recommendation.
[b] Level of evidence.

Recommendations on the use and clinical value of FFR and iwFR are found in Chapters 3 and 5. The table below provides recommendations on intracoronary imaging for procedural optimization.

Recommendations on intravascular imaging for procedural optimization		
Recommendations	**Class[a]**	**Level[b]**
IVUS or OCT should be considered in selected patients to optimize stent implantation.	IIa	B
IVUS should be considered to optimize treatment of unprotected left main lesions.	IIa	B

IVUS = intravascular ultrasound; OCT = optical coherence tomography.
[a] Class of recommendation.
[b] Level of evidence.

Recommendations for the treatment by PCI of specific lesion subsets are provided in the table below.

Recommendations on specific lesion subsets		
Recommendations	**Class[a]**	**Level[b]**
Stent implantation in the main vessel only, followed by provisional balloon angioplasty with or without stenting of the side branch, is recommended for PCI of bifurcation lesions.	I	A
Percutaneous revascularization of CTOs should be considered in patients with angina resistant to medical therapy or with a large area of documented ischaemia in the territory of the occluded vessel.	IIa	B
In true bifurcation lesions of the left main, the double-kissing crush technique may be preferred over provisional T-stenting.	IIb	B

Antithrombotic drugs for myocardial revascularization and their pharmacological targets are illustrated in Figure 9. Dosages are found in Table 7 below.

Table 7: Doses of antiplatelet and anticoagulant drugs used during and after myocardial revascularization

Antiplatelet drugs	
Aspirin	Loading dose of 150–300 mg orally or 75–150 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day.
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day.
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day. In patients with body weight <60 kg, a maintenance dose of 5 mg is recommended. In patients >75 years, prasugrel is generally not recommended, but a dose of 5 mg should be used if treatment is deemed necessary.
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg *b.i.d.*
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 µg/kg/min infusion (maximum 10 µg/min) for 12 hours.
Eptifibatide	Double bolus of 180 µg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 µg/kg/min for up to 18 hours.
Tirofiban	Bolus of 25 µg/kg over 3 min i.v., followed by an infusion of 0.15 µg/kg/min for up to 18 hours.
Cangrelor	Bolus of 30 µg/kg i.v. followed by 4 µg/kg/min infusion for at least 2 hours or duration of procedure, whichever is longer.
Anticoagulant drugs for PCI	
Unfractionated heparin	70–100 U/kg i.v. bolus when no GP IIb/IIIa inhibitor is planned. 50–70 U/kg i.v. bolus with GP IIb/IIIa inhibitors.
Enoxaparin	0.5 mg/kg i.v. bolus.
Bivalirudin	0.75 mg/kg i.v. bolus followed by i.v infusion of 1.75 mg/kg/h for up to 4 hours after the procedure as clinically warranted.
Oral anticoagulant drugs (concomitant treatment after PCI)	
Vitamin K antagonists (e.g. warfarin, phenprocoumon)	Dosing is based on INR value and the respective clinical indication.
Apixaban	Maintenance doses of 5 and 2.5[a] mg *b.i.d.*
Dabigatran	Maintenance doses of 150 and 110 mg *b.i.d.*
Edoxaban	Maintenance dose of 60 and 30[a] mg/day
Rivaroxaban	Maintenance doses of 20 and 15[a] mg/day and 2.5 mg *b.i.d.* (vascular dose).

b.i.d. = twice daily; GP = glycoprotein; INR = international normalized ratio; i.v. = intravenous; PCI = percutaneous coronary intervention.

[a] Specific criteria for reduced dose apply (see Recommendation Table here).

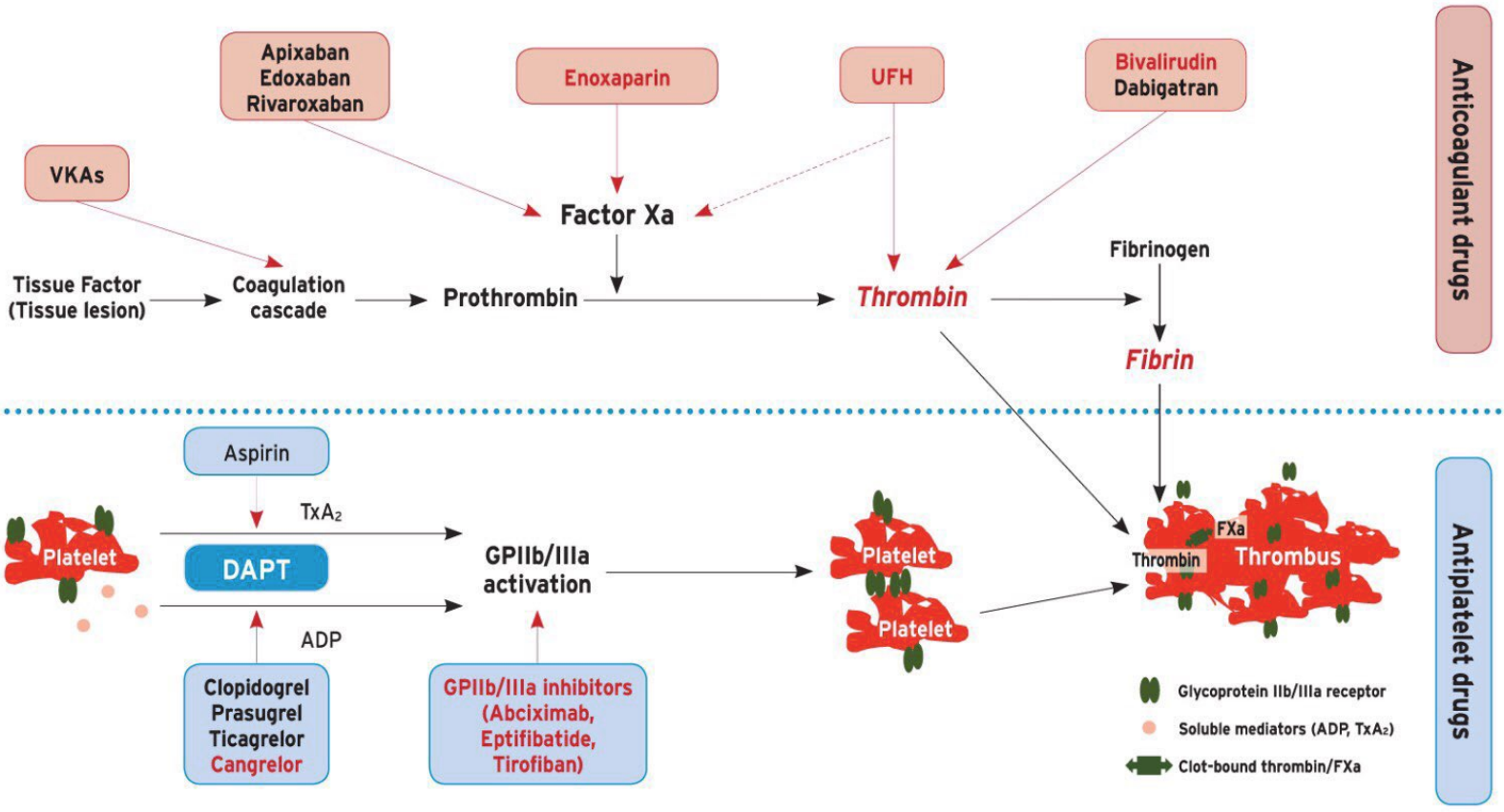
Figure 9 Antithrombotic treatment for myocardial revascularization and its pharmacological targets

Apixaban	Maintenance doses of 5 and 2.5[a] mg *b.i.d.*
Dabigatran	Maintenance doses of 150 and 110 mg *b.i.d.*
Edoxaban	Maintenance dose of 60 and 30[a] mg/day
Rivaroxaban	Maintenance doses of 20 and 15[a] mg/day and 2.5 mg *b.i.d.* (vascular dose).

b.i.d. = twice daily; GP = glycoprotein; INR = international normalized ratio; i.v. = intravenous; PCI = percutaneous coronary intervention.

[a] Specific criteria for reduced dose apply (see Recommendation Table here).

Figure 9 Antithrombotic treatment for myocardial revascularization and its pharmacological targets



The figure illustrates anticoagulant and antiplatelet drugs being used during and after myocardial revascularization (percutaneous coronary intervention or coronary artery bypass grafting). Drugs with oral administration are shown in black letters and drugs with preferred parenteral administration in red.

ADP = adenosine diphosphate; DAPT = dual antiplatelet therapy; FXa = factor Xa; GP = glycoprotein; TxA_2 = thromboxane A_2; UFH = unfractionated heparin; VKAs = vitamin K antagonists.

Recommendations for antithrombotic treatment in patients with stable CAD undergoing PCI are listed in the table below.

Recommendations for antithrombotic treatment in stable coronary artery disease patients undergoing percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
Pre-treatment and antiplatelet therapy		
Treatment with 600 mg clopidogrel is recommended in elective PCI patients once the coronary anatomy is known and a decision is made to proceed with PCI.	I	A
Pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
In patients on a maintenance dose of 75 mg clopidogrel, a new loading dose of 600 mg may be considered once the indication for PCI is confirmed.	IIb	C
Peri-interventional treatment		
Aspirin is indicated before elective stenting.	I	A
An oral loading dose of aspirin (150–300 mg p.o. or 75–250 mg i.v.) is recommended if the patient is not pretreated.	I	C
Clopidogrel (600 mg loading dose, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A
Glycoprotein IIb/IIIa antagonists should be considered only for bail-out.	IIa	C
Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g. history of stent thrombosis, left main stenting).	IIb	C
Unfractionated heparin is indicated as the standard anticoagulant (70–100 U/kg).	I	B
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for up to 4 hours after the procedure) is indicated in the case of heparin- induced thrombocytopenia.	I	C
Enoxaparin (i.v. 0.5 mg/kg) should be considered as an alternative agent.	IIa	B
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A

Enoxaparin (i.v. 0.5 mg/kg) should be considered as an alternative agent.	IIa	B
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A
Post-interventional and maintenance treatment		
Life-long single antiplatelet therapy, usually aspirin, is recommended.	I	A
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C
In patients with SCAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type[c].	I	A
In patients with SCAD treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
In patients with SCAD treated with DCB, DAPT should be considered for 6 months.	IIa	B
In patients with SCAD considered at high bleeding risk (e.g. PRECISE- DAPT ≥25), DAPT should be considered for 3 months[d].	IIa	A
In patients with SCAD who have tolerated DAPT without a bleeding complication and who are at low bleeding risk but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and up to 30 months may be considered.	IIb	A
In patients with SCAD in whom 3-month DAPT poses safety concerns, DAPT may be considered for 1 month.	IIb	C

BRS = bioresorbable scaffold; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; DES = drug-eluting stent; i.v. = intravenous; MI = myocardial infarction; PCI = percutaneous coronary intervention; p.o. = orally; PRECISE-DAPT = PREdicting bleeding

Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; SCAD = stable coronary artery disease.

[a] Class of recommendation.

[b] Level of evidence.

[c] These recommendations refer to stents which are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE mark.

[d] The evidence supporting this recommendation comes from two studies where the zotarolimus-eluting Endeavour stent was investigated in conjunction with a 3-month DAPT regimen.

Recommendations for pre- and peri-interventional antithrombotic treatment in patients with non-ST-elevation acute coronary syndromes undergoing PCI are listed in the table below.

Recommendations for antithrombotic treatment in patients with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
Pre-treatment and antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 75–250 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term.	I	A
A $P2Y_{12}$-inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel in $P2Y_{12}$-inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).	I	B
• Ticagrelor irrespective of the preceding $P2Y_{12}$-inhibitor regimen (180 mg loading dose, 90 mg *b.i.d.*).	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
For pre-treatment in patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg *b.i.d.*), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A
GP IIb/IIIa antagonist may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	C
Pre-treatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended.	III	A
Administration of prasugrel in patients in whom coronary anatomy is not known is not recommended.	III	B

is not recommended.		
Administration of prasugrel in patients in whom coronary anatomy is not known is not recommended.	III	B
Peri-interventional therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy.	I	A
It is recommended that anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy–safety profile of the chosen agent.	I	C
UFH is recommended.	I	C
In patients on fondaparinux, a single bolus UFH (85 IU/kg, or 60 IU in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated.	I	B
Enoxaparin should be considered in patients pre-treated with subcutaneous enoxaparin.	IIa	B
Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.	IIa	C
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for up to 4 hours after the procedure) may be considered as an alternative to UFH.	IIb	A
Crossover of UFH and LMWH is not recommended.	III	B

b.i.d. = twice daily; GP = glycoprotein; LMWH = low-molecular-weight heparin; NSTE-ACS = non-ST- segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

[a] Class of recommendation.

[b] Level of evidence.

Recommendations for post-interventional and maintenance antithrombotic treatment in patients with non-ST-elevation acute coronary syndromes or ST-elevation myocardial infarction undergoing PCI are listed in the table below.

Recommendations for post-interventional and maintenance treatment in patients with non-ST-elevation acute coronary syndromes and ST-elevation myocardial infarction undergoing percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$-inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as an excessive risk of bleeding (e.g. PRECISE-DAPT ≥25)	I	A
In patients with ACS and stent implantation who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$-inhibitor therapy after 6 months should be considered.	IIa	B
In patients with ACS treated with BRS, DAPT should be considered for at least 12 months and up to the presumed full absorption of the BRS, based on an individual assessment of bleeding and ischaemic risk.	IIa	C
De-escalation of $P2Y_{12}$-inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition.	IIb	B
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A
In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg *b.i.d.* for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B
In ACS patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel, low- dose rivaroxaban (2.5 mg *b.i.d.* for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

ACS = acute coronary syndrome; *b.i.d.* = twice daily; BRS = bioresorbable scaffold; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; PRECISE- DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; TIA = transient ischaemic attack.

[a] Class of recommendation - [b] Level of evidence - [c] Defined as at least 50 years of age, and had one of the following additional high-risk features: age 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance <60 mL/min.

Recommendations for pre- and peri-interventional antithrombotic treatment in patients with ST-elevation myocardial infarction undergoing PCI are listed in the table below. For recommendations on post-interventional and maintenance antithrombotic treatment in patients with ST-elevation myocardial infarction undergoing PCI see table here.

Recommendations for antithrombotic treatment in ST-elevation myocardial infarction patients undergoing percutaneous coronary intervention

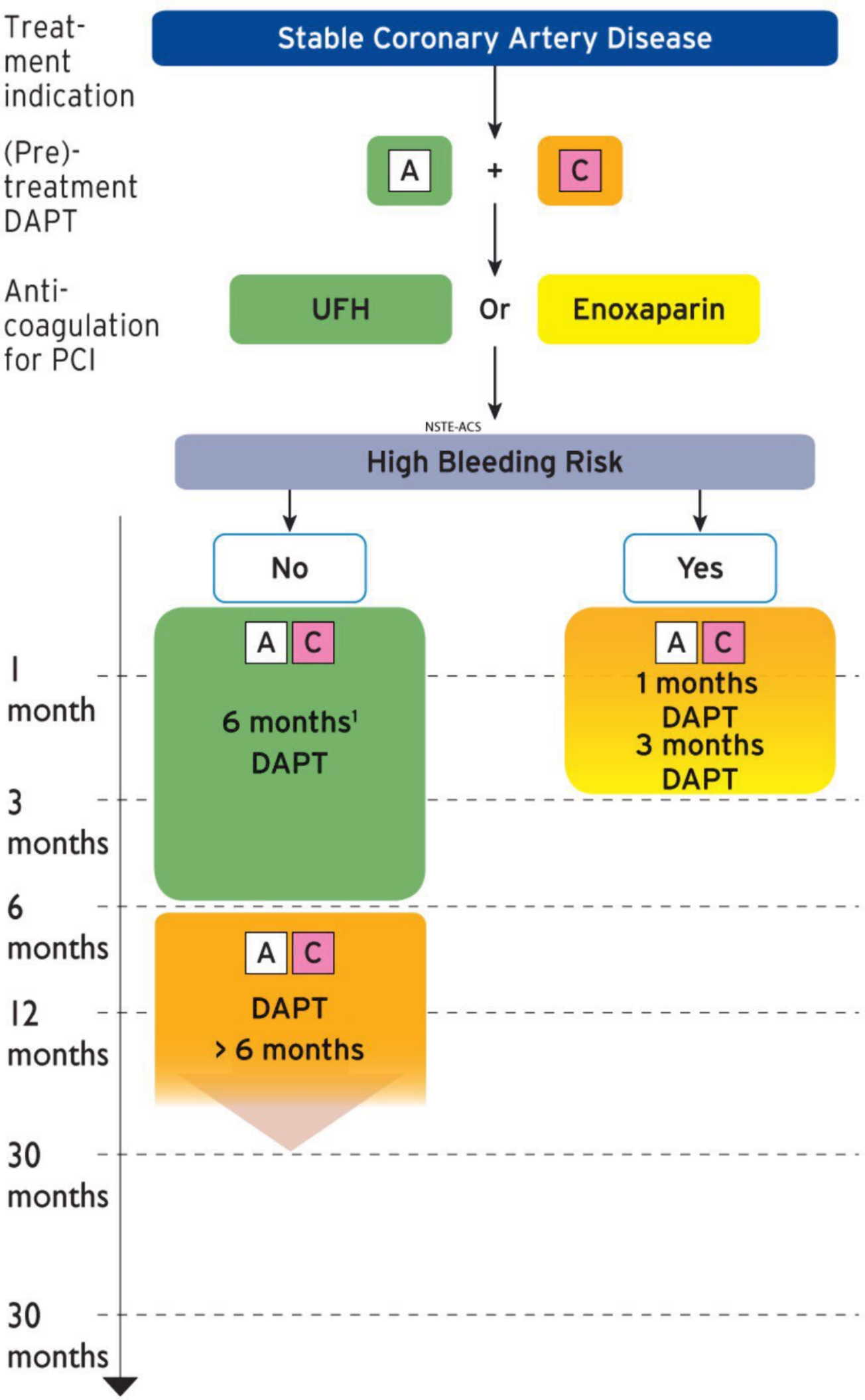
Recommendations	Class[a]	Level[b]
Pre-treatment and antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 75–250 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A potent $P2Y_{12}$-inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A
GP IIb/IIIa inhibitors should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A
GP IIb/IIIa antagonist may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	C
Peri-interventional therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.	I	A
Routine use of UFH is recommended.	I	C
Routine use of enoxaparin should be considered.	IIa	B
Routine use of bivalirudin may be considered.	IIb	A

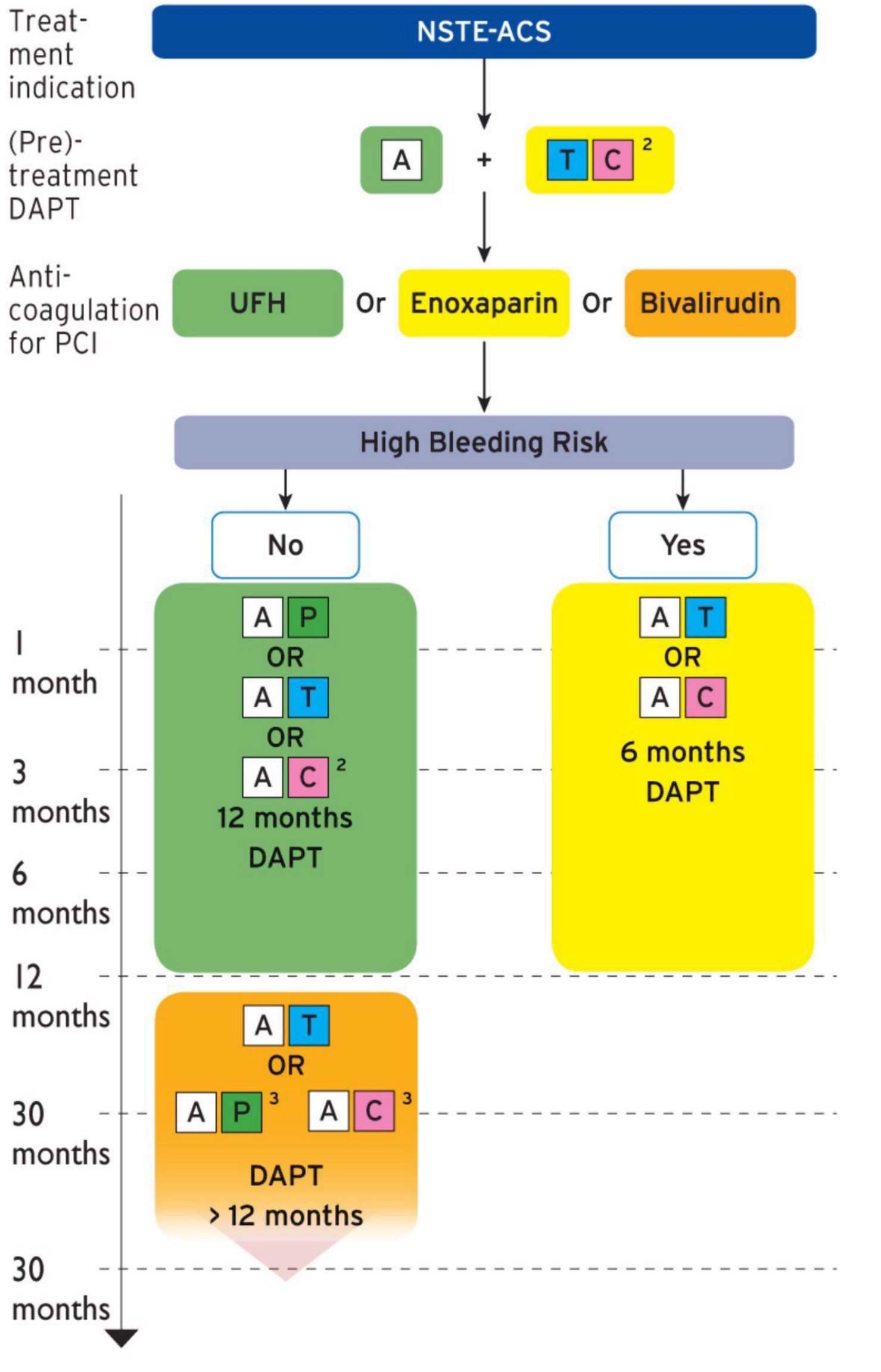
GP = glycoprotein; i.v. = intravenous; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

[a] Class of recommendation - [b] Level of evidence.

Summarizing the recommendations listed, Figure 10 illustrates the algorithm for antithrombotic drugs in patients undergoing percutaneous coronary intervention.

Figure 10 Algorithm for antithrombotic drugs in patients undergoing percutaneous coronary intervention




Treat-ment indication
NSTE-ACS
(Pre)-treatment DAPT
A + T C 2
Anti-coagulation for PCI
UFH
Or
Enoxaparin
Or
Bivalirudin
High Bleeding Risk
No
Yes
A P
OR
A T
OR
A C 2
12 months DAPT
A T
OR
A C
6 months DAPT
A T
OR
A P 3 A C 3
DAPT > 12 months
1 month
3 months
6 months
12 months
30 months
30 months

Algorithm in patients undergoing PCI

Treatment indication: **STEMI**

(Pre)-treatment DAPT: **A** + **T P C**[4]

Anti-coagulation for PCI: **UFH** Or **Enoxaparin** Or **Bivalirudin**

High Bleeding Risk

	No	Yes
1 month	A P OR A T OR A C[2]	A T OR A C
3 months	12 months DAPT	6 months DAPT
6 months		
12 months	A T OR A P[3] A C[3] DAPT > 12 months	
30 months		
30 months		

Antiplatelet drugs: A = Aspirin; C = Clopidogrel; T = Ticagrelor; P = Prasugrel

DAPT = dual antiplatelet therapy; DCB = drug-coated balloon; NSTE-ACS = non-ST-elevation acute coronary syndrome; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; UFH = unfractioned heparin.

Colour-coding refers to the ESC classes of recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).

[1]After PCI with DCB 6 months DAPT should be considered (class IIa) - [2]Clopidogrel if patient is not eligible for a treatment with prasugrel or ticagrelor; or in a setting of DAPT de-escalation (Class IIb). [3]Clopidogrel or prasugrel if patient is not eligible for a treatment with ticagrelor. [4]Pretreatment before PCI (or at the latest at the time of PCI); clopidogrel if potent P2Y12 inhibitors are contraindicated or not available. (For scores see Supplementary Table 4.). High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).

Recommendations and dual antiplatelet therapy in patients undergoing cardiac surgery are shown in the table below.

Dual antiplatelet therapy in patients undergoing cardiac surgery

Recommendations	Class[a]	Level[b]
It is recommended that the Heart Team estimates the individual bleeding and ischaemic risks and guides the timing of CABG as well as the anti-thrombotic management.	I	C
In patients on aspirin who need to undergo non-emergent cardiac surgery, it is recommended to continue aspirin at a low daily regimen throughout the peri-operative period.	I	C
In patients treated with DAPT after coronary stent implantation who subsequently undergo cardiac surgery, it is recommended to resume $P2Y_{12}$-inhibitor therapy post-operatively as soon as it is deemed safe so that DAPT continues until the recommended duration of therapy is completed.	I	C
In patients with ACS (NSTE-ACS or STEMI) treated with DAPT who are undergoing CABG and do not require long-term OAC therapy, resumption of $P2Y_{12}$-inhibitor therapy as soon as deemed safe after surgery and its continuation up to 12 months is recommended.	I	C
In patients on $P2Y_{12}$-inhibitors who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, at least 5 days after clopidogrel, and at least 7 days after prasugrel should be considered.	IIa	B
In CABG patients with prior MI who are at high risk of severe bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$-inhibitor therapy after 6 months should be considered.	IIa	C
Platelet function testing may be considered to guide the decision on the timing of cardiac surgery in patients who have recently received $P2Y_{12}$-inhibitors.	IIb	B
In patients perceived to be at high ischaemic risk with prior MI and CABG who have tolerated DAPT without a bleeding complication, treatment with DAPT for longer than 12 months and up to 36 months may be considered.	IIb	C

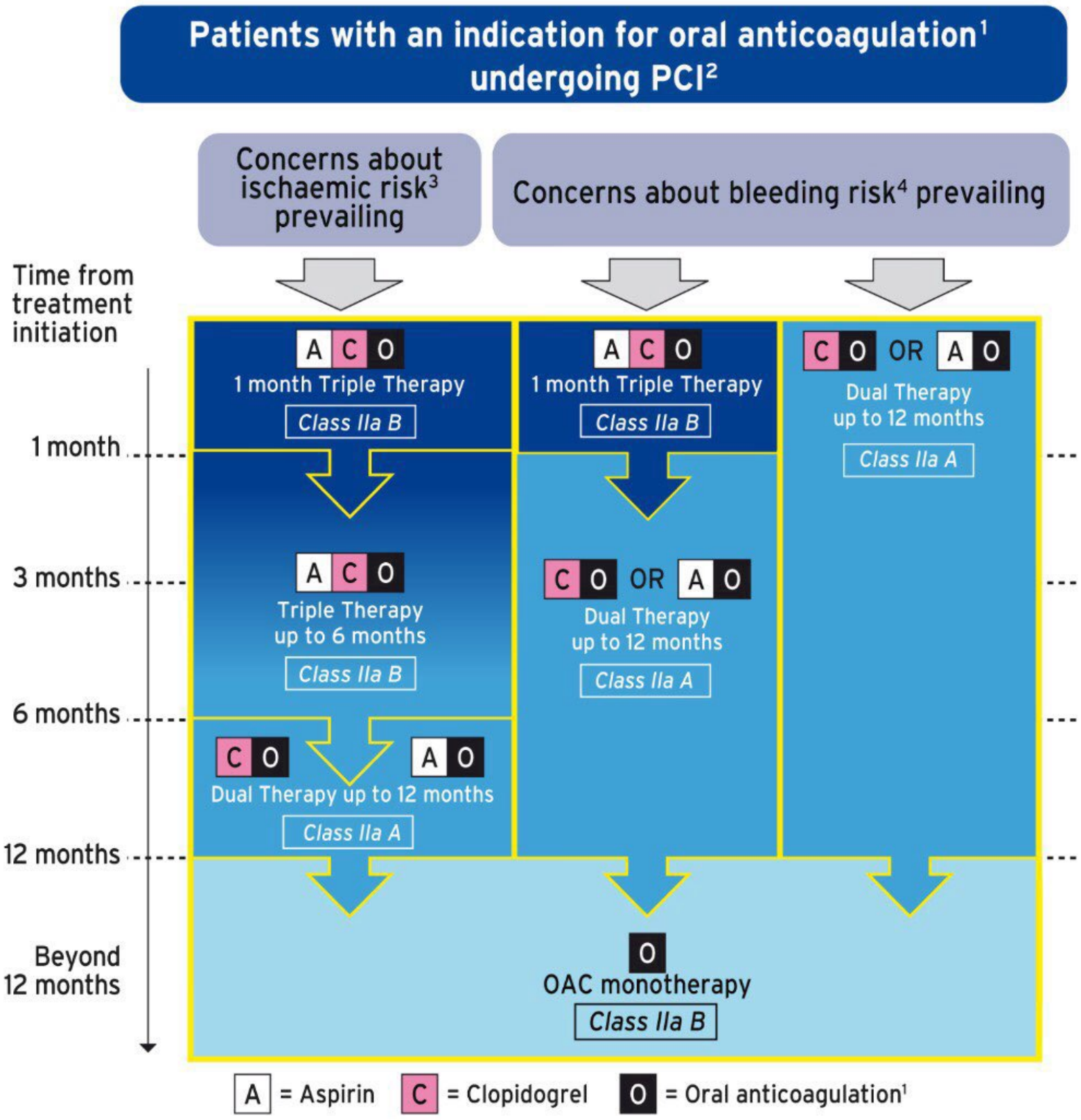
ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; DAPT = dual antiplatelet therapy; NSTE-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; STEMI = ST-elevation myocardial infarction. PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

[a] Class of recommendation - [b] Level of evidence.

In patients with an indication for anticoagulation undergoing PCI the choice of concomitant antiplatelet therapy is critical and depends on the assessment of the risk of ischaemic complications relative to the risk of bleeding complications.

Figure 11 shows the suggested algorithm based on the recommendations. In addition, Tables 8 to 10 specify strategies to avoid bleeding as well as high-risk features for ischaemic events and unfavourable patient profiles for a combination of oral anticoagulant and antiplatelet therapy.

Figure 11 Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



Colour-coding refers to the number of concomitant antithrombotic medication(s). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment with a single antiplatelet agent (aspirin or clopidogrel) plus OAC.

ABC = Age, Biomarkers, Clinical history; AF = atrial fibrillation; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; VKA = vitamin K antagonist. [1] Non-vitamin K antagonist oral anticoagulant (NOAC) preferred over VKA in patients with non-valvular AF. (Class IIaA). [2] Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy. [3] High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction. [4] Bleeding risk can be estimated by HAS-BLED or ABC score.

Table 8 Strategies to avoid bleeding complications in oral anticoagulation patients
Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
One should consider the use of NOAC instead of VKA when NOACs are not contraindicated.
Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65%) when VKA is used.
Clopidogrel is the $P2Y_{12}$-inhibitor of choice.
Use low-dose (≤100 mg daily) aspirin.
Routine use of PPIs.

ABC = Age, Biomarkers, Clinical history; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years (doubled), Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism (doubled), Vascular disease, Age 65–74 years, Sex category; HAS-BLED = Hypertension, Abnormal renal/ liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly; INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.

Table 9 High-risk features for ischaemic events
• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stented length >60 mm
• Treatment of a chronic total occlusion
• History of STEMI

STEMI = ST-elevation myocardial infarction.

Table 10 Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy
• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and an OAC should be considered for 1 month, irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel and an OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and an OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A
In patients with non-valvular AF requiring anticoagulation and antiplatelet treatment, a NOAC should be preferred over VKAs.	IIa	A
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.	IIa	B
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target INR in the lower part of the recommended target range and time in the therapeutic range >65%.	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered[c].	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*	IIb	B
When dabigatran is used in combination with aspirin or clopidogrel, a dose of 150 mg b.i.d may be preferred over a dose of 110 mg b.i.d.	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

ACS = acute coronary syndrome; AF = atrial fibrillation; *b.i.d.* = twice daily; INR = international normalized ratio; OAC = oral anticoagulant; NOAC = non-vitamin K oral anticoagulant; *q.d.* = once daily; VKA = vitamin K antagonist.

[a] Class of recommendation.

[b] Level of evidence.

[c] Apixaban 5 mg *b.i.d.* or apixaban 2.5 mg *b.i.d.* if at least two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L); dabigatran 110 mg or 150 mg *b.i.d.*; edoxaban 60 mg *q.d.* or edoxaban 30 mg *q.d.* if any of the following: creatinine clearance of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil, quinidine, or dronedarone; rivaroxaban 20 mg *q.d.* or rivaroxaban 15 mg *q.d.* if creatinine clearance 30–49 mL/min.

Operator experience impacts outcomes, in particular in critical, complex situations. Increased experience of an entire hospital team consisting of supporting members in the operating room or catheterization laboratory and those responsible for the post-operative care are associated with favourable outcomes.

The tables below provide recommendations for training, proficiency, and operator/ institutional competence in CABG and PCI.

Recommendations for operator/institutional volume in myocardial revascularization

Recommendations	Class[a]	Level[b]
CABG		
It should be considered that CABG be performed at institutions with an annual institutional volume of at least 200 CABG cases.	IIa	C
PCI		
It should be considered that PCI for ACS be performed by trained operators with an annual volume of at least 75 procedures at institutions performing at least 400 PCIs per year with an established 24-hour/7-day service for the treatment of patients with ACS.	IIa	C
It should be considered that PCI for SCAD be performed by trained operators with an annual volume of at least 75 procedures at institutions performing at least 200 PCIs per year.	IIa	C
It should be considered that institutions with annual volumes of fewer than 400 PCIs collaborate in networks with higher-volume institutions (>400 PCIs per year), with shared written protocols and exchange of operators and support staff.	IIa	C
It should be considered that PCI for LM be performed by trained operators with annual volumes of at least 25 LM PCI cases per year.	IIa	C
It should be considered that non-emergency high-risk PCI procedures - such as for LM disease, single remaining patent coronary artery, and complex chronic total occlusions - are only performed by adequately experienced operators at centres that have access to circulatory support and intensive care treatment.	IIa	C

ACS = acute coronary syndromes; CABG = coronary artery bypass grafting; LM = left main; PCI = percutaneous coronary intervention; SCAD = stable coronary artery disease.

[a] Class of recommendation.

[b] Level of evidence.

Recommendations for training in myocardial revascularization		
Recommendations	**Class[a]**	**Level[b]**
Training in CABG		
It is recommended that trainees in cardiac surgery and interventional cardiology follow a competency-driven residency programme with regular evaluation of progression.	I	C
It should be considered that trainees in cardiac surgery perform at least 200 CABG procedures under supervision before being independent.	IIa	C
Training in PCI		
It should be considered that trainees in interventional cardiology perform at least 200 PCI procedures as first operator, with one-third of PCI procedures in emergency or ACS patients under supervision, before being independent.	IIa	C
It should be considered that trainees in interventional cardiology complete formal training according to a 1–2 year curriculum at institutions with at least 800 PCIs per year and an established 24-hour/7-day service for the treatment of patients with ACS.	IIa	C

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

[a] Class of recommendation.

[b] Level of evidence.

Recommendations for outcome registration, monitoring, and benchmarking		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that specific quality performance measures for CABG are adopted at a national level to allow outcome monitoring and benchmarking.	I	C
It is recommended that national societies establish national databases on CABG practice and outcomes.	I	C
It is recommended that CABG outcome data are reported by hospitals to national databases.	I	C

CABG = coronary artery bypass grafting.

[a] Class of recommendation.

[b] Level of evidence.

Secondary prevention and cardiac rehabilitation are an integral part of the management after revascularization because such measures reduce future morbidity and mortality in a cost-effective way and can further improve symptoms. Specific recommendations for long-term medical therapy, secondary preventions and cardiac rehabilitation programmes are provided in separate dedicated guideline documents. Recurrence of symptoms or ischaemia due to disease progression or restenosis after myocardial revascularization deserves attention.

Recommendations on strategies for follow-up and management of patients after myocardial revascularization are provided in the table below.

Strategies for follow-up and management in patients after myocardial revascularization

Recommendations	Class[a]	Level[b]
After CABG or PCI for AMI participation in a cardiac rehabilitation programme is recommended to improve patient outcomes.	I	A
It is recommended that secondary prevention measures, including medical therapy and lifestyle changes, are started and reinforced after myocardial revascularization.	I	A
It is recommended that patients are re-evaluated after myocardial revascularization (e.g. at 3 months and thereafter, at least on an annual basis) in order to reassess symptoms and adherence with secondary prevention measures, and reinforce medical therapy and lifestyle changes when appropriate.	I	C
Symptomatic patients		
Coronary angiography is recommended in patients with intermediate- to high-risk findings[c] at stress testing.	I	C
An imaging stress test should be considered in patients with prior revascularization over stress ECG.	IIa	B
Asymptomatic patients		
Surveillance by non-invasive imaging-based stress testing may be considered in high-risk patient subsets 6 months after revascularization.	IIb	C
After high-risk PCI (e.g. unprotected LM stenosis), late (3–12 months) surveillance angiography may be considered, irrespective of symptoms.	IIb	C
Routine non-invasive imaging-based stress testing may be considered 1 year after PCI and >5 years after CABG.	IIb	C

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; LM = left main; PCI = percutaneous coronary intervention.

[a] Class of recommendation.

[b] Level of evidence.

[c] Intermediate- and high-risk findings at stress imaging are ischaemia at low workload with exercise stress testing, early onset ischaemia with pharmacological stress testing, inducible wall motion abnormality or reversible perfusion defect in ≥10% of LV myocardium.

2017 ESC Pocket Guidelines

Committee for Practice Guidelines

DAPT

Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease

ESC
European Society of Cardiology

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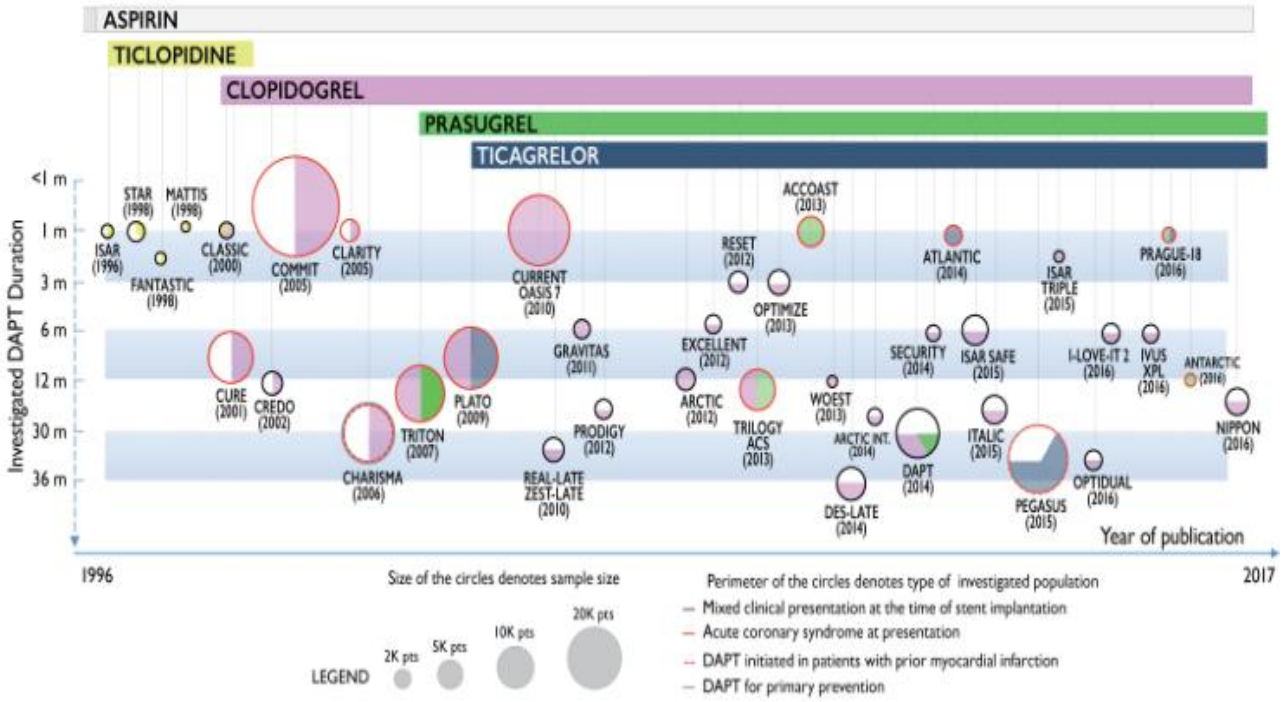
Based on population estimates from 2015, in the region of 1 400 000 and 2 200 000 patients per year may have an indication for DAPT after coronary intervention or myocardial infarction (MI), respectively in Europe.

In 2017, it is the 21st anniversary of the publication of the first randomized clinical trial establishing the superiority of DAPT over anticoagulant therapy among patients undergoing percutaneous coronary intervention (PCI) (Figure 1). Based on over 35 randomized clinical trials, including more than 225 000 patients, DAPT is among the most intensively investigated treatment options in the field of cardiovascular medicine (Figure 1).

Figure 1 History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease



The size of the circles denotes sample size. The colours of perimeters identify the type of included patient populations within each study. The colours within each circle identify the antiplatelet agent(s) investigated. Head-to-head studies comparing similar durations of two different antiplatelet strategies are shown with a vertical line, whereas those investigating different treatment durations are shown with a horizontal line.

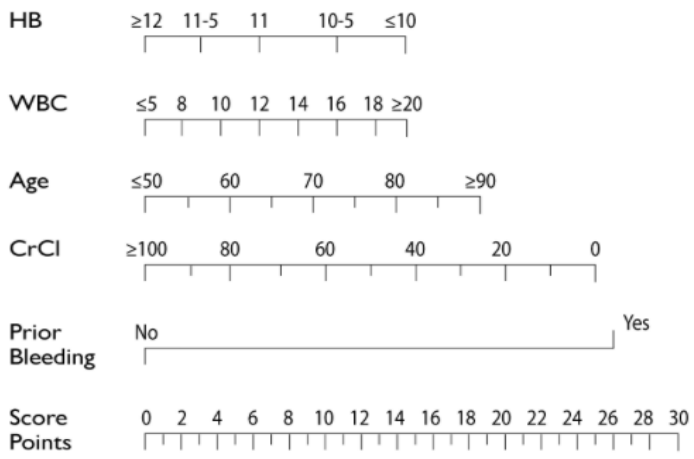
Studies investigating different treatment strategies or regimens and not treatment durations or type (e.g. pre-treatment in ACCOAST, tailored therapy in GRAVITAS, double dose of clopidogrel in CURRENT OASIS 7, etc.) are represented with a single colour indicating the $P2Y_{12}$ inhibitor, which was tested on top of aspirin.

Risk scores

Given the trade-off between ischaemic vs. bleeding risks for any given DAPT duration, the use of scores might prove useful to tailor DAPT duration in order to maximize ischaemic protection and minimize bleeding risks in the individual patient. The use of risk scores, which were specifically designed to guide and inform decision-making on DAPT duration, should be prioritized over other available risk scores (Table 3).

The table below provides an overview for the risk scores, which have been validated for dual antiplatelet therapy duration decision-making

Table 3 Risk scores validated for dual antiplatelet therapy duration decision making

PRECISE-DAPT score	
Time of use	At the time of coronary stenting
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)
Score calculation[a]	
Score range	0 to 100 points
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT
Calculator	www.precisedaptscore.com

DAPT score		
Time of use	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]	Age	
	≥75	–2 pt
	65 to <75	–1 pt
	<65	0 pt
	Cigarette smoking	+1 pt
	Diabetes mellitus	+1 pt
	MI at presentation	+1 pt
	Prior PCI or prior MI	+1 pt
	Paclitaxel-eluting stent	+1 pt
	Stent diameter <3 mm	+1 pt
	CHF or LVEF <30%	+2 pt
	Vein graft stent	+2 pt
Score range	–2 to 10 points	
Decision making cut-off suggested	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.daptstudy.org	

PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications
In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; WBC = white blood cell count.
[a]For the PRECISE-DAPT score use the score nomogram: mark patient's value for each of the five clinical variables of the score and draw a vertical line to the 'Point' axis to determine the number of points obtained for each clinical variable.Than summate the points obtained for each clinical variable to the total score.

Recommendations

Use of risk scores

The table below provides a recommendation on the use of risk scores as guidance for the duration of dual antiplatelet therapy.

Recommendations for the use of risk scores as guidance for the duration of dual antiplatelet therapy

Recommendation	Class[a]	Level[b]
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations[c] may be considered.	IIb	A

DAPT = dual antiplatelet therapy.
[a]Class of recommendation.
[b]Level of evidence.
[c]The DAPT and PRECISE-DAPT scores are those currently fulfilling these requirements.

P2Y12 inhibitor selection and timing

Recommendations on $P2Y_{12}$ inhibitor selection and timing

Recommendations	Class[a]	Level[b]
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin[c] is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications[c].	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications[c]	I	B
Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI.	I	A
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
In patients with stable CAD pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C

Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC.	I	A
Clopidogrel (300 mg loading dose in patients aged ≤75, 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis.	I	A
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT) risks.	IIb	C
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.	III	B

ACS = acute coronary syndrome; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; NSTE-ACS = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery.

[a]Class of recommendation - [b]Level of evidence - [c]Contra-indications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contra-indications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack or ongoing bleeds; prasugrel is not recommended for patients ≥75 years of age or with a bodyweight <60 kg.

Measures to minimize bleeding

Recommendations on measures to minimize bleeding while on dual antiplatelet therapy

Recommendations	Class[a]	Level[b]
Radial over femoral access is recommended for coronary angiography and PCI if performed by an expert radial operator.	I	A
In patients treated with DAPT, a daily aspirin dose of 75–100 mg is recommended.	I	A
A PPI in combination with DAPT is recommended.[c]	I	B
Routine platelet function testing to adjust antiplatelet therapy before or after elective stenting is not recommended.	III	A

DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention; PPI proton pump inhibitor.

[a]Class of recommendation - [b]Level of evidence - [c]While the evidence that a PPI does not increase the risk of cardiovascular events was generated with omeprazole, based on drug-drug interaction studies, omeprazole and esomeprazole would appear to have the highest propensity for clinically relevant interactions, while pantoprazole and rabeprazole have the lowest.

Switching oral P2Y12 inhibitors

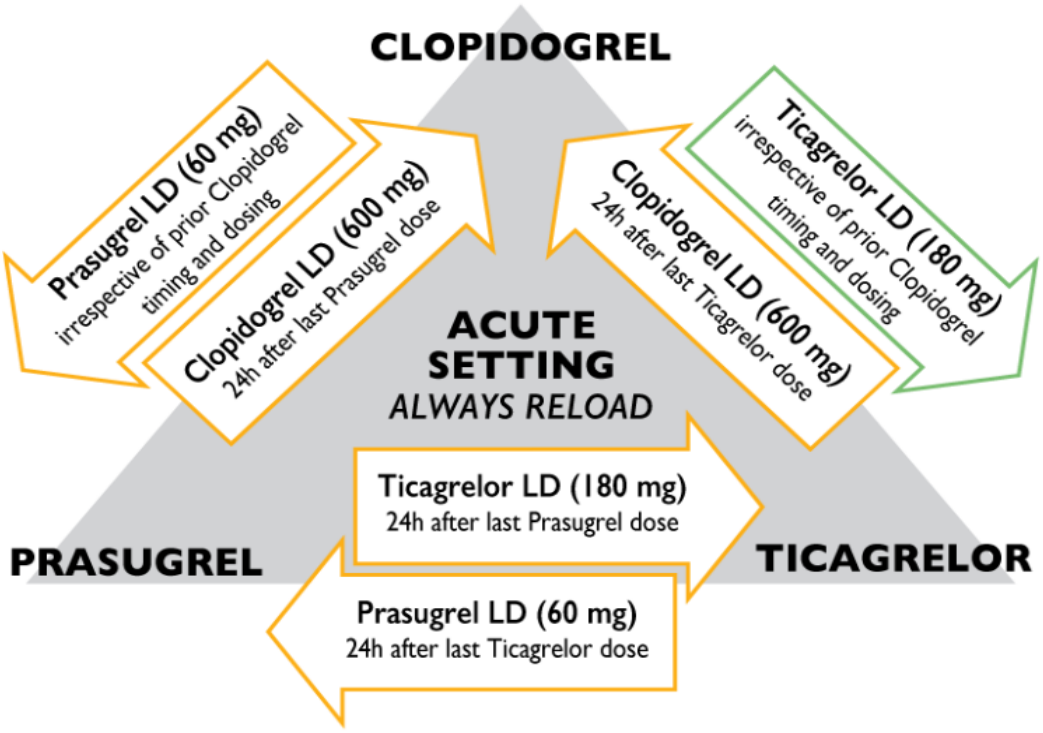
Recommendations for switching between oral $P2Y_{12}$ inhibitors

Recommendations	Class[a]	Level[b]
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.[c]	I	B
Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

ACS = acute coronary syndrome.
[a]Class of recommendation - [b]Level of evidence.
[c]Contra-indications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds.

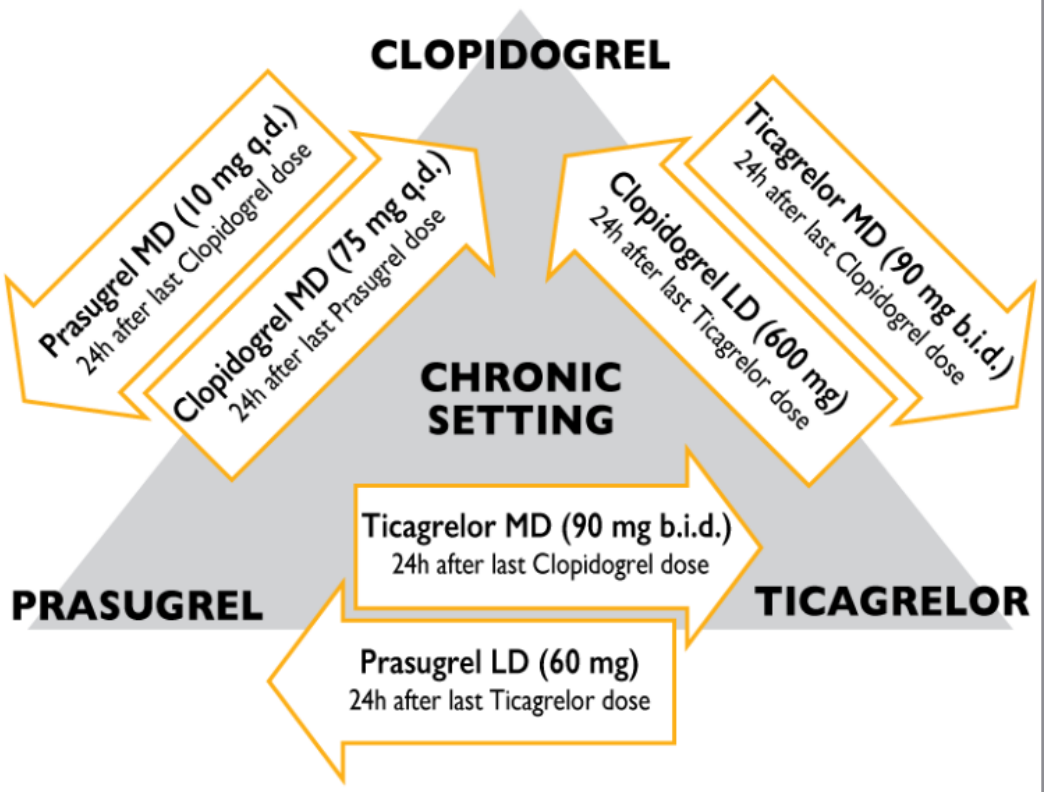
Switching algorithms

Figure 2 Algorithm for switching between oral $P2Y_{12}$ inhibitors in the acute setting



LD = loading dose; MD = maintenance dose
Colour-coding refers to the ESC class of recommendation (green = Class I; orange = Class IIb).
The green arrow from clopidogrel to ticagrelor highlights the only switching algorithm for which outcome data are available in patients with acute coronary syndrome. No outcome data (orange arrows) are available for all other switching algorithms. Acute setting is considered as a switching occurring during hospitalization.

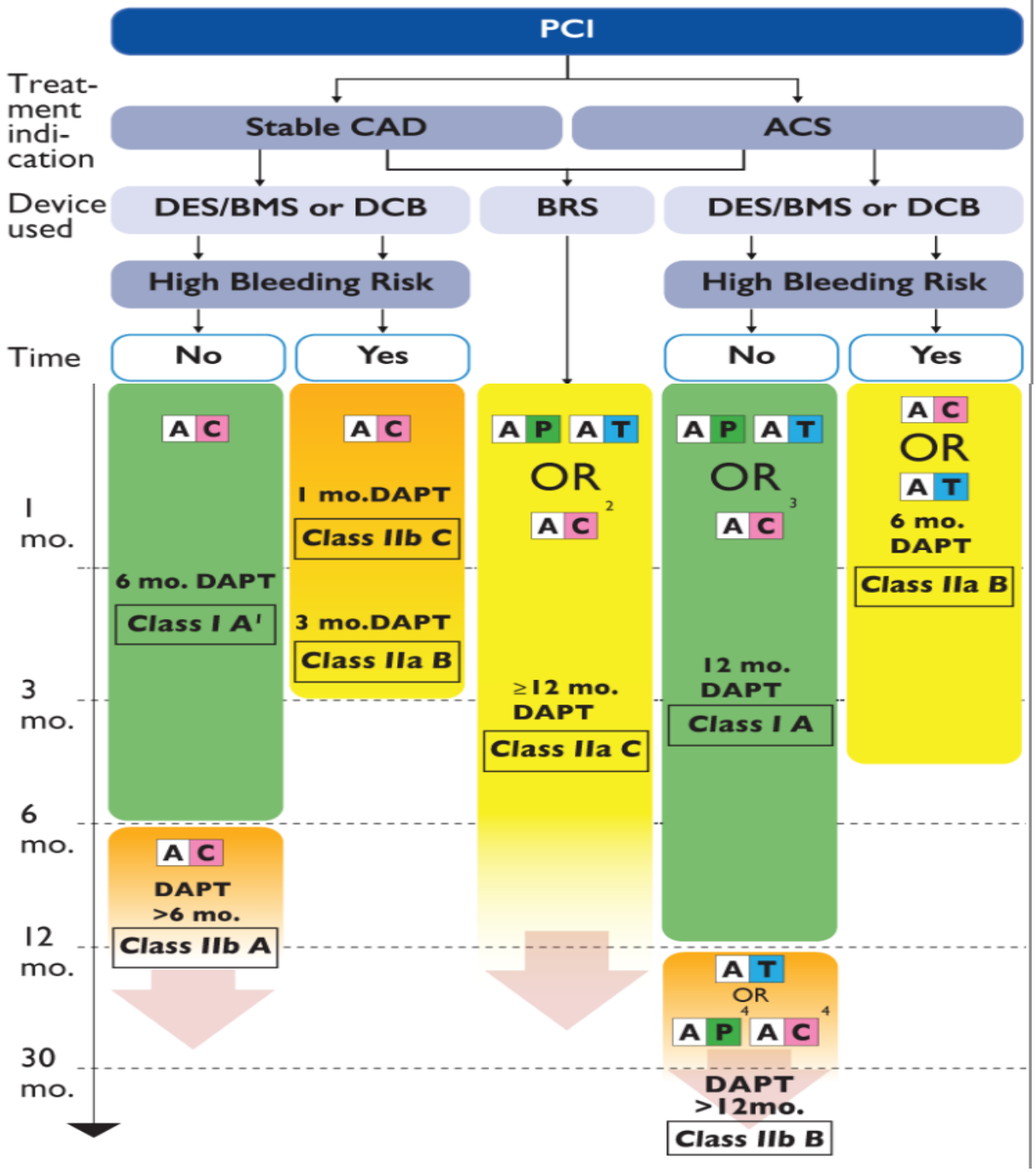
Figure 2bis Algorithm for switching between oral $P2Y_{12}$ inhibitors in the chronic setting

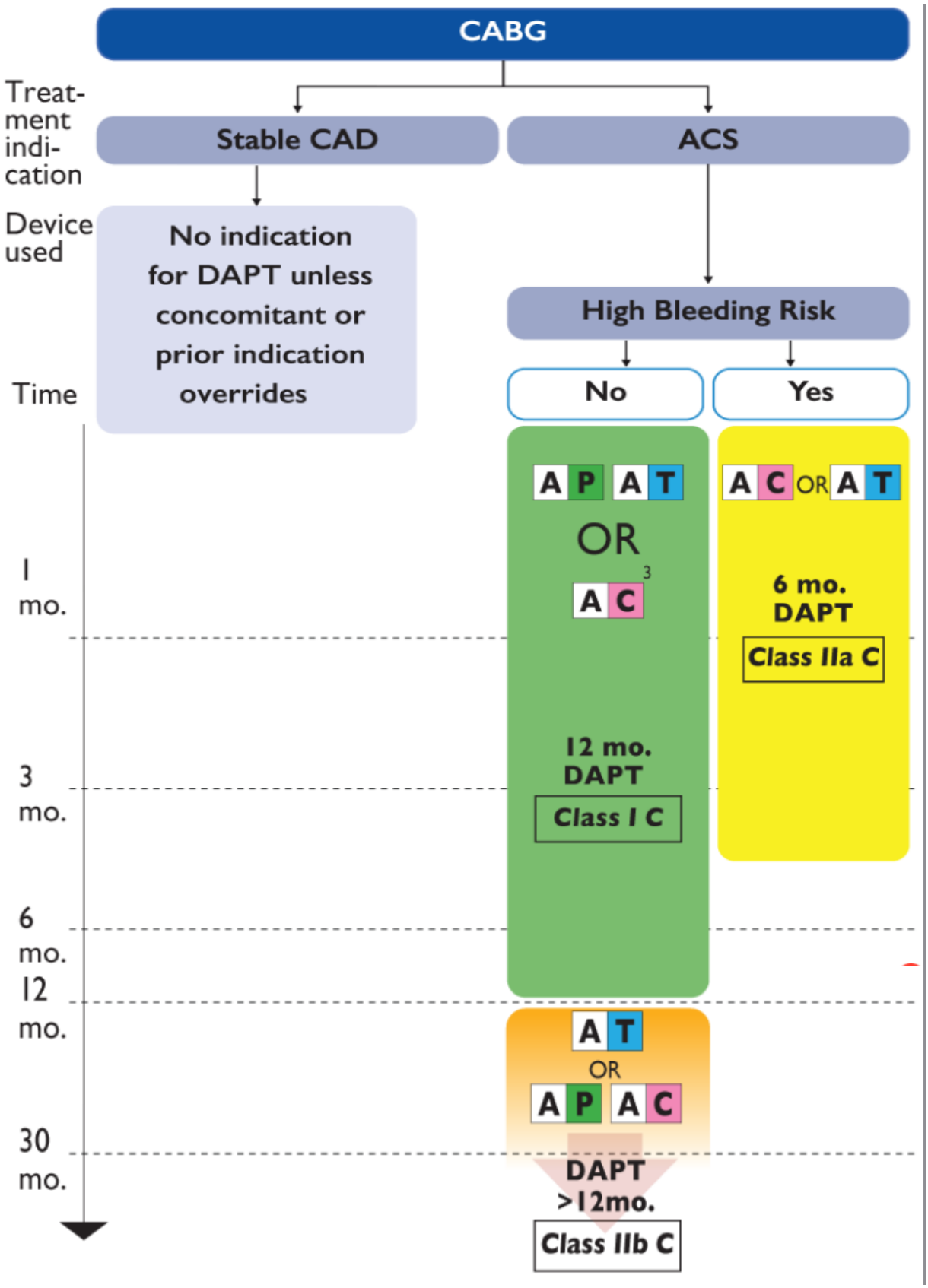


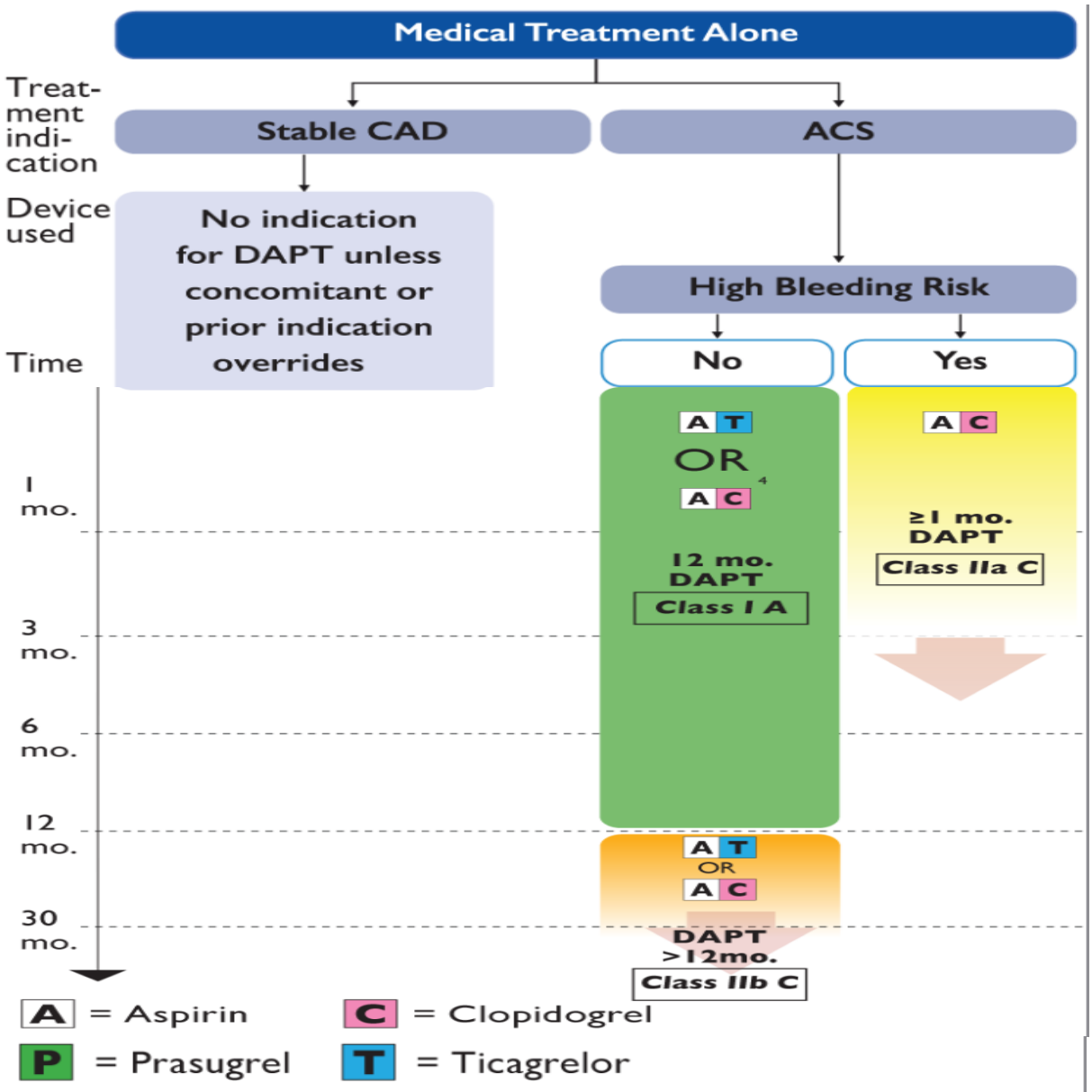
LD = loading dose; MD = maintenance dose
Colour-coding refers to the ESC class of recommendation (orange = Class IIb).
The green arrow from clopidogrel to ticagrelor highlights the only switching algorithm for which outcome data are available in patients with acute coronary syndrome. No outcome data (orange arrows) are available for all other switching algorithms.

An overview of recommendations endorsed by these guidelines regarding DAPT duration after PCI, as well as after CABG or in medically managed ACS patients, is provided in Figure 3 (see below).

Figure 3 Algorithm for dual antiplatelet therapy (DAPT) in patients with coronary artery disease. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).




CABG
Treat-ment indi-cation
Stable CAD
ACS
Device used
No indication for DAPT unless concomitant or prior indication overrides
High Bleeding Risk
Time
No
Yes
A P A T
OR
A C 3
6 mo. DAPT
Class IIa C
12 mo. DAPT
Class I C
1 mo.
3 mo.
6 mo.
12 mo.
30 mo.
A C OR A T
A T
OR
A P A C
DAPT >12mo.
Class IIb C



ACS = acute coronary syndrome; BMS = bare-metal stent; BRS = biore-sorbable vascular scaffold; CABG = coronary artery bypass graft ; DCB = drug-coated balloon; DES = drug-eluting stent; PCI = percutaneous coronary intervention; Stable CAD= stable coronary artery disease.
High bleeding risk is considered as an increased risk of spontaneous bleed-ing during DAPT (e.g. PRECISE-DAPT score ≥25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
[1]After PCI with DCB 6 mo. DAPT should be considered (Class IIa B).
[2]if patient presents with Stable CAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
[3]if patient is not eligible for a treatment with prasugrel or ticagrelor.
[4]if patient is not eligible for a treatment with ticagrelor.

Recommendations on dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type.[c]	I	A
Irrespective of the intended DAPT duration, DES is the preferred treatment option.[c]	I	A
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months should be considered.[d]	IIa	B
In patients with stable CAD treated with drug-coated balloon, DAPT for 6 months should be considered.	IIa	B
In patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and up to ≤30 months may be considered.	IIb	A
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month[e] may be considered.	IIb	C

CAD = coronary artery disease; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; PRECISE-DAPT= PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

[a]Class of recommendation.

[b]Level of evidence.

[c]These recommendations refer to stents which are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE-mark as detailed in Byrne *et al.* (see Full Text at www.escardio.org/guidelines).

[d]The evidence supporting this recommendation comes from two studies where zotarolimus-eluting Endeavour sprint stent has been investigated in conjunction with a 3-month DAPT regimen.

[e]1-month DAPT following implantation of zotarolimus-eluting Endeavour sprint stent or drug coated stent reduced risks of re-intervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration. It is unclear if this evidence applies to other contemporary DES.

Recommendations on dual antiplatelet therapy duration in patients with acute coronary syndrome treated with percutaneous coronary intervention

Recommendations	Class[a]	Level[b]
In patients with ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ inhibitor on top of aspirin is recommended for 12 months unless there are contra-indications such as excessive risk of bleeding (e.g. PRECISE-DAPT ≥ 25).	I	A
In patients with ACS and stent implantation who are at high-risk of bleeding (e.g. PRECISE-DAPT ≥ 25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	B
In patients with ACS treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with ACS who have tolerated DAPT without a bleeding complication, continuation of DAPT for longer than 12 months may be considered.	IIb	A
In patients with MI and high ischaemic risk[c] who have tolerated DAPT without a bleeding complication, ticagrelor 60 mg b.i.d. for longer than 12 months on top of aspirin may be preferred over clopidogrel or prasugrel.	IIb	B

ACS = acute coronary syndrome; b.i.d. = bis in die; DAPT = dual antiplatelet therapy. PRECISE-DAPT= PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

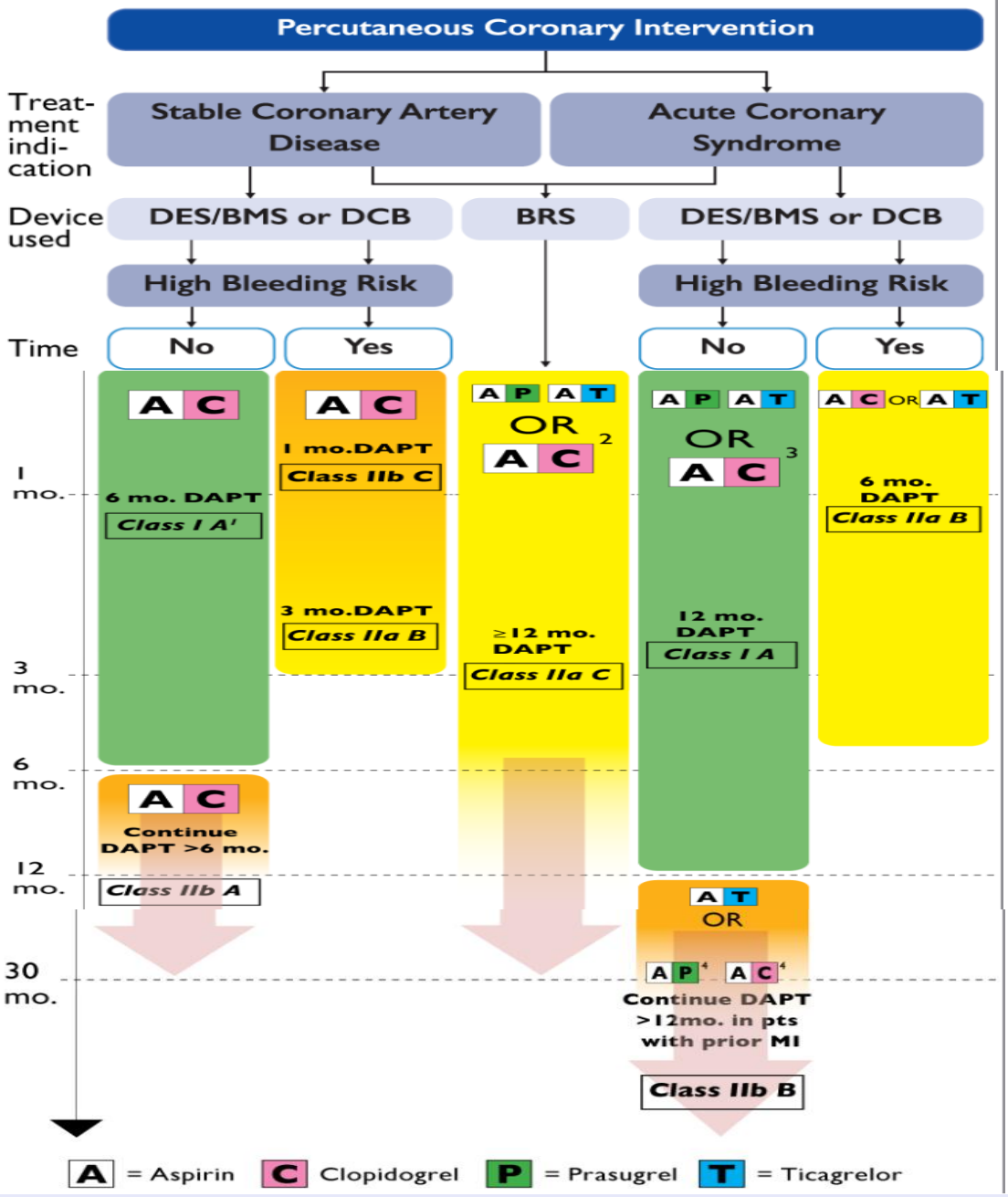
[a]Class of recommendation.

[b]Level of evidence.

[c]Defined as at least ≥50 years of age, and one or more of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance <60 mL per minute.

These recommendations refer to stents that are supported by large-scale randomized trials with clinical endpoint evaluation leading to unconditional CE mark, as detailed in Byrne et al. (see Full Text at www.escardio.org/guidelines)

Figure 4 Algorithm for dual antiplatelet therapy (DAPT) in patients treated with percutaneous coronary intervention.



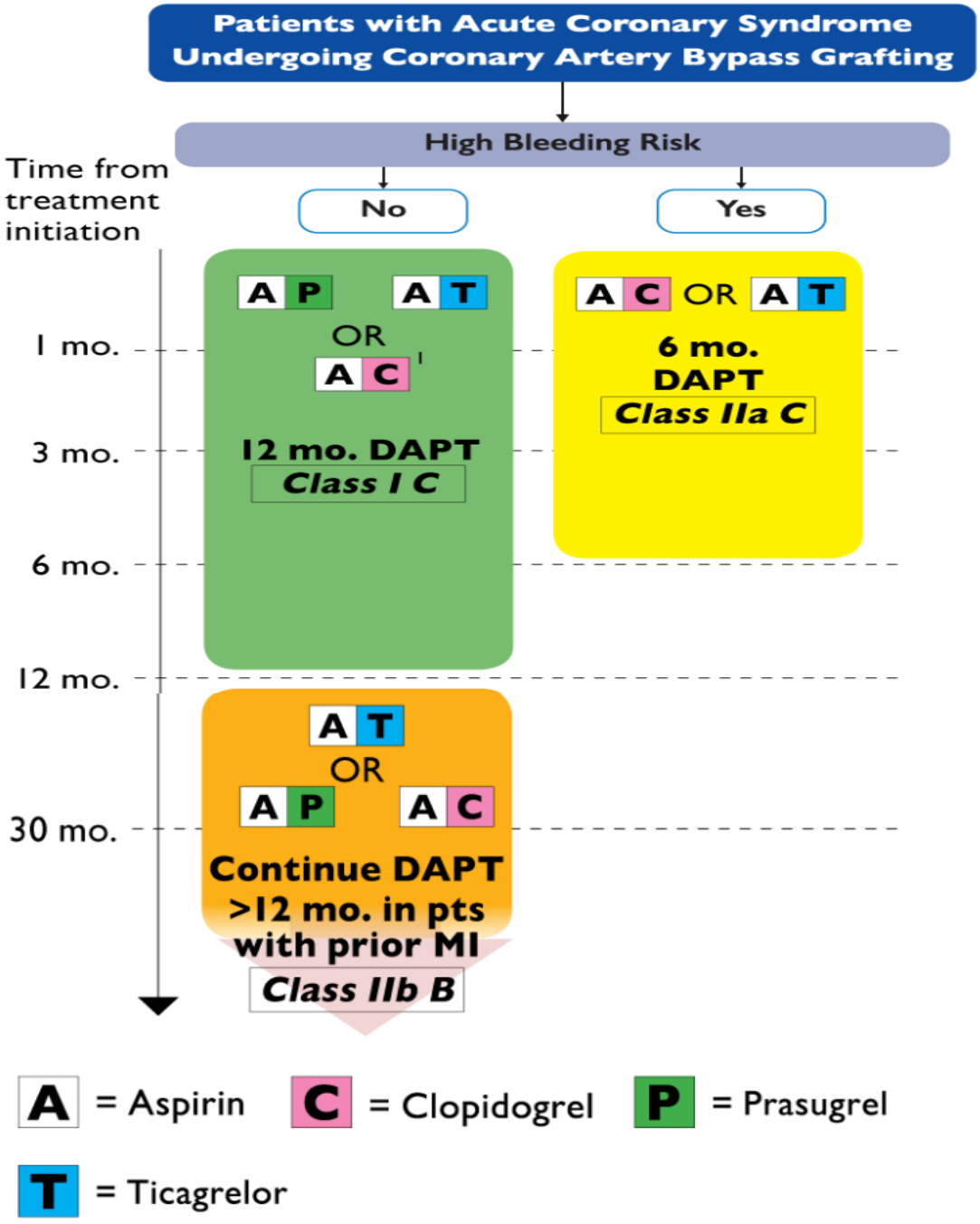
ACS = acute coronary syndrome; BMS = bare-metal stent; BRS = bioresorbable vascular scaffold; CABG = coronary artery bypass graft surgery; DCB = percutaneous coronary intervention; Stable CAD = stable coronary artery disease. High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥ 25).
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).
Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.
[1]After PCI with DCB 6 mo. DAPT should be considered (Class IIa B).
[2]if patient presents with SCAD or, in case of ACS, is not eligible for a treatment with prasugrel or ticagrelor.
[3]if patient is not eligible for a treatment with prasugrel or ticagrelor.
[4]if patient is not eligible for a treatment with ticagrelor.

Recommendations on dual antiplatelet therapy in patients treated with cardiac surgery with stable or unstable coronary artery disease

Recommendations	Class[a]	Level[b]
It is recommended that the Heart Team estimates the individual bleeding and ischaemic risks and guide the timing of CABG as well as the antithrombotic management.	I	C
In patients on aspirin who need to undergo non-emergent cardiac surgery, it is recommended to continue aspirin at a low daily regimen throughout the peri-operative period.	I	C
In patients treated with DAPT after coronary stent implantation who subsequently undergo cardiac surgery, it is recommended to resume $P2Y_{12}$ inhibitor therapy postoperatively as soon as deemed safe so that DAPT continues until the recommended duration of therapy is completed.	I	C
In patients with ACS (NSTE-ACS or STEMI) treated with DAPT and undergoing CABG and not requiring long-term OAC therapy, resumption of $P2Y_{12}$ inhibitor therapy as soon as deemed safe after surgery and continuation up to 12 months is recommended.	I	C
In patients on P2Y12 inhibitors who need to undergo non-emergent cardiac surgery, postponing surgery for at least 3 days after discontinuation of ticagrelor, at least 5 days after clopidogrel, and at least 7 days after prasugrel should be considered.	IIa	B
In CABG patients with prior MI who are at high-risk of severe bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months should be considered.	IIa	C
Platelet function testing may be considered to guide decisions on timing of cardiac surgery in patients who have recently received $P2Y_{12}$ inhibitors.	IIb	B
In patients perceived at high ischaemic risk with prior MI and CABG who have tolerated DAPT without a bleeding complication, treatment with DAPT for longer than 12 and up to 36 months may be considered.	IIb	C

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; DAPT = non-ST-elevation acute coronary syndrome; OAC = oral anticoagulant; PRECISE-DAPT= PREdicting bleeding Complications in patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy; STEMI = ST-elevation myocardial infarction.

Figure 5 Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing coronary artery bypass grafting



Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.

High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥25).

Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa;
orange = Class IIb).

[1]if patient is not eligible for a treatment with prasugrel or ticagrelor.

Recommendations on dual antiplatelet therapy duration in patients with acute coronary syndrome undergoing medical therapy management

Recommendations	Class[a]	Level[b]
In patients with ACS who are managed with medical therapy alone and treated with DAPT, it is recommended to continue $P2Y_{12}$ inhibitor therapy (either ticagrelor or clopidogrel) for 12 months.	I	A
Ticagrelor is recommended over clopidogrel, unless the bleeding risk outweighs the potential ischaemic benefit.	I	B
In patients with medically managed ACS who are at high-risk of bleeding (e.g. PRECISE-DAPT ≥ 25), DAPT for at least 1 month should be considered.	IIa	C
In patients with prior MI at high ischaemic risk[c] who are managed with medical therapy alone and have tolerated DAPT without a bleeding complication, treatment with DAPT in the form of ticagrelor 60 mg b.i.d. on top of aspirin for longer than 12 months and up to 36 months may be considered.	IIb	B
In patients with prior MI not treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not eligible for treatment with ticagrelor, continuation of clopidogrel on top of aspirin for longer than 12 months may be considered.	IIb	C
Prasugrel is not recommended in medically managed ACS patients.	III	B

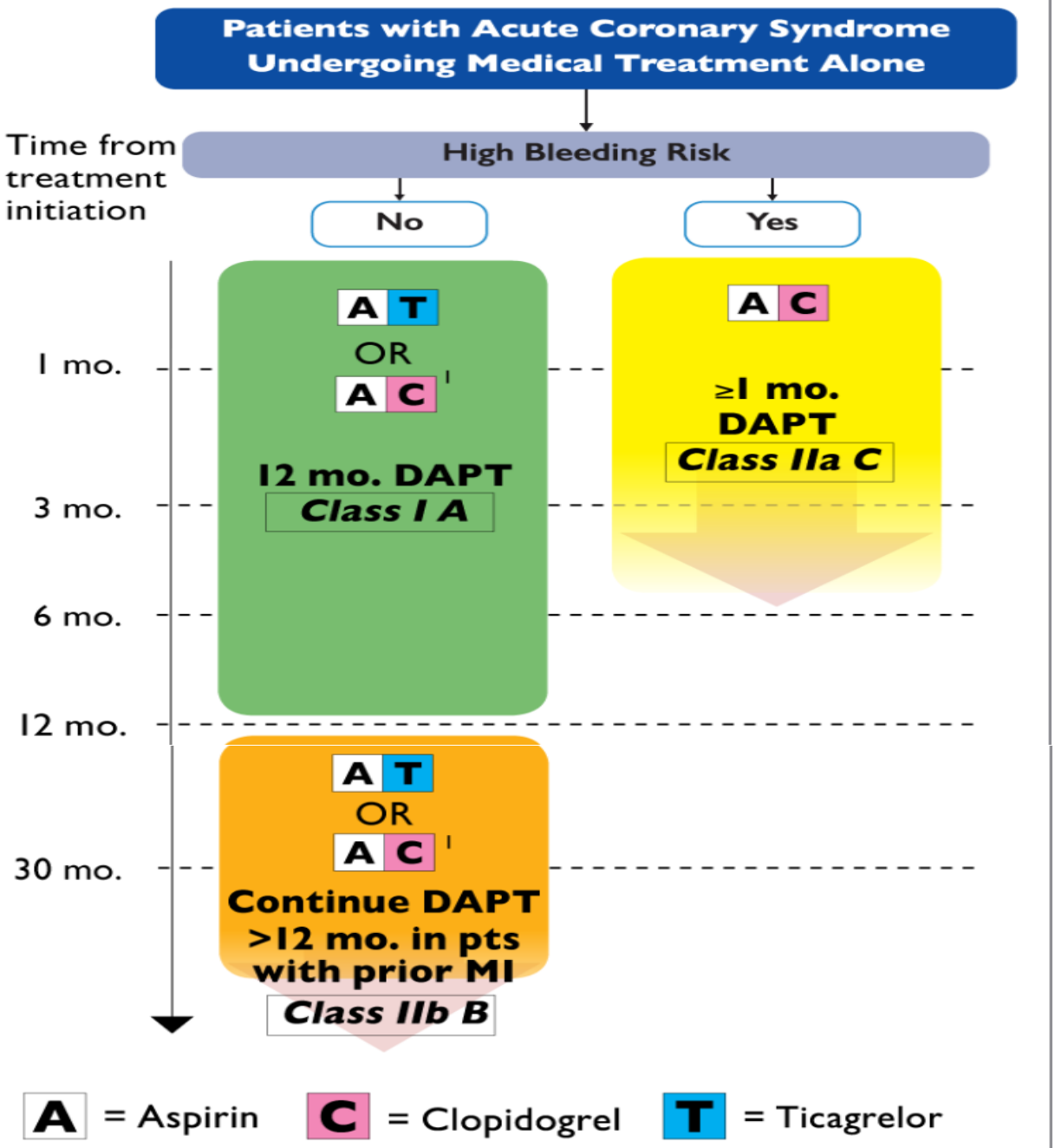
ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; MI = myocardial infarction. PRECISE- DAPT= PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual Anti Platelet Therapy.

[a]Class of recommendation.

[b]Level of evidence.

[c]Defined as ≥50 years of age, and one or more of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance <60 mL per minute.

Figure 6 Algorithm for dual antiplatelet therapy (DAPT) in patients with acute coronary syndrome undergoing medical management



Treatments presented within the same line are sorted in alphabetic order, no preferential recommendation unless clearly stated otherwise.

High bleeding risk is considered as an increased risk of spontaneous bleeding during DAPT (e.g. PRECISE-DAPT score ≥ 25).

Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).

[1]if patient is not eligible for a treatment with ticagrelor

Strategies to avoid bleeding complications in patients treated with oral anticoagulant are summarised in the table below.

Table 4 Strategies to avoid bleeding complications in patients treated with oral anticoagulant

• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
• Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤100 mg daily) aspirin.
• Routine use of PPIs.

ABC = Age, Biomarkers, Clinical history; CHA_2DS_2-VASc = Congestive heart failure, Hypertension,Age ≥ 75 years (doubled), Diabetes mellitus, prior Stroke or transient ischaemic attack or thromboembolism (doubled),Vascular disease, Age 65–74 years, Sex category; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR = non-vitamin-K oral anticoagulant; INR = international normalized ratio; PCI = percutaneous coronary intervention; PPIs = proton pump inhibitors;VKA = vitamin K antagonist.

[a]Apixaban 5 mg b.i.d. or apixaban 2.5 mg b.i.d. if at least two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L); dabigatran 110 mg b.i.d.; edoxaban 60 mg q.d. or edoxaban 30 mg q.d. if any of the following: creatinine clearance (CrCl) of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone; rivaroxaban 20 mg q.d. or rivaroxaban 15 mg q.d. if CrCl 30–49 mL/min.

DAPT and concomitant OAC

Stent-related high ischemic risk features

Table 5 High-risk features of stent-driven recurrent ischaemic events
• Prior stent thrombosis on adequate antiplatelet therapy
• Stenting of the last remaining patent coronary artery
• Diffuse multivessel disease especially in diabetic patients
• Chronic kidney disease (i.e. creatinine clearance <60 mL/min)
• At least three stents implanted
• At least three lesions treated
• Bifurcation with two stents implanted
• Total stent length >60 mm
• Treatment of a chronic total occlusion

DAPT and concomitant OAC

Unfavourable pt. profile for OAC & APT

Table 6 Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy
• Short life expectancy
• Ongoing malignancy
• Poor expected adherence
• Poor mental status
• End stage renal failure
• Advanced age
• Prior major bleeding/prior haemorrhagic stroke
• Chronic alcohol abuse
• Anaemia
• Clinically significant bleeding on dual antithrombotic therapy

Recommendations on dual antiplatelet therapy duration in patients with indication for oral anticoagulation

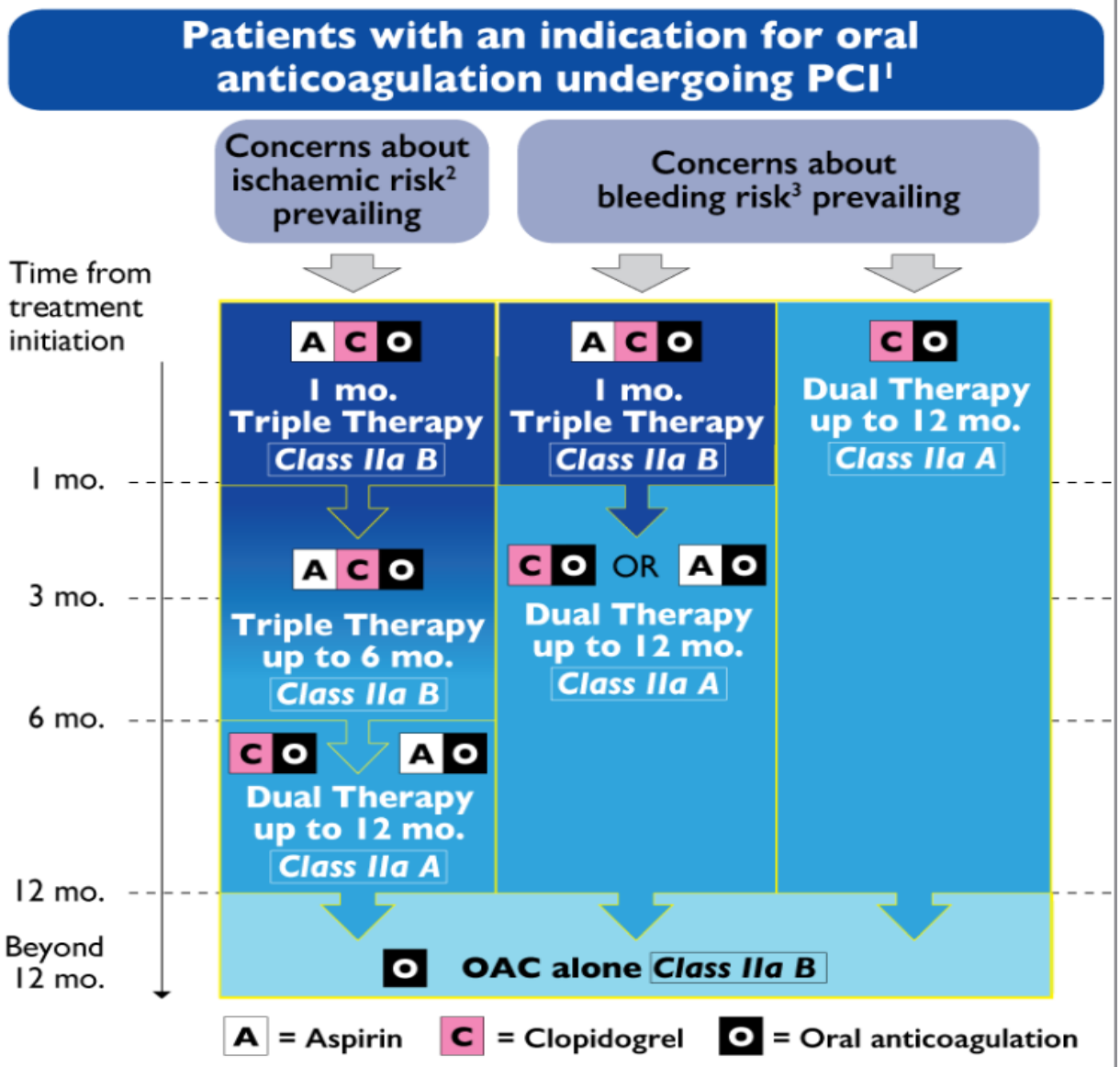
Recommendations	Class[a]	Level[b]
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and OAC should be considered for 1 month, irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.[c]	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d.	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

ACS = acute coronary syndrome; INR = international normalized ratio; OAC = oral anticoagulant; NOAC = non-vitamin K oral anticoagulant; *q.d.* = *quaque die*; VKA = vitamin K antagonist.

[a]Class of recommendation - [b]Level of evidence.

[c]Apixaban 5 mg *b.i.d.* or apixaban 2.5 mg b.i.d. if at least two of the following: age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL (133 µmol/L); dabigatran 110 mg *b.i.d.*; edoxaban 60 mg q.d. or edoxaban 30 mg *q.d.* if any of the following: creatinine clearance (CrCl) of 30–50 mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone; rivaroxaban 20 mg *q.d.* or rivaroxaban 15 mg *q.d.* if CrCl 30–49 mL/min.

Figure 7 Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



Colour-coding refers to the number of concomitant antithrombotic medication(s). Triple therapy denotes treatment with DAPT plus oral anticoagulant (OAC). Dual therapy denotes treatment with a single antiplatelet agent (aspirin or clopidogrel) plus OAC.

ABC = age, biomarkers, clinical history; ACS = acute coronary syndrome; mo. = month(s); PCI = percutaneous coronary intervention

[1]Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy.

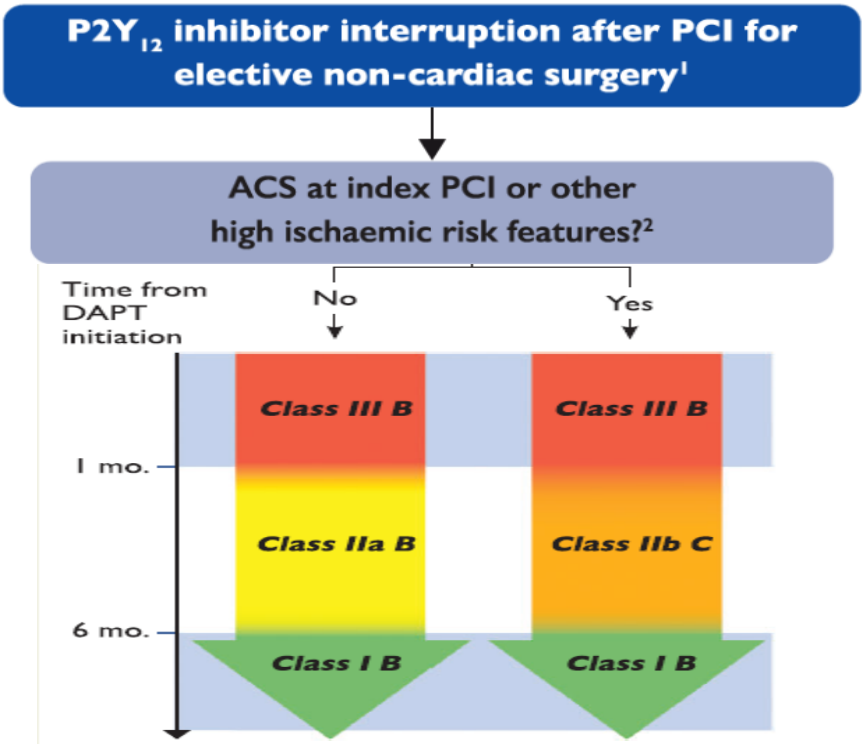
[2]High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction. 3: Bleeding risk can be estimated by HAS-BLED or ABC score.

The table below summarizes the recommendations on dual antiplatelet therapy in patients undergoing elective non-cardiac surgery.

Recommendations on dual antiplatelet therapy in patients undergoing elective non-cardiac surgery

Recommendations	Class[a]	Level[b]
It is recommended to continue aspirin perioperatively if the bleeding risk allows, and to resume the recommended antiplatelet therapy as soon as possible post-operatively.	I	B
After coronary stent implantation, elective surgery requiring discontinuation of the $P2Y_{12}$ inhibitor should be considered after 1 month, irrespective of the stent type, if aspirin can be maintained throughout the peri-operative period.	IIa	B
Discontinuation of $P2Y_{12}$ inhibitors should be considered at least 3 days before surgery for ticagrelor, at least 5 days for clopidogrel and at least 7 days for prasugrel.	IIa	B
A multidisciplinary expert team should be considered for pre-operative evaluation of patients with an indication for DAPT before elective surgery.	IIa	C
In patients with recent MI or other high ischaemic risk features[c] requiring DAPT, elective surgery may be postponed for up 6 to months.	IIb	C
If both oral antiplatelet agents have to be discontinued perioperatively, a bridging strategy with intravenous antiplatelet agents may be considered, especially if surgery has to be performed within 1 month after stent implantation.	IIb	C
It is not recommended to discontinue DAPT within the first month of treatment in patients undergoing elective non-cardiac surgery.	III	B

Figure 8 Timing for elective non-cardiac surgery in patients treated with dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI)



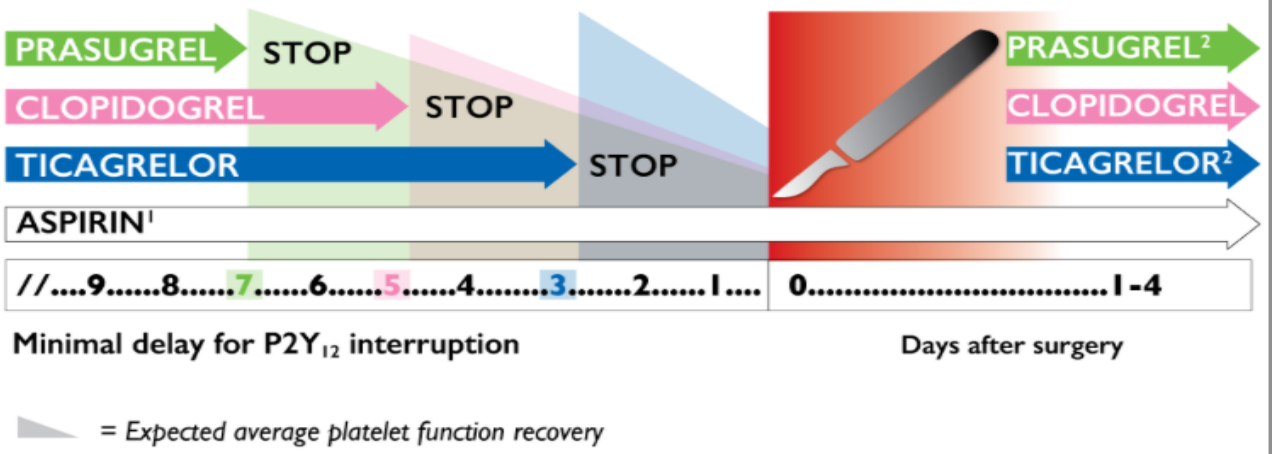
Colour-coding refers to the ESC Classes of Recommendations (green = Class I; yellow = Class IIa; orange = Class IIb).

ACS = acute coronary syndromes.

[1]Availability of H24 cath-lab service in place is suggested in case of major surgery within 6 months after PCI.

[2]High ischaemic risk features are presented in Table 5.

Figure 9 Minimal discontinuation and re-implementation time frames of dual antiplatelet therapy (DAPT) for patients undergoing elective surgery



[1]Decision to stop aspirin throughout surgery should be made on a single case basis taking into account the surgical bleeding risk.

[2]In patients not requiring

OAC = oral anticoagulant.

Gender and special populations

Recommendations related to gender considerations and those for special populations are shown in the table below.

Recommendations on gender considerations and those for special populations

Recommendations	Class[a]	Level[b]
Similar type and duration of DAPT are recommended in male and female patients.	I	A
It is recommended to reassess the type, dose and duration of DAPT in patients with actionable bleeding complication while on treatment.	I	C
Similar type and duration of DAPT should be considered in patients with and without diabetes mellitus.	IIa	B
Prolonged (i.e. >12 months[c]) DAPT duration should be considered in patients with prior stent thrombosis, especially in the absence of correctable causes (e.g. lack of adherence or correctable mechanical stent-related issues).	IIa	C
Prolonged (i.e. >12 months) DAPT duration may be considered in CAD patients with LEAD.	IIb	B
Prolonged (i.e. >6 months) DAPT duration may be considered in patients who underwent complex PCI.[d]	IIb	B

CAD = coronary artery disease; DAPT = dual antiplatelet therapy; LEAD = lower-extremities artery disease; PCI = percutaneous coronary intervention.

[a]Class of recommendation.

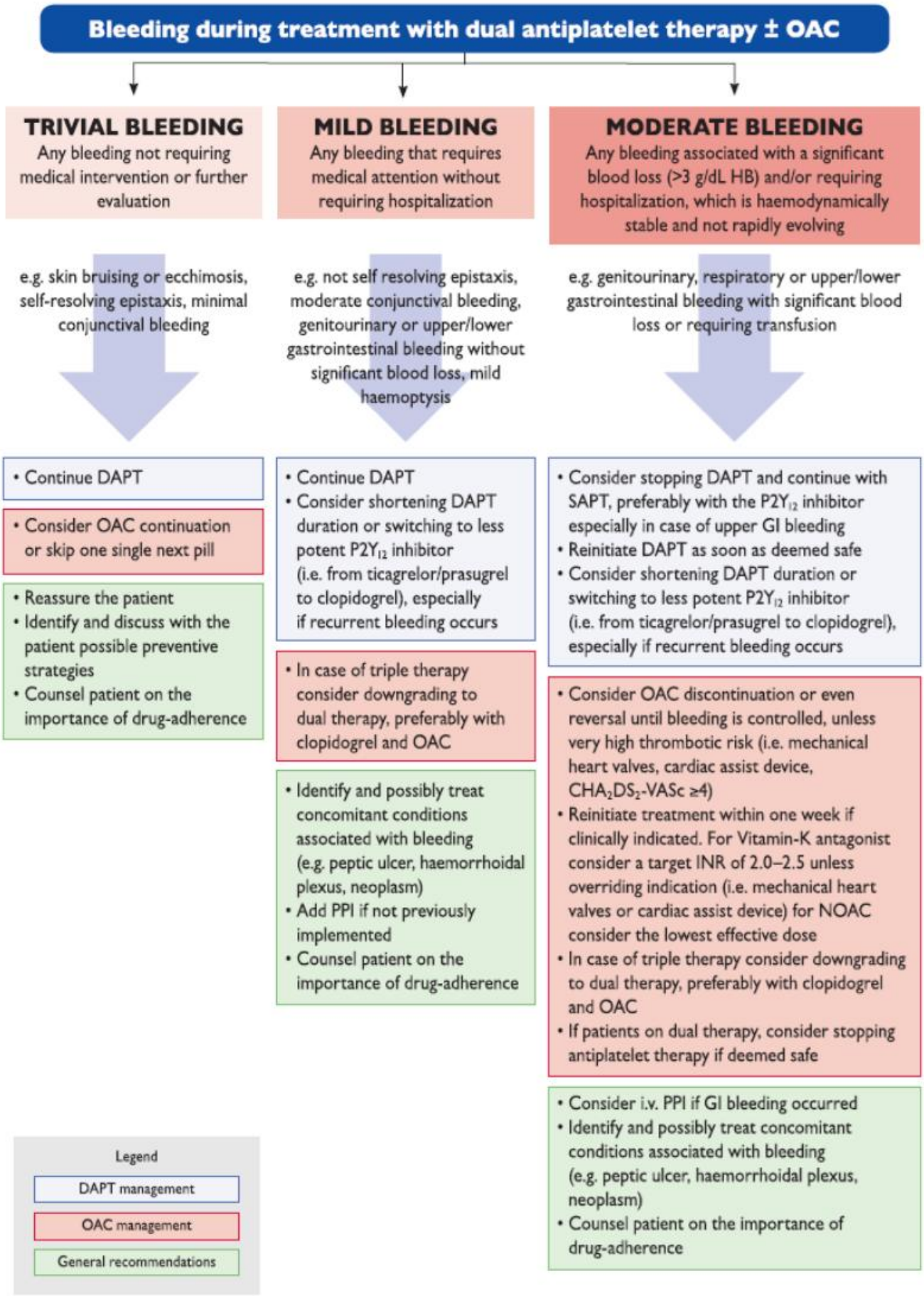
[b]Level of evidence.

[c]And possibly as long as tolerated.

[d]Complex PCI defined as the composite of ≥ three stents implanted, ≥ three lesions treated, bifurcation with two stents implanted, total stent length >60 mm and chronic total occlusion as target lesion.

Practical recom. for management

Practical recommendations for the management of bleeding in patients treated with dual antiplatelet therapy with or without concomitant oral anticoagulation are showed in the figure 10.


Bleeding during treatment with dual antiplatelet therapy ± OAC
TRIVIAL BLEEDING
Any bleeding not requiring medical intervention or further evaluation
MILD BLEEDING
Any bleeding that requires medical attention without requiring hospitalization
MODERATE BLEEDING
Any bleeding associated with a significant blood loss (>3 g/dL HB) and/or requiring hospitalization, which is haemodynamically stable and not rapidly evolving
e.g. skin bruising or ecchimosis, self-resolving epistaxis, minimal conjunctival bleeding
e.g. not self resolving epistaxis, moderate conjunctival bleeding, genitourinary or upper/lower gastrointestinal bleeding without significant blood loss, mild haemoptysis
e.g. genitourinary, respiratory or upper/lower gastrointestinal bleeding with significant blood loss or requiring transfusion
• Continue DAPT
• Consider OAC continuation or skip one single next pill
• Reassure the patient
• Identify and discuss with the patient possible preventive strategies
• Counsel patient on the importance of drug-adherence
• Continue DAPT
• Consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC
• Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm)
• Add PPI if not previously implemented
• Counsel patient on the importance of drug-adherence
• Consider stopping DAPT and continue with SAPT, preferably with the P2Y12 inhibitor especially in case of upper GI bleeding
• Reinitiate DAPT as soon as deemed safe
• Consider shortening DAPT duration or switching to less potent P2Y12 inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs
• Consider OAC discontinuation or even reversal until bleeding is controlled, unless very high thrombotic risk (i.e. mechanical heart valves, cardiac assist device, CHA2DS2-VASc ≥4)
• Reinitiate treatment within one week if clinically indicated. For Vitamin-K antagonist consider a target INR of 2.0–2.5 unless overriding indication (i.e. mechanical heart valves or cardiac assist device) for NOAC consider the lowest effective dose
• In case of triple therapy consider downgrading to dual therapy, preferably with clopidogrel and OAC
• If patients on dual therapy, consider stopping antiplatelet therapy if deemed safe
• Consider i.v. PPI if GI bleeding occurred
• Identify and possibly treat concomitant conditions associated with bleeding (e.g. peptic ulcer, haemorrhoidal plexus, neoplasm)
• Counsel patient on the importance of drug-adherence
Legend
DAPT management
OAC management
General recommendations
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Bleeding during treatment with dual antiplatelet therapy ± OAC

SEVERE BLEEDING

Any bleeding requiring hospitalisation, associated with a severe blood loss (>5 g/dL HB) which is haemodynamically stable and not rapidly evolving

e.g. severe genitourinary, respiratory or upper/lower gastrointestinal bleeding

- Consider stopping DAPT and continue with SAPT, preferably with the $P2Y_{12}$ inhibitor especially in case of upper GI bleeding
- If bleeding persists despite treatment or treatment is not possible, consider stopping all antithrombotic medications
- Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the $P2Y_{12}$ inhibitor especially in case of upper GI bleeding
- If DAPT is re-started, consider shortening DAPT duration or switching to less potent $P2Y_{12}$ inhibitor (i.e. from ticagrelor/prasugrel to clopidogrel), especially if recurrent bleeding occurs

- Consider stopping and reversing OAC until bleeding is controlled unless prohibitive thrombotic risk (i.e. mechanical heart valve in mitral position, cardiac assist device)
- Reinitiate treatment within one week if clinically indicated. For vitamin-K antagonists consider a target INR of 2.0–2.5 unless overriding indication (i.e. mechanical heart valves or cardiac assist device) for NOAC consider the lowest effective dose
- If patient on triple therapy consider downgrading to dual therapy with clopidogrel and OAC. If patients on dual therapy, consider stopping antiplatelet therapy if deemed safe

- Consider i.v. PPI if GI bleeding occurred
- RBC transfusion if HB <7-8 g/dL
- Consider platelet transfusion
- Urgent surgical or endoscopic treatment of bleeding source if deemed possible

LIFE-THREATENING BLEEDING

Any severe active bleeding putting patient's life immediately at risk

e.g. massive overt genitourinary, respiratory or upper/lower gastrointestinal bleeding, active intracranial, spinal or intraocular haemorrhage, or any bleeding causing haemodynamic instability

- Immediately discontinue all antithrombotic medications
- Once bleeding has ceased, re-evaluate the need for DAPT or SAPT, preferably with the $P2Y_{12}$ inhibitor especially in case of upper GI bleeding

- Stop and reverse OAC

- Fluid replacement if hypotension
- Consider RBC transfusion irrespective of HB values
- Platelet transfusion
- Consider i.v. PPI if GI bleeding occurred
- Urgent surgical or endoscopic treatment of bleeding source if deemed possible

Legend

- DAPT management
- OAC management
- General recommendations

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ACS = acute coronary syndrome; CHA2DS2-VASc= cardiac failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points)–vascular disease, age 65–74, sex category; DAPT = dual antiplatelet therapy; GI = gastrointestinal; HB = haemoglobin; INR = international normalized ratio; i.v. = intravenous; OAC = oral anticoagulant; NOAC = non-vitamin-K antagonist; PPI = proton pump inhibitor; RBC = red blood cell; SAPT = single antiplatelet therapy.

Circulation

ESC/ACC/AHA/WHF EXPERT CONSENSUS DOCUMENT

Fourth Universal Definition of Myocardial Infarction (2018)

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Keywords: AHA Scientific Statements ■ Myocardial infarction ■ Type 1 MI ■ Type 2 MI ■ Type 3 MI ■ Type 4a MI ■ Type 4b MI ■ Type 4c MI ■ Type 5 MI ■ Cardiac troponin ■ High sensitivity cardiac troponin ■ Myocardial injury ■ Prior myocardial infarction ■ Silent myocardial infarction ■ Recurrent myocardial infarction ■ Re-infarction ■ Cardiac procedural myocardial injury ■ Takotsubo syndrome ■ Myocardial infarction with nonobstructive coronary arteries (MINOCA)

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The American Heart Association requests that this document be cited as follows: Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD: the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138:e000–e000. DOI: 10.1161/CIR.0000000000000617.

Abbreviations and Acronyms

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
ARC-2	Academic Research Consortium-2
AUC	Area under the curve
CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
CKD	Chronic kidney disease
CK-MB	Creatine kinase MB isoform
CMR	Cardiac magnetic resonance
CTCA	Computed tomographic coronary angiography cTnCardiac troponin
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CT	Computed tomography
CV	Coefficient of variation
EF	Ejection fraction
ECG	Electrocardiogram or electrocardiographic
HF	Heart failure
hs-cTn	High-sensitivity cardiac troponin
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
ISFC	International Society and Federation of Cardiology
LAD	Left anterior descending artery
LBBB	Left bundle branch block
LoD	Limit of detection
LGE	Late gadolinium enhancement
LGE-CMR	Late gadolinium enhancement cardiac magnetic resonance
LV	Left ventricular
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
MONICA	MONItoring of trends and determinants in CArdiovascular disease
MPS	Myocardial perfusion scintigraphy
NHLBI	National Heart, Lung, and Blood Institute
NSTEMI	Non-ST-elevation myocardial infarction
PET	Positron emission tomography
PCI	Percutaneous coronary intervention
POC	Point of care
RBBB	Right bundle branch block
SPECT	Single photon emission computed tomography
STEMI	ST-elevation myocardial infarction
ST-T	ST-segment–T wave
TIMI	Thrombolysis in Myocardial Infarction
TTS	Takotsubo syndrome
UDMI	Universal Definition of Myocardial Infarction
URL	Upper reference limit
WHF	World Heart Federation
WHO	World Health Organization

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1. WHAT IS NEW IN THE UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION?

What's new in the universal definition of myocardial infarction?
New concepts
• Differentiation of myocardial infarction from myocardial injury.
• Highlighting peri-procedural myocardial injury after cardiac and non-cardiac procedures as discrete from myocardial infarction.
• Consideration of electrical remodelling (cardiac memory) in assessing repolarization abnormalities with tachyarrhythmia, pacing, and rate-related conduction disturbances.
• Use of cardiovascular magnetic resonance to define aetiology of myocardial injury.
• Use of computed tomographic coronary angiography in suspected myocardial infarction.
Updated concepts
• Type 1 myocardial infarction: Emphasis on the causal relationship of plaque disruption with coronary athero-thrombosis; *new Figure 3*.
• Type 2 myocardial infarction: Settings with oxygen demand and supply imbalance unrelated to acute coronary athero-thrombosis; *new Figures 4 and 5*.
• Type 2 myocardial infarction: Relevance of presence or absence of coronary artery disease to prognosis and therapy.
• Differentiation of myocardial injury from type 2 myocardial infarction; *new Figure 6*.
• Type 3 myocardial infarction: Clarify why type 3 myocardial infarction is a useful category to differentiate from sudden cardiac death.
• Types 4–5 myocardial infarction: Emphasis on distinction between procedure-related myocardial injury and procedure-related myocardial infarction.
• Cardiac troponin: Analytical issues for cardiac troponins; *new Figure 7*.
• Emphasis on the benefits of high-sensitivity cardiac troponin assays.
• Considerations relevant to the use of rapid rule-out and rule-in protocols for myocardial injury and myocardial infarction.
• Issues related to specific diagnostic change ('delta') criteria for the use of cardiac troponins to detect or exclude acute myocardial injury.
• Consideration of new non-rate-related right bundle branch block with specific repolarization patterns.
• ST-segment elevation in lead aVR with specific repolarization patterns, as a STEMI equivalent.
• ECG detection of myocardial ischaemia in patients with an implantable cardiac defibrillator or a pacemaker.
• Enhanced role of imaging including cardiac magnetic resonance imaging for the diagnosis of myocardial infarction; *new Figure 8*.
New sections
• Takotsubo syndrome.
• MINOCA.
• Chronic kidney disease.
• Atrial fibrillation.
• Regulatory perspective on myocardial infarction.
• Silent or unrecognized myocardial infarction.

ECG = electrocardiogram; MINOCA = myocardial infarction with non-obstructive coronary arteries; STEMI = ST-elevation myocardial infarction.

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2. UNIVERSAL DEFINITIONS OF MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION: SUMMARY

Universal definitions of myocardial injury and myocardial infarction

Criteria for myocardial injury

The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

Criteria for acute myocardial infarction (types 1, 2 and 3 MI)

The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following:

- Symptoms of myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MIs).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*. Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*.

Criteria for coronary procedure-related myocardial infarction (types 4 and 5 MI)

Percutaneous coronary intervention (PCI) related MI is termed *type 4a MI*.

Coronary artery bypass grafting (CABG) related MI is termed *type 5 MI*.

Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for *type 4a MI* and > 10 times for *type 5 MI* of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5 or > 10 fold increase and manifest a change from the baseline value of > 20%. In addition with at least one of the following:

- New ischaemic ECG changes (this criterion is related to *type 4a MI* only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization.

Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include *type 4b MI* stent thrombosis and *type 4c MI* restenosis that both meet *type 1 MI* criteria.

Post-mortem demonstration of a procedure-related thrombus meets the *type 4a MI* criteria or *type 4b MI* criteria if associated with a stent.

Criteria for prior or silent/unrecognized myocardial infarction

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischaemic causes.
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology.
- Patho-anatomical findings of a prior MI.

CABG = coronary artery bypass grafting; cTn = cardiac troponin; ECG = electrocardiogram; MI = myocardial infarction; PCI = percutaneous coronary intervention; URL = upper reference limit.

3. INTRODUCTION

In the late 19th century, post-mortem examinations demonstrated a possible relationship between thrombotic occlusion of a coronary artery and myocardial infarction (MI).[1] However, it was not until the beginning of the 20th century that the first clinical descriptions appeared describing a connection between the formation of a thrombus in a coronary artery and its associated clinical features.[2,3] Despite these landmark observations, considerable time elapsed before general clinical acceptance of this entity was achieved, in part due to one autopsy study that showed no thrombi in the coronary arteries of 31% of deceased patients with an MI.[4] The clinical entity was referred to as coronary thrombosis, although use of the term 'MI' ultimately prevailed. Over the years, several different definitions of MI have been used, leading to controversy and confusion. Hence, a general and worldwide definition for MI was needed. This occurred for the first time in the 1950–70s, when working groups from the World Health Organization (WHO) established a primarily electrocardiographic (ECG)-based definition of MI intended for epidemiological use.[5] The original description, with minor modifications, is still used in epidemiological surveys (*Figure 1*).[6–8]

With the introduction of more sensitive cardiac biomarkers, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) collaborated to redefine MI using a biochemical and clinical approach, and reported that myocardial injury detected by abnormal biomarkers in the setting of acute myocardial

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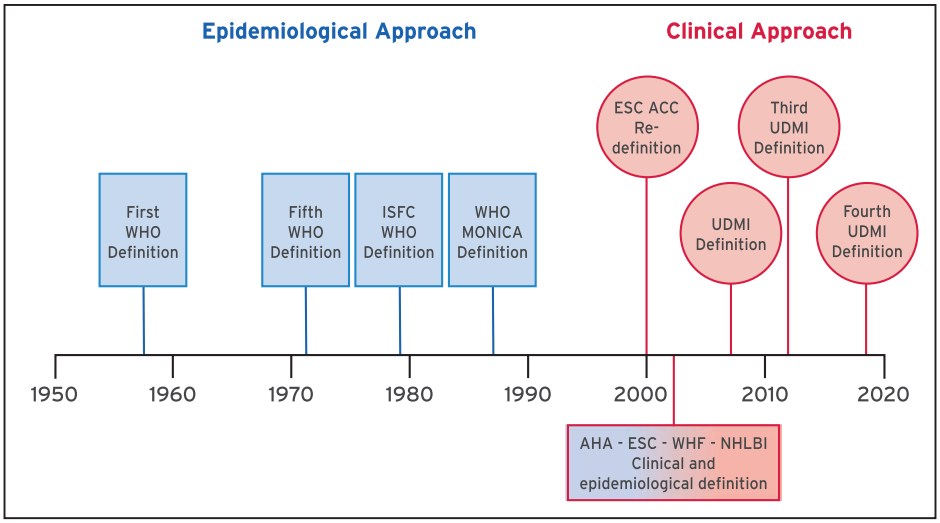

Figure 1. History of documents on the definition of myocardial infarction.
ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; ISFC = International Society and Federation of Cardiology; MONICA = MONItoring of trends and determinants in CArdiovascular disease; NHLBI = National Heart, Lung, and Blood Institute; UDMI = Universal Definition of Myocardial Infarction; WHF = World Heart Federation; WHO = World Health Organization.

ischaemia should be labelled as MI.[9] The principle was further refined by the Global MI Task Force, leading to the Universal Definition of Myocardial Infarction Consensus Document in 2007, introducing a novel MI classification system with five subcategories.[10] This document, endorsed by the ESC, the ACC), the American Heart Association (AHA), and the World Heart Federation (WHF), was adopted by the WHO.[11] The development of even more sensitive assays for markers of myocardial injury made further revision of the document necessary, particularly for patients who undergo coronary procedures or cardiac surgery. As a result, the Joint ESC/ACC/AHA/WHF Task Force produced the Third Universal Definition of Myocardial Infarction Consensus Document in 2012.[12]

Studies have shown that myocardial injury, defined by an elevated cardiac troponin (cTn) value, is frequently encountered clinically and is associated with an adverse prognosis.[13,14] Although myocardial injury is a prerequisite for the diagnosis of MI, it is also an entity in itself. To establish a diagnosis of MI, criteria in addition to abnormal biomarkers are required. Non-ischaemic myocardial injury may arise secondary to many cardiac conditions such as myocarditis, or may be associated with non-cardiac conditions such as renal failure.[15] Therefore, for patients with increased cTn values, clinicians must distinguish whether patients have suffered a non-ischaemic myocardial injury or one of the MI subtypes. If there is no evidence to support the presence of myocardial ischaemia, a diagnosis of myocardial injury should be made. This diagnosis can be changed if subsequent evaluation indicates criteria for MI. The current Fourth Universal Definition of Myocardial Infarction Consensus Document reflects these considerations through adhering to the clinical approach of the definition of MI.

Clinical Criteria for MI

The clinical definition of MI denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia.

4. PATHOLOGICAL CHARACTERISTICS OF MYOCARDIAL ISCHAEMIA AND INFARCTION

MI is defined pathologically as myocardial cell death due to prolonged ischaemia. Diminished cellular glycogen, and relaxed myofibrils and sarcolemmal disruption, are the first ultrastructural changes and are seen as early as 10–15 min after the onset of ischaemia.[16] Mitochondrial abnormalities are observed as early as 10 min after coronary occlusion by electron microscopy and are progressive.[17] It can take hours before myocyte necrosis can be identified by post-mortem examination in humans; this is in contrast to animal models, in which biochemical evidence of myocardial cell death due to apoptosis can be detected within 10 min of induced myocardial ischaemia in association with myocyte death.[15] Experimentally, necrosis progresses from the subendocardium to the subepicardium over several hours. The time course may be prolonged by increased collateral flow, reduced determinants of myocardial oxygen consumption, and intermittent occlusion/reperfusion, which can precondition the heart.[18] Timely imple-

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mentation of reperfusion therapy, when appropriate, reduces ischaemic injury of the myocardium.[19,20]

5. BIOMARKER DETECTION OF MYOCARDIAL INJURY AND INFARCTION

Cardiac troponin I (cTnI) and T (cTnT) are components of the contractile apparatus of myocardial cells and are expressed almost exclusively in the heart.[21,22] Increases in cTnI values have not been reported to occur following injury to non-cardiac tissues. The situation is more complex for cTnT. Biochemical data indicate that injured skeletal muscle expresses proteins that are detected by the cTnT assay, leading to some situations where elevations of cTnT could emanate from skeletal muscle.[23–27] Recent data suggest that the frequency of such elevations in the absence of ischaemic heart disease may be higher than originally thought.[28,29] cTnI and cTnT are the preferred biomarkers for the evaluation of myocardial injury,[12,21,22,30] and high-sensitivity (hs)-cTn assays are recommended for routine clinical use.[22] Other biomarkers, e.g. wwm (CK-MB), are less sensitive and less specific.[31] Myocardial injury is defined as being present when blood levels of cTn are increased above the 99th percentile upper reference limit (URL).[12,21,22,30] The injury may be acute, as evidenced by a newly detected dynamic rising and/or falling pattern of cTn values above the 99th percentile URL, or chronic, in the setting of persistently elevated cTn levels.

Criteria for Myocardial Injury

Detection of an elevated cTn value above the 99th percentile URL is defined as myocardial injury. The injury is considered acute if there is a rise and/or fall of cTn values.

Although elevated cTn values reflect injury to myocardial cells, they do not indicate the underlying pathophysiological mechanisms, and can arise following preload-induced mechanical stretch or physiological stresses in otherwise normal hearts.[32–34] Various causes have been suggested for the release of structural proteins from the myocardium, including normal turnover of myocardial cells, apoptosis, cellular release of cTn degradation products, increased cellular wall permeability, the formation and release of membranous blebs, and myocyte necrosis.[27,35] Yet, it is not clinically possible to distinguish which increases of cTn levels are due to which mechanisms.[36] However, regardless of the mechanism, acute myocardial injury, when associated with a rising and/or falling pattern of cTn values with at least one value above the 99th percentile URL and caused by myocardial ischaemia, is designated as an acute MI.[12,21,22,30] Histological evidence of myocardial injury with myocyte death can be detected in clinical conditions associated with non-ischaemic mechanisms of myocardial injury as well[37,38] (*Figure 2*).

Myocardial ischaemic or non-ischaemic conditions associated with increased cTn values are presented in *Table 1*. The complexity of clinical circumstances may sometimes make it difficult to discriminate specific individual mechanism(s) of myocardial injury. In this situation, the multifactorial contributions resulting in myocardial injury should be described in the patient record.

6. CLINICAL PRESENTATIONS OF MYOCARDIAL INFARCTION

Onset of myocardial ischaemia is the initial step in the development of MI and results from an imbalance between oxygen supply and demand. Myocardial ischaemia in a clinical setting can most often be identified from the patient's history and from the ECG. Possible ischaemic symptoms include various combinations of chest, upper extremity, mandibular, or epigastric discomfort during exertion or at rest, or an ischaemic equivalent such as dyspnoea or fatigue. Often, the discomfort is diffuse; not localized, nor positional, nor affected by movement of the region. However, these symptoms are not specific for myocardial ischaemia and can be observed in other conditions such as gastrointestinal, neurological, pulmonary, or musculoskeletal complaints. MI may occur with atypical symptoms such as palpitations or cardiac arrest, or even without symptoms.[12] Very brief episodes of ischaemia too short to cause necrosis can also cause cTn release and elevations. The involved myocytes can subsequently die due to apoptosis.[42]

If myocardial ischaemia is present clinically or detected by ECG changes together with myocardial injury, manifested by a rising and/or falling pattern of cTn values, a diagnosis of acute MI is appropriate. If myocardial ischaemia is not present clinically, then elevated cTn levels may be indicative of acute myocardial injury if the pattern of values is rising and/or falling, or related to more chronic ongoing injury if the pattern is unchanging.[14] Similar considerations are relevant when evaluating events that are potentially related to procedures that may cause myocardial injury and/or MI. Additional evaluations may lead to a need for the initial diagnosis to be revised.

Patients with suspected acute coronary syndrome (ACS) that are ruled out for MI with normal cardiac biomarker values (≤ 99th percentile URL) may have unstable angina or an alternative diagnosis. These patients should be evaluated and treated accordingly.[11,43]

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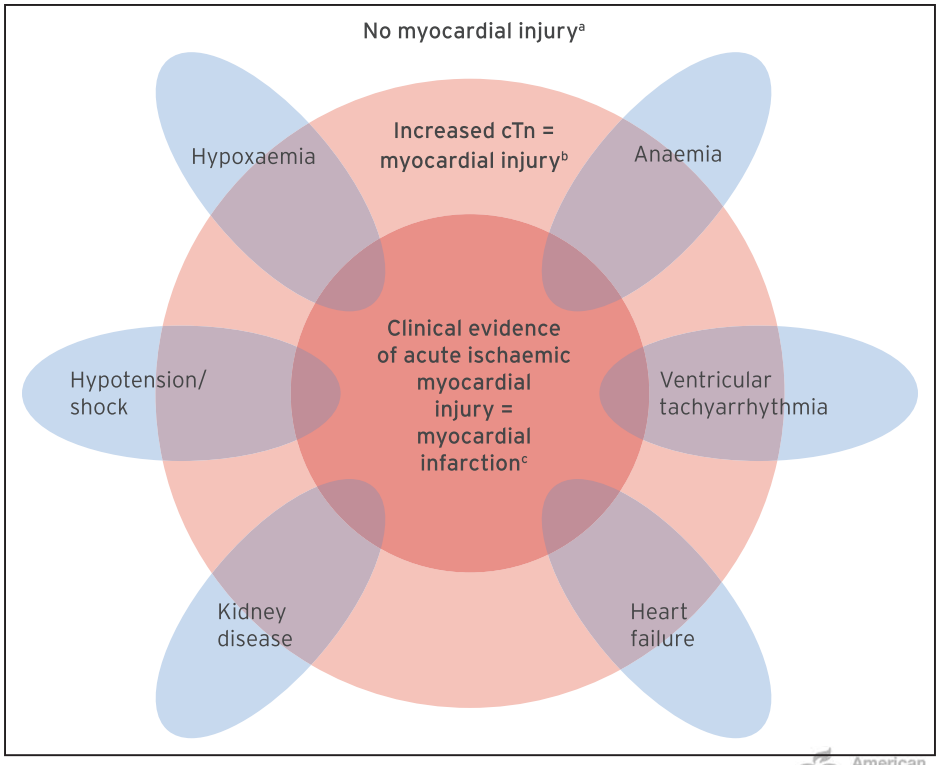

Figure 2. Spectrum of myocardial injury, ranging from no injury to myocardial infarction.
Various clinical entities may involve these myocardial categories, e.g. ventricular tachyarrhythmia, heart failure, kidney disease, hypotension/shock, hypoxaemia, and anaemia. cTn = cardiac troponin; URL upper reference limit. [a]No myocardial injury = cTn values ≤ 99th percentile URL or not detectable. [b]Myocardial injury = cTn values > 99th percentile URL. [c]Myocardial infarction = clinical evidence of myocardial ischaemia and a rise and/or fall of cTn values > 99th percentile URL.

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7. CLINICAL CLASSIFICATION OF MYOCARDIAL INFARCTION

For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate MI in patients with chest discomfort or other ischaemic symptoms, who develop new ST-segment elevations in two contiguous leads or new bundle branch blocks with ischaemic repolarization patterns as an ST-elevation MI (STEMI) (see section 27). In contrast, patients without ST-segment elevation at presentation are usually designated non-ST-elevation MI (NSTEMI). The categories of patients with STEMI, NSTEMI, or unstable angina are customarily included in the concept of ACS. In addition to these categories, MI may be classified into various types based on pathological, clinical, and prognostic differences, along with different treatment strategies.

7.1. Myocardial Infarction Type 1

MI caused by atherothrombotic coronary artery disease (CAD) and usually precipitated by atherosclerotic plaque disruption (rupture or erosion) is designated as a type 1 MI. The relative burden of atherosclerosis and thrombosis in the culprit lesion varies greatly, and the dynamic thrombotic component may lead to distal coronary embolization resulting in myocyte necrosis.[44,45] Plaque rupture may not only be complicated by intraluminal thrombosis but also by haemorrhage into the plaque through the disrupted surface (*Figure 3*).[44,45]

Criteria for Type 1 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.[a]

cTn = cardiac troponin; ECG = electrocardiogram; URL = upper reference limit.
[a]Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values.

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Table 1. Reasons for the Elevation of Cardiac Troponin Values Because of Myocardial Injury

Myocardial injury related to acute myocardial ischaemia
Atherosclerotic plaque disruption with thrombosis.
Myocardial injury related to acute myocardial ischaemia because of oxygen supply/demand imbalance
Reduced myocardial perfusion, e.g.
• Coronary artery spasm, microvascular dysfunction
• Coronary embolism
• Coronary artery dissection
• Sustained bradyarrhythmia
• Hypotension or shock
• Respiratory failure
• Severe anaemia
Increased myocardial oxygen demand, e.g.
• Sustained tachyarrhythmia
• Severe hypertension with or without left ventricular hypertrophy
Other causes of myocardial injury
Cardiac conditions, e.g.
• Heart failure
• Myocarditis
• Cardiomyopathy (any type)
• Takotsubo syndrome
• Coronary revascularization procedure
• Cardiac procedure other than revascularization
• Catheter ablation
• Defibrillator shocks
• Cardiac contusion
Systemic conditions, e.g.
• Sepsis, infectious disease
• Chronic kidney disease
• Stroke, subarachnoid haemorrhage
• Pulmonary embolism, pulmonary hypertension
• Infiltrative diseases, e.g. amyloidosis, sarcoidosis
• Chemotherapeutic agents
• Critically ill patients
• Strenuous exercise

For a more comprehensive listing, see[39–41].

It is essential to integrate the ECG findings with the aim of classifying type 1 MI into STEMI or NSTEMI in order to establish the appropriate treatment according to current Guidelines.[46,47]

7.2. Myocardial Infarction Type 2

The pathophysiological mechanism leading to ischaemic myocardial injury in the context of a mismatch between oxygen supply and demand has been classified as type 2 MI.[10,12] By definition, acute atherothrombotic plaque disruption is not a feature of type 2 MI. In patients with stable known or presumed CAD, an acute stressor such as an acute gastrointestinal bleed with a precipitous drop in haemoglobin, or a sustained tachyarrhythmia with clinical manifestations of myocardial ischaemia, may result in myocardial injury and a type 2 MI. These effects are due to insufficient blood flow to the ischaemic myocardium to meet the increased myocardial oxygen demand of the stressor. Ischaemic thresholds may vary substantially in individual patients depending on the magnitude of the stressor, the presence of non-cardiac comorbidities, and the extent of underlying CAD and cardiac structural abnormalities.

Studies have shown variable occurrences of type 2 MI depending on criteria used for diagnosis. Some reports rely on specific predetermined oxygen mismatch criteria,[48,49] whereas others apply more liberal criteria. Most studies show a higher frequency of type 2 MI in women. The shortand long-term mortality rates for patients with type 2 MI are generally higher than for type 1 MI patients in most but not all studies due to an increased prevalence of comorbid conditions.[49–57] Coronary atherosclerosis is a common finding in type 2 MI patients selected for coronary angiography. In general, these patients have a worse prognosis than those without CAD.[54–57] Prospective evaluations of the importance of CAD with type 2 MI using consistent definitions and approaches are needed.

It has been shown that the frequency of ST-segment elevation in type 2 MI varies from 3–24%.[53] In some cases, coronary embolism caused by thrombi, calcium or vegetation from the atria or ventricles, or acute aortic dissection may result in a type 2 MI. Spontaneous coronary artery dissection with or without intramural haematoma is another non-atherosclerotic condition that may occur, especially in young women. It is defined as spontaneous dissection of the coronary artery wall with accumulation of blood within the false lumen, which can compress the true lumen to varying degrees (*Figure 4*).[58]

All of the clinical information available should be considered in distinguishing type 1 MI from type 2 MI. The context and mechanisms of type 2 MI should be considered when establishing this diagnosis (*Figure 5*). The myocardial oxygen supply/demand imbalance attributable to acute myocardial ischaemia may be multifactorial, related either to: reduced myocardial perfusion due to fixed coronary atherosclerosis without plaque rupture, coronary artery spasm, coronary microvascular dysfunction (which includes endothelial dysfunction, smooth muscle cell dysfunction, and the dysregulation of sympathetic innervation), coronary embolism, coronary artery dissection with or without intramural haematoma, or other mechanisms that reduce oxygen supply such as severe bradyarrhythmia, respiratory failure with severe hypoxaemia, severe anaemia, and hypotension/shock; or to increased myocardial oxygen demand due to sustained tachyarrhythmia or severe hypertension with or without left ventricular hypertrophy. In patients who undergo timely coronary angiography, description of a ruptured plaque with throm-

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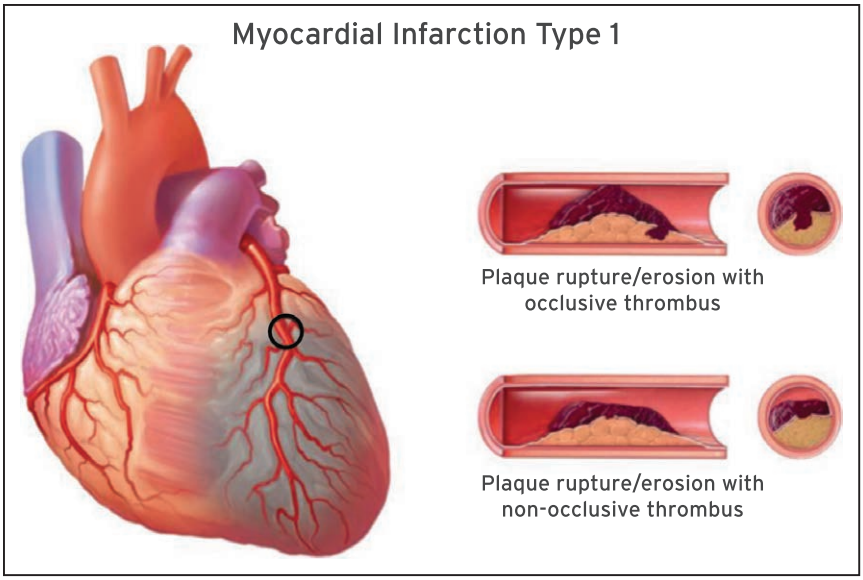

Figure 3. Myocardial infarction type 1.

bus in the infarct-related artery may be helpful in making the distinction between type 2 MI vs. type 1 MI, but angiography is not always definitive, clinically indicated, or required to establish the diagnosis of type 2 MI.

Criteria for Type 2 MI

Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:

- Symptoms of acute myocardial ischaemia;
- New ischaemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

It appears advisable in the acute setting to treat the underlying ischaemic imbalance of oxygen supply and demand. This treatment may include volume adjustment, blood pressure management, administration of blood products, heart-rate control, and respiratory support.[47,48] Depending on the clinical situation, coronary evaluations may be indicated to assess the likelihood of CAD. If it is present, the MI Guidelines may be applied in accordance with the ECG findings of STEMI or NSTEMI.[46,47] However, if CAD is absent, the benefits of cardiovascular risk reduction strategies with type 2 MI remain uncertain.

7.3. Myocardial Infarction Type 2 and Myocardial Injury

Type 2 MI and myocardial injury are frequently encountered in clinical practice and both are related to a poor outcome.[13,14,49,51,56] A conceptual model to facilitate the clinical distinction between acute ischaemic myocardial injury with or without an acute atherothrombotic event (type 1 or type 2 MI) vs. conditions without acute ischaemic myocardial injury is displayed in *Figure 6*. Acute MI requires a rising and/or falling pattern of cTn values. Acute myocardial injury may also manifest such a pattern but if the injury is related to structural heart disease, the cTn values may be stable and unchanging. Type 2 MI and non-ischaemic myocardial injury may coexist. It should be recognized that some disease entities may be on both sides of the diagram, e.g. acute heart failure that may occur in the context of acute myocardial ischaemia. Nevertheless, abnormal cTn values in the setting of acute and/or chronic heart failure are often better categorized as a myocardial injury condition. Few studies have compared the incidence and clinical features of type 2 MI vs. myocardial injury without acute myocardial ischaemia.

7.4. Myocardial Infarction Type 3

The detection of cardiac biomarkers in the blood is fundamental for establishing the diagnosis of MI.[10,12] However, patients can manifest a typical presentation of myocardial ischaemia/infarction, including presumed new ischaemic ECG changes or ventricular fibrillation, and die before it is possible to obtain blood for cardiac biomarker determination; or the patient may succumb soon after the onset of symptoms before an elevation of biomarker values has occurred. Such patients are designated as having a type 3 MI, when suspicion for an acute myocardial ischaemic event is high, even when cardiac biomarker evidence of MI is lacking.[10,12] This category allows the separation of fatal MI events from the much larger group of sudden death episodes that

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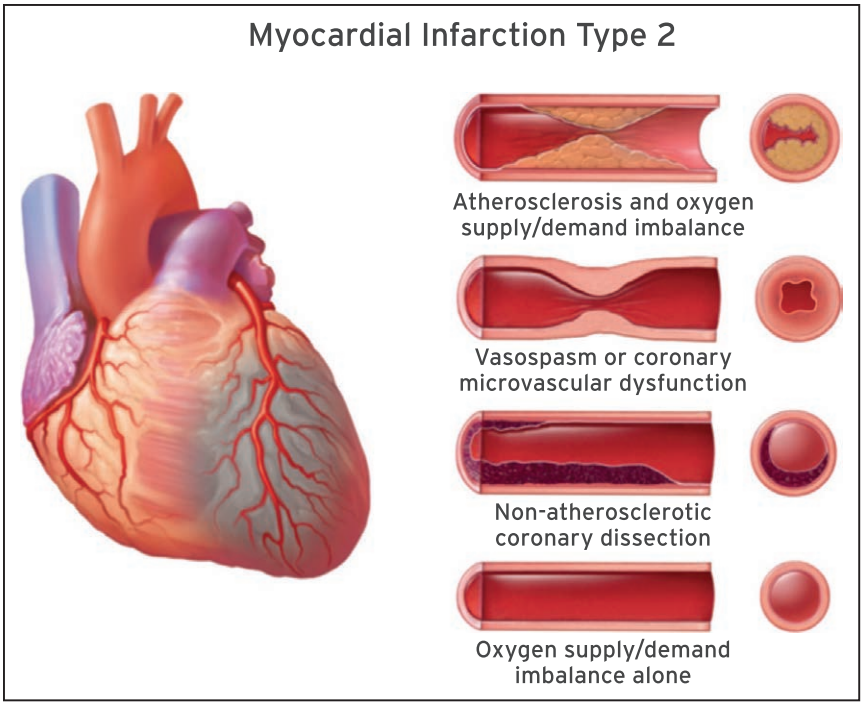

Figure 4. Myocardial infarction type 2.

may be cardiac (non-ischaemic) or non-cardiac in origin. When a type 3 MI is diagnosed and a subsequent autopsy reveals recent evidence of an MI, with a fresh or recent thrombus in the infarct-related artery, the type 3 MI should be reclassified to a type 1 MI. Original investigations addressing the incidence of type 3 MI are sparse, but a study showed an annual incidence below 10/100 000 person-years and a frequency of 3–4% among all types of MI.[60]

Criteria for Type 3 MI

Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation, but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

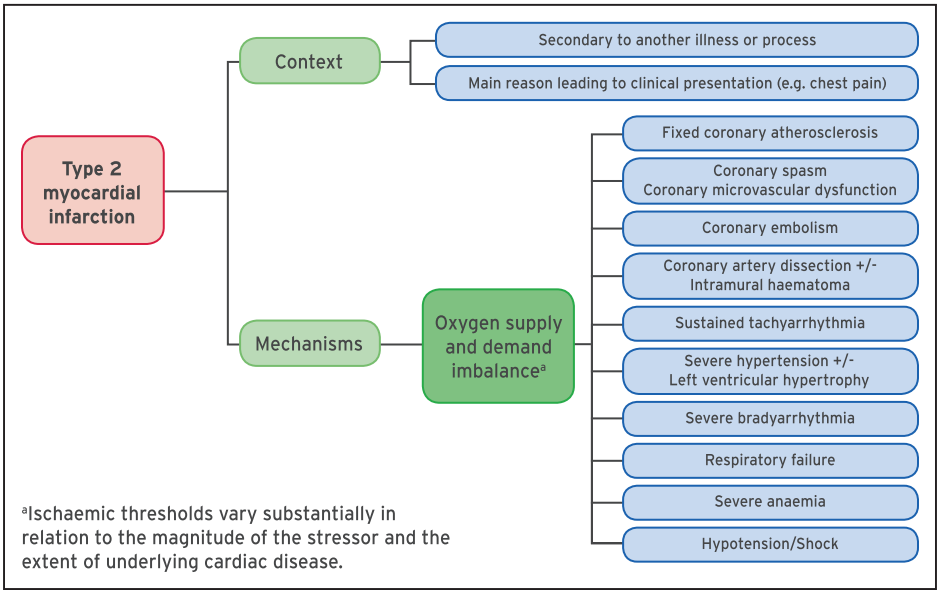

Figure 5. Framework for type 2 myocardial infarction considering the clinical context and pathophysiological mechanisms attributable to acute myocardial ischaemia.
The illustration above is modified from Januzzi and Sandoval.[59]

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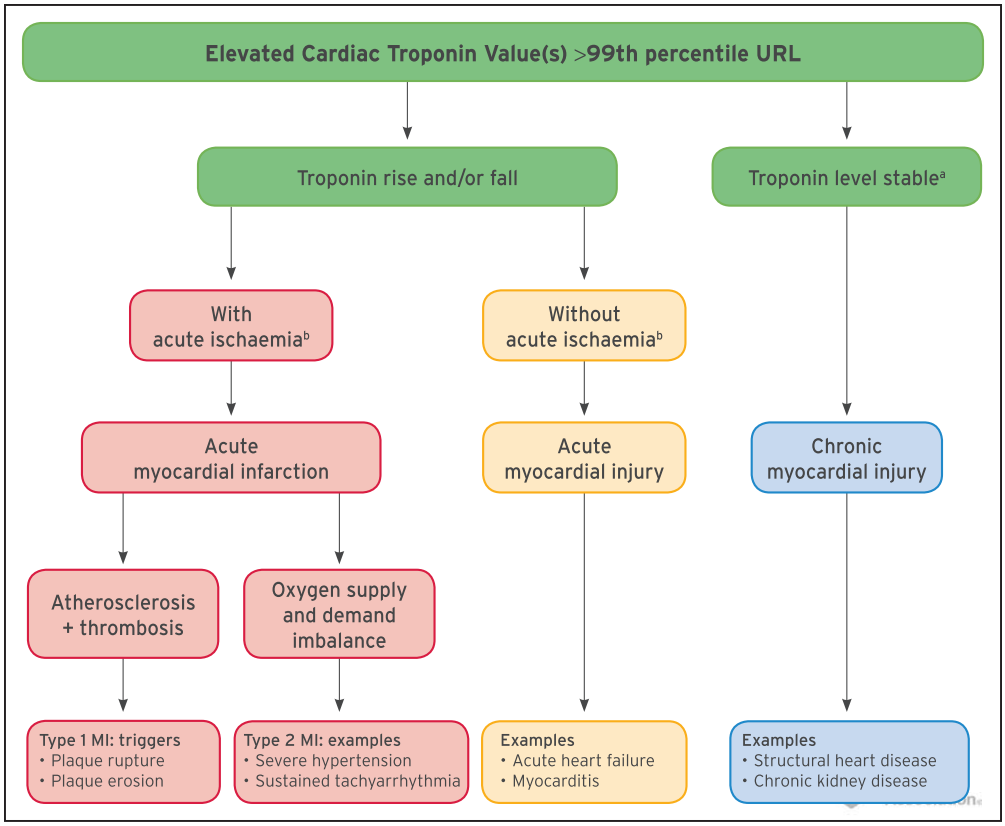

Figure 6. A model for interpreting myocardial injury.
Ischaemic thresholds vary substantially in relation to the magnitude of the stressor and the extent of underlying cardiac disease. MI = myocardial infarction; URL = upper reference limit. [a]Stable denotes ≤ 20% variation of troponin values in the appropriate clinical context. [b]Ischaemia denotes signs and/or symptoms of clinical myocardial ischaemia.

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8. CORONARY PROCEDURE-RELATED MYOCARDIAL INJURY

Cardiac procedural myocardial injury related to coronary revascularization procedures, whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), may be temporally related to the procedure itself, reflecting periprocedural issues, or may occur later reflecting complications of a device, such as early or late stent thrombosis or in-stent restenosis for PCI, or graft occlusion or stenosis with CABG. Late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR) allows assessment of procedural myocardial injury[61–63] When quantifying procedural injury using LGE-CMR before and shortly after PCI or CABG, it was found that 32% of patients had evidence of procedural myocardial injury.[63] Furthermore, it has been shown that patients with elevation of cTnI values after PCI or after CABG have evidence of procedural myocardial injury on CMR imaging.[61,62] For that reason, increased cTn values detected following a coronary revascularization procedure may reflect procedural myocardial injury. Of importance, if the baseline value before the procedure is above the 99th percentile URL, it is essential that cTn levels are stable prior to the evaluation in order to reliably establish the presence of acute procedural myocardial injury. It is not possible to determine, when intervening in a patient with an acute MI event resulting in an increased cTn level, how much of any given increase is related to the MI and how much is due to the procedure.

Criteria for Cardiac Procedural Myocardial Injury

Cardiac procedural myocardial injury is arbitrarily defined by increases of cTn values (> 99th percentile URL) in patients with normal baseline values (≤ 99th percentile URL) or a rise of cTn values > 20% of the baseline value when it is above the 99th percentile URL but it is stable or falling.

A large proportion of patients have abnormal values of cTn after PCI, ranging from ~20–40% in stable CAD to 40–50% in MI.[64] The occurrence of procedural myocardial injury can be detected by the measurement of cTn before the procedure and repeated 3–6 h later. Where the second value is rising, further sampling

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should be performed to document the peak cTn value. Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal (≤ 99th percentile URL), or if they are stable or falling. For patients that present with an ACS and undergo a prompt coronary revascularization procedure resulting in only a single pre-procedural baseline value that is normal or mildly elevated, followed by subsequent postprocedural values that continue to increase, the post-procedural increase should be attributed to the index event. Recent data corroborate the importance of elevated pre-procedure cTn values as a prognostic marker in patients that have values that rise after the procedure.[65] To diagnose procedural myocardial injury in the clinical setting of only a single pre-procedural cTn value, the cardiac Tn values would need to be stable or falling post-procedure, followed by a subsequent increase that exceeds the 99th percentile URL, and if the value has not returned to baseline, the increase should be > 20% with an absolute value > the 99th percentile URL.

9. MYOCARDIAL INFARCTION ASSOCIATED WITH PERCUTANEOUS CORONARY INTERVENTION (TYPE 4A MYOCARDIAL INFARCTION)

Stand-alone post-procedural increases of cTn values are sufficient to establish a diagnosis of procedural myocardial injury but not for the diagnosis of type 4a MI. Type 4a MI requires an elevation of cTn values greater than five times the 99th percentile URL in patients with normal baseline values or, in patients with elevated pre-procedure cTn in whom the cTn levels are stable (≤ 20% variation) or falling, the post-procedure cTn must rise > 20% to an absolute value more than five times the 99th percentile URL. In addition, there should be evidence of new myocardial ischaemia, either from ECG changes, imaging evidence, or from procedure-related complications associated with reduced coronary blood flow such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, slow flow or no-reflow, or distal embolization. The use of hs-cTn assays to diagnose type 4a MI (and type 5 MI) is an area of active research. Many hs-cTn assays are available, which have wide dynamic ranges. Different criteria may be required for different assays. However, it has recently been shown that the optimal hs-cTnT thresholds to predict cardiovascular events at 30 days and 1 year were very close to the five-fold increase suggested by the Third Universal Definition of Myocardial infarction.[12,66,67] These criteria are therefore retained because of a lack of new scientific evidence that identifies superior criteria for defining this MI subtype. Other criteria that meet the definition of type 4a MI, regardless of hs-cTn or cTn values, are the development of new pathological Q waves or autopsy evidence of recent procedure-related thrombus in the culprit artery.

Criteria for PCI-Related MI ≤ 48 h After the Index Procedure (Type 4a MI)

Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable (≤ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:

- New ischaemic ECG changes;
- Development of new pathological Q waves;[a]
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization.[b]

[a]Isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but more than five times the 99th percentile URL.
[b]Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria.

10. STENT/SCAFFOLD THROMBOSIS ASSOCIATED WITH PERCUTANEOUS CORONARY INTERVENTION (TYPE 4B MYOCARDIAL INFARCTION)

A subcategory of PCI-related MI is stent/scaffold thrombosis, type 4b MI, as documented by angiography or autopsy using the same criteria utilized for type 1 MI. It is important to indicate the time of the occurrence of the stent/scaffold thrombosis in relation to the timing of the PCI procedure. The following temporal categories are suggested: acute, 0–24 h; subacute, > 24 h to 30 days; late, > 30 days to 1 year; and very late > 1 year after stent/scaffold implantation.[68]

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11. RESTENOSIS ASSOCIATED WITH PERCUTANEOUS CORONARY INTERVENTION (TYPE 4C MYOCARDIAL INFARCTION)

Occasionally MI occurs and—at angiography, in-stent restenosis, or restenosis following balloon angioplasty in the infarct territory—is the only angiographic explanation since no other culprit lesion or thrombus can be identified. This PCI-related MI type is designated as type 4c MI, defined as focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

12. MYOCARDIAL INFARCTION ASSOCIATED WITH CORONARY ARTERY BYPASS GRAFTING (TYPE 5 MYOCARDIAL INFARCTION)

Numerous factors can lead to procedural myocardial injury during a CABG procedure. Many of them are related to the details of the cardiac preservation, the extent of the direct traumatic injury to the myocardium, as well as any potential ischaemic injury. For that reason, increases in cTn values should be expected after all CABG procedures,[69,70] which need to be taken into account when comparing the extent of procedural myocardial injury after cardiac surgery with that associated with less invasive approaches. Depending on whether it is off-pump or on-pump surgery, procedural myocardial injury is observed among 32–44% of CABG patients when quantified by LGE-CMR.[61,63] The area under the curve (AUC) and routine cTn sampling has demonstrated an excellent linear relationship with the mass of the new injury as defined by LGE-CMR. AUC for CK-MB is also good, although clearly inferior to cTnI.[69] However, these relationships vary depending on the nature of the procedure, the nature of the cardioplegia, and the specific assay used to measure cTn. Very high cTn values are most often associated with coronary arteryrelated events.[61,63,69] Thus, although cardiac biomarkers and especially cTn appear robust for the detection of procedural myocardial injury and also, in the presence of new myocardial ischaemia, for the detection of type 5 MI, a specific cut-off value for all procedures and all cTn assays is difficult to define. However, in order to ensure consistency with the analogous standards of the preceding definition of type 5 MI[12] and because of the lack of new scientific evidence that identifies superior criteria for defining this MI subtype, it is suggested that a cTn value > 10 times the 99th percentile URL is applied as the cut-off point during the first 48 h following CABG, occurring from a normal baseline cTn value (≤ 99th percentile URL), for diagnosing type 5 MI. It is important that the post-procedural elevation of cTn values is accompanied by ECG, angiographic, or imaging evidence of new myocardial ischaemia/new loss of myocardial viability.[71] The higher cut-off of MI after CABG than after PCI (10 times vs. 5 times the 99th percentile URL) has been arbitrarily selected due to the occurrence of more unavoidable myocardial injury during surgery than during PCI.

It should be recognized that ST-segment deviation and T wave changes are common after CABG due to epicardial injury, and are not reliable indicators of myocardial ischaemia in this setting. However, ST-segment elevation with reciprocal ST-segment depression or other specific ECG patterns may be a more reliable finding of a potential ischaemic event.

Criteria for CABG-Related MI ≤ 48 h After the Index Procedure (Type 5 MI)

CABG-related MI is arbitrarily defined as elevation of cTn values > 10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-procedure cTn in whom cTn levels are stable (≤ 20% variation) or falling, the postprocedure cTn must rise by > 20%. However, the absolute postprocedural value still must be > 10 times the 99th percentile URL. In addition, one of the following elements is required:

- Development of new pathological Q waves;[a]
- Angiographic documented new graft occlusion or new native coronary artery occlusion;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology.

[a]Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.

Marked isolated elevation of cTn values within the 48 h postoperative period, even in the absence of ECG/angiographic or other imaging evidence of MI, indicates prognostically significant cardiac procedural myocardial injury.[72] The presence of significant procedural myocardial injury in patients with operative problems (e.g. difficulty coming off bypass, technically difficult anastomoses in a heavily calcified aorta, of perioperative evidence of myocardial ischaemia, etc.) should prompt clinical review of the procedure and/or consideration of additional diagnostic testing for possible type 5 MI.

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13. OTHER DEFINITIONS OF MYOCARDIAL INFARCTION RELATED TO PERCUTANEOUS CORONARY INTERVENTION OR CORONARY ARTERY BYPASS GRAFTING

There is no universal consensus on the cTn or hs-cTn cut-off points that clearly distinguish cardiac procedural myocardial injury from MI. The distinction is made on the basis of an injury created by a flowlimiting complication during the procedure that results in sufficient myocardial ischaemia to generate a procedure-related MI. The size of the insult will determine the magnitude of the cTn release. Various groups have used multiples of the 99th percentile URL and set thresholds to diagnose periprocedural MIs for clinical trials.[68,73] Unless a standard assay is used for all analyses, given the heterogeneity of cTn assays, this approach could lead to very different values depending on the assay used locally. The Academic Research Consortium-2 (ARC-2) suggests a post-procedural cTn value ≥ 35 times the 99th percentile URL for both PCI and CABG in patients that have a normal baseline cTn value or in patients with elevated pre-procedure cTn values in whom the cTn levels are stable or falling. ARC-2 proposes that one ancillary criterion be required in addition to the ≥ 35 cTn rise to fulfill the definition of periprocedural MI. The ancillary criteria are one or more of the following: new significant Q waves (or equivalent), flow-limiting angiographic complications in a major epicardial vessel or > 1.5 mm diameter branch, or a substantial new loss of viable myocardium on echocardiography related to the procedure.[68] Furthermore, ARC-2 has defined standalone criteria for significant procedural myocardial injury if the rise in cTn is ≥ 70 times the 99th percentile URL (where the baseline is lower than the URL, elevated and stable, or falling).[68]

14. RECURRENT MYOCARDIAL INFARCTION

Incident MI is defined as the individual's first MI. When features of MI occur in the first 28 days after an incident event, the second event is not counted as a new MI for epidemiological purposes. If characteristics of MI occur after 28 days following an incident MI, it is considered to be a recurrent MI.[11]

15. RE-INFARCTION

The term re-infarction is used clinically for an acute MI that occurs within 28 days of an incident or recurrent MI.[11] The ECG diagnosis of suspected re-infarction following the initial MI may be confounded by the initial evolutionary ECG changes. Re-infarction should be considered when ST-elevation ≥ 1 mm recurs or new pathognomonic Q waves appear in at least two contiguous leads, particularly when associated with ischaemic symptoms. However, re-elevation of the STsegment can also be seen in threatened myocardial rupture or in cases of pericarditis, and should lead to additional diagnostic evaluation.

In patients where re-infarction is suspected from clinical signs or symptoms following the initial MI, an immediate measurement of cTn is recommended. A second sample should be obtained 3–6 h later or earlier with more sensitive cTn assays. If the cTn concentration is elevated, but stable or decreasing at the time of suspected re-infarction, the diagnosis of re-infarction requires a > 20% increase of the cTn value in the second sample.[74] If the initial cTn concentration is normal, the criteria for new acute MI apply.[12]

16. MYOCARDIAL INJURY AND INFARCTION ASSOCIATED WITH CARDIAC PROCEDURES OTHER THAN REVASCULARIZATION

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Cardiac procedures such as transcatheter valve interventions may cause myocardial injury, both by direct trauma to the myocardium and by creating regional ischaemia secondary to coronary obstruction or embolization. Ablation of arrhythmias involves controlled procedural myocardial injury by application of warming or cooling of the tissue. The extent of procedural myocardial injury can be assessed by serial cTn measurements. Increases of cTn values in this context should be considered as a procedural myocardial injury and not labelled as an MI unless the biomarker criteria and one of the ancillary criteria for acute myocardial ischaemia listed for type 5 MI are present.[75,76]

17. MYOCARDIAL INJURY AND INFARCTION ASSOCIATED WITH NON-CARDIAC PROCEDURES

Perioperative MI is one of the most important complications in major non-cardiac surgery and it is associated with a poor prognosis.[77,78] Most patients who have a perioperative MI will not experience ischaemic symptoms due to anaesthesia, sedation, or pain relieving medications. Nevertheless, asymptomatic perioperative MI is as strongly associated with 30 day mortality as symptomatic MI.[77,78] Knowledge about hs-cTn values at baseline can help to identify patients having chronic cTn elevation before surgery, as well as those at increased risk during and after the procedure.[79,80] Measurement of hs-cTn in post-operative samples reveals

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Circulation. 2018;138:00–00. DOI: 10.1161/CIR.0000000000000617

that as many as 35% of patients have levels above the 99th percentile URL, and 17% have an elevation and a rising pattern of values indicative of evolving myocardial injury.[81] Those with a rising pattern of elevated hs-cTn values are at particular risk; the greater the rise, the greater the risk.[82,83]

The pathophysiological mechanism of perioperative MI is subject to debate. It is recognized that the perioperative period is characterized by increased cardiac metabolic demand that may lead to MI in patients with otherwise stable CAD.[84,85] Thus, an angiographic investigation has identified demand myocardial ischaemia as the predominant aetiology of perioperative MI,[84,85] which together with a rise and/or fall of cTn values indicates type 2 MI. However, other angiographic studies have detected coronary plaque rupture in 50–60% of patients with perioperative MI,[86,87] which qualifies as type 1 MI. On the other hand, perioperative myocardial injury without ancillary ischaemic evidence indicative of MI is a common complication after non-cardiac surgery that is associated with substantial shortand long-term mortality on a level with perioperative MI.[83]

Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the aetiology of elevated postoperative values, a baseline pre-operative value is necessary to determine whether the increase is acute or more chronic. However, a diagnosis of MI still requires, in addition to an increase of cTn values, evidence of myocardial ischaemia that may be evident from the periand post-operative period, e.g. ST-segment changes on telemetry/ECG, repeated episodes of hypoxia, hypotension, tachycardia, or imaging evidence of MI. In the absence of evidence for acute myocardial ischaemia, a diagnosis of acute myocardial injury is more appropriate. Ongoing research suggests the possibility that interventions may be helpful in this clinical situation.

18. MYOCARDIAL INJURY OR INFARCTION ASSOCIATED WITH HEART FAILURE

Depending on the assay used, detectable to clearly elevated cTn values being indicative of myocardial injury may be seen in patients with heart failure (HF), both with reduced ejection fraction (EF) and with preserved EF.[88] Using hs-cTn assays, measurable hs-cTn concentrations may be present in nearly all patients with HF, with a significant percentage exceeding the 99th percentile URL, particularly in those patients with more severe HF syndromes, such as in acutely decompensated HF.[87]

Beyond type 1 MI, multiple mechanisms have been proposed to explain measurable to pathologically elevated cTn concentrations in patients with HF.[88,89] For example, type 2 MI may result from increased transmural pressure, small-vessel coronary obstruction, endothelial dysfunction, anaemia, or hypotension. Besides type 1 MI or type 2 MI, cardiomyocyte apoptosis and autophagy due to wall stretch have been experimentally demonstrated. Direct cellular toxicity related to inflammation, circulating neurohormones, and infiltrative processes may present with HF and abnormal cTn measurements indicating myocardial injury. Finally, exocytosis of the early releasable cytosolic troponin pool into the blood stream from stressed cardiomyocytes has also been suggested as a cause of elevated cTn values.[89]

In the context of an acutely decompensated HF presentation, cTn should always be promptly measured and the ECG recorded, with the goal of identifying or excluding myocardial ischaemia as the precipitant. In this setting, elevated cTn values should be interpreted with a high level of suspicion for type 1 MI if a significant rise and/or fall of the marker is seen, especially if it is accompanied by chest discomfort or other symptoms suggestive of myocardial ischaemia, and/ or if new ischaemic ECG changes or loss of myocardial function on non-invasive testing are found. Shortness of breath, the cardinal symptom of acutely decompensated HF, may be an ischaemic equivalent, but in the absence of corroborating evidence for a coronary mechanism, caution is advised in its interpretation. Coronary artery anatomy may be known and this knowledge may be used to interpret abnormal cTn results. However, further information—such as renal function, myocardial perfusion studies, coronary angiography, or CMR—is often required to better understand the cause of deviant cTn values.

19. TAKOTSUBO SYNDROME

Takotsubo syndrome (TTS) can mimic MI and is found in 1–2% of patients presenting with suspected STEMI.[90] The onset of TTS is often triggered by intense emotional or physical stresses, such as bereavement. Over 90% of patients are post-menopausal women. Cardiovascular complications occur in 50% of patients presenting with TTS, and the inpatient mortality is similar to STEMI (4–5%) due to cardiogenic shock, ventricular rupture, or malignant arrhythmias.[90] TTS usually presents similar to ACS. ST-segment elevation is frequent (44%), but the extent of the ST-segment elevation is usually widespread across the lateral and precordial leads, beyond that of a single coronary artery distribution. ST-segment depression occurs in < 10% of patients and after 12–24 h, deep, symmetric T wave inversion and QTc prolongation are typically observed.[91,92]

There are usually transient elevations in cTn levels (> 95% of cases), but the peak cTn values observed are modest, and contrast with the large territory of ECG changes or left ventricular (LV) dysfunction. The rise

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and fall in cTn levels support an acute myocardial injury, secondary to the high catecholamine surges that are known to trigger cTn release from cardiomyocytes. Coronary vasospasm, high myocardial strain hypercontractility, or high ventricular afterload may also contribute to myocardial ischaemia. The diagnosis of TTS should be suspected when the clinical manifestations and ECG abnormalities are out of proportion to the degree of elevation of cTn values, and when the distribution of the LV wall motion abnormalities does not correlate with a single coronary artery distribution. However, coronary angiography and ventriculography are often needed to secure the diagnosis.

In most cases, the coronary arteries are angiographically normal, and where CAD is present (15% cases) it is not sufficient to explain the observed pattern of regional wall motion abnormalities. Left ventriculography during catheterization and/or echocardiography may show a variety of LV regional wall motion abnormalities including apical (82% of patients), mid-ventricular (14.6%), basal (2.2%), or focal (1.5%) akinesis or hypokinesis in a circumferential pattern involving more than one coronary artery territory. Evidence of myocardial oedema is often seen on CMR imaging during the acute phase but LGE is usually absent. The recovery time for LV function varies from hours to several weeks.[93] Cardiac function may not return to normal, with persisting abnormalities of diastolic function, myocardial reserve during exercise, or rhythm disturbances at long-term follow-up in 10–15% of patients. In the absence of recovery of regional wall motion abnormalities, LGE-CMR is recommended to exclude MI with spontaneous recanalization.

The distinction between MI and TTS can be challenging, particularly when concurrent CAD is present (15% in the International Takotsubo Registry).[91] Two additional features that are helpful in distinguishing TTS from acute MI are QTc prolongation > 500 ms during the acute phase and the recovery of LV function over 2–4 weeks. There are rare cases described where MI and TTS coexist, e.g. MI-induced TTS or TTS with secondary plaque rupture, but this occurs where the acute regional wall motion abnormalities are more extensive than the culprit coronary artery territory, and fulfil the pattern and definition of TTS.[94]

20. MYOCARDIAL INFARCTION WITH NON-OBSTRUCTIVE CORONARY ARTERIES

It is increasingly recognized that there is a group of MI patients with no angiographic obstructive CAD (≥ 50% diameter stenosis in a major epicardial vessel), and the term myocardial infarction with nonobstructive coronary arteries (MINOCA) has been coined for this entity.[95,96] The diagnosis of MINOCA, like the diagnosis of MI, indicates that there is an ischaemic mechanism responsible for the myocyte injury (i.e. non-ischaemic causes such as myocarditis have been excluded). Furthermore, the diagnosis of MINOCA necessitates that obstructive CAD has not been inadvertently overlooked (e.g. spontaneous coronary artery dissection). The prevalence of MINOCA is estimated to be 6–8% among patients diagnosed with MI and more common in women than men, as well as in patients presenting with NSTEMI compared with those presenting with STEMI.[96–98] Atherosclerotic plaque disruption and coronary thrombosis may be a cause of MINOCA, i.e. type 1 MI. However, coronary spasm and spontaneous coronary dissection may be involved as well, i.e. type 2 MI, along with other possible causes. Additional coronary imaging and functional testing methods may be useful to elucidate the mechanisms of ischaemia in MINOCA.[46]

21. MYOCARDIAL INJURY AND/OR INFARCTION ASSOCIATED WITH KIDNEY DISEASE

Many patients with chronic kidney disease (CKD) have elevation of cTn values.[99,100] With hs-cTn assays, the majority of patients with end-stage renal disease will have elevation of hs-cTn values above the 99th percentile URL.[99,101] This is particularly the case for hs-cTnT, which is more often elevated compared with hs-cTnI.[99,102] It has been shown using hs-cTn assays that renal dysfunction is commonly associated with cardiovascular abnormalities.[102–104] In autopsy studies, elevation of cTn values was invariably associated with evidence of myocardial injury.[15] Recently, a minor effect on renal clearance of cTn has been shown when levels are low, but not in response to acute episodes of myocardial injury.[105] The mechanisms include increased ventricular pressure, small-vessel coronary obstruction, anaemia, hypotension, and possibly direct toxic effects on the myocardium associated with the uraemic state.[89] Cardiomyocyte apoptosis and autophagy due to acute wall stretch have been demonstrated experimentally.[18] Thus, baseline elevation of cTn values is common, and because they reflect myocardial injury, such elevation is highly prognostic over time.[99]

Diagnosing MI in patients with CKD and elevated cTn levels may be difficult if symptoms or ECG changes indicating myocardial ischaemia are absent. However, studies suggest that serial changes in cTn levels are equally effective in diagnosing MI in patients with CKD and in those with normal renal function.[106] If the level of elevated cTn values is unchanging, and the timing of the event makes a rising and/or falling pattern unlikely, the elevated level, even if substantial, is likely a reflection of chronic myocardial injury. This does not imply

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that these patients are free of CAD, since renal dysfunction and CAD are correlated. However, if a rising and/or falling pattern is present then the aetiology of the abnormal cTn values could be acute volume overload, congestive HF, or MI. If a rising and falling pattern is seen, and it is accompanied by ischaemic symptoms, new ischaemic ECG changes, or loss of viable myocardium on imaging, a diagnosis of acute MI is likely. There are no data to suggest that different criteria for the cTn decision levels are needed for these patients. At times, additional imaging studies may be necessary to determine the appropriate diagnosis. It should be noted that if CKD patients present late after the onset of chest pain, it may be difficult to observe a rise and/or fall of cTn values in the short-term, particularly when the baseline value is elevated. Such a situation should not obviate the diagnosis of MI when the clinical evidence is strong.

22. MYOCARDIAL INJURY AND/OR INFARCTION IN CRITICALLY ILL PATIENTS

Elevations of cTn values are common in patients in the intensive care unit and are associated with adverse prognosis regardless of the underlying disease state.[107,108] Some elevation of cTn values may reflect type 2 MI due to underlying CAD and increased myocardial oxygen demand,[109] whereas in other patients, type 1 MI may occur because of plaque disruption leading to thrombosis in a coronary artery. However, other patients may have elevated cTn values and marked decreases in EF due to sepsis caused by endotoxin, with myocardial function recovering completely with normal EF once the sepsis is treated. It is frequently challenging for the clinician caring for a critically ill patient with a severe single organ or multiorgan pathological condition to decide on a plan of action when the patient has elevated cTn values. If and when the patient recovers from the critical illness, clinical judgement should be employed to decide whether, and to what extent, further evaluation for CAD or structural heart disease is indicated.[110]

23. BIOCHEMICAL APPROACH FOR DIAGNOSING MYOCARDIAL INJURY AND INFARCTION

cTnI and cTnT are the preferred biomarkers recommended to both rule in and rule out myocardial injury, and thus to define MI and each specific subtype of MI.[12,22,23,31] Detection of a rise and/or fall of cTn values is essential, and a key early component along with other elements of the clinical evaluation to establish the diagnosis of acute MI. Criteria for determining a pathological rise between two serial cTn values are assay-dependent and continue to evolve. An idealized view of troponin kinetics in patients with acute MI is shown in *Figure 7*.

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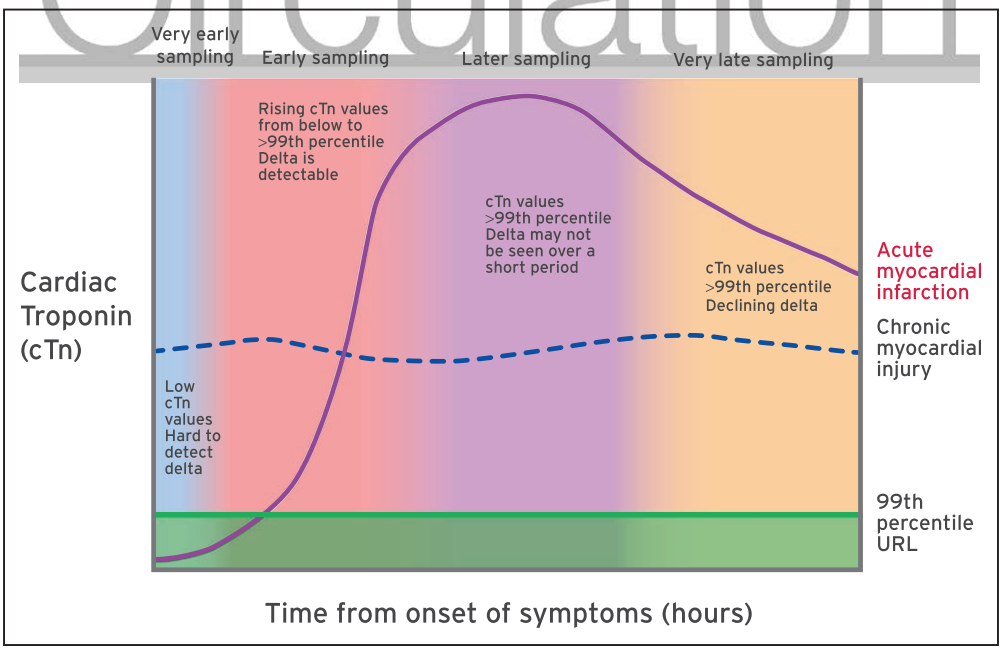

Figure 7. Illustration of early cardiac troponin kinetics in patients after acute myocardial injury including acute myocardial infarction.
The timing of biomarker release into the circulation is dependent on blood flow and how soon after the onset of symptoms samples are obtained. Thus, the ability to consider small changes as diagnostic can be problematic. In addition, many comorbidities increase cTn values and, in particular, hs-cTn values, so that elevations can be present at baseline even in those with myocardial infarction who present early after the onset of symptoms. Changes in cTn values or deltas can be used to define acute compared with chronic events, and the ability to detect these is indicated in the figure. Increased cTn values can often be detected for days after an acute event. cTn = cardiac troponin; URL = upper reference limit.

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It should be appreciated that because biomarker release is substantially dependent on blood flow,[111,112] there is significant variability in the time to peak value (velocity), the time when a normal value may become greater than the 99th percentile URL, or when a changing pattern of values can be observed. The ability to define a changing pattern will also depend on timing. For example, around peak values, it may be difficult to observe a changing pattern of values. Similarly, the downslope of the time–concentration curve is much slower than the upslope. These issues need to be taken into account when defining whether or not a changing pattern is present. In addition, it is important to make sure that a given change is greater than can be anticipated by variability alone. This is defined for conventional cTn assays as a change greater than or equal to three times the standard deviation around the measurement of the individual assay at relevant values.[12,22] For hs-cTn assays, biological variation also needs to be considered. In most studies, conjoint analytical and biological variation is in the range of 50–60%.

For that reason, this percentage has been suggested for use when initial baseline values are ≤ the 99th percentile URL.[23,31,113] However, for individuals with an initial value greater than the 99th percentile URL, a lesser degree of change during serial measurements is necessary to achieve improved clinical sensitivity (as compared with individuals with initial values ≤ the 99th percentile URL). Thus, an expert consensus group has recommended serial changes > 20% be used in this situation.[22] Absolute changes are assay dependent but appear superior to relative per cent changes with hs-cTn assays,[114] and in some studies this is especially the case when the initial value is increased.[115] The use of a fixed absolute value change criteria translates into a smaller percentage or relative change as absolute values rise, and therefore provides greater sensitivity. The use of a changing pattern is important in allowing clinicians to differentiate an acute from a chronic cTn increase above the 99th percentile URL.[113–115] Using criteria less than conjoint analytical and biological variation will reduce the clinical specificity of hs-cTn assays.[113,116] An imprecision of ≤ 10% coefficient of variation (CV) at the 99th percentile URL is also mandatory for hs-cTn assays.[31] The use of non-hs-cTn assays that do not have imprecision (≤ 10% CV at the 99th percentile URL) makes the determination of a significant serial change more difficult but does not cause false positive results. Assays with CVs between 10–20% are acceptable for clinical use. However, assays with CVs>20% at the 99th percentile URL should not be used.[117]

If a cTn assay is not available, the best alternative is CK-MB measured by a mass assay. As with cTn, an increased CK-MB value is defined as a measurement above the 99th percentile URL, which is designated as the decision level for the diagnosis of MI. Sex-specific CK-MB values should be employed.[118]

24. ANALYTICAL ISSUES OF CARDIAC TROPONINS

The analytical sensitivity [limit of detection (LoD)] of cTnI and cTnT assays varies 10-fold.[31,119] Because assays are not standardized, values from one assay cannot be directly compared with those from another assay. Furthermore, values may be different between assay generations[120] and changes can even occur when the same assay reagents are measured on different instruments.[121] Thus, clinicians must learn about their local assay and should look for reliable information, e.g. available on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) website (http://www.ifcc.org/executive-board-and-council/eb-task-forces/task-force-on-clinical-applications-of-cardiac-bio-markers-tf-cb/), when they have questions concerning analytical issues. The current guidelines accommodate all assays, whether hs-cTn, contemporary (conventional) cTn, or point of care (POC) cTn. While hs-cTn assays are able to measure relatively low values and document small increases above the 99th percentile URL, many contemporary and POC cTn assays may not detect small increasing values within the reference interval or slightly above the 99th percentile URL, leading to substantial differences in the frequency of events based solely on the cTn assay used. These differences are amplified when multiples of the 99th percentile URL are used. At present, IFCC guidelines support the concept that hs-cTn assays are differentiated from contemporary or POC cTn assays by their ability to measure cTn values above the assay's LoD in > 50% of healthy individuals.[31,118,119,122] This provides a rough estimate of assay sensitivity. It is recommended that values for cTn assays be reported as whole numbers in nanograms per litre to avoid interpretation problems associated with multiple zeros and decimal points that can often result in confusion.[31] Clinicians should avoid mixing the units from contemporary assays with those from hs-cTn assays. All assays, including cTn assays, have some analytical problems resulting in false positive and false negative results, but these are uncommon (< 0.5%).[22] These problems are less common with hs-cTn assays.[23]

Conjoint biological and analytical variation of hs-cTn assays is in the range of 50–60%.[123] When values are elevated, analytical variation is less and a value of 20% can be used to determine that values are stable in the proper clinical context. For example, changes may be difficult to observe over short periods of time in those who present early after the onset of symptoms of acute MI, those who present late and are on the downslope of the time-concentration curve, and those who have

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values near peak where they may be transitioning from a rising to a falling pattern.[113,123]

25. THE 99TH PERCENTILE UPPER REFERENCE LIMIT

The 99th percentile URL is designated as the decision level for the presence of myocardial injury and must be determined for each specific assay with quality control materials used at the URL to validate appropriate assay imprecision. The cTn assay 99th percentile URL values used in clinical practice and research can be found both in manufacturers' package inserts, in peer-reviewed publications, and on the IFCC website.[118–120] Clinicians should be aware that for all cTn assays, including hs-cTn assays, there is still no expert opinion or consensus about specific criteria for how the 99th percentile URL should be defined.[124] We endorse IFCC guidelines on the technical issues related to hs-cTn assays, including how studies should be configured to determine 99th percentile URLs.[120] The guidelines include the clinical or surrogate biomarker screening that may be needed to better define the 99th percentile URL and the statistical methods that can be applied, but do not include a requirement for cardiac imaging.[120] Screening of apparently healthy subjects with imaging has been shown to lower the observed 99th percentile URL value, but is not a practical standard for the *in vitro* diagnostic industry to use.[124,125] Thus, there is the possibility of false negative values using the manufacturer's reported 99th percentile URL values. hs-cTn assays demonstrate shifts to higher values for the 99th percentile URL in association with comorbidities and age over > 60 years.[101,125–127] However, at present, age-dependent cut-off points are not recommended for clinical use. Clinicians should rely instead on changing values during serial measurements of cTn for the diagnosis of acute myocardial injury, including MI. Significantly lower values are observed among women compared with men, and therefore sex-specific 99th percentile URLs are recommended for hs-cTn assays.[31,118–120] For some hs-cTn assays, sex-specific cut-off values have been reported to improve diagnostic and prognostic information in patients with possible acute MI.[128,129] However, there is controversy as to whether this approach provides valuable additional information for all hs-cTn assays.[130]

26. OPERATIONALIZING CRITERIA FOR MYOCARDIAL INJURY AND INFARCTION

Blood samples for the measurement of cTn should be drawn on first assessment (designated as 0 h) and repeated 3–6 h later, or earlier with hs-cTn assays. The sampling interval will impact the clinical cut-off at baseline and what is determined to be a pathological rise and/or fall of the biomarker. Sampling beyond 6 h may be required if further ischaemic episodes occur, or in high-risk patients. To establish the diagnosis of an acute MI, a rise and/or fall in cTn values with at least one value above the 99th percentile URL is required, coupled with a high clinical and/or ECG likelihood of myocardial ischaemia. hs-cTn assays shorten the time to diagnosis in many patients to within 3 h of onset of symptoms, but there are still some patients who may rule in late (at 6 h).[131] Furthermore, some patients with acute myocardial injury presenting late after the onset of acute MI (> 12–18 h) and who are on the downslope of the time-concentration curve may require longer periods of time for a changing pattern to be detected.[131] In addition, it should be noted that with the implementation of cTn and hs-cTn assays, the frequency of unstable angina will decrease and the diagnosis of NSTEMI will increase.[132,133] The magnitude of these changes using hs-cTn assays have been reported in the range of 18–30%.[134] Assuming proper timing of symptoms, acute ischaemia should result in a change in hs-cTn; however, there may be patients in whom it is difficult to ascertain the timing of symptom onset. Thus, despite typical chest discomfort, these patients may have hs-cTn values that are not elevated. Other patients with symptoms suggestive of unstable angina may have increased hs-cTn values as a result of structural heart disease with or without acute myocardial ischaemia. This latter group may be particularly difficult to distinguish from patients presenting with late NSTEMI with a slow decline in troponin values that can be observed in late presenters.[131] Finally, some patients may manifest a changing pattern of troponin values with a magnitude that does not exceed the delta suggested for diagnosis or who fail to manifest a value greater than the 99th percentile URL. This is a group of patients that deserves close scrutiny because they may be at high risk. The triage of these patients can only be accomplished based on clinical evaluation.

Strategies employing either very low levels of hs-cTn on presentation or the lack of any change and persistently normal hs-cTn values over a 1–2 h period after presentation have been advocated to exclude acute myocardial injury, and MI as well. A single sample rule out strategy using a very low value (in many cases the LoD of the assay) has high sensitivity for myocardial injury and therefore high negative predictive value to exclude MI.[135] This strategy should not be used in those who present early, i.e. < 2 h after the onset of chest discomfort. Some studies indicate that the single sample approach provides optimal sensitivity and negative predictive accuracy in patients otherwise at low risk and those with a normal ECG.[136–138] However, one concern about very short rule out periods is that

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the precision of the assays may not permit small differences to be distinguished.[139–142] These criteria have not, and should not, be applied to patients with hs-cTn elevations.

The clinical specificity and positive predictive value of such 1–2 h sampling approaches for ruling in MI are limited by the substantial proportion of individuals who meet the proposed biomarker criteria with diagnoses other than MI.[136,141] Thus, the use of a rapid rule in/ out MI protocol does not absolve the clinician from considering other causes of acute myocardial injury.[142] In addition, considering a broader population of patients—inclusive of those who present atypically, those with end-stage renal disease, and the critically ill—the cut-off points to be used will likely need to be altered.[139] Such patients have been excluded from the majority of emergency department evaluation studies.[108,136,142]

The demonstration of a rising and/or falling pattern is needed to distinguish acute injury from chronic conditions associated with structural heart disease that can have chronic increases of cTn values. For example, patients with renal failure[99,143,144] or LV hypertrophy[145] can have significant chronic increases in cTn values. These increases can be marked but do not change acutely during serial sampling. However, a falling pattern may take longer to be observed in patients with a high pre-test risk of MI who present late after symptom onset.[146] These patients who have cTn values on the downslope of the time–concentration curve have a slow decline in values (*Figure 7*). Thus, detecting a changing pattern over short periods of time may be difficult.[117] Depending on the extent of myocardial injury, cTn values may remain above the 99th percentile URL for a longer period of time.[22,23] An increased cTn value above the 99th percentile URL, with or without a dynamic change of values, or in the absence of clinical evidence of ischaemia, should prompt a search for other diagnoses associated with myocardial injury, as shown in *Table 1*.

27. ELECTROCARDIOGRAPHIC DETECTION OF MYOCARDIAL INFARCTION

The ECG is an integral part of the diagnostic workup of patients with suspected MI, and should be acquired and interpreted promptly (i.e. target within 10 min) after first medical contact.[47,147] Pre-hospital ECGs reduce the time to diagnosis and treatment, and can facilitate the triage of STEMI patients to hospitals with PCI capability if within the recommended time interval (120 min from STEMI diagnosis).[46,148] Acute myocardial ischaemia is often associated with dynamic changes in ECG waveform and serial ECG acquisition can provide critical information, particularly if the ECG at initial presentation is non-diagnostic. Recording several standard ECGs with fixed electrode positions at 15–30 min intervals for the initial 1–2 h, or the use of continuous computer-assisted 12-lead ECG recording (if available) to detect dynamic ECG changes, is reasonable for patients with persistent or recurrent symptoms or an initial non-diagnostic ECG.[149] Serial or continuous ECG recordings may be helpful in determining reperfusion or reocclusion status. Reperfusion is usually associated with a large and prompt reduction in ST-segment elevation.

More profound ST-segment shifts or T wave inversions involving multiple leads/territories are associated with a greater degree of myocardial ischaemia, and a worse prognosis. For example, ST-segment depression ≥ 1 mm in six leads, which may be associated with ST-segment elevation in leads aVR or lead V_1 and haemodynamic compromise, is suggestive evidence of multivessel disease or left main disease. Pathologic Q waves increase the prognostic risk. Other ECG signs associated with acute myocardial ischaemia include cardiac arrhythmias, intraventricular bundle branch blocks, atrioventricular conduction delays, and loss of precordial R wave amplitude, a less specific finding. The ECG by itself is often insufficient to diagnose acute myocardial ischaemia or infarction, since ST deviation may be observed in other conditions, such as acute pericarditis, LV hypertrophy (LVH), left bundle branch block (LBBB), Brugada syndrome, TTS, and early repolarization patterns.[150] A prior ECG is often helpful in distinguishing a new from a chronic finding, but should not delay the decision for treatment.

Prolonged new convex ST-segment elevation, particularly when associated with reciprocal ST-segment depression, usually reflects acute coronary occlusion and results in myocardial injury with necrosis. Reciprocal changes can help to differentiate STEMI from pericarditis or early repolarization changes. As in cardiomyopathy, Q waves may also occur due to myocardial fibrosis in the absence of CAD. Some of the earlier manifestations of myocardial ischaemia are typical T wave and ST-segment changes. Increased hyperacute T wave amplitude, with prominent symmetrical T waves in at least two contiguous leads, is an early sign that may precede the elevation of the ST-segment. In general, the development of new Q waves indicates myocardial necrosis, which starts minutes/hours after the myocardial insult. Transient Q waves may be observed during an episode of acute ischaemia or (rarely) during acute MI with successful reperfusion. *Table 2* lists ST-segment–T wave (ST-T) criteria suggestive of acute myocardial ischaemia that may or may not lead to MI. The J-point (junction between QRS termination and ST-segment onset) is used to determine the magnitude of the ST-segment shift with the onset of the QRS serving as the reference point. In patients with a stable baseline, the TP segment (isoelectric interval) is a more accurate method to assess

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the magnitude of ST-segment shift, and in distinguishing pericarditis (PTa depression) from acute myocardial ischaemia. Tachycardia and baseline shift are common in the acute setting and can make this determination difficult. Therefore, QRS onset is recommended as the reference point for J-point determina-tion (*Figure 8*).

New, or presumed new, J-point elevation ≥ 1 mm (1 mm = 0.1 mV) is required in all leads other than V_2 and V_3 as an ischaemic response. In healthy men under age 40, J-point elevation can be as much as 2.5 mm in leads V_2 or V_3, but it decreases with increasing age. Sex differences require different cut-off points for women, since J-point elevation in healthy women in leads V_2 and V_3 is less than in men.[5] The criteria in *Table 2* require that the ST shift be present in two or more contiguous leads. For example, ≥ 2 mm of ST-elevation in lead V_2 and ≥ 1 mm in lead V_1 would meet the criteria of two abnormal contiguous leads in a man ≥40 years old. However, ≥ 1mm and < 2 mm of ST-elevation, seen only in leads V_2–V_3 in men (or < 1.5 mm in women), may represent a normal finding.

It should be noted that lesser degrees of ST displacement or T wave inversion than those described in *Table 2* can also represent anacute myocardial ischaemic response. In patients with known or high likelihood of CAD, the clinical presentation is critical to enhance the specificity of these findings.

Absence of ST-elevation in the precordial leads, tall, prominent, symmetrical T waves in the precordial leads, upsloping ST-segment depression > 1 mm at the J-point in the precordial leads, and in most cases ST-segment elevation (> 1 mm) in lead aVR or the symmetrical, often deep (> 2 mm), T wave inversions in the anterior precordial leads are associated with significant left anterior descending artery (LAD) occlusion.[151–153] ST-elevation in lead aVR > 1 mm may accompany anterior or inferior STEMI, and is associated with increased 30 day mortality in patients with acute MI.[154] Pulmonary embolism, intracranial processes, electrolyte abnormalities, hypothermia, or perimyocarditis may also result in ST-T abnormalities and should be considered in the differential diagnosis.

The ECG diagnosis of atrial infarction should be suspected in the context of ventricular infarction (particularly when the right ventricle is involved) if small, transient elevations and reciprocal depressions of the PR (PTa) segment are noted associated with changes in configuration of the P wave.

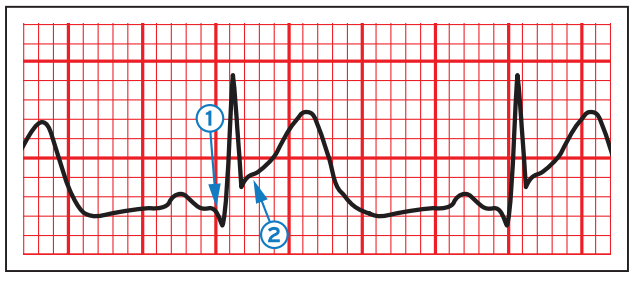

Figure 8. Electrocardiogram example of ST-segment elevation.
The initial onset of the Q wave shown by arrow 1 serves as the reference point and arrow 2 shows the onset of the ST-segment or J-point. The difference between the two identifies the magnitude of displacement. Measurements of both arrows should be made from the top of the electrocardiogram line tracing.

Table 2. Electrocardiographic Manifestations Suggestive of Acute Myocardial Ischaemia (In the Absence of Left Ventricular Hypertrophy and Bundle Branch Block)

ST-elevation
New ST-elevation at the J-point in two contiguous leads with the cut-point: ≥ 1 mm in all leads other than leads V_2–V_3 where the following cut-points apply: ≥ 2 mm in men ≥ 40 years; ≥ 2.5 mm in men < 40 years, or ≥ 1.5 mm in women regardless of age.[a]
ST-depression and T wave changes
New horizontal or downsloping ST-depression ≥ 0.5 mm in two contiguous leads and/or T inversion > 1 mm in two contiguous leads with prominent R wave or R/S ratio > 1.

[a]When the magnitudes of J-point elevation in leads V_2 and V_3 are registered from a prior electrocardiogram, new J-point elevation ≥ 1 mm (as compared with the earlier electrocardiogram) should be considered an ischaemic response. For bundle branch block, see section below.

28. APPLICATION OF SUPPLEMENTAL ELECTROCARDIOGRAM LEADS

Supplemental leads, as well as serial ECG recordings, should be deployed with a very low threshold in patients who present with ischaemic chest pain and a non-diagnostic initial ECG.[155,156] ECG evidence of myocardial ischaemia in the distribution of a left circumflex artery is often overlooked. Isolated ST-segment depression ≥ 0.5 mm in leads V_1–V_3 may indicate left circumflex occlusion and can best be captured using posterior leads at the fifth intercostal space (V_7 at the left posterior axillary line, V_8 at the left mid-scapular line, and V_9 at the left paraspinal border). Recording of these leads is strongly recommended in patients with high clinical suspicion of acute circumflex occlusion (e.g. initial ECG non-diagnostic or ST-segment depression in leads V_1–V_3).[156] A cut-off point of 0.5 mm ST elevation is recommended in leads V_7–V_9; specificity is increased at a cut-off point ≥ 1 mm ST-elevation and this cut-off point should be used in men < 40 years old. ST-segment depression in leads V_1–V_3 may be suggestive of inferobasal myocardial ischaemia (previously termed posterior infarction), especially when the terminal T wave is positive (ST-elevation equivalent); however, this is non-specific.

In patients with inferior and suspected right ventricular infarction, leads aVR or V_1 may exhibit ST-segment elevation ≥1 mm. The early recording of right precordial leads V_3R and V_4R should be performed, since ST-elevation ≥ 0.5 mm (≥ 1 mm in men < 30 years old) provides supportive criteria for the diagnosis.[157] Changes in right

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precordial leads may be transient, and an absence of ECG changes in leads V_3R and V_4R does not exclude right ventricular infarction. Myocardial imaging can be helpful in this clinical setting.

29. ELECTROCARDIOGRAPHIC DETECTION OF MYOCARDIAL INJURY

It is not possible to initially distinguish ECG manifestations of acute or chronic myocardial injury from acute myocardial ischaemia. Rapidly developing dynamic ECG changes that temporally match the clinical presentation may be helpful in diagnosing a symptomatic patient with elevated cTn values as having acute myocardial ischaemia resulting in MI. However, ECG abnormalities are also common in patients who have myocardial injury, e.g. myocarditis or TTS.[158–160]

30. PRIOR OR SILENT/UNRECOGNIZED MYOCARDIAL INFARCTION

Q wave criteria associated with MI and an increased relative risk of death are illustrated in *Table 3*, and are contained in Q wave coding algorithms such as the Minnesota Code and the WHO MONItoring of trends and determinants in CArdiovascular disease (MONICA) code[11,161,162]

The specificity of the ECG diagnosis for MI is greatest when Q waves occur in several leads or lead groupings, or are > 0.04 s. When the Q waves are associated with ST deviations or T wave changes in the same leads, the likelihood of MI is increased; for example, minor Q waves ≥ 0.02 s and < 0.03 s that are ≥ 1 mm deep are suggestive of prior MI if accompanied by inverted T waves in the same lead group. Non-invasive imaging techniques also provide important supportive evidence of prior MI. In the absence of non-ischaemic causes, regional myocardial thinning, scar or reduced wall motion shown by echocardiography, myocardial perfusion scintigraphy (MPS) with single photon emission computed tomography (SPECT) or positron emission tomography (PET), or magnetic resonance imaging provide strong evidence for prior MI, particularly when ECG criteria are equivocal.

Table 3. Electrocardiographic Changes Associated With Prior Myocardial Infarction (In the Absence of Left Ventricular Hypertrophy and Left Bundle Branch Block)

Any Q wave in leads V_2–V_3 > 0 .02 s or QS complex in leads V_2–V_3.
Q wave ≥ 0 .03 s and ≥ 1 mm deep or QS complex in leads I, II, aVL, aVF or V_4–V_6 in any two leads of a contiguous lead grouping (I, aVL; V_1–V_6; II, III, aVF).[a]
R wave > 0 .04 s in V_1–V_2 and R/S > 1 with a concordant positive T wave in absence of conduction defect.

[a]The same criteria are used for supplemental leads V_7–V_9. s = seconds.

Asymptomatic patients who develop new Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging that cannot be directly attributed to an interim coronary revascularization procedure or an ACS admission, should be termed 'silent or unrecognized MI'. In studies where serial ECG analysis was applied, silent or unrecognized Q wave MI accounted for 9–37% of all non-fatal MI events and was associated with a significantly increased mortality risk.[163,164] Improper lead placement, QRS abnormalities, or technical errors (e.g. lead reversal) may result in the appearance of new Q waves or QS complexes, as compared with a prior tracing. Thus, the diagnosis of a new silent Q wave MI should be confirmed by a repeat ECG recording with correct lead placement, focused questioning about potential interim ischaemic symptoms, or by an imaging study. Imaging techniques are useful if there is abnormal myocardial motion, thickening, or thinning in the region of interest, but the absence of these does not exclude MI.[165]

Criteria for Prior or Silent/Unrecognized MI

Any one of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Pathological Q waves as described in *Table 3*, with or without symptoms, in the absence of non-ischaemic causes;
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology;
- Pathological findings of a prior MI.

31. CONDITIONS THAT CONFOUND THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF MYOCARDIAL INFARCTION

A QS complex in lead V_1 is normal. A Q wave < 0.03 s and < 0.25 of the R wave amplitude in lead III is normal if the frontal QRS axis is between –30° and 0°. A Q wave may also be normal in aVL if the frontal QRS axis is between 60–90°. Septal Q waves are small, nonpathological Q waves < 0.03 s and < 0.25 of the R-wave amplitude in leads I, aVL, aVF, and V_4–V_6. Preexcitation, cardiomyopathy, TTS, cardiac amyloidosis, LBBB, left anterior hemiblock, LVH, right ventricular hypertrophy, myocarditis, acute cor pulmonale, or hyperkalaemia may be associated with Q waves or QS complexes in the absence of MI. Clinicians should be aware of confounders to the ECG diagnosis of myocardial ischaemia, since ST-T wave abnormalities are commonly observed with different pathological cardi-

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ac conditions, such as pre-excitation, pericarditis, and cardiomyopathy.

32. CONDUCTION DISTURBANCES AND PACEMAKERS

The diagnosis of MI is more difficult in the presence of conduction disturbances, related in part to ST-T wave changes caused by the conduction disturbance and the fact that the conduction disturbance itself may be heart-rate dependent.[166,167] Comparison to a preadmission ECG may be helpful in determining if the conduction defect or ST-T wave changes are new, as long as it does not delay time to treatment. Ischaemic symptoms, and presumed new LBBB or right bundle branch block (RBBB) that is not rate-related, are associated with an adverse prognosis. In patients with LBBB, ST-segment elevation ≥ 1 mm concordant with the QRS complex in any lead may be an indicator of acute myocardial ischaemia. Similar findings can be useful in detecting ECG evidence for acute myocardial ischaemia in patients with right ventricular paced rhythms.[167] Recording an ECG trace with the pacemaker temporarily switched off may also be useful in patients who are not pacemaker dependent, but careful interpretation of repolarization is needed due to the possible presence of stimulation-induced changes (electrical memory). The ECG diagnosis of acute myocardial ischaemia in patients with biventricular pacing is more difficult. In patients with RBBB, new or presumed new STsegment elevation ≥ 1 mm, or ST-segment or T wave abnormalities (excluding leads V_1–V_4) (*Table 2*), may indicate acute myocardial ischaemia. New, or presumed new, RBBB without associated STsegment or T wave changes is associated with thrombolysis in myocardial infarction (TIMI) 0–2 flow in as many as 66% of patients (compared with > 90% in those with ST-segment or T wave changes).[168]

33. ATRIAL FIBRILLATION

In patients with atrial fibrillation and rapid ventricular rate or paroxysmal supraventricular tachycardia, ST-segment depression or T wave inversion may occur in the absence of CAD.[169,170] The causes are not completely understood. Cardiac memory, an electrical remodelling phenomenon characterized by marked diffuse T wave inversions following periods of abnormal ventricular activation, which may also be caused by transient rate-related conduction disturbances or pacing, may explain these findings. In some patients, the tachycardia may result in an insufficient increase in coronary flow to match myocardial oxygen demand, resulting in cellular hypoxia and abnormal repolarization.[171,172] For these reasons, a patient with new-onset atrial fibrillation, elevated baseline cTn concentration, and new ST-segment depression should not automatically be classified as type 2 MI without additional information. In this clinical setting, signs of overt ischaemic symptoms, the timing of symptoms relative to atrial fibrillation onset, a changing pattern of cTn, and imaging and/or angiographic findings may be helpful in establishing the diagnosis. However, in the absence of evidence for myocardial ischaemia, the aetiology of the elevated cTn values should be attributed to myocardial injury.

34. IMAGING TECHNIQUES

Non-invasive imaging plays many roles in patients with known or suspected MI, but this section concerns only its role in the diagnosis and characterization of myocardial injury and MI. The underlying rationale is that regional myocardial hypoperfusion and ischaemia lead to a cascade of events including myocardial dysfunction, cell death, and healing by fibrosis. Important imaging parameters are therefore myocardial perfusion, myocyte viability, myocardial thickness, thickening and motion, and the effects of myocyte loss on the kinetics of paramagnetic or radio-opaque contrast agents indicating myocardial fibrosis or scar.

Commonly used imaging techniques in acute and prior MI are echocardiography, MPS using SPECT or PET, CMR, and possibly computed tomography (CT).[173] There is considerable overlap in their capabilities and each of the techniques can assess myocardial viability, perfusion, and function to a greater or lesser extent. Only the radionuclide techniques provide a direct assessment of myocyte viability because of the inherent properties of the tracers used. Other techniques provide indirect assessments of myocardial viability, such as the contractile response to dobutamine by echocardiography, or increased extracellular space secondary to myocyte loss by CMR or CT.

34.1. Echocardiography

The strength of echocardiography is the combined assessment of cardiac structure and function, in particular myocardial thickness, thickening/thinning, and motion. Regional wall motion abnormalities induced by ischaemia can be detected by echocardiography almost immediately after onset when > 20% transmural myocardial thickness is affected.[174–176] These abnormalities, when new and without alternative aetiology, support the diagnosis of MI when cTn values show a rising and/or falling pattern. Echocardiography also allows detection of non-coronary cardiac pathologies known to cause chest pain, e.g. acute pericarditis, severe aortic stenosis, and hypertrophic cardiomyopathy among others. The technique is useful in diagnosing mechanical complications in patients with MI and haemodynamic compromise (shock), or other potentially fatal entities

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such as acuteaortic dissection or massive pulmonary embolism where the clinical presentation might be similar to that seen with acute MI.

Intravenous echocardiographic contrast agents can improve visualization of the endocardial border, and can be used to assess myocardial perfusion and microvascular obstruction. Tissue Doppler and strain imaging permit the quantification of global and regional function.[177,178] Intravascular echocardiographic contrast agents that are targeted at specific molecular processes have been developed, but these techniques have not yet been applied in the setting of MI.[179]

34.2. Radionuclide Imaging

Several radionuclide tracers allow viable myocytes to be imaged directly, including the SPECT tracers ^{201}TI chloride, ^{99m}Tc sestamibi, and tetrofosmin, and the PET tracers ^{18}F 2-fluorodeoxyglucose and ^{82}Rb.[173] A strength of the radionuclide techniques is that they are the only commonly available methods for assessing viability directly, although the relatively low resolution of the images limits them for detecting the smallest areas of MI. Phantom studies suggest that myocyte loss as little as 4% of the myocardium can be detected, corresponding to 5–10 g of muscle.[180] ECG-gated imaging provides a reliable assessment of myocardial motion, thickening, and global function. Evolving radionuclide techniques relevant to the assessment of MI include imaging of sympathetic innervation using ^{123}I-labelled meta-iodobenzylguanidine,[181] imaging of matrix metalloproteinase activation in ventricular remodelling,[182,183] and the assessment of myocardial metabolism.[184]

34.3. Cardiac Magnetic Resonance Imaging

The high tissue contrast and resolution of CMR provides an accurate assessment of myocardial structure and function. Although less commonly used in the acute setting, it has similar capabilities to echocardiography in suspected MI. Paramagnetic contrast agents can be used to assess myocardial perfusion and the increase in extracellular space that is associated with the fibrosis of prior MI (detected by LGE-CMR). These techniques have been used in the setting of acute MI[185,186] and localized delay in contrast enhancement is able to detect even small areas of subendocardial MI, thought to be as little as 1 g.[187] CMR also has the ability to identify the presence and extent of myocardial oedema/inflammation, allowing the distinction of acute vs. chronic myocardial injury. The patterns of LGE when reflecting ischaemic and non-ischaemic myocardial injury are shown in *Figure 9*.

The gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scarring (white arrows). The different patterns of scarring are divided into ischaemic and non-ischaemic. Typically, an ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely, a non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel).

34.4. Computed Tomographic Coronary Angiography

Infarcted myocardium is initially visible as a focal area of decreased LV myocardial enhancement, but later imaging shows hyperenhancement as with LGE-CMR.[188] This finding is clinically relevant because contrastenhanced CT may be performed for suspected pulmonary embolism and aortic dissection, conditions with clinical features that overlap with those of acute MI, but the technique is not used routinely. Similarly, CT assessment of myocardial perfusion is technically feasible but not widely applied.[189] CT coronary angiography (CTCA) may be used to diagnose CAD in patients with an ACS in the emergency department or chest pain unit, particularly in low- to intermediate-risk patients with normal cTn at presentation.[189–193] The only randomized trial in these patients that included both hs-cTn and CTCA found that imaging did not reduce the length of stay in hospital, but it did decrease subsequent outpatient testing and costs.[189] A diagnosis of MI cannot be established based on a CTCA scan alone.

35. APPLYING IMAGING IN ACUTE MYOCARDIAL INFARCTION

Imaging techniques can be useful in the diagnosis of acute MI because of the ability to detect wall motion abnormalities or loss of viable myocardium in the presence of elevated cardiac biomarker values. Demonstration of new loss of myocardial viability in the absence of non-ischaemic causes supports the diagnosis of MI. Normal function practically excludes significant MI, but a small MI cannot be ruled out.[194] Thus, imaging techniques are useful for early triage and discharge of patients with suspected MI. However, if biomarkers have been measured at appropriate times and are normal, this excludes acute MI and takes precedence over the imaging criteria.

Abnormal regional myocardial motion and thickening may be caused by acute MI, or by one or more of several other conditions including prior infarction,

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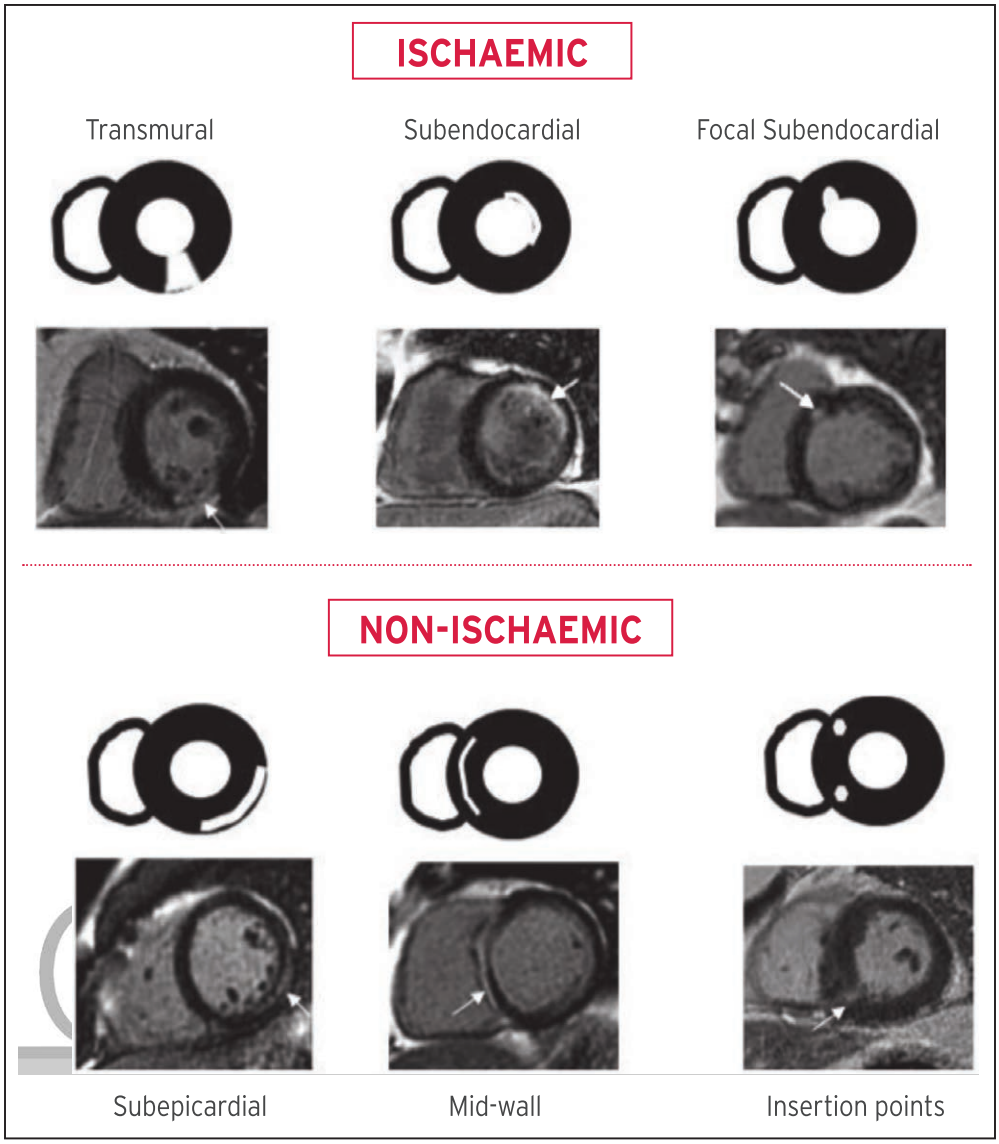

Figure 9. Post-contrast cardiac magnetic resonance images.
The gadolinium-based contrasts wash out slowly from myocardium with increased extracellular space such as fibrosis, thus enhancing areas of scarring (white arrows). The different patterns of scarring are divided into ischaemic and non-ischaemic. Typically, an ischaemic scar/fibrosis (upper panel) extends from the subendocardium to the epicardium (subendocardial, non-transmural scar vs. transmural scar). Conversely, a non-ischaemic fibrosis/scar can be encountered at the epicardium, in the mid-wall, or at the insertion points of the right ventricle (lower panel).

acute ischaemia, stunning, or hibernation. Non-ischaemic conditions such as cardiomyopathy, and inflammatory or infiltrative diseases, can also lead to regional loss of viable myocardium or functional abnormality. Therefore, the positive predictive value of imaging for acute MI is not high unless these conditions can be excluded, and unless a new abnormality is detected or can be presumed to have arisen in the setting of other features of acute MI.

In the setting of acute MI, CMR can also be used to assess the presence and extent of myocardium at risk (myocardial oedema), myocardial salvage, microvascular obstruction, intramyocardial haemorrhage, and infarct size, all markers of myocardial injury that have prognostic value.[190] In patients with possible acute MI but unobstructed coronary arteries, CMR can help to diagnose alternative conditions such as myocarditis, TTS, embolic infarction, or MI with spontaneous recanalization.[189]

36. APPLYING IMAGING IN LATE PRESENTATION OF MYOCARDIAL INFARCTION

In the case of late presentation after suspected MI, the presence of a regional abnormality of myocardial motion, thickening, thinning, or scar in the absence of a non-ischaemic cause provides supportive evidence of past MI. The resolution and specificity of CMR for the

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detection of myocardial scarring has made this a valuable technique. In particular, the ability to distinguish between subendocardial and other patterns of scars helps to differentiate between ischaemic heart disease and other myocardial pathologies. Imaging techniques are also useful for risk stratification after a definitive diagnosis of MI.

37. REGULATORY PERSPECTIVE ON MYOCARDIAL INFARCTION IN CLINICAL TRIALS

In drug and device development programmes, MI may be an entry criterion or be used as an efficacy endpoint, commonly as a component of the primary endpoint, as well as a safety endpoint of interest in drug development programmes.[195,196] A universal definition of MI is of great benefit for clinical studies, since it will allow a standardized approach for meaningful interpretation and comparison across different trials, or the pooling of results for the detection of safety signals. For the harmonization of the MI definition it is important to standardize the reporting of MI events by clinical events committees. This would allow a more optimal comparison of MI rates among drug and device trials.

One cannot presume that values from one cTn assay are equivalent to those of another. These differences are amplified when multiples of the values are used. This could affect results, especially in trials that compare strategies such as PCI and CABG. The use of one single assay and/or a central core laboratory within a trial could help to decrease this variability, and might be particularly relevant in decreasing variability in trials of a drug or intervention in which cTn concentration is a principal safety endpoint. However, the uniform use of a single assay is generally not feasible in trials with follow-up post-discharge, since recurrent ischaemic events may occur in different hospitals using different cTn assays. In clinical trials, a standardized approach to establish the 99th percentile URL for a particular assay should be established. One approach in large multicentre trials is to use the manufacturer's recommended 99th percentile URL for a particular assay to reduce site-to-site variability in the selection of the MI decision cut-off point.

Multiples for hs-cTn vs. conventional cTn could have markedly different prognostic implications. The assay types should be reported when possible. Multiples of the 99th percentile URL should be indicated and reported, both for those with cardiac procedural myocardial injury and those diagnosed with types 4a and 5 MI. Cumulative frequency distribution of peak cTn measurements for MI endpoint assessments by treatment group should also be provided. This will facilitate the comparison of trials and meta-analyses.

38. SILENT/UNRECOGNIZED MYOCARDIAL INFARCTION IN EPIDEMIOLOGICAL STUDIES AND QUALITY PROGRAMMES

ECG monitoring for unrecognized or silent Q wave MI is usually acquired annually in epidemiological studies and clinical trials that assess cardiovascular endpoints. These events are associated with adverse outcomes.[197] There is no firm consensus on how frequently to monitor for ECG evidence of silent Q wave MI or whether surveillance for silent MI events should be routinely implemented. Serial monitoring of patients who have had a symptomatic Q wave MI event revealed Q wave regression in a substantial number of patients.[198] An annual ECG is reasonable in clinical trials to monitor for silent Q wave MI events if the study population is expected to have an accelerated rate of atherosclerotic events. The review should consider the baseline tracing, interim event ECG tracings, and protocolmandated annual tracings, along with the review of imaging studies if available.

39. INDIVIDUAL AND PUBLIC IMPLICATIONS OF THE MYOCARDIAL INFARCTION DEFINITION

Revision of the definition of MI has a number of implications for individuals, health professionals, and society at large. A tentative or final diagnosis is the basis for advice about further diagnostic testing, lifestyle changes, treatment, and prognosis for the patient. The aggregate of patients with a particular diagnosis is the basis for healthcare planning, and policy and resource allocation.

One of the goals of good clinical practice is to reach a definitive and specific diagnosis, which is supported by current scientific knowledge. The approach to the definition of myocardial injury and MI outlined in this document meets this goal. In general, the conceptual meaning of the term myocardial infarction has not changed, although new sensitive methods have been developed to diagnose this entity. Thus, the diagnosis of an acute MI is a clinical diagnosis based on patient symptoms, ECG changes, and highly sensitive biochemical markers, as well as information gleaned from various imaging techniques.

It should be appreciated that the universal definition of MI may be associated with consequences for patients and their families with respect to psychological status, life and health insurance, and professional career, as well as driving and pilot licences. The diagnosis is also associated with societal implications with regards to diagnosis-related coding, hospital reimbursement, public health statistics, sick leave, and disability attestation. In order to meet these challenges, physicians must be adequately informed of the diagnostic criteria. Hence,

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educational materials will need to be created and treatment guidelines must be appropriately adapted.

40. GLOBAL PERSPECTIVES OF THE DEFINITION OF MYOCARDIAL INFARCTION

Cardiovascular disease is a global health problem and prevalence is increasing in the developing world. Understanding the burden and effects of CAD in populations is of critical importance. Changing clinical definitions, criteria, and biomarkers add challenges to our understanding and ability to improve the health of the public. For clinicians, the definition of MI has important and immediate therapeutic implications. For epidemiologists, the data are often retrospective, so consistent case definitions are critical for comparisons and trend analysis. The standards described in this report are suitable for epidemiology studies and for international classification of diseases.[199] However, to analyse trends over time, it is important to have consistent definitions and to quantify adjustments when biomarkers or other diagnostic methods change,[200] considering that the advent of cTn has dramatically increased the number of diagnosable MIs for epidemiologists.[11,201]

In countries with limited economic resources, cardiac biomarkers and imaging techniques may not be available except in a few centres, and even the option of ECG recordings may be lacking. The WHO recommends the use of the ESC/ACC/AHA/WHF Universal Definition of MI in countries without resource constraints, but recommends more flexible standards in resource-constrained locations. Thus, when the only information available is the clinical history and ECG, and when data on cardiac biomarkers are not available or incomplete, the diagnosis of MI can be confirmed by the development of pathological Q waves.[11]

41. USING THE UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION IN THE HEALTHCARE SYSTEM

Arriving at a diagnosis of MI using the criteria set forth in this document requires the integration of clinical findings, patterns on the ECG, laboratory data, observations from imaging procedures, and on occasion pathological findings, all viewed in the context of the time horizon over which the suspected event unfolds. Contemporary healthcare systems are increasingly using electronic medical records where medical information is entered, curated, and available for retrieval at a later date. This evolution offers the advantages of a modern electronic database that is useful for a variety of purposes, including scientific discovery and quality improvement in clinical care, but carries with it the challenges of sifting through variable locations and formats where key data elements for confirming a diagnosis of MI are located. Also, use of the electronic medical record as an epidemiological and research tool of the future is likely to require efforts to verify the accuracy of an acute MI diagnosis, rather than accepting the coded diagnoses used for administrative and billing purposes. Such an effort to create a computable phenotype of MI (further categorized as types 1–5 MI) will require input from informaticians and experts in implementation science to translate the recommendations from this Universal Definition of MI into the routine practice of healthcare delivery and documentation.

Given the evolution of biomarker assays used to support the diagnosis of MI, it is important that a consistent approach be used in the construction of the computable phenotype of MI so as to reliably make comparisons across institutions and track epidemiological trends. Ideally, the information provided should include the assay used to make the diagnosis of MI, the 99th percentile of the URL, and the full sequence of values obtained to discern a rise and fall in biomarker levels.[196]

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This article has been copublished in the *European Heart Journal*, the *Journal of the American College of Cardiology*, and *Nature Reviews Cardiology*.

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Acknowledgment

We are indebted to Karen A. Hicks for valuable advice.

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APPENDIX

Approved by the ESC Committee for Practice Guidelines (CPG) on behalf of the ESC Board 2016–2018.

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Approved by the WHF Board.

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CVD DURING PREGNANCY

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Figure 1 Selected revised and new recommendations

A) Selected revised recommendations

Comment, comparison with 2011	2018
Strengthening modified World Health Organization (mWHO) classification of maternal risk.	It is recommended to perform risk assessment in all women with cardiac diseases in childbearing age and before conception, using the mWHO classification of maternal risk. (IC)
Upgrade in class of recommendation - Patients with severe MS should undergo intervention before pregnancy.	Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2. (IC)
2011, OACs were recommended during the 2nd and 3rd trimesters until the 36th week. Now separate recommendations for women with low and high dose are given for VKA use during the 2nd and 3rd trimesters.	During the 2nd and 3rd trimesters until the 36th week, VKA are recommended in women needing a low dose. (Low dose VKA: warfarin <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day.) (IC)
Sotalol deleted.	Flecainide† or propafenone† are recommended for prevention of SVT in patients with WPW syndrome. (IC)
Changed in high-risk patients from UFH to LMWH. Dosing based on body weight introduced.	LMWH is the drug of choice for the prevention and treatment of VTE in all pregnant patients. (IB) It is recommended that the therapeutic dose of LMWH is based on body weight. (IC)
Changes: dose adjustment of UFH or LMWH dose within 36 hours now recommended.	In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose adjustment (within 36 hours). (IC)
Upgrade of recommendation, IIb to IIa.	Catheter ablation with electroanatomic systems should be considered in experienced centres in case of drug- refractory and poorly tolerated SVT. (IIaC)
Changed from D-dimers to imaging as the first line of investigation as D-dimers are unreliable in pregnancy.	If compression ultrasound is negative, magnetic resonance venography should be considered to diagnose VTE. (IIaC)
FDA categories A to X were used for all drugs in 2011.	Decision-making based on former FDA categories is no longer recommended. (IIIC)
“Pre-pregnancy surgery” is now deleted. Now also information on Turner syndrome with aortic diameter corrected for BSA.	Pregnancy is not recommended in patients with severe dilatation of the aorta (heritable thoracic aortic disease such as Marfan syndrome >45 mm, bicuspid aortic valve >50 mm or >27 mm/m^2 body surface area, Turner syndrome ASI >25 mm/m^2 body surface area). (IIIC)

B) Selected new recommendations

Right heart catheterization is recommended to confirm the diagnosis of PAH. This can be performed during pregnancy but with very strict indications. (IC)
LMWH in therapeutic dose is recommended in pregnant patients with chronic thromboembolic pulmonary hypertension. (IC)
In patients with pulmonary embolism, thrombolytic therapy is recommended only in severe hypotension or shock. (IC)
In women at high-risk for thromboembolism, it is recommended to convert LMWH to UFH at least 36 hours prior to delivery and stop the UFH infusion 4–6 hours prior to anticipated delivery. aPTT should be normal before regional anaesthesia. (IC)
In women at low-risk for thromboembolism on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 hours after the last dose of LMWH. (IC)
In women considering pregnancy and requiring heart valve surgery, it is recommended to choose the prosthesis in consultation with a pregnancy heart team. (IC)
It is recommended to manage pregnancy in women with mechanical heart valves in a centre with a pregnancy heart team (IC)
In treatment naive pregnant PAH patients, initiating treatment should be considered. (IIaC)
In patients with (history of) aortic dissection caesarean delivery should be considered. (IIaC)
β-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases. (IIaC)
Induction of labour should be considered at 40 weeks gestation in all women with cardiac disease. (IIaC)
In patients with PPCM, bromocriptine treatment may be considered to stop lactation and enhance recovery (LV function). (IIbB)
Pregnancy is not recommended in patients with vascular Ehlers–Danlos syndrome. (IIIC)
Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin (from Chapter 7, see Chapter 12) (III C)

C) New concepts

Enforcing mWHO classification of maternal risk.
Introduction of the pregnancy heart team.
More attention for assisted reproductive therapy.
Discussion of the use of bromocriptine in PPCM.
Introducing specific levels of surveillance based on low/medium/high-risk for arrhythmia with haemodynamic compromise at delivery.
New information on pharmacokinetics in pregnancy, more detailed information on pharmacodynamics in animal experiments on all drugs (Supplementary Data).
Perimortem caesarean section is discussed.
Advice on contraception and termination of pregnancy in women with cardiac disease is now provided.

ASI = aortic size index; aPTT = activated partial thromboplastin time; BSA = body surface area; FDA = US Food and Drug Administration; LMWH = low molecular weight heparin; LV = left ventricular; MS = mitral stenosis; mWHO = modified World Health Organization; OAC = oral anticoagulant; PAH = pulmonary arterial hypertension; PPCM = peripartum cardiomyopathy; UFH = unfractionated heparin.

Hypertensive disorders are the most frequent cardiovascular disorders during pregnancy, occurring in 5–10% of all pregnancies (see Chapter here). Among the other disease conditions, congenital heart disease is most frequent present during pregnancy in the western world (75–82%). Rheumatic valvular disease dominates in non-western countries, comprising 56–89% of all CVDs in pregnancy. Cardiomyopathies are rare, but represent severe causes of cardiovascular complications in pregnancy.

Pregnancy induces changes in the cardiovascular and coagulation system. The risk of pregnancy depends on the underlying cardiac diagnosis and individual conditions. Risk estimation should be individualized and be based on the modified World Health Organization (mWHO) classification (Table 3)

Table 3 Modified World Health Organization classification of maternal cardiovascular risk

	mWHO I
Diagnosis (if otherwise well and uncomplicated)	Small or mild • pulmonary stenosis • patent ductus arteriosus • mitral valve prolapse Successfully repaired simple lesions (atrial or ventricular septal defect, patent ductus arteriosus, anomalous pulmonary venous drainage) Atrial or ventricular ectopic beats, isolated
Risk	No detectable increased risk of maternal mortality and no/mild increased risk in morbidity
Maternal cardiac event rate	2.5–5%
Counselling	Yes
Care during pregnancy	Local hospital
Minimal follow-up visits during pregnancy	Once or twice
Location of delivery	Local hospital

Table 3 Modified World Health Organization classification of maternal cardiovascular risk (continued)

	mWHO II
Diagnosis (if otherwise well and uncomplicated)	Unoperated atrial or ventricular septal defect Repaired tetralogy of Fallot Most arrhythmias (supraventricular arrhythmias) Turner syndrome without aortic dilatation
Risk	Small increased risk of maternal mortality or moderate increase in morbidity
Maternal cardiac event rate	5.7–10.5%
Counselling	Yes
Care during pregnancy	Local hospital
Minimal follow-up visits during pregnancy	Once per trimester
Location of delivery	Local hospital

WHO classification of maternal CV risk

Table 3 Modified World Health Organization classification of maternal cardiovascular risk (continued)

	mWHO III
Diagnosis (if otherwise well and uncomplicated)	Moderate left ventricular impairment (EF 30–45%) Previous peripartum cardiomyopathy without any residual left ventricular impairment Mechanical valve Systemic right ventricle with good or mildly decreased ventricular function Fontan circulation. If otherwise the patient is well and the cardiac condition uncomplicated Unrepaired cyanotic heart disease Other complex heart disease Moderate mitral stenosis Severe asymptomatic aortic stenosis Moderate aortic dilatation (40–45 mm in Marfan syndrome or other HTAD; 45–50 mm in bicuspid aortic valve, Turner syndrome ASI 20–25 mm/m^2, tetralogy of Fallot <50 mm) Ventricular tachycardia
Risk	Significantly increased risk of maternal mortality or severe morbidity
Maternal cardiac event rate	19–27%
Counselling	Yes: expert counselling required
Care during pregnancy	Expert centre for pregnancy and cardiac disease
Minimal follow-up visits during pregnancy	Monthly or bimonthly
Location of delivery	Expert centre for pregnancy and cardiac disease

Table 3 Modified World Health Organization classification of maternal cardiovascular risk (continued)

	mWHO IV
Diagnosis	Pulmonary arterial hypertension Severe systemic ventricular dysfunction (EF <30% or NYHA class III–IV) Previous peripartum cardiomyopathy with any residual left ventricular impairment Severe mitral stenosis Severe symptomatic aortic stenosis Systemic right ventricle with moderate or severely decreased ventricular function Severe aortic dilatation (>45 mm in Marfan syndrome or other HTAD, >50 mm in bicuspid aortic valve, Turner syndrome ASI >25mm/m^2, tetralogy of Fallot >50 mm) Vascular Ehlers-Danlos Severe (re)coarctation Fontan with any complication
Risk	Extremely high-risk of maternal mortality or severe morbidity
Maternal cardiac event rate	40–100%
Counselling	Yes: pregnancy contra-indicated. If pregnancy occurs termination should be discussed
Care during pregnancy	Expert centre for pregnancy and cardiac disease
Minimal follow-up visits during pregnancy	Monthly
Location of delivery	Expert centre for pregnancy and cardiac disease

ASI = aortic size index; EF = ejection fraction; HTAD= heritable thoracic aortic disease; mWHO = modified World Health Organization classification; NYHA = New York Heart Association; WHO = World Health Organization.

Table 4 Predictors of maternal and neonatal events

Predictors of maternal cardiovascular events
Prior cardiac event (heart failure, transient ischaemic attack, stroke, arrhythmia)
NYHA Class III/IV
Left heart obstruction (moderate to severe)
Reduced systemic ventricular systolic function (ejection fraction <40%)
Reduced subpulmonary ventricular function (TAPSE <16 mm)
Systemic atrioventricular valve regurgitation (moderate to severe)
Pulmonary atrioventricular valve regurgitation (moderate to severe)
Pulmonary arterial hypertension
Cardiac medication before pregnancy
Cyanosis (O_2 saturation <90%)
Natriuretic peptide levels (NT-proBNP >128 pg/mL at 20 weeks predictive of event later in pregnancy)
Smoking history
Mechanical valve prosthesis
Repaired or unrepaired cyanotic heart disease
Predictors of neonatal events
NYHA Class III/IV or cyanosis during baseline pre-natal visit
Maternal left heart obstruction
Smoking during pregnancy
Low maternal oxygen saturation (<90%)
Multiple gestations
Use of anticoagulants throughout pregnancy
Cardiac medication before pregnancy
“At birth” cyanotic heart disease
Mechanical valve prosthesis
Maternal cardiac event during pregnancy
Maternal decline in cardiac output during pregnancy
Abnormal uteroplacental Doppler flow

NT-proBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; TAPSE = tricuspid annular plane systolic excursion. Predictors identified in references (See Full Text).

In women with a moderate or high-risk of complications during pregnancy (mWHO II–III, III and IV), pre-pregnancy counselling and management during pregnancy and around delivery should be conducted in an expert centre by a multidisciplinary team, the pregnancy heart team. The minimum team requirements are a cardiologist, obstetrician and anaesthetist, all with expertise in the management of high-risk pregnancies in women with heart disease. The conclusions and recommendations should be filed and made available 24 hours per day.

Transthoracic echocardiography is the preferred imaging method in pregnancy. Physiological exercise testing is an integral part of follow-up in grown-up congenital heart disease and valve disease, and should be performed in patients with known heart disease who plan pregnancy.

If possible, procedures using ionizing radiation should be delayed until at least the completion of the period of major organogenesis (>12 weeks after menses). Cardiac catheterisation and MRI can be necessary to guide diagnosis and interventional procedures.

Presently, options for pre-natal genetic testing are increasingly available for those patients with an identified genetic defect (either chromosomal defects such as insertions/deletions/ translocations or single gene defects). This includes (i) pre-gestational diagnosis or (ii) pre-natal diagnosis, chorionic villus sampling or amniocentesis. Counselling should be provided by an experienced centre with an interdisciplinary expert team.

Measurement of nuchal fold thickness around the 12th week of pregnancy to screen for chromosome abnormalities also screens for foetal congenital heart disease.

All women with congenital heart disease should be offered foetal echocardiography in the 19th to 22nd week of pregnancy with 45% of all congenital cardiac malformations identified.

If an intervention is absolutely necessary, the best time is after the fourth month in the second trimester. Maternal mortality during cardiopulmonary by-pass is now similar to that in non-pregnant women. However, foetal mortality remains high (around 20%). Cardiac surgery is recommended only when medical therapy or interventional procedures fail and the mother's life is threatened. Delivery before necessary surgery should be considered when the fetus is viable.

A delivery plan should be made with details of induction, management of labour, delivery, and post-partum surveillance.

Vaginal delivery is associated with less blood loss and lower risk of infection, venous thrombosis and embolism, and should be advised for most women. Caesarean section should be considered for obstetric indications and for patients presenting in labour on oral anticoagulants (OACs), with aggressive aortic pathology and in acute intractable HF and is advised in severe forms of pulmonary hypertension (PH) (including Eisenmenger syndrome).

Antibiotic prophylaxis is not recommended during vaginal or caesarean delivery. IE should be diagnosed and treated in the same way as in the non-pregnant patient. Antibiotics should be given according to guidelines, guided by culture and antibiotic sensitivity results considering the potential fetotoxic effects of antibiotics (see Table 7: Drugs and safety data).

The risk of using a particular type of contraception needs to be balanced against the risk of pregnancy, estimated using the modified WHO classification. Advice on contraception should be provided to all women with heart disease.

The rates of subfertility are likely to be as similar in most women with heart disease as in the general population, but their management is more complex. Hysteroscopy and laparoscopy can be life-threatening procedures in women with some forms of heart disease (PH, Fontan) and should be undertaken in an experienced centre with appropriate support. Assisted reproduction has added risks above those of pregnancy alone.

General recommendations		
	Class[a]	Level[b]
Pre-pregnancy risk assessment and counselling is indicated in all women with known or suspected congenital or acquired cardiovascular and aortic disease.	I	C
It is recommended to perform risk assessment in all women with cardiac diseases in childbearing age and after conception, using the mWHO classification of maternal risk.	I	C
It is recommended to treat high-risk patients in specialized centres by a multidisciplinary pregnancy heart team.	I	C
Foetal echocardiography by experienced specialists is recommended when there is an elevated risk of foetal abnormalities.	I	C
Echocardiography is recommended in any pregnant patient with unexplained or new cardiovascular signs or symptoms.	I	C
If cardiac surgery is to be performed after 24 weeks and before 37 weeks of gestation, then corticosteroids are recommended for the mother.	I	C
Vaginal delivery is recommended as first choice in most patients; for most important exceptions see below.	I	C
Induction of labour should be considered at 40 weeks of gestation in all women with cardiac disease.	IIa	C
Genetic counselling should be considered in women with congenital heart disease or congenital arrhythmia, cardiomyopathies, aortic disease or genetic malformations associated with CVD.	IIa	C
MRI (without gadolinium) should be considered if echocardiography is insufficient for a definite diagnosis.	IIa	C
In patients with severe hypertension, vaginal delivery with epidural analgesia and elective instrumental delivery should be considered.	IIa	C
Delivery before necessary surgery should be considered when gestational age is ≥26 weeks.	IIa	C
Caesarean delivery should be considered for obstetric indications or for patients with dilatation of the ascending aorta >45 mm, severe aortic stenosis, pre-term labour while on oral anticoagulants, Eisenmenger syndrome or severe heart failure.	IIa	C
A chest radiograph may be considered if other methods are not successful in clarifying the cause of dyspnoea.	IIb	C
Cardiac catheterization may be considered with very strict indications.	IIb	C
CT and electrophysiological studies may be considered in selected patients for vital indications.	IIb	C
Coronary bypass surgery or valvular surgery may be considered during pregnancy when conservative and medical therapy has failed, in situations that threaten the mother's life and that are not amenable to percutaneous treatment.	IIb	C
Prophylactic antibiotic therapy to prevent endocarditis during delivery is not recommended.	III	C

CT = computed tomography; CVD = cardiovascular disease; MRI = magnetic reso-

Introduction

In most women with congenital heart disease, pregnancy is well tolerated. Maternal cardiac complications are present in approximately 10% of completed pregnancies and are more frequent in mothers with complex disease.

PH has many causes and is defined by an elevation in mean pulmonary arterial pressure (PAP) ≥25 mmHg at right heart catheterization.

Maternal outcome, which varies according to the PH subset, has improved but mortality remains high in women with PAH (16–30% maternal mortality). Therefore, the recommendation to avoid pregnancy remains and when pregnancy occurs, termination should be discussed.

There is increased foetal and neonatal (0–30%) mortality particularly if there is preterm delivery, reduced maternal cardiac output (CO) and/or hypoxaemia.

Eisenmenger patients require special consideration because of the additional complications of cyanosis, right-to-left shunting, and paradoxical embolism. Maternal mortality is high (20–50%) and termination of pregnancy should be discussed. However, termination also carries a risk.

Foetal and neonatal risks are increased and relate to maternal CO and cyanosis. Miscarriage is common. Maternal hypoxaemia is the most important predictor of outcome.

Many of the principles of caring for non-Eisenmenger PAH apply. However, patients with Eisenmenger syndrome are at increased risk of thrombocytopenia, deficiencies in vitamin K-dependent clotting factors, and bleeding. Caution is therefore needed if prescribing antiplatelet therapy or LMWH.

Maternal complications (HF, thrombosis, arrhythmias, endocarditis) occur in at least 15% of cyanotic pregnant patients.

If oxygen saturation is >90%, then there is usually a better foetal outcome (10% foetal loss). If oxygen saturation is <85%, foetal growth restriction, prematurity, and foetal death are common and pregnancy should be discouraged (live birth rate of only 12%).

The principles for managing supravalvular or subvalvular LV outflow tract obstruction are the same as those for valvular aortic stenosis (AS) (see Chapter here). Balloon valvuloplasty is not, however, a therapeutic option.

Pregnancy is well tolerated by most women with repaired atrial septal defect (ASD) (WHO risk Class I).

For a secundum defect, catheter device closure can be performed during pregnancy but is rarely indicated.

Small or repaired ventricular septal defects (VSDs) (without left heart dilatation or ventricular dysfunction) have a low-risk of complications during pregnancy (mWHO I and II).

The risk of HF is low and only exists in women with severe regurgitation or impaired ventricular function.

Offspring mortality has been reported in 6% of cases, primarily due to the recurrence of congenital heart disease.

Pregnancy is often well tolerated in women after repair of coarctation of the aorta (CoA) (WHO risk class II).

In women with unrepaired CoA and those repaired who have systemic hypertension, residual CoA or aortic aneurysms have an increased risk of complications including dissection. Other risk factors include aortic dilatation and bicuspid aortic valve.

Pulmonary stenosis (PS) is generally well tolerated. However, severe stenosis may result in complications including RV failure and arrhythmias.

In severely symptomatic PS which is unresponsive to medical therapy and bed rest, percutaneous valvuloplasty can be appropriate.

Women with repaired tetralogy of Fallot usually tolerate pregnancy well (WHO risk class II). Cardiac complications have been reported in 8% of repaired patients.

In women with uncomplicated Ebstein's anomaly, pregnancy is often tolerated well (WHO risk class II). Symptomatic patients with cyanosis and/or HF should be counselled against pregnancy.

In patients with transposition of the great arteries (TGA), the risks associated with pregnancy are mainly attributable to women with a previous atrial (Senning and Mustard) switch, not arterial switch.

Though many women with an atrial switch operation tolerate pregnancy relatively well, there is an increased risk of developing arrhythmias (sometimes life- threatening) and HF (WHO risk class III). An irreversible decline in RV function and worsening TR are also described. Patients with more than moderate impairment of RV function or greater than moderate TR should be advised against pregnancy.

The risk of low birth weight and preterm delivery is 38%.

Complications include arrhythmias and HF (WHO risk class III). These patients are also predisposed to developing AV block. Some 10% of patients have an irreversible decline in RV function. Patients in New York Heart Association (NYHA) class III or IV, ventricular dysfunction (ejection fraction [EF] <40%), or severe TR should be counselled against pregnancy.

The rate of foetal loss is increased, especially if there is cyanosis.

Patients with a Fontan circulation have an increased risk of fertility issues but successful pregnancy can occur. However, these are high- to very high-risk pregnancies (WHO risk class III or IV). Patients with saturations <85%, depressed ventricular function, moderate to severe AV regurgitation, refractory arrhythmia or protein-losing enteropathy should be counselled against pregnancy (mWHO IV). Fontan patients have a high-risk of miscarriage (30%). Antenatal and peripartum bleeding is common. There is an increased risk of premature birth, small for gestational age, and neonatal death.

Fontan patients are at risk of thromboembolic complications and therapeutic anticoagulation should be considered (balanced with the risk of bleeding). Atrial arrhythmias should be treated promptly and this often requires electrical cardioversion.

Pregnancy and pulmonary arterial hypertension		
Recommendations	**Class[a]**	**Level[b]**
Right heart catheterization is recommended to confirm the diagnosis of PAH (group 1). This can be performed during pregnancy but with very strict indications.	I	C
Treatment dose LMWH is recommended in pregnant patients with chronic thromboembolic pulmonary hypertension.	I	C
If a PAH patient conceives on targeted PH therapies consideration should be given to withdrawing embryotoxic drugs taking into account the risks of withdrawal.	IIa	C
In treatment naive pregnant PAH patients, initiating treatment should be considered.	IIa	C
Pregnancy is not recommended in patients with PAH.	III	B

LMWH = low molecular weight heparin; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

[a] Class of recommendation

[b] Level of evidence.

Congenital heart disease

Recommendations	Class[a]	Level[b]
Patients with a systemic right ventricle (Mustard/Senning or congenitally corrected TGA), in NYHA Class III/IV, systemic ventricular dysfunction (EF <40%), or severe TR should be advised against pregnancy.	IIa	C
Anticoagulation treatment should be considered during pregnancy in Fontan patients.	IIa	C
Symptomatic patients with Ebstein's anomaly with saturations <85% and/or heart failure should be advised against pregnancy.	IIa	C
In patients with a Fontan circulation and saturations <85%, depressed ventricular function, moderate to severe AV regurgitation, refractory arrhythmia or protein-losing enteropathy pregnancy is not recommended.	III	C

AV = atrioventricular; EF = ejection fraction; NYHA = New York Heart Association; TGA = transposition of the great arteries; TR = tricuspid regurgitation.

[a] Class of recommendation.

[b] Level of evidence.

Aortic diseases

Due to haemodynamic and hormonal changes, pregnancy is a high-risk period for all patients with aortic pathology, which is rare during pregnancy but associated with very high mortality. Dissection occurs most often in the last trimester of pregnancy (50%) or the early post-partum period (33%).

The overall risk of a woman with Marfan syndrome having an aortic dissection associated with pregnancy is approximately 3%. Pregnancy should be avoided in Marfan patients with an aortic root diameter >45 mm. When the aorta is 40–45 mm, other factors should be considered such as family history of dissection and rate of aortic growth.

In patients with a bicuspid aortic valve, if the ascending aorta is not visible with echocardiography, an MRI or CT should be performed pre-pregnancy. The risk of dissection is small. Risk factors are type of bicuspid aortic valve morphology, aortic dilatation, and CoA. Pregnancy should be avoided when the aorta diameter is >50 mm.

In patients with Ehlers-Danlos syndrome, serious vascular complications occur almost exclusively in type IV (vascular). Maternal mortality is significant. Pregnancy is therefore considered as a very high-risk undertaking and not advised.

Turner syndrome is associated with an increased risk of congenital heart disease, aortic dilatation, hypertension, diabetes and atherosclerotic events. Risk factors for aortic dissection include aortic dilation, bicuspid aortic valve and CoA. Pregnancy should be avoided when the aortic size index (ASI) is >25 mm/m^2.

Table 5 Aortic diseases

	Marfan	**Bicuspid aortic valve**
Location of aneurysm/ dissection	Everywhere (sinus of Valsalva)	Ascending aorta
Risk of dissection	High: 1–10%	Low: <1%
Comorbidity	Dural abnormalities Mitral regurgitation Heart failure Arrhythmias	Aortic stenosis or regurgitation
Advise not to become pregnant	Ascending aorta >45 mm (or >40 mm in family history of dissection or sudden death)	Ascending aorta >50 mm

Table 5 Aortic diseases (continued)

	Loeys Dietz	**Turner**
Location of aneurysm/ dissection	Everywhere	Ascending aorta, arch and descending aorta
Risk of dissection	High: 1–10%	High: 1–10%
Comorbidity	Dural abnormalities Mitral regurgitation	Low height Infertility Hypertension Diabetes Bicuspid aortic valve Coarctation
Advise not to become pregnant	Ascending aorta >45 mm (or >40 mm in family history of dissection or sudden death)	ASI >25 mm/m^2

Table 5 Aortic diseases (continued)

	Vascular Ehlers–Danlos
Location of aneurysm/ dissection	Everywhere
Risk of dissection	High: 1–10%
Comorbidity	Dural abnormalities Uterine rupture
Advise not to become pregnant	All patients

ASI = aortic size index

Recommendations	Class[a]	Level[b]
All aortic diseases		
It is recommended that women with aortic disease have counselling about the risk of aortic dissection.	I	C
Imaging of the entire aorta (CT/MRI) is recommended before pregnancy in patients with a genetically proven aortic syndrome or known aortic disease.	I	C
In bicuspid aortic valve patients imaging of the ascending aorta is recommended before pregnancy.	I	C
When a woman with known aortic dilatation, (history of) dissection or genetic predisposition for dissection becomes pregnant, strict blood pressure control is recommended.	I	C
Repeated echocardiographic imaging every 4–12 weeks (depending on diagnosis and severity of dilatation) is recommended during pregnancy and 6 months post-partum in patients with ascending aorta dilatation.	I	C
For imaging of pregnant women with dilatation of distal ascending aorta, aortic arch or descending aorta, MRI (without gadolinium) is recommended.	I	C
It is recommended to deliver all women with aortic dilatation or (history of) aortic dissection in an experienced centre with a pregnancy heart team, where cardiothoracic surgery is available.	I	C
In patients with an ascending aorta <40 mm vaginal delivery is recommended.	I	C
In patients with an ascending aorta >45 mm caesarean delivery should be considered.	IIa	C
In patients with (history of) aortic dissection, caesarean delivery should be considered.	IIa	C
Prophylactic surgery should be considered during pregnancy if the aorta diameter is >45 mm and increasing rapidly.	IIa	C
When the foetus is viable, delivery before necessary surgery should be considered.	IIa	C
In patients with an aorta 40–45 mm vaginal delivery with epidural anaesthesia and expedited second stage should be considered.	IIa	C
In patients with an aorta 40–45 mm caesarean section may be considered.	IIb	C
Pregnancy is not recommended in patients with (or history of) aortic dissection.	III	C
When possible the use of ergometrine is not recommended in women with aortic disease.	III	C
Specific syndromes		
In patients with vascular Ehlers–Danlos syndrome celiprolol is recommended.	I	C
β-blocker therapy throughout pregnancy should be considered in women with Marfan syndrome and other heritable thoracic aortic diseases.	IIa	C
Pregnancy is not recommended in patients with severe dilatation of the aorta (heritable thoracic aortic disease such as Marfan syndrome >45 mm, bicuspid aortic valve >50 mm or >27 mm/m^2 BSA, Turner syndrome ASI >25 mm/m^2 BSA).	III	C
Pregnancy is not recommended in patients with vascular Ehlers– Danlos syndrome.	III	C

In stenotic valve diseases, increased CO causes an increase in transvalvular gradient of approximately 50%, mainly between the first and second trimesters, which increases the risk of maternal and foetal complications. Mechanical valve prostheses raise specific problems during pregnancy.

Heart failure occurs in one-third of pregnant women with moderate mitral stenosis and in half of those with severe mitral stenosis, most often during the second trimester. Atrial fibrillation, NYHA Class ≥II, systolic PAP >30 mmHg, severe stenosis and older age are associated with maternal complications. Prematurity rates are 20–30%, intrauterine growth retardation 5–20%, and foetal death 1–5%.

When symptoms or clinically significant PH (echocardiographically estimated systolic PAP ≥50 mmHg) develop, activity should be restricted and β-1 selective blockers (preferably metoprolol or bisoprolol) commenced. Diuretics may be used if symptoms persist. The persistence of severe symptoms or PH under medical therapy should lead to consider percutaneous mitral commissurotomy during pregnancy. Anticoagulation is recommended in the case of paroxysmal or permanent AF, left atrial thrombosis, or prior embolism.

All patients with significant MS should be counselled against pregnancy and intervention should be considered pre-pregnancy, favouring percutaneous intervention, even if asymptomatic, and even more so if the valve area is <1.0 cm^2.

The main cause of AS is bicuspid aortic valve followed by rheumatic heart disease. Cardiac morbidity is related to baseline severity of AS and symptoms. Even in patients with severe AS, pregnancy is often well tolerated if prior exercise tolerance was normal. Pre-term birth, intrauterine growth retardation, and low birth weight occur in 20–25% of the offspring of mothers with moderate and severe AS and are increased in severe AS.

All symptomatic patients with severe AS or asymptomatic patients with impaired LV function or a pathological exercise test should be counselled against pregnancy, and surgery should be performed pre-pregnancy.

During pregnancy in patients who are severely symptomatic despite medical therapy, percutaneous valvuloplasty can be undertaken by an experienced operator.

Women with severe regurgitation and symptoms or compromised LV function are at high-risk of HF. Heart failure occurs in 20–25% of women with moderate or severe rheumatic MR. Acute severe regurgitation is poorly tolerated.

Ascending aortic diameters should be measured in women with bicuspid valves. Pre-pregnancy surgery favouring valve repair should be performed according to guidelines.

In acute severe regurgitation with therapy-refractory HF, surgery is sometimes unavoidable during pregnancy. If the foetus is sufficiently mature, delivery should be undertaken prior to cardiac surgery (see Table "General Recommendations").

A high thromboembolic risk is associated with AF in native heart valve disease, in particular in clinically significant MS. Immediate anticoagulation is required.

In young women who wish to become pregnant in the future, the pregnancy heart team should be involved in the choice of a specific prosthesis, taking into account the advantages and disadvantages of the different options for that woman.

The risk of maternal cardiovascular complications in women with a bioprosthesis is low in those with no or minimal bioprosthesis dysfunction and uncompromised ventricular function. When significant bioprosthesis dysfunction is present, the risk of complications can be significant. In women with mechanical valves, pregnancy is associated with a very high-risk of complications (WHO risk classification III). A recent study from the UK reported a favourable outcome for mother and baby in only 28% of cases. The main risks are related to the need for anticoagulation therapy (valve thrombosis and haemorrhagic complications). Additional risks are related to ventricular and valvular dysfunction.

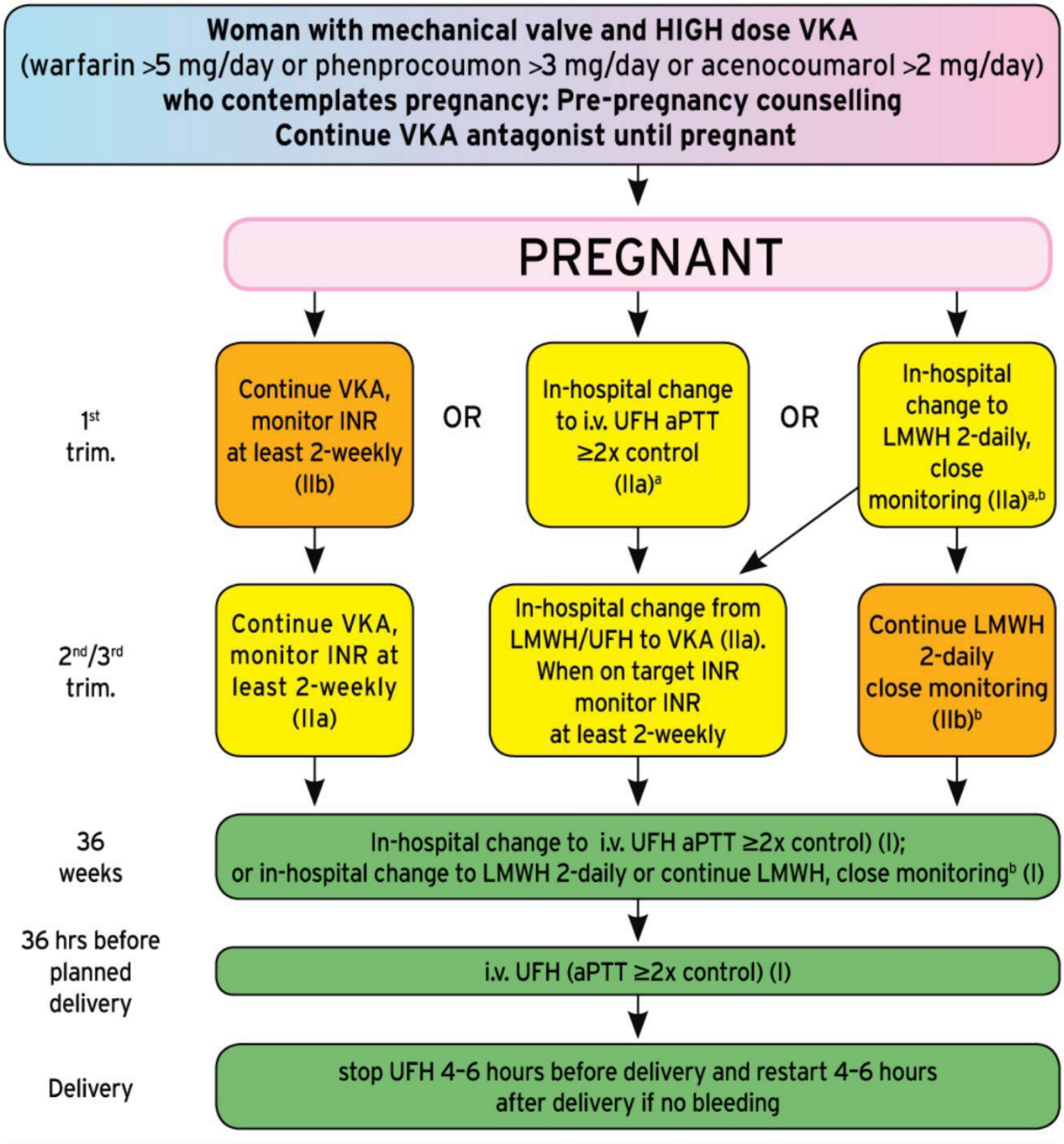
Current evidence (lacking adequate randomized studies) indicates that VKAs throughout pregnancy, under strict INR control, is the safest regimen to prevent valve thrombosis. LMWH is possibly superior to UFH for preventing valve thrombosis. All anticoagulation regimens carry an increased risk of miscarriage and haemorrhagic complications, including post-partum haemorrhage and retroplacental bleeding leading to premature birth and foetal death. VKAs during the first trimester are associated with an increased risk of miscarriage compared to LMWH or UFH, and the live birth rate is lower, Vaginal delivery while the mother is on VKAs is contra-indicated because of the risk of foetal intracranial bleeding. The option to avoid pregnancy should be discussed with women who have a mechanical valve prosthesis.

These high-risk pregnancies should be managed by a pregnancy heart team in an expert centre. The effectiveness of the anticoagulation regimen should be monitored weekly or every 2 weeks depending on the anticoagulation regimen (see Table 7: Drugs and safety data) and clinical follow-up including echocardiography should be performed monthly.

Dyspnoea and/or an embolic event are reasons for immediate transthoracic echocardiography to search for valve thrombosis, usually followed by transoesophageal echocardiography.

Planned delivery is necessary. Vaginal delivery requires a prior switch to i.v. heparin. The use of epidural anaesthesia requires a prolonged interruption of anticoagulant therapy, which may contra-indicate its use in women with a mechanical prosthesis. A planned caesarean section may therefore be considered as an alternative. Caesarean section should be performed if labour onset occurs while the patient is still on VKAs.

VKA



aPTT = activated partial thromboplastic time; INR, international normalized ratio; i.v. = intravenous; LMWH = low molecular weight heparin; LVEF = left ventricular ejection fraction; UFH = unfractionated heparin; VKA = vitamin K antagonist.

[a] Weeks 6–12 - [b] Monitoring LMWH: - starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously; -In-hospital daily anti-Xa levels until target, then weekly (I); -target anti-Xa levels: 1.0–1.2 U/mL (mitral and right sided valves) or 0.8–1.2 U/mL (aortic valves) 4–6 hrs post-dose (I); -pre-dose anti-Xa levels >0.6 U/mL (IIb).

Figure 2B Flowchart on anticoagulation in mechanical valves and (B) low dose VKA

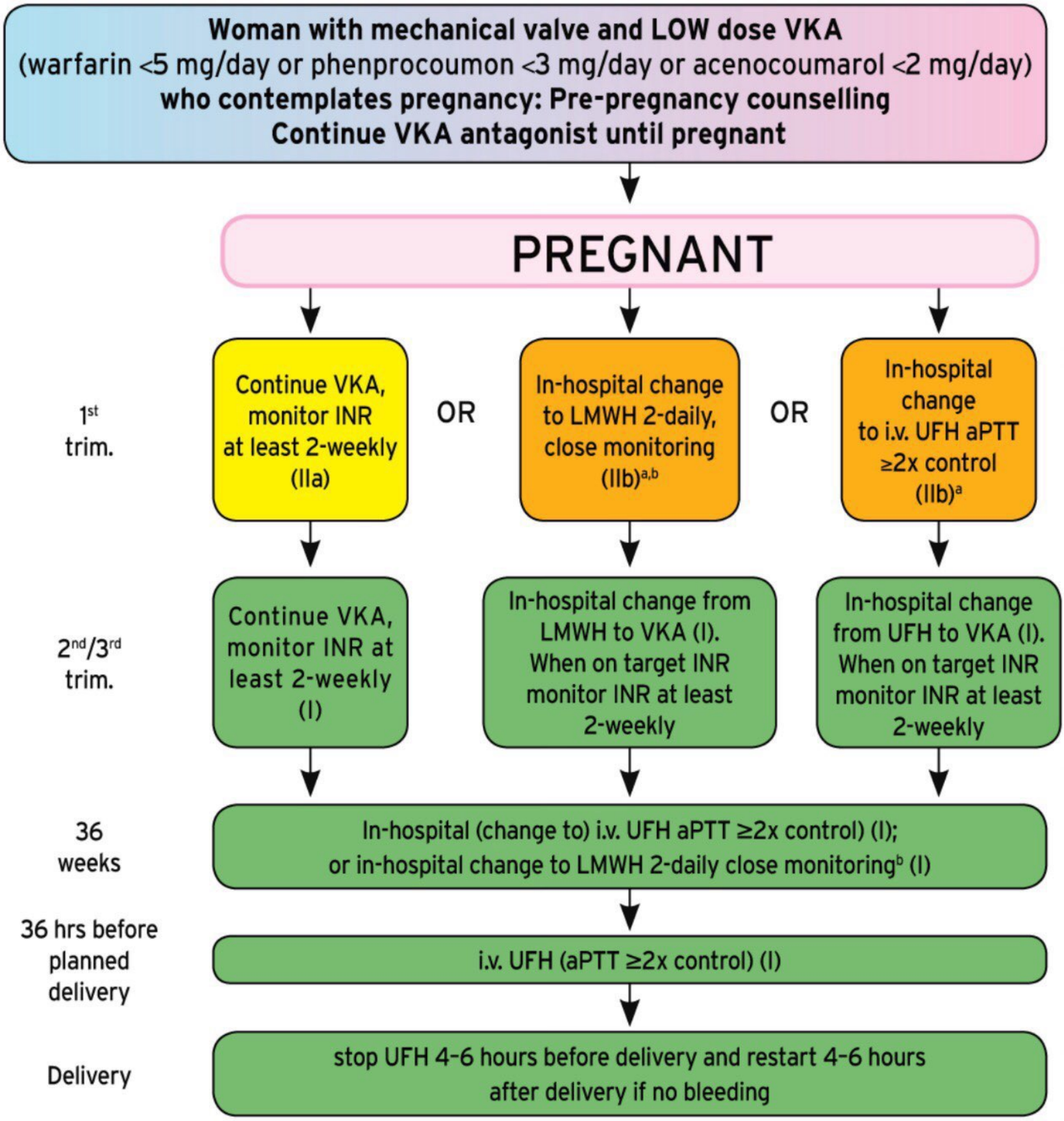


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Figure 2c Target INR for mechanical prostheses

Target INR for mechanical prostheses

Prosthesis thrombogenicity	Patient-related risk factors[a]	
	None	≥1
Low[b]	**2.5**	**3.0**
Medium[c]	**3.0**	**3.5**
High[d]	**3.5**	**4.0**

[a]Mitral or tricuspid valve replacement, previous thromboembolism, atrial fibrillation, mitral stenosis of any degree, LVEF <35% - [b]Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon - [c]Other bileaflet valves with insufficient data - [d]Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Björk-Shiley and other tilting-disc valves,any pulmonary valve prosthesis.

Management of native valvular heart disease		
Recommendations	**Class[a]**	**Level[b]**
Pre-pregnancy evaluation, including echocardiography, and counselling is recommended for any woman with known or suspected valvular disease.	I	C
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and β-1 selective blockers are recommended.	I	B
Diuretics are recommended when congestive symptoms persist despite β-blockers.	I	B
Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2.	I	C
Therapeutic anticoagulation using heparins or VKA is recommended in case of atrial fibrillation, left atrial thrombosis, or prior embolism.	I	C
Intervention should be considered before pregnancy in patients with MS and valve area <1.5 cm^2.	IIa	C
Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure >50 mmHg despite medical therapy.	IIa	C
Aortic stenosis		
Intervention is recommended before pregnancy in patients with severe AS if:		
• they are symptomatic	I	B
• OR LV dysfunction (LVEF <50%) is present	I	C
• OR when they develop symptoms during exercise testing.	I	C
Intervention should be considered before pregnancy in asymptomatic patients with severe AS when a fall in blood pressure below baseline during exercise testing occurs.	IIa	C
Balloon aortic valvuloplasty should be considered during pregnancy in patients with severe AS and severe symptoms.	IIa	C
Chronic regurgitant lesions		
Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation and symptoms or impaired ventricular function or ventricular dilatation.	I	C
Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.	I	C

AS = aortic stenosis; LV = left ventricular; LVEF = left ventricular ejection fraction; MS = mitral stenosis; VKA = vitamin K antagonist. [a]Class of recommendation - [b]Level of evidence.

Management of native valvular heart disease		
Recommendations	**Class[a]**	**Level[b]**
Pre-pregnancy evaluation, including echocardiography, and counselling is recommended for any woman with known or suspected valvular disease.	I	C
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and β-1 selective blockers are recommended.	I	B
Diuretics are recommended when congestive symptoms persist despite β-blockers.	I	B
Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2.	I	C
Therapeutic anticoagulation using heparins or VKA is recommended in case of atrial fibrillation, left atrial thrombosis, or prior embolism.	I	C
Intervention should be considered before pregnancy in patients with MS and valve area <1.5 cm^2.	IIa	C
Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure >50 mmHg despite medical therapy.	IIa	C
Aortic stenosis		
Intervention is recommended before pregnancy in patients with severe AS if:		
• they are symptomatic	I	B
• OR LV dysfunction (LVEF <50%) is present	I	C
• OR when they develop symptoms during exercise testing.	I	C
Intervention should be considered before pregnancy in asymptomatic patients with severe AS when a fall in blood pressure below baseline during exercise testing occurs.	IIa	C
Balloon aortic valvuloplasty should be considered during pregnancy in patients with severe AS and severe symptoms.	IIa	C
Chronic regurgitant lesions		
Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation and symptoms or impaired ventricular function or ventricular dilatation.	I	C
Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.	I	C

AS = aortic stenosis; LV = left ventricular; LVEF = left ventricular ejection fraction; MS = mitral stenosis; VKA = vitamin K antagonist. [a]Class of recommendation - [b]Level of evidence.

Management of prosthetic heart valves		
Recommendations	**Class[a]**	**Level[b]**
In women contemplating pregnancy, selection of a valve prosthesis should be undertaken in consultation with a pregnancy heart team.	I	C
It is recommended to manage pregnancy in women with mechanical valves in a centre with a pregnancy heart team.	I	C
If delivery starts while on VKA or in less than 2 weeks after discontinuation of VKA caesarean section is recommended.	I	C
It is recommended to discontinue VKA and start adjusted-dose intravenous UFH (aPTT ≥2x control) or adjusted-dose LMWH[c] (see separate recommendations) at the 36th week of gestation.	I	C
In pregnant women on LMWH or UFH, it is recommended to perform weekly anti-Xa level monitoring or aPTT monitoring with dose- adjustment (within 36 hours).	I	C
In pregnant women on VKA, it is recommended to perform INR monitoring weekly or every 2 weeks.	I	C
In pregnant women with LMWH, it is recommended to target anti-Xa levels 4–6 hours post-dose at 0.8–1.2 U/l (aortic valve prosthesis) or 1.0–1.2 IU/mL (mitral and right-sided valve prostheses).	I	C
It is recommended to replace LMWH with intravenous UFH (aPTT ≥2x control) at least 36 hours before planned delivery. UFH should be continued until 4–6 hours before planned delivery and restarted 4–6 hours after delivery if there are no bleeding complications.	I	C
It is recommended to anticipate timing of delivery to ensure safe and effective peripartum anticoagulation.	I	C
Immediate echocardiography is recommended in women with mechanical valves presenting with dyspnoea and/or an embolic event.	I	C
It is recommended to implement changes in the anticoagulation regimen during pregnancy in hospital.	I	C
During the second and third trimester until the 36th week VKAs are recommended in women needing a low dose.	I	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	C
During the second and third trimester until the 36th week VKAs should be considered in women needing a high dose.	IIa	C
Continuation of VKAs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.	IIa	C

During the second and third trimester until the 36th week VKAs should be considered in women needing a high dose.	IIa	C
Continuation of VKAs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day), after patient information and consent.	IIa	C
Discontinuation of VKA between weeks 6 and 12 and replacement with adjusted-dose intravenous UFH (aPTT ≥2x control) or adjusted- dose LMWHc twice daily (see separate recommendations) should be considered in patients with a warfarin dose >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).	IIa	C
During the second and third trimesters, LMWH with anti-Xa level monitoring and dose adjustment (see separate recommendations) may be considered in women who need a high dose of VKA[e] after patient information and consent.	IIb	C
In pregnant women with LMWH, in addition to monitoring peak anti-Xa levels, monitoring predose levels targeted at ≥0.6 IU/mL may be considered.	IIb	C
LMWH is not recommended when weekly anti-Xa level monitoring and dose-adjustment is not available.	III	C

aPTT = activated partial thromboplastin time; INR = international normalized ratio; LMWH = low molecular weight heparin; UFH = unfractionated heparin; VKA = vitamin K antagonist.

[a]Class of recommendation - [b]Level of evidence - [c]The starting dose for LMWH is 1 mg/kg body weight for enoxaparin and 100 IU/kg for dalteparin, twice daily subcutaneously - [d]Low dose VKA: warfarin <5 mg/day (or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day) - [e]High dose VKA: warfarin >5 mg/day (or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day).

Pregnancy is associated with a three- to four-fold increase in AMI risk compared with age-matched non-pregnant women. The majority of CAD are of non-atherosclerotic causes, including pregnancy-related spontaneous coronary artery dissection (P-SCAD) (43%), angiographically normal coronary arteries (18%) and coronary thrombosis (17%).

Clinical presentation is the same as the non-pregnant population. Serum troponin rise should suggest myocardial ischaemia. Where the ECG is non-diagnostic, echocardiography may be helpful.

Management

AMI management in pregnancy is similar to that in the general population, including revascularization techniques. In P-SCAD, enhanced vascular vulnerability should be considered when applying revascularization strategies.

Therapy

Low-dose aspirin appears to be safe, but there is little information regarding P2Y inhibitors. Clopidogrel should be used only when strictly necessary. The effects of ionizing radiation should not prevent primary PCI in pregnant patients with standard indications for revascularization in AMI. The majority of reports regarding STEMI management in pregnancy relate to bare metal stents, however, new generation drug-eluting stents (DES) are recommended according to the 2017 AMI STEMI Guidelines. Stents usage has been reported in spontaneous coronary artery dissection; however, currently there is no evidence to recommend them in pregnancy.

Pregnancy may be considered in patients with known CAD in the absence of residual ischaemia and clinical signs of LV dysfunction.

Management of coronary artery disease

Recommendations	Class[a]	Level[b]
ECG and measurement of troponin levels are recommended when a pregnant woman has chest pain.	I	C
Primary coronary angioplasty is recommended as the preferred reperfusion therapy for STEMI during pregnancy.	I	C
An invasive management strategy should be considered for NSTE-ACS with high-risk criteria.	IIa	C
Conservative management should be considered for stable NSTE-ACS with low-risk criteria.	IIa	C
Follow-up should be considered over at least the next 3 months after NSTE-ACS	IIa	C
Breastfeeding is not recommended in mothers who take antiplatelet agents other than low-dose aspirin due to lack of data (see Chapter here).	III	C

ECG = electrocardiogram; LV = left ventricular; NSTE-ACS = non-ST-elevation acute coronary syndrome; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

[a] Class of recommendation - [b] Level of evidence.

Management of native valvular heart disease		
Recommendations	**Class[a]**	**Level[b]**
Pre-pregnancy evaluation, including echocardiography, and counselling is recommended for any woman with known or suspected valvular disease.	I	C
Mitral stenosis		
In patients with symptoms or pulmonary hypertension, restricted activities and β-1 selective blockers are recommended.	I	B
Diuretics are recommended when congestive symptoms persist despite β-blockers.	I	B
Intervention is recommended before pregnancy in patients with MS and valve area <1.0 cm^2.	I	C
Therapeutic anticoagulation using heparins or VKA is recommended in case of atrial fibrillation, left atrial thrombosis, or prior embolism.	I	C
Intervention should be considered before pregnancy in patients with MS and valve area <1.5 cm^2.	IIa	C
Percutaneous mitral commissurotomy should be considered in pregnant patients with severe symptoms or systolic pulmonary artery pressure >50 mmHg despite medical therapy.	IIa	C
Aortic stenosis		
Intervention is recommended before pregnancy in patients with severe AS if:		
• they are symptomatic	I	B
• OR LV dysfunction (LVEF <50%) is present	I	C
• OR when they develop symptoms during exercise testing.	I	C
Intervention should be considered before pregnancy in asymptomatic patients with severe AS when a fall in blood pressure below baseline during exercise testing occurs.	IIa	C
Balloon aortic valvuloplasty should be considered during pregnancy in patients with severe AS and severe symptoms.	IIa	C
Chronic regurgitant lesions		
Surgical treatment is recommended before pregnancy in patients with severe aortic or mitral regurgitation and symptoms or impaired ventricular function or ventricular dilatation.	I	C
Medical therapy is recommended in pregnant women with regurgitant lesions when symptoms occur.	I	C

AS = aortic stenosis; LV = left ventricular; LVEF = left ventricular ejection fraction; MS = mitral stenosis; VKA = vitamin K antagonist. [a]Class of recommendation - [b]Level of evidence

The aetiology of pregnancy-associated cardiomyopathy includes acquired and inherited diseases, such as peripartum cardiomyopathy (PPCM), toxic cardiomyopathies, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), Takotsubo cardiomyopathy, and storage diseases.

Important predisposing factors include multiparity, African ethnicity, smoking, diabetes, pre-eclampsia, malnutrition, advanced age, and teenage pregnancy. PPCM presents with HF secondary to LV systolic dysfunction towards the end of pregnancy and in the months following delivery, with the majority diagnosed post-partum. The LV may be non-dilated, but the EF is usually <45%. Although symptoms and signs are often typical for HF, diagnosis is frequently delayed. Echocardiography is the imaging modality of choice. Initial LVEF <30%, marked LV dilatation (LV end diastolic diameter ≥6.0 cm), and RV involvement are associated with adverse outcomes. 6-month mortality ranges from 2.0% in Germany to 12.6% in a large cohort from South Africa or 24% over 24 months in Turkey. When the EF has not recovered to >50–55%, subsequent pregnancy should be discouraged.

Although PPCM and DCM are distinct disease entities, patients may share a genetic predisposition, and differentiation during pregnancy may be impossible. Pregnancy is poorly tolerated in some women with pre-existing DCM, with the potential for significant deterioration in LV function.

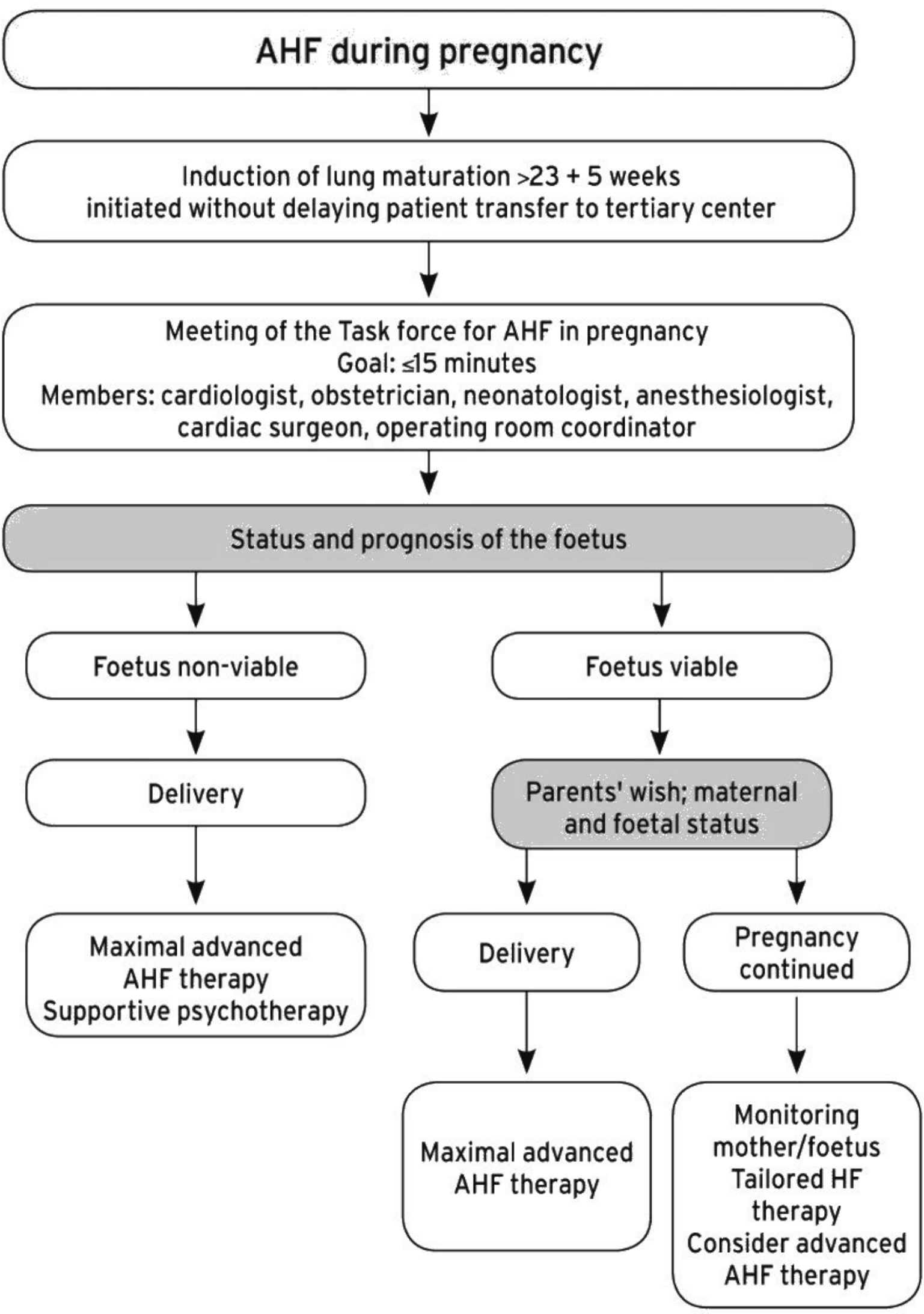
Pre-pregnancy management includes modification of existing HF medications to avoid foetal harm. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs) and ivabradine are contra-indicated and should be stopped prior to conception. β- blockers should be switched to β-1-selective blockers.

HF in DCM or PPCM can develop rapidly and guidelines for the management of acute HF and cardiogenic shock apply. (Figures 3 and 4). Patients with symptoms and signs of acute HF should be evaluated according to acute HF guidelines.

If a patient is in cardiogenic shock or dependent on inotropes or vasopressors, mechanical circulatory support and urgent delivery by caesarean section (irrespective of gestation) should be considered.

Management goals are similar to non-pregnant acute HF, while avoiding fetotoxic agents (ACE inhibitors, ARB, ARNI, MRA, ivabradine, and atenolol) during pregnancy. HF with pulmonary congestion is treated with loop diuretics and thiazides if required. Standard indications for anticoagulation in PPCM and DCM apply during and after pregnancy. Addition of bromocriptine to standard HF therapy may improve LV recovery and clinical outcome in women with acute severe PPCM. Given the high rate of improvement of LV function during optimal HF drug therapy, early implantation of an implantable cardioverter-defibrillator (ICD) in patients with newly diagnosed PPCM or DCM is not appropriate. Cardiac transplantation is reserved for patients where mechanical circulatory support is not possible or desirable.

Figure 3 Management of acute heart failure (AHF) during pregnancy

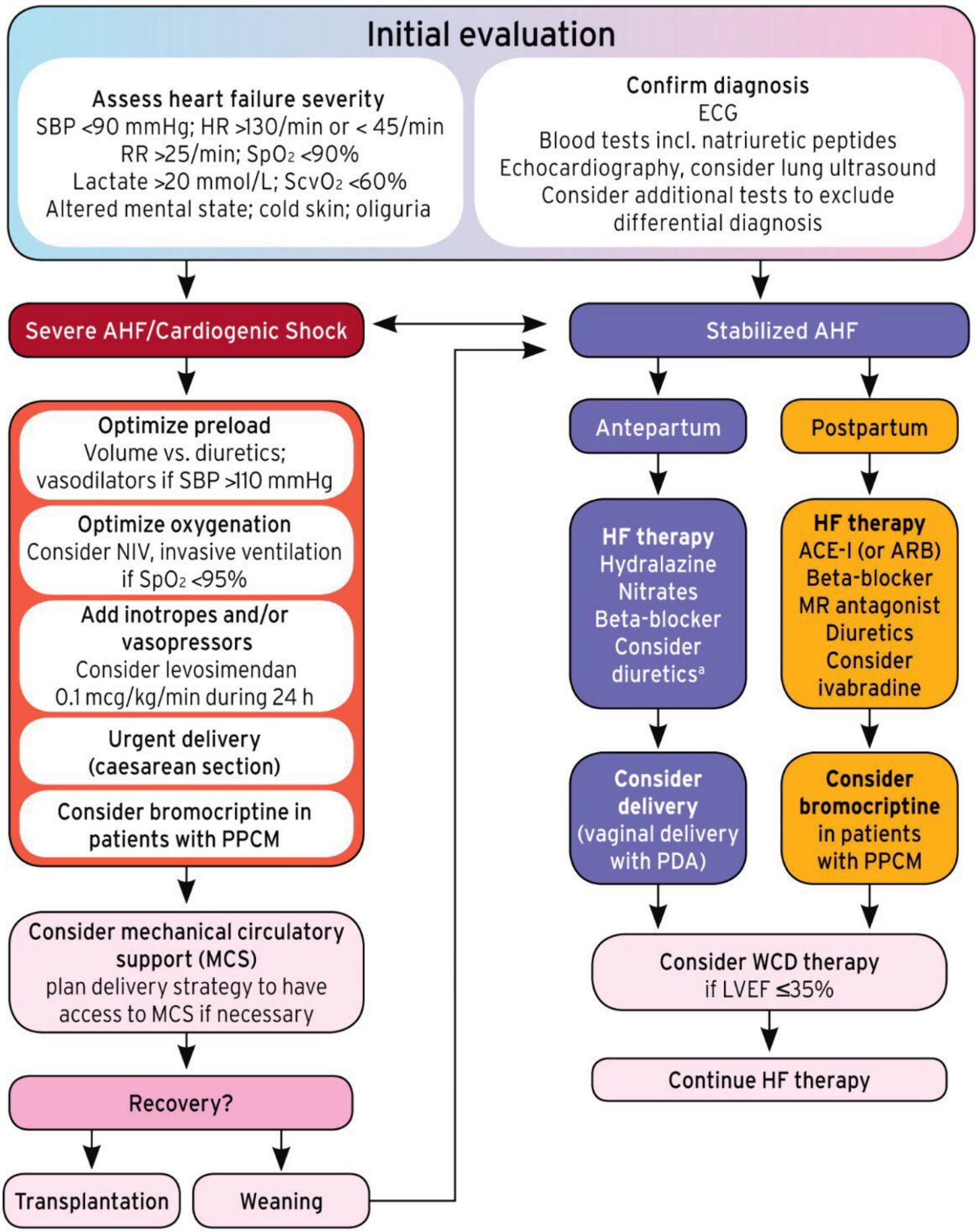


Example of a prespecified protocol of interdisciplinary work-up (modified from Bauersachs et al, EJHF 2016)

For interactivity see here

Figure 4 Management of acute heart failure (AHF) during/after pregnancy

Figure 4 Management of acute heart failure (AHF) during/after pregnancy



[a]Diuretics have to be used with caution due to potential reduction in placental blood flow.

Modified from Bauersachs et al, EJHF 2016: 18, 1096–1105

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; (A)HF = (acute) heart failure; HR = heart rate; NIV = non-invasive ventilation; MR = mineralocorticoid receptor; PDA = peridural analgesia; PPCM = peripartum cardiomyopathy; RR = respiratory rate; SBP = systolic blood pressure; $ScvO^2$ = central venous oxygen saturation; SpO^2 = peripheral oxygen saturation; WCD = wearable cardioverter-defibrillator.

In stable congestive HF vaginal delivery is preferred with spinal/epidural analgesia. Urgent delivery by Caesarean section should be considered in women with advanced HF and haemodynamic instability. Epidural anaesthesia may be the method of choice.

In HF with reduced EF (HFrEF), breastfeeding is discouraged in more severe cases (e.g. NYHA III/IV).

Women with HCM usually tolerate pregnancy well (maternal mortality 0.5%, complication or worsening of symptoms in 29%). Foetal mortality by spontaneous abortion (15%), therapeutic abortion (5%), or stillbirth (2%) is comparable to the general population.

Cardioversion should be considered for poorly tolerated persistent AF. Therapeutic anticoagulation is recommended for those with paroxysmal or persistent arrhythmias. Patients with a past history or family history of sudden death need close surveillance.

Low-risk cases may have a spontaneous labour and vaginal delivery. Caesarean section should be considered in patients with severe LV outflow tract obstruction, pre-term labour while on OAC, or severe HF.

Management of cardiomyopathies and heart failure		
Recommendations	**Class[a]**	**Level[b]**
Anticoagulation is recommended in patients with intracardiac thrombus detected by imaging or with evidence of systemic embolism.	I	A
It is recommended to treat women with HF during pregnancy according to current guidelines for non-pregnant patients, respecting contraindications for some drugs in pregnancy (see Table 7).	I	B
It is recommended to inform women with HFrEF about the risk of deterioration of the condition during gestation and peripartum.	I	C
Therapeutic anticoagulation with LMWH or vitamin K antagonists according to stage of pregnancy is recommended for patients with atrial fibrillation.	I	C
In HFrEF it is recommended that β-blockers are continued in women who used them before pregnancy or are installed with caution, if clinically indicated.	I	C
In patients with PPCM and DCM counselling for recurrence risk during subsequent pregnancy is recommended in all cases, even if LV function has recovered.	I	C
As rapid diagnosis and decision making is crucial for all pregnant women with acute HF, a prespecified management algorithm and an interdisciplinary team should be established.	IIa	C
Patients in cardiogenic shock/dependent on inotropes should be transferred early to a facility where mechanical circulatory support is available.	IIa	C
Bromocriptine treatment should be accompanied by prophylactic (or therapeutic) anticoagulation (see Chapter here).	IIa	C
Due to high metabolic demands of lactation and breastfeeding, preventing lactation may be considered in patients with severe HF.	IIb	B
In patients with PPCM, bromocriptine treatment may be considered to stop lactation and enhance recovery (LV function).	IIb	B
In women with PPCM and DCM subsequent pregnancy is not recommended if LVEF does not normalize.	III	C
Hypertrophic cardiomyopathy (HCM)		
In patients with HCM the same risk stratifications as for non- pregnant women is recommended.	I	C
In patients with HCM, it is recommended that β-blockers are continued in women who used them before pregnancy.	I	C
In patients with HCM, β-blockers should be started in women who develop symptoms due to outflow tract obstruction or arrhythmia during pregnancy.	IIa	C
In HCM, cardioversion should be considered for persistent atrial fibrillation.	IIa	C

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LMWH = low molecular weight heparin; LV = left ventricular; LVEF = left ventricular ejection fraction; PPCM = peripartum cardiomyopathy.

[a] Class of recommendation - [b] Level of evidence.

AF (27/100 000) and paroxysmal supraventricular tachycardia (PSVT) are, apart from premature beats, the most frequent arrhythmias. AF is associated with an increased mortality risk. Patients with a known history of any symptomatic supraventricular or ventricular tachycardia should be considered for catheter ablation prior to pregnancy.

Pregnant PSVT subjects have worse obstetric and foetal outcomes, with higher adjusted ORs (1.54–3.52) for severe maternal morbidity, caesarean delivery, low birth weight, preterm labour, foetal stress and foetal abnormalities, than those without PSVT.

Recommendations for acute termination of PSVT are outlined in the tables below. Intravenous administration of adenosine is recommended as first drug of choice for acute conversion of PSVT. For prevention of PSVT, β-blockers (exception for atenolol) or verapamil are first-line agents, except for patients with Wolff-Parkinson-White (WPW) syndrome.

Electrical cardioversion is recommended whenever ongoing AF is haemodynamically unstable or a considerable risk for the mother or the foetus. Cardioversion should generally be preceded by anticoagulation (see here). Intravenous β-blockers are recommended for rate control.

SCD is recognized as an increasing risk factor in pregnancy. Inherited arrhythmogenic disorders should always be looked for with appropriate diagnostic tests during or after pregnancy. Women with congenital LQTS are at substantial risk of cardiac events during the post-partum period. The choice of prophylactic antiarrhythmic drug therapy relates to the presence of underlying structural heart disease and LV function.

ICD implantation is recommended if an indication emerges during pregnancy. Non- selective β-blockers should be continued throughout pregnancy and during the post-partum period (at least 40 weeks after delivery) in patients with congenital LQTS and those with catecholaminergic polymorphic VT.

Bradyarrhythmias and conduction disturbances usually have a favourable outcome in the absence of underlying heart disease.

Sinus node dysfunction

Rare cases of sinus bradycardia may be related to the supine hypotensive syndrome of pregnancy. Symptomatic bradycardia should be managed by changing the position of the mother to a left lateral decubitus position. For persistent symptoms, a temporary pacemaker may be necessary.

Atrioventricular block

Isolated congenital complete heart block in the mother has a favourable outcome during pregnancy, especially when the escape rhythm has a narrow QRS complex.

Electrical cardioversion

Cardioversion seems safe in all phases of pregnancy as it does not compromise foetal blood flow and the risk of inducing foetal arrhythmias or initiating preterm labour seems small. The foetal heart rate should routinely be controlled after cardioversion.

Catheter ablation

Catheter ablation should be postponed to the second trimester if possible and performed at an experienced centre using non-fluoroscopic electroanatomic mapping and catheter navigation systems.

Implantable cardioverter-defibrillator and pacing

The implantation of an ICD should be considered prior to pregnancy in patients with high-risk factors for SCD. Treatment with an ICD during pregnancy does not cause an increased risk of major ICD-related complications and is recommended if an indication emerges. Implantations, for ICD preferably one chamber, can be performed safely, especially if the foetus is beyond 8 weeks' gestation. Echocardiographic guidance or electro-anatomical mapping may be helpful.

Table 6 Recommended surveillance levels at time of delivery in women with arrhythmias

	Level of surveillance[a]	Class[b]	Level[c]
Risk for arrhythmia with haemodynamic compromise at delivery: Low-risk			
PSVT, AF, idiopathic VT, low-risk LQTS, WPW syndrome.	1	I	C
Risk for arrhythmia with haemodynamic compromise at delivery: Medium-risk			
Unstable SVT, VT, those with an implanted ICD, VT and structural heart disease, Brugada syndrome. Moderate risk: LQTS, catecholaminergic polymorphic VT.	2	I	C
Risk for arrhythmia with haemodynamic compromise at delivery: High-risk for life threatening arrhythmia			
Unstable VT in structural heart disease/congenital heart disease, unstable VT/TdP in high-risk LQTS patients, short QT syndrome, high-risk catecholaminergic polymorphic ventricular tachycardia.	3	I	C

Descriptions of actions to be planned	**Surveillance level**		
	Low 1	**Medium 2**	**High 3**
Consult cardiologist	X		
Consultation with multidisciplinary team including arrhythmologists at specialized centre.		X	X
Mode and location of delivery as advised by obstetricians.	X	X	
Caesarean delivery recommended.			X
Monitor cardiac rhythm (telemetry, external rhythm monitor).		(X)	X
Intravenous line.		X	X
Arterial line.			X
Prepare for intravenous administration of adenosine.		X	
Prepare for intravenous administration of a β-blocker.		X	X
Prepare for intravenous administration of selected antiarrhythmic drugs.			X
External cardioverter defibrillator at site.		X	X
Delivery at thoracic operating theatre			X
Prepare for transfer to cardiac intensive care unit post- partum if needed			X

AF = atrial fibrillation; ICD = implantable cardioverter-defibrillator; LQTS = long QT syndrome; PSVT = paroxysmal supraventricular tachycardia; SVT = supraventricular tachycardia; TdP = torsade de pointes; VT = ventricular tachycardia, WPW = Wolfe-Parkinson-White.

[a] The risk stratification should follow published Guidelines for the particular disease.

[b] Class of recommendation - [c] Level of evidence.

Management of arrhythmias		
Recommendations	**Class[a]**	**Level[b]**
Acute management (intravenous administration of drugs) of SVT and AF		
Vagal manoeuvres, and if these fails, adenosine, are recommended for acute conversion of PSVT.	I	C
Immediate electrical cardioversion is recommended for any tachycardia with haemodynamic instability and for pre-excited AF.	I	C
β-1-selective blockers should be considered for acute conversion of PSVT.	IIa	C
Ibutilide or flecainide may be considered for termination of atrial flutter and AF in stable patients with structurally normal hearts[c].	IIb	C
Long-term management (oral administration of drugs) of SVT and AF		
β-1-selective blockers or verapamil[d] is recommended for prevention of SVT in patients without pre-excitation on resting ECG.	I	C
Flecainide[e] or propafenone[e] are recommended for prevention of SVT in patients with WPW syndrome.	I	C
β-selective blockers are recommended for rate control of AT or AF.	I	C
Flecainide[e], propafenone[e] or sotalol[f] should be considered to prevent SVT, AT and AF if AV nodal blocking agents fail.	IIa	C
Digoxin[d], verapamil[d] should be considered for rate control of AT or AF if β-blockers fail.	IIa	C
Catheter ablation with electroanatomic systems should be considered in experienced centres in case of drug-refractory and poorly tolerated SVT.	IIa	C
Acute management (intravenous administration of drugs) of Ventricular tachyarrhythmias		
Immediate electrical cardioversion is recommended for sustained both unstable and stable VT.	I	C
For acute conversion of sustained, haemodynamically stable, monomorphic VT (e.g. idiopathic VT), a β-blocker, sotalol[f], flecainide[e], procainamide or overdrive ventricular pacing should be considered.	IIa	C
Long-term management (oral administration of drugs) of Ventricular tachyarrhythmias		

case of drug-refractory and poorly tolerated SVT.		
Acute management (intravenous administration of drugs) of Ventricular tachyarrhythmias		
Immediate electrical cardioversion is recommended for sustained both unstable and stable VT.	I	C
For acute conversion of sustained, haemodynamically stable, monomorphic VT (e.g. idiopathic VT), a β-blocker, sotalol[f], flecainide[e], procainamide or overdrive ventricular pacing should be considered.	IIa	C
Long-term management (oral administration of drugs) of Ventricular tachyarrhythmias		
ICD (preferably one chamber) is recommended prior to pregnancy if clinically indicated. If indication emerges during pregnancy, ICD implantation is recommended using echocardiographic guidance or mapping, especially if foetus is beyond 8 weeks' gestation.	I	C
β-blocking agents are recommended during pregnancy and post- partum in patients with long QT syndrome or catecholaminergic polymorphic ventricular tachycardia.	I	C
β-blocking agents or verapamil[d,e] are recommended for prevention of idiopathic sustained VT if associated with severe symptoms or haemodynamic compromise.	I	C
In idiopathic sustained VT sotalol[f] or flecainide[e] should be considered for prevention if other drugs fail.	IIa	C
Catheter ablation with electroanatomic mapping systems may be considered in experienced centres in sustained drug-refractory and poorly tolerated VT if there are no other alternatives.	IIb	C

AF = atrial fibrillation; AT = atrial tachycardia; AV = atrioventricular; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; PSVT = paroxysmal supraventricular tachycardia; SVT = supraventricular tachycardia; TdP = torsade de pointes; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White.

[a] Class of recommendation - [b] Level of evidence - [c] Cardioversion of AF and atrial flutter should generally be preceded by anticoagulation (see below). - [d] AV nodal blocking agents should not be used in patients with pre-excitation on resting ECG or pre-excited AF - [e] Flecainide and propafenone should be combined with AV nodal blocking agents for certain atrial tachycardias, but structural heart disease, reduced left ventricular function and bundle branch block should be excluded - [f] Vaughan Williams class III antiarrhythmic drugs should not be used in patients with prolonged QTc.

Hypertensive disorders in pregnancy are the most common medical complications, affecting 5–10% of pregnancies worldwide.

Repeated BP readings should be performed, preferably on two occasions in the sitting position (or the left lateral recumbent during labour) with an appropriately- sized arm cuff at heart level and using Korotkoff V for diastolic BP (DBP). The diagnosis of hypertension in pregnancy by ambulatory BP monitoring (ABPM) is superior to routine BP measurement for the prediction of pregnancy outcome. Only devices validated according to recognized protocols should be used in pregnancy. Basic laboratory investigations include urinalysis, blood count, haematocrit, liver enzymes, serum creatinine, and serum uric acid. All pregnant women should be assessed for proteinuria in early pregnancy to detect pre-existing renal disease and, in the second half of pregnancy, to screen for pre-eclampsia.

The definition of hypertension in pregnancy is based only on office (or in-hospital) BP values (systolic BP [SBP] ≥140 mmHg and/or DBP ≥90 mmHg) and distinguishes mildly (140–159/90–109 mmHg) or severely (≥160/110 mmHg) elevated BP. Hypertension in pregnancy is not a single entity but comprises:

- Pre-existing hypertension: precedes pregnancy or develops before 20 weeks' gestation. It usually persists for more than 42 days post-partum and may be associated with proteinuria.
- Gestational hypertension: develops after 20 weeks' gestation and usually resolves within 42 days post-partum.
- Pre-eclampsia: gestational hypertension with significant proteinuria (>0.3 g/24h or ≥30 mg/mmol albumin/creatinine ratio). It occurs more frequently during the first pregnancy, in multiple pregnancy, in hydatidiform mole, in antiphospholipid syndrome, or with pre-existing hypertension, renal disease or diabetes. The only cure is delivery.
- Pre-existing hypertension plus superimposed gestational hypertension with proteinuria.
- Antenatally unclassifiable hypertension

Women at high or moderate risk of pre-eclampsia should be advised to take 100–150 mg of aspirin daily from week 12 to weeks 36–37.

Overview

Management of hypertension in pregnancy depends on BP, gestational age and the presence of associated maternal and foetal risk factors.

Most women with pre-existing hypertension and normal renal function have non- severe hypertension (140–159/90–109 mmHg) and are at low-risk for cardiovascular complications. Some are able to withdraw their medication in the first half of pregnancy because of the physiological fall in BP.

Evidence-based data regarding treatment of hypertension in pregnancy are lacking. In terms of treatment benefit, tight versus less tight control of hypertension in pregnancy in the Control of Hypertension in Pregnancy Study (CHIPS) was associated with less severe maternal hypertension, but no difference in the risk of adverse perinatal outcomes and overall serious maternal complications.

Non-pharmacological management of hypertension during pregnancy has a limited role to play with randomized studies of dietary and lifestyle interventions showing minimal effects on pregnancy outcome. Regular exercise might be continued with caution and obese women (≥30 kg/m^2) are advised to avoid a weight gain of more than 6.8 kg.

While the goal of treating hypertension is to reduce maternal risk, the agents selected must be effective and safe for the foetus.

Treatment of severe hypertension

There is no agreed definition of severe hypertension, with values ranging between 160 and 180 mmHg/>110 mmHg. This Task Force recommends considering an SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman an emergency, and hospitalization is indicated. The selection of the antihypertensive drug and its route of administration depend on the expected time of delivery. ACE inhibitors, ARBs and direct renin inhibitors are strictly contraindicated (see Chapter 12). Pharmacological treatment with i.v. labetalol, oral methyldopa, or nifedipine should be initiated; i.v. hydralazine is no longer the drug of choice. However, hydralazine is still commonly used when other treatment regimens have failed. Intravenous urapidil can also be considered. Sodium nitroprusside should only be used as the drug of last choice. The drug of choice when pre-eclampsia is associated with pulmonary oedema is nitroglycerin (glyceryl trinitrate).

Treatment of mild-to-moderate hypertension

Despite lack of evidence, the European guidelines recommend to initiate drug treatment in all women with persistent elevation of BP ≥150/95 mmHg and at values >140/90 mmHg in women with: gestational hypertension (with or without proteinuria); with pre-existing hypertension with the superimposition of gestational hypertension and hypertension with subclinical organ damage or symptoms at any time during pregnancy.

Methyldopa, β-blockers (most data available for labetalol) and calcium antagonists (most data available for nifedipine) are the drugs of choice. β-blockers appear to be less effective than calcium antagonists and may induce foetal bradycardia, growth retardation and hypoglycaemia. Women with pre-existing hypertension may continue their current antihypertensive medication unless on ACE inhibitors, ARBs, and direct renin inhibitors, which are contra-indicated due to adverse foetal and neonatal outcomes. Diuretic therapy is best avoided unless in the context of oliguria when low-dose furosemide may be considered. Intravenous magnesium sulfate is recommended for the prevention of eclampsia and treatment of seizures.

Delivery is indicated in pre-eclampsia with visual disturbances or haemostatic disorders and at 37 weeks in asymptomatic women. Breastfeeding does not increase BP in the nursing mother.

Post-partum hypertension is common in the first week. Methyldopa should be avoided because of the risk of post-partum depression.

Women experiencing hypertension in their first pregnancy are at increased risk in a subsequent pregnancy. The earlier the onset of hypertension in the first pregnancy, the higher the risk of recurrence in a subsequent pregnancy.

Women who develop gestational hypertension or pre-eclampsia are at increased risk of hypertension, stroke, and ischaemic heart disease in later adult life. Lifestyle modifications are primarily indicated to avoid complications in subsequent pregnancies and to reduce maternal cardiovascular risk in the future. Therefore, regular visits to a primary care physician to check BP and metabolic factors are recommended.

Management of hypertension		
Recommendations	**Class[a]**	**Level[b]**
Low-dose aspirin (100–150 mg daily) is recommended in women at high or moderate risk of pre-eclampsia from week 12 to weeks 36–37.	I	A
In women with gestational hypertension or pre-existing hypertension superimposed by gestational hypertension or with hypertension and subclinical organ damage or symptoms, initiation of drug treatment is recommended at SBP >140 mmHg or DBP >90 mmHg. In all other cases, initiation of drug treatment is recommended if SBP ≥150 mmHg or DBP ≥95 mmHg.	I	C
SBP ≥170 mmHg or DBP ≥110 mmHg in a pregnant woman is an emergency, and hospitalization is recommended.	I	C
Methyldopa, labetalol, and calcium antagonists are recommended for the treatment of hypertension in pregnancy.	I	B methyldopa C (labetalol, calcium antagonists)
In women with gestational hypertension or mild pre-eclampsia, delivery is recommended at 37 weeks.	I	B
It is recommended to expedite delivery in pre-eclampsia and with adverse conditions such as visual disturbances or haemostatic disorders.	I	C
In pre-eclampsia associated with pulmonary oedema, nitroglycerin given as an intravenous infusion is recommended.	I	C
In severe hypertension, drug treatment with intravenous labetalol or oral methyldopa or nifedipine is recommended.	I	C
Limitation of weight gain to <6.8 kg should be considered in obese women.	IIa	C
ACE inhibitors, ARBs or direct renin inhibitors are not recommended.	III	C

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
[a] Class of recommendation - [b] Level of evidence.

VTE, encompassing PE and deep vein/venous thrombosis (DVT), represents a significant cause of pregnancy-related morbidity and mortality. The risk of VTE is highest in the immediate post-partum period with rates of nearly 0.5% reported. In women with previous VTE, recurrence rates are 7.6% despite the use of LMWH.

All women should undergo a documented assessment of risk factors for VTE before pregnancy or in early pregnancy. Based on this, women can be classified as being at high, intermediate or low-risk of VTE and preventative measures applied accordingly. Previous unprovoked recurrent VTEs and previous VTE—unprovoked or oestrogen related—are considered high-risk factors.

LMWH has become the drug of choice for the prevention and treatment of VTE in pregnant patients. The initial dose of LMWH for thromboprophylaxis should be based on the booking weight (body weight at the first antenatal appointment with the gynaecologist) Patients at high-risk for VTE should receive prophylactic enoxaparin at 0.5 IU/kg of body weight once daily or other LMWH at equivalent doses, according to local practice. In morbidly obese women a weight-based dosing instead of a fixed dosing is more appropriate in order to achieve adequate anti-Xa concentrations.

Pulmonary embolism

For diagnosis, a high index of suspicion is important and all pregnant women with signs and symptoms suggestive of VTE should have objective testing performed urgently and receive therapeutic anticoagulation until the diagnosis is established. D-dimer levels increase physiologically with each trimester. Thus, a positive D-dimer test in pregnancy is not necessarily indicative of VTE and normal D-dimer concentrations have been reported in pregnant women with VTE, meaning that imaging remains the diagnostic test of choice during pregnancy.

LMWH: In suspected DVT or PE, therapeutic LMWH should be given until the diagnosis is excluded by objective testing The recommended therapeutic dose is calculated on early pregnancy body weight aiming for 4–6 hour peak anti-Xa values of 0.6–1.2 IU/mL.

UFH: Typically, UFH is used in the acute treatment of massive pulmonary emboli. (Chapter here).

Thrombolysis: Thrombolytics should only be used in patients with severe hypotension or shock

Fondaparinux: Fondaparinux (7.5 mg once a day in normal-weight pregnant woman) can be considered if there is an allergy or adverse response to LMWH (Chapter here).

Post-partum management:

In patients with recent PE, pre-partum heparin treatment should be restarted 6 hours after a vaginal birth and 12 hours after a caesarean delivery, if no significant bleeding has occurred, with subsequent overlap with VKAs for at least 5 days. VKAs may be started on the second day after delivery and continued for at least 3 months or for 6 months if PE occurred late in pregnancy. The INR should be between 2 and 3 and needs regular monitoring, ideally every 1–2 weeks.

Acute deep vein thrombosis

Leg swelling is a frequent finding in pregnancy, giving rise to the suspicion of DVT. Since DVT is left sided in >85% of cases swelling of the left leg is more suspicious. Three clinical variable – left leg presentation, >2 cm calf circumference difference, and first trimester – allowed a negative predictive value of 100% if ultrasound of the legs was negative.

Compression ultrasound is the diagnostic imaging procedure of choice for suspected DVT in pregnancy with a high sensitivity and specificity for proximal DVT. In acute DVT, treatment with therapeutic doses of weight adjusted LMWH should be given twice daily (as in PE).

Prevention and treatment of venous thromboembolism		
Recommendations	**Class[a]**	**Level[b]**
LMWH is recommended for the prevention and treatment of VTE in pregnant patients.	I	B
For high-risk women it is recommended to give a weight-related prophylactic dose of LMWH (e.g. enoxaparin 0.5 mg/kg once daily).	I	B
A documented assessment of risk factors for VTE before pregnancy or in early pregnancy is recommended in all women.	I	C
It is recommended that the therapeutic dose of LMWH is based on body weight.	I	C
Thrombolytics to manage patients with pulmonary embolism is only recommended in patients with severe hypotension or shock.	I	C
In high-risk women, it is recommended to convert LMWH to UFH at least 36 hours prior to delivery and stop the UFH infusion 4–6 hours prior to anticipated delivery. aPTT should be normal before regional anaesthesia.	I	C
In low-risk women on therapeutic LMWH, induction or caesarean section is recommended to be performed 24 hours after the last dose of LMWH.	I	C
For women after in vitro fertilization complicated by OHSS thromboprophylaxis with LMWH is recommended during the first trimester.	I	C
In women who are on antenatal anticoagulation it should be considered to actively manage the third stage of labour with oxytocin.	IIa	C
If compression ultrasound is negative, using magnetic resonance venography should be considered to diagnose pelvic thrombosis before using computed tomography pulmonary angiography or ventilation perfusion scanning.	IIa	C
In women on therapeutic LMWH, planned delivery should be considered at around 39 weeks to avoid the risk of spontaneous labour while fully anticoagulated (LMWH is only partially reversed with protamine).	IIa	C
Direct oral anticoagulants are not recommended in pregnancy.	III	B

aPTT = activated partial thromboplastin time; LMWH = low molecular weight heparin; OHSS = ovarian hyperstimulation syndrome; UFH = unfractionated heparin; VTE = venous thromboembolism.

[a] Class of recommendation - [b] Level of evidence.

There are no uniform recommendations for the treatment of pregnant women yet. In case of emergency, drugs that are not recommended by international agencies during pregnancy and breastfeeding should not be withheld from the mother. The potential risk of a drug and the possible benefit of the therapy must be weighed against each other.

US Food and Drug Administration classification

On 30 June 2015 the US Food and Drug Administration (FDA) changed the previously used classification system for counselling of pregnant women and nursing mothers requiring drug therapy. The former A to X categories have been replaced by the Pregnancy and Lactation Labelling Rule (PLLR), which provides a descriptive risk summary and detailed information on animal and clinical data. PLLR applies immediately for prescription drugs approved after 30 June 2015, and the former FDA categories have to be removed for all other drugs until 29 June 2018. However, the former FDA categories will be present in the literature for a longer period of time, and therefore Table 7 (Drugs and safety data) provides information on both systems.

The previous classification consisted of category A (safest) to Category D (evidence of human foetal risk) and, X (known danger—do not use!).

Drug use in pregnancy

Recommendations	Class[a]	Level[b]
Before pharmacological treatment in pregnancy is started, it is recommended to check drug Table 7 for clinical safety data.	I	C
In the absence of clinical safety data it is recommended to check electronic drug table (www.safefetus.com) for preclinical safety data.	I	C
In the absence of adequate human safety data, decision-making should be based on individual drug efficacy and safety profile, and available animal data, and the decision must be made together with the patient.	IIa	C
Decision-making based on former FDA categories alone is no longer recommended.	III	C

FDA = Food and Drug Administration.
[a] Class of recommendation - [b] Level of evidence.

Table 7: Drugs and safety data is available in the Full text of the ESC Guidelines for cardiovascular Diseases during pregnancy at: www.escardio.org/guidelines

2017 ESC Pocket Guidelines

Committee for Practice Guidelines

VHD

2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease

ESC
European Society of Cardiology

EACTS

www.escardio.org/guidelines

Since the previous version of the Guidelines on the management of VHD was published, in 2012, new evidence has accumulated, particularly on percutaneous interventional techniques and on risk stratification with regard to timing of intervention in VHD making the present update necessary. This document focuses on acquired VHD and is oriented towards management. It does not deal with endocarditis or congenital valve disease, including pulmonary valve disease, as separate guidelines have been published by the ESC on these topics.

Patient evaluation

Essential questions in the evaluation

The aims of the evaluation of patients with VHD are to diagnose, quantify, and assess the mechanism of VHD as well as its consequences. Decision-making for intervention should be made by a "Heart Team" with a particular expertise in VHD, comprising cardiologists, cardiac surgeons, imaging specialists, anaesthetists, and if needed, general practitioners, geriatricians, and heart failure, electrophysiology or intensive care specialists. The "Heart Team" approach is particularly advisable in the management of high-risk patients and is also important for other subsets, such as asymptomatic patients where the evaluation of valve reparability is a key component in decision-making. The essential questions in the evaluation of a patient for valvular intervention are summarized in Table 3.

Table 3 Essential questions in the evaluation of patients for valvular intervention

Questions
• How severe is VHD?
• What is the aetiology of VHD?
• Does the patient have symptoms?
• Are symptoms related to valvular disease?
• Are any signs present in asymptomatic patients that indicate a worse outcome if the intervention is delayed?
• What are the patient's life expectancy[a] and expected quality of life?
• Do the expected benefits of intervention (versus spontaneous outcome) outweigh its risks?
• What is the optimal treatment modality? Surgical valve replacement (mechanical or biological), surgical valve repair, or catheter intervention?
• Are local resources (local experience and outcome data for a given intervention) optimal for the planned intervention?
• What are the patient's wishes?

[a]Life expectancy should be estimated according to age, sex, comorbidities, and country-specific life expectancy.

Overview

Precise evaluation of the patient's history and symptomatic status as well as proper physical examination, in particular auscultation and search for heart failure signs, are crucial for the diagnosis and management of VHD. In addition, assessment of the extracardiac condition – comorbidities and general condition – require particular attention. Echocardiography is the key technique to diagnose VHD and to assess its aetiology, severity, mechanisms, pathophysiologic consequences (cardiac chamber size, ventricular function, pulmonary artery pressure) and prognosis. Other non-invasive investigations such as stress testing, CMR, CT, fluoroscopy, and biomarkers are complementary, and invasive investigation beyond preoperative coronary angiography is restricted to situations where non-invasive evaluation is inconclusive.

Echocardiographic criteria for the definition of severe valve stenosis are indicated in the corresponding sections, and quantification of regurgitant lesions is summarized in Table 4. An integrated approach including various criteria is strongly recommended instead of referring to single measurements. Indications for coronary angiography are summarized in the Table "Management of CAD in patients with VHD".

Risk stratification

Risk stratification applies to any sort of intervention and is required for weighing the risk of intervention against the expected natural history of VHD as a basis for decision-making. Most experience relates to surgery and TAVI. While EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard, it is nevertheless provided in this document for comparison as it has been used in many TAVI studies/ registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality. Both scores have, however, major limitations for practical use by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc. It remains essential not to rely on a single risk score figure when assessing patients, nor to determine unconditionally the indication and type of intervention. Patient's life expectancy, expected quality of life, and patient preference should be considered, as well as local resources and results. The futility of interventions in patients unlikely to benefit from the treatment has to be taken into consideration, particularly for TAVI and mitral edge-to- edge repair. The role of the Heart Team is essential to take all of these data into account and adopt a final decision on the best treatment strategy.

Table 4 Echocardiographic criteria for the definition of severe valve regurgitation: an integrative approach (adapted from Lancellotti *et al.*)		
Aortic regurgitation		
Qualitative		
Valve morphology	Abnormal/flail/large coaptation defect	
Colour flow regurgitant jet	Large in central jets, variable in eccentric jets[a]	
CW signal of regurgitant jet	Dense	
Other	Holodiastolic flow reversal in descending aorta (EDV >20 cm/s)	
Semiquantitative		
Vena contracta width (mm)	>6	
Upstream vein flow[c]	–	
Inflow	–	
Other	Pressure half-time <200 ms[f]	
Quantitative		
EROA (mm^2)	≥30	
Regurgitant volume (mL/beat)	≥60	
+ enlargement of cardiac chambers/vessels	LV	
Mitral regurgitation		
Qualitative		
Valve morphology	Flail leaflet/ruptured papillary muscle/large coaptation defect	
Colour flow regurgitant jet	Very large central jet or eccentric jet adhering, swirling, and reaching the posterior wall of the LA	
CW signal of regurgitant jet	Dense/triangular	
Other	Large flow convergence zone[a]	
Semiquantitative		
Vena contracta width (mm)	≥7 (>8 for biplane)[b]	
Upstream vein flow[c]	Systolic pulmonary vein flow reversal	
Inflow	E-wave dominant ≥1.5 m/s[d]	
Other	TVI mitral/TVI aortic >1.4	
Quantitative	**Primary**	**Secondary[h]**
EROA (mm^2)	≥40	≥20
Regurgitant volume (mL/beat)	≥60	≥30
+ enlargement of cardiac chambers/vessels	LV,LA	

Tricuspid regurgitation	
Qualitative	
Valve morphology	Abnormal/flail/large coaptation defect
Colour flow regurgitant jet	Very large central jet or eccentric wall impinging jet[a]
CW signal of regurgitant jet	Dense/triangular with early peaking (peak <2 m/s in massive TR)
Other	–
Semiquantitative	
Vena contracta width (mm)	≥7[a]
Upstream vein flow[c]	Systolic hepatic vein flow reversal
Inflow	E-wave dominant ≥1 m/s[e]
Other	PISA radius >9 mm[g]
Quantitative	
EROA (mm^2)	≥40
Regurgitant volume (mL/beat)	≥45
+ enlargement of cardiac chambers/vessels	RV, RA, inferior vena cava

CW = continuous wave; EDV = end-diastolic velocity; EROA = effective regurgitant orifice area; LA = left atrium/ atrial; LV = left ventricle/ventricular; PISA = proximal isovelocity surface area; RA = right atrium/right atrial; RV = right ventricle; TR = tricuspid regurgitation; TVI = time-velocity integral.

[a]At a Nyquist limit of 50–60 cm/s - [b]For average between apical four- and two-chamber views - [c]Unless other reasons for systolic blunting (atrial fibrillation, elevated atrial pressure) - [d]In the absence of other causes of elevated LA pressure and of mitral stenosis - [e]In the absence of other causes of elevated RA pressure - [f]Pressure half-time is shortened with increasing LV diastolic pressure, vasodilator therapy, and in patients with a dilated compliant aorta, or lengthened in chronic aortic regurgitation - [g]Baseline Nyquist limit shift of 28 cm/s- [h]Different thresholds are used in secondary mitral regurgitation where an EROA >20 mm^2 and regurgitant volume >30 mL identify a subset of patients at increased risk of cardiac events.

Management of coronary artery disease in patients with VHD (adapted from Windecker *et al.*)

Recommendations	Class[a]	Level[b]
Diagnosis of coronary artery disease		
Coronary angiography[c] is recommended before valve surgery in patients with severe VHD and any of the following: • history of cardiovascular disease • suspected myocardial ischaemia[d] • LV systolic dysfunction • in men aged over >40 years and postmenopausal women • one or more cardiovascular risk factors.	I	C
Coronary angiography is recommended in the evaluation of moderate to severe secondary mitral regurgitation.	I	C
CT angiography should be considered as an alternative to coronary angiography before valve surgery in patients with severe VHD and low probability of CAD or in whom conventional coronary angiography is technically not feasible or associated with a high-risk.	IIa	C
Indications for myocardial revascularization		
CABG is recommended in patients with a primary indication for aortic/ mitral valve surgery and coronary artery diameter stenosis ≥70%.[e]	I	C
CABG should be considered in patients with a primary indication for aortic/mitral valve surgery and coronary artery diameter stenosis ≥50–70%.	IIa	C
PCI should be considered in patients with a primary indication to undergo TAVI and coronary artery diameter stenosis >70% in proximal segments.	IIa	C
PCI should be considered in patients with a primary indication to undergo transcatheter mitral valve interventions and coronary artery diameter stenosis >70% in proximal segments.	IIa	C

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CT = computed tomography; LV = left ventricular; MSCT = multislice computed tomography; PCI = percutaneous coronary intervention; TAVI = transcatheter aortic valve implantation;VHD = valvular heart disease.

[a]Class of recommendation - [b]Level of evidence - [c]MSCT may be used to exclude CAD in patients who are at low risk of atherosclerosis - [d]Chest pain, abnormal non-invasive testing - [e]≥50% can be considered for left main stenosis.

Special considerations in elderly patients

Poor mobility, as assessed by the 6-minute walk test, and oxygen dependency are the main factors associated with increased mortality after TAVI and other VHD treatments. The combination of severe lung disease, post-operative pain from sternotomy or thoracotomy, and prolonged time under anaesthesia in patients undergoing traditional surgical aortic valve replacement may contribute to pulmonary complications. There is a gradual relationship between the impairment of renal function and increased mortality after surgical and catheter interventions. Coronary, cerebrovascular, and peripheral artery disease have a negative impact on early and late survival.

Endocarditis prophylaxis

Antibiotic prophylaxis should be considered for high-risk procedures in patients with prosthetic valves including transcatheter valves or repairs using prosthetic material and those with previous episodes of infective endocarditis. Detailed recommendations are given in dedicated guidelines.

Prophylaxis for rheumatic fever

Prevention of rheumatic heart disease should preferably be orientated to preventing the first attack of acute rheumatic fever. Antibiotic treatment of Group A Streptococcus sore throat is key in primary prevention. In patients with rheumatic heart disease, secondary long-term prophylaxis against rheumatic fever is recommended. Lifelong prophylaxis should be considered in high-risk patients according to the severity of VHD and exposure to Group A Streptococcus.

Heart Team and heart valve centres

The main purpose of heart valve centres as centres of excellence in the treatment of VHD is to deliver better quality of care. This is achieved through greater volumes associated with specialization of training, continuing education, and clinical interest. Specialization will also result in timely referral of patients before irreversible adverse effects occur, and evaluation of complex VHD conditions. Techniques with a steep learning curve may be performed with better results in hospitals with high volumes and more experience. These main aspects are presented in Table 5.

Table 5 Recommended requirements of a heart valve centre (modified from Chambers *et al.*)

Requirements
Multidisciplinary teams with competencies in valve replacement, aortic root surgery, mitral, tricuspid and aortic valve repair, as well as transcatheter aortic and mitral valve techniques including reoperations and reinterventions. The Heart Teams must meet on a regular basis and work with standard operating procedures.
Imaging, including 3D and stress echocardiographic techniques, perioperative TOE, cardiac CT, MRI, and positron emission tomography-CT.
Regular consultation with community, other hospitals, and extracardiac departments, and between non-invasive cardiologists and surgeons and interventional cardiologists.
Back-up services including other cardiologists, cardiac surgeons, intensive care and other medical specialties.
Data review: • Robust internal audit processes including mortality and complications, repair rates, durability of repair, and reoperation rate with a minimum of 1-year follow-up. • Results available for review internally and externally. • Participation in national or European quality databases.

Management of CAD and atrial fibrillation are summarized in the according tables.

Management of atrial fibrillation in patients with VHD

Recommendations	Class[a]	Level[b]
Anticoagulation		
NOACs should be considered as an alternative to VKAs in patients with aortic stenosis, aortic regurgitation, and mitral regurgitation presenting with atrial fibrillation.	IIa	B
NOACs should be considered as alternative to VKAs after the thirdmonth of implantation in patients who have atrial fibrillation associated with a surgical or transcatheter aortic valve bioprosthesis.	IIa	C
The use of NOACs is not recommended in patients with atrial fibrillation and moderate to severe mitral stenosis.	III	C
NOACS are contra-indicated in patients with a mechanical valve.	III	B
Surgical interventions		
Surgical ablation of atrial fibrillation should be considered in patients with symptomatic atrial fibrillation who undergo valve surgery.	IIa	A
Surgical ablation of atrial fibrillation may be considered in patients with asymptomatic atrial fibrillation who undergo valve surgery, if feasible, with minimal risk.	IIb	C
Surgical excision or external clipping of the LA appendage may be considered in patients undergoing valve surgery.	IIb	B

Aortic regurgitation

Overview

Aortic regurgitation (AR) can be caused by primary disease of the aortic valve cusps and/or abnormalities of the aortic root and ascending aortic geometry. Degenerative tricuspid and bicuspid AR are the most common aetiologies in Western countries. Other causes include infective and rheumatic endocarditis. Acute severe AR is mostly caused by infective endocarditis and less frequently by aortic dissection, and is addressed iin the relevant guidelines.

Evaluation

Echocardiography is the key examination to describe valve anatomy, quantify AR, evaluate its mechanisms, define the morphology of the aorta, and determine the feasibility of valve-sparing aortic surgery or valve repair. Essential aspects of this evaluation include:

- Assessment of valve morphology: tricuspid, bicuspid, unicuspid, or quadricuspid valve.
- Determination of the direction of the AR jet in the long-axis view (central or eccentric) and its origin in the short-axis view (central or commissural).
- Identification of the mechanism, following the same principle as for MR: normal cusps but insufficient coaptation due to dilatation of the aortic root with central jet (type 1); cusp prolapse with eccentric jet (type 2); retraction with poor cusp tissue quality and large central or eccentric jet (type 3).
- Quantification of AR should follow an integrated approach considering all qualitative, semiquantitative, and quantitative parameters (Table 4).
- Measurement of LV function and dimensions. Indexing LV diameters for body surface area (BSA) is recommended in patients with small body size (BSA <1.68 m^2). New parameters obtained by three-dimensional (3D) echocardiography, tissue Doppler, and strain rate imaging may be useful, particularly in patients with borderline left ventricular ejection fraction (LVEF) where they may help in the decision for surgery.
- Measurement of the aortic root and ascending aorta in the 2-dimensional (2D) mode at four levels: annulus, sinuses of Valsalva, sinotubular junction, and tubular ascending aorta. Measurements are taken in the parasternal long- axis view from leading edge to leading edge at end diastole except forthe aortic annulus, which is measured in mid systole. As it will have surgical consequences, it is of importance to differentiate three phenotypes of the ascending aorta:1) aortic root aneurysms (sinuses of Valsalva >45 mm); 2) tubular ascending aneurysm (sinuses of Valsalva <40–45 mm); 3) isolated AR (all diameters <40 mm). The calculation of indexed values has been recommended to account for body size.
- Definition of the anatomy of the aortic valve cusps and assessment of valve reparability should be provided by preoperative TOE if aortic valve repair or a valve-sparing surgery of the aortic root is considered.

CMR should be used to quantify regurgitant fraction when echocardiographic measurements are equivocal. In patients with aortic dilatation, gated MSCT is recommended to assess the maximum diameter. CMR can be used for follow-up but indication for surgery should preferably be based on CT measurements.

The indications for intervention in chronic AR are summarized in the table of recommendations on indications for surgery in severe AR and aortic root disease and in Figure 1, and may be related to symptoms, status of the LV, or dilatation of the aorta.

Indications for surgery in (A) severe aortic regurgitation and (B) aortic root disease (irrespective of the severity of aortic regurgitation)

Indications for surgery	Class[a]	Level[b]
A. Severe aortic regurgitation		
Surgery is indicated in symptomatic patients.	I	B
Surgery is indicated in asymptomatic patients with resting LVEF ≤50%.	I	B
Surgery is indicated in patients undergoing CABG or surgery of the ascending aorta or of another valve.	I	C
Heart Team discussion is recommended in selected patients[c] in whom aortic valve repair may be a feasible alternative to valve replacement.	I	C
Surgery should be considered in asymptomatic patients with resting ejection fraction >50% with severe LV dilatation:LVEDD >70 mm,or LVESD >50 mm (or LVESD >25 mm/m^2 BSA in patients with small body size).	IIa	B
B. Aortic root or tubular ascending aorta aneurysm[d] (irrespective of the severity of aortic regurgitation)		
Aortic valve repair, using the reimplantation or remodelling with aortic annuloplasty technique, is recommended in young patients with aortic root dilation and tricuspid aortic valves,when performed by experienced surgeons.	I	C

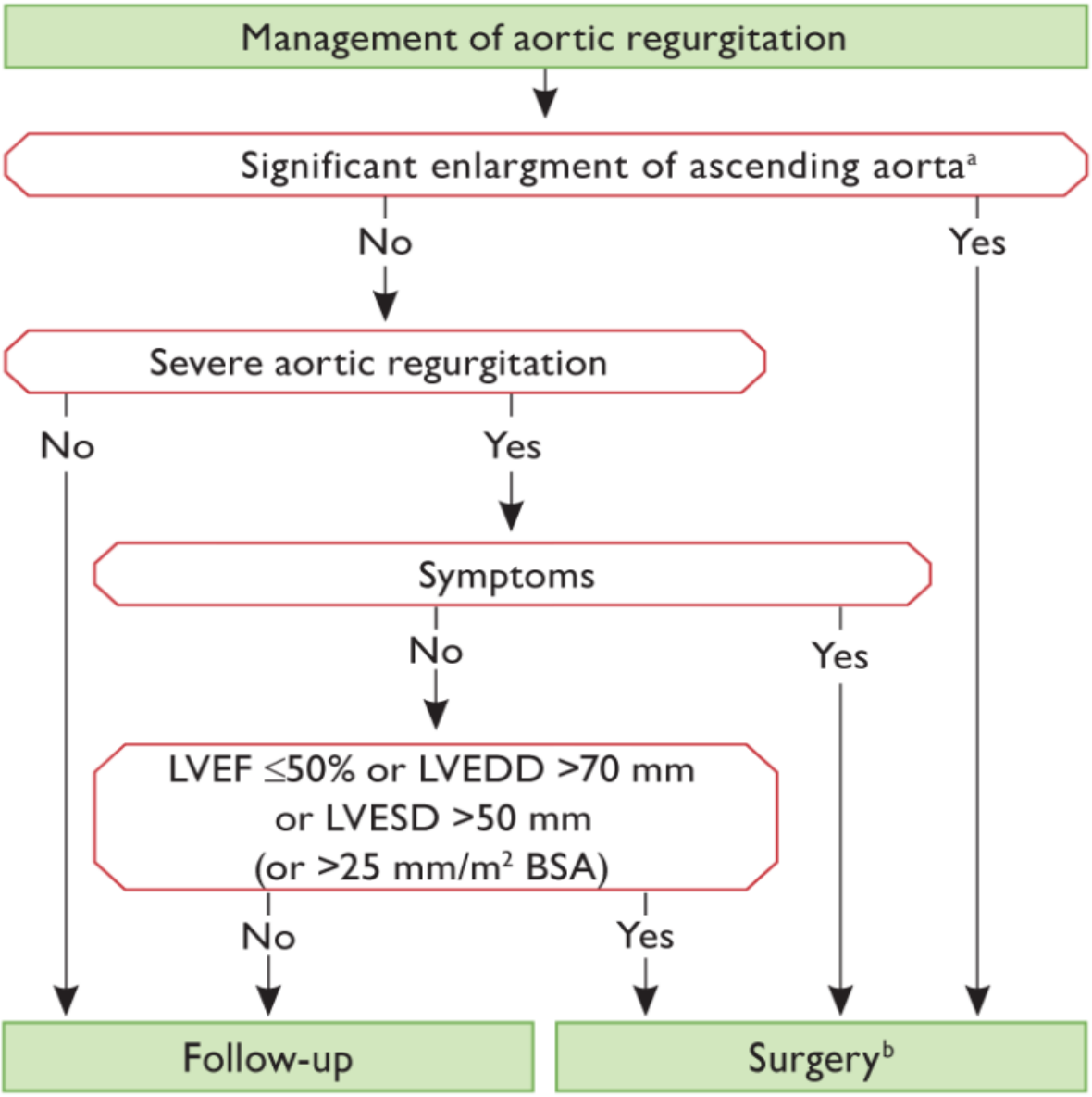
Surgery is indicated in patients with Marfan syndrome, who have aortic root disease with a maximal ascending aortic diameter ≥50 mm.	I	C
Surgery should be considered in patients who have aortic root disease with maximal ascending aortic diameter: • ≥45 mm in the presence of Marfan syndrome and additional risk factors,[e] or patients with a *TGFBR1* or *TGFBR2* mutation (including Loeys-Dietz syndrome).[f] • ≥50 mm in the presence of a bicuspid valve with additional risk factors[e] or coarctation. • ≥55 mm for all other patients.	IIa	C
When surgery is primarily indicated for the aortic valve, replacement of the aortic root or tubular ascending aorta should be considered when ≥45 mm, particularly in the presence of a bicuspid valve.[g]	IIa	C

BSA = body surface area; CABG = coronary artery bypass grafting; CT = computed tomography; ECG = electrocardiogram; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter.

[a] Class of recommendation - [b] Level of evidence - [c] Patients with pliable non-calcified tricuspid or bicuspid valves who have a type I (enlargement of the aortic root with normal cusp motion) or type II (cusp prolapse) mechanism of aortic regurgitation - [d] For clinical decision-making, dimensions of the aorta should be confirmed by ECG-gated CT measurement - [e]Family history of aortic dissection (or personal history of spontaneous vascular dissection), severe aortic regurgitation or mitral regurgitation, desire of pregnancy, systemic hypertension, and/or aortic size increase >3 mm/year (on repeated measurements using the same ECG-gated imaging technique, measured at the same level of the aorta with side-by-side comparison and confirmed by another technique) - [f]A lower threshold of 40 mm may be considered in women with low BSA, in patients with a TGFBR2 mutation, or in patients with severe extra-aortic features - [g] Considering age, BSA, aetiology of valvular disease, presence of a bicuspid aortic valve, and intraoperative shape and thickness of the ascending aorta.

Algorithm Mgmt. of aortic regurgitation

Figure 1 Management of aortic regurgitation



AR = aortic regurgitation;BSA = body surface area;LVEDD = left ventricle end-diastolic diameter; LVEF = left ventricular ejection fraction;LVESD = left ventricle end-systolic diameter.

[a]See table of recommendations on indications for surgery in severe aortic regurgitation and aortic root disease in section 4.2 for definition - [b]Surgery should also be considered if significant changes in LV or aortic size occur during follow-up (see table of recommendations on indications for surgery in severe aortic regurgitation and aortic root disease in section 4.2).

Medical therapy

In patients with Marfan syndrome, beta-blockers and/or losartan may slow aortic root dilatation and reduce the risk of aortic complications, and should be considered before and after surgery. By analogy, while there are no studies that provide evidence, it is common clinical practice to advise beta-blocker or losartan therapy also in patients with bicuspid aortic valve if the aortic root and/ or ascending aorta is dilated.

Serial testing

All asymptomatic patients with severe AR and normal LV function should be seen at least every year. In patients with a first diagnosis, or if LV diameter and/or ejection fraction show significant changes or come close to thresholds for surgery, follow-up should be continued at 3–6 month intervals. In inconclusive cases, BNP may be helpful. Patients with mild-to-moderate AR can be reviewed on a yearly basis and echocardiography performed every 2 years. If the ascending aorta is dilated (>40 mm) it is recommended to perform CT or CMR.

Special patient populations

If AR requiring surgery is associated with severe MR, both should be addressed during the same operation. In patients with moderate AR who undergo coronary artery bypass grafting (CABG) or mitral valve surgery, the decision to treat the aortic valve is controversial as data show that progression of moderate AR is very slow in patients without aortic dilatation. The Heart Team should decide based on the aetiology of AR, other clinical factors, the life expectancy of the patient, and their operative risk.

Aortic stenosis

Overview

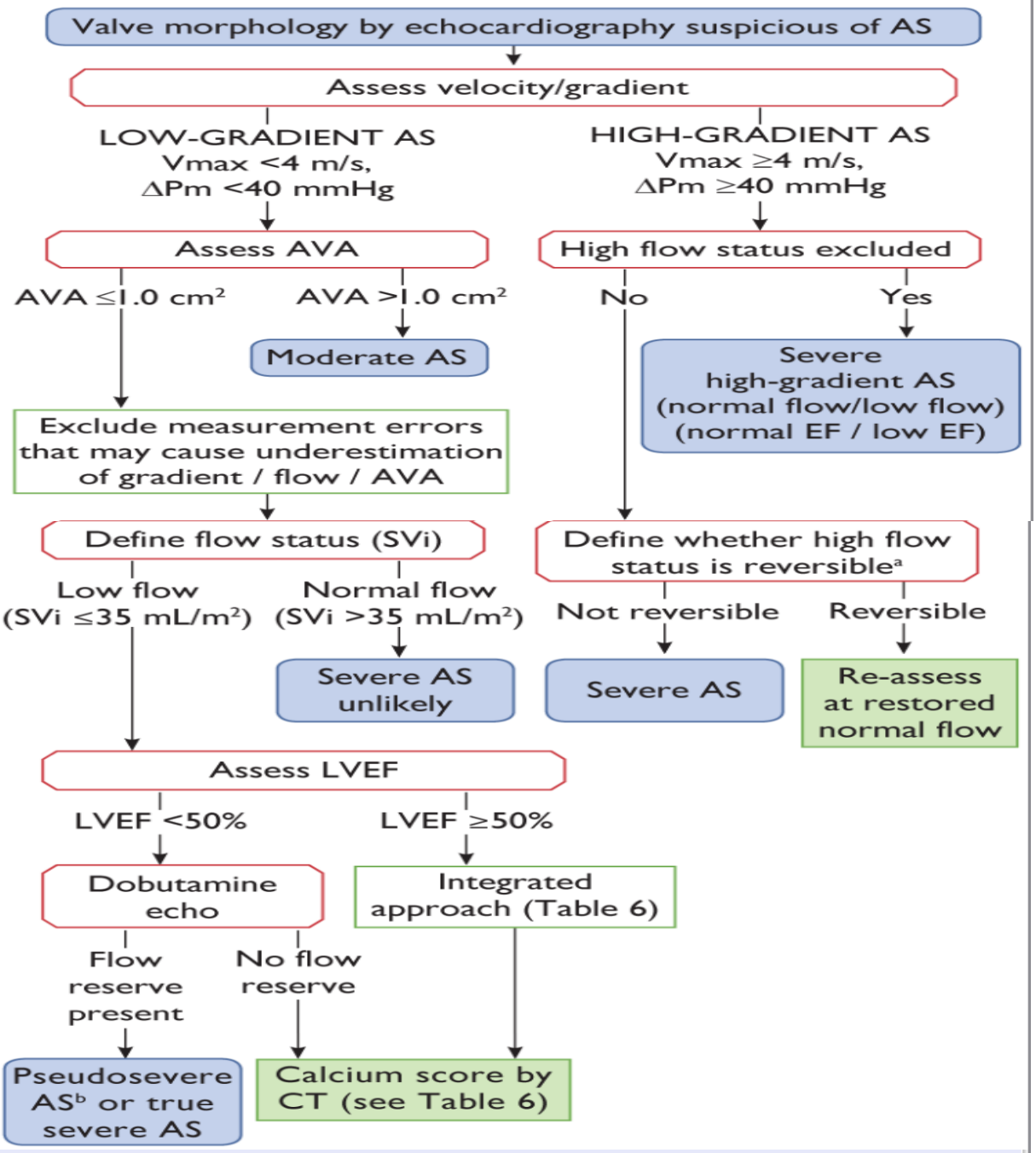
Aortic stenosis (AS) is the most common primary valve disease leading to surgery or catheter intervention in Europe and North America, with a growing prevalence due to the ageing population.

Evaluation

Introduction

Echocardiography is the key diagnostic tool. It confirms the presence of AS, assesses the degree of valve calcification, LV function and wall thickness, detects the presence of other associated valve disease or aortic pathology, and provides prognostic information. Doppler echocardiography is the preferred technique for assessing the severity of AS. Figure 2 and Table 6 provide a practical stepwise approach for the assessment of AS severity. Details can be found in a recent position paper of the European Association of Cardiovascular Imaging (EACVI).

Figure 2 Stepwise integrated approach for the assessment of AS severity (modified from Baumgartner *et al*). High flow may be reversible in settings such as anaemia, hyperthyroidism, arteriovenous shunts. Pseudosevere AS is defined by an increase to an AVA >1.0cm^2 with flow normalization



ΔPm = mean transvalvular pressure gradient; AS = aortic stenosis; AVA = aortic valve area; CT = computed tomography; EF = ejection fraction; LVEF = left ventricular ejection fraction; SVi = stroke volume index; Vmax = peak transvalvular velocity.
[a]High flow may be reversible in settings such as anaemia, hyperthyroidism, arteriovenous shunts.
[b]Pseudosevere AS is defined by an increase to an AVA >1.0 cm2 with flow normalization.

Table 6 Criteria that increase the likelihood of severe aortic stenosis in patients with AVA <1.0 cm² and mean gradient <40 mmHg in the presence of preserved ejection fraction (modified from Baumgartner *et al.*)

Criteria	
Clinical criteria	• Typical symptoms without other explanation • Elderly patient (>70 years)
Qualitative imaging data	• LV hypertrophy (additional history of hypertension to be considered) • Reduced LV longitudinal function without other explanation
Quantitative imaging data	• Mean gradient 30–40 mmHg[a]
	• AVA ≤0.8 cm²
	• Low flow (SVi <35 mL/m²) confirmed by techniques other than standard Doppler technique (LVOT measurement by 3D TOE or MSCT; CMR, invasive data)
	• Calcium score by MSCT[b] Severe aortic stenosis very likely: men≥ 3000; women≥ 1600 Severe aortic stenosis likely: men≥ 2000; women≥ 1200 Severe aortic stenosis unlikely: men <1600; women <800

3D = three-dimensional; AVA = aortic valve area; CMR = cardiovascular magnetic resonance; LV = left ventricular; LVOT = left ventricular outflow tract; MSCT = multislice computed tomography; SVi = stroke volume index; TOE = transoesophageal echocardiography.

[a]Haemodynamics measured when the patient is normotensive.

[b]Values are given in arbitrary units using Agatston method for quantification of valve calcification.

Additional diagnostic aspects, including assessment of prognostic parameters:

Exercise testing is recommended in physically active patients for unmasking symptoms and for risk stratification of asymptomatic patients with severe AS. TOE provides additional evaluation of concomitant mitral valve abnormalities. It has gained importance in the assessment before TAVI and after TAVI or surgical procedures.

MSCT and ***CMR*** provide additional information on the dimensions and geometry of the aortic root and ascending aorta and the extent of calcification. MSCT has become particularly important for the quantification of valve calcification when assessing AS severity in low-gradient AS. CMR may be useful for the detection and quantification of myocardial fibrosis, providing additional prognostic information regardless of the presence of CAD.

Natriuretic peptides have been shown to predict symptom-free survival and outcome in normal and low-flow severe AS, and may be useful in asymptomatic patients to determine optimal timing of intervention.

Retrograde LV catheterization to assess the severity of AS is no longer routinely performed. Its use is restricted to patients with inconclusive non- invasive investigations.

Diagnostic work-up before transcatheter aortic valve implantation: MSCT is the preferred imaging tool to assess anatomy and dimensions of the aortic root, size and shape of the aortic valve annulus, its distance to the coronary ostia, the distribution of calcifications, and the number of aortic valve cusps. It is essential to evaluate the feasibility of the various access routes as it provides information on minimal luminal diameters, atherosclerotic plaque burden, presence of aneurysms or thrombi, vessel tortuosity, and thoracic and LV apex anatomy. CMR–as an alternative technique–is, in this context, inferior to MSCT with regards to assessment of inner vessel dimensions and calcifications. 3D TOE can be used to determine aortic annulus dimensions but remains more operator- and image- quality–dependent than MSCT.

The indications for aortic valve interventions are summarized in the table of indications for intervention in AS and recommendations for the choice of intervention mode and in Table 7, and are illustrated in Figure 3.

Indications for intervention in aortic stenosis and recommendations for the choice of intervention mode

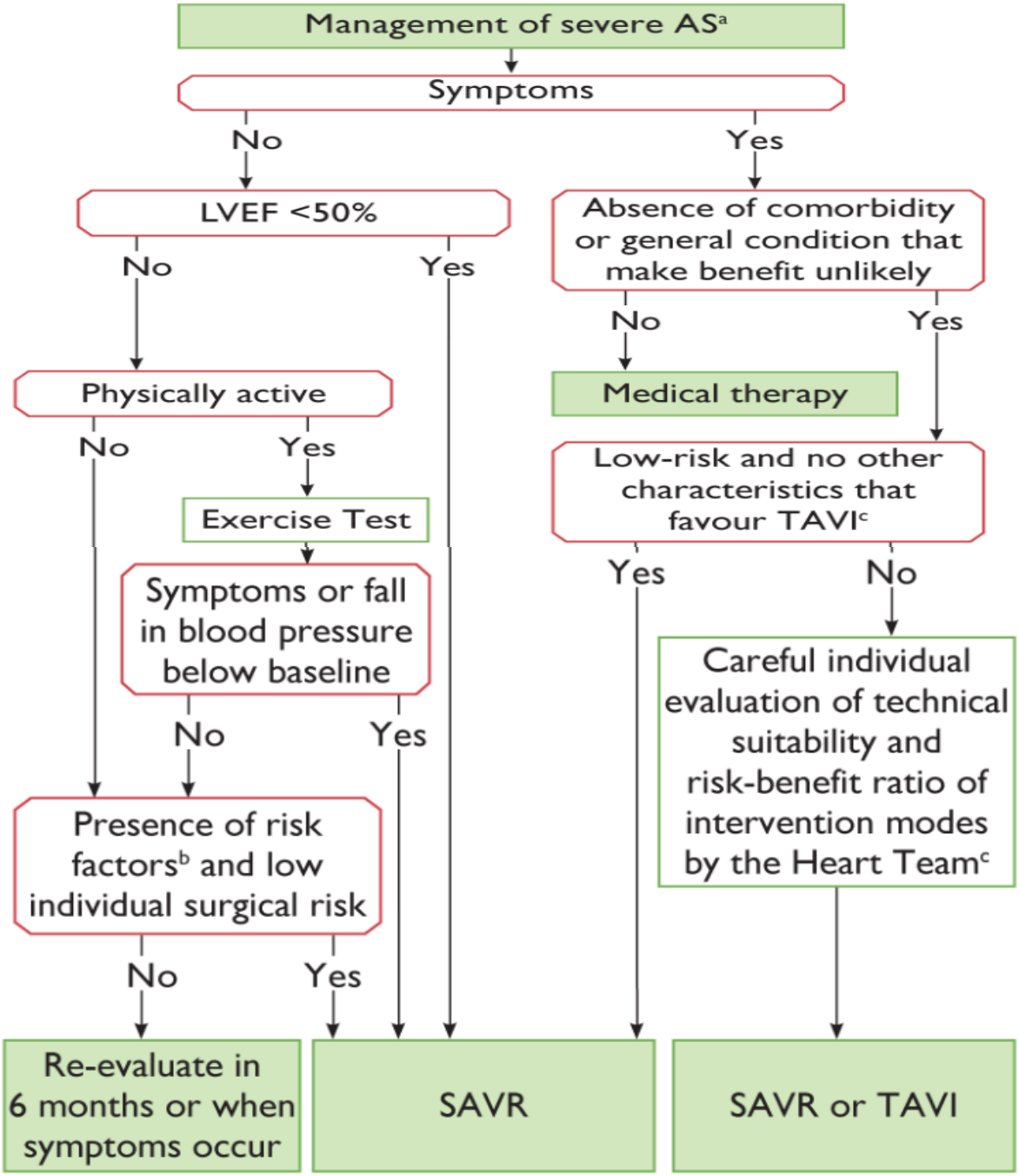
Recommendations	Class[a]	Level[b]
a) Symptomatic aortic stenosis		
Intervention is indicated in symptomatic patients with severe, high-gradient aortic stenosis (mean gradient ≥40 mmHg or peak velocity ≥4.0 m/s).	I	B
Intervention is indicated in symptomatic patients with severe low-flow, low-gradient (<40 mmHg) aortic stenosis with reduced ejection fraction, and evidence of flow (contractile) reserve excluding pseudosevere aortic stenosis.	I	C
Intervention should be considered in symptomatic patients with low-flow, low-gradient (<40 mmHg) aortic stenosis with normal ejection fraction after careful confirmation of severe aortic stenosis[c] (see Figure 2 and Table 6).	IIa	C
Intervention should be considered in symptomatic patients with low- flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis.	IIa	C
Intervention should not be performed in patients with severe comorbidities when the intervention is unlikely to improve quality of life or survival.	III	C

b) Choice of intervention in symptomatic aortic stenosis		
Aortic valve interventions should only be performed in centres with both departments of cardiology and cardiac surgery on-site, and with structured collaboration between the two, including a Heart Team (heart valve centres).	I	C
The choice for intervention must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each modality (aspects to be considered are listed in Table 7). In addition, the local expertise and outcomes data for the given intervention must be taken into account.	I	C
SAVR is recommended in patients at low surgical risk (STS or EuroSCORE II <4% or logistic EuroSCORE I <10%[d] and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation).	I	B
TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team.	I	B
In patients who are at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%[d] or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics (see Table 7), with TAVI being favoured in elderly patients suitable for transfemoral access.	I	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients or in patients with symptomatic severe aortic stenosis who require urgent major non-cardiac surgery.	IIb	C
Balloon aortic valvotomy may be considered as a diagnostic means in patients with severe aortic stenosis and other potential cause for symptoms (i.e. lung disease) and in patients with severe myocardial dysfunction, pre-renal insufficiency or other organ dysfunction that may be reversible with balloon aortic valvotomy when performed in centres that can escalate to TAVI.	IIb	C
c) Asymptomatic patients with severe aortic stenosis (refers only to patients eligible for surgical valve replacement)		
SAVR is indicated in asymptomatic patients with severe aortic stenosis and systolic LV dysfunction (LVEF <50%) not due to another cause.	I	C
SAVR is indicated in asymptomatic patients with severe aortic stenosis and abnormal exercise test showing symptoms on exercise clearly related to aortic stenosis.	I	C
SAVR should be considered in asymptomatic patients with severe aortic stenosis and abnormal exercise test showing fall in blood pressure below baseline.	IIa	C

SAVR should be considered in asymptomatic patients with normal ejection fraction and none of the above-mentioned exercise test abnormalities if the surgical risk is low and one of the following findings is present: • Very severe aortic stenosis defined by a V_{max} >5.5 m/s • Severe valve calcification and a rate of V_{max} progression ≥ 0.3 m/s/year • Markedly elevated BNP levels (>threefold age- and sex-corrected normal range) confirmed by repeated measurements without other explanations • Severe pulmonary hypertension (systolic pulmonary artery pressure at rest >60 mmHg confirmed by invasive measurement) without other explanation.	IIa	C
d) Concomitant aortic valve surgery at the time of other cardiac/ ascending aorta surgery		
SAVR is indicated in patients with severe aortic stenosis undergoing CABG, or surgery of the ascending aorta or of another valve.	I	C
SAVR should be considered in patients with moderate aortic stenosis[e] undergoing CABG, or surgery of the ascending aorta or of another valve after Heart Team decision.	IIa	C

[a]Class of recommendation - [b] Level of evidence - [c]In patients with a small valve area but low gradient despite preserved LVEF, explanations for this finding other than the presence of severe aortic stenosis are frequent and must be carefully excluded. See Figure 2 and Table 6 - [d]STS score (calculator: http://riskcalc.sts.org/stswebriskcalc/#/calculate); EuroSCORE II (calculator: http://www.euroscore.org/calc.html); logistic EuroSCORE I (calculator: http://www.euroscore.org/calcge.html); scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc. EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard; it is nevertheless provided here for comparison as it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality - [e]Moderate aortic stenosis is defined as valve area 1.0–1.5 cm^2 or mean aortic gradient 25–40 mmHg in the presence of normal flow conditions. However, clinical judgement is required.

Figure 3 Management of severe aortic stenosis



AS = aortic stenosis; LVEF = left ventricular ejection fraction; SAVR = surgical aortic valve replacement; TAVI = transcatheter aortic valve implantation.

[a]See Figure 2 and Table 6 for the definition of severe AS.

[b]Surgery should be considered (IIa C) if one of the following is present: peak velocity >5.5 m/s; severe valve calcification + peak velocity progression ≥0.3 m/s per year; markedly elevated neurohormones (>threefold age-and sex-corrected normal range) without other explanation; severe pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg

Table 7 Aspects to be considered by the Heart Team for the decision between SAVR and TAVI in patients at increased surgical risk (see Table of Recommendations in section 5.2.)

	Favours TAVI	Favours SAVR
Clinical characteristics		
STS/EuroSCORE II <4% (logistic EuroSCORE I<10%)[a]		+
STS/EuroSCORE II ≥4% (logistic EuroSCORE I ≥10%)[a]	+	
Presence of severe comorbidity (not adequately reflected by scores)	+	
Age <75 years		+
Age ≥75 years	+	
Previous cardiac surgery	+	
Frailty[b]	+	
Restricted mobility and conditions that may affect the rehabilitation process after the procedure	+	
Suspicion of endocarditis		+
Anatomical and technical aspects		
Favourable access for transfemoral TAVI	+	
Unfavourable access (any) for TAVI		+
Sequelae of chest radiation	+	
Porcelain aorta	+	
Presence of intact coronary bypass grafts at risk when sternotomy is performed	+	
Expected patient–prosthesis mismatch	+	
Severe chest deformation or scoliosis	+	
Short distance between coronary ostia and aortic valve annulus		+
Size of aortic valve annulus out of range for TAVI		+
Aortic root morphology unfavourable for TAVI		+
Valve morphology (bicuspid, degree of calcification, calcification pattern) unfavourable for TAVI		+
Presence of thrombi in aorta or LV		+

Cardiac conditions in addition to aortic stenosis that require consideration for concomitant intervention		
Severe CAD requiring revascularization by CABG		+
Severe primary mitral valve disease, which could be treated surgically		+
Severe tricuspid valve disease		+
Aneurysm of the ascending aorta		+
Septal hypertrophy requiring myectomy		+

cle; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons;TAVI = transcatheter aortic valve implantation.

[a]STS score (calculator: http://riskcalc.sts.org/stswebriskcalc/#/calculate); EuroSCORE II (calculator: http://www.euroscore.org/calc.html); logistic EuroSCORE I (calculator: http://www.euroscore.org/calcge.html); scores have major limitations for practical use in this setting by insufficiently considering disease severity and not including major risk factors such as frailty, porcelain aorta, chest radiation etc. EuroSCORE I markedly overestimates 30-day mortality and should therefore be replaced by the better performing EuroSCORE II with this regard; it is nevertheless provided here for comparison as it has been used in many TAVI studies/registries and may still be useful to identify the subgroups of patients for decision between intervention modalities and to predict 1-year mortality.

Medical therapy

No medical therapy for AS can improve outcome compared with the natural history. Randomized trials have consistently shown that statins do not affect the progression of AS. Patients with symptoms of heart failure, who are unsuitable candidates for surgery or TAVI, or who are currently awaiting surgical or catheter intervention, should be medically treated according to the heart failure Guidelines. Co-existing hypertension should be treated. Medical treatment should be carefully titrated to avoid hypotension and patients should be re-evaluated frequently. Maintenance of sinus rhythm is important.

Serial testing

In the asymptomatic patient, the wide variability in the rate of progression of AS stresses the need for patients to be carefully educated about the importance of follow-up and reporting symptoms as soon as they develop. Asymptomatic severe AS should be re-evaluated at least every 6 months for the occurrence of symptoms (change in exercise tolerance, ideally using exercise testing if symptoms are doubtful), and if there is change in echo parameters. Measurement of natriuretic peptides should be considered. In the presence of significant calcification, mild and moderate AS should be re-evaluated yearly. In younger patients with mild AS and no significant calcification, intervals may be extended to 2 to 3 years.

Patients in whom CABG is indicated and who have moderate AS will in general benefit from concomitant SAVR. It has also been suggested that if age is <70 years and, more importantly, an average rate of AS progression of 5 mmHg per year is documented, patients may benefit from valve replacement at the time of coronary surgery once the baseline peak gradient exceeds 30 mmHg. Individual judgement is recommended, taking into consideration BSA, haemodynamic data, leaflet calcification, AS progression rate, patient life expectancy and associated comorbidities, as well as the individual risk of either concomitant valve replacement or late reoperation.

Patients with severe symptomatic AS and diffuse CAD that cannot be revascularized should not be denied SAVR or TAVI.

Combined PCI and TAVI has been shown to be feasible, but requires more data before a firm recommendation can be made. The chronology of interventions should be the subject of individualized discussion based on the patient's clinical condition, extent of CAD, and myocardium at risk.

When MR is associated with severe AS, its severity may be overestimated in the presence of the high ventricular pressures, and careful quantification is required. As long as there are no morphological leaflet abnormalities (flail or prolapse, post-rheumatic changes, or signs of infective endocarditis), mitral annulus dilatation, or marked abnormalities of LV geometry, surgical intervention on the mitral valve is in general not necessary.

Concomitant aneurysm/dilatation of the ascending aorta requires the same treatment as in AR (see Section 4).

For congenital AS, see the ESC Guidelines on Grown-up Congenital Heart Disease.

Mitral regurgitation

Overview

Mitral regurgitation (MR) is the second most frequent indication for valve surgery in Europe. It is essential to distinguish primary from secondary MR, particularly regarding surgical and transcatheter interventional management.

Primary mitral regurgitation

Introduction

In primary MR, one or several components of the mitral valve apparatus are directly affected. The most frequent aetiology is degenerative (prolapse, flail leaflet). Endocarditis as another cause is discussed in specific ESC Guidelines.

Evaluation

Echocardiography is the principal investigation used to assess the severity and mechanism of MR, its consequences for the LV (function and remodelling), left atrium (LA), and pulmonary circulation, as well as the likelihood of repair. For quantification see Table 4. A precise anatomical description of the lesions, using the segmental and functional anatomy according to the Carpentier classification, should be performed to assess the feasibility of repair. TTE also assesses mitral annular dimensions and the presence of calcification. It is diagnostic in most cases, but TOE is recommended, particularly in the presence of suboptimal image quality. Determination of functional capacity and symptoms assessed by cardiopulmonary exercise testing may be useful in asymptomatic patients. Exercise echocardiography is useful to quantify exercise-induced changes in MR, in systolic pulmonary artery pressure, and in LV function. It may be particularly helpful in patients with symptoms and uncertainty about the severity of MR based on measurements at rest.

The use of global longitudinal strain could be of potential interest for the detection of subclinical LV dysfunction but is limited by inconsistent algorithms used by different echo systems.

Neurohormonal activation is observed in MR, with a potential value of elevated BNP levels and a change in BNP as predictors of outcome (particularly of symptom onset). In particular, low plasma BNP has a high negative predictive value and may be helpful in the follow-up of asymptomatic patients.

As echocardiographic measures of pulmonary pressure may show disagreement with invasive measures, the measurement should be invasively confirmed by right- heart catheterization if this is the only indication for surgery.

Indications for intervention

Recommendations

Indications for interventions in severe chronic primary MR are shown in the table of recommendations for indications for intervention in severe primary MR and in Figure 4.

Indications for intervention in severe primary mitral regurgitation		
Recommendations	**Class[a]**	**Level[b]**
Mitral valve repair should be the preferred technique when the results are expected to be durable.	I	C
Surgery is indicated in symptomatic patients with LVEF >30%.	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm[c] and/or LVEF ≤60%).	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45 mm and LVEF >60%) and atrial fibrillation secondary to mitral regurgitation or pulmonary hypertension[d] (systolic pulmonary pressure at rest >50 mmHg).	IIa	B
Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40–44 mm[c] when a durable repair is likely, surgical risk is low, the repair is performed in heart valve centres, and at least one of the following findings is present: • flail leaflet or • presence of significant LA dilatation (volume index ≥60 mL/m^2 BSA) in sinus rhythm.	IIa	C
Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when likelihood of successful repair is high and comorbidity low.	IIa	C
Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to medical therapy when likelihood of successful repair is low and comorbidity low.	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team, avoiding futility.	IIb	C

BSA = body surface area; LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary artery pressure.

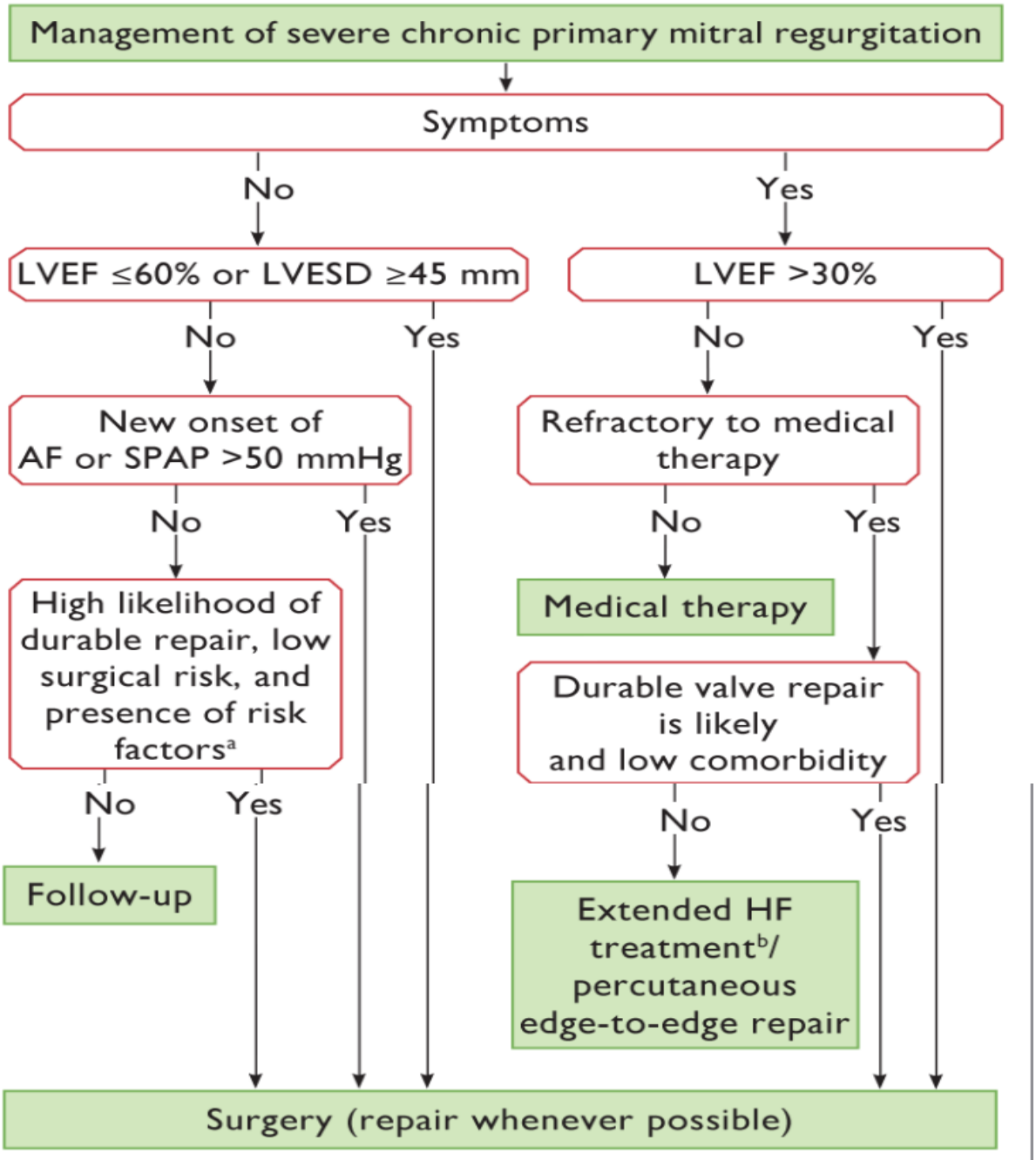
[a]Class of recommendation.

[b]Level of evidence.

[c]Cut-offs refer to averaged sized adults and may require adaption in patients with unusually small or large stature.

[d]If an elevated SPAP is the only indication for surgery, the value should be confirmed by invasive measurement.

Figure 4 Management of severe chronic primary mitral regurgitation



AF = atrial fibrillation; BSA = body surface area; CRT = cardiac resynchronization therapy; HF = heart failure; LA = left atrial; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; SPAP = systolic pulmonary arterial pressure.

[a]When there is a high likelihood of durable valve repair at a low-risk, valve repair should be considered (IIa C) in patients with LVESD ≥40 mm and one of the following is present: flail leaflet or LA volume ≥60 mL/m² BSA at sinus rhythm - [b]Extended HF management includes the following: CRT; ventricular assist devices; cardiac restraint devices; heart transplantation.

Medical therapy

In chronic MR with good ventricular function, there is no evidence to support the prophylactic use of vasodilators, including ACE-inhibitors. However, ACE-inhibitors should be considered when heart failure has developed in patients who are not suitable for surgery or when symptoms persist after surgery. Beta-blockers and spironolactone (or eplerenone) should also be considered as appropriate.

Serial testing

Asymptomatic patients with severe MR and LVEF >60% should be followed clinically and echocardiographically every 6 months, ideally in the setting of a heart valve centre. Closer follow-up is indicated if no previous evaluation is available and when measured variables show significant dynamic changes or are close to the thresholds. When guideline indications for surgery are reached, early surgery–within 2 months–is associated with better outcomes. Asymptomatic patients with moderate MR and preserved LV function can be followed on a yearly basis and echocardiography should be performed every 1–2 years.

Secondary mitral regurgitation

Introduction

In secondary MR (previously also referred to as "functional MR"), the valve leaflets and chordae are structurally normal and MR results from an imbalance between closing and tethering forces on the valve secondary to alterations in LV geometry. It is most commonly seen in dilated or ischaemic cardiomyopathies. Annular dilatation in patients with chronic atrial fibrillation and LA enlargement can also be an underlying mechanism.

Evaluation

Echocardiography is essential to establish the diagnosis of secondary MR. In secondary MR, lower thresholds have been proposed to define severe MR compared with primary MR (20 mm^2 for effective regurgitant orifice area [EROA] and 30 mL for regurgitant volume) owing to their association with prognosis. However, it is unclear if prognosis is independently affected by MR compared with LV dysfunction. So far, no survival benefit has been confirmed for reduction of secondary MR.

For isolated mitral valve treatment (surgery or percutaneous edge-to-edge repair) in secondary MR, thresholds of severity of MR for intervention still need to be validated in clinical trials. Severity of secondary MR should be reassessed after optimized medical treatment. Severity of tricuspid regurgitation and RV size and function should also be evaluated.

Secondary MR is a dynamic condition; echocardiographic quantification of MR during exercise may provide prognostic information of dynamic characteristics. Myocardial viability testing may be useful in patients with ischaemic secondary MR who are candidates for revascularization.

Indications for MR intervention in severe secondary MR are summarized in the table below.

Indications for mitral valve intervention in chronic secondary mitral regurgitation[a]

Recommendations	Class[b]	Level[c]
Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF >30%.	I	C
Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF <30% but with an option for revascularization, and evidence of myocardial viability.	IIa	C
When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and have a low surgical risk.	IIb	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30%, who remain symptomatic despite optimal medical management (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	IIb	C
In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.

[a]See section 6.2.1. for quantification of secondary mitral regurgitation, which must always be performed under optimal treatment - [b]Class of recommendation - [c]Level of evidence.

Medical therapy

Optimal medical therapy in line with the Guidelines for the management of heart failure should be the first step in the management of all patients with secondary MR. Indications for CRT should be evaluated in accordance with related Guidelines. If symptoms persist after optimization of conventional heart failure therapy, options for mitral valve intervention should be evaluated.

Mitral stenosis

Introduction

The incidence of rheumatic mitral stenosis (MS) has greatly decreased in industrialized countries. Degenerative calcific mitral valve disease is now encountered mainly in elderly patients. Percutaneous mitral commissurotomy (PMC) has had a significant impact upon the management of rheumatic MS.

Evaluation

Echocardiography is the preferred method for diagnosing MS, and for assessing its severity and haemodynamic consequences. Valve area using planimetry is the reference measurement of MS severity, whereas mean transvalvular gradient and pulmonary pressures reflect its consequences and have a prognostic value. TTE usually provides sufficient information for routine management. Scoring systems have been developed to help assess suitability for PMC. TOE should be performed to exclude LA thrombus before PMC or after an embolic episode. Echocardiography also plays an important role in monitoring the results of PMC during the procedure. Stress testing is indicated in patients with no symptoms or symptoms equivocal or discordant with the severity of MS. Exercise echocardiography may provide additional objective information by assessing changes in mitral gradient and pulmonary artery pressure.

Indications for intervention are summarized in Figure 5, the according table of indications and Tables 8 and 9.

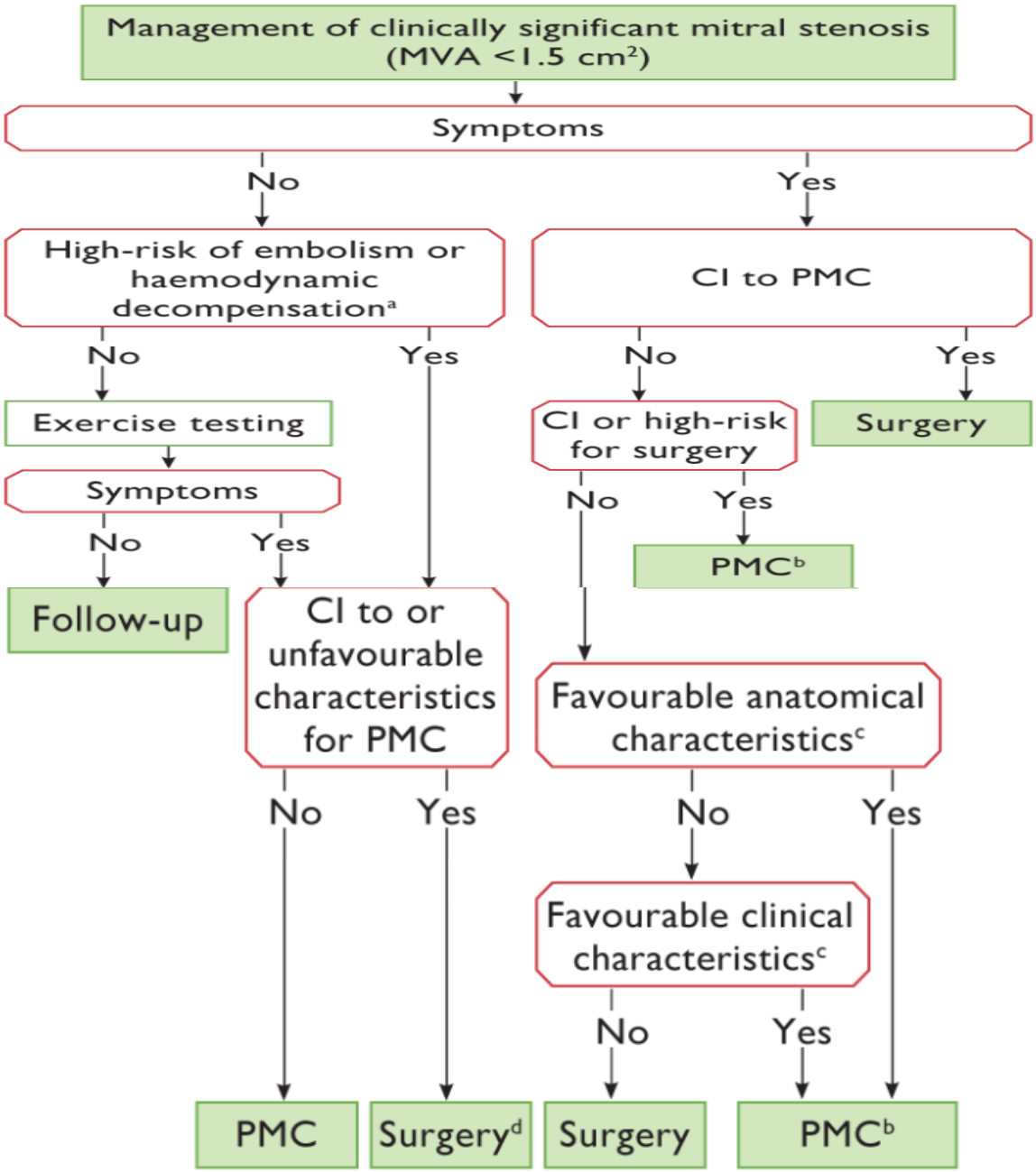
Indications for PMC and mitral valve surgery in clinically significant (moderate or severe) mitral stenosis (valve area ≤1.5 cm²)

Recommendations	Class[a]	Level[b]
PMC is indicated in symptomatic patients without unfavourable characteristics[c] for PMC.	I	B
PMC is indicated in any symptomatic patients with a contra-indication or a high-risk for surgery.	I	C
Mitral valve surgery is indicated in symptomatic patients who are not suitable for PMC.	I	C
PMC should be considered as initial treatment in symptomatic patients with suboptimal anatomy but no unfavourable clinical characteristics for PMC.[c]	IIa	C
PMC should be considered in asymptomatic patients without unfavourable clinical and anatomical characteristicsc for PMC and • high thromboembolic risk (history of systemic embolism, dense spontaneous contrast in the LA, new-onset or paroxysmal atrial fibrillation); and/or • high-risk of haemodynamic decompensation (systolic pulmonary pressure >50 mmHg at rest, need for major non-cardiac surgery,desire for pregnancy).	IIa	C

LA = left atrium; NYHA = New York Heart Association; PMC = percutaneous mitral commissurotomy.

[a]Class of recommendation - [b]Level of evidence - [c]Unfavourable characteristics for PMC can be defined by the presence of several of the following characteristics. Clinical characteristics: old age, history of commissurotomy, NYHA class IV, permanent atrial fibrillation, severe pulmonary hypertension. Anatomical characteristics: echo score >8, Cormier score 3 (calcification of mitral valve of any extent, as assessed by fluoroscopy), very small mitral valve area, severe tricuspid regurgitation. For definition of scores see Table 9.

Figure 5 Management of clinically significant mitral stenosis



CI = contra-indication; MS = mitral stenosis; PMC = percutaneous mitral commissurotomy.
[a]High thromboembolic risk: history of systemic embolism, dense spontaneous contrast in the left atrium, newonset atrial fibrillation. High-risk of haemodynamic decompensation: systolic pulmonary pressure >50 mmHg at rest, need for major non-cardiac surgery, desire for pregnancy - [b]Surgical commissurotomy may be considered by experienced surgical teams or in patients with contra-indications to PMC - [c]See table of recommendations on indications for PMC and mitral valve surgery in clinically significant mitral stenosis in section 7.2 and see echo scores - [d]Surgery if symptoms occur for a low level of exercise and operative risk is low.

Table 8 Contra-indications for percutaneous mitral commissurotomy (PMC)[a]
Contra-indications
Mitral valve area >1.5 cm^{2a}
Left atrial thrombus
More than mild mitral regurgitation
Severe or bi-commissural calcification
Absence of commissural fusion
Severe concomitant aortic valve disease, or severe combined tricuspid stenosis and regurgitation requiring surgery
Concomitant CAD requiring bypass surgery

CAD = coronary artery disease. [a]PMC may be considered in patients with valve area >1.5 cm^2 with symptoms that cannot be explained by another cause and if the anatomy is favourable.

Table 9 Echo scores: Wilkins score, Cormier score, and Echo Score "Revisited" for immediate outcome prediction	
Assessment of mitral valve anatomy according to the Wilkins score	
Grade	**Mobility**
1	Highly mobile valve with only leaflet tips restricted
2	Leaflet mid and base portions have normal mobility
3	Valve continues to move forward in diastole, mainly from the base
4	No or minimal forward movement of the leaflets in diastole
	Thickening
1	Leaflets near normal in thickness (4–5 mm)
2	Mid leaflets normal, considerable thickening of margins (5–8 mm)
3	Thickening extending through the entire leaflet (5–8 mm)
4	Considerable thickening of all leaflet tissue (>8–10 mm)
	Calcification
1	A single area of increased echo brightness
2	Scattered areas of brightness confined to leaflet margins
3	Brightness extending into the mid portions of the leaflets
4	Extensive brightness throughout much of the leaflet tissue

	Subvalvular thickening
1	Minimal thickening just below the mitral leaflets
2	Thickening of chordal structures extending to one third of the chordal length
3	Thickening extended to distal third of the chords
4	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles)
The total score is the sum of the four items and ranges between 4 and 16.	

Assessment of mitral valve anatomy according to the Cormier score	
Echocardiographic group	**Mitral valve anatomy**
Group 1	Pliable non-calcified anterior mitral leaflet and mild subvalvular disease (i.e. thin chordae ≥10 mm long)
Group 2	Pliable non-calcified anterior mitral leaflet and severe subvalvular disease (i.e. thickened chordae <10 mm long)
Group 3	Calcification of mitral valve of any extent, as assessed by fluoroscopy, whatever the state of subvalvular apparatus

Echo Score "Revisited" for immediate outcome prediction	
Echocardiographic variables	**Points for Score (0 to 11)**
Mitral valve area ≤1cm^2	2
Maximum leaflet displacement ≤12mm	3
Commissural area ratio ≥1.25	3
Subvalvular involvement	3

Risk groups for Echo score "Revisited": low (score 0–3); intermediate (score 4–5); high (score 6–11).

Diuretics, beta-blockers, digoxin, or heart-rate regulating calcium channel blockers can transiently improve symptoms. Anticoagulation with a target international normalized ratio (INR) between 2 and 3 is indicated in patients with either new-onset or paroxysmal atrial fibrillation. In patients in sinus rhythm, oral anticoagulation is indicated when there has been a history of systemic embolism, or a thrombus is present in the LA (recommendation Class I, level of evidence C) and should also be considered when TOE shows dense spontaneous echo contrast or an enlarged LA (M-mode diameter >50 mm or LA volume >60 mL/m^2) (recommendation Class IIa, level of evidence C). Patients with moderate to severe MS and persistent atrial fibrillation should be kept on vitamin K antagonist (VKA) treatment and not receive NOACs.

Cardioversion is not indicated before intervention in patients with severe MS, as it does not durably restore sinus rhythm. If atrial fibrillation is of recent onset and the LA only moderately enlarged, cardioversion should be performed soon after successful intervention.

Serial testing

Asymptomatic patients with clinically significant MS who have not undergone intervention should be followed up yearly by means of clinical and echocardiographic examinations and at longer intervals (2 to 3 years) in case of moderate stenosis. Management of patients after successful PMC is similar to that of asymptomatic patients. Follow-up should be more frequent if asymptomatic restenosis occurs. When PMC is not successful, surgery should be considered early unless there are definite contra-indications.

Special patient populations

When restenosis with symptoms occurs after surgical commissurotomy or PMC, reintervention in most cases requires valve replacement, but PMC can be proposed in selected candidates with favourable characteristics if the predominant mechanism is commissural refusion.

In the elderly population with rheumatic MS when surgery is high-risk, PMC is a useful option, even if only palliative. In other elderly patients, surgery is preferable. However, in elderly patients with degenerative MS with severely calcified mitral annulus, surgery is very high-risk. As there is no commissural fusion in these cases, degenerative MS is not amenable to PMC. If degenerative MS is severe, very preliminary experience has suggested that transcatheter valve implantation of a TAVI bioprosthesis in the mitral position is feasible in symptomatic elderly patients who are inoperable if the anatomy is suitable.

In patients with severe tricuspid regurgitation (TR), PMC may be considered in selected patients with sinus rhythm, moderate atrial enlargement, and functional TR secondary to pulmonary hypertension. In other cases, surgery on both valves is preferred.

Tricuspid regurgitation

Introduction

Pathological tricuspid regurgitation (TR) is more often secondary, due to RV dysfunction following pressure and/or volume overload in the presence of structurally normal leaflets. Possible causes of primary TR are infective endocarditis (especially in intravenous drug addicts), rheumatic heart disease, carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, Ebstein's anomaly and congenitally dysplastic valves, drug-induced valve diseases, thoracic trauma, and iatrogenic valve damage.

Evaluation

Echocardiography is the ideal technique to evaluate TR. In primary TR, the aetiology can usually be identified from specific abnormalities of the valve structure. In secondary TR, the degree of dilatation of the annulus, the RV dimension and function, and the degree of tricuspid valve deformation should be measured. Evaluation of TR severity (integration of multiple qualitative and quantitative parameters) and pulmonary systolic pressure should be carried out as currently recommended (Table 4). It has to be noted that the problem of elevated pulmonary vascular resistance may be disguised in the presence of severe TR because its velocity may be lower than expected in the case of pulmonary hypertension.

Evaluations of the RV dimensions and function should be conducted, despite existing limitations of current indices of RV function. The presence of associated lesions (looking carefully at the associated valve lesions, particularly on the left side) and LV function should be assessed. When available, CMR is the preferred method for evaluating RV size and function and represents the gold standard for assessing RV volumes and function.

Cardiac catheterization is not needed to diagnose TR or estimate its severity, but should be obtained in patients in whom isolated tricuspid valve surgery is contemplated for secondary TR to evaluate haemodynamics, in particular pulmonary vascular resistance.

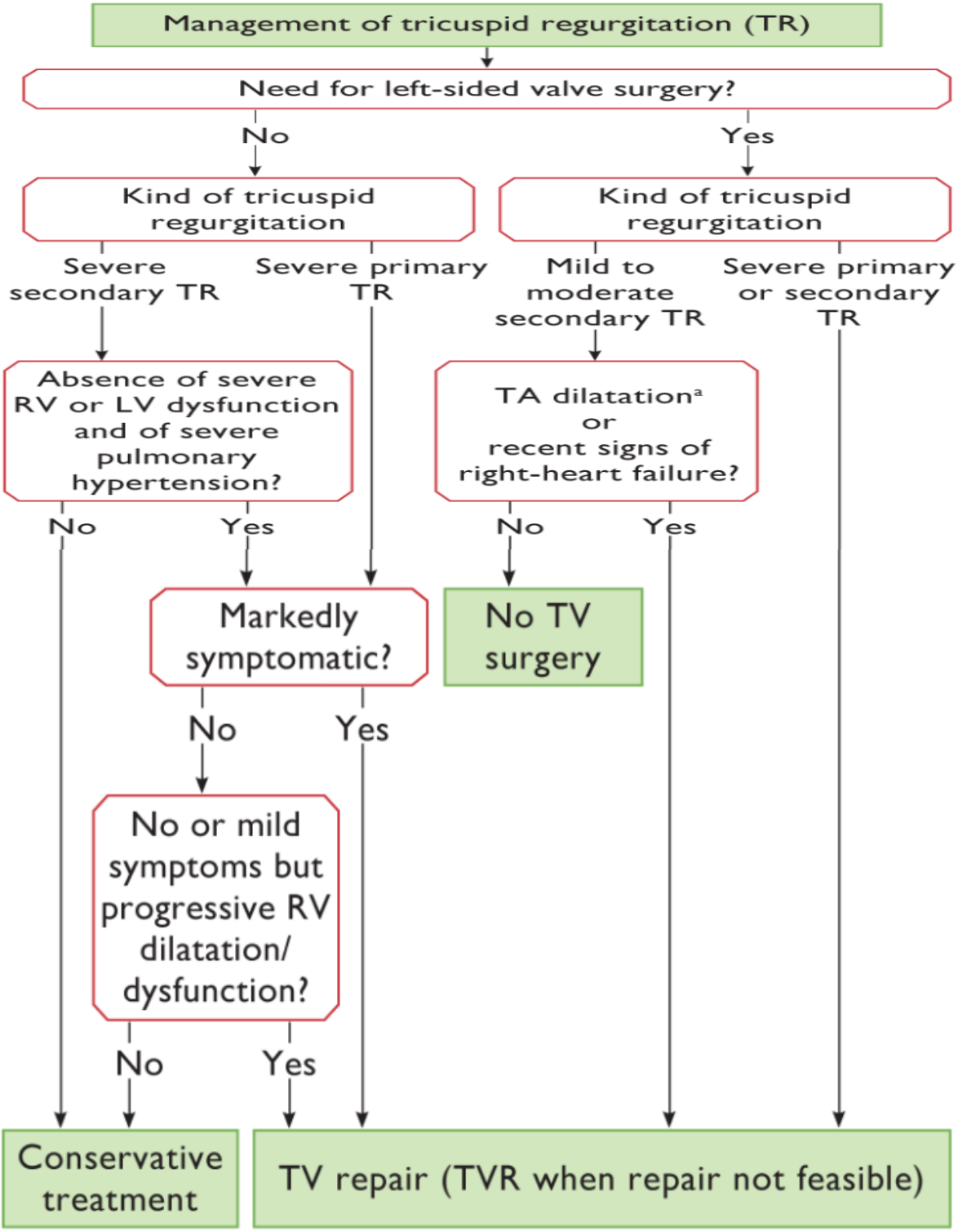
Indications for intervention are summarized in the table below and Figure 6.

Indications for tricuspid valve surgery		
Recommendations on tricuspid stenosis	**Class[a]**	**Level[b]**
Surgery is indicated in symptomatic patients with severe tricuspid stenosis.[c]	I	C
Surgery is indicated in patients with severe tricuspid stenosis undergoing left-sided valve intervention.[d]	I	C
Recommendations on primary tricuspid regurgitation		
Surgery is indicated in patients with severe primary tricuspid regurgitation undergoing left-sided valve surgery.	I	C
Surgery is indicated in symptomatic patients with severe isolated primary tricuspid regurgitation without severe right-ventricular dysfunction.	I	C
Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery.	IIa	C
Surgery should be considered in asymptomatic or mildly symptomatic patients with severe isolated primary tricuspid regurgitation and progressive right-ventricular dilatation or deterioration of right-ventricular function.	IIa	C
Recommendations on secondary tricuspid regurgitation		
Surgery is indicated in patients with severe secondary tricuspid regurgitation undergoing left-sided valve surgery.	I	C
Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with dilated annulus (≥40 mm or >21 mm/m^2 by 2D echocardiography) undergoing left-sided valve surgery.	IIa	C
Surgery may be considered in patients undergoing left-sided valve surgery with mild or moderate secondary tricuspid reguargitation even in the absence of annular dilatation when previous recent right- heart failure has been documented.	IIb	C
After previous left-sided valve surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe tricuspid regurgitation who are symptomatic or have progressive right-ventricular dilatation/dysfunction, in the absence of severe right or LV dysfunction, and severe pulmonary vascular disease/hypertension.	IIa	C

2D = two-dimensional; LV = left ventricular; PMC = percutaneous mitral commissurotomy.

[a]Class of recommendation - [b]Level of evidence - [c]Percutaneous balloon valvuloplasty can be attempted as a first approach if tricuspid stenosis is isolated - [d]Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve

Figure 6 Indications for surgery in tricuspid regurgitation



LV = left ventricular; RV = right ventricular; TA = tricuspid annulus; TR = tricuspid regurgitation; TV = tricuspid valve; TVR = tricuspid valve replacement. [a]TA ≥40 mm or >21 mm/m^2. See recommendations

Tricuspid stenosis

Introduction

Tricuspid stenosis (TS) is often combined with TR, most frequently of rheumatic origin. It is therefore almost always associated with left-sided valve lesions, particularly MS, that usually dominate the clinical presentation. Other causes are rare: congenital, drug-induced valve diseases, Whipple's disease, endocarditis, or large right atrial tumour.

Evaluation

Echocardiography provides the most useful information. TS is often overlooked and requires careful evaluation. Echocardiographic evaluation of the anatomy of the valve and its subvalvular apparatus is important to assess valve reparability. No generally accepted grading of TS severity exists, but a mean gradient ≥5 mmHg at normal heart rate is considered indicative of clinically significant TS. Catheterization is no longer used for evaluating the severity of TS.

Indications for intervention

The lack of pliable leaflet tissue is the main limitation for valve repair. Even though this is still a matter of debate, biological prostheses for valve replacement are usually preferred over mechanical ones because of the high-risk of thrombosis carried by the latter and the satisfactory long-term durability of the former in the tricuspid position. Percutaneous balloon tricuspid dilatation has been performed in a limited number of cases, either alone or alongside PMC, but frequently induces significant regurgitation. There is a lack of data on long-term results. See table of indications for tricuspid valve surgery (see Section 8.2).

Medical therapy

Diuretics are useful in the presence of heart failure but are of limited long-term efficacy.

Combined & multiple valve diseases

Significant stenosis and regurgitation can be found on the same valve. Disease of multiple valves may be encountered in several conditions, particularly in rheumatic and congenital heart disease but also, less frequently, in degenerative valve disease. There is a lack of data on combined or multiple valve diseases. This does not allow for evidence-based recommendations.

The general principles for the management of combined or multiple valve disease are as follows:

- When either stenosis or regurgitation is predominant, management follows the recommendations concerning the predominant VHD. When the severity of both stenosis and regurgitation is balanced, indications for interventions should be based on symptoms and objective consequences rather than on the indices of severity of stenosis or regurgitation. In this setting, consideration of the pressure gradient that reflects the haemodynamic burden of the valve lesion becomes more important than valve area and measures of the regurgitation for the assessment of disease severity.
- It is necessary to take into account the interaction between the different valve lesions.
- Indications for intervention are based on global assessment of the consequences of the different valve lesions (i.e. symptoms or presence of LV dilatation or dysfunction). Intervention can be considered for non-severe multiple lesions associated with symptoms or leading to LV impairment.
- The decision to intervene on multiple valves should take into account the extra surgical risk of combined procedures.
- The choice of surgical technique should take into account the presence of the other VHD; repair remains the ideal option.

The management of specific associations of VHD is detailed in the individual sections of this document.

The choice between a mechanical and a biological valve in adults is determined mainly by estimating the risk of anticoagulation-related bleeding and thromboembolism with a mechanical valve versus the risk of structural valve deterioration with a bioprosthesis, and by considering the patient's lifestyle and preferences. Rather than setting arbitrary age limits, prosthesis choice should be discussed in detail with the informed patient, cardiologists, and surgeons, taking into account the factors detailed.

Choice of the aortic/mitral prosthesis – in favour of a mechanical prosthesis; the decision is based on the integration of several of the following factors

	Class[b]	Level[c]
A mechanical prosthesis is recommended according to the desire of the informed patient and if there are no contra-indications to long-term anticoagulation.[c]	I	C
A mechanical prosthesis is recommended in patients at risk of accelerated structural valve deterioration.[d]	I	C
A mechanical prosthesis should be considered in patients already on anticoagulation because of a mechanical prosthesis in another valve position.	IIa	C
A mechanical prosthesis should be considered in patients aged <60 years for prostheses in the aortic position and <65 years for prostheses in the mitral position.[e]	IIa	C
A mechanical prosthesis should be considered in patients with a reasonable life expectancy[f], for whom future redo valve surgery would be at high-risk.	IIa	C
A mechanical prosthesis may be considered in patients already on long-term anticoagulation due to high-risk for thromboembolism.[g]	IIb	C

[a]Class of recommendation - [b]Level of evidence - [c]Increased bleeding risk because of comorbidities, compliance concerns, or geographic, lifestyle, or occupational conditions - [d]Young age (<40 years), hyperparathyroidism. [e]In patients aged 60–65 years who should receive an aortic prosthesis, and those between 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age. [f]Life expectancy should be estimated >10 years, according to age, sex, comorbidities, and country-specific life expectancy - [g]Risk factors for thromboembolism are atrial fibrillation, previous thromboembolism, hypercoagulable state, severe LV systolic dysfunction.

Choice of the aortic/mitral prosthesis – in favour of a bioprosthesis; the decision is based on the integration of several of the following factors	Class[b]	Level[c]
A bioprosthesis is recommended according to the desire of the informed patient.	I	C
A bioprosthesis is recommended when good-quality anticoagulation is unlikely (compliance problems, not readily available) or contra-indicated because of high bleeding risk (previous major bleed, comorbidities, unwillingness, compliance problems, lifestyle, occupation).	I	C
A bioprosthesis is recommended for reoperation for mechanical valve thrombosis despite good long-term anticoagulant control.	I	C
A bioprosthesis should be considered in patients for whom there is a low likelihood and/or a low operative risk of future redo valve surgery.	IIa	C
A bioprosthesis should be considered in young women contemplating pregnancy.	IIa	C
A bioprosthesis should be considered in patients aged >65 years for a prosthesis in the aortic position, or age >70 years in a mitral position, or those with life expectancy[c] lower than the presumed durability of the bioprosthesis.[d]	IIa	C

[a]Class of recommendation - [b]Level of evidence - [c]Life expectancy should be estimated according to age, sex, comorbidities, and country-specific life expectancy - [d]In patients aged 60–65 years who should receive an aortic prosthesis and those between 65–70 years in the case of mitral prosthesis, both valves are acceptable and the choice requires careful analysis of factors other than age.

Management after valve intervention

General remarks

Thromboembolism and anticoagulant-related bleeding present the majority of complications experienced by prosthetic valve recipients. Endocarditis prophylaxis and management of prosthetic valve endocarditis are detailed in separate ESC Guidelines.

All patients require lifelong follow-up by a cardiologist after valve surgery to detect early deterioration in prosthetic function or ventricular function or progressive disease of another heart valve. Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. TTE should be performed if any new symptoms occur after valve replacement or if complications are suspected. After transcatheter as well as surgical implantation of a bioprosthetic valve, echocardiography – including the measurement of transprosthetic gradients – should be performed within 30 days (preferably around 30 days for surgery) after valve implantation (i.e. baseline imaging), at 1 year after implantation, and annually thereafter. TOE should be considered if TTE is of poor quality and in all cases of suspected prosthetic dysfunction or endocarditis. Cinefluoroscopy for mechanical valves and MSCT scanning provide useful additional information if valve thrombus or pannus are suspected to impair valve function.

Indications for antithrombotic therapy in patients with a prosthetic heart valve or valve repair		
Mechanical prosthesis	**Class[b]**	**Level[c]**
Oral anticoagulation using a VKA is recommended lifelong for all patients.	I	B
Bridging using therapeutic doses of UFH or LMWH is recommended when VKA treatment should be interrupted.	I	C
The addition of low-dose aspirin (75–100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C
The addition of low-dose aspirin (75–100 mg/day) to VKA may be considered in the case of concomitant atherosclerotic disease.	IIb	C
INR self-management is recommended provided appropriate training and quality control are performed.	I	B
In patients treated with coronary stent implantation, triple therapy with aspirin (75–100 mg/day), clopidogrel (75 mg/day), and VKA should be considered for 1 month, irrespective of the type of stent used and the clinical presentation (i.e. ACS or stable CAD).	IIa	B
Triple therapy comprising aspirin (75–100 mg/day), clopidogrel (75 mg/ day), and VKA for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweighs the bleeding risk.	IIa	B
Dual therapy comprising VKA and clopidogrel (75 mg/day) should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A
In patients who have undergone PCI, discontinuation of antiplatelet treatment should be considered at 12 months.	IIa	B
In patients requiring aspirin and/or clopidogrel in addition to VKA, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in therapeutic range >65–70%.	IIa	B
The use of NOACs is contra-indicated.	III	B

Bioprostheses	Class[b]	Level[c]
Oral anticoagulation is recommended lifelong for patients with surgical or transcatheter implanted bioprostheses who have other indications for anticoagulation.[c]	I	C
Oral anticoagulation using a VKA should be considered for the first 3 months after surgical implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation using a VKA should be considered for the first 3 months after surgical mitral or tricuspid valve repair.	IIa	C
Low-dose aspirin (75−100 mg/day) should be considered for the first 3 months after surgical implantation of an aortic bioprosthesis or valve-sparing aortic surgery.	IIa	C
Dual antiplatelet therapy should be considered for the first 3–6 months after TAVI, followed by lifelong single antiplatelet therapy in patients who do not need oral anticoagulation for other rea-	IIa	C
Single antiplatelet therapy may be considered after TAVI in the case of high bleeding risk.	IIb	C
Oral anticoagulation may be considered for the first 3 months after surgical implantation of an aortic bioprosthesis.	IIb	C

ACS = acute coronary syndrome; CAD = coronary artery disease; INR = international normalized ratio; LMWH = low-molecular-weight heparin; LV = left ventricular; PCI = percutaneous coronary intervention; NOAC = non-vitamin K antagonist oral anticoagulant; TAVI = transcatheter aortic valve implantation; UFH = unfractionated heparin;VKA = vitamin K antagonist.

[a]Class of recommendation - [b]Level of evidence - [c]Atrial fibrillation, venous thromboembolism, hypercoagulable state, or − with a lesser degree of evidence − severely impaired LV dysfunction (ejection fraction <35%).

Table 10 Target INR for mechanical prostheses

Prosthesis thrombogenicity	Patient-related risk factors[a]	
	None	≥1 risk factor
Low[b]	2.5	3.0
Medium[c]	3.0	3.5
High[d]	3.5	4.0

INR = international normalized ratio; LVEF = left ventricular ejection fraction.

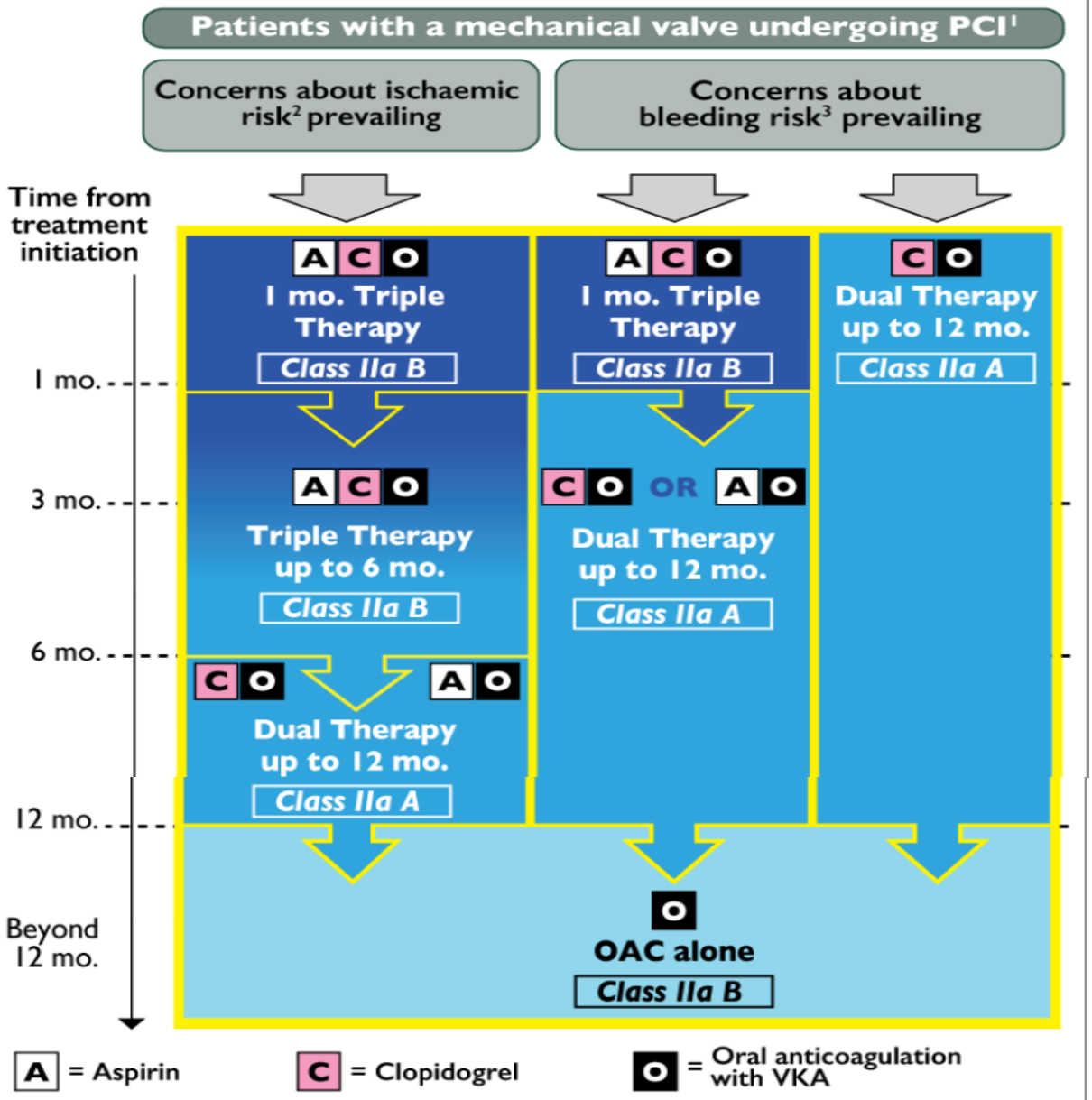
[a]Mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; LVEF <35%.

[b]Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On-X, Sorin Bicarbon.

[c]Other bileaflet valves with insufficient data.

[d]Lillehei-Kaster, Omniscience, Starr-Edwards (ball-cage), Bjork-Shiley and other tilting-disc valves.

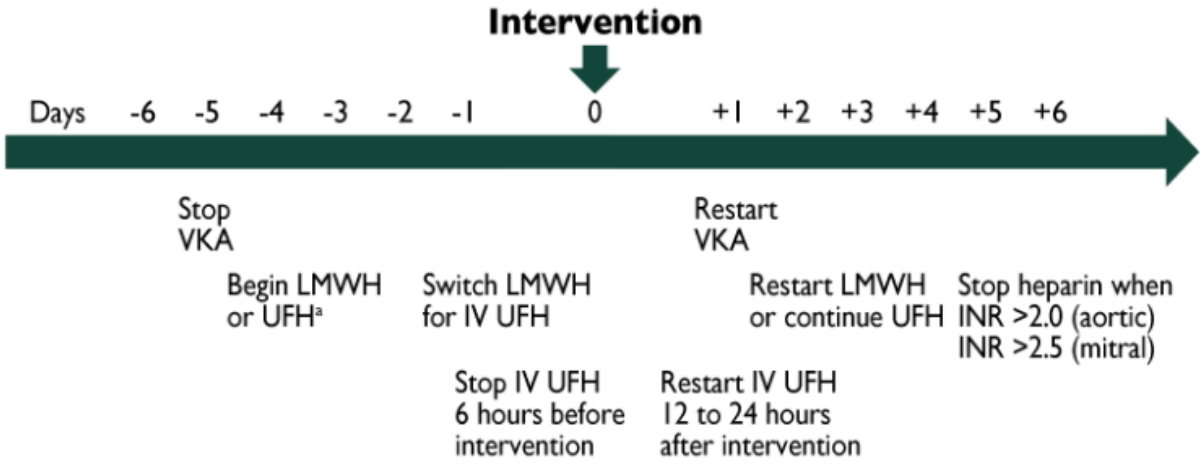
Figure 7 Antithrombotic therapy in patients with mechanical valve prosthesis after undergoing PCI (adapted from the 2017 ESC Focused Update on Dual Antiplatelet Therapy)



A = aspirin; ABC = age, biomarkers, clinical history; ACS = acute coronary syndrome; C = clopidogrel; mo. = month(s); O = oral anticoagulation with a vitamin K antagonist; PCI = percutaneous coronary intervention.
For more details regarding estimation of bleeding risk (HAS-BLED and ABC score) see the 2017 ESC Focused Update on Dual Antiplatelet Therapy (www.escardio.org/guidelines).
[1]: Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy.
[2]: High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction.
[3]: Bleeding risk can be estimated by HAS-BLED or ABC score

Anticoagulation during non-cardiac surgery requires careful management based on risk assessment. It is recommended not to interrupt oral anticoagulation for most minor surgical procedures (including dental extraction, cataract removal) and those procedures where bleeding is easily controlled. Major surgical procedures require an INR <1.5. In patients with a mechanical prosthesis, oral anticoagulant therapy should be stopped before surgery and bridging using heparin is recommended. UFH remains the only approved heparin treatment in patients with mechanical prostheses; intravenous administration should be favoured over the subcutaneous route. The use of subcutaneous LMWH, although off-label, is an alternative to UFH for bridging. When LMWHs are used they should be administered twice-a-day using therapeutic doses, adapted to body weight and renal function, and if possible, with monitoring of anti-Xa activity with a target of 0.5–1.0 U/mL. Fondaparinux should not be used for bridging in patients with mechanical prosthesis. Practical modalities of anticoagulation bridging are detailed in Figure 8.

Figure 8 Main bridging steps for an intervention requiring interruption of oral anticoagulation in a patient with a mechanical prosthesis. Timing should be individualized according to patient characteristics, actual INR, and the type of intervention (reproduced with permission from Iung and Rodes-Cabau)



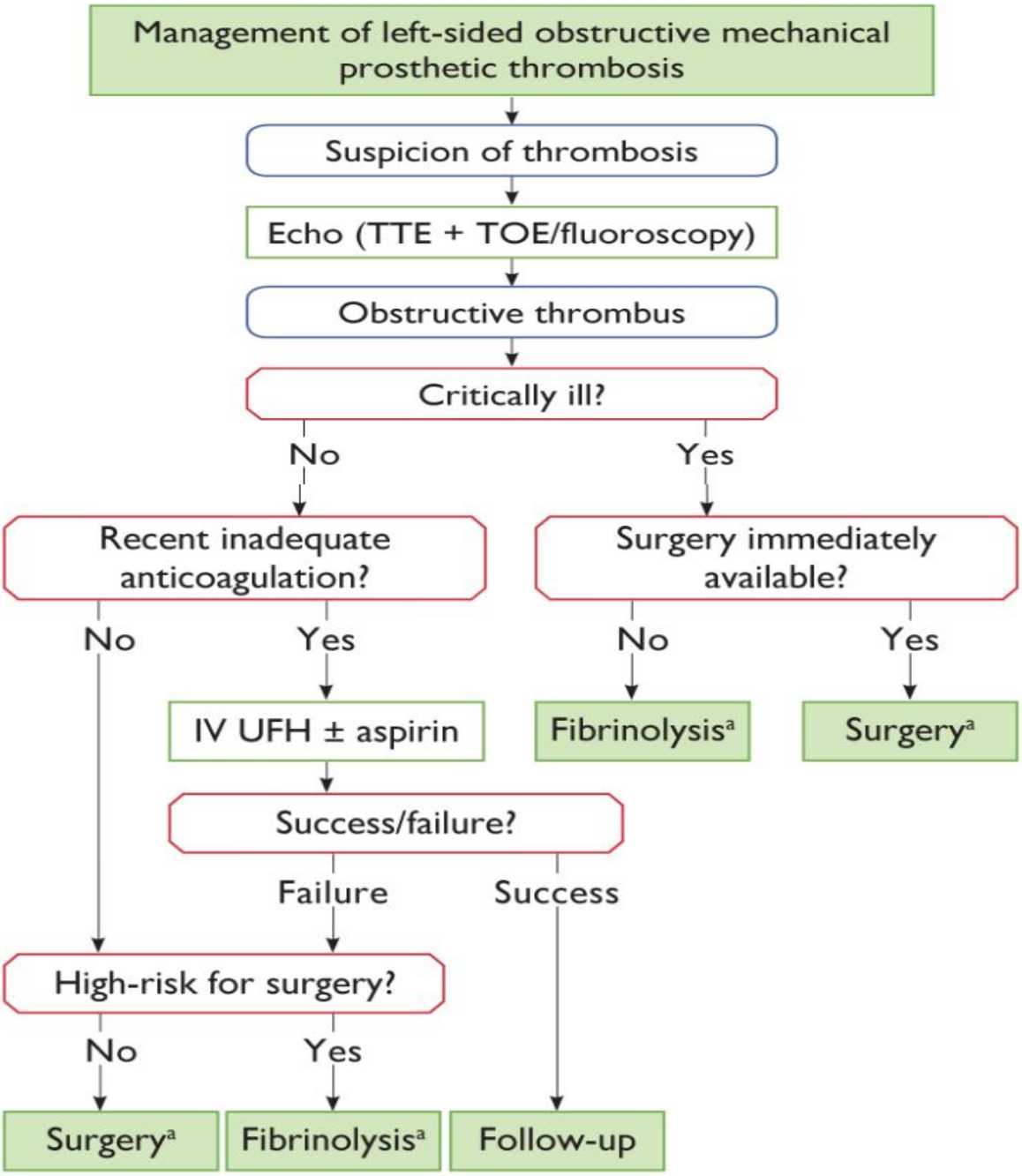
INR = international normalized ratio; IV = intravenous; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin;VKA = vitamin K antagonist.

[a]IV UFH may be favoured in patients at high thrombotic risk.

Management of prosthetic valve dysfunction		
Mechanical prosthetic thrombosis	**Class[b]**	**Level[c]**
Urgent or emergency valve replacement is recommended for obstructive thrombosis in critically ill patients without serious comorbidity.	I	C
Fibrinolysis (using recombinant tissue plasminogen activator 10 mg bolus + 90 mg in 90 minutes with UFH, or streptokinase 1 500 000 U in 60 minutes without UFH) should be considered when surgery is not available or is very high-risk, or for thrombosis of right-sided prostheses.	IIa	C
Surgery should be considered for large (>10 mm) non-obstructive prosthetic thrombus complicated by embolism.	IIa	C
Bioprosthetic thrombosis		
Anticoagulation using a VKA and/or UFH is recommended in bioprosthetic valve thrombosis before considering reintervention.	I	C
Haemolysis and paravalvular leak		
Reoperation is recommended if paravalvular leak is related to endocarditis or causes haemolysis requiring repeated blood transfusions or leading to severe symptoms.	I	C
Transcatheter closure may be considered for paravalvular leaks with clinically significant regurgitation in surgical high-risk patients (Heart Team decision).	IIb	C
Bioprosthetic failure		
Reoperation is recommended in symptomatic patients with a significant increase in transprosthetic gradient (after exclusion of valve thrombosis) or severe regurgitation.	I	C
Reoperation should be considered in asymptomatic patients with significant prosthetic dysfunction, if reoperation is at low-risk.	IIa	C
Transcatheter valve-in-valve implantation in aortic position should be considered by the Heart Team depending on the risk of reoperation and the type and size of prosthesis.	IIa	C

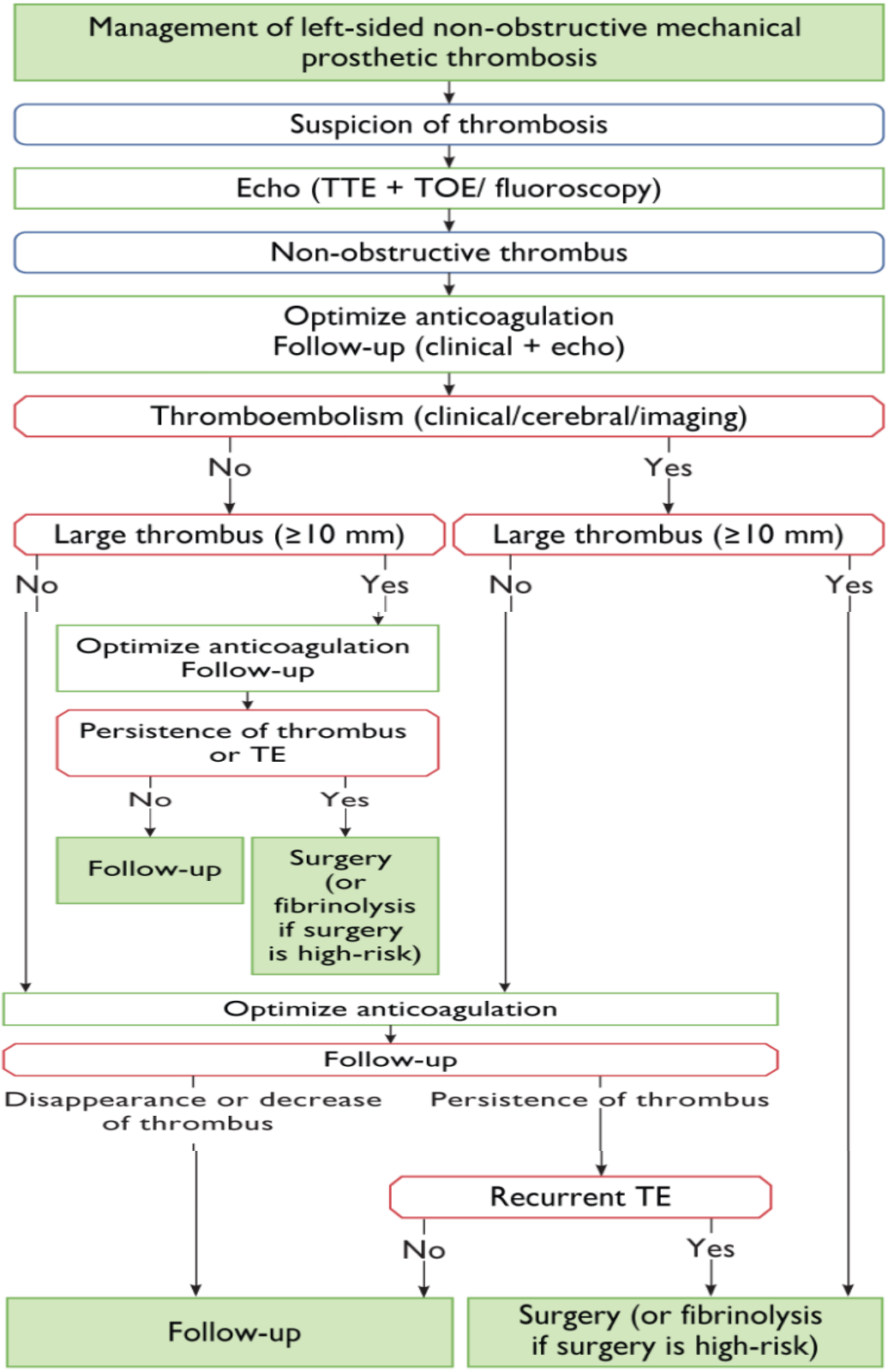
Management of valve thrombosis, hemolysis and paravalvular leak, and bio-prosthetic failure are summarized in the following tables and figures.

Figure 9 Management of left-sided obstructive mechanical prosthetic thrombosis



IV = intravenous; TOE = transoesophageal echocardiography; TTE = transthoracic echocardiography; UFH = unfractionated heparin. [a]Risk and benefits of both treatments should be individualized. The presence of a first-generation prosthesis is an incentive to surgery.

Figure 10 Management of left-sided non-obstructive mechanical prosthetic thrombosis



Management during non-cardiac surgery

Overview

Cardiovascular morbidity and mortality are increased in patients with VHD who undergo non-cardiac surgery. Symptomatic severe aortic stenosis or mitral stenosis may require valve replacement or percutaneous intervention before non- cardiac surgery. A detailed description of these recommendations is available in dedicated Guidelines (www.escardio.org/guideines).

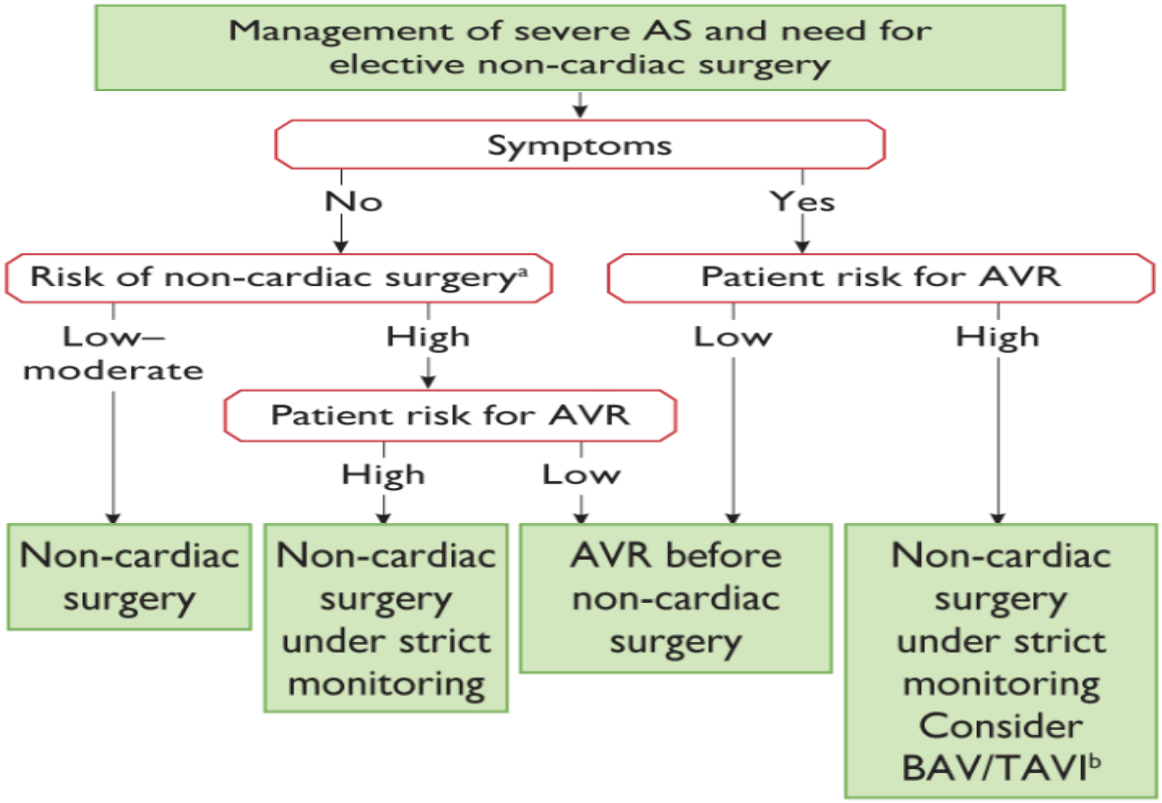
Preoperative evaluation

Echocardiography should be performed in any patient with VHD. Determination of functional capacity is a pivotal step in preoperative risk assessment, measured either by exercise test or ability to perform activities in daily life. The decision for the management should be taken after multidisciplinary discussion involving cardiologists, surgeons, and anaesthesiologists.

Specific valve lesions

In patients with severe aortic stenosis, urgent non-cardiac surgery should be performed under careful haemodynamic monitoring. Recommendations for the management of patients with severe AS who require elective non-cardiac surgery are summarized in Figure 11.

Figure 11 Management of severe aortic stenosis and elective non-cardiac surgery according to patient characteristics and type of surgery



AS = aortic stenosis; AVR = aortic valve replacement; BAV = balloon aortic valvuloplasty; TAVI = transcatheter aortic valve implantation.

[a]Classification into three groups according to the risk of cardiac complications (30-day death and myocardial infarction) for non-cardiac surgery (high-risk >5%; intermediate risk 1–5%; low-risk <1%).[196] - [b]Non-cardiac surgery performed only if strictly needed. The choice between percutaneous aortic valvuloplasty and TAVI should take into account patient life expectancy.

For interactivity see here

Non-cardiac surgery can be performed safely in patients with non-significant mitral stenosis (valve area >1.5 cm^2), and in asymptomatic patients with significant MS and a systolic pulmonary artery pressure <50 mmHg. In symptomatic patients or in patients with systolic pulmonary artery pressure >50 mmHg, correction of mitral stenosis, by means of PMC whenever possible, should be attempted before non-cardiac surgery if it is high-risk.

Non-cardiac surgery can be performed safely in asymptomatic patients with severe mitral regurgitation or aortic regurgitation and preserved LV function. The presence of symptoms or LV dysfunction should lead to consideration of valvular surgery, but this is seldom needed before non-cardiac surgery. If LV dysfunction is severe (ejection fraction <30%), non-cardiac surgery should be performed only if strictly necessary, after optimization of medical therapy for heart failure.

Perioperative monitoring

Heart rate control (particularly in mitral stenosis) and careful fluid management (particularly in aortic stenosis) are needed. TOE monitoring may be considered.

Management during pregnancy

Overview

Detailed Guidelines on the management of cardiovascular disease during pregnancy are available in a specific document (www.escardio.org/guidelines).

The decision for management during pregnancy should be taken after multidisciplinary discussion involving cardiologists, obstetricians, and anaesthesiologists. Valve disease should be evaluated before pregnancy and treated if necessary. Pregnancy should be discouraged in severe mitral stenosis, severe symptomatic AS, and aortic diameter >45 mm in Marfan syndrome or >27.5 mm/m^2 in Turner syndrome.

Caesarean section is recommended for patients with severe mitral or AS, ascending aortic diameter >45 mm, or severe pulmonary hypertension, as well as women on oral anticoagulants in preterm labour.

Native valve disease

Moderate or severe mitral stenosis with valve area <1.5 cm^2 in pregnant women is usually poorly tolerated. PMC should be considered in severely symptomatic patients (NYHA Class III–IV) and/or those with systolic pulmonary artery pressure >50 mmHg despite optimal therapy. PMC should be performed after the 20th week of pregnancy in experienced centres.

Complications of severe AS occur mainly in patients who were symptomatic before pregnancy and among those with impaired LV function. Evaluation with exercise test is recommended before pregnancy.

Chronic mitral regurgitation and aortic regurgitation are well tolerated, even when severe, provided LV systolic function is preserved.

Surgery under cardiopulmonary bypass is associated with a foetal mortality rate of between 15% and 30% and should be restricted to the rare conditions that threaten the mother's life.

Prosthetic valves

Maternal mortality is estimated at between 1% and 4%, and serious events in up to 40% of women with mechanical valves.
Therapeutic anticoagulation is extremely important to avoid complications. In patients requiring ≤5 mg warfarin, oral anticoagulants throughout pregnancy and change to UFH before delivery is favoured. In patients requiring higher doses, switch to LMWH during the first trimester with strict anti-Xa monitoring (therapeutic range 0.8–1.2) and use of oral anticoagulants afterwards is favoured.

2017 ESC Pocket Guidelines

Committee for Practice Guidelines

PAD

2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases

ESC
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Introduction

The term “peripheral arterial diseases” (PADs) encompasses all arterial diseases other than coronary arteries and the aorta. This should be clearly distinguished from the term “peripheral artery disease” often used to name lower extremity artery disease (LEAD). Indeed, other peripheral localizations (Figure 1) are also frequently affected, mainly by atherosclerosis, and complete the family of PADs.

Because of multiple presentations and therapeutic options, a multidisciplinary management of these patients is mostly necessary, and cardiologists should be sensitive in regard to the diagnosis and management of patients with PADs, as many of them are seen and managed for concomitant cardiac conditions. Major efforts are still necessary to sensitize healthcare providers, decision makers and the general population about the need for awareness, screening, prevention and management of the 40 million individuals in our continent affected by PADs.

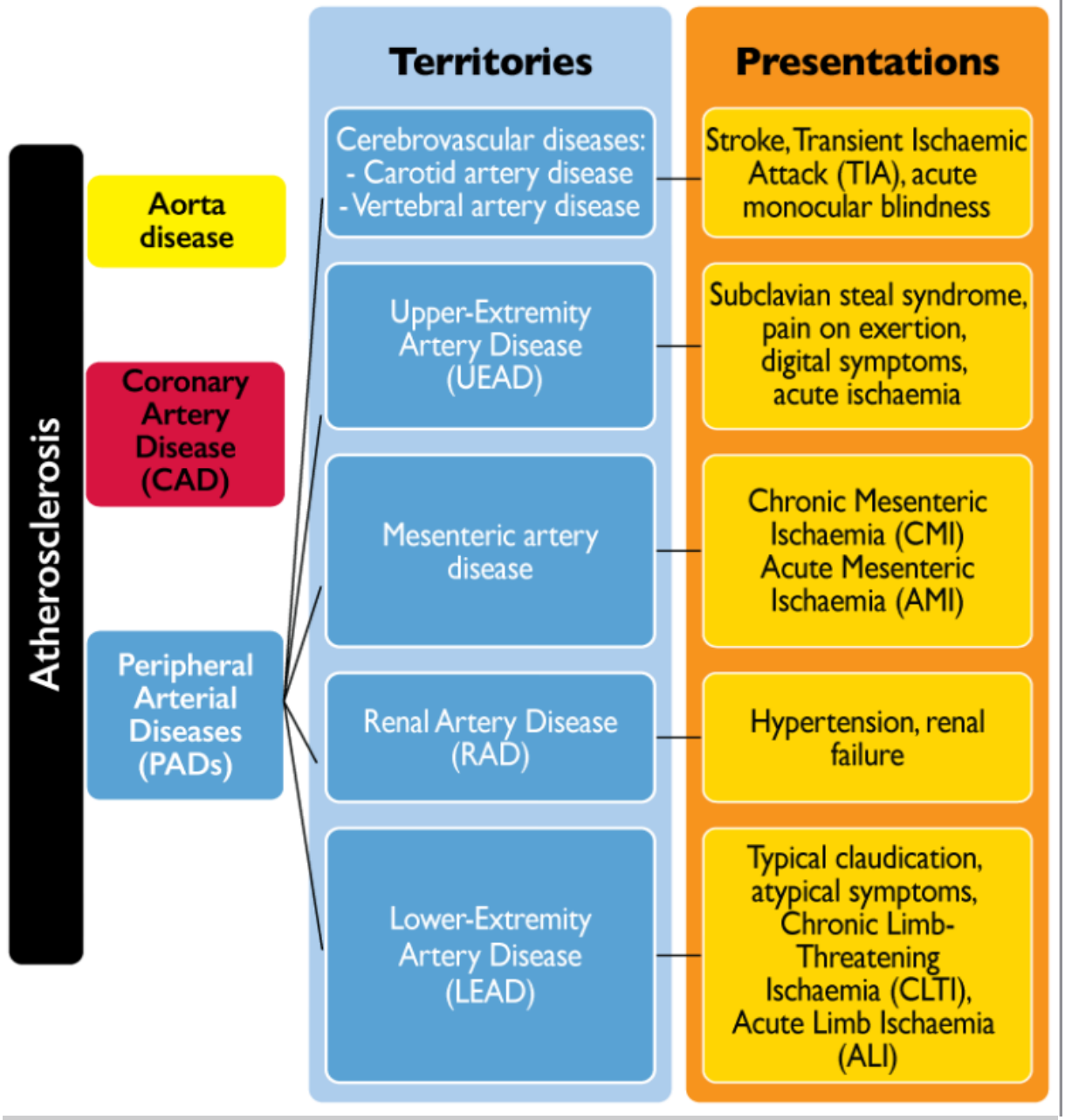
General recommendations on the management of patients with peripheral arterial diseases

Recommendations	Class[a]	Level[b]
In healthcare centres, it is recommended to set up a multidisciplinary Vascular Team to make decisions for the management of patients with PADs.	I	C
It is recommended to implement and support initiatives to improve medical and public awareness of PADs, especially cerebrovascular and lower extremity artery diseases.	I	C

Epidemiology and risk factors

The risk of different localizations of PADs increases with age and with exposure to major CV risk factors: smoking, hypertension, dyslipidaemia and diabetes. The strength of association between each risk factor and each vascular territory is variable. When a vascular territory is affected by atherosclerosis, not only is the corresponding organ endangered (e.g. the brain for carotid artery disease) but also the total risk of any cardiovascular event is increased (e.g. coronary events).

Figure 1 Presentations of Peripheral Arterial Diseases (PADs)



Overview

Thorough clinical history and physical examination are key steps in PADs management (Tables 1 & 2).

Laboratory testing (Table 3) is a key component especially for assessing the risk factors and end organ damages.

The Ankle-Brachial Index (ABI) has a specific particularity since it can not only diagnose LEAD but can be used as marker of atherosclerosis and risk of mortality and CV events (Table 4).

Table 1 Main points of medical history for assessment of peripheral arterial diseases

Family history of CVD (coronary artery disease, cerebrovascular disease, aortic aneurysm, LEAD), and premature CVD (fatal or non-fatal CVD event or/and established diagnosis of CVD in first degree male relatives before 55 years or female relatives before 65 years).
Personal history of: • Hypertension • Diabetes • Dyslipidaemia • Smoking (present and/or past), passive smoking exposure • Prior CVD • Chronic kidney disease • Sedentary life • Dietary habits • History of cancer radiation therapy • Psycho-social factors
Transient or permanent neurological symptoms.
Arm exertion pain, particularly if associated with dizziness or vertigo.
Symptoms suggesting angina, dyspnoea.
Abdominal pain, particularly if related to eating and associated with weight loss.
Walking impairment/claudication: • type: fatigue, aching, cramping, discomfort, burning • location: buttock, thigh, calf, or foot • timing: triggered by exercise, uphill rather than downhill, quickly relieved with rest; chronic • distance
Lower limb pain (including foot) at rest, and evolution at upright or recumbent position.
Poorly healing wounds of the extremities.
Physical activity assessment: • Functional capacity and causes of impairment.
Erectile dysfunction.

CVD = cardiovascular disease; LEAD = lower extremity artery disease.

Table 2 Physical examination for assessment of peripheral arterial diseases

Auscultation and palpation of cervical and supraclavicular areas.
Careful inspection of upper extremities, including hands (i.e. colour, skin integrity).
Palpation of upper extremity pulses.
Blood pressure measurement of both arms and notation of inter-arm difference.
Auscultation at different levels including the flanks, peri-umbilical region, and groin.
Abdominal palpation, palpation of femoral, popliteal, dorsalis pedis, and posterior tibial artery pulses, temperature gradient assessment.
Careful inspection of lower limbs, including feet (i.e. colour, presence of any cutaneous lesion). Findings suggestive of lower extremity arterial disease, including calf hair loss and muscle atrophy, should be noted.
Peripheral neuropathy assessment in case of diabetes or LEAD: sensory loss (monofilament testing), ability to detect pain and light touch (sharp examination pin, cotton wool), vibration impairment (128 Hz tuning fork); deep tendon reflexes examination; sweating.

Table 3 Laboratory testing in patients with peripheral arterial diseases

Routine tests
Fasting plasma glucose.
Fasting serum lipid profile: • total cholesterol • triglycerides • high-density lipoprotein cholesterol • low-density lipoprotein cholesterol
Serum creatinine and creatinine clearance.
Urine analysis: urinary protein by dipstick test, microalbuminuria.
• Blood count • Uric acid
Additional tests, based on findings from clinical history, physical examination and routine tests
Either glycated haemoglobin if fasting plasma glucose >5.6 mmol/L (101 mg/dL) or impaired glucose tolerance test when there is doubt.
Lipoprotein(a) if there is a family history of premature cardiovascular disease.
Quantitative proteinuria if positive dipstick test.

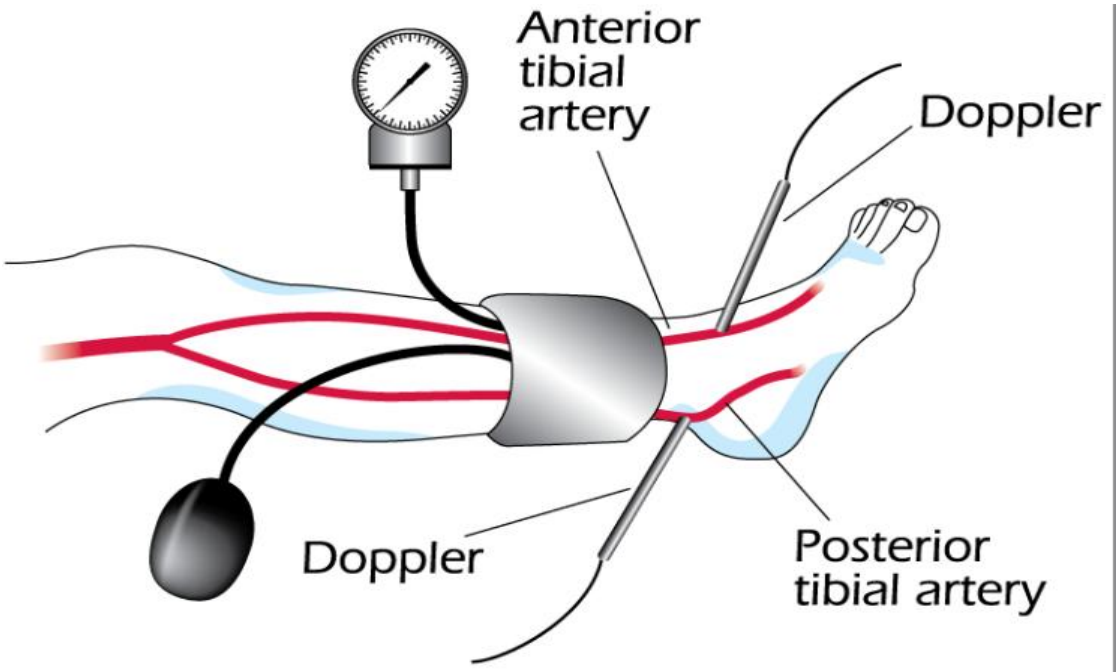
Table 4 The Ankle-Brachial Index

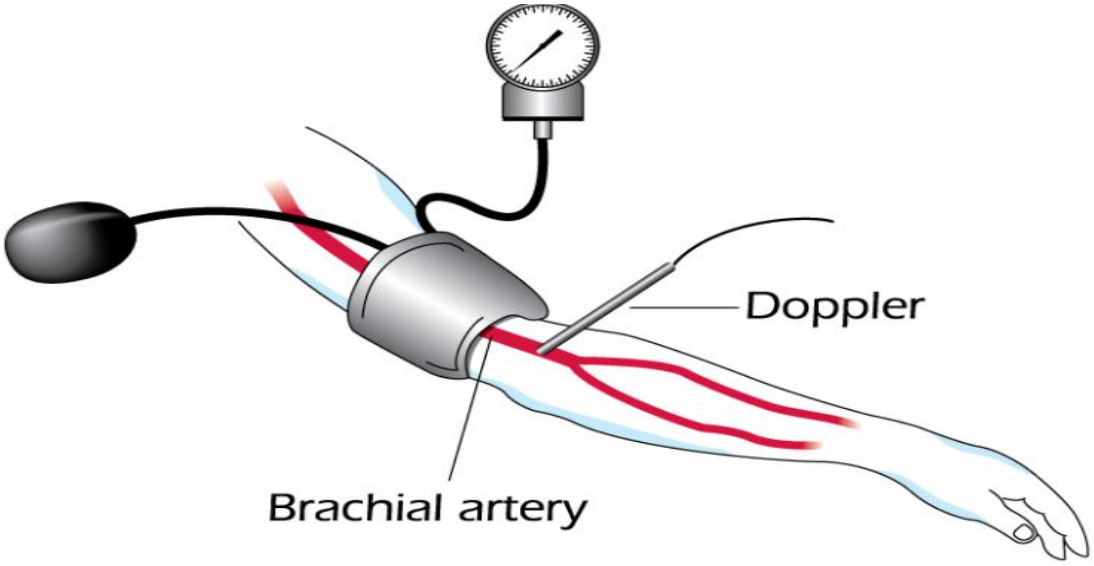
1. Who should have an ABI measurement in clinical practice?

- **Patients with clinical suspicion for LEAD:**
  - Lower extremities pulse abolition and/or arterial bruit
  - Typical intermittent claudication or symptoms suggestive for LEAD
  - Non-healing lower extremity wound
- **Patients at risk for LEAD because of the following clinical conditions:**
  - Atherosclerotic diseases: CAD, any PADs
  - Other conditions: AAA, CKD, heart failure
- **Asymptomatic individuals clinically-free but at-risk for LEAD:**
  - Men and women aged >65 years
  - Men and women aged <65 years classified at high CV risk according the ESC Guidelines[a]
  - Men and women aged >50 years with family history for LEAD

2. How to measure the ABI?

In supine position, with cuff placed just above the ankle, avoiding wounded zones. After a 5–10 minute rest, the SBP is measured by a Doppler probe (5–10 MHz) on the posterior and the anterior tibial (or dorsal pedis) arteries of each foot and on the brachial artery of each arm. Automated BP cuffs are mostly not valid for ankle pressure and may display overestimated results in case of low ankle pressure. The ABI of each leg is calculated by dividing the highest ankle SBP by the highest arm SBP.





3. How to interpret the ABI?

- For diagnosis of LEAD interpret each leg separately (one ABI per leg).
- For the CV risk stratification: take the lowest ABI between the two legs.
- Interpretation:

[a]Subjects with: markedly elevated single risk factors; diabetes mellitus (except for young people with type 1 diabetes without other major risk factors); a calculated SCORE ≥5% and <10%.

The management of patients with PADs includes both interventions to address specific arterial symptoms and general CV risk prevention. Best medical therapy includes CV risk factor management with non-pharmacological measures (i.e. smoking cessation, healthy diet, weight loss and regular physical exercise) and optimal pharmacological therapy.

Recommendations in patients with peripheral arterial diseases: best medical therapy

Recommendations	Class[a]	Level[b]
Smoking cessation is recommended in all patients with PADs.	I	B
Healthy diet and physical activity are recommended for all patients with PADs.	I	C
Statins are recommended in all patients with PADs.	I	A
In patients with PADs, it is recommended to reduce LDL-C to <1.8 mmol/L (70 mg/dL) or decrease it by ≥50% if baseline values are 1.8–3.5 mmol/L (70–135 mg/dL).	I	C
In diabetic patients with PADs, strict glycaemic control is recommended.	I	C
Antiplatelet therapy is recommended in patients with symptomatic PADs.	I	C[d]
In patients with PADs and hypertension, it is recommended to control blood pressure at <140/90 mmHg.	I	A
ACEIs or ARBs should be considered as first line therapy in patients with PADs and hypertension.[c]	IIa	B

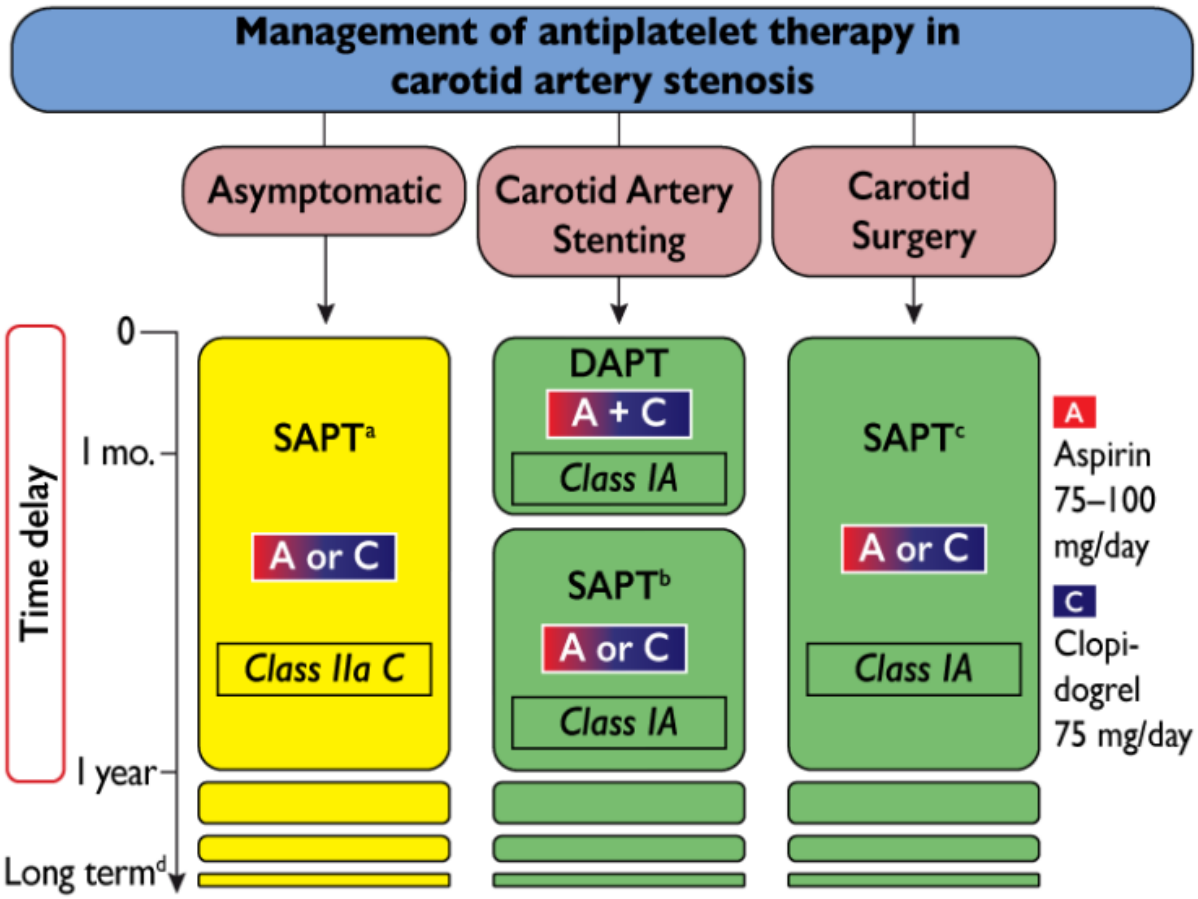
ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin-receptor blockers; BP = blood pressure; HbA1c = glycated haemoglobin; LDL-C = low-density lipoprotein cholesterol; LEAD = lower extremity artery disease; PADs = peripheral arterial diseases.

[c]Calcium channel blockers should be proposed in black individuals.

[d]Evidence is not available for all sites.When evidence is available, recommendations specific for the vascular site are presented in the corresponding sections.

This chapter addresses specifically the antithrombotic therapy, as part of best medical therapy, in most frequent cases. Other cases with PADs (e.g. renal artery disease) without any specific indication for oral anticoagulation (e.g. atrial fibrillation) require long-term antiplatelet therapy.

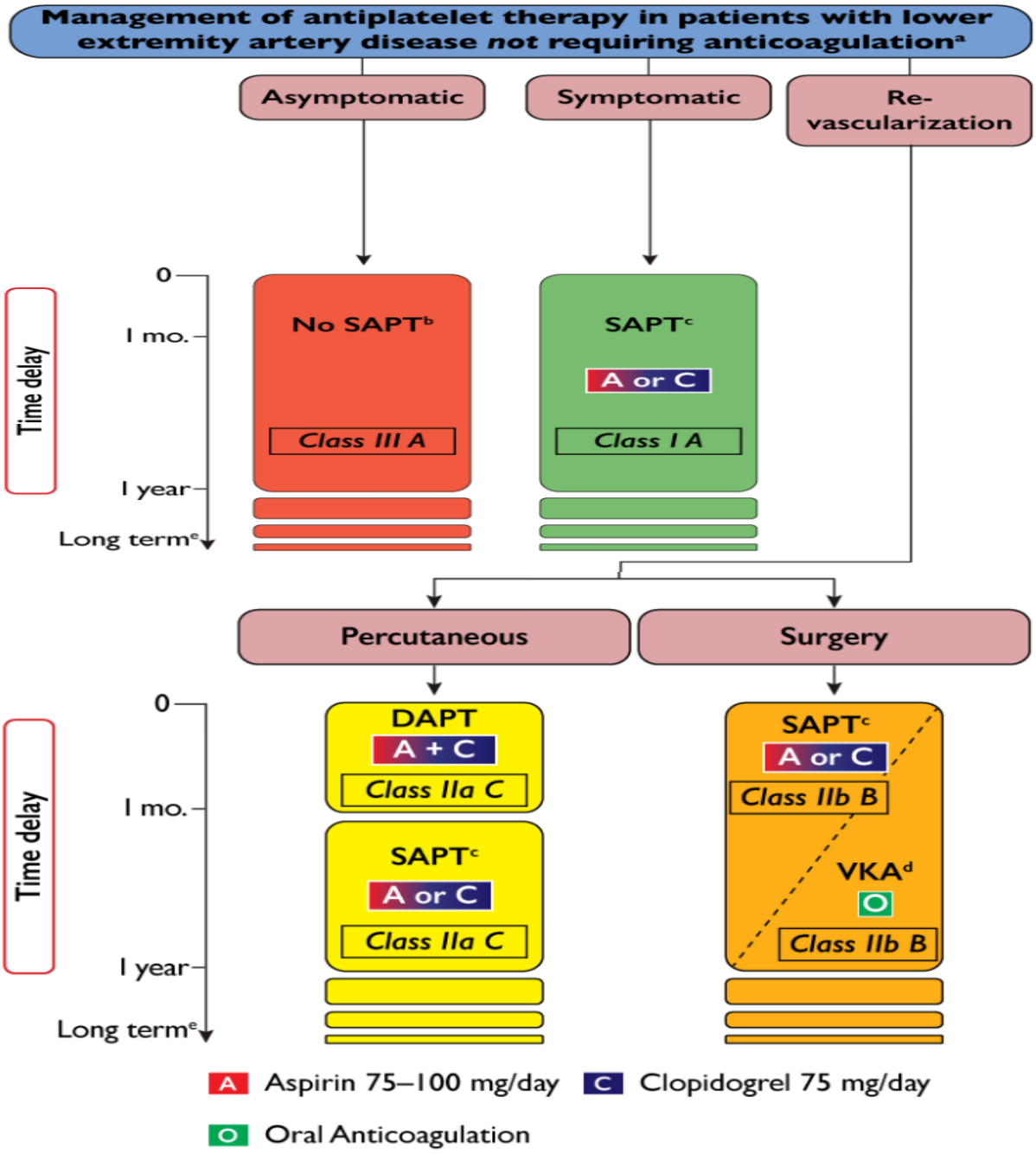
Figure 2 Management of antithrombotic treatment in patients with carotid artery stenosis



DAPT = dual antiplatelet therapy, a daily combination of aspirin (75–100 mg) and clopidogrel (75 mg); CAS = carotid artery stenting; SAPT = single antiplatelet therapy; TIA = transient ischaemic attack.

[a]At the exception of patient at very high bleeding risk - [b]DAPT may be used if another indication supersedes that of carotid artery stenting such as acute coronary syndrome or percutaneous coronary intervention of less than 1 year - [c] In case of recent minor stroke or TIA.A loading dose of aspirin (300 mg) and/or clopidogrel (300/600 mg) is recommended at the acute phase of stroke/TIA or during CAS - [d]Stands for as long as it is well tolerated.

Figure 3 Antiplatelet therapy in patients with lower extremity artery disease



DAPT = dual antiplatelet therapy; SAPT = single antiplatelet therapy;VKA = vitamin K antagonist.

[a]e.g. concomitant AF or mechanical valve prosthesis.

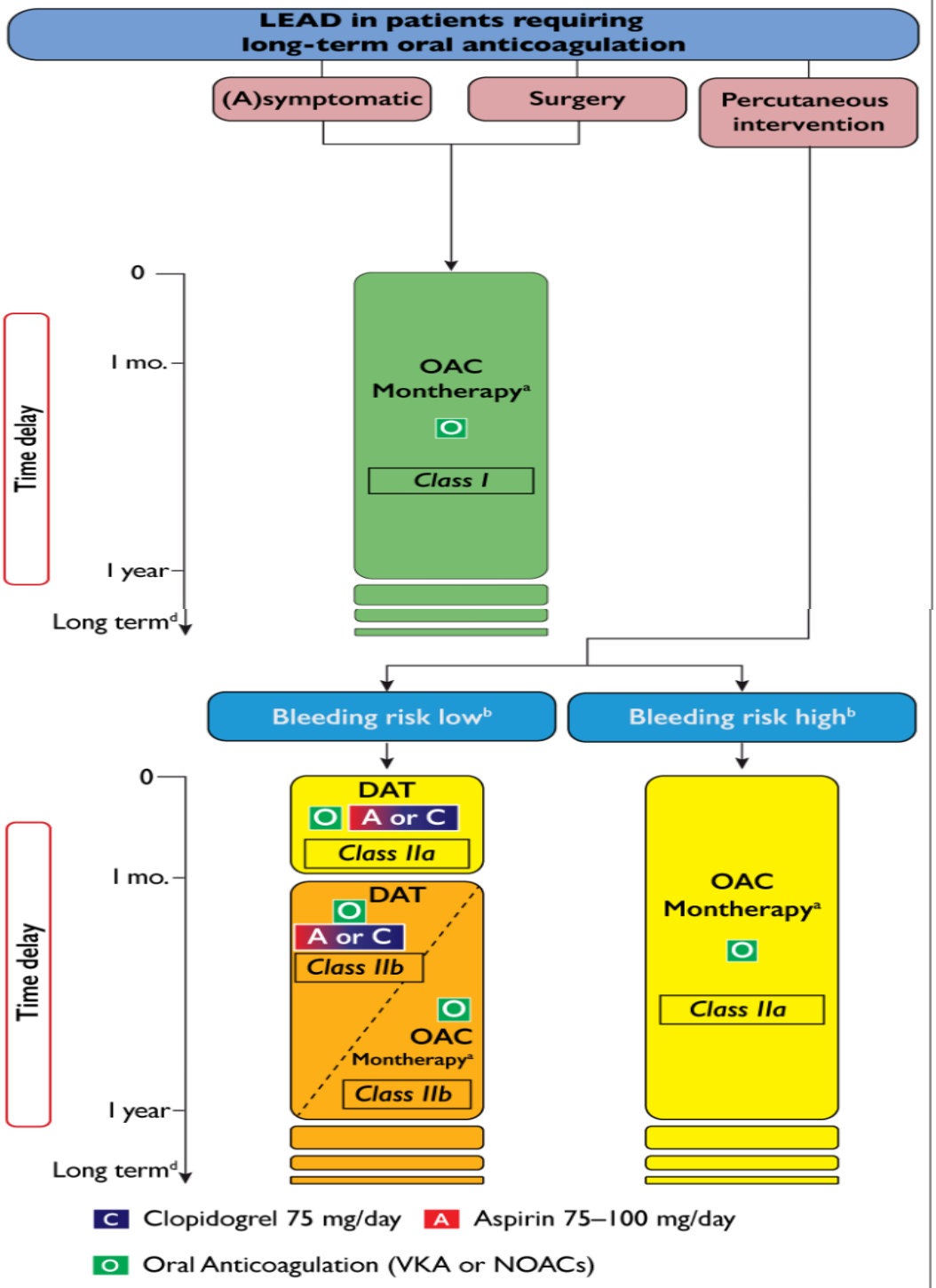
[b]SAPT should be considered if there is another concomitant atherosclerotic disease (e.g. coronary artery disease).

[c]DAPT may be considered in patients with recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization.

[d]Evidence is weak and bleeding doubles as compared to SAPT.

[e]Stands for as long as it is well tolerated.

Figure 4 Antithrombotic therapy in patients with LEAD requiring oral anticoagulation



ACS = acute coronary syndrome; CAD = coronary artery disease; CLTI = chronic limb-threatening ischaemia; DAT = dual antithrombotic therapy;LEAD = lower extremity artery disease; OAC = oral anticoagulation.

[a]DAT may be considered in high ischaemic rick patients defined as prior stent thrombosis, acute limb ischaemia on OAC and concomitant CAD (recent ACS, stenting of the last patent coronary artery, multiple coronary vessel disease in diabetic patients with incomplete revascularization).

[b]Compared to the risk for stroke/CLTI due to stent/graft occlusion.

[c]Stands for as long as it is well tolerated.

Recommendations on antithrombotic therapy in patients with peripheral artery diseases

Recommendations	Class[a]	Level[b]
Carotid artery disease		
In patients with symptomatic carotid stenosis, long-term SAPT is recommended.	I	A
DAPT with aspirin and clopidogrel is recommended for at least one month after CAS.	I	B
In patients with asymptomatic >50% carotid artery stenosis, long-term antiplatelet therapy (commonly low dose aspirin) should be considered when the bleeding risk is low.[c]	IIa	C
Lower extremity artery disease		
Long-term SATP is recommended in symptomatic patients.	I	A
Long-term SATP is recommended in all patients who have undergone revascularization.	I	C
SATP is recommended after infra-inguinal bypass surgery.	I	A
In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin.	IIb	B
Vitamin K antagonists may be considered after autologous vein infra- inguinal bypass.	IIb	B
DAPT with aspirin and clopidogrel for at least one month should be considered after infra-inguinal stent implantation.	IIa	C
DAPT with aspirin and clopidogrel may be considered in below-knee bypass with prosthetic graft.	IIb	B
Because of a lack of proved benefit, antiplatelet therapy is not routinely indicated in patients with isolated[d] asymptomatic LEAD.	III	A

Antithrombotic therapy for PADs patients requiring oral anticoagulant		
In patients with PADs and AF, oral anticoagulation:		
• is recommended when CHA_2DS_2-VASc score ≥2	I	A
• should be considered in all other patients	IIa	B
In patients with PADs who have an indication for OAC (e.g.AF or mechanical prosthetic valve), oral anticoagulants alone should be considered.	IIa	B
After endovascular revascularization, aspirin or clopidogrel should be considered in addition to OAC for at least I month if the bleeding risk is low compared to the risk of stent/graft occlusion.	IIa	C
After endovascular revascularization, OAC alone should be considered if the bleeding risk is high compared to the risk of stent/graft occlusion.	IIa	C
OAC and SAPT may be considered beyond one month in high ischaemic risk patients or when there is another firm indication for long-term SAPT.	IIb	C

AF = atrial fibrillation; CAS = carotid artery stenting; DAPT = dual antiplatelet; LEAD = lower extremity artery disease; OAC = oral anticoagulation; PADs = peripheral arterial diseases; SAPT = single antiplatelet therapy.

CHA_2DS_2-VASc score is calculated as follows: Congestive heart failure history (1 point), Hypertension (1 point),Age >75 years (2 points), Diabetes mellitus (1 point), Stroke or TIA or arterial thromboembolic history (1 point),Vascular disease history (1 point), Age between 65 and 74 years (1 point), Sex category (1 point if female).

[a]Class of recommendation.

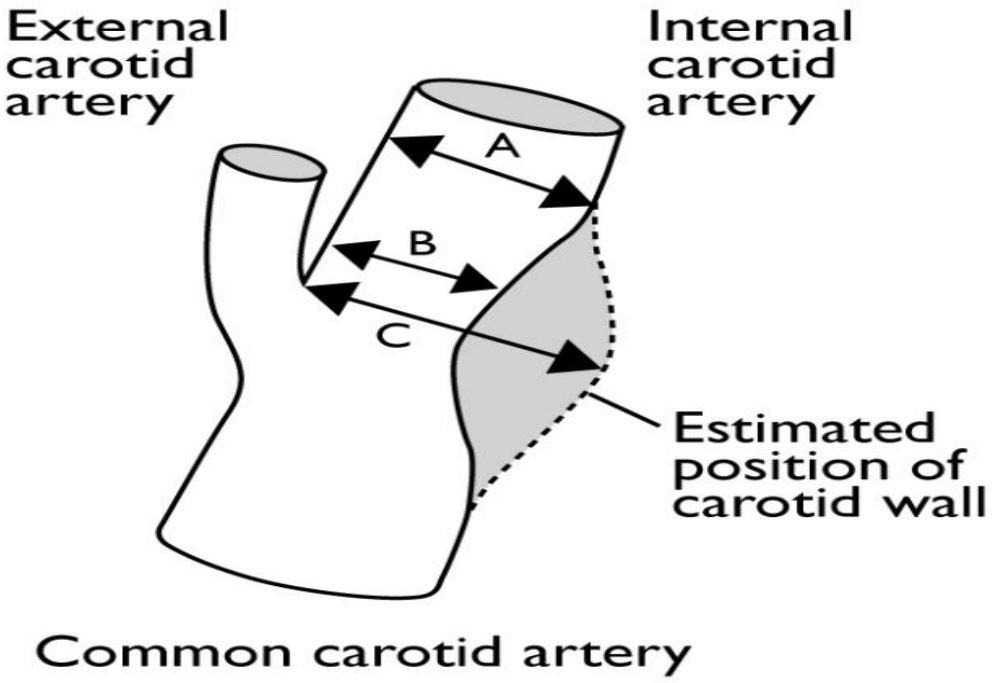
[b]Level of evidence.

[c]With the exception of patients with an indication for long-term oral anticoagulation.

[d]Without any other clinical cardiovascular condition requiring antiplatelet therapy (e.g. coronary artery disease or other multi-site artery diseases).

The management of carotid artery disease mostly depend on the symptomatic/asymptomatic characteristic, as well as the stenosis degree (Figure 4 and 5). Other characteristics can stratify the risk for patient with asymptomatic stenosis (Table 3).

Figure 5 Angiographic carotid stenosis according to different methods.



NASCET $\frac{A-B}{A}$	ECST $\frac{C-B}{C}$
NASCET	**ECST**
30	65
40	70
50	75
60	80
70	85
80	91
90	97

Approximate equivalent degrees of internal carotid artery stenosis used in NASCET and ESCT according to recent comparisons

ECST = European Carotid Surgery Trial; NASCET = North American Symptomatic Carotid Endarterectomy Trial

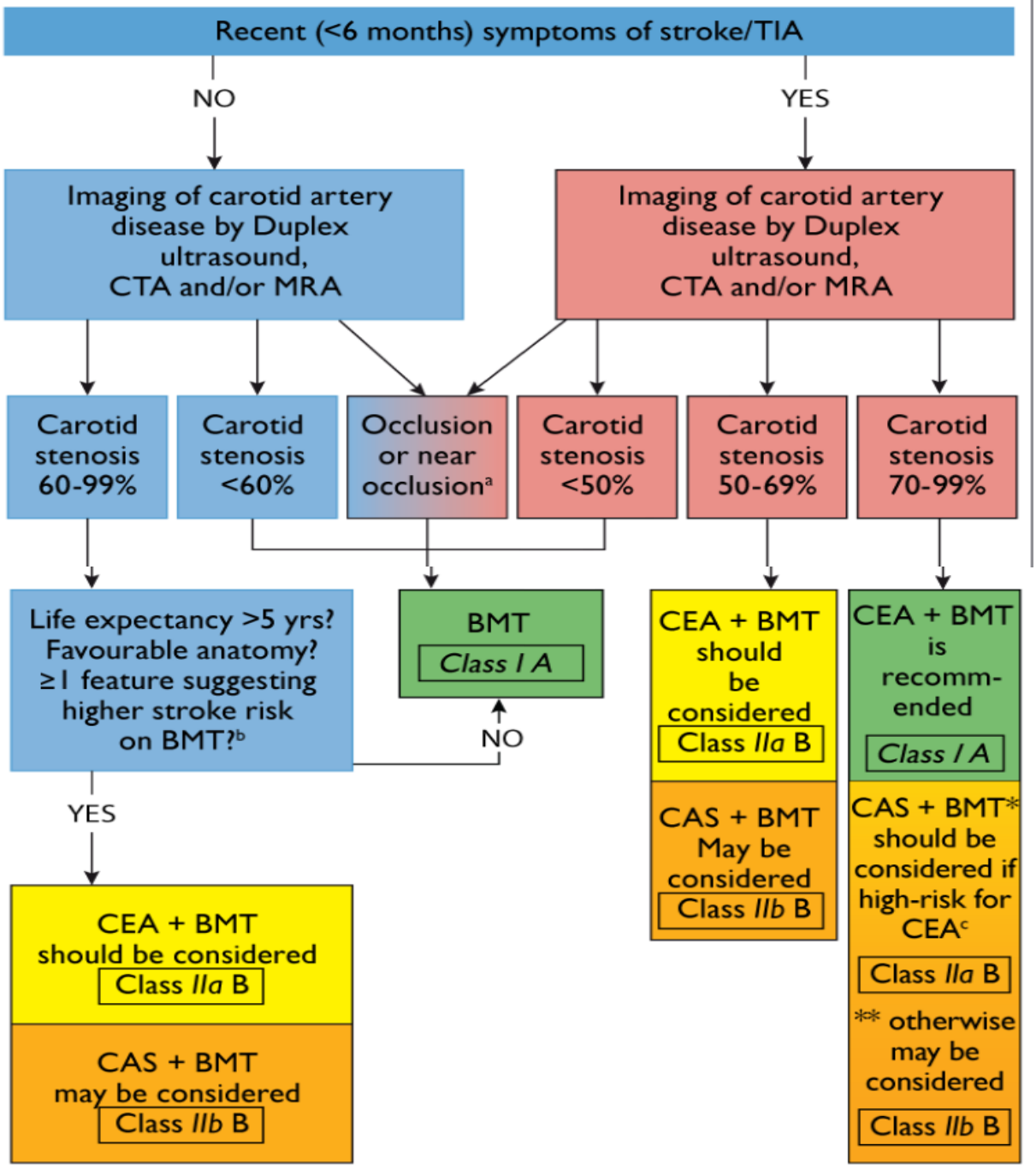
Recommendations for imaging of extracranial carotid arteries		
Recommendations	**Class[a]**	**Level[b]**
DUS (as first-line), CTA and/or MRA are recommended for evaluating the extent and severity of extracranial carotid stenoses.	I	B
When CAS is being considered, it is recommended that any DUS study be followed either by MRA or CTA to evaluate the aortic arch, as well as the extra- and intracranial circulation.	I	B
When CEA is considered, it is recommended that the DUS stenosis estimation be corroborated either by MRA or CTA (or by a repeat DUS study performed in an expert vascular laboratory).	I	B

CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; DUS = duplex ultrasound; MRA = magnetic resonance an-

Recommendations for management of asymptomatic carotid artery disease		
Recommendations	**Class[a]**	**Level[b]**
In "average surgical risk" patients with an asymptomatic 60–99% stenosis, CEA should be considered in the presence of clinical and/or more imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIa	B
In asymptomatic patients who have been deemed "high-risk for CEA"[d] and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[c] that may be associated with an increased risk of late ipsilateral stroke, CAS should be considered, provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIa	B
In "average surgical risk" patients with an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics[d] that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years.	IIb	B

BP = blood pressure; CAS = carotid artery stenting; CEA = carotid endarterectomy. [a]Class of recommendation - [b]Level of evidence. - [c]See Table 5 - [d]Age > 80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

Figure 6 Management of extracranial carotid artery disease



BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy; CTA = computed tomography angiography; MRA = magnetic resonance angiography;TIA = transient ischaemic attack.

[a]With post-stenotic internal carotid artery narrowed to the point of near occlusion -
[b]See Table 5.

[c]Age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral internal carotid artery occlusion, contralateral recurrent laryngeal nerve palsy, previous radical neck surgery or radiotherapy and recurrent stenosis after CEA.

Table 5 Features associated with increased risk of stroke in patients with asymptomatic carotid stenosis treated medically (for details see Web Table 5, see Web Addenda online*)	
Clinical[a]	• Contralateral TIA/stroke
Cerebral imaging	• Ipsilateral silent infarction
Ultrasound imaging	• Stenosis progression (> 20%) • Spontaneous embolization on transcranial Doppler (HITS) • Impaired cerebral vascular reserve • Large plaques[b] • Echolucent plaques • Increased juxta-luminal black (hypoechogenic) area
MRA	• Intraplaque haemorrhage • Lipid-rich necrotic core

HITS = high intensity transient signal; MRA = magnetic resonance angiography; TIA = transient ischaemic attack.
[a]Age is not a predictor of poorer outcome -[b]More than 40 mm^2 on digital analysis.

Recommendations on revascularization in patients with symptomatic carotid disease[c]		
Recommendations	**Class[a]**	**Level[b]**
CEA is recommended in symptomatic patients with 70–99% carotid stenoses, provided the documented procedural death/stroke rate is <6%.	I	A
CEA should be considered in symptomatic patients with 50–69% carotid stenoses, provided the documented procedural death/stroke rate is <6%.	IIa	A
In recently symptomatic patients with a 50–99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them "high-risk for CEA", CAS should be considered, provided the documented procedural death/stroke rate is <6%.	IIa	B
When revascularization is indicated in "average surgical risk" patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/ stroke rate is <6%.	IIb	B
When decided, it is recommended to perform revascularization of symptomatic 50–99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.	I	A
Revascularization is not recommended in patients with a <50% carotid stenosis.	III	A

[a]Class of recommendation - [b]Level of evidence - [c]Stroke or TIA occuring within the 6 months.

Recommendation on the use of embolic protection device during carotid stenting		
Recommendations	**Class[a]**	**Level[b]**
The use of embolic protection devices should be considered in patients undergoing carotid artery stenting.	IIa	C

Recommendations for management of vertebral artery stenoses		
Recommendations	**Class[a]**	**Level[b]**
In patients with symptomatic extracranial vertebral artery stenoses, revascularization may be considered for lesions ≥50% in patients with recurrent ischaemic events, despite optimal medical management.	IIb	B
Revascularization of asymptomatic vertebral artery stenosis is not indicated, irrespective of the degree of severity.	III	C

Upper extremity artery disease (UEAD) due to atherosclerosis is mostly situated at the brachio-cephalic trunk, the subclavian and axillary arteries. Other aetiologies should be considered (Table 6). When suspected, it can be assessed by DUS, CTA or MRA.

Table 6 Differential diagnosis in upper limbs artery disease

Causes	Subclavian	Axillary	Brachial	Forearm	Hand
Atherosclerosis	•				
Thoracic outlet syndrome	•				
Giant cell arteritis	•				
Takayasu arteritis	•	•			
Radiation artery fibrosis	•	•			
Embolic		•	•	•	•
Fibromuscular dysplasia		•			•
Buerger's disease				•	•
Ergotism				•	•
Connective tissue disease				•	•
Cytotoxic drugs					•
Arterial drug injection					•
Diabetes mellitus					•
Myeloproliferative disorders					•
Hypercoagulative status					•

Cryoglobulins					•
Repetitive trauma					•
Vinyl chloride exposure					•
Iatrogenic lesions	•	•	•	•	•

Recommendations on the management of subclavian artery stenosis		
Recommendations	**Class[a]**	**Level[b]**
In symptomatic patients with subclavian artery stenosis/occlusion revascularization should be considered.	**IIa**	C
In symptomatic patients with a stenotic/occluded subclavian artery, both revascularization options (stenting or surgery) should be considered and discussed case by case according to the lesion characteristics and patient's risk.	**IIa**	C
In asymptomatic subclavian artery stenosis, revascularization:		
• should be considered in the case of proximal stenosis in patients undergoing CABG using the ipsilateral internal mammary artery.	**IIa**	C
• should be considered in the case of proximal stenosis in patients who already have the ipsilateral internal mammary artery grafted to coronary arteries with evidence of myocardial ischaemia.	**IIa**	C
• should be considered in the case of subclavian artery stenosis and ipsilateral arteriovenous fistula for dialysis.	**IIa**	C
• may be considered in the case of bilateral		

Mesenteric artery disease is underdiagnosed and highly lethal. The prerequisite of diagnosis is clinical suspicion, followed by imaging.

Acute mesenteric ischaemia is more often related to embolism than to thrombotic occlusion. Outcome is very time-sensitive, and dependent on clinical suspicion.

Recommendations on the management of acute mesenteric ischaemia

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected acute mesenteric ischaemia, urgent CTA is recommended.	I	C
In patients with suspicion of acute mesenteric ischaemia,the measurement of D-dimer should be considered to rule out the diagnosis.	IIa	B
Treatment		
In patients with acute thrombotic occlusion of the superior mesenteric artery, endovascular therapy should be considered as first line therapy for revascularization.	IIa	B
In patients with acute embolic occlusion of the superior mesenteric artery, both endovascular and open surgery therapy should be considered.	IIa	B

The classical symptoms of CMI are postprandial abdominal pain, weight loss, diarrhoea or constipation, and food aversion.

Recommendations for management of chronic mesenteric artery disease

Recommendations	Class[a]	Level[b]
Diagnosis		
In patients with suspected CMI, DUS is recommended as the first line examination.	I	C
In patients with suspected CMI, occlusive disease of a single mesenteric artery makes the diagnosis unlikely, and a careful search for alternative causes should be considered.	IIa	C
Treatment		
In patients with symptomatic multivessel CMI, revascularization is recommended.	I	C
In patients with symptomatic multivessel CMI, it is not recommended to delay revascularization in order to improve the nutritional status.	III	C

CMI = chronic mesenteric ischaemia; DUS = duplex ultrasound.

Atherosclerotic renal artery disease (RAD) is the most common cause of "renovascular hypertension". The clinical situations raising suspicion for RAD are enlisted in Table 7.

Table 7 Clinical situations raising suspicion for renal artery disease

Onset of hypertension before the age of 30 years.
Onset of severe hypertension after the age of 55 years, when associated with CKD or heart failure.
Hypertension and abdominal bruit.
Rapid and persistent worsening of previously controlled hypertension.
Resistant hypertension (i.e. other secondary form unlikely and target not achieved despite four drug classes including a diuretic and a mineralocorticoid-receptor antagonist in appropriate doses).
Hypertensive crisis (i.e. acute renal failure, acute heart failure, hypertensive encephalopathy, or grade 3–4 retinopathy).
New azotaemia or worsening of renal function after treatment with RAAS blockers.
Unexplained atrophic kidney or discrepancy in kidney size, or unexplained renal failure.
Flash pulmonary oedema.

CKD = chronic kidney disease; RAAS = renin-angiotensin-aldosterone system.

Recommendations for diagnostic strategies for renal artery disease

Recommendations	Class[a]	Level[b]
DUS (as first-line), CTA[c] and MRA[d] are recommended imaging modalities to establish a diagnosis of RAD.	I	B
DSA may be considered to confirm a diagnosis of RAD when clinical suspicion is high and the results of non-invasive examinations are inconclusive.	IIb	C
Renal scintigraphy, plasma renin measurements before and after ACEI provocation, and vein renin measurements are not recommended for screening of atherosclerotic RAD.	III	C

ACEI = angiotensin-converting enzyme inhibitor; CTA = computed tomography angiography; DSA = digital subtraction angiography; DUS = duplex ultrasound; eGFR = estimated glomerular filtration rate; MRA = magnetic resonance angiography; RAD = renal artery disease.

[a]Class of recommendation - [b]Level of evidence - [c]When eGFR is ≥60 mL/min - [d]When eGFR is ≥30 mL/min.

Recommendations for treatment strategies for renal artery disease		
Recommendations	**Class[a]**	**Level[b]**
Medical therapy		
ACEIs/ARBs are recommended for treatment of hypertension associated with unilateral RAS.	I	B
Calcium channel blockers,beta-blockers and diuretics are recommended for treatment of hypertension associated with renal artery disease.	I	C
ACEIs/ARBs may be considered in bilateral severe RAS and in the case of stenosis in a single functioning kidney, if well-tolerated and under close monitoring.	IIb	B
Revascularization		
Routine revascularization is not recommended in RAS secondary to atherosclerosis.	III	A
In cases of hypertension and/or signs of renal impairment related to renal arterial fibromuscular dysplasia, balloon angioplasty with bailout stenting should be considered.	IIa	B
Balloon angioplasty, with or without stenting, may be considered in selected patients with RAS and unexplained recurrent congestive heart failure or sudden pulmonary oedema.	IIb	C
In the case of an indication for revascularization,surgical revascularization should be considered for patients with complex anatomy of the renal arteries, after a failed endovascular procedure, or during open aortic surgery.	IIa	B

ACEI(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin-receptor blocker(s); RAS = renal artery stenosis.

Clinical presentation

Most patients with LEAD are asymptomatic. Walking capacity must be assessed to detect clinically "masked LEAD". Atypical symptoms are frequent. Even asymptomatic patients with LEAD are at high-risk of CV events and must benefit from most CV preventive strategies.

Table 8 Clinical stages of lower extremity artery disease

Fontaine classification		
Stage		Symptoms
I		Asymptomatic
II	IIa	Non-disabling intermittent claudication
	IIb	Disabling intermittent claudication
III		Ischaemic rest pain
IV		Ulceration or gangrene

Rutherford classification		
Grade	Category	Symptoms
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
II	4	Ischaemic rest pain
III	5	Minor tissue loss
III	6	Major tissue loss

Diagnostic tests

Recommendations for ankle-brachial index measurement

Recommendations	**Class[a]**	**Level[b]**
Measurement of the ABI is indicated as a first-line non-invasive test for screening and diagnosis of LEAD.	I	C
In the case of incompressible ankle arteries or ABI >1.40, alternative methods such as the toe-brachial index, Doppler waveform analysis or pulse volume recording are indicated.	I	C

ABI = ankle-brachial index; LEAD = lower extremity artery disease.
[a]Class of recommendation - [b]Level of evidence.

Recommendations on imaging in patients with lower extremity artery disease		
Recommendations	**Class[a]**	**Level[b]**
DUS is indicated as first-line imaging method to confirm LEAD lesions.	I	C
DUS and/or CTA and/or MRA are indicated for anatomical characterization of LEAD lesions and guidance for optimal revascularization strategy.	I	C
Data from an anatomical imaging test should always be analyzed in conjunction with symptoms and haemodynamic tests prior to treatment decision.	I	C
DUS screening for AAA should be considered.	IIa	C

AAA = abdominal aorta aneurysm; CTA = computed tomography angiography; DUS = duplex ultrasound; LEAD = lower extremity artery disease; MRA = magnetic resonance angiography.

Recommendations on revascularization of aorto-iliac occlusive lesions[c]		
Recommendations	**Class[a]**	**Level[b]**
An endovascular-first strategy is recommended for short (i.e. <5 cm) occlusive lesions.	I	C
In patients fit for surgery, aorto-(bi)femoral bypass should be considered in aorto-iliac occlusion(s).	IIa	B
An endovascular-first strategy should be considered in long and/or bilateral lesions in patients with severe comorbidities.	IIa	B
An endovascular-first strategy may be considered for aorto-iliac occlusive lesions, if done by an experienced team and if it does not compromise subsequent surgical options.	IIb	B
Primary stent implantation, rather than provisional stenting, should be considered.	IIa	B
Open surgery should be considered in fit patients with an aortic occlusion extending up to the renal arteries.	IIa	C
In the case of ilio-femoral occlusive lesions, a hybrid procedure combining iliac stenting and femoral endarterectomy or bypass should be considered.	IIa	C
Extra-anatomical bypass may be indicated only for patients with no other alternatives for revascularization.	IIb	C

[a]Class of recommendation - [b]Level of evidence - [c]These recommendations apply both for patients with intermittent claudication and severe chronic limb ischaemia.

Recommendations on revascularization of femoro-popliteal occlusive lesions[c]

Recommendations	Class[a]	Level[b]
An endovascular-first strategy is recommended in short (i.e. <25 cm) lesions.	I	C
Primary stent implantation should be considered in short (i.e. <25 cm) lesions.	IIa	A
Drug-eluting balloons may be considered in short (i.e. <25 cm) lesions.	IIb	A
Drug-eluting stents may be considered for short (i.e. <25 cm) lesions.	IIb	B
Drug-eluting balloons may be considered for the treatment of in-stent restenosis.	IIb	B
In patients who are not at high-risk for surgery, bypass surgery is indicated for long (i.e. ≥25 cm) superficial femoral artery lesions when an autologous vein is available and life expectancy is >2 years.	I	B
The autologous saphenous vein is the conduit of choice for femoro- popliteal bypass.	I	A
When above-knee bypass is indicated, in the absence of any autologous saphenous vein, the use of a prosthetic conduit should be considered	IIa	A
In patients unfit for surgery, endovascular therapy may be considered in long (i.e. ≥25 cm) femoro-popliteal lesions.	IIb	C

[a]Class of recommendation - [b]Level of evidence - [c]These recommendations apply both for patients with intermittent claudication and chronic limb-threatening ischaemia.

Recommendations on revascularization of infra-popliteal occlusive lesions

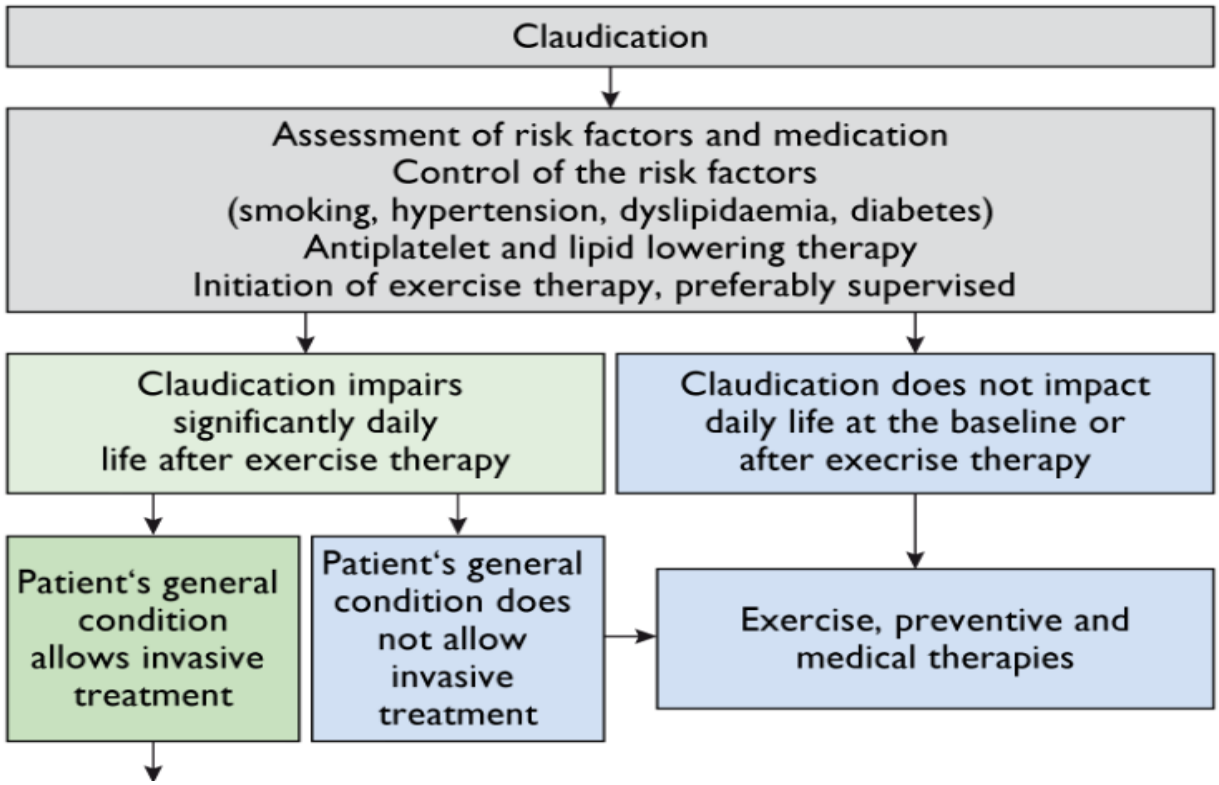
Recommendations	Class[a]	Level[b]
In the case of CLTI, infra-popliteal revascularization is indicated for limb salvage.	I	C
For revascularization of infra-popliteal arteries:		
• bypass using the great saphenous vein is indicated	I	A
• endovascular therapy should be considered.	IIa	B

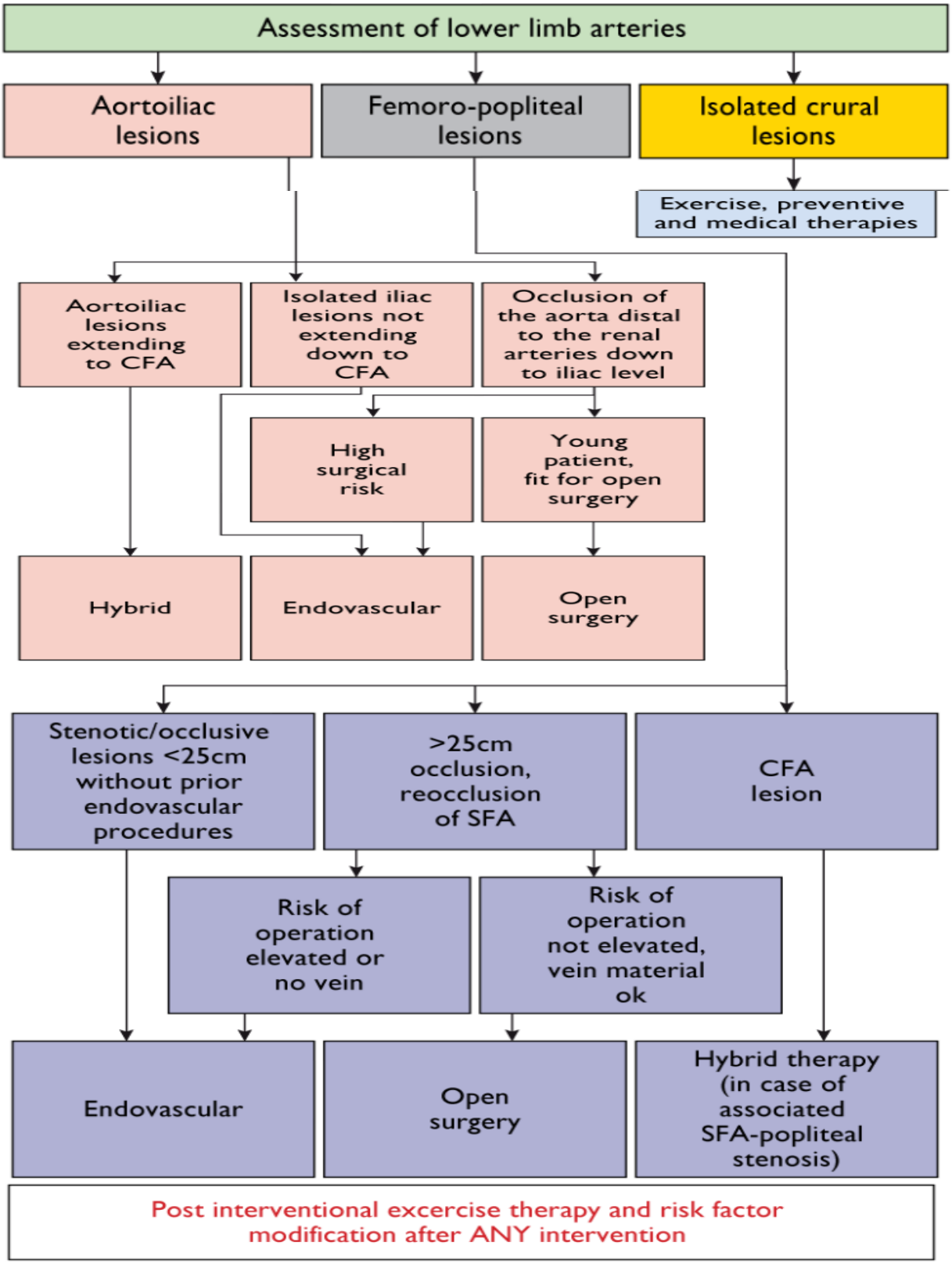
CLTI = chronic limb-threatening ischaemia. [a]Class of recommendation - [b]Level of evidence.

Recommendations for the management of patients with intermittent claudication

Recommendations	Class[a]	Level[b]
On top of general prevention, statins are indicated to improve walking distance.	I	A
In patients with intermittent claudication:		
• supervised exercise training is recommended.	I	A
• non-supervised exercise training is recommended when supervised exercise training is not feasible or available.	I	C
When daily life activities are compromised despite exercise therapy, revascularization should be considered.	IIa	C
When daily life activity is severely compromised, first line revascularization should be considered, in association with exercise therapy.	IIa	B

Figure 7 Management of patients with intermittent claudication[a]





CFA = common femoral artery; SFA = superficial femoral artery.
[a]Related to atherosclerotic lower extremity artery disease (LEAD).

CLTI specifies clinical patterns with vulnerable limb viability, related to ischaemia, wounds, and infection (Table 9 & Figure 8). Risk stratification and early recognition of tissue loss and/or infection and referral to the vascular specialist is mandatory for limb salvage by a multidisciplinary approach. Revascularization is indicated whenever feasible.

Table 9 Assessment of the risk of amputation: the WIFI classification

Score	Description		
W (Wound)			
0	No ulcer (ischaemic rest pain)		
1	Small, shallow ulcer on distal leg or foot without gangrene		
2	Deeper ulcer with exposed bone, joint or tendon ± gangrenous changes limited to toes		
3	Extensive deep ulcer, full thickness heel ulcer ± calcaneal involvement ± extensive gangrene		
I (Ischaemia)			
	ABI	Ankle pressure (mmHg)	Toe pressure or $TcPO_2$
0	≥0.80	>100	≥60
1	0.60–0.79	70–100	40–59
2	0.40–0.59	50–70	30–39
3	<0.40	<50	<30
fI (foot Infection)			
0	No symptoms/signs of infection		
1	Local infection involving only skin and subcutaneous tissue		
2	Local infection involving deeper than skin/subcutaneous tissue		
3	Systemic inflammatory response syndrome		

Example: A 65-year-old male diabetic patient with gangrene of the big toe and a <2 cm rim of cellulitis at the base of the toe, without any clinical/biological sign of general infection/inflammation, whose toe pressure is at 30 mmHg would be classified as Wound 2, Ischaemia 2, foot Infection 1 (WIfI 2-2-1).
The clinical stage would be 4 (high-risk of amputation). The benefit of revascularization (if feasible) is high, also depending on infection control.
[a]Adapted from Mills JL et al. J Vasc Surg 2014;59(1):220–234.

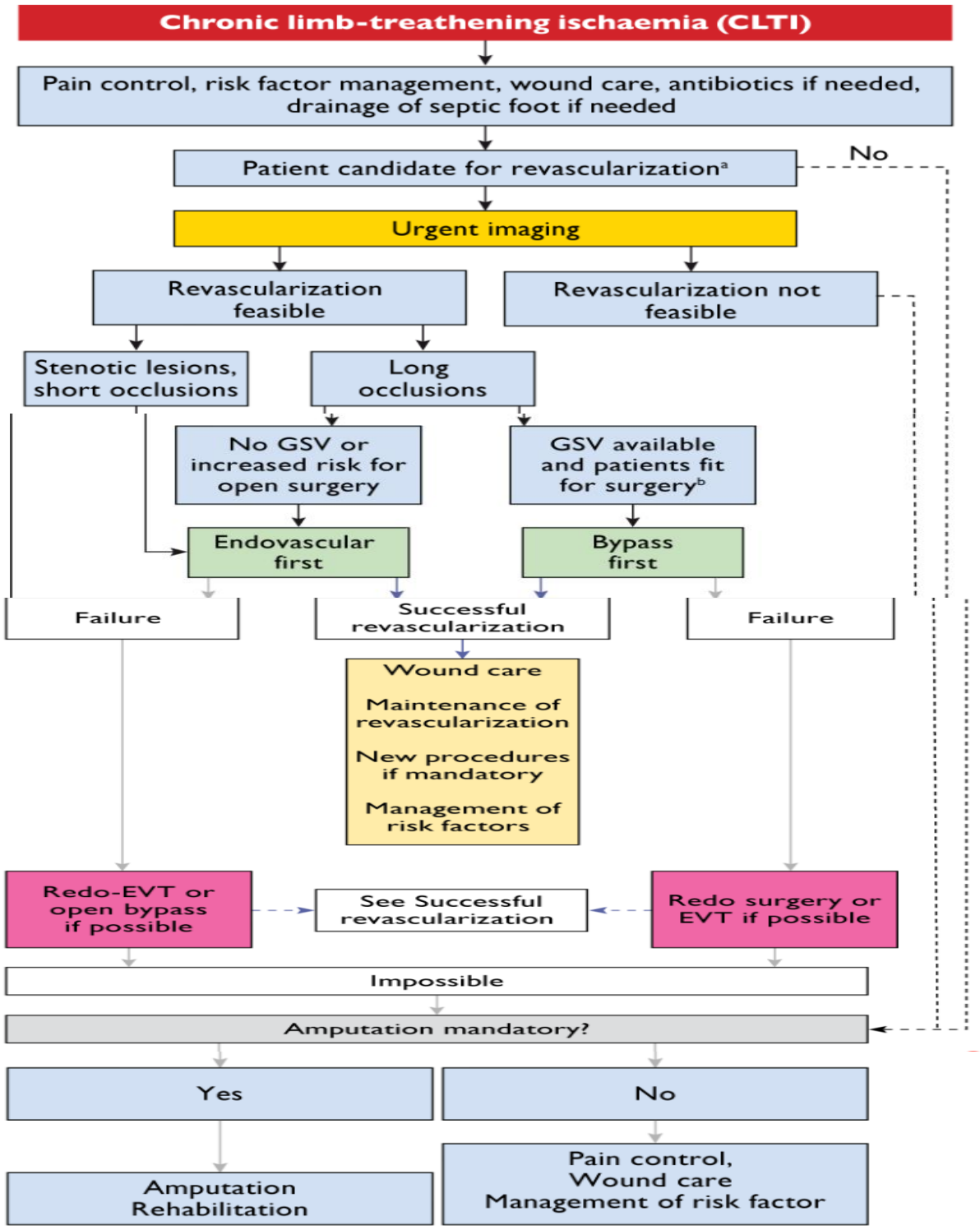
ABI = ankle-brachial index;TcPO2 = transcutaneous oxygen pressure.

Figure 8 Estimation of the amputation risk according to the WIfI classification (see also Table 7)[a]

Estimate risk of amputation at I year for each combination				
	Ischaemia-0			
W-0	VL	VL	L	M
W-1	VL	VL	L	M
W-2	L	L	M	H
W-3	M	M	H	H
	fI-0	fI-1	fI-2	fI-3
	Ischaemia-1			
W-0	VL	L	M	H
W-1	VL	L	M	H
W-2	M	M	H	H
W-3	H	H	H	H
	fI-0	fI-1	fI-2	fI-3
	Ischaemia-2			
W-0	L	L	M	M
W-1	L	M	H	H
W-2	M	H	H	H
W-3	H	H	H	H
	fI-0	fI-1	fI-2	fI-3
	Ischaemia-3			
W-3	L	M	M	H
W-3	M	M	H	H
W-3	H	H	H	H
W-3	H	H	H	H
	fI-0	fI-1	fI-2	fI-3

fI = foot infection; H = high-risk; L = low-risk; M = moderate risk;VL = very low risk;W = wound.

Figure 9 Management of patients with chronic limb-threatening ischaemia



EVT= endovascular therapy;
GSV = great saphenous vein.
[a]In bedridden, demented and/or frail patients, primary amputation should be considered.
[b]In the absence of contra-indication for surgery and in the presence of adequate target for anastomosis/runoff.

Recommendations on the management of chronic limb-threatening ischaemia		
Recommendations	**Class[a]**	**Level[b]**
Early recognition of tissue loss and/or infection and referral to the vascular team is mandatory to improve limb salvage.	I	C
In patients with CLTI, assessment of the risk of amputation is indicated.	I	C
In patients with CLTI and diabetes, optimal glycaemic control is recommended.	I	C
For limb salvage, revascularization is indicated whenever feasible.	I	B
In CLTI patients with below-the-knee lesions, angiography including foot runoff should be considered prior to revascularization.	IIa	C
In patients with CLTI, stem cell/gene therapy is not indicated.	III	B

CLTI = chroniclimb threatening ischaemia·

Acute limb ischaemia

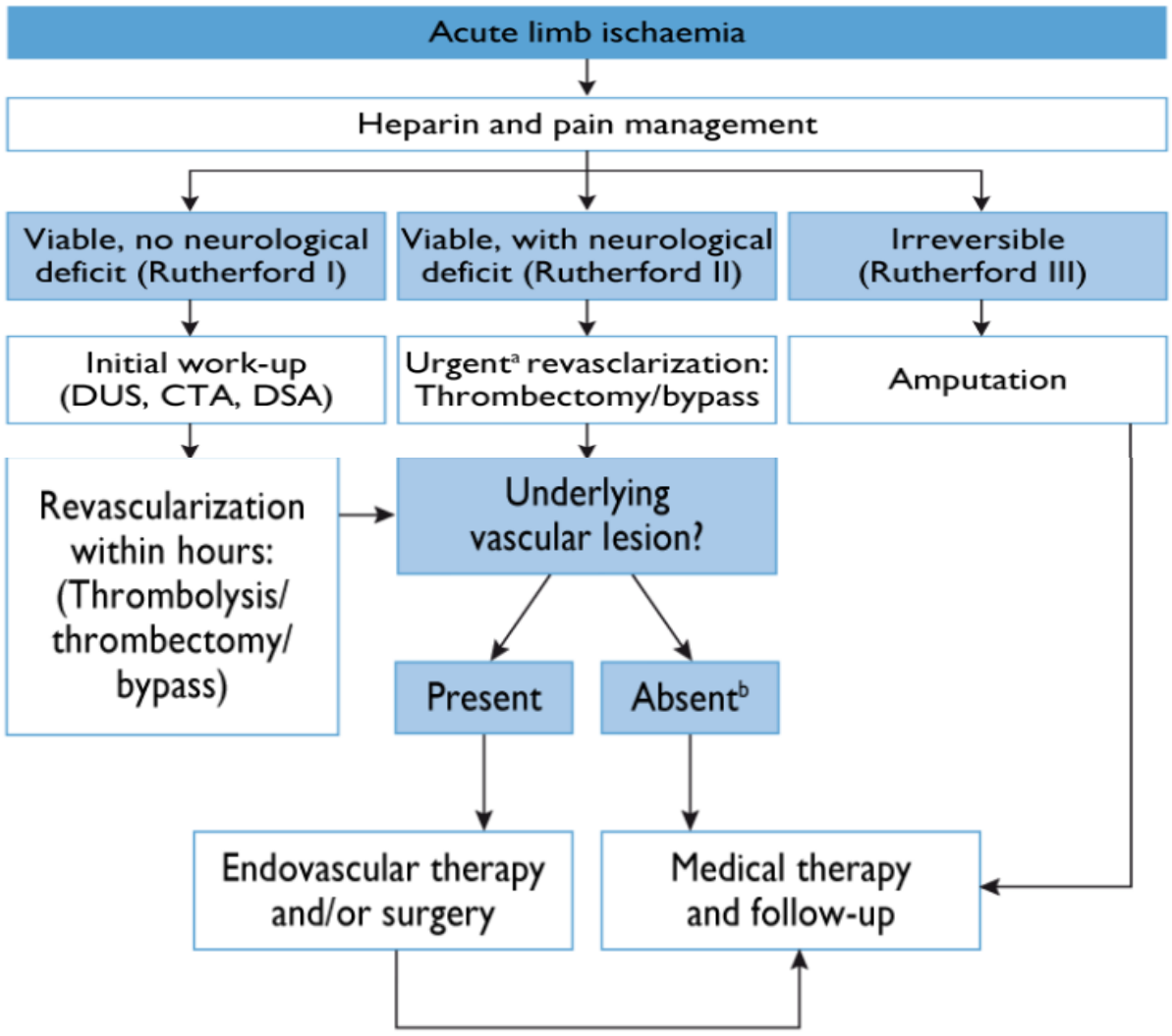
Acute limb ischaemia with neurological deficit mandates urgent revascularization.

Table 10 Clinical categories of acute limb ischaemia	
Grade I	
Category	Viable
Sensory loss	None
Motor deficit	None
Prognosis	No immediate threat
Grade IIA	
Category	Marginally threatened
Sensory loss	None or minimal (toes)
Motor deficit	None
Prognosis	Salvageable if promptly treated
Grade IIB	
Category	Immediately threatened
Sensory loss	More than toes
Motor deficit	Mild/moderate
Prognosis	Salvageable if promptly revascularized
Grade III	
Category	Irreversible
Sensory loss	Profound, anaesthetic
Motor deficit	Profound, paralysis (rigor)
Prognosis	Major tissue loss, permanent nerve damage inevitable

Recommendations for the management of patients presenting with acute limb ischaemia		
Recommendations	**Class[a]**	**Level[b]**
In the case of neurological deficit, urgent revascularization is indicated.[c]	I	C
In the absence of neurological deficit, revascularization is indicated within hours after initial imaging in a case to case decision.	I	C
Heparin and analgesics are indicated as soon as possible.	I	C

[a]Class of recommendation - [b]Level of evidence - [c]In this case imaging should not delay intervention.

Figure 10 Management of acute limb ischaemia

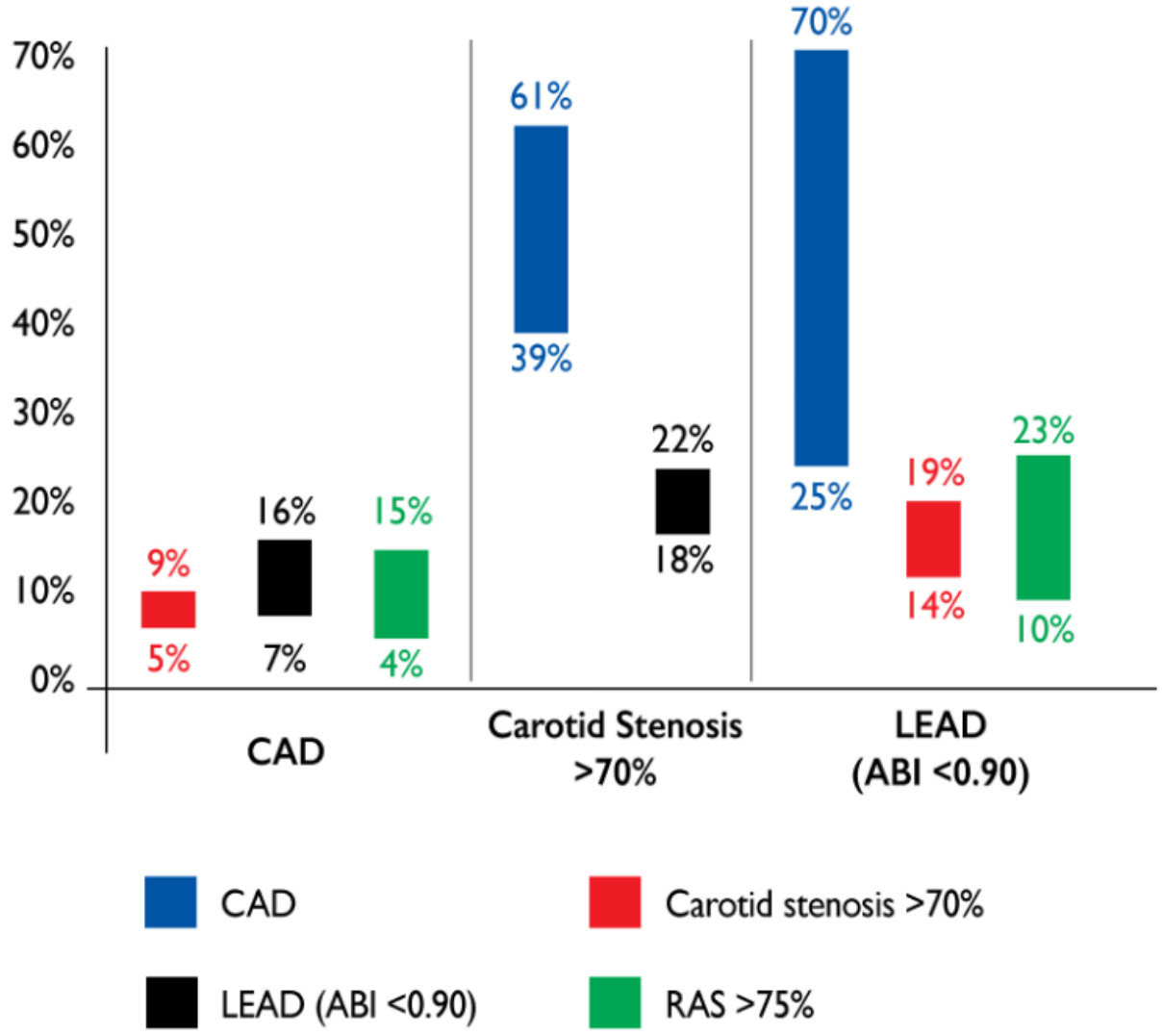


CTA = computed tomography angiography; DSA = digital subtraction ultrasound; DUS = duplex ultrasound.

[a]Imaging should not delay revascularization - [b] Specific etiological work-up is necessary (cardiac, aorta).

Multisite artery disease (MSAD) is defined by the simultaneous presence of clinically relevant atherosclerotic lesions in at least two major vascular territories ranging from 10–15% in patients with CAD to 60–70% in patients with severe carotid stenosis or LEAD (Figure 12).

Figure 11 Reported rate ranges of other localizations of atherosclerosis in patients with a specific arterial disease



The graph reports the rates of concomitant arterial diseases in patients presenting an arterial disease in one territory (e.g. in patients with CAD, 5–9% of cases have concomitant carotid stenosis >70%).

ABI = ankle-brachial index; CAD = coronary artery disease; LEAD = lower extremity artery disease; RAS = renal artery stenosis.

MSAD is invariably associated with worse clinical outcomes; however, systematic screening for asymptomatic disease in additional vascular sites has not been proven to improve prognosis and is yet not indicated. In patients with any presentation of PADs, clinical assessment of symptoms and physical signs of other localizations and/or CAD is necessary, and in case of clinical suspicion, further tests may be planned. Screening for asymptomatic lesions may be interesting in some cases (Table 11). This is the case for patients undergoing CABG, where ABI measurement may be considered especially when saphenous vein harvesting is planned, and carotid screening should be considered in a subset of patients at high risk of carotid artery disease.

Table 11 Indication for screening of associated atherosclerotic disease in additional vascular territories

Landing disease \ Screened disease	CAD	LEAD	Carotid	Renal
CAD				
Scheduled for CABG		IIa[a]	IIb[c] / I[b]	U
Not scheduled for CABG		IIb	NR	U
LEAD				
Scheduled for CABG	I[d]		NR	U
Not scheduled for CABG	NR		NR	U
Carotid stenosis				
Scheduled for CEA/CAS	IIb	NR		U
Not scheduled for CEA/CAS	NR	NR		U

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CAS = coronary endarterectomy; CKD = chronic kidney disease; ECG = electrocardiogram; LEAD = lower extremity artery disease; NR = no recommendation (not enough evidence to support systematic screening); TIA = transient ischaemic attack; U = uncertain.

[a]Especially when venous harvesting is planned for bypass - [b]In patients with symptomatic cerebrovascular disease.

[c]In patients with asymptomatic carotid disease and: age ≥ 70 years, multivessel CAD, associated LEAD or carotid bruit. [d]Screening with ECG is recommended in all patients and with imaging stress testing in patients with poor functional capacity and more than two of the following: history of CAD, heart failure, stroke or TIA, CKD, diabetes mellitus requiring insulin therapy.

Recommendations on screening for carotid disease in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, DUS is recommended in patients with a recent (<6 months) history of TIA/stroke.	I	B
In patients with no recent (< 6 months) history of TIA/stroke, DUS may be considered in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit.	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C

CABG = coronary artery bypass grafting; DUS = duplex ultrasound; LEAD = lower extremity artery disease; TIA = transient ischaemic attack.
[a]Class of recommendation - [b]Level of evidence.

Recommendations on the management of carotid stenosis in patients undergoing coronary artery bypass grafting

Recommendations	Class[a]	Level[b]
It is recommended that the indication (and if so the method and timing) for carotid revascularization be individualized after discussion within a multidisciplinary team, including a neurologist.	I	C
In patients scheduled for CABG, with recent (<6 months) history of TIA/stroke:		
• Carotid revascularization should be considered in patients with 50–99% carotid stenosis.	IIa	B
• Carotid revascularization with CEA should be considered as first choice in patients with 50–99% carotid stenosis.	IIa	B
• Carotid revascularization is not recommended in patients with carotid stenosis <50%.	III	C
In neurologically asymptomatic patients scheduled for CABG:		
• Routine prophylactic carotid revascularization in patients with a 70–99% carotid stenosis is not recommended.	III	B
• Carotid revascularization may be considered in patients with bilateral 70–99% carotid stenoses or 70–99% carotid stenosis + contralateral occlusion.	IIb	B
• Carotid revascularization may be considered in patients with a 70–99% carotid stenosis, in the presence of one or more characteristics that may be associated with an increased risk of ipsilateral stroke, [c] in order to reduce stroke risk beyond the perioperative period.	IIb	C

CABG = coronary artery bypass grafting; CAS = carotid artery stenting; CEA = carotid endarterectomy

Recommendations for screening and management of concomitant lower extremity artery disease and coronary artery disease		
Recommendations	**Class[a]**	**Level[b]**
In patients with LEAD, radial artery access is recommended as the first option for coronary angiography/intervention.	I	C
In patients with LEAD undergoing CABG, sparing the autologous great saphenous vein for potential future use for surgical peripheral revascularization should be considered.	IIa	C
In patients undergoing CABG and requiring saphenous vein harvesting, screening for LEAD should be considered.	IIa	C
In patients with CAD, screening for LEAD by ABI measurement may be considered for risk stratification.	IIb	B

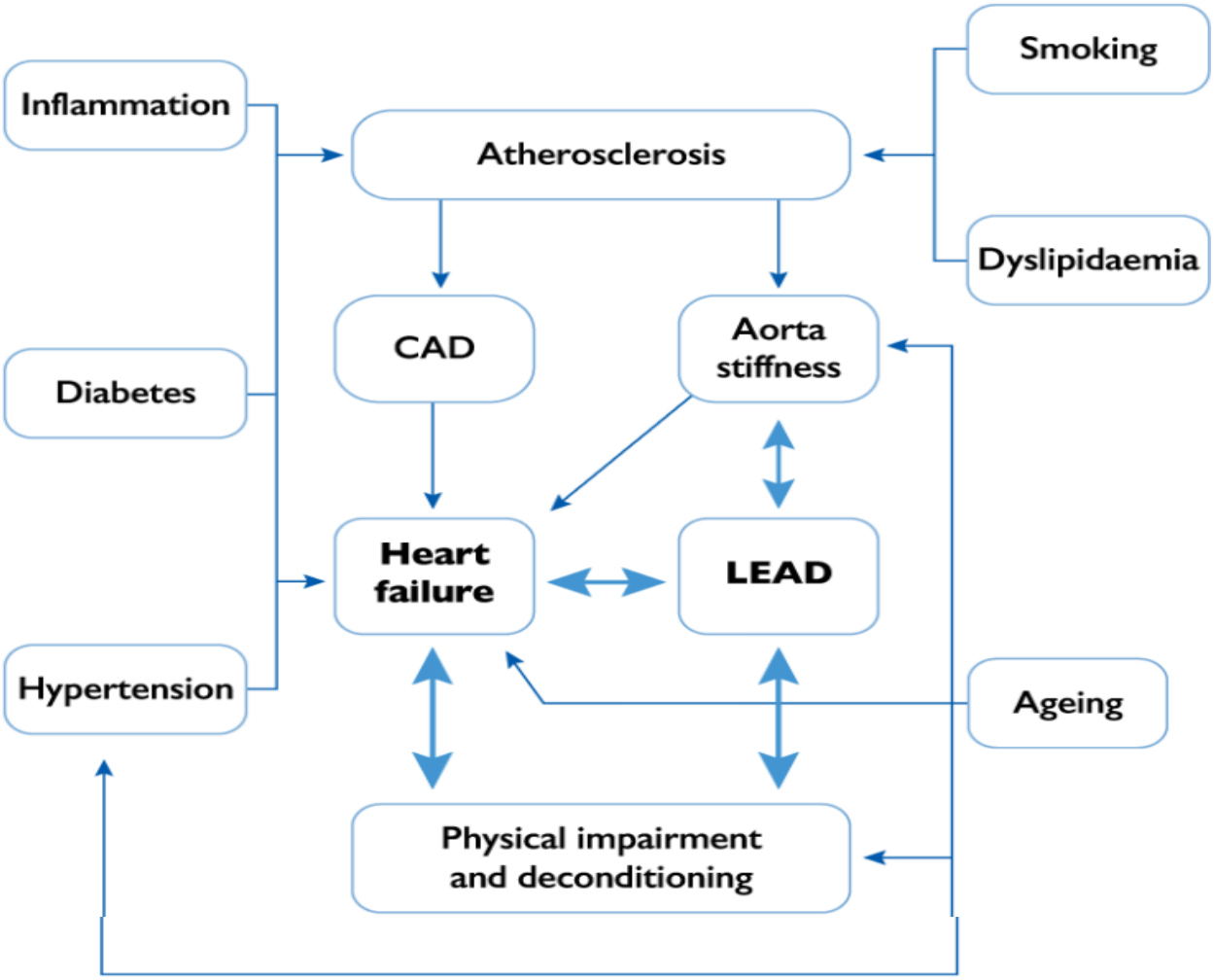
ABI = ankle-brachial index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; LEAD = lower extremity artery disease;TIA = transient ischaemic attack.

[a]Class of recommendation - [b]Level of evidence.

Recommendation on screening for coronary artery disease in patients with carotid disease		
Recommendations	**Class[a]**	**Level[b]**
In patients undergoing elective CEA, preoperative CAD screening, including coronary angiography, may be considered.	IIb	B

Cardiac conditions other than CAD are frequent in patients with PADs. This is especially the case for heart failure and atrial fibrillation in patients with LEAD.

Figure 12 Interrelations between heart failure and lower extremity artery disease



Recommendations on the management of heart failure associated with PADs

Recommendations	Class[a]	Level[b]
Full vascular assessment is indicated in all patients considered for heart transplantation or cardiac assist device implantation.	I	C
In patients with symptomatic PADs, screening for heart failure with TTE and/or natriuretic peptides assessment should be considered.	IIa	C
Screening for LEAD may be considered in patients with heart failure.	IIb	C
Testing for renal artery disease may be considered in patients with flash pulmonary oedema.	IIb	C

LEAD = lower extremity artery disease;TTE = transthoracic echocardiography; PADs = peripheral arterial diseases

Recommendations on the management of atrial fibrillation associated with PADs

Recommendations	Class[a]	Level[b]
In patients with LEAD and atrial fibrillation, oral anticoagulation:		
• is recommended when CHA_2DS_2-VASc score ≥2	I	A
• should be considered in all other patients.	IIa	B

LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; CHA2DS2VASC = Congestive heart failure; Hypertension; Age ≥75 years; Diabetes mellitus; prior Stroke or TIA; Vascular disease; Age 65–74 years; Sex Category female.

Recommendations on the management of valvular heart disease associated with PADs

Recommendations	Class[a]	Level[b]
Screening for LEAD and UEAD is indicated in patients undergoing TAVI or other structural interventions requiring an arterial approach.	I	C

LEAD = lower extremity artery disease; PADs = peripheral arterial diseases; TAVI = transcatheter aortic valve implantation; UEAD = upper extremity artery disease.

Advances in Experimental Medicine and Biology 1067
Advances in Internal Medicine

Md. Shahidul Islam *Editor*

Heart Failure: From Research to Clinical Practice

Volume 3

Springer

Advances in Experimental Medicine and Biology

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Volume 1067

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Heart Failure: From Research to Clinical Practice

Volume 3

Springer

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ISSN 0065-2598 ISSN 2214-8019 (eBook)
Advances in Experimental Medicine and Biology
ISSN 2367-0177 ISSN 2367-0185 (eBook)
Advances in Internal Medicine
ISBN 978-3-319-78279-9 ISBN 978-3-319-78280-5 (eBook)
https://doi.org/10.1007/978-3-319-78280-5

Library of Congress Control Number: 2017931583

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Printed on acid-free paper

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The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Dedicated to the living memory of my younger brother
Md. Mahabubul Islam (1957–2017)

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 1–3
DOI 10.1007/5584_2018_181
© Springer International Publishing AG 2018
Published online: 3 March 2018

Heart Failure: From Research to Clinical Practice

Md. Shahidul Islam

Abstract

"Heart failure: from research to clinical practice", a collection of selected reviews, which comes out also as a book, covers essentially all important aspects of heart failure, including the pathogenesis, clinical features, biomarkers, imaging techniques, medical treatment and surgical treatments, use of pacemakers and implantable cardioverter defibrillators, and palliative care. The reviews include essential background information, state of the art, critical and in-depth analysis, and directions for future researches for elucidation of the unresolved issues. Everyone interested in heart failure is expected to find this compilation helpful for a deeper understanding of some of the complex issues.

Keywords

Diagnosis of heart failure · treatment of heart failure · Palliative care of heart failure · Cardiac magnetic resonance imaging in heart failure · Heart failure with reduced ejection fraction · Heart failure with preserved ejection fraction · Cardiomyopathies

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"Heart failure: from research to clinical practice" is a collection of reviews that cover diverse aspects of the pathophysiology, clinical features, diagnosis, treatment, follow up, and palliative care of patients with different types of heart failure in diverse clinical settings. Heart failure is a major and expensive public health problem, requiring numerous office-visits, and hospitalizations, in all countries of the world: in the developing countries it is more often due to hypertension and valvular heart diseases, whereas in the developed countries it is more often due to ischemic heart diseases and cardiomyopathies. Worldwide, the prevalence of heart failure, particularly heart failure with preserved ejection fraction (HFpEF) is increasing. Some heart failure patients whose left ventricular ejection fraction is in the "mid-range", resemble HFpEF patients, while others resemble HFrEF (heart failure with reduced ejection fraction). The factors that determine the recovery of HFrEF to HFmrEF (heart failure with mid-range ejection fraction), or the deterioration of HFpEF to HFmrEF or HFrEF, and the prognostic importance of such changes in the ejection fraction over time, will continue to be active areas of research in the coming years. Our understanding of HFpEF, which is highly heterogeneous, and highly prevalent, is still poor and numerous studies will be needed to clarify many of the unresolved issues. Echocardiography is the most commonly used imaging technique for evaluation of heart failure, but in many countries

even this basic resource is not available. On the other hand, in many developed centers, advanced imaging techniques, like the cardiac magnetic resonance imaging are being used as a highly reliable and powerful technique for morphological and functional assessment of the heart, including for the identification of fibrosis and infiltrations, and for the identification of the major types of cardiomyopathies.

Based on strong evidence, most HFrEF patients are treated with angiotensin converting enzyme inhibitors (ACE-I), or angiotensin receptor blockers (ARB), and beta-blockers. However, many eligible HFrEF patients are not receiving ACE-I/ARB and beta-blockers in maximal tolerable doses in real life. On the other hand, the benefits of ACE-I/ARB plus beta blockers in HFpEF and HFmrEF are less clear. Still many HFpEF and HFmrEF patients are treated with ACE-I/ARB plus beta blockers, mostly because the patients have hypertension. Treatment of HFrEF patients with the neprilysin inhibitor sacubitril plus angiotensin receptor inhibitor valsartan (ARNI) improves clinical outcomes and reduces mortality further. It is likely that the use of ARNI for the treatment of HFrEF will keep increasing. There is some evidence suggesting that ARNI is beneficial even in the treatment of HFpEF, but we have to wait for more convincing results.

Heart failure patients with congestion must be treated with loop diuretics taking care to avoid both overuse, and under-use of the diuretics. Those who are truly resistant to the loop diuretics, may need treatment with bolus injection plus continuous infusion of the loop diuretics, or by sequential nephron blockade with loop diuretics plus a thiazide diuretic. It is necessary for the clinicians to be familiar with the basic pharmacodynamics and pharmacokinetics of the diuretics, and to know how to use the diuretics optimally in different clinical settings.

For optimal care of the heart failure patients, it is useful to have well-structured plans for regular follow up of the patients, preferably through outpatient units dedicated to the treatment of such patients. It is important to identify groups of patients who are likely to benefit most from management by the primary care physicians, specialists in internal medicine, or cardiologists. In addition to clinical assessments, serial measurement of cardiac biomarkers, and if possible, estimation of the left ventricular filling pressure by echocardiography can be helpful during follow up of the heart failure patients. It is expected that mobile monitoring devices and telecommunication technologies will be developed through multidisciplinary approaches, and will be increasingly used for the management and follow up of heart failure patients in the future. It is also beneficial for the heart failure patients to participate in cardiac rehabilitation programs for trying different modalities of exercise training.

Treatment of heart failure patients must be tailored to individual patients taking into consideration the co-existing diseases that many patients have. Many heart failure patients have chronic obstructive lung diseases, chronic kidney disease, diabetes, and central sleep apnea. About half of the heart failure patients have moderate renal failure. Treatment by ACE-I/ARB is beneficial even in HFrEF patients with moderate renal failure. The benefits of ACE-I/ARB in HFrEF patients with severe renal failure is not well established. In many such patients ACE-I/ARB may severely impair the renal function, and in some it may be essential to discontinue these medicines. Some HFrEF patients who do not tolerate ACE-I/ARB may benefit from hydralazine plus isosorbide dinitrate, a treatment modality, which is probably underused. In the treatment of heart failure patients with diabetes, sodium-glucose-co-transporter 2 inhibitors appear highly promising. Some heart failure patients may have hypothyroidism, hyperthyroidism, or “low T3 syndrome”, which aggravates heart failure; early detection and cautious treatment of these conditions are essential for successful treatment of heart failure.

Many heart failure patients develop different types of bradyarrhythmias that require pace maker implantation. Others need implantation of pacemaker and implantable cardioverter defibrillator. It is important to carefully choose the most appropriate types of devices (pacemakers, implantable cardioverter defibrillator), and the most appropriate pacing modes for treating these

heterogeneous group of patients. The choice of the devices and the pacing modes need to be made following a structured approach based on many factors including the aetiological factors. Some selected heart failure patients with moderate to severe mitral regurgitation can be helped by the treatment of mitral regurgitation by percutaneous interventions using transcatheter technologies.

A selected group of heart failure patients, including those who are waiting for heart transplantation, will benefit from implantation of left ventricular assist devices. Technological advances and clinical experiences in this field are increasing although prevention and management of serious complications remain challenging obstacles. Heart failure is a progressive disease; patients with advanced heart failure will eventually approach the end of life like anyone else. It is reasonable to initiate a conversation with the patients, on palliative care at an "appropriate" time, and integrate palliative care with ongoing curative treatment for a while, to improve patient satisfaction and quality of life. Clinicians need to be more familiar with the methods of palliative care of heart failure patients, aimed at reducing the symptoms, reducing the level of distress among the patients and the families, reducing the rates of hospitalization, and improving the quality of life as much as possible.

The reviews included in "Heart failure: from research to clinical practice", which also comes out as a book, cover most of the topics mentioned above to a considerable detail, including essential background information, through critical and in depth analysis of the controversial issues, to the directions for future researches. Everybody, including the nurses, doctors, students and scientists, from the beginners to the experts, are likely to find at least some of the contents of this collection informative, useful, interesting, and stimulating to a variable extent.

Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 5–15
DOI 10.1007/5584_2018_178
© Springer International Publishing AG 2018
Published online: 8 March 2018

Transition of Left Ventricular Ejection Fraction in Heart Failure

Yasuhiko Sakata, Kanako Tsuji, Kotaro Nochioka, and Hiroaki Shimokawa

Abstract

Along with a worldwide epidemiological transition and dramatic increase in the elderly population, both the incidence and prevalence of heart failure (HF) are increasing worldwide. This epidemic of HF is characterized by an increase of HF with preserved left ventricular ejection fraction (LVEF) (HFpEF) and a decrease of HF with reduced LVEF (HFrEF). Of note, transition between HFpEF and HFrEF has been recently highlighted, since it significantly relates with prognosis. Our recent studies indicated that temporary changes in LVEF are common and associated with prognosis in patients with HF. In this chapter, we summarize recent findings on temporal changes in LVEF and their prognostic impact in HF patients, acknowledging that further studies are needed to fully elucidate the pathophysiology of LVEF recovery and deterioration to improve clinical outcomes of HF patients, and also to develop therapies targeting novel pathways of myocardial recovery.

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Keywords

Epidemiologic transition · Heart failure · Ischemic heart disease · Left ventricular ejection fraction · Prognosis

1 Burden of HF

Along with the aging of society, the increase in patients with HF is an emerging public healthcare issue worldwide (Benjamin et al. 2017; Ambrosy et al. 2014; Shimokawa et al. 2015). In the United States, data from the National Health and Nutrition Examination Survey (NHANES) 2011–2014 indicate that 6.5 million people aged ≥20 years have HF (Benjamin et al. 2017), and prevalence of HF is projected to increase 46% from 2012 to 2030, resulting in more than 8 million people aged ≥18 years with HF (Heidenreich et al. 2013). In Europe, although precise estimates of HF are scarce, Bleumink et al. reported in 2004 from the Rotterdam Study that lifetime risk for HF at age of 55 was 33% for men and 29% for women, indicating that among individuals at this age, almost 1 in 3 will develop HF during their remaining lifespan (Bleumink et al. 2004). Information from Asia is also limited (Sakata and Shimokawa 2013; Guo and Lip 2013; Pillai 2013). However, it is assumed that a considerable number of patients develop HF every year, particularly when a recent epidemiologic transition and a dramatic increase in the elderly population

are taken into consideration (Sakata and Shimokawa 2013; Omran 1971; Zuckerman et al. 2014; Yusuf et al. 2001; Reddy and Yusuf 1998).

2 Geographic Differences in the Burden of HF

Significant geographic differences exist in the etiologies and risk factors for HF (Benjamin et al. 2017; Sakata and Shimokawa 2013). While hypertension is strongly associated with HF incidence in all regions, this association is particularly strong in Latin America, the Caribbean, Eastern Europe, and sub-Saharan Africa. In contrast, IHD is the leading cause of HF in the developed countries, while HF due to valvular and/or rheumatic heart disease remains common in East Asia, South Asia and Asia-Pacific countries (Benjamin et al. 2017). Notably, along with epidemiologic transition, the prevalence of HF with IHD has recently increased, especially in Asia and developing countries (Sakata and Shimokawa 2013; Reddy and Yusuf 1998). In particular, in certain areas of Asia and Africa, a considerable number of younger patients with cardiovascular disease have susceptibility to HF (Benjamin et al. 2017; Sakata and Shimokawa 2013). Indeed, it is reported that, despite a minimal association of IHD with HF in sub-Saharan Africa (Khatibzadeh et al. 2013), more than 40% of patients with newly diagnosed cardiovascular disease have HF, whereas only 10% have IHD, and HF is observed individuals in sub-Saharan Africa at a much younger age than in Western countries (Damasceno et al. 2012; Sliwa et al. 2008).

3 Classification of HF by LVEF

Although not the perfect parameter by which to stratify patients with HF, left ventricular ejection fraction (LVEF) has been historically used in clinical trials for this purpose. An unintentional result of this has been the realization that LVEF can be used to discern the benefits of HF therapies; namely, between HF with reduced LVEF (HFrEF) and HF with preserved LVEF (HFpEF) (Ponikowski et al. 2016; Yancy et al. 2013). There has been a debate as to whether HFrEF and HFpEF have different pathophysiological entities. It is now recognized, however, that they are distinct entities despite the fact that patients with HFrEF and HFpEF have similar clinical signs and symptoms (Komajda and Lam 2014). It is because of bimodal distribution of LVEF in epidemiologic studies and registries for HF (Borlaug and Redfield 2011; Gaasch et al. 2009) as well as the differences between HFrEF and HFpEF in patient characteristics (Bursi et al. 2006; Owan et al. 2006; Tsuji et al. 2017); LV remodeling patterns (Zile et al. 2004; Kitzman et al. 2002; Lam et al. 2007); functional consequences (particularly in the LV end-systolic pressure–volume relationship) (Borlaug et al. 2009; Lam et al. 2007; Kawaguchi et al. 2003; Schwartzenberg et al. 2012); cellular, subcellular, and interstitial characteristics (van Heerebeek et al. 2006; Borbely et al. 2005; van Heerebeek et al. 2008; Aurigemma et al. 2006); and responsiveness to HF therapies (Massie et al. 2007, 2008; Lee et al. 2004). Importantly, in the era of HF burden, it is well recognized that the proportion of HFpEF is increasing, while that of HFrEF is decreasing (Owan et al. 2006; Steinberg et al. 2012; Shiba et al. 2011). From Japan, we recently revealed that an increase in symptomatic HF with IHD was mostly attributable to the increase in HFpEF with IHD among patients registered in the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) Studies (Fig. 1) (Ushigome et al. 2015).

4 HF with Mid-range LVEF

Until recently, the most appropriate LVEF cut-off to differentiate HFrEF and HFrEF could not be agreed upon, since cut-offs for HFrEF or HFpEF vary among studies (Lam and Solomon 2014). Meanwhile, an LVEF cut-off of 50% for HFpEF has been embraced in the clinical guidelines so as to clearly discern HFpEF from HFrEF, leaving an LVEF gap around 40–50% as a grey zone, termed "HF with mid-range LVEF (HFmrEF)" for HF patients with an LVEF of 40–49% in the European Society of Cardiology (ESC) (Ponikowski et al. 2016) and "HFpEF, borderline" for HF patients with an

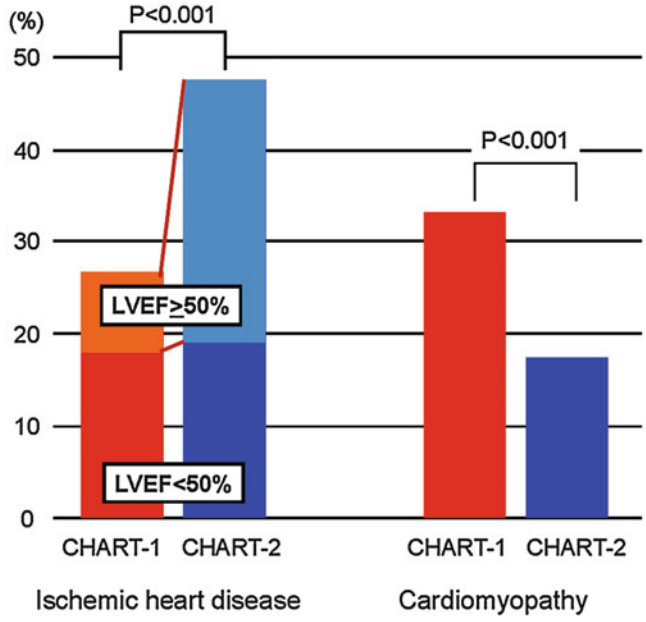

Fig. 1 Trends in etiologies of symptomatic HF in the CHART Studies. As an etiology of symptomatic HF, prevalence of IHD was significantly increased from the CHART-1 (Registration period 2000–2004, N = 1,006) to the CHART-2 (Registration period 2006–2010, N = 3,676) Study, while that of cardiomyopathy was decreased. Increase of HF with IHD was mostly attributable to that of HF with IHD and LVEF > 50%. CHART, Chronic Heart Failure Analysis and Registry in the Tohoku District; *HF* heart failure, *IHD* ischemic heart disease, *LVEF* left ventricular ejection fraction. This figure was made based on the data by Ushigome et al. (2015)

LVEF of 41–49% in the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) (Yancy et al. 2013). To examine the clinical features of HFmrEF patients, several studies have examined HFmrEF patients in the setting of hospitalized acute HF (Cheng et al. 2014; Kapoor et al. 2016) and reported that HFmrEF may generally resemble HFpEF, although HFmrEF with an etiology of ischemia exceptionally may more resemble HFrEF. Lam et al. summarized available data from studies comparing HFmrEF with HFrEF and HFpEF. While acknowledging slightly different LVEF cut-offs among studies, they found (1) the clinical characteristics of HFmrEF are intermediate between those of HFrEF and HFpEF; (2) patients with HFmrEF are younger and more predominantly male compared with those with HFpEF; (3) several cardiovascular risk factors are common among HFrEF, HFmrEF, and HFpEF, but patients with HFmrEF more likely have hypertension (60–77%) than those with HFrEF; (4) a significant proportion of patients with HFmrEF are diabetic (28–48%); and (5) patients with HFmrEF are more likely to have IHD (65–72%) than those with HFpEF, but to have a similar rate to those with HFrEF (Lam and Solomon 2014). In the CHART-2 Study, we examined 3480 consecutive HF patients with echocardiography data, consisting of 2154 HFpEF (LVEF $\geq$ 50%), 596 HFmrEF (LVEF 40–49%) and 730 HFrEF (LVEF < 40%). We found that clinical characteristics of HFmrEF were intermediate between those of HFrEF and HFpEF (Tsuji et al. 2017), consistent with former studies (Cheng et al. 2014; Kapoor et al. 2016). In addition, we also found that the prognostic factors of HFmrEF were intermediate between those of HFrEF and HFpEF. In contrast, the prognosis of HFmrEF more resembled that of HFpEF, while the prognostic impacts of cardiovascular medications in HFmrEF were similar to those in HFrEF: use of beta blockers was associated with better prognosis in both HFrEF and HFmrEF, but not in HFpEF, while statin use

was associated with better prognosis in HFpEF, but in neither HFrEF nor HFmrEF (Tsuji et al. 2017). These results indicated that HFmrEF may represent an overlap zone between HFrEF with higher-end LVEF and HFpEF with lower-end LVEF, rather than an independent entity of HF.

5 Changes in LVEF and Transitions Among HF Categories

Recent clinical guidelines have clearly classified patients into HFrEF, HFmrEF, or HFpEF on the basis of LVEF at HF diagnosis (Ponikowski et al. 2016; Yancy et al. 2013). However, little is known about changes in EF after the initial diagnosis. Dunlay et al. examined temporal changes in LVEF by echocardiography from initial HF diagnosis (to death or last follow-up) in a community cohort of incident HF patients in Olmsted County, Minnesota, USA (Dunlay et al. 2012). Among 1233 HF patients diagnosed between 1984 and 2009, LVEF increased in HFrEF patients by an average 6.9% over 5 years ($P < 0.001$), while it decreased in HFpEF patients (45.3%, N = 559) by an average 5.8% over 5 years ($P < 0.001$). Overall, 39% of HFrEF patients had an EF $\geq$ 50% and 39% of HFpEF patients at the initial diagnosis had an EF < 50% at some point there (Dunlay et al. 2012). Clarke et al. examined 2413 patients in Kaiser Permanente Colorado with a primary discharge diagnosis of HF between 2001 and 2008 and at least 2 measurements of LVEF separated by $\geq$ 30 days. On estimation of transition probabilities at 5-year follow-up, there was a 13% probability for HFrEF patients to transition to HFpEF (95% CI, 10–17%), a 31% probability to remain as HFrEF (95% CI, 23–38%), and a 56% probability of death (95% CI, 47–66%). In contrast, there was a 15% probability for HFpEF patients to remain as HFpEF (95% confidence interval [CI], 11–19%), a 33% probability to transition to HFrEF (95% CI, 26–40%), and a 52% probability of death (95% CI, 43–61%) (Clarke et al. 2013). We also examined transitions in LVEF among 2154 HFpEF (LVEF $\geq$ 50%), 596 HFmrEF (LVEF 40–49%) and 730 HFrEF (LVEF < 40%) patients registered in the CHART-2 Study (Tsuji et al. 2017) (Fig. 2). We found that HFmrEF and HFrEF, but not HFpEF, dynamically transitioned to other categories, mostly within a year; from registration to 1 year, HFrEF transitioned to HPpEF and HFmrEF by 18% and 22%, respectively, and HFmrEF transitioned to HFpEF and HFrEF by 44% and 16%, respectively. It was noted, however, that unlike patients with HFmrEF and HFrEF, HFpEF patients transitioned to HFmrEF and HFrEF by only 8% and 2%, respectively, indicating that subsequent progressive systolic contractile dysfunction is not a representative manifestation of HFpEF. This finding is inconsistent with that of Clarke et al. (Clarke et al. 2013), in which HFpEF patients dramatically transitioned to HFrEF or death. These observations, however, clearly indicate that LVEF dramatically changes after diagnosis, warranting a need to establish when and in which HFrEF, HFmrEF, and HFpEF patients we should repeat LVEF measurement. In the 2016 ESC guidelines (Ponikowski et al. 2016), however, echocardiography is only recommended for the assessment of myocardial structure and function in subjects with suspected HF in order to establish a diagnosis of either HFrEF, HFmrEF or HFpEF, but there is no recommendation for the LVEF follow-up. In this regard, our finding may indicate that we should repeat LVEF measurement at least within a year after the initial evaluation, particularly in HFrEF and HFmrEF patients. However, serial LVEF assessments after 1-year could be clinically important in each patient, since dynamic LVEF fluctuation is often observed after the 1-year follow-up in the CHART-2 Study (Tsuji et al. 2017).

6 HF with Recovered LVEF

It should be emphasized that patients with mid-range EF are not necessarily transitioning from HFpEF to HFmrEF then HFrEF: the ACCF/AHA guidelines also categorized a subset of patients with LVEF > 40% who previously had

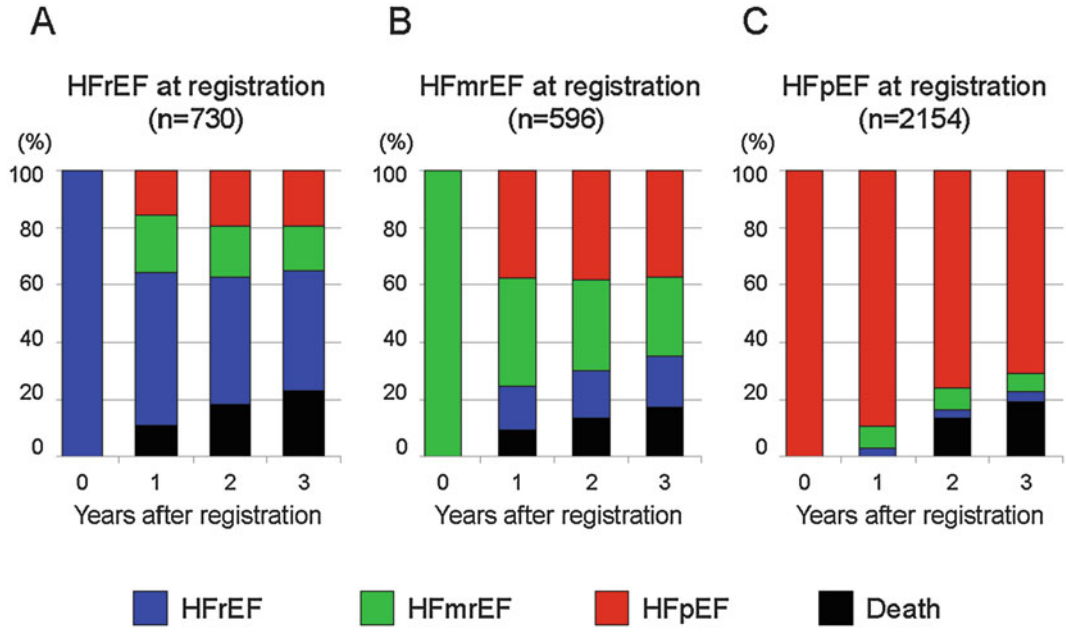

Fig. 2 Transitions of HF among heart failure patients by LVEF. (**a**) HFrEF, (**b**) HFmrEF, and (**c**) HFpEF patients. HF, heart failure; HFmrEF, HF with mid-range left ventricular ejection fraction; HFpEF, HF with preserved left ventricular ejection fraction; HFrEF, HF with reduced left ventricular ejection fraction; LVEF, left ventricular ejection fraction. This figure was made based on the data by Tsuji et al. (2017)

HFrEF as "HFpEF, improved", since these patients with improved or recovered EF may be clinically distinct from those with persistently preserved or reduced EF (Yancy et al. 2013). Indeed, substantial heterogeneity exists within patients with HFmrEF, since HFmrEF includes both patients with de novo HF and those who have recovered their systolic function from HFrEF (Nadruz et al. 2016; de Groote et al. 2014; Basuray et al. 2014). Studies of implantable cardioverter-defibrillator (ICD) therapy also suggest a subpopulation of HF patients with recovered LVEF (Naksuk et al. 2013; Zhang et al. 2015). Naksuk et al. reported that 25 of 91 (27%) patients undergoing ICD generator exchange had LVEF improvement from 31 ± 7% at baseline to 49 ± 8% at the time of ICD generator replacement ($P < 0.0001$) (Naksuk et al. 2013), while Zhang et al. reported that 40% of 538 patients with repeated LVEF assessments after ICD implantation for primary prevention of sudden cardiac death had an improved LVEF during follow-up and 25% had LVEF improved to ≥ 35% (Zhang et al. 2015).

7 Prognostic Impacts of Changes in LVEF

It has remained unknown whether changes in LVEF are associated with subsequent clinical outcomes in patients with HF. Dunlay et al. reported that decreases in LVEF over time were associated with increased mortality whereas increases were associated with improved survival, indicating that progressive systolic contractile dysfunction may, at least in part, contribute to the outcomes of HFpEF (Dunlay et al. 2012). Among patients with chronic HF registered in the CHART-2 Study, we also reported that, regardless of HF stage at registration, HFrEF patients at 1 year had increased incidence of death, while HFpEF at 1 year had better prognosis (Tsuji et al. 2017). These observations strongly

indicate that LVEF changes are obvious prognostic predictors.

Nadruz et al. studied 944 patients with HF, consisting of 620 with HFrEF, 107 HF with midrange LVEF and no recovery of LVEF (LVEF was consistent between 40% and 55%) (non-recovered HFmrEF), 170 HF with recovered midrange LVEF (LVEF 40–55% but previous LVEF < 40%) (recovered HFmrEF) and 47 HFpEF (LVEF > 55%) (Nadruz et al. 2016). They found that the clinical characteristics and values of predicted peak oxygen consumption and the minute ventilation/carbon dioxide production slope in cardiopulmonary exercise testing were comparable between non-recovered HFmrEF and recovered HFmrEF, which were intermediate between HFrEF and HFpEF. Importantly, the multivariable Cox regression analysis showed that a composite incidence of death, left ventricular assistant device implantation and transplantation in recovered HFmrEF was comparable to that in HFpEF, and was significantly lower than those in HFrEF (HR, 0.25; 95% CI 0.13–0.47) and non-recovered HFmrEF (HR, 0.31; 95% CI 0.15–0.67). Based on these observations, they concluded that recovered systolic function within the HFmrEF population is a marker of a more favorable prognosis (Nadruz et al. 2016).

LVEF improvement may have less effect in reducing arrhythmogenicity. In their prospective cohort study, Zhang et al. also reported that LVEF changes after ICD implantation for primary prevention of sudden cardiac death were inversely associated with all-cause mortality and appropriate shocks for ventricular tachyarrhythmias. Ruwald et al. reported that only one ventricular arrhythmia event occurred among 55 subjects with LVEF recovery > 50% in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) trial (Ruwald et al. 2014). However, it remains to be elucidated whether LVEF recovery after ICD implantation is essentially beneficial, particularly for arrhythmogenicity, since Zhang et al. also reported that the risk of an appropriate shock remained in patients whose follow-up LVEF improved to > 35%, albeit that this risk was markedly decreased (Zhang et al. 2015). Naksuk et al. also reported that the incidence of appropriate ICD shocks was similar between those with and without LVEF recovery after ICD implantation (Naksuk et al. 2013).

8 Factors Related to Changes in LVEF

Although little is known about factors related to changes in LVEF, the presence of IHD has recently been considered to play an important role in the clinical course of HFpEF patients (Hwang et al. 2014). HFpEF patients with IHD had greater decreases in LVEF and increased mortality during the follow-up. Thus, it is possible that HFmrEF may constitute a precedent stage of HFrEF among the subpopulation of HFpEF with IHD, possibly consisting of those in the early phase of cardiac remodeling after acute ischemic myocardial damage or those with chronic myocardial ischemia. In contrast, patients with partially recovered or early stages of myocarditis or cardiomyopathy and those who have just started to be treated with cardiovascular medications, including renin-angiotensin system (RAS) inhibitors and beta-blockers, may subsequently constitute a subset of recovered LVEF population.

Dunlay et al. reported that greater declines in LVEF were observed in older individuals and those with coronary disease, while greater increases were observed in women, younger patients, individuals without coronary disease, and those treated with evidence-based medications (Dunlay et al. 2012). Using multistate Markov modeling, Clarke et al. reported that patients who were adherent to beta-blockers were more likely to transition from HFrEF to HFpEF (HR 1.53; 95% CI 1.10–2.13) than those who were nonadherent, whereas adherence to neither angiotensin-converting enzyme nor angiotensin II receptor blocker was associated with LVEF transition, and that patients with a previous myocardial infarction were more likely to transition from HFpEF to HFrEF (HR 1.75; 95% CI 1.26–2.42), underlining that LVEF is a dynamic

factor related to sex, coexisting conditions, and drug therapy. In the CHART-2 Study, the simple linear regression analysis indicated that IHD etiology was negatively and female sex was positively associated with LVEF increase at 1-year in all three groups, indicating that an increase in LVEF in the HFrEF and HFmrEF groups was greater and a decrease in LVEF in the HFpEF group was smaller in females and in those without IHD (Tsuji et al. 2017). Importantly, the multivariable linear regression analysis revealed that patients with HFpEF, HFmrEF and HFrEF had different sets of factors related to LVEF change from baseline to 1-year: female sex was significantly associated with increase in LVEF, while history of stroke with LVEF decrease in HFpEF, IHD histology and LV dilatation were significantly associated with LVEF decrease in HFmrEF, and hyperuricemia, elevated BNP levels, IHD histology, and LV dilatation were significantly associated with LVEF decrease in HFrEF (Tsuji et al. 2017). These observations indicate that different approaches are required to preserve or improve LVEF by LVEF categories.

9 LVEF Maintenance After Recovery

It is unclear whether pharmacotherapy should be continued in patients with HF with recovered LVEF (Hopper et al. 2014). Moon et al. retrospectively examined 42 patients with idiopathic dilated cardiomyopathy who recovered from systolic heart failure (LVEF 26.5 ± 6.9% at initial presentation) to a near-normal state (LVEF ≥ 40%, and a ≥ 10% increase in absolute value) (Moon et al. 2009). Patients were monitored for recurrence of LV systolic dysfunction for 41.0 ± 26.3 months after recovery (LVEF 53.4 ± 7.6%) from LV dysfunction. LV systolic dysfunction reappeared (LVEF 27.5 ± 8.1%) during the follow-up period in 19% (8 of 42) of patients and the recurrence was significantly correlated with the discontinuation of anti-heart failure drugs. Park et al. retrospectively studied 85 consecutively enrolled patients with dilated cardiomyopathy (DCM) who achieved a restoration of LV systolic function and were followed up for 50 ± 33 months after recovery from LV dysfunction without discontinuation of standard medication for heart failure (Park et al. 2014). They observed recurrence of LV dysfunction in 33 patients, which was associated with age, diabetes, and LV end-diastolic dimension (LVEDD) at initial presentation in the multivariate analysis.

Studies on withdrawal of these drugs in HF are scarce and small. Hopper et al. examined whether withdrawal of beta-blockers or RAS inhibitors could be a risk in mixed populations of chronic stable HF trials and reported that withdrawal of beta-blockers and RAS inhibitors likely had untoward effects on cardiac structure, symptoms, and major outcomes (Hopper et al. 2014). Swedberg et al. examined 15 patients with congestive cardiomyopathy who had improved conspicuously on chronic administration of a beta-blocker: after withdrawal of the beta-blocker, they observed a pronounced deterioration of clinical condition in 6 patients (40%), and a significant decrease in LVEF, and signs of compromised diastolic function with pathological apex curves and an increase in third heart sound in all of the remaining patients (Swedberg et al. 1980). Importantly, they also reported that all these changes were reversed within a few weeks to a few months after re-administration of beta-blockers. Morimoto et al. examined the influence of tapering and then stopping metoprolol over a period of 14 weeks in 13 patients with DCM who had been receiving this agent for ≥30 months, 10 of whom were in NYHA functional class I (Morimoto et al. 1999). They reported that, while 6 patients remained stable, 7 patients deteriorated (2 sudden deaths and 2 deaths from worsening HF) during the 4-month follow-up period, and that LVEF fell from 38 ± 14% to 34 ± 14% ($P < 0.05$). With these observations, they concluded that beta-blockers should not be stopped in DCM patients treated with BB. Regarding discontinuation of RAS inhibitors, Maslowski et al. reported that after discontinuation of long-term captopril treatment in 5 patients with heart failure, cardiac

performance was not impaired and electrolyte balance was not adversely affected by the abrupt withdrawal of captopril in the short term (Maslowski et al. 1981). However, at least middle-term discontinuation of RAS inhibitors appears to be harmful in patients with chronic HF although any effect on LVEF itself has not been reported (Pflugfelder et al. 1993). Pflugfelder et al. reported that withdrawal of quinapril from patients with heart failure resulted in a slow progressive decline in clinical status among 224 participants with stable chronic HF; exercise tolerance, NYHA functional class, quality of life, and clinical status of HF deteriorated in patients withdrawn to placebo after $\geq$10 weeks of single-blind quinapril therapy, which occurred gradually over a 4–6-week period (Pflugfelder et al. 1993). These lines of evidence clearly indicate that continuation of medical therapy is mandatory to prevent reoccurrence of LV systolic dysfunction in HF patients with recovered LVEF.

However, given a report that discontinuation of HF medications after recovery did not lead to decompensation over 29 months' follow-up in patients with peripartum cardiomyopathy (PPCM), further investigations to confirm the harm of drug discontinuation after LVEF recovery are warranted (Amos et al. 2006). Furthermore, it should be noted that we cannot conclude any cause-effect relationships between drug discontinuation and outcomes based on the findings of retrospective studies, since the observations could be confounded by other reasons that may modulate the risk of recurrence independently. Indeed, patients who have blood pressure- or renal function-related intolerance of HF medications are most likely to have their medications discontinued, as well as to have the highest risk of future adverse outcomes.

10 Conclusion

Temporary changes in LVEF are common and associated with prognosis in patients with HF. Further prospective observational studies or randomized clinical trials are needed to fully elucidate the pathophysiology of LVEF recovery and deterioration to improve clinical outcomes of HF patients, and also to develop therapies targeting novel pathways of myocardial recovery.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 17–30
DOI 10.1007/5584_2018_179
© Springer International Publishing AG 2018
Published online: 15 March 2018

Combination Therapy of Renin Angiotensin System Inhibitors and β-Blockers in Patients with Heart Failure

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Abstract

Renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system play crucial roles in heart failure with reduced ejection fraction (HFrEF). Clinical trials provide strong evidence of prognostic benefits for combination therapy with angiotensin-converting enzyme inhibitor (ACEI) and β-blocker in the treatment of HFrEF. Angiotensin receptor blocker (ARB) is not superior to ACEI in improving mortality and an alternative for patients who are intolerant to ACEI. Prognostic evidence for triple therapy which combined angiotensin receptor blocker (ARB) and ACEI in addition to β-blocker therapy, is still controversial in HFrEF. Moreover, a recent clinical trial showed that triple therapy did not provide additional benefit compared with ACEI or ARB therapy alone in mildly symptomatic HFrEF. Of note, the triple therapy can even cause harm and renal dysfunction in HF with a history of hypertension. Direct renin inhibitor (DRI) has the theoretical benefit of upstream RAAS inhibition at the point of pathway activation. However, the results from clinical trials do not support upstream renin inhibition by DRI in addition to standard therapy with ACEI in patients with HFrEF. Angiotensin receptor-neprilysin inhibitor (ARNI) which combines a neprilysin inhibitor and ARB valsartan have a unique mode of action targeting both RAAS and the natriuretic peptide systems. In contrast to the evidence in HFrEF, clinical value of combination therapy with RAAS inhibitors and β-blocker is not well established in HF with preserved EF (HFpEF). The heterogeneity of diagnostic criteria and baseline characteristics of HFpEF need further evidence for the combination therapy. However, a recent clinical trial of LCZ696 showed promising results in reducing NT-proBNP in patients with HFpEF.

Keywords

Angiotensin receptor blocker · Angiotensin receptor-neprilysin inhibitor · Angiotensin-converting enzyme · Direct renin inhibitor · Ejection fraction · Heart failure · Mineralocorticoid receptor antagonist · Prognosis · Renin-angiotensin-aldosterone system · β-blocker

1 Introduction

The renin-angiotensin-aldosterone system (RAAS) is a signaling pathway responsible for regulating blood pressure and fluid balance (Garg and Yusuf 1995; Yusuf et al. 2003; Paul et al. 2006; Kobori et al. 2007). (Fig. 1) The RAAS

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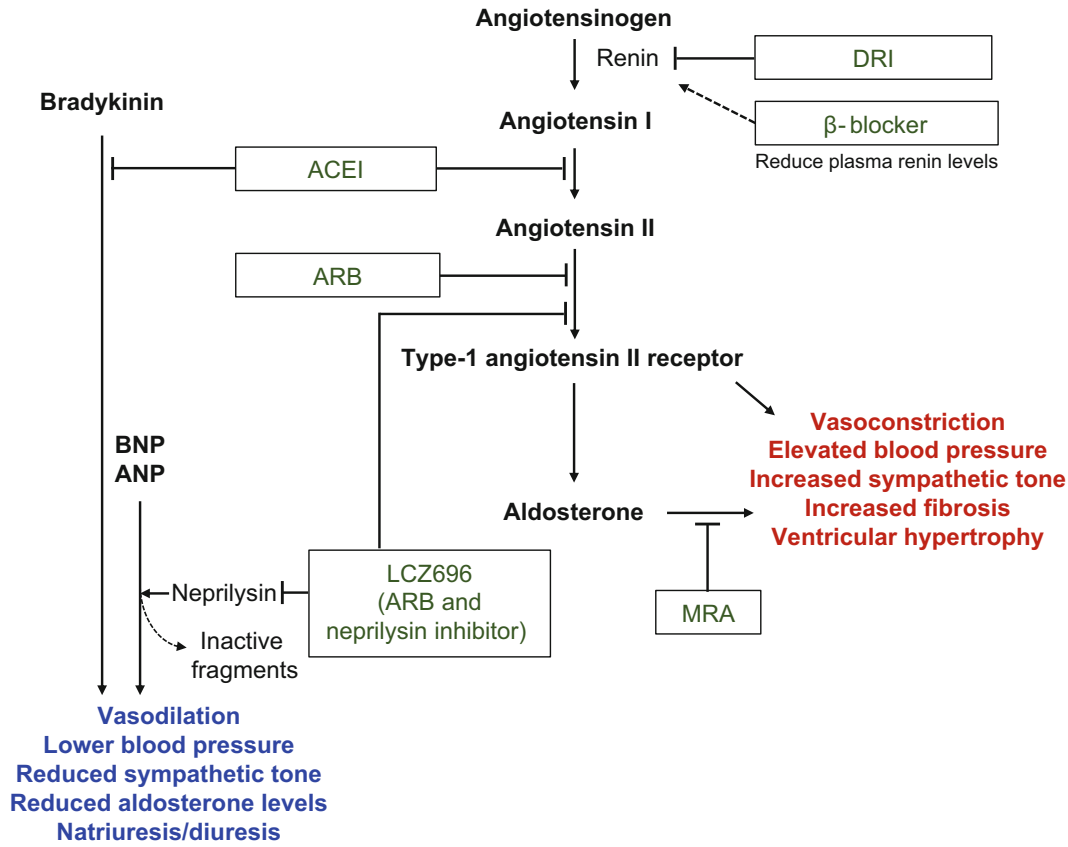

Fig. 1 Renin-angiotensin-aldosterone pathway. Abbreviations; *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DRI* direct renin inhibitor, *MRA* Mineralocorticoid receptor antagonist

plays a crucial role in heart failure with reduced ejection fraction (HFrEF). Blocking RAAS by angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB) and mineralocorticoid receptor antagonist (MRA) improve prognosis in HFrEF and are recommended by professional guidelines (Writing Committee et al. 2013; Ponikowski et al. 2016a) β blocker has ability to reverse the neurohumoral effects of the sympathetic nervous system (Eichhorn et al. 1991) and lowers plasma renin levels (Holmer et al. 1998) with ensuing symptomatic and prognostic benefits, and thus attained recommendation by the guidelines (Writing Committee et al. 2013; Ponikowski et al. 2016a). This section summarizes evidence of combination use with RAAS inhibitors and beta blockers in HF, especially in HFrEF.

2 ACEI in HFrEF

The first study demonstrating prognostic benefit by ACEI in HFrEF patents was the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) in 1987 (Group CTS 1987; Swedberg and Kjekshus 1988). The CONSENSUS demonstrated that, in 253 HFrEF patients with NYHA (New York Heart Association) class IV, treatment with enalapril (2.5-40 mg/day) significantly reduced the risk of mortality at 6-month (26% in enalapril vs. 44% in placebo) and 1-year (36% vs. 52%). In the CONSENSUS, the reduction in mortality by enalapril was attributed to significantly lower risk of mortality resulting from progression of HFrEF (a reduction of 50%) (Group CTS 1987). The findings from the CONSENSUS was confined to severe HFrEF

patients and no data on prognosis were available for patients with mildly symptomatic HF. Following the accomplishment of the CONSENSUS, the SOLVD (Studies of Left Ventricular Dysfunction) trial showed that treatment with enalapril over a mean of 41.4 months reduced the risk of death by 16% (95% confidence interval; 5–26%) among HFrEF patients with mild-to-moderate symptoms (SOLVD Investigators et al. 1991; The SOLVD Investigators 1990). Align with the CONSENSUS, the beneficial effect of enalapril for prognosis in the SOLVD was due to reduction of death from progression of HF. Besides survival benefits, patients receiving enalapril experienced hypotension more frequently than those receiving placebo in both the CONSENSUS and SOLVD.

3 ARB in HFrEF

ARBs (angiotensin II receptor blockers) are antagonists of angiotensin II type I receptor, which have less side effects, such as coughs and angioedema, as compared with ACEIs. Evidence of ARB in HFrEF is still limited. Head-to-head comparison between ACEI and ARB was conducted in the ELITE (Evaluation of Losartan in the Elderly) II trial enrolling 3,152 HFrEF (EF $\leq$ 40%) patients age 60 years or older with NYHA class II-IV. The results of ELITE II demonstrated no significant difference in mortality between ARB losartan and ACEI captopril (Pitt et al. 2000; Willenheimer 2000). In addition, the investigators observed significant fewer adverse event rates in losartan group (Pitt et al. 2000; Willenheimer 2000). Furthermore, the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity)-Alternative trial showed that an ARB candesartan comparing placebo was generally well tolerated and reduced cardiovascular mortality and morbidity in 2,028 HFrEF (EF < 40%) patients who are intolerance to ACE inhibitors (Granger et al. 2003). Based on these results, professional guidelines recommended ARB is considered as an alternative for patients who cannot tolerate ACEI due to cough or angioedema which are adverse effects of ACEI (Writing Committee et al. 2013; Ponikowski et al. 2016a).

4 MRA in HFrEF

Increasing evidence suggested that ACEI did not effectively suppress the production of aldosterone based on the pathophysiological observations (Borghi et al. 1993; Staessen et al. 1981; Struthers 2004; Andrew 2002). Hence, the RALES trial was initialized to evaluate the role of MRA in addition to ACEI in the treatment of advanced HFrEF (Pitt et al. 1999; Weber 1999). Specifically, the RALES (Randomized Aldactone Evaluation Study) aimed to determine whether spironolactone would reduce mortality in patients with advanced HF and an EF < 35%, who were already on standard medical therapy (ACEI, if tolerated, and diuretics). The RALES clearly demonstrated that adding 25 mg of spironolactone to standard therapy reduced all-cause mortality in HFrEF (EF < 35%) patients (Pitt et al. 1999). The success of the RALES with severe HFrEF patients prompted the subsequent EMPHASIS-HF trial (Zannad et al. 2011) which investigated MRA eplerenone in the treatment of moderate HFrEF with mild symptoms, reinforcing the benefits of MRA in HFrEF. Evidence from these trials established ACEI (ARB if in non-tolerated to ACEI) (Writing Committee et al. 2013; Ponikowski et al. 2016a; Cohn and Tognoni 2001) and MRA as standard therapies in HFrEF.

5 β-Blocker in HFrEF

β-blockers have ability to reverse the neurohumoral effects of the sympathetic nervous system (Eichhorn et al. 1991) and lowers plasma renin levels (Holmer et al. 1998) with ensuing symptomatic and prognostic benefits with recommendation by the guidelines (Writing Committee et al. 2013; Ponikowski et al. 2016a). In 1974, Finn Waagstein et al. first reported that practolol

dramatically improved patient's clinical status in a 59-year woman with HFrEF and suggested benefits of a β-blocker, practolol in patients with HFrEF (Waagstein et al. 1974; Waagstein and Rutherford 2017). A subsequent study from his group demonstrated the clinical benefits of the β-blocker in patients with HFrEF (Waagstein et al. 1974, 1975; Waagstein and Hjalmarson 1976).

6 Combination Therapy with ACEI and β-Blocker in HFrEF

Since angiotensin II increase the sympathetic drive, which was proven to be harmful in patients with HF. Combining ACEI/ARB with β blocker could provide summed blockage to the sympathetic nervous system with additional benefit. (Fig. 1) The prognostic value of the combination therapy with ACEI and β-blocker was demonstrated by the US Carvedilol trial (Packer et al. 1996). In NYHA II-IV HFrEF (EF < 40%) patients receiving ACEI, a mean daily dose of 45 ± 27 mg of carvedilol had a 65% lower risk of death than those given placebo during follow-up of 6.5 months and of extended 15 months. (Table 1) The results from the US Carvedilol were clear in terms of survival benefit by carvedilol. However, since carvedilol exerts pharmacologic effects atypical of and in addition to its action on adrenergic receptors, (Yoshikawa et al. 1996; Foody et al. 2002) it was not clear that all β-blockers would prolong survival in HFrEF patients. The beneficial effects of other β-blockers were confirmed in the CIBIS-II (Cardiac Insufficiency Bisoprolol Study II; bisoprolol) and MERIT (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; mrtoprolol) (Packer et al. 1999a, b). The value of carvedilol was further confirmed in severe HFrEF by the COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) trial, which enrolled 2,289 HFrEF (EF < 25%) patients with HF symptom at rest or on minimal exertion (Packer et al. 2001). In the COPERNICUS, the addition of carvedilol to ACEI, diuretics, and digitalis for a mean of 10.4 months decreased the rate of death by 35% (95%CI; 19–48%, P < 0.001) and the rate of death or hospitalization by 24% (13–33%, P < 0.001). (Table 1) The COPERNICUS provided further evidence that suppressing the neurohormonal axis can delay the progression of HF in HFrEF and improve survival in the acute setting.

Along with recognition of improved prognosis in HFrEF by combination therapy with β-blocker and ACEI, one question arose on the order of treatments, β-blocker first or ACEI first? To answer this, the CIBIS-III trial was designed comparing initial monotherapy with either bisoprolol or enalapril for 6 months followed by their combination for 6–24 months on mortality and hospitalization (Willenheimer et al. 2005). Regardless of order of initiation treatment, the combination use of a β-blocker to an ACE inhibitor further reduces mortality. Of note, the investigators observed the bisoprolol-first arm was associated with numerically increased risk of worsening HF (HR 1.25 [95%CI 0.87–1.81], P = 0.23). The risk of worsening HF in bisoprolol-first strategy, however, could be improved with greater experience of up titration of the β-blocker.

7 Triple Therapy of ACEI, ARB and β-Blocker in HFrEF

There is no study to test specifically prognostic impact of triple therapy, such as ARB add-on therapy to ACE inhibitor and β-blocker in the large clinical HF trial. However, the role of triple therapy in HF patients has also been evaluated in three trials, the Val-Heft (Valsartan Heart Failure Trial), the CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity)-Added, and the SUPPORT (supplemental benefit of ARB in hypertensive patients with stable heart failure using olmesartan) (Cohn and Tognoni 2001; McMurray et al. 2003; Sakata et al. 2015). (Table 2) In 2001, the Val-Heft evaluated the long-term effects of the addition of an ARB valsartan to standard therapy (approximately 93% in ACEI use; 35% in β-blocker use) in 5,010 HFrEF (EF < 40%) patients with NYHA

Table 1 The results of combination therapy with RAASI and β-blocker in HF patients and reduced ejection fraction

Trial	β-blocker	N	Age	Women	Mean EF	ACEI/ARB	HR for all-cause death	HR for CV death	HR for HF hosp.
US Carvedilol (1996)	Carvedilol (C)	1,094	58(P)/(C)	24% (P)/23% (C)	22% (P)/23% (C)	95%(P)/(C)	0.35 (0.20–0.61) $p < 0.001$	NA	NA
CIBIS-II (1999)	Bisoprolol (B)	2,647	61 (P)/(B)	20% (P)/19% (B)	27.6% (P)/27.5% (B)	96% (P)/(B)	0.66 (0.54–0.81) $p = 0.0011$	0.71 (0.56–0.90) p = 0.0049	0.64 (0.53–0.79) p = 0.0001
MERIT-HF (1999)	Metoprolol (M)	3,991	63.7 (P)/63.9 (M)	22% (P)/23% (M)	28% (P)/28% (M)	96% (P)/(M)	0.66 (0.53–0.81) $p = 0.00009$	NA	NA
COPERNICUS (2001)	Carvedilol (C)	2,289[a]	63.4 (P)/63.2 (C)	80% (P)/79% (C)	19.8% (P)/19.9% (C)	97% (P)/(C)	0.65 (0.53–0.81) p = 0.00013	NA	NA

Abbreviations; *P* placebo, *B* bisoprolol, *C* carvedilol, *M* metoprolol
[a]All patients have NYHA functional class IV

Table 2 Results of triple therapy of ACEI, ARB and β-blocker in patients with HF

Trial	ARB	N	Age	Women	Mean EF	ACEI/ARB	β-blocker	HR for all-cause death	HR for CV death	HR for HF hosp.
CHARM-added (2003)	Candesartan (C)	2,548	64.1 (P)/64.0 (C)	21.4% (P)/ 21.2% (C)	28.0% (P)/(C)	99.8% (P)/100% (C)	55.9% (P)/55.0% (C)	NA	0.84 (0.72–0.98), $p = 0.029$	0.83 (0.71–0.96), $p = 0.014$
Val-Heft (2001)	Valsartan (V)	5,010	63.0 (P)/62.4 (V)	20.0% (P)/20.1% (V)	26.9% (P)/26.6% (V)	92.8% (P)/92.6% (V)	35.3% (P)/34.5% (V)	1.02 (0.88–1.18), p = 0.80	NA	NA
SUPPORT (2015)	Olmesartan (O)	1,147	65.5 (con.)/65.8 (O)	24.8% (con.)/25.8% (O)	53.7% (con.)/53.7% (O)	81.1% (con.)/81.0% (O)	73.2% (con.)/70.1% (O)	1.15 (0.86–1.54), $p = 0.338$	1.26 (0.82–1.93), $p = 0.29$	1.15 (0.88–1.50), $p = 0.14$

Abbreviations; *P* placebo, *C* candesartan, *con.* control arm, *V* valsartan, *O* olmesartan

II-IV who randomly assigned to receive ARB valsartan or placebo. Mortality was similar in the two treatment groups. However, a post-hoc analysis of the Val-Heft revealed that patients who received triple therapy of ACEI, ARB and β-blocker had a significantly increased mortality (P = 0.009), and a trend toward an increase in the composite endpoint defined as cardiac arrest with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for 4 h or more without hospitalization (P = 0.10) (Cohn and Tognoni 2001). In contrast, in the CHARM-Added which enrolled 2,548 HFrEF (EF < 40%) patients with NYHA II–IV, triple therapy (56% in β-blocker use) was associated with a reduction in the composite of cardiovascular death or HF hospitalization (0·85 [95% CI 0.75–0.96], P = 0.011), when compared to placebo. In addition, there was no difference in all-cause death (HR 0·88 [0.72–1.08], P = 0.22) (McMurray et al. 2003; Swedberg et al. 1999).

Given the different results between Val-Heft and CHARM-added, the value of ARB add-on therapy to ACEI was controversial. In 2015, the SUPPORT, which investigated whether an additive treatment with an ARB olmesartan, reduces the mortality and morbidity in 1,147 HF patients with a history of hypertension (7% in NYHA class III; 72% in β-blocker use; 81% in ACEI use; 19% of EF ≤ 40%), provided additional information of triple therapy (Sakata et al. 2015; Sakata et al. 2013). The composite event rates of all-cause death, non-fatal acute myocardial infarction, non-fatal stroke, and hospitalization for worsening HF were not different between olmesartan and control groups (HR 1.18 [0.96–1.46], P = 0.112), whereas renal dysfunction developed more frequently in the olmesartan group (HR 1.64 [1.19–2.26], P = 0.003). Furthermore, a post-hoc analysis of the SUPPORT trial suggested that triple therapy may be harmful in patients with HF: among patients already receiving an ACEI and β-blocker, adding olmesartan was associated with increased incidence of the primary endpoint (HR 1.47 [1.11–1.95], P = 0.006), all-cause death (HR 1.50 [1.01–2.23], P = 0.046), and renal dysfunction (HR 1.85 [95% CI 1.24–2.76], P = 0.003) (Sakata et al. 2015). The results of the SUPPORT and Val-Heft indicate no benefit of triple therapy, which is in contract to what was observed in the CHARM-added trial (Cohn and Tognoni 2001; McMurray et al. 2003; Danser and van den Meiracker 2015). This discrepancy could be explained by the differences in patients' demographics; the majority of the patients in the CHARM-Added had NYHA class III (73%), in contrast to 38% in the Val-Heft, and 7% in the SUPPORT. Thus, although the routine use of triple therapy may be avoided in mildly symptomatic HF with a history of hypertension, it remains to be examined whether the triple combination therapy could be beneficial for HF patients with severe symptoms. A large trial comparing ARB added on to ACEI, β-blocker, and MRA (quad therapy) has not been performed yet (Table 3).

8 Comprehensive Blockade with Direct Renin Inhibitor, Aliskiren, ACEI and β-Blocker in HFrEF

The pathophysiological concept of a complete RAAS blockade was further tackled by direct renin inhibitor (DRI) (Rahuel et al. 2000; Wood et al. 2003). DRI provides another pharmacologically distinct means of suppressing the RAAS, with the theoretical advantages of blocking an enzyme with only one known substrate, angiotensinogen, providing the theoretical benefit of upstream RAAS inhibition at the point of pathway activation. (Fig. 1) Adding Aliskiren, a first-in-class orally active DRI on ACEI and β-blocker has shown favorable neurohumoral effects in terms of reducing plasma BNP (brain natriuretic peptide) levels compared with placebo in the ALOFT (Aliskiren Observation of Heart Failure Treatment) study (McMurray et al. 2008) which included HFrEF patients with NYHA II-IV, current or past history of hypertension, and plasma BNP > 100 pg/mL who had been treated with an ACEI and β-blocker (mean age 68 years; mean EF 31%; NYHA II 62%). Furthermore, aliskiren was associated with a significant

Table 3 Combination of Aliskiren with ACEI in heart failure and reduced ejection fraction

Trial	N	Age	Women	Mean EF	ACEI/ ARB	β blocker	HR for all-cause death	HR for CV death	HR for HF hosp.	Composite renal outcome
ASTRONAUT (2013)	1,639	64.6	22.8%	27.9%	84.2%	82.5%	0.99 (0.78–1.24) $p = 0.92$	0.92 (0.68–1.26) $p = 0.60$	0.90 (0.72–1.12) $p = 0.35$	NA
ATMOSPHERE (2016)	4,676*	63.3 (E)/62.4 (A + E)	21.4% (E)/21.1% (A + E)	28.3% (E)/28.5% (A + E)	100% (ACEI)	91.9% (E)/ 92.0% (A + E)	0.91 (0.82–1.02) $p = 0.12$	0.93 (0.82–1.05) $p = 0.23$	0.93 (0.82–1.06) $p = 0.29$	2.17** (1.24–3.79) $p = 0.007$

Abbreviations; *E* enalapril, *A* + *E* aliskiren and enalapril

*Exclude the aliskiren group (n = 2,340)

**Reference = The enalapril group

reduction in urinary aldosterone excretion, supporting the hypothesis that a DRI strategy may reduce aldosterone escape with prognostic benefit. However, the results of the ASTRONAUT (AliSkiren TRial ON Acute heart failure oUTcomes) and ATMOSPHERE (Aliskiren Trial to Minimize OutcomeS in Patients with HEart failuRE) trials did not support this hypothesis in terms of prognosis (Gheorghiade et al. 2013; McMurray et al. 2016). In the ASTRONAUT, HFrEF (EF $\leq$ 40%,) patients with BNP $\geq$ 400 pg/mL (or N -terminal pro-BNP [NT-proBNP] $\geq$1,600 pg/mL), and signs and symptoms of fluid overload were randomized to aliskiren or placebo. Patients assigned aliskiren experienced a significant and sustained drop in blood levels of NT-proBNP through 12 months follow-up (Gheorghiade et al. 2013). However, no statistical difference was observed in the event rates for composite of cardiovascular death or HF hospitalization (aliskiren, 35.0% vs. placebo 37.3%; HR 0.93; 95%CI [0.79–1.09], P = 0.36) at 12 months. In addition, hyperkalemia, renal dysfunction and hypotension were reported more frequently in the aliskiren group. Given by the non-beneficial impact with greater side effect by aliskiren, the ASTRONAUT trial implies that there might be a ceiling to the benefit with RAAS modulation, and further inhibition beyond ACEI does not provide any incremental benefit. This argument was reinforced by the results from the ATMOSPHERE trial. The ATMOSPHERE trial randomized 2,336 patients with NYHA II-IV and elevated BNP to receive enalapril alone, 2,340 to receive aliskiren, and 2,340 to receive combination therapy with aliskiren and enalapril (combination therapy) (McMurray et al. 2016; Krum et al. 2015). The primary composite outcome of all-cause death and HF hospitalization occurred in 32.9% of the combination therapy group, in 34.6% in the enalapril group (HR 0.93; 95%CI [0.85–1.03], P = 0.17) and in 33.8% in the aliskiren group (vs. enalapril, 0.99 [0.90–1.10], P = 0.91). Adverse event rates for aliskiren alone group were similar to those of enalapril alone. However, like the ASTRONAUT trial, in the ATMOSPHERE trial, there was a higher risk of hypotensive symptoms in the combination therapy group than in the enalapril alone group (13.8% vs. 11.0%, P = 0.005), and higher risks of an elevated serum creatinine level (4.1% vs. 2.7%, P = 0.009) and an elevated potassium level (17.1% vs. 12.5%, P < 0.001). The results from the ASTORONOUT and ATMOSPHERE do not support upstream renin inhibition in addition to standard therapy with ACEI in patients with HFrEF.

9 Comprehensive Blockade for RAAS and Natriuretic Peptide System in HFrEF

LCZ696 (sacubitril/valsartan) is a new class of agents called angiotensin receptor-neprilysin inhibitors (ARNIs) which combines a neprilysin inhibitor and an ARB valsartan. LCZ696 has a unique mode of action targeting both RAAS and the natriuretic peptide systems because sacubitril inhibits the neprilysin, which increases the level of natriuretic peptides rather than leading to additional blockage. (Fig. 1) Recent data from the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial suggests more comprehensive RAAS modulation with other RAAS axis blocking agents may have led to clinical benefit in HF patients and reduced EF (McMurray et al. 2014; McMurray et al. 2013). The PARADIGM-HF randomized 8,399 NYHA II-IV HFrEF ($\leq$40% and $\leq$35% were used at different time points in the trial) patients to LCZ696 or enalapril. With a median follow-up of 27 months, the trial was stopped early due to a positive interval efficacy analysis. The LCZ696 added to standard therapy with 93% of patients already taking β-blocker and 54% taking MRA led to a reduction in the primary composite outcome of cardiovascular death or HF hospitalization (21.8% vs. 26.5%; HR 0.80 95%CI [0.73–0.87], P < 0.001) as well as each of the individual components of the composite outcome. Of note, LCZ696 had a significant reduction in all-cause death (17.0% vs. 19.8%; HR 0.84 95%

CI [0.76–0.93], P < 0.001). LCZ696 was generally well tolerated except for a higher rate of hypotension and there was no difference in the rates of angioedema. Following the PARADIGM-HF, the US Food and Drug Administration approved LCZ696 for the treatment of HF. Furthermore, professional HF guidelines endorse LCZ696 as a class I recommendation for the management of symptomatic HFrEF (Ponikowski et al. 2016b; Jessup et al. 2016). Although this high-quality clinical study is the largest and the most globally represented trial in HFrEF patients, concerns have been raised regarding the generalizability of the trial results in real-world HF population due to inclusion/exclusion criteria, run-in period and lower dose of enalapril in the control arm (Yandrapalli et al. 2017; Yancy et al. 2017).

10 RAAS Inhibitor, β-Blocker and Those Combination in HF and Preserved EF (HFpEF)

Approximately half of HF patients have an EF of 50% or higher (heart failure and preserved ejection fraction; HFpEF) (Owan et al. 2006). The randomized trials with RAASI [ACEI (Cleland et al. 2006) or ARB (Massie et al. 2008)] monotherapy failed to show prognostic benefits in HFpEF patients. For instance, a prespecified subgroup analysis of I-PRESERVED (Irbesartan in Heart Failure with Preserved Ejection Fraction Study) suggested that ARB monotherapy did not provide beneficial impact on prognosis in HFpEF (HR0.87[0.75–1.02], P for interaction of ARB to β-blocker = 0.14) Moreover, the effect of β-blockers monotherapy has not been evaluated in an adequately powered study with HFpEF patients (Conraads et al. 2012; Liu et al. 2014; van Veldhuisen et al. 2009; Yamamoto et al. 2013). In addition, evidence of combination therapy of RAAS inhibitor and β-blocker is predominant in HFrEF. However, several data exist on combination therapy for prognosis in HFpEF by three large clinical trials; CHARM-preserved, I-PRESERVED, and SUPPORT (Yusuf et al. 2003; Massie et al. 2008; Miura et al. 2016).

The CHARM-Preserved enrolled 3,025 patients with HFpEF (EF > 40%) and NYHA II-IV, and a history of hospitalization for a cardiac reason. In the CHARM-Preserved, there was no difference in the primary outcome of cardiovascular death or HF hospitalization between the candesartan and placebo groups (22% vs. 24%; HR 0.89 [95%CI 0.77–1.03], P = 0·118) (Yusuf et al. 2003). However, a signal was observed toward lower event rate for HF hospitalization in candesartan (0.85 [0.72–1.01], P = 0·072). Similar results were observed in the I-PRESERVED including 4,128 symptomatic HF (NYHA II-IV) patients with HFpEF (EF ≥ 45%) who were 60 years or older (Massie et al. 2008; Carson et al. 2005). In the I-Preserved, ARB Irbesartan did not improve the outcome defined by the composite of death from any cause or hospitalization for a cardiovascular cause (heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke) in HFpEF. Post-hoc analysis from the SUPPORT, in HFpEF, the addition of olmesartan to β-blocker was significantly associated with lower event rate for all-cause death (HR 0.32 [0.12–0.90] P = 0.03), whereas addition to ACEI (1.85 [0.87–3.96], P = 0.11) or that to combination of ACEI and β-blocker (1.65 [0.93–2.94], P = 0.09) was not (Miura et al. 2016). In 2014, the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial including patients with EF ≥45%, who had to have either a HF hospitalization within 12 months before randomization or, if not, an elevated brain natriuretic peptide (BNP; BNP ≥100 pg/mL or N-terminal pro-BNP ≥360 pg/mL) within 60 days before randomization, showed no difference between MRA spironolactone and placebo groups in the primary composite outcome of cardiovascular death, aborted cardiac arrest, or HF hospitalization (Pitt et al. 2014; Desai et al. 2011). However, in post-hoc analysis of the TOPCAT trial, spironolactone was associated with a significant reduction in the primary outcome for those in the United States, Canada, Brazil, and Argentina but not those in Russia/Georgia (Pfeffer et al. 2015). These lines of evidence call for further trials to assess clinical effect of combination therapy of

RAAS inhibitor and β-blocker in HFpEF (Desai and Jhund 2016). To assess efficacy and safety of LCZ696 in HFpEF, the PARAMOUNT (Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion) trial was conducted in HFpEF (≥45%) patients with NYHA II-III, and NT-proBNP>400 pg/mL comparing LCZ696 (200 mg) with valsartan (160 mg) for 36 weeks (Solomon et al. 2012). NT-proBNP was significantly reduced at 12 weeks in the LCZ696 group compared with the valsartan group suggesting that LCZ696 may improve prognosis in HFpEF (Solomon et al. 2012). In near future, PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) trial (Solomon et al. 2017; Filippatos et al. 2015) will provide evidence of whether LCZ696 is prognostically superior to ARB alone in patients with chronic symptomatic HFpEF (EF ≥ 45%).

11 Conclusions

With concrete evidence, RAAS blockade by combination with ACEI and β-blocker is a gold standard in the treatment of HFrEF. ARB clearly represent an alternative of treatment for patients who are intolerant to ACEI. Triple therapy with ACEI, ARB and β-blocker does not provide additional benefit in mildly symptomatic HFrEF. Furthermore, triple therapy can even cause harm and renal dysfunction in HF with a history of hypertension. Sacubitril inhibits the neprilysin which increases the level of natriuretic peptides rather than leads to additional blockage, and reduces NT-proBNP levels greater than an ARB in HFpEF. Whether this effect would translate into improved outcomes, is tested by PARAGON-HF trial. Given by the heterogeneity of diagnostic criteria and baseline characteristics of HFpEF, clinical benefit of combination therapy with RAASIs and β-blocker is controversial, and we need further evidence in HFpEF.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 31–45
DOI 10.1007/5584_2017_112
© Springer International Publishing AG 2017
Published online: 31 October 2017

Combination of Hydralazine and Isosorbide-Dinitrate in the Treatment of Patients with Heart Failure with Reduced Ejection Fraction

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Abstract

The use of direct acting vasodilators (the combination of hydralazine and isosorbide dinitrate -Hy+ISDN-) in heart failure with reduced ejection fraction (HFrEF) is supported by evidence, but rarely used.

However, treatment with Hy+ISDN is guideline-recommended for HFrEF patients who cannot receive either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers due to intolerance or contra-indication, and in self-identified African-American HFrEF patients who are symptomatic despite optimal neurohumoral therapy.

The Hy+ISDN combination has arterial and venous vasodilating properties. It can decrease preload and afterload, decrease left ventricular end-diastolic diameter and the volume of mitral regurgitation, reduce left atrial and left ventricular wall tension, decrease pulmonary artery pressure and pulmonary arterial wedge pressure, increase stroke volume, and improve left ventricular ejection fraction, as well as induce left ventricular reverse remodelling. Furthermore, Hy+ISDN combination has antioxidant property, it affects endothelial dysfunction beneficially and improves NO bioavailability. Because of these benefits, this combination can improve the signs and symptoms of heart failure, exercise capacity and quality of life, and, most importantly, reduce morbidity and mortality in well-defined subgroups of HFrEF patients.

Accordingly, this therapeutic option can in many cases play an essential role in the treatment of HFrEF.

Keywords

Direct vasodilators · Hydralazine · Isosorbide dinitrate · Heart failure with reduced ejection fraction

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1 Introduction

The use of the combination of hydralazine and isosorbide-dinitrate (Hy+ISDN) was the first therapeutic intervention in heart failure with reduced ejection fraction (HFrEF) whose beneficial effect on survival was proven in a placebo-controlled, randomized trial (Cohn et al. 1986). Two randomized, placebo-controlled trials have now demonstrated a significant reduction in all-cause mortality in well-defined HFrEF patient populations due to the effects of this direct vasodilator drug combination (Cohn et al. 1986; Taylor et al. 2004), nonetheless, the use of Hy+ISDN is almost negligible worldwide (Golwala et al. 2013; Maggioni et al. 2013; Damasceno et al. 2012). There is no other therapeutic option which is supported by such high-level evidence but is neglected to such an extent by physicians.

The fact that the combination of Hy+ISDN takes a back seat in HFrEF therapy is partly due to changes in the concept of the pathophysiology of heart failure. While in the 1950s and 1960s the cardiorenal paradigm prevailed and heart failure was predominantly treated with the use of digitalis and diuretics, the haemodynamic concept, which established the use of vasodilators, came to dominate in the 1970s and 1980s. From the 1990s onwards, the treatment of heart failure based on the neurohumoral concept became prevalent, supplemented by highly effective neurohumoral antagonists (ACE inhibitors -ACEi-, beta receptor blockers -BB-, mineralocorticoid receptor antagonists -MRA-, angiotensin receptor blockers -ARB-, and angiotensin receptor neprylisin inhibitors -ARNI-). However, due to the dominance of this paradigm, treatment based on the haemodynamic concept was largely overlooked, along with the potential use of vasodilator treatment. Hydralazine is no longer available in many European countries, and where it is available it is very rarely used. However, much research indicates that, despite the unequivocal pathophysiological significance of abnormally elevated neurohumoral activation, we should not ignore the hemodynamic approach either when interpreting the processes of chronic heart failure, or when optimizing therapies (Johnson et al. 2002; Lisy et al. 2000; Stevenson 1999; Stevenson et al. 1995).

When treating a patient with heart failure, using optimal doses of neurohumoral antagonists is essential, but we must also strive to create the optimal hemodynamic status. This involves supporting an appropriate reduction in the heart rate, peripheral vascular resistance, left atrial filling pressure, and an increase in stroke volume and cardiac output, which in some cases cannot be achieved only with the use of neurohumoral antagonists (Stevenson 1999; Stevenson et al. 1995). In chronic heart failure, reduction of the preload and afterload, as well as atrial and ventricular wall tension, is also an important therapeutic goal, the achievement of which often unavoidably involves the use of direct vasodilators (Lisy et al. 2000; Stevenson 1999; Stevenson et al. 1995). In addition, neurohumoral antagonists sometimes cannot be used due to contraindications or intolerance, or patients may remain symptomatic despite use of the neurohumoral antagonists. In such cases, it is important to remember the direct-acting vasodilator combination Hy+ISDN, which if used with caution and according to the evidence and current guideline recommendations (Ponikowski et al. 2016; Yancy et al. 2013) can reduce symptoms and improve quality of life of many HFrEF patients, and reduce morbidity and mortality in some clinical situations.

This chapter presents an overview of the mechanism of action of the Hy+ISDN combination and a review of evidence, guideline recommendations, and practical guidance.

2 Mechanism of Action

2.1 Hydralazine

Hydralazine is primarily an arterial vasodilator that mainly reduces the tone of arterioles, while influencing venous tones less. The exact

intracellular pathways mediating its effects are not completely understood, but it reduces peripheral vascular resistance directly by relaxing vascular smooth muscle cells (Knowles et al. 2004). As an arterial vasodilator, it reduces systemic peripheral resistance, relieves the left ventricular ejection, and therefore – by lowering the afterload – increases left ventricular stroke volume and improves the left ventricular ejection fraction. Further beneficial hemodynamic consequences of afterload reduction include a decrease in the severity of mitral regurgitation, which is often observed in HFrEF due to left ventricular spherical remodelling. Moreover, a decrease in the volume of mitral regurgitation reduces left atrial wall tension, and beneficially affects redistribution of blood flow. One drawback of the effect of arteriolar vasodilation is that it causes a reflex increase in sympathetic activity with all the adverse consequences of this, particularly in cases of mild heart failure. It is notable that the use of hydralazine, particularly in advanced heart failure, does not decrease blood pressure significantly and does not affect kidney perfusion unfavourably. The drug is also known to have antioxidant properties (Daiber et al. 2005) and a beneficial effect on endothelial dysfunction. Hydralazine can prevent nitrate tolerance presumably by inhibition of a membrane-associated oxidase. Previous studies demonstrated that nitrate tolerance is associated with an increase in vascular reactive oxygen species production. The membrane-associated oxidase is likely involved in this process. Hydralazine inhibits this oxidase and reduces the production of reactive oxygen species and prevents nitrate tolerance (Bauer and Fung 1991; Gogia et al. 1995; Münzel et al. 1996).

2.2 Nitrates

Nitrates are primarily venodilators, although their arterial vasodilator activity is not negligible if there is a marked rise in systemic vascular resistance. They decrease the tone of veins and therefore decrease venous inflow into the right heart, decrease pulmonary artery pressure and pulmonary arterial wedge pressure, decrease left atrial pressure, and – as a consequence of the decrease in diastolic inflow into the left ventricle – decrease left ventricular preload, as well as left ventricular diastolic volume and pressure. They reduce the size of the mitral ostium in the dilated left heart, thus reducing relative mitral regurgitation. Isosorbide dinitrate, like nitrites and organic nitrates, is considered an NO donor. Nitrates can inhibit mitogenesis, proliferation of vascular smooth muscle cells and development of myocardial hypertrophy (Garg and Hassid 1989; Calderone et al. 1998) as well as mitigate left ventricular remodelling (Jugdutt and Khan 1994). When nitrates are used, nitrate tolerance should be taken into account. Nitrate tolerance can be avoided not only by temporarily discontinuing the nitrate effect or by temporarily lowering plasma nitrate levels, but with the use of certain drugs such as hydralazine (Gogia et al. 1995), ACEi (Elkayam et al. 1999), or carvedilol (Watanabe et al. 1998).

By means of the hemodynamic effects described above, hydralazine and nitrate reduce left ventricular and left atrial wall tension, both of which play a pathophysiologic role in heart failure (e.g. by inducing and maintaining neurohumoral activation). The combination of hydralazine and nitrate reduces both left and right ventricular filling pressure and increases cardiac output. As a result of the beneficial haemodynamic effects of the Hy+ISDN combination, left ventricular ejection fraction is improved, left ventricular end-systolic and end-diastolic diameters are decreased, thus reverse left ventricular remodelling is developed.

3 Evidence

Although several observational studies have demonstrated the favourable hemodynamic and clinical effects of hydralazine (Franciosa et al. 1977; Chatterjee et al. 1980) and nitrates

(Franciosa et al. 1978a, b; Leier et al. 1983) as individual treatments, clearly beneficial results in hard endpoints have only been achieved with the combination of the two agents.

3.1 V-HeFT I Trial (Vasodilator Heart Failure Trial I) (Cohn et al. 1986)

The first large, multicentre, randomized, placebo-controlled study that assessed the survival of HFrEF patients was the V-HeFT I trial, published in 1986. In the study 642 men with mild-to-moderate heart failure who were being treated with digoxin and diuretics were enrolled. Eligibility criteria were as follows: left ventricular dilatation (cardiothoracic ratio >0.55 on chest x-ray or left ventricular end-diastolic diameter index >2.7 cm/m^2 on echocardiography) or left ventricular ejection fraction <45% on radionuclide ventriculography and reduced exercise tolerance as assessed by spiroergometry (peakVO_2 <25 ml/kg/min). Patients were randomized to placebo, alpha-receptor blocking prazosin, and Hy+ISDN using a ratio of 3:2:2. The starting dose of prazosin was 2.5 mg four times daily, and the target dose was 5 mg four times daily (20 mg), the average prescribed dose was 18.6 mg per day, the starting dose of hydralazine was 37.5 mg four times daily and the target dose 75 mg four times daily (300 mg), the average dose was 270 mg per day, and the isosorbide dinitrate starting dose was 20 mg four times daily, while target dose was 40 mg four times daily (160 mg) with an average dose of 136 mg per day. Mean follow-up time was 2.3 years.

Within the primary endpoint of the study, defined as the cumulative mortality at 2 years, the Hy+ISDN combination resulted in a relative risk reduction of 34% ($p < 0.028$) compared to placebo. For the entire follow-up period however, the reduction in mortality in the Hy+ISDN group was only at the border of statistical significance ($p = 0.053$). Use of prazosin did not improve patient survival.

In addition to the survival benefit of Hy+ISDN, the combination also increased left ventricular ejection fraction significantly in both the short- (8 weeks) and long term (1 year) (2.9% and 4.2%, respectively, $p < 0.001$). This effect was absent for the placebo and prazosin groups. It is notable that treatment with Hy+ISDN did not significantly reduce systolic blood pressure in the short- or long-term, although a slight but statistically significant short-term decrease in diastolic blood pressure (−1.8 mmHg, $p < 0.05$) was detected. In the long-term, this minimal decrease in diastolic blood pressure was not found to be significant.

In summary, the V-HeFT I study demonstrated that the combination of Hy+ISDN can improve the survival of HFrEF patients significantly.

3.2 V-HeFT II Trial (Vasodilator Heart Failure Trial II) (Cohn et al. 1991)

After the appearance of ACEi and the demonstration of their positive effects on morbidity and mortality, the V-HeFT II study was organized to compare the therapeutic effects of ACEi and the Hy+ISDN combination. In this study, published in 1991, 804 men on digitalis and diuretic therapy for mild-to-moderate heart failure were enrolled. Patients were randomized to treatment groups with ACEi enalapril, or Hy+ISDN in a 1:1 ratio. The inclusion criteria, as well as the starting and the target doses of hydralazine and isosorbide dinitrate, were identical to those used in the VeHFT I trial. The target dose of enalapril was 20 mg. The average daily dose of enalapril (15 mg) in this study was similar to the average daily dose of enalapril in the overwhelmingly successful ACEi studies (CONSENSUS I (The CONSENSUS Trial Study Group 1987) – 18.4 mg/day; SOLVD-Treatment (The SOLVD Investigators 1991) – 16.6 mg/day; SOLVD Prevention (The SOLVD Investigators 1992) – 16.7 mg/day). The average dose of hydralazine was 199 mg, while the average dose of isosorbide dinitrate was 100 mg, both of which were somewhat lower than the average doses given in V-HeFT I. Patients were followed on average for 2.5 years.

Mortality after 2 years, predetermined as a major end-point for the trial, was significantly lower in the enalapril arm (18%) than in the Hy +ISDN arm (25%) ($p = 0016$). This trend persisted in the later study, but the difference in mortality across the entire follow-up period was no longer found to be significantly different between the two groups ($p = 0.08$). We emphasize that the favourable mortality rate observed in the enalapril-treated group was the consequence of a lower incidence of sudden cardiac death in this group ($p = 0.015$ without premonitory symptoms, $p = 0.032$ with premonitory worsening). There was no significant difference between the two groups in terms of mortality from pump failure ($p = 0.44$). Also notable is the fact that only the survival probability of patients with mild heart failure (NYHA I-II) was significantly different ($RR = 0.52$) in the enalapril and Hy +ISDN arms. The survival effect of the two treatment groups containing patients of NYHA III-IV class (nearly half the whole sample) was similar ($RR = 0.99$).

There was no significant difference in heart-failure-related (18.9% – enalapril vs. 18.4% – Hy +ISDN) and other CV-related hospitalization (26.7% in each group) across the whole VeHFT II patient population.

A significant improvement was observed in left ventricular ejection fraction for both the Hy +ISDN and enalapril treated patients ($p = 0.0001$); however, the beneficial effect of Hy+ISDN was significantly more pronounced than that of enalapril ($p = 0.026$). Peak VO2 measured by spiroergometry significantly increased during Hy+ISDN treatment ($p < 0.0001$), while this benefit was absent in the enalapril-treated group. Exercise capacity of patients also significantly improved in the Hy +ISDN group compared to enalapril-treated patients (Ziesche et al. 1993).

Blood pressure decreased in both treatment groups, but the reduction in systolic (−5 mmHg) and diastolic blood pressure (−4 mmHg) in the enalapril group was higher than that in the Hy+ISDN group (0 mmHg in systolic, −1 mmHg in diastolic blood pressure). Heart rate was significantly higher in patients treated with Hy+ISDN than in the enalapril group during the follow-up.

The two forms of treatment were associated with side effects almost in the same proportions, but the treatments were well tolerated in both groups. In the Hy+ISDN group, headaches ($p < 0.05$) were significantly more frequent, while enalapril was associated with a higher proportion of hypotension ($p < 0.05$) and coughing ($p < 0.05$) as well as a significantly higher increase in serum urea ($p < 0.01$) and creatinine ($p = 0.02$) and a significantly higher level of potassium.

In summary, the V-HeFT II study showed that the combination of the direct-acting vasodilator Hy+ISDN is less favourable in terms of survival than the ACEi enalapril. However, this weaker survival effect of Hy+ISDN was predominantly attributable to higher mortality (in particular, a higher proportion of sudden cardiac death) in the subgroup of patients with mild heart failure. It is reasonable to assume that the arrhythmogenic side effects of the Hy+ISDN combination were primarily a consequence of the reflex increase in sympathetic activity due to the effect of arterial vasodilator hydralazine, an effect which has been well documented in patients with mild heart failure. An important subgroup observation of the V-HeFT I study is consistent with the above statement – that the use of the Hy+ISDN combination in patients with mild heart failure and left ventricular ejection fraction of over 35% does not improve survival (Carson et al. 1996).

3.3 A-HeFT (African American Heart Failure Trial) (Taylor et al. 2004)

After the V-HeFT I trial evaluating the effect of Hy+ISDN compared to placebo, and the V-HeFT II study assessing the effect of the direct vasodilator combination compared to ACEi enalapril, a

further trial was organised to evaluate the effect of Hy+ISDN treatment in addition to optimal drug therapy in HFrEF. The A-HeFT study, published in 2004, compared the effect of a fixed-dose Hy+ISDN combination (37.5 mg Hy + 20 mg ISDN per tablet) with placebo in 1050 self-identified African American patients in NYHA functional class III and IV despite optimal background heart failure therapy. The starting dose of Hy+ISDN was one tablet three times daily, and the target dose was two tablets three times daily. A further inclusion criterion was the evidence of left ventricular dysfunction: The left ventricular ejection fraction was required to be $\leq$35%, or left ventricular ejection fraction of <45% combined with dilated left ventricle (left ventricular end-diastolic diameter > 6.5 cm, or left ventricular end-diastolic diameter index >2.9 cm/m^2 on the basis of echocardiography). Patients were treated with ACEi (69.5%) or ARB (16.9%), BB (73.8%), digoxin (59.6%), spironolactone (38.9%), and diuretics (89.8%). Seventeen percent had an implantable cardioverter defibrillator, and 2% had received cardiac resynchronization therapy.

The A-HeFT study was terminated prematurely. The mean duration of follow-up was 10 months. Termination was due to the extremely high decrease (43%) in the relative risk of death in the Hy+ISDN group ($p = 0.01$). The Hy+ISDN combination reduced mortality due to heart failure at the highest rate (75%); however, the decrease in sudden cardiac death was not significant.

A further significant positive effect was observed in the Hy+ISDN group according to the composite endpoint defined as the primary endpoint of the study (death from any cause, first hospitalization for heart failure during the 18 months of the study, and change in the quality of life at 6 months) ($p = 0.01$). The risk of first hospitalization for heart failure decreased by 33% ($p = 0.001$), quality of life score improved significantly ($p = 0.02$), and, according to later analysis, left ventricular ejection fraction increased and left ventricular end-diastolic dimension decreased significantly (Cohn et al. 2007).

Compared to placebo, Hy+ISDN decreased blood pressure slightly but significantly. Systolic blood pressure decreased by 1.9 Hgmm in the Hy+ISDN group and 1.2 Hgmm in the placebo group, while diastolic blood pressure decreased by 2.4 Hgmm in Hy+ISDN but increased 0.8 Hgmm in the placebo group ($p < 0.001$). There was no significant difference in heart rate between the two groups.

As far as side effects are concerned, headaches and dizziness were more frequently experienced in the Hy+ISDN arm, while heart failure progressed in significantly more cases in the placebo arm.

In summary, the A-HeFT study demonstrated that the fixed-dose combination of Hy+ISDN on top of standard therapy for HFrEF, including neurohumoral antagonists, can increase survival among African American patients with advanced heart failure.

The extension of the A-HeFT trial (X-A-HeFT) (Yancy et al. 2007), designed for ethical reasons to make the Hy+ISDN fixed-dose combination available from the time of A-HeFT study termination until FDA approval, further confirmed the beneficial effects of Hy+ISDN in this patient population. The study demonstrated low mortality and morbidity, symptomatic improvement, good compliance, and safety and tolerability of Hy+ISDN in the former 198 A-HeFT patients for about 7 months.

3.4 Summary of the Evidence

These three placebo-controlled, randomised mortality trials and their retrospective analyses proved that the Hy+ISDN combination improves the left ventricular ejection fraction significantly compared to both placebo (Cohn et al. 1986) and enalapril (Cohn et al. 1991). Beyond improving left ventricular ejection fraction, the vasodilator combination also decreases left ventricular end diastolic dimension (that is, it causes left

ventricular reverse remodelling) (Cohn et al. 2007), which is currently regarded as one of the strongest predictors of survival in HFrEF. Furthermore, Hy+ISDN treatment increases peak VO2 and exercise tolerance significantly (Ziesche et al. 1993), which is also considered to be a very important prognostic parameter. The Hy+ISDN combination significantly reduces heart muscle mass compared to placebo, where the opposite tendency is observed (Cohn et al. 2007). The vasodilator combination affects left ventricular sphericity index beneficially (Cohn et al. 2007) and decreases the level of plasma natriuretic peptides significantly (Cohn et al. 2007). In addition, Hy+ISDN decreases symptoms and improves quality of life.

In addition to these effects on surrogate endpoints the direct vasodilator combination can decrease the morbidity and mortality of HFrEF patients.

3.5 Systematic Reviews, Meta-Analyses, Registry Data

Since the publication of the three large, randomized, placebo-controlled mortality studies, several reviews and meta-analyses have evaluated the efficacy of the Hy+ISDN combination. A systematic review and meta-analysis that evaluated the data from seven randomized trials and 2626 patients published by Farag et al. (2015) confirmed that the Hy+ISDN combination significantly reduced total mortality and cardiovascular mortality in HFrEF compared to placebo. However, according to this review the evidence is not sufficient to support the sole use of either drug in HFrEF.

Using data from the American Heart Association's *Get With The Guidelines – Heart Failure* (GWTG-HF) registry, linked to Medicare claims, Khazanie et al. (2016) assessed the use and outcomes of Hy+ISDN among African American patients and patients of other races not on ACEi or ARB due to contraindications or intolerance during hospitalization for heart failure. The use of the combination of Hy+ISDN at discharge was low among both African American patients (22.7%) and patients of other races (18.2%). However, the cumulative incidence rates of mortality, all-cause readmission, and cardiovascular readmission at 3 years were similar between treated and untreated African American and non-African American patients, meaning that – taking into account the remarkable differences in baseline treatment and significant potential for selection bias – interpretation of the results of this study is challenging (Taylor 2016). Moreover, the findings of this observational study do not in any way reduce the value of the results of earlier randomized, controlled survival trials.

3.6 Ongoing Clinical Trials

There is currently no ongoing clinical trial in chronic heart failure that is using the Hy+ISDN combination, either in HFrEF or in HFpEF.

The GALACTIC trial (NCT00512759) is currently ongoing in acute heart failure assessing whether it is safe, effective and cost-effective to reduce preload and afterload by the combination of hydralazine and nitrate and additional vasodilators early in the non-ICU setting, targeting a systolic blood pressure of 90–110 mmHg.

4 Guideline Recommendations

The current guidelines for the management of heart failure published by the European Society of Cardiology (ESC) in 2016 (Ponikowski et al. 2016) and the American College of Cardiology and American Heart Association (ACCF/AHA) in 2013 (Yancy et al. 2013) recommend the use

of the direct vasodilator combination in two clinical situations:

1. *In case of ACEi and ARB intolerance or contraindication.*
   (a) ESC guideline: "Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death." This is a Class IIb recommendation with a "B" level of evidence.
   (b) ACCF/AHA guideline: "A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated." This is a Class IIa recommendation with a "B" level of evidence.
2. *In self-identified African-American HFrEF patients with NYHA Class III-IV despite optimal treatment.*
   (a) ESC guideline: "Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF <35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I, a beta-blocker and an MRA to reduce the risk of HF hospitalization and death." This is a Class IIa recommendation with a "B" level of evidence.
   (b) ACCF/AHA guideline: "The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated." This is a Class I recommendation with an "A" level of evidence.

Although the 2013 ACCF/AHA guidelines were updated in 2016 (Yancy et al. 2016) and 2017 (Yancy et al. 2017), they were not modified concerning the use of the Hy+ISDN combination.

4.1 The Use of Hy+ISDN Combination in Case of ACEi and ARB Intolerance or Contraindication

When a patient cannot receive either an ACEi or an ARB because of intolerance or contraindication, use of the Hy+ISDN combination is supported by the results of the V-HeFT I study (Cohn et al. 1986), which clearly demonstrated that the survival of patients receiving digitalis and diuretic therapy without an RAAS antagonist was significantly improved by the use of the direct vasodilator combination.

However, patients who presently cannot tolerate either an ACEi or an ARB can be treated with survival-enhancing treatment strategies (BB, and MRA) in addition to diuretics and/or digitalis, and it has not been demonstrated that direct vasodilators maintain their favourable mortality-reducing effects when BB and MRA are in use. However, considering the cases of ACEi and ARB intolerance, the beneficial effect of direct vasodilator treatment in these clinical situations seems to be at least likely.

Combined ACEi and ARB intolerance are most common in patients with significant hypotension and renal function impairment. The cough caused by ACEi as a result of bradykinin accumulation usually disappears with the use of ARB. However, hypotension, renal function impairment and hyperkalaemia, which is related to angiotensin suppression, are common side effects of ACEi and ARB.

Patients who are intolerant to ACEi and ARB due to significant hypotension or renal function impairment are generally hemodynamically unstable with advanced heart failure. If these patients are treated with only digitalis and diuretics, the introduction of BB is usually unsuccessful due to haemodynamic instability. Moreover, patients who cannot tolerate an ACEi because of impaired renal function cannot receive MRA either. Thus, ACEi and ARB intolerant patients, despite the fact that they should receive BB and MRA in accordance with the guidelines, still receive only digitalis and diuretics in the majority of cases. In this situation, the findings of the V-HeFT I study most probably hold true.

It is also important to note that if these ACEi-, ARB-, BB-, and MRA-intolerant severe heart failure patients receive direct vasodilator combinations in addition to diuretics and/or digitalis, they usually achieve hemodynamic stability, their blood pressure increases, and renal function improves. In this stable hemodynamic situation an attempt can be made to reintroduce ACEi, and then BB and MRA. Thus, instead of treating patients solely with diuretics and/or digitalis, which usually leads to a rapid progression of disease or even death, a much more advantageous optimal treatment strategy may be created for patients. Based on these considerations, the Hy+ISDN combination may currently be considered the most effective tool for breaking through ACEi and ARB intolerance.

However, it should be emphasized that all ACEi- and ARB-intolerant patients who can tolerate BB and MRA therapy should receive them, in addition to direct vasodilators. The Hy+ISDN combination should not be used to treat patients who have not previously showed intolerance or contraindication to ACEi and ARB.

The introduction of ARNI in HFrEF therapy does not affect this indication as patients who cannot receive either an ACEI or an ARB due to intolerance or contraindication should not receive an ARNI either.

4.2 The Use of the Hy+ISDN Combination in Self-Identified African-American HFrEF Patients with NYHA Class III-IV Despite Optimal Treatment

This indication is supported by the results of the A-HeFT study (Taylor et al. 2004) performed in an African-American patient population. According to the indication, in all self-identified African-American HFrEF patients who remain symptomatic despite optimal treatment with ACEi or ARB, BB and MRA, treatment should be supplemented with the combination of Hy+ISDN according to the ACCF/AHA guideline (Yancy et al. 2013), or at least the use of Hy+ISDN should be considered in accordance with the ESC guideline (Ponikowski et al. 2016).

The introduction of ARNI in the treatment of HFrEF may slightly modify the use of the Hy+ISDN combination in this patient population. The appropriate therapeutic strategy seems to be the following: As first step, replacement of ACEi or ARB with ARNI therapy is recommended in all patients who remain symptomatic despite optimal treatment with ACEi or ARB, BB and MRA. If still symptomatic, the addition of Hy+ISDN therapy should be considered in self-identified African-American HFrEF patients as second step. However, the combination of Hy+ISDN and ARNI has not yet been investigated, therefore caution is advised, especially as regards careful blood pressure monitoring.

As well-known that African-Americans respond to ACEi and some BB treatment less favourably; however, they respond to the Hy+ISDN combination better than Caucasian patients (Exner et al. 2001; Carson et al. 1999). In the background of these observations there are partly genetic differences. The DNA sub-study of the A-HeFT trial proved that NO synthase and aldosterone synthase polymorphism is associated with an enhanced Hy+ISDN effect (McNamara et al. 2006, 2009). McNamara et al. (2014) found that GNB3 825 T homozygotes respond in an outstandingly favourable way to Hy+ISDN

therapy. Moreover, all three polymorphisms are much more common in African-Americans than in other populations (McNamara et al. 2006, 2009, 2014; Rosskopf et al. 2002; Marroni et al. 2005; Barbato et al. 2004).

Confirmation of the results of the A-HeFT study in other racial groups was obtained from a small study (Mullens et al. 2009) in which the proportion of Caucasian patients was 80%. This study demonstrated the beneficial hemodynamic, mortality, and morbidity effects of Hy+ISDN in combination with optimal neurohumoral therapy in mostly Caucasian patients. Many experts consider the use of direct vasodilators in other racial patient populations with advanced heart failure despite optimal heart failure therapy as a beneficial treatment option. It is important to note, that the previous ESC guideline for the diagnosis and treatment of acute and chronic heart failure (published in 2012) (McMurray et al. 2012) recommended the use of the Hy+ISDN combination regardless of race: "Hy+ISDN may be considered to reduce the risk of HF hospitalization and risk of premature death in patients with an EF $\leq$45% and dilated LV (or EF $\leq$35%) and persisting symptoms (NYHA class II–IV) despite treatment with a BB, ACE inhibitor (or ARB), and an MRA (or ARB)." This recommendation was Class II/b with a "B" level of evidence.

According to the available data, the direct vasodilator combination may have a more favourable effect in African-Americans, but its beneficial hemodynamic and mortality effect (similar to that of ACEi enalapril in advanced heart failure -NYHA III-IV-) was demonstrated in the V-HeFT II study with predominantly Caucasian patients. It is important to note that direct vasodilators do not cause neurohumoral activation in cases of severe heart failure compared to mild heart failure, and therefore have no or less arrhythmogenic effects, and presumably do not increase the risk of sudden death, or increase it minimally. The beneficial effect of the vasodilator combination may increase independently of race when it is administered with neurohumoral antagonists, particularly with such BB that have been proven to be effective at treating heart failure and reducing sudden cardiac death.

A large, randomized, controlled, multicentre trial which assesses the effect of Hy+ISDN in non-African-American patients who remain symptomatic despite optimal neurohumoral antagonist therapy is warranted.

5 Practical Guidance (Following the Structure of the Web Addenda of 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure) (Ponikowski et al. 2016)

It is very important that the recommendations of the guidelines are closely followed in daily clinical practice. The Web Addenda of 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al. 2016) provide excellent practical guidance about the use of ACEi, ARB, BB, MRA, diuretics and ivabradine. Based on this practical guidance, we now review the optimal use of Hy+ISDN.

Why?

– Because HY+ISDN therapy improves symptoms, quality of life, and exercise capacity, as well as reduces hospitalization and mortality.

To whom?

– *Indications:*
  - In patients with HFrEF who cannot receive either an ACEi or an ARB due to intolerance or contraindication
  - In self-identified African-American patients with LVEF $\leq$35% or with an LVEF <45% combined with a dilated left ventricle in NYHA class III-IV despite optimal treatment with ACEi or ARB, BB and MRA
– *Contraindications:*
  - Known allergic reaction to either hydralazine or isosorbide dinitrate

  - Isosorbide dinitrate should not be given with avanafil, riociguat, sildenafil, tadalafil, or vardenafil
- *Cautions:*
  - Symptomatic or severe asymptomatic hypotension (systolic blood pressure < 90 mmHg).
  - Hydralazine is metabolised in the liver and its inactive degradation products are excreted in the urine. However, the effects of renal or hepatic failure on the pharmacokinetics of hydralazine are still not exactly known. Caution is needed in cases of renal and hepatic failure.
  - Hydralazine can increase the bioavailability of drugs that undergo significant first-pass metabolism (e.g. lidocaine, morphine, propranolol).

What dose?

- Hydralazine: starting dose 37.5 mg three-four times daily, target dose: 75 mg three-four times daily (in case of low blood pressure the starting dose may be lower, as low as 12.5 mg three times daily)
- Isosorbide dinitrate: starting dose 20 mg three-four times daily, target dose: 40 mg three-four times daily (in case of low blood pressure the starting dose may be lower, as low as 20 mg o.d. or b.i.d.)

Where and when?

- In the community in stable patients
- In hospital in patients hospitalized with worsening heart failure
  - after relieving fluid retention
  - the Hy+ISDN combination may be initiated with caution before achieving euvolaemia in selected patients who are intolerant to ACEi and ARB and who are intolerant to BB due to unstable heart failure.

How to use?

- Start with a low dose
- Dose should be increased at not less than 4 weeks in the community. More rapid dose up-titration may be performed in patients who are in hospital or who are otherwise closely monitored. If a non-fixed-dose combination is used, hydralazine and isosorbide dinitrate can be titrated separately
- Efforts should be made to reach the target dose or, if this fails, to reach the maximum tolerated dose
- Attention should be paid to blood pressure
- Patient education is particularly important in this treatment to increase adherence

Side effects and their frequencies:

- hypotension (symptomatic 5–6%)
- headaches (18–48%)
- dizziness/light-headedness (22–29%)
- fainting (2–3%)
- flushing of the face and neck (8–10%)
- gastrointestinal complaints (10–12%)
- rash (7–9%)
- arthralgia (15–17%)
- drug-induced lupus erythematosus (5%)

Problem solving:

- Asymptomatic hypotension
  - no treatment modification is usually required
- Symptomatic hypotension
  - Before reducing the dose of hydralazine and/or isosorbide dinitrate because of symptomatic hypotension, check whether the patient is taking any other non-disease-modifying blood-pressure-lowering agent (such as calcium-channel blockers) and reduce dose of this drug or stop, if possible
  - If the patient has no signs or symptoms of fluid retention, reduce the dose of diuretic or stop diuretic therapy

- If a patient tolerates ACEi/ARB, BB and MRA, dose-titration of these drugs should be preferred. Do not stop or decrease the dose of neurohumoral antagonists in order to introduce or increase the dose of hydralazine and/or isosorbide dinitrate

– Headache
  - Headaches are common but often improve with time
– Drug-induced lupus erythematosus (a rare side effect of hydralazine therapy which can arise months to years after introduction of the drug).
  - This is a reversible adverse reaction and resolves after discontinuation of treatment with drug

Advice to the patient:

– Explain the beneficial effects of treatment (improvement of symptoms, quality of life and exercise capacity, decrease in morbidity and mortality)
– Encourage patients to report adverse effects (i.e. symptomatic hypotension, dizziness/light-headedness, fainting, flushing of the face and neck, gastrointestinal complaints headache, rash, arthralgia)
– Alcohol and hot weather may increase dizziness/light headedness and fainting. Advise patients to avoid them, if possible.
– To prevent dizziness/light-headedness and fainting, advise patients to sit up or stand up slowly, especially in the morning, and to sit or lie down at the first sign of any of these side effects.

6 Summary

Despite the current lack of use of the Hy+ISDN combination, it can be a very effective element in HFrEF therapy when used in accordance with guidelines. Appropriate use of direct vasodilators can contribute to reducing the symptoms, improving the quality of life, and reducing the morbidity and mortality of self-identified African American patients who receive optimal neurohumoral antagonist therapy. In a well-selected HFrEF population under close control, the direct vasodilator combination may be used in patients of other races who are symptomatic despite optimal pharmacological and device therapy.

The Hy+ISDN combination can also play an important role in treating patients who cannot receive either ACEi or ARB due to intolerance or contraindication. This is partly because it can reproduce the balance vasodilator properties, preload and afterload decreasing effects of ACEi and ARB, despite the lack of a direct effect on the RAAS system. This property is also of relevance in treating patients who, despite ACEi and ARB intolerance, tolerate BB and MRA. Moreover, and perhaps even more importantly, Hy+ISDN can be successfully used to treat patients with advanced heart failure who, besides having ACEi- and ARB-intolerance, do not tolerate either BB or MRA. In this latter case, Hy+ISDN can be used not only as a therapeutic alternative to ACEi or ARB, but can help overcome ACEi- and ARB-intolerance, thereby facilitating the introduction of optimal neurohumoral antagonist therapy (ACEi/ARB/ARNI, BB, MRA) instead of digitalis and diuretic treatment.

Taking these factors into consideration, it is clear that the direct vasodilator combination Hy+ISDN is in many cases indispensable, and plays an important role in the treatment of HFrEF.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 47–65
DOI 10.1007/5584_2018_182
© Springer International Publishing AG 2018
Published online: 3 March 2018

The Art and Science of Using Diuretics in the Treatment of Heart Failure in Diverse Clinical Settings

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Abstract

It is important to understand the rationale for appropriate use of different diuretics, alone or in combination, in different heart failure patients, under diverse clinical settings. Clinicians and nurses engaged in heart failure care, must be familiar with different diuretics, their appropriate doses, methods of administration, monitoring of the responses, and the side-effects. Inappropriate use of diuretics, both under-treatment and overtreatment, and poor follow-up can lead to failures, and adverse outcomes. Adequate treatment of congestion, with rather aggressive use of diuretics, is necessary, even if that may worsen renal function temporarily in some patients. Diuretic treatment should later be titrated down, by early recognition of the euvolemic sate, which can be assessed by clinical examination, measurement of the natriuretic peptides, and when possible, echocardiographic estimation of the left ventricular filling pressure. You need to treat patients, who are truly resistant to the loop diuretics, by administering the diuretics as intravenous bolus injection followed by continuous infusion, and/or by sequential nephron blockade by adding the thiazide diuretics. You need to use the diuretics based on a sound understanding of the pathophysiology of the disease process, the pharmacokinetics and pharmacodynamics of the diuretics, even when strong evidences for your choices might be lacking. Some patients may benefit from injection of loop diuretics together with hypertonic saline, and others from injection of loop diuretics with albumin. Patient education, and regular follow up of the treatment of heart failure patients, in out-patient settings are important for reducing the rates of complications, and for reducing the needs for urgent hospitalizations.

Keywords

Albumin in heart failure · Bumetanide in heart failure · Diuretic algorithm in heart failure · Diuretic dose in heart failure · Diuretic infusion in heart failure · Diuretic resistance in heart failure · Diuretics in heart failure · Hypertonic saline in heart failure · Loop diuretics in heart failure · Sequential nephron blockade · Thiazides in heart failure · Torsemide in heart failure

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1 Introduction

Diuretics are used in the treatment of heart failure to reduce volume overload, the symptoms of congestion, and death from acute decompensation of heart failure. It is important to use diuretics appropriately and adequately: inadequate use of diuretics in acute decompensation of heart failure (ADHF) may lead to death, or will increase the risk for re-admission to the hospital, whereas overtreatment with diuretics will reduce tissue perfusion and impaired renal function. Treatment of chronic heart failure patients by loop diuretics reduces mortality, acute deterioration of heart failure, hospitalization, and improves symptoms and exercise capacity (Faris et al. 2012; Ponikowski et al. 2016).

It is important to assess the volume status of heart failure patients carefully to decide whether diuretic treatment is necessary, and once started, treatment with diuretics must be followed up regularly. Clinicians assess the right heart filling pressure, and the left heart filling pressure by integrating the following findings from the physical examination: increased jugular venous pressure, hepatojugular reflux, dependent edema, ascites, gallop heart sounds, and pulmonary rales. Accurate clinical assessment of right heart filling pressure and left heart filling pressure by physical examination is, however, difficult. In one study, trainee doctors in cardiovascular medicine accurately assessed, by physical examination, the right heart pressure in 67% of the cases, and the left heart pressure in 55% of the cases. The accuracy was higher for the experienced cardiologists (82% and 71% for the right heart pressure, and left heart pressure respectively) (From et al. 2011). The accuracy of assessment of the right heart pressure and the left heart pressure was not increased by including echocardiographic data or by knowing plasma natriuretic peptide level. It is, therefore, essential that doctors are taught and trained in physical examination skills during bedside teaching. The accuracy of the clinical assessment of the right and left heart filling pressures is better when the physicians are more experienced.

Heart failure patients with congestion must be treated by loop diuretics, given orally or through intravenous routes. Some heart failure patients will need infusion of loop diuretics, others may need loop diuretics in combination with other types of diuretics. It is necessary to be familiar with the basic pharmacokinetics and the pharmacodynamics of the commonly used diuretics, their dosage, and the rationale for combining different diuretics, when that is needed. In this review, I shall discuss the use of different diuretics for the treatment of chronic heart failure, and ADHF in different clinical settings, mainly from the perspective of a practicing clinician. For a better understanding of the issues involved, it is desirable that the readers read the whole review rather than only a few selected sections. In your day do day practice, you may also need to take into consideration the local traditions, and guidelines used in your hospital, and the updated guidelines from major societies.

2 The Parenteral Loop Diuretics

The most widely used intravenous loop diuretic is furosemide. When administered intravenously, the efficacy of the three loop diuretics furosemide, torsemide, and bumetanide, is the same, only the potency, and the duration of action are different. This means that you need to inject less mg of a diuretic that is more potent. Torsemide is more potent than furosemide, and bumetanide is more potent than torsemide. When given intravenously, 40 mg of furosemide is roughly equivalent to 10 mg of torsemide and 1 mg of bumetanide. When maximally effective, these loop diuretics cause excretion of 20% of the filtered sodium, which means that about 200–250 mmol of sodium is excreted in 3–4 l of urine in 3–4 h (Brater 2011).

Clinically, the natriuretic efficacy of a loop diuretic is more relevant than its potency. As alluded to earlier, the natriuretic efficacy, or the maximal natriuresis, as estimated from the upper plateau (the "ceiling") of the sigmoid-shaped

dose-response curve, is the same for the three loop diuretics. Once the ceiling of a single intravenous dose of a loop diuretic is reached, increasing the dose further, will cause more natriuresis, merely by prolonging the time during which the concentration of the diuretic in the plasma remains above the natriuretic threshold. High doses, above the nominal "ceiling" will increase the risk of the dose-related side effects of the diuretic. To induce further diuresis, it is preferable to inject the diuretic more frequently, (depending on the half-life, and duration of action of the diuretics), or give it as a continuous intravenous infusion after a bolus injection. In congestive heart failure, the elimination half-life of furosemide is 2.7 h, that of torsemide is 6 h, while that of bumetanide is only 1.3 h (Brater 1998).

The loop diuretics inhibit the Na^+-K^+-$2Cl^-$ cotransporter type 2 (NKCC2, product of the gene *SLC12A1*), which is located on the apical plasma membrane of the cells in the thick ascending limb of the loop of Henle. They also inhibit the Na^+-K^+-$2Cl^-$ cotransporter type 1 (NKCC1, product of the gene *SLC12A2*) expressed in many tissues. The NKCC1 of the inner ear may mediate the ototoxicity, and that of the vascular smooth muscle cells may mediate the direct vasodilation caused by intravenous injection of the loop diuretics.

Subcutaneous Administration of Furosemide: Furosemide has a pH of about 8.5–9, and for this reason it can cause skin reactions and discomfort when administered subcutaneously. More recently, a buffered furosemide preparation with pH 7.4 has been developed. Subcutaneous administration of this pH-neutral furosemide was as effective as intravenous furosemide in inducing natriuresis, urine-output, and weight loss in patients with ADHF (Gilotra et al. 2018). If larger studies confirm these findings, then subcutaneous furosemide can provide a new method of treating a selected group of heart failure patients at home. This may facilitate palliative treatment of heart failure.

3 Choice of the Oral Loop Diuretics

Most heart failure patients with symptoms and signs of congestion are treated by one of the three oral loop diuretics. The newer loop diuretics, torsemide and bumetanide have several theoretical and pharmacokinetic advantages over the commonly used furosemide. Oral absorption of furosemide is on the average ~ 50%. In contrast, the oral absorption of torsemide and bumetanide is about 80–100%, and the absorption is less variable compared to that of furosemide. In fact, oral absorption of furosemide is highly variable (from 10% to 100%) both from patient to patient, as well as in the same patient (Brater 2011; Murray et al. 1997). Absorption of the retard preparation of furosemide is even more variable, and it should not be used in the treatment of heart failure with congestion. In heart failure with congestion, the absorption of orally administered furosemide can be much slower because of the congestion of the intestinal walls, making it difficult for the plasma concentration of the drug to rise to the threshold for the induction of diuresis. In heart failure of NYHA class II or III the diuretic response to the loop diuretics is reduced by 1/3rd to 1/4th of the maximally effective dose (Brater 1998).

Note that in heart failure, absorption of the total amount of the orally ingested loop diuretics is not reduced (i.e. there is no malabsorption), but the absorption is delayed, especially during ADHF. After oral ingestion of a loop diuretic, it may take about 4 h (instead of normal about 1 h) for the concentration of the diuretic to reach the effective concentration at the luminal side of the nephron. For rapid action, as in the case of treatment of ADHF, inject the loop diuretic intravenously.

Another advantage of torsemide over furosemide, and bumetanide is its longer average duration of effect, which means that it may be enough to give it once per day. Because of the short half-life, furosemide, and bumetanide, when given once per day, or less frequently, can cause "post diuretic sodium retention", especially when

dietary salt intake is high. Such "rebound" reabsorption of sodium is less likely with torsemide, which is present in the tubular lumen for a longer period because of its longer half-life. Furosemide is mainly eliminated by the kidney, whereas torsamide and bumetanide are metabolized by the liver. In renal failure furosemide, but not torsamide or bumetanide can accumulate.

There is no good prospective randomized clinical trial that has studied the effects of torsemide as compared to furosemide. One study demonstrated that torsemide was better (compared to furosemide) in reducing the risk of readmission for heart failure (Murray et al. 2001). Another observational study found lower one-year mortality among patients treated with torsemide compared to those treated with furosemide (Cosin et al. 2002). However, torsemide (and bumetanide) are not available in many countries, and these drugs are more expensive. If the availability and the costs are not important considerations, some physicians would prefer to use torsemide instead of furosemide, for many heart failure patients. Most physicians, however, start with furosemide and switch to torsemide only when the effect of furosemide appears less satisfactory. An obvious alternative, in the latter situation, however, is just to increase the dose of furosemide, instead of switching to torsemide (or bumetadine).

4 Clinical Use of the Loop Diuretics

Understanding the mechanisms of actions of the loop diuretics is essential for their rational use in different clinical settings. As mentioned before, the loop diuretics block the NKCC2 located on the *luminal* surface of the cells of the thick ascending loop of Henle. The diuretics must reach the ultrafiltrate in the lumen of the nephron to exert their action. The concentration of the loop diuretics in the ultrafiltrate in the lumen of the nephron must reach a threshold level for blocking the NKCC2 for inducing diuresis. The loop diuretics are essentially *not* filtered through the glomerular membrane because they are >95% protein bound; instead they are actively secreted into the lumen of the proximal tubule through the organic anion transport 1 (OAT1, product of *SLC22A6* gene), organic anion transport 2 (OAT2, product of product of *SLC22A6* gene), and the multidrug-resistance associated protein 4 (product of the gene *ABCC4*). Nonsteroidal anti-inflammatory drugs, uric acid, and some uremic toxins can compete with the loop diuretics for transport through these transporters leading to resistance to the loop diuretics.

You need to identify the "threshold" dose of the loop diuretic that induces diuresis, when given as a single dose. The effect of a given dose of furosemide can be assessed clinically from the diuretic response, change in the bodyweight, and measurement of urine volume. Normal people are very sensitive to furosemide, but heart failure patients with congestions, and especially those with impaired renal function have higher thresholds.

Start furosemide at a dose of 20–40 mg orally once per day, and if necessary, titrate the dose up, based on the response. Maximal single oral dose of furosemide in patients with normal kidney function is usually 80 mg. In patients with impaired kidney function, the maximal single dose of furosemide can be as high as 240. (There are also 1 g tablets of furosemide). For people who need high dose, you can use 500 mg tablets. The maximal daily dose of furosemide in patients with impaired renal function is 600 mg, but some may need much higher dose, sometimes as high as 2000 mg, given in 4–6 divided doses per day.

If furosemide is not so effective, you can choose to increase the dose of furosemide or to change it to a more potent and better absorbed loop diuretic like torasemide. Start torasemide at a dose of 5–10 mg once in the morning. You can increase the dose up to 200 mg per day, based on the response. Maximal single dose of torsemide is 100 mg. Alternatively, you can use another more potent and well-absorbed loop diuretic bumetanide at a starting dose of 0.5–1 mg, and increase the dose, if necessary, up to 5 mg per day. Maximal daily dose of bumetanide is 10 mg. Because of its short duration of action, bumetanide should be given more frequently to avoid "post-diuretic sodium retention".

If you give short-acting loop diuretics like furosemide or bumetanide, once every other day, or even once per day, and if the patient's dietary salt intake remains high, then it is less likely to achieve negative sodium balance because of "post diuretic sodium retention".

5 Intermittent Injections Versus Continuous Intravenous Infusion of Loop Diuretics

It is common to give loop diuretics as intermittent intravenous injections, which result in variable concentrations of the diuretic in the lumen of the nephron. This approach works in the vast majority of the heart failure patients, but does not induce sufficient diuresis in some patients, especially in those with renal failure. If you first give a loop diuretic first as a bolus injection, followed by as a continuous intravenous infusion, that will maintain the concentration of the diuretics in the lumen of the nephron at an effective level during the infusion (Brater 2011). It is important that a loading dose of the loop diuretic is injected first before starting the continuous infusion. These patients must be treated in the hospital often in the intensive care unit. Continuous infusion is better than bolus injections in inducing diuresis and reducing the concentrations of the brain natriuretic peptides in the plasma (Ng and Yap 2018).

The intravenous loading doses of furosemide, bumetanide, and torsemide are 40 mg, 1 mg, and 20 mg respectively.

If creatinine clearance is >75 mL/min, then infuse furosemide, bumetanide, or torsemide at a rate of 10 mg, 0.5 mg, or 5 mg/h respectively.

If creatinine clearance is <25 mL/min, infuse furosemide first at a rate of 20 mg/h. Then, if necessary, give a second bolus dose of furosemide, and increase the infusion rate to 40 mg/h. For bumetanide the initial rate of infusion is 1 mg/h, which can be increased to 2 mg/h. For torsemide the initial rate of infusion is 10 mg/h, which can be increased to 20 mg/h.

If the creatinine clearance is 25–75 mL/min, infuse furosemide at a rate of 10 mg/h, and later on, if necessary, increase to 20 mg/h. For bumetanide, the initial rate is 0.5 mg/h, which can be increased later to 1 mg/h. Torsemide infusion can be started at a rate of 5 mg/h, and can later be increased to 10 mg/h.

Note that, in all cases, before changing to a higher infusion rate, you will need to inject a second loading dose of the respective diuretic.

6 Use of Diuretics in the Treatment of Acute Decompensated Heart Failure (ADHF)

It is essential to understand the limitations of diuretic treatment in ADHF; overreliance on the diuretic treatment alone may lead to fatal outcome. Rapid clinical assessment by an experienced physician is essential for the diagnosis of the cause of acute dyspnea, and for choosing the most appropriate treatment for an individual patient with ADHF. When available, point of care ultrasonography performed by an experienced person can give additional useful information than can be obtained by clinical examination alone (e.g. lung ultrasound can identify whether the patient has pulmonary edema, and ultrasound examination of the inferior vena cava can identify intravascular volume overload).

When patients present with acute pulmonary edema, hypoxemia, and particularly with hypercapnia, they will need rapid treatment by noninvasive ventilation (NIV), if treatment by supplemental oxygen does not relieve dyspnea, and does not correct hypoxia/hypercapnia. If they have contraindications to NIV, if they do not tolerate NIV, or do not improve with NIV (in about 30–120 min), then they should be intubated, and mechanically ventilated.

Patients who have flush pulmonary edema due to severe hypertension or renal artery stenosis, acute mitral- or aortic-regurgitation, will require afterload reduction by vasodilator therapy, for instance, by intravenous nitroglycerine. Patients with normal blood pressure and volume overload are more likely to benefit from intravenous loop diuretic therapy, but in case of poor response to

the diuretic therapy, they may need concomitant vasodilator therapy.

Many patients with ADHF have volume overload, while others have volume redistribution (Fallick et al. 2011). While diuretic therapy is more effective in those patients with volume overload, it can also reduce symptoms and improve oxygenation to some extent, even in those patients with volume redistribution. In most cases, initial therapy of ADHF patients with evidence of volume overload should include intravenous injection of a loop diuretic. It is important to administer intravenous furosemide early since the onset of diuresis may take up to 30 min (peak diuresis at 1–2 h). Some patients, for instance, those with end stage renal failure, or severe hypotension, are less likely to benefit from diuretics alone.

If the patient is not already on any diuretics, and if the kidney function is normal then give 20–40 mg furosemide intravenously as bolus. If there is no response inject double the dose i.e. 40–80 mg furosemide after 2 h. Two or more bolus injections per day of furosemide may be necessary. Usually 40–80 mg bolus injection of furosemide will be sufficient to induce adequate diuresis in patients who have nearly normal kidney function. Those patients, who have renal insufficiency or severe ADHF, will need higher bolus injections e.g. 160–200 mg of furosemide. When high doses of loop diuretics are necessary, it is better to give the diuretics as infusions (see below). This reduces risk of toxicity and ensures uniform concentration of the diuretics.

Initial doses of the loop diuretics for treating ADHF are often empirical, but it is useful to follow some method for the determination of the initial doses of the intravenous loop diuretics. For treating patients with ADHF, who are on chronic treatment with oral loop diuretics, the initial dose of the i.v. furosemide should be 2.5 times the patient's usual total daily oral maintenance dose, and this dose should be divided into two injections daily, as intravenous bolus injections. For instance, a patient is chronically on 40 mg oral furosemide daily, which is equivalent to 20 mg i.v. furosemide daily; give 2.5 times this dose i.e. $20 \times 2.5 = 50$ mg in two divided doses intravenously daily (total dose, in this case, 50 mg intravenous injection of furosemide daily). As mentioned before, if there is no response to the initial dose, then the dose may need to be doubled and repeated at 2 h intervals. In the DOSE (Diuretic Optimization Strategies Evaluation) trial, the patients in the "high dose strategy" group received a median dose of 773 mg furosemide in 3 days (Felker et al. 2011). Loop diuretic therapy using this "high dose strategy", causes significantly greater improvement of dyspnea, and greater fluid and weight loss (Felker et al. 2011). It has been shown that use of aggressive diuretic treatment in the emergency department can enable a faster transition to the oral diuretic therapy (Catlin et al. 2018). However, treatment according to the "high dose strategy" causes "worsening renal function" in significantly larger number of patients, but you should not worry about that since transient worsening of renal function during aggressive decongestion therapy does not alter prognosis negatively (Greene et al. 2013). Oral loop diuretics should be stopped at the time the patient is receiving intravenous loop diuretics, and should be restarted when congestion is sufficiently relieved, according to clinical assessment. Short-term changes in the hemoglobin concentration can be used as a surrogate marker for decongestion (van der Meer et al. 2013). In one study, oral loop diuretics were re-started after about 3 days of aggressive intravenous loop diuretic therapy (Catlin et al. 2018).

In addition to having a method for choosing the initial dose of the intravenous loop diuretic, it is also useful to have a preplanned algorithm for subsequent intravenous diuretic therapy. A convenient algorithm for this, especially in patients with worsening renal function, is to increase the dose of the bolus and the infusion rate of the diuretic, if necessary, in combination with a thiazide diuretic, in a stepwise fashion, guided by the daily urine output (Grodin et al. 2016a). The steps of this algorithm are as follows:

Step 1. Current oral dose of furosemide: ≤ 80 mg/day.
Suggested dose of intravenous furosemide:
Intravenous bolus: 40 mg
Infusion rate: 5 mg/h

Step 2. Current oral dose of furosemide: 81–160 mg/day.
Suggested dose of intravenous furosemide:
Intravenous bolus: 80 mg
Infusion rate: 10 mg/h
Oral dose of thiazide diuretic: Metolazone 5 mg once daily

Step 3. Current oral dose of furosemide: 161–240 mg/day.
Suggested dose of intravenous furosemide:
Intravenous bolus: 80 mg
Infusion rate: 20 mg/h
Oral dose of thiazide diuretic: Metolazone 5 mg twice daily

Step 4. Current oral dose of furosemide: > 240 mg/day.
Intravenous bolus: 80 mg
Infusion rate: 30 mg/h
Oral dose of thiazide diuretic: Metolazone 5 mg twice daily

Choose one of the four steps mentioned above based on the urine output assessed at the start, after 24 h, 48 h, 72 h, and 96 h as listed below:

At the start:
If the urine output is >5 L/day: reduce the current dose of diuretic
If the urine output is 3–5 L/day: continue current dose of diuretic
If the urine output is <3 L/day: Choose step 1, 2, 3, or 4 (as mentioned above) depending on the current oral dose of furosemide.
B. At 24 h:
If the urine output is >5 L/day: reduce the current dose of diuretic
If the urine output is 3–5 L/day: continue current dose of diuretic
If the urine output is <3 L/day: Advance to the next step: if you chose step 1 before, advance to step 2, and so on.
C. At 48 h:
If the urine output is >5 L/day: reduce the current dose of diuretic
If the urine output is 3–5 L/day: continue current dose of diuretic
If the urine output is <3 L/day: Advance to the next step: if you chose step 2 before, advance to step 3, and so on.
C. At 48 h:
If the urine output is >5 L/day: reduce the current dose of diuretic
If the urine output is 3–5 L/day: continue current dose of diuretic
If the urine output is <3 L/day: Advance to the next step: if you chose step 2 before, advance to step 3, and so on. If there is persistent volume overload consider adding levosimendan, or nitroglycerine
C. At 72 and 96 h:
If the urine output is >5 L/day: reduce the current dose of diuretic
If the urine output is 3–5 L/day: continue current dose of diuretic
If the urine output is <3 L/day: Advance to the next step: if you chose step 3 before, advance to step 4. If there is persistent volume overload, consider levosimendan or nitroglycerine, left-ventricular assist device, dialysis or ultrafiltration.

It has been reported that treatment of persisting congestion in ADHF by using the algorithm outlined above results in more fluid loss, and weight loss, compared to the standard diuretic therapy, without further impairment of the renal function (Grodin et al. 2016a).

Note that every patient is different. You need to choose the appropriate dose and regime for intravenous diuretic therapy for the individual patient based on different factors some of which are not mentioned above. For instance, you need to be cautious in using intravenous diuretics in patients who have aortic stenosis, and in some patients who have right ventricular dysfunction.

In right ventricular failure with normal afterload (as in acute right ventricular infarction), the preload should not be reduced excessively by excessive use of diuretics. Often right ventricular diastolic filling pressure of 8–12 mm Hg is optimal in right ventricular failure.

Use of Dopamine. Patients with ADHF and renal dysfunction may benefit from treatment with low dose dopamine (2 μg/kg/min) combined with loop diuretics. However, improved clinical outcomes were achieved only in the patients with HFrEF, and not in patients with HFpEF (Wan et al. 2016).

7 Use of Two Different Classes of Diuretics in the Treatment of Heart Failure

Loop Diuretic Plus a Mineralocorticoid Receptor Antagonist (MRA): Many patients with heart failure are already on treatment with a loop diuretic, and an MRA (spironolacton or eplerenone). If not already on an MRA, add a MRA to the treatment of heart failure patients, who qualify for treatment with a MRA, for improving survival (see the section "use of the mineralocorticoid receptor antagonists (MRA) in the treatment of heart failure"). In addition, it may be reasonable to add MRA to the treatment of heart failure patients, who are on loop diuretic, and who have low or low-normal plasma potassium. Combining a loop diuretic, and a MRA may have the effects of "sequential nephron blocking" (see below) since they block sodium reabsorption in two different parts of the nephron. For improving the survival of the eligible patients, spironolacton is used at a low dose (usually 12.5–25 mg/day). If the aim of adding a MRA to the loop diuretic therapy is to increase diuresis or to treat hypokalemia then you need to use spironolactone at a higher dose (up to 100 mg/day). However, high dose spironolactone (100 mg/day) to treat congestion in ADHF, and to overcome diuretic resistance does not improve clinical outcomes (Butler et al. 2017).

Loop Diuretic Plus a Thiazide Diuretic: Treat heart failure patients initially with only a loop diuretic (often in combination with a MRA), and if necessary, increase the dose of the loop diuretic successively to the maximal recommended dose. Over the time, the natriuretic response to a given dose of a loop diuretic gradually decreases. Some people call it the "breaking phenomenon". The mechanism of the "breaking phenomenon" include decrease of extracellular volume, activation of the renin-angiotensin-aldosterone system, as well as functional and structural "nephron remodeling". The advantage of the "breaking phenomenon" is that it provides an adaptive mechanism to protect from volume depletion during long term diuretic therapy. On the other hand the same mechanisms that lead to the "breaking phenomenon" can lead to "diuretic resistance" if the congestion persists.

If the loop diuretic alone fails to achieve decongestion you may need to add a thiazide diuretic on top of the loop diuretic therapy. In this scenario, the loop diuretic will block the reabsorption of sodium chloride in the thick ascending limb of the loop of Henle, and the thiazide diuretic will do the same in the distal segments of the nephron. This approach, which is called "sequential nephron blocking" can induce large diuresis, when resistance to the loop diuretics develops. As alluded to in the previous paragraph, one major mechanism of resistance to the loop diuretic is "nephron remodeling". While the loop diuretics inhibit sodium chloride reabsorption in the loop of Henle, these drugs, indirectly, stimulate sodium chloride reabsorption in the distal nephron. In fact, prolonged use of the loop diuretics leads to the hypertrophy of the distal convoluted tubule, the connecting tubule and the collecting duct. The thiazide diuretics inhibit the Na^+-Cl^- cotransporters (NCC, product of *SLC12A3* gene) located in these sites. Multiple signaling mechanisms, including increased delivery of sodium to the distal nephron, aldosterone, hypokalemia, metabolic alkalosis, circulating proteases filtered into the nephron, increase the activity of the thiazide-sensitive NCC by direct or indirect mechanisms.

Any of the thiazide diuretics can be used for sequential nephron blockade. For the treatment of ADHF patients in the hospital, you can use hydrochlorothiazide at doses of 25–50 mg twice daily, chlortaidone at a dose of 50 mg once daily or metolazon at a dose of 5 mg once (or twice) daily. It probably does not matter which thiazide diuretic you choose. Many use metolazon partly because it has a longer duration of action compared to hydrochlorothiazide. However, metolazone is poorly absorbed, has elimination half-life of 2 days which makes titration of its dose in acute situations difficult (Brater 2011). Metolazone is effective in patients with GFR < 20 ml/min, but this is not a special property of metolazon; other thiazide diuretics can be given in equivalent doses if metolazon is not available. The loop diuretic and the thiazide diuretics can be given at the same time; thiazide diuretics have longer duration of action compared to the loop diuretics. When given together the thiazide diuretics support continued diuresis after the diuresis induced by the shorter acting loop diuretics start to diminish. For outpatient use, the longer acting thiazide diuretics can be given 2–3 times weekly, rather than daily (for example metolazone 2.5 mg or other thiazide diuretic in equivalent doses 2–3 times weekly) (Jentzer et al. 2010).

Some clinicians prefer to combine a thiazide diuretic with a loop diuretic at an earlier stage instead of first trying loop diuretics at a maximal recommended dose. Others prefer not to do so, since combining a thiazide diuretic with a loop diuretic increases the risk of massive diuresis, and hypokalemia. Before starting long term treatment with a loop diuretic plus a thiazide diuretic, make sure that you have a plan for regular follow up to monitor the plasma sodium and potassium concentration.

If hypokalemia develops, it may be necessary to add a potassium-sparing diuretic that act on the distal tubule. The choices in this situation are spironolactone, triamterene, and ameloride. Spironolactone may not be an obvious choice because it is possible that the patient is already on low dose spironolactone (which is not effective in preventing hypokalemia when given in low dose). Moreover, it is difficult to titrate the dose of spironolactone. Tiamterene should not be used because it must be converted to the active drug in the liver. The best choice, in this situation, is ameloride which acts directly and is easy to titrate.

Loop Diuretic Plus Acetazolamide: The most well-known action of acetazolamide is inhibition of carbonic anhydrase, but it also inhibits or downregulates the Cl^-/HCO_3 exchanger plendrin, which is expressed in the distal nephron (Soleimani 2015). Acetazolamide by itself is a weak diuretic, but can cause profound diuresis when combined with a thiazide diuretic, or a loop diuretic. An occasional heart failure patient, who has severe metabolic alkalosis during treatment with a loop diuretic may benefit from addition of acetazolamide (Imiela and Budaj 2017).

8 Thiazide and Thiazide-like Diuretics

Thiazides are weak diuretics and you will not use thiazide diuretics alone for the treatment of vast majority of your heart failure patients. Thiazides and thiazide-like diuretics inhibit the NCC located in the distal convoluted tubules of the kidney. As mentioned before, in selected cases of heart failure patients, usually, those, who do not respond to maximal recommended doses of loop diuretics, you may need to add a thiazide diuretic to the treatment by a loop diuretic (see the section "Loop diuretic plus a thiazide diuretic"). Commonly used thiazide and thiazide-like diuretics are hydrochlorothiazide, bendroflumethiazide, chlorthalidone, metolazone, and indapamide. Equipotent doses of these are hydrochlorothiazide 25 mg, bendroflumethiazide 2.5 mg, chlorthalidone 12.5 mg, metolazone 2.5 mg, and indapamide 2.5 mg.

Usual initial dose of bendroflumethiazide is 2.5 mg and usual daily dose is 2.5–10 mg. Initial dose of hydrochlorothiazide is 25 mg and usual daily dose is 12.5–100 mg. Initial dose of metolazone is 2.5 mg and usual daily dose is 2.5–10 mg. Initial dose of indapamide is 2.5 mg and usual daily dose is 2.5–5 mg (Ponikowski et al. 2016).

The duration of action of bendroflumethiazide and metolazone is 12–24 h (up to 48 h), that of

hydrochlorotiazide is 6–12 h (up to 24 h), that of chlorthalidone is 24–72 h, and that of indapamide is 36 h (Roush et al. 2014). In renal failure, the duration of action of hydrochlorothiazide, bendroflumethiazide, and chlorthalidone can be dramatically prolonged.

9 Monitoring of Kidney Function in Heart Failure Patients During Treatment with Diuretics

It is essential to monitor kidney functions during treatment of heart failure patients with diuretics. For this, it is useful to measure both plasma urea and creatinine since the ratio between the two gives useful information. In SI units the normal range of plasma urea is 2.5–10.7 mmol/L, and that of plasma creatinine is 62–106 μmol/L. A urea: creatinine >100:1 suggests prerenal cause, 40–100:1 suggests normal or postrenal cause, and < 40:1 suggests renal cause. In some laboratories urea is measured as Blood Urea Nitrogen (BUN), which is expressed as mg/dl, and plasma creatinine is also expressed as mg/dl. In this system a BUN:creatinine of > 20:1 suggests prerenal cause, 10–20:1 suggests normal or postrenal cause, and < 10:1 suggests renal cause.

A marked increase of plasma urea with little or minimal increase of plasma creatinine (urea:creatinine > 100:1) during treatment with diuretics, indicates dehydration (during dehydration the passive absorption of urea increases). In such situation you may choose to reduce the dose of the diuretic, if the patient does not have acute pulmonary edema or acute symptoms of congestion. You may consider to reduce the dose of the ACE-I/ARB temporarily during the use of the diuretic, in some patients who have heart failure with preserved left ventricular ejection fraction (HFpEF).

On the other hand, you should continue treatment with the diuretic using the same dose or even a higher dose, if the patient has pulmonary edema or marked symptoms and signs of congestion. This will probably cause further rise of urea and creatinine, but you will need to continue the treatment with the diuretic. In fact, continued treatment with the diuretic under such situations may eventually reduce the plasma creatinine by reducing the central venous pressure, and thereby reducing the renal venous pressure, which when elevated, contributes to the reduction of the GFR.

It is important that you do not stop treatment with the diuretic because of excessive fear of impaired renal function or hypotension, as long as there are signs of volume overload. It has been demonstrated that continued treatment with diuretics, to reduce volume overload, even when the diuretic treatment impairs renal function, reduces mortality (Testani et al. 2010).

10 Follow Up of Heart Failure Patients Treated with Diuretics in Outpatient Units

It is very useful to have an outpatient unit dedicated to the follow up of the heart failure patients. In these units, trained nurses can follow up the patients through telephone contacts, and regular office visits. The nurse titrates the doses of not only the diuretics but also of other heart failure medicines. It is useful for nurses to have clear written instructions specifically designed for the follow up, and the nurses must be able to consult doctors experienced in the treatment of heart failure, whenever needed.

The nurses will give information to the patients about heart failure in general, and about the diuretic treatment in particular. Patients should receive written instructions about the use, monitoring of weight, and the side effects of the treatment by the diuretics. They should receive information about restriction of intake of fluids, and salt, and information about low salt diets. They will limit fluid intake to about 1.5–2 l per day. They should take the diuretics before breakfast or lunch so that the salts consumed during the meals can be excreted. Absorption of loop diuretics is better if taken on an empty stomach. They should not take the diuretics after 16:00 if they want to avoid nocturia. Patients will weigh themselves before breakfast, and dressing, after voiding every morning. They will contact the nurse if they have increased breathlessness,

swelling of the legs, or if the body weight increases more than 1 kg over 3 days. They should contact the nurse if they feel dizziness or lightheadedness, which may indicate excessive use of diuretics. In this regard measurement of blood pressure by the patients at home can be very helpful. They should contact the nurse if they have diarrhea or vomiting that persists for more than 2–3 days.

Start treatment by a loop diuretic, usually furosemide, at a low dose e. g. 20–40 mg once daily. After initiating a diuretic or increasing the dose, follow up the patient after 3 days (it can often be done through telephone contacts). Measure plasma sodium, potassium, creatinine, urea and eGFR prior to the office visits. During the office visit enquire about symptoms, examine for signs of congestions, dehydration, and hypovolemia; measure heart rate, blood pressure and bodyweight. Examine for jugular venous pressure, pulmonary rales, edema of the legs or sacrum. Ascertain the cause of fluid retention (excessive intake of fluid or salt, non-compliance, NSAID, atrial fibrillation, infection). Usually, treatment by a diuretic should reduce body weight at a rate of about 0.5 kg/day. If the rate of weight reduction is satisfactory then maintain the current dose of the diuretic; if the rate of weight reduction by furosemide 40 mg once daily, is less than expected, increase the dose of furosemide to 80 mg once daily. Increase furosemide doses by 40 mg increments. If the patient is on furosemide 80 mg once daily, and the rate of weight reduction is not satisfactory, then increase the dose to 80 mg + 40 mg + 0 mg daily, and later on, if necessary, to 80 mg + 80 mg + 0 mg. If you prefer to use torsemide or bumetanide remember that 40 mg oral furosemide is roughly equivalent to 10 mg torsemide, and 0.5 mg bumetanide. In fact, oral torsemide is preferable to furosemide because of its more reliable, near 100% absorption, and longer duration of action.

The nurse will consult with the heart failure specialist doctor if the patient's symptoms do not improve, if the patient doesn't attain dry weight, and if the patient appears to need higher doses of furosemide. The nurse will not combine a loop diuretic with a thiazide diuretic; this should be done in consultation with the heart failure specialist doctor keeping in mind that these patients will need frequent monitoring of plasma electrolytes.

Some of these patients cannot be treated in the outpatient settings. If the patient's symptoms are not improving despite furosemide in doses more than 80 mg twice daily, if the patient's body weight have increased excessively, if the patient has signs of severe decompensated heart failure, if the patient has edema in the legs reaching above the knees, if the patient's general condition is poor, or if the patient has multiple concurrent illnesses, it may be essential to admit the patient to the hospital. This decision must be based on consultation with the heart failure specialist doctor.

Avoid overtreatment by diuretics. Reduce the dose of the diuretic after the dry weight has been restored, to avoid dehydration and impaired renal function. The goal is to use the lowest possible dose of a diuretic that maintains the dry weight. In many stable chronic heart failure patients, it is possible to down-titrate the diuretics (Martens et al. 2018). Remember that treatment with diuretics must be individualized; in some patients diuretics can be stopped as cardiac function improves, while others will need a maintenance dose of the diuretic to maintain the dry weight. If the patient is on the maintenance dose of a diuretic, then reduce the dose only if there are signs of volume depletion e. g. weight loss more than 1 kg compared to the dry weight, symptomatic postural hypotension, or rise of plasma urea by more than 25%. If you reduce the dose of a diuretic, contact the patient after 48 h to assess the consequences of the dose reduction. Do not reduce the maintenance dose of a diuretic if the patient has signs of congestion like peripheral edema, and elevated jugular venous pressure, even if the patient has hypotension or an increase in the plasma urea. Such patients often need hospitalization and attention by heart failure specialist doctors.

Many problems can arise during the treatment with diuretics, and the problems need to be handled promptly. In case of hypotensive symptoms, you can temporarily withhold 1–3 doses of the diuretic, reduce the dose of the diuretic by one

tablet, and reassess the blood pressure in 3 days. Patients may avoid hypotensive symptoms if they do not change positions abruptly. In patients who have heart failure with reduced ejection fraction (HFrEF), treatment with ACE-I/ARB should be continued during the treatment with diuretics. In some patients who have heart failure with preserved ejection fraction (HFpEF), the treatment with ACE-I/ARB may sometimes be reduced or withhold, temporarily, during the treatment with diuretics.

Hypokalemia can be treated by long acting potassium chloride tablets 750 mg three times daily for 3 days, and perhaps by addition of spironolactone if there are indications to add MRA. Note that spironolactone, used at a low dose, for improving survival in heart failure, does not act as a good potassium sparing agent. It is also not easy to titrate spironolactone for treating hypokalemia. If a potassium-sparing diuretic is desired, and if there is no indication for adding an MRA, then it is better to try amiloride.

Hyponatremia may be treated by reducing the intake of fluid. Do not reduce the dose of the diuretic for treating hyponatremia, if the patient needs diuretic for the treatment of congestion. If the response to the diuretic is inadequate make sure that the patient is not drinking too much fluid, consider increasing the dose of the diuretic, consider giving diuretic in 2–3 divided doses, instruct patients to take the diuretic in empty stomach, and consider changing to torsemide, or bumetanide, which are better absorbed. In case of impaired renal function during treatment by the diuretics, check for signs of dehydration, eliminate the nephrotoxic drugs like NSAID, and perhaps in patients with HFpEF, consider reducing the dose of ACE-I/ARB.

Metabolic alkalosis can often develop in patients treated with diuretics, especially when patients also have hypokalemia. This is due to reduced effective arterial blood volume leading to increased secretion of renin, angiotensin II, and aldosterone. A reduction in the glomerular filtration rate reduces the filtered load of bicarbonate. Angiotensin II increases Na^+-H^+ exchange and increased HCO_3^- absorption in the proximal tubule due to increased H^+ in the lumen. Aldosterone increases H^+ secretion in the distal tubule which generates new HCO_3^-, which is reabsorbed together with Na^+. Moreover, Cl^- depletion causes failure of pendrin a Cl^--HCO_3^- exchanger. Hypokalemia causes metabolic alkalosis also by shifting hydrogen ions from the plasma to the intracellular compartment in exchange for potassium. All these processes aggravate metabolic alkalosis. Metabolic alkalosis is often corrected by administering potassium chloride or potassium sparing diuretics. In rare cases, severe metabolic alkalosis, may need to be treated by acetazolamide given at a dose of 250–500 mg twice daily.

Diuretic treatment must be titrated down once the euvolemic state has been reached. Early recognition of the euvolemic state is necessary for avoiding excessive use of diuretics with risks for worsening of the renal function. Clinical examination alone is often not enough for early identification of the euvolemic state. Serial measurement of the B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) can be helpful for early identification of the euvolemic state. For each patient it is possible to identify a "dry" natriuretic peptide level, which corresponds to clinical stability, and lack of volume overload. The aim of the diuretic treatment should be to reduce the concentration of the natriuretic peptide level to as close as possible to the "dry" level. Combining clinical examination, measurement of the natriuretic peptides, and when possible, Doppler echocardiographic biomarkers of left ventricular filling pressure, can help optimal use of the loop diuretics, and optimization of heart failure care in outpatient settings (Dini et al. 2017).

Treatment by Intravenous Diuretics in the Outpatient Unit: A cost-effective method for treating patients with intravenous diuretic could be to treat the patients, for short period, in the outpatient unit, instead of admitting them to the hospital. This approach is suitable for patients who have modest volume overload. Buckley et al. combined bolus injection of loop diuretics with continuous infusion over 3 h in an outpatient unit

(Buckley et al. 2016). They used a standardized algorithm for choosing the dose of the bolus injection of the diuretic from the patient's home oral diuretic dose. For instance, people who were on 80 mg oral furosemide received 40 mg i.v. furosemide as bolus followed by continuous infusion. Those who were on more than 160 mg oral furosemide received 200 mg. i.v. furosemide as bolus followed by continuous infusion. If this group of patients did not have adequate urine output by 90 min, they received a second bolus injection of 200 mg furosemide followed by infusion. In addition to the i. v. bolus injection of furosemide, all the patients received continuous intravenous infusion of furosemide at a rate of 20 mg/h for 3 h (total 60 mg infused over 3 h). Patients who were on 300 mg oral furosemide received also pretreatment by a thiazide diuretic (metolazone 1.25–10 mg, or hydrochlorothiazide 12.5–50 mg). This treatment resulted in a median urine output pf about 1 l and a median weight loss of 1 kg in 3 h (Buckley et al. 2016).

11 Monitoring of Plasma Sodium and Potassium Concentration in Heart Failure Patients during Treatment with Diuretics

After starting treatment with a loop diuretic, the maximum natriuresis (and diuresis) occurs often with the first dose. Subsequent doses of the diuretics also cause large diuresis if the patient is still in a state of volume overload. Later on, as the volume status improves, the sodium retaining mechanisms are activated, and the effects of the loop diuretic are diminished (this is sometimes called "diuretic breaking").

After starting the treatment with, or after increasing the dose of a loop diuretic, it takes, on the average about 2–3 weeks to reach a steady state, when the intake of sodium and potassium is equal to the excretion of sodium and potassium. Once the steady state is reached, continued treatment with the same dose of the loop diuretic will maintain the weight loss that has been achieved. Thus, plasma potassium and sodium concentrations should be measured frequently during the first 2–3 weeks. After 2–3 weeks, there is no need to measure the plasma sodium and potassium routinely. However, if the dose of the loop diuretic is increased, if a new diuretic is added, or if there is increased volume overload, then you need to check the concentrations of plasma sodium and potassium again.

The kaliuretic effect of the loop diuretic lasts longer than the natriuretic effect. Some patients will need oral potassium tablet supplements during this period. Hypokalemia is less common when only loop diuretic is used, but, it is more common when a thiazide diuretic is combined with a loop diuretic. While loop diuretics induce hypokalemia and hyponatremia usually during the first 2–3 weeks, the thiazide diuretics can induce hyponatremia and hypokalemia at any time, ever after several months or years after starting the therapy (Barber et al. 2015). Thus, if a thiazide diuretic is used, plasma concentration of potassium and sodium should be measured regularly during the treatment by the drug.

Most patients with heart failure are treated with loop diuretics. If the patient is already on a thiazide diuretic (for instance as part of the treatment for hypertension) at the time when you start treatment with a loop diuretic, then it is better to stop the thiazide diuretic. Combine thiazide diuretics with loop diuretics, usually, when the loop diuretics given in maximal recommended doses do not work satisfactorily. As mentioned before, these patients are at high risk for developing hypokalemia, and hyponatremia, at any time after starting the treatment, and they must be followed up by measurement of plasma potassium and sodium frequently.

In heart failure, hypokalemia caused by the loop diuretics and the thiazide diuretics increases overall mortality, cardiovascular deaths, and deaths due to cardiac arrhythmia (Cooper et al. 1999). The risk for hypokalemia is less in patients who receive mineralocorticoid receptor antagonists (MRA), either alone, or in combination with the potassium-losing diuretics. However, these latter group of patients have higher risk of developing hyperkalemia. About 2–5% of patients develop severe hyperkalemia (plasma potassium

concentration > 6 mmol/I) during the treatment with MRAs. For this reason, plasma potassium concentration should be measured 1 week after starting the treatment with the MRA, 1 month later, when the dose of the drug is increased, and when an worsening of the electrolyte status is suspected (for instance, in case of vomiting, diarrhea, worsening heart failure or renal failure). During recent years, the use of MRA in heart failure has increased, and this has led to an increase in the rate of hospital admission due to hyperkalemia, and even deaths from hyperkalemia, in some countries (Juurlink et al. 2004). Heart failure patients who are on MRA must be followed up by frequent monitoring of plasma potassium concentration, but in practice, it turns out that this is often not done (Shah et al. 2005).

If hyperkalemia develops, check if the patient is on NSAID, potassium-containing salt-substitutes, or any herbal preparations, which should be discontinued. Advise the patients to avoid potassium-rich foods. In some cases it will be appropriate to add a loop diuretic that can increase kaliuresis. If the patient has metabolic acidosis, you can give sodium bicarbonate, which will reduce plasma potassium concentration. If the plasma potassium concentration still remains above > 5.5 mmol/l, then you need to reduce the dose of, or discontinue the MRA, and in some cases even ACE-I or ARB, temporarily or permanently.

12 Use of the Mineralocorticoid Receptor Antagonists (MRA) in the Treatment of Heart Failure

In heart failure, the MRAs (spironolactone and eplerenone) are not used primarily as diuretics. The doses of MRAs used in the treatment of heart failure are usually 12.5–50 mg per day. At such low doses MRAs do not have much diuretic action although they reduce potassium excretion to some extent, and thereby reduce the risk of hypokalemia. (For comparison, in the treatment of ascites due to cirrhosis of liver, MRAs are used in doses as high as 200–400 mg per day for inducing diuresis). The pharmacokinetics of spironolactone is complicated because it is converted to many active metabolites. Note also that high dose of spironolactone (e.g. 100 mg/day), which is a diuretic dose, does not improve congestion or symptoms in ADHF (Butler et al. 2017).

MRAs reduce mortality in heart failure partly by reducing the risk of hypokalemia, and consequent cardiac arrhythmias, but mainly by blocking the direct action of aldosterone on the heart. Before starting treatment with MRAs you need to make sure that the patient can be frequently monitored for changes in the plasma potassium and creatinine concentration. Do not start MRAs in patient whose plasma potassium concentration is $\geq$5 mmol/L, and the estimated glomerular filtration rate is $\leq$30 ml/min per 1.73 m^2. The indications for treatment with MRAs in heart failure are based on several randomized clinical trials. Give MRAs to: 1. patients who have symptomatic heart failure and LVEF <35%; 2. to patients after STEMI and with LVEF<40% and symptomatic heart failure or diabetes mellitus. 3. In the treatment of HFpEF the effect of spironolactone is less clear. Post-hoc analysis of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study suggests that spironolactone reduces hospitalization and cardiovascular death in HFpEF, but only in "the Americas".

Start treatment with spironolactone 12.5 mg or 25 mg daily, and after 4 weeks double the dose. Endocrine side effects occur in about 10% of patients treated with spironolactone. If endocrine side effects occur then switch to eplerenone starting with 25 mg daily, and then switching after 4 weeks to 50 mg daily. If the eGFR is 30–49 ml/min/1.73 m2 then start spironolactone at a dose of 12.5 mg daily or every other day and double the dose after 4 weeks. If you want to switch to eplerenone because of endocrine side effects, start treating with 25 mg every other day, and then double the dose to 25 mg daily after 4 weeks.

13 Use of the Vasopresin Receptor Antagonists (VRA) in the Treatment of Heart Failure

VRAs increase excretion of electrolyte-free water (aquaresis), and should theoretically be useful in the treatment of hospitalized heart failure patients with congestion, and severe hyponatremia (P-Na <120 mmol/l) despite water restriction. Recent studies, however, have shown that tolvaptan, a VRA, does not induce clinical improvement despite greater weight- and fluid-loss (Felker et al. 2017; Konstam et al. 2017). Unlike MRAs, VRAs do not reduce mortality. The prohibitive costs of VRAs, risk for hepatotoxicity, risks for overcorrection of hyponatremia, are additional reasons for extremely low use of VRAs in clinical practice in the treatment of heart failure.

14 Diuretic Treatment of Heart-Failure Patients with Hyponatremia

About 20% of patients hospitalized for heart failure have hyponatremia. In most cases hyponatremia in heart failure is not primarily due to diuretic treatment *per se* rather due to multiple other factors related to heart failure. These factors include increased secretion of ADH due to low cardiac output, increased thirst due to high angiotensin II, reduced ability of the kidney to excrete free water due to reduced renal perfusion, and reduced urine flow through the distal segment of the nephron. In some cases hyponatremia is due to diuretics especially when a thiazide diuretic is combined with a loop diuretic. In heart failure, even mild hyponatremia is associated with worse prognosis. In one study, patients who had serum sodium 132–135 mmol/l had significant increase in in-hospital, and 30 day mortality (Klein et al. 2005). Heart-failure patients who have serum sodium <125 mmol/l, due to heart failure, often have "end-stage" heart failure.

It is important to determine whether hyponatremia is mainly depletional or dilutional. This can be done by clinical assessment, and by assessment of the relevant laboratory parameters. For instance, if a patient with hyponatremia is on oral furosemide 160 mg twice daily, and does not have any obvious signs of congestion, then his hyponatremia could probably be depletional. Intravenous infusion of isotonic saline may be sufficient to treat depletional hyponatremia. Severe depletional hyponatremia (serum sodium < 125), however, should be treated by slow infusion of hypertonic (3%) saline making sure that serum sodium concentration does not increase at a rate faster than 10 mmol/l per 24 h (better aim for 6 mmol/l per 24 h). During treatment, serum sodium must be measured frequently. At the same time potassium and magnesium stores should also be replenished (Verbrugge et al. 2015).

On the other hand, dilutional hyponatremia in heart failure is more difficult to treat. If hyponatremia is severe (<120 mmol/l), or if there are symptoms attributable to hyponatremia, then it should be treated by fluid restrictions (< 1000 ml/day). ACE-I/ARB should be continued. If the patient is on a thiazide diuretic combined with a loop diuretic, then the thiazide diuretic should be stopped. The loop diuretic should not be stopped especially if the patient has congestion. The loop diuretics can indirectly promote free water excretion by reducing the concentration gradient in the renal medulla; this reduces water reabsorption in the collecting duct. Some patients with hyponatremia and persistent congestion may benefit from infusion of small volume hypertonic saline combined with high dose furosemide (see the section "use of hypertonic saline infusion with high dose loop diuretic in the treatment of heart failure").

VRAs (e.g. tolvaplan) have a potential role in the treatment of severe hyponatremia in heart failure, when other measures fail. These drugs increase serum sodium, but they are rarely used because of prohibitive cost, risk for overcorrection, and potential for liver toxicity.

In one study, 32% of the heart failure patients with hyponatremia received no specific therapy, 55% was treated by fluid restriction, 6% by

isotonic saline, 3% by hypertonic saline, and 4% by tolvaplan (Dunlap et al. 2017). Most of these patients had hyponatremia at the time of discharge from the hospital. There is no evidence that treatment of hyponatremia in heart failure improves clinical outcome.

15 Diuretic Treatment of Heart-Failure Patients with Hypoalbuminemia

In hypoalbuminemia, the delivery of free loop diuretics to the luminal site of action is reduced. Loop diuretics are >95% protein bound. In hypoalbuminemia less loop diuretic binds to the albumin, and more diuretic diffuses into the tissue. Thus, less loop diuretic is secreted into the nephron. If the patient has albuminuria, then the secreted loop diuretic binds to the albumin in the lumen of the nephron, which reduces the free form of the loop diuretic at the site of the action.

In treatment of heart failure patients with hypoalbuminemia, the main option is not to infuse albumin rather to increase the dose of the diuretic so that sufficient loop diuretics bind to albumin, secreted into the nephron, and are available in free form at the site of the action. To achieve this, the dose of the loop diuretic should be 2–3 times higher than normal dose. If the patient, in addition to hypoalbuminemia, has decreased glomerular filtration rate, then you may need to increase the dose of the loop diuretic another 2–4 fold (Brater 2011). Thus, these patients may need huge dose of loop diuretics, which may need to be given in repeated doses. Another approach is to add a thiazide diuretic to the regime of the loop diuretic therapy (see the section "Loop diuretic plus a thiazide diuretic").

The benefits of using loop diuretics combined with albumin in hypoalbuminemia remains controversial. If the treatment approach mentioned in the preceding paragraph does not give result, and if the patient has severe hypoalbuminemia (e. g. <20 g/l), then you can try treatment with loop diuretic combined with albumin. If combination of loop diuretics with albumin induces more diuresis than loop diuretics alone, then you can repeat the treatment; otherwise do not repeat this expensive treatment.

There are different ways of combining the loop diuretics and albumin. You can premix a maximal dose of a loop diuretic with 25 g albumin, and infuse the mixture over about 30 min. Alternatively, you can first infuse 25–50 g of albumin, and after 30 min infuse the loop diuretics. Albumin expands intravascular volume within 30–60 min (Duffy et al. 2015).

Note that modest hypoalbuminemia in heart failure is not associated with short-term adverse clinical outcome in patients treated with diuretics (Grodin et al. 2016b).

16 Use of Hypertonic Saline Infusion with High Dose Loop Diuretic in the Treatment of Heart Failure

In some patients with refractory congestive heart failure, infusion of small-volume hypertonic saline, combined with high dose furosemide, improves weight loss, reduces length of hospitalization, improves mortality, and reduces re-hospitalization rate (Gandhi et al. 2014).

Investigators have used different protocols for combining furosemide with hypertonic saline. Some have used i.v. furosemide 125–1000 mg with 150 ml f 1.4–4.6% hypertonic saline, two times per day (Paterna et al. 2015; Licata et al. 2003). Others have used i.v. furosemide 250 mg plus 150 ml 3% hypertonic saline two times per day (Paterna et al. 2011). (If you add 80 mmol NaCl to 500 ml of normal saline, you get 3% hypertonic saline). Mix furosemide with 150 ml of 3% saline and infuse it over 30 min two times per day for 1–2 days (Paterna et al. 2011).

The mechanism by which hypertonic saline increases the effect of high dose furosemide is not fully clear. Hypertonic solution increases availability of furosemide in its intraluminal site of action (it shifts the dose response curve of furosemide at the top and to the left). Due to its osmotic effect, hypertonic saline mobilizes fluid from the interstitial space to the vascular

compartment. It is also possible that hypertonic saline alters the autoregulation of blood flow in the kidney resulting in an increase of blood flow to the superficial nephrons which has short loop of Henle (the salt-losing nephrons).

17 Resistance to the Loop Diuretics

When loop diuretics given in maximal recommended doses fail to relieve congestion, then it is said that there is resistance to the loop diuretics. There is however, no standardized operative definition of diuretic resistance. In clinical practice, it is important to monitor response to the diuretics by monitoring the daily weight changes. Some patients who apparently have resistance to the loop diuretics are probably not receiving maximal recommended doses of the diuretics. In other cases, apparent diuretic resistance could be due to poor compliance, unrestricted fluid/salt intake, or intake of NSAID. It has been shown that, in most cases, true diuretic resistance, is due to resistance at the tubular level, rather than due to reduced delivery of the diuretic to its luminal site of action (Ter Maaten et al. 2017). True diuretic resistance should be treated by continuous infusion of the loop diuretics and/or sequential nephron blockade by addition of a thiazide diuretic (see section on "loop diuretic plus a thiazide diuretic"). In some selected cases, for instance, in patients with acute pulmonary edema, respiratory failure, and oliguria, ultrafiltration should be tried, when maximal doses of the diuretics given in frequent doses fail to relieve the symptoms (Regolisti and Fiaccadori 2013; Costanzo et al. 2007).

18 Concluding Remarks

Treatment of chronic heart failure with congestion, and ADHF, in the hospitals or in the outpatient settings, needs careful considerations, for choosing the most appropriate regime of treatment, for an individual patient, depending on many factors. Treatment must be individualized, avoiding both under-treatment and overtreatment, over time. In some patients, aggressive diuretic therapy, even in the face of worsening renal function, can be necessary for decongestion. Patient education, regular follow-up, and monitoring through outpatient "heart-failure units" are important ingredients for success. Treatment of severe heart failure patients with congestion, who are resistant to the loop diuretics, can be challenging, but good results can be obtained by bolus injections followed by continuous infusion of the loop diuretics, and sequential nephron blockade, following a structured step-up approach.

Clearly, many large, prospective, clinical trials will be needed for understanding many of the unresolved issues; meanwhile navigating the diuretic treatment through different phases of the natural history of chronic heart failure, will remain an art based on experiences of the clinicians. It is important for the clinicians to familiarize themselves with the treatment protocols that others have tried in different clinical situations, and try those in their own practices, when necessary, even in the absence of strong evidence.

Acknowledgement Financial support was obtained from the Karolinska Institute, Stockholm, Sweden, and the Uppsala County Council, Uppsala University Hospital, Department of Emergency Care and Internal Medicine, Uppsala University, Sweden.

Conflicts of Interests The author declares that he has no conflicts of interest concerning the publication of this paper.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 67–87
DOI 10.1007/5584_2018_149
© Springer International Publishing AG 2018
Published online: 2 March 2018

Treatment of Heart Failure with Preserved Ejection Fraction

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a growing epidemiologic problem affecting more than half of the patients with heart failure (HF). HFpEF has a significant morbidity and mortality and so far no treatment has been clearly demonstrated to improve the outcomes in HFpEF, in contrast to the efficacy of treatment in heart failure with reduced ejection fraction (HFrEF).

The failure of proven beneficial drugs in HFrEF to influence the outcome of patients with HFpEF could be related to the heterogeneity of the disease, its various phenotypes and multifactorial pathophysiology, incompletely elucidated yet. The diagnosis of HFpEF could be demanding or even inaccurate. Moreover, the therapeutic strategies were influenced by different cut-offs used to define preserved ejection fraction (EF). From this perspective, the current guidelines have classified HFpEF by an EF $\geq$ 50%, together with a distinct entity, heart failure with mid-range ejection fraction (HFmrEF), defined by an EF ranging from 41–49%.

New therapies have been developed to interfere with the mediator pathways of HFpEF at the cellular and molecular level, including mineralocorticoid receptor antagonists, soluble guanylate cyclase stimulators, or angiotensin receptor-neprilysin inhibitors. A number of antidiabetic drugs, such as sodium/glucose cotransporter 2 inhibitors and dipeptidyl peptidase-4 inhibitors are promising options, being under research in large clinical trials. Until the results of ongoing trials shed light on these therapies, guidelines recommend empirical treatment for established HFpEF, and emphasize the crucial role of addressing cardiovascular comorbidities leading to HFpEF, in particular arterial hypertension.

Keywords

Clinical trials · Comorbidities · Heart failure · Preserved ejection fraction · Prognosis · Treatment

Heart failure with preserved ejection fraction (HFpEF) has emerged as a distinct form of heart failure along with the increased prevalence of the elderly population. In epidemiological studies there is less morbidity and mortality from HFpEF compared to heart failure with reduced ejection fraction (HFrEF), but the commonly associated cardiovascular and non-cardiovascular comorbidities have an unfavorable impact on its evolution (Chioncel et al. 2017). Therapies that have proven effective in HFrEF have not been shown to improve long-term prognosis in HFpEF, and data on potential therapies

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targeting the pathophysiologic pathways of HFpEF are still inconclusive, so the current guidelines do not contain any firm indication on the therapy of choice in patients with HFpEF.

1 Therapies Proven to Be Beneficial in Heart Failure with Reduced Ejection Fraction

1.1 Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Targeting the renin-angiotensin-aldosterone system (RAAS) activation by counteracting the deleterious effects of angiotensin II on cardiovascular system (hypertrophy, fibrosis, vasoconstriction and remodeling) using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), along with aldosterone blockade by mineralocorticoid receptors antagonists (MRAs), has been shown to improve the outcome in HFrEF. The evidence for RAAS blockade as a therapeutic target in HFpEF is less clear, since the treatment has not demonstrated similar benefits.

Small studies using ACEIs (quinapril and enalapril) or ARBs (losartan and valsartan) had inconsistent results on different end-points such as exercise tolerance, NYHA functional class, quality of life or hospitalization in HFpEF patients (Zi et al. 2003; Aronow and Kronzon 1993; Warner et al. 1999; Parthasarathy et al. 2009).

The three large randomized controlled trials (RCTs) using ACEIs (perindopril) and ARBs (candersartan and irbesartan) in HFpEF patients had as primary composite endpoint death or time to first hospitalization.

In the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial, the efficacy of perindopril 4 mg/day compared with placebo was assessed in 850 elderly patients (>70 years) with HFpEF, EF > 45% and evidence of diastolic dysfunction (Cleland et al. 2006). The study was neutral, without significant reduction in the primary endpoint, although a significant reduction in heart failure hospitalizations was observed after 1 year, but not for the entire study duration. The study was prematurely stopped and was underpowered due to lower than expected enrolment and event rate and a high proportion of discontinued treatment in the perindopril group, with 35% cross-over to open-label ACEI at the end of the study.

In the CHARM-Preserved arm of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program of trials, the efficacy of candesartan was evaluated on the composite endpoint of cardiovascular death and heart failure hospitalization in HFpEF patients. 3023 elderly patients with NYHA functional class II–IV, prior hospitalization for heart failure and EF > 40% were enrolled. At baseline, 19% of the patients were taking ACEI, 61% had NYHA functional class II, and the mean EF was 54%. The primary outcome was not significantly different between the candesartan group versus placebo, but candesartan had a modest benefit in reducing the hospitalizations for heart failure which was marginally statistically significant only after adjustment for small differences in baseline characteristics (unadjusted $p = 0.118$; adjusted $p = 0.051$) (Yusuf et al. 2003).

The second and largest RCTs trial assessing ARBs efficacy in HFpEF after CHARM-Preserved was The Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-Preserve) (Massie et al. 2008). 4128 patients ≥60 years, with NYHA class II–IV and EF > 45% were assigned to irbesartan (targeting the dose to 300 mg) or placebo. The main composite outcome of the study was all-cause death or cardiovascular hospitalization for heart failure, myocardial infarction, unstable angina, arrhythmia, or stroke. At the end of the study there were no significant differences in the irbesartan arm vs placebo for the main outcome and for the secondary outcomes, including death, cardiovascular hospitalizations or worsening heart failure. Of note, there was a high rate (34%) of irbesartan discontinuation by the end of the study, and a considerable number of the patients had concomitant use of multiple RAAS inhibitors (ACEI, spironolactone) and also beta-blocker during the study.

The different results between CHARM-Preserved and I-PRESERVE trials may rely on the differences in the baseline characteristics of patients. CHARM–Preserved enrolled younger patients, with less severe symptoms of heart failure, fewer women, much higher proportions of ischemic heart disease, lower baseline ACEI use and lower baseline EF (55% vs. 60%), contributing to the noted, minor differences in the results. Although CHARM–Preserved did not achieve its primary end point, the positive result on hospitalizations for heart failure leads to a class IIb indication, level of evidence B, for the ARBs to decrease hospitalizations for patients with HFpEF in the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al. 2013).

1.2 Mineralocorticoid Receptor Antagonists

Aldosterone, by activation of the vascular and cardiac mineralocorticoid receptors, induces fibrosis, hypertrophy and endothelial dysfunction contributing to the vascular and cardiac remodeling and increased left ventricular (LV) diastolic stiffness (Komajda and Lam 2014; Borlaug and Paulus 2011; Weber 1989, 2001; Weber and Brilla 1991; Brilla et al. 1993a; Chapman et al. 1990; Weber et al. 1992; Brilla et al. 1993b). MRAs might have promising effects in HFpEF by improving LV diastolic dysfunction, the major pathophysiologic mechanism of the disease. After the beneficial effects of aldosterone on LV diastolic function in several small studies the impact of aldosterone on LV diastolic dysfunction (assessed by echocardiography) and maximal exercise capacity was tested in Aldosterone receptor Blockade in Diastolic Heart Failure (Aldo-DHF) trial (Roongsritong et al. 2005; Mottram et al. 2004; Mak et al. 2009; Edelmann et al. 2013). Aldo-DHF included 422 ambulatory patients with HFpEF (EF > 50%), NYHA class II-III and peak O2 $\leq$ 25 mL/Kg/min. In patients treated with spironolactone, there was an improvement in LV diastolic dysfunction (E/E′ ratio modestly but significantly decreased compared to placebo group over 12 months along with decrease in LV mass and natriuretic peptides), but maximal exercise capacity, NYHA class or quality of life did not improve. The mild symptoms of patients with HFpEF randomized in the trial and the minimal effect of spironolactone on functional exercise capacity in HFrEF trials are some possible reasons for the neutral results of Aldo-DHF trial. Nevertheless, MRAs are strongly recommended (class I indication) in HFrEF and LV ejection fraction (LVEF) $\leq$35%, to reduce mortality and HF hospitalization (Pitt et al. 1999; Zannad et al. 2011).

In the large TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, the effects of spironolactone in elderly patients with HFpEF were evaluated on a composite outcome of cardiovascular mortality, aborted cardiac arrest, or hospitalization for heart failure (Pitt et al. 2014). TOPCAT trial included 3445 patients $\geq$50 years old, with HFpEF and EF $\geq$ 45%, the majority with symptomatic NYHA class II, with a mean follow-up of 3.3 years. At the end of the study, spironolactone did not significantly reduce the incidence of primary composite end-point compared with placebo. However, when each component was separately analyzed, spironolactone significantly reduced the risk of heart failure hospitalizations with 17% (12% vs. 14.2%, HR 0.83; 95% CI 0.69–0.99; $P = 0.04$). So, despite the neutral result on the main composite outcome, the morbidity in the elderly patients with HFpEF was reduced by spironolactone treatment.

The lack of positive results for the primary composite outcome of TOPCAT trial deserves some considerations. There were marked and unusual regional variation between Russia/Georgia (which contributed to 49% of the total enrollment) and North and South Americas (Americas). The post hoc analysis performed in order to clarify these regional differences, pointed out that the population enrolled in Russia/Georgia had a low risk profile, with a fourfold lower rates of the primary end-point than in Americas (Pfeffer et al. 2015). Also the rates of hospitalizaton for heart failure in the placebo-arm in Russia/Georgia were fivefold lower than in HFpEF patients enrolled in large ARBs trials

(CHARM- PRESERVED and I-PRESERVED) being quite similar with rates reported in some hypertension trials (ALLHAT, VALUE and LIFE, while in Americas the event rates were comparable to those in other HFpEF trials (Yusuf et al. 2003; Massie et al. 2008; ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group 2002; Julius et al. 2006; Dahlöf et al. 2002). Moreover, there was a considerably lower effect of spironolactone compared with placebo on potassium, creatinine and blood pressure in Russia/Georgia than in Americas and, in a sample from the active arm of this population, the spironolactone metabolite was nondetectable. These post hoc analyses, beside the significant limitations, showed the efficacy of spironolactone in HFpEF patients on primary outcome and on its two individual components, cardiovascular death and heart failure hospitalization, only in the Americas (HR = 0.83), but not in Russia/Georgia (HR = 1.10). The result of TOPCAT trial supported the class IIb recommendation in the recent 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure (Yancy et al. 2017a). The significant interaction between the TOPCAT recruitment strategy, based either on prior heart failure hospitalization, or natriuretic peptides level, and the efficacy of spironolactone treatment, emphasizes the need for diagnosis accuracy of HFpEF in future studies.

1.3 Beta-blockers

Beta-blocker (BB) therapy reduces mortality and morbidity in HFrEF patients, but their efficacy on the prognosis of patients with HFpEF remains unclear.

Betareceptor blockade has been proven to improve myocardial relaxation and diastolic function and to prolong diastole, promoting diastolic filling and improving myocardial perfusion. Patients with diastolic dysfunction and higher heart rates seem to benefit more from BB treatment by an improvement in early filling in particular. BB could reduce arrhythmias and sudden death in HFPEF patients, having similar effects as in HFrEF patients (Andersson et al. 2002; Wallhaus et al. 2001).

The treatment with carvedilol resulted in a significant improvement in E/A ratio, an echocardiographic marker of LV diastolic dysfunction, in 113 patients with diastolic heart failure enrolled in the double blind multi-center trial Swedish Doppler-echocardiographic study (SWEDIC) (Bergström et al. 2004). However, exercise capacity was not improved by nebivolol compared with placebo in 116 subjects with HFPEF from the trial "Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and LV function of patients with Diastolic Dysfunction (ELANDD)" (Conraads et al. 2012).

The effect of BB therapy on outcome in patients with HFpEF was evaluated in some small clinical studies. Carvedilol had no effect on mortality or hospitalizations neither in the SWEDIC trial, nor in the "Japanese Diastolic Heart Failure" (J-DHF) study on the primary endpoint of cardiovascular death or unplanned HF hospitalization (Yamamoto et al. 2013). The "Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure" (SENIORS) trial enrolled 2128 elderly patients with a history of heart failure or with an EF < 35% (Flather et al. 2005). Treatment with nebivolol was associated with a 14% reduction in the primary composite end-point of all-cause mortality or cardiovascular hospitalizations in elderly patients. However a small number of randomized patients had HFpEF (LVEF>35%), encompassing only one-third of the heart failure population with known EF.

In summary, due to the inconsistent data from these small randomized controlled trials, not adequately powered, considering BB treatment in HFPEF remains questionable.

The effects of BB therapy on outcome in patients with HFpEF were analysed in two recent metaanalysis. The impact of BB treatment on mortality and hospitalization was assessed in HFpEF patients with EF ≥ 40% in the first

metaanalysis comprising 21,206 patients from 12 clinical studies between 2005 to 2013 (Liu et al. 2014). BB treatment was associated with a lower risk of all-cause mortality, but did not reduce the risk of all-cause hospitalization or cardiovascular hospitalization.

In a recent meta-analysis of 25 RCTs from 1996 to 2016 including a number of 18,101 patients patients with HFpEF and EF ≥40%, BB therapy significantly reduces all-cause mortality (RR: 0.78, 95%CI 0.65 to 0.94, p = 0.008) compared with placebo (Zheng et al. 2017).

The prognosis of patients with HFPEF treated with BB was assessed from the Swedish Heart Failure Registry (Lund et al. 2014). In a propensity score-matched cohort for β-blocker use study including 19.083 patients with HFpEF, 4054 patients were treated with BB. The treatment was associated with 8% reduction in all-cause mortality, but did not have a significant effect on combined all-cause mortality or heart failure hospitalization.

In light of the results of these meta analyses and registry which demonstrated the beneficial effect of BB on mortality in HFpEF a prospective large randomized trial is needed in order to clarify the efficiency of BB treatment in HFpEF. According to current evidence, the treatment with BB is not recommended in HFpEF, but patients with HFpEF could benefit from BB use in uncontrolled arterial hypertension treated with other drugs or in atrial fibrillation for symptomatic improvement (Whelton et al. 2017; Kirchhof et al. 2016).

1.4 Ivabradine

Ivabradine, by blocking the "funny channel" ($I_{(f)}$) in the sino-atrial node, slows down the spontaneous depolarization slope of the pacemaker cells, thus reducing heart rate. Current guidelines recommend ivabradine for the treatment of stable, symptomatic patients HFrEF with heart rate > 70 bpm on maximally tolerated BB doses or in those who are BB intolerant, in order to reduce hospitalizations for heart failure (Yancy et al. 2017a; The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) 2016).

In HFpEF, ivabradine use might be beneficial by reducing heart rate, leading to prolonged diastolic filling time with improvement in stroke volume, reduced LV filling pressures and decreased wall stress, a stimulus for myocardial fibrosis (Kanwar et al. 2016).

After the promising results from experimental studies in a mouse model of HFpEF suggesting that ivabradine improves vascular stiffness, LV systolic and diastolic function, the clinical efficacy of ivabradine was investigated in EDIFY trial (Effect of ivabradine in patients with heart failure with preserved ejection fraction) (Becher et al. 2012; Komajda et al. 2017). It was a randomised placebo-controlled trial, in which 171 patients with heart failure NYHA class II–III, in sinus rhythm, with heart rate ≥ 70 bpm, NT-proBNP ≥220 ng/mL or BNP ≥ 80 pg/mL, and EF ≥45% were included, being randomized to ivabradine or placebo. Although in patients treated with ivabradine there was a significant reduction in heart rate compared with placebo, there were no significant improvements in diastolic function (assessed by changes in E/e′ ratio), exercise capacity (evaluated by six minute walk test) or NT-proBNP. The lack of positive effect of ivabradine could be explained by the presence of extensive myocardial fibrosis and increased LV stiffness, with severe diastolic restriction to filling and a very limited stroke volume reserve, not significantly influenced by the lengthening of the filling time through heart rate reduction (Komajda et al. 2017). The neutral results of the EDIFY trial does not support the use of ivabradine in HFpEF.

1.5 Digoxin

Digitalis glycosides have the longest history in the treatment of heart failure based on their positive inotropic effect. However, over the last decades, digoxin use has narrowed considerably, as more effective drugs, with fewer side effects have been developed. Digoxin currently has a IIbB class

indication in HFrEF in patients in sinus rhythm who remain symptomatic despite optimal treatment (The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) 2016). A potential benefit in HFpEF could be due to neurohormonal effect of digoxin (Massie and Abdalla 1998; Smith et al. 1984). Low dose digoxin improves baroreceptor sensitivity, thus increasing vagal tone and reducing sympatheticactivation (Gheorghiade and Ferguson 1991). Digoxin might also provide antifibrotic effects by interfering with aldosterone and by suppressing the RAAS (Sundaram et al. 2002; Torretti et al. 1972). Digoxin has positive inotropic effect at doses of 0.25 mg/day or higher, whilst at lower doses the neurohormonal effect is dominant (Gheorghiade et al. 2004). Hence, digoxin capacity to modulate the neurohormonal imbalance, major contributor to HFrEF and HFpEF progression, suggests its possible benefits in all patients with heart failure. Another mechanism recently explored is the improvement in early energy-dependent diastolic function of the myocardium, that might support digoxin use in HFpEF (Wang et al. 1990).

The usefulness of digoxin in diastolic heart failure was investigated in DIG (Digitalis Investigation Group) ancillary trial, carried out concomitantly with the primary DIG trial. The objective of DIG trial was to evaluate the effect of digoxin on heart failure hospitalization and death in patients with heart failure in sinus rhythm. Patients with LV ejection fraction $\leq 45\%$ ($n = 6800$) constituted the main study group, whilst patients with LV ejection fraction >45% ($n = 988$) were enrolled in the ancillary study, being randomized to digoxin at a median daily dose of 0.25 mg ($n = 492$) or placebo ($n = 496$). Digoxin had no effect on mortality and all-cause or cardiovascular hospitalizations. Patients treated with digoxin had a nonsignificant 18% lower risk of heart failure hospitalization or mortality, and a nonsignificant 21% reduction in hospitalization for heart failure ($p = 0.094$) (Digitalis Investigation Group 1996, 1997; Ahmed et al. 2006). The favorable effects of digoxin treatment in HFpEF might be due to its neurohormonal effects (Chirinos et al. 2005). However, there is a consensus on the lack of information about the effect of digoxin in patients with HFpEF that does not support its use in these patients (Massie and Abdalla 1998).

2 Treatment with Drugs Targeting Mediator Pathways of Heart Failure with Preserved Ejection Fraction

2.1 Proof of Concept Studies Targeting the Nitric Oxide – Cyclic Guanosine Monophosphate – Protein Kinase G Axis

The recently developed HFpEF paradigm focused on chronic microvascular inflammation which induced an unfavorable molecular cascade in the cardiomyocytes resulting in increased myocardial stiffness, hypertrophy and interstitial fibrosis leading to LV diastolic dysfunction (Paulus and Tschope 2013). The involved pathway is the decreased concentration and impairing signaling of cyclic guanosine monophosphate (cGMP) and reduced activity of protein kinase G (PKG) in the cardiomyocyte, which became therapeutic targets. This observation provides a compelling rationale to pharmacologically modulate this pathway in HFpEF patients. There are two types of guanylate cyclases (GC) enzymes, which convert the guanosine triphosphate to cGMP. The soluble guanylate cyclase (sGC) is functioning as a receptor for nitric oxide (NO) and the transmembrane-associated particulate guanylate cyclase serves as a receptor for natriuretic peptides. The reduced NO bioavailability is associated with decreased NO stimulation and/or the responsiveness of soluble guanylate cyclase. NO donors and nitrates and orally active soluble guanylate cyclase (sGC) stimulators have been developed. The cardiac up-regulation and overexpression of phosphodiesterase-5 (PDE5) with enhanced cGMP degradation represent another mechanism that can be prevented by PDE5 inhibition. The reduced synthesis of the transmembrane-associated particulate guanylate cyclase due to natriuretic peptide activation is a mechanism targeted by neprilysin inhibitors (Greene et al. 2013).

2.2 Exogenous Nitrates

Nitrates decrease the number of anginal attacks in ischemic heart disease and and symptoms in patients with HFrEF, by decreasing the pulmonary congestion and improving exercise tolerance. In HFpEF, nitrates increase peripheral venous capacitance, thus reducing ventricular preload and LV filling pressure and may improve exercise capacity. At the molecular level, exogenous nitrates or NO donors activate soluble guanylyl cyclase increasing cGMP synthesis with subsequent PKG activation, leading to vasodilation.

However, the Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction (NEAT-HFpEF) trial failed to demonstrate beneficial effects of isosorbide mononitrate on exercise tolerance in HFpEF patients with limited activity related to symptoms (dyspnea, fatigue, or chest pain) (Zakeri et al. 2015). Although nitrates may improve endothelial function, chronic therapy with long-acting nitrates can paradoxically increase oxidative stress and local endothelin activation, augmenting the endothelial dysfunction (Oelze et al. 2013). Based on NEAT-HFpEF trial, the routine use of nitrates in patients with HFpEF is ineffective and is not recommended in the 2017 update Guideline for the Management of Heart Failure, except for patients with HFpEF and coronary artery disease, for symptoms relief (Yancy et al. 2017a).

2.3 Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE5) inhibitors prevent the intracellular catabolism of cGMP by phosphodiesterases, upregulating cGMP activity and hence augmenting the vascular and myocardial effects of nitric oxide. Consequently, there is a decreased stiffness of titin, modulated through PKG, and improvement in LV diastolic function (Oelze et al. 2013; van Heerebeek et al. 2006; Kruger et al. 2009; Bishu et al. 2011).

In a small study, in 44 patients with HFpEF, EF $\geq$ 50%, pulmonary hypertension and recent onset dyspnea, PDE5 inhibitor sildenafil improved LV diastolic function, LV remodeling and reduces pulmonary hypertension compared with placebo after 12 months (Guazzi et al. 2011).

However, the beneficial effects of sildenafil were not confirmed in another trial, PDE5 inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) (Redfield et al. 2012). 216 patients with HFpEF, NYHA class II–IV, LVEF $\geq$50 and reduced exercise tolerance, were randomized to sildenafil at different doses or placebo. At baseline, the patients were on stable heart failure therapy and had elevated LV filling pressure and mild increase in pulmonary artery systolic pressure. After 24 weeks, there were no significant differences between the sildenafil and placebo group in the median change in peak VO_2, nor in exercise tolerance or in the LV diastolic function.

The neutral results of the RELAX trial may be explained by the enrollment of HFpEF patients without associated pulmonary hypertension or by the coexistence of cronothropic incompetence as a contributor to the exercise intolerance. Another explanation could be the limited efficacy of PDE5 inhibitors in preventing cGMP breakdown, when the dominant mechanism of low molecular level of cGMP was the deficient generation of cGMP.

Based on RELAX trial, PDE5 inhibitors are not recommended for the treatment of HFpEF in the 2017 update Guideline for the Management of Heart Failure.

2.4 Soluble Guanilate Cyclase Stimulators

In HFpEF, reactive oxygen species (OS) and endothelial dysfunction contribute to the reduction of NO bioavailability, with inadequate stimulation of soluble guanilate cyclase (sGC) and reduced generation of cGMP. Furthermore, OS induces a shift of native sGC to a dysfunctional form at the molecular level, unresponsive to endogenous and exogenous NO (Greene et al. 2013). Evidence shows that cGMP deficiency is rather due to diminished production rather than increased PDE5-mediated degradation in HFpEF.

The attempt to increase cGMP by PDE5 inhibition could be efficient if PDE5 synthesis was up-regulated, such as in pulmonary arterial hypertension (Redfield et al. 2013). The increase in NO bioavailability by nitrates, ACEIs or other molecules may not be sufficient to improve microvascular function in patients with heart failure (Cole et al. 2011). Direct small molecule sGC agonists appear particularly promising, as they might overcome these limitations.

Recently available, the oral treatment with direct sGC stimulators had encouraging results in patients with heart failure before hospital discharge or early post-hospitalization (Stasch et al. 2011; Gheorghiade et al. 2013). The SOluble guanylate Cyclase stimulatoR in heArT failurE Studies (SOCRATES) programme aimed to assess the effects of the novel once-daily oral sGC stimulator vericiguat (BAY 1021189) in patients with HFrEF or HFpEF stabilized after hospitalization or under intravenously diuretic therapy for worsening heart failure. SOCRATES programme was designed as two parallel phase II trials, SOCRATES-REDUCED in HFrEF and SOCRATES-PRESERVED in HFpEF. In SOCRATES-REDUCED trial there was a significant reduction in NTproBNP levels and a trend towards decreased hospitalizations for heart failure in vericiguat arm compared with placebo, a rationale for further Phase 3 trials (Pieske et al. 2014; Gheorghiade et al. 2015). SOCRATES-PRESERVED, a phase 2b dose-finding trial, aimed to evaluate the safety, tolerability, and pharmacodynamic effects of optimal doses of vericiguat in patients with HFpEF (LVEF $\geq$45%) (Pieske et al. 2014). The primary endpoints were changes in NT-proBNP levels and left atrial volume from baseline at 12 weeks. Patients (n = 477) were randomized to vericiguat (n = 384) or placebo (n = 93) within 4 weeks of hospitalization for heart failure (75%) or outpatient treatment with intravenous diuretics for heart failure (25%). Although there was no change in the NT-proBNP level and left atrial volume at 12 weeks in the active arm compared with placebo, patients treated with vericiguat had significant improvements in the quality of life (Pieske et al. 2017). Riociguat currently has no indications in patients with HFpEF, but given the encouraging results of SOCRATES-PRESERVED trial, further research is warranted.

2.5 Angiotensin II Receptor Blocker Neprilysin Inhibitors

Angiotensin II receptor blocker neprilysin inhibitor (ARNI) is a new therapeutic class of agents acting on the RAAS and the neutral endopeptidase system. LCZ696, the first drug in the class, is a combination of valsartan, an angiotensin AT1 receptor blocker, and sacubitril, a neprilysin inhibitor. LCZ696 acts both by suppressing the RAAS system, and by enhancing the protective effects of natriuretic peptide (NP). Sacubitril, by inhibiting neprilysin, the primary enzyme that degrades NP, increases the bioavailability of NP which exerts natriuretic, vasodilator and antiproliferative effects. After the beneficial results on morbi-mortality in the PARADIGM-HF trial, ARNI is strongly indicated (class 1 level of evidence) in patients with chronic symptomatic HFrEF in both European and American heart failure guidelines (Yancy et al. 2017a; The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology(ESC) 2016).

LCZ696, by its mechanism of action, could improve LV diastolic dysfunction, by reducing myocardial hypertrophy and fibrosis and consequently reducing LV diastolic stiffness, important pathophysiologic mechanisms of HFpEF. The efficacy of LCZ696 on NT–proBNP as a marker of LV wall stress (which is not a substrate for neprilysin) was assessed by the phase II trial "Prospective Comparison of ARNI with ARB on Examination of Heart Failure with Preserved Ejection Fraction" (PARAMOUNT) (Solomon et al. 2012). In 301 patients with HFpEF, NYHA class II-III, EF $\geq$45% and elevated NT-proBNP plasma levels, the efficacy and safety of LCZ696 from baseline to 12 weeks were assessed in comparison with valsartan. NT-proBNP was significantly lower at 12 weeks in the LCZ696 group compared with the valsartan group and the drug was well tolerated. Of note,

NYHA functional class and left atrial dimensions, marker of sustained elevations in LV filling pressures, were also significantly reduced in the LCZ696 group after 36 weeks.

2.6 Ranolazine

Ranolazine inhibits late inward sodium current (I_{Na}) in cardiac muscle, thus reducing intracellular calcium levels and therefore decreasing LV wall tension and oxygen requirement. Ranolazine also reduces LV end-diastolic pressure by the improvement in ventricular relaxation and increases the coronary blood flow (Noble and Noble 2006). Currently used as an antianginal agent, ranolazine was thought to provide favourable outcomes in HFpEF based on its effect on LV diastolic function through late sodium current inhibition and possibly through a direct effect on myofilament calcium sensitivity and myofilament cross-bridging (Lovelock et al. 2012).

RALI-DHF (The Ranolazine for the Treatment of Diastolic Heart Failure) trial was designed to evaluate the effect of ranolazine in patients with HFPEF. It was a small, prospective, single-center, randomized, double-blind, placebo-controlled trial, in which 20 patients with heart failure and LVEF $\geq$45% had been included. Patients received ranolazine or placebo in iv bolus followed by 24 h continuous infusion and then ranolazine 1 g twice daily or placebo. Although in patients treated with ranolazine there was an improvement in some hemodynamic parameters, there was no improvement in relaxation parameters (Jacobshagen et al. 2011; Maier et al. 2013).

3 Unsolved Issues Related to HFpEF Syndrome

In the past years, HFpEF became a recognized clinical entity with a steadily increasing prevalence and high morbidity and mortality. In contrast to HFrEF, in which the therapeutic management significantly improved patients' outcome, there is no effective therapy in HFpEF so far, since the drugs used in large clinical trials failed to prove beneficial effects. There are many unsolved issues in this heterogeneous HF syndrome with a variety of phenotypes.

HFpEF pathophysiology is incompletely elucidated. LV diastolic dysfunction, a consequence of myocardial stiffening and relaxation abnormalities, was considered a dominant and constant component. However, it has been demonstrated that HFpEF syndrome is a complex interaction between elevation of LV filling pressures and other concomitant cardiovascular patologies such as abnormal ventriculo-arterial coupling, chronotropic incompetence, intrinsic pulmonary vascular disease associated with pulmonary hypertension and, notably, subclinical systolic dysfunction despite preserved EF.

There are distinctive demographic characteristic of HFpEF patients in contrast with patients with HFrEF. The clinical profile of the HFpEF patient is an elderly, more often woman, with comorbid conditions, in particular arterial hypertension (with the prevalence of hypertension between 60% and 90%), but also with atrial fibrillation, and, less commonly, ischemic heart disease (Mant et al. 2009).

Non-cardiovascular comorbid conditions, such as obesity, diabetes, chronic kidney disease, anemia, chronic obstructive pulmonary disease or obstructive sleep apnea, are common, contributing to the progression of HFpEF and to the higher noncardiac hospitalization and mortality than in patients with HFrEF. In a new paradigm, these comorbidities induce a systemic proinflammatory state, responsible for structural and functional changes in the myocardium and vascular system of HFpEF patients. The low grade inflammation with increased oxidative stress, impaired NO bioavailability, and endothelial dysfunction appear to be the link between comorbidities and HFpEF progression (Paulus and Tschope 2013).

The negative result of major clinical trials testing different drugs classes proved to have favorable effects on outcome in HFrEF could have multiple explanations, relying on disease characteristics, patients selection or trial design.

A lower level of neurohormonal activation in HFpEF compared to HFrEF is suggestive for different pathway of cardiac remodeling, which are less responsive to neurohormonal inhibition with RAAS or sympathetic antagonists. Myocardial fibrosis and excessive extracellular matrix are major determinants of myocardial stiffness and diastolic dysfunction in HFpEF and remains important therapeutic targets in future clinical studies. The differences in the severity of the disease in patients with HFpEF enrolled in differents trials are another confounding factor, as some patients with severe disease could be less responsive to pharmacological treatment.

Another reason for the heterogenous results in different trials is the challenge to select the "true" HFpEF patient. The accurate diagnosis of HFpEF is difficult and relies mostly on the exclusion of other causes of the symptoms. In some trials, patients with non-cardiac dyspnea and with incident LV hypertrophy, but without true HFpEF were enrolled, leading to the negative results.

An important weakness of epidemiological studies and registries in HFpEF was the lack of consensus regarding the definition of preserved EF. While HFrEF or systolic heart failure is defined by an EF $\leq$ 40%, different cut-off of EF were applied for HFpEF definition in the clinical trials ($\geq$ 40% (CHARM) $\geq$ 45% (I-Preserved, PEP-HF, TOPCAT) or $\geq$50% (ALDO-DHF), while HFpEF was defined by an EF $\geq$50% in heart failure guidelines (Yancy et al. 2013).

Retrospective subgroup analyzes from large RCTs (CHARM, TOPCAT) and registry data revealed differences in etiology and in the response to treatment between patients with heart failure and EF between 41 and 49% compared to those with heart failure and EF $\geq$50%. For these reasons, in the recent heart failure guidelines, heart failure and EF between 41 and 49% is recognized as a new entity, heart failure with mid range EF (HFmrEF) or borderline HFpEF (Yancy et al. 2017a; The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology(ESC) 2016). In a recent prospective heart failure long-term European registry, the epidemiological data after 1 year of follow-up revealed that in comparison with HFrEF, HFpEF patients were older, hypertensive, with atrial fibrillation and were less likely to have an ischemic heart disease. The HFmrEF patients had more similarities with the HFrEF being younger, males and more often with ischemic heart failure (Chioncel et al. 2017).

The current heart failure Guidelines recommendations on HFpEF treatment emerged from RCTs, patients with HFmrEF being included in HFpEF patients. The future clinical trials will shed light on this new entity, better defining each heart failure category and as much as new data become available, further Guidelines recommendations would be presumably distinct for each heart failure phenotype.

4 Current Guidelines' Recommendations in Heart Failure with Preserved Ejection Fraction

In the absence of effective treatments to improve the prognosis of HFpEF patients, heart failure guidelines recommend therapies for symptomatic control of the disease (Table 1). Diuretics are by now the only recommended intervention firmly proven to alleviate symptoms in patients with HFpEF and congestion. Patients with stage C HFpEF and persistent arterial hypertension should be treated with ACEIs, ARBs, and BB after the management of volume overload with diuretics in order to reach lower blood pressure (BP) goals. The BP target in HFpEF is lower than 130/80 mmHg, as recommended by the recent American Heart Failure and High Blood Pressure guidelines (Whelton et al. 2017; Yancy et al. 2017b).

Atrial fibrillation, a common comorbidity in patients with HFpEF, should be treated in order to reduce the risk of thromboembolic events and to control either the heart rate, or the cardiac

Table 1 Therapies for stage C HFpEF in clinical trials and the recommendations of ACC/AHA/HFSA guideline for the management of heart failure

Drug	Trial Phase Year	Number of patients	LVEF cut-off	Primary end points	Results	ACC/AHA/HFSA Guideline for the Management of Heart Failure (Yancy et al. 2017b) Class of Recommendation and Level of Evidence for Stage C HFpEF
Therapies proven to be beneficial in HFrEF						
Beta-blockers						
Carvedilol	SWEDIC II 2004	113	≥ 45%	Echocardiographic assessment of LV diastolic function	Only E/A ratio significantly improved	**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF**
Carvedilol	J-DHF II 2013	245	>40%	CV death/unplanned heart failure hospitalization	No benefit	**IIaC**
Nebivolol	SENIORS III 2005	752 (35% of 2128 patients enrolled)	>35%	All-cause mortality or cardiovascular hospitalizations	Inconsistent data (small number of HFpEF patients)	
Nebivolol	ELANDD II 2012	116	>45%	exercise capacity (6 min walking test)	No benefit	
Renin-angiotensin-aldosterone axis inhibition						
Perindopril	PEP-CHF III 2006	850	>45%	All-cause mortality/heart failure hospitalization	No benefit (underpowered study)	**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF** **IIaC**
Candesartan	CHARM-Preserved II 2003	3023	>40%	CV death/heart failure hospitalization	No benefit Only modest benefit in reducing heart failure hospitalizations	**The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF**
Irbesartan	I-PRESERVE III 2008	4128	>45%	All-cause death/CV hospitalization	No benefit	**IIaC** **The use of ARBs might be considered to decrease hospitalization for patients with HFpEF** **IIbB**

(continued)

Table 1 (continued)

Drug	Trial Phase Year	Number of patients	LVEF cut-off	Primary end points	Results	ACC/AHA/HFSA Guideline for the Management of Heart Failure (Yancy et al. 2017b) Class of Recommendation and Level of Evidence for Stage C HFpEF
Spironolactone	Aldo-DHF IIb	422	≥50%	Echocardiographic assessment of LV diastolic function (E/e' ratio)/ maximal exercise capacity	No benefit in maximal exercise capacity	**In appropriately selected patients with HFpEF (with EF ≥ 45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate > 30 mL/min, creatinine < 2.5 mg/dL, potassium < 5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations.**
	2013				Only improvement in LV diastolic function	**IIb B-R**
Spironolactone	TOPCAT III 2013	3445	≥ 45%	CV death/heart failure hospitalization/aborted cardiac arrest	No benefit Only benefit in reducing HFpEF hospitalizations	
Other proven therapies						
Digoxin	DIG III 2006	988 in HFpEF subgroup	>45%	All-cause/heart failure/CV mortality	No benefit (trend towards reduction in heart failure hospitalization)	**Use not supported**
Ivabradine	EDIFY III 2017	171	≥45%	Echo-Doppler E/e' ratio/distance on 6-min walking test/plasma NT-proBNP	No benefit	**Use not supported**
Drugs targeting mediator pathways of heart failure with preserved ejection fraction						
Exogenous nitrates						
Isosorbide mononitrate	NEAT-HFpEF III 2015	110	≥50%	Effects on activity levels and exercise tolerance	No benefit	**No benefit*** **III B-R** ***Nitrates may provide symptomatic relief in patients with HFpEF and symptomatic CAD**

Phosphodiesterase-5 inhibitors						
Sildenafil	RELAX	216	≥50%	Oxygen consumption or exercise tolerance/diastolic function	No benefit	**No benefit**
	II					**III B-R**
	2012					
Soluble guanilate cyclase stimulators						
Vericiguat, riociguat	SOCRATES-PRESERVED	477	≥45%	Changes in NT-proBNP levels and left atrial volume	No benefit	**No indication**
	IIb				Significant improvements in quality of life	Further research warranted
	2017					
Ranolazine	RALI-DHF	20	≥45%	Hemodynamic and relaxation parameters after ranolazine infusion (cardiac catheterization)	No benefit	**No indication**
	II					
	2011					

HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, LVEF = left ventricular ejection fraction, CV = cardiovascular, SWEDIC = Swedish Doppler-echocardiographic study, J-DHF = Japanese Diastolic Heart Failure, SENIORS = Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure, ELANDD = Effects of Long-term Administration of Nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with Diastolic Dysfunction, PEP-CHF = perindopril in elderly people with chronic heart failure, ACE = angiotensin converting enzyme, CHARM = Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity, ARB = angiotensin receptor blockers, I-PRESERVE = Irbesartan in patients with heart failure and preserved ejection fraction,Aldo-DHF = Effect of spironolactone on diastolic function and exercise capacity in patients with heartfailurewith preserved ejectionfraction, TOPCAT = Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist, DIG = Digitalis Investigation Group, EDIFY = Effect of ivabradine in patients with heart failure with preserved ejection fraction, NEAT-HFpEF = Nitrate's Effect on Activity Tolerance in Heart Failure With Preserved Ejection Fraction, CAD = coronary artery disease, RELAX = PDE5 inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure, SOCRATES-PRESERVED = Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with PRESERVED EF, RALI-DHF = RAnoLazIne for the treatment of diastolic heart failure in patients with preserved ejection fraction: the RALI-DHF proof-of-concept study.

rhythm, for the improvement of heart failure symptoms (Kirchhof et al. 2016). The treatment of coronary artery disease should be managed according to guidelines, including coronary revascularization strategies, since myocardial ischemia has a detrimental role on outcome and symptoms in HFpEF patients. ARBs and, in selected patients, aldosterone receptor antagonists might be advised to reduce hospitalizations for heart failure. Non-cardiovascular comorbidities, such as obesity, diabetes, chronic kidney disease, anaemia, chronic obstructive pulmonary disease, sleep apnea, are commonly associated with HFpEF and the current guidelines strongly recommend their screening and their proper management (Yancy et al. 2017a; The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) 2016).

One of the major challenges is the prevention of HFpEF development. BP control in patients at increased risk for heart failure remains an essential goal. In a large RCT trial in patients at high cardiovascular risk, strict BP control (systolic BP <120 mmHg) was associated not only with a significantly lower incidence of heart failure, but also with a decrease in cardiovascular mortality, leading to a new approach for BP control (The SPRINT Research Group 2015). In the last American Heart Failure and High Blood Pressure guidelines, the recommended optimal BP target measured in the office setting is lower than 130/80 mmHg in patients with increased cardiovascular risk, which is less than the BP target proposed by the latest European Arterial Hypertension Guidelines (systolic BP < 140 mmHg) (Whelton et al. 2017; Yancy et al. 2017b; The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC) 2013). Attaining BP target in patients with increased CV risk, defined as age > 75 years, established vascular disease, chronic renal disease, or a Framingham Risk Score > 15% is a mandatory strategy to prevent heart failure.

5 Emerging Treatment Strategies and Ongoing Clinical Trials in Heart Failure with Preserved Ejection Fraction (Table 2)

5.1 Exercise Training

Some recent studies were designed to evaluate the efficacy of exercise training (ET) as a complementary therapeutic strategy in patients with HFpEF and their results support the beneficial effect of ET on exercise capacity and quality of life (Gary et al. 2010; Edelmann et al. 2011; Alves et al. 2012; Smart et al. 2012; Kitzman et al. 2013). In Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study, the exercise capacity measured as peak oxygen uptake (mL/kg/min) significantly increased in patients undergoing supervised physical training programme in addition to the usual care compaired with patients receiving usual care (Edelmann et al. 2011). The quality of life, estimated using Minnesota living with heart failure score, was also significantly improved in patients undergoing ET.

Although ET improved systolic function in patients with HFrEF it is still debatable if it might improve diastolic function in patients with HFpEF (Haykowsky et al. 2007). However, in clinical studies using more specific diastolic function parameters (E/E′ ratio), there was a significant improvement in diastolic function with ET. ET significantly improves E/e′, (marker of left ventricular filling pressures), and left atrial volume index (Edelmann et al. 2011).

Various mechanisms could explain the positive effect of ET in patients with HFpEF. ET has been shown to improve endothelial function, to reduce systemic inflammation and to diminish age-related stiffening of the heart and LV diastolic dysfunction (Hambrecht et al. 1998, 2000; Linke et al. 2001; Adamopoulos et al. 2001). ET also induces favorable changes within the peripheral arterial blood flow and in the function of metabolically active skeletal muscle leading to an increased oxygen uptake (Sullivan et al. 1988).

Table 2 Emerging therapies for HFpEF – ongoing clinical trials

Drug/intervention	Trial name	n	Primary outcomes	End
Exercise training				
Individually prescribed, supervised, combined endurance/strength training for 12 months (≥3x/week)	Exercise Training in Diastolic Heart Failure (**Ex-DHF**)	320	Composite outcome score: all cause mortality, cardiovascular hospitalizations, NYHA class, global self-assessment, exercise capacity and diastolic function.	?
Aldosterone Antagonists				
Spironolactone	Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction (**SPIRRIT**)	3500	Time to death from any cause [Time Frame: Collected at data base lock, 5 years after study start].	2021
			Information on Death from the Swedish Causes of death registry.	
Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI)				
Sacubitril/Valsartan; Valsartan	Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction (**PARAGON-HF**)	4822	Cumulative number of primary composite events of cardiovascular death and total (first and recurrent) HF hospitalizations. [Total follow up time (up to 57 months)].	2019
Sacubitril/Valsartan; Enalapril; Valsartan	A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (**PARALLAX**)	2200	Change from baseline in N-terminal pro-brain natriuretic peptide (NT-proBNP) after 12 weeks.	2019
			To demonstrate that LCZ696 is superior to individualized medical therapy for comorbidities in reducing NT-proBNP from baseline after 12 weeks of treatment in patients with HFpEF.	
Antidiabetic drugs with evidence- based cardiovascular outcomes improvement				
Empagliflozin (Sodium glucose co-transporter-2 (SGLT-2) inhibitor)	EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (**EMPEROR-Preserved**)	4126	Composite primary endpoint – Time to first event of adjudicated Cardiovascular death or adjudicated hospitalization for Heart Failure in patients with HFpEF [Time Frame: up to 38 months].	2020
Teneligliptin (Dipeptidyl peptidase-4 inhibitors (DPP-4i))	Teneligliptin on the Progressive Left Ventricular Diastolic Dysfunction With Type 2 Diabetes Mellitus Study (**TOPLEVEL**)	936	Change of the ratio of peak velocity of early transmitral diastolic filling by echocardiography (E) to early diastolic mitral annular velocity by tissue Doppler echocardiography (E/e') [Time Frame: Up to 2 years].	2019

Current guidelines recommend combined endurance/resistance training as a safe therapy to improve maximal exercise capacity, LV diastolic function, and quality of life for patients with HFpEF. In patients at high risk for HFpEF (sedentary, overweight or obese women with arterial hypertension), ET has been also proven effective in improving exercise tolerance (Church et al. 2007).

However, the long-term impact of ET on patient-related outcomes in HFpEF is still unclear, since none of the studies published so far have been designed to address hospitalizations and mortality in these patients.

Exercise training in Diastolic Heart Failure (Ex-DHF) trial was designed as the first multicenter RCT to evaluate the effects of physical training on clinical outcomes in patients with HFpEF (Edelmann et al. 2011). The primary objective of Ex-DHF trial is to establish whether a 12 month supervised ET program can improve a composite outcome score in HFpEF patients. The effect of supervised ET in addition to usual care compared to usual care alone on the primary end point (all cause mortality, cardiovascular hospitalizations, NYHA class, global self-assessment, exercise capacity and diastolic function) will be assessed in 320 patients with stable HFpEF. The ET effects on inflammatory, metabolic and collagen turnover biomarkers, as well as on cardiac and vascular function and ventriculo–arterial coupling will also be evaluated in Ex-DHF substudies.

5.2 Aldosterone Antagonist – Spironolactone

Occurring early in the evolution and present in variable degrees in all patients with HFpEF, myocardial and vascular fibrosis, a major contributor to the impairment of LV diastolic function, represents a meaningful therapeutic target. Collagen synthesis within the extracellular matrix, the major mechanism of fibrosis, is increased by RAAS activation (Borlaug and Paulus 2011). Aldosterone stimulates cardiac fibroblasts and also stimulates the expression of profibrotic molecules through inflammation and oxidative stress mediated mechanisms (Marney and Brown 2007). Mineralocorticoid receptor antagonism (MRA) seems reasonable for the improvement of LV diastolic function and data from clinical studies are promising supporting the hypothesis that MRAs may improve outcomes in HFpEF. Uncertainties in the past will probably be elucidated by ongoing trials and new anti-fibrotic therapies would bring important benefits in HFpEF.

The TOPCAT trial, although with neutral results, suggested that the effects of spironolactone varies according to LV EF, having greatest benefit at the lower end of the EF spectrum (Solomon et al. 2016). Based on this data, the "Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction" (SPIRRIT) trial was designed as a unique registry-randomized clinical trial including HFPEF patients from the Swedish Heart Failure Registry. The primary objective the trial was the effects of spironolactone on all-cause mortality in symptomatic HFpEF patients with EF > 40% and elevated elevated NTproBNP. The trial will include about 3500 patients during 5 years period and is projected to end by 2021.

5.3 Angiotensin II Receptor Blockerneprilysin Inhibitors

5.3.1 PARAGON – HF Trial

Sacubitril-valsartan (LCZ696), the first in the class of angiotensin receptor neprilysin inhibitors (the primary enzyme that degrades the natriuretic peptides with antriproliferative and natriuretic effects), significantly reduced the composite endpoint of cardiovascular death or heart failure hospitalization in HFrEF in PARADIGM-HF trial and is indicated in HFrEF patients who remain symptomatic as an alternative to ACEi/ARB therapy in the current heart failure guidelines (McMurray et al. 2014).

In PARAMOUNT trial, in patients with HFpEF there was a significant reduction in NT-proBNP at 12 weeks and significant improvement in left atrial size and NYHA class in patients randomized to sacubitril-valsartan compared to valsartan at 36 weeks (Solomon et al. 2012).

After the positive results of sacubitril-valsartan in these trials, the effect of sacubitril-valsartan compared to valsartan on morbidity and mortality

in HFpEF will be assessed in PARAGON-HF (Efficacy and Safety of LCZ696 Compared to Valsartan, on Morbidity and Mortality in Heart Failure Patients With Preserved Ejection Fraction).

5.3.2 PARALLAX – HF Trial

The mechanisms of action of sacubitril-valsartan (LCZ696) suggest that it may have an impact on the pathophysiology of HFpEF, in which excessive fibrosis and myocyte hypertrophy may lead to abnormal LV relaxation and filling, impaired diastolic distensibility and increased vascular stiffness, generating elevated cardiac filling pressures. The purpose of the PARALLAX-HF study is to prove the superiority of sacubitril-valsartan over individualized medical therapy for comorbidities in reducing NT-proBNP and improving heart failure symptoms and functional capacity in patients with HFpEF.

5.4 Antidiabetic Drugs

Heart failure is among the most worrisome complications of diabetes. On the other hand diabetes is a major comorbidity contributing to progression and prognostic in HFpEF. Treating diabetes with optimum metabolic control is an important target, especially in patients with HFpEF. Moreover, recent data also demonstrated the beneficial effect of some classes of antidiabetic drugs on HFpEF prognosis, explained by their mechanism of action interfering heart failure pathogenic pathways. These drugs are currently under investigation in large outcome trials.

5.5 Sodium Glucose Co-transporter-2 Inhibitors

5.5.1 EMPEROR – Preserved Trial

Empagliflozin belongs to glifozins class, being an inhibitor of the sodium glucose co-transporter-2 (SGLT-2), which is found almost exclusively in the proximal tubules in the kidneys. SGLT-2 accounts for about 90% of glucose reabsorption into the blood. Blocking SGLT-2 in patients with type 2 diabetes and high blood sugar levels reduces blood glucose by blocking glucose reabsorption in the kidney and thereby augmenting urinary glucose excretion. Inhibition of SGLT2 with empagliflozin increases excretion of salt (i.e. sodium) from the body and reduces intravascular volume. Excretion of sugar, salt and water after the initiation of treatment with empagliflozin may therefore contribute to the improvement in cardiovascular outcomes. The aim of the EMPEROR – Preserved study is to evaluate efficacy and safety of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HFpEF.

5.6 Dipeptidyl Peptidase-4 Inhibitors (DPP-4i)

5.6.1 TOPLEVEL Trial

Dipeptidyl peptidase-4 inhibitors (DPP-4i) have recently become widely used to treat type 2 diabetes mellitus. Animal studies report numerous pleiotropic effects of DPP-4i: cardioprotective effects on hypertension, HFrEF, HFpEF, myocardial infarction, and cardiac hypertrophy. Therefore, DPP-4i are expected to inhibit cardiovascular events in clinical trials, by preventing cardiomyocyte hypertrophy and perivascular fibrosis, and improving endothelial function (Yamamoto et al. 2017).

The TOPLEVEL clinical trial is designed to assess the LV diastolic function of long term treatment with teneligliptin in patients with type 2 diabetes mellitus by two arms: one with patients showing E/e′ by echocardiography less than 8, the other including patients with E/e′ higher than 8. The results of the study are expected by 2019.

In conclusion, HFpEF is a heterogeneous form of heart failure, incompletely defined, with multiple pathophysiological mechanisms, numerous phenotypic aspects and many unknowns. To date, no drug treatment has been shown to be effective in lowering the morbidity or mortality

of HFpEF. A deeper understanding of the mechanisms of the disease, which could become therapeutic targets, the elucidation of numerous uncertainties of the epidemiological and clinical studies, as well as the results of ongoing trials with various new classes of drugs could bring therapeutic benefits and improve the prognosis of this highly prevalent form of heart failure.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 89–108
DOI 10.1007/5584_2017_140
© Springer International Publishing AG 2018
Published online: 2 February 2018

Circulating Biomarkers in Heart Failure

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Abstract

Biological markers have served for diagnosis, risk stratification and guided therapy of heart failure (HF). Our knowledge regarding abilities of biomarkers to relate to several pathways of HF pathogenesis and reflect clinical worsening or improvement in the disease is steadily expanding. Although there are numerous clinical guidelines, which clearly diagnosis, prevention and evidence-based treatment of HF, a strategy regarding exclusion of HF, as well as risk stratification of HF, nature evolution of disease is not well established and requires more development. The aim of the chapter is to discuss a role of biomarker-based approaches for more accurate diagnosis, in-depth risk stratification and individual targeting in treatment of patients with HF.

Keywords

Heart failure · Biomarkers · Prediction · Stratification · Biomarker guided-therapy

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Abbreviations

ADM	adrenomedullin
ANP	atrial natriuretic peptide
ARNI	angiotensin receptor neprilysin inhibitors
BNP	brain natriuretic peptide
BRPs	bone related proteins
cGMP	cyclic guanylyl monophosphate
CITP	carboxy-terminal telopeptide
CNP	C-type natriuretic peptide
CRP	C-reactive protein
CT-proET-1	C-terminal-pro-endothelin-1
CV	cardiovascular
EMPs	endothelial microparticles
EPCs	endothelial progenitor cells
Gal-3	galectin-3
GDF-15	Growth differentiation factor-15
HF	heart failure
hFABP	heart type of fatty acid binding protein
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LV	left ventricular
MMP	matrix metalloproteinase
MPs	micro particles
MR-proANP	mid-regional pro-atrial natriuretic peptide

MR-proADM	mid-regional pro-adrenomedullin
NPs	natriuretic peptides
NT-proBNP	NT-pro-brain natriuretic peptide
PICP	carboxy-terminal propeptide
sST2	soluble suppressor of tumorigenicity-2 receptor

1 Introduction

Heart failure (HF) is a leading cause of premature cardiovascular (CV) death in patients with established CV disease (Ponikowski et al. 2016). Prevalence of HF has been exhibiting a tendency to worldwide, despite the scientific progress in the field of the two past decades. HF is also characterized by an elevated rate of primary and secondary hospitalization and increased economic burden for patients and their families. Although there are numerous clinical guidelines, which clearly indicated diagnosis, prevention and evidence-based treatment of HF, a strategy regarding exclusion of HF diagnosis, as well as risk stratification of HF, nature evolution of disease is not well established and requires more development (Wettersten and Maisel 2016). In this context, biological markers reflected several pathophysiological stages of HF have become a powerful and convenient noninvasive tool for diagnosis of HF, a stratification of HF patients at risk of progression, HF severity, and biomarker-guided therapy (Ledwidge et al. 2013). The aim of the chapter is to discuss a role of biomarker-based approaches for more accurate diagnosis, in-depth risk stratification and individual targeting in treatment patients with HF.

2 Conventionally Used Biomarkers of Heart Failure

According to The Biomarkers Definitions Working Group Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group (National Institutes of Health) 2001).There are numerous of biomarkers, which reflect several pathophysiological stages of HF and allow stratifying individuals at risk (Fig. 1). Currently updated clinical recommendations have been reported that the natriuretic peptides (NPs), including brain NP (BNP), mid-regional pro-atrial NP (MR-proANP), NT-pro-brain NP (NT-proBNP), mid-regional pro-brain NP (MR-proBNP), are the most frequently used biomarkers in clinical practice to stratify patients at risk of cardiac dysfunction, a risk of admission/readmission to the hospital due to HF-related reasons, and a risk of death (Pouleur 2015), while galectin-3, high-sensitivity cardiac troponins and soluble suppressor of tumorigenicity-2 (sST2) receptor are thought to be promising biomarkers in this respect (Table 1). Most data on cardiac biomarkers have been derived from chronic HF individuals. In contrast, risk prediction in patients admitted to hospital with acute HF remains a challenge.

2.1 Natriuretic Peptides

First NPs were recommended by the European Society of Cardiology and American Heart Association for exclusion HF, and then they were discussed as a tool for risk stratification, and NPs-guided therapy (Ponikowski et al. 2016; Wettersten and Maisel 2016). The majority of NPs' family members (Atrial NP [ANP] and brain [BNP] apart from C-type of NP [CNP]) are mechanical stress-related markers. They are actively released by cardiomyocytes as a result in fluid overload, cardiac stretching, as well as due to exposure to other causes, e.g. ischemia/ necrosis, metabolic and toxic damage, membrane stability loss, and inflammation (Berezin 2017a). ANP is released from atrial granules upon acute volume overload, whereas BNP is stressed-related peptide that does not accumulate before stimulation. In contrast, CNP is secreted from activated endothelial cells and renal cells in response to cytokine activation and through endothelium-dependent

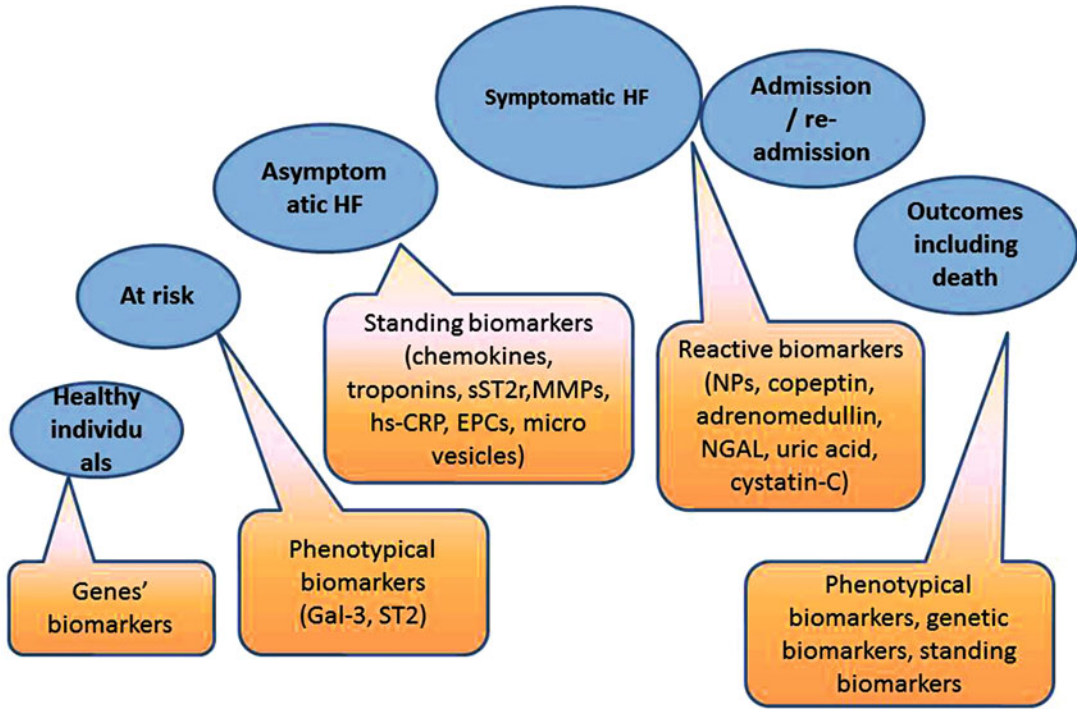

Fig. 1 Schema of practical use of various biomarkers in HF development and progression

agonists, e.g. acetylcholine (Berezin 2017a). The biological effects of ANP and BNP are mediated by binding with appropriate NP receptor type A (NPRA). NPRA are expressed at the surfaces of the target cells and are linked with cGMP mediating water/electrolyte homeostatic effects, i.e. diuresis/natriuresis, increasing glomerular filtration rate, volume of circulating plasma, suppressing systemic sympathetic activities, maintenance of cardiac output and regulation of blood pressure. NPs may demonstrate anti-proliferative activity and anti-mutagenic effect, mediate vascular dilatation and prevent vascular wall hypertrophy (Berezin 2017a). Additionally, NPs show modest anti-aldosterone and endothelin-1 effects.

In patients with HF the plasma levels of BNP and NT-proBNP are typically >100 pg/ml and >250 pg/mL, respectively, while there is high individual biological variability of both biomarkers irrespective of presentation of HFrEF or HFpEF (Felker et al. 2017). Elevated levels of NPs are well correlated with clinical status and severity of HFrEF/HFpEF patients, a risk of developing acute HF regardless etiology of the disease, risk of hospital admission/re-admission, as well as all-cause mortality, CV and HF death in individuals with established HF including at discharge from the hospital after treating HF decompensation (Feng et al. 2017). More recent evidence suggests that NPs along with the next generation of CV biomarkers could provide added predictive value to drug therapy of HF, which could potentially lower HF-related risk of outcomes (Fonarow 2017; Chow et al. 2017).

2.2 Biomarkers of Myocardial Fibrosis

2.2.1 Galectin-3

Galectin-3 is a soluble β-galactoside-binding protein, which is actively secreted by activated mononuclears and macrophages due to inflammatory stimulation. The main biological function

Table 1 Utility of biomarkers in HF management

Suggestions for use	Patients	COR	LOE
NPs (BNP, NT-proBNP or MR-proANP)			
Rule-in or support of initial working diagnosis	Patients with suspected HF in non-acute setting condition with dyspnea	I	A
	Patients with suspected acute and chronic HF, when the etiology of dyspnea is unclear	I	A
	Patients with suspected HF in acute setting condition	IIb	C
Exclusion of important cardiac dysfunction	Outpatients with uncertain signs and symptoms of HF	I	A
Prognosis of HF	Outpatients/inpatients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
	Postdischarged patients	IIa	B
Prevent development of LV dysfunction or new-onset HF	Patients at risk of HF development	IIa	B
Target therapy	Outpatients with established HF in euvolemic condition	IIa	B
Biomarkers of myocardial injury (cardiac troponins)			
Risk stratification	Patients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
Biomarkers of myocardial fibrosis (galectin-3)			
Risk stratification	Outpatients with established chronic HF	IIb	B
	Inpatients with established acute and chronic HF	IIb	A
	Post-discharged patients	IIa	B
sST2			
Prognosis of HF	Outpatients/inpatients with established HF	I	A
	Patients who were admitted to the hospital with acute HF	I	A
	Post-discharged patients	IIa	B

Abbreviations: *HF* heart failure, *NPs* natriuretic peptides, *BNP* brain NP, *NT-proBNP* N-terminal fragment of brain NP, *sST2* soluble suppressor of tumorigenicity-2, *MR-proANP* mid-regional pro-atrial NP, *COR* classes of recommendations, *LOE* level of evidence

of galectin-3 is to activate the fibroblasts for further collagen synthesis (Yancy et al. 2017). Recent pre-clinical and clinical studies have revealed the pivotal role of galectin-3 in progressive accumulation of extracellular matrix leading to cardiac fibrosis, cardiac remodeling, and worsening cardiac performances associated with impaired cardiac systolic and diastolic function, dilation of cardiac cavities, and induction of cardiac arrhythmias (Boulogne et al. 2017a; Souza et al. 2017). Galectin-3 in elevated concentrations was measured in a serum of the patients at risk of HF and CV disease (Lala et al. 2017). In patients with acute HF galectin-3 associated with NT-proBNP levels and the estimated glomerular filtration rate but not with age and serum cardiac troponins (Imran et al. 2017). Galectin-3 was not superior to NT-proBNP, sST2 receptor, Growth Differentiation Factor (GDF)-15 or high-sensitive C-reactive protein (hsCRP) in prediction of CV mortality and HF death, while the combination of galectin-3 and NPs was more accurate in predicting HF death compared to either of the biomarkers alone (Besler et al. 2017a).

2.2.2 Soluble Suppressor of Tumorigenicity-2 Receptor

Soluble suppressor of tumorigenicity-2 receptor (sST2) belongs to the interleukin (IL)-1 receptor family members, which has two isoforms, i.e. membrane-bound (ST2L) and soluble (sST2) isoforms. sST2 interacts with its ligand IL-33 and through myocardial mRNA expressions of Th1-related cytokines (tumor necrosis factor-alpha) may directly enhance

cardiac hypertrophy, fibrosis, cavity dilation with impaired cardiac function (Berezin 2017a).

The serum levels of sST2 in acute HF were dramatically increased on admission and appeared to be decreased rapidly depending on clinical improvement. Therefore, sST2 in HF has well correlated with BNP and GDF15 levels (Srivatsan et al. 2015). sST2 levels at discharge were better predictor of HF re-admission than ones at admission (Boulogne et al. 2017b). Although both biomarkers of myocardial fibrosis (sST2 receptor and galectin-3) are predictive of HF-related admission to the hospital and CV death (Billebeau et al. 2017), direct head-to-head comparison of sST2 and galectin-3 revealed superiority of sST2 over galectin-3 in HF risk stratification (Bayes-Genis et al. 2014).

2.3 Biomarkers of Myocardial Injury

Development and progression of HF strongly relates to direct and indirect damages of cardiac cells by effect of etiological factors of cardiac dysfunction (i.e. ischemia/necrosis, inflammation, hypoxia, hypertrophy, fibrosis) as well as by other factors contributing to the pathogenesis of HF (i.e., biomechanical stress due to cardiac remodeling, iron deficiency, oxidative stress/mitochondrial dysfunction). Biomarkers of myocardial injury may be detected in peripheral blood in elevated concentration as a result of leakage through cardiac cell membranes and due to injury of cells. However, regardless of the main cause of cell dysfunction, biomarkers of cardiac cell injury reflect a wide range of pathophysiological process: from instability of lipid layers of membrane due to lipid peroxidation to destroying cell due to necrosis/apoptosis (Berezin 2017a).

There are some biomarkers of myocardial injury and necrosis (cardiac troponins T and I, myoglobin, heart type of fatty acid binding protein, glutathione transferase P1), which are investigated in details as potential predictors of HF onset and HF-related outcomes (Anguita 2017). Since last two decades high-sensitivity cardiac troponins had been suggested to be prognosticators of high risk of CV mortality and combined adverse CV outcomes in HF (Nagarajan et al. 2012; Masson et al. 2010).

3 Biomarker-Guided Therapy of HF

It had been found that NP guided HF therapy improved titration of medications (Feng et al. 2017; Fonarow 2017), but did not lead to better HF clinical outcomes (Wettersten and Maisel 2016; Berezin 2017a). Meanwhile, serial measurements of NPs could be useful for determining the severity of HF for decision about ambulatory and in-hospital medical care. Additionally, NT-proBNP, but not BNP, is better suited during HF therapy based on the new angiotensin-receptor-neprilysin-inhibitor (ARNI) (Malek and Gaikwad 2017). The clinical trials have shown that neprilysin inhibition together with chronic renin-angiotensin system blockage with Sacubitril/Valsartan may increase the bioavailability of NPs and promotes additional cardio-renal benefits and thereby reduce all-cause mortality, CV mortality and HF death (Wong et al. 2017). Because biologically active BNP is degraded by neprilysin, in HF patients treated with ARNI circulating level of BNP sufficiently increases, whereas NT-proBNP concentration declines dramatically. In such situations the principles of NPs-based HF guided therapy are become complicated. Apparently, monitoring of BNP levels is not suitable for risk stratification and HF adjusted medical care, when ARNIs are used, however, NT-proBNP remains useful for risk assessment and HF stratification regardless drug prescriptions (Luchner et al. 2017; Aspromonte et al. 2016; Skaf et al. 2017; Nakanishi et al. 2017). Finally, majority of experts believe that a combination of biomarkers may ultimately prove to be more informative in their predictive ability than single biomarker (Nymo et al. 2017).

4 Limitations in Use of Conventional Biomarkers in HF

Confusingly, the role of NPs in modification of treatment considerably relates to aging, CV disease, metabolic co-morbidities, kidney clearance, metabolism (neprilysin for BNP, glycosylation, methylation, oxidation for other NPs), toxic effect (cardiotoxicity) (Berezin 2016a). Therefore, higher individual biological variability of these biomarkers may impair interpretation of the measured results (Favresse and Gruson 2017). There is a big list of diseases associated with increased level of NPs beyond HF development (Table 2).

Although galectin-3 is an independent predictor of all-cause mortality, CV death and occurrence of HF, there is an inverse relationship

Table 2 The potential causes of changes in circulating NPs' levels

Diseases	Types of changes	Causes for NP evolution	
		Primary	Other
Acute and chronic HF	↑↑↑	Over-production due to myocardial wall stretching/fluid overload	Lowered kidney clearance, cardiac injury
MI/ACS	↑↑	Cardiac injury	Fluid overload, biochemical stress, ischemia/hypoxia
Atrial fibrillation/ atrial flutter	↑↑	Leakage through cardiac myocyte membrane	Cardiac injury
Myocardities/ cardiomyopathy	↑-↑↑↑	Cardiac injury	Leakage through cardiac myocyte membrane due to inflammation, fluid overload, biochemical stress
Cardiac hypertrophy	↑	Leakage through cardiac myocyte membrane	Biochemical stress
Cardioversion	↑	Cardiac injury	Metabolic myocardial damage
Cancer chemotherapy	↑	Toxic-metabolic myocardial insults	Biochemical stress
Valvular and pericardial disease	↑-↑↑	Leakage through cardiac myocyte membrane	Biochemical stress, fluid overload, cardiac injury
Pulmonary hypertension	↑-↑↑	Leakage through cardiac myocyte membrane	Fluid overload, biochemical stress, ischemia/hypoxia
Cardiac surgery	↑	Leakage through cardiac myocyte membrane	Biochemical stress, fluid overload, cardiac injury
Aging	↑	Lowered kidney clearance	Biochemical stress
DM	↑-↑↑	Lowered kidney clearance	Cardiac injury, fluid overload, biochemical stress
COPD	↑↑	Myocardial wall stretching	Fluid overload, cardiac injury
Obesity	↓	Increased degradation by enzymes (glycosylation for NT-poBNP, nephrylisin for BNP)	Increased kidney clearance
Anemia	↑	Leakage through cardiac myocyte membrane	Metabolic myocardial damage, biochemical stress, cardiac injury, ischemia/hypoxia
Renal failure	↑	Lowered kidney clearance	Biochemical stress, metabolic myocardial damage
Critical illness, bacterial sepsis, severe burns	↑-↑↑	Lowered kidney clearance	Metabolic myocardial damage, biochemical stress, cardiac injury, ischemia/hypoxia

Abbreviations: *NP* natriuretic peptide, *HF* heart failure, *ACS* acute coronary syndrome, *MI* myocardial infarction, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, ↑ mild increase, ↑↑ moderate increase, ↑↑↑ severe increase, ↓ decrease

between serum galectin-3 level and estimated glomerular filtration rate (Besler et al. 2017b). Accordingly, lowered kidney clearance should be taken into consideration, when data of galectin-3 measurement are interpreted. Therefore, older patients contributed to higher galectin-3 concentrations than younger individuals (Krintus et al. 2017). Amongst other biomarkers (NPs, GDF-15, high-sensitivity troponin T, sST2, aldosterone, phosphate, parathyroid hormone, plasma renin, and creatinine), galectin-3 had the lowest individual biological variability, whereas NPs and GDF-15 had the highest ones (Meijers et al. 2017). In contrast to NPs serum galectin-3 levels did not appear to be significantly related to circulating level of cardiac troponins, left ventricular (LV) ejection fraction and LV mass index (Agnello et al. 2017). However, there was a positive correlation between galectin-3 levels and NT-proBNP in HF individuals. Thus, galectin3 and NPs might be considered as the best markers for both short- and long term death prediction in HF regardless kidney function and age. Unfortunately, no biomarker predicted the short-term composite HF endpoints in acute HF (Miró et al. 2017). Additionally, there are controversial findings related to the lack of association of galectin-3 concentration with adverse outcomes in chronic HF (Wojciechowska et al. 2017).

Even sST2 was not associated with age, female sex, LV structure or LV systolic or diastolic function (Maisel and Di Somma 2016; Berezin 2016b; AbouEzzeddine et al. 2017). Thus, these findings confirmed that the sST2 is a marker of systemic inflammation and fibrosis with predictive ability regarding all-cause and CV death in HF (AbouEzzeddine et al. 2017; Aimo et al. 2017).

5 Novel Biomarkers for HF Management

The discovery of new biomarkers is promising, but rarely novel molecules prove to be significantly better in diagnostic and predictive value than the established biomarkers. In addition to the various types of NPs, galectin-3, sST2, high-sensitive cardiac troponins, several other biomarkers have been investigated to be better predictors in HF (Table 3).

5.1 Procalcitonin

Procalcitonin is propeptide of calcitonin, which is normaly produced and actively secreted by the parafollicular C cells of the thyroid gland (Ryu et al. 2015). Procalcitonin/calcitonin axis is essential for regulation of calcium homeostasis and immunity (Berezin 2017a). The preclinical and clinical studies have shown that extrathyroidal production of procalcitonin markedly increases in cases of systemic inflammatory reaction, severe infections (viral, bacterial, fungal and parasitic), and shock (Reiner et al. 2017; Hayashida et al. 2017; Simon et al. 2004). Although serial measurements of procalcitonin are recommended to discriminate of in-hospital mortality in various diseases associated with pro-inflammatory activation (pneumonia, chronic obstructive pulmonary disease, acute respiratory tract infections, sepsis, etc.), there is evidence that the serum procalcitotin levels might be a predictive biomarker for chronic HF (Simon et al. 2004). Large clinical trials are required to obtain evidence for a predictive role of procalcitonin in exacerbated HF individuals.

5.2 Copeptin

Copeptin is C-terminal derivative of the arginine vasopressin that normally acts as regulator of water and electrolyte homeostasis (Morgenthaler 2006). Although plasma levels of copeptin are very variable and tightly relate to blood/urine osmolality, copeptin appears to be in higher concentrations in sever hypertension, stroke, acute and chronic HF, myocardial infarction,

Table 3 The promising novel biomarkers for HF depending on HF phenotypes

Related pathophysiological processes in HF	HF phenotype	Biomarkers	Relevance to clinical outcomes in HF
Myocardial biochemical stress	Any	MR-proANP	All-cause, CV and HF-related mortality, risk of hospital re-admission at discharge, risk of HF deterioration
Neurohumoral activation	HFrEF	Copeptin	All-cause and HF-related death, CV mortality, hospital admission rate
	HFrEF	CT-proET-1	NYHA stage
	HFrEF	ADM/MR-proADM	All-cause mortality, CV mortality and HF-related death in acute HF
Myocardial fibrosis	HFpEF/ HFmrEF	PICP	AF, CV mortality, MI, HF-related death
	HFpEF/ HFmrEF	CITP	AF, CV mortality, MI, HF-related death
	HFpEF/ HFmrEF	PIIINP	All-cause mortality, CV mortality, MI, HF-related death
	HFpEF, HFmrEF	MMPs	All-cause, CV and HF-related mortality in acute HF, ADHF, risk of HF admission in HF
Myocardial necrosis	Any	hFABP	CV and HF-related mortality
	Any	GSTP1	MI mortality, CV events and HF admission
Vascular remodeling	Any	OPN	CV mortality, MI, HF onset
	HFpEF/ HFmrEF	OPG	CV mortality, MI, HF onset
	Any	Signature of miRNAs	All-cause and CV mortality, MI, HF onset, HF progression
Inflammation	HFrEF	hs-CRP	NYHA stage of HF, risk of death in ADHF
	HFrEF	Procalcitonin	ADHF, acute HF, CV death, readmission rate
	HFrEF	GDF-15	CV mortality, HF deterioration
Oxidative stress	HFrEF	Uric acid	All-cause and CV mortality
	HFrEF	Myeloperoxidase	All-cause and CV mortality in ADHF, acute HF, HF-related outcomes in chronic HF
	HFpEF/ HFmrEF	Ceruloplasmin	Risk of HF deterioration, NYHA-stage
	HFpEF/ HFmrEF	8-OHdG	
	HFpEF/ HFmrEF	Trx1	
Renal dysfunction	HFrEF	Cystatin C	All-cause and CV mortality, HF-related death, HF readmission in acute HF
	HFrEF	NGAL	HF-related death in acute HF and ADHF
Metabolomic state	HFrEF	Signature of metabolomics (fatty and amine acids, Krebs cycle components, DNAs, lipids, glucose, variable very-long chain carbons, proteins, hormones, enzymes ets.)	HF-related death, CV mortality, hospital re-admission rate

(continued)

Table 3 (continued)

Related pathophysiological processes in HF	HF phenotype	Biomarkers	Relevance to clinical outcomes in HF
Endothelial dysfunction	HFpEF, HFrEF, HFmrEF (?)	EPCs	All-cause mortality, CV mortality, HF-related death, admission/ readmission rate
	Any	EMPs	

Abbreviations: *ADHF* acutely decompensated heart failure, *AF* atrial fibrillation, *MR-proANP* mid-regional pro atrial natriuretic peptide, *ADM* adrenomedullin, *MR-proADM* mid-regional pro-adrenomedullin, *PICP* carboxy terminal propeptide, *CT-proET-1* C-terminal-pro-endothelin-1, *CITP* carboxy-terminal telopeptide, *PIIINP* amino-terminal peptide of procollagen type III, *HF* heart failure, *hs-CRP* high-sensitive C-reactive protein, *hFABP* high-sensitive fatty acid binding protein, *GDF* growth differentiation factor, *EPCs* endothelial progenitor cells, *EMPs* endothelial cell-derived micro particles, *MI* myocardial infarction, *MMP* matrix metalloproteinase, *NGAL* neutrophil gelatinase-associated lipocalin, *8-OHdG* 8-hydroxy-2′-deoxyguanosine, *Trx1* thioredoxin 1, *GSTP1* glutathione transferase P1

diabetes mellitus, advanced kidney diseases, and in critical conditions. As quantitative biomarker of endogenous biomechanical stress elevated level of copeptin was found in close positive association with increased CV mortality and CV disease in out-patients and all-cause mortality in critical states (Remde et al. 2016). There is a large body of evidence that the serial measurements of copeptin level may be provide an important information for discrimination of a risk of all-cause mortality, HF-related outcomes and CV events and diseases (Moayedi and Ross 2017; Krane et al. 2017; Yan et al. 2017a; Berezin 2015a). Although both increased NT-proBNP levels and copeptin levels were recognized significant independent predictors of adverse clinical outcomes in HF, the role of dual marker contribution in HF risk stratification remains to be clarified (Savic-Radojevic et al. 2017; Smaradottir et al. 2017; Sahin et al. 2017; Herrero-Puente et al. 2017).

5.3 Heart Type of Fatty Acid Binding Protein

The heart type of fatty acid binding protein (hFABP) is normally essential for the long-chain fatty acids re-uptake, regulation of calcium homeostasis in cardiomyocytes and mediating inflammatory reaction (Chmurzynska 2006). Because hFABP is tissue-specific biomarker of myocardial injury and necrosis, it is reserved as predictor of myocardial infarction at the early hours of development of the disease. Recent studies have shown that circulating levels of hFABP are elevated in cardiac dysfunction and closely predicted CV outcomes and HF-related events in in-patients especially in those who had fluid retention and lung congestion (Savic-Radojevic et al. 2017; Chmurzynska 2006; Qian et al. 2016; Kitai et al. 2017). Although elevated serum level of hFABP yielded better prognostic information on survival in individuals with acute and advanced HF when compared to NPs, cardiac troponins and even galectin-3 taken alone, there is confusion about the improved precision of entire predictive model after incorporating hFABP to NPs and/or galectin-3 (Savic-Radojevic et al. 2017; Qian et al. 2016; Kitai et al. 2017).

5.4 Growth Differentiation Factor-15

Growth differentiation factor (GDF)-15 is multifunctional cytokine that belongs to the transforming growth factor-β superfamily (Kempf and Wollert 2009). GDF-15 is normally expressed in various cells including immune cells, fibroblasts, myocardial cells, endothelial cells, and mononuclears. Additionally, GDF-15 is actively secreted into circulation by cardiac myocytes due to stretching and biochemical stress (Berezin 2015a; Kempf and Wollert 2009; Chan et al. 2016).

Serum levels of GDF-15 are associated with increased risk of all-cause death independent of age, clinical signs and symptoms of cardiac dysfunction, LVEF, renal function and NPs in HF (Hage et al. 2017). Interestingly, in in-patients with acute HF the serum levels of GDF-15 were not better to NPs and galectin-3 taken alone in accuracy to predict HF-related outcomes including death and re-admission to the hospital after discharge (Demissei et al. 2017). In contrast, out-patients with chronic HFrHF/HFpEF may be candidates to multiple predictive biomarker strategy based on collective measurement of NPs, GDF-15, and galectin-3 (Berezin et al. 2015a; Berezin 2015b).

5.5 Endothelial Cell-Derived Micro Particles and Endothelial Progenitor Cells

Impaired endothelial function plays a pivotal role in HF development and HF-related complications and also associates with an appearance in the peripheral blood of specific circulating biomarkers, i.e. endothelial microparticles (EMPs) and endothelial progenitor cells (EPCs) (Berezin et al. 2015a; Berezin 2015b; Berezin at al. 2016). Recent clinical studies have shown that an ability of mature endothelial cells and their precursors to release of secretom progressively worse depended on HF stage and severity (Berezin 2015b, c; Berezin et al. 2014a, 2015b, 2016c). There is novel HF risk prediction score created by means of biomarkers, e.g. NPs, galectin-3, high sensitive CRP and estimated ratio between both numbers of apoptotic EMPs and EPCs (Berezin et al. 2015b; Berezin 2015d). However, it is not clear whether new predictive models would be effective in HF treatment. More clinical trials are required to improve our understanding in the field of individualized therapy of HF under biomarker control.

5.6 Biomarkers of Collagen Metabolism

Recent studies have shown that impaired collagen metabolism may alter the myocardial collagen network, enable cardiovascular remodeling, and mediates HF complications, i.e. atrial fibrillation/flutter, sudden death, and decline in LV pump function (Löfsjögård et al. 2014). Interestingly, there is evidence regarding causative role of BNP in alterations in collagen type I metabolism in HFrEF (Berezin 2016c). The OPTIMAL (The Optimizing Congestive Heart Failure Outpatient Clinic trial) revealed that disturbances of collagen type I metabolism are independent predictors of long-term, all-cause mortality and CV mortality in HFrEF individuals (Löfsjögård et al. 2017). Therefore, circulating CITP is probably an independent predictor of survival in patients with HFrEF (Tziakas et al. 2012).

5.7 Matrix Metalloproteinases

Development of HF strongly associates with CV remodeling, biomechanical and oxidative myocardial stress, neurohormonal and inflammatory activation that are modulated by matrix metalloproteinases (MMPs). It has demonstrated that MMPs determine extracellular accumulation of collagen and mediate pro-fibrotic processes (Berezin and Samura 2013). Recent pre-clinical and clinical studies have shown that an impairment of cardiac function may relate to the collagen accumulation due to an imbalance between expression of MMPs, predominantly MMP-1, MMP-3, MMP-6, MMP-9, and suppression of their tissue inhibitors (Collier et al. 2011; Hutchinson et al. 2010; Berezin et al. 2015c). However, the predictive value of these biomarkers was not confirmed and requires more future investigations.

5.8 Biomarkers of Oxidative Stress

5.8.1 Serum Uric Acid

Observational and clinical studies have shown that the elevated level of serum uric acid (SUA) is a common feature in patients with HF, hypertension, atherosclerosis, obesity, diabetes mellitus and chronic renal disease (Grassi et al. 2013; Borghi et al. 2015). The role of SUA in pathogenesis of CV disease is controversial. On the one hand, SUA induces an oxidative stress through over-production of reactive oxygen species. SUA often impairs vascular function via enhancement of inflammatory damage, inducing vascular calcification and directly via cell membranes deterioration effect (Grassi et al. 2013). On the other hand, low-grading inflammation that is frequently found in HF may cause xanthine oxidase over-activity and leads to increased tissue SUA accumulation, which acts as scavenger of free radicals and protects against an damaging effect of oxidative stress (Berezin and Kremzer 2013; Berezin 2014). Additionally, an increase of SUA may be an attribute of lowered kidney clearance in a progress of HF. Therefore, there is evidence regarding the regulatory role of SUA in EPC differentiation that allow discussing uric acid as a mediator of reparation of tissues in HF (Berezin et al. 2014b).

Numerous clinical studies have emphasized the predictive role of baseline SUA for early post-discharge HF outcomes (Amin et al. 2017; Okazaki et al. 2016, 2017). Interestingly, the activity of xanthine oxidoreductase that is a key rate-limiting enzyme of purine degradation may be more accurate predictor of HFrEF severity and HF clinical outcomes than SUA (Otaki et al. 2017; Huerta et al. 2016; Kim et al. 2013). Consequently, SUA remains an established risk factor of clinical outcomes in acute HF (Berezin 2017b), while poor prognosis in patients with chronic HF is not elucidated (Berezin 2017c).

5.8.2 Other Biomarkers of Oxidative Stress

Serum levels of myeloperoxidase, vitamin D3, ceruloplasmin and 8-hydroxy-2-′-deoxyguanosine correlate with staging of chronic HF regardless of LVEF and predict a development of HFrEF, while the role of these biomarkers of oxidative stress remains under discussion (Chan et al. 2016; Mozos et al. 2017). Although there is evidence regarding the close link between vascular remodeling (Berezin 2017d; Mozos and Marginean 2015), endothelial dysfunction and CV disease the predictive role of vitamin signature in serum (i.e., vitamin A, B12, D, K, C and E) in HF individuals is not still clear and requires to be investigated (Berezin 2017c).

5.9 Biomarkers of Renal Dysfunction in HF

5.9.1 Cystatin C

Cystatin C is an endogenous inhibitor of cysteine proteases and this biomarker is discussed as an alternative predictor of CV events in acute and chronic HF patients with any types of cardiorenal syndrome (Kim et al. 2013). The patients with HFrEF demonstrated elevated serum cystatin C, especially in cases with serious risk of CV complications (Kim et al. 2013). Additionally, increased cystatin C level in hypertensive patients with HFpEF was found (Berezin 2017d). It appears to be associated with LV diastolic dysfunction and alterations in collagen metabolism regardless of estimated GFR (Berezin 2017d). Although cystatin C has now validated a powerful predictor of CV outcomes and kidney injury, its sensitivity in patients with chronic HF is inferior to that of hs-CRP and NPs (Berezin 2017c). In contrast, in acute HF Cystatin C provided an incremental value for prognosis more than NT-proBNP and uric acid (Kim et al. 2015; Taub et al. 2012).

5.9.2 Other Biomarkers of Kidney Injury in HF

There are many perspective biomarkers of kidney injury that could be useful for stratification of HF at risk, i.g. stromal cell-derived factor-1, exosomes, MPs, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1, interleukin-18 and miRNAs (Berezin 2017d; Taub et al. 2012). Although they are at the early stages of renal dysfunction prior to any elevations in serum creatinine, the prognostication of clinical outcomes in acute HF and chronic HF require more investigations.

5.10 Genetic Biomarkers

By now, genetic testing has incorporated as a part of patient evaluation for suspected inherited cardiomyopathies (Teekakirikul et al. 2013; Teo et al. 2015). It turns out the epigenetic modifications through DNA methylation, ATP-dependent chromatin remodeling, histone modifications with an involvement of microRNA-related mechanisms might be sufficient pathophysiological factors contributing to adverse cardiac remodeling and altered cardiac function (Hershberger and Siegfried 2011). In this context, the novel risk scores reflecting variabilities in genetic and epigenetic features in HF development appear to be promising (Berezin 2016d; Yang et al. 2015; Lopes and Elliott 2013). Indeed, some early studies have reported interesting results with respect to genetic precursors of HFpEF and HFrEF (Berezin 2016e; Fazakas et al. 2016; McNamara et al. 2014; Friedrich et al. 2013; Hofman et al. 2010; Sutter et al. 2013; Kolder et al. 2012). There are numerous studies depicted the role of single nucleotide polymorphisms (SNPs) of genes encoding enzymes related to oxidative stress (Berezin 2016e), genotype of guanine nucleotide-binding proteins (G-proteins) beta-3 subunit (GNB3) (Fazakas et al. 2016), transcription factor Islet-1 gene (McNamara et al. 2014), troponin T (Friedrich et al. 2013), CYP2D6 polymorphism (Hofman et al. 2010), cardiac myosin binding protein-C mutations (Sutter et al. 2013), renin-angiotensin-aldosterone system polymorphism (Kolder et al. 2012) etc. in HF development and progression. It is well known that angiotensin-converting enzyme (ACE) I/D gene D allele was associated with higher overall mortality as compared with the I allele in HF patients and that the effect could be modified by ACE inhibitors' given (Wu et al. 2010). Additionally, ACE DD and angiotensin-1-receptor 1166 CC genotypes may synergistically increase the predisposition to HFpEF (Kolder et al. 2012; Wu et al. 2009, 2010).

The ARIC (Atherosclerosis Risk in Communities) study reported that none of the metabolite SNPs including pyroglutamine, dihydroxy docosatrienoic acid were individually associated with incident HF, whereas a genetic risk score created by summing the most significant risk alleles from each metabolite determined 11% greater risk of HF per allele (Yu et al. 2013). (Ganna et al. 2013) have reported that amongst 707 common SNPs associated with 125 diseases including HF it would not be easy to obtain explainable results by common genetic variants related to HF development. Consequently, a close gene-gene interaction may determine an individual's risk of HF through different pathways including epigenetic modifications. All these findings lead to the assumption that genes score might be a powerful tool for prediction of HF development.

More successful genome-wide linkage studies toward genes-related contribution in HF have been done by incorporating SNPs of several genes (i.g. the bradykinin type 1 receptor gene, angiotensin-II type I receptor gene, the β1-adrenoceptor gene and CYP2D6 polymorphism) in predictive score to benefit and suffer harm from HF therapy. Although these pharmacogenetic studies have focused on promised topics, the obtained results have not been absolutely consistent (Ganna et al. 2013; Yip and Pirmohamed 2013; Nelveg-Kristensen et al. 2015). In contrast, there is evidence that the gene expression profiles might be useful rather for risk prediction in HF than for choosing HF treatment regime (Bondar et al. 2014; Berezin

2016f). Thus, the clinical implementation of the HF therapy based on genes scoring remains uncertain and requires more evaluation in the future (Poller et al. 2017).

5.11 Micro-RNAs

It has been established that microRNAs (miRNA) are involved in the development and progression of HF across all pathophysiological stages of the disease (Berezin 2016d). miRNA are epigenetic regulators of myocardial response and fibrosis, growth of cardiac myocytes, cardiac and vasculature reparation, immunity, angiogenesis, and inflammation (Berezin 2016e). The altered miRNA' signature was found in patients with asymptomatic and symptomatic HF (Jin et al. 2017; Vegter et al. 2017; Yan et al. 2017b). It has suggested the signatures of non-coding RNAs would be candidate to improve diagnosis and prognostication of HF (Wong et al. 2014).

5.12 Mid-Regional pro-Adrenomedullin

Mid-regional pro-adrenomedullin (MR-proADM) is the prohormone of the CV protein adrenomedullin and it is well-established neurohumoral marker of cardiac biochemical stress that is raised in patients with infections, acute dyspnea, acute HF, severe chronic HFrEF/HFpEF, unstable angina pectoris/myocardial infarction, and throughout the first week after stroke (Bustamante et al. 2017). There is evidence that the MR-proADM is an early predictor of in-hospital mortality due to various reasons, i.e. respiratory infections, surgical procedure and CV diseases (Odermatt et al. 2017; Dres et al. 2017; Lopes and Menezes Falcão 2017). MR-proADM as a marker of biomechanical stress and fibrosis was not better than NPs and did not exhibit equal predictive value to sST2r and galectin-3 in HFrEF/HFpEF (Lopes and Menezes Falcão 2017). Interestingly, sST2 was better to MR-proADM, because it is more closely related to left ventricular remodeling and cardiac fibrosis. Moreover, MR-proADM did not improve a risk stratification based on NPs in patients with chronic HFrEF and moderate anaemia (Welsh et al. 2017). Thus, the role of MR-proADM as a component of biomarker-based stratification is discussable, may contribute to determine the short-term outcomes of critical ill patients with acute severe dyspnea, respiratory infection and acute HF.

6 Validation of Multiple Biomarker Predictive Scores

Despite several predictive scores based on biomarkers' measurement and approved for chronic HF, predictive scores for acute HF have not been validated (Bayes-Genis and Ordonez-Llanos 2015; Cohen-Solal et al. 2015). Current multiple biomarker scores for prognostication, risk stratification and diagnosis of HF (Fig. 2) are based on NPs in combination with biomarkers of myocardial injury and fibrosis (galectin-3 and sST2 receptor). A new score was validated by the American Heart Association/American College of Cardiology (2017), suitable for patients at risk of HF, with established chronic HF (for both HFrEF and HFpEF), with suspected and documented acute HF (at admission), as well as patients with HF at discharge from the hospital.

Interestingly, there are several attempts regarding use of biomarkers to stratify at risk patients with HFrEF and HFpEF. Whether add-on biomarkers are needed to improve cumulative predictive value for wide spectrum of HF individuals with different HF phenotypes, co-morbidities, ages and sex-related peculiarities is not fully clear. There is no clarity and consistent evidence for multiple biomarker strategy in improvement in CV mortality and CV outcomes. It has been suggested that sST2 and galectin-3 could improve prognosis in HF-related hospitalization and CV death, when added to NPs. This strategy is confirmed by experts of various

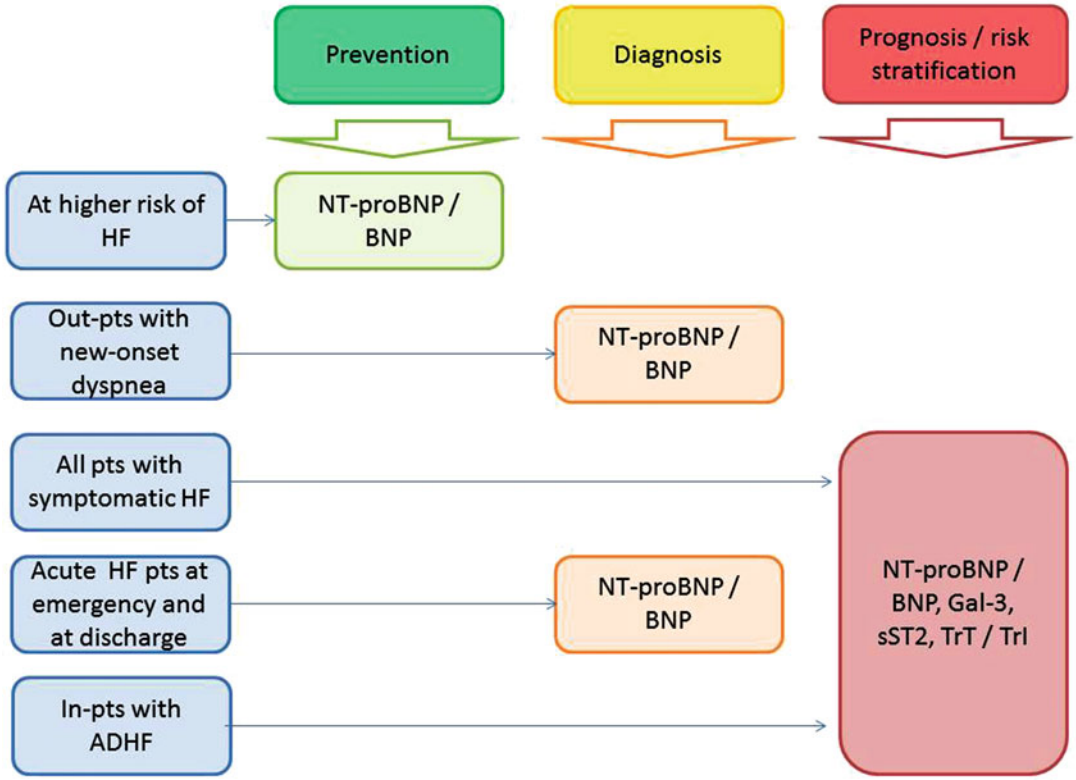

Fig. 2 Practical use of various biomarkers in HF development and progression
Abbreviations: *ADHF* actually decompensated heart failure, *pts* patients, *Gal-3* galectin-3, *NT – proBNP* NT-pro-brain natriuretic peptide, *BNP* brain natriuretic peptide, *TrT* troponin T, *TrI* troponin I, *sST2* soluble suppressor of tumorigenicity-2 receptor

medical associations and is the only one that is validated now (Chow et al. 2017).

7 Conclusions

There are many controversies regarding the importance of biomarkers as predictors of survival and in diagnosis of HF. Improvement of clinical guideline recommendations for optimizing HF therapy in routine clinical practice under biomarkers' control is required. Obviously, galectin-3 or sST2r would be optimal for improving NPs- based biomarker strategy in HF individuals, while there is evidence regarding other biomarkers that could individualize stratification of risk and treatment. There is need of larger clinical trials in order to head-to-head compare different biomarkers and clarify their role in diagnosis and guided therapy of HF.

Acknowledgements This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest Not declared.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 109–131
DOI 10.1007/5584_2018_143
© Springer International Publishing AG 2018
Published online: 7 February 2018

Evolving Role of Natriuretic Peptides from Diagnostic Tool to Therapeutic Modality

Ines Pagel-Langenickel

Abstract

Natriuretic peptides (NP) are widely recognized as key regulators of blood pressure, water and salt homeostasis. In addition, they play a critical role in physiological cardiac growth and mediate a variety of biological effects including antiproliferative and anti-inflammatory effects in other organs and tissues. The cardiac release of NPs ANP and BNP represents an important compensatory mechanism during acute and chronic cardiac overload and during the pathogenesis of heart failure where their actions counteract the sustained activation of renin-angiotensin-aldosterone and other neurohormonal systems. Elevated circulating plasma NP levels correlate with the severity of heart failure and particularly BNP and the pro-peptide, NT-proBNP have been established as biomarkers for the diagnosis of heart failure as well as prognostic markers for cardiovascular risk. Despite activation of the NP system in heart failure it is inadequate to prevent progressive fluid and sodium retention and cardiac remodeling. Therapeutic approaches included administration of synthetic peptide analogs and the inhibition of NP-degrading enzyme neutral endopeptidase (NEP). Of all strategies only the combined NEP/ARB inhibition with sacubitril/valsartan had shown clinical success in reducing cardiovascular mortality and morbidity in patients with heart failure.

Keywords

Natriuretic peptides · ANP · BNP · NT-proBNP · CNP · Heart failure · Biomarker · NP receptors · Neprilysin · ARNI · Sacubitril/valsartan

1 Natriuretic Peptides – Characterization and Biological Effects

The family of natriuretic peptides (NP) comprises genetically distinct but structurally homologous peptides including atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) (Potter et al. 2009). Some publications also attribute Dendroaspis natriuretic peptide (DNP) (Schweitz et al. 1992; Burnett 2006) and urodilatin (Forssmann et al. 1998) to this group which continues to expand with new peptides being discovered (Nobata et al. 2010). The typical 17 amino acid ring structure of the NPs is determined by an intramolecular disulfide bridge and contains several common amino acids. Particularly ANP is well preserved among different

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species, suggesting an important phylogenetic role for these peptides in osmoregulation (Vlasuk et al. 1986).

NPs mediate their actions via the activation of membrane-bound guanylyl cyclase-coupled receptors (NPR-A and NPR-B) (Tremblay et al. 2002) and the subsequent formation of cyclic guanosine monophosphate (cGMP) (Hamet and Tremblay 1991) (Fig. 1a). The physiological effects of the NP are terminated by either the cleavage of the peptides by neutral endopeptidase (NEP 24.11, neprilysin) (Charles et al. 1996), or the binding to a transmembrane clearance receptor (NPR-C) (Rademaker et al. 1997) followed by intracellular degradation. Whereas ANP and BNP are synthesized and released from atrial or ventricular cardiomyocytes, CNP is predominantly secreted by endothelial cells upon various stimuli. The main biological function of the NPs along the cardiorenal axis is regulation of electrolyte and water homeostasis in response to changes in intravascular volume and blood pressure. Furthermore, antiproliferative effects involving cardiomyocytes and non-myocytes play an important role in maintaining myocardial structure and function (Burnett 2006). More recently, an important role of NPs in the regulation of metabolic processes such as lipolysis, mitochondrial fatty acid oxidation and glucose homeostasis has been revealed (Schlueter et al. 2014) (Fig. 1b).

1.1 ANP

As the first in this group ANP was discovered in 1981 by *de Bold* and colleagues (1981) who found that the injection of atrial extracts elicited a potent natriuretic effect in rats. Subsequent studies revealed that this peptide hormone is predominantly expressed in atrial cardiomyocytes and stored in preformed granules (Corthorn et al. 1991); only a small percentage is found in ventricles under physiological conditions. In humans, ANP is synthesizes as a 151 amino acid (aa) prohormone (prepro-ANP) and, after cleavage of a signal peptide, 126 aa proANP is stored in the atrial granules. Upon secretion of the C-terminal 28 aa biologically active ANP an equimolar amount of N- terminal peptide, NT-proANP, is released into the blood (Mathisen et al. 1993), the final step being facilitated by the cardiac serine protease corin (Yan et al. 2000).

In response to atrial stretch (Dietz et al. 1995) ANP released into the circulation, binds selectively to the NPRs and promotes natriuresis, diuresis and vasodilation; the same effect could be observed after volume or salt load (Eskay et al. 1986), mineralocorticoid administration (Gardner et al. 1986), rapid atrial pacing (Espiner et al. 1985), angiotensin II or endothelin-1 administration (Ruskoaho et al. 1997), hypoxia (Chen 2005) and adrenergic stimulation (Wong et al. 1988). The renal effects can be attributed to an augmented intrarenal perfusion with increased renal blood flow, increased glomerular filtration rate as well as reduced tubular sodium reabsorption (Weidmann et al. 1986; Marin-Grez et al. 1986). Hemodynamic effects are caused by a direct, endothelium-independent vasorelexation that leads to a reduction of the peripheral resistance, a shift of intravascular fluid to the extracellular space (Lang et al. 1987) in combination with a reduction of cardiac output, and inhibition of the activity of the renin-angiotensin-aldosterone (RAAS) and arginine vasopressin systems (AVP). The net effects include a reduction of intravascular fluid and cardiac filling and a reduction of systemic and pulmonary arterial pressure. This mechanism is particularly relevant in conditions with systemic neurohormonal activation such as heart failure and hypertension. Interestingly, no reflex tachycardia was observed after ANP-induced blood pressure reduction, an effect that is due to the modulatory effect of ANP on cardiac baroreceptors (Volpe 1992).

Adding yet another facet to the spectrum of their properties, NPs are emerging as important regulators of energy consumption and metabolism, pointing towards a "*heart-adipose tissue connection*" (Schlueter et al. 2014; Ramos et al. 2015; Collins 2014). Recent studies demonstrate that NPs are able to promote adipocyte lipolysis (Sengenes et al. 2000), lipid oxidation and mitochondrial respiration via a cGMP-dependent pathway. ANP infusion in humans induced lipolysis systemically and in subcutaneous adipose

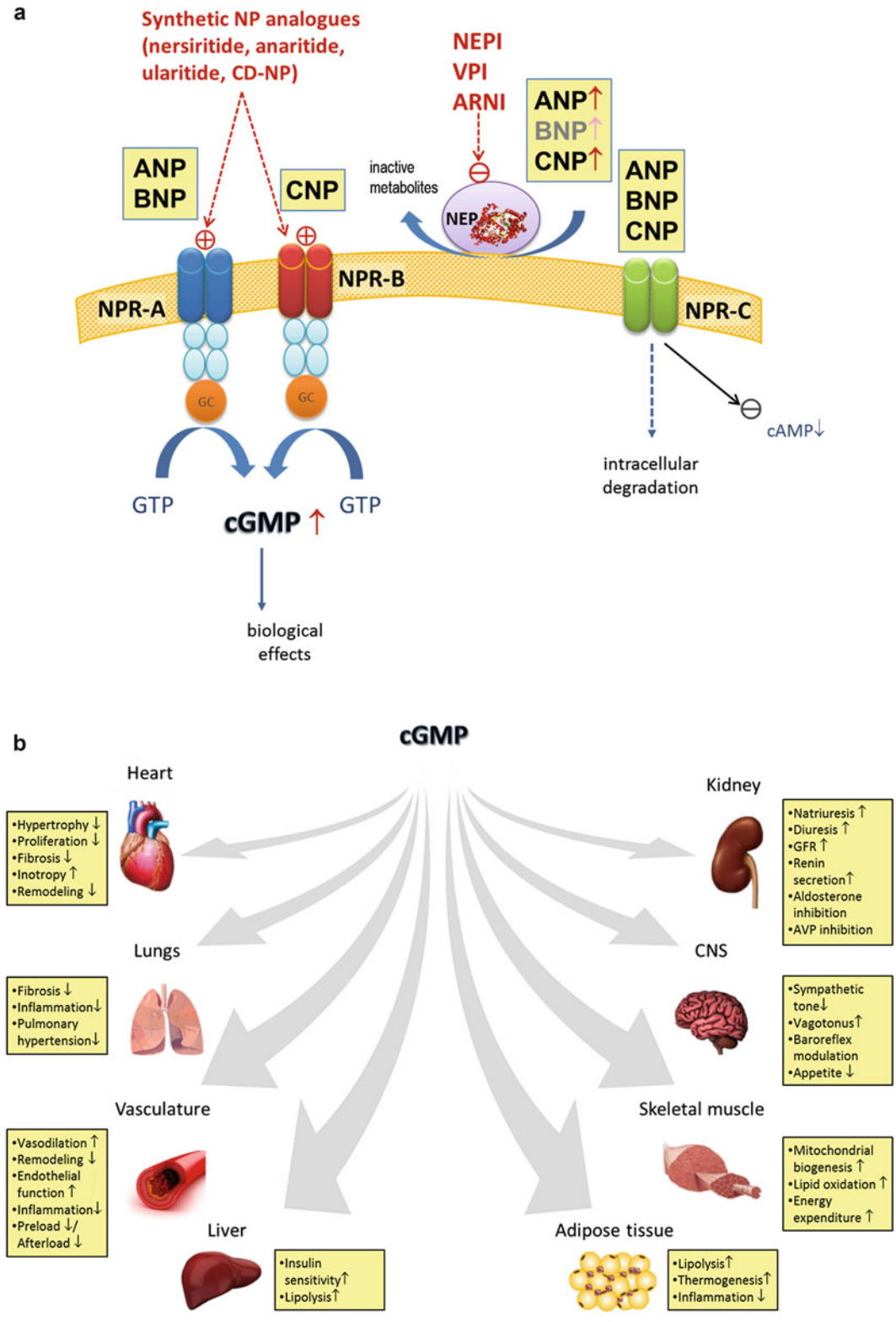

Fig. 1 (**a**) NP signaling and therapeutic modalities (in red), (**b**) physiological effects

tissue. These effects were associated with increased oxidative capacity of skeletal muscle and postprandial energy expenditure (Birkenfeld et al. 2008). The complex regulatory pathway that leads to activation of lipid oxidation and oxidative phosphorylation involves the orchestration of local adipose tissue concentrations of NPs through regulation of their clearance, mitochondrial biogenesis via upregulation of peroxisome proliferator-activated receptor (PPAR)-γ coactivator (PGC)-1α, nuclear receptor PPARδ as well as downstream genes encoding components of the respiratory chain complexes (Engeli et al. 2012). Mitochondrial biogenesis in turn plays a critical role in the pathophysiology of insulin resistance in diabetes (Pagel-Langenickel et al. 2010) and targeting this signaling cascade could represent an attractive therapeutic approach in patients with cardiovascular diseases complicated by metabolic syndrome. Taken together, these metabolic effects could contribute to a relative protection against diet-induced obesity and insulin resistance. This hypothesis is further supported by the observation that mice lacking NPR-A are more susceptible to weight gain and insulin resistance while BNP transgenic mice are relatively resistant when fed on a high-fat diet (Miyashita et al. 2009).

1.2 BNP

Despite being first isolated from porcine brain (Sudoh et al. 1988), BNP is the major NP of the cardiac tissue and is synthesized in both atria and ventricles (Kambayashi et al. 1990; Luchner et al. 1998). In atrial granules BNP is stored together with ANP (Hasegawa et al. 1991) and co-secretion of both peptides has been described (Toth et al. 1994), explaining the close correlation of plasma ANP and BNP levels in healthy individuals. Similar to ANP, the precursor preproBNP is synthesized by cardiomyocytes and processed to proBNP involving the convertases corin and furin (Ichiki et al. 2013). The C-terminal 32 aa fragment is secreted as active BNP together with the inactive N-terminal fragment, NT-proBNP that consists of 76 aa. Ventricular stretch seems to be the main stimulus for BNP release and elevated BNP levels have been found in conditions with elevated left ventricular enddiastolic pressure and pulmonary artery wedge pressure (Richards et al. 1993). The physiological effects of BNP are comparable to ANP although the biological half-life of BNP is longer: in humans it is 19 min for BNP compared to 4.5 min for ANP (Florkowski et al. 1994; Biollaz et al. 1987) which results from slower degradation by neprilysin. Similar to ANP, BNP has been identified as a potential regulator of metabolic pathways. An inverse relationship between plasma BNP levels and those of the anorexigenic peptide leptin has been found in patients with heart failure (Melenovsky et al. 2013). BNP infusion reduced plasma glucose level and, similarly, BNP overexpression has been associated with improved glucose tolerance and lower blood glucose levels. Conversely, low BNP levels were correlated with insulin resistance and type 2 diabetes in an epidemiological study (Kroon et al. 2012).

1.3 CNP

As the third member of the NP family the 22 aa peptide CNP has been identified by Sudoh et al. in 1990. In contrast to ANP and BNP, the heart is not the main source of CNP synthesis. It is abundant in the brain, particularly in the cerebellum and hypothalamus, chondrocytes and cardiac tissue. CNP shows high expression levels in the kidney (Mattingly et al. 1994) involving proximal, distal and medullary collecting duct tubular cells and has been detected in urine samples. Similar to the other NPs, mature CNP is generated after several cleavage steps from a 126 aa pre-pro peptide. Important stimulators of CNP secretion are cytokines and growth factors including TNF-α, interleukins, TGF β, and shear stress. In addition, ANP and BNP directly stimulate the endothelial synthesis and secretion of CNP. CNP is thought to mediate its action in a paracrine fashion predominantly in the vasculature (Ueno et al. 1997) and can be detected at very low levels in the blood. The different spectrum of activity

(Clavell et al. 1993) with almost no effect on sodium and water balance can be explained by higher affinity for the NPR-B compared to the NPR-A. Important effects of CNP are the potent arterial and venous vasodilation as well as antiproliferative effects due to inhibition of mitogenesis in the fibroblasts (Horio et al. 2003; Cao and Gardner 1995), endothelial and smooth muscle cells (Furuya et al. 1995). In addition, CNP ameliorates pulmonary hypertension along with a reduction of fibrosis and inflammation in animal models (Itoh et al. 2004; Kimura et al. 2016).

1.4 DNP

Dendroaspis natriuretic peptide (DNP) has been first described in snake venom (Schweitz et al. 1992) but has also been detected in human plasma (Schirger et al. 1999). The peptide shows a high structural homology to ANP and causes comparable diuretic and natriuretic effects when given as infusion in dogs (Lisy et al. 1999). This was accompanied by a significant reduction in mean arterial pressure and increase in circulating levels of the second messenger cGMP, indicating that the GC activation after binding to the NPR plays a role for its biological effect. DNP binds with high affinity to the NPR-A and does not seem to be susceptible to degradation by neprilysin (Dickey and Potter 2011).

1.5 Urodilatin

Lacking a circulating form in the blood, urodilatin was first detected in urine and found to be synthesized in the kidney where it is secreted into the lumen of the distal tubules. In contrast to the other NPs there is also no storage of an urodilatin precursor in the renal tissue. The high homology to ANP with only a 4 aa extension at the N-terminus gave rise to the perception that urodilatin may represent a tissue-specific splice variant of the ANP gene (Feller et al. 1989).

Urodilatin induces a potent diuretic and natriuretic response that even exceeds the efficacy of ANP. The longer duration of action of urodilatin compared to ANP is a result of a relative resistance of urodilatin to enzymatic degradation by neprilysin. Despite the systemic hemodynamic effect, including a reduction of arterial blood pressure, increase of cardiac output and reduction of pulmonary pressure that is seen after IV administration (Kentsch et al. 1992) it is thought that urodilatin exerts its physiological actions predominantly in the kidney where it is involved in the regulation of renal perfusion and electrolyte homeostasis.

2 NP Receptors

The presence of natriuretic peptide receptors has been described in a variety of tissues and cells, including endothelial and smooth muscle cells, cardiomyocytes, adrenals, lungs, brain, neurons (Kuhn 2016). First insights into the distribution came from autoradiography studies and showed a high abundance of the receptors in the kidney (Chai et al. 1986) with localization in renal arteries, afferent and efferent arterioles, glomerular epithelial and mesangial cells, tubular epithelium, papillae and renal cortex.

Currently, four receptor subtypes have been characterized of which two, NPR-A and NPR-B, mediate the NP actions via GC activation and cGMP production. The structure of these receptors is characterized by an extracellular ligand-binding domain, a short transmembrane region and an intracellular portion consisting of the GC, a hinge region and the regulatory kinase homology domain (KHD). Phosphorylation of the KHD is required for ligand-dependent receptor activation and subsequent production of cGMP (Pandey et al. 1988; Potter and Hunter 1998).

ANP has the highest affinity to NPR-A but also binds to NPR-B and NPR-C. By contrast, BNP and DNP bind only NPR-A and C while CNP seems to be the exclusive ligand for NPR-B (Koller et al. 1991). NPR-A is expressed in the kidney, vascular smooth muscle cells, endothelial cells, adipose tissue, adrenal gland, liver, brain, and – at lower levels – in the heart (Potter 2011).

NPR-B is highly expressed in vascular endothelial cells and smooth muscle cells (Hutchinson et al. 1997), implying its role in the regulation of vascular tone and blood pressure. NPR-C lacks the intracellular guanylyl cyclase and is considered a NP clearance receptor (Nussenzveig et al. 1990). Upon binding of its ligands, the NPR-C-ligand complex is internalized resulting in lysosomal hydrolysis of the ligand and recycling of NPR-C to the cell surface. However, an intrinsic effect of NPR-C activation involving the inhibition of adenylate cyclase has been discussed (Anand-Srivastava and Trachte 1993). Another receptor, NPR-D, has been cloned and its ligand binding properties have been characterized (Kashiwagi et al. 1995). It is abundant in the brain but its physiological relevance in mammals remains unclear.

3 Transgenic Models Illustrating the Function of the NP system

While the exogenous administration of NPs provided valuable information on their main actions, the observed effects were typically of short duration and the receptor-selectivity was lost when supra-physiological doses were given. To overcome these constraints, genetic models of either overexpression or targeted deletion have been employed to facilitate the understanding of the physiological functions of NP and their receptors thereby providing additional insights into their role in health and disease states.

The transgenic overexpression of the ANP gene in mice that resulted in a fivefold increase in plasma ANP levels was associated with a significantly lower blood pressure compared to their littermates reflecting a reduction in vascular resistance (Barbee et al. 1994). These mice also showed a 27% reduction in heart weight while cardiac output, stroke volume and heart rate remained unaltered. Conversely, ANP deficiency by targeted deletion of the proANP gene resulted in salt-sensitive hypertension and cardiac hypertrophy that seemed to be independent of blood pressure (John et al. 1995; Feng et al. 2003).

The genetic modification of BNP showed a similar pattern: overexpression of human BNP in mice was associated with arterial hypotension while BNP deficiency through disruption of the preproBNP gene led to cardiac fibrosis (Ogawa et al. 1994; Tamura et al. 2000).

Mice lacking NPR-A were characterized by cardiac hypertrophy and fibrosis along with a reduced survival (Oliver et al. 1997). These mice had elevated blood pressure and died prematurely due to the development of congestive heart failure or aortic dissection.

Mice with targeted deletion of either CNP (Chusho et al. 2001) or NPR-B were not viable as their intrauterine growth was significantly impaired, highlighting the role of NPR-B in normal development (Tamura et al. 2004). However, a rat model overexpressing a dominant-negative NPR-B mutant that was associated with blunted NPR-B signaling had a normal phenotype at birth but developed progressive myocardial hypertrophy primarily due to increased cardiomyocyte size in the absence of marked fibrosis (Langenickel et al. 2006). The important role of NPR-C in clearing NPs from the circulation became evident in mice lacking NPR-C that showed a prolonged ANP half-life associated with hypotension, mild diuresis and volume contraction (Matsukawa et al. 1999).

Taken together, these animal models revealed the importance of the NP system in the regulation of blood pressure, water and electrolyte balance as well as cardiac growth.

4 Regulation of Natriuretic Peptides in Heart Failure

Heart failure is a complex clinical syndrome that is characterized by impaired left ventricular function and typically manifests with fluid retention leading to pulmonary congestion and dyspnea, peripheral edema and decreased exercise tolerance (Yancy et al. 2013). These maladaptive changes can be attributed to systemic neurohormonal activation involving RAAS, endothelin, vasopressin and the sympathetic nervous system, which, initially acting as compensatory

mechanism to maintain systemic circulation, lead to a vicious cycle of sustained activation.

Under physiological conditions, both ANP and BNP are predominantly stored in the atria and continuously secreted, the resulting plasma levels ranging between 3–20 and 1.4–12 pM, respectively (Rademaker and Richards 2005). In heart failure, plasma ANP and BNP levels increase primarily in response to cardiac filling in the presence of cardiac congestion. Initially, acute volume load leading to atrial distention triggers the release of pre-formed ANP while at a later stage increased atrial and ventricular synthesis of both ANP and BNP contribute to a persistent elevation of their plasma concentrations. According to immunohistological studies, the peptide concentrations of ANP, BNP and CNP are significantly increased in ventricles of human failing hearts (Wei et al. 1993a). In recent studies, ANP has been shown to positively correlate with the pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and left ventricular hypertrophy thereby representing an indicator for the severity of heart failure (Raine et al. 1986; Dietz et al. 1986; Tsutamoto et al. 1989). These observations initiated the utilization of NPs as diagnostic and prognostic markers in the management of heart failure.

The activation of NP system in heart failure represents an important compensatory mechanism which ultimately fails to effectively prevent fluid retention and to maintain water and electrolyte homeostasis. Several underlying mechanisms have been discussed: (1) an inadequate NP release in response to stimuli, (2) downregulation of NPRs (Matsumoto et al. 1999; Tsutamoto et al. 1992; Cabiati et al. 2010), (3) impaired NP signaling due to desensitization of NPRs leading to relative peripheral NP resistance (Schroter et al. 2010), (4) upregulation of NP degrading enzyme neprilysin (Knecht et al. 2002), (5) upregulation of cGMP-degrading enzyme phosphodiesterase-5 (Nagendran et al. 2007; Pokreisz et al. 2009). Nevertheless, the NP system has been recognized as an important regulatory system in CHF and therapeutic strategies promoting the effectiveness of NPs in individuals with heart failure have shown beneficial effects.

5 Use of NPs As Biomarkers in Heart Failure

Based on the observations that heart failure is associated with elevated plasma levels of ANP and BNP, these peptides became an attractive tool aiding in the diagnosis and management of HF (Omland et al. 1996). As the N-terminal fragments of the ANP and BNP prohormones are secreted in equimolar amounts but do not undergo the same fast enzymatic degradation except renal excretion, they have a longer half-life resulting in higher plasma levels. Plasma NP levels can be measured using commercial assays, including point of care devices, making them suitable biomarkers for rapid diagnosis (Weber and Hamm 2006; Nayer et al. 2014). While ANP is the dominant circulating peptide in healthy individuals, the rise of BNP levels is more pronounced in the presence of heart failure or other conditions that are associated with increased ventricular wall stress. Today, NPs play an important role as biomarkers in three different aspects of heart failure and also in the more general context of cardiovascular diseases: (1) primary prevention: assessment of cardiovascular risk in an apparently "healthy" individuals, (2) diagnosis of heart failure in acute care setting of patients presenting with dyspnea, (3) stratification and management of patients with chronic heart failure.

5.1 Biomarkers Predicting CV Risk in the General Population

Large epidemiological studies have established the use of NPs as predictors for heart failure and cardiovascular events in healthy subjects or patients with preexisting CV diseases (Agarwal et al. 2012; Wang et al. 2006; Chahal et al. 2015). In the context of the Framingham Heart Study, the use of CV biomarkers was assessed in more than 3000 participants and it was found that BNP

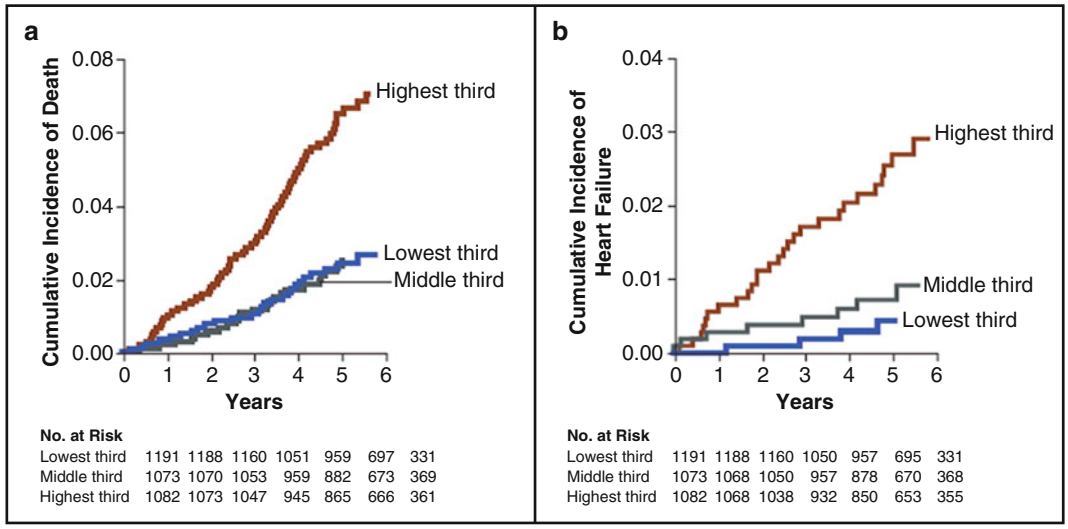

Fig. 2 The use of plasma BNP levels in predicting the incidence of death and heart failure in the general population (Data from the Framingham Heart Study, Wang et al. 2006)

was the most informative predictor for future major cardiovascular events and death (Fig. 2). Similarly, elevated plasma BNP levels were found to be a key risk factor for the incidence of heart failure (Velagaleti et al. 2010). The value of adding the measurement of NT-BNP to the risk stratification beyond conventional clinical risk factors has also been demonstrated in several trials (Kistorp et al. 2005). McKie et al. compared the potential of ANP, NT-pro ANP and pro-BNP as predictive markers for heart failure in a large community-based cohort that was followed over 9 years (McKie et al. 2011). While ANP was found to correlate with the onset HF, it did not predict mortality or the risk for MI. By contrast, NT-proBNP was associated with increased mortality, HF and MI. Overall, NT-pro BNP was identified as the most robust marker to predict mortality and CV risk in the general population. Another study in patients with chronic heart failure found that mid-regional proANP (MR-proANP) showed a better correlation with poor survival than NT-pro BNP, thus adding prognostic information in these patients (von Haehling et al. 2007).

Based on cumulative evidence showing BNP and NT-BNP as strong predictors for the new onset of heart failure in the general population, these biomarkers are currently recommended for clinical use by the AHA (Chow et al. 2017).

5.2 Diagnosis of HF in Acute Settings

The measurement of plasma NP levels has been proven extremely useful in addressing a common problem in clinical cardiology, which is the accurate diagnosis of heart failure in patients presenting with dyspnea in the emergency room or outpatient clinic. Early studies indicated that both plasma ANP and BNP levels increase with the extent of hemodynamic load and left ventricular dysfunction (Schrier and Abraham 1999). More recent studies found that BNP and NT-proBNP were superior to ANP in establishing the diagnosis of heart failure (Maeda et al. 1998). In the **B**reathing **N**ot **P**roperly study, plasma BNP levels correlated well with the symptoms according to the New York Heart Association class (Maisel et al. 2002). Furthermore, when 100 pg/ml was used as a cut-off, the sensitivity of BNP to diagnose heart failure in patients presenting with dyspnea was 90% while the specificity was 76% (Fig. 3). A similar

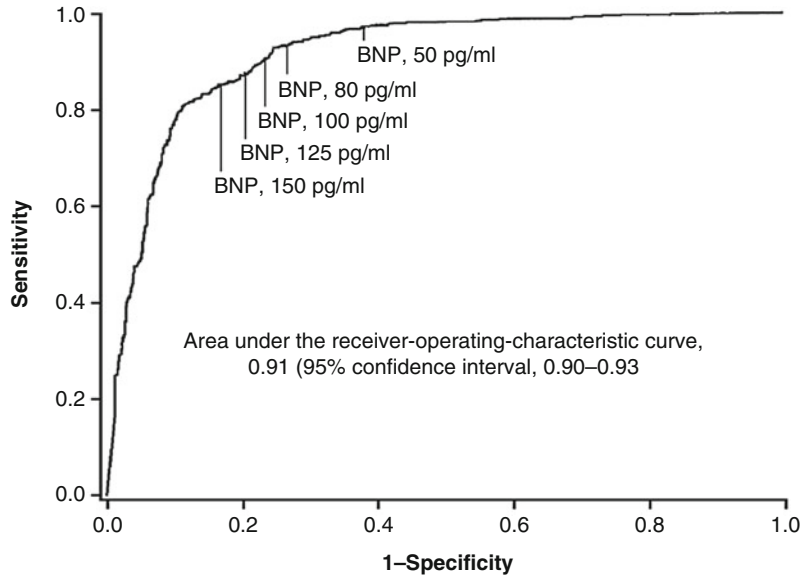

Fig. 3 Diagnostic sensitivity and specificity of plasma BNP levels in patients presenting with dyspnea (Data from the Breathing Not Properly trial, Maisel et al. 2002)

BNP pg/ml	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Accuracy
	(95 percent confidence interval)				
50	97 (96–98)	62 (59–66)	71 (68–74)	96 (94–97)	79
80	93 (91–95)	74 (70–77)	77 (75–80)	92 (89–94)	83
100	90 (88–92)	76 (73–79)	79 (76–81)	89 (87–91)	83
125	87 (85–90)	79 (76–82)	80 (78–83)	87 (84–89)	83
150	85 (82–88)	83 (80–85)	83 (80–85)	85 (83–88)	84

accuracy was found for NT-proBNP (Roberts et al. 2015). Defining the threshold of NT-proBNP at 300 pg/ml resulted in a 99% accuracy to rule out heart failure according to the PRIDE study (Januzzi et al. 2005).

Based on these data, the concept of utilizing NPs in the differential diagnosis of heart failure has now been adapted by ESC, AHA and ACC guidelines that recommend the use of BNP and NT-proBNP for decision making as well as assessment of severity and prognosis (Ponikowski et al. 2016; Yancy et al. 2016). Accordingly, FDA approved BNP and NT-proBNP immunoassays to aid the diagnosis of heart failure (FDA 2001).

When interpreting the results of NP testing, medical conditions that have an impact on circulating plasma NP levels need to be taken into account. Such confounding factors that lead to increased plasma levels include: higher age, impaired renal function, anemia, atrial fibrillation, pulmonary hypertension or embolism, right ventricular dysfunction and sepsis (Chow et al. 2017; Collins et al. 2015; Richards et al. 2013). Conversely, NP levels were found to be lower in patients with obesity, pericarditis and end-stage cardiomyopathy. For the clinical practice, the use of different cut-off points for different age groups, kidney function parameters and BMI have been discussed (Hill et al. 2014).

5.3 NPs for Guidance in HF Management

The therapeutic management of patients with heart failure is complex despite the availability of drugs including beta blockers (BB), ACE

inhibitors (ACEi), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRA) that have a proven benefit for long-term survival. Nevertheless, the individual treatment regimen is often chosen based on symptoms rather than on objective criteria. As BNP and NT-proBNP are excellent marker for CV mortality and have shown to improve with treatment of chronic heart failure (Anand et al. 2003; Fruhwald et al. 2007; Tsutamoto et al. 2001), it is reasonable to assume that changes in plasma NP levels reflect the progression or prognosis of heart failure. Therefore, their role in guiding the management of patients with existing heart failure has been evaluated.

One of the first clinical studies to demonstrate a significant benefit of NP-guided therapy was published in 2000 and showed a reduction in 6-month mortality in patients hospitalized with decompensated heart failure and impaired left ventricular function (Troughton et al. 2000). Here, patients whose therapy was modified based on periodic plasma NT-proBNP level measurement had a reduced risk to experience a cardiovascular event including death, hospital admission or outpatient heart failure. Conversely, the intensified medical treatment in the NP-guided treatment was associated with a reduction in plasma NT-proBNP levels.

A recent meta-analysis that pooled data of 11 studies enrolling 2000 patients with heart failure compared the outcome of patients undergoing NP-guided versus clinically guided treatment showed that utilizing BNP or NT-proBNP in the management of heart failure reduced all-cause mortality (Troughton et al. 2014). In this treatment group the prescription of ACEi/ARB, BB and MRA was also higher. However, the benefit seemed to depend on the age and was limited to patients younger than 75 years as the survival benefit was abolished in patients above 75. In the TIME-CHF study that compared intensified (based on NT-proBNP levels) and standard therapy in elderly heart failure patients and used a target of 400 pg/ml in patients <75 years or 800 pg/ml in patients >75, no difference was seen with respect to heart failure symptoms or hospital admission-free survival (Pfisterer et al. 2009). While NT-proBNP guided treatment reduced the number of hospitalizations for heart failure, this effect was again limited to those patients less than 75 years. When selecting a threshold of 1000 pg/ml NT-proBNP for the outpatient management of individuals with chronic left ventricular function (PROTECT), the effect was striking showing a 42% reduction in total cardiovascular events after an average of 10 months follow-up (Januzzi et al. 2011). By contrast, a recently published study that based the intensified treatment on NT-proBNP levels at discharge from hospital did not show any difference from the control group (Carubelli et al. 2016). Furthermore, when comparing the value of (NT-pro)BNP guided treatment in patients with heart failure and reduced (HFrEF) versus preserved (HFpEF) ejection fraction, it was noted that the beneficial effect is limited to the HFrEF population (Brunner-La Rocca et al. 2015).

Taken together, the evidence for the benefit of NPs in heart failure management remains ambiguous and this can be in part attributed to the heterogeneity in the design of the heart failure trials, enrolling different patient populations and defining different cut-off points and criteria for therapy adjustment. Reflecting the controversy resulting from recent studies, the use of BNP/NT-proBNP in guiding the therapy in patients with decompensated heart failure is currently not recommended (Ponikowski et al. 2016; Yancy et al. 2016).

6 Therapeutic Implications for NPs in Heart Failure

6.1 Synthetic NPs

Based on the observation that NPs elicit profound natriuretic and vasodilatory effects, several synthetic NPs were explored as a potential therapeutic strategy in heart failure to counteract progressive sodium and water retention.

6.1.1 Anaritide and Carperitide (ANP)

The synthetic human ANP-analog anaritide, which corresponds to the 25 aa carboxy terminus of the mature peptide had been investigated in healthy subjects and shown to have the expected renal effects and also reduced systemic and pulmonary blood pressure along with a suppression of plasma renin and aldosterone levels. When administered in patients with congestive heart failure, however, some of the hemodynamic effects were comparable while the renal effects were blunted (Cody et al. 1986). A similar renal hyporesponsiveness was observed by other groups upon infusion of the full-length peptide in patients with heart failure (Saito et al. 1987) while others were able to demonstrate beneficial renal effects in these patients (Fifer et al. 1990). As a result, carperitide, a synthetic full-length peptide was approved for the treatment of acute decompensated heart failure in Japan but is not approved in other countries.

6.1.2 Neseritide (BNP)

Despite its approval for the treatment of acute decompensated heart failure in the US in 2001 the data on the use of nesiritide has sparked a lot of controversy, which ultimately led to a decline in its clinical application (Hauptman et al. 2006). Initial trials demonstrated natriuretic and mild hypotensive responses to the infusion of human BNP in healthy volunteers that could be reproduced in patients with congestive heart failure (Yoshimura et al. 1991; Marcus et al. 1996).

The largest early study in 432 patients hospitalized with symptomatic heart failure that received incremental doses of nesiritide in comparison to intravenous standard therapy showed a sustained hemodynamic and clinical improvement over 1 week (Colucci et al. 2000). Similarly, the VMAC trial published in 2002 showed that nesiritide administration was more effective in improving hemodynamic function and reducing heart failure symptoms than placebo or nitroglycerin (VMAC 2002), although the latter effect was modest.

However, a meta-analysis of five subsequent studies including more than 1200 patients suggested that the administration of nesiritide in heart failure could be associated with a risk of worsening renal function at least at higher doses (Sackner-Bernstein et al. 2005). The ASCEND-HF trial enrolling over 7000 patients was conducted to alleviate these concerns and it did not show any differences between nesiritide and placebo with respect to deterioration of renal function in patients with heart failure. Surprisingly, no benefit on symptomatic improvement, cardiovascular mortality or hospitalization rate was found (O'Connor et al. 2011). The latest metaanalysis assessing data of 38,000 patients from 22 randomized trials provided the final confirmation that, while the concerns about negative effects on renal function could be ruled out, there is no lasting cardiovascular benefit associated with the use of nesiritide. Instead, the risk of symptomatic hypotension was significantly increased (Gong et al. 2016). As a consequence, nesiritide has not been approved in Europe with the exception of Switzerland, and is not recommended for treatment of symptomatic heart failure by the current guidelines.

6.1.3 Ularitide (Urodilatin)

The latest in the group of synthetic NPs that advanced into late stage clinical development for heart failure is ularitide, a 32 aa urodilatin analogue. The peptide combines the renal properties of ANP while presenting with a relative resistance to the degradation by neprilysin. Administered in patients with decompensated heart failure, ularitide increased cardiac output and preserved renal function without affecting systemic blood pressure (Luss et al. 2008).

Despite promising effects and a favorable safety profile in the recently published outcomes study TRUE-AHF that enrolled more than 2000 patients the short-term hemodynamic effects did

not translate into a reduction of long-term cardiovascular mortality (Packer et al. 2017).

6.1.4 Cenderitide (CD-NP)

The dual chimeric NP receptor activator was created by Lisy et al. adding the carboxyl terminus of DNP to human CNP (Lisy et al. 2008). The resulting 37 aa peptide targets NPR-A and NPR-B, is resistant to enzymatic degradation by neprilysin (Dickey and Potter 2011) and combines renal and antifibrotic properties (Lee et al. 2016).

Chronic infusion of cenderitide in a rat model of left ventricular hypertrophy showed a significant reduction of cardiac hypertrophy and fibrosis along with improved left ventricular diastolic function (Martin et al. 2012). This effect was observed in the absence of any blood pressure reduction or change in heart rate.

Similarly, in the first trial in healthy volunteers cenderitide infusion over 4 h resulted in a significantly increased diuresis and natriuresis along with suppression of plasma aldosterone levels while the blood pressure response was minimal (Lee et al. 2009). Recognizing the therapeutic potential of the predominant antiproliferative actions of cenderitide in restenosis prevention after vascular interventions a cenderitide-eluting stent (CES) was developed and implanted in porcine coronary arteries. Despite the detection of CD-NP in the systemic circulation, indicating a sustained release of the peptide after stent implantation, CES was not superior in reducing neointima formation than control stents (Huang et al. 2016). Clinical trials in heart failure and other cardiovascular indications are still ongoing and a clinical benefit has yet to be demonstrated.

6.1.5 Others

Synthetic DNP has been investigated in animal models of heart failure and was found to improve cardiac and renal function by reducing cardiac filling pressure, right atrial and pulmonary wedge pressure and to increase diuresis and natriuresis along with glomerular filtration rate (GFR) (Lisy et al. 2001; Chen et al. 2002). Despite these favorable effects, no clinical development has been reported to date.

Vasonatrin (VNP), a synthetic peptide combining CNP with the 5 C-terminal aa of ANP, has potent arterial and venous vasodilating properties in combination with natriuretic effects (Wei et al. 1993b). This peptide was also shown to be superior to ANP and CNP with respect to its antiproliferative effect in smooth muscle cells (SY et al. 2005).

Finally, a new method of NP delivery has been explored with conjugated oral human BNP that was successfully tested in dogs where it led to blood pressure reduction and increased sodium excretion (Cataliotti et al. 2005, 2008).

6.2 Neprilysin Inhibition

Known for more than 40 years when it was first isolated from renal brush border (George and Kenny 1973), the zinc-dependent endopeptidase NEP 24.11 (neprilysin) has only recently moved to the focus of attention in heart failure therapy.

Enzymatic degradation of NPs by neprilysin is the final step that terminates the action of circulating NPs (Bayes-Genis et al. 2016; Stephenson and Kenny 1987a). Since its discovery neprilysin has been found in various organs and tissues including brain, heart (in cardiomyocytes and fibroblasts), peripheral vasculature, adrenal gland, lungs, gastrointestinal secretory epithelial brush borders, thyroid, epithelia, fibroblasts, and neutrophils. Its soluble form has been detected in urine and cerebrospinal fluid. While NPs, particularly ANP and CNP, have high affinity for this enzyme, they are not specific substrates but share this degradation pathway with other vasoactive peptides such as angiotensins, bradykinin, adrenomedullin, endothelin and arginine vasopressin (Stephenson and Kenny 1987b).

Despite elevated NP levels in patients with heart failure it has been postulated that the increased NP secretion is inadequate to compensate the progressive fluid retention and vasoconstriction caused by systemic neurohormonal activation. Thus, preventing NP degradation

could be a viable strategy to restore the functionality of the NP system under these conditions.

6.2.1 First Generation Neprilysin Inhibitors

Early studies by Wilkins et al. (1992) already showed that specific neprilysin inhibition by candoxatrilat enhanced the natriuretic effect of acute ANP infusion in rats while the neprilysin inhibition alone did not have a renal effect. Interestingly, in a rat model of experimental heart failure characterized by elevated plasma ANP levels and cardiac hypertrophy candoxatrilat alone was able to induce natriuresis and attenuate cardiac hypertrophy (Abassi et al. 2005). However, when candoxatril was administered in patients with mild chronic heart failure, the hemodynamic improvement was comparable to the effect seen with furosemide (Westheim et al. 1999). Similarly, the improvement in exercise tolerance was comparable to the effect seen in the captopril- treated group (Northridge et al. 1999).

6.2.2 Dual Neprilysin/ACE Inhibitors

Given the lack of clinical or hemodynamic benefit of candoxatrilat in patients with heart failure, (Westheim et al. 1999) the development of the dual neprilysin/ACE inhibitor omapatrilat seemed to be promising as it resulted in augmenting NP effects while avoiding stimulation of angiontensin II. Indeed, treatment with this vasopeptidase inhibitor in the OCTAVE study led to a more potent blood pressure reduction in patients with hypertension than ACEI alone (Kostis et al. 2004). However, the concomitant inhibition of bradykinin was associated with an increased incidence of angioedema. The OVERTURE trial that enrolled more than 5000 patients with chronic heart failure and assessed cardiovascular mortality and morbidity revealed that omapatrilat was not superior to enalapril (Packer et al. 2002). Instead, the incidence of angioedema was 60% higher in the omapatrilat treated group (0.8% vs. 0.5%) and safety concerns ultimately led to the termination of the clinical development.

6.2.3 Dual ECE/Neprilysin and Triple ACE/Neprilysin/ECE Inhibitors

A different approach that also targets the neurohormonal activation in heart failure is the simultaneous inhibition of neprilysin and endothelin-1, with or without concurrent ACE inhibition (von Lueder et al. 2013). Dual ECE/neprilysin inhibition lowered blood pressure and left-ventricular enddiastolic pressure without affecting heart rate or left ventricular contractility (Mulder et al. 2004). As echocardiographic studies revealed, the dual inhibitor reduced left ventricular end-diastolic and systolic diameters indicating improved cardiac remodeling after experimental myocardial infarction. Another dual inhibitor, daglutril (SLV306), had been evaluated in patients with congestive heart failure that underwent invasive hemodynamic assessment. Compared to placebo, daglutril lowered pulmonary artery pressure, right atrial pressure and PCWP in a dose-dependent fashion but did not affect systemic blood pressure or heart rate (Dickstein et al. 2004). Although initially promising in this indication, daglutril was not further developed for treatment of heart failure.

Analyzing the effects of triple inhibitor in an experimental model of heart failure, it was demonstrated that triple inhibition for 4 weeks reduced blood pressure more than ACEI or dual ECE/neprilysin inhibition while the increase in cardiac output was comparable among the three groups. However, the triple inhibitor was superior in reducing left ventricular remodeling (Mellin et al. 2005).

Given the controversial results (Xiong et al. 2017) on endothelin antagonism in heart failure trials, the development of combined inhibitors with neprilysin is not likely to move forward.

6.2.4 Angiotensin Receptor/Neprilysin Inhibitors (ARNI)

A new drug class of ARNI combining ARB and neprilysin inhibition has recently been introduced, and with sacubitril/valsartan (also known as LCZ696) the first drug in this class has been approved for treatment in heart failure. Avoiding the bradykinin-related adverse events

seen with omapatrilat and using an ARB instead of an ACEI, the concept of blocking RAAS while augmenting NP system has proven to be beneficial on heart failure symptoms as well as cardiovascular outcome.

In the PARADIGM-HF study more than 8000 patients with heart failure and reduced ejection fraction (<40%) showing mild to moderate symptoms were randomized to receive either sacubitril/valsartan or enalapril (McMurray et al. 2014). The study was stopped early after a median follow-up of 27 months due to overwhelming benefit in the sacubitril/valsartan group (Fig. 4a). In these patients, the rate of hospitalizations for heart failure was reduced by 23% compared to enalapril and this effect became already evident after 30 days (Fig. 4c). Post-hoc analysis of the study data confirmed that the beneficial effect of sacubitril/valsartan exists irrespective of the baseline left ventricular ejection fraction (Solomon et al. 2016). A strong correlation between NT-proBNP levels and CV risk after treatment with sacubitril/valsartan or enalapril was seen in PARADIGM further affirming the role of NT-proBNP as prognostic marker in patients with heart failure (Zile et al.

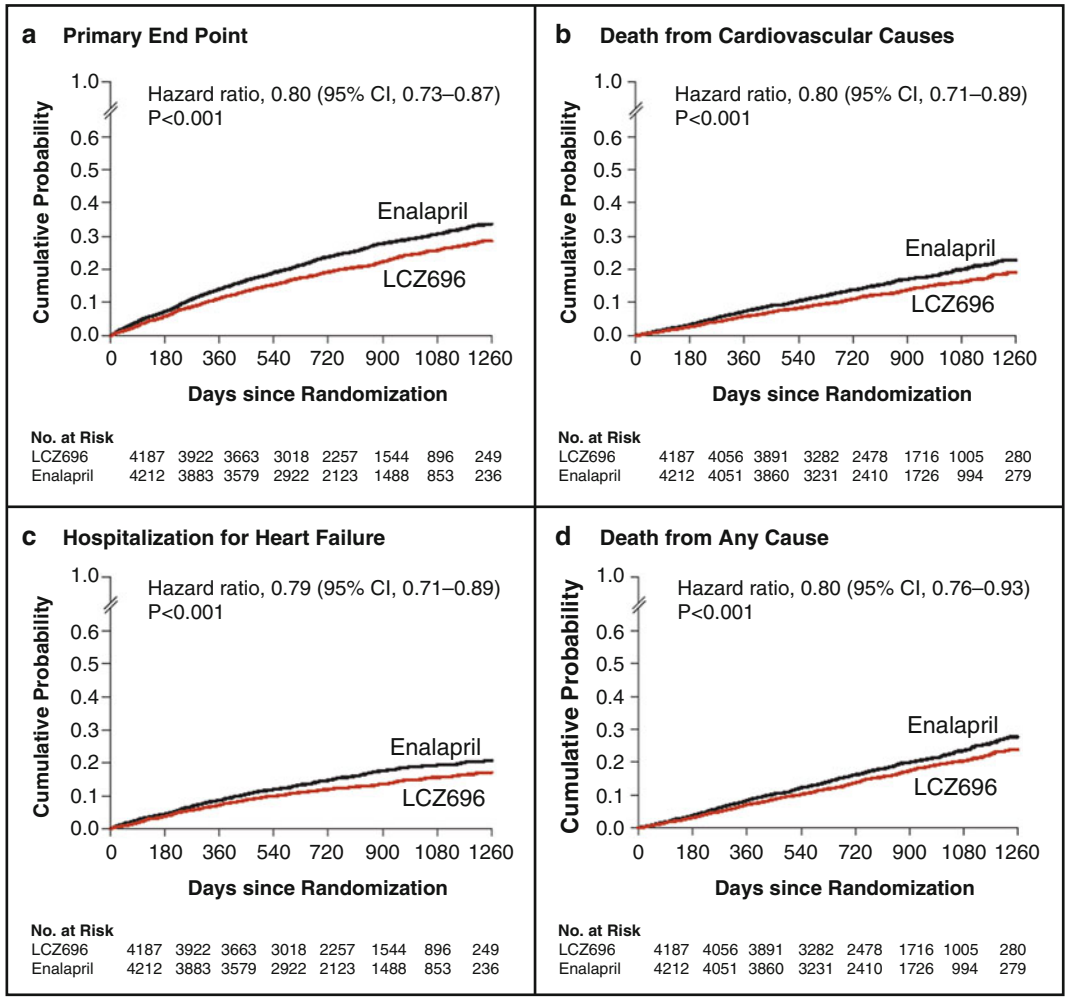

Fig. 4 Effect of sacubitril/valsartan on cardiovascular mortality and morbidity in patients with heart failure and reduced left ventricular function. Primary endpoint was the composite endpoint of death from cardiovascular causes or hospitalization for heart failure (Data from the PARADIGM study, McMurray et al 2014)

2016). Current ESC and AHA guidelines recommend the replacement of ACEIs in ambulatory patients with heart failure and reduced ejection fraction (HFrEF) who remain symptomatic despite optimal treatment (Ponikowski et al. 2016; Yancy et al. 2016).

After establishing the therapeutic value of ARNI in patients with HFrEF, additional trials have been design to investigate the beneficial effect in the HFpEF population. Using NT-proBNP as a surrogate marker for long-term outcome in patients with heart failure, the PARAMOUNT study was able to demonstrate that treatment with sacubitril/valsartan reduced NT-proBNP levels to a greater extent than valsartan (Solomon et al. 2012). The ongoing PARAGON (Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction) study will determine if these promising results translate into improved outcomes and if treatment with sacubitril/valsartan is more potent in reducing cardiovascular mortality and morbidity in patients with in symptomatic HFpEF than the comparator valsartan (Solomon et al. 2017).

Finally, the concept of NP system playing a pivotal role in the crosstalk between cardiac function and metabolic regulation was further supported by a recent mechanistic study that demonstrated improved insulin sensitivity and subcutaneous lipolysis in patients with obesity and hypertension treated with sacubitril/valsartan (Jordan et al. 2017). Further studies are required to evaluate if the favorable metabolic effects have additional therapeutic potential in other indications such as metabolic syndrome.

7 Conclusion

The important role of NP in the maintenance of fluid and salt homeostasis and blood pressure regulation has been known for several decades. As revealed more recently, the physiological properties extend beyond the cardio-renal axis and include favorable metabolic effects.

Despite promoting vasodilation, diuresis and natriuresis which effectively counteracts renin-angiotensin-system, vasopressin, endothelin and sympathetic activation in healthy individuals, the system ultimately fails under conditions of sustained neurohormonal activation such as heart failure. Here, maladaptive changes lead to progressive water and sodium retention, increased cardiac preload and afterload leading to cardiac hypertrophy.

Cardiac synthesis and secretion of NPs have been demonstrated to increase with cardiac load and plasma NP levels correlate closely with the severity of heart failure. Hence, they are being employed as prognostic markers and are now established as analytical tools in the diagnosis of heart failure.

Due to the described physiological effects the NP system has become an attractive therapeutic target to counteract the unfavorable hemodynamic changes, neurohormonal activation and pathological cardiac remodeling typically found in heart failure. To date the most successful treatment strategy in heart failure patients has been the dual neprilysin/ARB inhibition with sacubitril/valsartan which showed a mortality benefit in these patient as first drug in its class.

In addition, there is potential for improvement of insulin resistance and obesity and manipulating the NP system is a promising strategy to simultaneously address cardiovascular and metabolic disorders.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 133–144
DOI 10.1007/5584_2017_120
© Springer International Publishing AG 2017
Published online: 3 November 2017

The Role of Cardiologists in the Management of Patients with Heart Failure

Vera Maria Avaldi and Jacopo Lenzi

Abstract

Heart failure is a complex clinical syndrome with a remarkable impact on health care systems in terms of patients' morbidity and mortality, as well as direct and indirect costs. It is essential to redesign models of care for patients with heart failure that are tailored on personalized health care needs and carried out in the most appropriate setting. There is some debate about the role of cardiologists in the management of patients with heart failure. Indeed, results regarding the inclination of cardiologists' patients to achieve better outcomes are controversial, given the heterogeneity of studies in terms of study design, population, setting and variables considered. The aim of this chapter is to describe and synthesize the current state of knowledge about the role of specialists in the management of patient with heart failure, and to assess whether there is a type of patients for which cardiologists demonstrate the greatest value or a setting of care where they add more benefit.

Keywords

Heart failure · Cardiologist care · Mortality · Readmissions

1 Introduction

Heart failure (HF) is a complex clinical syndrome that affects 1–2% of the adult population in Western countries and whose prevalence increases up to 10% among people older than 70 years of age (Mosterd and Hoes 2007; Dunlay and Roger 2014). HF is considered a major public health issue given its leading role in affecting morbidity, mortality and hospital admissions, which represent the majority of HF-related costs (Ponikowski et al. 2016; Lloyd-Jones et al. 2009). Over the last decades, advances in treatments and management have improved survival, but readmission rates after an index hospitalization for HF remain high (Jhund et al. 2009;

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Bueno et al. 2010; Maggioni et al. 2013). It is thus urgent to redesign health care systems to develop evidence-based practices and create seamless pathways of care that join community and hospital settings in order to improve quality of care and outcomes for patients with HF (Driscoll et al. 2016).

In light of this, in the last years there has been some debate about the most appropriate role of specialists in the management of HF and other chronic conditions as well. It is possible to imagine that cardiologists have more experience in caring HF patients and provide a more accurate risk-benefit assessment of diagnostic procedures and treatments. Nevertheless, it is unthinkable that all patients with HF will receive specialty care from cardiologists. In the last two decades some articles have compared, with controversial results, cardiologist care with care provided by generalists or other physicians in relation to mortality and readmissions (Lowe et al. 2000; Auerbach et al. 2000; Bellotti et al. 2001; Di Lenarda et al. 2003; Jong et al. 2003; Ansari et al. 2003; Ahmed et al. 2003; Indridason et al. 2003; Ezekowitz et al. 2005; Foody et al. 2005; Lee et al. 2010; Boom et al. 2012; Uthamalingam et al. 2015; Selim et al. 2015; Masters et al. 2017). These studies differ in setting, length of follow-up, outcomes and variables considered in statistical adjustment. However, the approach of "either- or" in comparison of generalists and specialists was limited, and generally the key question was not whether specialists provide more value in HF care, but for what type of patients cardiologists demonstrate the greatest value or in which setting they might add more benefit (Ayanian 2000).

In this chapter we are going to describe and synthesize the current state of knowledge about the role of cardiologists in the management of patient with HF, hoping that it can serve to stimulate thought among readers and suggest policy strategies to improve health care services. The complete list of studies reviewed in this chapter is provided in Table 1.

2 What Is the Effect of Cardiologist Management on HF Patients' Outcomes?

One of the first studies on this topic was published in 2000, and is a prospective cohort study (Lowe et al. 2000) evaluating 257 over 60-year patients with HF managed in-hospital by cardiologists (40.1%) or generalists (59.9%) and followed up to 1 year after hospital discharge. Patients admitted to a cardiology department presented predominantly cardiovascular diseases and less comorbidities. No differences were found in all-cause readmissions between the two groups at 28 and 365 days. On the contrary, mortality at 30 days was higher among patients seen by cardiologists and stayed higher at 3, 6 and 12 months, although this gap diminished over time and was no more significant at 1 year. Authors explained that these findings were mostly due to different baseline characteristics rather than to differences in the quality of care provided. It is also worth noticing that this study was carried out in Australia, where general physicians and cardiologists are trained in specialty care and general medicine respectively, and this training could minimize differences in patterns of care between physicians.

Another study (Auerbach et al. 2000) found no survival advantage attributable to specialty care in the short term after discharge. In particular, Auerbach et al. analyzed the survival of 1298 patients up to 1 year after admission to 5 teaching hospitals for congestive HF between 1989 and 1994. After adjusting for severity of illness and other variables, compared to patients managed by generalists, cardiologists' patients had a lower mortality hazard ratio only at 180 days after admission with a weak statistical significance (0.72; 95% CI 0.54 to 0.96). This result suggests that different outcomes for HF patient may be more likely due to patients' characteristics than to differences in the management or in the type of care provided.

Table 1 Summary of studies comparing cardiologist care with care provided by generalists or other physicians for patients with heart failure

	Country	Study design	Study population	Comparison groups	Population size	Duration of follow-up, days	Main results
Lowe et al. (2000)	Australia	Cohort study	Patients aged ≥60 years hospitalized with HF	Cardiologists vs. Generalists	257	365	No differences were found in all-cause readmissions between the two groups at 28 and 365 days. On the contrary, mortality at 28 days was higher among patients seen by cardiologists and stayed higher at 90, 180 and 365 days, although this gap diminished over time and was no more significant at 1 year.
Auerbach et al. (2000)	United States of America	Cohort study	Patients hospitalized with an exacerbation of HF	Cardiologists vs. Generalists	1298	365	Cardiologists' patients had a significant lower mortality rate at 180 days after admission.
Di Lenarda et al. (2003)	Italy	Prospective, cross-sectional survey	Patients with HF admitted to hospital	Cardiology Department vs. Internal Medicine Department	2127	180	No differences in in-hospital and 6-month mortality or readmissions between the two groups.
Uthamalingam et al. (2015)	United States of America	Cohort study	Patients discharged with acute decompensated HF	Cardiologists vs. Hospitalists/Non-hospitalists	496	180	Mortality at 6 months did not differ between groups; cardiologists' patients were less likely to be readmitted at 6 months; the composite outcome was favorable for cardiologists' patients.
Selim et al. (2015)	United States of America	Cohort study	Patients hospitalized with acute decompensated HF	Cardiologists vs. Generalists	7516	60	The cardiologist group had a lower mortality rate at 60 days; no difference in in-hospital mortality; the cardiologists' patients had a lower readmission rate at 30 and 60 days for both all and the systolic HF subgroup.

(continued)

Table 1 (continued)

	Country	Study design	Study population	Comparison groups	Population size	Duration of follow-up, days	Main results
Boom et al. (2012)	Canada	Cohort study	Patients newly hospitalized for HF	Cardiologists vs. Generalists alone vs. Generalists with cardiologist consultation	7634	365	Patients managed by generalists alone had a higher risk of 30-day and 1-year mortality, as well as of 1-year death and/or all-cause readmission. The beneficial effect of cardiologists was stronger for the elderly and for patients in the highest mortality risk score categories.
Jong et al. (2003)	Canada	Cohort study	Patients with first-time hospitalization for HF	Cardiologists vs. General internists vs. Family practitioners vs. Other physicians	38702	365	The risk-adjusted mortality was favorable for patients treated by cardiologists from 72 hours after admissions until 1 year of follow-up. The effect of cardiologist care was beneficial for patients at medium to high risk (defined as a function of age or comorbidities), but did not emerge for patients at low risk. Readmissions for HF at 1 month were similar between patients seen by different physicians, but higher at 1 year for cardiologists' patients than for other groups. The composite outcome of death and/or readmission for HF at 1 month was lower for cardiologists' patients than for those seen by all the other physicians, but at 1 year cardiologists lost the advantage over general internists.
Ansari et al. (2003)	United States of America	Cohort study	Patients with new-onset HF	Cardiologists vs. Primary care physicians	403	730	Patients managed by cardiologists had a reduction in the risk of composite outcome of death and/or hospital admission for cardiovascular diseases at 24 months after adjusting for potential confounders.

Ezekowitz et al. (2005)	Canada	Cohort study	Patients with first-time hospitalization for congestive HF	Specialists (Cardiologists or General internists) vs. Family physicians vs. both Specialists and Family physicians	3136	365	Patients with specialists follow-up visits had improved survival at 30 days and 1 year compared to patients seen by FP alone. Patients with a high disease burden seen by both a specialist and a FP had a lower mortality rate
Ahmed et al. (2003)	United States of America	Cohort study	Patients aged ≥65 years hospitalized with HF	Cardiologists vs. Generalists	1075	90	Patients receiving consultative care had lower adjusted rates of 90-day all-cause readmission compared to those who received generalist care.
Indridason et al. (2003)	United States of America	Cohort study	Patients hospitalized with chronic HF	Follow-up visits by: only Cardiologists (CARD-only) vs. only Generalists (GM-only) vs. Cardiologist and Generalist (MIXED) vs. no follow-up visits (no-GM-CARD)	11661	365	Using MIXED group as reference, both the GM-only group and the no-GM-CARD group had significant increase in risk of death. There was no significant difference in survival between the MIXED and CARD groups.
Lee et al. (2010)	Canada	Cohort study	Patients with an Emergency Department visit for HF	30-days follow-up visits by: Primary Care physicians (PCPs) alone vs. Cardiologists alone vs. both PCPs and Cardiologists vs. neither PCPs nor Cardiologists	10599	365	Collaborative care, compared with PCP alone, was associated with a significant reduction in 1-year mortality and 1-year death and/or readmission and/or repeated emergency department visits for HF.
Masters et al. (2017)	United Kingdom	Retrospective service evaluation	Patients with a primary diagnosis of HF	Patients with HF managed by a multidisciplinary inpatient heart failure team (HFT) vs. Patients with HF with usual care before the implementation of HFT	407	365	Patients cared for by HFT had significantly lower in-hospital and 1-year mortality compared to patients managed with usual care before the introduction of the HFT.

HF Heart failure

Consistent with this argument are the results of the study by Di Lenarda et al. (2003) that compared characteristics, treatment and outcomes of 2127 patients admitted for HF to 167 cardiology departments and 250 internal medicine departments. Cardiology patients were younger, had more severe HF-related symptoms and underwent more often both invasive and non-invasive procedures; conversely internal medicine patients were older and more often women, and had more frequently a preserved left ventricular (LV) function. Also, cardiologists prescribed more β-blockers than generalists. Nevertheless, after adjusting for patients' characteristics and drug use, there were no differences in in-hospital mortality and 6-month mortality or readmissions between the two groups.

These studies clearly suggest that multivariate analyses are critical, and that the effect of specialist management might be related to selection bias of patients.

There is evidence that patients managed by cardiologists are more frequently male, younger, have more cardiovascular comorbidities than other diseases and are at lower risk of contraindications or intolerance to treatments, (Lowe et al. 2000; Auerbach et al. 2000; Bellotti et al. 2001; Jong et al. 2003; Boom et al. 2012; Selim et al. 2015) and probably for this reason receive more evidence-based drug prescriptions and invasive procedures (Di Lenarda et al. 2003; Jong et al. 2003; Ansari et al. 2003; Foody et al. 2005; Boom et al. 2012; Uthamalingam et al. 2015; Selim et al. 2015). On the contrary, patients cared by non-specialists tend to be older and with more severe comorbidities, and might have more contraindications to evidence-based treatments. In particular, the pattern of drug prescriptions has been shown to be a key element to improve outcomes and reduce mortality and the hospitalization burden for HF patients, (Al-Gobari et al. 2013; Vaduganathan et al. 2013; Sakata et al. 2013; Corrao et al. 2015; Fischer et al. 2015; Chowdhury et al. 2013; Yancy et al. 2017) and could be a process of care strictly related to the performance of cardiologists. Therefore, it is essential to take into consideration and control for differences in the patient case mix, when comparing the performance of different physicians.

Still, results are not fully consistent across studies. More recent articles underlined the beneficial effect of hospital specialist management on HF patients' outcomes even after adjusting for potential confounders. Uthamalingam et al. (2015) studied the outcomes of 496 patients discharged with acute decompensated HF, comparing the management of cardiologists with the management of hospitalists and non-hospitalists. After adjustment for patients' characteristics, comorbidities and clinical variables, mortality rates at 6 months did not differ between groups, while patients treated by cardiologists were less likely to be readmitted at 6 months for HF; also the composite outcome of mortality and/or readmissions for HF at 6 months was favorable for specialists. Still, the authors stated that patients treated by non-cardiologists were different for HF clinical manifestation, age or comorbidities, less adherent to evidence-based drugs and less likely to undergo a LV systolic dysfunction evaluation—all elements that might have a strong impact on outcomes.

Also Selim et al. (2015) highlighted the favorable effect of specialist management. They evaluated the impact of in-hospital cardiologist management on 30 and 60-day mortality and all-cause readmissions. The study population comprised of 7516 patients, 19% treated by cardiologists and 81% by generalists, and authors compared the outcomes of the two groups adjusting for patients' characteristics, comorbidities and clinical variables; they also reran analysis for a subgroup of patients with systolic HF. The cardiologist group received more evidence-based drug prescriptions and presented a lower mortality rate at 60 days compared with the generalist group, but there was no difference at 30 days and for in-hospital mortality. Concerning HF and all-cause readmissions at 30 and 60 days, results were favorable for patients managed by cardiologists for both all and the systolic HF subgroup. The authors concluded that the potential benefit of cardiologist- vs. generalist-centered care should be acknowledged, although cardiologist care was

not associated with a strong improvement in short-term outcomes. These results suggest that involvement of cardiologists could improve outcomes especially for HF patients with specific characteristics of clinical severity. This is confirmed by Boom et al. (2012) that analyzed 7634 patients newly hospitalized for HF in 81 hospitals of Ontario and evaluated the specialty-related differences in processes of care and outcomes. The authors distinguished the in-hospital care provided by cardiologists, generalists alone, and generalists with cardiologist consultation. The involvement of cardiologists had impact on prescriptions of evidence-based drugs and on execution of both invasive and non-invasive procedures. Patients managed by generalists alone had a higher risk of 30-day and 1-year mortality, as well as of 1-year death and/or all-cause readmission. The beneficial effect of cardiologists was stronger for the elderly and for patients in the highest mortality risk score categories, suggesting that specialty care could be most advantageous for high-risk patients, who typically benefit most from evidence-based therapies.

All of these studies evaluated the general survival and readmission of hospitalized patients, given the assumption that the in-hospital management is a primary determinant of post-discharge outcomes. Anyway, these results were also confirmed in studies evaluating the outpatient and primary care setting.

A Canadian study (Jong et al. 2003) analyzed a cohort of 38,702 subjects hospitalized for the first time between 1994 and 1996 and compared processes of care and outcomes of patients managed by cardiologists in hospital (14.2%) vs. those managed by general internists (35%), family practitioners (41%) and physicians of other disciplines (9.9%). Patients seen by cardiologists were more likely to be younger, male and with a history of cardiovascular diseases, and more likely to undergo invasive procedures. The risk-adjusted mortality was favorable for patients treated by cardiologists from 72 h after admissions until 1 year of follow-up. In particular, the effect of cardiologist care was beneficial for patients at medium to high risk (defined as a function of age or comorbidities), but did not emerge for patients at low risk. Moreover, readmissions for HF at 1 month were similar between patients seen by different physicians, but higher at 1 year for cardiologists' patients than for other groups. The composite outcome of death and/or readmission for HF at 1 month was lower for cardiologists' patients than for those seen by all the other physicians, but at 1 year cardiologists lost the advantage over general internists. We think that these results are noteworthy, as they caught the heterogeneity that characterizes the setting of hospital and community care.

Given these evidences, the involvement of cardiologists seems to be advantageous especially for the most complex and impaired HF patients. In addition, as highlighted by the studies described above, there is proof that specialty management affects the outcomes of patients with a new onset of HF.

This is also confirmed by a retrospective cohort study, (Ansari et al. 2003) in which Ansari et al. evaluated characteristics, treatment and outcomes of patients with HF at early stage managed in outpatient setting by primary care physicians and cardiologists. They compared 198 patients managed by cardiologists with 205 patients managed by primary care physicians. Patients treated by cardiologists tended to be men, younger and with more cardiovascular comorbidities. In addition, cardiologist care was associated with a higher adherence to guidelines recommendations as far as prescriptions of evidence-based drugs for HF and related comorbidities. Cardiologists prescribed more ejection fraction evaluations and their patients had a reduction in the risk of composite outcome of death and/or hospital admission for cardiovascular diseases at 24 months after adjusting for potential confounders.

Another study (Ezekowitz et al. 2005) evaluated the impact of specialist follow-up on outcomes of patients with new-onset congestive HF. Of 3136 study patient, 34% received no follow-up cardiovascular visits, 24% were seen only by family physician (FP), 1% only by specialist (cardiologists or general internists), 42%

by both specialist and FP. Patients who received combined care had higher Charlson Index comorbidity scores, more outpatient visits and accesses to emergency department, and were more frequently readmitted for cardiovascular care at 30 days and 1 year compared to those seen solely by FPs. However, after adjusting with a Cox proportional hazards time-dependent covariate model for different follow-up periods, frequency of visits, days spent in hospital during the follow-up, age and some comorbidities, patients seen by specialists had improved survival at 30 days and 1 year compared to patients seen by FP alone. In this study, patients with a high disease burden seen by both a specialist and a FP had a lower mortality rate, and a possible interpretation is that they had more access to health services and more opportunities to detect a worsening health status or to adjust their medical treatment.

That being said, despite the heterogeneity and the substantial differences between the studies until now considered, we can argue that the involvement of cardiologists could influence and improve the management of HF. This is evident in any setting of care and especially for patients with a more severe clinical impairment, who receive more benefit from appropriate diagnostic assessment and pharmacological treatments—all interventions mostly carried out by cardiologists rather than by other physicians.

3 Are Cardiologists Able to Respond to Any Needs of Care of Patients with HF?

It is essential to consider that for chronic conditions, including HF, the more patients seek care from specialists, the higher are medical costs related to procedures, interventions and types of medication prescribed that are not necessarily useful to achieve an improved quality of care (Starfield et al. 2009). In addition, given that patients with HF are elderly and generally affected by other comorbidities, it is necessary to adopt an approach that takes into consideration all of the care needs of these patients.

HF guidelines (Ponikowski et al. 2016; Yancy et al. 2013) recommend a collaborative model in which generalists, cardiologists and other professionals provide care together to optimize outcomes and quality of life. Although there is evidence that multidisciplinary approach improves quality and outcomes of care of HF, (Rich et al. 1995; McAlister et al. 2004; Hansen et al. 2011; Metra and Teerlink 2017) such models of care do not always delineate the specific role of specialists nor preferential settings where cardiologists should be involved with generalists for a better care of patients.

Some studies in this field have compared HF treatments and outcomes based on the specialty of admitting or attending physicians, and assessed whether cardiologists collaborated as consultants in the care of patients directly managed by non-specialists.

A retrospective cohort study (Ahmed et al. 2003) compared the management of 1075 patients with HF, 65 years and older, provided by cardiologists (13%), generalists (55%) or both in consultative care (32%). Patients receiving consultative care were more likely to undergo an LV ejection fraction evaluation and to receive ACE inhibitors compared to those managed in solo care. In addition, they had lower adjusted rates of 90-day all-cause readmission compared to those who received generalist care.

Another study (Indridason et al. 2003) evaluated the 1-year survival of a cohort of almost 12 000 patients with chronic HF discharged from the Department of Veterans Affairs hospitals in 1991 and 1992. Patients were subdivided in 4 groups in relation to the outpatient specialist care received: only cardiologists (CARD-only, 7%), only generalists (GM-only, 56%), cardiologist and generalist (MIXED, 29%), and no follow-up visits (no-GM-CARD, 8%). After a Cox proportional hazards analysis, using MIXED group as reference the GM-only group and the no-GM-CARD group had a 26% and 48% significant increase in

risk of death, respectively. There was no significant difference in survival between the MIXED and CARD groups. These results were compared with analyses carried out in a second cohort observed between 1994 and 1995, and no differences emerged. Authors suggested that the patterns of outpatient care had impact on survival and that the involvement of cardiologists, when in collaboration with generalists, improved survival. A limitation of the study was the use of administrative data and the lack of some important patients' characteristics, including LV function. In addition, patients in the MIXED group had on average more visits compared to others, and it is possible that the intensity of follow-up contributed to better outcomes.

Another Canadian study (Lee et al. 2010) evaluated the impact of outpatient care after an emergency department visit for HF. The study population comprised 10 599 patients seen within 30 days of discharge by primary care physicians (PCPs) alone (62.2%), cardiologists alone (5.1%), both PCPs and cardiologists (13.9%), or neither PCPs nor cardiologists (18.8%). Patients managed in collaborative care received more evidence-based drug prescriptions and were more likely to undergo an assessment of LV function or both invasive and non-invasive procedures compared to those visited only by a PCP. In addition, collaborative care, compared with PCP alone, was associated with a significant reduction in 1-year mortality (HR 0.79; 95% CI 0.63 to 1.00) and 1-year death and/or readmission and/or repeated emergency department visits for HF (HR 0.86; 95% CI 0.78 to 0.94).

Lastly, we want to mention the presence of some specific models of HF management, implemented especially in the UK, based on collaborative care with a multidisciplinary HF specialist team. A very recent study (Masters et al. 2017) evaluated in a UK University Hospital the impact on HF patients' outcomes of a multidisciplinary inpatient heart failure team (HFT), composed by a cardiologist, two nurses specialist in HF, a pharmacist and a clinical fellow. The goal of the HFT was to review and improve patient care and to manage the early follow-up after discharge. Compared to patients admitted 6 months before the introduction of the HFT, patients cared for by HFT had significantly lower in-hospital and 1-year mortality and were more likely to be discharged with evidence-based treatments. No difference between the 2 groups was found in all-cause and HF readmission rates.

These evidences suggest that patients with HF could benefit from collaborative care between specialists and non-specialists—indeed, a multidisciplinary approach is intended to guarantee the management of complex needs related not only to HF, but also to other comorbidities.

4 From Evidence to Practice: Should Cardiologists Be Routinely Involved in the Management of Patients with HF?

Although there is no clear answer to this question, specialty care seems to be associated with improved outcomes for patients with HF. In particular, patients at high risk or with a new onset of HF could benefit the most from specialist care because of the cardiologists' inclination to appropriately manage diagnostic procedures and prescribe evidence-based treatments. In general, specialty approach should be required whenever the clinical conditions are worsening or there is a transition between the inpatient and outpatient setting and vice versa. The collaboration between specialists and non-specialists is also crucial, and might lead to a patient-centered care, rather than a professionally centered care, to achieve patients' health and equity in access to health care.

Nevertheless, the current state of knowledge does not allow to identify specific clinical characteristics of HF patients that require the involvement of specialists as main professionals or consultants. In particular, there is a lack of studies investigating the different impact of cardiologist care for HF patients with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF)—two groups of patients whose clinical characteristics and prognosis require a tailored approach to treatment. Probably EF is

not routinely collected, especially in non-specialist wards, so it is difficult to distinguish these patients. In addition, the diagnosis of HFpEF is more challenging than the diagnosis of HFrEF, (Ponikowski et al. 2016) and is largely based on exclusion criteria (Ferrari et al. 2015). However, on the basis of clinical practice, it might be argued that cardiologists could improve management of patients with HFrEF, for which there are indications for evidence-based treatments, and patients with de-novo HF, for which cardiologists probably could have more experience and training in recognizing underlying cardiovascular etiology of HF.

In addition, there is lack of evidence about the specific impact of cardiologists in post-discharge period. While it is relatively easy to compare specialist and non-specialist management of HF in hospital, in the primary care setting several multidisciplinary strategies for HF management (Rich et al. 1995; McAlister et al. 2004; Takeda et al. 2012; Garin et al. 2012; Jackevicius et al. 2015) have been implemented to take into account the complex needs of patients not only related to HF, and it is difficult to recognize the competing role of different physicians. Further research is needed to identify if there are some "critical changes in care" (e.g., changes in pharmacological treatments, first signs of decompensation) for which cardiologists could add more benefit in comparison to other professionals.

Available literature does not even clarify if cardiologist care has more impact on mortality or readmissions, because of the heterogeneity of study designs and timeframes that makes results difficult to compare. It is worth noticing that differences across studies also subtend other substantial differences in health care organization that are specific to each context. Some of these could be related to: professionals' capabilities, specialized or not, to manage the patients; local procedures, after an emergency department access, for the referral of HF patients to a cardiology ward instead of a generalist or internal medicine ward; local procedures for the request of specialists' consultation when HF patients are admitted in a non-specialist ward. It should also be noted that in some settings there is a lack of standardized referral processes, and the choice of directing patients with HF to a cardiologist is at complete discretion of each professional. All these issues should be taken into consideration when analyzing the literature on this topic and discussing which professional could guarantee the best quality of care.

We can thus argue that each evidence or evaluation on this topic is significant for the context from which it is derived, but only suggestive for other contexts that have different systems of care with specific characteristics in terms of socio-economic background, population or integration between different specialists. A process of care effective in one setting might indeed be less effective or not effective at all in other settings. In conclusion, it is necessary to study and implement management strategies, specific to each context, that identify the best way to deliver cardiologist care and favor the interactions between different health professionals for patients with HF. Further research should assess the impact of cardiologist management by focusing on HF clinical manifestation, in order to identify specific clusters of patients that could benefit more from specialist care. It is also worth considering death as a competing risk for hospital readmission, and evaluating differences between outcomes in the short- long-term period.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 145–159
DOI 10.1007/5584_2017_137
© Springer International Publishing AG 2018
Published online: 28 January 2018

Optimizing Management of Heart Failure by Using Echo and Natriuretic Peptides in the Outpatient Unit

Frank Lloyd Dini, Gani Bajraktari, Cornelia Zara, Nicola Mumoli, and Gian Marco Rosa

Abstract

Chronic heart failure (HF) is an important public health problem and is associated with high morbidity, high mortality, and considerable healthcare costs. More than 90% of hospitalizations due to worsening HF result from elevations of left ventricular (LV) filling pressures and fluid overload, which are often accompanied by the increased synthesis and secretion of natriuretic peptides (NPs). Furthermore, persistently abnormal LV filling pressures and a rise in NP circulating levels are well known indicators of poor prognosis. Frequent office visits with the resulting evaluation and management are most often needed. The growing pressure from hospital readmissions in HF patients is shifting the focus of interest from traditionally symptom-guided care to a more specific patient-centered follow-up care based on clinical findings, BNP and echo. Recent studies supported the value of serial NP measurements and Doppler echocardiographic biomarkers of elevated LV filling pressures as tools to scrutinize patients with impending clinically overt HF. Therefore, combination of echo and pulsed-wave blood-flow and tissue Doppler with NPs appears valuable in guiding ambulatory HF management, since they are potentially useful to distinguish stable patients from those at high risk of decompensation.

Keywords

Heart failure · Natriuretic peptides · Pulmonary capillary wedge pressure · Echocardiography · Ejection fraction · Diastolic dysfunction · Prognosis · Hemodynamic profiles · Cardiac output

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Heart failure (HF) is a complex clinical syndrome characterized by recurrent episodes of acute decompensation, requiring frequent hospitalizations and readmissions. The prognosis of HF has improved markedly in the past 30 years as a result of many advances in the diagnosis and treatment of this condition (Ponikowski et al. 2016). However, the rate of adverse outcome remains high, underscoring the need for additional disease specific monitoring and treatment strategies (Krumholtz et al. 2000). It has been estimated that 1–2% of the healthcare expenditure is devoted to HF and that most of these costs are related to hospitalization (Heidenreich et al. 2013). The highest risk period for re-hospitalization is in the first weeks to months after discharge (Ross et al. 2010; Desai and Stevenson 2012).

Over the years, it has become apparent that ambulatory patients who receive a regular follow-up have fewer exacerbations and readmissions and that a personalized and tailored management is a fundamental step to achieve a better quality of care and to improve the outcome. Therefore, a number of strategies have recently been implemented to reach these targets (Shah et al. 1998; Fonarow et al. 1997). This evidence strongly supports the thought that HF patients, after discharge from hospital, should be followed-up by cardiologists or internists with particular expertise in HF. Nowadays, new evidences have supported the concept that better optimization of cardiovascular drugs and device therapies can be achieved by combining echo and natriuretic peptides (NPs), i.e., B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP), in the follow-up evaluation of outpatients with chronic HF (Fig. 1).

1 Biomarker-Guided Management

BNP is a 32-aminoacid polypeptide synthetized by the ventricular myocytes in response to excessive stretching of the heart muscle and correlated with LV filling pressures (LVFP) (Maisel et al. 2002, 2008). This molecule is secreted attached to 76-aminoacid N-terminal fragment called NT-proBNP. BNP and NT-proBNP are measured immunogically and their elevated levels are strong indicators of HF. However, these assays may measure multiple forms of these peptides. These altered molecules, nicknamed as "junk NPs", are immunoreactive, but minimally hormonally active (Hobbs and Mills 2008).

A modern way of managing HF patients is to apply biomarker-guided therapy. Plasma levels of NPs reflect heart condition, since NPs are known to be overloaded in HF patients, and may supplement clinical findings and can be used to titrate HF medications (Fig. 2).

The use of NP levels to guide HF therapy has been studied extensively in the last decade (Troughton et al. 2014). Elevated BNP (above approximately 125 pg/mL) or NT-proBNP (above approximately 1000 pg/mL) values are prognostically meaningful in chronic HF, and a rising pattern is predictive of impending adverse outcome, irrespective of other subjective and objective prognostic metrics. The results of several studies support the use of serial NP testing to monitor the response to therapy and improve outcome in patients with chronic HF and reduced EF (Table 1) (Jourdain et al. 2007; Januzzi et al. 2011; Eurlings et al. 2010; Shah et al. 2011; Pfisterer et al. 2009). However, not all studies in which therapy has been guided by NPs have shown superiority over the standard strategy (Lainchbury et al. 2010; Gaggin et al. 2012). An important limitation of all these prospective trials was that fixed cut-points for NPs were established *a priori*, independently from patients' characteristics (e.g., age, LV EF, LVFP, renal function etc.). Since the clinical stability of individual patients may be expressed by different NP values, attempting to lower NP levels below a fixed threshold may be impracticable or even counterproductive. It is, therefore, important to individualize NP targets by means of so-called "dry" NP levels, which can be defined as the NP value that corresponds to clinical

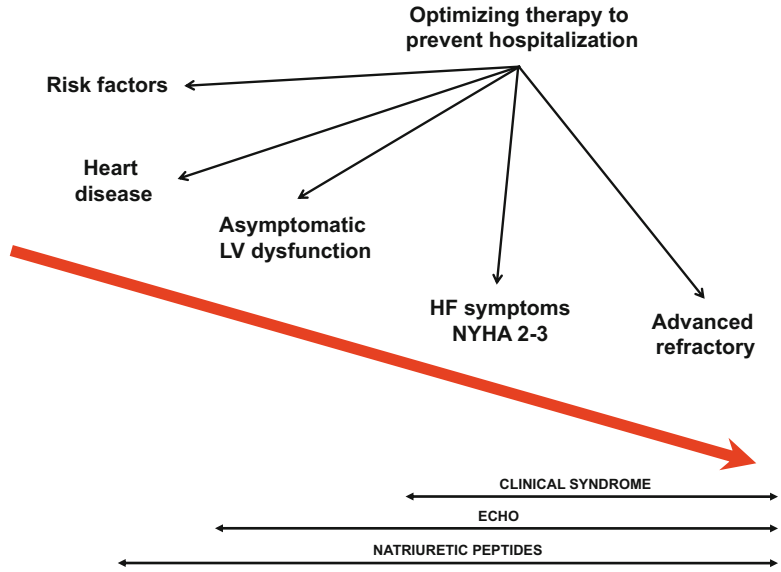

Fig. 1 Optimization of cardiovascular drugs and device therapies can be achieved by combining echo and natriuretic peptides

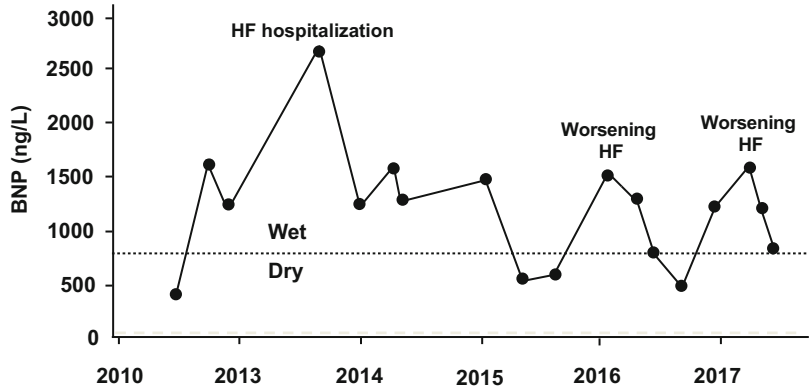

Fig. 2 Time-course of B-type natriuretic peptide levels in a patient with heart failure with reduced left ventricular ejection fraction

stability with no signs of fluid overload. Reaching low BNP or NT-proBNP, bringing the patient as close as possible to his "dry" level, can reduce the rate of both events and re-hospitalizations (Maisel et al. 2002; 2008). Relative changes of 40% in BNP values and of 25% in NT-proBNP values have been suggested as meaningful thresholds for detecting whether a significant variation has occurred (Stienen et al. 2015). With the introduction of neprilysin inhibitors, guided therapy with NT-proBNP should be recommended to prevent disease progression, optimize treatments and improve quality of life and prognosis (Zile et al. 2016).

2 Assessing Left Ventricular Filling Pressures by Echo

Several pressure measurements at cardiac catheterization has been referred to LV diastolic filling pressures. They include mean left atrial pressure, pulmonary capillary wedge pressure (PCWP) and LV end-diastolic pressure. Assessing LVFP in HF patients is of outmost importance inasmuch as more than 90% of hospitalizations due to worsening HF result from elevations of LVFP and fluid overload. Specifically, it has been recognized that PCWP is the ideal

Table 1 Strategies to lower circulating natriuretic peptide levels and reduce left ventricular filling pressures

Uptitrate or add ACEI, ARB or ARNI
Uptitrate or add beta-blockers (if not unstable)
Increase loop diuretic dosage, especially if BNP >500 pg/ml or NT-proBNP >2000 pg/ml
Add oral thiazide diuretic agents (including metolazone)
Add digoxin
Uptitrate or add MRA if tolerated by renal function and potassium
If in AF, maximize rate control or consider more aggressive attempts to restore sinusrhythm
Intensified or repeated HF education regarding sodium restriction and water intake
Consider potential indication for CRT
Consider optimization of CRT (if CRT device implanted)
Consider rehabilitation and exercise training

Legend: *AF* Atrial fibrillation, *ACE* Angiotensin converting enzyme inhibitors, *ARB* Angiotensin receptor blockers, *ARNI* Angiotensin receptor neprilysin inhibitors, *CRT* Cardiac resynchronization therapy, *MRA* Mineralcorticoid receptor antagonists

candidate to reflect the hemodynamic goal (Stevenson 2006).

LV diastolic filling pressures can be estimated reliably by echocardiography (Nishimura and Tajik 1997). Echocardiography offers a unique opportunity to identify the presence of increased LVFP (Table 2). Since the backward transmission of elevated mean left atrial and LV end-diastolic pressures is a prerequisite to cardiogenic pulmonary congestion, echo-derived assessment of filling pressures may be considered a surrogate marker of impending decompensation (Fig. 3) (Lester et al. 2008).

In recent years, knowledge and interpretation of echo Doppler measures have provided a non-invasive means for evaluating LVFP. A number of indices have been used, including: LV pulsed-wave transmitral filling velocities (E:A ratio, E wave deceleration time [EDT]), pulmonary venous flow (ratio of systolic wave velocity and diastolic wave velocity and the difference in duration between pulmonary venous flow and transmitral flow at atrial contraction), Doppler tissue imaging (DTI) and left atrial volume index (Table 2).

In patients with LV dysfunction, diastolic filling abnormalities as assessed by pulsed Doppler include three different transmitral flow velocity patterns: the impaired relaxation (stage I), characterized by a prolonged EDT with an E:A ratio $\leq$0.8, the pseudonormal (stage II), characterized by an EDT $\geq$150 ms and an E:A ratio >0.8, and the restrictive (stage III) (Fig. 4) (Nagueh et al. 2016).

An EDT <150 ms, i.e., restrictive transmitral flow pattern, has been shown to correlate well with a PCWP >15 mmHg, symptoms and advanced NYHA functional class (Nishimura and Tajik 1997). The restrictive pattern has been documented to be an important predictor of cardiac morbidity and mortality (The MeRGE Heart Failure Collaborators 2008). In patients with depressed LVEF (<40%), the presence of a stage I pattern usually reflects normal PCWP (Giannuzzi et al. 1994).

The classification based on transmitral flow velocity patterns is especially useful in patients with depressed LV EF, but in mildly reduced or preserved LV EF a prolonged EDT with an E:A ratio <1 (impaired relaxation pattern) may be sometimes associated with increased LVFP (Yamamoto et al. 1997). Therefore, in the presence of near normal (>40%) or normal EF (>50%), transmitral velocity should be considered an insensitive marker of diastolic dysfunction and combination of several variables, including the ratio of transmitral blood flow to myocardial early diastolic velocities (E/e′), left atrial size and pulmonary artery pressures, are often necessary for reliably estimating filling pressures. In these patients, a comprehensive approach that combines several echocardiographic and Doppler findings was found to be superior of any estimation of the filling pressures

Table 2 Echocardiographic and Doppler criteria to assess elevated left ventricular filling pressures

Measurement	Modality	Variable
Major criteria of elevated left ventricular filling pressures		
Transmitral velocities	Pulsed-wave blood flow Doppler	E wave deceleration time <150 ms
Transmitral and annular velocities	Pulsed-wave tissue and blood flow Doppler	Ratio of transmitral to myocardial early velocities (E/e′): medial >15, lateral ≥13, average ≥13
Pulmonary vein flow	Pulsed-wave blood flow Doppler	Difference in duration between pulmonary venous flow and transmitral flow at atrial contraction ≥30 ms
Pulmonary vein flow	Pulsed-wave blood flow Doppler	Ratio of systolic wave velocity and diastolic wave velocity ≤40%
Minor criteria of elevated left ventricular filling pressures		
Left atrial size	2D echocardiography	Left atrial volume index ≥40 ml/m^2
End-diastolic pulmonary regurgitant velocity	Continuous-wave blood flow Doppler	Estimated pulmonary artery diastolic pressure >13 mmHg
Systolic tricuspid regurgitant velocity	Continuous-wave blood flow Doppler	Estimated pulmonary artery systolic pressure ≥40 mmHg

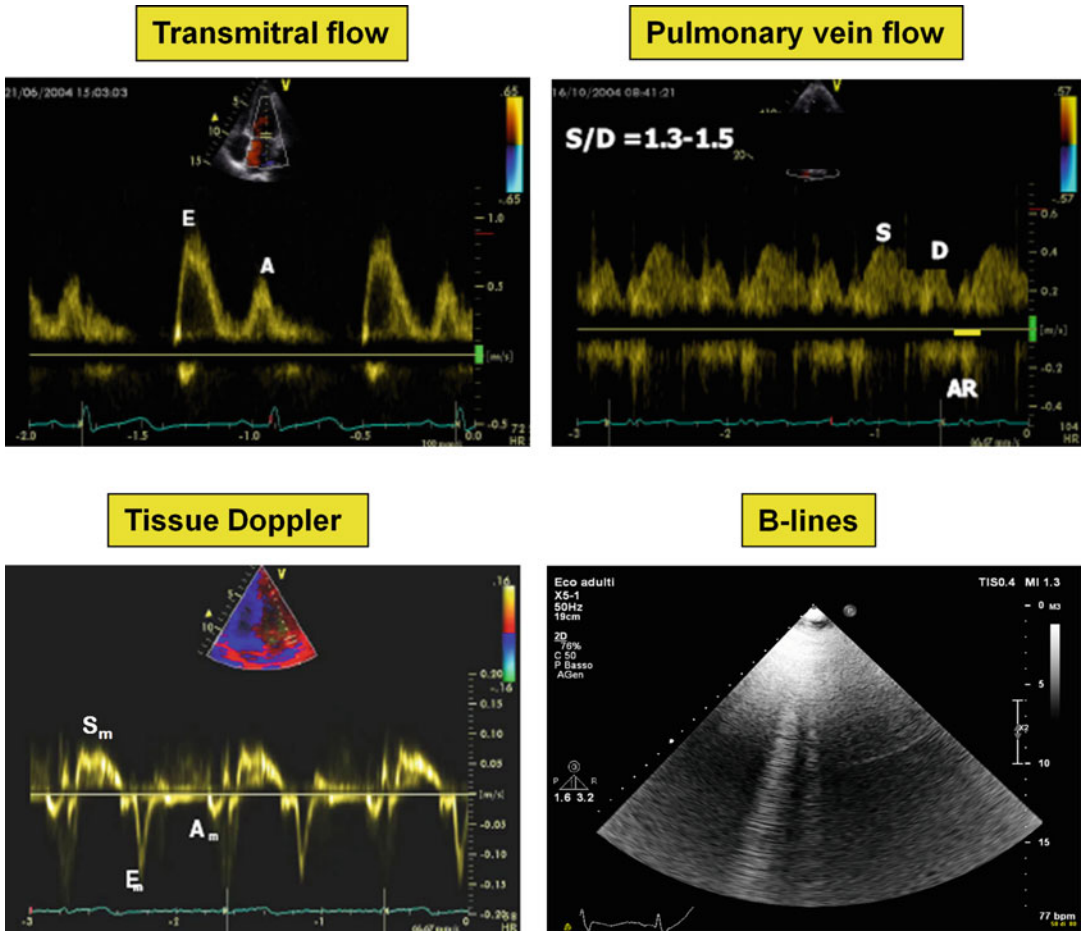

Fig. 3 Assessing left ventricular filling pressure by echo Doppler (transmitral flow, pulmonary vein flow and tissue Doppler) and pulmonary congestion by lung ultrasound

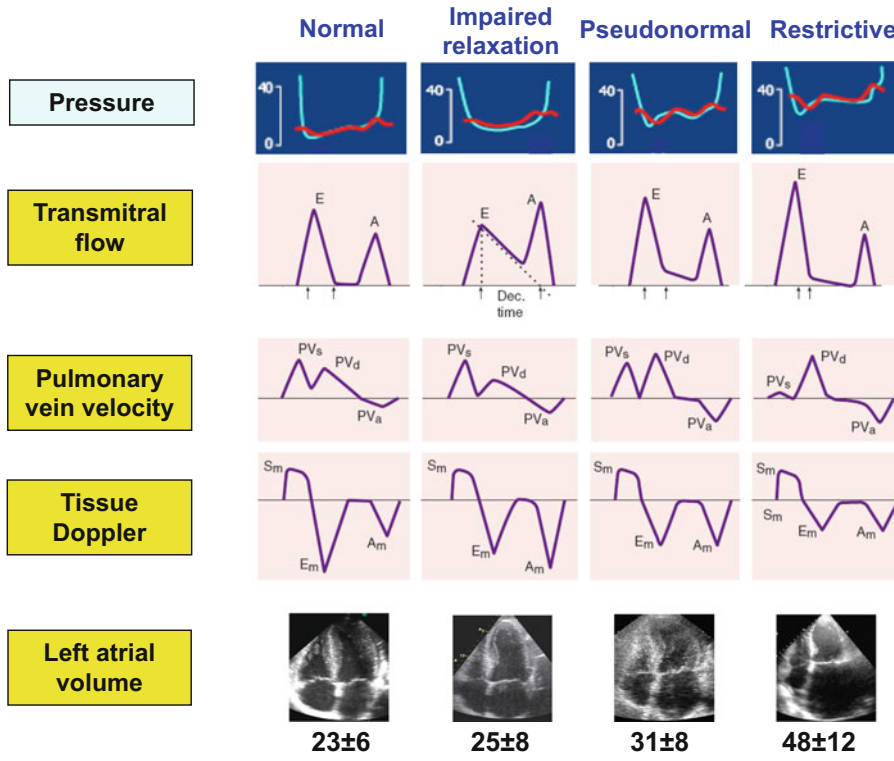

Fig. 4 Progression of the disease from normal to restriction. Note that there are four transmitral flow velocity patterns that corresponds to changes in pulmonary vein and tissue Doppler profiles as well as increases in left atrial volumes

provided by a single parameter (Dini et al. 2010). The use of echocardiographic HF risk scores has been proposed to stratify ambulatory HF patients with preserved or mildly reduced or reduced LV EF (Carluccio et al. 2013).

A clinically useful noninvasive measurement of PCWP should be able to detect meaningful changes in PCWP with therapy. Over the years, several authors have emphasized the value of reversible restrictive diastolic filling, that reflects the transition to more stabilized hemodynamic conditions. A restrictive LV filling pattern that becomes nonrestrictive after treatment or Valsalva maneuver has been associated with improved survival (Temporelli et al. 1998; Whalley et al. 2002). Patients with HF and depressed LV EF who had a restrictive flow and who did not reverse this alteration after unloading therapy had the worst prognosis.

Pulmonary venous flow patterns have provided an additional contribution to the assessment of the filling pressures (Appleton et al. 1993; Dini et al. 2000a). Analysis of the difference in duration of pulmonary venous and transmitral flow at atrial contraction has been shown to identify patients with increased LV end-diastolic pressure irrespectively of patients' LV EF. A valuable categorization has been accomplished using a cut-off value of 30 ms. Pulmonary venous A duration minus transmitral A duration >30 ms was found to be a powerful predictor of cardiac death or hospitalization for worsening HF (Dini et al. 2000b).

Diastolic dysfunction that brings about increases in LVFP very often leads to left atrial enlargement. Left atrial dilation can indicate the presence of longstanding structural heart disease and has a prognostic meaning (Rossi et al. 2002; Dini et al. 2002). The left atrium is considered to be a marker of long-term increased filling pressure analogous to the role of HbA1c as a measure of average glucose level in diabetes.

More recently, Doppler tissue imaging – particularly E/e′ – has entered the clinical scenario, thus providing additional prognostic information. Studies that have evaluated E/e′ in order to monitor PCWP in an outpatient setting have demonstrated that a ratio of E/averaged myocardial early velocity (averaged E/e′) ≥13 reliably reflects increased LVFP (Nagueh et al. 1997). In patients with near normal (>40%) LV EF, E/e′ is recommended for the estimation of LVFP, but adequate assessment of diastolic dysfunction often requires the combined use of transmitral and DTI parameters integrated with left atrial size and pulmonary artery pressures.

3 Lung Ultrasound

Lung ultrasound (LUS) is a novel technique that may detect and quantify pulmonary congestion. B-lines (previously known as lung comets) are sonographic reverberations artifacts, which originate from water-thickened pulmonary interlobular septa. Bilateral multiple B-lines are present in pulmonary congestion and are also helpful in outpatients with chronic HF failure to recognize impending signs of decompensation. B-line assessment has the advantage of being rapid, quick to learn, easy to perform and inexpensive (Frassi et al. 2007).

It has been clearly demonstrated that the presence of B-lines significantly correlated with E/e′ and NP levels, suggesting that assessing lung ultrasound can be feasible and accurate in detecting decompensation (Miglioranza et al. 2013; Gargani et al. 2015). In studies performed in patients admitted for acute HF, persistent pulmonary congestion at LUS before hospital discharge was associated with adverse outcomes of mortality and hospitalization for worsening HF (Gargani et al. 2015; Coiro et al. 2015).

Even though a number of studies have shown that LUS evaluation of pulmonary congestion is useful in the risk stratification of patients with chronic HF, the prognostic value of extravascular lung water in HF outpatients is less certain. In addition, lung comets tend to appear late during the course of the disease, and have low specificity in distinguishing between patients with pulmonary congestion and those with fibrosis. Hence, since the appearance of B-lines is a late evidence it is more reasonable to rely on echocardiographic modalities to assess elevated LVFP, which are a prerequisite to LV decompensation, rather than to depend on markers of increased pulmonary tissue water, which are obviously later findings.

4 Combining Echo and Natriuretic Peptides During Follow-Up

Early diagnosis of nonacute HF is crucial because prompt initiation of evidence-based treatment can prevent or slow down further progression. To diagnose new-onset HF in primary care is challenging and, when based on presenting clinical features alone, there may remain considerable diagnostic uncertainty. Therefore, additional testing, particularly measurements of NPs, may be of great value to refine diagnosis and improve management (Kelder et al. 2011).

In hospitalized patients with symptomatic acute HF, knowledge of LVFP is important for clinical decision making, and physical examination can provide important insight for treatment decision with very little contribution of NPs and echocardiographic findings (From et al. 2011).

In contrast with the acute setting, the clinical utility of integrated use of echocardiography and circulating NP levels has become increasingly apparent in the outpatient unit. Worsening of diastolic dysfunction and increasing NP levels often precede the development of signs and symptoms of HF, suggesting the role for preventing interventions (Fig. 1).

In chronic HF, health societies recommend the use of echocardiography for initial diagnosis when a change in the patient's clinical status occurs and when new data from an echocardiogram would result in the physician changing the patient's care. Health societies do not recommend routine testing when the patient has no change in clinical status or when a physician is

unlikely to change care for the patient based on the results of the exam (Douglas et al. 2007). However, assessment of clinical status is generally conducted with the use of the subjective NYHA classification and this measure is based on expert opinion of the presence of HF symptoms rather than objective evidence. Assessing patients with only NYHA classification may miss an objective measure that gives complimentary information and superior prognostication (Stevenson and Perloff 1989).

In recent years, the idea that a change in clinical status was the only prerequisite to performing echocardiography during follow-up of HF outpatients has been challenged (Tavazzi et al. 2013). It has become apparent that most symptoms and signs of HF have little sensitivity with regard to the detection of elevated PCWP, despite good specificity (Gheorghiade et al. 2010). The ADHERE registry data highlighted the limited reliability of clinician interpretation, as evidenced by incomplete symptom relief, in many patients with HF after hospital discharge (Adams et al. 2005).

Patients with HF are at high risk of death, but perhaps equally burdensome is the high rate of readmission. Recently, the prevention of hospital readmissions has been recognized as a primary goal for asymptomatic or mildly asymptomatic outpatients with HF has given important momentum to the role of follow-up echocardiography. With the introduction of more portable devices and focused cardiac ultrasound, a new window of opportunity has emerged for the more widespread use of echocardiography for serial evaluations of patients (Spencer et al. 2013). The value of repeated echocardiograms during follow-up visits has been supported by the ESC Guidelines on HF. Echocardiographic assessment was recommended not only to assess cardiac structure and function, including LV diastolic function, but also to plan and monitor treatment and to obtain prognostic information.

In HF outpatients, increasing the frequency of follow-up visits with the optimization of medical therapy, particular after hospital discharge, has been associated with improved outcomes, less hospitalizations and reduction of costs. To date, new evidences have supported the concept that better management and tailoring of cardiovascular therapies can be achieved by combining echo and NPs (Yin et al. 2012; Scali et al. 2014). This strategy may be proficiently combined with the standard components of the patient follow-up visit. Indeed, NPs and Doppler echocardiography, when utilized serially in an integrative and personalized manner, can be valuable in monitoring patients who are high risk of clinical exacerbation, with a significant benefit for the outcome. Patients whose BNP levels and echo-derived assessment of LVFP decrease in response to therapy had a better survival during follow-up (Fig. 5a).

The complimentary use of NP and echo-guided strategies can balance their intrinsic limitations, with crucial benefits for the patient. The limitations of the NP-based approach (including biological variability, slow time-course, poor specificity and lack of conclusive scientific evidence) may be overcome by this strategy. By contrast, assessment of NP concentrations seems especially useful in patients in whom Doppler echocardiographic parameters are inconclusive in the determination of LVFP.

The value of integrated circulating NP levels and echo-guided management of outpatients with chronic HF can be established when this strategy is compared with the standard of care. In a recent retrospective study, we observed a greater survival benefit in patients in the echo- and BNP-guided group than in a clinically-guided group (Simioniuc et al. 2016).

In echo-BNP-guided group, patients were first clinically evaluated (history, clinical examination, up-titration of therapy, measure of renal

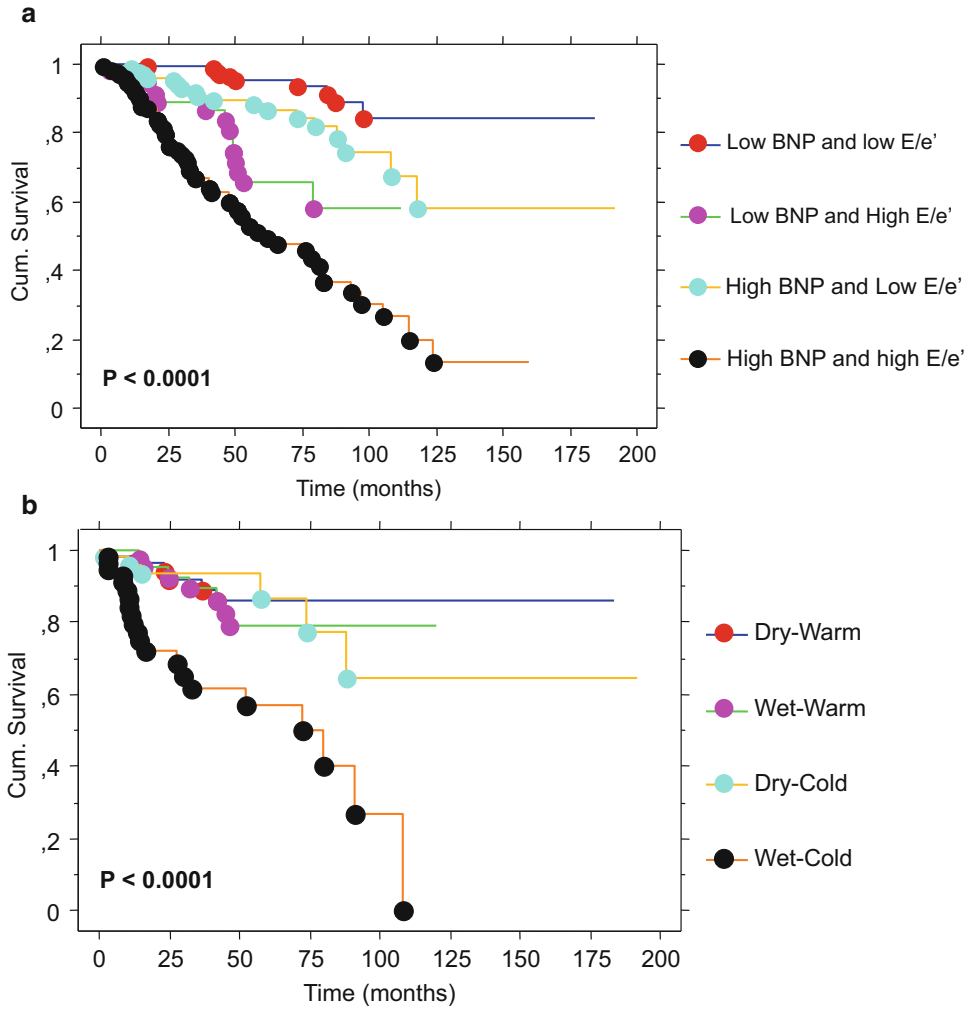

Fig. 5 (**a**) All-cause mortality in patients with chronic heart failure categorized according to B-type natriuretic peptide (BNP) levels and the ratio of transmitral blood flow to myocardial early diastolic velocities (E/e′). (**b**) All-cause mortality in patients categorized according to echo-assessed hemodynamic profiles (Simioniuc et al. 2016)

function) and BNP levels were assessed. If patients fulfilled the Framingham criteria for symptomatic HF or exhibited BNP levels at or above 125 pg/ml, echocardiography was performed as an adjunct to the physical examination, focused on the evaluation of echocardiographic signs of elevated LV filling pressures. Therapeutic decisions, including clinical interventions to lower BNP and/or elevated LV filling pressures, were made, thereafter, based on physical, biochemical and echo findings. A closer follow-up (2–4 weeks) was planned in symptomatic and asymptomatic patients exhibiting echo-Doppler signs of elevated LV

filling pressures and/or a clinically relevant rise in BNP concentration, while the frequencies of visits were extended out to 4–6 months in patients who were doing well.

The survival gain observed in the latter study was associated with a better management of renal function. Patients whose follow-up was based on standard of care had a significantly higher prevalence of worsening renal function, which was likely related to higher diuretic dosages. Patients in whom diuretic requirements were guided by NPs and echo had an advantage. In fact, diuretics were temporarily increased in those with elevated BNP concentrations and/or restrictive mitral flow with or without clinical signs of decompensation, whereas they were cautiously reduced when patients improved, especially if stabilized BNP levels and nonrestrictive mitral flow had been reached. As a result, increased necessity of diuretics or their excessive dosing were more easily identified or prevented by the echo-BNP guided care. A plausible reason behind these observations is that the early recognition of the euvolaemic state, i.e., normal tissue water content, by the echo and BNP guided strategy helps to prevent excessive dosing of loop diuretics, that may predispose patients to renal dysfunction and adverse prognosis (Harjai et al. 1999; Ahmed et al. 2006; Dini et al. 2013; Damman et al. 2016; McKie et al. 2014). We can, therefore, assume that clinical findings are of limited value to assess diuretic requirements during follow-up, whereas the echo and BNP driven approach is important to overcome this limitation and to optimize HF treatment, including loop diuretic regimen. Since renal dysfunction is known to be one of the most predictive markers for adverse outcomes in chronic HF, guiding HF care with echo and NPs seems valuable to reduce patients' risk in the outpatient setting Eliminate and substiture with (Dini et al. 2017).

In another study that compared ambulatory HF patients submitted to an echo and BNP guided follow-up versus patients who underwent a symptom-guided follow-up and those receiving no organized follow-up, management directed by echo and BNP was associated with a better survival. In the echo and BNP-guided group, raised LV filling pressure, as assessed by E/e′, and BNP levels were the best predictors of all-cause mortality, whereas presence of B-lines at LUS were independently associated with the combined end-point of death and HF hospitalization. We can, therefore, assume that clinical findings are of limited value in optimizing HF therapy during follow-up, whereas the echo- and BNP-driven approach is important in order to overcome this limitation and provide the patients with a more tailored therapy (Dini et al. 2017).

5 Hemodynamic Profiles in Patients with Chronic Heart Failure

Management of HF, improvement of survival and avoidance of HF hospitalization depend largely on correct assessment of systolic function and pulmonary congestion (Nohria et al. 2003). Classifying patients with advanced HF by baseline measures of perfusion and pulmonary congestion has been used to estimate hemodynamic status and to select and titrate therapy (Stevenson et al. 1990).

In 1976, Forrester et al. (1977) demonstrated that among patients who had an acute myocardial infarction, Swan-Ganz catheterization identified four hemodynamic profiles. These profiles were based on the presence or absence of congestion (PCWP $>$ or $\leq$18 mm Hg) and adequacy of perfusion (cardiac index [CI] $>$2.2 l/min/m^2). Profile A (dry-warm) represented no congestion or hypoperfusion; profile B (wet-warm), congestion without hypoperfusion; profile C (dry-cold), hypoperfusion without congestion; and profile D (wet-cold), both congestion and hypoperfusion. Furthermore, invasive hemodynamic profiles predicted survival, with increased mortality when congestion was present (profile B) and even worse outcomes when both congestion and hypoperfusion were evident (profile D). Conversely, profile A (dry-warm)

describes a group of well-compensated patients with a good overall prognosis.

The hemodynamic assessment of HF patients is a fundamental strength of echocardiography (Nagueh et al. 2016). According to international guidelines, echocardiography is the single most useful diagnostic test in the evaluation of patients with HF because of its ability to accurately and noninvasively provide measures of LV function and assess causes of structural heart disease. It can also detect and define the hemodynamic and morphologic changes in HF over time and might be equivalent to invasive measures in guiding therapy.

Doppler echocardiography is not only useful for noninvasive determination of LVFP, it can provide reliable and repeatable measures of cardiac output and stroke volume, which can be evaluated across any cardiac orifice, such as the LV outflow tract (Quiñones et al. 2002). The estimation of stroke volume depends on accurate assessment of LV outflow tract, errors of which are squared in the course of cross-sectional area calculations. Luckily, this measurement is facilitated by the dimensions of the LV outflow tract that are highly correlated with body surface area (Shiran et al. 2009; Leye et al. 2009). Like the Forrester hemodynamic classification, echo-directed categorization of HF patients according to hemodynamic profiles can provide information that reflects the patient's fluid status and tissue perfusion. This strategy can also be used in outpatients since it based upon noninvasive variables and does not require the presence of symptoms of decompensation for diagnosis. The value of echo-directed hemodynamic profiles is well depicted in Fig. 5b, where outpatients with HF who manifested low output and increased LVFP had the worst outcome.

Another prospective development is to integrate measures of NPs and echo markers of increased LVFP with parameters that indicate low cardiac output or depressed stroke volume (Fig. 6). The significance of this approach is that it facilitates the early recognition of the high risk patient (B, C and D), on the basis of changes in NP levels from "dry" to "wet" and modifications of echo-Doppler variables, which reflect the evolution toward congestion or low perfusion (Dini et al. 2017). The inclusion of patients in subsets A, B, C, or D may be used not only to better interpret the patient's hemodynamic status but also for prognostic stratification. Our preliminary results show that when high-risk patients do not revert to a lower risk profile on therapy, the event-rate tends to increase substantially. Finally, echo-directed hemodynamic profiling may help guide titration of medical therapy. Patients with profile A may tolerate initiation and up-titration of beta-blockers with the success observed in major trials, whereas profile B might represent a population where chronic beta-blocker therapy could be maintained but initiation or up-titration deferred until restoration of profile A. Conversely, determination of profile C might lead to a decrease or withdrawal of recently initiated beta-blockers until better compensation is achieved. The greater use of beta-blockers on admission in patients with profile A relative to those with profiles B and C is consistent with this management strategy.

6 Conclusions

There are a number of reasons to use echo and NPs in combination to optimize management during follow-up of HF outpatients. Echo parameters, including LUS, have been correlated with LVFP and are useful to identify patients with a higher than normal PCWP and incipient pulmonary congestion. However, echo variables have a significant "gray zone" in which they are often inconclusive in the assessment of LVFP. Integration of echocardiographic estimates of LVFP with the determination of NP circulating levels and measures of LV pumping capacity, such as cardiac output and cardiac index, can be used to reach a comprehensive understanding of patients' hemodynamic status. This findings can be proficiently used to distinguish stable patients form those who at high risk of clinical decompensation and may be utilized to better titrate cardiovascular medications and interventions, with clinical benefit and the reduction of costs of hospitalization.

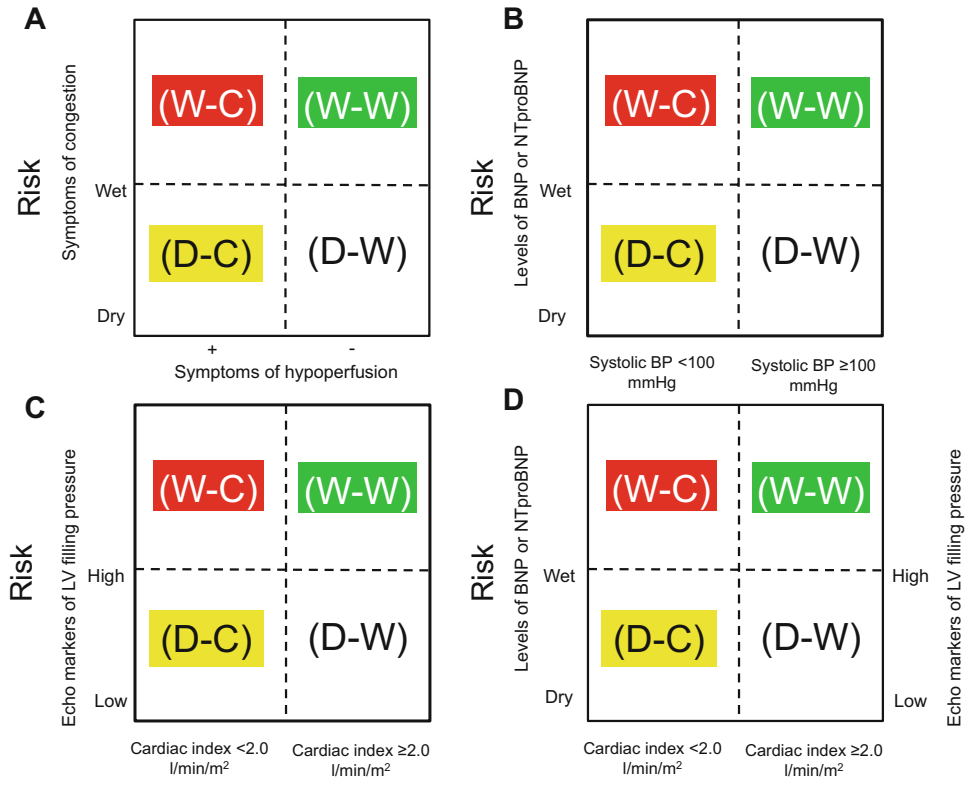

Fig. 6 (**a**) Assessment of clinical profiles. Congestion is assessed by presence of orthopnea, jugular venous distension, rales, hepatojugular reflux, ascites, peripheral edema. Compromised perfusion is assessed by the presence of asthenia, narrow pulse pressure, oliguria. (**b**) Assessment of stability by natriuretic peptides and systolic blood pressure. (**c**) Assessment of hemodynamic stability by echo. (**d**) Assessment of hemodynamic stability by natriuretic peptides and echo. D-W (dry-warm) well-perfused without congestion, D-C (dry-cold) low-perfused without congestion, W-W (wet-warm) well-perfused and congested, W-C (wet-cold) hypoperfused and congested

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 161–181
DOI 10.1007/5584_2018_144
© Springer International Publishing AG 2018
Published online: 17 February 2018

Physical Training and Cardiac Rehabilitation in Heart Failure Patients

Cesare de Gregorio

Abstract

Regardless of advances in medical and interventional treatment of cardiovascular disease (CVD), a limited number of patients attend a cardiac rehabilitation (CR) programme on a regular basis. Due to modern therapies more individuals will be surviving an acute cardiovascular event, but the expected burden of chronic heart failure will be increasing worldwide.

However, both in high- and low-income countries, secondary prevention after an acute myocardial infarction or stroke has been implemented in less than a half of eligible patients.

Combined interventions are still needed to reduce decompensations, hospitalizations and mortality in heart failure patients from any origin. In addition to medical treatments, regular exercise has been demonstrated to improve metabolic and hemodynamic conditions in both asymptomatic risk factor carriers and cardiac patients. Risk factor control and exercise should gather together for an effective management of patients.

Exercise-based training is a core component of primary and secondary prevention. It should involve healthy carriers of cardiovascular risk factors, and patients with cardiomyopathy as well. The supposed attenuated effect of CR in the era of advanced revascularization and structural interventions is due to the heterogeneity of training models and physical training in the literature. Moreover, lifestyle modification, psycho-social challenges and patient's compliance are potential confounders.

In this chapter the most recent evidences about training modalities and potential benefit of CR in heart failure patients are discussed.

Keywords

Cardiac rehabilitation · Cardiovascular disease · Exercise · Functional evaluation · Heart failure · Clinical outcomes · Physical training

Acronyms

AF	Atrial Fibrillation
CET	Cardiopulmonary Exercise Test
CHF	Chronic/Congestive Heart Failure
CO_2	Carbon Dioxide Oxygen
CR	Cardiac Rehabilitation
CT	Continuous Training
CV	Cardiovascular
CVD	Cardiovascular Disease

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HR	Heart Rate
ICD	Intracardiac Implantable Defibrillator
IMT	Inspiratory Muscle Training
IT	Interval Training
LV	Left Ventricle/Ventricular
O_2	Oxygen
VO_2	Oxygen Consumption
SET	Strength-exercise Training
TAVI	Transcatheter Aortic Valve Implantation

1 Introduction

Cardiac rehabilitation (CR) is the sum of interventions needed to ensure the best physical, psychological and social conditions to the patient with chronic heart failure (CHF) or post-acute cardiovascular (CV) event (Wenger et al. 1995; Fletcher et al. 2001) [Table 1].

Despite advances in medical and interventional treatment of cardiovascular diseases (CVDs), there are only a few patients attending at CR programme on a regular basis. Therefore, more individuals are expected to survive an acute CV event, but the occurrence of CHF as a chronic complication will be increasing worldwide. Though secondary prevention with medical drugs is habitually promoted after an acute event, CR programmes following an acute myocardial infarction or stroke have been implemented in less than a half of eligible patients. Due to limited access resources to healthcare systems, especially in low-income countries, coverage for primary and/or secondary prevention is less than expected (Piepoli et al. 2014; Rauch et al. 2016; Piepoli et al. 2017).

Table 1 Essential features in cardiac rehabilitation programmes

People's needs centred
Refining patient's ability and skills for daily routines
Encouraging social activities and return to work
Enabling patient's psychological course
Improving people's relationship with relatives
Responding to changes in people's needs
Taking patients part of their therapy
Helping patients in order to change lifestyle
Providing interdisciplinary team counselling
Reducing re-hospitalization and clinical outcomes

However, combined interventions are still needed in order to reduce decompensations, hospitalizations and mortality in CHF patients from any origin. Above drug use, regular exercise has been demonstrated to improve metabolic balance and cardiovascular condition in both cardiac patients and asymptomatic carriers of CV risk factors. Risk factor control, combined exercise and medical therapy should be patient-tailored for a better management of CHF, regardless of nationwide healthcare organization difficulties (Stephens 2009; Pulignano et al. 2016).

Exercise-based CR programmes have been recognized to be as cost-effective as medical treatment. Decreased hospital admissions and benefits in both clinical condition and quality of life have been reported by the majority of studies, and such a low mortality rate has been observed during CR time frame. The underutilization of CR is a crucial issue when successful return to work has to be warranted after an acute CV event in people of working age (Taylor et al. 2014; Ambrosetti et al. 2017).

In these clinical settings, exercise training should be encountered as a core component of secondary prevention, but also of primary prevention in healthy carriers of risk factors. The supposed attenuated effect of CR in the era of advanced revascularization and structural interventions may be linked to the heterogeneity of patients from the available studies. Also, different training models, factual lifestyle modification, psycho-social challenges, and patient's compliance are unforeseen factors (Taylor et al. 2004, 2014; Rauch et al. 2016; Piepoli et al. 2017).

2 From Risk Factor Control to Post-acute Cardiac Event

The mainstream approach to CHF patients necessarily encompasses major risk factors control. For instance, the straightforward management of systemic hypertension is class IA and tobacco smoking cessation class IC level of recommendation.

According to the ESC/ACC guidelines, counselling is strongly encouraged, especially in CHF patients routinely consuming alcohol drinks. Naturally, each patient shows individual characteristics that should be considered on the basis of their specific aetiology and pathophysiology (Arena et al. 2007; Balady et al. 2007; James et al. 2014; Ponikowski et al. 2016; Piepoli et al. 2017).

A substantial number of deaths have been likely demonstrated as a consequence of continued cigarette smoking after an acute CV event. Smokers, in fact, were shown to have 2–4 fold higher risk of new coronary and/or ischemic brain events than non-smokers. Continuing to smoke after an acute myocardial infarction or coronary revascularization leads to high probability of re-infarction and increased mortality in the mid- and long-term follow-up (Suskin et al. 2001).

Diabetes and hypercholesterolemia are very common risk factors among CHF patients, and their presence can lead to myocardial and muscle functional deterioration. Nonetheless, the benefits of rigorous glucose control have been widely debated, because deleterious effects of repeated hypoglycaemic crisis have been demonstrated in comparison with patients keeping moderately, but steady, hyperglycaemia (Aguilar et al. 2009; MacDonald et al. 2010).

However, higher HbA1c is associated with a greater risk of CV events in untreated diabetic patients with CHF (Goode et al. 2009).

Regarding obesity, in a large population-based study on 120,813 nondiabetic obese individuals (aged 51 $\pm$ 4 years), the risk of CV events was related to overweight. During a mean follow-up of 10 $\pm$ 7 years, the risk of developing cardio-metabolic multi-morbidity was 5 times higher in class I obesity individuals (OR 4.5, 3.5–5.8; $p < 0.0001$). It was almost 15 times higher in those from classes II and III combined (14.5, 10.1–21.0; $p < 0.0001$), irrespective of gender, age and race. In view of the risk of death related to cardio-metabolic decompensation, this study likely confirmed that obesity must be carefully managed in order to reduce the risk of diabetes and CVD. Thus, regular exercise should be mandatory for lifestyle to change (Kivimäki et al. 2017).

However, the most important conditions in which CR takes the greatest advantage are post-acute cardiac events. Despite important benefits of CR in combination with stringent risk factors control in patients with first coronary event (Steca et al. 2017), a recent Norwegian study reported low participation rates (20–30%) to a CR pathway among patients undergoing a first percutaneous coronary intervention. Their participation was also dependent on the geographical location. The typical participants were young, overweight and well-educated patients (Olsen et al. 2017).

Another prospective cohort study of patients with a first myocardial infarction referred to 3 different tertiary care teaching hospitals in Switzerland, Poland and Ukraine demonstrated substantial differences in treatment and secondary prevention measures according to their socioeconomic condition (Kämpfer et al. 2017).

More than 7 million people worldwide experience a myocardial infarction every year. Twelve-month mortality rates are now in the range of 10%, and the consequence is that 20% of the survivors suffer a second event. Approximately 50% of major coronary events occur in patients previously hospitalized for ischaemic heart disease (Piepoli et al. 2017).

A call for much stronger secondary prevention is nowadays crucial in order to reduce population risk and recurrences (Fig. 1).

Beyond CV risk factors control and appropriate lifestyle changes, the European Society of Cardiology is determined to embrace current challenges by updated documents aimed at covering present gaps for secondary prevention strategies, which include physical activity and exercise on a regular basis (Piepoli et al. 2014, 2017).

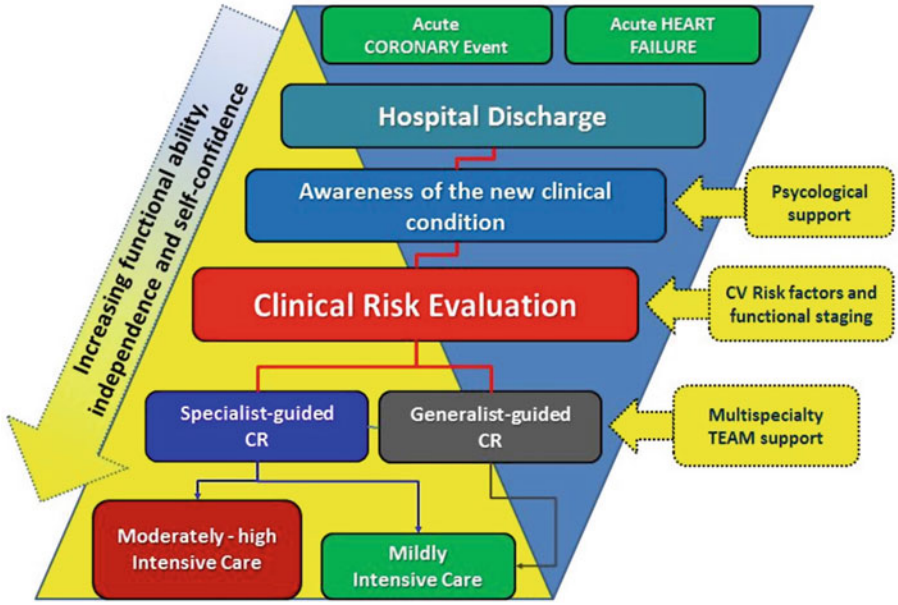

Fig. 1 Cardiac rehabilitation pathway for patients experiencing first cardiac event. Training is aimed at improving functional capability, independence and self-confidence

3 Physical Training in CHF Patients

Diagnosis of CHF is based on established criteria by the international guidelines (Ponikowski et al. 2016). Major causes of CHF with and without LV dilatation are summarized in Table 2.

Several modalities and intensity of training exercise have been tested in CHF patients. Both, progressively rising or steady intensity levels, up to 95% of peak heart rate (HR), have been shown to be beneficial on their hemodynamic status (O'Connor et al. 2009; Taylor et al. 2004). However, training protocols are still debated because of a large methodological heterogeneity (Pollock et al. 2000; Taylor et al. 2014; Cornelis et al. 2016; Ambrosetti et al. 2017).

The *Francais Groupe pour exercice réadaptation et sport (National Society of Cardiology)* has demonstrated such a variability in the management of CR protocols from various Cardiac Centres. For instance, cardiopulmonary exercise test (CET) was performed in 86% of the individuals before a CR programme. Training intensity was established on the basis of gas exchanges and peak VO_2, when available. Alternatively, patients were trained on symptoms (Borg scale), or a combination of both these latter. The amount of daily exercise sessions varied from 2 to 4 (Tabet et al. 2009).

In most cases, intensity of daily activities and exercise refers to the metabolic equivalent (MET), which is the resting metabolic rate (the amount of O_2 consumption at rest) approximately corresponding to 3.5 ml O_2/kg/min (1.2 kcal/min for a person weighing 75 kg). Working at 4 METS improves the metabolism up to 14.0 ml O_2/kg/min (Jetté et al. 1990).

Tables 3 and 4 show various activities and related METS to be applied for a CR programme in either healthy carriers of risk factors or CHF patients.

4 Exercise Modalities

Exercise involves skeletal and cardiac muscles in both mechanical (static or isometric, and dynamic or isotonic) and ventilatory-metabolic properties (aerobic and anaerobic).

Table 2 Main causes of chronic left heart failure

With left ventricular dilatation
Ischemic heart disease and previous myocardial infarction
Primary or secondary dilated cardiomyopathy
Previous myocarditis
End-stage hypertensive heart disease
End-stage hypertrophic cardiomyopathy
Aortic regurgitation
Without left ventricular dilatation
Hypertensive heart disease
Ischemic heart disease
Hypertrophic cardiomyopathy
Left ventricular (pseudo)hypertrophy from storage/infiltrative/systemic disease
Restrictive cardiomyopathy

Table 3 Range definitions of exercise intensity levels for CR

Intensity	effort	METS	Peak VO_2[a]	Peak VO_2 (%)	HR max (%)	Borg scale	Aerobic	Anaeobic	Lactate prod[b]
Low	Light	≤3	≤10.0	<40	<55	≤11/20	√		<2.0
Moderate	Intermediate	3.5–5	11.0–18.0	40–60	55–69	≤13/20	√	√	2.0–3.0
High	Vigourous	5.5–8.5	18.0–25.0	61–79	70–90	≤16/20	√	√	>3.0
Maximal	Very hard	>9	>25.0	>80	>90	≤19/20		√	>4.0

HR heart rate (bpm), *PVO_2* peak oxygen upload
[a](ml/kg/min)
[b]Lactate production (mmol/L)

Isometric exercise results in a static muscular strain, with minimal or absent limb movement. On the contrary, **isotonic exercise** leads to more or less extensive movement of the limb or body, and thus to muscle fibres changes in lengthening. This latter can also be classified as concentric (shortening of the myofibrils against gravity or a weight) or eccentric (lengthening of the muscle fibres, as a weight is lowered against gravity). Alternatively, *metabolic classification* refers to O_2 consumption, available for the muscle contraction. Exercise can be aerobic (in O_2 environment, without lactate production) or anaerobic. Both metabolic and mechanic components are usually present in a variable proportion in all exercises, as well as varying with intensity during the same exercise. Likewise, testing the response to exercise can be challenging in function of the frameworks chosen (Arena et al. 2007; Tabet et al. 2009; Fletcher et al. 2013; Hollings et al. 2017).

Endurance exercise has a predominant *dynamic–aerobic* component, but at a higher intensity it can move into a *dynamic-anaerobic* feature, related to the increased O_2 demand, primarily from the most involved muscles.

Resistance (strength) exercise refers to activities using low-mid-repetition movements against resistance, thus with a prevalent *isometric/static/eccentric* component. For these characteristics, resistance exercise should not be encouraged in patients with high peripheral resistances or systemic hypertension, although it could yield modest reduction in blood pressure.

Endurance-strength exercise is a delicate compendium of the aforementioned modalities. Though challenging, it can improve athletic performance in healthy individuals and shortening the workout time in cardiac patients. From a physiological point of view, muscles dedicate to endurance exercise are different from those involved in strength exercise. There is a

Table 4 Metabolic costs of various physical activities

Exercise	METS	O_2 uptake (ml/Kg/min)
Writing	1.7	5.9
Playing accordion/flute	1.8–2	6.3–6.5
Playing trumpet/flute	2	7
Directing an orchestra	2.2–2.5	7.7–8
Ride a horse	2.3	8–8.5
Playing the piano	2.3	8–8.5
Playing pool	2.4–2.6	8.1–8.6
Golf (assisted)	2.5	8.7
Walking (slow)	2.5	8.7
Swimming (sea)	2–4	7–14
Bowling	2–4	7–14
Dancing (cool)	2.9	10.7
Gardening (weeding)	3	10–11
Yoga	3.2–3.5	10.5–12.3
Washing floor (housework)	3.3	11
Walking (4 kmph)	3.3–3.5	11–12
Riding a bike (<10 kmph)	3.5–3.8	12–13
Sailing (assisted)	3.8	13.5
Rhythmic gymnastic	4	14
Ping pong (light)	4	14
Tennis (double)	4.2–5	15.4–17
Volleyball (light)	4.5–5	15.7–16
Swimming pool (light)	4.5–5	15.7–16
Walking (5–6 km/h)	4.5–5	15.7–16
Golf (unassisted)	4.8–4.9	17–18
Table tennis	4–8	14–24
Ice skating (<25 km/h)	5	17–18
Carpentry	5–7	17.5–22
Bicycling (10–20 km/h)	5–7	17.5–22
Skiing (alpine)	5–9	17–25.8
Modern dance	5.5	19–19.5
Aerobic/classic dancing	6	21
Tennis (singles)	6–7	21–23.5
Surfing	6	21
Free climbing	6.9	24,15
Ice skating (26–32 km/h)	9–11	24–27
Soccer (moderate-heavy)	10–11	25–29
Swimming pool (mid-heavy)	11–14	28–33

documented reciprocal interference phenomenon, because endurance muscle (red) fibres are chiefly devoted at improving aerobic metabolic capacity and facilitating body weight loss, whereas muscle mass and potency are due to strength (white) fibres, with only minor changes in aerobic capacity. Sports science has been working hard to find the best combination of both these components, but not a single solution is available to each patient yet. In cardiac patients, this is a suitable combination of exercises to improve their working ability and wellness, but the proportion of strength exercise should not exceed 30–40% of the whole training programme (Fletcher et al. 2013; Hollings et al. 2017).

5 Training Modalities

Among CR training modalities, the following have been chiefly tested in CHF patients: continuous training; interval training; inspiratory muscle training; strength exercise; and a combination of these (Fletcher et al. 2013; Mezzani et al. 2013; Cornelis et al. 2016; McGregor et al. 2016; Hollings et al. 2017).

Continuous training (CT), basically known as ***endurance training***, is characterized by a low-mid intensity, steady exercise. Usually submaximal and aerobic, it has to be performed for considerable time (eg. sauntering or jogging). It improves respiratory gas exchanges, heart rate (HR) reserve, peripheral vascular resistances and blood pressure. It also facilitates body weight loss, but needs long-term training. If a cardiopulmonary testing (CET) has been performed, training intensity should be started at 30–40% of peak VO_2, rising up to 50–60% over time.

During CT, the cardiac output increases due to the Frank-Starling mechanism and the rise in HR (cardiac output = systolic output × HR). At moderately-high intensity exercise, the cardiac output is chiefly due to HR, because the stroke volume typically reaches a plateau at 50–60% of the maximal VO_2 (Balady et al. 2007; Arena et al. 2007; Fletcher et al. 2013; Hollings et al. 2017).

Interval training (IT) is characterized by short sessions of aerobic high-load (strength) exercise alternating with resting periods (Fig. 2). Apparently more risky than CT, it has been reported as safe as the low-intensity CT. It was demonstrated to get good cardiac improvement even in populations of elderly patients with stable post-infarction CHF (WislØff et al. 2007; Mezzani et al. 2013).

In the study of Wisloff et al. (2007), CT protocol consisted of a combination of exercise at 70% (for CT) and 95% (for aerobic IT) of peak HR, for 12 weeks. Based on available literature, both European and American guidelines committees have endorsed IT as a safe modality of CR (Balady et al. 2007; Mezzani et al. 2013). More recently, high-intensity IT was proven to be beneficial as well, and individualized models of high-intensity training have been proposed according to clinical condition (McGregor et al. 2016; Ribeiro et al. 2017).

Moreover, functional capacity and atrial fibrillation recurrences were demonstrated to ameliorate in CHF patients with non-permanent atrial fibrillation after 12-month aerobic IT in comparison with CT (Malmo et al. 2016).

Inspiratory muscle training (IMT) is a modality of exercise aimed at improving respiratory functional capacity. Mechanisms of dyspnoea are multifactorial and interacting each other in CHF patients. Dominant catabolic processes, caused by LV impairment and low cardiac output, lead to respiratory and skeletal muscle myopathy which weakens exercise tolerance in the advanced stages of CHF. It has been demonstrated that abnormal increase in work of breathing due to the imbalanced ventilatory rate probably contributes to exercise intolerance and symptoms. Also, the central nervous system's perception of huge inspiratory output increases dyspnoea as well (Borghi-Silva et al. 2008).

Bosnak-Guclu et al. (2011) demonstrated that 6-week IMT (after 1-week familiarization with the method) can improve functional capacity, respiratory and peripheral muscle strength in patients with CHF. Likewise, fatigue perception, mood disorders and depression ameliorate.

More recently, IMT was also tested in intensively treated patients with prolonged use of mechanical ventilation. In this group, inspiratory training with the help of an electronic device (the manual mode consisted of 3 series of 10 repetitions with 1-min break between each series, twice a day) increased muscular inspiratory performance and shortened their weaning time significantly (Tonella et al. 2017).

Strength-exercise training (SET)**,** also defined ***resistance training*****,** is a relatively recent modality of training that was unlikely to be applied in CHF patients until a few years ago. Power exercise has been demonstrated to be feasible in a wide number of patients, when tailored to their initial functional capacity, muscle mass and muscular tone. Studies have demonstrated that intensity can be progressively increased

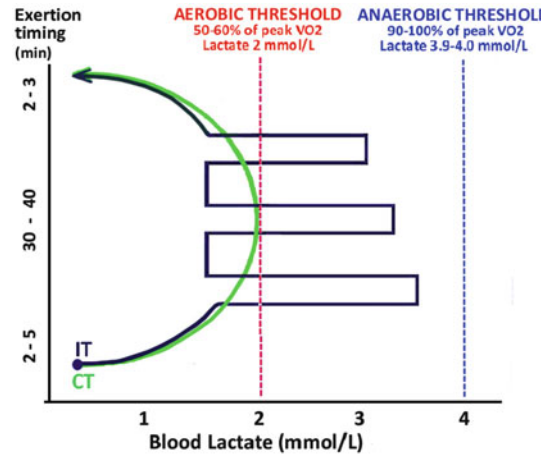

Fig. 2 Comparison of continuous training (CT) with interval training (IT) modality in a cardiac rehabilitation session, according to lactate production (Modified from Tabet et al. 2009)

from low (2–4 sets of exercises at less than 60% of pVO_2) to high-intensity level (8–10 sets, at 80–90% of pVO_2) at no clinical risk (Seguin and Nelson 2003).

Moderate to high intensity resistance training performed 2–3 days per week (for 3–6 months) was really effective in both men and women with heart disease (Pollock et al. 2000; Seguin and Nelson 2003; Ribeiro et al. 2017).

6 Eligibility for Cardiac Rehabilitation

Patients experiencing an acute CV event can be eligible for a CR programme early after hospital discharge. However, the best timing for training to be started cannot be established without considering at least the following factors: (1) magnitude of cardiac damage and persistent ventricular dysfunction; (2) residual myocardial ischemia; (3) electrical instability; (4) clinical deterioration and comorbidities; (5) pulmonary function. As expected, uncomplicated patients can be eligible for physical training earlier than those remaining symptomatic despite intensive therapy and interventional procedures, as well as when complicated by severe cardiac dysfunction, electrical instability and/or advanced kidney disease (Taylor et al. 2004; Balady et al. 2007; Taylor et al. 2014). A three-level risk classification for establishing eligibility to CR is displayed in Fig. 3. Stages A to D refer to the ACC heart failure classification reported by Hunt (2006), still valid.

Fortunately, less severe dysfunctional outcomes are expected in cardiac patients undergoing modern treatments and procedures than in the past (Piepoli et al. 2011; Piepoli et al. 2014; Ponikowski et al. 2016). For instance, a growing number of elderly patients is undergoing transcatheter aortic valve implantation (TAVI) for aortic stenosis. They represent a new class of CR candidates, whose risk level has not been established yet. Although early experimental studies demonstrated no benefit of training in mice with LV hypertrophy from aortic stenosis (exercise induced LV impairment, increased collagen expression, pulmonary congestion and worsening biomarkers) (van Deel et al. 2011), nowadays CR is recommended to patients receiving surgical aortic valve replacement (Hansen et al. 2015; Lund et al. 2016).

Better survival rate and functional capacity, but controversial mental health outcomes, have been reported by Sibilitz et al. (2016).

A recent pilot study on combined SET after TAVI demonstrated a significant improvement in exercise capacity, muscular strength, and quality of life in comparison with the usual care, without new cardiac events or prosthetic valve dysfunction (Pressler et al. 2016).

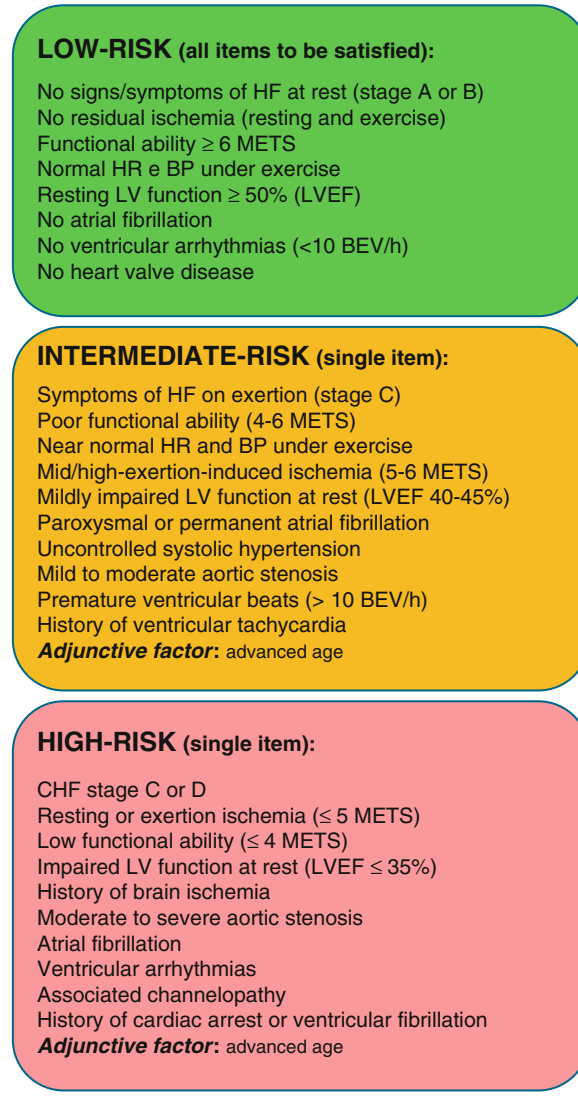

Fig. 3 Assessment of cardiac risk in CHF patients and eligibility requirements for CR. Based on the ACC guidelines, asymptomatic or sporadically symptomatic patients, thus at risk of HF (NYHA class I) can be classified as **stage A** (risk factor carriers) or **B** (presence of cardiac damage, like hypertensive heart disease, LV hypertrophy or dilatation, valve disease, previous myocardial infarction). As they become symptomatic, **stage C** refers to patients with treatable heart failure (NYHA class 2–3) and **stage D** is the most advanced stage (NYHA class III-IV), usually eligible for intensive therapy, resynchronization therapy, ventricular assistance device or heart transplant. High blood pressure can be further prognosticator also in low-risk patients

Overall, unstable and risky clinical conditions remain a warning for a safe CR programme in the CHF patient population (Fig. 3). High-risk patients should not undergo CR unless any cause of instability has been resolved. They require to be reclassified onto moderate-risk class before deciding about a CR program. These patients usually need to follow the entire pathway across all rehabilitation services, which include intensive CR program in skilled Medical Centres. Patients with a higher clinical risk need a safer modality of training (Piepoli et al. 2014; Ambrosetti et al. 2017; Karagiannis et al. 2017).

Low-risk stable patients do not deserve particular attention and can be addressed to either a centre-based or home-based CR. Both models have been demonstrated to ensure CV benefit and wellbeing. Services should be commissioned to warrant a smooth transition across all elements of their pathway. Of note, it is likewise important for patients to have easy access to hospital and local healthcare services, possibly choosing the

same one where they have been discharged from. Regular communication between outpatient hospital services and each patient is a requirement for best clinical achievements (de Gregorio et al. 2015; Pulignano et al. 2016; NHS England. 2016).

As aforementioned the recent meta-analysis by Anderson et al. (2017a, b) demonstrated no differences between home- and centre-based CR in terms of clinical outcomes at 1-year follow-up in many patients with ischemic heart disease or overt CHF. The authors also confirmed the continued expansion of evidence-based utility of CR programmes in the community.

Furthermore, no differences between home-based with tele-monitoring guidance and centre-based training were found to reach impressive health-related quality of life. Home-based training, however, was associated with a higher patient satisfaction and, as expected, it was more cost-effective than centre-based programme. Lacking territorial facilities in order to get nursing home-assistance and tele-monitoring were the main limitations of less organized communities (Kraal et al. 2017).

7 How to Assess Functional Capacity

In order to establish exercise capacity in CHF patients before starting a CR programme and during the training period, different protocols have been suggested. Many times, peak exercise values have been investigated using an effort perceived scale during exertion test, as initially proposed by Borg et al. (1984).

A short-time exercise of 8–12 min was suggested by Hansen et al. (1984) for assessing patient's perception of fatigue and/or dyspnoea. The initial 20-point Borg scale has been occasionally used for strength exercise due to its complexity. A 15-point scale was then preferred to support an easy-to-do, reliable, and instrument-independent estimation of exercise intensity. More recently, a modified 10-point scale was demonstrated to be easier to use for evaluating exercise training intensity, rehabilitation and perception, after adequate validation against objective markers of intensity. A ramp protocol on bike or treadmill test with a modified Bruce protocol has been suggested in CHF patients (Noble and Robertson 1996; Day et al. 2004).

However, **cardiopulmonary exercise testing** (CET) has become the most useful method to estimate functional capacity in cardiac patients on treadmill or cycling test. A ramping protocol of 8–12 min is encouraged to the patient performing exercise until symptoms of chest discomfort or dyspnoea become intolerable. Breath-to-breath gas exchange by a covering nose and mount mask is analysed with a metabolimeter. Minute ventilation, instant VO_2 uptake and carbon dioxide (CO_2) production are collected on a regular basis. Peak VO_2 consumption reflects the highest attainable rate of transport and use of O_2 during the incremental ramp protocol. Under normal circumstances, peak VO_2 is expressed as an absolute value (ml/Kg/m) or percent between her/his measured and reference value (Balady et al. 2010; Arena and Sietsema 2011; Schraufnagel and Agostoni 2017).

The ***aerobic threshold***, a concept based on the principle that energy production shifts from aerobic metabolism to a metabolism that combines both anaerobic and aerobic patterns during increasingly workload exercise, can be calculated with CET. Aerobic threshold differs from the ***anaerobic threshold*** on lactate production. Below the aerobic threshold, the muscles are working in optimal aerobic interval, and blood lactate level is <2 mmol/L. Overcoming the aerobic threshold means that the subject is working above 60% of the individual peak VO_2, thus in a borderline condition of O_2 debt, consistent with a moderate lactate production (2–4 mmol/L).

This latter interval still allows a CV benefit, because systemic distribution of blood flow during exercise is homogeneous, according to the rise in HR. However, as exercise intensity or lengthening increases, metabolism becomes totally anaerobic (***anaerobic threshold***) and lactacid (>4 mmol/L). At this step CO_2 production overcomes O_2 uptake, and HR no longer increases (plateau). Also, CHF patients may have uneven distribution of blood flow to muscles

and their O_2 consumption cannot be established easily. Whereas the aerobic-anaerobic time frame shortens with training in athletes, it can be really difficult to establish in patients with depressed myocardial performance (Milani et al. 1996; Lavie et al. 2004; Arena and Sietsema 2011; Schraufnagel and Agostoni 2017).

Even if initially limited to severely compromised patients who should have undergone heart transplant, indication to perform CET has been broadened to other conditions by a recent position paper of the Heart Failure Association of the ESC (Corrà et al. 2017).

In this document, the functional stratification by CET has been extended to the whole CHF population. Peak $VO_2 \leq 10$ ml/kg/min (8 ml/kg/min on beta-blocker therapy) is suggested as a high-risk condition in patients with depressed LV ejection fraction. On the contrary, a low-risk class may be attributed to patients with $VO_2 > 18$ ml/kg/min (12 ml/kg/min on beta-blocker therapy). In the relatively new patient's functional class (CHF with preserved LV ejection fraction), a moderate risk category has been suggested for peak $VO_2 < 50$ ml/kg/min.

It has been suggested that a single MET increment on treadmill test at the peak VO_2 resulted in a 13% reduction in all-cause mortality and 15% cardiovascular death (Kodama et al. 2009).

Conconi test is an alternative way to establish patient's functional capacity based on her/his walking or cycling capacity with just a moderate perception of discomfort or fatigue (based on the Borg scale). It is necessary to register the HR increase approximately every 200 m. As the HR slope does not change anymore (deflection point), this step corresponds to the anaerobic threshold (Grazzi et al. 2005; Arena et al. 2007; Kjertakov et al. 2016).

More recently, the group of Grazzi (Chiaranda et al. 2013) proposed a modified protocol in which the patient was asked to perform a single km at a moderate perceived fatigue (11–13 Borg 15-point scale). The patient began the test by walking on the level at 2.0 km/h, with subsequent increase of 0.3 km/h every 30 s up to the greater walking speed corresponding to 11–13 Borg scale until the end of the km. This study demonstrated an exponential relationship between quartiles all of average walking speed and relative risk of death. Patients with a walking rate below 4.4 km/h had worse prognosis.

Exercise ECG testing is a simple and cost-effective tool capable of providing diagnostic and prognostic evaluation of patients with known or suspected coronary heart disease. It is widely used in daily routine for making diagnosis of active ischemic heart disease, and it can offer further insights by data derived from exercise parameters like effort duration, behaviour of HR, blood pressure and occurrence of arrhythmias (Fletcher et al. 2013).

The **6-min walking test** is the easiest method to assess functional capacity in most patients with CHF, included elderly patients and those being evaluated for cardiac transplantation. It has been often used for staging patients with chronic pulmonic disease. The distance ambulated during the test predicts peak VO_2 and short-term event-free survival (Cahalin et al. 1996; Kervio et al. 2003). However in some patients with disturbed coupling between HR and walking distance, like in those with neuromuscular disease, the HR-adjusted walking distance (walked meters/mean HR) was found to be a stronger prognosticator than the absolute walking distance (Prahm et al. 2014). Particularly in the elderly, the 6-min test has to be considered a submaximal exercise, not greater than 80% of their peak VO_2. Also, to be suitable for clinical use, one or two familiarization attempts are required to bound the learning effect (Kervio et al. 2003).

Echocardiography is a cost-effective technique that provides useful information on cardiac morphology and function both at rest and exertion. Left ventricular function is a crucial marker of the patient's clinical history, and depressed LV ejection fraction has been considered the most important prognosticator. The use of echocardiography in establishing a CR programme has two kinds of indication: the first one is to assess baseline cardiac performance, which is a useful marker of CV risk and also helps to arrange the training pathway adequately (see also Fig. 2). The second and more important application is to check for morphofunctional improvement after

exercise training, beyond the individual mood or wellbeing. However, current guidelines and literature data do not recommend challenging markers to be used as strong clinical prognosticators. Among them, LV ejection fraction remains a commonly used functional index, but its measurement must be provided and verified carefully. Recent studies suggest three-dimensional as a more accurate modality than two-dimensional echocardiography to estimate cardiac chamber size and function (Squeri et al. 2017; Medvedofsky et al. 2017).

In patients with CHF the presence of myocardial tissue fibrosis and abnormal collagen content is a limiting factor for attaining clinical benefit from either medical therapy or exercise. The use of gadolinium-enhanced cardiac magnetic resonance imaging (cMRI) has definitively improved our knowledge on the pathophysiology of several cardiac diseases, especially in patients with inflammatory heart disease and cardiomyopathy (Dickerson et al. 2013; Peterzan et al. 2016).

The good relationship between tissue delay enhancement (accumulation of gadolinium as a consequence of myocardial damage or fibrosis) and ultrasound-derived functional indices confirms the need for "multi-modality" technology to investigate the cardiac function properly.

In this regard, tissue Doppler and deformation (strain) analysis have been demonstrated to be excellent noninvasive tools. For instance, LV global longitudinal strain (GLS, which is a modern marker of myocardial fibres' shortening/deformation) and untwisting (a marker of the whole heart rotation) rates were found to be closely related to cardiopulmonary functional response in CHF patients (Li et al. 2017).

Figure 4 depicts an example of the use of echocardiography for checking cardiac functional benefit out of short-term CR in CHF patients, irrespective of LV ejection fractional changes.

Likewise, peak atrial longitudinal strain can be considered as a novel and more independent marker of left atrial dysfunction in various

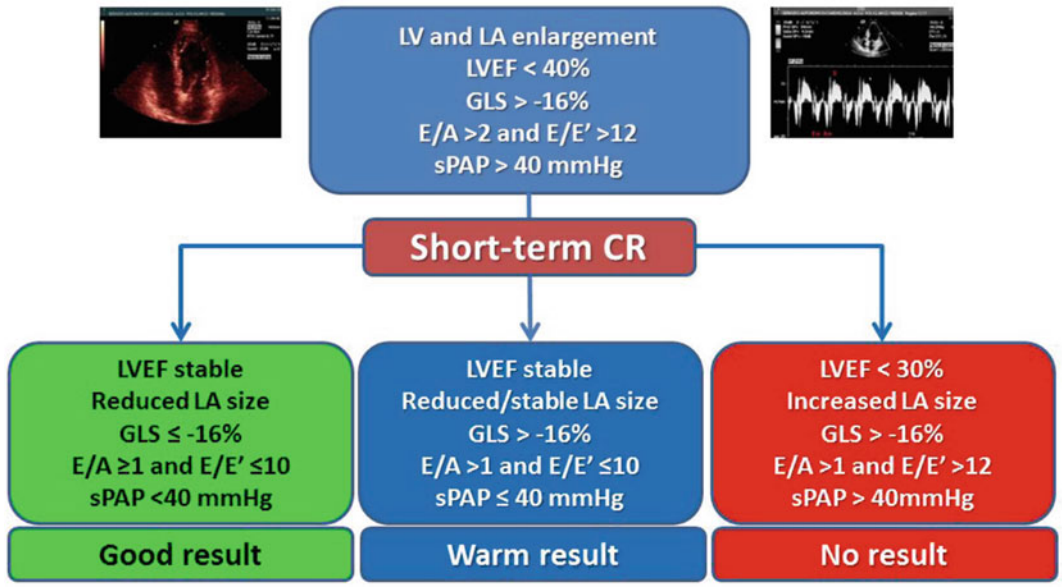

Fig. 4 Example of echocardiography functional marker changes related to short-term CR training efficacy, even in the absence of significant changes (≥10 point percent) in LV ejection fraction. E/A: is the ratio measured from the mitral valve inflow velocity (early/late mitral valve velocity ratio); E/E′: is the ratio between mitral early velocity (E-wave) and the early tissue velocity (E′ wave), measured as a mean value of the lateral mitral annulus and the basal septum; *GLS* global longitudinal strain (is a negative value, thus < is better), *LVEF* left ventricular ejection fraction, *sPAP* systolic pulmonary artery pressure

clinical conditions (de Gregorio 2016; de Gregorio et al. 2016).

Finally, multimodality echocardiography imaging provides strong information on the need for cardiac resynchronization therapy in CHF patients who have been maximized on therapy (Bertini et al. 2016).

8 Clinical Benefit of Physical Training by Meta-Analysis

In a recent meta-analysis Hollings et al. (2017) demonstrate that SET leads to an increase in both lower and upper limbs' dynamism, and improves aerobic fitness as much as aerobic CT alone in coronary heart disease cohorts. In their study, isotonic training was better than isometric and isokinetic modality, with an overall low prevalence of adverse events. Clinical gaps were identified for women and older adults in long-term outcomes. Therefore, safety and effectiveness of high-intensity training remain to be proven through large trials in such clinical settings.

Actually, fewer women than men participate in CR programmes because of a complex array of economical, medical and social challenges experienced. A recent systematic review of 31 studies demonstrated that improvement of participation has been tested through different solutions: automatic and systematic referral methods were seen to improve CR participation by 2–7 times compared to usual care, whereas early access to clinic by 8 times (both had strength of recommendation class I) (Supervía et al. 2017).

Also, liaison intervention increased referral rates as by 3 times than usual care, and other facilities like home visit, nursing phone call, motivational interviewing, gender-tailored intervention, letter, community program, telemedicine support, or smartphone-based program, were demonstrated to be useful as well (Grace et al. 2011; Gravely et al. 2014; Supervía et al. 2017).

Main results from 2 large meta-analyses on CR-related prognosis in both CHF and coronary heart disease (CHD) are displayed in Table 5 (Taylor et al. 2004; Abell et al. 2017).

Kraschnewski et al. (2016) also reported only 20–30% of older adults, with or without cardiac disease, to currently meet criteria of recommendations for strength training to be performed at least twice a week.

These findings likely emphasize the need for additional education campaigns as previously suggested (Naci and Ioannidis 2013).

In addition, generalists, internists, cardiologists, pulmonologists should encourage their patients to maintain physical activity all lifelong, as simply as they can by Table 6.

On the other hand, even if facilities to access training arenas or centres can be unsatisfactory in some Countries, studies support conclusions that home- and centre-based CR programmes are similarly effective in improving health-related quality of life in patients after myocardial infarction or with CHF (Anderson et al. 2017a; b; Kraal et al. 2017).

Older patients with limited opportunities of attending health care services may get benefit from dancing commensurate to their physical

Table 5 Results of large meta-analyses on total (A) and cardiac mortality (B) in CHF patients after CR

	Year	Studies (n)	Patients (n)	Controls (n)	Heterogeneity	Risk reduction	p-value
A							
Taylor	2004	34	326/4295 CHF	381/4137	32.53 (p = 0.49)	0.80 (0.68–0.93)	0.005
Abell	2017	47	701/5792 CHD	763/5487	NA	0.90 (0.83–0.99)	0.03
B							
Taylor	2004	18	211/2706 CHF	267/2665	14.39 (p = 0.50)	0.74 (0.61–0.90)	0.002
Abell	2017	43	288/3527 CHD	384/3399	38.90 (p = 0.63)	0.74 (0.65–0.87)	<0.0001

Table 6 Examples of exercise prescription to patients at risk of or with overt CHF

	Patients at risk of CHF (Hypertensive patients[a] or apparently healthy risk factor carriers) **NYHA CLASS 1, ACC CLASS A-B**		**Patients with CHF** (Ischemic cardiomyopathy, dilated or hypertrophic cardiomyopathy)[a] **NYHA CLASS 2–3, ACC CLASS C**	
Usual lifestyle	Sedentary	Active	Sedentary	Mildly active
Learning curve	Required (trainer-guided)	Unnecessary	Required (trainer-guided)	Required (trainer-guided)
Modality/ frequency	CT (3–4 days/week)	CT (3 days/week)	CT (2–3 days/week)	CT (2–3 days/week)
	IT (1 day/week)[b]	IT (1–2 day/week)[b]	IT (1 day/week)[c]	IT (1 day/week)[c]
Intensity	50–70% max HR (CT)	50–70% max HR (CT)	50–70% max HR (CT)	50–70% max HR (CT)
	70–80% max HR (IT)	70–90% max HR (IT)		
Type and timing of exercise	CT: walking, biking, dancing or jogging for 30–60 min/day	CT: running, biking, dancing or jogging for 60–80 min/day	CT: walking or biking for 30 min/day	CT: walking or biking for 45 min/day
	OR	OR	OR	OR
	Intermittent bouts (max **4 per session**) of 10 min each of walking, cycling, jogging, running, skating, up to max 40 min session length	Intermittent bouts (max **6 per session**) of 10 min each of walking, cycling, jogging, running, skating, up to max 60 min session length	Intermittent bouts (**2–3 per session**) of 10 min each of walking, biking or jogging, up to max 40 min session length	Intermittent bouts (**max 4–6 per session**) of 10 min each of walking, biking or dancing up to max 60 min session length
	PLUS	PLUS	PLUS	PLUS
	IT (1 session gym per week, 8–10 exercises: 1–2 sets of 10–12 repetitions per exercise with interval resting length of 120–150 s)	IT (1–2 session gym per week, 10–12 exercises: 1–2 sets of 10–12 repetitions per exercise with interval resting length of 120–150 s)	IT (1 session gym per week, 6–7 exercises: 1–2 sets of 10–12 repetitions per exercise with interval resting length of 150–180 s)	IT (1–2 session gym per week, 8–10 exercises: 1–2 sets of 10–12 repetitions per exercise with interval resting length of 150–180 s)

[a]Exercise session can be initiated with blood pressure $\leq$150/90 mmHg. Exercise should be stopped as for systolic values $\geq$200 mmHg, or the patient is complaining with chest pain, dizziness, strong fatigue (Borg scale >15)
[b]IT should be performed in a gym, usually in the middle of the week, between CT sessions
[c]After the learning period and 30–45 days of CR training programme

capability, as an alternative way of wellness (Merom et al. 2016).

9 Exercise Training in Particular Clinical Settings

9.1 Cardiac Resynchronization Therapy and Defibrillator

Cardiac resynchronization therapy (CRT) may lead to a significant improvement in functional capacity and quality of life in selected patients (especially women) with dilated CHF and left bundle branch block (Randolph et al. 2017).

Despite initial doubts and uncertainties, exercise training has been demonstrated to ameliorate hemodynamic measures in some out of these patients (Patwala et al. 2009).

Interval training was demonstrated to improve functional capacity, endothelium-dependent vasodilatation and quality of life in 52 CHF male patients with intracardiac implantable defibrillator (ICD) irrespective of cardiac resynchronization therapy (Belardinelli et al. 2006).

However, it should be taken into consideration that ICD uses exercise-independent HR as the primary method of tachycardia detection. Thus, before initiating a CR training program, the cut-off HR of the device should be known

exactly. Exercise intensity should be limited to a maximal HR at least 10–15 beats lower than the threshold discharge rate of the ICD (Fletcher et al. 2013).

Baseline functional status and severity of ventricular dysfunction will have an impact on exercise prescription and grading exercise tolerance before a CR training programme in ICD carries. In general, moderate- or high-intensity competitive athletics are not allowed, especially in activities at risk of chest traumas. Low-intensity sporting activities that do not constitute a significant risk of device damage are permitted, after 6 months since the last arrhythmia requiring an ICD intervention (Lampert et al. 2013; Zipes et al. 2015; de Gregorio and Magaudda 2017).

In a retrospective comparative survey on ICD patients, fewer shocks were registered in rehabilitated patients than in those who did not participate to training programmes (Davids et al. 2005).

Of interest, in the HF-ACTION study, a large assessment of the impact of exercise in 490 ICD patients with stable CHF, only one patient experienced appropriate shock on exertion (O'Connor et al. 2009).

9.2 Heart Transplantation

Patients undergoing cardiac transplantation are almost inactive before surgery and remain deconditioned after the operation. They receive a denervated donor heart with altered physiological response to exercise. Bradycardia is a common condition and the blunted chronotropic and inotropic responses tend to limit their exertional capacity.

However, peripheral resistances, right atrial strain and blood pressure adjustment allow the patient to perform quite good physical activity. These mechanisms support some studies showing exercise training to increase endurance capacity in heart recipients (Hermann et al. 2011; Fletcher et al. 2013).

Generally speaking, patients should enter a medically supervised CR programme as soon as they are discharged from the hospital. However, there is a lengthy delay in time from discharge to CR referral centres. Extended waiting lists are associated with adverse effects on body composition. Once referred, however, patients gain significant benefit in functional capacity (Marzolini et al. 2015).

Though similar to other patients with CVD, prescription of exercise intensity can be challenging in heart transplant recipients because their HR rises more slowly in response to exercise and can remain elevated after the end of exercise. Also, it is difficult to use HR to check for exercise intensity, and then other markers of patient' tolerance (Borg scale, workload, peak VO_2) have to be identified in this clinical setting. Evidence for exercise-based CR to improve functional capacity was recently found, but no effect was observed on quality of life, 1-year after heart transplant. Cardiac rehabilitation appears to be safe, but long-term trials are needed to confirm definite benefits (Marzolini et al. 2015; Anderson et al. 2017b).

9.3 Atrial Fibrillation

There is controversial relationship between exercise and atrial fibrillation (AF) both in apparently healthy individuals ("lone" AF) and in patients with CVD. Light to moderate physical activity, particularly leisure time activity and walking (approximately 600–800 kcal/week, walking distance of 5–10 km per week, pace >2 km/h) showed >40% risk reduction of recurrences in elderly patients with paroxysmal atrial fibrillation (Mozaffarian et al. 2008). On the contrary, another study reported that high-intensity endurance training was associated with increased incidence of AF or flutter in the general population (Mont et al. 2009).

Actually, such discrepancies can be due to inhomogeneous study populations, because aging individuals likely get an arrhythmic risk greater than younger patients when performing mild to moderate exercise.

In a recent retrospective study on 14,094 patients referred for treadmill exercise test at the Mayo Clinic Rochester (MN, USA), a better cardiorespiratory fitness was associated with a lower

risk of incident AF, stroke, and overall mortality. Similarly, the risk of stroke and death was inversely associated with cardiorespiratory fitness (Hussain et al. 2018).

Intense training can lead to a higher incidence of supraventricular arrhythmias in older patients because of the coexistence of multiple risk factors, like hypertension and obesity. These factors may promote (left) atrial chamber enlargement and fibrosis, thus facilitating the occurrence of AF. Nevertheless, in view of potential benefit of exercise in CHF patients, current guidelines do not discourage exercise training in this clinical setting (Fletcher et al. 2013).

Thoughtfulness, however, is needed as the patient enters a training programme. For instance, HR tends to increase as far as in patients with sinus rhythm, but with a challenging trend on warm-up, peak exertion and cool-down. Therefore, HR cannot be considered a suitable marker of the aerobic or anaerobic threshold, nor training effectiveness, also considering the frequent use of beta-blockers and digitalis for HR control.

Finally, recent studies have demonstrated a relationship between obesity and incidence of AF. The pathophysiological mechanisms linking these two entities are highly complex and remain incompletely understood: dysregulation in either hemodynamic, neurohumoral, inflammatory, metabolic and/or autonomics has been demonstrated in a high proportion of such patients (Wong et al. 2016; Lavie et al. 2017).

Among 1415 patients with AF and high body mass index screened for participating to CARDIO-FIT study, 308 patients were selected for a cardiorespiratory fitness training programme. Atrial fibrillation burden, symptom severity, and their functional status improved significantly in the group with a cardiorespiratory fitness gain ≥ 2 METs than in the group <2 METs, and fewer recurrences were registered in symptomatic individuals with paroxysmal AF (Pathak et al. 2015).

In patients with permanent AF, 12-week IT increased skeletal muscle strength (but not mass), exercise capacity and quality of life. It also significantly reduced resting HR. Moreover, such a gain in muscle strength was also relevant for mobility and posture of patients. Conclusions were that regular mild-intensity exercise should be encouraged to majority of patients with AF (Osbak et al. 2012).

Conflict of Interest None to declare.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 183–196
DOI 10.1007/5584_2018_183
© Springer International Publishing AG 2018
Published online: 2 March 2018

Advanced Non-invasive Imaging Techniques in Chronic Heart Failure and Cardiomyopathies

Focus on Cardiac Magnetic Resonance Imaging and Computed Tomographic

Gianluca Di Bella, Fausto Pizzino, Rocco Donato, Dalia Di Nunzio, and Cesare de Gregorio

Abstract

Cardiomyopathies (Cs) are a heterogeneous group of myocardial diseases with structural and/or functional abnormalities.

The aetiology is due to genetic-family substrate in most cases, however, the correct and detailed analysis of morphofunctional abnormalities (severity and distribution of hypertrophy, ventricular dilatation, ventricular dysfunction) and tissue characteristics (myocardial fibrosis, myocardial infiltration) are a crucial element for a definite diagnosis.

Among the different diagnostic imaging modalities applied in clinical practice (echocardiography, nuclear medicine), cardiac magnetic resonance (CMR) has emerged as a non-invasive diagnostic tool having high ability to quantify systolic function and tissue abnormalities that represent the substrates of many Cs.

The main added value of CMR is the ability to identify cardiomyopathies with respect to ischemic heart disease and, above all, to discriminate the major types of cardiomyopathies based on morpho-functional presentation patterns and the presence and location of myocardial fibrosis.

Many CMR elements allow increasing diagnostic accuracy but CMR data should be integrated with an appropriate clinical and instrumental context.

Computed Tomographic (CT) scan technology has showed a complementary role in patients having Cs and HF.

In this chapter, the diagnostic, pathophysiologic and prognostic value of CMR and CT in heart failure due to the most common cardiomyopathies will be discussed.

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Keywords
Cardiac magnetic resonance · Cardiomyopathy · Dilated cardiomyopathy · Hypertrophic cardiomyopathy · Myocarditis

1 Introduction

Cardiomyopathies (Cs) are a heterogeneous group of myocardial diseases with structural and/or functional deficiencies unrelated to anomalies of coronary arteries, pericardial diseases, arterial hypertension, valvulopathies and congenital heart disease. Although, a genetic-family substrate is the aetiology in most cases, the correct and detailed analysis of morpho-functional abnormalities (severity and distribution of hypertrophy, ventricular dilatation, ventricular dysfunction) and tissue characteristics (myocardial fibrosis, myocardial infiltration) are a crucial elements for a proper diagnostic and therapeutic work out.

The morpho-functional approach to cardiomyopathy distinguishes myocardial diseases into "hypertrophic," "dilatative," "restrictive", arrhythmogenic dysplasia and non-classified cardiomyopathies.

The most common clinical presentation of Cs is heart failure (HF).

In the last 15 years, cardiac magnetic resonance (CMR) has emerged as a non-invasive diagnostic tool having high ability to quantify systolic function and tissue abnormalities (oedema, fat and fibrosis) that represent the substrates of many Cs (Maron et al. 2006).

The main added value of CMR is the ability to identify cardiomyopathies with respect to ischemic heart disease and, above all, to discriminate the major types of cardiomyopathy based on the biventricular morpho-functional presentation patterns and the presence and location of myocardial fibrosis (Maron 2008).

The CMR with late gadolinium enhancement (LGE) identifies fibrotic tissue as an area of ⁇hyperintensity (hyperenhancement) compared to the healthy myocardium that appears to be hypo-intense. It should be noted that although some CMR elements allow for an increase in diagnostic accuracy, CMR data evaluation should be integrated in the light of an appropriate clinical and instrumental context. (Rovai et al. 2007; Di Bella et al. 2010a, b; Aquaro et al. 2010a, b).

From the practical point of view, the main phenotypic presentations of cardiomyopathies are the following: 1) increase in thickness/hypertrophy (hypertrophic phenotype) and 2) left ventricular dilation/dysfunction ("dilated "phenotype).

2 Hypertrophic Phenotype Cardiomyopathies

Hypertrophic phenotype cardiomyopathies are characterized by an increase in wall thickness in the absence of systolic load conditions that may justify its secondary development such as high blood pressure or valve abnormalities.

These manifestations may depend either on true hypertrophy, that is, by the increase in the mass of the individual myocardial cells, or by a pseudoepertrophy due to the infiltration of extracellular material or the accumulation of intracellular substances. Typically, these conditions occur in hypertrophic cardiomyopathy, infiltrative diseases such as amyloidosis and accumulation diseases such as Anderson-Fabry disease. (Elliott et al. 2008).

Using clinical data, electrocardiogram and ecocardiographic data, it is not easy to obtain a differential diagnosis between these forms, since the phenotypic appearance is extremely similar, especially in the early stages. The CMR 's added value is represented by the ability to obtain morphological images with high spatial resolution and the ability to distinguish peculiar tissue alterations based on signal characteristics in the different sequences (Fig. 1).

3 Hypertrophic Cardiomyopathy

Sarcomeric hypertrophic cardiomyopathy (HCM) is caused by mutations in sarcomeric protein genes. HCM is characterized by an increase in wall thicknesses (15 mm in at least one LV

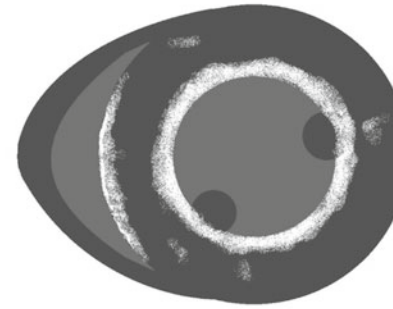
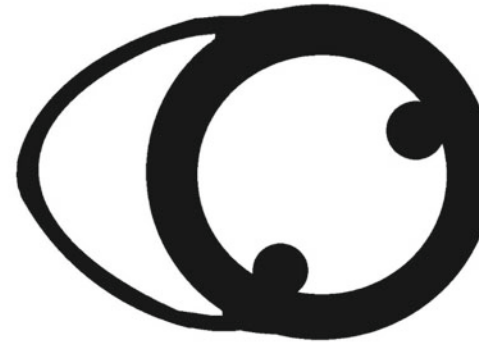
CMR findings in hypertrophic cardiomyopathies	
Sarcomeric HCM	**Cardiac Amiloidosis**
	
• Asymmetric hypertrophy (usually) • Focal LGE in LV junction and septum • Hypertrophy of papillar muscles	• LV Concentric hypertrophy • RV Hypertrophy • Low contrast myocardium-cavity (blood) • Subendocardial circumferential LGE • "zebra" appearance • More focal LGE areas
Anderson-Fabry disease	**Athlete's heart**
	
• LV Concentric hypertrophy • Inferolateral mid-wall (epicardial) LGE	• Eccentric hypertrophy • Small wall thickening • Dilated both LV and RV volumes • No LGE

Fig. 1 Late gadolinium enhancement (LGE) patterns in hypertrophic cardiomyopathies that one may encounter in clinical practice. According with LV hypertrophy and LGE localization a suspected diagnosis of sarcomeric HCM, Athlete's heart, Anderson-Fabry disease can be made. Typical CMR findings in CA permit to make an accurate and early diagnosis

segment) in the presence or not of an increased heart mass.

According to hypertrophy localization and systolic movement of the anterior mitral leaflet (SAM) that may lead to obstruction of outflow tract of the left ventricle, HCM can be defined symmetric, asymmetric, obstructive and non-obstructive. (Authors/Task Force members et al. 2014).

CMR can provide detailed information on all aspects of the disease. Using cine CMR (SSFP) sequences, it is possible to accurately measure the parietal thicknesses of all left ventricular segments, including apical, often difficult to evaluate with echocardiography. It is therefore possible to identify the different hypertrophic patterns depending on the localization of the affected segments (apical, mid-ventricular, symmetric, asymmetric). Generally the interventricular septum is the most affected by hypertrophic phenomena, an infero-lateral septum/wall ratio greater than 1.3 identifies asymmetric hypertrophy. (Maron 2012; Wicker et al. 1983).

In the event of left ventricular obstruction, it is often possible to observe a signal void (hypointense line) in the tract of the left ventricle efflux during the systolic phase.

If present, it is often possible to observe the SAM, new CMR flow study methods have proven to be able to detect obstruction and calculate the gradient with high precision. (Allen et al. 2015).

The common CMR findings are reduction of volumes and increased of ejection fraction and left ventricular mass. Other findings that may increase suspicion of HCMs are the findings of myocardial crypts, especially in the inferior and inferior walls, and the presence of hypertrophic papillaries and/or the presence of adjunctive papillaries. In the mid-ventricular forms, frequent identification of apical aneurysms is common. But the real strength of the CMR is tissue characterization; it allows identifying both ischemic-inflammatory phenomena and fibrosis, typical of this cardiomyopathy. The ischemia present in HCM is predominantly microvascular, resulting in inflammatory phenomena leading to tissue oedema and increased interstitial water content. T2 weighed sequences are very sensitive to the presence of free water and allow to detect ooedema. These findings have a strong diagnostic and prognostic value, as the presence of ooedema has been associated with increased arrhythmic risk. (Todiere et al. 2014).

Myocardial fibrosis is another common feature of HCM. The LGE technique allows identifying with great accuracy the fibrotic areas, which almost always exhibit non-ischemic patterns, predominantly intra-myocardial, with frequent localization to septal junctions between right and left ventricles and in the most hypertrophic segments. In the case of apical aneurysm, the walls of the aneurism are often thinned and with transmural fibrosis. The presence of fibrosis has a significant impact on the prognosis, leading to a five-fold greater risk of cardiovascular events than patients who cannot be identified. (Bruder et al. 2010).

A progressive increase in the risk of arrhythmia death has been observed with the increased degree of fibrosis, a percentage increase in fibrosis greater than 15% of the myocardial mass is associated with a risk twice as high as a sudden cardiac death. (Chan et al. 2014).

Some advanced methods such as measuring and mapping the native T1 allow to identify microfibrosis (interstitial fibrosis) by an indirect calculation of the extracellular volume. (Brouwer et al. 2014).

Such alterations are not measurable by the LGE technique that requires a certain percentage of fibrosis in the single voxel to be identified. However, these methods are still applied only in experimental contexts (Hinojar et al. 2015).

4 Cardiac Amyloidosis

Systemic amyloidosis is an accumulation disease due to the presence of an abnormal circulating protein that usually comes from the light chains of immunoglobulins (primitive forms) or transthyretin (genetic and senile forms). These proteins tend to precipitate in different tissues, including myocardium, accumulating in the form of "amyloid" and leading to structural and functional damage. (Di Bella et al. 2014).

Cardiac amyloidosis (CA) is a hypertrophic phenotype cardiomyopathy characterized by an increase in parietal LV thickness and mass that represents the paradigm of restrictive cardiomyopathy.

CMR plays a primary role in diagnosing CA, since this pathology has morphological characteristics and peculiar signal on different CMR sequences. From a morphological point of view, the CMR allows us to appreciate the LV hypertrophy, most frequently symmetrical, with increased of LV myocardial mass. Other often identifiable features are the increase of the interatrial septal and the right ventricle thickness, the increased of the atrio-ventricular valves thickness, dilated atria and the presence of pericardial effusion. (Di Bella et al. 2016a, b; Maceira et al. 2005).

The typical CMR findings of CA after the injection of gadolinium are a low contrast between myocardium and blood (reduced T1 signal strength difference between myocardial blood) at different inversion times, an increased accumulation of contrast on subepicardial and subendocardial area (subendocardial circumferential LGE) or a diffuse LGE localization. Additionally, LGE deposition can be located in the AV valves, right ventricle and atrial wall (Fontana et al. 2015; Syed et al. 2010).

These "typical patterns" are accompanied by alternative patterns, in which the LGE may have a homogeneous focal distribution and locate more frequently in the inferior or inferolateral walls with a mid-wall (non-ischemic pattern) localization as the same observed in other cardiomyopathies such as Fabry's disease.

More advanced techniques allow identification of the alterations of T1 mapping to diagnose CA. Native T1 mapping in CA is almost always increased by amyloid deposition. These techniques also allow to indirectly calculate the volume of myocardial extracellular space, an increase of more than 32% can identify the AC with a sensitivity of 79% and a specificity of 97% (Barison et al. 2015a, b).

Some characteristics allow discriminating which type of amyloid infiltrates the heart. Transthyretin CA show a greater increase in thickness and mass and a greater involvement of the right ventricle compared to those with light chain CA. (Kristen et al. 2015).

5 Fabry Disease

Anderson-Fabry's disease (FD) is an X-linked genetic disease characterized by the deficiency of a lysosomal enzyme, α-galactosidase, which determines the build up of globotriaosylceramide and other sphingolipids. The disease mainly affects the myocardium, the kidney, and the nervous system. Cardiomyopathy is characterized by a hypertrophic phenotype with diastolic dysfunction, valve disorders and conduction defects with progressive evolution towards terminal heart failure (Pieruzzi et al. 2015).

The echocardiographic findings are similar to other forms of hypertrophic cardiomyopathy. The CMR's added value in this pathology includes the possibility of a precise and accurate morphological evaluation (LV mass, thickness, and shape) and functional (volumes, ejection fraction) similar to that already described for HCM. LGE is present in about less than 50% of MAF cases and, in the classical form, is located in the basal and mid segments of infero-lateral wall, with an intramyocardial distribution. Although this finding is common in FD, inferolateral LGE is not specific for this subtype of disease (Madonna et al. 2014).

The variable presence of LGE in this pathology depends on the fact that fibrosis is a late phenomenon. In FD lipid accumulation is intracellular, while gadolinium is an exclusively extracellular contrast media. However, the presence of marked hypertrophy in a young male with familial history associated with LGE intra-myocardial infero-lateral, must induce the suspicion of a FD. Obstruction is rare but a possible finding. The diagnosis of FD is perhaps one of the conditions in which the new experimental analysis and mapping methods of native T1 (pre-contrast) have so far proved to be more useful. Some studies have shown that native T1 is significantly shorter in FD patients than patients with other forms of hypertrophy and healthy controls. T1 shortening is due to sphingolipid accumulation (fat has T1 short). T1 shortening is

proportional to the degree of hypertrophy but may also be present in patients with early-stage FD where hypertrophy has not yet been manifested (Sado et al. 2013). The development of these new methods has therefore opened up new promising perspectives in these patients.

6 Athlete's Heart

The athlete's heart (AH) is a condition that, at times, needs to be differentiated from other cardiomyopathies. Adaptation to intense training develops frequently eccentric hypertrophy in endurance athletes, while power athletes can see concentric hypertrophy (Galderisi et al. 2015). Because athletes are one of the most at risk of sudden cardiac death, distinguishing the AH from other cardiomyopathies having an unfavourable prognosis is of paramount importance (de Gregorio and Andò 2014).

The CMR may be helpful in the exclusion of other cardiomyopathies, although its use is not always consistent. Generally CMR shows increased cardiac mass and parietal thicknesses increased (especially at the septal level), and/or left ventricular dilatation, especially in resistance athletes (cyclists, marathons, etc.). However, dilation is rarely severe, and is associated with a conserved overall systolic function (often at the lower limit of the standard): in addition, usually, there is a balanced dilatation of the right ventricle while the atrial chambers often exhibit normal volumes. A recent study has shown that among the morphological parameters, the ratio between the maximum end-diastolic parietal thickness and indexed end-diastolic volume is the best index to distinguish AH from other forms of pathological hypertrophy (Petersen et al. 2005a, b).

LGE is generally absent in patients with AH. However, small areas of LGE can be identified in these patients or because they are secondary to other pathological processes (myocarditis, ischemia, sarcoidosis, traumas, etc.) or because sometimes it may be possible to detect the least nuanced areas of fibrosis even in healthy subjects (especially septal RV junction). In these cases, instrumental follow-up after appropriate de-training is the most well-known strategy because in most AH cases, there is a partial or total regression of hypertrophy after 3 months (Maron et al. 1993).

For high reproducibility in the estimation of volumes and mass, CMR remains the reference method for the follow up of these patients (Rovai et al. 2007; Di Bella et al. 2010a, b; Aquaro).

7 Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by LV dilatation and systolic dysfunction in the absence of load conditions (hypertension, valve disease, congenital malformations) or coronary heart disease. The prevalent aetiology is genetic, although in many cases it is not possible to identify the responsible defect (idiopathic forms). CMR can provide valuable information regarding the evaluation of cardiac volume, function and LGE presence and extent.

CMR use may be useful for accurate estimate of the EF when echocardiography documents borderline value in patients who are candidate for cardioverter-defibrillator implant. The left atrium volume evaluation also proved to be an important prognostic factor; patients with a volume greater than 72 ml/m^2 showed high risk of death or transplantation (Gulati et al. 2013).

Fibrosis evaluation by LGE technique is useful in the first instance to exclude other causes potentially determining ventricular dysfunction. In particular, the absence of subendocardial or transmural LGE with a distribution corresponding to one coronary territory excludes ischemic damage. Much more difficult is the distinction between familial DCM respect to other end-stage cardiomyopathies such as hypertrophic cardiomyopathy or myocarditis (Di Bella et al. 2016a, b).

The presence of fibrosis can be found in about 35% of patients with DCM and is associated with greater risk of death, hospitalization and higher incidence of sudden cardiac death and ventricular tachycardia. An increase in extracellular volume measured by T1 mapping can be found in patients with DCM and represents an independent risk

factor for major cardiovascular events (Barison et al. 2015a, b; Aquaro et al. 2010a, b).

DCM phenotype can be found in patients with muscular dystrophies such as Duchenne or Becker. Usually LV dysfunction and dilatation appear at young age and it is slowly progressive. Additionally, myocardial fibrosis is common finding located in the lateral wall with subepicardial distribution, rarely involving the septum. The presence of fibrosis is associated with development of negative remodeling and with higher degree of dysfunction (Silva et al. 2007;Puchalski et al. 2009).

Myocardial fibrosis can also be found in female carriers and even in this population represents a predictor of LV dysfunction (Mavrogeni et al. 2013).

8 Myocarditis

Myocarditis is an inflammatory cardiomyopathy usually due to viral aetiology and characterized by inflammatory infiltrate at myocardial level. Usually, myocarditis is associated with a flue-like syndrome (acute phase). Clinical presentation is very heterogeneous (Yilmaz et al. 2013).

CMR has demonstrated high diagnostic accuracy in patients with infarct like presentation that usually showed preserved EF but impaired LV longitudinal function (Di Bella et al. 2010a, b). However, endomyocardial biopsy remains the standard gold standard method in heart failure and arrhythmic presentation. In addition to morpho-functional evaluation, CMR allows to identify many of the tissue characteristics typical of inflammation (hyperoemia, oedema, and fibrosis).

9 Lake Louise Criteria

Lake Louise criteria is useful for evaluation and accurate diagnosis of oedema, hyperaemia and fibrosis. The diagnosis of myocarditis (78% accuracy) with CMR can be achieved if at least 2 criteria are positive. If there is only one criterion or no criterion exists, but myocardial/clinical suspicion is strong, then the examination can be repeated at 1–2 weeks (Friedrich et al. 2009).

It should be emphasized that the accuracy of the criteria is more relevant in patients with a high clinical suspicion of myocarditis.

Oedema is due to the increased permeability of vascular walls and cell membranes, as a consequence of the release of pro-inflammatory cytokines increasing interstitial and intracellular water content. T2 weighted images show water signal (oedema) as extremely hyperintense in comparison with other tissues. The distribution of the oedema may be diffuse and/or focal (anterior and lateral wall with predominantly subepicardial distribution and septal wall with mid wall distribution). Diffuse oedema is characterized by a > 1.9 ratio between the intensity of the entire myocardial signal and the intensity of the skeletal muscle used as a healthy muscle reference. Although oedema is a distinctive sign of inflammation, it may still be absent or difficult to detect in patients with borderline myocarditis, even for the low signal-to-noise ratio of T2 inversion recovery sequences. Oedema can also be present in other pathologies that come into differential diagnosis with myocarditis, first of all acute coronary syndromes, but in these cases oedema is generally transmural or subendocardial, never subepicardial.

The typical vasodilatation observed in inflammation causes hyperaemia and consequently a greater concentration of gadolinium in the affected areas. This phenomenon (termed "early gadolinium enhancement") occurs within a few minutes of intravenous administration. The gadolinium significantly shortens the T1 of the tissues in which it is located. A 4–5 ratio (depending on the MRI scanner used) between myocardial and healthy skeletal muscle is diagnostic for myocardial hyperaemia. However, the presence of muscular inflammation involvement can affect this method. In addition, an increase of 45% is considered a diagnostic of myocardial hyperaemia. Another hyperaemia method is SSFP sequences after gadolinium.

In the acute myocarditis, LGE is due to the inability of the cells injured to maintain the membrane integrity, allowing the gadolinium to

penetrate the cytoplasm. In late phases, the presence of LGE is due to the increased interstitial space (interstitial fibrosis) due to inflammatory necrosis. The presence of fibrosis allows gadolinium to occupy greater volumes than healthy tissue, resulting in delayed washout. Localization of LGE in myocarditis is characteristic, affecting the sub-epicardium or the mid-ventricular layer. The lateral walls and the interventricular septum are the walls most frequently affected. The amount of LGE detected in acute phase is generally greater than in the following phases. In some cases, you can have restitution with substantial LGE disappearance. The presence of LGE in patients with myocarditis has proven to be a very useful independent predictor of mortality and should always be sought in patients with clinical suspicion.

10 Additional CMR Criteria that Support the Diagnosis of Myocarditis

Although not included in the Lake Louise criteria, the presence of left ventricular dysfunction, pericardial inflammation and/or inflammation are additional information in the diagnosis of acute myocarditis. Another diagnostic element is the temporary increase of the mass and the parietal thicknesses (diffused or localized), which represents the "swelling" and is the macroscopic expression of the oedema.

11 Non-compaction Cardiomyopathy

Non-compaction cardiomyopathy (NCC) is a form of congenital cardiomyopathy with an unknown aetiology that depends on the lack of myocardial compaction of embryonic myocardial trabecules. The ventricular walls appear jagged, with numerous trabeculations and deep recesses extending towards the cavity. These alterations may involve the entire left ventricular endocardial surface but most commonly involve only lateral and apical LV segments. Right ventricle can be involved but because trabeculations are common physiological features, pathological findings are not yet defined. NCC may be a completely asymptomatic condition, so some authors do not consider it a true cardiomyopathy; in other cases, however, progression towards left ventricular dilatation and left ventricular dysfunction may occur, with increased risk of arrhythmia and death. Some forms of NCC may also be associated with hypertrophy and restriction. Some authors consider the NCC not as a cardiomyopathy but as a phenomenon found in other cardiomyopathies such as hypertrophic or dilated (Petersen et al. 2005a, b; Jacquier et al. 2010; Grothoff et al. 2012). Thanks to the high spatial resolution and the ability to effectively analyse all segments, CMR is useful for diagnosing NCC (Fig. 2).

The most commonly used CMR criterion for its simplicity is to evaluate the relationship between myocardial thickness and compact size in the affected segment. A > 2.3 ratio would identify patients with NCC with sensitivity and specificity of 86% and of 99% respectively (Petersen et al. 2005a, b). The most commonly used sequences for measurements are SSFP. Although simple and rapid use this criterion was strongly criticized for having led to an excess of pathology diagnosis.

Other criteria are based on uncompacted myocardial mass. Some authors have suggested that a non-compact bulk percentage of the total mass > 20% would have a sensitivity and specificity of 93.7% 39 (Jacquier et al. 2010). Others Authors have proposed a non-compact index mass of 15 g/m2 and a non-compact mass greater than 25% would be highly specific criteria. Grothoff et al. suggets an index based noncompact/compact ratio > 3 in basal segments at least one segment; this approch would showed a sensitivity and specificity close to 100% (Grothoff et al. 2012).

Mass-based criteria have been shown to be more accurate, however, computational mass calculation is difficult and not entirely reproducible, so there is no unanimous consensus on the parameters to be used to diagnose NC Mass-based criteria have been shown to be more accurate, however, computational mass calculation is undeniable and not entirely reproducible, so there

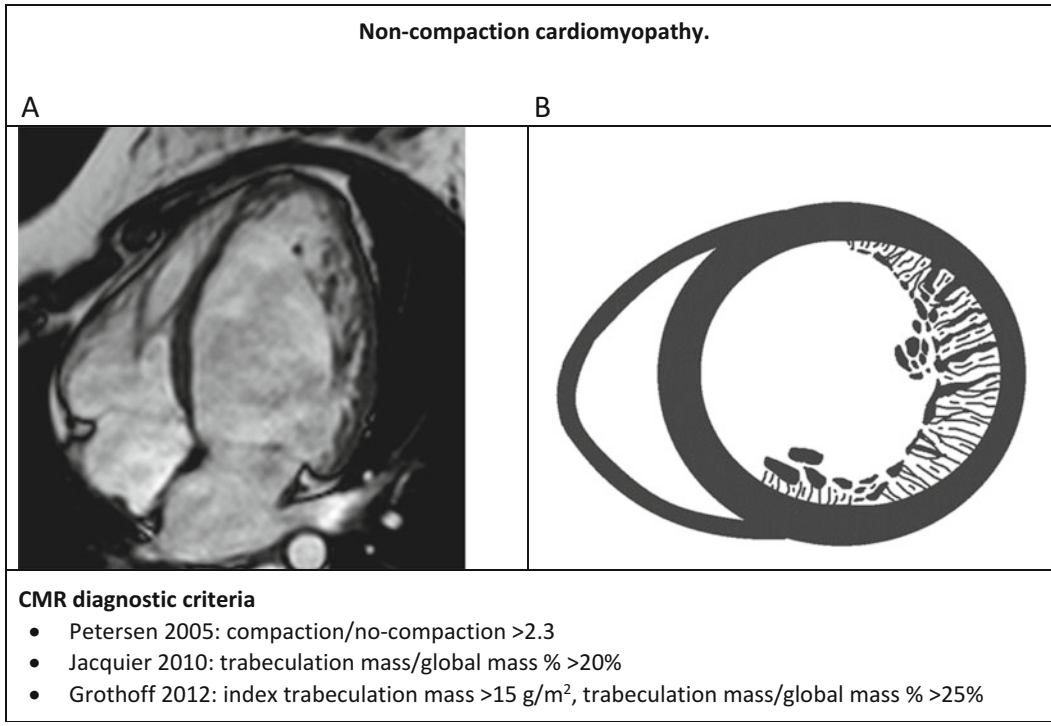


Fig. 2 Cine CMR image on horizontal long axis (panel A) and typical pattern on short axis (panel B) in Non-compaction cardiomyopathy. Lower panel shows the different CMR criteria proposed

is no unanimous consensus on the parameters to be used to diagnose NCC. Some authors would have identified an important prognostic element in the number of segments involved. (Punn and Silverman 2010). Fibrosis can be found in patients with NCC but no specific pattern has been identified and has not proven to be an important predictor of dysfunction or death.

12 Arrhythmogenic Cardiomyopathy

Arrhythmogenic dysplasia is a genetic cardiomyopathy that is characterized by right ventricular involvement and/or involvement of both ventricles (biventricular subtype) or left ventricle (subtype with predominantly left ventricular involvement). Arrhythmogenic cardiomyopathy is a progressive disease that in the initial phase of the right ventricular form is characterized by morphofunctional abnormalities located in specific areas of the right ventricle (sub-tricuspidic right ventricular area, right ventricle apex and right ventricle out-flow, called "triangle dysplasia ") followed by a right ventricular dilatation and dysfunction.

The CMR in addition to allowing the evaluation of the right ventricular size and function can identify fibro-adipose infiltration/replacement areas. In 2010, major and minor diagnostic criteria for the diagnosis of arrhythmia dysplasia were reviewed (Marcus et al. 2010).

From these it can be seen that ventricular kinetics (akinesia/dyskinesia) segmental abnormalities must be associated with right ventricular dilatation or a right ventricular dysfunction (major criterion: ejection < 40%). Although in the 2010 criteria don't have included CMR parameter derived from tissue information (fatty or fibrous infiltration), numerous scientific evidence has demonstrated the additive diagnostic value of both fatty and fibrous infiltration detected using CMR. In particular, various

studies show the negative prognostic impact of the presence of tissue alterations in patients with frequent premature ventricular complexes at right ventricular origin (Aquaro et al. 2010a, b).

In addition to the usual acquisition plans (long horizontal axis, vertical axis, short axis) in SSFP sequences, T-1 weighed, T-1 fat-sat and LGE, and also the acquisition of transaxial or oblique planes oriented to the right ventricular outflow tract are included in CMR protocol.

13 Hemochromatosis

Hemochromatosis is a disease characterized by accumulation of considerable amounts of iron in different tissues including the heart.

Iron causes structural and functional damage to the organs affected mainly by the excessive production of free radicals of oxygen (Gulati et al. 2014). Iron accumulation causes alterations of diastolic function, progressive dilation and left ventricular dysfunction. The CMR plays a decisive role in evaluating hemochromatosis patients. In fact it allows to evaluate the accumulation of myocardial iron by exploiting the effect of metal ferromagnetic properties on relaxation times, particularly on T2. Iron, in fact, results in a T2 shortening proportional to the concentration of metal present in myocardial tissue. The T2 * (T2 star) is the true decay time of the T2 not influenced by 180 ° refund pulses. The most commonly used method is called multi-echo T2 *, which, with the use of dedicated software, allows to obtain the values ⍰⍰of T2 * on both global and segmental LV. Some authors use average septum values ⍰⍰as they have been shown to be more accurate and reproducible. An iron tissue overload is indicated by values < 20 ms while a value <10 ms is a warning of a severe accumulation.The utilization of the T2 * method has allowed better management of iron chelation therapy in hemochromatosis patients without the need for biopsies. Fibrosis may be present in patients with myocardial iron overload and is associated with lower T2 * values and Remodeling negative (Ramazzotti et al. 2009).

14 CT Scan in Cardiomyopathies and Heart Failure

Diagnostic advantage of Computed Tomographic (CT) scan technology in cardiac patients (HF and Cs) is as well as in other clinical settings. High speed of execution, high spatial resolution, good temporal resolution and wide field of view result in high-quality anatomical imaging (Taylor et al. 2010).

Also, the high-field of view allows detecting pulmonary congestion and pleural effusions, inferior cava vein disease and hepatomegaly which can be present in HF patients (Cademartiri et al. 2015).

Of strategic importance, CT can identify all the coronary artery tree, with powered diagnostic value on coronary wall calcifications, intra-coronary plaques, coronary anomalies and intra-myocardial course of coronary branches (Taylor et al. 2010).

Recent studies have demonstrated the chance for a morpho-functional characterization of the myocardial wall like CMR. Cardiac anatomical structures, such as chamber and wall thickness, valves, vessels can be seen in detail, and recent studies confirmed that CT can give strategic information on Cs (Taylor et al. 2010; Cademartiri et al. 2015; Lloyd-Jones et al. 2002).

On the other hand, CT has some disadvantage including the use of ionizing radiation and contrast agents.

In HF patients, CT scan allows a proper diagnosis (or exclusion) of coronary artery disease (CAD, both in acute and chronic clinical settings (Lloyd-Jones et al. 2002).

High sensitivity (98–100%) and good negative predictive value (94–100%) were demonstrated for CT scan when ruling out diagnosis of CAD, and CT became a increasingly used investigation in the general population (Meijboom et al. 2008).

In a recent meta-analysis, CT scan was as accurate as coronary angiography (the gold standard) to rule out CAD as the leading mechanism of heart failure in patients with left ventricular ejection fraction (LVEF) < 35% of unrecognized origin (Bhatti et al. 2011).

The study of the cardiac chambers and the myocardium is not a strong indication for CT

scan. Its use is mainly limited to patients with contraindications to undergo cardiac MRI examination (e.g in patients with metallic devices) or to individuals with poor acoustic window for an echocardiogram, who need important information for their clinical management (Taylor et al. 2010).

A good reliability was confirmed for CT with regard to the most common morpho-functional cardiac parameters (ventricular end-diastolic and end-systolic volumes, ejection fraction, stroke volume, myocardial mass and wall motion abnormalities) in comparison with cardiac MRI, echocardiography or gated SPECT (Schroeder et al. 2008; Fischbach et al. 2007).

A relatively recent clinical application of CT scan is myocardial tissue characterization. Myocardial fibrosis can be recognized with a delay enhancement technique, like that used in gadolinium-enhanced cardiac MRI.

Comparative studies with MRI showed a good correlation between the two methods for the identification of myocardial fibrosis in dilated or hypertrophic cardiomyopathy, cardiac amyloidosis, myocarditis and cardiac sarcoidosis. Moreover, it could be a possible alternative for patients unable to perform cardiac MRI (Lee et al. 2017; Cerny et al. 2017; Takaoka et al. 2017).

Of clinical interest, CT scan can also play a diagnostic role in diagnosis of hypertrophic cardiomyopathy in adult patients, and for a screening of their relatives. In Tako-Tsubo cardiomyopathy, CT scan has been demonstrated to be such an useful tool to exclude CAD, wall motion abnormalities and cardiac complication like apical aneurysm and intra-ventricular thrombosis, (Ugo et al. 2015).

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 197–217
DOI 10.1007/5584_2017_105
© Springer International Publishing AG 2017
Published online: 5 October 2017

Pathogenesis, Clinical Features and Treatment of Diabetic Cardiomyopathy

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Abstract

Patients with type 1 and type 2 diabetes mellitus (T1D and T2D) show an increased incidence of heart failure (HF) even after adjustment for well established risk factors for HF such as hypertension and ischaemic heart disease. The resulting specific form of cardiomyopathy is known as diabetic cardiomyopathy" (DCM). Pathogenetic mechanisms underlying DCM are likely to be multifactorial, from altered myocardial metabolism (hyperglycaemia, hyperinsulinaemia, increased circulating fatty acids and trglycerides) to microvascular disease, autonomic neuropathy, and altered myocardial structure with fibrosis. Current medical treatment recommendations from scientific societies on HF in patients with diabetes mellitus (DM) do not differ from those for patients without DM. Regarding the effect of different hypoglycaemic drugs on HF in patients with DM, and considering the best available current evidence, the sodium-glucose-co-transporter 2 inhibitors and metformin seem to be especially advantageous regarding the effects in patients with T2D and HF.

Keywords

Heart failure · Diabetes mellitus · Diabetic cardiomyopathy · Cardiac lipotoxicity · Left ventricular ejection fraction · Diastolic dysfunction · Systolic dysfunction

1 Heart Failure and Diabetes: Definition, Diagnosis and Epidemiology

Heart failure (HF) is currently one of the medical care problems of greater relevance in the developed countries. Although the treatment of these

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patients has improved in recent years, the high prevalence (0.4–2% in the European population) and incidence of this disease has lead to cause significant morbidity and mortality (50% of patients will die in 5 years, and 90% in 10 year), while generating a large number of hospital admissions with the consequent health expenditure. HF affects between 1–2% of the adult population in developed countries, rising to more than 10% in the elderly (Mosterd and Hoes 2007).

Heart Failure is a complex clinical syndrome due to structural and/or functional cardiac alterations whose diagnosis is difficult especially in the initial stages given that symptoms are not specific, and therefore it is difficult to distinguish between HF and other problems (Oudejans et al. 2011). It is widely accepted that individuals may progress through an asymptomatic phase of left ventricular systolic dysfunction (ejection fraction (EF) <50%) before the development of overt HF, even when only mild impairment of EF is present (Wang et al. 2003). In these patients, treatment with an angiotensin-converting enzyme inhibitor has demonstrated to reduce the incidence of HF and the rate of related hospitalizations (SOLVD Investigators et al. 1992). According to the European Society of Cardiology (ESC) guidelines of HF, patients with this condition can be classified into three groups taking according to left ventricular ejection fraction (LVEF): 1) HF with reduced ejection fraction (HFrEF): LEVF <40%; 2) HF with preserved ejection fraction (HFpEF): LEVF >50%; 3) HF with mildly reduced EF (HFmrEF): LEVF 40–49% (Ponikowski et al. 2016). Frequently, patients have both systolic and diastolic HF at the same time, but the term for this condition is still systolic HF. The diagnosis of HF in a non-acute context should be first evaluated on the patient's medical history, symptom presentation (shortness of breath at rest or during exercise, fatigue, tiredness, swelling of ankles), physical examination (tachycardia, tachypnea, pulmonary rales, pleural effusion, elevation of venous jugular pressure, peripheral edema, hepatomegaly) and a resting electrocardiogram. If these elements are normal, the diagnosis of HF is very improbable. If one of the elements is abnormal, the plasma level of natriuretic peptides (NPs) should be determined, with an indication to perform an echocardiogram in those patients with NPs concentrations higher than the exclusion threshold. The diagnosis of HFpEF may be difficult given the absence of obvious signs of central fluid retention. For this reason, the diagnosis should be based on objective measures of cardiac dysfunction which include elevated levels of NPs and an the evidence of cardiac functional and structural alterations underlying HF (Ponikowski et al. 2016). Key structural alterations include a left atrial volume index >34 mL/m^2 or a left ventricular mass index ≥115 g/m^2 in men and ≥95 g/m^2 in women (Caballero et al. 2015). Key functional alterations include an E/e′ ≥13 and a mean e' septal and lateral wall <9 cm/s.

Cardiovascular complications are the leading cause of diabetes-related morbidity and mortality. Further, diabetes is associated with an increased risk of HF after adjustment for well-known HF risk factors as observed in several population-based studies (Vaur et al. 2003). The Framingham Heart Study showed, after correcting for cardiovascular risk factors and coronary artery disease (CAD), that the frequency of HF was twice and five times higher in men and women with diabetes, respectively, than in age-matched non-diabetic subjects (Kannel and McGee 1979). Indeed, HF is one of the most common initial manifestations of cardiovascular disease in patients with type 2 diabetes mellitus (T2D). The risk of HF is also increased in patients with type 1 diabetes mellitus (T1D). These patients have been described as having a four-fold increase in the risk of being admitted to the hospital with HF, compared with population-based controls

(Rosengren et al. 2015). In both type 1 (Rosengren et al. 2015) and T2D (Lind et al. 2012), poor glycaemic control has been described to be associated with an increased incidence of HF. Moreover, as shown in both observational and clinical studies, diabetes is associated with a poor subsequent prognosis in subjects with HF (Gustafsson et al. 2004). In fact, in patients with T2D, mortality is increased ≈10-fold in patients with versus those without HF (Standl et al. 2016).

2 Diabetic Cardiomyopathy: Definition, Prevalence and Characteristics

The presence of left ventricular dysfunction in diabetic subjects without CAD or hypertension led to the use of the term diabetic cardiomyopathy (DCM). The usual definition of DCM includes the presence of structural and functional abnormalities of the myocardium in subjects with diabetes without coronary artery disease, hypertension or significant valvular disease. The existence of this specific form of cardiomiopathy was first proposed in 1972 after postmortem studies (Rubler et al. 1972), based on the findings of HF in diabetic individuals free of detectable CAD. Subsequent studies provided more definitive evidence for DCM in diabetic subjects without CAD (Regan et al. 1977).

Functionally, DCM is characterized by cardiac hypertrophy, loss of cardiomyocytes, interstitial fibrosis and diastolic dysfunction followed by systolic dysfunction (Boudina and Abel 2007). The disease course consists of a silent asymptomatic subclinical, and usually long, period during which cellular structural damage initially leads to diastolic dysfunction, thereafter to systolic dysfunction, and eventually to HF (Velez et al. 2014). A relevant characteristic of the myocardium in diabetes is cardiac hypertrophy. The evidence from 2 large studies (Strong Heart study and the Cardiovascular Health study) showed that there is an association between diabetes and cardiac hypertrophy (increased left ventricular mass and wall thickness), together with deranged systolic and diastolic functions (Devereux et al. 2000). These myocardial structural changes were later confirmed independently in the Framingham study, in which independently of blood pressure, there was a correlation between glycaemic control and cardiac hypertrophy (Kannel and McGee 1979). Diastolic dysfunction, an early functional alteration in the diabetic myocardium described as correlated with diabetes duration, could be the first sign of DCM (From et al. 2009). The presence of subclinical diastolic dysfunction in these subjects is associated with the development of heart failure, and also with mortality, independent of the presence of hypertension and CAD. Additionally, in population-based cohorts, diastolic dysfunction has been associated with development of HF after a 6-year follow-up period (Kane et al. 2011).

Using conventional ultrasound imaging and Doppler imaging, diastolic dysfunction is detected in 25–60% of subjects with diabetes (Boyer et al. 2004). According to the recommendations of the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF, in at risk individuals for HF, a transthoracic echocardiography protocol with the assessment of tissue Doppler velocities and deformation indices should be considered to identify myocardial dysfunction at the preclinical stage. The available evidence indicates that in diabetic subjects left ventricular (LV) diastolic dysfunction might precede LV systolic dysfunction (From et al. 2009; Poirier et al. 2001). Studies that have used tissue Doppler imaging in patients with T2D have demonstrated impairment of diastolic function, even in patients with short duration of the disease (Di Bonito et al. 2005). In these patients, duration of DM of over 4 yr is correlated with significant LV diastolic dysfunction (From et al. 2009). The fact that systolic dysfunction may develop at a later stage of the disease is a challenge for the diagnosis using conventional echocardiography. Moreover, it must be noted that, although echocardiographic abnormalities are very common in outpatients with T2D, it has recently been reported that neither cardiac symptoms nor

clinical characteristics are effective for identifying patients with echocardiographic abnormalities (Jørgensen et al. 2016). The use of cardiac ultrasound screening by application of age-and sex-adjusted normal myocardial velocity ranges has demonstrated that 36% of diabetic patients without coronary artery disease or left ventricular hypertrophy have significant subclinical left ventricular dysfunction (Fang et al. 2005). Diastolic dysfunction is considered the first marker of DCM. However, the evaluation of myocardial dysfunction by echocardiography with speckle-tracking imaging has demonstrated that systolic strain alteration may exist in the presence of normal diastolic function, suggesting that diastolic dysfunction might not be regarded as the first marker of a preclinical stage of diabetic cardiomyopathy (Ernande et al. 2011). In patients with T1D, the prevalence described for myocardial dysfunction in a recent study performed in 1093 T1D patients was 15.5% (1.7% with LVEF <45%, and 14.4% with evidence of diastolic dysfunction) (Jensen et al. 2014). Whether screening and aggressive management of diabetic patients with preclinical diastolic dysfunction might delay the progression to HF with improved outcomes is not yet known.

Because treatment for HF improves survival and quality of life, clinicians should be observant of signs of HF in the management of patients with diabetes, starting at early stages. Echocardiography might be warranted, especially in the presence of poor glycaemic control, long duration of diabetes, an adverse risk factor profile or micro/macro albuminuria.

3 Mechanisms Involved in the Pathophysiology of Diabetic Cardiomyopathy

The metabolic milieu associated with diabetes is characterized by alterations in multiple molecular pathways in the cardiomyocytes, leading to an impairment of cardiac contractility and promoting myocyte dysfunction, injury and eventually death. Thus, the pathogenetic mechanisms underlying diabetic heart disease are likely to be multifactorial, ranging from altered myocardial metabolism (hyperglycaemia, hyperinsulinaemia, increased circulating fatty acids and triacyclglycerols) to endothelial dysfunction, microvascular disease, autonomic neuropathy, and altered myocardial structure with fibrosis. The main potential pathophysiological factors that drive the development of DCM are shown in Fig. 1.

3.1 Cardiac Lipotoxicity

In the normal heart, a constant energy supply is primarily met by the β-oxidation of long-chain fatty acids (FAs). β-oxidation accounts for

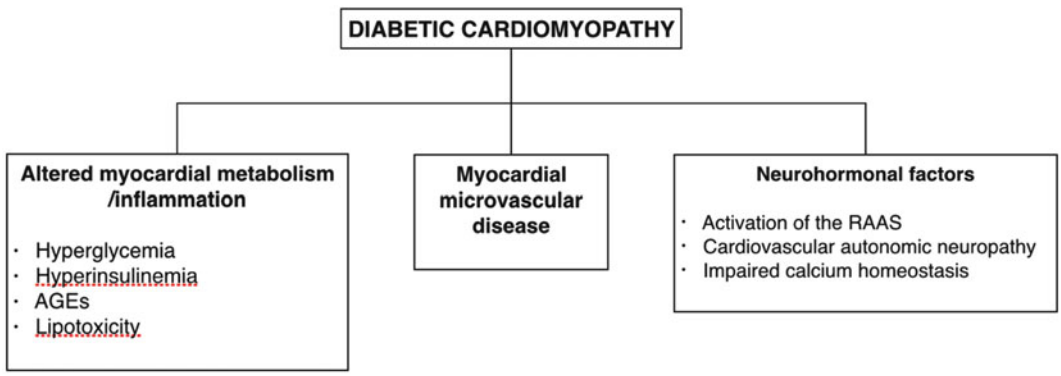

Fig. 1 Schematic depiction of the potential pathophysiological pathways that have been implicated in diabetic cardiomyopathy. These can be divided into: (1) altered myocardial metabolism/inflammation, (2) myocardial microvascular disease and (3) neurohormonal factors

approximately 50–70% of the energy production of the heart, with the remainder primarily accounted for by carbohydrate (glucose and lactate) oxidation and the oxidation of ketone bodies (Asrih et al. 2012). Fatty acids are delivered to the heart from two sources: (a) FAs esterified as triglycerides (TGs) contained in circulating TG-rich lipoproteins (chylomicrons and very-low density lipoproteins (VLDL)) and liberated by lipoprotein lipase (LpL)-mediated lipolysis associated with proteoglycans and glycosylphosphatidylinositol-anchored high density lipoprotein–binding protein 1 (GPIHBP1) on the luminal surface of endothelial cells; and b) non-esterified FAs, referred to as free FAs (FFAs), bound to serum albumin. Fatty acids can be taken up passively by cardiomyocytes via diffusion across the cell membrane (20%), or by a protein-mediated mechanism involving fatty acid binding proteins (FABPs) and CD36 (80%) on the cell membrane. Ectopic fat accumulation (cardiac steatosis) within (intramyocardial) or around (epicardial/pericardial) the heart has been described to be greater in obesity and in patients with T2D. In patients with T2D, myocardial TG content has been described to be associated with impaired left ventricular diastolic dysfunction, independent of age, body mass index, visceral fat, and diastolic blood pressure (Levelt et al. 2016). In some studies, it has been reported that intramyocardial TG content was correlated with left ventricular diastolic dysfunction (Ng et al. 2010). In addition, it has been shown in cardiac imaging studies performed with different metabolites that patients with T2D have lower uptake of glucose and greater uptake and oxidation of FAs (Rijzewijk et al. 2009). Epicardial fat depots have also been reported to be increased in patients with diabetes (From et al. 2009). Interestingly, the Framingham Heart Study and the Multi-Ethnic Study of Atherosclerosis revealed that the size of fat depots around the heart are risk predictors for CV dysfunction and coronary disease (Mahabadi et al. 2009). Remarkably, studies have also shown that patients with T1D have higher epicardial fat thickness than individuals without diabetes, independent of body mass index, age or level of glycated haemoglobin. In recent years, ectopic fat deposition in another organ different from the heart (i.e., the liver) has been described to be associated with both myocardial steatosis and dysfunction (Bonapace et al. 2012).

There are two possible scenarios to explain the accumulation of intramyocardial TGs described in patients with diabetes: (1) oversupply of FA and (2) impaired FA oxidation. A number of factors, including elevated levels of insulin, contribute to high concentrations of FFAs. Insulin accelerates TG synthesis and inhibits lipolysis in adipocytes. In the setting of insulin resistance, such as in T2D, lipolysis in the adipose tissue and hydrolysis of TGs are increased and lead to elevated concentrations of circulating FFAs. Cardiac insulin resistance is accompanied by a persistent relocation of the fatty acid transporters CD36 and FABP from the cytosol to the cell membrane, leading to chronic elevation of FAs uptake and oxidation (Goldberg et al. 2012), and internalization to an intracellular location of the glucose transporter GLUT4. The preferential use of FAs for myocardial metabolism, instead of glucose, is an important contributing factor to the development of DCM. CD36 is a transmembrane protein that transports long-chain FAs, and it is highly expressed in the heart, adipose tissue and skeletal muscle (Pepino et al. 2014). In both heart and skeletal muscle, FA uptake rates have been found to run in parallel to the expression level of CD36. Thus, CD36 overexpression results in elevated rates of FA uptake (Steinbusch et al. 2011), whereas CD36 knockout (KO) or knockdown impairs the transport of FA across the plasma membrane (Angin et al. 2012). The results obtained in aged CD36-deficient mice have provided evidence that CD36 mediates age-induced cardiomyopathy in these mice (Koonen et al. 2007). After the uptake of FAs by target tissues, these may have 3 major different fates in the cell. They can be converted into sphingolipids, such as ceramide; alternatively, they can be esterified into TGs, diglycerides, or phospholipids; or they can undergo oxidation to obtain energy. When the balance between FA uptake and oxidation is altered, excess FAs are

directed towards the synthesis of complex lipids, such as TG, diacylglycerols (DAGs) and phospholipids. An alternative route to use fatty acid surplus is via the ceramide biosynthetic pathway. DAGs and ceramides are signalling lipids believed to be toxic when their intracellular concentrations are increased. Animal experiments have implicated ceramide in the pathogenesis of cardiac dysfunction associated with obesity and diabetes (Park and Goldberg 2012). However, whether ceramide is relevant to cardiac failure in humans is still unclear. Finally, it should be noted that saturated long-chain FAs, most notably palmitate, are associated with toxicity in cells, either because of their direct actions or their incorporation into phospholipids.

3.1.1 Lipid Abnormalities in Patients with T2D

Patients with T2D often present with atherogenic dyslipidaemia, which is characterized by hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, an increase in small and dense LDL particles and hyper-apolipoprotein B (apoB). These patients show elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs), a mixture of lipoproteins derived either from the intestine (chylomicrons) or the liver (VLDL). Patients with T2D also show an increase in the concentration of modified forms of LDL particles (oxidized LDL (ox LDL), glycosylated LDL (glLDL) and electronegative LDL, the last generated by mechanisms such as lipolysis and non-esterified fatty acid loading). This modified forms of LDL are mainly increased in patients with T2D who have a predominance of small dense LDL (sdLDL) particles (phenotype B) (Sánchez-Quesada et al. 2013). Regarding the effect of modified LDL on cardiomyocytes it has been described that under hypoxic conditions the supply of FFAs from LDL-negative to the cardiomyocyte is increased. This increase of FFAs favours intracellular TG synthesis that is accompanied by inefficient sequestering of FFAs into lipid droplets and promotes the production of reactive oxygen species (Revuelta-López et al. 2015). Given that TG accumulation in the myocardium has been described to cause deleterious lipotoxicity, a potential pathogenic pathway of electronegative LDL particles on cardiomyocyte function should further be explored.

3.1.2 Lipid Abnormalities in Patients with T1D

In patients with T1D, an altered lipid pattern has been described, especially in women with poor glycaemic control, consisting of increased triglyceride levels and decreased HDL concentrations, which except for HDL-c are normalized by the optimization of glycaemic control (Pérez et al. 2000). Regarding the quality of lipoproteins, intensive diabetes therapy has recently been reported to be associated with potentially favourable changes in circulating LDL and HDL subclasses in T1D (Vinagre et al. 2014).

3.2 Microvascular Disease

The alterations of myocardial composition and the consequent diastolic properties and left ventricular filling pressure might be mediated by changes in coronary microcirculation. Although heart disease due to diabetes is mainly associated with complications in large vessels, microvascular abnormalities are also believed to be involved in altering cardiac structure and function. Three major defects, endothelial dysfunction, alteration in the production/release of hormones, and shifts in the metabolism of smooth muscle cells, have been suggested to produce damage to the small arteries and capillaries (microangiopathy) due to hyperglycaemia and to promote the development of DCM. These factors might either act alone or in combination to oxidative stress as well as changes in cellular signalling and gene transcription, in turn causing vasoconstriction and structural remodelling of the coronary vessels (Adameova and Dhalla 2014). In fact,

histological examination of human diabetic post-mortem hearts has shown the presence of microangiopathy in this organ (Bloch et al. 1980). Among the possible mechanisms promoting microangiopathy in DCM are hyperglycaemia, hyperlipidaemia, and activation of the neurohumoural system (Adameova and Dhalla 2014). As a consequence, alterations in the function and permeability of the endothelium, increased reactivity of the smooth muscle cells and adhesion of monocytes, as well as thrombocytes, might induce vasoconstriction and stimulation of the signalling pathways that promote fibrosis. In patients with T2D, coronary microvascular dysfunction has been described to be associated with concomitant albuminuria (von Scholten et al. 2016). In the Strong Heart Study (Liu et al. 2003), after adjustment for multiple known contributing factors, including CAD, the degree of diastolic dysfunction was shown to be proportional to the level of microalbuminuria. Also in patients with T1D without known heart disease, micro- and macroalbuminuria have been described to be associated with subclinical myocardial dysfunction (Jensen et al. 2014). Thus, these results suggest a common lesion occurring in multiple microvascular beds. Moreover, in patients with T2D coronary flow reserve, which reflects coronary microvascular function, left ventricular dysfunction has been described (Kawata et al. 2015).

3.3 Hyperglycaemia and Advanced Glycation End Products (AGEs)

During long standing hyperglycemic state in diabetes mellitus, glycation is the non-enzymatic process through which glucose forms covalent adducts with proteins (Du et al. 2003). This results in stable compounds that slowly accumulate during life; these glycated proteins induce structural and physiologic changes in the CV system: increased myocardial and vascular, atherosclerotic plaque formation, endothelial dysfunction, and altered responses to vascular injury. The enhanced generation and accumulation of advanced glycation end-products (AGEs) have been linked to increased risk for macrovascular and microvascular complications associated with diabetes mellitus. A correlation has also been reported between AGEs levels and isovolumetric relaxation time and diastolic left ventricular diameter (Kilhovd et al. 1999). The influence of glycaemic optimization on the risk of cardiovascular events in diabetic subjects with heart failure has not been clearly established. A meta-analysis that included 8 randomized trials showed that more intensive glycaemic control in patients with T2D did not reduce the occurrence of HF events (Castagno et al. 2011). In contrast, the results regarding optimization of glycaemic control and its effects on diastolic dysfunction in patients with T2D have been conflicting. In T2D patients with mild diastolic function and good glycaemic control (mean HbA1c of 6%) without confounding comorbidities, the Diabetes mellitus and Diastolic Dysfunction (DADD) investigators reported, in a controlled clinical trial, that glycaemic control did not result in improvement in either diastolic LV function or myocardial perfusion reserve (Jarnert et al. 2009). Conversely, in an earlier small, observational study, von Bibra et al. described in a small group of T2D with comorbidities that the intensification of glycaemic control was associated with an improvement in myocardial diastolic function (von Bibra et al. 2004).

3.4 Cardiovascular Autonomic Neuropathy

Cardiovascular autonomic neuropathy in patients with diabetes is caused by an alteration of the autonomic system. The prevalence of this form of neuropathy varies between 20 and 65% depending on the duration of DM and the study methods for its assessment (Debono and Cachia 2007). Cardiovascular autonomic neuropathy is associated with rest tachycardia, exercise intolerance, orthostatic hypotension and silent

myocardial ischemia. In patients with T2D, cardiovascular autonomic neuropathy diagnosed by autonomic function tests, has been described to be associated with left ventricular diastolic dysfunction (LVDD) suggesting that patients with LVDD have cardiovascular autonomic neuropathy and hence are at increased risk of mortality due to sudden cardiac death (Mythri and Rajeev 2015). However, it should be noted that this is an area of knowledge that is largely unexplored.

3.5 Inflammation

Diabetes mellitus is considered as a pro-inflammatory state (Diamant et al. 2005). In this sense, several groups have reported increased circulating levels of inflammatory biomarkers such as cytokine IL-6 and C-reactive protein in patients with T2D. Expression of inflammatory cytokines is also markedly increased in experimental models of diabetes. These inflammatory markers are influenced by a wide range of clinical and pathologic conditions such as metabolic syndrome and the presence of DM, and thus might not specifically reflect alterations in myocardial inflammatory processes (Frangogiannis 2014). Animal models of T1D and T2D have revealed increased myocardial inflammation driven in part by increased activation of M1 macrophages (Jadhav et al. 2013). In the Zucker diabetic fatty rats, the polarization of macrophages toward anti-inflammatory macrophage M2 phenotype in cardiac tissue is described to be associated with an improvement of cardiac hemodynamic parameters such as ventricular contractility (Jadhav et al. 2013). Even though it is difficult to distinguish between ischemic/non-ischemic causes of cardiomyopathy, in the presence of a myocardial infarction, certain cell types involved in the inflammatory response can migrate across the vascular wall, and promote cytotoxic effects on cardiomyocytes, thereby potentially extending ischemic/non ischemic injury. To our knowledge, in humans, there is not yet any evidence of myocardial inflammation. These results point to the necessity of conducting further studies on myocardial inflammation and the potential utility of the role of anti-inflammatory strategies to prevent cardiac dysfunction in subjects with diabetes.

3.6 Activation of the Renin-Angiotensin-Aldosterone System (RAAS)

In the diabetic heart, there is an increased density and expression of the angiotensin II receptor (Khatter et al. 1996). Activation of RAAS in the myocardium promotes remodelling processes. In patients with preserved ejection fraction, it has been described that treatment with a mineralcorticoid receptor antagonist is associated with a reduced risk of hospitalization for HF and that this treatment also reverses cardiac remodelling (Orea-Tejeda et al. 2007). In animal models of diabetes, aldosterone antagonism (spironolactone) attenuated the increased content of myocardial content of connective tissue in diabetic mice (Westermann et al. 2007). This treatment has also been described to attenuate cardiac failure by decreasing cardiac inflammation and normalizing metalloproteinase activity in streptozotocin-induced diabetic cardiomyopathy (Westermann et al. 2007).

3.7 Impaired Calcium Homeostasis

It is known that calcium and other ion homeostasis is altered in diabetic cardiomyocytes (Cesario et al. 2006). Failing heart muscle generally exhibits distinct changes in intracelular Ca^{2+} handling, including impaired removal of cytosolic Ca^{2+}, reduced calcium loading of the cardiac sarcoplasmic reticulum, and defects in this sarcoplasmic reticulum Ca^{2+} release accompanied by an impairment of cardiac relaxation and systolic function. In streptozotocin-induced diabetic rats, decreased activity of the

sarcoplasmic reticulum Ca^{2+}ATP ase has been reported; this reduced enzymatic activity contributes to the pathogenesis of cardiac dysfunction in this animal model of diabetes (Zhao et al. 2006; Lopaschuk et al. 1983).

4 Medical Therapy for Heart Failure in Patients with Diabetes

Current guidelines from the European (Ponikowski et al. 2016) as well as the American (WRITING COMMITTEE MEMBERS and ACC/AHA TASK FORCE MEMBERS 2016) cardiology societies do not recommend specific treatment approaches in patients with diabetes. In this section, our approach takes into consideration treatments according to LVEF and is divided into: (1) treatment in patients with reduced EF (HFrEF), and treatment in patients preserved EF (HFpEF) or mild-range EF (HFmEF). Likewise, treatment in patients with HFrEF is divided into the first line medical treatment and other treatments.

4.1 Pharmacological Treatment of Heart Failure with Reduced Ejection Fraction (HFrEF)

The main aims of the medical treatment for patients with HF include the improvement of quality of life and clinical status, and the avoidance of hospitalizations and reduction of mortality. Several clinical trials have provided the evidence base for the medical treatment of chronic heart failure. Regarding HFrEF, neurohormonal antagonists (such as angiotensin-converting enzyme inhibitors (ACEIs), mineralcorticoid receptor antagonists (MRAs) and β-blockers) proved to reduce morbidity and mortality. Thus, these groups of drugs are the main medical treatment. Furthermore, ivabradine and more recently sacubitril/valsartan have demonstrated benefit in terms of mortality and hospitalizations in subjects with EF < 35% in clinical trials (McMurray et al. 2014; Swedberg et al. 2010; Shekelle et al. 2003).

However, no pharmacological treatment has been shown to reduce mortality in patients with HFpEF, and the existing evidence to improve morbidity or prevent hospitalizations is poor. For this reason, current clinical guidelines just recommend the control of congestion, symptoms and comorbidities in this group of patients.

Because diabetes confers a poorer prognosis in terms of morbidity and mortality in subjects with HF, the implementation of evidence-based treatment is imperative. Below, we include the mains details of the current recommendations about medical treatment in chronic HF according to European Society of Cardiology (Ponikowski et al. 2016).

4.1.1 First Line Medical Treatment in HFrEF

Angiotensin Converting Enzyme Inhibitors (ACEIs) /Angiotensin II Receptor Blockers ACEIs significantly reduce the number of hospitalizations for HF, myocardial infarction and CV mortality in subjects with asymptomatic or symptomatic left ventricular systolic dysfunction (Ponikowski et al. 2016). For this reason, they are strongly recommended in the absence of contraindications in all patients with HF. The dose of ACEIs ought to be increased to the maximum tolerated dose to achieve optimal inhibition of the RAAS (Masoudi and Inzucchi 2007). In patients who cannot tolerate ACEIs, angiostensin receptor blockers (ARBs) are recommended (Ponikowski et al. 2016).

In patients with symptomatic chronic HF and intolerance to ACEIs, treatment with the ARB candesartan reduced CV mortality and morbidity (Granger et al. 2003). Treatment with valsartan, another angiotensin-receptor blocker, was reported to reduce the combined end-point of mortality and morbidity and to improve clinical signs and symptoms in patients with HFrEF when added to prescribed therapy which included ACEIs (Masoudi and Inzucchi 2007; Granger et al. 2003; Cohn and Tognoni 2001). The benefits of ACEIs in subjects with diabetes

and HFrEF are similar to those of subjects without DM (McMurray et al. 2014). Thus, ACEIs should be used in all subjects with diabetes and HFrEF.

Beta-Blockers The results obtained in clinical trials performed in more than 20,000 patients with HFrEF have demonstrated that β-blockers significantly decrease the risk of death and hospitalization due to HF and improves symptoms despite treatment with an ACEIs (Packer et al. 2001). β-blockers and ACEIs are complementary, and both are strongly recommended in patients with HFrEF. Beta-blockers should be initiated in clinically stable patients. It is recommended that treatment is started at low doses and the dose should be increased according to the tolerance of the patient until the maximum tolerated dose. Current guidelines recommend the use of β-blockers in patients with coronary heart disease given its effectiveness in patients with myocardial infarction. Thus, they are also recommended in subjects with previous myocardial infarction and asymptomatic left ventricular systolic dysfunction (LVSD) (Ponikowski et al. 2016).

Recent studies have shown that the benefit of treatment with β-blockers in HFrEF is mainly in patients in sinus rhythm (Kotecha et al. 2014). However, current guidelines maintain the recommendation for the use of β-blockers in all patients with depressed EF in sinus rhythm, and even in atrial fibrillation. The use of β-blockers in patients with diabetes and HFrEF, as in patients without diabetes, is associated with a decreased risk of all-cause, cardiovascular and cardiac mortality. Thus, this treatment should be considered, in addition to ACEIs, in all diabetic subjects with HFrEF and stable symptoms of HF.

Mineralcorticoid Receptor Antagonists (MRAs) In two clinical trials (the RALES study and the EPHESUS study) (Pitt et al. 1999, 2003), MRAs on top of standard therapy in subjects with HFrEF were reported to improve symptoms, decrease the risk of hospitalization and reduce mortality. Therefore, MRAs are recommended in all symptomatic patients with HFrEF and LV ejection fraction below 35% (Ponikowski et al. 2016). Heart failure guidelines recommend routine surveillance of serum potassium and renal function in patients treated with MRAs. This is especially important in diabetic subjects. These patients have a higher prevalence of chronic kidney disease, and some of them might also have type IV renal tubular acidosis; these two factors clearly increase the risk of hyperkalaemia, particularly if they are already receiving treatment with ACEIs.

4.1.2 Second Line Medical Treatment in HFrEF

Sacubitril/Valsartan This is a first-in-class drug that contains an angiotensin II receptor blocker (valsartan) and a neprilysin inhibitor (sacubitril). In the cardiovascular system, neprilysin cleaves numerous vasoactive peptides. Some of these peptides have vasodilatory effects (including natriuretic peptides, adrenomedullin and bradykinin), and others exert vasocontricting effects (angiotensin I and II and endothelin-1, among others). The inhibition of neprilysin leads to a slower degradation of NPs. High circulating NPs inhibits the secretion of renin and aldosterone. Additionally, NPs increase natriuresis, diuresis, and myocardial relaxation.
In the PARADIGM-HF trial, in symptomatic patients with HFrEF, LVEF below 35–40%, elevated NPs and glomerular filtration rate over 30 mL/min/1.73 m^2, received either sacubitril/valsartan or enalapril (Zhao et al. 2006). Sacubitril/valsartan was superior to enalapril in terms of hospitalizations for HF, and cardiovascular and overall mortality. Moreover, this treatment resulted in a greater long-term reduction of HbA1c than in patients receiving enalapril (Seferovic et al. 2017).

Sacubitril/valsartan is therefore indicated in patients with HFrEF and EF $<$ 35% who are symptomatic despite standard treatment (Ponikowski et al. 2016). Combined treatment

with an ACEIs (or ARB) and sacubitril/valsartan is contraindicated. To avoid the occurrence of angioedema, ACEIs should be stopped 36 h before starting treatment with sacubitril/valsartan.

Ivabradine Increased resting heart rate is a well-established risk factor for adverse events. Ivabradine decreases the heart rate by inhibiting of the I_f channel in the sinus node. In the Systolic Heart failure Treatment with the I_f inhibitor Ivabradine Trial (SHIFT), treatment with ivabradine versus placebo in patients with symptomatic HFrEF, LVEF $\leq$35% and heart rate over 70, was associated with an improvement of clinical outcomes that included admissions for worsening HF (Swedberg et al. 2010; Shekelle et al. 2003). Therefore, ivabradine is recommended in patients with HFrEF that fit these criteria and are symptomatic despite standard treatment (Ponikowski et al. 2016).

Table 1 Summarizes the results obtained from clinical trials assessing the effect of drug therapy on HF mortality and morbidity in patients with reduced LVEF

4.1.3 Other Medical Treatments in HFrEF

A. **Diuretics:** The main clinical manifestations of HF are due to the retention of fluids; thus, treatments aimed at improving congestive symptoms play a central role in this treatment approach. Thus, diuretics are one of the cornerstones of HF treatment, to reduce symptoms of congestion although they have not shown reduction in mortality (Ponikowski et al. 2016). The proper use of these agents requires adequate knowledge of their pharmacodynamics and pharmacokinetics, their interactions and possible causes of inefficiency, as well as their potential dangers. To avoid the latter, basic rules should be maintained, including the use of the lowest possible doses that can keep the patient free from oedema and periodic monitoring of renal function and serum electrolytes. In comparison with thiazides, loop diuretics induce a more intense and shorter diuresis, although they may act synergistically; for the treatment of resistant oedema, this combination may be used.

B. **Hydralazine and isosorbide dinitrate** may be used in combination in symptomatic subjects with HFrEF, in whom ACEIs or ARB are contraindicated or are not well tolerated, although this recommendation is based on old studies in which the standard treatment did not include ACEIs, β-blockers or ARMs (Cohn et al. 1986).

C. **Digoxin** may be used in subjects who keep sinus rhythm with symptomatic HFrEF despite all the other medical treatment described, to reduce the risk of hospitalization (all-cause and heart failure hospitalizations) (Digitalis Investigation

Table 1 Clinical trials evaluating drug benefit in patients with reduced ejection fraction

	Mortality	Morbidity
ACEi (Ponikowski et al. 2016)	↓	↓
ARBs (Masoudi and Inzucchi 2007; ranger et al. 2003; Cohn and Tognoni 2001)	↓	↓
B-receptor blockade (acker et al. 2001)	↓	↓
Mineralcorticoid/aldosterone receptor antagonists (Kotecha et al. 2014; Pitt et al. 1999)	↓	↓
I_f –channel inhibitors (Ivabradine) (Swedberg et al. 2010; Shekelle et al. 2003)	↓	–
Angiotensin receptor neprilysin inhibitor (Zhao et al. 2006)	↓	↓

ACEi (Angiotensin-converting enzyme inhibitor): captopril, enalapril, lisinopril, ramipril, trandolapril; **ARBs** (Angiotensin receptor blockers): candesartan, valsartan; **β-receptor blockade:** bisoprolol, carvedilol, metroprolol succinate; **Mineralcorticoid/aldosterone receptor antagonists:** eplerenone, spironolactone; **Ivabradine:** in symptomatic HF patients with LVEF $\leq$35%, sinus rhythm and heart rate $\geq$ 70 beats $\times$ minute; **Angiotensin receptor neprilysin inhibitor:** in symptomatic HF patients with LVEF $\leq$35–40%, elevated natriuretic peptides and glomerular filtration rate $>$ 30 ml/min

Group 1997), although its effect on top of β-blockers has never been assessed. In subjects with symptomatic HF and atrial fibrillation, digoxin is a useful resource to slow a rapid ventricular rate when other therapeutic options cannot be pursued.

Finally, there are few studies that have examined the effect of statin treatment on vascular markers of inflammation and echocardiographic findings in patients with non-ischemic forms of HF. These studies have shown that treatment with statins (atorvastatin) in patients with reduced LVEF improves LVEF and attenuates adverse LV remodelling (Sola et al. 2006; Yamada et al. 2007).

4.2 Current Therapies for Treatment of Heart Failure with Preserved (HFpEF) or Mid-Range Ejection Fraction (HFmEF)

Until now, patients with EF between 40–49% (HFmrEF) had been excluded from HF clinical trials or, alternatively, they were included in the HFpEF group (EF $\geq$ 50%); therefore, the evidence regarding treatment response of patients in this "grey area" is poor (McMurray et al. 2003; Smith et al. 2003). Although the pathophysiology is heterogeneous, for the time being, current HF guidelines recommend the same medical treatment for HFmrEF and HFpEF patients.

Treatment with ACEIs, ARBs, β-blockers, MRAs or ivabradine in patients with HFpEF or HFmrEF was not shown to decrease mortality in any of the trials in which it has been evaluated, and evidence to improve morbidity or prevent hospitalizations is poor.

Patients with HFpEF or HFmrEF are usually elderly subjects, highly symptomatic and with low quality of life. A main aim of medical therapy in these patients is to improve clinical symptoms. In the SENIORS study, 2128 patients over 70 years of age with previous HF were randomized to the β-blocker nebivolol or placebo. Treatment with nebivolol reduced the combined endpoint of death or cardiovascular hospitalization (Flather et al. 2005).

The different studies that have analysed the cause of death in subjects with HF have suggested that the proportion of non-cardiovascular deaths is higher in subjects with HFpEF compared to HFrEF. This is consistent with the belief that comorbidities may play an important role in outcomes in patients with HFpEF compared with HFrEF. This was confirmed in a national ambulatory cohort of Veterans with HF (Ather et al. 2012), in which it was shown that those patients with HFpEF had a higher non-cardiac morbidity burden associated with higher non-HF hospitalizations compare to HFrEF suggesting that comorbidities should be treated aggressively in patients with HFpEF (Ponikowski et al. 2016).

5 Treatment of Diabetes in Patients with HF

Given the associations of cardiac dysfunction with glucose metabolism, cardiac energy reserve, and steatosis, metabolic interventions aiming to improve glucose metabolism might have beneficial impacts on cardiac function. Nevertheless, the best treatment strategy in diabetic patients with HF remains controversial, and only some glucose-lowering medications have specifically been studied in patients with HF. Although intensive glycaemic control does not seem to impact the outcomes of HF, the choice of the glucose-lowering drug may have a major impact on the development of HF and other cardiovascular outcomes.

(a) Metformin: Currently, the main clinical practice guidelines unanimously recommend the use of metformin as the initial therapy of choice in the vast majority of patients with T2D. There are no data from randomized trials specifically designed to evaluate the effects of metformin on HF, either on incident HF or on safety and efficacy in patients with established HF. Until now, there are data that support the

evidence that metformin is at least as safe as other hypoglycemic agents in patients with DM and HF, even in those cases with decreased ejection fraction (Eurich et al. 2013). In a systemic review of observational studies, metformin was reported to be associated with a 20% lower adjusted death rate compared with other antihyperglycaemic medications, mainly sulfonylureas (Eurich et al. 2013). Moreover, data from observational studies showed that metformin leads to a reduction in all-cause mortality in patients with T2D with congestive HF and appears to reduce the admissions from congestive HF in patients with congestive HF or with moderate chronic nephropathy (Eurich et al. 2013). Furthermore, metformin has not been reported to be associated with an increased risk of lactic acidosis in patients with chronic HF or with mild chronic kidney disease (Inzucchi et al. 2014). Hence, these data have prompted regulatory authorities to remove HF from the earlier list of product-label contraindications for metformin therapy (Inzucchi et al. 2007). The Food and Drug Administration withdrew congestive HF as a contraindication for the use of metformin in 2006. Also, in April 2016, the agency reviewed its warning regarding chronic nephropathy to restrict the use of metformin only in patients with severe disease (glomerular filtration rate < 30 ml/min/1.73m^2), thus allowing its administration in subjects with moderate chronic nephropathy (30–60 ml/min/1.73 m2). For this reason, in the absence of severe ventricular dysfunction, metformin is currently recommended as first-line therapy in clinically stable subjects with HF.

(b) Sulfonylureas and insulin: As with metformin, clinical trial data are scarce concerning the impact on HF in subjects with established cardiovascular disease treated with either sulfonylureas or insulin. No difference in HF events was recorded in the UK Prospective Diabetes Study (UKPDS) comparing sulfonylureas or insulin treatment with dietary intervention in 3867 newly diagnosed patients with diabetes (Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) 1998). Regarding sulfonylureas, population-based observational studies have provided discordant results (McAlister et al. 2008; Tzoulaki et al. 2009). Conversely, no increase in HF hospitalization or cardiovascular events was observed in the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial (ORIGIN Trial Investigators et al. 2012). In summary, based on this limited evidence, the presence of HF is not a contraindication for the use of sulfonylurea therapy, but an alternative option of using metformin seems preferable. Moreover, as with insulin therapy, severe hypoglycaemia is common with sulfonylurea therapy with potential adverse cardiac effects; thus, sulfonylurea therapy should be reconsidered in patients with HF if hypoglycaemia occurs.

(c) Thiazolidinediones: The thiazolidinedione (TZD) family of Peroxisome proliferator-activated receptor gamma (γ) (PPARγ) agonists initially provided a promising therapeutic option in T2DM owing to antidiabetic efficacy combined with pleiotropic beneficial cardiovascular effects. However, the utility of TZDs in T2D has declined in the past decade, largely due to concomitant adverse effects of fluid retention and edema formation attributed to salt-retaining effects of proliferator-activated receptor γ activation on the nephron. The two major cardiovascular outcome trials with these drugs, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia and Diabetes (RECORD) and PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), identified a substantial increase in risk of

HF, although HF was not a pre-specified adjudicated endpoint in PROACTIVE (Dormandy et al. 2005). In this latter study, a significant reduction in the secondary outcome (cardiovascular death, and non-fatal myocardial infarction or stroke) occurred (HR 0.84), although there was no significant reduction in the primary endpoint, that included also re-vascularization procedures. More recently, treatment with pioglitazone showed superiority for major cardiovascular events in a population of 3895 patients with recent stroke and insulin resistance (although not T2D) randomized to pioglitazone versus placebo in the Insulin Resistance Intervention After Stroke trial, with no significant increase in HF outcomes (Kernan et al. 2016). However, thiazolidinediones have a fluid retention potential, leading to increased heart failure events. Already in 2003, the American Diabetes Association and the American Heart Association recommended that TZDs should be used with caution in subjects with class I-II of the New York Heart Association, while they should be avoided in subjects with class III and IV (Nesto et al. 2003). The European Society of Cardiology stated in their 2016 guidelines that thiazolidinediones are not recommended in any patient with HF (Ponikowski et al. 2016).

(d) dipeptidyl peptidase IV (DPP-4) Inhibitors: DPP4 is a serine peptidase that is widely distributed and may be found as a membrane-anchored surface protein or in a soluble form. Studies in different experimental models suggest that these drugs may have renoprotective and cardioprotective effects. However, conflicting findings have been described in other preclinical animal models and also in clinical studies. The cardiovascular effects of DPP-4 inhibitors remain controversial. While these drugs did not reduce or increase the risk of primary, pre-specified composite cardiovascular outcomes, one DPP-4 inhibitor (sitagliptin) demonstrated no effect on HF (Green et al. 2015), another (saxagliptin) increased the ~~increased the~~ risk of hospitalization for HF in the overall population (Scirica et al. 2013), and a third (alogliptin) demonstrated inconsistent effects on heart failure hospitalization across subgroups of patients (Zannad et al. 2015). The mechanisms related to the increased HF risk with saxagliptin and the evident heterogeneity with regard to HF effects within the DPP4 inhibitor class require further elucidation.

(e) GLP-1 receptor agonists (GLP-1RA): No increased risk of hospitalization for HF has been reported with GLP-1RAs in meta-analyses of phase-II/III trials (exenatide, albiglutide, dulaglutide, liraglutide) (Li et al. 2016), demonstrating the safety of this pharmacological class, and these findings have been confirmed in three large prospective cardiovascular outcome trials (Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) with lixisenatide, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER) with liraglutide and the Trial to Evaluate Cardiovascular and other long-term outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) with semaglutide). In particular, the LEADER trial reported a trend towards a reduction in HF hospitalization (−13%, $P = 0.14$), together with a significant reduction in cardiovascular and all-cause mortality in patients with T2D at risk for cardiovascular disease. These results are reassuring in the face of the somewhat negative results of the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) trial, which evaluated the effects of liraglutide in patients with advanced HF and low LVEF, such that further studies and caution are now required when using this agent to treat these patients in clinical practice.

(f) Sodium-glucose transporter type 2 (SGLT2) inhibitors: The first prospective, randomized, controlled trial assessing CV safety in patients with T2D was the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus patients (EMPA-REG OUTCOME) trial, which was also the first clinical trial to demonstrate that an antidiabetic agent, empagliflozin, could reduce cardiovascular events (Zinman et al. 2015). Empagliflozin is a highly selective inhibitor of the sodium glucose contransporter 2 (SGLT2) in the kidney. Results obtained in the EMPA-REG trial showed that treatment with empagliflozin versus placebo, in addition to standard of care in subjects with T2D and high cardiovascular risk, is associated with significant reductions in the primary 3-point major adverse CV events outcome (a composite of CV death, non-fatal myocardial infarction and non-fatal stroke) (14% risk reduction), a 38% relative risk reduction in CV death, a 32% relative risk reduction in all-cause mortality and a 35% risk reduction in hospitalization for HF.

Empagliflozin has been shown to delay the progression of kidney disease and to reduce clinical renal events, including dialysis. Importantly, empagliflozin decreased the number of hospitalizations for HF and mortality by one-third. However, the mechanisms by which empagliflozin exerts CV protection are currently unknown. The early impact of empagliflozin on CV and hospitalization for HF suggest early haemodynamic effects of the drug. Furthermore, SGLT2 inhibition has been found to increase the concentration of circulating ketone bodies, which might provide an alternative energy source for the diabetic heart in the presence of insulin resistance. In addition, other potential mechanisms, such as weight loss, reduced blood pressure, sodium depletion, reduced oxidative stress, and arterial stiffness, as well as a reduction in sympathetic nerve activation, are currently being discussed (Neal et al. 2017). Recently, a large multinational study using real-world clinical practice databases from different countries compared hospitalization for HF and death in patients newly initiated on any SGLT-2 inhibitors (empagliflozin, dapagliflozin, canagliflozin) versus other glucose-lowering drugs. The results obtained showed that treatment with SGLT-2-inhibitors was associated with a lower risk of HF and death, suggesting that the benefits seen with empagliflozin in a randomized trial might be a class effect applicable to a broad population of T2D patients in real-world practice(CVD-REAL). According to 2016 ESC guidelines, empagliflozin should be considered in patients with T2D to prevent or delay HF and to prolong life (Ponikowski et al. 2016).

To date, prospective CV outcome trials are ongoing with other SGLT2 inhibitors (dapagliflozin in the DECLARE-TIMI) to determine whether the beneficial cardiovascular outcome effects reported from the EMPA-REG OUTCOME trial are a class effect or unique to empagliflozin. Recently, combined results from the Canagliflozin Cardiovascular Assessment Study (CANVAS) and the CANVAS renal end-points trial (CANVAS-R) have been reported. In these studies, patients with T2D, 65.6% with a history of cardiovascular disease, were randomized to canagliflozin (300 mg daily or 100 mg daily) or placebo. Results obtained show that the rate of the primary outcome, a composite of CV death, and non-fatal myocardial infarction or stroke, was lower in the group of patients treated with canagliflozin than in the placebo group (occurring in 26.9 vs. 31.5 participants per 1000 patient-years; hazard ratio, 0.86; $P < 0.001$ for noninferiority; $P = 0.02$ for superiority). However, the CANVAS data also revealed a significant doubling in the risk for amputations, primarily on the toe or metatarsal (6.3 vs 3.4 cases per 1000 patient-years, hazard ratio, 1.97) (Zannad et al. 2015). Additionally, the effects of various agents, including empagliflozin, on cardiovascular morbidity and mortality in patients with HFpEF will be determined by future trials in heart failure (e.g., EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved

Ejection Fraction [EMPEROR-Preserved; NCT03057951]; and Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and PRESERVED Ejection Fraction Heart Failure [PRESERVED-HF; NCT03030235]); however, thus far, symptom control is the major therapeutic goal (Lehrke and Marx 2017).

In conclusion, the choice of a glucose-lowering drug in subjects with diabetes should be individualized. The American Diabetes Association and European Association for the Study of Diabetes emphasize the importance of personalized treatment in patients with DM and list different conditions to be taken into consideration when choosing a drug: risk of hypoglycaemia, effect on body weight, side effects and costs among the different factors. Moreover, it will also have to be taken into account if the patient has a history of cardiovascular disease or HF (Fitchett et al. 2017).

Take Home Messages

1. The risk of HF in patients with DM is significantly increased, and it is one of the most common initial manifestations of CVD in patients with T2D.
2. Diabetes is associated with worse outcomes in patients with HF.
3. In diabetic cardiomyopathy, the disease course consists of a silent asymptomatic subclinical, and usually long period, during which cellular structural damage initially leads to diastolic dysfunction, thereafter to systolic dysfunction, and eventually to HF.
4. The pathogenic mechanisms underlying DCM are likely to be multifactorial, ranging from altered myocardial metabolism to endothelial dysfunction, microvascular disease, autonomic neuropathy, and altered myocardial structure with fibrosis.
5. The presence of subclinical diastolic dysfunction in patients with T2D is associated with the subsequent development of HF and mortality, independent of hypertension and coronary disease.
6. The presence of albuminuria in a patient with diabetes is associated with an increased risk of having subclinical abnormal myocardial function.
7. Current guidelines from the European, as well as the American, cardiology societies do not recommend specific therapeutic approaches in subjects with diabetes compared with those without the disease.
8. Considering the best available current evidence, the sodium-glucose-co-transporter 2-inhibitors and metformin seem to be especially advantageous with regard to HF effects, with their use associated with reduced HF events and improved mortality.

Acknowledgments This work wfrom Instituto de Salud Carlos III, Ministry of Economy and Competitiveness, Spain; CIBERDEM, a research network initiative of Instituto de Salud Carlos III, Spain and from la Fundació Marató TV3 (Grant number 201602.30.31) of Spain.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 219–238
DOI 10.1007/5584_2017_126
© Springer International Publishing AG 2017
Published online: 21 November 2017

Heart Failure and Kidney Disease

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Abstract

Kidney disease is commonly found in heart failure (HF) patients. They share many risk factors and common pathophysiological pathways which often lead to mutual dysfunction. Both haemodynamic and non-haemodynamic mechanisms are involved in the development of renal impairment in heart failure patients. Moreover, the presence of a chronic kidney disease is a significant independent predictor of worse outcome in chronic as well as in acute decompensated HF. As a consequence, an accurate evaluation of renal function plays a key role in the management of HF patients. Serum creatinine levels and glomerular filtration rate (GFR) estimates are the corner stones of renal function evaluation in clinical practice. However, to overcome their limits, several emerging glomerular and tubular biomarkers have been proposed over the last years. Alongside the renal biomarkers, imaging techniques could complement the laboratory data exploring different pathophysiological pathways. In particular, Doppler evaluation of renal circulation is a highly feasible technique that can effectively identify HF patients prone to develop renal dysfunction and with a worse outcome. Finally, some classes of drugs currently used in heart failure treatment can affect renal function and their use can be influenced by the presence of chronic kidney disease.

Keywords

Biomarkers · Cardio-renal syndrome · Chronic kidney disease · Doppler · Haemodynamics · Heart failure · Prognosis · Renal function · Renal resistance index · Venous Doppler

1 Introduction

Renal dysfunction is a common condition in cardiovascular diseases. The burden of renal impairment is especially relevant in the heart failure (HF) population, regardless of the phenotype of cardiac dysfunction and the acute or

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chronic clinical setting, because of the close relationship between heart and kidney function (Chong et al. 2015). Renal and heart diseases share common risk factors and pathophysiological pathways which can lead to an acute or chronic mutual dysfunction, termed cardiorenal syndrome (Table 1). Cardiorenal syndrome has been classified in five subtypes: type 1 refers to acute heart failure as the cause of acute kidney disease; type 2 refers to chronic heart failure as the cause of chronic kidney disease; in type 3 the acute worsening of kidney function causes heart dysfunction; in type 4, chronic kidney disease (CKD) leads to heart failure; in type 5 there is a simultaneous injury of heart and kidneys caused by systemic diseases (Ronco et al. 2008). About half of the patients with heart failure suffers from at least moderate chronic kidney disease, defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m2, compared to the 10.6% of the general population (Damman et al. 2014a; Hill et al. 2016). The prevalence of CKD is higher among the patients with acute decompensated heart failure (ADHF), ranging from 30 to 60%, depending on the definition used (Adams et al. 2005). Similarly, in-hospital worsening renal function (WRF) is observed in 23% of HF patients, even if the optimal definition for WRF is still debated, leading to some heterogeneity in the results from the various cohorts (Damman et al. 2014a; Smith et al. 2006; Metra et al. 2008). Among patients with chronic heart failure (CHF), up to 42% have CKD (Damman et al. 2014a). Renal impairment is an independent risk factor for adverse outcome in subjects with ADHF and CHF (Smith et al. 2006; Hillege et al. 2000; Damman et al. 2009a; Chang et al. 2010).

2 Pathophysiology

Heart and kidney are two organs tightly linked in physiological and pathological conditions, because they both contribute to preserve the homeostasis of water and electrolytes and the cardio-circulatory function. Heart is greatly dependent on fluid homeostasis regulated by the kidney and renal function is subordinated to perfusion pressure through hemodynamic, neurohormonal, inflammatory and local mechanisms (Damman and Testani 2015). Moreover, heart and kidney diseases frequently coexist because they share pathophysiological pathways and risk factors (such as hypertension, diabetes and atherosclerosis). In heart failure several mechanisms are involved in the pathogenesis of renal impairment, e.g. haemodynamic alterations due to reduced cardiac output and renal venous congestion, neurohormonal deregulations, systemic and local inflammation (Colombo et al. 2012), high-dose of diuretics.

Renal haemodynamic factors are main determinants of renal impairment (and GFR reduction) in HF patients (Damman and Testani 2015). GFR is dependent on renal blood flow and filtration fraction and it is maintained in a normal range by autoregulation despite significant reduction of cardiac output. When these mechanisms are exhausted, as in HF, GFR declines with cardiac output (Braam et al. 2012). Renal hypoperfusion with "forward" underfilling triggers renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system activation which causes arteriolar vasoconstriction both at glomerular and tubular level. Especially in the acute setting, relevant drop of cardiac output can lead to tubular hypoxia and acute tubular necrosis (Schefold et al. 2016).

Table 1 Consensus Conference of Acute Dialysis Quality Initiative Group classification of cardiorenal syndromes

Type	Primary dysfunction	Consequences
Type 1	Acute worsening of heart function	Kidney injury and/or dysfunction
Type 2	Chronic abnormalities in heart function	Kidney injury and/or dysfunction
Type 3	Acute worsening of kidney function or AKI	Heart injury and/or dysfunction
Type 4	CKD	Heart injury and/or dysfunction
Type 5	Systemic conditions	Simultaneous heart and kidney injury and/or dysfunction

However, the haemodynamic interaction between heart and kidney is even more complex and other mechanisms are involved, considering the modest association between renal impairment and left ventricular systolic function in a large registry of HF patients (Heywood et al. 2007). Emerging data on the interaction between venous congestion and renal dysfunction in HF have lead to a reappraisal of this relationship (Nohria et al. 2008). High central venous pressure and renal venous hypertension can impair GFR through an increase in interstitial pressure and a reduction of artero-venous gradient (Mullens et al. 2009).

Among the non-haemodynamic factors, the hyperactivation of RAAS and sympathetic nervous system has an important role in HF. In addition to the direct effect on the arteriolar tone, at renal level RAAS increases in the long term the secretion of proinflammatory molecules, promotes fibrosis and leads to reduced response to natriuretic peptides (Ruiz-Ortega et al. 2002; Charloux et al. 2003). Moreover, the sympathetic hypertone provokes renin release from juxtaglomerular cells and RAAS activation, oxidative stress and endothelial dysfunction (together with RAAS) (Damman and Testani 2015; Goldsmith et al. 2010).

On the other hand, chronic kidney disease is an established and increasingly recognized risk factor for cardiovascular disease, particularly heart failure. The risk of cardiac impairment increases gradually with kidney dysfunction. In particular, a 15 times higher cardiovascular mortality has been observed in end-stage renal disease (ESRD) patients compared to general population (Granata et al. 2016). In this group of patients, the myocardial structural changes are mainly characterized by left ventricular hypertrophy and fibrosis responsible for diastolic dysfunction; however also dilatation of the left ventricle and impairment of systolic function can occur (Alhaj et al. 2013). Among the several mechanisms involved in the development of heart failure in ESRD patients, an increased preload, caused by fluid overload and a high flow state, related to arterio-venous fistulas, can promote the eccentric remodeling of the left ventricle. On the other hand, an increased afterload, due to high arterial systemic resistances (systolic and diastolic hypertension) and a reduced arterial compliance (vascular calcification), can promote a ventricular concentric remodeling. In addition to the changes in preload and afterload, myocardial fibrosis can be enhanced by a number of non-haemodynamic factors as uremic toxins, oxidative stress, inflammatory status, hyperparathyroidism, hypovitaminosis D and hyperphosphatemia (Alhaj et al. 2013; Tumlin et al. 2013).

3 Markers of Glomerular Function

Taking into account its relevant prognostic role, the evaluation of kidney function in subjects with heart failure is extremely important. A number of laboratory examinations are available to assess renal function and, in particular, the filtration ability of the kidney (Table 2).

3.1 Serum Creatinine and Glomerular Filtration Rate

Serum creatinine levels and GFR estimation are the corner stone for renal function evaluation and are routinely recommended in HF patients management for assessing renal dysfunction and filtration impairment (Ponikowski et al. 2016). Serum creatinine is the product of creatine phosphate breakdown at muscular level. It is produced at relatively constant rate and eliminated by the kidney through glomerular filtration and partially by active secretion in the tubules (Levey et al. 2006). Empirical formulas can be used to easily estimate GFR based on serum creatinine levels, age, gender and weight. The most commonly used formulas are Cockroft-Gault, simplified Modification of Diet in renal disease (MDRD) and, recently, Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) (Stevens et al. 2006). These equations have been validated in CKD populations with good results. Among these formulas, CKD EPI has been shown to be less biased in GFR estimation, especially within the population with preserved

Table 2 Advantages and limitations of renal biomarkers and imaging techniques

Technique	Advantages	Limitations
Serum creatinine	Easy to interpret; cheap	Biased due to age, diet, gender and muscle wasting
BUN	Cheap; strong prognostic value	Less reliable marker of filtration function
Cystatin C	Unbiased; reliable in GFR estimation	Relatively expensive
Microalbuminuria	Easy; early marker of renal impairment; prognostic value independent of GFR	Low specificity
Tubular markers	Early markers of renal impairment; strong markers of AKI; prognostic value independent of GFR	Costs; low specificity
Bidimensional ultrasonography	Feasible; it excludes obstructive uropathy and some parenchymal alterations	Low specificity; no hemodynamic information
Renal resistance index	Feasible; prognostic value independent of GFR	Influenced by renal obstructive arterial disease; lower accuracy with irregular rhythms
Venous Doppler	Feasible; prognostic value independent of GFR	Lack of standardization
Computed tomography	High spatial resolution	Nephrotoxicity of constrast medium; exposure to radiations; no indications in clinical practice
Nuclear imaging	Low radiation dose	Exposure to radiations
MRI	No radiation exposure; unique functional information	Expensive; time consuming; lack of standardization; no indications in clinical practice

renal function (Stevens et al. 2010). In the setting of CHF patients, it leads to a more accurate classification of renal functional stages and a better risk stratification, particularly in those patients with normal or near normal renal function (McAlister et al. 2012; Valente et al. 2014). For this reason, it has recently become the most used estimate of GFR in clinical practice. Serum creatinine levels can also be used to identify patients with WRF, who are at higher risk for events (Smith et al. 2006; Metra et al. 2008). In HF patients, it is generally defined as an absolute increase of >0.3 mg/dl and/or a relative increase of >25% in serum creatinine levels within two-time points (Damman et al. 2009a). In the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines, CKD progression has been defined as a decline in the stage of CKD accompanied by a 25% or greater drop in eGFR from baseline (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013).

Creatinine concentration and GFR estimation are currently recommended to assess renal impairment in HF and to classify renal dysfunction based on GFR category (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). However, some limitations in the use of serum creatinine exist, as its levels are biased due to age, diet, gender and body mass. A decrease in creatinine levels (with overestimation of GFR) is observed in muscle wasting, a common condition seen in advanced HF. Additionally, GFR estimation can be hampered when filtration function decreases as the relative effect of active secretion is more pronounced, leading to an overestimation of GFR (Damman et al. 2012). On the basis of these limitations, new biomarkers have been proposed to better evaluate glomerular function.

3.2 Blood Urea Nitrogen (BUN)

Urea is produced by protein catabolism, filtered at glomerular level and reabsorbed in the collecting ducts by an AVP-mediated system. In conditions of low cardiac output, the increased RAAS and adrenergic stimulation lead to enhanced fluid and sodium retention.

Consequently, distal flow is reduced and urea reabsorption increases. Urea has been shown to be a strong prognostic marker in both acute and chronic HF populations, being an important predictor of morbidity and mortality (Damman et al. 2012; Aronson et al. 2004; Cauthen et al. 2008). In the acute setting, blood urea nitrogen, together with blood pressure and serum creatinine, has been used to estimate in-hospital mortality with a tree algorithm in the ADHERE registry (Fonarow et al. 2005). The prognostic value of urea could also be greater than serum creatinine (Klein et al. 2008), probably because urea levels take into account other factors than glomerular filtration, as protein intake (and thus nutritional status), catabolic state and reabsorption coupled with sodium at tubular level as a marker of low flow (Schrier 2008). Urea levels are therefore dependent both on glomerular function and on a number of factors related to HF severity. This could explain its strong prognostic role, but it cannot be considered a reliable marker of filtration function. The ratio between urea and creatinine has been extensively used for the differentiation of prerenal renal dysfunction from intrinsic renal parenchymal disease. In prerenal renal dysfunction significant renal neurohormonal activation causes a disproportionate reabsorption of urea compared to creatinine, leading to an urea/creatinine ratio $>$ 100 (or a BUN/creatinine ratio $>$ 20). In patients with HF and renal dysfunction, an elevated urea/creatinine ratio could differentiate a renal impairment due to hypoperfusion from CKD. Furthermore, high urea/creatinine ratio has been associated with congestion and long-term mortality in HF patients (Parrinello et al. 2015).

3.3 Cystatin C

Cystatin C belongs to cysteine proteinase inhibitor family and is secreted by all nucleated cells. It is filtered freely through the glomerulus and then reabsorbed but not secreted by tubular cells, where it is catabolised. As opposed to creatinine, it is relatively independent from age, body mass, nutritional status and cachexia (Newman et al. 1995). The only concerns are inflammation and thyroid dysfunction which could influence Cystatin C levels (Fricker et al. 2003; Singh et al. 2007). Empirical formulas have been proposed to estimate GFR, with better results compared to serum creatinine in different clinical settings and particularly in normal and near normal renal function (Damman et al. 2012; Dharnidharka et al. 2002). Cystatin C has also shown to be accurate in stratifying the risk in the elderly, in diabetic patients and in patients affected by coronary artery disease (Shlipak et al. 2005a; Ix et al. 2006; de Boer et al. 2009). Limited data exist on the role of Cystatin C in HF; however, it appears to be a promising prognostic marker both in acute and chronic HF (Arimoto et al. 2005; Shlipak et al. 2005b; Lassus et al. 2007). Despite these interesting proprieties, Cystatin C is not widely used in clinical practice, perhaps because of its relative high cost compared to creatinine. However, current KDIGO guidelines for CKD state that Cystatin C could be used as a confirmatory test in circumstances when GFR estimation based on creatinine alone is less accurate (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013)

3.4 Albuminuria

Albumin is the most abundant protein in blood. Because of its size, its negative electric charge (the same as the glomerular basement membrane) and the tubular absorption, it is normally present at very low level in the urine. The urinary excretion of albumin is generally evaluated by the ratio between urinary albumin and creatinine (UACR). Albuminuria is present when UACR is $>$30 mg/g, an UACR between 30 and 300 mg/g is termed microalbuminuria, an UACR $>$300 mg/g is defined macroalbuminuria (Miller et al. 2009). Albuminuria is the effect of glomerular membrane damage due to endothelial dysfunction, inflammation, increased glomerular pressure and atherosclerosis (Comper et al. 2008). For this reason, it should be considered a marker of glomerular permeability rather than an

estimate of filtration. Microalbuminuria is highly prevalent in CHF (van de Wal et al. 2005). In this setting other mechanisms could be involved, i.e. renal venous congestion and reduced renal perfusion (Damman et al. 2009b). It has been shown to be associated mortality and HF related hospitalization, independently from creatinine levels and GFR. This association remains significant even in CHF patients with normal GFR, suggesting that microalbuminuria could be an early sign of renal impairment (Jackson et al. 2009; Masson et al. 2010). In the management of patients with renal dysfunction, albuminuria classification, together with GFR category, is recommended as a marker of kidney damage in CKD definition and risk stratification (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013).

4 Markers of Tubular Damage

Another component of acute kidney injury is tubular cell damage, which may be damaged earlier than the glomerulus. Therefore, different markers of tubular damage are being studied to better evaluate and predict renal impairment.

4.1 Neutrophil Gelatinase Associated Lipocalin (NGAL)

NGAL is a small protein produced by the kidney and other organs. It is freely filtered through the glomerulus and completely reabsorbed in the proximal part of the tubule. In normal conditions very low urinary and blood concentrations are observed (Schmidt-Ott et al. 2007). When tubular damage occurs, NGAL cannot be completely reabsorbed, leading to increased urinary levels. In renal diseases, higher plasma levels are also common but relatively less specific, being also found in sepsis, inflammation and cancer (Schmidt-Ott et al. 2007). In case of acute kidney injury, NGAL precedes the rise of serum creatinine by at least 24 h, as the other tubular markers (Mishra et al. 2005). In the acute decompensated heart failure setting, it is associated with the occurrence of WRF and with adverse clinical outcome (Collins et al. 2012; Alvelos et al. 2013). In CHF patients, NGAL levels are markedly increased compared to controls, but they were not able to predict adverse events. Thus, NGAL should be considered as a marker of tubular damage in the acute rather than in the chronic setting (Damman et al. 2010).

4.2 N-Acetyl Beta Glucosaminidase (NAG)

NAG is a lysosomal protein of the proximal tubule, excreted into urine in case of tubular damage (Bazzi et al. 2002). NAG levels are associated with tubular injury in acute kidney disease where it predicts worse prognosis (Liangos et al. 2007). In the intensive care setting, NAG is related to the risk of acute kidney injury (Westhuyzen et al. 2003). In patients with CHF it showed to predict an increased risk of death or HF-related hospitalizations, independently from GFR (Damman et al. 2010). These results were also confirmed in the large cohort of CHF patients of the GISSI HF trial, where it was the only tubular marker related to prognosis and risk of WRF (Damman et al. 2011). Few data are available on the prognostic role of NAG in acute decompensated heart failure.

4.3 Kidney Injury Molecule (KIM1)

KIM1 is a transmembrane glycoprotein which is expressed in proximal tubule cells after hypoxic tubular injury almost 1 day before the increase in serum creatinine (Han et al. 2002). KIM1 urinary levels have high sensitivity for early detection of acute kidney injury. CHF patients have higher KIM1 levels compared to controls. In these setting, urinary KIM1 predicts poor prognosis independently from GFR (Damman et al. 2010).

4.4 Fatty Acid-Binding Proteins (FABPs)

FABPs are proteins that bind free fatty acids. Different tissue-specific FABs have been identified (Veerkamp et al. 1990). In the kidney, liver specific FABP (FABP-1) and heart specific FABP (FABP-3) have been respectively expressed in the proximal and in the distal tubule (Maatman et al. 1991). Urinary FABP-1 and FABP-3 levels have been associated with ischemic tubular injury and risk for AKI (Noiri et al. 2009). In CHF patients persistently high FABP-3 levels are associated with cardiovascular events (Niizeki et al. 2008).

4.5 TIMP-2 and IGFBP7

Tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7) are cell-cycle arrest biomarkers found to be elevated in renal tubule damage (Niizeki et al. 2008). The product of the urinary concentrations of these two biomarkers, [TIMP-2] × [IGFBP7], has been demonstrated to predict short term acute kidney injury in acute decompensated heart failure with good sensitivity and specificity (Schanz et al. 2017). Furthermore, patients with AKI and elevated [TIMP-2] × [IGFBP7] show a trend toward reduced survival within 1 year (Schanz et al. 2017).

5 Imaging

Several different imaging techniques can explore renal function in terms of anatomy and haemodynamics (Table 2). Ultrasound and Doppler examinations represent an easy and widespread technique used to evaluate parenchymal abnormalities and estimate perfusion pressures with parameters correlated with prognosis in the setting of HF patients. On the other hand, there are several promising second level techniques, especially involving nuclear and magnetic resonance imaging (MRI), which are confined only to an experimental role, so far.

5.1 Renal Ultrasonography

Bidimensional renal ultrasound is a low cost and easy to perform technique which allows an anatomical examination of renal parenchyma. Unfortunately, there are no morphological abnormalities specifically related to heart failure. The observed renal anatomy is greatly dependent on the stage of heart failure and on the severity of the concurrent kidney disease, so the bidimensional examination mostly differentiate an acute from a chronic renal impairment and can exclude an obstructive uropathy as a cause for renal dysfunction. Renal dimensions are related to body surface area, and are generally between 10 and 12 cm in length (Emamian et al. 1993).

In case of renal dysfunction associated with chronic heart failure, there is a non-specific sonographic appearance, common with other causes of CKD: kidneys are smaller, with reduced cortical thickness and cortex-medulla ratio (Moghazi et al. 2005). The parenchyma appears relatively echogenic compared to the liver, due to interstitial fibrosis related to chronic disease (Page et al. 1994). During de novo acute decompensated heart failure renal anatomy is frequently preserved, provided no prior CKD is present. Kidneys have normal dimension and cortex-medulla ratio, with a fairly echolucent appearance of the parenchyma compared to the liver. An echogenic appearance can be rarely observed in case of long-standing renal hypoperfusion (Di Lullo et al. 2012). Both in the acute and in the chronic setting signs of urinary obstruction are generally absent, unless urologic co-morbidities occur.

5.2 Vascular Renal Doppler

The Doppler study of renal arterial flow allows a more comprehensive evaluation of the complex mechanisms involved in the relationship between

renal dysfunction and HF, considering renal haemodynamics and, in particular, arterial resistances. Renal resistances are determined by a number of factors: arteriolar tone, parenchymal anatomy and renal venous congestion.

Glomerular filtration is strictly related to glomerular (blood) hydrostatic pressure and, in turn, to renal blood flow, together with capsular hydrostatic pressure and colloid osmotic pressure. In normal conditions, glomerular filtration and renal perfusion are in parallel stabilized by intrinsic and extrinsic regulation mechanisms with low changes despite wide fluctuations of systemic blood pressure between 70 and 180 mmHg. Out of this range filtration is highly dependent on blood pressure. Renal blood flow is mainly regulated by intrinsic autoregulation (namely myogenic reflex and tubulo-glomerular feedback) and neurohormonal factors as opposed to perfusion of other organs, which are primarily dependent on oxygen demand (Braam et al. 2012; Smilde et al. 2009). Renal blood flow, in theory, is dependent on perfusion pressure (and therefore on cardiac output) and on arterial resistances. In case of a normal autoregulatory system, a reduced cardiac output will not affect net filtration because autoregulation will determine a decrease of arterial resistances ensuring a normal renal blood flow. However, in the setting of heart failure, autoregulatory mechanisms could be altered, being depleted or overruled by sympathetic activation and leading to high renal resistances. Therefore, a reduced cardiac output may cause a disproportional fall of glomerular filtration (Braam et al. 2012). A long-standing increase of renal resistances due to hyperstimulation of arteriolar tone can lead to a functional and then to a structural vascular rarefaction. The former is caused by a prolonged vasoconstriction which causes a reduced number of perfused vessels without anatomical vascular abnormalities. A sustained vasoconstriction may lead to local ischemia, endothelial dysfunction, release of both growth factors and enzymes and, finally, to fibrosis and vascular remodeling. This condition, labeled as "structural rarefaction", refers to an actual reduction in the number of anatomical vessels embedded in the tissue. The vascular remodeling could be considered a cause of persistent increase of renal resistances (Prewitt et al. 1982; Chade 2013). Whatever the mechanism involved, functional rarefaction due to neurohormonal activation or anatomical rarefaction due to remodeling, it is clear that high resistances are associated with reduced renal blood flow and could eventually identify a subset of HF patients prone to renal dysfunction.

Renal arterial haemodynamics could be quantitatively evaluated through renal resistive index (RRI) of Doppler arterial waveform. RRI is derived from Pourcelot's formula: (peak systolic velocity – end diastolic velocity) / peak systolic velocity. The relationship between RRI and arterial resistances is not completely linear. A number of other variables are involved in this interaction, such as vascular stiffness and rhythm disturbances (Mostbeck et al. 1990; Bude and Rubin 1999; Tublin et al. 1999; Murphy and Tublin 2000). Moreover, central venous pressure (CVP) has shown to be positively correlated with RRI: an increase in central venous and intra-abdominal pressure could be transmitted to the renal parenchyma by the stiff capsule leading to an increase in renal interstitial pressure and consequently in arterial resistances (Ciccone et al. 2014). Doppler evaluation of arterial circulation is performed with an anterior approach and a convex probe or with a posterior approach in sitting position and an echocardiographic phased-array probe. Renal arteries are sampled at the level of segmental arteries with a good feasibility. The median value of RRI in healthy adults is 0.60, with slight variations between right and left kidneys (Darmon et al. 2010). RRI evaluation is generally reproducible, with low intraobserver and interobserver variability (Lubas et al. 2014). RRI values above 0.70 are considered abnormal.

The prognostic role of RRI has been evaluated first in patients with chronic nephropathy, where higher values have been shown to correlate with greater degree of parenchymal fibrosis, an increased risk for progression of kidney disease and a generally poor outcome (Platt et al. 1990; Parolini et al. 2009; Hanamura et al. 2012). In the population of patients with HF, RRI has proven

to be useful in risk stratifying patients with both preserved (HFpEF) and reduced (HFrEF) ejection fraction. In the HFpEF population, it has been correlated with poor prognosis, i.e. a greater risk for death and HF related hospitalization (Ennezat et al. 2011). Later on, RRI has been also evaluated in the cohort of outpatients with HFrEF. In this setting, it was associated with a number of endpoints related to progression of heart failure. Patients with higher RRI values are considered at higher risk for HF related hospitalization, all cause death, death due to HF and urgent heart transplantation (Ciccone et al. 2014). RRI could also identify CHF patients prone to poorer renal prognosis, such as those at risk for diuretic resistance (considered as the need for higher diuretic doses) and WRF, during a mid and long-term follow up (Iacoviello et al. 2015; Iacoviello et al. 2016). The prognostic role of RRI in HF has been demonstrated to be independent and incremental, when compared to renal function evaluated with serum creatinine and GFR (Ciccone et al. 2014). RRI could be used together with established laboratory renal markers to better characterize renal function of HF patients, thus integrating information provided by estimated GFR and microalbuminuria (Leone et al. 2016). However, further studies are needed to confirm clinical usefulness of this imaging approach.

In a similar way, scientific efforts should be made to clarify the possible role of renal venous Doppler pattern, which has been recently proposed as a tool to better evaluate renal congestion. Indeed, the renal venous congestion plays a key role in kidney physiology. This has been already demonstrated in the first decades of the last century in an experimental ex-vivo model. High renal venous pressure more than low renal perfusion pressure was associated with a reduction of glomerular filtration rate (Winton 1931). This has been recently observed also in acute as well as in chronic heart failure (Mullens et al. 2009; van de Wal et al. 2005). Renal congestion can lead to a fall in glomerular filtration in two ways. High venous pressure can be transmitted upstream to capillaries at glomerular and tubular level, causing in turn a reduced artero-venous gradient through renal circulation. Moreover, because of the tight renal capsule, high pressure can be transmitted to renal interstitial and then to tubular space. Tubular hypertension can affect upstream capsular hydrostatic pressure, one of the driving forces of glomerular filtration (Tublin et al. 2003). According to this pathophysiological background, the evaluation of renal venous flow could provide information about the presence of increased renal pressure due to peripheral congestion (Jeong et al. 2011). Venous impedance index (VII) has been used as a measure of venous pulsatility. It is calculated as peak maximum flow velocity minus maximum flow velocity at nadir, divided by peak maximum flow velocity (Ishimura et al. 1997). However, as minimum velocity is considered, VII is useful unless intermittent flow is observed. On the other hand, intrarenal venous flow pattern has been shown to be significantly associated with central venous pressure. In the setting of HF patients, venous flow has been classified as continuous or discontinuous, and among those as monophasic or biphasic discontinuous. Discontinuous patterns identify the subset of patients with worse renal function and high central venous pressure. Finally, they were associated with poor prognosis, considered as cardiovascular death and HF hospitalization (Iida et al. 2016). In other series of patients, venous flow has been divided into five groups: continuous with a normal velocity decrease in diastole, continuous with reduced modulation, monophasic with short presystolic interruption or reversal (corresponding to atrial systole), polyphasic intermittent and monophasic intermittent flow. Even in this cohort of patients, the last two intermittent flow patterns are observed in more compromised patients who show worse outcome. Interestingly, the pattern with short presystolic interruption represents a group at intermediate risk, with mild increase in central venous pressure and probably an early renal involvement (Puzzovivo et al. 2016).

5.3 Other Imaging Techniques

Other imaging techniques have been explored for the functional evaluation of the kidneys. Nuclear imaging is based on the use of radioisotopes bound to non-metabolized molecules with known pharmacokinetics. Among the different radioisotopes, Technetium (^{99m}Tc) is the molecule of choice because of its short half-life and low radiation exposure. For assessment of GFR, ^{99m}Tc–DTPA (diethylenetriaminepentaacetic acid) is used. DTPA is eliminated by filtration without entering the cells, and being neither secreted nor reabsorbed by the tubules. GFR values obtained with ^{99m}Tc–DTPA are slightly lower compared to inulin (Haufe et al. 2006). ^{99m}Tc–MAC3 (mercaptoacetyltriglycine) is used for renal blood flow estimation. In the setting of pre-renal azotemia (as in HF), ^{99m}Tc–MAC3 uptake is generally normal in the first 1–2 min, whereas it is reduced in vascular and parenchymal causes and in acute tubular necrosis. After 20 min, MAC3 uptake is increased in pre-renal azotemia, vascular causes and acute tubular necrosis, while it is reduced in parenchymal and obstructive diseases (Kalantarinia 2009). Positron emission tomography (PET), especially combined with CT to enhance spatial resolution, allows a functional and molecular evaluation of the kidney. It could be useful to determine GFR, renal blood flow and to assess the tissue activity of transporters, enzymes and receptors. However, this technology is not widely available for clinical purposes and at the moment it is limited only to the experimental setting (Haufe et al. 2006; Kalantarinia 2009).

Computed tomography (CT) is considered the gold standard for the diagnosis of nephrolithiasis, renal masses and parenchymal diseases. Triphasic helical CT after contrast injection can be used to evaluate functional parameters, as GFR and renal blood flow (Hackstein et al. 2004). However, in the clinical setting of HF, especially in patients with renal impairment, it has limited feasibility and scarce literature because of the high risk of contrast induced nephrotoxicity.

Magnetic resonance imaging (MRI) is a fast growing field in the setting of kidney disease especially because it combines anatomical and functional evaluation of the kidney. The main limitations to its widespread use is the lack of standardized sequences and postprocessing softwares, and for this reason it is confined, so far, to the research field (Michaely et al. 2007). MRI could be used to estimate classical parameters such as GFR and renal blood flow. GFR quantification is based on the kinetics of a gadolinium-containing contrast medium which is eliminated only through glomerular filtration, being not reabsorbed nor secreted by the tubules (Hackstein et al. 2003; Boss et al. 2007). On the other hand, renal blood flow can be evaluated with phase-contrast MRI of the renal artery. This method relies on magnetically excited arterial water molecules used as endogenous tracer for perfusion imaging (Roberts et al. 1995). Together with these approaches, used to assess these conventional parameters, some other techniques are under development for further functional evaluations. With this regard, BOLD (blood oxygenation level dependent) MRI seems to be a promising tool; it works by exploiting the magnetic properties of haemoglobin in order to evaluate the degree of tissue oxygenation of renal parenchyma. Deoxygenated haemoglobin has paramagnetic activity as opposed to oxygenated haemoglobin which is diamagnetic. The increase in tissue deoxygenated haemoglobin during oxygen extraction leads to a decrease in T2* signal, corresponding to the degree of tissue oxygenation. Since renal parenchyma shows a physiological heterogeneous oxygenation with the medulla working at lower oxygen levels, in the setting of HF, BOLD MRI of this region could be especially sensitive to early prerenal kidney injury (Simon-Zoula et al. 2006; Artunc et al. 2011).

6 Renal Dysfunction and HF Treatment

Current recommended therapies for HF patients have been shown to improve functional status

and survival but, in some cases, they could negatively interact with renal function. Patients with HF and renal dysfunction are usually underrepresented in randomized controlled trials on cardiovascular diseases and there are relatively limited data on the baseline renal function and on the effects of treatment on renal disease (Coca et al. 2006). The subgroup of patients with severely decreased renal function (GFR <30 mL/min/1.73m^2) has been generally excluded from clinical trials and therefore there is lack of evidence-based therapies in this population (Ponikowski et al. 2016).

6.1 ACE Inhibitors and Angiotensin II Receptor Blockers

The favourable effect of Angiotensin-converting enzyme inhibitors (ACE-I) and Angiotensin II receptor blockers (ARB) on cardiac function and survival in patients with HF has been well established (Ponikowski et al. 2016). They have shown to improve symptoms and exercise capacity, reduce the risk of hospitalization and mortality (Chang et al. 2010; Garg and Yusuf 1995). ACE-I are recommended, unless contraindicated, in all symptomatic HF patients, while ARB are recommended in patients who are ACE-I intolerant (Chang et al. 2010). In the last European guidelines, ACE-I are also recommended in patients with asymptomatic LV systolic dysfunction to reduce the risk of symptoms development, hospitalization and death (Ponikowski et al. 2016). In the subgroup of patients with HF and moderate renal dysfunction (GFR 30–59 ml/min/1.73 m^2) there is evidence of favorable outcome with ACE-I therapy (Bowling et al. 2012; Massie et al. 2001; Tokmakova et al. 2004). ACE-I might also be beneficial and considered in patients with severe renal dysfunction (GFR <30 ml/min/1.73 m^2), however there are no conclusive data (Bowling et al. 2012). Analogously, there is moderate evidence for the use of ARB in the population of patients with HF and moderate renal dysfunction, whereas there are no data available on the effect of ARB in severe renal disease (Granger et al. 2003). ACE-I and ARB are contraindicated in pregnancy, history of angioedema, bilateral renal artery stenosis and previous allergy to ACE-I/ARB. Recommended dose of ACE-I/ARB should be adjustment according to GFR (Table 3) (Damman et al. 2014b). Caution is advised in patients who experience hyperkalemia (>5 mmol/l) and/or severe renal dysfunction. An early increase in serum creatinine is relatively common during initiation and uptitration of ACE-I/ARB therapy (10–35% of patients). This deterioration in renal function is usually small and does not have the same adverse prognostic implications as other kind of WRF in HF natural history (Testani et al. 2011). However, an extreme decrease in renal filtration function is dangerous. In patients with severe renal dysfunction, the renin-angiotensin system blockade is known to impair the autoregulatory mechanisms and make glomerular filtration critically dependent on renal blood flow (Metra et al. 2012). The degree of creatinine increase that should warrant therapy discontinuation is uncertain. The European guidelines suggest that an increase in creatinine of up to 50% above baseline or an increase in potassium to $\leq$5.5 mmol/L is acceptable (Ponikowski et al. 2016). If greater rises in creatinine or potassium are observed, the dose of ACE-I/ARB should be reduced. If creatinine increases by $>100\%$ or to >3.5 mg/dl and/or GFR <20 ml/min/1.73 m^2, therapy should be discontinuated. Renal function and electrolytes should be checked before initiation of ACE-I/ARB therapy, 1–2 weeks after initiation and final uptitration, and every 4 months after the final dosage is achieved. Blood chemistry should be also checked after dose reduction in case of WRF.

6.2 Mineralcorticoid Receptor Antagonists

Mineralcorticoid receptor antagonists (MRA) act by blocking the receptor that binds aldosterone. Two MRAs, spironolactone and eplerenone, have been demonstrated to reduce mortality and hospitalization in HF with reduced ejection

Table 3 Dose adjustment of treatments in patients with impaired renal function (Tokmakova et al. 2004)

Drug	Dose Adjustment
ACE-I	
Captopril	GFR >40: no adjustment
	GFR 20–40: 1/2 dose
	GFR 10–20: 1/4 dose
	Dialysis: 1/8 dose
Enalapril	GFR 30–80: no adjustment
	GFR 10–30: 1/2 dose
	Dialysis: only dose on dialysis days
Lisinopril	GFR 30–80: no adjustment
	GFR 10–30: 1/2 dose
	Dialysis: only dose on dialysis days
Ramipril	GFR 30–60: no adjustment
	GFR 10–30: 1/2 dose
	Dialysis: only dose on dialysis days
ARB	
Candesartan	GFR >15: Starting dose 4 mg/die than dose uptitration based on response
	GFR <15 or dialysis: no experience
Valsartan	GFR >10: no adjustment
	GFR <10 or dialysis: no experience
Losartan	No adjustment
MRA	
Spironolactone	GFR >60: no adjustment
	GFR 30–60: every other day regimen
Eplerenone	GFR >60: no adjustment
	GFR 30–60: every other day regimen

fraction (Pitt et al. 1999, 2003; Zannad et al. 2011). Therefore, MRA are recommended in all symptomatic patients with HF and reduced ejection fraction (LVEF $\leq$35%) despite treatment with an ACE-I/ARB and beta-blockers (Ponikowski et al. 2016). The beneficial effects of spironolactone and eplerenone have shown to be consistent irrespective of baseline renal function. There is convincing evidence for the use of MRA in patients with HF and moderate renal dysfunction. However, no data are available the setting of severe renal dysfunction because these patients were excluded from the randomized clinical trials (Vardeny et al. 2012). Therefore, MRA are contraindicated in patients with baseline GFR <30 ml/min/1.73 m^2 and/or potassium >5.0 mmol/l and in patients with previous allergic reaction. Spironolactone and eplerenone should be initiated at a dose of 25 mg daily, increasing to 50 mg daily. For patients with moderate renal dysfunction or concerns of hyperkalemia an initial regimen of every-other-day dosing is advised (Table 3). As for ACE-I/ARB, MRA can determine an initial increase in serum creatinine. In the RALES trial, an increase in creatinine was more common in the spironolactone group compared to placebo. However, WRF was not associated with worse outcome in this group, in contrast to WRF of the placebo group (Vardeny et al. 2012). The main concern associated with use of MRA is hyperkalemia, which is relatively common in the clinical practice (25% of patients) and occurs mostly in patients with reduced baseline GFR. The development of potassium >5.5 mmol/l and/or creatinine >2.5 mg/dl and/or GFR <30 ml/min/1.73 m^2 should trigger dose reduction of MRA. In case of potassium levels

>6.0 mmol/l and/or creatinine >3.5 mg/dl and/or GFR <30 ml/min/1.73 m^2, MRA should be discontinuated. Renal function and electrolytes should be checked at 1 and 4 weeks after initiation/uptitration, monthly for the first 3 months and every 3–4 months thereafter.

6.3 Angiotensin Receptor Neprilysin Inhibitors

Angiotensin receptor neprilysin inhibitors (ARNI) is a new class of drugs recently developed. LCZ696 is the first agent of this class and combines the neprilysin inhibitor prodrug sacubitril and the ARB valsartan. The active metabolite of sacubitril inhibits neprilysin, leading to a slowed degradation of natriuretic peptides and bradikinin. Higher blood levels of vasoactive peptides are responsible for the favourable cardiovascular effects, such as increased diuresis and natriuresis, vasodilatation and myocardial anti-remodeling effect (McCormack 2016). In the recent PARADIGM-HF trial, sacubitril/valsartan has demonstrated to be superior over enalapril in reducing mortality and hospitalization in a population of ambulatory HFrEF patients with LVEF <40% (later amended to <35%) and high BNP levels (McMurray et al. 2014a). Sacubitril/valsartan is therefore recommended as a replacement for ACE-I in patients with these characteristics who remained symptomatic despite optimal medical treatment (Ponikowski et al. 2016). In the PARADIGM-HF, 37% of enrolled patients had a baseline GFR <60 ml/min/1.73 m^2 (McMurray et al. 2014b). Reduced GFR at the enrolment did not modify the effect of sacubitril/valsartan on mortality and morbidity, as shown in a subgroup analysis (McMurray et al. 2014a). Up to now, there is very limited clinical experience in patients with severe renal dysfunction, as those patients were excluded from the previous studies. Sacubitril/valsartan is contraindicated with concomitant use of an ACE inhibitor. Other contraindications related to valsartan should also be considered. The initial recommended dose of sacubitril/valsartan is 49/51 mg twice daily, increased to 97/103 mg after 2–4 weeks. An initial dose of 24/26 mg twice daily should be considered in patients with moderate renal dysfunction. The effect of sacubitril on renal dysfunction is of interest because neprilysin inhibition is expected to have favourable effect on kidney function (Judge et al. 2015). This renoprotective effect is probably related to the slower degradation of natriuretic peptides and it has been observed in both the studies on sacubitril/valsartan. In the PARAMOUNT trial, GFR decreased to a greater extent in the valsartan group compared to the sacubitril/valsartan group (Solomon et al. 2012). In the PARADIGM-HF, significant increase in creatinine levels (>2.5 mg/dl) and discontinuation of the treatment because of renal impairment were less frequent in the sacubitril arm in comparison to the enalapril group (McMurray et al. 2014a). Further data on the renoprotective role of sacubitril/valsartan will come from the ongoing Heart and Renal Protection III (UK HARP-III) trial, which will compare sacubitril/valsartan with irbesartan in a population of CKD patients with proteinuria and GFR between 20 and 60 ml/min/1.73m^2.

6.4 Hydralazine and Nitrates

In CHF hydralazine is generally used in combination with high doses of oral nitrates, as isosorbide dinitrate (ISDN). Both these molecules are vasodilator drugs with a complementary "nitroprusside-like" hemodynamic effect, caused by the predominant venodilatory action of ISDN and the arterial-dilatory effect of hydralazine (Bauer and Fung 1991). The first data on the clinical effects of the association of hydralazine and isosorbide dinitrate (H-ISDN) come from a small RCT on 642 men treated with digoxin and diuretics. In this population, H-ISDN was associated with a trend towards mortality reduction compared to placebo (Cohn et al. 1986). In a subsequent study, the African-American Heart Failure Trial (A-HeFT), the

addition of H-ISDN to conventional therapy significantly reduced mortality and HF hospitalizations in African-American patients affected by HF (Taylor et al. 2004). The results of A-HeFT are difficult to translate to non-African-American patients, therefore in this population the mortality benefit remains uncertain. In the HF European guidelines, H-ISDN is recommended in self-identified African-American patients with HFrEF, symptomatic despite standard treatment. H-ISDN may also be considered in symptomatic patients intolerant or with contraindications to RAAS blockers (Ponikowski et al. 2016). In patients with advanced HF, the acute treatment with intravenous hydralazine showed positive changes on the renal hemodynamics. Hydralazine decreased total renal resistance and significantly increased renal blood flow, with preservation of GFR (Cogan et al. 1980). Similar results were observed after oral hydralazine therapy. The favorable hemodynamic effect was associated with a significant increase in creatinine clearance (Pierpont et al. 1980). Data from a post-hoc analysis of the A-HeFT, demonstrate that the beneficial effects of H-ISDN on event-free survival were consistent across subgroups, in particular in patients with and without history of chronic heart failure (Taylor et al. 2007). Because of its neutral effect in kidney disease, H-ISDN is frequently prescribed, in clinical practice, to patients with HF and renal failure or hyperkalemia, in whom ACE-I/ARB use could be complicated or contraindicated (Ziaeian et al. 2017; Giamouzis et al. 2011).

6.5 Diuretics

Despite the beneficial effects on renal haemodynamics due to the RAAS inhibition, the sodium excretion capacity of kidneys remains often poor, leading to sodium retention and fluid overload. The goal of diuretic therapy in HF is to relieve signs and symptoms of congestion by stimulating diuresis and natriuresis. Diuretics act by inhibiting the reabsorption of sodium at tubular level. The loop diuretics (furosemide, bumetanide and torasemide) operate at the level of the ascending limb of the loop of Henle and are the cornerstone of symptoms management in HF patients. On the other hand, thiazide diuretics act in the distal convoluted tubule and are mainly used as antihypertensive agents. Diuretic treatment is generally initiated with the minimum effective dose and then adjusted according to the therapeutic response. The symptomatic benefit of diuretics is universally accepted; nevertheless, no randomized controlled trial has prospectively evaluated their effects on morbidity and mortality. A small meta-analysis on loop and thiazide diuretics showed a possible favorable effect on mortality and hospitalization in the HF general population (Faris et al. 2012), but no prognostic data are available in the specific setting of HF and renal dysfunction (Damman et al. 2014b).

However, diuretics may have detrimental effects of renal function. Because of their mechanism of action, a prolonged use has been shown to worsen renal function in patients with both normal and reduced filtration capacity (Bayliss et al. 1987). The mechanisms involved are hypovolemia with renal hypoperfusion which, in turn, causes a reduction of glomerular perfusion pressure and renal arteriolar constriction mediated by neurohormonal upregulation (Bayliss et al. 1987). The degree of renal dysfunction has been shown to influence the variability of diuretic response among HF patients. Indeed, renal impairment is associated with a downward and right shift of the dose-response curve, leading to higher doses required to achieve the same level of sodium excretion (Ellison 2001). An altered dose-response relationship could lead to a self-perpetuating vicious circle with higher loop diuretic dosages needed for symptoms relief, which have been demonstrated to be independently associated with mortality (Eshaghian et al. 2006).

Furthermore, renal disease is one of the main causes of diuretic resistance, i.e. the lack of treatment response and the inability to achieve a negative fluid balance. In patients with impaired renal function, poor kidney perfusion as well as low protein levels are responsible for the reduced

concentration of loop diuretics that reach peritubular capillaries. Moreover, high levels of urate and other endogenous organic anions compete with loop diuretics for the organic anion transporter. Finally, filtered albumin can bind loop diuretics in the tubular lumen, preventing their effect at their site of action (Verbrugge et al. 2016). Diuretic resistance frequently requires an adequate fluid and/or sodium restriction and increasing loop diuretic dose is often a solution to the problem. Furthermore, adding either thiazides or metolazone, and eventually MRA, on top of loop diuretic therapy could be of further help in case of severely impaired renal function. Indeed, the sequential nephron blockade may be useful in order to overcome the upregulation of thiazide-sensitive sodium transporter and the renal adaptation of distal tubules that increase the capacity to reabsorb sodium (Verbrugge et al. 2016). Unfortunately, the combined diuretic therapy is associated with enhanced risk of electrolytes disturbances (hypokalemia, hypomagnesemia, hyponatremia), hypovolemia and renal impairment. Blood chemistry and volume status should be periodically checked in order to adjust the diuretic dose and maintain euvolemia. In case of significant hypokalemia (<2.5 mmol/l) and/or severe renal dysfunction a dose reduction or the discontinuation of thiazide diuretics should be considered.

7 Conclusion

Kidney disease is highly prevalent in subjects affected by heart failure and has a negative prognostic value independently of the degree of cardiac dysfunction. Therefore, an accurate renal function evaluation is relevant to identify patients prone to worse outcome. GFR estimation based on serum creatinine levels is considered the easiest way to assess overall kidney function in clinical practice and it is routinely used in HF patients management. However, several limitations in the use of serum creatinine exist. To overcome some of the caveats related to creatinine, several new glomerular and tubular markers have been studied. Emerging renal biomarkers have demonstrated to carry incremental diagnostic and prognostic information in renal diseases and identify renal impairment at an earlier stage. In addition to laboratory data, imaging techniques have shown to give complementary information in HF-related renal dysfunction. In particular, Doppler evaluation can explore renal arterial and venous haemodynamics, giving independent and incremental prognostic information. Finally, the management of patients with significant renal impairment and concomitant heart failure is still a major challenge. Unfortunately, because of the underrepresentation of patients with renal dysfunction in HF clinical trials, limited data are available for this specific subgroup. With this regard, current evidences support the use of HF drugs in patients with moderate renal dysfunction, but data on the population with severe and end-stage renal dysfunction are still lacking. Lastly, the new ARNI class showed a promising renoprotective effect in recent clinical trials, but further data are expected about its safety in patients with severe renal dysfunction.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 239–253
DOI 10.1007/5584_2017_132
© Springer International Publishing AG 2017
Published online: 13 December 2017

Dysthyroidism and Chronic Heart Failure: Pathophysiological Mechanisms and Therapeutic Approaches

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Abstract

Among comorbidity in chronic heart failure (CHF), dysthyroidism represents a relevant problem especially in the ageing CHF patients worldwide. Thyroid greatly affects many cardiovascular activities and its dysfunction may worsen a CHF condition. In particular, hypothyroidism has a relative high prevalence in patients with heart failure and it plays a key role in influencing CHF onset, progression and prognosis. Hyperthyroidism, is less frequent in this clinical context but it necessitates of immediate treatment because of its negative effects on cardiovascular balance. Also, it must be considered that dysthyroism may also be iatrogenic and the main responsible drug is Amiodarone.

Based on the best available evidence and our cumulative clinical experience, this manuscript analyzes the prevalence, the pathophysiology and the prognostic impact of thyroid disorders in chronic heart failure.

Keywords

Chronic heart failure · hypothyroidism · hyperthyroidism · Amiodarone

1 Introduction

Comorbidity and multimorbidity in chronic heart failure (CHF) represent an emerging problem especially in the ageing CHF patients worldwide. In particular the well-known adaptive or maladaptive modifications of the neuroendocrine and the immune system are heavily involved in the pathogenesis as well as in the worsening of CHF, leading to functional and structural modifications of the cardiovascular system (Fiore et al. 2013). In addition, several hormone deficits and comorbid endocrine and metabolic conditions have been described, with a strong

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impact on the prognosis of these patients (Arcopinto et al. 2015a). Specifically, thyroid dysfunction (Triggiani and Iacoviello 2013; Triggiani et al. 2016), hypogonadism (Giagulli et al. 2013a, b) GH/IGF1 axis impairment (Arcopinto et al. 2017), diabetes (Dei Cas et al. 2015), especially when associated with depression (Fiore et al. 2015) and obesity (De Pergola et al. 2013) can influence either the development and the progression and prognosis of CFH itself. The therapy of endocrine and metabolic conditions, moreover, can be very challenging in patients with CHF (Triggiani and Iacoviello 2013; Triggiani et al. 2016; Giagulli et al. 2013; Arcopinto et al. 2017; Dei Cas et al. 2015; Fiore et al. 2015; De Pergola et al. 2013; Arcopinto et al. 2015b; Butler et al. 2008).

Thyroid function greatly affects cardiovascular balance, particularly heart rate, systemic vascular resistance, arterial pressure, and cardiac excitability as well as lusitropic properties. Thyroid dysfunction, therefore, may have a negative impact on the symptoms of patients with CHF and it can be associated with a poor prognosis. An early diagnosis and treatment of thyroid disorders, therefore, should be considered of importance to better treat CHF patients and to prevent worsening of the heart failure (Butler and Kalogeropoulos 2008; Jessup et al. 2009; Dalström 2005; Manowitz et al. 1996).

2 Hypothyroidism and Heart Failure

Subclinical hypothyroidism is characterized by a TSH above the normal range with thyroid hormones free fractions still normal, and it can be mild when TSH is between 4.5 and 9.9 mU/L or severe when TSH is $\geq$10 mU/L. It is frequently "asymptomatic", even though many patients actually can develop mild symptoms of thyroid hormone deficiency. Furthermore, these patients can develop an overt hypothyroidism, characterized by a reduction of thyroid hormones, over the time, at a rate of about 2–5% per year (Cooper and Biondi 2012; Cooper 2001; Huber et al. 2002; Turnbridge et al. 1977).

The prevalence of overt hypothyroidism has been estimated to be between 14 and 19/1000 for women and less than 1/1000 for men whereas the prevalence of subclinical hypothyroidism shows higher figures: 75/1000 for women and 28/1000 for men. This percentage increases with age, up to 15–20% more in the ninth decade of life (Vanderpump et al. 1995; Hollowell et al. 2002; Canaris et al. 2000; Ruggeri et al. 2017).

When dealing with elderly people, however, it should be take into account that there is a large body of evidence that TSH distribution curves shift to higher concentrations with increasing age and such a rise in TSH serum concentrations does not reflect a real increase in the prevalence of hypothyroidism with age, but rather a change in age-specific population distribution of TSH. This may be due to an age-associated alteration in TSH set point caused by a diminished sensitivity of the pituitary gland to the negative feedback by thyroid hormones, a decrease in TSH biological activity or in thyroid gland sensitivity to TSH. For these reasons, the use of an age-specific reference range for TSH has been recommended, especially in patients over 70 years, to avoid subjects being misclassified with subclinical hypothyroidism and even inappropriately treated with thyroid hormone with possible consequent negative effects (Klein and Ojamaa 2001).

2.1 Hypothyroidism and Heart Failure: Pathophysiologic Aspects

The reduced production of thyroid hormones results in adverse cardiac effects, represented by reduced contractility with impaired left ventricular systolic function on exercise and impaired ventricular filling (diastolic dysfunction) associated with increased systemic vascular resistance and diastolic hypertension (Klein and Danzi 2007; Biondi and Cooper 2008). In subclinical hypothyroidism, the abnormalities in cardiac function observed are the same but less severe than those showed in the overt form (Dillmann 2002).

Reduction in cardiac contractility and diastolic dysfunction are partly due to changes in heart gene expression. Thyroid hormones, in fact, affect the expression of genes involved in contractile properties and intracellular calcium handling through interaction with Thyroid-Responsive Elements (TREs), thus regulating cardiomyocytes contractility (Dillman 1990; Van Tuyl et al. 2004; Chen et al. 2000). Moreover, chronic hypothyroidism is also characterized by the stimulation of the activity of fibroblasts resulting in myocardial fibrosis (Van Bilsen and Chien 1993), and can lead to loss of small coronary arteries, impaired blood flow, and cardiomyocytes' shape alterations.

The pattern of cardiac gene expression observed in hypothyroid subjects is very similar to that developed in response to hypertension, ischemia, myocardial infarction and valvulopaty, conditions that can cause pathological hypertrophy and CHF (Nakao et al. 1997; Lowes et al. 1997; Feldman et al. 1986).

As a consequence, in HF, the cardiac gene expression is similar to that of subjects affected by hypothyroidism. This genetic pattern of expression is called "fetal gene program recapitulation". This is a typical condition of intrauterine life when placental type 3 deodinase (D3) converts T4 into inactive reverse T3, resulting in a low T3 concentration in fetal blood, a condition that promotes cell proliferation more than cell differentiation. After birth, there is a replacement with a new gene expression program (Gerdes 2015). However, it can be reversed in case of chronic hypothyroidism, in low T3 syndrome, in myocardial hypertrophy and HF, raising the question whether CHF itself may be in part due to a deficit of cardiomyocytes' thyroid hormone receptor stimulation and response, due to the expression of different thyroid receptors isoforms and an increased expression of D3, with impaired genomic and non-genomic signaling (Pantos et al. 2008) and whether hormone replacement therapy could be an effective therapy to improve cardiac function in CHF patients (Brenta et al. 2007; Cappola et al. 2006).

Non-treated hypothyroidism also increases coronary heart disease's risk factors such as LDL and Apolipoprotein B (Christ-Crain et al. 2003; Squizzato et al. 2007). This condition leads to a lower expression of liver receptors for LDL, with a reduction of their clearance. HDL (high density lipoproteins) are normal or often increased due to a lesser CEPT (Cholesteryl ester transfer protein) and liver lipase activity. This causes a reduced transport of cholesterol esters from HDL to VLDL (very low density lipoprotein) and IDL (intermediate low density lipoproteins). In addition, hypothyroidism increases plasma cholesterol oxidation primarily because its capture pattern is altered. In this setting, particular attention should be paid to the subclinical forms, which are often left untreated for a long period (Monzani et al. 2004). A significant increase in mortality for cardiovascular causes, particularly ischemic disease, in patients with subclinical hypothyroidism compared to euthyroid subjects is reported by Iervasi et al. (2007). In fact thyroid hormones play an important role in regulating myocardial morphology, metabolism and cell response to stress, increasing heart tolerance to ischemia, and improving, by inotropic and anti-apoptotic actions, hemodynamics in setting of ischemia-reperfusion.

2.2 Hypothyroidism and Heart Failure: Prognostic Implications

Different studies have evaluated the prognostic impact of thyroid hormone deficiency in patients with CHF. Hamilton et al. demonstrated the role as a marker of the fT3 / reverse T3 ratio in predicting a worse prognosis in terms of death or need for cardiac transplantation, in patients hospitalized for advanced cardiac heart failure (Hamilton et al. 1990).

Pingitore et al. (2005) evaluated the role of low T3 levels in predicting mortality in 281 CHF patients. A multivariate model has highlighted the only two independent predictors of mortality for any cause: the ejection fraction and the total T3 level. In this study a high percentage of patients

showed a low total T3 value (43%). This was probably due to severe systolic insufficiency (20% of patients showed an ejection fraction <20%) associated with a functional status that may have affected T3 levels. Finally, in this study population, the presence of a low percentage of patients receiving ACE inhibitors and beta-blockers may have affected hemodynamics and thyroid function.

The relationship between serum FT3 levels, hemodynamic parameters and prognosis was also evaluated in a small population of patients with dilated cardiomyopathy (Kozdag et al. 2005). In this study, 21% of the subjects had abnormalities in thyroid function tests. The results also showed that the free triiodothyronine (fT3) / free thyroxine (fT4) ratio was significantly correlated with echocardiographic parameters that reflect cardiac remodeling and systolic-diastolic function. In addition, the fT3 / fT4 ratio, considered as a continuous variable and fT3 / fT4 < 1.7, were both associated with an increased risk of mortality, regardless of other prognostic markers. Once again only a small percentage of patients were treated with ACE inhibitors and beta-blockers at the time of enrollment. Low fT3 level was also associated with adverse outcomes in patients hospitalized for Acute Decompensated HF (Okayama et al. 2015).

In an Italian study based on a population of CHF outpatients (93% treated with ACE inhibitors or angiotensin receptor blockers, 88% beta-blockers), in a 15-month of follow-up, it has been proven that in a univariate analysis model, TSH, thyroid hormones and the ratio fT3/fT4 were all associated with the events (cardiac failure exacerbations); however, a multivariate analysis, after correcting for other variables associated with events, showed that only TSH was independently associated with the occurrence of the events (Iacoviello et al. 2008).

Another study by the same authors, involving a larger sample of patients, has confirmed the role of hypothyroidism in CHF outpatients (Triggiani et al. 2012). Patients with pre-diagnosed hypothyroidism, new diagnosis of hypothyroidism at the enrollment and hypothyroidism developed during follow-up showed a higher risk of progression of HF compared to the euthyroid patients. These evidence suggests that in patients with stable CHF, hypothyroidism plays a role in determining worsening of heart failure.

In a pooled analysis of individual participant data performed on 25,390 subjects from six prospective cohorts in the USA and Europe, the risk for acute HF events, hospitalization or death for HF events was higher in the subjects with higher TSH concentration. In particular, the HR was 1.01 for TSH 4.5–6.9 mU/L, 1.65 for TSH 7.0–9.9 mU/L, and 1.86 for TSH 10.0–19.9 mU/L (Gencer et al. 2012).

In a prospective follow up study of a large cohort of 5,599 patients with HF by Chen et al. (2014) a high TSH concentration and a low concentration were both associated with an increased mortality rate in CHF patients, and the mortality in the highest quartile of TSH was 36% higher than that in the second quartile. Moreover, a TSH between 4.5 mU/L and 10.0 mU/L was associated with a 40% higher mortality, whereas a TSH >10.0 mU/L was associated with a more than twofold increase in mortality. In a meta-analysis of 13 studies by Ning et al. (2015) both overt hypothyroidism and subclinical hypothyroidism were associated with increased risk of all-cause mortality, cardiac death and/or hospitalization in patients with HF. In a paper by Hayashi et al., the role of TSH as a marker of worse prognosis and the negative impact of subclinical hypothyroidism were confirmed also in patients admitted for acute decompensated HF: higher TSH, but not free T3 and free T4, was independently associated with composite cardiovascular events, including cardiac death and re-hospitalization for heart failure in these patients. Therefore, subclinical hypothyroidism was an independent predictor, whereas low-T3 syndrome as well as subclinical hyperthyroidism were not (Hayashi et al. 2016).

Figure 1 summarizes the pathophysiological mechanisms through which hypothyroidism can alter the progression of HF.

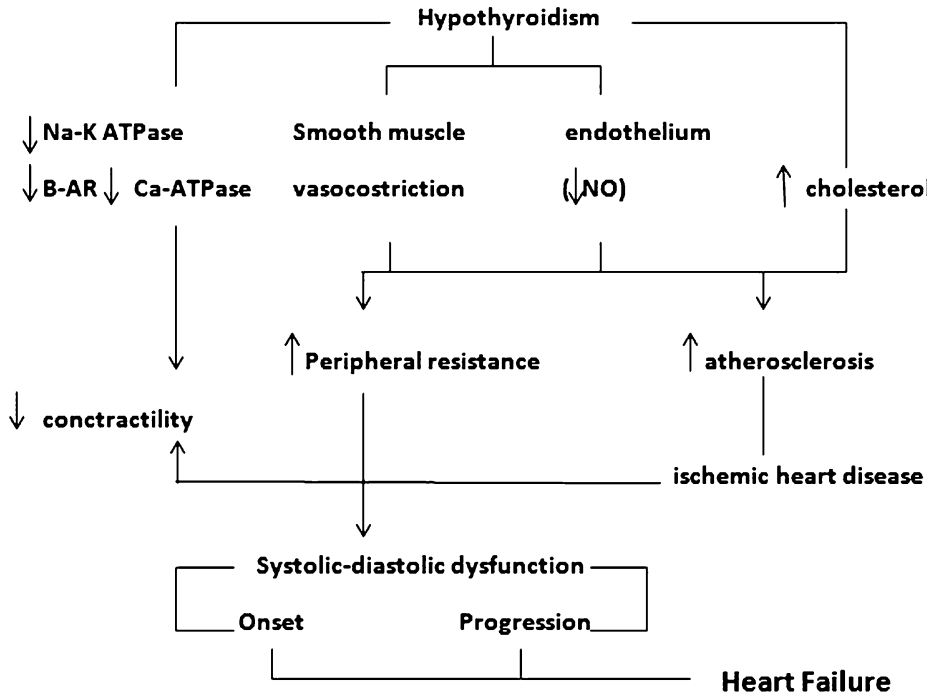

Fig. 1 Hypothyroidism and heart failure: pathophysiological mechanisms
Na-K ATPase: Sodium-potassium pump, Ca2 + −ATPase: calcium pump, β-AR: Beta adrenergic receptor, NO: Nitric oxide
Hypothyroidism causes cardiovascular and metabolic alterations. On the one hand it reduces contractility, due to a decreased activity of the Sodium Potassium ATPase and CA2 + −ATP-ase pump. On the other hand, it increases peripheral resistances by acting on the endothelial and smooth muscle cells causing vasoconstriction. It also determines an increase in serum cholesterol levels, causing possible ischemic disease. All these result in a systolic-diastolic dysfunction that may favor the onset or progression of heart failure

2.3 Hypothyroidism and Heart Failure: Therapeutic Aspects

The treatment of hypothyroidism is based on Levothyroxine (L-T4). The replacement treatment with thyroid hormones allows the control of cardiovascular manifestations of hypothyroidism. Levothyroxine treatment, although increasing myocardial oxygen consumption, because of the inotropic and cronotropic effect, in fact, is also responsible for the reduction of ventricular volume and diastolic pressure, with benefits for patients with HF. The initial dose of levothyroxine is generally 12.5–25 mcg/day, with TSH control at 6–8 weeks and with gradual titration over time, avoiding both too low and too high doses, with a target represented by the normal TSH reference range for the age of the patient, which is: 21–54 years: 0.4–4.2 mIU / L and 55—87 years: 0.58.9 mIU/L (Triggiani and Iacoviello 2013).

While there is no doubt about the need for replacement therapy for overt hypothyroidism, the treatment of subclinical hypothyroidism, especially for TSH values under 10.0 mUI/L still remains controversial, in particular in the elderly (Ruggeri et al. 2017). We are waiting for the full results of the cardiovascular outcomes of the TRUST Study (Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism), (Stott et al. 2017a) in which, preliminary reports, do not find any beneficial effect of Levothyroxine therapy versus placebo in improving symptoms of hypothyroidism, tiredness as well as health-related quality of life,

cognitive and physical performance (Stott et al. 2017b). Moreover, considering the apparent beneficial influence of subclinical hypothyroidism reported by the Leiden 85+ Study in the "oldest old"(Gussekloo et al. 2004) the IEMO 80+ Thyroid Trial (The Institute for Evidence-based Medicine in Old age) will probably shed light on the real utility to treat those patients by means of Levothyroxine (Mooijaart and IEMO 80-Plus Thyroid Trial Collaboration 2014).

3 Low T3 Syndrome ("Euthyroid Sick Syndrome")

"Euthyroid sick syndrome" or "low T3 syndrome" is a condition characterized by an alteration in thyroid profile with typically low circulating T3 levels in the presence of normal TSH, and normal or reduced T4 levels, in patients with cardiac disease and more generally in patients with non-thyroid disease (for example malnutrition, diabetic ketoacidosis, chronic renal failure). The pathophysiologic mechanisms involved have not been fully clarified, but the most acclaimed hypothesis is a reduction in the enzymatic activity of 5′-monodeiodinase, which is responsible for the peripheral conversion of T4 to T3 (Chopra 1997). This syndrome is viewed as an adaptation in the presence of severe systemic pathology, reducing the production of active thyroid hormone T3 and, consequently, lowering energy consumption. It is not therefore a pathological condition. Several cross-sectional case control studies have shown that about 30% of patients with CHF have low T3 levels and T3 in serum decreases proportionately to the severity of heart disease (Pingitore et al. 2005) (Fig. 2).

However, the reduction in serum T3 concentrations levels could alter the cardiovascular system and enhance the progression of heart failure. In fact, cardiac myocytes lack an appreciable deiodinase activity, depending therefore on the plasma T3. Low T3 syndrome, therefore, can be considered at the beginning as a response aiming at reducing proteins and energy loss. This adaptive response, however, when persistent, becomes a maladaptive response, contributing to an unfavorable prognosis in these patients (Triggiani and Iacoviello 2013). In a study of 281 patients hospitalized for CHF, the presence of low T3 values was associated with an increased risk of mortality. In multivariate analysis, the concentration of T3 was the most important independent predictor of mortality, after correction for the conventional prognostic markers (Kozdag et al. 2005). Pingitore et al. (2008) studied the acute effects of substitution therapy with T3 in CHF patients with low T3 syndrome. Twenty clinically stable patients were randomly assigned to synthetic L-T3 or placebo for 3 days. In the first group an increase in serum fT3 concentration was observed reaching a plateau after 24–48 h. No side effects were observed, but a significant improvement in neuro-hormonal status, due to a significant reduction in plasma noradrenaline, NT-proBNP and serum aldosterone levels. Furthermore, a significant increase in systolic output has been observed. Conversely, no significant variations in neuro-hormonal profile and heart rate were observed in placebo-treated patients. The main problem in administering T3 is the need for intravenous administration and its short half-life which is a pharmacokinetic parameter indicating the time required to reduce the bioavailability of a drug by 50%, i.e. the amount of a drug or protein in plasma or serum. Better results could be achieved with the development of new long-term oral formulations to improve the therapeutic profile of this drug.

4 Hyperthyroidism and Heart Failure

The overt form of hyperthyroidism has a prevalence of 0.5–2% in women, ten times greater than that in men (Levey and Klein 1994). The subclinical form seems to be a more frequent condition (Surks et al. 2004). It has a prevalence of 0.5–6.3% in the general population, with the highest figures in the elderly.

The excess of thyroid hormone has important effects on the cardiovascular system (Klein and Danzi 2007). The relative reduction of peripheral

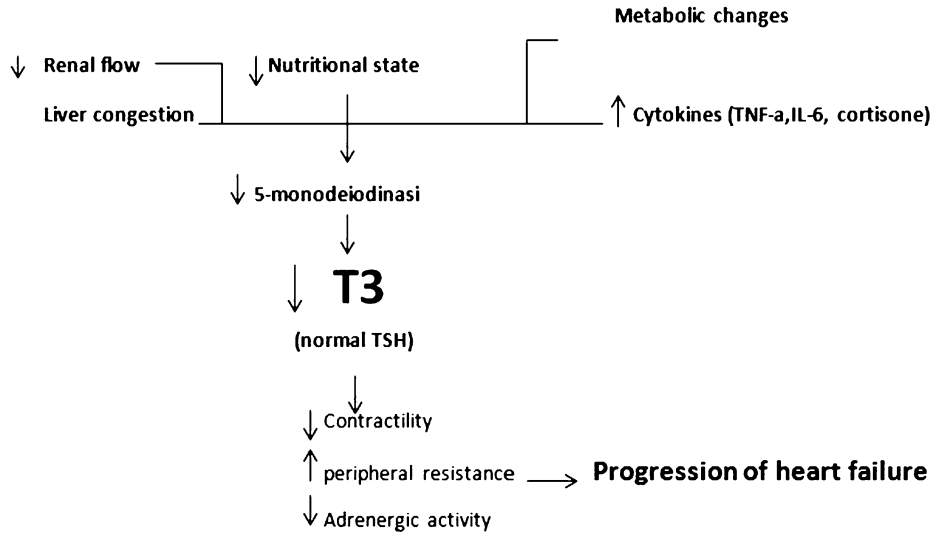

Fig. 2 Low T3 syndrome and progression of heart failure TNF-α: tumor necrosis factor α; IL-6: interleukin-6; T3: triiodothyronine; TSH: thyrotropin
Any condition that reduces the activity of 5′-monodeiodinase leads to a reduction of T4 to T3 conversion, in presence of normal TSH values. This could alter the function of the cardiovascular system (reduced contractility and adrenergic activity, increased peripheral resistance) and enhance the progression of heart failure

resistance and the increase in circulating blood volume and heart rate cause a hyper-dynamic circulatory state (Vanderpump 2005; Biondi et al. 2005). This condition can often lead to symptoms of heart failure. An impairment of left ventricular ejection fraction, however, is rarely observed in hyperthyroidism (Shirani et al. 1993; Umpierrez et al. 1995; Watanabe et al. 1995).

Thyrotoxicosis is characterized by an increase in heart rate, with possible onset of arrhythmias, a selective increase in blood flow to the muscles, skin and heart, vasodilatation with decreased diastolic blood pressure, decreased renal perfusion and subsequent activation of the Renin-angiotensin-aldosterone (RAAS) system, with increased blood volume (Klein and Danzi 2007; Biondi and Cooper 2008). The combination of increased diastolic relaxation and augmented blood volume leads to an increase in preload. Conversely, the increase in myocardial contractility associated with reduced systemic vascular resistance leads to a after-load reduction. This explains the increase in systolic output which, combined with increased heart rate, leads to an increase in cardiac output up to three times the standard (Biondi and Cooper 2008; Watanabe et al. 1995; Kasper et al. 1994; Siu et al. 2007; Kahaly and Dillmann 2005).

The demand for oxygen and energy consumption are both increased at rest with impossibility to increase further and adequately during physical activity (Fazio et al. 2004). These hemodynamic changes are the consequence of thyroid hormone excess that acts both at vascular and cardiac level, increasing the production of Nitric Oxide and directly acting on vascular smooth muscle cells, and increasing the expression of sarcoplasmic reticulum Ca2 + −ATPase and alpha-myosin heavy chain as well as the number of beta1 adrenergic receptor, while reducing the activity and/or expression of phospholamban, sodium/calcium exchanger and beta-myosin heavy chain (Biondi and Cooper 2008; Kasper et al. 1994).

Over time, hyperthyroidism may lead to a myocardial hypertrophy similar to that seen during pregnancy, with an increase in both length and cross section of cardiomyocytes, (Fazio et al.

2004; Biondi et al. 2002) with adverse effects on morphology and cardiac function, increasing the ventricular mass and the left atrial size with impairment of systolic and diastolic function. The most well-known form of heart failure caused by hyperthyroidism is the high output, essentially caused by a high peripheral demand rather than by a pump deficit. However, the onset of CHF may also be related to other factors (Biondi and Cooper 2008). Coronary vasodilatation, already present in resting conditions to increase blood flow to hyperkinetic cardiac muscle, results in reduced capacity for further dilation during stress, resulting in myocardial ischemia. In the presence of hyperthyroidism, in patients already affected by coronary artery disease, the onset of myocardial ischemia is further favored by the increased oxygen consumption by myocardium and tachycardia (Klein and Danzi 2007). Heart failure may also be favored by the variations in the duration of the action potential and refractory period and the consequent onset of atrial fibrillation (Frost et al. 2004). Regarding this point, an experimental study, conducted on hypothyroid rats because they were thyroidectomized and on hyperthyroid rats because they were treated with Levothyroxine, demonstrated that the duration of the repolarization phase of the action potential was highly prolonged in the atria from the first group and shortened in the atria of the second group. Thyroid hormone may abbreviate the duration of the action potential by accelerating sodium extrusion as a consequence of increased metabolic turnover. These changes could account for a reduced probability of arrhythmias such as atrial fibrillation and atrial flutter in hypothyroidism, and the opposite in hyperthyroidism (Freedberg et al. 1970).

Signs and symptoms generally attributed to heart failure in hyperthyroid subjects, such as exercise intolerance, fatigue, peripheral edema are caused by hyper-dynamic circulatory state due to the inability of cardiac output to cope with the exercise. In some cases, symptoms such as resting dyspnea, liver congestion, and pleural effusion may also appear. Generally, these tend to improve with the restoration of euthyroidism and the use of diuretics and beta-blockers (Cruz et al. 1990). This condition, however, if untreated, can worsen over time and lead to a "pathological" type of hypertrophy, ventricular dilatation and a "true" chronic heart failure. Low-cardiac output heart failure is rare in hyperthyroidism. It is described in about 6% of patients, especially elderly and with a long history of untreated or not well-controlled hyperthyroidism, often with pre-existing cardiomyopathy, atrial fibrillation or tachycardia (Umpierrez et al. 1995). In these cases myocardial contractility is reduced, while systemic vascular resistance and circulating blood volume are both increased (Hak et al. 2000). Some longitudinal studies and the analysis of the pooled data from six cohort studies showed, that HF events are increased in overt but also in patients affected by subclinical hyperthyroidism (Gencer et al. 2012).

Figure 3 summarizes the pathophysiological mechanisms through which hyperthyroidism can enhance the progression of heart failure.

4.1 Hyperthyroidism and Heart Failure: Therapeutic Aspects

In hyperthyroid patients with CHF the aim of the therapy is to rapidly restore the euthyroidism using thionamides, surgery and/or radioiodine.

In Italy, Metimazole is the preferred drug for the treatment of hyperthyroidism. It induces blockade of thyroid hormone synthesis by inhibiting the oxidation of iodide to organic iodine. Secondly, it determines the inhibition of the production of TSH antibodies. In fact, Metimazole accumulates in the thyroid where it inhibits the activity of thyroid lymphocytes, the main source of antibody synthesis against thyroid hormone receptors. The initial dose is ranged between 15 and 60 mg per day (divided into three doses); the maintenance dose is 5–15 mg per day. Metimazole cannot be taken for more than two consecutive years, then it should be suspended and 1 year should be expected for a new intake. Carbimazole is the drug for the treatment of hyperthyroidism in British territory. It should be taken for 1–2 years, given the high risk of post-suspension hyperthyroidism. It may

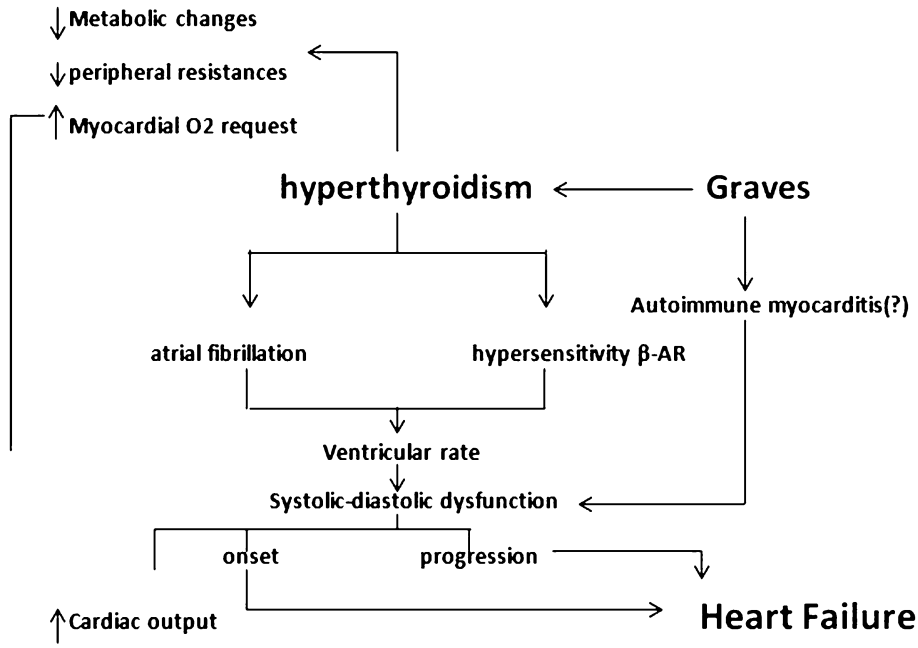

Fig. 3 Hyperthyroidism and heart failure. Pathophysiological mechanisms
O_2: oxygen, β-AR: Beta adrenergic receptor
Hyperthyroidism acts both at vascular and cardiac levels, resulting in a reduction in peripheral resistances and metabolic changes and an increase in myocardial O_2 demand by an rise in heart rate and possible onset of arrhythmias such as atrial fibrillation. This causes, moreover, an increase in ventricular rate and, in time, a systolic-diastolic dysfunction. This leads to hyper-dynamic circulatory state that can favor the onset or progression of the heart failure

cause itching and skin rashes. These side effects can be kept under control by the administration of antihistamines. Propylthiouracil should be used if the patient is allergic to carbimazole. It belongs to the class of thionamides and has its therapeutic action as an immunosuppressor. Potassium perchlorate is also used to treat hyperthyroidism. It represents a second-choice drug after Metimazole and Propylthiouracil. It is a ion sterically similar to iodine. It is able to compete for binding to specific channels, capable of transporting this ion, in the form of iodides, from the vascular lumen to the thyrocytes. The reduced absorption of iodides prevents thyroide synthesis of thyroid hormones re-balancing the blood profile of these hormones. It is available in the form of 200 mg tablets to take 3–4 times daily (600–800 mg) in three doses. Iodine 131 is the drug of radiometabolic therapy, widely used to treat hyperthyroidism in surgically inoperable patients. The medication is usually taken by mouth. The therapeutic effects of the drug are only observed after 4–-5 weeks of treatment. In CHF patients, pharmacological therapy should be preferred. Radiometabolic therapy is considered a second choice because of a slow control of hyperthyroidism and the possibility of re-emergence of illness. However, it is preferable to surgery in the cardiopath.

Beta blockers can improve cardiac function reducing heart rate (Bahn et al. 2011). One of the most used drugs for this purpose is Propanolol, at an indicative dose of 120–240 mg/day. Other least known drugs of the category are Atenolol and Metoprolol.

Surgical therapy is used in patients where hyperthyroidism recurs after medical therapy.

Longitudinal studies are required to asses wether the treatment is effective also in the subclinical form of hyperthyroidism.

5 Amiodarone-Induced Thyroid Diseases and CHF

Amiodarone is a class III antiarrhythmic drug. It is a benzofuranic derivative containing two iodine atoms. It contains 37.2 mg iodine per 100 mg of active substance. With standard daily dosage (200 mg/day), therefore, a significant amount of iodine is administered, with an increase of more than 40 times of its plasma and urinary levels. The drug is stored in the fat tissue; therefore, iodine levels can remain elevated for more than 6 months from its suspension (Vassallo and Trohman 2007).

The incidence of amiodarone-induced hyperthyroidism varies from 1 to 23% and may occur at any time of treatment, even months after its suspension. Two main mechanisms are involved: metabolic and inflammatory-toxic, responsible respectively for type I and type II Amiodarone-induced hyperthyroidism (Martino et al. 2001; Bogazzi et al. 2003).

Type I occurs in subjects with pre-existing thyroid pathologies and is caused by the increased synthesis of thyroid hormones induced by iodine in subjects with nodular goiters or latent Graves' disease; it is linked to an alteration of the mechanisms leading to the blockade of iodine uptake and hormone synthesis when the intrathyroidal concentration of inorganic iodine exceeds a certain threshold.

It is characterized by low TSH concentration, high levels of fT4 or fT3 and low radioiodine uptake. The eco-color Doppler of the thyroid shows a hypervascularization, as in Graves's disease.

Type II occurs in a normal gland. It is probably secondary to a destructive thyroid process caused by iodine or the same amiodarone. In the latter case, amiodarone can induce antibodies against the thyrotropin receptor causing hyperthyroidism. The cytotoxic mechanism leads to an excessive release of preformed T3 and T4 by the follicles, resulting in a destructive process. The main mechanism responsible for this seems to be the mono-N-desethyl amidarone (MDEA), an active metabolite of the amiodarone. The eco-color Doppler of the thyroid shows a hypovascularization and there is an increase of serum interleukin-6 level.

At the onset of hyperthyroidism, amiodarone treatment should be stopped (Loh 2000). It should, however, be considered that the half-life of the drug, about 50 days, implies that it continues to affect thyroid function even after its effective withdrawal. In addition, discontinuation of therapy may be associated with adverse effects, such as potentially fatal arrhythmias.

A different therapeutic approach was proposed for the two forms of thyrotoxicosis (Martino et al. 2001). For type I, treatment should be a combination of a thionamide (metimazole or propylthiouracil) to inhibit hormone biosynthesis, and potassium perchlorate to block the thyroid transporter of iodine. As the usual therapeutic dosage becomes ineffective for high iodine intracellular concentration, a higher thionamide dose than normal (metimazole 40–60 mg/day; propylthiouracil 600–800 mg/day) should be used. Potassium perchlorate should be used for a period not exceeding 1 month (30–40 days maximum). The treatment should not be prolonged because of the risk of severe side effects such as agranulocytosis, aplastic anemia and nephrotic syndrome, but it should not be reduced to a shorter period because this seems to favor the onset of recurrences of thyrotoxicosis. For Type II, considering the presence of a destructive thyroiditis, the use of corticosteroids alone or in combination with thionamides has been considered an effective therapy (Loh 2000). The dosage and therapeutic pattern changes depending on the type of steroid used (15–80 mg/day of prednisone or 3–6 mg/day of dexamethasone). The most common scheme is the use of prednisone starting at 80 mg/day, reducing the dose every 2 weeks for about 3 months. Premature suspension of cortisone therapy may result in recurrence of thyrotoxicosis; in these patients, steroid treatment must be restarted (Martino et al. 2001).

It is also necessary to observe in Type II for a transition to hypothyroidism after amiodarone withdrawal. In this case it is desirable to resume therapy with hormone replacement therapy for the restoration of euthyroidism. In mixed forms it would be helpful to use an initial combination of propylthiouracil or metimazole and potassium perchlorate, at the dosages already mentioned, with the addition of steroids for 2 weeks in the absence of improvement (Triggiani et al. 2012). Surgical thyroidectomy should be considered in those cases refractory to medical treatment.

In a study by our group, (Kannan et al. 1984) a high prevalence and incidence of hypothyroidism has been demonstrated among CHF patients and the key role played by amiodarone therapy in its genesis has been clearly shown.

The mechanisms through which amiodarone can induce hypothyroidism are at least three: (1) modification of the natural course of a pre-existing autoimmune thyroiditis; (2) the lack of adaptation to the overload of iodine induced by amiodarone and (3) the direct cytotoxic damage (Forfar et al. 1982).

Besides the possible development of hypo and hyperthyroidism, the most important metabolic effect of the amiodarone is definitely the inhibition of the 5′-monodeiodase type I enzyme, which results in a moderate and persistent increase in T4 and fT4 and a mild but persistent reduction of the total T3 and fT3, sometimes associated with a slight transient increase in TSH (Butler and Kalogeropoulos 2008; Baker et al. 1994). Such changes in the hormonal pattern begin to manifest after about 3–4 months of treatment. The action is exerted through the binding of its main metabolite to thyroid hormone receptors alpha 1(Bogazzi et al. 2001) and beta 1 (Franklyn et al. 1989), inhibiting T3 binding and causing a condition of "local hypothyroidism" which would explain its therapeutic efficacy as antiarrhythmic and antianginal, but also its adverse effects on cardiac function.

Amiodarone can directly induce the so-called "fetal gene program recapitulation"(Franklyn et al. 1989), further compromising myocyte function. These additional effects, not mediated by thyroid hormone deficiency, may explain why restoration of euthyroidism by substitution therapy can not completely counter the adverse effects of amiodarone therapy in the progression of heart failure.

6 Conclusions

Thyroid hormones are involved in cardiovascular balance. They affect the heart rate, systemic vascular resistances, arterial pressure and cardiac contractility. Dysthyroidisms, therefore, have a negative impact on the symptoms on the prognosis of patients with heart failure.

In particular, hypothyroidism, which can be *subclinical* (TSH above the normal range with thyroid hormones free fractions still normal) or *overt* (reduction of thyroid hormones), leads to progression of HF trough the reduction of myocardial contractility and the increased peripheral resistances and serum cholesterol, causing possible ischemic disease. On the other hand, the excess of thyroid hormones (hyperthyroidism), through the relative reduction of peripheral resistance, the increase in circulating blood volume and the increase in myocardial O_2 demand, by a rise in heart rate and possible onset of arrhythmias, leads to hyperdynamic circulatory state that can favor the onset or progression of the heart failure. Moreover, about 30% of patients with CHF have low T3 level, in the presence of normal TSH and normal or reduced T4 levels, and T3 in serum decreases proportionately to the severity of heart disease, causing the progression of heart failure. This condition is known as "low T3 syndrome" and is caused by a reduction in the activity of 5′-monodeiodinase, the enzyme which peripherally converts T4 to T3. This is initially viewed as an adaptation to reduce energy consumption in the presence of severe systemic pathologies, but when persistent, it becomes "maladaptive".

Finally, dysthyroism may also be iatrogenic. One of the most commonly used antiarrhythmic drug in patients with CHF is Amiodarone, which may induce hyperthyroidism trough two main mechanisms: metabolic in type I and inflammatory-toxic in type II.

Whatever is the underlying mechanism, an early diagnosis and treatment of thyroid disorders is important to better treat CHF patients and to prevent worsening of the heart failure: Levothyroxine in patients with overt hypothyroidism; Thionamides, Potassium perchlorate, surgery and/or radioiodine in hyperthyroidism and in amiodarone-induced hyperthyroidism; substitution therapy with T3 in CHF patients with low T3 syndrome, while considering the problems associated with the existence of an exclusive intravenous formulation; corticosteroids in type II amiodarone-induced hyperthyroidism.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 255–269
https://doi.org/10.1007/5584_2017_136
© Springer International Publishing AG 2017
Published online: 27 December 2017

Management of Bradyarrhythmias in Heart Failure: A Tailored Approach

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Abstract

Patients with heart failure (HF) may develop a range of bradyarrhythmias including sinus node dysfunction, various degrees of atrioventricular block, and ventricular conduction delay. Device implantation has been recommended in these patients, but the specific etiology should be sought as it may influence the choice of the type of device required (pacemaker vs. implantable cardiac defibrillator). Also, pacing mode must be carefully set in patients with heart failure (HF) and left ventricular systolic dysfunction.

In this chapter, we summarize the knowledge required for a tailored approach to bradyarrhythmias in patients with heart failure.

Keywords

Heart failure reduced ejection fraction · Heart failure preserved ejection fraction · Bradyarrhytmias · Implantable cardioverted defibrillator · Pacemaker · Cardiomyopathies

1 Introduction

Rhythm disturbances in patients with heart failure (HF) are not confined to tachyarrhythmias (Stevenson et al. 2002). While the ever-increasing percentage of HF patients implanted with devices capable of pacing interfere quantification of bradyarrhythmias at the current time, earlier registries illustrated that bradyarrhythmias with electromechanical dissociation are the mechanism of sudden cardiac

The original version of this chapter has been revised. An erratum to this chapter can be found at https://doi.org/10.1007/5584_2018_198

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death in a significant number of selected HF patients (Luu et al. 1989).

Also in the Euro Heart Failure survey, 6% of patients with a HF-related admission also had bradycardia, and a bradyarrhythmia complicated their clinical course in about one in six patients (Cleland et al. 2000). HF is an umbrella term comprising a wide range of different patients, those with preserved (>50%) left ventricular ejection fraction (LVEF), those with reduced LVEF (LVEF <40%) and those with mid-range ejection fraction (LVEF >40 <50%) (Ponikowski et al. 2016).

Differentiation of patients with HF based on LVEF is important due to different demographics, etiology, co-morbidities and indication/response to therapies; the last is particularly true for the bradyarrhythmias in which the management is closely dependent on underlying etiologies. In this chapter, we briefly discuss the etiology and the pathophysiology of the conduction system disorders and then focus on the specific knowledge and skills that cardiologists must achieve for a "*personalized*" management of bradyarrhythmias in patients with Heart Failure with reduced EF (HFrEF). Heart Failure with mid-range Ejection Fraction (HFmrEF) and Heart Failure with preserved Ejection Fraction (HFpEF).

2 Etiology and Pathophysiology of Bradyarrhythmias

Bradyarrhythmias are most commonly caused by the failure of impulse formation (sinus node dysfunction) or by the failure of impulse conduction over the atrioventricular (AV) node/His-Purkinje system (Rubart and Zipes 2014). Bradyarrhythmias may be caused by a disease that directly alters the structural and functional integrity of the sinus node, atria, AV node and His-Purkinje system or by extrinsic factors (e.g., autonomic disturbances, drugs) without causing structural abnormalities (Table 1) (Bayés de Luna 2011).

2.1 Sinus Node Dysfunction

Sinus node dysfunction (SND) can result from various conditions, which cause depression of the automaticity and electrical conduction from the sinus node, perinodal and atrial tissue (Sneddon and Camm 1992). These conditions may be intrinsic (diseases that directly alter the sinus node or sinoatrial structure) or extrinsic (most often cardiovascular drugs or systemic illness). In most of cases, SND is caused by both structural and molecular remodeling of sinus node caused by aging (idiopathic SND) (Dobrzynski

Table 1 The potential etiologies of bradyarrhytmias include both intrinsic and extrinsic causes, however in half of more of the cases, no specific causes are identified, and the block is felt to be related to idiopathic progressive cardiac conduction disease with myocardial fibrosis and/or sclerosis that affects the conduction system

Intrinsic	Extrinsic
Idiopathic degenerative disorder	Antiarrhythmic agents
	Class IA quinidine, procainamide
	Class IC propafenone, flecainide
	Class II blockers
	Class III sotalol, amiodarone, dronedarone
	Class IV diltiazem, verapamil
Ischemic heart disease	Increased vagal tone
Hypertensive heart disease	Carotid sinus hypersensitivity
Infiltrative cardiomyopathy	Hypothyroidism
Trauma	Intracranial hypertension
Inflammation	Hypothermia
Collagen vascular disease	Hyperkalemia
Infection	Hypoxia
Neuromuscular disorder	Sleep apnea

et al. 2007). Also, any process that results in damage of the sinoatrial node (e.g., collagen vascular diseases, ischemia, infiltrative diseases or surgical trauma) can be a causative/contributing factor (Bharati et al. 2012). At least 50% of patients with sick sinus syndrome develop alternating bradycardia and tachycardia, also known as tachy-brady syndrome (Mangrum and DiMarco 2000; Brignole 2002).

In patients with HF, the most common etiologies of SND are brady-tachy syndrome and ischemia; the remaining are called idiopathic forms. In patients with tachy–brady syndrome, atrial fibrillation or flutter with rapid ventricular response are particularly frequent in older patients with advanced sinoatrial nodal disease in whom sinoatrial node fibrosis may favor re-entrant beats or tachycardia (Choudhury et al. 2015). However recently it has been demonstrated that atrial arrhythmias can be the cause of SND. Indeed, in patients undergoing electrical cardioversion for persistent atrial fibrillation, an increase of sinus node recovery time and a reduction in both maximal and intrinsic heart rate it has been documented (Manios et al. 2001). Acute or chronic ischemia, due to disease of the right coronary artery or sinus node artery, are often quoted as a cause of SND. The pathogenesis of this is still unknown, however some evidence showed that stenosis of sinus node artery leads to longer sinus node recovery time and prolonged sinoatrial conduction time (Morris and Kalman 2014). Finally, idiopathic SND is not only caused by fibrosis of the sinoatrial node but also related to "electrical remodeling" of the atria and the sinoatrial node (i.e., reduced expression of ion channels and some gap junction) (Tellez et al. 2011).

2.2 Atrioventricular Node Dysfunction

Acquired atrioventricular (AV) block is caused by several extrinsic and intrinsic conditions already discussed with sinus node dysfunction. First degree AV block is commonly associated with idiopathic progressive degeneration of the cardiac conduction system, but it can also be due to drug effect (e.g., beta-blockers) (Waller et al. 1993; McVay 1984).

Type I 2nd-degree AV block almost always results from impaired conduction in the AV node (rather than more distally in the conduction system). It is usually benign and may be seen in children, trained athletes, and people with high vagal tone, particularly during sleep. It may also occur during an acute myocardial infarction because of increased vagal tone or ischemia of the AV node, but the block is usually temporary.

Finally type II 2nd-degree or 3rd-degree AV block are often associated with ischemia or myocardial disease (Barold and Hayes 2001).

In patients with HFrEF ischemia accounts for about 40% of cases of high-grade AV block (Zoob and Smith 1963). Conduction can be disturbed with either chronic ischemia or during an acute myocardial infarction (Mullins and Atkins 1976). In case of ischemia of the right coronary artery, the AV nodal artery may be involved with subsequent necrotic changes in the AV node while the His-Purkinje system is usually spared.

In case of ischemia of left coronary artery and circumflex branch, necrotic changes are seen most often in the distal His bundle and in the bundle branches.

Less frequent causes are represented by neuromuscular disorders (muscular dystrophy, Kearns-Sayre syndrome) (Limongelli et al. 2013), systemic disease (cardiac sarcoidosis) (Hamzeh et al. 2015) and Lyme myocarditis (Lo et al. 2003).

In patients with HFpEF apparently, idiopathic progressive cardiac conduction defects are the most common cause of AV block (Schwartzmann 2014) while hypertensive heart disease (Masarone et al. 2017), diabetes and infiltrative cardiomyopathies (amyloidoses, Fabry disease) represent less frequent causes (Falk 2005; O'Mahony and Elliot 2010).

3 Diagnosis of Bradyarrhythmias

Patients presenting with bradyarrhythmias complain of dizziness, vertigo and syncope (Vogler et al. 2012). To establish the diagnosis of SND, it

is crucial to find a causal relationship between the patients' symptoms and the electrocardiogram (ECG) abnormalities. Apart from a thorough medical history, a 12-lead surface ECG, Holter ECG recording, and exercise testing are usually adequate.

Whenever surface ECG and repetitive Holter recordings are incapable of documenting the cause of a patient 's symptoms, an external event recorder or an implantable loop recorder should be considered (Solbiati et al. 2016).

Diagnosis of AV block can be achieved in most of these cases, non-invasively, in fact, the surface ECG (if the recording is sufficiently long) usually provides the information to characterize the type of the AV block (Haines et al. 2014). In patients with intermittent AV block, Holter ECG and exercise testing are important to establish a correlation between symptoms and cardiac rhythm.

With rare exceptions, such as persistent 2:1 AV block or failure to establish a symptom-rhythm correlation, the invasive electrophysiologic study does not make a significant contribution to the management of patients with bradyarrhythmias (Adan and Crown 2003).

The diagnosis of bradyarrhythmias represents a starting point and not the end of the diagnostic process. In fact, it is crucial to recognize the presence of red flags (Tables 2 and 3) (Rapezzi et al. 2013) suggesting the presence of a cardiomyopathy whose recognition is essential for proper treatment.

4 Therapy of Bradyarrhythmias

Treatment for bradyarrhythmias is divided into acute and chronic phases (Link et al. 2015). Acute therapy depends on the presence of bradycardia-related symptoms and is aimed at the prevention of acute HF and asystole. Intravenous drug therapy (atropine, isoprenaline, or epinephrine) and transcutaneous or transvenous temporary pacing can be used during this phase (Wung 2016). The decision to proceed from temporary to permanent pacing (chronic therapy) and which device must be used (pacemaker vs. implantable cardioverter defibrillator) is determined by the type of HF and by the etiology of the bradyarrhythmias (i.e., tailored treatment).

5 Tailored Treatment of Bradyarrhythmias in Patients with HFrEF/HFmrEF

Patients with HFrEF/HFmrEF can manifest SND, various degrees of AV block and interventricular conduction delay. In older adults, the main cause of bradyarrhythmias is ischemic heart disease. The onset of AV conduction defects in middle age or earlier should prompt an evaluation for non-ischemic etiology (e.g., inflammatory or genetic cardiomyopathy) (Barra et al. 2012).

According to the tailored approach, we proposed a different management based on specific etiology (Fig. 1).

5.1 Ischemic HFrEF/HFmrEF

Bradyarrhythmias can be caused by both acute or chronic ischemia.

In acute coronary syndromes with right coronary artery as culprit's vessel, high-grade AV block has been described in up to 17% of cases (Tans et al. 1980). Most of these cases are transient and resolve either spontaneously or with revascularization, about 9% will ultimately require a permanent pacemaker (Nicod et al. 1988).

Management of patients with HFrEF/HFmrEF of ischemic etiology must be conducted according to 2012 ACCF/AHA/HRS Guidelines for Device-Based Therapy (Tracy et al. 2012) that indicates permanent pacing in:

- Permanent 3rd-degree AV block complicating acute coronary syndrome in whom the block does not resolve with revascularization,
- Transient advanced 2nd or 3rd-degree infranodal AV block and associated bundle branch block.

In both cases, careful evaluation of the device must be considered, in fact, according to the

Table 2 In patients with cardiomyopathies and bradyarrhythmias the red flags must be sought to reach an etiologic diagnosis

Family and personal history
First degree relative with cardiomyopathies
Unexplained sudden death in the first-degree relative
Unexplained pacemaker implantation in the first-degree relative
Age of onset of bradyarrhythmias <55 y/o
Symptom and clinical examination
Learning difficult/mental retardation
Sensorineural deafness
Visual impairment
Muscle weakness
Paraesthesiae/sensory abnormalities/neuropathic pain
Bilateral carpal tunnel
Angiokeratomata
Laboratory finding
↑ Serum creatine phosphokinase
↑ Transaminase
Leukocytopenia
Proteinuria with/without reduction of glomerular filtration rate
Myoglobinuria
Lactic acidosis
Electrocardiography
Low QRS voltage (or normal voltages despite LVH)
Short PR interval
Echocardiography
Concentric LVH with MWT ≥ 15 mm
Concentric LVH with MWT ≥13 mm in patients with family history for HCM
Symmetric LVH
Increased interatrial septum thickness
Increased atrioventricular valve thickness
Increased right ventricle free wall thickness
Ground glasses appearance of ventricular myocardium
Mild/moderate pericardial effusion
LV non-compaction
Postero-lateral akinesia/dyskinesia
Cardiac magnetic resonance imaging
Postero-lateral LGE + concentric and symmetric LVH
Diffuse subendocardial LGE
Intense myocardial "avidity" for gadolinium
Patchy mid-wall LGE

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (Priori et al. 2015) and 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (Ponikowski et al. 2016):

- In patients with HFmrEF, a pacemaker (PM) is reccomended.
- In patients with HFrEF with severe reduction of LVEF (<35%) and no bundle branch block an implantable cardioverter defibrillator (ICD) is reccomended after 40 days of myocardial infarction,
- In patients with HFrEF with severe reduction of LVEF (<35%) despite 3 months of optimal medical therapy and bundle branch block

Table 3 In patients with cardiomyopathy, the identification of the clinical-echocardiographic phenotype (hypertrophic, dilatative, restrictive) is only the first diagnostic step. The next step is to search red flags to reach an etiologic diagnosis of cardiomiopathies

Laminopathies
Autosomal dominant inheritance pattern
Muscle weakness
Dilated cardiomyopathy
AV block
↑ Serum creatine phosphokinase
Sarcoidosis
AV block
Postero-lateral pseudo infarction pattern on ECG
↑ Serum angiotensin converting enzyme level
Hypokinetic non-dilated cardiomyopathy
LGE at the anterobasal septum or papillary muscles
Muscular dystrophies
Autosomal dominant inheritance pattern (rarely X linked)
Muscle weakness
AV block
Postero-lateral pseudo infarction pattern on ECG
↑ Serum creatine phosphokinase
Dilated cardiomyopathy with postero-lateral akinesia/dyskinesia
LGE at the anterobasal septum or papillary muscles
Anderson-Fabry disease
X liked inheritance pattern
Visual impairment (cataracts, corneal opacities)
Angiokeratomata
Short P-R /preexcitation
AV block
Proteinuria with/without reduction of glomerular filtration rate
Concentric LVH
RV free wall thickness
Posterolateral LGE
Amyloidosis
Autosomal dominant inheritance pattern (familial TTR amyloidosis)
Bilateral carpal tunnel syndrome (TTR amyloidosis)
AV block
Low QRS voltage (or normal voltages despite LVH)
Proteinuria with/without reduction of glomerular filtration rate
Concentric LVH
Global hypokinesia (late stage)
Increased RV free wall thickness
Mild pericardial effusion
Diffuse subendocardial LGE
Mitochondrial disease
Matrilinear inheritance pattern
Sensorineural deafness
Learning difficult
Muscle weakness
Short P-R /preexcitation
AV block
↑ Serum creatine phosphokinase
↑ Transaminase
Leukocytopenia (TAZ gene/Barth syndrome)
Concentric LVH
Global hypokinesia (late stage)

(QRS > 150 msec) a cardiac resynchronization therapy device with a defibrillator backup (CRT-D) is reccomended,

- In patients with HFrEF with severe reduction of LVEF (<35%) despite 3 months of optimal medical therapy and left bundle branch block (QRS > 130 msec <150 msec) a CRT-D is reccomended,
- In patients with HFrEF with severe reduction of LVEF (<35%) and in patients with HFmrEF and expected high percentage of ventricular pacing CRT-D may be considered

In patients with chronic ischemic heart disease the indications for pacing are the same as for the general population:

- PM implantation is indicated in symptomatic bradycardia,
- PM implantation is indicated in patients with 3rd or 2nd-degree type 2 AV block irrespective of symptoms,
- PM implantation should be considered in patients with 2nd-degree type 1 AV block which causes symptoms or is found to be located at intra- or infra-His levels at the electrophysiological study,
- When PM is planned an ICD is recommended in patients with HFrEF and severe reduction of LVEF (EF < 35%).

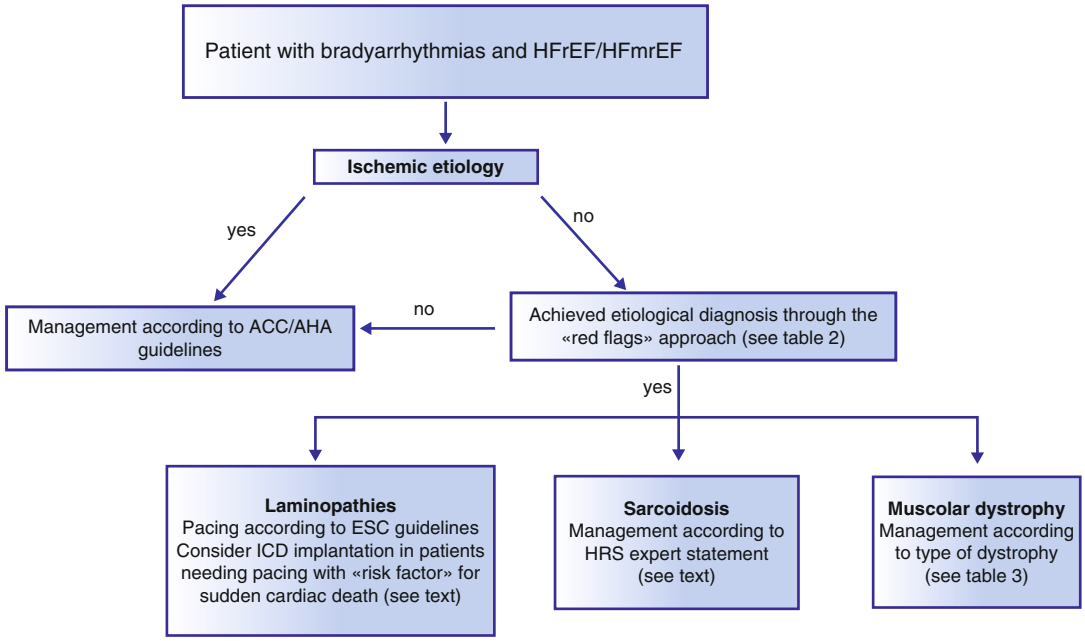

Fig. 1 Algorithm for clinical management of bradyarrhythmias in patients with heart failure reduced ejection fraction/mild reduced ejection fraction. *HFrEF* Heart Failure Reduced Ejection Fraction, *ACC/AHA* American College of Cardiology/American Heart Association, *ESC* European Society of Cardiology, *ICD* Implantable Cardioverter Defibrillator, *HRS* Heart Rythm Society

5.2 Non-ischemic HFrEF/HFmrEF

Non-ischemic dilated cardiomyopathy is an umbrella term comprising a variety of different etiologies with a different approach to bradyarrhythmias. In patients with non-ischemic HFrEF/HFmrEF management of bradyarrhythmias is the same as for patients with ischemic etiology; however, recently the indication to ICD implantation has been questioned. Generally, in these patients according to results of large randomized clinical trials including Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (Bardy et al. 2005) and Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) (Moss et al. 2002) ICD implantation carries a class I recommendation for patients with symptomatic HFrEF and LVEF $\leq$35%.

The benefit of ICD implantation is considered to be similar in patients with non-ischemic vs. ischemic HFrEF even though the majority of patients in SCD-HeFT and all of the patients in MADIT-II had HFrEF of ischemic origin. However, the recent Defibrillator Implantation in Patients with Non ischemic Systolic Heart Failure (DANISH) showed at 68 months of follow-up that all-cause of mortality was not significantly lower in the ICD group compared to the control group (Køber et al. 2016). Nevertheless, a relatively high rate of non cardiovascular mortality in the study (31%), may have masked out any potential benefit from ICD therapy, as ICD placement do not have effects on non cardiovascular death. Furthermore, an age-by-therapy analysis was observed whereby patients $<$59 years old derived a mortality benefit from ICD therapy whereas older patients did not. Likewise, patients with more severe HFrEF as determined by NT-proBNP level and functional class also appeared to benefit from ICD. Ultimately, the DANISH trial suggests that routine ICD therapy for all patients with non-ischemic HFrEF with LVEF $\leq$35% may not result in the strong mortality benefit previously extrapolated from data in patients with ischemic cardiomyopathy. For this reason, the decision to place an ICD in these patients should likely be considered on an

individual basis considering the severity of underlying disease and concomitant arrhythmia risk versus age/life expectancy and comorbidities. For some etiology (discussed below) specific considerations are required.

5.3 Laminopathies

Lamin A/C gene mutations can be associated with myocardial diseases, usually characterized by dilated cardiomyopathy and arrhythmic disorders (cardiolaminopathies) (Cattin et al. 2013). Patients with cardiolaminopathies may present a wide range of arrhythmic disturbances, which include either bradyarrhythmias (AV blocks, sinus node dysfunction, atrial standstill) (Sylvius and Tesson 2006) or tachyarrhythmias (atrial fibrillation, ventricular tachycardia, and ventricular fibrillation) (Finsterer et al. 2016), in varying combinations, and with frequent association with HFrEF.

In cardiolaminopathies the incidence of sudden cardiac death in patients with pacemakers is very high (Rankin and Ellard 2006) for this reason we recommend ICD implantation in pacemaker candidates with "specific" risk factors for sudden cardiac death (male sex, LVEF $< 45\%$, non-sustained ventricular tachycardia, non-missense mutation) (Van Rijsingen et al. 2012).

5.4 Myocarditis

Myocarditis is a common cause of transient cardiac rhythm disturbances; supraventricular and ventricular arrhythmias are the main findings. However, symptomatic bradycardia/AV blocks can occur in about 30% of cases, particularly in children and in some etiologies (Chagas disease, Lyme disease, diphtheria) (O'Rourke 1972; Sinagra et al. 2016). In myocarditis associated AV block recovery occurs in most of the cases, and rarely permanent PM implantation is required (Batra et al. 2003). For this reason, in patients with "de novo" HFrEF/HFmrEF and bradyarrhythmias, the diagnosis of myocarditis should be excluded (also through cardiac magnetic resonance and cardiac biopsy) to avoid improper PM/ICD implants.

5.5 Sarcoidosis

Sarcoidosis is a systemic inflammatory disease of unknown cause, characterized by the formation of non-caseating granulomas and resultant scarring of affected organs (Newman et al. 1997). Myocardial involvement occurs in 20–30% of cases, though only roughly one-quarter of these patients are diagnosed ante mortem (Kim et al. 2009). AV block is a common presentation of clinically manifest cardiac sarcoidosis because of the involvement of the basal septum by scar tissue, granulomas, or the involvement of the nodal artery (Kandolin et al. 2011). However, although conduction abnormalities are the most common cardiac presentation, the risk of sudden death from ventricular arrhythmias is high in the presence of significant cardiac involvement (Kumar et al. 2015). Recent Heart Rhythm Society expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis recommend (Birnie et al. 2014):

- PM implantation can be useful in patients with cardiac sarcoidosis with an indication for pacing even if the AV block reverses transiently.
- Immunosuppression can be useful in patients with cardiac sarcoidosis presenting with type II 2nd-degree and 3rd-degree AV block.
- ICD implantation can be useful in patients with cardiac sarcoidosis and an indication for PM implantation.

5.6 Muscular Dystrophies

Muscular dystrophies are a group of inherited diseases affecting skeletal muscle that also affect cardiac muscle (Hermans et al. 2010). Cardiac involvement is characterized from a

pathophysiologic point of view by a degenerative process with fibrosis and fatty replacement of the myocardium and of conduction system (Yilmaz and Secthem 2012) and from a clinical point of view by HF, conduction disease, atrial and ventricular arrhythmias, and sudden cardiac death (Groh 2012).

Since the incidence of sudden cardiac death is high in this group of disorders, and because conduction system disease tends to be unpredictable, the development of 2nd or 3rd-degree AV block, even in the absence of symptoms, is considered an absolute indication for permanent pacing implantation (Table 4) (Finsterer et al. 2012).

The benefit of an ICD implantation compared with pacemaker implantation in patients with muscular dystrophies remain under evaluation.

6 Mode of Pacing in Patients with HFrEF

Careful individual decision-making is required in selecting the optimum pacing mode in patients with HF and reduced LVEF (Fig. 2). In patients with SND, but intact atrioventricular conduction atrial pacing alone might be considered; on the other hand, patients with AV block (present or expected) will require ventricular pacing. Dual chamber pacing with AV delay optimization has beneficial functional and clinical effects when applied to the appropriate patients, namely, symptomatic patients in sinus rhythm with a long PR interval, functional mitral regurgitation and a ventricular filling time of less than 200 msec at rest (Auricchio and Salo 1997).

Pacing the right ventricle can be deleterious, resulting in a relative delay in left ventricular activation and may induce ventricular asynchrony, possibly due to a site of activation being distant from the left ventricle (Sweeney and Prinzen 2006). For similar reasons pacing the right side of the heart in patients with dilated cardiomyopathy and grossly uncoordinated ventricular contraction due to left sided conduction abnormalities, can do little to improve coordination (Dresing and Natale 2001). In the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial it was documented that the dual chamber (right atrial and right ventricular) pacing was detrimental in patients with HFrEF/HFmrEF, with increased HF admissions and mortality compared to sinus rhythm (Wilkoff et al. 2002). Also, support for the deleterious effect of right ventricular pacing was provided by a posthoc analysis of data from "The mode selection" (MOST) trial in sinus node dysfunction (Sweeney et al. 2003). Of the 2010 patients enrolled in the MOST trial, this analysis was restricted to the 1339 participants who had a baseline QRS duration <120 msec. Among these patients, 707 were assigned to dual-chamber rate-modulated and 632 to the single-chamber sensor-based, rate-modulating pacemakers pacing. Regardless of pacing mode, patients with a higher cumulative percentage of ventricular paced beats had significantly higher rates of subsequent hospitalization and atrial fibrillation.

For this reason, in selected patients with HFrEF/HFmrEF with PM indication and expected high percentage of ventricular pacing bi-ventricular pacing appears the best choice.

7 Tailored Treatment of Bradyarrhythmias in Patients with HFpEF

SND and AV block are common in elderly patients with HFpEF, because idiopathic fibrosis of sinus node is age related and for the presence of comorbidities such as hypertension diabetes and chronic ischemia that favors the sinus node fibrosis (Josephson 2008). The onset of bradyarrhythmias in the middle age or the association between bradyarrhythmias and moderate/severe left ventricular hypertrophy should raise the suspicion of genetic disease (Fig. 3).

7.1 Anderson-Fabry Disease

Anderson-Fabry disease is an X linked multisystemic disorder caused by the deficiency of α-galactosidase A, which leads to abnormal

Table 4 Cardiac conduction defects are common and progressive in neuromuscular Disorders and often requiring permanent pacemaker implantation

Type of dystrophy	Conduction system involvement	Indication to permanent pacing
Duchenne's muscular dystrophy	Frequent	2nd or 3rd -degree AV block, especially in the setting of a widened QRS complex
Becker muscular dystrophy	Possible	2nd or 3rd -degree AV block, especially in the setting of a widened QRS complex
Myotonic muscular dystrophy	Frequent	HV interval > 70 msec (perform EPS in all patients even in the absence of high-degree AV block)
Emery-Dreyfuss muscular dystrophy	Possible	2nd or 3rd -degree AV block, especially in the setting of a widened QRS complex
Limb girdle muscular dystrophy	Frequent	Family history of heart block or sudden death (familial form)
		2nd or 3rd -degree AV block, especially in the setting of a widened QRS complex (sporadic form)

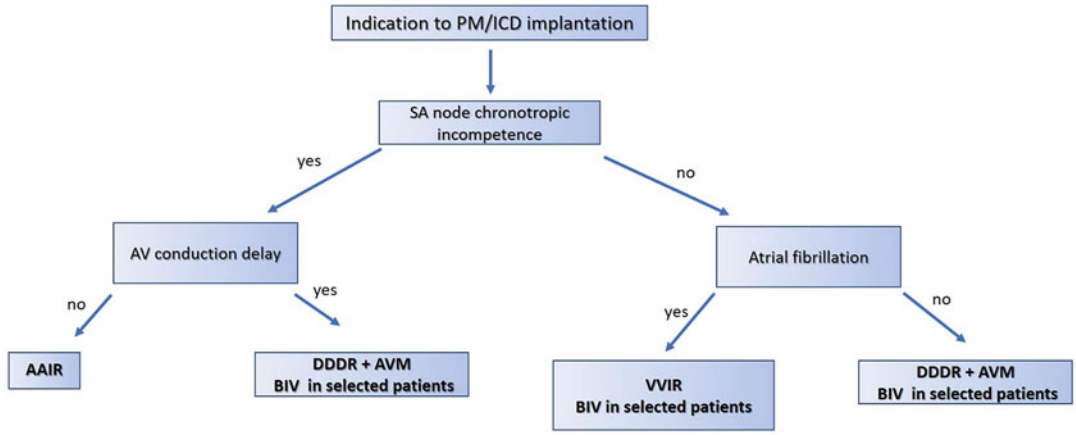

Fig. 2 Optimal pacing mode in HFrEF/HFmrEF. *PM* Pacemaker, *ICD* Implantable cardioverter defibrillator, *SA* Sinoatrial, *AV* Atrio-ventricular, *AVM* Atrio-ventricular delay management, *AAIR* Atrial pacing with rate responsive, *DDDR* Dual chamber pacing with rate responsive, *VVIR* Ventricular pacing with rate responsive, *BIV* Biventricular pacing

lysosomal accumulation of glycolipids (Garman and Garboczi 2004).

Even though left ventricular hypertrophy and ventricular arrhythmias are the most prominent cardiac manifestation, bradyarrhythmias, and progressive AV conduction disease have been reported and these may cause sudden cardiac death (Linhart et al. 2007).

Considering that the enzyme replacement therapy does not affect the bradyarrhythmias once they are established (but early therapy may prevent them) symptomatic bradycardia or asymptomatic patients with progressive conduction system abnormalities, intermittent AV block, and/or significant bradycardia should be treated with permanent pacing (Kim et al. 2016).

In the absence of specific guidelines and indications for device therapy for Anderson-Fabry disease, it is our experience to discuss an ICD implantation in patients with an indication for pacing and/or in patients with ventricular arrhythmias and a severe cardiac phenotype (hypertrophy, fibrosis). Recently O′ Mahony and coll. Showed, in a retrospective cohort study including 208 patients with Anderson-

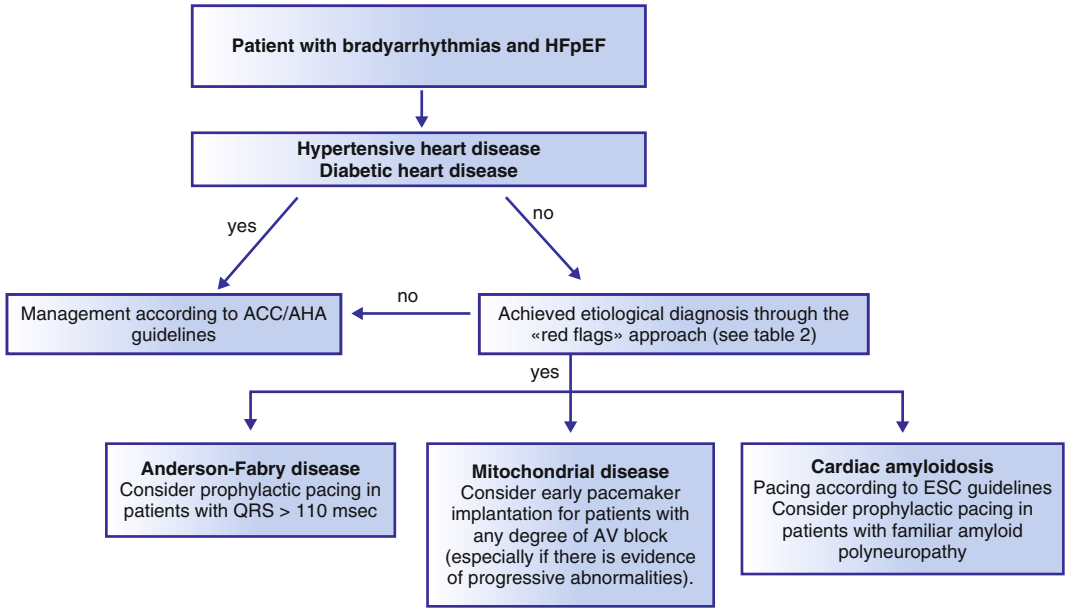

Fig. 3 In patients with HFpEF, the search for specific etiologies is essential for a tailored approach to pacing therapy. *HFpEF* Heart Failure Preserved Ejection Fraction, *ACC/AHA* American College of Cardiology/American Heart Association, *ESC* European Society of Cardiology, *AV* Atrio-Ventricular

Fabry disease, that 6% of patients need a pacemaker implantation for anti bradycardia therapy. At multivariate analysis, the most accurate predictor of future anti-bradycardia pacing is a wide QRS (O'Mahony et al. 2011). For this reason, in all patients with Anderson-Fabry disease and a QRS duration >110 msec a "prophylactic" ICD implantation should be considered.

7.2 Mitochondrial Disease

Mitochondrial diseases include a wide range of clinical entities involving tissues that have high energy requirements (Limongelli et al. 2012). Abnormalities in the mitochondrial function cause cardiomyopathies, arrhythmias, and abnormalities of the conduction system disorders (Bindoff 2003). Of note, in patients with mitochondrial disease progression to high-grade AV block is often unpredictable; for this reason, early pacemaker implantation for patients with any degree of AV block (including first-degree AV block with PR interval >300 ms), or any fascicular block with or without symptoms, especially if there is evidence of progressive abnormalities should be considered (Limongelli et al. 2016).

7.3 Amyloidosis

Amyloidosis comprises a unique group of diseases that share the extracellular deposition of insoluble fibrillar proteins in organs and tissues (Weatherall et al. 2010). Cardiovascular amyloidosis can be primary, a part of systemic amyloidosis, or a result of chronic systemic diseases elsewhere in the body. The most common presentation is congestive HF, mainly with normal left ventricular ejection fraction, high pulmonary capillary wedge pressure (Fig. 4) and conduction system disturbances (García Ropero et al. 2015). There are no specific indications for device therapy in cardiac amyloidosis, however, for patients with familial amyloid polyneuropathy with conduction disorder,

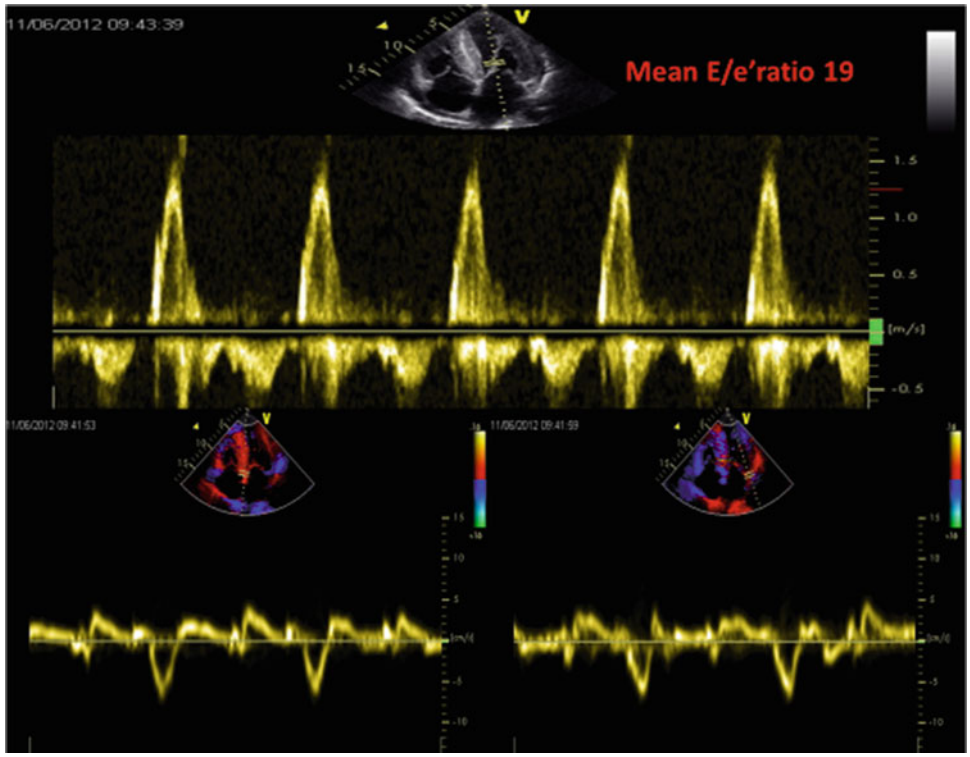

Fig. 4 Echocardiographic evidence of diastolic dysfunction in patients with AL Amyloidosis. Note the high E/e′ ratio suggestive of high pulmonary capillary wedge pressure

early "prophylactic" pacing should be considered (Rapezzi et al. 2010; Algalarrondo et al. 2012).

8 Mode of Pacing in Patients with HFpEF

Compared to patients with HFrEF/HFmrEF less evidence is present regarding the choice of pacing mode in patients with HFpEF. In patients with HFpEF due to hypertension, diabetes or ischemia, we proposed to select a pacing mode according to current ESC guidelines on cardiac pacing and cardiac resynchronization therapy (Brignole et al. 2013). In patients with Anderson-Fabry cardiomyopathy and mitochondrial disease, the pacing mode is selected according to the presence of left ventricular tract obstruction (Fig. 5). In fact in patients with left ventricular tract obstruction, we propose to set PM/ICD in DDD mode, regardless of the presence of AV blocks, to reduce left ventricular outflow gradient (Lucon et al. 2013; Montaigne and Pentiah 2015), while in patients without left ventricular outflow gradient we set PM/ICD mode according to international guidelines.

Finally, in our view, biventricular pacing should be the mode of choice in patients with cardiac amyloidosis, as conventional right ventricular pacing may lead to LV dyssynchrony and thus further decrease the stroke volume (Mathew et al. 1997).

9 Conclusion

The overall burden of a conduction disease is high in patients with HF and its management is complex and multifaceted. The current guidelines propose a general, evidence based approach relying on the type of bradyarrhythmias in patients with HF. A future personalized

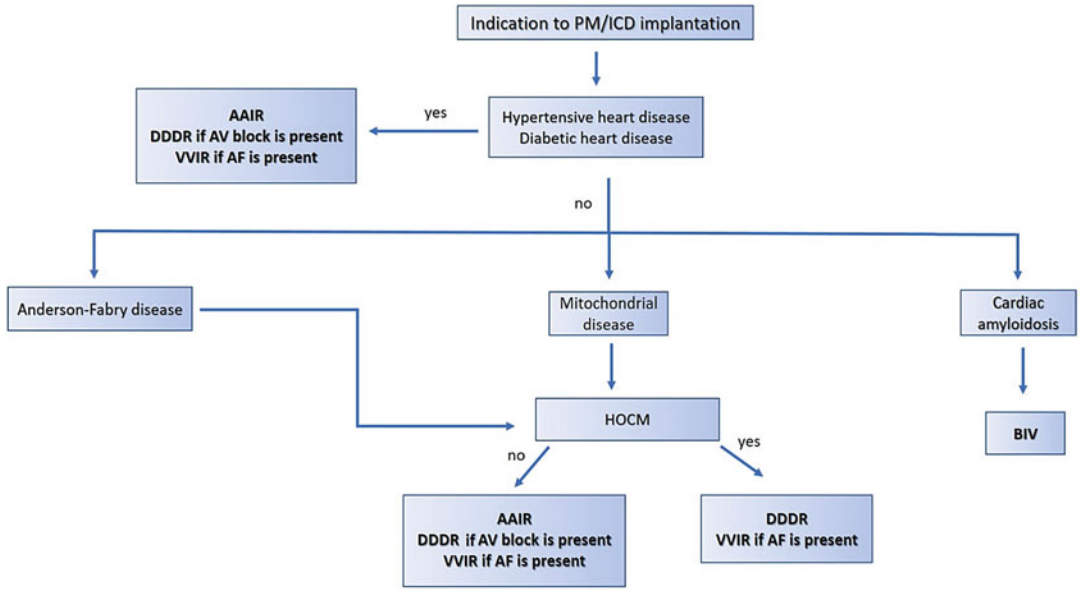

Fig. 5 Optimal pacing mode in HFpEF *PM* Pacemaker, *ICD* Implantable cardioverter defibrillator, *AAIR* Atrial pacing with rate responsive, *DDDR* Dual chamber pacing with rate responsive, *VVIR* Ventricular pacing with rate responsive, *BIV* Biventricular pacing

approach is warranted in this wide and heterogeneous cohort of patients. On this ground, HF specialist and electrophysiologist should broaden the horizon of the "ischemic vs non-ischemic HF" to provide a much tailored and personalized therapeutic approach in these patients.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 271–285
https://doi.org/10.1007/5584_2017_142
© Springer International Publishing AG 2018
Published online: 27 December 2017

Percutaneous Mitral Valve Interventions and Heart Failure

Abhishek Sharma, Sunny Goel, and Sahil Agrawal

Abstract

Mitral regurgitation (MR) is the most frequent Valvular Heart Disease (VHD) and is an important cause of heart failure. MR can be caused by primary valve abnormality (Degenerative MR/Primary MR) or it can be secondary to cardiomyopathy (Functional MR/Secondary MR). Medical management alleviates symptoms but does not alter the progression of the disease. Current guidelines recommend surgery for moderate-to-severe (Grade $>$ 3) MR in patients with symptoms or evidence of left ventricular dysfunction. Despite current practice guidelines, the majority of patients with severe MR do not undergo surgery. The reasons include high surgical risk from advanced age or multiple comorbidities, and a lack of clear data supporting valve surgery for secondary MR with LV dysfunction. The recent emergence of percutaneous interventional approaches in treating MR has expanded therapeutic options for patients who are at high risk for conventional Mitral Valve (MV) surgery. In this chapter, we will review the novel advancements in the field of percutaneous MV interventions that could potentially become the standard of care for patients with MR and heart failure.

Keywords

Mitral regurgitation · Heart failure · Percutaneous mitral valve intervention · Leaflet repair · MitraClip · Chordae repair · Direct annuloplasty · Left ventricle remodeling · Transcatheter mitral valve replacement

1 Introduction

Mitral regurgitation (MR) is the most prevalent VHD and is an important cause of congestive heart failure (CHF). MR affects up to 2% of the general population, with an incidence increasing with age. Approximately 10% of population older than 70 years of age is affected by MR

The original version of this chapter has been revised. An erratum to this chapter can be found at https://doi.org/10.1007/5584_2018_204

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(Jones et al. 2001). MR can be caused by primary abnormality of the valve apparatus (degenerative/primary) or it can be secondary to cardiomyopathy (functional/secondary). Degenerative MR is relatively uncommon, found mostly in younger patients and is potentially curable with repair of the damaged valve. Functional MR in comparison is caused by left ventricular (LV) dysfunction leading to mitral annular dilatation, tethering of the valve and inadequate leaflet coaptation (Nishimura et al. 2014; Hammerstingl et al. 2013; Kaul et al. 1991). Because valve abnormality is not the primary pathology in functional MR, valve surgery by itself is not curative but can help ameliorate symptoms.

Severe MR leads to progressive LV dysfunction and CHF (Trichon et al. 2003). Without intervention, symptomatic patients have an annual mortality of ≥5% (Carabello 2008; Carabello 2009). Medical management may alleviate symptoms but does not alter progression of the disease (Carabello 2008). Current practice guidelines recommend valve surgery for severe MR in patients with symptoms or evidence of LV dysfunction (American College of Cardiology/American Heart Association 1998; Bonow et al. 2006; Bonow et al. 2008). A substantial proportion of patients with severe symptomatic MR are not offered valve surgery despite clear indications (Bach et al. 2009; Mirabel et al. 2007; Vahanian et al. 2012). The reasons for this lack of surgical referral include high surgical risk from advanced age or multiple comorbidities, and lack of clear data supporting valve surgery for secondary MR with LV dysfunction (Bach et al. 2009; Mirabel et al. 2007; Vahanian et al. 2012). The advent of percutaneous approaches to treating MR has expanded therapeutic options for patients who are at high risk for conventional MV surgery. In this chapter, we will discusses the novel advancements and the future developments in the rapidly expanding field of percutaneous MV interventions that could potentially become the standard of care for patients with MR who are unable to undergo traditional surgery.

2 Mitral Regurgitation and Heart Failure

Normal MV function depends on a balance between closing forces of LV contraction and tethering forces of the papillary muscles (Levine and Hung 2003). MR results when this balance is perturbed by abnormalities of the valve itself or those resulting from cardiomyopathy- annular dilation, leaflet tethering, and loss of force and/or synchrony of LV contraction [Ref]. In the early stages of chronic MR, the resulting volume overload is tolerated until the left atrium reaches its maximum compliance, beyond which symptoms start to develop. A vicious cycle develops, as the regurgitant volume in the left atrium returns to the LV during diastole, resulting in LV volume overload and progressive LV dilatation with subsequent fall in LV ejection fraction. Progressively, chamber dilatation results in annular dilation, lateral and apical displacement of the papillary muscles, and malcoaptation of the mitral leaflets (Gaasch and Meyer 2008).

Papillary muscle displacement may occur because of global LV enlargement or focal myocardial scarring, and can affect one or both papillary muscles (Ray 2010). With chronic MR, the mitral leaflet area may increase up to 35% over time, an adaptive response that minimizes the degree of regurgitation; insufficient leaflet remodeling may contribute to severe MR (Chaput et al. 2008; Saito et al. 2012). However, even in patients with increased mitral leaflet area, papillary muscle displacement with subsequent decreased coaptation length may still result in significant MR (Saito et al. 2012). The normal saddle-shape of the annulus is also important for maintaining normal leaflet stress (Dal-Bianco and Levine 2013). Loss of this shape and annular flattening with LV remodeling result in increased

leaflet stress with secondary MR. In addition, LV systolic dysfunction reduces the strength of MV closing, which opposes the leaflet tethering forces created by papillary muscle displacement. These pathological changes culminate in failure of leaflet coaptation and decreased valvular closing forces due to LV dysfunction, resulting in MR and propagating the vicious cycle of heart failure and MR.

3 Treatment Options

The goals of therapy for patients with MR and heart failure are aimed at reducing symptoms, increasing exercise capability, improving quality of life (QoL) and decreasing MR-associated complications. There is considerable debate regarding the optimal approach, timing of intervention, indications, and efficacy of interventions. Treatment options include medical therapy and valvular interventions, which include surgery and percutaneous MV repair/replacement. Patients with functional MR caused by ischemic cardiomyopathy undoubtedly benefit from revascularization while cardiac resynchronization therapy (CRT is recommended for suitable patients with CHF who meet guideline criteria.

4 Medical Therapy

The most recent American College of Cardiology/American Heart Association/ (AHA/ACC) guidelines on valve disease recommend guideline-directed medical therapy (GDMT) as the first-line treatment for patients with MR and CHF, although the morbidity and mortality for patients with LV dysfunction and secondary MR remain high (Nishimura et al. 2014). Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, aldosterone antagonists, and diuretic agents should be considered for all patients with CHF. In the absence of LV dysfunction or CHF symptoms, there is little evidence that vasodilators are useful for treatment of the MR (Nishimura et al. 2014; Seneviratne et al. 1994)

5 Cardiac Resynchronization Therapy

CRT is a well-established treatment in select CHF patients with LV dyssynchrony (Cleland et al. 2005). In addition to improving CHF outcomes, it is shown to improve secondary MR from resynchronization of LV contraction (Madaric et al. 2007). Improved myocardial contractility increases closing forces of the MV while reverse LV remodeling reduces leaflet tethering by improving LV geometry (Breithardt et al. 2003; Abraham et al. 2002). Unfortunately, severe secondary MR improves in only one-half of patients after CRT, but such improvement identifies a cohort with improved prognosis (Cleland et al. 2005). CRT is a reasonable front-line therapy for secondary MR in CHF patients (along with GDMT), and should be considered prior to surgery or percutaneous valvular intervention.

6 Surgical Intervention

Surgical correction is the gold standard for patients with degenerative MR (Carabello 2008). Valve surgery may be attempted for secondary MR but has never been clearly demonstrated to alter the natural history of the primary cardiomyopathy or improve survival (Wu et al. 2005; Silberman et al. 2006; Calafiore et al. 2013; O'Gara 2012). Although practice guidelines currently recommend MV repair or chordal sparing replacement for functional MR, they do not specify the choice of operation. The 2014 ACC/AHA VHD guidelines contain three recommendations for valve surgery in secondary MR (Nishimura et al. 2014) (Table 1).

Table 1 ACC/AHA valvular heart disease guidelines for surgical management of functional MR

1. MV surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR **[COR- IIa, LOE- C]**
2. MV surgery may be considered for severely symptomatic patients (NYHA class III/IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for heart failure **[COR- IIb, LOE- B]**
3. MV repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery **[COR- IIb, LOE- C]**

AVR aortic valve replacement, *CABG* coronary artery bypass graft, *COR* class of recommendation, *LOE* level of evidence, *MR* mitral regurgitation, *MV* mitral valve

7 Percutaneous Intervention for MV

Several transcatheter technologies mimicking surgical techniques of MV repair have emerged for treating high surgical risk MR patients. Whereas transcatheter aortic valve replacement has now become standard of care for high and prohibitive surgical risk patients with aortic stenosis, transcatheter MV replacement has been lagging. The primary deterrent is the unique challenge posed by the non-symmetrical shape of the mitral annulus; which is noncircular, relatively large, dynamic in shape, and subject to cyclical, high LV systolic pressures. In addition, the subvalvular apparatus is complex, is variable in anatomy, and lies in close proximity to the LV outflow tract (LVOT) making it difficult to successfully deploy and anchor a percutaneous prosthesis (Goel et al. 2014). Need for trans-septal puncture and the pathologic heterogeneity of MR further add to these challenges (Table 2).

7.1 Leaflet Repair

The common goal of the various transcatheter mitral leaflet repair techniques is to increase the coaptation surface between the anterior and posterior mitral leaflets. The first and the foremost device in this category is the MitraClip®(Abbott Vascular, Santa Clara, California). This device, CE marked since 2008, has since been used to treated more than 35,000 patients (Ladich et al. 2011; Feldman et al. 2011). The MitraClip is a polyester-covered cobalt-chromium clip inserted via the femoral vein and advanced under transesophageal echocardiographic guidance into the LA following trans-septal puncture. The clip is opened, positioned above the regurgitant jet, and advanced into the LV. It is then retracted to grasp the free edges of the mitral leaflets, the grippers are dropped, and the clip is closed and released, emulating the Alfieri surgical edge-to-edge repair**.** Multiple clips may be safely placed, if necessary. MitraClip is effective to treat both degenerative MR and functional MR. Currently, the MitraClip® is approved by the Food and Drug Administration for transcatheter repair in selected high-risk patients with symptomatic primary and degenerative MR (Goel et al. 2014).

The MitraClip system was initially evaluated in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trials (Ladich et al. 2011; Feldman et al. 2011). The EVEREST-II trial randomized treatment of 279 patients in a 2:1 ratio to either MitraClip® or surgery (Feldman et al. 2011). 73% of patients had primary MR, and 27% had secondary MR. At 5 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was lower in the percutaneous repair than the surgical group (44.2% versus 64.3%, respectively; $p = 0.01$) (Mauri et al. 2013). The difference was driven by higher rates of 3+ to 4+ MR (12.3% vs. 1.8%; $p = 0.02$) and more need for surgery (27.9% vs. 8.9%; $p = 0.003$) with percutaneous repair. Patients treated with percutaneous repair more commonly required surgery for residual MR during the first year after treatment, but between 1- and 5-year follow-up, rates of surgery with either therapy were similarly low. Five-year mortality was similar for either treatment strategy. Both MitraClip and surgery

Table 2 Summary of percutaneous interventions for MV in current clinical use or under investigation

Therapeutic target	Device and Manufacturer	Device mechanism of action	MR etiology treated
Leaflet	Mitraclip [Abbott vascular] (Ladich et al. 2011)	Edge-to-edge leaflet plication using a clip, resulting in a double orifice valve	Primary and secondary MR
	PercuPro (MitraSpacer) [cardio-solutions]	Provides a coaptation surface for the leaflets by placing a space occupier across the MV orifice	Primary and secondary MR
	Thermocool SmartTouch [Biosense Webster] (Williams et al. 2008)	Leaflet ablation resulting in reduced motion or structural alteration	Primary MR
	Middle peak [middle peak medical]	Implantation of a posterior neoleaflet	Primary and secondary MR
Chords	NeoChord DS (NeoChord) (Sack et al. 2009; Pedersen et al. 2008)	Artificial chordae implantation anchored to the prolapsed leaflet and the LV apex	Primary MR
	V-chordal [Valtech] (Kim et al. 2009)	Artificial chordae implantation anchored to the prolapsed leaflet and the papillary muscle tip	Primary MR
	Babic [Edward Lifesciences] (Harnek et al. 2011)	Artificial chord implantation anchored to the prolapsed leaflet and the LV	Primary MR
	MitraFlex [Transcardiac therapeutics]	Combination of artificial chord implantation anchored to the prolapsed leaflet and the LV, and edge-to edge leaflet plication using a clip creating a double orifice valve	Primary and secondary MR
Annulus [direct annuloplasty]	Mitralign Bident(Mitralign)	Reducing mitral annulus (MA) circumference by plication of pledgets placed on the posterior MA and connected by a suture	Primary and secondary MR
	AccuCinch GDS (guided delivery systems [GDS])	Reducing MA circumference by implanting a ring of anchors at the posterior annulus interlinked with a cable that can be restrained	Primary and secondary MR
	Cardioband (Valtech)	Reducing MA circumference by anchoring an adjustable partial ring at the posterior MA	Primary and secondary MR
	QuantomCor (QuantomCor) (Rahman et al. 2010; Heuser et al. 2008)	Reducing MA circumference by using radiofrequency energy to cause scarring and constriction of the MA	Primary and secondary MR
	Milipede (Milipede)	Reducing MA circumference by self-expanding ring annuloplasty	Primary and secondary MR
	ReCor [ReCor medical] (Jilaihawi et al. 2010)	Reducing MA circumference by using heat to induce collagen, and thus MA, shortening	Primary and secondary MR

(continued)

Table 2 (continued)

Therapeutic target	Device and Manufacturer	Device mechanism of action	MR etiology treated
Annulus [indirect annuloplasty]/ coronary sinoplasty	CARILLON (cardiac dimensions) (Schofer et al. 2009)	Reducing MA antero-posterior diameter by indirect anterior displacement of the posterior MA following plication of the posterior periannular tissue	Secondary MR
	MONARC (Edwards) (Webb et al. 2006)	Reducing MA antero-posterior diameter by coronary sinus reshaping	Secondary MR
	Mitral cerclage (NIH) (Kim et al. 2009)	Reducing MA circumference by creating a loop around the MA and LVOT anchored to the CS	Secondary MR
	Valcare (Valcare medical) (Sack et al. 2009)	Rigid "D"-shaped annuloplasty using percutaneous annuloplasty ring	Primary and secondary MR
Left ventricle remodeling	Mardil BACE [Mardil medical Inc]	Reducing MA and LV circumference by implantation of a pouch around the heart with a saline inflatable bladder to externally compress the LV	Secondary MR
	PARACHUTE (CardioKinetix)	Ventricular partition of damaged ischemic muscle, isolating the non-functional muscle segment from the functional segment, thereby decreasing the overall volume and restoring a more normal geometry and function in the left ventricle.	Secondary MR
	Coapsys (Myocor) (Grossi et al. 2010)	Transventricular reshaping with 2 extracardiac epicardial pads that are connected by a flexible tether running through transventricular subvalvular space and anchored on the other side of epicardial surface. The chord can be shortened to reduce MR during the operation	Secondary MR
Valve replacement	Caisson TMVR (caisson interventional)	Transfemoral trans-septal MV replacement	Primary and secondary MR
	CardiAQ (CardiAQ) (Swaans and van der Heyden 2013)	Transfemoral trans-septal, self-anchoring MV replacement	Primary and secondary MR
	Cardia AQ 2nd generation (cardia AQ) (Ussia et al. 2016)	Transapical MV replacement. Anchored through leaflet engagement, chordal preservation and annular attachment	Primary and secondary MR
	Tiara (Neovasc Inc) (Cheung et al. 2014)	Transapical device with three bovine pericardial tissue leaflets mounted on self-expanding D-shaped metal alloy frame	Primary and secondary MR
	Tendyne (Tendyne holding) (Lutter et al. 2014)	Transapical self-expanding bovine pericardial valve in-stent with atrial and ventricular fixation	Primary and secondary MR
	High life (HighLife SAS) (Lange and Piazza 2015)	Transatrial MV replacement	Primary and secondary MR

(continued)

Table 2 (continued)

Therapeutic target	Device and Manufacturer	Device mechanism of action	MR etiology treated
	Medtronic TMVR (Medtronic) (Piazza et al. 2014)	Self-expanding nitinol ring and a cylindrical, tri-leaflet pericardial valve	Primary and secondary MR
	Fortis (Edwards) (Abdul-Jawad Altisent et al. 2015)	Transapical MV replacement using bovine pericardial tissue and cloth-covered self-expanding frame	Primary and secondary MR
	MitrAssist (MitraAssist)	Transventricular or transapical prosthesis positioned within native valve	Primary and secondary MR
	CardioValve (Valtech)	Transfemoral, trans-septal two-step MV replacement system	Primary and secondary MR
	Navigate TMVR (NCSI)	Self-expandable MV replacement device featuring a nitinol stent and dehydrated tissue	Secondary MR

demonstrated sustained reductions in mitral regurgitation and improvements in functional class and LV dimensions compared with baseline.

Although currently approved for only degenerative MR in the US, data from registries have demonstrated high rates of procedural success and favorable short-term outcomes in high or prohibitive risk patients with functional MR in large patient cohorts. The REALISM (Real World Expanded Multi-center Study of the MitraClip System Continued Access) study was a prospective, multicenter, continued access registry to collect data on the real-world use of the MitraClip device with high-risk (estimated STS PROM $\geq$12%) and non-high risk arms. Recently, aggregate data from the REALISM and EVEREST-II High Risk registries on 351 patients with symptomatic $\geq$3+ MR (functional MR = 70%) was published (Glower et al. 2014). 327 of 351 patients completed 12 month follow-up. MitraClip reduced MR to less than 2+ in 86% of patients at discharge ($P < 0.0001$). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1%, and stroke in 2.6%. At 12 months, 84% of patients had less than 2+ MR and rate of surgery was 2.2%. Significant improvements were seen in NYHA functional class and QoL scores (Glower et al. 2014). Among the 127 patients with degenerative MR, initial success rate was 95% and 30-day mortality was 6.3%. Although the 1-year mortality rate of 23.6% was high, it reflects the patients' baseline comorbidities. Importantly, 57.5% demonstrated New York Heart Assosication (NYHA) functional status of I or II at 1 year compared with only 12.6% with NYHA I or II at baseline.

The TRAMI (Transcatheter Mitral Valve Interventions) study is the largest published registry evaluating transcatheter MV repair conducted at 20 centers in Germany enrolling 1064 patients (Schillinger et al. 2013). The median age was 75 years; 87% had NYHA functional class III/IV CHF symptoms; 69% had LVEF <50%; secondary MR was present in 71% of patients; and the median STS score was 10%. Procedural success was achieved in 95% of patients, with no procedural deaths. At 3-month follow-up, although 12% of patients had died and 12% had been hospitalized for CHF; 66% remained in NYHA functional class I/II (Schillinger et al. 2013). At 1 year follow up, out of 749 (90.5%) patients that were available for

follow-up, the mortality rate was recorded to be 20.3%. and 63.3% of patients pertained to NYHA functional classes I or II (compared with 11.0% at baseline). Importantly, a significant proportion of patients regained the complete independence in self-care after MitraClip implantation (independence in 74.0 vs. 58.6% at baseline) (Puls et al. 2016)

In the ACCESS-EU (MitraClip Therapy Economic and Clinical Outcomes Study Europe) registry, the MitraClip was implanted in 567 patients at 14 sites across Europe (Puls et al. 2016). The mean logistic EuroSCORE was 23, and 77% of patients had secondary MR. The clip implant rate was 99.6%, with multiple clips used in 40% of patients. MR was reduced to $\leq$2+ in 91% of patients, and there were no procedural deaths. NYHA functional class and 6-min walk distance (6MWD) substantially improved at 1-year follow-up (Maisano et al. 2013).

The efficacy of the MitraClip device in inoperable patients with secondary MR is currently being evaluated in randomized controlled trials. The COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy) trial, RESHAPE-HF (MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation) and MITRA-FR (Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) studies will compare MitraClip device to standard GDMT in CHF patients with functional MR.

Other leaflet repair techniques are currently under clinical development. These include leaflet ablation for primary MR that aims to structurally alter leaflet anatomy and reduce leaflet motion (Thermocool irrigation ablation electrode), the implantation of a posterior neoleaflet to restore leaflet coaptation in either functional or degenerative MR (Middle Peak Medical) as well as an indirect approach to improve leaflet coaptation by filling of the coaptation gap between the anterior and posterior leaflet using a space occupier device across the mitral annulus (Percu-Pro MitraSpacer).

7.2 Chordae Repair

Transcatheter implantation of adjustable synthetic chordae tendinae to restore leaflet coaptation in patients with MR due to flail leaflets is currently under development. By adjusting the length of the chord, the MR can be reduced or abolished. The NeoChord uses a mini-thoracotomy transapical approach to capture the leaflet, and the chords are then exteriorized, adjusted, and tightened to the LV myocardium. This technology is mainly designed for degenerative MR with posterior leaflet prolapse. The V-Chordal system (Valtech Cardio Ltd., Or Yehuda, Israel) uses a slow rotation of a helical element to attach the chordae to the papillary muscle. The chordae are then sutured to the through a minithoracotomy left atriotomy approach. A clip attaching mechanism is under development, to allow for transfemoral access.

The Babic device creates two continuous guiding tracks from the LV puncture site through the target leaflet. The device is then exteriorized via the transseptal catheter and femoral vein. A polymer loop is apposed onto the venously exteriorized guiding tracks via docking adapters and is anchored onto the atrial leaflet surface by retracting the guiding tracks from the epicardial end. An elastic polymer tube is interposed between the leaflet and the free myocardial wall and secured to the epicardial surface by an adjustable knot. The MitraFlex device places an anchor in the inner LV myocardium and another on the leaflet via a transapical approach and connects the two with a synthetic chord; it can also perform an edge-to-edge repair at the same time.

7.3 Direct Annuloplasty

Transcatheter MV annuloplasty techniques attempt to abolish MR by reducing MV annulus circumference in an effort to increase leaflet coaptation. In the direct annuloplasty techniques; the posterior mitral annulus is targeted and the

mitral annulus is approached either from the left atrium (LA) through a transseptal approach or transapically via the LV. An attempt is made to reduce the mitral annulus circumference by implanting adjustable rings or purse-string sutures that cinch the mitral annulus or by delivering radiofrequency energy that shrinks the mitral annulus by creating a scar. Presence of annular calcification or causing potential damage to circumflex artery or valve leaflet poses challenge to successful direct annuloplasty.

The Mitralign device uses a retrograde transfemoral approach via the aortic valve into the LV to deliver pairs of pledgets which anchor through the posterior annulus. Each pledget pair can be cinched to achieve selective plications of the annulus and more than two pairs of pledgets can be implanted along the posterior annulus. Mitralign Percutaneous Annuloplasty first in man study was reported in 71 patients with moderate to severe Functional MR. Device success rate was 70.4% (n = 50 of 71). 30 day (n = 45) and 6-month (n = 41) rates for all-cause mortality, stroke, and myocardial infarction were 4.4%, 4.4%, and 0.0% and 12.2%, 4.9%, and 0%, respectively. At 6 months, non-urgent mitral surgery was performed in 1 patient (2.4%) and non-urgent percutaneous repair in 7 patients (17.1%). Core lab echocardiographic analysis showed MR reduction in 50% of treated patients by a mean of 1.3 grades after 6 months. There was significant reduction of anterior-posterior (–0.31±0.4 cm) and septal-lateral dimensions (–0.21±0.3 cm), a decrease in MV-tenting area (–0.57±1.1 cm^2) and increase in MV coaptation length (0.13±0.2 cm). Reverse LV remodeling with reduction of LV end-diastolic diameter (–0.20±0.4 mm) and volume (–22±39 ml) was also seen. Treatment was associated with significant improvement in 6 MWD (56.5±92.0 m) and improvements in NYHA functional class at 6 months (Nickenig et al. 2016).

The Accucinch (Guided Delivery Systems, Santa Clara, California) annuloplasty system which is also delivered via a retrograde transfemoral route, is designed to implant a series of anchor elements circumferentially under the posterior mitral annulus, from trigone to trigone. All anchors are connected by a cable that is used to cinch the annulus and the basal portion of the LV to reduce annulus circumference and MR. The feasibility and the safety of the device was shown in 10 patients, with no conversion to surgery and no 30- day major events; however, mitral regurgitation reduction was inconsistent (Kleber 2012).

The Cardioband system (Valtech Cardio, OrYehuda, Israel) is a transcatheter-implantable surgical-like ring which utilizes placement of a series of small corkscrew anchors on the atrial side of the left atrium. The anchors are connected by a Dacron sleeve that can be subsequently tensioned to reduce the mitral annular circumference. It is delivered anterograde via the right femoral vein through a transseptal puncture. Results in 15 swine using a transatrial access have been promising (Maisano et al. 2012) and recently early (1 month) outcomes of the first-in-man pre-CE-mark feasibility and safety trial were reported (Maisano et al. 2016). .The study enrolled 31 high-risk adult individuals with symptomatic functional mitral regurgitation (MR) despite optimal medical therapy, and who received the full implant of a Cardioband. Adjustment of the Cardioband resulted in significant reduction in the septolateral dimension in all but two patients (septolateral dimension from 36.8+4.8 to 29+5.5 mm after the procedure, $P < 0.01$). Following Cardioband adjustment (29 of 31 patients) MR was none or trace in 6 (21%), mild in 21 (72%), and moderate in 2 (7%) patients. No patient had severe MR after adjustment. Procedural mortality was zero and in-hospital mortality was 6.5% (2 of 31 patients, neither procedure nor device related). At 30 days, 22 of the 25 patients (88%) had MR $\leq$2+ (Maisano et al. 2016).

Another device in this category, the Millipede (Millipede, LLC, Ann Arbor, Michigan) is a repositionable and retrievable ring fixing the entire mitral annulus placed via a percutaneous or minimally invasive approach.

Several radiofrequency energy based annuloplasty techniques are in various stages of development. The QuantumCor (QuantumCor, Lake Forest, California), placed by the transseptal route, consists of a 40-mm loop with

7 electrodes and 14 thermocouples. RF energy is delivered to the circumference of the mitral annulus leading to tissue scarring and reduction of the mitral annulus dimensions, thereby improveming leaflet coaptation and reducing MR (Rahman et al. 2010; Heuser et al. 2008).

7.4 Indirect Annuloplasty/Coronary Sinoplasty

Percutaneous indirect mitral annuloplasty systems use implantable wires or systems placed through the coronary sinus to indirectly shrink the posterior mitral annulus and reduce MR. Although less invasive, this approach has some important limitations – (1) The CS is at a variable distance from the mitral annulus which is frequently increased in case of severe MR with annular dilation thereby reducing chances of successful abolition of MR (Maselli et al. 2006) (2) Left circumflex coronary artery compression has been frequently observed with this procedure (Sponga et al. 2012).

The Carillon Mitral Contour System, the most popular device in this category, consists of a nitinol device with two anchors connected by a bridge. After cannulation of the coronary sinus, the distal anchor is positioned at the end of the great cardiac vein in close vicinity with the anterolateral commissure of the MV and the bridge is retracted to plicate the posterior mitral annulus under fluoroscopy and TEE guidance. The device is placed percutaneously via the right internal jugular vein approach and can be easily retrieved if MR reduction is not favorable or coronary artery compromise develops. The device has undergone several design modifications to prevent slippage during implantation and now has reinforcement at its ends to prevent late fracture. Once significant MR reduction is achieved, the proximal anchor is deployed in the selected position. Due to the associated risk of impingement of the circumflex coronary artery, coronary angiography is performed throughout the deployment.

The CARILLON Mitral Annuloplasty Device European Union Study (AMADEUS) was the first to assess the safety and efficacy of the Carillon device (Schofer et al. 2009). Forty eight patients with dilated cardiomyopathy, moderate to severe FMR, an EF $<$ 40%, and a 6MWD between 150 and 450 m were enrolled in the study. Eighteen patients did not receive a device because of access issues, insufficient acute FMR reduction, or coronary artery compromise. Major adverse event rate was 13% at 30 days. At 6 months, the degree of FMR reduction ranged from 22% to 32%. 6MWD improved from 307+/−87 m at baseline to 403+/−137 m at 6 months ($P < 0.001$). Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved from 47+/−16 points at baseline to 69+/−15 points at 6 months ($P < 0.001$) (Siminiak et al. 2012). The Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial was a prospective nonrandomized trial in which 53 patients with symptomatic FMR were enrolled for CARILLON device therapy (Siminiak et al. 2012). Thirty-six patients received a permanent implant; 17 had the device recaptured. Patients in whom the device was placed then acutely recaptured for clinical reasons served as a comparator group. Safety and key functional data were assessed in the implanted cohort up to 24 months. The 30-day major adverse event rate was 1.9%. In contrast to the comparison group, the implanted cohort demonstrated significant reductions in FMR as represented by regurgitant volume [baseline 34.5 ±11.5 mL to 17.4 ±12.4 mL at 12 months ($P < 0.001$)]. There was a corresponding reduction in LV diastolic volume [baseline 208.5 ±62.0 mL to 178.9 ±48.0 mL at 12 months ($P = 0.015$)] and systolic volume [baseline 151.8 ±57.1 mL to 120.7 ±43.2 mL at 12 months ($P = 0.015$)], compared with progressive LV dilation in the comparator group. The 6MWD markedly improved for the implanted patients by 102.5 ±164 m at 12 months ($P = 0.014$) and 131.9 ±80 m at 24 months ($P < 0.001$) (Siminiak et al. 2012).

The Cerclage System creates a loop around the mitral annulus and the LV outflow tract (LVOT), entering through the CS ostium, passing through the anterior interventricular vein and returning near the CS ostium, perforating the myocardium either coming out in the right

ventricle and passing through the anterior tricuspid commissure, or directly coming out through the septum in the right atrium; the loop is then tightened and secured near the CS ostium (Kim et al. 2009). Different from the other coronary sinus devices, the Cerclage system allows for circumferential remodeling of the mitral annulus. The development of other indirect percutaneous mitral annuloplasty devices such as the Edwards Monarc and the Viacor was halted due to the relatively high rate of device-related adverse events including circumflex artery occlusion and fatal CS perforation (Noble et al. 2011; Machaalany et al. 2013).

7.5 Left Ventricle Remodeling

LV remodeling devices improve mitral leaflet coaptation and reduce functional MR by restoring LV shape and reducing mitral annulus dimensions. These technologies force reduction of the septo-lateral annular dimension through approximation of two devices connected by a bridge. The Mardil-BACE (Mardil, Inc., Morrisville, North Carolina) is a silicone band with an inflatable chamber that is slipped externally around the atrio-ventricular groove of the beating heart without cardiopulmonary bypass through a mini thoracotomy. The chamber can be inflated by saline through subcutaneous ports, and their volume can be adjusted intra- and postoperatively, thus remodeling the MV annulus and the sub-valvular apparatus. The surgical device seems effective in reducing functional MR and a percutaneous development is ongoing (Raman et al. 2011).

The Myocor i-Coapsys device consists of two epicardial pads (anterior and posterior) connected by a load-bearing transventricular chord, all deliverable through a port inserted in the pericardium via a percutaneous sub-xiphoid approach [Fig. 7]. Under TEE guidance the flexible cord is shortened to reduce the LV and mitral annulus anteroposterior dimension, improving leaflet coaptation and MR. In the Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve (RESTORE-MV) trial, 165 patients were randomly assigned to undergo CABG with or without Coapsys ventricular reshaping. Patients treated with the device had greater reductions in LV end-diastolic diameter, and lower mortality at 2 years, compared with the conventional annuloplasty control arm. A percutaneous approach was developed but despite the positive results of the trial, this device is no longer manufactured as the sponsor failed to secure funding (Grossi et al. 2010).

7.6 Percutaneous MV replacement

Transcatheter mitral valve replacement (TMVR) systems that can replace or be implanted into the native valve may be a feasible solution to treat MR independently of the underlying mechanism and have the potential to become an alternative to treat severe MR in high surgical risk patients. One of the many key obstacles in designing successful TMVR is anchorage of the bioprosthesis to the mitral annulus because of difficulty anatomy of mitral valve. Although these procedures were technically successful, the clinical outcomes have been mixed. Several of these devices are under clinical development.

The CardiAQ-Edwards transcatheter MV implantation system consists of a self-expanding trileaflet bovine bioprosthesis mounted on a nitinol frame. The foreshortening frame that allows for controlled deployment and self-positioning within the native mitral annulus preserving mitral leaflets and chordae, LV contractility. The valve can be implanted through a transseptal or transapical route and no rotational alignment is required. Supra-annular implantation avoids LVOT obstruction and a polyester skirt reduces risk of paravalvular leak. The first human implantation was in 2012 and the RELIEF prospective registry is currently ongoing and plans to recruit 200 patients to assess the safety of this device [Ref]. The FORTIS which consisted of a bovine pericardial valve within a cloth-covered self-expandable frame and a unique anchoring system to minimize

paravalvular leakage. The trial was terminated after a high incidence of valve thrombosis was noted and the valve is not currently available.

The Neovasc Tiara device consists of a trileaflet bovine pericardial valve on a self-expanding nitinol frame. The D-shaped orifice conforms to the saddle shape of the mitral annulus. The flat part of the frame is positioned anteriorly avoiding impingement of the LV outflow tract. The ventricular part of the valve has a covered skirt structure that prevents paravalvular leakage and 3 anchors (2 anteriorly to the trigone and 1 behind the posterior mitral leaflet) that stabilize the position of the valve within the mitral annulus along with the atrial flange. The valve is implanted through a transapical approach, and the valve is retrievable and repositionable. Initial clinical experience has been encouraging and a feasibility study will enroll 30 patients (Banai et al. 2012).

The Tendyne is a transcatheter transapical self-expanding nitinol prosthesis supporting a trileaflet porcine pericardial valve (effective orifice area of >3.2 cm^2, 34 Fr delivery sheath). Novel aspects of the Tendyne device include an outer D-shape with an asymmetric sealing cuff and a braided polyethylene tether that helps to anchor the prosthesis to an apical epicardial pad [Fig. 8]. Recently, the authors published the global feasibility data for the device in 30 patients with symptomatic MR and high surgical risk (Banai et al. 2012). Patients (mean age 76 years, 83% male) had a mean Society of Thoracic Surgery predicted risk of mortality of 7.3%. The majority (77%) had secondary MR and nearly one-half had LV EF of $<50\%$. The device was successfully implanted in 28 patients (93%) and was retrieved without complications in the other 2 patients. Grade 0 MR was reported in all but 1 patient. There were no device embolizations, no strokes, and no LV outflow tract obstruction. At 30 days, there was 1 death due to pneumonia and only 1 patient had mild MR. Overall freedom from major adverse events was 83%, and there was significant improvement in NYHA functional class, walk time, and QoL (Muller et al. 2017).

The Intrepid TMVR is a tri-leaflet bovine pericardial valve within in a self-expanding nitinol frame delivered transapically using a 33 Fr sheath The frame consists of a circular inner stent housing a 27-mm valve, and a conformable outer fixation ring (available in 3 sizes) which engages the mitral annulus. The outer fixation ring is designed to accommodate the variability of the native mitral annulus and facilitates anchoring through a 'champagne cork' like effect. The native leaflets and chordae are preserved and leveraged to seal around the device.

8 Conclusion

Transcatheter techniques for mitral regurgitation are still largely in their infancy but hold great promise for the management of select high-risk patients with severe MR who otherwise have a grave prognosis. MitraClip has emerged as a durable alternative to surgery in selected high-risk population groups and is currently approved in the US for patients with symptomatic primary MR. Encouraging progress has also been made in transcatheter MV replacement despite the technical challenges posed by the complex anatomy of the MV and the subvalvular apparatus. Progression from conventional surgery through minimally invasive surgery to transcatheter therapies can be viewed as a natural and inevitable procedural evolution. Further research involving a wider spectrum of patients and devices would shape the future of this exciting field of cardiology.

Conflict of Interest None.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 287–294
DOI 10.1007/5584_2018_145
© Springer International Publishing AG 2018
Published online: 13 March 2018

Left Ventricular Assist Devices – A State of the Art Review

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Abstract

Cardiovascular diseases are the leading cause of mortality rates throughout the world. Next to an insufficient number of healthy donors, this has led to increasing numbers of patients on heart transplant waiting lists with prolonged waiting times. Innovative technological advancements have led to the production of ventricular assist devices that play an increasingly important role in end stage heart failure therapy. This review is intended to provide an overview of current implantable left ventricular assist devices, different design concepts and implantation techniques. Challenges such as infections and thromboembolic events that may occur during LVAD implantations have also been discussed.

Keywords

End-stage heart failure · Mechanical circulatory support · Ventricular assist device · VAD

Keywords and Abbreviations

VAD	Ventricular assist device
LVAD	Left ventricular assist device
RVAD	Right ventricular assist device
BVAD	Biventricular assist device
UMTS 3G	Universal Mobile Telecommunications System, 3. Generation
FDA	U.S. Food and Drug Administration
CE	Communauté Européenne
HTx	Heart transplantation
NYHA	New York Heart Association
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ICS	Intercostal space

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1 Introduction

Cardiovascular disease is the leading cause of worldwide morbidity rates. Chronic ischemic heart disease, acute heart failure and myocardial infarction are among the primary causes of mortality in Europe (45% of all deaths), the United States of America (34,3%) and worldwide (45% of noncommunicable diseases) (Lloyd-Jones et al. 2010; WHO|NCD mortality and morbidity [Internet] 2016; Wilkins et al. 2017).

There are different options for treating heart failure depending on the severity, cause and course of heart failure. They include adjustments to patients lifestyle (e.g. more sports, diet), drug administration and surgical interventions.

Surgical therapies includes but are not limited to coronary artery bypass grafting, implantation of stents in affected coronary arteries, the repair or replacement of an failing heart valve and finally the heart transplantation, which serves as a gold standard for terminal end stage heart failure in refractory patients. The discrepancy between the number of patients waiting for a heart transplant and the number of donor hearts at hand, shows that this therapy is not available for everyone who needs it (Eurotransplant – Statistics [Internet] 2016). Implantation of long term left ventricular assist devices, offers an alternative treatment for patients falling in this gap or are not eligible for heart transplantation for reasons like comorbidities (Mancini and Colombo 2015). According to the seventh INTERMACS annual report, over 13,000 patients received implants for left ventricular support in the United States of America in 2014, out of whom 955 were implanted pulsatile flow LVADs and 12,030 – continuous flow LVADs respectively (Kirklin et al. 2015). Next to these implantable long term VADs, there are catheter-based, para- and extracorporeal blood pumps. Catheter based rotational pumps like Impella 2.5, RP (Abiomed) or HeartMate PHP (Abbott) provide temporary mechanical circulatory left of right ventricular support in case of e.g. acute cardiogenic shock or percutaneous coronary intervention. Paracorporeal systems, like Excor (BerlinHeart GmbH) are mainly implanted in children with heart failures. Other blood pumps (peristaltic or rotary pumps, e.g. Rotaflow, Maquet, or Centrimag, Abbott) are used in extracorporeal membrane oxygenation systems (ECMO) or heart lung machines for short and midterm support of the circulatory system. Despite this high variety of blood pumps in mechanical circulatory support, this chapter offers a focused overview of the current implantable, rotary left ventricular assist devices (LVAD, also abbreviated as VAD), along with their characteristic designs and implantation strategies. Current challenges involving LVAD implantation have also been discussed.

2 Left Ventricular Assist Devices – Indications and Implantation

A left ventricular assist devices (LVAD) is used for hemodynamic support of the left ventricle in patients suffering from terminal refractory left ventricular failure.

Heart failure standard of care in the form of mechanical circulatory support by left ventricular assist devices may differ between countries and is often dependent on the funding available for LVAD implantation programs (Birks 2010). The clinical indications for VAD implantation may vary with patients. Such indications include VAD support either until a suitable donor heart is transplanted (bridge to transplant or BTT), or until the patient stabilizes such that eventual entry on the heart transplant waiting list is possible (bridge to candidacy or BTC), or until a decision on further treatment options for patient into question can be made (bridge to decision or BTD). VAD implantation may also serve as an alternative lifelong treatment for patients on cardiac transplant lists (destination therapy or DT) or until myocardial recovery occurs (bridge to recovery or BTR). The LVAD is then usually explanted, in other cases it remains in place, the outflow graft is ligated and the driveline is removed (Rodriguez et al. 2013; Frazier et al. 2015; Khvilivitzky et al. 2012). A special application of LVADs is the support of both, the left and the right ventricle (biventricular assist device, BVAD) or as a total artificial heart (TAH). Both implantation scenarios are very rare and off-label uses (Frazier et al. 2010). The distribution between the implantation purposes differ from country to country mainly due to approval status of the devices and availability of donor hearts. As stated by the INTERMACS registry, the distribution between BTT, BTR and DT implantations were 53.5%, 45.7%, and 0.2% respectively in 2014 in the US (0.5% of all implantation were rescue and other) (Kirklin et al. 2015). This chapter focuses on long-term, implantable VAD system with the main implantation purpose BTT, BTR and DT.

Costs of LVAD therapy depends on several entries like device costs, hospitalization frequency, duration, costs, as well as follow-up length and costs. Literature presents wide spread data for total LVAD costs and should be interpreted carefully. Total LVAD costs found in literature ranges from $316,078 to $1,025,500 (Seco et al. 2017), a German-French group presented accumulated 2-years costs of €281,361 ± 156,223 (Aissaoui et al. 2017). The key component of a ventricular assist device is the blood pump. The pump establishes a parallel blood flow path (ventricles > cardiac support pump > aorta ascendens) to physiological bloodstream (ventricles > aortic valve > aorta ascendence). The pump draws blood from the left ventricle by an inflow cannula which is connected to the apex by a suture ring with a fixing and sealing mechanism, and giving it back into the systemic circulation by means of an outflow graft. Typically the outflow graft is sewn to the ascending aorta. In a few cases it can also be useful to anastomose the descending aorta (Zucchetta et al. 2014). The blood pump is connected with a powersupply by means of a cable (driveline). The driveline passes from the pump, through the musculus rectus abdomini and fascial layers into the abdominal region of the patient. The cable exits the body through a small incision in the skin (Slaughter et al. 2010). The cable sheath (usually made of silicone or polyurethane) is covered in the implanted part with a woven or non-woven material, which ensures an optimal ingrowth (Dean et al. 2015; Camboni et al. 2016). The driveline is immobilized close to the exit site to the skin by means of a fixing system and to protect the exit site from mechanical manipulation. The exit site of the cable is protected from possible infections, by a mandatory sterile dressing. The pump is externally connected to a control unit (controller). Constant power supply through the controller is ensured either by two batteries or a battery and an AC adapter. Some VAD manufacturers still offer other options, such as a 12 V AC adapter, which provides power supply through a car battery. Peripheral components (such as controller and batteries) may be carried in a portable system (a bag, rucksack, etc.), giving the patient mobility for several hours. To enable constant power supply the patient receives a replacement controller and spare batteries. The batteries are charged at home using a special battery charging station.

Additional devices for adjusting the VAD-speed and other VAD parameters are available at the clinical centers: Every complete VAD system contains a monitor which can be connected to the controller with a cable. One manufacturer (ReliantHeart, Inc.) provides an additional remote monitoring system that transmits the VAD parameters to a server by means of a UMTS mobile phone standard (3G). The parameters can then be accessed by the clinical VAD team using a web-based interface.

The implantation procedure is individual for each VAD type. The Instruction of Use (IFU) of the specific LVAD provides all requirements and implantation and application instructions to be followed by the physician. The following section should give an simplified principle of the implantation steps of VADs:

- The chest is opened by median sternotomy or minimally invasive techniques
- The sewing ring is sutured to the apex with felt pad sutures
- The myocardium within the suture ring is punched out as an access for the inflow cannula (also in reverse order to the fixation of the suture ring)
- The ventricle is checked for thrombi, any existing thrombi are removed
- Positioning and fixation the inflow cannula of VADs in sewing ring
- Placement and anastomosis of outlet graft at the aorta ascendens
- Subcutaneous placement of the connecting cable, with the exit point at the right or left upper quadrant of the abdomen
- Fixation of the cable
- After hemostasis the thorax and the cable exit point are closed and the wounds are dressed

Prior to LVAD application, it is necessary to prepare the pump in the sterile field in the operating room. The sterile system components

removed from the sterile outer packaging are visually inspected for integrity. Inlet and outlet cannula are mounted as required and the driveline is connected to the control unit and power line. A test run is performed in a bowl with sterile dextrose solution. The pump, sewing ring, outflow graft and driveline are usually soaked with antibiotic solution dependent on the pump type.

A default access for pump implantation is full sternotomy. After the pericardium is opened the heart and great vessels are exposed. The heart lung machine (HLM) is cannulated right-atrial and aortic. This approach provides a good overview of the heart and adjacent large vessels, the larger surgical field allows more options for treatment. This approach is favorable, if concomittant interventions such as heart valve replacement and repair, closing of an atrioventricular septal defect or implantation of epicardial pacemaker leads are required.

There are also less invasive techniques available with two access points to the thorax defined by the apex of the left ventricle (pump inlet placement) and upper mediastinum (outlet graft anastomosis) (Schmitto et al. 2014; Hanke et al. 2015). The opening to the apex is performed through a left thoracotomy at the level of the 6th intercostal space (ICS). The exact position of the left ventricular apex and thus the thoracotomy is detected by echocardiography before incision. For the opening of the upper mediastinum two approaches are possible: an upper hemisternotomy that is only partially opening the sternum, or a right-sided thoracotomy at the level of 1–2 ICS. After opening the thorax, the pericardium is only partially opened as far as it is necessary to provide access. The pericardium surrounding the right ventricle is left largely uninspected and the heart remains in its original position. Both facilitate the prevention of a possible right heart failure in the course. This technique is linked to additional benefits such as less adhesion complications, less bleeding complications, shorter ICU stays, potential reduction of infections, and cosmetic aspects. The implantation is performed using an extracorporeal circulation, heart-lung machine (HLM). A cardioplegia of the heart is not always carried out ("beating heart" approach).

There are several strategies for placement and anastomosis of the outlet graft includingthe anastomosis to the descending aorta, and placement of outlet graft in the sinus transversus pericardii or a bulge in the pericardial cavity (Hanke et al. 2016a, b).

The driveline is typically implanted in a large arc in the abdominal fascia and/or in the muscle sheath of the rectus, it exits the body in the abdomen (usually upper right or left quadrant). Here there are different tunneling techniques with one, two or three small incisions to implant the longest possible part of the driveline cable as an infection barrier. The driveline exit site is then supplied with a sterile wound dressing and a cable fixation, which is changed regularly. The patient retains the sterile dressing procedure even after the wound has healed, in order to constantly protect against infection and (micro) injuries (Slaughter et al. 2010; Fleissner et al. 2013).

3 Left Ventricular Assist Device – Design Aspects of the LVAD

Various types of blood pumps are currently used in clinical treatment. These mechanical pumps are used for extracorporeal circulation, as part of a cardiopulmonary bypass, extracorporeal membrane oxygenation system, or dialysis system, as an implantable version for a ventricular assist or as a total artificial heart (Der Deutsche Herzbericht [Internet] 2016). The application timespan can vary from a few hours for the short-term usage up to several years for long-term usage. Depending on the application, blood pumps can be built as positive displacement pumps or rotary pumps. Implantable ventricular assist pumps for long-term applications in terms of LVAD application nowadays employ only rotary pumps and will be discussed in this section. The VADs design implements wide-spread user specification areas, including hemodynamic function, hemo- and biocompatibility, durablility, usability during the implantation and explantation and daily in later handling, storage and transport conditions before implantation and during subsequent application (Girdhar et al. 2012; Schmitto et al. 2014; Geidl et al. 2009; Sabashnikov et al. 2013; Pagani et al. 2009; Schmitto et al. 2015).

The historical development of implantable cardiac assist pumps started with the pulsatile displacement pumps with pneumatic or electromechanical drives from the 1970s ("1st generation"), which, while still paracorporeal, were often not fully implantable. Rotary pumps with mechanical rotor bearings ("2nd generation") came up in the 1980s and 1990s, while last generation ("3rd generation") rotary pumps with contactless bearing concepts were first reported in the 1990s and 2000s (Reul and Akdis 2000; Heart Assist Devices – Texas Heart Institute [Internet] 2016; Tang et al. 2009). The currently approved systems in use for adults are 2nd and 3rd generation systems, which are significantly smaller and lighter than their predecessors from the first generation. They can be implanted in the mediastinum above the diaphragm, smaller pump types may be implanted within the pericardium. These turbine-like machines transmit energy through the swirl on the blood to move the blood forward. The designs vary between axial-flow rotors, diagonal- or mixed-flow rotors, and radial- or centrifugal-flow rotors. In general, as the size and the hydraulic power of axial to radial designs increase, the number of revolutions per minute decreases correspondingly.

The forces acting on the rotor from the blood flow and the motor drive are leveled with a suitable hemocompatible bearing. There are two bearing design principles applicable for for axial, radial or mixed rotor forms: mechanical contact bearings, or free-floating, contactless bearings which may be hydrodynamic, passive-magnetic or active-magnetic.

Mechanical bearings are used in the 2nd generation LVAD, which arefriction type, "lubricated" mechanical bearing forms such as a ball-cup bearing antagonizing axial and radial forces on the rotor. They are relatively easy to manufacture and maintain the rotor stable in its position. Disadvantages of these contact bearings include heat development, high shear forces or insufficient wash out and stagnation areas, resulting in subsequent insufficient haemocompatiblity (hemolysis and thrombus formation). Appropriate operation of the bearing is only assured when completely immersed in blood (or blood substitute).

Wearless rotor bearings are typical for 3rd generation LVADs. Hydrodynamic bearing surfaces are designed to produce a local pressure in a fluid film between rotating rotor and housing, thus creating a fluid force. This is achieved with tilted surfaces or spiral grooves. Such bearings solely operate in moving liquid environments with a specific viscosity range. With increasing rotational speed a fluid film is built up and the bearing functions effectively. Disadvantage of this bearing design includes operating point dependency, narrow gaps, which are required for moderate hydrodynamic forces, subsequent tight manufacturing tolerances, which require a complex and expensive manufacturing process, and generation of high shear stresses on the blood, resulting in elevated blood damage as well as activation of coagulation.

Magnetic bearing types contain permanent magnets or active magnetic systems. While permanent magnet deposits do not produce stable equilibriums of forces and are therefore used mainly in hybrid bearings, active magnetic systems with the help of distance sensors are able to control rotor-position in housing and work with larger rotor to housing gap dimensions. These design characteristics result in excellent hemocompatibility (Loree et al. 2001; Schmitto et al. 2017; Wieselthaler et al. 2010). As far as disadvantages are concerned, complexity (many active components, including sensors and regulation hardware and software) and the associated overall size of pump itself and its external system components should be mentioned. Table 1 provides an overview of actual LVADs in clinical application.

3.1 Additional Components

Along with the pump, additional components and tools complete the LVAD system. Surgical tools include a circular knife or punching system for opening of the left ventricular apex. Depending on the manufacturer and system another tool

Table 1 Information on clinically relevant VADs

LVAD (manufacturer)	Pump type	Generation	CE/FDA approval	Characteristics
HeartAssist 5 (ReliantHeart, Inc.)	Axial	2.	2014/IDE trial	Implantable blood flow sensor, remote monitoring
HeartMate II (Abbott.)	Axial	2.	2005/2010	First continuous VAD with FDA approval
HeartMate 3 (Abbott.)	Centri-fugal	3.	2015/IDE trial	Latest VAD with CE approval
HVAD (Medtronic)	Centri-fugal	3.	2009/2012	First LVAD with minimally invasive implant approval
Incor (BerlinHeart GmbH)	Axial	3.	2003/–	First implantable VAD with active-magnetic bearing
Jarvik 2000 (JarvikHeart, Inc.)	Axial	2.	2005/clinical trial	Retroauricular implantable plug for power supply

Berlin Heart [Internet] (2016), Welcome to Reliant Heart [Internet] (2016), HeartWare [Internet] (2016), Thoratec – Innovative Therapies for Advanced Heart Failure [Internet] (2016), Jarvik Heart Inc. The Jarvik 2000 [Internet] (2016) and Food (2016)

(dynamometric key) is necessary to fix the pump inlet in the sewing ring. For intramuscular and subcutaneous implantation of the driveline, a tunneling tool (trocar) is used, that may be pre-bent and has a tip along with a connecting mechanism for the cable connector. A small incision to penetrate the skin is created with either a surgical standard tool (scalpel or scissors) or a small circular knife, which is included in the pump-set. Finally, a sterile extension cable is often used, which is later removed, in order to connect a non-sterile control unit with a sterile cable in the sterile field.

4 Achievements and Current Research Topics

Since the first use of cardiac assist pumps, physicians and developers have learned a lot about the systems and their interaction with the human body. In addition to improvements and adjustments in patient management and operating techniques, this experience led to numerous technical improvements and new developments which in its turn brought radical changes into the concepts of the blood pump. Fatigue strength was improved immensely with the transition from pulsatile displacement pumps to centrifugal pumps and non-contact bearing concepts. The downsizing of the systems has improved implantability and reduced surgical trauma, especially when combined with new surgical techniques. Advancements in electrical engineering such as battery, microprocessor technology and (electro) magnets have contributed to both the internal and external components of the VAD systems to be smaller and lighter. Though the control and regulation of the pumps have become more complex but also more potent and consequently an increased quality of life for patients could be achieved. The hemocompatibility, biocompatibility and interaction with the (hemodynamic) system were substantially improved by adapting materials and surfaces, rotor and housing design taking into consideration hemodynamics and blood flow in the system including global and local shear stresses as well as residence times. This technical progress has been flanked by new manufacturing and development processes as well as further developments in the field of materials science.

Despite the rapid technical and clinical advancements, LVAD therapy still has to deal with serious complications. As the latest annual report of US-based VAD register INTERMACS (over 15,000 patients included) shows, the overall complication rate has decreased (Kirklin et al. 2015). The rate of hemolysis, strokes, renal dysfunction and lung failure, however, increased. Major complications accompanying the months after implantation include infection, bleeding, system malfunction, stroke or death.

These statistics provide a good overview of the challenges arising during the therapy with implantable cardiac support pumps in the future.

Firstly, it is not enough to focus solely on a technical optimization of the devices, but it also is necessary to examine the relation between the pump and physiology of patients along with a deeper understanding of infections and (anti-) coagulant events. Current research topics deal with new and optimized diagnostic procedures for early complication detection and intervention or complication prevention. Secondly, new technical and/or pharmaceutical therapy options need to be developed to address encountered complications fast and in a conservative manner. The psychological and ethical as well as quality of life aspects of a VAD implantation are addressed in additional research areas. To avoid infection and improve the quality of life of patients with ventricular assist pumps, ongoing work is focused on systems that allow transcutaneous energy transfer (TET). Feasibility was shown in few patients, today's and future developments in battery and pump technology may contribute for successful translation in clinical practice (Mehta et al. 2001). Telemonitoring is another current research topic, which will allow clinicians to view patient data online and thus assist them immediately. As a consequence (as known from other areas of heart failure therapy), patients may benefit from less routine clinic visits, early detection of complications and subsequent early and presumably more safe and cost-saving therapy (Welcome to Reliant Heart [Internet] 2016; johan.van.der.heide[at]itea3.org J van der H. 14003 Medolution [Internet] 2016).

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 295–311
DOI 10.1007/5584_2017_115
© Springer International Publishing AG 2017
Published online: 14 October 2017

Palliative Care in the Management of Patients with Advanced Heart Failure

Susan E. Lowey

Abstract

Globally, there are 18-million individuals living with heart failure, a disease that is responsible for 12–15 million office visits and 6.5 million inpatient hospitalizations each year. As HF becomes advanced or end-stage, patients often live in a cycle of frequent transitions between care settings, and with unmet needs, including distress from inadequately managed symptoms. Prognostication in patients with heart failure can be challenging due to the unpredictable exacerbating-remitting illness trajectory that is associated with this progressive disease. Recurrent hospitalizations, worsening functional status and refractory symptoms, despite optimal therapies, are among the most salient predictors indicating that patients with advanced heart failure are nearing the end of life. Palliative care is a specialized form of medical care that has been shown to help improve severity of symptoms, facilitate discussions regarding medical decision making/advance care planning, and provide support for patients and their families. Palliative care can be used alongside curative treatments and has been shown to improve patient satisfaction and quality of life. Anorexia-cachexia syndrome, dyspnea, fatigue, pain and depression are among the most common symptoms experienced by patients suffering from advanced heart failure. Palliative care can help alleviate these symptoms and also facilitate conversations about decision making surrounding resuscitation status and use or deactivation of medical devices, such as an implantable-cardioverter-defibrillator (ICD). Clinical practice guidelines from the American College of Cardiology and American Heart Association report that aggressive life-sustaining treatments and therapies should not be utilized in patients with advanced heart failure who have refractory symptoms that are not responding to medical therapy. The focus of care should switch to controlling symptoms, reducing hospital admissions and improving health-related quality of life, which can be supported by the incorporation of palliative care into the treatment plan.

Keywords

Advanced care planning · Advanced heart failure · End-of-life care · Heart failure · Palliative care · Symptom management

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1 Introduction to Advanced Heart Failure

The heart is one of the most complex organs in the body. It is at the center of the circulatory system pumping oxygen-rich blood to all parts of the body (U.S. Department of Health and Human Services, National Heart Lung and Blood Institute 2011). The performance and health of the heart muscle is vital to ensure survival. Over time, the ability of the heart to adequately pump blood to other parts of the body can weaken. It can affect either the left or right side of the heart or both (U.S. Department of Health and Human Services, National Heart Lung and Blood Institute 2015a). This condition is known as heart failure and it is the progressive outcome from a variety of cardiovascular diseases, such as coronary artery disease, hypertension, arrhythmias and cardiomyopathy (U.S. Department of Health and Human Services, National Heart Lung and Blood Institute 2015b). Congestive heart failure occurs when blood backs up into various organs, such as the lungs and kidneys, due to the inefficiency of the heart to pump. This can affect the function of those organs and can cause significant distress from presenting symptoms. Although not all heart failure is classified as congestive, its effects can contribute to a host of adverse symptoms and stressors on the body of those who are affected (American Heart Association 2017a).

According to the American College of Cardiology/American Heart Association (ACC/AHA), the progression of heart failure is categorized into 4 stages (Hunt et al. 2009). Individuals who have risk factors for heart failure but have no structural heart disease are classified as stage A, whereas patients who have risk factors and the presence of asymptomatic heart disease are classified as stage B. Stage C encompasses the largest percentage of patients and includes patients who have active symptomatic disease. Stage D represents advanced or end-stage heart failure and is characterized by the presence of refractory symptoms despite the implementation of available medical therapies (Hunt et al. 2009). This paper will focus exclusively on the management of patients who present with advanced, or stage D, heart failure and the use of palliative care interventions in their overall treatment plan.

1.1 Prevalence

Heart failure has become an all too common chronic illness affecting nearly 6 million people in the United States and nearly 18 million people globally (World Health Organization 2017a). Heart disease is the leading cause of death worldwide affecting men and women alike, regardless of ethnicity or racial origin. Of the 6 million people who are diagnosed with heart failure, approximately 10% have advanced, or stage D, heart failure (American Heart Association 2017b). Heart failure has no cure and although there are treatments available to manage the disease, it is a progressive disorder that will eventually worsen despite the best medical therapies.

This disease is costly, both in terms of mortality and economics. One in every three deaths in the United States is the result of heart disease, contributing to the deaths of 2240 people each day (American Heart Association 2017c). Heart failure is responsible for 12–15 million office visits and 6.5 million inpatient hospitalizations each year (Hunt et al. 2009). According to the American Heart Association, the estimated cost of cardiovascular disease in 2010 was $863 billion and is expected to rise to $1044 billion by 2030 (American Heart Association 2017c). Patients with heart failure live with many distressing symptoms that can affect their functional status and quality of life (Heo et al. 2014). Heart failure affects older adults more than any other age category, with 80% of patients who are hospitalized with this disease aged 65 years or older. The incidence and prevalence of heart failure will escalate alongside the projected growth of the older adult population expected to reach 83.7 million by the year 2050 (United States Census Bureau 2014).

1.2 Illness Trajectories in Advanced Heart Failure

An illness trajectory is the common course or pattern of progression that is associated with a specific type of illness. The term trajectory is defined as "a path or course", therefore illness trajectory can be defined as "a course of illness" and is the usual pattern or progression of an illness or disease (Merriam-Webster 2017a). It is important to understand which illness trajectory is most commonly associated with heart failure in order to be able to anticipate prognosis and inform the patient and family what to expect. Many patients want to know what will happen to them when they are diagnosed with an illness. This is especially true if the disease is not fully curable and the patient will have to live with the illness for the rest of his/her life.

Illness trajectories were first studied by Glaser and Strauss (Glaser and Strauss 1965) who examined the various illness trajectories that people who were dying often went through. Three trajectory types were classified: surprise deaths, expected deaths, and entry-reentry deaths. Surprise deaths were usually unexpected and occur without any warning, such as a car accident. Expected deaths occur in individuals diagnosed with a known terminal illness in which death was the expected outcome with disease progression. Entry-reentry deaths reflect the trajectory that is most aligned with heart failure and describes a typically slower illness trajectory characterized by intermittent acute exacerbations followed by periods of remission. There is a slower decline associated with this type of trajectory and while patients may recover from an exacerbation, they often do not return to their previous level of functioning, losing a little more function with each subsequent exacerbation.

2 Prognostication in Advanced Heart Failure

The exacerbating-remitting illness trajectory can make prognostication difficult in patients with advanced heart failure, as it is difficult to predict with any certainty when the next exacerbation will occur. Prognostication in heart failure can be challenging because of the unpredictability with the course of the illness and severity of exacerbations. Previous research has examined this topic with much variation in their results. In a sample of 1433 patients with advanced heart failure, the estimated 1-year survival was 71.9% (Costanzo et al. 2008) whereas another similar study found the 6-month survival to be only 67% (Allen et al. 2008). The estimated 1-year survival was found to be 25% in a randomized control trial that compared two cohorts of patients; one undergoing destination ventricular assist device (VAD) therapy compared with a cohort receiving only medical management (Rose et al. 2001). Despite this variation, heart failure research has continued to grow and subsequently findings have supported the most salient clinical indicators to help physicians with accurate prognostication of patients with heart failure.

2.1 Predicting Prognosis in Advanced Heart Failure

Although prognostication can be difficult due to an unpredictable illness trajectory and other factors that may be involved, there are several key components that can assist providers with predicting prognosis for a patient with heart failure. Previous research has shown several indicators that strongly correlate with a limited prognosis in patients with heart failure (Reisfield and Wilson 2007). These include: decreased left ventricular ejection fraction equal or less than 45%, elevated blood-urea nitrogen and/or creatinine 1.4 mg/dl or higher, recent cardiac hospitalization, ventricular dysrhythmias that are resistant to treatment, reduced functional status, anemia, hyponatremia, cachexia, and presence of other co-morbidities (Reisfield and Wilson 2007).

More recent research has supported the use of biomarkers for the diagnosis, treatment, and prognostication in patients with heart failure

(Schmitter et al. 2014). Three well-established biomarkers for heart failure include the brain natriuretic peptide (BNP), N-terminal pro-hormone of brain natriuretic peptide (NT-proBNP), and mid-regional sequence of pro-atrial natriuretic peptide (MR-proANP) (Schmitter et al. 2014). Another recent study found increased levels of pro-atrial natriuretic peptide (MR-proANP) to be associated with 10-year all cause mortality and adverse clinical outcomes in community dwelling patients (Odermatt et al. 2017). Since many patients with advanced heart failure die following a visit to emergency care, Lee and colleagues (Lee et al. 2016) conducted the first phase of their ACUTE study to examine the validity of an emergency heart failure mortality risk tool. This will help physicians to accurately identify level of risk among patients who present to the emergency room with symptoms of acute heart failure (Lee et al. 2016).

2.2 Conversations About Goals of Care

Goals of care are the desired outcomes patients have for their medical care and are based on their values and beliefs (Vermont Ethics Network 2011). Goals of care can change over time as patients' circumstances and stage of illness changes and therefore it is important for providers to ask patients about their individual goals of care periodically throughout the illness trajectory. Understanding the unpredictable nature of this the illness trajectory associated with heart failure can be a useful starting point in helping inform patients about what they might expect as their illness progresses. Previous research has demonstrated the lack of these types of conversations early enough in patients' illness trajectories (Hupcey et al. 2016). Often the conversation about goals for care does not occur until the patient is already in the advanced stage of disease. It is important to understand that patients' care preferences may change from a previous hope for a cure and focus on extending length of life, to a new aim on improving comfort and quality of life. When this shift in care preferences occurs, a conversation about the incorporation of palliative care should be initiated.

It is vitally important for providers to have a good understanding about what palliative care is and what it is not, in order to provide accurate and honest information to the patient and family. Family members may be present and involved in conversations about goals of care and there may be discrepancies between what the patient wants and the wishes of the family. Since this can pose a challenge, several family meetings alongside social work, may need to be held before there is resolution in a clear plan of care moving forward. The initiation of palliative interventions can occur alongside of curative medical therapies, and that is an important point to share with patients and families during goals of care conversations.

3 Palliative Care

3.1 Origins of Palliative Care

Palliative care originates from the term "palliate" and is defined as "to reduce the violence of (a disease) and/or to ease (symptoms) without curing the underlying disease" (Merriam-Webster 2017b).

The World Health Organization defines palliative care to be "an approach to care that improves the quality of life for patients with life-limiting illnesses and their families through the prevention and relief of physical, psychosocial and spiritual suffering" (World Health Organization 2014). Although most end-of-life care programs and hospices utilize the underlying philosophy of palliative care, it in itself has become a specialty of care found in over half of all 100+ bed hospitals in the United States (National Hospice and Palliative Care Organization 2014). This equivocates to a 138% increase since the year 2000. Palliative care programs and services are found in both inpatient and outpatient health care settings.

Although palliative care first began alongside the hospice movement, it is its own specialty of care that is widely used by patients who are diagnosed with serious illnesses. It uses a team-based approach to assess and treat adverse symptoms that accompany serious illnesses (National Hospice and Palliative Care Organization 2014). The goal of palliative care is to mitigate or lessen distressing symptoms that affect patients, which will ultimately benefit their quality of life. In addition to a focus on symptom management, palliative care often bridges the gap between medical care and end-of-life care by initiating difficult conversations surrounding prognosis and goals of care. It helps patients with decision making and care planning. Lastly, palliative care helps to provide emotional support for patients and families who are living with serious life threatening illnesses (National Hospice and Palliative Care Organization 2014).

3.2 Provision of Palliative Care

Palliative care can be incorporated into the care of patients who have been diagnosed with a serious life limiting illness. It can be used by patients of any age or alongside any stage of illness because the overarching goal is to improve quality of life (Center to Advance Palliative Care 2011). There is no pre-determined life expectancy required to be eligible to receive palliative care. This differs from hospice care, which requires patients to have a life expectancy of 6-months or less in order to qualify for its services (Center to Advance Palliative Care 2011). Some healthcare organizations may offer one or more sub-specialties of palliative care focused on a specific population. Geriatric and pediatric palliative care are two examples of sub-specialties that focus on improving the quality of life for older adults and children, respectively. Palliative care is covered by Medicare, Medicaid and most private insurances or HMO's (Start the Conversation.Org 2017).

In addition to the requirement of a 6-month life expectancy, the other marked difference between palliative care and hospice are the regulations governing curative versus comfort care. Palliative care can be used alongside life-sustaining or curative treatments in patients who are diagnosed with a serious life limiting illness. This differs from hospice care in that hospice requires patients to forgo all curative or life-sustaining medical treatments and elect to receive solely comfort care measures (National Hospice and Palliative Care Organization 2014).

Palliative care might be a better option than hospice for patients who are living with certain chronic illnesses, such as heart failure. This is because some of the regulations that stipulate what is covered or allowable treatments by hospice may not be consistent with patients' wishes or goals of care. This pertains to patients, such as those with heart failure, who have periodic exacerbations of illness that require inpatient care and the administration of medications that are not routinely covered by hospice because they are considered to be curative in nature. Patients with advanced heart failure may find more benefit with the provision of palliative care interventions alongside their treatment plan rather than electing solely hospice care. This is because many of the interventions routinely used for symptom management are considered curative and would not be reimbursable through the current regulations of the hospice benefit (Lowey et al. 2014).

3.3 Indication for Palliative Care

The benefits of palliative care for patients with heart failure have been recognized by the American Heart Association, American College of Cardiology and the Heart Failure Society of America (Diop et al. 2017). The ideal timing for initiation of palliative care is not well understood despite consensus statements and panels that have advocated for its delivery alongside curative medical care. What we do know is that patients who are diagnosed with ACC/AHA Stage D heart failure and/or patients who develop symptoms classified by the New York Heart Association as Class III or IV, may benefit from palliative interventions (Teuteberg 2016).

Additionally, discussion surrounding palliative care should be initiated with "patients who have more frequent inpatient hospitalizations for heart failure exacerbations, present with refractory angina, have recurrent implantable cardiac device (ICD) shocks, and levels of anxiety or depression that adversely affect quality of life" (Teuteberg 2016). Lastly, early conversations with patients to establish their goals of care and periodic re-visitation of these goals, is an essential component that will enable providers to determine when their patients would most benefit from the incorporation of palliative care into their treatment plan.

4 Management of Symptoms in Advanced Heart Failure

4.1 Anorexia/Cachexia

Anorexia is a common symptom that accompanies many types of advanced illnesses. It is defined as the "reduction or loss of desire to eat" (Wholihan 2015). In acute diseases, anorexia can be corrected or reversed when the illness resolves. In progressive advanced illnesses, such as heart failure, anorexia can be more challenging to manage. If patients are not able to consume enough calories, it will lead to protein-calorie malnutrition and subsequent weight loss (Wholihan 2015). Unresolved anorexia can lead to cachexia, and the presence of both together has been coined anorexia-cachexia syndrome in progressive disease or cardiac cachexia when associated primarily with heart failure (von Haehling et al. 2009). Cardiac cachexia is estimated to arise in 16–36% of patients with advanced heart failure (Wholihan 2015). Cachexia is defined as wasting away from lack of adequate nutritional intake and/or progressive weight loss (Wholihan 2015). Decreased appetite typically accompanies both anorexia and cachexia, however the latter can occur without the presence of a decreased appetite (Wholihan 2015). Wasting of skeletal muscle and fatigue often accompany anorexia-cachexia syndrome (Wholihan 2015) which may be difficult to treat in patients who are nearing the end of life.

Early signs of anorexia-cachexia syndrome include: reduced appetite, alterations in taste, and early satiety (Wholihan 2015). These signs can lead to weight loss, wasting of muscle and adipose tissue, fatigue and decreased functional status (Wholihan 2015). Decreased food intake will lead to metabolic alterations, decreased immune response and systemic inflammation (Wholihan 2015) which can develop into a devastating cycle and progressive worsening of patients' underlying condition. In addition to its physiological effects, anorexia-cachexia syndrome contributes to psychological and spiritual distress for the patient and family. It can have profound effects on quality of life. Assessment should include a thorough nutritional intake and appetite evaluation. There are several validated tools available to assess nutritional status including the Subjective Global Assessment for Nutrition (Wholihan 2015), which focuses exclusively on nutrition or the Memorial Symptom Assessment Scale (Wholihan 2015), which focuses on several symptoms including appetite.

Palliative management of patients with anorexia-cachexia syndrome should be focused on reducing the distress caused by anorexia and subsequent weight loss in an effort to improve comfort and quality of life. Non-pharmacological interventions include: encouraging small meals served at room temperature, initiating more heavily caloric or nutritional foods/liquids first in the meal, avoiding foods and liquids with little or no nutritional value, introducing over-the-counter nutritional supplements, and supporting patients and families to continue to offer cultural dishes and maintain family mealtime rituals (Wholihan 2015). Pharmacological interventions include megestrol acetate, which has shown to stimulate appetite and promote weight gain. The majority of these studies were in cancer patients, and therefore the benefit in non-cancer illnesses such as heart failure, are not well known (Wholihan 2015). Some studies have found a positive correlation between fluid retention and megestrol use, however, larger multisite studies are needed to provide stronger validation of this

side effect in heart failure patients (von Haehling et al. 2009).

The use of artificial nutrition and hydration is a common topic that arises during conversations about management of anorexia and cachexia. Although administering nutrition and fluids through artificial means might have good benefits for patients with an acute trauma or illness, the benefits for patients with advanced or terminal illnesses are less known. We do know that the use of artificial nutrition and hydration can contribute to several unwanted complications among patients with advanced disease. This includes: nausea and vomiting, loose stools, aspiration, shortness of breath, edema and dumping syndrome (End of Life Nursing Education Consortium (ELNEC) n.d.). Patients who are nearing or at the end of life may have little to no benefit from artificial feedings and have been found to contribute to increased discomfort and further reduction in quality of life (End of Life Nursing Education Consortium (ELNEC) n.d.). Providers should evaluate the patient's goals of care in conjunction with stage of illness before deciding whether artificial nutrition or hydration should be initiated.

4.2 Confusion

It is not atypical for patients with heart failure to present with cognitive impairments, confusion or delirium. This has been found to be related to decreased cardiac output and reduced cerebral blood flow (Whellen et al. 2014). These cognitive deficits can be compounded by the age of most heart failure patients, as normal age related changes may also be present. Patients may be subject to higher rates of hospitalization, greater functional deficits and increased mortality (Heidrich and English 2015). Certain medications, such as benzodiazapines, opioids and even some cardiac medications, such as beta blockers and ACE inhibitors, can further contribute to confusion and delirium. Among hospitalized patients, delirium has been reported in 14–56% of patients and up to 80% of patients who were mechanically ventilated in ICU's (Heidrich and English 2015).

The Confusion Assessment Method (CAM) and Memorial Delirium Assessment Scale (MDAS) are two clinical instruments that can easily be used to evaluate patients' cognition in the clinical setting (Heidrich and English 2015). In patients who are not actively dying, palliative management includes removing the source that is contributing to confusion or delirium, such as reducing medication dosages or treating underlying medical conditions, such as an infection. Terminal restlessness is a term used to describe increased agitation, confusion and restlessness experienced by some patients as they near the end of life (Heidrich and English 2015). If the patient is exhibiting other signs that indicate their condition is rapidly progressing and they are actively dying, palliative management would focus on reducing the distress associated with the symptom/behavior and ensuring the safety of the patient and those around him/her. Antipsychotic medications, particularly haloperidol, is the medication of choice for management of terminal restlessness or agitation (Heidrich and English 2015). This medication typically has fewer side effects than anticholinergics or benzodiazepine medications, and can be given in a variety of routes. Lorazepam should ideally not be used because it has been demonstrated to worsen delirium in older adults (Heidrich and English 2015).

4.3 Cough

Cough can be a common occurrence in patients with heart failure. Cough can be dry or productive, depending on the origin. Patients with heart failure can develop a cough due to pulmonary congestion, the presence of an underlying infection or result from the use of an ACE inhibitor used to manage their heart condition (Whellen et al. 2014). Cough is often worse at night, when the patient is lying down. Frequent coughing can lead to irritation in the respiratory tract and trachea, pain, nausea from retching, and even fractured ribs (Dudgeon 2015). It can contribute to

poor sleep, nutrition and increased fatigue, which can greatly decrease the patient's quality of life.

Management for cough begins by evaluating the underlying cause or source of the cough. This includes ruling out any underlying infection or escalating exacerbation. For patients whose cough is caused by ACE inhibitor, an angiotensin receptor blocker (ARB) can be substituted (Katz and Konstam 2009). Palliative treatment for a non-productive cough can include: antitussive medications, such as dextromethorphan, opioids, and inhaled anesthetics for severe cases (Dudgeon 2015). Treatment for a productive cough can include: expectorants, mucolytics, antihistimines, and anticholinergics to decrease sputum production. Oxygen and chest physiotherapy may also be used (Dudgeon 2015).

4.4 Dyspnea

Dyspnea, also referred to as shortness of breath or breathlessness, is a common and distressing symptom experienced by patients with advanced heart failure. A recent systematic review found that 60–88% of patients with cardiac disease experience some type of dyspnea (Solano et al. 2006). Breathlessness has been described by patients as a profound heaviness or weight sitting on their chest and the inability to take in enough air to breathe (Lowey et al. 2013). This can be a frightening experience and has been associated with increased levels of anxiety and depression (Lowey et al. 2013). The cause of dyspnea is often multidimensional and its treatment can be difficult in patients with advanced heart failure. Dyspnea may become refractory in advanced or end-stage heart failure, which means that the underlying cause cannot be reversed and the focus of care should shift to interventions aimed at palliation (Abernathy et al. 2003).

In palliative care, the gold standard management for refractory dyspnea in end-of-life care is the use of an opioid medication (Lanken et al. 2008). Caution should be taken when prescribing an opioid medication to patients with heart failure, because their increased age and presence of other co-morbidities can contribute to the build-up of toxic metabolites (Dudgeon 2015). Benzodiadapines have also been shown to help reduce anxiety that is associated with breathlessness. The benefits associated with administering opioids and benzodiazapines for patients who are nearing the end of life or actively dying, may outweigh the risks, since the focus of palliative care is on maximizing comfort and improving quality of life (End of Life Nursing Education Consortium (ELNEC) n.d.).

Some non-pharmacological interventions may help alleviate the sensation of breathlessness in patients with advanced heart failure. Several systematic review articles on this topic found that interventions that promote muscle strengthening, such as cardiac rehabilitation and respiratory muscle training, have produced the most positive results in clinical trials (Buckholz and von Gunten 2009; Bausewein et al. 2008). Activities that promote energy conservation, such as the use of walking aids, have also been found to help reduce dyspnea. Although the literature lacks strong evidence that supports the benefit for complementary therapies, such as acupuncture, some of these therapies have shown promise (Buckholz and von Gunten 2009). Lastly, since the presence of anxiety is strongly associated with the dyspnea experience, interventions that support emotional and cognitive factors can be beneficial. This includes counseling, psychotherapy, and relaxation techniques. Eliciting changes in the patient's environment, such as ensuring enough surrounding open space and keeping the air well circulated through the use of a fan and/or open window, have been reported to promote comfort with breathing by patients (Dudgeon 2015). More large multi-site controlled trials that examine the benefits of these and other non-pharmacological therapies are needed.

4.5 Edema

Fluid overload associated with poor cardiac output and issues with perfusion can contribute to the development of edema and/or ascites in patients with advanced heart failure (Whellen et al. 2014). This can be very uncomfortable

and contribute to or worsen other symptoms, such as pain and shortness of breath (Adler 2009). Edema is especially prevalent in right-sided heart failure, which causes a buildup of blood behind the heart which precipitates increased systemic venous pressure (Katz and Konstam 2009). The presence of excess fluid in soft tissues causes swelling, which can be classified as pitting or non-pitting edema. "Cardiac edema" is edema that is most pronounced in the lower extremities in patients with right-sided failure (Katz and Konstam 2009). Chronic edema caused by an underlying illness can develop into lymphedema (Fu and Lasinski 2015).

Treatment for edema involves the administration of diuretic medications, elevation of the affected extremity and compression stockings (Adler 2009). Medications and foods that contribute to increasing levels of sodium and/or fluids should be avoided (Whellen et al. 2014). Evaluation of daily weights with subsequent titration of diuretic medications should also be part of the treatment plan.

4.6 Fatigue

Fatigue is one of the most common and chronic symptoms associated with many serious diseases. Research that has examined symptom clusters, which are described as "concurrent and related symptoms that may or may not have a common etiology" has found the presence of fatigue in 7 out of the 9 studies that were evaluated (Bookbinder and McHugh 2010). It is a common and prevalent symptom that is associated with heart disease, chronic obstructive pulmonary disease, cancer, renal disease, HIV/AIDS and multiple sclerosis (O'Neil-Page et al. 2015).

Two theoretical models have been reported in the literature that offers an explanation for the underlying pathophysiology of fatigue: the accumulation and depletion hypotheses. The accumulation hypothesis suggests that fatigue is caused by the body's inability to dispose of waste products that have accumulated in the body. Whereas the depletion hypothesis suggests the opposite; that the lack of certain substances that are vital for the body to function, are reduced or missing (O'Neil-Page et al. 2015). The presence of other co-morbidities, such as anemia, dehydration, cachexia, electrolyte imbalance, thyroid dysfunction and infection have also been identified as contributing factors associated with the development of fatigue (Adler 2009).

Palliative management of fatigue can be complex due to the multi-factorial components that may be involved. The first step is a thorough evaluation of fatigue severity, onset, duration, usual pattern or presentation, alleviating and exacerbating factors, and impact on functional abilities and quality of life (Yennurajalingam and Bruera 2007). There are several validated scales available to assist with the evaluation and diagnosis of fatigue including: the Multidimensional Fatigue Inventory, Multidimensional Fatigue Symptom Inventory, and the Edmonton Symptom Assessment Scale (Yennurajalingam and Bruera 2007). In palliative care, if reversal or discovery of the underlying condition causing fatigue is not possible, management should be aimed at treating the associated and distressing symptoms. This can include the management of pain, depression, delirium, and anorexia (Yennurajalingam and Bruera 2007).

Pharmacological management of fatigue includes the administration of corticosteroids, methylphenidate, or modafinil (O'Neil-Page et al. 2015; Yennurajalingam and Bruera 2007). Research has also found some benefit with the addition of megestrol, normally used to promote appetite, also improves fatigue and sense of wellness (Yennurajalingam and Bruera 2007). Non-pharmacological management includes the use of energy conservation, which was identified as the most frequently utilized treatment for fatigue (Yennurajalingam and Bruera 2007). Resistance training and exercise were also noted to have benefits (Yennurajalingam and Bruera 2007).

4.7 Insomnia

Insomnia and problems related to sleep are common among patients with advanced heart failure and are most often related to the presence of orthopnea or paroxysmal nocturnal dyspnea. Previous research found the prevalence of insomnia among patients with cardiac disease to be as high as 44% (Evangelista et al. 2009) with 50% of patients diagnosed with sleep disordered breathing, such as obstructive sleep apnea (Whellen et al. 2014). The primary treatment for patients with sleep disordered breathing is continuous positive airway pressure (CPAP). This therapy, however, may not be well tolerated by patients in advanced stages of the disease.

Palliative management of insomnia includes trying to remediate the underlying cause, if possible, and then focusing on alleviating any adverse effects. Pharmacological management could include medications used for anxiety/depression, such as benzodiazapines, if those symptoms are found to result from sleep deprivation. Low dose zolpidem can also be trialed for patients whose symptoms are affecting quality of life (Whellen et al. 2014). Providers should educate patients to be wary of side effects from these medications, particularly in older adults. Patients should be encouraged to maintain bedtime routines and to minimize noise and external lighting at bedtime. The room temperature should be tailored to individual patient preferences.

4.8 Pain

Patients with heart failure can be subject to experience various types of pain. Some pain can be related to their cardiac health, such as chest pain associated with angina, while others may be related to osteoarthritis or peripheral vascular disease. One study found 89% of end-stage heart failure patients have pain (Evangelista et al. 2009). Pain is classified by its etiology (somatic, visceral, or neuropathic) and also by pattern of presentation, which can be acute or chronic. (Coyle and Layman-Goldstein 2001).

Patients with heart failure should be asked about their current location of pain, duration, intensity, quality, aggravating and alleviating factors and current pain management regimen (End of Life Nursing Education Consortium (ELNEC) n.d.). Once the origin of pain is determined, the provider can determine the most optimal pain management plan for the patient. It is ideal to include both pharmacological and non-pharmacological interventions in the pain management plan. In palliative care, pain that is acute and determined to resolve in a short period of time is treated using a short-acting analgesic whereas pain that is chronic should include the use of both a long-acting and short-acting analgesic medication (End of Life Nursing Education Consortium (ELNEC) n.d.). Since the majority of patients with advanced heart failure are older adults, pain medications should be used according to the World Health Organization (WHO) three-step ladder for pain in adults (World Health Organization 2017b). The aim of pain management is to treat pain with the lowest type of analgesia that will mitigate the pain and limit unwanted side effects.

Opioid medications are the most widely used pharmacological treatment for patients who have moderate to severe pain (Adler 2009). Combination medications and non-steroidal inflammatory medications should be avoided in older adult patients, such as those with heart failure (Adler 2009). Although providers should use caution when prescribing narcotic medications, particularly in older adults because it may contribute to falls, delirium, and urinary retention (Eliopoulos 2014), the focus of palliative care is to improve quality of life, and the benefits for reducing symptoms should be weighed against any minimal risks.

4.9 Anxiety & Depression

The chronic and progressive nature of advanced heart failure includes periods of exacerbations when the disease worsens. The unpredictable nature of exacerbations can contribute to feelings of anxiety and depression among patients. Depression has been found to be present in 21–36% of patients with heart failure and with even greater prevalence among patients who have advanced disease (Adler 2009). The presence of depression and anxiety have been shown to correlate with greater symptom burden and more frequent hospitalizations (Goodlin 2009) and patients who report depression have greater fatigue and other symptoms than patients without depression.

The evidence suggests that many of the traditional medications used to treat depression can contribute to adverse effects in patients with heart failure. Selective serotonin reuptake inhibitors (SSRI's) can place patients at risk for fluid retention and/or hyponatremia and these medications can also take several weeks to be fully titrated (Goodlin 2009). Tricyclic antidepressants are another class of medications that can be used instead of SSRIs. They have however, been found to contribute to prolonged QT intervals at higher doses and also have a 1–2 week lead time for full titration to occur (Goodlin 2009). To date, the best evidence suggests the use of methylphenidate due to its minimal adverse effects with this patient population (Goodlin 2009). Benefit from this and/or other psycho-stimulant medications can be seen in 1–2 days rather than weeks, as with the before mentioned classes of medications. Benzodiazapines have also been found to be effective in reducing anxiety among patients with heart failure at any stage of the disease (Goodlin 2009).

Non-pharmacological interventions for depression and anxiety include measures aimed at providing emotional support, such as support groups and mindfulness education programs (Sullivan et al. 2009). These interventions promote patients to increase their sense of control related to heart failure symptoms, which can subsequently reduce feelings of anxiety and depression (Sullivan et al. 2009).

5 Quality of Life and Functional Status

Patients with advanced heart failure can experience a wide range of adverse and uncomfortable symptoms that accompany disease progression. This can significantly impact the quality of daily life and contribute to physiological, psychological and spiritual distress. Worsening of the heart also leads to functional limitations and disability which can both have a profound effect on patients and their caregivers. Limitations can include all of the activities of daily living (ADLs). There are six basic ADLs which are: bathing, dressing, eating, toileting, transferring (ambulating) and continence (Eliopoulos 2014). The symptoms associated with heart failure can impact any or all of the patient's ability to complete their ADLs. This can then contribute to other issues and concerns, which in turn can worsen the patient's overall health and well being. Additionally, loss of these functional abilities not only impact the patient, but their family members, many of whom may be the assisting the patient by providing informal care.

The loss of a patient's functional ability and subsequent loss of independence in being able to carry out the activities of daily living, are both losses that can contribute to feelings of grief. Grief is a universal experience that individuals go through when dealing with a loss. Although losses are often defined in terms of a loss of a family member or friend, non-human types of losses, such as loss of independence, can also precipitate feelings of grief (End of Life Nursing Education Consortium (ELNEC) n.d.).

5.1 Caregiver Support

There has been a multitude of research aimed at understanding the caregiver experience and interventions aimed at providing better support for this population. The burden associated with caregiving can impact both physical and mental health of caregivers, which can ultimately impact the care of the patient (Pressler et al. 2013). Caregivers may also experience a financial impact as a result of the time devoted to caregiving (Pressler et al. 2013). Caregivers for patients with heart failure have been found to experience increased levels of depression and anxiety and report decreased quality of life (Pressler et al. 2013).

Early intervention and assistance to the caregiver is vital because of the extended length of time that most caregivers will be providing care to their loved ones with heart failure. McMillan and colleagues conducted an intervention for the caregivers of hospice patients with advanced heart failure and found caregivers have greater benefit with early intervention rather than when their loved one was in the later stages of disease (McMillan et al. 2013).

6 Ethical Challenges

Patients who live with serious and progressive illnesses are often faced with making medical decisions as their illness worsens and they near the end of life. Some of these decisions involve a determination of what the patient wishes or wants done for them medically in the event they are no longer able to make decisions. As difficult as it is to engage in advance care planning, it is most ideal for the patient to make these decisions known before they become incapacitated (Martinez-Selles et al. 2017). This future care planning should ideally include discussion about patient preferences for resuscitation status, withholding and/or withdrawing care, artificial nutrition/hydration and use/discontinuation of device therapy (Martinez-Selles et al. 2017).

6.1 Resuscitation Status and Advance Directives

An advance directive is a legal document that states the types of medical care a patient wants in the event that they are no longer able to make their own decisions (Patients Rights Council 2013). Instituting a living will, identifying a health care proxy and designating a durable power of attorney for health care are three of the most common activities that can be done with advance care planning. These documents or designations enable the patient to identify their wishes for medical care beforehand and/or identify an individual to make those medical decisions on behalf of the patient (Patients Rights Council 2013).

Do Not Resuscitate (DNR)/Do-Not-Attempt Resuscitation (DNAR) In previous years, the acronym (DNR) was used for do-not-resuscitate, which meant that a patient elected to forgo medical intervention if they went into cardiopulmonary arrest (Breault 2011). Another acronym (DNAR), do-not-attempt resuscitation, has recently been added by the American Heart Association (Breault 2011). This is viewed as a less "harsh" term used for the decision to not intervene medically in the event a patient goes into cardiac arrest. If a patient has elected their resuscitation status to be DNR/DNAR, they have decided against initiation of cardiopulmonary resuscitation if they go into cardiac arrest. This includes the use of chest compressions, administration of cardiac medications and the placement of a respiratory/breathing tube (Breault 2011).

The majority of patients with advanced heart failure are older adults. Advanced age was found to be a factor associated with having poor outcomes with use of CPR (Berry and Griffie 2015). CPR was found to only be successful in about 18% of hospitalized patients (Berry and Griffie 2015) with an even lower success rate among patients with advanced illnesses, such as cancer or end stage heart failure.

Allow Natural Death (AND) Allow natural death is a term being used in some health care institutions in place of the traditional DNR/DNAR terminology. Patients who have an AND order want only comfort measures taken for symptom management as they go through the dying process (End of Life Nursing Education Consortium (ELNEC) n.d.). The goal of AND is to ensure that the patient is as comfortable as possible while allowing the natural process of dying to progress (End of Life Nursing Education Consortium (ELNEC) n.d.).

6.2 Withholding and Withdrawing Care

Withholding and/or withdrawing care is a controversial topic that has been debated in the literature (Manalo 2013). Both relate to the use of medical interventions at the end of life and can range from minor, such as the use of a non-life sustaining medication, to more complex, such as mechanical ventilation. Withholding medical care means that a medical treatment or intervention available is not initiated whereas withdrawing medical care denotes the cessation or removal of existing treatments that are already being used (End of Life Nursing Education Consortium (ELNEC) n.d.). The rationale behind withholding or withdrawing medical interventions is based on an evaluation of the benefits and burdens for the patient associated with the treatment. Sometimes treatments are determined to be futile in which patients do not receive any beneficial outcome from the intervention (Martinez-Selles et al. 2017). Some life-sustaining treatments could even worsen patients' suffering and decrease their quality of life.

Educating patients with advanced heart failure about illness progression and what they might expect is essential so that patients can identify goals of care. Any interventions used for the patient are solely for comfort or palliative care. This reinforces the importance of patients having an advance directive in place because this can help to decrease the initiation and use of futile medical care from the outset (End of Life Nursing Education Consortium (ELNEC) n.d.).

6.3 Artificial Nutrition and Hydration

Artificial nutrition or hydration (ANH) is defined as a medical intervention that delivers nutrition and/or hydration through artificial means. This involves administering food or fluids through a non-oral route, such as subcutaneously or intravenously (Arenella n.d.). According to the American Hospice Foundation, ANH should not be considered more than basic care rather than as a medical treatment (Arenella n.d.). Previous research suggests that dying patients derive some benefit from not being able to eat or drink. It has been found to reduce nausea and subsequent vomiting, shortness of breath and edema (Brody et al. 2011), some of which are common symptoms found among patients with advanced heart failure.

6.4 End of Life Decisions Regarding Device Therapy

An implantable-cardioverter-defibrillator (ICD) is a medical device utilized in patients at risk for sudden cardiac death with known ventricular tachycardia or fibrillation (American Heart Association n.d.). ICDs help to prevent cardiac arrest in patients at risk for ventricular arrhythmias and newer models can also dually serve as a pacemaker device (American Heart Association n.d.). Providers should discuss the benefits and risks associated with this device in patients who may be viable candidates for this option. Patients who already have an ICD whose illness has progressed and who are at the end of life should re-evaluate the usage of this device. The ICD should be deactivated in patients who are actively dying in order to avoid the receipt of multiple shocks which can contribute to great suffering and significant distress at the end of life (Martinez-Selles et al. 2017). The

deactivation of the ICD will not hasten death and patients should be informed that resynchronisation therapy will continue even in the absence of defibrillation. Conversations surrounding the discontinuation of an ICD device can be distressing and patients and families should be well supported during these difficult decisions. Management of symptoms using palliative care is especially important to be included in the treatment plan for patients who elect ICD deactivation (Martinez-Selles et al. 2017).

6.5 Active Death Help/Physician-Assisted Suicide

Active death help or physician assisted suicide is common terminology used to describe the purposeful ending of one's life (American Academy of Hospice and Palliative Medicine n.d.). A patient living with a terminal illness may request a prescription from a physician to obtain a lethal dose of medication which the patient will self-administer to end his/her life (American Academy of Hospice and Palliative Medicine n.d.). This differs from palliative care because its goal is to improve overall quality of life, through symptom management and relief of suffering without the intentional hastening of death (American Academy of Hospice and Palliative Medicine n.d.). Most professional associations governing medical providers in the realm of end of life care take a neutral or antagonistic position towards active death help (American Academy of Hospice and Palliative Medicine n.d.).

7 Clinical Practice Guidelines

According to the American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines (Yancy et al. 2017; Yancy et al. 2013), aggressive life-sustaining treatments and therapies should not be utilized in patients with advanced or end-stage heart failure who have refractory symptoms that are not responding to medical therapy. Patients who are in their last months of life should not receive treatments that do not contribute to their recovery or improve their quality of life. This includes intubation, the use of mechanical ventilation, and implantation of a cardiac defibrillator (Yancy et al. 2013). The focus of therapy for patients with stage D disease is to: control symptoms, reduce hospital admissions, improve health-related quality of life, and to establish end of life goals (Yancy et al. 2013). It is during this stage that the incorporation of palliative care or hospice should be initiated and the deactivation of ICDs should be instituted.

8 Conclusion

Palliative care should be incorporated into the management plan for patients with advanced heart failure. It has been demonstrated to help reduce severity of symptoms, encourage advance care planning and identification of goals of care and reduce patient and family distress affecting quality of life. Understanding the common illness trajectory for patients with heart failure can help providers inform patients about what to expect with illness progression. Palliative care can be initially be instituted alongside curative treatments, and its focus in the overall plan of care can increase as the patient's condition worsens and curative treatments offer less of a benefit. Clinical practice guidelines support the provision of palliative care as an option for the management of patients with ends-stage heart failure.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 313–325
DOI 10.1007/5584_2018_176
© Springer International Publishing AG 2018
Published online: 13 March 2018

Athlete's Heart and Left Heart Disease

Cesare de Gregorio, Dalia Di Nunzio, and Gianluca Di Bella

Abstract

Physical activity comprises all muscular activities that require energy expenditure. Regular sequence of structured and organized exercise with the specific purpose of improving wellness and athletic performance is defined as a sports activity.

Exercise can be performed at various levels of intensity and duration. According to the social context and pathways, it can be recreational, occupational, and competitive. Therefore, the training burden varies inherently and the heart adaptation is challenging.

Although a general agreement on the fact that sports practice leads to metabolic, functional and physical benefits, there is evidence that some athletes may be subjected to adverse outcomes. Sudden cardiac death can occur in apparently healthy individuals with unrecognized cardiovascular disease.

Thus, panels of experts in sports medicine have promoted important pre-participation screening programmes aimed at determining sports eligibility and differentiating between physiological remodeling and cardiac disease.

In this review, the most important pathophysiological and diagnostic issues are discussed.

Keywords

Athlete's heart · Cardiomyopathy · Exercise · Functional evaluation · Left ventricular hypertrophy · Physical training · Sports · Sudden cardiac death

Acronyms

AH	Athlete's heart
CVD(s)	Cardiovascular disease(s)
ECG	Electrocardiogram
ECHO	Echocardiography
HCM	Hypertrophic cardiomyopathy
LA	Left atrial/atrium
LV	Left ventricle/ventricular
PHA	Physical activity
pVO2	Peak oxygen uptake
SA	Sports activity
SCD	Sudden cardiac death

1 Introduction

Physical activity (PHA) comprises all muscular activities that require energy expenditure. Regular sequence of structured and organized exercise

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with the specific purpose of improving wellness and athletic strength is named sports activity (SA). Both PHA and SA can be performed at various level of intensity. According to the social context and pathways, sports can be differentiated into recreational, occupational, and competitive (Bauman et al. 2002).

In developed countries, daily time is more organized than in the past: people are spending more time in PHA, irrespective of how much they are used to do in the workplace. This is also a result of successful information campaigns promoting wellness, in an attempt to prevent the general population from cardiovascular diseases (CVD), reduce risk factors in young people and sarcopenia in the elderly, and promote rehabilitation after acute events (King et al. 2002; Bauman et al. 2002; Giles-Corti et al. 2005; Elferink-Gemser et al. 2011; Abdullah et al. 2016; Harada et al. 2017).

Although there is a general agreement on such benefits from SA, athletes may be subjected to traumas requiring a training break or showing disproportionate cardiac adaptation, unlikely with a physiological remodeling. Some of these conditions may be at risk for arrhythmias and sudden cardiac death (SCD), thus requiring differential algorithms, especially in young athletes (Asif and Drezner 2013; Corrado et al. 2003, 2011a, b; de Gregorio 2012; Risgaard et al. 2014; Link 2017). The fact that professional athletes may harbor potentially lethal heart diseases has been a matter of concern to the cardiovascular medicine. Astonishing SCD in the arena has a terrible impact on the general thought, at times encouraging media and newspapers to spread the message that SA can be risky. However, SA per se does not represent a risk factor for SCD but it can be triggering arrhythmic events in the presence of misjudged CVD, chest traumas or drugs abuse (Corrado et al. 2003, 2011a, b; Risgaard et al. 2014; de Gregorio and Magaudda 2017; Link 2017).

In general, the incidence of SCD in male athletes was largely unexplained until publication of an Italian study demonstrating that arrhythmogenic right ventricular cardiomyopathy and coronary anomalies are often responsible for a large number of events in apparently healthy athletes, in whom training burden and exercise intensity are important determinants (Corrado et al. 2011a, b). Also full-contact SAs can be life-threatening in male athletes (de Gregorio and Magaudda 2017).

More recently, a particular prognosticator has been identified based on cardiac magnetic resonance imaging. It has been demonstrated that athletes with right bundle branch block and ventricular arrhythmias may show a so-called "stria" pattern (subtle intra-myocardial mid-layer linear image of delay enhancement), as a consequence of (subclinical) acute myocarditis (Zorzi et al. 2016).

Therefore, pre-participation screening has become mandatory to recognise CV anomalies in both competitive and uncompetitive athletes. However, some criticisms have arisen about its cost-effectiveness, chiefly in those countries where screening does not have a reasonable economical coverage. The introduction of eligibility criteria has significantly diminished the number of athletes at risk of SCD but also increased the number of false positive verdicts (Corrado et al. 2003; de Gregorio 2012; Leikin et al. 2012; La Gerche and Heidbuchel 2014; Risgaard et al. 2014; Maron et al. 2016;).

Disqualification might have a destroying impact on professional athletes' career. To date, there is no legal precedent holding a physician liable for refusing or admitting an athlete. In a famous old lawsuit, some cardiologists were blamed of negligence because of misdiagnosed cardiomyopathy in a basketball player. Against another medical opinion that disqualified the athlete from competitions, the athlete played in spite of everything and died on the arena. The court, awkwardly, was unable to establish the case as malpractice (Mitten 1993).

Almost restrictive criteria have been adopted by the 2013 European Guidelines (Biffi et al. 2013a, b; Heidbuchel et al. 2013) for professional athletes. On the contrary, the 2015 American recommendations were less stringent due to the fact that incidence of SCD among young American athletes was as far as that achieved by European and Italian population registries, after the introduction of the pre-participation screening programmes (Maron et al. 2009, 2015; Leikin et al. 2012; Corrado et al. 2015).

However, studies carried out by the University of Padua (Italy) have shown the importance of nationwide clinical and electrocardiographic screening in all young sports players. Urinalysis, spirometry and exercise ECG test (and echocardiography, if necessary) are performed in competitive athletes only (Corrado et al. 2003, 2010, 2011a, b; Biffi et al. 2013a, b).

Pathophysiology of AH and differential diagnosis with left heart disease will be discussed in this review.

2 Classification of Sports

An ideal classification of SAs should endorse three important requirements: clarity, easy availability and precision. However, there is no agreement about which criteria should be used to classify individual characteristics and athlete's needs.

According to physiological standards, in 1969 Antonio Dal Monte proposed a classification based on the energy source of the muscular mass during exercise (anaerobic or aerobic), revised many times and then published in a book (Dal Monte and Faina 1999). From then, further innovative criteria have been proposed worldwide until publication of the recent US classification (Mitchell et al. 2005).

Sports disciplines are classified according to the cardiovascular involvement and muscle strength, which are both crucial determinants for sports eligibility. The American Task force included both static (measured as the progressive increasing in voluntary muscle contraction) and dynamic [gradual improvement in peak oxygen uptake (pVO2) with submaximal muscle contraction] components in competition. The rise in pVO2 is expression of increased cardiac output and global heart efficiency. As the static component increases, blood pressure and peripheral resistances increase as well, both resulting in a higher cardiovascular demand. This classification is almost clear, but it can fail to classify highly trained athletes performing strong disciplines (Mitchell et al. 2005; Levine et al. 2015).

In a different way, the Italian task force (Biffi et al. 2013a, b) approved a four-task classification of SAs, as follows:

(a) **Group A,** neurogenic disciplines with mild increase in heart rate and trivial effects on cardiac output and blood pressure, due to predominant emotional involvement of the athlete (e.g. bowling, golf, shooting, recreational fishing);
(b) **Group B** disciplines are characterized by a greater increase (even submaximal) of heart rate, with minor impact on the peripheral vascular resistances and blood pressure (e.g. riding, aviation, motorsport, skydiving);
(c) **Group C** consists of disciplines characterized by prevalent blood pressure rising than cardiac output. Thus, heart rate and peripheral resistance range from medium to maximal (e.g. climbing, athletic, cycling, swimming, skiing, surfing, artistic gym).
(d) **Group D** includes all sports with mid-high cardiovascular involvement. This subgroup includes two subsections according to cardiovascular parameters:
   – **D1)** variable trend of heart rate, peripheral resistance, and cardiac output (e.g. soccer, football, water polo, volleyball, hockey).
   – **D2)** characterized by a regular increase in heart rate, blood pressure and a decrease in peripheral resistance (e.g. biathlon, rowing, cycling, skiing, swimming).

SAs can also be classified according to the type and intensity of exercise performed, being divided into a predominant dynamic (isotonic) or static (isometric) component. Dynamic exercise usually consists with forces developing from changes in muscles length and joint movements. Static exercise chiefly consists of intramuscular work force devoid of significant changes in fibre length or joint movements. However, isotonic and dynamic exercise does not necessarily mean aerobic exercise, because aerobic or anaerobic characteristics depend on intensity, duration and

pulmonary capacity. High-intensity static exercises are usually anaerobic, while high-intensity dynamic exercises can be performed in either aerobic or anaerobic modality. The aerobic threshold, in fact, corresponds to lactate serum concentration of at least 2 mmol/L, whereas the anaerobic threshold of 4 mmol/L. Some SAs, like skiing, running and soccer, are highly dynamic, but often above the aerobic threshold. The cardiovascular demand is challenging because of mixed dynamic and static components. Aerobic and anaerobic stages can be unpredictably coexisting at the same time. The interval between the aerobic and anaerobic threshold defines such activity as intermediate with a mild increase in blood lactate which does not limit athletic performance (Jetté et al. 1990; Levine et al. 2015).

3 Training Burden

Despite accuracy is required, each classification of sports disciplines should be as flexible as possible. In fact, athletes from the same category can deserve really different completion and placement. Sports practice has important physical effects with an involvement of almost all parts of the body, mainly of the CV and respiratory systems.

Physical training is a process whereby sportive performances are maximized and improved: it consists of repetitive and/or continuous exercise aimed at enhancing performance, resistance, ability, and delaying fatigue. Athletes improve their performance by increasing frequency, duration and intensity of training.

Sharma et al. (2000) established a minimum burden of 5 h per week in organized exercise sessions for identifying trained athletes.

Besides, the scientific approach to define the training burden requires an objective and quantifiable method. In particular, the training load has been defined as "external" when the amount of exercise is unconditioned by the individual perception of stressful activity. On the contrary, an "internal" workload concerns exercise-induced physiological/psychological internal environment. It was also termed as the "milieu interieur" in biological homeostasis by Bernard (1966) and then by Noble (2008).

Likewise, the "external" perception does not represent the actual workload imposed by exercise. In fact, two athletes performing the same exercise may perceive a different feeling of effort according to their strength. On the other hand, similar competence may lead to different game performance and ensuing physical stress, based on training and genetic background (Hopkins 1991; Noble 2008; La Gerche et al. 2014).

Therefore, the correct recognition of training burden remains challenging for physicians. However, it appears to be a critical issue when deciding whether the athlete has adequate, insufficient or excessive cardiac adaptation to exercise. In fact, this is such a necessary background when differentiating physiological from pathological LV remodelling (Fig. 1).

4 Cardiac Adaptation to Exercise (Athlete's Heart)

Changes in cardiac morphology and function are physiological responses to regular exercise. The original definition of AH dates back to late nineteenth century, when a dilatation of the heart was seen in Nordic skiers and crew runners from a university college (Darling 1899).

During the same period, Morganroth and colleagues described two types of left ventricular (LV) remodeling by using M-mode echocardiography, as follows: a) concentric hypertrophy (LV wall thickness greater than the chamber volume), as the consequence of strength exercise, and b) eccentric hypertrophy (LV dilatation greater than wall thickness) after endurance exercise. The stimulus for hypertrophy was attributed to blood pressure rise with increased peripheral vascular resistance during strength exercise, both resulting in high ventricular systolic stress. On the contrary, the blood volume overload during endurance exercise may lead to wall stretching and fibrils' elongation, and then to LV dilatation (Morganroth et al. 1975).

It is important to understand the concept of ***LV hypertrophy*** that corresponds to an increase in

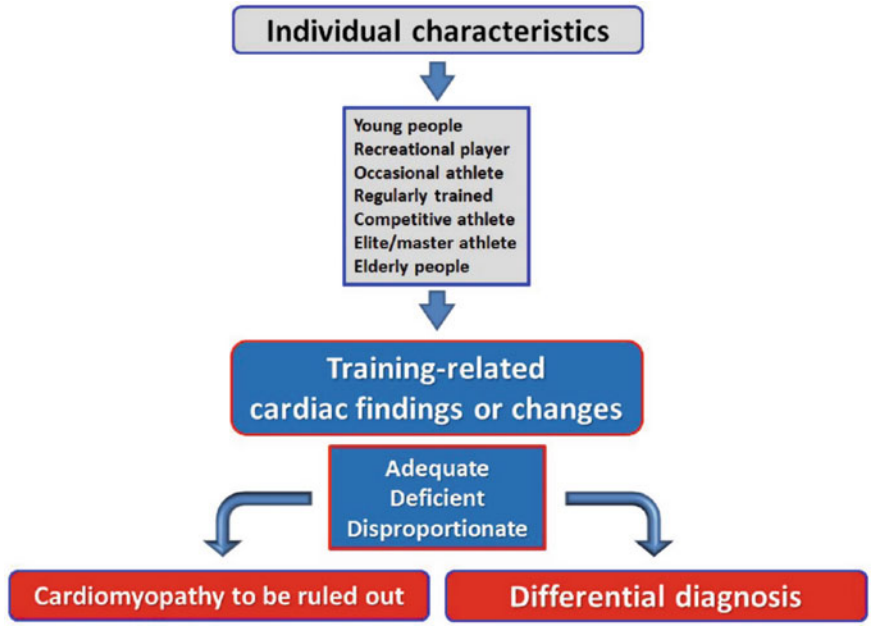

Fig. 1 General approach to the athlete for differentiation between AH and cardiac disease

LV mass. Thus, the term hypertrophy should indicate a change in muscle mass and/or chamber volume. However, generally speaking, it means LV wall thickening.

Based on the Laplace's equation

$$\text{LV systolic stress} = \frac{(\text{LV radius}^* \text{SBP})}{\times/2^* \text{LV wall thickness}}$$

the increase in LV wall thickening counteracts the internal LV systolic stress. This is a natural pathophysiological model of compensatory hypertrophy. However, clinical concern arises when explaining such adjustments in resistance athletes who usually perform different training modality. Moreover, due to a decrease in both cardiac output and systemic vascular conductance, post-exercise hypotension may occur in some individuals, as a consequence of central disregulation, and this further has an influence on the LV remodeling (Romero et al. 2017).

More recent theories suggest that regularly trained athletes show a well-balanced LV remodeling (Haykowsky and Tomczak 2014). However, approximately 30% of Olympic endurance athletes (eg. marathoners) show biventricular dilatation, sometimes belonging to the "grey-area" subset. Scuba apnea divers may present with a mild dilatation of the ventricular chambers, possibly associated with transient wall motion abnormalities due to their performance in hypoxic conditions (de Gregorio et al. 2006; Gempp et al. 2013).

Myocardial hypertrophy is more evident in master Afro-American than Caucasian athletes, irrespective of their training modality (Beaudry et al. 2016; Oláh et al. 2016; D'Ascenzi et al. 2017).

In fact, ethnicity is a well documented determinant of cardiac remodelling, especially in younger athletes: different blood pressure modulation, endothelial function, arterial stiffness, angiotensin-converting enzyme polymorphisms and insulin-like growth factor-1 expression, are all related to ethnicity and can lead to a different adaptive response to exercise. Accordingly, the prevalence of repolarisation anomalies (at times, surprising) is more frequent in black athletes (Prior and La Gerche 2012; Drezner et al. 2013; Maron et al. 2016; Dores et al. 2017; Sharma et al. 2017). ST-T wave changes suggestive of LV hypertrophy have also been found in

240 highly-trained black women (Rawlins et al. 2010).

ECG findings suggestive of LV hypertrophy, left atrial and right atrial enlargement are so common among young athletes and require careful interpretation because they can be expressions of a "juvenile pattern" (Anderson et al. 2014; Leikin et al. 2012; Speranza et al. 2014).

Based on current knowledge, limits for normal LV wall thickness have been established in different groups of athletes: trained adolescents usually show a maximum wall thickness of 12–13 mm (generally limited to ventricular septum), whereas 15–16 mm in those aged between 25 and 30 (Table 1). Intermediate (young) athletes with 13–15 mm septum thickness enter the "grey-zone" of hypertrophy and need further differentiation with hypertrophic cardiomyopathy (HCM). Because of hormonal characteristics, cardiac remodeling is trivial in women, and a septum wall thickness > 13 mm is considered such an exceptional finding (Maron et al. 2009; Corrado et al. 2010; Prior and La Gerche 2012; D'Ascenzi et al. 2017).

Furthermore, the atrial chambers tend to increase in size with exercise. Mild enlargement occurs more frequently in young and highly-trained athletes. Atrial enlargement can be suspected at ECG and diagnosed by echocardiography. Even if the left atrial (LA) diameter has been the unique measurement to consider in the majority of athletes, recent evidences suggest that LA volume corrected for body surface area should be preferred (Kebed et al. 2017).

Pelliccia and collaborators (2005) found an enlarged LA in about 30% of athletes, but this finding was not suggestive of pathological remodelling. More recently, D'Andrea et al. (2010) also reported mild LA dilatation (29–33 mL/m^2) in 24% of 615 endurance athletes, whereas it was moderate ($\geq$ 34 mL/m^2) only in 3% of cases, largely commensurate to the LV end-diastolic volume.

As compared to hypertensive patients with similar atrial chamber enlargement, a normal LA wall deformation (reservoir function) has been demonstrated in trained athletes by strain-echocardiography (Gjerdalen et al. 2015; D'Ascenzi et al. 2016). However, a higher incidence of atrial fibrillation has been reported in some strained athletes. Arrhythmic crisis usually begins at night or after meals, possibly associated with changes in vagal tone. However, atrial fibrillation in the athlete is typically short-termed. Length of training (eg. in veteran athletes), recurrence of premature atrial beats, autonomic nervous system and chronic structural changes following heavy training have been identified as potential triggers (Hubert et al. 2018).

5 Athlete's Heart or Cardiomyopathy?

Beneficial effects of PHA on the heart have been well substantiated in the literature, and training is an essential part of cardiac rehabilitation. However, studies have questioned this paradigm. A potential cellular damage has been seen after exhaustive exercise, and some mechanisms have been also discussed (Ostojic 2016).

Physiological LV hypertrophy should not be associated with myocyte structural anomalies or death. However, intense and lengthy exercise can lead to myocardial inflammation and fibrosis in endurance athletes free of heart disease before competition (La Gerche et al. 2012). Conversely, cardiomyocyte inflammation and myocardial fibrosis are representative of pathological hypertrophy and proceed along with functional decompensation over time. To explain abnormal findings in the athlete, an "ischemic core" hypothesis has been made: the cardiomyocytes would become ischemic when their surface exceeds the distance across which the O_2 diffuses down its concentration gradient from adjacent capillaries. This mechanism, promoted by reiterated intense training, may be leading to spot cellular death and subsequent contractile depression (La Gerche et al. 2012; Ostojic 2016; D'Ascenzi et al. 2017).

A recent study was carried out to assess changes in cardiac troponin I levels and the main biomarkers of skeletal muscle damage after an uphill-only marathon (Supermaratona dell'Etna, Sicily, Italy, 43 km, from ground to 2850 m) and any possible relationship with

Table 1 Markers suggestive of non-physiological left heart remodeling, requiring further evaluation

Findings	Notes
Family history of HCM or SCD	Sudden cardiac death in relatives should be carefully verified and confirmed. Only arrhythmic sudden death or fatal stroke can be related to HCM.
ECG: *Typical pattern of hypertrophy or pathological Q waves (pseudo-necrosis)*	Q waves without previous myocardial infarction can be seen in individuals with either HCM or dilated cardiomyopathy.
ECG: *Negative T waves (other than precordial leads V1 and V2) or high-voltage positive T waves*	
ECHO: *LV wall thickness*	Asymmetric septal, posterior-lateral wall or apical wall hypertrophy is such an unusual finding.
≥ 15 mm (elite/master athletes aged > 30 years)	
≥ 13 mm (elite young athletes aged 20–30 years)	
≥ 12 mm (young women OR young member of a HCM family)	
ECHO: *LV antero-posterior diameter < 45 mm or LV volume index < 50 ml/m^2, and/or narrow outflow tract*	Dynamic obstruction is a typical feature of HCM
ECHO: *Atrial enlargement (>34 cm/m^2)*	Parasternal longitudinal diameter > 40 mm has been demonstrated to be a poor prognostic marker in young patients with HCM, but it can also be found in healthy athletes
ECHO: *Diastolic dysfunction and/or impaired global longitudinal strain (GLS)*	There is no defined GLS cut-off value in athletes suspected to have HCM. In some studies, it was > − 16%.
ECHO: *LV dilatation > 60 mm or > 75 ml/m^2, especially if associated to wall motion anomalies*	Prior myocarditis, familiar dilated cardiomyopathy and coronary anomalies should be ruled out
FOLLOW-UP: *Unmodified wall thickening and ECG findings after detraining*	Also in young patients with HCM, detraining can lead to a decrease in wall thickness and partial normalization of T waves
CARDIOPULMONARY TESTING: *Peak VO_2 < 45 ml/kg/min or < 110% of predicted*	Trained athletes usually show peak VO_2 greater than 45ml/kg/min
CARDIAC MRI: *wall thickness > 15 mm whether associated with delay enhancement or ischemic pattern*	Delay enhancement can be expression of acute myocardial injury (oedema) or chronic fibrosis in patients with heart disease
EXERCISE-ECG: *sign of myocardial ischemia, angina, arrhythmias, or poor systolic pressure rising*	Ischemia can be expression of either coronary anomalies (e.g. tunnelled arteries) or atherosclerosis, even in apparently healthy athletes
HOLTER-ECG: *frequent premature beats, sustained or nonsustained ventricular tachicardia*	

ECG electrocardiogram, *ECHO* echocardiography, *GLS* global longitudinal strain, *HCH* hypertrophic cardiomyopathy, *LV* left ventricle/ventricular *SCD* sudden cardiac death

athletes' physiological parameters. Mean troponin I levels increased significantly in all athletes (mean + 900%), and in 52% of them values were over the normal range, indicating that uphill-only marathon may dramatically increase cardiac and skeletal muscle blood biomarkers of injury, unrelated with common physiological cofactors like age, body mass index, VO2max and training status (Da Ponte et al. 2018).

A particular clinical picture related to SA is the LV noncompaction. It has been described in the general population and also in endurance athletes, as a rare genetic disorder. ***Left ventricular noncompaction*** is characterized by endomyocardial trabeculations and deep recesses due to abnormal embryology of the heart, which lead to a significant (more than 50%) reduction in the compacted layer of the myocardium. As a consequence, some LV wall segments are thinner and trabeculated than the rest of the myocardium, gradually losing their contractile function. In fact, depending on the extent of the noncompacted layer, this anomaly consists with a continuum in LV dysfunction from

asymptomatic (and benign) picture to advanced heart failure with arrhythmic complications. Trabeculations, without any other features of noncompaction or ECG repolarization changes, can be found as a transitory finding in highly trained athletes, especially when a disproportionate preload is imposed by exercise. As per usual, this form of noncompaction reverses with detraining (de Gregorio et al. 2008; La Gerche et al. 2012; Gati et al. 2013; Poscolieri et al. 2014; Dores et al. 2015).

Overall, the most important task for physicians is to differentiate AH from all forms of pathological hypertrophy or dilatation (Table 1 and Fig. 2).

Athlete's heart usually consists of a balanced increase in LV wall thickness and chamber volume, associated with possible mild atrial chambers enlargement but normal or supranormal resting function (Beaudry et al. 2016).

Of note, from large athlete populations we learned that all ventricular wall segments (mainly the septum) are mildly thickened in healthy athletes, whereas isolate apical, inferior or lateral wall hypertrophy is unusual. In these cases, differential diagnosis needs an ECG and echocardiogram, and, at times, cardiac magnetic resonance imaging, to be performed. Differentiation of AH from HCM usually depends on LV wall thickness being in the ambiguous "grey-zone" of hypertrophy (13–15 mm in male and 12–13 mm in female athletes, aged 18–30 years).

The dilemma can be resolved by applying consolidated algorithms, like small LV end-diastolic cavity (<45 mm), diastolic dysfunction, impaired LV strain, atrial dilatation, which are summarized in Table 1 and Fig. 2. However, identification of sarcomeric gene mutation and family history of cardiomyopathy are potential markers of HCM. Individuals with a LV hypertrophy within the grey-zone should observe a 3-month detraining period at least to discriminate between AH (normalization of wall thickness, about 2–3 mm less, and ECG findings) and HCM (persistence of such anomalies). Electrocardiographic abnormalities (i.e., increased R- or S-wave voltages, small Q waves, and repolarisation abnormalities) are frequently seen in healthy young athletes. According to the most recent guidelines, a careful interpretation of the ECG is encouraged in the presence of widespread negative T-waves (more than in the precordial leads V1-V2). Of note, the coexistence of systemic hypertension should also be considered as a confounder (Corrado et al. 2010; Borjesson and Dellborg, 2011; de Gregorio 2012; Calore et al. 2016; Sharma et al. 2017; Zorzi et al. 2017).

Howsoever, HCM remains one of the main causes of SCD among young athletes in the U.S.A. (Maron et al. 2016). Although less challenging than HCM, dilated cardiomyopathy must be differentiated from AH when LV end-diastolic diameter is >65–70 mm (normal finding in less than 15% of athletes). To find a normal LV ejection fraction with no wall motion anomalies generally rule out a pathologic dilatation. As aforementioned, cardiac magnetic resonance and/or computed tomographic scan allow recognising myocardial oedema, ischemia and/or fibrosis as expressions of ischemic heart disease, dilated cardiomyopathy or previous myocarditis (Spence et al. 2011).

6 Conclusions

Regular exercise is responsible for cardiac chamber remodeling (AH) which includes mild LV hypertrophy or dilatation, atrial remodeling and fine modification of the myocardial structure. This is a benign condition and does not require medical treatment. However, an increase in LV mass can also be due to non physiological conditions, such as hypertensive heart, HCM, dilated cardiomyopathy or storage disease. To discriminate between AH and these latter conditions is a crucial step in order to reduce adverse clinical outcomes in athletes. One of the most innovative developments in prevention of SCD is the recent portable ECG technology. The US Food and Drug Administration approved the use of a mobile heart monitoring. The smartphone's app holds an algorithm alerting the patient when an abnormal heart rate or rhythm is detected. Thanks to a wireless connection, the ECG trace can be shared with referral physicians or the hospital. In a recent study, this app was

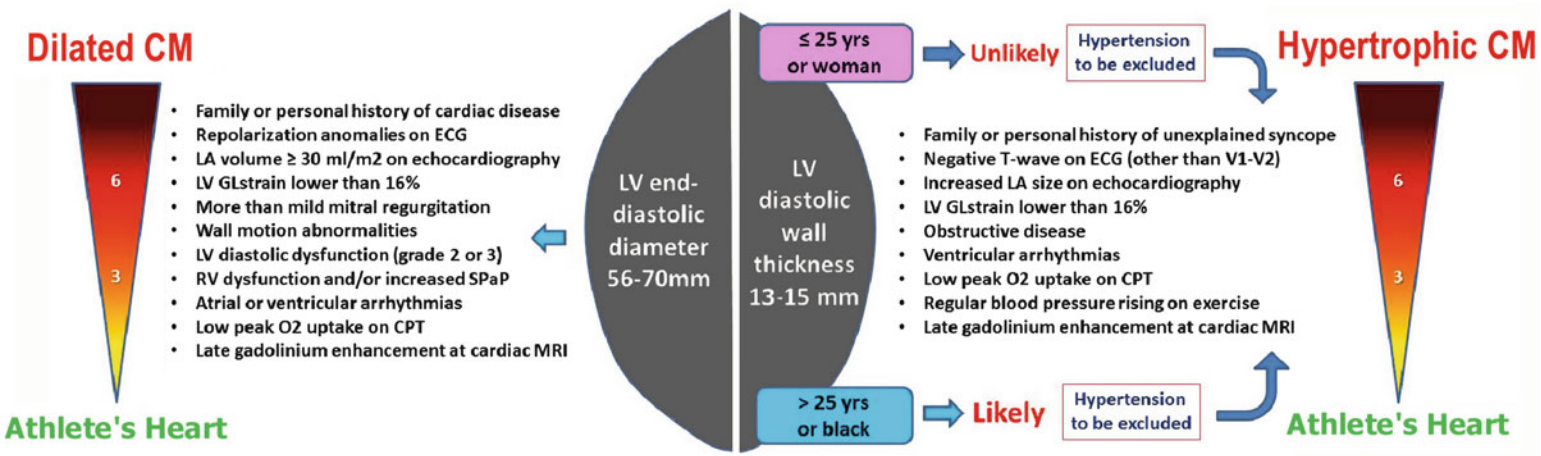

Fig. 2 Differential criteria based on the most important studies aimed at making diagnosis of dilated or hypertrophic cardiomyopathy (CM) in young athletes classified within the grey-area of LV hypertrophy. There are no cut-off values, but all these items have to be considered as a continuum between athlete's heart (AH) and CM

In both dilated and hypertrophic CM, systemic hypertension must be ruled out. CPT, cardiopulmonary testing; GL, global longitudinal; LA, left atrial/atrium; LV, left ventricle/ventricular; MRI, magnetic resonance imaging. Likely and unlikely refer to presence of LV wall thickness of 13 to 15 mm

>99% specific for atrial fibrillation (Haberman et al. 2015).

In spite of current knowledge, some (young) athletes may get a challenging diagnosis, even if advanced technologies are carried out. In such cases, generalists, cardiologists, internists or sports physicians are called to qualify them for competitive SA, but overdiagnosis of cardiac disease can be detrimental to the interest of professional athletes, with ensuing avoidable removal from competitive sports, and loss of psychologic investment and economic opportunities. However, a do-nothing attitude or missing diagnosis of potentially life-threatening CVDs is disappointing and dangerous as well.

Conflict of Interest None to declare

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 327–351
DOI 10.1007/5584_2018_146
© Springer International Publishing AG 2018
Published online: 7 February 2018

Central Sleep Apnea with Cheyne-Stokes Breathing in Heart Failure – From Research to Clinical Practice and Beyond

K. Terziyski and A. Draganova

Abstract

Characterized by periodic crescendo-decrescendo pattern of breathing alternating with central apneas, Central sleep apnea (CSA) with Cheyne-Stokes Breathing represents a highly prevalent, yet underdiagnosed comorbidity in chronic heart failure (CHF). A diverse body of evidence demonstrates increased morbidity and mortality in the presence of CSB. CSB has been described in both CHF patients with preserved and reduced ejection fraction, regardless of drug treatment. Risk factors for CSB are older age, male gender, high BMI, atrial fibrillation and hypocapnia.

The pathophysiology of CSB has been explained by the loop gain theory, where a controller (the respiratory center) and a plant (the lungs) are operating in a reciprocal relationship (negative feedback) to regulate a key parameter (partial pressure of carbon dioxide (pCO_2)). The temporal interaction between these elements is dependent on the circulatory delay. Increased chemosensitivity/chemoresponsiveness of the respiratory center and/or augmented ascending non- CO_2 stimuli from the C-fibers in the lungs (interstitial pulmonary edema), overly efficient ventilation when breathing at low volumes and prolonged circulation time are involved. An alternative hypothesis of CSB being an adaptive response of the failing heart has its merits as well. The clinical manifestation of CSB is usually poor, lacking striking symptoms and complaints. Witnessed apneas and snoring are infrequently reported by the sleep partner. Sometimes patients may report poor sleep quality with frequent awakenings, paroxysmal nocturnal dyspnea and frequent urination at night. Standard instrumental and laboratory studies, performed in CHF patients, may present clues to the presence of CSB. Concentric remodeling of the left ventricle and dilated left atrium (echocardiography), high BNP and C-reactive protein levels, increased ventilation-carbon dioxide output ($VEVCO_2$) and lower end-tidal CO_2 (cardiopulmonary exercise testing), reduced diffusion capacity (pulmonary function testing) and hypocapnia (blood-gas analysis) may indicate the presence of CSB.

CSB and cardiovascular disease are probably linked through bidirectional causality. Cyclic variations in heart rate, blood pressure, respiratory volume, partial pressure of arterial oxygen (pO_2) and pCO_2 lead to sympathetic-adrenal activation. The latter worsens ventricular energetism and survival of cardiomyocytes and exerts antiarhythmogenic effects. It causes cardiac remodeling,

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potentiating the progression and the lethal outcome in CHF patients. Several treatment modalities have been proposed in CSB. The most commonly used are continuous positive airway pressure (CPAP), adaptive servoventilation (ASV) and nocturnal home oxygen therapy (HOT). Novel therapies like nocturnal supplemental CO_2 and phrenic nerve stimulation are being tested recently. The current treatment recommendations (by the American Academy of Sleep Medicine) are for CPAP and HOT as standard therapies, while ASV is an option only in patients with EF > 45%. BPAP (bilevel device) remains an option only when there is no adequate response to previous modes of treatment. Acetazolamide and theophylline are options only after failing the above modalities and if accompanied by a close follow-up.

Keywords
Heart failure · Cheyne-Stokes breathing · Central sleep apnea · CPAP · Home oxygen therapy · Loop gain · Pathophysiology · Controller gain · Plant gain · Circulatory delay

1 Historical Perspective

In 1818 Dr. John Cheyne (1818) published a paper "A case of Apoplexy", where he described a specific breathing pattern which he monitored in a patient, suffering from heart failure and a neurologic disorder, without linking it to a specific etiology. Thirty-six years later, in 1854, Dr. William Stokes (1854) published a description of a disturbed breathing pattern in a patient with a "fat degeneration of the heart" and aortic valve defect, emphasizing the role of the cardiac disorder. These two papers present the first scientific description of the periodic breathing, which later became well-known as Cheyne-Stokes breathing.

Despite almost 200 years of history, at present the CSB invokes a vivid contrast between its high social-economic and medical value and still insufficient understanding and recognition of the problem. Its importance is defined by the high prevalence (of heart failure and CSB) among the population, as well as by the negative impact it may imply on the prognosis of heart failure.

2 Definition

Central sleep apnea (CSA) with Cheyne-Stokes Breathing (CSB) is the most common of 8 types of central sleep apnea, according to the newest version of the international classification of sleep disorders (ICSD-3) (AASM 2014). It is usually associated with chronic heart failure (CHF).

Shorter cycle length indicates a different type of CSA (AASM 2014). A typical representation of CSB is shown on Fig. 1. Alternatively, CSB may present with central hypopneas, instead of apneas.

> CSB is characterized with periodic crescendo-decrescendo pattern of breathing alternating with central apneas with a cycle length > 40 s (most commonly 45–60 s). (AASM 2014)

3 Diagnostic Criteria (ICSD-3) (AASM 2014)

According to ICSD-3, the diagnosis CSA with CSB should satisfy the following criteria: the presence of symptoms (A) OR atrial fibrillation/flutter, congestive heart failure, or a neurologic disorder (B) AND specific polysomnography (PSG) characteristics (C) AND the disorder is not better explained by another cause (D).

The symptoms criterion (A) includes one or more of the following: sleepiness; difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep; awakening short of breath; snoring; witnessed apneas.

PSG findings (C) should present ALL of the following: >5 central apneas and/or central hypopneas per hour of sleep; central events are >50% of all events; the pattern of ventilation

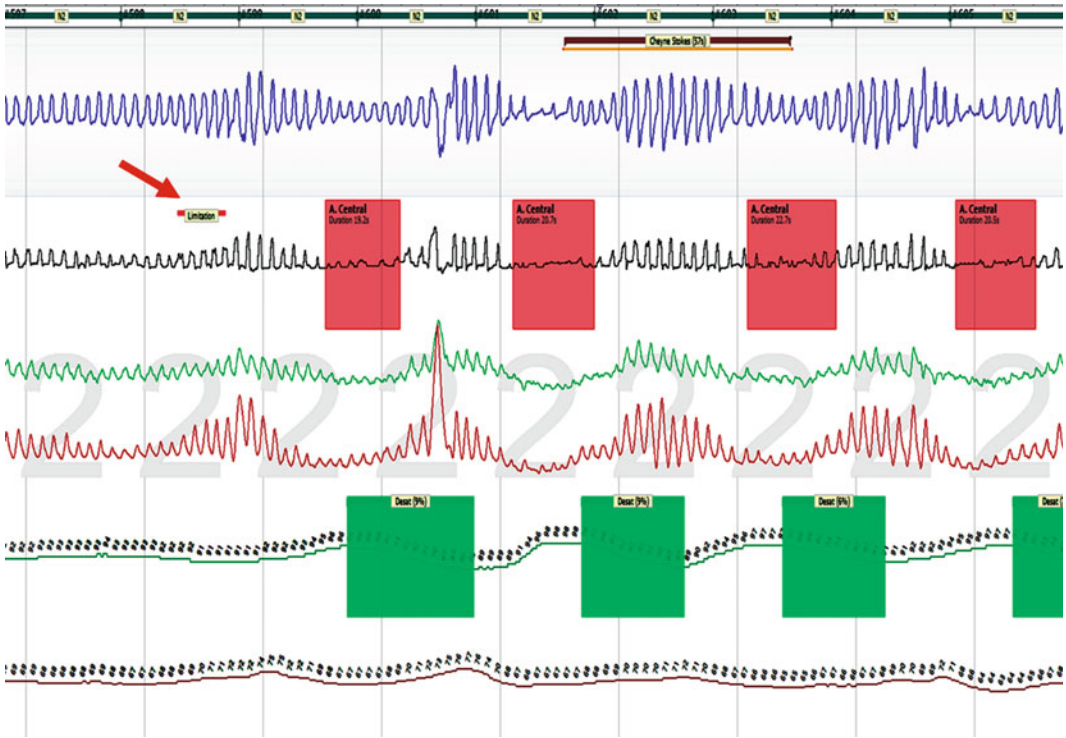

Fig. 1 A typical presentation of CSB. 5-min sample of the "ventilatory part" of a polysomnography (thermistor, nasal cannua, thoracic and abdominal belts, oxygen saturation, heart rate – from top to bottom). Crescendo-decrescendo pattern of ventilation is observed, mirrored by respective fluctuations in effort and followed by desaturations. The length of a single cycle is about 55 s falling within the definition for CSB. Similar variability in heart rate is observed. One may notice the flattening of the nasal flow (red arrow), preceding the start of the CSB sequence
Legend: *CSB* Cheyne-Stokes breathing

meets criteria for CSB. PSG findings are defined according to the newest AASM criteria (Berry et al. 2012; Iber 2007).

An important remark is that the diagnosis CSA with CSB does not exclude the diagnosis OSA (AASM 2014).

4 Prevalence

The prevalence of CSB in CHF is strikingly high, but the condition is being seriously underdiagnosed. Though, a big body of data in support of that has been accumulated, the numbers reported by different studies are varying in a wide range due to the lack of coherence in the methodology, population characteristics (severity of HF, medication therapy, atrial fibrillation, body-mass index (BMI), age), diagnostic and severity criteria, scoring criteria, etc. The difficulties in differentiating central from obstructive hypopneas (Krawczyk et al. 2013) and the frequent coexistence of central and obstructive events in a single CHF patient (Javaheri et al. 1998; Sin et al. 1999; Tkacova et al. 2006) may explain the discrepancy in the ratio OSA/CSA in these studies. The most important of them are presented on Fig. 2.

Furthermore, elements of Cheyne-Stokes breathing pattern with a gradual increase and decrease of ventilation may be present during obstructive events (Tkacova et al. 2006). Tkacova et al. hypothesize that both breathing disturbances are a part of a vicious cycle, involving cardiovascular, pulmonary and autonomous mechanisms, contributing to the progressive heart decline. In general, the obstructive events are concentrated during the first half, while the

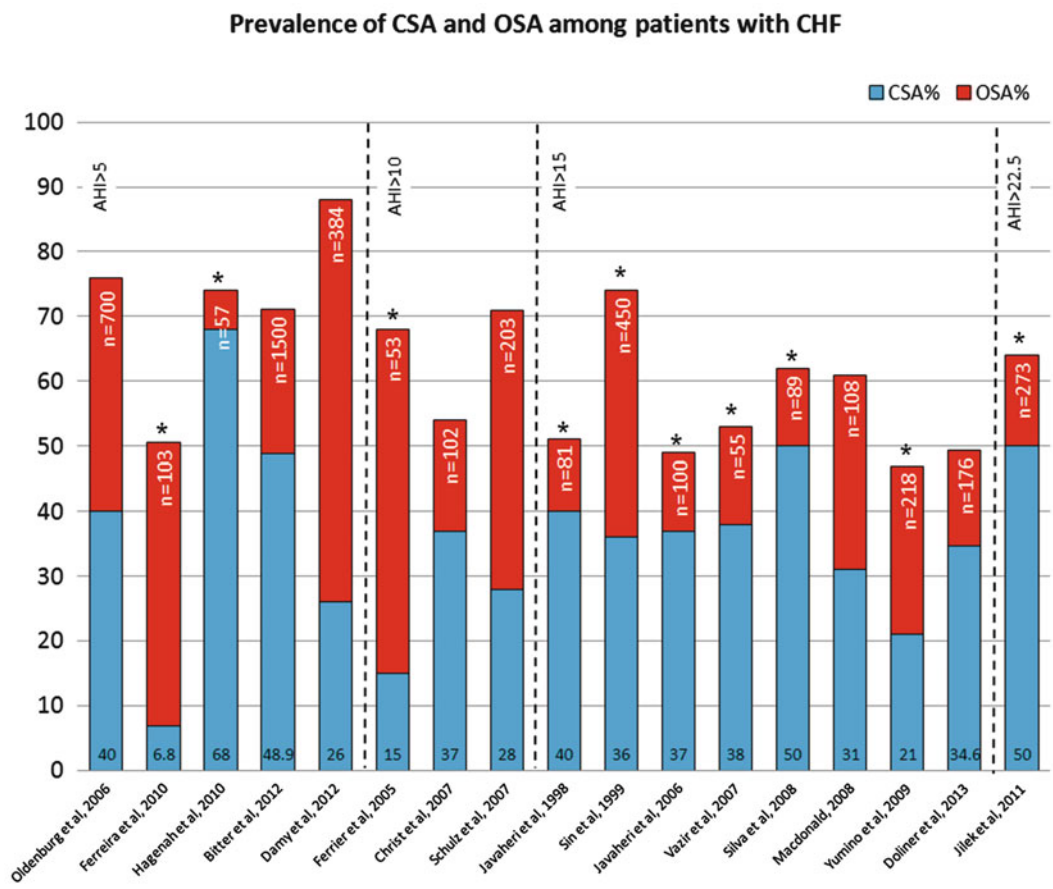

Fig. 2 Prevalence of CSA and OSA among patients with CHF (Javaheri et al. 1998; Sin et al. 1999; Oldenburg et al. 2007; Ferreira et al. 2010; Hagenah et al. 2010; Bitter et al. 2012; Damy et al. 2012; Ferrier et al. 2005; Christ et al. 2007; Schulz et al. 2007; Javaheri 2006a; Vazir et al. 2007; Silva et al. 2008; MacDonald et al. 2008; Yumino et al. 2009; Dolliner et al. 2013; Jilek et al. 2011)
Legend: *CSA* central sleep apnea, *OSA* obstructive sleep apnea, *CHF* chronic heart failure, *AHI* apnea-hypopnea index
Blue bars represent CSA frequency in % (shown as a number at the bottom of the respective bar) of the total number of CHF patients (n = at the top of each bar) in the study (indicated below). Red bars stand for OSA frequency. Combined bar height (blue + red) corresponds to the frequency of sleep disordered breathing in each study. * indicates polysomnography (gold standard study), while its absence – polygraphy (no sleep data). The studies are grouped (vertical dotted line) by the AHI threshold for diagnosing sleep apnea.

central events – during the second half of the night (Tkacova et al. 2001). The shift OSA-CSA is accompanied by a decrease in the arterial partial pressure of CO_2 (pCO_2), increase in the circulation time and duration of periodic breathing cycles. The inversed relation between the latter and the cardiac output (Hall et al. 1996) suggests that the shift from OSA to CSA within a single night is associated with an analogical impairment of the cardiac function, characterized by an increase in the left ventricular filling pressure and a decrease in the cardiac output (Tkacova et al. 2006). The increased venous return due to the rostral fluid shift in supine position is probably a significant contributor to that effect.

5 Etiology

By definition (AASM 2014) CSB has been linked to the presence of CHF.

However, a significant proportion of the CHF patients do not develop CSB. Several risk factors for its occurrence have been identified so far.

1. Age

Patients with CHF and CSB are generally older than CHF patients without the disorder (Bitter et al. 2012; Ancoli-Israel et al. 2003; Javaheri et al. 2017). However, in the study of Bitter et al. CSA regression analysis excluded age as an independent risk factor (Bitter et al. 2012).

2. Gender

Male gender was determined as an independent risk factor for CSA in a large study on 1506 patients with CHF (Bitter et al. 2012). The reasons for gender differences have not yet been fully understood.

Central events usually appear in light sleep, at the wake-sleep transition and especially after an arousal or sleep phase change (Sahlin et al. 2005). Relatedly, males have been found to have a more fragmented and unstable sleep, decreased amount of slow-wave sleep and increased number of wake-sleep transitions, as compared to women (Silva et al. 2008), (Hume et al. 1998). Additionally, central events are usually triggered by a phenomenon, causing hyperventilation hypocapnia, such as an obstructive apnea (Tkacova et al. 2001, 2006; Yumino et al. 2009; Naughton and Lorenzi-Filho 2009). Therefore, the higher prevalence of OSA in men (Young et al. 1993) may contribute significantly to the higher prevalence and severity of CSA in male patients with CHF. The androgens are known to stimulate the deposition of fat in the truncus and the neck region, but also modulate muscle tone of the upper airways during sleep (Phillips and Ancoli-Israel 2001).

Dai Yumino et al. reported approximately 2.5 times higher prevalence of both OSA and CSA in men in a study of 218 stable CHF patients, despite the insignificant differences in BMI, EF and New York Heart Association (NYHA) class (Yumino et al. 2009). Javaheri et al. also reported higher prevalence of CSA with higher obstructive AHI in men (Javaheri et al. 2017).

3. Race and genetic factors

Race has not been found to influence the prevalence of CSB among CHF patients (Javaheri et al. 2017).

Though gene-dependent development of the respiratory center, influencing its functionality and proneness to periodic breathing under provocation (hypoxia, hypocapnia) has been supposed to play a role in CSB generation (Champagnat et al. 2009), studies showing involved genes are scarce and in limited populations (Wang et al. 2016).

4. Anthropometric parameters

Obesity is a classic risk factor for OSA, both in the general population and among CHF patients (Bitter et al. 2012). It could be speculated, that obesity might be among the risk factors for CSA, taking into account the influence of adipokines on respiratory control (Cundrle et al. 2014) and the fact, that obstructive events might trigger CSA in predisposed subjects (Tkacova et al. 2001, 2006; Yumino et al. 2009; Naughton and Lorenzi-Filho 2009).

Neck circumference is a simple anthropometric parameter, used for OSA prediction. As White et al. suggested, it is influenced by the rostral fluid shift during the night, commonly observed in CHF patients. However, the latter affects the lungs as well, increasing pulmonary congestion, which is a part of CSA pathophysiology. Thus, enlarged neck size, although not directly associated with the development of CSA, may be a potentiating factor (White and Bradley 2013).

5. Atrial fibrillation

The relationship between atrial fibrillation (AF) in CHF and presence of CSA has been proven (Sin et al. 1999; Bitter et al. 2012). The association is probably bilateral, since AF may be both a cause and a consequence of CSA, mediated

by circulatory delay and sympathetic-adrenal activation, respectively.

6. Hypocapnia

Hypocapnia is a significant risk factor for CSB in CHF. CO_2 levels in arterial blood were lower in the presence of CSA in the majority of the studies (Bitter et al. 2012; Christ et al. 2007; Szollosi et al. 2008; Bradley et al. 1992). These findings are in consent with the loop gain theory as a mechanism underlying CSB (Lorenzi-Filho et al. 1999; Bradley and Floras 1996; Bradley et al. 2001; Leung and Bradley 2001). Accordingly, nocturnal CO_2 application corrects the disturbance (Lorenzi-Filho et al. 1999; Xie et al. 2002; Andreas et al. 1998; Khayat et al. 2003). It should be noted, however, that the reported data suggest that the majority of the patients with CSA in these studies were nevertheless normocapnic ($pCO_2 > 35$).

7. Others

Low **leptin** concentrations were found in CHF patients with CSA (Cundrle et al. 2014) and subsequently demonstrated as a risk factor for its presence (Cundrle et al. 2017).

Smoking (pack-years) was more prevalent among CHF patients with CSA in 1 study (Javaheri et al. 2017). However, it is not clear if it is a risk factor or an associated factor.

Treatment

Although, as discussed below, the severity of CHF (as measured by NYHA class and ejection fraction (EF)) does not significantly differ between patients with and without CSA (Bitter et al. 2012; Christ et al. 2007; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005), applying contemporary and adequate medication therapy is the important first step towards CSA treatment in these patients. Diuretics and angiotensin-converting enzyme inhibitors reduce the ventricular pre- and afterload and improve the cardiac output (Walsh et al. 1995) and beta-blockers blunt the excessive sympathetic activation effects (Tamura et al. 2007), and therefore could diminish to a certain extent the severity of CSA (Solin et al. 1999). Nevertheless, no differences in the medication profile of the patients with or without CSA were found in the study of Bitter et al. on 1500 CHF patients with optimal treatment (Bitter et al. 2012). The same results were reported in another study on 700 patients (Oldenburg et al. 2007).

6 Pathophysiology of CSB

6.1 Control of Breathing According to the Loop Gain Theory

Control of breathing has been explained by the loop gain theory. Loop gain (LG) is the engineering term describing a system with negative feedback control by quantitative assessment of its (in) stability. LG is a product of the controller gain (CG) and the plant gain (PG) and their temporal interaction (time delay). CG describes the controller response to a certain change ($y = f(x)$) and PG is the resultant effect on the amplitude of the controlled parameter ($x = f(y)$). If LG > 1 the system is unstable due to repeating overshoot/undershoot (the corrective response leads to oversized effects, surpassing the initial changes and creating an abnormal imbalance in the opposite direction). On the other hand, LG < 1 is characteristic to a stable system, reacting with a moderate response to a certain change. It is important to understand that a very small response would not destabilize the system, but rather would need prolonged period of time to restore the equilibrium. The time delay influences the size of the overshoot/undershoot in the first scenario and the time to equilibrium in the second, thus also playing an important role.

Translated to the control of breathing, the controller gain represents the magnitude of the breathing drive produced by the respiratory center with respect to the pCO_2, the plant gain is the efficiency of the lungs to eliminate CO_2 and time delay is the lung-to-chemoreceptor time, a.k.a. circulatory delay (Fig. 3).

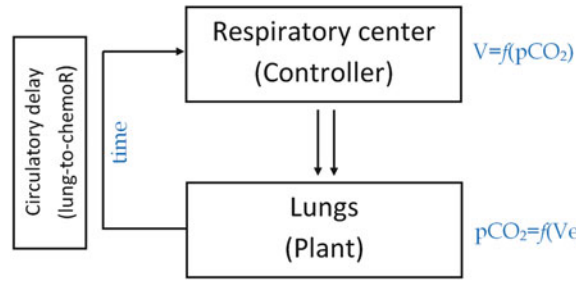

Fig. 3 Components of the loop gain in breathing

The main component of the CG is the chemosensitivity of the respiratory center, i.e. the slope of the function $V = f(pCO_2)$. Significant inter- and intrapersonal variability in the CO_2 sensitivity (Moore et al. 1976; Mountain et al. 1978; Weil 1984; Saunders et al. 1976; Kawakami et al. 1984) has been described with the exact mechanisms behind it still unclear (Orr et al. 2017). An important factor that may influence it is hypoxia (Lloyd et al. 1958). Chemosensitivity represents the "metabolic" control of breathing and may be termed also intrinsic gain. This intrinsic gain is modified by factors such as the upper airway patency to produce the chemoresponsiveness (Orr et al. 2017). One may think of chemosensitivity and chemoresponsiveness as the desired and the actually executed command.

This type of exclusively metabolic breathing control is typical during sleep (Naughton and Lorenzi-Filho 2009), but is not sufficient to respond adequately to various physiologic states and activities during wakefulness (talking, singing, exercising, etc.). Therefore, in addition to the intrinsic gain, other factors, such as the wakefulness/arousal ventilatory drive and conscious cortical overdrive of breathing (descending control) are important for the cumulative CG. Additionally, ascending non-CO_2 stimuli from the C-fibers in the lungs are also an important modulator of the respiratory center, especially under pathologic conditions (Naughton and Lorenzi-Filho 2009; Wellman and White 2011).

The plant gain describes the efficiency of the ventilation to eliminate CO_2 and more specifically the change in pCO_2 in response to executing the ventilatory command ($pCO_2 = f(V)$). It has been shown that lower functional residual volume (FRC) is less effective in terms of buffering of CO_2 changes, thus increasing the PG (Szollosi et al. 2008; Khoo et al. 1982).

As it may be seen (Fig. 3), the PG and the intrinsic part of the CG are in reciprocal relationship. To better illustrate the loop gain mechanism, PG and CG may be plotted on a single graph by inverting the axes of the PG, which would produce the metabolic hyperbole (Fig. 4).

The crossing point between the CG and the metabolic hyperbole is the "static" equilibrium point of the ventilation and pCO_2 if breathing was solely under metabolic control. However, due to the wakefulness drive (WD) it is shifted to the left (at lower pCO_2). Other non-CO_2 stimuli may additionally contribute to that effect. The intersection between the CG and the 0X axis corresponds to $V = 0$ and a pCO_2 level known as apneic threshold (AT). Once, the actual pCO_2 falls below the AT, cessation of breathing occurs. The angle between the CG and the 0X axis corresponds to the chemosensitivity. The steeper the slope is, the greater are the changes in the ventilatory drive per unit of pCO_2 (CG) invoking greater changes in pCO2 at the lungs (metabolic hyperbole). The position at the metabolic hyperbole at which the same changes in the ventilation occur would differently impact the pCO_2 levels due to the non-linear function of the metabolic hyperbole (almost linear in the section around normal pCO_2 and much steeper in the hypocapnic region). Finally, the V/pCO_2 equilibrium in the control of breathing is "dynamic", rather than static and at any given moment is gravitating around the intersection (in blue),

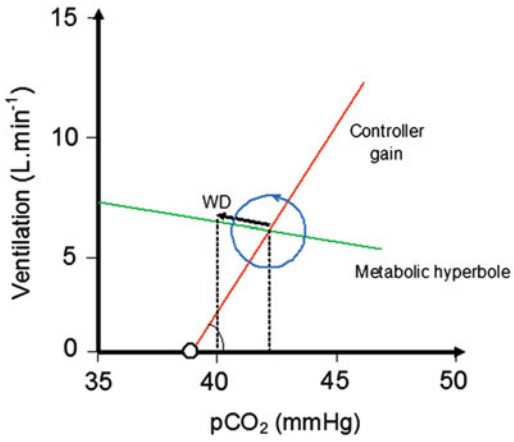

Fig. 4 Control of breathing, according to the theory of loop gain (Modified after Wellman and White 2011)

with the radius of the circle corresponding to the circulatory delay (arbitrary units). Thus, longer circulatory delay would produce greater deviations from the intersection point.

Significant changes in the control of breathing occur during wake-sleep transitions having important implications to periodic breathing. Under normal conditions the eupneic pCO_2 increases by 3–6 mmHg (withdrawn WD), and the AT decreases to prevent breathing pauses (Xie et al. 2002). The cortical descending control during wakefulness supports the breathing even if pCO_2 is below the AT (Khoo et al. 1982; Bradley and Phillipson 1992; Skatrud and Dempsey 1983; Phillipson 1978), while its absence during sleep would result in a central apnea under these circumstances. As a result of the apnea, the pCO_2 gradually increases and after surpassing the AT, the breathing and the equilibrium is restored. If, however, this is accompanied by a (micro)arousal, the momentary level of pCO_2 is relatively hypercapnic for the AT (swiftly changing to levels corresponding to wakefulness). As a result, a fast increase in ventilation, corresponding to the hyperpneic phase of the periodic breathing follows (Xie et al. 1994).

6.2 Causes of CSB in Patients with CHF, According to the Loop Gain Theory

CSB occurs due to increased LG as a result of increased CG, PG and circulatory delay, frequently in combination.

A number of factors may increase the CG in CHF patients. For example, moderate hypoxia affects the chemoresponsiveness increasing the chemosensitivity (the intrinsic gain) (Orr et al. 2017; Lloyd et al. 1958), but also by influencing the upper airway patency (Wellman et al. 2008). The latter may be already disadvantageously altered in patients with obstructive sleep apnea (Wellman et al. 2008). Obstructive events also trigger respiratory associated arousals and hence, an abrupt change in the AT and fluctuations of pCO_2 under and over the AT (Bradley and Floras 1996; Bradley et al. 2001; Leung and Bradley 2001; Lorenzi-Filho and Bradley 2002). Any other cause of sleep fragmentation and increased arousability would elicit the same result. This mechanism may be facilitated further by the inadequate decrease of the AT during sleep, found by Xie et al. in a group of CHF patients (Xie et al. 2002). CHF patients, who are already hypocapnic during wake are especially vulnerable with the withdrawal of the descending effects on the respiratory center (Hanly et al. 1993), (Naughton et al. 1995). On the contrary, application of CO_2 eliminates the central events (Lorenzi-Filho et al. 1999). The chemosensitivity curve may be shifted to the left by non-CO_2 stimuli, other than the WD. The C-fibers reflex is especially important in CHF patients. Pulmonary congestion increases the pulmonary capillary wedge pressure (PCWP) and triggers the reflex resulting in tachypnea and hyperventilation, followed by hypocapnia and central apnea (Paintal 1969; Roberts et al. 1986; Churchill and Cope 1929). PCWP has been correlated with pCO_2 levels and the severity and

number of the central apneas (Solin et al. 1999). Additionally, left ventricle end-diastolic and end-systolic volumes were twice bigger in patients with CHF and concomitant CSB than in CHF only in the study of Tkacova et al. (1997). The presence of CSB has also been associated with left atrium distension (Lloyd 1988) and increased levels of NT-proBNP (Carmona-Bernal et al. 2005; Poletti et al. 2009). In the same regard, optimizing the drug therapy for CHF may result in improving the CSB in some cases (Oldenburg et al. 2009; Olson et al. 2007). The carotid bodies may also play a role in the chemosensitivity, as shown by animal models (Ding et al. 2011; Schultz et al. 2015).

The importance of the interstitial edema is even greater, since it increases the elasticity of the lungs, reducing the FRC (Agostoni et al. 2002) and increasing the plant gain. The importance of PG is underlined by the positive effect of CPAP on CSB, which has been at least partially explained by recruitment of lung volume (Orr et al. 2017).

CHF is also associated with increased arterial circulatory time, causing increased circulatory delay and hence, increasing the LG by mediating "the right changes at the wrong time" (Khoo et al. 1982). Though the importance of circulatory delay is not equivocally accepted, most of the studies support its leading role (Hall et al. 1996; Lorenzi-Filho and Bradley 2002; Naughton et al. 1993; Mortara et al. 1999; Lorenzi-Filho et al. 2008).

An alternative theory for the CSB pathogenesis is the central hypothesis, which describes CSA as an internal oscillation within the CNS and modulating the breathing either indirectly via changes in heart rate and blood pressure or directly through activation of the respiratory center (Yajima et al. 1994).

It is important to note that the importance of the loop gain theory extends beyond being a theoretical canvas of CSB. Recently, it has been successfully used to determine treatment efficacy on central apneas (Stanchina et al. 2015).

6.3 CSB As an Adaptation of the Failing Heart

Naughton et al. proposed the controversial hypothesis of CSB being an adaptive response of the failing heart, rather than a detrimental complication (Naughton 2012). It has been gaining popularity recently with the evidence for increased mortality in CHF-CSB patients when treated with ASV (SERVE-HF) (Cowie et al. 2015). The CANPAP study also failed to produce convincing evidence for a positive outcome in terms of mortality with CPAP treatment in these patients (Bradley et al. 2005), although post-hoc analysis showed otherwise (Arzt et al. 2007). Actually, Naughton et al. structured their hypothesis around several logical arguments related to potential pathophysiological benefits of the hyperpneic phase of CSB, such as: increased FRC; vagal stimulation; improved tissue O_2 extraction (Haldane effect); improved cardiac filling (respiratory pump); increased end-expiratory pressure, etc. (Naughton 2012). It should be noted that the changes in the above-mentioned features are opposite during the apneic phase and the net effect may not be beneficial. For example, it has been proven that CSB is associated with increased sympathetic-adrenal activity (Solin et al. 2003; Carmona-Bernal et al. 2005; Oldenburg et al. 2008a).

Overall, with the lack of experimental studies, directly testing the hypothesis and the proves for higher morbidity, mortality and hospitalization rates in CHF patients with CSB (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003) and treatment benefits (Arzt et al. 2007, 2009), this hypothesis should not be accepted as mainstream.

7 Clinical Manifestation

7.1 Signs and Symptoms

Patients with CHF report a number of somatic complaints, such as generalized fatigue, insomnia, impaired neuro-psychologic functions (Bitter et al. 2012; Braunwald 1988). Although most of the symptoms could be attributed to the cardiac dysfunction, some of them could possibly be granted to the disturbed sleep structure and, to a certain degree, result in the presence of daytime sleepiness. The clinical manifestation of CSA/CSB itself is usually poor, lacking striking symptoms and complaints. Witnessed apneas and snoring are infrequently reported by the sleep partner. Sometimes patients may report poor sleep quality with frequent awakenings, paroxysmal nocturnal dyspnea and frequent urination at night (Javaheri 2006a).

One may pay attention to the fact that the diagnosis CSA with SDB does not need the manifestation of any symptoms (criterion A – sleepiness; difficulty initiating or maintaining sleep, frequent awakenings, or non-restorative sleep; awakening short of breath; snoring; witnessed apneas) in the presence of CHF or AF (criterion B) (ICSD-3 (AASM 2014)), once gain demonstrating the low clinical profile of these patients.

7.2 NYHA Functional Class and Echocardiography

Most of the studies failed to present any significant differences in the NYHA functional class and the ejection fraction between patients with and without sleep-disordered breathing (Christ et al. 2007; Javaheri et al. 2017; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005). Though a correlation between the severity of the CHF and CSA frequency has been reported (Arzt et al. 2003), CSB showed high prevalence among patients with heart failure with preserved ejection fraction (HFpEF) (Berger et al. 2002; Herrscher et al. 2011).

Other EchoCG parameters, however, were found to differ between groups with and without CSA. Javaheri et al. (2017) related concentric remodeling of the ventricle (expressed by elevated left ventricular mass/volume ratio) to be associated with CSA. Left atrial size has also been linked to CSB (Oldenburg et al. 2007; Calvin et al. 2014) through increased chemosensitivity. Calvin et al. speculated that the association between the enlarged left atrium and the enhanced CO_2 chemosensitivity, found in CHF patients, is partially mediated by the J-reflex (Calvin et al. 2014). Right ventricle involvement was also reported (Calvin et al. 2014; Javaheri et al. 2007). Right ventricular systolic pressure is increased in CHF patients in the presence of CSA (Calvin et al. 2014), probably mediated by the hypoxia induced pulmonary hypertension (Javaheri et al. 2007).

7.3 Laboratory Parameters

Increased BNP levels in CHF are associated with poor outcome (Berger et al. 2002; Richards et al. 2001; Omland et al. 2002). The BNP was even further increased in patients with CSB (Carmona-Bernal et al. 2005; Poletti et al. 2009).

C-reactive protein levels are elevated in CHF (Pye et al. 1990; Kaneko et al. 1999; Sato et al. 1999) and influence its prognosis (Anand et al. 2005). In a study on 996 patients with CHF, Schmalemeier et al. reported a significant correlation between the CRP and the severity of CSA (Schmalgemeier et al. 2014). However, the reported effects of the therapy for CSA in CHF on the CRP levels have been controversial (Koyama et al. 2010; Bitter et al. 2012).

7.4 Cardiopulmonary Exercise Testing (CPET)

No clear proof for an association between exercise capacity and the presence of CSA in CHF is present so far. Peak oxygen uptake (VO_{2peak}) was reported to be lower with CSA as an absolute measure (Meguro et al. 2005; Roche et al. 2008)

or percent of predicted (Vazir et al. 2006; Roche et al. 2008) in some studies or without significant differences in others (Arzt et al. 2003). No difference was found in the anaerobic threshold (Roche et al. 2008). The most consistent finding is the increased ventilation-carbon dioxide output ($VEVCO_2$) in CHF with CSB (Arzt et al. 2003; Meguro et al. 2005; Roche et al. 2008; Cundrle et al. 2015). End-tidal CO_2 was lower at peak and at 50% of the exercise intensity in the group with CSB in the study of Cundrle et al. (2015). Periodic pattern of breathing may be observed in the first 4 min of a CPET (Roche et al. 2008).

7.5 Arterial Blood Gases

As already mentioned hypocapnia is a typical finding in CSB patients (Bitter et al. 2012; Christ et al. 2007; Szollosi et al. 2008; Bradley and Phillipson 1992). On the other hand, lower pO_2 is not present (Bitter et al. 2012) or not an independent risk factor (Bitter et al. 2012) in CHF with CSA.

7.6 Pulmonary Function Testing (PFT)

Reduced diffusion capacity of the lungs has been found to be an independent risk factor for CSA and correlated moderately with the AHI in the study of Szollosi et al. (2008). Despite the fact that low lung volumes have been implicated in the pathogenesis of CSB (see above), no difference in PFT parameters in patients with CSA has been reported.

7.7 Periodic Breathing During Wakefulness

CSB may be observed during wakefulness as well (Poletti et al. 2009; Mortara et al. 1999; Brack et al. 2007; Leite et al. 2003) and is associated with increased mortality and poor transplant-free survival (Brack et al. 2007). It has been attributed to low cardiac index and increased circulatory time (Mortara et al. 1999) and linked to increased sympathetic-adrenal activity and BNP levels (Poletti et al. 2009) and lower EF, exercise capacity and hypocapnia (Leite et al. 2003).

8 Consequences of CSB

Breathing disturbances, present in patients with stable CHF, are not just an acute pathological condition, but provoke chronic effects, which could promote a number of diseases, as well as further deterioration of cardiac function. In fact, Somers et al. (Somers 1999) hypothesize that CSA and cardio-vascular disease are linked through bidirectional causality as a part of a vicious cycle.

CSB is accompanied by cyclic variations in heart rate (tachycardia-bradycardia), blood pressure (hypertension-hypotension), respiratory volume (hyperpnoea-hypo/apnea), partial pressure of arterial oxygen (pO_2) (hypoxia-hyperoxia) and carbon dioxide (pCO_2) (hypercapnia-hypocapnia). The pathophysiological mechanisms, responsible for the adverse prognosis in CSA patients include hypoxia with/without hypoxemia, (micro)arousals from sleep, increased negative intrathoracic pressure. Each of them, and especially their combination, leads to sympathetic-adrenal activation.

Hypoxia, followed by an apnea or hypopnea, could provoke bradycardia or even several-seconds asystole (Guilleminault et al. 1983), whereas severe hypoxia could provoke acute ventricular arrhythmia (Leung et al. 2004). It should be noted that mild hypoxia was not related to ventricular arrhythmia in the same study (Leung et al. 2004). The combination between hypoxia and tachycardia impairs myocardial contractility, as it leads to a decreased myocardial oxygen delivery and an increase in the left ventricular afterload (Serizawa et al. 1981). The frequent desaturations and multiple arousals elicit structural changes to the heart as well as left and right ventricular hypertrophy (Ancoli-Israel et al. 2003) and contribute to the development of systemic oxidative stress in OSA (Lavie and Lavie 2009), and may invoke similar effects in CSB.

The arousals, following each respiratory disturbance contribute to the increased instability of respiratory control (Phillipson 1978; Naughton et al. 1993; Xie et al. 1994), increased release of catecholamines (Naughton et al. 1995; Horner et al. 1995), and overactivation of the sympathetic nervous system (Solin et al. 2003; Carmona-Bernal et al. 2005; Oldenburg et al. 2008a). Naughton et al. found increased nocturnal urinary norepinephrine levels and increased daytime norepinephrine plasma levels in patients with CHF and CSB, as compared to those without CSB and an association between the norepinephrine levels with increased frequency of arousals (Naughton et al. 1995). Sympathetic overactivation leads to a decreased survival of cardiomyocytes, exerts antiarrythmogenic effects and worsens ventricular energetism. It relates to myocyte hypertrophy, apoptosis and focal myocardial necrosis, which are factors for cardiac remodeling (Costanzo et al. 2015). All of these potentiate the progression and the lethal outcome in CHF patients (Mansfield et al. 2003).

Although the increased negative intrathoracic pressure is a typical consequence of OSA, it could also be present in CSA as well, even though to a lesser extent, as a result of pulmonary congestion and decreased compliance of lungs.

The Inflammatory Pathway According to the cytokine hypothesis, the activation of the immune system plays an important role in the pathogenesis of CHF, pointing out the participation of some pro-inflammatory cytokines for the development of the ventricular dysfunction (Seta et al. 1996; Vasan et al. 2003). Besides, the increased levels of some inflammatory markers show an independent correlation with adverse events and mortality (Anand et al. 2005) and those patients exhibit more severe CHF. Several studies suggest that the presence of obstructive sleep apnea leads to increased levels of some markers of systemic inflammation (Ciftci et al. 2004; Dyugovskaya et al. 2002; Schulz et al. 2000), which could be associated with a further progression of the cardiac dysfunction, forming a vicious cycle. Some markers of systemic inflammation are elevated in CSB (Schmalgemeier et al. 2014), so the aforementioned mechanism may play a role in CSB, as well.

The pathogenesis of the negative consequences of CSB on CHF is summarized in Fig. 5.

8.1 Quality of Life

Patients with CHF have a considerably decreased quality of life as compared with individuals, matched by age and gender (Lesman-Leegte et al. 2009). Undoubtedly, heart failure affects quality of life (QoL) to a greater extend, compared with other chronic conditions (Jaarsma et al. 2010). The influence of the CSB on QoL in patients with CHF is still debated with some studies reporting no effect (Ferrier et al. 2005), while others finding considerable worsening in the group with CSB (Carmona-Bernal et al. 2008), but the correlation with objective indices of its severity was poor (ODI) to moderate (AHI).

8.2 Morbidity and Mortality

The negative impact of the combination CHF/CSB is supported by a diverse body of evidence for increased morbidity and mortality in the presence of CSB (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003; Lanfranchi et al. 1999; Hanly and Zuberi-Khokhar 1996). These findings were confirmed when corrected for the CHF severity (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005; Mansfield et al. 2003; Hanly and Zuberi-Khokhar 1996). The severity of SDB probably plays an important role, as demonstrated in the study of Lanfranchi et al where only severe CSA (AHI $\geq$ 30) was associated with adverse prognosis (Lanfranchi et al. 1999).

Obstructive sleep apnea is a risk factor for arterial hypertension (Nieto et al. 2000). However, the impact of CSA on blood pressure, though expected (Fig. 5) has not been proven yet. In two studies (Bitter et al. 2012; Yumino et al. 2009) arterial hypertension was more

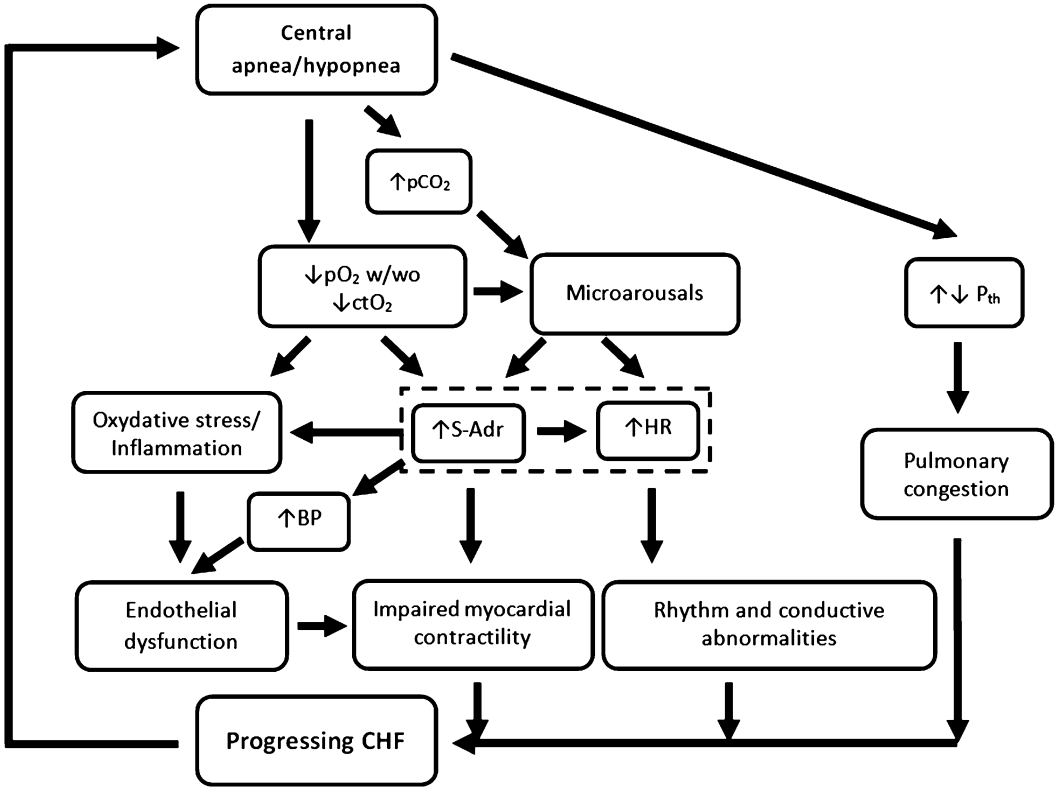

Fig. 5 Pathophysiology of the detrimental effects of CSB on chronic heart failure
Legend: pCO_2 – partial pressure of carbon dioxide, pO_2 – partial pressure of oxygen, ctO_2 – oxygen concentration (in arterial blood); P_{th} – intrathoracic pressure; S-Adr – sympathetic-adrenal activity; HR – heart rate; BP – blood pressure

prevalent in CSA compared to CHF patients without sleep disordered breathing, but the difference was not significant. No difference was found in the prevalence of diabetes mellitus as well (Bitter et al. 2012).

9 Diagnosis and Polysomnographic Pattern

The diagnostic process of patients with CHF, suspected to have CSA, follows the standard steps and includes a profound clinical interview, assessment of the HF condition and a sleep study, each of them having its importance for an adequate diagnostic outcome. A detailed description of the day-time and night-time symptoms is collected, preferably with the participation of the bed-partner, although a negative history of the latter does not exclude a clinically significant disorder. The recommended type of diagnostic study is the standard in-laboratory polysomnography (type 1 device), as it provides detailed information on sleep structure, respiratory and electro-physiological parameters. The polysomnographic characteristics of CSA include:

From the respiratory part: crescendo-decrescendo ventilatory pattern, accompanied by a partial (hypopnea) or complete cessation of breathing without thoracic and abdominal effort, followed by a decrease in the oxygen saturation. Respiratory effort is best measured by esophageal pressure, but currently this method is rarely used in clinical practice.

From the EEG part: CSB usually occurs during the transition from wakefulness to NREM 1 and 2 sleep stages. It is alleviated in a non-supine body position (Szollosi et al. 2006), while during slow wave sleep and REM sleep the ventilation tends to normalize. Usually a CSB sequence is preceded by an obstructive event or an arousal. Unlike obstructive events, ending with arousals, EEG arousals in CSB appear at the peak of the hyperventilation phase of the CSB cycle.

The severity of CSA is usually expressed by measuring the apnea-hypopnea index (AHI), which is calculated as the number of apneas and hypopneas, divided by the hours of sleep. Another metrics, although quite less commonly used, is the percentage of sleep time in which CSA/CSB occurs (Naughton and Andreas 2010).

10 Predictors

There is enough body of evidence that the presence of CSA/CSB in CHF patients worsens the overall prognosis (Ancoli-Israel et al. 2003; Carmona-Bernal et al. 2005) and needs targeted treatment (Arzt et al. 2007, 2009), therefore, a reliable screening system for its timely detection is required. Presently, the golden standard for diagnosing CSA/CSB is laboratory polysomnography, an expensive, laborious and highly specialized procedure, which can differentiate the various types of SDB (AASM 2014), (Ferrier et al. 2005) and determine the need of treatment. In order to optimize polysomnography use, a predictive system could be created, aiming at selecting the appropriate patients.

We have proposed a pathophysiological approach to the selection of some predictors, based on parameters, reflecting the etiology, the pathogenesis and the consequences of CSA/CSB in CHF (Draganova et al. 2016) – Table 1.

11 Therapy of CSB

Treatment of CSB aims at improving the cardiac function, quality of life and life expectancy in these patients. Despite the variety of treatment modalities proposed, it is important to note that, so far, guidelines do not offer a uniform treatment strategy for CSA in patients with CHF.

11.1 Optimization of CHF Therapy

Although according to some authors severity of CHF (as measured by NYHA class and ejection fraction) does not significantly differ among patients with and without CSA (Bitter et al. 2012; Christ et al. 2007; Vazir et al. 2006; Arzt et al. 2003; Meguro et al. 2005), applying

Table 1 Pathophysiological approach to prediction of CSB in CHF (With permission from Draganova et al. 2016)

PREDICTORS				
Etiologic	**Pathogenetic**			**Symptomatic**
✓ Anthropometry ✓ Medical history ✓ EchoCG ✓ NYHA class ✓ Laboratory parameters	Controller	Plant gain	Mixing gain	Symptoms
	✓ Respiratory control	✓ PFT ✓ EchoCG	✓ EchoCG	✓ ESS ✓ MLHFQ
	Loop gain in general			Complications
	✓ Cardiopulmonary exercise testing (CPET) ✓ Hypoxic provocation			✓ ECG/ HRV ✓ CPET

Legend: *EchoCG* echocardiography, *NYHA* New York Heart Association, *ESS* Epworth sleepiness scale, *MLHFQ* Minnesota Living with Heart Failure Questionnaire, *ECG* electrocardiography, *HRV* heart rate variability

contemporary and adequate medication therapy, is the important first step towards CSA treatment in these patients. The diuretics, aiming at reducing the cardiac filling pressures, together with angiotensin-converting enzyme inhibitors to reduce ventricular afterload and improve cardiac output (Walsh et al. 1995) and beta-blockers to blunt the sympathetic nervous activation effects (Tamura et al. 2007), could to a certain extent diminish CSA severity (Solin et al. 1999).

Other therapeutic approaches, applied in advanced CHF like resynchronizing therapy (RT), may also have a beneficial effect on CSA. RT improves cardiac pumping function, which is a prerequisite for improved quality of life and sleep, as well as decreased mortality rate (Abraham et al. 2015). A meta-analysis, comprising 170 patients with CHF after RT, shows a considerable decrease of AHI in CSA patients, but not in patients with OSA (Lamba et al. 2011). Atrial overdrive pacing on top of RT in some of the patients in the same study, has led to a minor additional improvement of CSA (Lüthje et al. 2009).

However, despite the optimal CHF therapy, the presence of CSA requires specific treatment. The golden standard is application of positive airway pressure during sleep, although other treatment modalities have been tried.

11.2 Non-positive Airway Pressure Modalities

11.2.1 Nocturnal Oxygen Supplementation

Noxturnal home O_2 therapy (HOT) has been successfully used to treat CSA in CHF patients (Shigemitsu et al. 2007; Seino et al. 2007; Toyama et al. 2009; Sasayama et al. 2006; Nakao et al. 2016). The possible mechanisms involved are improvement in oxygen delivery to cardiomyocytes and influencing the controller gain by decreasing hypoxemia and increasing the cerebral CO_2 (Badr 2009). The effect of O_2 therapy on AHI in CHF with CSA is comparable to CPAP (Teschler et al. 2001). Additional benefits of the therapy are decrease in the nocturnal norepinephrine and the BNP levels (Shigemitsu et al. 2007), improved physical capacity (Toyama et al. 2009; Hanly et al. 1989; Andreas et al. 1996; Staniforth et al. 1998; Krachman et al. 1999) and quality of life (Seta et al. 1996) and lower hospitalization rate and duration (Seta et al. 1996). Unlike reported previously (Hanly et al. 1989; Staniforth et al. 1998; Krachman et al. 1999), EF increased after 3 months of HOT in the study of Toyama et al. (2009).

It should be noted, however, that noxturnal oxygen supplementation may not eliminate upper airway obstruction (frequently co-existing with central event), unless it is caused by an increased loop gain (Wellman et al. 2008).

11.2.2 Nocturnal Supplemental CO_2

Nocturnal inhalation of small amounts of CO_2 or the artificial increase of dead space (and, thus pCO_2) leads to suppression of CSB by shifting pCO_2 above the apneic threshold (Lorenzi-Filho et al. 1999; Xie et al. 2002; Andreas et al. 1998; Khayat et al. 2003). However, sleep quality and quality of life are not improved (Szollosi et al. 2004).

To avoid undesirable side effects of the CO_2 implementation, such as increased sympathetic activity, Mebrate et al. proposed a system with dynamic delivery of CO_2 (Mebrate et al. 2009). Yet, CO_2 therapy is not recommended for clinical use.

11.2.3 Theophylline

Theophylline is a respiratory stimulant (Eldridge et al. 1985; Javaheri et al. 1989) and has been able to decrease the periodic breathing and the AHI and improve oxygen saturation during sleep in the study of Javaheri et al. (1996). No improvement in cardiac function or sleep architecture was found (Javaheri et al. 1996).

11.2.4 Acetazoleamide

The positive effect of Acetazoleamide on high-altitude central sleep apnea and idiopathic CSA (White et al. 1982; DeBacker et al. 1995; Sutton et al. 1979; Hackett et al. 1987) is probably mediated by reduction in the pulmonary

congestion and lowering the apneic threshold through neural plasticity. Analogously, its use in CSA with CHF has been tested in a single small randomized trial on 12 CHF patients. Acetazoleamide for 6 nights has led to a decrease in periodic breathing by 38%, improved the quality of sleep and reduced of daytime sleepiness (Javaheri 2006b).

11.2.5 Phrenic Nerve Stimulation

A novel approach to eliminate CSB is the unilateral transvenous stimulation of the phrenic nerve. A pulse generator is implanted to stimulate the diaphragm during sleep, aiming at maintaining normal respiratory excursions (Ponikowski et al. 2012). Abraham et al. reported a 55% decrease in AHI (on behalf of the central events) at 3 months and a considerable improvement of sleep efficiency, oxygen saturation and quality of life (Abraham et al. 2002).

11.2.6 Heart Transplantation and Supportive Devices

Data showing the effect of heart transplantation and supportive devices are still limited to case reports and no reliable conclusions are possible. Heart transplantation was demonstrated to eliminate CSB in several studies (Fox et al. 2014; Vermes et al. 2009), in the first case the resolution was delayed over time (Fox et al. 2014). Ventricular assistant device eliminated successfully CSB in several cases (Vermes et al. 2009; Vazir et al. 2010).

11.3 Positive Airway Pressure Modalities

11.3.1 CPAP

At present, CPAP therapy is considered the gold standard in the treatment of CSA in CHF. It reduces AHI and improves the saturation profile (Naughton and Lorenzi-Filho 2009; Bradley et al. 2005; Arzt et al. 2007, 2009; Mansfield et al. 2003; Kaneko et al. 2003). According to its effect on AHI, the patients are divided into "responders" and "non-responders" (Javaheri 2000). With adequate titration CPAP increases transplant-free survival among these patients (Arzt et al. 2007; Sin et al. 2000). However, this effect is observed only in responders to the therapy (AHI on CPAP <15) (Arzt et al. 2007). It should be noted, that CPAP response is time-dependent (Arzt et al. 2009) and typically AHI decreases with less than 50% at the first night of treatment (Arzt et al. 2009; Teschler et al. 2001). In the study of Arzt et al., an additional reduction of 42% in the AHI (to the initial 47%) were observed after 12 weeks in the absence of any changes to the therapeutic pressure or medications (Arzt et al. 2009). Therefore, response assessment after at least 2 weeks of CPAP treatment is recommend (Arzt et al. 2009).

Additional benefits of the CPAP are improvement in EF (Bradley et al. 2005; Mansfield et al. 2003; Sin et al. 2000) physical capacity (Bradley et al. 2005), quality of life (Bradley et al. 2005) and sympathetic activity (Bradley et al. 2005; Mansfield et al. 2003; Kaye et al. 2001). CPAP does not affect sleep macroarchitecture, while data on arousals are controversial (Yumino et al. 2009; Kaneko et al. 2003).

CPAP treatment effects are consistent with the loop gain theory. It decreases plant gain by increasing the FRC which serves as a buffer for pCO_2, preventing large swings in it (Sands et al. 2011; Krachman et al. 2003). Controller gain is decreased as well, due to improved oxygenation of the blood affecting chemosensitivity (Lloyd et al. 1958; Arzt et al. 2009). It alleviates cardiogenic pulmonary edema and thus, decreases the non-CO_2 stimuli to the respiratory center (Lenique et al. 1997). The stability of the upper airway may also be improved in some patients (Jobin et al. 2012). Additionally, CPAP serves as a "cardiac assist device", decreasing the preload and the afterload to the heart (Naughton and Bradley 1998; Mehta et al. 2000; Steiner et al. 2008; Philip-Joët et al. 1999). Increasing blood oxygen levels also bears the benefits of reduced sympathetic-adrenal activity (Naughton et al. 1995; Kaye et al. 2001) and improved myocardial oxygen.

Table 2 Treatment recommendations for CSB (AASM)

Treatment modality	Statement	Recommendation
CPAP	CPAP therapy is indicated for the initial treatment of CSAS related to CHF.	STANDARD
O_2	O_2 therapy is indicated for the treatment of CSAS related to CHF.	STANDARD
ASV	ASV is indicated for the treatment of CSAS related to CHF with EF > 45%.	OPTION
BPAP	BPAP therapy in ST mode may be considered only if there is no response to adequate trials of CPAP, ASV, and O_2 therapies.	OPTION
Acetazolamide/ theophylline	Acetazolamide and theophylline have limited supporting evidence but may be considered after optimization of standard medical therapy, if PAP therapy is not tolerated, and if accompanied by close clinical follow-up.	OPTION

11.3.2 BPAP

Bilevel positive airway pressure (BPAP) supports a lower pressure during exhalation, thus facilitating the expiration and increasing tidal volume. In theory, the latter may cause hypocapnia and hence, provoke periodic or worsen breathing in CHF patients with CSA. Additionally, a large difference between the inspiratory and the expiratory pressures (>7 cmH_2O) causes periodic breathing in most healthy individuals (Badr 2009).

Consistent with the abovementioned, worsening of central breathing disturbances with BPAP was shown in the study of Johnson et al. (Johnson and Johnson 2005). On the contrary, several small studies demonstrated positive effect of the therapy (Köhnlein et al. 2002; Willson et al. 2001; Dohi et al. 2008; Kasai et al. 2005), with even superior results compared to CPAP (Köhnlein et al. 2002; Willson et al. 2001).

However, the scarcity of data and the contradictory results pose questions to BPAP therapy in CHF patients with CSA.

11.3.3 Adaptive Servoventilation

Adaptive servo-ventilation (ASV) is a relatively new approach in the CSA therapy in CHF. Its key characteristic is the variable pressure support to prevent hyperventilation, adding to the cardiocirculatory benefits of the CPAP (Teschler et al. 2001). Low expiratory pressures improve the cardiac output and also the compliance to the therapy (Hastings et al. 2010). Meanwhile, the servo-controlled inspiratory support stabilizes the ventilation at about 80% of minute ventilation during rest, avoiding the risk of hyperventilation and improving the efficacy in eliminating central events (Naughton and Lorenzi-Filho 2009). Indeed, studies have shown superiority of ASV over CPAP in eliminating CSB and better compliance (Teschler et al. 2001; Philippe et al. 2006).

ASV therapy has been shown to improve physical capacity, EF, N-pro-BNP levels in CHF patients (Oldenburg et al. 2008b). A positive effect of ASV on echocardiographic parameters has been reported even in patients with heart failure with preserved ejection fraction (Bitter et al. 2010). Additionally, ASV decrease sympathetic-adrenal activation, reduces nicturia and improves sleep architecture and quality of life (Philippe et al. 2006; Pepperell et al. 2003). In that regard ASV also proved superior to CPAP (Teschler et al. 2001; Philippe et al. 2006).

Despite these promising initial data, the results of the biggest multi-center randomized trial on ASV so far – SERVE-HF (Cowie et al. 2015) were disappointing. ASV therapy does not result in a significant improvement in quality of life or symptoms of CHF. More importantly, a considerable increase in cardiovascular and all-cause mortality with ASV treatment were found (Cowie et al. 2015). The results of another large-scale study (SAVIOR-C) show no effect of ASV therapy on EF and plasma BNP levels (Momomura et al. 2015).

The results of the SERVE-HF study provoked an update in the AASM recommendations for treatment of CSA in CHF (Aurora et al. 2012, 2016) which are summarized in Table. 2.

12 Future Perspectives

Though, CSB in CHF has been an extensively studied area lately, a lot of uncertainties remain. Naughton et al. have questioned the necessity of treatment of CSB, proposing an adaptive nature of the disorder (Naughton 2012). This hypothesis was reinforced the SERVE-HF study results (Cowie et al. 2015). It may be even the case of magnitude determining the adaptive or pathological nature of SDB. In that regard, the lack of uniform threshold for its presence and lack of severity metrics may be strongly impeding progress on the topic. Even the use of AHI as a key parameter by analogy to OSA has to be questioned (Naughton 2016). The recent changes in hypopnea definition (Berry et al. 2012) lead to scoring more events (Duce et al. 2015; Ward et al. 2013), though that does not seem to impact the proportion of central and obstructive events in CHF (Ward et al. 2013). Novel therapeutic approaches taking into account the pathophysiology of CSB were attempted (Mebrate et al. 2009; Ponikowski et al. 2012) and need further investigation. Phenotyping patients based on the loop gain seems especially promising in improving therapeutical efficacy (Stanchina et al. 2015). Early diagnosis is of no less importance and reliable laboratory markers for prediction of CSB are still needed.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 353–371
DOI 10.1007/5584_2017_99
© Springer International Publishing AG 2017
Published online: 5 October 2017

The Evolution of mHealth Solutions for Heart Failure Management

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Abstract

In the last decade, the uptake of information and communication technologies and the advent of mobile internet resulted in improved connectivity and penetrated different fields of application. In particular, the adoption of the mobile devices is expected to reform the provision and delivery of healthcare, overcoming geographical, temporal, and other organizational limitations. mHealth solutions are able to provide meaningful clinical information allowing effective and efficient management of chronic diseases, such as heart failure. A variety of data can be collected, such as lifestyle, sensor/biosensor, and health-related information. The analysis of these data empowers patients and the involved ecosystem actors, improves the healthcare delivery, and facilitates the transformation of existing health services. The aim of this study is to provide an overview of (i) the current practice in the management of heart failure, (ii) the available mHealth solutions, either in the form of the commercial applications, research projects, or related studies, and (iii) the several challenges related to the patient and healthcare professionals' acceptance, the payer and provider perspective, and the regulatory constraints.

Keywords

Data mining · Diagnosis · Ecosystem · Heart failure · Holistic environment · mHealth applications taxonomy · mHealth challenges · mHealth evolution · mHealth HF interventions · Patient management · Treatment

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1 Introduction

Mobile telecommunication technologies have penetrated multiple sectors, such as commerce, media, and finance with health being the one with the greatest potential (Clarke 2014). The acceleration of the electronic health records (EHRs) uptake by the Health Information Technology for Economic and Clinical Health Act legislation and the access of patients to mobile devices enabled the advent of the mobile health technology (mHealth) (Mennemeyer et al. 2016). Specifically, the last years, the concept of mHealth as "the use of mobile computing and communication technologies in healthcare and public health" is continuously gaining place and expanding. Governments are interested in involving mHealth as a complementary approach for improving healthcare delivery and achieving the health-related Millennium Development Goals (MDGs) in low- and middle- income countries (http://www.who.int/topics/millennium_development_goals/accountability_commission/en/). This interest has enhanced the development and application of several mHealth systems in Europe and worldwide, which provide early evidence for mobile and wireless technologies potential.

One of the key factors for this rapid mHealth growth is the healthcare transformation and the penetration of the mobile technology in the everyday life. The number of smartphone devices surpassed the world population, which accounts for 7.22 billion (https://www.gsmaintelligence.com/research/?file=357f1541c77358e61787fac35259dc92&download). About 80% of the world's population has access to a smartphone device with advanced technical capacities (Martínez-Pérez et al. 2013a). From 2011 to 2014, there was a remarkable increase from 35–64% in the proportion of Americans who owned a smartphone (http://www.mobihealthnews.com/42077/pew-64-percent-of-us-adults-own-a-smartphone-now). Smartphones may include several sensors, such as accelerometers and cameras, which can be used in different application areas. The spread and sophistication of such devices are growing rapidly. Wearable devices, such as smart watches, wristbands, and clothing, have been designed and fabricated incorporating physiological sensors, and they are able to collect and transmit data to the smartphones in order to be analyzed locally or to the Cloud. Taking into account the popularity, availability, and technological capacity of the smartphones, their integration with the mHealth has the potential to address the issue of disease management.

The mHealth technology is able to address specific needs and serve a wide range of purposes of heterogeneous audiences, including healthcare professionals, caregivers, patients, or even healthy people (http://www.springer.com/gp/book/9783319233406). The mHealth solutions are evaluated in diverse scenarios: (i) timely access to emergency and general health services, (ii) patient monitoring and management, (iii) reducing drug shortages at healthcare institutions, (iv) improving clinical diagnosis, and (v) assisting in overall adherence. One of the key characteristics of mHealth is the ability to serve the patients not only in the everyday life but also during hospitalization or even rehabilitation. The acquisition and collection of patient-specific information and the use of mHealth strategy in the clinical practice have been shown to be an easy and efficient way for improving service delivery in healthcare systems and in turn for providing health benefits to the patients (http://www.who.int/goe/publications/goe_mhealth_web.pdf).

1.1 mHealth in Chronic Diseases

Chronic diseases are among the leading cause of mortality and morbidity (Durstine et al. 2013; Viswanathan et al. 2012). The management of

chronic diseases requires a long-term treatment. Patients spend about 1 h per year with their healthcare professional and around 10,000 h to manage their health and disease symptoms by themselves. Self-management involves the management of symptoms and disease monitoring to prevent further complications. This can be achieved through the adherence to the suggestions provided by the experts. The adherence is one of the key factors for improved health outcomes and quality of life; however 50% of the patients with chronic diseases are non-adherent (Burkhart and Sabaté 2003). This burden is higher in the developing countries (Beaglehole et al. 2008). According to the World Health Organization (WHO), "increasing adherence may have a greater effect on health than improvements in specific medical therapy" (http://www.who.int/chp/knowledge/publications/adherence_introduction.pdf). Given the growing prevalence of chronic diseases combined with the increasing adoption of smartphone devices, the use of mHealth for patient self-management and disease monitoring seems promising. Several studies have shown the benefits gained for the patients after the adoption of mHealth systems. A meta-analyses on mHealth interventions for self-management of diabetes (Free et al. 2013) showed that significant improvements in the control of glycemic levels for diabetes patients can be achieved. The interactive approach of mHealth for monitoring blood glucose, diet, physical activity, and medication adherence was revealed by Saffari et al. (2014). Various analysis on diabetes self-management approaches through the utilization of mHealth showed that the monitoring of specific features, such as measured hemoglobin A1c, can result in significant health outcomes (Krishna and Boren 2008). Parkinson's disease is a movement disorder of the central nervous system affecting about 6.3 million worldwide (Liu et al. 2017; Darweesh et al. 2016). The integration of sensors in smartphone sensors resulted in a powerful tool, allowing the accurate measurement and evaluation of different movement-related metrics, and it has gained the interest of researchers (Patel et al. 2008, 2009, 2010).

1.2 mHealth for Cardiovascular Diseases

Cardiovascular disease (CVD) is a chronic disease with a high prevalence (http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf), and it consists a clinical field in which mHealth could provide several advantages. A variety of unhealthy lifestyle behaviors are related to CVD. The on time and continuous monitoring of these factors could significantly lower individuals CVD onset risk. For example, obesity is associated with several physical and mental health conditions, such as CVD, and according to evidence, a weight loss of 3–5% may delay or even prevent CVD onset and progression (https://www.researchgate.net/publication/12144466_Long-term_weight_loss_and_changes_in_blood_pressure_results_of_the_Trials_of_Hypertension_Prevention_phase_II; Look AHEAD Research Group and Wing 2010). In recent years, the use of smartphones and the provided functionalities for weight loss interventions have increased exponentially (Bacigalupo et al. 2013; Stephens and Allen 2013). In addition, for those at risk, the access to diagnostic tools, which are able to detect the disease at an earlier stage and provide outpatient monitoring with the associated improved care delivery and quality of life (QoL), has great promise. This can be achieved by the incorporation of informative ECG tools in smartphone-enabling technologies, which provides diagnostic ability in a scalable and cost-efficient way (Eapen et al. 2016).

1.3 mHealth and Heart Failure

Heart failure (HF) is a chronic cardiovascular life-threatening condition. It is characterized by high rates of hospitalizations, readmissions, and outpatient visits. These facts transform HF to a substantial economic burden for healthcare systems. The statistics show that (i) 26 million adults globally are diagnosed with HF, (ii) 3.6 million are newly diagnosed, every year, and (iii) 3–5% of hospital admissions are attributed to HF incidents. Recent studies reveal that the direct and indirect costs are up to 2% of all the healthcare expenditure (Ponikowski et al. 2014; Authors/Task Force Members et al. 2012; Blecker et al. 2013). All these, in combination with the fact that the HF population is rapidly growing, make the improvement of the HF management the main objective and priority of cardiovascular healthcare systems. The available approaches and interventions assisting HF patients in disease management include (i) nurse or healthcare professional group consultations (Feldman et al. 2009), (ii) -internet-based tools (Nolan et al. 2014), (iii) printed materials (Taylor-Clarke et al. 2012), and (vi) mHealth applications (Martínez-Pérez et al. 2013b) being the most promising (Karhula et al. 2015).

The mHealth-based interventions can have several characteristics that give them the potential to be more effective, among which the most important are (i) *interactivity* that allows the bidirectional communication and the care delivery, as a form of personal coach, (ii) *personalization* that makes the mHealth interventions customizable to the individual's needs, (iii) *timeliness* which permits the evaluation and delivery of targeted information at the right time point, (iv) *context sensitivity* expressing the ability of interventions to be adapted on the circumstances and/or the individual's environment, and (v) *ubiquity and accessibility* of the technology to all segments of population (Dicianno et al. 2015).

The use of mobile technology in HF management has attracted the interest of several researchers, resulting thus to the presence of a large number of reviews in the literature. The reviews focus on the description and comparison of different existing, in the last decade, mHealth interventions, as well as on their impact (Louis et al. 2003; Martínez et al. 2006; Chaudhry et al. 2007a; Maric et al. 2009; Cajita et al. 2016). The aim of this study is to present a short review of the mHealth HF interventions including also commercial available mHealth HF interventions and mHealth research projects related to HF patient management.

2 Heart Failure Clinical Problem and Current Practices

HF is a clinical syndrome that results from any structural or functional impairment of heart function, including (i) dilated and familial cardiomyopathies, (ii) endocrine and metabolic causes of cardiomyopathy (obesity, diabetic cardiomyopathy, thyroid disease, acromegaly and growth hormone deficiency, alcoholic cardiomyopathy, etc.), (iii) tachycardia-induced cardiomyopathy, (iv) myocarditis, (v) peripartum cardiomyopathy, (vi) cardiomyopathy caused by iron overload, (vii) amyloidosis, (viii) cardiac sarcoidosis, and (ix) stress cardiomyopathy. The HF patients suffer from a variety of symptoms, such as dyspnea, fatigue, low exercise tolerance, retention of pulmonary and/or peripheral fluid, urinary disorder (Tannenbaum and Johnell 2014), fast or irregular heartbeat (Pastor-Pérez et al. 2010), and breathing difficulties during sleep (Sharma et al. 2011), at rest, or at exercise (Bozkurt and Mann 2003). According to the ESC guidelines (Authors/Task Force Members et al. 2012), the procedure for evaluating the disease in HF patients in a non-acute setting includes the following steps:

Step 1: *History and physical examination*. The healthcare professional, during the first step of the HF evaluation process, estimates the probability of HF based on the following parameters: (i) family history, (ii) NYHA class, (iii) weight, (iv) duration and severity of symptoms,

(v) received medication, (vi) history of rehospitalization, (vii) lifestyle of the patient (nutrition and exercise), (viii) medical condition – comorbidities, and (ix) adherence to treatment.

Step 2: *Electrocardiogram* (*ECG*). The resting ECG provides information regarding the presence of abnormalities, such as atrial fibrillation and left ventricular (hypertrophy and repolarization). In case all elements (collected during first and second step of the diagnosis process) are normal, HF is unlikely; otherwise laboratory tests (third step) should be performed.

Step 3: *Laboratory tests*. Laboratory tests include routine blood and urine analysis and examination of natriuretic peptide (NT-proBNP) (Ewald et al. 2008; Maisel et al. 2008), cardiac troponin T or I (Horwich et al. 2003), and other emerging biomarkers. Based on these measurements, the experts are able to identify the patients who need echocardiography. Echocardiography is the method that is followed in patients with suspected HF, due to its high accuracy, increased safety, and low cost.

Step 4: *Noninvasive and invasive testing*. Other imaging modalities, such as chest X-ray, stress echocardiography, cardiovascular magnetic resonance imaging, *single photon emission computed tomography radionuclide ventriculography*, and positron emission tomography, can complement echocardiography in case specific clinical questions must be answered. Invasive tests, such as coronary angiography, right-heart catheterization, and endomyocardial biopsy, can be performed when they have a meaningful clinical consequence.

Step 5: *Risk scoring*. Certain risk scoring to homogenize the daily clinical practice and to assist the healthcare professionals in making therapeutic decision (Seattle HF, CHARM Risk Score, CORONA Risk Score, EFFECT Risk Score, etc.) is currently used in the clinical practice.

Framingham, Boston, the Gothenburg, and the ESC criteria are among the most common criteria used in the clinical practice for the determination of the presence of HF (Roger 2010). For the estimation of HF severity, the experts use the New York Heart Association (NYHA) or the American College of Cardiology/American Heart Association (ACC/AHA) guidelines classification systems. These criteria/classification systems are based on the combination of information collected through the diagnosis process and allow the experts to determine the most appropriate treatment for the HF patients (Dickstein et al. 2008).

The objectives of treatment in patients with HF are to improve their clinical status, functional capacity, and QoL, prevent hospital admission, and reduce mortality. Among the recommendations for the treatment of HF patients are (Yancy et al. 2013; McKelvie et al. 2013; National Clinical Guideline Centre (UK) 2010) (i) medication treatment, (ii) nutrition suggestions, (iii) exercise training, (iv) education, and (v) adherence.

The evolution in the field of medicine contributed to a widely available amount of medication for HF. In specific HF stages, patients are more likely to be prescribed more than one kind of medication (Paulus and van Ballegoij 2010). Lifestyle modifications (nutrition and physical activity) should also be performed by HF patients on a daily basis. Specific attention should be paid to the weight monitoring since it is a key element in HF self-management (Krum et al. 2011; Writing Committee Members et al. 2013), associated with repeated hospitalization (Chaudhry et al. 2007b) and increased mortality (Fiutowski et al. 2008). Non-adherent behavior places barriers to the exploitation of existing knowledge and thus has a negative impact on the patient's clinical status and overall QoL. Even though the HF patients have at their disposal a plethora of health-based knowledge, the adoption of this knowledge in their life is lacking. Recent evidence reveal that less than 50% of the HF patients are regularly monitoring their weight, while about 33% of HF patients do not take any action (van der Wal et al. 2005). This percentage is in accordance with the fact that patients' nonadherence is among the major factors contributing to the increase of hospitalizations (Fitzgerald et al. 2011).

3 mHealth-Based HF Interventions

The barriers, reported in the previous section, can be overcome by the use of mobile technology. mHealth enables the promotion of health intervention and can positively affect health-related behavior in real time (Riley et al. 2011). A large pool of primary and review studies are available in the literature describing, comparing, and evaluating the mHealth solutions, with the mHealth-based HF solutions attracting the highest number (Kitsiou et al. 2013). The clinical, structural, behavioral, and economic effects of mHealth solutions on HF are among the objectives of primary studies, while the systematic review focuses on different aspects. A systematic review of mHealth-based HF interventions was presented recently by Cajita et al. (2016). This study describes the already available interventions and their impact in terms of all causes of mortality, cardiovascular mortality, HF-related hospitalizations, length of stay, NYHA functional class, left ventricular ejection fraction, QoL, and self-care. According to the authors, the most commonly presented solutions are those that are able to remotely monitor the HF patient's status, using a mobile communication device in combination with a blood pressure sensor, weight scale, and an ECG recorder. Similar observations are reported in (Scherr et al. 2006; Piotrowicz et al. 2012), which indicate the feasibility of portable home-monitoring devices connected to a smartphone to monitor the HF patients with high diagnostic quality and integrity of vital measurements. Specifically, the study of Ledwidge et al. (2013) showed that the weight could be monitored through a wireless weight scale. Specifically, the patient's daily weight data were transmitted to a mobile phone and analyzed by an algorithm to predict the clinical deterioration in HF patients. The TEMA-HF 1 RCT used a telemonitoring system for enabling the healthcare professionals and the HF clinic communication (Dendale et al. 2012). The study included 160 HF patients from seven hospitals who used different sensors for measuring the daily weight, blood pressure (BP), and heart rate (HR). In case the predefined limits were exceeded, automatic alerts were created. The results of TEMA-HF 1 RCT showed that this telemonitoring system achieved a reduction in the hospitalization rate. A telemonitoring system which was used in 50 HF patients showed its value and impact on self-care, disease management, and health-related outcomes (Seto et al. 2012a). The quantitative outcomes revealed the empowerment of the HF patients and the ability of the clinicians to monitor and manage their patients in a more efficient and effective way. Another, similar study suggested that the use of the mobile phone telemonitoring approach could result in improved patient's medication regimen (Seto et al. 2012b). Additionally, this mHealth system provided the HF patients with automated suggestions related to lifestyle behavior. 120 patients from eight clinical centers who participated in the MOBITEL prospective, randomized study (Scherr et al. 2009) were equipped with a smartphone device, a weight scale, and a sphygmomanometer for BP and HR measurements. All the measured vital parameters were transmitted to the mHealth application, while the patients were able to manually insert the perceived medication. Then, the data were collected and analyzed to a secure website, which enabled the numerical and graphical data representation. This mHealth system allowed the remote monitoring of the patients by the physicians, and in case the transmitted values exceeded the personalized limits and/or early warning signs of decompensation existed, an automatic alert was created. The inclusion of the ECG sensor in mHealth systems has also been examined by several studies. Yap et al. (2012) used a chest belt of an ECG device and a specific mHealth application. Leijdekkers and Gay (2008) showed that a self-test mHealth application enables the HF patients to evaluate their clinical condition and support them in avoiding heart attacks, without the need of a healthcare professional. The main concept included (i) the collection and analysis of the ECG data depending on the patient's status, (ii) informed the patient and suggested a visit to

the doctor, and (iii) automatically alerted the emergency services providing the location and the status of the patient. Based on the findings of the previous studies, Seto et al. (2012b) created a rule-based HF mHealth system for measuring the weight, the BP, the HR, and the ECG. After the data collection by the mHealth application, an analysis by the hospital data servers was followed. The aim of this mHealth solution was to create and send alerts to the patients and the clinicians automatically, taking into account the clinical guidelines.

On the other hand, the systematic reviews aimed to summarize the available evidence (Kitsiou et al. 2015). Kitsiou et al. (2015) reviewed the effectiveness of home telemonitoring interventions for HF patients aiming to inform the policy makers, the practitioners, and the researchers. The authors collected, evaluated, and combined existing evidence from 15 reviews published from 2003 to 2015. The evaluation revealed that (i) a better investigation is needed regarding the process by which home telemonitoring provides improved outcomes, (ii) an optimal strategy should be followed for such systems, (iii) the optimal follow-up duration for achieving the expected benefits should be defined, and (iv) further investigation of the differential effectiveness between chronic HF patients and types of home telemonitoring is proposed. Whitehead and Seaton (2016) examined the effectiveness of mobile phone and tablet apps in the self-management of key symptoms of long-term condition management, among which was HF. The authors concluded that mobile phone and tablet apps have the potential to improve symptom management through enhanced symptom control. However, further innovation, optimization, and rigorous research around the field are suggested for allowing the provision of improved healthcare and outcomes. The design, implementation, and evaluation of mHealth technologies for chronic diseases management, like HF, are approached in the review study of Matthew-Maich et al. (2016). The authors concluded that in order to develop a feasible, well-acceptable, and usable mHealth system, the following should be taken into consideration: (i) A user-center design approach should be followed. (ii) A multidisciplinary approach, in which all ecosystem actors are involved in the disease management process, should be applied. (iii) An iterative development process supported by theoretical background knowledge should be designed. (iv) The evaluation of the end user's experience should be based on feasibility, acceptability, usability, and health-related criteria. (v) Barriers regarding organizational and system readiness to adopt mHealth solutions, the perception of different group of end users, user-technology interface that is used, and the existing sociodemographic disparities should be taken into account.

In consideration of the primary and review studies (Cajita et al. 2016; Kitsiou et al. 2015; Fiordelli et al. 2013), a taxonomy of mHealth-based HF interventions is presented in Table 1.

4 Commercial Available mHealth-Based HF Applications

Transformation of research results to a commercial product lead to commercial available mHealth-based HF solutions. The solutions are presented in the table below (Table 2) along with their privacy policy (Masterson Creber et al. 2016), their Institute for Healthcare Informatics (IMS) functionality scoring (IMS Institute for Healthcare Informatics 2017), their Mobile Application Rating Scale (MARS) score (Stoyanov et al. 2015), and their Heart Failure Society of America (HFSA) guidelines score (Masterson Creber et al. 2016). A short description of IMS, MARS, and HFSA scores is presented in Tables 3, 4, and 5, respectively.

Based on the HFSA guidelines score, the application that addresses all the HF-specific self-care behaviors is the Heart Failure Health Storylines (https://itunes.apple.com/us/app/heart-failure-health-storylines/id1062725794?mt=8). *AskMD* application followed by *WebMD*, *Symple*, *Heart Failure Health Storylines*, and *ContinuousCare Health App*

Table 1 Taxonomy of mHealth-based HF interventions

Dimension		
Functionality	Remote monitoring	Clinical monitoring
		Home monitoring
		Self-monitoring
	Training/education	
	Point of care diagnostic	Embedded software application
		Connected devices
		Sensors
		Mobile attachments
	Behavior modification	Cessation
		Promotion
		Self-management
	Efficiency and productivity	Data collection
		Communication
		Telemonitoring
	Compliance	Treatment
		Medication
		Self-testing
Technical modalities	Mobile features	Text messaging
		Features developed ad hoc for a specific condition
		Add-ons
		Voice
		Video
		Multimedia messaging services
	Type of devices	Mobile devices, including a blood pressure measuring sensor, weight scale, electrocardiogram recorder, or an implantable defibrillator equipped with a heart rhythm monitoring function
		Videoconference equipment
		Automated telemonitoring stations
		Mobile phones
		Tablets
	Technological approach employed for the collection and transmission of data	Central monitoring center/platform
		Automatic data transfer between the participants and the monitoring center
		Manually input and transfer of patients data to the monitoring center
		Algorithms determining whether the patient's values are outside their predefined limits which would then trigger an alert message to be sent to the participants physicians
		Nurses and physicians in their central monitoring centers who regularly monitored the participants status
		Structured approach in contacting participants regarding their status
Design process	User-centered design	
	Multidisciplinary team approach	
Policy consideration	Data management	On-device storage
		On-site servers
		Cloud computing
	Food and Drug Administration regulation	
	Mobile security	

Table 2 The scoring of the commercially available mHealth applications for HF

Application name (platform)[a]	Privacy policy	HFSA guidelines score	IMS	MARS
ASCVD[c] *Risk Estimator* (Apple)	No	3	6	3.6
AskMD (Apple)	No	4	9	4.9
BloodPressureDB (Google)	Yes	3	7	3.2
Cardiograph (Google)	Yes	2	5	3.2
Continuous Care Health App (Apple and Google)	Yes	6	11	4.0
FAQs in Heart Failure (Google)	No	0	2	3.6
Health Manager (Apple)	Yes	4	7	2.5
Healthy Ally (Google)	Yes	1	6	3.8
Healthy Heart (Google)	No	0	1	0.8
Healthy Heart Numbers (Amazon)	No	1	2	1.3
Heart Disease (Google and Amazon)	No	0	1	2.2
Heart Disease & Symptoms (Google)	No	1	0	2.7
Heart Failure Health Storylines (Apple and Google)	Yes	8	10	4.1
Heart Guide (Google)	Yes	1	4	3.4
Heartkeeper (Google)	Yes	4	7	3.9
Heart Log (Apple)	No	2	5	3.8
Heart Services (Google)	No	0	3	2.5
iTreat-Medical Dictionary (Apple and Google)	Yes	0	4	1.7
iTriage (Apple and Google)	Yes	5	9	3.5
mediSOS (Google)	Yes	2	4	3.9
Miniatlas Hypertension (Apple)	No	0	3	3.5
My Cardiologist (Google)	No	1	2	2.0
My Health Tracker (Amazon)	No	1	3	1.7
My Heart Rate Monitor & Pulse Rate (Apple)	No	2	5	2.4
MyHeartApp (Apple)	No	4	4	3.7
Pulse Pro (Apple)	Yes	2	4	2.9
REKA (Google)	Yes	2	3	3.5
SelfCare-My Health Record (*MHR*) (Apple)	No	2	5	3.4
Symple (Apple)	Yes	3	11	4.3
Track your Heart Failure Zone (Amazon)	No	0	2	1.3
Urgent Care 24/7 (Apple)	Yes	4	9	3.7
URI Life (Google)	Yes	5	6	3.1
WebMD (Apple and Google)	No	7	11	4.4
WOW ME 2000 mg (Apple and Google)	No	7	7	3.4

[a]Applications are available in Android Google Play, Apple iTunes, and Amazon Appstore

had the highest average MARS score. The evaluation of the applications in terms of 4 subscale scores (engagement, functionality, aesthetics, and information) revealed that *AskMD* has the highest score for engagement, functionality, aesthetics, and information, while *Heart Failure Health Storylines* application is on the top of the list for behavior change (Masterson Creber et al. 2016). The commercially available applications were also evaluated regarding the functionalities they provide based on the IMS score. The results indicated that the *WebMD*, *Symple*, and *ContinuousCare Health App* had a total of 11 functionalities, while *Heart Failure Health Storylines* follow with 10 functionalities (Masterson Creber et al. 2016). The five top applications based on the three scores are the following: *Heart Failure Health Storylines*, *Symple*, *ContinuousCare Health App*, *WebMD*, *and AskMD*. A description of the Heart Failure Health Storylines application is provided in Table 6.

Table 3 IMS Institute for Healthcare Informatics functionality scoring criteria

IMS Institute for Healthcare Informatics functionality scoring criteria	
Functionality scoring criteria	Description
1. *Inform*	Provides information in a variety of formats (text, photo, video)
2. *Instruct*	Provides instructions to the user
3. *Record*	Capture user-entered data
Collect data	Able to enter and store health data on individual phone
Share data	Able to transmit health data
Evaluate data	Able to evaluate the entered health data by patient and provider, provider and administrator, or patient and caregiver
Intervene	Able to send alerts based on the data collected or propose behavioral intervention or changes
4. *Display*	Graphically display user-entered data/output user-entered data
5. *Guide*	Provide guidance based on user-entered information, may further offer a diagnosis, or recommend a consultation with a physician/a course of treatment
6. *Remind or alert*	Provide reminders to the user
7. *Communicate*	Provide communication with healthcare provider/patients and/or provide links to social networks

5 mHealth Projects Related to HF Management

Several projects are related to HF management. A short description of indicative projects accompanied with their comparison is depicted in Table 7.

The objective of RENEWING HEALTH (Regions of Europe Working together for Health) project (http://www.renewinghealth.eu/) was to implement, validate, and assess innovative telemedicine solutions for chronic diseases' management. Specifically, the project follows a patient-centered approach with the patient having a central role in the management of his/her own disease. It allows the (i) choice and dosage of medications for improving the medication adherence and (ii) early detection of early signs of worsening.

The exploitation and further deployment of the telemedicine services implemented within the RENEWING HEALTH project are the main objectives of the United4Health project (http://united4health.eu/). The patient-centered approach and the use of telemonitoring for the treatment of patients with diabetes, chronic obstructive pulmonary disease, or CVD diseases are applied to all the service solutions. Services engage patients in the management of their disease, optimize the choice and dosage of medications, promote compliance to treatment, and help professionals to detect early signs of worsening. The patients use medical devices to measure the heart rate, blood pressure, pulse oximetry, and weight. The collected data are wirelessly forward from the medical device to a central gateway, and a clinical operator evaluates them. The telemedicine solution is able to detect abnormal measurements and triggers an alert to the operator to investigate further the collected data and proceed to the appropriate decisions and actions.

The HeartCycle project (http://www.heartcycle.eu/) proposed a disease management solution, based on Phillips commercial platform Motiva® (http://www.healthcare.philips.com/main/products/telehealth/products/motiva.wpd), for supporting and empowering the patients with HF. This is achieved by monitoring and analyzing vital signs and other measurements, including weight and physical activity activities. The patients are using a shirt with an embedded sensor for collecting the patient's vital signs during exercising. The communication between patient and healthcare professional is enabled through the patient's television. Personalized suggestions and educational material related to the patient's disease are projected through television after being analyzed by specific algorithms.

Table 4 MARS – Mobile Application Rating Scale score

Engage	Fun, interesting, customizable, interactive (e.g., sends alerts, messages, reminders, feedback, enables sharing), well targeted to the audience
	1. Entertainment: Is the app fun/entertaining to use? Does it use any strategies to increase engagement through entertainment (e.g., through gamification)?
	2. Interest: Is the app interesting to use? Does it use any strategies to increase engagement by presenting its content in an interesting way?
	3. Customization: Does it provide/retain all necessary settings/preferences for apps features (e.g., sound, content, notifications, etc.)?
	4. Interactivity: Does it allow user input, provide feedback, and contain prompts (reminders, sharing options, notifications, etc.)? Note: These functions need to be customizable and not overwhelming in order to be perfect.
	5. Target group: Is the app content (visual information, language, design) appropriate for your target audience?
Function	App functioning, easy to learn, navigation, flow logic, and gestural design of app
	6. Performance: How accurately/fast do the app features (functions) and components (buttons/menus) work?
	7. Ease of use: How easy is it to learn how to use the app; how clear are the menu labels/icons and instructions?
	8. Navigation: Is moving between screens logical/accurate/appropriate/ uninterrupted; are all necessary screen links present?
	9. Gestural design: Are interactions (taps/swipes/pinches/scrolls) consistent and intuitive across all components/screens?
Aesthetics	Graphic design, overall visual appeal, color scheme, and stylistic consistency
	10. Layout: Are arrangement and size of buttons/icons/menus/content on the screen appropriate or zoomable if needed?
	11. Graphics: How high is the quality/resolution of graphics used for buttons/icons/menus/content?
	12. Visual appeal: How good does the app look?
Information	Contains high-quality information (e.g., text, feedback, measures, references) from a credible source
	13. Accuracy of app description (in app store): Does app contain what is described?
	14. Goals: Does app have specific, measurable, and achievable goals (specified in app store description or within the app itself)?
	15. Quality of information: Is the app content correct, well written, and relevant to the goal/topic of the app?
	16. Quantity of information: Is the extent coverage within the scope of the app and comprehensive but concise?
	17. Visual information: Is visual explanation of concepts – through charts/graphs/images/videos, etc. – clear, logical, and correct?
	18. Credibility: Does the app come from a legitimate source (specified in app store description or within the app itself)?
	19. Evidence base: Has the app been trialed/tested (must be verified by evidence (in published scientific literature))?
Satisfaction	
	20. Would you recommend this app to people who might benefit from it?
	21. How many times do you think you would use this app in the next 12 months if it was relevant to you?
	23. Would you pay for this app?
	24. What is your overall star rating of the app?
Behavior change	
	25. Awareness: This app is likely to increase awareness of the importance of addressing [insert target health behavior]
	26. Knowledge: This app is likely to increase knowledge/understanding of [insert target health behavior]
	27. Attitudes: This app is likely to change attitudes toward improving [insert target health behavior]

(continued)

Table 4 (continued)

	28. Intention to change: This app is likely to increase intentions/motivation to address [insert target health behavior]
	29. Help seeking: Use of this app is likely to encourage further help seeking for [insert target health behavior] (if it's required)
	30. Behavior change: Use of this app is likely increase/decrease [insert target health behavior]

Table 5 HFSA – Heart Failure Society of America – recommended nonpharmacologic management behaviors

Weight	Daily weighing
Check swelling	Checking extremities for swelling
Physical activity	Doing physical activity or exercise
Diet	Eating a low-salt diet
Medication	Taking daily medications
MD appointment	Attending doctor's appointments
Monitor symptoms	Daily monitoring of HF symptoms
Symptom response	Actively responding to symptoms when they change

Table 6 Heart Failure Health Storylines application short description

	Heart Failure Health Storylines *By Self Care Catalysts Inc.* https://play.google.com/store/apps/details?id=com.selfcarecatalyst.healthstorylines.hf&hl=el
Developed in partnership with the Heart Failure Society of America and is powered by the Health Storylines™ platform from Self Care Catalysts Inc.	
Heart Failure Health Storylines provides tools to better manage and monitor heart failure	
Medication reminder: Sends reminders for medication intake in the users mobile device	
Symptom tracker: Allows tracking of symptoms and side effects and provides patterns that should be shared with the healthcare provider	
Daily vitals: User can keep a record of important vital measurements and provides graphical representation of them over time	
Physical activity tracker: Keeps track of physical activity levels	
Sync a device: User can import data from other health and fitness applications	
Daily moods and journal: Track and understand users' emotions and what might be driving them. Additionally, keep a journal for increasing well-being	

The HeartMan project (http://cordis.europa.eu/project/rcn/199014_en.html) developed a personal mHealth system for assisting the HF patients and providing them personalized advice and support. The key components include (i) the development of evidence-based predictive models, (ii) the creation of long-term models which focus on modifiable parameters, (iii) the delivery of a cognitive behavioral approach including mindfulness exercises, and (iv) the use of advanced health monitoring devices for monitoring the physical and psychological state of the patient.

HEARTEN (http://www.hearten.eu/) takes advantage of the cloud technologies for computing and serving information. HEARTEN is a solution which can be used from all actors involved in the management of a HF patient,

Table 7 Comparison of mHealth research projects related to HF

	RENEWING HEALTH (http://www.renewinghealth.eu/)	United4Health (http://united4health.eu/)	HeartCycle (http://www.heartcycle.eu/)	HeartMan (http://cordis.europa.eu/project/rcn/199014_en.html)	HEARTEN (http://www.hearten.eu/)
Users					
Patients	✓	✓	✓	✓	✓
Medical professionals	✓	✓	✓	✓	✓
Nurses	✓	✓	X	X	✓
Caregivers	X	X	X	X	✓
Patient-centered ecosystem	X	X	X	X	✓
Devices					
Smartphones	X	X	X	✓	✓
Medical devices/ sensors	✓	✓	✓	✓	✓
Developed new medical devices/ sensors	X	X	X	X	✓
Communication hub/ mobile device	✓	✓	✓	✓	✓
Breath/ saliva biosensors	X	X	X	X	✓
Data monitoring					
Real-time monitoring	✓	✓	✓	✓	✓
Integrated DSS	✓	✓	✓	✓	✓
Real-time triggers to healthcare professionals	✓	✓	✓	✓	✓
Real-time triggering to patients	X	X	✓	✓	✓
Real-time triggering to other ecosystem actors	X	X	X	X	✓
Use of artificial intelligence					
Artificial intelligence on evaluation and predictive model for collected data	X	X	X	✓	✓
DSS patient personalization	X	X	X	✓	✓
Data mining techniques	X	X	X	✓	✓
Sharing and communication					
Medical data available across all users	X	X	✓	✓	✓
Automated notifications/ reminders to the users aiming the patients	X	X	X	✓	✓
Escalation of notifications depending on the importance	X	X	X	X	✓
Automatic change of communication channel and/or route in case of no response within a time period	X	X	X	X	✓
Real-time communication between the users	X	X	X	✓	✓
Platform – infrastructure					
Cloud services and services	X	X	X	✓	✓
Web access	✓	✓	✓	✓	✓
mHealth	X	X	X	✓	✓
Common data repository	X	X	X	N/A	✓

including caregivers and other ecosystem actors. The integrated Knowledge Management System and the Dynamic Patient Communication Protocol provide real-time monitoring, notifications, and reminders, overcoming the barrier of non-personalized patient management and treatment. This is achieved through the employment of artificial intelligence and data mining techniques. Furthermore, HEARTEN's alerting mechanism adapts the behavior of its users and can change the channel and route of communication, enabling the active communication and interaction.

6 Challenges to the Development and Adoption of mHealth Solutions

Although the impact of mHealth solutions is well accepted, several challenges for the development and adoption of the mHealth solutions should be addressed (Eapen et al. 2016; Matthew-Maich et al. 2016). Among the factors which support or hinder the implementation of mHealth solutions include (i) the institutional environment such as culture, policies, and readiness to change and integrate such systems, (ii) the availability of a comprehensive business and exploitation plan, (iii) personal factors of the different end users including perceived value of the mHealth solutions, and (iv) factors related to the solution itself, such as usability by the different types of end users. The challenges can be categorized to the following perspectives: (i) patient and healthcare professionals, (ii) payer, (iii) provider, and (iv) regulatory bodies.

Patient and Healthcare Professionals

A barrier to the adoption of mHealth solutions by the patients and the healthcare professionals is that the applied approaches neglect to address the impact of the solution to the workload adjustments, to the practice preferences, and to the existing daily routines of the end users. Healthcare professionals will not be positive to the adoption of such a solution in case they are not convinced about the benefits and the added value in terms of professional role support. Furthermore, the perception that the solution can act as a supportive tool of organizational micromanagement reduces their willingness to adopt the solution. On the other side, patients prefer solutions that can be seamlessly integrated in their daily activities without consuming their functional and time capacity. Beside the perceived value, factors related to the usability of the solution and the level of engagement they provide to the different type of end users are important factors for the adoption of the mHealth solutions. Solutions that are considered time-consuming, unreliable, burdensome, which require the entry of information and/or provide feedback through nonuser-friendly interfaces or even create doubts to the users regarding the protection of health information, remain a central concern.

The dispersion of mHealth solutions is affected by socioeconomic and demographic disparities. For instance, elderly and patients with low income are those most benefited by the mHealth solutions. However, such groups in general have the least amount of access to the mobile devices.

Payers

The adoption/acceptance of a mHealth solution depends on payers. Payers should take into account the healthcare incentives and implementation reimbursement. Beyond the financial motivation, payers can aggregate and synthesize evidence to enhance learning and use of mHealth solutions. Additionally, the interaction of patients with payers through the utilization of mHealth allows patients' outcomes and experiences to be measured. Through mHealth-based care management programs, payers and self-insured employees can manage previously outsourced prevention and wellness programs.

Providers

The mHealth tools focus on providers as the purchasers of the tools. Clinicians present the

lowest rate of mHealth tools adoption. This could potentially be attributed to (i) the clinicians' frustration with current health information technologies, (ii) the poor workflow integration and lack of interoperability that result to the provider's reluctance to health information technology acceptance, (iii) the uncertainty about the reliability of the data, (iv) the lack of adequate decision support, (v) the need of being provided with a holistic personalized care and delivering clinically meaningful support based on data analysis, (vi) the lack of high-quality mHealth evidence-based diagnostic and treatment strategies, (vii) the concern about the related ethical and legal issues, and (viii) the lack of clear reimbursement strategy.

Regulatory Bodies

The rapid proliferation of mHealth products created regulatory challenges. The Food and Drug Administration has issued guidance to assist the manufactures to further understand what items fall under the purview of regulators. It limits its scope to mobile medical applications intended to "be used as an accessory to regulated medical device" or to "transform a mobile platform into a regulated medical device" (https://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf).

7 Conclusions

A taxonomy of mHealth-based HF interventions, a comparison of commercially available applications of HF, and a review of research projects related to HF are presented in the current study. Through this overview, the evolution of mHealth solutions for HF management is depicted concluding to several challenges, concerning patients, healthcare professionals, payers, providers, and regulatory bodies, which should be addressed. It is clear that the advancements in mobile technology have spurred growth and innovation in the health sector. More specifically in the field of HF management, this is expressed through the increasing number of researchers and the corresponding studies focusing on the HF management (diagnosis, severity estimation, prediction, adherence estimation, etc.) and the transformation of the studies to European Union funded projects and consequently to consumer applications. Although the rapid evolution of mHealth solutions for HF management, the assessment of the impact of those solutions on patients' life and especially in HF outcomes should be further studied. Some initial studies indicate that, in order for the mHealth solutions for HF to have substantial impact, a multidisciplinary approach should be followed where representatives of healthcare and technology fields should closely cooperate not only between each other but also with patients.

Acknowledgments This work is supported by the HEARTEN project that has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 643694.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 373–385
DOI 10.1007/5584_2017_106
© Springer International Publishing AG 2017
Published online: 28 September 2017

New Insights in Cardiac Calcium Handling and Excitation-Contraction Coupling

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Abstract

Excitation-contraction (EC) coupling denotes the conversion of electric stimulus in mechanic output in contractile cells. Several studies have demonstrated that calcium (Ca^{2+}) plays a pivotal role in this process. Here we present a comprehensive and updated description of the main systems involved in cardiac Ca^{2+} handling that ensure a functional EC coupling and their pathological alterations, mainly related to heart failure.

Keywords

Calcium · RyR · Mitochondria · SerCa · Contraction · Heart Failure

1 Introduction

Each heartbeat is the result of calcium (Ca^{2+}) release and reuptake. During this cycle, the presence of this cation is essential to convert electric stimulation (action potential) in mechanic output (contraction), in a process commonly termed excitation-contraction (EC) coupling (Santulli et al. 2017a; Fabiato and Fabiato 1975). The action potential is the electrical signal that depolarizes the plasma membrane of cardiac myocytes, allowing the entrance of a relatively low amount of extracellular Ca^{2+}, which in turn induces high Ca^{2+} release from the sarcoplasmic reticulum (SR) (Lenzi and Caniggia 1953). Cytosolic Ca^{2+} binds to myofilaments, activating contractile machinery (Ebashi et al. 1967; Reddy and Honig 1972). This "Ca^{2+}-induced Ca^{2+} release"

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(CICR), represents a positive feedback mechanism that allows the functional coupling between plasma membrane and SR (Katz 1967; Fabiato and Fabiato 1979; Fabiato 1983; Isenberg and Han 1994).

2 Microanatomy of EC Coupling

In cardiac cells, the structural units that mediate CICR are termed "diads" (Page et al. 1971; Soeller and Cannell 1997), consisting in specialized cellular micro-domains each composed by terminal cisternae of SR, also known as junctional SR, localized in close proximity to a tubular invagination of the plasma membrane, the transverse tubule (T-tubules) (Soeller and Cannell 1997; Shacklock et al. 1995; Clark et al. 2001). On the side of plasma membrane, along T-tubules, there are voltage-gated Ca^{2+} channels (T-Type and L-type, also known as dihydropyridine receptors, DHPRs), whereas on the side of SR cisternae there are intracellular Ca^{2+} release channels (ryanodine receptors, RyRs) (Pinali et al. 2017; Crocini et al. 2016; Li et al. 2015; Fameli et al. 2014).

Ca^{2+} channels on T-tubules are activated by depolarization and through them Ca^{2+} from the extracellular compartment goes in the cytosol, and activates RyR channels located on the SR of the same diad (Keizer and Levine 1996; Nakai et al. 1997). It has been estimated that for each Ca^{2+} channel opened on T-tubules, about 4–6 RyR channels are activated on SR, which in turn can activate neighboring RyR channels, resulting in massive release of Ca^{2+} from SR (Wang et al. 2001; Paolini et al. 2004).

3 Troponin, Tropomyosin, and Ca^{2+}: How Force Is Produced

The troponin complex consists of three subunits: tropomyosin-binding (T), inhibitory (I), and Ca^{2+} sensor (C). Troponin-T anchors the other two subunits on tropomyosin. Troponin I, under resting intracellular levels of Ca^{2+}, competes with tropomyosin for a common binding site on actin myofilaments, forcing tropomyosin into a position where it sterically blocks the binding of myosin heads (Lehman et al. 2013; Rao et al. 2014). The binding of cytosolic Ca^{2+} to Troponin-C induces conformational changes leading to the so-called activated state, in which myosin-binding sites on actin are exposed (Wang et al. 1999; Lehman et al. 2009). Then, the formation of cross-bridges between actin and myosin produces the sliding of myofilaments one over the other, eventually resulting in muscle contraction (Brunello et al. 2014; Kawai et al. 2006; Piazzesi and Lombardi 1996).

The inodilator levosimendan is a Ca^{2+} sensitizer that acts via binding the Ca^{2+}-saturated Troponin-C (Gustafsson et al. 2017). In particular, hydrogen-bond donor and acceptor groups on the pyridazinone ring and on the mesoxalonitrile–hydrazone moieties of levosimendan bind to a hydrophobic pocket of the Ca^{2+}-saturated amminoterminal domain of Troponin-C (Robertson et al. 2008). The main consequence of levosimendan binding is that the Ca^{2+}-saturated Troponin-C is stabilized in the presence of the drug, thereby promoting contractile force without an increase in the amplitude of intracellular Ca^{2+} transient. Levosimendan also acts via activation of ATP-sensitive K^+ channels (Grossini et al. 2009). In clinical trials levosimendan exhibited non-consistent results, especially in terms of mortality (Mebazaa et al. 2007; Polzl et al. 2017; Landoni et al. 2017).

Ca^{2+} handling within cardiac myocytes is in a delicate and dynamic equilibrium, which relies on several physiological modulators and subcellular systems, structurally and functionally related. Importantly, the amount of Ca^{2+} extruded by the cell during relaxation must be the same as the amount entering during the contraction (Karlstad et al. 2012). After the contraction phase, several mechanisms contribute to relaxation. Notably, Ca^{2+} is a fundamental determinant also during relaxation, since the correct functioning of channels responsible for cytosolic Ca^{2+} removal strictly depends on Ca^{2+} concentration (Allen et al. 1988; Plummer et al. 2011; Subramani et al. 2005).

4 Ca^{2+} Handling in the Pathogenesis of Heart Failure: New Insights

An accurate cardiac Ca^{2+} handling warrants the appropriate contraction that allows the heart to pump sufficient blood to meet the metabolic demand of the body. Impairment in cardiac pump function characterizes the pathological condition of heart failure (HF) (Karlstad et al. 2012; Kitsis and Narula 2008). Malfunction of the processes involved in Ca^{2+} handling plays an important role in the pathogenesis of HF, and this kind of alteration in myocytes is a primary defect causing contractile dysfunction in HF (Yano et al. 2005). Modifications in the expression and/or activity of Ca^{2+} channels, alongside with alterations of cardiomyocyte architecture (T-tubules), seem to have a determinant role in failing myocytes (Balke and Shorofsky 1998). The involvement of different Ca^{2+} transporters has been related to the stage and etiology of HF; indeed, studies in human failing hearts suggest that patients with ischemic cardiomyopathy are characterized by impaired Ca^{2+} uptake, while patients with idiopathic dilated cardiomyopathy exhibits mainly modifications in Ca^{2+} release (Sen et al. 2000).

Cardiac contraction is the result of isometric force (or ventricular pressure) and rapid shortening to allow ejection of the blood (Caremani et al. 2016; Colomo et al. 1994). Both of them rely on Ca^{2+}, specifically on amplitude/duration of Ca^{2+} transients, and on sensitivity of myofilaments to Ca^{2+}. To allow the generation of Ca^{2+} transients appropriate in terms of duration and amplitude, cardiac myocytes need a high – and at the same time flexible – capacity of Ca^{2+} buffering. Normally the amount of Ca^{2+} bound is in a 100:1 ratio compared to Ca^{2+} free in the cytosol, and during contraction such ratio immediately increases (about tenfold) in favor to free Ca^{2+} (MacGowan et al. 2006). Ca^{2+} buffering should ensure an optimal removal of free Ca^{2+} from cytosol in order to have an appropriate amount of Ca^{2+} available to the contraction in the next beat.

Each cycle of EC coupling needs a dynamic interplay between Ca^{2+} transient and myofilaments. The sensitivity of myofilaments to Ca^{2+} is high when the myofilaments are stretched, *i.e.* in the phase of cardiac blood filling (diastole) (Zhao et al. 2016). Therefore, right after relaxation the myofilaments are more responsive to Ca^{2+} binding. Such autoregulation is a key mechanism underlying the coordination in EC coupling. Hence, when a perfect overlap of high Ca^{2+} transient and high myofilaments sensitivity to Ca^{2+} is obtained, an appropriate force is generated, leading to an optimal contraction.

Although the exact mechanisms involved in cardiac Ca^{2+} handling are not entirely understood, it is known (Benitah et al. 2003) that EC coupling and cardiac performance are mainly based on two mechanisms: (1) Synchronized Ca^{2+} release during contraction; (2) Effective Ca^{2+} reuptake that ensure a good and robust termination of Ca^{2+} dependent contraction.

To satisfy the first point, there are systems that mediate Ca^{2+} flux towards the cytosol, from extracellular compartment or from intracellular Ca^{2+} stores, *i.e.* SR, during EC coupling (Fig. 1). For the second one, there are systems involved in retrograde Ca^{2+} flux, to terminate EC coupling (Fig. 2).

5 Ca^{2+} Fluxes during Systole

Ca^{2+} flux towards the cytosol starts with the entrance of a small amount of Ca^{2+} from extracellular space, triggering EC coupling: the depolarization wave is "transformed" in high Ca^{2+} release from intracellular store for contraction (Nanasi et al. 2017). The individual events of local Ca^{2+} release from SR are named Ca^{2+} sparks and reflect the activation of a cluster of about 6–20 Ca^{2+} channels on SR (Xie et al. 2013). Single Ca^{2+} sparks occur also at rest, and a crucial difference from Ca^{2+} sparks events during EC coupling is the synchronization; indeed, the action potential is able to synchronize several thousand of Ca^{2+} sparks within the same cell (Louch et al. 2013). Thus, individual events of

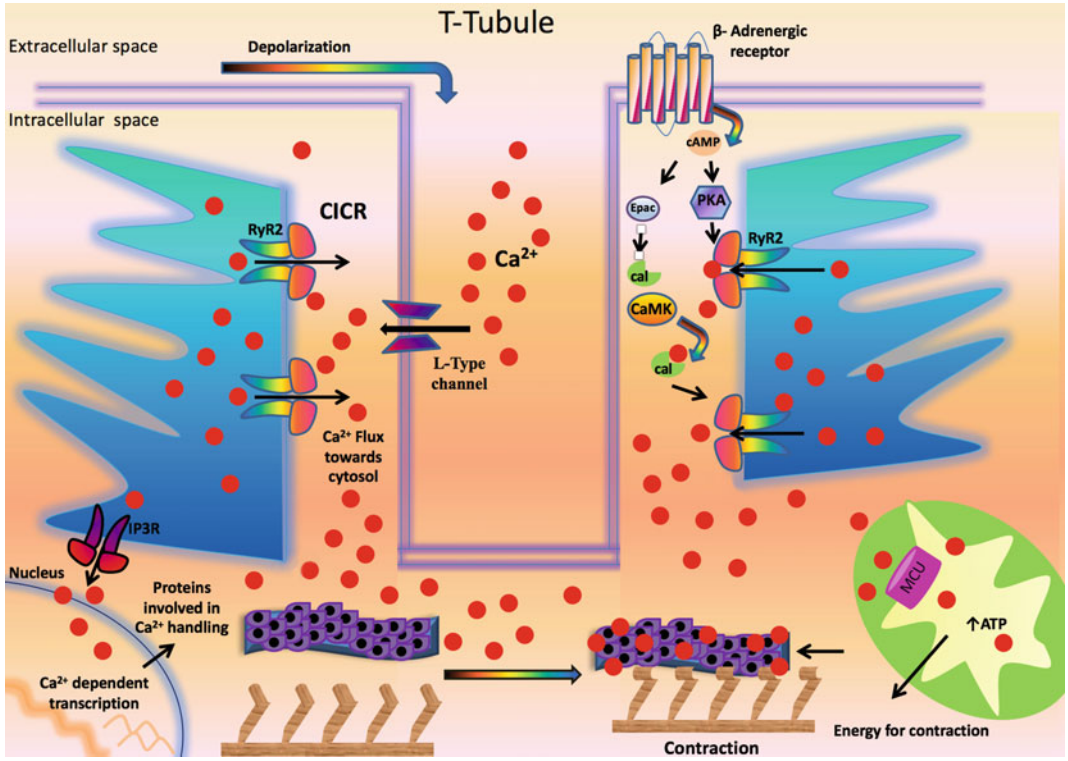

Fig. 1 Role of Ca^{2+} in excitation-contraction coupling in cardiomyocyte. Ca^{2+}: calcium; cal: calmodulin; CaMK: Ca^{2+}/calmodulin-dependent protein kinase; CICR: Ca^{2+}-induced Ca^{2+} release; Epac: exchange protein directly activated by cAMP; IP3R: inositol 1,4,5-trisphosphate receptor; MCU: mitochondrial Ca^{2+} uniporter; PKA: Protein Kinase A; RyR2: Type 2 ryanodine receptor Ca^{2+} release channel

local Ca^{2+} release are overlapping in time and space during EC coupling.

The main cellular complexes mediating Ca^{2+} flux towards cytosol for EC coupling are: voltage sensitive Ca^{2+} channels (T- and L-type) on the plasma membrane and RyRs on the SR.

6 Voltage-Dependent Ca^{2+} Channels

In myocytes there are two main types of voltage-dependent Ca^{2+} channels: T-type and L-type Ca^{2+} channels (Gonzalez-Rodriguez et al. 2015; Shaw and Colecraft 2013). The T-type channels are not preferentially located in the junctional region inside the diads, and the Ca^{2+} current generated by this kind of channels is negligible, with a minimal contribute to EC coupling (Zhou and January 1998). The L-type channels, also known as dihydropyridine receptors (DHPRs), are the main voltage dependent Ca^{2+} channels involved in EC coupling; they mainly localize on the T-tubule, in close proximity of Ca^{2+} channels on SR terminal cisternae (Bodi et al. 2005). DHPRs are activated by depolarization, allowing the Ca^{2+} to enter inside the cytosol and trigger CICR. A strategic auto-regulation of the CICR mechanism occurs at this level: indeed, DHPRs are inhibited by Ca^{2+} itself at the cytosolic side, limiting the amount of Ca^{2+} entry after depolarization. This local inhibitory effect on DHPRs is mediated by calmodulin, which binds the C-terminal domain on the receptor (Pott et al. 2007). Ca^{2+} released from SR in the same sarcolemmal-SR junction has also a modulatory effect on L-type receptors: when SR Ca^{2+} release occurs, the Ca^{2+} flux through DHPRs is reduced (Shiferaw et al. 2003). These events confirm that the Ca^{2+} needed for the contraction primarily derives from SR,

since Ca^{2+} channels on plasma membranes are quickly inhibited after the entrance of small amount of Ca^{2+}.

As mentioned above, action potential is responsible for synchronization of Ca^{2+} release from SR. The specific organization of ion channels on the plasma membrane, and in particular on the specialized invaginations of the T-tubules, plays a pivotal role in EC coupling (Oyehaug et al. 2013; Galbiati et al. 2001). Indeed, the loss of these structures leads to aberrant Ca^{2+} handling with blunted contractility, and such alteration has been mechanistically associated to HF (Wei et al. 2010).

In humans, HF secondary to dilated, hypertrophic, and ischemic cardiomyopathy, is related to aberrant alterations of T-tubule structure and the subsequent not-appropriate organization of voltage-dependent Ca^{2+} channels (Lyon et al. 2009). These anomalies could also be related to impaired function of junctophilins, proteins that are responsible for appropriate positioning of voltage-gated Ca^{2+} channels on T- tubules (Pinali et al. 2017; Schobesberger et al. 2017).

7 Key Role of RyR2 in Cardiac EC Coupling

RyRs are intracellular release channels, deputed to Ca^{2+} release from intracellular stores; the RyR2 isoform represents the most abundant isoform of this family in cardiomyocytes (Tunwell et al. 1996). This name was attributed based on the molecule with a high binding affinity to these receptors: the ryanodine, a natural product, known to induce a paralytic effect on striated muscle (Sutko et al. 1997; Rumberger and Ahrens 1972).

These channels have a tetrameric structure, similar to a mushroom, with the stalk across the SR membrane and the cap towards the cytosol. In this large structure, it is possible to identify at least two functional domains: C-terminus, which represents the ion pore across the membrane, and N-terminus that contains numerous modulatory sites (Gao et al. 1997). Indeed, RyR activity is highly regulated by several molecules – including calmodulin, FK-506 binding protein (FKBP), sorcin, junctin, and triadin (Balshaw et al. 2001; Anthony et al. 2007) – linked to the receptor, which thus represents the scaffold of a large macromolecular complex (Santulli et al. 2017b). Calmodulin and sorcin, two small proteins with high affinity for Ca^{2+}, are able to inhibit RyR when Ca^{2+} levels in the cytosol are higher than a threshold value, preventing further Ca^{2+} release from SR. This phenomenon is involved in EC coupling termination.

RyR has also several sites modulated by Ca^{2+}, Mg^{2+}, phosphorylation, and oxidation, making this receptor also a sensor of intracellular redox state (Hain et al. 1995; Chugun et al. 2007; Xie et al. 2015). Therefore, RyR activity is the result of a multifaceted interactome specialized in Ca^{2+} handling.

Inositol-1,4,5, trisphosphate (IP3) receptors (IP3Rs) represent another example of intracellular Ca^{2+} release channel. Located on the SR as RyR, they are activated by a second messenger, IP3, involved in several pathways. These receptors are closely related to the RyR family, sharing a high structural homology (Santulli et al. 2017a, b; Maltsev et al. 2017). Although there are several stimuli that induce IP3 accumulation, the physiological depolarization of cardiac myocyte, does not seem to activate IP3Rs and their involvement seem to be limited to the regulation of transcription of important modulator of Ca^{2+} handling machinery (*e.g.* CamKII, calcineurin), indirectly contributing to regulate the capacity of the cells to maintain Ca^{2+} homeostasis, indispensable for appropriate EC coupling and contractility (Santulli et al. 2017a; Santulli and Marks 2015). Moreover, IP3R has a different distribution in atrial and ventricular myocytes, compared to RyR2; in particular, IP3Rs are principally located in the atrial myocyte and also in Purkinje fibers (Luo et al. 2008; Mignery et al. 1990). Purkinje fibers are a specialized conduction system, and IP3Rs can modulate the transfer of depolarization wave through ventricular mass.

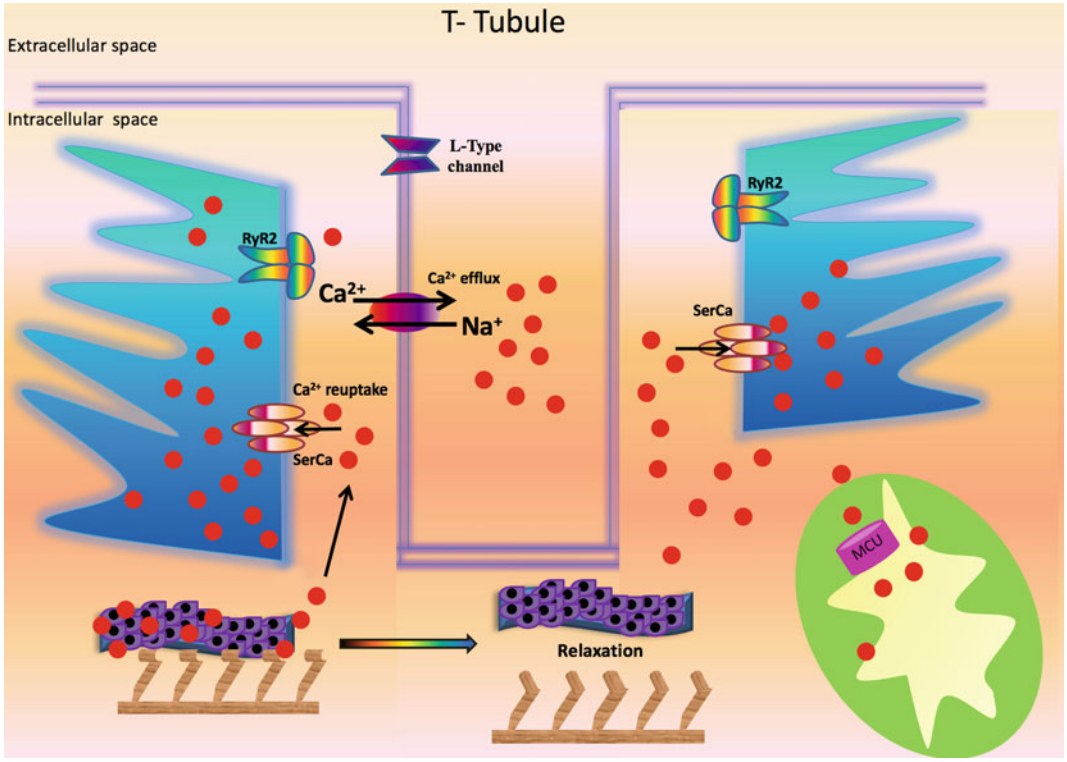

Fig. 2 Mechanistic role of Ca^{2+} in the relaxation phase. Ca^{2+}: calcium; MCU: mitochondrial Ca^{2+} uniporter; Na^{+}: sodium; RyR2: Type 2 ryanodine receptor Ca^{2+} release channel; SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase

8 Ca^{2+} Fluxes During Diastole

To ensure muscle relaxation, mechanisms of Ca^{2+} reuptake from the cytosol actively mediate a retrograde Ca^{2+} flux. The main "cytosolic Ca^{2+} scavengers", Sarco-Endoplasmic reticulum Ca^{2+} ATPase (SerCa) and Na^{+}/Ca^{2+} exchanger, achieve this function (Fig. 2). A large portion of Ca^{2+} is pumped by SerCa from the cytosol back to the SR, but the relative contribute of different Ca^{2+} removal systems can depend on the species.

9 Functional Role of Na^{+}/Ca^{2+} Exchanger in Ca^{2+} Reuptake

Na^{+}/Ca^{2+} exchanger mediates reversibly influx or efflux of Ca^{2+}, depending on concentration of free Ca^{2+} inside the cytosol, but normally it works in Ca^{2+} efflux mode (Fujioka et al. 2000; Luongo et al. 2017). In cardiomyocytes this channel represents the major Ca^{2+} efflux system, with a critical role in the regulation of Ca^{2+} cellular content (Zhu et al. 2015; Acsai et al. 2011). Indeed, some alterations of ionic equilibrium inside the cell, that induce increase in Na^{+} intracellular levels, can trigger changes in the activity of the channel, which starts to work in reverse mode, mediating Na^{+} efflux, with influx of Ca^{2+} ions (Kang and Hilgemann 2004).

10 SerCa-ATPase

SerCa ATPase represents a fundamental pump system mediating Ca^{2+} reuptake in the SR/ER (Zima et al. 2014). In cardiomyocytes, SerCa removes the Ca^{2+} from cytosol during relaxation with an active process (ATP hydrolysis), in order to terminate the EC coupling cycle and to restore Ca^{2+} levels inside SR, necessary for the next contraction.

The correct activity of SerCa, and the indirect interplay with RyR2 that promotes Ca^{2+} flux in the opposite direction, are essential to have an EC coupling cycle with appropriate amplitude and synchronization in space and time. Ca^{2+} itself plays a pivotal role in mediating such interplay (Collins and Thomas 2001). SerCa, as well as RyR2, is highly regulated not only directly by Ca^{2+}, but also by other molecules that are sensitive (CaMKII) or not (PKA) to Ca^{2+}. These two kinases, as seen for RyR2, are able to regulate SerCa, but not via direct phosphorylation, but through phosphorylation of the most important regulator of SerCa, phospholamban. Phospholamban (PLB), is an endogenous inhibitor of SerCa that limits the affinity of the pump for Ca^{2+}. PKA can phosphorylate PLB at Ser^{16}, inhibiting PLB and therefore activating SerCa, increasing its pumping rate (Simmerman et al. 1986). CaMKII, whose activation relies also on the exchange protein directly activated by cAMP (Epac) pathway (de Rooij et al. 1998; Lymperopoulos et al. 2014; Parnell et al. 2015), is able to phosphorylate PLB at Thr^{17}, leading also in this case to an acceleration of SR Ca^{2+} uptake (Simmerman et al. 1986). SerCa is also regulated by the metabolic state of the cell in terms of ATP/ADP ratio, and redox-status (Zima et al. 2014). Alterations in expression or activity of SerCa, strongly contribute to HF development and progression, through dysfunctional Ca^{2+} handling. In particular, several studies show that both mRNA and protein levels of SerCa pump are downregulated in HF (Currie and Smith 1999; Armoundas et al. 2007). The decrease in SerCa/PLB ratio results in impaired SR Ca^{2+} uptake (Linck et al. 2000). Moreover, the regulation of SerCa by both PKA (Schwinger et al. 1998) and CaMKII (Schwinger et al. 1999) is significantly impaired in failing hearts.

11 Intracellular Ca^{2+} Leak: Definition, Pathophysiology, and Interventions

RyR2 interactome ensures the appropriate amplitude and kinetics of Ca^{2+} cycling, indispensable for cardiac contractility. Alterations in RyR2 and/or in RyR2 interactome, are among the main identified aspects of HF (Ono et al. 2000; Kohno et al. 2003). All the events that are able to affect the opening frequency of RyR2, determining changes in amplitude or duration of Ca^{2+} release, can predispose to contractility dysfunction (Patel et al. 2000). In particular, the phenomenon of Ca^{2+} leak, defined as inappropriate release of Ca^{2+} from the SR (*e.g.* during the diastolic phase), is determinant in HF progression (Hofer et al. 1996). In pathological conditions such as HF, there is a high release of Ca^{2+} from SR during diastole, reducing the availability of SR Ca^{2+} for the subsequent contraction, thereby impairing contractility (Santulli et al. 2017b).

FKBP12.6, also known as Calstabin2, plays an important pathophysiological role in the regulation of RyR2 function. Indeed, it stabilizes a conformation of the channel that prevents Ca^{2+} leak (Timerman et al. 1996; Lam et al. 1995; Xin et al. 1999; Yuan et al. 2014). There are numerous events, both acute and chronic, that trigger instability of RyR macromolecular complex. One typical example is represented by its phosphorylation, which induces the dissociation from the receptor of its stabilizing molecule, FKBP12.6 (Yuan et al. 2014). Chronic activation of beta-adrenergic system increases PKA activity (Santulli et al. 2013), with consequent phosphorylation of RyR (Takasago et al. 1991). Phosphorylation of RyR by CaMKII has also been reported in HF (Kushnir et al. 2010). Furthermore, ROS-linked oxidation of RyR affects the normal Ca^{2+} handling, compromising the correct contraction of myocytes during HF (Santulli et al. 2015).

Several benzothiazepine derivatives, including *JTV519* (also known as *K201*, 4-[−3{1-(4-Benzyl) piperidinyl}propionyl]-7-methoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine) (Kohno et al. 2003; Hachida et al. 1999a, b; Sacherer et al. 2012) and its substructure *S107* (7-methoxy-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine) (Thevis et al. 2009; Matecki et al. 2016; Lukyanenko et al. 2017) have shown cardioprotective and antiarrhythmic

properties by decreasing Ca^{2+} leak (Santulli et al. 2017a; Xie et al. 2013, 2015).

Henceforth, RyR2 represents the central target of many pathways dysregulated in cardiac pathological conditions, including adrenergic dysfunction, metabolic disorders, ROS production: all of these conditions are accompanied by alterations in Ca^{2+} handling and subsequent impairment in contractility.

12 Role of Mitochondrial Ca^{2+} in Metabolism-Contraction Coupling

Mitochondria play a strategic role in ensuring an adequate EC coupling (Miragoli and Cabassi 2017; Umanskaya et al. 2014; Gambardella et al. 2017; Torrealba et al. 2017). Indeed, cardiac myocytes are critically dependent on constant and appropriate energy supply, alongside with a finely tuned Ca^{2+} handling (Torrealba et al. 2017; Sorriento et al. 2017; Sheeran and Pepe 2017). Mitochondria and SR are functionally and structurally associated and, at the point of interaction (mitochondrial associated membranes) Ca^{2+} transits from SR to mitochondria (Min et al. 2012; Bononi et al. 2017). Ca^{2+} that enters in mitochondria is able to increase their bioenergetics, but at the same time, mitochondria, allowing Ca^{2+} entrance through the mitochondrial Ca^{2+} uniporter (De Stefani et al. 2011; Liu et al. 2017; Granatiero et al. 2017), can act as local Ca^{2+} buffers, actively participating in Ca^{2+} handling (Walsh et al. 2009; Gunter and Sheu 2009; Drago et al. 2012; Morciano et al. 2017). However, mitochondrial Ca^{2+} overload has been shown to be detrimental in various cell types (Liu et al. 2016; Kostic et al. 2015; Charles et al. 2017), and, specifically, it has been proven to play a mechanistic role in the pathogenesis of HF (Santulli et al. 2015). Therefore, our hypothesis is that whereas transient mitochondrial Ca^{2+} uptake promotes ATP production, prolonged or excessive Ca^{2+} uptake can be harmful.

The ability of mitochondria to respond to changes in Ca^{2+} levels, increasing metabolic outcome, and acting as Ca^{2+} scavenger, contributes to the adequate contractile response of cardiomyocytes. Indeed, alterations in these processes can lead to increase in cytosolic Ca^{2+} with potential activation of detrimental pathways that have been associated with HF, including CaMKII (Zhang and Brown 2004). Additionally, alterations in SR-mitochondria contacts have been found in cardiac dysfunction and HF (Lopez-Crisosto et al. 2017).

Whether mitochondrial Ca^{2+} transients exist during physiological EC coupling, in a beat-to-beat fashion, remains to be determined. Anyway, an important aspect of these phenomena is that Ca^{2+} proves once again its ability to act as a messenger, communicating to mitochondria the energetic demand of the cell, for adequate contraction.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 387–403
DOI 10.1007/5584_2017_135
© Springer International Publishing AG 2017
Published online: 20 December 2017

Critical Appraisal of Multivariable Prognostic Scores in Heart Failure: Development, Validation and Clinical Utility

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Abstract

Optimal management of heart failure requires accurate risk assessment. Many prognostic risk models have been proposed for patient with chronic and acute heart failure. Methodological critical issues are the data source, the outcome of interest, the choice of variables entering the model, the validation of the model in external population. Up to now, the proposed risk models can be a useful tool to help physician in the clinical decision-making. The availability of big data and of new methods of analysis may lead to developing new models in the future.

Keywords

Heart failure · Risk model · Prognosis

1 Introduction

Average outcome of patients with heart failure (HF) is poor, with relevant mortality and morbidity: the absolute mortality rates for HF remains close to 50% within 5 years of diagnosis (Roger et al. 2004; Levy et al. 2002); however, the risk among subgroups of patients may vary several-fold.

Prognosis is one of the main charge of medical practice: clinicians need to understand the likely course of a disease to treat patients with confidence.

Patients and their relatives are concerned about the risk of future events, therefore communicating an accurate prognosis is a basic part of the physician-patient interaction. An accurate

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prediction of the future course of the disease could help patients in their decision-making.

Correct prognostication of HF patients is mandatory to select high-risk subjects for mortality, or for hospitalization, allowing the selection of patients who can gain the most benefit from advanced procedures, like heart transplantation and mechanical support, at the same time avoiding overtreatment of low-risk or terminal patients.

Furthermore accurate prognostication of disease trajectory may suggest the modality and frequency of follow up, selecting, for example, patients for tele-monitoring systems, or eventually, to refer patients to hospice for palliative treatments.

Evaluation of risk profile of acute heart failure (AHF) patients, at hospital admission, should help physicians to identify low risk patients that can be safely discharged at home, pursuing both patients best outcome and correct resource allocations.

Finally, in clinical trials, risk stratification is useful to define eligibility criteria associated with higher event rate (when researchers are interested in recruiting a cohort of high-risk patients) or to forecast the likely benefit of a treatment on an individual basis, leading to a personalized medicine with targeted treatments.

However, age, aetiology, comorbidities, different pathophysiological patterns, treatments and non-medical factors may influence disease trajectory, making the prediction of clinical course difficult. Previous studies demonstrated that the holistic medical judgment about prognosis is inaccurate and highly variable; in particular, differences between physician predicted and actual survival of HF patents is remarkable in intermediate risk patients (Yamokoski et al. 2007). Moreover, physicians are unable to predict survival for end-stage patients (Hauptman et al. 2008).

Many individual factors have been associated with poor prognosis in heart failure such as demographic data, functional status, severity of heart dysfunction, biomarkers of neurohormal activation, non-cardiovascular co-morbidities and clinical events. However, the clinical applicability of a single predictor is limited. Then again, for such a complex disease, as heart failure is, a single predictor unlikely fits for all patients; rather a multivariable approach to prognosis is required. Multivariable prognostic models have been developed to overcome the limitations of single predictor approach; they give predictions based on multiple factors and are called prognostic models, prediction models, prediction rules or risk scores (Moons et al. 2012a, b). These models can be used to identify patient cohorts with high, medium, or low risk for death or another relevant clinical outcome.

2 Risk Prediction Models: Development and Validation

Statistical techniques for single-outcome are logistic regression for binary conditions and the Cox proportional hazards model for time-to-event analysis (Hosmer and Lemeshow 2000; Clark et al. 2003a, b). The logistic regression model takes the natural logarithm of the odds as a regression function of k predictors:

$$\ln\left(p/(1-p)\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \ldots + \beta_k x_k$$

where p is the probability of event, β_0 is the model intercept term and β_i represents the estimated regression coefficient of each risk factor. In the case of unequal length of follow-up, the prediction of time-to-event requires specific regression techniques. The most popular approach is the Cox proportional hazards model for assessing the hazard function $h(t)$ given a set of k independent multiple predictors

$$h(t; x_1, x_2, x_3, \ldots, x_k) = \lambda_0(t) \times \exp(\lambda_1 x_1 + \lambda_2 x_2 + \lambda_3 x_3 + \ldots + \lambda_k x_k)$$

where $\lambda_0(t)$ is the baseline hazard at time t, λ_i represents the estimated regression coefficient for the k independent covariates. The linear predictor allows the calculation of patient's outcome probability on the basis of subject's risk profile

(values observed for the k variables x_1,x_2,x_3,..., x_k). In the case of more than two possible discrete outcomes, logistic regression may be extended to multinomial logistic regression where each mutually exclusive outcome has its own coefficients (LaValley 2008). In the case of time-to-event analysis with more failure outcomes, competing risks regression models evaluate the relationship of covariates to cause-specific failures (Rao and Schoenfeld 2007).

Developing a Predictive Model Before starting to develop a multivariable model, in order to avoid bias, some relevant issues should be considered: the representativeness of the population of interest, the accuracy of dataset, the missing values handling, the sample size, the number of observed events and the number of predictors (Royston et al. 2009; Bradburn et al. 2003).

The first crucial step is the selection of the data source. Patient's information may be obtained from community, registry, state-wide databases, population cohorts, clinical trials. The next pivotal step is the selection of variables making up the score: a prognostic model is only as good as the variables from which is derived. The aim is to reduce scoring system complexity without lost in predictive performance. Factors highly correlated with others may be excluded considering as predictors those with the highest independent contribute in explaining outcome (Harrell et al. 1996). Well-known predictors already reported as prognostic would be candidates without excluding those not significant at univariate analysis. Stepwise parsimonious technique, as forward selection or backward elimination approach, analyses all candidate variables. All regressive approaches allow the use of categorical predictors and continuous variables. A strong violation of linearity assumption between risk of outcome and continuous factors may lead to erroneous predictions (Royston et al. 2009). Several approaches exist to model non-linear relationships (Harrell et al. 1996). Categorization of continuous variables is possible by using established cut-points that have clinical meaning; more than two categories reduce the loss of information (Clark et al. 2003a, b). Simple bedside risk score may be derived from regression coefficients of original model developed on categorised data. A scoring system with summation of points assigned for each predictor allows an accurate bedside stratification of prognosis without solving the equation. Alternatively, tools are commonly available as web-calculator or mobile app to estimate directly the exact probability of outcome occurrence given patient' features.

Assessing Performance The models' performance is assessed in terms of discrimination and calibration of predictions. The concordance statistic C-index (Harrell et al. 1996) or the area under the receiver-operating curve (ROC) measure the ability of risk scores in distinguish between individuals with and without the outcome. A value of 0.50 could be achieved randomly, whereas an index of 1.0 represents perfect discrimination. Calibration is one of the most important model performance characteristics necessary to produce valid risk estimates and to avoid errors into decision-making. Goodness-of-fit statistics for calibration can be obtained by comparing, for groups of predicted risks, the observed events against the expected values. The underlying hypothesis is that the estimated and observed frequencies agree. A statistically significant finding indicates lack of fit (Hosmer ad Lemeshow 2000).

Often, investigators evaluate the performance of a model when a new predictor is added. Two common measures are used for assessing improvement in model performance (Pencina et al. 2008, 2011): the Integrated Discrimination Improvement (IDI) and the Net Reclassification Improvement (NRI). Figure 1 shows an example of models comparison.

Validating a Prognostic Model A good model should allow a reliable classification of patients into risk groups. External validation examines the generalisability of the model, for which it is necessary to use new data collected from a similar population in a different institution. Model's performance can be assessed using new data

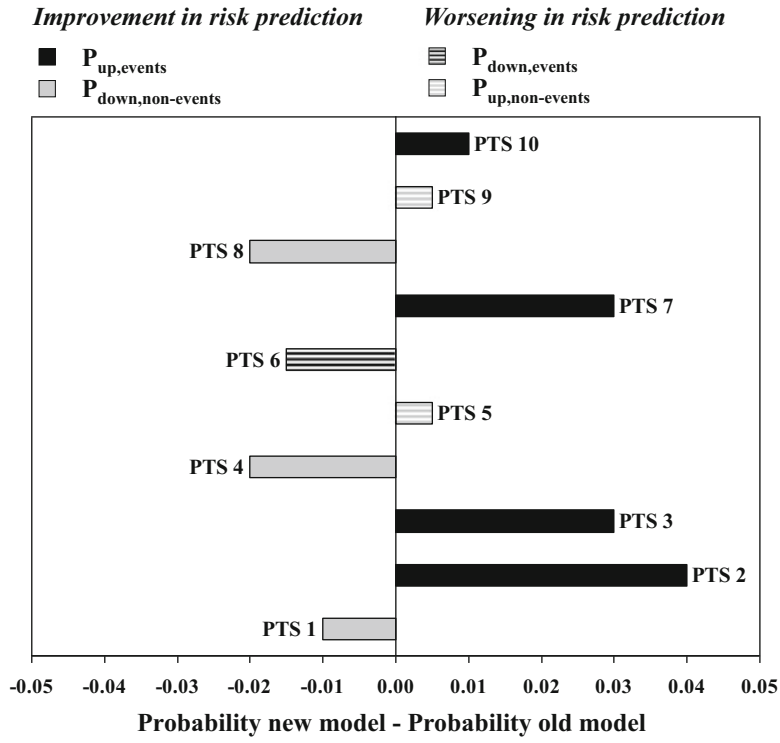

Fig. 1 Ten example patients (PTS) classified by an old risk model and re-classified by a new one including a new predictor. An improvement is obtained on the right of 0 in patients who develop the event (patients 2,3,7,10) and on the left of 0 in those who do not develop the outcome of interest (patients 1,4,8)

from the same source as the derivation sample, but a true evaluation of transportability requires data from another population (Moons et al. 2012a, b). Discrimination and calibration are re-assessed over the validation population. Internal validation is helpful, but it cannot provide information about the model's performance elsewhere. With the internal validation strategy, dataset is randomly split into two parts that separately are used to develop the model and to assess predictive accuracy. The two datasets are very similar and results tend to be optimistic. Non-random splitting may be preferable as it reduces the similarity of the two sets of patients (for example by hospital). If data are limited, the model can be developed using the whole dataset and the performance can be evaluated by cross validation or bootstrapping procedures.

Figure 2 summarizes the scoring system development process.

3 Risk Models in Heart Failure

Acute worsening with functional and clinical deterioration interrupts the trajectory of chronic heart failure; the predictors of prognosis of these two stages may be different, so separated multivariable models for heart failure have been developed. Tables 1 and 2 report the main features of risk scores for chronic and acute heart failure.

3.1 Chronic Heart Failure

Heart Failure Survival Score (HFSS) Keith D. Aaronson et al. (1997) developed a predictive model using data from 268 ambulatory patients with advanced heart failure from a single center

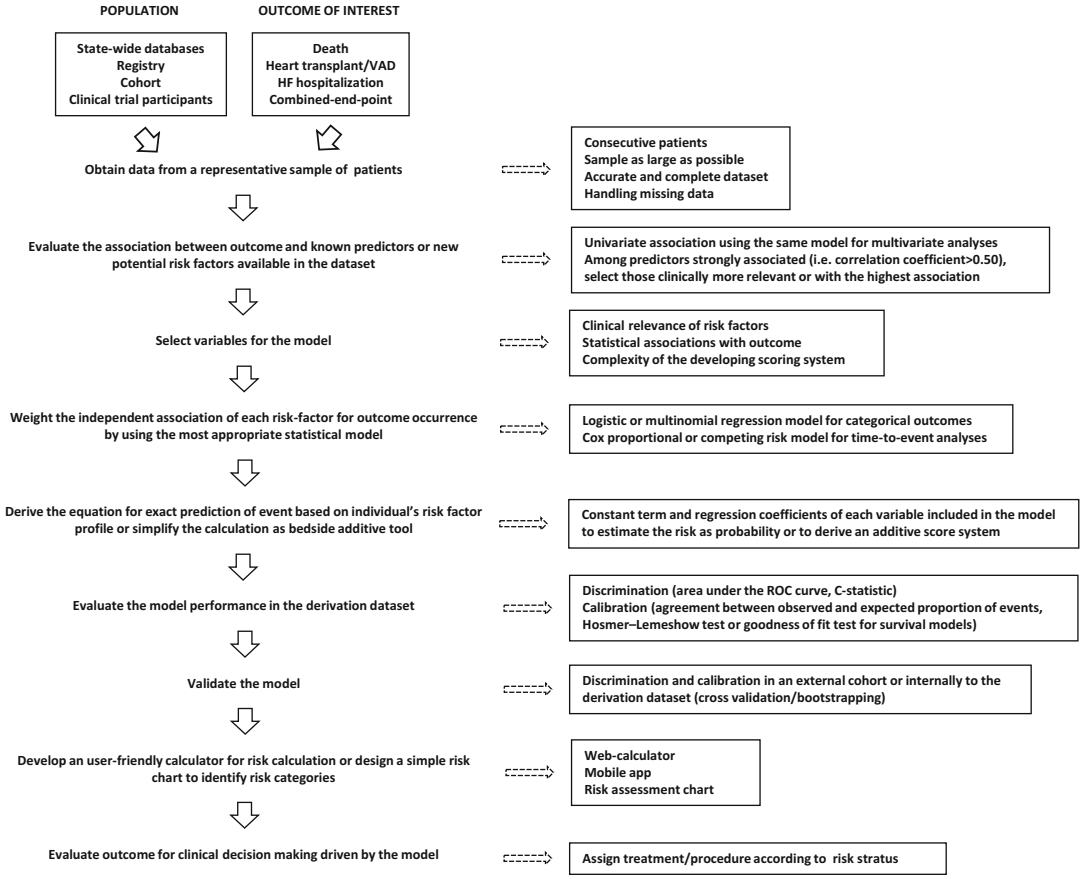

Fig. 2 Scoring system development process

(derivation sample) to predict a composite outcome of death, urgent heart transplant and ventricular assist device implantation. The predictive model contained the following seven variables: ischemic cardiomyopathy, resting heart rate, left ventricular ejection fraction (LVEF), QRS duration $\geq$0.12, mean resting blood pressure, peak $\dot{V}O_2$ and serum sodium. The model has been prospectively validated in 2240 patients from 8 independent single center cohorts (Bilchick et al. 2012; Zugck et al. 2001; Koelling et al. 2004; Parikh et al. 2009; Lund and Mancini 2010). The HFSS was calculated for each patient in the validation sample from the final model; scores were divided in three risk group: low, medium and high risk, with a 1-year survival of respectively 93%, 72% and, 43%. Patients in medium- and high-risk groups should be considered for cardiac transplantation, while transplantation can be safely deferred in patients in the low-risk group. However, C-statistics of HFSS in validation cohorts ranged from 0.56 to 0.78, being far from optimal. The worsening of model's calibration in validation cohorts, with more frequent use of beta-blockers or automatic implantable defibrillators (Alba et al. 2013), raises doubts about the applicability of HFSS to current heart failure patients.

The Seattle Heart Failure Model (SHFM)

Wayne C. Levy et al. (2006) developed and validated a multivariate risk model to estimate survival from death, urgent heart transplantation and ventricular assist device in heart failure patients with both reduced (HFrEF) and preserved (HFpEF) ejection fraction. The model

Table 1 characteristics of risk score for chronic heart failure

Risk score	Variables in the model	C-statistic (derivation cohort)	End point
HFSS	Ischemic cardiomyopathy, resting HR, LVEF, QRS duration ≥0.12 s, mean resting blood pressure, peak $\dot{V}O_2$, serum sodium.	0.74	1-year composite end point (death, urgent transplant, VAD implantation)
SHFM	Age, sex, aetiology, LVEF, blood pressure, serum sodium, cholesterol, haemoglobin, percent lymphocytes, NYHA class, WBCC, creatinine, uric acid, allopurinol.	0.725	1-year composite end point (death, urgent transplant, VAD implantation)
HF-Action	Exercise duration on cardiopulmonary exercise test, quality of life (KCCQ), symptom stability, BUN, sex.	0.70	Composite end point (death, hospitalization)
MAGGIC	Age, sex, BMI, current smoker, SBP, diabetes, NYHA class, LVEF, COPD, HF duration, creatinine, beta-blocker, Ace-inhibitor or angiotensin receptor antagonist assumption	–	1–3 year mortality
MECKY score	Haemoglobin, serum sodium, kidney function, LVEF, peak oxygen consumption, VE/VCO_2 slope	0.804	1-year composite end point (cardiovascular death, urgent heart transplant)
BARLERA	Age, NYHA class, eGFR LVEF, COPD, sex, SBP, diabetes mellitus, haemoglobin level, high uric acid level, aortic stenosis, BMI	0.75	2-year mortality

Abbreviations: *HR* Heart rate, *LVEF* Left ventricular ejection fraction, *NYHA* New York Heart Association, *WBCC* White blood cell count, *KCCQ* Kansas City Cardiomyopathy Questionnaire, *BUN* Blood urea nitrogen, *BMI* Body mass index; *SBP* Systolic blood pressure, *COPD* Chronic obstructive pulmonary disease, *eGFR* Estimate glomerular filtration rate

incorporates easily obtainable clinical and laboratory variables, heart failure medications, and devices. The SHFM was derived in a cohort of 1125 heart failure patients from the clinical trial "the Prospective Randomized Amlodipine Survival Evaluation PRAISE1" (Packer et al. 1996), with the use of a multivariate Cox model. Five other cohorts (n = 9942) were used to prospectively validate the model: ELITE2 (n = 2987), UW (n = 148), RENAISSANCE (n = 925), Val-HeFT (n = 5010), IN-CHF(n = 872). The variables used as a survival predictor were 14: age, gender, aetiology, LVEF, blood pressure, serum sodium, cholesterol, haemoglobin, percent lymphocytes, New York Heart Association (NYHA) class, white blood cell count, creatinine, uric acid and allopurinol.

The 1-year ROC in the derivation cohort was 0.725. In the validation cohorts, the 1-year ROC was 0.682 for ELITE2, 0.810 for UW, 0.682 for RENAISSANCE, 0.694 for Val-HeFT, and 0.749) for IN-CHF. The combined data set of all 6 trials had a 1-year ROC of 0.729. C-index increase from 0.72 to 0.78 when brain natriuretic peptides are added to the model (May et al. 2007).

Because the calculation of estimated survival is impractical for computation by hand, a Web-based calculator (http://www.SeattleHeartFailureModel.org) has been developed, allowing convenient interactive calculation of estimated survival and also of the predicted effects on survival of adding (or subtracting) medications or devices to a patient's regimen.

The HF-ACTION Predictive Risk Score Model The "Heart Failure: A Controlled Trial Investigating Outcomes of Exercise TraiNing (HF-ACTIONtrial)" (O'Connor et al. 2009) included 2331 well-characterized ambulatory patients with HFrEF and NYHA class II to IV. Study participants received guideline-based therapies (β-blockade, 95%; use of an angiotensin-converting enzyme inhibitor, 74%; implantable cardioverter-defibrillator, 40%; biventricular pacing, 18%) and were

Table 2 Characteristics of risk score for acute heart failure

Risk score	Variables in the model	C-statistic (derivation cohort)	End point
In-Hospitals risk models			
ADHERE	BUN, creatinine, SBP	0.75	In hospital death
AHFI	Sex, CAD, diabetes, lung disease, SBP, HR, respiratory rate, temperature, BUN, sodium, potassium, WBCC, acute myocardial infarction o myocardial ischemia at ECG, pulmonary congestion or pleural effusion radiographic examination	–	In hospital death
OPTIMIZE-HF	Creatinine, sodium , age, HR, liver disease, previous CVA/TIA, peripheral vascular disease, race, left ventricular systolic dysfunction, COPD, SBP, previous HF hospitalization	0.75	In hospital death
GWTG-HF	Older age, low SBP, elevated HR, COPD, non- black race	0.75	In hospital death
EHMRG	HR, creatinine, systolic blood pressure initial oxygen saturation, serum troponin	0.805	7-days death
PROTECT	BUN, respiratory rate, HR, albumin, cholesterol, diabetes, previous HF hospitalization.	0.72	Death or re-hospitalization at 30 days
Post-discharge risk models			
EFFECT	Age, SBP, BUN, sodium concentration, cerebrovascular disease, Dementia, COPD, hepatic cirrhosis, Cancer, Hemoglobin	0.80 (30 days) 0.77 (1-YEAR)	30-days/1-year mortality
OPTIME-CHF	Age, BUN, SBP, Sodium, NYHA class	0.77	60-days mortality
OPTIMIZE – HF	Age, weight, SBP, serum creatinine, History of liver disease, history of depression, history of reactive airway disease	0.72	60-days mortality
ELAN	NT-proBNP at discharge, NT-ProBNP reduction, age, peripheral oedema, SBP, sodium, BUN, NYHA class	0.78	180-days mortality
ADHF/NT-proBNP risk score	COPD, SBP , eGFR, serum sodium, hemoglobin, NT-proBNP; LVEF, tricuspidal regurgitation	0.84	1-year mortality
ESCAPE	Age, BUN, six minute walking test, sodium, CPR/ Mechanical ventilation, diuretic dose at discharge, no betablocker at discharge, BNP	0.76	6-months mortality

CAD Coronary heart disease, *CVA* Cerebral vascular accident, *NT-proBNP* N-terminal brain natriuretic peptide, *BNP* Brain natriuretic peptide. Other abbreviations as in Table 1

systematically followed with standardized assessments of clinical outcomes, which included the primary composite end point of death or hospitalization from any cause and the secondary end point of death alone. A multivariable statistical model for risk stratification was developed from the trial population (O'Connor et al. 2012). The analysed variables were exercise duration on cardiopulmonary exercise test (CPET), quality of life, evaluated by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ), symptom stability, serum urea nitrogen and sex. The strongest baseline predictor of both the primary and the mortality end points was exercise duration on the CPET: for every additional minute of exercise duration, there was an associated 8% reduction in risk for the primary end point and an 18% reduction in risk for mortality. The risk score of the primary end point had a C-index of 0.63. The risk score for mortality had a C-index of 0.70. For this study the investigators used an internal validation while has not been externally validated in an independent cohort of patients with HF because there are

no known similar HF data sets that include peak VO_2, CPET duration, and KCCQ data.

The Meta-analysis Global Group in Chronic Heart Failure (MAGGIC) (Pockok et al. 2013). This study included individual data on 39,372 patients with HF, with both reduced and preserved LVEF, from 30 cohort studies, 6 randomized controlled trials (24,041 patients) and 24 registries (15,331 patients). Using Poisson regression models for survival with forward stepwise variable selection, adjusting for study and follow-up time, 13 independent predictor variables were selected: age, gender, body mass index (BMI), current smoker, systolic blood pressure (SBP), diabetes, NYHA class, LVEF, chronic obstructive pulmonary disease, HF duration, creatinine, beta-blocker, Ace-inhibitor or angiotensin receptor antagonist assumption. Each variable contributes to creating an integer risk score (accessible by the website www.heartfailurerisk.org) that allows calculating the 1-year probability of death and the 3-year probability of death. Two different risk scores have been created for patients with reduced or preserved ejection fraction, respectively. Nearly all predictors display a similar influence on mortality in the two subgroups. Two exceptions are age (HFpEF has a better prognosis in younger patients) and SBP, which have a stronger inverse association with mortality in patients with HFrEF. The authors did not report neither AUC nor C-statistic, making impossible the comparison with other risk models.

Metabolic Exercise Test Data Combined with Cardiac and Kidney Indexes (MECKY Score) Agostoni et al. build a new risk score for patient with HFrEF, integrating measures with potential prognostic value from CPET with established clinical, laboratory and echocardiographic risk factors, in order to identify patients at risk of cardiovascular death and urgent heart transplant (Agostoni et al. 2013). The MECKI score was derived from a cohort of 2716 with HFrEF systolic HF patients followed in 13 Italian centres. Ability to perform a CPET was an inclusion criterion. The prognostic variables used are six: haemoglobin, serum sodium, kidney function, LVEF, peak oxygen consumption and VE/VCO_2 slope. The study end-point was a composite of cardiovascular death and urgent heart transplant.

The MECKI score AUC was 0.804 at 1 year, 0.789 at 2 years, 0.762 at 3, and 0.760 at 4 years.

A major criticism of the MECKI score is that it is only applicable to HF subjects who have performed a maximal CPET. However, at present, MECKI is the long-term prognostic score for HFrEF with the highest AUC. In a comparative analysis of four risk models (HFSS, SHFM, MAGGIC, MECKI), MECKI score showed the best discrimination ability for the composite end-point of all death and urgent transplantation with an AUC of 83%, resulting, furthermore, well calibrated (Freitas et al. 2017).

Predictors of Mortality in 6975 Patients With Chronic Heart Failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure Trial. Proposal for a Nomogram (Barlera et al. 2013). The aim of the present study was to develop a model for predicting mortality in a contemporary cohort of Italian patients recruited in the GISSI-HF trial (Tavazzi et al. 2008), followed for 4 years. The study population consisted of 6975 outpatients with chronic heart failure. 12 independent predictors of mortality, (age, NYHA class, estimate glomerular filtration rate, LVEF, chronic obstructive pulmonary disease, sex, SBP, diabetes mellitus, haemoglobin level, high uric acid level, aortic stenosis, and BMI) entered the model. The authors represented the model with a nomogram that can be used to calculate a prognostic score and to estimate the risk for death for individual patients. The predicted probabilities associated with each factor are mapped into points on a scale from 0 to 100. The presence or the level of each predictive factor is associated with a point system allowing us to sum up the points for all of the factors. The total points accumulated by the various

covariates correspond with the predicted probability of survival at 2 or 4 years. The study revealed that the most significant predictive determinants of mortality were older age, more advanced HF symptoms, and reduced renal function. Then a subset of 1231 patients with cardiac biomarkers (hs-cTnT and NT-proBNP) available at baseline was analysed; the multivariable Cox model for mortality showed that NT-proBNP was the strongest predictor (hazard ratio, 1.51 for 1 unit increase on a log scale, $P < 0.0001$) followed by hscTnT (hazard ratio, 1.50 for each unit increase on a log scale, $P < 0.0001$). The C-statistic of the model was 0.75. A major limitation of this study is the lack of an external validation.

3.2 Acute Heart Failure

Several prognostic models have been developed to predict in-hospital mortality as well as to estimate outcomes between 30 days up to 6 months post-discharge.

3.3 In-Hospital Risk Models

Adehre A risk stratification model to predict in-hospital mortality in patients admitted with acutely decompensated heart failure was derived from data of 33.046 patients from the Acute Decompensated Heart Failure National Registry (ADHERE) (Fonarow et al. 2005). The validity of the model was prospectively tested using data from 32.229 hospitalization. The best single predictor for mortality was blood urea nitrogen (BUN) level of 43 mg/dL or higher. The second best predictor in both the higher and lower BUN nodes was admission SBP, at a discrimination level of <115 mm Hg. Eventually serum creatinine levels of 2.75 mg/dL or higher provided additional prognostic value in patients with BUN levels ≥43 mg/dL and SBP ≤ 115 mm Hg. By the CART method, a risk tree was derived to identify ADHF patients at low, intermediate and high risk for in-hospital mortality in the validation cohort. Mortality in the low and high-risk group was respectively 2.1 and 22%.

The ADHERE algorithm has some strengths: it was derived from a real world population; it was adequately validated in another cohort of patients; it is a parsimonious model requiring the measure only three variables. The ADHERE algorithm may allow immediate and simple triage at admission in the emergency department, not requiring complex calculation. The model has some limitations: the registry entries reflect individual hospitalization, and repeated hospitalizations of the same patient were entered as separated records. Moreover, the mortality of low risk group was too high in comparison with other models.

Acute Heart Failure Index (AHFI) This model was derived by the data of 33.533 patients admitted in the Emergency department (ED) with a diagnosis of heart failure (Auble et al. 2005). Authors derived a prediction rule to identify heart failure patients at low-risk of in-hospital death. The AHFI resulted from the combination of demographic, biochemical and non-invasive diagnostic factors.

The AHFI was validated in 8.383 patients from two cohorts with respect to inpatients death, serious medical complication before hospital discharge, and 30-day death. The performance decreased in the validation cohort: mortality rates in low risk group were almost threefold higher in the validation cohort in comparison with two derivation cohorts (0.7–1.7 vs. 0.3%) (Hsieh et al. 2008; Hsiao et al. 2011).

Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) This model derived by the analysis of the national hospital-based registry and quality improvement program OPTIMIZE-HF registry, including data of 48,612 patients (Abraham et al. 2008). The Authors developed a point scoring system to predict in-hospital mortality screening forty-five

potential predictor variables. Multivariable predictors of mortality included age, heart rate, SBP, sodium, creatinine, HF as primary cause of hospitalization, and presence/absence of left ventricular systolic dysfunction. The ability of the logistic regression model to discriminate mortality was tested by a classification and a regression tree (CART) analysis. The final risk-prediction nomogram included age, heart rate, SBP, serum creatinine, serum sodium, primary cause of admission (HF or other), left ventricular systolic dysfunction. For each value of these variables, a score is associated to the probability of in-hospital mortality. The model had a C-statistic of 0.75; however, validation of the score is missing.

Get With the Guidelines-Heart Failure (GWTG-HF) The GWTG-HF program of the American Heart Association provided a risk score that applies to a broad spectrum of heart failure patients, including those with HFpEF (Peterson et al. 2010). 27.850 patients belonged to the derivation sample; 11.933 patients entered the validation sample. The score combined seven clinical factors (older age, low SBP, elevated heart rate, presence of chronic obstructive pulmonary disease, and non-black race). The risk score had good discrimination, with a C-index of 0.75 in both derivation and validation data set. Model calibration evaluated by plots of predicted versus observed mortality and by the Hosmer-Lemeshow test was good. In-hospital mortalities in the lower and higher risk group were 0.4 and 9.7% respectively.

Emergency Heart Failure Mortality Risk Grade (EHMRG) Lee DS et al proposed a multivariate risk index for 7-days death using initial vital signs, clinical, presentation features, and readily available laboratory tests for patients with AHF (Lee et al. 2012). 7433 patients presenting to the emergency department of 86 hospitals composed the derivation cohort. The model was validate in a cohort of 5158 patients. Higher heart rate, creatinine concentration and lower SBP, initial oxygen saturation, no normal serum troponin levels entered the score. Areas under the ROC curves of the multivariate model were 0.805 for the derivation data set and 0.826 for validation data set.

PROTECT This model was derived from 2033 patients enrolled in the clinical trial "Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT)" (Massie et al. 2010; Cleland et al. 2014). Patients were hospitalized for AHF; they had mild or moderate impairment of renal function. Outcomes at 30 days were death or rehospitalisation for any reason; death or rehospitalisation for cardiovascular or renal reasons; and, at both 30 and 180 days, all-cause mortality. Authors identified 37 baseline clinical characteristics as candidate predictor variables. Notably no single factor had a C-index >0.70, and few had values >0.60. Eighteen variables had independent prognostic value, but a reduced model using only eight variables (age, previous heart failure hospitalization, peripheral oedema, SBP, serum sodium, urea, creatinine, and albumin) performed similarly: the model C-index was 0.72 for both all variables model and eight items model. C-indices were lower for composite outcomes than for mortality. The model underwent external validation in study population of another clinical trial; C-index in validation population was 0.67.

Patients on inotropic agents, with severe pulmonary disease, recent ischemia and preserved ejection fraction were not included, so the applicability of PROTECT risk score to a wide range of community base population is limited.

4 Post-discharge Risk Models

Enhanced Feedback for Effective Cardiac Treatment (EFFECT) Study Authors of the EFFECT study analysed multiple variables available at hospital presentation of more than 4000

patients (Lee et al. 2003). They developed and validated a model able to predict all cause 30-day and 1-year mortality. Older age, lower SBP, higher respiratory rate, higher urea nitrogen level, hyponatremia, and co-morbidities were multivariable predictors of mortality at both 30 days and 1 year. Mortality rate in the very low risk group was of 0.4% at 30 days and 7.8% at 1 year. Mortality in the very high-risk group was 59% at 30 days and 78.8% at 1 year.

Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study This model was derived from study population of the OPTIME-CHF (Cuffe et al. 2002); this risk score predicts post-discharge outcomes in 949 patients hospitalized for acute decompensated heart failure for 48 to 72 h of infusion of either milrinone or placebo (Felker et al. 2004). The study population consisted entirely of patients with HFrEF, while patients with significant renal dysfunction or on inotropes were excluded from the study.

The study outcomes were 60-day mortality or the composite of death or rehospitalisation at 60 days. Increased age, lower systolic blood pressure, NYHA class IV symptoms, elevated blood urea nitrogen, and decreased sodium were the variables at presentation predicted death 60 days-mortality. C-index for mortality at 60 days was 0.77 but less for the composite endpoint (C-index 0.69).

Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) The data source used to develop this score is comprehensive hospital-based registry. 4402 patients were included in this analysis. Eight variables (age, serum creatinine, reactive airway disease, liver disease, lower SBP, lower serum sodium, lower admission weight, and depression) were used to calculate a score to predict the risk of mortality within 60 days after discharge. The model C-index was 0.72 (O'Connor et al. 2008).

A European coLlaboration on Acute decompeNsated Heart Failure (ELAN-HF) Data from seven prospective cohorts with in total 1301 patient were pooled by Salah et al. to develop a predictive discharge score based on the strongest predicting variables regarding mortality (Salah et al. 2014). Differently from previous studies, the model included natriuretic peptide dosage. The model that incorporated NT-proBNP levels at discharge as well as the changes in NT-proBNP during hospitalisation in addition to age $\geq$75 years, peripheral oedema, SBP $\leq$115 mm Hg, hyponatremia at admission, serum urea of $\geq$15 mmol/L and NYHA class at discharge, had the best C-statistic (AUC 0.78). The addition of NT-proBNP to a reference model significantly improved the net reclassification (62%).

ADHF/NT-proBNP Risk Score Scrutinio confirmed the relevance of natriuretic peptide measurements in patients with acutely decompensated heart failure, studying the improvement in the risk reclassification of 824 patients with acutely decompensated heart failure (453 in the derivation cohort, 371 in the validation cohort) by adding NT-proBNP to other common clinical variables (Scrutinio et al. 2013). The ADHF/NT-proBNP risk score contains eight variables: NT-proBNP chronic obstructive pulmonary disease, estimated glomerular filtration rate, sodium, haemoglobin, LVEF, and moderate to severe tricuspid regurgitation. The score (range 0–22) proved to be effective in predicting one-year mortality. In the derivation cohort, the risk score had a C-index of 0.839 and the Hosmer-Lemeshow statistic was

1.23 ($p = 0.542$), indicating good calibration. In the validation cohort, the risk score had a C-index of 0.768.

The addition of NT-proBNP to the reference model did not improve model discrimination, but resulted in significant risk reclassification.

Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) The ESCAPE trial enrolled 433 patients hospitalized with AHF randomly assigned to receive clinical assessment or pulmonary artery catheter-guided therapy (Binanay et al. 2005). Data from this trial were used to derive a predictive model; the end point was time to death at 6 months (O'Connor et al. 2010). Among the analysed variables, high discharge BNP level showed the strongest association with death. The score proposed included eight variables (Age, BUN, 6-min walk test, sodium, CPR/mechanical ventilation, diuretic dose at discharge, no-betablocker at discharge, BNP) with 1 point possible for each, except for BUN and BNP where additional points were assigned for the highest value with a maximum possible of 13 points. Data from FIRST (Flolan International Randomized Survival Trial) (Califf et al. 1997) were used to externally validate the ESCAPE study. C-index for 6 months mortality was 0.78 in the derivation data set, but decreased to 0.65 in the validation population.

5 Heart Failure Risk Scores: Usefulness and Criticisms

Risk stratification of patients with heart failure is a complex pivotal medical task aimed to improve patient's outcome and efficiency of health care delivery system. To this day, even if a large number of variables has been associated to prognosis, predicting mortality and/or HF hospitalization remains difficult.

Risk score are multivariable predictive models in which each variable is weighted to calculate the probability of the occurrence of an outcome. Risk score should allow an unbiased risk stratification, transferring the result of prognostic studies in the clinical practice.

Nevertheless, despite all the proposed prognostic models, the clinical application is challenging and clinical scores are not yet considered part of the standard of care.

Critical Issues Against the redundancy of models published in the last years, a critical analysis is needed. Only a small percentage of studies qualifies from a methodological point of view.

In their systematic review, Alba et al found out that only 25% of event free survival models in ambulatory patients with HF received validation in some external population (Alba et al. 2013). In other two reviews, 69 of 117 and 41 of 64 models respectively, were not validated (Ouwerkerk et al. 2014; Rahimi et al. 2014). Not validate models generally overestimate the prediction power.

Moreover, when validation is reported, the discrimination, evaluated by the C-index, generally results significantly lower than that found in the derivation model (Alba et al. 2013). Therefore, the generalization and the external applicability of the proposed models remain a main issue. Notably some models may underestimate the mortality risk in elderly patients or at approaching the end of life (Nutter et al. 2010).

Another major limit of risk scores studied at this day is the lacking accuracy in predicting HF hospitalization (a major health problem in western countries): in most studies, the C-index of models predicting HF hospitalization was lower than that of model predicting mortality (Ross et al. 2008; Giamouzis et al. 2011). In a meta-analysis, there was a highly significant difference in C-statistics between models predicting mortality and HF hospitalization (Ouwerkerk et al. 2014). Maybe, some non-medical factors, not included in the risk models, may influence the risk hospitalization. Biomarkers, such as natriuretic peptides, are more promising for this purpose (Jannuzzi et al. 2006, 2010).

Risk scores evaluate the prognosis of a cohort of patients, but prediction of outcome in individual patients is inherently inaccurate. Therefore,

the applicability of a model to the single patient is arguable. It is clear and understandable the meaning of a risk of death of 20% for a cohort (it means that during the follow up about 20 of 100 patients are expected to die). It is less clear the meaning of such a probability for a single patient, for which, the actual survival has only to possible values: 0 or 100%.

Risk scores should improve the process of care. However, there are few evidences (none in acute heart failure) that clinical decision making guided by risk score could allocate correctly patients to different therapies.

In a previous study, the HFSS was able to identify patient who get the best benefit from heart transplant (Lim et al. 2005). More recently, Bilchick et al. reported the successful use of the SHFM to predict implantable Cardioverter defibrillator benefit in a large cohort of patients (Bilchick et al. 2017).

A further limit of risk score is their time horizon, ranging from one to 5 years, which may not be an adequate period in younger patients.

Eventually, risk score may predict death or (less well) hospitalizations, but do not account for quality of life changes, that in some subgroups of patients, (like in the elderly) may be the most relevant outcome. Study using the trade-off utility has shown that patients with decompensated heart failure will trade more than 30% of their predicted life expectancy in order to have a better quality of life (Howlett 2013).

Risk Scores and Guidelines Recommendations According to 2013 ACCF/AHA heart failure guidelines (Yancy et al. 2013), "validate" multivariable risk scores have a class IIa recommendation (it is reasonable to perform procedure/administer treatment, but additional studies with focused objectives needed) to estimate subsequent risk of mortality in heart failure patients.

It is worth noting that in the same guidelines a class I recommendation (Procedure/treatment should be performed/administered) is given to the dosage of natriuretic peptides for establishing prognosis in acutely decompensated HF. The following risk scores have been selected and cited by the guidelines 's authors: SHFM, HFSS, Charme risk score, Corona risk score for chronic heart failure; I-preserve score for heart failure with preserved ejection fraction; ADHERE model, GWTG-HF, EFFECT risk score, ESCAPE risk score, OPTMIZE risk score for acutely decompensated heart failure. Oddly guidelines' authors have cited some models that have not been adequately validated.

The guidelines of European Society of Cardiology highlight the limitations of clinical scores, remembering that their clinical applicability is limited and precise risk stratification in HF remains challenging (Ponikowski et al. 2016).

The 2016 International Society for Heart and Lung Transplantation listing criteria for heart transplantation recommend the use of prognosis scores along with CPET to guide listing for transplantation for ambulatory patients in circumstances of ambiguity (e.g. peak $VO_2 > 12$ and < 14 ml/kg per min). An estimate 1-year survival as calculated by the SHFM of $<$ 80% or an HFSS in the medium/high risk range should be considered as reasonable cut points for listing (Class IIb). According to these guidelines, listing patients solely on the criteria of risk score is not indicated (class III) (Mehra et al. 2016). On the contrary, CPET to guide transplant listing has a class I recommendation.

What Risk Model Should Be Used? First, physician involved in the care of patients with heart failure should evaluate the quality of research that produced the model.

Risk scores derived by registries and population studies have a better external validity in comparison with models derived from clinical trial, and, generally, a better accuracy (Alba et al. 2013). Clinical trial populations are usually younger, more carefully characterized, and may be better managed. Only models with a good discrimination in validation cohort are recommended. No single model fits for all heart

failure patients, because some variables may have a different relevance in specific subgroups.

For estimating prognosis in older patients, models focused on comorbidities are perhaps advisable, while, for heart transplant listing of ambulatory younger patients, models including exercise capacity, (i.e. maximum oxygen consumption), should be preferred.

In the setting of AHF, when quickness of decision is a crucial factor, it is advisable to stratify risk by a simple model, with few easily, measurable variables (like ADHERE Tree).

Predictors of Prognosis More than 200 variables have been used in different models; a few common and strong markers of risk, however, emerged the most frequent factors: age, sex, blood urea nitrogen, sodium, renal function, SBP, natriuretic peptides, LVEF, and NYHA class. In a meta-analysis blood urea nitrogen and sodium had the highest predictive value (Ouwerkerk et al. 2014). These variables should always be considered in the clinical practice and in the development of new models.

Future Direction Two of the most popular risk scores, HFSS and SHFM, were derived from 286 and 1125 patients respectively. Today, these figures result infinitesimal if compared to what we are going to manage: the rapid adoption of electronic health records (EHRs) is changing the world of clinical research. The growth of EHRs will make it possible to access unprecedented amounts of clinical data and offers the potential for collecting accurate information about millions of patients. Even if ethical and legal issues have to be resolved, and big data analyses are not immune to some limitations, in the next future it will be possible to derivate and validate in real time risk scores from hundreds of thousands patients. Big data approach needs new methods for analysis in the field of artificial intelligence (AI). Machine learning, deep learning and cognitive computing are the AI techniques involved in the analysis of big data (Krittanawong et al. 2017). System biology approach, that incorporate data from biomarker, genomic, metabolomics and proteomic, is promising. The acquisition of these techniques should lead up to a precision cardiovascular medicine, an approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.

6 Conclusions

Many risk scores have been proposed in the previous years, however, these models have not been widely implemented in clinical practice. In populations different from that from which the risk models were derived, their discrimination capability is far from optimal. Validate models, however, could be a useful tool to help, not substitute, medical judgment, to guide clinical decision making, especially in borderline patients, or in the grey zone of single validates predictors of prognosis. The research of new more accurate models should carry on, benefitting from the availability of big data analyses and system biology approach.

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Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 405–406
https://doi.org/10.1007/5584_2018_198
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Published online: 11 April 2018

Erratum to: Management of Bradyarrhythmias in Heart Failure: A Tailored Approach

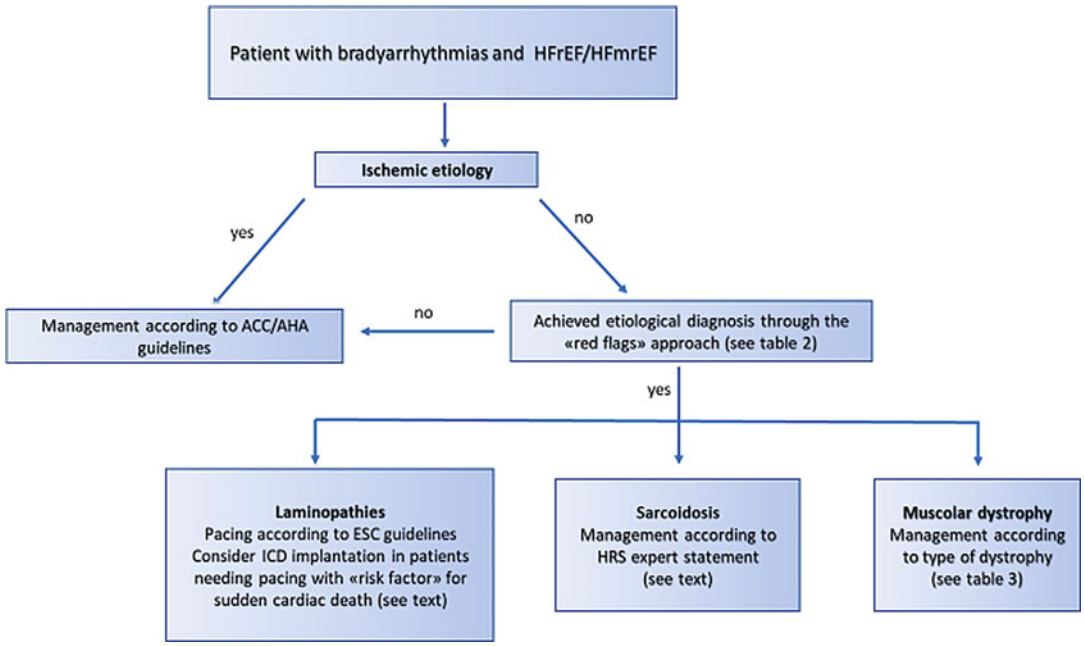
Daniele Masarone, Ernesto Ammendola, Anna Rago, Rita Gravino, Gemma Salerno, Marta Rubino, Tommaso Marrazzo, Antonio Molino, Paolo Calabrò, Giuseppe Pacileo, and Giuseppe Limongelli

Erratum to:
Chapter "Management of Bradyarrhythmias in Heart Failure: A Tailored Approach" in:
D. Masarone et al., Adv Exp Med Biol - Advances in Internal Medicine,
https://doi.org/10.1007/5584_2017_136

Fig. 3 of this chapter was initially published incorrectly. The correct presentation is given below.

The updated online version of the original chapter can be found under
https://doi.org/10.1007/5584_2017_136

Incorrect Figure



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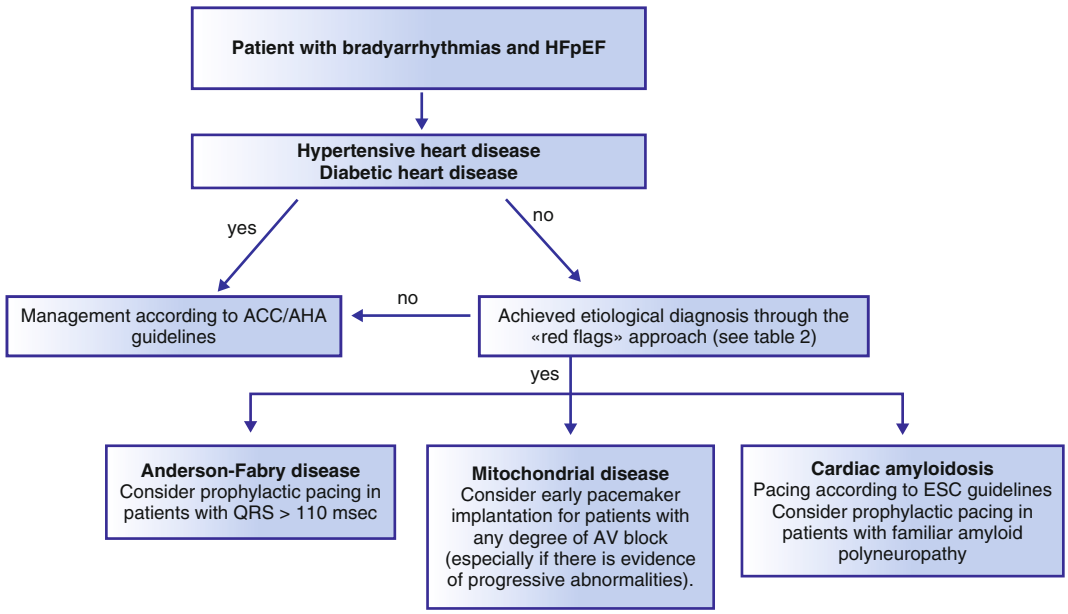

Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 407
https://doi.org/10.1007/5584_2018_204
© Springer International Publishing AG, part of Springer Nature 2018
Published online: 11 April 2018

Erratum to: Percutaneous Mitral Valve Interventions and Heart Failure

Abhishek Sharma, Sunny Goel, and Sahil Agrawal

Erratum to:
Chapter "Percutaneous Mitral Valve Interventions and Heart Failure" in:
A. Sharma et al., Adv Exp Med Biol - Advances in Internal Medicine,
https://doi.org/10.1007/5584_2017_142

In the original version of this chapter, the last name of the third author was incorrectly listed as Sahil Agarwal. It should actually read Sahil Agrawal and this has been corrected.

The updated online version of the original chapter can be found under
https://doi.org/10.1007/5584_2017_142

Adv Exp Med Biol - Advances in Internal Medicine (2018) 3: 409–418
https://doi.org/10.1007/978-3-319-78280-5
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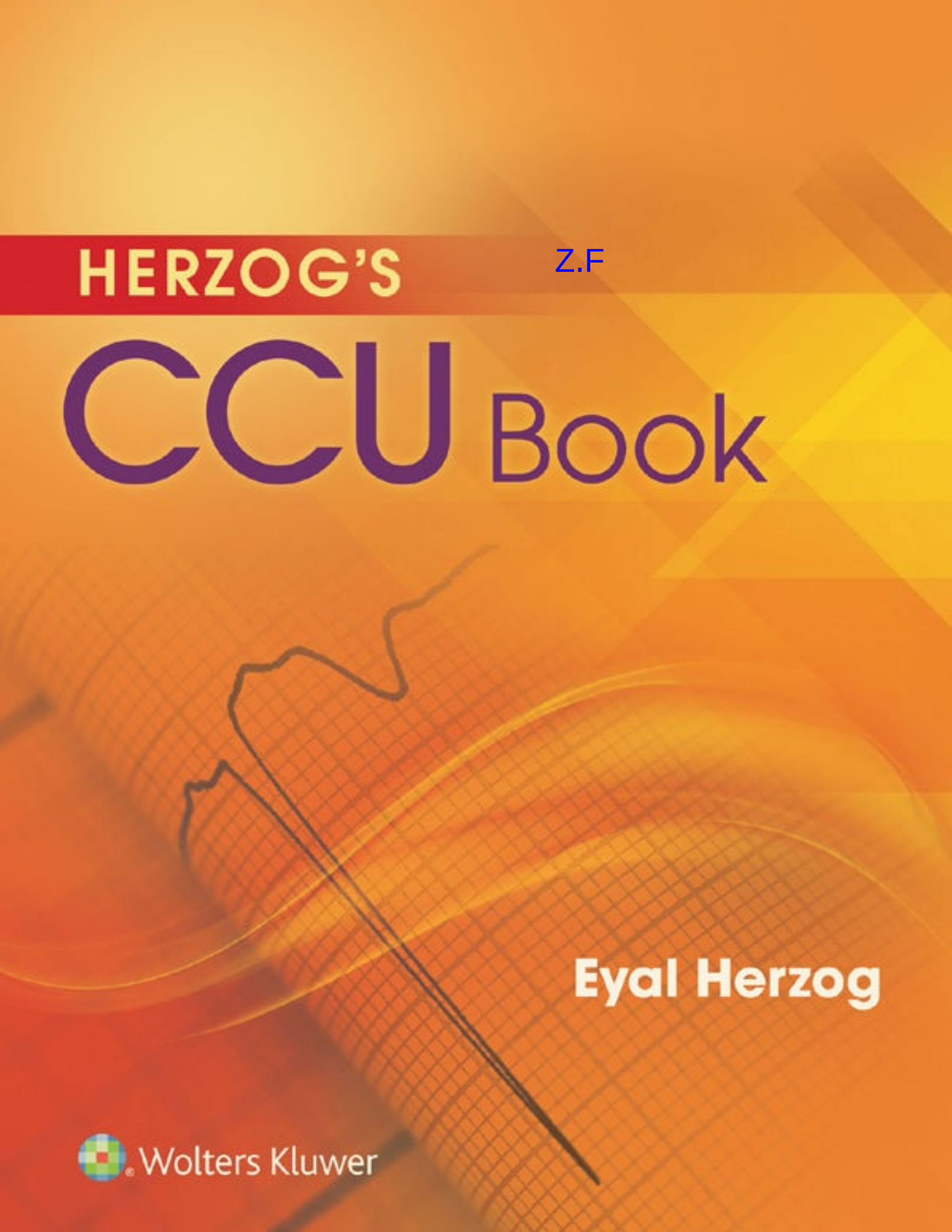

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Editorial Coordinator: Lauren Pecarich
Production Project Manager: Linda Van Pelt
Design Coordinator: Holly McLaughlin
Manufacturing Coordinator: Beth Welsh
Marketing Manager: Rachel Mante Leung
Prepress Vendor: S4Carlisle Publishing Services

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9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data
Names: Herzog, Eyal, editor.
Title: Herzog's CCU book / [edited by] Eyal Herzog.
Other titles: CCU book | Cardiac care unit book
Description: Philadelphia: Wolters Kluwer Health, [2018] | Includes bibliographical references and index.
Identifiers: LCCN 2017044559 | eISBN 9781496362681
Subjects: | MESH: Heart Diseases | Critical Care
Classification: LCC RC682 | NLM WG 210 | DDC 616.1/2—dc23 LC record available at https://lccn.loc.gov/2017044559

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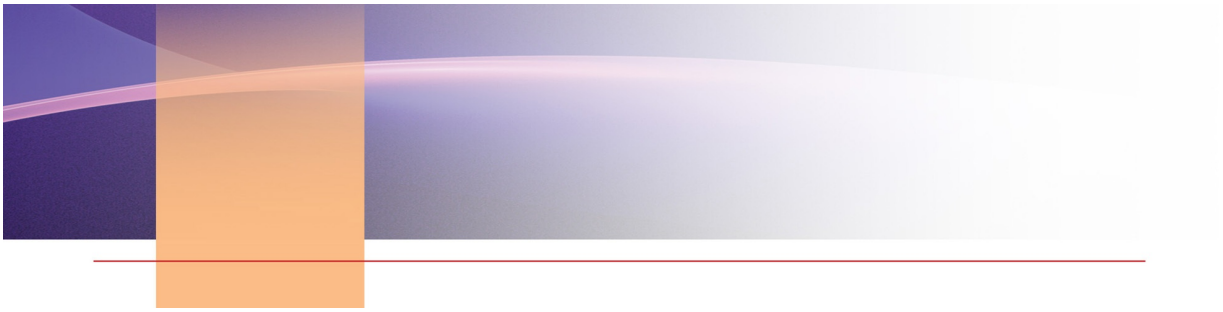

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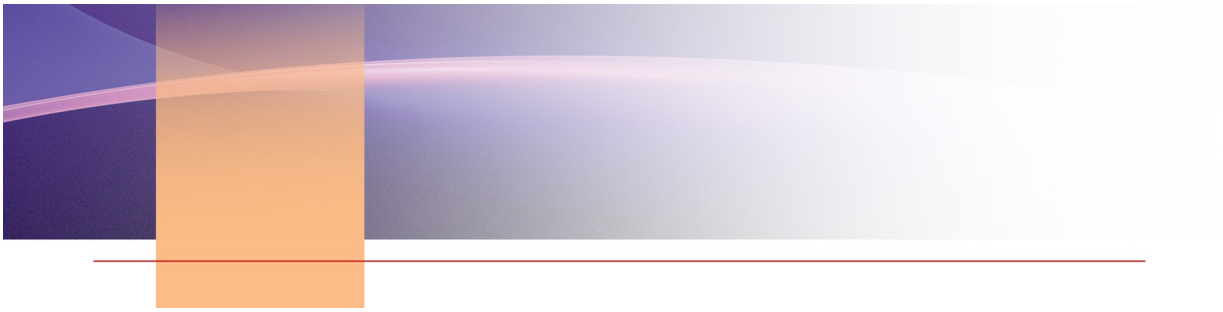
† Deceased. His untimely passing at the end of 2016 has left a void in our hearts and minds.



Preface

Heart disease is the leading cause of death in the world. Advances in the treatment of heart disease are considered among the greatest achievements of modern medicine. Physicians, nurses, and all health care providers who care for patients with heart disease consider the cardiac care unit (CCU) the most exciting place in the hospital.

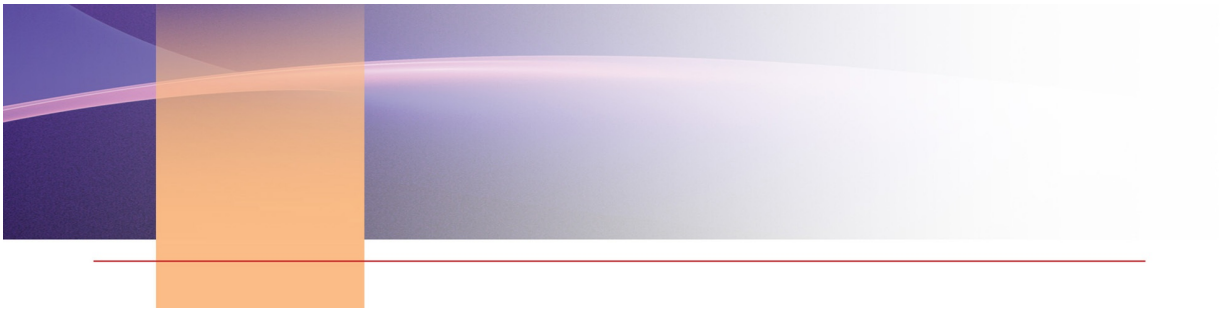
The *CCU Book* is essentially two books combined into one. Most chapters have two sections: the first is for physicians and other health care providers, and the second is for patients and their families.

The first section of each chapter is aimed toward physicians (interns, residents, fellows, and attendings), medical students, nurses, physician assistants, and other health care providers who rotate or practice in the CCU. It is organized such that readers will not need to consult any textbooks regarding the topics discussed and will be able to understand the simplified pathophysiology and management of the disease. This includes diagnostic modalities, initial critical care management in the CCU, follow-up care in a step-down unit, and plans for discharge. Algorithms and pathways for management are provided for easy implementation in any health care system.

The second part of each chapter covers the same topics previously discussed but is directed toward the patients and their families. The language and the medical terminology are simpler and geared toward the general public.

It is my hope that this book will serve as a teaching tool to save the lives of patients with heart disease in the CCU.

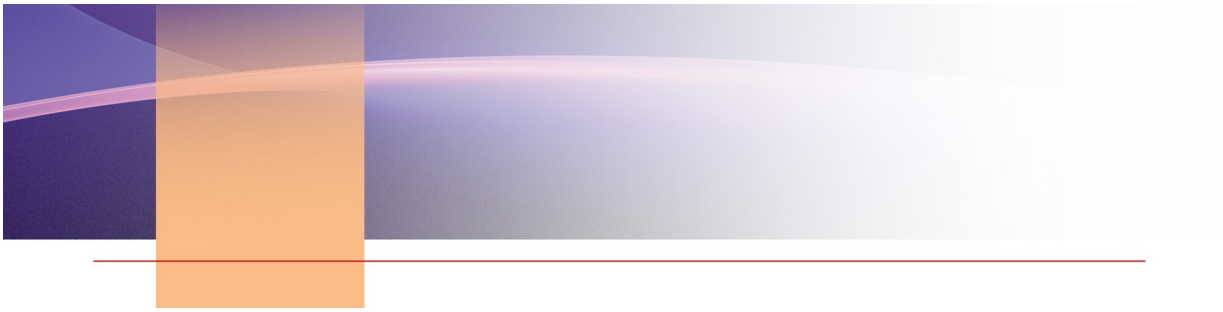
Eyal Herzog



Acknowledgments

I would like to acknowledge the extraordinary work of LaToya Selby and Candice Francis from my office at Mount Sinai St. Luke’s Hospital in New York; they are my right hand in assisting my trainees and patients in the hospital and are also the editing coordinators for this book.

Thank you,
Eyal Herzog



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ACUTE CORONARY SYNDROME

1

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Pathway for the Management of Acute Coronary Syndrome

The practice of medicine is changing at unprecedented speed. Today's reasonable assumption is outlined by tomorrow's evidence. We face a deluge of data as we confront the onslaught of acute coronary syndrome (ACS). ACS subsumes a spectrum of clinical entities, ranging from unstable angina (UA) to ST-elevation myocardial infarction (STEMI). The management of ACS is deservedly scrutinized because it accounts for about 2 million hospitalizations and a remarkable 30% of all deaths in the United States each year. Clinical guidelines on the management of ACS, which are based on clinical trials, have been updated and published.[1–3]

In this chapter, we describe a novel pathway for the management of ACS in our health care system.[4, 5]

The pathway has been designated with the acronym PAIN (***P***riority risk, ***A***dvanced risk, ***I***ntermediate risk, and ***N***egative/Low risk), which reflects the patient's most immediate risk stratification upon admission (**Figure 1.1**). This risk stratification reflects the patient's 30-day risks for death and myocardial infarction (MI) following the initial ACS event.

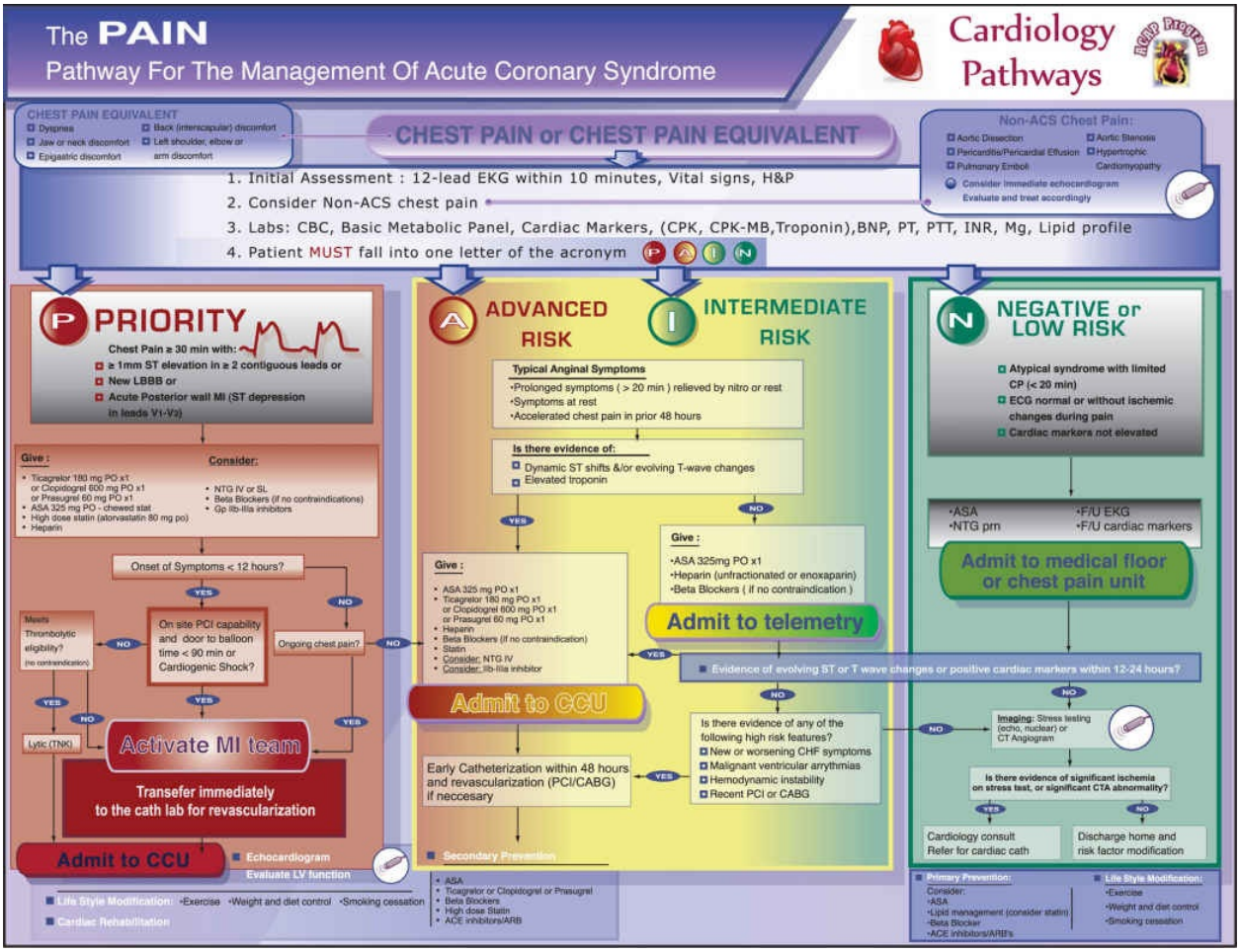

FIGURE 1.1 The PAIN pathway for the management of acute coronary syndrome. ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CABG, coronary artery bypass surgery; CHF, congestive heart failure; CCU, coronary care unit; CPK, creatine phosphokinase; CPK-MB, CPK-muscle and brain; ECG, electrocardiogram; INR, international normalized ratio; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; PT, prothrombin time; PTT, partial thromboplastin time.

The pathway is color coded with the “PAIN” acronym (P—red, A—yellow, I—yellow, N—green), which guides patient management according to the patient’s risk stratification. These colors—similar to the traffic light code—have been chosen as an easy reference for the provider about the sequential risk level of patients with ACS.[6]

In comparison with the North American and European guidelines for ACS,[1–3] in the proposed PAIN algorithm, P (priority) is equivalent to STEMI or STE (ST-elevation)-ACS; A (advanced) and I (intermediate) are equivalent to non–STE-ACS; and N (negative) means that there is no evidence of ACS.

INITIAL ASSESSMENT OF PATIENTS WITH CHEST PAIN OR CHEST PAIN EQUIVALENT

Patients who present to emergency departments with chest pain or chest pain equivalent will be enrolled into this pathway.

Figure 1.2 shows the chest pain equivalent symptoms. The initial assessment is seen in **Figure 1.3**. All patients should have an electrocardiogram (ECG) performed within 10 minutes as well as a detailed history and physical examination.

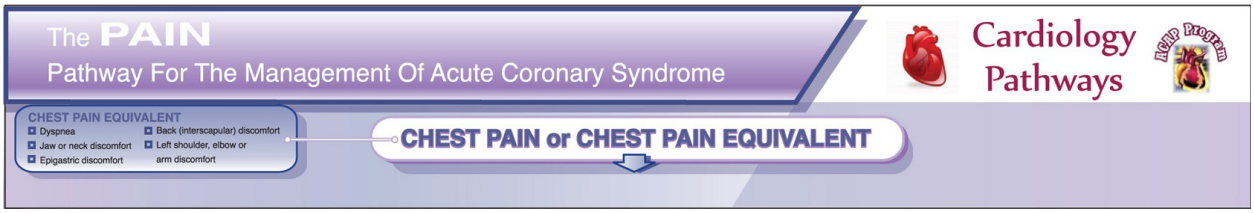

FIGURE 1.2 Chest pain and chest pain equivalent symptoms.

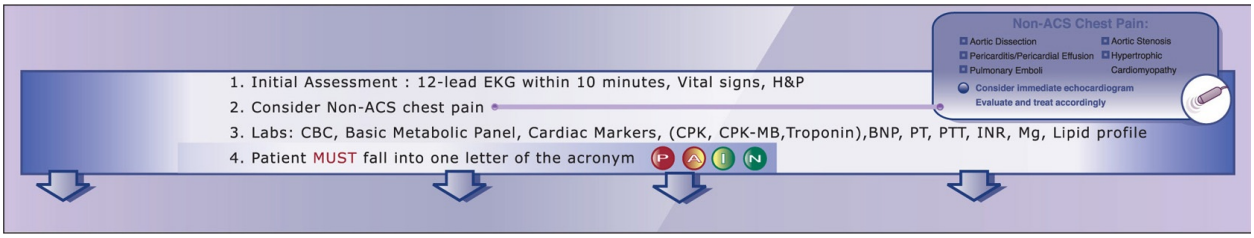

FIGURE 1.3 Initial assessment of patients with chest pain. ACS, acute coronary syndrome; CBC, complete blood count; CPK, creatine phosphokinase; CPK-MB, CPK-muscle and brain; BNP, brain natriuretic peptide; ECG, electrocardiogram; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

Non-ACS chest pain should be excluded urgently. These conditions include aortic dissection, pericarditis and pericardial effusion, pulmonary emboli, aortic stenosis, and hypertrophic cardiomyopathy. If any of these emergency conditions is suspected, we recommend immediately obtaining an echocardiogram or a computed tomography (CT) scan and treating accordingly.

Our recommended initial laboratory tests include complete blood count, basic metabolic panel, cardiac markers (to include creatine phosphokinase [CPK], CPK-muscle and brain [CPK-MB], and troponin), brain natriuretic peptide (BNP), prothrombin time, partial thromboplastin time, international normalized

ratio, magnesium level, and a lipid profile.

INITIAL MANAGEMENT OF PRIORITY PATIENTS

Priority patients are those with symptoms of chest pain or chest pain equivalent lasting longer than 30 minutes with one of the following ECG criteria for acute MI:

1. Group (1): New ST-elevation at the J point in at least two contiguous leads: ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3 and/or ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads
2. Group (2): New left bundle branch block (LBBB) or
3. Group (3): Acute posterior wall MI (ST-segment depression in leads V1–V3)

The initial treatment of these patients includes obtaining an intravenous line; providing oxygen; treating patients with oral aspirin (chewable 325 mg stat) and a loading dose of one of the following agents: ticagrelor (180 mg), clopidogrel (600 mg), or prasugrel (60 mg); and giving high-dose statin (atorvastatin 80 mg po). We also recommend considering a bolus of IV heparin (1 mg/kg to a maximum dose of 4000 units) and nitroglycerin if it will not delay the transfer of the patient to the Cardiac Catheterization Laboratory (**Figure 1.4**).

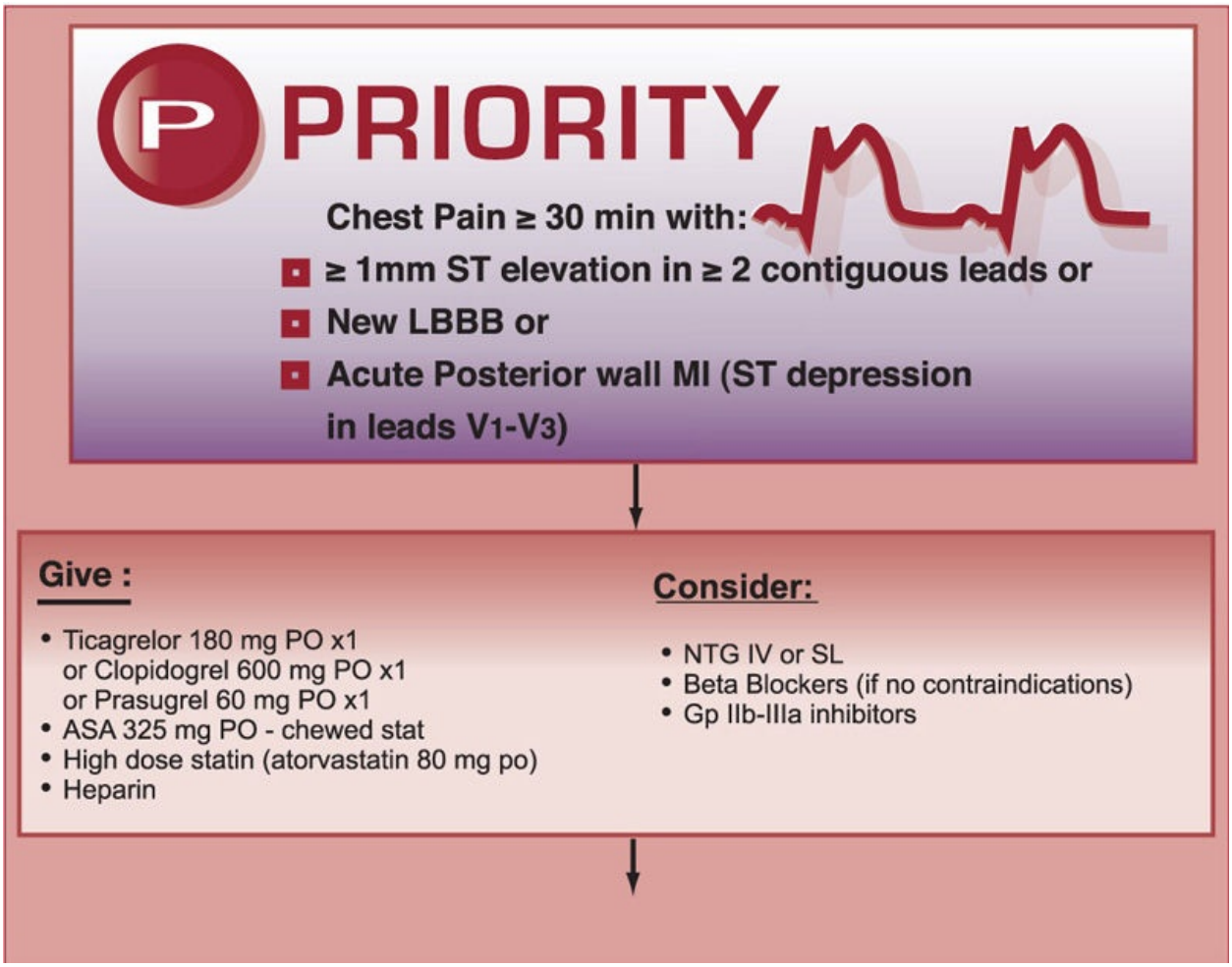

FIGURE 1.4 The initial management of priority patients (those with ST-elevation myocardial infarction). LBBB, left bundle branch block; MI, myocardial infarction.

The key question for further management of these patients is the duration of the patients' symptoms. For patients whose symptoms exceed 12 hours, presence of persistent or residual chest pain determines the next strategy. If there is no evidence of continued symptoms, these patients will generally be treated as though they had been risk stratified with the advanced risk group.

For patients whose symptoms are less than 12 hours or with ongoing chest pain, the decision for further management is based on the availability of on-site angioplasty (percutaneous coronary intervention [PCI]) capability or the ability to transfer the patient to a PCI-capable hospital for immediate PCI within 120 minutes, and the clinical condition of the patient. Patients presenting to a PCI-capable hospital or patients presenting to a non–PCI-capable hospital but who can be transferred to a PCI-capable hospital with an expected "first door to balloon" time of less than 120 minutes should be transferred immediately to the

cardiac catheterization laboratory for revascularization. The MI team is activated for this group of patients (**Figure 1.5**). Furthermore, patients with cardiogenic shock should be transferred immediately to the cardiac catheterization laboratory even if they present to a non–PCI-capable hospital and anticipated time to transfer is more than 120 minutes.

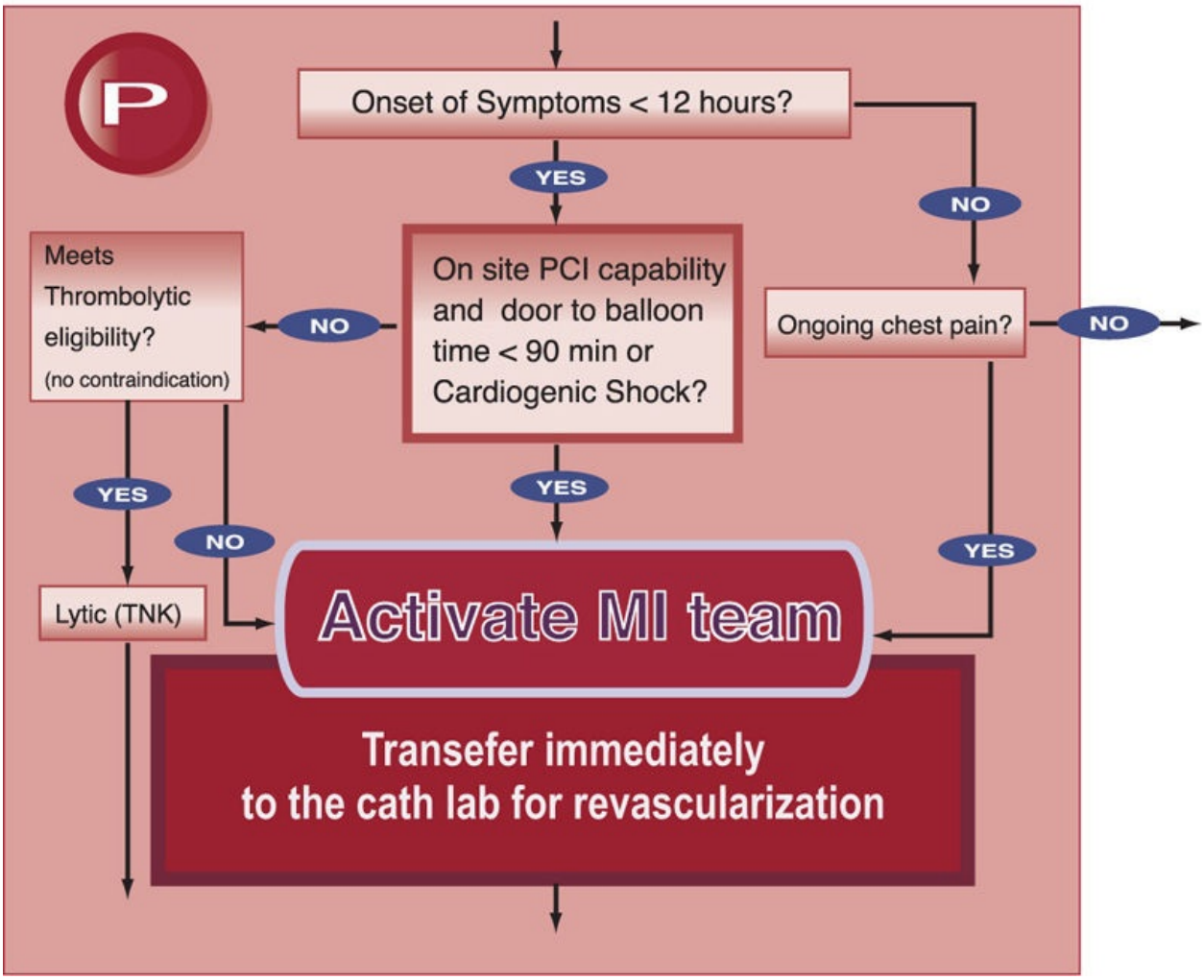

FIGURE 1.5 Advanced management of priority myocardial infarction patients. MI, myocardial infarction; PCI, percutaneous coronary intervention.

In our health care system, a single call made by the emergency department physician to the page operator activates the MI team, which includes the following healthcare providers:

1. The interventional cardiologist on call (who is considered the team leader
2. The director of the Coronary Care Unit (CCU)

3. The cardiology fellow on call
4. The interventional cardiology fellow on call
5. The catheterization laboratory (cath lab) nurse on call
6. The cath lab technologist on call
7. The CCU nursing manager on call
8. The senior internal medicine resident on call

Activating these groups of people has been extremely successful in our institution and has reduced markedly our door to balloon time as well as our first medical contact to device time.

For hospitals without PCI capability and with expected first door-balloon time of more than 120 minutes, we recommend thrombolytic therapy if there are no contraindications.

CORONARY CARE UNIT MANAGEMENT AND SECONDARY PREVENTION FOR PATIENTS WITH PRIORITY MYOCARDIAL INFARCTION

Patients with priority MI should be admitted to the CCU (**Figure 1.6**). All patients should have an echocardiogram to evaluate left ventricle systolic and diastolic function and to exclude valvular abnormality and pericardial involvement. We recommend a CCU stay of 24 to 48 hours to exclude arrhythmia or mechanical complications. For patients with no evidence of mechanical complications or significant arrhythmia, secondary prevention drugs should be started, including aspirin, one of the additional antiplatelet drugs (ticagrelor, clopidogrel, or prasugrel) a high-dose statin, a beta-blocker, and an angiotensin converting enzyme (ACE) inhibitor, or an angiotensin receptor blocker (ARB). Aldosterone blocking agents should be considered for patients with diabetes or LV ejection fraction less than 40%.

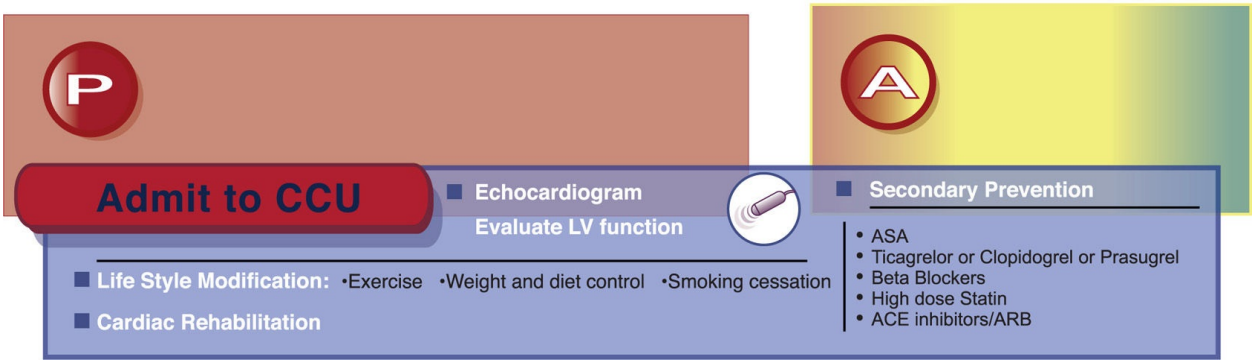

FIGURE 1.6 Coronary care unit management and secondary prevention for patients with priority myocardial infarction. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCU, coronary care unit.

Most patients can be discharged within 48 hours with recommendation for lifestyle modification, including exercise, weight and diet control, smoking cessation, and cardiac rehabilitation. Secondary prevention drugs should be continued on discharge.

MANAGEMENT OF ADVANCED RISK ACUTE CORONARY SYNDROME

Typical anginal symptoms are required to be present in patients who will be enrolled into the advanced or intermediate risk groups.

These symptoms include the following:

1. Prolonged chest pain (>20 minutes) relieved by nitroglycerine or rest
2. Chest pain at rest or
3. Accelerated chest pain within 48 hours

To qualify for the advanced risk group, patients must have dynamic ST changes on the ECG (>0.5 mm), dynamic ischemic T-wave changes, or elevated cardiac biomarkers (troponin >0.2 ng/mL) (**Figure 1.7**).

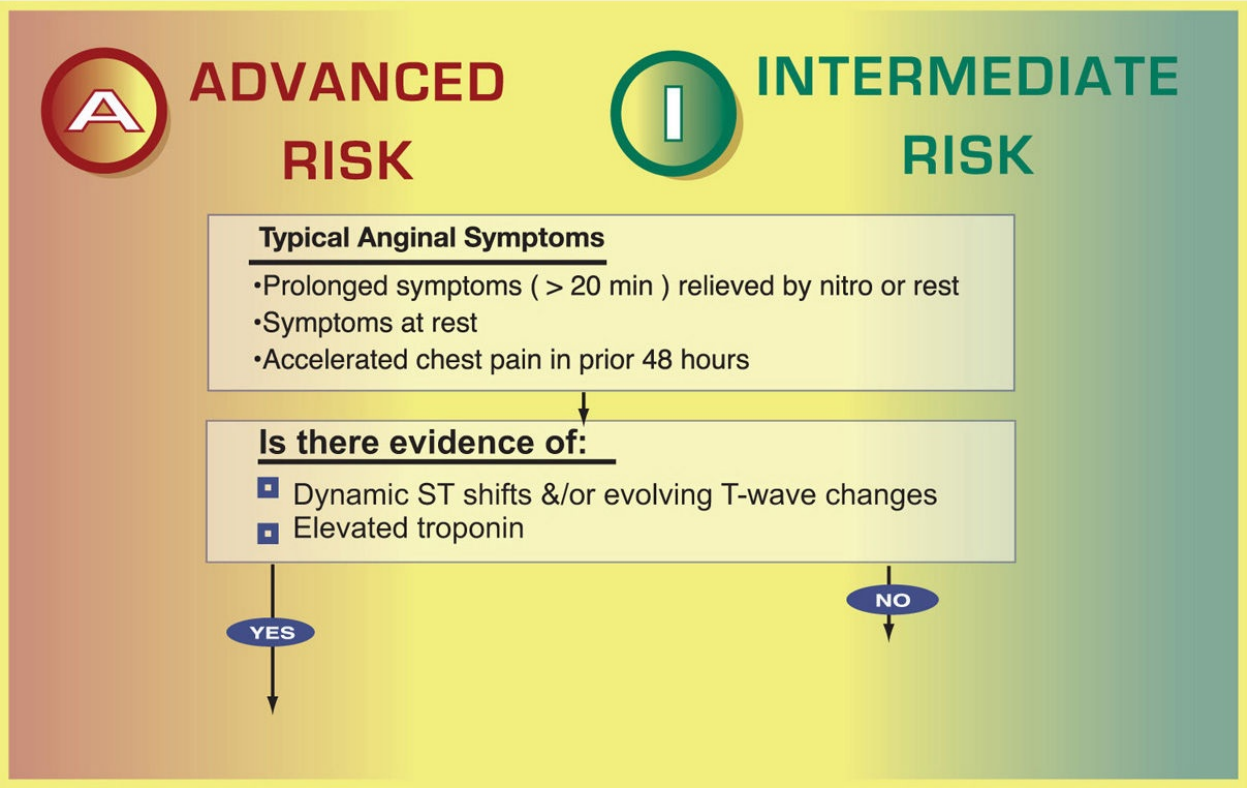

FIGURE 1.7 Risk stratification as advanced risk acute coronary syndrome.

We recommend that patients be admitted to the CCU and be treated with aspirin; ticagrelor or clopidogrel; anticoagulation, including either intravenous heparin or low molecular weight heparin; a beta-blocker; and a statin; consider glycoprotein IIb–IIIa inhibitor or nitroglycerin if there are no contraindications (**Figure 1.8**).

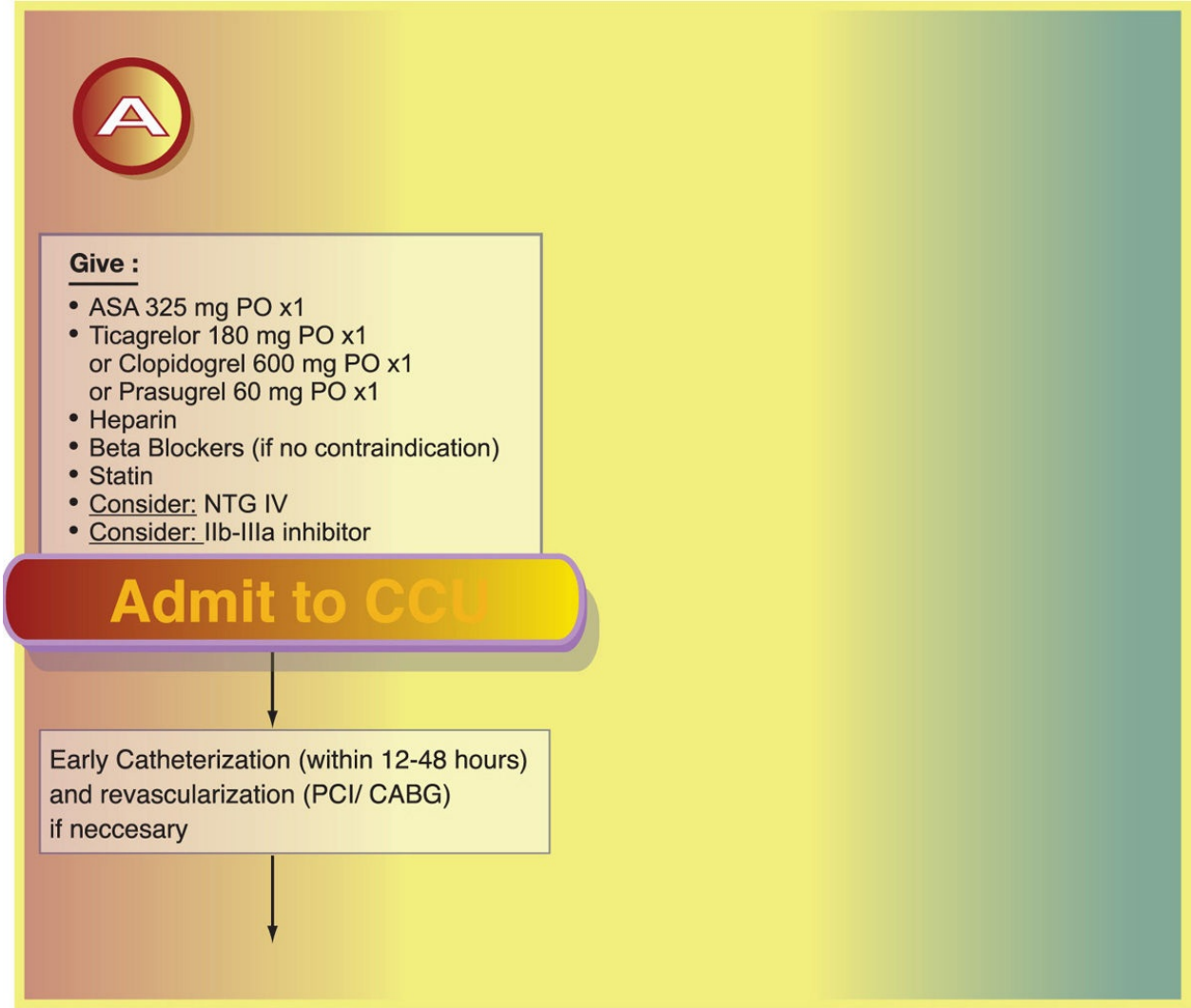

FIGURE 1.8 Management of patients with advanced risk acute coronary syndrome. CCU, coronary care unit; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.

These patients should have early cardiac catheterization within 48 hours and revascularization by PCI or coronary artery bypass surgery (CABG) if there is obstructive coronary artery disease noted on coronary angiography. All patients should have an echocardiogram to evaluate left ventricular (LV) function. Recommendation for secondary prevention medication, lifestyle modification, and cardiac rehabilitation should be provided as in the case of patients in the priority risk group (**Figure 1.6**).

MANAGEMENT OF INTERMEDIATE RISK GROUP

Both the intermediate risk group and the advanced risk patients present to the hospital with typical anginal symptoms. Compared with the advanced risk patients, the immediate risk patients *do not* have evidence of dynamic ST changes or ischemic T-wave changes on the ECG or evidence of positive cardiac markers. These patients should be admitted to the telemetry floor and be given aspirin, heparin, and a beta-blocker if there is no contraindication (**Figure 1.9**). We recommend a minimum telemetry stay of 12 to 24 hours. During this period of time, if there is evidence of dynamic ST changes or ischemic T-wave changes on the ECG or evidence for positive cardiac markers, the patients should be treated as if they had been stratified to the advanced group.

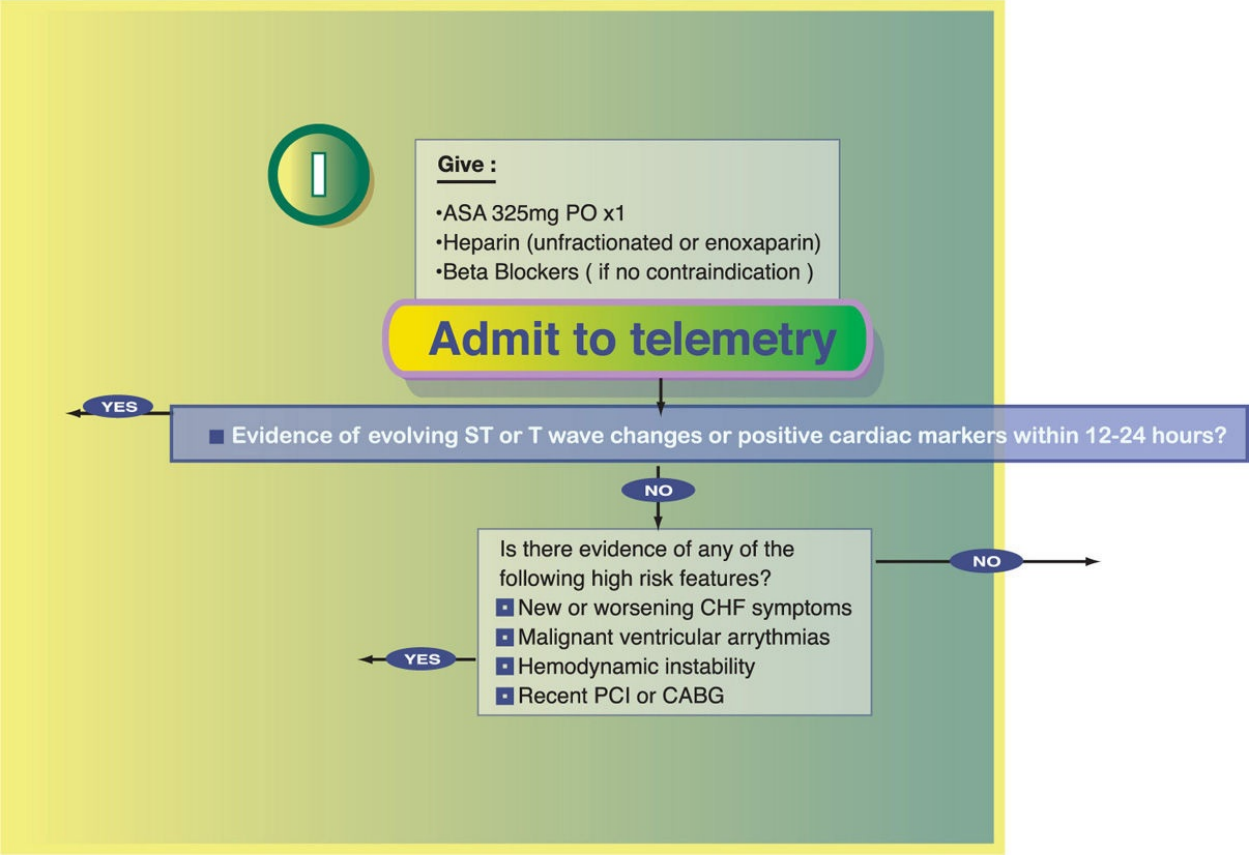

FIGURE 1.9 Management of patients with intermediate risk acute coronary syndrome. CHF, congestive heart failure; CABG, coronary artery bypass surgery; PCI, percutaneous coronary intervention.

The intermediate risk group patients are assessed again for the following high-risk features:

1. New or worsening heart failure symptoms

2. Malignant ventricular arrhythmias
3. Hemodynamic instability
4. Recent PCI or CABG

If there is evidence of any of these high-risk features, we recommend cardiac catheterization within 48 hours and revascularization by PCI or CABG if necessary. Patients with no evidence of high-risk features should be referred for cardiac imaging and stress testing (stress echocardiography or stress nuclear test) or for CT angiography.

MANAGEMENT OF NEGATIVE- OR LOW-RISK GROUP PATIENTS

These groups of patients have atypical symptoms, do not have significant ischemic ECG changes during pain, and do not have elevated cardiac biomarkers.

These patients should be treated only with aspirin and given sublingual nitroglycerin if needed. If a decision is made to admit them to the hospital, they should be admitted to a chest pain unit or to a regular medical floor. They should be followed up for 12 to 24 hours with repeated ECG and cardiac biomarkers (**Figure 1.10**). If there is evidence of evolving ST changes or ischemic T-wave changes on the ECG or any evidence of positive cardiac markers, the patients should be treated aggressively, as for the advanced risk group patients.

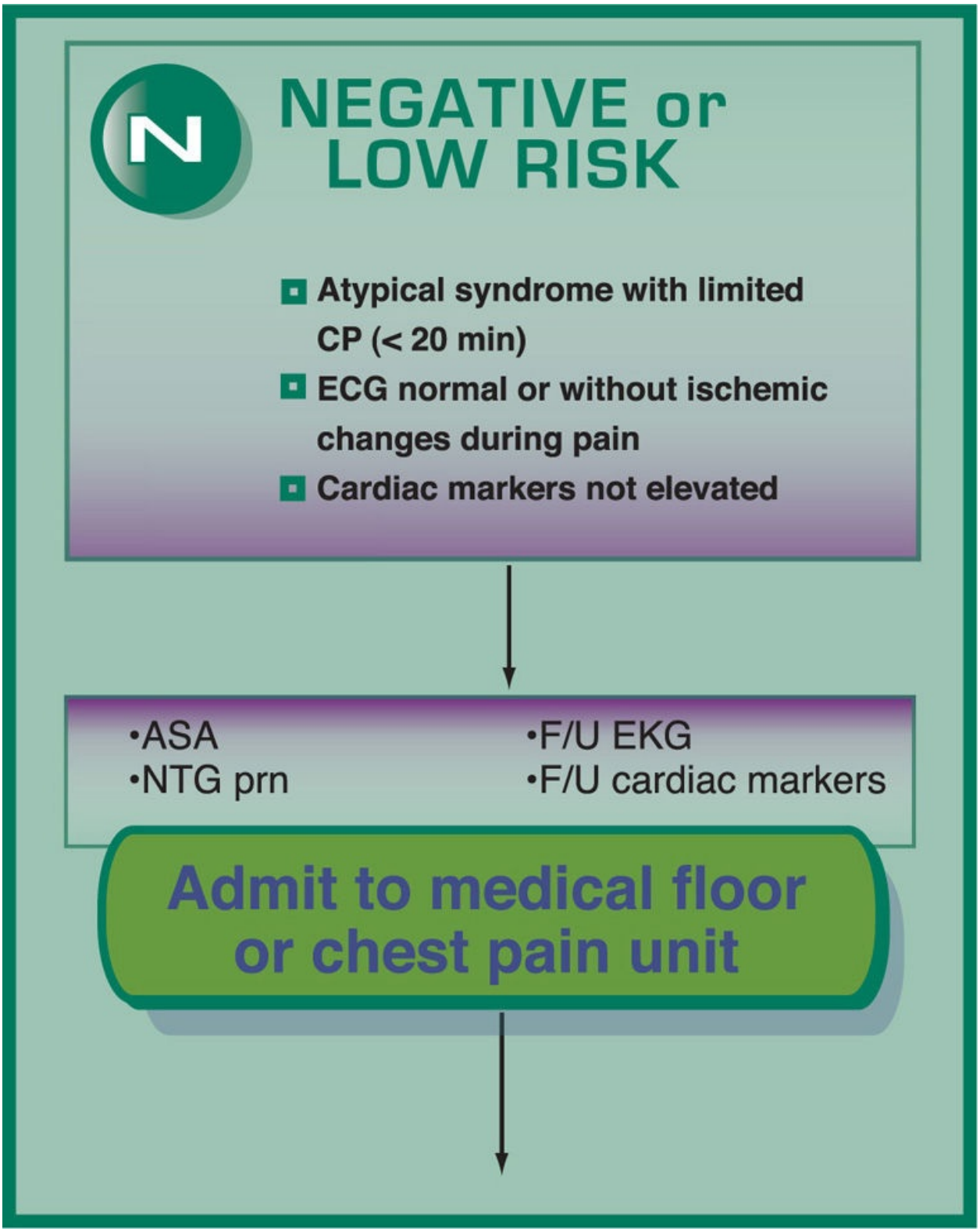

FIGURE 1.10 Initial management of patients with negative- or low-risk acute coronary syndrome; ASA, acetylsalicylic acid; CP, chest pain; ECG, electrocardiogram; NTG, nitroglycerin.

If there are no significant ECG changes and all cardiac markers are negative, we recommend cardiac imaging and stress testing by stress echocardiography or stress nuclear test or a CT angiography (**Figure 1.11**).

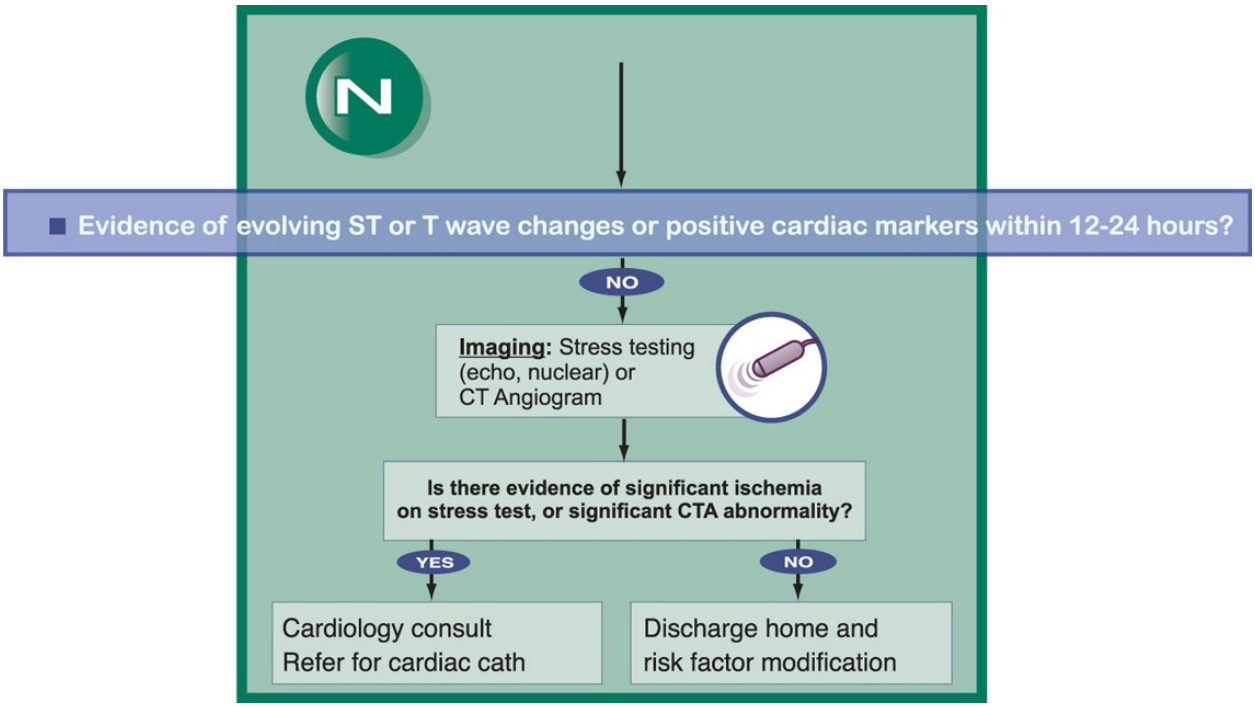

FIGURE 1.11 Risk stratification of low-risk patients by using cardiac imaging stress testing.

Evidence of significant ischemia on any of these stress imaging modalities will be followed by a referral for cardiac catheterization. If there is no evidence of significant ischemia on stress testing, the patients will be discharged home with a recommendation for risk factor modification, to include primary prevention medication and lifestyle modification (**Figure 1.12**).

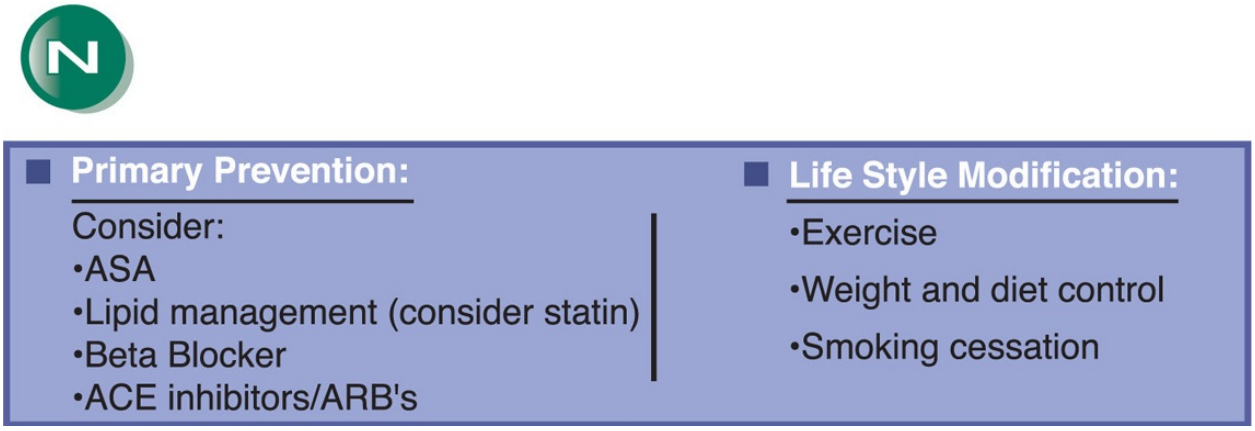

FIGURE 1.12 Primary prevention for low-risk patients. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid.

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2

Chirag Bavishi
Eyal Herzog
Jacqueline E. Tamis-Holland

ST-Segment Elevation Myocardial Infarction

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) represents the most urgent form of acute coronary syndromes (ACS). Pathophysiologically, it is characterized by occlusive intracoronary thrombus formation, resulting in the total cessation of coronary artery blood flow, and the characteristic pattern of ST-segment elevation on the electrocardiogram (ECG), indicative of an acute current of injury from transmural ischemia. Prompt recognition is the key step in the management of such patients to ensure early revascularization, thus limiting the extent of ischemic myocardium and minimizing early and late morbidity and mortality associated with STEMI.

EPIDEMIOLOGY

STEMI remains a major public health problem in both developed and developing nations. In the United States, there are approximately 1 million hospitalizations each year for ACS, and STEMI comprises 25% to 40% of these cases.[1, 2] Approximately one-third of the patients with STEMI are women. In the

past decade, there has been a marked decline in the incidence of STEMI, presumably as a result of the widespread institution of aggressive preventive therapies. In-hospital mortality for patients with STEMI ranges from 5% to 6%, whereas 1-year mortality is variable and estimated to range from 7% to 18%.[1] However, important age-related, sex-related, and geographic differences exist.

PATHOPHYSIOLOGY

The occlusive intracoronary thrombus is usually the result of rupture, ulceration, or erosion of an atherosclerotic plaque. Plaque rupture accounts for the majority of the cases. This leads to either partial obstruction, which generally causes myocardial ischemia in the absence of ST-segment elevation (non–ST-segment elevation ACS), or complete occlusion and STEMI. The myocardium supplied by the culprit artery loses its contractile ability, which leads to the following abnormal contractile patterns: dyssynchrony, hypokinesis, akinesis, and dyskinesis. The remaining noninfarcted myocardium usually manifests hyperkinesis unless there is underlying coronary artery disease affecting the territory supplied by these arteries. If a large area of myocardium is jeopardized, left ventricular pump function becomes depressed. Diastolic dysfunction is invariably associated with systolic dysfunction. Severely reduced systolic function leads to a decrease in left ventricular stroke volume, which lowers systemic pressures and coronary perfusion pressure, potentiating myocardial ischemia and leading to a vicious cycle. In extreme cases of severe myocardial damage, this will eventually lead to cardiogenic shock.

CLINICAL DIAGNOSIS AND ASSESSMENT

The diagnosis of STEMI generally requires symptoms suggestive of myocardial ischemia associated with persistent ST-segment elevation on ECG and evidence of myocardial necrosis, which is typically supported by an elevation in cardiac enzymes.

SYMPTOMS

The sudden onset of chest discomfort is the most common presenting symptom. The chest discomfort is usually retrosternal, with a mid- to left-sided

predisposition. The pain is usually described as “pressure-like,” “crushing,” “squeezing,” or “compressing.” The pain may sometimes radiate to the left arm, left shoulder, neck, or jaw. These symptoms may be associated with shortness of breath, diaphoresis, nausea, or vomiting. These typical clinical symptoms are present in many, but not all, patients with STEMI. Women, elderly patients, and patients with diabetes may present with atypical symptoms. Such symptoms can include epigastric pain, shortness of breath, back pain, or nausea and diaphoresis alone. In some patients, the presentation of STEMI is manifested by symptoms of ventricular tachycardia or symptoms of left ventricular failure. Occasionally, patients with STEMI may present with cardiac arrest. A focused history and physical exam should be performed on all patients with suspected STEMI, to aid in making the diagnosis and identifying high-risk patients.

ELECTROCARDIOGRAM

A 12-lead ECG should be acquired and interpreted promptly (within 10 minutes) in all suspected cases of acute myocardial infarction (MI). In the presence of a strong clinical suspicion, if the initial ECG is nondiagnostic, a repeat ECG should be performed 5 to 10 minutes later to assess for evolving ST elevation. Hyperacute T waves are the earliest ECG manifestations of a STEMI and may precede the characteristic ST-segment elevation. On the other hand, up to 15% of patients with STEMI can have a normal ECG. In these circumstances, the left circumflex artery is often the culprit vessel.

The European Society of Cardiology/ACCF/AHA/World Heart Federation Task Force for the Universal Definition of MI and the ACCF/AHA/SCAI Guidelines for the Management of ST Elevation Myocardial Infarction include the following criteria for the ECG definition of ST elevation infarction[1, 3]:

1. New ST elevation at the J point in at least two contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads.
2. New ST depressions in ≥2 precordial leads (V1–V4) are indicative of a transmural posterior infarction.
3. New or presumably new left bundle branch block (LBBB). (While this may be a STEMI equivalent, the diagnostic accuracy of this finding has recently been questioned.[1] There are algorithms that may help to further differentiate a true STEMI in the setting of LBBB.)

In patients with suspected right ventricular infarction, right precordial leads (V3R and V4R) could further aid in the diagnosis. In addition, in cases of a suspected posterior infarction, recording of posterior leads is strongly recommended (V7 lead should be recorded at the left posterior axillary line, V8 lead should be recorded at the left midscapular line, and V9 lead should be recorded at the left paraspinal border).[3] The presence of "reciprocal changes" in the form of ST-segment depression in the leads that are opposite to the location of the ST elevations is a characteristic finding that greatly increases the specificity of the diagnosis of STEMI. Multilead ST-segment depression with coexistent ST elevation in lead aVR alone has been described in patients with left main or proximal left anterior descending artery occlusion.

It is important to recognize that the ECG changes that are depicted in a patient with suspected STEMI are a dynamic finding. The ST-segment changes will evolve throughout the patient's postinfarction course and will often reflect the extent to which the patient has achieved restoration of myocardial blood flow at the tissue level. **Figure 2.1** outlines the evolution of ECG changes in a patient with a large anterior infarction who received prompt reperfusion therapy.

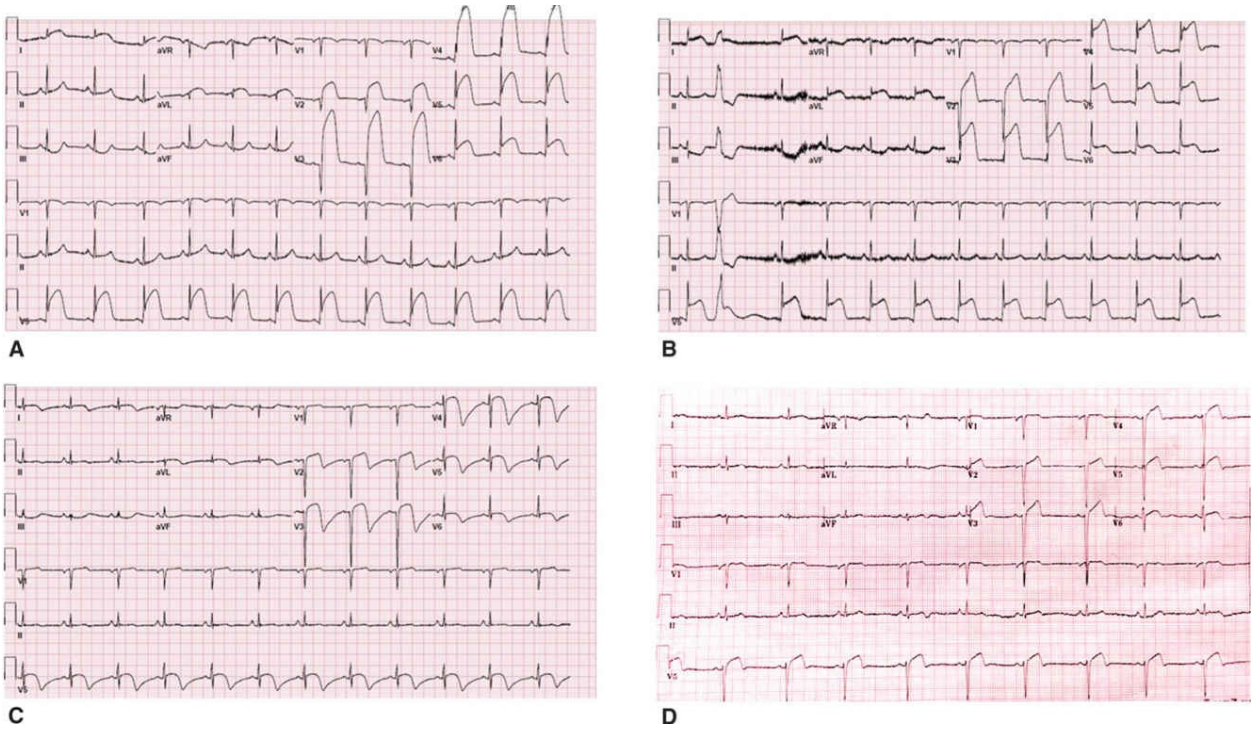

FIGURE 2.1 The evolution of the ECG during an acute infarction. A, The ECG of a 54-year-old male presenting 2 hours after the onset of severe chest pain demonstrating a large anterolateral infarction. B, The ECG in this same patient immediately after reperfusion therapy with primary PCI. Despite restoration of

TIMI III flow in the infarct artery and complete relief of chest pain, there remains moderate ST-segment elevation. Note, however, that the ST-segment elevation has been reduced by more than 50% in the lead with the greatest degree of ST elevation on initial ECG. This usually indicates achievement of tissue-level reperfusion. C, The ECG 48 hours after the acute infarction. The patient was asymptomatic at the time the ECG was performed, and his cardiac enzymes were downtrending. Note the marked ST and T wave changes and the prolongation of the QT interval. This finding is not uncommon postinfarction even in patients treated successfully with reperfusion therapy. D, The ECG was performed 2 weeks after the infarction. Note the marked improvement in the ST and T wave abnormalities. ECG, electrocardiogram; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

BIOMARKERS

Serum biomarkers can be detected when they are released from damaged myocardial cells. Because this is a time-bound process, serum biomarkers are not useful for early detection of STEMI but can confirm myocardial injury if a patient is presenting late after symptom onset. Established cardiac biomarkers used to detect acute MI are cardiac-specific troponins (troponin I and troponin T), creatine kinase (CK) and CK isoenzymes (CK-MB fraction), and myoglobin. **Figure 2.2** depicts the Kinetic profiles of the various biomarkers used in the diagnosis of acute STEMI. Myoglobin elevations peak early but are not cardiac-specific. Cardiac troponin is the preferred biomarker for the diagnosis of MI because of its high specificity and sensitivity. The biomarkers of myocardial injury, however, do not provide any information on the cause of injury. Elevated levels should always be correlated clinically because it could be secondary to nonischemic insults. In STEMI, clinicians should not wait for the results of cardiac biomarkers to initiate treatment. Clinical presentation and 12-lead ECG should serve as the initial diagnostic tools. CK and CK-MB are the tests of choice to define a recurrent MI in the early days after STEMI.

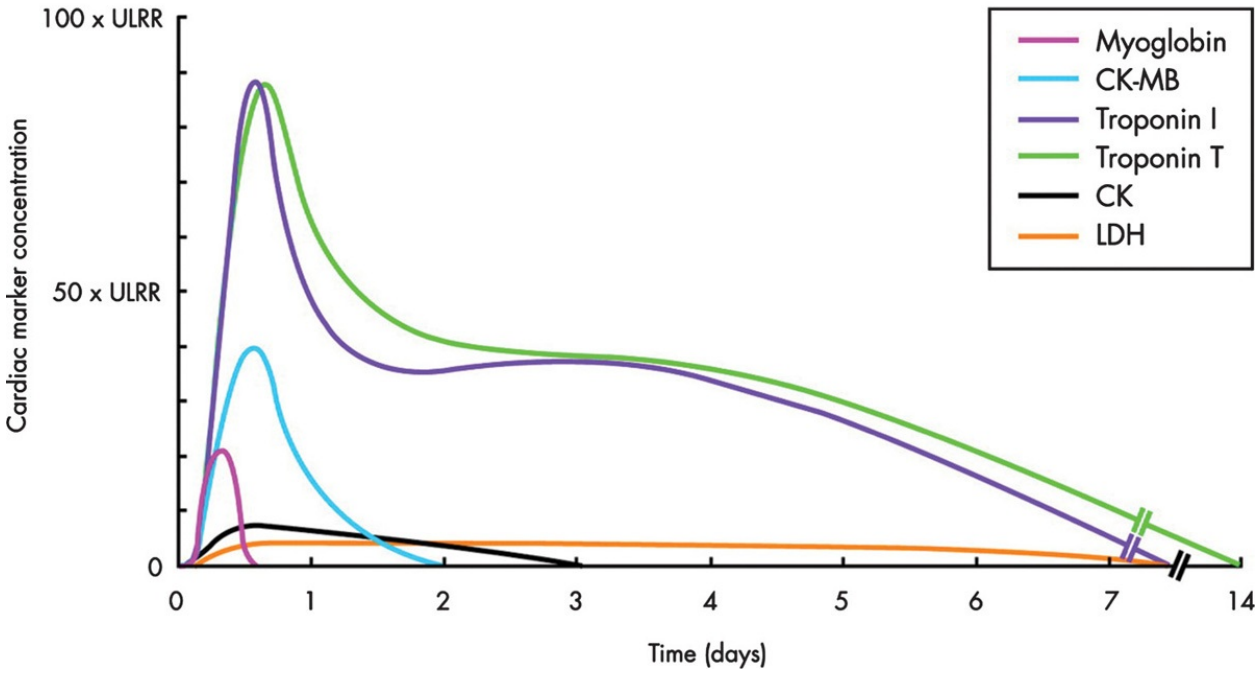

FIGURE 2.2 Cardiac biomarkers in STEMI. These biomarker profiles are schematic and do not differentiate the course of the occlusion (ie, early reperfusion vs persistent occlusion). ST-segment elevation myocardial infarction. CK, creatine kinase; CK-MB, creatine kinase muscle–brain; LDH, lactate dehydrogenase; STEMI, ST-elevation myocardial infarction; URLL, upper limit reference range. (Reproduced from French JK, White HD. Clinical implications of the new definition of myocardial infarction. *Heart*. 2004;90(1):99-106, with permission of the publisher. Copyright 2016, BMJ Publishing Group Ltd & British Cardiovascular Society.)

RISK ASSESSMENT

It is important to perform a risk assessment for all patents with STEMI. This assessment should be done on initial presentation, and repeat assessments should be performed throughout the hospital stay. A risk assessment provides the physician with important estimates of the patient's overall prognosis and guides the health care team on the most appropriate therapies on the basis of this risk. For example, in a post hoc analysis of the DANish trial in Acute Myocardial Infarction-2 (DANAMI-2),[4] primary percutaneous coronary intervention (PCI) was associated with a significant reduction in 3-year mortality compared with fibrinolysis (25% vs 36%) in high-risk patients with a thrombolysis in myocardial infarction (TIMI) risk score ≥5. Risk assessments also allow the physician to provide realistic information to patients and their families regarding a patient's prognosis. A risk assessment is often based on the historical and clinical information that is available to the health care team when the patient first presents to the hospital, and is further modified by the patient's subsequent

hospital course.

Scoring systems such as the TIMI risk score[5] or the Global Registry of Acute Coronary Events (GRACE) score[6] are tools that provide a qualitative assessment of risk and the likelihood that the patient will suffer a subsequent ischemic or terminal event in the short term. The TIMI risk score is an easy to use risk score for patients with STEMI. The TIMI score was derived from a dataset of patients enrolled in the TIMI-II trial and validated using information from those patients enrolled in the TIMI-9 trial. The score comprises eight variables, each of which is assigned a certain number of points. The variables include the following: (1) Age: 65 to 74 years = 2 points; and ≥75 years = 3 points; (2) Systolic blood pressure < 100 mm Hg = 3 points; (3) Heart rate > 100 beats/min = 2 points; (4) Kilip class II–IV = 2 points; (5) History of diabetes or hypertension or angina = 1 point; (6) Weight < 67 kg = 1 point; (7) Anterior infarct or LBBB = 1 point; and (8) Time to treatment > 4 hours = 1 point. Across the spectrum of risk, mortality at 30 days varies from less than 1% for low-risk patients (those with a TIMI score of 1) to over 35% for high-risk patient (those with a TIMI score of 8).

The GRACE risk score assesses the likelihood of in-hospital and 6-month mortality among patients with ACS, including STEMI, non–ST-elevation MI, or unstable angina. The score was derived using variables from an unselected population of patients enrolled in the GRACE Registry, an international clinical registry of all patients with ACS admitted to selected hospitals. The GRACE risk score gives a broader range of weighted values for each particular risk factor. Because the GRACE score was derived from an unselected population of patients (rather than data from patients enrolled in clinical trials), it incorporates a larger range of clinical variables than the TIMI risk score. Eight factors are used in this score: (1) Age, (2) Heart rate, (3) Systolic blood pressure, (4) serum creatinine, (5) Cardiac arrest on presentation, (6) ST-segment deviation, (7) Elevated/abnormal cardiac enzymes, and (8) Rales or jugular venous distension versus pulmonary edema versus shock. The GRACE score calculator is available as a web-based tool for easy use (http://www.outcomes-umassmed.org/grace/). The GRACE score was validated using the clinical data of the patients enrolled in the Global Use of Strategies to Open Occluded Arteries IIb (GUSTO IIb) study. The predicted mortality for the patients in the GUSTO IIb study calculated with the GRACE scoring system was strongly correlated with the observed mortality (*c*-statistic = 0.791), thus emphasizing the strong predictive accuracy of this scoring system.

REPERFUSION THERAPY

The management of STEMI involves an integrated strategy that begins with early recognition of symptoms and diagnosis, contact with emergency medical services, time-efficient practices in emergency departments to shorten door-to-balloon times or door-to-needle times, and a skilled heart team to ensure timely revascularization. To achieve these goals, the American Heart Association recommends that each community develops a STEMI system of care, which includes[1, 7]:

1. A process for prehospital identification of STEMI and prehospital activation of the cardiac catheterization laboratory, with destination protocols in place to bypass non-PCI hospitals and direct patients with suspected STEMI diagnosed in the field to PCI-capable hospitals.
2. Protocols enabling the rapid diagnosis and treatment of STEMI at non–PCI-capable hospitals, including the facilitation of transfer of such patients to PCI-capable hospitals and/or the rapid and early use of fibrinolytic therapy for those patients who present to hospitals without PCI capability and who cannot be transferred to PCI-capable hospitals in a timely manner.
3. Ongoing multidisciplinary team meetings (including emergency medical services, non-PCI hospitals, and PCI centers) to evaluate outcomes and quality improvement metrics.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Current guidelines recommend that reperfusion with either fibrinolysis or primary PCI be performed as soon as possible after arrival at the hospital.[1] In general, primary PCI is the preferred reperfusion therapy. Several randomized controlled trials (RCTs) and observational studies have shown the superiority of primary PCI compared with fibrinolytic therapy.[8, 9] In a meta-analysis of 23 randomized trials, primary PCI was associated with a reduction in short-term and long-term major adverse cardiovascular events, including death, nonfatal Recurrent MI, and stroke.[8] The benefits of PCI over fibrinolytic therapy were seen irrespective of the type of fibrinolytic agent used, and even when reperfusion was delayed because of transfer for primary PCI. Restoration of TIMI-3 flow has a major impact on short- and long-term mortality. Primary PCI can achieve TIMI-3 flow in the infarct artery in >85% of patients,[9, 10] compared

with only about 60% to 63% of patients using thrombolytic therapy.[11] Conceivably, PCI has been shown to limit infarct size and salvage greater myocardium compared with fibrinolysis.[12] Primary PCI also reduces recurrent ischemia, resulting in fewer revascularization procedures and a shorter length of stay compared with fibrinolysis.[13] Primary PCI should be performed in patients with ischemic symptoms of <12 hours' duration presenting to PCI-capable hospitals, and for patients presenting to non–PCI-capable hospitals only if PCI can be performed within 120 minutes of first hospital arrival (see below). For patients with a delayed presentation of 12 to 24 hours after symptom onset, PCI can still be considered. Patients who present to hospitals without PCI capabilities should be transferred for primary PCI if they have contraindications to fibrinolytic therapy or cardiogenic shock, irrespective of the time delay from first medical contact.[1]

Transfer for Primary Percutaneous Coronary Intervention

Several trials have shown benefits in transferring patients with STEMI for primary PCI from a non–PCI-capable hospital to a PCI-capable hospital. The DANAMI-2 trial[14] conducted in Denmark was the largest of such studies, involving 1572 patients. The trial found that the transfer of patients with STEMI from a non–PCI-capable hospital to a PCI-capable hospital for primary PCI was superior to the use of fibrinolytic therapy at the referring hospital. The median transfer time was 67 minutes, and average first door-to-device time was approximately 110 minutes. Most of these transfer studies were performed in European centers where transfer times are generally relatively short, and efficient systems with protocols for transport are already in place. Data from the recent AHA Mission: Lifeline Program of 14,518 patients transferred from non–PCI-capable hospitals for primary PCI between 2008 and 2012 in the United States showed that more than one-third of the patients with STEMI who were transferred for primary PCI failed to achieve a first door-to-device time ≤120 minutes, despite estimated transfer times of less than 60 minutes.[15] If the time to treatment with primary PCI falls beyond the window of 120 minutes, it is possible that the relative benefit from primary PCI as compared with fibrinolytic therapy may be lost. These findings suggest that ongoing efforts to optimize STEMI systems across the country are still needed to achieve primary PCI care for transfer patients as mandated by the guidelines.

FIBRINOLYTIC THERAPY

When it is anticipated that primary PCI cannot be performed within 120 minutes of first medical contact and the onset of ischemic symptoms is within 12 hours, then fibrinolytic therapy should be given. As stated earlier, myocardial salvage is a time-dependent process, and successful epicardial perfusion can be achieved if fibrinolytic therapy is administered early after symptom onset. In fact, studies have demonstrated the superiority of fibrinolysis over primary PCI when therapy is administered within 1 to 2 hours of symptom onset (concept of the "golden hour").[16] The efficacy and utility of fibrinolytic agents diminish with time, and their benefit in patients who present >12 hours after symptom onset is uncertain; however, the guidelines still provide a window of use within 12 to 24 hours of symptom onset for large infarct or patients with ongoing symptoms. It is recommended that when fibrinolytic therapy is indicated or chosen as the primary reperfusion strategy, it should be administered within 30 minutes of arrival at the hospital. Unfortunately, not all patients are candidates for fibrinolytic therapy because of possible contraindications, but should instead be considered for transfer for primary PCI.[1] **Table 2.1** outlines the absolute and relative contraindications to fibrinolytic therapy. Major complications of fibrinolytic therapy include bleeding, particularly intracranial hemorrhage (<1%) and other serious bleeding (<2%). Approximately 20% to 25% of patients have failure of reperfusion,[17] and an additional 25% to 30% have reocclusion,[18] which is associated with increased in-hospital mortality and significant impairment in left ventricular function.[19]

TABLE 2.1 Contraindications to Fibrinolytic Therapy

ABSOLUTE	RELATIVE
Any prior intracranial hemorrhage	History of chronic, severe poorly controlled hypertension
Known structural cerebral vascular lesion (ie, arteriovenous malformation)	Severe hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg)
Malignant cerebral neoplasm (primary or metastatic)	History of prior ischemic stroke >3 mo
Ischemic stroke within 3 mo	Dementia
Active bleeding or bleeding diathesis (excluding menses)	Other known intracranial pathology

Important closed-head or facial trauma within 3 mo	Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Intracranial or intraspinal surgery within 3 mo	Major surgery (<3 wk)
Severe and uncontrolled hypertension unresponsive to therapies	Recent (within 2–4 wk) internal bleeding
For planned streptokinase use: streptokinase within 6 mo	Noncompressible vascular punctures
	Pregnancy
	Active peptic ulcer

MEDICAL MANAGEMENT

GENERAL MEASURES

Oxygen is provided to treat hypoxia. In a randomized study evaluating the benefits of oxygen therapy administered routinely to patients at 8 L/min (in the absence of clinical hypoxia), oxygen therapy was associated with increased rates of recurrent MI and ventricular arrhythmias and increased infarct size.[20] For this reason, oxygen should be reserved for those patients with signs of hypoxia, including an oxygen saturation of <95% on room air. In patients with severe pulmonary edema compromising the respiratory status, endotracheal intubation and mechanical ventilation may be necessary. Morphine or nitrates should be given to control pain and associated increased sympathetic activity, but these therapies have little effect on overall clinical outcome. Nitrates are contraindicated in patients with suspected right ventricular infarction, hypotension, or recent use of 5′ phosphodiesterase inhibitors.

ANTIPLATELET THERAPY

A cascade of thrombotic processes follow rupture, fissure, or erosion of an atherosclerotic plaque. Circulating platelets become activated on contact with the lipid-filled core, collagen, and other thrombogenic contents. Activated platelets release adenosine diphosphate (ADP) and thromboxane A_2 and cause expression of the glycoprotein IIb/IIIa receptors, which bind to adhesive proteins such as von Willebrand factor and fibrinogen and amplify the thrombotic process at the

ruptured plaque. Of the various receptors involved in the process, the P2Y12 receptors activated by ADP play a key role in platelet activation, adhesion, and aggregation. A thrombus rich in platelets promotes reocclusion after successful fibrinolysis[21] and even after primary PCI.[22] Antiplatelet agents thus play a central role in the treatment of patients with STEMI. **Figure 2.3** illustrates the various receptors seen on the surface of the platelet and the interaction of the platelet receptor inhibitors with these receptors.

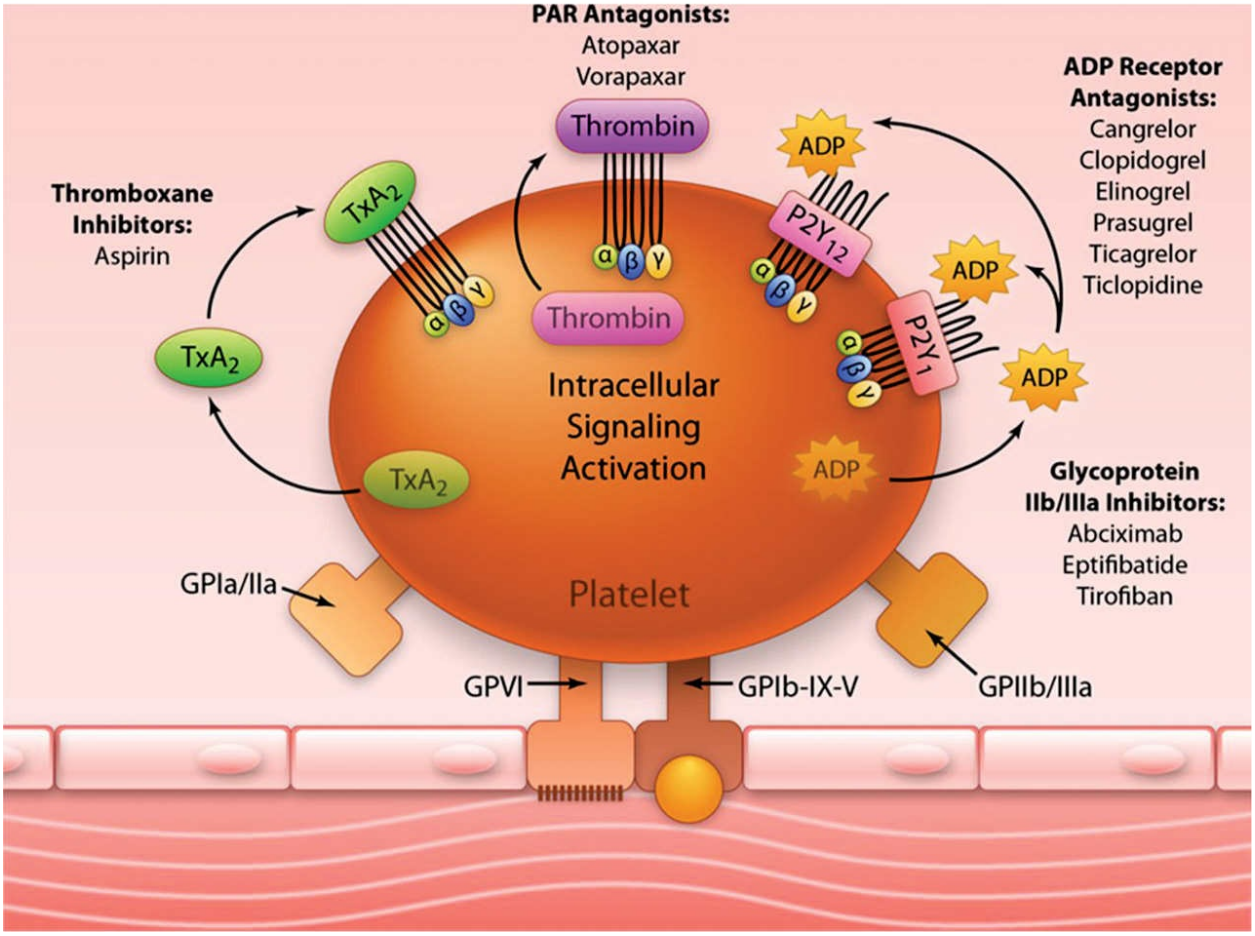

FIGURE 2.3 Schematic diagram of the interplay of platelet receptors and platelet receptor inhibitors. There are various targets of action for antiplatelet therapies. ADP, adenosine diphosphate; GP, glycoprotein; PAR, protease-activated receptor; Tx, Thromboxane. (Reproduced from Bhatt DL, Hulot J-S, Moliterno DJ, et al. Antiplatelet and anticoagulation therapy for acute coronary syndromes. *Circ Res*. 2014;114:1929-1943, with permission of the publisher. Copyright 2016, American Heart Association.)

Aspirin

Aspirin irreversibly inhibits the cyclooxygenase enzyme, which is the mediator of the initial step in the synthesis of thromboxane A_2 and arachidonic acid. Non–enteric-coated aspirin in doses of 162 to 325 mg should be given to patients to "chew" immediately on initial presentation. After primary PCI or fibrinolysis, the preferred maintenance dose is 81 mg. In the CURRENT-OASIS 7 trial,[23] there were no differences in the efficacy and safety end points between aspirin 325 mg and aspirin 81 mg in patients with ACS undergoing invasive treatment. Observational studies, however, have suggested increased bleeding in follow-up with higher doses of maintenance aspirin,[24] and hence the lower dose is generally advised.

P2Y12 Inhibitors

The P2Y12 inhibitors include oral (clopidogrel, prasugrel, and ticagrelor) and intravenous (cangrelor) agents. These medications block the binding of ADP to the P2Y12 receptor, thus inhibiting the P2Y12 receptor–mediated activation of the glycoprotein IIb/IIIa receptor and subsequent platelet aggregation. Adding P2Y12 inhibitors to aspirin offers added benefit in patients with MI, and benefits have been noted in medically treated patients as well. **Table 2.2** outlines the properties of the currently available oral P2Y12 inhibitors.

TABLE 2.2 Comparison of P2Y12 Inhibitors

P2Y12 INHIBITOR	CLOPIDOGREL	PRASUGREL	TICAGRELOR
Class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine
Prodrug	Yes	Yes	No
Receptor binding	Irreversible	Irreversible	Reversible
Onset of effect	2–4 h	30 min	30 min
Duration of effect	3–10 d	5–10 d	3–4 d
Metabolism	Hepatic	Hepatic	Hepatic
Clearance	Renal 50%, fecal 46%	Renal 68%, fecal 27%	Renal 26%, fecal 58%
Loading dose	300–600 mg	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily	90 mg twice daily
Withdrawal before surgery	5 d	7 d	5 d

Clopidogrel

Clopidogrel, a prodrug, converts to active metabolite and binds irreversibly to the P2Y12 receptor on platelets. Numerous RCTs have demonstrated that pretreatment with clopidogrel reduces cardiovascular mortality and ischemic events post-PCI.[25] Clopidogrel administered at a loading dose of 600 mg (as compared with 300 mg) is associated with a 42% relative reduction in the rates of definite stent thrombosis.[23] The AHA/ACC guidelines recommend a loading dose of 600 mg to be given as early as possible for those patients planned for

primary PCI.[1] The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) study[26] showed that the use of clopidogrel for medically treated STEMI benefited patients through a 9% reduction in the composite end point of death, recurrent MI, and stroke; further, a 7% reduction in all-cause death was noted among patients randomized to clopidogrel treatment. A 300 mg loading dose of clopidogrel is advised for medically treated patients (fibrinolytic-treated patients or patients who did not receive reperfusion therapy), followed by a maintenance dose of 75 mg daily. A loading dose is not recommended for medically treated patients over 75 years old.

Prasugrel

As with clopidogrel, prasugrel is a prodrug that, on converting to active metabolite, irreversibly blocks the P2Y12 receptor. As compared with clopidogrel, prasugrel achieves faster and more potent platelet inhibition. In a prespecified subgroup analysis of patients with STEMI enrolled in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI 38),[27] prasugrel, as compared with clopidogrel, was associated with a 32% reduction in the primary composite end point of cardiovascular death, MI, or stroke without any increase in non–coronary artery bypass graft (CABG) bleeding. Prasugrel was also associated with a 52% reduction in stent thrombosis in follow-up. It is important to note that despite the absence of an increase in bleeding events in the patients with STEMI enrolled in the TRITON-TIMI 38 trial, a higher rate of non-CABG major bleeding was noted in the overall trial. Therefore, prasugrel should be used with caution in patients who are ≥75 years of age or whose body weight ≤60 kg. Prasugrel is contraindicated in those patients with a history of prior stroke or transient ischemic attack. The recommended loading dose of prasugrel is 60 mg, followed by a maintenance dose of 10 mg daily.

Ticagrelor

Ticagrelor is a direct acting selective antagonist that binds reversibly to the P2Y12 receptor. In a subgroup analysis of patients with STEMI enrolled in the Platelet Inhibition and Patient Outcomes (PLATO) trial,[28] ticagrelor showed a 13% reduction in the combined end point of cardiovascular death, MI, or stroke with no increase in the risk of any bleeding, compared with clopidogrel.

Mortality was also significantly reduced with ticagrelor. The recommended loading dose of ticagrelor is 180 mg, and the recommended maintenance dose is 90 mg twice a day. When ticagrelor is used, the maintenance dose of aspirin is 81 mg daily. Dyspnea is one of the frequently reported side effects of ticagrelor, with about 14% of patients reporting dyspnea in the main PLATO trial; however, drug discontinuation caused by dyspnea was less than 1%.[29]

Cangrelor

Cangrelor is an intravenous, nonthienopyridine, direct P2Y12 receptor blocker that has rapid onset and rapid offset (within minutes) of its effects. Pooled analysis of the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) trials[30] showed that cangrelor decreased periprocedural outcomes of all-cause death, MI, ischemia-driven revascularization, or stent thrombosis. An increase in minor bleeding, but not major bleeding, was noted. Although these trials came under scrutiny because of their designs and timing of administration of clopidogrel, the results of the trials collectively support the use of cangrelor in those patients who are "inadequately" pretreated with clopidogrel before PCI.

Glycoprotein IIb/IIIa Receptor Inhibitors

Glycoprotein IIb/IIIa receptor inhibitors (GPI) block the binding of the glycoprotein IIb/IIIa receptors to fibrinogen, thereby inhibiting fibrinogen-platelet bridging. They are potent parenteral platelet inhibitors. Three agents are available—abciximab, eptifibatide, and tirofiban. In the setting of primary PCI, abciximab has been studied the most. Compared with unfractionated heparin (UFH) or low-molecular-weight heparin alone, GPIs are associated with a significant reduction in cardiovascular events, largely driven by a reduction in periprocedural MI.[31] An increased risk for bleeding was also observed in the trials studying GPI use. Studies supporting the use of these agents during PCI were largely performed before the widespread use of dual antiplatelet therapy, and the role of GPI in the current era is less well defined. Furthermore, data on the benefits of these agents in the setting of STEMI have shown variable results.[32, 33] Per guidelines, it is reasonable to begin treatment with GPI at the time of primary PCI in selected patients (large thrombus burden or inadequate P2Y12 receptor antagonist loading) with STEMI who are receiving UFH.

ANTICOAGULATION THERAPY

Anticoagulant therapy is used in the acute setting of STEMI in preparation for primary PCI. It is also used in medically treated patients following fibrinolysis, or in those patients who are not otherwise eligible for reperfusion therapy. The choice of anticoagulation depends on the patient's risk of bleeding and the treatment strategy.

Unfractionated Heparin or Bivalirudin in Primary Percutaneous Coronary Intervention

UFH titrated to an appropriate activated clotting time (approximately 250 seconds) and bivalirudin are the most commonly used therapies for primary PCI. UFH can be used with or without planned GPI, whereas bivalirudin is typically administered with provisional use of GPI. Many studies have compared the use of bivalirudin with UFH in patients with STEMI. These studies consistently demonstrated a lower rate of major bleeding with bivalirudin and lower net adverse cardiac events but a higher risk of stent thrombosis. A meta-analysis of randomized trials comparing these two anticoagulants in patients undergoing primary PCI demonstrated a 19% reduction in all-cause mortality, a 32% reduction in cardiac mortality, and a 38% reduction in major bleeding with bivalirudin.[34] Bivalirudin, however, was associated with a 3-fold higher rate of stent thrombosis. Prolonged bivalirudin infusion post-PCI may help to mitigate this early risk of stent thrombosis in patients with STEMI; in those with higher risk for bleeding, bivalirudin is preferred.

Unfractionated Heparin, Enoxaparin, or Fondaparinux with Fibrinolytic Therapy

Patients undergoing fibrinolysis should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the index hospitalization, or until revascularization is performed.[1] Based on age, weight, and renal function, either UFH, enoxaparin, or fondaparinux can be used. The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)- TIMI 25 study[35] demonstrated a 17% reduction in the rates of death or recurrent MI at 30 days with the use of enoxaparin as compared with UFH following fibrinolytic therapy, but a higher rate of major bleeding was observed. Despite the higher rates of major bleeding, net adverse events, including a composite of death, nonfatal recurrent MI, and nonfatal intracerebral

hemorrhage, was lower with enoxaparin. If anticoagulation therapy is extended beyond 48 hours, enoxaparin is preferred. In patients undergoing PCI post–fibrinolytic therapy, heparin is a reasonable alternative. Finally limited data have shown some benefit to fondaparinux for medically treated and fibrinolytic-treated patients with STEMI.[36] It should be noted, however, that if PCI is planned, fondaparinux should not be used as the sole anticoagulant to support the PCI because of the risk of catheter-related thrombosis.[36]

β-BLOCKERS

β-Blockers decrease the risk for ventricular arrhythmias, reduce remodeling, improve left ventricular hemodynamics, and may reduce infarct size.[37] Oral β-blockers should be initiated within the first 24 hours in all patients with STEMI, in the absence of any contraindication. Patients with initial contraindications to β-blockers should be reevaluated after 24 hours for β-blocker therapy. Intravenous β-blockers can be given at the time of presentation in patients who are hypertensive or have ongoing ischemia, but the routine use of IV β-Blockers has not been proven beneficial. β-Blockers are contraindicated in patients with signs of heart failure, evidence of a low output state, increased risk for cardiogenic shock, or other contraindications to use (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).

STATIN THERAPY

In stabilized patients, a fasting lipid panel should be obtained, and high-intensity statin therapy (atorvastatin or rosuvastatin) should be initiated or continued if there are no contraindications. Numerous studies have demonstrated that statins lower the risk of future cardiovascular events and the need for coronary revascularization in patients with ACS.[38] Statin therapy is beneficial even in patients with baseline low-density lipoprotein cholesterol levels <70 mg/dL.[39]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS OR ANGIOTENSIN RECEPTOR BLOCKERS

In a meta-analysis of four RCTs and >98,000 patients in which angiotensin-converting enzyme (ACE) inhibitors were started within 36 hours of MI, compared with placebo, ACE inhibitors significantly reduced 30-day mortality and heart failure.[40] Although data have shown a benefit of ACE inhibitors in all

patients with STEMI, the benefits appear most pronounced in patients with large areas of myocardium involved or in patients with congestive heart failure. Therefore, ACE inhibitors should be administered within the first 24 hours to all patients with STEMI with anterior location, heart failure, or ejection fraction ≤40%, unless contraindicated. ACE inhibitors can also be given to otherwise stable and low-risk patients with STEMI as well. The major contraindications of ACE inhibitors/ARBs (angiotensin receptor blockers) are hypotension, worsening renal function, or drug allergy. ARBs are indicated for patients who are ACE inhibitor–intolerant.

ALDOSTERONE ANTAGONISTS

Spironolactone and eplerenone are aldosterone antagonists. The AHA/ACC guidelines recommend initiation of an aldosterone antagonist in patients with STEMI and no contraindications in those who are already receiving an ACE inhibitor and β-blocker and who have an ejection fraction ≤0.40 and either symptomatic congestive heart failure or diabetes mellitus.[1] This recommendation is supported by the results from the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival trial,[41] which studied the effect of eplerenone in addition to standard therapy in patients with acute MI and an ejection fraction ≤40% and signs of heart failure. Eplerenone resulted in a 15% reduction in total mortality and a 17% reduction in cardiovascular mortality mainly because of a reduction in sudden cardiac death. Aldosterone antagonists should not be given to patients with renal failure (creatinine ≥ 2.5 mg/dL in men and ≥2.0 mg/dL in women) and hyperkalemia (potassium ≥5.0 mEq/L).

ADDITIONAL MANAGEMENT

ECHOCARDIOGRAPHY

An echocardiogram is a simple tool to assess post-MI ejection fraction and can provide useful information regarding a patient's overall prognosis. All patients with STEMI should receive an echocardiogram before hospital discharge and ideally within the first 24 hours of presentation. Echocardiography can also aid in identifying stunned or jeopardized myocardium, evaluate ejection fraction following reperfusion, and can help detect mechanical complications of STEMI such as free wall rupture, acute ventricular septal defect, and mitral regurgitation (see section on Mechanical Complications). Finally, in patients with ST

elevation of uncertain etiology, echocardiography performed on initial presentation can help distinguish myocardial ischemia from common nonischemic causes of chest pain such as perimyocarditis, valvular heart disease, pulmonary embolism, or aortic dissection.

CORONARY ANGIOGRAPHY

Although the majority of patients with STEMI will be treated with primary PCI, a substantial minority of patients will present to hospitals without timely access to primary PCI and will therefore be treated with fibrinolytic therapy; these patients should be considered for coronary angiography at some point during the hospital course. In general, patients with severe heart failure or cardiogenic shock should be transferred for immediate coronary angiography following fibrinolytic therapy. It is also recommended that patients who do not demonstrate evidence for restoration of myocardial blood flow following fibrinolytic therapy be considered for immediate transfer for coronary angiography.

Over the last decade, numerous studies have supported a strategy of early coronary angiography (within 3 to 24 hours) following fibrinolytic therapy even in seemingly stable patients.[42, 43] The Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) study[42] was the largest of all such trials evaluating the benefit of routine early angiography following fibrinolytic therapy, and reported a 36% reduction in clinical events, including 30-day death, recurrent MI, worsening heart failure, or shock in the group of patients assigned to early catheterization. A meta-analysis of all such trials reported a 64% reduction in the rate of death or recurrent infarction at 30 days with early coronary angiography following fibrinolytic therapy, which was particularly pronounced among the trials enrolling high-risk patients.[43] As a result of these data, routine early coronary angiography (within 3 to 24 hours of fibrinolytic therapy) should be considered for all stable patients. For the remaining patients who may not have been referred for early angiography, the AHA/ACC guidelines give a class I recommendation for coronary angiography in cases of spontaneous or inducible ischemia.[1] In the absence of these findings, routine coronary angiography before hospital discharge (to define the anatomy) may still be considered.

STRESS TESTING

For those medically treated patients who do not undergo initial coronary

angiography, noninvasive stress testing should be performed. This allows the clinician to assess for residual ischemia post-MI (both in the infarct-related artery and to assess ischemia in areas remote from the infarct which might be indicative of multivessel disease). After the first 48 to 72 hours, pharmacologic stress testing may be performed and has been shown to be safe and effective. Alternatively, a submaximal exercise stress test might also be considered to help guide recommendations for postdischarge exercise plans but should be followed with a maximal stress test within 6 weeks once the patient is fully recovered.

PERCUTANEOUS CORONARY INTERVENTION OF THE NONCULPRIT ARTERY

In patients with STEMI, approximately 50% will have multivessel disease.[44] There are three options for the treatment of multivessel disease in STEMI. These include: (1) Treatment of the culprit artery only with ischemia-guided management of nonculprit arteries; (2) performing multivessel PCI at the time of primary PCI; or (3) treatment of the culprit artery only during the primary PCI followed by staged PCI of nonculprit arteries at a later date. Several randomized trials evaluating these strategies have reported benefits from PCI of the nonculprit artery (done either at the time of primary PCI or as a staged procedure).[45, 46] The Preventive Angioplasty in Acute Myocardial Infarction trial[45] randomized 465 patients to a strategy of multivessel PCI performed at the time of the primary PCI or usual care. This study demonstrated a 65% reduction in major cardiovascular events with multivessel PCI, including a composite of death from cardiac causes, nonfatal MI, and refractory angina. Although the study was not powered to show a reduction in the individual components of the composite end points, the benefits reported in this study were consistent across all of the individual components of the composite end point. In the Third Danish Study of Optimal Acute Treatment of Patients with ST-Segment Elevation Myocardial Infarction (DANAMI 3-PRIMULTI) trial,[46] the patients were randomized to a strategy of fractional flow reserve (FFR)–guided staged PCI or conservative care. In this study of 607 patients, FFR-guided staged PCI was associated with a 44% reduction in the composite of death, nonfatal MI, or ischemia-driven revascularization. This appeared to be entirely driven by a lower rate of ischemia-driven revascularization. It is important to note that all of the trials to date examining PCI strategies for patients with STEMI and multivessel disease have been small or moderate in size and none of the trials were powered

to evaluate the individual components of the composite end point. The Complete versus Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE) trial[47] will randomize 3900 patients to a strategy of staged multivessel PCI or culprit artery only revascularization and should provide us with important information regarding staged PCI for patients with STEMI and multivessel disease. Until we have a larger data set of results, it is important to remember that the management of multivessel disease in STEMI should be individualized. Factors that might influence the decision to proceed with additional revascularization include patient-related factors (the presence of severe left ventricular dysfunction, recurrent angina, or arrhythmias might favor complete revascularization; on the other hand, older patients or patients with chronic kidney disease might benefit from a more conservative approach to care), coronary anatomy (patients with relatively discrete lesions with a low complexity might be appropriate for multivessel PCI performed at the time of primary PCI), and patient preferences.

COMPLICATIONS ARISING AFTER STEMI

BLEEDING

Bleeding after MI is associated with increased mortality, recurrent MI, longer hospital stay, and increased cost.[48] Major bleeding may occur in up to 5% to 10% of patients undergoing PCI; however, the incidence rates vary depending on patient population, antithrombotic combinations, and bleeding definition.[49] Various definitions and risk scores have been developed to assess the severity and prognosis of bleeding.[50] Access-site bleeding accounts for the majority of bleeding; however, gastrointestinal and intracerebral bleeding may occur (in particular in fibrinolytic-treated patients) and could be life-threatening. Bleeding risk increases with age and is particularly notable in patients with low body weight, female sex, femoral access, or those receiving fibrinolytic therapy or GPI. There is an exponential increase in the risk of bleeding when triple therapy is required during or after hospitalization. Every effort should be made to minimize bleeding complications. Bleeding risk can be mitigated with the use of bivalirudin anticoagulant therapy during PCI or through radial access PCI. In addition, when triple therapy is indicated, careful titration of the international normalized ratio with a narrower goal of 2.0 to 2.5 is recommended.

LEFT VENTRICULAR RUPTURE

Left ventricular rupture is a rare complication of acute MI occurring in 0.17% to 0.31% of cases.[51] Rupture develops after a large STEMI usually at the junction of infarcted and normal myocardium and is often lethal. Rupture typical occurs about 2 to 5 days following acute infarction but has been shown to occur as early as day 1 post-MI. Risk factors for rupture include delayed time to reperfusion, advanced age, and female sex. Rupture can occur at the free wall, resulting in immediate death, or present subacutely with signs of shock because of contained rupture and cardiac tamponade. Frank free wall rupture is often immediately fatal, whereas survival in a contained rupture will depend on the timing to the recognition of the rupture, hemodynamic stabilization and, most importantly, surgical repair. A telltale sign of a contained rupture is the sudden onset of hypotension or shock with clear lungs and elevated jugular venous pressure. Another form of left ventricular wall rupture includes ventricular septal rupture. Anterior infarctions are associated with rupture of the septum in an apical location, whereas ruptures associated with inferior infarctions usual involve the basal septum. In these cases, patients typically present with hemodynamic instability, heart failure, and development of a loud, holosystolic murmur. Echocardiography is instrumental in the diagnosis of any of these forms of rupture. Definitive management for all forms of rupture is surgical repair; however, the feasibility of surgical repair and timing of surgery are controversial and vary with clinical presentation.

ACUTE MITRAL REGURGITATION

Significant mitral regurgitation is noted in approximately 3% of cases of acute MI.[52] The etiology of acute mitral regurgitation includes ischemic papillary muscle displacement/rupture, left ventricular dilatation, or true aneurysm. Papillary muscle rupture, partial or complete, is a life-threatening complication. This usually occurs 2 to 7 days after the infarct. Clinical manifestation includes hypotension, pulmonary edema, and a mid- to late systolic murmur in the mitral area. Diagnosis is confirmed by echocardiography (with color flow Doppler). The management includes prompt diagnosis, afterload reduction with nitrates, diuretics, intra-aortic balloon pump, and emergent surgery. Nevertheless, mortality remains high.

LEFT VENTRICULAR ANEURYSM

True aneurysms consist of a discrete, dyskinetic area of thin left ventricular wall with a broad neck. Rupture of these aneurysms is uncommon. This should be differentiated from a *pseudoaneurysm,* which is a contained ventricular rupture (see above). Aneurysms are most often noted in patients who are not treated with reperfusion therapy or who have lack of evidence of tissue level reperfusion following fibrinolytic therapy or PCI (persistent ST-segment elevation noted on the ECG in the immediate hours and days after treatment). Diagnosis is made by noninvasive imaging modalities. Possible sequelae of left ventricular aneurysm include congestive heart failure, ventricular arrhythmias, and left ventricular thrombus. Because of the risk for mural thrombosis and systemic embolization, oral anticoagulation therapy should be considered in patients with aneurysms, especially in the first 3 months post-MI. Surgical aneurysmectomy is reserved for select cases of patients who are severely symptomatic.

LEFT VENTRICULAR THROMBUS

Although the incidence of left ventricular thrombus has decreased with the use of primary PCI and the use of potent antithrombotic therapies, it is not an uncommon complication after STEMI, occurring in 4% to 8% of cases and usually associated with anterior wall infarctions.[53] Systemic embolization is always a potential risk. High-risk features for embolization on echocardiography include increased mobility, protrusion into the ventricular chamber, and contiguous zones of akinesis and hyperkinesis. Cardiac MRI can also be helpful to aid in diagnosis. Treatment requires anticoagulation with warfarin for at least 3 to 6 months.

ATRIOVENTRICULAR BLOCK

Ischemic injury can produce a variety of conduction blocks. Complete atrioventricular block is more common in inferior than in anterior infarct. It is usually transient and improves with revascularization. Some patients may require temporary pacing, but permanent complete heart block associated with an inferior infarction is generally rare.

VENTRICULAR ARRHYTHMIAS

Ventricular tachycardia and ventricular fibrillation are the most dreaded complications. Nonsustained ventricular tachycardia in the first 24 hours postinfarct is generally benign and not associated with a worse prognosis.[54]

Correction of electrolyte abnormalities, including hypokalemia, hypomagnesemia, and institution of β-blockers serve as prophylaxis for occurrence of malignant arrhythmias. Occasionally, postinfarction arrhythmias can indicate reocclusion and may necessitate additional coronary angiography even in the absence of other signs or symptoms of reocclusion. Treatment of unstable ventricular tachycardia/ventricular fibrillation consists of electrical defibrillation, administration of antiarrhythmic agents such as amiodarone or lidocaine, and repeat coronary angiography if clinically warranted. Generally, the presence of sustained ventricular arrhythmias beyond 48 to 72 hours in the absence of evidence of reocclusion is associated with a poor prognosis, and consideration should be given to the placement of a cardiac defibrillator.

CARDIOGENIC SHOCK

Cardiogenic shock is the most common cause of death in patients with STEMI, occurring in 5% to 15% of all acute infarctions.[55] Cardiogenic shock can either be a manifestation of severe pump failure in the setting of a large infarct or a sequela of mechanical complications of MI. It is characterized by a constellation of findings reflecting systemic hypotension, low cardiac output, and evidence of vital organ hypoperfusion (eg clouded sensorium, cool extremities, oliguria, acidosis). The formal diagnostic criteria for cardiogenic shock will vary depending on the dataset examined, but, in general, cardiogenic shock requires refractory (not transient) hypotension in the absence of any other underlying causes with evidence of a low output state. **Table 2.3** outlines the diagnostic criteria for shock taken from the Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial.[56] The diagnosis of shock can be confirmed through the use of right heart catheterization measurements; however, the clinical presentation and use of Doppler and 2D echocardiography provide similar information to right heart catheterization, and therefore right heart catheterization is not always indicated. Early revascularization with PCI or CABG is the recommended reperfusion strategy for patients with STEMI and shock, irrespective of the time delay.[56] For patients who are unsuitable candidates for PCI or CABG, fibrinolysis can be given if there are no contraindications. Inotropes and vasopressor agents can be used to maintain hemodynamic stability and organ perfusion. Norepinephrine, dopamine, or dobutamine are used for the initial pharmacologic management. However, in patients with elevated systemic vascular resistance, vasopressor agents and high-

dose inotropes may be counterproductive, and these patients should be evaluated for mechanical circulatory support devices.

TABLE 2.3 Criteria for Cardiogenic Shock

CLINICAL CRITERIA
Persistent hypotension (a systolic blood pressure of <90 mm Hg for at least 30 min or the need for supportive measures to maintain a systolic blood pressure of ≥90 mm Hg)
End-organ hypoperfusion Altered mental status Cool extremities Urine output of <30 mL/h Elevated serum lactate levels
Heart rate of ≥60 beats/min
HEMODYNAMIC CRITERIA
Cardiac index (<1.8 L/min/m^2 without support or <2.0 to 2.2 L/min/m^2 with support)
Adequate or elevated filling pressure (left ventricular end-diastolic pressure >18 mm Hg or right ventricular end-diastolic pressure >10 to 15 mm Hg or pulmonary capillary wedge pressure of ≥15 mm Hg)

Intra-aortic balloon pumps (IABP) can be used in patients with cardiogenic shock who do not stabilize with pharmacologic therapies. Although observational data support the use of IABP in patients with cardiogenic shock demonstrating improved outcomes,[57] the Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial[58] failed to show any benefit from the use of IABP in patients with acute MI complicated by cardiogenic shock. The study examined patients presenting with acute MI and shock who were planned for early revascularization. The primary end point, 30-day all-cause mortality, was not significantly reduced with the use of IABP in shock. The study, however, did not address the optimal management of patients who develop shock later in the hospital course following revascularization. Fewer data are available to guide the use of IABP in cases of shock that develop after reperfusion, and most physicians would try to support these patients with mechanical circulatory support devices as a bridge to recovery, or as a bridge to additional revascularization and/or surgical repair of complications. Other temporary mechanical circulatory support devices such as Impella 2.5 or Impella CP, Tandem Heart, and percutaneous extracorporeal membrane oxygenator, may

be helpful in severe cases of shock, but randomized data are not available. There are advantages and limitations to each of the support devices, and the decision to initiate hemodynamic support should be individualized.

DISCHARGE PLANNING

TIMING OF DISCHARGE

The timing of discharge is highly variable and often influenced by the clinical and Socio-demographic variables of the patient. There are no recommendations as to what constitutes appropriate duration of hospitalization for patients with STEMI. In low-risk patients with single vessel disease, who undergo successful primary PCI and are free of early sustained ventricular tachyarrhythmias, hypotension, heart failure, or any bleeding episodes, discharge home at 48 hours is generally reasonable.

PATIENT EDUCATION AND COUNSELING

One of the critical aspects of discharge planning is education of patients and their families. The plan of care for the patients should include the following domains of care:

1. Review of medications, including the importance of adherence
2. Follow-up appointments and testing
3. Dietary counseling
4. Physical and sexual activities counseling
5. Smoking cessation (if applicable)
6. Secondary prevention
7. Cardiac rehabilitation

CARDIAC REHABILITATION

Cardiac rehab is a medically supervised exercise program that has been shown to improve the cardiovascular health of patients with acute MI. The goals of exercise-based cardiac rehabilitation after STEMI are to increase functional capacity, improve symptoms, decrease potential disability, improve the quality of life, help the patient to modify coronary risk factors and thereby reduce morbidity and mortality.[1, 59] Core components include a baseline and follow-up patient assessment, exercise counseling, nutritional counseling, smoking

cessation counseling, psychosocial counseling, and management of blood pressure, lipids, and diabetes mellitus with pharmacologic treatment, as appropriate.[59] In spite of the proven benefits of cardiac rehabilitation, it is underutilized because of several hospital-level factors and insurance issues.[60] Efforts must be concentrated on ensuring timely access to cardiac rehabilitation in patients with STEMI.

FUTURE DIRECTIONS

There remains a strong need to improve public awareness and educate the general population about symptoms of heart attacks and the importance of timely care, to improve the time from symptom onset to presentation for medical evaluation. Multicultural and multilingual efforts should be made, especially in those for whom English is not the first language. Research into newer therapies should continue. Research into treatments to minimize or reverse ventricular remodeling, and novel therapies involving stem cell or bone marrow precursor cells, stent technology, antiplatelets, and anticoagulants are ongoing.

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Patient and Family Information for: ST-ELEVATION MYOCARDIAL INFARCTION

WHAT IS A STEMI?

ST-elevation myocardial infarction (STEMI) or “heart attack” is a life-threatening emergency condition that occurs when one of the arteries supplying blood to the heart muscle suddenly becomes completely blocked. This is more commonly referred to as a heart attack and is one of the leading causes of death in the United States. A STEMI heart attack is considered an emergency because within a very short period of time, a part of the heart muscle can become permanently damaged because of the absence of blood flow from the blocked artery; therefore, urgent medical attention and treatment is required. Studies have shown that the major delay in treatment of a patient with a STEMI is often related to the patient’s ability to recognize the symptoms and call for help. This is why all patients with chest pain or discomfort lasting more than 10 minutes are encouraged to call 911 for immediate evaluation.

WHAT CAUSES A STEMI?

Patients at risk for a heart attack often have mild or intermediate blockages caused by plaque buildup in the arteries of the heart (coronary arteries). Normally, these blockages do not cause any symptoms because the blood flow to the heart muscle is not usually compromised. However, if these plaques rupture (or crack), the blood in the artery is then exposed to the sticky material inside of the plaque, and this will lead to the formation of a large blood clot that will

completely block the flow of blood down the artery. Some conditions may increase a patient's risk of developing a heart attack. These are referred to as risk factors. It is important to understand that the presence of risk factors increases a patient's chance of developing a heart attack. However, even if a patient has a lot of risk factors, it does not mean that he or she will definitely have a heart attack. On the contrary, some patients without any risk factors may still have a heart attack. The major risk factors that have been identified to cause coronary artery disease and heart attacks include a family history of heart attacks or coronary artery disease, a history of diabetes, high blood pressure, or high cholesterol levels, smoking cigarettes or other types of tobacco products, being overweight, not being physically active, and male gender. Some of these conditions can be changed or controlled by living a healthier lifestyle and/or taking medications to control the condition.

HOW DO DOCTORS DIAGNOSE A STEMI?

The presentation of heart attacks can be variable, but most commonly patients experience profound chest discomfort or chest pain. Patients may describe this chest pain as a chest "squeezing," "tightness," or "heaviness," and sometimes a patient may have shortness of breath, cold sweats, and nausea. The chest pain is typically located in the center of the chest and often described as radiating to the left shoulder, arm, or jaw. The patient may instead have symptoms of upper belly pain, shoulder or back pain, or shortness of breath in the absence of chest pain. Older patients, female patients, and patients with diabetes are more likely to have these less typical symptoms. When an individual presents with these complaints, medical personnel use a chest pain protocol to allow a rapid evaluation in order to quickly confirm the patient's diagnosis so as to allow for immediate treatment.

The mainstay of diagnosis of a STEMI is the electrocardiogram (ECG). During an ECG, electrodes are attached to the outside of the chest wall with a sticky material, and these electrodes measure the electrical conduction through the heart. If the patient is having a "STEMI" the ECG will have a characteristic appearance, known as ST segment elevation. This characteristic appearance helps to distinguish a STEMI heart attack from other heart conditions or other non–heart-related conditions. It is essential to perform and interpret an ECG early after a patient presents for evaluation. Doctors may also order blood tests

called cardiac enzymes (cardiac troponin or creatinine kinase CPK-MB). These enzymes are normally contained within the heart cells; When the heart cells die during a heart attack, the heart cells are destroyed and the enzymes are released into the bloodstream. If the health care team strongly suspects, on the basis of symptoms and the abnormalities seen on ECG, that a patient is having a heart attack, then treatment will be given even before the results of the blood tests are reported.

There are two options doctors may use to reopen blocked arteries. The first treatment is the administration of fibrinolytic medications. These medications dissolve the blood clot in the artery of the heart. The second treatment is a procedure called an angioplasty or stent, commonly referred to as primary percutaneous coronary intervention (PCI). During primary PCI, a balloon and/or stents are used by a cardiologist to physically open up the blocked artery. Extensive research involving multiple studies have shown that primary PCI is the best treatment to restore blood flow for a patient with STEMI. However, not all hospitals have the ability to perform emergency primary PCI. If a patient lives in a region in which there are no nearby hospitals that can provide emergency angioplasty or stent, the doctor may first treat the patient with fibrinolytic medications and later transfer him or her to a hospital for possible angioplasty or stent. Regardless of the type of treatment a patient receives, the goal is to rapidly provide the therapy to open the blocked arteries: Fibrinolytic therapy should be administered within 30 minutes; Primary PCI should be performed within 90 minutes of presentation.

WHAT OTHER TREATMENTS DO PATIENTS WITH STEMI RECEIVE?

Once a patient is diagnosed with a STEMI, doctors will begin therapy with medications that thin the blood and decrease its stickiness. Blood thinners are referred to as anticoagulants. Agents that decrease the stickiness of the blood are referred to as antiplatelet agents. All patients with a STEMI will also be placed on a cardiac monitor, and their vitals signs (blood pressure, heart rate, and breathing rates) will be closely monitored. The next step for treating patients with STEMI is to open the blocked artery. As previously mentioned, if a patient is admitted to a hospital that offers emergency primary PCI, the blocked artery will be opened by inflating a balloon in the artery and placing a stent. If a patient

is admitted to a hospital that does not have the capability of performing emergency stenting, the patient will be transferred to another hospital that can perform primary PCI. If there are no nearby hospitals that have the capability of performing primary PCI, the patient might first receive fibrinolytic therapy and later be transferred to another hospital as needed. On most occasions, when an angioplasty is performed a stent is placed in the coronary artery to prevent reocclusion. The two types of stents that are used are bare-metal stents and drug-eluting stents. Drug-eluting or "coated" stents are less likely to narrow again compared with bare-metal stents, but they require a more prolonged duration of treatment with antiplatelet medications. In some cases, the best way to treat the blocked arteries is open-heart surgery. In addition to antiplatelets therapy, other medications may be given. These include angiotensin-converting enzyme inhibitors and beta-blockers. These medications decrease the work required by the heart, and they help the heart to recover and get stronger after a heart attack. Cholesterol lowering medications, called statins, are an important medication used to treat patients with a heart attack. They help to prevent the occurrence of another heart attack.

PREVENTION AND FOLLOW-UP

There are two types of heart attack prevention. Primary prevention is aimed at decreasing a patient's chance of having a "first" heart attack. The goal of secondary prevention is to prevent the occurrence of another heart attack (a "second heart attack"). In patients with STEMI, the focus is on secondary prevention so that the patient will be less likely to suffer from another heart attack. This requires rigorous efforts and attention to living a good lifestyle and taking medications on a regular basis. It is important that patients eat a heart-healthy diet. Heart-healthy diets are diets that are rich in fruits and vegetables and whole grains, and low in saturated fats, trans fats, sweetened drinks, and processed foods. If possible, patients should begin a regular exercise plan (with a doctor's guidance). Although individual recommendations may vary, the goal is to do at least 30 minutes of moderate-intensity exercise most days of the week. Weight loss, avoidance of excess alcohol, and cessation of smoking are also important components of a healthy lifestyle. It is critical that patients also adhere to taking all of their prescribed medications on a regular basis and discuss any concerns about their medications with their doctor before stopping a prescribed

medication. Patients should closely follow up with their cardiologist for regular monitoring to ensure compliance with lifestyle measures and medications so as to prevent the complications from the heart attack and lower the risk of recurrences. From a public health perspective, CPR could save the lives of patients who suffer heart attack and sudden death, and everyone should ideally be certified in CPR.

3

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Non–ST-Elevation Acute Coronary Syndromes

NON–ST-ELEVATION MYOCARDIAL INFARCTION: DEFINITION AND CLINICAL SPECTRUM

The term non–ST-elevation myocardial infarction (NSTEMI) refers to acute coronary syndrome (ACS) in which myocardial ischemia results in tissue necrosis in the absence of ST-segment elevation on the electrocardiogram (ECG). By definition, NSTEMI is accompanied by elevated levels of cardiac biomarkers, signifying loss of myocardial tissue and differentiating NSTEMI from unstable angina. The clinical spectrum of NSTEMI ranges from mild ischemic insults with preserved left ventricular function to life-threatening ischemic events associated with global myocardial ischemia and hemodynamic compromise as well as cardiac arrest. Detailed practice guidelines have been published by the European Society of Cardiology in 2016,[1] the American Heart Association (AHA), and American Society of Cardiology (ACC) in 2014.[2] A comparison between the two documents has also been published.[3]

PATHOPHYSIOLOGY

Myocardial infarction typically results from formation of a coronary thrombus at the site of an existing atherosclerotic plaque.[4] The degree of coronary stenosis at the culprit site before the acute ischemic event is frequently mild or moderate. Coronary thrombosis is caused by disruption of the fibrous cap that forms a barrier between the blood and procoagulant constituents within the plaque. Postmortem studies as well as intravascular imaging studies indicate that most events are triggered by rupture of a thin-cap fibrous atheroma overlying a lipid-rich necrotic core. Superficial plaque erosions are responsible for most of the remainder of cases. In contrast to ST-elevation myocardial infarction (STEMI), the culprit coronary lesion in most NSTEMI cases is not totally occlusive. Embolization of particulate matter from the thrombus within the epicardial coronary artery to the distal microvasculature, as well as intermittent coronary occlusion, leads to myocardial necrosis in these cases. Rarely, NSTEMI is caused by total occlusion of a major coronary artery without associated elevation of the ST-segment in the ECG.

EPIDEMIOLOGY

Currently, NSTEMI outnumbers STEMI by a ratio of 3:1, with an estimated annual US incidence of around 500,000.[5] Patients with NSTEMI have more comorbidities than those with STEMI. In-hospital mortality is similar for patients with NSTEMI and STEMI (9.5% vs 9.7%); however, 1-year postdischarge mortality is higher in patients with NSTEMI (18.7% vs 11.4%).[6, 7]

DIAGNOSIS

HISTORY

Precordial chest pain is a frequent presenting symptom in patients with NSTEMI. Typical angina involves a sensation of retrosternal heaviness or pressure radiating to the left arm. Chest pain may be atypical, may radiate to any anatomic location between the umbilicus and the mandible, and in some cases may be absent. Alternatively, patients may complain of angina equivalents such as dyspnea, palpitations, and generalized weakness. Atypical presentation is more common in females, diabetics, patients with renal failure, and the elderly. Presence of risk factors for atherosclerosis such as diabetes mellitus,

hypertension, hyperlipidemia, renal failure, a family history of coronary disease, a history of smoking, advanced age, and a previous diagnosis of coronary or peripheral vascular disease are common in patients with NSTEMI. It is important to document current medications the patient is receiving (which may interact with medications to be administered) and to inquire about use of illicit drugs such as cocaine, which may trigger myocardial ischemia. In a patient with ACS, it is crucial to rule out a history of bleeding before initiating antithrombotic and anticoagulant therapy. Allergy to intravascular contrast media should be ruled out and renal function assessed before referring the patient for cardiac catheterization.

PHYSICAL EXAMINATION

Examination may be normal in patients with NSTEMI. It is important to detect signs of hemodynamic compromise if present (reduced blood pressure, accelerated heart rate, signs of peripheral hypoperfusion, jugular venous distention, pulmonary congestion) because these patients may benefit from intensive care and an early invasive strategy. A hypertensive crisis may trigger myocardial ischemia and should be diagnosed and treated rapidly. A systolic murmur may signify a mechanical complication such as acute ischemic mitral regurgitation. A detailed physical examination is crucial for detecting findings, which may point to an alternative diagnosis such as pericarditis (friction rub and pulsus paradoxus), aortic stenosis (systolic murmur), aortic dissection (differences in blood pressure between limbs), musculoskeletal disorders (sensitivity to palpation of the chest wall), and so on. Irregular heart rhythm may also be present in NSTEMI with premature beats and atrial fibrillation. Rapid rate may play a role in the pathophysiology of NSTEMI and should be documented and referred to in the therapeutic strategy.

ELECTROCARDIOGRAM

The ECG may show a variety of anomalies such as ST-segment depression, transient ST-segment elevation, T wave inversion, as well as tachyarrhythmias and bradyarrhythmias. In more than 30% of patients, the ECG is normal. It is important not to misdiagnose a true posterior-wall STEMI (ST-depression and tall R waves in leads V1–V3) and new-onset left bundle branch block (LBBB), which warrant emergency coronary reperfusion.

CARDIAC BIOMARKERS

Measurement of cardiac troponin (cTn) serum levels using regular assays or high-sensitivity assays (hs-cTn) is an effective quantitative method for identifying myocardial necrosis in patients suspected of having NSTEMI. Many hospitals still use regular troponin assays. cTn is a more sensitive and specific marker for myocardial injury than creatine kinase and its muscle–brain isoenzyme. Whereas elevations up to 3-fold the upper reference limit are a nonspecific finding with limited positive predictive value for diagnosis of acute myocardial infarction (MI), elevations beyond 5-fold the upper reference limit have high (>90%) positive predictive value. High-sensitivity troponin assays detect myocardial necrosis within 1 hour of onset of symptoms and typically remain elevated for several days. A variety of conditions other than MI may be accompanied by troponin elevations including critical illness (e.g. burns), nonischemic cardiac injury (e.g. myocarditis, infiltrative disease), aortic dissection, pulmonary embolism, and renal failure. Renal failure can modify the pathognomonic levels of troponin, but dynamic changes in troponin are indicative of myocardial necrosis.

ANCILLARY TESTING

A variety of functional and anatomic imaging modalities may be used to noninvasively detect and quantify myocardial ischemia, to assess prognosis, and to identify high-risk patients. Chest X-ray may demonstrate noncardiac causes of chest discomfort such as pneumonia, pneumothorax, and rib fracture and should be performed in all patients in whom the diagnosis of an ACS is deemed unlikely. Echocardiography assesses left ventricular ejection fraction, reveals regional wall motion abnormalities suggestive of acute or chronic coronary disease, and is crucial for assessment of patients who are hemodynamically unstable. Echocardiography may assist in diagnosing alternative causes of chest pain such as aortic stenosis, pericarditis (pericardial effusion), pulmonary embolism (pulmonary hypertension and right ventricular dilatation), Takotsubo cardiomyopathy, and aortic dissection. Stress echocardiography (during exercise or administration of dipyridamole or dobutamine) may diagnose and quantify degree of myocardial ischemia and offers superior prognostic information compared with a regular exercise test. Contrast echocardiography may be used to assess myocardial perfusion. Cardiac magnetic resonance may be used to assess myocardial perfusion and wall motion and to diagnose myocardial scar

formation (late gadolinium hyperenhancement). Nuclear myocardial perfusion imaging detects myocardial ischemia and may be used to assess myocardial viability and ejection fraction. Multidetector computed tomography enables noninvasive detection of coronary disease; however, efficacy may be limited in patients with severe coronary calcification, prior stent implantation, and irregular and fast heart rhythms.

DIFFERENTIAL DIAGNOSIS

A majority of patients presenting to the emergency department with chest pain have a noncardiac etiology for their complaints. The differential diagnosis of NSTEMI in individuals presenting with chest pain includes STEMI (diagnostic ECG); unstable angina (lack of biomarker elevation); thoracic emergencies such as acute aortic syndromes (e.g. aortic dissection) and pulmonary embolism; infectious or inflammatory conditions such as pneumonia, myocarditis, and pericarditis; gastrointestinal disorders; and musculoskeletal disorders of the chest wall. A detailed history and physical examination are crucial for diagnosing these conditions and should be complemented by judicious use of imaging studies.

DIAGNOSTIC ALGORITHM

In patients presenting with chest pain who are suspected of having an ACS, a key priority is to identify those with indications for emergency coronary reperfusion (eg, STEMI, new-onset LBBB, ongoing ischemia, hemodynamic instability) (**Figure 3.1**). Life-threatening conditions that can mimic NSTEMI such as acute aortic syndromes and pulmonary embolism should be rapidly excluded on the basis of the history, examination, and appropriate imaging studies (e.g. “triple rule out” CT angiography). The remainder should undergo a diagnostic protocol, which is designed to rapidly rule-in or rule-out myocardial ischemia as the underlying cause of their symptoms. cTn assays, preferably hs-cTn assays, are crucial for rapid triage of these patients because serum levels increase rapidly in patients with myocardial damage. A dynamic rise in serum cTn levels above the 99th percentile in patients with a compatible clinical presentation is diagnostic of MI. A typical 0 h/3 h algorithm in patients suspected to have sustained an NSTEMI is based on testing of hs-cTn serum levels on admission to the emergency department. Levels below the upper limit of normal in patients in whom chest pain began more than 6 hours previously

effectively rules out the diagnosis. Repeat testing of hs-cTn levels is performed 3 hours later in those who developed chest pain less than 6 hours before presentation, when initial levels were not elevated. Patients in whom hs-cTn levels are not elevated may be discharged or referred for further noninvasive evaluation. In those with elevated hs-cTn levels on admission, a dynamic rise in levels is required to confirm the diagnosis of NSTEMI. Patients with a diagnosis of NSTEMI are referred for invasive management unless contraindicated. An alternative 0 h/1 h algorithm may be used; however, it is less well validated.

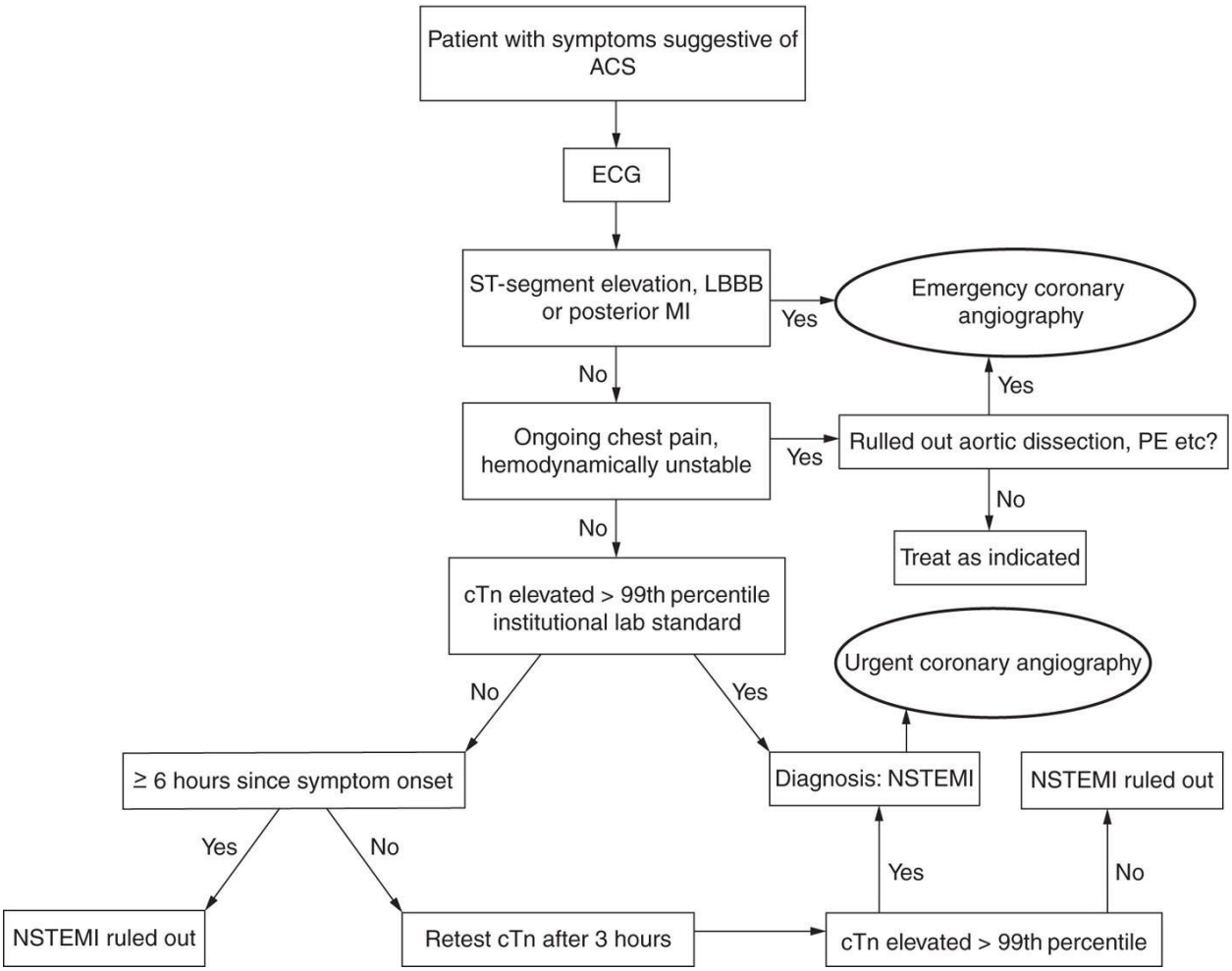

FIGURE 3.1 Diagnostic algorithm in patients with suspected NSTEMI. ACS, acute coronary syndrome; cTn, cardiac troponin; ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; PE, pulmonary embolism.

RISK STRATIFICATION

Early triage of patients with NSTEMI is crucial in order to identify individuals who are at high risk for development of further myocardial damage. Ongoing chest pain, dynamic ST-changes on the ECG, and hemodynamic instability suggest need for emergency revascularization. Assessment of the risk for life-threatening cardiac arrhythmias is crucial for selecting the appropriate hospital environment and degree of monitoring required for these patients. Predictors of serious arrhythmias include hemodynamic instability, documented major arrhythmias, ejection fraction ≤40%, untreated significant coronary lesions on angiography, and complications related to coronary intervention. Patients with

NSTEMI and risk factors for serious arrhythmias should be kept in cardiac care unit.

Several scores provide quantitative assessment of ischemic risk and prognostication up to 3 years. The thrombolysis in myocardial infarction (TIMI) risk score (online calculator: http://www.timi.org/index.php?page=calculators) uses seven metrics to assess prognosis. The variables included in the risk score are: age ≥65 years, presence of ≥3 risk factors for coronary disease, known coronary disease, recent aspirin use (within the past week), severe angina (≥2 episodes within the past 24 hours), ST deviation ≥0.5 mm on the ECG, and elevated cardiac biomarkers. The Global Registry of Acute Coronary Events (GRACE) 2.0 risk score (online calculator: http://www.gracescore.org/WebSite/default.aspx?ReturnUrl=%2f) has been shown to provide superior prognostication compared with the TIMI risk score. Variables included in the GRACE 2.0 risk score are: age, blood pressure, heart rate, renal function, cardiac arrest, Killip class, elevated cardiac biomarkers, and ST-segment deviation.

Assessment of risk for bleeding is crucial before administration of anticoagulant and antiplatelet drugs. Current risk scores are relevant mainly for predicting bleeding in patients with NSTEMI undergoing coronary angiography; however, their relevance to patients selected for noninvasive treatment or those receiving oral anticoagulants is unclear. The ***C***an ***R***apid risk stratification of ***U***nstable angina patients ***S***uppress ***AD***verse outcomes with ***E***arly implementation of the ACC/AHA guidelines (CRUSADE) bleeding risk score (online calculator: http://www.crusadebleedingscore.org) uses the following variables: female sex, diabetes, peripheral vascular or cerebrovascular disease, heart rate, blood pressure, heart failure, hematocrit, and creatinine clearance. The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) bleeding risk score takes into account the following variables: female sex, advanced age, elevated serum creatinine, white blood cell count, anemia, and presentation as NSTEMI or STEMI. These scores may require updating in view of recent changes in clinical practice, which include increasing use of transradial vascular access, diminishing popularity of glycoprotein IIb/IIIa inhibitors, substitution of clopidogrel for more potent oral antiplatelet drugs, and shift in anticoagulant regimens from heparin to bivalirudin.

MEDICAL TREATMENT

ANTI-ISCHEMIC AGENTS

The objective of medical therapy is to correct the imbalance between myocardial supply and demand and to reduce thrombus-related events (**Figure 3.2**). Some of the research relating to pharmacologic treatment of NSTEMI dates back to the era before the advent of current antiplatelet and anticoagulant medications and preceded modern invasive treatment strategies.

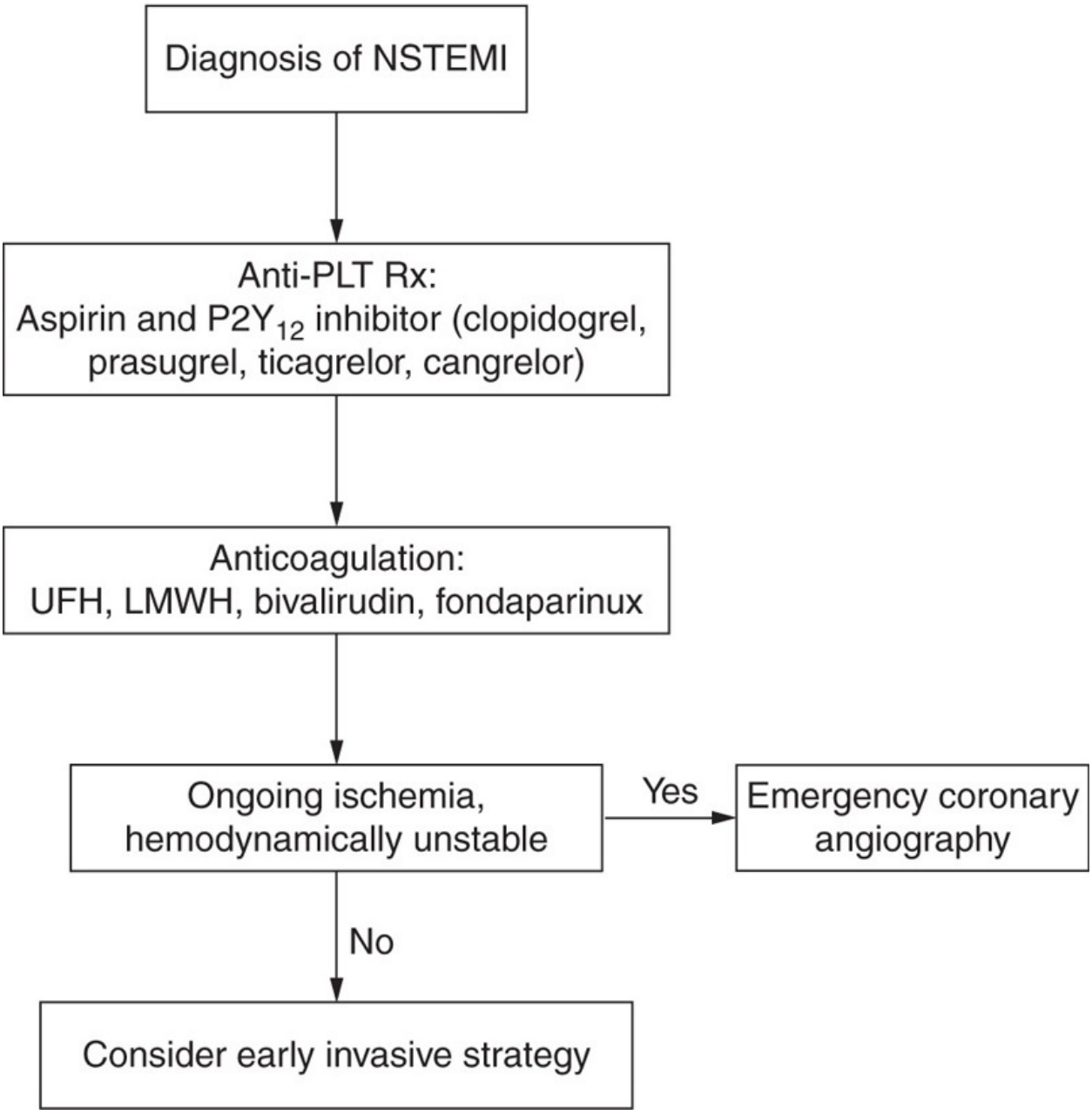

FIGURE 3.2 Treatment algorithm in patients with diagnosis of NSTEMI. Anti-PLT Rx, antiplatelet therapy; LMWH, low-molecular-weight heparin; NSTEMI, non–ST-elevation myocardial infarction; UFH,

unfractionated heparin.

General Measures

Bed rest minimizes physical activity, reduces myocardial oxygen demand, and enables effective patient monitoring. Oxygen should not be administered universally, but only to hypoxic patients with arterial oxygen saturation <90%. Opiates reduce chest pain and anxiety and therefore myocardial oxygen demand; however, they may reduce intestinal absorption of oral antiplatelet medications and may lower blood pressure in hypotensive patients—especially in those given concomitant nitrates. Nitrates may lower blood pressure in hypertensive patients and facilitate regression of ST-segment depression on the ECG. Their role is symptom relief with no proven impact on patient outcome. Nitrates should be given cautiously to hemodynamically unstable patients and are contraindicated in patients who have received phosphodiesterase type 5 inhibitors (sildenafil, tadalafil) within the past 24 to 48 hours.

β-Adrenergic-Blocking Agents

β-Blockers reduce myocardial oxygen demand (reduced contractility, heart rate, and blood pressure). Early studies found a mortality benefit for administration of β-blockers; however, they should be given cautiously to hypotensive and bradycardic patients because they may increase the incidence of cardiogenic shock. β-Blockers may worsen coronary spasm in patients who have used cocaine.

ANTIPLATELET THERAPY

Combined antiplatelet therapy with aspirin and an inhibitor of the $P2Y_{12}$ receptor decreases the occurrence of recurrent ischemic event and improves clinical outcomes in patients with NSTEMI compared with aspirin monotherapy. Dual therapy also increases the risk of bleeding, especially if ticagrelor or prasugrel is substituted for clopidogrel. This bleeding risk is especially relevant to the estimated 10% of NSTEMI patients who are referred for coronary artery bypass surgery (CABG). Prasugrel administration should be withheld until coronary angiography has been performed and need for CABG has been excluded.

Aspirin

Aspirin suppresses platelet thromboxane A_2 production by irreversibly inactivating cyclooxygenase-1. Pivotal trials of aspirin in ACS, performed before the recognition of the importance of an early invasive strategy, found a reduction in occurrence of MI and death. High-dose (300 to 325 mg/d) and low-dose (75 to 100 mg/d) aspirin are equally effective and should be given following a loading dose of 150 to 300 mg of a nonenteric-coated formulation.

$P2Y_{12}$ Receptor Blockers

Clopidogrel

Clopidogrel irreversibly inactivates platelet $P2Y_{12}$ receptors and inhibits adenosine diphosphate (ADP)-induced platelet aggregation. Clopidogrel is a pro-drug that undergoes hepatic metabolism via the cytochrome p450 to release an active metabolite. In patients with ACS, combined treatment of aspirin and clopidogrel decreases ischemic events. Some patients have inadequate response to clopidogrel and may be at risk for increased ischemic events and stent thrombosis. Individual responsiveness to clopidogrel may be related to gene polymorphisms; however, the role of screening for platelet responsiveness to clopidogrel in clinical practice is unclear. The loading dose of clopidogrel is 300 to 600 mg and maintenance dose is 75 mg/d. In the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events−Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS7) study, doubling the maintenance dose during the first week reduced the risk of ischemic events.[8]

Prasugrel

Prasugrel irreversibly inactivates platelet $P2Y_{12}$ receptors and inhibits ADP-induced platelet aggregation with faster onset and greater inhibitory effect than clopidogrel. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI 38) study, prasugrel reduced the risk of MI and stent thrombosis compared with clopidogrel but increased the risk of bleeding.[9] Prasugrel is contraindicated in patients with known cerebrovascular disease, elderly patients (>75 years old) and those with low body weight (<60 kg). Loading dose is 60 mg and the maintenance dose is 10 mg/d.

Ticagrelor

Ticagrelor reversibly inhibits platelet $P2Y_{12}$ receptors with onset of action and efficacy similar to prasugrel. The half-life of 6 to 12 hours mandates that ticagrelor is taken twice daily. In the Platelet Inhibition and Patient Outcomes (PLATO) study, ticagrelor decreased death, MI, and stroke as well as stent thrombosis compared with clopidogrel but increased the risk of nonfatal bleeding.[10] Side effects include dyspnea. Loading dose is 180 mg, and maintenance does is 90 mg twice daily.

Cangrelor

Cangrelor is administered intravenously and induces short-term (1 to 2 hours) inhibition of platelet $P2Y_{12}$ receptors. Cangrelor reduces thrombotic events and stent thrombosis compared with clopidogrel but increases the risk of bleeding.[11]

Glycoprotein IIb/IIIa Receptor Inhibitors

Glycoprotein IIb/IIIa receptor inhibitors effectively prevent platelet aggregation; however, their use is associated with an increased risk of bleeding. Studies performed before the era of oral $P2Y_{12}$ antagonists suggested a clinical benefit; however, the safety of administering these drugs concomitantly with ticagrelor and prasurel is unknown. Currently, administration of these agents is recommended only in the setting of thrombotic complications of PCI.

ANTICOAGULATION

Anticoagulants target thrombin generation and fibrin formation and act in synergy with antiplatelet agents. A challenge in treating these patients is to achieve the optimal balance between the need to safely and effectively prevent thrombus-related events and the desire to reduce bleeding complications.

Unfractionated Heparin

Unfractionated heparin (UFH) is composed of an assortment of molecules of variable size that generate a conformational change in antithrombin and inactivate factors II (thrombin) and X. UFH is administered intravenously, the dose–response of UFH is unpredictable, the therapeutic window narrow, and the treatment predisposes patients to development of heparin-induced thrombocytopenia (HIT). Anticoagulation can be reversed by administration of protamine sulfate, and the degree of anticoagulation can be assessed by

measuring the activated Partial Thromboplastin Time (aPTT).

Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH) is administered subcutaneously and achieves more predictable anticoagulant effect compared with UFH. Protamine achieves partial reversal of LMWH-induced anticoagulation. LMWH causes HIT less often than UFH, and the LMWH dose should be reduced in patients with renal failure.

Fondaparinux

Fondaparinux is a reversible selective inhibitor of factor X. Fondaparinux is administered subcutaneously and does not induce HIT. Fondaparinux lowers rates of bleeding and mortality compared with LMWH without increasing ischemic events; however, UFH should be added during PCI to avoid catheter thrombosis.[12, 13]

Bivalirudin

Bivalirudin is an intravenously administered direct thrombin inhibitor. Bivalirudin with bailout administration of glycoprotein IIb/IIIa inhibitors achieves an anti-ischemic effect comparable to UFH or LMWH with routine co-administration of glycoprotein IIb/IIIa inhibitors, but with reduced bleeding complications.

INITIAL CONSERVATIVE VERSUS INITIAL INVASIVE APPROACH

Routine coronary angiography in patients with NSTEMI enables rapid confirmation of the diagnosis of ACS by identification of the culprit lesion in an epicardial coronary artery, risk assessment based on the coronary anatomy and performance of early coronary revascularization. Randomized trials have shown that an invasive strategy achieved superior clinical outcomes (reduced mortality and rehospitalization) compared with a strategy of selective angiography based on positive findings in noninvasive tests.[14, 15] Selection of patients for an early invasive strategy should be individualized and should take into consideration the presence of comorbidities, cognitive impairment, renal failure, frailty, etc. An

early invasive strategy (angiography with 12 to 48 hours of hospital admission) reduced the risk of adverse cardiac events compared with a delayed invasive strategy, especially in high-risk patients (GRACE risk score > 140).[16] Coronary angiography and intervention via transradial vascular access decreases mortality and vascular complications compared with transfemoral access[17] and complete revascularization is associated with superior clinical outcomes compared with culprit-only revascularization.[18] Revascularization should be performed after demonstration of a hemodynamically significant flow-limiting coronary stenosis. Stenting is generally performed in discrete coronary lesions, whereas patients with diffuse coronary disease (SYNTAX score > 23 to 33) should be considered for CABG.

DISCHARGE PLANNING

Secondary prevention of coronary events is crucial in patients being discharged after hospitalization for NSTEMI. Patients should be educated about the importance of modifying their risk profile and instructed regarding the importance of a healthy lifestyle, smoking cessation, weight reduction, routine aerobic exercise, optimal blood pressure control, and consumption of a Mediterranean diet low in saturated fats and rich in vegetable products. Enrollment in a cardiac rehabilitation program may enhance patient compliance, reduce cardiac mortality and hospital admissions, and improve quality of life.[19]

STATINS

High-intensity statin therapy is recommended to reduce low-density lipoprotein (LDL)-cholesterol levels to below 70 mg/dL or as low as possible, depending on the specific hospital's protocol. Ezetimibe treatment may be considered in patients who are intolerant to high-dose statins and those who fail to reach the desired LDL levels.

BETA BLOCKERS AND ACE INHIBITORS

Beta Blockers and ACE Inhibitors are indicated in patients with a reduced left ventricular ejection fraction (<40%); however, their efficacy in patients with preserved left ventricular ejection fraction in the current era of routine coronary revascularization is unproven.

ANTIPLATELET THERAPY

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is mandatory after coronary stenting and also in patients who did not undergo coronary revascularization. Tailoring the duration of DAPT involves a tradeoff between reductions in stent thrombosis and MI and increases in major hemorrhage.[20] DAPT should be continued for at least 1 year, and continuation of DAPT beyond that time frame has been suggested to reduce ischemic events[21]; however, duration of DAPT should be individualized according to the estimated patient's risk of future ischemic events as well as bleeding risk.[22]

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Patient and Family Information for: NON–ST-ELEVATION ACUTE CORONARY SYNDROMES

WHAT IS CORONARY ARTERY DISEASE, AND WHAT IS A HEART ATTACK?

Coronary disease results from blockages in the arteries that supply oxygenated blood to the heart muscle. Coronary disease results from atherosclerosis, which is a process in which cholesterol accumulates in cells within the vessel wall. Atherosclerosis is very common in the general population and is linked to several risk factors such as smoking, obesity, high blood pressure, diabetes, and a family history of coronary disease. A heart attack results from sudden development of a blood clot on top of an atherosclerotic plaque, which occludes the coronary artery and prevents blood flow to the heart muscle. Because the pumping heart needs a constant blood supply, occlusion of a coronary artery may cause irreversible damage and replacement of the normal muscle cells with scar tissue. The typical symptom during a heart attack is crushing chest pain radiating to the left arm; however, the presenting symptoms of a heart attack may be atypical, and many other diseases may be associated with symptoms that mimic a heart attack.

HOW IS A HEART ATTACK DIAGNOSED?

Diagnosis of a heart attack is based on assessment of the patient’s complaints, physical examination, the ECG, and various blood tests and ancillary tests.

ELECTROCARDIOGRAM

The ECG in a patient with a heart attack may show a finding called ST-elevation, which usually signifies complete blockage of a coronary artery. Heart attack patients with ST-elevation on the ECG are usually referred for emergency coronary catheterization in order to open the blocked artery immediately and prevent further damage to the heart muscle. More often, the ECG in patients with a heart attack does not show ST-elevation. These patients usually do not require emergency catheterization, but are typically referred for catheterization within 1 to 2 days in order to evaluate the patency of the coronary arteries and select the best treatment approach.

BLOOD TESTS

Even minimal damage to the heart muscle may lead to secretion of a protein called troponin into the blood stream. Measurement of blood troponin levels enables accurate diagnosis of a heart attack.

ADDITIONAL TESTS

- Echocardiography uses ultrasound to evaluate the structure and functioning of the heart. This noninvasive test is very useful for detecting damage to the heart muscle following a heart attack.
- Exercise testing: During physical exercise, the workload on the heart increases in order to supply larger volumes of oxygenated blood to the skeletal muscles. This increased cardiac workload means that the heart muscle itself requires increased blood supply through the coronary arteries. Obstruction to blood flow in the coronaries during exercise may cause an imbalance between oxygen supply and demand in the heart muscle, which is called myocardial ischemia. ECG changes during exercise may reflect ischemia and signify that catheterization should be performed in order to accurately analyze the anatomy of the coronary arteries.
- Myocardial perfusion scans measure the uptake of radioactive substances in the heart muscle at rest and during exercise to detect ischemia.
- Cardiac CT is a noninvasive test that enables accurate mapping of the coronary anatomy and detection of blockages within these arteries.

TREATMENT

MEDICATIONS

Various medications have proven benefit in patients with coronary artery disease. Aspirin is a blood thinner, which is used to prevent development of blood clots within the coronaries. In patients with a heart attack, an additional oral blood thinner is usually given to enhance the effect of aspirin. Three commonly used blood thinners are clopidogrel (Plavix), prasugrel (Effient), and ticagrelor (Brilinta). Statins are cholesterol-lowering drugs that may prevent heart attacks and death in patients with coronary disease. β-Blockers are drugs that lower the heart rate and blood pressure and therefore decrease the workload on the heart. Nitrates are drugs that improve blood supply to the heart muscle in patients with coronary disease.

CARDIAC CATHETERIZATION

During catheterization, a thin tube (catheter) is inserted via an artery in the groin or in the wrist to the heart. The procedure is performed in a special room, which is called a catheterization laboratory where X-ray is used to study the heart and coronary arteries. Injection of a fluid called contrast media enables accurate mapping of the course and patency of the coronary arteries and detection of blockages within them.

CORONARY ANGIOPLASTY

Angioplasty is a technique that enables opening of blockages within the coronary arteries through a catheter. A small balloon is used to open the blockages. A stent is a metallic cylinder that is placed within the blockage to keep it open. Modern stents (drug-eluting stents) have special drugs attached to them that prevent renarrowing of the arteries.

CORONARY BYPASS SURGERY

Bypass surgery is open-heart surgery in which alternative blood vessels (bypass grafts) are connected to the diseased coronary arteries beyond the point at which they are blocked. This is done in order to renew blood supply to the heart muscle. Bypass surgery is usually performed in patients with multiple blockages in the coronary arteries who are not considered good candidates for angioplasty, especially in diabetics.

RECOVERY

- Diet: Patients with coronary disease should use a “Mediterranean” diet with a high consumption of vegetables and fruit and low in saturated fats and red meat. Patients should lower their calorie consumption in order to achieve an ideal body weight.
- Exercise: Aerobic exercise has proven benefit in preventing future heart attacks, lowering blood pressure, and achieving weight loss. A typical exercise regimen entails walking an hour a day at a speed of 3 mph.
- Smoking: Continued smoking after a heart attack significantly increases the risk of repeated heart attacks, stroke, and death. Smoking cessation is crucial in patients with coronary disease and may be assisted by special counseling.
- Medications: Patients with coronary disease require life-long aspirin to prevent future heart attacks and statins to lower the blood cholesterol. Patients who have received coronary stents require an additional blood thinner (clopidogrel, prasugrel, ticagrelor) for a period ranging between several months and 1 year. Some patients require additional medications to control high blood pressure and diabetes, to treat heart failure or rhythm disturbances, and to reduce chest pain (angina).

4

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Indra Warren

Echocardiography in Acute Coronary Syndrome

INTRODUCTION

The past few decades have witnessed remarkable progress in the understanding of the pathophysiology of acute coronary syndrome (ACS). This, in turn, has led to advances in various imaging techniques for diagnosis and therapeutic options. Developments in the field of echocardiography have paralleled the progress made in ACS. The initial use of echocardiography was to detect pericardial effusions and cardiac tumors. However, the current applications of various forms of echocardiography include an extended list of pathologic and therapeutic indications. Advances in echocardiographic techniques and instrumentation have rivaled those in management of ACS.[1] This chapter is focused on the role of echocardiography in ACS.

ASSESSMENT OF REGIONAL SYSTOLIC FUNCTION IN ACUTE CORONARY SYNDROME

Occlusion of an epicardial coronary artery at the time of ACS may lead to a loss of contractile function in the myocardial segments subtended by that vessel. The magnitude and duration of wall motion abnormalities depend on the severity,

extent, and duration of the coronary occlusion.

In unstable angina, left and right ventricular wall motion may be normal unless transthoracic echocardiography happens to be performed during an episode of chest pain.

Non–ST-elevation myocardial infarction (NSTEMI) usually results from an occlusion of a coronary branch vessel often in an elderly patient with pre-existing collateral coronary circulation. Typically, the loss of contractile function is restricted to the subendocardial layer, which is most vulnerable to ischemia. However, on standard echocardiography, the contractility loss may be observed in the entire thickness of the affected myocardial segment. This overestimation of contractile loss is attributed to tethering (an apparent passive loss of contractility in normal segments because of contractile loss in an adjacent area).

ST-elevation myocardial infarction (STEMI) often results from an acute occlusion of a major coronary vessel and tends to occur in a younger age group compared with NSTEMI. If the total session of coronary flow lasts for more than 3 to 6 hours, myocardial necrosis will occur and the myocardium in the affected segments will be replaced with a fibrous tissue over the ensuing weeks.[2]

The magnitude of regional contractile loss in ACS is usually assessed semiquantitatively. It is usually interpreted clinically as follows[2]:

1. Interpretation of wall motion abnormalities:
   Normal: Contractility preserved
   Hypokinesis: Partial loss of contractility
   Akinesis: Complete loss of contractility
   Dyskinesis: Paradoxical movement of the affected segment away from the center of the ventricle during systole
   Aneurysmal: Outward movement of the affected segment during both systole and diastole
2. Extent and location of affected segments
3. Suspected coronary artery distribution (left anterior descending artery [LAD] vs right coronary artery vs left circumflex artery).

ASSESSMENT OF GLOBAL SYSTOLIC FUNCTION IN ACUTE CORONARY SYNDROME

Global ventricular systolic function in ACS is assessed through both wall motion scoring and global ventricular ejection fraction (EF).

Wall Motion Scoring

Wall motion scoring analysis assigns a numeric value to the degree of contractile dysfunction in each segment. The most common scoring criteria are seen in **Table 4.1**.[3]

TABLE 4.1 Left Ventricular Wall Motion Scoring

	Score
Normal or hyperkinetic	1
Hypokinetic (reduced thickening)	2
Akinetic (absent or negligible thickening)	3
Dyskinetic (systolic thinning or stretching, aneurysmal)	4

Wall Motion Score Index = Sum of Individual Segment Scores/Number of Evaluated Segments.

Once all segments are assigned individual scores, a total score is calculated as a sum of individual scores. A Wall Motion Score Index (WMSI) is then calculated as a ratio between the total score over the number of evaluated segments. The WMSI is a dimensionless index.

A 17-segment model is commonly used to allow for standardized communication within echocardiography and with other imaging modalities. In this 17-segment model, the apex is divided into five segments (septal, anterior, inferior, lateral, and an "apical cap" defined as the myocardium beyond the end of the left ventricular [LV] cavity).[3] For a fully visualized normal ventricle, the total score is 17 (all segments have normal contractility). Because all 17 segments are evaluated, the WMSI of a normal heart is 17/17 = 1. For abnormal ventricles, the higher the WMSI, the more significant the wall motion abnormally is. A score above 1.7 represents significant wall motion abnormality.

Assessment of Ventricular Ejection Fraction

Numerous studies have consistently shown left ventricular ejection fraction (LVEF) as one of the most powerful predictors of future mortality and morbidity in patients with heart disease.[4] LVEF is the single most powerful predictor of mortality and the risk for developing life-threatening ventricular arrhythmias after myocardial infarction.[5] Furthermore, once the ACS resolves, the residual

LVEF is important for treatment options as LVEF cutoff values are built into recommendations for both medical and electrical device therapies. Even with treatment and clinical stabilization of heart failure, there is an inverse, almost linear, relationship between LVEF and survival in patients whose LVEF is less than 45% (**Figure 4.1**).[6]

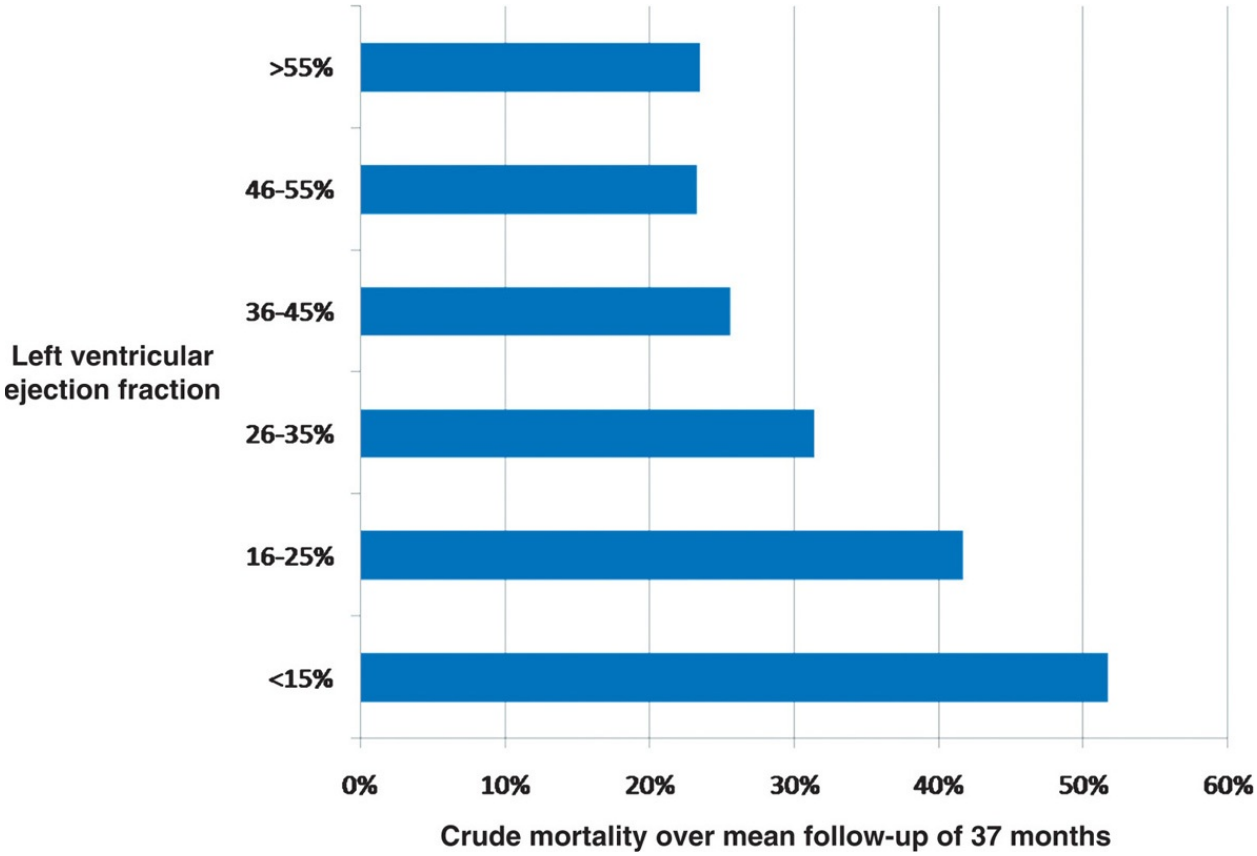

FIGURE 4.1 Relationship between left ventricular ejection fraction and survival. Note the negative, almost linear, relationship between survival and left ejection fractions <45%. (Based on numeric data from Curtis et al.[6])

By definition, LVEF is the percentage of the end-diastolic volume that is ejected with each systole as the stroke volume. Thus, to calculate the LVEF, one needs to estimate the end-systolic and end-diastolic volume of the left ventricle.

For two-dimensional echocardiography, biplane Simpson's rule is routinely used for estimation of the LVEF.[7, 8] Most modern ultrasound systems provide a semiautomated software package for the Simpson's rule analysis. Operators are usually only required to trace the LV endocardial border at end-diastolic and end-systolic in the apical four-chamber and two-chamber views; the software

package then automatically calculates the LV end-diastolic volume, end-systolic volume, and LVEF (**Figure 4.2**).

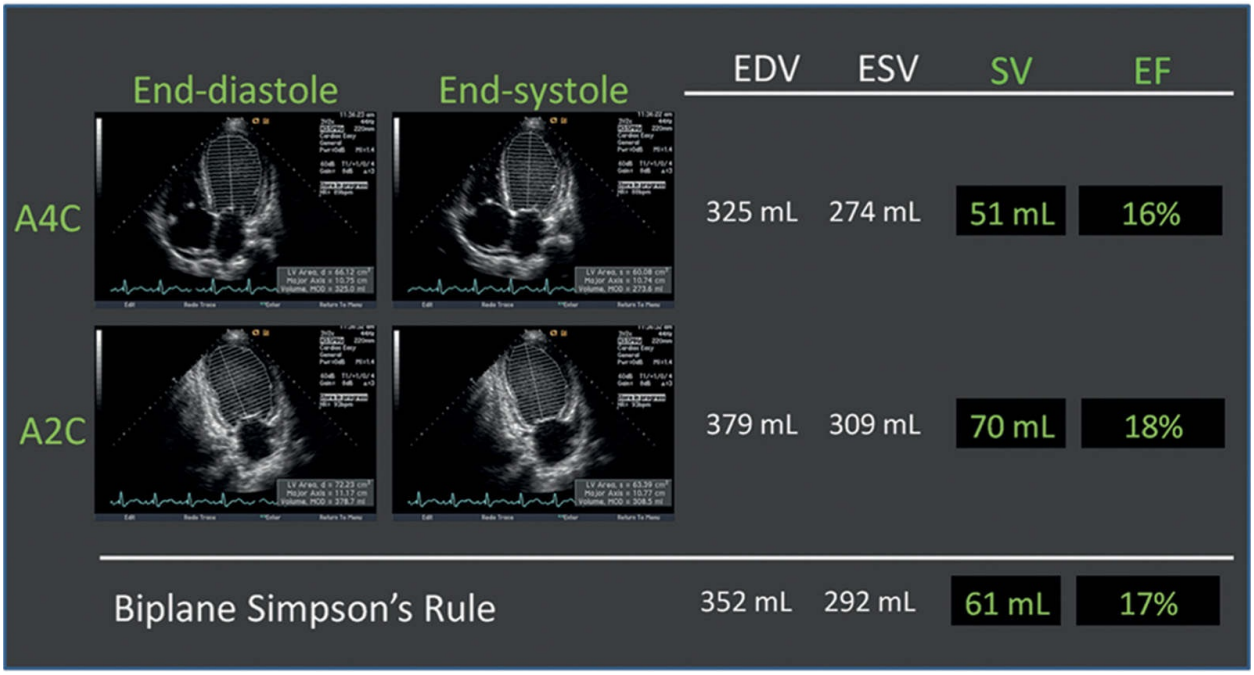

FIGURE 4.2 Calculation of LVEF by biplane Simpson's rule. The operator of an ultrasound system is required to trace the endocardial border of an end-diastolic and an end-systolic frame in the A4C and A2C views. The system then calculates the EDV, ESV, SV, and LVEF. A4C, apical four-chamber; A2C, apical two-chamber; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; SV, stroke volume.

With the advent of real-time three-dimensional (RT3D) transthoracic techniques, LV volumes and LVEF can now be calculated with even greater accuracy than is possible with the biplane Simpson's rule (**Figure 4.3**). RT3D-derived LV volume data are now comparable to those obtained by cardiac magnetic resonance imaging, the prior gold standard for such calculations.[8]

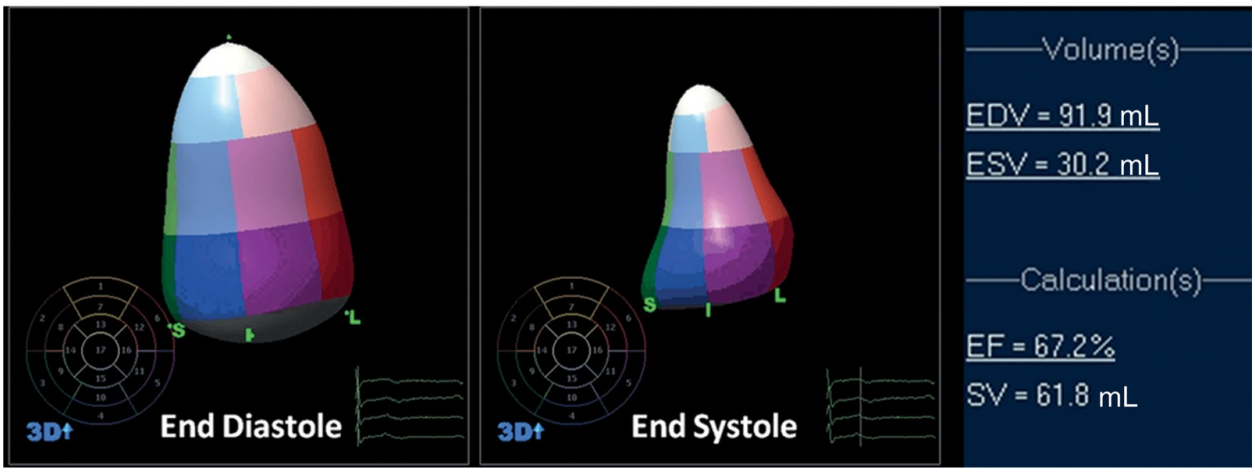

FIGURE 4.3 Calculation of left ventricular volumes and EF by three-dimensional echocardiography. A three-dimensional ultrasound system calculates the EDV, ESV, SV, and LVEF automatically from a three-dimensional data set after an operator manually enters key reference points of the left ventricle. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LVEF, left ventricular ejection fraction; SV, stroke volume.

Thus, whenever available, LV volumes and LVEF in ACS should be calculated from an RT3D system; the biplane Simpson's rule should be the next best method for such calculations when only a two-dimensional ultrasound system is available.

THE ISCHEMIC CASCADE

The ischemic cascade refers to a sequence of events that occurs in the myocardium after the onset of ischemia.[9] Myocardial perfusion is determined by coronary blood flow and myocardial oxygen consumption. Any imbalance in this supply-and-demand relationship results in myocardial ischemia.[10] The mechanical, electrographic, and clinical events that follow the development of ischemia were formally described in 1985 by Hauser et al.[11] and were later termed the "ischemic cascade."[12] Classically, the observable changes occur sequentially (**Figure 4.4**) starting with perfusion abnormalities leading to abnormalities in wall function, then ischemic electrocardiogram (ECG) changes, and finally angina.[13] Echocardiography has the ability to detect these pathophysiologic changes in the myocardium at the most initial stages and therefore is more sensitive than history, physical examination, and ECG for identification of myocardial ischemia.[14] **Figures 4.5** and **4.6** depict

echocardiographic views of the left ventricle, demonstrating the LV wall segments and their typical corresponding coronary distributions.[3] Additionally, the utilization of image-enhancing agents (echocardiographic contrast microbubbles) has improved the detection of even subtle wall motion abnormalities, improving the confidence in the presence or absence of ischemia, and thereby facilitating further management.

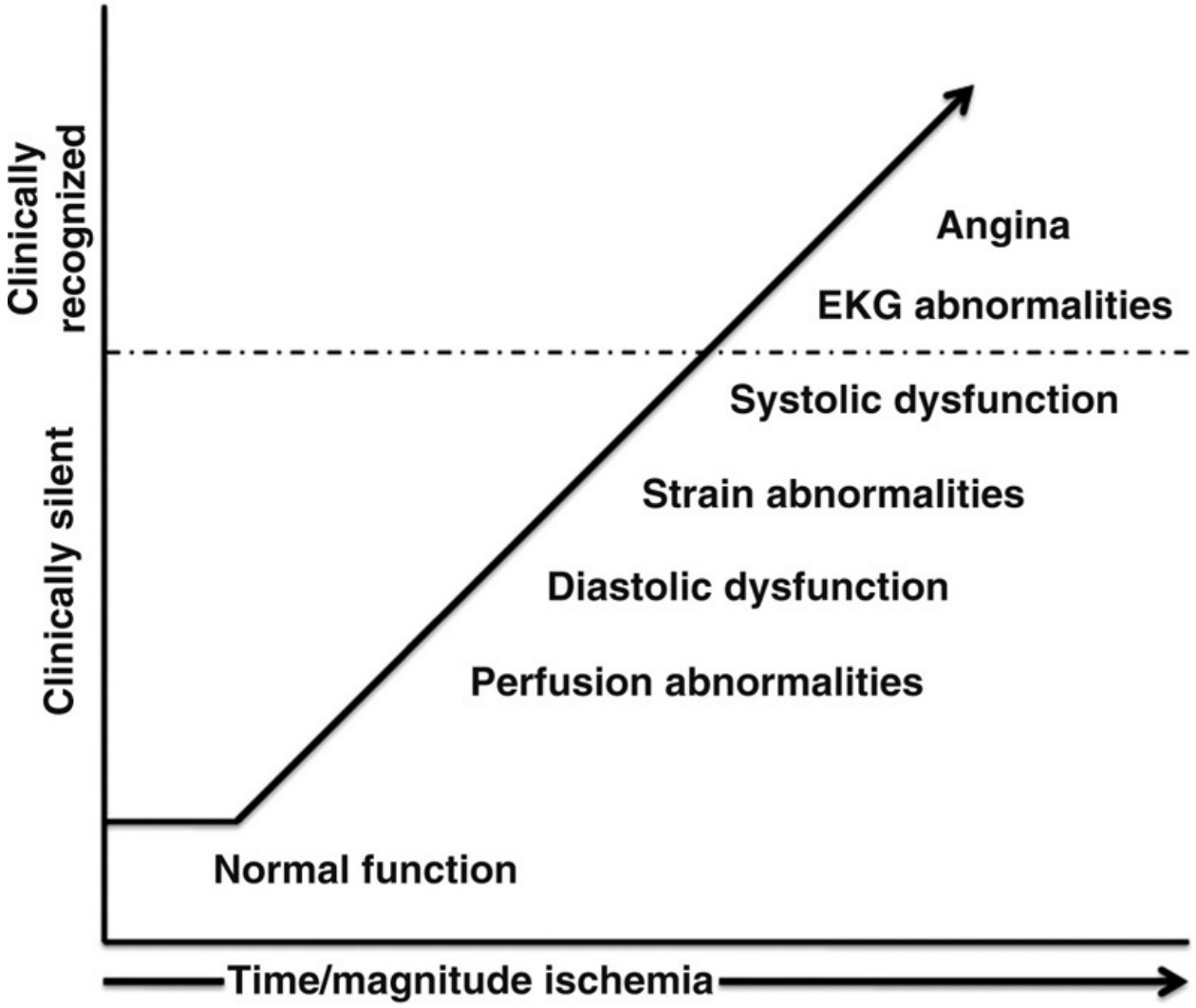

FIGURE 4.4 The ischemic cascade. Myocardial dysfunction occurs in a predictable sequence, which is detectable before clinical symptoms. ECG, electrocardiogram.

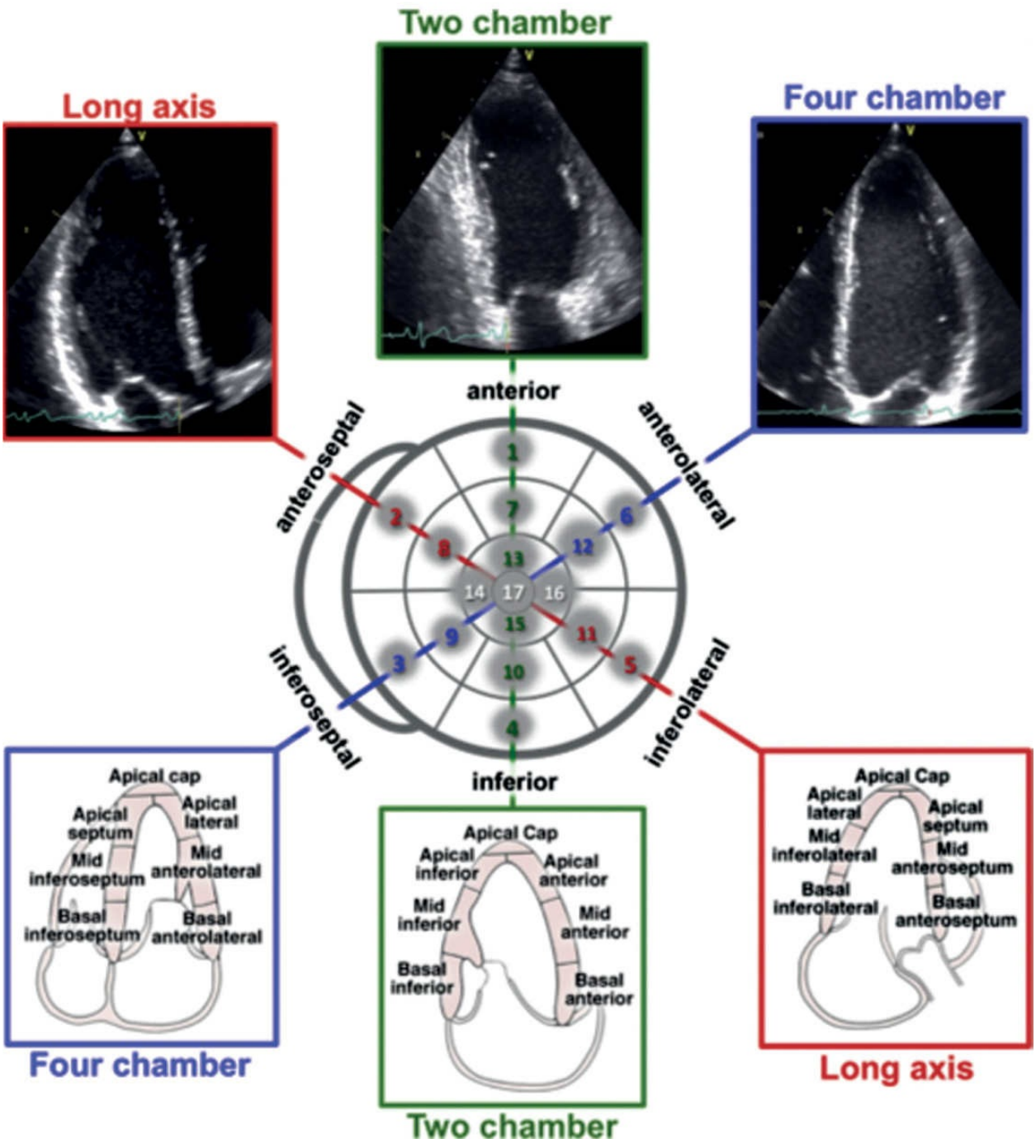

FIGURE 4.5 A4C, A2C, and ALX views in relation to the bull's-eye display of the left ventricular segments (center). Top panels show echocardiographic images and bottom panels depict the left ventricular wall segments visualized in each view. A4C, apical four chamber; A2C, apical two chamber; ALX, apical long axis. (Courtesy of Lang et al.[3])

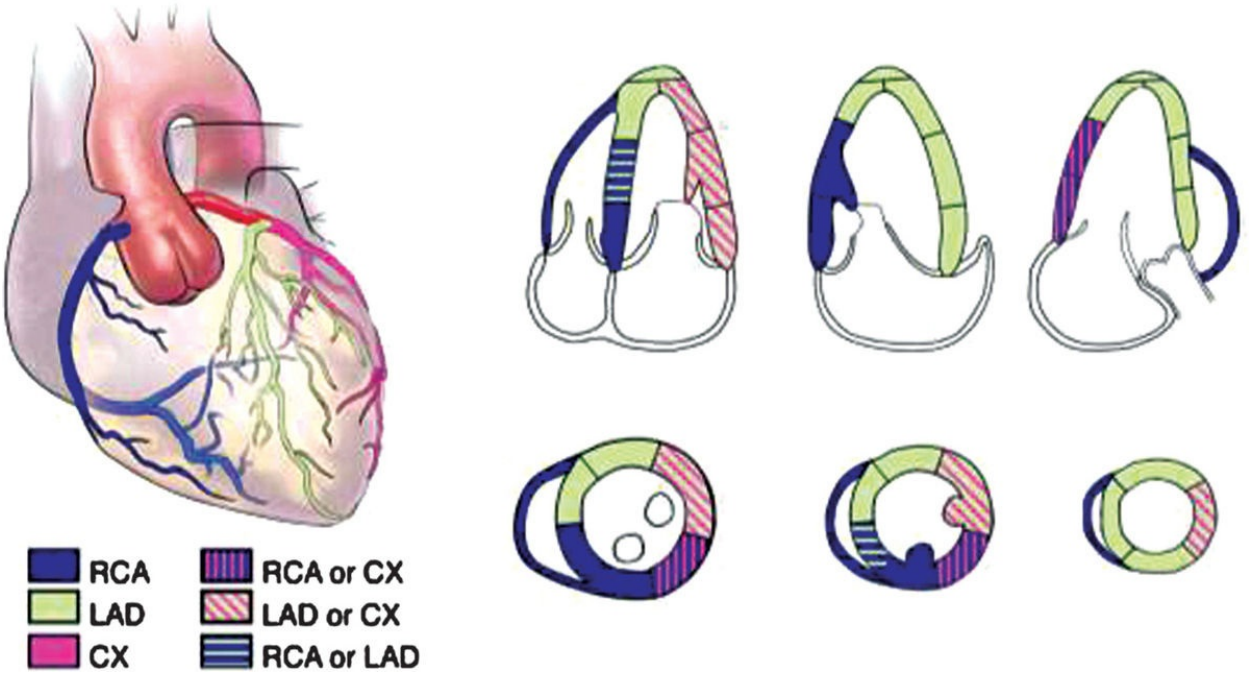

FIGURE 4.6 Distributions of the RCA, LAD, and CX. CX, circumflex coronary artery; LAD, left anterior descending artery; RCA, right coronary artery. (Courtesy of Lang et al.[3])

Echocardiography for the diagnosis of suspected acute ischemia is most helpful in subjects with a high clinical suspicion but nondiagnostic electrocardiograms, as it allows real-time assessment of myocardial function. Additionally, through stress modalities, it offers assessment and risk stratification in patients who present to the emergency department with chest pain.

Of note, troponin elevation with chest pain may not be related to an ACS, but rather be secondary to other cardiovascular pathology such as valvular disease (eg, severe aortic stenosis or regurgitation), which can induce ischemia by causing LV wall stress; acute heart failure due to systolic and/or diastolic dysfunction; or even acute pulmonary embolism with right ventricular strain. Echocardiography is a valuable tool to detect and quantify these other abnormalities, regardless of whether the patient is having an ACS.

STRESS ECHOCARDIOGRAPHY

There are different types of stress echocardiography that can be used in the evaluation of patients with coronary artery disease.[15] For patients who are able

to exercise, treadmill and supine bicycle stress echocardiograms are the preferred techniques. For patients unable to exercise, pharmacologic stress testing using dobutamine, dipyridamole, or adenosine is an alternative method to provoke ischemia.

Table 4.2 outlines the methods to induce stress. The basic principle of stress echocardiography is the identification of new wall motion abnormalities that occur in the presence of provocable ischemia. This involves the comparison of baseline echocardiographic images obtained under resting conditions with those obtained immediately postexercise in the case of treadmill or during peak exercise in the case of bicycle protocol. Parasternal long and short axes as well as apical two-chamber, three-chamber, and four-chamber views are acquired at baseline and Post-stress testing. The left ventricle is divided into 17 segments as per the recommendation of the American Society of Echocardiography. All images are digitized in a continuous-loop format utilizing a quad-screen format to facilitate the detection of new segmental wall motion abnormalities. The best Post-exercise image is selected and compared with the baseline image by side-by-side comparison in the quad-screen image format.

TABLE 4.2 Methods to Induce Stress

Exercise	Pharmacologic
Treadmill	Dobutamine
Supine bicycle	Dipyridamole
Isometric exercise	Adenosine

In the United States, the most commonly used method for provoking ischemia in patients able to exercise is treadmill testing. The sensitivity of exercise testing is strongly dependent upon attaining adequate heart rate and cardiovascular workload. The use of treadmill or bicycle methods of exercise requires the patient to achieve a target heart rate of 85% of the age-predicted maximum heart rate or attain a workload of at least six metabolic equivalents in order to achieve satisfactory sensitivity. In patients who can achieve these workloads, exercise testing is the method of choice to provoke myocardial ischemia.

The most common treadmill protocol used is the Bruce protocol, although other protocols such as the modified Bruce can be used depending upon the level of fitness of the patient. According to standard stress testing protocol, the patient

has continuous ECG monitoring with exercise and blood pressure is checked every 3 minutes. With treadmill exercise, the Post-exercise images are obtained ideally within less than 1 minute.

The exercise test should be terminated if any of the following occurs:

1. Severe symptoms such as chest pain or dyspnea
2. Severe ST depressions
3. Hemodynamically significant arrhythmia
4. Severe hypertensive response (BP > 220/120 mm Hg)
5. Hypotension (a decrease of >20 mm Hg)

PHARMACOLOGIC STRESS ECHOCARDIOGRAM

For those patients who cannot exercise, dobutamine or dipyridamole stress echocardiograms can alternatively be performed. By far, dobutamine is the most common pharmacologic agent used to provoke ischemia in stress echocardiograms. Dobutamine is a synthetic catecholamine that binds to β-1 and β-2 receptors. The affinity of dobutamine for β-1 cardiac muscle receptors results in positive inotropic and chronotropic effects. Therefore, dobutamine induces myocardial ischemia in patients with flow-limiting coronary stenosis by increasing LV contractility, heart rate, wall stress, and therefore myocardial oxygen demand. Dobutamine has a short half-life and is rapidly metabolized once the infusion is discontinued. Any adverse side effects or arrhythmias can usually be quickly terminated by discontinuation of the drip or by intravenous β-blockers.[16]

Pathway for Management of Patients Based on Stress Echocardiography Results

Risk stratification of patients undergoing stress echocardiography should be based both on peak WMSI (which includes both extent and severity of ischemia/infarction) and on LVEF (resting). **Figure 4.7** represents a schematic for the risk stratification of patients with known or suspected coronary artery disease referred for stress echocardiography. These data for risk stratification are based on an analysis of 3259 patients (59 ± 13 years; 48% males) followed for up to 4 years.[17]

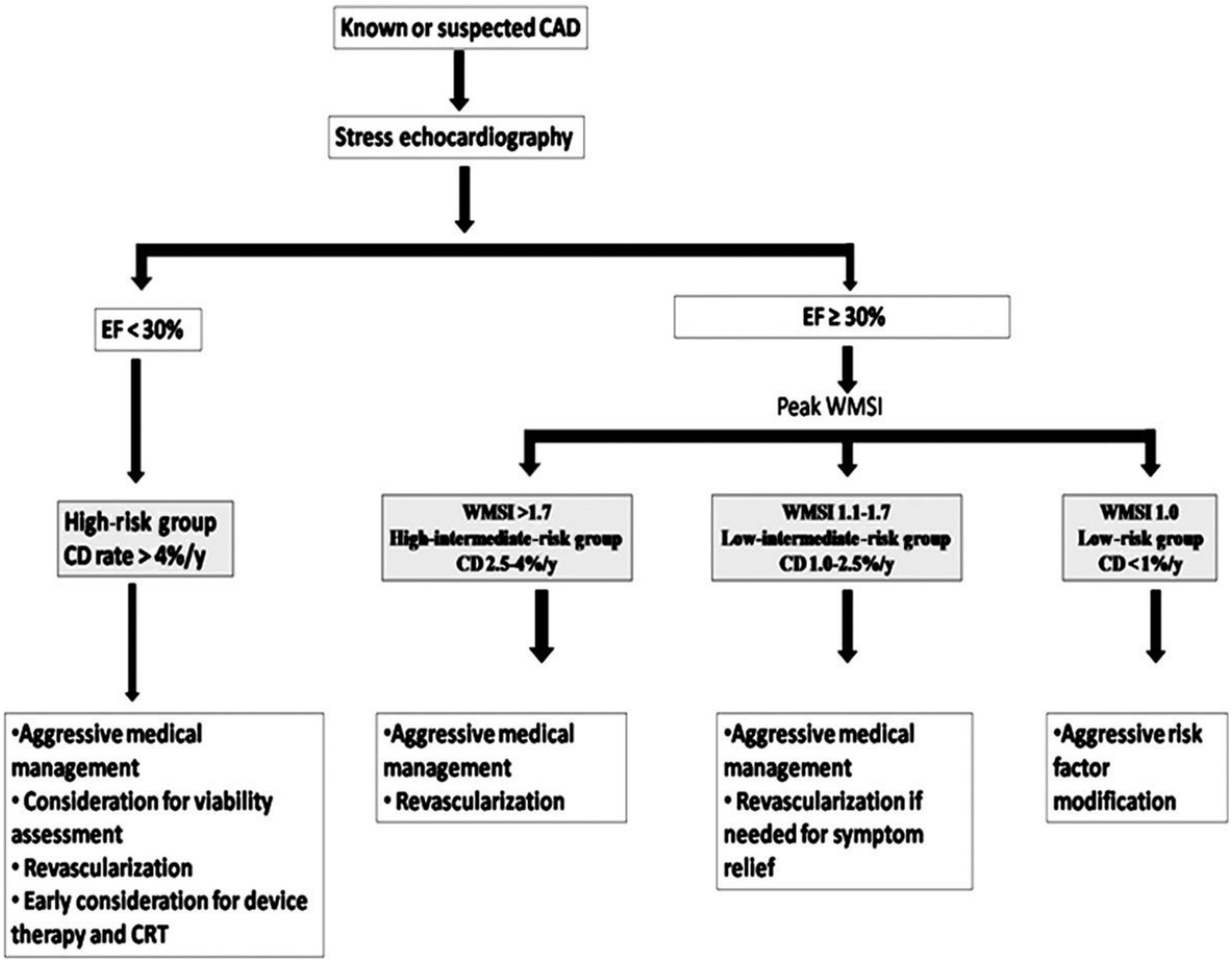

FIGURE 4.7 Schematic for risk stratification of patients undergoing stress echocardiography. CAD, coronary artery disease; CD, cardiac death; CRT, cardiac resynchronization therapy; EF, ejection fraction; WMSI, Wall Motion Score Index.

The first step in the risk stratification process is evaluation of LVEF. Patients with EF <30% are a high-risk group with a cardiac death (CD) rate of >4%/y regardless of the peak WMSI. Such patients should be aggressively managed. These patients may also benefit from viability assessment and consideration for revascularization as deemed necessary. They should also be considered for early device therapy (implantable cardioverter defibrillator/cardiac resynchronization therapy) and for cardiac transplant evaluation.

In patients with EF ≥ 30%, peak WMSI can further risk stratify the patient subgroup into a low-risk group (peak WMSI = 1.0) (CD <1%/y), low-intermediate (peak WMSI 1.1–1.7) (CD 1%–2.5%/y), and a high-intermediate (peak WMSI > 1.7) (CD 2.5%–4.0%/y) risk groups. Patients in the low-risk category will benefit from aggressive risk factor modification. Those in the low-

intermediate risk group may benefit from aggressive medical management and consideration of revascularization for symptom relief only. Patients in the high-intermediate risk group may benefit from aggressive medical management and revascularization therapy. Such a risk stratification approach would potentially avoid unnecessary revascularization procedures for low-risk individuals and at the same time provide a framework for the management of intermediate and high-risk subgroups.

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Patient and Family Information for: ECHOCARDIOGRAPHY IN ACUTE CORONARY SYNDROME

INTRODUCTION

The echocardiogram is an ultrasound device that visualizes the heart and surrounding structures in a real-time fashion, which in turn provides important anatomic and physiologic information to the cardiologist. The echocardiogram, like a radar, emits and receives ultrasound waves and constructs an image by employing the differences in the signal properties. At the end of this sophisticated and fast process, an impressive and informative animation of the heart moving in the chest is displayed for further interpretation. In the cardiac care unit (CCU), echocardiography has become an essential tool for real-time bedside diagnosis of heart disease, especially in critical situations. Furthermore, echocardiography lacks any major side effects and is mostly noninvasive.

THE DEVICE STRUCTURE

The echocardiogram itself is made of two major components: the first is the transducer, which is the “radar dish” that relays the ultrasounds waves and is in touch with the patient’s body, and the second is a computer console that functions as the “brain” performing the computation. The transducer is filled with multiple crystals (called piezoelectric crystals) that have the natural property of sending and receiving ultrasound waves. Different transducers have different properties. Lower frequency transducers can emit ultrasound waves deeper into the body, but lack the picture quality of the higher frequency ones.

When placing the transducer over the chest (this common procedure is referred to as a transthoracic echocardiogram or TTE), a real-time moving image of the heart appears. By rotating and manipulating the transducer over the chest, different areas of the heart are seen; those are referred to as windows. Gel is used to improve the contact between the transducer and the skin, which helps with improving image quality. In TTE, four major areas over the chest are used to create heart images. These include the left chest area between the third and fourth ribs (parasternal), the tip of the heart (apical), under the ribs (subcostal), and above the chest (suprasternal). Several views of the heart are created in each location by rotating the transducer.

THE ECHOCARDIOGRAM ROLE IN THE CCU

In the CCU, echocardiography studies are performed to answer complex clinical questions. Of particular concern in the CCU are the function and integrity of the heart muscle walls (myocardium), the valves, and the heart sac (pericardium). The echocardiogram can provide information such as which chamber of the heart is involved in the disease, the heart's squeezing efficiency, the amount of fluid in the heart's sac, and the presence of clots in the heart chambers.

In the case where there is fluid in the heart sac that compresses the heart (a condition called pericardial tamponade), the echocardiogram can detect this acute life-threatening situation promptly and guide an immediate draining procedure.

"HEART ATTACKS" AND ECHOCARDIOGRAPHY

The majority of disease treated in the CCU is of coronary origin. The coronary arteries are the vessels that feed blood to the heart muscle itself. "Heart attack" or acute myocardial infarction is the condition where a coronary vessel is blocked and thereby prevents oxygenated blood from being delivered to the heart muscle. This in turn causes the heart muscle to start dying, and losing its ability to contract and pump blood. In contrast to a complete blockage, a partial blockage of the coronary artery may result in symptoms such as chest pressure on exertion (referred to as angina), but no impairment in the heart's squeezing function. Interestingly, the patient's symptoms are the last to develop in the

cascade of coronary artery blockage. After complete cessation of blood supply to the heart muscle, a sequence of event occurs that is referred to as the ischemic cascade, where the heart muscle wall motion is affected before any ECG changes and before the patient develops symptoms. Therefore, the echocardiogram potentially can detect, in a noninvasive way, heart wall motion contraction impairments in situations where the ECG is nondiagnostic and the patient's symptoms are unclear. During a complete coronary occlusion, the echocardiogram is able to show which wall of heart is not contracting and is thus affected directly by the occlusion. The degree of muscle contraction impairment has a scoring system that provides information about the extent of occlusion and function of the muscle. The walls of the heart are divided into 17 segments. Normal wall motion gets a score of 1; *hypokinesis* is the term used to describe decreased contractility and receives a score of 2; *akinesis* is when no wall motion is seen, with a score of 3; and *dyskinesis* is when the wall motion direction is occurring in the opposite direction, with a score of 4. The sum of the scores of each segment is then divided by 17. A normal score would be 1 (17 divided by the 17 segments) and a score above 1.7 represents significant wall motion abnormality.

There are three major coronary arteries in the heart, and each of them provides blood supply to a certain muscle wall of the heart (with some overlap). The echocardiogram is able to pinpoint the culprit vessel that is occluded. The occluded coronary artery is represented in the echocardiographic study by a specific area of impaired contraction. The assessment of the heart muscle contraction is also assessed as a whole, that is, the heart's overall pumping efficiency. This is referred to as EF. The EF denotes the percentage of blood squeezed from the left ventricle of the heart in one heartbeat to the rest of the body (normal value is 60%). It is known from numerous studies that the lower the EF is, the worse the outcome of the patient.

For example, a patient with an acute myocardial infarction is admitted to the CCU with a LAD occlusion. The LAD supplies blood to the front side of the left heart chamber (main pumping chamber). During the performance of the echocardiogram study, the cardiologist notices that the front portion of the left heart chamber is not squeezing optimally (ie, there is hypokinesis), with an EF of 30%, and there is also some valve leak. Occlusion of an artery can influence the function of a heart valve because the valve's movement relies on muscles attached to the heart wall. The patient is sent thereafter for a cardiac catheterization where the occluded coronary artery is opened. An

echocardiogram performed 2 days after the procedure shows some recovery in the wall motion of the front wall with resolution of the valve leakage, as blood supply was restored to the region. The echocardiogram provided up-to-date functional information of various structures of the heart such as the muscle wall and the valves. In contrast, a patient whose echocardiogram shows global LV hypokinesis without any regional wall abnormalities likely had a remote myocardial infarction that initially affected the region of the heart distributed by the occluded coronary artery but progressed to a dilated left ventricle, or had small vessel disease that reduced global perfusion.

MANAGEMENT AFTER THE ACUTE EPISODE

The echocardiogram has a role for diagnosing new or recurrent symptoms during the admission of a patient in the CCU after the primary diagnosis was made. For example, if a patient has recurrent chest pain or shortness of breath, or if the patient's blood pressure is coming down without a reason, the echocardiogram can provide answers. New heart wall motion abnormalities could point to new or recurrent coronary vessel occlusions. A new murmur that is first detected on physical exam with a stethoscope could be the result of a new valve problem (eg leakage), or even a rupture between the heart chambers. These conditions require prompt interventions, and at times may require surgery. The echocardiogram can help in diagnosing dehydration (the main pumping chamber of the heart becomes smaller), fluid overload (due to heart failure or administration of too much fluids), or fluid in the heart sac that compresses the heart (eg pericardial effusion, tamponade).

STRESS TESTING

Some patients who are admitted with chest pain with a high suspicion of a coronary artery disease without an overt heart attack require more testing to confirm the diagnosis. This could be accomplished by performing an echocardiogram while the patient's heart is being "stressed," that is, walking on a treadmill or giving the patient a medication that will make the heart beat faster. Actual stressing or exercising is not performed when the patient is suspected of an evolving heart attack (ACS). Images of the patient's heart muscle contraction

are obtained before, during, and after the stress—the muscle could be inspected for wall motion abnormalities that denote probable coronary disease.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Some echocardiographic information could be better acquired by using the device in a semi-invasive method called transesophageal echocardiogram—echocardiogram obtained through the esophagus (food pipe). Because there is a short distance between the transducer and the heart while the transducer is positioned in the esophagus, the quality of pictures is better. It is especially useful when imaging cardiac structures that are located at the back part of the heart (eg the left atrium).

LIMITATIONS

There are some limitations in performing an echocardiogram at the bedside as compared with the echocardiography laboratory settings. Usually, the patient is asked to lie on his left side to obtain some of the windows and then to lie on his back for the rest of the images. In the CCU, the patient could be mechanically ventilated, sedated, and might not be able to cooperate. Thus, some of the pictures may be much harder to obtain in order to produce high-quality images.

CONCLUSION

Echocardiography in the CCU provides important anatomic, structural, and clinical information that aids the cardiologist in the diagnosis and treatment of acute heart diseases. It helps to establish a diagnosis in a real-time fashion. It shows the heart muscle function, and this information helps to designate which coronary artery is occluded during heart attacks. It also shows the integrity and function of the heart valves, the amount of fluid in the heart’s sac, and the body’s fluid balance. Echocardiography aids in managing severely sick patients in the CCU by performing sequential studies. Echocardiography has changed the way cardiologists treat patients in the CCU by having the ability to get live, real-time images of the heart apparatus at the bedside.

5

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Use of Radionuclide Imaging in Acute Coronary Syndrome

INTRODUCTION

Chest pain is a common complaint and is often the presenting symptom in patients with acute coronary syndrome (ACS). The evaluation of chest pain as a presenting symptom for ACS is complicated by: (1) the numerous etiologies that can cause chest pain, (2) the lack of an “ideal” diagnostic test available at the time of initial evaluation, (3) poor clinical outcomes of patients in whom a diagnosis of ACS is missed, and (4) the medicolegal implications. Because patients with ACS are at a high risk for poor outcomes, the ability to identify these patients rapidly during the initial evaluation is critical. The initial diagnostic workup in patients presenting with symptoms suspicious of ACS include a history, physical examination, electrocardiogram (ECG), and serum cardiac biomarkers (such as cardiac troponins). The ECG is the key diagnostic test used to determine whether the patient has ongoing myocardial ischemia. Unfortunately, the ECG is often nondiagnostic in many patients who present with symptoms suspicious for ACS. Although serum troponin has been shown to be a sensitive test for myocardial damage, there are certain drawbacks to the test, for example, the need for ischemia of sufficient time for myocardial necrosis to take place, and thus the initial serum troponin is often negative in patients with

ACS. Patients with unstable angina often do not have significant troponin elevation. Although the newer generation assays (“high-sensitivity troponin”) may affect the accuracy and timing of ACS diagnosis significantly, one should bear in mind that troponin elevation (especially mild degrees) is not exclusive to ACS but may happen in other conditions, primarily nonischemic cardiovascular diseases, for example, pulmonary embolism, acute heart failure, and severe sepsis. Based on the pathophysiology of coronary artery plaque rupture as the cause of ACS, one of the earliest signs of ACS is the decrease in blood flow to the myocardium (**Figure 5.1**). This decrease in myocardial blood flow can be evaluated using single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), which images the relative amount of myocardial blood flow to all segments of the left ventricle. The use of SPECT MPI in the patient presenting with chest pain has developed over the last several decades to allow for rapid triage in chest pain patients with a view to initiating the necessary medical therapy and revascularization. However, we would also like to identify those patients whose chest pain is not caused by ACS so they are not unnecessarily admitted to the hospital, thus better utilizing health care resources. Stress SPECT MPI can be used for risk stratification in low-risk patients admitted for suspected ACS. It can also identify areas of ischemia in patients with ACS who were not fully revascularized. Finally, radionuclide imaging can assist in assessment of myocardial viability. In this chapter, we will explore the technical, physiologic, and current outcome data of using SPECT MPI in patients with acute chest pain.

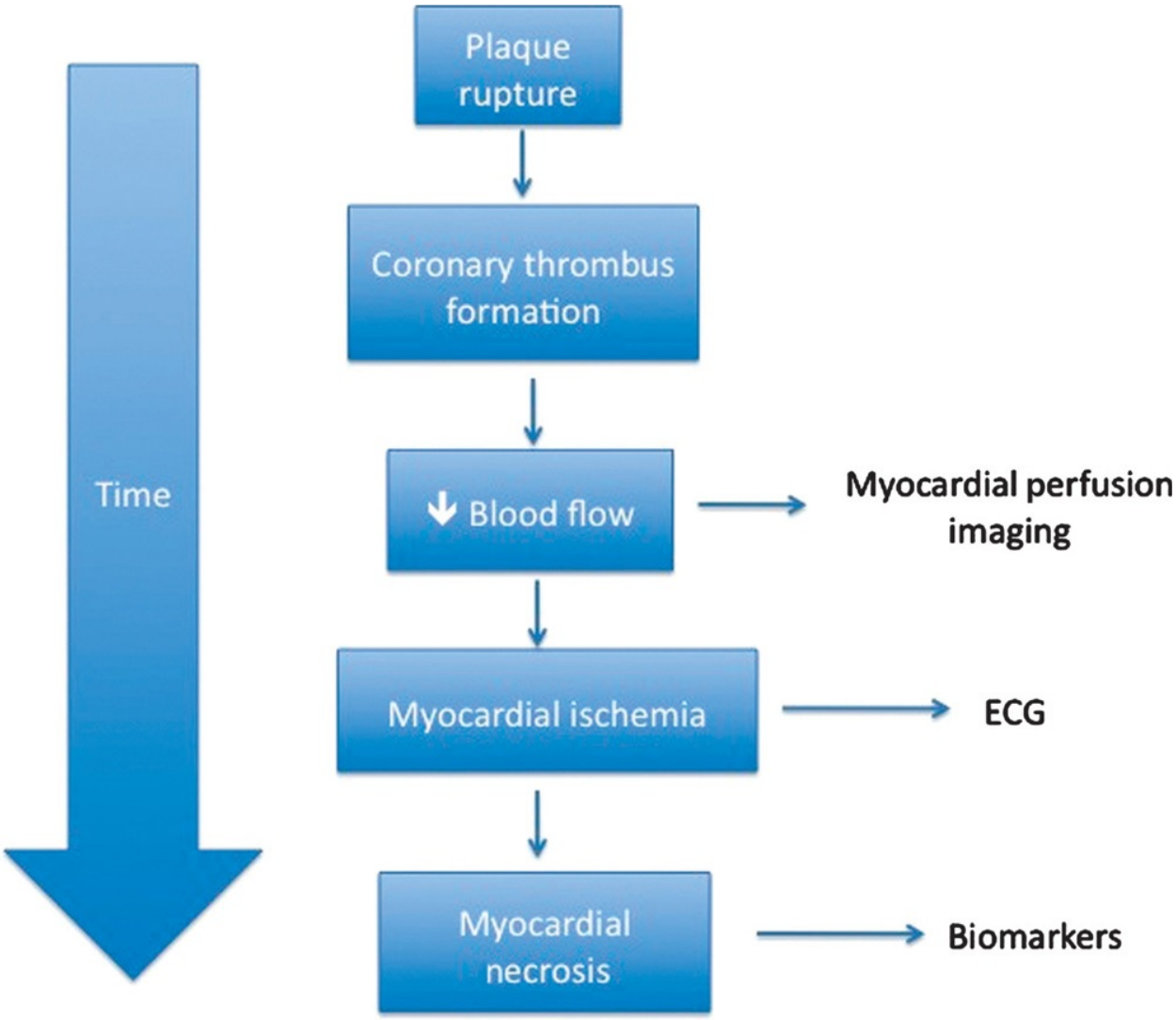

FIGURE 5.1 The ischemic cascade. ECG, electrocardiogram.

OVERVIEW OF SPECT MYOCARDIAL PERFUSION IMAGING

MPI was introduced into clinical practice in the 1970s as a tool to noninvasively assess for myocardial ischemia. In the 1980s, planar imaging gave way to the more robust SPECT imaging most commonly used today. The theory behind SPECT MPI relies on the fact that blood flows preferentially down the path of least resistance, that is, the vessel without coronary occlusion versus the vessel with coronary occlusion (**Figure 5.2**). When comparing myocardial regions with each other, a decrease in tracer uptake in a region is a sign of myocardial

hypoperfusion. SPECT MPI utilizes radiotracers whose activity can be detected with a special camera called a scintillation camera. The most commonly used radiopharmaceuticals are Thallium-201 (Tl-201), Technetium-99m (Tc-99m) sestamibi, and Tc-99m tetrofosmin. Radiopharmaceuticals contain atoms that undergo radioactive decay by emitting a particle that can be detected using a SPECT camera. Once injected intravenously, the radiotracer is taken up by the myocardium proportionally to regional coronary blood flow, and the relative "amount" of tracer in each region of the myocardium can be measured and imaged.

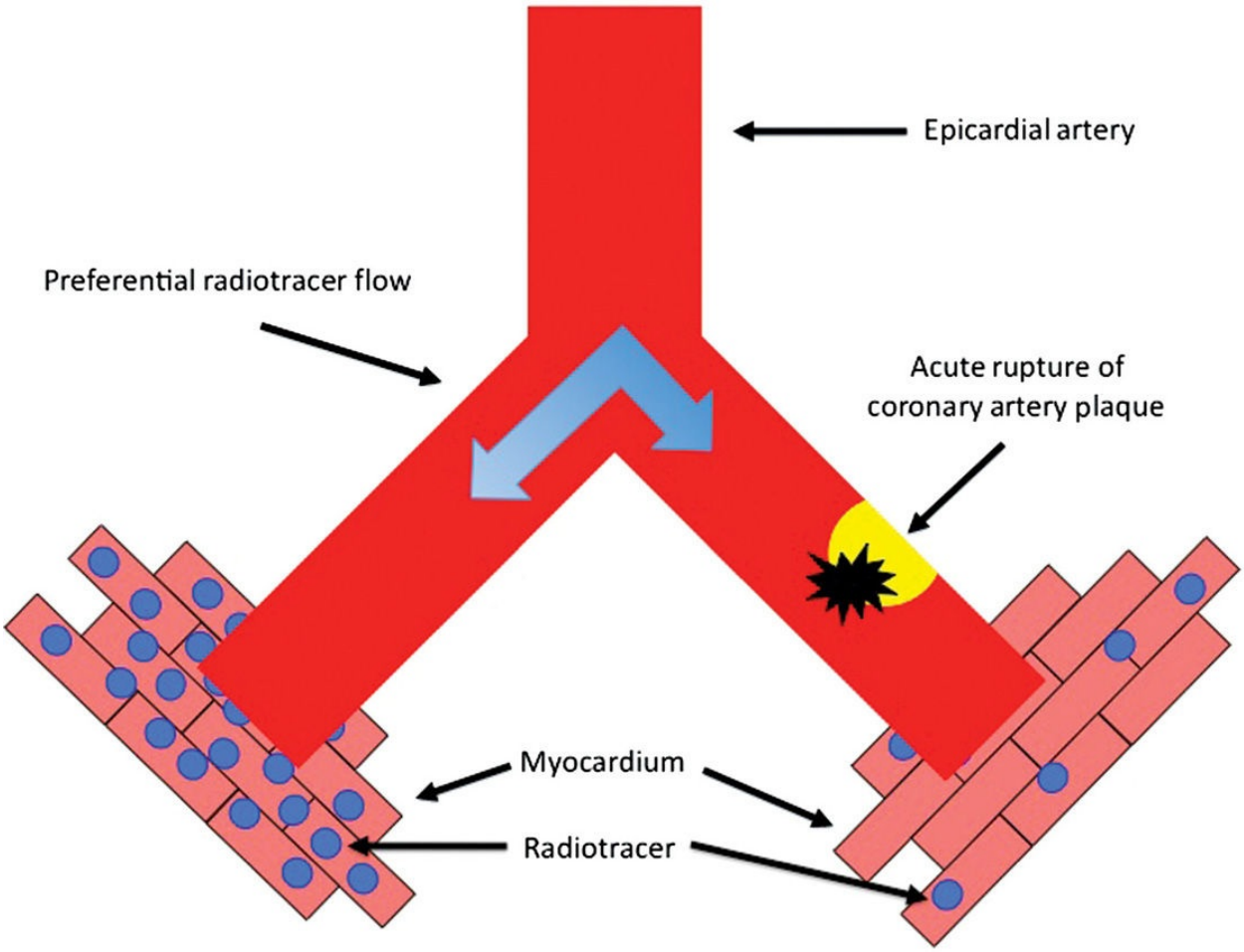

FIGURE 5.2 Differential myocardial radiotracer uptake in myocardium subtended by a normal coronary and a coronary with a ruptured atherosclerotic plaque.

SPECT CAMERA

The SPECT camera is designed to detect the radioactivity emitted from a patient

after injection of a radiotracer. After injection of the radiotracer, patients are placed in the camera and the images are acquired.

RADIOTRACERS

Radiotracers are tagged molecules that emit radioactivity. The ideal radiotracer has several features:

1. Linear relationship between myocardial uptake and blood flow.
2. High myocardial extraction rate.
3. Low extracardiac uptake.

The most commonly used radiotracers in nuclear cardiology are Tl-201 and Tc-99m. Tc-99m has several advantages over Tl-201, including a shorter half-life, higher energy photons, no redistribution, and availability on site from a Mo-99 generator or in unit doses from a local commercial radiopharmacy. The process whereby Tl-201 decays is called electron capture or isomeric transition (Tl-201 + e^- → Hg-201 + ϒ), whereas Tc-99m decays by a process called gamma decay (Tc-99m → Tc-99 + ϒ).

RESTING MYOCARDIAL PERFUSION IMAGING

MPI imaging is based on the concept that the injected radiotracer is taken up by the myocardium in proportion to the amount of blood flow that the myocardial region receives. If the blood flow to an area of myocardium is reduced at rest because of coronary occlusion, this area of the myocardium will receive less radiotracer relative to those areas in which blood flow is not reduced (**Figure 5.2**). The resulting SPECT images will have a decrease in tracer activity in the myocardial segments subtended by the diseased coronary artery. In patients with chest pain caused by ACS, there is rupture of coronary plaque, resulting in the formation of intracoronary thrombus and a subsequent decrease in myocardial blood flow to the myocardium supplied by that artery. On the other hand, in patients without coronary occlusion, there will be no decrease in blood flow to the myocardium, and no decrease in tracer activity will be seen.

STRESS MYOCARDIAL PERFUSION IMAGING

In patients with coronary artery disease but with preserved resting blood flow to the myocardium, MPI may appear normal at rest. Stress testing can be used to

diagnose physiologically significant coronary artery stenosis in these patients. Stress testing can be performed using exercise or pharmacologic agents. In nuclear cardiology, pharmacologic stress testing is typically performed using a vasodilator agent (such as adenosine, dipyridamole, and regadenoson). During exercise, there is disproportional increase in coronary blood flow to the nondiseased coronary arteries compared with the stenosed coronary arteries. Similarly, during vasodilator pharmacologic stress, coronary vasodilation and increase in blood flow are attenuated in areas supplied by stenosed coronary arteries. As a result, stress testing creates inhomogeneity in myocardial perfusion with decreased regional radiotracer uptake in patients with hemodynamically significant coronary artery disease that can be detected and quantified by MPI.

INTERPRETATION OF SPECT MYOCARDIAL PERFUSION IMAGING

By convention, SPECT images are displayed in three orientations: short axis, vertical long axis, and horizontal long axis (**Figure 5.3**). The left ventricle can be divided into the anterior wall, lateral wall, inferior wall, and septum. While interpreting stress SPECT MPI, images are displayed with the poststress images on the top line and the rest images below (**Figure 5.4**). The short axis images are displayed apex to base, followed by the vertical long axis and the horizontal long axis. As previously discussed, SPECT MPI measures relative blood flow to the various segments of the myocardium. When interpreting stress SPECT MPI, one compares the amount of tracer uptake on the stress images with the amount of tracer uptake in the rest images for each myocardial segment. Broadly speaking, if the tracer uptake is homogeneous in both the rest and stress images, there is no decrease in blood flow to the myocardium, that is, no ischemia or scar (**Figure 5.4**). However, if there is a decrease in perfusion on the stress images in a region of normal tracer uptake on the resting images, that is termed a “reversible” defect and may be indicative of ischemia (**Figure 5.5**). If there is a matched in tracer uptake in both the stress and rest images, that is termed a “fixed” defect and may be indicative of myocardial scar (**Figure 5.6**).

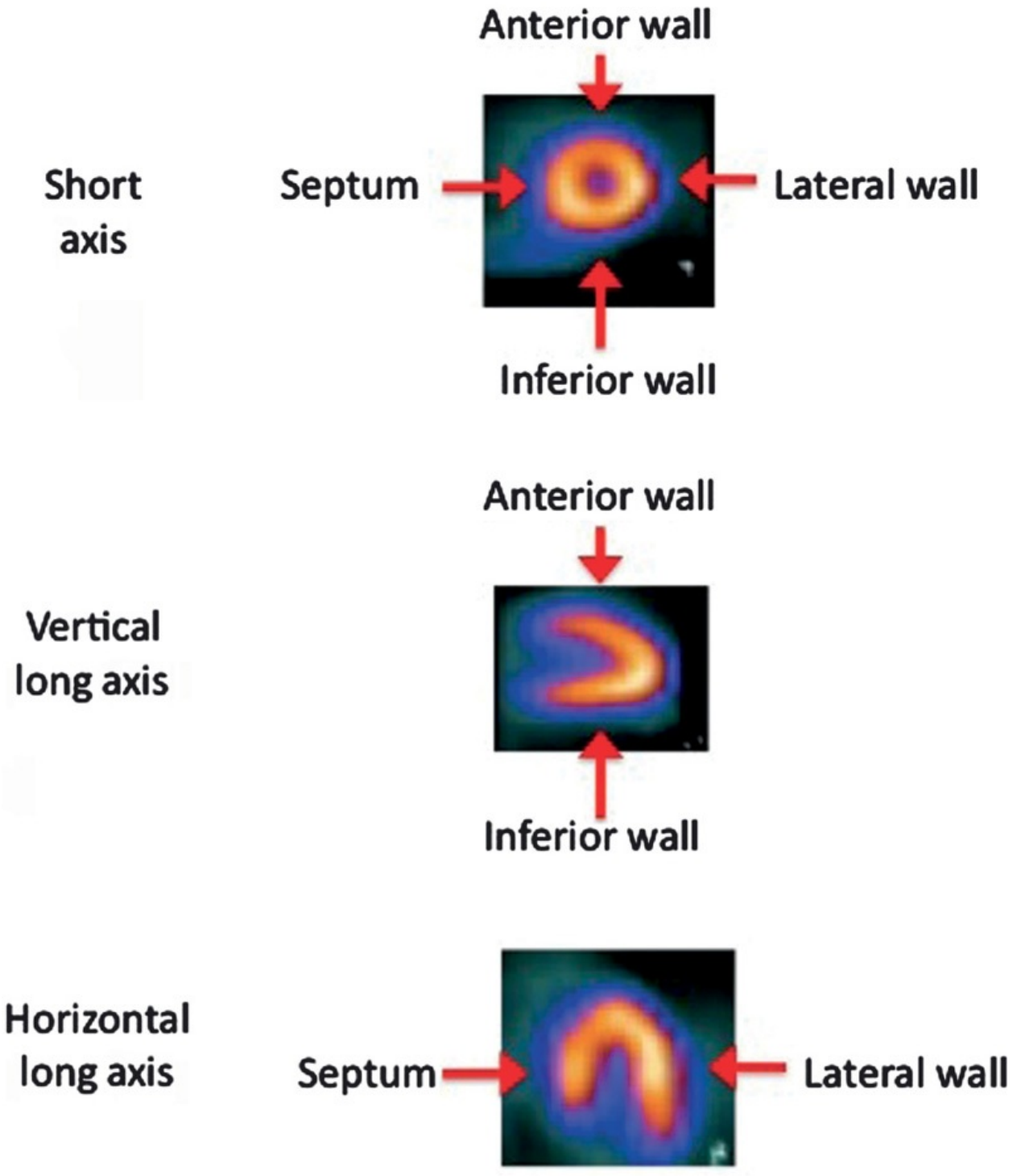

FIGURE 5.3 Short-axis, vertical long-axis, and horizontal long-axis slices with labeled myocardial regions.

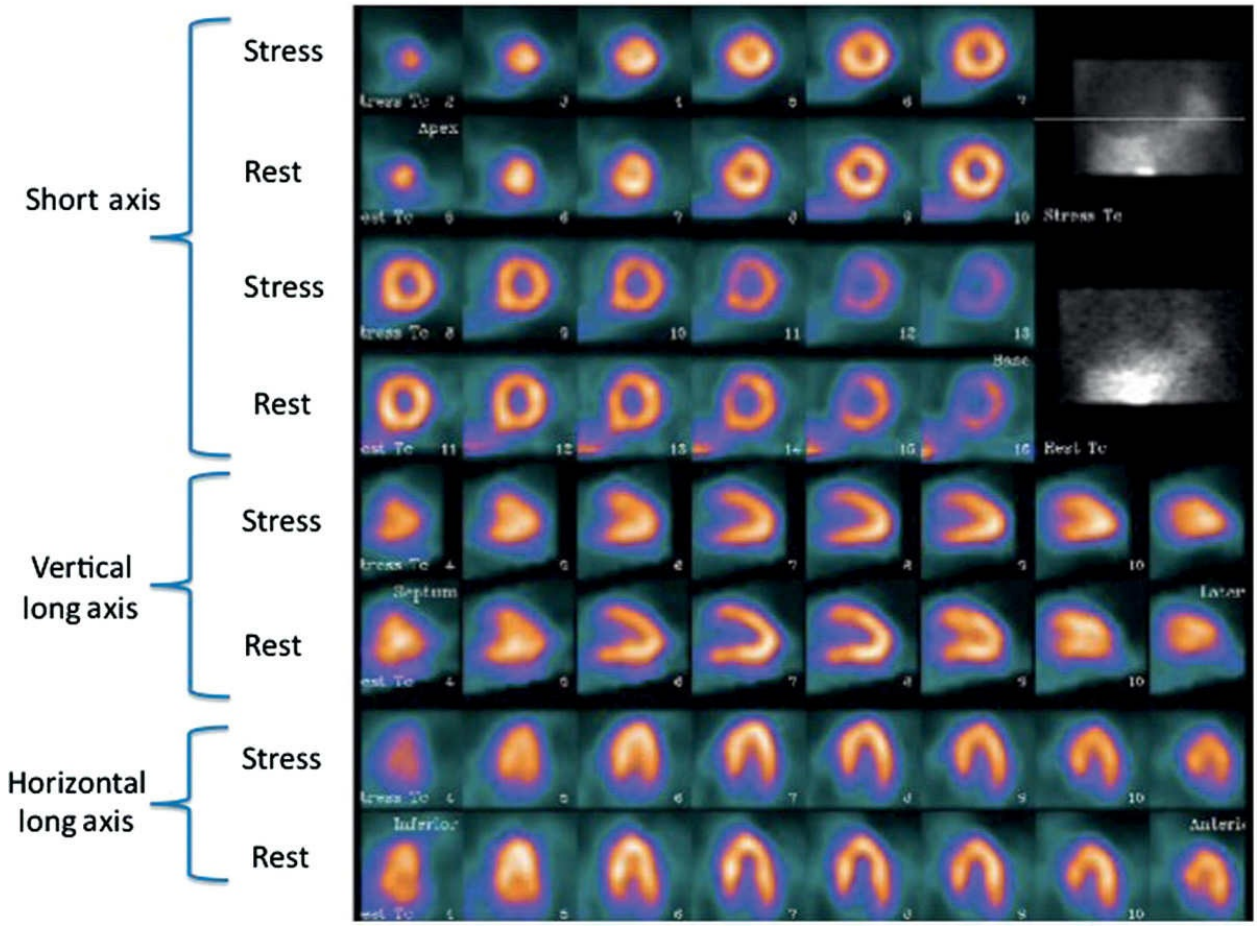

FIGURE 5.4 Normal single photon emission computed tomography myocardial perfusion imaging with homogeneous tracer uptake.

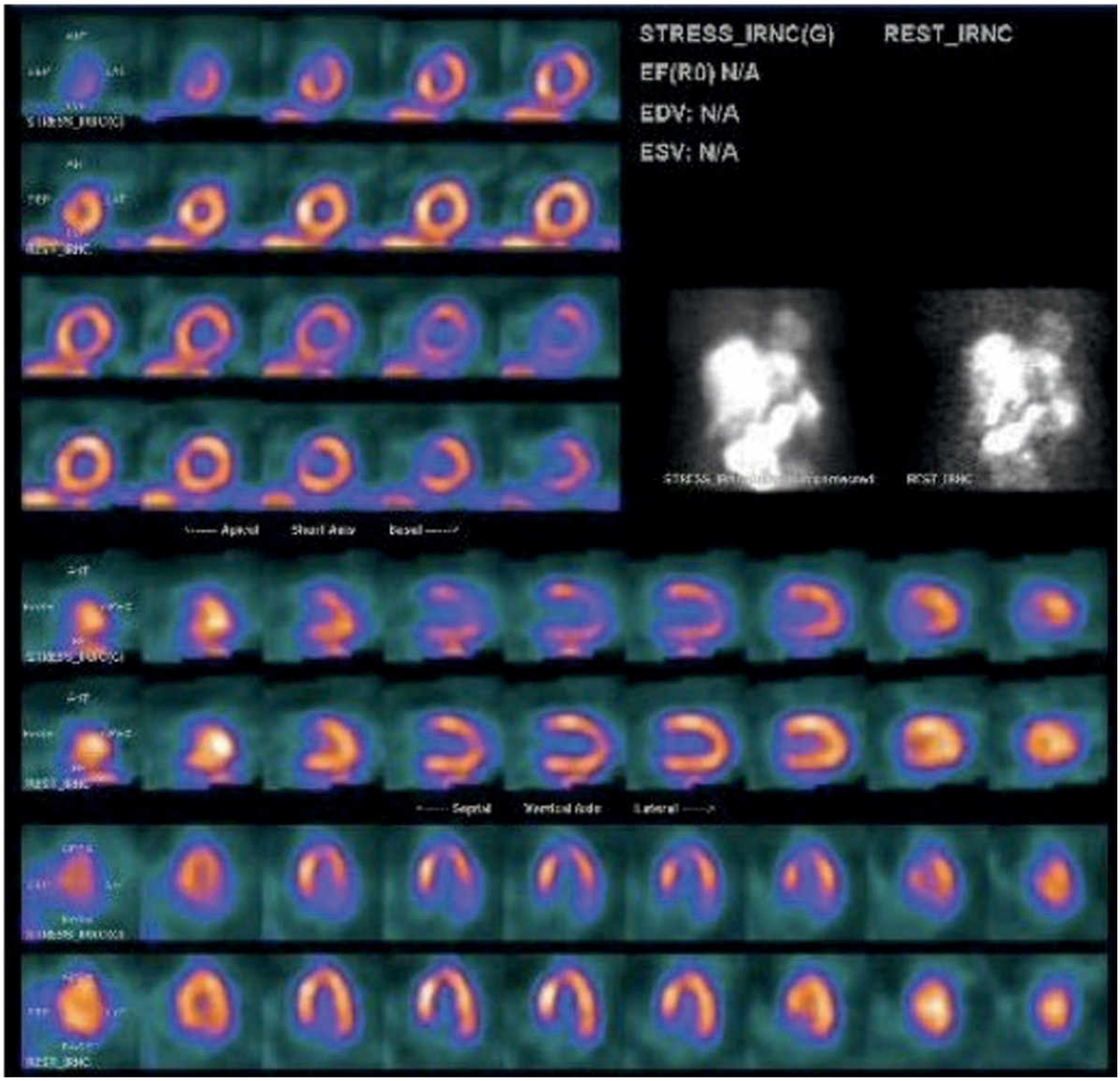

FIGURE 5.5 An example of a reversible perfusion defect. A decrease in tracer uptake is noted in the apical region that reverses on the resting images. This is a reversible perfusion defect and is indicative of ischemia in the distribution of the left anterior descending artery.

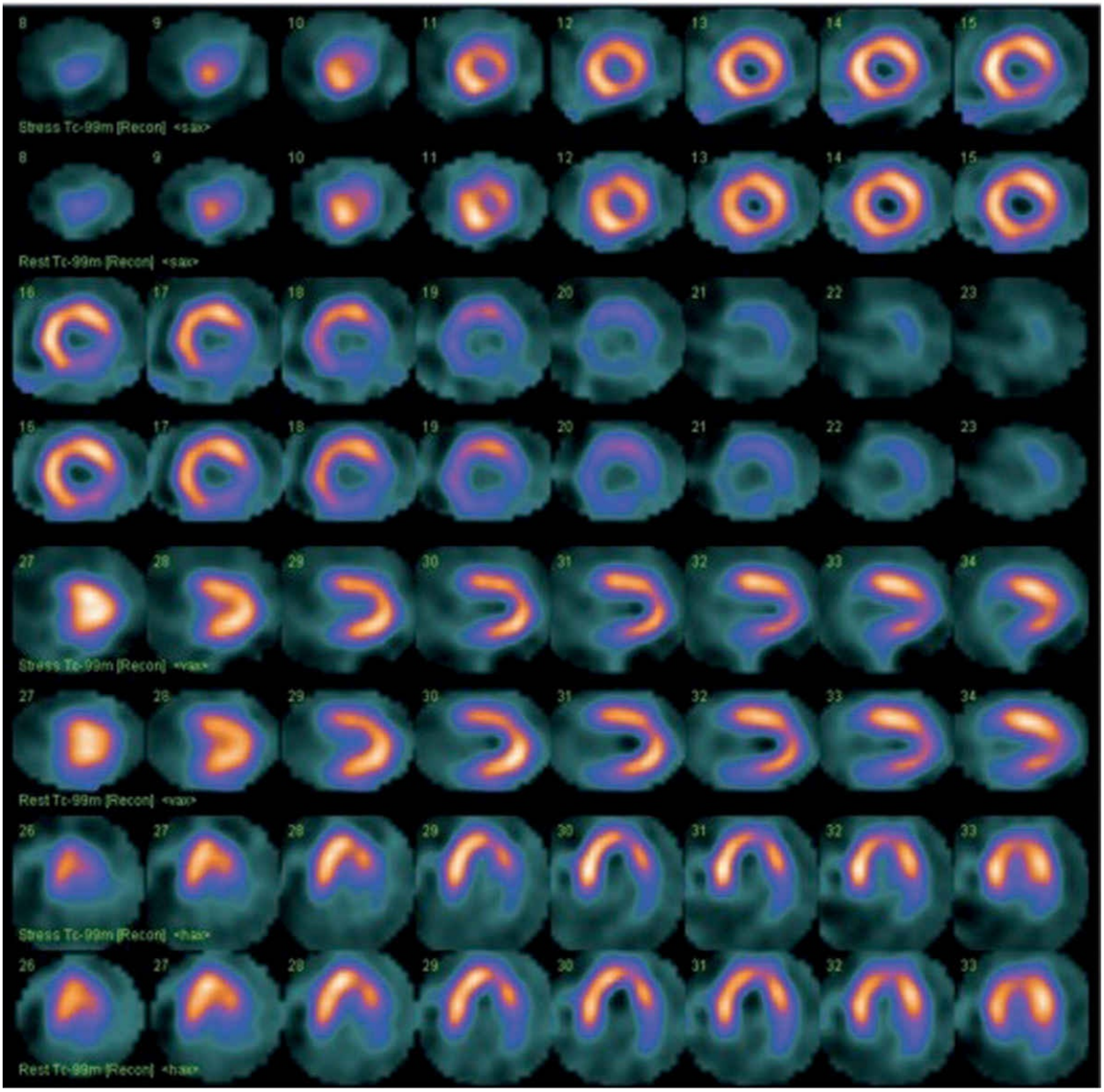

FIGURE 5.6 An example of a fixed perfusion defect. There is a decrease in tracer uptake noted in the lateral and inferior walls at the midventricle and at the base of the stress images. This finding is also noted in the rest images and is termed a fixed defect indicative of myocardial scar.

VIABILITY ASSESSMENT

In patients with established coronary artery disease and ischemic cardiomyopathy, resting wall motion abnormalities may be present, signifying areas of noncontractile myocardium. However, noncontractile myocardium is not synonymous with scarred and nonviable myocardium. In patients with acute ischemic event, the myocardium can still be viable but stunned (ie regionally

decreased contractile function) and may recover contractility over time. In patients with a high-degree coronary stenosis and limited resting blood flow, the myocardium can be in a state of hibernation and can maintain viability. With the restoration of blood flow, the hibernating myocardium can return to its contractile state and improve systolic heart function. SPECT imaging can discern viable myocardial tissue from myocardial scar by taking advantage of the redistributive properties of Tl-201. When Tl-201 is injected, it is initially distributed and taken up by the myocardium with good blood flow. Myocardial segments with limited blood flow that are viable and those myocardial segments that are scarred do not take up Tl-201 initially. Over several hours, Tl-201 will redistribute and be taken up by the myocardium that is alive but has limited blood flow, that is, the viable myocardium. Initial defects on imaging study may show reversibility upon redistribution imaging, and the extent of viable myocardium can be assessed.

ROLE OF SPECT MYOCARDIAL PERFUSION IMAGING IN PATIENTS WITH SUSPECTED ACUTE CORONARY SYNDROME

RESTING SPECT MYOCARDIAL PERFUSION IMAGING

The ideal test in patients with suspected ACS enables the clinician to diagnose it early in the course of the disease as well as stratify those patients who are at low risk and can be safely discharged compared with those who are at high risk and need further workup. As previously stated, the combination of history, physical examination, ECG, and serum troponin may be indeterminate at the time of initial evaluation, and the clinician cannot confidently determine whether the patients are experiencing an ACS. Resting SPECT MPI protocols have been developed and well studied in patients with suspected ACS having active ongoing chest pain. Multiple studies have shown that resting SPECT MPI can identify patients undergoing ACS and also those who can be safely discharged. Heller et al. studied 357 patients who presented with chest pain suspicious for myocardial ischemia and a non-diagnostic EKG. Patients underwent rest SPECT MPI with Tc-99m.[1] Among the 20 patients with myocardial infarction, 18 (90%) had abnormal SPECT images, whereas 2 had normal SPECT images, for a negative predictive value of 99%. In this study, SPECT MPI gave incremental diagnostic value over clinical and ECG variables alone, and an abnormal SPECT

was the strongest predictor of myocardial infarction. The Emergency Room Assessment of Sestamibi for Evaluation of Chest Pain (ERASE) trial was a prospective multicenter randomized trial of 2475 patients who presented with chest pain and a normal or nondiagnostic ECG.[2] The patients were randomized to usual care or usual care plus rest SPECT MPI. The authors report that there was no difference in the rate of hospitalization between the study arms among the patients with myocardial infarction. However, among those without ACS, fewer patients were hospitalized in the rest SPECT strategy than in standard care (42% vs 52%).

TRIAGING LOW-RISK PATIENTS HAVING CHEST PAIN WITH SUSPECTED ACUTE CORONARY SYNDROME

Low-risk patients with chest pain evaluated in the acute settings often have nondiagnostic initial ECG and negative cardiac biomarkers. Stress SPECT MPI can be used safely in this patient group for diagnosis and risk stratification. Multiple studies have addressed the role of different imaging modalities in assessing low-risk patients with chest pain in the emergency department and those admitted to the hospital. Most of the studies compared coronary computed tomography (CT) angiography with different stress testing modalities (such as traditional stress SPECT MPI, stress-only SPECT MPI, and stress echocardiography).[3–6] The studies showed largely comparable outcomes among patients assigned to different modalities, and the decision to proceed with a particular test should be determined by patient-specific and institution-specific characteristics. SPECT MPI tests the functionality of the heart (whether occluded coronary arteries cause ischemia of wall segments). In contrast, CTA shows the anatomy of the coronary arteries (whether there is any stenosis) but provides no information about the physiologic significance of the stenosis. Thus, both modalities can be used in complementary ways.[7]

ROLE OF SPECT IN MANAGING PATIENTS POST–MYOCARDIAL INFARCTION

Stress SPECT MPI can also be used in hemodynamically stable patients within 3 months of myocardial infarction to assess for the presence and degree of ischemia and for risk stratification purposes. It can also be used to evaluate for stent thrombosis or restenosis in patients who become symptomatic after revascularization. In general, stress testing is not used in asymptomatic patients

if they were fully revascularized, but it can be considered in asymptomatic patients with no or partial revascularization to evaluate for the usefulness of additional revascularization.[8] Myocardial perfusion SPECT using adenosine or dipyridamole infusion can be safely performed 48 hours post–myocardial infarction once the patient is hemodynamically stable.

ROLE OF RADIONUCLIDE IMAGING IN ASSESSING MYOCARDIAL VIABILITY

Thallium-201 SPECT can be used in patients with ischemic cardiomyopathy to assess viability, with the goal of revascularizing viable myocardium. Often, patients admitted to the hospital with heart failure symptoms are found to have new reductions in left ventricular ejection fraction (LVEF) without a known ischemic insult. These patients may have had silent myocardial infarction or may not have presented to the hospital when they had an acute myocardial infarction. Sometimes, patients with newly diagnosed reductions in LVEF may have nonischemic cardiomyopathy caused by long-standing hypertension or myocarditis, in which case revascularization would not be useful. SPECT MPI is useful in differentiating between ischemic and nonischemic cardiomyopathy. Other tests that are used to distinguish viable myocardium from irreversible injury include positron emission tomography, dobutamine echocardiography, and cardiac magnetic resonance.[9] Accumulating evidence is inconclusive about the role of routine viability assessment in patients with ischemic cardiomyopathy, but it can be useful in certain clinical scenarios.[10]

CONCLUSION

Although the cardiac imaging modalities have been rapidly evolving over the past decade, SPECT MPI has been shown to be a useful tool in diagnosing and risk stratifying patients with suspected ACS. It can also be occasionally used in patients post–myocardial infarction and for viability assessment in patients with ischemic cardiomyopathy.

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Patient and Family Information for: USE OF RADIONUCLIDE IMAGING IN ACUTE CORONARY SYNDROME

Radionuclide imaging, often called nuclear imaging, has been used since the 1970s to image the heart. Radionuclide imaging uses radiopharmaceuticals that are given via intravenous injection. One component of a radiopharmaceutical is a tracer, a substance that is taken up from the blood by the heart muscle. The amount of the tracer extracted from the blood by the heart muscle is proportional to the amount of the blood flow to the heart muscle. The radiopharmaceutical is a radioactive substance that emits photons that can be captured by a special camera. The information from the camera allows physicians to take pictures of the heart muscle. Essentially, those pictures represent “the map” of blood flow to the heart muscle and identify the areas where the blood flow is compromised because of a blockage in the blood vessels supplying the heart.

Although nuclear imaging employs radioactive substances, the dosage given to an individual patient is relatively small. Mostly, it is in the range of radioactivity comparable to other imaging procedures such as a CT scan and is considered safe. The injection is given by a technician or a doctor. The patient is then imaged by the camera that detects the photons emitted by the radiotracer. This part of the test is crucial: the technician explains to the patient the position they need to maintain and the necessity of staying still while the pictures are obtained. The patient needs to follow the instructions carefully so that high-quality images can be obtained.

Heart attacks are caused by a decrease in the blood flow that nourishes the heart muscle. If blood flow to a part of the heart muscle is blocked, the patient

will have a heart attack and the heart muscle can die. In patients who experience chest pain, it is often difficult to determine if the pain is a sign of heart disease. The initial tests for patients with chest pain include an ECG and blood tests. If these tests are inconclusive, the physician may opt to perform radionuclide imaging. Radionuclide imaging maps the blood flow to the heart and is useful in identifying a blood vessel blockage that may signify a heart attack. In patients who have experienced a heart attack, radionuclide imaging enables physicians to determine who will benefit from procedures that restore blood flow to the heart muscle.

The idea behind the stress test is to compare resting images of the heart to those obtained after the stress test. The stress portion can be performed with either exercise or medication. During an exercise stress test, the patient is asked to exercise on a treadmill or a stationary bicycle. If the patient cannot exercise or the physician thinks it is unsafe for the patient to exercise, a medication can be used. The physician or a trained health care professional is always present in the room for the stress test. In general, stress testing is safe and well tolerated, although some patients may experience brief side effects (headache, nausea, chest discomfort) from the medication. Serious events, including heart attacks and heart rhythm disturbances, are rare.

During radionuclide stress testing, two sets of heart images—the rest images and the stress images—are usually obtained as previously described. By comparing the two sets of images, the physician can determine whether there is an impairment of blood flow to the heart. If significant blood flow impairment is identified by the stress test, the patient may be referred for an invasive procedure called cardiac catheterization.

6

Ronen Rubinshtein
Harvey Hecht

Computed Tomographic Angiography in Acute Cardiac Care

INTRODUCTION

Contrast-enhanced multidetector computed tomography (MDCT), which provides high-quality noninvasive images of the heart, great vessels, and coronary vasculature, has been shown to be useful and reliable in the triage of patients with chest pain of possible ischemic origin and specifically in the diagnosis of acute coronary syndrome. Current generation computed tomography (CT) scanners (64-slice and higher) require minimal patient cooperation (short breath hold) and have improved image quality (better spatial and temporal resolution) and high diagnostic accuracy. MDCT can visualize coronary plaques and is also gaining a role in the evaluation of coronary stents and bypass grafts and for evaluation of patients undergoing structural or electrophysiologic cardiac interventions.

TECHNICAL CONSIDERATION

New generation CT scanners allow rapid scanning of the heart by a high gantry

rotation speed and wider coverage of the field of view than initial scanners, thus allowing a “freeze” in cardiac motion and overcoming many previously observed breathing artifacts. Some scanners allow a single beat acquisition and very rapid reconstruction of scanned data to be presented to the reader.

However, despite these advancements, it is still recommended to lower the patient heart rate to <65 beats/min to optimize image quality. In the absence of contraindications, it is also recommended to administer sublingual nitroglycerin just prior to scanning to allow coronary vasodilation and improved image quality.

The scan itself is performed using electrocardiogram (ECG) gating to image and reconstruct the heart and the coronary vessels during a certain phase in the cardiac cycle, usually diastole.

About 50 to 100 mL of intravenous contrast media (iodine-based) is typically used to allow opacification of the coronary vessels.

After scanning, the data can be viewed and manipulated on a PC-based or dedicated workstation that utilizes sophisticated software to optimize analysis and overcome artifacts.

CLINICAL USEFULNESS OF CARDIAC CT

NONCONTRAST CALCIUM SCORING

Quantitative assessment of the extent of coronary arterial calcification by electron beam CT had been available for several years before the advent of MDCT. When categorized according to a defined scoring system (eg, the Agatston calcium score), calcification can predict subsequent coronary events in various cohorts. However, calcium scoring is usually performed for screening asymptomatic subjects, especially those with intermediate risk for future cardiovascular adverse events. Those are the patients in whom calcium scoring may identify or rule out definite coronary atherosclerosis (coronary calcifications) and may impact the physician’s decision in regard to primary preventive therapies.

CONTRAST-ENHANCED CARDIAC CT APPLICATIONS

Coronary CT angiography (CCTA) is used to diagnose coronary atherosclerosis and coronary narrowing. CCTA is considered the noninvasive test with the highest sensitivity to diagnose coronary stenosis when compared to invasive

coronary angiography as the reference standard. This test has a very high negative predictive value (>98%), making it a useful tool to rule out coronary stenosis. On the other hand, because of motion artifacts and coronary calcifications, the positive predictive value is somewhat lower but still very good (85% to 92%).

One of the areas where CCTA has been shown to be especially useful is in the emergency department setting. Patients with acute chest pain but without high-risk features (such as elevated troponin, ECG changes indicative of ischemia, or recurrent/ongoing chest pain) are good candidates for CCTA. A normal or near-normal scan has been shown to be safe and effective in shortening hospital stay (**Figure 6.1**). Infrequently, a "triple rule out" protocol may be used to exclude pulmonary emboli or thoracic aortic dissection in addition to coronary stenosis.

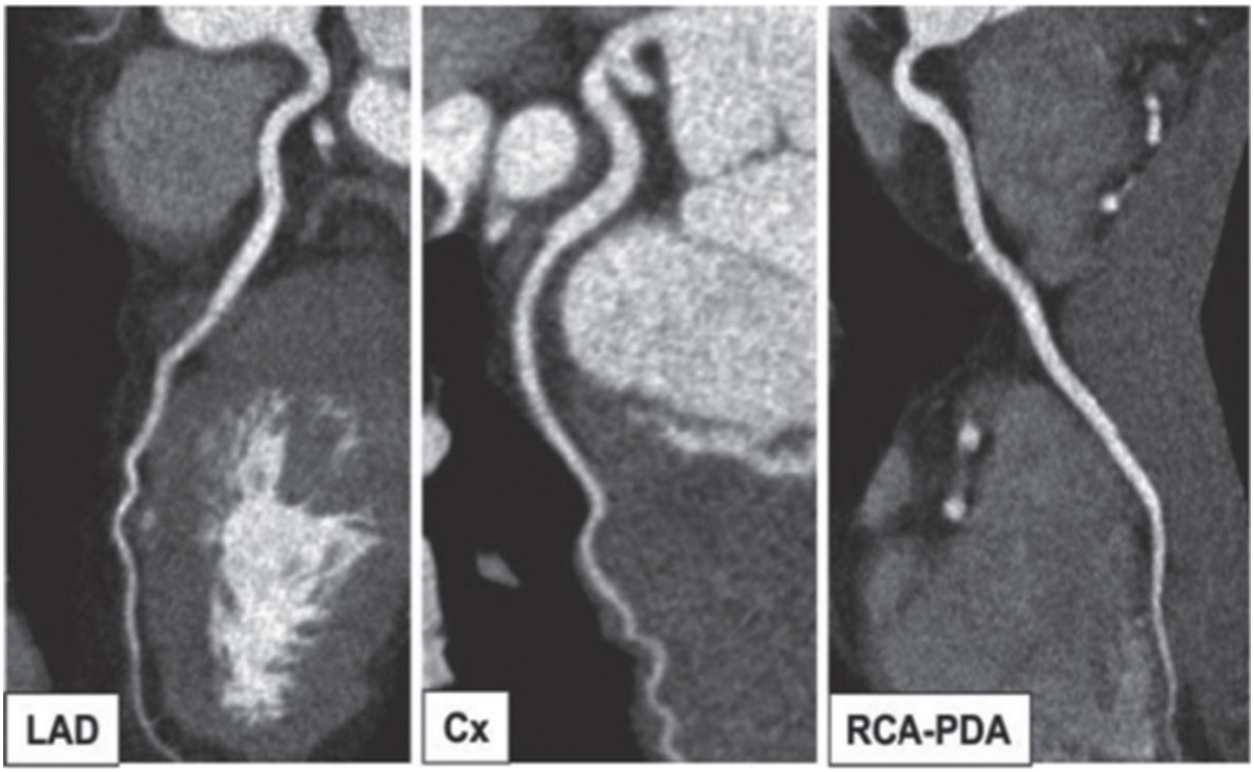

FIGURE 6.1 Normal coronary arteries by coronary computed tomography angiography in a patient with acute chest pain. Cx, circumflex coronary artery; LAD, left anterior descending artery; PDA, posterior descending artery; RCA, right coronary artery.

In contrast to conventional invasive coronary angiography, which allows visualization of the coronary lumen but provides only minimal details of the coronary plaque, CCTA can demonstrate the details of coronary plaques

(noncalcified/calcified/mixed), and several features that may be demonstrated by CCTA have been suggested to be associated with higher risk of adverse coronary events. Those include low attenuation plaque (<30 Hounsfield units), spotty calcifications (within a non-calcified plaque), and “napkin ring” sign (**Figure 6.2**). Other features shown to be of clinical relevance are plaque eccentricity and positive remodeling.

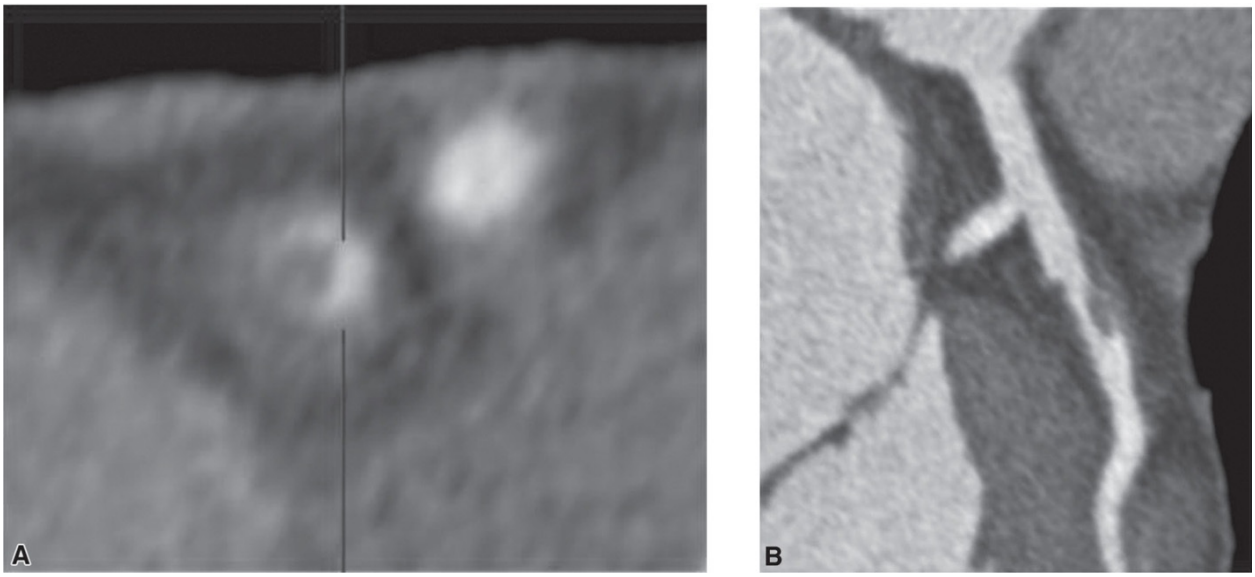

FIGURE 6.2 Cross-section view (A) and long axis (multiplanar reformation) (B) of the left anterior descending coronary artery showing a possible ruptured plaque (napkin ring sign) and stenosis.

The presence of nonobstructive coronary atherosclerosis as well as obstructive disease on CCTA has been shown to be of prognostic value. The higher the burden of disease, the higher the likelihood of future cardiovascular events (and vice versa).

Recently, it has been shown that CCTA can also be used to evaluate the physiologic significance of a coronary stenosis (computed tomographic fractional flow reserve) using complex models of computational flow dynamics.

Of note, this may also be shown by using CT for assessment of myocardial perfusion (rest or stress induced), where myocardial hypoenhancement limited to a vessel territory may be indicative of ischemia or infarction.

CCTA is also very useful in the characterization of coronary anomalies or myocardial bridging.

Beyond evaluation of the native coronary vessels, CCTA can evaluate the patency of coronary stents, especially stents ≥3 mm wide, albeit with reduced

diagnostic accuracy related to metallic artifacts (**Figure 6.3**). Diagnosis is also possible in patients with coronary bypass grafts (**Figure 6.4**), but again with somewhat reduced accuracy because of the presence of metallic clips in the distal anastomosis and the diffuse nature of calcified coronary atherosclerosis in those patients.

FIGURE 6.3 Patent stent in the left anterior descending coronary artery demonstrated by coronary computed tomography angiography.

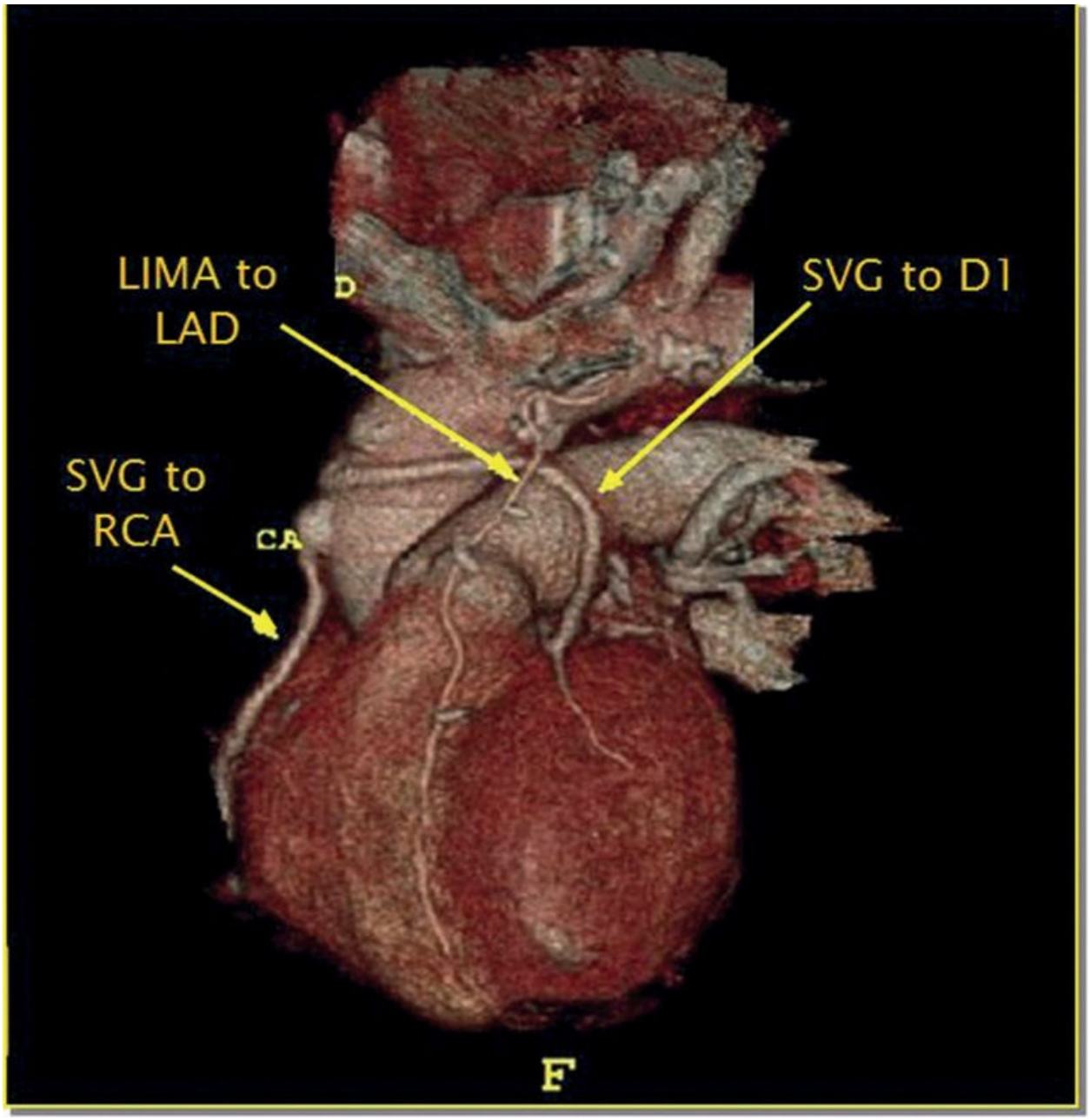

FIGURE 6.4 Volume-rendered image of the heart in a patient with a history of coronary bypass grafting. D1, first diagonal batch; LAD, left anterior descending artery; RCA, right coronary artery; SVG, saphenous vein graft; LIMA, left internal mammary artery.

An increasing indication is the evaluation of cardiac structures before interventional cardiac procedures, most importantly for evaluation of the aortic valve and root before transarterial aortic valve replacement or evaluation of the pulmonary veins draining into the left atrium before pulmonary vein isolation (ablation) in patients with atrial fibrillation.

SUMMARY

Cardiac CT is a powerful diagnostic tool, mostly used for the diagnosis of obstructive coronary atherosclerosis in symptomatic patients. Technical advancement in recent years has led to a significant reduction in radiation exposure to patients without compromising image quality. Several future trends in the development of cardiac CT systems may also increase its usefulness for clinical use. Those include the development of dual energy or spectral CT systems that may improve tissue diagnosis and the rapid development in the field of fusion imaging allowing visualization (even in real time) of images derived from two different modalities (eg, two-dimensional angiography and CT or echocardiography and CT).

The exponential increase in the number of structural heart interventions and the increased usefulness that may be derived from combining anatomic and physiologic assessment of the coronary tree are expected to accelerate the use of this imaging modality for cardiovascular diagnosis.

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Patient and Family Information for: COMPUTED TOMOGRAPHIC ANGIOGRAPHY IN ACUTE CARDIAC CARE

Coronary computed tomographic angiography (CTA) is a simple X-ray study involving injection of approximately 6 ounces of contrast containing iodine into an arm vein while the patients hold their breath for 5 seconds. This will be accompanied by a warm sensation throughout the body some patients may find this mildly uncomfortable.

If there is a known allergy to intravenous contrast, premedication with steroids and diphenhydramine will be required. There is no relationship between seafood and contrast allergies. Patients will be able to leave unaccompanied immediately afterward. The X-ray machine is open and does not produce claustrophobia. The CTA provides very detailed pictures of the coronary arteries that are very accurate in determining whether there is narrowing in the arteries. It also produces excellent pictures of the aorta and heart muscle.

7

Arpit Shah
Angela Palazzo

Coronary Angiography and Percutaneous Coronary Intervention

CARDIAC CATHETERIZATION AND ANGIOGRAPHY

Sones and colleagues performed the first coronary arteriography in 1959. Since its advent, cardiac catheterization and coronary angiography have remained the gold standard for diagnosis of coronary artery disease (CAD) as well as structural and valvular heart disease. Although advances in imaging, including cardiac computed tomography and cardiac magnetic resonance imaging, have enhanced the diagnosis of many forms of heart disease, coronary angiography along with advances in percutaneous coronary intervention (PCI) and structural heart disease intervention has revolutionized our ability to manage patients with ischemic, non-ischemic and structural heart disease.

Indications

The indications for cardiac catheterization and coronary angiography are varied. They include acute coronary syndromes such as ST-elevation myocardial infarction (STEMI) as well as non-ST-elevation myocardial infarction (NSTEMI), unstable coronary syndromes without infarction, heart failure,

valvular heart disease, arrhythmia, and sudden cardiac death. In some of these instances, the procedure will be for diagnostic purposes only, but for others, it will be a prelude to intervention.

STABLE ISCHEMIC HEART DISEASE

Coronary angiography is performed in patients with stable ischemic heart disease (SIHD) either as an initial strategy to assess risk or after a workup with noninvasive testing. The 2012 and 2014 multisociety guidelines on diagnosis and management of patients with SIHD have recommended diagnostic angiography based on clinical presentation, symptoms, and findings on noninvasive testing (**Tables 7.1 and 7.2**).[1, 2]

TABLE 7.1 Noninvasive Risk Stratification in Patients With Stable Ischemic Heart Disease[1, 2]

HIGH RISK (>3% ANNUAL DEATH OR MI)
Severe resting LV dysfunction (LVEF<35%) not readily explained by noncoronary causes
Resting perfusion abnormalities ≥10% of the myocardium in patients without prior history or evidence of MI
Stress ECG findings including ≥2 mm of ST-segment depression at low workload or persisting into recovery, exercise-induced ST-segment elevation, or exercise-induced VT/VF
Severe stress-induced LV dysfunction (peak exercise LVEF <45% or drop in LVEF with stress ≥10%)
Stress-induced perfusion abnormalities encumbering ≥10% myocardium or stress segmental scores indicating multiple vascular territories with abnormalities
Inducible wall motion abnormality (involving >2 segments or 2 coronary beds)
Wall motion abnormality developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate<120 beats/min)
CAC score >400 Agatston units
Multivessel obstructive CAD (≥70% stenosis) or left main stenosis ≥50% stenosis) on CCTA
INTERMEDIATE RISK (1-3% ANNUAL DEATH OR MI)
Mild/moderate resting LV dysfunction (LVEF 35% to 49%) not readily explained by noncoronary causes
Resting perfusion abnormalities in 5% to 9.9% of the myocardium in patients without a history or prior evidence of MI
≥1 mm of ST-segment depression occurring with exertional symptoms
Stress-induced perfusion abnormalities encumbering 5% to 9.9% of the myocardium or stress segmental scores (in multiple segments) indicating 1 vascular territory with abnormalities but without LV dilation
Small wall motion abnormality involving 1 to 2 segments and only 1 coronary bed
Coronary Artery Calcium score 100 to 399 Agatston units
One vessel CAD (≥70% stenosis) or moderate CAD stenosis (50% to 69% diameter stenosis) of CCTA in ≥2 arteries on CCTA
LOW RISK (< 1% ANNUAL DEATH OR MI)
Low-risk treadmill score (score ≥5) or no new ST segment changes or exercise-induced chest pain symptoms; when achieving maximal levels of exercise
Normal or small myocardial perfusion defect at rest or with stress encumbering <5% of the myocardium
Normal stress or no change of limited resting wall motion abnormalities during stress
CAC score <100 Agatston units
No coronary stenosis >50% on CCTA

CAC, coronary artery calcium; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 7.2 Indications for Coronary Angiography in Stable Ischemic Heart Disease[1, 2]

INDICATIONS FOR CORONARY ANGIOGRAPHY IN STABLE ISCHEMIC HEART DISEASE			
Class I	***Class IIA***	***Class IIB***	***Class III***
Coronary angiography is useful in patients with presumed SIHD who have unacceptable ischemic symptoms despite GDMT and who are amenable to, and candidates for, coronary revascularization. (Level of Evidence: C)	Coronary angiography is reasonable to further assess risk in patients with SIHD who have depressed LV function (Ejection Fraction <50%) and moderate risk criterion noninvasive testing with demonstrable ischemia. (Level of Evidence: C)	Coronary angiography might be considered in patients with stress test results of acceptable quality that do not suggest the presence of CAD when clinical suspicion of CAD remains high and there is a high likelihood that the findings will result in important changes to therapy. (Level of Evidence: C)	Coronary angiography for risk assessment is not recommended in patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbidities or individual preferences. (Level of Evidence: B)
Patients with SIHD who have survived sudden cardiac death or potentially life-threatening ventricular arrhythmia should undergo coronary angiography to assess cardiac risk. (Level of Evidence: B)	Coronary angiography is reasonable to further assess risk in patients with SIHD and inconclusive prognostic information after noninvasive testing or in patients for whom noninvasive testing is contraindicated or inadequate. (Level of Evidence: C)		Coronary angiography is not recommended to further assess risk in patients with SIHD who have preserved LV function (Ejection Fraction >50%) and low-risk criteria on noninvasive testing. (Level of Evidence: B)
Patients with SIHD who develop symptoms and signs of heart failure should be evaluated to determine whether coronary angiography should be performed for risk assessment. (Level of Evidence: C)	Coronary angiography for risk assessment is reasonable for patients with SIHD who have unsatisfactory quality of life because of angina, have preserved LV function (Ejection Fraction >50%), and have intermediate risk criteria on noninvasive testing. (Level of Evidence: C)		Coronary angiography is not recommended to assess risk in patients who are at low risk according to clinical criteria and who have not undergone noninvasive risk testing. (Level of Evidence: C)
Coronary arteriography is recommended for patients with SIHD whose clinical	Coronary angiography is reasonable to define the extent and severity of CAD in patients with suspected SIHD whose		Coronary angiography is not recommended to

characteristics and results of noninvasive testing indicate a high likelihood of severe IHD and when the benefits are deemed to exceed risk. (Level of Evidence: C)	clinical characteristics and results of noninvasive testing (exclusive of stress testing) indicate a high likelihood of severe IHD and who are amenable to, and candidates for, coronary revascularization. (Level of Evidence: C)	assess risk in asymptomatic patients with no evidence of ischemia on noninvasive testing. (Level of Evidence: C)
	Coronary angiography is reasonable in patients with suspected symptomatic SIHD who cannot undergo diagnostic stress testing or have indeterminate or nondiagnostic stress tests, when there is a high likelihood that the findings will result in important changes to therapy. (Level of Evidence: C)	

CAD, coronary artery disease; GDMT, guideline-directed medical therapy; IHD, ischemic heart disease; LV, left ventricular; SIHD, stable ischemic heart disease.

REDUCED LEFT VENTRICULAR EJECTION FRACTION

Coronary angiography is considered reasonable when ischemia may be a contributing factor for heart failure to assess the patency of coronary arteries.[3] This may be part of a workup that includes echocardiography, viability studies, and MRI.

SUDDEN CARDIAC DEATH OR VENTRICULAR ARRHYTHMIA

Coronary angiography is an important tool in the assessment of CAD in survivors of cardiac arrest and patients with life-threatening ventricular arrhythmia.[4] If cardiac arrest is associated with ST elevations, coronary angiography should be performed emergently.

PREOPERATIVE CORONARY ANGIOGRAPHY

Routine use of preoperative coronary angiography for noncardiac surgery is not recommended. Indications of coronary angiography are similar to those applied in a nonoperative setting.[5]

For patients who are undergoing cardiac surgery for valvular heart disease, aortic disease, or other structural heart disease, coronary angiography is recommended as part of the preoperative workup for nonemergency indications.

CORONARY ANATOMY

Optimal myocardial function is based on a delicate balance of supply and demand achieved through coronary arterial circulation. Coronary arterial circulation consists of two parts—the conduit vessels formed by large epicardial coronary arteries and resistance vessels formed by medium- and small-sized coronary arterioles. The coronary arterial circulation originates from the aorta as two main branches—the left coronary artery, which consists of the left main coronary artery (LMCA), the left anterior descending and the circumflex artery —and the right coronary artery (RCA). There can be some anatomic variations to this pattern. The left and right coronary arteries arise from the left and right coronary cusps, respectively. Dominance is referred to as right or left, depending on whether the RCA or the left coronary artery supplies the posterior descending artery (PDA). In about 70% of patients, the PDA is a branch of the RCA, and this is referred to as a right dominant circulation. In 20% of individuals, the PDA is codominant or balanced in both the left circumflex artery (LCx) and the RCA, and in 10% of individuals, the PDA arises from the LCx.

In order to correlate angiographic views with coronary anatomy, it is useful to consider the main coronary arteries in two orthogonal planes. The left anterior descending and the posterior descending arteries course along the plane of the interventricular septum. The LCx and the RCA run along the plane of the atrioventricular valve perpendicular to the plane of the interventricular septum.

LEFT CORONARY ARTERY

The LMCA is the first portion of the left coronary artery. The LMCA usually bifurcates into the left anterior descending artery (LAD) and the LCx. In some individuals, there may be a trifurcation into a ramus intermedius branch. The LAD artery initially runs along the anterior interventricular groove and terminates at the apex in most individuals. During its course, it gives out septal branches that supply the anterior two-thirds of the interventricular septum, and diagonal branches that supply the anterolateral wall of the left ventricle. The LCx travels along the left atrioventricular groove and gives rise to the obtuse marginal branches. The obtuse marginal branches supply the lateral wall of the left ventricle.

RIGHT CORONARY ARTERY

The RCA runs along the right atrioventricular groove in a mirror fashion to the LCx artery, perpendicular to the long axis of the heart. The first branch arising from the RCA is called the conus artery, which supplies the right ventricular outflow tract. The second branch arising from the RCA is a sinoatrial branch, which supplies the sinus node. It arises out of the RCA in about 60% cases and from the LCx in 40% of individuals. The acute marginal branch arises from the midsegment of the RCA supplying the right ventricle. The RCA gives off the PDA and at least one posterolateral branch in a right dominant circulation.

POSTERIOR DESCENDING ARTERY

The PDA runs along the posterior interventricular groove parallel to the LAD running in the anterior interventricular groove and meeting the LAD along the apical portion of the interventricular septum. It supplies the inferoposterior aspects of the left ventricle and gives off septal branches to supply the inferior aspect of the interventricular septum.

POSTEROLATERAL BRANCHES

The posterolateral branches arise as terminal portions of either the RCA after the origin of the PDA or the LCx. They supply the inferior and posterior segments of the left ventricle.

ANGIOGRAPHIC PROJECTIONS

An accurate assessment of coronary arteries requires obtaining multiple angiographic projections to avoid any overlap of vessels. The position of the image intensifier in relation to the patient's body defines the projections. Left anterior oblique (LAO) and right anterior oblique (RAO) describe the position of the image intensifier to the left or right of a patient's chest, respectively. The anteroposterior (AP) views describe the image intensifier directly over the patient. Cranial and caudal projections describe the position of the image intensifier toward the head (cranial) or feet (caudal). The left coronary system requires an AP caudal to assess the LMCA, LAO cranial for the LAD and its branches. The LAO caudal (spider view) is helpful for assessment of the LMCA, proximal LAD, and proximal LCx. The RAO caudal view is useful for the LCx and its obtuse marginal branches, and the RAO cranial view for mid- and distal

LAD along with diagonal branches (**Figure 7.1A** and **B**). The RCA should be visualized in LAO cranial, which shows the RCA along with the PDA and a RAO projection with cranial angulation for mid-RCA and the entire course of the PDA (**Figure 7.2**). Additional views may be obtained based on the individual patient's coronary anatomy.

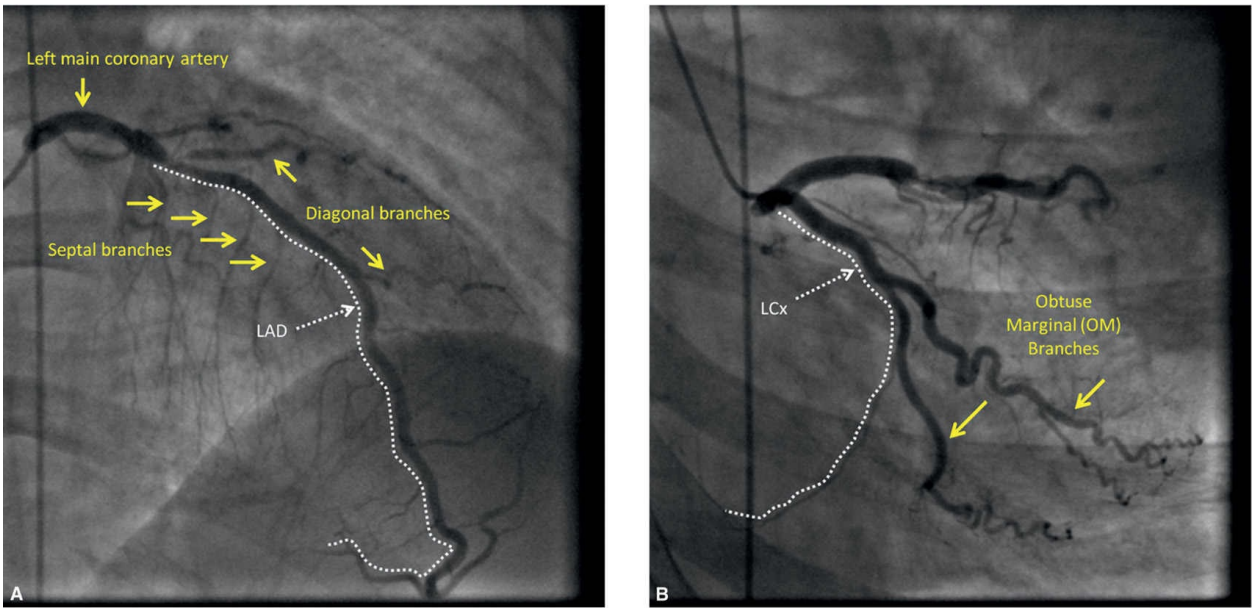

FIGURE 7.1 A, Left anterior descending artery (LAD) and its major branches visualized in a cranially and a slightly rightward angulated view (right anterior oblique [RAO] –9°; cranial +36°). B, Nondominant left circumflex (LCx) artery and its major branches visualized in a caudally and a slightly rightward angulated view (RAO –6°; caudal –21°).

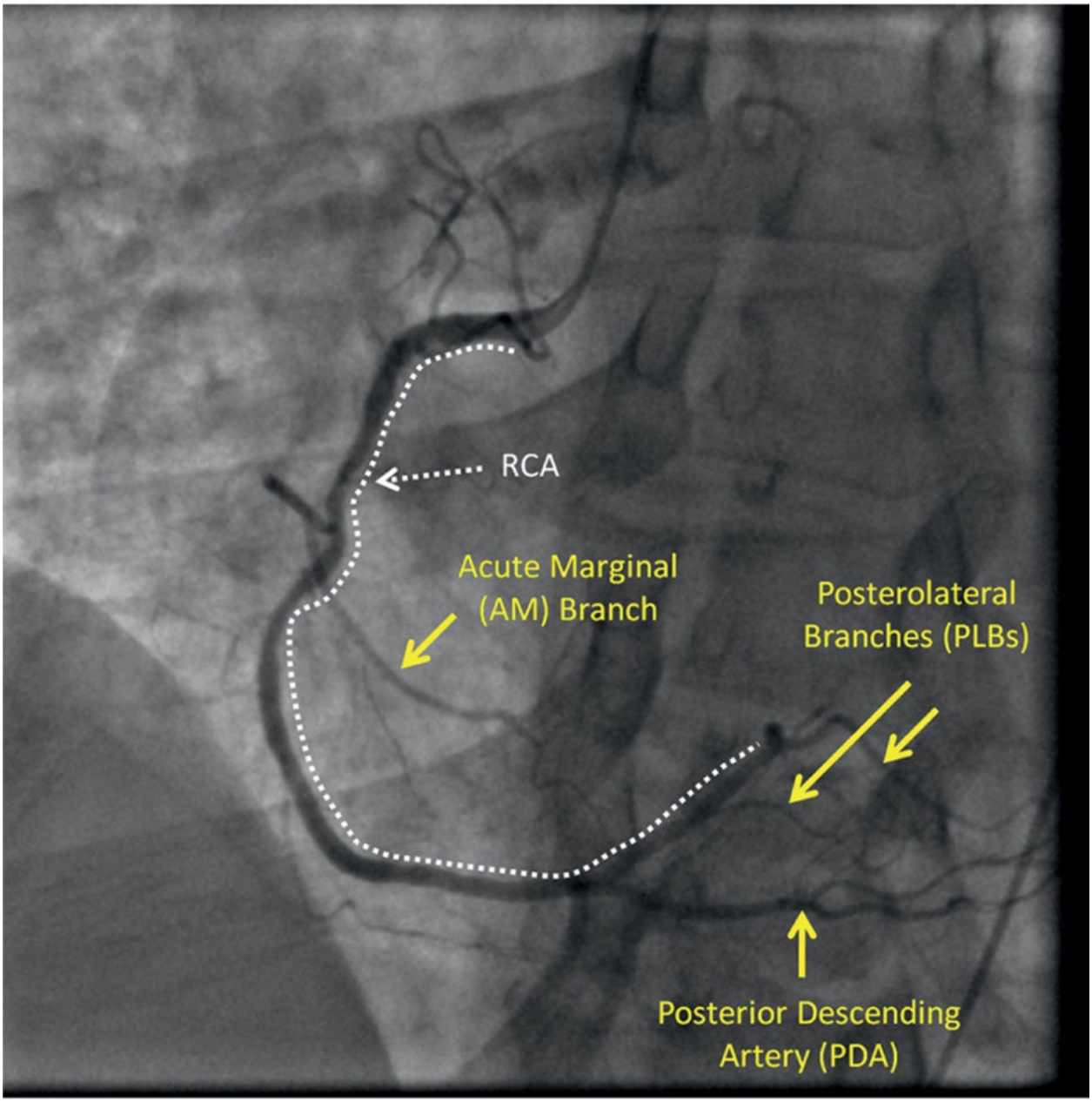

FIGURE 7.2 Dominant right coronary artery (RCA) and its major branches visualized in a slightly cranially angulated left anterior oblique (LAO) view (LAO +28°; cranial +3°).

PREPROCEDURE PREPARATION

CONSENT

The physician performing the cardiac catheterization should obtain informed consent from the patient. The discussion should include the indication for

coronary angiography and PCI if indicated, an overview of the procedure, and risk/benefits of the procedure. The following risks, although not inclusive, should be reviewed with the patient.[6]

Mortality (0.1%)
Myocardial infarction (0.05%)
Cerebrovascular accident (0.07%)
Arrhythmia (0.38%)
Vascular complications and bleeding (0.43%)
Contrast reaction (0.37%)
Hemodynamic complication (0.26%)
Perforation of heart chamber (0.03%)

MEDICATIONS AND ALLERGIES

Complete medication reconciliation along with a review of allergies should be performed before the procedure. Special attention should be given to prior allergies to contrast agents. Mild to moderate reactions can usually be pretreated with diphenhydramine and/or steroids. Careful assessment of risk and benefits along with allergy consultation should be done for more serious reactions. Metformin should be discontinued on the day of the procedure and 48 hours thereafter. Patients on chronic warfarin therapy should have an international normalized ratio < 1.8 for femoral access if anticoagulation can be withheld.[7] Alternatively, radial access can be considered for these patients. The timing of discontinuation for newer oral anticoagulants is guided by the patient's renal function and the particular agent but should be discontinued at least 1 to 2 days prior to the procedure.[7]

PREPROCEDURE WORKUP

A recent laboratory evaluation with baseline renal function, hemoglobin, and coagulation studies (if indicated) should be performed within 30 days in the outpatient setting and within 24 hours in the inpatient setting.[7] Patients with preexisting renal dysfunction or elevated risk scores[8] are at high risk for contrast-induced nephropathy (CIN) and should be considered for adequate hydration with normal saline pre- and periprocedural. The electrocardiogram should be reviewed for all patients because it can help localize the culprit vessel, particularly in the setting of ST-elevation myocardial infarction. Prior

angiograms and operative reports for patients with a history of coronary artery bypass grafting (CABG) should also be reviewed if available.

CONSCIOUS SEDATION

A complete assessment of comorbidities and physical examination should be performed before the procedure. Airway assessment using the Mallampati classification and the American Society of Anesthesiologists Physical Status Classification can help in assessing the patient's eligibility for conscious sedation. Conscious sedation is usually achieved with short-acting agents such as midazolam and fentanyl.

A physical exam should be performed prior to the procedure and include auscultation of the heart for previously undiagnosed murmurs and documentation of neurologic exam, including any pre-existing deficits. A careful assessment of peripheral pulses, including femoral, dorsalis pedis, and posterior tibial, should be recorded in the chart.

ARTERIAL ACCESS

Coronary angiography can be performed using a modified Seldinger technique at three possible sites:

1. Femoral artery
2. Radial artery
3. Brachial artery

FEMORAL ARTERY

The common femoral artery courses medial to the femoral head and bifurcates into the superficial femoral artery and profunda femoris artery distal to the midpoint of the femoral head. The femoral artery should ideally be accessed above the bifurcation and below the inferior epigastric artery. The femoral artery (right or left) is accessed using a modified Seldinger technique with anatomic landmarks and fluoroscopy guidance to locate the midpoint of the femoral head. A 5F or 6F sheath is usually used for diagnostic cardiac catheterization (**Figure 7.3**). There is a risk of retroperitoneal bleeding if the sheath is placed above the inguinal ligament. The risk of a pseudoaneurysm increases if the sheath is placed

below the bifurcation of the common femoral artery.

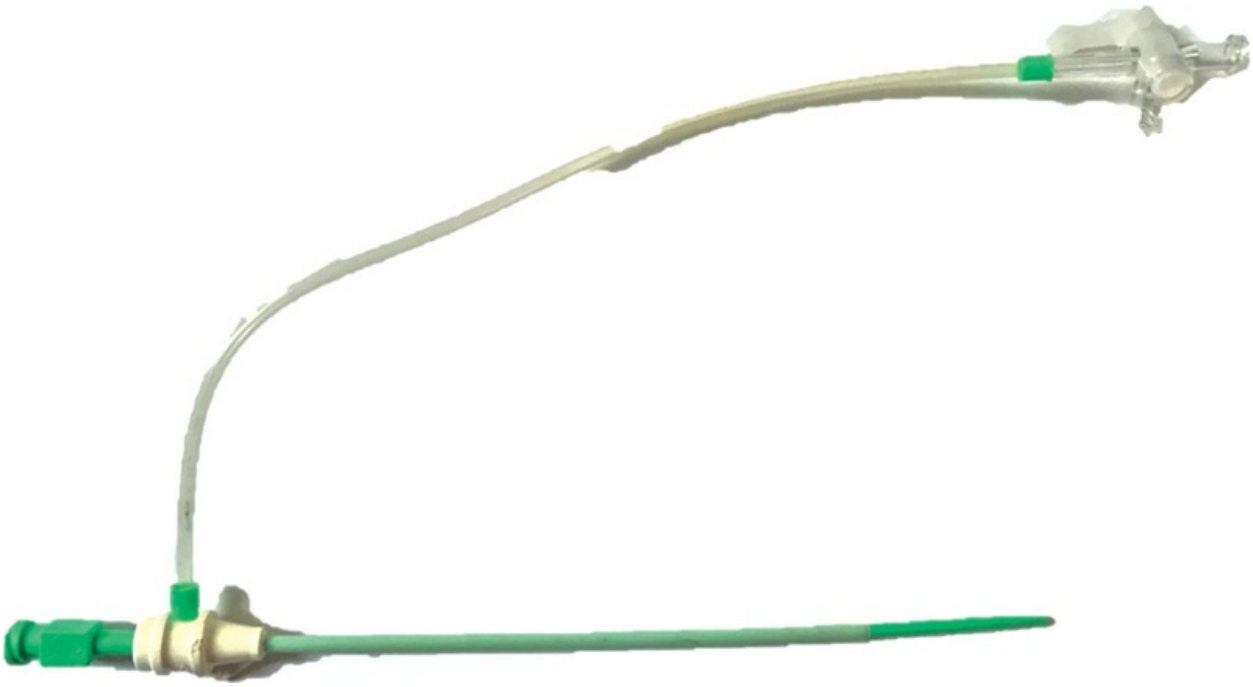

FIGURE 7.3 A 6F arterial sheath is shown here. This serves as the access point for left heart catheterization and coronary angiography.

RADIAL ARTERY

Radial artery catheterization has been shown to reduce mortality and major adverse cardiovascular events and reduce major bleeding and vascular complications across the entire spectrum of patients with CAD.[9] Before this procedure, an Allen test is performed to assess the patency of ulnar artery flow. The radial artery is accessed using a modified Seldinger technique. Heparin is injected directly into the sheath upon access to prevent thrombosis. Radial artery spasm is prevented by injecting nitroglycerin and Verapamil.

BRACHIAL ARTERY

The brachial artery can also be used for coronary angiography; however, there is a higher risk of compromising the blood supply to the hand in the event of vessel closure.

DIAGNOSTIC CARDIAC CATHETERIZATION

After access has been obtained from any of the sites previously mentioned, coronary angiography and left ventriculography are performed through the sheath. With the help of a J-tipped guidewire, the catheter is advanced through the sheath and into the ascending thoracic aorta under fluoroscopy. The guidewire is removed, and catheters are aspirated followed by a flush with heparinized saline.

CORONARY ANGIOGRAPHY

The LMCA is usually engaged using a Judkins left catheter (**Figure 7.4C**), and the RCA is engaged using a Judkins right catheter through the femoral approach (**Figure 7.4B**). In addition, other catheters are available in cases where Judkins catheters fail to engage the coronary arteries. Similarly, catheters are specially designed to access the coronary arteries from a radial approach. On successful cannulation of coronaries, contrast is injected under fluoroscopy, and various angiographic views are obtained as previously mentioned for each coronary artery.

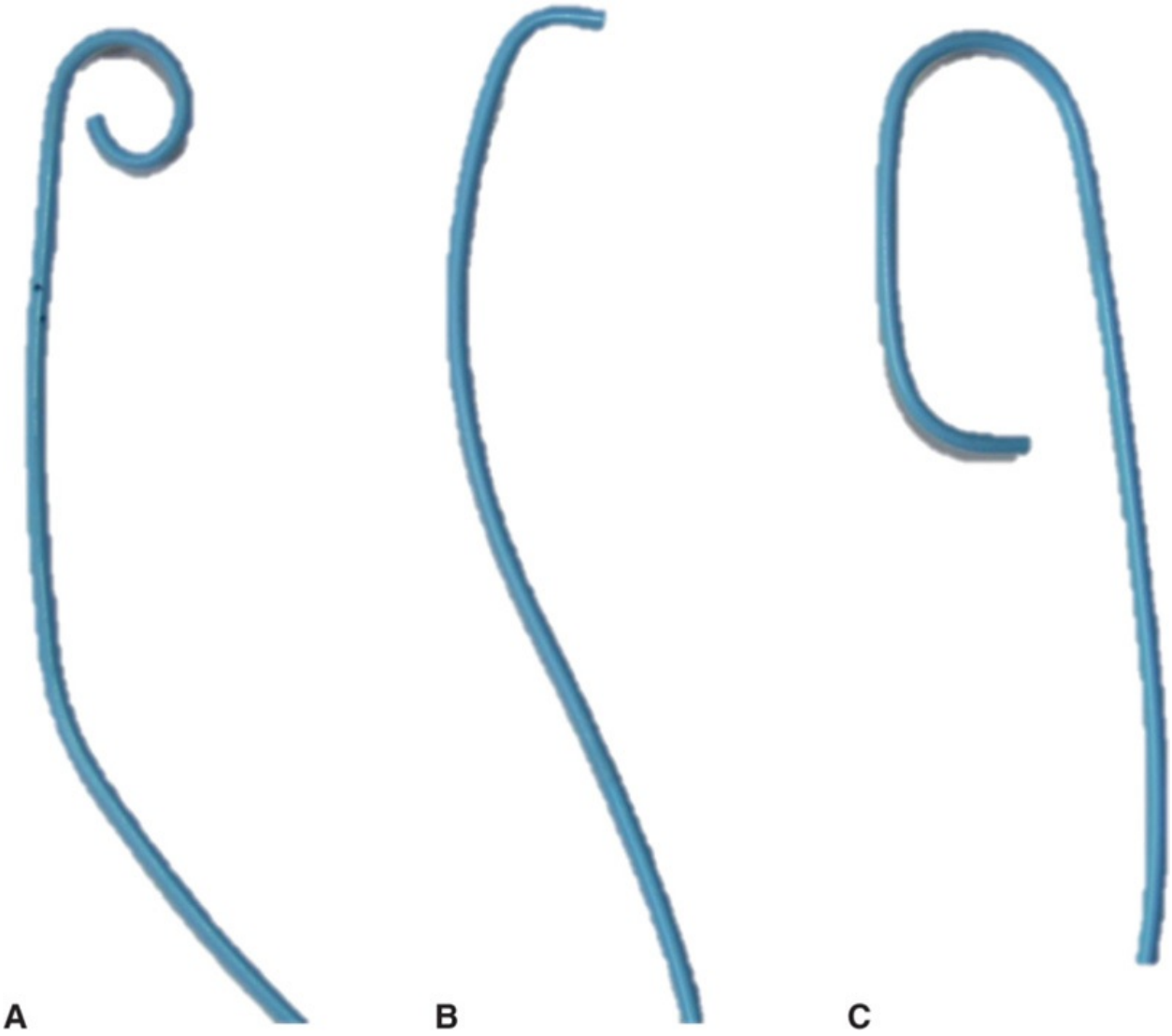

FIGURE 7.4 Coronary artery catheters used in coronary angiography and left heart catheterization. A, A pigtail catheter is placed across the aortic valve to assess left ventricular function and hemodynamics. B, A Judkins right catheter, shown here, is used to cannulate the right coronary artery. C, A Judkins left catheter, shown here, is used to cannulate the left coronary artery.

LEFT VENTRICULOGRAPHY

Left ventriculography is performed with the help of a pigtail catheter in most cases **(Figure 7.4A)**. The pigtail catheter is advanced through the aortic valve and positioned in the center of the left ventricle. An RAO projection is obtained as the contrast is injected into the left ventricle. The figure shows left ventriculography performed in an RAO view. This view gives an assessment of the anterolateral wall, inferior wall, and apex. An LAO projection can be performed to visualize the interventricular septum and lateral wall. Left

ventriculography can also be used to assess the severity of mitral regurgitation based on the degree of opacification of the left atrium. Left ventriculography should be avoided in patients with underlying chronic kidney disease unless deemed necessary for diagnosis.

SUPRA-AORTIC ANGIOGRAPHY

Positioning the pigtail catheter just above the aortic valve is useful for assessing the ascending aorta as well as evaluating aortic insufficiency.

LEFT HEART HEMODYNAMICS

Intracavitary pressure tracings can be obtained from the pigtail catheter placed in the left ventricle. Left ventricular end-diastolic pressure can be measured from these pressure tracings, which can help in the management of patients presenting with acute coronary syndrome, heart failure, and cardiogenic shock and to guide fluid strategy postprocedure. Aortic stenosis can be assessed from the transvalvular gradient obtained as the pigtail catheter is withdrawn from the left ventricle into the aorta or with simultaneous pressure measurements in the left ventricular (LV) and aorta. Mitral stenosis can be assessed by measurement of gradients between the pulmonary capillary wedge pressure and the LV cavity, and atrial septal defect as well as ventricular septal defect can be evaluated with an oxygen saturation series.

ARTERY BYPASS GRAFTS

It is helpful to know the anatomy of the bypass grafts before cardiac catheterization. Specialized catheters are available to engage the bypass grafts.

POSTPROCEDURE CARE

VASCULAR SITE HEMOSTASIS

After completion of cardiac catheterization, the femoral sheath is removed, and hemostasis is achieved either by manual compression or vascular closure devices. Manual compression can be applied directly at the access site for a minimum of 15 minutes, depending on the size of the sheath. If anticoagulation is given with heparin during the procedure, sheath removal and manual

compression can be done if activated clotting time (ACT) is less than 180 seconds. For patients receiving bivalirudin, the sheath can be removed 2 hours after the infusion has stopped. Bed rest of at least 4 hours is advised following manual compression for hemostasis.

A variety of vascular closure devices are available. These achieve hemostasis either with an extravascular plug (Angio-seal/Mynx) or through sutures (Perclose). The Angio-seal vascular closure (St. Jude Medical) device consists of a bioabsorbable intravascular anchor and a collagen extravascular plug to seal the arteriotomy site. Components are absorbed within 60 to 90 days, and the site is available after this time for access. A potential complication is embolization of the intravascular component. Mynx vascular closure (Access closure) uses a bioabsorbable sealant that absorbs blood and expands to seal the arteriotomy site. Perclose (Abbott Laboratories) is a suture-based vascular closure device that functions by percutaneous delivery of sutures. Perclose is also used as a preclosure device when managing a large femoral arteriotomy, as with the use of Impella or Transcatheter Aortic Valve Replacement. Careful assessment of distal pulses is a mandatory part of postprocedure care.

Compared to manual compression, vascular closure devices are noninferior regarding access-site complications but have a higher incidence of infection. They have been shown to have a reduced time to hemostasis and earlier time to mobilization.[10] Careful selection of patients is advised to avoid potential complications.

Radial artery hemostasis is achieved by immediately removing the sheath postprocedure irrespective of anticoagulation status and applying wristband compression devices. Radial artery occlusion is a potential complication. It is important to assess the radial artery flow with pulse oximetry of the corresponding finger by compressing the ulnar artery while using the wristband compression devices. There are no restrictions to ambulation after wristband compression devices, but the patient is advised not to perform strenuous activities using their hand for 2 to 4 hours after the procedure.[7, 11]

POSTPROCEDURE MONITORING

Complete bed rest for 2 hours is advised when a vascular closure device has been used in a patient who has not received anticoagulation. Manual compression requires 4 to 6 hours of bed rest. The patient should be recovered in an area with careful monitoring of vital signs and distal pulses to identify early

signs of bleeding or vessel closure. Postprocedure labs are recommended in patients undergoing PCI and those with preexisting renal dysfunction. Patients undergoing PCI may be considered for monitoring in a telemetry setting if they are at increased risk for postprocedural adverse cardiac event or CIN or require continuous use of intravenous medications.

COMPLICATIONS

The risk of major adverse cardiac and cerebrovascular events for diagnostic cardiac catheterization occurs in <0.1% of procedures. Vascular site complications include bleeding, retroperitoneal hemorrhage, hematoma, pseudoaneurysm, arteriovenous (AV) fistula formation, dissection, and embolization and are less than 0.5%. Patients with a small pseudoaneurysm (less than 2 cm) can be observed for spontaneous closure. Large pseudoaneurysms (more than 3 cm) require ultrasound-guided compression or, more frequently, ultrasound-guided thrombin injection. Retroperitoneal hemorrhage should be suspected in patients with back or flank pain along with hemodynamic instability. Diagnosis can be confirmed with CT scan without contrast. Management includes close monitoring of vitals and complete blood count in a coronary care unit setting, fluid resuscitation, and transfusion as indicated. Anticoagulation reversal may be indicated and vascular surgery consultation is advised. AV fistula is a relatively rare complication. Small AV fistulas can be followed serially with ultrasound. Large fistulas associated with swelling, deep vein thrombosis, or high-output failure may require ultrasound-guided compression or surgical closure.

The risk for CIN increases with preexisting renal insufficiency, DM, and with patients with elevated risk scores.[8] The ideal strategy for preventing CIN includes adequate hydration and minimizing the contrast load.[7]

Coronary artery spasm, dissection, and air embolism are infrequent complications. Cardiac perforation is a rare complication after right heart catheterization. Other complications include cardiac arrhythmia, particularly ventricular fibrillation after injecting the RCA, vagal response, heart failure, and rarely infection. Allergic reaction to contrast dye can range from mild to severe anaphylaxis. Patients at high risk should be premedicated as outlined earlier.

PERCUTANEOUS CORONARY INTERVENTION

Andreas Gruentzig ushered in a new era in the management of CAD when he performed the first percutaneous transluminal coronary angioplasty (PTCA) in 1977. PCI has now grown into a complex field of diagnosis and management of CAD. With a marked improvement in safety and efficacy, it is one of the remarkable achievements of modern cardiovascular medicine.

INDICATIONS FOR PERCUTANEOUS CORONARY INTERVENTION

The American College of Cardiology/American Heart Association task force has published guidelines on indications for PCI.[12] In addition, a multisociety committee has developed the appropriate use criteria for nonemergent PCI based on the severity of angina, findings on the noninvasive study, medical therapy, and extent of CAD.[13]

ST-ELEVATION MYOCARDIAL INFARCTION

Coronary angiography and PCI is a Class I indication in STEMI as primary therapy in patients with ischemic symptoms of less than 12 hours' duration or in patients in cardiogenic shock or acute severe heart failure regardless of time to presentation. Delayed PCI of the infarct-related artery in patients who were initially managed either with fibrinolytic or no reperfusion therapy should be performed in the setting of cardiogenic shock, high-risk findings on noninvasive testing, or spontaneous or easily provoked myocardial ischemia. It is not recommended to perform delayed PCI of a totally occluded artery more than 24 hours after STEMI presentation in stable patients (**Tables 7.3** and **7.4**).[14]

TABLE 7.3 Indications for Primary PCI in STEMI[14]

PRIMARY PCI IN STEMI			
Class I	***Class IIA***	***Class IIB***	***Class III***
	Primary PCI is reasonable in patients with STEMI if there	PCI of a noninfarct artery may be considered in selected patients	

Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 h duration. (Level of Evidence: A)	is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 h after symptom onset. (Level of Evidence: B)	with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure
Primary PCI should be performed in patients with STEMI and ischemic symptoms of less than 12 h duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from FMC. (Level of Evidence: B)		
Primary PCI should be performed in patients with STEMI and cardiogenic shock or acute severe HF, irrespective of time delay from MI onset. (Level of Evidence: B)		

ECG, electrocardiogram; FMC, first medical contact; HF, heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

TABLE 7.4 Coronary Angiography in Patients Who Received Firbrinolytic Therapy or No Reperfusion Therapy

CORONARY ANGIOGRAPHY IN PATIENTS WHO RECEIVED FIBRINOLYTIC THERAPY OR NO REPERFUSION THERAPY

Class I	*Class IIA*	*Class IIB*	*Class III*
Cardiac catheterization and coronary angiography with intent to perform revascularization should be performed after STEMI in patients with any of the following: • Cardiogenic shock or acute severe HF that develops after initial presentation. (Level of Evidence: B) • Intermediate- or high-risk findings on predischarge noninvasive ischemia testing. (Level of Evidence: B) • Myocardial ischemia that is spontaneous or provoked by minimal exertion during hospitalization. (Level of Evidence: C)	Coronary angiography with intent to perform revascularization is reasonable for patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy. Angiography can be performed as soon as logistically feasible. (Level of Evidence: B)		
	Coronary angiography is reasonable before hospital discharge in stable patients with STEMI after successful fibrinolytic therapy. Angiography can be performed as soon as logistically feasible, and ideally within 24 h, but should not be performed within the first 2–3 h after administration of fibrinolytic therapy. (Level of Evidence: B)		

HF, heart failure; STEMI, ST-elevation myocardial infarction.

NON–ST-ELEVATION ACUTE CORONARY SYNDROME

The management of non-ST-elevation acute coronary syndromes (NSTE-ACS) revolves around two pathways, either an invasive strategy or an ischemia-guided strategy. The invasive strategy is designed to perform coronary angiography initially, with intent to revascularize. In the ischemia-guided strategy, angiography is performed in patients who do not respond to medical therapy, have high-risk findings on noninvasive testing, or have a high non-ST-elevation acute coronary syndromes or Thrombolysis in Myocardial Infarction (TIMI) score (**Table 7.5**).[15]

TABLE 7.5 Management of Patients With NSTE-ACS[15]

Non--ST-Elevation Acute Coronary Syndromes

Class I	*Class IIA*	*Class IIB*	*Class III*
An urgent/immediate invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in patients (men and women) with NSTE-ACS who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). (Level of Evidence: A)	It is reasonable to choose an early invasive strategy (within 24 h of admission) over a delayed invasive strategy (within 25–72 h) for initially stabilized high-risk patients with NSTE-ACS. For those not at high/intermediate risk, a delayed invasive approach is reasonable. (Level of Evidence: B)	In initially stabilized patients, an ischemia-guided strategy may be considered for patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events. (Level of Evidence: B)	An early invasive strategy (ie, diagnostic angiography with intent to perform revascularization) is not recommended in patients with: a. Extensive comorbidities (eg, hepatic, renal, pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. (Level of Evidence: C) b. Acute chest pain and a low likelihood of ACS who are troponin-negative (Level of Evidence: C), especially women (Level of Evidence: B)
An early invasive strategy (diagnostic angiography with intent to perform revascularization if appropriate based on coronary anatomy) is indicated in initially stabilized patients with NSTE-ACS (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events. (Level of Evidence: B)		The decision to implement an ischemia-guided strategy in initially stabilized patients (without serious comorbidities or contraindications to this approach) may be reasonable after considering clinician and patient preference. (Level of Evidence: C)	

CHRONIC STABLE ANGINA

Revascularization in patients with chronic stable angina is recommended on the basis of either improved survival or improved symptoms and is outlined in a document termed the Appropriate Use Criteria. This is a detailed compilation of scenarios based on symptoms, extent of ischemia, and current medications. A full discussion is included in the reference.[13, 16]

For patients with complex coronary anatomy, left main disease, or severe LV dysfunction, a "heart team" approach is recommended with input from both cardiac surgery and interventional cardiology with regard to risks and benefits of each approach.

The success of PCI revolves around the following:

- Guiding catheters and guidewires
- Balloon dilatation and coronary stents
- Anticoagulation during PCI
- Lesion modification devices
- Embolic protection devices
- Diagnostic ancillary devices
- Mechanical supportive devices

GUIDE CATHETERS AND GUIDEWIRES

Appropriate choice of the guide catheter is a key first step in the treatment of a lesion. An ideal catheter should be of sufficient design to deliver equipment, provide adequate support to advance the equipment, and provide monitoring of aortic pressure. Similar to diagnostic angiography, luminal diameter size of guide catheters for PCI is denoted by French size (6F approximately 2 mm). In most cases, a 6F guide catheter will be adequate for percutaneous intervention. However, a large French size guide catheter (7F or 8F) is required for performing complex PCI. Despite the extra support provided by guide catheters, a flexible tip is available to reduce damage to the coronary ostium. Guide catheters also help in monitoring the aortic pressure and alert the operator in case of dampening or ventricularization of the waveform. Dampening of the pressure wave (drop in systolic pressure) is seen when a guide is larger than the coronary ostium or when the guide is deep-seated and pressing against the wall or plaque. In addition to appropriate choice of the guide catheter, additional maneuvers

such as a long arterial sheath, guideliner delivery system, or buddy wire techniques may be used to achieve optimal support.

GUIDEWIRES

The next step after the choice of the optimal guide catheter is an appropriate selection of coronary guidewire. An optimal guidewire will cross the lesion without trauma and provide a rail for device delivery. A coronary guidewire consists of an inner core, outer covering, and tip. The choice of guidewire depends on the lesion complexity and type of device delivery. In most cases, “workhorse” wires will suffice for the noncomplex lesion. Complex lesions such as chronic total occlusions may require more advanced techniques and different wires. Soft tip and hydrophilic wires can help navigate tortuous lesions but are more liable to cause dissection and perforation.

BALLOON DILATATION

After the guidewire is advanced distally across the lesion, the next step is to select balloon dilatation catheters. There are two types of balloon dilatation catheter: monorail and over-the-wire. Monorail or rapid-exchange system is designed for a single operator to advance the system while maintaining the distal wire. The over-the-wire system allows delivery to tortuous, calcified vessels and better support for certain devices. Inflation of the balloon is done with a device called an indeflator that measures and controls the amount of pressure. The purpose of predilatation prior to stent implantation includes evaluation of the characteristics and length of the stenosis, determination of the diameter of the stent to be used, and aid in the delivery of the stent. Successful predilatation of the stenosis occurs when both the pressure and the duration of inflation inside the balloon causes the stenotic lesion to yield completely in its entire length. With increasing balloon diameters and higher pressures, inflation can result in an increased risk of vessel injury. On the contrary, lower inflation pressures may not cause sufficient yielding of the stenosis, complicating adequate stent placement.

Compliance of the balloon must be considered while planning PTCA. Compliant balloons can increase in size by >20% when pressure is increased beyond nominal pressure, whereas noncompliant balloons change very little at higher pressures. Noncompliant balloons are better suited for the calcified or fibrotic lesions or for postdilatation of stents. There are many ways to approach

balloon inflation, including size, inflation time, and pressures, but the overall concept is to eliminate the “waist” or area of stenosis.

CORONARY STENTS

Before the advent of stents, plain old balloon angioplasty (POBA) was met with the risk of abrupt vessel closure, requiring CABG, in the short term and the risk of restenosis in the long term because of intense smooth muscle proliferation at the site of POBA. These problems were addressed with the introduction of bare metal stents (BMS) and improved upon in the current era of drug-eluting stents (DES). In its basic design, a DES consists of a mesh of metal that is polymer coated with an antiproliferative drug. Despite the reduction in the incidence of abrupt vessel closure with coronary stents, two issues have plagued the use of coronary stents—stent thrombosis and in-stent restenosis (ISR).

Stent thrombosis can be acute (<24 hours), subacute (<30 days), late (30 days to 1 year), and very late (>1 year). Stent thrombosis results from a lack of endothelialization of the stent, resulting in contact between stent struts and platelets. Endothelialization is usually completed within 4 weeks in BMS. This is markedly delayed in DES because of the release of the antiproliferative drug. In addition to the type of stent, several other factors, including lack of stent apposition or malposition/dissection, can increase the risk of stent thrombosis. The use of dual antiplatelet therapy (DAPT) has reduced the incidence of stent thrombosis, but very late thrombosis has been seen rarely after termination of DAPT beyond the 1-year mark. The duration of DAPT has been a matter of intense debate. The recent 2016 AHA/ACC focus update on the duration of DAPT recommends that patients with SIHD who are treated with DES should be treated for at least 6 months and for at least 1 month following BMS (Class I). Treatment beyond the recommended duration may be considered for those patients who can tolerate DAPT without significant bleeding risk (Class IIb). In patients with ACS treated with either BMS or DES, DAPT should be continued for at least 1 year, and continuation beyond that may be reasonable for patients without any bleeding complication or elevated risk for bleeding (Class IIb).[17]

ISR is caused by neointimal hyperplasia. Neointimal hyperplasia refers to smooth muscle proliferation leading to stenosis at the site of stent implantation. The incidence of ISR has significantly decreased with the use of DES. Risks for ISR include stent underexpansion, diabetes, small vessel size, and long lesions.

Besides neointimal hyperplasia, de novo neoatherosclerosis caused by chronic inflammation has been proposed as a potential mechanism for late ISR and thrombosis.[18]

ANTICOAGULATION DURING PERCUTANEOUS CORONARY INTERVENTION

Anticoagulation is required during PCI to prevent thrombus formation on the guide catheters, coronary wire, or at the site of any arterial injury.[12] There are several different anticoagulation alternatives for PCI.

UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is one of the most commonly used anticoagulants because of ease of use, rapid action availability of the reversal agent, and cost. The degree of anticoagulation with UFH is measured by the ACT using either Hemochron or Hemotec devices. The dosing of heparin is weight-based. UFH should be titrated to achieve an ACT of 200 to 250 seconds if glycoprotein IIb/IIIa receptor inhibitors (GPI) is administered; if no GPI is given, ACT should be targeted toward 250 to 350 seconds (Class I; Level of Evidence C).[12]

BIVALIRUDIN

Bivalirudin is a direct thrombin inhibitor that is used across the entire spectrum of patients undergoing PCI, including STEMI, where it has been shown to reduce cardiac mortality and major bleeding (Class I; Level of Evidence B).[14,19,20] However, recent trials have failed to show a mortality benefit or superiority over heparin.[21, 22] Bivalirudin should be the agent of choice for patients with heparin-induced thrombocytopenia. Bivalirudin is given as a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h for the duration of the procedure. If the patient receives a load of Prasugrel or Brilinta at the time of PCI or is on maintenance therapy with either drug, then bivalirudin can be stopped immediately after PCI. In patients receiving a plavix load at the time of PCI or within 2 hours of PCI, bivalirudin should be continued for at least 2 hours post-PCI until the antiplatelet effect has been achieved.

ENOXAPARIN

Enoxaparin, or low-molecular-weight heparin, can be used in patients with NSTE-ACS undergoing PCI. Enoxaparin may be considered for patients who have not received prior antithrombin therapy or who have received subcutaneous enoxaparin "upstream" for management of NSTE-ACS (Class IIb; Level of Evidence B).[12] An additional dose of enoxaparin is recommended if the patient has received less than 2 doses or if the last dose was received more than 2 hours before PCI (Class I; Level of Evidence B).[12]

FONDAPARINUX

Fondaparinux is an indirect thrombin inhibitor. It is not recommended for use because of an increased risk of catheter thrombosis.[12]

DIAGNOSTIC ANCILLARY DEVICES

Although considered "the gold standard," coronary angiography comes with some limitations. Coronary angiography merely outlines the vessel lumen and provides no information on the anatomic configuration of the vessel wall or functional significance of the lesion. These problems are addressed by recent advances in intravascular ultrasound (IVUS), optical coherence tomography (OCT), and fractional flow reserve (FFR).

INTRAVASCULAR ULTRASOUND

IVUS creates a cross-sectional tomographic image of the vessel wall. A standard IVUS image provides a minimal luminal area (MLA, plaque burden, and some characterization of lesion morphology and contents). Criteria for MLA with IVUS have been correlated with FFR. An MLA < 6.0 mm^2 is suggestive of significant hemodynamic lesion in left main, whereas an MLA of <4.00 mm^2 is used as cutoff for non–LMCA. In addition to assessment of lesion severity, IVUS has substantial clinical utility in coronary stenting. IVUS-guided coronary stenting can be useful in assessing vessel size, stent deployment, and proper stent apposition. It can also guide in the identification and management of complications post-stenting such as ISR and coronary dissection.

OPTICAL COHERENCE TOMOGRAPHY

OCT uses scattering and absorption of near infrared emitted from an optical fiber of an imaging catheter. Tomographic images are generated through an automated pullback requiring contrast infusion because OCT cannot image through blood. OCT has far superior resolution compared to IVUS. However, it falls behind in image penetration. OCT can identify thrombus, plaque rupture, stent malapposition, edge dissection, and prolapse of tissue (**Figure 7.5**). A 2014 consensus document of the Society of Cardiovascular Angiography and Interventions gives OCT a "probably beneficial" rating for stent deployment and "possibly beneficial" for plaque morphology.[23]

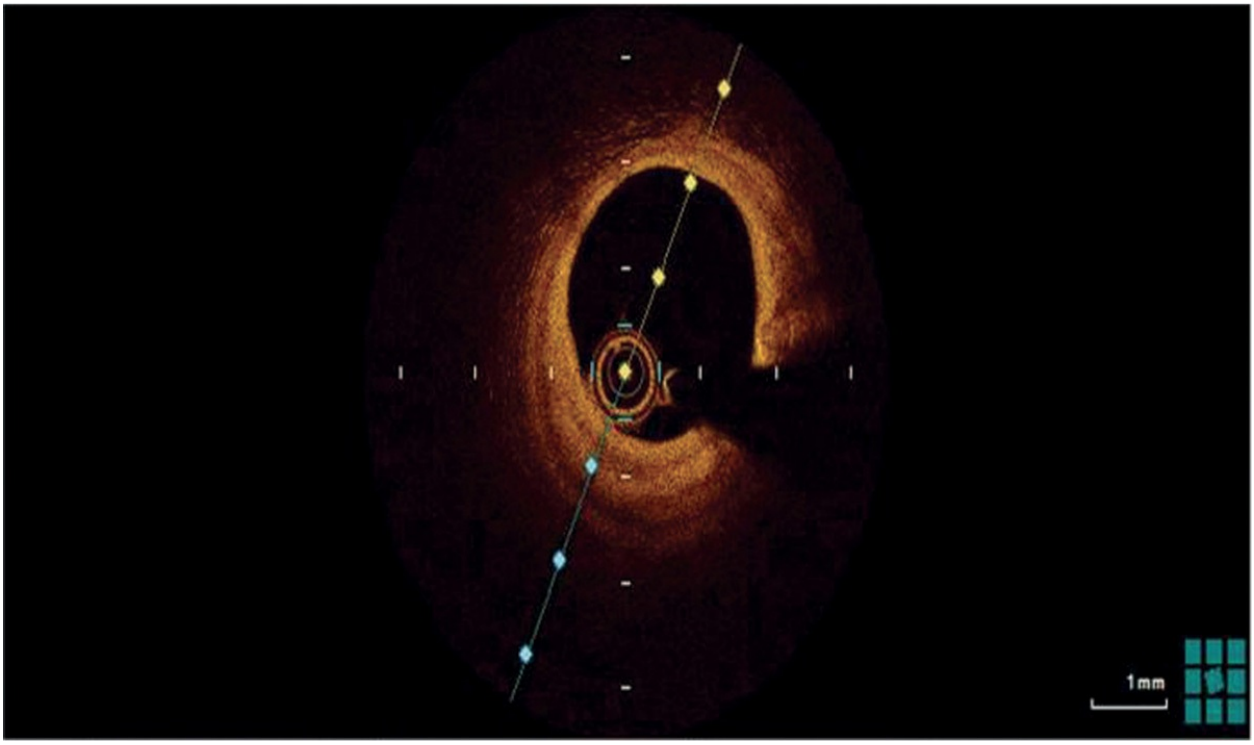

FIGURE 7.5 A cross-sectional optical coherence tomography image of coronary artery.

FRACTIONAL FLOW RESERVE

As compared to the anatomic assessment of lesion severity provided by IVUS and OCT, FFR provides physiologic significance of lesion severity. FFR is the ratio of mean distal coronary pressure after the lesion divided by mean pressure proximal to the lesion during maximal hyperemia achieved with IV adenosine (**Figure 7.6**). Although first validated at a significant level of 0.75, the value was extended to 0.80 to improve sensitivity. The FAME trial randomized patients with multivessel disease to either FFR-guided PCI or to angiographic-guided

PCI. The primary outcome of death, MI, or repeat revascularization was significantly lower in the FFR-guided PCI arm.[24] FAME 2 demonstrated that FFR-guided PCI with optimal medical therapy in patients with stable CAD showed better outcomes than did medical therapy alone.[25] FFR is useful in guiding the management of a patient with SIHD and in assessing the angiographic significance of intermediate lesions (Class IIa; Level of evidence A).[12]

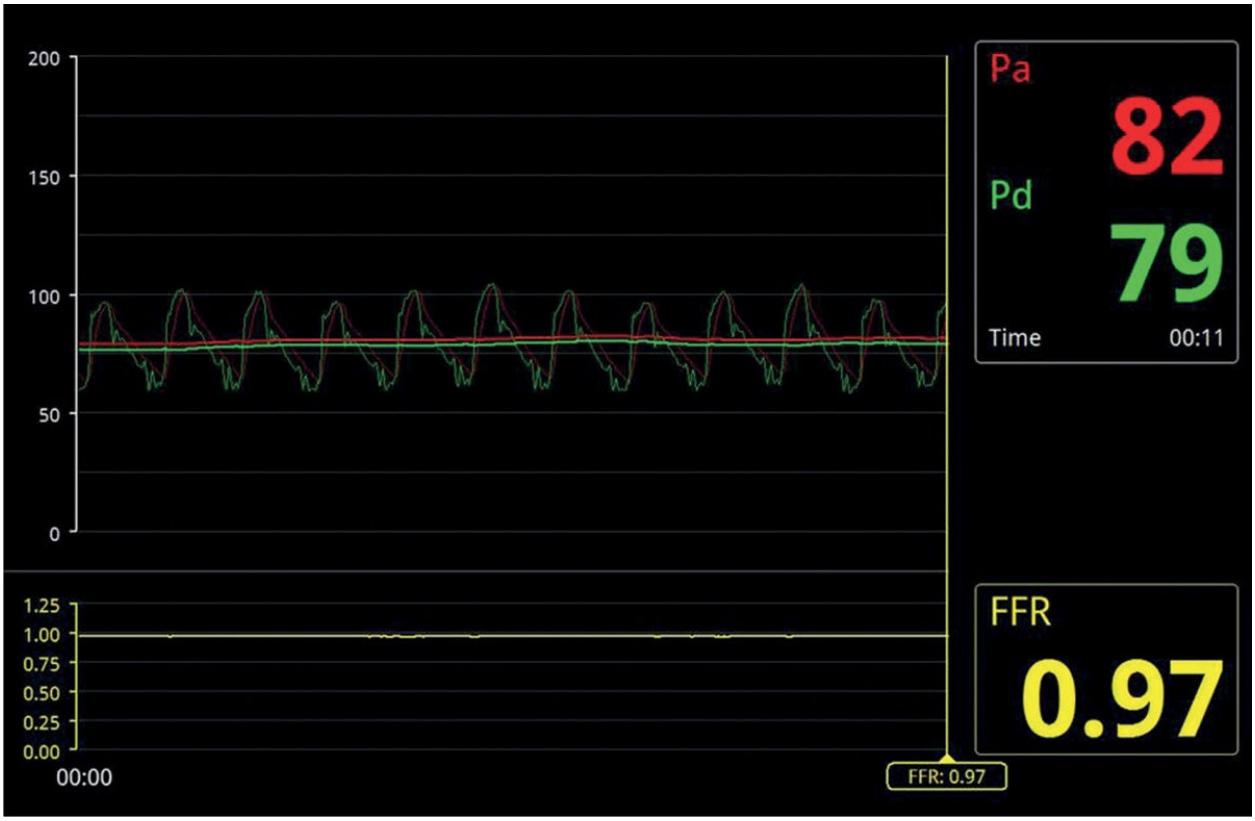

FIGURE 7.6 Normal fractional flow reserve of an indeterminate lesion coronary after IV adenosine infusion.

LESION MODIFICATION DEVICES

The procedural success of a calcified lesion depends on the adequate preparation of the vessel. Mild calcification can be managed with routine PTCA followed by stent. Moderate to severe calcification may require the use of the atherectomy devices to both debulk the lesion and modify the architecture of the vessel. Device selection is based on the degree of calcification, operator experience, and

clinical presentation of the patient.

Atherectomy devices include rotational atherectomy, orbital atherectomy, excimer laser atherectomy, and cutting balloon atherectomy.

Rotational atherectomy works on the principle of “differential cutting,” involving selective ablation of calcium, leaving healthy tissue intact, unlike balloon angioplasty, which causes several intimal tears. Rotational atherectomy ablates plaque using a diamond elliptical burr rotating concentrically on a wire at 140,000 to 160,000 revolutions per minute. It comes in sizes ranging from 1.25 to 2.5 mm. Particulates released from RA can pass through coronary microcirculation and eventually undergo phagocytosis in the body. Occasionally, the microparticles can cause microcirculation obstruction, thereby increasing the risk of slow flow or no-reflow.[26] This can be reduced by gradual burr advancement, short ablation runs, and avoidance of deceleration.[26] Despite its clinical utility, rotational atherectomy has not been shown to improve clinical outcomes. Current guidelines recommend that rotational atherectomy be used in the setting of severely calcified or fibrotic lesions that are not amenable to adequate balloon dilatation prior to stent implantation (Class IIa; Level of Evidence C).[12]

Diamondback 360 Coronary Orbital Atherectomy System works on the principle of differential sanding and centrifugal force for plaque modification. The system consists of a diamond-coated crown eccentrically mounted on a guidewire. The crown is available in a 1.25-mm size, but the maximum orbit is determined by the rotational speed of the crown. Compared to rotational atherectomy, orbital atherectomy produces microparticles that are smaller in size and allows continuous blood flow.

Excimer laser atherectomy uses laser energy to modify calcified lesions. Similar to rotational atherectomy, guidelines recommend use of excimer laser in fibrotic or moderately calcified lesions that cannot be adequately crossed or dilated with balloon angioplasty (Class IIb; Level of Evidence C).[12]

Cutting balloon atherectomy utilizes a balloon mounted with metallic blades that cut the plaque, allowing balloon dilatation at a lower pressure. Two such devices are available: The Flextome cutting balloon consists of three to four longitudinally directed microsurgical blades on the balloon surface. AngioSculpt consists of a nitinol cage over a balloon that cuts the plaque and also prevents balloon slippage. Cutting balloon atherectomy is frequently used in the setting of ostial lesions and mild- to moderate calcified lesions. Cutting balloon is also recommended to avoid coronary artery trauma caused by balloon slippage during

PCI of ISR (Class IIb; Level of Evidence C).[12]

THROMBECTOMY

Thrombectomy devices incorporate removal of complete or partially occluding thrombus in patients with ST-elevation myocardial infarction. In light of recent studies, the 2015 focused update on primary PCI for patients with ST-elevation myocardial infarction has modified the recommendation from Class IIa to Class III for Routine aspiration thrombectomy before primary PCI.[27] Aspiration thrombectomy is performed using a catheter to remove thrombus using negative pressure applied through a syringe with a locking plunger controlled with a three-way stopcock. Angiojet is a rheolytic device based on the Venturi Bernoulli principle. It consists of a flexible catheter, pump, and angiojet console. The console energizes the pump to send pressurized saline to the catheter tip. A vacuum effect is created as the saline jet travels backward in the catheter. The net result is disruption and aspiration of thrombus, which can then be retrieved. Although not routinely recommended, it is extremely useful in patients with heavy clot burden.

EMBOLIC PROTECTION DEVICES

Embolization of atherosclerotic debris into systemic circulation is a complication sometimes encountered during saphenous vein graft intervention. There are two devices currently available for prevention of embolization. The Filterwire EZ uses a distal filter over a fixed wire that is advanced across a saphenous vein graft lesion. The filter prevents embolization of debris but does not compromise the blood flow through the filter pores. The Guardwire uses a balloon mounted on the distal end of the wire. The balloon is inflated distal to the lesion followed by rapid stenting and aspiration of the content of the vessel. Unlike the filter wire, there is the possibility of compromise to blood flow and hemodynamic compromise.

MECHANICAL SUPPORTIVE DEVICES

One of the significant advances in interventional cardiology is the availability of mechanical circulatory support devices. The purpose of the mechanical support device is to provide end-organ and coronary perfusion and improve myocardial performance in the setting of cardiogenic shock or high-risk PCI.[28] The definition of high-risk PCI has been broad across the literature. It can be defined on the basis of patient-specific, lesion-specific, and clinical-specific variables.[29] Patient-specific characteristics include advanced age, depressed EF <35%, congestive heart failure, chronic kidney disease, diabetes mellitus, severe aortic stenosis, severe mitral regurgitation, or peripheral arterial disease. Lesion-specific characteristics include multivessel disease, left main disease, last patent conduit, bifurcation lesions, or chronic total occlusion. Lastly, clinical presentations include acute coronary syndromes, advanced heart failure, and cardiogenic shock.[29]

Cardiogenic shock and high-risk PCI represent a dynamic patient population group that can have marked hemodynamic and metabolic derangements. It is recommended that a multidisciplinary heart team approach is utilized for prompt identification of these patients. Providing optimal support to these patients may require this team approach and can be accomplished with an array of appropriate mechanical support devices.[30] The 2011 multisociety guidelines for PCI recommend elective insertion of a hemodynamic support device at the time of PCI in carefully selected patient populations as described above (Class IIb; Level of Evidence C).[12] Each device has a particular hemodynamic profile as well as indications and contraindications. It is imperative to carefully consider all clinical parameters before a mechanical support device is selected.

INTRA-AORTIC BALLOON PUMP

The intra-aortic balloon pump (IABP) remains one of the most commonly used support devices. The IABP, which works on the principle of counterpulsation, inflates during diastole to provide diastolic augmentation of pressure and increased coronary perfusion and deflates during systole to reduce afterload and improve cardiac output. The device consists of a balloon catheter and a console. The balloon catheter has a polyethylene balloon attached to its body with two lumens. One lumen is for guidewire insertion and pressure monitoring, and the other lumen is for balloon inflation with helium. The IABP is inserted through the femoral artery and placed in the descending thoracic aorta under fluoroscopic guidance. The position of the balloon should be 1 to 2 cm below the subclavian

artery and above the renal artery. A daily chest X-ray should confirm the tip of the IABP between the second and third intercostal spaces. The IABP uses either the electrocardiogram or pressure triggers for timing the balloon cycle. Moderate to severe aortic regurgitation is considered a contraindication for IABP placement, and careful attention is required for patients with severe peripheral arterial and aortic disease. Despite the widespread use of IABP, clinical trials have failed to show a mortality benefit. The Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trail randomized 600 patients with cardiogenic shock complicating acute myocardial infarction into IABP or no IABP. All patients received optimal medical therapy and were expected to undergo revascularization with either PCI or CABG. This trial failed to show a significant reduction in 30-day mortality between the two groups.[31] Despite the lack of evidence, the 2013 guideline for management of ST-elevation myocardial infarction recommends use of IABP for patients with cardiogenic shock who fail to stabilize with pharmacologic therapy (Class IIa; Level of evidence B).[14] Alternate devices for circulatory support may be indicated for patients with refractory cardiogenic shock (Class IIb; Level of Evidence C).[14]

IMPELLA

The Impella device provides a nonpulsatile axial flow of blood from the LV to the ascending aorta. It is available as Impella 2.5 and Impella CP, which can be inserted percutaneously, and as Impella 5.0, which requires a surgical cutdown. The device consists of a pigtail catheter that crosses the aortic valve and is connected to a cannula that contains the pump inlet and outlet.[29] Impella 2.5 can provide an outflow of 2.5 L/min, Impella CP provides support between 3.0 and 4.0 L/min, and Impella 5.0 can provide support of 5.0 L/min. Left ventricular thrombus is an absolute contraindication for the use of Impella. The PROTECT II trial randomized 452 symptomatic patients with complex three-vessel disease or unprotected left main CAD and reduced ejection fraction to intra-aortic balloon or Impella 2.5T support during nonemergent high-risk PCI. The Impella provided superior hemodynamic support compared to IABP, but the 30-day incidence of major adverse events was not statistically significant between the two groups. At 90 days, a trend toward improved outcomes was observed for the Impella 2.5 group.[32]

TANDEM HEART

The Tandem Heart provides extracorporeal circulation up to 5.0 L/min, utilizing a centrifugal pump from the left atrium to the femoral artery. It consists of an inflow cannula inserted into the left atrium through the femoral vein via the transseptal approach and an outflow cannula placed in the femoral artery.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) can be either Veno-venous ECMO to support oxygenation or veno-arterial ECMO to support both oxygenation and circulation. Veno-arterial is the device of choice for patients with biventricular failure requiring oxygenation and circulatory support.[29] The ECMO system consists of a venous reservoir, external centrifugal pump, membrane oxygenator, and a rewarming heparin-coated circuit.[28] Veno-arterial ECMO can provide circulatory flow up to 6 to 7 L/min, but its use can cause LV distension, and adequate venting with an Impella or IABP may be required.[30]

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Patient and Family Information for: CORONARY ANGIOGRAPHY AND PERCUTANEOUS CORONARY INTERVENTION

CARDIAC CATHETERIZATION AND CORONARY ANGIOGRAPHY

Cardiac catheterization is a procedure that is performed to obtain X-ray pictures of arteries that supply the muscles of the heart. It can also be used to measure the pressures in the right- and left-sided chambers of the heart. This procedure is performed through a blood vessel either in the leg or in the arm or wrist. The doctor may recommend this procedure for a variety of cardiac diseases:

1. CAD: If the doctor is suspecting blockages in coronary arteries, the blood vessels that nourish the heart walls, he/she may recommend cardiac catheterization for identification and assessment of severity of blockages by injecting the coronary arteries with a contrast material that is seen under X-ray.
2. Valvular heart disease: Diseases affecting valves of the heart can be assessed by measuring the pressures in the chambers of the heart and by injecting contrast in the ventricles or the aorta.
3. Congenital heart disease: Some forms of congenital heart disease can be evaluated with cardiac catheterization by pressure measurements and oxygen analysis in the chambers of the heart.

PREPARATION FOR THE PROCEDURE

The patient will most likely be asked not to eat several hours before the procedure, but most medications can be taken with a sip of water. If the patient takes any blood thinners other than aspirin, plavix, prasugrel, ticagrelor, or other antiplatelet drugs, the doctor may discontinue these or modify the doses before the test. For diabetic patients, the doctor may hold or reduce the dose of medications before the procedure.

When the patient arrives in the catheterization laboratory, an intravenous line is started in the arm by the nurse so that medication, including sedation, can be given to the patient during the test. An electrocardiogram and blood tests will be performed before the test. ECG monitoring electrodes will be placed on the chest so that continuous recordings of the heartbeat can be performed throughout the test. To reduce the risk of infection, hair will be shaved from the groin area if the doctor chooses to use the femoral artery in the leg for the insertion of the catheter. The doctor will review the procedure and obtain informed consent from the patient before the procedure.

PROCEDURE

Once the patient is inside the cardiac catheterization room, the doctor will give medications to help relax and relieve any anxiety. The patient will be most likely awake or in a light sleep. The entire body from neck to toe will be covered with a sterile drape. For the catheterization performed through the artery in the leg, the doctor will palpate the femoral artery in the groin. Thereafter, he will inject numbing medication to relieve any pain before inserting a thin plastic sheath into the artery. The doctor may place a similar sheath in the femoral vein that runs next to the femoral artery to measure the pressures in the right-sided chambers of the heart. A similar technique will be used if the catheterization is performed through the wrist of the hand by accessing the radial artery.

LEFT HEART CATHETERIZATION AND CORONARY ANGIOGRAM

After the plastic sheath is placed in the femoral artery, the doctor will pass the catheters through the sheath, which will be advanced under X-ray guidance up to the aorta, the main artery leading to the heart, and reach the left side of the heart. The doctor will then access the coronary arteries and inject “dye” to perform a “coronary angiogram.” Digital X-ray pictures will be obtained at the same time to diagnose blockages in coronary arteries. The doctor may also obtain pressures in the left ventricle, which is the main pumping chamber of the heart, by passing

a catheter into the left ventricle to perform “left heart catheterization.”

RIGHT HEART CATHETERIZATION

After the plastic sheath is placed in the femoral vein, the doctor will pass the catheter under X-ray guidance to the right-sided chambers of the heart. “Right heart catheterization” will be completed by obtaining the pressure measurements of the right-sided chambers of the heart. A combined “right heart catheterization” and “left heart catheterization” will be performed to diagnose the disease of heart valves and muscles of the heart.

POST PROCEDURE

The entire procedure of “left heart catheterization,” “coronary angiogram,” and “right heart catheterization” will be completed in approximately 30 to 45 minutes if no further procedure is planned. The doctor will then remove the small plastic sheath from the wrist or the leg. If the procedure were performed through the wrist, a small pressure band would be applied and removed in approximately 2 hours. For the procedure performed through the leg, the sheath will be removed, and either manual pressure will be applied for 15 to 20 minutes or a “closure device” will be used. The use of a “closure device” will allow the patient to ambulate earlier compared to the case with manual pressure. The doctor will provide information about postprocedure care required. Typically, the patient is required to stay in bed for about 2 to 4 hours.

After coronary angiogram is performed, the doctor will review the X-ray pictures and decide whether the patient requires an intervention. If the review of X-ray pictures reveals “blockages,” the doctor will review the best treatment option for the patient, which can range from medical treatment to PCI or bypass surgery. The choice of treatment option depends on the number of arteries involved and the complexity of the blockages, pumping function of the heart, symptoms of the patient, and presence or absence of diabetes.

The foregoing procedures of “coronary angiogram” and “PCI” may be performed in an elective setting or, in some cases, emergently if the patient presents with symptoms of a heart attack. Two scenarios may occur. In the first scenario, the patient presents with the clinical condition referred to as STEMI. Patients with STEMI have a coronary artery completely blocked by a blood clot known as a thrombus. If the hospital is capable of performing coronary angiogram and PCI, the patient will be rushed to the cardiac catheterization

laboratory. If such a capability does not exist, the patient will either be transferred to the nearest hospital and/or given medications to dissolve the clot occluding the artery. In the second scenario, patients may present with a condition referred to as NSTE-ACS, in which, unlike in the case of STEMI, the artery is not completely occluded. Patients presenting with NSTE-ACS are treated with either coronary angiogram and/or PCI within a few hours of presentation if indicated on the basis of clinical presentation, or they may undergo further noninvasive testing to determine the need for a coronary angiogram and/or PCI.

PERCUTANEOUS CORONARY INTERVENTION

We will review different forms of PCI if the doctor decides, on the basis of the coronary angiogram, that there is a need for it. The doctor may perform the PCI immediately after the angiogram or later. The percutaneous intervention is performed through the same small plastic sheath using a different set of catheters and wires.

CORONARY ANGIOPLASTY

This procedure is referred to in medical terminology as PTCA. It is usually performed as a precursor to implantation of stent to prepare the coronary artery. Rarely, it is performed as a “stand alone” procedure, but this is associated with increased risk of repeat blockages because of the formation of scar tissue. The procedure is performed by passing what is known as a guide wire across the coronary artery with “blockages.” Once the wire is positioned adequately across the blockage, a flexible catheter with a balloon attached to its distal tip is passed over the wire and placed at the site of the “blockage.” The balloon is inflated, compressing the plaque, and is deflated after a few seconds to open the blockage. This may be repeated as necessary to dilate the coronary artery and prepare it for subsequent stent implantation.

CORONARY STENTS

One of the problems with “stand alone” coronary angioplasty, as previously described, was repeat blockage of the coronary artery caused by the formation of scar tissue. This was greatly reduced with the advent of coronary stents.

Coronary stents are metallic devices that are placed at the site of the blockage usually after balloon dilatation or sometimes directly. There are two types of stents: (1) BMS and (2) DES. A DES delivers a drug locally at the site of the blockage and thereby reduces the problem of restenosis. However, the stent itself is considered a foreign material and is at risk for formation of clot because of the interaction of stent material and blood. This risk is greater with DESs because the release of drug prevents cell growth and keeps them "foreign" for a longer time. To prevent this complication of clotting of the stent, the doctor will prescribe two medications, aspirin and another antiplatelet drug such as plavix, prasugrel, or ticagrelor. This form of therapy is called "DAPT." Depending on type of the stent and clinical condition that prompted the stent implantation, the duration of the therapy may last from 1 month to 1 year or even longer. It is essential that the patient consult a doctor before stopping "DAPT."

ROTATIONAL ATHERECTOMY

In some patients, the coronary arteries are severely calcified at the site of the blockage, making the implantation of stent extremely difficult. In those cases, the doctor may decide to perform rotational atherectomy. Rotational atherectomy is performed with a specialized burr mounted on a catheter. The burr rotates at a very rapid speed to pulverize the calcification. This procedure is usually followed by balloon dilatation and stent implantation.

THROMBECTOMY

In patients presenting with STEMI, a blood clot is formed at the site of the blockage. The clot may be aspirated by a catheter with mechanical suction or by devices that generate suction effect by high-pressure saline jets.

INTRAVASCULAR ULTRASOUND

Because coronary angiogram is a two-dimensional image seen on X-ray films, several other devices may be used to determine the severity of blockages in the coronary artery. One such device is called IVUS. This consists of a miniature ultrasound mounted on top of a catheter. The catheter is inserted into the coronary artery and can help visualize the degree of narrowing, calcification, and composition of plaque. It can also help the doctor to guide the implantation of the stent.

OPTICAL COHERENCE TOMOGRAPHY

OCT is a device similar to IVUS to help better understand the severity of the blockage. It is based on fiber optics, and catheters emit near infrared light. The quality of pictures obtained with OCT is far superior to those obtained with IVUS.

FRACTIONAL FLOW RESERVE

FFR is a technique used to assess whether the blockage visualized by coronary angiogram is physiologically limiting the blood supply to heart muscles. A wire is passed across the blockage, and a medication called “adenosine” is given intravenously to simulate maximal blood flow. The wire compares the pressure before and after the blockage to provide a number. If the number is less than 0.80, the doctor will opt to put a stent at the site of the blockage.

MECHANICAL SUPPORT DEVICES

A doctor may insert mechanical support devices in two scenarios: (1) The patient is presenting with a critical condition called “cardiogenic shock,” where the patient’s blood pressure is extremely low, and the heart is not able to pump sufficient blood to the body despite the use of strong medications. (2) The doctor determines that the blockage is very complex and wants to provide extra support to the heart while the intervention is performed. Several devices are available for use but the most commonly used devices are the IABP and Impella.

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Coronary Artery Bypass Surgery

BACKGROUND

Coronary artery bypass surgery (CABG) is a safe and effective method of treating coronary artery disease.[1–3] Surgical bypass for coronary disease may be performed either in the elective setting or after acute myocardial infarction. The ACC/AHA guidelines for elective CABG in patients with coronary artery disease and emergency CABG after acute myocardial infarction are illustrated in **Tables 8.1** and **8.2**. The principles of surgical technique and postoperative care are similar; however, comorbidities strongly influence outcomes in the intensive care unit (ICU). A standardized approach is useful in the management of these complicated postoperative patients.

TABLE 8.1 ACC/AHA Guidelines for CABG in Patients With Coronary Artery Disease

1. ≥50% diameter stenosis in the left main coronary artery
2. ≥70% diameter stenoses in three major coronary arteries, with or without involvement of the proximal LAD artery
3. ≥70% diameter stenosis in the proximal LAD plus one other major coronary artery
4. Survivors of sudden cardiac death with presumed ischemia-mediated ventricular tachycardia caused by significant (≥70% diameter) stenosis in a major coronary artery
5. Patients with one or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite maximum medical therapy

CABG, coronary artery bypass surgery; LAD, left anterior descending.

TABLE 8.2 Guidelines for Emergency CABG after Myocardial Infarction

1. Patients with acute myocardial infarction (MI) and (a) primary PCI has failed or cannot be performed, (b) coronary anatomy is suitable for CABG, and (c) persistent ischemia of a significant area of myocardium at rest and/or hemodynamic instability refractory to nonsurgical therapy is present
2. Patients undergoing surgical repair of a postinfarction mechanical complication of MI
3. Patients with cardiogenic shock who are suitable for CABG irrespective of the time interval from MI to onset of shock and time from MI to CABG
4. Patients with life-threatening ventricular arrhythmias (believed to be ischemic in origin) in the presence of left main stenosis greater than or equal to 50% and/or 3-vessel CAD

CABG, coronary artery bypass surgery; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

BASIC SURGICAL TECHNIQUE AND INTRAOPERATIVE CONSIDERATIONS

CABG is performed under general anesthesia with endotracheal intubation. Patients receive prophylactic antibiotics within 60 minutes prior to incision. Treatment is aimed at normal skin flora; a first-generation cephalosporin is commonly used and redosed in 4 to 6 hours based on clearance during cardiopulmonary bypass (CPB). Vancomycin may be used in regions of high prevalence of methicillin-resistant Staphylococcus species or in those patients with a long preoperative hospital length of stay.[4, 5] Continuation of prophylactic antibiotics is not indicated beyond 24 to 48 hours postoperatively.

Intraoperative monitoring is essential in maintaining appropriate physiologic parameters across all body systems. Arterial, central venous, and pulmonary artery (PA) catheterization are used for hemodynamic monitoring. Placement of a PA catheter is not a necessity in those patients with a normal ejection fraction and uncomplicated surgical procedure. Intraoperative transesophageal echocardiograms provide excellent assessment of cardiac function during and after the time of CPB. A bladder catheter with a temperature probe is placed to monitor urine output and core body temperature. Alternatively, a rectal or esophageal temperature probe may be inserted for monitoring during the warming and cooling process of CPB.

Transesophageal echocardiography (TEE) is essential for the intraoperative evaluation of cardiac anatomy, ventricular function, valve anatomy, and pathology. TEE can also be used to confirm placement of intracardiac catheters and devices, evaluate for air or thrombus within the cardiac chambers, and

record postrevascularization ventricular function. Epicardial probes may be used by the cardiac surgeon to evaluate the ascending aorta for intraluminal plaque.

CPB and cardioplegic arrest are used in many procedures to provide a motionless and bloodless field during surgical revascularization. CPB uses an extracorporeal circuit to drain the venous system; push the patient's blood through an oxygenator, warmer and filter; and return the blood into arterial circulation. Acting as a gravity siphon, a venous cannula removes blood from the right atrium or inferior vena cava (IVC) and superior vena cava directly into a container called the venous reservoir. A pump then pushes the blood through an oxygenator and a specialized filter to remove particulate matter before returning the blood into arterial circulation. The arterial cannula is most commonly located via the ascending aorta. However, in the case of dense calcification or an aneurysmal ascending aorta, cannulation may be performed in the axillary or femoral vessels. Additional cannulas are placed to infuse cardioplegic solutions and/or vent air from the cardiac chambers. Understanding the location of cannulation sites can be vital to postoperative care in the rare cases that the patient bleeds from one of the suture lines, especially if it is in a location outside of the chest (ie, following axillary or femoral cannulation).

Initiating CPB requires systemic anticoagulation for the patient's entire blood volume will be circulating through an extracorporeal circuit. Intravenous heparin is infused, 300 to 400 units/kg, to achieve an activated clotting time >450 seconds. After CPB has been discontinued, heparin is reversed with intravenous protamine sulfate.[6] Protamine is a naturally occurring protein derived from fish and therefore carries a small risk of anaphylaxis-type reaction with its use. The onset of high pulmonary arterial pressures, systemic hypotension, and acute right heart failure during the administration of protamine is concerning for a protamine reaction. Specific patients at risk include those with known fish allergies, or those who have been previously sensitized (reoperations or diabetics using protamine-containing insulins).[7]

In addition to stopping the heart and substituting circulation and ventilation with CPB, another physiologic change is the systemic cooling of patients to temperatures ranging from 28°C to 34°C to reduce cellular metabolism.[6] This provides additional protection to all organ systems. The patient is rewarmed before discontinuing CPB; core temperature is monitored in the immediate postoperative setting to ensure normothermia and prevent abnormal coagulation or an increased risk of infection.[8]

CABG is accomplished by creating a route for blood to travel from a region of

good flow (the aorta or subclavian artery), around an occlusive coronary lesion, to an area deprived of adequate flow. Available conduits include the internal mammary arteries, the greater saphenous veins (GSV), and the radial arteries. The internal mammary vessels are most commonly left in situ proximally connected to the subclavian artery and anastomosed distally to the target coronary. When the GSV or radial arteries are used, they are free grafts, requiring anastomosis proximally to the aorta for inflow. Internal mammary arterial patency rates approach 90% at 10 years; GSV patency is reported 70% to 80% at 5 years and 40% to 60% at 10 years.[9] Because of the difference in the native architecture of the venous conduit, there is a higher rate of neointimal hyperplasia and atherosclerosis, leading to earlier stenosis. Radial artery grafts have greater than 80% patency at 5 years.[9]

At the completion of the procedure, the patient is slowly weaned off CPB, and the heart restarts the work of maintaining cardiac output (CO). CPB causes a number of physiologic changes that are evident immediately after its discontinuation and into the postoperative period. Circulating the patient's blood through the extracorporeal circuit activates coagulation, complement, fibrinolytic, and cytokine cascades. This can result in a clinically significant systemic inflammatory response syndrome (SIRS) and/or coagulopathy.[6] The nonpulsatile and relatively hypotensive nature of the CPB circuit leads to activation of the body's natural sympathetic system, which can lead to an increased incidence of postoperative arrhythmias.

CABG can be performed without the use of CPB, thereby decreasing or eliminating the physiologic alterations of the bypass circuit. Off-pump CABG (OPCAB) is performed with special instruments that stabilize the beating heart and allow the surgeon a small area of motionless myocardium to complete the required vascular anastomoses. OPCAB has documented benefits, including decreased hospital costs, length of stay, myocardial dysfunction, stroke, renal dysfunction, transfusion requirements, and gastrointestinal dysfunction.[6,10–14] OPCAB techniques are used mainly by surgeons experienced with this modality. Good candidates are those patients with good cardiac function, no significant valve disease, and good target vessels. Some high-risk patients with many systemic comorbidities may do poorly with the physiologic stresses of CPB and may be candidates for OPCAB.

INITIAL CRITICAL CARE MANAGEMENT

Management of postsurgical patients begins at the time of transfer from the operating room to the ICU. To ensure this safe transit, a team of transporters that includes a member of the surgical team and anesthesia should be present to treat life-threatening situations. Before leaving the operating room, a systematic review of the patient's physiologic status should be performed. Specifically, all monitoring devices are checked, and the patient's vital signs must be appropriate for transport. Significant bleeding, hypothermia, and acidosis should be corrected before leaving the operating room.

The patient is transported with continuous electrocardiogram (ECG) tracings, invasive blood pressure monitoring, and pulse oximetry. The transport team must be equipped with battery-operated infusion pumps to have uninterrupted delivery of the required cardiovascular medications until arrival in the ICU. Sudden changes in cardiac rate, rhythm, and systemic blood pressure can occur quickly, and the transporting team must be prepared to correct them en route. The transporting team must have additional emergency medications readily available. Mechanical breaths are given via bag-mask ventilation from a portable and full oxygen tank.

Upon arrival at the ICU, the team of transporters work together with the accepting ICU staff to provide a seamless transfer of care. The endotracheal tube is immediately connected to the awaiting mechanical ventilator. Cardiovascular medication dosages and rates are confirmed by the ICU staff and, ideally, continued on the same pumps used in transport to avoid any errors. Immediate pump exchange of infusions is made if needed based on pretransfer communication of medications between the operating room and the ICU nurse. The patient's thoracic drainage tubes are immediately connected to wall suction to evacuate any residual fluid that has collected during transport.

The patient is connected to continuous ECG, invasive and noninvasive blood pressure, pulse oximetry, and the appropriate pulmonary arterial catheter tracings. Immediately after the safe transfer from the operating room to the ICU monitors, a thorough physical examination is performed for vital signs, lateralizing neurologic findings, cardiac murmurs, breath sounds, abdominal distension, quality and quantity of urine and chest tube output, and evidence of extremity malperfusion by examining for color, palpable pulses, and tactile temperature. A 12-lead ECG is obtained upon arrival for postoperative baseline and daily thereafter to evaluate for myocardial ischemia. A portable chest X-ray is checked for placement of the endotracheal tube, the positions of the thoracic drainage tubes, the presence of hemo/pneumothorax, the width of the

mediastinum, and pulmonary vascular congestion. A full set of laboratory values is obtained: arterial blood gas, basic metabolic panel, complete blood count, serum magnesium and phosphorous, serum lactic acid, and a full coagulation profile consisting of prothrombin time, activated thromboplastin time, and international normalized ratio (INR).

Diagnosis and treatment of postoperative abnormalities should involve an algorithmic and systems-based approach. **Figure 8.1** illustrates the algorithm for management of low output state after CABG.

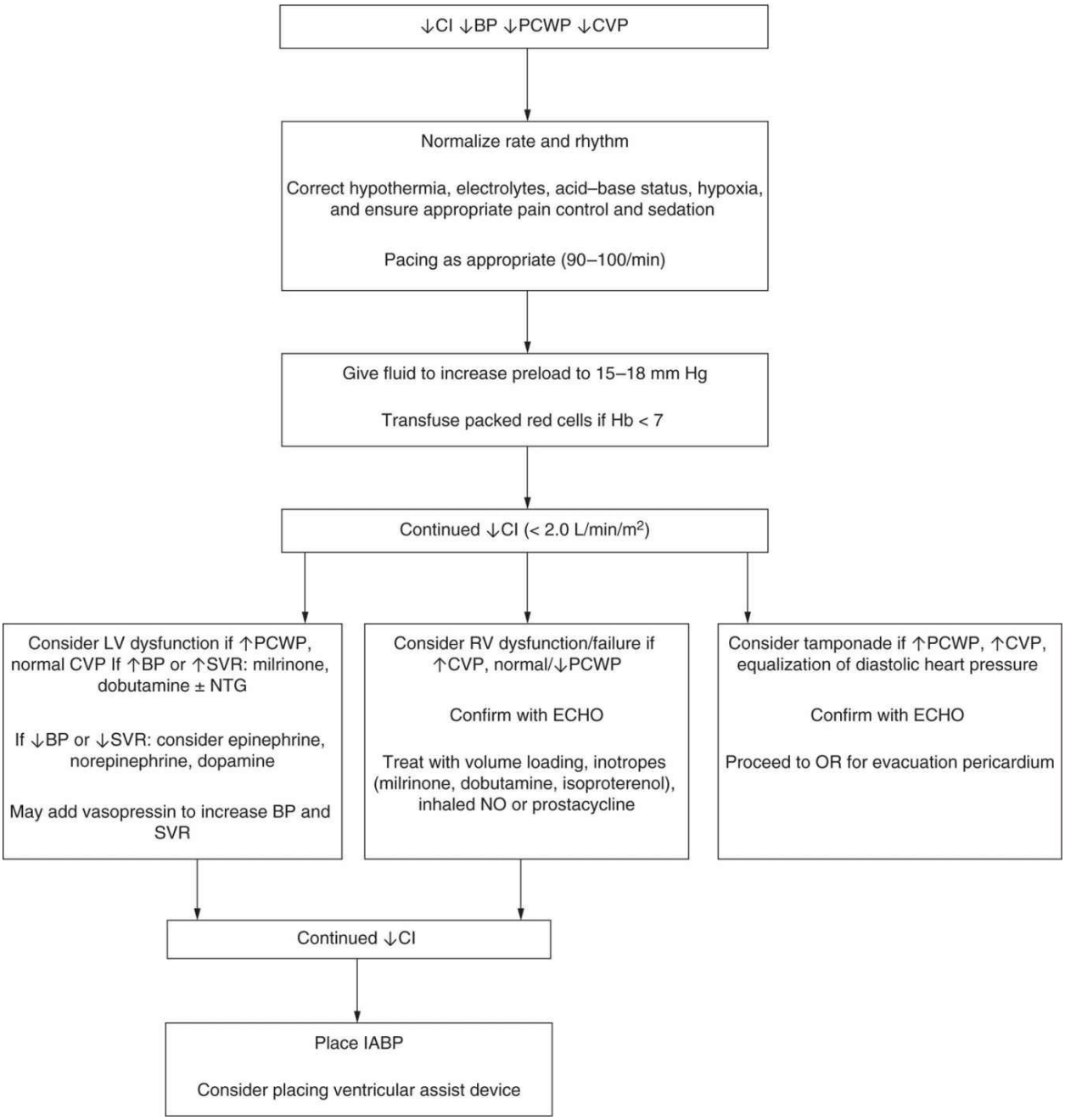

FIGURE 8.1 Algorithm for management of low output state after CABG. BP, blood pressure; CABG, coronary artery bypass surgery; CVP, central venous pressure; ECHO, echocardiogram; Hb, hemoglobin; IABP, intra-aortic balloon pump; LV, left ventricular; PCWP, pulmonary capillary wedge pressure; RV, right ventricle; SVR, systemic vascular resistance.

SYSTEMS MANAGEMENT

CARDIOVASCULAR

Postoperative cardiovascular issues can generally be divided into cardiac rate, rhythm, preload, afterload, contractility, or a combination of these. As discussed earlier, the use of a PA catheter can be omitted in patients with normal preoperative cardiac function; however, its use can provide a significant amount of information and guide management in the intensive care setting. When the PA catheter is not used, non-invasive hemodynamic monitoring, close physical examination, and clinical parameters such as urine output can be used to ensure adequate postoperative end-organ perfusion.

Rate

Rate disturbances are common in the immediate postoperative setting. Tachycardia can be caused by any number of physiologic disturbances such as CPB-induced sympathetic activation, pain, hypothermia, anemia, systemic hypoxemia, or pathologic postoperative conditions such as myocardial ischemia, tamponade, pneumothorax, or postpericardiotomy inflammation. Sinus tachycardia, although not inherently dangerous, contributes significantly to myocardial oxygen demand and should be avoided when possible in the immediate postoperative setting. Treatable causes of tachycardia should be addressed promptly. When secondary to sympathetic activation, atrioventricular (AV) nodal blockade with beta-blockers are considered first-line therapy; however, the use of beta-blockers in the immediate postoperative period is complicated by the depression of myocardial contractility. Postoperative myocardial depression usually dissipates within the first 12 to 24 hours of surgery, and beta-blockers are usually begun on postoperative day 1, with or without the presence of sinus tachycardia.

Asymptomatic bradycardia with or without conduction blockade and without changes to end-organ perfusion may not need to be treated urgently. However, when CO is inadequate, epicardial pacing may be accomplished via temporary ventricular and/or atrial wires placed routinely during the completion of the procedure. Transcutaneous pacing pads can be considered in an expedited fashion when urgent pacing is required in those patients without wires. Transvenous pacing wires can also be placed. When pacing is required, AV sequential pacing for AV nodal blockade or atrial pacing for sinus bradycardia is preferred to ventricular pacing alone to preserve the output of atrial systole, which increases preload and can contribute up to 30% of CO.

Rhythm

Rhythm disturbances, similarly, can be caused by the wide range of etiologies previously discussed, with the addition of electrolyte abnormalities (specifically potassium, magnesium, and calcium), acid–base disturbances, and myocardial irritation from indwelling catheters.

Atrial fibrillation (AF) is the most common post-CABG arrhythmia, occurring in up to 40% of patients. It usually occurs within the first 5 days of surgery but has a peak incidence at postoperative day 2. Risk factors associated with the development of AF include advanced age, history of paroxysmal AF, chronic obstructive pulmonary disease, the use of CPB, and longer intraoperative CPB times.[15, 16] Pharmacologic rate control and cardioversion are the two principles of treatment in new-onset AF. When AF is associated with rapid ventricular response, rate control is employed early to avoid a prolonged increase to myocardial oxygen demand, as is associated with other tachyarrhythmias. Beta-blockers are first-line therapy for acute rate control while corrections of the potential etiologies of the AF are explored.[17, 18]

In the absence of an identifiable and treatable cause of the AF in a stable patient, pharmacologic cardioversion may be performed with intravenous amiodarone. Administered as a bolus followed by continuous infusion, amiodarone acts both as a cardioverting agent with its Class III antiarrhythmic properties and as a sympatholytic and AV nodal blocker with its intrinsic beta receptor-blocking properties. Calcium channel blockers and digoxin are not typically used as first-line treatments in this setting.[19] Electrical cardioversion is reserved for patients with AF with rapid ventricular response with associated hemodynamic compromise. With significant hypotension or evidence of end-organ malperfusion associated with the onset of rapid AF, synchronized electrical cardioversion should be performed immediately. When AF persists, systemic anticoagulation with a heparin infusion should be initiated within 48 hours and bridged to therapeutic warfarin therapy with a target INR of 2.0 to 3.0.[18, 20]

Preload

Preload is the left ventricular end-diastolic volume (LVEDV), contributing to left ventricular (LV) myocyte stretch just prior to contraction. According to Starling’s law, increasing preload is associated with a predictable increase in LV contractility until a critical point is reached where further increases in preload lead to overdistension of the LV and a decrease in contractility. It is therefore

necessary to optimize preload to achieve the best CO. The most accurate measure of preload is by direct measurement of the left ventricular end diastolic pressure (LVEDP); this can be accomplished only via transarterial catheterization of the LV. Estimates of LVEDP can be made by measuring pulmonary artery wedge pressure (PAWP), pulmonary arterial diastolic pressure, or central venous pressure (CVP). In general, the further away the measurement from the LV, the less accurate the estimate of the LVEDP. In the postoperative period, however, these measurements can provide easy and rapid estimates of intracardiac volume status.

PAWP is measured after inflating the distally located PA catheter balloon in a segmental PA. This value approximates left atrial pressure, which in turn estimates LV pressure with the open mitral valve. Similarly, pulmonary arterial diastolic pressure, also measured by the PA catheter, estimates transmitted LA pressure. The PA diastolic pressure is, in general, slightly higher than the PAWP; it can be calibrated to the PAWP and trended in real time without having to frequently inflate the PA catheter balloon and risking PA rupture. Both PAWP and PA diastolic pressure are inaccurate in the setting of significant pulmonary hypertension or severe mitral valve disease. CVP provides the least accurate estimate of LVEDP; however, it is readily measured with a central venous catheter. CVP is an inaccurate estimation of LVEDP with right heart dysfunction, pulmonic or tricuspid valve disease. Trends, rather than direct measurements, are the most important aspect of these measurements. Fluctuations in pressure measurements mimic the changes in the LVEDP, and adjustments to postoperative resuscitation can be guided by those values.[6, 21]

Preload will be decreased when there is inadequate circulating volume. Active bleeding may be evident via increased chest tube output. More commonly, a postbypass inflammatory state results in a systemic response that includes capillary leakage and third-spacing of intravascular volume. Management is aimed at replacing lost volume, typically with colloid infusions. If there is active bleeding, packed red blood cells may be transfused to maintain adequate tissue oxygenation, as measured by the mixed venous calibration. A thick, stiffened left ventricle typical of patients with long-standing hypertension has poor compliance, and diastolic filling will be compromised. Patients with significant LV hypertrophy may require even higher filling pressures to maintain an adequate preload and normal CO.

Preload can also be compromised in the setting of cardiac tamponade. Postoperative bleeding into the pericardium increases the transmural pressure of

the cardiac chambers and compromises venous return to the right heart to restrict filling. Beck Triad (hypotension, distended neck veins, and distant/muffled heart sounds) is the classic finding in tamponade. **Table 8.3** lists the findings in acute tamponade. The diagnosis of tamponade may be subtle, however. The acute or gradual increase in CVP or PA pressures associated with hypotension may be an indication of tamponade without other physical examination findings. One can observe a trend toward equalization of the CVP, right atrial pressure, right ventricular diastolic pressure, PA diastolic pressure, and PAWP. A portable chest X-ray may show increased widening of the mediastinal silhouette, and echocardiography may demonstrate pericardial fluid with compression of the right heart and distension of the IVC. Diagnosis is critical and time-sensitive; treatment should be sought emergently. Evacuation of the pericardial blood is accomplished with resternotomy because this purely mechanical problem will be unresponsive to noninvasive treatments.[6]

TABLE 8.3 Findings of Acute Tamponade

Tachycardia and/or hypotension
Distended neck veins and elevated CVP (only if the patient is not hypovolemic)
Equalization of pressures including CVP, RA mean, RV diastolic, PA diastolic, and PA wedge (usually within 5 mm Hg)
Low voltage ECG tracings or electrical alternans
CXR findings including widening of the mediastinum or cardiac silhouette
TEE findings of RA or RV compression and IVC distension

CVP; central venous pressure; CXR, chest X-ray; ECG, electrocardiogram; IVC, inferior vena cava; PA, pulmonary artery; RA, right atrium; RV, right ventricle; TEE, transesophageal echocardiogram.

Afterload

Afterload is the pressure, or wall tension, generated by the left ventricle to overcome systemic vascular resistance (SVR) to produce adequate ejection of blood; the normal SVR range is 900 to 1200 dynes · seconds/m^5.[6, 21] Increased SVR in the postoperative period may occur secondary to increased sympathetic output after CPB, altered baroreceptor activity, hypothermia, pain, or anxiety. Patients with preoperative hypertension, diabetes, peripheral vascular disease, and chronic kidney disease are at higher risk for postoperative hypertension. The goal postoperatively is to achieve a pressure adequate for good organ perfusion, although not placing too much stress on the cardiac and vascular suture lines. This is especially true in older or frail patients with poor tissue strength. Systolic blood pressure is usually maintained between 90 and 130 mm Hg with a mean

arterial pressure of less than 90 mm Hg. A higher blood pressure may be needed in patients with significant peripheral arterial disease to maintain end-organ perfusion. Conversely, a high SVR may restrict flow through the systemic microvasculature, thereby decreasing organ perfusion. An elevated SVR places increased stress on the heart by increased LV wall tension and afterload, increasing myocardial oxygen demand and possibly worsening postoperative myocardial function.[6]

Postoperative sedatives such as propofol decrease SVR and blood pressure. Initially after arrival in the ICU, it is important that medications are both rapid onset and quickly cleared in the case of sudden hemodynamic changes.

Sodium nitroprusside lowers both SVR and pulmonary vascular resistance by relaxing arterial smooth muscle and can be used in the setting with an elevated SVR and systemic pressure. Nitroprusside is metabolized to cyanide and may therefore become toxic with prolonged use. Its toxicity is increased with liver dysfunction.

Nitroglycerin is commonly used in the setting of systemic hypertension following CABG. This venodilator increases venous compliance and reduces preload. It should be avoided in states of hypovolemia because it will significantly reduce ventricular filling and may induce a significant reflex tachycardia that will increase myocardial oxygen demand.

Short-acting beta-blockers can also be used for hypertension. However, negative inotropes are generally avoided in the immediate postoperative period. Dihydropyridine calcium channel blocking agents such as nicardipine are almost purely peripheral vasodilators and can be used to treat an elevated SVR. Caution should be exercised because this class of medication has a half-life that is significantly longer than that of nitroprusside and nitroglycerin.

A *low* SVR is also troublesome because it may cause a reflex tachycardia and an increase in CO to maintain peripheral perfusion. Decreased vasomotor tone as a result of SIRS following CPB is the most common cause of a decreased SVR. Other causes include peripheral vasodilation, sepsis, adrenocortical insufficiency, or anaphylaxis. Treatments include maintaining adequate preload, ensuring sufficient CO, and utilizing peripheral vasoconstrictors as needed. Norepinephrine is a first-line agent that may be supplemented with vasopressin or phenylephrine as needed. Epinephrine may also be used in the setting of a patient that requires both vasoconstricting and inotropic effects to maintain perfusion.

Contractility

Myocardial contractility is the intrinsic force of contraction and is generally estimated by left ventricular ejection fraction (LVEF). Patients with poor myocardial contractile function preoperatively have higher risks from surgical intervention. Those with a normal LVEF may also emerge from CABG with depressed myocardial contractility caused by ischemia-reperfusion injury, cardioplegic arrest, myocardial edema, or ischemia.

Intraoperatively, LVEF is recorded with TEE and is compared to the known preoperative values. Postoperatively, contractility may be estimated by measuring the CO using a PA catheter. Utilizing the principle of thermodilution, a small volume of cold saline is injected into the right atrial port, where it mixes with blood. The change in temperature is sensed by a probe at the tip of the catheter located distally in the pulmonary arterial tree. Cardiac output is estimated by the change in temperature of blood over time between the site of injection of cold saline and the tip of the pulmonary artery catheter. The faster the decrease in temperature, the higher the CO and vice versa. Other less invasive systems exist for estimating CO, including a FloTrac® sensor, which utilizes arterial line pressure measurements and waveforms to estimate the CO based on standardized values of SVR for the patient's height, weight, and age.

Post-CABG myocardial dysfunction is usually transient, especially in patients with normal preoperative function, and usually resolves within 12 to 48 hours. Normal CO is 4.0 to 6.0 L/min, but varies depending on the patient's size. The cardiac index (CI) is a measure of the CO, standardized to the patient's body surface area. The CI, measured in L/min/m^2, is a more effective measure of the patient's contractile function. An adequate CI should be greater than 2.0 L/min/m^2. With adequate preload and afterload, a depressed CI requires inotropic medications to augment myocardial contractility.[6]

Epinephrine is a strong alpha and beta-adrenergic agonist and can be simultaneously used as a positive inotrope and vasopressor. Dobutamine is a strong beta agonist and weak alpha agonist. Both exert strong inotropic effects and are titrated to achieve an adequate CO. Their use may be limited because of the intrinsic arrhythmogenic properties of the medications. Higher doses used to achieve an adequate CO may cause tachyarrhythmias that increase myocardial oxygen demand. Epinephrine causes fewer tachyarrhythmias at higher concentrations than does dobutamine, although both are acceptable for use in the immediate postoperative period.

Milrinone is a phosphodiesterase inhibitor that increases myocardial contractility while relaxing peripheral and pulmonary arterial smooth muscle. It is an ideal drug for an adequately volume-loaded patient with depressed myocardial contractility and an elevated SVR or pulmonary hypertension. Milrinone has a significantly longer half-life than epinephrine, and its use can have effects lasting for hours after it has been discontinued.

Other positive inotropes such as dopamine and isoproterenol exist, and their use varies depending on the clinical situation. Any medication used to treat impaired myocardial contractile function must be weighed against other systemic effects that they will induce on the critical care patient. In severe postoperative cardiogenic shock, placement of an intra-aortic balloon pump may be indicated to decrease afterload, increase coronary perfusion, and improve CO.

Although LV dysfunction is more commonly associated with a postoperative decrease in CI, right ventricular dysfunction may play an important role. Preexisting right heart failure, inadequate right ventricular protection during CPB, right ventricular infarction, and pulmonary hypertension may contribute to postoperative right heart dysfunction, which may present as a decreased CO. Common findings include elevated right ventricular filling pressures associated with relatively low or normal LV filling pressure. Echocardiography may demonstrate a hypokinetic and dilated right ventricle and/or new-onset tricuspid regurgitation.

Management of right heart failure is similar to that of left heart failure. The goal is to optimize preload for adequate myocardial stretch, provide inotropic support, and minimize afterload, which in this case is the pulmonary arterial vasculature. Milrinone can provide good inotropic support with pulmonary vasodilation in this setting. Dobutamine, isoproterenol, nitric oxide, prostacyclin, and sildenafil citrate may also be used as adjuncts in the ICU setting to improve RV function and decrease pulmonary hypertension.[22, 23]

BLEEDING AND HEMATOLOGIC DISTURBANCES

Bleeding in the immediate postoperative period is not uncommon post-CABG. Multiple reasons for this exist: preoperative antiplatelet agents or anticoagulants, disturbances to the coagulation cascade, hepatic dysfunction, CPB-associated platelet dysfunction, and hypothermia. The volume of hourly bleeding should trend downward from the time of sternal closure. A guideline for acceptable postoperative bleeding is 2 mL/kg for the first 3 hours, followed by 1 mL/kg for the next 3 hours, and then by 0.5 mL/kg up to postoperative hour twelve. We

define surgical bleeding mandating re-exploration vs. excessive bleeding with initial conservative measures as illustrated in **Figure 8.2**. Up to 4% of postoperative bleeding in CABG patients requires re-exploration.[24–26] Persistent hemorrhage is quickly communicated to the attending surgeon.

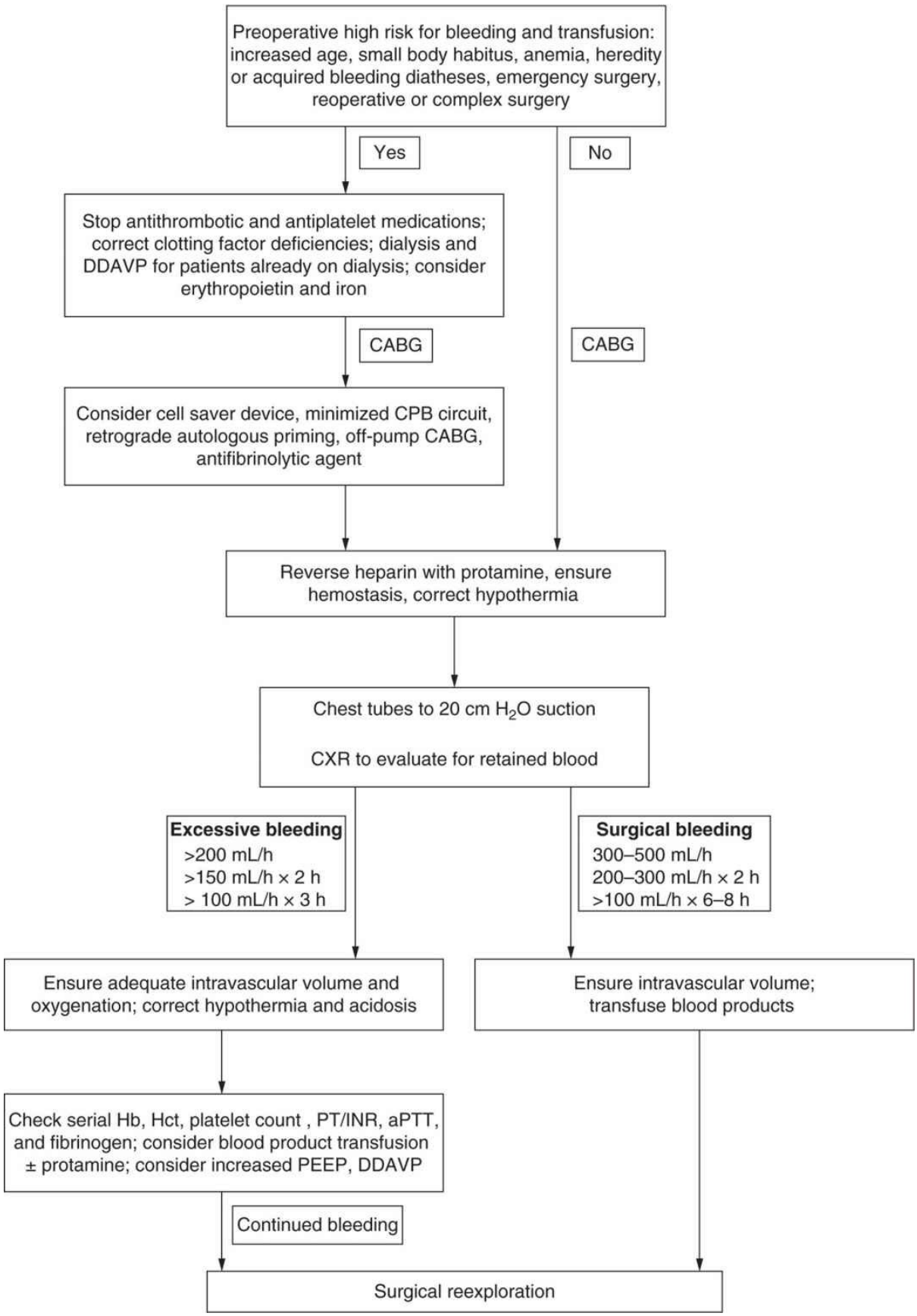
Preoperative high risk for bleeding and transfusion: increased age, small body habitus, anemia, heredity or acquired bleeding diatheses, emergency surgery, reoperative or complex surgery
Yes
No
Stop antithrombotic and antiplatelet medications; correct clotting factor deficiencies; dialysis and DDAVP for patients already on dialysis; consider erythropoietin and iron
CABG
CABG
Consider cell saver device, minimized CPB circuit, retrograde autologous priming, off-pump CABG, antifibrinolytic agent
Reverse heparin with protamine, ensure hemostasis, correct hypothermia
Chest tubes to 20 cm H_2O suction
CXR to evaluate for retained blood
Excessive bleeding
>200 mL/h
>150 mL/h × 2 h
> 100 mL/h × 3 h
Surgical bleeding
300–500 mL/h
200–300 mL/h × 2 h
>100 mL/h × 6–8 h
Ensure adequate intravascular volume and oxygenation; correct hypothermia and acidosis
Ensure intravascular volume; transfuse blood products
Check serial Hb, Hct, platelet count , PT/INR, aPTT, and fibrinogen; consider blood product transfusion ± protamine; consider increased PEEP, DDAVP
Continued bleeding
Surgical reexploration

FIGURE 8.2 Algorithm for the management of postoperative bleeding. aPPT, activated partial thromboplastin time; CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; CXR, chest X-ray; DDAVP, desmopressin; INR, international normalized ratio; Hb, hemoglobin; Hct, hematocrit; PEEP, positive end-expiratory pressure; PT, prothrombin time.

The quality and quantity of chest tube drainage are examined in the bleeding patient. Fresh, bright red blood with brisk flow may indicate arterial surgical bleeding and require re-exploration. Slow draining, dark red blood may be evidence of venous bleeding or oozing from raw surfaces and may be controlled with improved coagulation, warming to normothermia, clotting factors, or watchful waiting.

Frequent laboratory tests of serum hemoglobin, hematocrit, platelet count, prothrombin time, activated partial thromboplastin time (aPTT), and INR are indicated. Although no specific transfusion trigger exists, packed red blood cell transfusions are generally initiated to maintain hemoglobin of at least 7 mg/dL. In patients with relatively more systemic oxygen demand, such as those with a lower threshold for end-organ ischemia, hemoglobin levels are general kept higher, around 8 to 10 mg/dL. In the coagulopathic patient with an elevated INR, fresh frozen plasma (FFP) may be transfused if the INR is greater than 1.5. An elevated aPTT, greater than 1.5 times baseline, may be an indication of residual circulating heparin, and additional protamine may be infused in doses of 50 to 100 mg. Checking the intraoperative anesthesia record is important because the total amount of infused protamine should not exceed 1.3 mg/100 units of heparin given for CPB.[27]

Postoperative platelet dysfunction may be a result of CPB, uremia from chronic kidney disease, or antiplatelet medications. Platelet concentrations should be maintained at 100,000/μL if ongoing coagulopathy and bleeding are present. Desmopressin (DDAVP) may also be used as an adjunct to postoperative bleeding that is thought to originate in platelet dysfunction. It causes a release of von Willebrand factor from vascular endothelium and promotes the adherence of platelets to collagen. Its routine prophylactic use to treat CPB-induced platelet dysfunction is not recommended; it may be used in excessive hemorrhage or when bleeding is secondary to uremia or known von Willebrand disease, type I or II.[26]

Cryoprecipitate, which contains factors VII, VIII, fibrinogen, and von Willebrand factor, may also be used as an adjunct to the bleeding patient receiving packed red blood cells, FFP, and platelets to account for dilution of

these factors. When massive volumes of blood product are being transfused, the ratios of packed red blood cell, FFP, and cryoprecipitate should be relatively equal.[26, 28]

Increasing intrathoracic pressure may be beneficial by effectively tamponading slowly bleeding surfaces, particularly from the chest wall. This is accomplished by increasing positive end-expiratory pressure (PEEP) on the ventilator, usually from 5 up to 8 to 10 mm Hg. The intravascular fluid status of the patient is important because this increase in PEEP reduces venous return to the heart and may cause hypotension.

Persistent hemorrhage, particularly in the setting of hemodynamic compromise with increased vasopressor requirements and normalized coagulopathy, may be an indication for return to the operating room for re-exploration.

PULMONARY

During transfer to the ICU, patients are manually bag-ventilated on 100% oxygen; they are transitioned to mechanical ventilation immediately after arrival. After arrival, a volume-controlled mode is used to maintain set minute ventilation. This mode of delivery can be programmed via assist-control ventilation or synchronized intermittent mandatory ventilation (SIMV); with the patient fully sedated, SIMV will perform as assist-control mode. The fraction of inspired oxygen is titrated down from 100% to 40% as tolerated by the patient to maintain hemoglobin saturation above 95%. Tidal volumes are set according to the patient's weight, and both tidal volume and respiratory rate should be adjusted as needed to maintain adequate ventilation after examination of the first arterial blood gas.

Most patients will be ready for extubation within 6 hours of arrival in the ICU. Risk factors for prolonged mechanical ventilation include advanced age, tobacco smoking, COPD, female gender, renal failure, emergency surgery, persistent cardiogenic shock, and cerebrovascular accidents (CVA).[29, 30]

Hemodynamically stable patients who are fully awake, alert, and following commands can proceed to ventilator weaning. Several protocols exist to ensure safe weaning from mechanical ventilation, and all rely on the patient's ability to breathe spontaneously and ventilate adequately. Initiating a spontaneous breathing trial (SBT) with zero mechanically delivered breaths, a PEEP of 5 cm H_2O, and little pressure support will allow the patient to assume the work of

breathing. During the SBT, diaphoresis, agitation, hypoxemia, use of accessory respiratory muscles, or hemodynamic instability are sufficient evidence that the patient is not ready for extubation. After 30 minutes, if the patient does not exhibit signs of physiologic distress, an arterial blood gas is measured to evaluate for adequacy of ventilation and oxygenation. If the pH ≥ 7.32, Pa_{O_2} ≥ 60 mm Hg, and P_{CO_2} ≤ 45 mm Hg, the patient meets the criteria for extubation in the right clinical setting.[6]

The patient is transitioned from mechanical ventilation to supplemental oxygen via facemask delivering humidified air. This should be progressively weaned to nasal cannula as tolerated by the patient to maintain a hemoglobin saturation above 92%. Pulmonary toilet, pain control, and mobilization are critical in the immediate postoperative period to prevent atelectasis and effusions that can delay the patient's progress. Incentive spirometry is taught to each patient and recommended frequently throughout the ICU stay.

If clinically indicated, high-flow oxygen via nasal cannula or continuous positive airway pressure via mask can be used to decrease the work of breathing for the patient and improve oxygenation. This is particularly true in obese patients or those with known preoperative pulmonary dysfunction.

RENAL

Management of fluids following CABG can be divided into two phases: (1) volume loading and (2) diuresis. Initially, maintaining an adequate preload is critical to CO, and infusion of significant volumes of intravenous fluids may be required. A urinary catheter with a temperature probe is inserted before the start of surgery and is left in place for precise hourly measurements of urine output that confirm good organ perfusion. Urine output should be maintained at 0.5 mL/kg/h; oliguria may be evidence of inadequate end-organ perfusion, and addressing problems with preload, afterload, and/or contractile function is mandatory.

Up to 8% of patients will develop acute kidney injury (AKI), and up to 0.7% will require dialysis after CABG. The presence of AKI increases the risk of perioperative mortality to 14%, and that rate is doubled for those requiring dialysis.[27, 31]

Within the first 24 to 48 hours, the CPB-associated SIRS response improves, and loss of fluid to the extravascular space secondary to capillary leak will reverse. Oncotic pressure will draw fluid into the intravascular space, and the

total body fluid volume will begin to decrease as urine output increases. In some cases, urine output alone is insufficient to remove the excess fluid. CPB can both activate the renin–angiotensin–aldosterone system and stimulate antidiuretic hormone release, both reducing fluid excretion. After the volume loading phase, when managing preload is no longer a concern, typically on the first or second postoperative day, the patient may be started on furosemide or other loop diuretic to aid in volume unloading.

GASTROINTESTINAL

Enteral feeding of the post-CABG patient should be done as soon as it is safe. For patients extubated immediately postoperatively, liquids and then solid food are started on postoperative day 1. For patients who require longer periods of mechanical ventilation, adequate caloric intake is ensured with an orogastric or nasogastric tube placed at the time of surgery. For longer-term enteral nutrition, a soft Dobhoff feeding tube should be inserted.

Gastrointestinal complications occur in 1% to 3% of CABG patients, and, although rare, they increase morbidity and mortality. The most common ones include paralytic ileus (gastric, small bowel, or colonic in origin), upper gastrointestinal bleeding, mesenteric ischemia attributed to diffuse hypoperfusion or acute vascular occlusion, and acute acalculous cholecystitis.

Paralytic ileus of the small bowel or colon may present with abdominal cramping, distension, nausea with bilious emesis, and obstipation. Its cause in the post-CABG patient is usually secondary to the use of opioid analgesics; however, CPB-associated SIRS may play a role. Treatment is largely supportive and requires bowel rest; discontinuation of opioid medications; and maintenance of adequate electrolyte levels, intravenous hydration, and early mobilization. Nasogastric decompression is indicated in the setting of persistent nausea and emesis and should be maintained until evidence of bowel function returns.[32–34]

Upper gastrointestinal bleeding may occur from previously undiagnosed gastroduodenal lesions, stress ulcers, or diffuse gastritis secondary to hypoperfusion. Epigastric pain associated with nausea and bloody or “coffee-ground” emesis should immediately prompt further investigation with esophagogastroduodenoscopy EGD. Other findings include melena and increasing blood urea nitrogen (BUN) with a normal serum creatinine with decreasing serum hemoglobin. In all high-risk patients postoperatively, the use of acid-reducing medications is initiated to reduce the incidence of bleeding

caused by stress gastritis.[35–37]

Mesenteric ischemia can be a life-threatening disease that requires urgent work-up. In post-CABG patients, especially those suffering from decreased CO, systemic hypoperfusion may lead to diffuse ischemia. This may be exacerbated in patients with known mesenteric arterial occlusive disease. Presenting symptoms may include vague abdominal pain, abdominal distension, obstipation, or hematochezia, as the endothelium necroses and begins to slough. Acute thrombosis or embolism to a major mesenteric vessel may also produce ischemia. In this case, the onset of pain may be more acute and intense with a patient in more distress than clinical examination would indicate. In both cases, elevations of white blood cell count and serum lactic acid occur as the ischemic bowel transitions to anaerobic metabolism. In a hemodynamically stable patient, a suspicion for mesenteric ischemia should be worked up with computed tomography (CT) angiography. In a rapidly deteriorating patient with a high suspicion for mesenteric ischemia, surgical exploration of the abdomen, possibly with on-table mesenteric angiography and bowel resection, should be planned.

Acalculous cholecystitis is a classic disease of the ICU patient with poor CO and compromised foregut perfusion. Symptoms may include acute onset of right upper quadrant pain with tenderness, fever, rigors, nausea, and emesis. Laboratory studies may be normal or demonstrate a new leukocytosis and hyperbilirubinemia or mild transaminitis. Diagnosis is usually made with right upper quadrant abdominal sonography, specifically looking for thickening of the gallbladder wall, pericholecystic fluid, and usually the absence of gallstones. Patients with acalculous cholecystitis may be treated with antibiotics alone. If the patient begins to clinically deteriorate, and fails nonoperative management, the placement of a percutaneous cholecystostomy tube will usually treat the obstruction without the need for further immediate surgical intervention.[38, 39]

NEUROLOGIC

The post-CABG patient is at significant risk for neurologic insults. Clinically significant postoperative CVA following CABG are estimated at 1% to 2%. Risk factors include increasing age, diabetes, previous CVA, carotid artery occlusive disease, significantly calcified aorta, aortic or mitral valve, prolonged CPB time, and AF.[40, 41]

CVA can be divided grossly into embolic or hemorrhagic stroke, global hypoperfusion, or hypoxemia. Clinically evident strokes are usually identified

after the patient is wakened from anesthesia and a full neurologic examination is completed. Inability to fully regain consciousness once sedation is weaned, hemiplegia or other lateralizing deficits, dysarthria, and visual field abnormalities may be apparent. Immediate noncontrast CT of the head should be obtained in any patient for whom suspicion for CVA exists.

Confusion and agitation are also common neurologic disturbances that occur in the postoperative setting. Although gross agitation is usually clear to all, subtle signs of confusion may be apparent only to a patient's family or nurse who cares for the patient from day to day. A mental status examination should be performed to assess the patient's orientation. If the patient is a threat to himself or others, emergency sedation or 1:1 observation may be indicated.

In all cases, a full assessment of the potential causes of the change in mental status is performed. Etiologies of confusion include narcotic medications, CVA, hypoxemia or hypercapnia, alcohol withdrawal, metabolic derangements such as hypoglycemia, elevated BUN, ammonia or acidosis, and seizure activity. Treatment is aimed at correction of the underlying cause. When none can be reliably identified, noncontrast head CT and/or electroencephalogram may be required. Neurology consultation is always obtained.

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Patient and Family Information for: CORONARY ARTERY BYPASS SURGERY

BACKGROUND

CABG is a surgical procedure performed for patients who have blockages in the arteries that deliver oxygenated blood to their heart muscle. These blockages are caused by atherosclerosis, which occurs as a result of risk factors: smoking, hypertension, high cholesterol, diabetes mellitus, and family history.

Not all patients require surgery for these blockages; some can be treated with medications and others with minimally invasive procedures called stents. Surgery is recommended for those patients with a blockage in the main artery to their heart (left main artery) or multiple blockages in a patient with diabetes or decreased heart function. Some complex lesions also require surgical bypass.

Patients can be seen as outpatients to schedule their procedure. Others arrive in the hospital with a small or large heart attack, and it is recommended that they have surgery urgently to prevent complete blockage of the heart arteries that would result in a major heart attack and permanent loss of heart muscle function.

PROCEDURE

CABG surgery is performed with the patient asleep under general anesthesia. Most surgeries require between 3 and 6 hours, depending on the number of grafts that need to be placed. Although there are three main arteries to the heart, the branches of these arteries may be large and supply a significant amount of muscle. For that reason, patients may require between 1 and 6 grafts, depending

on the number of specific blockages and their specific anatomy.

The basis of the surgery is to use a vessel, or conduit, to bring new blood supply to the heart. The actual lesion itself is not removed. Rather, blood is rerouted from an area of high blood flow (such as the aorta), past the blockage, to an area of lesser blood flow. This procedure is often performed with the patient on a heart–lung machine, or CPB circuit. This device takes over the work of the heart and lungs while the surgeon is performing the operation. At the completion of the surgery, the patient is weaned off the machine, and the heart resumes beating on its own, pumping blood to the lungs and body.

CRITICAL CARE MANAGEMENT

Most patients are brought straight to the ICU after surgery. The first 48 hours are the most critical time after heart surgery. The patient is monitored closely for any changes in their blood pressure, heart rate, and organ function. Once they are awake after anesthesia and strong enough, they are removed from the ventilator and are able to breathe on their own.

In the ICU, the patients are watched closely for any signs of bleeding, irregular heart rates, and organ dysfunction. They are encouraged to deep breathe and cough to keep their lungs expanded. Pain control is very important for this process, and although they initially receive strong intravenous medications, they are slowly transitioned to oral medications as their pain improves. Respiratory therapists work with the patients immediately after arrival and throughout their hospital stay.

Another important part of recovery is mobilizing the patient after surgery. This helps lung function, bowel function, and overall strength. Deconditioning after heart surgery can be severe, and physical therapy is necessary to prevent this. Physical therapists work with all patients from the first day after surgery and continue to help them as they take a few steps, walk in the hallways, climb stairs, and mobilize on their own.

RECOVERY

Most patients are in the ICU for 24 to 48 hours after CABG surgery, barring any complications. The patient is then moved to a step-down monitored room in

preparation for discharge. In uncomplicated cases, families can expect their loved ones to return home within 5 to 7 days after surgery.

9

Basheer Karkabi
Eyal Herzog
Jacob Goldstein

Medications Used in the Management of Acute Coronary Syndrome

The pharmacologic management of an acute coronary syndrome (ACS) has evolved dramatically over the past three decades into a heavily evidence-based discipline. Contemporary treatment strategies have become more targeted, focusing on the unique pathophysiologic underpinnings of this disorder. Additionally, new therapeutic approaches are rigorously tested and proven in large clinical trials before becoming standard therapy. As our armamentarium of new therapeutics continues to grow, our diagnostic and management strategies will necessarily change over time. As such, practitioners caring for patients with ACS must become life-long students of this exciting and dynamic field in order to provide the best care for their patients in the years to come.

Appropriate medical therapy is indicated for all patients presenting with or suspected of having ACS. The goals of initial medical therapy are fourfold: to relieve pain, to halt the progression of disease, to reduce morbidity, and to improve survival. Because the term *ACS* encompasses a spectrum of severity with a common pathophysiology, the difficulty in the pharmacologic management comes in determining where in the spectrum a particular patient falls and balancing the risks and benefits in treating that patient to achieve the desired goals.

Once the diagnosis of ACS is established, the patient should quickly be

stratified by risk into one of several treatment strategies. Medical therapy should be immediately started in a rational manner to achieve the initial goals of treatment, namely, to interrupt platelet activation/aggregation and thrombus formation and to relieve pain. Patients diagnosed with an ST-segment elevation myocardial infraction (STEMI) should be emergently stratified to primary percutaneous coronary intervention (PCI) or fibrinolytic therapy, whereas those with unstable angina (UA)/non–ST-segment elevation myocardial infarction (NSTEMI) should be risk stratified into either an early invasive or an initial conservative approach. Regardless of what treatment strategy is initiated, patients should be continuously evaluated for high-risk features of disease, adverse hemodynamic consequences, and treatment failure. Such features often mandate deviation from the initial management strategy to a more aggressive one. Importantly, as a patient transitions from one treatment strategy to another, the pharmacologic approach can vary substantially.

In general, the pharmacologic approach to managing ACS should be prioritized with an emphasis on rapid treatment with medications known to provide morbidity and mortality benefit. Guidelines for treatment are useful; however, they cannot address every possible nuance experienced in clinical practice. Health care providers must have a thorough understanding of their institutional capabilities and preferences, as well as familiarity with the drugs, doses, indications, and side effects in order to provide patients with optimal benefit and minimal harm.

ANTI-ISCHEMIC AND ANALGESIC THERAPY

β-ADRENERGIC BLOCKERS

Rationale: β-Blockers are used to inhibit the actions of catecholamines on the β_1-adrenergic receptors located in the myocardium. Inhibition of these receptors leads to a reduction in myocardial contractility, atrioventricular (AV) node conduction, sinus node rate, and an overall reduction in systolic blood pressure. The net effect of these actions results in a decrease in cardiac work and myocardial oxygen demand. Additionally, β-blockers increase diastolic pressure-time, which may be important in increasing coronary blood flow. In patients with ACS undergoing PCI, a large meta-analysis showed a significant reduction in mortality at 30 days and 6 months for patients who received β-blocker therapy.[1] However, the COMMIT trial failed to demonstrate a mortality benefit with the

early use of β-blockers in patients with myocardial infarction.[2] This finding has been attributed to injudicious use of β-blockers in patients with heart failure or other risk factors for cardiogenic shock and has been instructive in the most recent guidelines involving recommendations for β-blocker usage in ACS. In contrast to the early aggressive use of β-blockers for acute myocardial infraction (MI), the CAPRICORN trial demonstrated a reduction in all-cause mortality, cardiovascular mortality, and nonfatal MI with β-blockers when 1959 patients with acute MI and left ventricular (LV) dysfunction were randomized to receive to low-dose carvedilol versus placebo and treated with a more gradual uptitration strategy.[3]

Indications: ACS (without contraindications), stable angina, compensated chronic heart failure.

Dosing: Multiple preparations available including intravenous (IV) and oral, β_1 selective and nonselective, short and long acting (**Table 9.1**).

TABLE 9.1 β-Blockers Used in ACS

DRUGS	SELECTIVITY	DOSE	COMMENT
Metoprolol tartrate	β_1	50–200 mg twice daily	Often initiated with 12.5–25 mg every 6–8 h
Metoprolol succinate	β_1	12.5–200 mg daily	Short-acting tartrate preferred for ACS; however, mortality benefit shown for stable patients with CHF
Carvedilol	β_1, β_2, α_1	3.125–25 mg twice daily	Started low and titrate up; mortality benefit for LV dysfunction
Bisoprolol	β_1	1.25–5 mg twice daily	
Atenolol	β_1	25–200 mg daily	
Labetalol	β_1, β_2, α_1	200–600 mg twice daily	
Propranolol	β_1, β_2	20–80 mg twice daily	
Esmolol	β_1	50–300 μg/kg/min	

ACS, acute coronary syndrome; CHF, congestive heart failure; LV, left ventricular.

Side effects: Hypotension, bradycardia, AV block, acute exacerbation of heart failure, bronchospasm, paradoxical hypertension (HTN) in setting of active cocaine use.

Contraindications: High-grade AV block, active bronchoconstriction, hypotension, bradycardia, severe LV dysfunction or heart failure (rales, S3 gallop), or in patients with myocardial infarction at high risk for cardiogenic shock (older age, female sex, relative hypotension, high Killip class, reflexive tachycardia).

Recommendations: The acute use of β-blockers in ACS is recommended in all patients without contraindications, especially in patients with ongoing angina and HTN. Short-acting, β_1 selective agents are typically used to minimize side effects and allow for dose titration. The common practice used to be a regimen of metoprolol 5 mg IV, repeated every 5 minutes, up to a total of 15 mg. Oral therapy can be started at metoprolol 25 to 50 mg every 6 hours, or bisoprolol 1.25 mg every 12 hours, and titrated to achieve the desired heart rate or blood pressure. Frequent heart rate and blood pressure checks, continuous electrocardiography (ECG) monitoring, and routine auscultation for rales and bronchospasm should be performed (preferably in an intensive care unit setting). Once stabilized, patients should receive maintenance doses of up to 100 mg metoprolol twice daily or bisoprolol 2.5 to 5 mg twice daily. In patients with LV dysfunction, β-blockers with proven mortality benefit such as bisoprolol, carvedilol, and metoprolol succinate should be utilized for long-term management.

CALCIUM CHANNEL BLOCKERS

Rationale: Calcium channel blockers (CCBs) inhibit myocardial and vascular smooth muscle contraction by reducing transmembrane inward calcium flux. In ACS, CCBs are useful in decreasing myocardial oxygen demand (by decreasing afterload, contractility, and heart rate) and in coronary vasodilatation. Meta-analyses of UA/NSTEMI trials involving CCBs have suggested no overall benefit in death or nonfatal MI.[4] Retrospective studies of verapamil and diltiazem have shown increased mortality in patients with LV dysfunction.[5, 6] Additionally, a trial using nifedipine was stopped early because of concern for harm when taken without concomitant β-blockers.[7]

Indications: In ACS, considered second-line therapy in β-blocker-intolerant patients for relief of angina, blood pressure control, and rate control of

supraventricular arrhythmias. CCBs are considered adjuncts to β-blockers and nitrates for the relief of ischemic symptoms. They are generally the preferred treatment for patients with cocaine-induced myocardial ischemia or variant angina.

Dosing: Multiple preparations both IV and oral, short and long acting (**Table 9.2**).

TABLE 9.2 Calcium Channel Blockers Used in ACS

DRUG	DOSE	DURATION OF ACTION	COMMENT
Nondihydropyridines			
Diltiazem	Immediate release: 30–90 mg every 6 h	Short	Avoid with known or suspected LV dysfunction
	Slow release: 120–360 mg 3 times daily	Long	
Verapamil	Immediate release: 80–160 mg every 8 h	Short	Avoid with known or suspected LV dysfunction
	Slow release: 120–480 mg daily	Long	
Dihydropyridines			
Amlodipine	5–10 mg daily	Long	
Felodipine	5–10 mg daily	Long	
Nisoldipine	20–40 mg daily	Short	

ACS, acute coronary syndrome; LV, left ventricular.

Side effects: Hypotension, bradycardia, myocardial depression (diltiazem and verapamil), flushing, edema, headache.

Contraindications: Hypotension, AV conduction abnormalities, LV dysfunction or congestive heart failure (CHF) (especially diltiazem and verapamil).

Recommendations: In patients with contraindications to β-blockers or in those whom β-blockers and nitrates have failed to achieve relief of ischemia or rate control with supraventricular arrhythmias, CCBs can be used to further reduce blood pressure and chest pain. Caution should be exercised when CCBs and β-

blockers are used concomitantly because of depressed AV nodal conduction. Diltiazem and verapamil should be avoided in patients with LV dysfunction. Use of dihydropyridines such as amlodipine and felodipine appear to be safe with LV dysfunction, although their benefit remains undefined in the treatment of ACS; nifedipine should be avoided altogether.

NITRATES

Rationale: Despite a paucity of rigorous clinical trial data, nitrates continue to remain important in the treatment of HTN and chest pain in patients with ACS. Nitrates cause a reduction of myocardial oxygen demand while enhancing myocardial oxygen delivery and affect both peripheral and coronary vascular beds. Nitroglycerin (NTG) increases venous capacitance, thereby decreasing preload and reducing ventricular wall tension. Furthermore, NTG promotes the dilation of the coronary arteries, and possibly has a mild inhibitory effect on platelet aggregation (although the clinical significance of this is not known).

Indications: Angina, HTN, CHF, variant angina.

Dosing: NTG is available in multiple preparations including sublingual tablets and spray, transdermal, and intravenously (**Table 9.3**).

TABLE 9.3 Nitrate Preparations Used in ACS

COMPOUND	ROUTE	DOSE	DURATION OF EFFECT
Nitroglycerin	Sublingual tablets	0.3–0.6 up to 1.5 mg	1 to 7 min
	Spray	0.4 mg as needed	Similar to sublingual tablets, however, has a longer shelf life
	Transdermal	0.2–0.8 mg/h every 12 h	8 to 12 h with intermittent therapy; efficacy improved with 12 h off period
	Intravenous	5–200 μg/min	Tolerance in 7 to 8 h
Isosorbide dinitrate	Oral	5–80 mg, every 8–12 h	Up to 8 h
	Oral, slow release	40 mg, every 12–24 h	Up to 8 h
Isosorbide mononitrate	Oral	20 mg twice daily	12 to 24 h

	Oral, slow release	60–240 mg daily

ACS, acute coronary syndrome.

Side effects: Headaches, hypotension, and tachyphylaxis are common with NTG usage.

Contraindications: NTG is contraindicated after the use of phosphodiesterase inhibitors used for the treatment of erectile dysfunction such as sildenafil, tadalafil, and vardenafil as concominant use can induce profound hypotension. Additionally, nitrates should be avoided in patients suspected of having a right ventricular infarct because its usage can result in severe hypotension even with low doses.

Recommendations: NTG use is typically initiated with three 0.4-mg sublingual NTG tablets taken 5 minutes apart with the concomitant administration of either an oral or IV β-blocker. For patients with ongoing chest pain, HTN, or decompensated heart failure, it is appropriate to switch to IV NTG. This is given at 10 μg/min through continuous infusion via nonabsorbing tubing and can be up titrated by 10 μg/min every 3 to 5 minutes to achieve symptomatic relief or desired blood pressure response. Although there is no published maximal ceiling dose, 200 μg/min is typically used because there is unlikely to be measurable clinical benefit beyond this rate. For blood pressure titrations, NTG should be titrated to less than 110 mm Hg in previously normotensive patients or to greater than 25% lower than the starting Mean Arterial Pressure (MAP) in hypertensive patients. NTG should generally be avoided in patients with starting systolic blood pressures of less than 90 mm Hg, in patients with marked bradycardia or tachycardia, or in patients who present with systolic blood pressures 30 mm Hg or more below their baseline. After a patient has been stable or chest pain free for 12 to 24 hours, it is prudent to attempt weaning IV NTG or transitioning to an oral preparation if still indicated.

MORPHINE

Rationale: Although there is a lack of randomized clinical trials, morphine sulfate provides analgesic and anxiolytic effects that might partially counteract the adrenergic drive associated with ACS. Additionally, it causes mild venodilation, a modest reduction in heart rate via increased vagal tone, and decreased blood pressure, which lowers myocardial oxygen demand.

Dosing: Morphine sulfate 1 to 5 mg IV PRN.

Side effects: Nausea, vomiting, respiratory depression, hypotension.

Recommendations: Morphine should be considered for anginal relief in patients not sufficiently controlled with nitrates, β-blockers, or CCBs and is often given in preparation for further invasive testing.

ANCILLARY THERAPIES

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN II RECEPTOR BLOCKERS

Rationale: Inhibition of the renin–angiotensin–aldosterone system has salutary effects on blood pressure, afterload reduction, and LV remodeling associated with myocardial infarction (MI)-induced LV dysfunction. Angiotensin-converting-enzyme (ACE) inhibitors have a proven track record in multiple clinical trials for decreasing mortality, particularly when started within 24 hours to 16 days after myocardial infarction in patients with depressed ejection fractions, heart failure, and diabetes mellitus.[8–12] Patients with higher risk gained greater benefit. Additionally, the VALIANT trial demonstrated that valsartan was as effective as captopril in the reduction of death following MI in patients with demonstrable LV dysfunction or clinical heart failure.[13] Therefore, in addition to their proven clinical role in stable CHF, angiotensin receptor blockers (ARBs) appear to also offer benefit in the ACS setting.

Indications: ACS with concurrent pulmonary congestion or LVEF ≤ 40%, in absence of contraindications. ARBs should be given to patients intolerant of ACE inhibitors.

Dosing: Multiple preparations both short and long acting. IV forms are not recommended for ACS (**Table 9.4**).

TABLE 9.4 ACE Inhibitors and ARBs Used in ACS

ACE Inhibitors				
Drug	***Starting dose***	***Typical dose***	***Maximum dose***	***Comments***
Benazepril	10 mg	20–40 mg	80 mg	May use bid dosing
Captopril	6.25–12 mg bid–tid	25–50 mg bid–tid	450 mg daily	Target dose in HF: 50 mg tid
Enalapril	2.5–5 mg daily–bid	10–40 mg	40 mg	Target dose in HF: 10 mg bid

Fosinopril	10 mg	20–40 mg	80 mg	
Lisinopril	2.5–5 mg	10–40 mg	80 mg	Target dose in HF: 20 mg daily
Moexipril	7.5 mg	7.5–30 mg	30 mg	
Perindopril	4 mg	4–8 mg	16 mg	
Quinapril	10 mg	20–80 mg	80 mg	Target dose in HF: 20 mg daily
Ramipril	2.5 mg	2.5–20 mg	20 mg	
Trandolapril	1 mg	2–4 mg	8 mg	Reduce dose in hepatic dysfunction
ARBs				
Candesartan	8–16 mg	16–32 mg	32 mg	
Eprosartan	600 mg	600–800 mg	800 mg	
Irbesartan	75–150 mg	150–300 mg	300 mg	
Losartan	25–50 mg	50–100 mg	100 mg	Reduce dose in hepatic dysfunction
Valsartan	20 mg	160 mg	320 mg	
Olmesartan	20 mg	20–40 mg	40 mg	
Telmisartan	20–40 mg	40–80 mg	80 mg	

ACE, angiotensin-converting-enzyme; ACS, acute coronary syndrome; ARBs, angiotensin receptor blocker; HF, heart failure.

Side effects: Hypotension, hyperkalemia, angioedema and cough (ACE inhibitors).

Contraindications: Hemodynamic instability, renal failure, hyperkalemia.

Recommendations: Typically initiated early, within the first 24 hours of hospital stay, in patients without contraindications. Use of short-acting formulations (ie, captopril 6.25 mg q8h) allows for dose titration. Once stable, once-daily dosing can be initiated. IV ACE inhibitors should be avoided in the management of ACS.

ALDOSTERONE RECEPTOR ANTAGONISTS

Rationale: Aldosterone receptor antagonists have been shown to prevent deleterious ventricular remodeling after acute MI, decrease the rate of death, and

reduce hospitalizations in patients with chronic severe heart failure. The EPHESUS trial further expanded the beneficial role in renin–angiotensin–aldosterone blockade by demonstrating a reduction in morbidity and mortality for patients presenting with acute MI complicated by heart failure and LV dysfunction (LVEF ≤ 40%) when treated with eplerenone.[14]

Indications: ACS with concurrent pulmonary congestion or LVEF ≤ 40%, in absence of contraindications.

Dosing: Eplerenone 25 mg daily with gradual uptitration to a maximum of 50 mg daily. Frequent monitoring of electrolytes, especially potassium and creatinine, is essential.

Side effects: Hypotension, hyperkalemia, renal dysfunction.

Contraindications: Hemodynamic instability, renal failure, hyperkalemia.

Recommendations: Given the totality of evidence to date, ACE inhibitors and ARBs remain preferred first-line therapy agents for renin–angiotensin–aldosterone blockade for patients with ACS and concurrent LV dysfunction. However, the addition of an aldosterone receptor blocker such as eplerenone may be considered in patients already receiving optimal medical treatment in the absence of contraindications.

HMG-COA REDUCTASE INHIBITORS (STATINS)

Rationale: Statins have been widely studied both in primary and secondary prevention for chronic coronary artery disease (CAD). The “pleiotropic” effects of statins include not only their well-established ability to lower the levels of low-density lipoprotein (LDL), but also their anti-inflammatory, antioxidant, and antithrombotic properties. The first clinical trial to demonstrate benefit of statins given early (24 to 96 hours) after ACS was MIRACL study—compared with placebo, atorvastatin given for 16 weeks reduced the composite end point of death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization by 16% (95% CI: 0.7 to 1.0, $P = 0.048$).[15] Also in the setting of ACS, PROVE IT-TIMI 22 showed a significant 16% reduction in the hazard ratio for death, MI, UA, revascularization and stroke in patients treated with intensive lipid-lowering therapy (atorvastatin 80 mg) compared with standard therapy (pravastatin 40 mg) and followed for 18 to 36 months.[16]

Indications: STEMI and UA/NSTEMI.

Dosing: Multiple agents; however, atorvastatin was the most studied for ACS.

They are typically given at 40 to 80 mg po daily (**Table 9.5**).

TABLE 9.5	Statins Used in ACS
DRUG	**DOSE**
Atorvastatin	10–80 mg daily
Fluvastatin	20–80 mg daily
Lovastatin	10–80 mg daily
Pravastatin	10–80 mg daily
Rosuvastatin	5–40 mg daily
Simvastatin	10–80 mg daily

Side effects: Dyspepsia, rash/pruritis, myalgias, hepatotoxicity, rhabdomyolysis (rare).

Contraindications: Caution should be exercised when used with cytochrome P450 inhibitors and in the setting of elevated transaminases.

Recommendations: Statins at high doses should be considered early in the course of patients presenting with ACS, irrespective of the baseline LDL-cholesterol levels. Statins should be considered standard therapy for secondary prevention in the absence of contraindications.

ANTIPLATELET MEDICATIONS

ASPIRIN (ASA)

Rationale: Aspirin is a potent, irreversible platelet COX-1 inhibitor that inhibits the production of thromboxane A_2 and results in decreased platelet aggregation at the site of intimal injury and thrombus formation. Although it is a relatively weak inhibitor of overall platelet aggregation, ASA confers a significant reduction in mortality.[17–21]

Indications: ACS (diagnosed or suspected), chronic CAD.

Dosing: Initial dosing should be 162 to 325 mg given orally as a nonenteric coated, chewable tablet to allow for rapid buccal absorption. If active nausea or vomiting, a 300-mg rectal suppository should be promptly administered. The maintenance dose of ASA is conventionally the lowest available dose, which

ranges from 75 to 100 mg/d in different countries (81 mg/d in North America).

Side effects: Nausea, vomiting, dyspepsia, gastrointestinal (GI)/genitourinary (GU) bleeding.

Contraindications: The only contraindication is patients with true ASA allergy (anaphylaxis, hives, nasal polyps, bronchospasm). Such patients should be given a thienopyridine such as clopidogrel, with strong consideration given for ASA desensitization treatment.

Recommendations: Aspirin 325 mg should be administered to all persons as soon as ACS is diagnosed or suspected, typically in the ambulance or the emergency department. In general, therapy with ASA should be continued indefinitely after the first presentation with ACS at a low dose of 75 to 81 mg daily.

$P2Y_{12}$ ADENOSINE DIPHOSPHATE RECEPTOR INHIBITORS

$P2Y_{12}$ inhibitors are inhibitors of adenosine diphosphate (ADP)-induced platelet aggregation and dual antiplatelet therapy (DAPT) of $P2Y_{12}$ inhibitors (thienopyridines and nonthienopyridines) along with ASA have become a cornerstone in the pharmacologic management of patients with ACSs and after coronary stent placement. The first thienopyridine introduced and used after coronary stenting was ticlopidine. Since the introduction of other agents of this group, ticlopidine use has been largely decreased mainly due to unfavorable side-effect profile including GI effects, neutropenia, and thrombotic thrombocytopenic purpura (TTP) in addition to long onset of action and frequent dosing. Therefore, ticlopidine is no longer recommended in the treatment of ACS. During the last two decades, another three oral $P2Y_{12}$ inhibitors have received the Food and Drug Administration (FDA) approval in the United States for use in ACS: clopidogrel, prasugrel, ticagrelor, and another IV agent introduced recently, cangrelor. Each of these drugs work by inhibiting the $P2Y_{12}$ ADP receptor on platelets, with ticagrelor being the only oral drug with reversible inhibition. They differ importantly with respect to their onset of action, side-effect profile, and overall potency. Evidence for the beneficial use of $P2Y_{12}$ inhibitors comes from multiple, large-scale randomized trials. Because DAPT with $P2Y_{12}$ inhibitors exert more robust platelet inhibition than ASA alone, the risk of subsequent bleeding is higher and therefore appropriate $P2Y_{12}$ inhibitors selection should be tailored to a patient's individual bleeding risk.

Clopidogrel

Rationale: Clopidogrel is an irreversible $P2Y_{12}$ receptor inhibitor, the most studied thienopyridine, and the most used until the introduction of ticagrelor. As the maximal therapeutic platelet inhibition of clopidogrel takes 3 to 7 days to reach, the administration of a loading dose of 300 to 600 mg, resulting in substantial inhibition within approximately 2 hours, has been used in ACS studies. In the CURE trial, patients with UA or NSTEMI were found to have a lower rate of cardiovascular death, nonfatal MI, or stroke when treated with ASA and clopidogrel than ASA alone (9.3% vs 11.4%, $P < 0.001$); however, this came at the expense of major bleeding, particularly in patients who subsequently underwent coronary artery bypass graft (CABG).[22] In STEMI patients, the COMMIT-CCS-2 study demonstrated a significant reduction in the composite end point of death, reinfarction, and stroke (9.2% clopidogrel vs 10.1% placebo, $P = 0.002$) in 45,852 patients treated with clopidogrel, 93% of whom had ST elevation.[23] The addition of clopidogrel to fibrinolytic therapy was proven beneficial in the CLARITY-TIMI 28 trial where 3491 patients with STEMI had a significant reduction in occluded infarct artery on angiography, death, or recurrent MI when treated with clopidogrel (15% clopidogrel vs 21.7% placebo, $P < 0.001$).[24] This was felt to be driven by the prevention of infarct-related reocclusion. Randomized controlled trials of clopidogrel versus placebo, added to ASA, in primary PCI for patients with STEMI has not been conducted and its efficacy in that setting has been assumed on the basis of the results of studies of patients with ACS undergoing elective PCI and patients with STEMI treated with fibrinolysis before PCI. On this background, the HORIZONS-AMI trial evaluated two loading doses, 600 versus 300 mg, of clopidogrel in STEMI patients undergoing primary PCI. The higher loading dose resulted in 28% reduction of 30 days' composite of mortality, reinfarction, and stent thrombosis without significantly increasing the rate of major bleeding.[25] The larger CURRENT-OASIS 7 trial has evaluated high dose of clopidogrel, 600 mg loading and 150 mg daily for a week with regular 75-mg daily dose thereafter, to regular loading and maintenance dose among 25,086 patients with ACS. A prespecified analysis of 17,263 individuals who underwent PCI revealed a reduction of cardiovascular events at 30 days, especially to be noticed a 46% reduction in the occurrence definite stent thrombosis with the high-dose regimen of clopidogrel compared with the regular dose.[26]

Indications: STEMI, UA/NSTEMI, alternative to ASA in patients with true

ASA intolerance.

Dosing: Loading dose 300 to 600 mg followed by 75 mg daily. When combined with fibrinolytics, a 300-mg loading dose should be used for patients under 75 years of age and no loading dose for patients over 75 years of age.

Side effects: Bleeding, GI intolerance, rash, TTP (rare).

Contraindications: High risk for intracranial/GI/GU bleeding, anticipated CABG within 5 days, high suspicion for diminished clopidogrel response (eg, CYP2C19 variant, stent thrombosis).

Special note on clopidogrel responsiveness: It has become increasingly recognized that there is considerable interindividual variability in platelet inhibition from clopidogrel, often leading to adverse clinical events. This is thought to be primarily related to genetic polymorphisms involving the metabolism of clopidogrel and other drugs by the hepatic CYP450 system, specifically the CYP2C19 isoenzyme, and has led to an FDA warning for the use of clopidogrel. Although genetic and platelet function testing are available, routine use is not specifically recommended at this time. However, patients deemed to be at moderate to high risk (previous history of stent thrombosis, recurrent ischemic events, planned complex interventions) should be considered for platelet function testing or alternative antiplatelet strategies including prasugrel or ticagrelor, two agents that do not appear to have these limitations.

Recommendations: Clopidogrel with loading dose of 300 to 600 mg followed by 75 mg daily alongside with ASA is indicated early in the treatment of UA/NSTEMI (both early invasive and initial conservative strategy), although it is reasonable to use ticagrelor in preference to clopidogrel in patients who are treated with an early invasive strategy. Clopidogrel should be continued for up to 12 months, with treatment beyond that time considered in specific patients. Halting clopidogrel and DAPT may be required in some clinical circumstances earlier than 12 months after the index event, such as with the occurrence of bleeding, the need for noncardiac surgery or if anticoagulant therapy for atrial fibrillation becomes indicated. With no clear answers from randomized controlled trials, it is important to utilize clinical judgment as to the length of DAPT duration for the scenarios mentioned here, taking into consideration the bleeding risk on the one hand and the risk of stent thrombosis on the other (based on clinical and anatomic findings of each patient and the stent type).

Because of the increased bleeding associated with CABG, clopidogrel should be held for at least 5 days and up to 7 days before elective CABG. In patients with a high likelihood of needing bypass, some centers opt to delay clopidogrel

loading until coronary anatomy has been defined if angiography can be done in a timely manner. If a loading dose is given and a patient is subsequently found to need urgent surgical revascularization, centers with experienced surgeons can often operate with an acceptable incremental bleeding risk.

For patients with STEMI, when fibrinolysis is planned, clopidogrel alongside with ASA is recommended with a 300-mg loading dose for patients <75 years. However, no loading dose is currently recommended for patients ≥75 years. For patients planned for primary PCI, a loading dose of 600 mg with 75 mg daily thereafter is recommended, but it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel in this setting.

Prasugrel

Rationale: Prasugrel is a newer irreversible $P2Y_{12}$ ADP receptor inhibitor that offers distinct advantages over clopidogrel. Like clopidogrel, prasugrel is a pro-drug that requires hepatic metabolism to its active metabolite. However, its metabolism is not affected by the CYP2C19 allele and does not appear to have the same interpatient variability found with clopidogrel. Additionally, its pharmacodynamic properties result in more rapid and consistent platelet inhibition when compared with clopidogrel. The TRITON-TIMI 38 study is the largest trial to date for prasugrel evaluation, comparing it to clopidogrel in patients with ACS scheduled to undergo PCI. Prasugrel was found to significantly reduce the combined rates of death, nonfatal MI, and stroke when compared with clopidogrel (9.9% prasugrel vs 12.1% clopidogrel, $P < 0.001$). Additionally, significant reductions in MI, urgent target vessel revascularization, and stent thrombosis were shown. However, the benefit of prasugrel came at the expense of significantly increased major bleeding, including fatal bleeding.[27] Patients with prior stroke or transient ischemic attack (TIA) had worse outcome with prasugrel, and bleeding rates were noted to be particularly high in patients with body weight <60 kg or age >75 years.

Indications: STEMI when fibrinolysis is not planned and UA/NSTEMI.

Dosing: Loading dose of 60 mg followed by 10 mg daily.

Side effects: Bleeding.

Contraindications: Age ≥75 years, body weight <60 kg (or use maintenance dose of 5 mg daily), history of stroke/TIA, high risk for intracranial/GI/GU bleeding, active bleeding, CABG planned within 5 to 7 days.

Recommendations: Prasugrel is currently recommended for the treatment of STEMI in patients undergoing primary PCI. For patients undergoing nonprimary

PCI, prasugrel should not be given if the patient has received a fibrinolytic. For UA/NSTEMI, prasugrel is a reasonable alternative thienopyridine in patients without the aforementioned contraindications and in whom clopidogrel would otherwise be indicated, especially after coronary stent placement. It must be noted that in TRITON-TIMI 38, patients with UA/NSTEMI treated with prasugrel were given the loading dose only *after* coronary anatomy was defined. Injudicious upstream loading in patients at high risk for surgical disease before knowledge of coronary anatomy may lead to excessive bleeding. This drawback and the introduction of ticagrelor have turned prasugrel to be less preferred in the setting of UA/NSTEMI. Additionally, prasugrel has not been studied in the early conservative management strategy.

Ticagrelor

Rationale: Ticagrelor is a nonthienopyridine reversible $P2Y_{12}$ ADP receptor inhibitor. Like prasugrel, it offers several potential advantages over clopidogrel, namely, it provides more rapid and consistent platelet inhibition. Additionally, because it is a reversible inhibitor, its antiplatelet effects dissipate more rapidly than other thienopyridines. The PLATO trial compared ticagrelor with clopidogrel in the treatment of patients presenting with ACS both with and without STEMI (n = 18,624). Ticagrelor was associated with a significant reduction in the primary composite end point of death, MI, and stroke compared with clopidogrel (9.8% vs 11.7%, $P < 0.001$). There was no significant difference in the rates of major bleeding between the two groups; however, the ticagrelor group did have a higher incidence of major bleeding not related to CABG, including more intracranial bleeding.[28] A substudy of PLATO trial including only patients planned for invasive strategy has reached the same results.[29] The PEGASUS-TIMI 54 trial examined the benefit and safety of extended treatment with ticagrelor among patients with previous MI. Comparing two doses of ticagrelor, 90 mg twice daily and 60 mg twice daily, with placebo for a median follow-up of 33 months revealed a significant reduction in the composite end point of cardiovascular death, MI, or stroke with the expense of increased risk of bleeding.[30]

Indications: STEMI when fibrinolysis is not planned and UA/NSTEMI (both early invasive or initial conservative strategy).

Dosing: Initial loading dose of 180 mg followed by 90 mg twice daily.

Side effects: Bleeding, dyspnea, ventricular pauses.

Contraindications: High risk for intracranial/GI/GU bleeding, active bleeding.

Recommendations: Ticagrelor is indicated in STEMI when percutaneous intervention is planned. As it has not been studied in conjunction with fibrinolytic agents, ticagrelor is not indicated when these agents are planned to be given or immediately after being given as in rescue PCI—in these circumstance clopidogrel is more appropriate. Ticagrelor is indicated for the treatment of UA/NSTEMI whether they planned for invasive strategy or conservative/medical management. Particularly advantageous is ticagrelor's reversible pharmacokinetic properties and short half-life, which make upstream loading possible irrespective of the patient's risk for surgical CAD.

Cangrelor

Rationale: Cangrelor is an IV nonthienopyridine blocker of the ADP activated $P2Y_{12}$ receptor. The rapid onset of action and the rapid return of platelets function after cessation of its infusion are thought to be its clinical advantage. The CHAMPION PHOENIX trial of 11,145 patients compared bolus and infusion of cangrelor to clopidogrel 300 or 600 mg in patients undergoing elective or urgent PCI. Cangrelor reduced the occurrence of primary end point (composite of death, MI, ischemia-driven revascularization, and stent thrombosis at 48 hours) by 22% to 4.7% in the cangrelor group versus 5.9% in the clopidogrel (95% CI: 0.66 to 0.93, $P = 0.005$). To be noted, the secondary end point of stent thrombosis at 48 hours was reduced to 0.8% with cangrelor in comparison with 1.4% with clopidogrel (95% CI: 0.43 to 0.90, $P = 0.01$).[31]

Indications: As adjunct to PCI in patients who have not been treated with $P2Y_{12}$ receptor inhibitors and who are not being given a glycoprotein IIb/IIIa inhibitors (GIPs).

Dosing: Cangrelor is given as 30 μg/kg bolus followed by 4 μg/kg/min infusion at the time of PCI for 2 hours up to a maximum of 4 hours.

Side effects: Bleeding, worsening renal function, hypersensitivity.

Contraindications: Significant active bleeding, hypersensitivity reaction.

Recommendations: Cangrelor is recommended as adjunct to PCI in patients who have not been treated with oral $P2Y_{12}$ receptor inhibitors at the time of PCI and who are not being given a GIP.

PLATELET GP IIB/IIIA RECEPTOR ANTAGONISTS

GPIs decrease platelet aggregation and thrombus formation by inhibiting the

ability of fibrinogen to cross-link platelets. Three GPI medications that are currently approved for use in the United States include abciximab, eptifibatide, and tirofiban. The benefit of GPI medications seems to be predominantly in patients managed invasively with PCI and with high-risk clinical features (positive troponins, diabetics). However, in the modern era of DAPT with aspirin plus a $P2Y_{12}$ inhibitor, the benefit of upstream use before PCI in the ACS population has become less apparent. For UA/NSTEMI patients, the *EARLY-ACS* trial compared routine upstream use of eptifibatide in addition to standard DAPT versus delayed use at the time of angiography. No significant reduction in ischemic complications was observed with early upstream use of GPI, even though eptifibatide was used in only approximately 25% of patients in the "delayed" arm.[32] Similarly, the *ACUITY Timing* trial failed to show benefit of the strategy of upstream GPI inhibitors when compared with provisional use at the time of PCI. For patients treated with upstream use, increased major bleeding was observed at 30 days.[33] As such, the routine *upstream* use of GPI is not recommended in NSTEMI.[34] Accordingly, in NSTEMI, guidelines recommend DAPT with aspirin plus *either* a $P2Y_{12}$ inhibitor or GPI, but not *routine* triple antiplatelet therapy with all three class of agents. GPIs should be used in addition to aspirin, especially at the time of PCI if there was no adequate pretreatment with ADP receptor blockers. If adequate pretreatment with an ADP receptor blockers was given, the administration of GPI at the time of PCI is according to class 2a recommendation.

For patients with STEMI, the FINESSE and BRAVE-3 studies showed no benefit with regard to infarct size or ischemic events in patients treated upstream with abciximab, as compared with administering GPI during primary PCI.[35, 36] According to STEMI 2012 European guidelines.[37] in primary PCI patients:

1. GPIs should be considered for bailout therapy if there is angiographic evidence of massive thrombus, slow or no-reflow, or a thrombotic complication as a class 2a recommendation.
2. Routine use of a GP IIb/IIIa inhibitor as an adjunct to primary PCI performed with unfractionated heparin (UFH) may be considered in patients without contraindications as a class 2b recommendation.
3. Upstream use of a GPI (vs in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI as a class 2b recommendation.

Additionally, the 2013 STEMI guidelines of ACC/AHA[38] emphasizes the

following points:

1. It is reasonable to administer GPI at the time of primary PCI in the cath-lab in selected STEMI patients treated with UFH irrespective of the pretreatment of ADP receptor blockers—a 2a recommendation. It is possible to consider intracoronary abciximab—a 2b recommendation.
2. Upstream administration of GPI in planed primary PCI—as a class 2b recommendation.

Many of these trials predated the routine use of P2Y12 inhibitors. Although the relative efficacy of prasugrel and ticagrelor in the trials appeared consistent among patients receiving and not receiving GIPs, the efficacy and safety of GPIs on top of these P2Y12 inhibitors have not been prospectively addressed.[27, 28] In patients treated with prasugrel or ticagrelor, GPIs should be limited to bail out situations *or* thrombotic complications during PCI. All GPIs should be used in conjunction with ASA and heparin or enoxaparin. Benefit must be weighed against increased incidence of bleeding, especially in patients at a higher risk for this adverse outcome such as elderly patients.

Abciximab

Rationale: Abciximab is a Fab fragment of a humanized murine antibody that inhibits the GP IIb/IIIa receptor, endothelial cell vitronectin receptors, and leukocyte MAC-1 receptors. Although it has a short half-life, its binding to GP IIb/IIIa receptors can persist for weeks although platelet aggregation gradually returns to normal 24 to 48 hours after discontinuation of the infusion. The role of abciximab in ACS was first established with the EPIC trial, which demonstrated a significant reduction in the rate of death, MI, or emergent revascularization in the group treated with a bolus and infusion of the drug before undergoing PCI.[39] In the contemporary era, the ISAR-REACT 2 trial demonstrated a significant reduction in death, MI, or urgent revascularization in high-risk (troponin positive) UA/NSTEMI patients treated with abciximab who underwent PCI (8.9% abciximab vs 11.9% placebo, $P = 0.03$).[40] However, for UA/NSTEMI patients who are risk-stratified to the early conservative strategy, the GUSTO IV-ACS trial showed abciximab to be of no additional benefit.[41]

Indications: UA/NSTEMI as adjunct to PCI in bailout situations or thrombotic complications during PCI, STEMI during primary PCI.

Dosing: 0.25 mg/kg 10 to 60 minutes before PCI followed by 0.125

μg/kg/min for 12 hours (maximum rate 10 μg/min).

Side effects: Bleeding, thrombocytopenia, hypersensitivity reactions.

Contraindications: Prior hypersensitivity, high risk for intracranial/GI/GU bleeding.

Recommendations: Abciximab should not be used in the treatment of UA/NSTEMI when PCI is not planned. For STEMI, it should be initiated at the time of primary PCI.

Eptifibatide

Rationale: A heptapeptide antagonist that reversibly inhibits GP IIb/IIIa. In the PURSUIT trial, patients with UA/NSTEMI treated with eptifibatide in addition to ASA and heparin had reduced rates of death and nonfatal MI at 96 hours and 6 months, particularly in those who underwent PCI.[42]

Indication: UA/NSTEMI treated with PCI with high-risk features. STEMI during primary PCI.

Dosing: Upstream ACS: Loading dose 180 μg/kg bolus followed by 2 μg/kg/min for 96 hours. If CrCl ≤ 50 mL/min, dose should be reduced to 1 μg/kg/min.

Primary PCI: Loading dose of 180 μg/kg bolus twice, separated by 10 minutes, followed by 2 μg/kg/min for 18 to 24 hours. If CrCl ≤ 50 mL/min, dose should be reduced to 1 μg/kg/min.

Side effects: Bleeding, thrombocytopenia (rarely severe).

Contraindications: Renal dialysis, severe thrombocytopenia, high risk for intracranial/GI/GU bleeding.

Recommendations: Eptifibatide use is acceptable in the management of UA/NSTEMI for patients as adjunct to PCI in bailout situations or thrombotic complications during PCI, or in addition to other standard antiplatelet medications for patients with high-risk features or recurrent ischemia. Daily monitoring of hemoglobin and platelets is recommended. For STEMI, eptifibatide should be initiated at the time of primary PCI.

Tirofiban

Rationale: Tirofiban is a nonpeptide antagonist that reversibly inhibits GP IIb/IIIa receptor. When combined with UFH, it has been shown to reduce death, MI, and refractory ischemia up to 30 days in patients with high-risk presentations (ischemic ECG features, elevated cardiac biomarkers).[43]

Dosing: High dose—25 µg/kg bolus, followed by 0.15 µg/kg/min infusion for 18 to 24 hours; standard dose—0.4 µg/kg/min for 30 minutes, then 0.1 µg/kg/min for 96 hours. Dose should be reduced by half for patients with CrCl < 30 mL/min.

Side effects: Bleeding, thrombocytopenia (rarely severe).

Contraindications: High risk for intracranial/GI/GU bleeding, severe thrombocytopenia.

Recommendations: Typically, its addition to other standard antiplatelet medications is reserved for patients with high-risk features or recurrent ischemia. Most contemporary trials utilize the high-dose regimen for patients undergoing PCI due to more robust platelet inhibition. Daily monitoring of hemoglobin and platelets is recommended.

ANTICOAGULANTS

UNFRACTIONATED HEPARIN

Rationale: Heparin accelerates the action of circulating antithrombin, which leads to inactivation of factor IIa (thrombin), factor IXa, and factor Xa. Ultimately, this prevents further clot propagation but not lysis of existing thrombus. A meta-analysis involving six trials showed a nonsignificant relative risk reduction of 33% ($P = 0.06$) in death or MI when combined with ASA.[44]

Indications: ACS (both STEMI and UA/NSTEMI).

Dosing: Weight-based nomogram preferred to fixed-dose regimens. Bolus: 60 U/kg (max 4000 U) with initial infusion at 12 U/kg/h (max 1000 U/h). The activated partial thromboplastin time (aPTT) should be monitored q6h until dosing is therapeutic (aPTT 50 to 70).

Side effects: Mild thrombocytopenia, bleeding, heparin-induced thrombocytopenia (HIT).

Contraindications: Severe thrombocytopenia, previously documented HIT.

Recommendations: UFH is recommended early in the management of STEMI and UA/NSTEMI (for both conservative and early invasive strategies) and during PCI. A weight-based dosing regimen should be utilized with frequent monitoring of aPTT, hemoglobin, and platelets. For conservative management strategy, UFH should be continued for at least 48 hours or until discharge (up to 8 days). For CABG or PCI, it should be continued up until the time of procedure (holding according to institutional practices).

LOW-MOLECULAR-WEIGHT HEPARIN: ENOXAPARIN

Rationale: Enoxaparin is a low-molecular-weight heparin (LMWH) that is more selective than UFH at inhibition of factor Xa. When compared with UFH, LMWHs have decreased binding to plasma proteins and endothelial cells, dose-independent clearance, a longer half-life, and more sustained and predictable anticoagulation. Multiple clinical trials have shown a reduction in death, MI, and recurrent angina up to 40 days when compared with UFH.[45–47] For patients with STEMI treated with fibrinolysis, the ExTRACT TIMI 25 study showed that enoxaparin was superior to UFH with regard to death, nonfatal reinfarction, and urgent revascularization but with increased rates of major bleeding.[48]

Advantages over UFH: More predictable anticoagulation, more cost-effective (less monitoring), less occurrence of HIT, twice-daily subcutaneous (SC) dosing, better reduction of nonfatal MI, death, or recurrent angina.

Disadvantages compared with UFH: Unable to give in setting of severe renal impairment, not reversible with protamine, increased major bleeding,[49] inability to reliably monitor ACT (Activated Clotting Time) during PCI.

Indications: UA/NSTEMI and STEMI.

Dosing: Enoxaparin 30 mg IV × 1 may be given early and then 1 mg/kg q12h for 2 to 8 days. It should be avoided in patients with CrCl < 30 (or reduction to q24h should be considered). Unclear dosing strategy for morbidly obese patients; however, often an anti-Xa level is measured, with a commonly accepted therapeutic target of 0.5 to 1.0 anti-Xa units/mL. For patients >75 years, no IV bolus should be given and dose at 0.75 mg/kg q12h.

Side effects: Bleeding, HIT (rare), injection-site complications.

Contraindications: CrCl < 30 mL/min.

Recommendations: In patients with UA/NSTEMI, use of enoxaparin is considered an acceptable alternative to UFH, especially in those being managed conservatively. Duration of treatment is at least 48 hours and typically until discharge (up to 8 days). If CABG is pursued, enoxaparin should be discontinued 12 to 24 hours prior and bridged with UFH according to institutional practice. Although there are limited data for the use of dalteparin for this indication, enoxaparin remains the preferred LMWH. For STEMI patients treated with fibrinolysis, enoxaparin has proven efficacy, albeit at increased risk for bleeding, and can be used throughout the index hospitalization up to 8 days.

DIRECT THROMBIN INHIBITORS: BIVALIRUDIN

Rationale: Direct thrombin inhibitors (DTIs) bind reversibly to thrombin and inhibit clot-bound thrombin more effectively than does UFH. Bivalirudin is a synthetic derivative of hirudin (older DTI no longer used clinically) with a shorter half-life. The ACUITY trial studied UA/NSTEMI patients undergoing PCI and showed noninferiority of bivalirudin monotherapy as compared with UFH or LMWH plus GPI with respect to ischemia (9% vs 8%, $P = 0.45$), but importantly a significant reduction in major bleeding (4% vs 7%, $P < 0.0001$).[50] The HORIZONS-AMI trial showed that STEMI patients undergoing primary PCI treated with bivalirudin alone compared with UFH plus GPI had significantly reduced 30-day rates of death from cardiac causes (1.8% vs 2.9%, $P = 0.03$) and a lower rate of major bleeding (4.9% vs 8.3%, $P < 0.001$).[51] When followed out to 1 year, patients classified as high risk had a decreased mortality (8.4% vs 15.9%, $P = 0.01$) and a decreased rate of recurrent MI (3.6% vs 7.9%, $P = 0.04$).[52] Yet, a recently published meta-analysis of 13 randomized controlled trials, involving 24,605 patients with ACS treated with PCI revealed a significant reduction in the rate of major bleeding with bivalirudin compared with UFH with routine use of GPIs, but not when provisional use of GPIs with UFH was attempted. Additionally, there was a significant increase in the rate of 30 days' definite stent thrombosis largely driven by a 4-fold increase in acute (<24 hours) stent thrombosis regardless of routine or provisional use of GPIs with UFH.[53]

Indications: UA/NSTEMI (early invasive strategy only); STEMI undergoing primary PCI.

Dosing: Bolus 0.75 mg/kg followed by infusion of 1.75 mg/kg/h up to 4 hours. Then it should be decreased to 0.2 mg/kg/h for up to 20 hours.

Side effects: Bleeding.

Contraindications: Dosing adjustments for renal impairment.

Recommendations: Bivalirudin is an acceptable alternative for treatment of UA/NSTEMI in patients undergoing early invasive strategy when used with $P2Y_{12}$ inhibitor given upstream of PCI. It is not recommended for UA/NSTEMI patients being treated with an initial conservative strategy. For STEMI, bivalirudin can be used during primary PCI with or without prior treatment with UFH.

FACTOR XA INHIBITORS: FONDAPARINUX

Rationale: Fondaparinux is a synthetic pentasaccharide that selectively binds to

and potentiates antithrombin thereby promoting factor Xa inhibition. Its dose-independent clearance and long half-life allow for once-daily administration and predictable and sustained anticoagulation effects. The OASIS 5 study compared fondaparinux with enoxaparin in the treatment of UA/NSTEMI. Patients treated with fondaparinux had similar rates of death, MI, and refractory ischemia at 9 days, but significantly less major bleeding. At 180 days, fondaparinux was associated with a significant reduction in all major end points.[54] However, there was an increased incidence of catheter-associated thrombus formation during PCI, which led to the open-labeled use of UFH. The OASIS 6 study found that patients with STEMI treated with fondaparinux and fibrinolysis had reduced mortality and reduced rates of reinfarction without increased bleeding or strokes,[55] although again there was evidence of increased thrombotic complications during coronary intervention. These adverse events have turned fondaparinux to be contraindicated as a sole anticoagulant to support PCI in ACS.[38]

Indications: UA/NSTEMI and STEMI.

Dosing: Initial dose of 2.5 mg IV followed by 2.5 mg SC injection daily (maximum antifactor Xa activity is reached in 3 hours).

Side effects: Bleeding, rash/pruritus at injection site, mild elevation of aminotransferases, thrombocytopenia.

Contraindications: CrCl < 30 mL/min, caution if body weight < 50 kg.

Recommendations: Fondaparinux is an alternative anticoagulant for the treatment of UA/NSTEMI patients being managed conservatively and should be continued for up to 8 days. Its use is preferred in the treatment of those with an increased bleeding risk. In the event of PCI, co-administration of UFH or bivalirudin is recommended to decrease the incidence of catheter-associated thrombosis. Fondaparinux should be avoided in patients with planned CABG within 24 hours owing to its long half-life. For STEMI, fondaparinux is an acceptable alternative to UFH in patients undergoing fibrinolysis and should be continued for up to 8 days. The incidence of catheter-associated thrombosis has limited its use for primary PCI and therefore fondaparinux should not be used in this setting.

WARFARIN

Rationale: Warfarin exerts its anticoagulant effect by inhibiting the hepatic synthesis of the vitamin K–dependent coagulation factors II, VII, IX, and X as

well as the anticoagulant proteins C and S. Although older, small studies found limited benefit when used in the post-MI setting, the role of warfarin for ACS in the modern era is primarily relegated to the treatment of LV thrombus, atrial fibrillation, or mechanical heart valves. Given the role of DAPT for ACS, the addition of warfarin ("triple antithrombotic therapy") for other indications introduces a greater overall risk of bleeding and can often be challenging to manage in clinical practice.

Indications: Atrial fibrillation, LV thrombus, mechanical heart valve, venous thromboembolism (VTE).

Dosing: 2 to 5 mg po daily should be started and adjusted according to international normalized ratio (INR). Standard nomograms or genotype-specific dosing strategies are available. Starting lower dose in elderly or debilitated patients should be considered. Target INR varies with indication.

Side effects: Bleeding, hypersensitivity reactions, skin/tissue necrosis (rarely).

Contraindications: Active bleeding or unacceptable bleeding risk, unsupervised patient with high nonadherence risk, pregnancy.

Recommendations: The use of warfarin during or after ACS is predominately guided by expert opinion with limited evidence in the current literature. Warfarin should generally be started or continued in high-risk patients with a clear indication for its use (atrial fibrillation, LV thrombus, mechanical heart valve, or VTE). When used in combination with aspirin and a thienopyridine, the benefit of warfarin should outweigh the incremental risk of bleeding, and it should be given for the minimal time necessary to achieve the desired protection. Patients on triple antithrombotic therapy should be closely monitored for bleeding with strict attention paid to maintaining a therapeutic INR.

NEW ORAL ANTICOAGULANTS

During the last decade, the oral DTI Dabigatran and the direct factor Xa inhibitors Rivaroxaban, Apixaban, and Edoxaban have gained widespread use to reduce the thromboembolic risk in nonvalvular atrial fibrillation (NVAF) and in VTE with superior efficacy and safety profile, as a group, over warfarin.[56] Therefore, they are used in patients with ACS mainly for above-mentioned indications, NVAF, and VTE. As with warfarin, the addition of one of these agents to DAPT after coronary syndrome and PCI is associated with increased risk of bleeding. For the meantime, no large randomized clinical trials to examine different protocols and combinations of these agents have been completed. Therefore, as with warfarin, triple antithrombotic therapy should be

given for the minimal time necessary, with reduced dosage of new oral anticoagulants (NOACs) and with addition of proton pump inhibitors. Additionally, when triple therapy is needed, it is a common practice to prefer clopidogrel to ticagrelor and prasugrel.[57] As the clearance of these agents is partly renal, they are not given with severe impairment of renal function (CrCl < 15 mL/min).

Except for their common use in NVAF and VTE, clinical trials have shown some reduction in ischemic events when NOACs were given to patients after ACS but with the expense of increased bleeding events.[58]

Indications: NVAF, VTE.

Dosing: Dabigatran 110 to 150 twice daily, rivaroxaban 20 mg once daily (15 mg for CrCl 15 to 49 mL/min) (15 mg twice daily for 21 days as a loading dose for VTE), apixaban 5 mg twice daily (2.5 mg twice daily when two of the following exists: Serum Creatinine > 1.5 mg%, age > 80, weight < 60 kg).

Side effects: Bleeding.

Contraindications: Active bleeding or unacceptable bleeding risk, advanced renal failure, pregnancy.

Recommendations: NVAF, VTE.

FIBRINOLYTICS

All fibrinolytic agents are plasminogen activators and work by catalyzing the cleavage of endogenous plasminogen to generate plasmin. Their thrombolytic action is derived from the ability of plasmin to degrade the fibrin matrix of the thrombus. Although contemporary practice favors the use of a catheter-based reperfusion strategy when available, fibrinolytic reperfusion still remains an important component in the treatment of STEMI in the United States and worldwide. The mortality benefit of fibrinolytic therapy is well proven and, when compared with control, fibrinolysis has been estimated to confer a significant 18% relative reduction in 35-day mortality.[59] Similar to primary PCI, fibrinolytic reperfusion offers the greatest benefit when given early, ideally within the 30 minutes of diagnosis. As a thrombus becomes more organized over time, the efficacy of fibrinolytic therapy decreases. Patients at higher risk for adverse consequences (anterior MI, diabetes, hypotension, left bundle branch block) seem to derive the most benefit when pharmacologic reperfusion is initiated early in the course.

Fibrinolytic agents differ substantially with regard to their antigenicity, specificity for clot-bound fibrin, dosing, and cost. There is no preferred fibrinolytic agent currently recommended by ACC/AHA guidelines. Instead, the choice of fibrinolytic agent should be selected on the basis of physician familiarity, timely availability, and, in the case of streptokinase, past exposure. The most feared and catastrophic adverse consequence of fibrinolytic therapy is intracranial hemorrhage, which is estimated to occur in 0.5% to 0.7% of patients. As such, the absolute contraindications for fibrinolytic therapy include patients with increased risk for intracerebral hemorrhage (ICH) (prior hemorrhagic stroke, prior ischemic stroke within 3 months, intracranial neoplasm or vascular lesions, or closed-head injury within 3 months). Fibrinolytic reperfusion is contraindicated in the treatment of UA/NSTEMI.

Concominant use of anticoagulants in patients treated with fibrinolytics: All patients receiving fibrinolytic reperfusion should receive anticoagulant therapy for a minimum of 48 hours and preferably for the duration of the hospitalization, up to 8 days. UFH, enoxaparin, and fondaparinux have established efficacy when used with fibrinolytics and are the recommended anticoagulants. UFH should be dosed according to recommended ACS weight-based dosing guidelines. However, use for greater than 48 hours is discouraged due to the increased risk of developing HIT and therefore should be changed to enoxaparin or fondaparinux. Enoxaparin should be dosed with specific attention to age, weight, and CrCl. In patients <75 years with normal creatinine, an initial 30-mg IV bolus is given followed by 1-mg/kg SC every 12 hours. If ≥75 years, the IV bolus is eliminated and 0.75 mg/kg SC every 12 hours is given. For all patients with CrCl < 30 mL/min, 1 mg/kg SC daily should be given. Fondaparinux is dosed with an initial 2.5-mg IV followed by 2.5-mg SC daily. It should be avoided in patients with creatinine less than 3.0 mg/dL.

STREPTOKINASE

Rationale: Streptokinase (SK) is a first-generation non–fibrin-specific lytic that exerts its effects both on clot-bound and circulating plasminogen. Although inexpensive by comparison, SK is limited by the possible development of neutralizing antibody titers in previously treated patients. Additionally, SK results in systemic fibrinolysis.

Indication: STEMI.

Dosing: 1.5 million IU over 60 minutes.

Side effects: Bleeding, bronchospasm, anaphylaxis, hypotension, angioedema,

periorbital swelling, fever, urticaria.

Contraindications: See **Table 9.6**.

TABLE 9.6 Contraindications for the Use of Fibrinolytic Agents in STEMI

ABSOLUTE CONTRAINDICATIONS
Any prior ICH
Known intracranial neoplasm or cerebral vascular lesion
Ischemic stroke within 3 mo (EXCEPT acute ischemic stroke within 3 h)
Suspected aortic dissection
Active bleeding or bleeding diathesis (excluding menopause) such as active peptic ulcer
Significant closed-head or facial trauma within 3 mo
RELATIVE CONTRAINDICATIONS
Severe, uncontrolled HTN on presentation (SBP > 180 mm Hg or DBP > 110 mm Hg)
History of ischemic stroke > 3 months, dementia, or intracranial pathology not specified above
Traumatic or prolonged (>10 min) CPR
Noncompressible vascular punctures
Pregnancy
Recent (2–4 wk) internal bleeding
Major surgery within past 3 weeks

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of the patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004;44:E1-E211.
CPR, cardiopulmonary resuscitation; DPB, diastolic blood pressure; ICH, intracerebral hemorrhage; HTN, hypertension; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

ALTEPLASE (RTPA)

Rationale: A second-generation fibrinolytic considered to be more specific for clot-bound fibrin. Compared with SK, alteplase was shown to confer a significant 30-day mortality reduction (15%) when administered with UFH.[60] However, alteplase is associated with a slightly higher risk of ICH than SK.

Indications: STEMI.

Dosing: Accelerated protocol—(for patients > 67 kg) 15 mg IV bolus, then 50 mg over 30 minutes, then 35 mg over 60 minutes (total dose = 100 mg). For patients ≤ 67 kg, 15 mg IV bolus, then 0.75 mg/kg (50 mg maximum) over 30 minutes, then 0.5 mg/kg (35 mg maximum) over 60 minutes (total dose < 100 mg).

Side effects: Bleeding, hypotension, nausea/vomiting.

Contraindications: See **Table 9.6**.

RETEPLASE (RPA)

Rationale: rPA is a third-generation fibrinolytic similar to alteplase but with less high-affinity fibrin binding and increased potency. Although no increased mortality was shown over alteplase in GUSTO III, its ability to be given as a double bolus may confer a theoretical advantage related to it by timely administration and less dosing errors.

Indications: STEMI.

Dosing: 10 units IV bolus followed by a second 10 units IV bolus in 30 minutes.

Side effects: Bleeding.

Contraindications: See **Table 9.6**.

TENECTEPLASE (TNK)

Rationale: TNK is a third-generation fibrinolytic that, compared with alteplase, has increased fibrin specificity, decreased clearance, and decreased inhibition from plasminogen activator 1. The ASSENT 2 trial showed similar 30-day mortality rates when compared with alteplase, however fewer mild-to-moderate systemic bleeding complications and need for blood transfusions.[61]

Indications: STEMI.

Dosing: Single 30-to-50-mg IV bolus given over 5 seconds, dosed by weight. For <60 kg, 30 mg should be given; for 60 to 70 kg, 35 mg; for 70 to 80 kg, 40 mg; for 80 to 90 kg, 45 mg; for ≥ 90 kg, 50 mg.

Side effects: Bleeding, hypotension.

Contraindications: See **Table 9.6**.

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atient and Family Information for: MEDICATIONS USED IN THE MANAGEMENT OF ACS

The medicines used to treat heart attacks in the modern-era stem from decades of laboratory and clinical trial research. As more and more is learned about CAD, the drugs used to treat heart attack victims will hopefully become even more safe and effective. Today, medical therapy forms the cornerstone of heart attack care. Early after diagnosis, much emphasis is placed on controlling chest pain, interrupting further heart damage, and maintaining a safe blood pressure and heart rate. Powerful blood thinners, pain medications, blood pressure–and cholesterol-lowering drugs, catheterization procedures, and sometimes even bypass surgery are used to varying degrees in the early treatment of heart attacks. Alongside these therapies, other medicines may be added to treat cardiac arrhythmias, CHF, diabetes, or tobacco addiction. The decisions underlying which medicines are used to treat a specific patient are complex and often change depending on one's age, cardiac risk factors, medical history, and type of heart attack encountered.

The following sections are divided into various classes and types of medications routinely used in the treatment of heart attacks. Many of the medicines described are also used to treat other conditions, both related and unrelated to the heart. The rationale behind each medication's use, both generic and commonly used trade names, potential side effects, and important details are provided. It is important to emphasize that the following pages should be used only as a general guide. Specific details about each drug, doses, and potential interactions with other medications should always be discussed with a physician and pharmacist.

TREATING THE PAIN OF A HEART ATTACK

A heart attack results from the interruption of blood flow to the muscle of the heart, most commonly by a small blood clot known as a thrombus. As heart muscle is dependent on the oxygen and nutrients carried by the blood, it quickly becomes starved in a process known as ischemia. Ischemia in most patients results in chest pain or angina. It is classically described as a chest pressure or tightness, often moving to the shoulder, neck, jaw, or arms. Other symptoms may include nausea, vomiting, or shortness of breath. For patients who have experienced chest pain or pressure in the past, the discomfort associated with a heart attack is usually more intense, more frequent, and even occurring at rest. In some patients, particularly diabetics and the elderly, symptoms may be more subtle and present only as mild stomach pain or indigestion, occasional palpitations, or even no symptoms at all. The onset of chest pain is often the first sign of a heart attack, and it provides warning that the heart muscle is threatened. While the primary goal in treating all heart attacks is to restore blood flow within the jeopardized coronary artery, the adequate treatment of pain is of paramount importance to all patients.

Medications used to specifically treat the pain of a heart attack are called “antianginals” and include nitrates, β-blockers, and CCBs. For pain unrelieved with these classes of drugs, various forms of narcotic medications, known as opioids, are commonly used.

NITRATES

Names: NTG (*Minitran, Nitro-Bid, Nitro-Dur, Nitro-Time, Nitrolingual, NitroQuick, Nitrostat*)

Related medications: Isosorbide mononitrate (*Imdur, Ismo, Monoket*), isosorbide dinitrate (*Isordil, Dilatrate-SR, Isochron*)

NTG is one of the most commonly used medicines for the treatment of chest pain. It is a “vasodilator” and primarily works by dilating, or expanding, the size of coronary arteries. The net effect is that more blood can get to the heart muscle. Even in patients with a completely blocked coronary artery, NTG is useful because it recruits blood flow to other, less diseased arteries. NTG lowers blood pressure, a property that is helpful in relieving pain and decreasing the amount of strain placed on the heart. NTG can be administered in a variety of forms, a feature that makes it particularly useful when treating someone with

ongoing nausea and vomiting. When given as permanent medication, people treated with nitrates develop a situation called “tolerance,” which means that the influence of nitrates decreases by time. On the other hand, when kept for only s.o.s. use as in heart attacks, nitrates retain their above-mentioned benefits.

Preparations: Sublingual (dissolved under the tongue), translingual (sprayed into the mouth), oral, transcutaneous (absorbed through the skin), and IV.

Side effects: Headache (most common), flushing, dizziness, lightheadedness, nausea, vomiting, blurred vision, swelling.

Important information: The patients who use medications to treat erectile dysfunction such as sildenafil (*Viagra*), tadalafil (*Cialis*), or vardenafil (*Levitra*) should not use NTG because combined use may result in a severe, rapid reduction in blood pressure or even death. The prior or ongoing use of any of these medications should immediately be reported to a physician.

β-BLOCKERS

Names: Metoprolol (*Lopressor, Toprol-XL*), carvedilol (*Coreg*), bisoprolol (*Zebeta*), atenolol (*Tenormin*), labetalol (*Trandate*), propranolol (*Inderal*), esmolol (*Brevibloc*)

β-Blockers are a class of blood pressure medications commonly used in the treatment of heart attacks, abnormal heart rhythms, and CHF. They work to relieve angina by both lowering blood pressure and reducing the heart rate. When the heart is forced to pump blood against a high blood pressure or beat at a fast rate, it requires greater amounts of oxygen and thus greater coronary blood flow. During exercise and especially during a heart attack, blood flow to the heart muscle is jeopardized and unable to meet the demands required. By lowering both the blood pressure and heart rate, β-blockers are useful at reducing this strain on the heart and often result in reduced levels of chest pain.

Preparations: Oral, IV.

Side effects: Dizziness, fatigue, lightheadedness, change in sexual ability or desire, depression, diarrhea, slow heartbeat.

Important information: Some patients with asthma, emphysema, bronchitis, or related diseases of the lungs may experience excessive wheezing or shortness of breath while taking β-blockers. Such reactions should be reported to a physician. Additionally, abruptly discontinuing β-blockers has been reported sometimes to result in worsening of chest pain.

CALCIUM CHANNEL BLOCKERS

Names: Diltiazem (*Cardizem, Cartia, Dilacor, Dilt, Diltia, Diltzac, Taztia, Tiazac*), verapamil (*Calan, Covera, Isoptin, Verelan*), amlodipine (*Norvasc*), felodipine (*Plendil*), nisoldipine (*Sular*), lercanidipine (*Zanidep*)

CCBs, a class of blood pressure medications, are also used to treat angina and abnormal heart rhythms. CCB have various effects, with part of them working similar to β-blockers, reducing the heart rate and blood pressure, thus reducing strain on the heart. Yet, it is a common practice to avoid this group of medications in heart attacks because they can result in significant decrease in heart contractility and may aggravate heart failure. On the other side, patients with a combination of heart attack and elevated blood pressure may gain benefit from CCB treatment.

Preparations: Oral, IV.

Side effects: Dizziness, lightheadedness, headache, nausea or vomiting, constipation, swelling, slow heartbeat.

NARCOTICS (OPIOIDS)

Names: Morphine (*Avinza, MS Contin, Roxanol*), fentanyl (*Sublimaze*), oxycodone (*OxyContin, OxyFast, Percocet, Endocet, Magnacet*), hydrocodone (*Lortab, Norco, Vicodin, Zydone*), hydromorphone (*Dilaudid*), meperidine (*Demerol*)

Narcotics such as morphine do not specifically treat angina. Rather, they act more generally to block pain signals in the body from reaching the brain. Narcotics are often prescribed for heart attack patients when other antianginal medications have failed to completely control pain. Additionally, they have several beneficial side effects, one of which is to help slow the heart rate. Like β-blockers and CCBs, this helps to reduce the work load exerted on the heart thereby reducing strain on the heart. Narcotics come in many different preparations, but in the context of heart attacks narcotics are used mainly intravenously; by this route, they provide the most rapid relief of symptoms needed at the initial phase of management.

Preparations: Oral, IV, transdermal (through the skin).

Side effects: Nausea, vomiting, constipation, dizziness, flushing, slow heartbeat, shallow breathing.

ANTIPLATELET MEDICATIONS

Platelets are specialized blood cells that constantly survey the body for areas of injury. In blood vessels, and in the coronary arteries in particular, platelets are responsible for identifying damaged areas of vessel wall and then sealing off these areas before further harm ensues. Unfortunately, other adverse processes, such as cholesterol deposits and thickening of arterial wall, may cause activation of platelets as these small cells recognize these arterial wall changes as damage to be sealed. When this occurs, platelets quickly change their shape, become sticky, and along with other platelets form a small blood clot—thrombus. Unfortunately, this small blood clot may often grow large enough to completely or incompletely impede flow through the entire artery. This, most simply, is the cause of a heart attack. Antiplatelet drugs are special medications that interfere with the ability of platelets to form clots, particularly large obstructive clots. Antiplatelet medications work particularly well at reducing heart attacks caused by blood clots in the coronary arteries. However, because they block the natural actions of platelets throughout the body, they can also increase the risk of unintended bleeding.

ASPIRIN

Names: Aspirin (*Bayer Aspirin*, *Ecotrin*, *Anacin*)

Aspirin is one of the oldest, most widely used, cheap, and effective antiplatelet medicines around. Even today, it remains an essential component in the treatment of heart attacks both during hospitalization and after discharge. With very few exceptions, aspirin therapy should be taken for life in individuals who suffer a heart attack.

Preparations: Oral, rectal.

Side effects: Upset stomach, heartburn, stomach bleeding, easy bruising.

Important information: Because aspirin remains such an important medicine in the treatment and prevention of heart attacks, patients should take it daily. This is especially important if a stent is used in the treatment of one’s heart disease. Although a true aspirin allergy exists, fortunately, it is rare and most side effects from aspirin can be overcome with the use of coated formulations and certain medicines to reduce stomach acid. Consultation with a cardiologist is recommended before stopping aspirin, even temporarily, for situations such as elective surgery.

$P2Y_{12}$ INHIBITOR

Names: Clopidogrel (*Plavix*), prasugrel (*Effient*), ticagrelor (*Brilinta*)

These medications each work as potent antiplatelet medications, most commonly taken in addition to aspirin, and work to greatly reduce the body's ability to form blood clots in the coronary arteries and elsewhere. Studies of patients with heart attacks have consistently proven that these drugs, when added to aspirin, help reduce the incidence of future heart attacks and prolong one's lifespan. In addition to their role in the treatment of heart attacks, they are critically important in patients who have been treated with coronary stents.

Preparations: Oral.

Side effects: Easy bruising or bleeding, nausea, dizziness.

Important information: Like with aspirin, patients prescribed medications from this class should strive to take them exactly as requested by a physician. In patients with coronary stents, this becomes of even greater importance because the abrupt discontinuation can result in new blood clots forming within the stent itself. Although such events are rare, they often lead to a second heart attack and can be fatal. As with aspirin, consultation with a cardiologist is recommended prior to electively stopping these medications for upcoming surgeries. Patients should avoid missing doses or running out before a prescription can be renewed.

PLATELET GLYCOPROTEIN IIB/IIIA RECEPTOR ANTAGONISTS

Names: Abciximab (*Reopro*), eptifibatide (*Integrilin*), tirofiban (*Aggrastat*)

Glycoprotein IIb/IIIa receptor antagonists are molecules named for the specific platelet receptor they bind. As with other antiplatelet medications, they work to decrease the ability of platelets to form clots within the coronary arteries. However, this class of medications is only given intravenously. Although these drugs are often used in addition to aspirin for the early treatment of heart attacks, they are most commonly used during coronary intervention during catheterization, including stent placements. Their highly potent platelet-blocking effects make them particularly well suited to prevent clot formation within stents, thereby increasing stent durability. Like with other antiplatelet medications, drugs from this class have been proven in thousands of patients who had heart attack to prolong life and reduce future heart attacks.

Preparation: IV.

Side effects: Easy bruising or bleeding, nausea, stomach aches.

ANTICOAGULANTS

A blood clot, or thrombus, is not only formed by platelets. Within the circulating blood exists a multitude of microscopic proteins that work alongside platelets to assist in the formation of blood clots at sites of vessel injury. When damage is detected, these proteins form long, thin threads call fibrin. In turn, these fibrin threads create a mesh-like plug that helps to stabilize blood clots. Whereas antiplatelet medications block the actions of platelets, anticoagulants block the body's ability to form fibrin. Because they work to prevent blood clot formation, they too are often referred to as "blood thinners."

HEPARIN AND RELATED MEDICATIONS

Names: Heparin

Related medications: Enoxaparin (*Lovenox*), bivalirudin (*Angiomax*), fondaparinux (*Arixtra*), dalteparin (*Fragmin*)

Heparin and its related medicines comprise a central role in the treatment of heart attacks. They are given early in the course of a heart attack and sometimes continued throughout the duration of a hospital stay. In addition to preventing blood clots associated with heart attacks, heparin or similar drugs are routinely used in the prevention of clots associated with other disorders. Typical uses may include the prevention of blood clots in the legs (deep vein thrombosis), those associated with mechanical heart valves, and those that may form with certain abnormal heart rhythms.

Preparations: IV, SC (under the skin) injections.

Side effects: Easy bruising or bleeding, pain at injection site, abnormal blood counts (especially platelets), rash.

Important information: A rare condition known as HIT can occur in some patients who have had previous exposure to heparin. This condition causes a dramatic drop in platelets and can lead to both excessive bleeding and clotting. Patients with a history of HIT should promptly notify their physicians during any hospital admission or office visit.

WARFARIN

Names: Warfarin (*Coumadin, Jantoven*)

Related medications: Dabigatran (*Pradaxa*)

Warfarin is an orally given blood thinner that has been used for decades to treat a multitude of conditions associated with blood clotting. Inherited clotting disorders, mechanical heart valves, abnormal heart rhythms, and prior blood

clots in the legs or lungs are all common reasons for warfarin to be prescribed. Although it is rarely used to specifically treat or prevent heart attacks, warfarin deserves special mention because it is often used in addition to the antiplatelet and anticoagulant medications commonly prescribed for patients who had heart attack. A unique and often frustrating feature of warfarin is that it requires frequent blood tests to monitor its activity.

Preparations: Oral.

Side effects: Easy bruising or bleeding, nausea, vomiting, altered sense of taste.

Important information: Each blood thinner added to a patient's list of medications introduces an incremental risk of unintended bleeding. In properly selected patients, these drug combinations can be safely followed but often require more aggressive monitoring and physician visits. It is not uncommon for warfarin dosing, even if stable for years, to need adjusting after the initiation of new medications. Patients should pay close attention to early signs of bleeding, especially bleeding related to the stomach or intestines, and report these to their physician.

NEW ORAL ANTICOAGULANTS (NOACS)

Names: Dabigatran (*Pradaxa*), Rivaroxaban (*Xarelto*), Apixaban (*Eliquis*)

This class of orally taken blood thinners was introduced during the last decade to treat several conditions that, until then, were treated by warfarin. There is no need to continuously monitor their activity by blood tests, and they have additional benefit in efficacy and safety over warfarin. Still, as blood thinners, they may increase the risk of unintended bleeding especially when taken with antiplatelet agents as in patients after heart attacks.

Preparations: Oral.

Side effects: Bleeding.

FIBRINOLYTICS OR "CLOT BUSTERS"

Names: Streptokinase (*Streptase*), alteplase (*Activase*), reteplase (*Retavase*), Tenecteplase (*TNKase*)

Fibrinolytics, also called "thrombolytics" or "clot busters," are a class of medications used to treat a specific type of heart attack where blood flow through a coronary artery is completely obstructed. Unlike antiplatelet and anticoagulant drugs, which prevent blood clots from forming or expanding,

fibrinolytics actually target and destroy clots that have already formed. These extremely potent medications work best when given very early in the course of a heart attack and typically are used in areas where a cardiac catheterization laboratory is not immediately available. Unfortunately, they have not proven to be useful in treating heart attacks caused by only partially obstructive clots.

Preparations: IV.

Side effects: Easy bruising or bleeding, stroke (rare).

OTHER IMPORTANT MEDICATIONS USED IN TREATING HEART ATTACKS

The immediate control of chest pain, addition of antiplatelet and anticoagulant medications, and often cardiac catheterization or use of fibrinolytics are crucially important during the early stages of a heart attack. These therapies are largely targeted at aborting further damage and salvaging heart muscle from permanent damage. Aggressive and early control of blood pressure, fluid volume, and cholesterol levels are equally important in achieving these goals. In many cases, additional blood pressure medications may be added to more closely control one's HTN. In other cases, they may be added simply for the unique and beneficial properties they provide to patients with heart disease.

ACE INHIBITORS AND ARB*S*

Names: **ACE inhibitors**—benazepril (*Lotensin*), captopril (*Capoten*), enalapril (*Vasotec*), fosinopril (*Monopril*), lisinopril (*Prinivil*, *Zestril*), moexipril (*Univasc*), perindopril (*Aceon*), quinapril (*Accupril*), ramipril (*Altace*), trandolapril (*Mavik*); **ARBs**—cadesartan (*Atacand*), eprosartan (*Teveten*), irbesartan (*Avapro*), losartan (*Cozaar*), olmesartan (*Benicar*), valsartan (*Diovan*), telmisartan (*Micardis*)

Medications from these two classes of blood pressure drugs are commonly used alongside other therapies to treat specific consequences of heart attacks, such as CHF, that is, a weakened heart muscle. Apart from being blood pressure–lowering drugs, these medications have shown to be beneficial in prolonging life, reducing the incidence of CHF, and protecting the kidneys in diabetic patients.

Preparations: Oral.

Side effects: Dizziness, lightheadedness, cough (ACE inhibitors), abnormal electrolyte levels, swelling.

DIURETICS

Names: furosemide (*Lasix*), bumetanide (*Bumex*), torsemide (*Demadex*), hydrochlorothiazide (*Esidrix, Microzide*), chlorothiazide (*Diuril*), metolazone (*Zaroxolyn*), amiloride (*Midamor*), triamterene (*Dyrenium*), spironolactone (*Aldactone*), eplerenone (*Inspra*).

Diuretics, commonly referred to as "water pills," are routinely used in the care of patients who had heart attack and who suffer from CHF or any condition characterized by increased fluid in the body, most often in the lower extremities or lungs. They work to remove excess fluid by stimulating urine production in the kidneys. Furosemide (*Lasix*) remains the most prescribed drug used in the hospital for this purpose. Some weaker diuretics are often added for their blood pressure–lowering properties, whereas others such as spironolactone (*Aldactone*) and eplerenone (*Inspra*) may be added in special circumstances characterized by severe CHF.

Preparations: Oral, IV.

Side effects: Dizziness, lightheadedness, dry mouth, thirst, hearing difficulty, abnormal electrolyte levels, and kidney function.

CHOLESTEROL-LOWERING MEDICATIONS

Names: atorvastatin (*Lipitor*), fluvastatin (*Lescol*), lovastatin (*Mevacor, Altoprev*), pravastatin (*Pravachol*), rosuvastatin (*Crestor*), simvastatin (*Zocor*)

Related medications: niacin (*Niaspan, Niacor*), gemfibrozil (*Lopid*), fenofibrate (*Tricor*), cholestyramine (*Questran*), colestipol (*Colestid*), colesevelam (*Welchol*), ezetimibe (*Zetia*)

Cholesterol-lowering medications, most notably the statins, have emerged as some of the most important drugs used in the treatment CAD in the past three decades. Stringent cholesterol control helps prevent both future heart attacks and strokes. Additionally, clinical trials have shown the benefits of statins, especially powerful agents as atorvastatin (*Lipitor*), simvastatin (*Zocor*), or rosuvastatin (*Crestor*), when given during the early phase of heart attack management. The related medications listed above are sometimes added to better control certain types of cholesterol or triglycerides abnormalities, most often in addition to statins.

Preparations: Oral.

Side effects: Muscle aches or pains, nausea, stomach aches, flushing or itching (niacin), insomnia (niacin), gas, diarrhea.

II

HEART FAILURE

10

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Pathway for the Management of Acute Heart Failure

EPIDEMIOLOGY AND IMPACT

Heart failure is a common and growing problem in the developed nations owing to an aging population. If the overall prevalence of heart failure among adults is 1% to 2%, it exceeds 10% in the elderly (over 70 years old).[1] Moreover, acute decompensated heart failure is among the most common causes of hospitalization among elderly patients. Besides being common and costly, heart failure hospitalization has important prognostic implications: it carries subsequent 1-year mortality risk close to 30%.[1] The current chapter is intended to outline a simple yet comprehensive approach to diagnosis and management of acute decompensated heart failure by synthesizing the evidence from multiple studies and major cardiology society recommendations.[1, 2] It is based on the initial acute heart failure management pathway published by our heart failure team (**Figure 10.1**).[3]

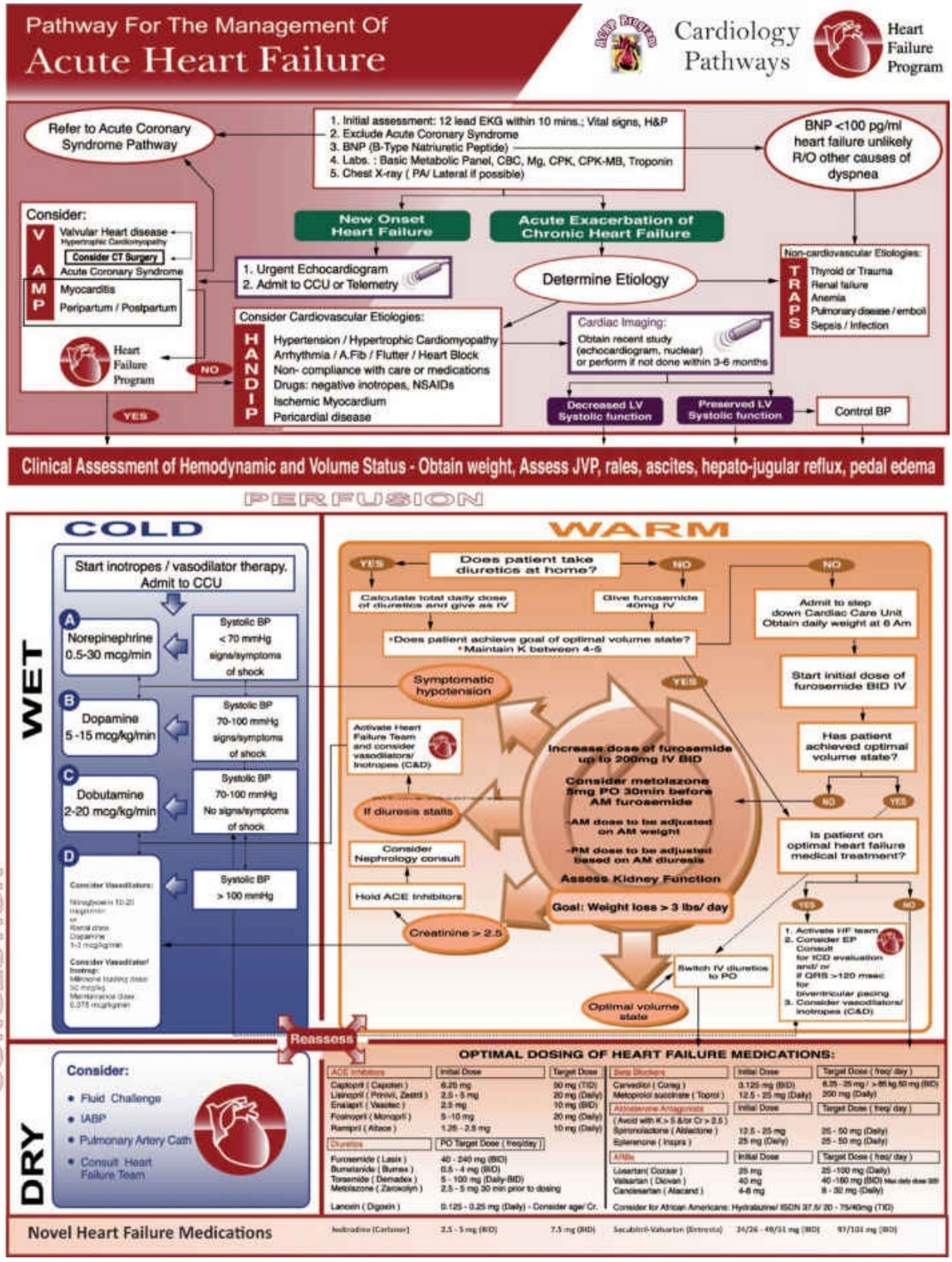

FIGURE 10.1 Pathway for the evaluation and management of acute decompensated heart failure. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptides; BP,

blood pressure; CBC, complete blood count; CCU, coronary care unit; CPK, creatine phosphokinase; CPK-MB, CPK-muscle and brain; CT, computed tomography; EKG, electrocardiogram; HANDIP, hypertension, arrhythmias, noncompliance with care, drugs, ischemic myocardium, and pericardial disease; IABP, intra-aortic balloon pump; IV, intravenous; JVP, jugular venous pressure; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; PA, pulmonary artery; TRAPS, thyroid, renal failure, anemia, pulmonary disease, and sepsis; VAMP, valvular disease, acute coronary syndromes, myocarditis, and peripartum/postpartum cardiomyopathy.

DEFINITIONS

Acute decompensated heart failure refers to the acute onset of symptoms (predominantly dyspnea, congestion, and fatigue) due to elevated cardiac filling pressures and/or decreased cardiac output. It can be newly diagnosed heart failure or exacerbation of preexisting chronic heart failure condition. Despite major advances in confirmatory laboratory and diagnostic modalities, heart failure remains a clinical diagnosis of a constellation of signs and symptoms. Careful history taking and focused physical examination are the cornerstones of the diagnosis. The diagnosis is established by the combination of symptoms of heart failure (such as dyspnea and orthopnea), signs of fluid overload (such as jugular venous distention, pulmonary crackles, and peripheral edema), signs of hypoperfusion (such as cold extremities, confusion, and narrow pulse pressure), and objective evidence of structural heart disease (such as third heart sounds, cardiac murmurs, and echocardiographic findings). Acute decompensated heart failure is a continuum of clinical presentations ranging from mild dyspnea to florid pulmonary edema to cardiogenic shock; therefore, urgent evaluation and triage of suspected acute decompensated heart failure are warranted.

Although initially described for patients with myocardial infarction, the Forrester classification can be applied to all patients with acute decompensated heart failure to guide the management.[4] It assigns patients to groups on the basis of bedside estimation of fluid overload status (“wet,” meaning apparent signs of congestion) and perfusion state (“cold,” meaning low perfusion state). “Wet” signs include pulmonary congestion, jugular venous distention, congestive hepatomegaly, and peripheral edema. “Cold” signs include cold extremities, confusion, narrow pulse pressure, and oliguria. Most but not all patients in the “cold” category are hypotensive. Most patients with acute decompensated heart failure fall into the “wet” and “warm” category: They have evidence of pulmonary congestion/pulmonary edema with normal or high blood pressure. Patients with pulmonary edema and hypoperfusion are in or at risk for

cardiogenic shock, which typically signifies bad prognosis unless a reversible cause is rapidly identified and corrected (eg, reperfusion therapy in a patient with acute myocardial infarction or a corrective surgery in a patient with acute valvular dysfunction). Sometimes patients with cardiogenic shock (“cold” state) have no evidence of pulmonary congestion and systemic hypoperfusion dominates the clinical picture. Patients with acute right ventricular infarction are a classic example in this category.

ETIOLOGY AND PRECIPITATING FACTORS

There is a long list of possible heart failure etiologies, but in reality a few causes account for the majority of cases. From long-term heart failure management perspective, the causes can be broadly divided into heart failure with reduced left ventricular ejection fraction (LVEF) and heart failure with preserved LVEF. Recently, a new category of heart failure with mid-range ejection fraction of 40% to 49% has been proposed, which represents a “gray zone” between the traditional categories.[1, 2] Coronary artery disease is the most common cause of heart failure with reduced LVEF. Less common causes include myocardial diseases resulting in dilated cardiomyopathy that can be idiopathic, genetic, or associated with other conditions (such as infections, toxins, immune-mediated condition, peripartum, and so on). The prevalence of heart failure with preserved LVEF increases with age and overall accounts for approximately 50% of heart failure cases. The etiology of heart failure with preserved ejection fraction is complex and relates to important cardiovascular risk factors such as hypertension. Some valvular diseases (such as aortic stenosis and mitral regurgitation), hypertrophic cardiomyopathy, and restrictive cardiomyopathy also present as heart failure with preserved LVEF.

In any patient who presents with new-onset acute decompensated heart failure or chronic heart failure exacerbation, the precipitating cause should be identified and adequately addressed. Myocardial ischemia is a common precipitating factor and should be considered in the differential diagnosis. Valvular pathology can cause acute heart failure if it develops suddenly: Typical examples include flail mitral valve with chordal rupture or aortic valve perforation in infective endocarditis. Similarly, mechanical complication of myocardial infarction (such as papillary muscle rupture and ventricular septal rupture) can cause sudden profound hemodynamic deterioration. Myocarditis and postpartum

cardiomyopathy can present as acute heart failure. VAMP (valvular disease, acute coronary syndromes, myocarditis, and peripartum/postpartum cardiomyopathy) is a useful mnemonic in evaluating a patient with new-onset acute heart failure (**Figure 10.2**).[3] Severe hypertension is another common condition that is typically associated with preserved LVEF and better in-hospital outcomes. Both supraventricular and ventricular arrhythmias can precipitate heart failure. It is important to know that patients with diastolic dysfunction are highly dependent on preload for left ventricular filling. Certain arrhythmias such as atrial fibrillation decrease diastolic filling by increasing heart rate and eliminating atria kick, and therefore they can provoke florid heart failure in an otherwise stable patient. Interestingly, frequent ventricular premature beats and right ventricular pacing can create dyssynchrony contributing to heart failure. Medication and diet noncompliance is one of the most common factors that precipitate acute exacerbation in patients with chronic heart failure. HANDIP (hypertension, arrhythmias, noncompliance with care, drugs, ischemic myocardium, and pericardial disease) is another useful mnemonic in evaluating patients with heart failure exacerbation from cardiac causes (**Figure 10.2**).[3]

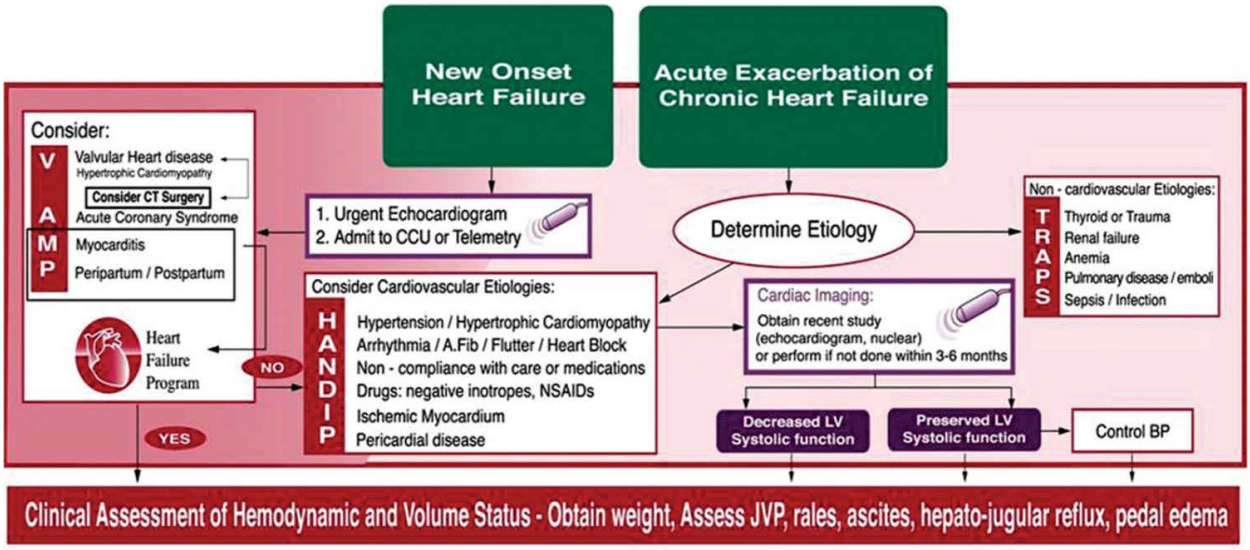

FIGURE 10.2 Differential diagnosis between new-onset heart failure and acute exacerbation of chronic heart failure, with timing of imaging and consideration of precipitating pathophysiology. BP, blood pressure; CCU, coronary care unit; CT, computed tomography; HANDIP, hypertension, arrhythmias, noncompliance with care, drugs, ischemic myocardium, and pericardial disease; JVP, jugular venous pressure; LV, left ventricular; NSAIDs, nonsteroidal anti-inflammatory drugs; TRAPS, thyroid, renal failure, anemia, pulmonary disease, and sepsis; VAMP, valvular disease, acute coronary syndromes, myocarditis, and peripartum/postpartum cardiomyopathy.

Noncardiac factors can precipitate heart failure in otherwise stable patients by creating high oxygen demand and inducing tachycardia (such as anemia, thyroid diseases, drugs, fever and infection, and pulmonary emboli), causing fluid overload (in-hospital intravenous fluid administration, renal failure, and nonsteroidal anti-inflammatory agents), or decreasing myocardial contractility (negative inotropes such as verapamil). TRAPS (thyroid, renal failure, anemia, pulmonary disease, and sepsis) is a mnemonic to help categorize noncardiac precipitants of heart failure exacerbation (**Figure 10.2**).[3]

DIAGNOSIS AND WORKUP

Once the history and physical examination findings consistent with heart failure are ascertained, further work-up is directed toward confirming the diagnosis, establishing the cause of the heart failure, addressing the precipitating factor(s), and identifying prognostic indicators. Physical examination should specifically focus on the degree of respiratory failure (tachypnea, accessory respiratory muscle use), vital signs, signs of fluid overload (pulmonary crackles, jugular venous distension and peripheral edema), and signs of hypoperfusion (cold extremities, confusion, feeble pulses). Cardiac assessment may provide important clues to the diagnosis (eg, a new murmur). Bedside rapid assessment of congestion status and systemic perfusion helps to assign the patient to one of the Forrester categories as described earlier. The essential set of initial tests includes electrocardiogram (ECG), laboratory work-up (complete blood count, electrolytes, renal function and liver function test, and coagulation profile), cardiac troponins, and chest X-ray. Thyroid function tests are recommended in patients with newly diagnosed acute decompensated heart failure. Up to one-third of patients with acute coronary syndrome have no chest pain upon presentation. Therefore, serial ECGs and cardiac biomarkers should be an essential part of the initial work-up. Of note, some repolarization abnormalities and QTc interval prolongation can be caused by acute heart failure per se, not necessarily myocardial ischemia. Similarly, small increase in cardiac biomarkers is often seen in acute decompensated heart failure. Other important findings on ECG include arrhythmias, conduction delays, and hypertrophy. Chest X-ray can confirm pulmonary congestion and can demonstrate some other relevant pathology (large pleural effusion, infiltrates, and cardiomegaly). Arterial blood gases provide information about oxygenation, ventilation, and acid–base status;

arterial blood gases should be considered in all patients with significant respiratory distress as well as low perfusion (“cold”) state.

B-type natriuretic peptides (BNP and pro-BNP) are released from myocardial cells in response to increase in the wall stress. Their levels are elevated in both heart failure with preserved LVEF and that with reduced LVEF, but on average they are lower in patients with heart failure with preserved LVEF. Measuring BNP level can supplement the evaluation of patients with suspected acute decompensated heart failure if used in the appropriate clinical context.[5] Low BNP levels (<100 pg/mL) have a high negative predictive value that makes the diagnosis of heart failure unlikely in a patient who presents to the emergency department with dyspnea. Values > 400 pg/mL are consistent with heart failure, whereas intermediate values (100 to 400 pg/mL) are in the gray zone. Studies showed linear correlation between the admission BNP levels in patients with acute decompensated heart failure and in-hospital mortality.[6] Of note, obese patients with heart failure have lower BNP levels, which should be factored in during clinical decision making. Sudden, “flash” pulmonary edema can sometimes be associated with falsely low BNP levels. At the same time, the positive predictive value of elevated BNP levels (especially gray-zone values) is not very high because they can be elevated in patients with atrial fibrillation, left ventricular hypertrophy, pulmonary hypertension, sepsis, renal dysfunction, and liver disease. For example, in a septic patient with persistent atrial fibrillation and possible heart failure, elevated BNP levels add little information to the clinical judgment. In the patients with preexisting chronic heart failure who come with acute exacerbation, one-time elevated BNP level conveys little information.

Echocardiography is an essential tool in evaluating patients with acute decompensated heart failure. The urgency of getting echocardiogram is determined by the clinical presentation. For example, in a patient suspected to have acute valvular pathology or an acute mechanical complication of myocardial infarction, a bedside echocardiogram can immediately confirm the diagnosis, whereas in a patient with known chronic heart failure, subacute symptoms, and medication noncompliance, the immediate test would add little information. In the acute settings, an echocardiogram helps to assess the presence and degree of systolic dysfunction, right ventricular size and function, and valvular and pericardial pathology. It can assess the diastolic dysfunction and give the estimate of right-sided pressures as well as left-sided filling pressures. Regional wall motion abnormalities and dyssynchrony can provide

clues to the possible causes of the symptoms. Determination of LVEF (heart failure with reduced LVEF vs preserved LVEF) is fundamental in long-term management of heart failure patients.

The routine insertion of a pulmonary artery catheter in patients with acute decompensated heart failure is *not* recommended because it has not been shown to improve major clinical outcomes.[7] It can be considered under specific circumstances to estimate left-sided filling pressures and cardiac output. Possible scenarios include complex patients with cardiac and pulmonary disease, persistent hypotension, worsening renal function, and so forth. The benefits of getting important hemodynamic information should be weighed in each individual patient against the complications of the invasive monitoring and limitations of the technique.

Coronary angiography is indicated in patients with acute decompensated heart failure believed to be precipitated by myocardial ischemia. Successful reperfusion in these settings has been shown to improve survival.

Comprehensive assessment of patients admitted for acute decompensated heart failure includes identification of prognostic indicators. The indicators of poor prognosis include clinical variables (age, poor functional status at baseline, low admission blood pressure, etc), Laboratory factors and ECG changes (wide QRS complex, certain arrhythmias, hyponatremia, positive cardiac biomarkers, marked elevation of BNP, etc), and imaging findings (low LVEF, restrictive mitral inflow pattern, abnormal RV function, etc).[1]

MANAGEMENT

The management of acute decompensated heart failure should be approached in systematic manner and tailored to each individual patient. **Figure 10.1** outlines the general approach to the management of acute decompensated heart failure. The following components of the therapy should be addressed: (1) oxygenation, (2) hemodynamics, (3) fluid overload, and (4) precipitating factors.

OXYGENATION

The range of respiratory distress varies along the spectrum of presentations in acute decompensated heart failure. Rapid assessment of oxygenation and respiratory status is an important initial step. Mild respiratory distress might

require oxygen supplementation via nasal cannula or a mask, with the goal of keeping the patient comfortable and maintaining oxygen saturation above 90% to 92%. Caution should be exercised in chronic CO_2 retainers because high-flow oxygen delivery in these patients can result in acute CO_2 retention and respiratory acidosis. Patients with significant respiratory distress need arterial blood gas analysis to assess oxygenation, ventilation, and acid–base status. Patients with pulmonary edema have been shown to benefit from noninvasive positive pressure ventilation, provided they do not have contraindications (eg, impaired level of consciousness, agitation, inability to protect airways, high risk of aspiration, etc). The benefits of noninvasive positive pressure ventilation result from improved V/Q mismatch and decreased cardiac preload. Meta-analyses of randomized clinical trials in patients with pulmonary edema suggest a decrease in the need of intubation and improvement in respiratory signs and symptoms.[8] Mortality benefit from noninvasive positive pressure ventilation in those patients has not been consistently demonstrated. Patients in significant respiratory distress and those who have contraindications to noninvasive positive pressure ventilation should be intubated and mechanical ventilation should be initiated.

HEMODYNAMICS

Rapid bedside assessment of hemodynamics as described earlier is important in initial management of acute decompensated heart failure. Most heart failure patients are in “warm” and “wet” category and need treatment with diuretics and vasodilators. Patients with borderline or low blood pressure, poor perfusion, and pulmonary edema (“cold” and “wet”) are in/at risk of cardiogenic shock and generally carry poor prognosis. Rapid correction of precipitating factors may improve their condition (eg, revascularization in acute coronary syndrome). Patients with borderline and low systolic blood pressure and poor perfusion (cold and clammy) and patients who are resistant to diuretic therapy experience symptomatic improvement from inotropic agents. Dobutamine, which is a β-adrenergic agonist, can be used in these settings. Phosphodiesterase inhibitors (such as milrinone) are potent inotropes and can also provide significant symptomatic relief. It is important to remember that inotropic agents should be used only as temporary measure and withdrawn as early as possible once adequate perfusion is restored and congestion has been relieved. Symptomatic relief provided by those agents comes at the expense of increased risk of

ischemia, arrhythmias, and myocardial damage. They have been shown to increase short-term and long-term mortality in patients with congestive heart failure.[1] Their use should be restricted to patients with known severe systolic left ventricular dysfunction. In addition, vasodilator effect of inotropic agents may cause hypotension. Vasopressor agents (preferably norepinephrine) can be used in these settings to maintain blood pressure. Finally, patients with hypotension and no signs of significant pulmonary congestion ("cold" and "dry" state) can receive a fluid challenge, if volume depletion and sepsis are a consideration. However, these patients are at risk of rapidly developing volume over load and edema. Careful monitoring is essential. In patients who develop symptomatic hypotension during aggressive diuresis, the diuretics should be held. Patients who are highly preload dependent (eg, severe aortic stenosis or severe concentric left ventricular hypertrophy and normal LVEF) are at a higher risk of hypotension with aggressive diuresis.

In patients with cardiogenic shock who do not have an adequate response to pharmacologic therapy, mechanical assist devices should be considered. These include intra-aortic balloon pump and ventricular assist devices. They can provide temporary hemodynamic support as a "bridge to decision" or bridge to longer-term intervention. The evidence behind using mechanical assist devices in these settings is limited and needs further study and validation.[1]

FLUID OVERLOAD

Symptoms of dyspnea in acute decompensated heart failure are attributed to elevated left-sided filling pressures. Most patients with decompensated heart failure are fluid overloaded owing to renal retention of sodium and water, whereas some patients with acute, especially precipitous, heart failure are normovolemic. Early diuresis and manipulation of preload are the most effective ways to bring symptomatic relief to those patients. Most patients with acute decompensated heart failure require intravenous loop diuretic therapy except "dry" patients and those with hypotension and shock. Patients with hypotension, severe acidosis, renal failure, and hyponatremia are less likely to respond to loop diuretics. The dosing of the intravenous loop diuretic (eg, furosemide) used in patients with acute decompensated heart failure should be based on the degree of fluid overload, renal function, and preadmission loop diuretic use (**Figure 10.3**). Interestingly, it has been shown that loop diuretics improve symptoms even before the diuretic effect by venodilation and a decrease in preload. Parameters

that need to be monitored during diuretic therapy include volume status, intake and output, blood pressure, electrolytes, and renal function. Patients with decreasing renal function upon diuresis (a form of “cardiorenal syndrome”) carry a worse prognosis. In patients who show suboptimal response to escalating doses of loop diuretics, the following options can be considered: addition of a thiazide diuretic, addition of mineralocorticoid receptor antagonist, inotropic therapy, and continuous infusion of a loop diuretic. In patients with renal dysfunction, metolazone added to loop diuretics might be used. Dopamine in low doses has been shown to improve renal perfusion, but the clinical implications of this finding were not supported in a large randomized clinical trial. Ultrafiltration is the last-resort therapy, especially in patients with severe renal dysfunction.

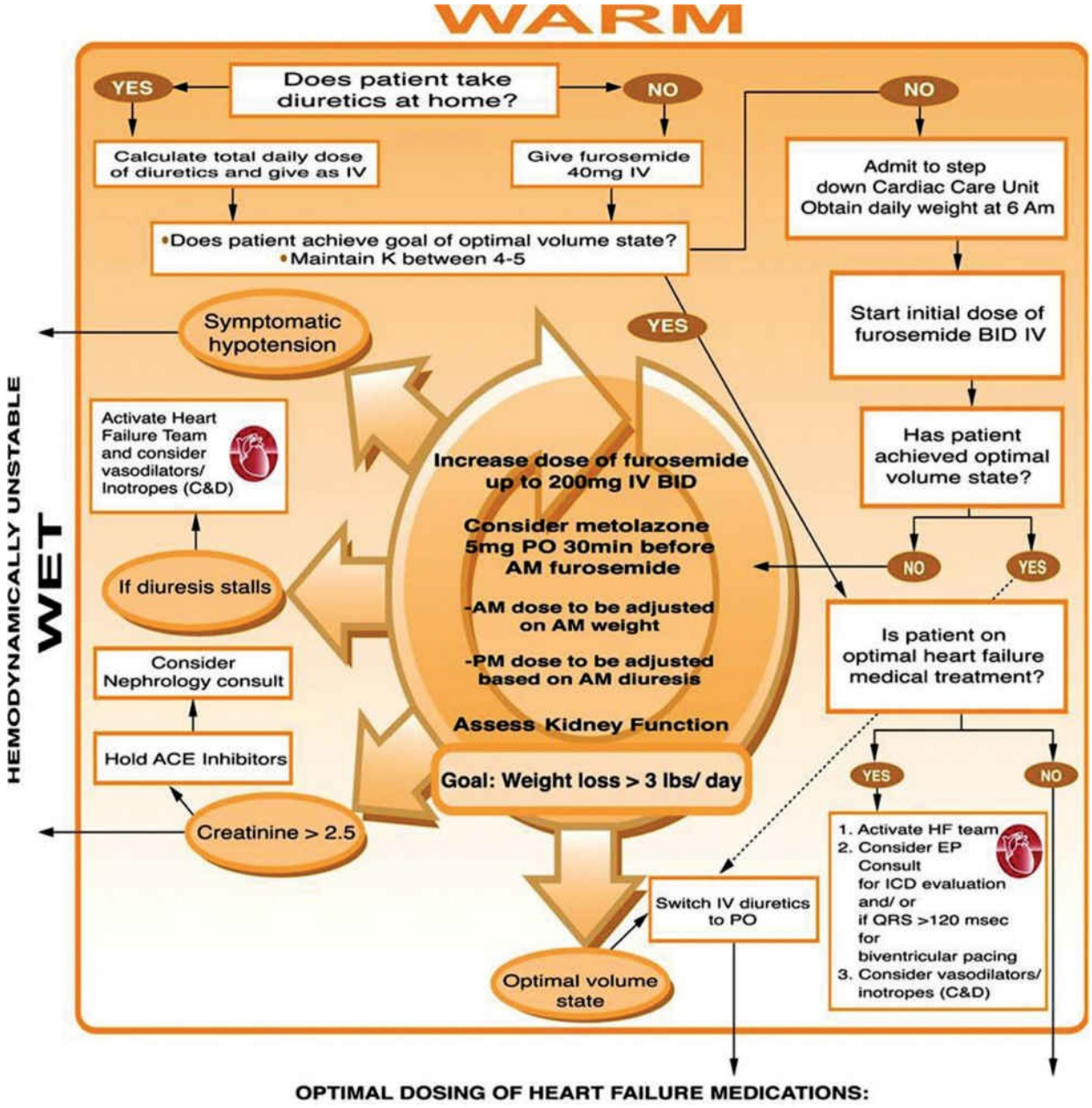

FIGURE 10.3 The "loop" concept of aggressive usage of loop diuretics to rapidly and safely diurese patients, shorten length of stay, and transition to oral therapy upon successful completion of diuresis. ACE, angiotensin converting enzyme; EP, electrophysiology; ICD, implantable cardioverter defibrillator.

Preload reduction brings significant symptomatic relief in patients with acute decompensated heart failure by decreasing left-sided filling pressures. It can be achieved by using venodilators such as nitroglycerine, isosorbide dinitrate, and nitroprusside. Nitroglycerin, typically in the form of intravenous infusion, can be used as add-on therapy to diuretics if systolic blood pressure is >110 mm Hg. In patients with systolic blood pressure <90 mm Hg, vasodilators should be

avoided, whereas in patients with systolic blood pressure of 90 to 110 mm Hg, they should be used with caution. Hypotension is the main side effect of nitroglycerine, especially in patients who are significantly preload dependent (eg, severe aortic stenosis, right ventricular infarction). Nitrates should be avoided in patients using phosphodiesterase inhibitors (eg, sildenafil). Headache is a common complaint, and tachyphylaxis develops with continuous use. Nitroprusside is a potent vasodilator that achieves significant afterload reduction along with preload reduction. This property is important in certain situations such as hypertensive emergencies and acute valvular pathology such as acute mitral regurgitation. Accumulation of cyanide is a potential side effect with continuous infusion. Nesiritide is an analog of brain natriuretic peptide. It produces vasodilation, reduces preload, and may bring symptomatic relief to patients with pulmonary congestion. However, a large randomized trial showed that nesiritide improves symptoms only marginally and does not improve the rates of death and rehospitalization. [9] Therefore, routine use of nesiritide is not recommended. Morphine reduces anxiety and sense of dyspnea and produces vasodilation in patients with pulmonary edema. However, retrospective studies raised some concerns regarding the use of morphine in these patients because of association with increased in-hospital mortality.[2] In patients with acute coronary syndrome and chest pain, morphine should not be withheld.

OTHER THERAPIES

Angiotensin-converting enzyme (ACE) inhibitors reduce morbidity and mortality in patients with chronic heart failure and decreased LVEF but their role in managing patients with acute decompensated heart failure is limited. They are generally avoided in these patients until they are stable due to the following concerns: ACE inhibitors can precipitate hypotension and worsening renal function in patients who are aggressively diuresed. Similarly, β-blockers are the mainstay of chronic heart failure treatment in patients with systolic left ventricular dysfunction, but they should be avoided in the settings of acute exacerbation. In patients who are already taking β-blockers, they can be cautiously resumed once the patients are stable. Thromboembolism prophylaxis should be ensured in all patients with acute decompensated heart failure.

PRECIPITANTS

Identifying the precipitating factors for acute decompensated heart failure should

be the part of the initial thought process. The common precipitating factors are described above, and some of them should be actively sought and corrected such as myocardial ischemia, hypertensive crisis, arrhythmias, and acute valvular pathology (see specific chapters on how to address those issues). Medication and diet noncompliance is a common precipitant, and it should be specifically inquired. Other precipitating factors such as infection, medications (eg, nonsteroidal antiinflammatory drugs), pulmonary disease, and so on could be more subtle and their identification requires a systematic approach to history taking, physical examination, and laboratory work-up.

END-STAGE HEART FAILURE

Patients with severe, "end-stage" heart failure that are resistant to optimal medical therapy often have symptoms at rest (NYHA functional class IV). They have frequent hospitalizations, long hospital stays, and poor quality of life. Options for those patients are limited to continuous inotrope infusion as palliative measure and mechanical support as "bridge" therapy to transplantation or as "destination" therapy. In addition, for refractory end-stage heart failure palliative and hospice care discussions should be initiated.[1, 2]

OPTIMAL DISCHARGE PLANNING

Optimal discharge planning involves patient education, proper follow-up, identification and correction of precipitants, and evidence-based therapy for heart failure. Patient education should include information about the nature of the disease, importance of diet and medication compliance, self-monitoring (eg, weight and edema), and early recognition of decompensation symptoms. Precipitating factors should be addressed, which in specific circumstances might include ischemic work-up, valvular disease surgery, long-term control of arrhythmias, control of hypertension, and the like. Chronic management of heart failure is based on the estimation of the LVEF. Patients with systolic left ventricular dysfunction should be placed on a β-blocker and an ACE inhibitor (or angiotensin receptor blocker) and optimal dosing of the agents should be achieved by slow uptitration during outpatient follow-up. Other therapies for those patients include aldosterone antagonists, hydralazine and isosorbide dinitrate combination, and digoxin (see Chapter 19 for specific drug discussion). Newer agents such as an angiotensin receptor-neprilysin inhibitor (sacubitril-

valsartan) and a selective sinus node inhibitor (ivabradine) have a role in the outpatient treatment of chronic systolic heart failure. Specifically, sacubitril-valsartan has been shown to be a superior agent compared with ACE inhibitor.[10, 11] Ivabradine can be considered to further lower heart rate in normal sinus rhythm despite patients' being on optimal doses of β-blockers or in patients intolerant of β-blockers.[12] The evidence for chronic management of diastolic heart failure is more limited; optimal volume control and treatment of hypertension seem to be the best strategy at this point.

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Patient and Family Information for: THE MANAGEMENT OF ACUTE HEART FAILURE

DEFINITION AND CAUSES

Heart failure is a common problem in the United States, especially in the elderly population. It is one of the most common reasons for hospital admission. Heart failure is a clinical syndrome and not a specific disease. It can have many causes. It results from decreased pumping function of the heart and its inability to propagate adequate amounts of blood to the tissues. Acute heart failure is a serious, life-threatening condition; it can be the presentation of newly diagnosed illness or an exacerbation of a preexisting disease. Shortness of breath is the most common symptom of acute heart failure. It results from fluid accumulation in the lungs. Other manifestations of heart failure include cough, swelling of the legs, fatigue, tiredness, and poor appetite. Some patients experience nighttime episodes of breathlessness and find it difficult to sleep flat in bed. Patients with preexisting chronic heart failure often experience slow and progressive shortness of breath on exertion, leg swelling, and weight gain, all symptoms of fluid accumulation in the body before they present to the hospital with breathlessness at rest. Acute heart failure is not synonymous to “heart attack,” but it can sometimes be precipitated by heart attack. In that case, it is common for patients to have chest pain, chest discomfort, or pressure-like sensation in the chest. The severe form of acute heart failure is called “pulmonary edema”; it causes significant distress and breathing difficulty due to rapid build-up of the fluid in the lungs. Another extreme form of heart failure is called “cardiogenic shock”; it causes poor perfusion of the tissues due to significant impairment of heart function. The patients appear cold and clammy, their blood pressure is low, and

their thinking can be impaired. Those patients are at a high risk of dying and often need drastic measures to correct the underlying problem and support the circulation.

Heart failure is not a single disease; it is a manifestation of a big variety of structural heart disorders. The most common disorder that results in heart failure is coronary artery disease. Blockage of the blood vessels that supply the heart muscle can result in a significant heart muscle damage, causing the heart to fail. High blood pressure, if unrecognized or untreated, causes pathologic changes in the heart muscle over months to years and can eventually result in heart failure. The heart valve narrowing or leakage is a relatively common cause of heart failure. Diseases of the heart muscle, itself termed “cardiomyopathy,” manifest as heart failure. Some causes of cardiomyopathy are known (such as infection, alcohol, and illegal drugs) and some are genetically inherited. A well-described form of cardiomyopathy is associated with pregnancy. Sometimes, there is no obvious cause for the heart muscle weakness, and in medical literature, it is referred to as “idiopathic.” Besides the structural heart disease that results in heart failure, it is important to realize that a variety of conditions can provoke an acute exacerbation of heart failure. Those conditions are called “precipitating factors.” Precipitating factors superimposed on the underlying structural heart disease are responsible for acute onset of symptoms in otherwise stable patient. A “heart attack” or inadequate blood supply to the heart muscle called “ischemia” is a common precipitating factor. Poorly controlled blood pressure puts excessive strain on the heart and precipitates heart failure. Noncompliance with the diet and medications is among the most common precipitating factors for acute heart failure. Other conditions that can precipitate or worsen heart failure include infection, certain medications (including painkillers), low blood count, heart rhythm disturbances (called “arrhythmias”), kidney disease, etc.

DIAGNOSIS AND TREATMENT

The physician establishes the diagnosis of acute heart failure by taking history (asking questions about the patient’s symptoms), performing physical examination, and ordering appropriate tests. Besides confirming the diagnosis, the physician needs to determine what the underlying structural heart disease is that causes heart failure and what the precipitating factor for the current acute exacerbation is. Blood tests are commonly sent, and ECG and chest X-ray are

also typically performed. Ultrasound examination of the heart (also known as echocardiogram) helps to visualize cardiac chambers, and it is the most commonly used tool to evaluate the structure and function of the heart. Other tests are performed as deemed necessary by the physician. Cardiac catheterization is an invasive test that includes placing catheters into the heart chambers and major vessels to diagnose vessel blockage or get important pressure readings from various heart chambers. It is also used for interventions if vessel blockage seems to be causing patient's symptoms.

Treatment of heart failure has several important components. Patients are given oxygen by nasal prongs or a mask to ensure adequate oxygen delivery to the tissues. In patients with significant breathing difficulty, assisted ventilation via special mask is employed (commonly called "continuous positive airway pressure"). Occasionally, a breathing tube is placed in the airway and mechanical ventilation is initiated. In patients with low blood pressure and poor perfusion, medications are used to maintain blood pressure. In severe cases, medications that enhance heart muscle contractility are used; unfortunately, those medications are associated with significant adverse effects and therefore their use is limited to refractory cases. As explained above, fluid overload underlies many symptoms of heart failure; therefore, diuretic medications are commonly administered to increase water and sodium excretion from the body. Other medications that help to relieve the symptoms include vasodilators; these medications dilate the blood vessels in the body decreasing the workload on the heart. These are commonly administered as intravenous drips. Precipitating factors are also addressed. These could include controlling abnormal heart rhythm, lowering blood pressure, treating infection, etc.

FOLLOW-UP AND PREVENTION

Once the acute phase is over, the long-term management plan should be discussed in detail. Medications used to treat chronic heart failure are often different from those used to treat acute exacerbation. β-Blockers (such as metoprolol or carvedilol), ACE inhibitors (such as lisinopril and enalapril), sacubitril-valsartan, and spironolactone are commonly used in the treatment of chronic heart failure. They help to maintain heart function and prevent acute exacerbation. They have also been shown to decrease the risk of death in certain patients with heart failure. Proper education of the patient includes teaching

them about the appropriate medication regimen, necessity of taking the medications daily, and compliance with low-salt diet. Sodium contained in salt retains fluid in the body and causes heart failure exacerbations. Besides, it commonly elevates blood pressure, putting excessive stain on the heart. Patients should not only follow appropriate diet but also be able to recognize early signs and symptoms of heart failure such as exertional shortness of breath, fatigue, inability to lay flat in bed, awakening from sleep short of breath, using several pillows to elevate the head and thereby making breathing at night easier, gradual weight gain, and ankle swelling. Weight gain is commonly the first manifestation of fluid build-up in the body; therefore, the patients should know their “dry weight” and try to follow their weight regularly. Proper follow-up after discharge is necessary to ensure stability of clinical symptoms and proper adjustment of medication doses. Some of the medications (such as β-blockers) need to be titrated up slowly during follow-up visits to avoid adverse effects. In case of coronary artery disease and valvular heart disease, certain interventions or surgery can fix the problem. Implantations of certain devices such as a pacemaker or defibrillator might be beneficial in certain groups of patients.

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Yaron Hellman

Heart Failure with Reduced Ejection Fraction

INTRODUCTION

This chapter provides the basic definitions, pathophysiology, clinical presentation, and the basis of treatment in patients with heart failure (HF) with reduced ejection fraction (EF). From an epidemiologic standpoint, HF is a growing problem with a substantial impact affecting millions of patients worldwide. About 5.7 million adults in the United States have HF, and half of those affected will die within 5 years of diagnosis.[1] In fact, HF is the leading cause of hospitalization among patients over the age of 65 in the United States.[2] The economic burden of HF is reflected in costs estimated to be as much as $30.7 billion/year in the United States alone.[3] This total includes the cost of health care services, medications to treat HF, and missed days of work.

DEFINITION

HF has a broad definition with no single diagnostic test as a gold standard. Impaired contractility and reduced EF are not an adequate definition—at least half of the patients with HF have a preserved EF (impaired relaxation or

"diastolic" HF). According to current clinical guidelines, the broadest definition of HF is "a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood."[4]

Older definitions include the "classic" definition by Braunwald—"A pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues."[5] Another classic definition emphasizing HF pathophysiology proposed by Poole-Wilson is "a clinical syndrome caused by an abnormality of the heart and recognized by a characteristic pattern of hemodynamic, renal, neural and hormonal responses."[6]

Currently, "heart failure" replaced the older term "congestive heart failure" because many patients present with symptoms of dyspnea and exercise intolerance rather than overt volume overload.[4]

SUBGROUPS

HF can be divided into several well-known subgroups. Left-sided HF refers to pulmonary congestion as opposed to right-sided HF representing peripheral edema, pleural effusion, and ascites. Forward failure is used to describe low cardiac output and poor peripheral perfusion. In contrast, backward failure consists of peripheral edema, pulmonary edema, and splanchnic congestion (ascites, hepatomegaly, abdominal fullness).

CLASSIFICATION ACCORDING TO LEFT VENTRICULAR EJECTION FRACTION

EF is the percentage expressed by (left ventricular end-diastolic volume—end-systolic volume)/left ventricular end-diastolic volume. EF is considered as a load-independent factor that can identify patients with a primary defect in cardiac contractility—systolic function. Many HF trials selected patients according to reduced EF because it can be measured objectively by echocardiography, magnetic resonance imaging (MRI), or radionuclide imaging. However, as mentioned earlier, approximately half of the patients with HF have preserved EF—diastolic dysfunction. The etiology, comorbidities, demographics, and response to therapy differ between patients with reduced

ejection fraction (HFrEF) and preserved EF (HFpEF). Therefore, patients with HF are generally divided into these two categories.[7] It is important to understand that diastolic dysfunction (impairment of myocardial relaxation) may coexist in the setting of systolic dysfunction. Conversely, patients with diastolic dysfunction may have impaired systolic function not identified by the EF. That is why the terms HFrEF and HFpEF are more accurate rather than systolic and diastolic HF. In addition, an intermediate group with a left ventricular ejection fraction (LVEF) of 40% to 50% has been added recently to reflect this mixture of systolic and diastolic dysfunction.[4, 7]

ETIOLOGY

HF has a wide range of causes varying from common causes (coronary artery disease, hypertension) to rare infiltrative diseases (amyloidosis, Fabry disease). These etiologies are categorized phenotypically in **Figure 11.1**. The initial classification includes non-myocardial diseases—valvular disease, pericardial disease, and congenital heart disease. Pericardial disease mainly refers to constrictive pericarditis, which typically presents with right-sided HF, although many patients have dyspnea as well. Valvular heart disease often results in myocardial disease over time because of compensatory mechanisms such as hypertrophy (eg, aortic stenosis and left ventricular hypertrophy [LVH]) and dilation (aortic regurgitation and dilated left ventricle [LV]). Congenital heart disease represents a diverse category, often with myocardial changes, even after palliative or correctional surgery.

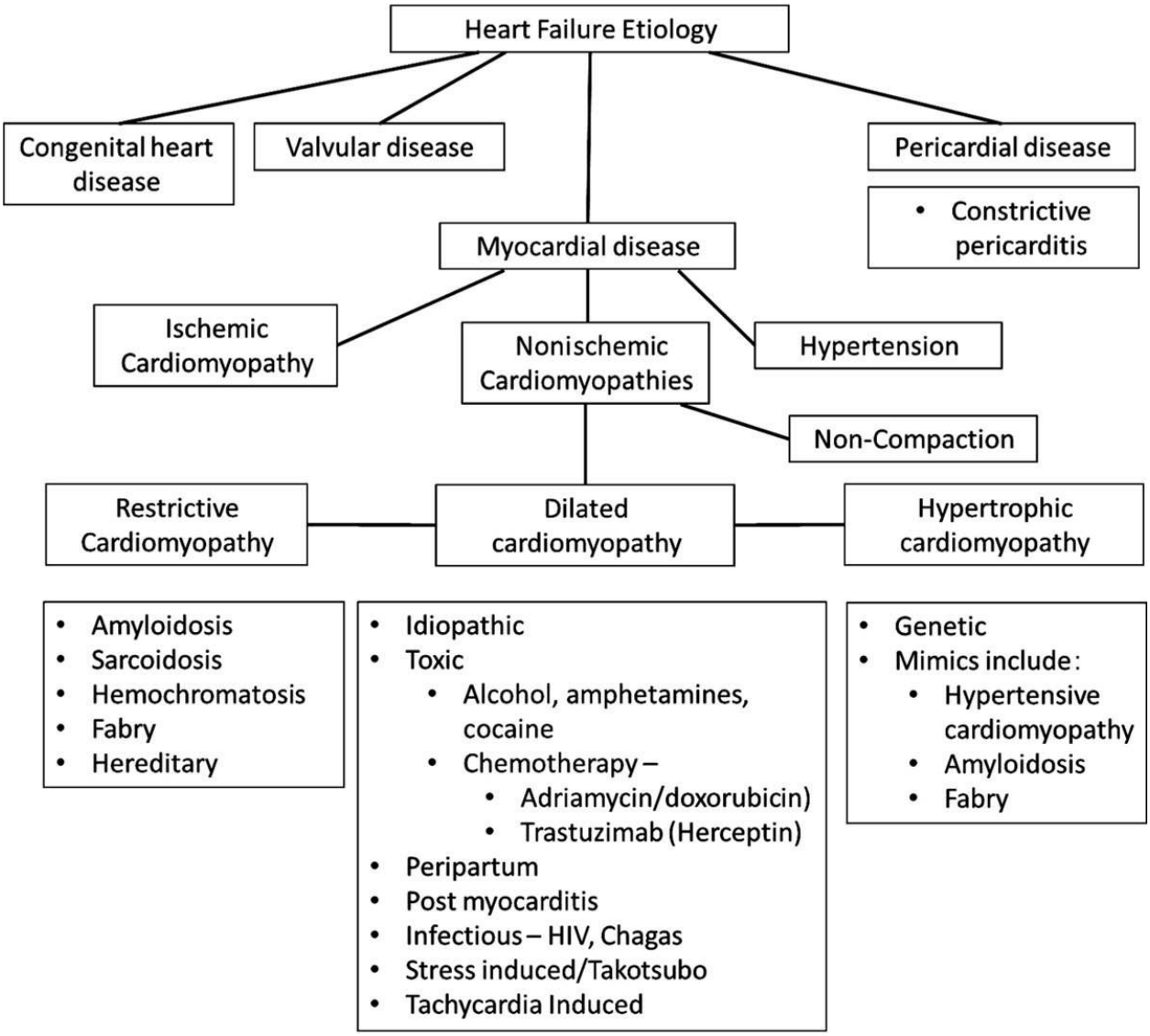

FIGURE 11.1 Heart failure etiologies.

Primary myocardial disease can be roughly divided to ischemic cardiomyopathy and nonischemic cardiomyopathies. Although hypertension is not a primary myocardial disease, it causes LVH over time (depending on treatment) and results in diastolic dysfunction. When blood pressure elevation is at extreme levels, systolic dysfunction may also occur (“afterload mismatch”)—reduced LVEF.

Coronary artery disease and myocardial infarction remain a leading cause of HFrEF even in the current era of timely reperfusion for ST-elevation myocardial infarction. Eventually, many patients post myocardial infarction will develop a global dilated cardiomyopathy after the initial insult (remodeling) or repeated

insults—ischemic cardiomyopathy. Some of these patients may present with HF without preceding angina (usually diabetics with "silent" ischemia). Nonischemic cardiomyopathies include a variety of myocardial diseases. These can be divided into dilated, restrictive, hypertrophic, and non compaction cardiomyopathies.

Dilated cardiomyopathy can be subdivided into several groups—genetic/idiopathic, post myocarditis, toxic, and peripartum cardiomyopathy. Alcohol is a common cause of toxic cardiomyopathy, often partially reversible after cessation of alcohol intake. Chemotherapy-induced cardiomyopathy is increasing in prevalence, especially due to the relatively high success rate in the treatment of leukemia/lymphoma, and the use of doxorubicin and Herceptin in breast cancer. This set the ground for a new subspecialty in itself—cardio-oncology.

PATHOPHYSIOLOGY

Several key pathophysiologic concepts are important to understand when dealing with HF.[8] Cardiac output is determined by heart rate (HR) × stroke volume (SV). One important consequence of this equation is that tachycardia is a proper response to increase cardiac output. Therefore, beta-blockers and HR–lowering therapy in patients with a fixed SV may be detrimental (eg, acute systolic HF, amyloidosis, aortic stenosis). The hazardous effects of tachycardia in the long term are discussed later.

SV is determined by three factors: preload, cardiac contractility (inotropic state), and afterload.

Preload is defined as the ventricular end-diastolic volume. The left ventricular preload is determined by venous return, atrial contraction (20%), and right ventricular function. An important relationship is the force–volume curve, more commonly known as the Frank-Starling curve. A useful analogy is visualizing the basic myocardial unit, the actin–myosin complex, as a spring **(Figure 11.2)**. If the spring is stretched (ie, filling the LV with volume—preload), it will contract with increased force. When the preload is excessive, the spring will reach a certain limit and may even generate a reduced force of contraction. The final end of the Frank–Starling curve is also explained by the right ventricle–left ventricle (RV–LV) interaction and septal displacement.

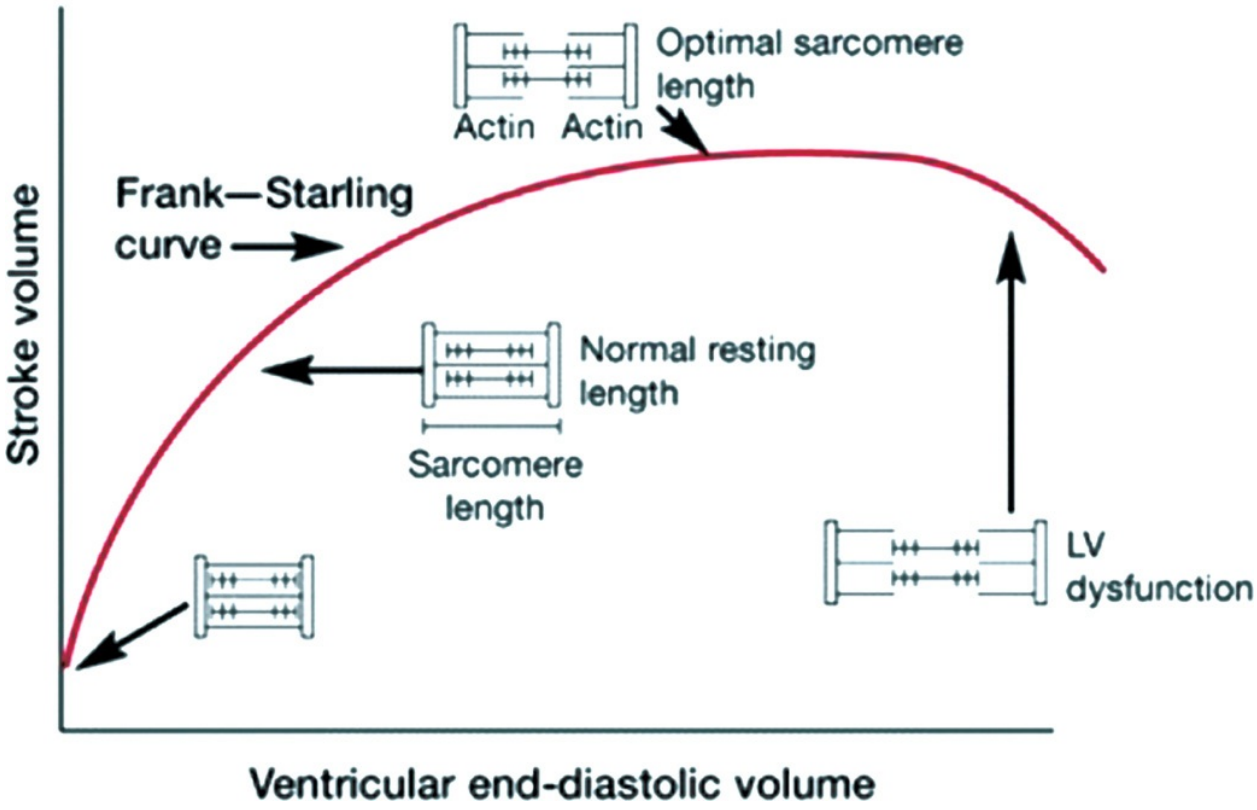

FIGURE 11.2 Relation between stroke volume and ventricular end-diastolic volume. LV, left ventricle.

Cardiac contractility is also known as the inotropic state. This is determined by the intrinsic ability of the myocardium to contract. Factors affecting the inotropic state are intracellular calcium, catecholamines, and pharmacologic agents at different levels (beta-adrenergic receptor, phosphodiesterase 3, NA/K exchanger, etc).

Afterload represents the resistance against which the heart ejects blood. This tension faced by the myocardium is determined by Laplace's law—$T = P*R/2D$, where P is the pressure faced by the LV, R is the radius of the ventricular chamber, and D is the wall thickness. Common situations of increased afterload are vasoconstriction, systemic hypertension, and aortic stenosis. Increased afterload results in reduced systolic function even in hearts with preserved cardiac contractility. This inverse relationship is markedly pronounced in patients with HFrEF **(Figure 11.3)**—patients with HFrEF are "afterload sensitive." This is why afterload reduction is such a crucial and important part of HF therapy.

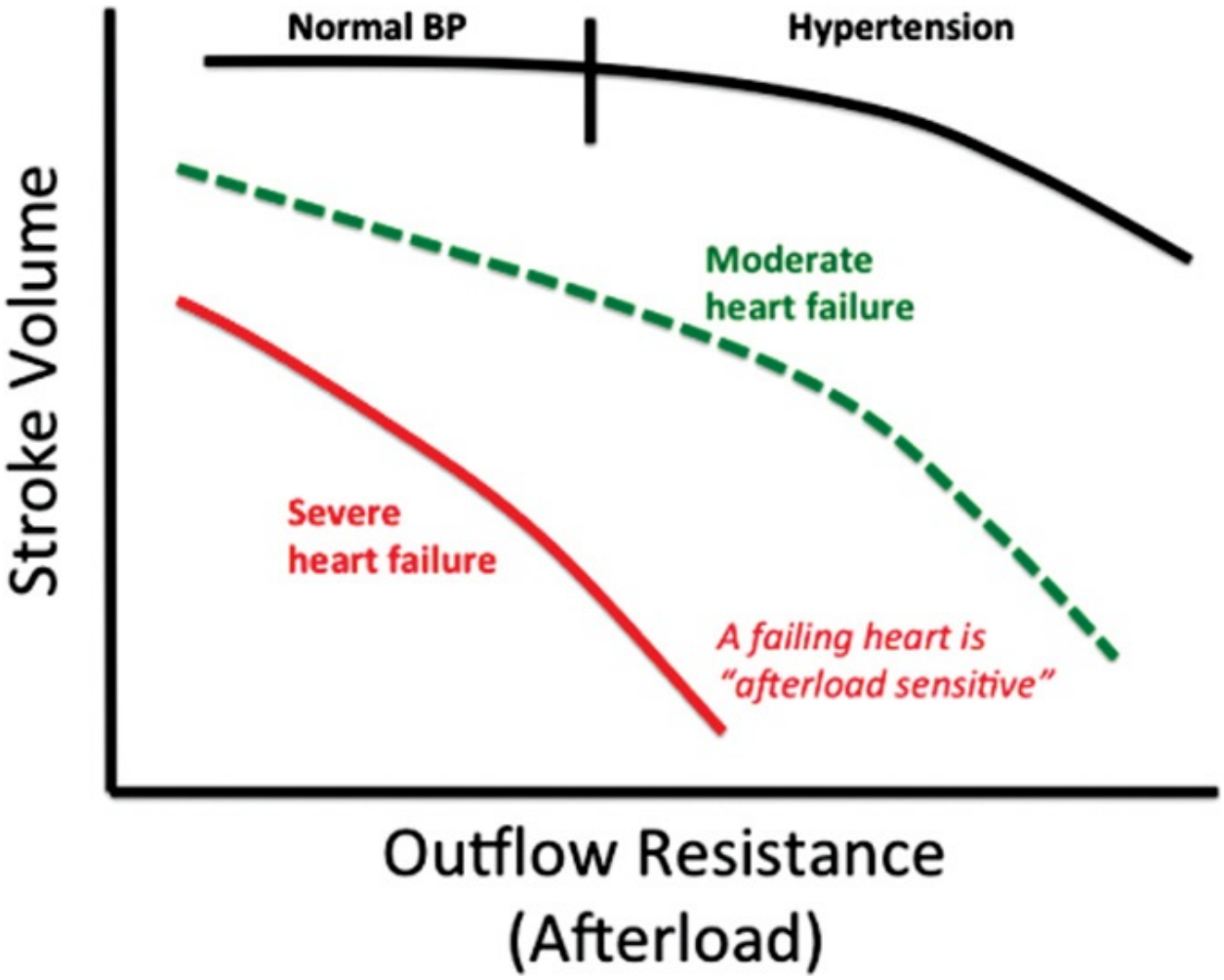

FIGURE 11.3 Relation between stroke volume and outflow resistance (afterload). BP, blood pressure.

REMODELING

Remodeling is a pathophysiologic concept describing the process in which an initial insult (eg, myocardial infarction, myocarditis) results in eccentric hypertrophy and LV enlargement. At first, LV enlargement increases SV and cardiac output allowing for initial compensation. However, the progressive ventricular enlargement (beyond the extent of the initial insult) results in thinning of the heart muscle and globally reduced contraction. This is analogous to a "bad remodeling" job done in the house. The official definition of remodeling is a "group of molecular, cellular and interstitial changes that clinically manifest as changes in size, shape and function of the heart resulting from cardiac injury," as published in an international consensus document.[9]

NEUROHORMONAL ACTIVATION AFTER MYOCARDIAL INSULT

The reduced SV in HFrEF along with elevated pressures lead to the activation of several neurohormonal pathways.

Activation of the sympathetic nervous system is an immediate consequence of any cardiac insult. Reduced cardiac output is sensed by baroreceptors, which in turn increase central nervous system sympathetic discharge and catecholamine production by the adrenal glands. Catecholamines act upon beta-receptors in the heart and alpha-receptors in the peripheral vasculature; resulting in tachycardia, increased venous return (preload), increased cardiac contractility (inotropic state), and peripheral vasoconstriction (which increases blood pressure and afterload). The sympathetic activation therefore increases cardiac output in the short term, allowing for compensation and meeting the body's metabolic demands. However, in the long term, catecholamines are detrimental with direct apoptotic effects on myocardial cells, pro-arrhythmia, and increase in afterload and cardiac work.

Another hormonal cascade activated post myocardial injury is the renin–angiotensin–aldosterone axis. Decreased cardiac output causes an increase in renin production, which in turn increases angiotensin production and vasoconstriction. In addition to vasoconstriction, angiotensin stimulates production of aldosterone. Aldosterone exerts its effect on the renal collecting ducts, promoting sodium reabsorption along with K and H secretion. Aldosterone also has a direct effect on myocardial cells, promoting apoptosis and fibrosis.

An inflammatory reaction occurs as well during HF, resulting in increased levels of cytokines such as tumor necrosis factor. In the long term, this is one of the causes of cardiac cachexia, similar to that in cancer patients.

In contrast to the deleterious "bad" neurohormones that cause salt and water retention and long-term damage to myocardial cells, there is a "positive" pathway providing natriuresis and vasodilation—the natriuretic peptides. These natriuretic peptides are secreted by the heart chambers and blood vessels. There are several natriuretic peptides; the most well known is the B-type natriuretic peptide (BNP) secreted mainly by the ventricles. Since natriuretic peptides are measurable, elevated BNP and N-terminal (NT)-pro-BNP levels provide a diagnosis of HF as well as an estimation of prognosis (extent of HF).

Myocardial energy metabolism is also modulated in HF—an "energy crisis."[10] Since free fatty acids require more O_2 and energy to derive adenosine triphosphate, glucose is a more efficient fuel for the failing heart. The implications of these energetic derangements are providing good nutritional support, in general, and appropriate glucose and insulin management during acute HF.

SYMPTOMS AND SIGNS OF HFrEF

Dyspnea is a cardinal manifestation of HF and may manifest in several forms. The basic underlying mechanism of dyspnea is increased hydrostatic pressure in the alveolar capillaries and transudation of fluids into the alveoli. Exertional dyspnea occurs because of the increased preload and cardiac demand. Dyspnea may also occur during the night, due to the supine position and increased preload. This is the mechanism of paroxysmal nocturnal dyspnea (PND) and orthopnea. PND is often described by patients as nightly rales or wheezing. Orthopnea is not as common as exertional dyspnea; but when it is described ("sleeping upright in a chair"), it is quite specific for HF rather than for other causes of dyspnea. A recently recognized symptom is bendopnea—dyspnea while bending over.[11] Bendopnea is quite common in HFrEF (especially in the patients with advanced HF), also due to increased preload. Many patients will complain of the inability to tie their shoe laces. Because the underlying cause of dyspnea in HF is increased hydrostatic pressure, it is not specific for HFrEF and is a common symptom of HFpEF as well. In addition, younger patients with a more compliant LV and atrium ("less stiff" compared to the aging fibrotic heart) may not necessarily complain of dyspnea. Dyspnea may also present as "cardiac asthma"—the alveolar fluid may cause bronchoconstriction and wheezing. This may sound exactly like asthma on clinical examination!

Patients with HFrEF may also manifest right-sided symptoms such as peripheral edema, abdominal fullness, or ascites. Often the liver/splanchnic congestion may cause right upper quadrant and epigastric pain, sometimes masquerading as cholecystitis (especially when the patient already has gallstones). Cachexia and unintended weight loss are late and ominous symptoms of advanced HF, usually marking the "point of no return" even with advanced therapies.

Important physical signs in patients with HFrEF include measurement of vital

signs (HR, blood pressure), estimation of jugular venous pressure (JVP), lung auscultation (crackles and wheezing), heart auscultation (S3), and lower extremity edema. JVP is an essential component, with a particular emphasis on the abdominojugular test (abdominal compression resulting in jugular venous distension), which correlates well with wedge pressure (not only occult right atrial pressures as previously thought).[12] Weight is another physical sign that reflects changes in body volume/fluids in the short term. In the long term, weight loss and cachexia are signs of advanced HF. In fact, obesity seems to have a "protective" effect in HF—hence the term "obesity paradox."

DIAGNOSTIC TESTS

The single most important test in HF is the echocardiogram. First, the echocardiogram provides us with the major distinction between HFrEF and HFpEF. Second, the echocardiogram allows for evaluation beyond LV function —including valvular disease (eg, mitral regurgitation, aortic stenosis), hemodynamics (estimation of pulmonary artery pressure, cardiac output), presence of thrombus, and RV function.

Natriuretic peptide measurement in HF is the equivalent of the troponin measurement in myocardial infarction. As mentioned earlier, the natriuretic peptide system is activated as part of the neurohormonal response in HF. BNP is released from the ventricles in response to increased wall stress, and reflects the degree of HF. During the late 1990s and early 2000s, the natriuretic peptides transformed from a basic science neurohormonal marker to a clinically relevant biomarker allowing for rapid diagnosis of dyspnea in the emergency room.[13] BNP is measured directly or as NT-pro-BNP, depending on the commercial kit used by the hospital biochemistry laboratory. In addition to ruling in or ruling out HF in patients with dyspnea, natriuretic peptides are also a useful marker of prognosis. Lastly, BNP may be used to guide therapy, suggesting that several measurements of BNP during the HF hospitalization are warranted.

The electrocardiogram (ECG) is a basic cardiac test and contributes in the diagnosis and management of HF. Although most patients with HF will have a pathologic ECG, it does not always provide specific information. However, the ECG can help support possible etiologies—such as low voltage in amyloidosis, Q waves with or without ST elevation in myocardial infarction, and LVH in patients with hypertension, hypertrophic cardiomyopathy or aortic stenosis. Left

bundle branch block (LBBB) is also important, because this is the main indication of biventricular pacing (cardiac resynchronization therapy). In addition, ECG findings are helpful in the diagnosis of hyperkalemia/hypokalemia, digoxin toxicity, and in the assessment of pacemaker function. Lastly, the ECG may demonstrate arrhythmias with important clinical implications. A common situation is the HF patient with atrial fibrillation, requiring the consideration of anticoagulation for the prevention of stroke and systemic thromboembolism.

The chest X-ray may demonstrate pulmonary congestion and an enlarged cardiac silhouette in patients with HF. In addition, the chest X-ray allows for further evaluation of other causes of dyspnea, such as lung disease, diaphragmatic paralysis, and pulmonary effusion.

MRI is a complex imaging modality that is currently used mainly for the diagnosis and risk stratification of infiltrative disorders (amyloidosis, hemochromatosis, and sarcoidosis), hypertrophic cardiomyopathy, myocarditis, and congenital heart disease. The MRI is useful in quantifying RV function (which is not always fully captured in the two-dimensional echo), presence of scar (late gadolinium enhancement), and LV chamber evaluation (non compaction, LVEF)

Cardiac catheterization is an essential part of evaluating HFrEF. Coronary artery disease is a common etiology of reduced LV systolic function. More importantly, revascularization (coronary artery bypass grafting, percutaneous coronary intervention) may significantly improve LV function and outcomes.[14] Therefore, coronary evaluation is mandated in most patients. In younger patients without significant coronary calcification, computed tomography (CT) angiography is a noninvasive alternative. Hemodynamic assessment via right heart catheterization is necessary in patients with borderline hemodynamics (precardiogenic shock, cardiogenic shock) and in candidates for ventricular assist device (VAD) or heart transplantation.

Cardiopulmonary exercise testing (CPET) offers a means of improved diagnosis (cardiogenic vs pulmonary vs other causes of dyspnea), as well as estimating prognosis. This test does not require the patient to reach a maximal HR because the anaerobic threshold is determined during the test itself. An important value to keep in mind is the VO_{2max} (peak oxygen consumption)—a value less than 14 mL/kg/min indicates a poor prognosis and a clear benefit from heart transplantation or left ventricular assist device (LVAD) rather than medical management.[15]

The 6-minute walk test is simpler and more readily available than the CPET. It provides useful prognostic information, although with limited accuracy and without the ability to differentiate between cardiac and noncardiac causes of exertional dyspnea and limitation.[16]

CLASSIFICATION OF HEART FAILURE

Patients with HF are typically categorized into two classification systems, in addition to the subgroups presented earlier.[4] The New York Heart Association (NYHA) functional classification allows semi-quantification of symptom severity. Class I patients have no symptoms, class II patients have symptoms during moderate to severe exertion, class III patients are symptomatic during mild to moderate exertion, and class IV patients are symptomatic at rest or with minimal exertion, including basic daily activities. The NYHA class serves as an important marker of prognosis and guides therapy accordingly.

A relatively recent classification scheme was introduced by the American College of Cardiology/American Heart Association (ACC/AHA), similar to the staging performed in oncology. Patients with stage A HF are only at risk for HF. These patients are asymptomatic; but if untreated, they might develop HF with time. Risk factors include hypertension, diabetes, and chemotherapy. Patients with stage B HF have already sustained a myocardial insult; however, they are still asymptomatic. Examples are patients post myocardial infarction, chemotherapy-induced cardiotoxicity with reduced LVEF. Stage C HF patients are the “typical” patients seen in clinical practice—symptomatic, requiring diuretics, angiotensin-converting enzyme inhibitors (ACEI), and beta-blockers. Stage D is an important distinction defining a subset of moribund patients who are repeatedly hospitalized and frequently inotrope dependent. These patients have a very limited prognosis, if not eligible for advanced HF therapy (LVAD, transplant). This recognition is also important to initiate proper palliative care.

HEART FAILURE TREATMENT

HF treatment requires several general measures, in addition to medical and device therapy. Sodium intake should be limited, because this is one of the major factors determining total body volume. However, recently the use of severe

sodium restriction has been criticized and even linked to excess mortality. Practically, patients should be informed of the following—do not add salt, do not add salt substitutes (which contain potassium and pose a risk of hyperkalemia when treated with ACEI and aldosterone antagonists), beware of sodium-rich foods (anything preserved in a can or box, pickles, deli, soy sauce, etc). Water restriction was also a common practice; however, the ability to excrete water is relatively independent from the sodium balance and total body volume. Therefore, this is mainly relevant in patients with problems of water balance—hyponatremia. In a recent study of patients hospitalized with acute decompensated HF, the use of an aggressive sodium and water restriction approach had no effect on outcome, except for increased perceived thirst in the water-restricted group.[17]

Alcohol and smoking should be avoided. Alcohol is directly toxic to the myocardium, especially when myocardial injury is already established. In addition to vasodilation, which lowers blood pressure along with the patient's vasodilating medications, alcohol may contribute to the occurrence of both atrial and ventricular arrhythmia. Obviously, alcohol cessation is especially important in alcoholic cardiomyopathy.

Smoking should also be discouraged for several reasons. First, this may improve the patient's lung function and dyspnea. Second, smoking is a major risk factor for coronary artery disease and may provoke subsequent myocardial infarctions. Lastly, owing to increased cancer risk and as a marker of poor compliance with medical advice, smoking is considered in most transplant centers a contraindication for heart transplantation.

Dietary modifications are required when the patient is obese, although the obesity paradox should be kept in mind. Excessive weight loss also might be harmful.

Physical activity should be encouraged, within the limitations of the patient's ability to perform exercise. This is where the role of a formal cardiac rehabilitation program is extremely important.

The patients should also be informed of hazardous medications—nonsteroidal anti-inflammatory drugs (NSAIDs). These are one of the most common causes for HF decompensation. NSAIDs disrupt renal function and interfere with the whole renin–angiotensin–aldosterone axis.

Medical therapy and device therapy are discussed in the following chapters.

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Patient and Family Information for: HEART FAILURE WITH REDUCED EJECTION FRACTION

WHAT IS HEART FAILURE?

The heart is the organ responsible for pumping blood throughout the body, delivering oxygen and essential nutrients. This muscular pump is divided into the right and left sides. The right side of the heart receives blood without oxygen from the rest of the body and delivers the blood to the lungs. After the blood flows through the lungs and receives oxygen, it arrives at the left side of the heart. The left side of the heart is much more muscular, because it has to eject the blood (which now has oxygen) to the rest of the body—from head to toe, except for the lungs. The force of flow is powerful enough to generate a blood pressure, which is routinely measured.

HF is defined as a problem with the heart's ability to eject blood and/or fill with blood. Various diseases cause the heart to weaken as a muscular pump, thereby resulting in HF. The ability of the heart to contract and eject blood is measured by the term EF.

WHAT IS EJECTION FRACTION?

EF represents the percentage of blood flowing out of the heart during each contraction. The EF is never 100%, because the heart cannot contract, totally empty out all of its contents, and then refill. Actually, the heart is usually half filled even at the end of its contraction. Therefore, the normal EF is 55% to 60%. An EF below 50% is considered abnormal. When the EF is reduced below 30%

to 35%, the heart's pumping action is considered severely reduced. HF can also occur with a "normal" EF—the heart can eject blood properly, but has trouble filling. A common cause of this situation is hypertension. After years of the heart trying to pump out blood against a high blood pressure, the heart muscle thickens (similar to the enlargement of muscles after lifting weights). The thickened heart muscle requires a much higher pressure to fill (think of trying to fill a balloon vs filling a tire). These high pressures cause the blood to go back to the lungs and fill with fluid, ending up with shortness of breath. The causes and treatment of HF differ according to EF—HFrEF and HFpEF. However, many of the symptoms and signs of HF are the same.

CAUSES OF HEART FAILURE

HF is the result of several diseases affecting the heart as a pump. Usually problems with the heart muscle cause HF. However, the heart as a pump also has valves and an encasement (pericardium). Therefore, diseases of the heart valves (aortic stenosis, aortic regurgitation, mitral stenosis, and mitral regurgitation) and pericardium (constrictive pericarditis) also result in HF.

Common diseases affecting the heart muscle include the following:

Coronary artery disease—Blockages in the heart's blood supply, previous "heart attacks."

Hypertension or high blood pressure—The EF is usually preserved in this situation.

Alcohol—The heart muscle can recover once alcohol intake is stopped.

Drugs—Cocaine, amphetamines; may result in irreversible damage.

Chemotherapy—There are several chemotherapies that are toxic to the heart muscle. Common examples include doxorubicin (Adriamycin) given for lymphoma and, sometimes, for breast cancer, and trastuzumab (Herceptin) given for breast cancer.

Familial/genetic heart disease—This may be a disease limited to the heart muscle, causing weakness and impaired contraction—dilated cardiomyopathy. Sometimes this is part of a general muscular disease (as in Duchenne muscular dystrophy).

Infection—Viruses can cause myocarditis, resulting in heart damage.

Congenital heart disease—These are complex diseases. HF is a problem even

after palliative or corrective surgery.

Peripartum—This rare form of HF can present following pregnancy.

SYMPTOMS AND SIGNS OF HFrEF

Shortness of breath—dyspnea—is a common symptom of HF and may appear in several forms. Shortness of breath occurs because of the increased pressure in the heart muscle, causing a backward flow of blood toward the lungs. The lungs then fill with fluid, resulting in breathing difficulty. Shortness of breath is worsened during exercise—the heart cannot keep up with the increased need for blood flow, and more blood remains in the lungs.

Dyspnea may also occur when lying down—during the day, gravity helps pull blood away from the heart (standing and walking). When lying down, this effect is neutralized. This is known as orthopnea. Patients with severe HF will complain of sleeping upright in a chair during the night.

Bendopnea is a similar symptom—shortness of breath while bending over. Many patients with advanced HF will have trouble tying their shoe laces or picking up objects. This is also due to the blood flow to the heart being affected by gravity.

Shortness of breath during the night—PND. In this situation, the patient awakens at night with shortness of breath, sometimes even wheezing.

"Cardiac asthma"—sometimes the fluid in the lungs can cause wheezing, mimicking the sounds heard during an asthma attack. Many times, HF episodes (especially before diagnosis) can be mistaken for bronchitis, chronic obstructive pulmonary disease exacerbation, or an asthma attack.

Peripheral edema/swelling—fluid can accumulate in the rest of the body, not only in the lungs. This commonly occurs in the legs, due to gravity.

Abdominal pain—accumulation of fluid in the liver and gut area causes abdominal pain, abdominal swelling, and loss of appetite.

Weight gain—this can be due to fluid accumulation.

Weight loss can occur in patients with very advanced HF—because of increased energy requirements by the failing heart and changes in body metabolism.

DIAGNOSTIC TESTS

There is no single test for the diagnosis of HF. Several tests are required:

Echocardiogram—ultrasound of the heart. The single most important test in HF is the echocardiogram. First, the echocardiogram provides us with the EF—the major distinction between HFrEF and HFpEF. Again, this is important because the medical treatment for HFrEF is different from the treatment for HFpEF. Second, the echocardiogram allows for evaluation beyond the percentage of heart muscle contraction—including valves, the heart's encasement (pericardium), and other important measures of heart function (right-sided function, flow in the right and left sides, estimation of filling pressures, and muscle thickness).

BNP—This is a blood test. In response to increased pressures inside the heart, the heart secretes a hormone named BNP. This hormone is measurable and can help diagnose HF. In addition to diagnosis, BNP can also provide a rough measure of the extent of HF—in patients with congestion and fluid retention, the BNP levels are high. Once the HF is treated and congestion is relieved (compensated HF), BNP levels can return to lower values. Therefore, in addition to HF diagnosis and assessment of severity, BNP may help guide therapy.

The ECG is a basic cardiac test demonstrating the electrical activation of the heart. The ECG is helpful in HF, because it can hint at possible causes and also direct medical decisions. For example, the ECG can demonstrate previous heart attacks. The ECG may also demonstrate a conduction problem known as LBBB. When this occurs in the setting of HFrEF, a biventricular pacemaker, which can synchronize the heart's contraction between the right and left sides, should be considered. In patients who already have a pacemaker, the ECG can help determine pacemaker function. Lastly, the ECG may demonstrate heart rhythm disturbances, which are not always felt by the patient.

The chest X-ray is also a basic test—in HF it can demonstrate fluid in the lungs and an enlarged heart. More importantly, it can help the physician look for other causes of shortness of breath, such as pneumonia or lung disease.

MRI—In this test, use of a powerful magnet and the detection of energy waves released by provoked hydrogen atoms generate a high-resolution picture of the heart tissue. Advances in computer technology and quick processing of images allow evaluation of serial images and heart function. The advantage over echo/ultrasound technology is that MRI is not angle dependent. MRI can also characterize tissues and detect abnormalities not "seen" by echo. However, MRI is expensive, not always widely available, and requires time. In addition, the examination takes place within a tube, which might pose a problem in patients

with claustrophobia. Lastly, metal objects are problematic because of the strong magnetic field. Therefore, only patients with MRI-safe pacemakers and without metal implants (orthopedic) are candidates for MRI.

Cardiac catheterization—this is usually an essential part of evaluating HFrEF. Coronary artery disease and heart attacks are a common cause of reduced heart function. More importantly, revascularization and opening of the blockages may improve heart function and outcomes. Therefore, coronary catheterization is mandated in most patients with reduced heart function. In younger patients, CT angiography is a noninvasive alternative. Direct measurement of pressures using a catheter inserted into the neck or groin veins is necessary in patients with advanced HF to determine medical therapy and plan for VAD or heart transplantation.

CPET is a test where the patient performs exercise (either on a bike or a treadmill) with a specialized mask measuring oxygen and carbon dioxide coming in and out of the lungs. This test does not require the patient to reach a maximal HR. The CPET offers a means of improved diagnosis whether the shortness of breath originates from HF, lung disease, muscle weakness, or a combination of problems. It is an objective test. One of the measurements is the peak oxygen consumption—a value less than 14 mL/kg/min indicates a clear benefit from heart transplantation or LVAD rather than medical management.

The 6-minute walk test is simpler and more readily available then the CPET. The patient is asked to walk for 6 minutes and the distance is measured. This test also provides useful information concerning the timing of heart transplantation or LVAD. However, it has limited accuracy and does not have the ability to differentiate between HF and other causes of shortness of breath.

CLASSIFICATION OF HEART FAILURE

Patients with HF are typically categorized into two classification systems.

The NYHA functional classification: NYHA class I patients have no symptoms, NYHA class II patients have symptoms during moderate to severe exercise, NYHA class III patients are symptomatic during mild to moderate activities, and class IV patients are symptomatic at rest or with minimal activities, including basic daily activities (bathing, toilet, etc).

A similar but different classification scheme was introduced by the ACC and AHA.

Patients with stage A HF are only at risk for HF. These patients are asymptomatic, but if untreated, they might develop HF with time. Risk factors include hypertension, diabetes, and chemotherapy. Patients with stage B HF have already sustained an injury to their heart muscle; however, they are still asymptomatic. Examples are patients after a heart attack, or patients after chemotherapy with a reduced EF. Stage C HF patients are the “typical” patients—symptomatic, requiring standard medical treatment with diuretics, ACE inhibitors, and beta-blockers. Stage D is an important distinction defining a subset of patients who are repeatedly hospitalized or cannot be discharged from the hospital. These patients are very sick—if they are not eligible for advanced HF therapy (LVAD, transplant), palliative care should be initiated. In addition to the importance of determining stage D, patients who feel well and are in stage A or B also deserve special attention—despite feeling well, they should receive medications to *prevent* future HF.

HEART FAILURE TREATMENT

HF treatment requires several general measures, in addition to medical and device therapy.

Salt—Sodium intake should be limited, because this is one of the major factors determining the amount of total body fluids. The basic rules: Do not add salt. Do not add salt substitutes (which contain potassium—this is usually a problem with the medications given in HF). Beware of sodium-rich foods (anything preserved in a can or box, pickles, deli, soy sauce, etc).

Water restriction was also a common practice; however, the ability to get rid of water is relatively independent from the ability to get rid of sodium. Therefore, this is mainly relevant in patients with problems in water balance—hyponatremia. In a recent study of patients hospitalized with acute HF, the use of an aggressive sodium and water restriction approach had no effect, except for increased perceived thirst in the water-restricted group.

Alcohol and smoking should be avoided. Alcohol is directly toxic to the heart, especially when injury to the heart muscle is already established. In addition, alcohol may lower blood pressure, which may be low anyway because of HF medications. Lastly, alcohol may contribute to the occurrence of electrical heart disturbances—arrhythmia. Obviously, alcohol cessation is especially important in HF resulting from alcoholism.

Smoking should also be discouraged for several reasons. First, this may improve the patient's lung function and decrease the sensation of shortness of breath. Second, smoking is a major risk factor for coronary artery disease and may provoke subsequent heart attacks. Lastly, owing to increased cancer risk and as a marker of poor compliance with medical advice, smoking is considered in most transplant centers a contraindication for heart transplantation.

Dietary modifications are required when the patient is obese. However, excessive weight loss also might be harmful.

Physical activity should be encouraged, within the limitations of the patient's ability to perform exercise. This is where the role of a formal cardiac rehabilitation program is extremely important.

Patients should also be informed of hazardous medications—NSAIDs. These medications (Advil, ibuprofen, naproxen) disrupt renal function and interfere with hormonal activation in HF. NSAIDs are a common cause of HF deterioration.

Medical therapy and device therapy are discussed elsewhere.

12

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Heart Failure with Preserved Ejection Fraction

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by the impaired ability of the heart to meet the metabolic needs of the body, resulting in breathlessness, fatigue, and/or fluid retention. HFpEF is defined by the left ventricular ejection fraction (LVEF) ≥ 50%. Patients with LVEF <40% are defined as having heart failure with reduced ejection fraction (HFrEF). The subgroup of patients in the borderline range (LVEF 40% to 49%) is termed borderline, intermediate, or as having heart failure with mid-range LVEF with characteristics and treatment patterns that need further research.[1]

Historically, diastolic heart failure has been the term used synonymously with HFpEF; but, currently, with new insights into the pathophysiology of the disease, diastolic dysfunction is thought to be one of the several factors contributing to the development of HFpEF and it is not necessarily the only component of the syndrome.

EPIDEMIOLOGY

Heart failure is a major source of morbidity and mortality in the United States with the estimated prevalence of 5.7 million cases, and nearly half of these cases are patients with HFpEF.[2] It has been projected that the prevalence of heart failure will increase by 46% by 2030.[3] The prevalence increases dramatically with age, and it is more common in women than in men at any age. The mortality rates are grossly similar in patients with HFrEF and HFpEF, with recent data showing some improvement in survival for patients with HFrEF.[4] This has been attributed to the use of guideline-directed medical therapies. However, no such evidence-based treatment strategies exist for HFpEF. Therefore, the development of medical and device therapies for HFpEF is a major unmet medical need.

PATHOPHYSIOLOGY

The pathophysiology of HFpEF is complex and is the subject of active ongoing research. It is postulated that HFpEF is a heterogeneous syndrome to which various mechanisms contribute. These mechanisms can contribute to various degrees in each individual patient and can be divided into the following categories:

1. Cardiac abnormalities
    a. Diastolic dysfunction
    b. Systolic dysfunction
    c. Atrial fibrillation and atrial dysfunction
    d. Pulmonary hypertension and right ventricular dysfunction
    e. Chronotropic incompetence
2. Vascular abnormalities and impaired ventricular–vascular coupling
3. Extra cardiac abnormalities
4. Cardiovascular aging

CARDIAC ABNORMALITIES

Diastolic Dysfunction

In a normal person, diastole is the summation of an active process of relaxation related to calcium reuptake and myofilament dissociation and passive stretching resulting from mechanical properties of the sarcomere and extracellular matrix at

the molecular level and the chamber and pericardium at the organ level. During the isovolumic relaxation phase of the cardiac cycle, the left ventricle relaxes and creates a sucking force that helps the ventricle fill up during diastole when the mitral valve opens. Many studies indicate that in HFpEF the rate of ventricular relaxation during isovolumic relaxation is decreased. Also, diastolic dysfunction is associated with reduced left ventricular compliance.[5] As a result, the left ventricle can only accommodate volumes similar to the normal heart at higher filling pressures. Also, due to impaired relaxation properties and chamber stiffening, patients with HFpEF poorly tolerate increased heart rates as seen with exercise and atrial fibrillation.

Systolic Dysfunction

The systolic function of the heart is commonly measured by LVEF, but LVEF does not reflect all aspects of the left ventricular systolic performance. The left ventricular systolic function is complex and can be fully evaluated using advanced echocardiographic techniques such as speckle tracking echocardiography. Several studies have demonstrated markedly impaired longitudinal systolic function in patients with HFpEF despite preserved LVEF. Further studies will help subdivide the HFpEF syndrome based on the different aspects of the left ventricular systolic performance beyond the LVEF assessment.

Atrial Dysfunction

The left atrium contributes to about 20% of cardiac output in a normal individual, and this number has been shown to be up to 45% in patients with diastolic dysfunction because the left ventricular filling depends on the ability of the left atrium to push blood at higher pressures.[6] Left atrial dysfunction is common in patients with HFpEF as measured by advanced echocardiographic techniques and may contribute to transition from asymptomatic diastolic dysfunction to symptomatic heart failure.

Atrial fibrillation is common in patients with HFpEF. It is poorly tolerated in these patients and can precipitate acute decompensated heart failure.

Pulmonary Hypertension and Right Ventricular Dysfunction

Pulmonary hypertension is common in patients with HFpEF and is associated with worse prognosis. Elevated left atrial pressure leads to elevated pulmonary pressures and then chronic elevation in the left atrial pressure causes pulmonary

arteriolar and venous remodeling, resulting in increased pulmonary vascular resistance. Right ventricular dysfunction can result from pulmonary hypertension and/or can be a part of the disease process independent of the elevated pulmonary pressures.

Chronotropic Incompetence

Studies have shown a blunted heart rate response to exercise and prolonged post-exercise heart rate recovery in patients with HFpEF.[7, 8] These findings may contribute to the symptoms and they have also been linked to worse prognosis.[9]

VASCULAR ABNORMALITIES

Vascular remodeling is a part of aging, but it is greatly amplified by cardiovascular risk factors such as diabetes mellitus and hypertension. Vascular stiffening results in impaired ability to accommodate an increased systemic load during stress and exercise. Vascular remodeling is a part of the same systemic process that affects the diastolic properties of the left ventricle. As a result, the ability of the cardiovascular system to function efficiently under various loading conditions and maintain low filling pressures is compromised because of impaired ventricular–vascular coupling.

EXTRA CARDIAC FACTORS

A range of extra cardiac contributing factors have been implicated in the pathogenesis of HFpEF. These include anemia, pulmonary disease, renal disease, and obesity. Obesity and metabolic syndrome are especially important because of the high prevalence in the general population; also, weight loss may improve diastolic properties of the left ventricle.

CARDIOVASCULAR AGING

HFpEF is predominantly a disease of the elderly that emphasizes the importance of age-related cardiovascular changes in the disease pathogenesis. Aging leads to a wide range of changes within the cardiovascular system, including alteration in the left ventricular diastolic function and vascular stiffening. Aging does not invariably result in heart failure, but age-related changes are greatly amplified by cardiovascular risk factors and disease states (such as atherosclerosis) and contribute to the development of the HFpEF phenotype.

CLINICAL FEATURES

The clinical presentation of HFpEF can be variable: patients can present with mild symptoms of exercise intolerance and tiredness or be admitted with acute pulmonary edema if an immediate precipitating factor (such as atrial fibrillation or uncontrolled hypertension) is present. The range of symptoms is similar to HFrEF and includes dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema, and weight gain. As with HFrEF, it is important to characterize and quantify the functional status in a standardized way such as the New York Heart Association functional classification **(Table 12.1)**.

TABLE 12.1 New York Heart Association Functional Classification for Cardiac Diseases

I	Patients have cardiac disease without limitation of physical activity. Ordinary physical activity does not cause symptoms such as fatigue, palpitation, dyspnea, or chest pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or chest pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. Less than ordinary activity causes fatigue, palpitation, dyspnea, or chest pain
IV	Patients have cardiac disease resulting in symptoms at rest, and physical activity causes further discomfort

Physical examination can demonstrate signs of fluid overload such as elevated jugular venous pressure, lung rales, hepatomegaly and hepatojugular reflux, ascites, and peripheral edema. The lateral displacement of the apical impulse and the third heart sound usually point toward HFrEF.

Besides the symptoms and signs of heart failure, the history and physical examination should also be directed toward identifying the risk factors that can lead to the development of HFpEF such as hypertension, coronary artery disease, obesity, and diabetes mellitus. In cases of acute decompensated heart failure, the precipitating factors should be explored; these include medication noncompliance, poorly controlled hypertension, arrhythmia, and thyroid disease.

DIAGNOSIS

Diagnosis of HFpEF is not always straightforward. The following components

should be considered in patients suspected to have HFpEF:[1, 10]

1. Symptoms consistent with heart failure diagnosis
2. Presence of physical signs of heart failure, mostly evidence of fluid overload
3. Preserved LVEF (≥50%)
4. Elevated natriuretic peptide levels
5. Evidence of structural or functional alterations underlying heart failure as assessed by echocardiography

Natriuretic peptide levels are elevated in patients with HFpEF, but they are on average lower than the levels seen in patients with HFrEF. The structural alterations commonly observed in patients with HFpEF include left atrial enlargement and left ventricular hypertrophy; the functional alterations include decreased annular tissue velocities, elevated *E/e′* ratio, and pulmonary hypertension. Advanced echocardiographic assessment may demonstrate impaired longitudinal left ventricular systolic function. If the diagnosis remains uncertain after initial testing, invasive hemodynamic evaluation may be helpful. Elevated left ventricular filling pressures at rest support the diagnosis of HFpEF; however, many individuals demonstrate hemodynamic compromise only with stress. In these patients, hemodynamic measurements during exercise can be performed using either echocardiography (diastolic stress test) or uncommonly invasive hemodynamic testing.

A 12-lead electrocardiogram (ECG) should be performed initially on all patients presenting with heart failure. Initial laboratory evaluation of patients presenting with heart failure should include complete blood count, comprehensive metabolic panel, hemoglobin A1c, fasting lipid profile, urinalysis, ferritin and transferrin saturation, and thyroid-stimulating hormone. Serial monitoring, when indicated, should include serum electrolytes and renal function. Echocardiogram is the cornerstone of patient evaluation, as described earlier.

Further testing should be tailored to the clinical scenario and may identify specific causes, risk factors, or precipitating factors for HFpEF phenotype. These include coronary artery disease, systemic diseases (such as sarcoidosis), infiltrative disorders (such as amyloidosis), and so on. Also, further testing may be necessary to exclude other conditions presenting with a similar phenotype such as hypertrophic cardiomyopathy and constrictive pericarditis.

MANAGEMENT

There are no consistently proven treatment strategies that would reduce mortality in patients with HFpEF. The basics of management revolve around symptomatic treatment of volume overload with diuretics, control of hypertension, and treatment of risk factors such as atrial fibrillation, coronary artery disease, and diabetes mellitus.

DIURETICS

One of the main goals of HFpEF therapy is to achieve euvolemia by judicious use of diuretics. Diuretic treatment provides a symptomatic benefit similar to that in patients with HFrEF.

DRUGS AFFECTING RENIN-ANGIOTENSIN SYSTEM

Among the various drug therapies tested in HFpEF, several trials have targeted the renin–angiotensin system, but they have largely failed to show any significant mortality benefit. The trials specifically studied an angiotensin-converting enzyme inhibitor perindopril and angiotensin receptor antagonists candesartan and irbesartan. The summary of various trials is shown in **Table 12.2**.[11–13]

TABLE 12.2 Summary of Randomized Controlled Trials with Various Pharmacologic Agents in Patients with HFpEF

	PEP-CHF	CHARM-PRESERVED	I-PRESERVE	TOPCAT	RELAX
Patients, number	850	3023	4128	3445	216
Drug	Perindopril	Candesartan	Irbesartan	Spironolactone	Sildenafil
Mean follow up (years)	2.1	3	4.1	3.3	24 weeks
Primary end point	All-cause death/HF hospitalization	CV death/HF hospitalization	All-cause death/CV hospitalization	CV death/aborted cardiac arrest/HF hospitalization	Change in peak O_2 consumption, median
Hazard	0.92 (0.70–	0.89 (0.77–	0.95 (0.86–	0.89 (0.77–1.04)	−0.2 (IQR,−1.7–

ratio	1.21)	1.03)	1.05)		1.11)
P value	0.54	0.12	0.35	0.14	0.9

CV, cardiovascular; HF, heart failure; HFpEF, heart failure with preserved ejection fraction.

It is now clear that HFpEF is a heterogeneous disease with variable contribution by different pathophysiologic components; and the trials that studied renin–angiotensin system antagonists applied broad criteria for patient selection and did not target any specific pathophysiologic component. Currently, the use of these agents is necessary for hypertension control and diabetes management, but there is no convincing evidence to support their role as disease-modifying agents for HFpEF. Use of a neprilysin inhibitor in combination with an angiotensin receptor blocker is being studied now in the HFpEF phenotype.

ALDOSTERONE ANTAGONISTS

The mineralocorticoid receptor antagonist spironolactone has been studied in a large randomized controlled trial in HFpEF (TOPCAT). The study showed no significant reduction in the composite primary end point of cardiovascular death, hospitalization for heart failure, or aborted cardiac death as compared with placebo. From the components of the primary outcome, spironolactone did show benefit in reducing hospitalizations (P = 0.04). As the pathophysiologic components of HFpEF phenotype are further refined, it is possible that certain subgroups of patients with HFpEF may benefit from an aldosterone antagonist.

PHOSPHODIESTERASE 5 INHIBITORS

Early animal study data showed improvement in ventricular structure and function with the use of sildenafil in pressure overload hypertrophy. However, when sildenafil was tested in a clinical trial of 216 patients with HFpEF, no significant benefits regarding exercise capacity, clinical status, or quality of life were noted with the follow-up period of 24 weeks.[14]

β-BLOCKERS

There are limited data on the use of β-blockers in patients with HFpEF. The potential theoretical advantage of using β-blockers in HFpEF comes from the possibility of prolonging the diastolic period because of the negative

chronotropic effect of β-blockers. However, there is significant prevalence of chronotropic incompetence in patients with HFpEF that offsets the potential benefit of β-blockers. Limited data comes from registries like the Organized Program to Initiate Life-saving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF).[15] The study evaluated 7154 hospitalized patients and showed that β-blockers had no effect on 1-year mortality and hospitalization rates in patients with HFpEF but significantly improved both end points in the HFrEF group.

CONTROL OF HYPERTENSION AND OTHER CONTRIBUTING FACTORS

Hypertension is an important factor in the development of HFpEF and precedes the development of HFpEF in the majority of the cases. Early blood pressure treatment is the most important intervention that could possibly prevent the progression of hypertensive heart disease to symptomatic HFpEF. The choice of drugs should follow the common practices for hypertension control unless compelling indications are present for specific drug use (eg, rate control of atrial fibrillation with a β-blocker). Other contributing factors that should be addressed in the treatment strategy include anti-ischemic therapies in patients with coronary artery disease, proper diabetes control, and so on.

ROLE OF EXERCISE

Exercise training in HFpEF has shown benefit in improving exercise tolerance and managing obesity. The HF-ACTION trial focusing on patients with HFrEF showed that exercise had a modest reduction for both all-cause mortality and rehospitalization. In one meta-analysis, exercise training was associated with an improvement in cardiorespiratory fitness and quality of life.[16]

CONCLUSIONS

In the past decade there have been several advances in the management of HFrEF, but no breakthrough treatment discoveries have been made for HFpEF. The efforts to understand the pathophysiology of HFpEF have broadened our

understanding of this phenotype from a disorder of diastolic function to a complex interplay of multiple abnormalities. Despite these advances, there is still a need to standardize the diagnostic criteria and better characterize the disease processes based on specific pathophysiologic features rather than LVEF alone. Future therapies targeting these pathophysiologic mechanisms may provide better clinical outcomes.

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Patient and Family Information for: HEART FAILURE WITH PRESERVED EJECTION FRACTION

DESCRIPTION AND CAUSES

Heart failure with preserved ejection fraction, also known as HFpEF, is a disease of the heart caused by increased stiffness of the heart and blood vessels and inability of the heart to relax properly. As a result, the heart function does not meet the demands of the body even though the pumping function of the heart (measured as “ejection fraction”) is preserved. Impaired heart function can cause fluid accumulation in the lungs and other organs of the body. Patients commonly feel shortness of breath and fatigue with exertion as initial symptoms. As the disease progresses, shortness of breath can develop at rest, commonly with inability to sleep lying flat. Patients can also notice swelling of the ankles and stomach discomfort due to fluid accumulation in the abdomen.

The exact cause of the disease is not quite clear, but several health problems are known to contribute to the development of HFpEF. Hypertension (high blood pressure) is considered the main one. High blood pressure over time causes abnormal thickening of the heart muscle and increased stiffness of blood vessels: these are the major contributors to HFpEF. Some patients have coexisting obesity and diabetes. Coronary artery disease (blockage of the arteries supplying blood to the heart) is seen in some patients and it can also precipitate HFpEF. Abnormal heart beats, most typically atrial fibrillation, commonly coexists with HFpEF and can contribute to inefficient pumping of the heart.

HFpEF is known as the disease of the elderly. The heart muscle and blood vessels become stiff as people age; therefore, aging increases the chances of developing HFpEF. Also, women are twice more likely to develop HFpEF as

compared to men. The reason for this is not fully understood.

ASSESSMENT AND TESTING

The physician establishes the diagnosis of HFpEF by taking history (asking questions about the patient's symptoms), performing physical examination, and ordering appropriate tests. Besides confirming the diagnosis, the physician needs to determine the underlying structural heart disease that causes heart failure and its contributing factors so that it can be effectively treated. Blood tests are commonly done, and ECG and chest X-ray are also typically performed. Ultrasound examination of the heart (also known as echocardiogram) helps visualize cardiac chambers, and it is the most commonly used tool to evaluate the structure and function of the heart. Other tests are performed as deemed necessary by the physician. Cardiac catheterization is an invasive test that includes placing catheters into the heart chambers and major vessels to diagnose vessel blockage or get important pressure readings from various heart chambers. It is also used for interventions if vessel blockage seems to be causing the patient's symptoms.

TREATMENT

Treatment of HFpEF is challenging because there are no proven therapies that can change the natural cause of the disease. Therefore, therapies are focused on symptom relief and modification of risk factors for this condition. Diuretics (also known as water pills) are of great benefit because they remove excess fluid from the lungs and other organs of the body. They help decrease shortness of breath and leg swelling. Blood pressure medications are also important because hypertension has been identified as a major risk factor for developing HFpEF. The blood pressure control is individualized by the physician based on patient's age and coexisting medical conditions. The patient needs to follow closely with the physician because blood pressure control can be challenging and may involve multiple adjustments of medication types and dosages. Lifestyle modifications should be a routine part of patient management in HFpEF. Exercise training has shown to improve the exercise capacity and quality of life in patients with HFpEF. The physician may recommend a cardiac rehabilitation

program with dynamic exercise training.

Salt restriction is recommended in patients who have symptoms of heart failure or have high blood pressure because excess salt can cause fluid buildup in the body.

The patient’s weight should be monitored routinely because weight gain may be the early sign of excess fluid in the body. Patients should avoid smoking because it increases the chances of heart attack and can worsen heart failure. Alcohol is one of the important contributors to high blood pressure and its use should be restricted in any patient with heart disease.

13

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Mechanical Complications of Myocardial Infarction

Mechanical complications of acute myocardial infarction (AMI) result in some of the deadliest cardiovascular outcomes. It is difficult to assess the true incidence of these complications because both clinical and autopsy series differ considerably. Nevertheless, they are thought to be responsible for about 15% of all AMI deaths.[1] It is important to realize that these catastrophic events can occur within minutes to hours of the inciting event, or even days to weeks later. Mechanical complications of AMIs can be divided into two major categories: acute phase complications and chronic phase complications. **Table 13.1** outlines these complications.

TABLE 13.1 Acute Phase Versus Chronic Phase Complications in Acute Myocardial Infarction

ACUTE PHASE	CHRONIC PHASE
Left ventricular free wall rupture	True ventricular aneurysm
Ventricular septal rupture	Ventricular pseudoaneurysm
Right ventricular infarction	Left ventricular thrombus
Acute mitral regurgitation	

LEFT VENTRICULAR FREE WALL RUPTURE

Left ventricular free wall rupture (LVFWR) is almost an entirely fatal complication of myocardial infarction (MI). Despite great progress in the reduction of both mortality and morbidity from AMI, death related to LVFWR has been high.

Among patients who die after an AMI, many large studies have found a 14% to 26% incidence of cardiac rupture.[2] According to the National Registry of Myocardial Infarction, which reviewed data from 350,755 patients with AMI, the incidence of cardiac rupture was <1%.[3] Approximately 50% of the time, myocardial rupture occurs within the first 5 days of MI and within 2 weeks in over 90% of cases.[4, 5] Regardless, acute or subacute myocardial rupture is a serious and predominantly fatal complication of AMI.[6]

Studies have also suggested a higher mortality from free wall rupture with thrombolytics because cardiac rupture was responsible for 7.3% of all deaths and 12.1% with thrombolytic agents. Thrombolytic therapy does not necessarily increase the risk of rupture but it may accelerate occurrence, often within the first 24 hours of drug administration.[7] In contrast, the incidence of cardiac rupture may be lower in patients treated with percutaneous coronary intervention. This was suggested in an observational study of 1375 patients who received a thrombolytic agent or underwent primary angioplasty, the incidence of rupture was 3.3% and 1.8% respectively.[8] It is well known that myocardial rupture after MI is less common in patients with successful reperfusion.[9]

One study found that myocardial rupture was 9.2 times more likely to occur in patients who had no prior history of angina or MI, ST-segment elevation or Q-wave development on the initial electrocardiogram (ECG), and peak MB-creatine kinase above 150 IU/L.[4] Absence of collateral blood flow and greater size of infarct territory correlate with a higher risk of myocardial rupture. Other risk factors for rupture include anterior location of the infarction, age >70, and female sex.[8, 10]

PATHOPHYSIOLOGY

Myocardial rupture more frequently involves the left ventricle than the right ventricle, and rarely involves the atria.[3] The infarct commonly affects the

anterior and lateral walls of the left ventricle near the junction of the infarct and normal myocardium. Ventricular free wall rupture is defined as an acute, traumatic perforation of the ventricles, which may include pericardial rupture.[6] With unsuccessful or no reperfusion, coagulation necrosis develops within the first 3 to 5 days.[5] As the necrosis progresses, neutrophils infiltrate the myocardial space and release lytic enzymes that disintegrate the necrotic myocardium leading to perforation. The rupture thus is a result of transmural infarction and the actual perforation can range in size from millimeters to centimeters depending on infarct size.[5] Early phase rupture is defined as within 72 hours post MI and late rupture is greater than 4 days.

The hallmark of rapid deterioration is primarily due to the extravasation of blood into the pericardial space with resultant instantaneous, acute pericardial tamponade. Because these events occur so quickly, the condition of patients usually deteriorates before any therapeutic intervention. Less commonly, subacute rupture can provide a longer therapeutic window because the rupture may be temporarily contained by pericardial adhesions or by thrombosis at the rupture site. It is in these patients that immediate, life-saving, cardiovascular surgery is possible **(Figure 13.1)**.[11]

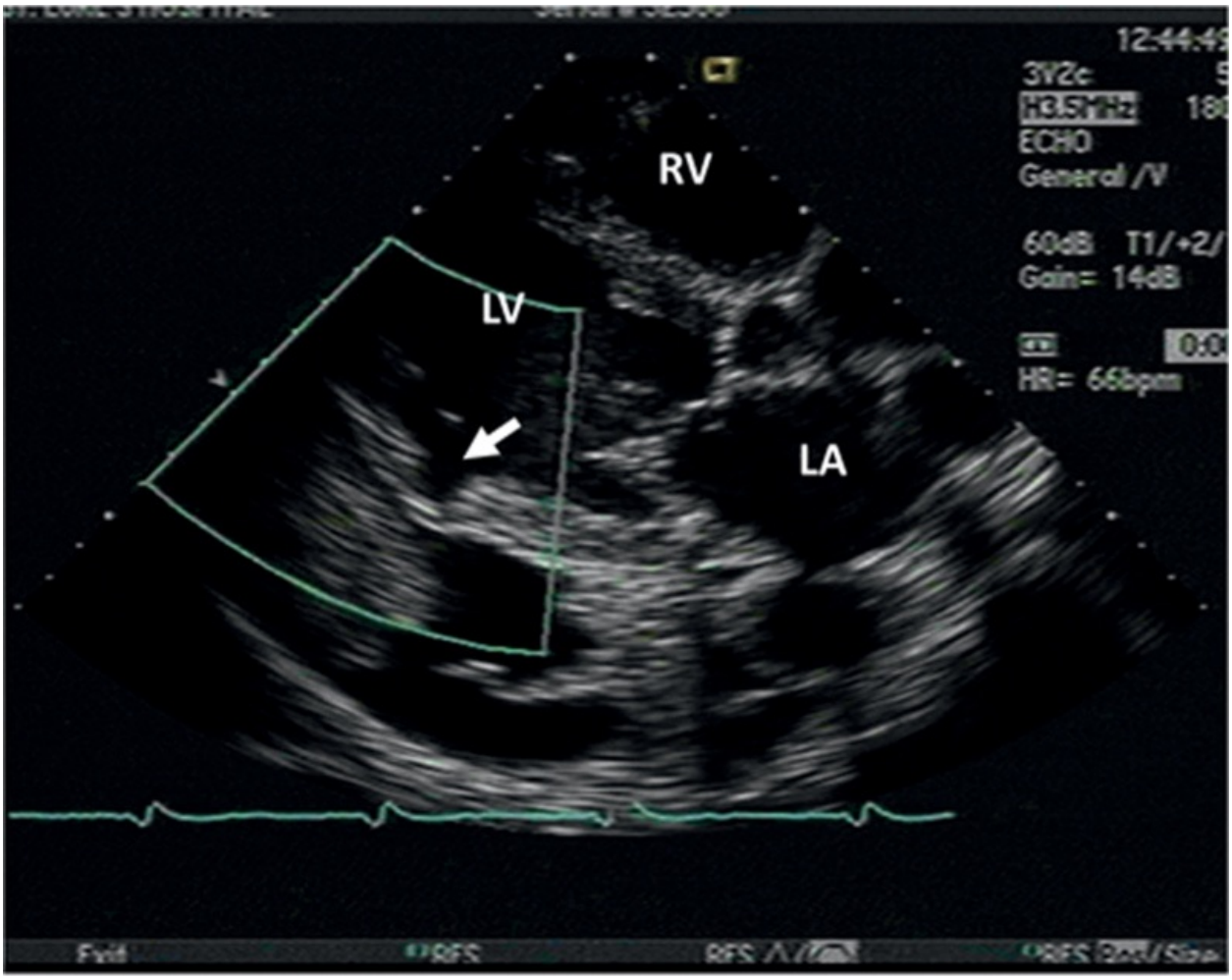


FIGURE 13.1 Parasternal long-axis view of a transthoracic echocardiogram demonstrating a posterior free wall rupture (*arrow*). LA, left atrium; LV, left ventricle; RV, right ventricle.

CLINICAL PRESENTATION

The clinical course of myocardial rupture is variable and challenging to diagnose, because patients may rapidly decompensate. Their clinical course parallels that of any patient suffering from pericardial tamponade. Thus, the presentation of rupture can vary from sudden death in an undetected or silent MI to incomplete/subacute rupture in those with known MI.[12] **Figure 13.2** demonstrates a case of LVFWR causing pericardial tamponade with thrombus formation in the pericardial space.

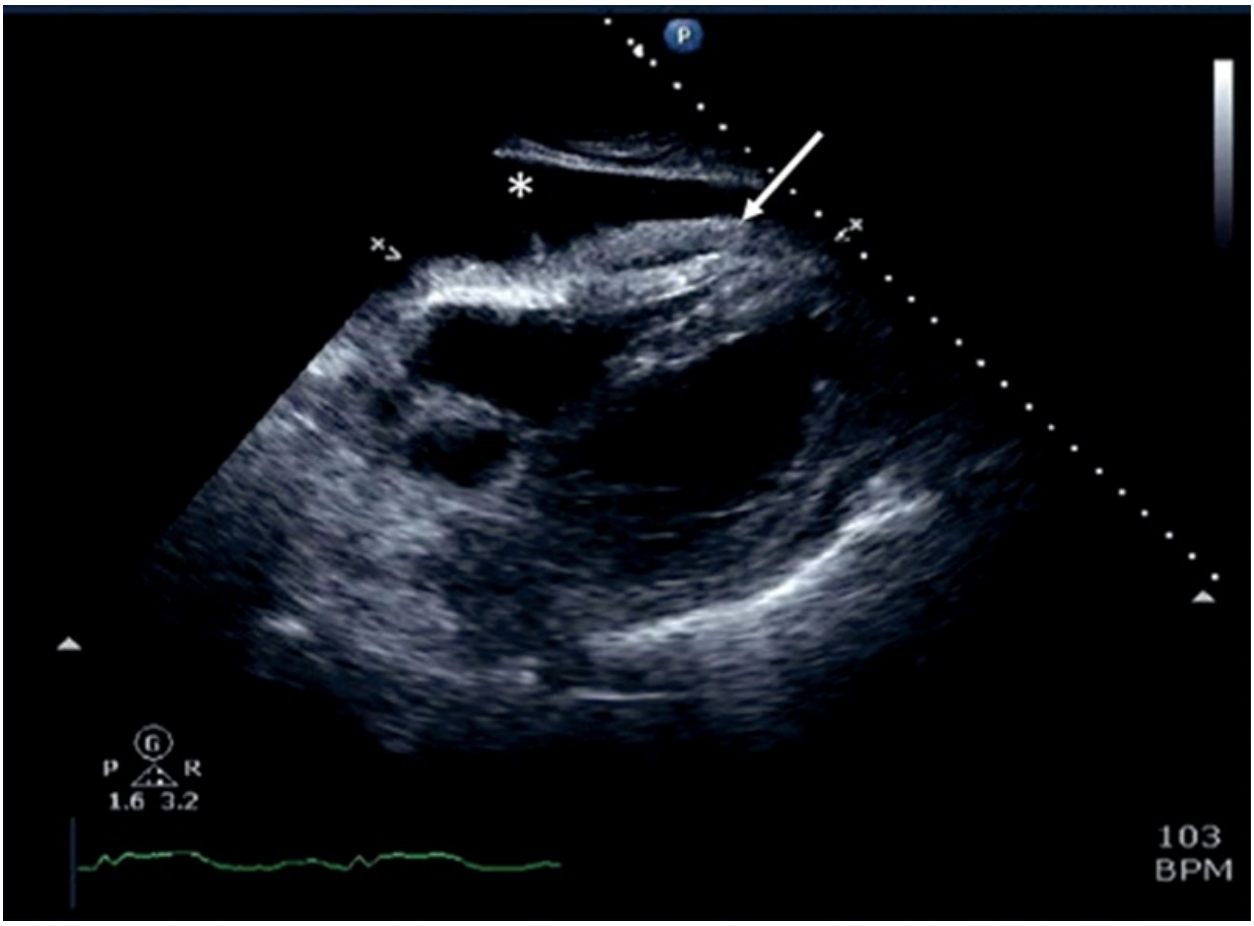


FIGURE 13.2 Subcostal view showing pericardial effusion (*asterisk*) with a thrombus in the pericardial space (*arrow*). This resulted from a ventricular free wall rupture after an acute myocardial infarction and the patient developed cardiac tamponade physiology.

Complete rupture of the left ventricular (LV) free wall usually leads to hemopericardium and death from cardiac tamponade. Patients may complain of transient chest pain or dyspnea. Acute tamponade can cause tachypnea, tachycardia, muffled heart sounds, elevated jugular venous pressure, and pulsus paradoxus. The presence of rupture is first suggested by the development of sudden profound right heart failure and shock, often progressing rapidly to pulseless electrical activity and death. Emergent transthoracic echocardiography (TTE) will confirm the diagnosis and emergent pericardiocentesis can transiently relieve the tamponade.[12]

Incomplete/subacute rupture of the LV free wall can occur when organized thrombus and the pericardium seal the ventricular perforation. Patients may present with persistent or recurrent chest pain (particularly pericardial pain), nausea, restlessness, agitation, abrupt hypotension, and/or electrocardiographic

features of localized or regional pericarditis.[4, 5] The diagnosis of incomplete/subacute rupture is again confirmed by TTE.[12]

There are three types of ventricular free wall rupture **(Figure 13.3)**. Type I is a slitlike or fissure full-thickness rupture, usually occurring within the first 24 hours with abrupt onset of symptoms. Type II is more subacute and occurs as a result of erosion of the myocardium at the infarct site. Type III has a later onset, occurring because of the expansion of the infarct zone with wall thinning and rupture through an aneurysmal segment.

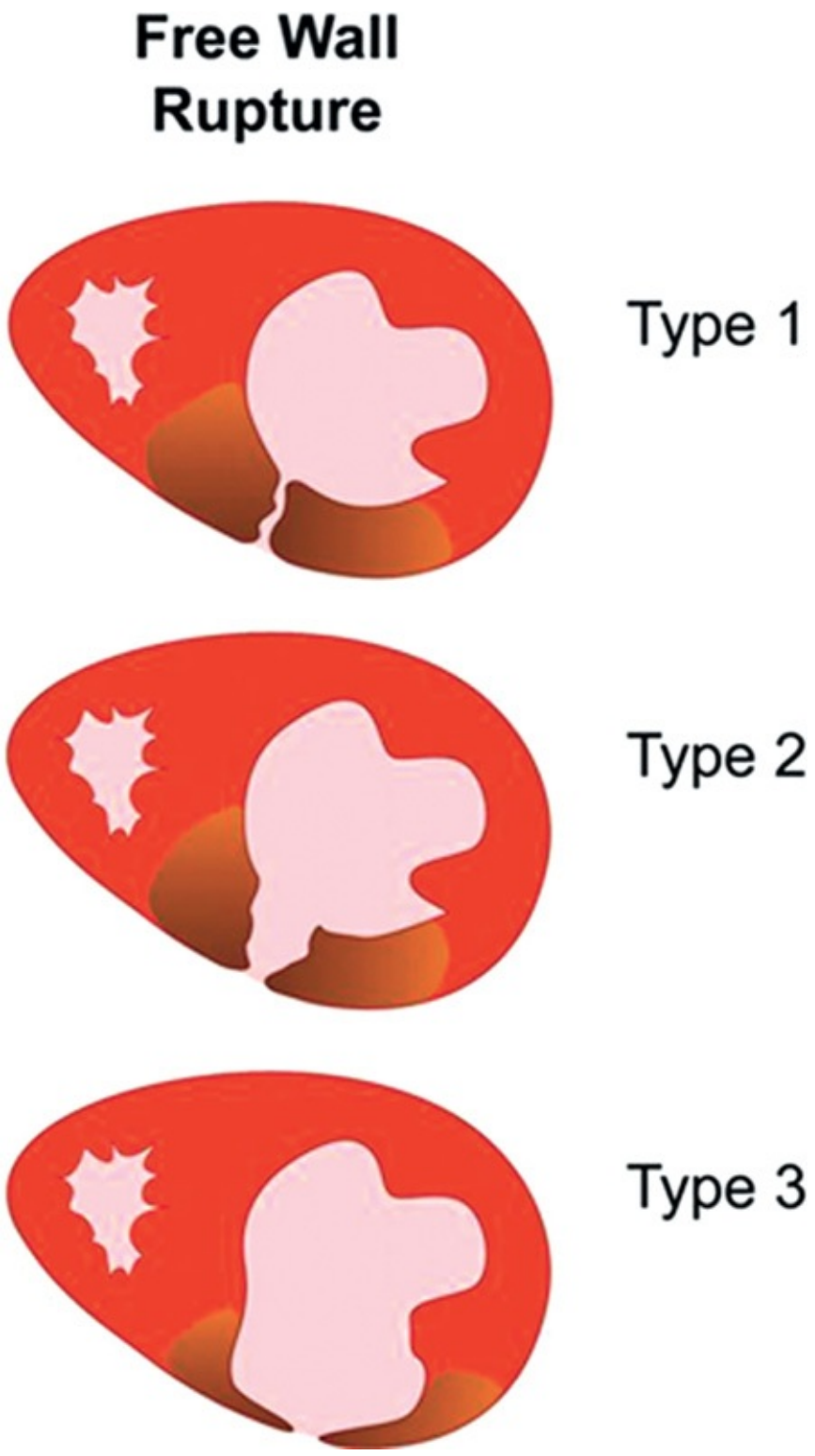


FIGURE 13.3 Classification of myocardial free wall rupture. (Adapted from Reynolds HR, Hochman JD. *Eur Heart J*. 2010;31:1433-1435, modified from Becker AE, van Mantgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol*. 1975;3:349-358.)

TREATMENT

As mentioned, the mortality for acute and subacute free wall rupture is high because of rapid clinical deterioration. Survival depends primarily on the prompt recognition of myocardial rupture and provision of immediate therapy. Patients displaying suggestive symptoms, signs, and ECG changes require emergent bedside echocardiogram and echocardiographically guided pericardiocentesis if fluid is visualized. Immediate surgical intervention is indicated if the pericardiocentesis identifies the fluid as blood. Medical therapy aimed at hemodynamic stabilization should also be instituted. In addition to pericardiocentesis, this includes fluids, inotropic support, vasopressors, and even intra-aortic balloon pump counterpulsation and percutaneous cardiopulmonary bypass when available and indicated.[4]

With rapid recognition and initiation of both medical and surgical therapy, the potential for survival, particularly with subacute rupture, can improve dramatically. In 1 study, 25 of 33 patients (76%) with subacute ventricular rupture survived the surgical procedure and 16 (48%) were long-term survivors.[13]

VENTRICULAR SEPTAL RUPTURE

Another deadly complication of AMI involves rupture of the interventricular septum. Rapid diagnosis, aggressive medical therapy, and prompt surgical intervention are essential to increase the chances of survival.

In the era before reperfusion therapy, rupture of the interventricular septum is thought to have occurred in 1% to 2% of patients with AMI and accounts for approximately 5% of deaths in this setting.[14] It typically occurs in the first week after infarction, with a mean time from symptom onset of 3 to 5 days.[15] The classic risk factors for septal rupture in the pre-reperfusion era include hypertension, advanced age, female sex, and the absence of a history of MI or angina.[16] Prognosis for ventricular septal rupture (VSR) in the prereperfusion era was very poor, with an in-hospital mortality of about 45% in those treated surgically and about 90% in those treated medically.[15] With the advent of thrombolysis and percutaneous intervention, incidence and outcomes have changed.

In the reperfusion era, studies show a much lower incidence and an

accelerated time to diagnosis of interventricular septal rupture than had been previously reported. Early reperfusion therapy may prevent the extensive myocardial necrosis that is associated with ventricular rupture.[15] Patients generally have a mean time of 1 day from infarction to development of a VSR. Many have postulated that this acceleration of rupture may be due to thrombolysis causing hemorrhage during the "lytic state," so that if a VSR occurs, its time course may be accelerated.[15] In the reperfusion era, advanced age, anterior infarct location, female sex, and no previous history of smoking were found to be the most potent predictors of a VSR.[15]

PATHOPHYSIOLOGY

The pathophysiology of interventricular septal rupture is similar to that of free wall rupture. Without reperfusion, coagulation necrosis develops within the first 3 to 5 days. The septum becomes necrotic and is infiltrated by neutrophils, which release lytic enzymes, thereby disintegrating the necrotic myocardium.[16] A transmural septal infarction underlies the rupture of the interventricular septum, with the tear ranging in size from millimeters to centimeters.[14]

The ventricular septum is a very vascular structure. The rarity of septal rupture and the variable infarct location relate to the fact that the interventricular septum has a dual blood supply. The anterior two-thirds is supplied by the left anterior descending (LAD) coronary artery and its branches. The posterior one-third is supplied by branches of the posterior descending artery, which come from the right coronary or the left circumflex artery, depending on the dominance of the circulation.[17] Studies have been conflicting in terms of which artery is predominantly responsible for septal rupture, but anterior MIs are considered to be more frequent, followed by inferior infarctions. Similar to free wall rupture, interventricular septal rupture occurs most frequently with a first MI when there is less likely to be collateral blood flow. In this setting, with an abrupt cessation of flow in the infarct-related artery, no collateral flow exists to support the infarcted zone, thereby making the septum prone to rupture **(Figure 13.4)**.

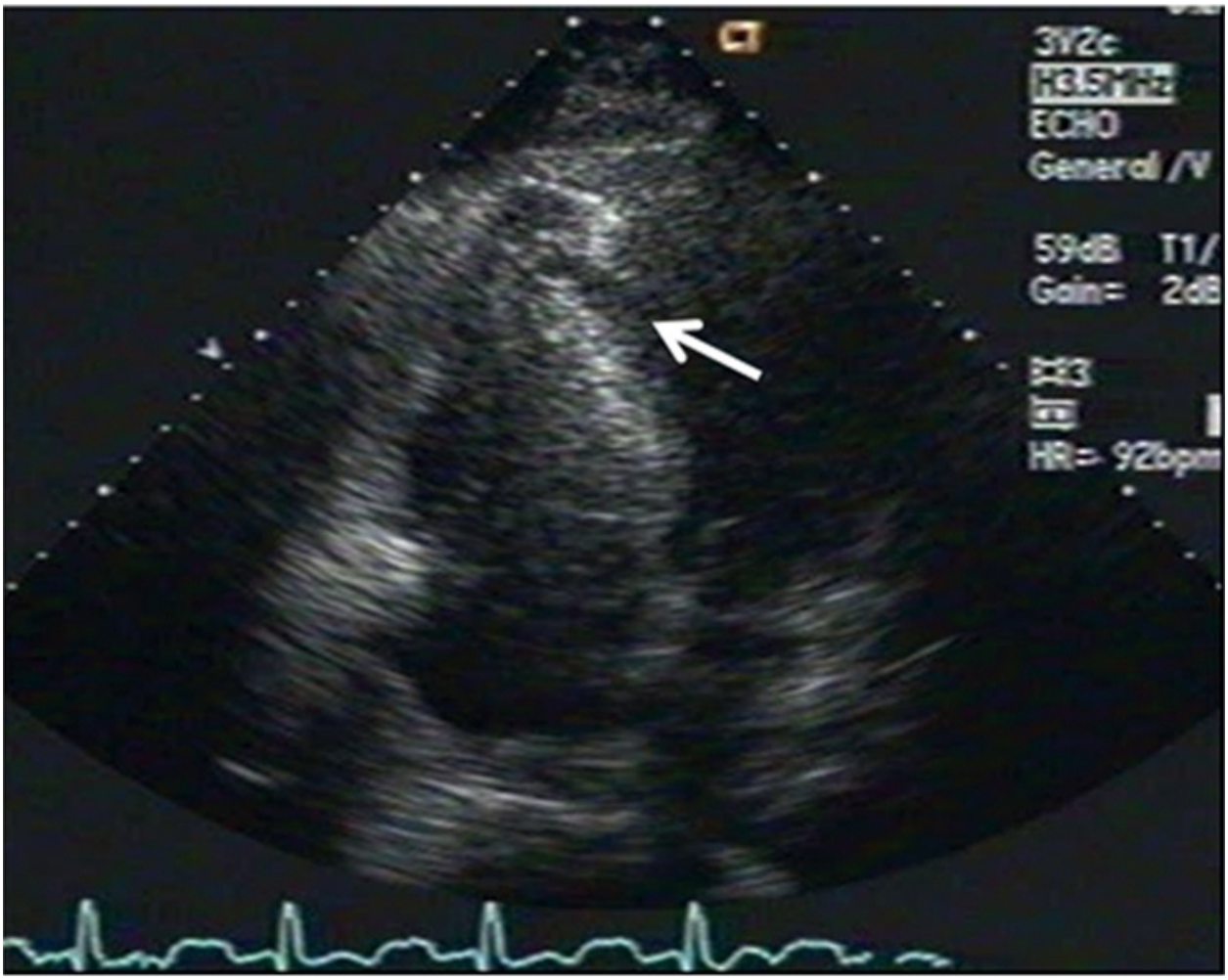


FIGURE 13.4 Apical four-chamber view of a transthoracic echocardiogram demonstrating a ventricular septal rupture in the distal portion of the interventricular septum (*arrow*).

CLINICAL PRESENTATION

Symptoms of rupture include shortness of breath, chest pain, signs of low cardiac output, and shock.[16] In 1934, Sager proposed a set of clinical criteria for suspecting a ruptured septum. The sudden onset of a systolic murmur, often accompanied by a thrill, in a patient with rapid hemodynamic decompensation is highly suggestive of a ruptured interventricular septum.[18] The rupture produces a harsh, loud, holosystolic murmur along the left sternal border, radiating toward the base, apex, and right parasternal area with a palpable thrill present in half of the patients. Compared to acute mitral regurgitation (MR), initially there is often right ventricular (RV) failure and absence of severe pulmonary edema before LV failure ensues. As the disease progresses, complete biventricular failure invariably occurs.[16]

In the setting of cardiogenic shock, the thrill and murmur may be difficult to appreciate because turbulent flow across the defect is reduced. Pulmonary hypertension may cause the pulmonic component of the second heart sound to be accentuated. RV and LV S3 gallops are often heard. Tricuspid regurgitation may be present and biventricular failure generally occurs within hours to days.[16]

TREATMENT

In the correct clinical setting, immediate echocardiogram is crucial to confirm the diagnosis. After the diagnosis is made, medical therapy may consist of mechanical support with an intra-aortic balloon pump, afterload reduction, diuretics, and inotropic agents.[16] Prompt surgical intervention is essential because most patients have a rapid deterioration and die. It was previously believed that shortly after an AMI, the myocardium was too fragile for safe repair of the rupture. A waiting period of 3 to 6 weeks, to allow the margins of the infarcted muscle to develop a firm scar to facilitate surgical repair, was standard before surgical intervention.[19] Medical therapy carries close to 100% mortality. While surgical therapy is associated with poor results—only about 13% survival, it is still considered the primary therapy.[20] Surgical therapy consists of placing a myocardial patch across the ruptured septum with concomitant coronary artery bypass as needed. A recent review in the European Heart Journal shows reported 30-day mortality at various time points after AMI, and outlines an approach for the management of VSR shown in **Figures 13.5** and **13.6**.[21] **Figure 13.7** demonstrates a case of apical VSR in a patient with an acute LAD territory MI.

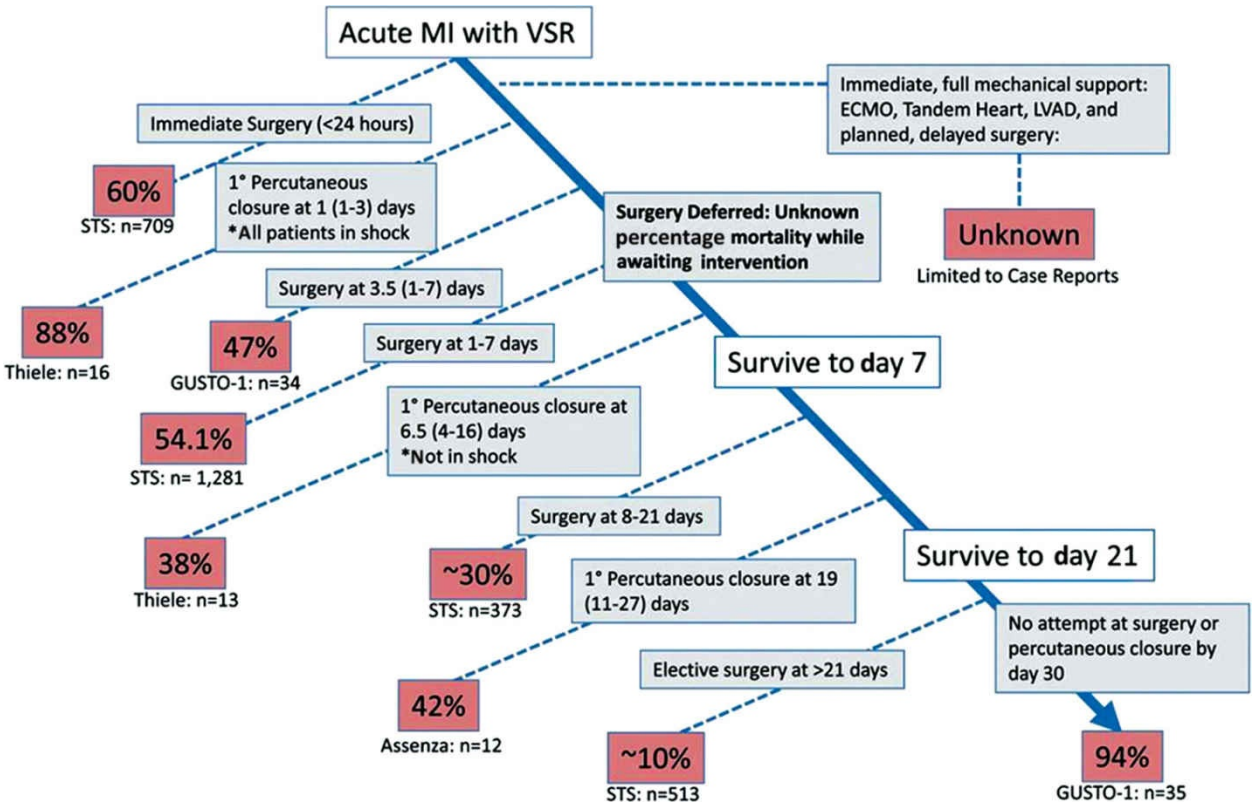


FIGURE 13.5 Reported 30-day mortality for VSR with immediate surgical management or at various time points of delayed intervention. ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; MI, myocardial infarction; VSR, ventricular septal rupture. (Adapted from Jones BM, Kapadia SR, Smedira NG, et al. *Eur Heart J*. 2014;35:2060-2068.)

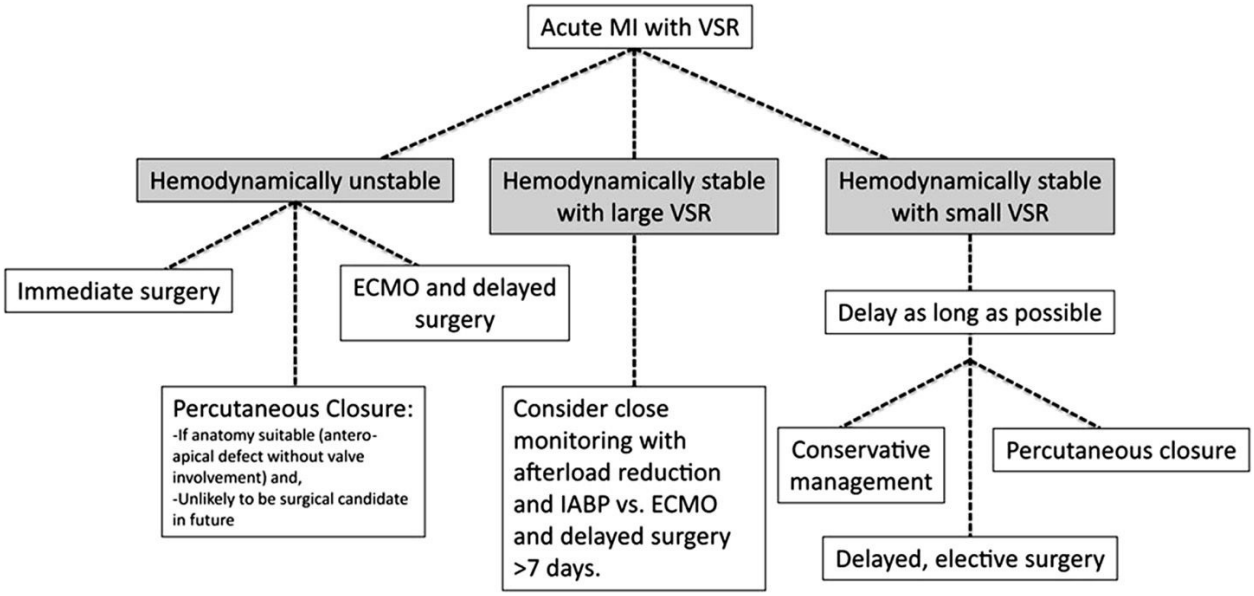
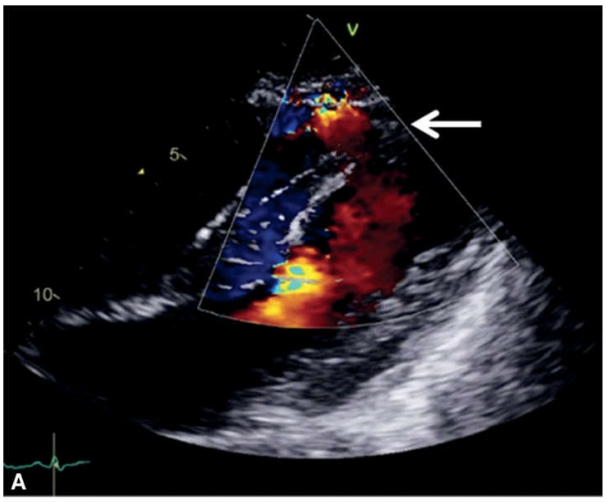


FIGURE 13.6 A multidisciplinary approach for managing acute VSR. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MI, myocardial infarction; VSR, ventricular septal rupture.

(Adapted from Jones BM, Kapadia SR, Smedira NG, et al. *Eur Heart J*. 2014;35:2060-2068.)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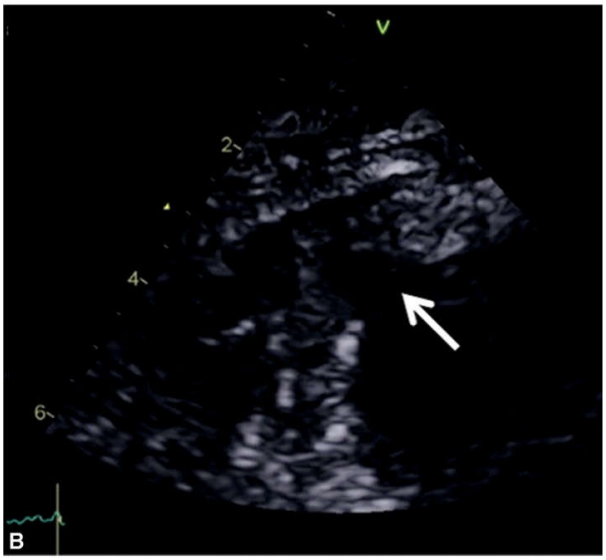
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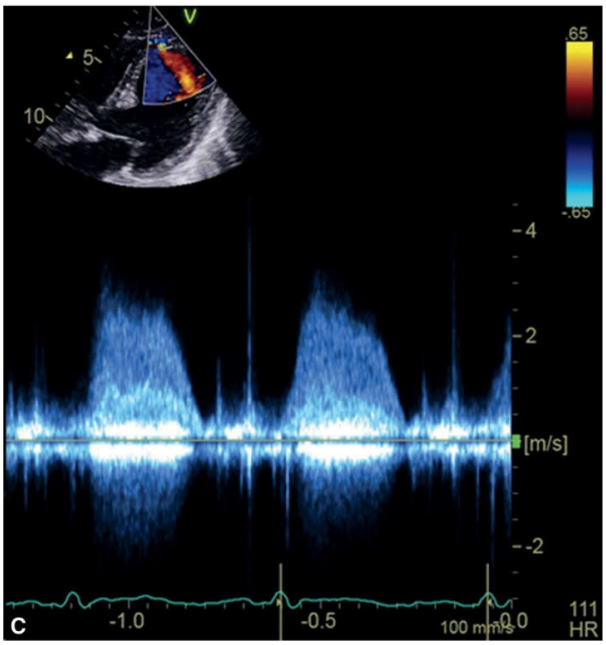
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FIGURE 13.7 Subcostal view showing apical VSR with flow from left ventricle to right ventricle (A) color Doppler flow, (B) VSR defect seen with 2D imaging highlighted by an arrow, (C) continuous wave Doppler demonstrating gradient across VSR. 2D, two-dimensional; VSR, ventricular septal rupture.

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction (RVI) was described over 60 years ago, but for decades it was not considered to be important because it showed no hemodynamic consequence in animal models.[22] Over time, it has become important to diagnose because it defines a specific clinical entity that is associated with considerable morbidity and mortality.[23] RVI complicates up to half of inferior wall LV infarctions.[22] Prompt recognition of this mechanical complication of AMI is crucial because its initial management differs from that of other types of infarction.

PATHOPHYSIOLOGY

The physiology of the right side of the heart varies considerably from that of the left. It is a low-pressure system that has one-sixth of the muscle mass of the left ventricle. Despite this, both ventricles have the same cardiac output.[22] This is due to the fact that the pulmonary vascular resistance is one-tenth that of the peripheral systemic resistance.[24] These factors are important in the hemodynamic consequences of RVI.

Coronary blood flow to the right ventricle is unique in that it occurs in both systole and diastole.[22] The right coronary artery (RCA) supplies the right ventricle through the acute marginal branches in the majority of patients, as well as the inferior wall and posterior interventricular septum through the posterior descending artery in right-dominant systems. Typically, RVI occurs when there is occlusion of the RCA proximal to the acute marginal branches. It can also occur with an occlusion of the left circumflex in those who have a left-dominant system. Although quite rare, occlusion of the LAD artery may result in infarction of the anterior right ventricle.[22]

The incidence of RVI in association with LV infarction ranges from 14% to 84% across different studies. Incidence of isolated RVI accounts for less than 3% of all cases of infarction.[22] When isolated to the right ventricle, the occlusion is usually in the acute marginal vessels or of a nondominant RCA.[24] Many RCA

occlusions do not result in RV necrosis.[23] Less than half of inferior MIs involve the right ventricle. This may be due to lower RV myocardial oxygen demand as a result of its smaller muscle mass, or from its improved oxygen delivery from the biphasic nature of the coronary blood flow during both systole and diastole. A rich left-to-right collateral system is also thought to play a part.[22]

Acute underperfusion of the RV free wall and adjacent interventricular septum leads to a stunned and noncompliant right ventricle. Loss of RV contractility results in a serious deficit in LV preload with a resultant drop in cardiac output, thereby causing systemic hypotension.[25] Augmented atrial contractility is necessary to overcome the increased myocardial stiffness associated with RVI.[26] Factors that impair filling of the noncompliant right ventricle and cause decreased preload are likely to have profound adverse effects on hemodynamics in patients with large RVIs. These factors include volume depletion due to the use of diuretics and nitrates or any diminution in atrial function caused by concomitant atrial infarction or the loss of atrioventricular (AV) synchrony.[22]

To complicate matters, acute RV dilatation causes a leftward shift of the interventricular septum, increasing LV end-diastolic pressure with a resultant decrease in LV compliance and cardiac output. LV compliance is further aggravated by increased intrapericardial pressure as a result of RV dilatation **(Figure 13.8)**. As a consequence, the LV filling and systolic function may be below normal.[23] If significant LV dysfunction complicates RVI, the results can be disastrous.

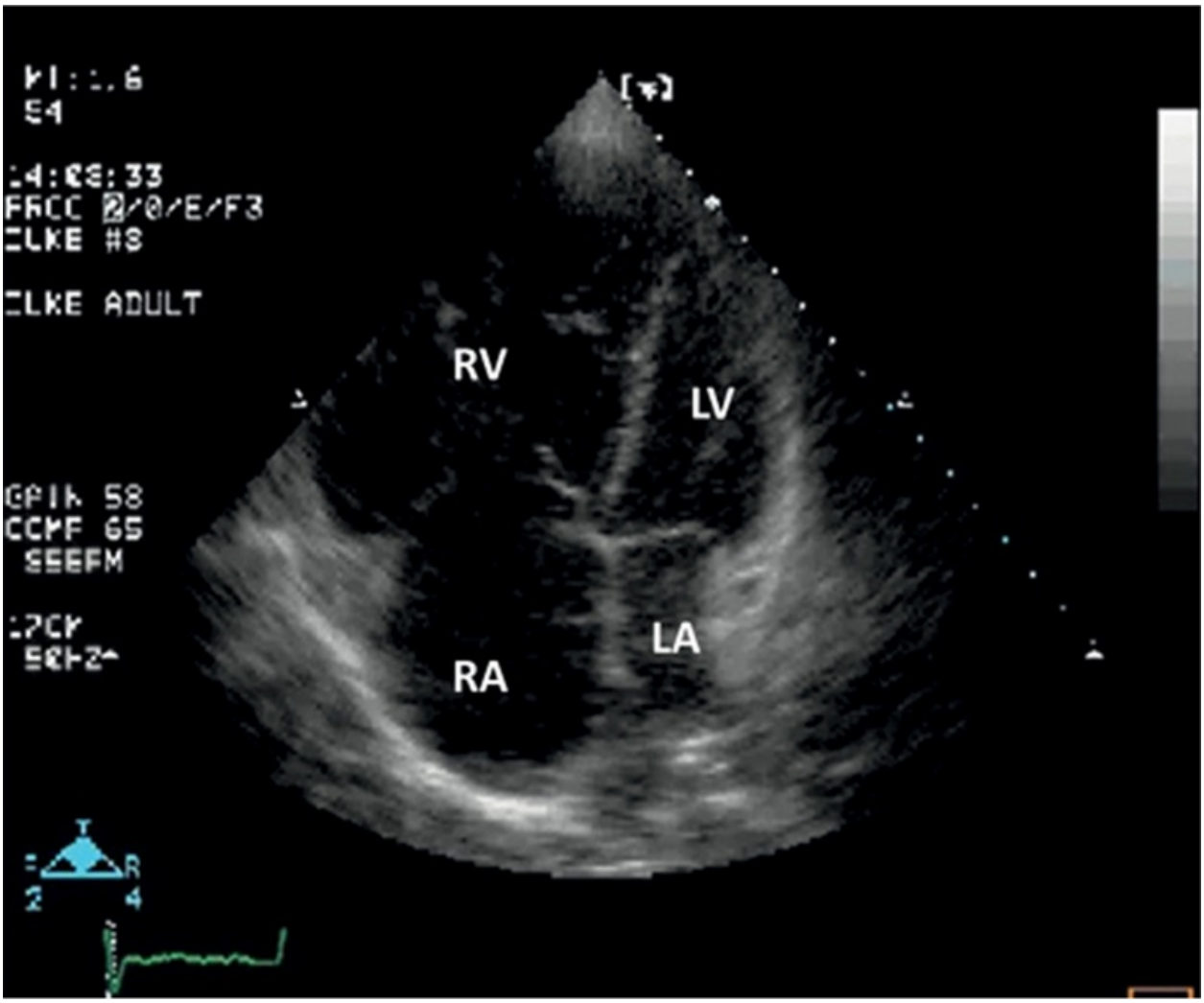


FIGURE 13.8 Apical four-chamber view of a transthoracic echocardiogram demonstrating a dilated and severely hypokinetic right ventricle with compression of the left ventricle. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

CLINICAL PRESENTATION

Given that management of RVI is quite different from LV infarction, recognizing its clinical presentation is paramount. A patient presenting with an inferior MI and the triad of hypotension, clear lung fields, and elevated jugular venous pressure, is virtually pathognomonic for RVI.[22] This triad is very specific, but has a sensitivity of less than 25%.[27] Auscultation may reveal a right-sided S3 and S4.[28] Tricuspid regurgitation may also be noted if the right ventricle is sufficiently dilated.

Pulsus paradoxus (decreased systolic blood pressure with inspiration) and Kussmal sign (elevated jugular venous distension with inspiration) have also

been reported in RVI.[28] Careful examination of neck veins in the setting of an inferior MI should alert the physician to the drastic consequences that use of nitrates, diuretics, and morphine can have. These agents should be avoided because they reduce preload and can promote or exacerbate hypotension.

The ECG is crucial for the diagnosis of RVI. The most frequent finding is any degree of ST elevation in leads II, III, and aVF with or without Q waves. Occlusion sufficiently proximal in the RCA to cause RV free wall injury also frequently compromises the blood supply to the sinoatrial node, atrium, and AV node, producing effects such as sinus bradycardia, atrial infarction, atrial fibrillation, and AV block.[25] Involvement of the RV free wall may be suspected with the presence of ST depression in precordial leads V2 and V3 when compared to V1. Confirmation of RV ischemia can be quickly obtained when right-sided leads V4R through V6R show ST-segment elevations greater than 1 mm **(Figure 13.9)**.[25] A 1-mm ST elevation in V4R is 70% sensitive and 100% specific for RVI.[22] ST-segment elevation in V4R has been shown to be a strong independent predictor of major complications and in-hospital mortality.[23] When the ECG shows signs of RVI, echocardiography can aid in the diagnosis.

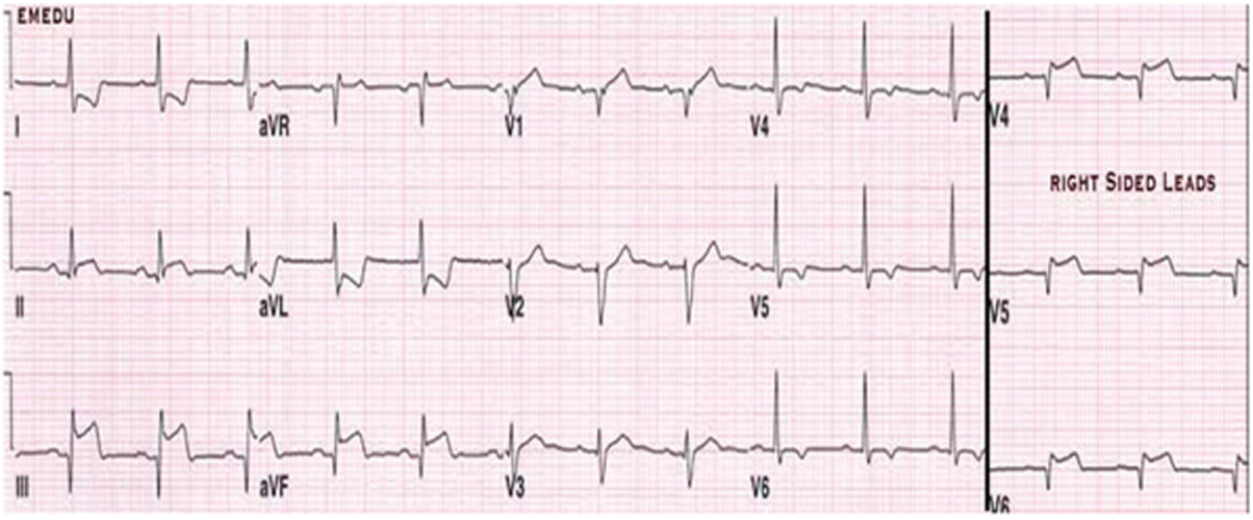


FIGURE 13.9 Electrocardiogram showing an inferior wall myocardial infarction with right-sided leads showing significant ST elevation in V4R through V6R.

TREATMENT

The treatment strategy of RVI includes early maintenance of RV preload, reduction of RV afterload, inotropic support of the dysfunctional right ventricle

and early reperfusion.[22] When the right ventricle is ischemic, use of drugs such as nitrates and diuretics will reduce preload and may reduce cardiac output and cause severe hypotension. Volume loading alone with normal saline will often increase filling of the right ventricle and in turn increase filling of the underfilled left ventricle and increase cardiac output.[23]

Excessive fluid administration can further elevate right-sided filling pressures without improvement in cardiac output. In some cases, volume loading will cause further RV dilatation, which in turn further compromises LV output through pericardial restraining effects.[22] Inotropic support with dobutamine should be initiated if the cardiac output fails to improve with up to 1 L of fluid administration.[23]

Often, inferior MI can result in bradyarrhythmias and AV dyssynchrony. When stroke volume is impaired, cardiac output depends on heart rate; therefore, bradycardia can be deleterious. The development of a high-degree AV block has been reported in as many as 48% of patients with RVI.[29] AV dyssynchrony causes loss of right atrial contribution to preload and can lead to further hemodynamic compromise. Several investigators have shown that AV sequential pacing in patients with complete heart block leads to significant increase in cardiac output and reversal of shock when ventricular pacing alone has no benefit.[30] Prompt cardioversion for atrial fibrillation should be considered to restore AV synchrony at the earliest signs of hemodynamic compromise.[22]

Reperfusion should be considered in the initial management of RVI. Recent studies have shown that those patients with predominant RV failure who underwent revascularization with either percutaneous angioplasty or coronary artery bypass grafting (CABG) had much better outcomes. Mortality was 42% for those revascularized versus 65% for those not revascularized. These numbers were similar for those with predominant LV failure (40% and 73%). The conclusion was made that RV failure complicating AMI carries a very high mortality risk similar to that for LV failure. Revascularization helps improve these numbers and should be considered immediately.[31]

Long-term prognostic data for those suffering from RVI is conflicting. It is generally thought that when patients survive to discharge, prognosis is favorable but large-scale studies are needed to confirm this theory.[22]

ACUTE MITRAL REGURGITATION

Acute MR is another major fatal mechanical complication of AMI. As with the other complications of AMI, the rapid recognition, diagnosis, and treatment can result in significant improvement in survival. The three main causes of MR in the setting of an AMI include ischemic papillary muscle dysfunction, papillary muscle or chordal rupture, and LV dilatation.[32]

MR of mild-to-moderate severity occurs in 14% to 45% of patients following an AMI. Most MR is transient in nature but sudden papillary muscle rupture can be a life-threatening event. Fibrinolysis for reperfusion may decrease the incidence of rupture; however, when administered, rupture may occur earlier in the post-MI period than in the absence of reperfusion. In the prefibrinolytic era, papillary muscle rupture was reported to occur between days 2 and 7 post AMI. However, it is now thought that a median time to papillary muscle rupture is 13 hours.[33] Papillary muscle rupture is found in 7% of patients in cardiogenic shock and contributes to 5% of the mortality after acute MI.[34]

Studies have shown that the risk factors for acute MR with papillary muscle rupture include advanced age, female gender, and absence of previous angina, inferoposterior AMI, single-vessel disease, and no history of diabetes. When considering acute MR without papillary muscle rupture, the risk factors also include female gender and advanced age; however, these patients are likely to have had a prior MI, recurrent ischemia, and multivessel coronary artery disease.[35]

PATHOPHYSIOLOGY

The mitral valve is located retrosternally at the fourth costal space and consists of an anterior and posterior leaflet. Any portion of the mitral apparatus can become anatomically disrupted and result in a portion of the mitral valve becoming flail and dysfunctional. The degree of resultant regurgitation is directly related to the extent of anatomic disruption. Most of the time in the setting of acute MI, the rupture of an entire papillary muscle or muscle head typically results in acute severe MR.[36] In most patients, the anterolateral papillary muscle receives dual blood supply from the LAD and circumflex coronary arteries and is less likely to be involved by the ischemic process than is the posteromedial papillary muscle, which is supplied solely by the posterior descending artery. Because of its single-vessel blood supply the posteromedial papillary muscle is 6 to 12 times more vulnerable to vascular compromise and rupture than the anterolateral papillary muscle. Often, the infarct expansion is

relatively small with poor collaterals, and up to 50% of patients have single-vessel disease, with many of them being a consequence of a first-time MI.[6, 37] Several studies support that acute MR is not only a common complication post AMI, but also that the degree of MR is predictive of patient survival. Large studies calculate the mortality of patients with moderately severe to severe MR during an acute MI to be 24% at 30 days and 52% at 1 year.[38] Mild MR in the setting of AMI is however not associated with clinically adverse events because it is likely reversible and secondary to the acute ischemic insult.

Of note, select patients with moderate-to-severe MR, but without papillary muscle rupture, are hemodynamically stable. In this setting, patients respond well to medical therapy and revascularization with or without eventual surgical intervention (mitral valve repair or replacement or CABG).[39]

TREATMENT

As with all of the acute phase complications of AMI, the proper treatment of acute, severe MR is emergent surgical correction of the mitral valve and CABG when indicated. Prompt diagnosis with echocardiogram and aggressive medical therapy before surgery markedly improve patient outcomes. **Figure 13.10** demonstrates an apical four-chamber view of a transthoracic echocardiogram showing MR as a result of an inferior wall MI. When considering hemodynamic compromise secondary to significant, acute MR, aggressive medical resuscitation involves improving forward flow by afterload reduction and thus improving the regurgitant fraction. Afterload reduction is accomplished with the use of nitrates such as sodium nitroprusside, diuretics, and intra-aortic balloon pump counterpulsation.

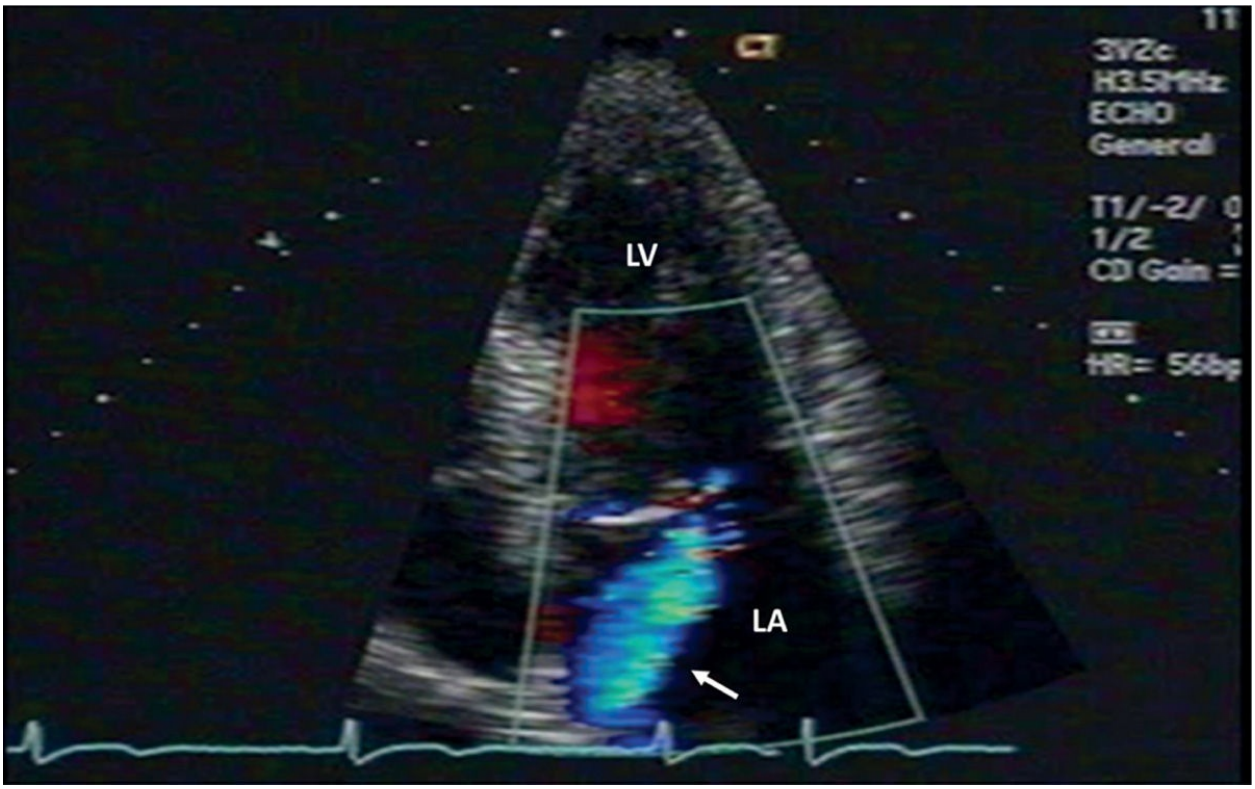
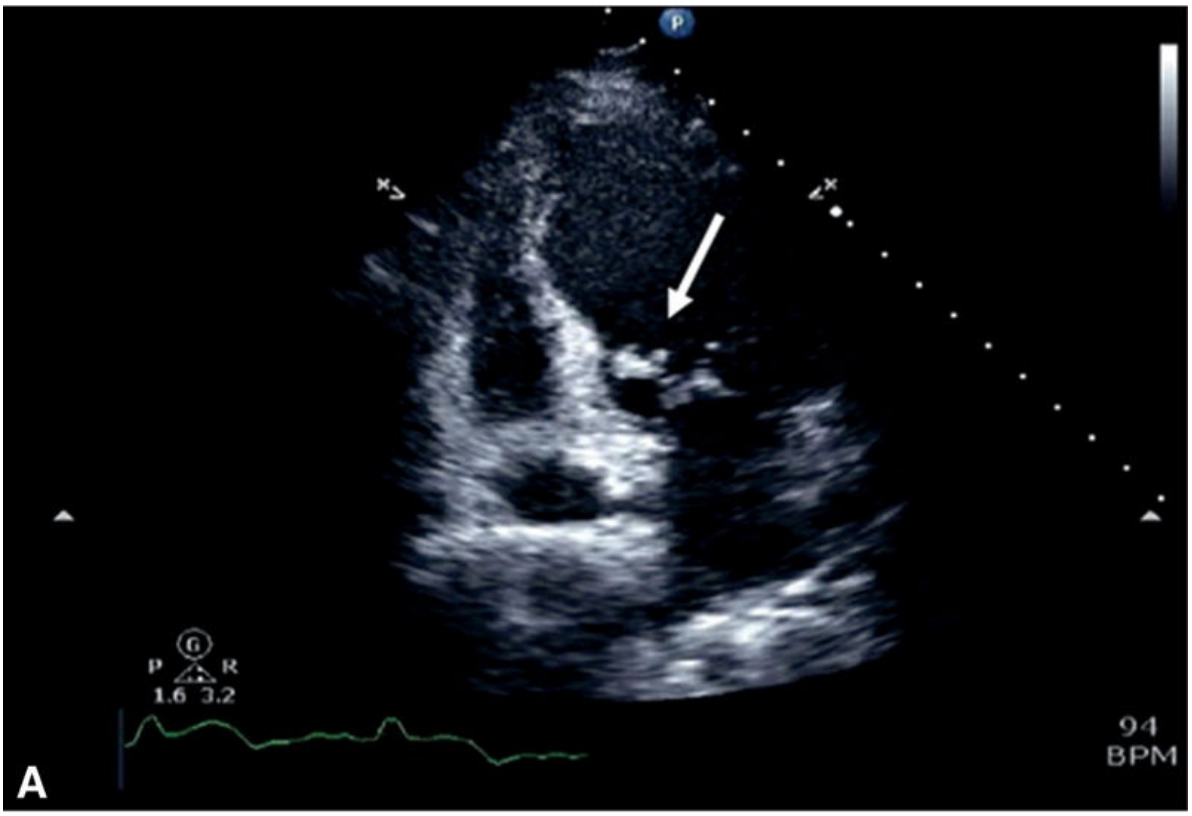


FIGURE 13.10 Apical four-chamber view of a transthoracic echocardiogram showing mitral regurgitation as a result of an inferior wall myocardial infarction (*arrow*). LA, left atrium; LV, left ventricle.

The operative mortality for these patients is an estimated 20% to 25% and heavily dependent on the timing of diagnosis and treatment. Despite such a high mortality, survival in patients restricted to medical therapy alone is significantly lower. Thus, emergent surgical intervention remains the treatment of choice for papillary muscle rupture.[40] Of note, mitral valve repair rather than replacement should be attempted in centers experienced in performing this procedure[38, 39]; and patients must meet the strict criteria for mitral valve repair, which includes the preserved integrity of the mitral apparatus (ie, intact papillary muscles and chordae). Interestingly, long-term results in 1 small study of 22 patients revealed a perioperative mortality of 27% and a 7-year survival for the survivors of surgery of 64% (the overall 7-year survival was 47%).[40] The only factor that improved both immediate and long-term survival was the concomitant performance of CABG. **Figure 13.11** shows a ruptured papillary muscle resulting in severe MR, requiring urgent surgical intervention.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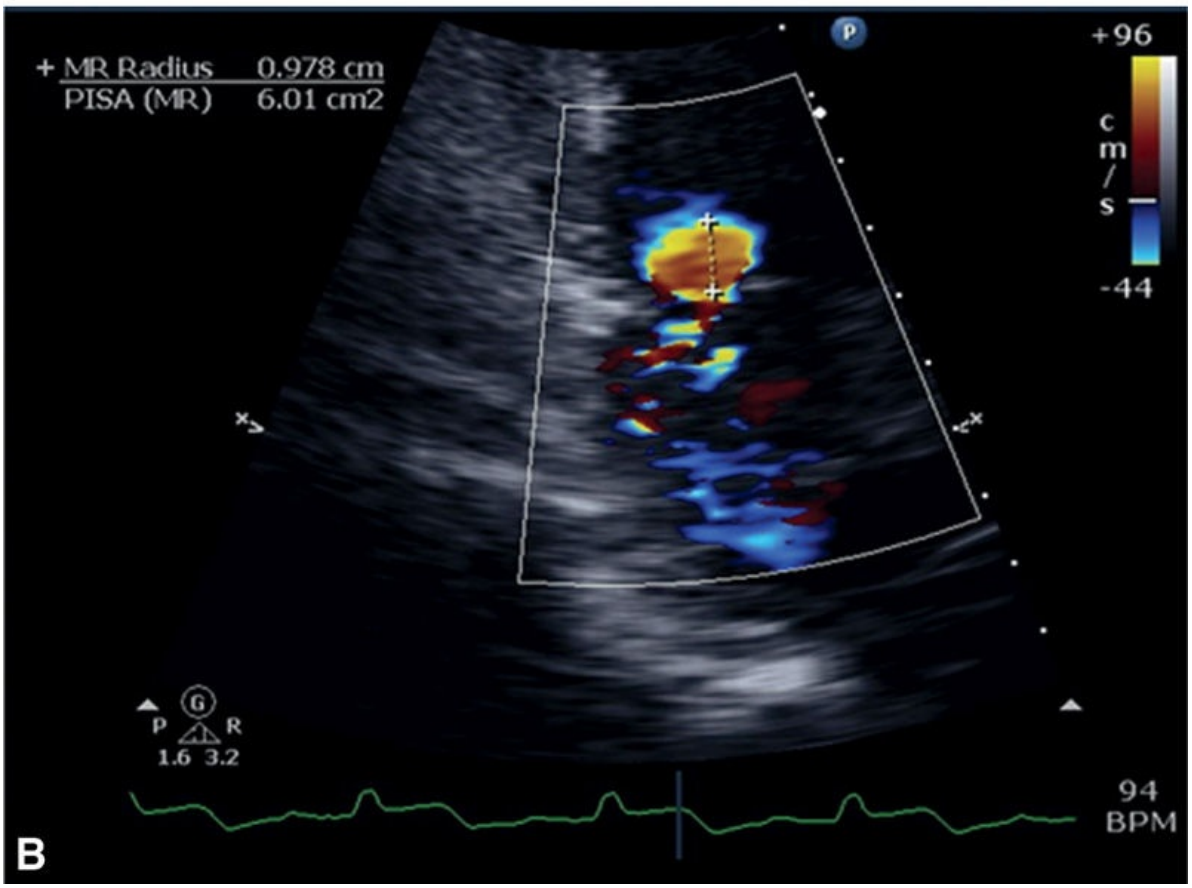
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FIGURE 13.11 Papillary muscle rupture. A, Apical four-chamber view showing ruptured head of the papillary muscle (*arrow*). B, Apical three-chamber view with color Doppler demonstrating severe mitral regurgitation with large proximal isovelocity surface area (PISA) radius.

TRUE VENTRICULAR ANEURYSM

In contrast to the acute complications of MI, the chronic complications of AMI are not immediately life-threatening. They have very different presentations and require different treatments. True left ventricular aneurysm (LVA) is a common chronic complication of AMI that is important to diagnose.

LVA is a common mechanical complication following an AMI, often occurring between 10% and 15% of patients. Before the era of current management, which includes strategies such as thrombolytic therapy, percutaneous coronary intervention, and the administration of afterload reducing agents, the incidence of LVA approached 40%.[41, 42] A recent analysis has shown that the incidence of LVA among 350 consecutive patients with ST-segment elevation MI, treated with thrombolytic therapy, was significantly lower in those with a patent infarct-related artery (7.2% vs 18.8%).[43] LVA of the apex and anterior wall are approximately four times more common than those of the inferior or inferoposterior walls.

Approximately 70% to 85% of LVAs are located in the anterior or apical walls, and in most cases are due to complete occlusion of the LAD coronary artery and the absence of collateralization. However, 10% to 15% of cases involve the inferior-basal walls because of RCA occlusion. A rare finding is a lateral LVA, which is the result of an occluded left circumflex coronary artery. Among patients with multivessel disease, LVA is uncommon if there is extensive collateralization or a nonoccluded LAD artery.

PATHOPHYSIOLOGY

LVA has been described as a well-delineated and distinct break, (“hinge point”) in the LV geometry and contour present in both systole and diastole. The walls consist of thin, scarred, or fibrotic myocardium, completely devoid of muscle, the result of a healed transmural AMI. The pathognomonic features include a wide mouth that enables communication with the aneurysmal cavity. Often, this is evident at 4 to 6 weeks following an AMI. The involved wall segment is either akinetic or dyskinetic during systole, and collapses inward when the ventricle is

fully vented during surgery **(Figures 13.12** and **13.13)**.

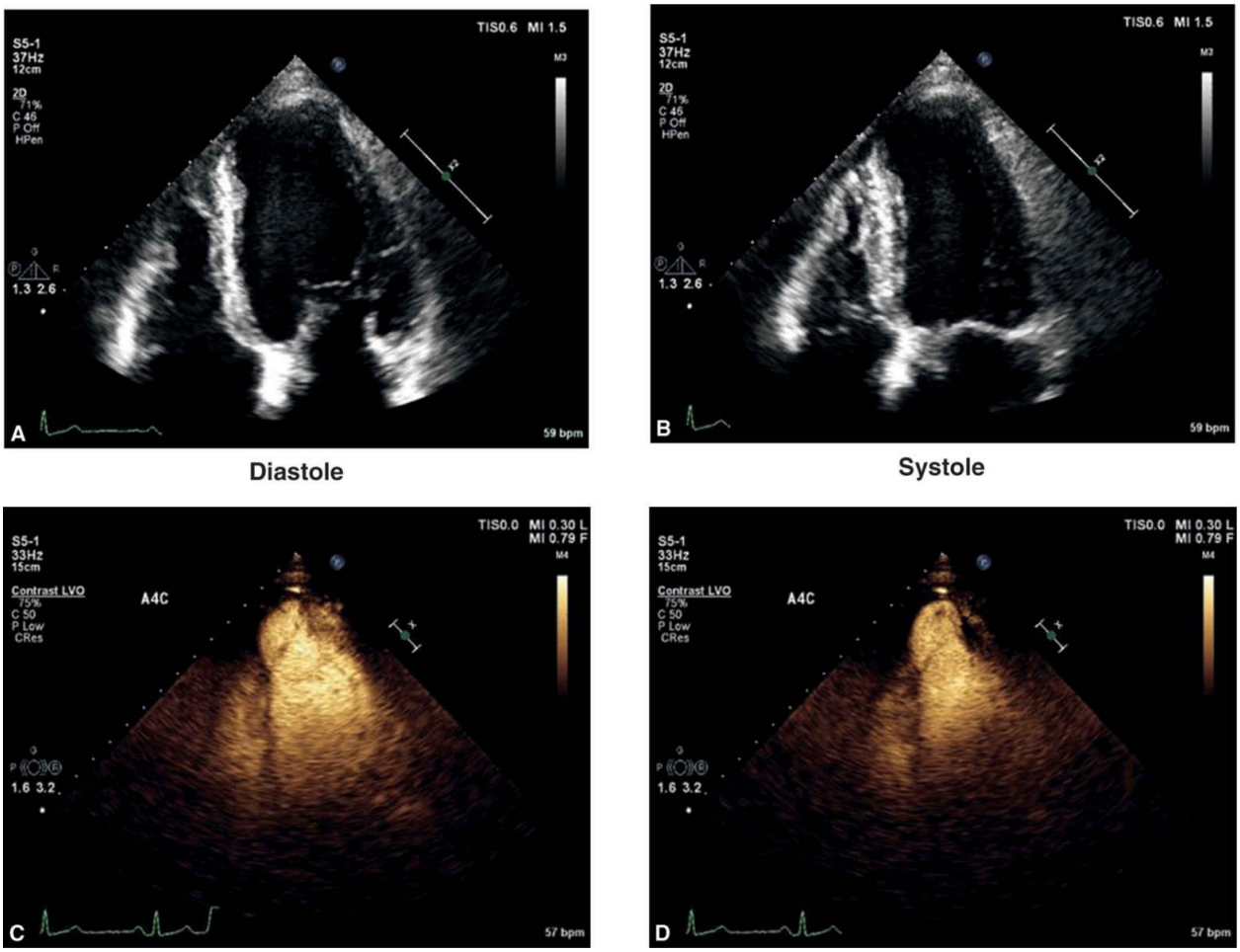

FIGURE 13.12 Apical four-chamber view in (A) dia stole and (B) systole and (C and D) with echo contrast, respectively, showing a large apical acute myocardial infarction with a large apical aneurysm with no clot.

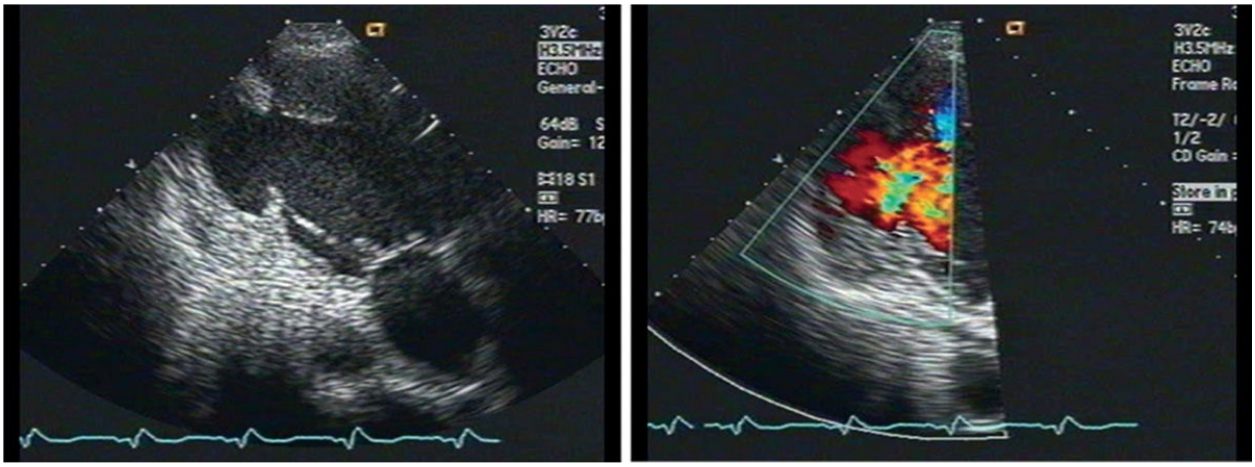

FIGURE 13.13 Apical three-chamber view **(left)** obtained from transthoracic echocardiogram revealing a large left ventricular aneurysm, enhanced with color flow Doppler **right)** establishing an area of

communication between the normal left ventricle and the aneurysmal portion.

Although the size of an aneurysm varies widely, most are within 1 to 8 cm in diameter. The wall of the aneurysm typically consists of a hybrid of necrotic myocardium and white fibrous scar tissue. This wall is extremely thin and delicate and may calcify over an extended period of time. Of note, it is imperative to distinguish between an LVA and a pseudoaneurysm, which is characterized by a narrow neck and a distinct "shelf-like" opening.

The endocardial surface is smooth and nontrabeculated. The aneurysm is filled with organized thrombus in more than 50% of cases, which has the tendency to calcify over time.[44] Dense adhesions between the aneurysm and the overlying pericardium are common phenomena. On a molecular level, initially, the ventricular wall is characterized by myocardial muscle necrosis and a concomitant intense inflammatory reaction, which eventually is replaced with scar tissue formation, and a mature aneurysm consists mostly of hyalinized fibrous tissue. The "border zone," that is, the layer between the aneurysm and the healthy myocardium, is characterized by patchy fibrosis and abnormal alignment of the muscle fibers.

CLINICAL PRESENTATION

A prior history of AMI is almost universally present in patients with an LVA that is not associated with other etiologies such as hypertrophic cardiomyopathy or Chagas disease. The physical examination may reveal one or more of the following findings; however, it may prove to be somewhat difficult to diagnose an LVA by physical examination because the findings are nonspecific.

- Cardiac enlargement with a diffuse apical impulse located to the left of the midclavicular line.
- An area of dyskinesis can occasionally be appreciated with palpation of the left lateral chest wall, in the area of the apex and anterior wall of the left ventricle.
- A third and/or fourth heart sound (S3 or S4) is often heard, which represents the onset of blood flow into a dilated and stiffened LV chamber.
- A MR-like systolic murmur may be appreciated because of the distortion of LV geometry that results in the absence of leaflet apposition, papillary muscle dysfunction, and/or annular dilatation.

The presence of an LVA should be suspected when a patient with a large, predominantly, anterior AMI develops one of the aforementioned physical examination findings. The ECG usually reveals evidence of a large AMI and there may be persistent ST-segment elevation; however, this finding is usually the result of a large area of scar and does not necessarily imply an aneurysm **(Figure 13.14)**.

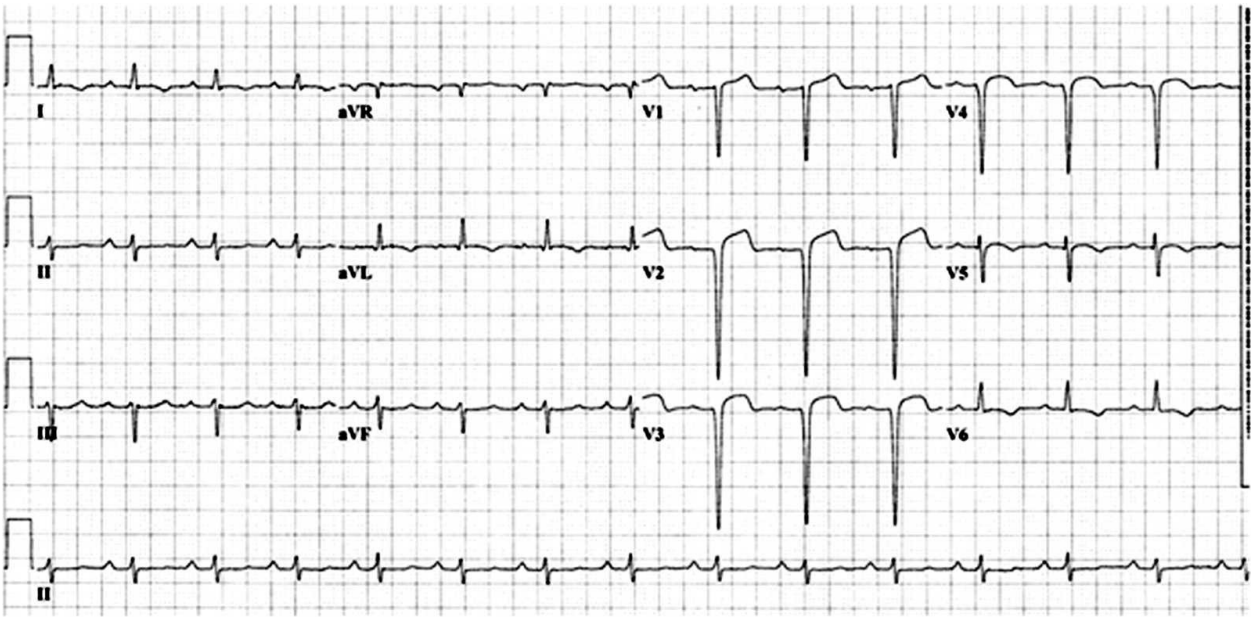

FIGURE 13.14 Electrocardiogram of a patient with a true left ventricular aneurysm displaying persistent ST elevation with Q waves in V1 through V4.

Although limited and rarely used today, chest radiography may aid in the diagnosis of an LVA; however, given the extreme limitations of chest radiography, the diagnosis is definitively made via two-dimensional echocardiography. A simple definition of an LVA on echocardiography imaging is the presence of a dyskinetic wall motion abnormality with the feature of diastolic deformity.[45, 46] TTE is most often used and has globally emerged as the diagnostic tool of choice. Even before the diagnosis is made, there are a number of serious complications that can result from an LVA, such as heart failure, ventricular arrhythmias, and thrombus formation.

During ventricular systole, the paradoxical bulging of the aneurysmal segment results in “stealing” part of the LV stroke volume, resulting in decreasing cardiac output and predisposing to LV volume overload. LV dilatation and increase in wall stiffness can increase oxygen demand. In the setting of underlying coronary

artery disease, the increase in oxygen demand may lead to myocardial ischemia with subsequent angina. The end result of long-standing volume overload and prolonged ischemia is a globally dilated, failing left ventricle. Heart failure symptoms are common.

The myocardial scarring present in LVA is a substrate for ventricular arrhythmias. Two mechanisms contribute to this possible deadly outcome. Firstly, myocardial ischemia and increased myocardial stretch can lead to enhanced cardiac automaticity. Secondly, the myocardium located at the border zone is made up of a mix of fibrotic tissue, inflammatory cells, and damaged muscle fibers, which is a suitable substrate for a reentrant tachycardia. Ventricular arrhythmias often result in sudden cardiac death.

As previously mentioned, a mural thrombus is identified in autopsy or surgery in >50% of patients with LVA. A possible fatal consequence of thrombus formation is possible systemic embolization, which can result in stroke, ischemic colitis, ischemic limbs, and a variety of other disastrous complications.

It is important to note that true LVAs may enlarge over time. However, unlike false aneurysms, a true LVA rarely ruptures because of the dense fibrosis that comprises the walls.[47, 48]

TREATMENT

Mild-to-moderate size asymptomatic aneurysms can be safely treated medically with an anticipated 5-year survival of up to 90%. Therapy includes reduction of afterload via angiotensin-converting enzyme inhibitors, nitrates, and anticoagulation (in the setting of significant LV dysfunction or evidence of thrombus formation). The optimal approach to the patient with a large, asymptomatic LVA remains a clinical dilemma. Concomitant repair of the aneurysm has been advocated when CABG or valve surgery is performed. In the absence of such indications for surgery, these patients should otherwise be treated with the same regimen as those with a small LVA; they should also be followed up closely for progressive LV dilation. Similar to other settings of chronic volume overload, a progressive increase in LV diameter and/or decrease in LV ejection fraction are a clear indication for surgery even before the presence of advanced heart failure or other symptoms.

As per the 2004 American College of Cardiology/American Heart Association (ACC/AHA) guidelines on ST-elevation MI, aneurysmectomy, accompanied by CABG, in patients with an LVA who have repetitive ventricular arrhythmias and/or heart failure unresponsive to medical and catheter-based therapy, is a

Class IIa recommendation and is therefore reasonable.[49] Surgical repair should be considered for symptomatic patients with either akinetic or dyskinetic segments, because they represent variants in the spectrum of the same disease. Surgical repair of an LVA is very effective, and results in a significant improvement in patient survival, symptoms, and functional class compared to medical treatment.[50–52] Furthermore, a marked decrease in surgical mortality has been achieved in the past 25 years. Endocardial mapping with subsequent endocardial resection and possible cryoablation are performed in patients with malignant ventricular arrhythmias.

LEFT VENTRICULAR PSEUDOANEURYSM

A left ventricular pseudoaneurysm (LVPA) or false aneurysm is a less common form of a ventricular aneurysm present in <1% of patients post MI. It is briefly discussed here.

PATHOPHYSIOLOGY

An LVPA forms when cardiac rupture is more or less contained by adherent pericardium or scar tissue. Unlike a true aneurysm, an LVPA is devoid of endocardium or myocardium and because these aneurysms are prone to rupture, a quick and accurate diagnosis is of extreme importance. Unlike a true LVA whereby the walls consist of dense fibrous tissue with excellent tensile strength, the wall of an LVPA is comprised of thrombus and varying portions of the epicardium and parietal pericardium. It is the result of an AMI (typically an inferior or posterolateral wall AMI) with myocardial rupture and hemorrhage into the pericardial space, becoming progressively compressive. Cardiac tamponade occurs, thereby preventing further hemorrhage into the pericardium. Over time, thrombus organizes with overall poor structural integrity, and thus is prone to inevitable rupture, which is a fatal event.[53]

CLINICAL PRESENTATION

It has been suggested that the most frequent symptoms associated with LVPA include chest pain and dyspnea. However, often symptoms can be somewhat vague and nonspecific. The other symptomatology includes that of tamponade, heart failure, syncope, arrhythmia, or systemic embolism. Cardiac murmurs are

present in about two-thirds of patients. The murmur is often indistinguishable from that of MR. Almost all patients have some degree of underlying ECG changes, which include ST-segment elevation and nonspecific T-wave changes. Evidence of a mass on chest X-ray is seen in more than one-half of patients; however, as previously mentioned, this is not specific or sensitive for the diagnosis of an LVPA.[54, 55]

The most reliable method for diagnosis of an LVPA is via echocardiography. A TTE is a reasonable first step, but a definitive diagnosis is made in only a fraction of patients. Echocardiography can usually distinguish a pseudoaneurysm from a true aneurysm by the appearance of the connection between the aneurysm and ventricular cavity. LVPAs have a narrow neck, typically less than 40% of the maximal aneurysm diameter, which causes an abrupt interruption in the ventricular wall contour (**Figures 13.15** and **13.16**). In contrast, true aneurysms are nearly as wide at the neck as they are at the apex. **Figures 13.17** compares true aneurysms versus false/pseudoaneurysms.

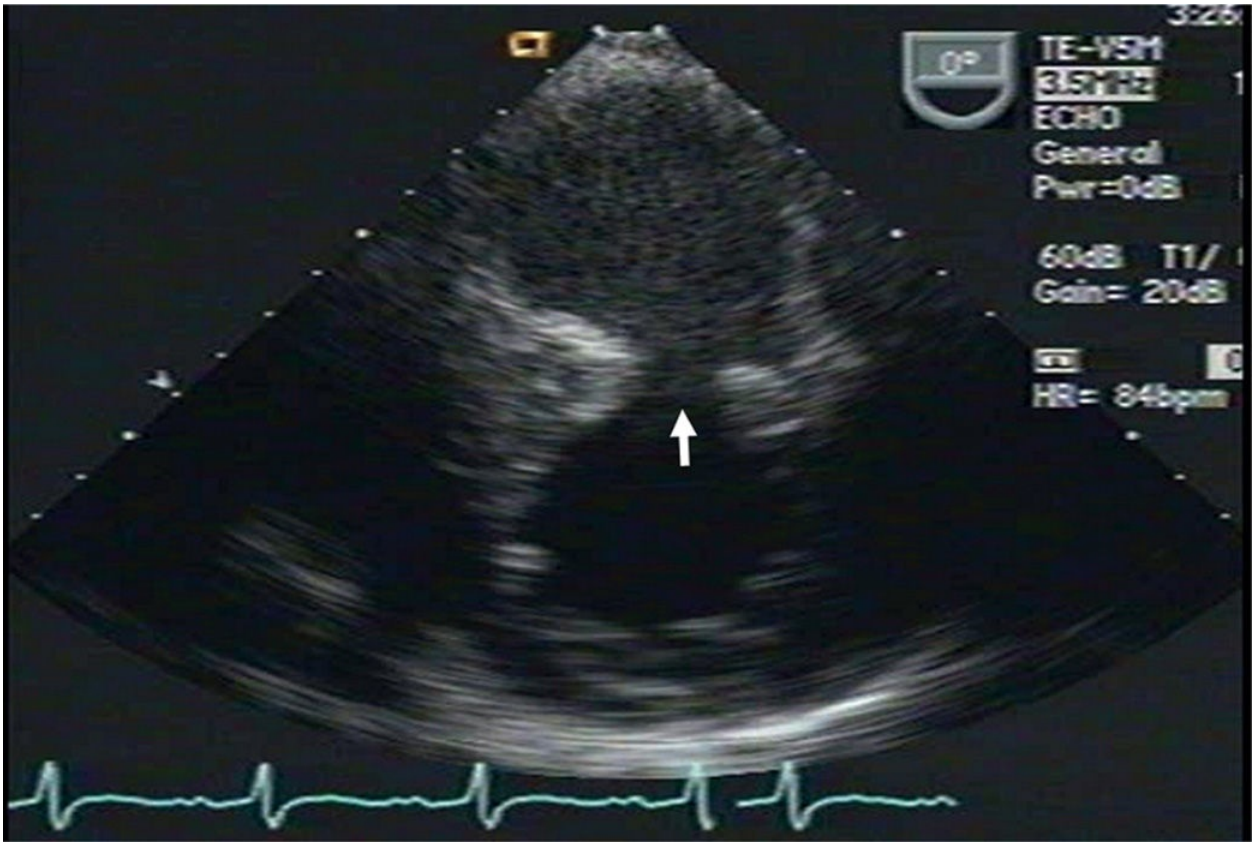

FIGURE 13.15 Short-axis view of the left ventricle (*lower cavity*) during transesophageal echocardiography. Large pseudoaneurysm (*higher cavity*). Notice the narrow "bottleneck" opening (*arrow*).

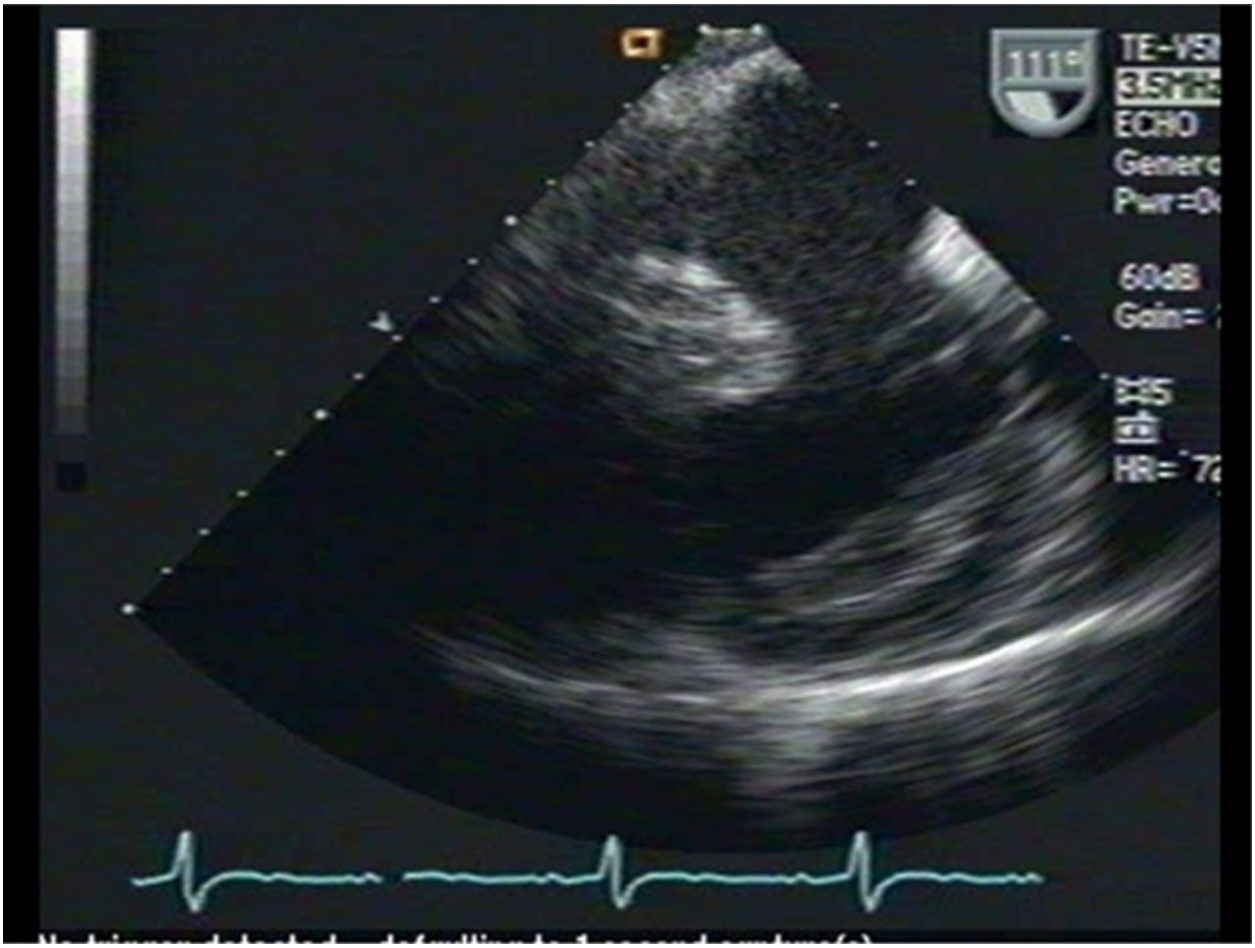

FIGURE 13.16 Short-axis view from transesophageal echocardiogram depicting a large pseudoaneurysm (*higher cavity*). Notice the narrow “shelf-like” opening into the aneurysmal cavity.

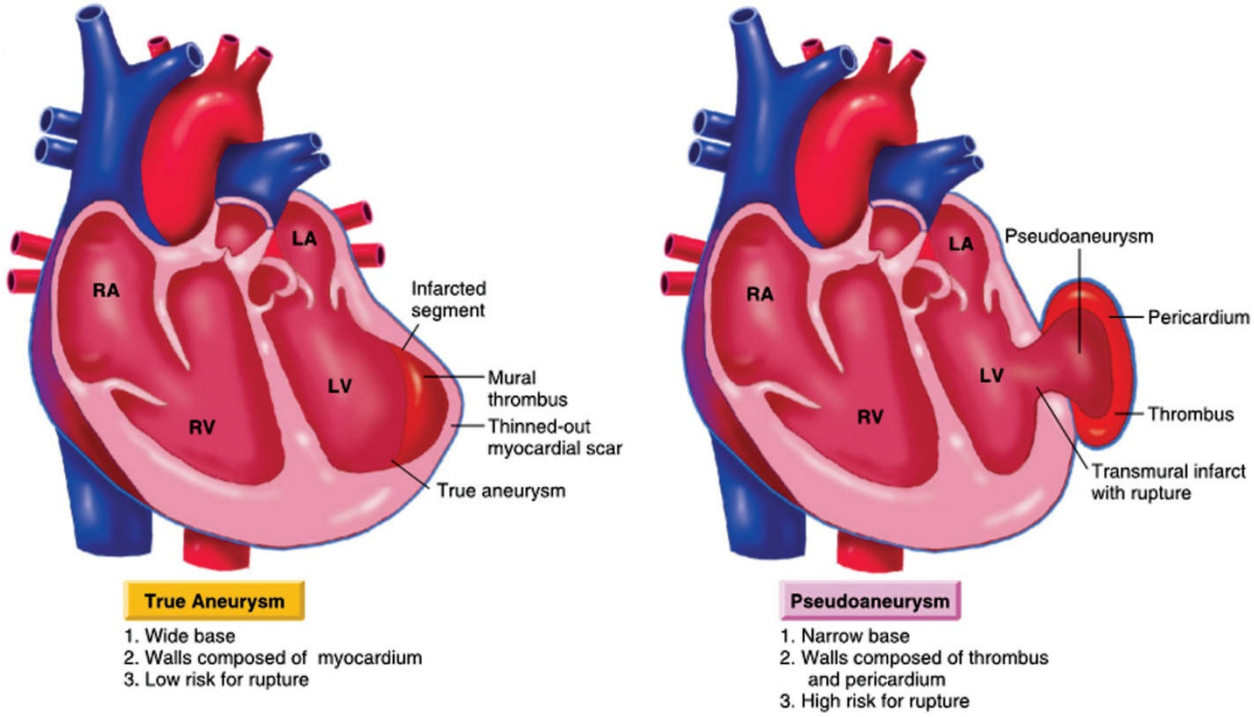

FIGURE 13.17 Differences between a pseudoaneurysm and a true aneurysm. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (Adapted from Mann DL, Zipes DP, Libby P, Bonow RO: *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine.* Philadelphia, PA: Elsevier, 2015; and from Shah PK. Complications of acute myocardial infarction. In: Parley W, Chatterjee K, eds. *Cardiology*. Philadelphia, PA: JB Lippincott; 1987.)

TREATMENT

Untreated LVPAs have a 30% to 45% risk of rupture and, with medical therapy, a mortality of almost 50%. Thus, surgery is the preferred therapeutic option. With current techniques, the perioperative mortality is less than 10%, although the risk is greater among patients with severe MR requiring concomitant mitral valve replacement.

LEFT VENTRICULAR THROMBUS

A mural LV thrombus is a common sequela of an AMI and most commonly develops in the presence of a large infarction. Thrombi are prone to originate in regions of stasis; they are most commonly noted to occur in the apex but may also occur in lateral and inferior aneurysms. With extensive transmural infarction, mural thrombi may overlie the infarcted myocardium. Before current conventional medical therapy, the incidence ranged between 25% and 40%.[54]

The initiation of heparin and perhaps thrombolysis can reduce the development of an LV thrombus by 50%. The major risk of a thrombus is subsequent distal embolization, which is highest during the first 2 weeks following an AMI with eventual reduction of risk by 6 to 8 weeks. This is attributed to a relative endothelialization of the thrombus with reduction in its embolic potential. Echocardiography has high sensitivity (95%) and high specificity (85%) for identification of an LV thrombus and has emerged as the diagnostic modality of choice. Characteristically, a thrombus has a nonhomogeneous echo density with a margin distinct from the underlying wall, which is akinetic to dyskinetic (**Figures 13.18** and **13.19**).[56] A thrombus is more likely to occur following an AMI in the LAD artery distribution (up to 33%) versus the right coronary or circumflex (<1%) coronary arteries.

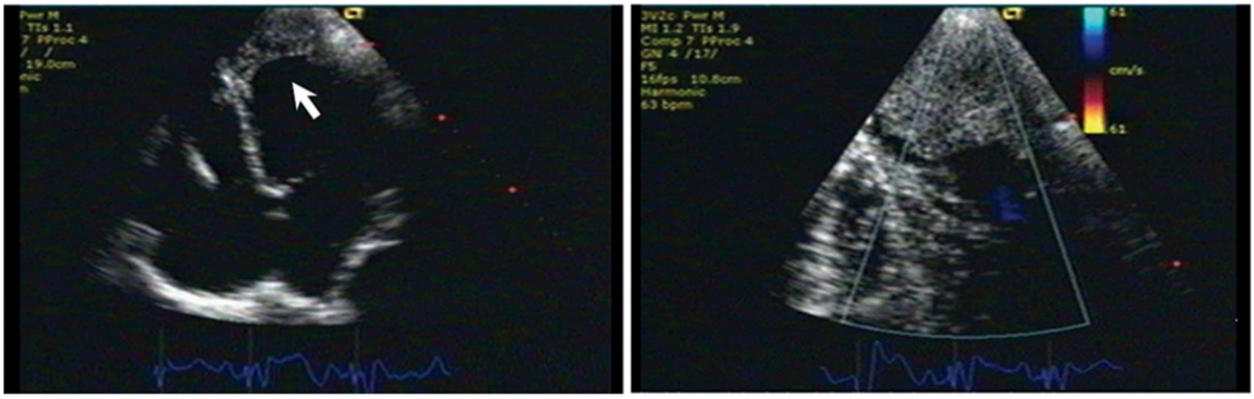

FIGURE 13.18 Apical four-chamber views of a transthoracic echocardiogram from a 74-year-old patient 3 months following AMI (*top*). Notice the large protruding apical thrombus (*arrow*). Color flow imaging (*bottom*) may be used to demonstrate abnormal flow patterns. AMI, acute myocardial infarction.

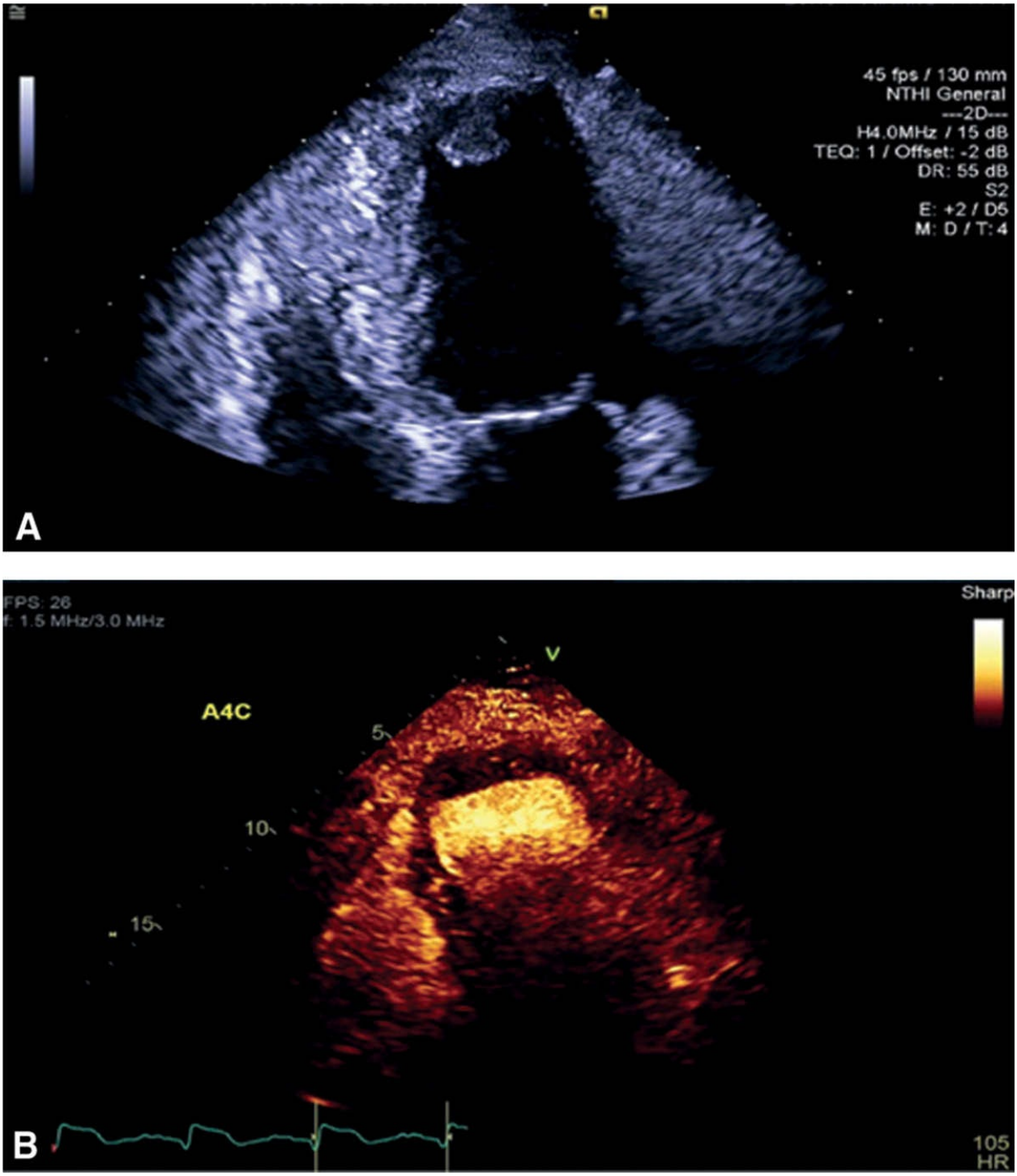

FIGURE 13.19 A, Apical four-chamber view of a transthoracic echocardiogram demonstrating a large left ventricular apical thrombus. B, Injection of an echo-contrast agent delineates the linear appearance of this large apical thrombus.

Current data on the correct treatment of LV thrombi is lacking. There are no large-scale trials that direct treatment; however, it is generally recommended that

patients who have an apical clot will receive full anticoagulation with traditional anticoagulant therapy, that is, warfarin. They should be initiated with heparin and converted to full-dose warfarin for at least 3 months with a goal international normalized ratio between 2 and 3.[1]

CONCLUSION

As outlined, mechanical complications of an AMI are important to recognize, to diagnose, and, especially, to treat. Recognizing the most important signs and symptoms should prompt an immediate echocardiogram and, in most cases, this may lead to surgical intervention. Most therapies carry with them a poor prognosis, but surgery is clearly a better option with improved survival over medical therapy alone. Physicians in cardiac care units (CCUs) must grasp all of these concepts to provide proper medical care.

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Patient and Family Information for: MECHANICAL COMPLICATIONS OF MYOCARDIAL INFARCTION

For decades, heart disease has consistently been the leading killer in the world. When a family member or loved one has a heart attack, it can be a terrifying experience for everyone involved. Most of the time, everything goes smoothly, and that family member or loved one walks out of the hospital with a new outlook on life. However, there are occasions when a patient's condition can rapidly deteriorate and circumstances drastically change. These potential complications can happen at home, in transit to the hospital, in the emergency room, or even in the CCU. An understanding of the complications that go hand in hand with an acute heart attack is crucial for comprehending the nature of the disease.

The heart is the most important muscle in the human body. Like all muscles, it needs oxygen to live. However, unlike all muscles, it continuously beats around 100,000 times a day. A heart attack involves the blockage of blood flow to that muscle; this results in the cutting off its oxygen supply, for all intents and purposes, suffocating the muscle. Without oxygen, the heart muscle will die. The intense chest pain that a patient senses during an acute heart attack is due to this muscle death. Relieving that blockage will restore blood flow to the damaged muscle, replenish its oxygen supply, and hopefully allow it to live. The timely nature of this intervention is paramount to the heart's survival.

Prompt recognition and initiation of therapy for an acute heart attack is the most important factor in that patient's survival. The longer the heart muscle goes without oxygen, the faster it dies, and the worse the prognosis. The signs and symptoms of a heart attack include a left-sided or central chest pressure accompanied by any combination of shortness of breath, nausea, vomiting,

sweating, and left arm or neck pain. The moment these symptoms commence, immediate medical attention should be sought.

Doctors have various methods to relieve the obstruction, including medications and direct intervention in the blocked vessel. Medical therapy involves the administration of an IV medication called a thrombolytic. This medicine will rapidly break up the blood clot in the coronary artery that has been blocked, thereby thwarting the heart attack. Interventional therapy involves the placement a tube or “catheter” into one of several arteries in the arms or the legs that lead to the heart. These catheters are then advanced to insert directly into the coronary arteries and through the use of a moving X-ray, the thrombosis can be directly visualized and extracted. Subsequently, a little piece of hollow metal, called a “stent,” can be inserted in the artery and allow blood to freely flow to the dying heart muscle. The faster the therapy is delivered, the better. There are times when a substantial amount of irreversible damage has been done, causing the muscle to die and possibly tear, leading to life-threatening complications. There are other times when the muscle does not tear, but simply dies, and causes more chronic complications. In this chapter we discuss the disastrous complications of a heart attack.

When the heart muscle dies, it can eventually tear and cause sudden clinical deterioration and possibly death. If there is a delay in a patient’s presentation to the emergency room, therapy cannot be initiated and the heart muscle will die. This delay can be from hours to days. If there is no delay, and therapy is administered immediately, there is always a possibility that the therapy may not be completely successful, the artery will remain blocked, and the heart muscle will die anyway. This is an unfortunate reality because not all treatments are successful. On these rare occasions, the area of the heart muscle between the dead and viable tissue will completely sever. This will result in free communication between two areas of the heart, causing brisk bleeding and inevitable death. There are three such scenarios that must be promptly recognized because surgical therapy usually provides the only means for survival. These three scenarios include ventricular free wall rupture, interventricular septal rupture, and papillary muscle rupture.

It is not as important to know the intricate details of these complications as it is important to understand their deadly potential. Any sudden deterioration in clinical condition should prompt suspicion of myocardial rupture. Development of increased chest pain or shortness of breath accompanied by a new murmur on physical examination, an accelerated heart rate, and a drop in blood pressure

must be followed by an immediate echocardiogram, or ultrasound of the heart. This will provide visualization of the cardiac muscle and diagnosis of a myocardial tear. If the situation arises, IV medications can be administered to temporarily stabilize the patient, but emergent surgical intervention is paramount to provide any chance of survival.

Emergent surgery should be performed within hours of recognition of the rupture. IV medications will support the patient's blood pressure and heart rate until the operating room is ready for patient transfer. The surgical procedure will involve opening the chest wall, directly visualizing the heart, and repairing the torn tissue. Often, bypass of any blocked arteries will accompany repair of the damaged cardiac muscle. The procedure will take many hours to complete; and even if successful, the probability of eventual death is still very high. When the ruptured myocardium is repaired and the bypass complete, the patient still has a long and dangerous road ahead.

The postoperative period is every bit as important as the procedure itself. Making it out of the operating room does not mean that long-term survival is guaranteed. There are many factors such as age and comorbidities that complicate both the surgical procedure and the recovery period. The older a person is, the more unlikely it is for the person to survive such a difficult surgery and the more difficult it is to recover. Coexisting medical conditions such as asthma, emphysema, kidney disease, cancer, and diabetes, among others, all increase mortality. Friends and family must be realistic about the severity of the situation and expectations for survival. Most studies quote far less than 50% survival, with the actual numbers being less than 25%.

The left ventricle is the most important of the four heart chambers for survival. Most of what has been discussed involves damage to this all important chamber. The right ventricle is a less muscular part of the heart that can also be damaged during a heart attack. It is important to recognize RV injury, because its treatment is very different from that of garden variety LV injury. There are specific clinical signs and ECG findings that will lead to the diagnosis of an RVI. When present, a physician must be careful not to administer certain medications, such as nitroglycerin or diuretics, because they can lead to clinical deterioration. The astute medical professional can easily diagnose this situation and provide appropriate therapy. As with all heart attacks, restoring blood flow to the right ventricle will prevent poor clinical outcomes and improve survival. Surgical intervention is generally not necessary and if the patient survives to discharge, outlook is favorable.

Chronic complications of a heart attack are probably more common than the acute ones. Depending on the timing of the revascularization, a certain amount of heart muscle invariably dies. As described earlier, the longer the muscle goes without oxygen, the more of it dies. The most common phrase used is: “time is muscle.” Patients who suffer large heart attacks and do not receive adequate therapy lose large amounts of muscle forever. The heart weakens, blood does not get pumped forward as it should, and over the following weeks an aneurysm can form. An aneurysm is described as a weakening of the muscle to the point that it forms a pocket within or outside the walls of the heart. To either side of the aneurysm is living tissue, and within the aneurysm is dead tissue. Aneurysms are divided into two categories that require different therapies: true aneurysms and pseudoaneurysms.

The more common and less dangerous of the two types of aneurysms are the true aneurysms. The entire aneurysm forms a pocket that is made of dead cardiac tissue. An indentation is created in the myocardium with a wide neck that contains the aneurysm. True aneurysms are entirely made of dead myocardial tissue. Because the muscle does not contract, there is invariably stasis of blood flow within the pocket, making it prone to forming blood clots. Often, a piece of the blood clot can break off and cause many complications including stroke. True aneurysms should be treated with the same aggressive medical therapy that all heart attack patients receive. This includes but is not limited to beta-blockers, angiotensin-converting enzyme inhibitors, and aspirin. If a blood clot is present, patients should be administered blood thinners to prevent against stroke. Rarely, surgical intervention is necessary to excise the aneurysm when there is evidence of deadly arrhythmias that are resistant to medical therapy.

Pseudoaneurysms are extremely rare and are very dangerous. A pseudoaneurysm represents a contained rupture of the cardiac tissue. As has been described previously, tearing of the heart muscle results in brisk bleeding and, often, death. Occasionally, this bleeding can be contained by the thin layer of tissue surrounding the heart called the pericardium. The pericardium is a rigid layer of tissue that encases the heart and at times will seal off a myocardial rupture, thereby preventing certain death. A pseudoaneurysm forms when the pericardium bubbles outward and contains a rupture during a heart attack.

Instead of the wide neck seen in true aneurysms, a pseudoaneurysm has a narrow neck that communicates with the left ventricle. There is no dead myocardium in the pseudoaneurysm because it is entirely made of pericardium. Invariably, the pocket of the pseudoaneurysm contains a blood clot, because

there is complete stasis of blood flow. A pseudoaneurysm is prone to rupture because it consists of only the thin pericardium that has sealed off the prior rupture. When demonstrated by echocardiogram or computed tomography scan, surgical consultation is appropriate. Surgical excision of the pseudoaneurysm is the only treatment that can be offered to prevent rupture and certain death.

Both acute and chronic complications of a heart attack have become less common as medical therapy has advanced. The development of thrombolytics and interventional procedures have improved survival and drastically reduced the number of disastrous complications that can occur. In the unfortunate cases when they do occur, advancements in surgical technology and techniques have further improved the chances of survival. Even with all these advancements in therapy, however, prompt recognition and timely diagnosis can be the difference between life and death. Survival to hospital discharge is not certain when these complications occur and family members must realize that there is a long road ahead.

When a patient does survive a complication of an AMI, he or she must realize that great care must be taken to improve the likelihood of long-term survival. Outpatient follow-up with a cardiologist, surgeon, and medical doctor should be in place before discharge. The patient will invariably be on a new regimen of medications that can be extremely complicated. Survivors will often need a significant amount of rehabilitation before they can return to their pre–heart attack state. Social support and family encouragement both increase the likelihood of recovery. Patients should not leave the hospital without a strict understanding of what medications they are to take and who they are to follow up with. A structured regimen of medication compliance, physician follow-up, and cardiac rehabilitation can turn a life-threatening situation into a rewarding experience for patients, families, and all medical professionals involved.

14

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Cardiogenic Shock Complicating Acute Myocardial Infarction

INTRODUCTION

Over the past several decades, both the incidence of acute myocardial infarction (AMI) and the mortality rate for AMI patients have shown a steady decline because of multiple factors, including effective risk factor modification as well as improved medical, surgical, and percutaneous therapies for coronary artery disease.[1–3] The incidence of cardiogenic shock complicating AMI, however, remains unaffected, and the mortality resulting from this condition remains high and is a leading cause of death among patients hospitalized for AMI.[4, 5]

Myocardial infarction–related cardiogenic shock is a heterogeneous clinical entity in both etiology and presentation but is most commonly the result of acute left ventricular (LV) dysfunction caused by extensive cardiac muscle necrosis in the setting of an ST elevation myocardial infarction (STEMI). As the stroke volume acutely declines, the heart attempts to maintain cardiac output by increasing heart rate as a compensatory response. Once this compensatory mechanism becomes inadequate, tissue hypoperfusion ensues, leading to a systemic inflammatory response, multiorgan dysfunction, and eventually circulatory collapse. This may be further precipitated by a vasodilatory response of the peripheral circulatory system, resembling a systemic inflammatory state.

Early signs of impending cardiovascular collapse may be evident on arrival at the hospital, but the majority of patients will present in a well-compensated state and progress to shock only after clinical presentation.[6]

In part because of the heterogeneity of its etiologies and manifestations, there is no universally accepted definition of cardiogenic shock. The SHOCK (SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK) trial required patients to meet both clinical criteria of cardiogenic shock (sustained hypotension and end-organ hypoperfusion) and either hemodynamic confirmation with a pulmonary artery catheter or radiographic confirmation of pulmonary edema in the setting of anterior wall infarction (**Table 14.1**: SHOCK inclusion criteria for which patients should be revascularized early).[7] It is important to note that these are stringent criteria set for the purposes of a randomized control trial and that in clinical practice the myocardial dysfunction associated with ischemia exists along a spectrum: patients may meet only some of these criteria at the time of their initial evaluation.[8] In the setting of physical and biochemical findings of peripheral organ hypoperfusion despite adequate intravascular volume status, the clinician should suspect cardiogenic shock by the bedside. Recognition of early signs of falling cardiac output may facilitate earlier and more aggressive treatment of patients with a more grave prognosis (**Table 14.2**: Killip Classification, which outlines the early signs of decompensating cardiac function).[9]

TABLE 14.1 Shock Inclusion Criteria

INCLUSION CRITERIA	PARAMETERS
Ischemic criteria	ST-segment elevation, Q-wave infarction, new left bundle-branch block, or posterior infarction with anterior ST-segment depression
Clinical Criteria	Hypotension: SBP <90 mm Hg for at least 30 min or the need for supportive measures to maintain blood pressure End-organ hypoperfusion: cool extremities or urine output < 30 mL/h despite a heart rate of ≥ 60 beats/min
Hemodynamic criteria	Cardiac index ≤ 2.2 L/min/m^2, pulmonary capillary wedge pressure ≥ 15 mm Hg (not necessary if radiographic criteria are met)
Radiographic criteria	Pulmonary congestion on chest radiograph in setting of anterior wall myocardial infarction

SBP, systolic blood pressure.

TABLE 14.2 Killip Classification

KILLIP CLASS	DESCRIPTION
I	No evidence of heart failure
II	Mild heart failure: rales over one-third or less of posterior lung fields, systolic blood pressure of 90 mm Hg or higher
III	Pulmonary edema involving more than one-third of lung fields, systolic blood pressure of 90 mm Hg or higher
IV	Cardiogenic shock: extensive rales, systolic blood pressure less than 90 mm Hg

INCIDENCE

Cardiogenic shock remains an infrequent but life-threatening complication of AMI. Evidence of shock is either present on arrival or develops after admission in 4% to 10% of patients hospitalized for ST elevation AMI.[5, 10] There is significant regional variation in temporal trends in incidence over time; it remains unclear to what extent this is driven by a changing burden of disease versus being reflective of changing definitions and evolving patterns of coding and classification.[11]

ETIOLOGY AND PATHOPHYSIOLOGY

Cardiac myocytes are among the most aerobically active cells in the body and are dependent on a blood supply commensurate with their relatively high oxygen demand.[12] When this relationship is disrupted through either acute plaque rupture (type 1 myocardial infarction) or through a mismatch in supply and demand (type 2), myocyte contractility is compromised, and the heart attempts to compensate through other mechanisms. When these mechanisms are inadequate, cardiac output begins to fall, and a downward spiral toward cardiogenic shock begins (**Figure 14.1**).[13]

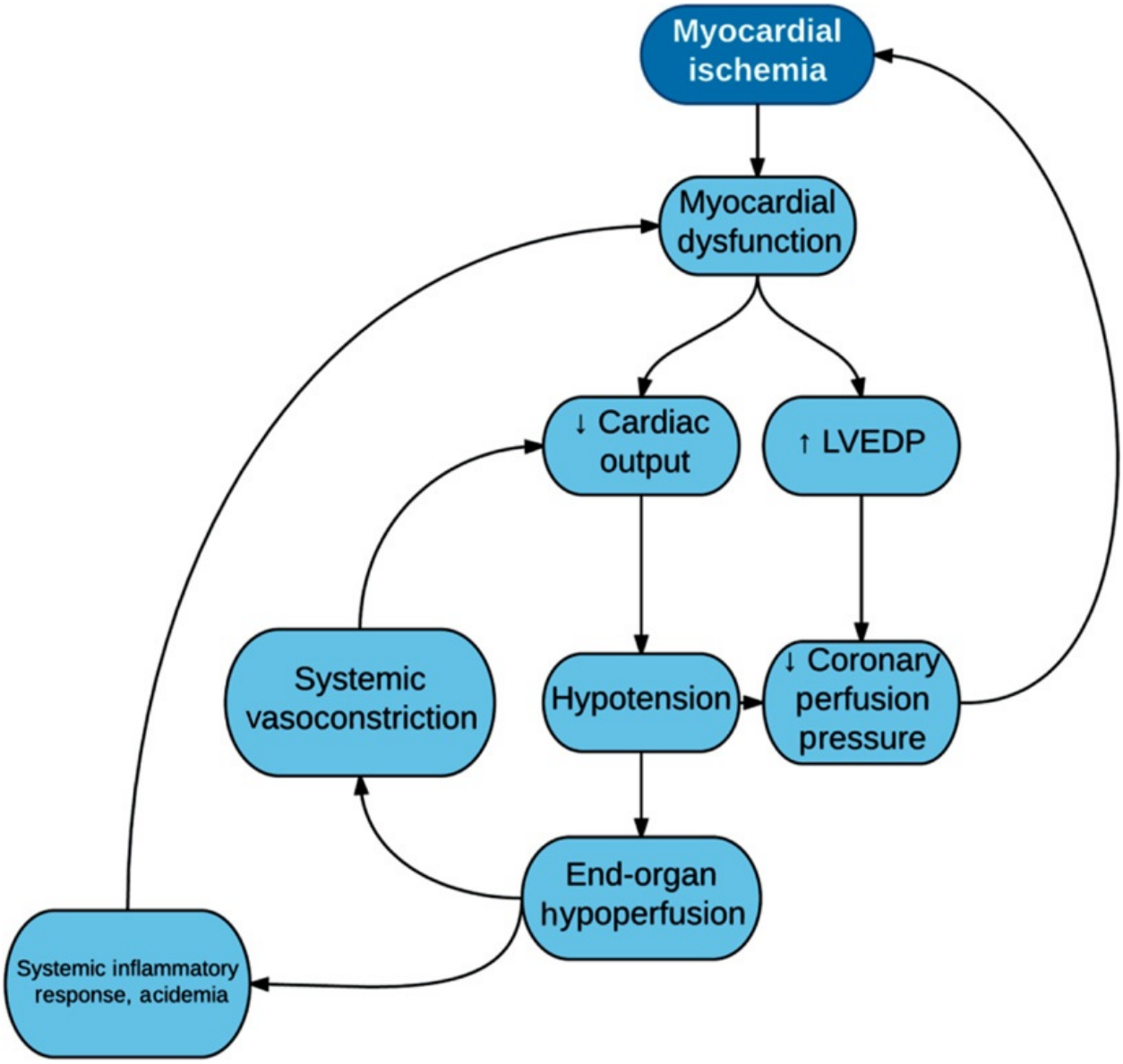

FIGURE 14.1 The hemodynamic and biochemical decompensation cascade of cardiogenic shock. LVEDP, left ventricular end diastolic pressure.

Coronary perfusion occurs primarily during diastole and is dependent on the gradient between the proximal aortic pressure and the left ventricular end diastolic pressure (LVEDP). As cardiac output begins to fall, LVEDP begins to rise and diastolic pressures begin to decrease, further reducing the coronary perfusion gradient in the culprit vessel as well as the coronary circulation as a whole. This can result in remote ischemia in the noninfarct regions and further compromises cardiac output, creating a vicious spiral that culminates in frank circulatory collapse.

Beyond the immediate hemodynamic effects, a similarly injurious biochemical cascade begins. The fall in cardiac output leads to a reflexive activation of the sympathetic nervous system and an ensuant catecholamine surge; renal hypoperfusion also activates the renin–angiotensin–aldosterone axis. The resulting increase in heart rate and vasoconstriction lead to an increase in myocardial oxygen demand through increased wall stress, heart rate, and contractility.

In parallel to this, tissue destruction related to both local myocardial ischemia and systemic end-organ damage leads to acidemia and the release of inflammatory cytokines, including IL-6; these trigger an increase in nitric oxide synthase production in vascular smooth muscle cells. This vasodilator response may be a dominant feature in a proportion of patients with cardiogenic shock. Both nitric oxide and acidemia itself may act as negative inotropes and exacerbate an acute decline in cardiac function.[14, 15]

In addition to the direct myocardial dysfunction and sequelae described above, AMI may also result from several mechanical complications, including mitral regurgitation (caused by acute LV dilatation or papillary muscle ischemia/rupture), ventricular septal rupture, or ventricular free wall rupture. Although relatively uncommon, early comprehensive bedside echocardiography is critical to rule out these complications because they portend a worse prognosis and mandate consideration for surgical intervention.

It is important to maintain a wide differential in patients with hemodynamic instability to ensure that syndromes with similar presentations such as underresuscitated sepsis or hemorrhagic shock are not missed. Noncoronary cardiovascular emergencies such as acute thoracic aortic dissection, pulmonary embolism, myocarditis/pericarditis, tension pneumothorax, and tamponade should also be considered and ruled out with further testing if necessary.

MANAGEMENT

DIAGNOSIS

The cornerstone of management of cardiogenic shock is prompt recognition and accurate diagnosis of the dominant mechanism affecting circulatory instability. A quick but comprehensive history should be taken with a focus on determination of risk factors, comorbidities, medication use, and allergies (particularly to antiplatelet agents or to contrast medium). A focused physical exam should also

be performed to screen for mechanical or valvular etiologies of shock (eg, a murmur suggestive of ventricular septal rupture or of acute mitral regurgitation) as well as to look for evidence of early cardiogenic shock (including but not limited to impaired mentation, cool extremities, pulmonary congestion, or an elevated jugular venous pressure).

STABILIZATION AND RESUSCITATION

In concurrence with planning for emergent revascularization, a physiologic baseline for the patient should be established and early resuscitative measures initiated. Initial measurements of relevant biomarkers such as cardiac enzymes (troponin T and CK-MB) and lactate should be made. Adequate intravascular volume status should be confirmed clinically if not invasively.

We perform routine invasive hemodynamic monitoring in this patient population. Placement of a pulmonary artery catheter receives a class I recommendation from the American College of Cardiology for patients with respiratory distress or clinical evidence of impaired perfusion in whom the adequacy or excess of intracardiac filling pressures cannot be determined from clinical assessment.[16, 17] A right heart catheter enables continuous monitoring of vital hemodynamic parameters such as cardiac index, cardiac power, and mixed venous oxygen saturations, all of which are strong prognostic outcome variables. It also enables quantification of systemic vascular resistance (SVR), which helps gauge the response of the periphery to the acute myocardial insult. Similarly, invasive arterial blood pressure monitoring is useful to assess the real-time response to vasoactive therapies or when indirect blood pressure monitoring is unreliable.

If hypotension persists despite adequate filling pressures, pharmacologic or mechanical support should be initiated. If a vasopressor is required, norepinephrine should likely be used over dopamine. A recent randomized trial failed to show a significant difference between norepinephrine and dopamine across all subtypes of shock; however, a predefined subgroup analysis of patients with cardiogenic shock showed a significant increase in mortality with dopamine therapy.[18] Vasopressin may also be considered in cases with persistently low SVR.

MECHANICAL CIRCULATORY SUPPORT

Although vasopressor therapy may play a critical role in temporizing a patient

with impending circulatory collapse, this must be weighed against the associated risks, including tachyarrhythmia, peripheral vasoconstriction leading to distal malperfusion, and an increase in myocardial oxygen demand triggering worsening myocardial ischemia. More definitive support can be offered by a mechanical assist device. Although mechanical support is not a new therapy and placement of an intra-aortic balloon pump (IABP) was an integral component of the early revascularization strategy of the SHOCK trial, other durable options have become available in recent years.

Mechanical circulatory support (MCS) devices fall into three primary categories: pulsatile flow devices (IABP), axial continuous-flow devices such as the Impella (with flow from left ventricle to aorta), and centrifugal continuous-flow devices such as the TandemHeart (with flow from left atrium to femoral artery) and venoarterial extracorporeal membrane oxygenation (VA-ECMO). In addition to different positions and modalities of support, each of these devices differs in the extent to which it is able to support the circulation of a patient with worsening left-sided cardiogenic shock (as seen in **Table 14.3**).[19]

TABLE 14.3 Mechanical Circulatory Support Devices

	IABP	IMPELLA	TANDEMHEART	VA-ECMO
Output	0.3–1 L/min	1–5 L/min	2.5–5 L/min	3–7 L/min
Flow/mechanism	Aortic counterpulsation	LV to aorta continuous flow	LA to aorta continuous flow	Venous to arterial continuous flow (multiple configurations possible)
Preload	↓	↓↓	↓↓	↓
Afterload	↓	↓	↑	↑↑
Contraindications	Severe AI Severe PAD	Severe AI, critical AS, mechanical AVR Severe PAD Contraindication to anticoagulation LV thrombus	Severe AI Severe PAD Contraindication to anticoagulation VSD LA thrombus	Severe AI Severe PAD Contraindication to anticoagulation

AI, aortic insufficiency; AS, aortic stenosis; AVR, aortic valve replacement; IABP, intra-aortic balloon pump;; LA, left atrial; LV, left ventricular; PAD, peripheral arterial disease; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VSD, ventricular septal defect..

The IABP is the most familiar, readily available, and easily insertable of the percutaneous MCS options. It is typically inserted transfemorally: arterial access

is obtained via the femoral artery, followed by advancement of a guidewire into the aorta; the balloon pump is subsequently advanced over the wire and placed in the descending aorta distal to the takeoff of the left subclavian artery. Once connected, the balloon pump is controlled either through electrocardiogram (ECG) gating or through pressure transduction to inflate during diastole and actively deflate during systole. This leads to a decrease in afterload because of the active deflation during LV ejection, augmenting cardiac output and reducing myocardial oxygen demand. In addition, the inflation during diastole raises the coronary perfusion pressure. IABP utilization is contraindicated in patients with severe aortic regurgitation, severe peripheral arterial disease, or significant coagulopathy. The most commonly used balloon size shifts approximately 40 mL of blood per inflation and increases cardiac output by up to 1 L/min.[20]

The Impella family of devices is offered in three primary sizes, two of which may be inserted percutaneously (the Impella 2.5 and CP) and one that must be inserted via surgical cutdown (the Impella 5.0). As with the IABP, these are typically inserted transfemorally. Arterial access is obtained via the femoral artery, followed by insertion of a guidewire. An introducer is advanced over the guidewire, and a diagnostic catheter is advanced into the left ventricle; a placement guidewire is then inserted into the apex of the ventricle, and the diagnostic catheter is removed. The Impella is then inserted over this guidewire and positioned so that it sits across the aortic valve with the inlet area 3 to 3.5 cm below the aortic annulus and the outlet in the ascending aorta. It is contraindicated in severe aortic stenosis or regurgitation; severe peripheral arterial disease; and in patients with mechanical aortic valves, LV thrombi, or contraindications to anticoagulation. The degree of support offered varies with device size: The Impella 2.5 offers up to 2.5 L/min of support, the CP offers up to 3.5 L/min, and the Impella 5.0 offers up to 5 L/min.[19] When long-term temporary support is anticipated, the Impella 5.0 is often placed via the axillary approach using a graft.

The TandemHeart device is also typically inserted transfemorally. Venous access is obtained via the femoral vein; a transseptal puncture technique is then used to enter the left atrium, and a guidewire is advanced into the left atrium. An inflow catheter is then inserted over this to access the left atrium, where it drains oxygenated blood back to the centrifugal pump of the TandemHeart. This oxygenated blood is then reintroduced into the circulation in the femoral artery. Contraindications include uncontrolled bleeding diatheses or contraindications to anticoagulation, severe aortic regurgitation, and left atrial thrombi. It offers up to

4.5 L/min of support.

VA-ECMO offers both the capability of biventricular support as well as treatment of concomitant respiratory and circulatory collapse. It is most often inserted in a femoral vein to femoral artery fashion but can be performed in a wide variety of configurations. Regardless of the site of insertion, deoxygenated blood is drained via a venous inflow catheter into a centrifugal pump, oxygenated, and reintroduced into the arterial circulation. Contraindications include severe aortic insufficiency, severe peripheral arterial disease, and contraindications to anticoagulation. It offers the most extensive hemodynamic support of current MCS devices, with up to 7 L/min of flow. When placed peripherally, it is important to place an antegrade cannula to perfuse the distal limb and avoid ischemic complications.

Most recently, percutaneous right ventricular assist devices have emerged as an option for patients with refractory cardiogenic shock in the context of isolated right ventricular failure. Early data suggest promising outcomes, but the technical difficulty of device insertion and relatively good prognosis for isolated right ventricular infarction may limit widespread use.[21]

Although options for MCS have proliferated in recent years and their use is rapidly becoming more widespread, the evidentiary base to support their more frequent use has lagged behind.[22] Trials comparing the newer MCS options versus IABP in cardiogenic shock complicating AMI have largely been underpowered, and although some have shown superiority in improvement of hemodynamic parameters, there is to date little evidence supporting a mortality benefit.[23, 24] Given equivocal clinical benefits and significantly higher cost associated with percutaneous ventricular assist devices (VADs), IABP may remain the preferred first-line choice for cardiogenic shock, with escalation to more support only when necessary.[25]

REVASCULARIZATION

Early diagnostic angiography and subsequent percutaneous or surgical revascularization should be pursued in patients with cardiogenic shock complicating either STEMI or non–ST elevation acute coronary syndrome. This is a class I recommendation for both patient populations and is driven primarily by findings from the SHOCK trial.[7,26,27] The SHOCK trial randomized 302 patients with AMI complicated by cardiogenic shock to either medical therapy alone (with delayed revascularization if needed) or to emergent revascularization

via either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) within 6 hours of randomization. Compared with medical therapy alone, urgent revascularization was associated with a nonsignificant reduction in 30-day all-cause mortality (46.7% vs 56.0%, $P = 0.11$); a lasting survival benefit was conferred with revascularization and was found to be significant at 6 months postrandomization (50.3% vs 63.1%, $P = 0.027$).

The ideal mode and extent of revascularization is an area of ongoing debate. For patients with only one- or two-vessel disease (including isolated left main disease), PCI of the infarct-related artery can be performed at the time of initial angiography.[28] The role for revascularization of nonculprit lesions is less clear; although restoration of blood flow to a wider area of the myocardium has strong theoretical benefits, this must be balanced against the additional procedural risk and contrast exposure inherent to a more extensive coronary intervention. Current guidelines recommend consideration of nonculprit vessel revascularization in the setting of broadly defined hemodynamic instability; although this is supported by observational studies and registry analysis, there is a paucity of randomized data.[29, 30] The ongoing CULPRIT-SHOCK trial will randomize patients with shock complicating AMI to either immediate multivessel PCI or to PCI of the culprit lesion only and should help to narrow this evidence gap.[31]

Emergent CABG offers definitive revascularization to patients with multivessel disease. In addition, prompt cardiopulmonary bypass may rescue a patient with impending circulatory collapse and halt the cycle of worsening end-organ perfusion described earlier. Within the SHOCK trial, CABG was recommended for patients with a left main stenosis of ≥ 50%, two or more total or subtotal occlusions, or stenoses of > 90% in two noninfarct major epicardial vessels. Based on these criteria, approximately 36% of patients in the emergent revascularization arm underwent CABG. Despite being a higher-risk population (higher incidence of diabetes, three-vessel disease, and left main disease), patients treated with CABG had similar rates of survival as those treated with PCI. In clinical practice, however, less than 5% of patients with cardiogenic shock currently receive early CABG.[11] Analysis of the National Cardiovascular Data Registry shows increasing rates of PCI in this setting, with only a small minority referred for CABG over a similar time frame.[32] Percutaneous intervention with its implicit commitment to dual antiplatelet therapy may preclude definitive surgical revascularization in these patients; it should thus be kept in mind that emergent CABG remains the treatment of choice and should be

considered for patients with complex left main disease, severe three-vessel disease not amenable to PCI, or with concurrent mechanical complications of AMI.

PERSISTENT SHOCK

Cardiogenic shock may not resolve despite aggressive revascularization and appropriate initial support. Persistent shock despite revascularization should prompt a reevaluation of the patient's situation with a focused physical examination, consideration of pulmonary artery catheter insertion if not already performed, and repeat echocardiography (**Figure 14.2** outlines the management of persistent shock).

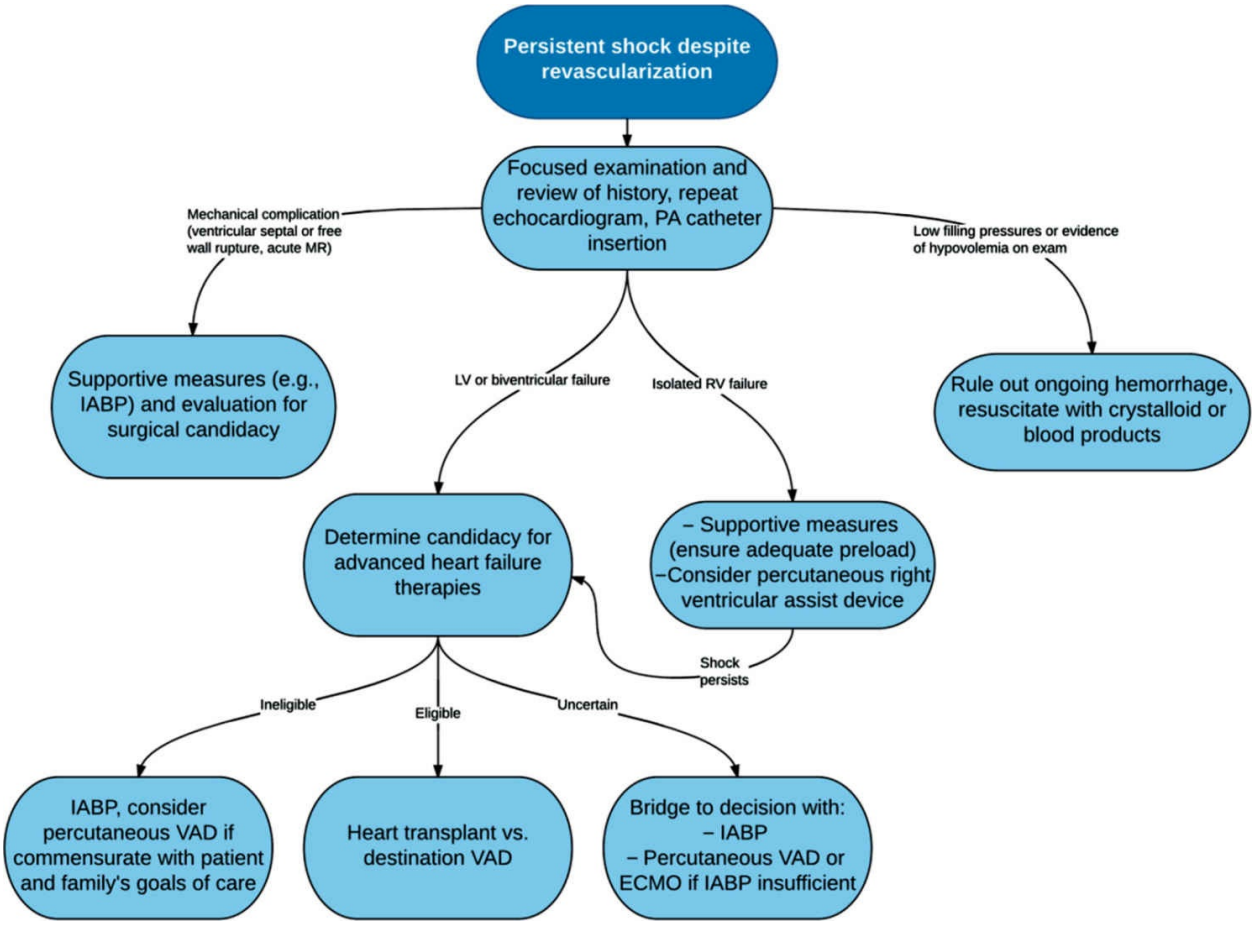

FIGURE 14.2 Management of persistent shock. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LV, left ventricular; MR, mitral regurgitation; PA, pulmonary artery; RV, right ventricular; VAD, ventricular assist device.

If persistent shock resulting from LV failure is confirmed, the patient's eligibility for advanced heart failure therapies (ie, transplantation or destination left ventricular assist device) should be assessed; if they are an appropriate candidate, an expedited evaluation should be initiated. If the patient is ineligible, a percutaneous VAD may still be an option, but this should be discussed in the context of the goals of care of the patient and family. If candidacy is unclear initially, consideration should be given to deploying a bridge-to-decision MCS. In patients with a dismal prognosis, especially those with poor prior functional status, significant comorbidities, especially established renal failure, palliative options should be considered.

DISCHARGE PLANNING

Survivors of cardiogenic shock after AMI will require aggressive medical management for secondary prevention. High-intensity statin therapy, smoking cessation, weight loss, and management of other risk factors should be emphasized before their discharge. All patients should be referred to cardiac rehabilitation at discharge. LV ejection fraction should be assessed both before discharge and again 6 weeks after their acute event to determine eligibility for implantable cardiac defibrillator insertion.

SUMMARY

Despite advances in medical therapy and revascularization techniques for coronary artery disease, cardiogenic shock remains a major source of morbidity and mortality among patients hospitalized with AMI. The mainstay of treatment of cardiogenic shock is early recognition, followed by prompt treatment of the underlying cause (with surgical or percutaneous revascularization) while providing appropriate hemodynamic support.

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Patient and Family Information for: CARDIOGENIC SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION

DEFINITION

Every organ in the body requires a continuous supply of oxygen in order to function properly. Blood, pumped by the heart, is what carries oxygen to all the organs. If the pumping function of the heart becomes weak enough that it is unable to provide sufficient blood flow to the organs, the body begins to shut down, and this is known as *cardiogenic shock*. Many different conditions can cause cardiogenic shock, but the most common one is *myocardial infarction*, also known as a heart attack.

As with the rest of the organs in the body, the human heart also requires a constant supply of oxygen. The *coronary arteries* carry the oxygen-carrying blood to the heart tissue. If this blood flow is interrupted by a blockage in one or more of the coronary arteries, a heart attack results because oxygen cannot get to the portion of the heart that has the blockage. The heart tissue stops functioning properly when blood flow is disrupted, and it can die if it lacks blood flow for long enough. Large heart attacks can cause such significant damage to the heart that it is unable to pump strongly enough for the blood to reach all the organs in sufficient amounts. When this occurs, it is known as cardiogenic shock.

SIGNS AND SYMPTOMS OF CARDIOGENIC SHOCK

Patients with cardiogenic shock will often complain of shortness of breath. Other symptoms such as chest, neck/jaw, or arm pain are also common in patients with cardiogenic shock caused by a heart attack. As a result of the weak condition of the heart, patients with cardiogenic shock will often have low blood pressures and high heart rates. It is also common for patients to be confused, have cool skin, and make only minimal amounts of urine.

MANAGEMENT AND TREATMENT

Cardiogenic shock is a medical emergency, and patients with this condition need urgent care in a critical care unit. When physicians are concerned that cardiogenic shock is present, they will act quickly in an attempt to gather information to see the cause of the shock. Blood work will be obtained to determine the amount of red blood cells in the body, how well the kidneys are functioning, and an ECG, which is a tracing of the heart rhythm, will be done to see if a patient is having a heart attack. Patients will have intravenous (IV) lines placed in their blood vessels so that medicines that act quickly can be given. At times, it may even be necessary to place a large (IV) line, known as a central venous line, so that numerous medications can be given at the same time. Patients will also receive an echocardiogram, which is an ultrasound, to be able to see the pumping function of the heart and to be able to evaluate the heart structures.

Patients who have evidence of an ongoing heart attack need blood flow to the heart restored quickly in order to minimize the amount of heart damage. Some hospitals have the ability to perform cardiac angiography, which is a procedure that allows for identification of the blocked artery. If there is a blockage, using balloons and *stents*, which are devices that prop the blood vessel open, blood flow can be restored to the heart. Some patients have such severe blockages that they require emergency *coronary artery bypass surgery* to restore blood flow or fix defects in the heart caused by the heart attack. If the nearest hospital that performs catheterization is too far away or not available in a timely manner, some patients may be treated with medications designed to dissolve the blood clot in the coronary artery.

Patients who have blood flow restored through one of these methods (or in patients with cardiogenic shock resulting from a cause other than a myocardial infarction) may require a mechanical assist device that improves the heart’s

ability to pump blood to the remainder of the body. The oldest and most commonly used device is an *IABP*. The IABP sits in a large blood vessel near the heart and inflates and deflates in a way that maximizes blood flow to both the heart and the rest of the body. Other types of mechanical assist devices are the Impella, TandemHeart, and ECMO, which are catheter-based heart pumps. The Impella is placed inside the heart chamber and uses a motor to pump the blood from the heart to the arteries that will carry the blood to the rest of the body. TandemHeart is a continuous-flow assist device that sits outside the heart. The pump withdraws oxygenated blood from the left upper chamber of the heart (the left atrium) and propels it by a magnetically driven, six-bladed impeller through the outflow port, and returns it to the arteries. ECMO uses technology derived from heart and lung bypass that allows gas exchange outside the body as well as providing circulatory support. Patients with cardiogenic shock are also often treated with *mechanical ventilators* to assist with breathing, have *pulmonary artery catheters* placed to measure blood pressures, and are given medications that improve the function of the heart.

OUTCOMES/QUALITY OF LIFE

Cardiogenic shock is a serious problem that results in the death of one out of every two patients; however, survival in patients with heart attacks can be improved with the rapid restoration of blood flow to the heart. The amount of time, size, and area of the heart that is without blood flow are the most important factors in determining whether patients will survive heart attacks complicated by cardiogenic shock. Other factors that are critical in determining how well a patient will do is the heart function, age of the patient, kidney function, and other illnesses or comorbidities that the patient has to simultaneously battle.

Although patients with cardiogenic shock are at high risk of death, about half of all patients will survive. Patients who had a normally functioning heart before the event that led to the cardiac shock and who survive their hospitalization have good outcomes and can live for long periods of time. In fact, the vast majority of patients who survive cardiogenic shock and are discharged home will have minimal signs of heart failure one year after their hospitalization.

SUMMARY

Cardiogenic shock is a serious problem that can result in death. The most common cause of cardiogenic shock is a major heart attack. The treatment of patients with heart attacks begins with rapid restoration of blood flow to the heart by either opening up a blocked coronary artery or by bypassing the diseased arteries with surgery. After blood flow is restored, patients are treated supportively with MCS devices and medicines to improve the function of the heart. Despite the high risk of death, patients who were healthy before their illness and can survive the hospitalization have a good chance of resuming a normal life.

15

Richard Ro
Patricia Chavez
Bette Kim

Hypertrophic Cardiomyopathy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is characterized by hypertrophy of the left ventricular (LV) myocardium without ventricular dilatation. It occurs without a secondary cause such as hypertension or systemic disease, and is marked by variable morphologic, clinical, and hemodynamic abnormalities. HCM is one of the great masqueraders of cardiology. It may be mistaken for coronary artery disease as it presents with typical angina chest pain owing to myocardial ischemia in the absence of epicardial coronary stenosis resulting from supply and demand mismatch. It is additionally misleading when HCM presents with ST depressions, T-wave inversions, or pathologic Q waves. It may masquerade as mitral or aortic valve disease with a systolic murmur and heart failure symptoms. It can also be mistaken as pulmonary disease with symptoms of dyspnea on exertion. Tragically, patients with HCM can be asymptomatic until their initial presentation is sudden death, which can occur at rest or on the athletic playing field. With this wide diversity of possible presentations, HCM patients are not infrequently encountered in the cardiac care unit (CCU), and therefore an understanding of the disease is vital in its diagnosis and therapy. The pathophysiology includes the understanding and interplay of the following factors: LV outflow obstruction, concurrent mitral regurgitation, myocardial ischemia, atrial fibrillation (if present), sudden death, diastolic dysfunction, and

aspects of molecular biology and genetics. Diagnostic testing with transthoracic echocardiography (TTE), nuclear scintigraphy, exercise stress testing, cardiac catheterization, 24-hour electrocardiogram (ECG), and cardiac magnetic resonance imaging (cMRI) may be applied. Treatment may involve pharmacologic agents, the implanted defibrillator, surgical septal myectomy, transcoronary intervention in the form of alcohol septal ablation (ASA), or, in very rare cases, pacing.[1]

GENETICS

HCM is inherited as an autosomal dominant trait and occurs in 1:500, or about 0.2% of the general population. Emerging data from genetic population-based studies suggest an increased prevalence of HCM estimated to be 1:200 people or greater.[2] The risk of transmission is 50% from an affected parent, but the mutation may also occur sporadically. Missense (insertions or deletions occur less frequently) mutations of at least 11 genes that code for components of the myocardial sarcomere such as the thick myosin filament, intermediate filament, thin actin filament, Z-disc, or supporting proteins have been identified as a cause of HCM. The most common mutations (accounting for the majority of established mutations) found are in the ***β***-myosin heavy chain and myosin-binding protein C. Despite the presence of a known gene mutation, there is a wide variation in phenotype, and some genes demonstrate higher penetrance compared to others.[3] In a cohort of referred, unrelated patients with HCM who underwent gene testing for the eight most common mutations, 38% of the patients were found to have sarcomeric mutations. The remainder were noted to be genotype negative. Younger age at diagnosis, marked wall thickness, and a family history of HCM increased the frequency that a patient will be found to be gene positive.[4] Once a patient is identified to have HCM, all first-degree family members should be referred for clinical or genetic screening. Genetic screening should be performed in an experienced laboratory, and preceded by genetic counseling so that an informed decision can be made by the patient and their family regarding the possible results and subsequent management. In addition, multiple concurrent mutations may portend increased severity of disease.[1] In patients who have a positive genotype with negative phenotype (absence of hypertrophy), first-degree family members where a known mutation was not identified in the index case, or if genetic screening was discussed and declined,

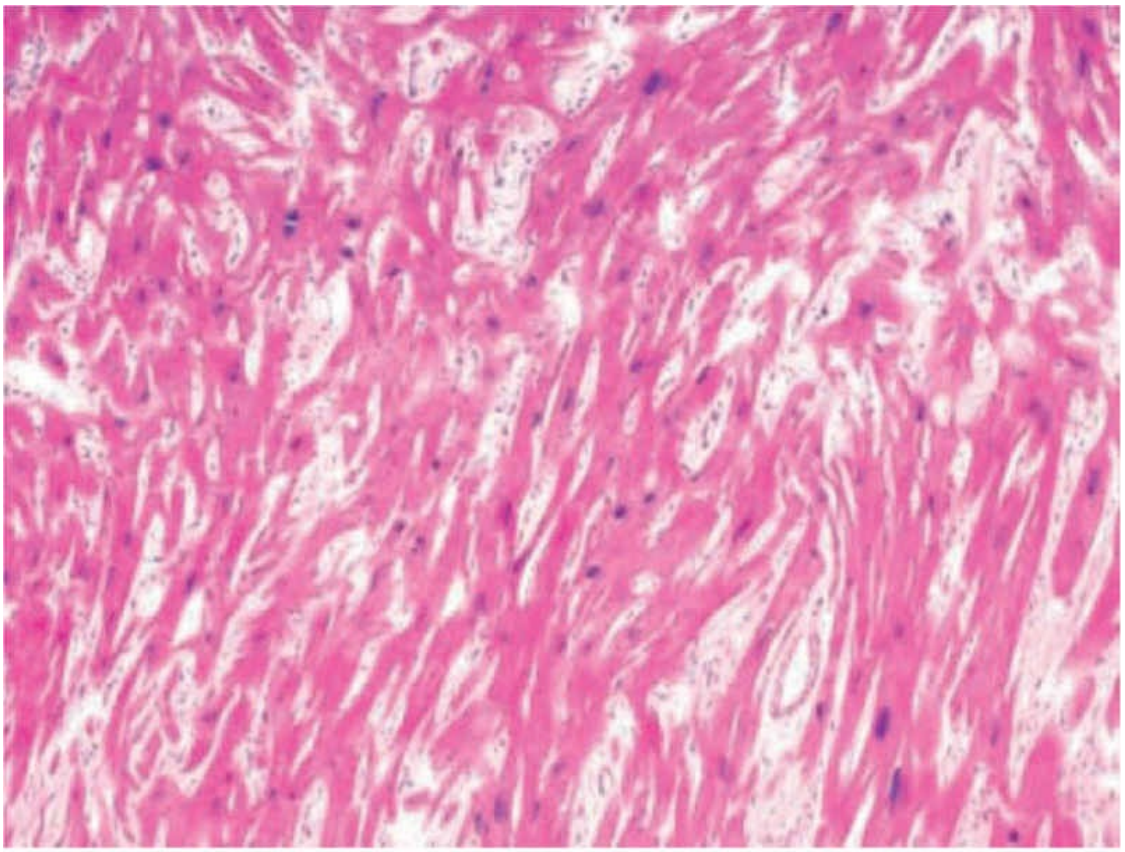
regular clinical screening via physical examination, ECG, and transthoracic echocardiogram should be utilized. This should be performed every 12 to 18 months for children and adolescents, and transitioned to every 5 years in adulthood.

Echocardiographic appearance also appears to predict a high likelihood of sarcomeric mutation in HCM; a reversed septal curvature causing a crescent-shaped LV cavity predicts gene-positive patients as compared with those with localized subaortic bulge and preserved septal curvature.[5] Although most genetically determined HCM occur on eight genes, many hundreds of HCM-causing mutations are dispersed over many gene loci. These genes may cause different phenotypes and may have different prognoses. Even among families with the same mutation on a particular locus, individuals vary with respect to phenotype and prognosis. This has markedly delayed genotype–phenotype correlation. The pathophysiologic linkage between mutations and hypertrophy appears to be mediated by mutation-induced functional abnormalities, most often because of increased contractile function. Recent theories about cause of hypertrophy have focused on inefficient utilization of ATP.

PATHOPHYSIOLOGY

On light microscopy, myocyte hypertrophy is noted, particularly in the subendocardium, as well as extensive myocardial fiber disarray—the combination of the two represent the pathognomonic abnormality. In normal individuals, myocytes are arranged in a linear and parallel configuration. However, patients with HCM demonstrate myocytes that are oblique or perpendicular to each other **(Figure 15.1)**. Furthermore, the nucleus of the cardiac myocyte is affected. Rather than having a central nucleus, enlarged nuclei are noted with pleomorphism and hyperchromasia. The myocyte myofibrillary architecture, which can be observed with phosphotungstic acid hematoxylin stain, is also disordered. Myocyte fiber disarray can be noted in other diseases, but myocyte hypertrophy and the percentage of the involved myocardium is less than 10%.[6] The interstitial connective tissue is also overly prolific with extensive fibrosis and is thought to account for the reduced LV chamber compliance and diastolic dysfunction seen **(Figure 15.2)**. Fiber disarray and myocardial fibrosis are thought to predispose to electrical reentry and sudden cardiac death (SCD). The coronary vasculature is not exempt from

adverse changes—smaller intramural arteries show intimal and medial smooth muscle hyperplasia and medial fibrosis, resulting in luminal narrowing **(Figure 15.3)**. The capillaries are similarly affected. These narrowings are thought to contribute to ischemia, which is well documented in HCM. Epicardial arteries can also be involved, less likely with stenosis than with myocardial bridging, which is noted in 15% to 30% of patients with HCM.



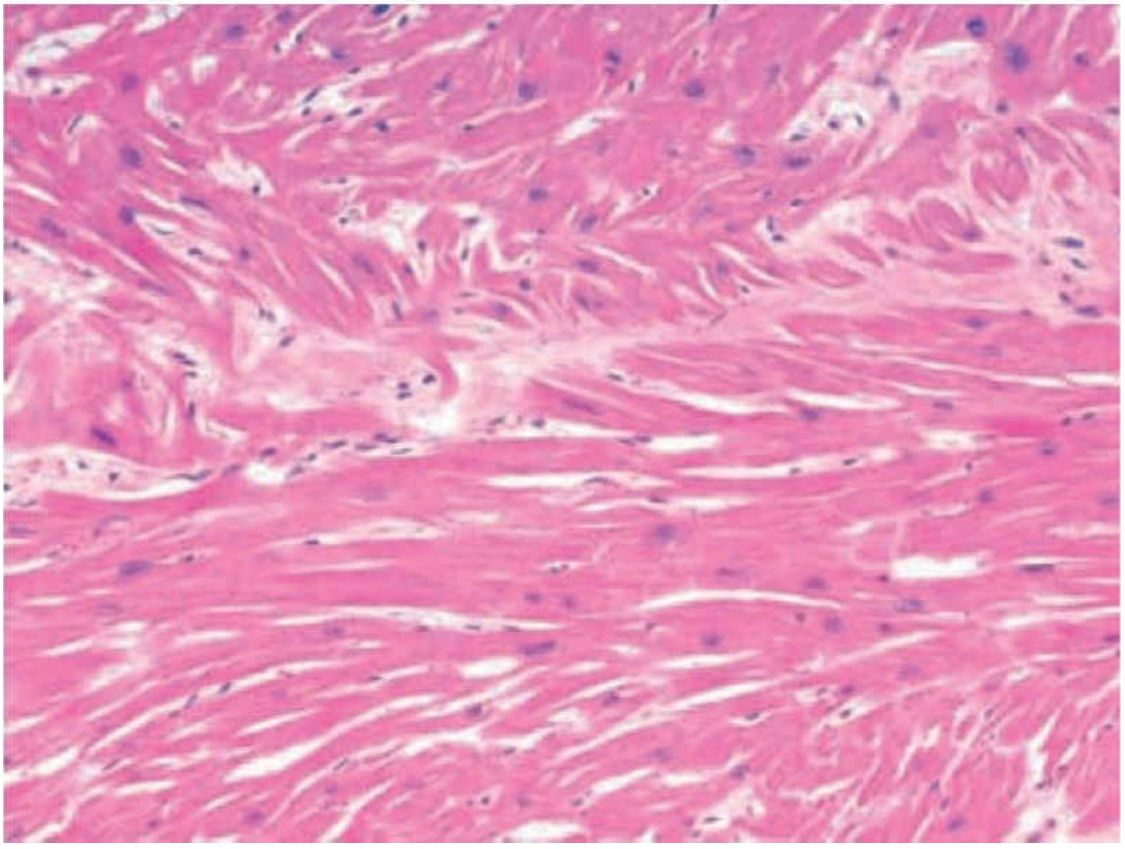


FIGURE 15.1 On light microscopy, myocyte hypertrophy is noted with extensive myocardial fiber disarray —the myocytes are oblique or perpendicular to each other, rather than being arranged in a linear and parallel configuration.

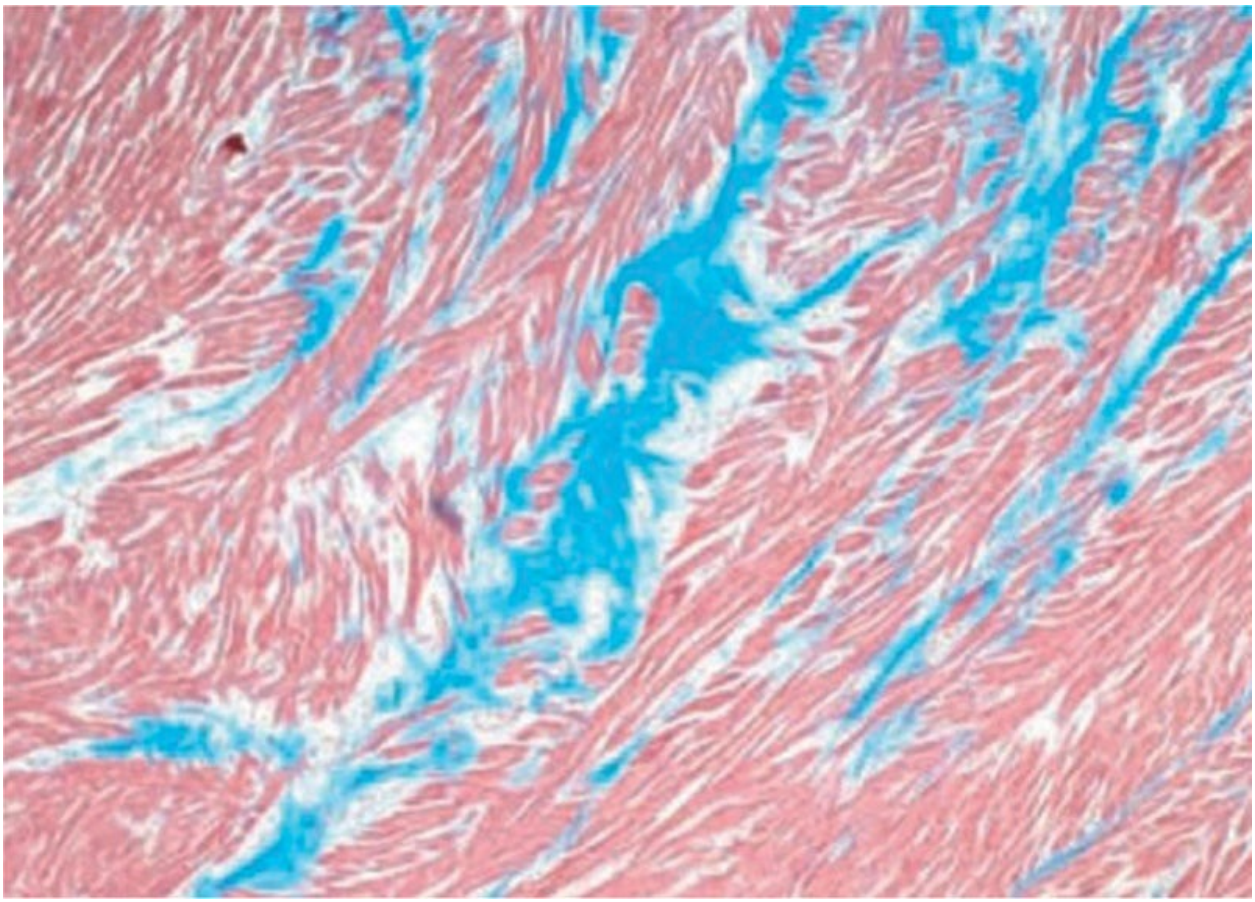


FIGURE 15.2 A modified Masson's trichrome stain of the myocardium is shown above and demonstrates extensive interstitial fibrosis with myocyte disarray.

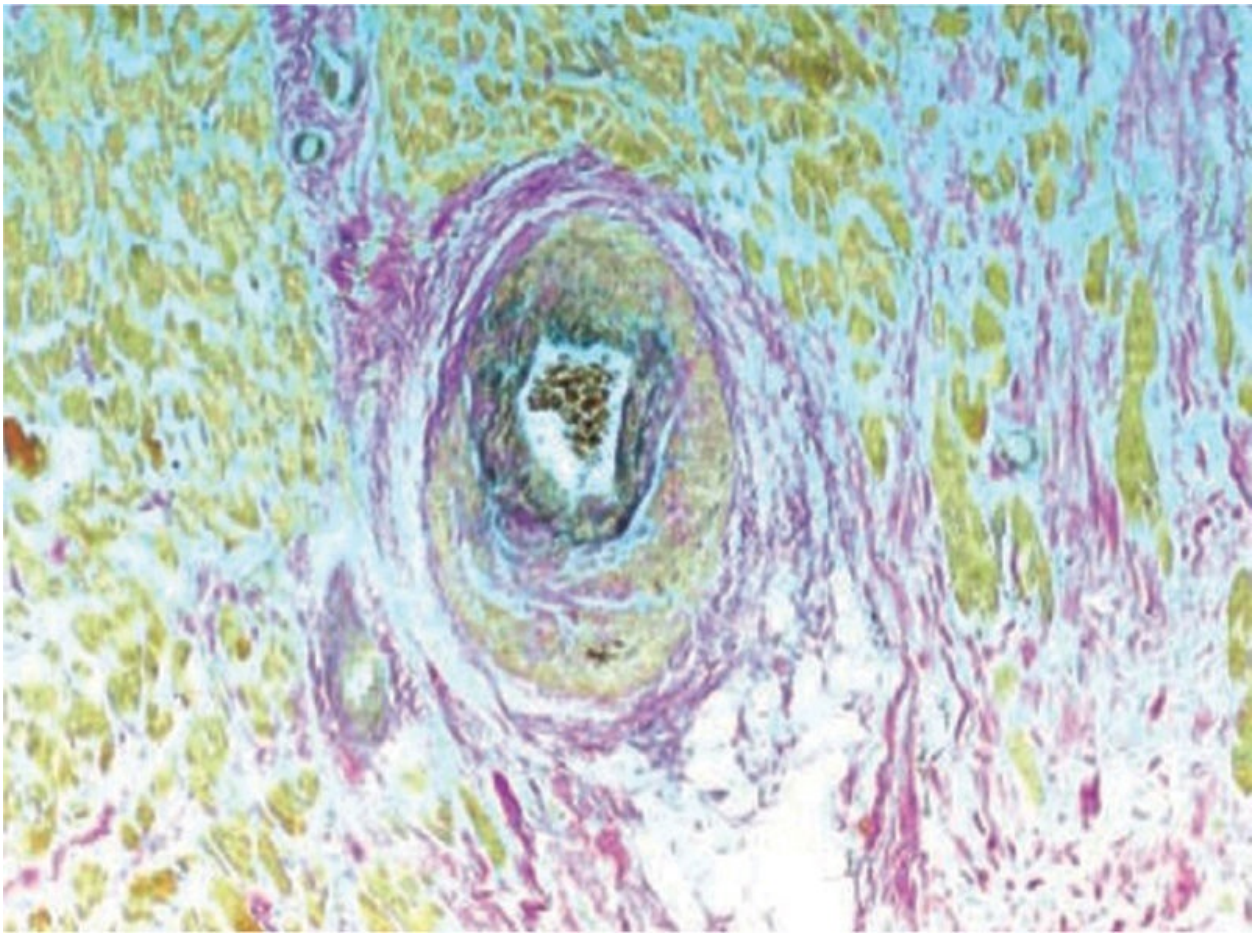


FIGURE 15.3 An intramural artery is shown above with intimal and medial smooth muscle hyperplasia and medial fibrosis, resulting in luminal narrowing. The capillaries are similarly affected. These narrowings are thought to contribute to ischemia.

DIAGNOSIS

The most common imaging modality used to establish a clinical diagnosis of HCM is TTE with an emerging role of cMRI. Additional testing in the initial evaluation of HCM should include an ECG, which is abnormal in up to 95% of patients.[7] A 24-hour ambulatory Holter monitor should be obtained to rule out episodes of nonsustained ventricular tachycardia, which generally adds prognostic information about risk of SCD. HCM is diagnosed when LV hypertrophy without dilatation occurs in the absence of a clinical condition that would cause the degree of hypertrophy noted.[1] Therefore, to make the diagnosis of HCM, it is important to evaluate for other cardiac or systemic conditions capable of producing the magnitude of hypertrophy evident (eg, aortic valve

stenosis, systemic hypertension, athlete's heart). Athlete's heart occurs in elite, highly trained competitive athletes, where wall thickness is increased but is usually less than 15 mm.[8] Compared to patients with HCM, these patients have normal or enlarged cardiac chambers, normal diastolic function, and have regression of their LV hypertrophy with temporary cessation of training. The location of abnormal hypertrophy in patients with HCM is most often the anterior septum, although the posterior septum and anterior wall can be involved as well. Typical of the heterogeneity of HCM is that hypertrophy can occur in any segment, even among relatives known to have the same genotype. Truly atypical HCM variants include thickening isolated to the lateral or posterior wall. Wall thickness should be evaluated for all patients with TTE, but may be limited by the obtained ultrasound window. MRI, which has become an important diagnostic tool in HCM, is useful in this situation. In a subset of patients, the site and extent of cardiac hypertrophy and abnormalities of the mitral valve result in obstruction to LV outflow. LV outflow tract (LVOT) obstruction is an important determinant of symptoms and is associated with adverse outcomes. This is caused by systolic anterior motion (SAM) of the mitral valve and contact of the valve with the hypertrophied septum (mitral–septal contact), which is demonstrated through echocardiography **(Figure 15.4)**.[9] The phenomenon of dynamic SAM is caused by a crucial anatomic overlap between the inflow and outflow portions of the left ventricle. **Figure 15.5** shows dynamic SAM as it progresses through the early moments of systole. The narrowing of the LVOT and the anteriorly positioned coaptation point of the mitral valve places the protruding leaflet into the edge of the flow stream, subjecting the undersurface of the leaflet to the pushing force of flow, as illustrated in **Figure 15.6**.

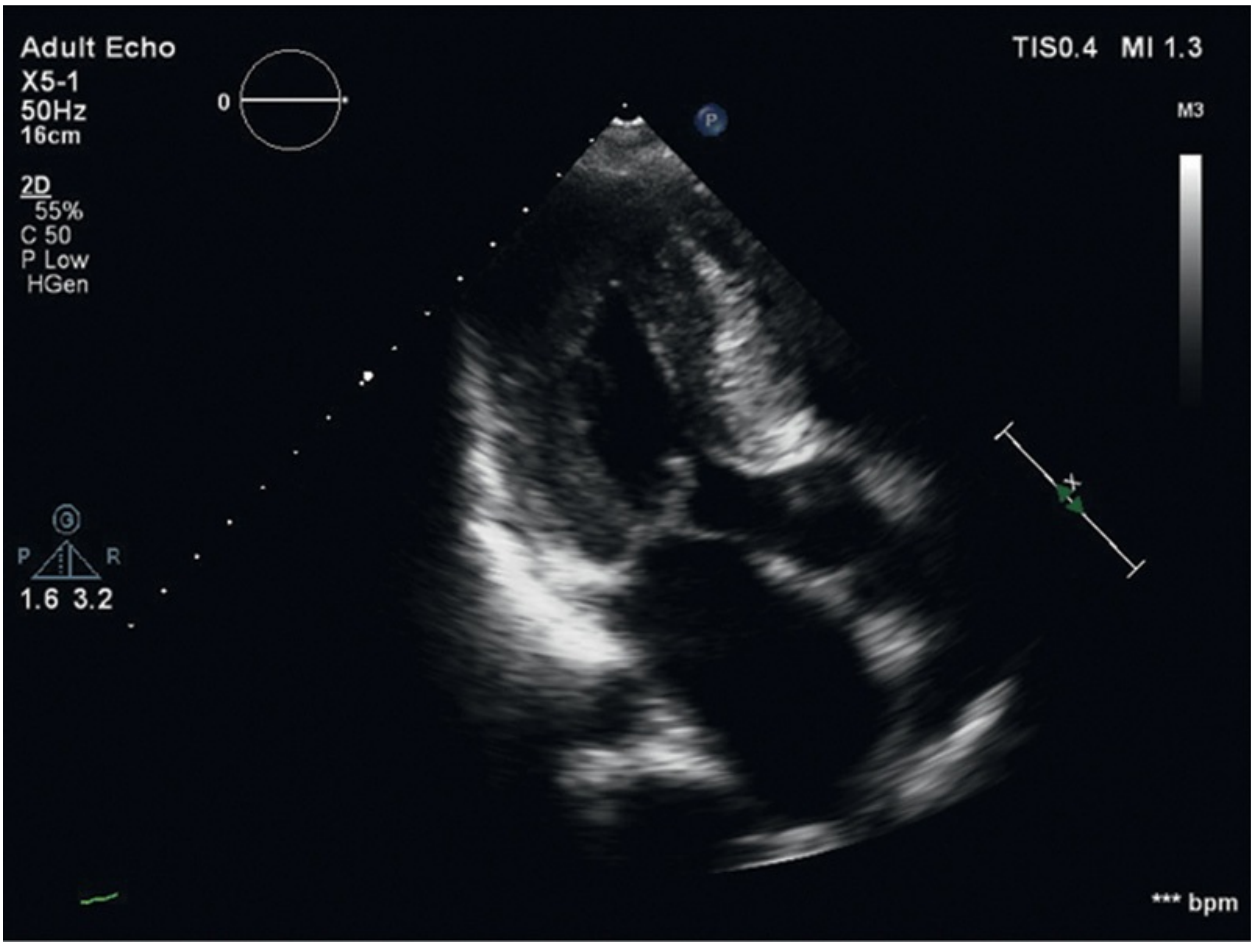


FIGURE 15.4 This apical three-chamber view on transthoracic echocardiography demonstrates systolic motion of the mitral valve with resulting mitral–septal contact. Note the hypertrophy of the left ventricular walls, particularly the anteroseptum.

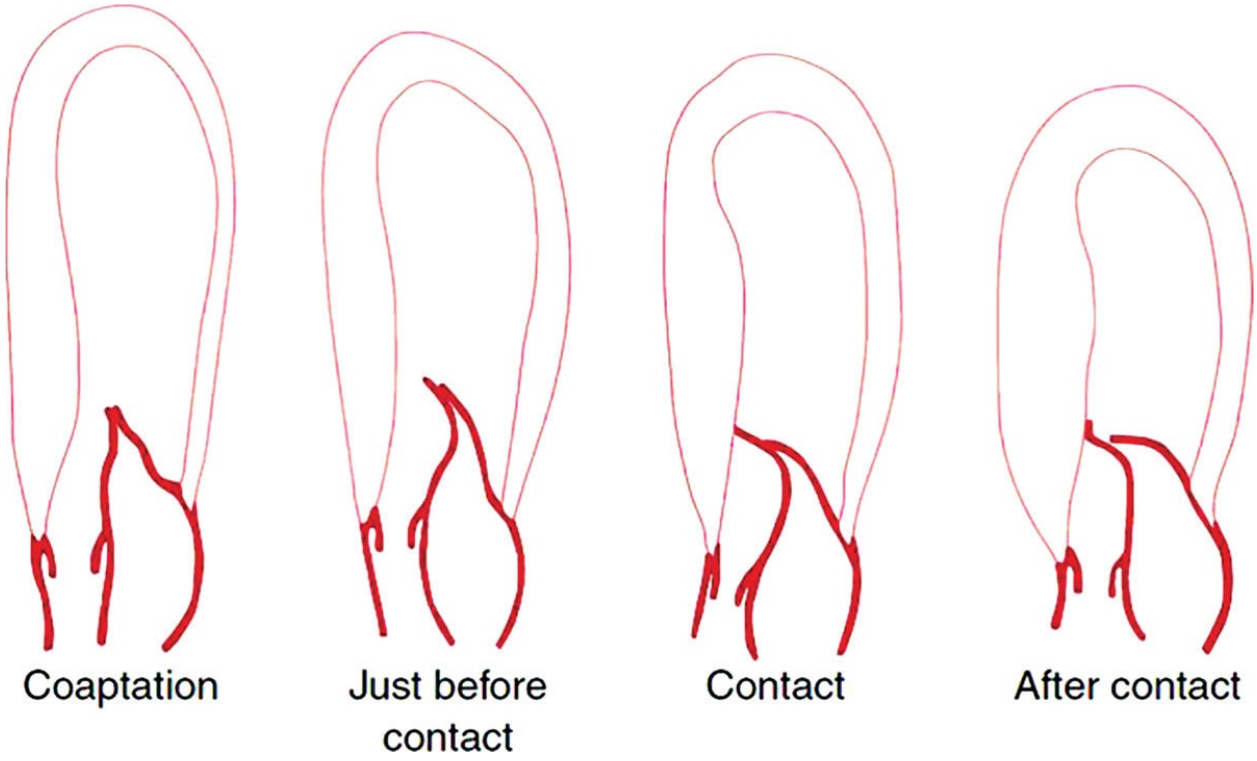


FIGURE 15.5 Systolic anterior motion of the mitral valve, schematically drawn from apical five-chamber view, as it proceeds in early systole. (Adapted from Sherrid MV, Chu CK, Delia E, et al. An echocardiographic study of the fluid mechanics of obstruction in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1993;22:816-825.)

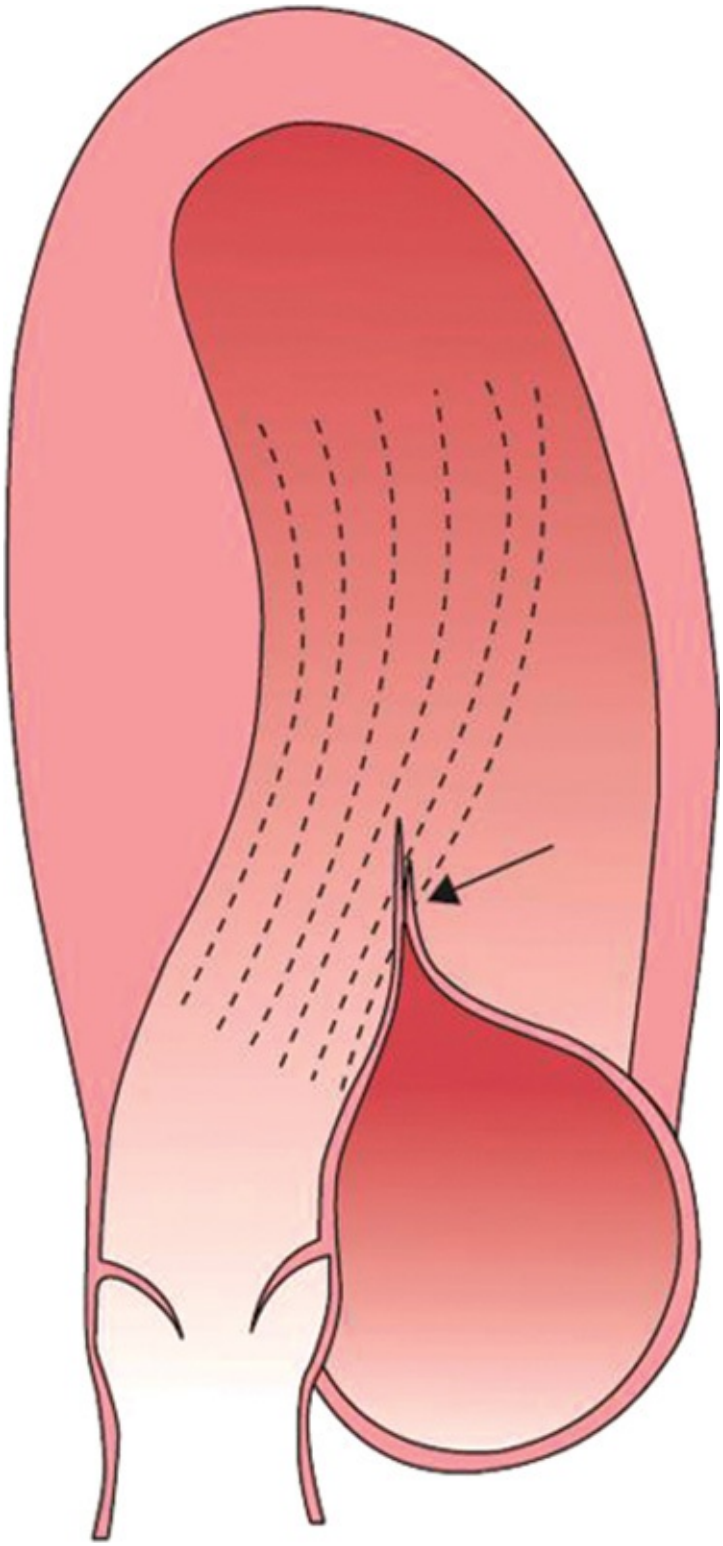


FIGURE 15.6 The pushing force of flow in the left ventricle is shown schematically above relative to the mitral valve in the apical five-chamber view. In obstructive hypertrophic cardiomyopathy, the mitral leaflet coaptation point is closer to the septum than normal. The protruding leaflets extend into the edge of the flow stream and are swept by the pushing force of flow toward the septum. Flow pushes the underside of the

leaflets (*arrow*). Note that the midseptal bulge redirects flow so that it comes from a relatively lateral and posterior direction; on the five-chamber view, flow comes from the "1 o'clock" direction. This contributes to the high angle of attack relative to the protruding leaflets. (Adapted from Sherrid MV, Gunsburg DZ, Moldenhauer S, et al. Systolic anterior motion begins at low left ventricular outflow tract velocity in obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2000;36:1344-1354.)

cMRI can provide additional clinically relevant information by quantifying LV mass, evaluating the right ventricle and mitral valve, identifying aberrant muscle bundles within the left ventricle (LV), and identifying myocardial fibrosis/scarring by late gadolinium enhancement (LGE). If myocardial mass has at least 15% with LGE, there is a 2-fold risk in SCD compared with those who are otherwise considered low risk. Finally, CMR can also play a role in distinguishing HCM from other cardiac pathology that may similarly demonstrate LV hypertrophy on echocardiography.[10]

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

The degree of obstruction is quantified by measuring the pressure drop and the gradient across the LVOT. This is most commonly done noninvasively with continuous wave Doppler echocardiography. Pulsed wave Doppler correlation with the two-dimensional echocardiogram allows for determination of the site of obstruction, which must be ascertained in every patient, especially if intervention is contemplated. LV outflow obstruction causes a midsystolic drop in LV ejection velocities and flow when the gradient is >60 mm Hg. This echocardiographic pattern has been termed the "lobster claw" abnormality because of its characteristic appearance **(Figure 15.7)**. Significant obstruction is considered to be present with a resting gradient greater than 30 mm Hg. Changing preload and afterload may provoke a gradient by increasing the overlap between the inflow and outflow portions of the LV, reflecting the dynamic nature of the obstruction. After completing initial echocardiographic imaging with no evidence of a resting gradient, patients with concern for HCM such as septal hypertrophy or SAM should be additionally imaged while asked to perform the Valsalva maneuver or standing to elicit a possible gradient. Two-thirds of patients with HCM have resting or provokable LVOT obstruction, and one-third are nonobstructive. Exercise, and on occasion exercise in the postprandial state, can also be used to uncover latent obstruction. However, exercise testing is not indicated in patients with gradients over 4 m/s at rest, New

York Heart Association class III or IV symptoms, or prior history of ventricular arrhythmia.[11] These maneuvers are helpful in order to correlate patient symptoms with degree of obstruction and to provide a target for therapy. In addition, patients with gradients in excess of 50 mm Hg at rest or with provocation should be considered for invasive intervention if they remain symptomatic despite medical management.

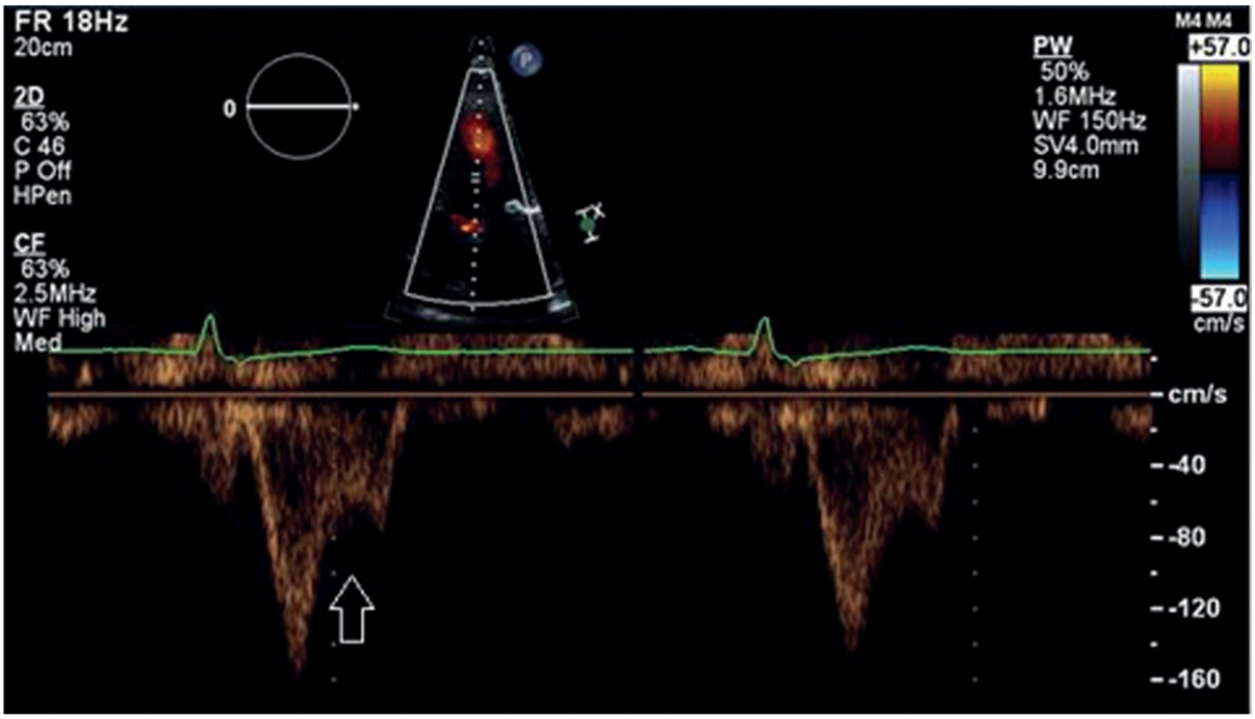


FIGURE 15.7 Midsystolic drop in LV ejection velocity in obstructive hypertrophic cardiomyopathy. On a pulsed wave Doppler recording just apical of the entrance to the LVOT in a patient with severe dynamic obstruction caused by systolic anterior motion and mitral–septal contact. The arrow points to the LV midsystolic drop in LV ejection flow velocity. This drop in velocity has been called the "lobster claw abnormality" because of its characteristic appearance. The drop in velocity results from the sudden imposition of afterload because of the mitral–septal contact and the gradient. LV, left ventricular; LVOT, left ventricular outflow tract.

TREATMENT

There are five aspects of care that should be covered in the treatment of every HCM patient, some of which may not necessarily be applicable in the setting of the CCU: (1) Risk of sudden death should be discussed, and individual stratification of risk should be done. The average risk of dying suddenly is 1%

per year for HCM patient populations, but the risk may be higher or lower depending on whether risk factors for sudden death are present. For patients deemed by their physicians to be at high risk, discussion of implantation of a defibrillator should be considered. (2) Treatment in hopes of alleviating symptoms should be initiated. (3) A discussion to avoid athletic competition and extremes of exertion should be conducted, as well as lifestyle modifications to avoid exacerbation of LVOT obstruction. (4) There should be an effort to detect and manage risk factors contributing to coronary artery disease such as hypercholesterolemia, diabetes mellitus, and cigarette smoking (HCM and coronary disease have an adverse synergistic effect on prognosis). (5) Clinical screening (physical exam, transthoracic echocardiogram and ECG) or genetic testing of first-degree family members should be performed to assess who is at risk or has inherited the gene mutation. Although many aspects of this evaluation can wait until a patient is stabilized after the CCU stay, it must be remembered that HCM is a lifelong condition and that these issues need discussion, management, and follow-up.

PHARMACOLOGIC TREATMENT OF SYMPTOMS

Figure 15.8 outlines an algorithm for the management of symptomatic HCM in patients grouped into obstructive and nonobstructive HCM categories.

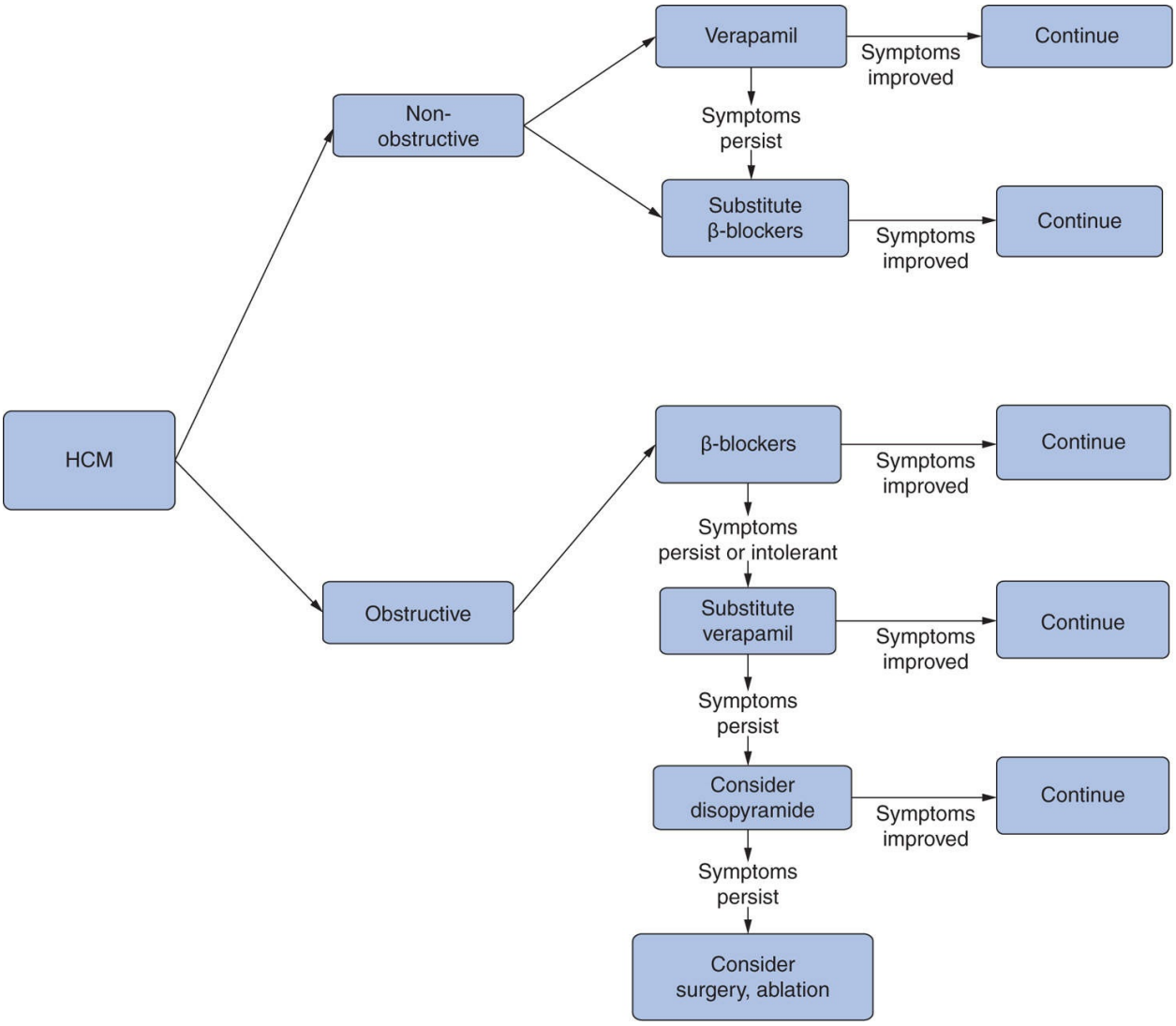


FIGURE 15.8 The management of patients with either obstructive or nonobstructive hypertrophic cardiomyopathy is detailed above. Pharmacologic therapy is driven by symptom response, and patients with obstruction who are refractory to medications are indicated for advanced intervention. HCM, hypertrophic cardiomyopathy.

NONOBSTRUCTIVE HCM

In nonobstructive HCM, symptoms are caused by diastolic dysfunction with impaired relaxation early in diastole and decreased chamber compliance in late diastole. This is coupled with small LV volumes and hypertrophy.

Few agents are available, and they are not particularly effective in improving severe symptoms owing to diastolic dysfunction. No pharmacologic agent has been consistently shown to improve LV relaxation and chamber compliance in HCM.[12] Therefore, treatment options for symptomatic nonobstructive HCM are

limited.[13] Two treatment goals are to improve LV diastolic function and to improve ischemia. Two classes of agents are currently used—***β***-blockade and calcium channel blockade. Neither class of agents has been shown to improve diastolic chamber compliance.[14] Verapamil's positive contribution in the pathophysiology of nonobstructive HCM appears to be relief of ischemia. Verapamil improves myocardial perfusion as assessed by stress radionuclide perfusion imaging and may thus improve symptoms.[15] Beta-blockade and, to a lesser degree, verapamil may cause chronotropic incompetence in HCM.[16] As diastolic dysfunction may limit the exercise-induced increase in stroke volume, patients with HCM often rely on increased heart rate to increase cardiac output. In such patients, pharmacologic limitation of increase in heart rate may impair exercise capacity. Whereas disopyramide has been shown to improve diastolic function in obstructed patients, by decreasing gradient and systolic load, it has not been shown to improve diastolic function in nonobstructed patients and should be avoided in this group, pending further investigation.[17, 18] For the patient with fluid retention, with edema or rales, diuretics may be helpful by relieving dyspnea and uncommon edema. Overdiuresis should be avoided because patients with HCM are often preload dependent for adequate cardiac output. If patients initially present with significant edema, another diagnosis should be sought as this is very unusual. Amyloid may be suspected in this clinical situation, especially if the ECG QRS voltage is low. The use of angiotensin receptor blocker losartan did not demonstrate improvement in exercise capacity or cardiac function. Clinical trials are ongoing because there is currently no good pharmacologic treatment for advanced symptoms in nonobstructive HCM.[19] Fortunately, patients with nonobstructive HCM appear to have a more benign clinical course compared with obstructed patients.[20]

OBSTRUCTIVE HCM

Pharmacologic therapy of symptoms in obstructive HCM (OHCM) is successful in two-thirds of patients. ***β***-blockers are initially used because of their negative inotropic effect. This improves dynamic LV outflow obstruction by decreasing ejection acceleration, which in turn lowers flow velocities early in systole and decreases early drag forces on the mitral valve. SAM and mitral–septal contact are delayed, thereby reducing the LVOT gradient. In addition, decreased myocardial tissue oxygen consumption alleviates possible myocardial ischemia, and negative chronotropy increases diastolic filling time.[13] ***β***-blockers also

decrease the sympathetically mediated rise in gradient and tachycardia. The doses should be titrated to cessation of symptoms, a heart rate ranging from 60 to 65 beats/min, or recommended maximum doses. However, ***β***-blockade is not expected to reduce resting gradient, and less than half of patients have sustained improvement in symptoms.[21] ***β***-blockers are effective in reducing exercise-induced LVOT obstruction.[22] For patients who are intolerant of ***β***-blockers or remain symptomatic verapamil therapy can be attempted in doses as high as 480 mg/day. Verapamil, a potent calcium channel blocker (CCB), also has negative inotropic properties but is also a vasodilator. It has been shown to decrease gradient and improve symptoms. Some studies have demonstrated an improvement in exercise tolerance as well. However, it is not used in patients with severe obstruction and severe symptoms because, on occasion, its vasodilating effects outweigh its negatively inotropic effects: the LVOT gradient may rise, and pulmonary edema and death have been reported. In addition, heart block and bradycardia may complicate its use. If there is no improvement with verapamil, disopyramide can be added to beta-blockade or verapamil.[23, 24] Disopyramide is a type I antiarrhythmic drug with potent negatively inotropic properties; in normal individuals, it can decrease echocardiographic fractional shortening by 28%. It is a sodium channel blocker and may have calcium channel blocking properties as well; however, it is not a vasodilator. Disopyramide is generally given to patients who are refractory to ***β***-blockade or verapamil and would otherwise require intervention with surgical septal myectomy or ASA. In a multicenter study, two-thirds of patients with OHCM treated with disopyramide combined with a ***β***-blocker could be managed medically with amelioration of symptoms and 50% reduction in LVOT gradient when followed for 3 years. The remaining one-third of patients could not be managed successfully with disopyramide and required invasive therapy secondary to inadequate symptom and gradient control or vagolytic side effects. There was a trend toward lower cardiac mortality and sudden death in the disopyramide group, without an increased risk of arrhythmia. The starting dose of disopyramide is 250 mg twice a day using the controlled-release preparation, and can be increased to 300 mg twice daily.[25] Disopyramide is generally given with a ***β***-blocker or verapamil to limit exercise-induced adrenergic response and to slow ventricular response, should atrial fibrillation occur. Mild vagolytic side effects, dry mouth, blurred vision, and constipation are common but generally subside. If they prove troubling, the dosage may be reduced, or controlled-release pyridostigmine may be added, 180 mg/day. A more serious vagolytic side

effect is urinary retention. Vagolytic side effects cause discontinuation of disopyramide in 7% of patients. Because of its impaired elimination in renal failure, disopyramide should be administered in reduced dosage or with serum monitoring. ECG surveillance of the QTc interval should be performed, and QTc prolonging medications should be carefully considered prior to initiation in patients who are on disopyramide.

DRUGS TO AVOID (OR DISCONTINUE) IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

All vasodilators should be avoided in OHCM, a drug class that is commonly used in the CCU. Vasodilators will worsen LVOT obstruction. These include all nitrate preparations (sublingual, topical, and IV), dihydropyridine CCBs (amlodipine and nifedipine), angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and alpha-adrenergic blockers that are used for prostatism. Furthermore, drugs that increase contractility will worsen obstruction and should also be avoided in OHCM such as dopamine, dobutamine, milrinone, and digoxin.

SURGICAL SEPTAL MYECTOMY

Myectomy is the treatment of choice for patients who fail medical therapy.[24, 25] Candidates for myectomy have persistent disabling symptoms and gradients of >50 mm Hg at rest or after physiologic provocation. Myectomy has been successfully performed for 30 years, and in experienced centers it can be performed with low surgical mortality of 1%. It is uniformly successful in reducing both gradient and symptoms.

Interventions are not always successful, and the reason for heterogeneity in response is not clear. Understanding the central role of flow drag in the pathogenesis of SAM may prevent treatment failures. Inadequate myectomy resection focused on just the subvalvular septum, targeted to widen the outflow tract and to reduce Venturi forces, may result in persistent SAM and obstruction. A limited myectomy misses the impact of the midventricular septal bulge that redirects LV flow so that it comes from a relatively posterolateral direction. This sort of resection results in persistent SAM and either outflow obstruction or

mitral regurgitation because flow must still course around the remaining septal hypertrophy, and it still catches the mitral valve and pushes it into the septum, causing mitral regurgitation. To alleviate this sort of residual SAM, investigators from Germany have popularized the extended myectomy. More extensive resection redirects flow away from the mitral valve, precluding drag-induced SAM. A large decrease in the angle of attack of flow relative to the mitral valve has been shown after successful myectomy; flow is made more parallel to the mitral valve. The myectomy resection must be extended far enough down toward the apex to allow flow to track anteriorly along the surgically reduced septum away from the mitral valve. Surgical septal myectomy also addresses abnormalities in the attachments of the papillary muscles, which are common in HCM and which can often contribute to LVOT obstruction.[25] In addition, HCM patients typically have intrinsic mitral valve pathology such as mitral valve prolapse, increased leaflet length, and abnormal chordal attachments that contribute to obstruction. Surgical myectomy has the advantage of addressing mitral valve abnormalities with a repair.[26, 27] Targeting the basal septum alone is unlikely to completely relieve SAM, obstruction, and mitral regurgitation. When surgery is selected, myectomy is preferred over mitral replacement for relief of LVOT obstruction in HCM patients refractory to pharmacotherapy.

ALCOHOL SEPTAL ABLATION

Percutaneous Alcohol Septal Ablation (ASA) can be considered an alternative to surgical septal myectomy for patients at high operative risk and advanced age. It can be done only if there is suitable anatomy. This procedure offers the attractive promise of septal reduction without cardiopulmonary bypass and its complications. After placement of a temporary right ventricular pacing lead, a small diameter balloon catheter is placed in a selected left anterior descending (LAD) septal branch, and after inflating the balloon, angiographic contrast is injected to ensure that contrast does not reflux back into the LAD. Diluted echo contrast is then injected during transthoracic or transesophageal echocardiographic imaging. In 8% of such injections, contrast is seen to flow to structures where alcohol injection would be disastrous: posterior LV wall, RV free wall, mitral papillary muscles, or the entire septum. With this information, the operator searches for a septal branch that can be demonstrated to supply just the upper septum, preferably including and extending past the point of mitral–

septal contact. A dose of 1 to 3 mL of absolute alcohol is instilled into the septal branch. Optimally, a controlled myocardial infarction occurs. This is accompanied by typical chest pain, enzyme elevation, and risk for potentially lethal ventricular arrhythmia. The acute gradient reduction of ASA is caused by reduced ejection acceleration from the infarct and decreased hemodynamic force on the mitral valve decreasing SAM identically as in negatively inotropic medications. Late improvement stems from septal thinning owing to septal scar. ASA is associated with a risk of pacemaker dependency in 10% to 15% of cases, and an increase in ventricular arrhythmias has been reported. In addition, ASA does not offer as complete relief of obstruction compared with surgical myectomy.[28, 29]

DUAL-CHAMBER PACING

Dual-chamber pacing with complete ventricular preexcitation through a short atrioventricular (AV) delay to reduce outflow tract gradient is not considered primary therapy for obstruction.[30] Select older patients who are ≥65 years old may benefit with modest improvement on LVOT gradient and functional improvement.[30] Therapeutic effect is often incomplete; SAM persists with mean gradients of 30 to 55 mm Hg after 3 months of pacing. The mechanism by which pacing benefits SAM is unclear at this time. It may be because of the dyssynchrony caused by the right ventricular pacing, or because of the short AV delay. It is usually considered for patients who already have a dual-chamber pacemaker present with comorbid medical conditions or old age given in conjunction with disopyramide and a ***β***-blocker.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Although not a decision made solely in the CCU, the Implantable defibrillator has a role in the spectrum of care for HCM patients. Situations may arise in CCU patients that may prompt the recommendation of implantable cardioverter defibrillator (ICD) insertion. These include presentation with syncope or ventricular tachycardia—nonsustained or persistent. Other risk factors that are associated with higher risk for SCD and may prompt ICD include massive segmental wall thickening ≥30 mm, family history of SCD from HCM in a

young family member, and apical akinetic aneurysm owing to mid-LV obstruction.

MANAGEMENT OF ACUTE DECOMPENSATION OF PATIENTS WITH HCM

The initial step in the management of acute decompensated HCM patients with obstruction should be discontinuation of any possible offending agents such as vasodilators. The clinician should also keep in mind that positive inotropes in this setting of hemodynamic instability secondary to obstruction may be deleterious and should also be avoided. When hemodynamics stability is preserved, ***β***-blockers constitute the first line of treatment. If hemodynamic stability is compromised (systolic blood pressure <90 mmHg), increasing afterload and preload is in order. **Figure 15.9** shows the progression of management in these patients. In the event atrial fibrillation ensues, rate and rhythm control are imperative.

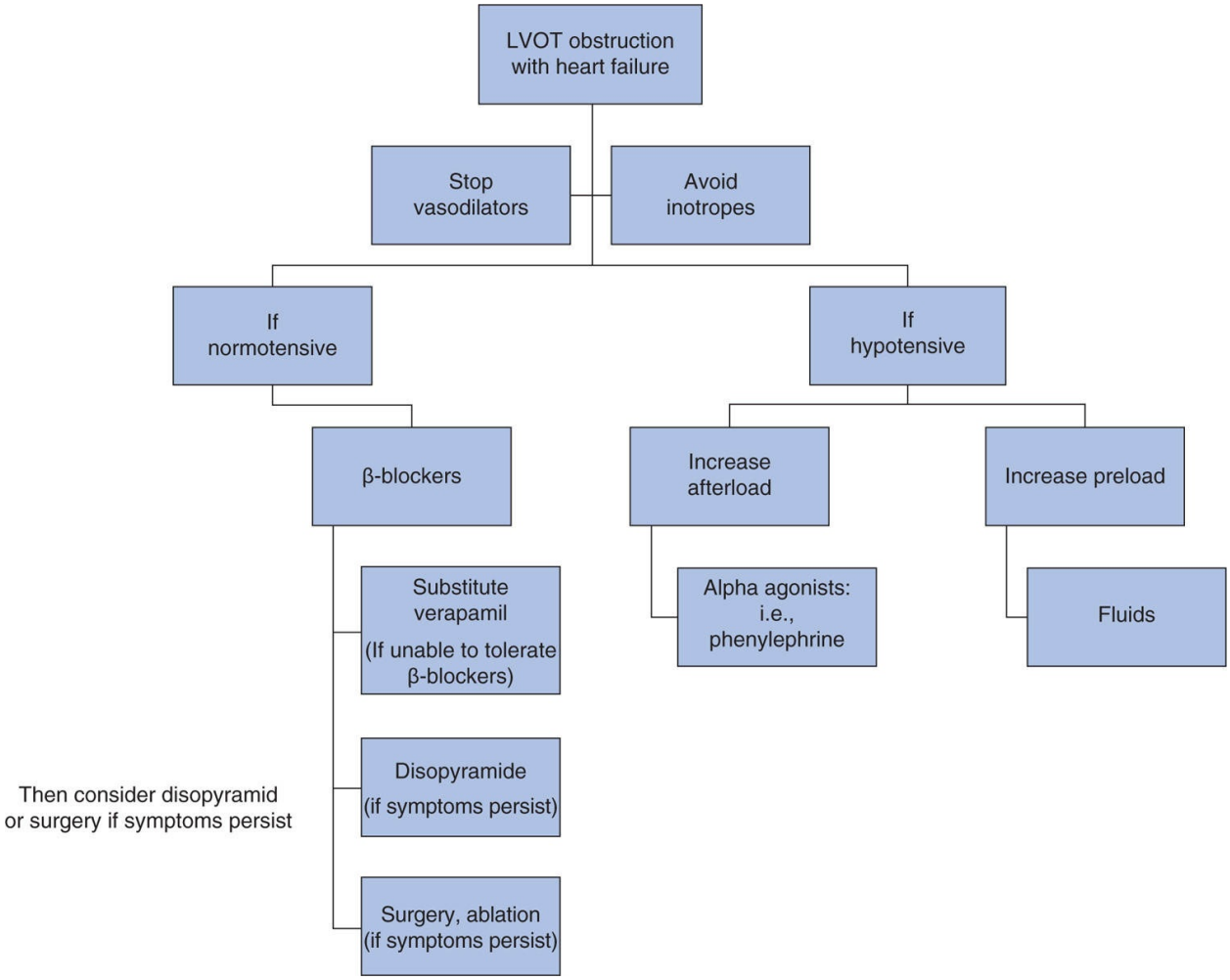


FIGURE 15.9 The management of patients being admitted into the cardiac care unit with heart failure symptoms secondary to left ventricular outflow tract obstruction is demonstrated above. Cessation of offending agents is the first step, and patients with hypotension should be treated with intravenous fluids and phenylephrine, if needed. Positive inotropes should be avoided because they can worsen obstruction. LVOT, left ventricular outflow tract.

The most common cause of acute decompensation in HCM patients is the acute onset of atrial fibrillation. The loss of the atrial kick and rapid heart rate on top of diastolic dysfunction can provoke heart failure symptoms. The first consideration should be whether the patient needs acute direct current cardioversion for severe heart failure or hemodynamic instability. For most other patients, slowing the ventricular rate with beta-blockade or nondihydropyridine CCBs is generally the best first treatment option. Verapamil may be used in nonobstructed patients but not in patients with resting obstruction because it has vasodilatory properties with a risk of pulmonary edema in severely obstructed patients. Amiodarone may be used to slow ventricular rate, but in non-

anticoagulated patients it should be used only in those who have recent (<48 hours) atrial fibrillation because the drug has the potential to restore sinus rhythm. Anticoagulation with parenteral heparin or low-molecular-weight heparin is indicated, because systemic embolism is very common in HCM patients. There should be a low threshold to refer patients for transesophageal echocardiogram (TEE) to exclude the presence of left atrial appendage thrombus before cardioversion. If there is no left atrial appendage thrombus noted, cardioversion may be performed either electrically or pharmacologically with a plan to continue warfarin or newer oral anticoagulants as an outpatient. The use of a newer oral anticoagulant agent should be considered, and although there are no data specifically looking at their use in this patient population, they are used in clinical practice with HCM patients who have atrial fibrillation. Frequent episodes of atrial fibrillation may warrant referral for catheter-based ablation, which may be an option for these patients. All patients with HCM and atrial fibrillation should continue long-term anticoagulation to reduce the risk of stroke and embolic events. In HCM patients who develop atrial fibrillation, the risk of embolic events is high (ie, incidence is 2.5%/year). Long-term anticoagulation regardless of CHADS–VASC score is indicated in these patients to reduce stroke and peripheral embolic events.[31]

ACUTE LVOT OBSTRUCTION AND TAKOTSUBO CARDIOMYOPATHY

Patients with HCM and latent obstruction may rarely present with acute, severe LV dysfunction consistent with apical ballooning, pulmonary congestion, and cardiogenic shock similar to Takotsubo cardiomyopathy. Besides apical ballooning and hypercontractile basal LV function, these patients are also noted to have SAM of the mitral valve and mitral–septal contact. Around 10% to 25% of Takotsubo cardiomyopathy cases have been documented showing SAM, with the etiology of this being unclear. It has been theorized that the hypercontractility of the basal myocardium narrows the LVOT, causes flow to course around the basilar septum posterior and laterally, and positions the mitral valve leaflets to be swept into the outflow tract by a Venturi or flow-drag mechanism.[32] Another proposed mechanism is that patients initially presenting with this variant of Takotsubo cardiomyopathy have underlying, undiagnosed HCM with latent obstruction. Severe increased afterload mismatch from SAM

can cause subendocardial ischemia with resulting LV dysfunction.[33] The complete reversal of these findings after relief of LVOT obstruction indicates that they were caused by the dynamic obstruction caused by SAM of the mitral valve and mitral–septal contact. These patients should be admitted to the CCU after cardiac catheterization to exclude severe coronary artery disease with a left ventriculogram (if able to be clinically tolerated). Intravenous fluids, beta-blockade, and phenylephrine should be administered so as not to exacerbate LVOT obstruction and for hemodynamic support.

ACKNOWLEDGMENT: We acknowledge the guidance and mentorship of Dr. Mark Sherrid without whose support this chapter would not be possible.

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Patient and Family Information for: HYPERTROPHIC CARDIOMYOPATHY

HCM is characterized by thickening of the left ventricle that occurs without clinical cause such as high blood pressure or aortic valve disease. It is marked by varying symptoms and abnormalities. HCM is the great masquerader of cardiology. It often masquerades as coronary artery disease because it presents with chest pain, but without significant coronary narrowings. It is particularly confusing when HCM may present with ECG abnormalities mimicking those found in coronary disease. HCM is characterized by thickening of the heart muscle, most commonly at the septum between the ventricles. This leads to stiffening of the walls of the heart and abnormal mitral valve function that may obstruct normal blood flow out of the heart. Many people with HCM have no symptoms or only minor symptoms and live a normal life. Other people develop symptoms that progress and worsen as heart function worsens. Symptoms of HCM can occur at any age and may include chest pain or pressure that can occur with exercise or physical activity or at rest as well. Shortness of breath especially with exertion and fatigue (feeling overly tired) are often experienced. Initial presenting symptom could be a fainting episode (syncope) caused by irregular heart rhythms or abnormal responses of the blood vessels. Some patients may experience palpitations (fluttering in the chest) because of abnormal heart rhythms (arrhythmias), such as atrial fibrillation or ventricular tachycardia. Sudden death may occur as the presenting symptom in a small number of patients with HCM. HCM can run in families as a dominant genetic trait, owing to a gene that is inherited in half of the first degree relatives. In other instances, the cause is unknown. HCM is diagnosed on the basis of medical history (symptoms and family history), a physical exam, and echocardiogram results.

Additional tests may include blood tests, ECG, chest X-ray, exercise stress test, cardiac catheterization, CT scan, and MRI. In a subset of patients, the site and extent of cardiac thickening and abnormalities of the mitral valve result in obstruction to LV outflow. LVOT obstruction is an important determinant of symptoms and is associated with adverse outcome. Obstruction is an important therapeutic target in HCM because relief of obstruction often leads to improved symptoms. The most common location of obstruction is in the LVOT, caused by SAM of the mitral valve and mitral–septal contact. The phenomenon of dynamic SAM is caused by a crucial anatomic overlap between the inflow and outflow portions of the left ventricle. There are five aspects of care that should be covered in the treatment of every HCM patient: (1) Risk of sudden death should be discussed, and individual stratification of risk should be done. The average risk of dying suddenly is 1%/year for HCM patient populations, but the risk may be higher or lower depending on other risk factors for sudden death that may be present. For patients deemed by their physicians to be at high risk, discussion of implantation of a defibrillator should be considered. (2) Treatment in hopes of alleviating symptoms should be initiated. (3) A discussion to avoid athletic competition and extremes of exertion should be conducted, as well as lifestyle modifications to avoid exacerbation of LVOT obstruction. (4) There should be an effort to detect and manage risk factors of coronary artery disease such as hypercholesterolemia, diabetes mellitus, and cigarette smoking (HCM and coronary disease have an adverse synergistic effect on prognosis). (5) Clinical screening (physical exam, transthoracic echocardiogram, and ECG) or genetic testing of first degree family members should be performed to assess who is at risk or has inherited the gene mutation. Although many aspects of this evaluation can wait until a patient is stabilized after the CCU stay, it must be remembered that HCM is a lifelong condition and that these issues need discussion and management when the dust clears. Lifestyle changes may alter the course of HCM. Simple things like drinking adequate amounts of fluids, and avoiding competitive sports are important. Regular visits with a cardiologist are highly important. Patients with HCM should seek at least one consultation with a cardiologist at a specialized HCM treatment center—such doctors treat many HCM patients, whereas the usual cardiologist will see few in his/her career. Patients with HCM may find themselves in a CCU setting because of acute onset of symptoms of chest pain, shortness of breath or syncope, or the new onset of atrial fibrillation, a rapid irregular heart rhythm. Pharmacologic therapy is the first line of treatment for symptoms of HCM. Drugs are used to treat symptoms

and prevent further complications of HCM. Medications are used to reduce the degree of obstruction in the heart so that it can pump more efficiently. ***β***-blockers, disopyramide, and CCB are medications that may be prescribed for obstruction. If there is an arrhythmia, medications to control heart rate or decrease the occurrence of arrhythmias may be prescribed. Certain medications may need to be avoided; these include nitrates (because they lower blood pressure and worsen obstruction in the heart) or digoxin, dopamine, and dobutamine (because they increase the force of the heart's contraction and worsen obstruction).

If fluid collection in the lungs occurs, treatment is aimed at controlling it through diuretics. Surgical procedures are used to treat HCM when pharmacologic therapy fails to improve symptoms and obstruction. The "gold standard" is surgical septal myectomy. During this open heart surgical procedure, the surgeon removes a small amount of the thickened septal wall of the heart to widen the outflow tract (the path the blood takes) from the left ventricle to the aorta. This highly effective operation is done at specialized centers with a surgical mortality of <1%. Another important complication is the need for permanent pacing because of interruption of the normal electrical pathway of the heart. Alcohol Septal Ablation is another approach that involves cardiac catheterization to locate the small coronary artery that supplies blood flow to the septum. Small amounts of pure alcohol are injected through the catheter, which kills the cells on contact, causing a small "controlled" heart attack. This therapy decreases the contractile force of the heart and decreases obstruction in that way acutely. Later, the septum shrinks back to a more normal size over the following months, widening the passage for blood flow. Most HCM centers reserve ASA for patients who have substantial complicating medical illnesses or old age and frailty because the procedural risks are comparable to surgical myectomy, but the results are overall not as satisfactory.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

ICD are suggested for people at risk for life-threatening arrhythmias or SCD. The ICD constantly monitors the heart rhythm. When it detects a very fast, abnormal heart rhythm, it delivers small electric currents or shocks to the heart muscle to cause the heart to beat in a normal rhythm again. A small number of people with HCM have an increased risk of SCD. People at risk include the

following: (1) Patients with massive thickening of the left ventricle wall (exceeding 3 cm). (2) Those who have family members who have had SCD at a young age, thought to be because of HCM. (3) Young patients with HCM with fainting without cause. Generally, this is considered most important when blackout has happened within the last 6 months. (4) Adults who have a history of arrhythmia with a fast heart rate originating from the ventricles, called ventricular tachycardia. (5) Those with severe symptoms and poor contractile heart function. If risk factors are present, the strategy of the ICD is discussed with the patient, and the decision to implant depends on physician judgment and patient choice.

MANAGEMENT OF ACUTE DECOMPENSATION IN PATIENTS WITH HCM

The initial step in treating patients with acute decompensated HCM with obstruction involves discontinuing any medications that could dilate the peripheral vessels and cause the blood pressure to drop. The most common cause of acute decompensation in HCM patients is an arrhythmia called atrial fibrillation. This arrhythmia may speed up the heart rate. Usually, slowing it with medications is sufficient. However atrial fibrillation may cause the heart to fail, which translates into a dramatic drop in blood pressure. In this case, the arrhythmia might need to be stopped by performing a cardioversion. Anticoagulation with blood thinners such as heparin or low-molecular-weight heparin is indicated because emboli are very common in HCM patients. There should be a low threshold to refer patients for TEE to exclude the presence of thrombus prior to cardioversion. If there is no left atrial appendage thrombus noted, cardioversion may be performed either electrically or with medications with a plan to continue oral blood thinners, such as warfarin or other newer oral anticoagulants. Frequent episodes of atrial fibrillation may warrant referral for definitive treatment of the arrhythmia with procedures such as catheter-based ablations. In HCM patients who develop atrial fibrillation, the risk of embolic events is high (ie, incidence is 2.5%/year). All patients with HCM and atrial fibrillation should continue lifelong anticoagulation to reduce the risk of stroke and embolic events.

16

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Cardiac Magnetic Resonance Imaging in the Cardiac Care Unit

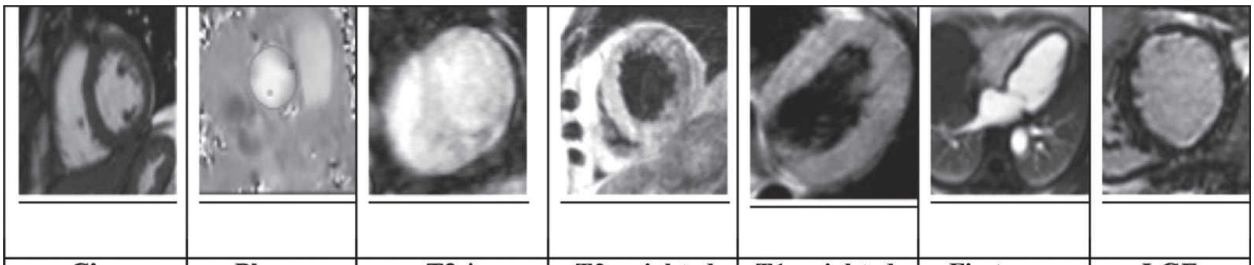
INTRODUCTION

The diagnosis and management of patients in the cardiac care unit (CCU) often requires the inclusion of data obtained by cardiac imaging. Although echocardiography and catheter-based coronary angiography are more commonly used, noninvasive cross-sectional imaging modalities such as cardiac computed tomography (CT) and cardiac magnetic resonance (CMR) are frequently necessary for clinical care as well. Without the use of ionizing radiation, CMR generates a signal (image) by altering the magnetic properties of hydrogen protons in the body through the application of radiofrequency pulses and magnetic gradients within a static magnetic field. The images generated can be very helpful in defining anatomy, function, and tissue characteristics of cardiac structures and the great vessels. In this chapter, we focus on CMR techniques and evaluations that would be relevant to the house staff who are on CCU rotation.

CARDIAC MAGNETIC RESONANCE SEQUENCES IN BRIEF

Different combinations of radiofrequency pulses and magnetic gradients,

generically termed sequences, enable acquisition of different types of images. Basic CMR sequences **(Figure 16.1)** include cine imaging, first-pass perfusion, phase-contrast, T1-, T2- and T2*-weighted imaging, early and late gadolinium enhancement (LGE) and magnetic resonance angiography (MRA).[1]



Cine	Phase Contrast	T2 *	T2 weighted	T1 weighted	First pass perfusion	LGE
Ventricular volumes, mass, ejection fraction, and wall motion assessment	Valvular stenosis and regurgitation, Qp/Qs	Iron deposition, intramyocardial hemorrhage	Presence of edema	Identification of fat, differentiation of chylous fluid and hemorrhage from simple fluid	Assessment of blood flow, microvascular obstruction	Assess for fibrosis/infarction

FIGURE 16.1 Common cardiac magnetic resonance sequences. LGE, late gadolinium enhancement.

- **Cine** imaging provides anatomic and functional details on chamber volumes and wall motion.
- **First-pass perfusion imaging** demonstrates perfusion defects, including microvascular obstruction (MVO).
- **Phase-contrast** imaging provides accurate data on the flow through the valves, including peak velocities, regurgitant volumes, and the ratio of pulmonary to systemic blood flows (Qp/Qs) as in the case of shunts.
- **T1- and T2-weighted** sequences assist with characterization of myocardial tissue, including myocardial edema, blood, thrombus, and fat. **T1- and T2-mapping** sequences provide more accurate and objective measures of tissue characterization compared to more subjective visual assessments. Although currently restricted largely to investigational use in the United States, these sequences are increasingly demonstrating abnormal myocardial parameters in various pathologies including, but not limited to, amyloidosis, cardiomyopathies, myocarditis, and autoimmune diseases.
- **T2*-weighted** sequences demonstrate the presence of myocardial iron and can

assist with identification of myocardial hemorrhage.

- **Early gadolinium enhancement** shows areas of no reflow and the presence of MVO, as well as increased myocardial signal intensity in myocarditis due to increased capillary leakage.
- **LGE** demonstrates areas of infiltration, necrosis, or fibrosis in characteristic patterns that can help diagnose the etiology of cardiac pathology.

MAGNETIC RESONANCE IMAGING SAFETY—PRACTICAL ASPECTS

CMR is a safe and valuable modality for the practicing cardiologist, but there are several important safety parameters to consider. To maximize image quality and minimize adverse events (which are rare), careful patient selection is crucial. The CCU patient will usually require an accompanying nurse and/or a physician for close monitoring and/or to administer medications as needed. The patient should be able to lie down flat for the duration of the examination up to 30 to 60 minutes, and he/she should ideally be able to follow breathing instructions. Typically, the patient is instructed to hold his/her breath for 10 to 15 seconds. Lack of cooperation can significantly impact image quality and even render the examination nondiagnostic. This may occur in patients who are in decompensated heart failure (HF) or who have underlying lung disease, altered mental status, or significant language barriers. The latter can be overcome by having a translator communicate with the patient from the control room. When patients are unable to the hold their breath, free-breathing alternatives such as real-time cine imaging often provide diagnostic image quality at the possible expense of a longer examination time.

A small proportion of patients (estimated around 2% to 4%) have significant claustrophobia. Of those, about half can be scanned by maximizing patient comfort with the use of blindfolds, appropriate lighting, and temperature control, or by having a family member available and maintaining verbal contact. Severe claustrophobia can be mitigated with a short-acting anxiolytic to be taken before the study (such as a low-dose benzodiazepine), avoiding oversedation that will impact cooperation with breathing instructions. Cardiac rhythm abnormalities are also important to consider. Tachyarrhythmias, including rapid atrial fibrillation/flutter and sinus tachycardia, can lead to blurry images, particularly on specific sequences. It may be helpful to control the heart rate with oral and/or intravenous (IV) beta-blocker before the examination, if medically appropriate. Frequent premature beats or bigeminy can have an impact on image quality. In

these cases, real-time cine imaging can also be helpful in improving image quality. While arrhythmias can reduce the accuracy of volumetric measurements, a diagnostic CMR study can be obtained in most cases.

The risks of CMR are primarily related to the generated static magnetic field, at a magnitude of 1.5 or 3.0 Tesla, representing 30,000 to 60,000 times the Earth's magnetic field strength. This can lead to ferromagnetic interactions causing motion or dislodgement of a ferromagnetic device or implant within the magnetic bore. Radiofrequency pulses can also result in local heating by concentrating energy around implanted wires or leads. Because of these risks, there are several devices that are categorized as unsafe because of their known hazard in all CMR environments. These are considered contraindicated and they include pacemakers (permanent or temporary), implantable cardioverter defibrillators (ICDs), and Swanz-Ganz catheters. A number of the newer pacemaker/ICDs are deemed magnetic resonance safe and are characterized as "MRI conditional" (magnetic resonance imaging conditional—meaning they can be scanned safely under specific conditions). Even though these devices are relatively safer, they can still produce significant artifacts that may render a cardiac scan nondiagnostic. Patients with these devices should be evaluated on a case-by-case basis and imaged at experienced CMR centers. Some of the transdermal medications (such as nitroglycerine patches) contain ferromagnetic components and should be removed before the CMR study. **Table 16.1** provides a comprehensive list of MRI-unsafe and MRI-safe or MRI-conditional devices.

TABLE 16.1 MRI Safety of Devices and Implants

MRI UNSAFE	MRI SAFE AND/OR CONDITIONAL (≤3.0 TESLA)
Permanent pacemakers[a]	Prosthetic heart valves
Implantable cardioverter defibrillators[a]	Intracoronary stents
Temporary transvenous pacemakers	Prosthetic joints
Insulin pumps	Dentures
Some medication patches	Implantable rhythm monitors[c]
Swan-Ganz catheters	Retained epicardial leads
Metal foreign bodies in the eyes	Occluder devices[d]

Brain aneurysm clips[b]	Peripheral stents[d]
Cochlear implants	Aortic aneurysm stents[d]
	Inferior vena cava filters[d]

[a]MRI-compatible pacemakers and implantable cardioverter defibrillators are now approved by the Food and Drug Administration and can be scanned under certain conditions at experienced cardiac magnetic resonance centers.
[b]More contemporary aneurysm clips are nonferromagnetic; however, confirmation with the implanting physician and manufacturer is absolutely required.
[c]Rhythm monitors can be conditional or unsafe, check with the manufacturer.
[d]If weakly ferromagnetic, it is recommended to wait 6 weeks post implantation.
MRI, magnetic resonance imaging.

One of the most significant (and avoidable) complications of contrast-enhanced CMR is nephrogenic systemic fibrosis (NSF). This occurs in patients with advanced renal insufficiency receiving gadolinium-contrast agents. Gadolinium is a lanthanide metal containing paramagnetic Gd^{3+} ions that enhances image contrast when administered intravenously. It is renally excreted with an elimination half-life of 60 to 90 minutes (18 to 34 hours in patients with renal insufficiency). NSF may occur in patients with advanced (stage 4 to 5) chronic kidney disease or acute kidney injury (AKI), particularly AKI of any severity in the setting of hepatorenal syndrome or in the liver peri-transplant period. It is characterized by fibrosis of skin, joints, eyes, and internal organs; approximately 5% of patients will have a debilitating course and, rarely, die.[2] Recommendations for NSF prevention are summarized in **Table 16.2**.

TABLE 16.2	MRI in Specific Patient Populations
Chronic kidney disease, renal insufficiency	eGFR <30 mL/min/1.73 m^2: use lowest possible dose (≤0.1 mmol/kg), avoid high-riska contrast agents
	ESRD: avoid contrast agents; if absolutely necessary, use lowest dose, avoid high-risk agents, consider hemodialysis 2 h afterward, and the following day
	AKI: avoid contrast agents (regardless of eGFR); if absolutely necessary, use lowest dose, avoid high-risk agents
Pregnancy	Gadolinium contrast agents should be avoided
	No evidence of teratogenic effects of noncontrast MRI studies

*High-risk contrast agents have a linear chemical structure, as compared with the safer macrocyclical contrast agents.
AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MRI, magnetic resonance imaging.

To enhance patient safety and selection for CMR, dedicated questionnaires that address all the important safety precautions have been developed. It is important to have a trained professional carefully administer these questionnaires and instruct the patient to provide accurate answers to all questions. It is also important to consider specific patient populations such as pregnant patients or patients with renal insufficiency **(Table 16.2)**.

CARDIAC MAGNETIC RESONANCE IN ACUTE CHEST PAIN

The differential diagnosis for acute chest pain (often with troponin elevation) is extensive and can be broadly divided into cardiac and noncardiac etiologies. In this chapter, we focus on the coronary causes of chest pain with troponin elevation in the acute and subacute phases as well as explore common noncoronary causes of chest pain and troponin elevation that are often seen in the CCU. **Table 16.3** briefly outlines some of the more common causes of chest pain, highlighting the disorders where CMR plays a significant role. It is important to realize that troponin elevation is sensitive but not specific for the detection of cardiac damage. It does not completely differentiate coronary from noncoronary causes of chest pain. Virtually any strain on the heart, whether from coronary occlusion, pulmonary embolism, or pneumonia, for example, can cause a troponin elevation. The decreased clearance of troponin in renal insufficiency can also lead to troponin elevation in nearly any setting.

TABLE 16.3 Differential Diagnosis of Chest Pain

CARDIAC	VASCULAR	GI	PULMONARY	OTHER
Acute coronary syndrome*	Aortic dissection*	Esophageal spasm	Pulmonary embolus	Rib fracture
Myocarditis*	Intramural hematoma*	Esophagitis	Pneumothorax	Costochondritis
Pericarditis*	Aortic ulcer*	Peptic ulcer disease	Pneumonia	Herpes zoster
Cardiac trauma*	Aortic aneurysm	Pancreatitis	Pleuritis	
Takotsubo cardiomyopathy*		Cholecystitis		

Boerhaave syndrome

* Conditions in which CMR is potentially useful for diagnosis

ACUTE CORONARY SYNDROME

One of the most common presentations seen in the CCU is the acute coronary syndrome (ACS). Thankfully, the mortality and morbidity rates have consistently declined for acute myocardial infarction (MI), in large part because of better diagnostics and treatment, such as statin therapy and early invasive angiography. Although the incidence of ST-segment elevation myocardial infarction (STEMI) has decreased, as the population ages, the consequences of ACS will continue to grow.

Cardiac Magnetic Resonance in Acute Coronary Syndrome

For the patient with acute STEMI or non-STEMI (NSTEMI)/unstable angina with high-risk features, an early invasive approach is favored. The initial use of CMR in these patients is limited because any delay in revascularization can lead to worse outcomes. CMR after revascularization, however, can provide important prognostic information after an ACS. For stable patients without a diagnosed ACS, an imaging modality initially can be very beneficial in determining the etiology of symptoms. CMR may prevent unnecessary invasive angiography as well as identify patients who would receive greater benefit from an early invasive strategy. Kwong et al[3] studied 161 patients with chest pain and a nondiagnostic electrocardiogram (ECG) who had a CMR combining different sequences within 12 hours of presentation. The sensitivity and specificity for acute MI or unstable angina was 84% and 85%, respectively. CMR was far more sensitive than strict ECG criteria for ischemia, peak troponin-I, and thrombolysis in myocardial infarction (TIMI) risk score, and was more specific than an abnormal ECG.[3] Plein et al[4] showed that CMR, also by combining different sequences, can identify high-risk patients with significant coronary stenosis in patients with chest pain in the absence of STEMI. In a study with 72 patients with NSTEMI/unstable angina, a comprehensive CMR protocol predicted the presence of coronary stenosis with greater accuracy than did the TIMI risk score.[4]

Outside of the acute phase of presentation, CMR also adds significant information in determining the extent of MI, ventricular remodeling, the

presence of MVO, and the degree of viability. These parameters provide useful information that can assist with prognosis and treatment.

Functional Assessment

Using CMR to detect the presence and extent of wall motion abnormalities can be a helpful tool to determine patients most at risk, who would then benefit from more aggressive medical therapy and an early invasive strategy.

Subtle wall motion abnormalities that may be missed on echocardiography can often easily be seen on cine imaging in CMR because of its superior image quality**.** Wall motion abnormalities that correlate with a coronary distribution can further provide support for ACS in patients without STEMI.

In stable, low-risk patients who present with acute chest pain, CMR can be highly predictive of ACS in the near future. In one study, the presence of wall motion abnormalities on CMR, regardless of perfusion abnormalities and infarction, had greater sensitivity and specificity than did troponin elevation in predicting ACS or a positive stress test within 8 weeks.[3]

Common sequelae of ACS include left ventricular (LV) dilation **(Figure 16.2)**, wall motion abnormalities, and the formation of aneurysms. Cine imaging provides quantitative assessment of LV volumes, wall motion abnormalities, and LV and right ventricular (RV) function with greater accuracy and reproducibility than two-dimensional echocardiography. The degree of LV dilatation and reduction in left ventricular ejection fraction (LVEF), in addition to scar burden and MVO, significantly predicts patients at risk for future cardiovascular events.[5]

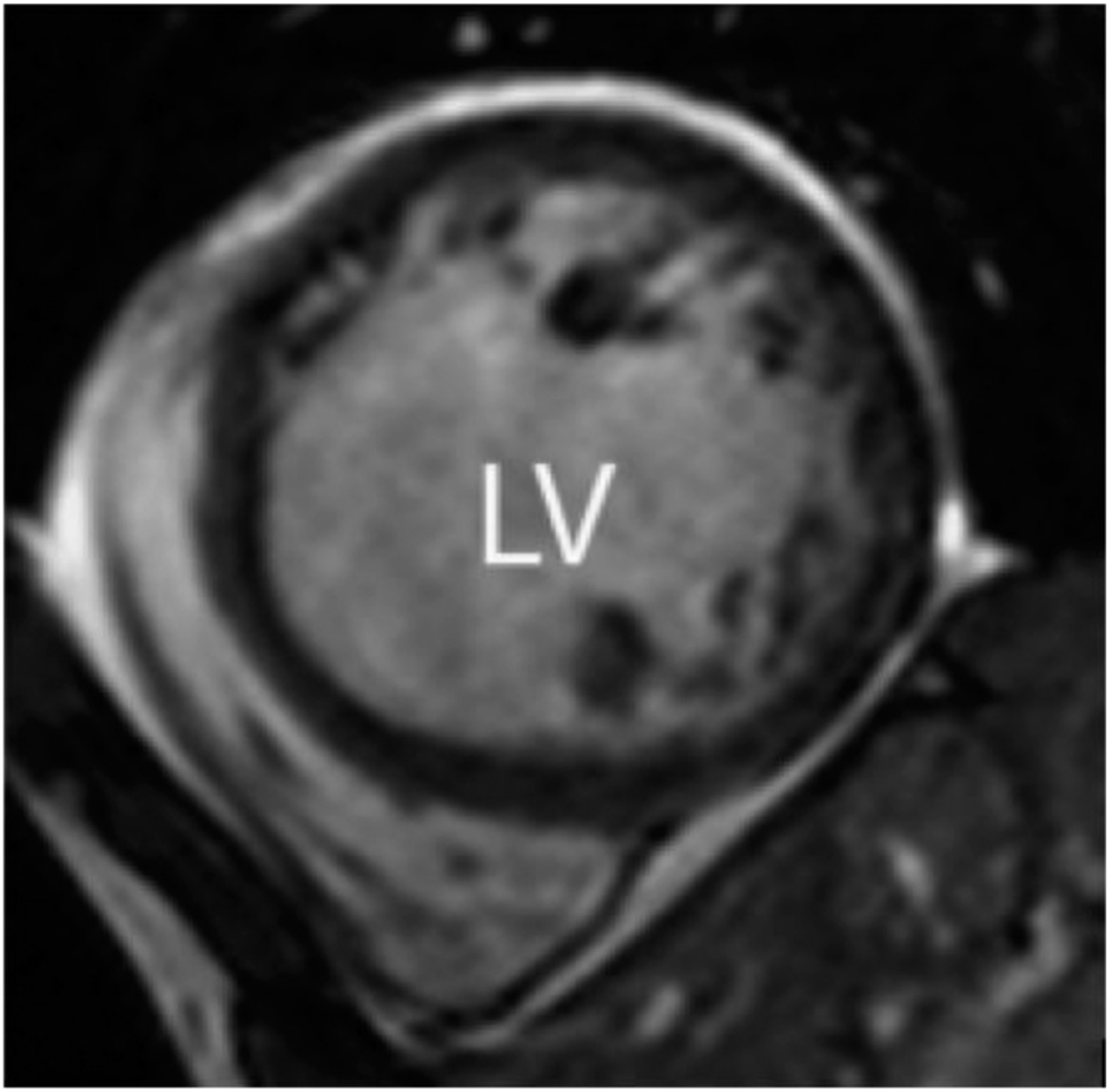


FIGURE 16.2 Short-axis view demonstrating a dilated left ventricle with a measured diastolic volume of 351 cc. LV, left ventricle.

Ischemia

The detection of ischemia on first-pass perfusion imaging can also reliably detect coronary disease even before wall motion abnormalities may be seen. Using a bolus of contrast with fast CMR sequences **(Figure 16.3)**, perfusion defects can become readily apparent. Normal myocardium will enhance, whereas relatively underperfused areas will appear dark for a certain amount of time.

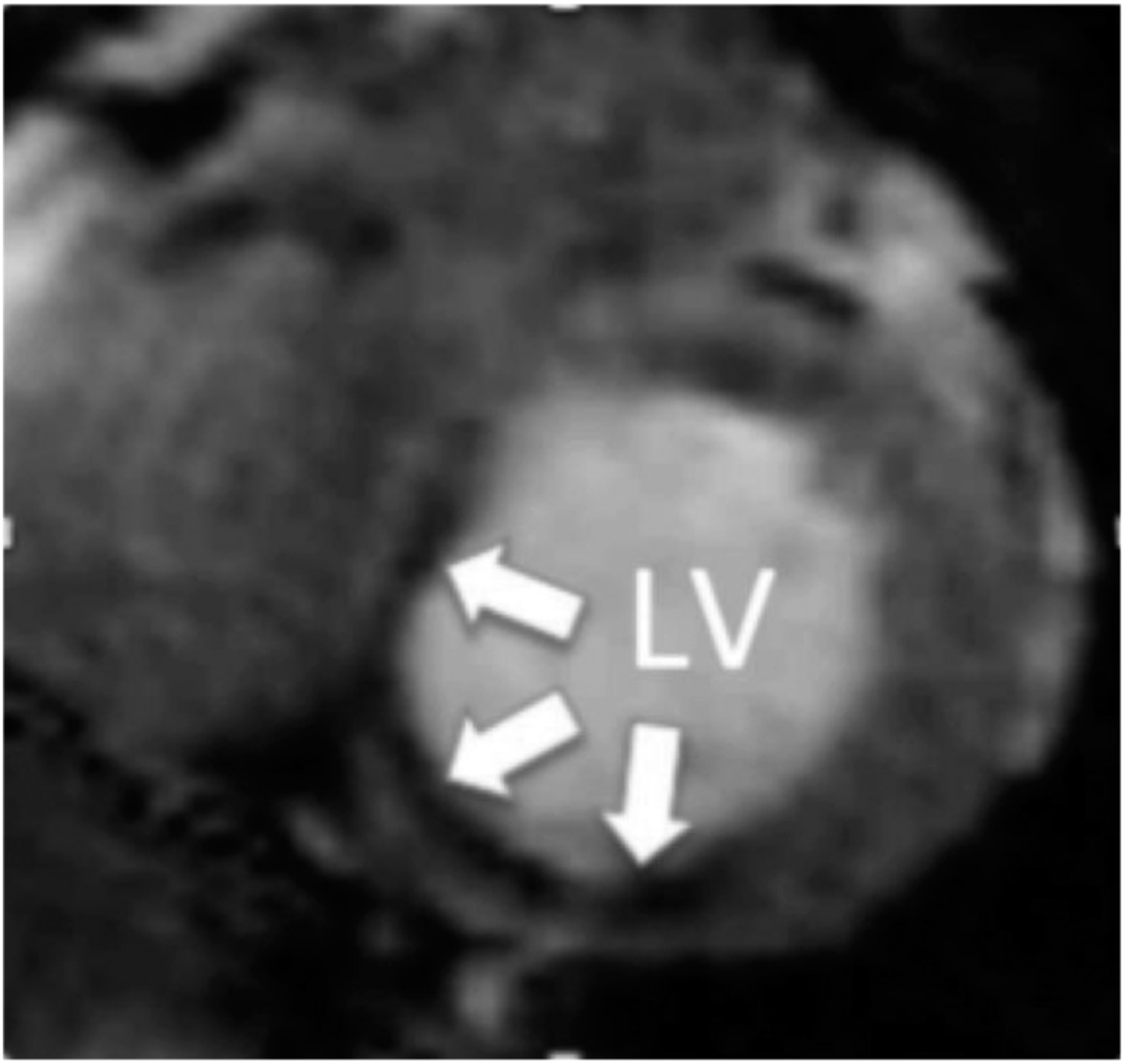


FIGURE 16.3 Short-axis view showing perfusion defects in the inferoseptal and inferior walls on first-pass perfusion imaging (white arrows). LV, left ventricle.

Myocardial Edema

Myocardial edema can be seen in many forms of myocardial injury and is not specific to acute MI. It can, however, be helpful in determining the acuity of an MI as well as the extent of injury. T2 relaxation time is a useful MRI parameter and is directly correlated to the percentage of free water. Myocardial edema in the setting of acute/subacute injury, myocyte swelling, and increased cell permeability in necrotic and ischemic areas accounts for the increase in free water and signal seen on T2-weighted imaging **(Figure 16.4)**. Of note, edema

after an ACS occurs in areas of both irreversibly and reversibly injured tissue and can overestimate the degree of myocardial necrosis. Myocardial edema may persist for weeks after infarction even after troponin levels have decreased to normal levels. A chronic infarct, on the other hand, will not have features of myocardial edema because water is resorbed and a fibrotic scar is formed, thus allowing CMR to distinguish between acute and chronic infarction. Cury et al[6] studied 64 patients presenting with chest pain, a normal ECG, and negative cardiac enzymes. Adding a T2-weighted sequence to cine imaging and LGE improved the specificity, positive predictive value, and accuracy in detecting ACS before a rise in serum biomarkers.[6]

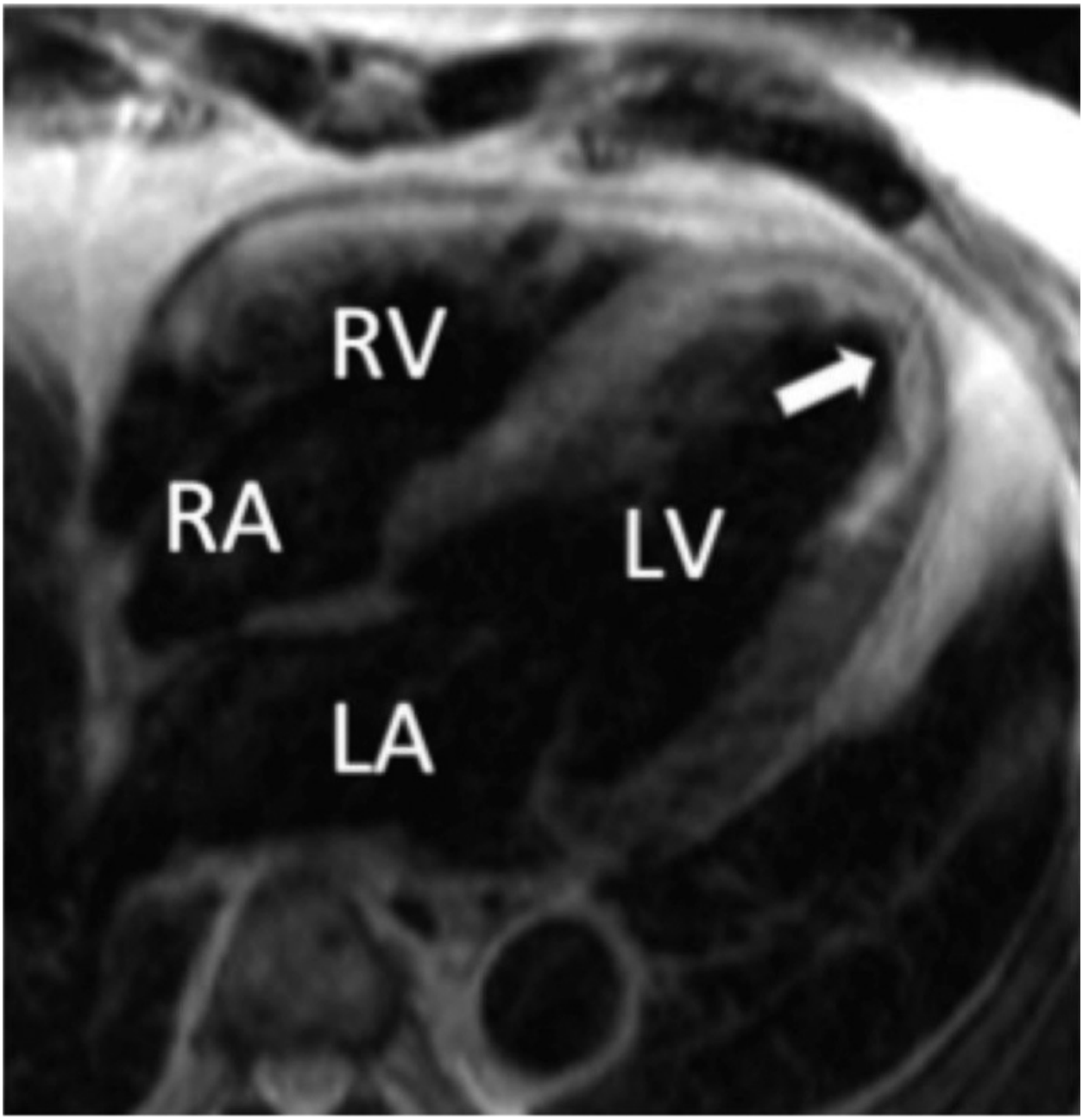


FIGURE 16.4 T2-weighted imaging demonstrating the presence of myocardial edema in the apical, apical lateral, and apical septal walls (*white arrow*) after acute myocardial infarction. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

In addition, combining T2-weighted imaging with LGE, a myocardial salvage index (MSI) can be calculated as the difference between the T2-intense region (area at risk) and final infarct (LGE), and used to predict outcomes after STEMI. Eitel et al[7] studied 208 patients with STEMI who had angioplasty within 12 hours of symptom onset and demonstrated that CMR-derived MSI can predict

long-term clinical outcomes, including major adverse cardiovascular events (MACE) and mortality.

Myocardial Infarction (Late Gadolinium Enhancement)

Gadolinium-contrast agents accumulate in extracellular space and do not enter healthy cells. In the acute MI phase, degradation of myocardial cell membranes allows contrast to enter the damaged cells if given enough time, appearing bright on LGE imaging. In the chronic setting, the contrast accumulates temporarily in the enlarged interstitial space occupied by fibrotic tissue **(Figure 16.5)**. Assessment of scar and viability is discussed subsequently**.**

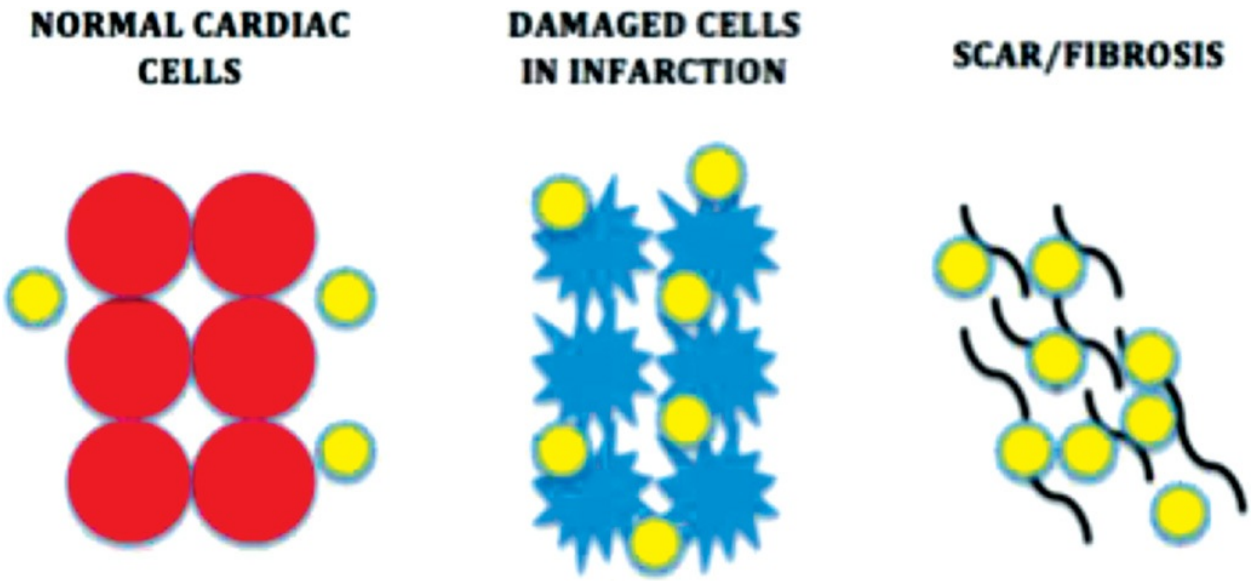


FIGURE 16.5 Deposition of gadolinium-contrast agents. Red—healthy cells; blue—acutely damaged cells; black—scar/fibrosis; yellow—gadolinium contrast.

Multiple studies have demonstrated the close correlation between LGE and histopathologic specimens of necrotic tissue. LGE is capable of detecting infarctions as small as 1 g due to the outstanding spatial resolution of CMR**.** Other imaging modalities are limited in their ability to differentiate small infarctions because of lower spatial resolution. The right ventricle, in particular, is poorly imaged by echocardiography, and acute RV infarction is more often demonstrated by LGE on CMR **(Figure 16.6)** than with the combination of ECG and echocardiography.

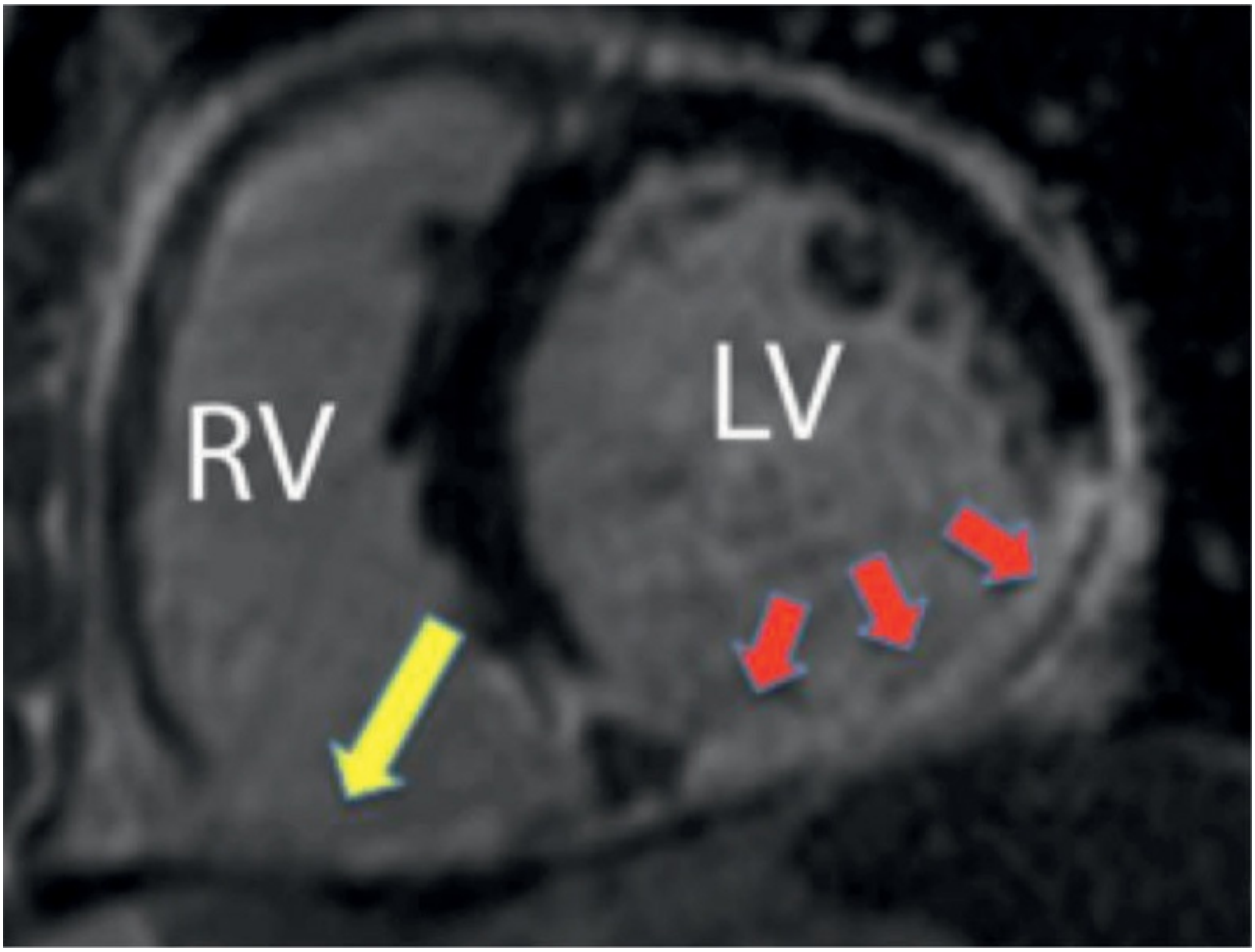


FIGURE 16.6 Short-axis view in delayed enhancement images demonstrating near transmural infarction of the inferior and inferolateral walls of the left ventricle (LV; *red arrows*) and near-transmural infarction of the inferior wall of the right ventricle (RV; *yellow arrow*). LV, left ventricle; RV, right ventricle.

Microvascular Obstruction and Intramyocardial Hemorrhage

Despite successful revascularization of their coronary arteries, subsets of patients have MVO**.** First-pass perfusion, early gadolinium enhancement, and/or LGE imaging can delineate these areas as a region without enhancement within the infarct core **(Figure 16.7)**, as a consequence of the lack of blood flow depositing contrast in these areas.

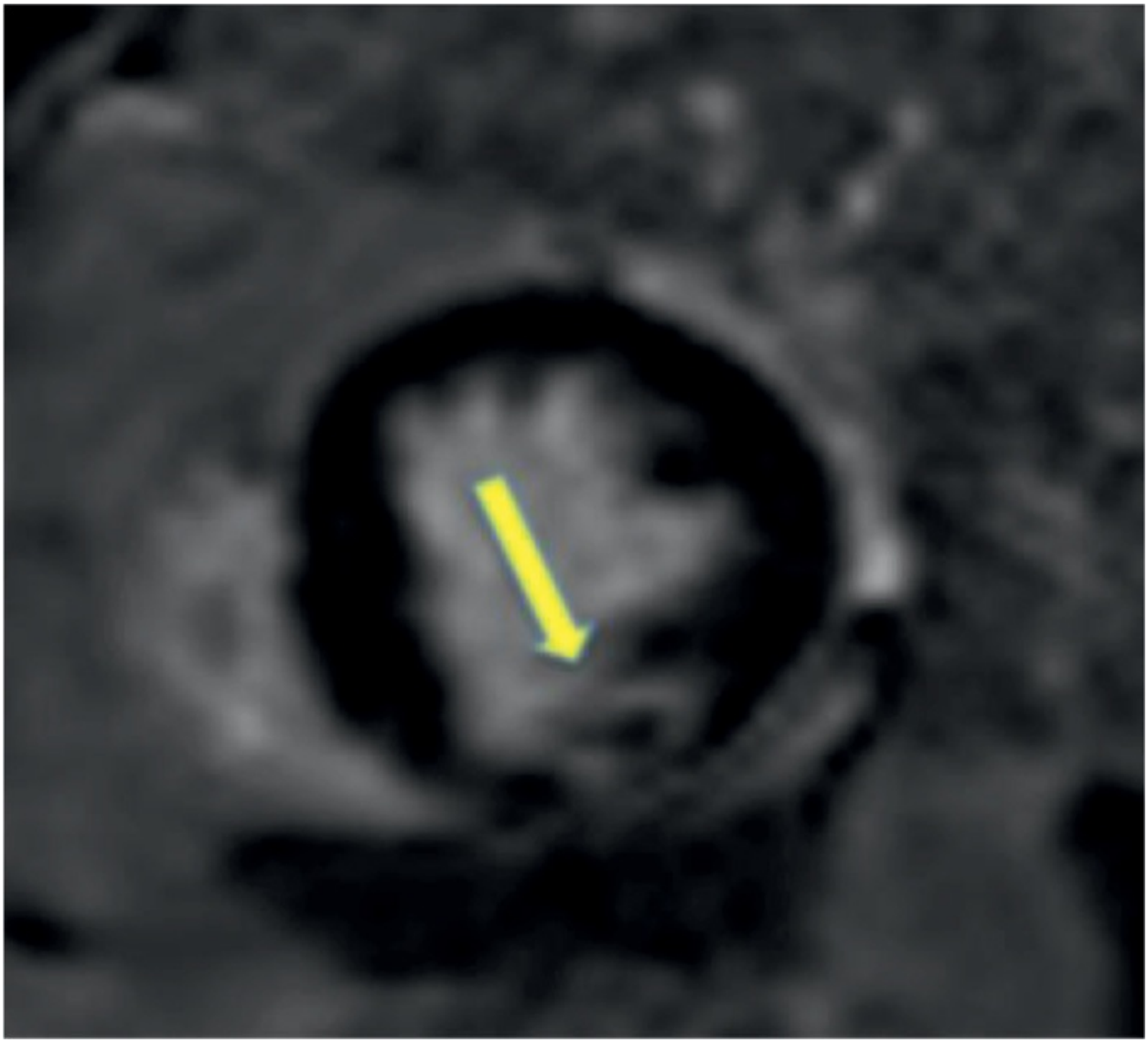


FIGURE 16.7 Short-axis view demonstrating a central hypointense core within an area of enhancement (*arrow*), signifying the presence of microvascular obstruction.

The presence of MVO has been demonstrated as an independent predictor of adverse LV remodeling and MACE. Hombach et al[5] studied 89 patients within 10 days of acute MI and concluded that, in addition to LV end-diastolic volume and LVEF, persistent MVO was a significant predictor of MACE.[5]

Viability

LGE is a useful tool to evaluate viability after ACS as well as provide prognostic information. The extent of the fibrosis is assessed by measuring the number of segments affected using a 17-segment model, as well as the percentage of

thickness involved in each segment. Segments with a small amount of fibrosis are often viable and can recover spontaneously if stunned and with revascularization in hibernating myocardium. Conversely, segments that have near transmural or transmural fibrosis are unlikely to recover. This can be a very helpful tool in determining which patients will benefit from revascularization.[8] Subendocardial enhancement that can progress to full transmural enhancement is characteristic of ischemic coronary disease. This is easily differentiated from nonischemic patterns of scar **(Figure 16.8)** that are described in more detail in section "Cardiac Magnetic Resonance in Heart Failure."

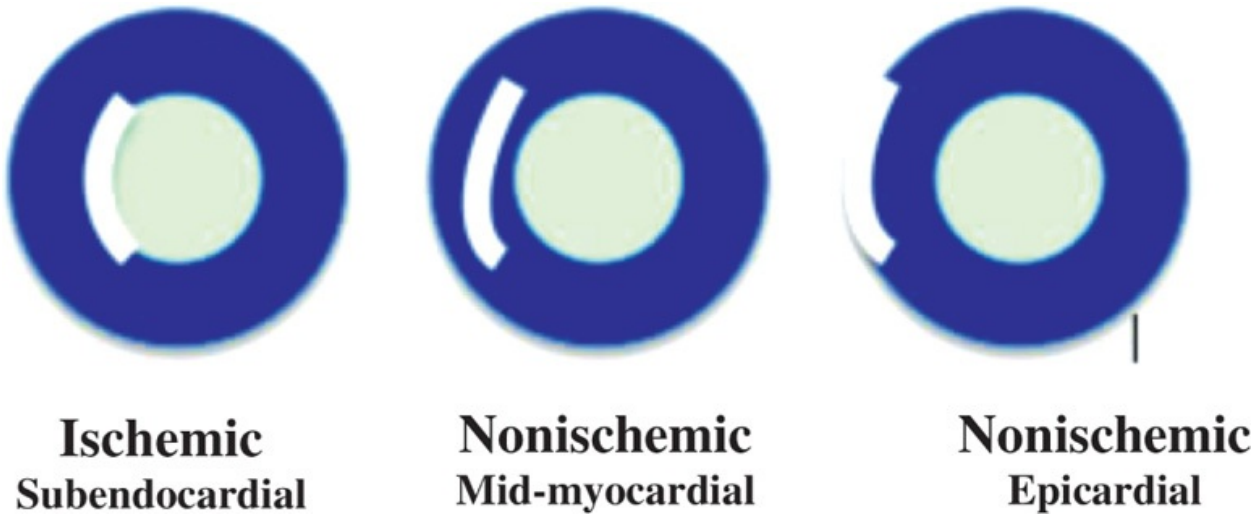


FIGURE 16.8 Fibrosis patterns in ischemic cardiomyopathies compared to nonischemic cardiomyopathies. Green—left ventricular (LV) cavity; blue—myocardium; white—fibrosis.

Cardiac segments with LGE evident in less than 25% to 50% thickness **(Figure 16.9)** are likely to regain function after revascularization, whereas segments with ≥75% enhancement **(Figure 16.10)** are most likely scarred and unlikely to benefit from further intervention. In addition, the amount of transmural infarction on LGE also predicts adverse LV remodeling.

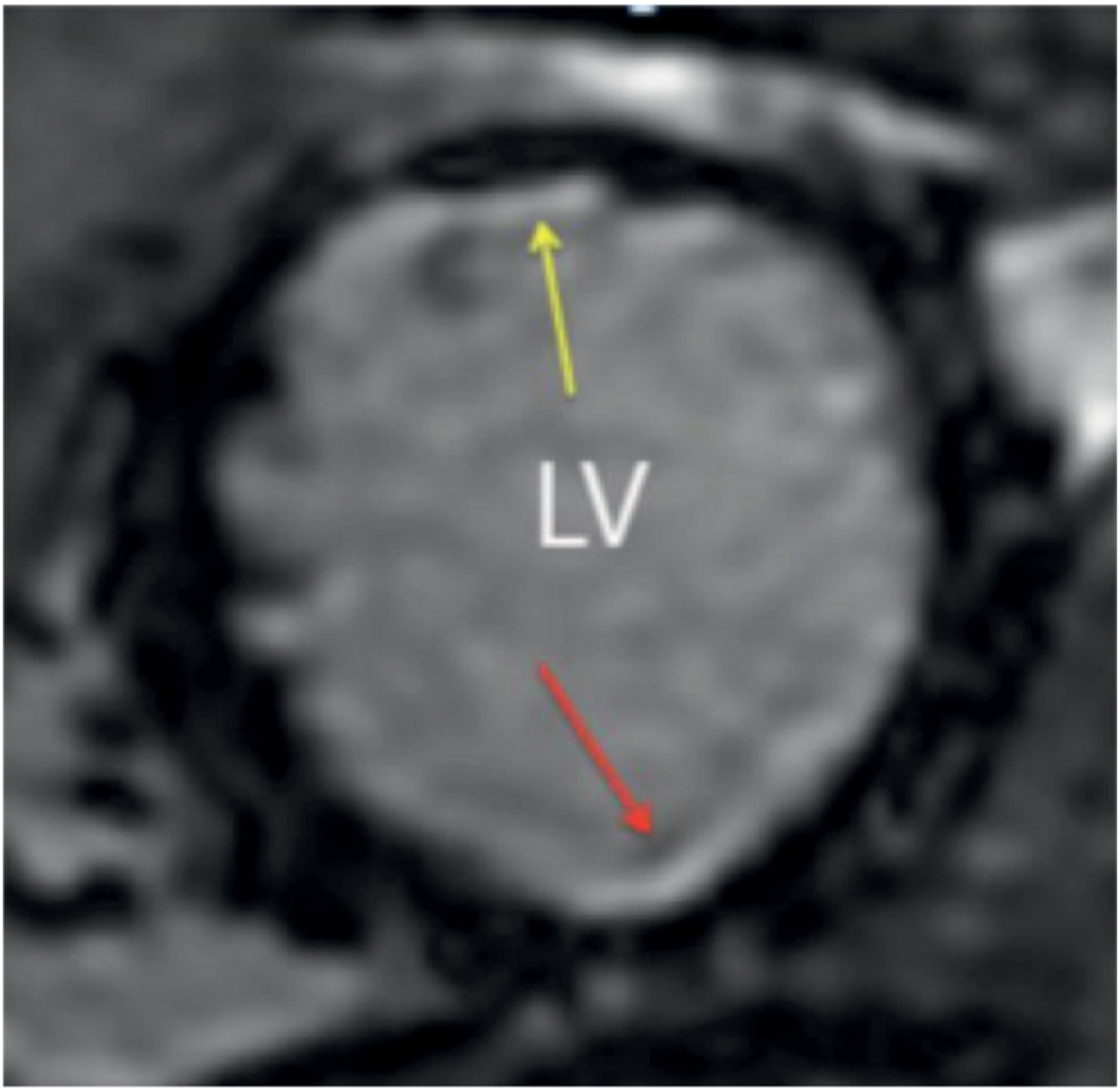


FIGURE 16.9 Short-axis view showing subendocardial infarctions of the anterior wall (*yellow arrow*) and inferior wall (*red arrow*) with a large area of preserved myocardium. LV, left ventricle.

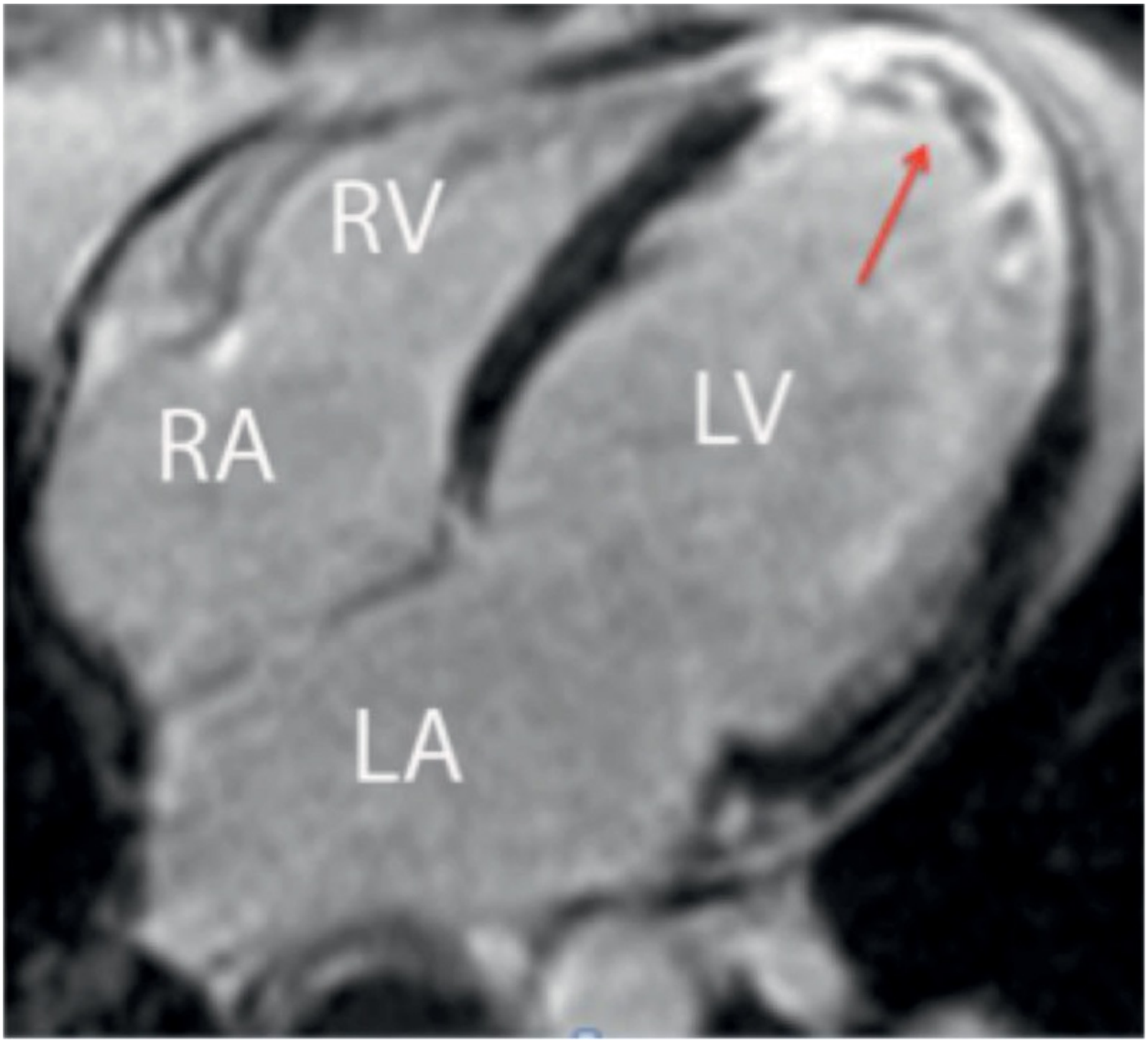


FIGURE 16.10 Four-chamber view demonstrating a large area of transmural infarction involving the LV apex, apical septal, and apical lateral walls (*arrow*). Note the central hypointensity within the area of enhancement, indicating the presence of microvascular obstruction. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

The peri-infarct region (also known as “gray zone” or “border zone”) on LGE imaging, is defined as an area with signal intensity above that of normal myocardium but less than dense scar. It has been recognized as a marker of arrhythmia risk. Whether the peri-infarct zone, overall scar amount, or LVEF alone are better predictors of spontaneous ventricular arrhythmias remains a question. Gouda et al[9] studied 48 patients post MI, half of whom had sustained monomorphic ventricular tachycardia (VT), and evaluated total scar, scar core, mean infarct transmurality, peri-infarct zone, and number of segments with LGE.

In multivariable analysis, total infarct size as percentage of LV mass was the only significant independent predictor of spontaneous and inducible VT.[9]

Post–Myocardial Infarction and Procedural Complications

With the advent of early percutaneous coronary intervention, the incidence of post-MI complications has dramatically decreased. When patients present late after onset of coronary occlusion, there is a greater risk (albeit still small) of dangerous post-MI complications. It is important to be aware of these phenomena because they are often acute and any delay in diagnosis can be fatal. Given the rapidity in onset and clinical deterioration, portable echocardiography is typically the most useful tool. However, if the patient is stable enough, post-MI complications can be more accurately assessed utilizing CMR.

Left Ventricular Thrombus

One of the most common complications of MI is the development of LV thrombus. Thrombus is most common in large anterior infarcts but can develop even in small isolated apical infarctions, as well as in other locations, particularly the septal and inferolateral walls.

Diagnosis by echocardiography, even with contrast administration, is far less sensitive than detection by CMR. Using simple CMR techniques, an LV thrombus can rapidly be distinguished from normal adjacent myocardium. Although contrast echocardiography significantly increased detection of thrombi compared to noncontrast echocardiography, LGE more accurately detected smaller and/or mural thrombi **(Figure 16.11)**.[10] Differentiation between thrombi and other cardiac masses is discussed in section “Miscellaneous.”

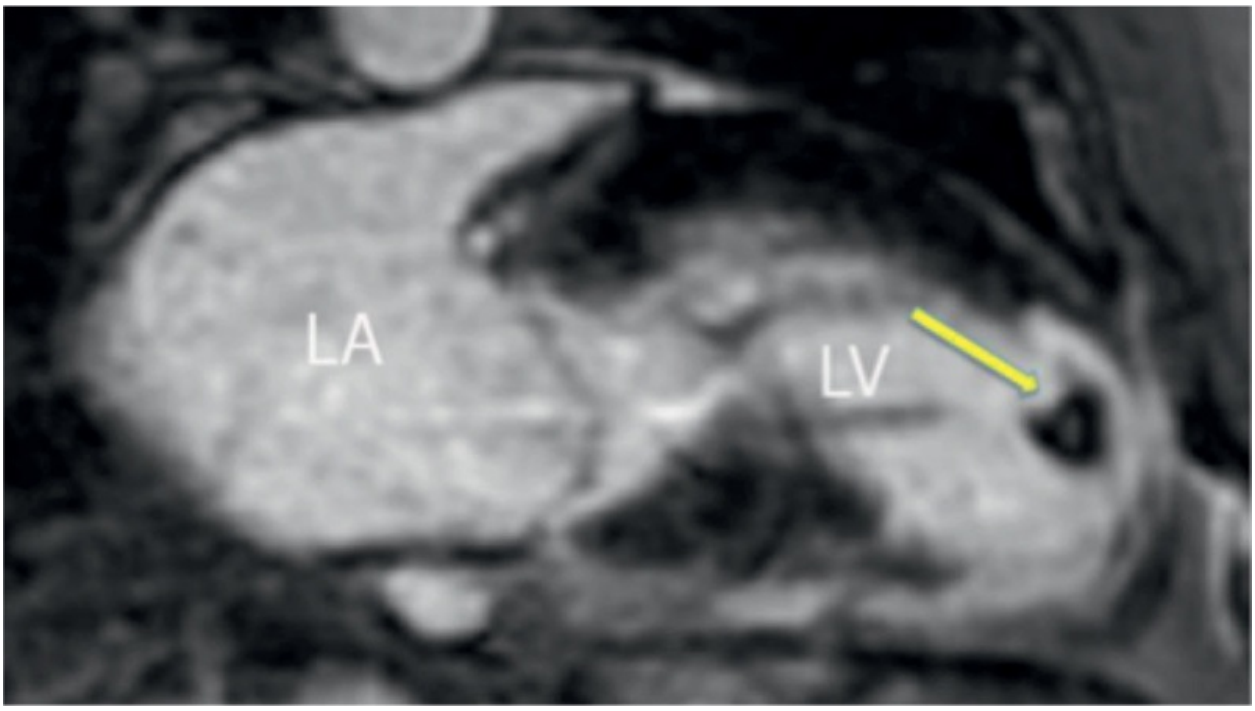
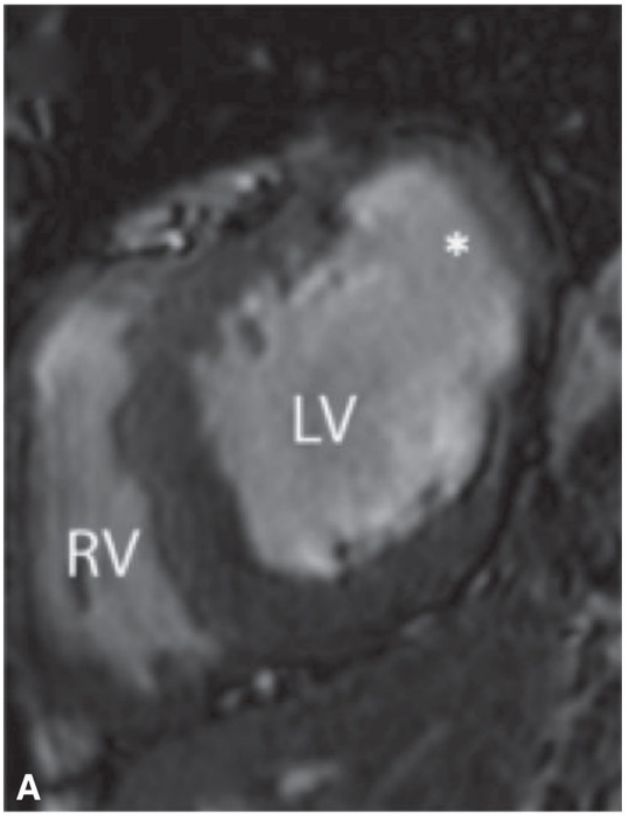


FIGURE 16.11 Two-chamber view demonstrating hypointense LV thrombus (*yellow arrow*) on late gadolinium enhancement imaging. LA, left atrium; LV, left ventricle.

Left Ventricular Aneurysm

Another common complication of acute MI is the development of an LV aneurysm. Typically, an infarcted, thin-walled left ventricle that has remodeled extensively causes the formation of aneurysms. Persistent ST-segment elevations on an ECG in the absence of chest pain or acute MI can indicate the presence of an LV aneurysm. Cine imaging and/or LGE sequences **(Figure 16.12)** can demonstrate the extent of aneurysm formation and clearly delineate the wide orifice that is characteristic of them.


*
LV
RV
A

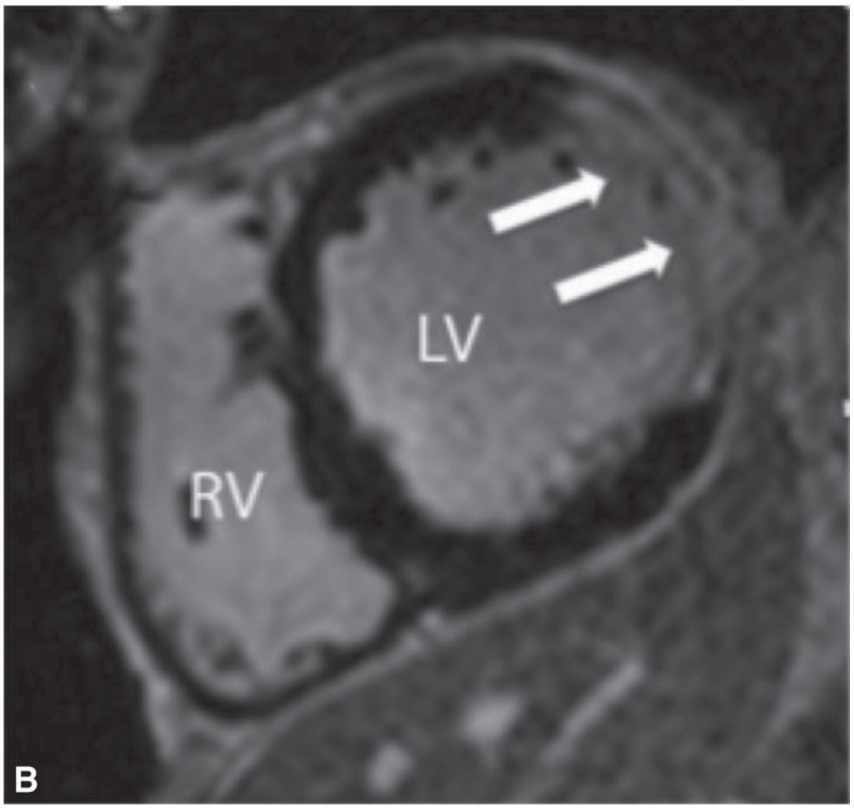

LV
RV
B

FIGURE 16.12 A, Short-axis view in cine images demonstrating a large aneurysm of the anterolateral wall. B, Short-axis late enhancement view demonstrating near-transmural infarction of the aneurysmal myocardial territory. LV, left ventricle; RV, right ventricle.

Left Ventricular Pseudoaneurysm/Free Wall Rupture

Less common, but more urgent, is the diagnosis of pseudoaneurysm/contained wall rupture. A true aneurysm contains all three layers of myocardial tissue (subendocardial, endocardial, and epicardial), whereas a pseudoaneurysm wall is constituted only by pericardium and fibrotic/inflammatory tissue (in essence, a contained free wall rupture) and is at high risk of losing that containment. A pseudoaneurysm typically has a narrow neck.

Uncontained free wall rupture is another rare post-MI complication that can be rapidly fatal. When suspected, immediate diagnosis with portable echocardiography and surgical intervention is often the only chance of survival. Patients are rarely, if ever, stable enough to have a CMR. In the rare case that a patient has a contained free wall rupture, CMR can provide detailed anatomic assessment of the rupture, including site, orifice, material containing the rupture, and other important parameters **(Figure 16.13)**.

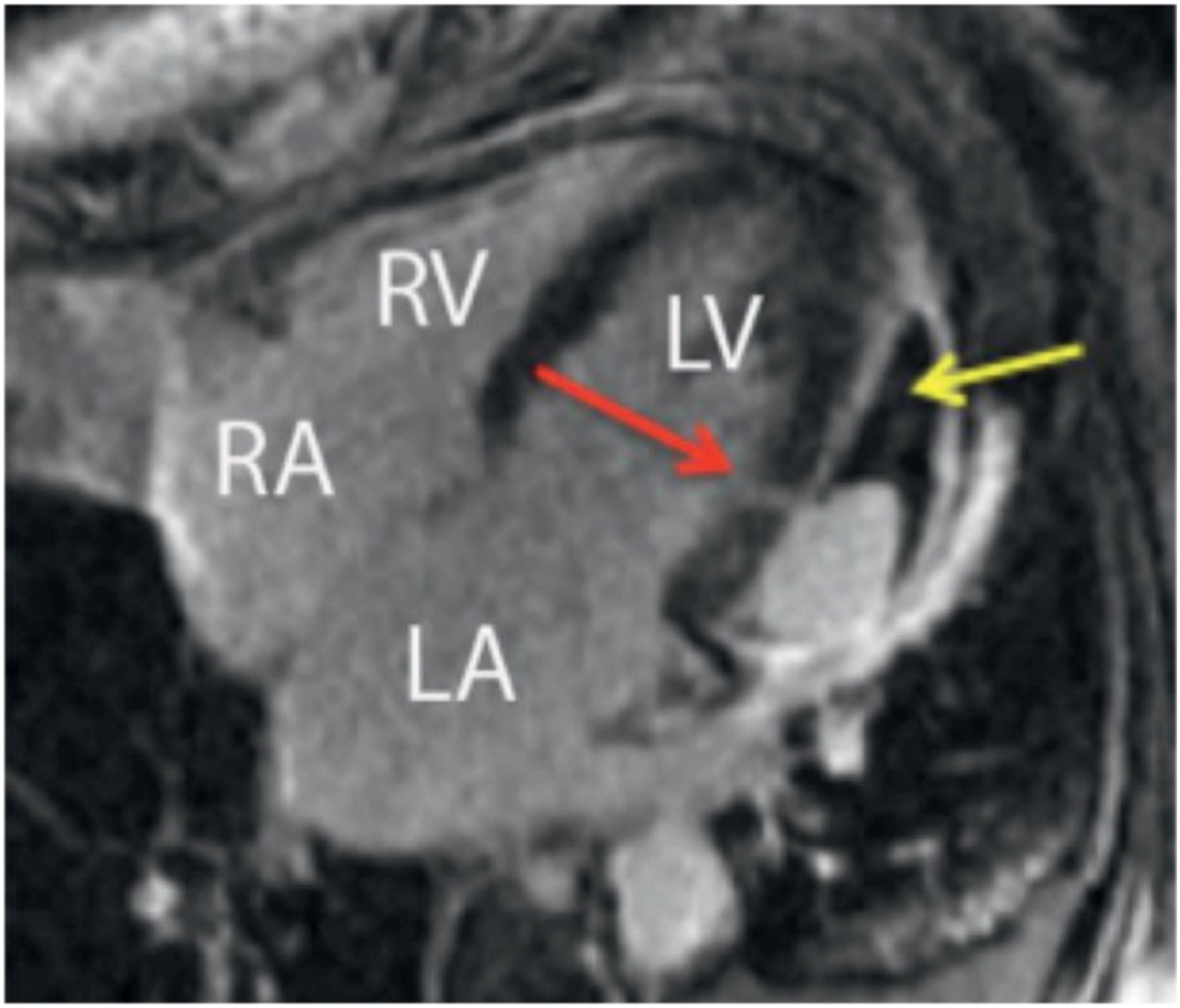


FIGURE 16.13 Free wall rupture contained only by thrombus (*yellow arrow*) and pericardium. Note the narrow neck at the point of rupture (*red arrow*). (Image courtesy of Jiwon Kim, MD, Weill Cornell Medical Center, New York, NY.) LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Ventricular Septal Defect

Ventricular septal defect (VSD) is another rare but potentially fatal complication that typically occurs within 1 week of acute MI. Patients typically present with a new holosystolic murmur, biventricular failure, and cardiogenic shock. Rapid diagnosis and surgical intervention are key to ensuring a patient's survival. Echocardiography is the diagnostic imaging modality of choice when VSD is suspected because of its portability and rapid image acquisition. Very rarely will a patient be stable enough to acquire a CMR to assist with diagnosis. If the patient is stable and there are poor acoustic windows on echocardiography, CMR

can provide excellent anatomic detail of the VSD and calculate the Qp/Qs for shunt quantification.

CARDIAC MAGNETIC RESONANCE IN NONCORONARY CAUSES OF ACUTE CHEST PAIN (WITH OR WITHOUT TROPONIN ELEVATION)

The most common cardiac causes of chest pain and troponin elevation in patients with nonobstructive coronary artery disease are myocarditis, myopericarditis, Takotsubo cardiomyopathy, and acute aortic syndromes.

Myocarditis

Myocarditis (both acute and chronic) remains a diagnostic challenge in clinical cardiology. Myocarditis should be considered in any patient with chest pain, elevated cardiac biomarkers, and normal coronary arteries. In addition, cardiomyopathy may result from chronic inflammatory disease in patients with inadequate immune response. Endomyocardial biopsy (EMB) with immunohistology is the “gold standard” for the diagnosis of myocarditis, but it is an invasive procedure with risks of complications.

CMR has been increasingly used as an aid in the diagnosis of myocardial inflammation in patients with suspected myocarditis. The International Consensus Group on CMR Diagnosis of Myocarditis was founded to establish recommendations on CMR techniques for myocarditis.[11] Infections are one of the most common etiologies of myocarditis, predominantly viral infections or post-viral immune-mediated reactions. Myocardial inflammation may also be triggered by reversible or irreversible toxic, ischemic, or mechanical injury, drug-related inflammation, transplant rejection, or some other immune response.[11] No single clinical or imaging finding confirms the diagnosis of myocarditis. The diagnostic approach should be an integrated synopsis of history, physical examination, noninvasive and invasive testing (LV function and volume as well as CMR tissue characterization) to guide medical therapy.

CMR has the ability to characterize inflammatory tissue changes. One approach is the Lake Louise Criteria (LLC): edema with T2-weighted imaging, hyperemia, or capillary leak with early gadolinium enhancement, and irreversible cell injury with LGE (besides other nonspecific findings such as LV dysfunction and pericardial effusion).[11] These CMR imaging techniques are used to determine the presence of edema, hyperemia, and myocardial

necrosis/fibrosis, which are part of the pathological process seen in myocarditis **(Figure 16.14)**. Several patterns of LGE may be seen in myocarditis, which usually follows a nonischemic pattern. Focal signal intensity may be seen in a subepicardial or intramyocardial pattern and can involve part or the entire extent of the myocardial wall **(Figures 16.15** and **16.16)**.

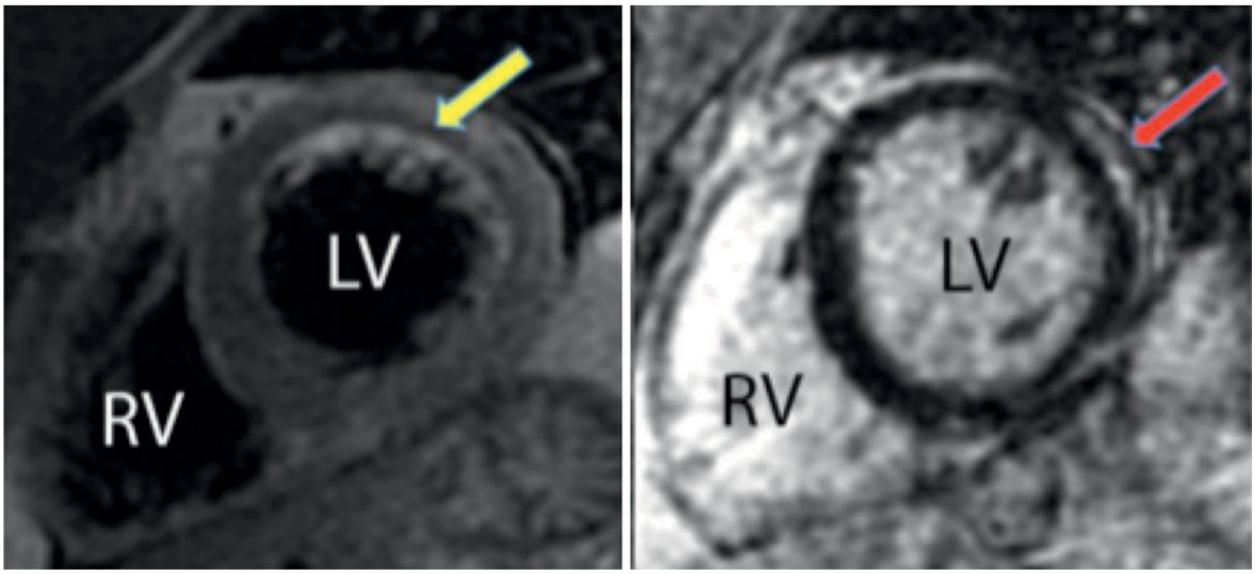


FIGURE 16.14 Myocardial edema on T2-weighted imaging (*yellow arrow*) and subepicardial late gadolinium enhancement (*red arrow*) in a patient with myocarditis. LV, left ventricle; RV, right ventricle.

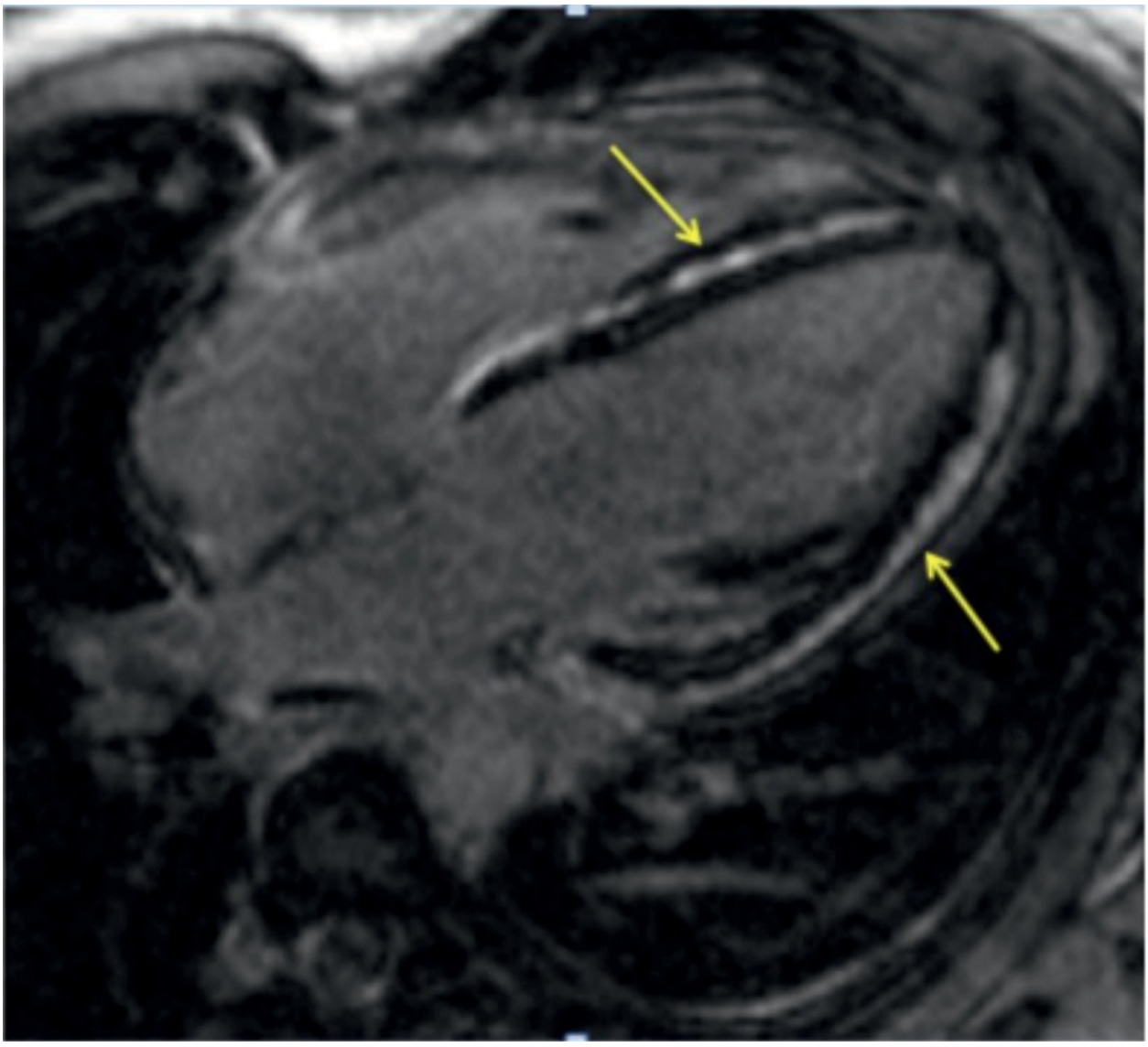


FIGURE 16.15 Late gadolinium enhancement (LGE) imaging in a patient with acute myocarditis. Note the diffuse subepicardial and intramyocardial enhancement, indicated by yellow arrows. (Image courtesy of Adam Jacobi, MD, Mount Sinai Hospital, New York, NY.)

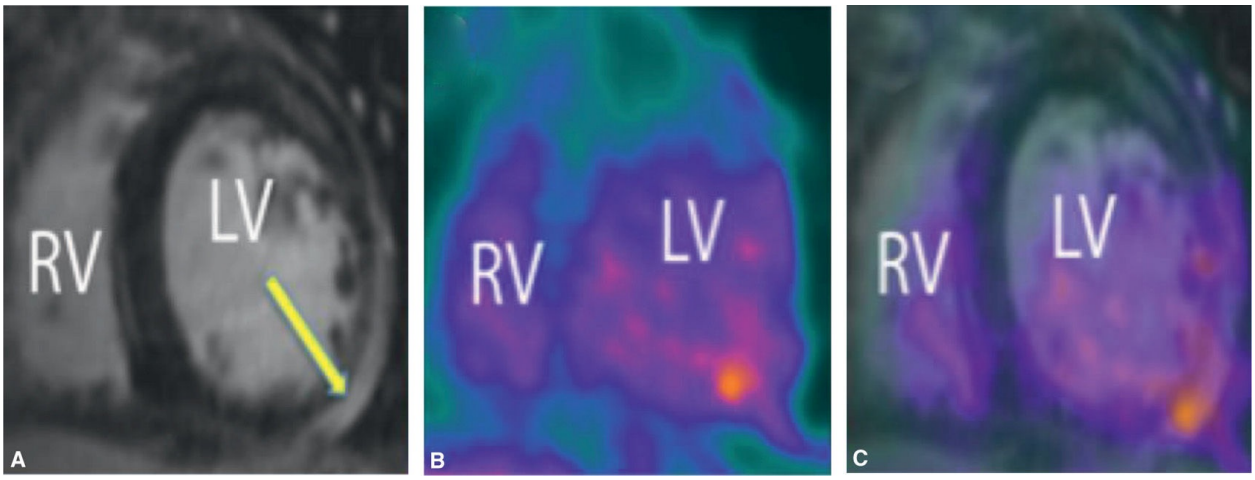


FIGURE 16.16 Panel (A) demonstrates a short-axis view of the LV with subepicardial (nonischemic) pattern of late gadolinium enhancement in the inferolateral wall in a patient with suspected myocarditis. Panel (B) demonstrates positron emission tomography (PET) imaging of the same patient. Panel (C) demonstrates fused PET magnetic resonance imaging (MRI): noteice the inflammatory activity in the area of LGE, consistent with active myocarditis. LV, left ventricle; RV, right ventricle. (Figure courtesy of Zahi Fayad, PhD, Maria Giovanna Trivieri, MD, and Phil Robson, PhD, Icahn School of Medicine, Mount Sinai Medical Center, New York, NY.)

More recently, T1 and T2 mapping with quantification of extracellular volume have provided additional information in the CMR diagnosis of myocarditis. Myocardial T1- and T2- relaxation times are significant parameters of active inflammation and edema in patients with acute myocarditis, as well as during the convalescent stage of the disease. In a recent publication, the MyoRacer Trial, Lurz et al[12] compared the diagnostic performance of CMR using T1 and T2 mapping versus the reference standard, EMB. They noted that in patients with acute myocarditis symptoms, T1- and T2-mapping techniques were even superior to the LLC (which have a sensitivity of 82% and a specificity of 98% for acute myocarditis). Therefore, T1 and T2 mapping may add useful information over T1- and T2-weighted imaging in the diagnosis of myocarditis.[12]

In summary, in patients suspected of having acute myocarditis, a comprehensive quantitative CMR is a useful tool that can reliably detect inflammatory alterations in the myocardium and should be implemented early if myocarditis is suspected.

Acute Pericarditis

Inflammation of the pericardium often presents as acute chest pain, with possible troponin elevation if there is concomitant myocardial involvement. The causes

of acute pericarditis are vast and include infectious (viral, bacterial, fungal, and mycobacterial), rheumatologic (eg, scleroderma, lupus, and rheumatoid arthritis), sequelae of radiation therapy, post-MI (ie, Dressler syndrome), trauma, and uremia.

Although systematic evaluation of the role of CMR in acute pericarditis is lacking, T2-weighted and LGE imaging can respectively demonstrate edema and enhancement of the pericardium **(Figure 16.17)** when there is ongoing inflammation.[13]

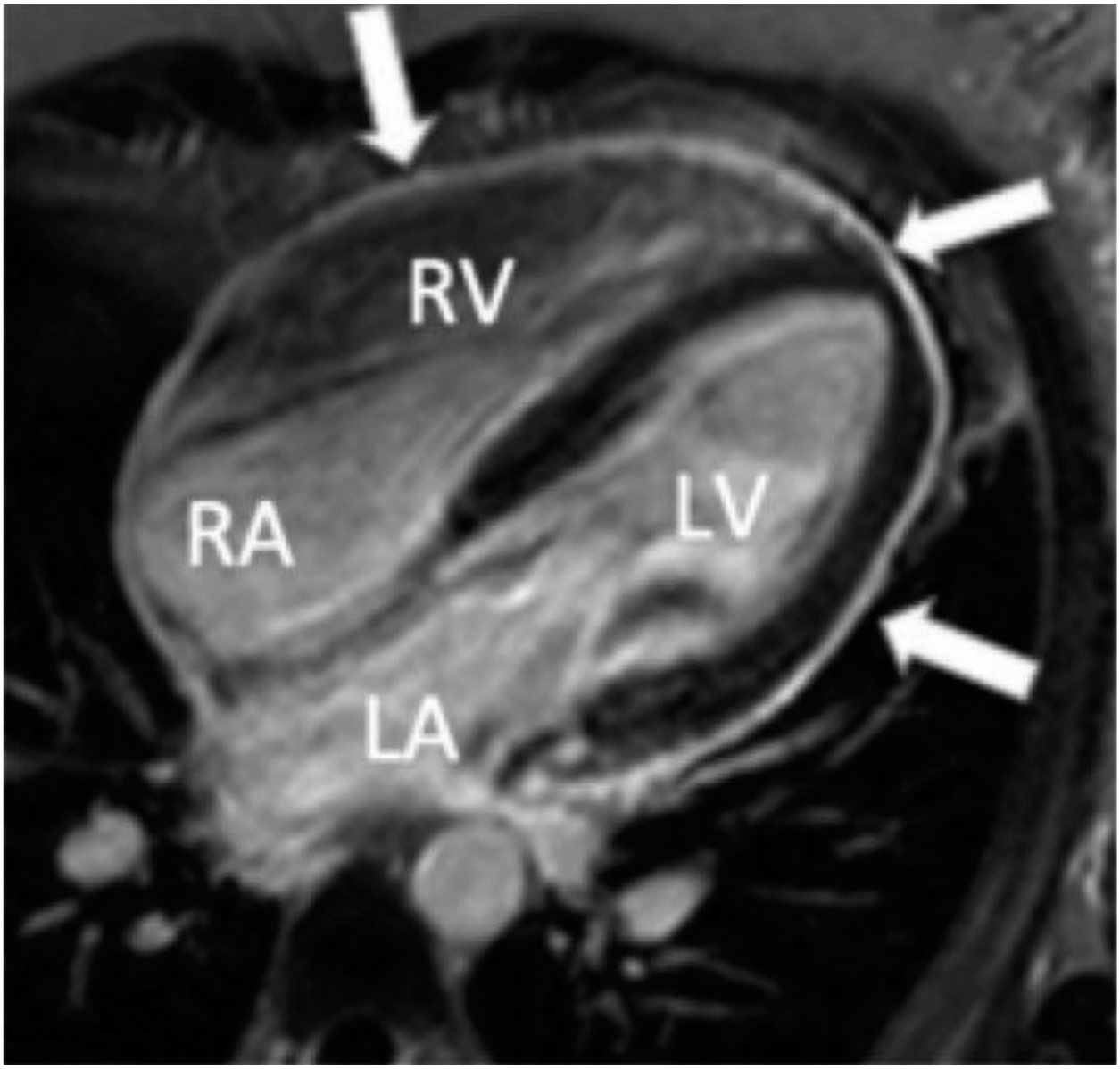


FIGURE 16.17 Diffuse delayed enhancement of the pericardium (*arrows*) in a patient with acute pericarditis. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy, also known as “apical ballooning syndrome” or “stress-induced cardiomyopathy,” is a unique syndrome that often presents similarly to an ACS or myocarditis **(Table 16.4)**. Among the hallmarks of the syndrome are wall motion abnormalities that do not correlate with a single coronary arterial territory. Takotsubo cardiomyopathy is classically described as a consequence of severe emotional stress, but virtually any stress, emotional or physical, can lead to this clinical entity. In some cases, no inciting event can be identified.

TABLE 16.4 Comparison of MRI Findings in Takatsubo Cardiomyopathy, Myocardial Infarction, and Myocarditis

	Takotsubo	Myocardial Infarction	Myocarditis
WMA in a coronary distribution	No	Yes	No
Edema	Yes (typically in areas of WMA)	Yes (typically in areas of WMA)	Yes (subepicardial/midmyocardial or transmural)
Late gadolinium enhancement	No or low intensity	Yes (subendocardial to transmural)	Yes (subepicardial/midmyocardial or “patchy”)
Resolution or follow up to 3 months	Majority = Yes	No	Majority = Yes

WMA, wall motion abnormality.

As of yet, the pathophysiology of Takotsubo cardiomyopathy is not well understood; theories range from multivessel spasm to catecholamine toxicity. Patients with Takotsubo cardiomyopathy often present with chest pain, ST-segment changes such as ST elevation or diffuse ST depression and prolongation of the QT interval. The classic wall motion abnormalities described are LV basal segment hyperkinesis with severe hypokinesis of the apical segments, and hence the term “apical ballooning.” Multiple variants of Takotsubo have been described including reverse Takotsubo with hyperkinesis of the apex and severe hypokinesis of the mid segments and a mid-wall variant where only the mid segments are hypokinetic.

Takotsubo cardiomyopathy remains a diagnosis of exclusion. The diagnosis is only in the absence of coronary artery disease on invasive or noninvasive angiography that matches with wall motion abnormalities. CMR is emerging as a

useful tool to readily distinguish between other causes of ACS and Takotsubo cardiomyopathy.

Cine imaging on CMR can accurately depict wall motion abnormalities that do not correlate with a coronary territory **(Figure 16.18)**. Myocardial edema on T2-weighted imaging, as described earlier, is often prominent in areas of wall motion abnormality. Edema and wall motion abnormalities can also be seen in the right ventricle.

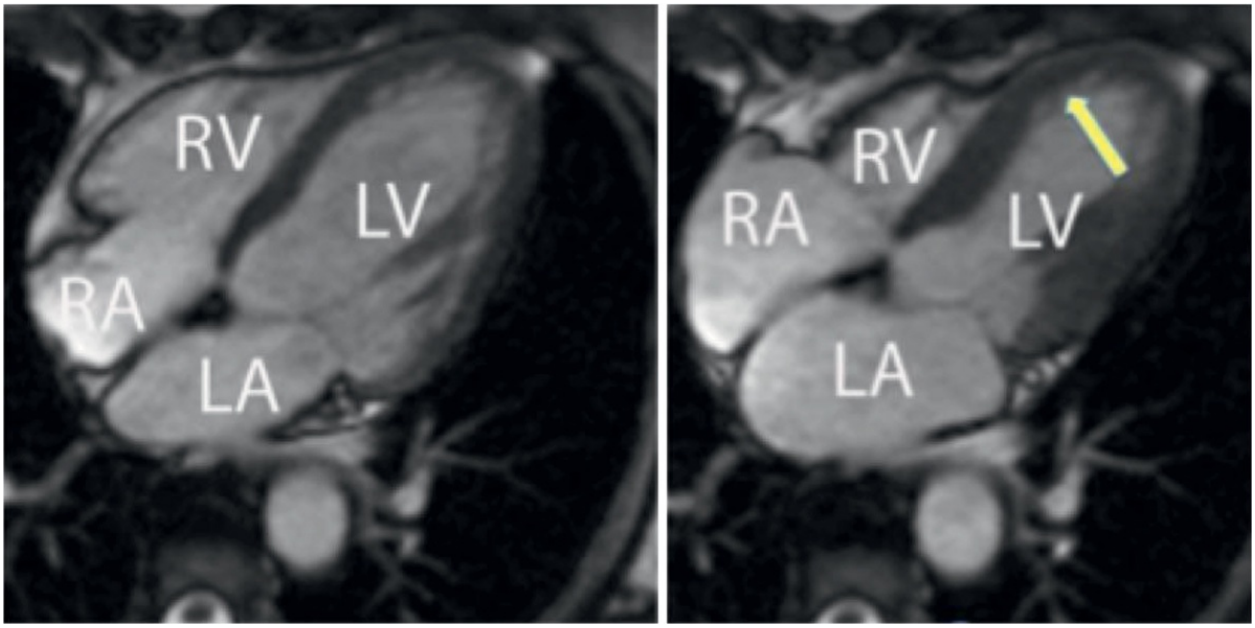


FIGURE 16.18 Four-chamber cine view (left: diastole; right: systole) demonstrating wall motion abnormalities in a patient with Takotsubo cardiomyopathy. Note the lack of movement of the mid-distal segments (*arrow*) compared to the basal segments. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

The lack of significant LGE in the areas of wall motion abnormality confirms the absence of MI**.** The degree of enhancement is almost never to the extent of a true MI and is sometimes termed “low-intensity LGE” **(Figure 16.19)**.[14]

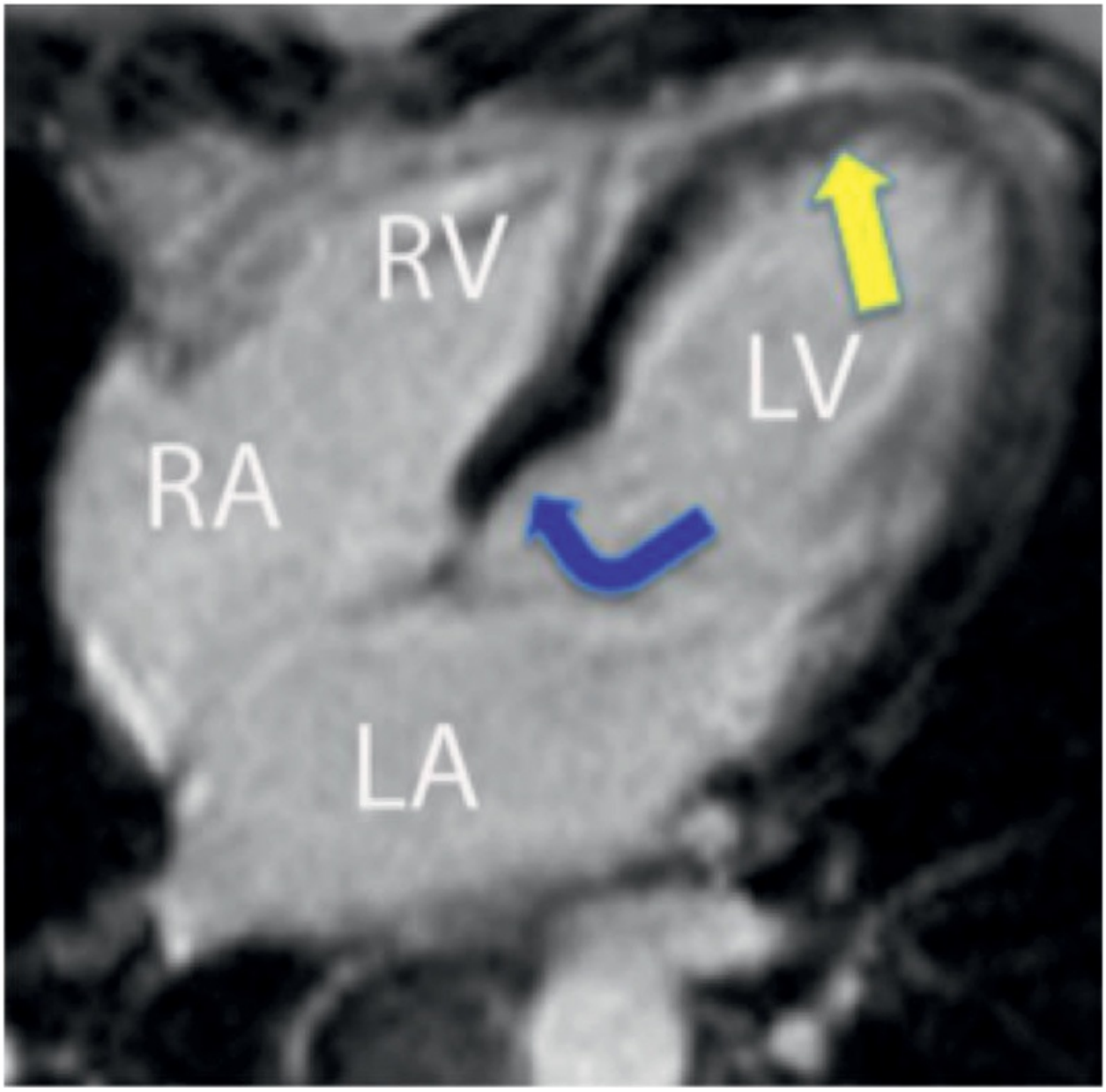


FIGURE 16.19 Four-chamber view demonstrating low-intensity late gadolinium enhancement (LGE) (*yellow arrow*) compared to normal myocardium (*blue arrow*) in the same patient as in the previous figure with Takotsubo cardiomyopathy. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

This constellation of findings (wall motion abnormalities beyond a coronary distribution, myocardial edema, and the lack of intense LGE) can assist in the diagnosis of Takotsubo cardiomyopathy. Patients often have a good prognosis, with the majority recovering LV function at 3 months.

Acute Aortic Syndromes

MRI can play an important role in determining the location and extent of involvement in patients with aortic dissection. When utilized, MRI provides a complete anatomic assessment of the intimal flap **(Figure 16.20)**, aortic valve morphology and severity of insufficiency, the presence of hemopericardium indicating impending aortic wall rupture, branch involvement of the great vessels, and the presence of an MI due to dissection into a coronary artery (usually the right coronary). MRI is also one of the most valuable imaging techniques for imaging aortic dissections after surgical intervention. Images are highly reproducible, making it an excellent modality for serial examinations. Residual dissection, thrombosis of the false lumen, suture dehiscence, and anastomotic leaks can be easily identified and help guide further management.[15]

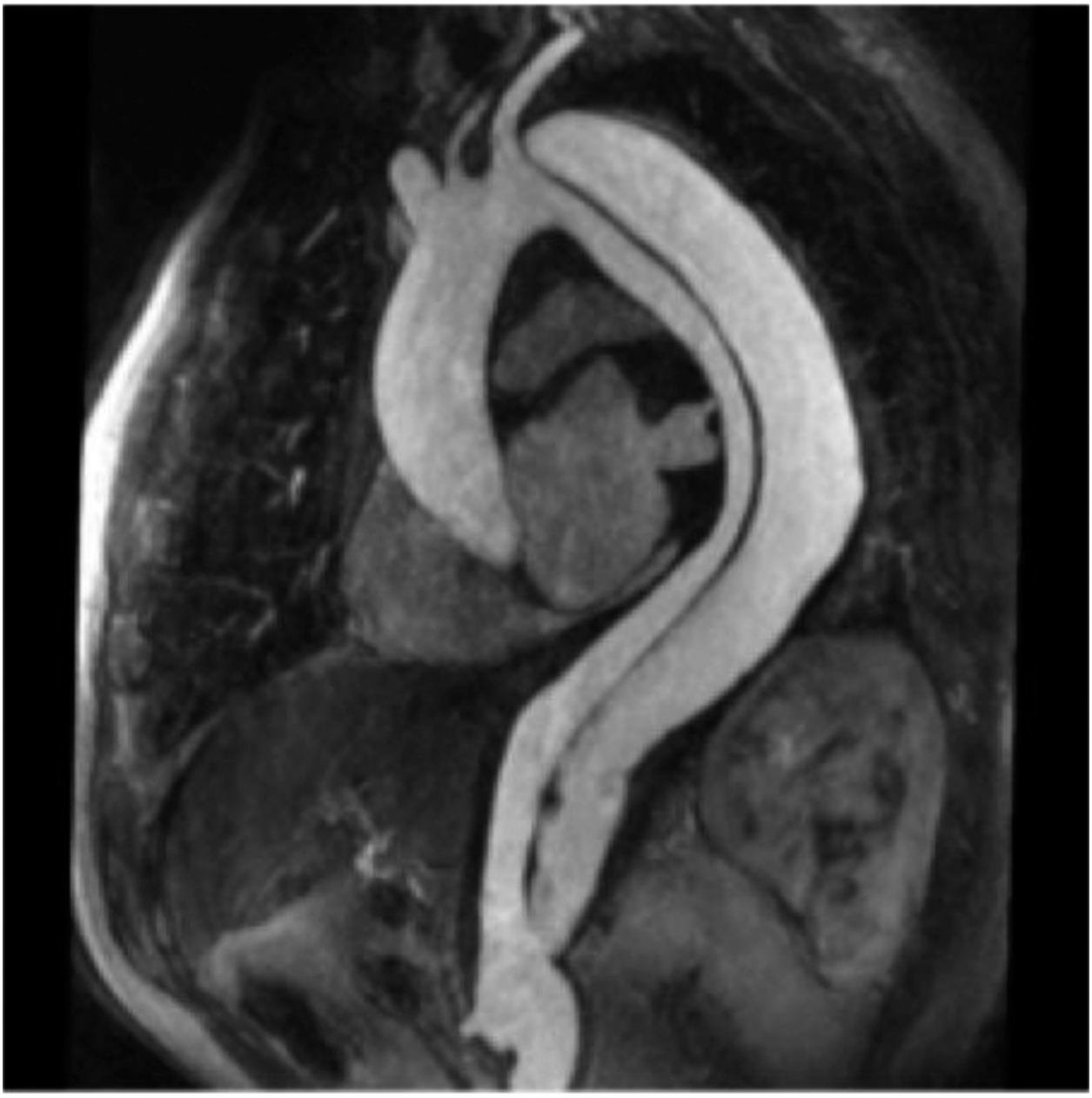


FIGURE 16.20 Contrast-enhanced aortic magnetic resonance angiography (MRA) demonstrating a type-B dissection flap extending from the origin of the left subclavian artery to the abdominal aorta.

CARDIAC MAGNETIC RESONANCE IN VENTRICULAR ARRHYTHMIAS

Sudden cardiac death (SCD) has been the leading cause of death in North America. It has been well documented that severely depressed LVEF (<35%) has been associated with SCD. Ventricular fibrosis or myocardial “scar” is the nidus

or “anatomic substrate” for ventricular arrhythmias in patients with ischemic cardiomyopathy (ICM) and nonischemic cardiomyopathy (NICM). In multiple randomized, controlled trials, with inclusion based on LVEF, the use of an ICD has reduced mortality. These studies are the basis of our current guidelines in primary prevention. However, only a fraction of patients (approximately 30%) receiving an ICD for primary prevention of SCD get appropriate therapy. The use of LVEF solely as the marker for ICD implantation is not ideal. SCD can occur also in patients with normal and mildly depressed LVEF. Therefore, a more in-depth need for risk stratification for primary prevention in patients with ICM and NICM (ie, myocarditis, sarcoidosis, and arrhythmogenic right ventricular cardiomyopathy [ARVC]) is necessary. CMR with LGE can be used to detect myocardial scar size and heterogeneity. Because myocardial scar is an important substrate for developing VT, CMR may be useful in predicting future ventricular arrhythmias.[16] CMR with contrast can be used to assess myocardial scar characteristics including scar transmurality, the border zone, and variations in the density of scar tissue and heterogeneity versus homogeneous scar appearance.

Disertori et al[16] performed a meta-analysis to evaluate the predictive value of LGE in CMR for ventricular tachyarrhythmia in ventricular dysfunction. Nineteen studies enrolling 2850 patients with ICM and NICM were included in the meta-analysis. The study demonstrated that LGE is a powerful predictor of ventricular tachyarrhythmic events in patients with ventricular dysfunction of ischemic and nonischemic etiology. The prognostic power of LGE for ventricular arrhythmias is particularly strong in patients with severely depressed LVEF (≤30%).

Regions of viable tissue within the gray zone detected by three-dimensional LGE-CMR correspond to conduction channels on endocardial voltage mapping and, therefore, may play a role in arrhythmia management and therapy.[16] As discussed also in section “Cardiac Magnetic Resonance in Heart Failure,” the presence or absence of fibrosis or, particularly, mid-wall fibrosis in NICM are indicators of high versus low risk of arrhythmic events.

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) remains the most common cause of SCD in young adults. Contrast-enhanced CMR with LGE has emerged as an in vivo marker of myocardial fibrosis and perhaps a marker for ventricular arrhythmias

and SCD **(Figure 16.21)**.[17]

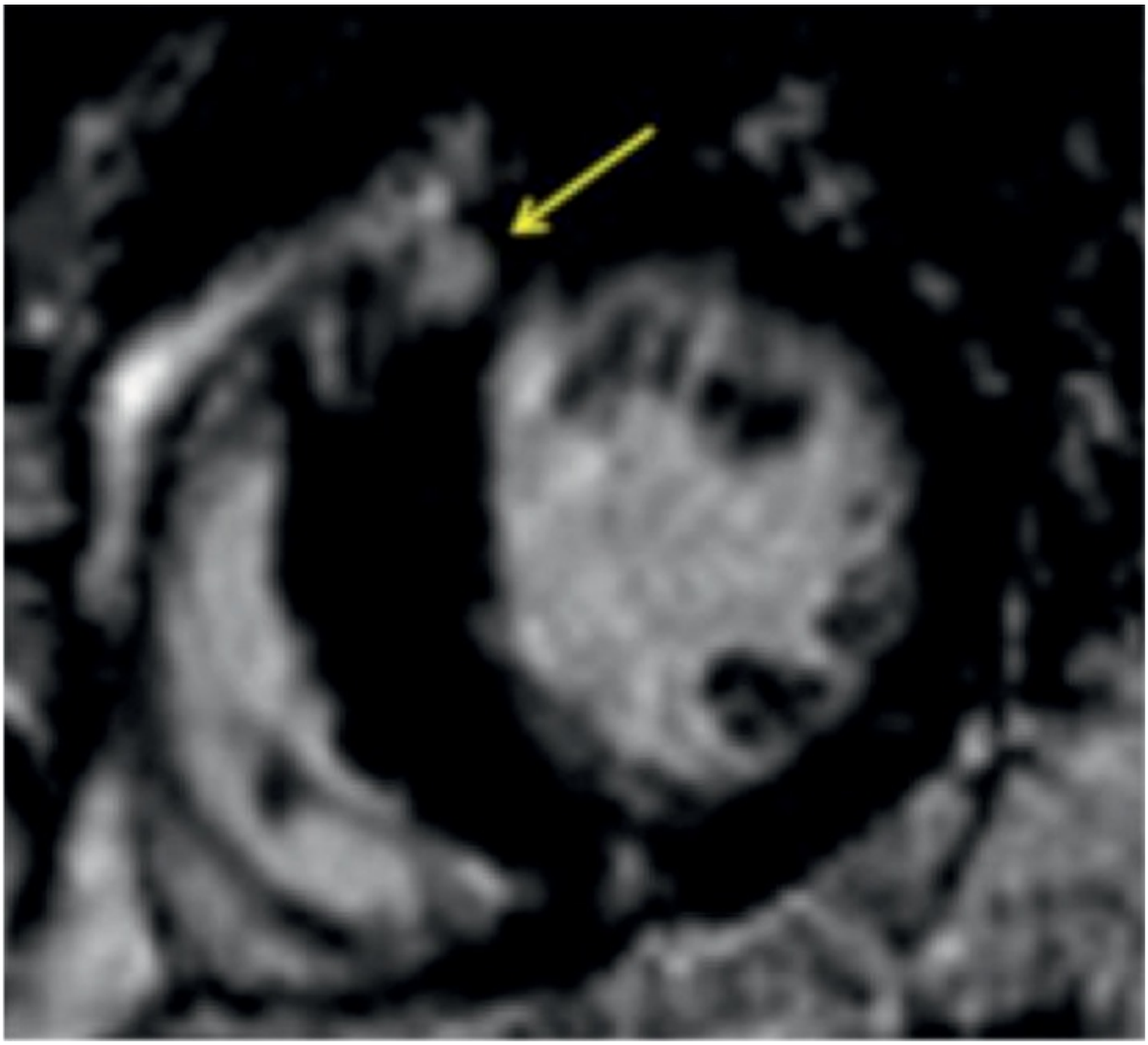


FIGURE 16.21 Short-axis view demonstrating mid-wall septal fibrosis at the right ventricular insertion point (*yellow arrow*), a characteristic pattern seen in hypertrophic cardiomyopathy.

In a recent publication by Chan et al,[17] the correlation between LGE and cardiovascular events were assessed in over 1200 patients with HCM. SCD events occurred in 37 patients (3%). The extent of LGE was associated with an increased risk of SCD events. LGE ≥15% of LV mass demonstrated a 2-fold increase in SCD event risk in those patients otherwise considered to be at lower risk. Performance of the SCD event risk model was enhanced by LGE (net reclassification index, 12.9%; 95% confidence interval, 0.3 to 38.3).[17] Absence

of LGE was associated with lower risk for SCD events in these patients.

CARDIAC SARCOIDOSIS

Inflammatory cardiomyopathies can be associated with ventricular arrhythmias at any time throughout their clinical course. Myocarditis is discussed in section "Cardiac Magnetic Resonance "Acute Chest Pain." Another potential cause of inflammatory cardiomyopathy is sarcoidosis, a systemic non-necrotizing granulomatous disease. This CD4+-mediated disease has multiorgan system involvement. The lungs are affected in more than 90% of patients, and the disease can also involve the heart, liver, spleen, skin, eyes, parotid gland, or other organs and tissues. An estimated 20% to 25% of patients with pulmonary or systemic sarcoidosis have asymptomatic cardiac involvement.[18] This finding was initially established on the basis of autopsy studies, which estimated the prevalence of cardiac involvement to be at least 25% among patients with sarcoidosis. These autopsy findings are consistent with recent data using LGE-CMR technology.

Cardiac involvement can include atrioventricular conduction disorders, atrial and life-threatening ventricular arrhythmias, and biventricular HF. Approximately 60% to 70% of patients with sarcoid-related deaths have evidence of intramyocardial infiltration. Although rare, isolated cardiac sarcoidosis does exist. Between 16% and 35% of patients presenting with complete atrioventricular block (age <60 years) or VT of unknown etiology have previously undiagnosed cardiac sarcoidosis as the underlying etiology.[18] EMB is considered to be the gold standard when positive. EMB is highly specific, but it is an invasive procedure. As cardiac involvement is not homogeneous and lesions are usually in a patchy distribution, EMB has poor sensitivity with a diagnostic yield as low as 19%. Thus, CMR is becoming the imaging modality of choice for the diagnosis of cardiac sarcoidosis and to guide the EMB to active intracavitary inflammatory lesions to increase the yield of biopsy.

There is no specific pattern of LGE on CMR that is diagnostic for cardiac sarcoidosis, although usually it is patchy and multifocal, with sparing of the endocardial border. CMR is increasingly utilized for assessment of clinically silent cardiac sarcoidosis, in view of its ability to identify small regions of myocardial damage, even in subjects with preserved LV systolic function.[18] In a recent meta-analysis including 760 patients, Coleman et al[19] noted that the presence of LGE on CMR imaging is associated with increased odds of both all-

cause mortality and arrhythmogenic events compared to those without myocardial involvement on LGE.

Positron emission tomography (PET)/CMR, which enables concurrent imaging of the two stages of the disease (inflammation and fibrosis/scar), has been also used recently in the diagnosis and management of cardiac sarcoidosis **(Figure 16.22)**.

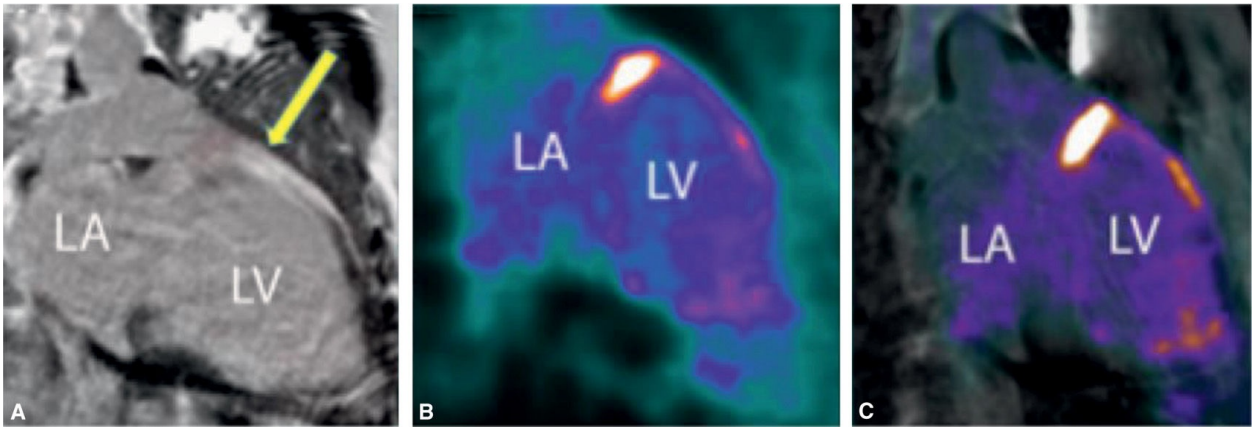


FIGURE 16.22 A, Two-chamber cardiac magnetic resonance (CMR) view of the LV with subepicardial (nonischemic) pattern of late gadolinium enhancement (LGE) in the basal to mid-anterior wall in a patient with known pulmonary sarcoidosis. B, **Positron** emission tomography (PET) imaging of the same patient. C, PET-CMR imaging: notice the inflammatory activity in the area of LGE consistent with active cardiac sarcoidosis. LA, left atrium; LV, left ventricle. (Image courtesy of Zahi Fayad, PhD, Maria Giovanna Trivieri, MD, and Phil Robson, PhD, Icahn School of Medicine, Mount Sinai Medical Center, New York, NY.)

The clinical situations where immunosuppression should be considered in patients with known cardiac sarcoidosis and myocardial inflammation include Mobitz II or third-degree heart block, frequent ventricular ectopy or nonsustained ventricular arrhythmias, sustained ventricular arrhythmias, and LV dysfunction.[18]

An electrophysiological study for SCD risk stratification may be considered in patients with LVEF >35% despite optimal medical therapy. ICD implantation should be considered when LVEF is <35% despite optimal medical therapy.[18] Patients with cardiac sarcoidosis have a worse prognosis than patients without cardiac involvement. Cardiac death is due to progressive HF or SCD. In patients with clinically manifest disease, the extent of LV dysfunction is the most important predictor of survival.

ARRYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Also known as arrythmogenic right ventricular dysplasia, ARVC is an inherited cardiomyopathy characterized by fibrofatty infiltration predominantly involving the right ventricle but that can also affect the left ventricle. Both can predispose patients to life-threatening ventricular arrhythmias. ARVC has a prevalence of 1 in 2000 to 5000 people, but can be as high as 1 in 1000 in certain regions because of underdiagnosis. Genetic testing for ARVC has developed over the past decade with associated mutations in desmosomal genes and non-desmosomal genes. Inheritance varies depending on the genes involved but most commonly is autosomal dominant with incomplete penetrance and variable expressivity.[20] Over the past decade, CMR has emerged as the gold standard imaging modality for in-depth evaluation of RV morphology, function, and tissue characterization.[20]

The diagnosis of ARVC is challenging and is based on the International Task Force criteria.[21] The Task Force set out to establish the major and minor CMR criteria for ARVC. Liu et al[21] evaluated the revised 2010 criteria in 968 consecutive patients referred for CMR with clinical suspicion for ARVC. The revised criteria in 2010 resulted in a reduction of total patients meeting any diagnostic CMR criteria for ARVC from 22.7% to 2.6% compared to the 1994 Task Force criteria.[21] This reinforced that perhaps ARVC was originally overdiagnosed before the 2010 revision. The new CMR major criteria include regional RV akinesia or dyskinesia plus RV enlargement (RV end-diastolic volume ≥110 ml/m^2 in males and ≥ 100 ml/m^2 in females) or RV ejection fraction ≤ 40% **(Table 16.5)**. Microaneurysms can also be present in the RV wall and are best seen on CMR cine imaging **(Figure 16.23C)**.

TABLE 16.5 Revised Imaging Task Force Criteria for the Diagnosis of ARVC[22]

2010 TASK FORCE CRITERIA
MAJOR CRITERIA
Two-dimensional echocardiographic criteria
Regional RV akinesia, dyskinesia, or aneurysm Plus one of the following (end-diastole): • PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) • PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) or fractional area change ≤33%

MRI imaging criteria
Regional RV akinesia, dyskinesia, or dyssynchrony Plus one of the following: • ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male) or ≥100 mL/m^2 (female) • or RV ejection fraction ≤40%
RV angiographic criteria
Regional RV akinesia, dyskinesia, or aneurysm
Minor criteria
Two-dimensional echocardiography criteria
Regional RV akinesia, dyskinesia, or aneurysm Plus one of the following (end-diastolic): • PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m^2) • PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m^2) or fractional area change >33% to ≤40%
MRI criteria
Regional RV akinesia, dyskinesia, or dyssynchrony Plus one of the following: • ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m^2 (male) or ≥90 to <100 mL/m^2 (female) • or RV ejection fraction >40% to ≤45%

ARVD, arrythmogenic right ventricular dysplasia; MRI, magnetic resonance imaging; RV, right ventricular.

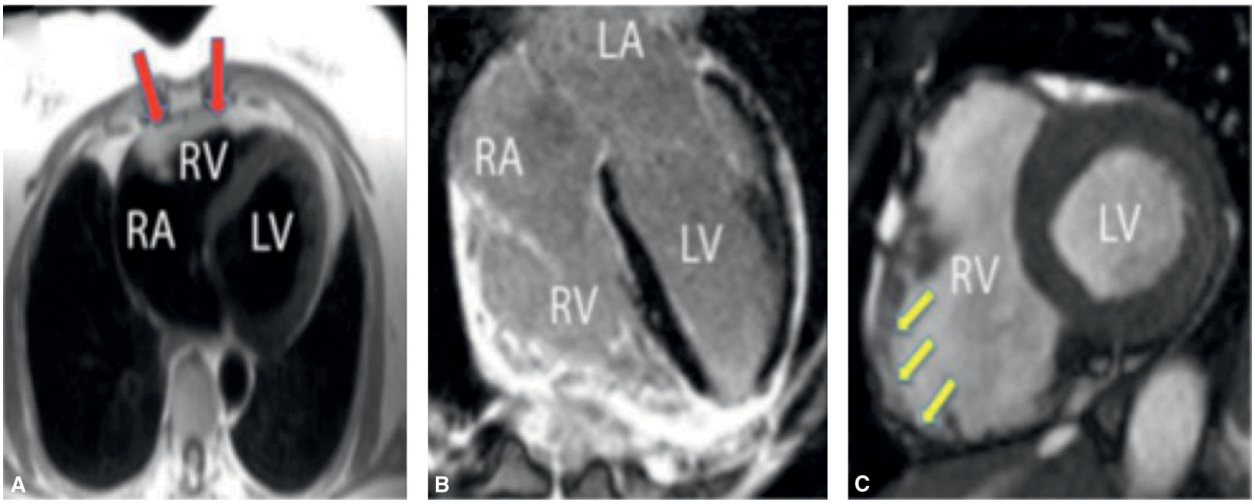


FIGURE 16.23 Axial black-blood imaging demonstrating fatty infiltration of the right ventricle (*red arrows*, A). Four-chamber view showing extensive late gadolinium enhancement (LGE) of the right ventricular free wall and apex (B). Short-axis cine view of the left and right ventricles with a large focal aneurysm of the right ventricular free wall (*yellow arrows*, C). LA, left atrium; LV, left ventricle; RA, right

atrium; RV, right ventricle.

Infiltration of fat in the right ventricle can be seen on T1-weighted CMR imaging, which is demonstrated as regions of increased signal intensity in the myocardium **(Figure 16.23A**). Fat–water separation imaging can further aid in the diagnosis of the fibrofatty infiltration. In addition, LGE of the RV myocardium can sometimes be seen **(Figure 16.23B**). New CMR sequences including high-resolution T1 mapping are evolving tools that may detect early and subtle changes in the right ventricle. In addition, quantification of RV regional wall motion abnormalities and evaluation of inter- and intraventricular dyssynchrony can provide novel tools for early detection of ARVC. Genetic testing using comprehensive cardiomyopathy panels and whole exome sequencing are also likely to significantly impact the diagnosis of ARVC and prevention of SCD. The diagnosis of ARVC with CMR is difficult and requires experienced imaging specialists for accurate diagnosis of the disease.

CARDIAC MAGNETIC RESONANCE IN HEART FAILURE

The presence of HF is a common indication of admission in the CCU. As discussed previously, CMR is most commonly reserved for the stable patient who is able to tolerate a decubitus position. The main roles of CMR include providing accurate quantification of biventricular size and function, and characterization of the myocardium for the presence of scar, necrosis, infiltration, or edema. Although reduced LVEF as measured with a variety of imaging modalities is a well-known marker of risk in HF, during the past few years, the presence of myocardial scar as demonstrated by LGE has emerged as an important powerful prognosticator independent of LVEF. In a series of 857 consecutive patients with HF, survival free from death or heart transplantation was similar in patients with severe LV dysfunction but no scar compared with those with preserved LVEF but evidence of LGE.[23] These findings, subsequently confirmed in other studies, suggest that myocardial scarring may be as powerful a prognosticator as measures of LV dysfunction.

For the purpose of the discussion, this section is divided into predominantly left-sided or right-sided HF, although there is certainly overlap between the two syndromes and their underlying etiologies. Additional information that can be obtained from CMR includes pericardial involvement, valvular disease severity,

or quantification of systemic to pulmonary shunts. It must be emphasized that data on CMR diagnostic and prognostic ability in HF has been obtained largely from stable cohorts and not from patients admitted to the CCU.

LEFT-SIDED HEART FAILURE

Dilated Cardiomyopathy

One of the most common causes of left-sided HF is dilated cardiomyopathy (DCM). DCM of specific etiologies, such as ischemia or sarcoid, have been discussed in section “Cardiac Magnetic Resonance in Ventricular Arrhythmias,” so here we address mainly DCM of unknown cause. In idiopathic DCM, two patterns of LGE are commonly observed: absent (approximately 65% to 70%) or nonischemic (approximately 20% to 25%). As described in sections “Cardiac Magnetic Resonance in Acute Chest Pain” and “Cardiac Magnetic Resonance in Ventricular Arrhythmias,” nonischemic LGE refers to areas of scar with a predominantly intramyocardial or subepicardial location, or transmural or subendocardial areas that do not conform to a coronary territory. Occasionally (around 10% of cases), “ischemic” LGE can be seen in patients with DCM and normal or nonobstructive coronary artery disease, raising the possibility of an ischemic etiology despite the absence of significant coronary stenoses (ie, embolization, vasospasm, thrombus autolysis, etc). A pattern of nonischemic, linear intramyocardial LGE in the interventricular septum can be often seen in idiopathic DCM and has received particular attention **(Figure 16.24)**.

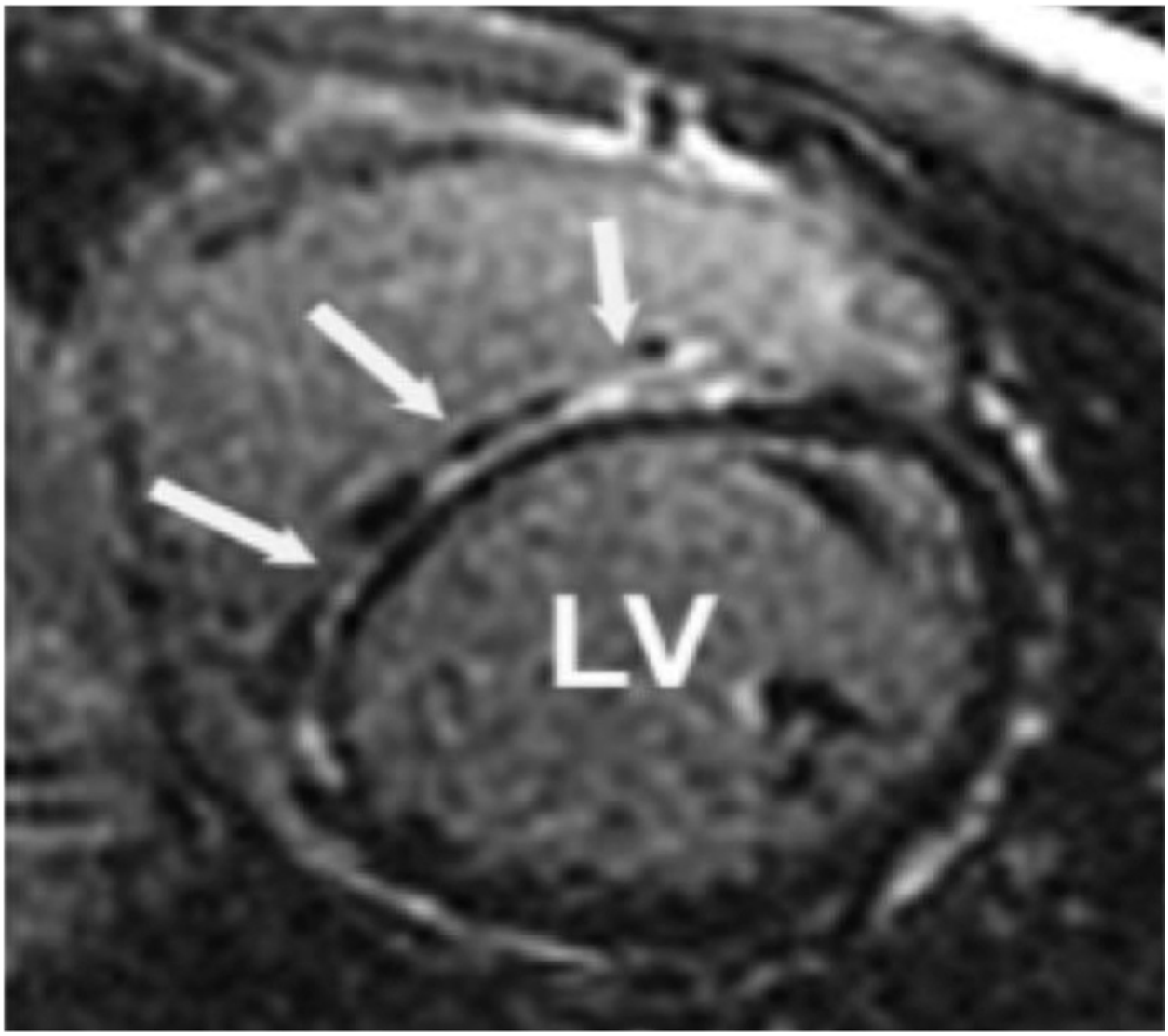


FIGURE 16.24 Short-axis image demonstrating linear intramyocardial late gadolinium enhancement (*arrows*) in a patient with idiopathic dilated cardiomyopathy. LV, left ventricle.

In a meta-analysis of nine studies including ≈1500 patients,[24] this pattern was associated with increased midterm risk of mortality (odds ratio = 3.27), malignant ventricular arrhythmias (odds ratio = 5.32), or HF hospitalization (odds ratio = 2.91; P <0.001 for all), independent of other conventional risk markers including LVEF. RV ejection fraction is also of prognostic value in these patients.

HEART FAILURE WITH PRESERVED EJECTION FRACTION

Many cases of HF do not have reduced LVEF, a situation commonly referred to

as heart failure with preserved ejection fraction (HFpEF). HFpEF is a multifactorial syndrome in which diastolic LV dysfunction is believed to represent a common pathophysiologic pathway. The role of CMR in HFpEF is not well defined because diastolic function is often better evaluated with echocardiography, although preliminary data suggest an association between localized scar (using LGE) or diffuse myocardial fibrosis (using novel T1-mapping sequences) with abnormalities in LV stiffness and impaired outcomes.[25]

RIGHT-SIDED HEART FAILURE

Restrictive Cardiomyopathy

CMR plays an increasingly important role in the evaluation of restrictive cardiomyopathy, one form of HFpEF associated with congestive symptoms, related to infiltrative heart disease. In developed countries, the most common cause of restrictive cardiomyopathy is cardiac amyloidosis. The typical features of amyloidosis include increased ventricular wall thickness in the absence of electrocardiographic hypertrophy, relatively preserved LVEF, biatrial enlargement, thickening of the mitral and tricuspid leaflets as well as of the interatrial septum, and pericardial and pleural effusions. These features are specific but have low sensitivity. Cardiac amyloid is associated with a typical pattern of diffuse LGE, more prominent toward the base of the heart, with a predominantly intramyocardial and subendocardial distribution **(Figure 16.25)**.

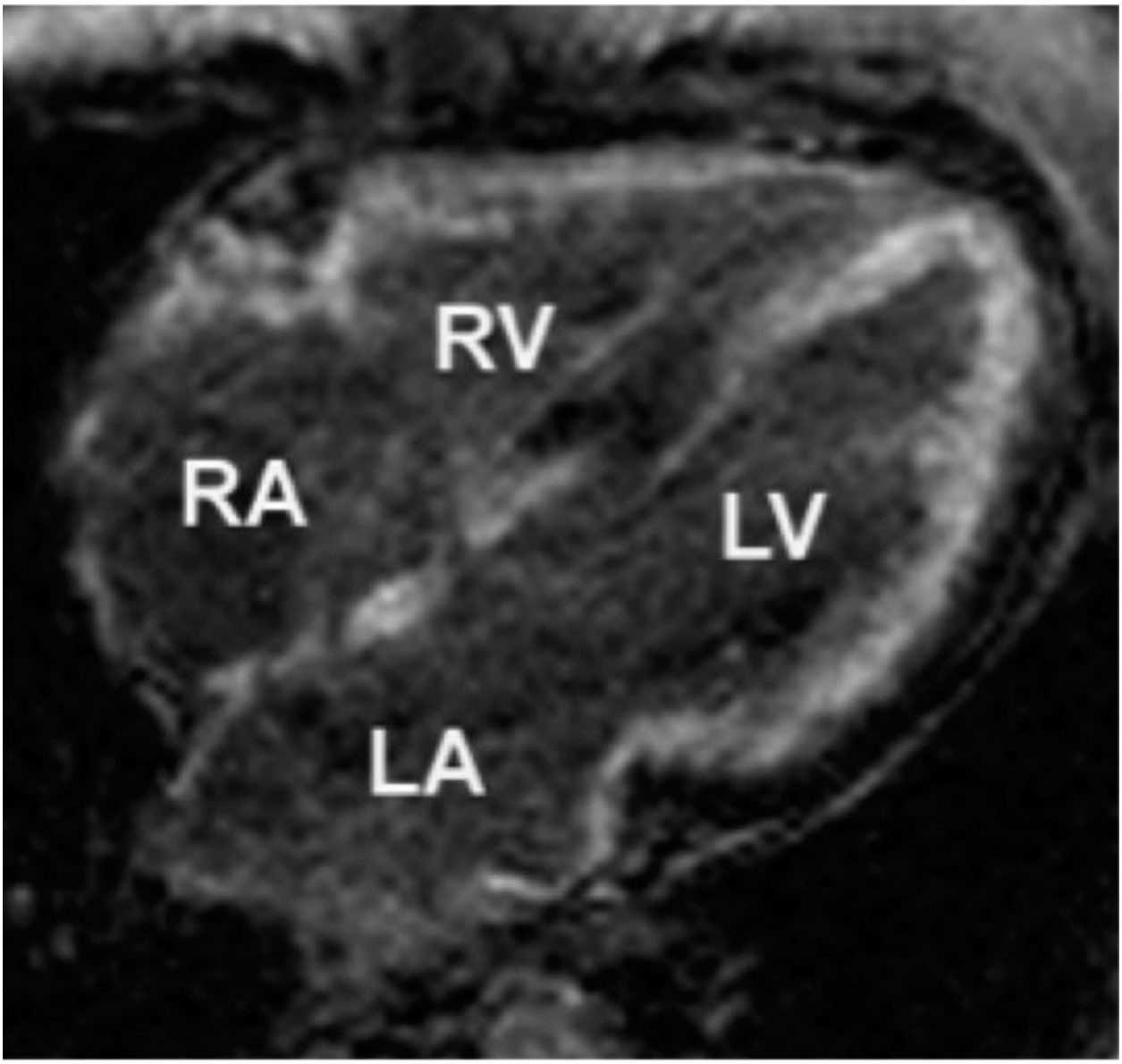


FIGURE 16.25 Four-chamber view demonstrating diffuse, predominantly subendocardial late gadolinium enhancement (LGE) in the LV of a patient with cardiac amyloidosis. LGE also noted in the RV and both atria. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

In addition, abnormal contrast kinetics between the blood and the myocardium can be observed and quantified. This pattern is highly specific to cardiac amyloidosis and, importantly, has been associated with increased mortality (hazard ratio = 5.2; P <0.001) after adjusting for LV systolic and diastolic function, LV mass index, and N-terminal pro-brain natriuretic peptide.[26] Some distinguishing CMR features may help in the differential diagnosis between light-chain and transthyretin amyloid, which has both prognostic and therapeutic

implications. Other less common etiologies of restrictive heart disease such as iron deposition or endomyocardial fibrosis **(Figure 16.26)** can also be accurately identified with CMR.

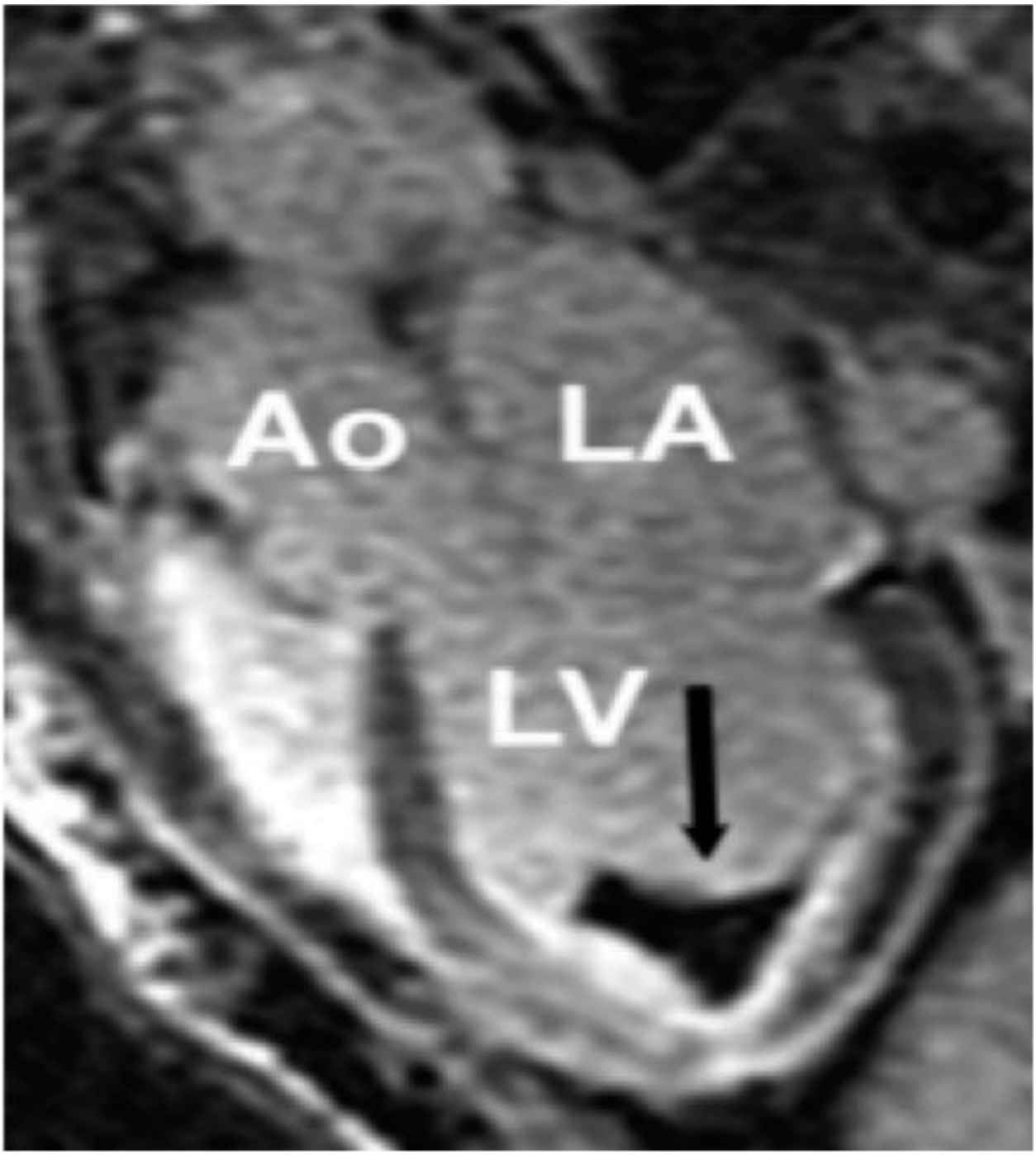


FIGURE 16.26 Three-chamber view in a patient with endomyocardial fibrosis demonstrating apical late gadolinium enhancement with superimposed thrombus (*arrow*). Ao, aorta; LA, left atrium; LV, left ventricle.

Constrictive Pericarditis

Constrictive pericarditis can be idiopathic as well as the end result of virtually any progressive inflammatory pericarditis process. The diagnostic standard of pericardial constriction is equalization of end-diastolic pressures in all cardiac chambers due to the pressure exerted by the thickened, and/or inflamed pericardium as well as increased ventricular interdependence. It is important to distinguish this entity from restrictive cardiomyopathies, which can present similarly, because patients with constrictive pericarditis, unlike those with restrictive cardiomyopathy, may benefit from pericardiectomy or anti-inflammatory therapy. CMR can assess the thickness of the pericardium; the presence of pericardial edema, effusion and inflammation; as well as demonstrate exaggerated ventricular interdependence. Other sequelae of constriction that support the diagnosis may also be seen, such as a dilated inferior vena cava and pleural effusions.

CMR is well suited for direct quantification of pericardial thickness **(Figure 16.27)**. Normal pericardial thickness in CMR (due to limitations in spatial resolution) is 1 to 2 mm. A thickness of 3 mm is considered borderline, whereas ≥4 mm is considered definitely abnormal.[13] Increased pericardial thickness can be focal or diffuse. The most common pattern of thickening includes prominence over the right heart as well as the atrioventricular groove. It is important to realize that constriction can occur with normal pericardial thickness in the presence of focally inflamed pericardium that significantly impairs filling. Similarly, the presence of pericardial thickening is not synonymous with constriction. Constrictive physiology can be assessed with CMR as increased ventricular interdependence with respiration, manifested by marked inspiratory flattening of the interventricular septum during free-breathing cine imaging **(Figure 16.28)**.[13]

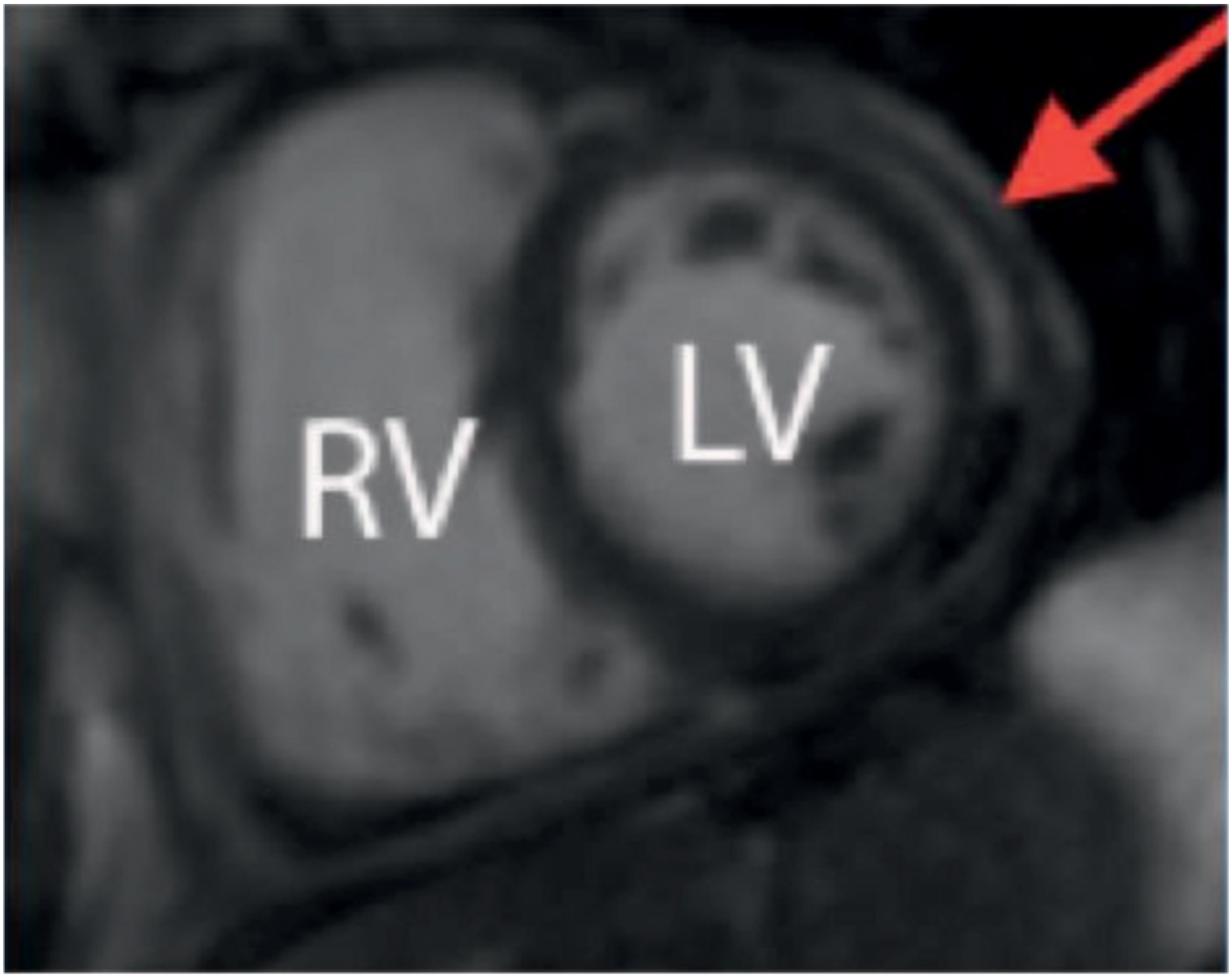


FIGURE 16.27 Short-axis view with prominent pericardial thickening (*arrow*) in a patient with constrictive pericarditis. LV, left ventricle; RV, right ventricle.

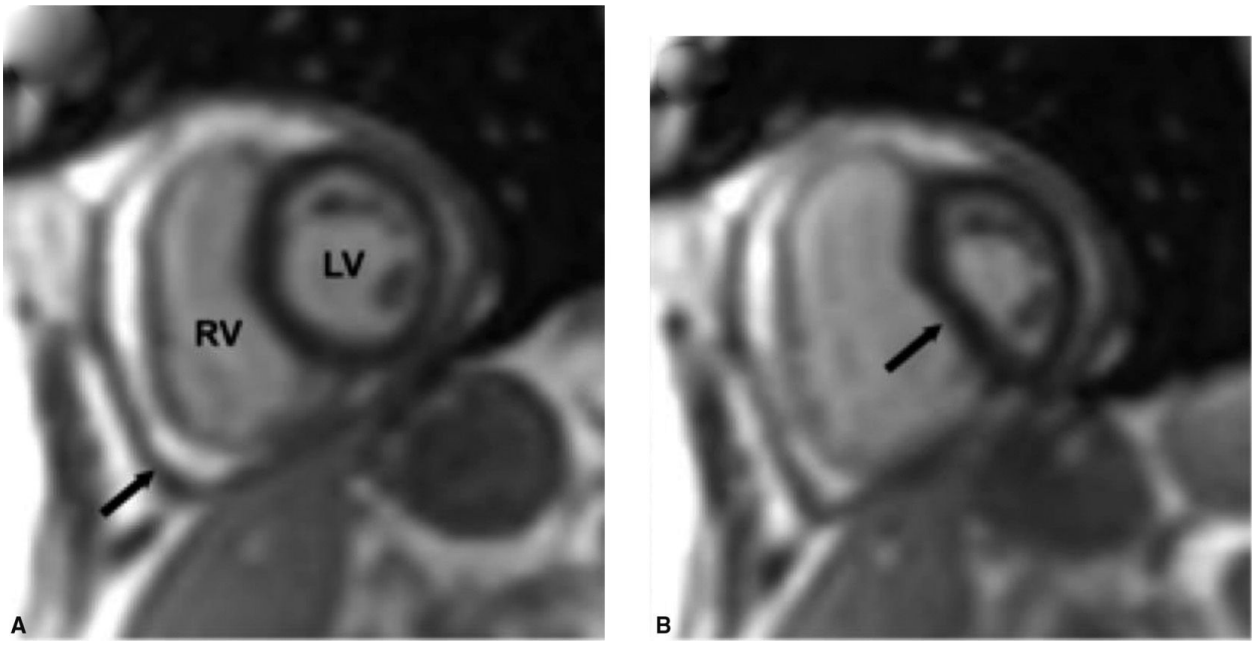


FIGURE 16.28 Expiratory (A) and inspiratory (B) short-axis views in a patient with pericardial constriction, demonstrating prominent flattening of the interventricular septum (*arrow* in B) with inspiration. Note also the thickened pericardium (*arrow* in A). LV, left ventricle; RV, right ventricle.

As in the case of acute pericarditis (see section “Cardiac Magnetic Resonance in Acute Chest Pain”), increased T2 signal intensity (compatible with edema) and post-contrast LGE in the pericardium **(Figure 16.29)** are indicative of active inflammation and can be seen in constrictive effusive pericarditis. Zurick et al[27] studied 25 patients with constrictive pericarditis who underwent pericardiectomy, imaging them with CMR and examining the histopathology of the pericardial specimens. They found that a subset of patients with LGE had more chronic inflammation and fibroblastic proliferation. These patients often had increased pericardial thickness compared to patients with a fibrotic, less inflamed pericardium. These findings may help guide treatment and identify patients who may benefit from anti-inflammatory therapies in lieu of immediate surgical treatment.[27]

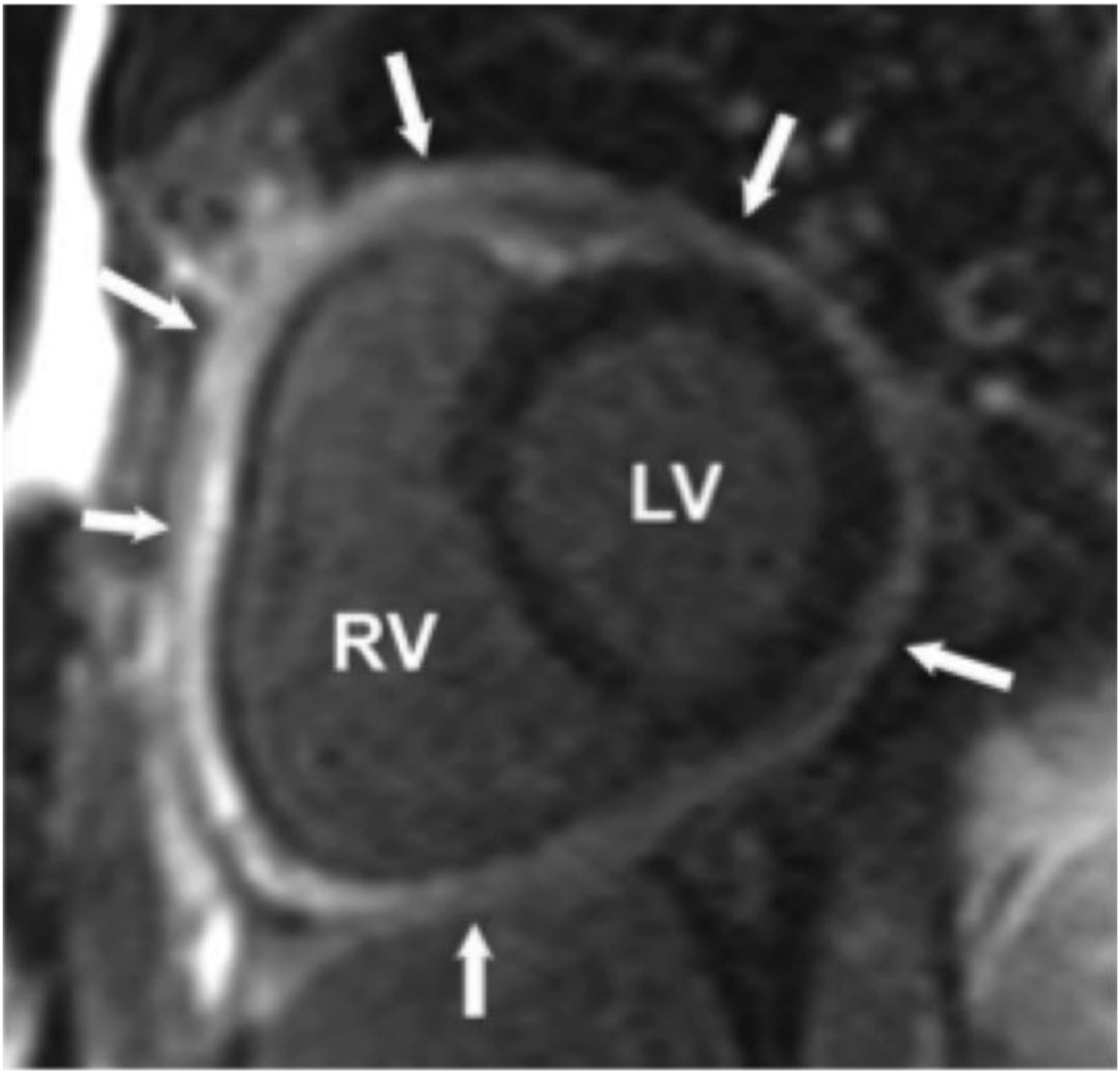


FIGURE 16.29 Short-axis image demonstrating extensive pericardial late gadolinium enhancement (*arrows*) in a patient with constrictive pericarditis. LV, left ventricle; RV, right ventricle.

CMR can help not only diagnose constriction but also provide important prognostic information. Aquaro et al[28] studied 70 patients with clinical suspicion of constrictive hemodynamics on echocardiography and/or catheterization. Constrictive pericarditis was present in 53 patients, whereas 12 had active inflammation, suggestive of a transient constrictive process. LGE was correlated with adverse events.[28]

Right Ventricular Dilatation

Dilatation involving only or predominantly the RV can be seen in ARVC (see section “Cardiac Magnetic Resonance in Ventricular Arrhythmias”), and in RV pressure or volume overload. In RV pressure overload (pulmonary hypertension, stenosis, and embolism), RV dilatation, hypertrophy (if chronic), predominantly systolic septal flattening and, eventually, reduced RV ejection fraction can all be identified with CMR and have been linked to impaired outcome.[29] Although identification of pulmonary embolism with MRA is feasible, CT is usually preferred for this application because of increased accuracy and speed of acquisition. RV volume overload is characterized by RV dilatation and dysfunction without hypertrophy and predominantly diastolic flattening of the interventricular septum. A common cause of RV volume overload is right-sided valvular regurgitation, such as can be seen in carcinoid heart disease. Both pulmonary and tricuspid insufficiency can be accurately quantified with CMR. If no valvular regurgitation is present, a systemic-to-pulmonary shunt should be suspected. CMR is well suited to depict shunts that may not be readily identified with echocardiography such as some ventricular and atrial septal defects, anomalous pulmonary vein drainage, or patent ductus arteriosus. CMR is the most accurate noninvasive modality for the quantification of shunt severity, which is accomplished by measuring systemic (aortic) and pulmonary output using phase-contrast imaging as described here.

FLOW IMAGING—VALVULAR HEART DISEASE

Phase-contrast (or flow) imaging is a technique that can quantify blood velocity and flow within a vessel and that, when applied to the pulmonary artery or the aorta, can respectively provide right- and left-sided stroke volume/output **(Figure 16.30)**.

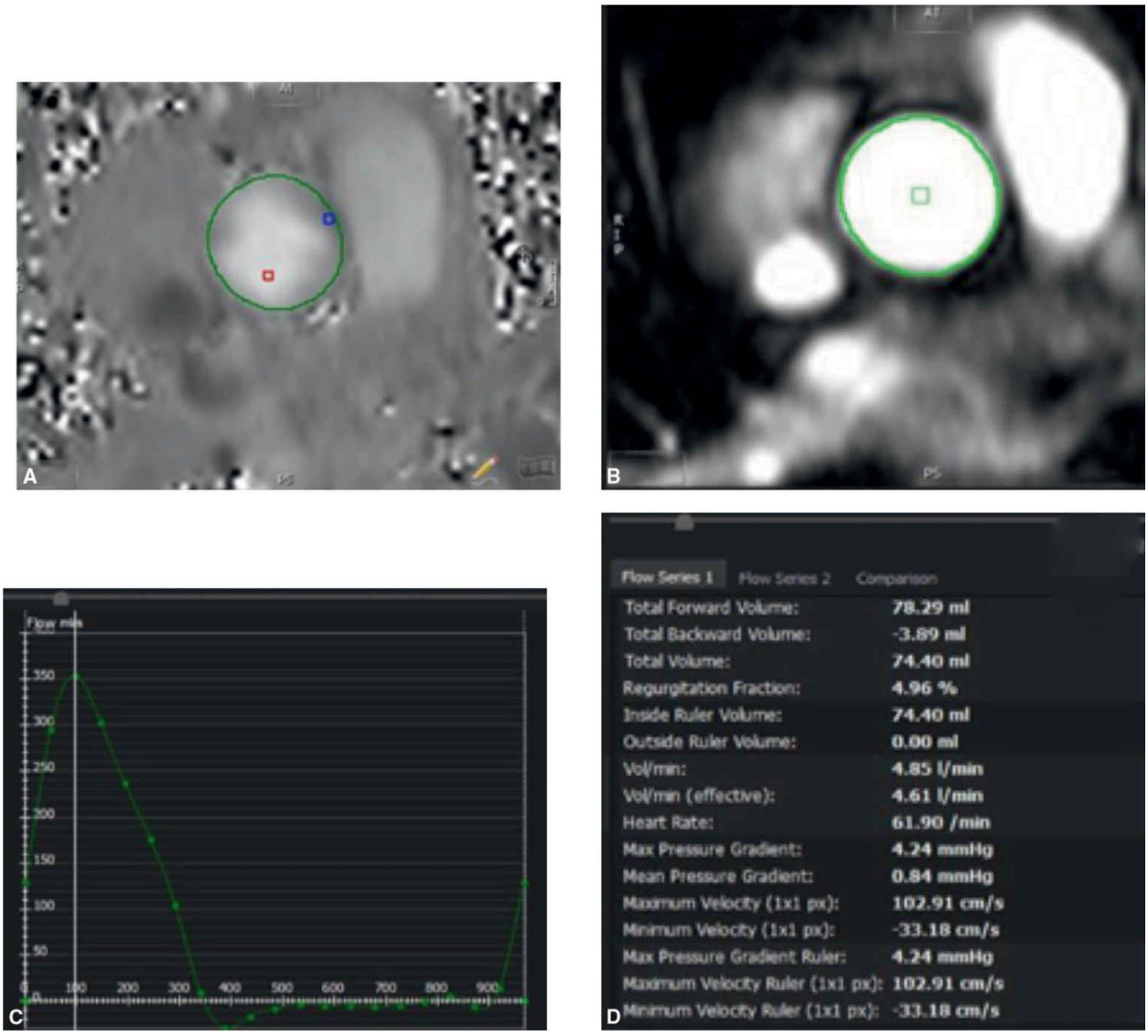


FIGURE 16.30 Phase-contrast imaging demonstrating a cross-section of the ascending aorta (*green contours*) in both the (A) velocity map and (B) anatomic reconstruction. C, Integration of the velocities within the aortic area enables determination of flow throughout the cardiac cycle and (D) quantification of parameters such as output, stroke volume, or degree of regurgitation. For example, the regurgitant fraction in this case is 5%.

As indicated, the difference between the two is used in congenital abnormalities to calculate the Qp/Qs. In addition, phase-contrast imaging in the same locations can be employed to assess valvular heart disease. Evaluation of valvular abnormalities is rarely the primary indication for CMR, so a detailed description of available techniques is beyond the scope of this chapter. Nonetheless, valvular assessment is appropriate if the patient is undergoing CMR for other reasons, or in situations where test results are discordant or

echocardiography may be limited (eg, quantification of pulmonary regurgitation, differentiation of bicuspid from trileaflet valves, identification of sub- or supravalvular stenoses, etc). Pulmonary and aortic regurgitation are measured as the difference between anterograde and retrograde flows in the pulmonary artery and ascending aorta, respectively (as illustrated in **Figure 16.30**). Mitral and tricuspid regurgitation are graded on the basis of the difference between the LV or RV stroke volume calculated with cine imaging, and the stroke volume in the aorta or pulmonary artery measured by phase contrast. Preliminary data indicate meaningful prognostic value of CMR-based indices of aortic and mitral regurgitation, although further confirmatory studies are needed. Finally, valve stenosis severity can be quantified by direct valve planimetry or measuring peak transvalvular gradients in a manner comparable to Doppler ultrasound (although gradients tend to be underestimated with CMR).

MISCELLANEOUS

CARDIAC CAUSES OF HYPOTENSION—BEYOND HEART FAILURE

In the reasonably stable patient with unexplained hypotension, and in the appropriate clinical scenario, CMR may be helpful to investigate potential underlying etiologies. A possible cause of unexplained hypotension in the CCU patient includes pericardial effusion and tamponade. Although this is more readily and efficiently evaluated with ultrasound, localized effusions or pericardial hematomas such as those seen after cardiac surgery may be difficult to identify on echocardiography. In addition, if CMR is performed in a patient with pericardial effusion, fluid signal characteristics can provide gross characterization on whether fluid is simple (ie, transudate) or complex (hemorrhagic, purulent, etc).[13]

Dynamic LV outflow tract obstruction can also cause hypotension, particularly in the postoperative settings after mitral valve replacement, or in patients with HCM, hypovolemia, and/or increased inotropic state. This complication is again usually identified with echocardiography, but CMR can be considered as an alternative if the ultrasound is not diagnostic.

ADULT CONGENITAL HEART DISEASE

Although a relatively uncommon indication for admission in the CCU, the increasing population of adults with surgically corrected complex congenital

heart disease is likely to result in an increasing number of patients presenting with decompensated HF, arrhythmias, or thromboembolic disease.

As mentioned in section “Cardiac Magnetic Resonance in Heart Failure,” CMR can be used to quantify the severity of systemic-to-pulmonary shunting, including Eisenmenger physiology, in simple and complex disorders. Additional important roles of CMR in these patients include the quantification of the volumes and function of the RV or the systemic ventricle, the evaluation of patency of surgical baffles and conduits, and the assessment of extracardiac structures such as the pulmonary arteries that can be difficult to study with echocardiography.

Regarding some specific malformations, Ebstein anomaly can present with right-sided HF, and the abnormal insertion of the tricuspid leaflets into the RV can be characterized with echocardiography and/or CMR. Patients with a repaired tetralogy of Fallot often develop RV dilatation and systolic dysfunction secondary to significant pulmonary insufficiency. CMR can provide absolute quantification of regurgitation severity, and guide the optimal timing of surgical or percutaneous pulmonary valve implantation before irreversible RV deterioration occurs. In addition, the presence of an RV scar has been linked to an increased risk of HF and ventricular arrhythmias. Patients with corrected transposition may develop dilatation and dysfunction of the systemic right ventricle in cases of atrial baffles, or narrowing of the pulmonary and reimplanted coronary arteries after arterial switch operations. Finally, in patients with a single-ventricle physiology, CMR can be used to determine ventricular performance (including dilatation, dysfunction, and LGE), patency of the Fontan circulation, and presence of cardiac or venous thrombi that is a common complication of associated chronic venous stasis.

CARDIAC MASSES

CMR can be very useful in the diagnostic evaluation of a cardiac mass, and in the differentiation between benign and malignant tumors. The most common primary cardiac tumors are benign, and they include myxomas, lipomas, and papillary fibroelastomas. Myxomas are mobile, pedunculated masses commonly in the atria and frequently attached to the interatrial septum **(Figure 16.31).**

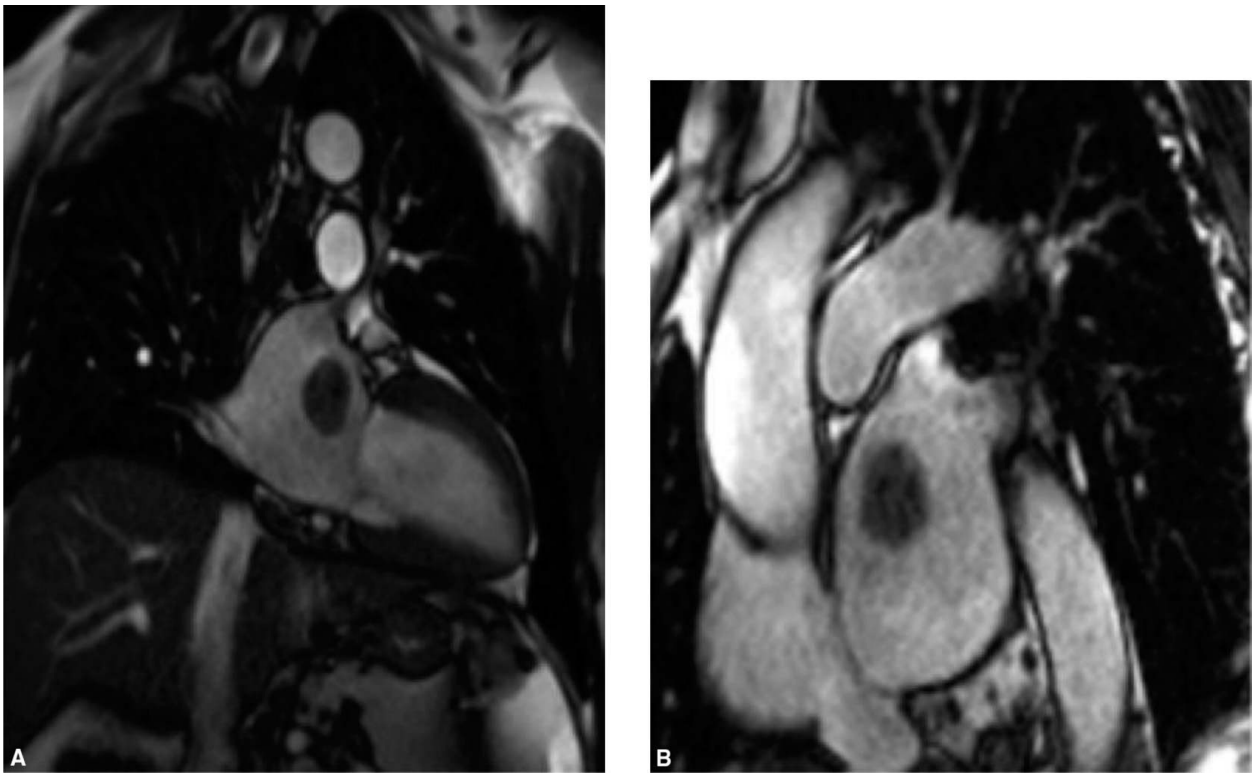


FIGURE 16.31 Two-chamber view demonstrating a left atrial myxoma (A). Short-axis stack at the level of the atria showing the large mass in the left atrium (B). Pathology confirmed the diagnosis of myxoma.

Fibroelastomas are valvular tumors that are small (<1 cm) and commonly involve the aortic side of the aortic valve. Cardiac lipomas are usually in the epicardial space, slow growing, and should be distinguished from the more prevalent lipomatous hypertrophy of the interatrial septum. The most common primary malignant cardiac mass is angiosarcoma, which classically involves the right atrium with extension into adjacent structures (pericardium, with associated pericardial effusion). Secondary tumors are much more common than primary cardiac tumors, and they involve the heart or pericardium either via direct invasion (lung and renal cell carcinoma) or by hematogenous spread (breast cancer, melanoma).

CMR offers several advantages in the imaging of cardiac masses over echocardiography. The combination of high resolution with a wide field of view can help define anatomy of the mass, attachment site, and adjacent structures. For example, the presence of a large pericardial effusion, lymphadenopathy, or involvement of more than one cardiac chamber or other mediastinal structures is consistent with a malignant process. The high temporal resolution of CMR (albeit less than that of echocardiography) can help assess mobility of the mass.

Most importantly, CMR can delineate tissue characterization with the use of T1-weighted, T2-weighted, and fat-saturation sequences. With IV contrast administration and evaluation of first-pass perfusion, CMR can demonstrate vascularity of a mass, and LGE allows further tissue characterization **(Figure 16.32)**. The post-contrast inversion time (TI) scout images are also helpful, and a combination of these findings can narrow the differential diagnosis (see subsequent text).

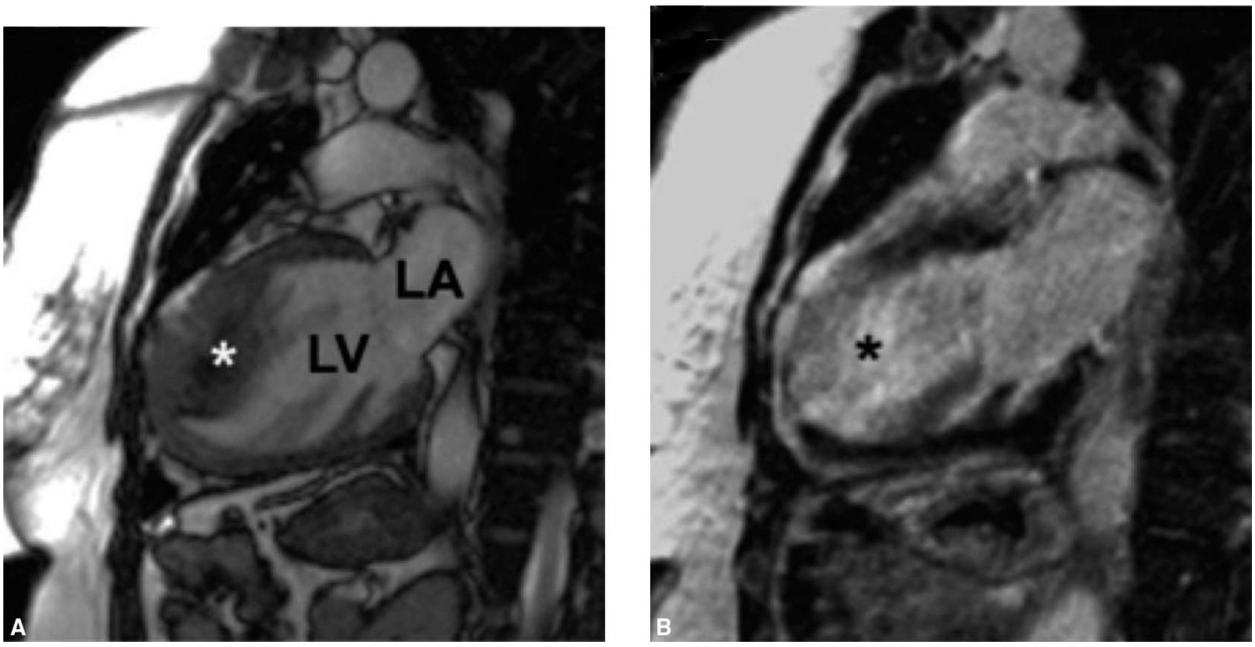


FIGURE 16.32 Two-chamber view demonstrating a mass in the left ventricular apex (*white asterisk*, A). Two-chamber view illustrating that the mass is a vascular structure on long TI imaging (B). Contrast this with the avascular thrombus in Figure 16.11. Pathology was consistent with a hamartoma. LA, left atrium; LV, left ventricle.

In the CCU setting, one of the most relevant applications of CMR for cardiac masses is the differentiation between tumor and thrombus. This is important in patients who present with ischemic cardioembolic stroke with underlying atrial fibrillation, prior MI (see section “Cardiac Magnetic Resonance in Acute Chest Pain”), LV aneurysm, rheumatic heart disease, or DCM. In such patients, several findings can identify thrombus with reasonable accuracy, as demonstrated in a recent retrospective CMR analysis of 116 patients with a definite cardiac mass.[30] In this study there were 84 thrombi, 17 benign tumors, and 25 malignant tumors. In comparison to benign or malignant tumors, thrombi were more often smaller, more homogeneous and less mobile. On the other hand, tumors were more often

hyperintense on T2-weighted imaging, first-pass perfusion, and LGE imaging when compared to thrombi. A key distinguishing characteristic with 95% accuracy was demonstrated on the TI scout images, where thrombi appeared hyperintense or isointense with short TI, and hypointense with long TI, whereas tumors demonstrated the opposite behavior.[30]

CONCLUSION

As demonstrated in this chapter, CMR is an increasingly useful imaging modality that can help diagnose and direct treatment in patients in the CCU. CMR can assist in the diagnosis of ACS, provide excellent tissue characterization, lend insights into HF etiology, precisely quantify LV and RV volumes and ejection fractions, demonstrate intracardiac shunts with precision, and assist with the identification of extracardiac structures, among other capabilities. Although not available at all cardiac centers because of its expense, it is a valuable tool when performed and read by experienced physicians.

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Patient and Family Information for: CARDIAC MAGNETIC RESONANCE IMAGING

MRI stands for magnetic resonance imaging. Cardiac MRI is a safe and painless imaging modality that uses a strong magnet to create pictures of the inner structures of the heart and help the referring physician determine many aspects of heart health. Unlike other types of imaging, MRI does not use harmful ionizing radiations such as X-rays or gamma rays. It can accurately determine the function of both sides of the heart, identify problems with valves, assess the presence of scar tissue in the heart, and provide information on many more structural and functional aspects of the heart.

PREPARATION FOR THE PROCEDURE

Some imaging facilities request that patients do not eat or drink anything before the procedure. It is important to check with the imaging facility to determine what their pre-MRI dietary guidelines are.

The magnetic field of an MRI machine extends beyond its physical boundaries and usually includes the room where the machine is placed. Any metallic object placed inside or close to the magnetic field can interfere with its function. As a result, jewelry and metal accessories, cell phones, electronic devices, and wallets containing credit or debit cards should be removed before the examination and preferably left at home.

A few types of metal implants are not safe for cardiac MRIs. Certain types of metal coils in brain aneurysms, cochlear implants (hearing aid implants placed inside the inner ear), “Triggerfish” contact lenses, insulin pumps, defibrillators,

and pacemakers are not MRI compatible. Virtually any metal-containing material can interfere with an MRI. These include, but are not limited to, bullets or shrapnels left in place and metallic rods, plates, or screws used in fixing fractured bones. All implantable and external devices should be reported to the physician before undergoing a cardiac MRI.

The examination requires that patients are able to lie flat for 30 to 60 minutes and hold their breath for 10 to 15 seconds multiple times over the course of the examination. If a patient has any difficulty lying flat or is unable to hold his/her breath, the referring physician should be informed.

Some patients will need injectable contrast with the examination depending on the clinical indication. The contrast used in cardiac MRI examinations is a gadolinium-based agent, which is distinctly different from the contrast used in CT scans. It should not be used if the patient's kidney function is very low. Gadolinium-based contrast agents have a much lower incidence of allergic reactions compared to iodinated contrast agents used in CT scans. If the patient has had an allergy to the iodinated contrast used in CT scans and has any other allergies, the physician should be informed to determine the best course of action.

If the patients have claustrophobia, which is a fear of being in enclosed spaces, they should alert their physician because some MRIs can appear to the patients as small and enclosed. In some cases, the physician may prescribe a medication to help with the claustrophobia.

Patients who are pregnant or think that they may be pregnant should alert their physician before having an MRI. There have been limited studies to determine the safety of an MRI in pregnant patients. The decision to do the examination is made individually in each case after careful consultation between the physician conducting the MRI and the referring physician.

THE DAY OF THE EXAMINATION

MRI units vary in size but are often quite large, with a cylinder-shaped tube where the patient will lie down. Some MRI units are open on the sides, "open MRI," whereas others are closed. Closed MRIs can make some patients claustrophobic. Many imaging facilities have headphones and some have videos that the patient can watch during the examination to ease the claustrophobia. The patients are given a handheld device that they can squeeze if they feel

uncomfortable at any point during the examination. This device alerts the technician to stop the examination and come into the room to check on the patient. The MRI technician will be able to speak with, and hear, the patient from the control room. While the patient will be alone in the MRI room, the control room is immediately adjacent to the MRI room with large windows so that the technician can see the patient at all times.

The patients will have stickers attached to their chest that will connect to a monitor to observe the heart rate and correlate the imaging with the cardiac cycle to obtain the best possible images. The examination has many sequences that require the patient to hold his/her breath for 7 to 8 seconds at a time. The breath-holding instructions will be clearly given by the technician. If the patient becomes tired with the breath holding, some sequences can be obtained with normal breathing, but this may affect the quality of the images.

Some patients will have an IV line placed if they need contrast. A series of images are often taken before the contrast is given, with another series of images taken afterward. The gadolinium-based contrast is usually well tolerated, but may make some patients feel warm, nauseous, and/or leave them with a metallic taste in their mouth. If the patient experiences any itching, hives, difficulty breathing, he/she should immediately press the handheld button and alert the technician.

The entire examination typically lasts between 30 and 60 minutes depending on the sequences that need to be obtained and whether contrast is being used.

AFTER THE EXAMINATION

After the examination, the patients can go about their normal day as long as they did not get any sedating medications. If they were given medication to ease anxiety, they should be accompanied by another person who would be able to safely take the patient home and monitor them for a few hours. The radiologist or cardiologist interpreting the examination will analyze the images and send a report to the referring physician. The referring physician will share the results with the patient. The time of reporting varies according to the policies at each imaging facility.

17

Noah Moss
Sean P. Pinney

Mechanical Circulatory Support in the Cardiac Care Unit

Cardiogenic shock refers to the disorder where cardiac dysfunction results in inadequate end-organ perfusion. The classic condition involves systemic hypotension and symptoms or signs of organ hypoperfusion despite adequate intravascular volume. Initial management is focused on treatment of reversible causes such as revascularization when appropriate in acute coronary syndromes. Following this or simultaneously, inotropic and vasopressor agents are administered to improve hemodynamics. Despite these measures, adequate perfusion to prevent end-organ dysfunction is often not restored or able to be maintained. As a result, morbidity and mortality from this disorder remain high, with a 30-day mortality, across many studies, exceeding 40%.[1] This has led to the development of mechanical circulatory support (MCS) devices that have been proven to reverse the poor hemodynamic profile of cardiogenic shock. It is important to note that although use of MCS clearly improves hemodynamics, data demonstrating a mortality benefit are lacking.

The decision to initiate MCS must not be taken lightly. Its use demands substantial resource allocation and carries tremendous cost. In addition, there is a high rate of serious complications when MCS is employed. Appropriate patient selection is of utmost importance. It is imperative that patients for whom temporary MCS is considered are thought to have a long-term option for

survival, because temporary MCS is merely a bridging therapy. Therefore, the medical providers must have a high index of suspicion that survival with the capacity for meaningful recovery of end-organ function and quality of life is possible. This may be accomplished by eventual improvement of native cardiac function, by placement of long-term MCS or through cardiac transplantation.

The MCS devices currently available differ in several ways, including the level of support provided, hemodynamic effects, site of vascular access, vessel size required for delivery, and associated complications (**Table 17.1**). In this chapter, we will discuss the most commonly used devices and highlight their important distinctive features.

TABLE 17.1 Characteristics of Mechanical Circulatory Support Devices

DEVICE	MECHANISM	HEMODYNAMIC SUPPORT (L/min)	DEVICE SIZE (Fr)	INSERTION
IABP	Pneumatic	0–1	8	Percutaneous: femoral or axillary artery
TandemHeart	Centrifugal	4	Inflow 21 Outflow 12–17	Percutaneous: inflow femoral vein (to left atrium via transseptal puncture), outflow femoral artery
Impella 2.5	Axial	2.5	13	Percutaneous: femoral artery
Impella CP	Axial	4	14	Percutaneous: femoral artery
Impella 5.0	Axial	5	23	Surgical cutdown: femoral or axillary artery
Impella RP	Axial	4	22	Percutaneous: femoral vein
VA-ECMO	Centrifugal	>4.5	Inflow 18–21 Outflow 15–22	Percutaneous ± cutdown: inflow femoral vein, outflow femoral artery
Durable LVAD	Axial or Centrifugal	>7	NA	Surgical: inflow from LV, outflow ascending aorta

Fr, French; IABP, intra-aortic balloon pump; LV, left ventricular; LVAD, left ventricular assist device; L/min, liters per minute; VA-ECMO, venoarterial-extracorporeal membrane oxygenation.

INTRA-AORTIC BALLOON PUMP

The intra-aortic balloon pump (IABP) was the first mechanical device developed, and its use has become widespread since its inception in the 1960s. It is placed in the descending thoracic aorta and acts by balloon inflation during diastole and active deflation in systole (see **Figure 17.1**). This results in a higher perfusion pressure in the coronary arteries during diastole and a reduction in left ventricular afterload during systole. The hemodynamic effects are variable and depend on the position in the aorta, heart rate, rhythm, aortic compliance, and systemic resistance. Overall, the potential hemodynamic effects include an increase in cardiac output (CO) of approximately 500 cc minute, an increase in mean arterial blood pressure (MAP), and a reduction in left ventricular end-diastolic pressure (LVEDP) with a resulting decrease in left ventricle (LV) wall stress and myocardial oxygen demand. Given the mechanism of action already described, the use of IABP has generally been studied in patients with cardiogenic shock resulting from myocardial infarction. The largest randomized trial evaluating the use of IABP in this group of patients was the IABP-SHOCK II Trial.[1] Six hundred patients with cardiogenic shock complicating acute myocardial infarction expected to undergo early revascularization were randomly assigned to IABP or usual care. No difference in the primary end point of 30-day all-cause mortality was found. Several smaller studies and meta-analyses have failed to show convincing evidence of a mortality benefit with the use of IABP in this setting. Of note, some benefit has been demonstrated with the use of an IABP in patients with myocardial infarction complicated by shock treated with thrombolytic therapy.[2, 3]

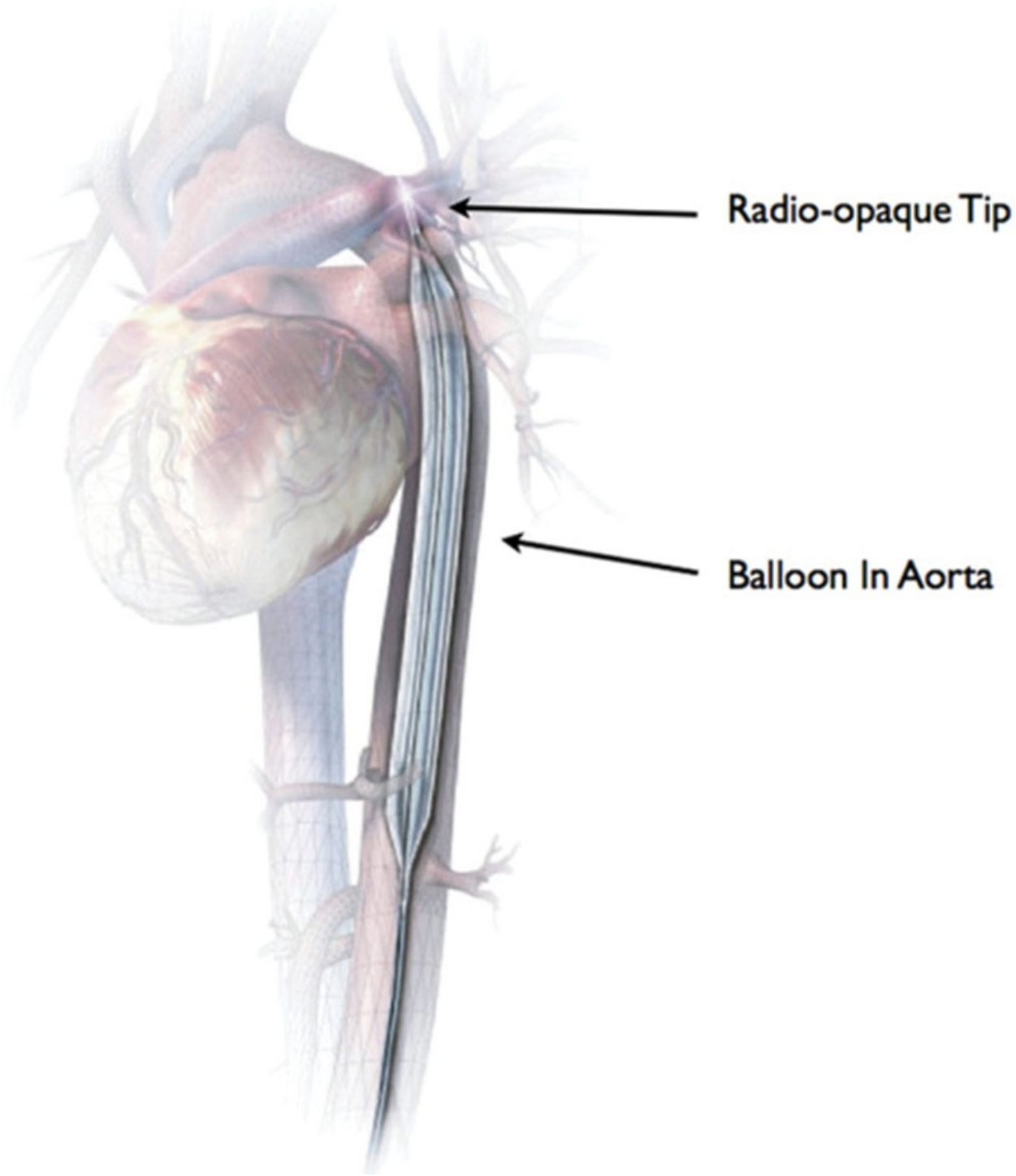

FIGURE 17.1 Intra-aortic balloon pump. It is shown placed in the descending thoracic aorta below the aortic knob. The radio-opaque tip is used to assess placement by X-ray.

CLINICAL USE

The IABP is typically placed in the femoral artery, although placement in the left

axillary/subclavian artery has been used when long-term support is planned. Its tip is advanced to the descending thoracic aorta up to the level of the carina and at least 2 cm below the aortic knob. An IABP should not be placed in patients with more than mild aortic regurgitation, because the degree of regurgitation will be increased by counterpulsation from the device. Aortic pathology such as dissection or a significant aneurysm would preclude the insertion of an IABP because of the risk of furthering aortic disease. In addition, severe peripheral vascular disease (or small vasculature) will limit its use in view of the development of ipsilateral limb ischemia.

A chest X-ray should be performed daily to confirm proper position. Distal pulses must be regularly checked following placement to screen for limb ischemia. The pressure waveform should be reviewed to ensure proper device function and timing (see **Figure 17.2**).

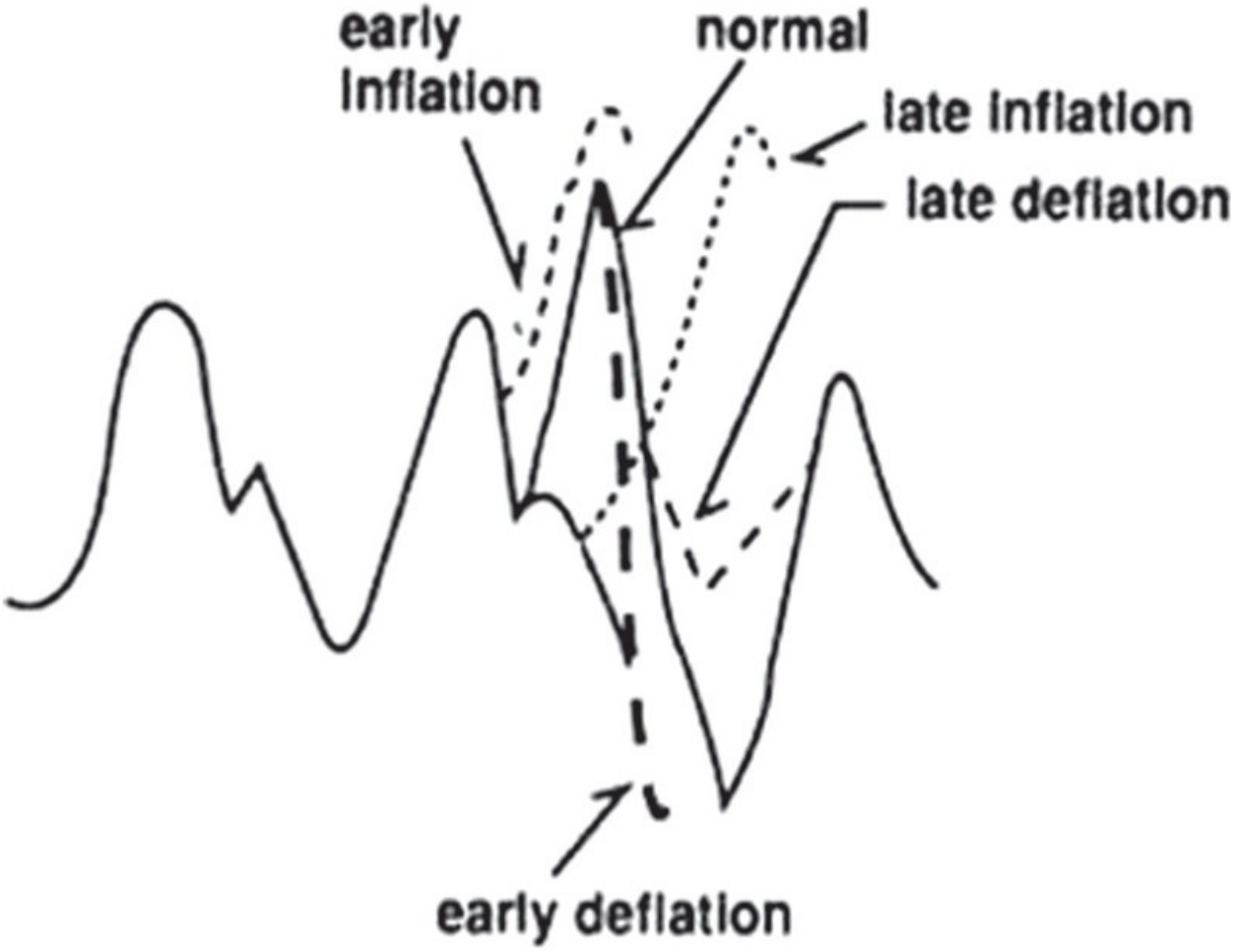

FIGURE 17.2 IABP tracing displaying normal and improper timings of balloon inflation. In a normal waveform, balloon inflation occurs at or slightly above the dicrotic notch, which represents the onset of diastole after aortic valve closure. Deflation occurs during isovolumetric contraction, just before the aortic valve opens. Early inflation, balloon inflation before aortic valve closure, can result in premature aortic valve closure and a reduced cardiac output. Late inflation, where the inflation point follows the dicrotic notch, leads to a reduction in coronary perfusion pressure. Early deflation will prevent the intended decrease in assisted systolic pressure and the resulting afterload reduction from occurring. Late deflation, occurring following aortic valve opening, will increase afterload and myocardial oxygen demand. IABP, intra-aortic balloon pump.

The use of anticoagulation with IABP support can be weighed in the context of patient-specific factors or based on institutional guidelines. Studies evaluating the routine use of anticoagulation have not demonstrated a reduced risk of thrombus formation, thromboembolism, or limb ischemia. Only an increased risk of bleeding has been found.[4]

COMPLICATIONS

The most common complications of IABP use are vascular in nature. These include limb ischemia and hemorrhage from the access site. A rare but serious complication resulting from the IABP is compromised perfusion in the aorta, leading to visceral (including renal) and spinal cord ischemia. These can be mitigated by proper placement, as discussed above.

INDICATIONS

The 2013 ACC/AHA guidelines for the management of ST-elevation myocardial infarction (STEMI) state, as a class IIa (level of evidence B) recommendation, that “the use of an IABP can be useful for patients with cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy.”[5] In addition, they highlight its use as a temporizing measure in mechanical complications of shock such as papillary muscle rupture with resulting mitral regurgitation and ventricular septal rupture.

TANDEMHEART

The TandemHeart (Cardiac Assist, Inc, Pittsburgh, PA) percutaneous assist device is a left atrial to femoral artery bypass continuous flow centrifugal pump system designed to provide complete hemodynamic support. It has been studied

in a randomized fashion for patients presenting with cardiogenic shock caused by ischemic[6] and nonischemic disease.[7] When compared to the IABP it has demonstrated superior hemodynamic effects and, among other parameters, results in larger increases in CO and MAP and a greater reduction in pulmonary capillary wedge pressure (PCWP). It was also evaluated in patients with severe refractory cardiogenic shock, a scenario in which its use would likely be of the greatest benefit, and it was shown to dramatically improve hemodynamic and clinical parameters.[8] No mortality benefit has been demonstrated, but the trials were not adequately powered to evaluate this outcome.

CLINICAL USE

An atrial drainage cannula (21F) is placed in the left atrium by means of a transeptal puncture, and oxygenated blood is drawn from there and returned via a centrifugal pump to an arterial cannula (most often 17 French) in the femoral artery (see **Figure 17.3**). Aortoiliac and femoral angiography is recommended before insertion to assess vessel size, as a 12F bilateral femoral artery access system is available to accommodate smaller vasculature. It is powered by an electromagnetic motor that drives a plastic impeller at a speed of 3000 to 7500 rpm and is capable of delivering flows up to 4.0 L/min. During use, anticoagulation is administered continuously to achieve a target partial thromboplastin time of 65–80 seconds or an activated clotting time (ACT) between 180 and 220 seconds.

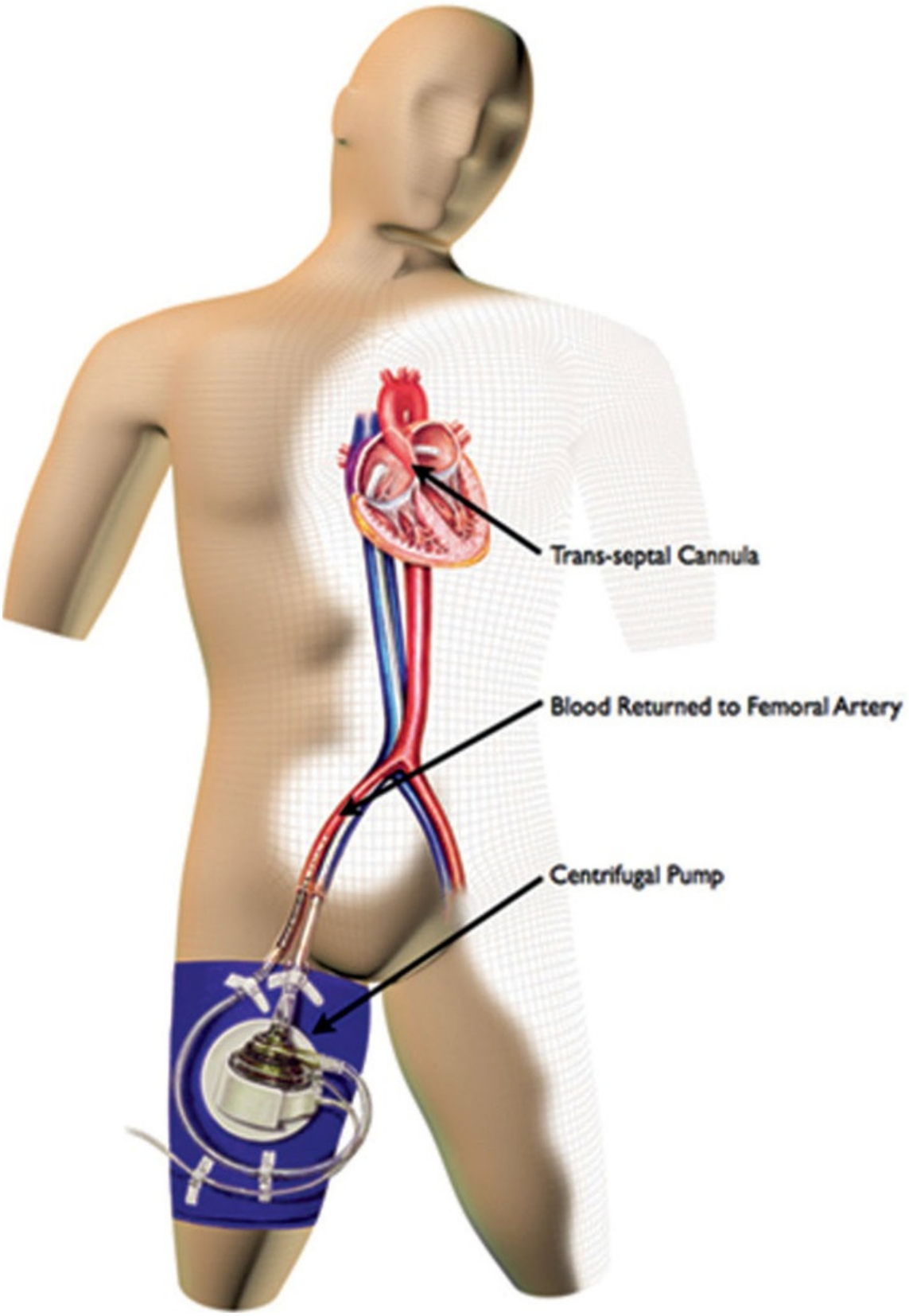
Trans-septal Cannula
Blood Returned to Femoral Artery
Centrifugal Pump

FIGURE 17.3 The TandemHeart percutaneous assist device. A drainage cannula is placed in the left atrium by means of a transseptal puncture, and oxygenated blood is drawn from there and returned via the centrifugal pump to a cannula in the femoral artery.

Despite the impressive hemodynamic benefits observed with the use of TandemHeart, its implementation is ultimately limited by the complexities of device insertion, which can be particularly challenging in emergency situations.

COMPLICATIONS

The most common complications of TandemHeart use are device-related limb ischemia and bleeding. These occur as a result of vascular access site trauma and the development of a coagulopathy. In trials, a high rate of blood transfusions was noted.

INDICATIONS

The 2013 ACC/AHA STEMI guidelines state, as a class IIa (level of evidence C) recommendation, that "LV assist devices for circulatory support may be considered in patients with refractory cardiogenic shock."[5]

The 2013 International Society for Heart and Lung Transplantation (ISHLT) guidelines for MCS state, as a class I (level of evidence C) recommendation, that the use of temporary mechanical support should be strongly considered in patients with multiorgan failure, sepsis, or on mechanical ventilation to allow successful optimization of clinical status and neurologic assessment before placement of a long-term MCSD.[9]

A 2015 clinical expert statement, endorsed by multiple organizations, concludes that patients with acute decompensated heart failure may benefit from early use of percutaneous MCS when they continue to deteriorate despite initial interventions.[10]

IMPELLA

The Impella (Abiomed, Inc, Danvers, MA) families of devices are axial flow pumps that work on the principle of the Archimedes screw. These devices deliver blood from the inlet area, which sits in the LV, through the impeller to the outlet opening in the ascending aorta (**Figure 17.4**). The left-sided Impella

device comes in three different sizes that differ on the basis of the degree of support it can deliver. The Impella 2.5 can provide up to 2.5 L/min, the Impella CP can deliver up to 4 L/min, and the Impella 5.0 up to 5 L/min. The family of devices has been shown to improve the hemodynamics of cardiogenic shock by unloading the LV, which results in an increased MAP, reduced myocardial oxygen demand, and a reduced PCWP. The Impella 2.5 is the only device of the group to be studied in a randomized fashion and has been shown to provide greater hemodynamic support compared to the IABP in patients with cardiogenic shock complicating AMI.[11] The Impella 5.0 was evaluated for use in postcardiotomy cardiogenic shock and was found to yield favorable outcomes.[12]

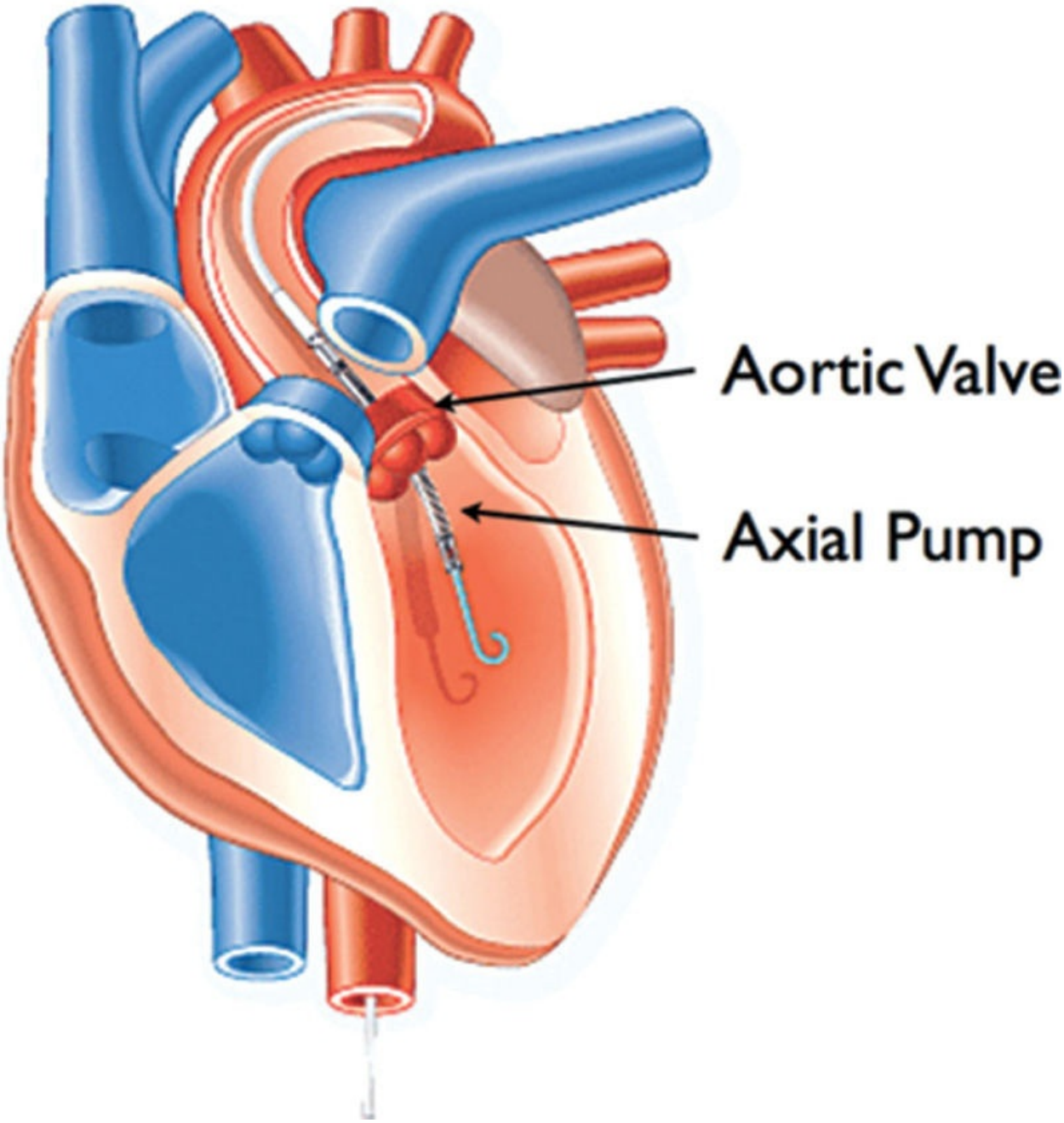

FIGURE 17.4 The Impella axial flow pump. The Impella is advanced retrograde across the aortic valve until the catheter with a pigtail tip sits in the LV. Blood is delivered from the inlet area through the impeller to the outlet area in the ascending aorta. LV, left ventricle.

CLINICAL USE

The Impella is inserted via arterial access and is advanced retrograde across the aortic valve until the catheter with a pigtail tip, which helps avoid myocardial injury and ensures a stable position, sits in the LV. The Impella 2.5 and Impella

CP can be inserted through a 14Fr introducer sheath using a percutaneous approach via the femoral artery. The Impella 5.0 uses a larger introducer sheath (23Fr) that requires a surgical cutdown for insertion and is often placed in the axillary artery. The Impella devices are typically placed under fluoroscopic guidance in the catheterization laboratory. To optimize device flow and avoid complications, proper positioning of the Impella tip in the LV is of utmost importance. Echocardiography can be used at the patient's bedside to confirm proper positioning of the device in the LV cavity. The degree of support is managed by graduation of pump speed.

The Impella requires sufficient LV preload for proper function, and its use is therefore contraindicated with significant right heart failure. Given the need for the system to cross the aortic valve, a mechanical prosthesis or severe AS precludes its use. It should be avoided when more than mild aortic insufficiency is present because a significant amount of blood that is pumped in the ascending aorta can flow back into the LV and reduce systemic perfusion. As with other devices that require arterial access, severe peripheral vascular disease limits its use. In addition, use of the Impella is contraindicated in the presence of an LV thrombus or a ventricular septal defect.

COMPLICATIONS

Major bleeding at the vascular access site is the most common complication of Impella use. Hemolysis is frequently seen owing to the high rotational speed of the impeller. If the catheter is advanced too far into the LV apex, there is a risk of ventricular arrhythmias and perforation, which may result in pericardial tamponade.[13] Limb ischemia remains a concern given the large arterial sheath required for placement.

INDICATIONS

In general, the recommendations from major society guidelines discuss all temporary mechanical support devices under the same heading. Therefore, the recommendations for Impella use in cardiogenic shock are identical to those listed for the TandemHeart.

The Impella 2.5 has received a separate indication from the FDA for use during high-risk percutaneous coronary interventions (PCI) performed in elective or urgent hemodynamically stable patients with severe coronary artery disease and depressed left ventricular ejection fraction, when a heart team,

including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option.

RIGHT VENTRICULAR SUPPORT

Right ventricular failure (RVF) can occur in multiple settings. It can be particularly devastating during the use of left-sided MCS devices because they rely on sufficient LV preload for proper function. The right ventricle (RV) can be placed under exceptional stress during MCS use for several reasons, including the rise in RV preload with normalization of CO, the alteration of normal RV geometry caused by septal shift resulting from LV unloading and an increase in pulmonary vascular resistance, which can typically be seen with critically ill patients and in the postoperative period. The RV often recovers over a short period of time, and patients can typically be stabilized with volume optimization along with the use of inotropes and pulmonary vasodilators. Right-sided MCS devices have been developed for use in RVF refractory to medical therapy. The Impella RP system works on the same principles previously described for the Impella family of pumps and can provide flow greater than 4 L/min at an impeller speed of 33,000 rpm. The device delivers blood from the inlet area, which sits in the inferior vena cava, through the cannula to the outlet opening in the pulmonary artery (PA). Its use was evaluated in a prospective trial comprising patients with RVF complicating left ventricular assist device (LVAD) implant and myocardial infarction or postcardiotomy.[14] Following initiation of support, there was a significant increase in cardiac index (CI) and a reduction in central venous pressure (CVP).

The TandemHeart system, described earlier, has been successfully converted to a right-sided support device. The inflow cannula draws blood from the right atrium (RA), and it is returned to the PA. Analysis of a registry of patients who received the device for management of RV failure found that its use led to an improvement in MAP, CVP, PA systolic pressure, and CI.[15]

CLINICAL USE

The Impella RP is inserted into the femoral vein via a 23Fr sheath and advance to the right heart with its tip passing through the RA, tricuspid valve, and pulmonic valve. During pump operation, an ACT of 160 to 180 is recommended.

Its use is contraindicated with right-sided mechanical valves, severe valvular stenosis or regurgitation of the tricuspid or pulmonary valve, and mural thrombus in the RA or vena cava.

The TandemHeart system can be placed percutaneously or surgically. Percutaneous implantation requires two areas of venous cannulation, and this can be accomplished via bifemoral or right internal jugular approaches using 21Fr cannulas. Surgical implantation is performed by direct cannulation of the RA and PA or by peripheral cannulation of the femoral vein and direct cannulation of the PA.

COMPLICATIONS

The most frequent complication with both devices is major bleeding. As described with the Impella systems above, hemolysis is seen with Impella RP use.

INDICATIONS

There are no societal recommendations for use of temporary right-sided mechanical support devices. The Impella RP is FDA approved for use in patients who develop acute right heart failure or decompensation following LVAD implantation, myocardial infarction, heart transplantation, or open-heart surgery.

EXTRACORPOREAL MEMBRANE OXYGENATION

Extracorporeal membrane oxygenation (ECMO) differs from the temporary devices already discussed in that it is able to provide full support in cases of severe biventricular failure. There are two forms of extracorporeal support, veno-venous (VV) and venoarterial (VA). The VV system provides only oxygenation. However, VA ECMO can provide complete cardiopulmonary support. The system consists of a continuous flow centrifugal pump and a membrane oxygenator (**Figure 17.5**). Blood is aspirated from the RA into the venous inflow cannula and, via the pump, is circulated through the membrane oxygenator. Oxygenated blood is then directed into the arterial circulation via the outflow cannula. ECMO can provide substantial hemodynamic support, with flows up to 6 L per minute, and increased LV afterload, which can have negative consequences discussed later. ECMO has been applied clinically in many forms

of circulatory failure, including cardiogenic shock from various etiologies and cardiac arrest, but no randomized controlled trials have been performed to study its use. For the most part, the data supporting its implementation come from prospective and retrospective single center experiences or pooled analysis of this data. In these, it has been suggested that ECMO use improves 30-day survival and neurologic outcomes in the cardiac arrest population but resulted in similar outcomes when compared to other forms of mechanical support, aside from IABP, in the cardiogenic shock patients.[16] When considering these data, one must recognize the nonrandomized nature of these studies and the potential large influence that confounders have on these results.

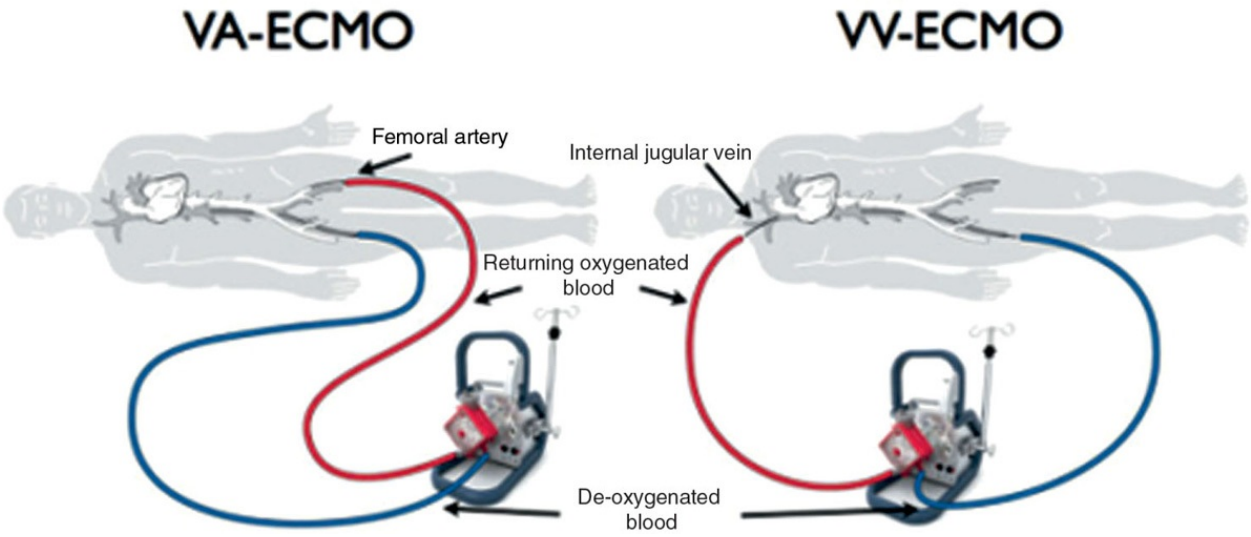

FIGURE 17.5 Diagrammatic representation of peripheral veno-venous (VV-ECMO) and peripheral veno-arterial (VA-ECMO) extracorporeal membrane oxygenation. With VA-ECMO, venous blood is circulated through the membrane oxygenator, and oxygenated blood is directed into the arterial circulation. With VV-ECMO, venous blood flows through the membrane oxygenator, and oxygenated blood is returned to the venous circulation. (From Cove ME, MacLaren G. Clinical review: MCS for cardiogenic shock complicating acute myocardial infarction. *Crit Care*. 2010;14:235.)

CLINICAL USE

The appeal of the ECMO system is the ability to provide complete cardiopulmonary support with rapid insertion peripherally at the bedside. A venous inflow cannula (ranging from 15 to 29 Fr) is inserted into the femoral vein and advanced to the RA; this is usually performed under transesophageal echocardiography guidance. The arterial outflow cannula (ranging from 15 to 23Fr) is typically placed in the femoral artery, but other arterial sites of

cannulation have been used. Adjusting the rotational speed of the device controls flow, and it should be placed at the lowest speed necessary to provide adequate perfusion. As flow is increased, the afterload rises as well. This results in a reduction in the heart's ability to unload and increases myocardial oxygen demand. In turn, there is an increase in the LVEDP/PCWP that can lead to the development of pulmonary congestion. In addition, it is thought that the unfavorable LV loading conditions created by ECMO use may adversely affect myocardial recovery. Several strategies can be employed to decompress or "vent" the LV when deemed necessary. These include inotropic support, IABP placement, Impella use, atrial septostomy, or direct LA or LV cannulation. When femoral cannulation is employed, arterial blood gases and pulse oximetry should be checked in the right arm, the farthest area from the cannulation site, to confirm uniform oxygenation throughout the arterial system. This is necessary because the ECMO device will preferentially perfuse the lower extremities with its fully saturated blood, whereas blood ejected from the heart will selectively perfuse the brain, coronaries, and upper extremities. This phenomenon can be exacerbated by improvement in native CO and IABP use.

Anticoagulation is necessary to prevent thrombus formation in the system, particularly in the membrane oxygenator, and ACTs are typically maintained between 180 and 250 seconds.

One disadvantage to ECMO use is that a cardiac perfusionist, whose availability is limited at many centers, is required for management of the system. The perfusionist plays an integral role in the ECMO circuit setup, priming, and optimization of settings during use.

COMPLICATIONS

The most frequent complication during ECMO use is hemorrhage that can occur at the sites of cannulation or other. Neurologic complications such as seizures, cerebral infarction, and hemorrhage have been reported. Cardiac thrombus formation, especially when CO remains low, is seen. Renal failure has been observed with a notable oliguric phase following implant. As with the other devices placed peripherally, limb ischemia is of concern, and in order to decrease the occurrence an additional cannula can be placed to perfuse the distal extremity. Given the multiple entry sites and large-size catheters, close monitoring for infectious complications is required.

INDICATIONS

ECMO carries a society recommendation similar to the other forms of percutaneous MCS, but strong consideration should be given to ECMO use when there is significant impairment in respiratory gas exchange.[10]

DURABLE MCS

Implantable MCS devices have become integral to the management of patients with end-stage heart failure. They have been shown to improve both survival and quality of life when compared to traditional care in this group of patients.[17] The newer-generation continuous flow pumps have proven to be more durable and carry a superior adverse event profile than the original pulsatile devices.[18] The two main indications for implantation are bridge to transplantation (BTT) and destination therapy (DT). The hope that these devices would routinely offer a path to recovery has been unrealized because this occurs in few cases.[19] BTT refers to implanting an LVAD to maintain hemodynamic support in those patients who are listed for cardiac transplantation. Given the prolonged wait times for donor organs, bridging is necessary, because many patients would not survive to the time of transplantation. Devices are placed as DT with the intent of providing prolonged support in patients who are ineligible for cardiac transplantation.

Implantation of durable mechanical support devices in patients with cardiogenic shock and multiorgan failure has traditionally been avoided in view of the concern that these critically ill patients would not tolerate the rigors of surgery and extended cardiopulmonary bypass. Registry data have indeed shown that early and midterm survival for patients implanted at INTERMACS profile 1, defined as critical cardiogenic shock, is significantly worse than for less sick patients, but despite the advanced disease state, 1-year survival is reported to be 76%.[20] Some centers have adopted strategies of inserting implantable LVADs as the primary therapy for refractory cardiogenic shock rather than attempts at hemodynamic stabilization with short-term mechanical devices.[21] This approach restores consistent CO to a greater degree and avoids the exposure to the multiple complications associated with the short-term devices.

CLINICAL USE

The two most commonly used commercially available LVADs are the Heartmate

II (St. Jude Medical, St. Paul, MN) and the HVAD (Medtronic Inc., Minneapolis, MN). Both pumps consist of a blood inlet, termed the inflow cannula, traditionally placed in the left ventricular apex, and an outlet, termed the outflow cannula, typically placed in the ascending aorta, separated by a single rotating element that imparts energy on the blood to increase flow and pressure. There is a percutaneous driveline connected to the LVAD pump that is tunneled outside the body and linked to a controller that is powered by connecting battery packs (**Figure 17.6**). The primary differences between the two devices lie in the mechanics of the rotating element and implant location. The Heartmate II is an axial flow pump whose impeller with its housing is positioned below the left rectus abdominis muscle or in the peritoneal cavity. The HeartWare HVAD is a centrifugal flow device with the impeller and its housing in the pericardial space (**Figure 17.7**). Of note, the Heartmate 3 (St. Jude Medical, Inc., St. Paul, MN), a centrifugal flow intrapericardial pump, is currently being studied in a clinical trial. Because of the continuous LV unloading and flow generated by these devices, patients most often lack a palplable pulse. Measurement of systemic pressure requires the use of a doppler device and manual blood pressure cuff, and in critically ill patients, the use of an arterial line is prudent. Patients are chronically maintained on warfarin with a goal international normalized ratio in the range of 2 to 3 and antiplatelet therapy to prevent device thrombosis.

FIGURE 17.6 Components of a ventricular assist device system. Pictured here is the Thoratec Heartmate II Left Ventricular Assist Device (HM-II LVAD). A, Pump, B, batteries, C, system controller, D, driveline, E, position of inflow cannula, F, position of outflow cannula. (Permission requested from Thoratec

Corporation of SJM.)

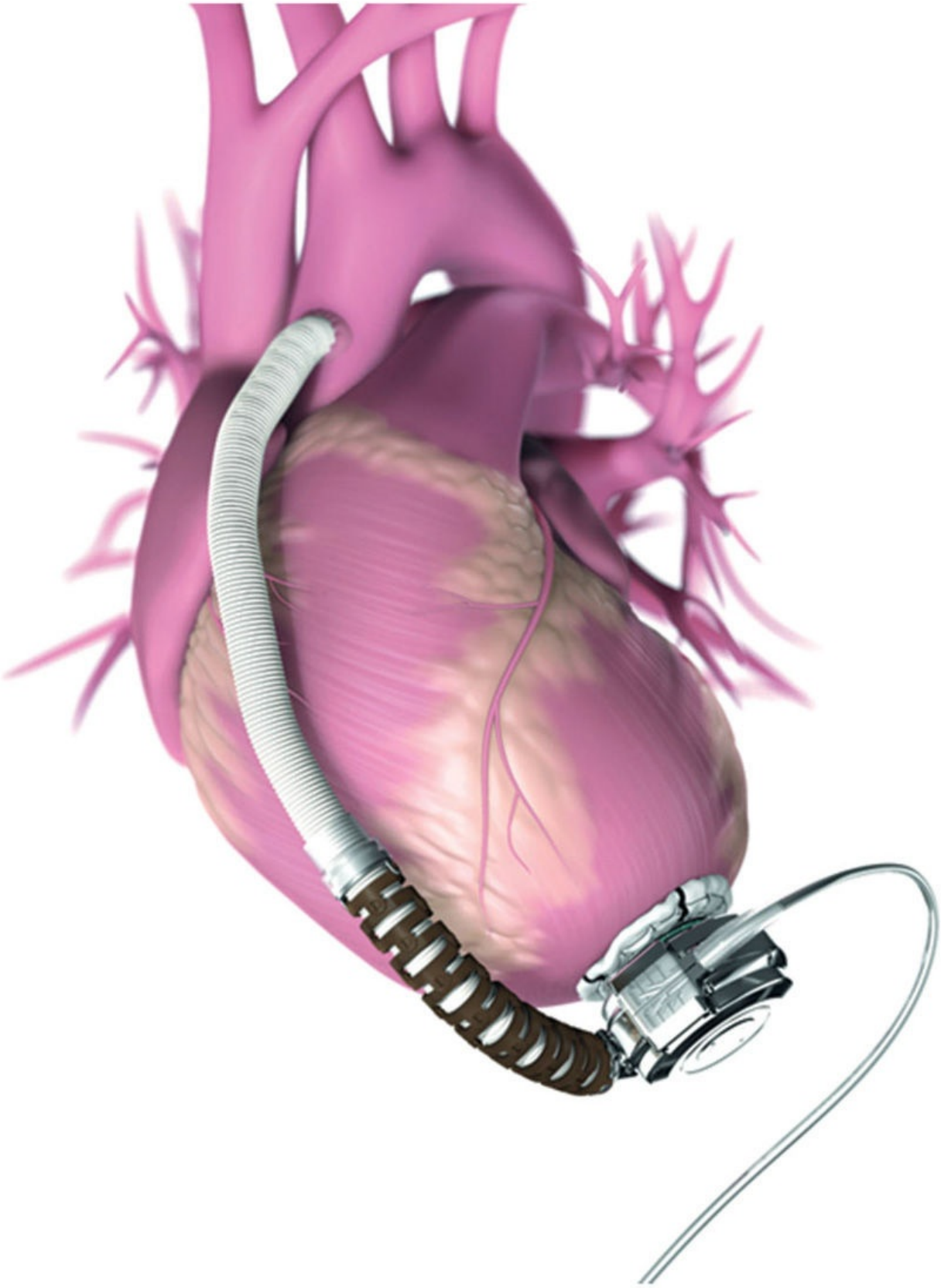

FIGURE 17.7 Position of an intrapericardial ventricular assist device. Pictured here is the HeartWare HVAD system. A, Pump, B, driveline, C, position of outflow cannula. (Permission requested from HeartWare.)

COMPLICATIONS

Several serious complications, including stroke, bleeding, and pump thrombosis, have been noted to occur both in the initial trials and in registry data.[20] Readmissions are common, and some adverse events require management in the CCU.

Bleeding requiring transfusion of packed red blood cells, most often from a gastrointestinal source, occurs at high rates. Formation of arteriovenous malformations and acquired von Willenbrand syndrome are thought to be responsible for these events. These typically resolve with brief periods off anticoagulation or with endoscopic treatment but can continue to occur at high rates in certain individuals.

Pump thrombosis can present with a wide range of clinical manifestations, depending on the extent of the clot. In its most benign form, only elevated markers of hemolysis with little change in device function or patient symptoms are found. On the other end of the spectrum, severe hemolysis with pump failure and resulting heart failure can occur. Features suggestive of thrombosis include signs of hemolysis such as red or reddish-brown urine, elevated serum lactate dehydrogenase, decreased serum haptoglobin, and increased plasma-free hemoglobin. The change in pump performance most suggestive of thrombosis is the development of a marked or gradual increase in pump power. Given the decline in output through the pump, increased pump speed may be required to maintain adequate flow. Pump thrombosis can initially be managed with intensification of anticoagulation, but pump exchange may be indicated depending on the severity and clinical scenario.

Right heart failure can be an early or late complication of LVAD support. For proper LVAD function, the RV must supply adequate preload across the pulmonary circuit. RV failure can manifest as low flow through the device, volume overload and end-organ dysfunction. It is thought that LVAD support can further weaken an already compromised RV by increasing systemic venous return and inducing geometric changes that can increase tricuspid regurgitation or reduce the septal contribution to RV stroke volume. In the perioperative period post-LVAD implant, management of right heart failure will include high doses of intotropic support or, in refractory cases, implantation of a temporary

right ventricular assist device.

Ventricular arrhythmias, typically sustained ventricular tachycardia (VT), have been observed to occur at high rates post-LVAD implant, even in patients who had not experienced these previously.[22] These can occur in the immediate postoperative period, when electrolyte imbalances and the use of arrythmogenic inotropes contribute to their cause, or later in the course. An echocardiogram should be performed to evaluate whether endocardial irritation in the setting of excessive ventricular unloading resulting in direct contact of the LVAD outflow cannula and endocardium, termed a "suction event," is the culprit. Initially, sustained VT is typically well tolerated, as the device will continue to provide support. When the event is protracted, right heart failure can develop, and the accompanying clinical manifestations previously discussed can follow. The management of VT in an LVAD patient is similar to that employed in the typical patient. First, reversal of inciting factors and correction of electrolyte imbalances should be tried. This may include cessation of proarrythmic medications or a speed reduction to prevent approximation of the outflow cannula and endocardium. Following this, treatment with antiarrhythmics, antitachycardia pacing or defibrillation should be implemented. Only rarely, in cases repeatedly refractory to the above treatments, is ablation considered.

INDICATIONS

The 2013 ISHLT guidelines[9] for MCS state, as a class IIa (level of evidence C) recommendation, that long-term MCS for patients who are in acute cardiogenic shock should be reserved for the following:

1. Patients whose ventricular function is deemed unrecoverable or unlikely to recover without long-term device support.
2. Patients who are deemed too ill to maintain normal hemodynamics and vital organ function with temporary MCS devices (MCSDs), or who cannot be weaned from temporary MCSDs or inotropic support.
3. Patients with the capacity for meaningful recovery of end-organ function and quality of life.
4. Patients without irreversible end-organ damage.

The Centers for Medicare and Medicaid Services (CMS) has laid down the following criteria for LVAD implantation as DT:

1. New York Heart Association class IV patients with end-stage heart failure that are not candidates for transplantation.
2. Patients who have failed to respond to optimal medical management for at least 45 of the last 60 days or have been balloon pump dependent for 7 days or IV inotrope dependent for 14 days.
3. Patients who have a left ventricular ejection fraction < 25% and have demonstrated functional limitation with a peak oxygen consumption of ≤14 mL/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.

CONCLUSION

Cardiogenic shock remains a devastating condition with high rates of morbidity and mortality. Over the past several decades, we have seen the development of MCS devices that are able to offer excellent hemodynamic support. The choice of device can be tailored to patient characteristics, degree of desired support, and institutional resources. **Figure 17.8** outlines an algorithm for deciding on the proper implementation of these therapies. Their use has become widespread, and the costs associated with them continue to rise. This is all occurring without concrete evidence of improvement in mortality with the use of these devices. Whether the benefit of reversing the hemodynamics of cardiogenic shock has not translated into improved long-term outcomes because of the high rate of complications associated with these devices or as a result of delayed initiation, to a time when multiorgan dysfunction has already developed, needs further evaluation in well-designed clinical trials. In addition, before instituting support it must be confirmed that there is a reasonable chance that a pathway to a meaningful recovery will be established.

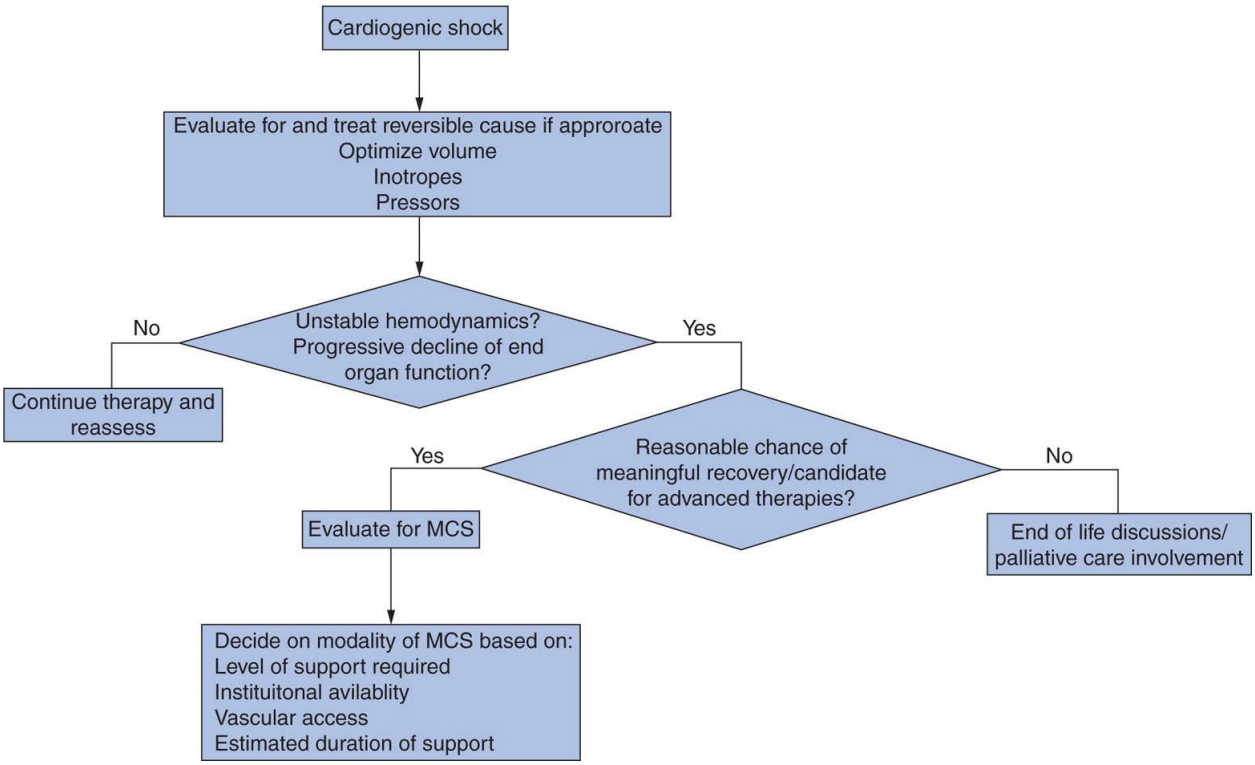

FIGURE 17.8 An algorithm for deciding on the use of mechanical circulatory support.

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Patient and Family Information for: MECHANICAL CIRCULATORY SUPPORT

The heart is responsible for providing the force to deliver oxygenated blood to the body's organs and tissues. The heart has a right and left side that serve different functions but work in tandem to maintain the circulation of blood. The right side of the heart sends blood through the lungs, where it picks up oxygen. The oxygenated blood then passes to the left side, where it is pumped to the rest of the body. When the heart suffers a serious injury, an insufficient amount of blood is delivered to the organs to meet their demands, and organ dysfunction follows. This clinical situation is termed cardiogenic shock. The heart can be weakened to this extent either by a new cardiac event, such as a heart attack, by progression of existing heart disease, or by an insult to an already impaired heart. Signs of cardiogenic shock include fatigue, altered mental state, cool extremities, low blood pressure, kidney failure, and liver failure. Initial management is focused on treatment of reversible causes, such as opening up blocked arteries, and attempting to augment heart function with intravenous medications. At times, these maneuvers are not sufficient to restore adequate circulation. It is in these situations that the use of mechanical circulatory support (MCS) is considered. MCS refers to a variety of devices that aim to improve or replace the heart's pumping function. They are placed in order to allow the heart to recover adequate function or until a more definitive treatment is implemented. These devices differ in several ways, including the way they function, the level of support provided, the manner in which they are placed, and the associated complications.

The *IABP* is typically used and is the best studied device in patients with cardiogenic shock resulting from a heart attack. The device imparts its impact by

timed inflation and deflation of a balloon that sits at its tip. It supports the failing heart by decreasing the pressure that the heart has to pump against and increasing blood flow to the coronary arteries. It is usually placed in the arteries of the lower extremities and advanced up the aorta to its proper position. The most common complications of IABP use are related to the artery in which it is placed. Complications include disruption of blood flow to the lower extremities and bleeding from the site of access.

The *TandemHeart* assist device is a continuous flow pump designed to provide a high level of support. A catheter is placed in the veins of the lower extremities and advanced to the heart, where its tip crosses from the right to the left side. Blood is drained from the left side of the heart and directed, using the force of the pump, to a catheter in the arteries of the lower extremities where it enters circulation. The most common complications of TandemHeart use are related to the blood vessels in which the catheters are placed. Complications include disruption of blood flow to the lower extremities and bleeding from the site of access. It is not uncommon to require a blood transfusion as a result of significant bleeding.

The *Impella* system is available in three distinct sizes that differ in the amount of support they can provide. They all function on the same principle. The system is inserted into the peripheral arteries, and its tip is advanced into the LV of the heart. Using the force of the pump, blood is pulled through the opening at the tip seated in the LV and pushed to the aorta. Complications include disruption of blood flow to the lower extremities and bleeding from the site of access. In addition, it is common to induce breakdown of blood cells given the force placed on them when passing through the pump.

ECMO is the only device system able to provide full cardiac support and oxygenate blood. A catheter is placed in the veins of the lower extremities and advanced to the right side of the heart. Blood is drained from the right side and directed, using the force of the pump, to a device that provides oxygen to the blood. The oxygenated blood is then passed to a catheter in the arteries, typically in the lower extremities, where it enters circulation. Complications include disruption of blood flow to the lower extremities and bleeding from the site of access. As a result of the disruption to normal blood flow, clot formation in the heart can occur. In addition, neurologic events such as seizures and strokes have been documented during use.

Placement of a long-term support device, called a *LVAD*, can be considered in cases where there is little hope of restoring adequate heart function in a

relatively short period of time. These pumps restore blood circulation in a reliable manner and are quite durable. They must be implanted surgically in the operating room with use of the heart–lung machine. Blood enters the system through a tube in the LV and flows through the pump. From the pump, it is passed through tubing and exits the system in the aorta, where it circulates to the rest of the body. LVADs can remain in place for months to years. They remain in use until the heart recovers its native function or until a heart transplant is available or permanently remain for those patients not eligible for heart transplantation. They have been proven to both improve survival and quality of life in patients with advanced heart failure. The impressive benefits of the device do not come without cost. There are several complications associated with LVAD support. These include bleeding, infection, stroke, device malfunction requiring exchange and ventricular arrhythmias.

The condition of cardiogenic shock, resulting from severely impaired cardiac function, carries a high risk of morbidity and mortality. This has led to the development of novel devices with the hope of improving outcomes. These mechanical devices have repeatedly been proven to enhance blood circulation dramatically, but studies have yet to demonstrate an overall improvement in survival. It is important to understand that it is not appropriate to employ MCS in all cases. Use of these devices comes with a high rate of complications, many of them serious, which can place further stress on an already critically ill patient. In addition, the health care costs associated with their use are significant. The physicians must have a high index of suspicion that the patient can recover from their critically ill state and enjoy a meaningful quality of life in the future. To reach this end, these devices can serve as a bridge to recovery of native heart function, to placement of a long-term mechanical device, or to cardiac transplantation.

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Selection and Care of the Heart Transplant Patient

INTRODUCTION

Despite making great advances in the medical treatment of heart failure over the last several decades, heart transplantation remains the definitive therapy for end-stage heart failure by extending survival and improving quality of life.[1, 2] Although the number of heart transplantations performed annually in the United States has remained static over the last decade, both short- and long-term survival rates have increased significantly.[3]

This chapter will discuss patient selection for transplantation as well as postoperative and follow-up care. It will focus on the first 6 months after transplantation, making references to later time points.

PATIENT SELECTION

Heart transplantation is indicated for the treatment of Stage D heart failure according to the American Heart Association/American College of Cardiology comprehensive heart failure guidelines. Transplantation may also be considered for the treatment of refractory arrhythmias; hypertrophic cardiomyopathy; severe

angina, valvular heart disease, or congenital heart disease not amendable to surgical repair; and, less frequently, selected cardiac neoplasms. A second transplant may be considered for patients with a history of heart transplant who develop allograft failure from vasculopathy, rejection, or other causes.

The specific criteria employed by transplant centers to decide patient eligibility may vary somewhat. The International Society for Heart and Lung Transplantation (ISHLT) has published consensus guidelines regarding patient selection.[4] Among the many criteria used, perhaps none is as variable as age. The ISHLT recommends that patients should be less than or equal to 70 years of age. Some centers draw the line at 65 years, whereas others have no absolute age criteria. Notably, in 2006, of the 2192 transplants performed in the United States, 243 (11%) occurred in patients over 65. Given that the majority of heart failure cases occur in patients older than 65, there is an implicit need for either transplantation or other destination therapies for patients in their seventh and eighth decades of life.

All patients should be without neoplasm. Select patients with recently treated localized cancers with a low chance of recurrence may be eligible if they are free of metastatic disease. Cancer screening includes colonoscopy in all patients over 50 years, a prostate-specific antigen in men, and mammography and a PAP smear in women. Cardiac transplantation has been successfully performed to treat cardiac neoplasms such as large atrial myxomas, and cardiac sarcomas without evidence of metastatic disease. Primary amyloidosis is an emerging indication for transplantation. Transplantation using extended-donor criteria followed by chemotherapy alone or in conjunction with bone marrow transplantation has been shown to extend survival in these patients.[5]

Although once excluded from consideration, diabetic patients can now be listed for transplant provided they have little or no evidence of end organ disease such as retinopathy, nephropathy or peripheral vascular disease. Patients with other debilitating chronic illnesses that may impact survival and those who lack the ability to provide self-care are generally excluded. Examples include dementia or hemiplegia after stroke. Patients with severe peripheral or cerebral vascular disease are excluded, as are those patients with significant restrictive or obstructive pulmonary disease (FEV***1*** <1 L).

Evaluation of liver and kidney function should be done at baseline and repeated at regular intervals. Patients with chronic kidney disease with a creatinine clearance of less than 34 mL/minface a high risk for developing chronic renal failure and should be considered for combined heart–kidney

transplantation. Patients with significant liver dysfunction are at risk for perioperative bleeding, vasoplegia, and organ failure. A transjugular liver biopsy may be required in those patients with significant liver dysfunction in order to exclude cirrhosis. This also permits measurement of hepatocaval and hepatic vein pressures to clarify the etiology and severity of the disease. Patients with significant irreversible disease, defined by bilirubin >2.5 or alanine transaminase/aspartate transaminase >3x normal, may be declined listing or, at select centers, considered for heart–liver transplant. Patients with reversible hepatic dysfunction with "nutmeg liver" from outflow obstruction may still be considered eligible for transplant because central venous pressure should fall with transplantation of a new cardiac allograft.

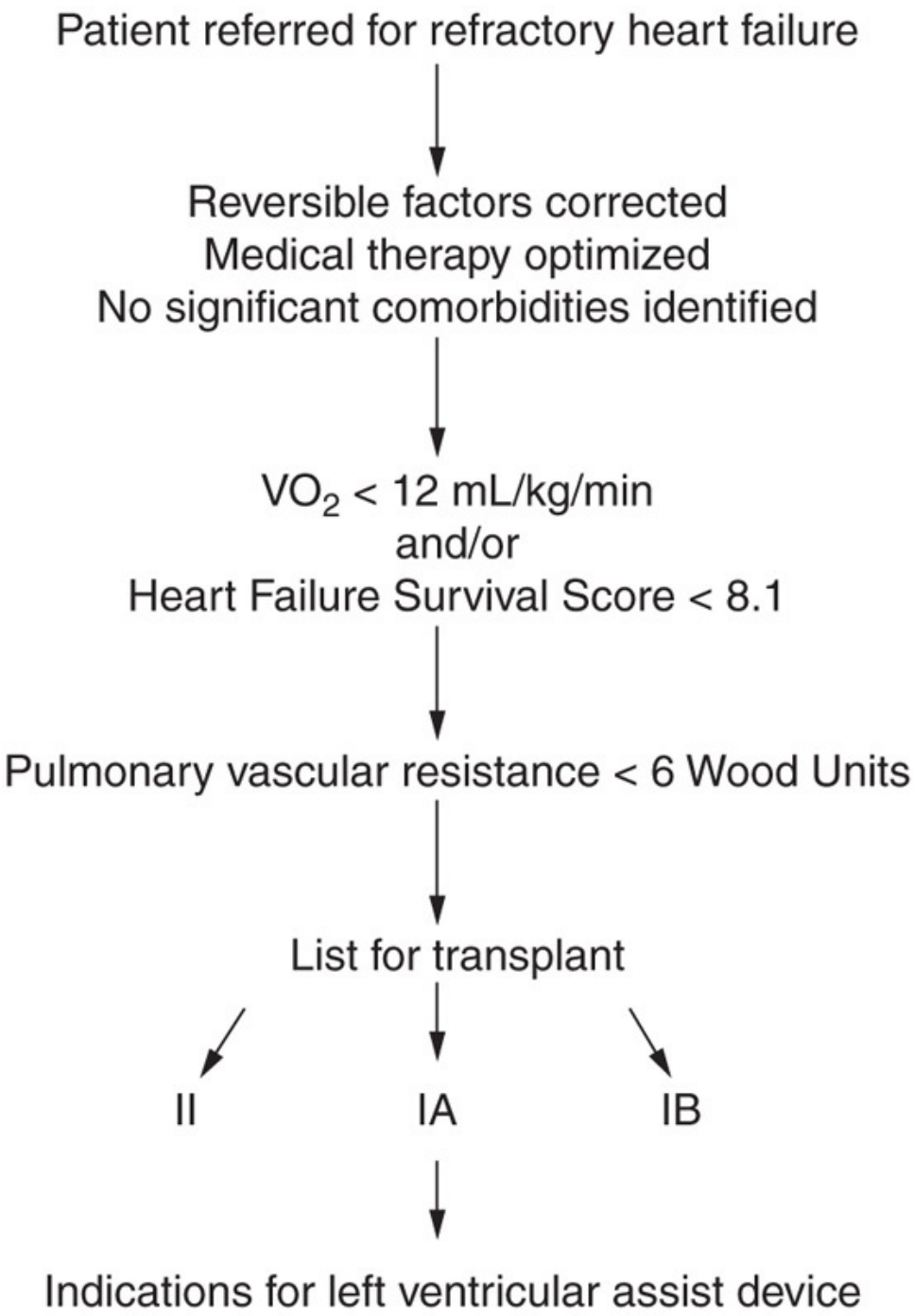
Screening for chronic viral infection should be performed before listing. Testing for herpes simplex virus (HSV), Epstein Barr virus (EBV), cytomegalovirus (CMV), hepatitis A, B, and C as well as HIV is recommended. Prophylaxis against reactivation of CMV and HSV is determined on the basis of the results of serologic testing. Controversy remains as to whether patients infected with hepatitis B and C should be transplanted in view of the risk of increased viral replication in the setting of immunosuppression. Infected patients with HIV have recently been considered eligible at some centers using extended-donor criteria. Eligible patients must have an undetectable viral load and a reconstituted immune system with normal CD4 count.[6, 7] Titers for *Trypanosoma cruzi* (Chagas) should be tested in all patients with nonischemic cardiomyopathy who are native or resided in South or Central America. Screening for strongyloides is recommended for those patients who lived or visited an endemic area such as Puerto Rico or the Dominican Republic.

Selection of heart transplant recipients should be reserved for those patients with a significant cardiovascular limitation resulting in reduced 1-year survival. Identifying such patients can be challenging, particularly in ambulatory patients. Cardiopulmonary exercise testing to measure peak oxygen consumption (VO_2 max) is a proven risk stratifying method and should be performed in all ambulatory patients.[8] A peak oxygen consumption of less than 12 mL/min/kg, or less than 14 mL/kg/min if intolerant of a beta-blocker, is considered the threshold for listing because it is predictive of reduced 1-year survival. Other noninvasive predictive models include the heart failure survival score, which incorporates peak oxygen consumption, or the Seattle Heart Failure model.[9, 10]

Patients with pulmonary hypertension are at increased risk for right heart failure following transplant because the unconditioned donor right ventricle (RV)

may struggle and fail in the face of increased afterload. Generally speaking, a pulmonary vascular resistance (PVR) of greater than 6 Wood Units or greater than 3 Wood Units following vasodilator testing with nitroprusside is considered a contraindication to transplantation. Long-term treatment with an inodilator, such as milrinone, or a ventricular assist device may help reduce PVR to safely allow transplantation. When PVR remains fixed, heart–lung transplantation may be considered. A summary of our transplant listing algorithm can be found in **Figure 18.1**.

Proposed Listing Algorithm



Hemodynamic instability despite high-dose inotropic therapy +/– intra-aortic balloon pump

Predictably prolonged waiting time in a tenuous 1A

FIGURE 18.1 The approach to evaluating patients for heart transplantation begins with referral to an advanced heart failure program. Reversible factors are corrected and medications are optimized. Persistently symptomatic patients will be risk stratified with a cardiopulmonary stress test and multivariable risk scores. Those with predicted high 1-year mortality will be formally evaluated, a process that includes right heart catheterization to screen for fixed pulmonary hypertension. Acceptable candidates will be listed for transplant and further stratified as 1A if they require intensive care hospitalization, 1B if they require continuous inotrope infusion, or II if they are otherwise stable.

The presence of alloantibodies increases the risk of experiencing either acute or chronic rejection. All potential recipients are screened against a panel of reactive antibodies (PRA). It is our practice to perform a donor-specific prospective crossmatch for all recipients with a PRA greater than 10% to reduce the chance of developing acute or hyperacute rejection. This step reduces the risk of allograft loss, but, because of the mechanics of performing the test, effectively reduces the donor pool. Further steps to minimize the risk of humoral sensitization include limiting blood product transfusion while awaiting transplantation. Patients who are more likely to have elevated levels of alloantibodies include postpartum women and prior recipients of organ transplants. A program of desensitization can be performed in patients whose PRA remains elevated. Both plasmapheresis and infusions of immunomodulatory drugs, such as intravenous gamma globulin (IVIG) and rituximab, have been employed with varying degrees of success.[11]

Obese patients experience a greater number of complications following cardiac surgery, including prolonged ventilatory times, renal failure, and wound infection.[12] The presence of obesity in heart transplant recipients is associated with poorer survival compared with nonobese patients. A body mass index (BMI) greater than 35 is considered a relative contraindication to transplantation at our center, and all patients are encouraged to reduce their BMI to less than 30 to improve their odds of long-term survival.

Other contraindications to heart transplantation include any psychological or social barrier that would preclude one’s ability to reliably comply with medical therapy and follow-up examinations. Active drug, alcohol, or tobacco use excludes consideration for transplantation. Nicotine blood levels, as well as blood alcohol levels and urine toxicology screens, can be used to test for compliance. Decisions about the severity of a patient’s substance dependency are generally made as part of a general evaluation of all patients by a psychiatrist. Social support is critical for the patient posttransplantation given the physical and psychosocial stressors encountered.

It is recommended that patients on the waiting list be formally reevaluated every 6 months to ensure that they still fulfill the necessary listing criteria. Occasionally, a patient's clinical condition will improve as a result of medical or device therapy. Those patients with significant improvement in cardiac function and symptoms should be considered for removal from the waiting list.

DONOR SELECTION

Following the establishment of brain death, organs are offered for transplantation by local organ donor networks following the rules established by the United Network for Organ Sharing. Because the specific criteria used to accept donor organs remain variable between transplant centers, a recent consensus statement provided recommendations to improve the evaluation and successful utilization of potential cardiac donors.[13] In general, donors should be younger than 50 years old, but older donors may be considered for extended criteria recipients. Donors with significant chest wall trauma are excluded from transplantation, although short periods of cardiopulmonary resuscitation or isolated rib fractures are acceptable. To ensure that the heart is of a sufficient size to match the recipient's needs, a donor's weight should not be less than 80% of that of the recipient, and the donor should be no more than 6 inches smaller than the recipient. Some believe that a male donor whose height exceeds 66 inches is sufficient for all recipients regardless of their height. Donors should be free of malignancy and should have negative blood and sputum cultures to reduce the risk of bacterial transmission. Donors with HIV or active hepatitis B infection are excluded from consideration. Although in the past donors with serologic evidence of hepatitis C infection have been used in some centers, a recent study called this practice into question. Gasink et al investigated the impact of transplanted hearts from hepatitis C seropositive patients into seronegative recipients.[14] One-, five- and ten-year mortality rates were significantly higher in those patients who received organs from seropositive donors. Donors who are seronegative for hepatitis B surface antigen but seropositive for the core antibody may be acceptable donors. When these hearts are used, recipients should receive prophylactic treatment with lamivudine and hepatitis B immune globulin to further reduce the risk of viral transmission. All patients should be offered hepatitis B vaccination while awaiting transplantation.[15] Patients infected with HIV or HTLV (Human T-lymphotropic Virus) are not acceptable donors.

To assess the heart's suitability for donation, one typically performs an electrocardiogram (ECG), echocardiogram, and, on occasion, coronary angiography. Cardiac enzymes may be minimally elevated in the setting of brain death because of the occurrence of myocardial contraction band necrosis. Markedly elevated levels of the MB fraction of creatine phosphokinase or troponin-I are more consistent with myocardial injury or infarction.

Echocardiography is particularly useful for evaluating cardiac structure and function. Left ventricular hypertrophy with a septal or posterior wall thickness greater than 13 mm is frequently a contraindication to donation because of the difficulty in preserving such a thickened myocardium. A significantly reduced ejection fraction or regional wall motion abnormalities suggestive of infarction will similarly exclude donation, as will severe regurgitant or stenotic valvular lesions.

Coronary angiography is recommended for male donors over 45 and females over 55 as well as younger patients with significant atherosclerotic risk factors. The use of computed tomography (CT) angiography in lieu of percutaneous angiography may be considered in those centers unable to provide coronary angiography. The presence of coronary disease can also be assessed by palpation of the coronary arteries at the time of harvesting. Inspection should include evaluation of significant valvular disease and the presence of congenital lesions or a large patent foramen ovale (PFO). Such PFOs are generally sutured closed at the time of transplantation to prevent paradoxical embolization. A summary of absolute and relative contraindications to donation can be found in **Table 18.1**.

TABLE 18.1 Absolute and Relative Contraindications to Donor Heart Selection

ABSOLUTE CONTRAINDICATIONS
Organ transport time > 4 h
Confirmed myocardial infarction with systolic dysfunction
LVEF < 30%
Severe valvular disease not amenable to repair
Active infection with transmissible pathogens including, but not limited to, HIV hepatitis B (HBSAg +) or C virus, or highly resistant bacteria
Bacterial endocarditis
A history of major extracranial or metastatic malignancy
Age > 65 years
Significant penetrating cardiac trauma
RELATIVE CONTRAINDICATIONS
Donor–recipient height mismatch > 6 inches
Age 50–65 years
Male donors > 45 years and female donors > 50 years with cardiovascular risk factors and an inability to perform coronary angiography

Previous high-risk behavior including intravenous drug use or risky sexual activity
Donor instability manifested by hypoxia, severe acidosis with pH < 7.2, hypotension requiring high-dose vasoconstrictors
Organ transport time 3–4 hours

LVEF, left ventricular ejection fraction.

PATIENT MANAGEMENT

The patient with a newly transplanted heart faces a number of physiologic challenges. Without having time to recover from cold ischemia and facing reperfusion injury, the denervated heart is expected to function fully and provide an adequate cardiac output as soon as possible after being weaned from cardiopulmonary bypass. The loss of sympathetic innervation makes the allograft dependent on circulating catecholamines in order to sustain cardiac output. Infusions of positive inotropic medicines, such as dobutamine or milrinone, are always given in sufficient quantity to assist the heart in providing an adequate cardiac output. This obligatorily requires continuous patient monitoring with arterial lines and a pulmonary artery catheter in an intensive care unit. Vasoconstrictors such as arginine vasopressin (AVP) and norepinephrine may be temporarily employed to counter the vasoplegia that often occurs after cardiopulmonary bypass in advanced heart failure patients. Because of their deleterious effects on the microcirculation, vasoconstrictors should be weaned and discontinued at the earliest possible time. Weaning of positive inotropic medicines generally begins 48 hours after transplantation after allowing the sinus node to recover from cold ischemia, and for the RV to accommodate itself to the increased afterload in those patients with preexisting pulmonary hypertension. Transfer out of the intensive care unit to a floor with continuous telemetry monitoring commonly occurs before weaning is completed.

Vasodilatory hypotension is commonly encountered postoperatively. The mechanism for this may be related to the pretransplant use of vasodilatory drugs, such as angiotensin converting enzyme inhibitors, and inodilators such as milrinone. Other suspected factors include a systemic inflammatory response to prolonged cardiopulmonary bypass and a reported depletion of AVP that occurs as consequence of long-standing advanced heart failure. Although vasoconstrictors such as norepinephrine have generally been used to treat vasodilatory hypotension, synthetic AVP may be more effective in this patient

population because it does not constrict pulmonary arteries or compromise renal function.

Renal dysfunction is a common posttransplant occurrence and contributes to both a prolonged hospital stay and increased risk of mortality. Postoperative renal failure is usually a consequence of ischemic injury that results from diminished renal perfusion during cardiopulmonary bypass, perioperative hypotension, and perhaps from embolization from an atherosclerotic aorta. Its presence not only contributes to the volume-overloaded state, but may also delay the initiation of immunosuppressive therapy, particularly the use of calcineurin inhibitors. Temporarily withholding the calcineurin inhibitor may allow time for renal function to improve.[16] When patients with reduced urine output are unable to match their obligatory inputs, such as blood products and intravenous medications, diuretics may be used. Frequently, oliguric renal failure will require mechanical renal replacement therapy. When clearance is not required, aquapheresis (Aquadex FlexFlow System, Sunshine Heart Inc., Eden Prairie, MN) may be employed. Slow, low efficiency dialysis or continuous veno-venous hemofiltration (CVVH) allows for removal of large volumes of fluid, provides clearance, and may facilitate renal recovery. Rarely, patients will develop fulminant renal failure postoperatively. These patients are typically patients with preexisting chronic kidney disease. Such patients may be managed with dialysis, but in consideration of poor long-term outcomes, renal transplantation is preferred.[17, 18]

Right heart failure is common in the posttransplant patient. Reasons for its occurrence include ischemia–reperfusion injury, preexisting pulmonary hypertension, and volume overload from infusion of intravenous fluids. Multiple blood product infusions, including packed red blood cells and fresh frozen plasma, may further volume load an already distended RV. In the face of this additional preload, ventricular function may deteriorate. A rising central venous pressure (CVP) in the setting of systemic hypotension will compromise myocardial perfusion and lead to ventricular ischemia with contractile dysfunction. Release of cytokines such as thromboxane from transfused platelets may further increase pulmonary arteriolar pressure and place additional afterload on a straining RV. Furthermore, transplantation of a smaller donor heart into a larger recipient predisposes to RV dysfunction more than to left ventricle (LV) dysfunction. RV failure should be suspected when CVP rises and cardiac output falls. Transthoracic echocardiography may not offer adequate RV visualization in postoperative patients because of an inability to obtain sufficient

echocardiographic windows or position the patient properly; thus, transesophageal echocardiography is preferred in endotracheally intubated patients.

Treatment is directed at improving the loading conditions for the RV while providing adequate inotropic support to maintain circulation. Aggressive diuresis to achieve a CVP of 12 to 15 mm Hg will lower RV preload and may help to reduce tricuspid regurgitation. When patients are diuretic resistant or in overt renal failure, or simply need large volumes of fluid removed quickly, aquapheresis or CVVH is indicated. Inhaled nitric oxide will reduce RV afterload by dilating pulmonary arteries. Nitric oxide also improves oxygenation and V/Q matching. When patients require positive inotropic support for a prolonged period of time, milrinone is preferred over dobutamine, because of its superior ability to dilate the pulmonary vasculature. Mechanical support, using a right ventricular assist device, may be necessary for some patients as a means of providing longer-term support. The ventricular assist device can be slowly weaned over a period of days or weeks as right heart function improves.

Bradyarrhythmias are frequently encountered, but their incidence has decreased with the use of bicaval anastamoses, which tend to spare the sinus node. Given that resting heart rate of a denervated heart is between 90 and 120 beats per minute (bpm), rates lower than this may be a result of sinus node dysfunction, ischemia, or preoperative use of amiodarone. Both isoproterenol and aminophylline were widely used in the past to elevate resting heart rate, but nowadays electronic pacing through temporary wires is preferred. Temporary pacing wires should remain in place long enough to ensure that sinus node function has adequately recovered. Temporary pacing can be considered for patients whose heart rates are below 90 bpm, especially if the patient has evidence of low cardiac output. Permanent pacemakers are reserved for patients with persistent sinus or atrioventricular nodal dysfunction.

Although infrequently encountered, tachyarrhythmias are usually a sign of an injured allograft. Atrial fibrillation is commonly seen in cardiac surgery, but less so following heart transplantation. This is believed to be a result of the left atrial anastamosis, which effectively isolates the pulmonary veins and prevents atrial fibrillation. When present, atrial arrhythmias are a sign of either ischemic injury or early rejection. Ventricular arrhythmias are also rare, but are generally not a sign of rejection but of myocardial ischemia or infarction. Congenital arrhythmias in the donor heart, such as Wolf Parkinson White syndrome, are occasionally seen and can be treated with catheter ablation.

ACUTE ALLOGRAFT DYSFUNCTION

Acute allograft dysfunction remains one of the most common causes of early posttransplant death. It occurs in up to 5% of transplants and has multiple etiologies. These include ischemia–reperfusion injury, poor preservation, and unrecognized or underappreciated predonation dysfunction. Both prolonged ischemia and the use of high-dose catecholamine infusions predispose to allograft dysfunction, perhaps by depleting myocardial energy stores. Hyperacute rejection, which occurs because of the presence of preformed antibodies to human leukocyte antigens, is now rarely seen because of the routine use of PRA screening. The struggling allograft can usually be adequately supported with infusions of epinephrine, dobutamine, or milrinone. More severe degrees of dysfunction require mechanical support with the use of intra-aortic balloon counterpulsation, or the placement of ventricular assist devices to rest the allograft and provide adequate organ perfusion. Patients who can be weaned successfully from the device have a survival rate similar to that of the general transplant population. Although urgent repeat transplantation is an option for these patients, the presence of multiorgan dysfunction often limits their candidacy. Causes of death in the posttransplant period are listed in **Table 18.2**.

TABLE 18.2 Causes of Death in the Posttransplant Period

Cardiac allograft vasculopathy	54 (1.7%)
Acute rejection	208 (6.5%)
Lymphoma	2 (0.1%)
Malignancy, other	2 (0.1%)
CMV	4 (0.1%)
Infection, non-CMV	414 (12.9%)
Primary graft failure	831 (26.0%)
Graft failure	445 (13.9%)
Technical	237 (7.4%)
Other	213 (6.7%)
Multiple organ failure	431 (13.5%)

Renal failure	18 (0.6%)
Pulmonary	134 (4.2%)
Cerebrovascular	205 (6.4%)

CMV, cytomegalovirus.
From Taylor DO, Edwards LB, Boucek MM, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-third official adult heart transplantation report—2006. *J Heart Lung Transplant*. 2006;25:869–879.

IMMUNOSUPPRESSION

Prior to the routine use of cyclosporine (CyA) in the early 1980s, heart transplantation survival was so poor that many physicians called for a moratorium on the procedure. Although advances in immunosuppression have improved outcomes dramatically, allograft rejection still accounts for 6.5% of early deaths following transplantation. Typical maintenance immunosuppression in the current era consists of a calcineurin inhibitor in combination with an antimetabolite and corticosteroids.

The use of induction immunosuppression, although once routine, has lately been called into question. It was thought that by passivating the immune system through the use of either monoclonal or polyclonal antibodies, induction therapy allowed time for the allograft to recover function without facing the threat of rejection. This period of induction also allowed for postoperative recovery of renal function prior to the initiation of a calcineurin inhibitor with its attendant risk of nephrotoxicity. In retrospect, this approach was limited by the fact that induction therapy induced T-cell anergy, but not clonal depletion. In effect, moderate-to-severe rejection was not prevented, but only delayed by 6 to 12 months. Nonetheless, upward of half of all transplant centers continue to use induction immunosuppression, although use of OKT3 and polyclonal antibodies, such as thymoglobulin, has declined, whereas use of selective interleukin-2 (IL-2) receptor antibodies has increased. The IL-2 receptor blocker basiliximab has been shown to reduce both the severity and the frequency of cardiac rejection as well as increase the time to a first rejection episode. Its use is not associated with the cytokine release syndrome or the significant side effects associated with OKT3.[19]

Cell cycle antagonists, either aziothioprine or mycophenelate mofetil (MMF), are started intraoperatively or on postoperative day one. Both drugs work by inhibiting the de novo pathway of purine synthesis, a step crucial to cellular proliferation. Because leukocytes and lymphocytes lack the salvage pathway,

these drugs particularly inhibit their proliferation. Azathioprine produces a greater degree of bone marrow suppression than does MMF. It is given as a single dose of 1.5 to 5 mg/kg adjusted for white blood cell and liver function. Azathioprine is metabolized by thiopurine methyltransferase (TPMT) in vivo. Small proportions of patients have very low levels of TPMT (roughly 0.3% of the general population) and are at greater risk of experiencing myelosuppresion.

Following the results of a large multicenter randomized clinical trial showing its benefits over azathioprine, MMF has become the preferred antiproliferative agent at most transplant centers.[20] Patients receiving MMF experienced fewer episodes of hemodynamically significant rejection and enjoyed a higher survival rate at the first year of follow-up, as well as a trend toward a lesser incidence of severe rejection. Opportunistic infections were seen more commonly in patients receiving MMF, but most of these resulted from either HSV or herpes zoster and were not life threatening. MMF is given as a fixed dose of 1500 mg twice daily for patients with preserved renal function. Lower doses of 500 to 1000 mg bid are used for patients with estimated creatinine clearance of less than 50 mL/kg/min. The dose of MMF may need to be reduced in the setting of gastrointestinal upset or leucopenia. Blood levels of mycophenolate and its metabolite can be measured, but are not available at all centers.

Inhibition of the calcineurin pathway is the cornerstone of solid organ transplantation. The introduction of the first calcineurin inhibitor, CyA, in 1983 revolutionized solid organ transplantation, essentially doubling the 1 and 5-year survival rates. They work by inhibiting calcineurin, a calcium calmodulin–dependent phosphatase that activates transcription factors responsible for transcription of IL-2. Calcineurin inhibition prevents both IL-2 transcription and T-lymphocyte activation.

CyA is a cyclic decapeptide that is derived from the fungus *Trichoderma polysporin*. Its major immunosuppressive effect is to inhibit the production of IL-2 and other cytokines by activated lymphocytes. CyA binds to cyclophilin in the cytoplasm of T-lymphocytes, and this complex then binds to and inhibits calcineurin, ultimately preventing transcription of IL-2. CyA affects T-helper and cytotoxic T-cells but has little or no effect on suppressor T-cells. The drug is metabolized by cytochrome P450 3A4, located in the liver and along the gastrointestinal tract. Approximately 5% to 10% of the parent compound is excreted unchanged in the urine. CyA has a half-life of 19 hours. Different formulations of CyA are supplied for both intravenous and oral administration. When given intravenously, CyA is mixed in a 1:1 concentration in either normal

saline or 5% dextrose and infused continuously. CyA (Sandimmune, Novartis, East Hanover, NJ) for oral use is provided in liquid (100 mg/mL) and capsule form and is administered 2 or 3 times daily. Neoral (Novartis, East Hanover, NJ) is a microemulsion formulation of CyA that has improved absorption and bioavailability and is given in two daily doses. CyA can be given as a continuous infusion immediately after transplant or delayed for 24 to 48 hours until it can be given enterally. A typical continuous infusion begins at 0.5 to 1.0 mg/h and is adjusted accordingly. When converting to oral CyA, approximately 3 times the total daily intravenous dose is given. In the early posttransplant period, CyA is administered to achieve a trough whole blood level of 300 to 350 ng/mL. Target levels decrease with time as rejection risk begins to wane. Typical target levels are 250 to 350 in the first 6 months, 150 to 250 in months 6 to 12, and 100 to 150 long-term. Side effects include nephrotoxicity, hypertension, hypertrichosis, gingival hyperplasia, tremor, and seizures. Serum levels of CyA are affected by many medications. Those that elevate levels are drugs that inhibit its metabolism through the cytochrome P450 system, such as erythromycin, fluconazole, and amiodarone and the antihypertensive diltiazem.

Tacrolimus (Prograf, also known as FK-506) is a macrolide antibiotic derived from the bacteria Streptomyces tsukubaensis. It has now become the preferred drug at many transplant centers. The major advantage of tacrolimus over CyA is the lesser degree of hypertension and hyperlipidemia. Some prescribers prefer its use in women for cosmetic reasons, because it produces less hirsutism and gingival hyperplasia than CyA. After binding with FKBP-12 (also referred to as the FK506 binding protein), tacrolimus inhibits calcineurin. Although its mechanism of activation is similar to that of CyA, it is much more potent but appears to produce less nephrotoxicity. Other side effects include seizures, insomnia, tremor, and hypertension. Tacrolimus is also associated with an increased risk of hyperglycemia, although whether the long-term incidence of diabetes is increased remains controversial. Tacrolimus can be administered either orally or intravenously. When given intravenously, an initial dose of 0.01 to 0.05 mg/kg/d is infused continuously and adjusted to achieve a level of around 12 to 15 ng/mL. When given enterally, a 1 mg dose test of tacrolimus is given to all patients because clearance of the drug may vary significantly between patients. Typical trough target levels are 10 to 15 ng/mL in the first 2 months, 8 to 12 ng/mL for the next 3 to 6 months, and 5 to 10 ng/mL thereafter.

Rapamycin (Rapamune) and everolimus (Zortress, Certican) are reserved for patients with transplant vasculopathy. When initiating these proliferation signal

inhibitors, one should discontinue antiproliferative drugs such as MMF or azathioprine. Doses of tacrolimus should be reduced to achieve trough levels of approximately 4 to 6 ng/mL. An initial rapamycin dose of 6 mg is given 6 hours after tacrolimus and is followed by a daily dose of 2 mg. This daily dose should be adjusted to achieve rapamycin levels of approximately 10 ng/mL in the first year of transplant and between 5 and 10 ng/mL thereafter.

Corticosteroids are the third class of medications used for maintenance immunosuppression. Intravenous methylprednisolone is given preoperatively and switched to prednisone once the patient can tolerate oral agents. Prednisone dosing is tapered down during the first several months of transplant. Corticosteroids have numerous troublesome side effects: they worsen glycemic control, increase serum lipids, and stimulate appetite, leading to obesity. They have profound effects on bone absorption, producing osteoporosis and a susceptibility to fracture. Avascular necrosis of the hips and shoulders from steroid use necessitates joint replacement surgery in some patients. Other debilitating side effects include cataract formation, colonic perforation, and, especially with higher doses, mood disorders such as psychosis. Motivated to limit these toxicities, many centers attempt to wean patients entirely off corticosteroids after 6 to 12 months.[21] The optimal timing of complete steroid withdrawal has yet to be determined, and the majority of patients remain on steroids indefinitely.

REJECTION SURVEILLANCE

Endomyocardial biopsy remains the gold standard for the diagnosis rejection. Biopsies are taken from the RV via the transvenous approach **(Figure 18.2)**. At the time of each biopsy, four to five samples are taken and graded using the 2004 revised ISHLT system. Both the revised and standard system, published in 1990, are summarized in **Table 18.3**. Biopsies are performed at a frequency that matches the time-dependent risk of rejection. A typical schedule would require biopsies on a weekly basis for the first month, then on a biweekly basis for the second and third months, and on a monthly basis for the fourth through sixth months, with the frequency diminishing thereafter. Routine performance of endomyocardial biopsy after the fifth transplant year is no longer required. Biopsies should be performed anytime rejection is suspected.

TABLE 18.3 **Standardized ISHLT Cardiac Biopsy Grading Scales**

(2005 Revised Version in Comparison with 1990 Version)			
1990 SCALE		**2005 SCALE**	
Grade	***Description***	***Grade***	***Description***
0	No rejection	0	No rejection
1A	Focal perivascular or interstitial infiltrate without necrosis	1R	Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage
1B	Diffuse but sparse infiltrate without necrosis	2R	Two or more foci of infiltrate with associated myocyte damage
2	One focus only with aggressive infiltration and/or focal myocyte damage	3R	Diffuse infiltrate with multifocal myocyte damage, edema, hemorrhage, vasculitis
3A	Multifocal aggressive infiltrates and/or myocyte damage		
3B	Diffuse inflammatory process with necrosis		
4	Diffuse aggressive polymorphous infiltrate, with or without edema, hemorrhage or vasculitis; with necrosis		

ISHLT, The International Society for Heart and Lung Transplantation.

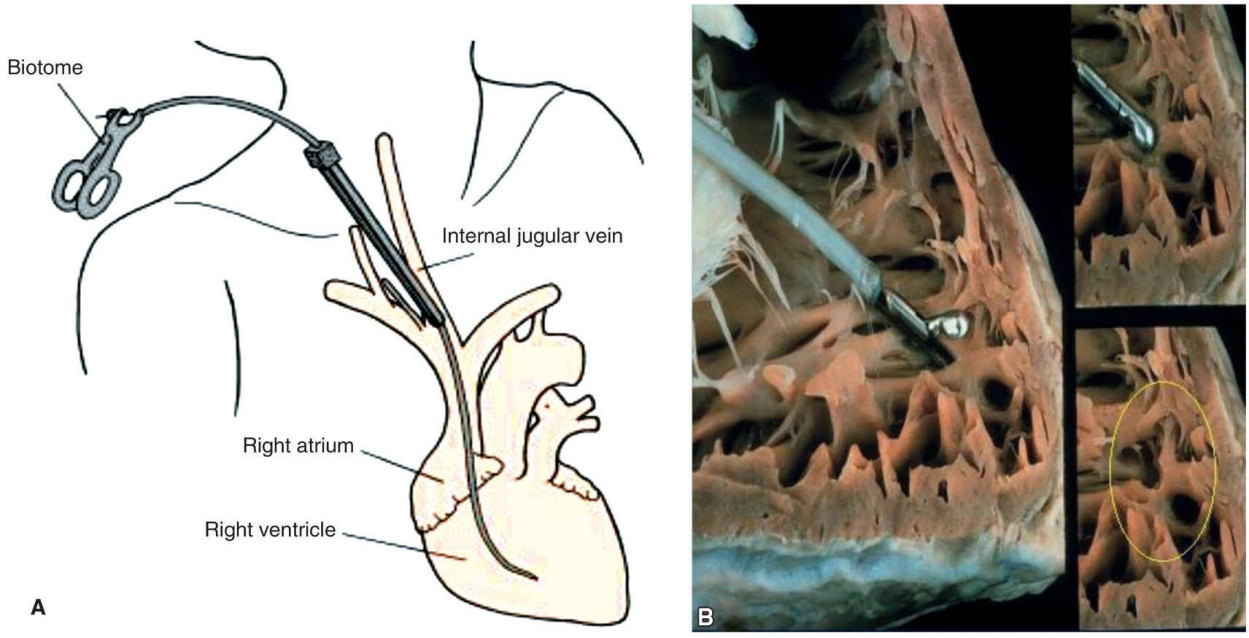


FIGURE 18.2 Endomyocardial biopsy is performed under fluoroscopic guidance. A bioptome is advanced through the jugular vein and directed across the tricuspid valve into the right ventricle and positioned against the interventricular septum (A). After the bioptome is closed and withdrawn, a small defect remains within the myocardium (B). During a typical biopsy session, four to six pieces of myocardium will be sampled and sent to pathology for review.

Symptoms of rejection are often absent, but can be insidious when present. They may include malaise or generalized fatigue, symptoms of heart failure (shortness of breath, peripheral edema), and palpitations. Arrhythmias, such as atrial fibrillation, may be present. Biopsy should be promptly arranged for in any

patient in whom rejection is suspected. Assessment of ventricular dysfunction should be performed using either echocardiography or magnetic resonance imaging. Depending on the degree of suspicion for rejection, empiric therapy may need to be given while awaiting endomyocardial biopsy results. A typical biopsy schedule is shown in **Table 18.4**.

TABLE 18.4 Typical Endomyocardial Biopsy Schedule for Rejection Surveillance

TIME POSTTRANSPLANT	FREQUENCY
1 month	Weekly
2 months	Biweekly
3–6 months	Monthly
7–12 months	Every 2 months
12–18 months	Every 3 months
>18 months	Every 6–12 months

Recent work suggests that detection of cellular rejection may be possible using less invasive methods. The Cargo Study evaluated the gene expression profile of peripheral blood mononuclear cells obtained from patients a minimum of one year after transplantation. Using this profile, a scoring system was created that could exclude the presence of ≥ ISHLT 2R (previously 3A) rejection with a negative predictive value of 99.6%. The system is currently approved for clinical use, and studies are ongoing to predict whether the test is useful in patients during the first year posttransplant.[22]

TREATMENT OF CELLULAR REJECTION

Strategies for the treatment of rejection differ significantly from center to center. Factors influencing one's decision to treat include grade of rejection, impact on cardiac function (as determined by echocardiogram and/or right heart catheterization), and time from transplantation. At our center, patients are treated as follows: Grade 0 and Grade 1R (previous grades 1A, 1B, and 2) biopsies do not require treatment in the absence of symptoms or abnormal hemodynamics. Care is taken to ensure that doses and levels of immunosuppressive medications are at their therapeutic targets. Patients with symptomatic rejection are treated with corticosteroids. Grade 2R (previous grade 3A) rejection may be treated with a short pulse of oral steroids, for example, prednisone 50 mg bid, if occurring more than 3 months posttransplant. Patients with grade 2R rejection that are

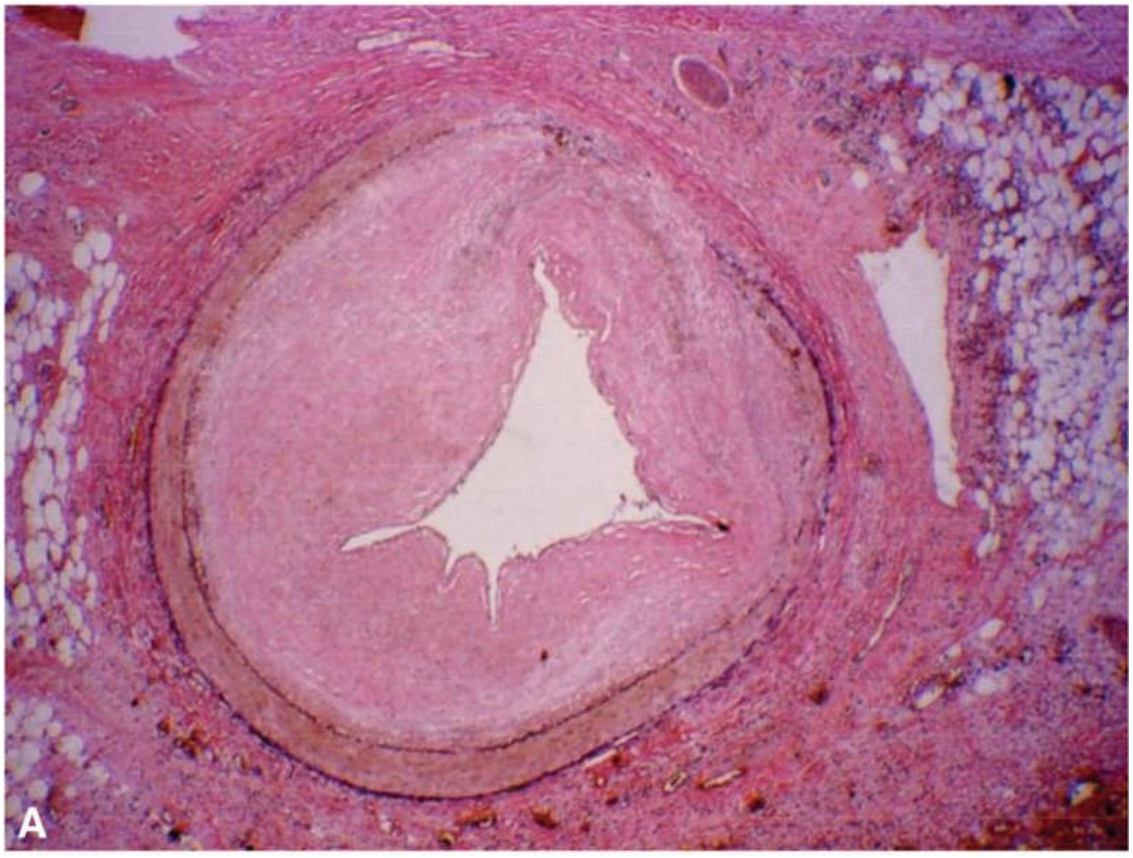
symptomatic or have hemodynamic consequences of rejection, as well as those patients less than 3 months posttransplant, are treated with intravenous methylprednisolone (1000 mg/d for 3 days) followed by a prednisone taper. Repeat biopsy is typically performed in 2 weeks. Hemodynamically severe rejection occurs in fewer than 5% of patients, but requires inpatient admission and treatment with cytolytic therapy consisting of thymoglobulin. Inpatient admission and hemodynamic monitoring are essential because patients are at risk of rapidly progressing cardiac failure and circulatory collapse.

HUMORAL REJECTION

Humoral rejection is a B-cell mediated process in which alloantibodies attach to major histocompatibility complex class I or II antigens usually in a perivascular pattern. It can present in a variety of ways, from an insidious process to fulminant hyperacute rejection. Its diagnosis is confirmed with either immunofluorescence or immunoperoxidase staining for the complement degradation products C4D or C3D. When the latter is used, a positive stain must be present in the setting of symptoms or other signs of rejection such as abnormal hemodynamics or left ventricular dysfunction to complete the diagnosis. Risk factors for its development include having an elevated pretransplant PRA, the development of specific antidonor antibodies, or the preoperative use of a left ventricular assist device. Treatment of humoral rejection is targeted at three distinct processes: clearance or neutralization of circulating antibodies, eradication of plasma cells, and prevention of sensitized B-cells transforming into plasma cells. Plasmapheresis with plasma exchange can quickly remove circulating alloantibodies and allow graft function to recover.[23] Up to 40% of circulating immunoglobulin G may not be cleared by plasmapheresis, but may be neutralized by administering IVIG. We typically prefer a sucrose-free preparation in order to avoid nephrotoxicity. Intravenous cyclophosphamide (0.5 to 1.0 g/m^2) may be given following plasmapheresis to eliminate alloantibody-producing plasma cells. More recently, the anti-CD20 monoclonal antibody rituximab (Genentech, San Francisco, CA), a chimeric humanized antibody directed against the pan–B-cell surface molecule CD20, has been used as the third component of therapy. It targets sensitized B-cells and interferes with their ability to transform into antibody-producing plasma cells. Ultimately, rituximab may provide long-term benefit by eliminating “memory” B cells and preventing the adverse late sequelae of humoral rejection.

CARDIAC ALLOGRAFT VASCULOPATHY

Cardiac allograft vasculopathy (CAV) is a diffuse arteriosclerosis that remains one of the most common long-term complications of cardiac transplantation. CAV resembles the arteriopathy of restenosis following balloon angioplasty **(Figure 18.3)**. Both processes represent an abnormal response to vessel injury. In the case of CAV, both immunologic and nonimmunologic arterial injury contributes to its development. The arteriopathy comprises both intimal proliferation and negative remodeling of the external elastic lamina. Because it produces concentric rather than eccentric luminal stenoses, the presence of CAV is often underestimated, but its prevalence may be as high as 55% by the third posttransplant year.[24] The presence of CAV limits the long-term success of cardiac transplantation. In a multicenter study of 2609 heart transplantation recipients, 42% had angiographic evidence of graft vasculopathy by 5 years following transplantation.[25] Up to 7% of transplant recipients will die or require repeat transplantation because of CAV.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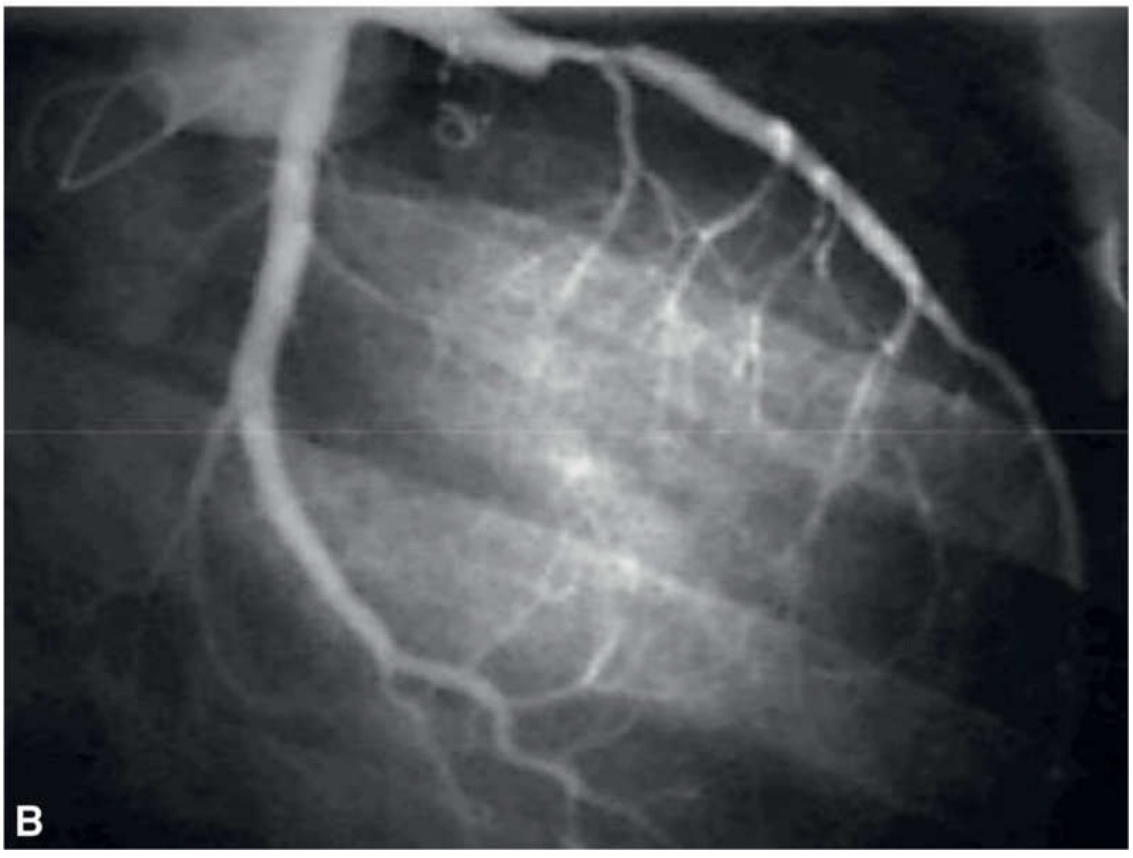
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FIGURE 18.3 Cardiac allograft vasculopathy (CAV) is a proliferative disorder that typically arises in the branches and distal vessels in response to both immunologic and nonimmunologic forms of injury. A cross section of an artery affected by CAV shows near obliteration of the lumen (A). Coronary angiography remains the most common modality to diagnose CAV. Typical pruning of the branch and distal vessels (B).

The development of CAV is an insidious process. Because the transplanted heart is denervated, patients will rarely, if ever, present with angina. Instead, they may experience atypical exertional symptoms, such as malaise or generalized discomfort, or, when allograft dysfunction is pronounced, symptoms of heart failure. Frequently, CAV remains asymptomatic, and therefore yearly screening is encouraged. Coronary angiography is the accepted method of assessing CAV. For those patients whose baseline angiogram is free of disease, angiography can be performed on an alternate year basis. In the intervening years, noninvasive imaging with either positron emission tomography or dobutamine echocardiography is acceptable. For those patients in whom CAV is detected, yearly angiography should be performed to track its progression. More recently, CT angiography has been employed for routine detection of CAV, avoiding the need for invasive angiography.[26]

Effective prevention of CAV includes the use of aspirin and HMG-CoA reductase inhibitors (statins). Pravachol is preferred because it is not metabolized by CYP 3A4, but other statins are equally effective in preventing CAV. Unfortunately, treatment options remain limited. Target of rapamycin inhibitors, such as sirolimus and evorolimus, have been shown to slow, and in some cases prevent, the progression of vasculopathy.[27] Revascularization with either coronary stenting or bypass surgery is frequently not an option because secondary and tertiary branches of the coronary arteries are often involved, reducing “downstream” blood flow. Intracoronary stenting may be an option for treating focal symptomatic lesions. Rates of restenosis are higher for CAV than for typical atherosclerotic lesions. The use of drug-eluting stents produces lower restenosis rates as compared to bare metal stents, but both have rates that are higher than those seen in nontransplant patients. For severe disease, retransplantation remains the only definitive treatment option.

ANTIMICROBIAL PROPHYLAXIS AND TREATMENT

Transplanted patients are at risk for infection from both common and opportunistic pathogens. Typical signs of infection may be less prominent in the setting of immune suppression, and fever may be suppressed by the use of

corticosteroids. The prevalence of infection in the early transplant period is 47% for bacterial infections, followed by viral (42%), fungal (8%), and protozoal (4%) infections.[28]

The risk of bacterial infection is particularly high during the immediate postoperative period and slowly abates over a 6-month period. Antibiotic prophylaxis to prevent surgical wound infection using an agent against gram-positive cocci (ie, cefazolin or vancomycin) is routinely used in all patients. Contact isolation with the use of gowns and gloves is recommended to prevent nosocomial infection. Respiratory isolation is not required for patients, but hand washing before and after patient contact is encouraged, as is the early removal of support lines and tubes. Visitors are certainly allowed, but they should also perform hand washing. Patients should not be exposed to fresh cut flowers and should handle fruit and vegetables only after they have been thoroughly cleaned or peeled. The use of a surgical mask may help prevent airborne transmission when venturing out of the hospital room.

The risk of fungal infection is greatest during the period of maximal immune suppression and tails off by the sixth postoperative month. The most commonly encountered infection is candidiasis, particularly oral thrush. It is easily prevented with nystatin swish and swallow or mycelex troches. Deep tissue infections require more aggressive treatment with systemic antimicrobial drugs such as fluconazole. Pneumocystis carinii is an opportunistic fungal pathogen that classically presents as an interstitial pneumonia producing cough and hypoxemia, particularly with exertion. Prophylaxis with trimethaprim/sulfamethoxazole is given throughout the first year to prevent fulminant infection. Dapsone or atovaqoune can be used as a substitute in the sulfa allergic patient. Other fungal pathogens like aspergillus or cryptococcus can produce life-threatening infections. Therapy for these more severe infections requires aggressive care with intravenous azole therapy or amphotericin.

The risk of protozoal infection peaks at month 3 and dissipates over the first year. All transplant donors and recipients should be tested for exposure to toxoplasmosis gondii. Seronegative recipients from a positive donor should receive pyrimethamine prophylaxis or high-dose trimethoprim/sulfamethoxazole for 6 weeks. Folinic acid is given concomitantly to prevent pyrimethamine hepatotoxicity. As more patients from endemic areas receive transplants, it is incumbent on the transplant team to consider reactivation of a broad spectrum of pathogens. These include strongyloides hyperinfection in those patients who lived for a time in Puerto Rico or the Dominican Republic. Reactivation of

Trypanosoma cruzi may be encountered in patients from South or Central America where Chagas cardiomyopathy is the leading cause of heart failure. Screening for both these pathogens should take place before listing for transplant.

Risk of viral infection, particularly from HSV, CMV, and varicella zoster virus, increases over the first 6 weeks after transplant, but falls by the sixth month coincident with the reduced dose of immunosuppressive therapy. Chronic infection may persist, particularly from viruses such as CMV, HBV, and EBV, and the latter may contribute to the risk of malignancy, particularly posttransplant lymphoproliferative disorder.[4]

Infection with CMV is of particular concern because it can occur from either latent viral reactivation or direct donor transmission. Seronegative patients who receive a heart from a seropositive donor have a 50% risk of developing infection. Symptoms of CMV can vary considerably, including flulike symptoms or a gastrointestinal syndrome with profuse watery diarrhea and elevation of liver transaminases. Leucopenia may be present as a consequence of bone marrow suppression. Other manifestations of CMV include pneumonitis, pancreatitis, retinitis, and encephalitis. Polymerase chain reaction is the most sensitive diagnostic test for the detection of viremeia, but the diagnosis can also be made from identification of virus from tissue biopsy (usually stomach or colon) or from the serum buffy coat.

ADJUVANT THERAPY FOR THE TRANSPLANT PATIENT

Routine treatment of the posttransplant patient with HMG-CoA reductase inhibitors (statins) decreases the incidence of CAV and increases long-term survival. In a landmark 1995 trial, cardiac transplant patients randomized to pravastatin had less rejection and CAV, and improved survival compared to controls.[29] These results were recently reconfirmed in a “real world” analysis of over 1000 transplant patients.[30] It is unclear whether the results are secondary to the anti-inflammatory effects of statins or to their lipid-lowering properties. Aspirin is routinely given to all heart transplant patients. Although data supporting antiplatelet therapy are not as robust as those for the statins, transplant patients are thought to be more likely to have activated platelets. Aspirin prophylaxis may consequently decrease the risk of myocardial infarction.[31, 32]

Concomitant use of corticosteroids and calcineurin inhibitors places the

transplant patient at increased risk for developing osteoporosis. To lower this risk, patients receiving chronic corticosteroid therapy should take a calcium and vitamin D supplement. Patients with dexa scan evidence of either osteopenia or osteoporosis, and any patient considered at increased risk for fracture, are encouraged to take one of the bisphosphanates, such as alendronate or risedronate. Calcitonin may be considered an alternative to the bisphosphonates.[33]

HOSPITAL DISCHARGE

Discharge planning should begin shortly after the patient leaves the intensive care unit. Physical therapy should be initiated as soon as the patient is medically clear to participate. Nutritionists should be consulted to provide education to patients about heart-healthy diets as well as drug–food interactions. Medical regimens are reviewed with the patient and family members. Before being cleared for discharge, patients must be hemodynamically stable without any need for vasoactive medicines, must have an endomyocardial biopsy free of rejection, and must have a therapeutic tacrolimus or CyA drug level. It is our general practice to ensure that patients can successfully recite the names of their immunosuppressive drugs before allowing home discharge. Follow-up appointments in the transplant clinic are generally performed within 1 week of discharge. Patients are instructed to stay near the transplant center for several months should the need for urgent hospitalization arise.

The goal of cardiac transplantation is to both extend life and restore productivity. Unfortunately, less than 30% of transplant recipients return to full-time employment. Although this is partially attributable to the advancing age of the transplant population, other obstacles exist. Patients may be severely deconditioned from their previous heart failure condition, and may require intensive physical therapy to regain full function. Chronic corticosteroid therapy, which produces proximal muscle weakness and central obesity, may contribute to this deconditioning. It is possible that a strategy that employs earlier implantation of bridging left ventricular assist devices will allow sufficient reconditioning prior to transplant to allow for quicker postoperative recovery. The denervated heart also limits full cardiovascular performance, because it produces a slightly diminished maximal cardiac output. This is particularly evident in size-mismatched recipients. Despite these limitations, the majority of heart transplant recipients enjoy a physically active lifestyle and an improvement in quality of life, especially when compared to their pretransplant state.

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Patient and Family Information for: Selection and Care of the Heart Transplant Patient

Patients with advanced heart failure (also referred to as Stage D or end-stage heart failure) experience symptoms of fatigue and shortness of breath in spite of optimal medical therapy. Once heart failure has progressed to this point, few treatment options remain. Heart transplantation has been performed since the 1960s. Over the years, refinements in both surgical technique and medical management have significantly improved patient survival and quality of life. In the early days of transplantation, most patients lived only a few months, whereas now heart transplant patients can expect to live many years with a good quality of life. About 90% of heart transplant recipients survive the first year. More than half of all recipients live for more than 10 years, and some live for more than 20 years with the same transplanted heart. The major downside to heart transplantation is that there simply are not enough donor hearts to go around. Currently in the United States, there are close to 200,000 patients living with advanced heart failure, but only 2000 heart transplants will be performed annually. This means that there is a constant need to increase awareness of organ donation to increase the pool of available organs.

Patients who are referred to an advanced heart failure program for consideration of heart transplantation must first undergo a standard evaluation. This evaluation is designed to answer two questions: first, is the patient sick enough to require transplant, and, second, are there any reasons why this patient should not receive a heart transplant. The typical evaluation includes consultations with a cardiologist, surgeon, and transplant coordinator. Additional visits with social work and psychiatry are necessary to screen for potential psychological, financial, or social barriers to living with a transplant. Typical

tests include a CT scan, ultrasound, and age-appropriate cancer screening. One invasive test, a right heart catheterization, will measure the pressures inside the heart and lungs to ensure that it is safe to perform the operation.

The decision to place a patient on the heart transplant waiting list is made by a committee of transplant professionals, the same individuals who met the patient during the evaluation process. Waiting times vary from state to state and are determined by a patient's body size, blood type, and heart failure severity. Those patients who require admission to an intensive care unit or who have a failing ventricular assist device are moved to the top of the list because they face the highest risk of dying in the near future.

The transplant operation takes about 6 to 8 hours to perform. Most patients will remain in the intensive care unit for at least 4 or 5 days and in the hospital for about 10 to 14 days. During this time, the transplanted heart will be supported by a number of intravenous medications and occasionally a temporary pacemaker to ensure that it beats fast enough. This is also the time when patients start to receive medications that suppress the immune system and prevent the heart from being rejected by the body. Even though it sounds severe, heart transplant rejection is rarely severe and can almost always be treated simply by increasing the dose of immune suppressive medications.

Before leaving the hospital, all patients must have a heart biopsy to check for rejection. This procedure takes less than half an hour to perform. A physician will place a tube in the jugular vein and pass a bioptome (a small scissor-like instrument) through it to sample a few pieces of heart tissue. These samples will be looked at by a pathologist to make sure there is no sign of rejection. This procedure is repeated throughout the first year at regular intervals to make sure the heart is not being rejected and to safely allow reductions in immune suppressive medications.

Most patients feel very well living with a transplant. Although some have run marathons and climbed mountains, most heart transplant recipients simply live life without experiencing fatigue and shortness of breath as they did when they had heart failure. To make sure that the transplanted heart continues to function well, patients will have to return for check-ups several times each year. Everyone will have an echocardiogram performed annually to make sure that the heart is still beating well. Patients will also have an annual angiogram to make sure that the transplanted arteries remain free of blockages that could weaken the heart over time. All patients who take immune suppressive medications are more vulnerable to infections. In addition to taking antibiotics to prevent infection,

transplant recipients should use common sense and avoid close contact with family or friends who are sick.

There are a number of long-term complications that can limit the success of heart transplantation. Some of the immune suppressive medicines can weaken the kidneys. About 5% of heart transplant recipients will have advanced kidney disease requiring dialysis or a kidney transplant. Although the immune suppressive drugs do not cause cancer, they do place transplant patients at higher risk for developing cancers. These include a rare form of lymphoma, which affects the immune system. Skin cancer is the most common form of cancer and should be prevented by wearing a hat, long-sleeved shirts, and sunscreen when outdoors.

19

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Eyal Herzog

Medications Used in the Management of Heart Failure

The past 30 years have provided remarkable advances in the pharmacotherapeutic management of patients with acute and chronic heart failure (HF). Major improvements in both survival and symptom management now provide practitioners with the ability to provide therapy that is well tolerated, decreases recurrent hospitalizations, and improves quality of life. As the incidence of HF continues to increase with the advancing age of the population, and there is improved post-infarction survival, maximizing the use of currently available agents, development of new class of drugs, and the continued development of implantable devices for treatment of mechanical and electrical complications of HF should further our ability to improve patient care.

In this chapter, we explore the various agents currently available for the management of HF.

INOTROPES

Intravenous inotropes dobutamine and milrinone are useful in patients with severe systolic dysfunction with relative hypotension and evidence of inadequate end-organ perfusion, who are not responsive to, or are intolerant of, vasodilators

and diuretics. Inotropic agents relieve acute HF symptoms and may preserve end-organ function, but have not been demonstrated to improve survival. On the contrary, several studies have demonstrated increased adverse outcomes, including increased mortality with chronic intravenous inotropic therapy.

DOBUTAMINE

Dobutamine, a synthetic catecholamine, is primarily a β adrenergic stimulant with minimal α_1 cardiac sympathetic activity. Its β_1 sympathetic activity accounts for its inotropic activity through β-receptor–mediated activation of intracellular cyclic-adenosine monophosphate (c-AMP). The resulting sarcoplasmic reticulum calcium release mediates myocardial contractility. Similar β_1 activity at the sinoatrial (SA) node accounts for its modest chronotropic activity. Patients taking β-blockers on admission may have an attenuated initial response to dobutamine, until the β-blocker has been metabolized or renally eliminated.[1] However, cardiac output response to increasing doses of dobutamine has been observed in patients on chronic carvedilol.[2] The dose-dependent β_2 effect produces mild peripheral arteriolar dilation. As with most intravenous sympathetic stimulants, dobutamine has a rapid onset of action (1 to 2 minutes) and has a peak effect within 10 minutes. The drug is rapidly methylated providing for a short duration of action ($t_{1/2}$—2 minutes), ideal for a drug requiring titration based on hemodynamic effects.

The hemodynamic effects of dobutamine in patients with HF include increased cardiac output, arteriolar dilation, reduction of pulmonary artery occlusion pressure (PAOP or wedge pressure), and small but variable change in blood pressure (**Table 19.1**). In responsive patients, the hemodynamic benefits of the drug increase end-organ perfusion, manifest by improving renal function and urine output, decreased pulmonary vascular congestion, and improved skin perfusion and mentation.

TABLE 19.1 Hemodynamic Effects of Intravenous Agents Used in the Treatment of Acute Decompensated Heart Failure

DRUG	DOSE	HR	MAP	PAOP	CO	SVR
Dobutamine	2.5–15 μg/kg/min	0/+	0	−	+	−
Milrinone	0.375–0.75 μg/kg/min	0/+	0/−	−	+	−

Dopamine	0.5–3 μg/kg/min	0	0	0	0/+	−
Dopamine	3–10 μg/kg/min	+	+	0	+	0
Dopamine	>10 μg/kg/min	+	+	+	+	+
Nesiritide	Bolus: 2 μg/kg Infusion: 0.01 μg/kg/min	0	0/−	−	+	−
Nitroglycerin	5–200 μg/min	0/+	0/−	−	0/+	0/−
Nitroprusside	0.25–3.0 μg/kg/min	0/+	0/−	−	+	−

CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAOP, pulmonary artery occlusive pressure; SVR, systemic vascular resistance.
Adapted from DiPiro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. New York, NY: McGraw Hill; 1999.

The adverse effects that should be monitored in patients with HF include dose-related tachycardia – most concerning in ischemic cardiomyopathy – as well as atrial arrhythmias (like atrial fibrillation) and ventricular arrhythmias (like ventricular tachycardia).

Dobutamine dosing begins at 2.5 to 5 μg/kg/min and is progressively increased on the basis of clinical and hemodynamic response. Because it is not a vasoconstrictor (pressor), dobutamine does not need to be administered through a central line. Dosing may be increased to 15 μg/kg/min, although maximum hemodynamic benefit may be achieved at lower doses, and ventricular ectopy risk increases as the dose is increased. Once hemodynamic stability has been accomplished, dobutamine infusions should be gradually tapered off. Although intermittent ambulatory dobutamine infusions have been used for quality-of-life enhancement in patients who are not candidates for transplantation or pump implantation, or as a pharmacologic bridge to cardiac transplantation, the practice has generally been replaced by implantation of ventricular assist devices.[3] In addition, randomized trials have demonstrated increased mortality with the use of ambulatory dobutamine infusions.[4]

MILRINONE

Milrinone is a selective inhibitor of phosphodiesterase III, an enzyme responsible for the intracellular breakdown of c-AMP. c-AMP accumulation increases intracellular calcium and thereby facilitates myocardial contractility. Although milrinone’s hemodynamic effects are similar to those of dobutamine,

milrinone produces more arterial and venous dilation, earning it the label "inodilator" (**Table 19.1**). Theoretical advantages of milrinone as compared to dobutamine include greater afterload reduction, augmenting the cardiac output produced by its inotropic effect, and its post-receptor mechanism of action, a potential benefit in patients receiving β-blockers for chronic HF. Hemodynamic improvement is usually observed within 15 minutes of initiation of therapy. The drug is renally eliminated with an elimination half-life of approximately 3 hours in patients with HF, and the maintenance infusion should be adjusted on the basis of creatinine clearance.

Although the package insert recommends a 50 μg/kg loading dose, many practitioners refrain from administering the loading dose to reduce the risk of hypotension. Typical maintenance doses of milrinone range from 0.375 to 0.75 μg/kg/min (**Table 19.2**). At maintenance doses above 0.5 μg/kg/min, once hemodynamic and clinical stability has been achieved, the infusion should be gradually tapered off. However, because the drug has a longer elimination half-life than does dobutamine, lower milrinone maintenance doses may be reduced more rapidly than dobutamine doses, provided hemodynamic stability has been achieved. In addition to hypotension, the most common side effects are tachyarrhythmias. Milrinone may produce less tachycardia than does dobutamine, but it also has the potential to produce both atrial and ventricular arrhythmias.

TABLE 19.2 Renal Dosing of Milrinone

CREATININE CLEARANCE (mL/min/1.73 m^2)	MILRINONE INFUSION RATE (μg/kg/min)
5	0.20
10	0.23
20	0.28
30	0.33
40	0.38
50	0.43

Despite the potential adverse long-term impact on morbidity and mortality related to intravenous inotropic therapy, patients with acute decompensated HF

benefit from the short-term hemodynamic improvement associated with the administration of these agents, pending the resolution of the underlying events that precipitated their hemodynamic deterioration.

DOPAMINE

Dopamine possesses dose-dependent hemodynamic effects, stimulating D_1 dopamine receptors, α_1-, β_1-, and β_2-receptors. Other than the diuretic effect of low-dose (renal dose) dopamine to enhance volume loss in patients with diuretic-resistant HF, dopamine use is typically reserved for use in patients with marked hypotension including those with cardiogenic shock. Inotropic doses in the 2 to 5 μg/kg/min range promote increase in cardiac output; however, intermediate- and high-dose dopamine increase systemic vascular resistance, increasing afterload and PAOP, and impeding cardiac output (**Table 19.1**). In the setting of cardiogenic shock, dopamine may be required to maintain mean arterial pressure and coronary perfusion pressure until the underlying etiology can be treated or resolved.

DIGOXIN

Digoxin is a moderately potent inotrope with additional neurohormonal modulating effects producing increased parasympathetic nervous system activity and decreased central sympathetic nervous system drive. Its inotropic effect is related to inhibition of sarcolemmal sodium-potassium-ATP-ase, resulting in increased myocardial cell calcium, the final common pathway for all currently available inotropic agents. The benefit of digoxin in HF was debated for most of its first 200-year history. The drug has little use in the treatment of acute HF in patients with sinus rhythm. Perhaps the least controversial use of the drug in patients with HF is to assist (in combination with β-blockers or amiodarone) in the management of rate control in patients with atrial fibrillation. The Digoxin Investigation Group (DIG) clarified the role of digoxin in the management of patients with HF with normal sinus rhythm.[5] This study demonstrated that digoxin, in addition to background angiotensin-converting enzyme inhibitor (ACEI) and diuretic therapy, improved exercise tolerance, and reduced HF-related hospitalizations, but did not improve survival. Therefore, digoxin therapy for HF may be considered in patients with atrial fibrillation or in patients in sinus rhythm on target doses (if tolerated) of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) and β-blockers who exhibit

continued exercise intolerance or recurrent HF-related hospitalizations.

Digoxin is primarily renally eliminated with a serum elimination half-life of 1.6 days in patients with normal renal function. Recent trials have demonstrated that the efficacy of digoxin in HF can be achieved with doses that produce serum concentrations of 0.5 to 1.0 ng/mL, lower than those previously defined as "therapeutic."[6] Higher serum concentrations provide no added benefit and increase the risk of digoxin toxicity.

Digoxin Toxicity

Digitalis intoxication is a clinical diagnosis based on the presence of signs and/or symptoms including anorexia, nausea, and vomiting, and atrial or ventricular arrhythmias. Given the establishment of lower effective serum concentration, the incidence of digoxin toxicity has likely diminished. It is important to understand that the diagnosis of digoxin toxicity is never based solely on the digoxin concentration. Elevated serum digoxin concentrations are only one etiology of drug toxicity, usually related to maintenance doses inappropriate for the level of renal function. Most patients with normal renal function require 0.125 mg digoxin daily. Patients with renal insufficiency typically require 0.125 mg every other day or less. Many other factors that do not produce elevated serum digoxin concentrations are capable of causing digoxin toxicity including diuretic-induced hypokalemia or hypomagnesemia, hypoxemia, acidosis, hyperthyroidism, and others. Concurrent amiodarone therapy may double the serum digoxin concentration, and typical digoxin dosing in these patients should be reduced by 50% of the usual dose, considering renal function.

DIURETICS

Classical descriptions of acute decompensated HF characterize patients as volume overloaded, but well perfused ("wet and warm") or hypoperfused and not volume overloaded ("cool and dry"). However, the majority of hospitalized patients will require acute diuretic therapy to relieve signs and symptoms associated with their acute presentation. Much of the efficacy data associated with diuretic therapy for acute HF has been derived from experience before the era of randomized controlled trials. Despite their effectiveness for symptom relief, diuretics have not been demonstrated to improve survival in HF. Because of their potency, and rapid onset of action, loop diuretics (furosemide, torsemide,

and bumetanide) are considered the mainstay of treatment (**Table 19.3**). These agents inhibit sodium and chloride reabsorption in the ascending limb of the loop of Henle. Their effect of reducing venous tone and therefore pulmonary capillary wedge pressure often begins to improve pulmonary symptoms before a significant increase in urinary output. It is important to recognize that patients with chronic HF may have increased pulmonary capillary pressures and progressive dyspnea in the absence of significant pulmonary crackles on physical examination. Conversely, patients with new-onset HF are more likely to demonstrate pulmonary vascular congestion (crackles) on examination.

TABLE 19.3 Diuretics Used in the Treatment of Heart Failure

DRUG	INITIAL DAILY DOSE(S)	MAXIMUM TOTAL DAILY DOSE	DURATION OF ACTION
Loop diuretics			
Bumetanide	0.5–1.0 mg once or twice	10 mg	4–6 h
Furosemide	20–40 mg once or twice	600 mg	6–8 h
Torsemide	10–20 mg once	200 mg	12–16 h
Potassium sparing diuretics			
Eplerenone	25 mg once	50 mg once	24 h
Spironolactone	12.5–25 mg once	50 mg	2–3 d
Triamterene	50–75 mg	200 mg	7–9 h
Sequential nephron blockade			
Metolazone	2.5–10 mg once plus loop diuretic		
Chlorothiazide (IV)	500–1000 mg once plus loop diuretic		

Dosing of loop diuretics is empiric. In general, a 40-mg oral dose is equivalent to a 20-mg intravenous dose. In volume-overloaded patients with normal renal function, an initial intravenous dose should be 1 to 2 times the chronic oral dose. Response to an individual intravenous dose can be assessed in several hours.

Patient response is based on relief of pulmonary vascular congestion, daily weight, hepatic congestion, and peripheral edema. Because loop diuretics require a threshold serum concentration to affect their natriuretic response, patients with chronic HF, and those with moderate-to-severe renal insufficiency will usually require higher initial doses than patients with normal renal function or new-onset HF (diuretic-naive patients). Alternative furosemide dosing strategies comparing bolus dosing to continuous infusions have been evaluated in a number of small uncontrolled trials. Earlier studies, in addition to a review of eight randomized trials, suggest that continuous intravenous infusions of furosemide ranging from 10 to 40 mg/h, depending on renal function, produce a greater diuretic effect than similar total doses administered by intermittent bolus dosing, with fewer adverse effects.[7] The DOSE (Diuretic Optimization Strategies Evaluation) trial, a randomized, open-label comparison between twice-daily bolus furosemide versus continuous infusion demonstrated no differences in outcomes in hospitalized, volume-overloaded patients with HF.[8] There was a trend toward less hypokalemia and hypotension in the continuous infusion group. Although no definitive data currently resolve the dosing route of administration controversy, it does not appear that continuous infusion offers a significant advantage over traditional bolus dosing of furosemide.

Monitoring of adverse effects of diuresis such as abnormal electrolytes, orthostatic hypotension, prerenal azotemia or increasing serum creatinine, is essential. Less commonly, patients with a history of chronic gout may experience an acute gout exacerbation. Excessive diuresis can enhance undesired neurohormonal activation, increasing the risk of excessive hypotensive effects from ACEI and β-blockers.

Diuretic resistance is not uncommon in patients with an acute exacerbation of chronic HF. A number of factors predispose to lack of diuretic response including worsening renal function, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) that antagonize the effects of diuretics, or renal hypoperfusion secondary to HF or overly aggressive diuresis or vasodilators. A number of strategies to produce effective diuresis in nonresponsive patients have been employed. First, if appropriate diuretic response is not achieved within 4 hours, the intravenous dose can be successively doubled until an intravenous dose of 120 mg is reached. Higher single doses are unlikely to enhance diuresis and are more likely to risk ototoxicity. Despite the lack of controlled data, anecdotal reports of successful diuresis with continuous furosemide infusions in diuretic-resistant patients may promote successful diuresis. Oral metolazone,

unlike other oral thiazide diuretics, can be effective in patients with renal insufficiency. An oral dose of 5 to 10 mg should be administered before intravenous furosemide—30 to 60 minutes is the accepted time frame, although pharmokinetically the distal tubule blockade requires at least several hours. Other distal convoluted tubule diuretics include oral hydrochlorothiazide, chlorthalidone, or intravenous chlorothiazide. However, metolazone, perhaps related to its efficacy in patients with renal insufficiency and its longer elimination half-life, seems to be preferred by most clinicians.

Diuretics that act more distally, such as spironolactone or amiloride, are less likely to overcome diuretic resistance, but may have a role in limiting hypokalemia and hypomagnesemia provoked by loop diuretics. These acute electrolyte disturbances in patients with HF increase the risk of hemodynamically compromising, or potentially life-threatening arrhythmias. Intravenous low-dose dopamine stimulates renal dopamine receptors and has been demonstrated to increase urine output; however, no controlled studies in patients with diuretic-resistant HF have been undertaken. Interpatient variability in response to the β_1 adrenergic inotropic effects of dopamine may play a role in its ability to increase urinary output in HF. The UNLOAD (***UN***load the ***L***eft ventricle in patients with ***AD***vanced heart failure) trial demonstrated that ultrafiltration produced greater weight and fluid loss, as well as fewer HF-related hospitalizations than intravenous diuretics in patients hospitalized for HF.[9] The CARRESS-HF (***CA***rdiorenal ***RES***cue ***S***tudy in Acute Decompensated ***H***eart ***F***ailure) trial was undertaken to demonstrate the efficacy of ultrafiltration in patients with HF having persistent congestion and worsening renal function. Unfortunately, the ultrafiltration had no benefit over stepped pharmacological therapy (diuretics).[10] In fact, ultrafiltration was associated with more adverse events—worsening renal failure, bleeding, and catheter-related events. Therefore, ultrafiltration is reserved for patients with refractory congestion who have failed to respond to diuretic-based strategies.[11]

ALDOSTERONE ANTAGONISTS

The adverse effects of aldosterone in HF are related to its sodium- and water-retaining potential initiated by activation of the rennin–angiotensin–aldosterone system (RAAS), and from decreased hepatic aldosterone clearance. As important is the impact of aldosterone on myocardial and vascular remodeling that

produces increased collagen deposition and fibrosis. These effects produce ventricular systolic and diastolic dysfunction and contribute to the progressive nature of chronic HF. Although both ACEIs and ARBs lower aldosterone production in the short term, long-term suppression may not be maintained. Aldosterone antagonists spironolactone and eplerenone have both been demonstrated to improve symptoms, reduce HF-related hospitalizations, and improve survival in selected patients. The ***R***andomized ***AL***dactone ***E***valuation ***S***tudy (RALES) trial evaluated the effect of spironolactone (maximum dose 25 mg daily) in patients with New York Heart Association (NYHA) class IV symptoms, or class III symptoms in recently hospitalized patients.[12] The EPHESUS (***E***pleronone ***P***ost-Acute Myocardial Infarction ***H***eart ***F***ailure ***E***fficacy and ***SU***rvival ***S***tudy) trial studied eplerenone (maximum dose 50 mg daily) in patients with HF or diabetes and left ventricular ejection fraction (LVEF) <40% within 14 days of myocardial infarction (MI). Both drugs demonstrated an improvement in survival and reduction in HF-related hospitalization.[13] The EMPHASIS (***E***plerenone in ***M***ild ***P***atients ***H***ospitalization ***A***nd ***S***urv***I***val ***S***tudy) trial expanded the use of aldosterone antagonists by evaluating the effect of eplerenone in patients with NYHA II symptoms and LVEF ≤35%, again resulting in reduction of mortality and hospitalizations.[14]

The benefits associated with the use of aldosterone antagonists must be carefully weighed against the potential for life-threatening hyperkalemia. Given that ACEI therapy has become a mainstay in the treatment of HF, and because some degree of renal insufficiency is common as the severity of HF increases, it is imperative that patients be chosen carefully, and that appropriate monitoring of serum potassium concentrations takes place. The major trials excluded patients with serum creatinine >2.5 mg/dL; however, serum creatinine is a poor predictor of creatinine clearance, especially in elderly patients. Aldosterone antagonists should not be administered to patients with creatinine clearances below 30 mL/min, and the dose should be reduced at creatinine clearances less than 50 mL/min. More frequent use of aldosterone antagonists in the general HF population, as opposed to patients enrolled in clinical trials, subsequent to the publication of the two major trials, has resulted in an incidence of hyperkalemia up to 24%.[15] Serum potassium concentrations should be monitored within 3 days of drug initiation and again at 1 week. Serum potassium concentrations greater than 5.5 mEq/L should promote discontinuation of the drug. The lack of routine monitoring has been well documented in the ambulatory care setting.[16]

Spironolactone may cause painful gynecomastia in approximately 10% of

patients, according to the RALES study, and probably increased rates in higher doses. This is attributed to the anti-androgenic and indirect estrogenic effect of spironolactone. Eplerenone is much more selective than spironolactone in aldosterone receptor blockade and does not exert anti-androgenic and estrogenic effects. However, it is less potent than its corresponding dose of spironolactone. Eplerenone is also more expensive than spironolactone, and is therefore usually administrated when patients complain of spironolactone-related side effects.

VASODILATORS

Nitroglycerin, nitroprusside, and nesiritide are all effective in improving hemodynamic and symptoms of pulmonary vascular congestions in patients who are not hypotensive. These agents are indicated in patients with ongoing pulmonary vascular congestion not responsive to diuretic therapy and standard oral therapy. Additional indications for intravenous vasodilator therapy include patients with HF and ongoing ischemia, hypertension, or significant mitral regurgitation.

NITROGLYCERIN

Nitroglycerin is primarily a venodilator with dose-dependent arteriolar dilating properties. At higher doses, nitroglycerin is a potent coronary vasodilator, making it an ideal agent for patients with ischemic cardiomyopathy. Nitrate-induced preload reduction results in reduced PAOP, myocardial oxygen demand, and improvement in dyspnea. Because of its short onset and duration of action, the infusion rate can be quickly adjusted, allowing easy titration toward maximal beneficial hemodynamic effects, and rapid correction of adverse effects. The risk of hypotension with nitroglycerin as with the other intravenous vasodilators is critically dependent on intravascular volume. Hemodynamic monitoring may be useful to assess the beneficial effects, and limit the risk of hemodynamic adverse effects with both nitroglycerin and nitroprusside, as well as with intravenous inotropes. Tolerance to the hemodynamic effects of nitroglycerin can be seen in 12 to 72 hours in patients on continuous nitroglycerin infusions.[17]

NITROPRUSSIDE

Nitroprusside is a more balanced arteriolar and venous dilator than nitroglycerin.

As a more potent arteriolar dilator, it has greater effect in increasing cardiac output in patients with elevated systemic vascular resistance, while retaining the preload lowering benefit of reducing PAOP and pulmonary congestion. Although nitroprusside has been associated with coronary steal in patients with obstructive coronary disease, in patients with HF the reduction in both preload and afterload generally decreases myocardial oxygen demand.[18] Obviously a significant reduction in aortic diastolic pressure has the potential to decrease coronary perfusion pressure and increase ischemia. As with nitroglycerin, nitroprusside is short acting, providing for easy titration. The most common side effect is hypotension. Two biochemical toxicities have potentially led to the underutilization of nitroprusside in acute decompensated HF—cyanide and thiocyanate toxicity. Malnourished patients or patients with liver disease are more prone to cyanide intoxication because of their inability to combine cyanide produced in the serum from nitroprusside with the hepatically produced sulfhydryl group to form thiocyanate. The accumulated cyanide produces elevated lactate levels and metabolic acidosis. Patients with decrease renal function are unable to eliminate the thiocyanate metabolite and develop neurotoxicity including headache, altered mental status, and seizures. Because thiocyanate has an elimination half-life of 4 days in patients with normal renal function, infusions of less than 3 μg/kg/min administered for less than 3 days in patients with a serum creatinine less than 3.0 mg/dL are unlikely to result in toxicity. Serum thiocyanate concentrations can be measured in the hospital laboratory.

NESIRITIDE

Nesiritide is an intravenous form of recombinant human brain natriuretic peptide (BNP). It produces a dose-dependent reduction in venous and arterial pressures, natriuresis, and diuresis. Its most consistent effect is decreased dyspnea and POAP, much like nitroglycerin. Questions remain as to the impact of nesiritide on hospitalization rates and mortality, especially in the face of its relatively high cost compared to nitroglycerin. In addition, in a review of a series of publications, nesiritide significantly increased the risk of worsening renal function.[19] The ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial enrolled 7141 patients hospitalized with acute HF randomly assigned to nesiritide or placebo. Nesiritide did not impact mortality or rehospitalization, and was not associated with

worsening renal function, but it was associated with an increase in rates of hypotension.[20]

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKING AGENTS

ACEIs have been demonstrated to improve survival in NYHA Class II to IV patients with systolic dysfunction, and improve symptoms in many patients (**Table 19.4**). Their pharmacologic effects, inhibiting the conversion of angiotensin I to angiotensin II, result in a decreased production of angiotensin II and aldosterone. Limiting aldosterone production decreases the progression of left ventricular dysfunction and reduces ventricular remodeling, myocardial fibrosis, cardiac hypertrophy, and dilatation. The chronic hemodynamic effects of ACEIs to reduce afterload (angiotensin is a potent vasoconstrictor), and, to a lesser extent, preload, improves exercise tolerance and quality of life. In addition to improving survival, ACEIs decrease the rate of HF-related hospitalizations, and limit the need for increasing diuretic doses. For post-MI patients, ACEIs reduce the risk of developing HF, recurrent MI, and HF-related hospitalizations. Angiotensin-converting enzyme is also responsible for the degradation of bradykinin. The cough and rare cases of angioedema observed in patients treated with ACEI are attributed to this elevation of bradykinin. Therefore, substitution of an ACEI with a direct ARB can bypass this effect without raising bradykinin levels. Owing to the significant cumulative data demonstrating the benefit for ACEI in the treatment of chronic HF, these drugs, as opposed to ARBs, are recommended as first-line therapy for chronic HF. ARBs, which probably possess similar symptom and survival benefit, should be reserved for the 10% to 15% of patients who develop ACEI-induced cough.

TABLE 19.4 Oral Agents FDA Approved for Treatment of Chronic Heart Failure

DRUG	INITIAL DOSE	TARGET DOSE	ELIMINATION
ACE inhibitors			
Captopril	6.25 mg tid	50 mg tid	Renal

Enalapril	2.5–5 mg bid	10 mg bid	Renal
Lisinopril	2.5–5 mg daily	20–40 mg daily	Renal
Quinapril	10 mg bid	20–40 mg bid	Renal
ARB			
Candesartan	4 mg daily	32 mg daily	Renal
Valsartan	40 mg bid	160 mg bid	Liver/some renal
ARNI			
Sacubitril-Valsartan	24–26 mg to 49–51 mg bid	97–103 mg bid	Sacubitril: renal/liver Valsartan: liver/some renal
β-Blockers			
Carvedilol	3.125 mg bid	<85 kg: 25 mg bid >85 kg: 50 mg bid	Liver
Carvedilol extended release	10 mg daily	80 mg daily	Liver
Metoprolol extended release	12.5 mg daily	200 mg daily	Liver
Ivabradine	2.5–5 mg bid	7.5mg bid	Liver/renal
Hydralazine-isosorbide dinitrate (Bidil)	Hydralazine 37.5 mg Isosorbide 20 mg tid	Hydralazine 75 mg Isosorbide 40 mg tid	Liver

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; FDA, U.S. Food and Drug Administration.

ACEI therapy for ischemic or nonischemic cardiomyopathy should be initiated at low doses, but may be titrated to maximum doses within a few days to weeks, provided blood pressure and renal function remain stable. It is important to note that patients with more severe HF may have relatively low blood pressures (systolic pressures in the 100 mm Hg range), and as long as symptomatic hypotension is not present, ACEI therapy should be maintained. Dose reduction or transient withholding of ACEI administration should not be based only on the systolic blood pressure reading, but on the presence of symptomatic hypotension. In addition, new-onset hypotension or an increase in serum creatinine, in the setting of ACEI therapy, warrants an evaluation for cause, especially overly aggressive diuretic therapy, or hyponatremia in the

setting of NYHA Class IV HF. Although survival enhancement can be achieved with low doses of ACEIs (lisinopril 5 mg or its equivalent), maximum symptom improvement and limitation of HF-related hospitalizations are best achieved with higher doses (20 to 40 mg lisinopril).

For patients with acute decompensations of chronic HF, ACEIs or ARBs have minimal acute hemodynamic benefit, but should remain part of the therapeutic regimen as long as they are hemodynamically tolerated.

The two most likely adverse effects associated with ACEI/ARB administration in hospitalized patients are hypotension and worsening renal function. The risks of both of these outcomes are enhanced by overly aggressive diuresis. Small (10%) increases in serum creatinine are commonly associated with initiating ACEI/ARB therapy in patients with HF, and should not provoke dosage reduction or drug withdrawal. Progressive increases in serum creatinine, however, are a typical manifestation of decreased renal blood flow, commonly the result of aggressive diuretic therapy, or worsening HF. Reducing the rate of diuresis, rather than holding the dose of ACEI/ARB, will usually allow renal function and/or blood pressure to return to its baseline level. It is not usually necessary to temporarily withhold administration of the ACEI/ARB, unless the rise in serum creatinine continues. Drug-induced hypotension, even in the face of total body volume overload, will usually require holding the diuretic until intravascular volume equilibrates.

A second common cause of worsening renal function associated with the administration of ACEIs/ARBs is the concomitant use of other nephrotoxic agents, most notably, intravenous contrast administered for coronary artery imaging. Because of the risk of nephrotoxicity associated with iodinated contrast, especially in the diabetic patient, withholding ACEIs/ARBs for patients with suspected dye-induced nephrotoxicity is appropriate until renal function returns to baseline. Although volume repletion is an effective method of reducing the risk of dye-induced nephrotoxicity, this may be more difficult in patients with HF than in patients with coronary artery disease without HF.[21] The presence of preexisting renal disease in patients with HF should not be considered a contraindication to ACEI/ARB therapy in chronic HF. Several trials in various patient populations including post-MI patients with decreased left ventricular function have demonstrated that ACEIs are more effective in the subset of patients with mild-to-moderate renal insufficiency than in patients with normal renal function.[22] Judicious routine monitoring of renal function is required in patients hospitalized for HF, irrespective of the addition of

ACEIs/ARBs. Prevention of hyperkalemia is especially important in patients with HF with chronic kidney disease receiving ACEI/ARB therapy.

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS

A new class of drugs was recently developed, combining inhibition of the RAAS via an ARB with a molecule that inhibits the endogenous peptidase neprilysin—an enzyme responsible for the degradation of natriuretic peptides, bradykinin and adrenomedullin (counterregulatory substances released in HF, among other conditions). By inhibiting neprilysin, these counterregulatory substances are upregulated allowing for natriuresis, diuresis, vasodilation, and anti-fibrotic/antiremodeling effects. As with ACEIs, angiotensin receptor–neprilysin inhibitors reduce the degradation of bradykinin (**Table 19.4**). This is why the neprilysin inhibitor molecule was combined with an ARB and not an ACEI. This decision stemmed from the results of a study combining neprilysin inhibition and ACE inhibition in one molecule—omapatrilat, a "super ACE inhibitor." Trials with this molecule had a disturbing rate of angioedema, probably due to the double inhibition of bradykinin degradation causing marked bradykinin elevation.[23] Therefore, a molecule combining valsartan (ARB) and sacubitril (neprilysin inhibitor) was constructed and initially termed LCZ696. After preclinical testing, a large-scale trial (PARADIGM-HF, ***P***rospective Comparison of ***AR***NI with ***A***CEI to ***D***etermine ***I***mpact on ***G***lobal ***M***ortality and ***M***orbidity in ***H***eart ***F***ailure, trial) enrolling patients with HF having reduced LVEF (<40% and then 35% during the trial) and NYHA Class II to IV symptoms was initiated. This trial compared enalapril 10 mg bid versus LCZ696 (Sacubitril/Valsartan) in a randomized double-blind design after two single-blind run-in periods (where patients were tested with enalapril and then with LCZ696 individually).[24] The PARADIGM-HF trial demonstrated superiority of LCZ696, later named Entresto, over enalapril. This was reflected in reduced cardiovascular mortality, as well as in hospitalizations. The main side effects are similar to ACEI/ARB—hypotension and angioedema. Following this trial, HF guidelines began to endorse Entresto instead of ACEI/ARB if a patient is still symptomatic despite optimal medical therapy.[25]

β-BLOCKERS

β-Blockers were originally considered contraindicated in patients with HF because of their negative inotropic effects (**Table 19.4**). Once the paradigm for the pathogenesis of HF shifted away from primary myocardial dysfunction to a syndrome resulting from the action of "compensatory" mechanisms related to the sympathetic nervous system and the renin–angiotensin–aldosterone axis, it became clear that agents that antagonize these mechanisms might be beneficial. Several large randomized trials in the 1990s demonstrated that β-blockers improve survival in patients with NYHA Class II to IV HF.[26–28] In addition, they decrease the risk of overt HF in patients with asymptomatic left ventricular dysfunction. The progression and degree of chronic HF severity are associated with the serum concentration of norepinephrine. Patients with the highest norepinephrine concentrations have the poorest prognosis. Hemodynamically, norepinephrine-induced tachycardia and inotropic effects increase myocardial oxygen demand. In addition, the peripheral vasoconstriction increases left ventricular afterload, further increasing oxygen demand and decreasing cardiac output. Chronically, sympathetic stimulation produces myocardial cell loss through apoptosis and cell necrosis, as well as downregulation of myocardial β_1 receptors and loss of sensitivity to sympathetic stimulants. As had been previously discovered with the use of ACEIs to interfere with the adverse effects of the RAAS on progressive ventricular dysfunction, survival, and symptoms, blocking the detrimental effects of catecholamines on the failing ventricle with β-blockers resulted in improved left ventricular function, attenuating ventricular remodeling, decreasing the risk of life-threatening arrhythmias, and decreasing myocardial oxygen demand.

A number of issues are relevant to the use of β-blockers in the patient hospitalized for HF. These include timing of drug therapy initiation, methods for increasing doses toward chronic target dosing, strategies for dosing in patients on chronic β-blockers who are admitted for acute HF decompensation, and choosing between various β-blockers approved for use in chronic HF.

β-Blocker therapy should be initiated in patients with new-onset HF only after volume status has been optimized. Patients who remain volume overloaded are more likely to develop increasing HF symptoms, whereas patients who are intravascularly volume depleted are more like to become hypotensive. Several studies have addressed the order in which ACEI/ARB or β-blockers should be administered, because initiation of both agents is recommended within 24 hours of the onset of MI.[29] These studies, however, have been performed in patients with mild-to-moderate chronic HF, not patients hospitalized with new-onset or

acutely decompensated HF. Although both β-blockers and ACEIs are effective for myocardial remodeling post MI, current guidelines recommend initiation of ACEI within 24 hours of the MI, and delaying the introduction of β-blockade until the signs and symptoms of HF have been resolved. It is not necessary to achieve the "target dose" of ACEI/ARB before initiating starting doses of the β-blocker.

Unlike the initial dosing strategy with ACEIs/ARBs, β-blockers should be titrated toward their target doses more gradually, with a minimum of 2-week intervals between dosage increases. It is well documented that many patients with chronic HF do not receive doses consistent with target doses determined by large controlled trials. As with ACEIs/ARBs, small doses of β-blockers do positively impact survival; however, greater reduction in HF hospitalizations and improvement in LVEF are achieved with dosing strategies intended to achieve target doses. It is common for ambulatory care providers to maintain patients on the low-dose β-blockers that were initiated during an acute hospitalization, presumptively based on concerns for worsening HF as the dose is increased, or assuming that the patient has achieved the ultimate level of symptom control. Clearly, monitoring for adverse effects such as worsening HF, symptomatic bradycardia, or hypotension are a requisite part of chronic monitoring during titration toward target doses of β-blocker therapy. Especially for patients with new-onset HF, however, maintaining a starting dose, without an attempt to titrate to target doses, diminishes the potential benefit that the combination of ACEI/ARB and β-blockers can achieve for prevention of disease progression.

Recent data have addressed the question of withdrawing β-blockers in patients on chronic therapy who present with an acute decompensation of HF. Until recently, the approaches have generally been either to temporarily discontinue the β-blocker or to decrease the chronic dose to some degree. The appropriate strategy clearly depends on the level of severity of the acute decompensation. Patients who present with severe hemodynamic decompensation (hypotensive, or approaching cardiogenic shock), or those with severe pulmonary vascular congestion are obvious candidates for transient withdrawal of β-blockers. Data prospectively analyzed from the OPTIMIZE-HF (Organized *P*rogram to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) demonstrated that patients who were withdrawn from β-blocker therapy had a higher risk for mortality, compared with those continued on β-blockers.[30] Patients who were eligible for β-blocker therapy, but did not receive them, had similar risk for mortality as those who had therapy withdrawn. During the 60- to 90-day follow-

up period, 94% of patients remained on β-blockers after discharge. Only 57% of patients who had their β-blocker withdrawn received β-blocker treatment during the 60- to 90-day follow-up period. Of the patients maintained on therapy during hospitalization, only 12% had their maintenance dose reduced during follow-up. The remaining 88% were maintained on their preadmission dose, or had their dose increased (12%). It appears therefore from limited registry data that patients with chronic HF admitted to the hospital on β-blocker therapy should not have this therapy withdrawn unless they are hemodynamically compromised. An additional risk associated with β-blocker withdrawal is failure to reinstate the drug after hospital discharge.

Two β-blockers are currently approved in the United States for the treatment of HF—metoprolol controlled release/extended release (CR/XL) and carvedilol. Bisoprolol has also been demonstrated to reduce the incidence of sudden death and of HF-related death, but is not approved by the U.S. Food and Drug Administration for this indication in the United States. Metoprolol is a cardioselective β-blocker, whereas carvedilol is a nonselective β-blocker with α-adrenergic blocking activity. Both agents have demonstrated similar reductions in morbidity and mortality in large randomized controlled studies of patients with HF. Subtle pharmacodynamic features may influence the decision to use one drug or the other. The cardioselectivity of metoprolol may be beneficial in patients with reversible airway disease such as asthma; however, cardioselectivity diminishes with increasing dosage. The recommended target dose of metoprolol of 200 mg daily likely provides little cardioselectivity. The α-blocking property of carvedilol has a theoretical advantage in patients with a history of cocaine abuse in whom pure β-blocker pharmacology leaves unopposed coronary artery α-receptors susceptible to the vasospastic potential of cocaine. Both metoprolol XL and carvedilol are available as once-daily dosing formulations to enhance patient compliance.

The most common adverse effects of β-blockers in patients with HF include worsening of HF symptoms, especially in volume-overloaded patients or in those whose dose titration has occurred too rapidly, symptomatic bradycardia, or hypotension.

IVABRADINE

Ivabradine is a drug that inhibits the If Current (If—“I funny”—because this

sodium channel current is triggered by hyperpolarization, as opposed to other sodium channels) in the SA node. If is the “pacemaker current” responsible for spontaneous depolarization of the SA nodal tissue. The rationale behind the development of this agent was to produce further lowering of the heart rate, in addition to β-blockers. Ivabradine does not have negative inotropic effects, so patients with β-blocker intolerance can receive a lower dose of β-blocker with ivabradine or ivabradine alone as a heart-rate–lowering agent. The SHIFT (***S***ystolic ***H***eart ***F***ailure Treatment with the **I**f Inhibitor Ivabradine ***T***rial) enrolled patients with HF having LVEF ≤35%, with NYHA class II to IV symptoms, and on optimal medical therapy with a heart rate >70. In this trial, ivabradine reduced the combined end point of hospitalizations and cardiovascular mortality.[31] Therefore, ivabradine (marketed as Corlanor) can be added on to optimal β-blocker therapy, along with ACEI/ARB and spironolactone in patients with LVEF ≤35% and are still symptomatic. Side effects include bradycardia and luminous phenomena—phosphenes, brightness in the visual fields. The visual changes are presumed to be the result of ivabradine inhibiting similar retinal channels.

HYDRALAZINE-ISOSORBIDE DINITRATE

The combination of the direct arteriolar dilator, hydralazine, and isosorbidedinitrate (ISDN), a long-acting nitrate venodilator was the first vasodilator regimen to demonstrate improved survival in chronic HF (V-HeFT, Vasodilator Heart Failure Trial).[32] Within a few years, ACEIs had been shown to enhance survival to a greater degree than did the original vasodilator combination, and had become the standard of care for chronic HF. A post hoc analysis of the original hydralazine-nitrate trial suggested that the combination was particularly effective in African-Americans. The A-HeFT (African-American Heart Failure Trial) compared a fixed combination of hydralazine and ISDN (maximum dose hydralazine 75 mg plus ISDN 40 mg 3 times a day) versus placebo in self-identified African-American patients on background ACEI, β-blocker, and a diuretic with or without digoxin and spironolactone.[33] The hydralazine-ISDN group had a significant reduction in mortality, in HF-related hospitalizations, and in an improvement in quality of life.

Oral vasodilator therapy with ACEIs and the combination of hydralazine have primarily been studied in patients with chronic HF. However, in patients

hospitalized with acute HF for whom ACEIs may be transiently withheld because of acute elevations of serum creatinine, hydralazine-isosorbide has been substituted for its beneficial hemodynamic effect.[34] Once stable renal function has been reestablished, ACEIs are the preferred choice for chronic management. In addition to its use in African-American patients, chronic hydralazine-isosorbide therapy may be appropriate for patients who do not tolerate either ACEIs or ARBs because of renal insufficiency or hyperkalemia.

The frequency of side effects such as headache and gastrointestinal complaints from the hydralazine-isosorbide combination in large trials is significant, and in both vasodilator HF trials many patients did not tolerate target doses of these drugs. In addition, the necessity of 3 times daily dosing increases the risk of noncompliance.

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Patient and Family Information for: MEDICATIONS USED IN THE MANAGEMENT OF HEART FAILURE

DRUGS FOR PATIENTS HOSPITALIZED WITH HEART FAILURE

Patients with HF symptoms often need hospitalization when their symptoms become severe. Several drugs are useful to relieve the symptoms of HF and to return them to the quality of life they experienced before the need for hospitalization. For most patients, relieving symptoms related to shortness of breath and swelling of their extremities are important goals. For patients who are more severely ill, improving their heart function will provide better blood flow to their organs and muscles. There are three drug categories that are frequently used for patients hospitalized for HF: drugs that relieve swelling and shortness of breath—diuretics such as furosemide (Lasix), drugs that improve heart pumping function (dobutamine or milrinone), and drugs that relax blood vessels and make it easier for the heart to pump blood into the blood vessels (nitroglycerin or nitroprusside).

Diuretic drugs decrease the amount of volume that is in the bloodstream by increasing the amount of salt and water that is removed by the kidneys. Patients with HF are often short of breath because the amount of fluid in the lungs makes it difficult for them to breathe. In addition, many patients have fluid accumulation in their ankles, legs, and even in their abdomen. The primary goal in patients hospitalized for HF is to eliminate fluid from the lungs, followed by a reduction of fluid in other parts of the body. It is important for these patients to

know their “dry weight,” the target weight they should maintain as outpatients. Appropriate use of diuretic drugs in the hospital should bring patients close to their dry weight. It is equally important for patients with HF to weigh themselves daily at home, because this is a practical method to determine fluid accumulation. Weight gain of more than 2 to 3 pounds within a few days is an indication that their HF may not be well controlled. Dietary salt intake has the greatest potential to promote fluid accumulation. Patients should be aware of the salt (sodium) content of the foods they eat, especially prepared foods such as canned vegetables and soups, prepared meats, and snack foods such as pretzels, potato chips, and similar items. They should also avoid adding salt to their meals at the table. Excessive salt intake can easily overcome the effects of diuretic drugs, and result in fluid accumulation. Some physicians have successfully educated patient to increase the dose of their diuretic drugs (furosemide or Lasix) when their weight increases by several pounds. If weight gain continues, or patients become increasingly short of breath with exertion, or when lying down at night, they should contact their physician. The side effects of diuretics that are closely monitored are decreases in blood pressure, kidney function, and other body salts such as potassium and magnesium. A careful balance is maintained between too much volume in the circulation, producing symptoms of shortness of breath and swelling, and too little volume, resulting in diminished kidney function or low blood pressure.

In addition to diuretics such as furosemide, which are used in the hospital, and chronically to manage fluid balance, two other diuretic drugs may be used in selected patients with HF with moderate-to-severe forms of HF. Spironolactone (Aldactone) and eplerenone (Inspra) are diuretic drugs that work by a mechanism different from that of furosemide, and, unlike other diuretic agents, have been shown to improve survival in selected patients with HF. Although they add to the ability of diuretic drugs to maintain appropriate fluid balance, their major impact is to add to the survival benefit of drugs like ACEIs and β-blockers (see subsequent text). The most important side effect of these added diuretics is their ability to increase the level of potassium in the blood. Because ACE inhibitors or ARBs also have the ability to cause the kidneys to hold on to potassium, serum potassium level should be closely monitored, especially in patients whose kidney function is impaired.

Intravenous drugs that increase the force of contraction in patients with HF are sometimes required in hospitalized patients when more conservative therapy has failed to improve symptoms and blood flow. Dobutamine and milrinone are both

drugs that increase the force with which the heart contracts, and therefore increase the amount of blood to the kidneys, muscles, and other vital organs. These drugs are intended for short-term use—several days—and are effective in improving blood flow, stabilizing blood pressure, and improving symptoms. Because these drugs have a short duration of action, doses can be easily adjusted to the heart pressures that are being closely monitored in severely ill patients. Most patients with HF have poorly contracting ventricles (lower heart chambers). Although it seems logical that drugs which improve the force of contraction of the heart should improve survival, the effect of these drugs is to improve symptoms and restore normal pressures in the circulation, rather than to benefit survival. The major side effect of dobutamine and milrinone include increased heart rate and heart rhythm disturbances. These potential side effects are closely monitored in patients in intensive care units. In rare cases, dobutamine may be used as an intermittent outpatient infusion to relieve symptoms in patients with severe HF who are not candidates for heart transplants or implantable heart pumps.

The only oral drug used in HF to increase the force of contraction is digoxin. The drug, used for more than 200 years in the treatment of HF, is much less powerful than agents such as dobutamine or milrinone. There are two circumstances in which digoxin may be used in HF. In hospitalized patients whose HF is complicated by the cardiac rhythm disturbance, atrial fibrillation, a rhythm disturbance of the upper chambers of the heart, digoxin may be used with other drugs to reduce pulse rate. In patients with chronic HF, digoxin may be added to other chronic HF medications to improve symptoms of exercise intolerance and to decrease the rate of hospitalizations for HF symptoms. Digoxin must be administered at lower dose or less frequently (every other day) to patients whose HF is complicated by reduced kidney function. Loss of appetite, nausea, and changes in heart rhythm are side effects that should be monitored in patients receiving digoxin therapy.

Nitroglycerin and nitroprusside are intravenous drugs that dilate arteries and/or veins and may also be used in patients with severe HF. By relaxing arteries, more blood can be ejected from the heart, increasing blood flow to vital organs. Because these drugs have the potential to lower blood pressure in patients whose heart function is already compromised, they must be administered under close supervision, making sure that blood flow is improved while blood pressure is maintained. Fortunately, both nitroprusside and nitroglycerin are very short-acting drugs, whose doses can be quickly altered if

necessary. Because nitroprusside has some side effects that occur more commonly in patients whose kidneys are not functioning normally, some physicians prefer nitroglycerin in such patients. Because nitroprusside is better able to dilate arteries than nitroglycerin, it may be preferred in patients with normal kidney function. Nitroglycerin dilates veins, to a greater extent than arteries, and is especially useful in patients with significant shortness of breath due to fluid accumulation in the lungs, and in patients with coronary artery disease, who may be experiencing chest pain associated with their HF symptoms.

DRUGS FOR CHRONIC HEART FAILURE

Most drugs used for the treatment of chronic HF will be continued when patients are hospitalized. At times during a patient's hospitalization, especially if the blood pressure decreases, or the kidney function worsens, these drugs may be withheld for short periods of time. However, once the patient's symptoms and vital organ function (especially kidneys) have improved, these agents will be restarted before discharge from the hospital.

ACEIs (lisinopril and others) are drugs that relax (dilate) blood vessels, making it easier for the heart to eject blood into the circulation. They thereby decrease the amount of work that the heart has to perform to provide adequate blood flow to vital organs and muscles. Most importantly, these drugs reduce the rate of deterioration of heart function responsible for the progression of HF, and prolong survival. Patients with HF and their caretakers should understand that although most patients experience some symptom improvement, continued compliance with the medication is critical, even in those whose symptoms do not improve, or improve only slightly, because the drugs prolong life. About 10% of patients experience a dry cough with ACEI therapy. The cough may occur at any time during therapy, and the patient's caretaker may notice the symptoms before the patient. Should the cough become bothersome, replacing the ACEI with an ARB will provide the same benefit without the associated cough. Many HF experts, however, prefer ACEIs as first-line therapy for HF. Rarely, patients may experience swelling of the lips, tongue, or throat from ACEIs. This reaction is a medical emergency and the patient should be taken to an emergency department for treatment to make sure that the airway is not blocked.

ARBs provide similar benefit for patients with HF, but are generally reserved

for patients who do not tolerate ACEIs. The incidence of swelling of the lips and throat is lower than with ACEIs, but there are rare cases of such swelling in patients receiving ARBs who had previous reactions with ACEIs. Patients receiving ACEIs of ARBs will require monitoring of blood pressure, kidney function, and potassium levels in the blood.

Similar to ACEIs, β-blocker drugs are an important part of the treatment of chronic HF. β-Blockers work in HF by preventing chemicals produced by the nervous system from interacting with heart muscle. This interaction is partially responsible for the chronic decrease in pump function with progression of symptoms experienced by patients with HF. β-Blockers, like ACE inhibitors and ARBs, may also be used to treat high blood pressure, but their use in HF is not primarily directed at blood pressure. Like ACEIs, β-blockers prevent the progression of pump function loss, improve survival, and, for most patients, improve exercise tolerance and other symptoms of HF. Also similar to ACEI therapy, lack of symptom improvement should not cause patients to stop taking the drug, because it also prolongs life. For patients with new-onset HF, β-blockers will be started at a low dose, whether the patient is in the hospital or is treated as an outpatient. However, β-blocker therapy will not be started until the patient's HF symptoms, especially fluid overload, have been treated, and the patient is considered stable. The dose of β-blocker will be gradually increased toward a maximum target dose no more frequently than every 2 weeks, provided no adverse effects are noticed. The most important β-blocker side effects are excessive slowing of heart rate or reduction of blood pressure, producing symptoms of dizziness or lightheadedness. Other side effects may be observed in patients with diseases such as asthma or diabetes. Patients with asthma may experience shortness of breath or wheezing. This side effect can be minimized with certain β-blocker drugs such as metoprolol (Toprol), but may still occur and should be closely monitored. Diabetic patients, especially those receiving insulin, should closely monitor their blood sugars at home since β-blockers may either increase or decrease blood sugar. In addition, these drugs may interfere with a patient's ability to recognize the symptoms of low blood sugar. Sweating and change in mental status may still occur, but the patient may not experience tremor, rapid heart rate, or anxiety typically observed with low blood sugar in the absence of β-blockers. β-Blockers should not be discontinued abruptly without close medical supervision because of the risk of heart attack or serious heart rhythm disturbances.

The combination of hydralazine and isosorbide, when added to standard

ACEI, β-blocker, and diuretic therapy in African-American patients has been shown to improve survival, reduce hospitalizations, and improve quality of life in patients with moderate-to-severe HF. These drugs relax arteries (hydralazine) and veins (isosorbide), improving blood flow, decreasing the work of the heart, and possibly preventing changes in the structure of the heart muscle associated with HF. This drug combination is available as a single fixed combination dosage form (Bidil) or as separate drug entities, which are less costly. A significant disadvantage of the combination is the necessity of administering the drugs 3 times a day. Because most drug therapies for HF are administered once or twice a day, the addition of this combination may challenge the likelihood of successful compliance. The incidence of side effects with this combination is also higher than with most other HF regimens. Headache, dizziness, and gastrointestinal distress increase with dose and are fairly common. Dosage should be gradually increased toward the target maximum dose (hydralazine 75 mg and isosorbide 40 mg 3 times daily) or to a dose which is tolerated by the patient.

There are a number of drugs that should be avoided in patients with HF. Most of these drugs are only available by prescription, and will be known by the physician. These include some drugs used for high blood pressure, diabetes, heart rhythm disturbances, and arthritis. Patients must be aware that some over-the-counter medications have the potential to worsen the symptoms of HF. Most important among these is NSAIDs such as ibuprofen (Motrin), naproxen (Aleve, Naprosyn) and similar drugs for pain and inflammation. Acetaminophen (Tylenol) in appropriate doses is safer. NSAIDs may cause salt and water retention, leading to edema (swelling), worsening shortness of breath, and to a decrease in kidney function. In addition, many herbal products including ginseng, licorice, and St. John wart should be avoided in patients with HF. It is best to consult with the pharmacist or physician before adding any new over-the-counter medication or herbal preparation to the prescribed regimen. Patients with HF are commonly prescribed complicated drug therapy regimens, and have other medical conditions related to heart disease including diabetes, high cholesterol, high blood pressure, or others. Behaviors that improve drug therapy compliance can help reduce the need for hospitalizations. Patients should always keep a list of their current drug therapy regimen with them, especially when visiting health care providers or on admission to the hospital.

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Pathway for the Management of Sleep Apnea in the Cardiac Patient

EPIDEMIOLOGY

Sleep-disordered breathing is a highly prevalent medical condition that is currently estimated to affect 5% to 10% of the general population, regardless of race and ethnicity; almost two-thirds of these are underdiagnosed.[1] More than 80% of patients with moderate-to-severe obstructive sleep apnea (OSA) have not been diagnosed by their health care providers.[2, 3] Undiagnosed sleep apnea leads to increased morbidity and mortality, particularly related to increased incidence of cardiovascular events.[4] The cost of untreated OSA is currently estimated to reach $3.4 billion.[5] It is therefore imperative that we identify patient population at high risk for sleep apnea and refer them to the appropriate therapy as early as possible.

SLEEP DISORDERS

OBSTRUCTIVE SLEEP APNEA

OSA is a highly prevalent disorder with an estimated prevalence 3% to 7% in

men and 2% to 5% in women.[6] It is characterized by repetitive episodes of airflow cessation (apnea) or reduction (hypopnea) despite persistent thoracic and abdominal respiratory effort, likely due to collapse of the pharyngeal airway that occurs during sleep.[7] This collapse generally occurs posterior to the tongue, uvula, and soft palate. These episodes result in hypoventilation as well as hypoxemia, and provoke awakenings (recurrent arousals) that restore pharyngeal dilator muscle tone and airflow. OSA is generally defined as five or more apneas and/or hypopneas per hour of sleep (Apnea-Hypopnea Index [AHI] > 5) assessed by a cardiorespiratory or full polysomnography (PSG) recording. Obstructive sleep apnea syndrome (OSAS), on the other hand, is defined as an AHI ≥ 5 accompanied by either excessive daytime sleepiness or two or more of the following symptoms such as witnessed apneas, recurrent awakenings, gasping for air, bed partners complaining of excessive snoring, waking unrefreshed, morning headache, daytime fatigue, or impaired concentration or memory.[8] Recurrent episodes throughout the night lead to frequent nocturnal awakenings, resulting in excessive daytime somnolence,[9] which is often the presenting complaint.

CENTRAL SLEEP APNEA

Central sleep apnea (CSA) is common, although less prevalent in the general population than OSA. In a population-based study that included 5804 community-dwelling adults aged 40 years and older, the overall prevalence of CSA on PSG was 0.9%.[10] Approximately half of the CSA cases were associated with Cheyne–Stokes breathing.[11] While the International Classification of Sleep Disorders identifies six different forms of CSA,[12] in general CSA is caused by a loss of ventilatory drive, either due to hyperventilation or hypoventilation leading to cessation of ventilation during sleep. Post-hypocapnia hyperventilation is the underlying pathophysiologic mechanism for central apnea associated with congestive heart failure (HF), high-altitude sickness, and primary CSA. These patients chronically hyperventilate in association with hypocapnia during wake and sleep and demonstrate increased chemoresponsiveness and sleep state instability. CSA due to hypoventilation results from the removal of the wakefulness stimulus to breathe in patients with compromised neuromuscular ventilatory control. Chronic ventilatory failure due to neuromuscular disease or chest wall disease may manifest with central apneas or hypopneas, at sleep onset or during phasic rapid eye movement (REM) sleep.

This is typically noted in patients with central nervous system disease, neuromuscular disease, or severe abnormalities in pulmonary mechanics.[13] The apnea episode is 10 seconds or longer in the absence of a respiratory drive, and five or more events occurring in 1 hour are considered abnormal. The diagnostic criteria for CSA depend on the etiology. A diagnosis of primary CSA requires four findings: five or more central apneas/hypopneas per hour of sleep on PSG in the absence of Cheyne–Stokes breathing; patient reports sleepiness, awakening with shortness of breath, witnessed apneas or insomnia; no evidence of daytime or nocturnal hypoventilation; and, finally, absence of a concurrent sleep disorder, medical or neurologic disorder, or substance use disorder than can better explain the patient's symptoms. CSA associated with Cheyne–Stokes respirations, which is typically characterized by an absence of air flow and respiratory effort followed by hyperventilation in a crescendo–decrescendo pattern and most often observed in patients with congestive HF.[14] Furthermore, obstructive and central apnea episodes can occur together in this condition.[15] Diminished upper airway muscle activation at a ventilatory nadir can result in pharyngeal collapse leading to obstruction.

The severity of sleep apnea is quantified using the AHI, which measures the number of episodes/hour. Mild sleep apnea is defined as AHI of 5 to 14 episodes/hour, moderate as 15 to 29, and severe sleep apnea as 30 or more episodes/hour.[16]

CARDIOVASCULAR CONSEQUENCES OF SLEEP APNEA

Prevalence of OSA is noted to be two to three times higher in patients with cardiovascular disease.[17] There is accumulating evidence linking atrial fibrillation,[18–20] hypertension,[21, 22] HF,[23, 24] and stroke[25] to sleep apnea. It is unclear if these conditions coexist or if a true causative relationship exists. Prior studies have shown that patients with OSA who were treated conservatively had increased mortality, with most deaths being cardiovascular in origin.[26–28]

There is a bidirectional relationship between OSA and weight gain; up to 80% of patients with sleep apnea are obese, which results in an anatomically small airway leading to recurrent pharyngeal collapse during sleep. However, OSA can also cause or worsen obesity by a number of proposed mechanisms. Frequent nocturnal arousals lead to daytime somnolence, which results in the body

craving caffeine and high-calorie sugary foods. These cravings are mediated by the hormone leptin, which is produced by adipose tissue.[29] In addition, patients with OSA have decreased REM sleep, during which the body burns the most calories. There is a significant association between insulin resistance and OSA as well as with atherosclerosis, advocating that the metabolic disturbances may well be a significant link between OSA and cardiovascular disease.[30] Moreover, reports from sleep clinics demonstrated the association between the degree of insulin resistance and severity of OSA.[31] Indeed, those patients with insulin resistance have 5-fold increase in the risk of developing diabetes mellitus, which in turn aggravates obesity.[32]

The prevalence of hypertension in sleep clinics is estimated to be 30% to 50%[33]; likewise, it is estimated that about 50% to 80% of patients with hypertension have OSA.[34, 35] Intermittent hypoxemia, sympathetic stimulation, chemoreceptor activation leading to systemic vasoconstriction, and the renin–angiotensin–aldosterone system have been linked to the development of hypertension in OSA.[36] OSA episodes produce surges in systolic and diastolic pressure that keep mean blood pressure (BP) levels elevated at night, resulting in blunted fall in nocturnal BP, or "nondipping phenomena."[37] In many patients, BP remains elevated during the daytime, when breathing is normal. Contributors to this diurnal pattern of hypertension include sympathetic nervous system overactivity and alterations in vascular function and structure caused by oxidant stress and inflammation.[35]

The prevalence of OSA in patients with HF ranges from 12% to 53%, with a higher incidence of Cheyne–Stokes respiration. Recurrent hypoxemia, sympathetic stimulation, and left ventricular (LV) wall stress due to recurrent apnea episodes, over time can lead to LV hypertrophy, dilatation, and systolic dysfunction.[38] OSA in HF has been shown to increase mortality.[39] Thus, a bidirectional relationship may exist between sleep apnea and HF, typically observed by a gradual shift from predominantly obstructive apneas at the beginning of the night to predominantly central apneas toward its end.[40] Salt and fluid retention in HF can contribute to the pathogenesis of OSA and CSA, and effects of the latter can worsen HF. This pathologic relationship may be attributed to marked neurohumoral activation, surges in BP and heart rate (HR), and a greater propensity to lethal arrhythmia induced by CSA.[41, 42]

Excessive daytime somnolence is the most common symptom of OSA. Recurrent episodes of nocturnal hypoxemia lead to recurrent arousals. This

daytime somnolence frequently results in work-related and motor vehicle accidents. Approximately 25% of patients with untreated OSA report falling asleep while driving. [43]

Cardiac arrhythmias are common in patients with sleep-disordered breathing due to alterations in sympathetic and parasympathetic activity that occurs during periods of hypoxemia.[44, 45] Bradycardia, first- to third-degree atrioventricular (AV) conduction block and sinoatrial node block during apneas have been reported in patients with OSA. Becker et al.[46] reported AV-block II–III and/or sinus arrest in 7% of an unselected group of patients with OSA and the prevalence was even higher (20%) in the subgroup with severe OSA. Transmural and intrathoracic pressure gradient changes lead to left atrial enlargement, which has also been linked to the development of atrial fibrillation.[47] The prevalence of atrial fibrillation is significantly higher in patients with OSA than that of the general population. According to the Sleep Heart Study, patients with severe OSA were four times more likely to have atrial fibrillation.[44] Untreated OSA has been shown in several studies to decrease the likelihood of successful rhythm control strategies; likewise, patients who undergo electrical cardioversion and those with untreated OSA are two times more likely to have atrial fibrillation recurrence at 1 year as compared to those who use continuous positive airway pressure (CPAP).[48] Antiarrhythmic drugs have also been shown to be less effective in patients with severe OSA.[49] Although OSA has been shown to increase the risk of atrial fibrillation recurrence after radiofrequency catheter ablation by 40%,[50] its treatment reduces the risk of atrial fibrillation recurrence after catheter ablation.[51]

The higher occurrence of life-threatening ventricular arrhythmias among patients with OSA[52] was suggested to contribute to the abnormal circadian pattern of sudden death in these patients. Gami *et al.53,54* showed a peak in sudden death from cardiac causes during sleeping hours, namely, 10 PM to 6 AM in patients with OSA in contrast to the traditional window of cardiovascular vulnerability which is 6 and 11 AM.

The Busselton Health Study[55] as well as an 18-year follow-up of the Wisconsin Sleep Cohort[56] showed that sleep apnea is an independent risk factor for all-cause mortality. OSA severity, particularly an AHI ≥ 20 as well as the degree of nocturnal hypoxemia have been shown to be directly related to the risk of sudden cardiac death.[54]

Numerous studies linked OSA to an increased risk of myocardial infarction[57,

[58] which is likely related to the intermittent hypoxemia, systemic vasoconstriction, unpredicted increase in BP, and the resultant changes in intrathoracic and intramural pressures.[59, 60] A 7-year prospective study demonstrated that untreated OSA was associated with a 5-fold increase of coronary artery disease (CAD) independent of age, sex, BP, diabetes, or smoking.[61] It has also been suggested that increased oxygen demand and reduced oxygen supply following OSA may trigger an attack of angina pectoris in patients with CAD, who already have reduced coronary flow reserve.[62]

Finally, OSA also appears to be linked to an increased risk of stroke, independent of other cardiovascular risk factors.[63] Nocturnal fluctuations in BP, nocturnal hypoxemia, reductions in cerebral blood flow, and systemic vasoconstriction appear to contribute to the development of stroke.[64] Habitual snoring and excessive daytime somnolence may also contribute to the risk of developing wake-up stroke.[65]

PATHWAY FOR THE MANAGEMENT OF SLEEP APNEA IN THE CARDIAC PATIENT

Owing to the high incidence of sleep apnea in patients with cardiovascular disease and the increased morbidity and mortality associated with these conditions, we propose a Sleep Apnea Pathway (SAP, **Figure 20.1**) to correctly identify and triage these patients to the appropriate therapy.

Pathway for Management of Sleep Apnea in Cardiology

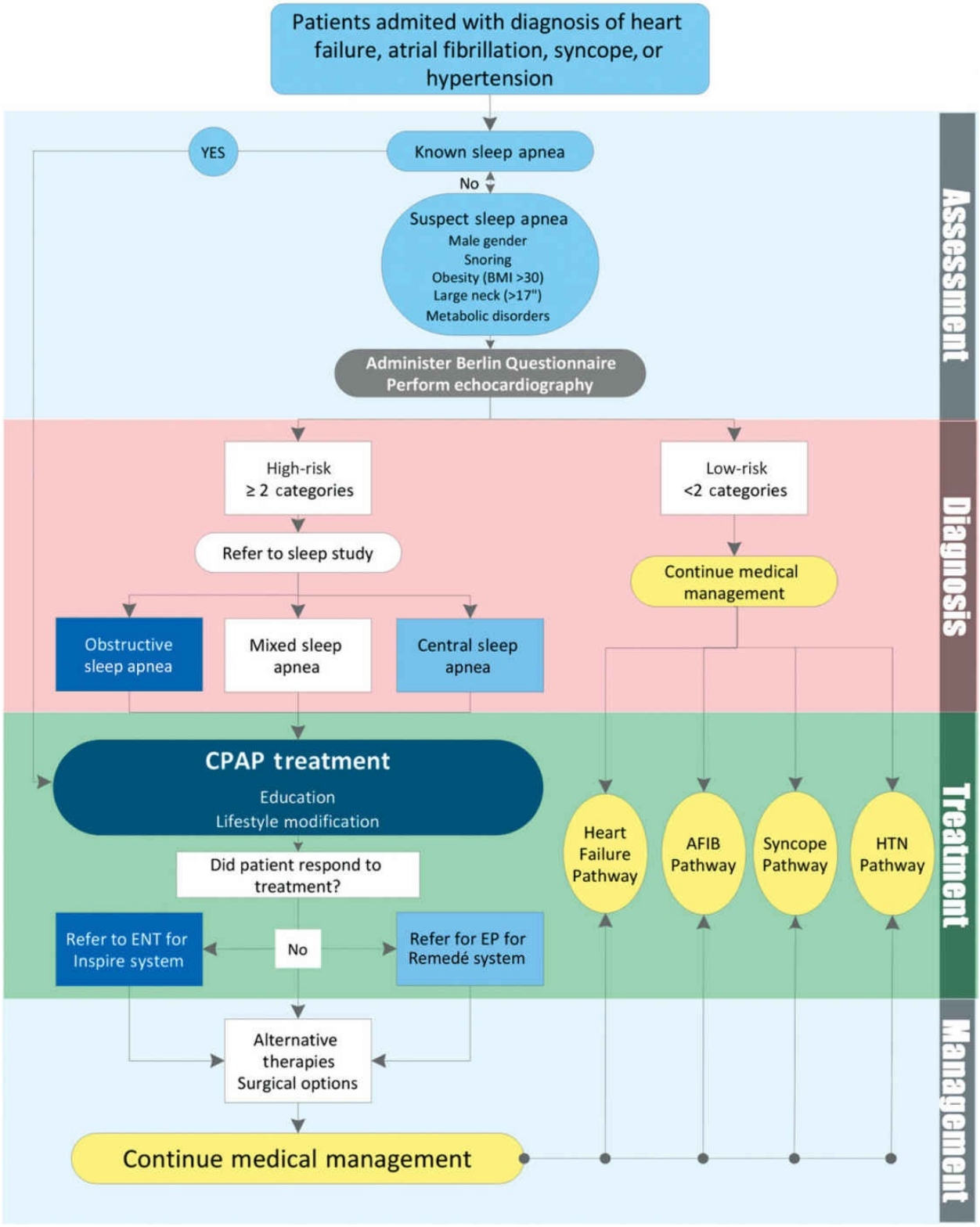

FIGURE 20.1 Pathway for the management of sleep apnea in cardiology. AFIB, atrial fibrillation; BMI, body mass index; CPAP, continuous positive airway pressure; ENT, ear-nose-throat; EP, electrophysiologist; HTN, hypertension.

STEP A: ASSESSMENT

All patients admitted with diagnosis of atrial fibrillation, syncope, hypertension, and HF should be evaluated for sleep apnea. Those patients with known sleep apnea diagnosis should be initiated on CPAP therapy according to their home setting. Those with suspected sleep apnea based on the following criteria, male gender, body mass index (BMI) > 30, snoring, neck circumference >17 inches, and metabolic disorders such as hyperlipidemia and insulin resistance will be screened by administrating the Berlin Questionnaire (BQ). We advise to perform an echocardiography as well on admission to evaluate heart function, pulmonary pressure, and any valvular disease.

STEP B: DIAGNOSIS

There are a number of tools available to screen for sleep apnea. These questionnaires are the BQ, the Epworth Sleepiness Scale (ESS), STOP, and STOP-Bang. These four questionnaires were compared in a cross-sectional study to determine effectiveness. The BQ, STOP, and STOP-Bang were shown to have the highest sensitivity, whereas the ESS was found to have higher specificity.[66] We have selected the BQ (**Figure 20.2**) as the screening tool for our SAP as it has shown better accuracy and is simpler to classify patients.[67] The BQ has also been shown to be predictive of those patients who are at higher risk for sleep apnea, limiting unnecessary PSG testing in patients who are lower risk and triaging them appropriately to medical management.[68] The BQ includes questions regarding snoring, daytime somnolence, hypertension, and BMI. The patient's family or bed partner is often used to confirm responses.[69]

Berlin Questionnaire

Sleep Evaluation in Primary Care

Please Complete the following:

height _____ age _____

weight _____ male/female _____

Category 1

1. Do you snore?

- ☐ yes
- ☐ no
- ☐ don't know

If you snore:

2. Your snoring is?

- ☐ slightly louder than breathing
- ☐ as loud as talking
- ☐ louder than talking
- ☐ very loud. Can be heard in adjacent rooms.

3. How often do you snore?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

4. Has your snoring ever bothered other people?

- ☐ yes
- ☐ no

5. Has anyone noticed that you quit breathing during your sleep?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

Category 2

6. How often do you feel tired or fatigued after your sleep?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

7. During your waketime, do you feel tired, fatigued or not up to par?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

8. Have you ever nodded off or fallen asleep while driving a vehicle?

- ☐ yes
- ☐ no

if yes, how often does it occur?

- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

Category 3

9. Do you have high blood pressure?

- ☐ yes
- ☐ no
- ☐ don't know

10. BMI > 30 (*See Chart*)

- ☐ yes
- ☐ no

Scoring Questions: Any answer within box outline is a positive response.

Scoring categories:

- ☐ Category 1 is positive with 2 or more positive responses to questions 1-5
- ☐ Category 2 is positive with 2 or more positive responses to questions 6-8
- ☐ Category 3 is positive with 1 positive responses to questions 9-10

Final Result: If 2 or more possible categories are positive, you have a high likelihood of sleep apnea.

Name _____

Address _____

_____

FIGURE 20.2 Berlin Questionnaire.

According to the BQ results, patients will be classified as high- and low-risk patients. High-risk patients are those who score positive in two or more categories, whereas low-risk patients only score positive in one category.

Patients who are deemed a high risk for sleep apnea achieve a score >2 on the BQ. These high-risk patients should then be referred for PSG testing. An AHI of 15 or an AHI of 5 or higher in conjunction with symptoms of daytime somnolence, unrefreshing sleep, waking up choking or gasping for breath, or bed partners confirming snoring or breathing interruptions during sleep warrants treatment. The test will classify patients as being pure OSA or CSA or a mixed picture. Regardless of the diagnosis, all patients should be considered for a treatment trial with CPAP therapy.

TREATMENT

Those patients who score <2 on the BQ are deemed low risk for sleep apnea. They should therefore be deferred to continue medical management of their comorbidities, such as atrial fibrillation,[70] hypertension,[71] syncope,[72] or HF,[73] according to our published pathways.

Although treatment with CPAP is the mainstay of treatment for sleep apnea, education and certain lifestyle modifications in concert with CPAP therapy have shown to be very effective.[74] Patient education program components are listed in **Table 20.1**. Behavioral treatment options include weight loss, exercise, positional therapy, and avoidance of alcohol and sedatives before bedtime; these have shown to decrease the upper airway muscle relaxation that occurs and can precipitate apnea episodes. Side sleeping has also been shown to decrease the upper airway collapse that occurs.[75] A study from Karolinksa Institute in Sweden showed that an average weight loss of 40 lb resulted in a 58% reduction in sleep apnea symptoms and decreased apnea episodes by 21/hour.[76]

TABLE 20.1 Components of Patient Education Programs

Findings of study, severity of disease
Pathophysiology of sleep apnea
Explanation of natural course and associated disorders
Risk factor identification, explanation of exacerbating factors, and risk factor modifications
Genetic testing when indicated
Treatment options
What to expect from treatment
Outline the patient's role in treatment, address concerns, and set goals

Consequences of untreated disease
Drowsy driving/sleepiness counseling

OSA treatment using CPAP has been shown to acutely decrease BP and nocturnal sympathetic tone. Several studies have shown that nocturnal CPAP can decrease daytime BP by approximately 2 mm Hg and seems to have the greatest effect in patients with uncontrolled hypertension and severe OSA.[77] Use of CPAP in sleep apnea has been shown to attenuate intrathoracic pressure changes and thus decrease preload, afterload, BP, and HR.[78, 79] Kaneko et al.[77] observed that 1 month after initiation of CPAP, the LV ejection fraction increased by 9% in patients with HF. Two observational studies have been performed comparing treated to untreated OSA patients; one study showed a 2-fold higher increase in mortality in the untreated group,[76] whereas the other showed a greater hospitalization-free survival in the treated group.

Treatment of CSA is more controversial; however, CPAP is still often employed to treat this condition. Multiple trials have been performed evaluating the role of CPAP in CSA. Canadian Positive Airway Pressure Trial for Patients With Congestive Heart Failure and Central Sleep Apnea (CANPAP) was a study that included 258 patients. Use of CPAP in this population reduced nocturnal desaturations and showed a modest improvement in LV ejection fraction.[81] However at 2 years, there were no significant differences in outcomes between the treated and untreated groups.

Mixed or complex sleep apnea exhibits signs of OSA; however, on initiation of CPAP therapy, central apneas persist or emerge.[80] Variable positive airway pressure (VPAP) is often used to treat mixed apnea.[82] VPAP normalizes breathing and suppresses CSA and Cheyne–Stokes respirations.

Failure of Continuous Positive Airway Pressure Therapy

If patients with OSA fail CPAP therapy, then we recommend referral to ear-nose-throat (ENT) specialists for consideration of implantation of the Inspire system (**Figure 20.3**). The Inspire system is an implantable device that senses breathing patterns and maintains airway patency during sleep by delivering stimulation to targeted airway muscles. The system consists of three implanted components including a small generator, breathing sensor lead, and stimulation lead, all controlled with the small handheld Inspire sleep remote. Patients who qualify for the Inspire system must have moderate-to-severe OSA (AHI 20 to 65, with <25% central apnea), be unable to use CPAP, and be free of complete concentric

collapse of the palate. Long-term study outcomes in patients using the Inspire system showed a 78% reduction in apnea–hypopnea events from baseline and an 80% reduction in oxygen desaturation levels.[83] In addition, patients had a clinically significant improvement in quality of life, including daytime somnolence that was measured by the ESS. Patients also showed a high adherence rate to therapy and significant improvement in important sleep-related quality-of-life outcome measures that are maintained across a 2-year follow-up period.[84, 85]

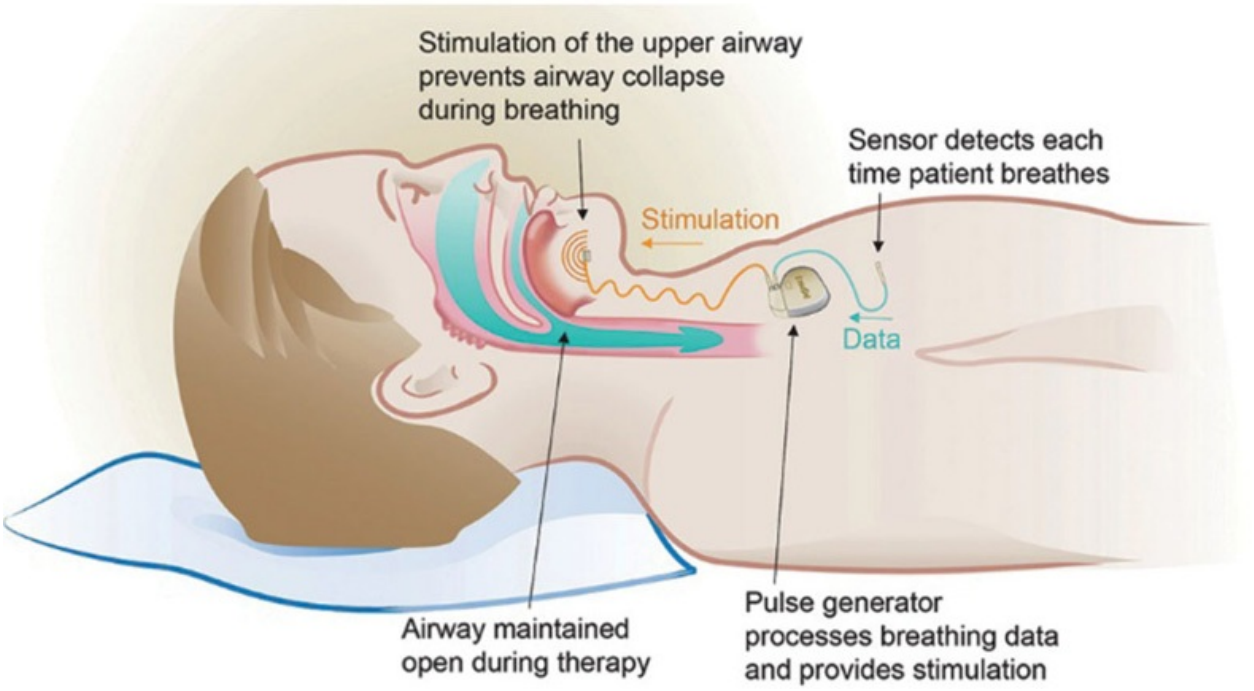

FIGURE 20.3 Inspire system.

Patients with CSA who fail CPAP therapy should be referred for consideration to the Remedé system. The system (**Figure 20.4**) is a phrenic nerve stimulator designed to restore the body's normal breathing pattern, which results in better oxygenation and less activation of the sympathetic nervous system. The settings of the device are monitored by the physician and can be changed remotely. Patients who are studied for indication of the Remedé system include those with AHI ≥ 20, Central Apnea Index (CAI) at least 50% of all apneas with at least 30 central apnea events, and Obstructive Apnea Index ≤ 20% of the total AHI. In the pilot study of the Remedé system, performed to evaluate outcomes at 3 and 6

months, CAI decreased by 84%, AHI decreased by 55%, Oxygen Desaturation Index improved by 52%, nocturnal arousals decreased by 35%, and REM by 29%.[86] Data published from the Remede–System Pivotal Trial Study Group showed that a significantly higher proportion of patients in the treatment versus control group achieved a ≥50% AHI reduction, and 91% 12-month freedom from serious adverse events related to the implant procedure, Remede–system, or delivered therapy.[87]

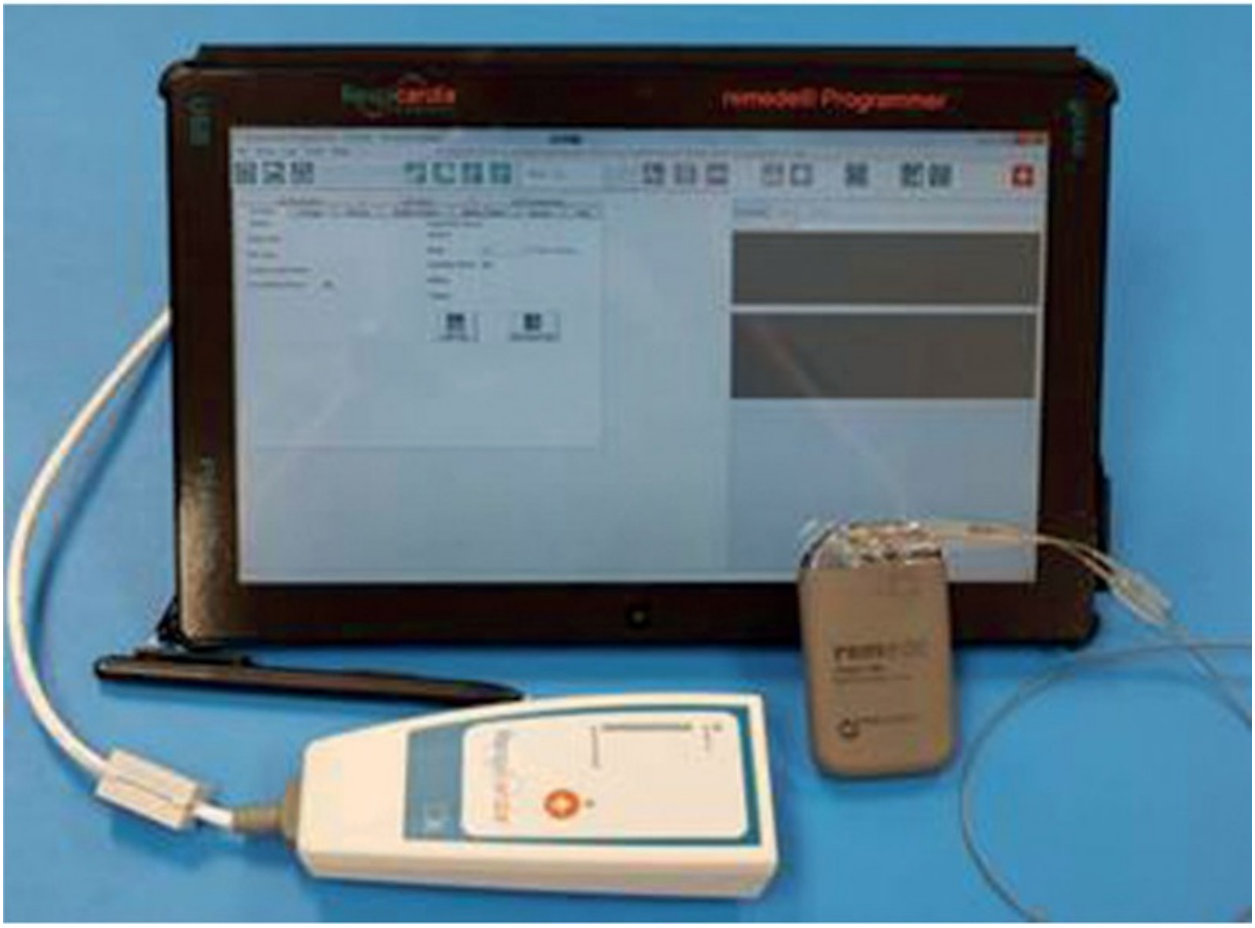

FIGURE 20.4 The Remedé system.

The findings of both the clinical trials of the Inspire system and the Remede–system indicate that by reducing AHI episodes and improving nocturnal oxygen levels, these novel devices may be helpful in reducing cardiovascular morbidity and mortality in those patients who fail CPAP therapy.

ALTERNATIVE AND SURGICAL TREATMENTS FOR THOSE WHO FAIL NOVEL THERAPIES

Oral Devices

There are currently over 100 FDA-approved dental devices that are available to patients to help relieve obstruction in sleep apnea.[88] These devices are designed to hold the lower jaw forward to prevent pharyngeal obstruction during sleep. This treatment is excellent for reducing snoring, although the effect on OSA is sometimes more limited. As a result, dental devices are best used for mild cases of OSA when relief of snoring is the main goal. Failure to tolerate and accept CPAP is another indication for dental devices. Although dental devices are not as effective as CPAP for OSA, some patients prefer a dental device to CPAP. Side effects of dental devices are generally minor, but may include changes to the bite with prolonged use.

Surgical Options

Surgery is an alternative therapy for patients who cannot tolerate or do not improve with nonsurgical treatments such as CPAP or oral devices. Surgery can also be used in combination with other nonsurgical treatments.

There are different types of surgical procedures that can be used in OSA to reshape structures or reposition bone and soft tissue.

1. Uvulopalatopharyngoplasty (UPPP) removes the uvula and excessive tissue in the throat, including the tonsils, if present, to help relieve upper airway obstruction. UPPP is the most common surgical procedure in OSA, but it has variable outcomes. The overall success rate is approximately 50%, with success defined as a 50% reduction in AHI and a post-surgical AHI reduction to less than 20 events/hour.[89] New UPPP variants have been showing more promise in improving OSA outcomes in ongoing clinical trials.
2. Other procedures, such as maxillomandibular advancement (MMA) and tracheotomy,[90] address both the upper and lower pharyngeal airway more globally. These two procedures have been shown to have high success rates and improved PSG outcomes. MMA may have a higher success rate, particularly in people with an abnormal jaw, but it is the most complicated procedure and is typically reserved for patients with severe OSA who have

failed prior targeted surgical attempts.[91] In a meta-analysis that included 627 patients undergoing MMA, the overall success rate, which was defined as an AHI <20 events/hour and reduced by at least 50%, was 86%. Cure of OSA, which was defined as an AHI less than five events per hour was achieved in 43% of patients.[92]

All surgical treatments require discussions about the goals of treatment, the expected outcomes, and potential complications.

SUMMARY

Sleep-disordered breathing is a highly prevalent medical condition, particularly in cardiac patients. Utilizing a system evidence-based pathway can identify patients who require treatment and direct them to the appropriate management plan.

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Patient and Family Information for: THE MANAGEMENT OF SLEEP APNEA IN THE CARDIAC PATIENT

Sleep apnea is a very common medical condition that affects 60 million Americans. There are different types of sleep apnea, the most common being obstructive sleep apnea or OSA. OSA is caused by collapse of the upper airway during sleep, leading to obstruction of breathing. Symptoms that suggest that one might have sleep apnea are excessive sleepiness during the day, waking up with headaches, insomnia, and frequent nighttime awakenings. Bed partners may also confirm that there is excessive snoring or periodic episodes of stopping breathing at night. CSA results in a lack of breathing during sleep caused by disrupted signals from the brain to initiate breathing.

Factors that may predispose patients to develop sleep apnea are male gender, obesity, and having a small mouth and throat. Sleep apnea also becomes more common as people age. Sleep apnea is common in patients with high blood pressure (BP), stroke, heart failure (HF), and atrial fibrillation. Undiagnosed and untreated sleep apnea in patients with any of these conditions can result in adverse outcomes. If a physician suspects sleep apnea based on known cardiovascular conditions and the presence of the risk factors previously stated, he may administer the Berlin Questionnaire (BQ) to determine the risk of having sleep apnea.

The BQ is a three-part questionnaire. Section one has five questions that address snoring habits. A bed partner may also be asked to help answer the questions. Section two addresses symptoms of daytime sleepiness. Section three has a question regarding the presence of high BP. The patient will also score a point if he/she is obese and has a BMI of 30 or higher. On the basis of the score, the physician might order a sleep study, also known as PSG testing.

The diagnosis of sleep apnea is confirmed by PSG testing. This is based on how many times per hour the patient stops breathing during the test. If diagnosed with sleep apnea, the physician will likely recommend CPAP for usage at nighttime in conjunction with lifestyle modifications, such as losing weight and avoiding alcohol and sedating medications before sleep. CPAP is a noninvasive method of providing oxygen while asleep. The oxygen is delivered by a face or nasal mask to keep the nasal passages open and to prevent collapse of the airway. Some oral dental devices are also available; however, they are not effective for every patient with sleep apnea.

If the attempt to use CPAP for sleep apnea does not work, there are new and emerging therapies that can be tried depending on the type of sleep apnea the patient has. The Inspire system is a new technology for patients with OSA who fail CPAP therapy. An implanted system, it delivers mild stimulation to important airway muscles to help keep the airway open during sleep. The device is controlled by a small, handheld remote. Patients with central sleep apnea who fail CPAP therapy can be referred for a Remedé system. The Remedé device is placed by a cardiologist in the electrophysiology laboratory. This is a minimally invasive procedure by which the device is placed under the skin and delivers impulses to the muscles that control breathing.

Surgery is also an option for patients who have severe OSA or do not respond or qualify for the abovementioned treatments. UPPP is the most common surgery for OSA and involves removing and repositioning the soft tissues in the throat to help relieve the obstruction that occurs during sleep. These surgeries have been shown to be very effective for some patients in resolving symptoms of sleep apnea. However, it is important that the patient discusses the treatment goals and concerns with the physician to decide what the best treatment option for sleep apnea is.

III

ARRHYTHMIA IN THE CCU

21

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Bradycardia and Heart Block

Normal heart rate (HR) is considered to range from 60 to 100 beats per minute (bpm). Therefore, bradycardia refers to an HR of 60 bpm or less. Bradycardia may be associated with symptoms such as weakness, fatigue, syncope or near-syncope, dizziness, shortness of breath with exercise, confusion, and symptoms of heart failure. On occasion, however, bradycardia may be asymptomatic. This occurs especially in otherwise healthy, young, athletic subjects and is usually responsive to exercise. Asymptomatic bradycardia can also happen during sleep secondary to reduced sympathetic and increased parasympathetic tone. These types of asymptomatic, physiologic bradycardias almost never warrant aggressive interventions. However, bradycardia due to extremely slow sinus rate or secondary to conduction block is usually pathologic even in the absence of symptoms because it carries a risk for further adverse cardiovascular outcomes.

The management of bradycardia is dependent on the symptom severity and the reversibility of the cause. A stable patient may be observed while being evaluated, but the unstable patient usually requires treatment with positive chronotropic drugs or temporary pacing until a more permanent solution can be employed.

ANATOMIC CONSIDERATION – SINOATRIAL NODE

Anatomically, the sinoartrial node (SAN) lies in the proximity to the junction of

the superior vena cava and the sulcus terminalis, at the high lateral border of the right atrium (RA). Blood supply derives from the SAN branch of the right coronary artery (RCA) in 60% and left circumflex coronary artery (lCx) in 40% of the population. Collateral blood supply is common, which explains the rarity of sinus node infarction.[1] The SAN is densely innervated by both the sympathetic and the parasympathetic (vagus nerve) nervous system. Conduction down to the atria and atrioventricular node (AVN) is through preferential pathways that help in uniform and synchronous activation of the atrial muscle and timely transfer of the generated impulse to the AVN. The main pathways include the anterior internodal tract from which the Bachman bundle separates and courses through the roof of the atria toward the left atrium (LA). The posterior internodal tract ("slow pathway") and the middle internodal tract also preferentially transmit SAN impulses to the AVN.

The AVN is located at the apex of the triangle of Koch in the inferomedial part of the RA and is located anterior and superior to the coronary sinus ostium. It derives its blood supply from a branch of the RCA (in 90% of the population) or the lCx artery. The bundle of His (HB) connects the distal part of the AVN with the bundle branches. It crosses the membranous interventricular septum to the left side and divides into the right bundle branch (RBB) and the left bundle branch (LBB). Blood supply to the HB is dual, both from the left anterior descending (LAD) coronary artery and posterior descending coronary artery. The RBB and the left anterior fascicle branch of the LBB are supplied mainly by septal branches of the LAD coronary artery. The left posterior fascicle, on the other hand, has dual blood supply, both from the LAD and the RCA.

SINUS RHYTHM

When the SAN is the dominant pacemaker of the heart, the sinus rhythm is present. It is characterized by a P wave that is positive (upright) in the inferior leads, and biphasic in lead V1 (first positive deflection from RA activation is followed by a negative deflection from LA activation). The P wave is negative in lead aVR. Leads V2–6 show positive P waves. The duration of the P wave is generally 120 ms (three small boxes) and its amplitude is <0.25 mV (2.5 small boxes). Larger values may indicate atrial pathology (enlargement) or conduction delay in the atria. The consecutive P waves are identical in morphology and the PR intervals are stable from beat to beat. The SAN has an intrinsic automaticity,

but the rate of impulse generation is controlled by the autonomic nervous system. Sympathetic stimulation increases, whereas parasympathetic (vagal) stimulation decreases the SAN firing rate.

SINUS ARRHYTHMIA

Sinus arrhythmia is defined as an irregular sinus rhythm (P-P variation >120 ms), with normal-looking P waves. It is very common and considered to be normal. Differential diagnosis of irregular sinus rate includes wandering atrial pacemaker or frequent premature atrial contractions, both with different P-wave morphologies. Respiratory sinus arrhythmia is the most common type and is related to alteration in the autonomic tone with respiration. Inspiration and expansion of the lung tissue inhibits the parasympathetic tone, thus increasing the sinus rate. This type is usually benign, very common in young individuals but may be associated with obesity and hypertension. In contrast, the effects of respiration on the sinus rate diminish with age and in patients with diabetic neuropathy. Nonrespiratory sinus arrhythmia may be seen in a normal or diseased heart, or may be associated with medications (such as digitalis). Ventriculophasic sinus arrhythmia is typically seen in patients with complete or second-degree heart block. P-P intervals that contain a QRS are shorter in comparison to the following P-P intervals that do not contain a QRS. The mechanism is probably related to increase in stroke volume, which triggers a baroreceptor response and results in widened P-P interval in the following beat.

SINUS NODE DYSFUNCTION

Sinus node dysfunction (SND) is an intrinsic disease of the sinus node and its presentations include the following:

1. Sinus bradycardia (SB), including sinoatrial exit block and sinus pauses
2. Tachycardia-bradycardia syndrome
3. Conversion pauses following termination of atrial arrhythmia
4. Chronotropic incompetence

SB is defined as sinus rate (with normal-appearing P waves) of less than 60

bpm (**Figure 21.1A**. The major causes of SB are depicted in **Table 21.1**. SB may be caused by intrinsic disease of the sinus node or by extrinsic causes, such as medications and metabolic and hormonal changes (see subsequent text).

TABLE 21.1 Major Causes of Sinus Bradycardia

INTRINSIC	EXTRINSIC
Idiopathic degeneration (aging)	Autonomical mediated
Ischemia	Neurocardiogenic syncope
Rheumatic fever	Carotid sinus hypersensitivity
Pericarditis	β-Adrenergic blockers
Infiltrative disease	Calcium channel antagonists
Sarcoidosis	Clonidine
Amyloidosis	Digoxin
	Antiarrhythmic agents
Systemic lupus erythematosus	Parasympathetic agents—pyridostigmine, donepezil
Rheumatoid arthritis	Sympatholytic agents—methyldopa, clonidine
Scleroderma	I_f blockers—ivabradine
Myotonic dystrophy	Lithium
Surgical trauma during cardiac surgery	Hepatitis C drugs—sofosbuvir, daclatasavir
Familial disease	Hypothyroidism
Infectious disease	Hypothermia
Chagas disease	Neurologic disorder
Infectious endocarditis	
Lyme disease	Hypokalemia Hyperkalemia Hypoxia Intracranial hypertension

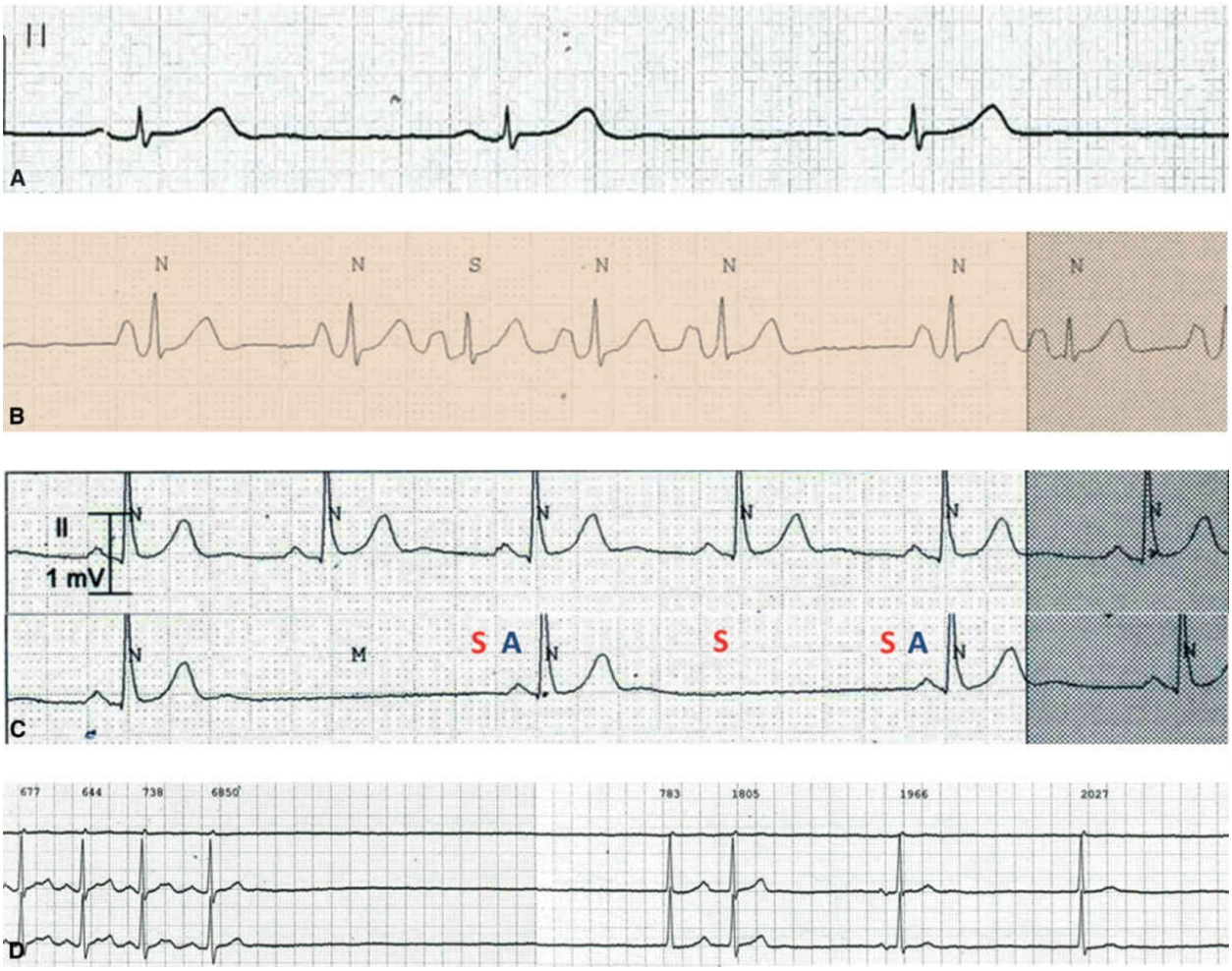

FIGURE 21.1 Sinus node dysfunction. A, Sinus bradycardia of 35 bpm in a young, trained, asymptomatic male. B, Second-degree sinoatrial block, type I (Wenckebach). Note a slight P-P interval prolongation. The pause duration is less than the two preceding P-P intervals. C, Second-degree type II sinoatrial block. The pause duration is exactly twice the regular P-P interval. *S* denotes the expected sinus activity and *A* denotes the atrial activity. D, Conversion pause due to prolonged sinus node recovery time shown in a Holter monitor of a woman with recurrent syncope. Following termination of atrial flutter, a prolonged pause of 6.85 seconds is seen with no P waves, and the first escape beat has no proceeding P wave. Therefore, it is a junctional escape beat.

ETIOLOGY OF SINUS BRADYCARDIA

Increased vagal tone—chronic increase in the parasympathetic tone is typical in trained athletes and during sleep (**Figure 21.1A**). Episodic increase in the vagal tone may occur during vasovagal response. Typically, conduction slowness (prolonged PR interval) and peripheral vascular dilatation also exists in addition to other vagal symptoms (pallor, diaphoresis, nausea), sometimes leading to hypoperfusion of the central nervous system and resultant brief episodes of loss of consciousness. Vagal tone may also be increased by the Valsalva manuever,

applying pressure on the carotid body or globe, cough, and acute myocardial infarction (MI), especially of the inferior wall (also known as the Bezold–Jarisch reflex).

Obstructive sleep apnea may also result in SB and pauses during apneic episodes. A large number of *medications* may cause SB, including sympathetic blockers (beta-blockers, methyldopa, clonidine), parasympathetic agents (digoxin, cholinomimetics), calcium channel antagonists, and antiarrhythmic drugs. Recently, the direct pacemaker-current (*If*) blocker, ivabradine, has been introduced for the treatment of heart failure and inappropriate sinus tachycardia. This medication may also cause SB.

Metabolic derangements that are associated with SB include hypothyroidism and myxedema coma, hypothermia, hypoxia, and hypokalemia. Common *infectious agents* associated with relative SB include *Legionella*, *Salmonella*, and *Trypanosoma cruzi* causing Chagas disease.

SINUS BRADYCARDIA OR PAUSE, SINUS ARREST, AND SINOATRIAL EXIT BLOCK

Sinus pause or arrest results from failure of sinus node impulse generation. It may occur because of intrinsic disease of the SAN, drugs that depress the SAN activity (beta-blockers, anti-arrhythmic drugs) or from increased vagal tone. Sinoatrial exit block occurs because of the failure to conduct the impulse generated by the SAN to the surrounding atrial tissue. On the surface electrocardiogram (ECG), it is manifested as a pause due to the absence of an expected P wave. The P-P cycle is longer than the P-P interval of the underlying sinus rhythm, but it is always less than two consecutive P-P intervals.

Sinoatrial Exit Block

This arrhythmia results from failure of the impulse generated in the sinus node to depolarize the surrounding atrial tissue. It is usually transient. It can occur because of ischemia or myocarditis, or secondary to medications and excessive vagal tone. With first-degree SA exit block, each SAN impulse is conducted to the atria with a delay. This cannot be diagnosed with surface ECG. **Figure 21.1B** shows an example of second-degree SA exit block of Wenckebach type (Mobitz I). The P-P interval slightly prolongs until a pause occurs. The pause is not a multiplication of the regular P-P interval and its duration is less than the two preceding P-P intervals. An escape from a lower pacemaker (i.e. from the AVN)

is often seen, and may result in retrograde conducting P waves with superior axis (negative P waves in II, III, and aVF). In **Figure 21.1C,** expected SAN activity is marked in S, whereas the atrial activity (the P wave) is marked in A. The pause seen is an exact multiplication of the P-P intervals; this is an example of type II second degree SA block.

Conversion Pauses

Following termination of an atrial arrhythmia, the diseased sinus may recover only after a pause (**Figure 21.1D**). Many times the atrial arrhythmia itself is asymptomatic, but the conversion pause can result in prolonged asystole and resultant syncope. Permanent pacemaker placement will eliminate the pauses and enable safe medical treatment for the atrial tachyarrhythmia.

TREATMENT

The treatment of SND depends mainly on symptoms. Asymptomatic SB is common and usually requires no therapy.[2] Symptomatic SND of any type may result in weakness, effort dyspnea, heart failure, and syncope. Here, permanent pacing is required. As a general rule, no oral medication can reliably increase the sinus rate. However, theophylline, a methyl xanthine which is also a phosphodiesterase inhibitor, may increase the sinus rate. It can be tried in patients with contraindications for pacing.[3]

ATRIOVENTRICULAR BLOCK

Atrioventricular block (AVB) is defined as a delay or interruption of impulse conduction from the atria to the ventricles. The conduction disturbance can be transient or permanent. Conduction may be delayed, intermittent, or absent (with or without a lower escape rhythm). The commonly used terminology includes the following:

First-degree AVB—slowed conduction without loss of AV synchrony, manifest in the surface ECG with prolonged PR interval, greater than 200 ms (**Figure 21.2A**). The conduction delay is usually at the level of the AVN. Normally, the PR will shorten during exercise test (due to physiologic shortening of the AV nodal refractory period) and a 1:1 conduction will be seen throughout the exercise despite increased sinus rate. Although no treatment is needed in most of the cases, caution should be taken with administration of negative chronotropic and nodal blocking agents (i.e. beta-blockers, calcium channel

antagonists, and anti-arrhythmic drugs).

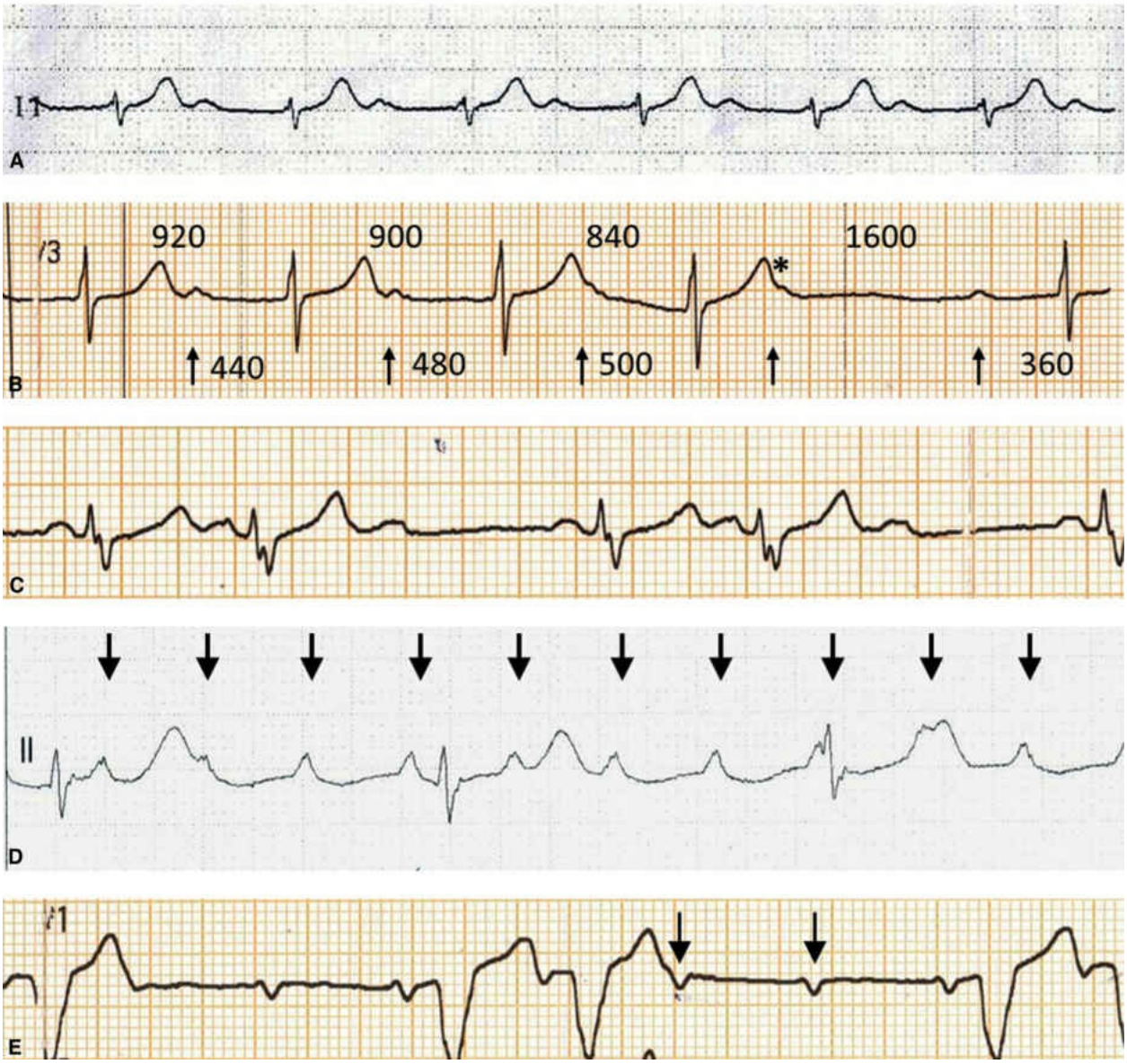

FIGURE 21.2 Types of AV conduction abnormalities.A, First-degree AV block with prolongation of the PR up to 440 ms in an asymptomatic man. B, Second-degree AV block, Mobitz type I (Wenckebach). Progressive PR prolongation is seen (P waves marked with an arrow and the values of the PR are given next to the arrows). Note the decrease in the ΔPR, resulting in a decrease in the RR intervals (denotes above the strip). Following a nonconducting P wave (*), PR shortening is seen and the pause is less than twice the preceding RR. The QRS is narrow, and the conduction delay is most probably at the level of the AV node. C, Second-degree AV block, Mobitz type II. Every third P wave is a block. The PR is fixed. The QRS is wide and the PR is normal (160 ms). The conduction delay is most probably below the level of the AV node. D, Complete AV block with no relationship between the P waves (arrows) and the QRS complexes. E, Advanced AV block with two consecutive blocked P wave (arrows). AV, atrioventricular.

Second-degree AVB—intermittent loss of AV conduction, often in a regular pattern (e.g. 2:1, 3:2, or higher degrees of block).

- In second-degree AVB type I (referred to as Wenckebach type), the PR interval progressively prolongs from beat to beat until AVBs occur and result in a dropped beat, which means failure of conduction of an SAN-generated impulse from the atria down to the ventricles. The PR interval following the pause returns to its baseline value and the sequence starts again. **Figure 21.2B** shows a typical example. The top numbers represent the R-R interval, whereas the bottom numbers represent the PR interval. The PR interval in the last conducted beat was 500 ms, and it was shortened to 360 ms after the blocked sinus beat. The pause following the blocked P wave (marked with an asterisk) is shorter than twice the preceding R-R. The QRS is usually narrow unless the underlying bundle branch block (BBB) is chronically present. The conduction delay is usually at the level of the AVN. Unless symptomatic, with a clear correlation between the ECG finding and the symptoms, this type of conduction abnormalities do not require therapy.
- Second-degree type II block (Mobitz II) is characterized in the surface ECG by a fixed PR interval before and after the blocked sinus beat (**Figure 21.2C**). The QRS is often wide. The conduction block is almost always below the level of the AVN. This type of AVB is usually permanent and often progresses to higher degree or even complete heart block. Implantation of a permanent pacemaker is required, regardless of symptoms.

Third-degree or complete AVB (CAVB)—no conduction is seen from the atria to the ventricles (**Figure 21.2D**). Lower escape rhythm may be seen. The higher the anatomic level of the conduction block, the faster and more stable the escape rhythm. AVB at the level of the AVN will usually give rise to a relatively fast escape rhythm of 40 to 60 bpm with a narrow QRS (unless BBB is chronically present). Lower anatomic level of the block, located at the His-Purkinje bundles, will result in a slow (<40 bpm) escape rhythm, often unstable with a wide QRS complex. As a general rule, the more distal the block, the slower will be the escape pacemaker. Low pacemakers have a rate of 40 bpm or less and are often unreliable, resulting in a very slow rate or asystole and often hemodynamic instability.

AVB should not be confused with other types of AV dissociation, in which there is no conduction from the atria to the ventricle due to other reasons, such as slowing of the sinus and accelerated nodal escape rhythm.

The term *advanced AVB* is referred to as two or more consecutive blocked sinus beats (**Figure 21.2E**).

The causes of AVB are depicted in **Table 21.2**. The main etiologies are discussed here in detail.

TABLE 21.2 Major Causes of Atrioventricular Block

PHYSIOLOGIC AND PATHOPHYSIOLOGIC	IATROGENIC
Increased vagal tone	
Fibrosis and sclerosis of the conduction system	Medications
Ischemic heart disease	β-Blockers, calcium channel antagonists, digitalis, antiarrhythmic medications
Cardiomyopathy and myocarditis	Cardiac surgery
Congenital heart disease	TAVI or closure of septal defects
Familial forms of AV block	Alcohol septal ablation for hypertrophic obstructive cardiomyopathy
Other	
Hyperkalemia, infiltrative malignancies and benign tumor, neonatal lupus syndrome, hypothyroidism, trauma, neuromascular diseases	

AV, atrioventricular; TAVI, transcatheter aortic valve implantation.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC ATRIOVENTRICULAR BLOCK

Increased vagal tone—enhanced vagal tone can normally occur during sleep, in athletes, and as a result of various vagal triggers such as pain, cough, carotid sinus massage, or carotid sinus hypersensitivity. All of these can result in AVB from Mobitz I to even complete AVB.[4] Typically, increased vagal tone results in SB in addition to the conduction abnormality and the QRS is narrow unless BBB is chronically present (**Figure 21.3**).

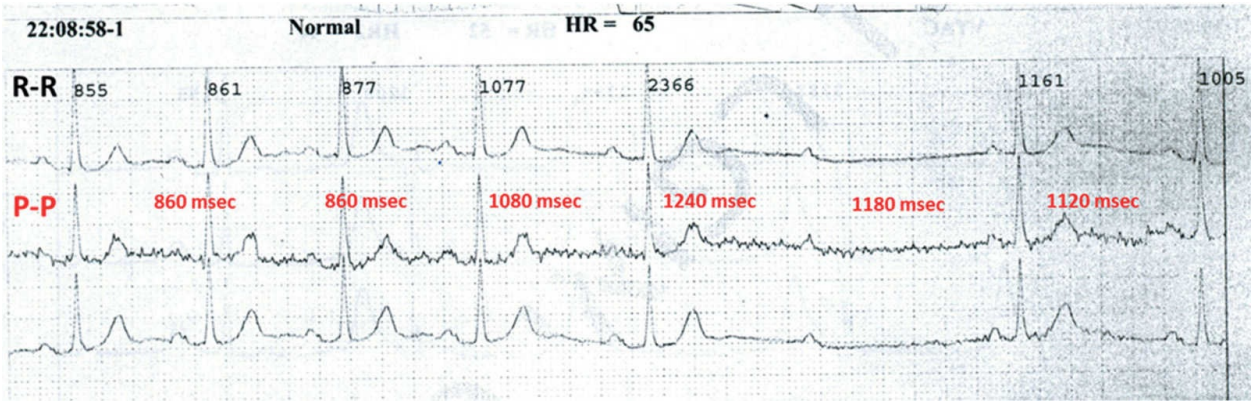

FIGURE 21.3 Vagal AV block. The top numbers (in black) denote the R-R intervals. The numbers in the middle (in red) denote the P-P intervals. Gradual prolongation of the P-P interval is present in addition to

the AV block. The patient was asleep during the recording. AV, atrioventricular; HR, heart rate.

IDIOPATHIC PROGRESSIVE CARDIAC CONDUCTION DISEASE

Fibrosis and sclerosis of the conduction system accounts for about one-half of cases of AVB. Progressive cardiac conduction defects, referred to as Lenegre or Lev disease, are characterized by progressive impairment of the conduction system:

- The term *Lenegre disease* has been traditionally used to describe a progressive, fibrotic disease of the conduction system in younger individuals. It is frequently associated with slow progression to complete heart block and may be hereditary.
- Lev disease refers to sclerosis of the left side of the heart in older patients. Common associated findings include aortic and mitral valve calcifications. Fibrosis of the mitral ring and central fibrous body is common in elderly patients and result in congenital atrioventricular block with a narrow QRS complex. Aortic valve calcifications are commonly associated with fibrosis of the HB and bundle branches. Thus, the QRS complex is usually wide.

ISCHEMIC HEART DISEASE

Both acute and chronic ischemia may result in any degree of AVB. Recognition of the blood supply of the conduction system is important for understanding the mechanism of AVB during ischemia (see the section “Anatomic Consideration”). Up to 20% of patients with acute MI develop conduction abnormalities, but most of these abnormalities are transient.[5] Inferior MI may cause a heightened vagal tone that results in an AVB at the level of the AVN. Prolonged PR, Wenckebach type, and CAVB may be seen, almost always transient and respond to intravenous (IV) atropine. The escape rhythm is of narrow QRS with a rate of 40 to 60 bpm, and thus usually the patients are asymptomatic. In contrast, anterior MI may cause ischemia of the septum, resulting in a slower escape rhythm (<40 bpm) with wider QRS. It is usually seen with an extensive MI due to occlusion of the proximal LAD, and therefore the prognosis is poor. Temporary pacing is often needed.

CARDIOMYOPATHY AND MYOCARDITIS

AVB can be seen in patients with cardiomyopathies, most commonly with infiltrative processes such as amyloidosis and sarcoidosis, and in patients with

myocarditis due to a variety of causes including rheumatic fever, Lyme disease, diphtheria, viruses, systemic lupus erythematosus (SLE), toxoplasmosis, bacterial endocarditis, and syphilis. The development of AVB in myocarditis is often a poor prognostic sign.

CONGENITAL HEART DISEASE

Congenital complete heart block may be an isolated lesion or may be associated with other types of congenital heart disease. When isolated, it results from transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antibodies in women with SLE. Treatment is indicated mainly in symptomatic patients.

FAMILIAL DISEASE

Familial AV conduction block, characterized by a progression in the degree of block in association with a variable apparent site of block, may be transmitted as an autosomal dominant trait. Genetic mutation may be observed, usually in the *SCN5A* gene, encoding the fast sodium channel. Presentation can occur at any age, but progression of the conduction abnormalities with aging is seen. When presenting at an older age, it is often called hereditary Lenegre disease. It has been proposed that heterozigosity combined with aging leads to a progressive decline in conduction.

AV conduction disturbance can also appear in the setting of inherited arrhythmic syndromes (long QT syndrome type 3, Brugada). In these conditions, ventricular arrhythmias are not uncommon and may result in sudden cardiac death. Therefore, an implantable cardioverter-defibrillator rather than a pacemaker may be required.

MUSCULAR DYSTROPHIES

Muscular dystrophies are often associated with conduction abnormalities. The major syndromes include myotonic dystrophy and Emery–Dreyfuss muscular dystrophy. Muscular symptoms are often easily noticed and aid in diagnosis.

ELECTROLYTE DISTURBANCE

Most commonly seen with hyper- and hypokalemia, the QRS is wide and the treatment is focused on correcting the potassium level. One should keep in mind that primary bradycardia may result in hypotension, acute renal failure, and

hyperkalemia, which exacerbates the conduction abnormality. In this setting, pacing is indicated.

IATROGENIC

Cardiac surgery may result in AVB, in particular replacement of calcified aortic and mitral valve and/or closure of ventricular septal defects. CAVB is seen in 5% to 20% of patients undergoing transcatheter aortic valve replacement, especially in patients with prior conduction abnormalities such as right BBB. Alcohol septal ablation for the treatment of hypertrophic obstructive cardiomyopathy is complicated with CAVB in 10% of the cases. AVB might happen during or following catheter ablation of certain arrhythmias, most commonly ablation of AV nodal reentrant tachycardia and focal tachycardias or ablation of accessory pathways located in the septal region. However, the frequency of this complication is low.

MEDICATIONS

A variety of drugs can impair AV conduction, occasionally resulting in AVB. Examples include β-blockers, digitalis, calcium channel antagonists (especially verapamil and, to a lesser extent, diltiazem), amiodarone, and adenosine. The block is usually in the AVN and may be reversible with discontinuation of the drug. In comparison, antiarrhythmic drugs that modulate the sodium channel, such as quinidine, procainamide, flecainide, propafenone, amiodarone, and sotalol can produce block in the more distal His-Purkinje system. Some of these medications (i.e. amiodarone and sotalol) exhibit significant beta-blockade activity and may cause a conduction delay at any level.

Most patients with AVB who are taking drugs that can impair conduction probably have underlying conduction system disease. This was suggested by a study of 169 patients with second- or third-degree AVB associated with medication. Drug discontinuation resulted in resolution of the AVB in 40% of the patients, but half of them recurred even after discontinuation of the drug.[6]

ATRIOVENTRICULAR DISSOCIATION

With AV dissociation, independent activation of the atria and ventricles is seen as a result of absent conduction through the AVN. There is no fixed relationship between the P waves and the QRS complexes, and the PR intervals are variable in a random manner. Assessment of the jugular venous waveform can disclose

"cannon" A waves, indicative of contraction of the RA against the closed tricuspid valve. Several conditions may result in AV dissociation (**Figure 21.4**):

FIGURE 21.4 Atrioventricular dissociation. A, Sinus bradycardia with junctional escape. The sinus and the junctional escape rate are similar. The first P wave conducts to the ventricle, whereas the second and the last P waves do not conduct (the PR interval is too short). The last P wave is buried in the QRS. The third P wave probably does conduct because the PR is normal and the R-R is shorter in comparison to other R-R in the strip. B, Accelerated idioventricular rhythm (AIVR) during reperfusion of an occluded coronary artery. Some P waves are marked with an arrow. C, AV dissociation due to complete AV block. N mark the QRS signal. All R-R intervals are equal, despite alternating relationship between the P wave and the R wave. D, AV dissociation due to ventricular tachycardia (VT). The QRS is relatively narrow because the VT's exit is near the septum. Arrow denotes the dissociated P waves.

- Slowing of the SAN with an escape junctional or ventricular rhythm without retrograde conduction to the AVN may result in AV dissociation. The junctional or ventricular rate is isorhythmic or faster than the sinus rate; thus, the interval between the QRS complexes is similar to or shorter than the PP interval. With isorhythmic AV dissociation, the PR may seem to be very short or the P waves may be buried within the QRS complex and therefore not seen (**Figure 21.4A**). As seen in the figure, the first P wave conducts, whereas the

second and the last P waves do not conduct to the ventricle (the PR interval is too short).

- Acceleration or enhanced automaticity of lower or subsidiary pacemakers, such as an accelerated junctional or ventricular rhythm, or with a ventricular tachycardia, and rarely with a junctional tachycardia, may cause AV dissociation. There is a retrograde block of impulse conduction through the AVN (no ventriculoatrial conduction); thus, there is no atrial activation and the sinus node is not suppressed. The RR interval is shorter than the PP interval. Accelerated idioventricular rhythm (AIVR) is a ventricular rhythm typically seen during reperfusion of cardiac ischemia (typically seen with thrombolysis in the setting of ST-elevation myocardial infarction) (**Figure 21.4B**).
- AVB, type II or III can result in AV dissociation (**Figure 21.4C**).
- Ventricular tachycardia with retrograde ventriculoatrial block (**Figure 21.4D**).

TREATMENT

The degree of the block and the presence or absence of reversible causes determines the treatment. First-degree and second-degree AVB of Wenckebach type usually requires no treatment. For advanced AVB with no reversible cause (second-degree Mobitz II and complete AVB), permanent pacemaker implantation is indicated regardless of symptoms.[7] An exception to that is asymptomatic congenital AVB. These patients usually have a reasonable inotropic response of the escape rhythm on one hand, and high rate of complications if a permanent pacemaker is implanted at a young age.

MANAGEMENT OF BRADYCARDIA AND HEART BLOCK

Initial assessment should focus on the stability of the patient, including symptoms of bradycardia (see preceding text) and hemodynamic status. **Figure 21.5** depicts the 2015 Advanced Cardiac Life Support (ACLS) bradycardia algorithm. A major modification in this algorithm, which was initially introduced in 2010, is to define the HR for intervention to less than 50 bpm (instead of the previously used formal definition of less than 60 bpm). One should keep in mind that while slow HR of 50 to 60 bpm usually will not cause symptoms and, in fact, may be physiologic, it may be inadequate for certain patients with other comorbidities (such as anemia, sepsis, heart failure). In these cases, holding

medications that may lower the HR and increasing HR with anticholinergics or sympathomimetics may be indicated.

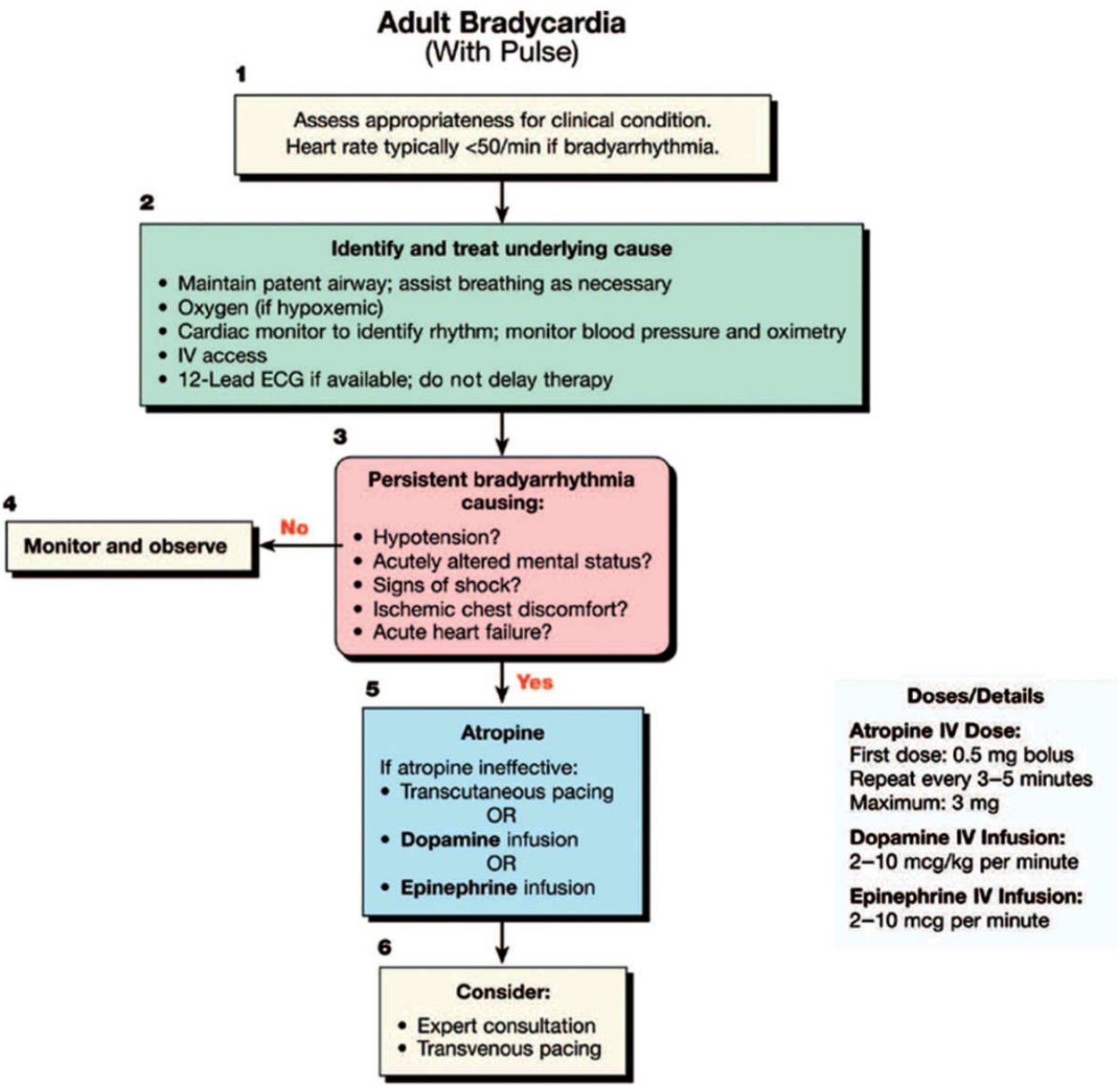

FIGURE 21.5 ACLS adult bradycardia algorithm. ACLS, Advanced Cardiac Life Support; ECG, electrocardiogram; IV, intravenous. (Reproduced from 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care.)

Mean blood pressure will often be relatively conserved because of compensatory vasoconstriction. Owing to increased stroke volume and prolonged diastolic time, systolic blood pressure increases while the diastolic blood pressure decreases, resulting in widened pulse pressure. The increased systolic pressure usually requires no treatment. Other patients may have signs and symptoms of hemodynamic compromise such as shock, orthostatic symptoms, oliguria, and confusion. Heart failure symptoms (shortness of breath,

orthopnea, and edema) and signs of congestion may appear. Unstable patients should be treated immediately regardless of the diagnosis (SB or AVB). Therapeutic options may include atropine (IV push of 0.5 to 1 mg), sympathomimetics (dopamine or epinephrine infusion), and temporary pacing (**Table 21.3**). However, caution should be exercised if atropine or sympathomimetics are given to a patient with infra-hisian AVB because these medications can increase the sinus rate and aggravate the degree of the block. Patients with asymptomatic bradycardia should be followed up without any immediate intervention. Reversible causes should be sought while a decision regarding placement of a temporary or permanent pacemaker is taken. Important reversible causes include hypothermia, electrolyte disturbance (especially hypokalemia and acidosis), hypoxia, cardiac ischemia, medication use, and overdose.

TABLE 21.3 Medication Used for Bradycardia

	MECHANISM OF ACTION	DOSE	SIGNIFICANT SIDE EFFECTS
Atropine	Anticholinergic (ACH-R antagonist)	IV, 0.5–2.0 mg	Tachyarrhythmia, glaucoma, bronchospasm, urinary retention
Isoprenaline	β-Receptor agonist	IV, 1–4 μg/min; IV drip of 15–60 mL/h of 0.4 mg/100 mL NS	Tachycardia, ischemia, hyper- or hypotension, headache
Theophylline	PDE-5 inhibitor	PO, 200 mg bid	Abdominal discomfort, tachycardia, restlessness

ACH-R, acetylcholine receptor; IV, intravenous; NS, normal saline; PDE-5, phosphodiesterase-5.

TEMPORARY PACING

Temporary pacing is indicated in symptomatic bradycardia whenever there is a potentially reversible cause, or when permanent pacing is not available or carries a high risk at that moment (i.e. ongoing infection, risk of bleeding due to drugs, thrombocytopenia, and coagulopathy). If the cause is irreversible and permanent pacing is available, it should be preferred over temporary pacing. However, many unstable patients will require the insertion of a temporary wire to allow safe implantation of a permanent pacemaker.

Temporary pacing may be achieved transcutaneously using external pads, transvenously using an electrode (“wire”), epicardially using an atrial or ventricular epicardial electrode placed during a cardiac surgery, or through an

esophageal electrode (mainly for atrial pacing).

TRANSCUTANEOUS PACING

External pads can deliver immediate pacing. Anteroposterior position is the most effective, although anterior-apical can also be tried (**Figure 21.6**). This is reserved for cases with asystole or severe bradycardia and hemodynamic instability and serves only until achieving pacing with other methods. **Figure 21.7A** shows an example of an external pacemaker-defibrillator unit from a specific manufacturer. The arrow indicates the location of the pacing button. In the external monitor-defibrillator, the current is programmed at a high energy (i.e. 80 mA). The pulsations need to be verified, ideally by palpating the radial or femoral pulses. Carotid artery palpation is best avoided in this situation. On occasion, an arterial line can deliver exact information about the blood pressure. Pacing artifacts are usually large and limit the ability to assess capture using the cardiac monitor. The capture should be assessed continuously as a slight movement by the patient or pad movement may result in noncapture. If palpation of the arterial pulse is absent, the pad location needs to be adjusted or the current needs to be increased. Pad malfunction owing to improper contact with the skin (usually due to diaphoresis or hair over the chest) should be excluded. It should be mentioned that most patients will need some sedation to tolerate the pain involved with pacing, due to cutaneous nerve stimulation and skeletal muscle contractions. The rate of pacing is typically between 60 and 80 bpm. Because of the limitations associated with transcutaneous pacing, this method should be considered only as a temporizing measure for unconscious patients or those in whom sedation can be administered, until either temporary or permanent transvenous pacing can be established.

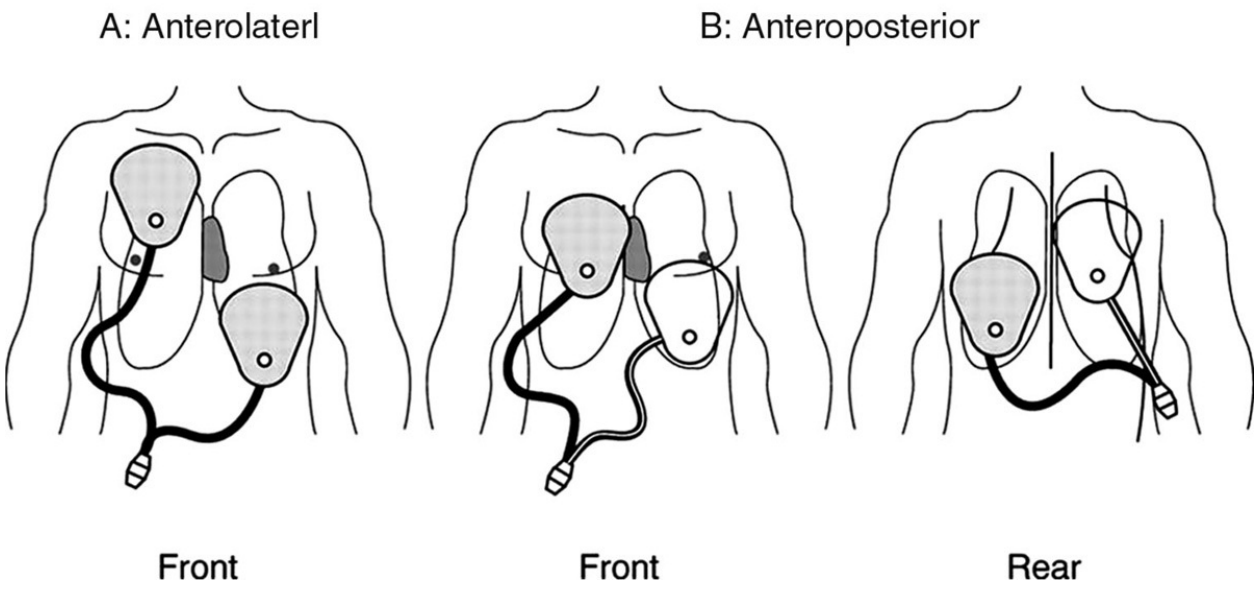

FIGURE 21.6 Pacemaker pads position. A, Apical and lateral. B, Anterior-posterior.

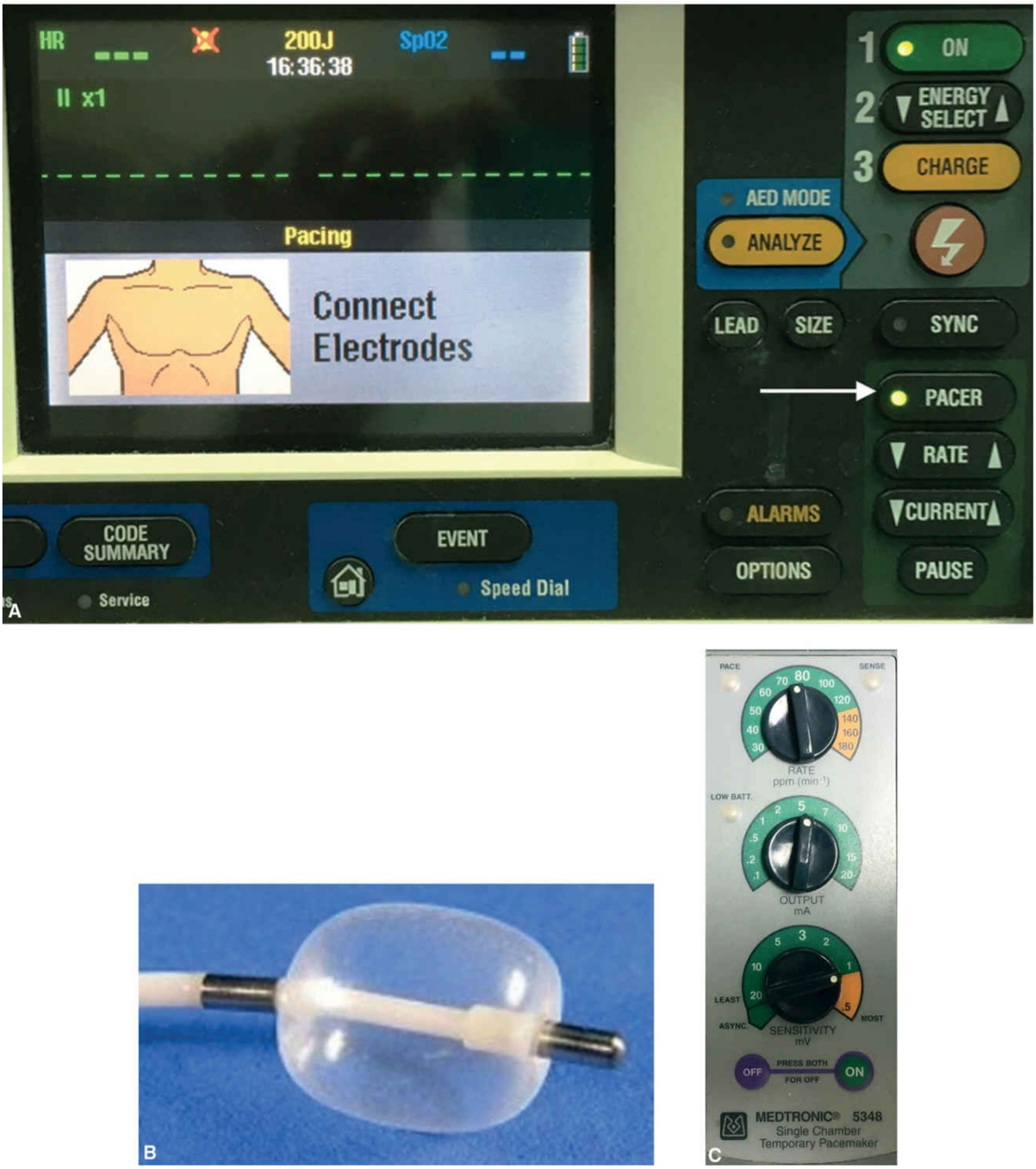

FIGURE 21.7 Temporary pacing units. A, External monitor-defibrillator. The white arrow denotes pacer button. Once pushed, the external pacemaker will pace at the set rate and output (notice green light on the left side of the button). The rate and current buttons are used for setting. Pacing may be started at 60 to 80 bpm with current of 80 mA. The current may be lowered, provided that capture is still manually verified. B, A tip of a temporary wire with distal inflatable balloon. C, Temporary pacing unit. The top button is used to set the rate, the middle button is used to set the output, and the lower button is used to set the sensitivity. The sensitivity is usually set to high (< 1 mV) to avoid pacing immediately after intrinsic activity, unless electrical noise is expected.

TRANSVENOUS PACING

Insertion of a temporary wire is best done by an expert physician under fluoroscopy guidance or at the bedside using a pacing wire with an inflatable balloon at the distal end (**Figure 21.7B**). The right jugular or subclavian veins are the optimal access sites for temporary pacing. These sites allow patient mobilization once the pacing wire is secured. However, access-related complications are high unless ultrasound guidance is used. The femoral vein may also be used, especially when done in the cardiac catheterization laboratory for a short duration. Disadvantages of using the femoral vein access include higher risk of infection and inability to mobilize the patient. The temporary wire is often positioned in the RV apex. Some of the wires contain a distal balloon (**Figure 21.7B**), to help advancing the tip of the wire under low-flow conditions. The balloon should be checked for leaks before insertion, inflated once in the vein, and deflated after positioning in the RV. The physician caring for paced patients should be familiar with the programming of the temporary pacing unit (**Figure 21.7C**). Once positioned in the RV apex, if there is an intrinsic activity, the sensing light will flash (top left of the pacing unit).

The upper button sets the pacing rate, usually at 60 to 80 bpm. The middle button sets the output delivered. The capture threshold is the minimal amount of output (in mA) required for capture. Threshold test is needed every 8 hours or whenever the patient position is changed (i.e. transferred to an intensive care unit [ICU] bed) (**Figure 21.8**). To test for the threshold, increase the pacing rate 10 to 20 bpm above the intrinsic rate (not less than 60 bpm) and slowly decrease the output till capture is lost (absence of QRS complex following the pacing artifacts). At that point, increasing the output should be done quickly. Output can be programmed to five times the threshold, usually at least 5 mA. This safety margin is required because the temporary electrode’s stability is less than those of the permanent leads.

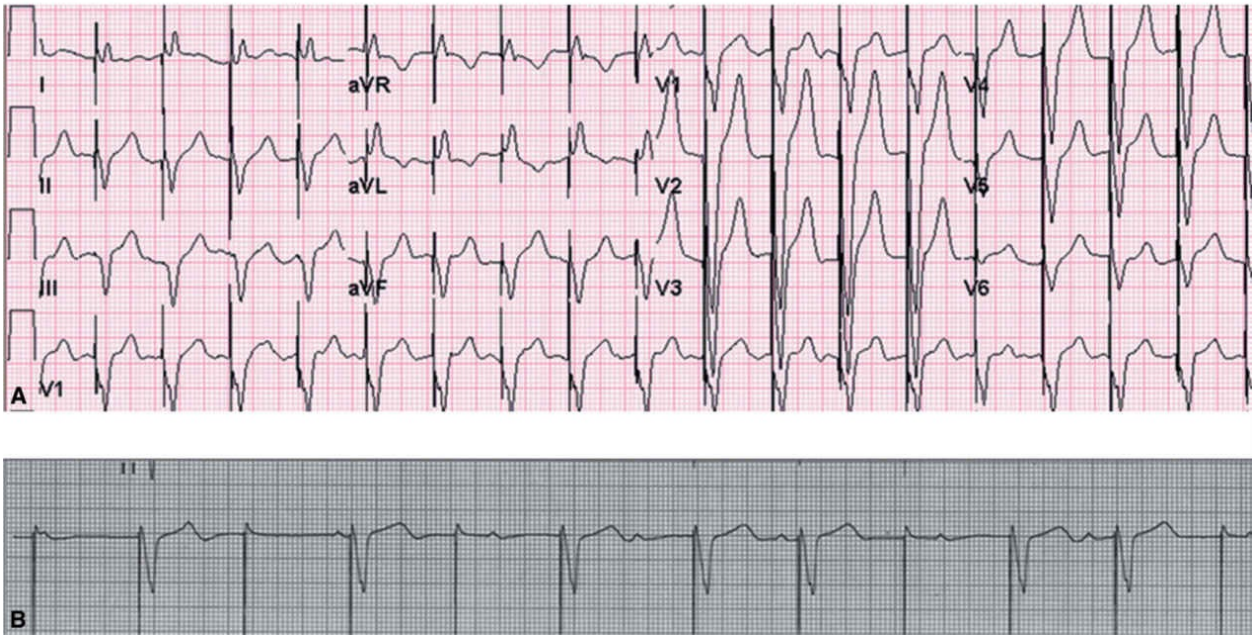

FIGURE 21.8 ECG recordings from patients with a temporary pacemaker. A**,** Paced ECG showing superior axis (negative in inferior limb leads) and LBBB pattern, typical for an electrode located in the RV apex. B, Pacemaker malfunction. Some of the pacemaker artifact (i.e. first, third, and fifth) are not followed by a QRS, indicating intermittent loss of capture. ECG, electrocardiogram; LBBB, left bundle branch block; RV, right ventricle.

SENSING

This term relates to the ability of the pacemaker to sense the intrinsic electrical activity. To determine an adequate sensing, set the pacemaker rate to 10 to 20 below the intrinsic rate, if possible. Set the sensitivity to the maximal level (**Figure 21.7C**, lower button, indicated by “least”). The sensing light (**Figure 21.7C**, top right) will stop flashing because it will not sense any activity. Slowly decrease the sensitivity threshold until the sensing light flashes. This is the sensing threshold, that is, the minimum intracardiac signal that will be sensed (seen) by the pacemaker and inhibit its activity. The sensitivity should be set to a low value (1 mV, indicated by “most”), not higher than the sensitivity threshold, to prevent pacing on intrinsic activity. However, when external noise is expected (during implantation of the permanent pacemaker with the use of electrocautery), the sensitivity should be programmed to the minimum (high value of 20 mV, depicted in **Figure 21.7C** as “least”).

Figure 21.8 shows examples of ECG from paced patients. In**Figure 21.8A**, typical pacing is shown. Each pacing artifact is followed by a QRS. The QRS morphology is typical for RV apical pacing with left BBB pattern and a superior

axis (negative QRS in the inferior limb leads). In **Figure 21.8B**, pacemaker intermittent loss of capture is seen. Notice how some of the pacing artifacts (first, third, fifth, ninth, and last) are not followed by a QRS.

The temporary wire is removed once the bradycardia is resolved or a permanent pacemaker is implanted. On occasion, temporary wires perforate the thin RV wall during implantation. It is not uncommon to observe pericardial effusion and tamponade upon removal of a temporary wire which had sealed a perforation, especially in anticoagulated patients.

PERMANENT PACEMAKER

Sinus node dysfunction resulting in bradycardia is an indication for pacemaker implantation mainly when symptomatic. Asymptomatic sinus bradycardia does not carry a risk for syncope or sudden death (2). In contrast, second-degree Mobitz type II, Advanced AV block and CAVB require permanent pacing regardless of symptoms.

Table 21.4 denotes the pacemaker nomenclature endorsed by the NASPE (North-American society of pacing and electrophysiology). The most common pacemaker is coded as DDDR, thus pacing and sensing is available in both atrium and ventricle, the sensing may trigger or inhibit pacing and rate modulation is possible. This type of pacemaker allows for atrio-ventricular synchrony. VDD pacing is a suitable option for patients with a conduction abnormality but a normal sinus function. This pacemaker has one lead which is positioned at the right ventricular apex, with a bipolar sensor located about 15 cm from the distal end of the lead and allows for sensing in the atrium. The nomenclature of this type of pacemaker (VDD) denotes that pacing is possible only in the ventricle (first letter, “V”, in the nomenclature). The major advantage of this type of pacemaker is that its single lead allows for AV synchronous pacing. VVI pacemakers can sense and pace the ventricle alone and is used mainly for patients in persistent atrial fibrillation or in patients in sinus rhythm but only infrequent bradycardic episodes. The last letter in the nomenclature, *I*, denotes that pacing is *inhibited* if the pacemaker senses an intrinsic ventricular activity of the patient. Similarly, AAI pacemaker allows for sensing and pacing in the atrium alone. While it is suitable for patients with sinus node dysfunction and intact AV conduction, it is only infrequently used for fear of later development of a conduction abnormality (**Table 21.5**). The routine management post-pacemaker implantations include prophylactic antibiotic therapy (usually for 24 hours with anti-staphylococcal agents), analgesics, chest X-ray to verify

lead position and rule out pneumothorax, and bed restriction (3 hours to overnight, depend in the local policy). Most patients will be discharged within 24 hours, unless their clinical status was not yet stabilize.

TABLE 21.4 NASPE Generic Code for Pacemakers

POSITION	I	II	III	IV
Category	**Chamber(s) paced**	**Chamber(s) sensed**	**Response to sensing**	**Rate modulation**
	O = none	O = none	I = inhibition	O = none
	A = atrium	A = atrium	T = triggered	R = rate modulation
	V = ventricle	V = ventricle	D = dual (I+T)	
	D = dual (A+V)	D = dual (A+V)		

NASPE, North American Society of Pacing and Electrophysiology.

TABLE 21.5 Types of Cardiac Pacemakers and NASPE Codes

CODE	MEANING
A(V)OO	Asynchronous atrial (ventricular) pacemaker without sensing of the patient's atrial (ventricular) rhythm
AA(VV)I	Sensing and pacing in the atrium (ventricle) only
DDD	Multiprogrammable physiologic dual-chamber pacemaker; can sense and pace in the atrium and ventricle
DDI	Dual chamber pacing and sensing in the lower rate only
VDD	Ventricular pacing, dual-chamber sensing with atrial synchronous ventricular pacing

NASPE, North American Society of Pacing and Electrophysiology.

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Patient and Family Information for: BRADYCARDIA AND HEART BLOCK

WHAT IS BRADYCARDIA?

Specialized heart cells in the right atrium are called sinus node and are responsible for electrical impulse formation, resulting in a resting HR in most healthy people of 60 to 100 beats per minute. Bradycardia is a slow heart beat (<60 bpm) caused either by abnormal electrical impulse formation (sick sinus syndrome) or by its delayed propagation to the rest of the heart (heart block). During sleep and in well-trained individuals, bradycardia is common and adequate and therefore does not require any treatment.

WHAT CAUSES BRADYCARDIA?

Bradycardia can be caused by the following:

- Changes in the heart that are the result of aging.
- Diseases that damage the heart's electrical system. These include coronary artery disease, heart attack, and infections such as endocarditis and myocarditis.
- Conditions that can slow electrical impulses through the heart. Examples include having a low thyroid hormone level (hypothyroidism) or an electrolyte imbalance, such as too much potassium in the blood.
- Some medicines for treating heart problems or high blood pressure, such as β-blockers, calcium blockers, antiarrhythmic drugs, and digoxin.

WHAT ARE THE SYMPTOMS?

As the HR declines, the heart may not pump enough blood to meet the body's needs. A very slow HR may cause a person to experience the following:

- Feel dizzy, lightheaded
- Feel short of breath and find it harder to exercise
- Feel tired
- Have chest pain or a feeling that the heart is pounding or fluttering (palpitations)
- Feel confused or have trouble concentrating
- Faint, if a slow HR causes a drop in blood pressure

Some people do not have symptoms, or their symptoms are so mild that they think these are just part of getting older. The pulse rate can be assessed by checking it manually with the fingers or with an electronic device such as blood pressure machines and smartphone applications.

If the heart beat is slow or uneven, talk to a doctor.

HOW IS BRADYCARDIA DIAGNOSED?

A doctor may be able to diagnose bradycardia by doing a physical examination, asking questions about past health, and doing an ECG. An ECG measures the electrical signals that control heart rhythm, so it is the best test for bradycardia. Bradycardia often comes and goes, so a standard ECG done in the doctor's office may not find it. An ECG can identify bradycardia only if the person is actually having it during the test. There may be a need to use a portable (ambulatory) ECG device. This lightweight device is also called a Holter monitor or a cardiac event monitor. The person wears the monitor for a day or more, and it records the heart rhythm while he/she goes about the daily routine. Blood tests may also be necessary to find out whether another problem is causing the slow HR.

HOW IS IT TREATED?

The treatment of a slow heartbeat depends on what is causing it and what are the accompanying symptoms. Sometimes, there is no need for any intervention,

especially if the bradycardia is asymptomatic.

If damage to the heart's electrical system causes the heart to beat too slowly, the person will probably need to have a pacemaker. A pacemaker is an electronic device, placed under the chest skin and connected to the heart with electrical wires, which helps correct the slow HR. Older people are most likely to have a type of bradycardia that requires a pacemaker. If another medical problem, such as hypothyroidism or an electrolyte imbalance, is causing a slow HR, treating that problem may cure the bradycardia. If a medicine is causing the heart to beat too slowly, the doctor may adjust the dose or prescribe a different medicine. If the person cannot stop taking that medicine, a pacemaker may be needed. The goal of treatment is to raise the HR so the body gets the blood it needs. If severe bradycardia is not treated, it can lead to serious problems. These may include fainting and injuries from fainting, as well as seizures or even death.

WHAT CAN BE DONE AT HOME FOR BRADYCARDIA?

Bradycardia is often the result of another heart condition, so taking steps to improve heart health will usually improve overall health. The best steps to take are to ensure the following:

- Control cholesterol and blood pressure
- Eat a low-fat, low-salt diet
- Get regular exercise; a doctor can tell what level of exercise is safe
- Stop smoking
- Limit alcohol
- Take medicines as prescribed
- See the doctor for regular follow-up care

People who get pacemakers need to be careful around strong magnetic or electrical fields, such as magnetic resonance imaging machines or magnetic wands used at airports because they may interfere with their functioning. If a pacemaker is placed, the doctor will give information about its type and what precautions are to be taken. Once a cardiac pacemaker is implanted, most patients enjoy a normal life without even noticing its presence.

22

Todd Kobrinski
Emad F. Aziz

Supraventricular Arrhythmias

INTRODUCTION

Of the supraventricular arrhythmias that are encountered in the cardiac care unit (CCU), sinus tachycardia and atrial fibrillation (AF) are most frequently seen owing to their higher incidences among patients with acute myocardial infarction (MI), respiratory failure, sepsis, structural or valvular heart disease, and cardiomyopathy. Because of the distinctness of AF as a clinical entity, it is discussed in conjunction with atrial flutter (AFL) in a separate chapter. This chapter focuses on the general approach to the classification and management of narrow QRS complex tachycardias followed by a description of the common forms of supraventricular tachycardias (SVTs). The algorithms defined in this chapter apply to the most typical clinical scenarios and are not intended to be exhaustive or highly specific.

SVTs are commonly seen in the CCU and in otherwise healthy patients without structural heart disease, with an overall prevalence estimate of 600,000 and annual incidence of 90,000 in the United States alone.[1]They represent a heterogeneous group of tachyarrhythmias that originate in the supraventricular tissue or utilize it as part of a reentrant circuit,[2] and are characterized by a spectrum of electrocardiogram (ECG) findings that are clinically important to understand, identify, and differentiate. SVTs typically present with a regular rate

(160–200 bpm) and a narrow QRS complex (<120 milliseconds) on ECG because they follow the normal pathway of atrioventricular (AV) conduction and ventricular activation via the His-Purkinje system. Occasionally, SVTs present with a wide QRS complex (≥ 120 milliseconds) because of baseline bundle branch blocks, rate-related aberrancy, or conduction via accessory pathways (APs).

Sinus tachycardia, by far the most common SVT, is not a pathologic arrhythmia (with the rare exception of inappropriate sinus tachycardia) but rather is an appropriate cardiac response to a physiologic event. Sinus tachycardia is gradual in onset and recession. The heart rate is regular and classically does not exceed 220 beats per minute (bpm) minus the patient's age. In sinus tachycardia, P waves precede the QRS complex. Sinus tachycardia is virtually always a compensatory response, and it should not be considered the cause of hemodynamic instability. Instead, the underlying precipitant of sinus tachycardia (eg, ischemia, infection, heart failure) must be identified and addressed.

GENERAL APPROACH TO NARROW QRS COMPLEX TACHYCARDIAS

SYMPTOMS AND HEMODYNAMIC IMPACT

SVTs are not usually life threatening to otherwise healthy individuals; however, patients admitted to the CCU who present with narrow QRS complex tachycardias should be thoroughly assessed for clinical signs and symptoms potentially *attributable to* the arrhythmia. These may include hypotension, diminished peripheral pulses and tissue perfusion, shortness of breath, and chest pain. In contrast to patients without organic heart disease, many CCU patients may have ischemic cardiomyopathy, severe valvular stenosis or regurgitation, or reduced left ventricular function. Among such patients, the tachycardia can lead to reduced diastolic filling and decreased cardiac output, which may hasten myocardial ischemia and decompensated heart failure. That said, it is equally important to differentiate these scenarios from those in which the underlying disease is the cause of hemodynamic instability and the precipitant for the SVT. For example, sepsis with vasodilatory shock or acute pulmonary embolism can be a *driver* of the tachyarrhythmia. After careful delineation of these relationships, if the SVT is thought to be the *cause* of hemodynamic instability, expeditious treatment (eg, electrical cardioversion) guided by established

Advanced Cardiac Life Support (ACLS) protocol is warranted (**Figure 22.1**).[3]

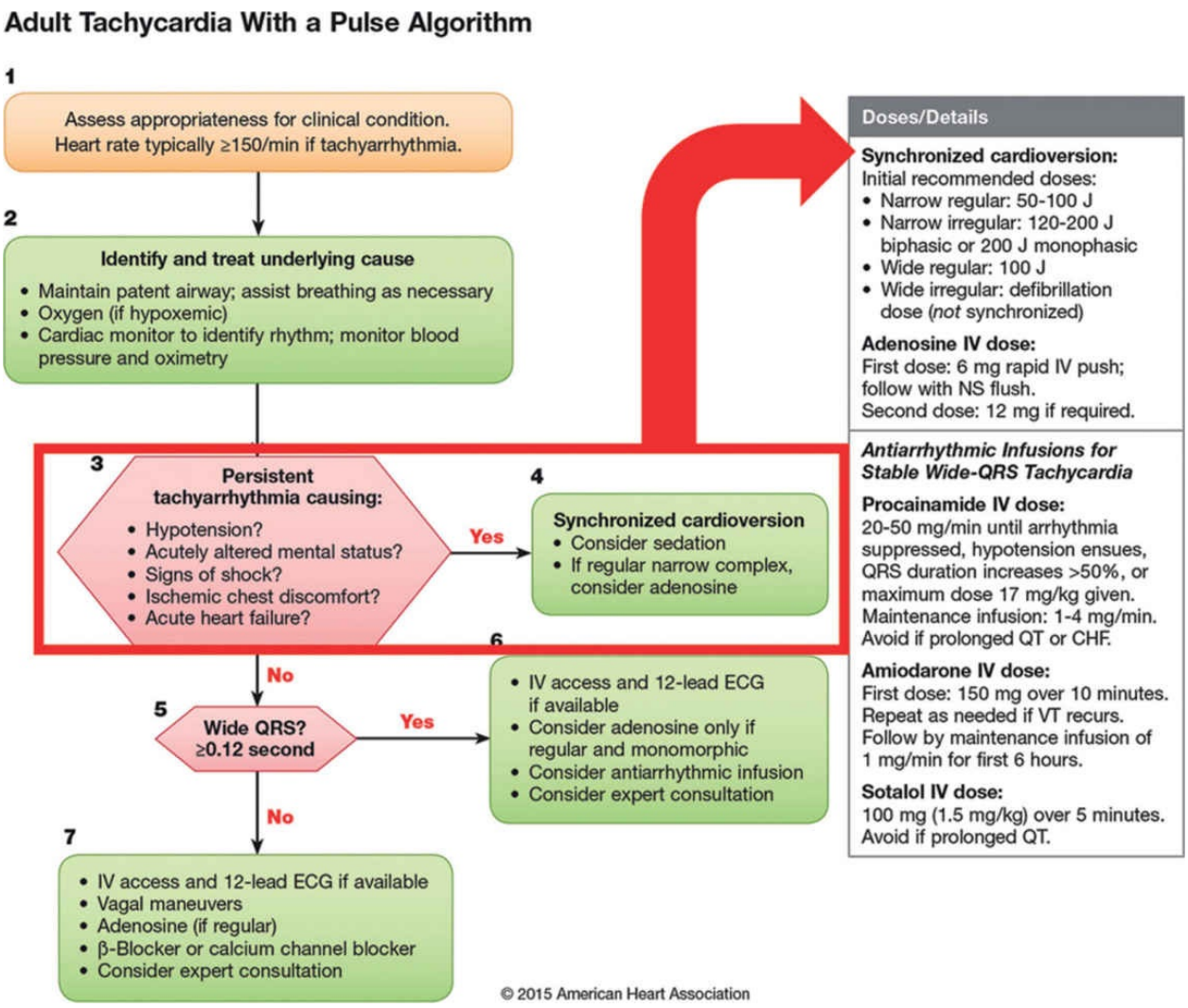

FIGURE 22.1 Algorithm for appropriate use of synchronized electrical cardioversion in the management of unstable patients with persistent narrow QRS complex SVTs. From the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) algorithm for adults with tachycardia and a pulse.[3]

CLASSIFICATION BASED ON ELECTROCARDIOGRAM FINDINGS

REGULARITY OF THE RHYTHM

A 12-lead ECG is the cornerstone in diagnosing SVT and should be carefully inspected for regularity of QRS complexes. This can be done most accurately using calipers to sequentially compare R-R intervals (**Figure 22.2**) and allows for rapid initial differentiation into two major categories: irregular and regular rhythms (**Figure 22.3**).[4–6] Careful inspection and repeat measurements are

usually sufficient to establish regularity; however, irregular SVTs including AF and AFL with variable AV conduction or multifocal atrial tachycardia (MAT) may exhibit very rapid ventricular conduction that can sometimes mask their irregularity. In such instances, the use of heart-rate–slowing maneuvers (ie, increased vagal tone) can be effective in resolving any ambiguity (**Table 22.1**).After the regularity has been assessed, the ECG should be analyzed for the presence of P waves and their morphology.

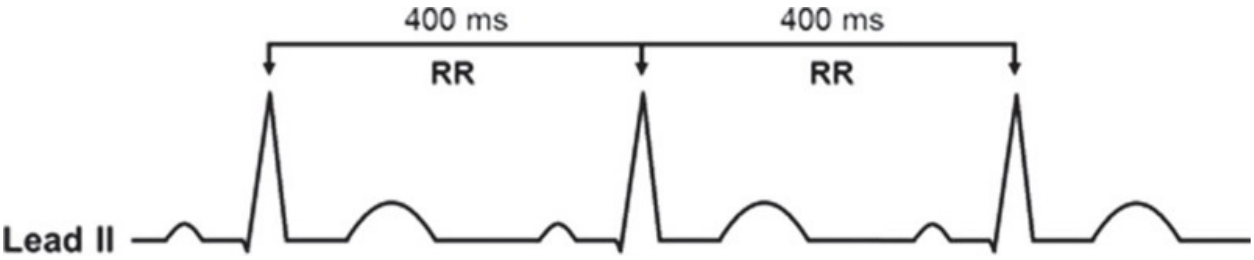

FIGURE 22.2 Determining the regularity of narrow QRS complex SVTs on ECG via measurement of the R-R interval. ECG, electrocardiogram; SVT, supraventricular tachycardia.

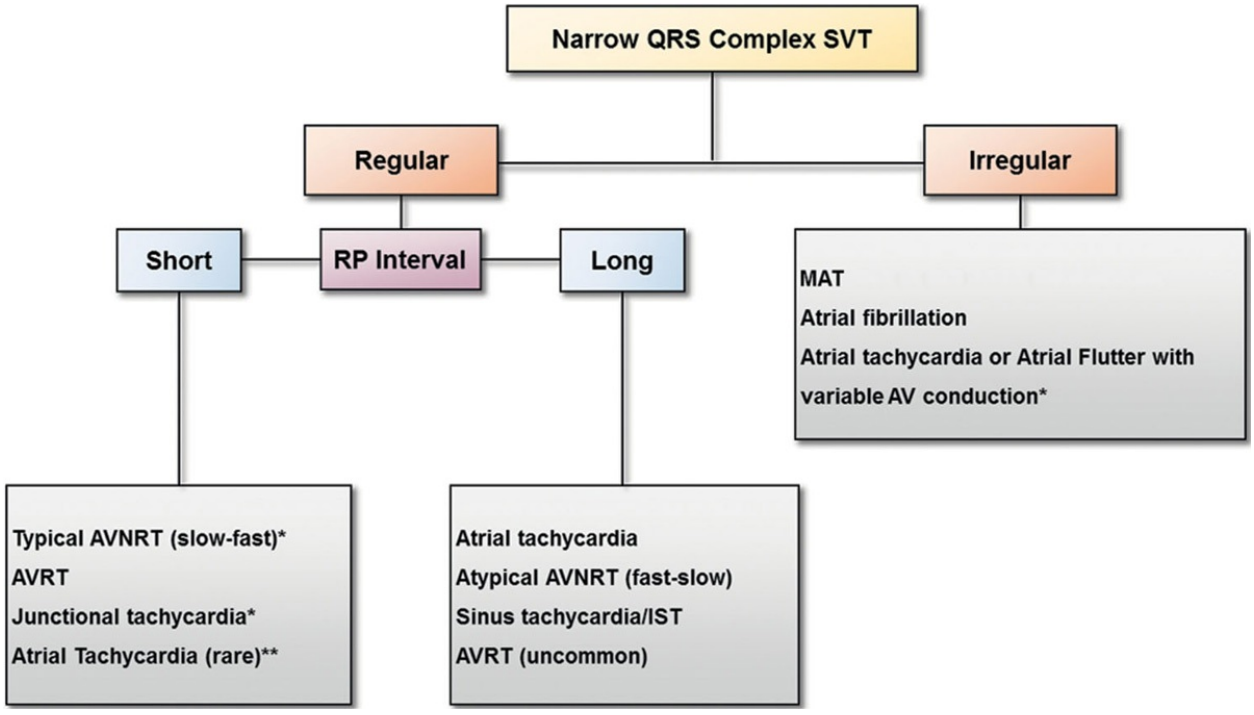

FIGURE 22.3 General approach to classifying narrow QRS complex tachycardias. AV, atrioventricular; AVNRT, atrioventricular nodal reentrant tachycardia; AVRT, atrioventricular reentrant tachycardia; IST, inappropriate sinus tachycardia; MAT, multifocal atrial tachycardia; SVT, supraventricular tachycardia.

TABLE 22.1 Common Methods of Transiently Slowing av Conduction to Allow for Definitive Diagnosis in the Classification of Narrow QRS Complex Tachycardias

Modalities that Transiently Slow Av Conduction:	Vagal Maneuvers: • Carotid Massage • Valsalva maneuvers	AV Nodal Medications: • Adenosine • β-blockers (metoprolol) • Nondihydropyridine calcium channel blockers (verapamil, diltiazem)	
Responses of Individual Svts to Transient Slowing ofAv Conduction:	**AVNRT**	**AVRT**	**AT**
Abrupt termination with a P wave after the last QRS complex.	Yes	Yes	Very unlikely
Abrupt termination with a QRS complex.	Yes	Yes	Yes
Some/gradual slowing of the ventricular rate without termination.	No (excludes)	No (excludes)	Common

AT, atrial tachycardia; AV, atrioventricular; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; SVT, supraventricular tachycardia.

PRESENCE AND MORPHOLOGY OF P WAVES

Identification of P waves and their morphologic patterns are essential for further characterization of regular narrow QRS complex SVTs, as well as their relative origin within the supraventricular conduction system (ie, sinoatrial [SA] node vs atrial vs AV node). This requires familiarity with P-wave appearance during normal (sinus) conduction on 12-lead ECG, and experience with recognition of oftentimes subtle variations.[7] Cases in which P waves are not well identified might indicate that the activation of the atria and ventricles is occurring almost simultaneously, resulting in a P wave that is buried within or just following the QRS complex. The most common etiologic example of this ECG pattern is atrioventricular nodal reentrant tachycardia (AVNRT), followed less commonly by unifocal atrial tachycardia (AT) and junctional tachycardia (JT). Sinus P waves are positive in the inferior leads (ie, II, III, and aVF) due to normal anterograde conduction, whereas P waves in AVNRT are always negative in the inferior leads (pseudo–S) due to retrograde conduction from the AV node to the atria (**Figure 22.4**). This is similarly seen in atrioventricular reentrant tachycardia (AVRT); however, nonretrograde P waves are sometimes present depending on the location of the AP. The importance of differences in P-wave

patterns and timing is not only inherent to AVNRT and AVRT. P waves originating from a different focus (ie, ectopic AT) or multiple foci (ie, MAT) in the atria can have variable morphologies and may even mimic sinus P waves (eg, crista terminalis origin). Therefore, comparison of P-wave characteristics with those found on the baseline ECG, as well as onset/termination properties of the tachycardia, is extremely useful in differentiating focal or reentrant tachycardia from sinus tachycardia.

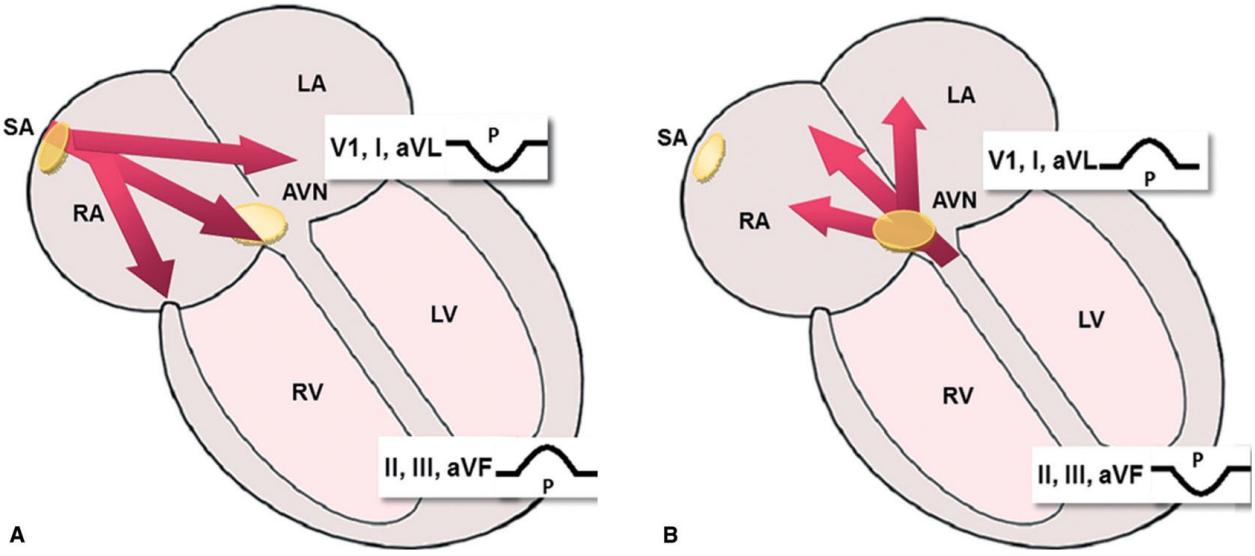

FIGURE 22.4 Differences in P-wave morphology in the inferior leads (II, III, aVF) based on direction of atrial activation. A, In normal antegrade sinus conduction positive P-wave deflections are seen in the inferior leads. B, With AVNRT, the atria are activated in a retrograde direction from the AV node, resulting in P waves that are negative in the inferior leads and positive in V1. AVN, atrioventricular node; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SA, sinoatrial node.

R-P INTERVAL

Following identification of P waves and their morphologies, the next step is examining the relationship of the P wave to the QRS complex. This is done by measuring an RR interval and then the distance from the initial R wave to the next discernable P wave. If the RP interval is less than one-half of the RR interval, the tachycardia is a short-RP tachycardia; otherwise, it is a long-RP tachycardia (**Figure 22.5**). The RP interval alludes to the relative timing of atrial (P) and ventricular (QRS) activation during SVT.

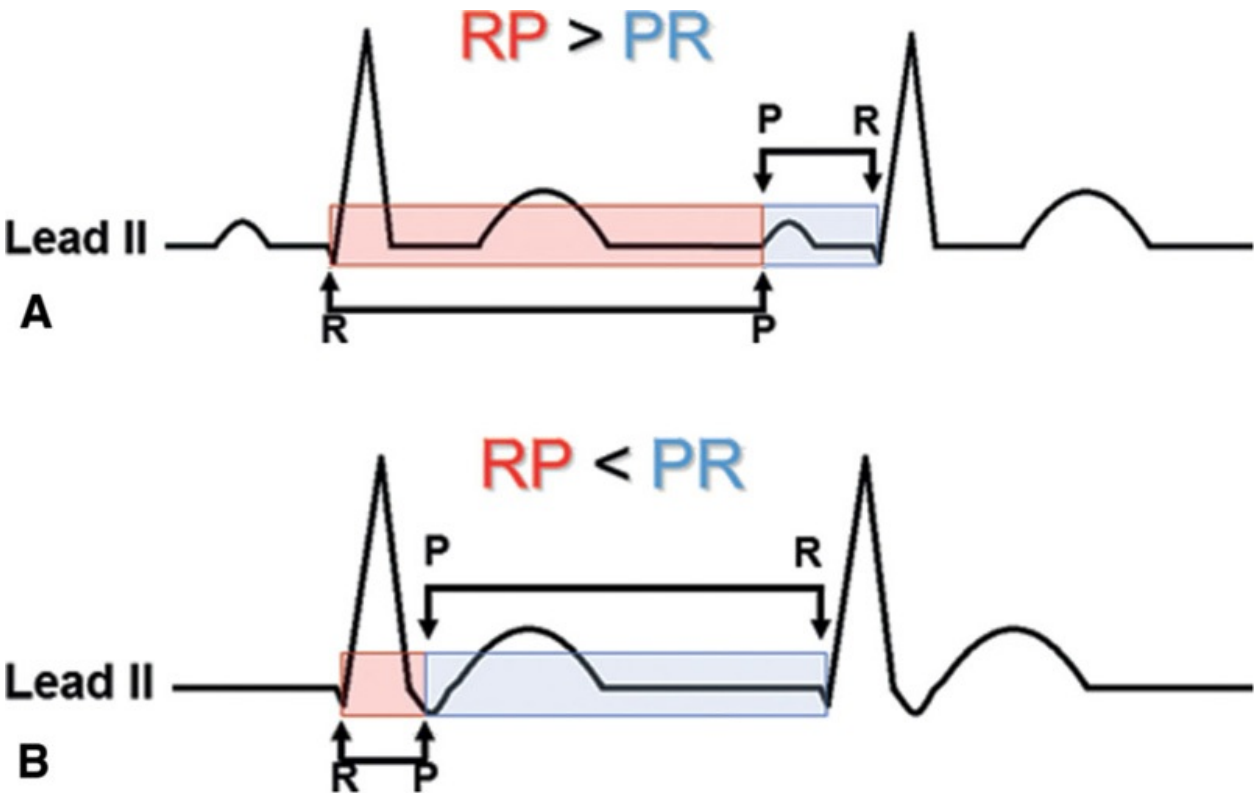

FIGURE 22.5 A, Measurement of the RP (and PR) intervals in ECG lead II. A, Narrow QRS complex tachycardias with RP intervals that are more than one-half of the RR interval (RP > PR) are called long RP tachycardias, whereas (B) those with an RP interval that is less than one-half of the RR interval (RP < PR) are known as short RP tachycardias.

As previously mentioned, atrial and ventricular activation occurs almost simultaneously (P waves buried within/just after QRS complex) in typical forms of AVNRT and AVRT, which represent the two most common short-RP tachycardias. AVNRT stems from dual-AV nodal physiology, whereas AVRT develops in patients with an extranodal AP that electrically connects the atrium and ventricle. Typical AVRT conducts down the AV node and up the AP resulting in a short-RP interval that may be slightly longer than that of AVNRT. Focal AT typically results in a long-RP tachycardia on ECG (**Figure 22.6A –B**).

FIGURE 22.6 A, 12-Lead ECG showing narrow QRS complex, *long-RP* tachycardia at a cycle length of 420 ms. Take note of the negative P waves preceding each QRS complex in the inferior leads (II, III, aVF; arrows). This patient subsequently underwent a successful radiofrequency catheter ablation for focal AT. B, CARTO-3 3D electroanatomic map for focal atrial tachycardia originating from the high crista terminalis.

ADDITIONAL DIAGNOSTIC MANEUVERS

As part of the systematic approach to identifying and classifying narrow QRS complex SVTs, it is often essential to transiently slow AV conduction to allow for more definitive assessment of regularity, presence of P waves, and RP intervals.[8, 9] This is commonly attempted first using bedside vagal maneuvers such as Valsalva and carotid sinus massage, followed by medications (commonly

adenosine, sometimes β -blockers and calcium channel blockers [CCBs]) that temporarily block or slow conduction through the AV node.

Before performing carotid sinus massage, it is crucial to revisit the patient's medical history and physical examination to check for contraindications such as cerebrovascular disease, recent MI, or carotid bruits. Maneuvers should always be performed with the patient in the supine position, and steady pressure should be applied unilaterally for 5 seconds. Bilateral carotid massage should never be performed. It is worthwhile to note that vagal maneuvers are not usually effective in terminating the tachycardia unless the AV node is part of a reentrant circuit (eg, AVNRT, AVRT).

If vagal maneuvers are ineffective, adenosine can be given as a rapid intravenous (IV) bolus followed by saline flush. Patients should be on continuous ECG monitoring during administration of adenosine to aid in diagnosis and to differentiate between treatment failure and termination with rapid reinitiation of SVT. The initial dose of adenosine is 6 mg, which can be followed by 12 mg if no response is seen. Patients should be forewarned that they are likely to experience side effects such as flushing, chest tightness, and shortness of breath, but these are very short-lasting. Although adenosine has a high tendency to terminate AVNRT and AVRT (AV node is part of the circuit), it is very unlikely to terminate AT or AFL. Nonetheless, it may unmask the underlying arrhythmia for more definitive diagnosis. Of note, adenosine can precipitate transient AF in up to 12% of patients, which poses a potential risk to patients with known Wolff–Parkinson–White (WPW) syndrome.[10] However, ventricular fibrillation (VF) and transient asystole in response to adenosine administration are rare.

Other agents such as IV β -blockers (eg, metoprolol) and CCBs (eg, diltiazem) may be effective in slowing AV conduction for di agnostic purposes, and may even terminate the SVT.[11] **Table 22.1** provides a listing of maneuvers and medications that are utilized diagnostically to transiently slow AV conduction, as well as the respective responsiveness of common SVT subtypes to these therapies.

OVERVIEW AND SAMPLES OF INDIVIDUAL SUPRAVENTRICULAR TACHYCARDIAS

ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA

AVNRT is the most frequently encountered of the regular narrow QRS complex tachycardias. The development of AVNRT and inherent behavior of the circuit is dependent on the presence of a particular electrophysiologic (EP) property of the AV node, termed dual-AV node physiology.[12] It is explained by the presence of two pathways with different conduction properties and refractoriness: the *fast pathway*, which conducts more rapidly with a longer refractory period, and the *slow pathway*, which conducts more slowly with a somewhat shorter refractory period (**Figure 22.7**).Normal (anterograde) AV conduction takes place in a forward direction down the *fast pathway*; however, if the *fast pathway* is refractory from a premature atrial complex (PAC), the sinus impulse may conduct over the *slow pathway*. If enough time passes for the *fast pathway* to recover, the impulse can conduct (retrograde) backward up the *fast pathway* and initiate a reentrant circuit that manifests on ECG as a regular tachyarrhythmia at 130 to 250 bpm (**Figure 22.8).**

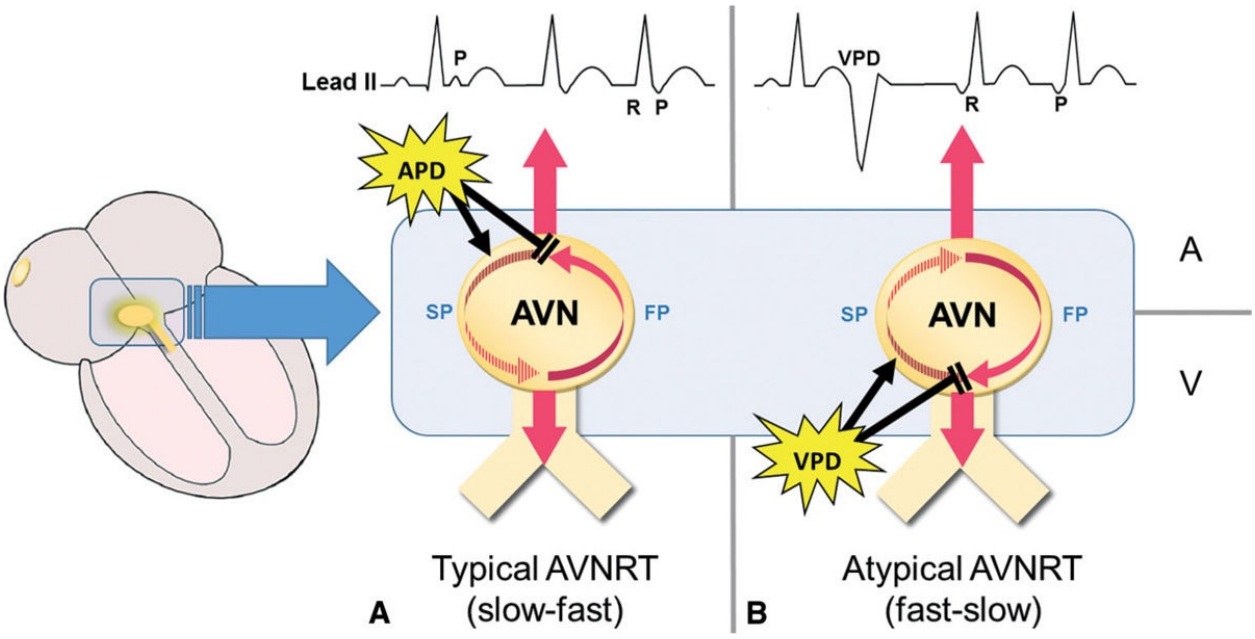

FIGURE 22.7 Mechanisms of atrioventricular nodal reentrant tachycardia (AVNRT), showing each atrioventricular node (bottom) and surface ECG lead (top). Solid arrows indicate conduction over the fast pathway (FP), and striped arrows represent conduction over the slow pathway (SP). A, Typical AVNRT: an APD blocks in the FP and conducts down the SP, followed by retrograde conduction up the FP. Note the nearly simultaneous timing of P waves and QRS complexes during typical AVNRT (RP < PR). Pseudo-S waves at the end of QRS complexes (inferior ECG leads) are a result of the retrograde P' waves. B, With atypical AVNRT, a VPD blocks at the FP and travels retrograde up the slow pathway, followed by antegrade conduction down the FP. Inverted P' waves are visible before the onset of the QRS complex in atypical AVNRT (RP > PR). A, atrial; APD, atrial premature depolarization (PAC); AVN, atrioventricular node; AVNRT, atrioventricular nodal reentrant tachycardia; P, P wave; R, R wave; V, ventricular; VPD, ventricular

premature depolarization (PVC).

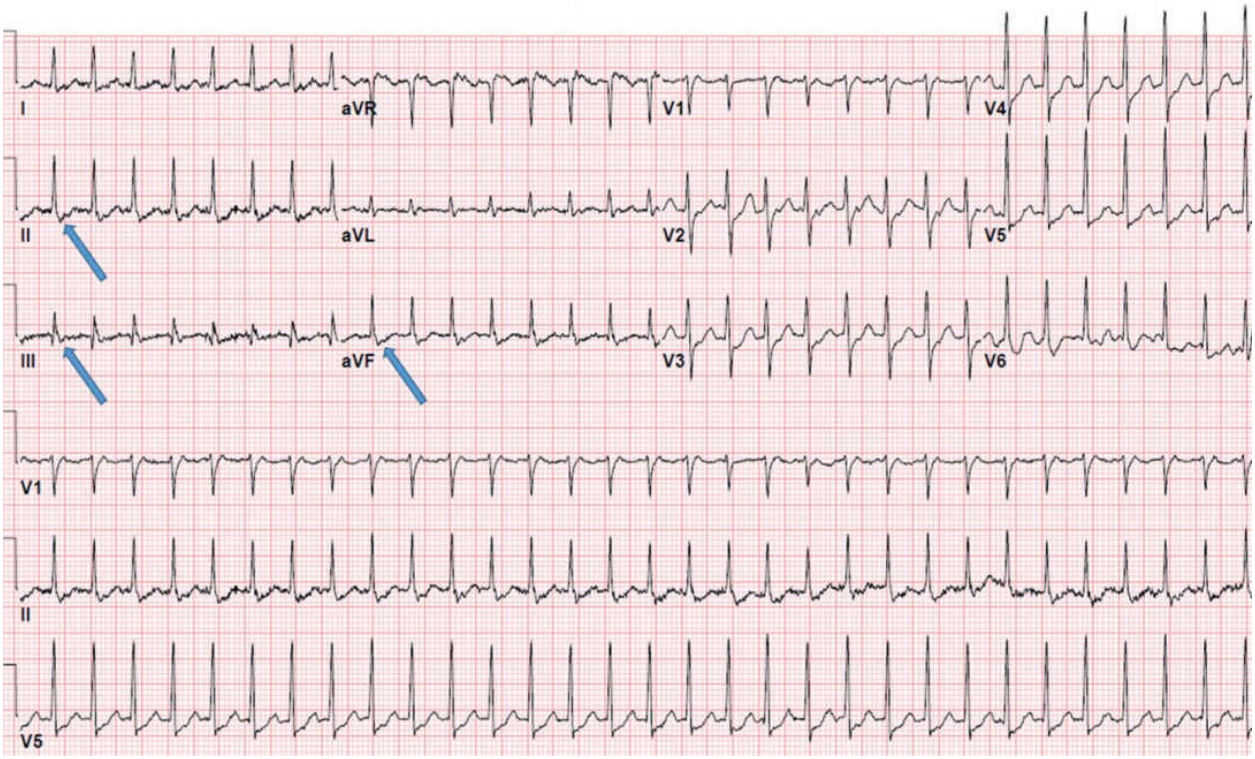

FIGURE 22.8 Typical (slow-fast) atrioventricular nodal reentrant tachycardia on 12-lead ECG. P waves are often not visible because they are buried in the QRS complexes owing to simultaneous activation of the atria and ventricles. In this example, take note of the pseudo s′ waves, which appear at the inferior leads (II, III, aVF) at the end of the QRS complex (arrows).

P waves are unidentifiable or can be seen just beyond the QRS complex because of the nearly simultaneous activation of the atria and ventricles. The P wave would look like a pseudo-S wave in leads II, III, aVF, and like an r’ wave in lead V1, which is the *sine qua non* in the diagnosis.

The rhythm is termed *typical* AVNRT (most common, 90%) if it follows the aforementioned EP properties, whereas in the *atypical* form of AVNRT the impulse travels down the *fast pathway* and up the *slow pathway* (uncommon, 10%) which manifests as a similar ECG finding except that P waves would be further away from the QRS.

As with any SVT, acute treatment of AVNRT should begin with assessment of hemodynamic stability, and patients who are hypotensive should be electrically cardioverted immediately. It is uncommon for AVNRT to cause major hemodynamic instability, and thus vagal maneuvers should be attempted to prolong the refractoriness of AV nodal conduction with a resultant transient

anterograde block and termination of the tachycardia. If vagal maneuvers are ineffective, administration of adenosine has been shown to terminate more than 95% of AVNRTs. [13, 14] Additional AV nodal agents such as IV (or PO) nondihydropyridine CCBs (ie, diltiazem) or β-blockers are second-line options.

Despite their effectiveness in terminating AVNRT, it is important to keep in mind that the ability of CCBs to slow AV nodal conduction may result in more rapid conduction down an AP in the presence of preexcited AF, leading to VF and sudden cardiac death (SCD). They can also be dangerous for patients with significant systolic heart failure because of their negative inotropic and vasodilatory properties. β-Blockers (ie, metoprolol) are a safer choice in that setting, and amiodarone might be a reasonable third-line option, although robust data on its efficacy is lacking.

ATRIOVENTRICULAR REENTRANT TACHYCARDIA

AVRT is a form of short-RP tachycardia that develops in patients with an AP, a cluster of extranodal tissue that provides an alternative atrio-ventricular electrical connection, which bypasses the AV node and His-Purkinje system. APs can conduct in antegrade, in retrograde, or in both directions. They are described as *manifest* if they conduct antegrade more rapidly than the AV node, demonstrating a characteristic *preexcitation* pattern on resting ECG with slurring of the QRS upstrokes known as *delta*waves, resulting in a broader QRS (> 110 ms) and shortened PR interval (less than < 120 ms); *concealed* if they conduct exclusively retrograde; or *latent* if they have the capability to conduct antegrade under certain conditions. When associated with paroxysms of SVT, this pattern is known as WPW syndrome, and the pre excitation pattern on ECG during sinus rhythm signifies early ventricular activation due to rapid anterograde conduction down the *manifest* AP (**Figure 22.9**).

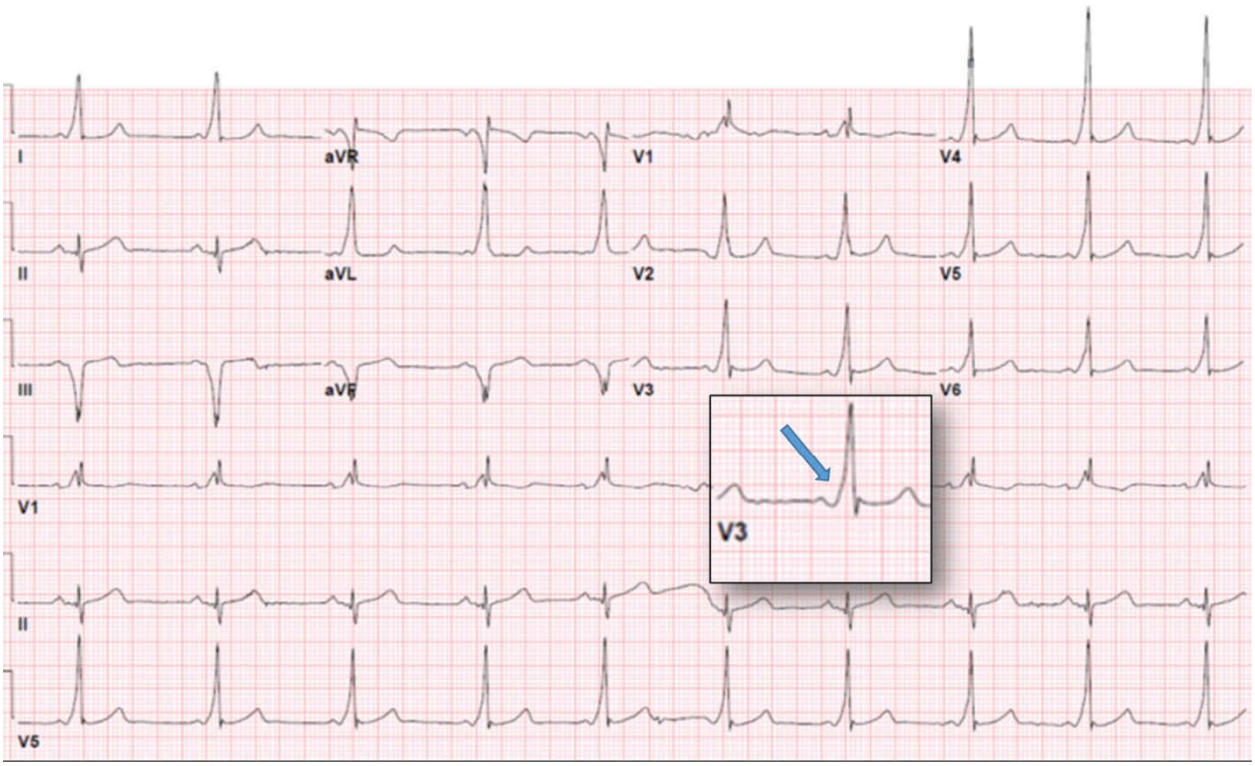

FIGURE 22.9A 12-lead ECG in sinus rhythm with preexcitation (delta wave). Delta waves on resting ECG are a result of ventricular preexcitation due to concomitant rapid anterograde conducting accessory pathway. Note the characteristic shortened PR interval and broad QRS with slurring of the initial upstroke (arrow).

The most common form, *orthodromic* AVRT (95%), results from an impulse (eg, PAC) that blocks at the AP (during refractory period), travels down the AV-node His-Purkinje system to the ventricle, then travels retrograde to the atrium via the AP, and reenters the AV node, continuing the tachycardia (**Figure 22.10**). The RP interval is slightly longer in *orthodromic* AVRT (P wave on top of ST segment) compared with AVNRT (P wave at end of QRS complex), but the difference may be subtle on ECG. *Antidromic* AVRT is a much less common form of AVRT (5%) in which an impulse blocks at the AV node, travels down the AP, and returns retrograde to the atrium via the AV node. This results in a distinctive *wide QRS complex* tachycardia on ECG. It is important to remember that preexcited *antidromic* AVRTs with a *manifest* AP that conducts rapidly from the atrium to the ventricle carry a low (< 1%) but tangible risk of SCD, particularly in the setting of AF, AFL, and AT. This is due to rapidly conducted atrial impulses via the AP to the ventricle, which can cause VF. The risk is most pronounced in the first two decades of life, but can be heightened in patients in the CCU receiving AV nodal blocking agents for rate control (ie, β-blockers,

CCBs), which could promote anterograde conduction down the AP.

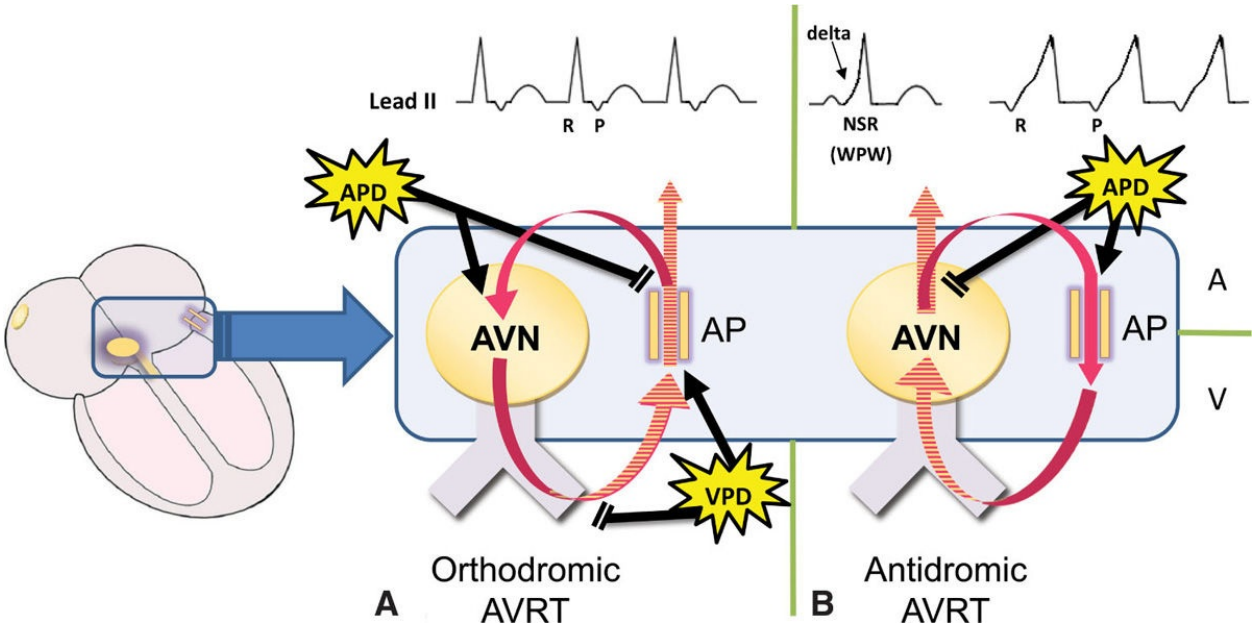

FIGURE 22.10 Mechanisms of atrioventricular nodal reentrant tachycardia (AVRT). A, During orthodromic AVRT, no delta wave is seen because all anterograde conduction is over the AV node (AVN) and His–Purkinje system. Retrograde P waves are seen after each QRS. B, Mechanism of AVRT in patients with the Wolff–Parkinson–White (WPW) syndrome. In sinus rhythm, the slurred QRS upstroke (delta wave) is due to rapid anterograde conduction over the accessory pathway (AP) and early activation of the ventricle (V). During antidromic AVRT, maximal preexcitation results in wide distorted QRS complexes due to V activation exclusively from anterograde conduction over the AP. A, atrium; APD, atrial premature depolarization; AVN, atrioventricular node; NSR, normal sinus rhythm; VPD, ventricular premature depolarization.

Acute treatment of AVRT may focus on either the AV node or on the AP. In *orthodromic* or *antidromic*AVRT, the AV nodal conduction is a viable target for maneuvers and medications that delay or block anterograde or retrograde impulses, respectively. As with AVNRT, vagal maneuvers may slow conduction at the AV node and lead to block and termination of the tachycardia. If unsuccessful, antiarrh tissue refractoriness and block AP conduction. However, these should not be used in patients with structural or ischemic heart disease.[1]Amiodarone is less efficacious than procainamide and may be considered as a last-line option for elderly patients or those refractory to other medications. Owing to its efficacy in delaying extranodal and blocking AP conduction, IV procainamide is considered first line for acute management of *antidromic*AVRT. Predictors of high-risk patients with WPW for SCD are younger males <40 years of age, manifest preexcitation on ECG at all times,

multiple APs, and short antegrade effective refractory period of the AP (< 240 msec).

ATRIAL TACHYCARDIA

AT is a less common form of SVT that initiates from the atria and (unlike AVNRT or AVRT) does not require that the AV node participates in sustaining the arrhythmia. In other words, the atrial origin *drives* the arrhythmia with an atrial rate that can range from 100 to 250 bpm (**Figure 22.11**). The course of AT is typically benign; however, sicker patients in the CCU may exhibit more incessant forms and be at higher risk for developing tachycardia-induced cardiomyopathy or decompensated heart failure.

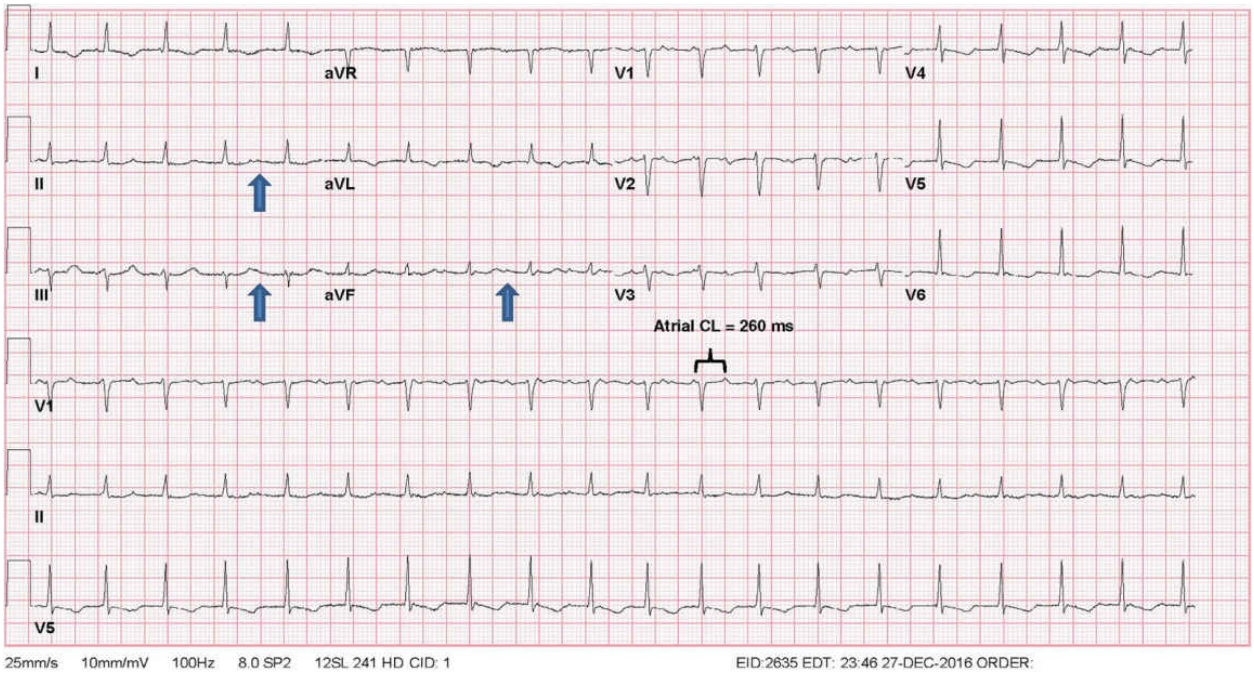

FIGURE 22.11 Atrial tachycardia on 12-lead ECG. Note the upright P waves in the inferior leads (II, III, AVF; arrows) with an atrial cycle length (CL) of 260 ms. ECG, electrocardiogram.

ATs can generally be divided into three types (**Figure 22.12**): (1) focal, (2) multifocal, and (3) macro-reentrant. Focal ATs are characterized by centrifugal spread of atrial activation from a small defined area, and are further described in terms of their EP mechanisms including abnormal automaticity, triggered activity, and microreentry.[16, 17] MAT is a less understood but not an uncommonly encountered AT in the CCU setting. It is typically seen as secondary to a number of underlying cardiopulmonary conditions, particularly

respiratory failure due to chronic obstructive pulmonary disease (COPD). ECG findings should include an irregular tachycardia (ventricular rate ≥100 bpm) with at least three distinct P-wave morphologies and an isoelectric baseline between P waves (**Figure 22.13**). Unfortunately, in the presence of rapid AV nodal conduction, ECG analysis is insensitive for differentiating between ATs.

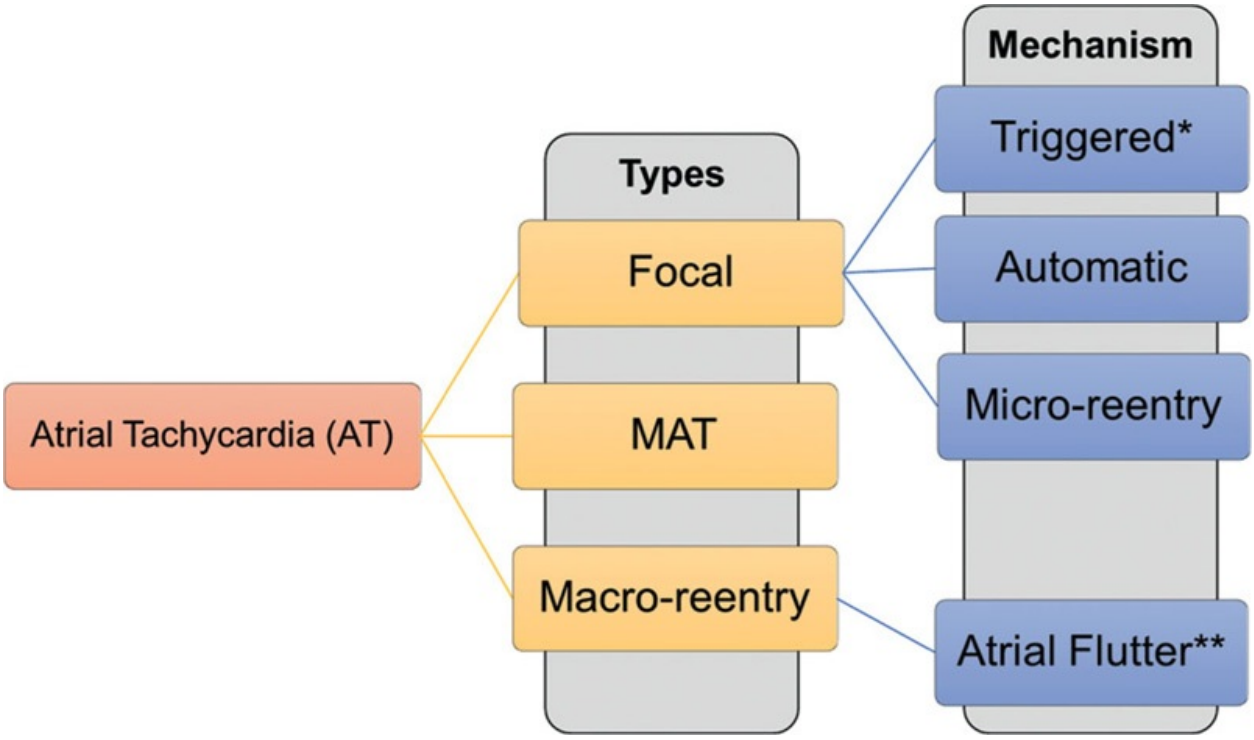

FIGURE 22.12 Classification of AT by type and mechanism. Focal atrial tachycardias (ATs) can commonly occur as a result of early or late afterdepolarizations (triggered activity) or cells with enhanced firing rates compared with normal pacemaker cells (automaticity), or as a result of a small reentrant loop (micro-reentry), which is frequently difficult to locate despite advanced EP mapping software in the lab. Multifocal atrial tachycardia (MAT) is a poorly understood, irregular form of AT characterized by at least 3 different P-wave morphologies. It is often seen as a feature of acute cardiopulmonary illness, especially respiratory failure due to COPD. *Likely etiologic mechanism of a majority of focal ATs. **Atrial flutter discussed in another chapter.

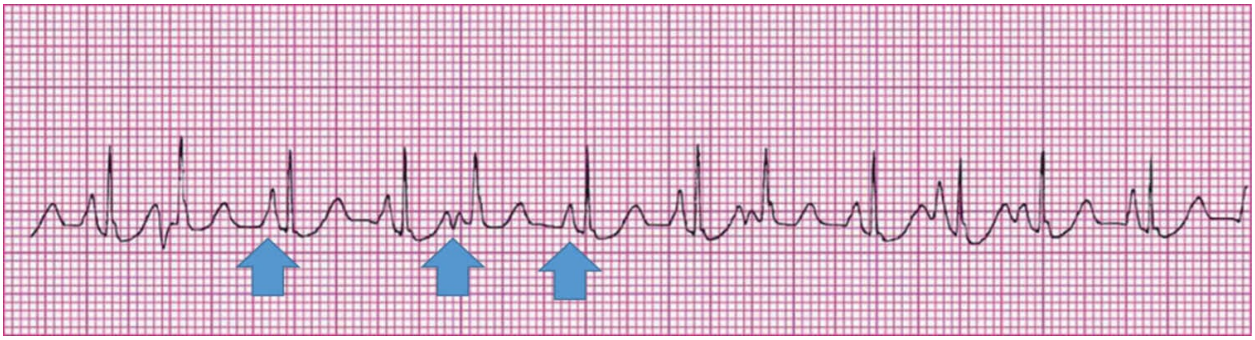

FIGURE 22.13 Multifocal atrial tachycardia (MAT) on a telemetry strip. It is characterized by three distinct P-wave morphologies, with irregular P-to-Pintervals, and ventricular rate >100 bpm. MAT is frequently seen during bouts of acute illness, especially respiratory failure due to decompensated COPD.

Thus, to make a definitive diagnosis, it is especially useful to employ vagal maneuvers or adenosine when encountering an AT. Vagal maneuvers usually do not terminate focal ATs, but can result in a transient AV nodal block that allows for clearer delineation of P waves. Similarly, the antiadrenergic and AV nodal blocking properties of adenosine are very effective in differentiating focal from macroreentrant (ie, AFL) ATs, and can provide additional mechanistic information based on resultant termination (eg, triggered AT) or suppression (eg, automatic AT) of the arrhythmia. The importance of a high-quality ECG rhythm strip during adenosine administration cannot be overstated in this scenario. Additional options for acute management of ATs include AV nodal blocking agents for ventricular rate control (ie, IV verapamil or β-blockers), as well as class IC drugs (flecainide, propafenone) with variable efficacy. In contrast to focal ATs, hospitalized patients with MAT may portend higher morbidity and mortality, and rate- or rhythm-controlling strategies that are typically employed tend to be ineffective. As a mainstay, their predisposing condition should be managed aggressively to offer the best outcomes. Electrical cardioversion is of variable utility depending on the mechanism of AT, and patients with sustained ATs or continued symptoms often benefit (at lower risk) from radiofrequency (RF) catheter ablation as first-line treatment.

INAPPROPRIATE SINUS TACHYCARDIA

In contrast to sinus tachycardia, which is always a normal secondary physiologic response, inappropriate sinus tachycardia (IST) is defined as a sinus tachycardia that cannot be explained by normal physiologic stressors. It is further described by associated symptoms such as weakness, dizziness, and palpitations, which are also not attributable to secondary causes such as thyroid disease, anemia, or drugs. Resting heart rates in patients with IST are typically > 100 bpm, with a mean 24-hour heart rate > 90 bpm.[1]Etiologies such as neurohormonal dysregulation, sinus node hyperactivity, and dysautonomia have been suggested, but the precise cause is uncertain. There has been some association seen with anxiety disorders, and anxiety can be a trigger. Overall, IST carries a benign prognosis, and no specific recommendations for acute management have been published. For ongoing management, ivabradine was found to reduce the

inherent pacemaker activity of the sinus node and has recently been approved by the U.S. Food and Drug Administration for use in patients with concomitant systolic heart failure.[19, 20]

JUNCTIONAL TACHYCARDIA

Junctional tachycardia (JT) is seen infrequently in adults, but may be encountered in patients in the CCU following cardiac surgery. The underlying mechanism is abnormal automaticity from a focus at the AV junction.[21] On ECG, JT manifests as a rapid, regular (occasionally irregular), narrow QRS complex tachycardia with ventricular rates ranging from 100 to 220 bpm, and retrograde (in or after the QRS) P waves (**Figure 22.14**). It is not uncommon to misdiagnose other SVTs (ie, AVNRT, AVRT, MAT) because of the often absent P waves and sometimes irregular appearance on ECG. The course of adult patients with JT is essentially benign, and given the low incidence of JT in this population, there is little data regarding diagnosis and management. Nonetheless, IV β -blockers, verapamil, diltiazem, and procainamide may be reasonable in the acute setting. A far more commonly encountered paroxysmal JT in adults is accelerated junctional rhythm. It exhibits a slower ventricular rate (60-100 bpm) than does JT and is frequently seen in the setting of acute MI or digoxin toxicity. Acute management primarily focuses on treating the underlying condition, but there are some data to suggest that β-blockers, verapamil, or adenosine may terminate the arrhythmia.

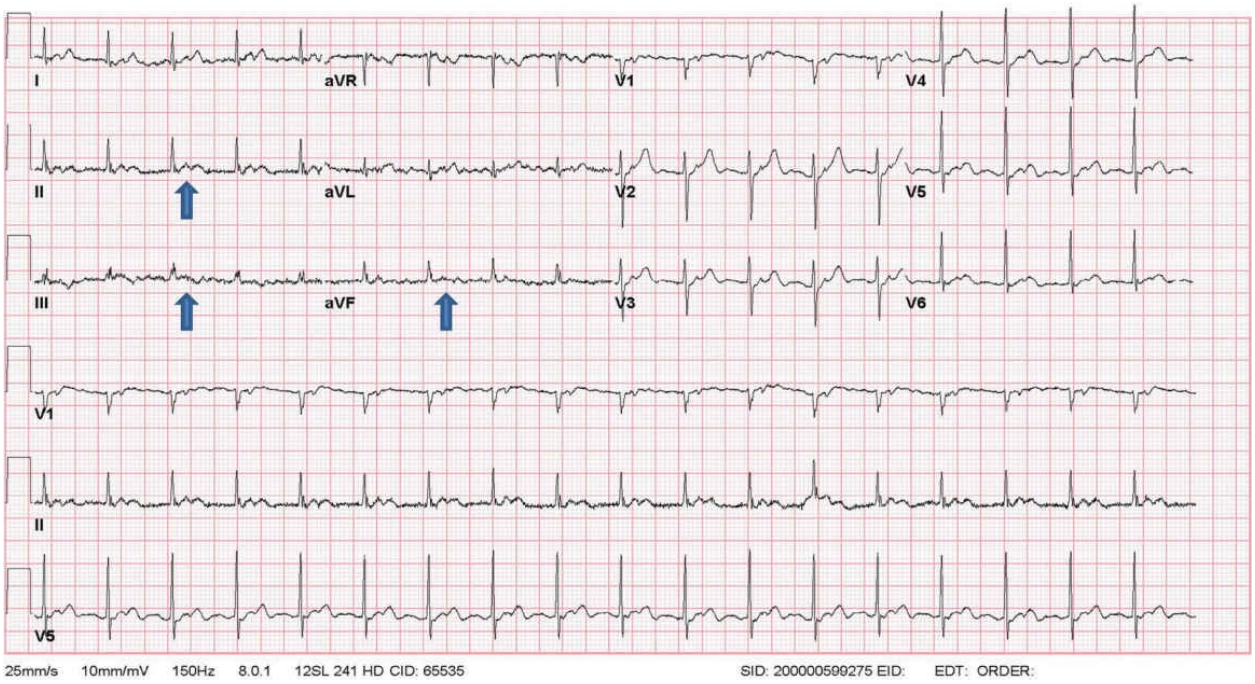

FIGURE 22.14 Junctional tachycardia (JT) or accelerated junctional rhythm. Note the absence of P waves preceding each QRS complex which appear to be buried in the proceeding T waves (arrows).

LONG-TERM MANAGEMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIAS

Patients with infrequent episodes of AVNRT that are well tolerated can be managed long term with prophylactic AV nodal blocking medications (eg, PO β-blockers, verapamil, diltiazem). Although antiarrhythmic medications such as flecainide and propafenone are reasonable secondary options in patients without structural or ischemic heart disease, their use in a younger patient is not preferred. Patients with frequent symptomatic episodes, intolerance to medication, or preference of not using long-term medications can undergo curative RF catheter ablation via *slow* pathway modification (**Figure 22.15**) as first-line therapy. [22, 23] Technological advances have greatly increased the safety, efficacy, and cost-effectiveness[24] of this approach with success rates of 95% to 99% and less than 1% risk of any complications.

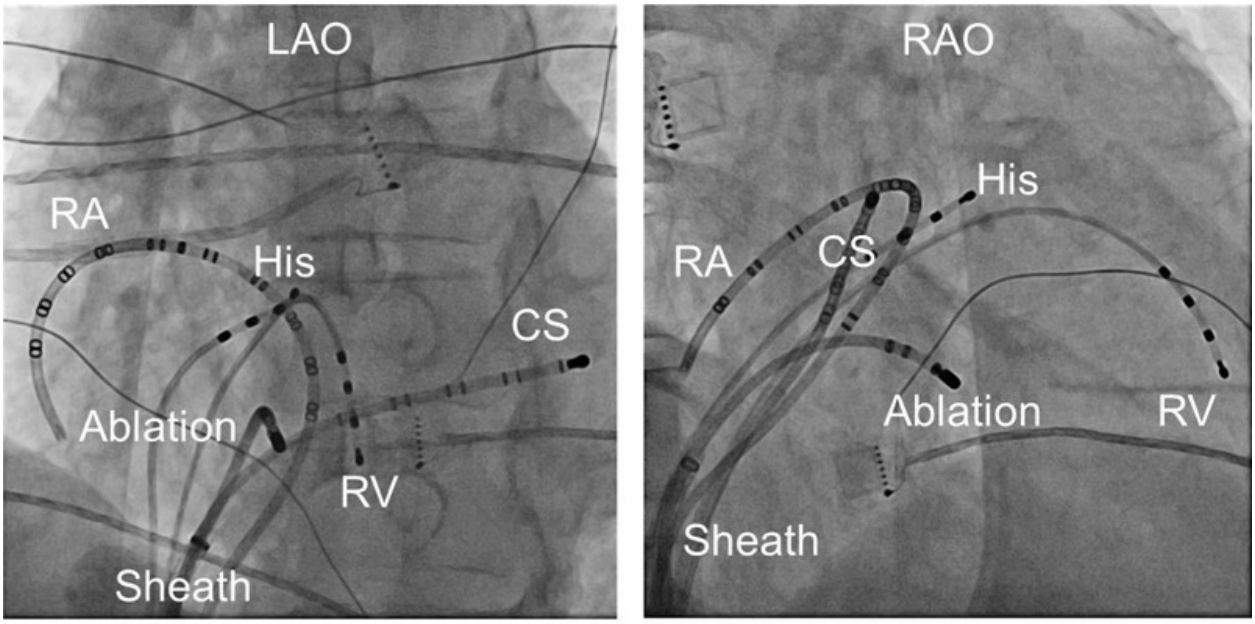

FIGURE 22.15 Catheter positions during slow-pathway modification via radiofrequency ablation for AVNRT. CS, coronary sinus; LAO, left anterior oblique; RA, right atrium; RAO, right anterior oblique; RV, right ventricle; AVNRT, AV nodal reentrant tachycardia.

With similarly high success rates, catheter ablation should be strongly considered for long-term management of symptomatic patients with AVRT and WPW syndrome with high-risk features for SCD. Patients who are not inclined to undergo ablation can be given PO class IC (flecainide, propafenone) or class III (amiodarone) agents in the setting of *antidromic* AVRT.

Controversies exist on the management of asymptomatic patients with WPW; this is due to the complexity of the nature of history of asymptomatic WPW. Certainly, the asymptomatic pediatric population is at higher risk of SCD than is the adult asymptomatic population. Intrinsic EP properties of APs, rather than symptoms can quantify this risk and further delineation with an EP study should be encouraged.

Focal ATs can be managed with a rate-control strategy utilizing AV nodal blocking medications such as PO verapamil, diltiazem, or β-blockers. Catheter ablation is a safe and viable option for symptomatic patients or those with incessant ATs, with variable success rates ranging from 70% to 100%.

MAT is most typically seen in patients with advanced lung disease, but can be additionally correlated to structural heart disease and congestive heart failure. Treatment entails a rate-control strategy with AV nodal agents, but remains centered on management of the underlying condition.

SUMMARY

SVTs are commonly encountered in the CCU. Aside from AF, the SVTs most typically seen (in order of frequency) are AVNRT, AVRT, and AT. Narrow QRS complex tachycardias require a systematic approach to differential diagnosis and treatment. Sinus tachycardia is virtually always a compensatory response that requires identification and treatment of the underlying cause. Early identification of patients with hemodynamic compromise due to SVTs with prompt electrical cardioversion is essential. The initial approach to hemodynamically stable patients with SVT should include vagal maneuvers, followed by medications that transiently slow AV conduction and may potentiate termination of the arrhythmia. Long-term management must be individualized and may include PO AV nodal agents and RF catheter ablation.

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Patient and Family Information for:SUPRAVENTRICULAR ARRHYTHMIAS

WHAT IS SUPRAVENTRICULAR TACHYCARDIA?

Supraventricular tachycardia (SVT) is a general term used to classify abnormally fast heartbeats (tachycardias) known as arrhythmias, which originate above (supra-) the ventricles (lower chambers) in the atria (upper chambers) of the heart. The term *paroxysmal* is sometimes used to describe SVTs that start and stop suddenly or intermittently, without warning. Although normal heart rates range from 60 to 100 beats per minute (bpm), heart rates during SVT are usually greater than 130 bpm and may climb above 200 bpm in some instances. The fast heartbeat can last minutes or even hours, and it can happen during rest or with exercise. In a hospital setting, additional stress from the patient's illness(es) may provide a trigger for SVT to occur more frequently. SVT is not a single disease; rather, it encompasses a number of arrhythmias that have different causes and may each require unique treatment strategies. The three most common types of SVT are called atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and atrial tachycardia (AT). Atrial fibrillation and atrial flutter with rapid heart rates are also types of SVT and are discussed in detail in a separate chapter.

HOW IS SUPRAVENTRICULAR TACHYCARDIA RECOGNIZED?

Some patients may not experience symptoms during episodes of SVT. If

symptoms are present, the patient may have a sensation that his or her heart is beating very rapidly, forcefully, and/or irregularly (also known as palpitations). In addition, the patient may feel tired, dizzy, faint, and, in some instances, pass out because of lack of adequate blood flow to the brain when the heart is beating very rapidly. Patients who also have coronary artery disease or congestive heart failure may also experience symptoms such as difficulty breathing and tightness or pain in the chest. Although symptoms are useful in recognizing arrhythmias, determining specific types of SVT requires careful examination of the 12-lead electrocardiogram (ECG). Because of the intermittent nature of most SVTs, longer-term monitoring is sometimes required. In the hospital or cardiac care unit (CCU) setting, this can be done readily using standard continuous telemonitoring devices worn by many or all patients. A cardiologist may ask the outpatient to wear an external monitoring device for up to one month or may refer him or her to a cardiac electrophysiologist (electrical specialist of the heart), who can implant a longer-lasting device under the skin to provide monitoring for two years or more. On some occasions, a more invasive study called an electrophysiology (EP) study is performed to better pinpoint the exact type of SVT. The procedure is done in a closely monitored laboratory setting using multiple catheters that are introduced into the heart from veins in the legs. Using this minimally invasive technique, abnormal electrical circuits in the heart can be accurately located and mapped.

SINUS TACHYCARDIA VERSUS SUPRAVENTRICULAR TACHYCARDIA

Not to be confused with SVT, sinus tachycardia refers to a fast heart rate, typically 100 to 130 bpm, which originates from and travels through the normal electrical circuits in the heart. It is a normal reaction of the heart to exertion, exercise, and stressors such as anxiety, fever, and pain. It is also commonly associated with various illnesses that directly or indirectly affect the heart such as heart failure, heart attack, infections (e.g., pneumonia), and blood clots in the lungs (pulmonary embolism). Thus, sinus tachycardia is almost always a means by which the body compensates during illness or stress, and it does not require specific treatments aside from managing the underlying stressor. In contrast, SVT is always abnormal (pathologic) and requires treatment.

HOW IS SUPRAVENTRICULAR TACHYCARDIA TREATED?

Paroxysmal SVT most often starts and stops abruptly, but when it occurs, it can result in a spectrum of clinical findings from uncomfortable palpitations to life-threatening hemodynamic instability (low blood pressure) or organ ischemia (low blood flow), requiring urgent intervention. If the patient is unstable, conversion (cardioversion) to normal sinus rhythm can be immediately attempted by applying an electric current (shock) over the chest to the heart. Electrical cardioversion is a generally safe and effective (over 90%) way to quickly restore a normal heart rhythm, and patients are given sedatives and pain medication prior to delivery of the shock if possible. In situations where blood pressure is stable and the patient has a good pulse, doctors may try vagal maneuvers to slow the heart rate and terminate the arrhythmia without medications. Vagal maneuvers affect the nervous system, which then signals the heart to respond by reducing the heart rate. One of these techniques used by doctors is called carotid sinus massage, and is performed by briefly pressing (for 5 to 10 seconds) on a specific area of the neck overlying the carotid arteries that carry blood to the brain. This is done while closely monitoring the patient's ECG and vital signs, as it can cause slowing of the heart rate and may lower the blood pressure. Carotid massage should not be performed by the patient or on patients who have blockages in their carotid arteries. Alternatively, doctors may instruct the patient to try Valsalva maneuvers such as holding a deep breath and straining (as during a bowel movement). Both carotid massage and Valsalva maneuvers can slow the heart rate to better identify the type of SVT or may terminate it completely.

If vagal maneuvers do not work, certain medications can be given orally or intravenously (IV) to try and terminate the SVT. The most commonly used medication is IV adenosine. This medication works by slowing the heart rate and temporarily blocking impulses traveling from the upper to the lower chambers of the heart, which can break the abnormal electrical circuit in the heart and terminate the arrhythmia. After injection, patients often feel brief uncomfortable symptoms such as skin flushing, chest tightness, and shortness of breath, which quickly subside because of adenosine's short duration of action. Other medications that may be used to slow the heart rate or terminate SVT include beta-blockers (e.g., metoprolol), specific calcium channel blockers (e.g., diltiazem, verapamil), and specialized antiarrhythmic medications. If the

episodes of SVT are infrequent and patients are not highly symptomatic, daily oral medications to control heart rates during episodes or prevent attacks may be sufficient. In patients with severe symptoms and frequent episodes, an EP study followed by an ablation procedure can be performed to cure the arrhythmia. Like EP studies, ablations are procedures that are done in the EP laboratory and use catheters that are guided into the heart. Catheters are then directed to the specific spots in the heart, from where the SVT is thought to originate, and then tiny controlled burns (called radiofrequency ablation) or extreme cold (cryoablation) is applied to destroy the abnormal electrical circuits that are causing the arrhythmia. In most patients with SVT, the arrhythmia is permanently cured after the ablation procedure.

SUMMARY

Supraventricular arrhythmias are commonly seen in the CCU. Sinus tachycardia should be differentiated from SVT in that it is almost always a normal means by which the body compensates for a stressor such as exercise, fever, or illness. As such, it does not require specific management other than identification and treatment of its underlying cause. In contrast, SVT is always abnormal and can result in a wide range of clinical findings from benign uncomfortable symptoms to ischemia or life-threatening hemodynamic instability. Careful examination of ECG findings can help narrow down specific types of SVT, but pinpointing specific types often requires long-term monitoring because of the intermittent nature of the arrhythmia. Patients who are hemodynamically unstable may require urgent electrical cardioversion to restore normal heart rhythm. After identifying SVT in a stable patient, doctors may attempt vagal maneuvers, followed by IV adenosine in an attempt to slow the heart rate and terminate the arrhythmia. Patients who have severe symptoms or frequent episodes of SVT can have an EP study followed by catheter ablation (radiofrequency or cryoablation) with a high likelihood of permanently curing the arrhythmia. A good basic understanding of the causes and issues related to SVT and its management is important for patients and their families.

23

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Fundamentals of Atrial Fibrillation and Atrial Flutter

ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common arrhythmia in the adult population, with continuously increasing prevalence as the population ages; currently, 6 million adults in the United States are diagnosed with AF. It represents a significant influence on morbidity and mortality rates as well as a large economic and public health burden.[1] AF predisposes to a greater risk of stroke and mortality while impairing quality of life.[2] The estimated cost of treating US citizens with AF is $26 billion a year. It is estimated that by year 2050 the prevalence of AF will be close to 12 million. This assumption is based on increasing mean age of population, obesity epidemic, as well as achievements in treatment of cardiovascular diseases.[3]

Men have a 1.5-fold higher risk for developing AF than women, derived from data adjusted for age and predisposing conditions.[4] Although it seems to be less common in African Americans, lifetime risk of developing AF is higher in men of European descent compared with women of European descent (26% vs 23%). AF is strongly age associated, most commonly presenting at age 80 or above (about 1 in 10) and only 1% of patients with AF are less than the age of 60.

Aging of the population is the main underlying factor for rapidly increasing prevalence of AF.[5, 6]

ETIOLOGY

Patients with underlying cardiovascular disease often have abnormal atrial size and function. Enlargement of the atrial chamber, fibrosis, fatty or amyloid tissue deposition, and inflammation can contribute to abnormal functionality and electrical remodeling of the atrium leading to pathologic evolution of AF. Some patients have AF occurring under the influence of autonomic nervous system: vagal form (after meals, during sleep) or adrenergic form (exercise induced).

RISK FACTORS

1. Increasing age: especially >80 year old, one in 10 patients above age 80 will develop AF. This represents >1/3 of patients with AF.[7]
2. Male sex: a 1.5-fold higher risk than in females.[8]
3. Tall stature and obesity: these are independently associated with increased incidence of AF.[9] In the Framingham Heart Study, every unit increase in body mass index (BMI) was associated with an approximate 5% increase in risk.
4. Metabolic syndrome[10]: with its components, hypertension (HTN),[8] obesity,[9] diabetes mellitus, hyperlipidemia, are all associated with higher risk of AF.[11] BMI, waist circumference, and sagittal abdominal diameter could similarly predict AF.[12]
5. Valvular heart disease: the most potent association is with mitral stenosis.
6. Myocardial infarction (MI): AF in the setting of acute MI independently predicts stroke and 30-day mortality[13]; can be seen in up to 10% of patients in the early period after acute MI.[8, 14]
7. Postsurgical AF: there are heterogeneous patterns of AF after cardiac surgery. The incidence is 20% to 25% in patients undergoing coronary artery bypass grafting and up to 40% after valvular surgery. A substantial minority of AF is short-lived and isolated, with no impact on length of stay; however, recurrent or prolonged AF significantly affects outcomes.[15]
8. Heart failure (HF): there is individual variation of cause–consequence relationship.[16]
9. Obstructive sleep apnea (OSA): predisposes by metabolic and autonomic

abnormalities, as well as structural cardiovascular changes.[17] Untreated OSA is associated with much higher risk of development of AF as well as recurrence after AF ablation.[18]

10. Chronic kidney disease.
11. Hyperthyroidism: clinically overt and subclinical, it is associated with higher risk of developing AF.
12. Excessive alcohol consumption, caffeine, cigarette smoking.
13. Excessive physical exertion: athletic lifestyle, especially the one involving endurance activities predisposes to higher risk especially in young patients (due to high vagal tone).
14. Genetic predisposition: parental AF predisposes the offspring by two to three times than in the general population.

PATHOPHYSIOLOGY

The pathophysiology of AF is multifactorial and complex, including genetic and neural system mechanisms. Haissaguerre et al were the first to evaluate and discover pulmonary veins (PVs) as the dominant triggers in the initiation of AF.[19] Focal triggers can lead to reentry in high-frequency rotors, and electrical activation from these rotors may fragment giving fibrillatory conduction. If this process continues for long periods, there is subsequent atrial remodeling at the cellular level (ion channels) and other triggers raise further perpetuating AF, in particular small and large reentrant wavelets. AF induction may occur in the presence of fibrotic and poorly conducting atria (eg, due to hemodynamic overload, as in HTN or HF); genetic disorders affecting refractory period and/or conduction velocity heterogeneously[20]; or AF itself. By shortening the atrial refractory period, reducing conduction velocity, and provoking contractile and structural remodeling, AF may set the stage for self-perpetuation (ie, “AF begets AF”).[21] Structural remodeling of both atria typically happens under the influence of previously mentioned risk factors. This remodeling is mediated by activations of fibroblasts, fibrosis, fatty infiltration, connective tissue deposition, myocyte hypertrophy, necrosis, and inflammatory infiltration. All these processes result in local conduction disturbances and electrical dissociation that leads to micro-reentrant circuits’ formation. Genetic mechanisms associated with AF development include abnormalities in potassium or sodium channels, connexin expression or function, and microRNAs[22] (**Figure 23.1**).

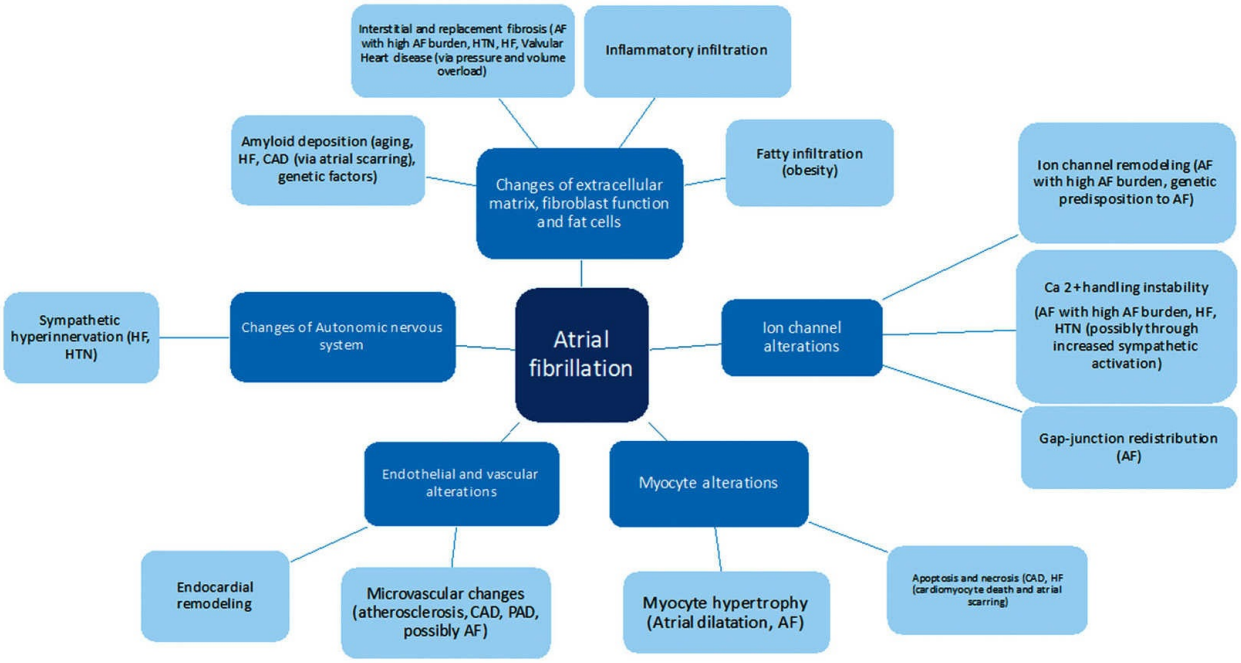


FIGURE 23.1 Key factors in the pathophysiology of atrial fibrillation (AF). CAD, coronary artery disease; HF, heart failure; HTN, hypertension; PAD, peripheral artery disease. Modified from ESC guidelines 2016: management of atrial fibrillation.[22]

CLASSIFICATION

Detecting asymptomatic or minimally symptomatic AF improved with implantable loop recorders (ILRs), pacemakers, and defibrillators.

1. **Lone AF or idiopathic AF:** It used to be defined as patients who have no precipitating cause or associated CV disease. However, the percentage of AF that is considered lone AF decreased from 30% in 1954 to 3% in 2014 based on studies that showed larger proportion of etiologic factors of AF. The term lone AF is generally avoided because it is not fully clear to what extent the workup should be done to consider AF to be idiopathic and also the term is not useful in making treatment decisions.[23]
2. **Asymptomatic AF** (subclinical): Early recognition of AF at times is difficult owing to its often "silent" nature. For one-third of patients with AF, they are not aware that they are in AF. Recent studies using different monitoring tools, ranging from transtelephonic monitoring to pacemakers, have indicated that the correlation between AF episodes and patient symptoms is very poor: many AF episodes are asymptomatic, whereas many AF-like symptoms are

not related to AF episodes.[24] Early detection of the arrhythmia might allow timely introduction of therapies to protect patients from AF complications as well as the possibility of interrupting the progression of AF from a potentially treatable condition to a refractory one. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (***ASSERT***) monitored patients 65 years or older who had HTN and no prior history of AF and a newly implanted pacemaker or cardioverter defibrillator for development of subclinical atrial tachyarrhythmias (defined as episodes of atrial rate >190 beats per minute [bpm] for more than 6 minutes). At 3 months, 10.1% of the enrolled patients had developed such episodes. Subclinical AF was indeed associated with both an increased risk of clinical AF and ischemic stroke and systemic embolization.[25] More intense and prolonged monitoring is justified in highly symptomatic patients, patients with recurrent syncope, and patients with a potential indication for anticoagulation (especially after cryptogenic stroke).[26]

3. **Paroxysmal AF:** Self-terminating (within 48 hours to 7 days).
4. **Persistent AF:** Continuously present for more than 7 days and up to 1 year.
5. **Long-standing AF:** Continuous AF lasting for ≥1 year.
6. **Permanent AF:** Duration longer than 1 year with failed attempts to restore and maintain sinus rhythm (SR).

ATRIAL FIBRILLATION, A PROGRESSIVE DISEASE

AF is a progressive disease that becomes more difficult to treat with increasing duration. In patients presenting with paroxysmal AF—progression to persistent AF is 10% in 1 year, 25% to 30% in 5 years, and more than 50% in 10 years. In patients with persistent AF lasting more than 1 year, only 40% to 60% remain in SR; and in patients with more than 3 years of duration, only 15% are maintained in SR. Clinical progression, supported by electrical contractile and structural atrial remodeling promotes AF stability and persistence.[21] The HATCH scoring system (based on underlying HTN, age >75 years, history of transient ischemic attack (TIA) or stroke, chronic obstructive pulmonary disease, and HF) was proposed to predict this risk of progression in patients receiving pharmacologic therapy.[27] The clinical outcomes of patients who exhibit progression of AF are worse with respect to hospital admissions and major adverse cardiovascular

events. In the Euro Heart survey, patients with AF who had progressed to persistent or permanent AF had higher rates of hospital admissions, TIA, stroke, MI, and death.[28]

WORKING UP ATRIAL FIBRILLATION

Diagnosis

On initial evaluation of the patient who presents with AF, it is important to obtain:

- Key history: Questions such as symptoms, frequency, and duration to establish the AF pattern, initial onset, history of cardiovascular conditions and noncardiovascular conditions that are associated with AF, and assess the risk of complications such as thromboembolism and left ventricular (LV) dysfunction.
- Electrocardiogram (ECG): To establish suspected diagnosis of AF, assess the rate, evaluate for possible conduction abnormalities, ischemic changes, and signs of structural heart disease.
- Echocardiography: To assess ventricular size and function, left atrial (LA) dimensions (left atrium shown to enlarge by about 5 mm in diameter over 1 year in patients with AF, LA enlargement [>55 to 60 mm] associated with failure to maintain SR after successful cardioversion), and to identify any structural disease such as valvular heart disease.
- Transesophageal echocardiography (TEE): To evaluate for presence of thrombus if patient is to undergo cardioversion; although the presence of spontaneous echo contrast (smoke) is not a contraindication for CV, the risk of stroke is increased in the presence of smoke or reduced left atrial appendage (LAA) emptying velocity.[29]
- Blood tests: Thyroid function, kidney function, and electrolytes abnormalities.
- Exercise stress testing or coronary angiogram: In those cases where there is LV dysfunction, ischemic signs are noted or patient has symptoms of ischemia.
- Monitoring: To assess the adequacy of rate control, relate symptoms with AF recurrences, and detect focal induction of bouts of paroxysmal AF. This can be achieved by a Holter monitor, AF auto-trigger monitor, or mobile cardiac outpatient telemetry. They all carry relative diagnosed yield ranging from 5% to 13% in the 24-hour Holter to 45% to 88% in the outpatient telemetry.[30] Previously undiagnosed AF was found in 1.4% of those aged >65 years,

suggesting a number needed to screen of 70. These findings encourage the further evaluation of systematic AF screening programs in at-risk populations.[31]

- ILR can be used when the AF burden is relatively small and in asymptomatic patients. They typically have the highest diagnosed yield of more than 80%.[32]

Complications

There are many consequences of AF that lead to disease states. Loss of organized atrial contraction often leads to exercise intolerance and HF.[33] Rapid ventricular rhythm can lead to tachycardia-induced cardiomyopathy and precipitate myocardial ischemia.[4] Certainly, aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or atrial myopathy, that can result in AF and thromboembolism. AF causes contractile dysfunction and stasis, which further increases the risk of thromboembolism. In addition, over time, the AF causes structural remodeling of the atrium, thereby worsening atrial myopathy and increasing the risk of thromboembolism even further. **Figure 23.2** depicts the recently adapted model of thromboembolic stroke in AF.[34]

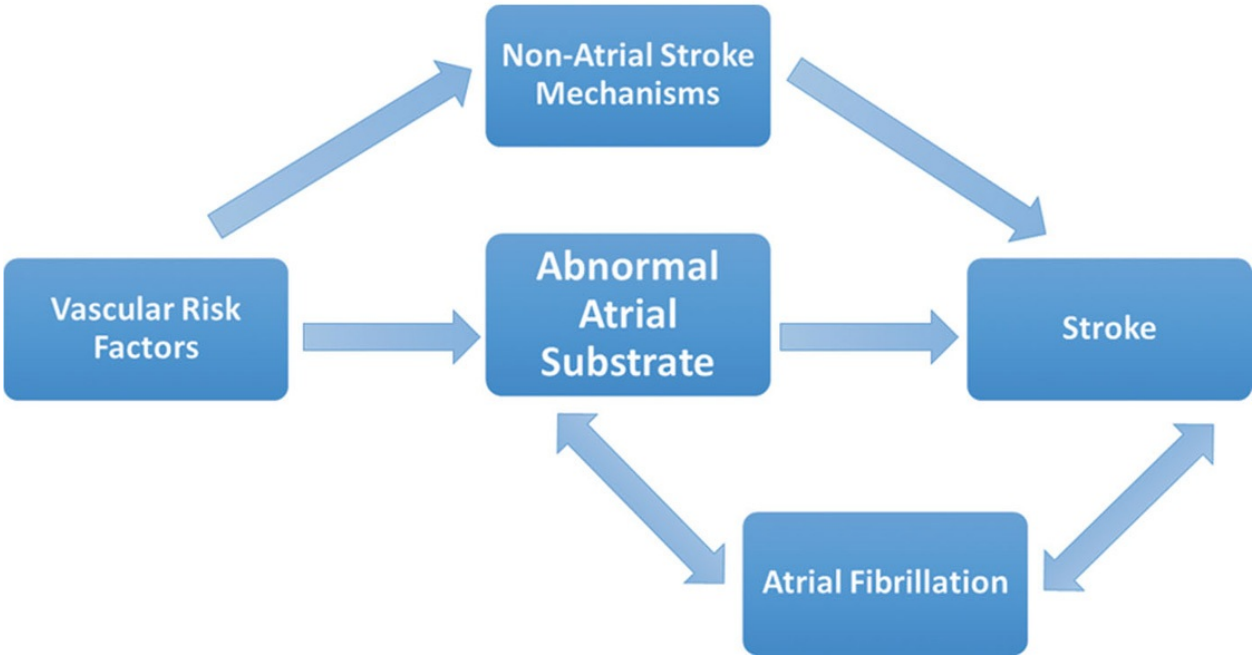


FIGURE 23.2 Recently adapted model of thromboembolic stroke in atrial fibrillation.

AF is associated with increased mortality; 1.5-fold for men and 1.9-fold for women.[35] Other complications are precipitation of ventricular electrical instability, anti-arrhythmic medication adverse effects, and pro-arrhythmic effects.[36]

ATRIAL FIBRILLATION AND STROKE

One in seven strokes is attributed to AF and it is suspected that subclinical AF is a cause of 1 in 4 ischemic strokes. Risk of death from AF-related stroke is 2-fold higher than that of stroke in patients without AF.[25] Premature atrial contractions,[37] paroxysmal supraventricular tachycardia,[38] ECG-defined LA abnormality,[39] and LA size[40] have been associated with stroke independently of AF. It is widely believed that failure of the fibrillating atrium to contract in patients with AF can lead to atrial stretch and dilatation, in turn promoting stasis and thrombus formation inside the LAA.[41] The LAA arises from the PVs and is an embryologic remnant of the left atrium and consists of a trabeculated 2- to 4-cm–long structure in direct continuity with the left atrium. Thus, its unique shape and anatomy may predispose to in situ thrombus formation.[42]

The individual stroke risk may be estimated using the CHA_2DS_2-VASc (C, congestive HF/LV dysfunction; H, hypertension; A_2, age [≥75 years]; D, diabetes; S_2, stroke/TIA attack; V, vascular disease; A, age 65 to 74 years; and S_c, sex category) classification scheme; classification is based on patient characteristics, with higher scores corresponding to a higher risk for stroke **(Table 23.1**). Thromboprophylaxis is the mainstay of stroke prevention in patients with AF.

TABLE 23.1 CHA_2DS_2-VASc Score

RISK FACTOR	POINTS
Congestive heart failure (symptoms of HF or evidence of HFrEF)	+1
Hypertension (BP>140/90 or ongoing treatment with anti-HTN drugs)	+1
Age >75	+2
DM (Fasting Glu>125 or HbA1C>6.5 or ongoing treatment)	+1

Previous stroke, TIA, or VTE	+2
Vascular disease (previous MI, PAD, or aortic plaque)	+1
Age 65–74	+1
Female sex	+1

DM, diabetes mellitus; HF, heart failure; HTN, hypertension; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack; VTE, venous thromboembolism.

ANTICOAGULATION

On the basis of clinical practice guidelines published by the American College of Cardiology, the American Heart Association, the American College of Chest Physicians, and the European Society of Cardiology, patients with AF should generally receive oral anticoagulation (OAC) with vitamin K antagonist (VKA) or novel oral anticoagulants (NOACs) such as apixaban, dabigatran, rivaroxaban, or edoxaban. OAC therapy has shown to prevent the majority of ischemic strokes in patients with AF and can prolong life.[43] VKA is still the only treatment with proven benefit for valvular AF (moderate or severe mitral stenosis or a mechanical valve). For nonvalvular AF, both VKA and NOACs are effective in preventing stroke. There have been multiple recent studies comparing NOACs with warfarin; and large cohort meta-analysis by Ruff et al that included 42,411 patients suggests that NOACS, while offering same level of stroke reduction as warfarin, is associated with greater reduction in mortality, less intracranial bleeding, and more frequent gastrointestinal bleed.[43] According to the 2016 ESC guidelines for the management of AF, NOACs are the preferred anticoagulants (ACs) over VKA for patients with nonvalvular AF.[22]

Antiplatelet therapy is inferior to AC for prevention of stroke and should not be used alone; however, when patients are required to be both on AC and dual oral antiplatelets (DAPTs), the risk of bleeding is increased.

In all patients who require ACs, bleeding risk should be assessed. The most widely used tool is the HAS-BLED score[45] (**Table 23.2**).

TABLE 23.2 HAS-BLED Score

RISK FACTOR	POINTS
Hypertension	+1
Abnormal renal function (dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L)	+1

Abnormal liver function (cirrhosis or bilirubin >2x Normal or AST/ALT/AP >3x Normal)	+1
Stroke history	+1
Prior major bleeding or predisposition to bleeding	+1
Labile INR (unstable/high INRs), time in therapeutic range < 60%)	+1
Elderly age >65	+1
Drugs/alcohol use history (≥ 8 drinks/week)	+1

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; INR, international normalized ratio.

The general consensus is that high bleeding score should not avert from using ACs, but the effort should be made to correct identifiable bleeding factors such as (HTN [systolic BP >160], labile international normalized ratio when on VKA, other drugs predisposing to bleeding—DAPTs or NSAIDs, excess alcohol intake [>8 drinks a week]) and potentially modifiable risk factors (anemia, impaired renal function, impaired liver function, and reduced platelet count or function).

Anticoagulation can be risky for some patients and, alternatively, LAA occlusion devices should be considered. Several indications for LAA occlusion may be taken into consideration. Such indications may include stroke reduction: (1) in those with absolute contraindications to OAC, (2) in patients with relative contraindications to OAC, or (3) as an alternative to OAC therapy for those with high fall risk.

Romero et al published data of computed tomography that demonstrated the four most common LAA morphologies: “Cactus” has a dominant central lobe with extending secondary lobes. “Windsock” has a dominant lobe larger than the distal portions of the LAA. “Cauliflower” has no dominant lobe, but has more complex characteristics than other morphologies. “Chicken-wing” presents an obvious bend in the proximal or middle part of the dominant lobe, or folding back on itself which can be a secondary lobe or twig[46] **(Figure 23.3)**. Three percutaneous devices to facilitate LAA closure have been developed and are in use: Watchman, Amplatzer, and the Lariat suture **(Figure 23.4)**. Although the randomized clinical trial PROTECT-AF[47] showed noninferiority of the Watchman device as compared with warfarin therapy for stroke prevention, there are still limited data as to whether the risk of stroke reduction is comparable to OAC and it is therefore recommended to continue OAC for at least 6 weeks after

implantation of the Watchman closure device. The Amplatzer plug has been utilized for percutaneous patent foramen ovale closure and has also been adopted as a method for LAA exclusion, although no randomized clinical trial of its use for this indication currently exists. The Lariat device is placed using a combined percutaneous endocardial and epicardial approach, and no OAC therapy is required after Lariat LAA closure.

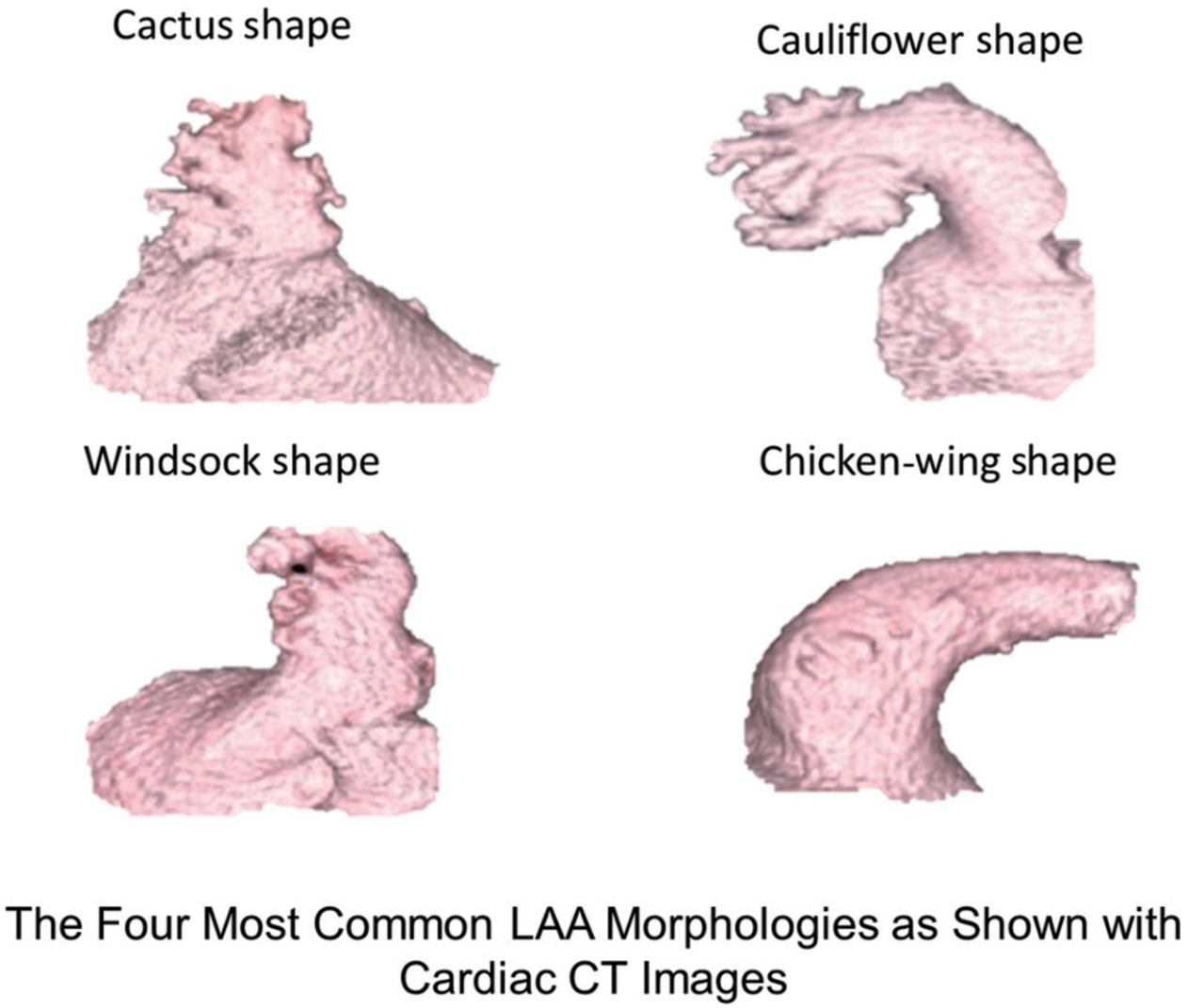


FIGURE 23.3 Left atrial appendage (LAA) morphology as seen by cardiac computed tomography (CT).

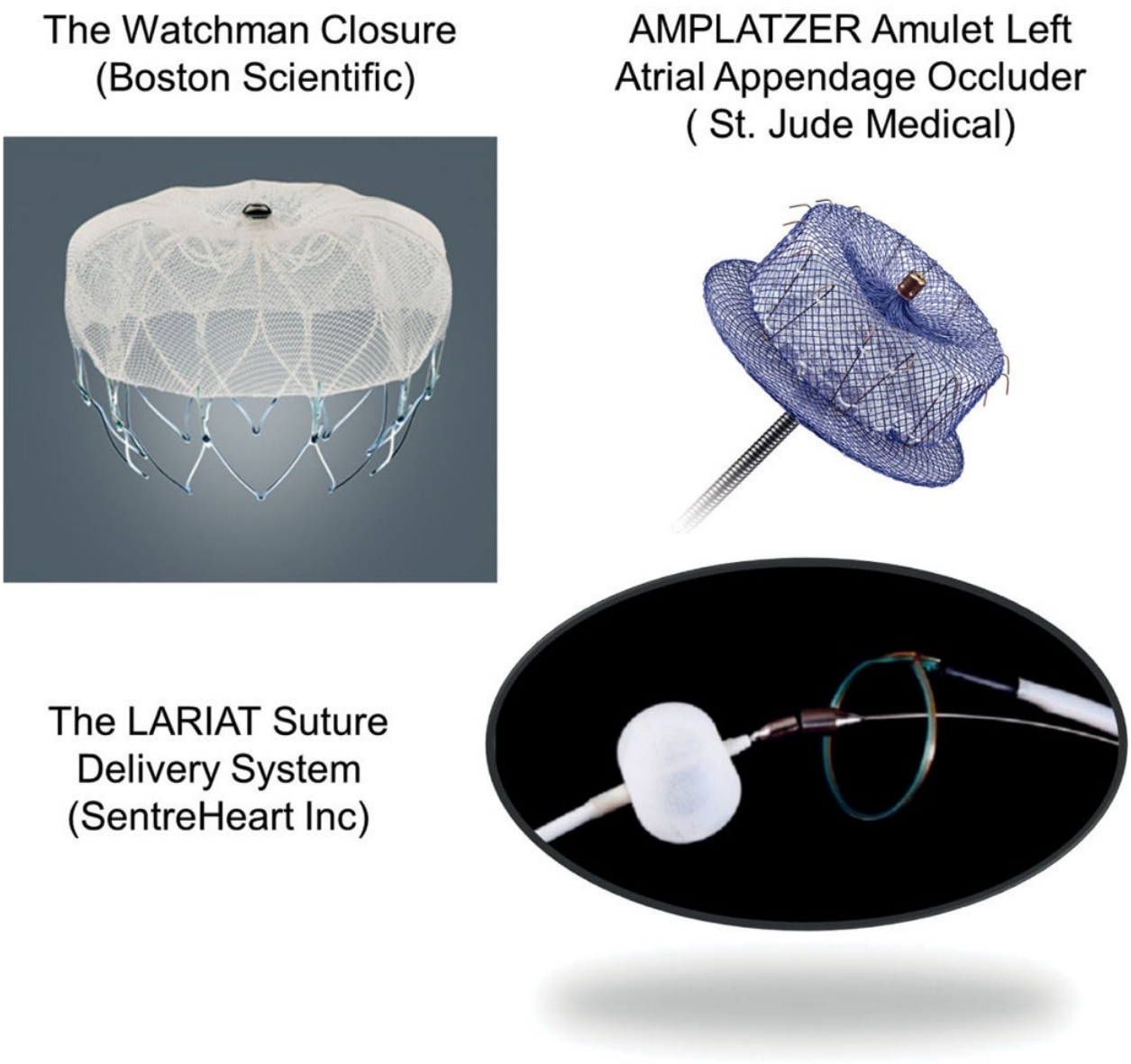


FIGURE 23.4 Available left atrial appendage closure devices.

In case of a TIA, OAC can be resumed 1 day after the event.

In case of a stroke, OAC can be resumed 3 to 12 days after the event, depending on the severity of the stroke.

A controversial question arises when a patient needs OAC and antiplatelet therapy. Two randomized clinical trials are currently testing different antithrombotic combinations for patients on OAC who require stent implantation. The Triple Therapy in Patients on Oral Anticoagulation After Drug

Eluting Stent Implantation (***ISAR-TRIPLE***, clinicaltrials.gov id NCT00776633) trial will address the hypothesis that reducing the length of clopidogrel therapy from 6 months to 6 weeks after implantation of a drug-eluting stent is associated with a reduced net composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months on top of treatment with aspirin and an oral anticoagulant. The Anticoagulation in Stent Intervention (***MUSICA-2***, clinical trials.gov id NCT01141153) trial is investigating the safety and efficacy of a triple antithrombotic regimen of acenocoumarol, low-dose (100 mg/d) aspirin, and clopidogrel versus high-dose (300 mg/d) aspirin and clopidogrel in patients with AF and low-to-moderate risk of stroke (CHADS2 ≤2) referred for percutaneous coronary intervention (PCI).

Currently, it is suggested that patients with AF who are at risk of stroke and who require antiplatelet therapy should minimize the time on triple therapy because of significantly increased risk of bleeding.

TREATMENT

The treatment strategies are subclassified to the acute or new onset of AF and treatment of established AF. **Figure 23.5** illustrates a typical diagram for treatment strategies for acute and chronic AF.

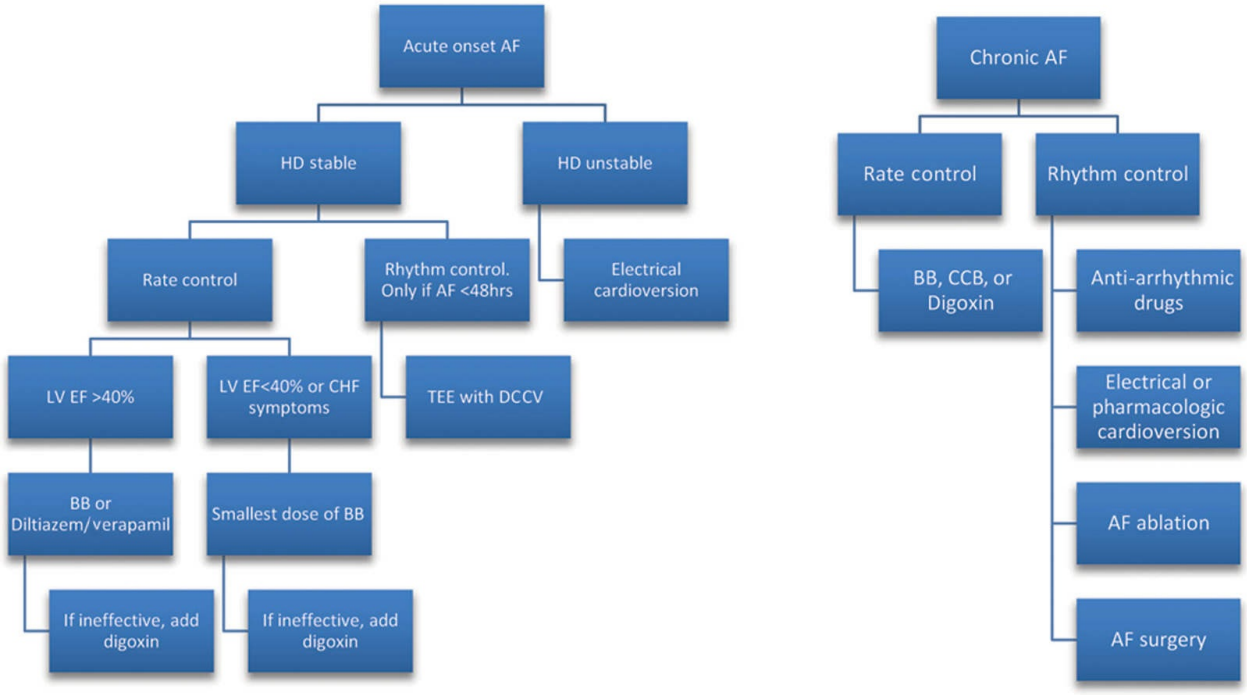


FIGURE 23.5 Treatment strategies for acute and chronic atrial fibrillation (AF). BB, β-blocker; CCB, calcium channel blocker; CHF, congestive heart failure; HD, hemodynamically; LVEF, left ventricular ejection fraction; TEE, transesophageal echocardiography.

Acute- or New-Onset Atrial Fibrillation

Many patients at presentation require heart rate (HR) control after other possible causes of increased HR are excluded such as infection, pulmonary embolism, and endocrine abnormalities. Agents preferred for acute rate control are β-blockers (BBs) and non–dihydropyridine calcium channel blockers (ND-CCBs), that is, diltiazem and verapamil given their rapid onset of action. However, the choice of the agent should be based on existing comorbidities. For example, in patients with left ventricular ejection fraction (LVEF) <40%, CCB should be avoided because of its negative inotropic effect and BBs should be used instead. The typical recommended initial controlled HR target should be <110 bpm. Patients who are hemodynamically unstable require immediate direct current cardioversion to restore cardiac output.

Established Atrial Fibrillation Diagnosis

There are two basic strategies for the treatment of AF, rate and rhythm control,

and each has its own benefits and drawbacks.

- **Rate control:** Target HR for rate control strategy is <110 bpm at rest. Early data from the RACE and the AFFIRM trials showed that there is no difference in CV events, NYHA class, or hospitalizations[48] between groups of patients with lenient or strict heart rate goals. However, the HR target should still be individually set given that some patients are symptomatic at the HR of 110 bpm. First-line rate control agents are BBs because of their potential beneficial effect on symptoms and lack of harm as well as having a good tolerance profile. Patients should be started on a low dose and uptitrated to achieve target HR control. Second-line agents are ND-CCBs (verapamil or diltiazem); however, this class should be avoided in patients with LVEF <40%. Also, avoid concomitant use with BBs. Digoxin can also be used in combination with BBs or CCBs to achieve better HR control (*ESC 2016 class IB recommendations for AF and class IB for AF with HFrEF*).[49] Amiodarone can be used when combination therapy fails to control HR. The last resort for rate control is the ablate and pace technique, in which AV junctional ablation is performed and a dual chamber of BiV pacemaker is implanted. A study by Queiroga et al showed that ablate and pace is associated with a low overall mortality and, interestingly, 48% of patients were still in SR at 72 months.[50]
- **Rhythm control:** Current 2014 AHA/ACC/HRS guideline for the management of patients with AF consider antiarrhythmic medications as the first-line, long-term treatment for symptomatic patients, however long-term follow-up studies have shown that these drugs can also have pro-arrhythmic effects.

Cardioversion to Normal Rhythm

Cardioversion, whether electrical or pharmacologic, is recommended for symptomatic patients with persistent or long-standing AF. Pretreatment with anti-arrhythmic drugs (AADs), usually class IC or III, is recommended to increase the effectiveness of cardioversion.[51] In a study by Cotiga et al, dofetilide had an unusually high pharmacologic conversion rate, demonstrated an incremental dose response, and was well tolerated and safe in a relatively healthy adult cohort with persistent AF.[52]It is recommended to perform TEE for patients who have had AF for more than 48 hours to exclude LAA thrombi before direct current cardioversion. For patients who were in AF for longer than 48 hours or for an unknown duration and who cannot undergo TEE, the

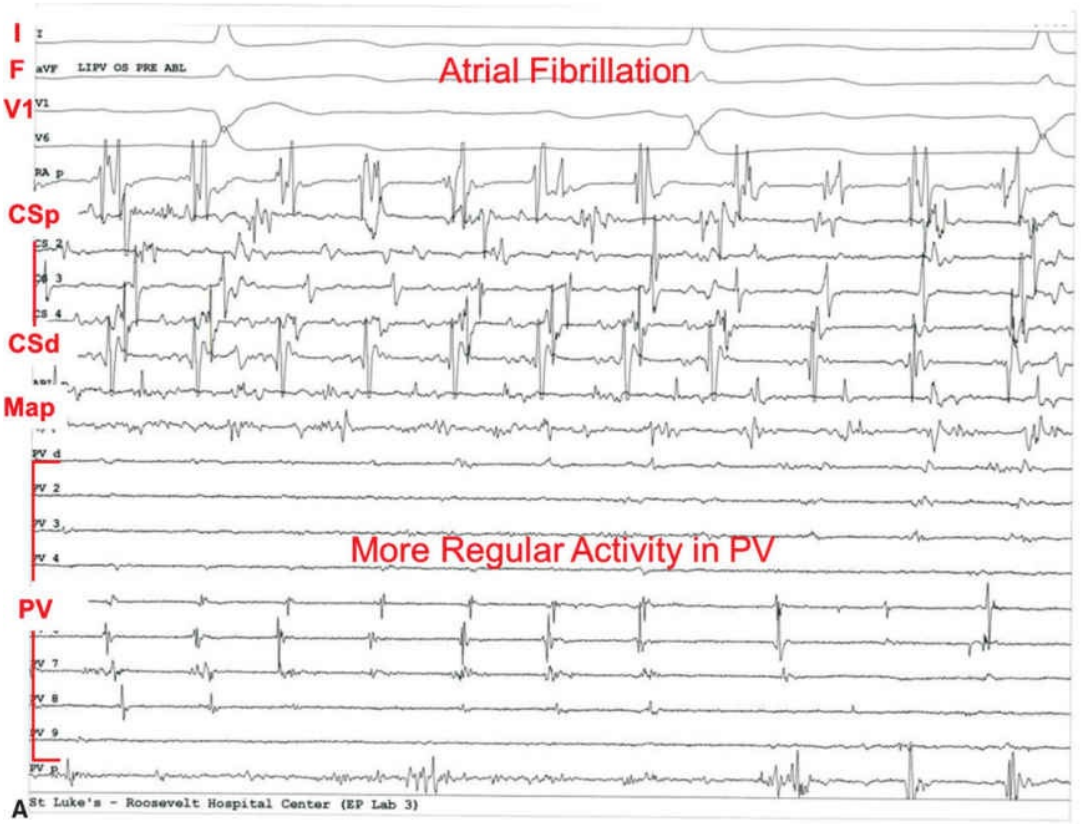
recommendation is to initiate AC for at least 3 weeks before cardioversion and to continue for 4 weeks after CV, unless longer AC is needed because of high stroke risk.

Catheter Ablation for Atrial Fibrillation

Catheter ablation (CA) to cure AF has now evolved as an established method for treating this common rhythm disorder. CA of AF is performed on a daily basis in electrophysiology laboratories in most regions of the world. Cure of AF has had a dramatic impact on quality of life, morbidity, and mortality. The first decade of AF ablation was characterized by new observations and concepts as well as improvement in technology. Most current treatment approaches for AF aim at ablation around the PVs with or without additional ablation lesion lines, a procedure that yields low complication rates and high success rates in both paroxysmal and chronic AF.[53]

Typical pulmonary vein antral isolation (PVAI) of PVs is performed guided by intracardiac echocardiography and a circular mapping catheter to more precisely identify the border of the PV antrum and reduce risk of PV stenosis. PVAI is performed by encircling all PVs based on anatomy, and demonstration of loss of PV potentials and, if possible, inability of signals to go from PV to atrium in the absence of PV potentials.

Figure 23.6A shows intracardiac electrograms (EGMs) from a patient in AF during a PVAI procedure. Note the unorganized atrial activities in the atrium seen on the coronary sinus (CS) catheter, and more organized EGMs seen within the PV circular mapping catheter after isolation of the veins and spontaneous termination of AF to SR. **Figure 23.6B** displays surface ECG in normal rhythm, organized sinus activity seen in the CS catheter, and completely silent (isolated) PV with no activities. In **Figure 23.6C** SR is seen on surface ECG and in the CS, whereas fibrillatory EGMs are seen confined to the PV, confirming complete isolation of the vein with exit block (no external connection to the atrium).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F
V1
CSp
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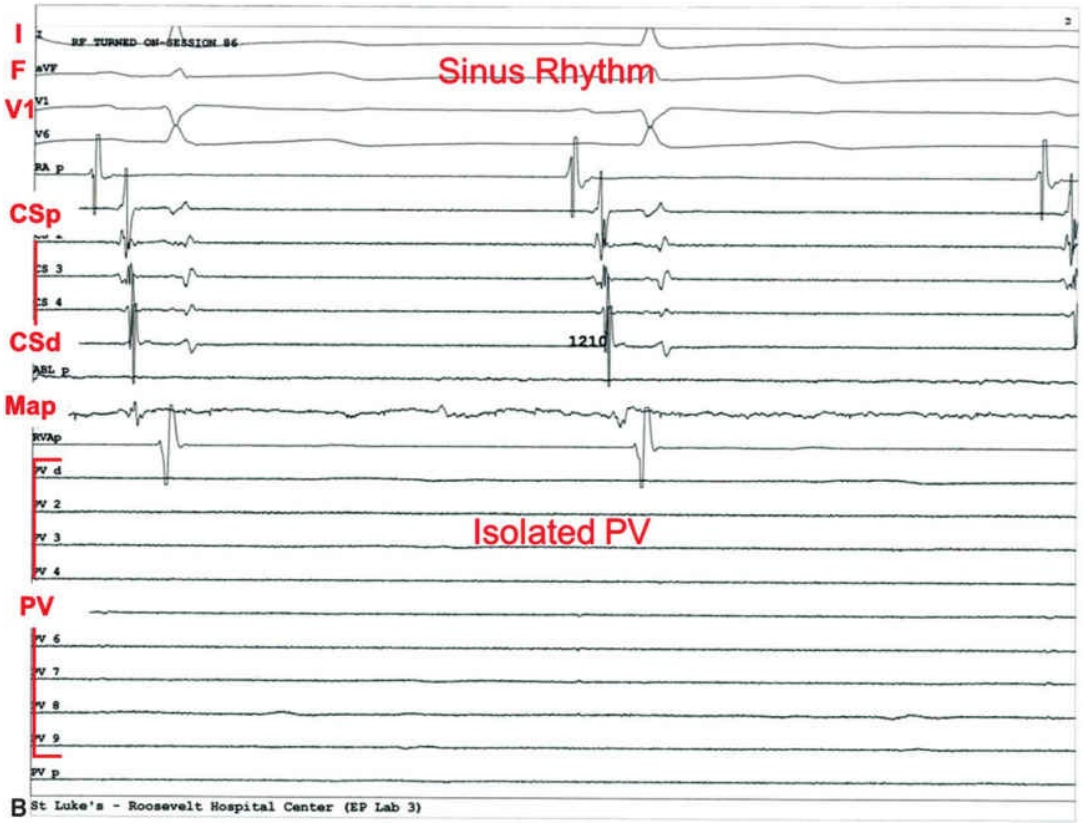
PV
Atrial Fibrillation
More Regular Activity in PV
St Luke's - Roosevelt Hospital Center (EP Lab 3)

A


I
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Sinus Rhythm
Isolated PV
1210
St Luke's - Roosevelt Hospital Center (EP Lab 3)

B

FIGURE 23.6 A, Intracardiac electrograms for a patient in atrial fibrillation. (*Note:* Atrial fibrillation seen in the coronary sinus and more organized activities seen in the pulmonary vein in a patient with atrial fibrillation during electrophysiology study.) B, Same patient after pulmonary vein (PV) antral isolation and conversion to sinus rhythm. (*Note:* Surface ECG shows normal rhythm, organized sinus activity in the coronary sinus, and completely silent [isolated] pulmonary vein with no activities.) CSd, distal coronary sinus catheter; CSp, proximal coronary sinus catheter; LLPV, left lower pulmonary vein; LUPV, left upper pulmonary vein; Map, mapping/ablation catheter; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

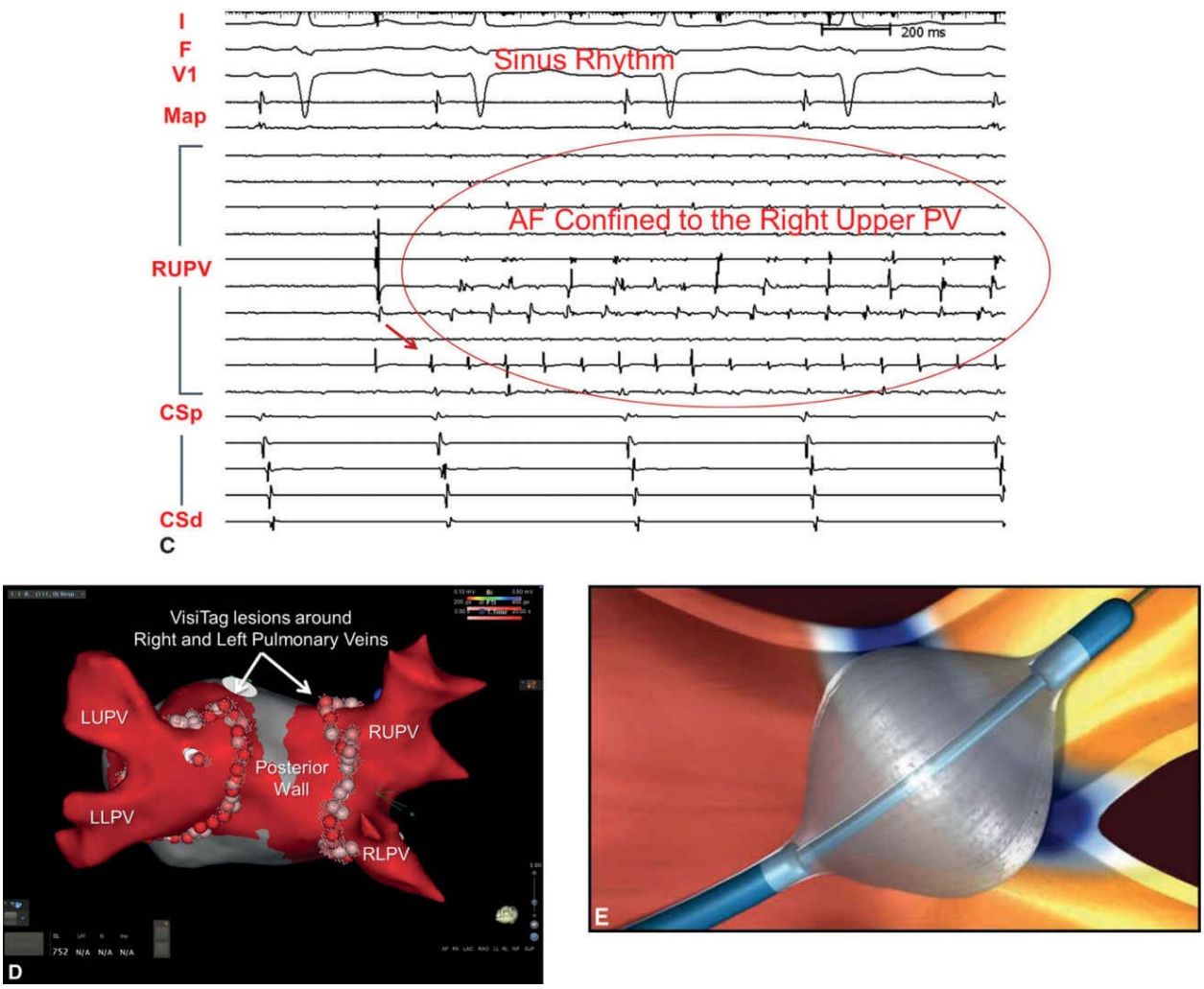


FIGURE 23.6 C, Atrial fibrillation, confined to a PV, while the rest of the heart is in normal sinus rhythm. *Note:* Sinus rhythm is seen on surface ECG and in the coronary sinus, while fibrillatory electrograms are seen confined in the pulmonary vein confirming complete isolation of the vein with exit block (no external connection to the atrium). CSd, distal coronary sinus catheter; CSp, proximal coronary sinus catheter; Map, mapping/ablation catheter; RUPV, right upper pulmonary vein. D, CARTO-3 electroanatomic 3D mapping of the left atrium after PV antral isolation. E, Arctic front balloon catheter for cryoballoon ablation *Note:* Red dots mark VisiTags indicating complete circumferential lesion sets around the antra of all pulmonary veins; also notice left atrial voltage map showing complete silence (red color) in the pulmonary veins and in the left atrial posterior wall. LLPV, left lower pulmonary vein; LUPV, left upper pulmonary vein; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein. E, Arctic front balloon catheter for cryoballoon ablation

Electroanatomic mapping is typically used during CA to guide in delineating the LA anatomy as well as the anatomy of PVs, and guide the electrophysiologist during the ablation procedure by placing automatic marks at the site of radiofrequency (RF) lesion applications. **Figure 23.6D** represents a CARTO-3

electroanatomic 3D mapping of the left atrium after complete PVAI, the red dots seen mark VisiTags indicating complete circumferential lesion sets around the antra of all PVs. LA voltage map shows complete silence (red color) in the PVs and in the LA posterior wall, indicating good lesion sets and confirming isolation as an endpoint for the ablation procedure.

In recent years, multiple clinical trials have clearly demonstrated the superiority of CA over AAD therapy in terms of long-term freedom from AF, improvement in quality of life, and reduction of hospitalizations.[54, 55] To date, there are few small studies that compared CA as a first line of treatment of AAD. The **RAAFT** was the first randomized trial to show the feasibility, safety, and effectiveness of CA as first-line therapy in patients with symptomatic paroxysmal AF. The outcomes assessed in this trial were recurrence of AF, hospitalization, and quality of life at 1-year follow-up. At the end of follow-up, 63% of patients assigned to AAD therapy experienced at least one recurrence of symptomatic AF, as compared with 13% of those assigned to the PVAI treatment arm, accounting for 80% relative risk reduction with CA ($P < 0.001$). Furthermore, PVAI was associated with a significantly lower rate of hospitalization (9% vs 54%, $P < 0.001$), and better quality of life.[56]

Presented data from the Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (**MANTRA-PAF**) trial[57] compared CA with AAD therapy as first-line therapy for symptomatic paroxysmal AF and showed that at 24 months, AF recurred in 15% of patients allocated to CA and in 29% of those receiving AAD, accounting for 48% relative risk reduction ($P = 0.004$). The corresponding number needed to treat with CA to prevent one episode of recurrent AF was 7. Patients assigned to CA also experienced significantly lower AF burden ($P = 0.007$) and improved quality of life.

More recently, the RF ablation versus antiarrhythmic drugs as first-line treatment of paroxysmal AF (**RAAFT-2**) trial showed that among patients with paroxysmal AF without previous antiarrhythmic drug treatment, RF ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 24 months.[58]

Finally, data from the CA versus antiarrhythmic drug treatment of persistent AF: a multicenter, randomized, controlled trial (**SARA study**) showed that CA was superior to medical therapy for the maintenance of SR in patients with persistent AF at 12-month follow-up.[59]

In recent years, cryoballoon ablation (**Figure 23.6E**), has gained some favor as an alternative approach to RF ablation for the treatment of symptomatic drug-

refractory AF with comparable immediate success and complications.[60] The most recent **FIRE AND ICE** trial showed that while patients treated with cryoballoon as opposed to RF ablation had significantly fewer repeat ablations, direct current cardioversions, all-cause rehospitalizations, and cardiovascular rehospitalizations during the follow-up period, both patient groups had improvement in quality-of-life scores after ablation.[61] The result of this study further establishes the call for ablation as the first-line therapy in younger patients with AF.

AC should be started and continue uninterrupted before the ablation with NOAC or VKA and continued for at least 6 months.[62] Generally it is recommended to continue AAD therapy for 12 weeks after ablation, as there is significant evidence showing prevention of early AF recurrences after ablation when AADs are continued for a few weeks.[63]

CA performed the first time has an efficacy of 60% to 80%, and only a few patients require a second procedure to achieve higher rates of effectiveness. If CA fails to restore rhythm, the patient and the cardiologist can decide between further available options: repeat ablation or hybrid therapy (AAD + ablation).

Outpatient Follow-Up of Patients with AF

Follow-up visits should be focused on assessment of patients' symptoms after initiation of the therapy, possibility of changing the strategy, or stepping to the next available treatment option if the patient is still symptomatic. Assessment of the presence of side effects should take place if the patient is on AAD. Special attention should be devoted to the treatment of comorbidities that could decrease the rate of AF recurrences (such as HF, OSA) as well as monitoring of anticoagulation and assessment for further need of it.

Prognosis

AF associated with increased risk of death independent of embolic stroke, partially because of its comorbidities (HF, coronary artery disease, HTN), but independently AF also increases risk of sudden cardiac death from ventricular arrhythmias.

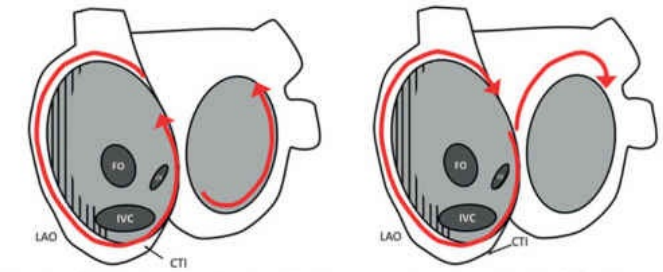
ATRIAL FLUTTER

Atrial flutter (AFL) is a regular atrial arrhythmia with rates up to 300 bpm, and is typically caused by a macroreentrant (MR) circular activation (reentrant) that revolves around a “large” obstacle, arbitrarily defined as being several centimeters in diameter. Typical AFL,[64] facilitated by the anatomic structure of the right atrium (RA), is the most frequent atrial MR tachycardia; however, owing to the increased incidence of heart surgery with atriotomy and to LA ablation for the treatment of AF, further MR tachycardia can be also seen.

The relationships between AFL and AF are complex. Both arrhythmias frequently occur at various times in the same patient and epidemiologic studies have demonstrated a tendency for patients who initially only present with flutter to develop fibrillation after several years. It is imperative to realize that AFL and AF are expressions of a single arrhythmogenic substrate. The background and diseases associated with AFL are similar to those of AF, including HTN, coronary disease, valvulopathy, chronic obstructive pulmonary disease, myocardiopathy, and 15% to 20% of apparently healthy hearts. In some cases, flutter initiates fibrillation and flutter ablation reduces the incidence of fibrillation.

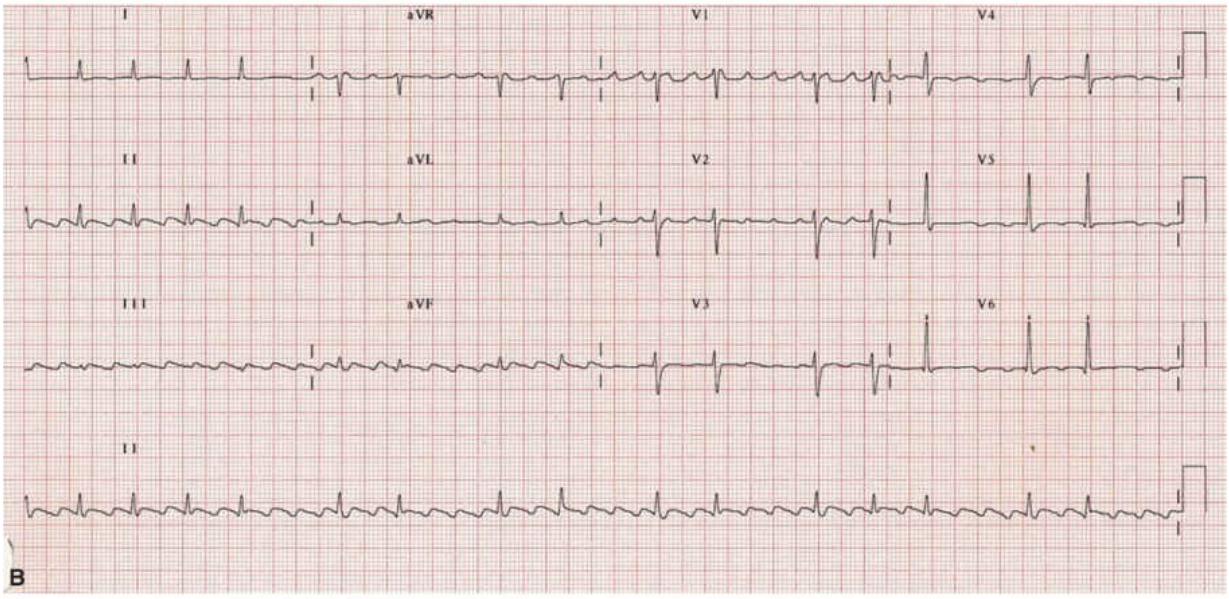
Typical AFL is an MR arrhythmia due to rotational activation around the RA. The circuit is bounded in front by the tricuspid ring and behind by a mixed anatomic and functional obstacle, formed by the vena cava and crista terminalis.[65] The activation wave goes down via the anterolateral RA and goes up via the septal RA (counterclockwise rotation in left anterior oblique view), necessarily passing between the inferior vena cava (IVC) and the lower tricuspid ring, an area known as the cavotricuspid isthmus (CTI). Cycle length (CL) is typically 200 to 240 ms, with great stability (variations of <20 ms), but under pharmacologic treatment or if there is delayed atrial conduction, the CL can reach 300 ms.

The combination of large valvular and venous orifices together with the functional obstacle in the crista terminalis makes the RA an ideal place for reentry, and this is probably the means by which typical AFL has such a characteristic electrocardiographic and functional image (**Figure 23.7A**). Counterclockwise activation (going down via the anterolateral RA) occurs in 90% of typical flutter, but in 10% there is a reverse or clockwise rotation (going up the anterolateral RA and going down the septal RA).



Typical Counterclockwise Flutter Reverse Typical Flutter

A



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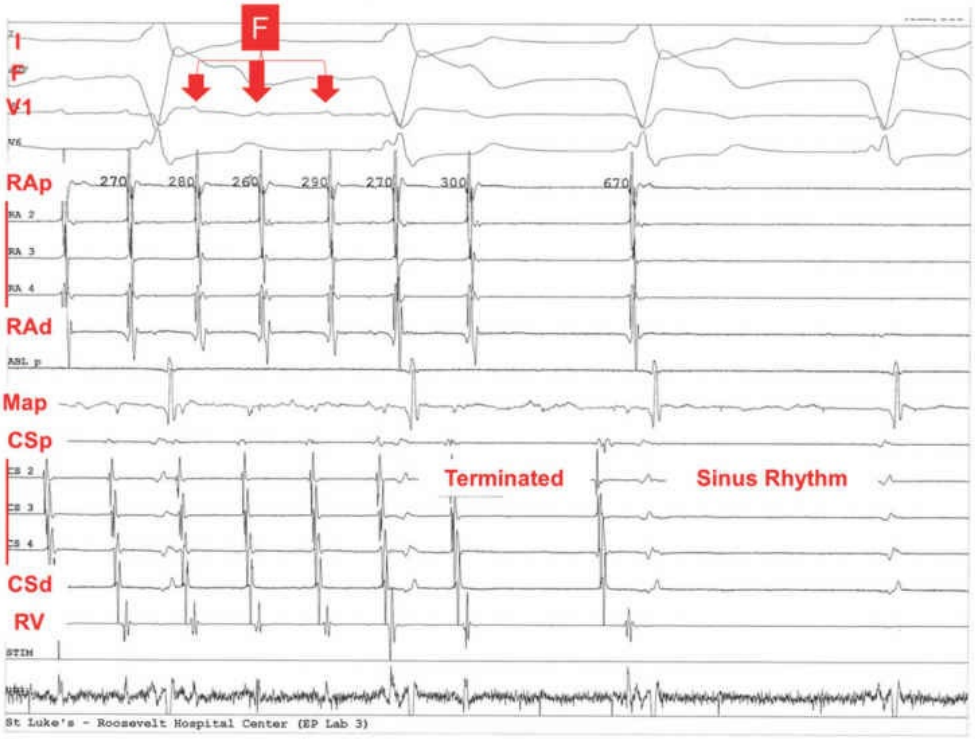

C

FIGURE 23.7 A, Mechanism of typical AFL and reverse typical AFL. B, Typical counterclockwise AFL. (Note the characteristic pattern in leads II, III, and aVF known as "sawtooth pattern." The wave is complex, with a slowly falling segment followed by a negative deflection that changes rapidly to positive to link with the following cycle.) C, Termination counterclockwise AFL during cavotricuspid isthmus (CTI) ablation. Note the beginning of the tracing [F] flutter waves that terminate during the CTI ablation to sinus rhythm. CS, coronary sinus; CSd, distal coronary sinus catheter; CSp, proximal coronary sinus catheter; FO, fossa ovalis; IVC, inferior vena cava; LAO, left anterior oblique; Map, mapping/ablation catheter; Rad, distal right atrium; Rap, proximal right atrium.

Typical AFL has a characteristic pattern in leads II, III, and aVF known as "sawtooth pattern." The wave is complex, with a slowly falling segment followed by a negative deflection that changes rapidly to a positive and links with the following cycle (**Figure 23.7B**). The pattern can be difficult to recognize if AV conduction is 2:1, but can be revealed by increasing the degree of block through massaging the carotid sinus or with intravenous adenosine. Clockwise typical AFL produces positive waves in the inferior leads, frequently with a sawtooth pattern, but what is most typical is a negative sawtooth wave, in lead V1.

AV conduction is frequently 2:1 during flutter, even while resting and under conduction-slowing agents; if the flutter rate is slower, conduction can be up to 1:1. However, ventricular rate can also be irregular because of complex block patterns in the AV node.

Indications for treatment are marked by poor tolerance, the poor or adverse response to antiarrhythmic agents, and the possibility of eliminating the circuit via CA. The ablation target is the CTI, being the narrowest part of the circuit, well delimited anatomically, easily accessible, and distant from the AV node.

RF ablation to produce a complete, bidirectional, and persistent CTI block normally requires several RF applications, between the tricuspid edge of the isthmus and the IVC. The use of irrigated-tip ablation catheter that produces deep lesions at lower energies, results in flutter termination (**Figure 23.7C**) and demonstrating bidirectional block across the CTI in 85% to 90% of cases with a complication risk of <1%.[66]

In general, the same guidelines have been adopted regarding anticoagulation therapy as in patients with AF; however, in cases with a high risk of hemorrhage, these standards could be made more flexible. TEE is typically performed before ablation to rule out a thrombus in the left atrium or the LAA and anticoagulation therapy is maintained for 4 weeks after ablation procedure. Once CTI block is

obtained, flutter recurs in 5% to 10% of cases, usually within 3 months, and reablation is, in general, technically easier.

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Patient and Family Information for: ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Atrial Fibrillation (AF) is the most common irregular heart rhythm abnormality. It is caused by abnormal electrical signals that cause the heart to beat irregularly and usually very fast.

Symptoms of AF are palpitations (racing heart, skipped beats, and irregular heartbeats), chest tightness, difficulty breathing, and dizziness.

This irregular heart rhythm can be constant or it can come and go. Sometimes it can be provoked by modifiable reasons such as alcohol, caffeine, or an overactive thyroid gland.

AF is classified according to how often the episodes occur and how quickly they terminate.

- Paroxysmal (intermittent): Irregular heart rhythm episodes that reoccur two or more times and stop on their own within 7 days. The heartbeat often normalizes as quickly as within a few seconds or after a few hours.
- Persistent: Irregular heart rhythm episodes that last more than 7 days, or last less than 7 days but necessitates medical therapy or a procedure to restore a normal heart rhythm (cardioversion). Cardioversion is most often done by sending electric shocks to the heart through electrodes placed on the chest.
- Longstanding persistent: Irregular heart rhythm episodes that continue for more than a year. The heart is in a constant state of fibrillation and the condition is considered permanent. In most cases, cardioversion is either ineffective or cannot be attempted.

When the HR stays fast and irregular for a prolonged time, it requires treatment to avoid complications such as stroke or developing a weak heart.

The two main problems with AF is the risk of developing a blood clot and the

risk of a fast HR that may weaken the heart.

- A blood clot can develop in the upper chambers of the heart because it is beating out of synchronization. The clot can travel outside of the heart along the blood vessels to the brain and cause a stroke. To decrease this risk, patients need to take anti-coagulants (blood thinners).
- Fast HR can be very uncomfortable for some patients, leading to the symptoms of palpitations. The heart is not pumping the blood effectively in this state. If fast HR persists for a long time, it can cause the heart to become weak. To keep the HR in the normal range, patients are prescribed medications to slow it down.

When a decision is made to attempt to restore regular heart rhythm, several options are available. There are medications called antiarrhythmic medications and they are directed to convert the heart rhythm to a normal rhythm. Another treatment option is called cardioversion and involves applying an electrical shock to the heart.

A unique treatment is called ablation. It is a procedural option that is based on the knowledge that areas of the heart are sending excessive signals and causing the upper chambers of the heart to beat irregularly. The procedure involves applying heat or cold (RF or cryoablation) to destroy small areas that are causing the abnormal heartbeat.

Atrial Flutter (AFL) is another common abnormal heart rhythm. In AFL, the upper chambers (atria) of the heart beat very fast. This results in atrial muscle contractions that are faster and out of synchronization with the lower chambers (ventricles). With AFL, the electrical signal travels along a pathway within the RA. It moves in an organized circular motion, or “circuit,” causing the atria to beat faster than do the ventricles. AFL makes a very distinct “sawtooth” pattern on an ECG, a test used to diagnose abnormal heart rhythms. AFL itself is not life threatening. If left untreated, the side effects of AFL can be potentially life threatening. AFL makes it harder for the heart to pump blood effectively. With the blood moving more slowly, it is more likely to form clots. If the clot is pumped out of the heart, it could travel to the brain and lead to a stroke. Ablation procedure is the treatment of choice for AFL, which is performed by inserting a small catheter through the femoral vein and advancing it to the heart till it reaches a specific area called the cavotricuspid isthmus. Delivering RF lesion typically terminates the flutter with a success rate of approximately 85% to 90% and with a complications risk of <1%.

24

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Pathway for the Management of Atrial Fibrillation and Atrial Flutter

Atrial fibrillation (AF) is the most common cardiac rhythm disturbance encountered in clinical practice, and its prevalence is increasing as the population ages.[1, 2] Electrocardiographically, AF is characterized by an irregularly irregular ventricular rhythm, with an absence of discrete P-wave activity. Rather, undulating fibrillatory activity (f waves) are seen on the electrocardiogram (ECG) between QRS complexes and T waves. The American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) established guidelines for the management of patients with AF.[3, 4]

In 2010, the estimated numbers of men and women with AF worldwide were 20.9 million and 12.6 million, respectively, with higher incidence and prevalence rates in developed countries. One in four middle-aged adults in Europe and the United States will develop AF in their lifetime.[4]

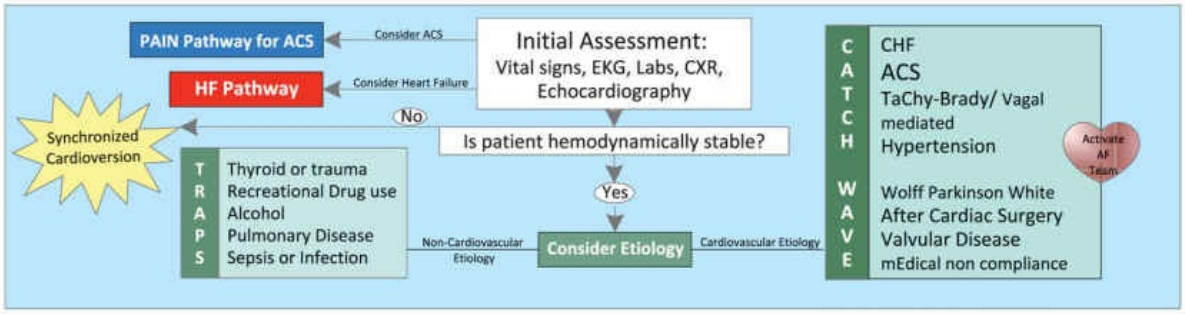
The increase in AF prevalence can be attributed to better detection of silent AF,[5–7] alongside increasing age and conditions predisposing to AF.[8]

Atrial flutter (Afl) is less common and is often associated with or preceded by AF or occurs in an isolated pattern. Guidelines for Afl management were included in the ACC/AHA/ESC Guidelines for the Management of Patients with Supraventricular Arrhythmias. The electrocardiographic findings of Afl in its

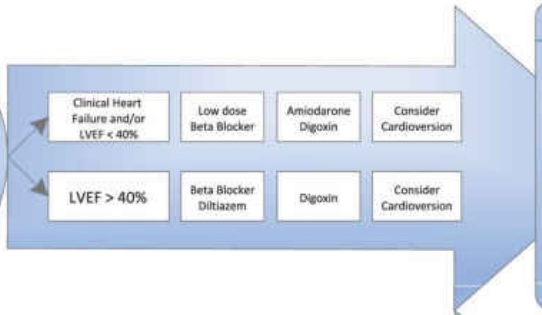
typical counterclockwise form include an atrial deflection with rapid regular undulations that gives rise to a “sawtooth” appearance, mainly in the inferior leads. The atrial rate is usually between 250 and 300 beats/min.

A major limitation of the currently published guidelines for the management of patients with AF and Afl is their complexity, the fact that official guidelines are published separately for each of these arrhythmias, and that they were published several years ago.[3] To address these deficiencies, we have developed a novel pathway for the management of AF and Afl (**Figure 24.1**).

RACE Pathway for Atrial Fibrillation and Atrial Flutter



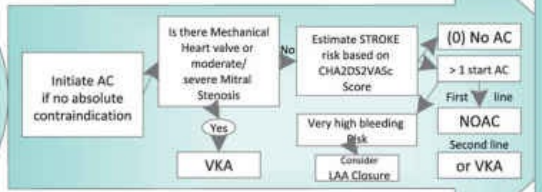
Rate Management



R = Rate Control Medications

	IV		PO
	Loading Dose	Maintenance Dose	Maintenance
Beta Blocker			
Metoprolol	2.5 - 5 mg IV bolus up to 3 doses	NA	25 - 100 mg bid
Esmolol	0.5 mg/kg IV over 1 min	0.05 mg/kg/min over 4 min	NA
Calcium Blocker			
Diltiazem	0.25 mg/kg IV over 2 min	5-15 mg/hr	120-360 mg/d
Verapamil	0.075-0.15 mg/kg IV over 2 min		120-360 mg/d
Digoxin	0.25 mg IV Q2hrs, up to 1.5 mg	0.125 - 0.25 mg daily	0.125 - 0.375 mg daily

Anticoagulation

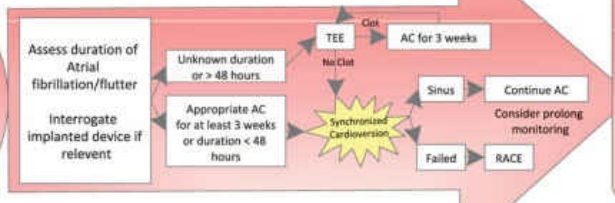


A = Anticoagulation Medications

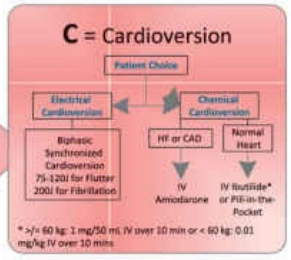
	Dabigatran (Re-LY)	Rivaroxaban (Rocket-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGAE-AF)
Dose	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily*
Dose for CKD	75 mg twice daily CrCl 15-30 mL/min	15 mg once daily CrCl 15-50 mL/min	2.5 mg twice daily if at least two of age ≥80yrs; weight ≤ 60 kg or Cr ≥ 1.5 mg/dL	30 mg once daily CrCl 15-50 mL/min
Reversal	Idarucizumab 5 g/100 mL infused rapidly	Awaiting Xa-inhibitors Approval		

* approved in US for CrCl 50-95 mL/min
All are not indicated with CrCl <15 mL/min

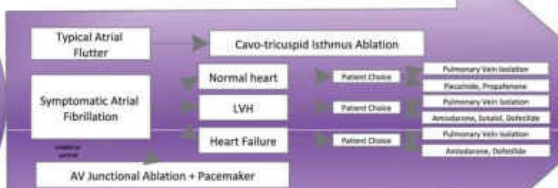
Cardioversion



C = Cardioversion



Electrophysiology Management



E = Electrophysiology / Antiarrhythmic Medication

Class IC	Starting PO dose	Maintenance PO Dose
Flecainide	50 mg Q 12 hrs	May titrate by 50 mg Q12hrs, Q4days to maximum 200 mg Q12hrs
Propafenone	150 mg Q 8 hrs	May titrate in 3-4 day intervals to 225 mg Q8hrs, then 300 mg Q8hrs

Class III	Oral Loading	IV Loading	Maintenance
Amiodarone	800 mg daily in divided doses x 1-3 weeks	150 mg IVPB over 10 mins, then, 1 mg/min x 6 hrs, then 0.5 mg/min x 18 hrs	200-600 mg PO daily
Sotalol*	80 mg bid		80-160 mg bid
Dofetilide* Dosed on CrCl	> 60 mL/min 500 mcg bid 40-60 mL/min 250 mcg bid 20-60 mL/min 125 mcg bid < 20 mL/min Contraindicated		adjust dose based on QTc 2 hrs after initial dose

* Requires 72 hours of telemetry monitoring and 12 lead EKG

FIGURE 24.1 Pathway for the management of atrial fibrillation and atrial flutter. AC, anticoagulant; ACS, acute coronary syndrome; AF, atrial fibrillation; AV, atrioventricular; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CXR, chest X-ray; ECG, electrocardiogram; HF, heart failure; IV, intravenous; IVPB, intravenous piggyback; LAA, left atrial appendage; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; NOAC, novel oral anticoagulation; TEE, transesophageal echocardiogram; VKA, vitamin K antagonist.

The necessity to develop such a pathway at our institution was compelling, yet typical of the need at many other large medical centers, where it has become increasingly difficult for all house staff to grasp all the subtleties in the management of AF and Afl and to rapidly, efficiently, and accurately implement clinical protocols. It should be emphasized that this pathway is the opinion of our group and may differ somewhat from the published guidelines. The pathway has been designated with the acronym of RACE, which reflects the four main components in patient management: ***R***ate control, ***A***nticoagulation therapy, ***C***ardioversion, and ***E***lectrophysiology/antiarrhythmic medication.

This pathway is an attempt to incorporate, in a user-friendly format, the key concepts of the initial diagnosis and management of these prevalent arrhythmias. This is followed by a comprehensive guideline for therapy using the RACE acronym.

INITIAL ASSESSMENT

All patients should undergo an initial assessment (**Figure 24.2**) on presentation to the emergency department, including a 12-lead ECG, history, and physical examination.

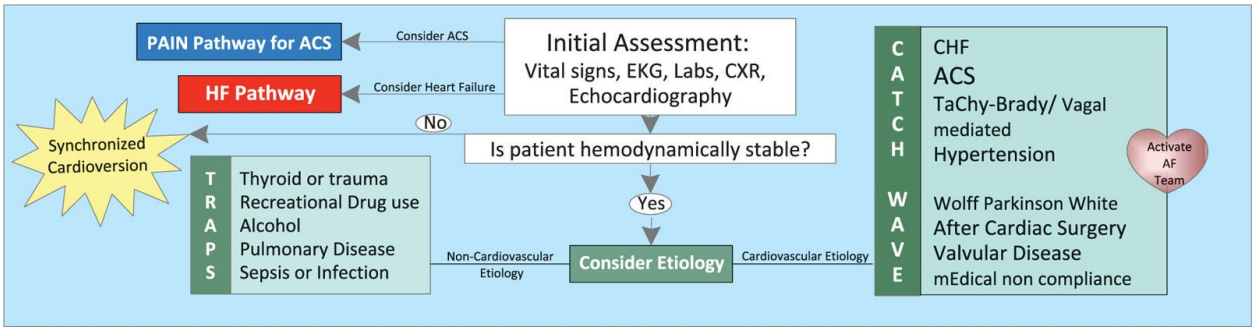


FIGURE 24.2 Initial assessment of patients with atrial fibrillation and atrial flutter. ACS, acute coronary syndrome; AF, atrial fibrillation; CHF, congestive heart failure; CXR, chest X-ray; HF, heart failure.

All patients should be immediately assessed for hemodynamic stability. If patients are hemodynamically unstable (low blood pressure, cold extremities, signs of heart failure, depressed mental status), emergency synchronized D/C cardioversion should be considered.

Patients should also be evaluated for acute coronary syndrome if they have suggestive symptoms, ECG changes, and/or elevated cardiac biomarkers. A comprehensive evaluation for acute heart failure is also essential, including an assessment of natriuretic peptide levels when appropriate. Prior studies have demonstrated a strong association between the heart failure syndrome and AF. Acute coronary syndrome and acute heart failure should be treated, respectively, per published guidelines and pathways.[9, 10]

Initial laboratory testing should include a comprehensive metabolic panel, complete blood count, magnesium level, thyroid function tests, and coagulation panel if a patient is on warfarin therapy. All patients should have a transthoracic echocardiogram for assessment of left and right ventricular function, valvular disease, and pericardial effusion.

Owing to recent advances in the management of AF, including complexities of medical and nonpharmacologic therapies, early involvement of an arrhythmia service (AF team) should be considered in all patients with AF/Afl.

We have developed a systematic approach to the pathophysiology of AF and Afl (**Figure 24.2**) using acronyms that can easily be remembered by physicians, nurses, and other health care personnel:

a. Non-cardiovascular etiology: **TRAPS**
- **T**—Thyroid disease
- **R**—Recreational drug use
- **A**—Alcohol
- **P**—Pulmonary disease
- **S**—Sepsis/infection

b. Cardiovascular etiology: **CATCH WAVE**
- **C**—Congestive heart failure
- **A**—Acute coronary syndrome/acute myocardial infarction (MI)
- **TC**—TaChy-brady syndrome/vagal mediated
- **H**—Hypertension
- **W**—Wolff–Parkinson–White syndrome
- **A**—After cardiac surgery
- **V**—Valvular heart disease
- **E**—mEdical noncompliance

RATE MANAGEMENT

In about 60% to 70% of patients with AF, a rapid ventricular rate is observed, and symptoms are usually present depending on the rapidity of the ventricular response, the length of time the arrhythmia is sustained, and the presence and type of underlying heart disease.[11] Acute ventricular rate control is the primary goal initially because patients' symptoms are chiefly governed by the rapid ventricular rate. In addition, a reduction in ventricular rate in AF results in a longer diastolic filling period and higher ventricular stroke volume. Acute ventricular rate control in AF can be achieved by pharmacotherapy, nonpharmacologic therapy, and early cardioversion to sinus rhythm. In addition, correction of precipitating factors often helps in controlling ventricular rates in addition to enhancing the chances for conversion to sinus rhythm.

We have defined the rate control goal in AF as a resting ventricular rate of less than 110 beats/min.

Atrioventricular (AV) node blocking agents including β-adrenergic blockers, non–dihydropyridine calcium channel blockers, and digoxin are usually effective in controlling ventricular rate in AF and Afl. Intravenous (IV) β-blocker and non–dihydropyridine calcium channel blockers are considered equally effective in rapidly controlling the ventricular rate. The addition of digoxin to the regimen is helpful, but digoxin as a single agent is generally less effective. Magnesium and amiodarone have also been used for acute ventricular rate control in AF. The agent of first choice is usually individualized depending on the clinical situation. β-Blockers are preferable in patients with myocardial ischemia, MI, and hyperthyroidism and in a postoperative state, but should be avoided in patients with bronchial asthma and chronic obstructive pulmonary disease, whereby non–dihydropyridine calcium channels blockers are preferred.β-blockers are preferred in AF during pregnancy. In addition, in AF with Wolff–Parkinson–White syndrome, β-Blockers, calcium channel blockers, and digoxin should be avoided, because these drugs are selective AV node blockers without slowing conduction through the accessory pathway, which can lead to increased transmission of impulses preferentially through the accessory pathway and precipitate ventricular fibrillation. The drug of choice for AF in pre-excitation syndrome is procainamide.

Figure 24.3 outlines our recommendations for rate control medications. It summarizes the IV loading and maintenance dose, as well as the oral dose for recommended medications.

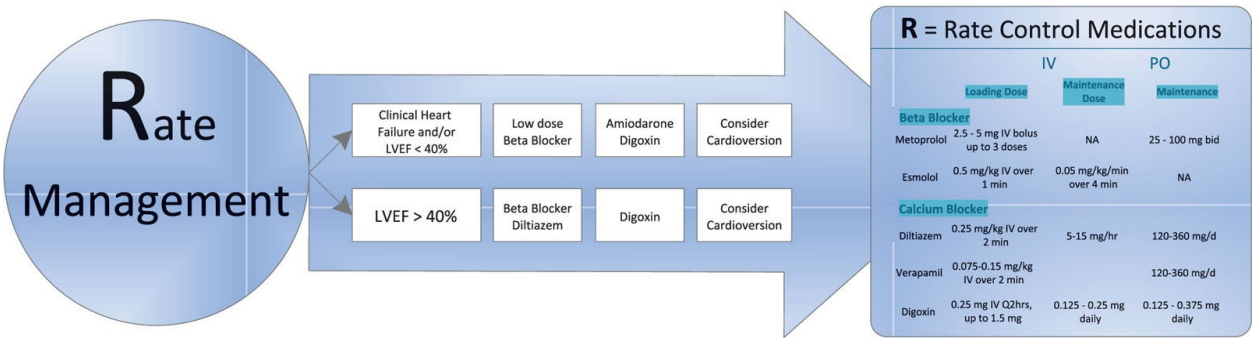


FIGURE 24.3 Rate management in patients with atrial fibrillation and atrial flutter. IV, intravenous; LVEF, left ventricular ejection fraction.

The first-line therapy to slow the ventricular rate in patients with AF and clinical heart failure and/or left ventricular ejection fraction (LVEF) <40% is a low-dose β-blocker.

The second-line therapy includes amiodarone or digoxin. Amiodarone can cause conversion to normal sinus rhythm in some patients and potentially precipitate a cardioembolic event in patients who are not adequately anticoagulated. If all these drugs fail to slow the ventricular rate, we suggest considering cardioversion.

For patients with LVEF >40%, we recommend using a β-blocker or diltiazem and as a second line to use digoxin.

If these agents fail to slow the ventricular rate, cardioversion should be considered.

ANTICOAGULATION

AF is thought to be responsible for approximately 15% to 25% of ischemic strokes.[12, 13] The pathophysiology of AF-associated stroke is complex, but it appears to arise as a result of the embolization of a thrombus formed within the dysfunctioning left atrium, especially the left atrial appendage (LAA). Clot formation is more likely to occur under the conditions of stasis accompanying impaired atrial contraction.

Stratification of thromboembolic risk is central to the current recommendation for anticoagulation of patients with AF.

The CHA_2DS_2-VASc stroke risk stratification score (**Table 23.1**), recommended for use by the 2014 AHA/ACC/HRS Guideline for the

Management of Atrial Fibrillation, is an expansion of the $CHADS_2$ score with three additional risk factors including female sex, age of 65 to 74 years, and history of vascular disease, such as prior MI, peripheral arterial disease, and aortic plaque.

The total score of the CHA_2DS_2-VASc is up to 9 points. On the basis of a strong level of evidence, the recommendation is to provide anticoagulation therapy for CHA_2DS_2-VASc scores of 2 or higher that indicates high risk for a thrombotic event. A CHA_2DS_2-VASc score of 1 indicates an intermediate risk of an event, and the clinician may consider offering antithrombotic therapy with either aspirin, an anticoagulant, or no therapy with continued monitoring with an implantable loop recorder for better understanding of the burden of AF. Assessing bleeding risk may assist with the decision process.

Several tools are available to assess the bleeding risk from anticoagulation for AF. The HAS-BLED score (**Table 23.2**) has been validated to predict clinically significant bleeding and has been demonstrated to outperform other scores.

Figure 24.4 outlines our summarized protocol for anticoagulation in the management of AF and Afl.

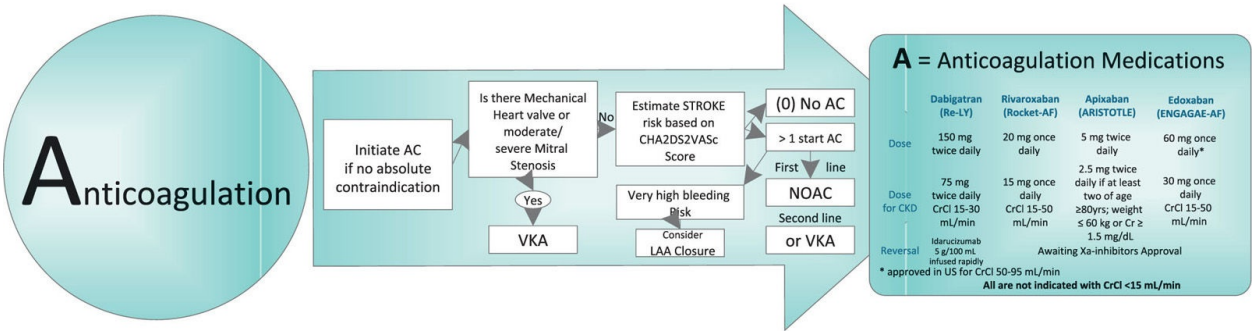


FIGURE 24.4 Anticoagulation in patients with atrial fibrillation and atrial flutter. AC, anticoagulant; LAA, left atrial appendage; NOAC, novel oral anticoagulation; VKA, vitamin K antagonist.

Our group decided to adopt the ESC definition of valvular AF as a mechanical heart valve or evidence of moderate or severe mitral stenosis. These patients will benefit from anticoagulation with only warfarin.

We recommend estimating the stroke risk based on the CHA_2DS_2-VASc scores and assessing bleeding risk based on the HAS-BLED score (**Table 23.2**).

Stroke risk of 0 does not require anticoagulation. If the stroke risk is above 1, we recommend assessing the bleeding risk for the purpose of mitigation of the

bleeding risk factors.

In patients with a very high risk of bleeding, in patients with bleeding on anticoagulation, and in patients who cannot tolerate long-term anticoagulation therapy, a LAA closure device can be considered.

Otherwise, we recommend anticoagulation and the first-line therapy should be one of the four available novel oral anticoagulation (NOAC) agents. Warfarin should be considered only as a second-line option.

Figure 24.4 outlines the dosing of the currently available NOAC agents.

CARDIOVERSION

The decision to electively cardiovert a patient to and maintain normal sinus rhythm are complex and requires careful consideration of patient-specific factors as well as shared decision making with the patient. Timing the duration of AF and Afl is sometimes difficult if the patient cannot pinpoint the starting time of the arrhythmia. It is well accepted that patients whose arrhythmia is less than 48 hours in duration can safely have a cardioversion performed, and those with arrhythmia over 48 hours may have developed atrial thrombus, which increases the risk of thromboembolic events post cardioversion.

Figure 24.5 outlines our recommendations for cardioversion in patients with AF or Afl. We recommend starting the evaluation of the patient by assessing the duration of AF and Afl.

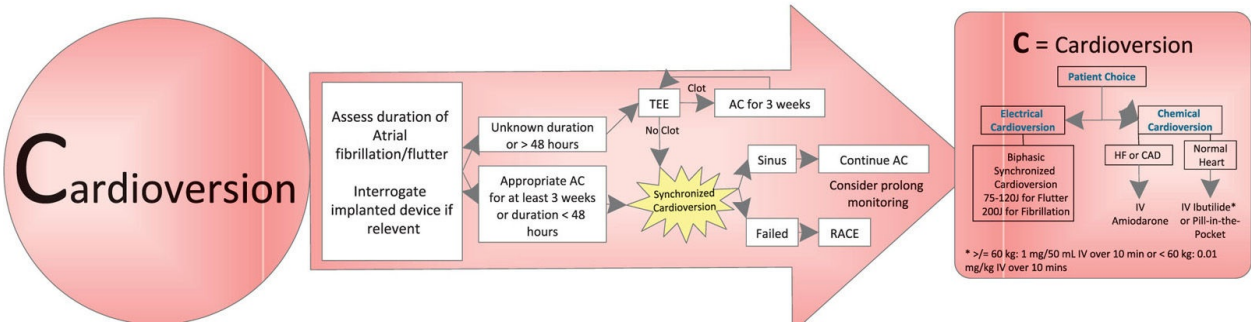


FIGURE 24.5 Cardioversion in patients with atrial fibrillation and atrial flutter. AC, anticoagulant; CAD, coronary artery disease; HF, heart failure; IV, intravenous; TEE, transesophageal echocardiogram.

This assessment can be quite easy if the patient has an implantable device—as the interrogation of the device will reveal the starting time of the arrhythmia.

For patients whose arrhythmia is *firmly established* to be less than 48 hours in duration, or if they have a *documented evidence* of appropriate anticoagulation for at least 3 weeks, a synchronized cardioversion can be safely performed.

When the onset of AF cannot be accurately determined or if AF is longer than 48 hours, anticoagulation should always be administered for at least 3 weeks before attempting cardioversion. Anticoagulation before cardioversion can be shortened if a transesophageal echocardiogram (TEE) is done and indicates the absence of thrombus in the left atrium and the LAA. The TEE-guided approach has been evaluated in the "Assessment of Cardioversion Utilizing Echocardiography (ACUTE) trial."[14, 15] With this approach, which we often employ, cardioversion is done immediately when the TEE suggests that there is no evidence of thrombus; anticoagulation is continued for at least 4 weeks or longer depending on the long-term cardioembolic risk.

The consideration to discontinue anticoagulation therapy after 4 weeks can be made when there is no recurrence of AF and there are no stroke risk factors.

Transthoracic electrical cardioversion is more successful than pharmacologic cardioversion, with an overall success rate of 75% to 93%, inversely related to the duration of AF, chest wall impedance, and left atrial size. The success rate for pharmacologic cardioversion in selected patients approaches 70% at best, and there is a risk of proarrhythmia. For this reason, we recommend electrical cardioversion.

Figure 24.5 outlines our recommended options for electrical or chemical cardioversion.

There are two conventional positions for the electrode placement: anterior-lateral and anterior-posterior. Several studies have shown that less energy is required and a higher success rate is achieved with electrodes in the anterior-posterior position. For this reason, we recommend the anterior-posterior location. The energy required for cardioversion of AF is often 200 joules. More energy is required in obese patients and for long-standing AF. The initial energy used depends in part on the waveform of the current delivered by the defibrillation. Biphasic devices have been shown to be more effective and require less energy than monophasic devices.

Although electrical cardioversion is the more widely used technique, chemical cardioversion using class III antiarrhythmic drugs such as ibutilide can certainly be used provided that the patient will be observed for at least 2 hours post cardioversion in a monitored setting. Dofetilide also has been shown to be effective in acute conversion of AF, typically after two doses with a documented

conversion rate up to 70%.[16, 17]

ELECTROPHYSIOLOGY MANAGEMENT

Over the past decades, various antiarrhythmic drugs and catheter-based procedures have been investigated for maintenance of sinus rhythm in patients with AF. Although the AFFIRM trial showed no significant difference in the outcome of patients using these medications, the long-term outcome of a population-based administrative databases from Quebec, Canada, from 1999 to 2007 in selected patients 66 years or older and followed up for more than 4 years showed rhythm control therapy to be superior in the long term, particularly as the study population got older.[18]

Figure 24.6 presents an abbreviated algorithm for selection of the most appropriate antiarrhythmic drug for maintaining sinus rhythm in selected categories of patients. The figure lists selected doses of our recommended class Ic and class III antiarrhythmic medications.

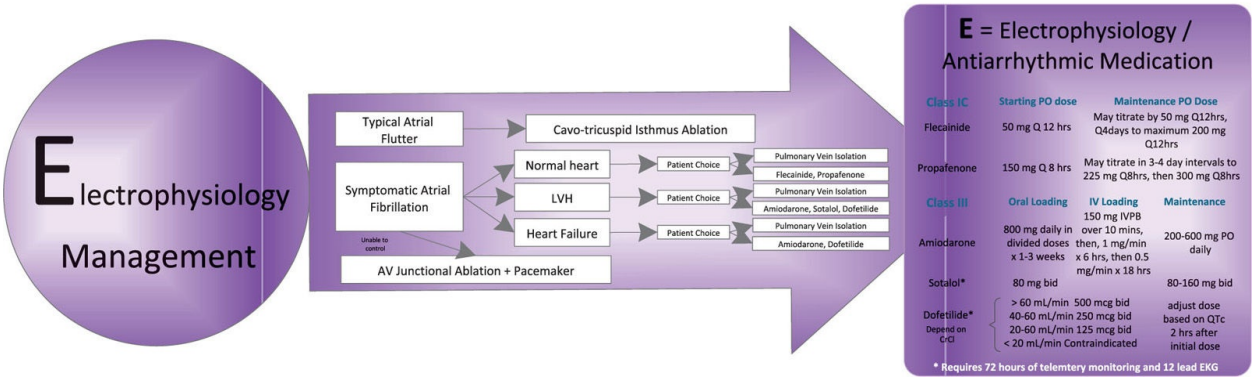


FIGURE 24.6 Electrophysiology management in patients with atrial fibrillation and atrial flutter. AV, atrioventricular; IV, intravenous; LVH, left ventricular hypertrophy.

That being said, several studies have shown that several class IA, IC, and III drugs, as well as class II drugs (β-blockers), are moderately effective in maintaining sinus rhythm; however, they are known to increase adverse events, including proarrhythmia, and some (eg, disopyramide, quinidine, and sotalol) may even increase mortality.[19]

Catheter ablation of AF has become an established therapeutic modality for the treatment of patients with symptomatic AF.

Pulmonary vein (PV) isolation using radiofrequency energy where a wide area or PV antral circumferential ablation strategy or the use of CRYO-ablation poses acute success rates documented in about 85% and long-term freedom from AF that is maintained at follow-up of at least 3 years with rates up to 80% in patients with paroxysmal Afl. Certainly, there are better outcomes when the procedure is performed by experienced operators.[20]

In rare cases when rate and rhythm control are unsuccessful despite maximally tolerated medical therapy and patients continue to be symptomatic because of the rapid Afl, treatment plans should include an electrophysiology (EP) consult to consider AV nodal junction ablation and permanent pacemaker implantation (ablate–pace technique).[21]

MANAGEMENT OF ATRIAL FLUTTER

The RACE pathway published in September 2005[1] was the first to include both AF and Afl in a single pathway. Because both arrhythmias will require anticoagulation and rate control medication, the initial assessment and management is similar. However, if the ECG is consistently Afl, we highly recommend consulting the EP team for consideration for Afl ablation, as shown in **Figure 24.6**.

EP studies have shown that Afl results from tachycardia using a reentry circuit. The reentry circuit occupies large areas of the atrium and is referred to as “macroreentrant.” The classic type of Afl (typical flutter) is dependent on the cavotricuspid isthmus. Catheter ablation of the cavotricuspid isthmus for isthmus-dependent flutter had been proved to be 95% to 100% successful,[22, 23] and is superior to antiarrhythmic therapy.[24]

Our recommendation is to consult the EP team for all patients with Afl for consideration of ablation. If medically treated, Afl resumes in the vast majority of patients within 6 months.[23]

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25

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Ventricular Arrhythmia

Ventricular arrhythmias (VAs) refer to a wide variety of tachyarrhythmias, which originate from the left or right ventricle. VA is a spectrum of arrhythmias ranging from premature ventricular contraction to ventricular tachycardia (VT) to ventricular fibrillation (VF). Various forms of VA are commonly seen in both the outpatient and inpatient clinical setting. However, it is prudent to review them while in the cardiac care unit (CCU), because patients with acute and life-threatening VAs will be treated here.

VA can be due to one of the following three mechanisms—Abnormal automaticity, triggered activity, or reentry.

a. **Abnormal automaticity:** Some of the cardiac tissue has the ability to automatically generate electrical impulse through spontaneous depolarization. Abnormal automaticity refers to the automatic firing of electrical impulse by cardiac tissue which, under normal conditions, does not demonstrate automaticity. Example: Right Ventricular Outflow Tachycardia.
b. **Triggered activity:** Triggered activity refers to an electrical impulse which is triggered by preceding impulse. Preceding impulse causes oscillations in the membrane potential of the abnormal cardiac tissue, which are called after-depolarizations. Once the after-depolarization crosses the threshold of depolarization, it creates abnormal electrical impulse. Example: Long QT Syndromes.
c. **Reentry:** This is the most common mechanism for VAs. Reentry refers to

propagation of impulse around a circuit that comprises two distinct electrical pathways with distinct electrical properties. As the circuit gets activated, it emits the electrical impulse at fixed cycle length. Example: Ischemic/scar-related VT.

BASIC DEFINITIONS

Table 25.1.describes some of the basic definitions related to VAs.

TABLE 25.1 Basic Definitions of Ventricular Arrythmia

Premature ventricular complexes (PVCs)	Ectopic beats originating from an abnormal automaticity focus. The depolarization of these beats is of ventricular origin and not conducted through the His–Purkinje system; they manifest as isolated wide QRS (>120 ms) complex beats on electrocardiogram (ECG).
Couplet	Two consecutive PVCs
Triplet	Three consecutive PVCs
Ventricular bigeminy	Occurrence of a PVC after every other normal/sinus beat
Ventricular trigeminy	Occurrence of a PVC every third beat
Nonsustained ventricular tachycardia (NSVT)	3 or more consecutive PVCs, at a rate of > 100 beats/min and spontaneously terminates within 30 s, without hemodynamic compromise
Ventricular tachycardia (VT)	Rapid (>100 beats/min), wide QRS complexes (>120 ms) of ventricular origin
Sustained ventricular tachycardia	VT that is greater than 30 s and/or is accompanied by hemodynamic instability and/or symptoms
Monomorphic ventricular tachycardia	VT in which all beats have the same morphology manifesting as uniform widened QRS complexes on ECG. Monomorphic VT originates from a single automaticity focus or reentry circuit within the ventricles
Polymorphic ventricular tachycardia	VT with widened QRS complexes that vary in amplitude and duration on ECG. Polymorphic VT originate from multiple ventricular foci firing together, leading to irregular ventricular depolarizations

Torsades de pointes	Type of polymorphic VT with widened QRS complexes that change in amplitude, giving the appearance of a “twisting pattern.” This is usually associated with long QT interval
Ventricular fibrillation	A rapid (typically > 300 beats/min) and irregular rhythm of chaotic electrical activity of ventricular origin, essentially leading to no meaningful cardiac output, and is a rapidly fatal rhythm

PREMATURE VENTRICULAR COMPLEXES

Premature ventricular complexes (PVCs) are extremely common in the population, and up to 40% of people without cardiac disease may have them. [1] PVCs originate from abnormal automaticity foci in the ventricles, which can be due to hypoxia, electrolyte abnormalities, or cardiac pathology. Common areas of these foci include the right ventricular outflow tract (RVOT), left ventricular outflow tract (LVOT), papillary muscle, or diseased cardiac tissue after a myocardial infarction (MI) or fibrosis. They manifest as isolated widened QRS complexes (>120 ms). Several studies have shown the presence of PVCs to be associated with increased risk of cardiovascular mortality in patients with structural heart disease. 2,3 **Figure 25.1** shows PVCs in a bigeminy pattern.

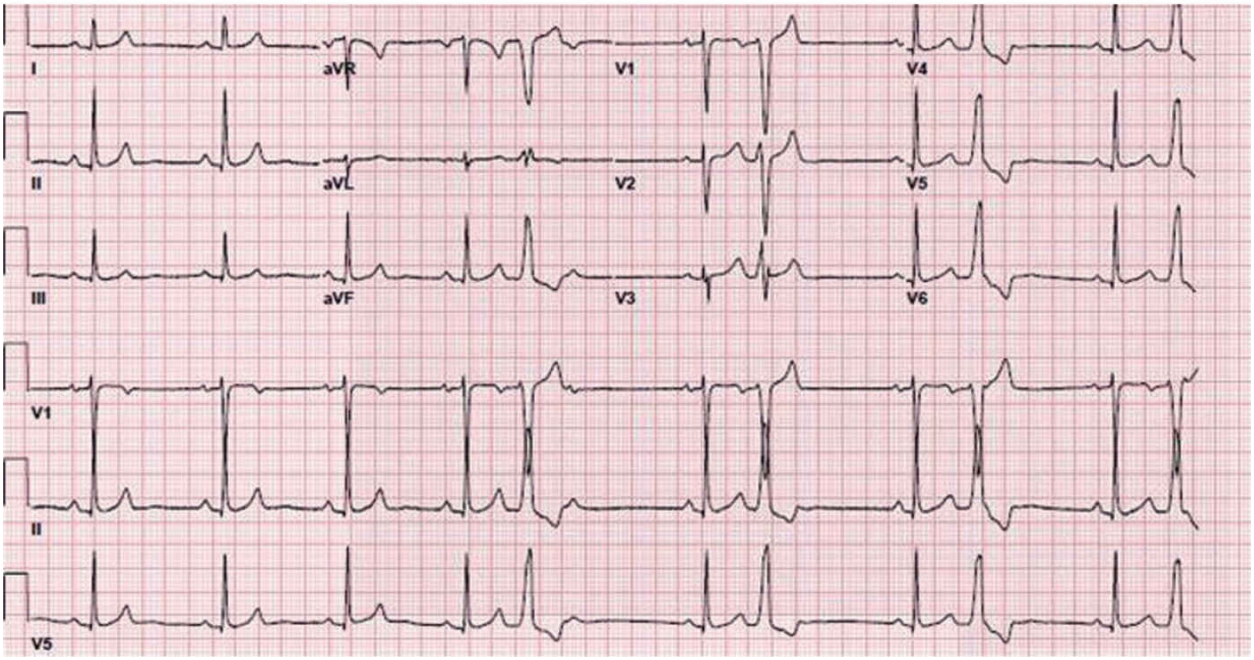

FIGURE 25.1 Normal sinus rhythm followed by ventricular bigeminy. This pattern involves the presence of a premature ventricular complexes (PVC) after every normal sinus beat. aVF; augmented vector foot; aVL; augmented vector left; aVR, augmented vector right.

In the vast majority of patients, PVCs do not produce symptoms, but they can manifest as palpitations and, rarely, lightheadedness or near syncope. Diagnosis of PVCs in the outpatient setting can be made by ambulatory Holter monitor or event monitor, specifically to quantify the burden of PVCs. Whether to treat the PVCs or not depends on the presence of structural heart disease, burden of PVCs, and presence of symptoms. Treatment options for symptomatic patients includes rectifying correctable causes or triggers such as ischemia, alcohol, illicit drugs, or caffeine and also includes workup to check electrolyte levels and thyroid stimulating hormone. For patients with structural heart disease, β - blockers may help reduce the frequency of PVCs. Catheter ablation should be considered for patients with high PVC burden (> 10%) that is associated with significant symptoms unresponsive to antiarrhythmic medications and/or left ventricular (LV) dysfunction. [4] PVCs originating from outflow tracts are relatively easily amenable to catheter ablation.

NONSUSTAINED VENTRICULAR TACHYCARDIA

Like PVCs, nonsustained ventricular tachycardia (NSVT) can be seen in a wide range of medical conditions as well as in healthy individuals. NSVT is mostly diagnosed on telemetry, Holter monitors, or event monitors. Typically, NSVT is not associated with hemodynamic compromise. However, it may produce lightheadedness, palpitations, or chest pain when it lasts for more than a few seconds. β-Blockers are recommended for symptomatic NSVT. In some cases, amiodarone can be used to suppress the NSVT in symptomatic patients.

Clinical relevance and prognostic value of NSVT remain the subject of debate in different clinical settings. Studies have shown that patients with significant coronary artery disease, left ventricular ejection fraction (LVEF) < 40%, and NSVT are at increased risk for sudden cardiac death (SCD), if sustained VT can be induced by electrophysiology study. These patients should have an implantable cardioverter defibrillator (ICD) placement (MUSTT trial).[5] However, such an association is absent for the first 48 hours post-MI. In hypertrophic cardiomyopathy patients, NSVT predicts elevated risk of SCD. Placement of defibrillator for primary prevention is justified in these patients.[6]

VENTRICULAR TACHYCARDIA

Sustained VT is characterized by wide complex tachycardia with a rate > 100 beats/min, lasting for more than 30 seconds, or any VT accompanied with hemodynamic compromise. Sustained VT has multiple etiologies-ischemic VT being the most common. Sustained VT can also be seen in patients with structurally normal heart. Refer to **Table 25.2** for details of types and etiologies of VT.

TABLE 25.2 Types and Etiologies of Ventricular Tachycardia (VT)

Structurally normal heart • Focal VT • Fascicular VT
VT due to structural heart disease • Ischemic VT • Dilated cardiomyopathy
Inherited channelopathies or genetic causes • Long QT syndrome • Brugada syndrome • Catecholaminergic polymorphic ventricular tachycardia • Hypertrophic cardiomyopathy • Arrhythmogenic right ventricular cardiomyopathy (ARVC)
Systemic disease or infiltrative disorders • Sarcoidosis (cardiac sarcoidosis) • Rheumatoid arthritis • Systemic lupus erythematous • Hemochromatosis • Amyloidosis • Myocarditis
Electrolyte abnormalities • Hypokalemia • Hypomagnesemia • Hypocalcemia
Congenital heart disease • Tetralogy of Fallot • Mitral valve prolapse
Drugs/medication induced • IV inotropes • Digitalis • Cocaine • Methamphetamine • Drugs that prolong the QT interval (class IA and class III antiarrhythmics, methadone, etc.)
Other • Commotio cordis

In patients with ischemic heart disease, VT and VF are often the result of scarring and fibrosis secondary to MI. Common nonischemic etiologies include dilated cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy (ARVC). Infiltrative disorders such as myocarditis, sarcoidosis, and amyloidosis can also cause VT. Finally, electrolyte abnormalities such as hypokalemia and hypomagnesemia can also precipitate VT.

Along with VF, sustained VT is a cause of sudden cardiac arrest and commonly also of syncope and chest pain in predisposed patients. Occasionally, if sustained VT is slow in rate, patients can be asymptomatic or may only have lightheadedness or dizziness.

One of the most challenging and clinically relevant issues while diagnosing VT from ECG is to distinguish it from supraventricular tachycardia (SVT) with aberrant conduction (**Table 25.3**). Both rhythms have wide QRS complexes (> 120 ms) with rates greater than 100 beats/min. In the emergent setting, recognizing the difference between the two is paramount. When doubt exists, it is safest to assume any wide complex tachycardia is VT, especially in patients with known cardiovascular disease. Presence of underlying structural heart disease is the strongest predictor of VT.[7, 8] Previous baseline 12-lead ECG obtained during sinus rhythm may also reveal the etiology of the tachycardia. Fusion or capture beats and atrioventricular (AV) dissociation (**Figure 25.2**) provide the strongest electrocardiographic evidence for differentiating VT from SVT with aberrancy, and are diagnostic of VT. However, in their absence, other clues from the electrocardiogram (ECG) may be required to help with this differentiation. Apart from the aforementioned features, several algorithms have been created for distinguishing VT from SVT with aberrancy, the most notable being Brugada criteria. In any young patient with irregular wide complex tachycardia with rate > 200 beats/min, atrial fibrillation caused by conduction over an accessory pathway should be suspected.

TABLE 25.3 Differentiating VT from SVT with Aberrancy

1. History of structural heart disease or coronary artery disease
2. QRS complexes of > 160 ms in absence of any class IC antiarrhythmic
3. True AV dissociation
4. Presence of capture or fusion beats
5. Extreme axis deviation (QRS positive in aVR and negative in I and aVF)
6. Presence of negative or positive concordance (all precordial leads are negative or

positive)

7. Presence of these signs:
   - **a.** Rsr′ (left R wave taller than right R wave) pattern or notched downslope of R wave in V1
   - **b.** Notching near the nadir of S wave (i.e., Josephson sign)
   - **c.** R wave > 30 ms in V1 or V2
   - **d.** QRS onset to nadir of S in V1 > 60 ms (i.e. Brugada sign)

AV, atrioventricular; aVF, augmented vector foot; aVR, augmented vector right; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

FIGURE 25.2 Sustained ventricular tachycardia (VT) with atrioventricular (AV) dissociation. This figure shows AV dissociation in a sustained VT, wherein the relationship between the P waves and the QRS complexes is completely lost. aVF; augmented vector foot; aVL; augmented vector left; aVR, augmented vector right.

MANAGEMENT OF VENTRICULAR TACHYCARDIA

Pulseless Sustained Ventricular Tachycardia

In any patient with pulseless sustained VT/VF (VT with cardiac arrest), cardiopulmonary resuscitation (CPR) should be initiated immediately. The patient should be treated per Acute Cardiac Life Support (ACLS) protocols. If return of spontaneous circulation is achieved, the patient should be started on chronic VT therapies along with post–cardiac arrest treatment. A detailed discussion of ACLS protocols and post–cardiac arrest treatment is beyond the scope of this chapter.

Sustained Monomorphic Ventricular Tachycardia with Pulse

Patients with hemodynamically compromised, unstable VT requires emergent cardioversion or defibrillation. If the patient is stable, he or she can be given antiarrhythmics while being carefully monitored in the critical care unit. Once the acute episode is resolved, workup should be initiated to identify the etiology, along with chronic medical and device therapies (**Table 25.4**). Current guidelines of the American College of Cardiology (ACC)/American Heart Association (AHA) recommend ICD therapy in patients who are survivors of cardiac arrest or who have had hemodynamically unstable VT for secondary prevention.[9]

TABLE 25.4 Acute and Chronic Management of Sustained VT with Pulse

SUSTAINED VT WITH PULSE	
Monomorphic	***Polymorphic***
Unstable: Emergent/urgent cardioversion	**Acute:** Emergent/urgent defibrillation
• Supplemental O_2 • 12-Lead ECG • Establish IV access • Initial labs—(electrolyte level, cardiac biomarkers, urine toxicology, magnesium level)	
Stable: Consider one of the following **antiarrhythmic medications**: • **Intravenous lidocaine** (1–1.5 mg/kg [typically 75–100 mg] at a rate of 25–50 mg/min; lower doses of 0.5–0.75 mg/kg can be repeated every 5–10 min as needed) • **Intravenous procainamide** (20–50 mg/min until arrhythmia terminates or a maximum dose of 17 mg/kg is administered) • **Intravenous amiodarone** (150 mg IV over 10 min, followed by 1 mg/min for the next 6 h; bolus can be repeated if VT recurs)	• If in setting of **myocardial ischemia**: consider IV nitroglycerin and urgent revascularization • **Short QT interval**: can use IV β-blocker or IV amiodarone (150 mg IV over 10 min, followed by 1 mg/min for the next 6 h; bolus can be repeated if VT recurs) • **Long QT interval**: IV isoproterenol can be used to increase the HR in patients with bradycardia • **Torsades de Pointes**: IV magnesium should be given even if the magnesium level is normal
Chronic therapies • β-Blockers • ICD implantation • Antiarrhythmic mediation • Radiofrequency catheter ablation • Surgical therapies—sympathetic denervation	

ECG, electrocardiogram; HR, heart tare; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

Sustained monomorphic VT (SMVT) (**Figure 25.3)** is commonly seen with

acute myocardial ischemia, chronic ischemic heart disease with LV scar formation as well as in the structurally normal heart. In patients with chronic ischemic heart disease, myocardial cells around the border of the scar act as a substrate for a reentrant circuit, causing monomorphic VT. Idiopathic focal VT is usually a monomorphic VT arising from areas of abnormal automaticity.

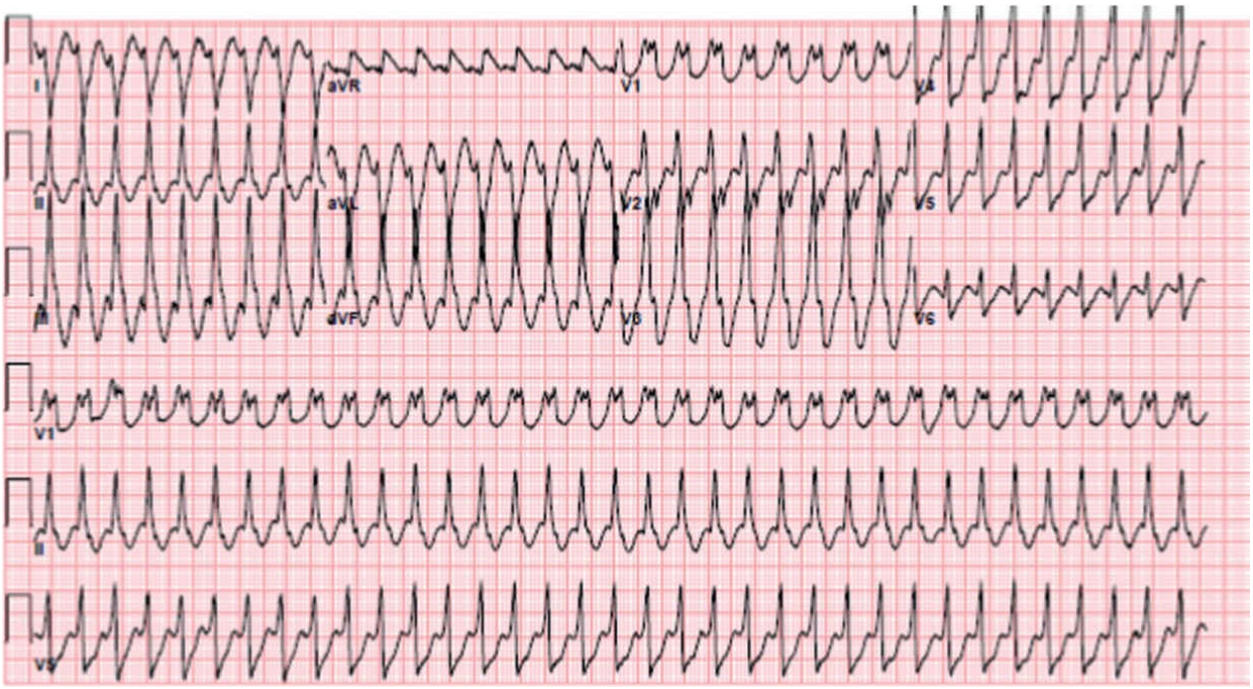

FIGURE 25.3 Sustained monomorphic ventricular tachycardia (SMVT). In SMVT, all beats have the same morphology manifesting as uniform widened QRS complexes on electrocardiogram. aVF; augmented vector foot; aVL; augmented vector left; aVR, augmented vector right.

All patients with sustained monomorphic VT should have basic workup to assess etiology. Features of instability include chest pain, dyspnea, hemodynamic instability, and altered mental status. Stable patients can be treated with any of three antiarrhythmic medications—lidocaine, amiodarone, or procainamide. Intravenous procainamide is not easily available in the United States. Lidocaine is usually more effective in VT associated with myocardial ischemia or infarction. Amiodarone acts slowly and is the most effective as well as most commonly used out of the three medications. Although IV administration of these medications can be stopped once the acute episode is over, infusion should be continued if there is recurrent SMVT. Intravenous amiodarone can be followed by oral amiodarone to prevent recurrent VT. Other concurrent managements include treatment of the reversible cause—electrolyte imbalance correction or urgent revascularization if myocardial ischemia is

present.

Once the acute episode is over, long-term medical therapy should be started, which commonly includes β -blocker with or without antiarrhythmic medication. ICD placement should be considered for secondary prevention. The European Heart Rhythm Association/Heart Rhythm Society (EHRA/HRS) recommends radiofrequency catheter ablation for patients with structural heart disease in the following situations: 1. recurrent VT that is not responding to antiarrhythmic drugs; 2. VT leading to recurrent ICD shocks with no response to or side effects with antiarrhythmic therapy; 3. incessant VT or VT storm not attributable to a reversible cause; 4. a patient who is not a candidate for ICD or refusing ICD.[10]

Surgical therapies for VT can be considered in patients who are undergoing cardiac surgery for another cause (coronary bypass graft placement/valve replacement) and have identifiable substrates such as ventricular aneurysms or large myocardial scars. Surgical approaches that have proven effective include LV aneurysmectomy, encircling endocardial ventriculotomy and subendocardial resection. In some patients with recurrent VT who have failed to respond to antiarrhythmic drugs and catheter ablation, bilateral surgical sympathectomy has been shown to be helpful.

Sustained Polymorphic Ventricular Tachycardia with a Pulse

Polymorphic VTs are classified on the basis of their QT interval. Polymorphic VT with normal QT intervals is most commonly caused by myocardial ischemia after acute MI, severe heart failure, or cardiogenic shock. When feasible, urgent myocardial revascularization should be undertaken. These patients have high mortality, especially when VT is associated with heart failure and cardiogenic shock. Antiarrhythmic drugs have limited success in improving their outcome.

Torsades de pointes (TdP) (**Figure 25.4**) is a specific type of polymorphic VT (which has characteristic ECG morphology in which QRS complexes appear to “twist” around the isoelectric line). When in sinus rhythm, an ECG classically shows prolonged QT interval. This can be congenital or acquired. Congenital long QT syndrome is caused by multiple genetic variants. Acquired long QT intervals are secondary to acute myocardial ischemia or drug administration. Medications known to contribute to QT prolongation include several antiarrhythmic drugs (Class III antiarrhythmics), antibiotics (specifically fluoroquinolones and macrolides), antipsychotics, and antihistamines.

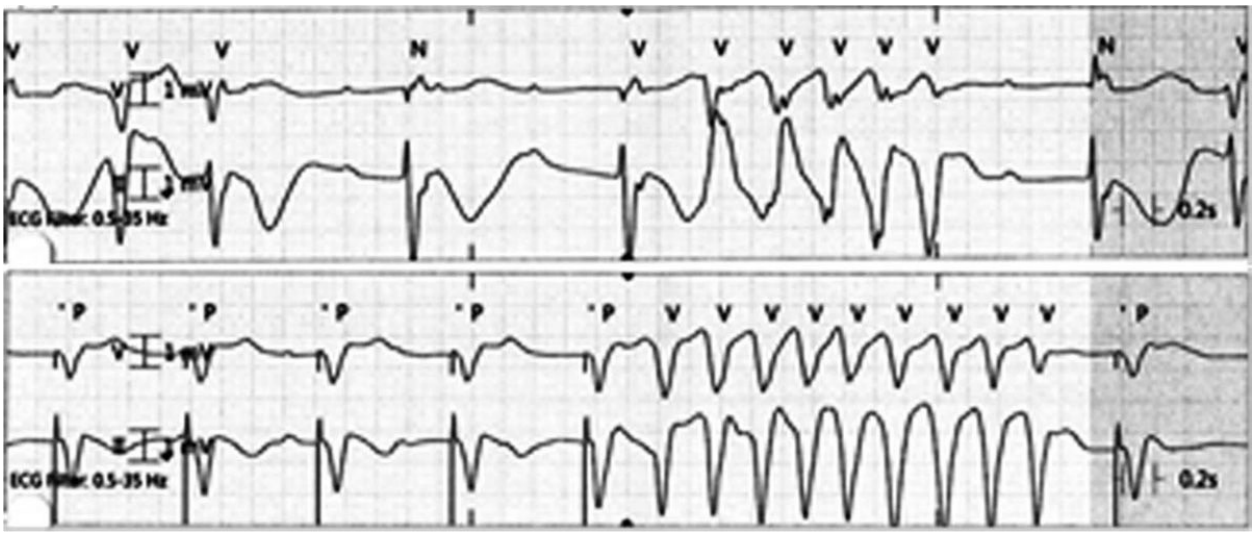

FIGURE 25.4 Torsades de pointes. Both rhythm strips showing electrocardiogram with baseline rhythm having prolonged QT interval and a short burst of polymorphic ventricular tachycardia, that is torsades de pointes. Upper panel: sinus bradycardia with prolonged QT interval. Lower panel: V-paced rhythm with prolonged QT interval.

There are other types of polymorphic VT without definitive association with QT interval. Bidirectional VT is a rhythm characterized by two distinct wide complex QRS (> 120 ms) morphologies (rate > 100 beats/min) that alternate every beat. Although bidirectional tachycardia is a rare occurrence in general, it is pathognomonic for digoxin toxicity. Catecholaminergic polymorphic ventricular tachycardia (CPVT), also known as familial polymorphic ventricular tachycardia (FPVT), is a congenital disorder caused by mutations in ryanodine receptors or other calcium channel binding proteins in the sarcoplasmic reticulum. It is a rare condition that manifests within the first or second decade of life, presenting as dizziness, syncope, or even sudden death, after exercise or emotional stress. Brugada Syndrome is a rare syndrome that is seen most commonly in South-East Asians. Resting ECGs show right-bundle branch block (RBBB) pattern with ST-elevations in the right precordial leads, specifically in V1 and V2, and have the potential to degenerate into polymorphic VT and even VF.

Most polymorphic VTs are unstable with hemodynamic compromise and require emergent or urgent defibrillation. In the patient with polymorphic VT and normal QT interval, the likely etiology is myocardial ischemia. β-Blockers and IV amiodarone can be used (bolus followed by infusion) to prevent recurrence of the arrhythmia. Urgent coronary angiography and revascularization is necessary to relieve the ischemia.

In the patient with congenital long QT syndrome, β -blockers may be used to reduce the frequency of PVCs and shorten the QT interval. ICD therapy is indicated if patients have recurrent syncope despite β-blocker therapy. Isoproterenol is used in patients with polymorphic VT triggered by sinus pauses or bradycardia. For patients with TdP, IV magnesium is first-line therapy (even in patients with normal serum magnesium) for both termination and prevention of recurrence of this rhythm. If the patient does not respond to intravenous magnesium, temporary intravenous pacing at 100 beats/min may be reasonable to prevent recurrence.

VENTRICULAR FIBRILLATION

VF is a rapid (typically > 300 beats/min) and irregular rhythm of chaotic electrical activity of ventricular origin. VF causes SCD because there is no cardiac output during this rhythm. Typically, this rhythm is seen during the acute phase of MI. VF is further divided into primary VF, which occurs less than 48 hours after a MI, and nonprimary VF, which does not occur in the setting of MI (but typically in the setting of heart failure or recurrent ischemia). Predictors of primary VF include ST-elevation MI (STEMI), early repolarization on baseline ECG during an acute coronary syndrome, hypokalemia, hypotension, large infarcts, male sex, and history of smoking. If not treated immediately, VF is almost universally lethal.

Treatment of VF involves defibrillation and pharmacotherapy. Defibrillation at an initial shock of 120 to 200 joules for biphasic defibrillators and 360 joules for monophasic defibrillators is currently recommended by ACLS guidelines. Pharmacotherapy involves epinephrine, which is to be administered as 1mg IV of 1:10,000 every 3 to 5 minutes. An initial bolus of 300 mg of IV amiodarone diluted in 20 to 30 mL of normal saline, followed by 150 mg IV boluses has been shown to increase the efficacy of electrical defibrillation in out-of-hospital cardiac arrest. Prior to the most recent guidelines regarding ACLS by the AHA, vasopressin was used, but is currently not recommended.[11] Lidocaine has been shown to have no evidence of efficacy in the management of VF. Chronic therapy for VF is similar to sustained VT, which includes ICD implantation for secondary prevention and β -blockers.

VENTRICULAR TACHYCARDIA—SPECIFIC VTS

VENTRICULAR TACHYCARDIA IN THE STRUCTURALLY NORMAL HEART

About 10% of patients with VT do not have any evidence of structural heart disease.[12] In general, these VTs present as monomorphic VT. Although idiopathic VT can originate from any ventricular site, the most frequent sites are RVOT, LVOT and Left ventricular fascicles.

Focal Ventricular Tachycardia

RVOT VT is seen in greater proportion in females compared to males, whereas the distribution of LVOT VT is more equal with respect to gender. They are both seen early in life, sometime between the third and fifth decades. The most likely mechanisms for these rhythms include triggered activity (catecholamine-mediated after-depolarizations). Symptoms include palpitations, dizziness, and, on occasion, syncope. On presentation, these rhythms commonly present as nonsustained repetitive monomorphic VT or paroxysmal exercise-induced VT. Frequent NSVT and high PVC burden can lead to ventricular dysfunction (tachycardia-induced cardiomyopathy) in these patients. On ECG, RVOT VT has a characteristic left bundle branch block morphology with inferior axis, where LVOT VT presents with RBBB morphology with inferior axis.

Idiopathic VTs are associated with good long-term prognosis. The decision to treat depends on the frequency and severity of symptoms, and presence of ventricular dysfunction. Acute termination can be achieved with adenosine and verapamil. RVOT and LVOT VTs respond well to β-blockers, calcium channel blockers, and antiarrhythmic drugs as well. As these patients have no structural heart disease, all antiarrhythmic drugs can be used. However, catheter ablation is preferred management option because it offers a permanent safe cure and has a high success rate, exceeding 90%.

Fascicular Ventricular Tachycardia

Fascicular VT originates from the fascicles in the left ventricle. Although commonly seen in the second to fourth decades of life, frequently patients may recall episodes of palpitations or dizziness at an earlier age. Up to 70% of these patients are males. This rhythm may be precipitated by emotional stress or exercise. Fascicular tachycardias are related to reentry in the His–Purkinje

system, most commonly in the left posterior fascicle. At times, the site of origin is a false tendon or a fibromuscular band that extends from the posteroinferior left ventricle wall to the basal septum, which has reportedly been observed on echocardiography.[13] On 12-lead ECG, fascicular VTs have a RBBB-like morphology and relatively short QRS interval (120 ms to 140 ms). Depending on the site of exit in the left ventricle, they are associated with left axis deviation (more commonly) or right axis deviation. Fascicular VT has good long-term prognosis and can be treated medically with β -blockers and calcium channel blockers. They are particularly sensitive to verapamil. Fascicular VT can be confused for SVT because of ECG characteristics and sensitivity to verapamil. Catheter ablation has high success rates (90–95%) and is preferred compared to lifelong medical therapy.

VENTRICULAR TACHYCARDIA IN THE STRUCTURALLY ABNORMAL HEART

Ventricular Tachycardia in Ischemic Heart Disease

This refers to VT that develops in the setting of both acute and chronic ischemic heart disease. Life-threatening VAs, including VT and VF, are infrequent but possible sequelae of acute STEMIs and acute non-ST-elevation MIs (NSTEMI), with an overall lower incidence in NSTEMIs compared to STEMIs. Life-threatening arrhythmias such as symptomatic VT and VF can be the first presentation of acute MI. These are primarily treated by coronary revascularization.

Patients with chronic ischemic heart disease usually have myocardial scarring and present with monomorphic VT. This involves a reentrant circuit involving damaged slow conducting myocardium and increased automaticity in the border zone of myocardial scars. On ECG, VT from old MIs are typically monomorphic, whereas VT in the acute MI presents as polymorphic. Patients who develop VT or VF in the acute MI phase, specifically in the first 24 to 48 hours, do not have an increased risk of sudden death and do not require an implantable cardioverter defibrillator (ICD) for secondary prevention.

For those who develop recurrent VT or VF, and are thus at risk for SCD, the primary treatment is ICD therapy. β-Blockers have anti-ischemic and bradycardic properties and have been shown to reduce SCD, if continued at least 90 days post-MI.[14] Antiarrhythmic medications such as sotalol and amiodarone may be used for recurrent VT and VF despite defibrillator implantation. Catheter

ablation has been shown to be highly successful for management of these patients and involves mapping and ablation of areas of slow conduction.

ICDs are indicated for primary and secondary prevention of sudden death in patients with chronic ischemic heart disease. Class IA indications for primary prevention include 1. patients with LVEF < 35% caused by prior MI who are at least 40 days post-MI and are in New York Heart Association (NYHA) Functional Class II or III, 2. patients with LVEF < 30% who are 40 days post-MI and are in NYHA Functional Class I. Class IA recommendation for ICD placement in the patient with ischemic cardiomyopathy for secondary prevention include those who are survivors of cardiac arrest caused by VT/VF.

Ventricular Tachycardia in Dilated Cardiomyopathy

This refers to VT that occurs in the setting of dilated cardiomyopathy (DCM). DCM is the most common cause of heart failure and is among the most common diagnosis that requires hospitalization in North America. The current prevalence of DCM in the United States is roughly 4.7 million, and the 5-year mortality rate in patients with heart failure caused by DCM is 50%.[15]

VT in the patient with dilated cardiomyopathy has been proposed by several different mechanisms: (1) arrhythmogenic substrates may result from myocardial fibrosis, leading to an irritable focus and (2) high catecholamine levels or stretching of myocardial fibers induced by increased LV end-diastolic volume. Acute management of VT in DCM is similar to that of ischemic cardiomyopathy. In addition, β-blockers show similar benefits as they do in ischemic cardiomyopathy. Current guidelines recommend ICD implantation for primary prevention in patients with new diagnosis of nonischemic dilated cardiomyopathy (NIDCM)with NYHA class II–III symptoms and EF <30%; or with at least 3 months of medical therapy in a patient with LVEF <35%.[16] Catheter ablation has been shown to have limited success in patients with VT and NIDCM, but it is particularly successful in a small proportion of these patients when VT is related to bundle branch reentry.

VENTRICULAR TACHYCARDIA RESULTING FROM INHERITED CHANNELOPATHIES OR CONGENITAL CAUSES

This section will focus on several different genetic and congenital causes of VT and their managements. Several of these causes of VT owe their arrhythmogenicity to channelopathies and receptor protein defects.

Long QT Syndrome

Long QT syndrome is a congenital disorder, which is characterized by a prolonged QT interval (greater than 450 ms in adult males and 470 ms in adult females) on baseline ECG. Several different mutations have been identified in patients with genetic long QT syndrome involving several different subunits of potassium and sodium channel proteins. Syncope provoked by being startled, exercise, or swimming in light of previous family history of SCD and an ECG showing prolonged QT may help make this diagnosis. As the QT interval may vary throughout the day, ambulatory ECG monitoring may provide some information to help confirm the diagnosis of long QT syndrome.

As discussed earlier, long QT syndrome can lead to a specific type of VT known as TdP, which is a polymorphic VT with a characteristic twisting pattern around an isoelectric point. TdP in these patients may develop from an adrenergic response precipitated by stress, electrolyte abnormality, or drug administration. Acute management to break TdP involves intravenous administration of magnesium, regardless of serum magnesium levels. β - Blockers and ICD therapy should be used for patients who are survivors of SCD and be considered for patients with a family history of SCD.

Brugada Syndrome

Brugada Syndrome is a rare autosomal dominant disorder that is seen most commonly in the Southeast-Asian male. Mutations in cardiac sodium channels are typically responsible for this condition. Resting ECG shows a right-bundle branch–like pattern with ST-elevations in the right precordial leads. Procainamide has been used as a diagnostic challenge test because it is able to provoke patients who do not have the baseline ECG findings. With Brugada pattern ECGs, ICD therapy is treatment of choice in patients with a history of syncope and aborted sudden death to prevent future SCD. Chronic therapy involving medications such as quinidine and cilostazol have been shown to suppress VAs in these patients, but currently should be used in conjunction with ICD therapy.

Catecholaminergic Polymorphic Ventricular Tachycardia

CP VT is a rare condition that manifests within the first or second decade of life, presenting as dizziness, syncope, or even sudden death, after exercise or emotional stress. Cardiac ryanodine receptor gene and calsequestrin 2 gene

mutations induce calcium release, leading to delayed after-depolarizations and triggered activity, which can lead to polymorphic ventricular tachycardia and VF; there are no characteristic baseline ECG findings. Chronic prevention recommendations include avoiding competitive sports and strenuous exercising. All adult patients without any documented VA history should be on a β -blocker. Survivors of cardiac arrest should be on β -blockers and have consideration of an ICD. In the patient who continues to have VAs despite being on a β -blocker and having an ICD, flecainide can be used for further suppression.

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic Cardiomyopathy (HCM) is a relatively common genetic disorder (1 in 500) caused by several mutations involving sarcomere genes, with a multitude of clinical manifestations and hemodynamic abnormalities (LV outflow obstruction, diastolic dysfunction, myocardial ischemia, and mitral regurgitation) that are related to profound hypertrophy and myopathic processes. Signs and symptoms are variable: Some patients are asymptomatic; some may experience dyspnea, palpitations or syncope; and some may experience advanced heart failure symptoms. Current Class I recommendations for treatment of symptoms such as angina or dyspnea include β-blockers and verapamil in patients with obstructive (referring to LV outflow obstruction) or nonobstructive HCM. Phenylephrine can be used for acute hypotension in patients with obstructive HCM who do not respond to fluid administration. Current class I recommendation for patients with severe treatment-refractory symptoms and LVOT obstruction is septal reduction either surgically (myomectomy) or percutaneously (alcohol septal ablation).

This condition may predispose to developing VAs and to SCD in young persons. Patients with a high risk of SCD include those with a previous history of VF, sustained VT or other SCD events, family history of SCD events, unexplained syncope, documented NSVT on Holter monitoring, and maximal LV wall thickness greater than or equal to 30 mm. These patients should be considered for ICD implantation.[2] There is no consensus on the role of electrophysiology testing in risk stratification of asymptomatic HCM patients who do not have any of the aforementioned criteria.

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC occurs in roughly 1 in 5000 patients and is characterized pathologically

by morphologic alterations caused by fibrofatty replacement of the right ventricle. ARVC is known as a cause of VAs developing after strenuous exercise, and 80% of cases are diagnosed before the age of 40. There are no specific findings on ECG, but electrocardiograms may reveal T-wave inversions in leads V1 to V3 in the presence of complete or incomplete RBBB. In addition, epsilon waves (characterized by small amplitude waves after the QRS complexes) have been seen in a large number of ECGs in patients with ARVC. With respect to pharmacologic treatment, β-blockers are reasonable recommendations, which should be added to ICD therapy if the patient has a history of frequent PVCs, NSVT, or sustained VT or VF. Patients with recurrent events should be treated with antiarrhythmic therapy and/or catheter ablation. Radiofrequency ablation in these patients can be attempted with limited success because of multiple arrhythmogenic foci.

Cardiac Sarcoidosis

Cardiac Sarcoidosis is being increasingly recognized as a cause of VTs in young patients. The involvement of cardiac muscle has been noted in 10 to 30% of patients with systemic sarcoidosis. A small proportion of these patients develop AV block and/or VT. Diagnosis is confirmed by the presence of myocardial granulomas in biopsy-proven systemic sarcoidosis. Patients with cardiac sarcoidosis and VT should get ICD. Prophylactic ICDs are indicated for patients with systemic sarcoidosis and large myocardial scar. Therapeutic options for management of recurrent VT in patients with cardiac sarcoidosis include antiarrhythmic drugs and, if need be, catheter ablation. Related to complex arrhythmia substrates, both endocardial and epicardial catheter ablation are often needed and are associated with limited success.

Other Congenital Heart Disorders (Tetralogy of Fallot and Mitral Valve Prolapse)

Tetralogy of Fallot (TOF) is a congenital heart defect classically involving four anatomic abnormalities of the heart (pulmonary stenosis, overriding aorta, ventricular septal defect, and right ventricular hypertrophy.) The prevalence of TOF in the United States is 4 to 5 in 10,000 live births. Pathophysiologically, the severity of symptoms largely depends on the degree of the RVOT obstruction. TOF itself is not responsible for VT; however, repair of the RVOT obstruction may involve scarring and patches that may provide an ideal substrate for reentry. Patients with a QRS longer than 180ms are at higher risk of developing

monomorphic VT. Because of the rarity of TOF, there is a lack of strong data for specific drug treatment in VAs in patients with this condition. ICD implantation may be useful in patients with a history of sustained VT or VF. Medical therapy or catheter ablation should be considered for these patients with recurrent VT.[17]

Mitral valve prolapse (MVP) is a valvular disease affecting 2% to 3% of the general population. Proteoglycan accumulation is responsible for leaflet thickening, leading to valvular abnormality. Patients with MVP have a variety of other cardiac complications like atrial fibrillation, congestive heart failure, endocarditis, and, rarely, VAs and sudden cardiac death. The logical explanation for VT in this patient population would be LV dysfunction seen with severe mitral regurgitation. However, multiple sudden cardiac deaths have been reported in MVP patients with mild MR and normal LV function. Etiology in these cases is believed to be caused by VA. VT should be suspected in all patients with MVP who present with presyncope or syncope.

MISCELLANEOUS CAUSES OF VT

Drug-Induced VT

Several drugs may lead to life-threatening VAs. In particular, polymorphic VT and TdP may result from medications that may cause prolongation of the QT interval, leading to acquired long QT syndromes. Antiarrhythmics, macrolide and fluoroquinolone antibiotics, antiprotozoals, antipsychotics, opiates, promotility agents, antihistamines, and toxins such as arsenic are recognized to prolong QT intervals in patients and should be used judiciously in patients with preexisting long QT intervals. Apart from intrinsic properties of the aforementioned medications, electrolyte abnormalities such as hypokalemia and hypomagnesemia should be recognized as potential side effects or from drug–drug interactions.

Commotio Cordis

Translated directly from Latin, meaning “agitation of the heart,” commotio cordis refers to VAs caused by chest trauma and has been recognized as a cause of SCD in young athletes. Young males are most affected, and this phenomenon has been reported in sports with physical contact (baseball, hockey, football). There is a 10 - to 30-millisecond window of the cardiac cycle (specifically in the ascending portion of the T wave), in which the heart is particularly vulnerable to mechanical trauma. When applied at the right time, even a small amount of

energy can disrupt the normal sinus rhythm into VF. This should be suspected when an athlete collapses following chest trauma even when relatively mild. It is the timing of the trauma with respect to the cardiac cycle rather than force that is important for precipitation of this arrhythmia. Treatment includes immediate initiation of CPR. Availability of automatic external defibrillators on playgrounds will improve survival from commotio cordis.

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Patient and Family Information for:VENTRICULAR ARRHYTHMIAS

WHAT IS A VENTRICULAR ARRHYTHMIA?

The heart is comprised of four chambers (two upper chambers called the left and right atria and two lower chambers called the left and right ventricles), and a coordinated sequence of electrical activation of these chambers (the atria pump first, followed by filling and pumping of the ventricles) is what allows the heart to effectively pump blood. A normal electrical sequence, also known as normal sinus rhythm, helps to generate adequate blood pressure in the arteries to deliver blood to the rest of the body and the brain. When this electrical sequence is interrupted, an arrhythmia is said to occur. Ventricular arrhythmias (VA) are disturbances of the rhythm of the heart when they originate in the lower chambers—the ventricles.

TYPES OF VENTRICULAR ARRHYTHMIAS

VA can be classified into the following categories:

1. Isolated Premature Ventricular Complexes (PVCs): These are single abnormal extra beats that originate in the ventricles.
2. Ventricular Tachycardia (VT): Refers to a longer sequence of abnormal ventricular beats, which if persistent, may be harmful to patients. VT is defined as more than 3 consecutive PVC. VT can be *nonsustained* if the patient's blood pressure remains stable, and the episode of VT is relatively short in duration (<30 seconds) or *sustained* if the patient is hemodynamically unstable and/or the episode lasts >30 seconds. VTs are

typically identified on electrocardiogram (ECG) as having a rate of more than 100 bpm.

3. Ventricular Fibrillation (VF): Ventricular fibrillation happens when the ventricles quiver but do not have an orchestrated contraction, resulting in essentially no meaningful pumping activity. This leads to no circulation of blood within the body and typically leads to death if not treated promptly.

SYMPTOMS

1. Isolated PVCs and nonsustained VT (NSVT) may cause palpitations, and/or dizziness; however, some patients do not feel anything at all.
2. Sustained VT lasts for more than 30 seconds, and many patients may lose consciousness and collapse.
3. VF will lead to collapse of the patient, loss of consciousness, and death if not treated promptly.

CAUSES OF VENTRICULAR ARRHYTHMIA

VAs may occur for a variety of reasons such as structural or inherited, or even on account of other physiologic abnormalities of the body.

1. Structural heart disease:
   a. Coronary Artery Disease (CAD): Many VAs occur in the setting of blocked coronary arteries in the heart after an acute heart attack. When a heart attack occurs, scarring and dead heart tissue cause electrical disruption. This disruption develops by several different mechanisms (explained in the above chapter). VA in the setting of heart attacks may even result in sudden cardiac death.
   b. Cardiomyopathies: This is a general term to describe various diseases of the heart (which may or may not be caused by blockage of the heart vessels such as in CAD). Cardiomyopathy can lead to weakness and/or stiffness of the heart muscle. Diseases that are not caused by CAD include viral infections, thickening of heart tissues, and dilatation of the chambers of the heart.
   c. Infiltrative heart disease: There are some other medical conditions that cause inflammation and scarring of the heart and that can lead to electrical disturbances and cause VAs.
2. VA without structural heart disease: There are some congenital conditions that affect the proteins that mediate the transport of ions (sodium, potassium, and calcium) in heart cells. Improper functioning of these channels causes disruption of electrical activity and increases the chances of VA.
3. Other reversible factors: Most commonly, abnormal levels of ions such as potassium or magnesium in the blood can cause VAs. Lack of oxygen, if

severe, has been known to irritate heart muscles and cause arrhythmias. Some medications, if not taken judiciously or combined with other medications, may affect different ions in the blood and lead to predisposition to VAs.

TREATMENT OPTIONS

Treatment of VA is divided into two parts. The first is to acutely treat and terminate the arrhythmia. The second is to prevent further arrhythmias from happening. Three different modalities of treatment currently exist today.

ANTIARRHYTHMIC MEDICATIONS

Antiarrhythmic medications are used to acutely treat rhythm disturbances, but may also be used to help maintain normal heart rhythms. β-blockers can slow down the heart rate and suppress the abnormal ventricular complexes. β-blockers are often used in the setting of a heart attack to help prevent VAs from happening. Traditional antiarrhythmic medications such as Amiodarone can also be used in the setting of VT—both to terminate the VT and to maintain a normal sinus rhythm. It is important to note that many antiarrhythmic medications are associated with the development of new and more severe arrhythmias, so care must be taken when given these medications to patients. Amiodarone is known to cause several side effects involving the liver, lungs, thyroid, and eyes when used chronically.

CATHETER ABLATION OF VENTRICULAR TACHYCARDIA

Patients can sometimes be taken into the electrophysiology lab and have abnormal rhythm pathways essentially destroyed. This is a rather invasive but safe procedure. During catheter ablation, abnormal electrical foci within the heart are identified by electrical stimulation. Heat energy is then delivered by a catheter to ablate/burn abnormal electrical pathways. This procedure can even be used in patients who experience a high enough burden of PVCs.

Depending on the type of disease, ablation may be extremely successful, with reported success rates of up to 95% in preventing recurrence of VAs.

Although they happen infrequently, some rare complications might occur with these procedures that include clot formation at the burn site and/or a collection of blood in the sac that surrounds the heart.

PACING AND ELECTRIC SHOCK

Devices known as implantable cardioverter defibrillators (ICDs) have been shown to reduce the death rate in patients who have experienced VT/VF or in those who are survivors of sudden cardiac death. ICDs can detect VAs and deliver two kinds of therapy that help maintain normal sinus rhythm: antitachycardia pacing (ATP) and electric shock. When a patient has VT, ATP can overdrive the pacing of the heart and slow the heart rate down. When a patient has a sustained VT or experiences VF, ICDs can deliver a shock and terminate the rhythm. This shock is similar to the therapy that is delivered by external defibrillators carried by paramedics and hospitals.

ICDs are placed in patients who have weak hearts after heart attacks, who have previously suffered cardiac arrest, or who are known to have high risks of sudden cardiac death.

26

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The Approach to the Patient with Syncope

Syncope is a syndrome consisting of a relatively short period of temporary and self-limited loss of consciousness caused by transient diminution of blood flow to the brain.[1, 2] The term derives from the Greek word *synkoptein*, which means "to cut short,"[3] and is used to classify a common clinical problem. The incidence of self-reported syncope was 6.2 per 1000 person-years in the Framingham study, with a cumulative incidence of 3% to 6% over 10 years.[4, 5] In selected patient populations, the lifetime prevalence of syncope could reach almost 50%. In the United States, 1 to 2 million patients are evaluated for syncope annually, making up 3% to 5% of emergency department visits, and 1% to 6% of urgent hospital admissions.[6]

Several guidelines have been published for the diagnostic approach to patients with syncope; however, they do not apply to every clinical situation encountered.[7, 8] The European Society of Cardiology[9] and the American College of Cardiology[10] have published detailed documents specifying a classification of the principal causes of syncope (**Table 26.1**). However, given the vast differential diagnosis, the varied therapies for patients presenting with syncope and the lack of consensus guidelines, a structured approach to the management of these patients was needed. To address this issue, we developed a standardized pathway which is comprehensive, yet simple, and provides guidelines for the

management of all patients presenting with syncope[11] (**Figure 26.1**).

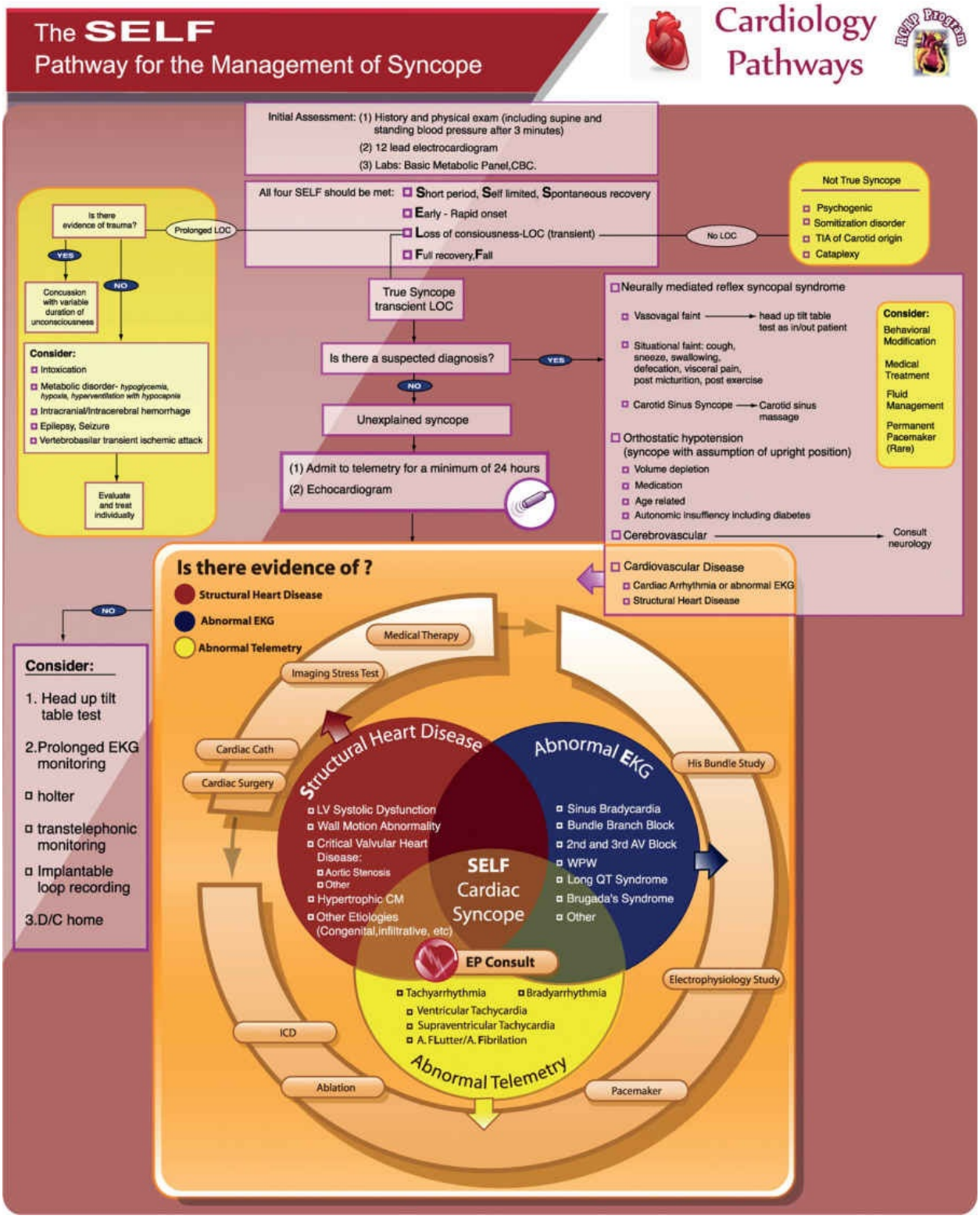

FIGURE 26.1 The SELF pathway for the management of syncope. CBC, complete blood count; ECG, electrocardiogram; EP, electrophysiologic; ICD. implantable cardioverter defibrillator; TIA, transient ischemic attack; WPW, Wolff–Parkinson–White.

TABLE 26.1 Classification of the Principle Causes of Syncope (Adapted from the European Society of Cardiology guidelines[9])

Reflex (neurally mediated) syncope

- Vasovagal:
  - Mediated by emotional distress: fear, pain, instrumentation, blood phobia
  - Mediated by orthostatic stress
- Situational:
  - Cough, sneeze
  - Gastrointestinal stimulation (swallow, defecation, visceral pain)
  - Micturition (post micturition)
  - Post exercise
  - Postprandial
- Carotid sinus syncope

Syncope due to orthostatic hypotension

- Primary autonomic failure:
  - Pure autonomic failure, Parkinson disease with autonomic failure, dementia
- Secondary autonomic failure:
  - Diabetes, amyloidosis, uremia, spinal cord injuries
- Drug-induced orthostatic hypotension:
  - Alcohol, vasodilators, diuretics, phenothiazine, antidepressants
- Volume depletion:
  - Hemorrhage, diarrhea, vomiting

Cardiac syncope (cardiovascular)

- Arrhythmia as primary cause:
  - Bradycardia:
    - Sinus node dysfunction (including bradycardia/tachycardia syndrome)
    - AV conduction system disease
    - Implanted device malfunction
  - Tachycardia:
    - Supraventricular
    - Ventricular (idiopathic, secondary to structural heart disease or to channelopathies)
  - Drug-induced bradycardia and tachyarrhythmias
- Structural disease:
    - Cardiac: cardiac valvular disease, acute myocardial infarction/ischemia
    - Hypertrophic cardiomyopathy, cardiac masses (atrial myxoma, tumors)
    - Pericardial disease/tamponade, congenital anomalies of coronary arteries, prosthetic valve dysfunction
- Others: pulmonary embolus, acute aortic dissection, pulmonary hypertension

AV, atrioventricular.

INITIAL ASSESSMENT OF A PATIENT WITH SYNCOPE

The initial assessment of a patient with syncope includes a meticulous and comprehensive medical history; incorporating eyewitness accounts can help determine the cause of syncope (**Table 26.2**).[7] Important questions to be asked in assessing patients with syncope are listed in **Table 26.3**. Orthostatic hypotension and autonomic dysfunction can be identified by measuring blood pressure and pulse rate in the upper and lower extremities in the supine and upright positions.

A 12-lead electrocardiogram (ECG) and basic laboratory tests, including a basic metabolic panel and complete blood count, should be performed in all patients with syncope.

TABLE 26.2 Initial Assessment of a Patient with Syncope

For every patient presenting with syncope:
- Detailed history
- Comprehensive physical examination
- Standard 12-lead ECG
- Basic labs (including basic metabolic panel, complete blood count)

For *all admitted patients (when appropriate):*
- Echocardiogram
- In-hospital 24-h telemetry monitoring (out-of-hospital telemetry may be applicable where available)
- Neurologic evaluation

ECG, electrocardiogram.

TABLE 26.3 Important Questions That Can Be Asked in Assessing Patients with Syncope

Questions about situations before syncope
- Position (supine, sitting, or standing)
- Activity (rest, change in posture, during or after exercise, during or immediately after urination, defecation, cough, or swallowing)
- Predisposing factors (crowded or warm places, prolonged standing, postprandial period) and precipitating events (fear, intense pain, neck movements)

Questions about onset of syncope
- Nausea, vomiting, abdominal discomfort, feeling of cold, sweating, pain in neck or shoulders, blurred vision, dizziness
- Trauma

Questions for eyewitness
- Way of falling (slumping forward, backward, or kneeling over), skin color (pallor, cyanosis, flushing), duration of loss of consciousness, breathing pattern (snoring), movements (seizure-like) and their duration, onset of movement in relation to fall, tongue biting

Questions after the episode
- Nausea, vomiting, sweating, feeling of cold, confusion, muscle aches, skin color, injury, chest pain, palpitations, urinary or fecal incontinence

Questions about past family and medical history
- Family history of sudden death, congenital arrhythmogenic heart disease or fainting
- Previous cardiac disease (coronary artery disease, heart failure)
- Neurologic history (epilepsy, narcolepsy)
- Metabolic disorders (diabetes, hypo or hyperthyroidism)
- Medication (antihypertensive, antianginal, antiarrhythmic, diuretics, and QT prolonging agents)
- In instance of recurrent syncope, information on recurrences such as the time from the first syncopal episode and on the number of spells

DEFINITION OF TRUE SYNCOPE

We use the acronym **SELF-1** which reflects the four criteria that should be met for an event to be considered true syncope. These criteria include

S—***S***hort period, self-limited, spontaneous recovery
E—***E***arly-rapid onset
L—***L***oss of consciousness—transient
F—***F***ull recovery—fall
Patients who did not lose consciousness are defined as “not true syncope.”

CLASSIFICATION OF SYNCOPE WHEN THERE IS A CERTAIN OR SUSPECTED DIAGNOSIS

These are certain disorders causing true syncope with a transient loss of consciousness:

1. *Reflex syncope:* Reflex syncope is a neurally mediated reflex syndrome[12] in the absence of structural heart disease. It refers to a reflex that, when triggered, gives rise to vasodilatation and bradycardia. These triggers include fear, pain, instrumentation, blood phobias, prolonged standing, crowded warm places, nausea, vomiting, and abdominal pain.
2. *Orthostatic hypotension syncope:* In orthostatic hypotension syncope, syncope occurs with assumption of an upright position. It can occur after starting of medications that can lead to hypotension, or can be due to an autonomic neuropathy.[13] Volume depletion is an important cause of orthostatic hypotension.
3. *Cardiovascular disease:* Structural heart disease can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output. Cardiac arrhythmia can cause a decrease in cardiac output, which usually occurs irrespective of circulatory demands.

RISK STRATIFICATION FOR ADMISSION

One of the main dilemmas that face emergency department physicians is whether

to admit patients to the hospital or to refer them for an outpatient evaluation. Many risk assessment scores have been developed. These include the San Francisco Syncope Rule (SFSR),[14] the *Osservatorio Epidemiologico della Sincopenel Lazio* (OESIL),[15] and the Evaluation of Guidelines in Syncope Study (EGSYS).[16] In all of these risk scores, there is a consensus to admit patients with abnormal ECG, hypotension, heart failure, and anemia. In our standardized SELF pathway,[11] we use the **SELF-2** criteria to evaluate the need for admission. These criteria include

S—***S***tructural heart disease
E—abnormal ***E*CG**
L—atrial f***L***utter
F—atrial ***F***ibrillation

Admitted patients should be monitored for a minimum of 24 hours, which could potentially reveal bradyarrhythmias or tachyarrhythmias. The management of bradyarrhythmias may include an electrophysiologic testing with or without subsequent pacemaker implantation. Tachyarrhythmias include ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, and atrial flutter. The treatment for these patients may include radiofrequency ablation or a device therapy with a pacemaker or an implantable cardioverter defibrillator (ICD). We recommend that all patients with a diagnosis of cardiac syncope be evaluated by an electrophysiologist during their hospitalization.

MANAGEMENT OF CARDIAC SYNCOPE

The major goal of the evaluation of syncope in patients with heart disease is to identify a potentially life-threatening diagnosis, particularly arrhythmias. Workup and management of these patients can include medical therapy, stress testing with cardiac imaging, cardiac catheterization, and possible revascularization with a percutaneous coronary intervention or cardiac surgery.

DIAGNOSTIC TOOLS THAT AID IN THE MANAGEMENT OF CARDIAC SYNCOPE

Electrocardiogram

Electrocardiography is essential in the workup of patients with unexplained syncope; however, it may only reveal a direct cause in 5% of patients. Abnormal

ECGs include the following findings: sinus bradycardia resulting from sinus node dysfunction or atrioventricular (AV) block resulting from AV node or His-Purkinje system dysfunction, pre-excitation patterns, a long/short QT-interval, Brugada syndrome, and characteristic ECG features of arrhythmogenic right ventricular dysplasia. Patients with unexplained bradycardia (heart rate of < 50 beats/min) should be evaluated for potential medical causes, specifically hypovolemia, hypoxia, acidosis, hypoglycemia, and hypothermia. Mild hyperkalemia when combined with a low *glomerular filtration rate* can also potentiate cardiac syncope in the elderly.[17] Hypothyroidism should also be considered in this age group.

Marked bradycardia can be the result of many medications such as β-blockers, calcium channel blockers, and digoxin, particularly in the presence of renal disease; this should be assessed and managed promptly. Lyme disease can be an unusual cause of heart block and needs to be considered in a patient from an endemic area. Finally, heart block can be a manifestation of myocardial infarction (MI), and patients with acute anterior wall MI and Mobitz type-II second-degree AV block, have a class IIa indication for a temporary transvenous pacing. This is in contrast to patients with inferior wall MI, where heart block can be a manifestation of the Bezold–Jarisch reflex (*this is a cardiovascular decompressor reflex involving a marked increase in vagal efferent discharge to the heart, elicited by stimulation of chemoreceptors, primarily in the left ventricle*). It causes a slowing of the heart beat and dilatation of the peripheral blood vessels with resultant lowering of the blood pressure. In patients with inferior wall MI, the heart block usually has a narrow escape rhythm and it usually resolves within a few days.

Echocardiography

Echocardiography should be performed in all patients with true syncope because it can identify patients with critical aortic stenosis, aortic dissection, severe pulmonary hypertension, acute pulmonary embolism, left atrial myxoma, and pericardial tamponade—situations that can lead to obstruction of flow in the heart and cause syncope.[18] These patients tend to be seriously ill and may require a lengthy intensive care stay. Echocardiography is considered the gold standard diagnostic tool for the finding of hypertrophic cardiomyopathy, segmental wall motion abnormalities suggestive of ischemic heart disease, and left ventricular systolic dysfunction.

Holter Monitoring

Holter monitoring enables correlation of symptoms with episodes of bradycardia; diagnostic clues are obtained in 50% to 70% of patients with bradycardia suspected on clinical grounds. However, events can be missed if symptoms do not occur in the 24- to 48-hour monitoring period. Holter monitoring can reveal sinus pauses, sinus arrest, second- or third-degree AV block, or severe sinus bradycardia with symptoms. Nocturnal asymptomatic bradycardia and pauses are not uncommon in the normal heart and are probably nondiagnostic. First-degree AV block or Mobitz type I AV block may be noted while patients are asleep owing to a high vagal tone. A long-monitored strip should be obtained because a 2:1 AV block is unlikely to persist. The other forms of AV block (Mobitz I or II) should then become apparent. Monitoring while the patient performs some form of exertion (eg, arm exercise, standing, and walking) may also help demonstrate the level of block. A block at the level of the AV node should improve with the adrenergic stimulation, but a block below the AV node in the His-Purkinje system may worsen as AV nodal conduction improves and increases the frequency of inputs to the His-Purkinje system.

Cardiac Event Monitoring

Cardiac event monitors, particularly those with auto-triggering capability, are widely used in the diagnosis of symptomatic and asymptomatic bradycardia and can be worn for up to 30 days. These devices can detect sinus pauses, sinus arrest, second- or third-degree AV block, or severe sinus bradycardia with symptoms[19]; however, their diagnostic yield for syncope and presyncope is only 6% to 25%.[20, 21]

Exercise Testing

A subnormal increase in heart rate after exercise (*chronotropic incompetence*) can be useful in diagnosing sick sinus syndrome. However, sensitivity and specificity are unclear and the results obtained may not be reproducible.[22] Exercise-induced AV block, even if asymptomatic, can be significant and suggests disease of the His-Purkinje system. Identifying symptoms due to sinus bradycardia can be difficult; nonetheless, exercise testing can be useful to help determine sinus node dysfunction as the cause of symptoms.

Electrophysiologic Testing

Electrophysiology testing is recommended when symptoms cannot be correlated clearly with a syncopal event and when significant bradyarrhythmias are suspected but cannot be diagnosed by noninvasive modalities. Sinus node dysfunction (*diagnosed as sinus node recovery time more than 1600 to 2000 milliseconds and/or corrected sinus node recovery time over 525 milliseconds*) serve only as an adjunct to clinical and noninvasive parameters because these tests are based on assumptions that limit their validity and clinical utility. There is little utility for electrophysiology testing in already-documented second- and third-degree AV block. Testing can be useful in patients with AV block and no clear symptom association; in patients with symptoms of bradycardia in whom AV block is suspected but not documented; and when the site of AV block cannot be determined reliably by surface tracings. His-ventricle interval of over *100 milliseconds* in a patient with bradycardia, even in the absence of symptoms, is a high-risk finding. Asymptomatic patients with Mobitz II AV block may benefit from this test to localize the site of block and to guide therapy. Overall, the role of electrophysiologic testing for bradycardia is limited, owing to low sensitivity and specificity. Positive findings may not be the reason for patient symptoms.[23]

MANAGEMENT OF PATIENTS WITH UNEXPLAINED SYNCOPE BUT WITH NO EVIDENCE OF CARDIAC ETIOLOGY

In the absence of underlying heart disease, syncope is not associated with excess mortality. Our recommendation for these patients is for early discharge, with consideration of head-up tilt-table testing and prolonged ECG monitoring (including Holter monitoring, trans-telephonic monitoring, and implantable loop recording).

OUTPATIENT DIAGNOSTIC TOOLS

Tilt-Table Testing

Tilt-table testing is used to evaluate the adequacy of the autonomic system, especially when there is suspicion of neurocardiogenic syncope.[24] The test can be performed either using head-upright tilting, which causes dependent venous pooling and thereby provokes the autonomic response, or by using adenosine to

facilitate the induction of vasovagal syncope. However, this test is limited by its poor sensitivity and the lack of uniformity.

Implantable Loop Monitor

Implantable loop recorders (ILRs) are subcutaneous monitoring devices that are typically implanted in the left parasternal or pectoral region and used for the detection of cardiac arrhythmias (**Figure 26.2**). The monitor has a loop memory and a battery life of 3 to 4 years. The current versions store an ECG that includes tracings recorded up to 40 minutes before and 2 minutes after activation by the patient and up to 7 hours of abnormal rhythm. If the patient activates the device when his consciousness returns, the probability of demonstrating a correlation between the ECG signals and the syncope is high. Krahn et al.[25] were among the first to describe a high diagnostic yield of the ILR in 16 patients with recurrent syncope. Extensive investigations including electrophysiology studies, treadmill testing, 48-hour ambulatory monitoring, and tilt-table testing failed to obtain a definite diagnosis in these patients. In 94% of the cases, recurrent syncope had occurred after implantation of the device revealing an arrhythmogenic cause in 60%. Consequently, in 40% of these patients, no arrhythmias were detected. In all patients with an arrhythmogenic cause, successful therapy was implemented. The Place of Reveal in the Care Pathway and Treatment of Patients with Unexplained Recurrent Syncope (*PICTURE*) registry,[26] a prospective, multicenter, observational study that followed up 570 patients with recurrent unexplained presyncope or syncope who received an ILR, showed that these patients were evaluated on average by three different specialists and underwent a median of 13 nondiagnostic tests (ranges between 9 and 20). Within the first year, syncope recurred in a third of the patients; the ILR provided a diagnosis in 78% of the patients, most commonly a cardiac etiology. In addition, the remote capability of these loops has revolutionized management for patients with syncope, as the patient is monitored continuously 24 hours a day, 7 days a week, and any abnormality is automatically transmitted through the Internet to the caring physician who then can take an action for management (**Figure 26.3**).

FIGURE 26.2 Example of commercially available implantable loop recorder; Reveal (Medtronic), Biomonitor II (Biotronik).

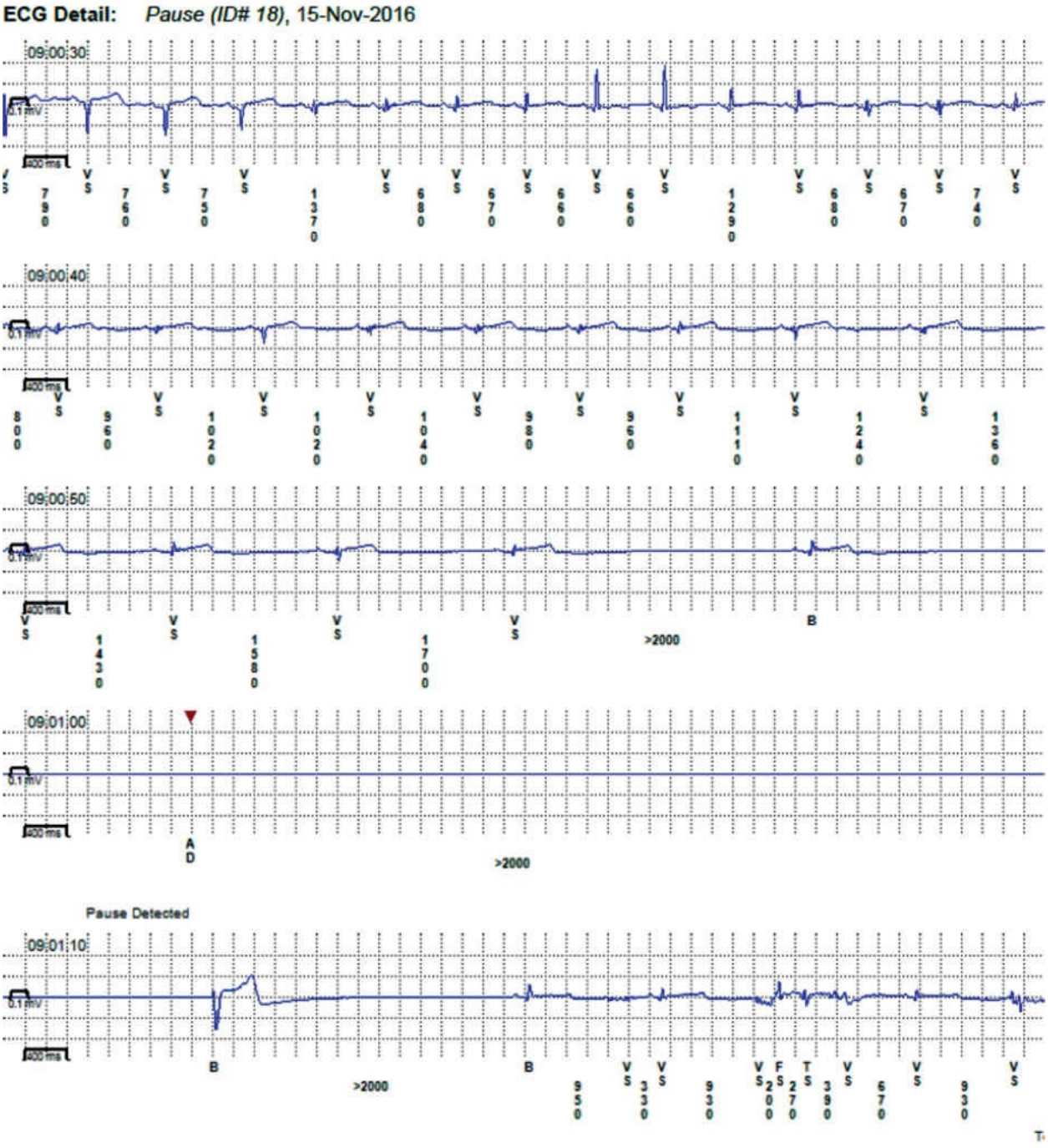

FIGURE 26.3 A long pause in a young patient who was mistakenly diagnosed with seizure for a long time. A long sinus pause of 12 seconds is seen and was transmitted by the implanted loop recorder.

Figure 26.3 demonstrates a long pause in a young patient who was mistakenly diagnosed as having seizure for a long time. A long sinus pause of 12 seconds is seen and was transmitted by the ILR.

Clinical validation of the SELF pathway from a database of 3100 patients who

were followed up longitudinally at our institution showed that this novel pathway is comprehensive, yet simple and provides effective risk stratification for patients presenting to the hospital with unexplained syncope and even with patients who could be missed by the standard risk stratification scores.[27] Also, implementing this pathway predicts the short- and long-term outcomes for those patients.[28]

CONCLUSION

In summary, having a standardized protocol for the management of patients with unexplained syncope should begin with a thorough medical history and a detailed physical examination including basic laboratory testing. High-risk patients (meeting SELF-2 criteria) should be admitted for at least 24-hour monitoring and echocardiography evaluation. Low-risk patients do not require hospital admission and they can be evaluated as outpatients with tilt-table testing or with a prolonged monitoring including ILR.

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Patient and Family Information for: THE APPROACH TO THE PATIENT WITH SYNCOPE

Syncope (sin-co-pee) is a medical term used to describe a temporary loss of consciousness that is caused by a sudden lack of blood flow to the brain. Syncope is commonly called fainting or “passing out.” If an individual is about to faint, he or she will feel dizzy, lightheaded, or nauseated and his field of vision may “white out” or “black out.” The skin may be cold and clammy. After fainting, an individual may be unconscious for a short time, but will eventually return to his baseline. Syncope can occur in otherwise healthy people and affects all age groups, but it is more common among the elderly. It can occur in many situations, such as standing up fast, working or playing hard especially in hot weather, breathing too fast (called hyperventilating), being upset, during long standing, during coughing, urinating, or all other situations that get in the way of the flow of oxygen to the brain.

There are several types of syncope. Vasovagal syncope usually has an easily identifiable triggering event such as emotional stress, trauma, pain, the sight of blood, or prolonged standing. Carotid sinus syncope is a medical term used for a situation in which there is pressure on the carotid artery in the neck and this may occur after turning the head, while shaving, or even when wearing a tight collar. Situational syncope is the term used when syncope occurs with urination, defecation, coughing, or as a result of gastrointestinal stimulation. Syncope is not usually a primary sign of a neurologic disorder, but it may indicate an increased risk for some neurologic disorders such as Parkinson disease, diabetic neuropathy, and other types of neuropathy. Certain medicines can cause fainting, including diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, nitrates, antipsychotic medications, antihistamines, levodopa, and

narcotics. Alcohol, cocaine, and marijuana can also cause fainting.

INITIAL EVALUATION OF A PATIENT WITH SYNCOPE

A doctor would like to know what exactly happened when the person fainted and all the details about how he or she felt. Symptoms vary from patient to patient; however, the most common symptoms are light headedness, dizziness, and nausea. Some people will feel very hot and clammy, sweaty, and will complain of visual and hearing disturbances. Information about current medications and preexisting medical conditions such as diabetes, heart disease, or psychiatric illness can help pinpoint the cause of syncope. There are certain tests and procedures that might be ordered to help guide management. These tests might lead the physician to a definitive diagnosis and would guide treatment.

PHYSICAL EXAMINATION AND LABORATORY TESTING

The doctor will compare the heart rate and blood pressure while the patient is lying down with the heart rate and blood pressure in a standing position. The doctor will listen to the heart beats for abnormal sounds that can be present in conditions such as narrowing of the aortic valve. The doctor will listen for *bruit* in the sides of the neck to rule out narrowing of the neck arteries (called carotid arteries). The doctor may firmly massage the carotid artery while the heart rate is closely monitored with an ECG. The heart's response to this maneuver can give clues to the cause of the syncope.

Laboratory tests may identify low red blood cell count (*anemia)* or other abnormalities including thyroid abnormalities and electrolyte imbalances (sodium, potassium, glucose, and magnesium).

ADDITIONAL DIAGNOSTIC TESTS

ELECTROCARDIOGRAM

An ECG will be performed on arrival. Sticky pads will be placed on the chest, arms, and legs, and will be connected to a recording device with long, thin cables. This is not a painful procedure and there is no risk involved. The ECG

provides a picture of the electrical activity throughout the heart muscle. A normal ECG does not necessarily mean that syncope is not caused by a heart rhythm problem. Heart rhythm problems are often brief, intermittent, and may not be present at the moment when the ECG is performed.

TILT-TABLE TESTING

Tilt-table testing is a noninvasive test performed to diagnose recurrent or unexplained light headedness or fainting spells. The test can define whether a patient has a condition called vasovagal syncope, in which there is malfunction of nerves that causes the heart to slow down and the blood pressure to drop with a change in position. The test takes about an hour to complete, and in preparation for it the patient would be asked not to eat or drink for 5 hours before the test including holding the medications. The patient will be asked to lie down on a special flat table. A nurse will insert an intravenous line in a vein in the arm. ECG electrodes will be attached to the chest to monitor the heart rate and the rhythm during the procedure. A blood pressure cuff will be placed on the arm. Safety straps will secure the patient to the table. After obtaining the blood pressure and ECG while lying on the table, the table will be tilted to a 60-degree angle. The patient will be standing on a footboard at the bottom of the table. The blood pressure and ECG will be monitored as the patient remains tilted up for 20 to 30 minutes. The patient will be instructed to tell the nurse if any symptoms, such as feeling sweaty, nauseous, lightheaded, or cold and clammy, are experienced. If the blood pressure starts to fall, the patient will be returned to the flat position. A doctor will be in the room during the entire procedure. If no symptoms are experienced, the table will be lowered to the flat position and the test will be terminated. On occasion, a short-acting medication may be given intravenously to assist in the test. The patient may need to rest for several minutes after the test before going home. A nurse will stay with the patient until the conditions for discharge are met.

ELECTROPHYSIOLOGY STUDY

An electrophysiology study is an invasive procedure performed in the hospital setting. Sedative medications are given before the procedure, but the patient may stay awake during the procedure. The physician uses a local anesthetic to numb a small area over the blood vessels (veins), usually in the groin, and then threads small catheters (thin electrical wires) through the blood vessels into the heart

using X-ray (fluoroscopic) guidance. Once in the heart, precise measurements of the heart's electrical function can be obtained. This procedure typically lasts 60 to 90 minutes.

IMPLANTABLE LOOP RECORDER

With ILR, the heart rate and rhythm can be monitored for a long time. The device has a memory and a battery that can last between 3 and 4 years. The ILR is implanted under the skin, usually in the upper left chest area. It stores events automatically according to programmed criteria, or it can be activated by the patient. The ILR may be useful if symptoms are sporadic and an arrhythmia is suspected, and other forms of testing were negative or inconclusive.

THERAPIES

PERMANENT PACEMAKER

A pacemaker is a small device, the size of a silver dollar, which is implanted under the skin just below the collarbone. The device is connected to wires threaded into the heart muscle, where they emit impulses that help regulate the heartbeat. Pacemakers are occasionally recommended if the syncope is caused by a very slow heartbeat, carotid sinus hypersensitivity, or by heart block. A pacemaker battery typically lasts 8 to 12 years and would require replacement after that time period with a simple procedure.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR

Certain dangerous conditions arise when irregular heartbeats originate from the lower chamber of the heart (ventricles), particularly in patients with a very weak heart. These patients may benefit from an ICD. Similar to a pacemaker, the ICD is typically implanted under the skin just below the collarbone. The device is connected to wires threaded into the heart muscle. However, in addition to its pacemaker capability, the ICD has the ability to detect fatal arrhythmias and deliver a high-energy electrical shock to the heart, which in turn will terminate the arrhythmia and return the heart to normal rhythm.

27

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Nektarios Souvaliotis

Basic Approach to Pacemaker and ICD Interrogation

INTRODUCTION

Cardiovascular implantable electronic device (CIED) is a term that encompasses pacemakers (PPM) for bradyarrhythmia treatment, implantable cardioverter defibrillators (ICD) for tachyarrhythmia management, and cardiac resynchronization therapy (CRT) devices for systolic dysfunction with conduction delays.[1] Cardiac arrhythmias have an estimated prevalence of 14.4 million patients in the United States, and they account for approximately 40,700 deaths annually.[2] As the indications for device placement continue to expand, these devices have evolved from a treatment of last resort to a first-line therapy to an increasing number of patients.[3] Approximately 1.6 million patients in the United States and Europe receive a PPM or ICD each year. Therefore, it is imperative that all physicians understand the operational basics of these devices and be able to retrieve and manage essential data when needed particularly in the critical care hospital setting.

A summary of the most updated pacing and defibrillator indications are seen in **Figures 27.1 and 27.2**.

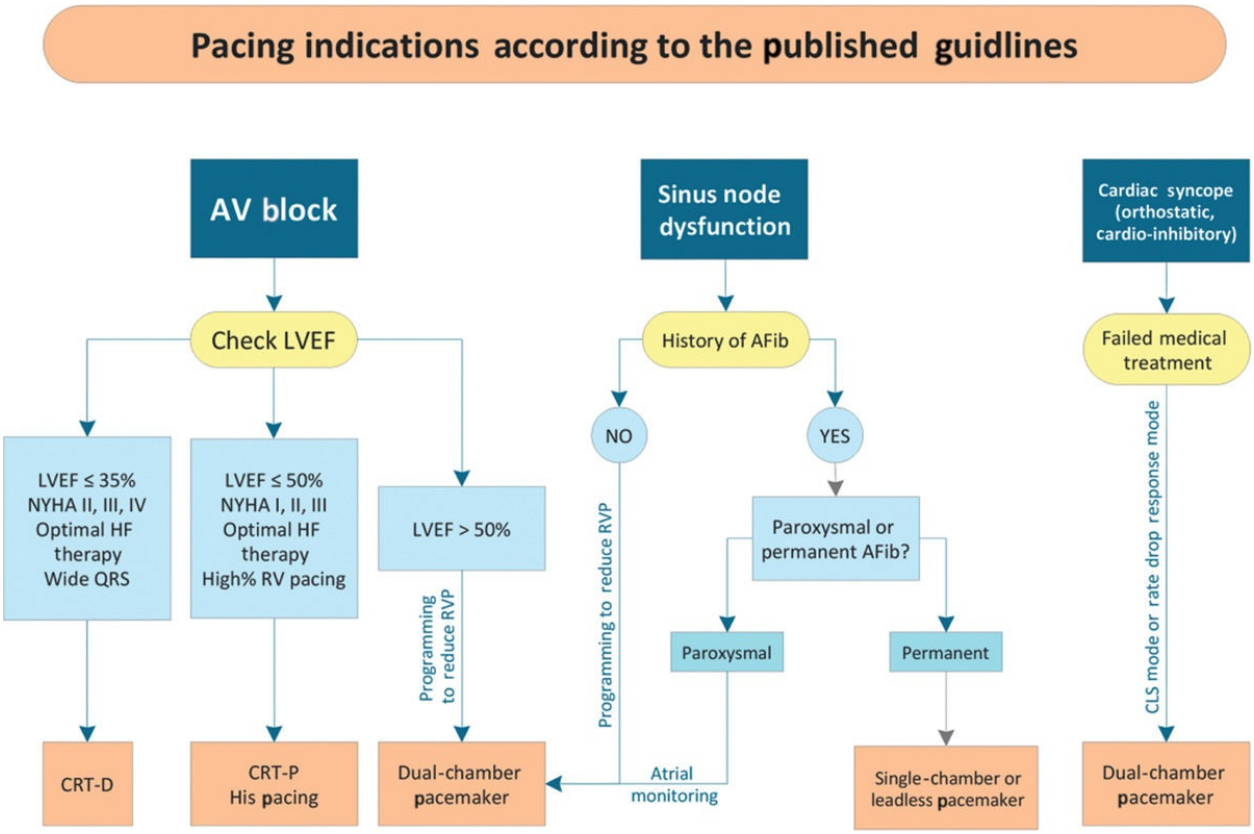


FIGURE 27.1 Class I pacing indications according to the published guidelines. AFib: atrial fibrillation; CLS: closed-loop system; HF: heart failure; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association Class; RVP: right ventricular pacing.

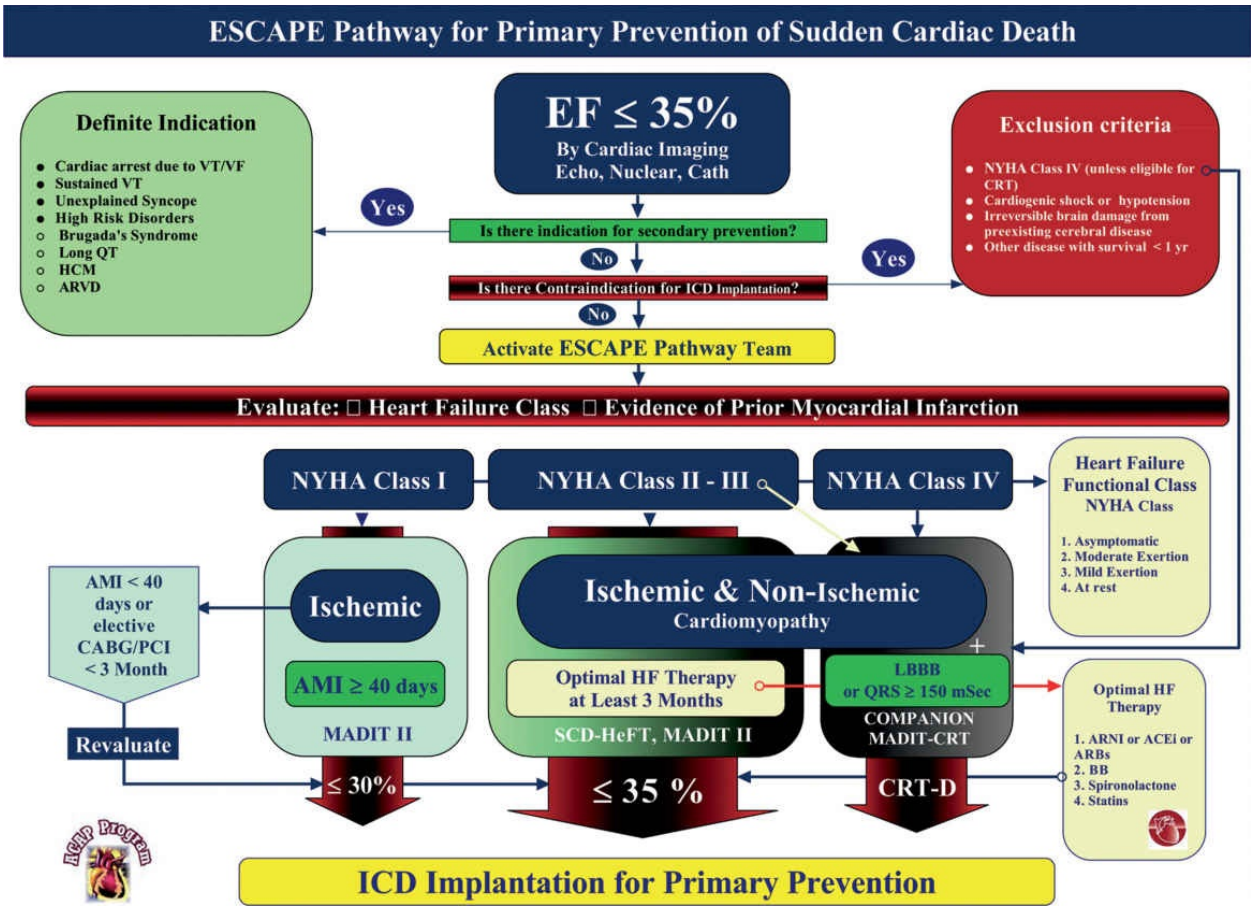


FIGURE 27.2 The ESCAPE pathway for prevention of sudden cardiac death.

EVALUATION OF CIED ON ADMISSION AND REASON FOR CONSULTATION

When called for a device evaluation consultation, it is imperative to identify the reason for the consult. This may include the evaluation for device functionality such as appropriate pacing and sensing, particularly if there is any question of device malfunction, or to identify arrhythmias like atrial fibrillation or ventricular tachycardia, or to rule out device-delivered therapy like antitachycardia therapy or firing. Device interrogation could also be appropriate after surgery, especially if device parameters were changed or cautery was used close to the device site.

IDENTIFICATION OF THE DEVICE MAKER

The first step is to identify the manufacturer of the device and the type of the device in order to utilize the proper programmer for the interrogation. Most patients carry a device identification card with them (**Figure 27.3**). If the card is not available, searching the patients' electronic medical records or manufacturers' patient registries can be of help. **Table 27.1** has the phone numbers for major device companies.

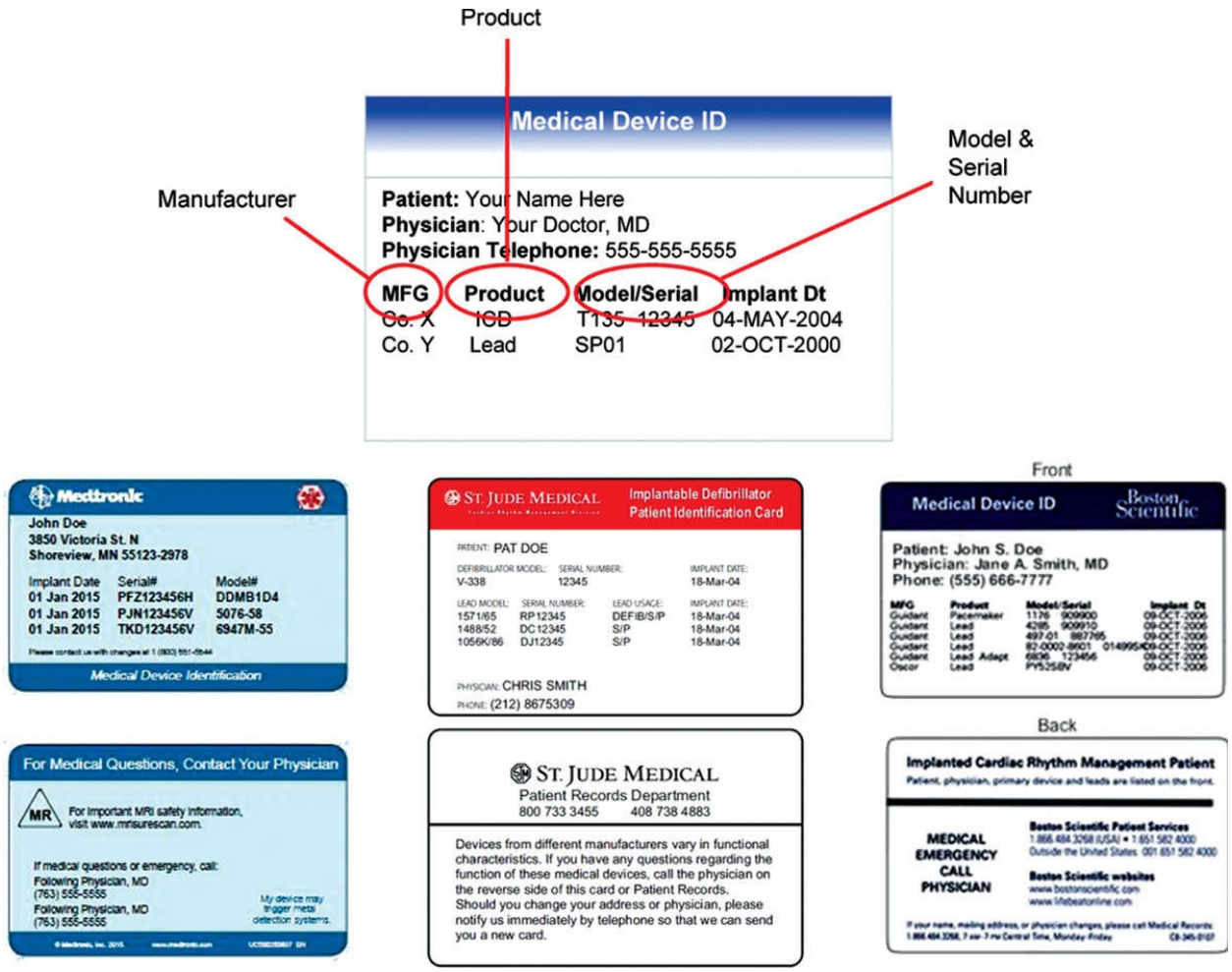


FIGURE 27.3 Patient identification cards examples from different manufacturers.

TABLE 27.1 Contact Number for Major Device Companies

Company	Contact Number
Biotronik	(800) 547-0394
Boston Scientific (Cameron, CPI, Guidant)	(800) CARDIAC
Medtronic (Vitatron)	(800) MEDTRONic
Sorin (ELA)	(877) 663-7674
St. Jude Medical (Pacesetter, Telectronics, Ventritex)	(800) SHOCKVF

In those instances where none of the above are available, or if the patient is

incoherent or intubated, one can identify the device from the CaRDIA-X algorithm (**Figure 27.4**) published by Jacob et al.[4] or the CRMD Finder app (**Figure 27.5**), which is based on the same source. This guide is unique as it utilizes a stepwise algorithm including device-specific radiopaque alphanumeric codes (ANC), device type (ICD, pacemaker, or ILR), the shape of the device, and the battery as well as the device leads. Currently in the United States, five major device manufacturers can be identified: Medtronic, St. Jude Medical, Boston Scientific, Biotronik, and Sorin.

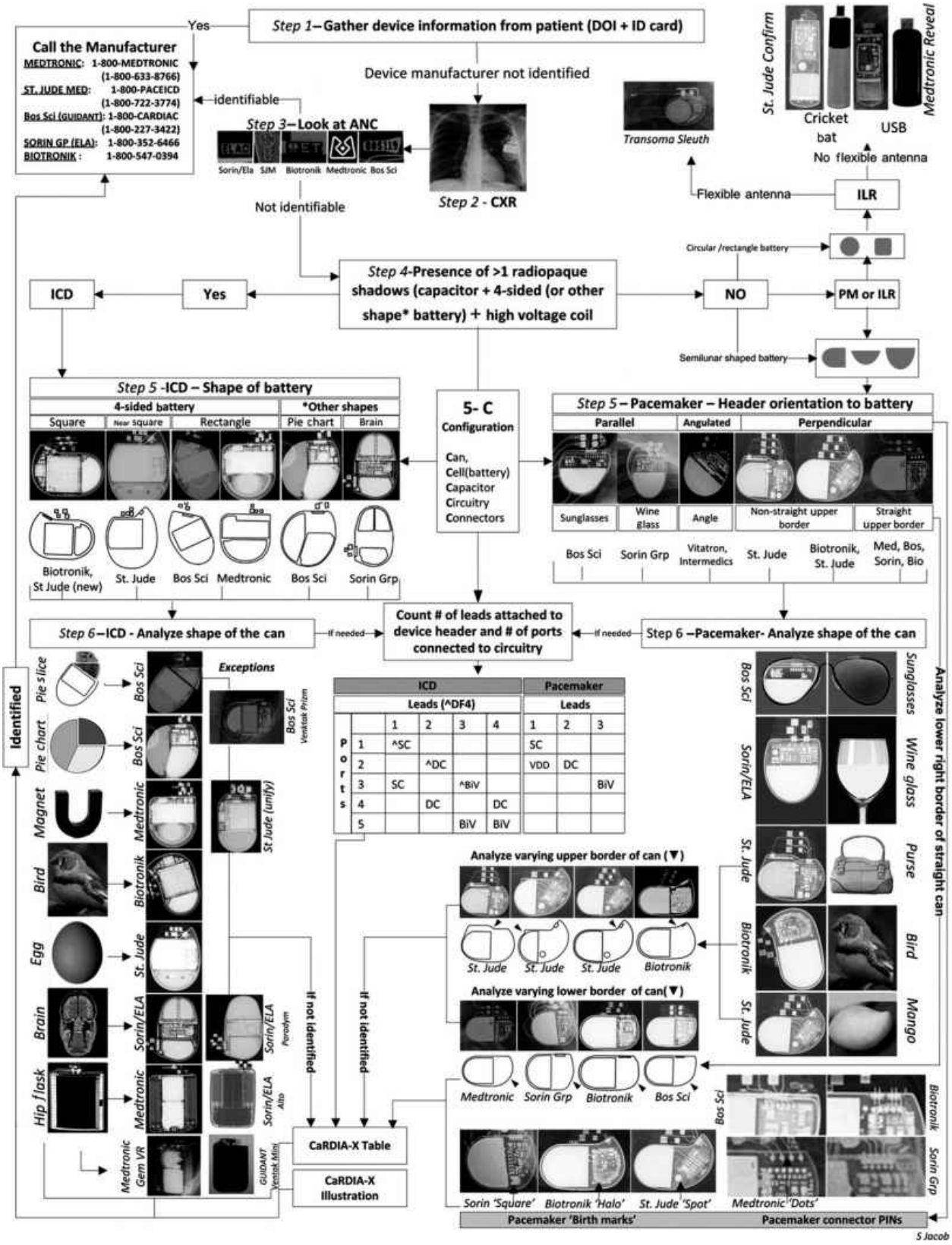

Step 1– Gather device information from patient (DOI + ID card)
Yes
Call the Manufacturer
MEDTRONIC: 1-800-MEDTRONIC (1-800-633-8766)
ST. JUDE MED: 1-800-PACEICD (1-800-722-3774)
Bos Sci (GUIDANT): 1-800-CARDIAC (1-800-227-3422)
SORIN GP (ELA): 1-800-352-6466
BIOTRONIK: 1-800-547-0394
Device manufacturer not identified
identifiable
Step 3– Look at ANC
Sorin/Ela SJM Biotronik Medtronic Bos Sci
Not identifiable
Step 2 - CXR
Transoma Sleuth
St. Jude Confirm
Medtronic Reveal
Cricket bat
USB
No flexible antenna
Flexible antenna
ILR
Circular /rectangle battery
Step 4-Presence of >1 radiopaque shadows (capacitor + 4-sided (or other shape* battery) + high voltage coil
ICD
Yes
NO
PM or ILR
Semilunar shaped battery
Step 5 -ICD – Shape of battery
4-sided battery
*Other shapes
Square
Near square
Rectangle
Pie chart
Brain
Biotronik, St Jude (new)
St. Jude
Bos Sci
Medtronic
Bos Sci
Sorin Grp
5- C Configuration
Can,
Cell(battery)
Capacitor
Circuitry
Connectors
Step 5 – Pacemaker – Header orientation to battery
Parallel
Angulated
Perpendicular
Sunglasses
Wine glass
Angle
Non-straight upper border
Straight upper border
Bos Sci
Sorin Grp
Vitatron, Intermedics
St. Jude
Biotronik, St. Jude
Med, Bos, Sorin, Bio
Step 6 –ICD - Analyze shape of the can
If needed
Count # of leads attached to device header and # of ports connected to circuitry
If needed
Step 6 –Pacemaker- Analyze shape of the can
Identified
Pie slice
Bos Sci
Pie chart
Bos Sci
Magnet
Medtronic
Bird
Biotronik
Egg
St. Jude
Brain
Sorin/ELA
Hip flask
Medtronic
Medtronic Gem VR
Exceptions
Bos Sci Ventak Prizm
St Jude (unify)
Sorin/ELA Parodym
Sorin/ELA Alto
GUIDANT Ventak Mini
If not identified
If not identified
ICD
Pacemaker
Leads (^DF4)
Leads
Ports
1 ^SC
2 ^DC
3 SC ^BiV
4 DC DC
5 BiV BiV
1 SC
2 VDD DC
3 BiV
Analyze varying upper border of can (▼)
St. Jude
St. Jude
St. Jude
Biotronik
Analyze varying lower border of can(▼)
Medtronic
Sorin Grp
Biotronik
Bos Sci
Sorin 'Square'
Biotronik 'Halo'
St. Jude 'Spot'
Medtronic 'Dots'
Pacemaker 'Birth marks'
Pacemaker connector PINs
Analyze lower right border of straight can
Bos Sci
Sunglasses
Sorin/ELA
Wine glass
St. Jude
Purse
Biotronik
Bird
St. Jude
Mango
Bos Sci
Biotronik
Sorin Grp
CaRDIA-X Table
CaRDIA-X Illustration
S Jacob

FIGURE 27.4 CaRDIA-X algorithm. (From Jacob S, Shahzad MA, Maheshwari R, et al. Cardiac rhythm device identification algorithm using X-Rays: CaRDIA-X. Heart Rhythm. 2011;8(6):915-922.)

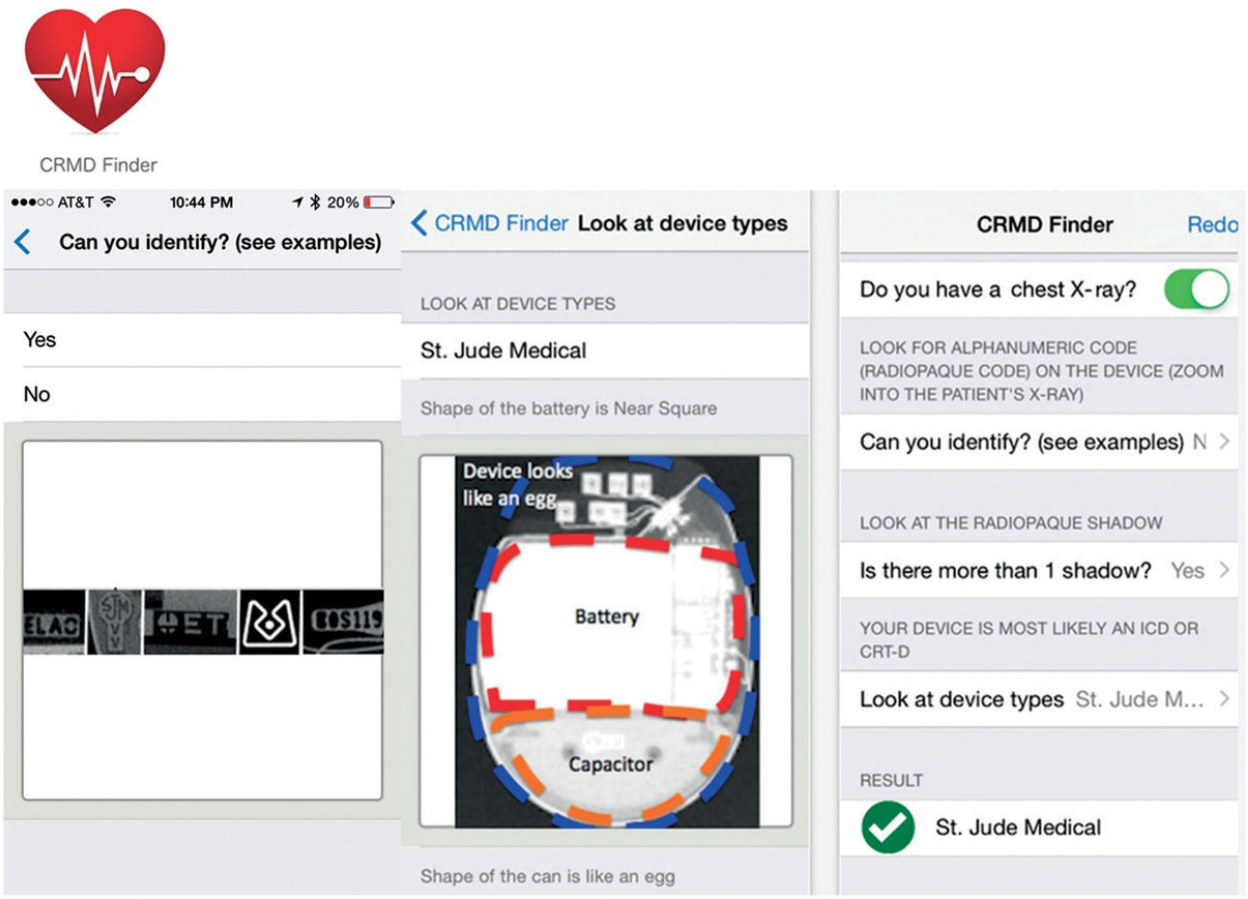


FIGURE 27.5 CRMD Finder app.

Once the device maker is identified, one should examine the x-ray for the following:

1. Identify device type: ILR, pacemaker, or ICD
2. If ILR, identify either Medtronic Linq, Transoma, or Biotronik (BioMonitor–II)
3. Identify if the device is a single, dual-chamber, or biventricular one
4. Epicardial leads or arrays
5. Recognize any further potential malfunctions like lead fractures, conductor externalization (Riata leads), dislodgment, twiddler syndrome, or any abandoned leads

After identifying the device manufacturer, the next step is to use the appropriate programmer and link it to the device by placing the wand at the device site. **Figure 27.6** illustrates the programmers of the five major device companies in the United States.

FIGURE 27.6 The programmers of the 5 major device manufacturers: Medtronic, St. Jude Medical, Boston Scientific, Biotronik, and Sorin.

ANALYZING THE PATIENTS' RHYTHM

1. Obtain presenting rhythm strip:
   - **a.** After the summary screen has been displayed, press the "25 mm" button on the programmer to print a presenting rhythm strip.
   - **b.** Press the "0 mm" button to stop printing.

c. This step will identify if the patient is (atrial, ventricular, or biventricular) paced.

2. Obtain underlying rhythm strip:

a. In this step, one must go to the Temporary Pacing Parameters screen. The Temporary Parameters screen allows you to change any and all pacing parameters in a temporary setting—without affecting any permanent settings.

b. Suggested Settings to view intrinsic rhythm: Mode: DDI; Rate: 30 bpm (if tolerated by patient); AV Delay: 300 ms (400 ms, if allowed); "DDI will allow backup ventricular pacing if needed, and allow you to see heart block by separating Atrial and Ventricular pacing function—and AV Delays greater than 300 ms. You must assess patient's ability to tolerate lower rate change prior to running test."

c. Run paper (press the 25-mm button) to document underlying rhythm. Press the "0 mm" button to stop printing.

INTERROGATION AND REPORTING

After placing the wand over the device, interrogation will either automatically begin or need to be initiated by pressing the interrogate button, depending on the programmer. At the end of the chapter, the appendix depicts examples from the initial page of each programmer with description of their most important functions.

BATTERY LIFE

Most device manufacturer will have a battery management screen that displays a battery "gauge," voltage graph, voltage, and/or estimated longevity (**Figure 27.7**). There are few abbreviations that one needs to be familiar with when evaluating a battery status; ***>ERI*** (elective replacement indicator), ***RRT*** (recommended replacement time), ***EOS*** (end of service), and ***EOL*** (end of life). The general rule of thumb is that ***ERI*** is about three months before reaching *EOL*.

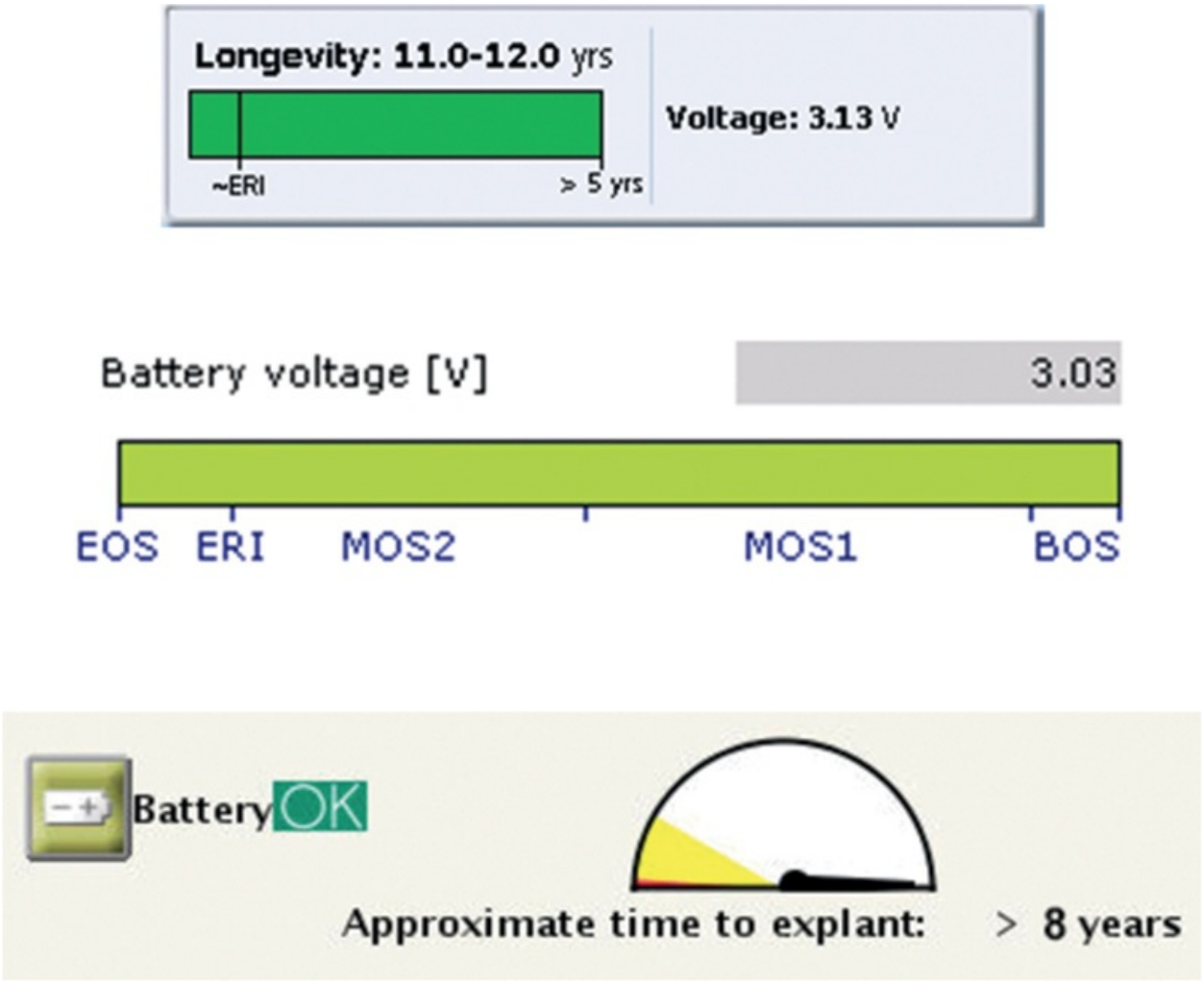


FIGURE 27.7 Examples of battery status, graphs, and gauges.

What to Do When ERI is Reached?

In Brady Devices (Pacemakers)

- Use all the available data, voltage, battery impedance, longevity predictors.
- Manufacturers can give accurate predictions with access to telemetry data.
- Look at follow-up intervals as ERI approaches; consider use of remote monitoring and consider changes at ERI (VVI).
- Have access to technical data; be aware of safety margins and errors in prediction.

In Tachy Devices (Defibrillators)

- Use remote monitoring to manage battery Middle of Life 2 (MOL2) → ERI period.
- Ensure patient is familiar with alarms/vibrations indicating ERI.
- Check advisories for changes in ERI point of some devices.
- Longer charge time usually indicates battery depletion; a charge time in excess of 20 seconds is abnormal.

SENSING TESTING

The ability of a pacemaker lead to sense an intrinsic electrical signal of the chamber that it is placed in is measured in millivolts (mV). The programmed sensitivity setting indicates the minimum intracardiac signal that will be sensed (seen) by the pacemaker to initiate the pacemaker response (inhibited or triggered). It is important to evaluate the trend of sensing of the chamber overtime rather than the actual sensed value of the (P) or (R) waves (**Figure 27.8**). There are certain conditions that can affect the sensing of a lead, such as dislodgment, chronic fibrosis at the lead tip, metabolic changes, and myocardial infarction.

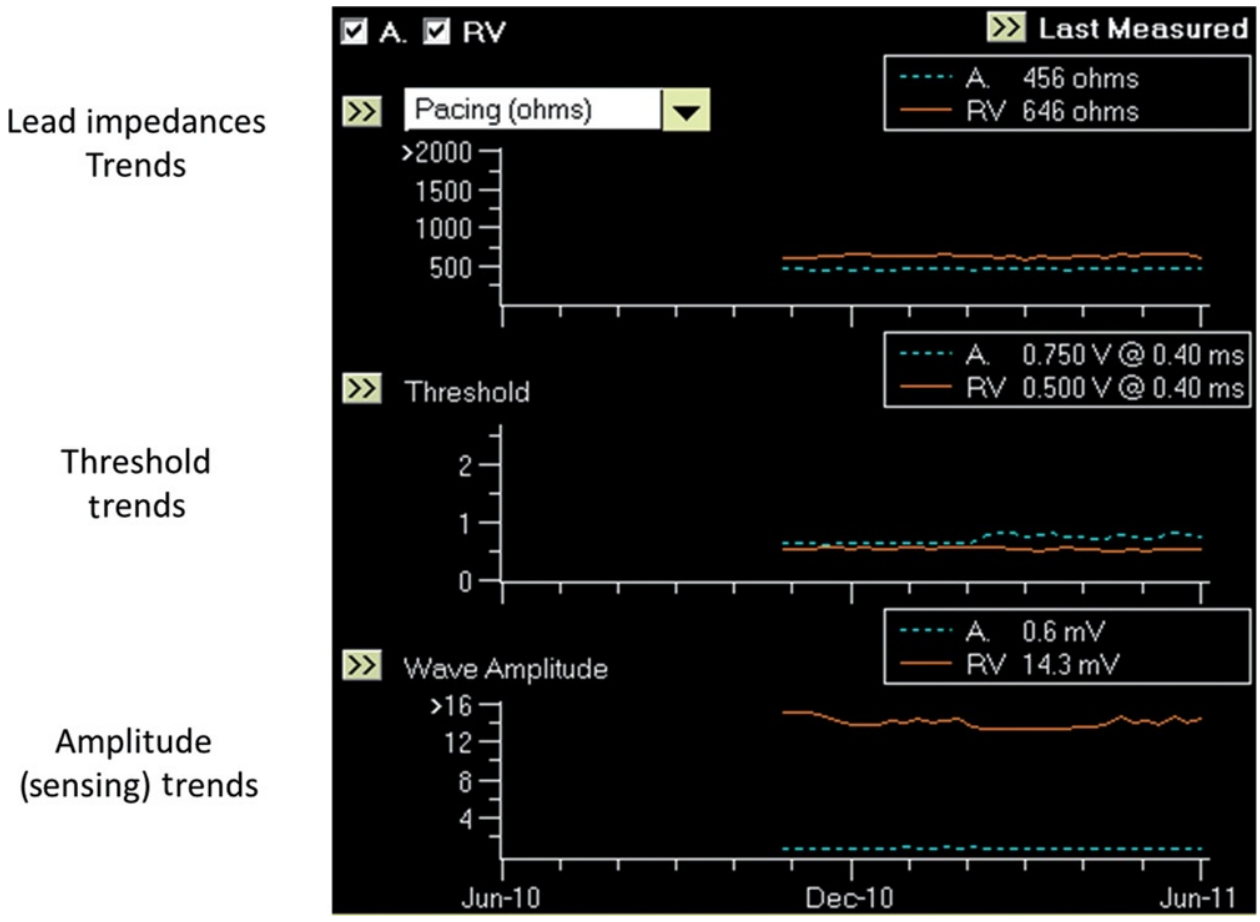


FIGURE 27.8 Example of a Medtronic device sensing, thresholds, and lead impedance trends.

We Recommend

- To evaluate the sensing of a chamber, adjust the Brady parameters if necessary to maintain proper device performance. (For pacemakers, the sensed P and R waves should be at least twice the sensitivity setting.)
- Suggested settings: Mode: DDI; Rate: 30 bpm; AV Delay: 300 ms (400 ms if allowed)

"DDI will allow backup ventricular pacing if needed, and allow you to see heart block by separating Atrial and Ventricular pacing function—and AV Delays greater than 300 ms. DDI is not available on some older pacemakers. Use DDD or VVI on these devices as appropriate."

It is very important to test the sensing of the device to avoid potential problems that could result from undersensing or oversensing.

- **Undersensing** occurs when the pacemaker fails to sense native cardiac

activity, which results in asynchronous pacing. This could be due to increased stimulation threshold at electrode site (exit block), poor lead contact, new bundle branch block, or programming problems.

- **Oversensing** occurs when electrical signal are inappropriately recognized as native cardiac activity and pacing is inhibited. These inappropriate signals may be large P or T waves, skeletal muscle activity, or lead contact problems.

LEAD IMPEDANCE TESTING

Lead impedance describes the sum of all resistance to current flow. It is a function of the characteristics of the conductor (wire), the electrode (tip), and the myocardium; thus, checking the lead impedances gives us information about the lead integrity. Normal lead impedance ranges from *300 to 1000* ohms (some leads have higher impedances by design). Similar to sensing amplitude, the steadiness of lead impedances overtime is more important than the number obtained (**Figure 27.8**). Lead impedance values can change as a result of lead fractures or insulation breakage.

- *Low-impedance* conditions, mainly insulation break exposing the lead wire to body fluids, which have low resistance, allows current to drain through the insulation break to the path of least resistance, leading to potential loss of capture and more rapid battery depletion.
- *High-impedance* conditions, mainly due to fractured conductor, are a result of not enough current flow from the device battery to the tissues. Other reason for high impedance is the lead not having properly seated in the pacemaker header.

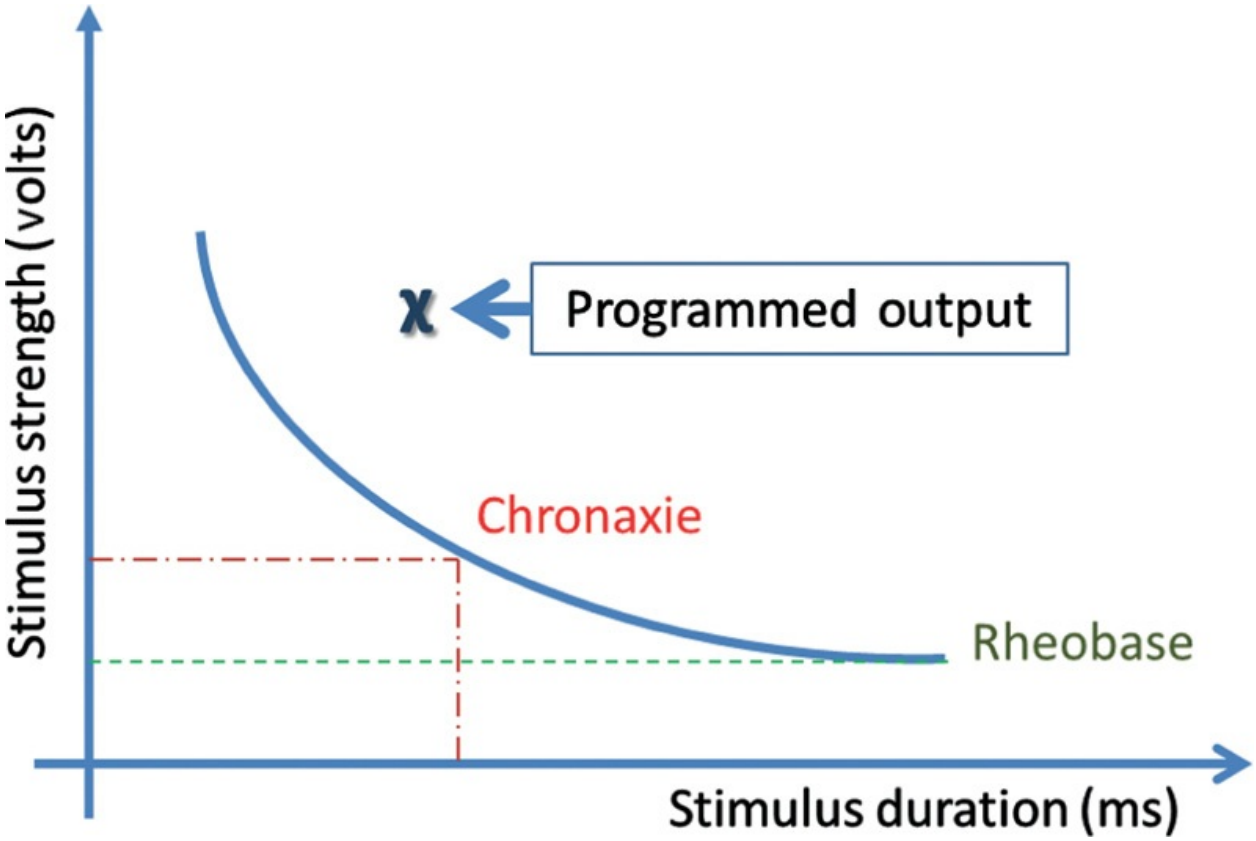
All devices perform automatic lead impedances in the course of the initial device interrogation. However, ICDs require you to test the pacing leads separately from the shocking lead impedance. Should you need to test impedance manually, look for the appropriate tabs on the Impedance screen to select which leads you are testing (ie, RA, RV, LV, and shocking lead impedance).

THRESHOLD (CAPTURE) TESTING

Capture threshold is the minimum electrical stimulus needed to consistently capture the myocardium. There are few factors that affect pacing thresholds. First, lead maturation as a result of the fibrotic capsule that develops around the tip of the lead can cause a slight rise in the threshold. Second, the newer leads

that are steroid eluted reduce the inflammatory process and allow the leads to maintain low chronic thresholds.

Myocardial capture is a function of amplitude, which is the strength of the impulse expressed in volts as it must be large enough to depolarize the heart and the pulse width, which is the duration of the current flow expressed in milliseconds. This is done using the strength–duration curve,[5] which illustrates the relationship of amplitude and pulse width as seen in **Figure 27.9**; any combination of pulse width and voltage on or above the curve will result in capture.



- The rheobase is the least voltage needed to depolarize the heart at infinite pulse duration.
- The chronaxie is the shortest pulse duration required to depolarize the heart at a voltage twice the rheobase.
- (X) is the programmed output equal 2x chronaxie.

FIGURE 27.9 The strength–duration curve.

By accurately determining capture thresholds, we can assure adequate safety

margins, keeping in mind that thresholds may differ in acute or chronic pacing systems and could slightly fluctuate on a daily basis.

The ultimate goal in performing capture threshold testing is to ensure patient safety and appropriate device performance as well as extend the service life of the battery if possible. A common output value is ≤2.5 V, but we should always maintain an adequate safety margin.

- To perform threshold testing, find the appropriate tab and adjust Brady parameters if necessary to maintain proper device performance.
  - Perform test using Voltage Testing criteria (fixed Pulse Width). Starting voltage should be approximately three-fourths of the programmed Amplitude setting.
  - Some older pacemakers will require Pulse Width testing (as the only option). Starting Pulse Width should be the current setting.
  - Thresholds are related to Amplitude and Pulse Width settings. When testing using Voltage, the programmed amplitude should be at least twice the measured threshold. When using Pulse Width, the programmed pulse width should be at least three times the measured threshold. The exception is when the auto capture is programmed ON.
- Useful tricks to performing Threshold testing:
  - **i.** Always test at a rate of at least 10 bpm above the patient's intrinsic rate —this helps to prevent fusion and makes loss of threshold seem as a pause related to a change in rate.
  - **ii.** When starting out, *always run paper during the entire test* (press the 25 button under the screen). This will make it easier for you to verify loss.
  - **iii.** Atrial Thresholds:
    1. The safest way to test Atrial Thresholds for any patient is in DDD mode. This will ensure ventricular support if the patient has any form of block—and for patients with intrinsic conduction, assist by adding another visual clue when Atrial capture is lost.
    2. If patient has intact intrinsic conduction, one can test it in two ways:
       - **a.** Atrial Thresholds in DDD mode will result in an Ap/Vs response at the paced atrial rate. Capture is verified by paced P waves and by QRS response. Loss of capture will result in a slight pause in rate (the difference between the intrinsic PR and the AV Delay), a loss of P wave capture, and will be immediately followed by a paced ventricular response (you will transition from a narrow upright QRS to a wide-paced QRS). *Suggested Settings: Mode:*

DDD, Rate: at least 10 bpm above intrinsic rate, AV Delay: max allowed (300 or 400 ms).

b. Atrial Thresholds in AAI mode will result in a ventricular response on the surface EGM at the paced atrial rate. Capture is verified by paced P waves and by QRS response. Loss of capture will result in a pause in rate as well as a loss in P wave capture. *Suggested Settings: Mode: AAI, Rate: at least 10 bpm above intrinsic rate.*

3. For patients with block, performing atrial thresholds in DDD mode is required to provide support for ventricular function. Here, capture is verified by loss of P waves only. Loss of capture will result in ventricular-only pacing. *Suggested Settings: Mode: DDD, Rate: 10 bpm max above intrinsic rate, AV Delay: 150 ms or greater. Increasing the AV Delay separates the P waves from the paced QRS, allowing the P waves to be seen easier. Keep the rate as low as possible when testing in this manner to allow the most space between paced QRSs.*

SPECIAL TESTING AND PARAMETERS FOR BRADYCARDIA THERAPY DEVICES

Pacemaker programming is very complex; however, for simplicity, medical personal should be at least familiar with the most common pacing modes. The North American Society of Pacing and Electrophysiology (NASPE) and British Pacing and Electrophysiology Group (BPEG) published as a joint effort the pacemaker code. This joint project is known as the *NBG pacemaker code*. The NBG was initially published in 1983 and was last revised in 2002.[6] It describes the five-letter code for operation of implantable pacemakers and defibrillators (**Figure 27.10**).

Generic Pacemaker Code (NBG): NASPE/BPEG

Position	I	II	III	IV	V
Function	Pacing chamber	Sensing chamber	Response(s) to sensing	Rate modulation	Multisite pacing
Specific Designations	O=none A=Atrium V=Ventricle D=Dual (A+V)	O=none A=Atrium V=Ventricle D=Dual (A+V)	O=none T=Triggered I=Inhibited D=Dual (T+I)	O=none R=Rate modulation	O=none A=Atrium V=Ventricle D=Dual (A+V)

- The first two positions of this code (Chamber Paced and Sensed) are relatively straightforward.
- The third position could be confusing. The most frequently used programs are the DDD (dual-chamber pacing and sensing both triggered and inhibited mode), VVI (for single-chamber, ventricular pacing in the inhibited mode), VDD (ventricular pacing with atrial tracking), and DDI (dual-chamber pacing and sensing, but inhibited mode only).
- The third position is described as follows:
  - D (Dual): In DDD pacemakers, atrial pacing is in the inhibited mode (the pacing device will emit an atrial pulse if the atrium does not contract). In DDD and VDD pacemakers, once an atrial event has occurred (whether paced or native) the device will ensure that an atrial event follows.
  - I (Inhibited): The device will pulse to the appropriate chamber unless it detects intrinsic electrical activity. In the DDI program, AV synchrony is provided only when the atrial chamber is paced. If on the other hand intrinsic atrial activity is present, then no AV synchrony is provided by the pacemaker.
  - T (Triggered): Triggered mode is only used when the device is being tested. The pacing device will emit a pulse only in response to a sensed event.
- The fourth position, rate modulation, increases the patient's heart rate in response to "patient exercise." A number of mechanisms (vibration, respiration, and pressure) are used to detect "patient exercise." As the exercise wanes, the sensor indicated rate returns to the programmed mode.
- The fifth position describes multisite pacing functionality. Atrial multisite pacing is being investigated as way to prevent atrial fibrillation. Ventricular multisite pacing is a treatment for pacing a patient with dilated cardiomyopathy.

FIGURE 27.10 The North American Society of Pacing and Electrophysiology (NASPE) and British Pacing and Electrophysiology Group (BPEG) published as a joint effort the pacemaker code. This joint project is known as the NBG pacemaker code. The NBG was initially published in 1983 and was last revised in 2002. It describes the five-letter code for operation of implantable pacemakers and defibrillators.

Main Pacing Modes

- The ***AAI or AAIR*** is an atrial demand pacing (atrium paced, atrium sensed, and pacemaker inhibited in response to sensed atrial beat) and is appropriate for patients with sinus node dysfunction who have intact AV nodal function. Patients with symptomatic sinus bradycardia or sinus pauses, but with an intact ability to accelerate their heart rate with exertion, can be programmed in an AAI mode. Those who cannot adequately accelerate their heart rate should have rate-responsive capability available.
- The *VOO* pacemaker is asynchronous ventricular pacemaker; there are no adaptive rate control or antitachyarrhythmia functions.
- The ***VVI or VVIR*** pacemaker is a ventricular "demand" pacemaker with electrogram-waveform telemetry; there are no adaptive rate control or

antitachyarrhythmia functions. Those who cannot adequately accelerate their heart rate should have rate-responsive capability available. The new leadless pacemaker (***Micra***) is VVI pacemakers.

- The ***VDD*** pacemaker is used for AV nodal dysfunction with intact and appropriate sinus node behavior.
- The **DDD *or DDDR*** pacemaker is a multiprogrammable "physiologic" dual-chamber pacemaker; there are no adaptive rate control or antitachyarrhythmia functions. Those who cannot adequately accelerate their heart rate should have rate-responsive capability available.
- The ***DDI*** pacer is used for a patient with a dual-chamber pacemaker that has episodes of paroxysmal atrial fibrillation. DDI prevents high ventricular rates. Some DDD pacemakers are programmed to enter the DDI mode when high atrial rates occur.

One of the most important aspects of checking the pacemaker function is to evaluate for percentage of pacing. BLOCK-HF trial[7] showed that the increased RV pacing can lead to RV-pacing-induced cardiomyopathy. Likewise, in patients with biventricular pacemakers, less than 90% pacing is considered inadequate. Investigations should be done to find the cause of less biventricular pacing (eg, higher LV thresholds than the programmed parameter, high frequency of PVCs, atrial fibrillation with rapid ventricular rates) and to correct it.

Important Programmable Features

Mode switching: This is the algorithm that identifies the presence of atrial tachyarrhythmias and switch the device to a nontracking mode (VVI, DVI, or DDI), allowing the pacing rate to be driven by the programmed lower-rate limit or sensor-indicated rate.

Minimizing ventricular pacing: *Managed ventricular pacing (MVP)*[8] from Medtronic and its likeness *ventricular pace suppression* (VPS) from Biotronik, *SafeR* pacing[9] from Sorin, *ventricular intrinsic preference* (VIP)[10] from St. Jude Medical, and *Rhythmiq* from Boston Scientific all have an atrial-based pacing mode that significantly reduces unnecessary right ventricular pacing by primarily operating in an AAI(R) pacing mode while providing the safety of a dual-chamber backup mode if necessary.

Rate-adaptive pacing: This refers to an increase in the pacing rate in response to a combination of sensors including association of an activity sensor giving a rapid response for short-duration exercise, a metabolic sensor, or minute ventilation sensor, to improve exercise capacity, particularly in patients with

chronotropic incompetence.

SPECIAL TESTING AND PARAMETERS FOR TACHYCARDIA THERAPY DEVICES

Appropriate ICD programming is crucial to deliver critical therapy to true arrhythmia (VT/VF) and to avoid unnecessary shock or inappropriate shocks. Multiple trials have been conducted with this aim in mind, namely, *PainFree I*,[11] *PainFree II*,[12] *PREPARE*,[13] *ShockLess*,[14] and *MADIT-RIT*[15] all of which showed that along with delivery of painless therapies and optimal programming, the use of discrimination algorithms play an important role in specifically reducing inappropriate shocks.

Tiered-therapy ICDs have 2 to 3 zones defined by the longest RR interval in each zone. The primary determinants of the boundaries of therapy zones are programming of specific therapies and SVT discrimination. The lower boundary between sinus and VT zone is programmed at approximately 180 to 188 bpm in primary prevention patients and at 30 to 60 ms greater than the cycle length of the slowest observed VT (150–160 bpm in most trials) in secondary prevention patients. Programming in the VT zone is focused on preventing therapy for SVT and nonsustained VT. We routinely program three zones in primary prevention patients, using the slowest VT zone for monitoring only at 160 to 166 bpm. In secondary prevention patients, the slower VT zone is programmed with three to four sequences of ramp/burst ATP compared with 1-burst ATP followed by shocks in the faster VT zone. The following are the SVT discriminators:

- *Onset:* Sudden onset is usually indicative of ventricular tachycardia.
- *Stability:* Wobbly R-R interval is indicative of atrial fibrillation.
- *Morphology:* Comparing the morphology of the tachycardia to an acquired template in sinus rhythm can help in discriminating supraventricular versus ventricular arrhythmias.
- *A/V counter:* More (V) than (A) is indicative of ventricular tachycardia.

ARRHYTHMIA REPORTING

One of the most important aspects in device interrogation is reporting on any documented arrhythmia on the device such as atrial fibrillation, ventricular tachycardia, supraventricular tachycardia, or pacemaker-mediated tachycardia.

When reporting these arrhythmias, it is essential to report the number of episodes and their length and the percentage of mode switching. Greater than

five and a half hours of atrial fibrillation has been associated with stroke, and these patients should be recommended for anticoagulation. Most devices will have a printed log of events for all arrhythmias and therapies and a report if the delivered therapies (whether ATP or ICD shocks) were appropriate or inappropriate.

In special situations, particularly cases with lead failure causing oversensing resulting in multiple inappropriate ICD firing, placing a magnet over the device will suspend all tachy therapies.

NEW ON THE HORIZON FOR PACING CARDIAC DEVICES

Leadless pacemakers: About 93% smaller than other modern-day pacemakers, the recent FDA-approved Micra pacemaker (Medtronic, Minneapolis, MN) (**Figure 27.11**) is the world's smallest pacemaker, yet it offers a complete set of features. The proprietary hybrid battery chemistry provides improved longevity, reliability, and predictable performance. It is MRI SureScan, which allows the patient to be safely scanned using either a 1.5-T or a 3-T full-body MRI. Currently, the device has a 99.2% implant success rate. About 96% of patients experienced no major complications at 6 months. The device has a 51% lower complication rate than traditional pacing systems, with no dislodgements or systemic infections.[16]

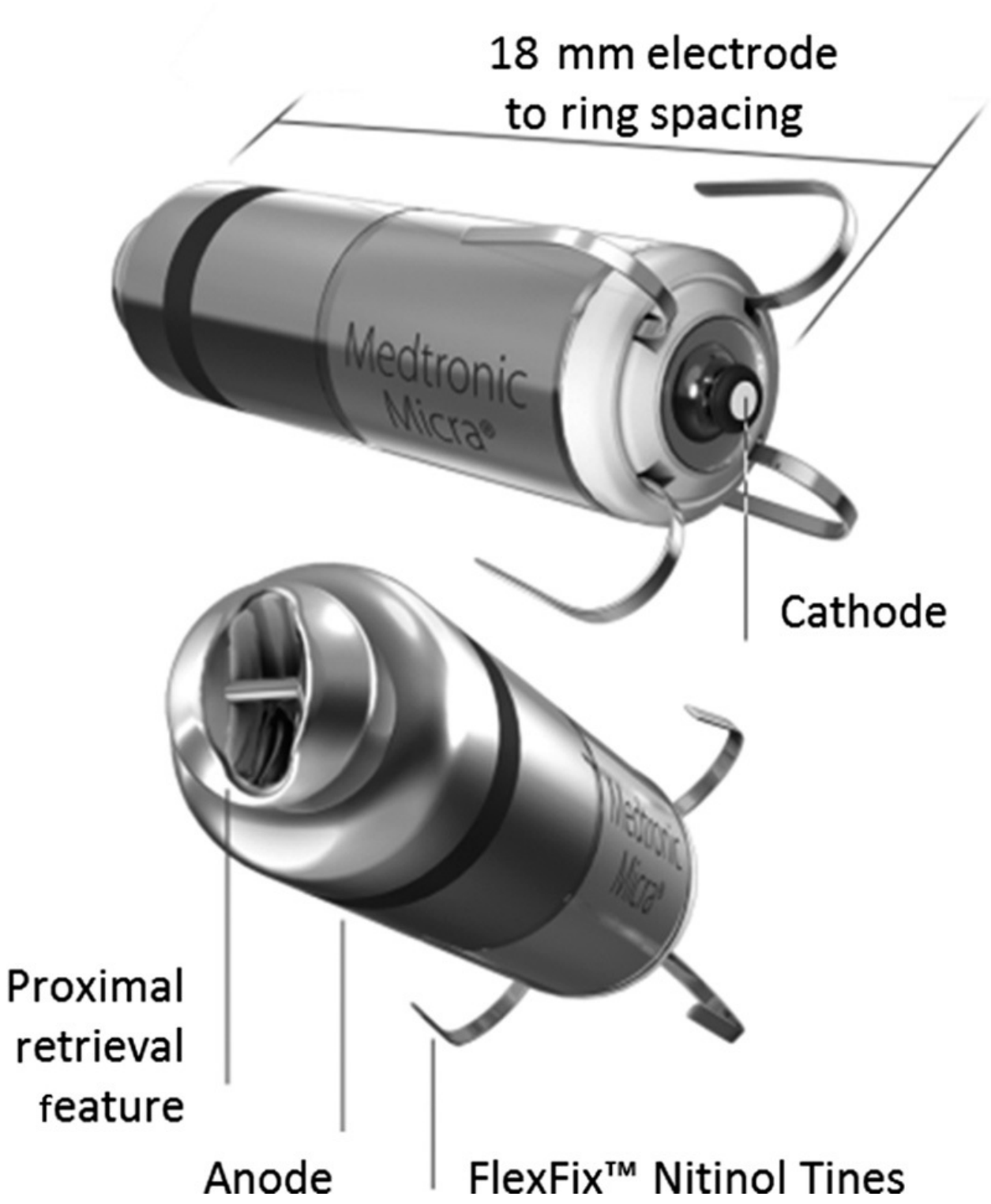


FIGURE 27.11 Leadless pacemaker Micra (Medtronic, Minneapolis, Minnesota).

SonR-Closed-Loop Optimization: The new Sorin SonR tip atrial lead is a

bipolar sugar-coated lead that picks up vibrations that reflect global contractility and not just local cardiac wall movements. The embedded sensor is a micro-accelerometer that detects cardiac muscle vibrations that reflect the first heart sound and are correlated with LV $dP/dt_{max.}$ The SonR tip lead performs automated V-V and A-V optimization at rest and during exercise. The recently published RESPOND-CRT trial[17] showed 30% reduction of all-cause mortality or heart failure hospitalization at 24-month follow-up (**Figure 27.12**).

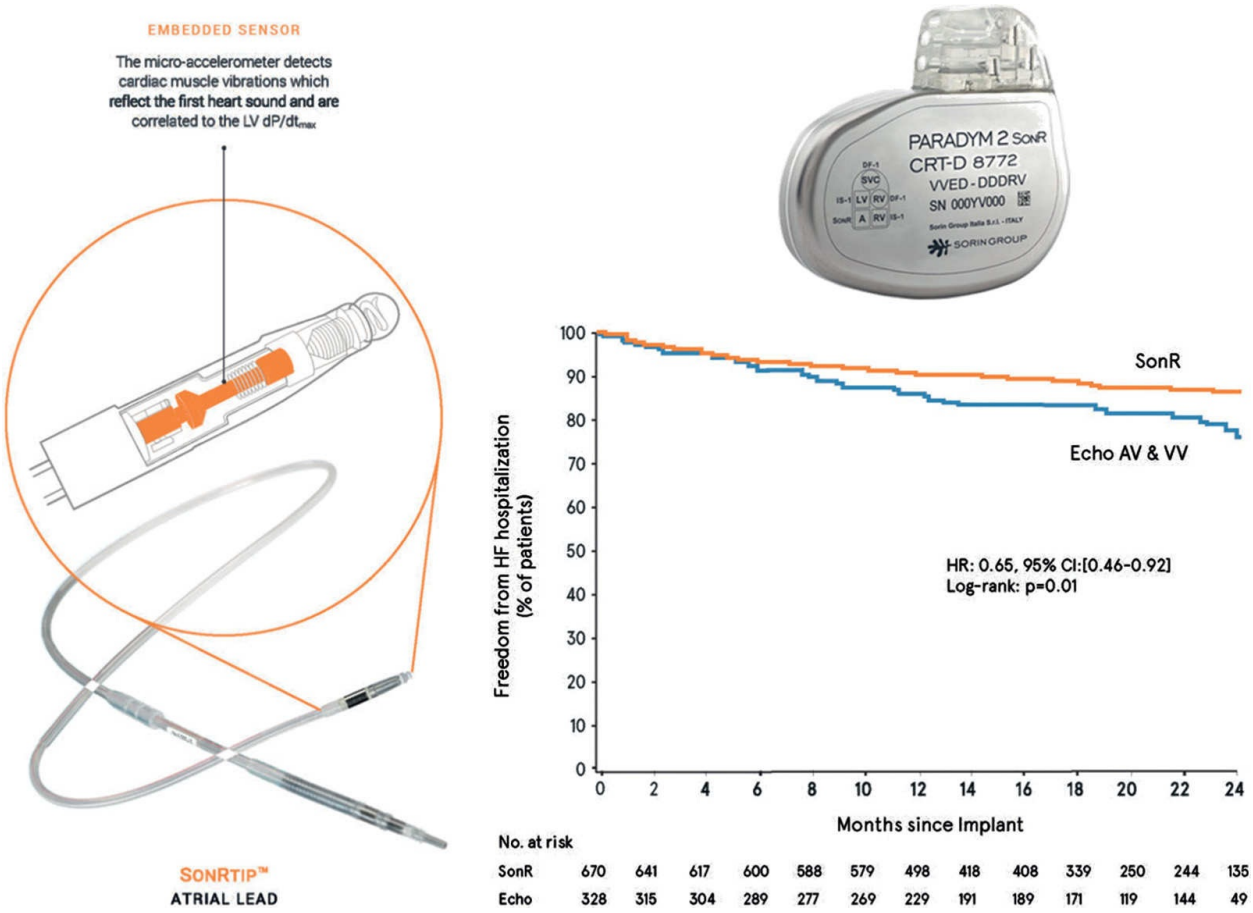


FIGURE 27.12 SonR tip atrial lead from Sorin, and the results of the RESPOND-CRT trial.

WiSE-CRT system: The WiSE-CRT system (EBR Systems, Sunnyvale, CA) uses a multicomponent strategy to provide leadless cardiac resynchronization. A tiny (9.1 mm × 2.7 mm, 0.05 cm^3) receiver electrode composed of polyester-covered titanium is implanted endocardially in the LV. A subcutaneous pulse generator is placed in the left lateral thorax and generates ultrasound pulses, which are converted to electrical pacing stimuli by the endocardial seed (**Figure 27.13**). All patients in the WiSE-CRT study had a traditional pacemaker or defibrillator; the subcutaneous WiSE-CRT pulse generator detected the RV pacing pulse from the standard system, which triggered endocardial LV pacing. In the initial trial, patients with failed coronary sinus lead placement, nonresponse to CRT, or need for an upgrade to CRT were enrolled. Data from small studies demonstrated significant QRS narrowing, absolute EF improvements of 5%, and improvements in composite clinical scores at 6 months.[18] The initial WiSE-CRT study was stopped for safety reasons.

Following delivery system redesign, early data from 14 patients demonstrated no implant-related adverse events.

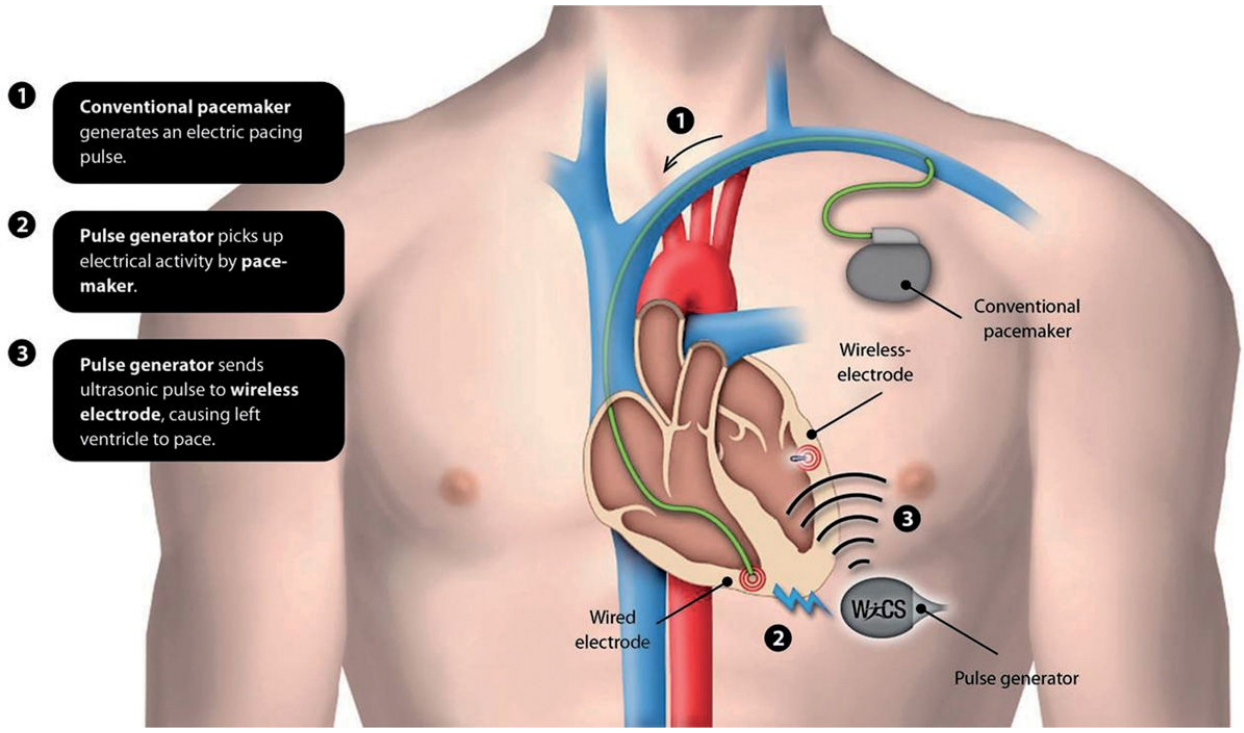


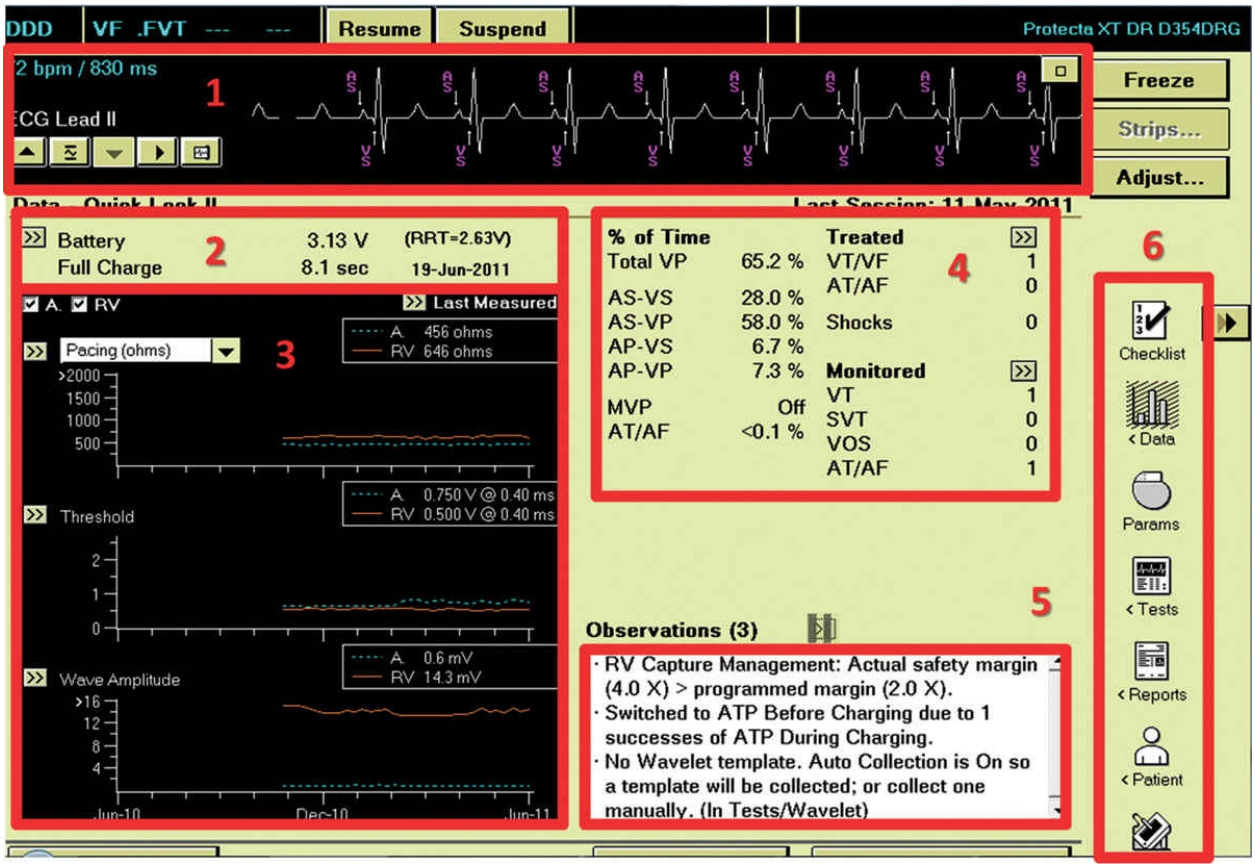
FIGURE 27.13 WiSE-CRT System.

CONCLUSION

Implantable devices are an essential part of medical management for a large number of cardiac patients. Basic knowledge is needed to perform a complete and thorough device evaluation.

APPENDIX: LIMITED KEY GUIDE OF THE FIVE MAJOR DEVICE MANUFACTURER PROGRAMMERS

1. Medtronic CareLink Programmer (**Figure 27.14**)

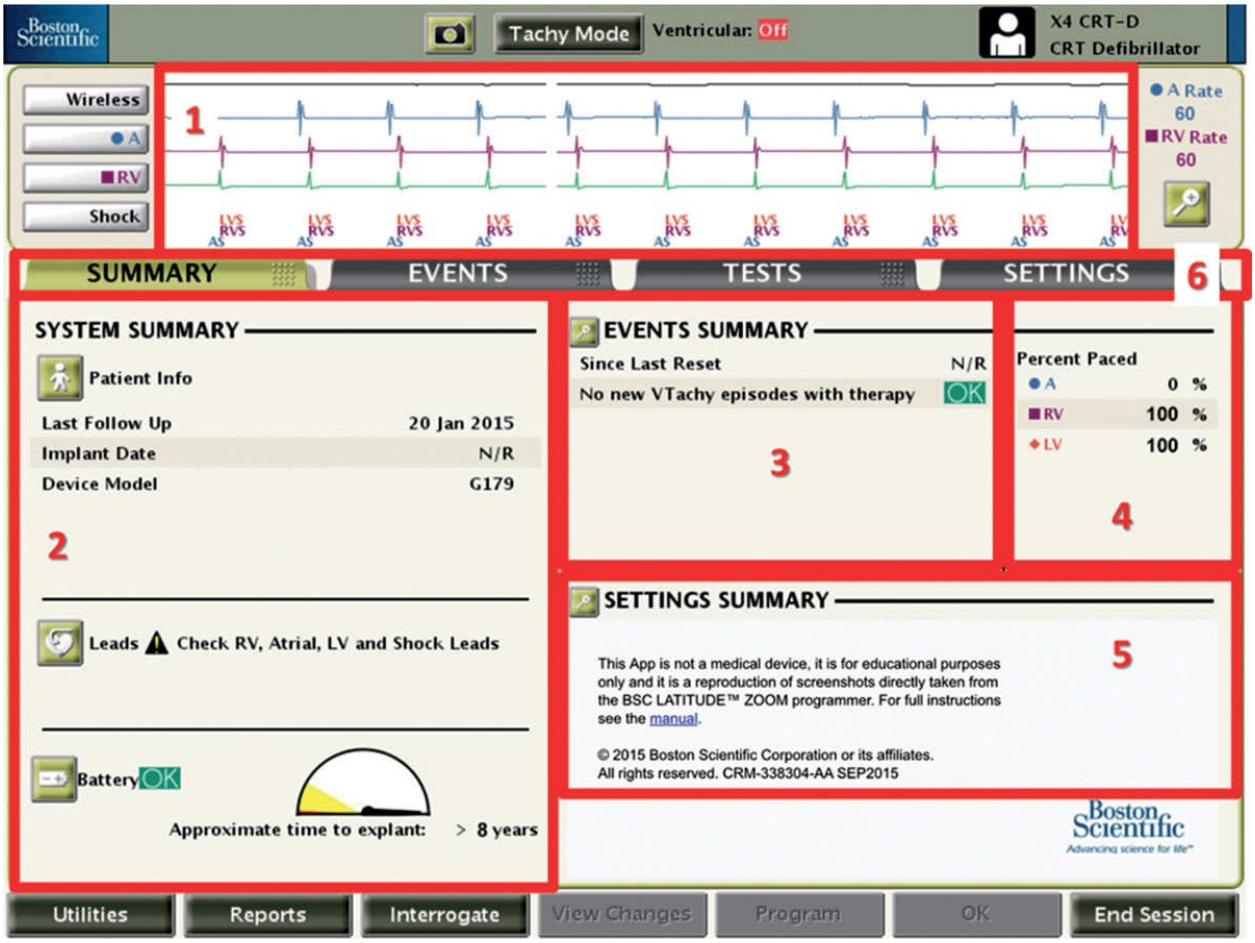


The initial screen of the Medtronic CareLink Programmer shows six main sections as marked in the figure.

1. Surface ECG
2. Battery management showing battery voltage as well as the marker for RRT
3. Trending section: This shows the trends overtime for measured amplitudes (sensing), thresholds, and lead impedances
4. Overview window for device statistics: This includes, percentage pacing over time, total atrial pacing (AP), and total ventricular pacing (VP). This section also shows the number of episodes of any arrhythmias including ventricular tachycardia/fibrillation (VT/VF), atrial tachycardia/fibrillation (AT/AF), and therapies if applicable for ICDs (shocks)
5. Observations window: This shows a short summary of most observation like fluid status (OptiVol), any thresholds issues (capture), or therapies
6. The sidebar set menu: This has a list of icons that help during the device interrogation, including checklist, statistical data, device setparameters, tests, reports and patient

FIGURE 27.14 Medtronic CareLink Programmer.

2. Boston Scientific ZOOM LATITUDE Programming System (**Figure 27.15**)



The initial screen of the Boston Scientific ZOOM LATITUDE Programming System shows six main sections as marked in the figure.

1. Surface ECG and intracardiac markers from the device leads (atrial, ventricular)
2. System summary window: This includes three sections, namely, patient information, leads notifications, and battery gauge showing indication of battery longevity with estimation for the time to explant
3. Events summary: This section shows the number of episodes of any arrhythmias, including ventricular tachycardia/fibrillation (VT/VF), atrial tachycardia/fibrillation (AT/AF), and therapies if applicable for ICDs (shocks)
4. Percentage paced: Total atrial pacing (AP) and total ventricular pacing (VP)
5. Setting summary: Device parameters setting
6. The upper ribbon tabs: These four tabs can take you directly to summary, events, tests, and device programmed settings. Reports printing can be selected by the button “reports” at the bottom of the screen

FIGURE 27.15 Boston Scientific ZOOM LATITUDE Programming System.

3. St. Jude Medical Merlin Programmer (**Figure 27.16**)

The initial screen of the St. Jude Medical Merlin Programmer shows eight main sections as marked in the figure.

1. Surface ECG and intracardiac markers from the device leads (atrial, ventricular)
2. Alerts windows: For any abnormalities, including lead issues, arrhythmia, or ICD therapy if applicable
3. Battery management window: This shows battery voltage as well as a graph depicting the estimated longevity
4. Daily test results summary window: This shows capturing thresholds, sensing amplitude, and lead impedances from most recent test check
5. Device setting summary
6. Percentage paced: Total atrial pacing (AP) and total ventricular pacing (VP)
7. Mode switching: This describes a percentage of automatic mode switching that occurs due to atrial arrhythmia. Mode-switching algorithms are designed to alleviate symptoms related to tracking of atrial arrhythmias
8. The sidebar set menu: This has a list of icons that help during the device interrogation, including FastPath summary, episodes, diagnostics, tests, parameters, and wrap-up overview from which reports are selected for printing

FIGURE 27.16 St. Jude Medical Merlin programmer.

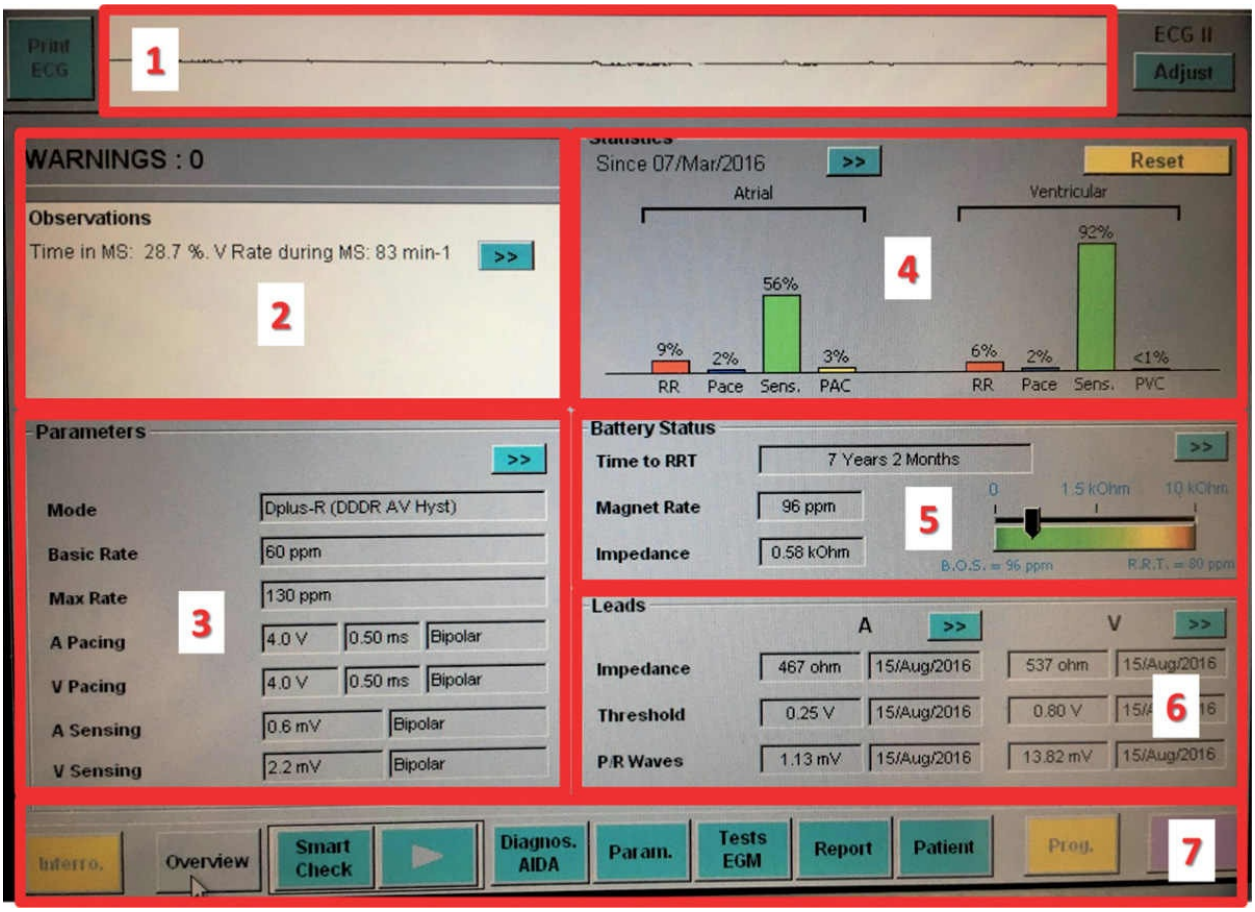
4. Biotronik Renaamic Programmer (**Figure 27.17**)

The initial screen of the Biotronik Renamic Programmer shows six main sections as marked in the figure.

1. Surface ECG and intracardiac markers from the device leads (atrial, ventricular)
2. Patient information, device parameters, and battery management window
3. Episodes windows: For any arrhythmia episodes SVT/VT/VF
4. Daily test results summary window: This shows capturing thresholds, sensing amplitude, and lead impedances from most recent test check
5. Diagnostics: Total percentage pacing for atrial pacing (A) and ventricular pacing (V) as well as atrial arrhythmia burden percentage
6. The sidebar set menu: This has a list of icons that help during the device interrogation, including follow-up, parameters, tests, recordings, diagnostics, and preferences. Reports printing can be selected by a button at the right lower part of the screen

FIGURE 27.17 Biotronik Renamic programmer.

5. Sorin Orchestra Plus Programmer (**Figure 27.18**)



The initial screen of the Sorin Orchestra Plus programmer shows seven main sections as marked in the figure.

1. Surface ECG and intracardiac markers from the device leads (atrial, ventricular)
2. Warnings and observations: This section also shows the number of episodes of any arrhythmias, including ventricular tachycardia/fibrillation (VT/VF), atrial tachycardia/fibrillation (AT/AF), and therapies if applicable for ICDs (shocks)
3. Device parameters and setting
4. Statistics: This shows the total percentage pacing for atrial pacing (A) and ventricular pacing (V) as well as atrial arrhythmia burden percentage
5. Battery management: This shows battery voltage and time to RRT
6. Leads: daily test results summary window: This shows capturing thresholds, sensing amplitude, and lead impedances from most recent test check
7. The lower bar menu: This has a list of buttons that help during the device interrogation, including interrogate, overview, smart check, diagnostics, parameters, tests, and reports

FIGURE 27.18 Sorin Orchestra Plus programmer.

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28

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Eyal Herzog

Strategies for the Prevention of Sudden Cardiac Death

INTRODUCTION

Sudden cardiac death (SCD), also known as sudden cardiac arrest, is a major health problem worldwide.[1] According to the American Heart Association (AHA) Statistical Data from 2015, each year 326,000 people experience EMS-assessed out-of-hospital cardiac arrests in the United States and approximately 60% of out-of-hospital cardiac arrests are treated by EMS personnel.[2–3] It is usually defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. Cardiac arrest is traditionally categorized as being of cardiac or noncardiac origin. A dynamic triggering factor usually interacts with an underlying heart disease, either genetically determined or acquired, and the final outcome is the development of lethal tachyarrhythmias or, less frequently, bradycardia.[4]

There is no comprehensible consensus on the definition of SCD, which is witnessed in only two-thirds of cases. Because the duration of symptoms preceding the terminal event usually defines the sudden nature of death, the World Health Organization defines SCD as unexpected death within 1 hour of symptom onset if witnessed or within 24 hours of the person having been observed alive and symptom free if unwitnessed.[5] Exclusion of noncardiac

causes, such as pulmonary embolus or drug overdose, is also critical because sudden cardiac arrhythmias may be the final common pathway in these disease states as well.

According to Framingham Heart Study, during a 20-year follow-up, 13% of the deceased have died of sudden death.[6] In more than 80% of cases, sudden death is caused by coronary disease.[7] The mechanism of sudden death is ventricular fibrillation (VF) in 65% to 85%, ventricular tachycardia (VT) in 7% to 10%, and electromechanical dissociation in 20% to 30%.

RISK FACTORS

About 80% of individuals who suffer SCD have coronary heart disease; the epidemiology of SCD to a great extent parallels that of coronary heart disease. On the basis of recent published data, the following variables have been associated with patients at higher risk of SCD: (1) syncope at the time of the first documented episode of arrhythmia, (2) NYHA class III or IV, (3) VT/VF occurring early after myocardial infarction (3 days to 2 months), and (4) history of previous myocardial infarction.[8] Other factors such as age, hypertension, left ventricular hypertrophy, intraventricular conduction block, elevated serum cholesterol, glucose intolerance, decreased vital capacity, smoking, relative weight, and heart rate are also postulated in identifying individuals at risk for SCD.[9–11] Even family history of myocardial infarction has been reported to be associated with the risk of primary cardiac arrest.[12] Another entity of patients at highest risk for early SCD are those with hereditary ion channel or myocardial defects, such as a long or short QT syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia (ARVD).

PATHOPHYSIOLOGY OF ARRHYTHMIA

The most common electric sequence of events in SCD is degeneration of VT (abnormal acceleration of ventricular rate) into VF, during which disorganized contractions of the ventricles fail to eject blood effectively, often followed by asystole or pulseless electrical activity.***7*** Polymorphic VT or torsade de pointes may be the initial arrhythmia in patients with genetic or acquired forms of structural heart disease.[13] Bradyarrhythmias or electromechanical dissociation

may be the primary electrical event in advanced heart failure or in the elderly patients.[14–15] Among patients with implantable cardioverter-defibrillators (ICDs), arrhythmic death accounts for 20% to 35% of deaths, and electromechanical dissociation after shock is a frequent cause of death. Asystole may be the first rhythm observed in the field, but this may be a marker of the duration of arrest because coarse VF ultimately degenerates into asystole.

MANAGEMENT

RISK STRATIFICATION

Current parameters for risk stratification of patients with CAD for SCD include medical history (presence of nonsustained VT or syncope), ejection fraction (EF), electrocardiogram (QRS duration, QT interval, QT dispersion), signal-averaged electrocardiogram, heart rate variability, and baroreflex sensitivity. However, the sensitivity and specificity of these parameters have not yet been studied in detail in large patient populations. The single major parameter associated with higher incidence and studied in many clinical trials is the left ventricular ejection fraction (LVEF). At present, only left ventricular (LV) dysfunction with reduced EF reliably defines “high risk” for SCD in patients with ischemic and nonischemic cardiomyopathy. The heart failure functional class and history of prior MI or CAD are also important prognostic risk factors along with sudden specific definite indications.[16]

PREVENTION

Prevention of sudden death means detection of high-risk patients and application of medical treatment in order to postpone it. The high risk of development of SCD is majorly attributed to fatal ventricular arrhythmias. Electrophysiologic anomalies in cells lead to development of ventricular ectopic activity or ventricular arrhythmias, which comes to the end with fibrillation and eventually death if not terminated in time. Because survival rates for out-of-hospital cardiac arrests are extremely low, ranging from 2% to 25% in the United States,[17] secondary prevention strategies only addresses a small portion of patient population at risk of SCD. The accumulated data have allowed guidelines to be formulated, which allow us to predict with more certainty patients at risk for

SCD and address the challenge to identify patients at risk before the first event as primary prevention. However, applying those guidelines in practice requires systems to structure the environment in which care is delivered so that "doing the right thing" becomes automatic.[18] This requires tools that simplify and provide focus by embedding the recommendations for evidence-based care into the care itself.

PHARMACOLOGIC THERAPY

β-Blockers

Of the different drugs that have been evaluated, only β-blockers have reduced sudden death in the myocardial infarction survivor.[19] The BHAT study showed that β-blockade with propranolol reduced all-cause mortality by 25% especially in patients with diminished LV function and/or ventricular arrhythmias.[20] A randomized trial of nearly 46,000 patients showed that, in the acute MI setting, early administration of high-dose β-blocker drugs orally has been shown to prevent VF.[21] In the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trial, 3,991 patients with NYHA class II-IV heart failure and EF ≤ 40% were randomized to long-acting metoprolol with a dose-escalation protocol.[22] At 1-year follow-up, overall mortality was lower in the treated group compared with placebo (7.2% vs. 11% per patient-years of follow-up). There was also a 41% relative risk reduction in sudden death with long-acting metoprolol. These data provide unequivocal benefit of β-blockade in acute MI, post-MI, and congestive heart failure for prevention of mortality and SCD.

Antiarrhythmic Drugs

The sine qua non for efficacy of common antiarrhythmic drugs in prevention against SCD based on well-designed, placebo-controlled clinical trials have shown no added benefit.[19–23] Class I drugs (mexiletine, flecainide), calcium antagonists, and class III drugs (d-sotalol, dofetilide) all failed to reduce, or even increased, the incidence of SCD after a myocardial infarction.[24] Amiodarone has also been shown to have no definitive effect on mortality in patients after MI in preventing SCD, as manifested in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[25]

Statins

The role of the statins has been well studied in the patients with CAD and has been shown to be extremely beneficial in reducing mortality but whether they play any significant role in preventing SCD remains controversial. A Multicenter Automatic Defibrillator Implantation Trial (MADIT II) substudy[26] demonstrated that, among patients treated with ICDs, those with background statin therapy had a lower rate of ventricular tachyarrhythmias. This finding was intriguing because it was unclear whether this observation was due to reductions in coronary events, decreased inflammation, unique antiarrhythmic properties, or unidentified confounders. Recently, the Cholesterol Lowering and Arrhythmia Recurrences After Internal Defibrillator Implantation (CLARIDI) study demonstrated that intensive lipid-lowering therapy using 80 mg of atorvastatin led to a 40% relative risk reduction (from 38% to 21%) in VT/VF recurrence in ICD patients during a 12-month follow-up. Yet, there are no definite guidelines supporting addition of statins as adjuvant therapy for prevention of SCD beyond conventional indications.

THE ROLE OF ICD DEVICES IN PRIMARY AND SECONDARY PREVENTION AGAINST SCD

Multiple prospective randomized multicenter clinical trials have documented improved survival with ICD therapy in high-risk patients with LV dysfunction due to either prior myocardial infarction or nonischemic cardiomyopathy. On a background of optimal medical therapy (with or without antiarrhythmic drug therapy), ICD therapy has been associated with a 23% to 55% mortality reduction due almost exclusively to a reduction in SCD. Superiority of an ICD over antiarrhythmic drug therapy for secondary prevention against SCD (predominantly amiodarone) was primarily noticed in the Antiarrhythmic Versus Implantable Defibrillator (AVID) trial.[27] The AVID trial enrolled 1,016 patients resuscitated from an episode of VT (if associated with hemodynamic collapse, cardiac symptoms, or occurring in the setting of an EF ≤ 40%) or VF. Patients were randomized to receive either medical therapy alone or in conjunction with an antiarrhythmic drug, which was most commonly amiodarone. The trial was stopped prematurely when a survival benefit was noted in patients receiving ICDs compared with those treated with sotalol or amiodarone. The unadjusted

survival rates for the ICD versus drug groups were 89% versus 82% at 1 year, 82% versus 75% at 2 years, and 75% versus 65% at 3 years. The major effect of the ICD was to prevent arrhythmic death (4.7% vs. 10.8% in patients treated with an antiarrhythmic drug). Results consistent with the AVID study were also reported from the CIDS[28] and the CASH[29] studies.

MADIT TRIAL

To test the efficacy of ICDs in prevention of SCD, the MADIT trial randomized 196 patients with ischemic cardiomyopathy,[30] EF ≤35%, a documented episode of nonsustained VT (NSVT), and inducible VT on electrophysiology study to ICD (n = 95) versus conventional medical therapy (n = 101). After a mean follow-up of 27 months, the relative risk reduction for all-cause mortality in the patients receiving ICDs was 54% (P = 0.009), thus showing the benefit of prophylactic ICD placement in a high-risk population.

MADIT II TRIAL

However, to make an impact on the overall population at risk for sudden death, high-risk patients need to be identified before an episode of VT or VF (primary prevention). The MADIT II study highlighted the possibility of preventing sudden death in patients with coronary artery disease (CAD). According to this trial, patients with a previous MI and low LVEF (≤30%) on optimal medical therapy were randomized to receive either an ICD or no ICD. Patients implanted with an ICD had a mortality rate of 14.2% versus 19.8% in the conventional therapy group (P = 0.016), with a 31% relative risk reduction in mortality during a follow-up period of 20 months. The survival benefit was entirely due to a reduction in the incidence of SCD and became apparent at 9 months after device implantation. This trial was novel in that there was no requirement for invasive electrophysiologic testing of prior ventricular arrhythmias. This trial expanded on the findings of MADIT I, which showed the superiority of ICD therapy in patients with CAD with an EF of 35% or less.

SCD-HEFT TRIAL

The significant role of ICD therapy in primary prevention against SCD in both ischemic and nonischemic cardiomyopathy patients was further clarified by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[31] This trial enrolled

2,521 patients with New York Heart Association[32] class II or III CHF and an EF of ≤35%. Patients were randomized to receive optimal medical therapy alone (847 patients), optimal medical therapy along with amiodarone (845 patients), or optimal medical therapy along with a conservatively programmed, shock-only, single-lead ICD (829 patients). Placebo and amiodarone were administered in a double-blind fashion. The primary end point of the study was all-cause mortality with mean follow-up of 3.8 years. A 23% reduction in mortality ($P = 0.007$) was observed with the ICD; the benefit of ICD was similar in both ischemic (hazard ratio, 0.79; $P = 0.05$) and nonischemic cardiomyopathy (hazard ratio, 0.73; $P = 0.06$). In contrast, mortality was similar in patients either on medical therapy alone or when combined with amiodarone. The benefit of ICD therapy was comparable for ischemic and nonischemic cardiomyopathy.

DEFINITE TRIAL

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial was the MADIT II counterpart. This trial included 458 patients with nonischemic dilated cardiomyopathy, EF ≤35%, nonsustained VT or premature ventricular contractions, and NYHA class I, II, or III who were randomly divided to standard medical therapy or ICD.[33] At a 2-year follow-up, there was a trend in mortality reduction with ICD (7.9% vs. 14.1%; hazard ratio = 0.65, $P = 0.08$). The largest benefit was seen in NYHA Class III patients (hazard ratio = 0.37). In part on the basis of the results of this trial, the Centers for Medicare & Medical Services expanded coverage for ICD implementation to patients with nonischemic cardiomyopathy for more than 9 months in duration who have NYHA class III or IV heart failure and EF ≤35%.

TIMING OF ICD IMPLANTATION

CABG PATCH TRIAL

In the CABG Patch study, 900 patients with LVEF of <36% and abnormal signal-averaged ECG who were undergoing elective coronary bypass surgery were randomized to ICD or no antiarrhythmic therapy.[34] This trail showed no difference in survival between the two groups at an average of 32-month follow-up. Of note, 88 patients enrolled were not randomized because they were deemed too unstable at the time of surgery for ICD placement. Additionally, EFs of these patients were not assessed postoperatively. Nevertheless, results suggest

that revascularization should be performed when feasible and SCD risk stratification should be performed after revascularization.

DINAMIT TRIAL

In this randomized, open-label trial comparing ICD therapy to optimal medical therapy, 674 high-risk patients (defined by an EF <35%) were enrolled 6 to 40 days after myocardial infarction.[35–36] The primary end point was death from any cause; death from arrhythmia was a secondary end point. During a mean follow-up of 30 months, there was no difference in overall mortality between two treatment groups. A reduction in arrhythmia was balanced by an increase in overall mortality (cardiac but nonarrhythmogenic) in the ICD group. The reason for this surprising finding is unclear but may be related to impaired cardiac autonomic function early after MI. The benefits of ICD therapy for prevention of SCD may not become evident until years after myocardial infarction and may not have been captured in the mean 30-month follow-up of DINAMIT Trial. Current guidelines therefore recommend deferring ICD implantation for at least 40 days following MI.

Aggressive treatment of myocardial ischemia, including revascularization, is the main treatment in these patients, and early implantation of ICD does not reduce overall mortality after early MI (the DINAMIT study). Implantation of ICD should be deferred in these cases as is currently recommended, with reassessment of LV function after 40 days to determine whether ICD is still required for primary prevention of SCD (if LVEF <35%), although in some individual circumstances it may be considered (eg, in patients with recurrent, sustained arrhythmias).

CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT), or biventricular pacing, can improve cardiac pump function in advanced heart failure by simultaneous activation of the left and right ventricles in those with underlying or pacing-induced bundle branch block. CRT[37] is approved in the United States for EF ≤ 35%, evidence of dyssynchrony, and class III–IV heart failure despite optimal medical therapy. A brief review of the clinical data supporting their current use follows.

COMPANION TRIAL

CRT with either a pacemaker or a pacemaker-defibrillator has been shown to be very beneficial in the COMPANION trial,[38] which randomized patients with class III or IV heart failure, normal sinus rhythm, LVEF <35%, LV end diastolic volume > 60 mm, and QRS interval > 120 milliseconds. In this trial CRT with a pacemaker decreased the risk of the primary end point (hazard ratio, 0.81; P = 0.014), as did CRT with a pacemaker-defibrillator (hazard ratio, 0.80; $P < 0.01$). The risk of the combined end point of death or hospitalization for heart failure was reduced by 34% in the pacemaker group ($P < 0.002$) and by 40% in the pacemaker-defibrillator group ($P < 0.001$). A pacemaker reduced the risk of the secondary end point of death from any cause by 24% (P = 0.059), and a pacemaker-defibrillator reduced the risk by 36% (P = 0.003).

CARE-CHF TRIAL

The Cardiac Resynchronization in Heart Failure Study (CARE-HF) trial was a nonblinded European trial, which enrolled patients with class III or IV heart failure, LVEF <35%, LV end diastolic volume >30 mm, QRS interval >150 milliseconds, or QRS >120 milliseconds with echocardiographic parameters of dyssynchrony.[39] This trial confirmed earlier trials that the benefits of CRT are in addition to those achieved with standard pharmacologic therapy in patients with moderate-to-severe heart failure due to LV systolic dysfunction with evidence of cardiac dyssynchrony. CARE-HF is the first study to show benefit with CRT with respect to survival and the first to show benefit and continued improvement for a period of over 2 years.

MADIT-CRT

In a large randomized study of NYHA Class I and II patients, the primary endpoint showed that CRT-D were associated with 34% relative reduction in the risk of all-cause mortality or first heart failure event; in addition, there were 41% relative reduction of heart failure events compared with ICD patients. One-year follow-up confirmed an improvement of 11% in LVEF compared with 3% improvement for ICD patients.[40] The trial showed the best benefit were for patients with left bundle branch block or with non–left bundle branch with QRS > 150 msec, which led to an update in the guidelines that was published in 2012.[42]

A GENERALIZED SIMPLE SYSTEMATIC APPROACH TOWARD PREVENTION OF SCD (ESCAPE PATHWAY)

Multiple pathways have been developed in recent past to address these complex issues faced in the management of SCD; however, most of them lack simplicity, and practicality of implementation, which in turn affect their overall outcome and patient care. Here, we describe the ESCAPE pathway,[41] which is a simple novel pathway for primary and secondary prevention of sudden cardiac arrest aiming to increase physician awareness and incorporate a tool for appropriate referral for ICD evaluation (**Figure 28.1**).

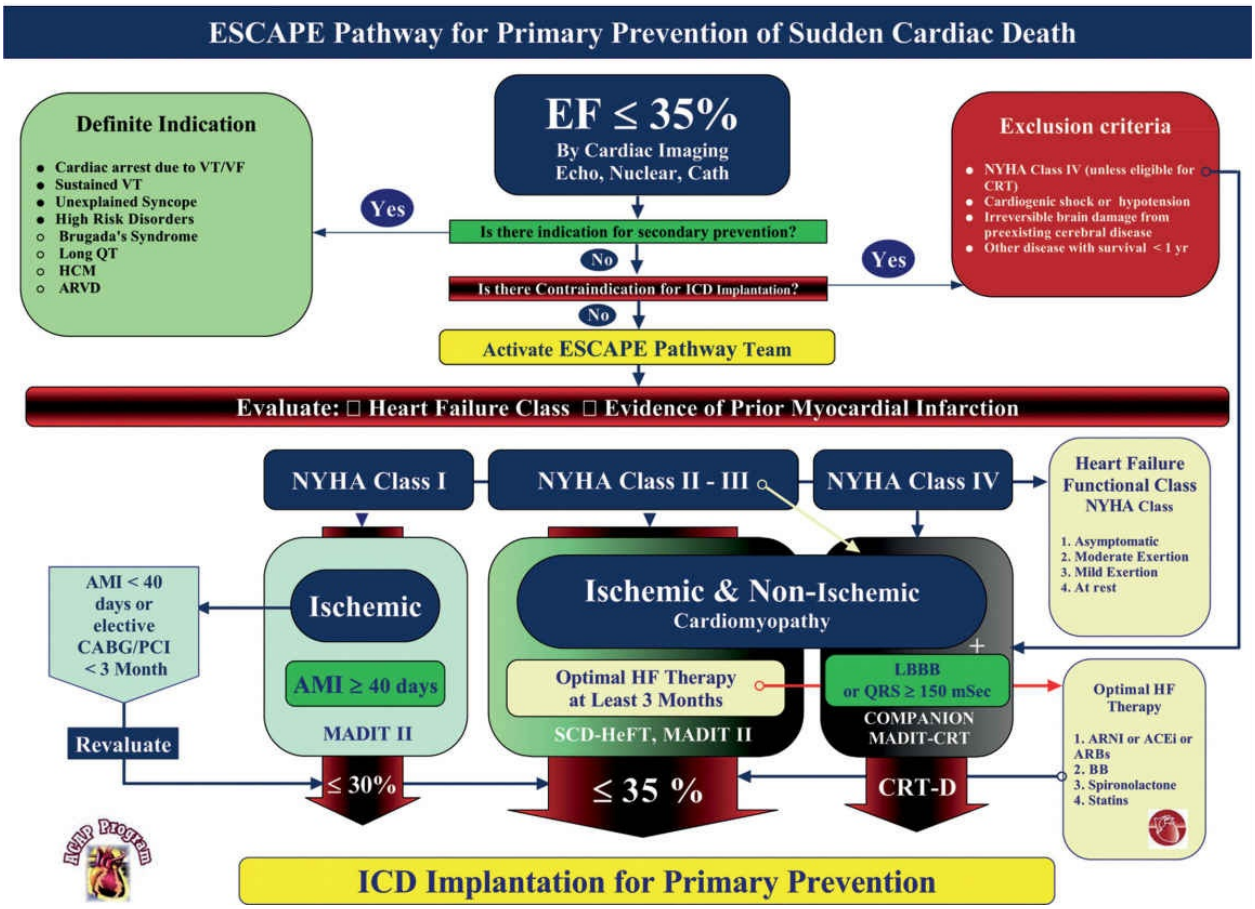

FIGURE 28.1 The ESCAPE pathway for prevention of sudden cardiac death.

STEP A: INITIAL EVALUATION OF PATIENTS

The initial and foremost thing to observe while assessing for the prevention against SCD is the EF. The ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of SCD criteria include patients with either ischemic or nonischemic cardiomyopathy with EF ≤ 35%, or NYHA class II or III heart failure.

On the basis of the initial evaluation of the patients with EF ≤ 35%, they can be divided into three subgroups: (A) patients with a clear indication for secondary cardiac arrest prevention, (B) patients who have a contraindication to ICD or have no proven benefit from ICDs for SCD prevention as per clinical data available to date, and (C) patients who neither have any indication for ICD placement at this time as a part of secondary prevention of SCD nor have any contraindication.

Group A involves the following patients (**Figure 28.2**):

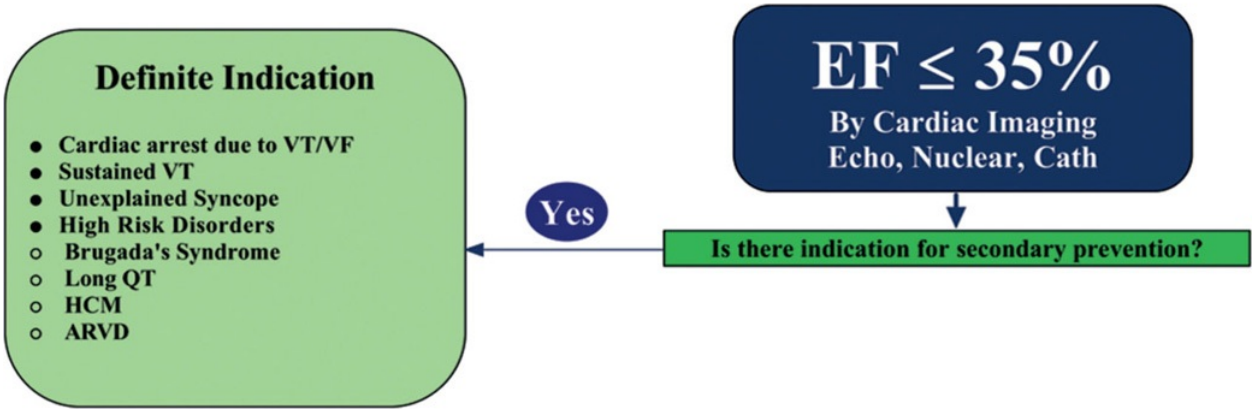

FIGURE 28.2 Indications for ICD implantation as secondary prevention of sudden cardiac death.

- Survivors of sudden cardiac arrest due to VT/VF
- Those with a previous documented episode of hemodynamically destabilizing sustained VT
- Those with unexplained syncope in the setting of underlying structural heart disease
- Those with high-risk short or long QT syndrome (LQTS or SQTS)
- Those with high-risk Brugada syndrome
- Those with high-risk hypertrophic cardiomyopathy
- Those with arrhythmogenic right ventricular dysplagia (ARVD)

This group of patient population on presentation should be referred directly for ICD implantation for secondary prevention against SCD.

Group B involves patients with a contraindication for ICD implantation and include the following (**Figure 28.3**):

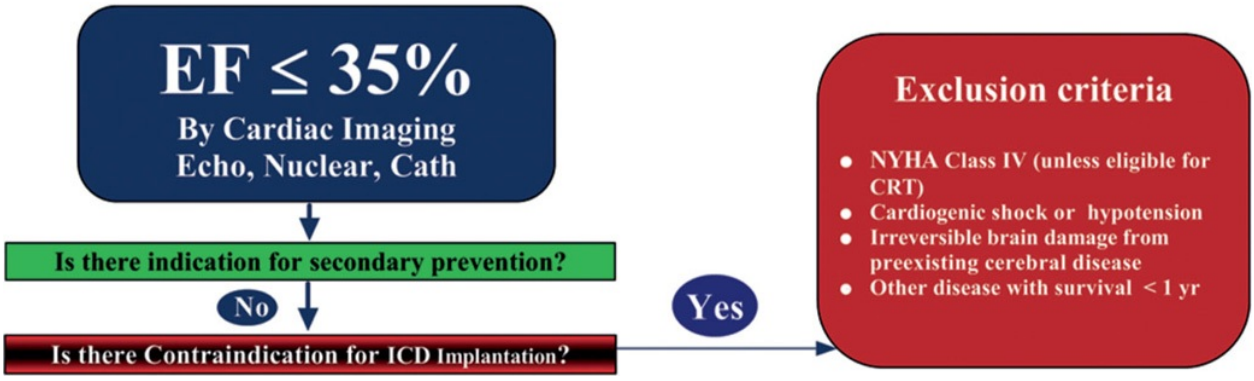

FIGURE 28.3 Contraindication for ICD implantation.

- NYHA class IV patients (unless QRS ≤ 120 milliseconds who are eligible for CRT)
- Those with cardiogenic shock or hypotension
- Those with irreversible brain damage from preexisting cerebral disease
- Those with other disease (eg, cancer, uremia, liver failure), associated with a likelihood of survival of less than 1 year

Group C patients need further work-up to decide whether or when they should get ICDs and should enter into step B.

STEP B: EVALUATION OF HEART FAILURE CLASSES

To determine the best course of therapy, these patients require assessment of the stage of heart failure according to the NYHA classification (**Figure 28.4**).[42–43]

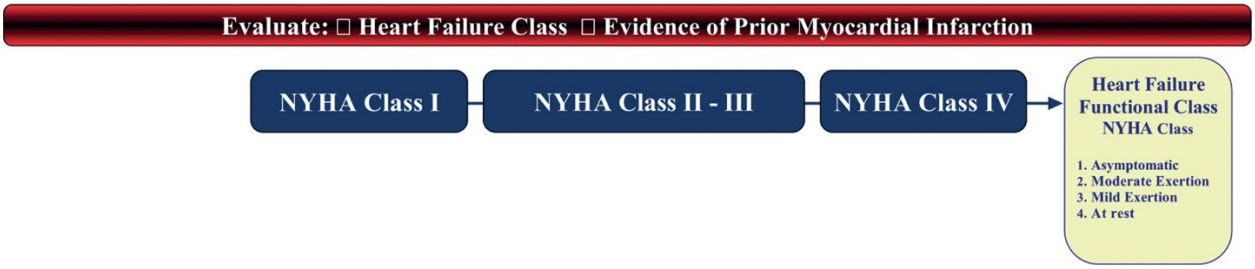

FIGURE 28.4 Evaluation of New York Heart Association classes.

- Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
- Class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
- Class III: Marked limitation of physical activity. Comfortable at rest, but less-than-ordinary activity causes fatigue, palpitation, or dyspnea.
- Class IV: Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

STEP C: EVALUATION OF CAD OR PRIOR MI IN NYHA CLASS I PATIENT

Evaluation for any evidence of prior MI or CAD requiring intervention is further necessary (**Figure 28.5**).

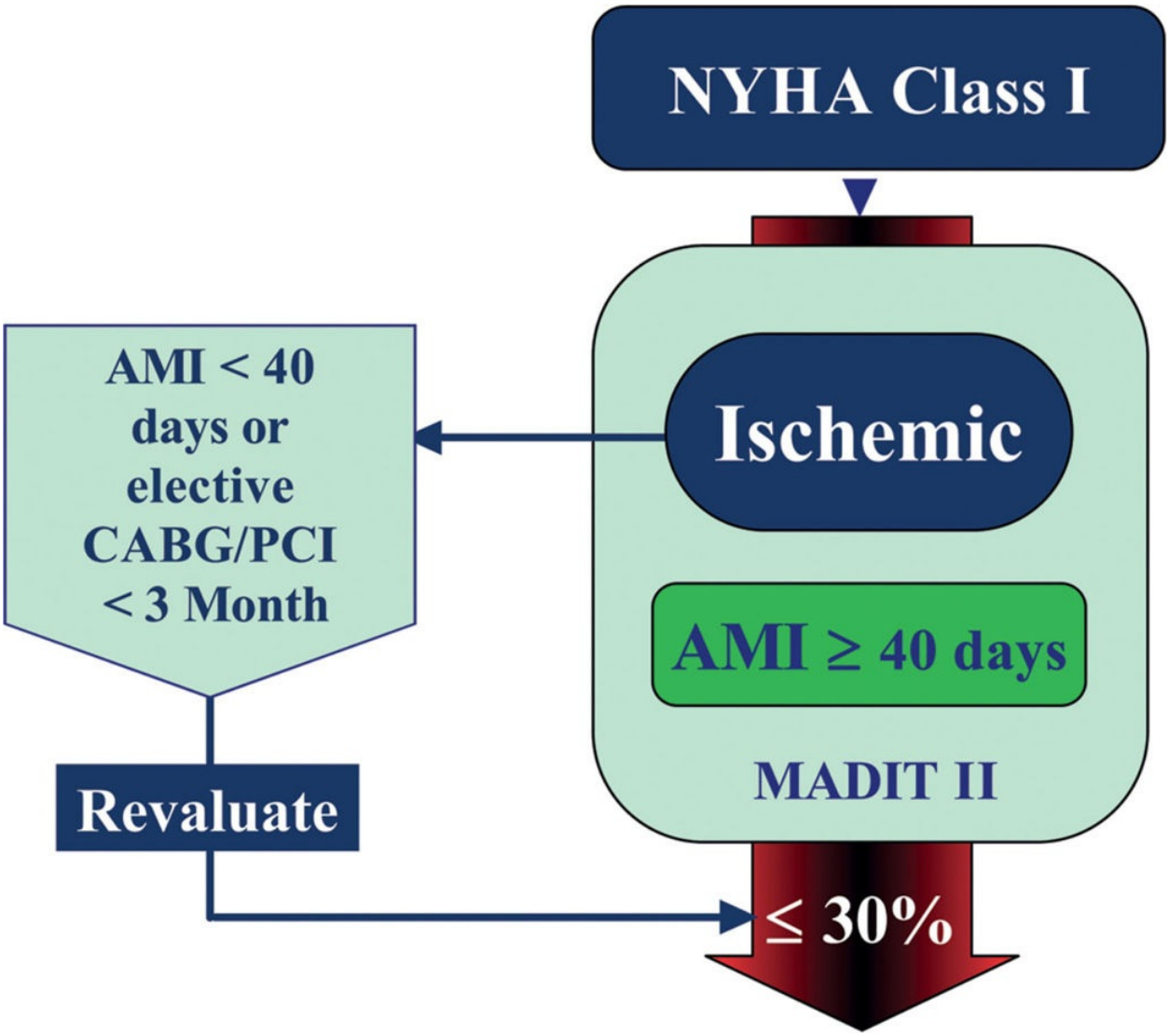

FIGURE 28.5 Evaluation of coronary artery disease or prior myocardial infarction in NYHA class I patients.

- Patients with NYHA class I heart failure whose EF is lower or equal to 30% and who are at least 40 days post-MI should be referred for an ICD implantation according to MADIT II trial.
- Patients with low EF and are ≤40 days post-MI should be managed medically for their heart failure at present.[44] If repeat imaging at 40 days confirms EF ≤ 30% (or ≤35% in patients with class II or III NYHA class CHF), these patients should be referred for an ICD implantation.
- Patients with low EF who underwent elective revascularization either by

percutaneous intervention or coronary bypass surgery in ≤3 months should be managed medically with optimal therapy for heart failure and if repeated imaging at 3 months confirms EF ≤ 30% (or ≤35% in patients with class II or III NYHA class CHF), these patients should be referred for an ICD implantation.

STEP D: PRIMARY PREVENTION OF SCD IN NYHA CLASS II–III PATIENTS WITH LOW EF

According to the ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2016 ACCF/AHA Guideline for the Management of Heart Failure[43] (**Figure 28.6**),

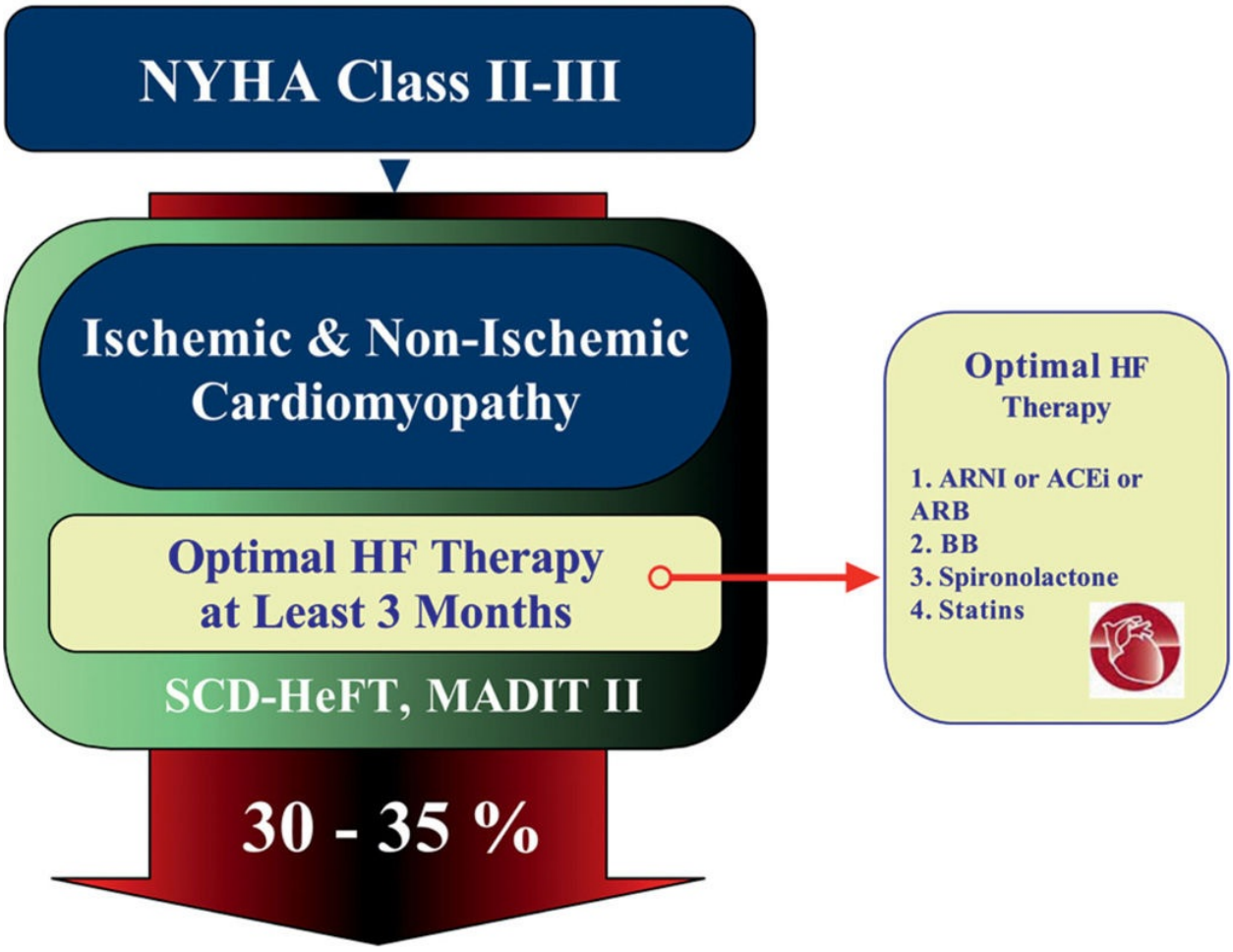

FIGURE 28.6 Primary prevention of sudden cardiac death in NYHA class II–III patients with low ejection

fraction.

- Angiotensin-converting enzyme (ACE) inhibitors are recommended for routine administration to symptomatic and asymptomatic patients with LVEF ≤40% (strength of evidence = A).
- β-Blockers shown to be effective in clinical trials of patients with HF are recommended for patients with an LVEF ≤ 40% (strength of evidence = A).
- Angiotensin-receptor blockers (ARBs) are recommended for routine administration to symptomatic and asymptomatic patients with an LVEF ≤40% who are intolerant to ACE inhibitors for reasons other than hyperkalemia or renal insufficiency (strength of evidence = A).
- Angiotensin-receptor/neprilysin inhibitor (ARNI), Valsartan/sacubitril may be used instead of an ACE inhibitor or an ARB in people with heart failure and a reduced LVEF (strength of evidence = A).
- Administration of an aldosterone antagonist should be considered in patients following an acute MI, with clinical HF signs and symptoms and an LVEF ≤40%. Patients should be on standard therapy, including an ACE inhibitor (or ARB) and a β-blocker (strength of evidence = A).

If repeated imaging at 3 months confirms EF ≤35% and still in NYHA class II to III, these patients will be referred for an ICD implantation.

STEP E: PRIMARY PREVENTION OF SCD IN NYHA CLASS III AND IV HEART FAILURE PATIENTS WITH LEFT BUNDLE BRANCH BLOCK OR NON–LEFT BUNDLE WITH PROLONGED QRS (≥150 MILLISECONDS)

Patients with left bundle branch block or non–left bundle with QRS ≥150 milliseconds and in NYHA class (II, III, and IV) according to COMPANION, CARE-HF, and MADIT-CRT trials will be referred for CRT with an ICD (CRT-D), whereas patients with NYHA class IV but QRS > 120 milliseconds should be treated with optimal medical therapy (**Figure 28.7**).[19]

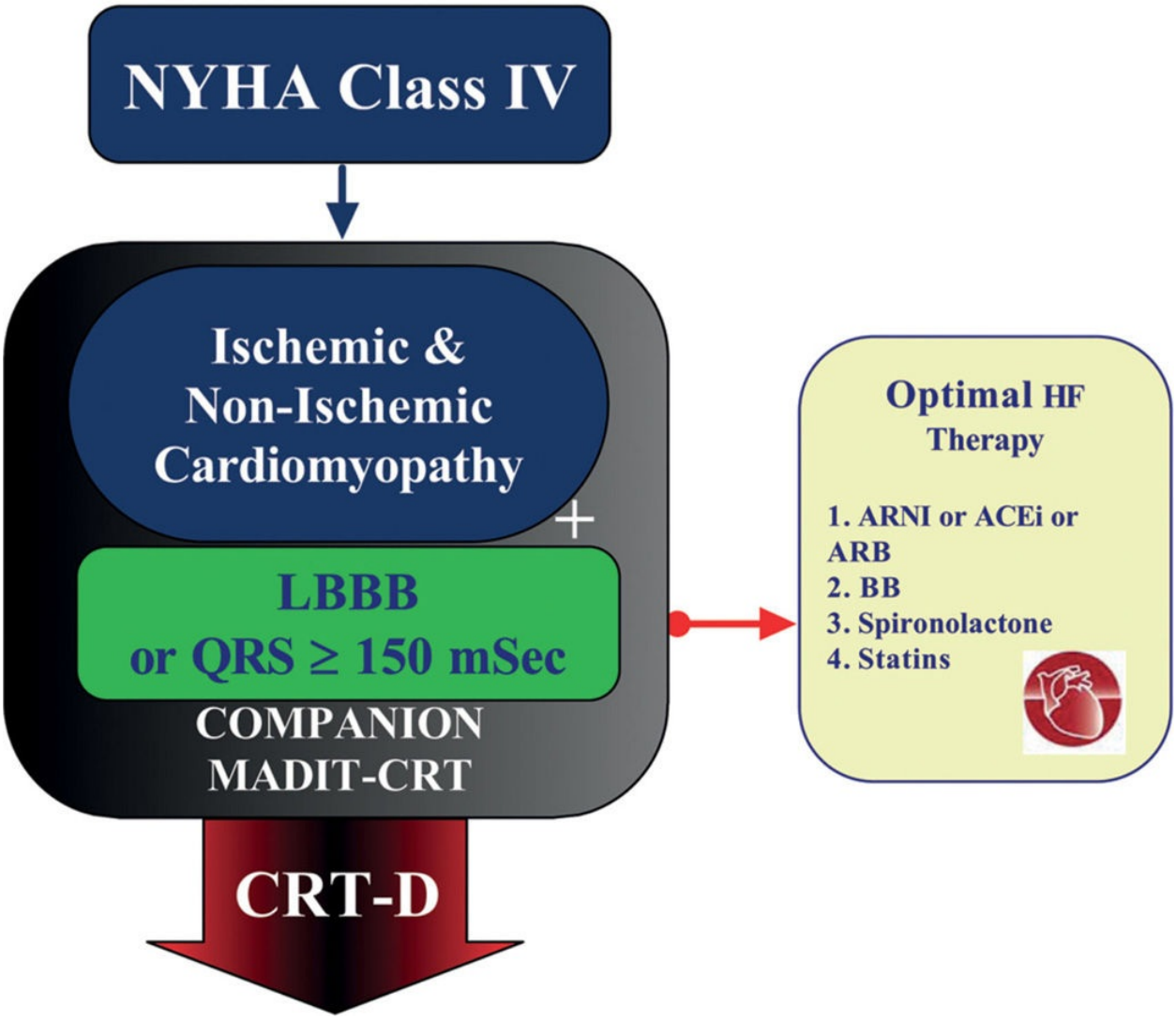

FIGURE 28.7 Primary prevention of sudden cardiac death in NYHA class III–IV heart failure patients with left bundle branch block (LBBB) or non-LBBB with prolonged QRS ≥150 ms.

CONCLUSION

Over the last three decades, revolutionary advances in the understanding and treatment of SCD have been accomplished. Structural and electrical mechanisms of terminal arrhythmias have been elucidated. Over two-dozen genetic mutations and polymorphisms have been identified, which in turn have increased our understanding of ion channel structure and function. At the same time, randomized trials that demonstrated harm from antiarrhythmic drugs have

curtailed the use of such drugs alone in the prevention of SCD. The ICD was developed and has proven to be a highly effective therapy in the prevention of SCD to date. However, most cases of SCD occur in patients without these high-risk features, and the biggest challenge still remains: to accurately identify patients at risk for SCD for primary prevention.

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29

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Cardiopulmonary Resuscitation and Cardiocerebral Resuscitation Using Therapeutic Hypothermia

DEFINING SUDDEN CARDIAC ARREST

Cardiac arrest is defined as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation. Cardiac arrest is traditionally categorized as being of cardiac or noncardiac origin. An arrest is presumed to be of cardiac origin unless it is known or likely to have been caused by trauma, submersion, drug overdose, asphyxia, exsanguination, or any other noncardiac cause as best determined by rescuers.[1]

It is challenging to define what “unexpected” or “sudden” death is. Current practice defines sudden cardiac death as unexpected death without an obvious noncardiac cause that occurs within 1 hour of symptom onset (witnessed) or within 24 hours of last being observed in normal health (unwitnessed).[2]

EPIDEMIOLOGY OF OUT-OF-HOSPITAL CARDIAC ARREST

Based on the American Heart Association (AHA) Statistical Data from 2015[1]

- Each year, 326,000 people experience emergency medical services (EMS)–assessed out-of-hospital cardiac arrests in the United States.
- Approximately 60% of out-of-hospital cardiac arrests are treated by EMS personnel.[3]
- Twenty-five percent of those with EMS-treated out-of-hospital cardiac arrest have no symptoms before the onset of arrest.[4]
- Among EMS-treated out-of-hospital cardiac arrests, 23% have an initial rhythm of ventricular fibrillation (VF) or ventricular tachycardia (VT) or are shockable by an automated external defibrillator (AED).[5]
- The incidence of cardiac arrest with an initial rhythm of VF is decreasing over time; however, the incidence of cardiac arrest is not decreasing.[6]
- The median age for out-of-hospital cardiac arrest is 66 years.[7]
- Cardiac arrest is witnessed by a bystander in 38.7% of cases, by an EMS provider in 10.9% of cases, and is unwitnessed in 50.4% of cases.[7]
- In the Cardiac Arrest Registry to Enhance Survival (CARES) registry, 31,127 out-of-hospital cardiac arrests were treated in 2013. Survival to hospital discharge was 10.6%, and survival with good neurologic function (Cerebral Performance Category 1 or 2) was 8.3%. For bystander witnessed arrest with a shockable rhythm, survival to hospital discharge was 33.0%.[7]
- According to the CARES registry, in 2013 the majority of out-of-hospital cardiac arrests occurred at a home or residence (69.5%).[7]
- A family history of cardiac arrest in a first-degree relative is associated with a 2-fold increase in risk of cardiac arrest.[8, 9]

EPIDEMIOLOGY OF IN-HOSPITAL CARDIAC ARREST

Based on the AHA Statistical Data from 2015[1]:

- Each year, 209,000 people are treated for in-hospital cardiac arrest in the United States.[10]
- According to the Get With The Guidelines (GWTG)-Resuscitation database from 2014, 25.5% of adults who experienced in-hospital cardiac arrest with any first recorded rhythm in 2013 survived to discharge.[1]

- In the United Kingdom National Cardiac Arrest Audit database between 2011 and 2013, the overall unadjusted survival rate was 18.4%. Survival was 49% when the initial rhythm was shockable and 10.5% when the initial rhythm was not shockable.[11]

CARDIOPULMONARY RESUSCITATION GUIDELINE EVOLUTION

The initial attempts to treat cardiac arrest focused on chest compressions. Closed chest defibrillation and closed chest cardiac massage were first described in the 1960s.

In the initial publication, some patients were treated with chest compression without positive pressure. However, with time, ventilation gradually became an essential pillar of cardiopulmonary resuscitation.

Given the prevalence and lethality of cardiac arrest, the AHA disseminated cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) information to health care professionals and the lay public in the 1970s.

The International Liaison Committee on Resuscitation (ILCOR) was formed in 1993. In 1999, the AHA hosted the first ILCOR conference to evaluate resuscitation science and develop common resuscitation guidelines. Since 2000, researchers from the ILCOR member councils have evaluated and reported their International Consensus on CPR and ECC Science With Treatment Recommendations(CoSTR) in 5-year cycles.[12]

HIGHLIGHTS OF THE 2015 AMERICAN HEART ASSOCIATION GUIDELINES UPDATED FOR CARDIOPULMONARY RESUSCITATION AND EMERGENCY CARDIOVASCULAR CARE

BASIC LIFE SUPPORT

Systems of Care

The 2015 AHA Updated Guidelines highlighted a new perspective on systems of care, differentiating in-hospital cardiac arrests (IHCAs) from out-of-hospital

cardiac arrests (OHCAs).[13]

The care for all post–cardiac arrest patients, regardless of the location of the arrests, converges in the hospital, generally in an intensive care unit (ICU) where post–cardiac arrest care is provided. The systems of care before that convergence are very different for the two settings. Patients who have an OHCA depend on their community for support. Lay rescuers must recognize the arrest, call for help, initiate CPR, and provide defibrillation (ie, public-access defibrillation [PAD]) until EMS assumes responsibility and transports the patient to an emergency department (ED) and/or cardiac catheterization lab. The patient is ultimately transferred to a critical care unit for continued care.

In contrast, patients who have an IHCA depend on a system of appropriate surveillance (ie, rapid response or early warning system) to prevent cardiac arrest. If cardiac arrest occurs, patients depend on the smooth interaction of the institution's various services and a multidisciplinary team of professional providers, including physicians, nurses, and respiratory therapists, among others.

Community Lay Rescuer Automated External Defibrillator Programs

It is recommended that PAD programs for patients with OHCA be implemented in public locations where there is a relatively high likelihood of witnessed cardiac arrest (eg, airports, casinos, sports facilities).

There is clear and consistent evidence of improved survival from cardiac arrest when a bystander performs CPR and rapidly uses an AED. Thus, immediate access to a defibrillator is a primary component of the system of care. The implementation of a PAD program requires 4 essential components: (1) a planned and practiced response, which, ideally, includes identification of locations and neighborhoods where there is high risk of cardiac arrest, placement of AEDs in those areas, and ensuring that bystanders are aware of the location of the AEDs, and, typically, oversight by an HCP; (2) training of anticipated rescuers in CPR and use of the AED; (3) an integrated link with the local EMS system; and (4) a program of ongoing quality improvement.

Figure 29.1 outlines the 2015 guidelines recommendations for the initial approach to a patient who is unresponsive.

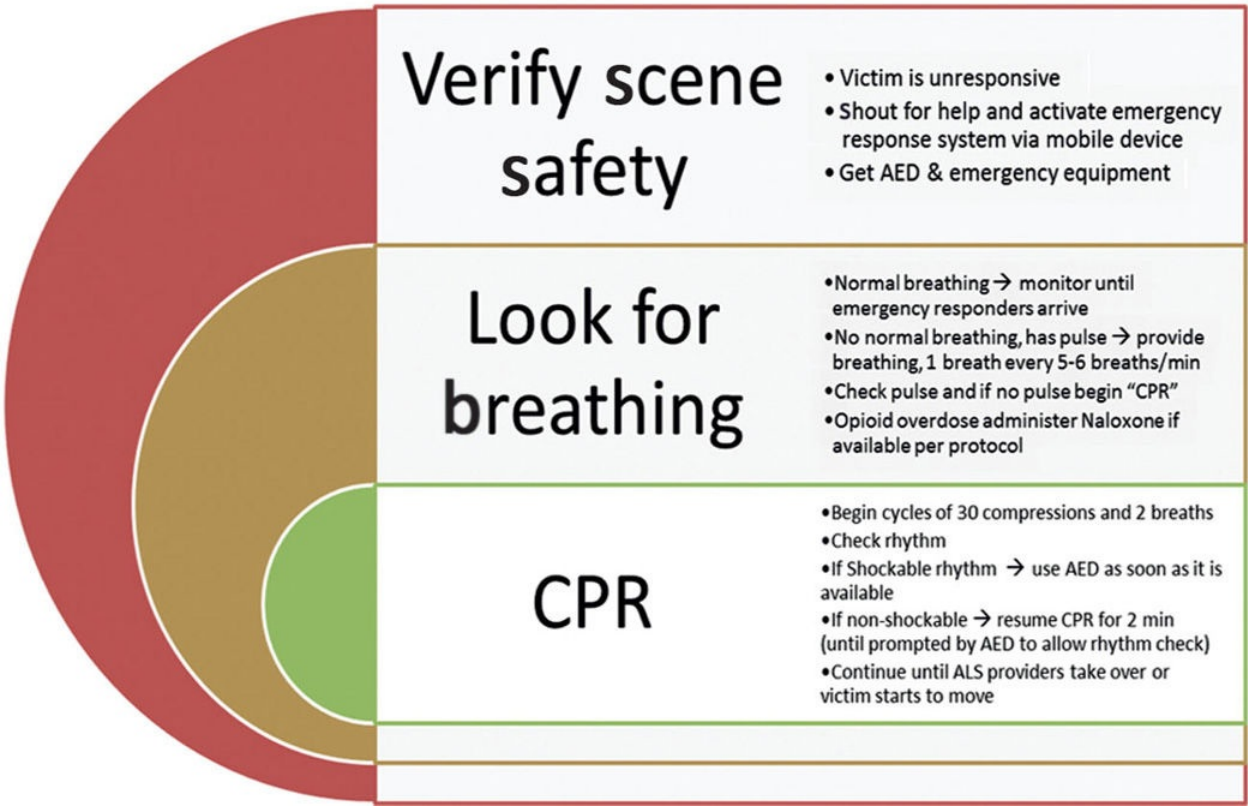


FIGURE 29.1 Updated 2015 guidelines recommendation for unresponsive patient management. AED, automated external defibrillator; ALS, advanced life support.

Chest Compressions

Untrained lay rescuers should provide compression-only (hands-only) CPR, with or without dispatcher guidance, for adult victims of cardiac arrest. The rescuer should continue compression-only CPR until the arrival of an AED or rescuers with additional training. All lay rescuers should, at a minimum, provide chest compressions for victims of cardiac arrest. In addition, if the trained lay rescuer is able to perform rescue breaths, he or she should add rescue breaths in a ratio of 30 compressions to 2 breaths. The rescuer should continue CPR until an AED arrives and is ready for use, EMS providers take over care of the victim, or the victim starts to move.

Chest Compression Rate

In most studies, more compressions are associated with higher survival rates, and fewer compressions with lower survival rates.

New to the 2015 Guidelines Update are upper limits of recommended compression rate and compression depth, based on preliminary data suggesting

that excessive compression rate and depth adversely affect outcomes.

For the critical outcome of survival to hospital discharge, evidence exists from two observational studies [14, 15] representing 13 469 adult patients. They compared chest compression rates of greater than 140/min, 120 to 139/min, less than 80/min, and 80 to 99/min with the control rate of 100 to 119/min. When compared with the control chest compression rate of 100 to 119/min, there was a 4% decrease in survival to hospital discharge with compression rates of greater than 140/min, a 2% decrease in survival to hospital discharge with compression rates of 120 to 139/min, a 1% decrease in survival to hospita l discharge with compression rates of less than 80/min, and a 2% decrease in survival to hospital discharge with compression rates of 80 to 99/min.

The study showed that chest compression depth declined with increasing chest compression rate. The relationship of reduced compression depth at different compression rates was as follows: for a compression rate of 100 to 119/min, 35% of compressions had a depth of less than 3.8 cm; for a compression rate of 120 to 139/min, 50% of compressions had a depth of less than 3.8 cm; and for a compression rate of 140/min or greater, 70% of the compressions had a depth of < 3.8 cm.

TREATMENT RECOMMENDATIONS

The 2015 guidelines recommend a manual chest compression rate of 100 to 120/min.

Chest Compression Depth

During manual CPR, rescuers should perform chest compressions to a depth of at least 2 inches (5 cm) for an average adult, while avoiding excessive chest compression depths (> 2.4 inches [6 cm]).

The reason for emphasis on accurate chest compression depth is the following: compressions create blood flow primarily by increasing intrathoracic pressure and directly compressing the heart, which in turn results in critical blood flow and oxygen delivery to the heart and brain. Rescuers often do not compress the chest deeply enough despite the recommendation to “push hard.” Although a compression depth of at least 2 inches (5 cm) is recommended, the 2015 Guidelines Update, as previously noted, incorporates new evidence about the potential for an upper threshold of compression depth (> 2.4 inches [6 cm]) beyond which complications may occur. Compression depth may be difficult to judge without use of feedback devices, and identification of upper limits of

compression depth may be challenging.

For the critical outcome of survival to hospital discharge, 3 observational studies [16–18] suggest that survival may improve with increasing compression depth. In the largest study (9,136 patients), a covariate-adjusted spline analysis showed a maximum survival at a mean depth of 4.0 to 5.5 cm (1.6 to 2.2 inches), with a peak at 4.6 cm (1.8 inches).[18]

Another important study showed injuries were reported in 63% with compression depth of more than 6 cm (more than 2.4 inches) and 31% with compression depth of less than 6 cm. Injuries were reported in 28%, 27%, and 49% with compression depths of < 5 cm (< 2 inches), 5 to 6 cm (2 to 2.4 inches), and > 6 cm (> 2.4 inches), respectively.[19]

Treatment Recommendations

The 2015 guidelines recommend a chest compression depth of approximately 5 cm (2 inches) while avoiding excessive chest compression depths (> 6 cm [> 2.4 inches] in an average adult) during manual CPR.

Compression–Ventilation Ratio

The critical outcome of survival with favorable neurologic outcome at discharge was studied in two observational studies.[20, 21] Of the 1,711 patients included, those who were treated under the 2005 guidelines with a compression–ventilation ratio of 30:2 had slightly higher survival than those patients treated under the 2000 guidelines with a compression–ventilation ratio of 15:2 (8.9% vs. 6.5%; RR 1.37 [0.98–1.91]).

The critical outcome of survival to hospital discharge was tested in 4 observational studies.[20–23] Of the 4,183 patients included, those who were treated under the 2005 guidelines with a compression–ventilation ratio of 30:2 had slightly higher survival than those patients treated under the 2000 guidelines with a compression–ventilation ratio of 15:2 (11.0% vs. 7.0%; RR 1.75 [1.32–2.04]).

For the critical outcome of survival to 30 days, 1 observational study[24] found that patients treated under the 2005 guidelines had slightly higher survival than those patients treated under the 2000 guidelines (16.0% vs. 8.3%; RR 1.92 [1.28–2.87]).

For the critical outcome of any return of spontaneous circulation (ROSC), 2 observational studies [20, 21] found that patients treated under the 2005 guidelines

had a ROSC more often than those patients treated under the 2000 guidelines (38.7% vs. 30.0%; RR 1.30 [1.14–1.49]).

Treatment Recommendation

The 2015 guidelines suggest a compression–ventilation ratio of 30:2 compared with any other compression–ventilation ratio in patients in cardiac arrest.

Ventilation During Cardiopulmonary Resuscitation with Advanced Airway

The 2015 guidelines suggest that it may be reasonable for the provider to deliver 1 breath every 6 seconds (10 breaths per minute) while continuous chest compressions are being performed (ie, during CPR with an advanced airway).

Bystander Naloxone in Opioid-Associated Life-Threatening Emergencies

New for the 2015 guidelines is that for patients with known or suspected opioid addiction who are unresponsive with no normal breathing but a pulse, it is reasonable for appropriately trained lay rescuers and basic life support (BLS) providers to administer intramuscular (IM) or intranasal (IN) naloxone in addition to providing standard BLS care.

In 2014, the naloxone autoinjector was approved by the US Food and Drug Administration for use by lay rescuers and HCPs.[3]

Shock First Versus Cardiopulmonary Resuscitation First

Numerous studies have addressed the question of whether a benefit is conferred by providing a specified period (typically 1½ to 3 minutes) of chest compressions before shock delivery, as compared to delivering a shock as soon as the AED can be readied. No difference in outcome has been shown.

For witnessed adult cardiac arrest when an AED is immediately available, it is reasonable that the defibrillator be used as soon as possible. For adults with unmonitored cardiac arrest or for whom an AED is not immediately available, it is reasonable that CPR be initiated while the defibrillator equipment is being retrieved and applied and that defibrillation, if indicated, be attempted as soon as the device is ready for use.

CPR should be provided while the AED pads are applied and until the AED is ready to analyze the rhythm.

Chest Recoil

On the basis of the 2015 guidelines, it is reasonable for rescuers to avoid leaning on the chest between compressions, to allow full chest wall recoil for adults in cardiac arrest.

Figure 29.2 summarizes the new 2015 guidelines recommendations for a high-quality CPR.

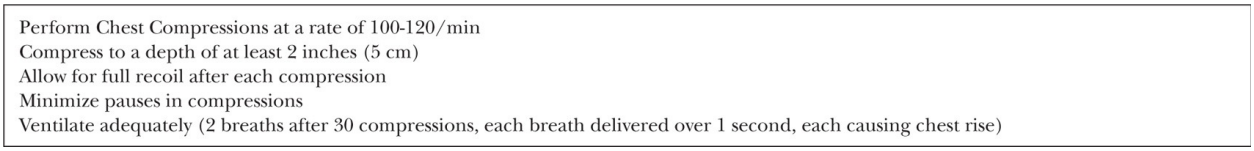


FIGURE 29.2 2015 guidelines recommendation for high-quality CPR.

ADVANCED LIFE SUPPORT

Mechanical Cardiopulmonary Resuscitation Devices

The 2015 updated guidelines recommend against the routine use of automated mechanical chest compression devices to replace manual chest compressions.[24]

For the critical outcome of survival to 1 year, 1 RCT[25] using the Lund University Cardiac Arrest System (LUCAS) device showed no benefit or harm when compared with manual chest compressions (survival 5.4% vs. 6.2%; RR, 0.87; 95% CI, 0.68–1.11).

For the critical outcome of survival to 180 days, 1 RCT[26] using a LUCAS device enrolling 2,589 OHCA patients showed no benefit or harm when compared with manual chest compressions when quality of chest compressions in the manual arm was not measured (survival 8.5% vs. 8.1%; RR, 1.06; 95% CI, 0.81–1.41).

Drugs During Cardiopulmonary Resuscitation

Epinephrine Versus Vasopressin

A single RCT[27] (n = 336) compared multiple doses of single- dose epinephrine (SDE) with multiple doses of standard-dose vasopressin in the ED after OHCA.

For the critical outcome of survival to discharge with favorable neurologic outcome (cerebral performance category [CPC] 1 or 2), there was no advantage with vasopressin (RR, 0.68; 95% CI, 0.25–1.82; P = 0.44).

For the important outcome of ROSC, there was no observed advantage with

vasopressin (RR, 0.93; 95% CI, 0.66–1.31; *P* = 0.67).

The 2015 guidelines suggest vasopressin should not be used instead of epinephrine in cardiac arrest.[24]

Epinephrine Versus Vasopressin in Combination with Epinephrine

For the critical outcome of survival to hospital discharge with CPC of 1 or 2, 3 RCTs [28–30] (*n* = 2,402) comparing SDE with vasopressin and epinephrine combination therapy showed no superiority with vasopressin and epinephrine combination (RR, 1.32; 95% CI, 0.88–1.98).

For the important outcome of ROSC, 6 RCTs [28–33] showed no ROSC advantage with vasopressin and epinephrine combination therapy (RR, 0.96; 95% CI, 0.89–1.04; *P* = 0.31).

The 2015 guidelines suggest against adding vasopressin to SDE during cardiac arrest.

Single-Dose Epinephrine Versus High-Dose Epinephrine

In adult patients in cardiac arrest in any setting, high-dose epinephrine (HDE) (at least 0.2 mg/kg or 5 mg bolus dose) was compared with SDE (1 mg bolus dose).

For the critical outcome of survival to hospital discharge with CPC 1 or 2, 2 RCTs comparing SDE with HDE [34, 35] (*n* = 1,920) did not show advantage with HDE (RR, 1.2; 95% CI, 0.74–1.96).

For the critical outcome of survival to hospital discharge, 5 RCTs comparing SDE with HDE (*n* = 2,859) did not show any survival to discharge advantage with HDE (RR, 0.97; 95% CI, 0.71–1.32).

The 2015 guidelines recommend against the routine use of HDE in cardiac arrest (weak recommendation, low-quality evidence).

Timing of Administration of Epinephrine

IN-HOSPITAL CARDIAC ARREST

For IHCA, for the critical outcome of survival to hospital discharge, one observational study[36] in 25,095 IHCA patients with a nonshockable rhythm showed an improved outcome with early administration of epinephrine. Compared to the reference interval of 1 to 3 minutes, adjusted OR for survival to discharge was 0.91 (95% CI, 0.82–1.00) when epinephrine was given after 4 to 6 minutes, 0.74 (95% CI, 0.63–0.88) when given after 7 to 9 minutes, and 0.63 (95% CI, 0.52–0.76) when given at more than 9 minutes after onset of arrest.

For IHCA, for the critical outcome of neurologically favorable survival at hospital discharge, an improved outcome was observed from early administration of epinephrine: compared with the reference interval of 1 to 3 minutes, adjusted OR was 0.93 (95% CI, 0.82–1.06) when epinephrine was given after 4 to 7 minutes, 0.77 (95% CI, 0.62–0.95) when given after 7 to 9 minutes, and 0.68 (95% CI, 0.53–0.86) when given at more than 9 minutes after onset of arrest.

For IHCA, for the important outcome of ROSC, an improved outcome from early administration of epinephrine: adjusted OR compared with reference interval of 1 to 3 minutes of 0.90 (95% CI, 0.85–0.94) when given after 4 to 7 minutes, 0.81 (95% CI, 0.74–0.89) when given after 7 to 9 minutes, and 0.70 (95% CI, 0.61–0.75) when given after 9 minutes.

Out-of-Hospital Cardiac Arrest

For the critical outcome of neurologically favorable survival at hospital discharge (assessed with CPC 1 or 2), 4 observational studies [37–40], involving more than 262,556 OHCAs, showed variable benefit from early administration of epinephrine.

For the important outcome of ROSC, there was very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 4 observational studies, 38,41–43 of more than 210,000 OHCAs, showing an association with improved outcome and early administration of adrenaline. One study[42] showed increased ROSC for patients receiving the first vasopressor dose early (<10 vs. >10 minutes after EMS call): OR, 1.91 (95% CI, 1.01–3.63).

The 2015 guidelines recommendations for cardiac arrest with an initial nonshockable rhythm are that if epinephrine is to be administered, it should be given as soon as possible after the onset of the arrest.

Antiarrhythmic Drugs for Cardiac Arrest

Antiarrhythmic drugs can be used during cardiac arrest for refractory ventricular dysrhythmias. Refractory VF/pVT is defined differently in many trials but generally refers to failure to terminate VF/pVT with 3 stacked shocks, or with the first shock.

For the important outcome of ROSC, 1 RCT, involving 504 OHCA patients, showed higher ROSC with administration of amiodarone (300 mg after 1 mg of adrenaline) compared with no drug (64% vs. 41%; $P = 0.03$; RR, 1.55; 95% CI, 1.31–1.85).[44]

The 2015 guidelines recommendations for antiarrhythmia drugs for cardiac arrest suggest the use of amiodarone in adult patients with refractory VF/pVT to improve rates of ROSC.

The guidelines also suggest the use of lidocaine or nifekalant (a Class III antiarrhythmic drug) as an alternative to amiodarone in adult patients with refractory VF/pVT.

The 2015 guidelines recommend against the routine use of magnesium in adult patients.

CARDIOCEREBRAL RESUSCITATION

Brief History of Therapeutic Hypothermia

The use of therapeutic hypothermia (TH) to mitigate various types of injury, in particular, posthypoxic injury to the brain, has been studied since the late 1930s.[45] Interest was initially kindled by reports of survival after prolonged exposure to cold, or submersion in ice-cold water, indicating a possible protective effect of low temperature on hypoxic injuries.[46]

Use of hypothermia after cardiac arrest was first described in the late 1950s [47, 48], but proof that hypothermia could improve outcome in these patients remained elusive. [49, 50] At the time it was thought that protective effects of TH were purely a result of hypothermia-induced lowering of metabolism; therefore, it was presumed that very low temperatures (25–28°C) were needed to provide significant neuroprotection.

This perception changed in the late 1980s, when animal studies demonstrated that significant protective effects also occurred with mild hypothermia (30–34°C), with far fewer side effects, and that a variety of destructive mechanisms were moderated by hypothermia rather than just reductions in brain metabolism.[49] In the late 1990s, a number of small nonrandomized, clinical trials provided better evidence for the efficacy of TH. [51–54] This led to the initiation of 2 landmark multicenter RCTs to test TH treatment, the results of which were published side by side in 2002. [55, 56] Both reported clear and significant improvements in outcome in cardiac arrest patients treated with therapeutic cooling.

The largest study, performed in 11 centers in Europe, enrolled 275 patients with witnessed cardiac arrest and an initial rhythm of VF or pulseless VT. The authors observed a 15.8% absolute (35.1% relative) improvement in outcome in

the hypothermia group ($P < 0.01$).[55] The other RCT enrolled 77 patients across 4 centers in Australia, reporting an absolute improvement of 22.3% (relative improvement of 43.7%) in patients with witnessed VT/VF treated with hypothermia compared with controls ($P < 0.05$).[56] A meta-analysis calculated that 1 additional case of good neurologic outcome would be gained for every 6 patients treated with TH.[57] Guidelines from various medical societies such as the AHA, European Resuscitation Council (ERC), and Neurocritical Care Society (NCS) began recommending cooling after cardiac arrest. [58, 59]

A larger RCT, the Therapeutic Temperature Management (TTM) study, compared temperature management at 33.0°C to maintaining a core temperature of 36.0°C.[60] The study enrolled 939 patients with witnessed cardiac arrest regardless of initial rhythm, including those with persistent hypoxia and hypotension who had been excluded from previous studies, with predefined subgroup analyses to correct for various risk factors. The results of this study were negative.[60] Rates of survival with good neurologic outcome were 46.5% in the 33°C group versus 47.8% in the 36°C group ($P = 0.78$). The rate of survival with excellent outcome (no neurologic residual) was 41.6% versus 39.4%, whereas survival with mild neurologic impairment was 4.9% versus 8.4%.[60] The authors concluded that maintaining core temperature at 36°C has equally good outcomes as cooling to 33°C.

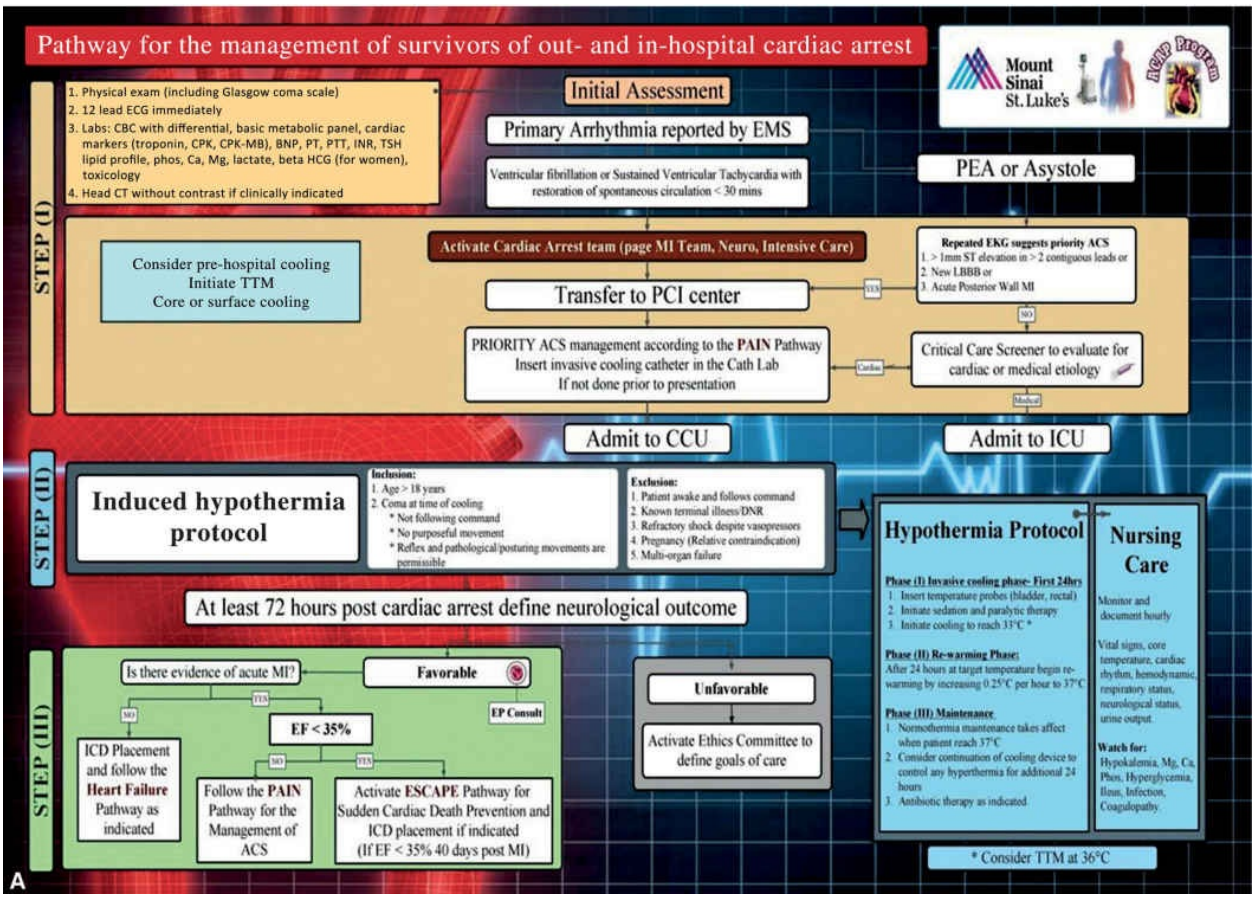
Pathways for the Management of Survivors of Out of and In-Hospital Cardiac Arrest

At our institution, similar to many tertiary medical centers, algorithms for the management of patients post–cardiac arrest have been developed.

Our first algorithm was published in 2010.[61] We continue to update it, as new scientific information and updated guidelines are published.[62]

The term therapeutic hypothermia has now been replaced with targeted temperature management(TTM).

Our 2015 updated TTM pathway is shown in **Figure 29.3A**.


Pathway for the management of survivors of out- and in-hospital cardiac arrest
Mount Sinai St. Luke's
ACHP Program
STEP (I)
1. Physical exam (including Glasgow coma scale)
2. 12 lead ECG immediately
3. Labs: CBC with differential, basic metabolic panel, cardiac markers (troponin, CPK, CPK-MB), BNP, PT, PTT, INR, TSH lipid profile, phos, Ca, Mg, lactate, beta HCG (for women), toxicology
4. Head CT without contrast if clinically indicated
Initial Assessment
Primary Arrhythmia reported by EMS
Ventricular fibrillation or Sustained Ventricular Tachycardia with restoration of spontaneous circulation < 30 mins
PEA or Asystole
Consider pre-hospital cooling
Initiate TTM
Core or surface cooling
Activate Cardiac Arrest team (page MI Team, Neuro, Intensive Care)
Repeated EKG suggests priority ACS
1. > 1mm ST elevation in > 2 contiguous leads or
2. New LBBB or
3. Acute Posterior Wall MI
YES
NO
Transfer to PCI center
PRIORITY ACS management according to the PAIN Pathway
Insert invasive cooling catheter in the Cath Lab
If not done prior to presentation
Cardiac
Critical Care Screener to evaluate for cardiac or medical etiology
Medical
Admit to CCU
Admit to ICU
STEP (II)
Induced hypothermia protocol
Inclusion:
1. Age > 18 years
2. Coma at time of cooling
* Not following command
* No purposeful movement
* Reflex and pathological/posturing movements are permissible
Exclusion:
1. Patient awake and follows command
2. Known terminal illness/DNR
3. Refractory shock despite vasopressors
4. Pregnancy (Relative contraindication)
5. Multi-organ failure
Hypothermia Protocol
Phase (I) Invasive cooling phase- First 24hrs
1. Insert temperature probes (bladder, rectal)
2. Initiate sedation and paralytic therapy
3. Initiate cooling to reach 33°C *
Phase (II) Re-warming Phase:
After 24 hours at target temperature begin re-warming by increasing 0.25°C per hour to 37°C
Phase (III) Maintenance
1. Normothermia maintenance takes affect when patient reach 37°C
2. Consider continuation of cooling device to control any hyperthermia for additional 24 hours
3. Antibiotic therapy as indicated
Nursing Care
Monitor and document hourly
Vital signs, core temperature, cardiac rhythm, hemodynamic, respiratory status, neurological status, urine output
Watch for:
Hypokalemia, Mg, Ca, Phos, Hyperglycemia, Ileus, Infection, Coagulopathy.
* Consider TTM at 36°C
At least 72 hours post cardiac arrest define neurological outcome
STEP (III)
Is there evidence of acute MI?
Favorable
EP Consult
NO
YES
EF < 35%
ICD Placement and follow the Heart Failure Pathway as indicated
Follow the PAIN Pathway for the Management of ACS
Activate ESCAPE Pathway for Sudden Cardiac Death Prevention and ICD placement if indicated (If EF < 35% 40 days post MI)
Unfavorable
Activate Ethics Committee to define goals of care
A

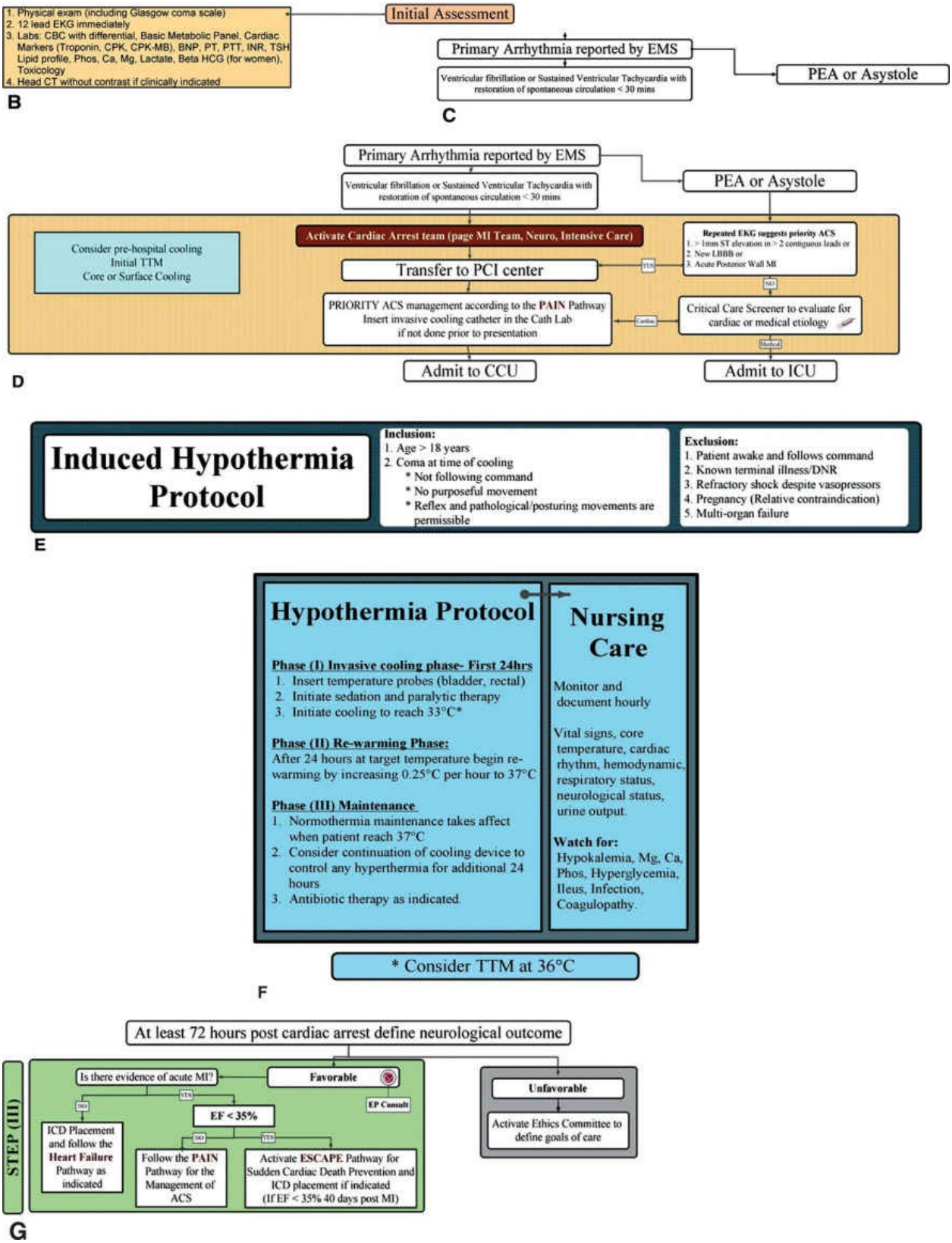


FIGURE 29.3 A, Pathway for management of survivors of out-of- and in-hospital cardiac arrest. B, Initial

assessment of patients who survive an out-of-hospital cardiac arrest. C, Identification of the primary arrhythmia that led to the cardiac arrest. D, Activation of the cardiac arrest team, transfer to percutaneous coronary intervention (PCI) center, and transfer to the critical care unit. E, Inclusion and exclusion criteria for patients who are candidates for the therapeutic hypothermia protocol. F, Induced therapeutic hypothermia protocol. G, Management of the post–rewarming phase including the recommendation for out-of-hospital therapy and the ethical decision to define goal of care.

The pathway is divided into three steps.

- Step I. From the field through the ED into the cardiac catheterization laboratory and to the critical care unit.
- Step II. Induced hypothermia protocol in the critical care unit.
- Step III. The management following the rewarming phase, including the recommendation for out-of-hospital therapy and the ethical decision to define goals of care.

STEP I

Presentation to the emergency department, proceeding to the cardiac catheterization laboratory and to the critical care unit.Upon arrival of a survivor of OHCA at the ED, the initial assessment (**Fig. 29.3B**) includes vital signs, physical examination, and neurologic examination with Glasgow coma score. Immediate 12-lead ECG is obtained and laboratory testing performed.

Initial laboratory testing includes complete blood count (CBC) with differential, basic metabolic panel, cardiac marker (troponin, CPK, CPK-MB), B-type natriuretic peptide (BNP), prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), lipid profile, phosphorus, calcium, magnesium, lactate, ß-HCG (for women), TSH, and toxicology screening. We recommend a head CT without contrast only if it is clinically indicated and will not delay transfer to the cardiac catheterization laboratory.

The patient is stabilized in the ED, where antiarrhythmic and vasopressor therapy may be administered, in addition to ventilator support.

The ED physician receives the emergency medical services (EMS) report of the primary rhythm and duration of cardiopulmonary resuscitation (CPR). This reported arrhythmia is the key decision point in our pathway.

The prognostically important distinction is between patients with documented VF or sustained VT who had a restoration of spontaneous circulation (ROSC) in <30 minutes and patients with reported asystole or pulseless electrical activity (PEA) (**Figure 29.3C**).

1. If the initial rhythm was VF or VT with an ROSC of ≤30 minutes, the cardiac arrest team is activated, and the patient will proceed to the cardiac catheterization laboratory (**Figure 29.3D**).
2. If the initial reported arrhythmia was PEA or asystole, the next step will depend on the ECG performed in the ED. If the ECG performed in the ED is suggestive of priority acute coronary syndrome (ACS), including ST elevation myocardial infarction (STEMI), left bundle branch block, or acute posterior wall MI, the MI team should be activated, and the care is similar to those patients with reported VF or VT arrest.
3. If priority ECG findings are not seen but the etiology of the arrest is most likely due to primary cardiac disease, the cardiology fellow will admit the patient to the cardiac care unit. We recommend an emergency echocardiogram.
4. If the etiology is likely noncardiac, the patient will be admitted to the medical ICU.

The cardiac arrest team includes the following 10 people.

The traditional (acute coronary syndrome) ACS-MI team comprises the following members:

1. Interventional cardiologist on-call team leader
2. Coronary care unit (CCU) director
3. Cardiology fellow on-call
4. Interventional cardiology fellow on-call
5. Cath lab nurse on-call
6. Cath lab technician on-call
7. CCU nurse manager on-call

In addition, the following personnel form the team:

8. The neurologist on-call
9. The critical care attending on-call
10. The medical resident screener

The MI team is activated by a single page to the central call center by the ED physician.

STEPS IN THE EMERGENCY DEPARTMENT

1. Decision to initiate induced hypothermia is made jointly by the ED physician and the cardiology or critical care physician. It is very important to review the hospital center's inclusion and exclusion criteria and decide whether the patient is a candidate for the TH protocol (**Figure 29.3E**).
2. The physician places an order to initiate hypothermia protocol.

Our goal is to transfer the patient to the percutaneous coronary intervention (PCI) center as soon as possible with a target door-to-balloon time of <90 minutes.

The management of the patient at this point is according to our Priority risk, Advanced risk, Intermediate risk, and Negative/low risk (PAIN) pathway following the priority ACS algorithm.[63]

Following cardiac catheterization, several steps occur while the patient is still in the catheterization laboratory:

1. The femoral arterial sheath can be maintained as an arterial catheter, which may be necessary to obtain blood pressure readings and arterial blood gas analyses.
2. The intravascular hypothermia catheter is inserted under strict aseptic technique (if it was not done earlier).

All patients are then transferred from the catheterization laboratory to the CCU where invasive hypothermia is initiated.

STEP II

Induced TH protocol in the critical care unit. The clinicians review the case and confirm the appropriateness of induced hypothermia (**Figure 29.3E**).

In summary, we recommend induced hypothermia for patients >18 years of age, who sustained a cardiac arrest and remain in coma. The patient must be comatose, not following commands or demonstrating purposeful movements. Patients excluded from the hypothermia protocol include patients who are awake, suffered prolonged ischemic times, experience refractory shock, demonstrate multiorgan failure, or have severe underlying illnesses, including terminal illnesses and do-not-resuscitate (DNR) status.

The hypothermia protocol is divided into three phases, as seen in **Figure 29.3F**:

Phase 1: Cooling phase for the first 24 hours

Phase 2: Rewarming phase

Phase 3: Maintenance phase

Phase 1: Cooling phase for the first 24 hours. We recommend 24 hours of the cooling therapy at a temperature goal of 33°C.

As will be discussed later in this chapter, the dose of the temperature management is controversial, and some centers cool patients to 36°C.

Endovascular catheters are an effective method of inducing TH (if a core cooling method is chosen). The catheters are usually inserted into the inferior vena cava through the femoral vein.

Continuous core temperature monitoring is required and generally accomplished using a temperature probe in the bladder (urinary catheter) or the rectum.

Monitoring of clinical condition and potential complications during the cooling phase.

As there are many physiologic effects of hypothermia, we recommend continuous monitoring and hourly documentation of vital signs; core temperature; cardiac rhythm; hemodynamic, respiratory, neurology status; and urine output. Common hemodynamic changes observed with cooling include hypertension, decreased cardiac output, and increased systemic vascular resistance. The hypertension and the increased systemic vascular resistance are believed to result from the cold-induced vasoconstriction.

Serum electrolyte imbalance is common during the cooling phase and results from the cooling-induced intracellular shifts of potassium, magnesium, calcium, and phosphate, leading to low levels of all these electrolytes. During the rewarming phase, these electrolytes shift back to the extracellular space.

Our protocol therefore recommends measurements of the basic metabolic panel every 4 hours for a total of 48 hours, measuring electrolytes (calcium, magnesium, and phosphate) PT, PTT, and INR, and a CBC every 12 hours up to 48 hours.

Additional possible side effects of cooling to be monitored include the following:

1. *Coagulopathy.* Coagulopathy is generally not significant with careful temperature monitoring and avoiding temperature of <33°C. If active bleeding occurs during the cooling phase, evaluation of coagulation factors and platelets should be performed and deficiencies corrected.
2. *Hyperglycemia. Hypothermia suppresses insulin release and causes insulin*

resistance. Our insulin infusion protocol for the management of hyperglycemia in critical care unit is used.[64]

3. *Infection.* Infection is usually multifactorial, including emergency intubation and intravenous catheter insertion and aspiration pneumonia at the time of arrest.

Furthermore, the hypothermia itself can suppress white blood cell production and impairs neutrophil and macrophage function. All measures to reduce ventilator-associated pneumonia are employed, including elevating the head of the bed.

4. *Shivering.* Our protocol aims to prevent shivering by administration of sedation and neuromuscular blocking agents on induction of hypothermia.

Phase 2: Rewarming phase. After 24 hours of the target temperature, the rewarming phase starts.

Controlled rewarming is a very important phase of this protocol.

Rewarming should be slow; at a rate of 0.25°C per hour, which we recommend, it typically requires 16 hours to rewarm to 37°C.

Potential complications during the rewarming phase include the following:

1. Hypotension—owing to peripheral vasodilation during the rewarming phase.
2. Electrolyte imbalance—increased levels of potassium, magnesium, calcium, and phosphate caused by intracellular shifting of these ions back to the serum during the rewarming phase.

Phase 3: Maintenance of normothermia phase. The maintenance phase is the last phase of the TH protocol.

Normothermia maintenance takes effect when the patient's temperature reaches 37°C.

We recommend continuation of the cooling device to maintain a temperature of 37°C and avoidance of fever that can potentially worsen a cerebral injury.

The duration of the additional maintenance phase is usually between 24 and 48 hours.

STEP III

The management following hypothermia and rewarming depends on the neurologic prognosis (**Figure 29.3G**).

At least 72 hours after cardiac arrest, the neurologic examination is performed by the neurology team. The neurologic examination may be affected by the

hypothermia protocol, including requirements for sedation and therapeutic paralysis, so the formulation of a neurologic prognosis may be delayed. In general, we defer neurologic prognostication until 6 days postarrest in patients undergoing hypothermia protocol.

Pathways for the patients will divide depending on whether the patient has a favorable neurologic prognosis or an unfavorable neurologic prognosis. An unfavorable neurologic prognosis would be defined as expectation of a persistent coma or vegetative state, or severe disability.

If the prognosis appears unfavorable, we recommend activating the ethics committee to meet with the family and clinicians to define the goals of care. From our experience, in most instances, life support is limited or withdrawn in such patients.

If the neurologic prognosis appears favorable, then the key question regarding further therapy is based on whether the cardiac arrest was because of MI.

If there is no evidence of acute MI (negative cardiac markers), then we recommend electrophysiology service consultation for consideration of implantable cardioverter defibrillator (ICD) placement and treatment of heart failure based on our heart failure pathway.[65]

If acute MI is confirmed by positive cardiac markers, we advise care based on the LV ejection fraction (LVEF) as it is defined by echocardiography or other imaging modalities. If LVEF ≤35%, we recommend activation of the ESCAPE pathway for sudden cardiac death prevention[66] and to consider ICD placement if EF ≤35% at 40 days post-MI. Also, we recommend managing heart failure according to our heart failure pathway.[65]

If EF >35%, we recommend following our PAIN pathway for the management of ACS,[63] including the following:

- Lifestyle modification
- Cardiac rehabilitation
- Secondary prevention medication (dual oral antiplatelet, ß-blocker, high-dose statin, ACE inhibitor/ARB)

Unresolved Practical Questions Regarding TTM

How Low Should We Go?

As mentioned earlier, the TTM study compared temperature management at 33°C to maintaining a core temperature of 36°C[60] and concluded that

maintaining core temperature at 36°C has outcomes that are as good as cooling to 33°C.

This observation seems to contradict the findings of all previous studies and may have been a result of selection bias.

Our group hypothesizes that a potential difference in outcome based on degree of cooling will depend on the severity of brain injury.

Our group opinion regarding this difference in outcome depending on the selection of patients for TTM appears in **Figure 29.4**.

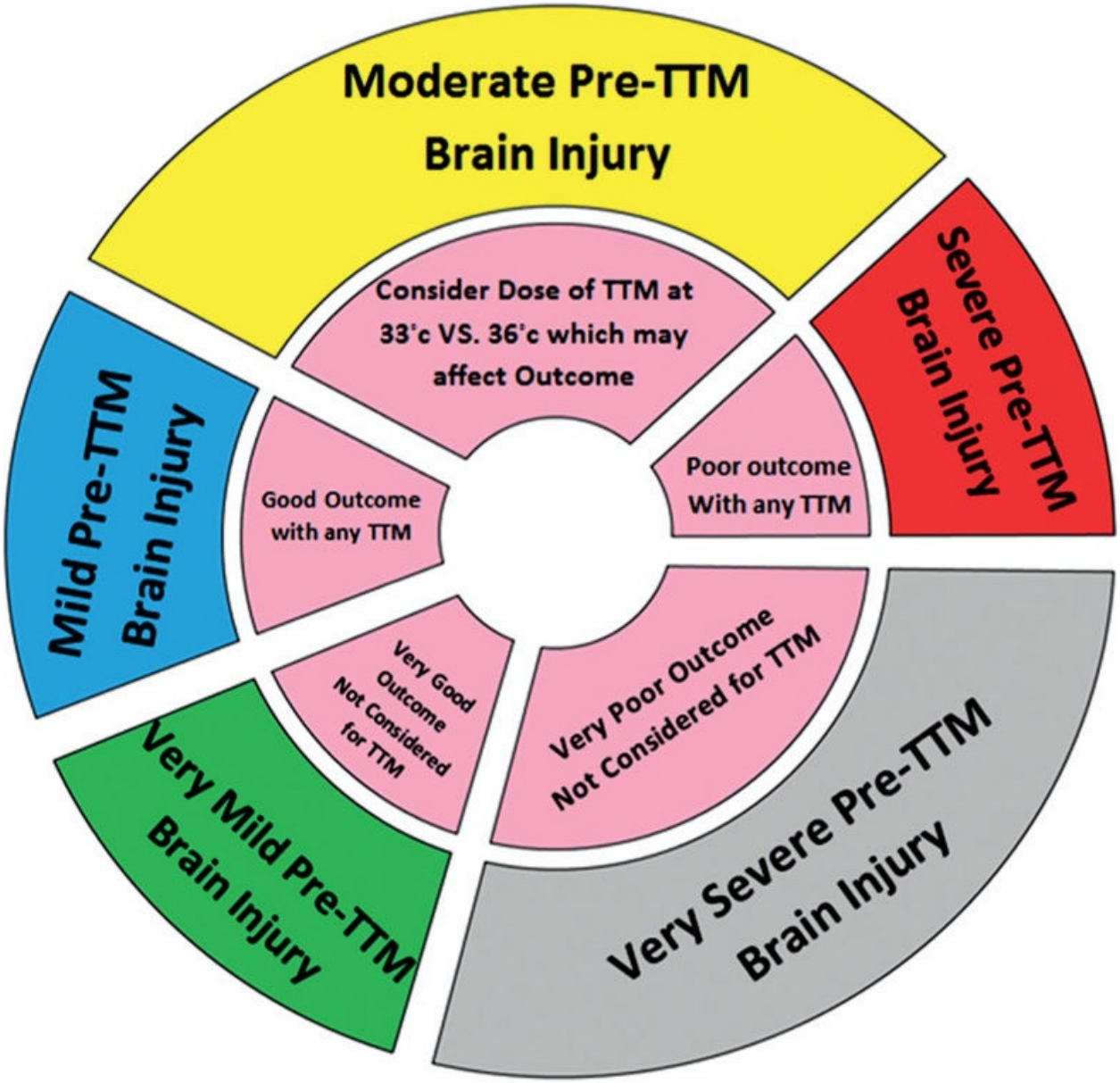


FIGURE 29.4 Degree of postarrest brain injury and proposed decision for Therapeutic Temperature

Management (TTM).

As seen in this figure, we can divide patients who survive cardiac arrest into 5 groups based on the degree of their postarrest brain injury.

1. Very severe brain injury
2. Severe brain injury
3. Moderate brain injury
4. Mild brain injury
5. Very minimal brain injury

Patients who fall into the first or the last category are unlikely to be considered for TTM in any health care system (as seen in the lower half of the figure).

- Patients who fall into groups 2, 3, and 4 are expected to have variable outcome.
- Patients in group 2, with severe brain injury, are expected to have poor outcome with any TTM.
- Patients in group 4 with mild brain injury are expected to have a good outcome with any TTM.

However, for patients in group 3, with moderate brain injury, the dose of TTM may affect outcome.

Our hypothesis is derived by applying Baye's theorem to the relationship between post-TTM degree of brain injury and pre-TTM degree of brain injury.

Our hypothesis is seen in **Figure 29.5**.

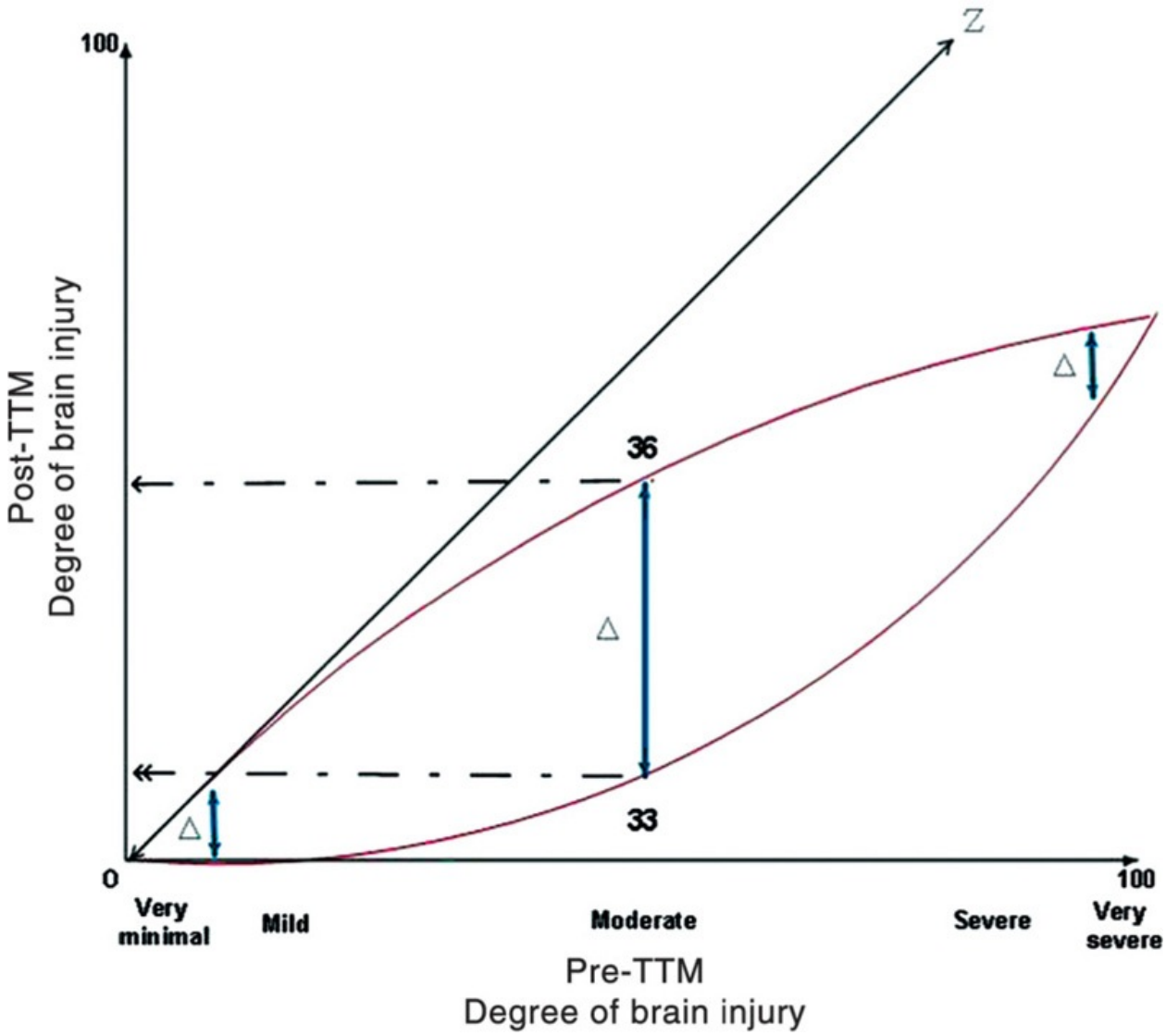


FIGURE 29.5 Applying Bayes' theorem to the relationship between post-TTM degree of brain injury and pre-TTM degree of brain injury. TTM, therapeutic temperature management.

In this figure, we have plotted the pre-TTM degree of brain injury on the x-axis, with score of 0 to 100 and the **post-TTM** degree of brain injury on the y-axis with score of 0 to 100, where a score of 0 mean no brain injury, and a score of 100 means irreversible brain injury.

As outlined earlier, we have five groups of patients based on their severity of brain injury:

- Very minimal, mild, moderate, severe, and very severe.
- The equivocal line (Z) represents where the pretreatment group brain injury is exactly the same as the posttreatment group brain injury.

- The other two lines represent the different temperature doses of 33°C and 36°C.
- It is the delta (Δ) between these lines that defines whether the therapy has potential benefits.

On the left end of this figure, the delta is very small for patients with very minimal or mild brain injury.

This is the same case for patients with severe or very severe brain injury where the delta between the two doses of therapy is very small.

However, for patients with moderate brain injury, the delta is quite large. In our hypothesized algorithm, there is a potential to reduce the post-TTM degree of brain injury from a high to a low score.

On the basis of this hypothesis, our group suggests that the dose of temperature management should be 33°C because it is difficult prognostically to determine moderate brain injury level.

We have to remember that this is only a hypothesis and larger studies enrolling solely patients with moderate brain injury should be conducted.

Our group believes that the Achilles heel of the field of TTM is our current limitations in the prognostication of postarrest brain injury.

Endovascular Versus Surface Cooling

Technologies can be broadly divided into invasive (core cooling) and noninvasive (surface cooling) methods.[67]

There is no evidence for a difference in outcome based on cooling method.

The advantages of invasive cooling over surface cooling are:

1. Greater speed of hypothermia/normothermia induction when core cooling is used; however, it is unclear whether more rapid induction improves outcome.
2. Fewer and smaller temperature fluctuations in the maintenance phase.
3. Continuous central temperature measurement in some types of endovascular catheter is possible.
4. No risk of surface cooling–induced skin lesions.
5. Ease of accessibility to patient, that is, no need to cover large areas of the skin to achieve cooling.
6. Less medication may be needed to control shivering because there is more effective shivering suppression with skin counterwarming (ie, the entire surface area can be warmed using warm air, leading to a significantly

diminished shivering response). [49,68,69]

The advantages of surface cooling over invasive cooling are as follows:

1. Ease of use; can be applied by nurses without the need for a physician to be present.
2. No invasive procedure required; therefore, no risk of mechanical complications.
3. Can be started immediately, without waiting for catheter insertion procedure, so potentially less delay in initiation of cooling.
4. No risk of catheter-induced thrombus formation.
5. Can be more easily applied outside the ICU setting.

A study by Deye and coworkers compared endovascular to surface cooling in a prospective, multicenter RCT.[70] The authors enrolled 400 patients; 203 were treated with endovascular cooling (using Zoll femoral Icy catheters) and 197 with external cooling (ice packs, fans, and a homemade tent). The main findings were as follows: significantly shorter time to target temperature (33°C), greater stability of temperature (defined as time within target ±1°C) in the maintenance phase, and reduced nursing workload (10 vs. 38 minutes, $P < 0.001$) in the endovascular group; more minor side effects in the endovascular group ($P = 0.009$); a nonsignificant trend toward more favorable outcome at 28 days (36.0% vs. 28.4%, OR 1.41 [0.93–2.16], $P = 0.107$; for shockable rhythm 53.7% vs. 37.1%, OR 1.97 [0.99–3.9], $P = 0.269$) and at 90 days (34.6% vs. 26.0%, OR 1.51 [0.96–2.35], $p = 0.07$) in the endovascular group; and fewer cases of severe overshoot (below 30°C) in the endovascular group ($n = 0$ vs. $n = 3$).[70] Strict fever control was maintained for a minimum of 3 days following rewarming in both groups.

This study had some limitations, especially the fact that newer and more powerful surface cooling devices such as the Arctic Sun system were not used and surface cooling was accomplished using fairly basic tools and devices.

We believe that the cooling method should be determined by institutional protocol.

Highlights from the 2015 Guidelines Recommendation for Post–Cardiac Arrest Care

Out-of-Hospital Cooling

Based on the 2015 guidelines: The routine prehospital cooling of patients with rapid infusion of cold IV fluids after ROSC is not recommended.[24]

Hemodynamic Goals After Resuscitation

It may be reasonable to avoid and immediately correct hypotension (systolic blood pressure < 90 mm Hg, mean arterial pressure < 65 mm Hg) during post–cardiac arrest care.[24]

Why: Studies of patients after cardiac arrest have found that a systolic blood pressure of < 90 mm Hg or a mean arterial pressure of < 65 mm Hg is associated with higher mortality and diminished functional recovery, whereas systolic arterial pressures of > 100 mm Hg are associated with better recovery. Although higher pressures appear superior, specific systolic or mean arterial pressure targets could not be identified because trials typically studied a bundle of many interventions, including hemodynamic control. Also, because baseline blood pressure varies from patient to patient, different patients may have different requirements to maintain optimal organ perfusion.

Early Coronary Angiography

Based on the 2015 guidelines: Coronary angiography should be performed emergently (rather than later in the hospital stay or not at all) for OHCA patients with suspected cardiac etiology of arrest and ST elevation on ECG. Emergency coronary angiography is reasonable for select (eg, electrically or hemodynamically unstable) adult patients who are comatose after OHCA of suspected cardiac origin but without ST elevation on ECG. Coronary angiography is reasonable in post–cardiac arrest patients for whom coronary angiography is indicated, regardless of whether the patient is comatose or awake.[24]

Targeted Temperature Management

All comatose (ie, lacking meaningful response to verbal commands) adult patients with ROSC after cardiac arrest should have TTM, with a target temperature between 32°C and 36°C selected and achieved, then maintained constantly for at least 24 hours.[24]

Continuing Temperature Management Beyond 24 Hours

Actively preventing fever in comatose patients after TTM is reasonable. In

observational studies, fever after rewarming from TTM is associated with worsened neurologic injury, although studies are conflicting. Because preventing fever after TTM is relatively benign and fever may be associated with harm, preventing fever is suggested.[24]

Prognostication After Cardiac Arrest

The earliest time to prognosticate a poor neurologic outcome using clinical examination in patients not treated with TTM is 72 hours after cardiac arrest, but this time can be even longer after cardiac arrest if the residual effect of sedation or paralysis is suspected to confound the clinical examination.[24]

Why: Clinical findings, electrophysiologic modalities, imaging modalities, and blood markers are all useful for predicting neurologic outcome in comatose patients, but each finding, test, and marker is affected differently by sedation and neuromuscular blockade. In addition, the comatose brain may be more sensitive to medications, and medications may take longer to metabolize after cardiac arrest. No single physical finding or test can predict neurologic recovery after cardiac arrest with 100% certainty. Multiple modalities of testing and examination used together to predict outcome after the effects of hypothermia and medications have been allowed to resolve are most likely to provide accurate prediction of outcome.

Organ Donation

All patients who are resuscitated from cardiac arrest but who subsequently progress to death or brain death should be evaluated as potential organ donors. Patients who do not achieve ROSC and who would otherwise have resuscitation terminated may be considered potential kidney or liver donors in settings where rapid organ recovery programs exist.[24]

Why: No difference has been reported in immediate or long-term function of organs from donors who reach brain death after cardiac arrest when compared with donors who reach brain death from other causes. Organs transplanted from these donors have success rates comparable to organs recovered from similar donors with other conditions.

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May Bakir

Principles of Antiarrhythmic Drug Therapy

INTRODUCTION

Ion channels in cardiac cells that generate the action potential are the basis for most arrhythmias. Thus, it is critical to know their function in order to understand the mechanisms of most arrhythmias and their treatment.[1]

The action potential is a representation of the changes in voltage of a single cardiac cell plotted over time.

There are five phases of the normal action potential ***(Figure 30.1)***[2]*:*

1. **Phase (4):** is the resting potential, which is stable at –90 mV in working myocardial cells. It is principally permeable to potassium ions.
2. **Phase (0):** is the rapid depolarization where there is a rapid increase in sodium permeability that forces the membrane potential into the positive range.
3. **Phase (1):** is the initial repolarization phase of the action potential, which is the result of a rapid decline in the sodium permeability and increase in potassium and chloride ions permeability.
4. **Phase (2):** is the plateau phase of the action potential, which is the result of a

balance of residual inward sodium and calcium currents and outward components of current carried by potassium ions.

5. **Phase (3):** is the phase of rapid repolarization, which is the result of a sustained increase in potassium permeability.

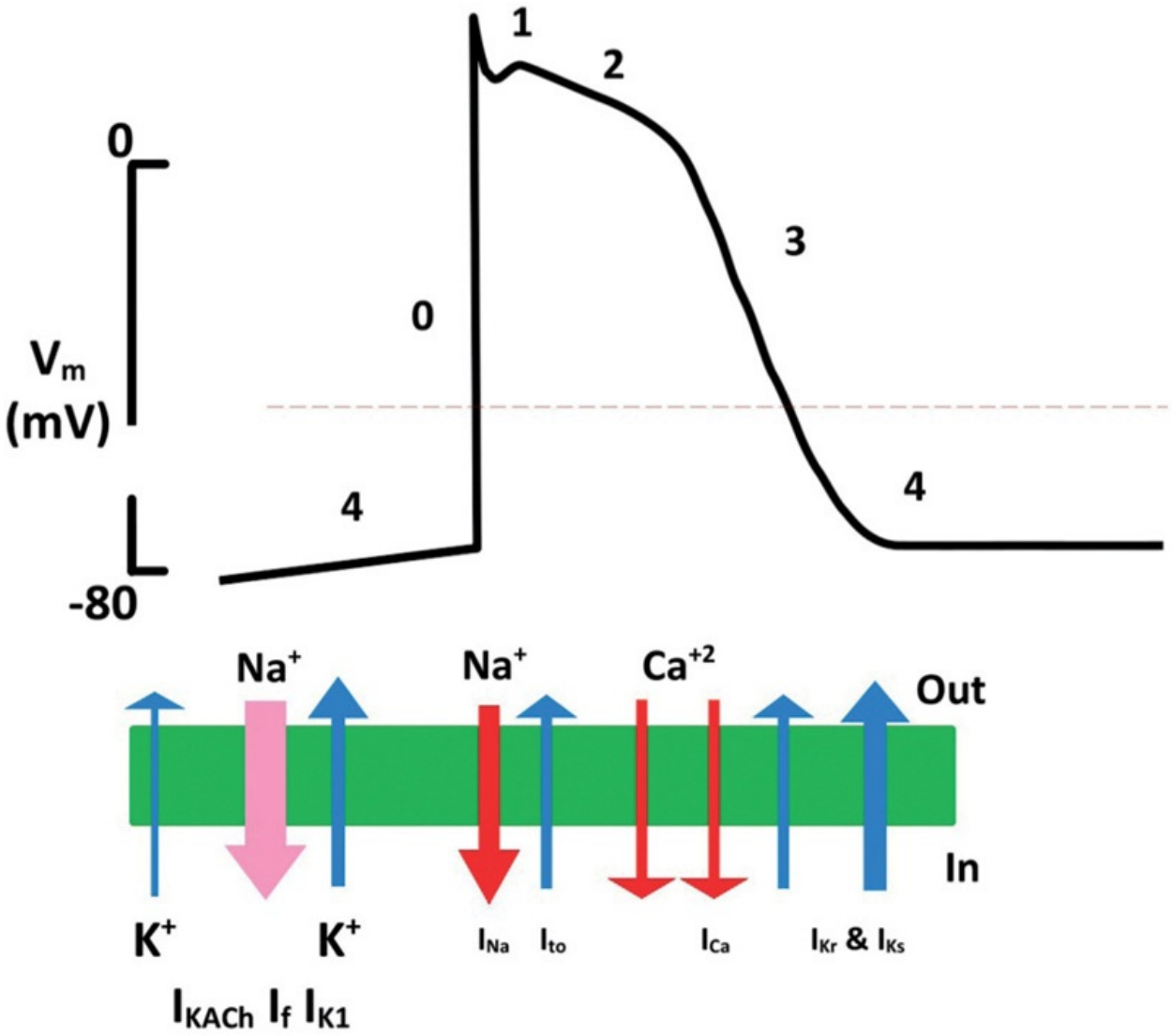


FIGURE 30.1 Action potential of cardiac cell depicting phases and ion movement across cell membrane. Downward arrows mark inward current; upward arrows mark outward current.

The pacemaker cells in the sinoatrial (SA) and atrioventricular (AV) nodes have significantly different action potential from the myocardial cells (**Figure 30.2**). Typically, phase (4) is resting at –50 mV and undergoes a slow depolarization that merges into phase (0). This is the effect of hyperpolarization-

activated current, I_F. Depolarization is much slower as a result of calcium ion carriers.

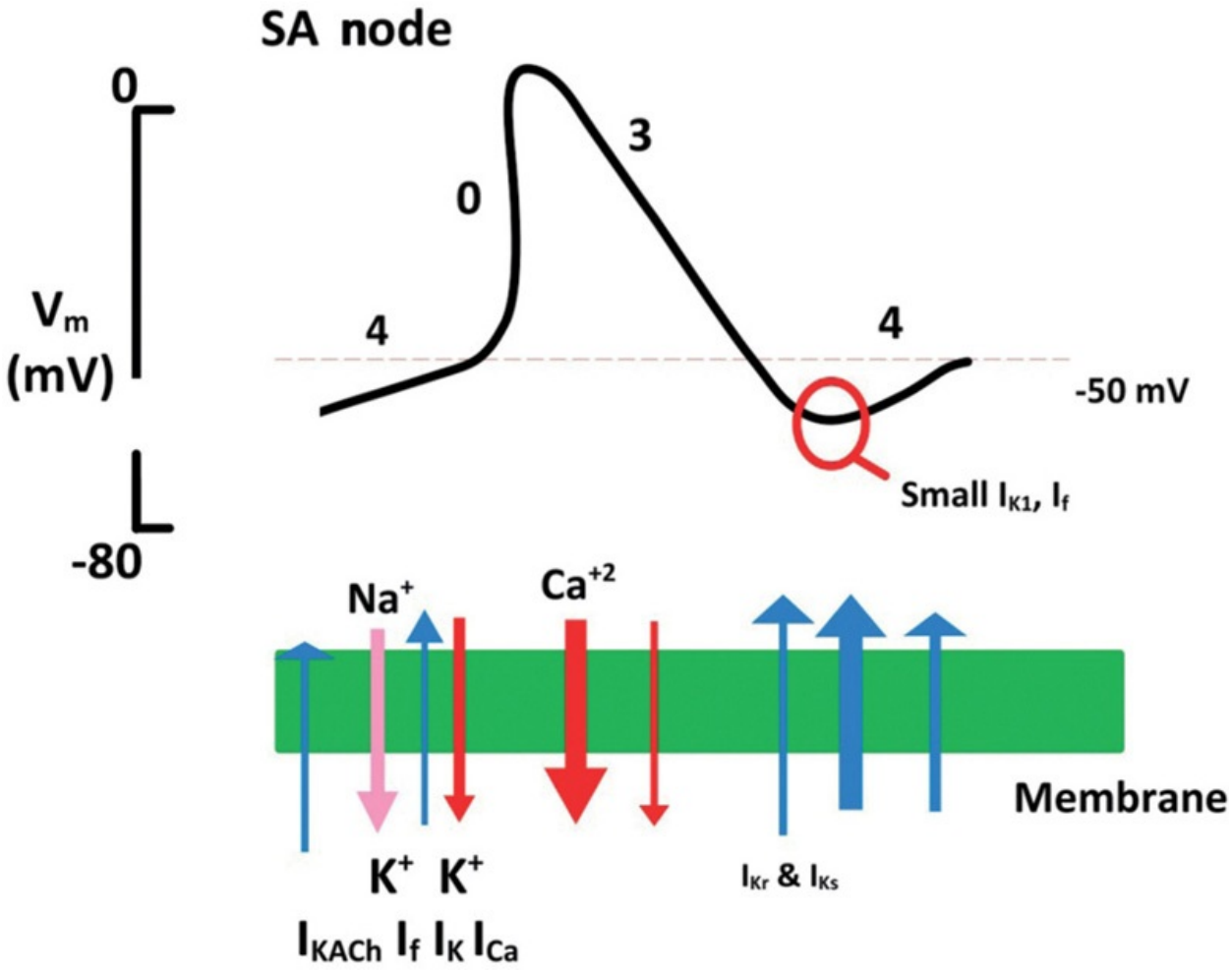


FIGURE 30.2 Action potential of cardiac pacemaker cells (SAN) depicting phases and ions movement across cell membrane. Downward arrows mark inward current; upward arrows mark outward current.

The sciences of ion channels are well correlated with the shape of the action potential, and this correlation is depicted in **Table 30.1**.

TABLE 30.1 Membrane Currents Controlling the Action Potential

ACTION POTENTIAL PHASE	CURRENT	DESCRIPTION	ACTIVATION MECHANISM
Phase (4)	I_{K1}	Inward rectifier	Depolarization
Phase (0)	I_{Na}	Sodium current	Depolarization

Phase (1)	$I_{to, f}$ $I_{to, s}$ I_{Kur}	Transient outward, fast Transient outward, slow Delayed rectifier, ultrarapid	Depolarization Depolarization Depolarization
Phase (2)	I_{CaL} I_{Na}	Calcium current, L-type Sodium current, late	Depolarization Depolarization
Phase (3)	I_{Kr} I_{Ks} I_{K1}	Delayed rectifier, rapid Delayed rectifier, slow Inward rectifier	Depolarization Depolarization Depolarization
Multiple Phases	I_B I_{KATP} Na-K, NCX	Background current ADP activated K^+ current Pump currents	Metabolism, stretch ADP/ATP Ionic concentrations

Spontaneous depolarization of the SA node activates the neighboring atrial myocardium through electrotonic interactions. Elevation of the atrial membrane potential from its resting level to more positive values activates voltage-dependent Na^+ channels, giving rise to the peak Na^+ current (I_{Na}), which further depolarizes the membrane potential and produces the upstroke of the atrial action potential (AP). Subsequent activation of L-type Ca^{2+} channels produces a small influx of Ca^{2+} into the cell ($I_{Ca,\ L}$), which triggers a much larger Ca^{2+} release from the intracellular stores of the sarcoplasmic reticulum (SR) through the cardiac ryanodine receptor channels (RyR2), a process termed Ca^{2+}-induced Ca^{2+} release.[3] The Ca^{2+} released into the cytosol (Ca^{2+} transient) binds to the contractile machinery and initiates contraction, thereby linking electrical excitation and mechanical contraction (excitation–contraction coupling). The Ca^{2+} transient also feeds back to the L-type Ca^{2+} channels, causing Ca^{2+}-dependent inactivation to prevent excessive Ca^{2+} influx.[4] Relaxation of the atrial myocytes occurs as Ca^{2+} is extruded from the cell via both the electrogenic Na^+–Ca^{2+} exchanger (NCX1; giving rise to I_{NCX}) and plasmalemmal Ca^{2+}-ATPase, and is resequestered into the SR via the SR Ca^{2+}-ATPase (SERCA2a). The latter is controlled by the inhibitory proteins phospholamban (PLN) and sarcolipin.[5] The depolarizing Na^+ and Ca^{2+} currents are countered by repolarizing currents, predominantly carrying K^+ ions. The transient outward K^+ current (I_{to}) produces a rapid repolarization immediately following the AP upstroke. A concerted effort of delayed rectifier K^+ currents with slow, rapid, and ultrarapid kinetics (I_{Ks}, I_{Kr},

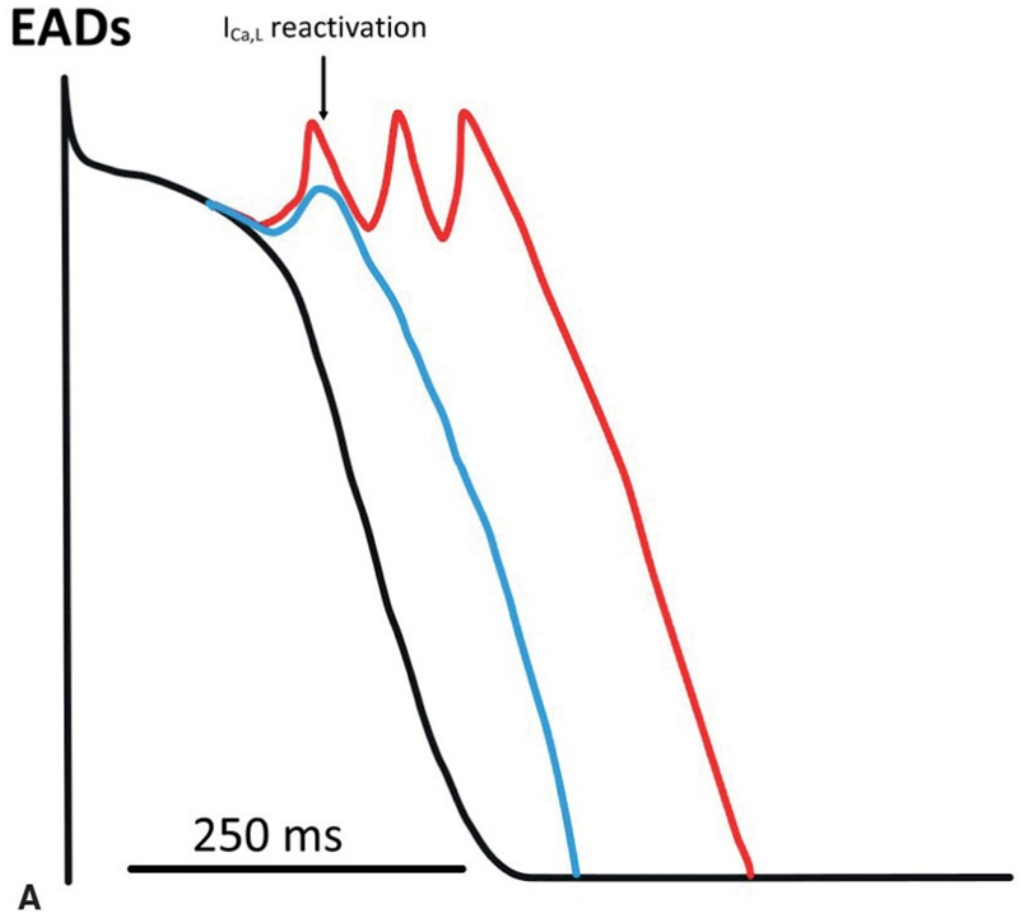
and I_{Kur}, respectively) and the Na^+–K^+ ATPase current (I_{NaK}) control AP duration (APD).

There is a change in the APD across the myocardium from endocardium to epicardium, with the action potential being the longest in the midmyocardial areas.[6] This dispersion can also be responsible for certain reentrant arrhythmias.

The average duration of the ventricular action potential is reflected in the QT interval on the surface electrocardiogram (ECG). It is this relationship that identifies the factors that produce QT-interval prolongation and the arrhythmias that are related to it, such as *torsade de pointes*.

Action potentials may be initiated within cells or groups of cells that have the property of automaticity. Diastolic depolarization during phase (4) of the AP is the basis of the automaticity in the SA and AV nodes. Abnormal automaticity may take other forms, such as early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs), which are examples of triggered activity because they are dependent on the preceding action potential.[7] Action potential prolongation is essential for EADs, with a net membrane current shift from outward to inward that, in consequence, produces oscillations of the membrane potential that may reach threshold; an example of this is torsade de pointes in long QT.[8] EADs can be abolished by interventions that return the APD toward normal or block the sodium current (I_{Na}) and calcium current (I_{Ca}). This can be achieved by increasing the heart rate with pacing or isoproterenol infusion; or by blocking the I_{Na} and I_{Ca} with class IC and class IV antiarrythmics, respectively.

On the other hand, DADs are characteristics of conditions that lead to Ca^{2+} overload. Ca^{2+} antagonists can block these. An example of DAD-mediated arrhythmias are the tachyarrhythmias that occur with digitalis toxicity. Characteristics of the modulation of EADs and DADs are depicted in (**Figure 30.3**).


EADs
$I_{Ca,L}$ reactivation
250 ms
A

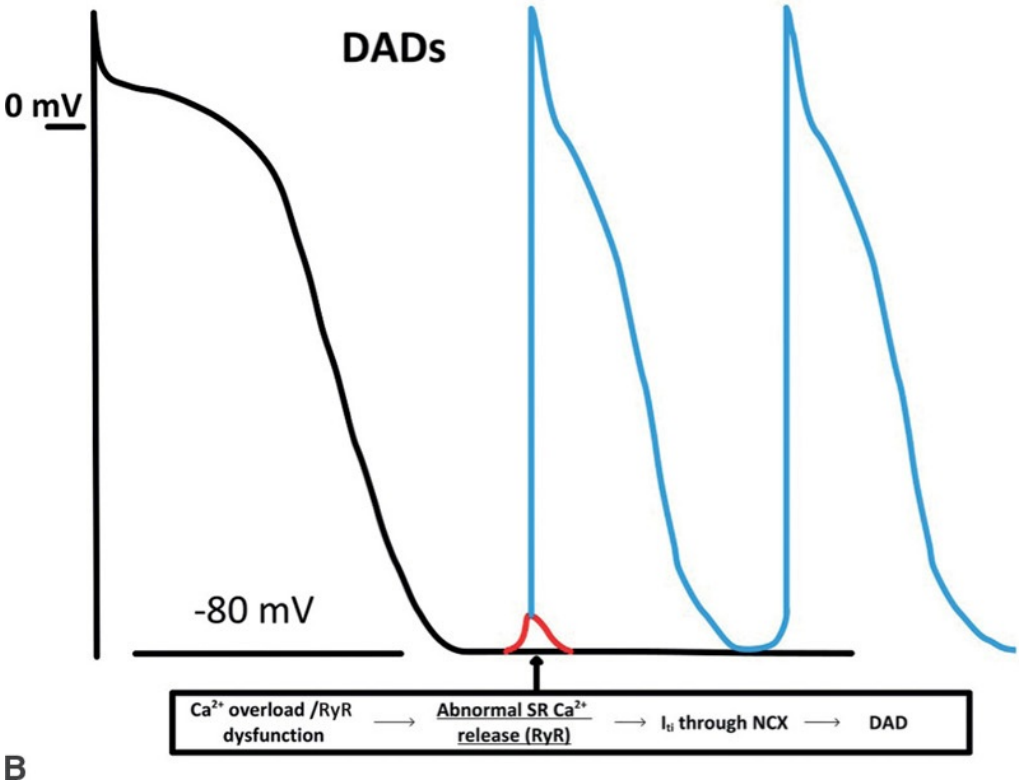

DADs
0 mV
-80 mV
Ca^{2+} overload /RyR dysfunction
Abnormal SR Ca^{2+} release (RyR)
I_{ti} through NCX
DAD
B

FIGURE 30.3 A, Early afterdepolarizations (EADs) are due to progressive prolongation of the action potential that results in oscillations at the plateau level of membrane potential. B, Delayed afterdepolarizations (DADs) are due to progressive prolongation of the action potential that results in oscillations during phase 4 of membrane potential.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS

For the past two decades, antiarrhythmic drugs have been differentiated according to the well-known classification system developed by Vaughan Williams[9] and subsequently modified by Harrison.[10] The original system includes four major groups of antiarrhythmic drugs: classes I, II, III, and IV. **Table 30.2** summarizes all the pharmacodynamic and pharmacokinetic properties of these drugs.

TABLE 30.2 Vaughan Williams Antiarrhythmic Drugs Pharmacodynamics a Properties

DRUG	EFFECT ON ION CURRENTS, CHANNELS	ECG CHANGES	ELIMINATION	BIOAVAILABILITY (%)	TIME TO PEAK PLASMA CONCENTRATION (HR)
Procainamide	I_{Na}, I_{Kr}	↑ QT	Hepatic (40–70%) Renal (30–60%)	100	1
Quinidine	I_{Na}, I_{Kr}, I_{to}	↑ QT	Hepatic (50–90%) Renal (10–30%)	70	1.5–3
Disopyramide	I_{Na}, I_{Kr}	↑ QT	Hepatic (20–30%) Renal (40–50%)	80–90	1–2
Lidocaine	I_{Na}		Hepatic		
Mexiletine	I_{Na}		Hepatic	90	2–4

Propafenone	I_{Na}, βB	↑ PR, ↑ QRS	Hepatic	10–50	2–3
Flecainide	I_{Na}	↑ PR, ↑ QRS	Hepatic (70%) Renal (30%)	90–95	2
Amiodarone	I_{Kr}, I_{Ks}, IK_{Ach}, Ca, I_{Na}, βB	↑ PR, ↑ QRS ↑ QT	Hepatic	50	3–7 (onset of action may take weeks)
Dronedarone	I_{Kr}, I_{Ks}, IK_{Ach}, Ca, I_{Na}, βB	↑ PR, ↑ QT	Hepatic	4–15	3–6
Dofetilide	I_{Kr}	↑ QT	Renal	90	2–3
Sotalol	I_{kr}, βB	↑ QT	Renal	90	2.5–4
Ibutilide	I_{Kr}	↑ QT	Hepatic		
Vernakalant	I_{Kur}, HERG, I_{KAch}	↑ QRS ↑ QT	Hepatic		

VAUGHAN WILLIAMS CLASS I: SODIUM CHANNEL BLOCKADE

Class I antiarrhythmic drugs block the rapid inward sodium channel during phase 0 of the action potential, slowing the rate of depolarization. The Hodgkin and Huxley[11] model describes these channels as existing in one of three states (open, closed, and inactivated), giving a different affinity for each drug.[12] These characteristics explain the feature of use dependence of drugs in this class, whereby block increases with increasing rate of stimulation, that is to say, with increased stimulation more sodium channels are in an open or inactivated state. Drugs that have greater affinity for their receptor when the sodium channel is open or inactivated bind more readily at faster stimulation rates. Drugs also show different rates for association or dissociation from their receptor, which is the basis for the subclassification refinement for class I drugs to (IA, IB, and IC).

Drugs with class IA action (eg, quinidine, procainamide, and disopyramide) prolong the depolarization and the refractoriness of myocardial cells in addition to blocking the rapid inward sodium channels. Thus, they may increase QRS duration and QT intervals. Class IB drugs (eg, lidocaine and mexilitine) shorten the action potential, but produce a minimum inhibition of the inward sodium channels, thus having a minimal effect on the QRS and QT durations. Drugs with class IC action (eg, flecainide and propafenone) are important sodium channel blockers that slow its conduction velocity and could thus increase the QRS duration more than any of the other class I drugs.

Class IA

These drugs have an intermediate rate of association and dissociation from sodium channels. In addition to blocking the sodium channels, they also decrease automaticity and excitability in the atria, ventricles, and Purkinje fibers because of the blockade of the rapidly activating potassium channel $I_{Kr.}$[13]

Quinidine

Quinidine depresses conduction and excitability, slows repolarization, and lengthens the AP duration. Because of its I_{kr} channel blockade, it reduces the maximum reentry frequency and thus slows tachycardia. It also possesses an α-adrenergic blocking property that promotes vasodilation and, in turn, causes a reflex increase in the SA node rate. It also has a greater potassium channel blockade than procainamide; thus, these drugs should be avoided in patients with heart failure because of their proarrhythmic and negative inotropic effect. In addition, quinidine decreases the potassium current during phase 1 of the action potential by blocking the I_{to} current. This effect may prevent the heterogeneity in membrane potentials during phase 2, which is believed to underlie the ST-segment elevation in the right precordial leads and initiation of ventricular fibrillation seen in Brugada syndrome.[14] This characteristic has been postulated in some studies for the management of electrical storm in Brugada syndrome patients.[15–17] Quinidine is predominantly metabolized by the P450 enzyme CYP3A4, and thus requires a lower dosage in patients with liver dysfunction. Importantly, it reduces the renal clearance of digoxin and may lead to digoxin toxicity.[18, 19] Metabolism of quinidine is inhibited by cimetidine and increased by phenytoin, phenobarbital, and rifampin. The main side effects of quinidine include hypotension, thrombocytopenia, hepatitis, and cinchonism, whose

symptoms include tinnitus, blurred vision, headaches, and dizziness.[20] It also can worsen symptoms in patients with myasthenia gravis.[21]

Disopyramide

In addition to its class IA characteristics, it exerts marked cardiac antimuscarinic effects leading to sinus node suppression as well as slow AV nodal conduction. Because of this anticholinergic effect, this drug can cause urinary retention, dry mouth, blurred vision, and closed-angle glaucoma and should thus be avoided in patients with glaucoma and men with symptomatic prostatic hyperplasia. For the past few years, disopyramide has emerged as an important drug in the management of patients with obstructive hypertrophic cardiomyopathy,[22–24] which may be its only use nowadays. It is eliminated by both renal and hepatic routes. It should be titrated up gradually from low doses because of its characteristics of saturable protein binding that can lead to disproportionally increased levels of the free drug.
Dosage: 150 mg every 8 hours up to 1 gm/day.

Procainamide

It is a derivative of the local anesthetic agent procaine, and its active metabolite N-acetylprocainamide (NAPA) is the reason for its I_{kr} blockade. It is indicated for acute conversion of ventricular and atrial dysrhythmias, and although it is less effective in suppressing abnormal ectopic pacemaker activity, it has more effective Na^+ channel blockers in depolarized cells. Procainamide given intravenously in a maximal dose of 10 mg/kg body weight over a 5-minute period during sinus rhythm produced complete anterograde block in the accessory pathway.[25] The usual effective concentration of procainamide is 4 to 8 mcg/mL and NAPA 7 to 15 mcg/mL.[26] Because of its Variable hepatic metabolism in relation to NAPA, monitoring of both procainamide and NAPA levels is needed during initiation of the drug or up titration of dosage because each component reaches steady-state levels at different times. The QT interval should be monitored during initiation to assess the risk of torsade de pointes. Procainamide can cause a drug-induced lupus-like syndrome that appears in about 20% of patients, with positive antinuclear antibodies in all patients, these symptoms range from arthralgia, arthritis, fever, and malar rash to pleural and cardiac effusions. It is also associated with the development of agranulocytosis.[27] It certainly has negative inotropic properties that may lead to

hypotension with rapid IV infusion, and it is thus contraindicated in patients with heart failure.
Dosage: Acute: 17 mg/kg at 20 mg/min (50 mg/min, if urgent). Infusion: 1–4 mg/min (depends on renal function).

Class IB

These drugs block fast sodium channels, decreasing V_{max}, the rate of depolarization during phase 0 of the action potential. They are typically used in treatment of ventricular tachycardia because they have no significant effect on atrial tissue. Both lidocaine and mexiletine are metabolized in the liver by the P450 enzyme CYP2D6; thus drugs that inhibit this enzyme (ie, amiodarone, quinidine, citalopram, cimetidine) can increase their plasma levels and the risks of toxicity.

Lidocaine

It is indicated in acute management and treatment of ventricular arrhythmia and is administered intravenously only to treat arrhythmias associated with myocardial infarction.[28] It is rapidly acting exclusively on Na^+ channels and may slightly shorten action potential duration and effective refractory period of normal conducting tissues, thus prolonging diastole and extending the time to recovery. However, some studies have suggested a facilitation of subnodal block in patient with abnormal conduction[29]; thus, when it is used as a local anesthetic, it should be given with caution in patients with heart block.[30] Lidocaine can cause sinus node standstill, in addition to causing neurologic system toxicity, which can be manifested by paresthesias, tremor, nausea, lightheadedness, hearing disturbances, slurred speech, and convulsions.
Dosage: 1.0–1.5 mg/kg IV push over 1–2 min; repeat every 5–10 min with 0.5–0.75 mg/kg, as needed, until 3 mg/kg total dose. Typical maintenance dose: 1.0 to 4.0 mg/min.

Mexilitine

It is an overall analog of lidocaine and can be safely used in patients with severe systolic dysfunction. It has an approximately 90% bioavailability, with only 1% of total body content within the plasma. Side effects of mexilitine include severe gastritis, tremor, blurred vision, nausea, dysphoria, dizziness, and agranulocytosis.

Dosage: 200 mg every 8 hours; consider lower dose in renal dysfunction patients.

Class IC

Flecainide and propafenone slow conduction velocity and V_{max} by blockade of sodium channels, with slow association/dissociation channel kinetics, resulting in marked use-dependent characteristics. Both prolong the PR and QRS durations, although flecainide can slightly increase the QT interval. The concomitant use of a β-blocker or nondihydropyridine calcium channel antagonist is generally recommended to prevent rapid atrioventricular conduction in the event of atrial flutter. Both can be effective at maintaining sinus rhythm with recurrence rates of 31% to 70%, as seen in the RAFT trial.[31]

Flecainide

It slows conduction in all cardiac tissue, has negative inotropic effect, and is shown to block the delayed rectifier potassium channels.[32] It is used primarily in patients with supraventricular tachycardia and atrial fibrillation (AF). It should be avoided in patients with coronary artery disease, reduced ventricular function, and ventricular arrhythmia, as seen in clinical trials, including the Cardiac Arrhythmia Suppression Trial (CAST)[33] and the Cardiac Arrest Study Hamburg (CASH).[34]

Flecainide can cause sinus node dysfunction and can increase pacing thresholds as well as increased levels of digoxin.

Dosage: 100 to 200 mg every 12 hours.

Propafenone

It blocks both open and inactivated sodium channels; in addition, it blocks both voltage-dependent calcium currents and potassium currents such that the action potential duration is essentially unchanged.[35] It has β-blocking properties that are particularly obvious in patients who poorly metabolize propafenone to 5-hydroxy propafenone. It is metabolized in the liver by enzyme CYP2D6 and thus increases the levels of digoxin, metoprolol, and warfarin.

Dosage: 450–900 mg every 8 hours.

Pill-in-the-Pocket

Class IC medication has been tested for safety and efficacy to be used in the emergency room with patients who have recent-onset atrial fibrillation; treatment was successful in 94% of the episodes occurring during the 15 months' follow-up, with conversion occurring over the mean of two hours.[36] The major concern of this approach was the possibility of ventricular tachyarrhythmias that ranged up to 5%. The pill-in-the-pocket approach should be considered an outpatient self-administration of single oral loading dose only in patients with lone AF and normal hearts, after being initially used in an in-hospital monitor setting that proved to have a safe response to single-dose therapy[37] with reported conversion rates of 70% to 80%.[38]

Dosage: depending on patient weight < 70 kg: immediate-release propafenone 450 mg once and flecainide 200 mg once, for weight ≥ 70 kg: 600 mg once and 300 mg once, respectively.

VAUGHAN WILLIAMS CLASS II: β-RECEPTOR BLOCKADE

This class of medications include those that selectively block receptors in cardiac tissue (β_1) or nonselectively including receptors in the lung and the blood vessel (β_2). Their predominant actions include a reduction in automaticity in cardiac tissue and conduction through the AV node. B_1 selective drugs like metoprolol, bisoprolol, and atenolol are better rate control drugs particularly in patients with heart failure.[39] Nonselective drugs that block both β_1 and β_2 receptors include propranolol, nadolol, and carvedilol, which, in addition, block α_1-adrenergic receptor, making it a great drug for rate control in patients with heart failure and hypertension.[40]

VAUGHAN WILLIAMS CLASS III: POTASSIUM BLOCKADE

Medications in this class block potassium channels, resulting in prolongation of the action potential. This group includes amiodarone, dronadarone, sotalol, ibutilide, and dofetilide. Vernakalant is a new agent that blocks potassium channels selectively in the atrial tissue.

Agents that block the rapidly activating inward rectifying potassium channels (I_{kr}) display reverse use dependence, wherein block is greater at slower heart rate. Therefore, drugs that block I_{kr} result in delays in repolarization and QT prolongation predominantly at slower heart rate (eg, dofetilide).

Amiodarone

It is the most commonly used antiarrhythmic drugs by far because it exerts effects across all Vaughan Williams classes. It increases the action potential duration and the refractory period via potassium channel blockade in a use-dependent manner, and noncompetitive inhibition of α- and β-receptors.[41] It increases the refractory period in all cardiac tissues, and decreases automaticity by slowing phase 4 depolarization. Although it might increase QT interval, torsade de pointes very rarely occurs (<1%).[42]

Amiodarone possesses class I effects by blocking activated sodium channels[43, 44] and also blocks L-type calcium channels. Amiodarone and dofetilide are second-line agents for patients without heart disease but are first-line agents for patients with heart failure. When given intravenously, it can cause hypotension that is related to the solvents polysorbate 80 and benzyl alcohol.[45] The iodine moiety in amiodarone is responsible for hypothyroid or hyperthyroid status. Iodine released from amiodarone in its metabolism directly inhibits thyroid function and hormone synthesis, producing a state of hypothyroidism.[46] Hyperthyroidism can occur in up to 10% of patients with two forms described.[47] Type-I hyperthyroidism, occurs in populations with an underlying thyroid pathology such as autonomous nodular goiter or Graves' disease. In these patients, there is accelerated thyroid hormone synthesis secondary to the iodide load from the amiodarone therapy (the Jod-Basedow phenomenon). In type-II hyperthyroidism, there is an inflammatory thyroiditis with release of stored thyroid hormone.[48, 49]

Amiodarone-induced pneumonitis may develop after several months or years, with cumulative prevalence estimated between 1% and 15%, depending on daily dose.[50] In addition, amiodarone may cause optic neuritis (0.1–2%), skin discoloration (4–9%), peripheral neuropathy (0.3%),[51] and hepatitis (0.6%), although an increase in transaminases can occur without it to hepatic toxic effect.[41]

It has a large volume of distribution, as a result of accumulation in fatty tissue and in the liver, lung, and spleen. Elimination is by excretion into bile, with a slow but valuable elimination rate and a half-life ranging between 13 and 103 days.[52]

There is a strong correlation between amiodarone and warfarin potentiation; thus, the warfarin dose should be reduced with close monitoring of the international normalized ratio. Other examples of drug-drug interactions are

those documented with digoxin, risk of rhabdomyolysis when given in combination with statins and prolongation of the QT interval when given with fluoroquinolone and macrolides.[41]

Dosage:

An oral dosing protocol

- 15 mg/kg/day × 1 week (~400 mg TID)
- 10 mg/kg/day × 2 weeks (~400 mg BID)
- 5 mg/kg/day (~400 mg QD)
- Eventually reduce to 100–200 mg daily

General IV load

- All arrhythmia: Monitor heart rate and blood pressure
  - 150 mg over 10 minutes
  - 1 mg/min × 6 hours
  - 0.5 mg/min × 18 hours or longer
- Ventricular fibrillation
  - 300 mg IVP; may repeat w/150 mg IVP
- Ventricular tachycardia
  - 150 mg over 10 min; repeat as needed to a total of 2.2 gm in 24 hours

For chronic use, the prescriber should consider at least twice yearly assessment of pulmonary, hepatic, eye, and thyroid function during amiodarone therapy.

Dronedarone

Dronedarone is, like amiodarone, a benzofuranyl compound with iodine removed and a methane sulfonyl group added. Removing iodine from the molecule was intended to eliminate or reduce iodine-related organ toxicity. Dronedarone retains many of amiodarone's electrophysiologic effects. It is a multichannel blocker with effects on the rapid and slow components of the delayed rectifier potassium channels (I_{Kr} and I_{Ks}), slow L-type calcium currents, ($I_{Ca\text{-}L}$), the inward sodium current (I_{Na}), and the inward rectifier potassium current (I_{K1}). It also inhibits the acetylcholine receptor–dependent K^+ current (I_{KAch})[53] and the pacemaker current (I_f) and is a noncompetitive α- and β-adrenergic antagonist,[54] thus reducing sinus rate and prolonging AV nodal conduction and refractoriness.[53] Dronedarone has been shown to prevent atrial

fibrillation/flutter (AF/AFl) recurrences in several multicenter trials.[55, 56] In addition to its rhythm control properties, dronedarone has rate control properties and slows the ventricular response during AF. In patients with decompensated heart failure, dronedarone treatment increased mortality and cardiovascular hospitalizations.[57] Results of the PALLAS trial suggested that dronedarone should not be used in the long-term treatment of patients with permanent AF.[58] As a result, the usage of dronedarone has fallen out of favor.[59] In our opinion, its use is limited only to cases when other medications are contraindicated, as in patients with atrial tachycardia who have underlying pulmonary disease. It is metabolized by CYP3A4 and thus subject to interactions with drugs that inhibit this enzyme such as verapamil, diltiazem ketoconazole, as well as macrolides, which could increase dronedarone levels and in turn worsen bradycardia or AV conduction block. It can increase digoxin levels by interacting with P-glycoprotein.[60]

Dosage: 400 mg every 12 hours.

Dofetilide

The most potent drug in this class,[61] it works by blocking the fast component of the delayed rectified potassium current, I_{kr}. Thus, it is indicated for chemical cardioversion as well as maintenance of sinus rhythm in patients with AF/AFl.[62] No negative inotropic effects are associated with this drug, and it could be used in patients with heart failure.[63] The EMERALD trial[61] showed that a full dose of dofetilide (500 mcg twice daily) was superior to low-dose dofetilide (250 mcg twice daily), low-dose sotalol (80 mg twice daily), and placebo.

The risk for torsade de pointes at doses of 250 to 500 mcg twice daily was less than 1% but as high as 2.9% in the DIAMOND-MI trial[64] and 3.3% in DIAMOND-CHF.[65] For this reason, the FDA recommends that dofetilide therapy be initiated in the hospital over a period of 3 days. It is excreted mainly by the kidneys (80%) through both glomerular filtration and cationic renal (active tubular) secretion, which is inhibited by cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol. Dofetilide carries a black box warning. Verapamil has a relative contraindication because it increases peak plasma level of dofetilide by 42% and was shown in the DIAMOND trial to increase the risk of torsade de pointes. Thiazide diuretics also have a block box warning in view of the risk of hypokalemia because they were shown to increase dofetilide AUC by 27% and further increased the QTc over time by 197%. In

addition, any other drug that prolongs the QT interval or promotes hypokalemia or hypomagnesemia should be avoided with dofetilide.

As previously mentioned, the FDA recommends that dofetilide therapy be initiated in the hospital over a period of 3 days and prescribed and dispensed by certified personnel. Generally, three half-lives should be used after stopping a previous antiarrhythmic before starting dofetilide. However, in the case of amiodarone, a waiting period of 3 months should be allowed (or until amiodarone concentration < 0.3 mcg/mL is reached).

Dosage is determined on the basis of renal function, calculated by creatinine clearance.

Dosage:

> 60 mL/min	500 mcg twice daily
40 – 60 mL/min	250 mcg twice daily
20 – 39 mL/min	125 mcg twice daily
< 20 mL/min	contraindicated (or if QTc is >440 msec)

If the QTc increases by more than 15% after the drug initiation, dofetilide dose is to be decreased by 50%; while, if the QTc exceeds 500 msec after the second dose, dofetilide should be stopped entirely.

Sotalol

It is prepared as a mixture of d- and l-isomers, of which the l-isomer is responsible for β-blockade. Both isomers block the rapid component of the delayed potassium rectifier channel (I_{Kr}). The initial d-Sotalol drug was found to have a higher mortality in patients with a history of myocardial infarction, as seen in the SWORD trial[66]; however, the racemic mixture of d- and l-isomers does not increase mortality.[67]

It prolongs the action potential by prolonging the repolarization by blockade of I_{Kr} channels, in both atrial and ventricular tissue. As a result of both β-blockade and potassium channel blockades, there is an overall slowing of the heart rate, AV node conduction, conduction across accessory bypass tracts,[68] and increase in AV nodal refractory period.[69] Class III effects are seen at more than 160 mg daily; at dosages of up to 640 mg/d, the QT interval is increased by 40 to 100 msec and the corrected QT interval by 10 to 40 msec.[70] Sotalol carries a dose-related proarrhythmic risk of torsade de pointes, which increases in the

setting of bradycardia, female gender, history of heart failure, or preexisting QT prolongation. Sotalol is excreted by the kidneys, and thus caution is indicated in patients with renal dysfunction. Antacids should be avoided within 2 hours because they may reduce peak serum concentrations and area under the plasma concentration curve. For a creatinine clearance of 30 to 59 mL/min, sotalol should be administered at an interval of 24 hours, starting at a low dose of 80 mg. Because of its β-blocking effect, sotalol should be used with caution in asthmatic patients, or in patients with other drugs that affect AV conduction.
Dosage: 80 – 320 mg orally twice daily can also be administered intravenously at 75 mg IV over 5 hours.

Precautions:
- Do not initiate if QTc > 450 msec
- Accepted QTc < 500 msec the for first 3 days to keep the risk of torsades de pointes under 2%.
- QTc < 520 msec could be accepted thereafter.
- Dosage greater than 320 mg/day may be lead to a substantial increase in the incidence of torsades de pointes (as high as 11% in patients whose corrected QT interval exceeds 550 ms).

Ibutilide

Ibutilide has antiarrhythmic effects through blockade of the rapid component of the delayed rectified potassium current, I_{kr}, as well as enhancing the slow inward sodium current; therefore, it prolongs the action potential duration and the QT interval in proportion to its plasma concentration.[71] There is no significant effect on the heart rate, the PR interval, or QRS duration and no significant change in the cardiac output or the blood pressure. When administered as a 1 mg dose followed by a second dose of 0.5 or 1 mg, ibutilide converted 47% of patients compared with 2% of placebo.[71] The overall risk for torsade de pointes is about 5%,[72] and thus the patient should be monitored for 4 hours after administration of the drug. If ibutilide fails to convert, it may at least enhance the response to electrical cardioversion. Because it is extensively metabolized by first pass, it must be given intravenously. It can be administered to patients receiving digoxin, calcium channel blockers, or β-blockers without interaction; however, the risk of proarrhythmia may increase.
Dosage: 1 mg (0.01 mg/kg < 60 kg) over 10 min; repeat, if needed, after 10 min. In our practice, we preload the patient with magnesium to keep the magnesium

level above >2.

Vernakalant

Vernakalant is an atrial-selective, multiple ion channel blocker that is approved in Europe for the treatment of AF; however, the FDA judged that additional information was necessary for approval. Vernakalant blocks the rapidly activating delayed rectifier potassium channel I_{Kur}, which is present in higher density in the atria, making it relatively atrial selective. It also blocks other potassium currents (I_{to}, hERG, and $I_{KAch)}$ and exhibits rate- and voltage-dependent blockade of the fast inward sodium current I_{Na}. Vernakalant has, therefore, a much greater effect in fibrillating atria than in the ventricle and is less likely to be proarrhythmic.

In the ACT II trial[73] that was performed in patients with new-onset atrial fibrillation or flutter after cardiac surgery, 47% converted to sinus rhythm opted for infusions of Vernakalant, compared with 14% who received placebo with median time to conversion of 12 minutes. In a recently published controlled randomized trial, Vernakalant was found to have significant advantages: it achieved conversion to a normal sinus rhythm within an average of 10 minutes, compared to ibutilide with an average of 26 minutes. Approximately 90 minutes after treatment began, 69% of Vernakalant-treated patients were in sinus rhythm, compared to 43% of patients treated with ibutilide.[74] Most studies were performed on patients with recent-onset atrial fibrillation <7 days, and the conversion rate changed from 45% to 61% within the first 10 to 15 minutes after intravenous administration with the most commonly used regimen (2 mg/kg bolus followed by 3 mg/kg 30 minutes later if AF continued).[73, 75]

Vernakalant is hepatically metabolized by CYP2D6; it is not clear what effect abnormal liver function has on the metabolism of the drug. Differences in renal function, age, sex, race, blood pressure, and heart failure status have not been shown to affect the pharmacokinetics of Vernakalant.[76] The new European guidelines added IV Vernakalant as a first-line treatment for chemical cardioversion for recent-onset atrial fibrillation in patients with coronary artery disease, moderate heart failure, and left ventricular hypertrophy.[77]

VAUGHAN WILLIAMS CLASS IV: CALCIUM CHANNEL BLOCKADE

Diltiazem and verapamil block the L-type calcium channels, resulting in the

relaxation of arterial smooth muscle and vasodilation, and decreased contractility in cardiac myocytes. These drugs also slow AV nodal conduction and increase AV nodal refractoriness. Verapamil also blocks sodium channels, but this is not believed to be a clinically important effect. They are both well absorbed from the gastrointestinal tract and undergo significant first pass effects in the liver, giving a bioavailability of 20% for verapamil and about 40% of diltiazem. They are metabolized in the liver by CYP3 A4; levels can thus be increased in the presence of inhibitors of this P450 enzyme such as ketoconazole and human immunodeficiency virus antiviral agents.

OTHER ANTIARRHYTHMIC DRUGS

Ranolazine

Ranolazine has antianginal properties and is currently approved for use in chronic angina. It reduces myocardial ischemia by its effects on the late inward Na current (I_{NaL}). Ranolazine inhibits peak I_{Na} in the atrium but not the ventricle. This effect results in reduced atrial excitability and a rate-dependent increase in postrepolarization atrial refractoriness. Ranolazine has variable systemic availability after oral administration because of its extensive first pass metabolism in the gut and liver. Metabolism is mainly via CYP3A4 and, to a lesser extent, CYP2D6. The terminal elimination half-life is 7 hours. The recommended dosage in patients with angina is 500 to 1000 mg twice daily. Ranolazine results in a 2- to 6-ms mean increase in the QTc interval, but drug-induced polymorphic ventricular tachycardia has not been observed. The MERLIN-TIMI 36 trial showed significant decreases in the frequency of nonsustained ventricular and supraventricular tachycardia and in the trend toward less frequent new-onset atrial fibrillation.

Pearls

Greater caution should be used when treating women with antiarrhythmic drugs that prolong repolarization, especially when additional risk factors for developing torsade de pointes are present (**Table 30.3**). Patient synchronic class I a or class III drugs should have regular follow-up so that electrocardiogram can be checked for conduction changes or prolongation of the QT interval. Periodic monitoring of laboratory data is also important, including electrolytes, creatinine, and liver enzymes as appropriate for the particular antiarrhythmic

agent. Both sotalol and dofetilide are renally excreted, and their use should be carefully monitored in patients with renal disease.

TABLE 30.3 Risk factors for Developing Drug-induced Torsade De Pointes

Congenital long QT
Female gender
Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)
Diuretic use
Bradycardia
Cardiac hypertrophy
Myocardial fibrosis
Congestive heart failure
Renal and liver insufficiency
Co-administration of drugs blocking P450 isoenzyme CYP3A4
High doses or rapid intravenous infusion of the drug
Baseline electrocardiographic abnormalities
Prolonged QT, T wave lability

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Patient and Family Information for: PRINCIPLES OF ANTIARRHYTHMIC DRUG THERAPY

Antiarrhythmic drugs are medicines that are used to treat abnormal heart rhythms resulting from irregular electrical activity of the heart. Antiarrhythmics correct irregular heartbeats and slow down hearts that beat too fast. Normally, the heart beats at a steady, even pace. The pace is controlled by electrical signals that begin in one part of the heart and quickly spread through the whole heart. If something goes wrong with this control system, the result may be an irregular heartbeat, or an arrhythmia. Antiarrhythmic drugs control these irregular heartbeats. If the heart is beating too fast, these drugs will slow it down. By correcting these problems, antiarrhythmic drugs help the heart work more efficiently. These medications only control abnormal heart rhythms, not cure them, and therefore you may have to take them for life. There are many different types of antiarrhythmic drugs, and your doctor will decide what class and medication is best for you. We will explain the purpose and how to use the most commonly used medications here.

Antiarrhythmic medicines are split into four categories:

- **Class I antiarrhythmic** medicines are sodium channel blockers, which slow electrical conduction in the heart.
  - **Flecainide**: Take this medication by mouth with or without food, usually twice daily.
    - Supraventricular tachycardia: 100 to 200 mg/day every 12 hours
    - Paroxysmal atrial fibrillation: 50 to 300 mg/day taken 2 to 3 times daily
    - Should not be used in people with liver impairment

    - **Propafenone**: Generally needs to be started in a hospital setting to ensure ECG monitoring of the patient.
        - There are many different dosages of propafenone, depending on clinical presentation of the arrhythmia. The treatment is generally begun with relatively high dosages (450–900 mg/day), decreasing to near 300 mg/day.
        - This medicine works best when there is a constant amount in the blood. To help keep the amount constant, do not miss any doses. Also, it is best to take each dose at evenly spaced times day and night. For example, if you are to take 3 doses a day, doses should be spaced about 8 hours apart.
        - If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.
    - These two drugs can be used as a "pill-in-the-pocket" method for use with single dosage in patients with lone AF episodes. This method can be utilized only in patients with normally structured hearts, with initial dose delivered in a hospital setting.
- **Class II antiarrhythmic** medicines are β-blockers, which work by blocking the impulses that may cause an irregular heart rhythm and by interfering with hormonal influences (such as adrenaline) on the heart's cells. By doing this, they also reduce blood pressure and heart rate.
    - **Metoprolol**: A β-blocker that works by blocking the effects of epinephrine, causing the heart to pump more slowly and with less force.
        - Metoprolol tartrate (short-acting) dosage: 50 to 200 mg taken every 12 hours.
        - Toprol XL (long-acting) dosage**:** 50 to 200 mg taken once daily
- **Class III antiarrhythmic** medicines slow the electrical impulses in the heart by blocking the heart's potassium channels.
    - **Amiodarone**: Most commonly used antiarrhythmic medication.
        - Maintenance dose: 100 to 200 mg daily
        - Avoid eating grapefruit or drinking grapefruit juice while using this medication unless your doctor instructs you otherwise. Grapefruit can increase the amount of this medication in your bloodstream.
        - Nausea, vomiting, constipation, loss of appetite, shaking, or tiredness may occur.
        - Tell your doctor right away if you have any of the following serious side

effects: easy bruising/bleeding, loss of coordination, tingling/numbness of the hands or feet, uncontrolled movements, new or worsening symptoms of heart failure (such as ankle/leg swelling, increased tiredness, increased shortness of breath when lying down).
    - Amiodarone may rarely cause thyroid problems. Either low thyroid function or overactive thyroid function may occur. Tell your doctor right away if you develop any symptoms of low or overactive thyroid, including cold or heat intolerance, unexplained weight loss/gain, thinning hair, unusual sweating, nervousness, irritability, restlessness, or lump/growth in the front of the neck (goiter).
    - Amiodarone has many interactions with medications, so be sure to discuss all the medications you are taking with your doctor.
    - Many patients who are prescribed amiodarone are also on the blood thinner coumadin, also known as warfarin. The blood levels of coumadin are higher when used with amiodarone, and therefore the dose of coumadin will need to be adjusted.
    - Digoxin dose will also most likely need to be lowered to prevent levels of digoxin in the blood from being too high.
    - Muscle breakdown can happen when taking amiodarone with cholesterol medications.
    - Amiodarone can cause other electrical disturbances within the heart when taken with certain antibiotics, so be sure to inform any primary care provider before taking any additional medication when treating an infection.
- **Sotalol**: Maintaining a normal heartbeat in patients who have AF or AFl.
    - Dosage: take one tablet 80 to 320 mg every 12 hours.
    - Patients who begin taking or restart sotalol should be observed in a hospital or similar setting in which heart and kidney function monitoring may be performed for at least 3 days after starting sotalol. Close monitoring of your heart or kidney function may also be needed if your dose is changed.
    - Sotalol may sometimes cause a new or worsened irregular heartbeat (prolonged QT interval), which could be life threatening. Talk with your doctor if you have prolonged QT interval or kidney problems.
    - Sotalol has many drug and herbal interactions, so be sure to go over everything you are taking and have recently taken with your health care provider before starting sotalol.

- **Dofetilide**: Used for the maintenance of sinus rhythm in individuals prone to the occurrence of AF and AFl arrhythmias, and for chemical cardioversion to sinus rhythm from AF and AFl.
  - There is risk of fatal heart rhythm when starting this medication, and therefore it must be initiated in a hospital setting where heart and kidney monitoring can occur for 3 days.
  - If you have been taking amiodarone, it should be stopped for 3 months before starting dofetilide.
  - There is a very specific dosing regimen when initiating dofetilide, which will be carried out by a trained professional in the hospital. The home dose is 500 mcg twice daily.
- **Class IV antiarrhythmic** medicines slow the electrical impulses in the heart by blocking the calcium channels in the heart.
  - **Diltiazem**: This medication is used to treat high blood pressure and chest pain as well as heart rhythm problems. Diltiazem affects the movement of calcium ions within heart tissue that occur during each heartbeat. This helps to relax the muscles of the heart and also open up blood vessels around the heart. It is known as a calcium channel blocker.
    - Diltiazem should not be used if you have heart failure.
    - Extended release tablets dosage: 180 to 480 mg daily.

31

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Modern Anticoagulation Therapy

BACKGROUND

Atrial fibrillation (AF) is among the most common sustained cardiac tachyarrhythmia in hospitalized patients.[1] The lifetime rate of developing AF in individuals 40 years and older is approximately 25%; with an estimated 16 million Americans with AF by 2050. There is about a 5-fold increased risk in developing an acute ischemic stroke in patients with AF.[1] In a meta-analysis, the rate of ischemic stroke in patients managed for AF with adjusted-dose warfarin reduced by 66% and antiplatelet agents by 22%.[2] To that end, adjusted-dose warfarin has traditionally been the gold standard in those with AF who are at risk for stroke.

Warfarin, however, is a complicated anticoagulant to manage, with a diverse mechanism of action profile on the clotting cascade.[3] Therefore, to improve the effectiveness of antithrombotic therapy in AF and reduce the relative risks of bleeding, newer modern anticoagulants have been developed with more direct-acting mechanisms on the clotting cascade that yield a more predictable anticoagulant effect.[3] As such, the purpose of this chapter is to provide clinicians with an overview of the evolving field of anticoagulation therapy as it pertains to AF, particularly when cardiac valves are not involved, such as mechanical valve repairs and replacements.

As research advances and the understanding of the incidence and etiologies of AF evolves in the context of valvular conditions, we recognize that at the time this chapter was developed, there were established differences in the worldwide definition of nonvalvular atrial fibrillation (NVAF) that only recently emerged.[4, 5] The American College of Cardiology (ACC), American Heart Association (AHA), and the Heart Rhythm Society (HRS) definition of NVAF can be summarized by the presence of AF in the absence of rheumatic mitral valve stenosis, a mechanical or bioprosthetic heart valve, or a mitral valve repair.[4] In contrast, the 2016 consensus of the European Society of Cardiology (ECS), European Heart Rhythm Association, and European Stroke Organisation removed the term "nonvalvular" AF, but rather references the specific underlying contributory clinical conditions.[5] Such scenarios may include AF secondary to structural heart disease, mitral stenosis, or prosthetic heart valves, suggesting the need for being more specific when selecting an anticoagulant or estimating stroke risk. For the purposes of this chapter, we refer to the ACC/AHA/HRS definition of NVAF.

The United States Food and Drug Administration (US FDA) has approved traditional and modern anticoagulants for the prevention of stroke and systemic embolism in patients with NVAF, thromboprophylaxis postoperatively in orthopedic and other procedures, as well as in treatment and in risk reduction of recurrent venous thromboembolism, such as deep vein thrombosis and pulmonary embolism. The scope of this chapter is a focus on the use of anticoagulants for AF with an emphasis on NVAF. The goal is to provide a decision analysis of anticoagulant drug selection and use based on clinical pharmacology, evidence, and patient characteristics.

ESTABLISH STROKE AND BLEEDING RISK

CHA2DS2-VASc SCORE

In addition to the shared decision making between clinician and patient, selecting the appropriate antithrombotic therapy for NVAF is often based on assessing the risk of thromboembolic stroke and bleeding.[4] The CHA_2DS_2-VASc stroke risk stratification score (**Table 31.1**), recommended for use by the 2014 AHA/ACC/HRS Guideline for the Management of Atrial Fibrillation, is an expansion of the $CHADS_2$ score with three additional risk factors including female sex, age of 65 to 74 years, and history of vascular disease, such as prior

myocardial infarction, peripheral arterial disease, and aortic plaque.[4] Therefore, the CHA_2DS_2-VASc score is said to be a more accurate predictor of stroke risk in patients with a $CHADS_2$ score of 0 or 1 and thus improving guidance on the need for anticoagulant therapy.

TABLE 31.1 CHA_2DS_2-VASc and HAS-BLED Risk Stratification Tools

CHA2DS2-VASc		HAS-BLED	
CONDITION	**POINTS**	**CONDITION**	**POINTS**
Chronic heart failure	1	Hypertension (ie, uncontrolled)	1
Hypertension	1	Abnormal renal/liver function	1 or 2
Age ≥ 75 y	2	Stroke	1
Diabetes mellitus	1	Bleeding tendency or predisposition	1
Stroke/TIA or thromboembolism, prior	2	Labile INR	1
Vascular disease (MI, PAD, or aortic plaque)	1	Age (eg, >65 y)	1
Age 65–74 y	1	Drugs (eg, concomitant aspirin or NSAIDs) or alcohol	1 or 2
Sex category (female)	1		
Total possible score	9	Total possible score	9

INR, international normalized ratio; MI, myocardial infarction; NSAIDs, non-steroidal anti-inflammatory drugs; PAD, peripheral arterial disease; TIA, transient ischemic attack.

The total score of the CHA_2DS_2-VASc is up to 9 points. On the basis of a strong level of evidence, the recommendation is to provide anticoagulation therapy for CHA_2DS_2-VASc scores of 2 or higher that indicate high risk for a thrombotic event. A CHA_2DS_2-VASc score of 1 indicates an intermediate risk of an event and thus the clinician may consider offering antithrombotic therapy with either aspirin, an anticoagulant, or no therapy with continued monitoring. Assessing bleeding risk may assist with the decision process.

When the decision is to initiate anticoagulation therapy, several considerations need to be evaluated. Warfarin remains the gold-standard anticoagulant method

for AF due to a mechanical or bioprosthetic heart valve.[4] The intensity of warfarin anticoagulation to a target international normalized ratio (INR) of 2.5 (range 2 to 3) is recommended for mechanical aortic valves without risks for thromboembolism (eg, CHA_2DS_2-VASc = 0), bioprosthetic aortic or mitral valves, and mitral valve stenosis or regurgitation. On the other hand, a target INR of 3 (range 2.5 to 3.5) is recommended for mechanical aortic valves with risks for thromboembolism (eg, CHA_2DS_2-VASc ≥ 2) and mechanical mitral valves.[6] When introducing warfarin, a parenteral anticoagulant with complete anticoagulant activity using either unfractionated heparin (UFH) as a continuous infusion with a steady-state target-activated partial thromboplastin time (aPTT) 1.5 to 2 times the upper limit of the "normal" range or a low-molecular-weight heparin (LMWH), such as enoxaparin, is recommended concomitantly with warfarin until the INR is at target on two separate samples 24 hours apart after at least 5 days of overlap.[3] The timing in which therapeutic INR is achieved is dependent on the half-lives of vitamin-K–dependent clotting factors II, VII, IX, and X. On average, a therapeutic INR is achieved by day 5, which is based on complete depletion of factor II, which has the longest half-life of approximately 48 to 64 hours.[7]

For NVAF with a CHA_2DS_2-VASc score of 2 or greater, oral anticoagulation therapy with either warfarin to a target INR 2 to 3 or a novel oral anticoagulant (NOAC) is recommended.[4] The NOAC agents include dabigatran, which elicits its anticoagulant effect by directly inhibiting thrombin activity, similar to argatroban; and apixaban, edoxaban, and rivaroxaban that inhibit factor Xa (FXa) activity similar to that of LMWHs.[8–11]

HAS-BLED

Several tools are available to assess the risk of bleeding from anticoagulation for AF. The HAS-BLED score (**Table 31.1**) has been validated to predict clinically significant bleeding and has been demonstrated to outperform the HEMORR(2)HAGES and ATRIA (***A***n***T***icoagulation and ***R***isk factors ***I***n ***A***trial fibrillation) assessment tools that are more complicated to complete.[12, 13] The components of the HAS-BLED tool include modifiable and nonmodifiable risk factors such as hypertension, abnormal renal and/or liver function, stroke, bleeding tendencies, labile INR, age (eg, older than 65 years), and drug (eg, aspirin, $P2Y_{12}$ antiplatelet agents, nonsteroidal anti-inflammatory drugs

[NSAIDs]) or alcohol use that increases the risk of bleeding. The highest possible HAS-BLED score is 9, whereby a score of 0 suggests a low risk of bleeding, 1 to 2 an intermediate risk of bleeding, and 3 or higher indicating a high risk of bleeding. In patients with a high risk of bleeding, improvements of modifiable risk factors, such as blood pressure control and avoidance of alcohol, may assist in determining anticoagulation selection during follow-up.

Although the clinical utility of these scoring systems requires additional evidence,[4] their results are useful in identifying those at a high risk of bleeding and may aid in the decision-making process between the clinician and patient. To illustrate a thought process for clinically evaluating stroke and bleeding risks, **Figure 31.1** illustrates a decision pathway that incorporates the CHA_2DS_2-VASc in the context of the HAS-BLED score. For example, an intermediate risk of stroke (eg, CHA_2DS_2-VASc score of 1) may result in one of three therapeutic options including no antithrombotic therapy, aspirin, or oral anticoagulation therapy. To help guide the clinician and patient in this scenario, using the HAS-BLED scoring system may lead to a more conservative approach from the standpoint of bleeding risk, such as selecting no antithrombotic therapy or aspirin. On the other hand, a high risk of stroke (eg, CHA_2DS_2-VASc score of 2 or greater) and a high risk of bleeding (eg, HAS-BLED score greater of 3 or equal) is a therapeutic challenge often encountered that requires careful consideration of the risks and benefits. One approach may be to address modifiable bleeding risk factors during routine follow-up while selecting an anticoagulant with complete reversibility.

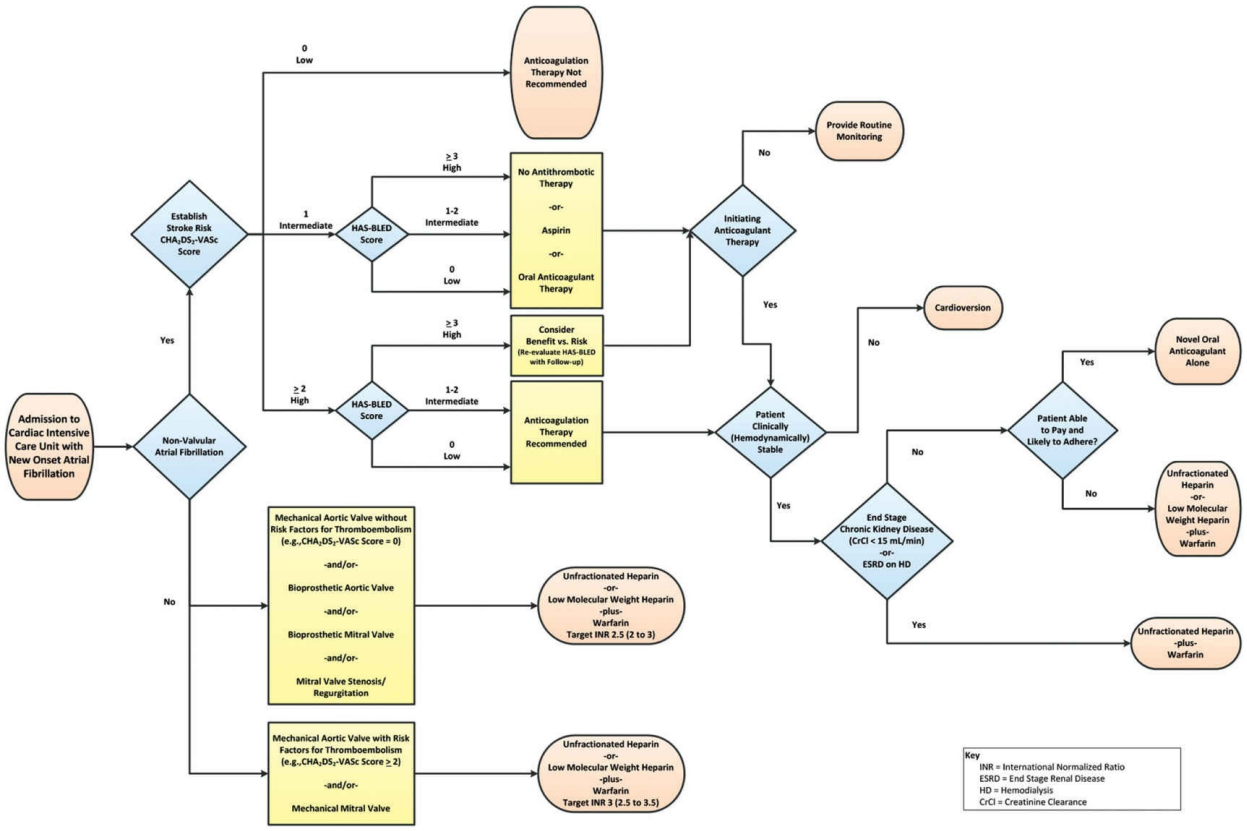

FIGURE 31.1 Anticoagulation pathway for atrial fibrillation in the cardiac intensive care unit.

Once the decision has been confirmed to initiate anticoagulation therapy in the cardiac intensive care unit, patient characteristics need to be considered for selecting an agent(s).

ANTICOAGULANT DECISION BASED ON PATIENT CHARACTERISTICS

>HEMODYNAMICALLY UNSTABLE REQUIRING CARDIOVERSION

Details surrounding patient selection criteria for and procedures involved with synchronized direct current electrical cardioversion are not discussed in this section because the technique extends beyond the scope of this chapter. For the hemodynamically unstable patient, it is important to first rule out AF as, indeed, the primary problem and not a compensatory response of another underlying condition, such as sepsis or hemorrhage.

Synchronized direct current electrical cardioversion is preferred for hemodynamically unstable patients presenting with new-onset AF greater than

48 hours for restoration of normal sinus rhythm, but does carry a risk for cardioembolic events, particularly during the first 72 hours after the procedure.[4] Anticoagulation should be initiated immediately following the procedure and continued for at least 4 weeks with life-long anticoagulation dependent upon the CHA_2DS_2-VASc score.[4, 5] Following cardioversion in hemodynamically unstable patients with AF or atrial flutter less than 48 hours, the decision to provide anticoagulation is dependent upon the patient's CHA_2DS_2-VASc score.

Warfarin has traditionally been the preferred agent for anticoagulation in combination with either UFH or an LMWH until a therapeutic INR is achieved in this setting; however, growing evidence supports the use of NOACs in this population.[4, 5] Selecting the specific anticoagulant therapy is discussed in further detail based on specific patient characteristics.

HEMODYNAMICALLY STABLE WITH ELECTIVE CARDIOVERSION

In a nonurgent setting for those who are hemodynamically stable with AF greater than 48 hours or unknown duration, transesophageal echocardiography (TEE) should be performed to exclude the left atrial thrombus for elective cardioversion.[4, 5] When a thrombus is present, anticoagulation should be initiated for 3 weeks and a repeat TEE should be completed to verify resolution to proceed with cardioversion.[4, 5] In the absence of a thrombus, the patient should proceed with immediate anticoagulation with UFH, starting with a weight-based bolus, followed by continuous infusion to attain target-aPTT, or weight-based LMWH, or a NOAC. The results of a recent trial utilizing data from the Finnish CardioVersion (FinCV) study demonstrated that peri-procedural anticoagulation reduced the risk for thromboembolic complications (TEC) by 82% and the CHA_2DS_2-VASc score provided a strong predictor for TEC post cardioversion in those without anticoagulation.[14] Following cardioversion, anticoagulation should be continued for a period of 4 weeks and life-long therapy is guided by the CHA_2DS_2-VASc score. Both warfarin and NOACs have been used for anticoagulation in this population of patients. To further consider anticoagulant selection, patient-specific factors including renal function needs to be considered.

CHRONIC KIDNEY DISEASE OR END-STAGE RENAL DISEASE ON HEMODIALYSIS

In the setting of stage 5 chronic kidney disease (CKD), defined as a creatinine clearance (CrCl) less than 15 mL/min or end-stage renal disease (ESRD) requiring hemodialysis, the NOACs have minimal data to support the use in NVAF. This is because all of these agents are, to some extent, renally excreted and thus pose an increased risk for accumulation and bleeding.[15] CKD itself poses an increased risk for bleeding as well as thromboembolism.[5] In addition, with a moderate reduction in renal function, when the CrCl calculated by the Cockcroft–Gault equation is less than 50 mL/min, NOACs have been demonstrated to differ from one another in their relative risk for major bleeding.[15] **Table 31.2** compares the differences in dosing with renal impairment for anticoagulants. LMWH as an alternative to NOAC is also not preferred in this patient population because the use is relatively contraindicated in CrCl less than 15 mL/min**.**

TABLE 31.2 Clinical Pharmacology Overview of Anticoagulants for Nonvalvular Atrial Fibrillation

	DABIGATRAN DIRECT THROMBIN INHIBITOR	APIXABAN FACTOR XA INHIBITOR	EDOXABAN FACTOR XA INHIBITOR	RIVAROXABAN FACTOR XA INHIBITOR	DALTEPARIN FACTOR XA INHIBITOR	ENOXAPARIN FACTOR XA INHIBITOR	WARFARIN VITAMIN K ANTAGONIST	UNFRACTIONATED HEPARIN
Dosing for stroke and systemic embolism prevention in nonvalvular atrial fibrillation	150 mg PO twice daily	5 mg PO twice daily	60 mg PO once daily (for patients with CrCl 51–95 mL/min)	20 mg PO once daily with evening meal	100 units/kg (actual body weight) SubQ every 12 h	1 mg/kg (actual body weight) SubQ every 12 h (Consider unfractionated heparin or anti-FXa monitoring when actual body weight exceeds 190 kg)	Initial (usual): 5 mg PO daily (Consider lower initial dose in patients with hepatic disease, CHF, malnutrition, age > 65 y, clinical hyperthyroidism, those at high risk of bleeding and those taking medications that can increase INR such as amiodarone, metronidazole, TMP/SMX, erythromycin, azole antifungals, and fluoroquinolones)	Bolus optional, if given 60 units/kg (max 4000 units) Initial infusion: 12 units/kg/h (max 1000 units/h), then titrate to institution-specific protocol based on aPTT
Onset of action for complete therapeutic effect	0.5–2 h	3–4 h	1–3 h	2–4 h	1–2 h	3–5 h	5–7 d	20–30 min
Protein binding (%)	35	78	55	92–95	Not applicable	Not applicable	Not applicable	Not applicable
Renal dose adjustments	CrCl 15–30 mL/min: 75 mg PO twice daily CrCl < 15 mL/min or on dialysis: avoid use	CrCl < 15 mL/min or on dialysis: no data Any two of the following: age ≥ 80, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL then use: 2.5 mg PO twice daily	CrCl > 95 mL/min or <15 mL/min: avoid use CrCl 15–50 mL/min, body weight < 60 kg, or if on P-gp inhibitor: 30 mg PO once daily	CrCl 15–50 mL/min: 15 mg PO once daily CrCl ≤ 15: avoid use	CrCl < 30 mL/min: monitor anti-FXa levels to determine dose, consider unfractionated heparin alternative Dialysis: avoid use	CrCl < 30 mL/min: 1 mg/kg (actual body weight) SubQ once daily Dialysis: avoid use	Not applicable	Severe renal impairment: half-life and elimination may be prolonged
Hepatic impairment	Mild: no dosage adjustments Moderate–severe: not recommended	Mild: no dosage Moderate: use caution adjustments Severe: not recommended	Mild: no dosage adjustments Moderate–severe: not recommended	Mild: no dosage adjustments Moderate–severe: not recommended	Dosage adjustments unknown, use caution or consider unfractionated heparin	Dosage adjustments unknown, use caution or consider unfractionated heparin	Consider lower initial dose and monitor PT/INR	Cirrhosis: half-life and elimination may be prolonged

Routine laboratory monitoring (considerations)	Not routinely recommended (aPTT, ECT)	Not routinely recommended (anti-FXa, PT/INR)	Not routinely recommended (anti-FXa, PT/INR)	Not routinely recommended (anti-FXa, PT/INR)	Not routinely recommended (anti-FXa)	Not routinely recommended (anti-FXa)	PT/INR	aPTT (anti-FXa)
Half-life	14 h (up to 34 h with severe renal impairment)	12 h (prolonged with renal impairment)	10–14 h Elderly: relatively unchanged (prolonged with renal impairment)	5–9 h Elderly: 11–13 h (prolonged with renal impairment)	3–5 h	4.5–7 h	20–60 h mean: 40 h (highly variable among individuals)	1.5–2.5 h
Metabolism and transport	P-gp	CYP3A4 and P-gp	Minimal CYP3A4 (primarily unchanged in urine)	CYP3A4 and P-gp	Not applicable	Not applicable	CYP2C9 (primary pathway), 2C19, 2C8, 2C18, 1A2, 3A4	Complex metabolism
Removed by dialysis	Yes (62%–68%)	No	No	No	No	No	No	No
Box warnings	Discontinuation in patients without adequate continuous anticoagulation increases risk of stroke Spinal/epidural hematoma: may occur with neuraxial anesthesia or undergoing spinal puncture; consider benefits and risks, and monitor for neurologic impairment	Discontinuation in patients without adequate continuous anticoagulation increases risk of stroke	Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl ≥ 95 mL/min Premature discontinuation increases the risk of ischemic events Spinal/epidural hematoma: may occur with neuraxial anesthesia or undergoing spinal puncture; consider benefits and risks, and monitor for neurologic impairment	Discontinuation places patients at an increased risk of thrombotic events Spinal/epidural hematoma: may occur with neuraxial anesthesia or undergoing spinal puncture; consider benefits and risks, and monitor for neurologic impairment	Spinal/epidural hematoma: may occur with neuraxial anesthesia or undergoing spinal puncture; consider benefits and risks, and monitor for neurologic impairment	Spinal/epidural hematoma: may occur with neuraxial anesthesia or undergoing spinal puncture; consider benefits and risks, and monitor for neurologic impairment	Can cause major or fatal bleeding Perform regular monitoring of INR in all treated patients Drugs, dietary changes, and other factors affect INR levels Instruct patients about prevention measures to minimize risk of bleeding and to report signs and symptoms of bleeding	None

anti-Fxa, antifactor Xa activity; aPTT, activated partial thromboplastin time; CrCl, creatinine clearance; ECT, ecarin clotting time; INR, international normalized ratio; kg, kilograms; P-gp, P-glycoprotein (transport); PO, per oral; PT, prothrombin time; SubQ, subcutaneously.

Warfarin therefore remains the oral anticoagulant option for patients with CKD stage 5 (CrCl < 15 mL/min) or ESRD requiring hemodialysis or renal replacement therapy. To achieve therapeutic INR, warfarin must be initiated with an infusion of UFH until therapeutic INR is achieved, as previously described.

HEMODYNAMICALLY STABLE WITH ADEQUATE RENAL FUNCTION

All anticoagulants are potential options for the hemodynamically stable patient with adequate renal function (defined as those with up to CKD stage 3 with CrCl > 30 mL/min). Therefore, the decision to select an anticoagulant is multifactorial. Factors to consider for anticoagulant selection are baseline risk assessment for bleeding and thromboembolic events, potential for drug interactions, patient medication adherence, compliance with provider follow-up, cost, and drug tolerability. **Table 31.2** provides an overview of the anticoagulant options for NVAF. UFH or an LMWH transitioning to warfarin has traditionally been the gold-standard anticoagulation regimen. The time in therapeutic range for target INR is an important consideration for those on warfarin because there

is a direct correlation with the annual risk for stroke or systemic embolism when frequently above or below the target range.

The NOACs include the direct thrombin inhibitor, dabigatran, and FXa inhibitors apixaban, edoxaban, and rivaroxaban. Their primary difference from that of warfarin is the rapid onset of action, which eliminates the need for bridging with UFH or an LMWH and the elimination of required laboratory monitoring for therapeutic efficacy. However, there are notable differences between each of the NOACs, which should be taken into consideration when selecting the optimal agent.

NOAC DOSING COMPARISON

Dabigatran etexilate is a prodrug that is rapidly converted into its active form dabigatran independently of the cytochrome P-450 (CYP) pathway. The lack of direct involvement with the CYP pathway is attractive to patients who may be on multiple medications, because this minimizes the risk for drug interactions, which are extensively hepatically metabolized by this means. The adverse effect of dyspepsia (5% to 10%) seen in the RE-LY (***R***andomized ***E***valuation of ***L***ong-Term Anticoagulation Therap***Y***) trial is attributed to its formulation with tartaric acid,[8] thereby making it a pH-dependent environment for absorption within the gastrointestinal tract. Thus, the medication should not be crushed or chewed and the contents of the capsule cannot be opened for administration down feeding tubes because this will increase the risk of bleeding. Taking dabigatran with food delays the onset of action up to 2 hours. It is suggested that patients requiring acid-suppressive therapy for peptic ulcer disease and individuals with total or subtotal gastrectomy as well as gastric bypass surgery should avoid this anticoagulant or use it with caution.[16]

Despite its twice-daily dosing being an issue for medication compliance, apixaban has demonstrated superiority to warfarin in NVAF. In ARISTOTLE, patients with a CHA_2DS_2-VASc score greater than 1, apixaban is associated with a lower annual incidence of stroke or systemic embolism (1.27% vs 1.60%) while having a decreased rate of lower major bleeding (2.13% vs 3.09%) than warfarin.[9] Apixaban tablets may be chewed or crushed for ease of administration down feeding tubes and are administered without regard to meals.

Edoxaban is not yet incorporated into the ACC/AHA/HRS guidelines for AF because the publication of its utility versus warfarin in NVAF in ENGAGE AF-TIMI 48 was published after the cutoff for inclusion into the most recent

guidelines.[4] However, a class I, level A recommendation in the ESC guidelines for AF yields preference to edoxaban along with the other NOACs over vitamin K antagonists (VKAs) such as warfarin.[5] Edoxaban may be administered independent of meals, but may have some benefit when administered with food, because bioavailability has been shown to increase from 6% to 22%.[16] Presently, there is no existing data on the effects of bioavailability if this medication is chewed or crushed to administer down a feeding tube.

Rivaroxaban must be administered with food because bioavailability is significantly increased from 66% to greater than 80%.[16] As with apixaban, rivaroxaban may be chewed or crushed for ease of administration down feeding tubes. The pharmacokinetic profile of this medication along with dabigatran is not affected by extremes in body weight.

Medication adherence may be a concern with both dabigatran and apixaban because they are both administered twice daily. Edoxaban and rivaroxaban may be more suitable for patients who are at risk for issues with adherence because they are administered once daily. All NOACs have shorter half-lives than their counterpart warfarin. Thus, the importance of not missing doses should be strongly emphasized during patient education because of the increased risk for embolic events.

HEPATIC AND RENAL IMPAIRMENT AND OTHER DOSAGE CONSIDERATIONS

Unlike rivaroxaban and dabigatran, apixaban is minimally excreted by the kidneys and predominantly through multiple nonrenal mechanisms including fecal and hepatic. This provides an advantage of apixaban over dabigatran, edoxaban, and rivaroxaban, with the potential for its use with moderate hepatic dysfunction. All NOACs require renal dose adjustments and should not be used in patients with an estimated CrCl < 15 mL/min depending on the individual agent.

In the ENGAGE AF-TIMI 48 study, NVAF patients with CrCl > 95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared with patients treated with warfarin.[10] Although uncommon for the majority of patients with NVAF, this anticoagulant is recommended for use only for those with a CrCl less than 95 mL/min. Apixaban and dabigatran should be used with caution in patients at and older than 80 years of age. With respect to lower extremes of weight, apixaban and edoxaban require dosage adjustment in

patients less than 60 kg.

DRUG INTERACTIONS

There are two primary considerations for drug interactions with the NOACs: CYP450 isoenzyme metabolism, specifically CYP3A4, and P-glycoprotein (P-gp) transport. Each of these mechanisms may take the form of either inhibiting or inducing drug metabolism. Inhibition may increase NOAC exposure leading to toxicities, such as major or minor bleeding events. Induction may decrease NOAC exposure leading to insufficient NOAC exposure, resulting in thrombotic events.

The CYP3A4 isoenzyme is involved in the metabolism of all NOACs, with the exception of dabigatran. Despite this advantage, many medications commonly metabolized by CYP3A4 are also involved with P-gp transport for elimination, which must be considered with concomitant use of dabigatran. Common CYP3A4 and P-gp inhibitors include erythromycin, clarithromycin, grapefruits and grapefruit juice, and protease inhibitors. Common inducers include barbiturates, phenytoin, rifampin, and carbamazepine. Additional monitoring is recommended when these agents are concomitantly administered.

CONVERTING FROM ONE ANTICOAGULATION REGIMEN TO ANOTHER

Throughout the course of an inpatient hospitalization, it may be necessary to convert between different anticoagulation regimens for NVAF. This may be particularly relevant for the patient admitted to the intensive care unit, where there may be acute changes in hemodynamics and organ function. **Table 31.3** outlines the specific details on transitioning between anticoagulation regimens.

TABLE 31.3 Converting Novel Oral and Other Anticoagulants

	APIXABAN (ELIQUIS) FACTOR Xa INHIBITOR	EDOXABAN (SAVAYSA) FACTOR Xa INHIBITOR	RIVAROXABAN (XARELTO) FACTOR Xa INHIBITOR	DABIGATRAN (PRADAXA) DIRECT THROMBIN INHIBITOR
Warfarin to NOAC	Discontinue warfarin, initiate when INR < 2	Discontinue warfarin, initiate when INR ≤ 2.5	Discontinue warfarin, initiate when INR < 3	Discontinue warfarin, initiate when INR < 2
				CrCl > 50

NOAC to warfarin	Start parenteral anticoagulant plus warfarin at next time of apixaban dose Discontinue parenteral anticoagulant when INR is within therapeutic range	(Oral option): reduce edoxaban dose in half and begin warfarin concomitantly. Measure INR at least weekly and just before edoxaban dose. Once INR stable ≥ 2, discontinue edoxaban (Parenteral option): Start parenteral anticoagulant and warfarin at time of next dose	Initiate warfarin and a parenteral anticoagulant 24 h after discontinuation of rivaroxaban	mL/min: Initiate warfarin 3 d before discontinuation of dabigatran CrCl 31–50 mL/min: initiate warfarin 2 d before discontinuation of dabigatran CrCl 15–30 mL/min: initiate warfarin 1 d before discontinuation of dabigatran
NOAC to non-warfarin oral anticoagulants	Discontinue apixaban, start new agent at time of next scheduled apixaban dose	Discontinue edoxaban, start new agent at time of next scheduled edoxaban dose	Initiate the new agent 24 h after discontinuing rivaroxaban	Discontinue dabigatran, start new agent at time of next scheduled edoxaban dose
Non-warfarin oral anticoagulants to NOAC	Discontinue current agent, start apixaban at time of next scheduled dose	Discontinue current agent, start edoxaban at time of next scheduled dose	Discontinue current agent, initiate rivaroxaban within 2 h of the next scheduled dose	Discontinue current agent, initiate dabigatran within 2 h of the next scheduled dose
LMWH to NOAC	Discontinue LMWH, start apixaban at time of next scheduled dose	Discontinue LMWH, start edoxaban at time of next scheduled dose	Discontinue the LMWH, initiate rivaroxaban within 2 h of next dose	Discontinue the LMWH, initiate dabigatran within 2 h of next dose
NOAC to LMWH	Discontinue apixaban, start LMWH at time of next dose	Discontinue edoxaban, start LMWH at time of next dose	Discontinue rivaroxaban, start LMWH at time of next dose	Discontinue dabigatran, start LMWH at time of next dose

CrCl, creatinine clearance; INR, international normalized ratio; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant.

NOAC MONITORING

Routine laboratory monitoring is not required for the novel oral anticoagulants.

The aPTT test provides an approximation of dabigatran's anticoagulant effect.

Anti-FXa activity with apixaban and rivaroxaban can be used to determine the degree of anticoagulation. Signs and symptoms of bleeding should be part of a

daily routine and managed accordingly if bleeding should occur.

ACTIVE BLEEDING AND REVERSING ANTICOAGULANTS

In the emergent need for surgery or urgent need for a procedure that might result in clinically significant bleeding, there may be a requirement for reversing the anticoagulant effects. In addition, bleeding is a heterogeneous phenomenon with management that requires individualized treatment approaches.[17] **Figure 31.2** illustrates a decision pathway for addressing bleeding while on anticoagulants, and **Tables 31.4 to 31.6** provide information on reversal strategies for anticoagulants used when treating AF. The use of a reversal agent is probably not warranted in most cases when active bleeding is responding to supportive care, attempting to accelerate the time to an elective procedure, a response to high drug serum concentrations, or elevated laboratory parameters.[4]

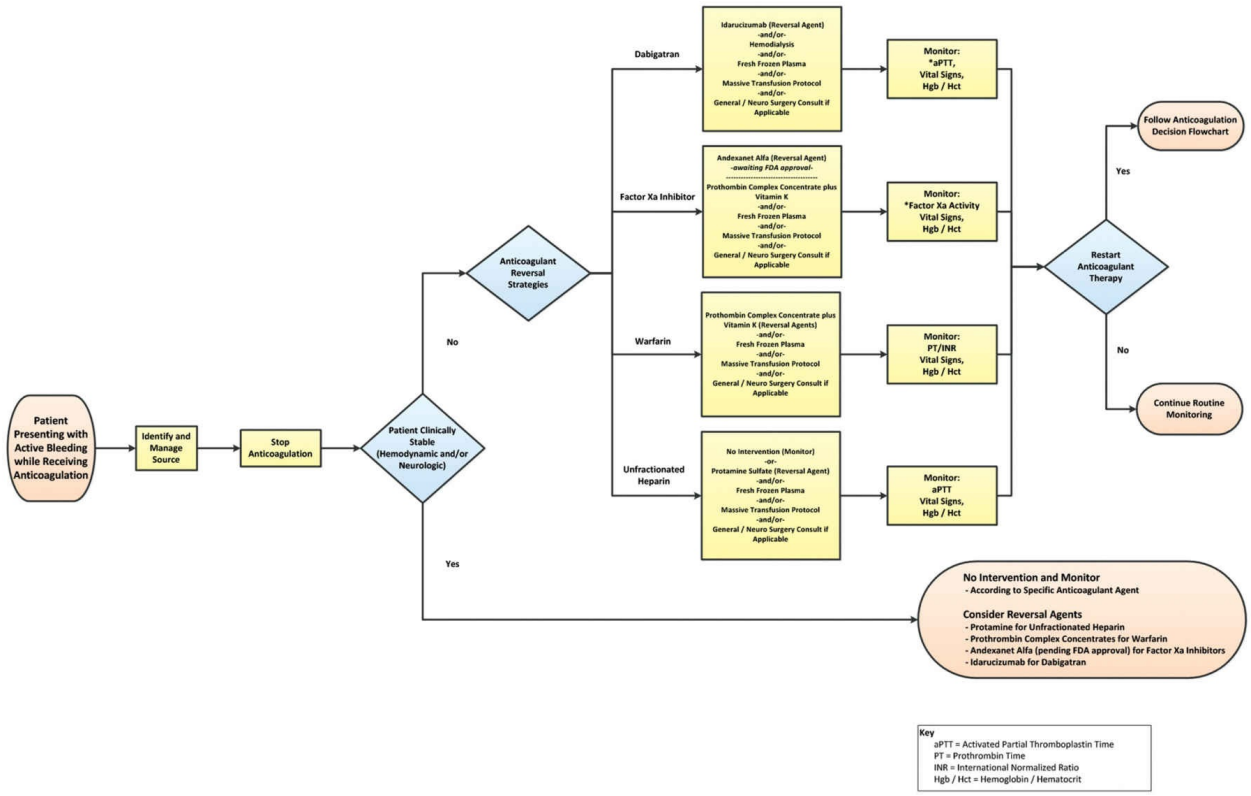

FIGURE 31.2 Pathway for active bleeding with anticoagulation.

TABLE 31.4 Reversal Strategies for Anticoagulants

	APIXABAN FACTOR XA INHIBITOR	EDOXABAN FACTOR XA INHIBITOR	RIVAROXABAN FACTOR XA INHIBITOR	ENOXAPARIN FACTOR XA INHIBITOR	DABIGATRAN DIRECT THROMBIN INHIBITOR	WARFARIN VITAMIN K ANTAGONIST	UNFRACTIONATED HEPARIN
Reversal agents	Prothrombin complex concentrate, 4-factor	Prothrombin complex concentrate, 4-factor	Prothrombin complex concentrate, 4-factor	Prothrombin complex concentrate, 4-factor	Idarucizumab	Prothrombin complex concentrate, 4-factor-plus-vitamin K[c]	Protamine sulfate
Alternative reversal agents	Andexanet alfa[a] (pending US FDA approval)	Andexanet alfa[a] (pending US FDA approval)	Andexanet alfa[a] (pending US FDA approval)	Protamine sulfate[b] Andexanet alfa[a] (pending US FDA approval)	None	Fresh frozen plasma-plus-vitamin K[c]	None
Reversal dosing	Andexanet alfa[a] 400 mg IV bolus over 15–30 min, then 480 mg IV infusion over 2 h (if apixaban last dose > 7 h)	Andexanet alfa[a] 800 mg IV bolus over 15–30 min, then 960 mg IV infusion over 2 h (if edoxaban last dose ≤ 7 h or unknown time)	Andexanet alfa[a] Low dose: 400 mg IV bolus over 15–30 min, then 480 mg IV infusion over 2 h; or High dose: 800 mg IV bolus over 15–30 min, then 960 mg IV infusion over 2 h Higher dose used if rivaroxaban last dose ≤ 7 h or unknown time	Andexanet alfa[a] 800 mg IV bolus over 15–30 min, then 960 mg IV infusion over 2 h if ≤7 h since last dose or unknown time	5 mg (2 × 2.5 g vials) as a slow IV push or infusion	PCC 4-factor: INR 2–3.9: 25 units/kg, max 2500 units INR 4–6: 35 units/kg, max 3500 untis INR > 6: PCC 50 units/kg, max 5000 units vitamin K[c] 10 mg infused IV over 30 min when used with PCC	Each 1 mg protamine reverses 100 units of heparin Maximum dose: 50 mg IV An additional 50% of the initial dose may be needed
Hemodialysis removal	No	No	No	20%	Yes 62%–68%	No	Partial
Activated charcoal	Consider use if appropriate	Consider use if appropriate	Consider use if appropriate	Not recommended	Consider use if appropriate	Not recommended	Not recommended

INR, international normalized ratio; IV, intravenous; PCC, prothrombin complex concentrate.
Prothrombin complex concentrate, 4-factor use is off-label for reversing apixaban, edoxaban, rivaroxaban, and enoxaparin.
[a]Andexanet alfa is not yet approved by the United States Food and Drug Administration, doses adapted from the ANNEXA-4 interim analysis study.
[b]Evidence does not support complete reversal of the anticoagulant effect. Use clinical judgment and consider other treatment options.

TABLE 31.5 Reversal of Warfarin for Elevated INR and/or Bleeding

INR < 5 without significant bleeding	Lower or hold next dose, then resume at lower dose when INR is therapeutic
INR between 5 and 9 without significant bleeding	Hold warfarin until INR is in therapeutic range, then resume at a lower dose May consider PO vitamin K 2.5 mg
INR > 9 without significant bleeding	Hold warfarin and give PO vitamin K 2.5–5 mg, expect INR reversal in 24–48 h
Significant bleeding with any INR	Hold warfarin Administer prothrombin complex concentrate (PCC) 25–50 units/kg-or-FFP 15 mL/kg (1 unit = 200–250 mL) plus vitamin K IV[a] 10 mg over 30 min depending on clinical situation Note: Expect INR reversal with vitamin K within 12–48 h, FFP within 1–4 h, and PCC within

15 min PCC preferred option in patients with TBI and/or ICH

[a]Evidence does not support complete reversal of the anticoagulant effect. Use clinical judgment and consider other treatment options.
FFP, fresh frozen plasma; ICH, intracranial hemorrhage; INR, international normalized ratio; IV, intravenously; PCC, prothrombin complex concentrate; PO, per oral; TBI, traumatic brain injury.

TABLE 31.6 Protamine Sulfate Dosing for Low-Molecular-Weight and Unfractionated Heparins

TIME SINCE LAST LMWH DOSE	PROTAMINE DOSE FOR EACH: DALTEPARIN 100 UNITS OR ENOXAPARIN 1 MG
<8 h	1 mg (or 50 mg fixed dose)
8–12 h	0.5 mg (or 25 mg fixed dose)
>12 h	Not likely useful (consider 25 mg fixed dose)
TIME SINCE LAST HEPARIN DOSE	**PROTAMINE DOSE FOR EACH 100 UNITS OF HEPARIN**
Immediate	1 mg (or 25 mg fixed dose)
30 min	0.5 mg (or 10 mg fixed dose)
>2 h	0.25 mg (or 10 mg fixed dose)
Consider a second protamine dose (50% of first dose) if prolonged aPTT continues	

aPTT, activated partial thromboplastin time; LMWH, low-molecular-weight heparin.

The source of bleeding has to be appropriately identified, managed, and treated such that rapid reversal of anticoagulation will not necessarily solve the underlying bleeding.[4] Thus, once bleeding is identified, the first priority is to locate the source and discontinue the anticoagulant agent. The clinical stability of the patient should serve as a guide for the next steps. For example, significant blood loss causing hypovolemic shock from a gastrointestinal bleed may require volume administered with blood transfusions. In addition, directly reversing the anticoagulant effect may also aid in restoring the bleeding diathesis. On the other hand, an intracranial hemorrhage generally requires less volume, but directly reversing the anticoagulant effect may be preferred. Volume restoration during hemorrhage, for example, with crystalloids, colloids, and/or blood transfusion protocols is beyond the scope of this chapter, but an overview of anticoagulant reversal agents is provided.

Reversal agents and strategies discussed include idarucizumab for dabigatran,

andexanet alfa (andexanet) for anti-FXa NOACs and LMWHs, prothrombin complex concentrates (PCCs) with vitamin K for warfarin, and protamine sulfate for UFH. Andexanet is currently in later phases of premarketing clinical trials. An additional agent, ciraparantag, is in very early stages of development with a broader spectrum of anticoagulants potentially reversed by this agent.

IDARUCIZUMAB FOR DABIGATRAN REVERSAL

Idarucizumab is a monoclonal antibody fragment that binds dabigatran with a 350-fold or so higher affinity to that of thrombin.[18] As a result, idarucizumab adheres to thrombin-bound dabigatran and neutralizes its activity. Currently, idarucizumab is approved by the US FDA for the reversal of the anticoagulant effects of dabigatran, needed for emergency surgery/urgent procedures or in life-threatening or uncontrollable bleeding.

The RE-VERSE AD trial examined the safety and reversal capacity of idarucizumab on dabigatran in patients who had a serious bleeding event or required reversal for an urgent procedure.[18] Serious bleeding was defined as overt, uncontrollable, or life-threatening bleeding that was judged by the treating clinician to require a reversal agent, and an urgent procedure was defined as requiring surgery or other invasive procedures that could not be delayed for at least 8 hours and for which normal hemostasis was required.[18] Idarucizumab was administered as a 5-g dose divided into two separate bolus infusions of 2.5 g in 50 mL within 15 minutes of one another. The results demonstrated rapid and complete reversal effects of dabigatran in 88% to 98% of patients.[18]

Idarucizumab is not without potential side effects that may include direct effects of the agent such as anaphylaxis, other hypersensitivity reactions, and serious reactions with hereditary fructose intolerance because sorbitol is a component of the preparation. A prothrombotic effect of dabigatran reversal by idarucizumab leading to thrombosis may also occur once the anticoagulant effects have been reversed, for example, in those with a high CHA_2DS_2-VASc score. In some patients, a delayed increase in dabigatran serum concentrations, such as 12 to 24 hours after idarucizumab administration, may reflect an increase in clotting time markers possibly due to intravascular redistribution of dabatran.[18] It is unknown whether additional doses of idarucizumab would be effective and safe in such scenarios.[18]

Because the cost of each dose of idarucizumab is currently in the several thousands of US dollars, it may be fiscally prudent for hospitals and health

systems to create multidisciplinary policies, procedures, and standardized protocols. Components of such consensus documents may include selecting appropriate clinical scenarios for use, monitoring parameters and frequencies, procurement quantities, and location of refrigerator storage within the institution to avoid waste.

ANDEXANET ALFA FOR FACTOR XA INHIBITOR REVERSAL

Not yet approved by the US FDA, andexanet alfa (andexanet) is a recombinant modified human FXa decoy protein that reverses the inhibitory effects of anti-FXa agents.[19] These counteractive effects of FXa inhibition by NOACs and LMWHs restore FXa activity and therefore the potential for clot formation.

The ANNEXA-4 trial is actively evaluating the activity of andexanet in patients with acute major bleeding within 18 hours of the administration of an FXa inhibitor, including apixaban, edoxaban, rivaroxaban, and enoxaparin.[19] Andexanet was administered by an initial bolus infusion over 15 to 30 minutes followed by a 2-hour infusion to maintain activity against the anti-FXa agent. Doses were relatively lower for patients who had taken apixaban or rivaroxaban more than 7 hours before the administration of andexanet and higher for patients who had taken enoxaparin, edoxaban, or rivaroxaban 7 hours or less before the administration of the bolus dose or at an unknown time. Clinical monitoring parameters for efficacy endpoints included changes in anti-FXa activity and hemostasis within a 12-hour period.[19] The most updated preliminary analysis of this ongoing trial demonstrated 79% of patients with relatively effective hemostasis after receiving the bolus and 2-hour infusion of andexanet. There were no reported serious side effects attributed directly to andexanet; however, thrombotic events occurred in 18% of patients.[19]

Additional data from the ongoing ANNEXA-4 trials, as well as from controlled trials, are needed to determine the safety of thrombotic event frequency compared with what is expected.[19] Further research is necessary to understand how this antidote will be used in clinical practice.

PROTHROMBIN COMPLEX CONCENTRATES WITH VITAMIN K FOR WARFARIN REVERSAL

The traditional approach to treat bleeding associated with warfarin is to administer fresh frozen plasma (FFP). However, there are significant drawbacks with using FFP. All clotting factors are included in FFP, derived from human

plasma, which often contains numerous antibodies. This increases the risk of infusion-related reactions, with the most severe consequence being transfusion-related acute lung injury. In addition, an extensive volume (15 mL/kg per unit) is required for reversal, which may be a limiting factor for volume-restricted patients with poor cardiovascular status. FFP also possesses its own intrinsic INR ranging from 1.5 to 1.7, owing to the presence of all clotting factors.

PCC is a concentrated form of factors II, VII, IX, and X and proteins C and S, which specifically targets all mechanisms involved with warfarin and includes those involved with NOACs. This product requires a higher degree of purity for processing compared with FFP, which dramatically lessens the likelihood of transfusion-related complications. The major advantages of PCC is that reversal requires much smaller volumes (1 to 2 mL/kg per unit), which can be infused over a shorter period of time.

Vitamin K may be administered as an individual agent in the setting of INR elevations with warfarin without significant bleeding. When administered as a single agent as intravenous or po, it is extremely slow to reverse the effects of INR, which will not be evident until approximately 24 to 48 hours after administration.

Over time, concentrated vitamin-K–dependent clotting factors have been used until recently with the introduction of 4-factor (4F)-PCC with vitamin K. In a multicenter, open-label, randomized, plasma-controlled noninferiority clinical trial using FFP versus 4F-PCC in patients with acute bleeding associated with VKA therapy for the achievement of effective hemostasis within 24 hours was evaluated. Superiority was also examined through reduction of INR to ≤1.3 within 30 minutes of the completed infusion.[20] Effective hemostasis was defined as cessation of bleeding within 4 hours of the end of the infusion and no additional coagulation intervention required within 24 hours. Within 24 hours, hemostasis was achieved in 72.4% of those receiving 4F-PCC versus 65.4% receiving FFP, demonstrating noninferiority.[20] There was no statistically significant difference detected for mortality or length of stay between 4F-PCC and FFP. Serious adverse events associated with reversal of VKAs with 4F-PCC were reported in 31% of patients, of which only 10 were deemed directly related to treatment.[20] When compared with FFP, rates of serious adverse events appeared similar; however, no clinical trial has been powered to specifically evaluate differences in safety.

Tables 31.4 and 31.5 outline the specific information regarding the dosing for FFP, PCC, and vitamin K for anticoagulation reversal.

PROTAMINE FOR REVERSAL OF HEPARINS

Particularly relevant to those patients requiring bridging with UFH when initiating therapy with warfarin, protamine will provide an effective means for stopping acute bleeding. There is no role for the use of protamine for reversal of NOACs. Protamine provides complete reversal of anticoagulant effects from UFH and partial reversal with LMWH, enoxaparin and dalteparin. See **Table 31.6** for dosing recommendations for protamine, which is based on administration times for each anticoagulant. Protamine should be administered slowly, with a maximum dose of 50 mg over 10 minutes to minimize the adverse effect of hypotension. If outcomes are promising from the future reversal agent in the pipeline, ciraparantag may end up replacing protamine for these agents, noting its broad effect upon reversal of anticoagulants.

REINITIATING ANTICOAGULATION POST BLEEDING

When bleeding occurs, especially from the gastrointestinal or urinary tracts, the presence of an underlying occult lesion should always be considered.[3] Once hemostasis is achieved, the decision whether and when to reinitiate anticoagulation therapy after reversing the anticoagulant effects for a severe bleeding episode may be necessary and should be considered on an individualized basis.[4] The ongoing use of the $CHADS_2$-DS_2-VASc and HAS-BLED systems together may provide guidance in this particular decision-making process. In patients for whom anticoagulation therapy is needed after hospitalization for a gastrointestinal bleed, reinitiating anticoagulation within 90 days of the event demonstrated positive outcomes on thrombotic events and death.[21, 22]

PERIOPERATIVE BRIDGING FOR SURGERY AND PROCEDURES

When chronic anticoagulation therapy is required, such as in AF, adequate anticoagulation before and after surgery or an invasive procedure may be needed, particularly when the risk of thromboembolism is high. The concept of anticoagulant “bridging” is essentially administering a short-acting anticoagulant (eg, UFH or LMWH) during the time when a long-acting warfarin is being withheld before the surgery, then continued after the surgery or procedure until

the long-acting anticoagulant is again within the target therapeutic range.[23] Because the NOACs have a faster offset of action compared with warfarin and a rapid onset of action, bridging with UFH or an LMWH may not be necessary, unless the patient is not able to take oral therapy such as with gastric resection or postoperative ileus.[23]

Not all procedures require anticoagulants to be held, for example, minor dental and skin procedures, cataract extraction, and selected cardiac device implantation.[23] The NOACs need to generally be held for 1 to 4 days before the procedure, with the interruption interval depending on the specific agent, patient's renal function, and type of bleeding risk of the procedure.[24] **Table 31.7** provides recommendations by the manufacturers and from clinical trials for the timing of discontinuing anticoagulants before surgery or procedures. Postoperative resumption of NOACs should take into account their rapid onset of action (1 to 3 hours postingestion), and can be restarted approximately 24 hours after low-bleed risk and 48 to 72 hours after high-bleed risk procedures.[24] With urgent surgery, there is no evidence suggesting higher bleeding rates with NOACs as compared with patients treated with warfarin.[24]

TABLE 31.7 Periprocedural Bridging: Anticoagulation Interruption for Surgery and Procedures

	APIXABAN FACTOR XA INHIBITOR	EDOXABAN FACTOR XA INHIBITOR	RIVAROXABAN FACTOR XA INHIBITOR	ENOXAPARIN FACTOR XA INHIBITOR	DABIGATRAN DIRECT THROMBIN INHIBITOR	WARFARIN VITAMIN K ANTAGONIST	UNFRACTIONATED HEPARIN
Procedures to not withhold anticoagulation	Not all procedures require anticoagulation to be held. Examples include minor dental procedures (such as cleaning, scaling, extraction), minor skin procedures, cataract extraction, selected cardiac device implantation, and routine endoscopy. Design a plan with the clinician performing the procedure and the patient.						
Elective low risk surgery and procedures	Discontinue apixaban at least 24 h before elective procedure	Discontinue edoxaban at least 24 h before invasive or surgical procedures. Risk of bleeding should be considered against the urgency of intervention if surgery cannot be delayed	Discontinue rivaroxaban at least 24 h before the procedure	Discontinue 12–18 h before the procedure	CrCl ≥ 50 mL/min Discontinue dabigatran 1–2 d before elective procedure CrCl < 50 mL/min Discontinue dabigatran 3–5 d before elective procedure	Discontinue until desired INR is reached (usual target < 1.5, acheived over 4–5 d)	Discontinue 6–12 h before procedure
Elective moderate to high-risk surgery and procedures	Discontinue apixaban at least 48 h before elective procedure	Discontinue edoxaban at least 24 h before invasive or surgical procedures. Risk of bleeding should be considered against the urgency of intervention if surgery cannot be delayed	Consider longer times based on clinical judgment	Discontinue 12–18 h before the procedure	Consider longer times for major surgery, spinal puncture, or spinal or epidural catheter or port placement	Discontinue until desired INR is reached (usual target < 1.5, acheived over 4–5 d)	Discontinue 6–12 h before procedure

CrCl, creatinine clearance; INR, international normalized ratio.

The BRIDGE investigators conducted a randomized, double-blind, placebo-controlled trial to determine whether foregoing anticoagulant bridge therapy in patients with AF treated with warfarin is noninferior to bridging with the LMWH dalteparin and superior with respect to major bleeding.[25] The mean $CHADS_2$ score was 2.3 (CHA_2DS_2-VASc score was not used for risk stratification at the time of the trial) with only about one-third with a score of 3 or higher, suggesting a relatively lower risk of thrombosis. It is important to point out that patients at high risk for thrombosis, such as those with CHA_2DS_2-VASc scores 2 or greater, and/or those requiring higher intensity warfarin, for example, with mechanical mitral valves may still require perioperative bridge therapy because these scenarios were excluded in the study.[25] In addition, surgical procedures associated with high risks of thrombosis, such as carotid endarterectomy, major cancer surgery, cardiac surgery, or neurosurgery were excluded from the trial. The results of this trial, demonstrated in patients with

AF on warfarin therapy, that LMWH perioperative bridge therapy did not prevent thromboembolic events, but did increase the risk of major bleeding.

It therefore may be reasonable to forego bridging warfarin with UFH or an LMWH in patients at relatively low thromboembolic risk and undergoing procedures to avoid clinically significant bleeding. Using this approach, the patient would therefore discontinue warfarin usually until the INR decreases to below 1.5 (approximately 5 days) before the procedure without being additionally anticoagulated. The perioperative treatment plan should therefore be designed in collaboration with the operating clinician and the patient.

ANTIPLATELET THERAPIES WITH ATRIAL FIBRILLATION

The Stroke Prevention in Atrial Fibrillation-1 (SPAF-1) trial from the early 1990s is the only trial among eight or so evaluated in a meta-analysis to show the benefit of aspirin alone in preventing stroke among patients with AF.[4] The dose seemingly effective was aspirin 325 mg once daily. Aspirin was not effective in those older than 75 years of age, did not prevent severe stroke, and has not been studied in low-risk populations.[4]

Clopidogrel 75 mg once daily plus aspirin 75 to 100 mg once daily was evaluated for stroke prevention in the ***A***trial Fibrillation ***C***lopidogrel ***T***rial With ***I***rbesartan for Prevention of ***V***ascular ***E***vents (ACTIVE-W) trial and terminated early because in patients with a mean $CHADS_2$ score of 2, the combination of antiplatelet agents was inferior to warfarin (target INR 2 to 3).[4] The ACTIVE-A trial compared clopidogrel plus aspirin versus aspirin alone and demonstrated superiority in stroke prevention of the combination antiplatelet therapy to aspirin alone; however, the benefits were diminished by the increases in severe bleeding rates.

The AVERROES study was a direct comparison between aspirin and the FXa inhibitor apixaban.[4, 26] This double-blind study of 5,599 patients deemed unsuitable for warfarin therapy were randomized to apixaban 5 mg twice daily (2.5 mg twice daily for those who had two of the following three: age ≥ 80 years, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL) or to aspirin 81 or 325 mg once daily. The trial was prematurely terminated owing to the observed superiority of apixaban over aspirin for the occurrence of any stroke or systemic embolism.

Major bleeding rates were similar between apixaban and aspirin.

With respect to triple antithrombotic therapy with concomitant dual antiplatelet agents and NOACs, there is a paucity of literature for evaluation. Several landmark trials that studied NOACs for stroke prophylaxis with NVAF excluded the combination of aspirin with a $P2Y_{12}$ inhibitor (eg, clopidogrel, prasugrel, ticagrelor).[8–11,26] Therefore, an important remaining unanswered question is in patients with AF requiring anticoagulation and at the same time dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor for coronary intervention such as stenting.

The SAFE-A study that compares 1-month versus 6-month $P2Y_{12}$ inhibitor therapy in combination with aspirin and apixaban, in patients with AF who undergo drug-eluding stent implantation, is currently under way.[27] The primary outcome will be the incidence of all bleeding complications occurring within 12 months. Ultimately, this study will provide data that may guide the optimal management of triple antithrombotic therapy.

Additional medications that have antiplatelet properties should be used with caution when taken concomitantly with NOACs. Such agents include NSAIDs, such as naproxen, ibuprofen, celecoxib, diclofenac, and meloxicam. In addition, selective serotonin reuptake inhibitors (SSRIs) commonly used as antidepressants, such as paroxetine, fluoxetine, sertraline, citalopram, and escitalopram, and serotonin norepinephrine reuptake inhibitors (SNRIs) commonly used as antidepressants and neurogenic pain analgesics, such as duloxetine and venlafaxine, should be used with caution.

ABILITY TO PAY AND LIKELY TO ADHERE TO THERAPY

Perhaps the greatest risk factor for thrombotic events with AF is the inability to take the prescribed anticoagulant on a daily basis.[4] This is particularly important with NOACs because the duration of action is shorter than that of warfarin, so missing even one dose of a NOAC increases the risk of thrombosis.

The reasons for nonadherence to a drug therapy regimen are multifaceted and highly individualized. Barriers that cause patients not to take their medication as prescribed may include the health literacy of the patient and/or caregiver, emotional state and acceptance of the need for chronic daily medications, side effects and intolerances, and the inability to obtain the drug because of cost or

other reasons. Discontinuing a NOAC should not occur without proper anticoagulant coverage, such as with warfarin and/or LMWH for patients who will still require treatment.[4] During the transitions of care when patients are admitted to and discharged from the hospital and/or patient care units, it is critical to accurately reconcile the medication regimen, including anticoagulant therapy to avoid thromboembolic events from omission errors. Prescribers are encouraged to discuss outpatient prescription drug coverage and the patient's intentions and ability to continue the oral anticoagulant therapy upon hospital discharge.

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Patient and Family Information for: MODERN ANTICOAGULATION THERAPY

ATRIAL FIBRILLATION

AF is an irregular heart beat that increases the risk of forming a blood clot in the heart. If the blood clot travels from the heart, it can cause a stroke. Anticoagulants are medications that lower the chances of having a stroke by thinning the blood and therefore helping to prevent clots from forming.

A patient who stops taking the prescribed anticoagulant may have an increased risk of forming a clot in the heart and bloodstream. Do not stop taking the prescribed anticoagulant without talking to the doctor who prescribed it. Missing even one dose may increase the chances of forming a blood clot. In case the anticoagulant medicine has to be stopped, be sure to tell the doctor.

TAKING ANTICOAGULANT MEDICATIONS

Take medication exactly as prescribed by the doctor. If the instructions are not clear, ask the doctor or pharmacist to explain.

- Do not change the dose or stop taking the anticoagulant unless the doctor says so.
- The doctor will tell how much medicine to take and when to take it.
- The doctor may change the dose if needed.

SIDE EFFECTS

All medications have the potential to cause side effects, and anticoagulants are no exception. There is a difference between an allergic reaction and a side effect. Allergic reactions are types of side effects, for example, a rash, which usually means the patient never takes the medicine again. Side effects, for example, bleeding or an upset stomach, due to an anticoagulant are usually dealt with simply by stopping the medication or changing to another similar alternative. It is important to report any side effects the patient may think he or she is having and to get medical help right away if the patient thinks he or she is bleeding. It is important to learn the signs or symptoms of bleeding.

Anticoagulants can cause bleeding in the brain that can be serious and can cause internal bleeding, which on rare occasions lead to death. This is because anticoagulants are blood thinner medications that reduce blood clotting. While on anticoagulants, the patient is likely to bruise more easily and it may take longer for the bleeding to stop. Do not stop taking the anticoagulant without notifying the doctor on noticing bruising.

SIGNS AND SYMPTOMS OF BLEEDING

Examples of unexpected bleeding or bleeding that lasts a long time may include the following:

- Unusual bleeding from the gums
- Nose bleeds that happen often
- Menstrual bleeding that is heavier than normal or vaginal bleeding
- Bleeding that is severe or cannot be controlled
- Red, pink, or brown urine
- Bright red or black tarry stools
- Coughing up blood or blood clots
- Vomiting blood or the vomit looks like “coffee grounds”
- Headaches and feeling dizzy or weak
- Pain, swelling, or new drainage at wound sites

DRUG INTERACTIONS

There is a chance that while on anticoagulants the patient may have a higher likelihood of bleeding if he or she takes other medicines that cause bleeding. These medications may include aspirin or aspirin-containing products, clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), NSAIDs, SSRIs, SNRIs, or any other medicines to prevent or treat blood clots. Inform the doctor about taking any of these medicines and ask the doctor or pharmacist if unsure whether the medicine is one among those listed earlier. Also ask the doctor or pharmacist before taking any new medications, over-the-counter medications, vitamins, or herbal supplements.

SPINAL OR EPIDURAL BLOOD CLOTS

People who take a blood thinner medicine and have an injection into their spinal and epidural area or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move.

It is important to recognize the signs and symptoms of spinal or epidural blood clots if receiving spinal anesthesia or a spinal puncture. Tell the doctor immediately in case of back pain, tingling, numbness, muscle weakness (especially in the legs and feet), and loss of control of the bowels or bladder (incontinence).

Do not take an anticoagulant, without first talking to the doctor, under the following conditions:

- If the patient has certain types of abnormal bleeding
- If the patient is allergic to the prescribed medication or any of the ingredients; a pharmacist can help identify these ingredients

What to tell the doctor before taking an anticoagulant medication: Inform the doctor about the following:

- Bleeding problems
- Liver or kidney problems
- Any other medical condition
- Being pregnant or planning to become pregnant
- Breastfeeding or plan to breastfeed

Tell the doctor about all the medicines the patient takes, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Also inform all the doctors and dentists about taking an anticoagulant medication.

They should talk to the doctor who prescribed the anticoagulant before the patient has any surgery and medical or dental procedure.

How to take anticoagulant medications:

- Take the medication exactly as prescribed by the doctor.
- Do not change the dose or stop taking the anticoagulant unless the doctor says so.
- The doctor will tell how much anticoagulant to take and when to take it.
- The doctor may change the dose if needed.

How to store anticoagulant medication:

- Anticoagulant medications should be stored at room temperature between 68°F to 77°F (20°C to 25°C).
- Be sure to keep all medicines out of the reach of children.

VI

RISK FACTORS: FROM THE ACUTE SETTING TO CHRONIC MANAGEMENT

32

Alan F. Vainrib
Muhamed Saric

Acute Aortic Syndrome

INTRODUCTION

Acute aortic syndrome (AAS) represents a spectrum of life-threatening conditions with similar clinical presentation and the need for urgent management. It includes classic acute aortic dissection (CAAD), intramural hematoma (IMH), and penetrating aortic ulcer (PAU). Although not included in the original definition of AAS, traumatic aortic rupture (TAR) and aortic aneurysm rupture have also been considered to be part of the AAS spectrum.

AAS is characterized by disruption of the media layer of the aorta and typically presents with acute chest pain. The term “acute aortic syndrome” was first coined in 2001 by the Spanish cardiologists Vilacosta and San Román, who described AAS as a spectrum of interlinked lesions[1] with the intent to increase awareness and to speed up diagnosis and appropriate treatment (**Figure 32.1**).

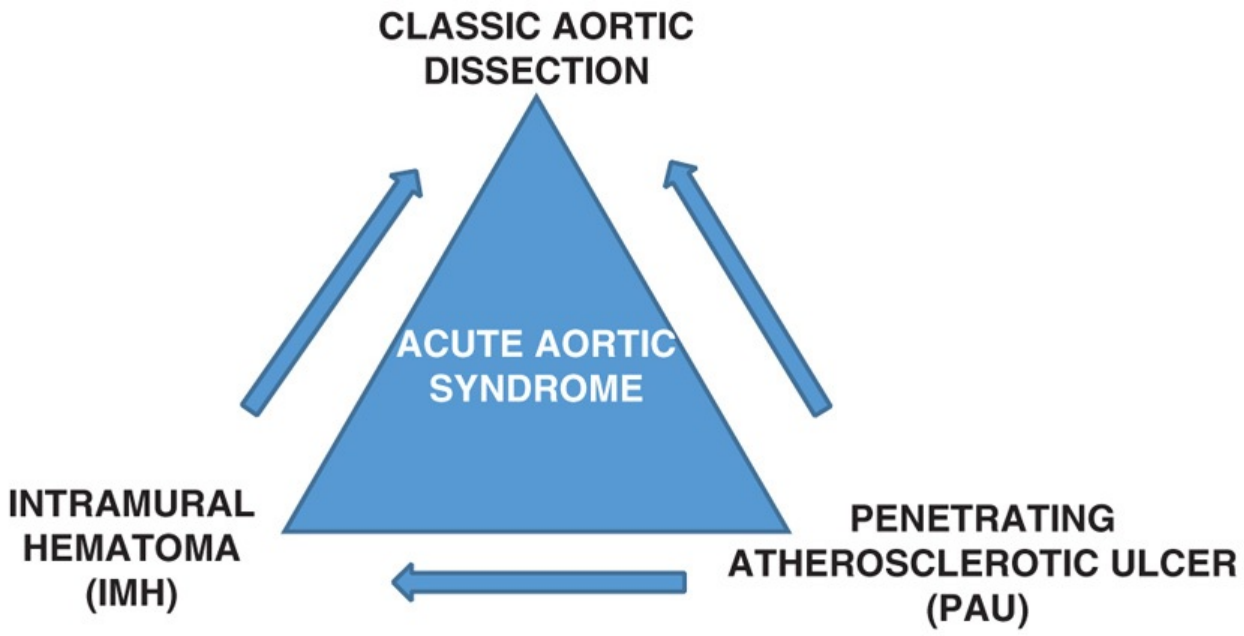

FIGURE 32.1 Acute aortic syndrome. The acute aortic syndrome triad first described by Vilacosta and San Román. Arrows signify possible progression of aortic lesions (penetrating aortic ulcer to IMH, penetrating aortic ulcer to classic dissection, IMH to classic dissection). IMH, intramural hematoma.

Although the incidence of AAS is lower than that of acute coronary syndrome (ACS), AAS carries a higher mortality, and is therefore a critical component of the differential diagnosis of chest pain in the Cardiac Care Unit (CCU). Overall incidence of AASs is 2 to 4 cases per 100,000 individuals. Because AAS is rare, the International Registry of Acute Aortic Dissection (IRAD) was created in 1996 as a way to combine data acquired from multiple top institutions in Europe, North America, and Asia.[2] The 2010 intersocietal guidelines for the diagnosis and management of patients with thoracic aortic disease proposed a standard approach to the diagnosis and treatment of AAS.[3]

Although clinical history and physical examination are important, imaging is essential in the diagnosis of AAS. Transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI) are the preferred imaging modalities and angiography is rarely needed.

CLASSIFICATION OF ACUTE AORTIC SYNDROMES

Historically, CAAD was the first recognized form of AAS. The classification schemes used for the classic aortic dissection were subsequently extended to

include IMH and PAU.

AASs are classified on the basis of the location and extent of involvement of the aorta. Two systems have been proposed, the DeBakey and the Stanford systems (**Figure 32.2**). The DeBakey system, which was proposed in 1965 by the Lebanese-American surgeon Michael Ellis DeBakey, divided aortic dissection into three types based on the anatomic location. Type I originates in the ascending aorta and propagates beyond the aortic arch, type II is limited to the ascending aorta only, and type III is limited to the descending aorta.[4]

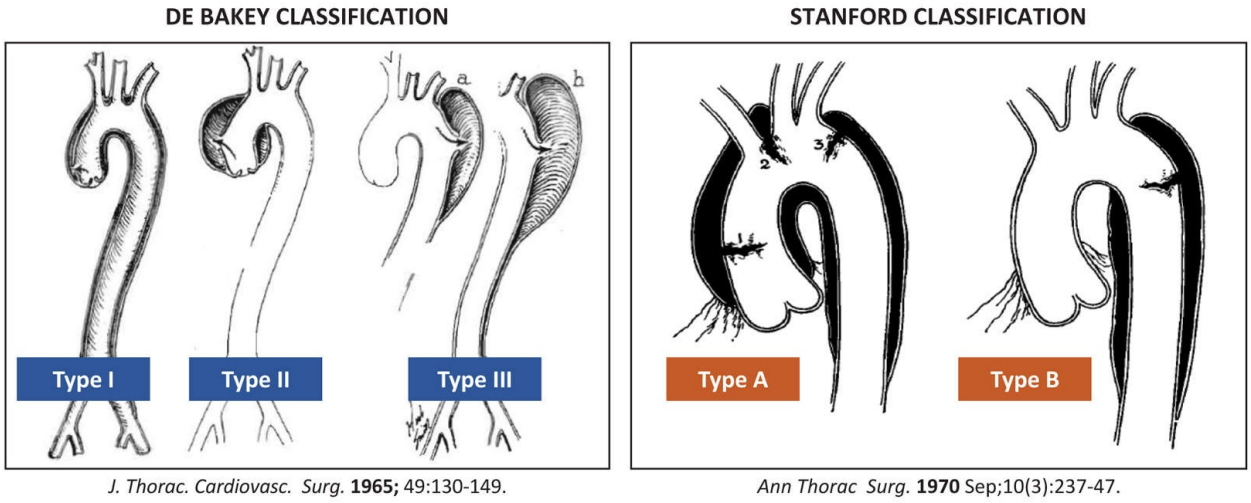

FIGURE 32.2 DeBakey and Stanford classifications. Left: DeBakey classification of aortic dissection. Type I includes the ascending and descending aorta, type II includes the ascending aorta only, and type III includes the descending thoracic aorta only. (DeBakey ME, Henly WS, Cooley DA, et al. Surgical management of dissecting aneurysms of the aorta. *J Thorac Cardiovasc Surg.* 1965;49:130-149.) Right: Stanford classification. Type A aortic dissection involves the ascending thoracic aorta, and type B involves the descending thoracic aorta only. All three AAS conditions; CAAD, IMH, and PAU use the Stanford classification. CAAD, classic acute aortic dissection; IMH, intramural hematoma; PAU, penetrating aortic ulcer. (Daily PO, Trueblood HW, Stinson EB, et al. Management of acute aortic dissections. *Ann Thorac Surg*. 1970;10[3]:237-247.)

The Stanford system, which was created by researchers at Stanford University in 1970, divides aortic dissections into two types. Type A includes any dissection that involves the ascending aorta, whereas type B dissections are limited to the descending thoracic aorta.[5] The Stanford classification appears to have wider acceptance and is now used for all three AAS types: CAAD, IMH, and PAU.

INTRAMURAL HEMATOMA

IMH is defined by crescentic or circumferential thickening of the media layer of

the aortic wall. IMH is likely due to a ruptured vasa vasorum resulting in intramural bleeding but without a detectable intimal tear. It was first described in 1920 by the German pathologist Ernst Kruckenberg, who is also well known for his description of the so-called Kruckenberg tumors (transperitoneal ovarian metastases from stomach and colon cancers). On TEE, CT, or MRI, IMH is typically visualized as a crescentic or concentric thickening of the aortic wall > 5 mm (**Figure 32.3**). The natural history of IMH often includes progression to CAAD, which accounts for its high morbidity and mortality.

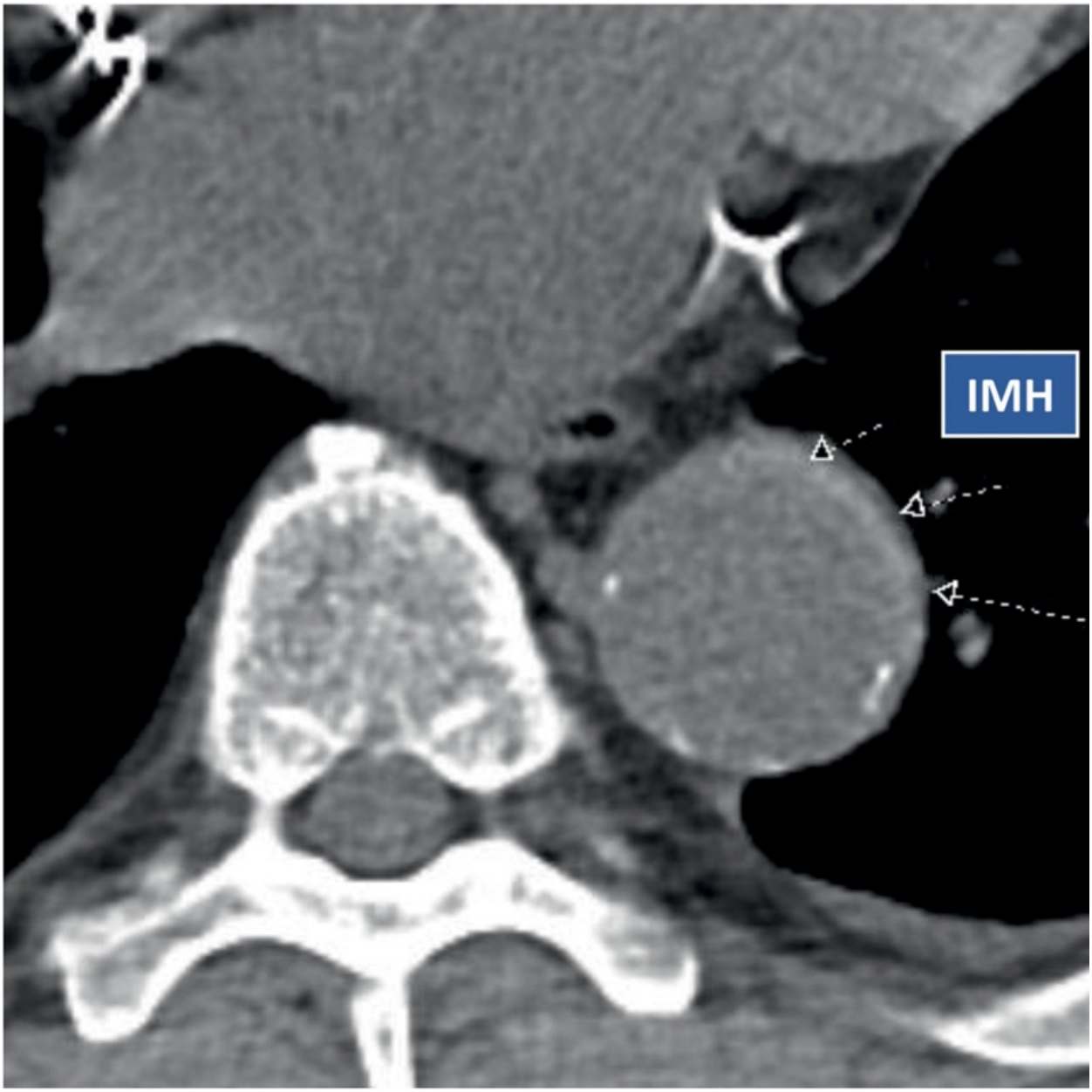

FIGURE 32.3 Intramural hematoma: CT. CT of the chest shows the descending thoracic aorta. The crescentic-shaped lesion on the patient's left signifies an IMH (dashed arrows). CT, computed tomography; IMH, intramural hematoma.

Etiology and Pathophysiology

IMH may account for up to 6% to 30% of all AAS, with a higher reported prevalence among the Korean and Japanese populations as compared with Western subjects.[6] It is unclear whether this is a true discrepancy in prevalence versus a reflection of differing classification, evaluation, or treatment practices. Often, IMH is diagnosed as such even though very small intimal tears indicative of limited aortic dissection may be present but missed by modern imaging modalities. This may overestimate the true prevalence of IMH as opposed to CAAD.

The characteristic feature of IMH is its location in the portion of the media closer to the adventitia, as opposed to CAAD which is typically located in the media closer to the intima. Although the most cited hypothesis of the pathophysiologic mechanism of IMH is rupture of the vasa vasorum, there is very little corroborating clinical or experimental evidence. Owing to the low incidence of IMH and the close association with CAAD, a definitive etiology still remains unclear.[7]

Clinical Manifestations

According to the IRAD experience, IMH typically presents with the symptoms of severe chest and back pain, similar to CAAD. However, IMH is less likely to present with manifestations of severe aortic regurgitation and pulse deficits.[6] IMH is rarely stable. It may either progress to CAAD or regress spontaneously, and therefore serial imaging is crucial. Stanford type B lesions in the descending aorta are more common than type A lesions in the ascending aorta (60% vs 35% of all IMH, respectively). Cardiogenic shock may be present in 14% of patients, more typically with type A IMH.[8] Pericardial effusion and tamponade may also be present, which are also more common in type A IMH. When compared with CAAD, type A IMH has a significantly higher risk of rupture (26% vs 8%, respectively).[9] A widened mediastinum may be present on chest X-ray; however, this is neither sensitive nor specific to IMH.

Diagnosis

As with all types of AAS, rapid diagnosis is paramount in IMH. TEE, CT, and MRI are the preferred diagnostic tools. CT is often chosen because of widespread availability, rapid acquisition, and its ability to diagnose other causes of acute chest pain such as trauma and pulmonary embolism.

Classically, absence of an intimal flap or tear differentiates IMH from CAAD. Often, IMH can be identified even on non–contrast-enhanced CT. On contrast CT scans, a crescentic or circular area of high attenuation that does not enhance with contrast is present. Similar findings are seen on MRI, which has the advantage of not requiring iodinated contrast.

On TEE, IMH is diagnosed if there is regional thickening of the aortic wall > 5 mm in a crescentic or circumferential pattern without an intimal flap or tear (**Figure 32.4A, B**). Limitations of TEE in diagnosing IMH arise from the TEE's inability to visualize all portions of the aorta including the area around the origin of the brachiocephalic artery and all but the most proximal portions of the abdominal aorta. TEE is very useful in diagnosing complications of IMH, such as pericardial effusion or aortic regurgitation.

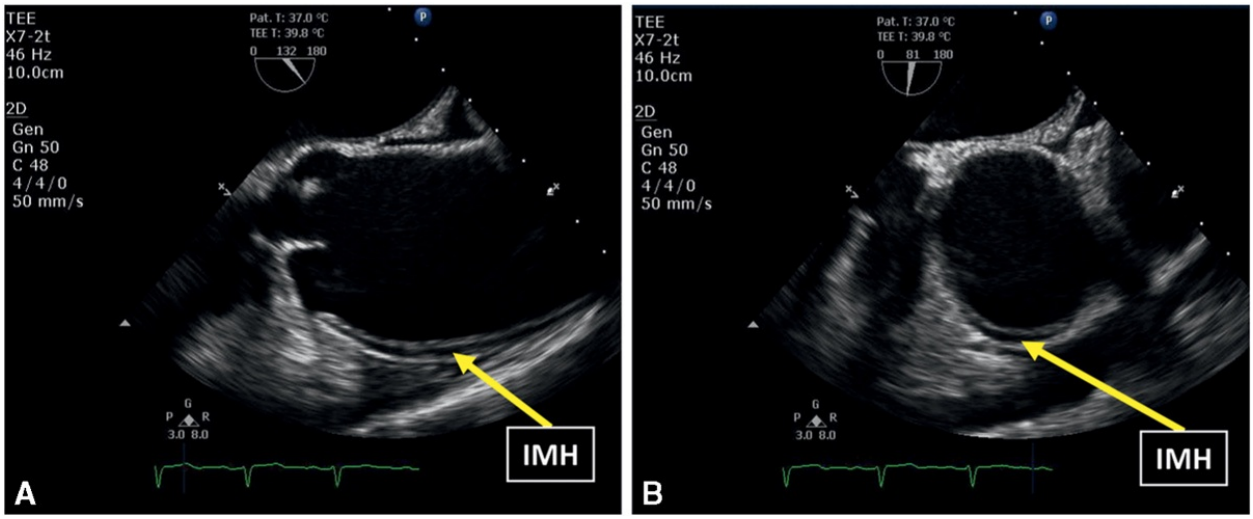

FIGURE 32.4 Intramural hematoma: TEE. Two-dimensional (2D) TEE of the ascending thoracic aorta in the long-axis (A) and short-axis (B) views. Yellow arrows point to a crescentic thickening of the anterior portion of the ascending thoracic aortic wall, consistent with a type A IMH. IMH, intramural hematoma; TEE, transesophageal echocardiography.

Small intimal tears may be missed by any modern imaging technique, challenging the diagnosis of classic IMH.

Management and Prognosis

The prognosis of IMH is somewhat better than that of CAAD. As in all AAS, the main determinant of prognosis is its aortic location. According to the IRAD registry, the mortality of type A IMH is approximately 27%, compared with 4% in type B IMH. Invasively managed patients with type A IMH typically fare better than medically managed patients. Invasive options include open surgical repair and percutaneous thoracic endovascular aortic repair. Medical management typically consists of heart rate (HR), blood pressure, and pain control. Surgical mortality for IMH is similar to that for other forms of AAS.

Type B IMH is often managed medically. Approximately 50% of type B patients may improve with medical management alone, 15% will remain stable, and 35% may progress to aneurysm formation, CAAD, or focal aortic rupture (pseudoaneurysm).[10]

Intramural Hematoma in Pregnancy

Although there are no specific guidelines in pregnancy for patients with IMH, pregnancy is considered a risk factor for the development of aortic pathology, especially in Marfan syndrome. As with other forms of AAS, expedited delivery via caesarian section is considered reasonable for pregnant patients with acute IMH, if possible.

CLASSIC ACUTE AORTIC DISSECTION

CAAD is the most common form of AAS.[2] It occurs in approximately 66% to 75% of all AAS. The overall incidence of CAAD is low, estimated at 0.5 to 4.0 cases per 100,000 per year, and is thought to affect men more than women in a 2:1 ratio.

Risk factors for CAAD include connective tissue disorders such as Marfan (fibrillin gene), Loeys–Dietz (transforming growth factor β receptor 1 and 2 genes), Ehlers–Danlos type 4 (collagen gene), and Turner syndrome (X monosomy), as well as the aortopathy associated with bicuspid aortic valve (*NOTCH1* gene). In addition, hypertension is a significant risk factor and is more prevalent among older patients. Last, aortic instrumentation or surgery, as well as cardiac catheterization, are rare but reported causes of aortic dissection.

CAAD was first described in 1555 by Andreas Vesalius (1514–1564) who reported traumatic abdominal aortic aneurysm in a man who fell off a horse.[11] Intimal tear, the hallmark of CAAD, was first described by Daniel Sennert (1572–1637), a German anatomist and published in 1650 posthumously.[12] A

very famous description of CAAD was by the British royal physician Frank Nichols (1699–1778) who provided the first unmistakable account of CAAD (deemed a “Transverse fissure of the aortic trunk”) in his autopsy of King George II, who died in 1760 while straining in the lavatory. Successful surgical repair of descending aortic dissection was not reported until 1955, by Michael Debakey (1908–2008) and his colleagues, and ascending dissection until 1962 by Frank Spencer and Hu Blake.[13,14]

Etiology and Pathophysiology

CAAD is characterized by an intimal tear, which leads to abnormal blood flow from the aortic lumen into the media (**Figure 32.5**). Consequently, there is a longitudinal separation of the media layers by the blood flow, which tears an intimomedial flap from the remainder of the aortic wall (**Figure 32.6A–C**). This flap separates the abnormal false lumen from the true aortic lumen. Intimal tears typically occur at the locations within the aorta with the highest shear stress. These are at the right side of the ascending aorta immediately distal to the ostium of the right coronary artery (type A dissections) and immediately distal to the ostium of the subclavian artery adjacent to the insertion of the ligamentum arteriosus (type B dissections).

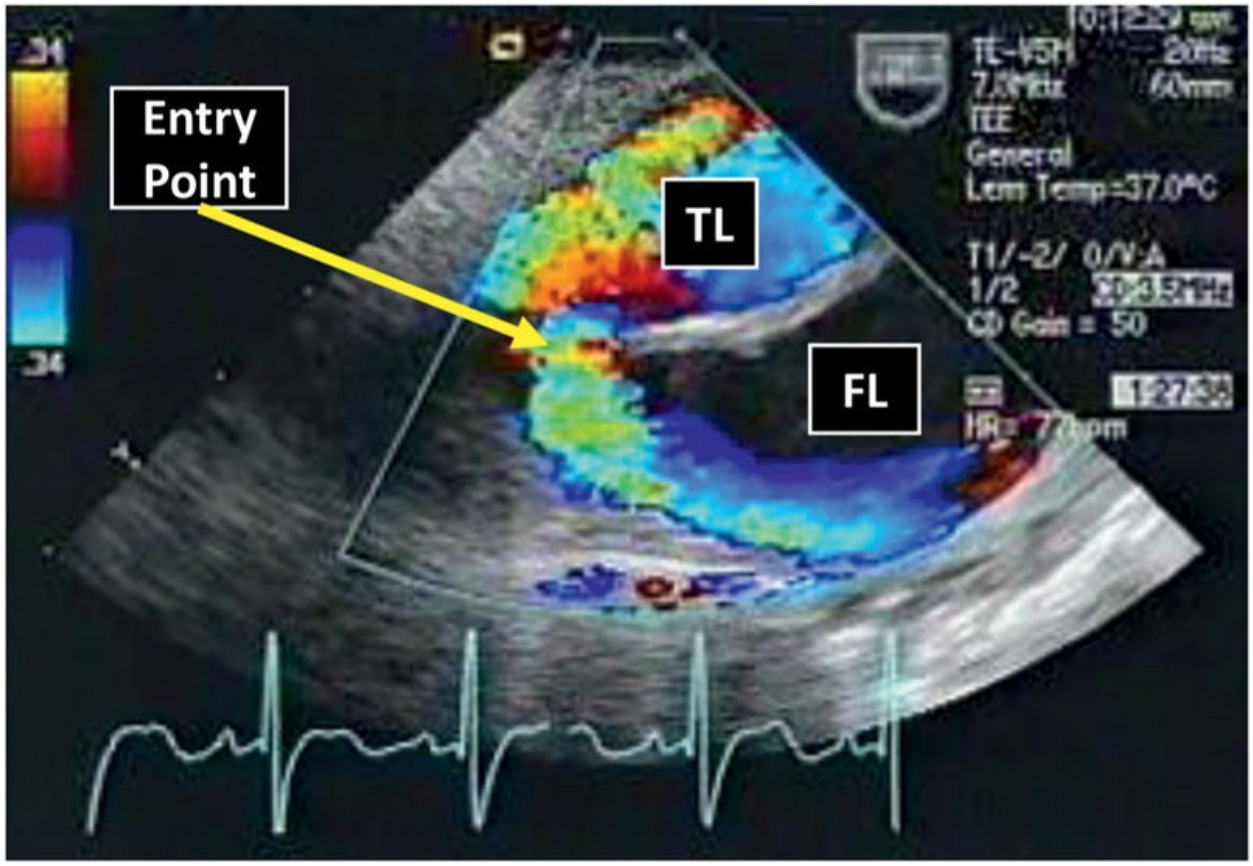

FIGURE 32.5 Classic acute aortic dissection: entry point on TEE. Two-dimensional (2D) TEE with color Doppler of the aortic arch in the upper esophageal view. Yellow arrow points to the entry point of flow from the true lumen to the false lumen, characteristic of CAAD. CAAD, classic acute aortic dissection; FL, false lumen; TEE, transesophageal echocardiography; TL, true lumen.

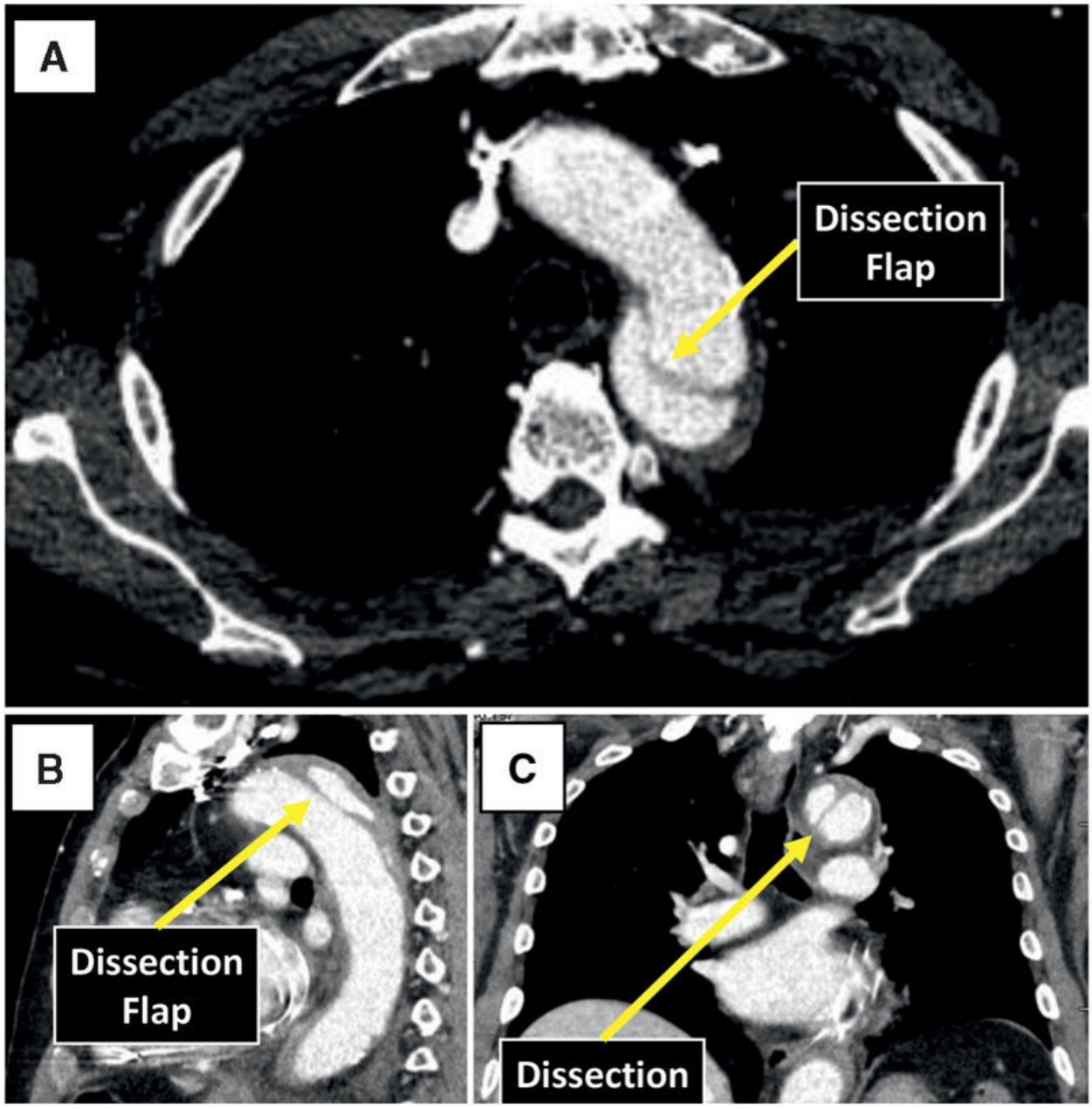

FIGURE 32.6 Classic acute aortic dissection: CT. Multidetector row CT with intravenous iodinated contrast in the axial view (A), sagittal view (B), and the coronal view (C). Yellow arrows point to dissection flap at the junction of the aortic arch and descending thoracic aorta, consistent with CAAD. CAAD, classic acute aortic dissection; CT, computed tomography.

Complications such as aortic regurgitation and pericardial tamponade can occur; and, over time, chronic changes such as false lumen thrombosis and aneurysm are common.

Clinical Manifestations

The typical symptom of acute aortic dissection is “aortic pain” similar to other forms of AAS. Acute, severe, tearing chest pain is the hallmark symptom of CAAD. Pain limited to the chest is typical of type A CAAD, and pain in the back is more often the symptom of type B CAAD. One study found older patients are less likely to abrupt onset of pain as compared with younger patients.[15]

Pulse deficit, present in up to 33% of patients according to the IRAD study, reflects impaired or absent blood flow to peripheral vessels. This is manifested by weak carotid, brachial, or femoral pulses on physical examination.

Other physical examination findings of CAAD include diastolic murmur or aortic regurgitation, hypotension related to either tamponade or aortic rupture, focal neurologic deficits reflecting propagation of the dissection toward involvement of carotid or cerebral arteries, and syncope.

Electrocardiogram (ECG) may be useful in distinguishing the chest pain of AAS from ACSs; unlike ACS, uncomplicated CAAD does not present with ischemic ECG changes. However, if the aortic dissection leads to coronary ischemia through involvement of coronary ostia (type A), the ECG will be less helpful with differentiation of symptoms.

Chest X-ray (CXR) imaging occasionally shows widening of the mediastinum, a nonspecific finding seen with other syndromes such as mediastinal hematoma. Other CXR findings are double aortic knob (40% of patients), tracheal displacement to the right, and enlargement of the cardiac silhouette.

Serum biomarkers such as D-dimer are often elevated in CAAD, but this is a nonspecific finding. In contrast, a normal D-dimer level may help exclude the diagnosis of CAAD. Investigational biomarkers such as elastin degradation products, calponin, fibrinogen, fibrillin, and smooth muscle myosin heavy chain are currently being evaluated.

Diagnosis

As with other forms of AAS, the 2010 intersocietal guidelines for the diagnosis and management of patients with thoracic aortic disease provide a useful decision tool to help guide diagnostic and management strategies for CAAD with a special emphasis on a combination of clinical risk assessment and rapid imaging.

CT with intravenous iodinated contrast is often the diagnostic modality of choice for CAAD because of its superb spatial resolution, rapid acquisition times, widespread availability, and its ability to diagnose other causes of acute

chest pain such as trauma and pulmonary embolism. The reported sensitivity of CT for CAAD is 87% to 94% and specificity is 92% to 100%. CT features of CAAD are intimal tear, dissection flap with a true and false lumen, dilatation of the aorta, and pericardial effusion.

TEE is especially useful in the diagnosis of CAAD when a CT with contrast cannot be performed, such as in hemodynamically unstable patients or in patients in whom the risk of iodinated intravenous contrast is high such as renal insufficiency or severe allergy. The reported sensitivity of TEE is 98% and specificity is 63% to 93%. Findings on TEE are a dissection flap separating the true and false lumen, site of intimal tear represented by flow from the true lumen into the false lumen on color Doppler (**Figure 32.7**). Spectral Doppler may help corroborate the diagnosis by demonstrating "to and fro" flow into and out of the false lumen.

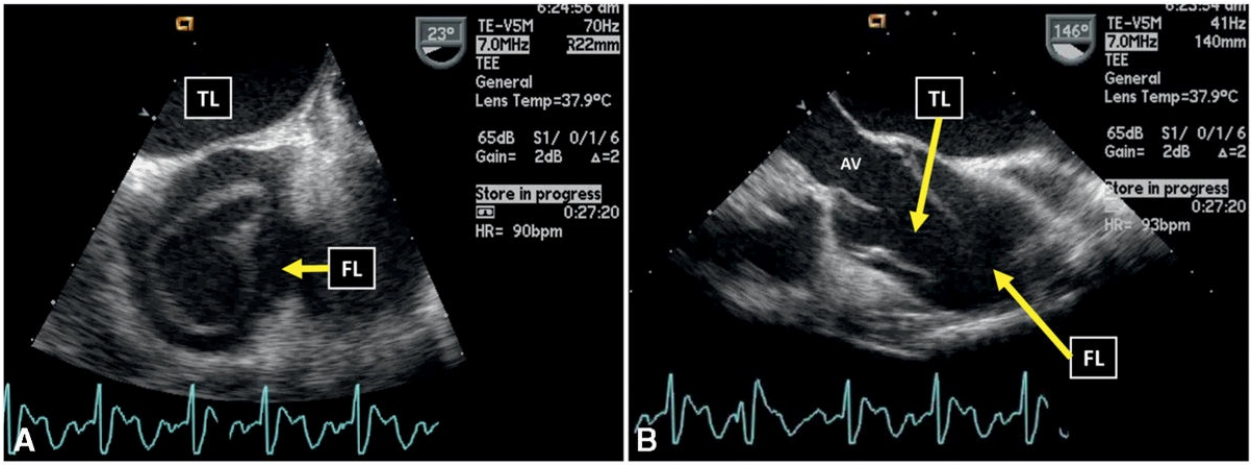

FIGURE 32.7 Classic acute aortic dissection: dissection flap on TEE. Two-dimensional (2D) TEE of the ascending thoracic aorta in short axis (A) and long axis (B) demonstrating CAAD. In this case, the dissection flap is circumferential with a 360° separation of the true and false lumens. CAAD, classic acute aortic dissection; FL, false lumen; TEE, transesophageal echocardiography; TL, true lumen.

The true lumen is identified by its expansion with systole and contraction in diastole. The true lumen is often smaller than the false lumen. In early stages, the false lumen may be echo free or may contain spontaneous echo contrast (also known as "smoke") due to stasis of blood flow. In later, more chronic stages, the false lumen may be partly or completely obliterated by thrombus formation.

Complications of CAAD may be seen on echocardiography such as aortic regurgitation, pericardial effusion/tamponade, and wall motion abnormalities indicative of ischemia if there is coronary ostial involvement.

It is important not to confuse the intimomedial flap of CAAD with either artifacts or surrounding vascular structures. Linear reverberation artifacts in the ascending aorta should not be mistaken for type A aortic dissection. Typically, reverberation artifacts are located twice as deep as the anterior aortic wall. In addition, a dilated azygos vein adjacent to the descending thoracic aorta may give an illusion of a type B dissection. Color or spectral Doppler imaging in both instances may help distinguish true aortic dissection from its masqueraders (**Figure 32.8**).

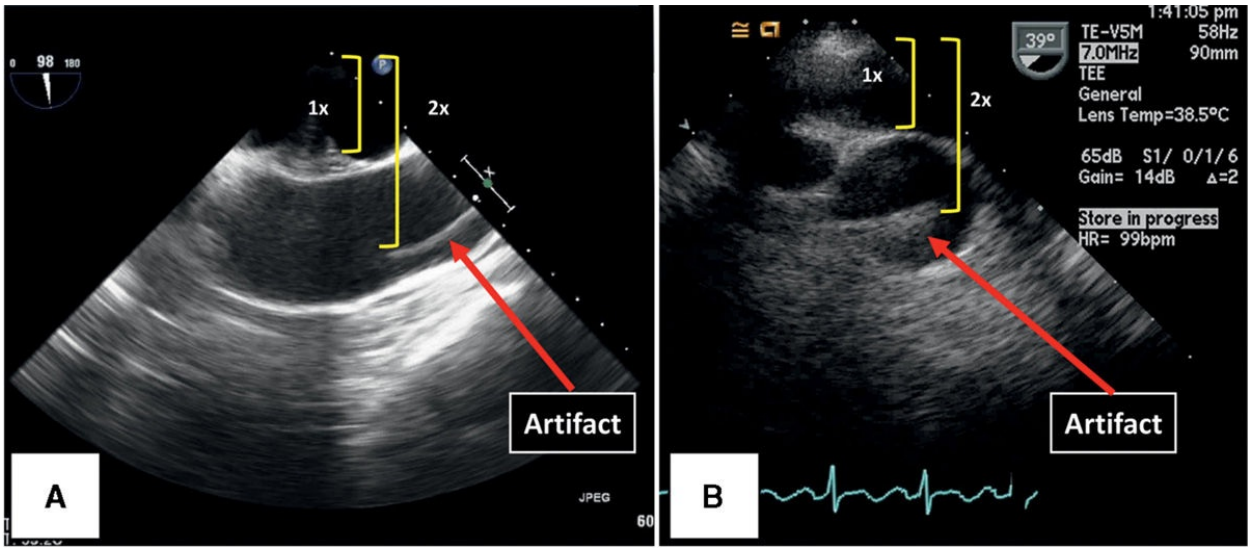

FIGURE 32.8 Reverberation artifact masquerading as type A dissection on TEE. Two-dimensional (2D) TEE of the ascending thoracic aorta in a long-axis view (A) and a short-axis view (B). Red arrows point to linear reverberation artifact. Note that the reverberation artifact is located twice as deep (2×) as the anterior aortic wall, characteristic of reverberation artifacts. TEE, transesophageal echocardiography.

Although on transthoracic echocardiography (TTE) aortic dissection can occasionally be seen, TTE should only be used as a screening tool owing to lack of sufficient sensitivity and specificity.

MRI and aortography also may reveal aortic dissection; however, they are reserved for specific situations. MRI may be used when the patient cannot receive iodinated contrast for CT nor undergo TEE. Aortography is of limited use and is typically performed during invasive endovascular therapeutic procedures.

Management and Prognosis

Type A CAAD is a true medical emergency, requiring immediate surgical repair

because the mortality increases by the hour. Approximately 90% of medically managed patients with type A CAAD die within 3 months of presentation. On the other hand, the prognosis is more favorable for patients with type B CAAD in whom medical management is often preferred over surgical repair because surgically managed patients have been shown to have higher mortality compared with those on medical therapy alone. Medical therapy generally consists of tight blood pressure control and β-blockade. Surgical management of type A CAAD typically consists of excision of the intimal tear if possible and obliteration of entry into the false lumen, as well as implantation of a graft to replace the ascending aorta.[16] Surgical therapy for type B is more complicated because of the presence of many spinal artery branches, and therefore has a risk of paraplegia. Nevertheless, surgical therapy of type B dissection is often necessary when there is aortic branch ischemia and end-organ damage. Endovascular graft therapy to treat type B CAAD has shown promise (**Figure 32.9**).[17]

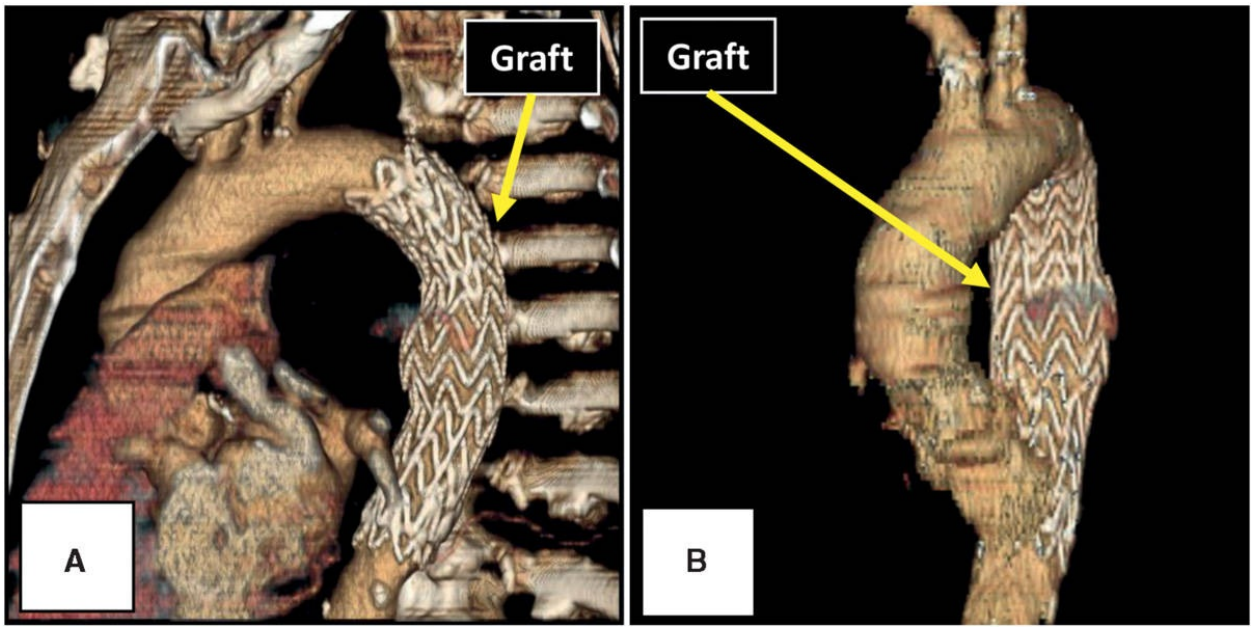

FIGURE 32.9 Endovascular graft repair: 3D CT. Three-dimensional (3D) reconstruction of contrast-enhanced chest CT in a sagittal view (A) and coronal view with surrounding structures removed (B) demonstrating an endovascular stent graft located between the junction of the aortic arch and descending thoracic aorta, extending to the distal descending thoracic aorta. CT, computed tomography.

It is important to identify risk factors for higher mortality in type A CAAD such as advanced age, prior cardiac surgery, hypotension or shock, pulse deficit, cardiac tamponade, and ischemic ECG changes.

Classic Acute Aortic Dissection in Pregnancy

The 2010 intersocietal guidelines for the diagnosis and management of patients with thoracic aortic disease recommends expedited fetal delivery via caesarian section for patients with CAAD during pregnancy given the high mortality of the disease (class IIa recommendation). The diagnostic imaging modality of choice is MRI without gadolinium to avoid exposing the mother and fetus to ionizing radiation.[18] TEE is an option and is considered safe in pregnancy; however, caution must be used when providing procedural sedation because the medications typically administered (midazolam and fentanyl) may be teratogenic, especially in the first trimester. In these cases, topical anesthesia with viscous lidocaine is crucial. There have been reports recommending monitoring fetal HR and uterine tone during TEE.[19]

PENETRATING AORTIC ULCER

PAU represents the process by which an atherosclerotic plaque erodes and penetrates through the elastic lamina into the media layer of the aorta, causing ulceration (**Figure 32.10**). PAU may further erode through the adventitia leading to either focal (pseudoaneurysm) or complete aortic rupture (**Figure 32.11**). Thrombus occasionally forms within PAU. In addition, PAU may lead to either IMH or aortic dissection, which is why PAU is characterized as an AAS.

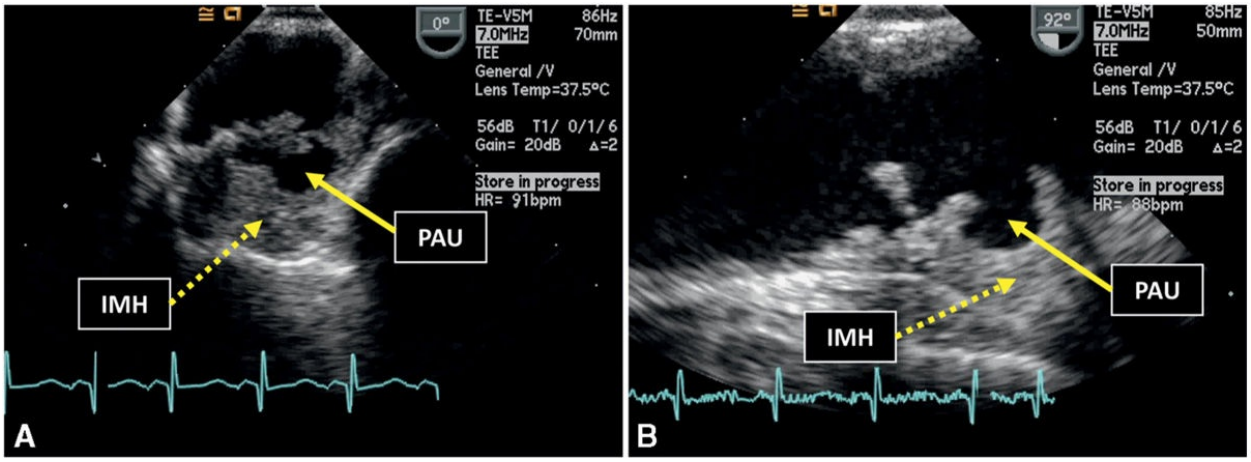

FIGURE 32.10 Penetrating aortic ulcer: TEE. Two-dimensional (2D) TEE of the descending thoracic aorta in the midesophageal short-axis view (A) and long-axis view (B). Yellow arrows point to demonstrating severe atherosclerotic plaque and PAU; yellow dashed arrows point to an area with developing IMH. IMH, intramural hematoma; PAU, penetrating aortic ulcer; TEE, transesophageal echocardiography.

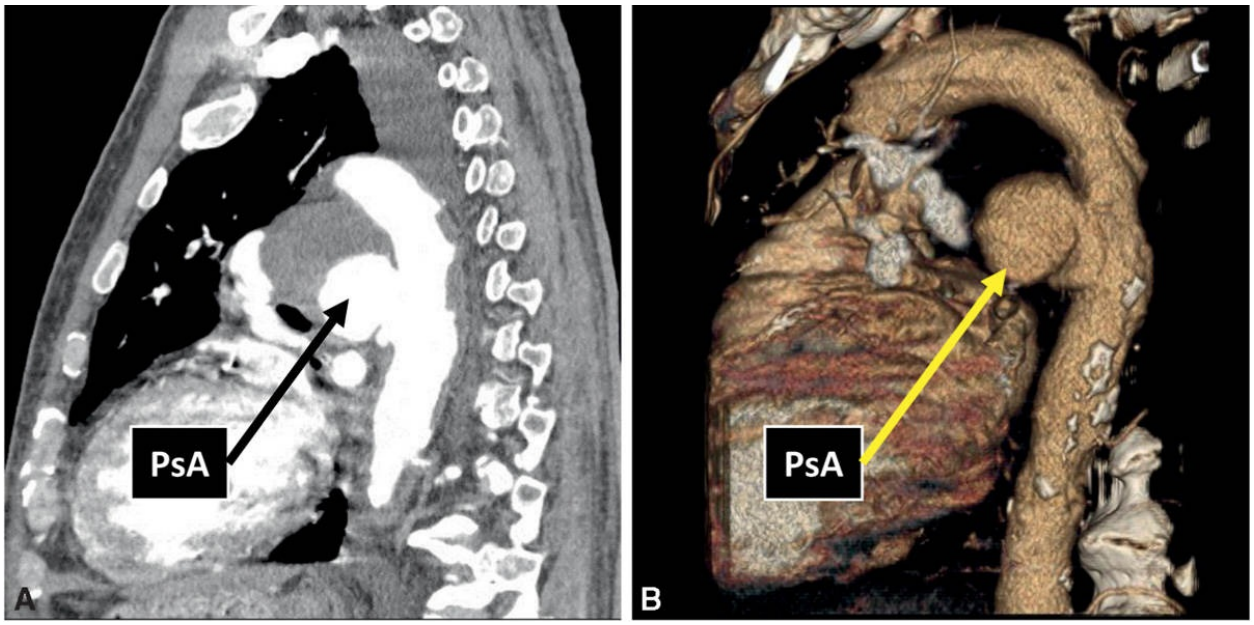

FIGURE 32.11 Penetrating aortic ulcer with rupture/pseudoaneurysm visualized by contrast-enchanced 2D (A) and 3D CT (B). Arrows point to PAU with aortic rupture and pseudoaneurysm of anterior portion of the proximal descending thoracic aorta. CT, computed tomography; PsA, pseudoaneurysm.

Etiology and Pathophysiology

PAU accounts for 2% to 11% of all AASs.[20,21] It was first described in 1986 by Anthony Stanson and colleagues.[22] Patients with PAU typically are older (>70 years old) and have risk factors for atherosclerosis including hypertension, smoking, and hyperlipidemia.

The natural history of PAU is not well described. PAU may cause remodeling of the aortic wall and aneurysm formation, contained rupture through the aortic wall and attendant pseudoaneurysm formation, complete aortic rupture with mediastinal or pleural hemorrhage, or progression to IMH and CAAD.

Clinical Manifestations

Symptoms of PAU are similar to that of other AASs. The pain associated with PAU is variable, and dependent on the location of the ulceration. Type A PAU typically presents with chest pain and type B PAU is more likely to present with back pain. Unlike IMH or CAAD, there have been reports of PAU as an incidental finding in asymptomatic patients.

Diagnosis

The diagnosis of PAU is primarily made by CT, TEE, and MRI. Aortography is

not typically used for PAU because of lack of direct visualization of the aortic wall. All three techniques are able to image atherosclerotic changes, ulceration, and complications such as pseudoaneurysm, rupture, and mediastinal and pleural hemorrhage. Identification of an ulcer crater distinguishes PAU from IMH. PAU lesions are typically focal as opposed to those of CAAD and IMH, which are more extensive.

Management and Prognosis

The natural history of PAU is poorly understood. On one hand, PAU is considered to be a surgical emergency with risk similar to or worse than other forms of AAS. On the other, reports have described the progression of PAU as slow, with a low prevalence of life-threatening complications.[23] There is therefore equipoise regarding the optimal medical versus surgical treatment strategies. Nevertheless, surgical management of PAU with aortic grafting is considered appropriate in the presence of aortic rupture, persistent or recurrent pain, hemodynamic instability, or rapidly expanding aortic diameter.

Penetrating Aortic Ulcer in Pregnancy

Because PAU is a disease that primarily affects older people (>70 years of age), it is highly unlikely that it will occur during pregnancy. There is therefore no available guideline to direct optimal management.

TRAUMATIC AORTIC RUPTURE

Although TAR is not considered to be a part of the original AAS triad, it is a life-threatening aortic emergency with only a 15% to 20% survival.[24] TAR is typically caused by deceleration injuries sustained in motor vehicle accidents (MVAs) and falls greater than 3 m.[25] It is the second leading cause of death after blunt trauma, occurring in approximately 1.5% to 1.9% cases.[26]

Etiology and Pathophysiology

The most common site of injury in TAR is at the aortic isthmus, immediately distal to the left subclavian artery at the site of the ductus arteriosus. This location is considered to be the most vulnerable to torsional and shear forces because it is thought to be a transition zone between the semi-mobile aortic arch and the fixed descending thoracic aorta. Other possible sites of injury are the transverse arch, ascending aorta, and descending aorta proximal to the

diaphragm.[27] Typically, the intima and medial layers rupture first, followed by rupture of the adventitia after an unpredictable interval of time.[28] Multiple tears may occur.

Clinical Manifestations

There is no specific symptom associated with TAR. Chest pain in the patient with trauma should, however, raise suspicion, especially in the presence of the "seat belt sign" (seat belt imprint on the surface of the skin). Pulse deficit and murmur of aortic regurgitation may be present. CXR may show a widened mediastinum, obscured aortic knob, and left hemothorax.

Diagnosis

TAR is best diagnosed using either contrast-enhanced CT or TEE because both modalities have high diagnostic sensitivity and specificity (**Figure 32.12**). Findings seen on CT include intimal flap, periaortic hematoma, luminal filling defects, pseudoaneurysm, or active extravasation of contrast from the aorta. It is important to distinguish TAR from a ductus arteriosus diverticulum, which is helped by the improved special and temporal resolution of modern multidetector row CT scanners. However, TEE may be more specific in differentiating ductus arteriosus diverticula from TAR. Another very useful advantage of TEE is its portability, with the ability to be performed at the bedside of hemodynamically unstable patients, a common scenario in TAR. The main limitation of TEE is an apparent "blind spot" at the distal ascending aorta and proximal aortic arch caused by bronchial shadowing. Aortography, the former gold standard, may be performed; however, it is invasive and can result in worsening of the aortic rupture in as many as 10% of patients and is therefore not the preferred diagnostic modality.

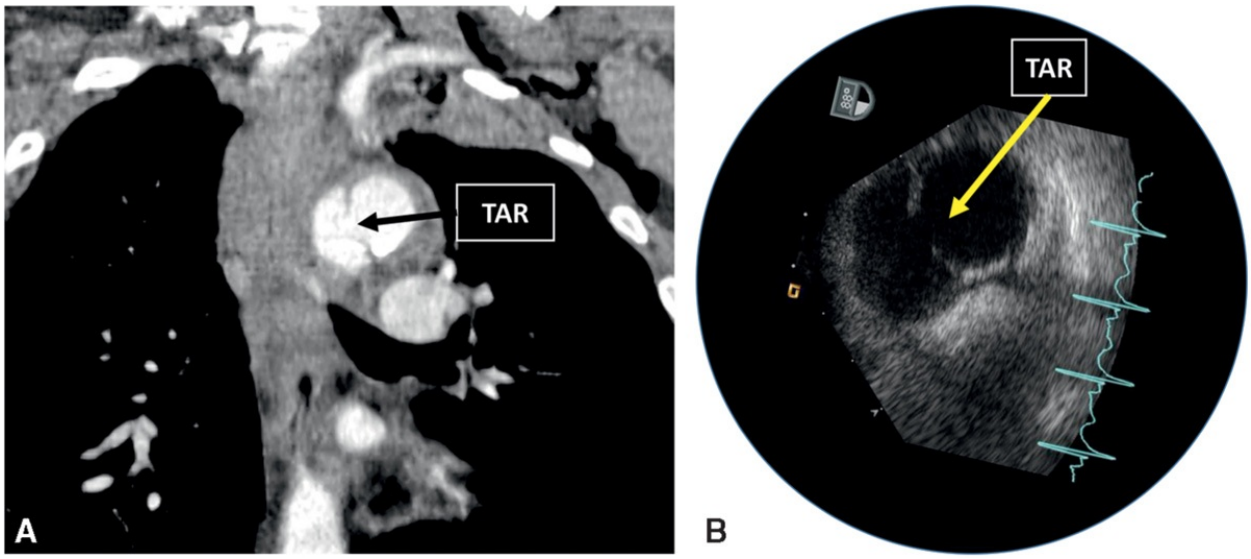

FIGURE 32.12 Traumatic aortic rupture. CT of the chest with iodinated contrast, coronal view (A), and TEE upper esophageal view (B) of the aortic arch. Arrows point to traumatic aortic rupture. Note that the TEE image was rotated to align with the CT image. CT, computed tomography; TAR, traumatic aortic rupture; TEE, transesophageal echocardiography.

Management and Prognosis

Emergent surgical therapy is the standard of care for TAR. As with AAS, medical therapy consists of very close blood pressure and HR control. Hemodynamically unstable patients should be operated on immediately. Surgical options comprise open repair with prosthetic grafts, and endovascularly delivered fabric-covered stents. Endovascular repair has been shown to have decreased overall mortality compared with surgical repair and is recommended when possible. The overall survival of TAR is approximately 10% to 18%. Survival to emergency room care greatly improves the odds of long-term survival, and survival to surgical therapy improves the odds even more, to approximately 70% to 90%.[29]

Traumatic Aortic Rupture in Pregnancy

Although there are no specific guidelines for the management of TAR in pregnancy, expedited delivery via caesarian section with emergent aortic surgery is a reasonable therapeutic approach given the high mortality both to the mother and fetus.

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Patient and Family Information for:
ACUTE AORTIC SYNDROME

GENERAL CONCEPTS OF ACUTE AORTIC SYNDROME

WHAT IS THE ILLNESS?

AAS refers to four related diseases of the large vessel that leaves the heart, called the aorta. These are CAAD, IMH, PAU, and TAR. These conditions involve damage to the wall of the aorta and require prompt care because they are associated with a high chance of dying unless treated rapidly.

HOW WILL THE PATIENT BE TREATED?

Once the diagnosis of AAS is established by CT, TEE, or MRI, the disease is typically treated with mediations that lower blood pressure and HR. The doctor will determine the type of AAS (type A or type B) based on the location of involvement in the aorta. A cardiothoracic surgeon may be consulted, who will assess the need for surgery. Surgery is often needed as soon as possible.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

Given the high mortality of AAS and the frequent need for emergency cardiac surgery, the doctor may recommend expedited delivery. If at risk of AAS because of genetic conditions that may affect the aorta, the patient should consult the doctor to assess the risk if she is thinking about becoming pregnant.

INTRAMURAL HEMATOMA

WHAT IS THE ILLNESS?

IMH is described as bleeding into the wall of the aorta due to breakage of the internal blood vessels of the aorta. Symptoms of IMH are sudden severe chest or back pain. IMH is best diagnosed by imaging the aorta using CT, TEE, or MRI. On experiencing symptoms suggestive of IMH, the patient or a family member should seek medical care immediately because the risk of dying from this condition increases by the hour.

HOW WILL THE PATIENT BE TREATED?

Once the diagnosis of IMH is established, medications will be given to reduce the blood pressure and HR. A cardiothoracic surgeon may be consulted, who will assess the need for surgery. Surgery will often involve either replacement of the diseased portions of the aorta or placement of special type of stent within the aorta that will help contain the bleeding and prevent the aorta from bursting.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

IMH carries a high risk of mortality, and often requires emergency surgery. The doctor will tailor the medications for IMH to include only those with minimal risk to the baby. If the pregnant patient or family member requires emergency surgery, expedited delivery is prudent. Rapid consultation with an obstetrician is crucial. If the person has a condition that puts her at risk for IMH such as Marfan syndrome or other genetic disorders of the aorta, consult the doctor to assess the risk if thinking about becoming pregnant.

CLASSIC ACUTE AORTIC DISSECTION

WHAT IS THE ILLNESS?

CAAD is the most common type of AAS. It is caused by a tear of the inner layer of the aorta, called the intima. This tear can then propagate, leading to separation of the layers of the aorta. There are hereditary disorders such as Marfan syndrome and bicuspid aortic valve that may put the person or a family member at risk of CAAD because of weakening of the aortic wall.

Symptoms typically experienced are severe “tearing” chest or back pain that occurs at rest. If the person or a family member experiences such symptoms,

seek medical care immediately.

CAAD will be diagnosed using CT, TEE, or MRI, which are widely available and can be performed and interpreted rapidly.

HOW WILL THE PATIENT BE TREATED?

As with other types of AAS, the doctor will prescribe medications that lower blood pressure and HR. A cardiothoracic surgeon may be consulted immediately, who will assess the need for surgery. The location of the dissection is a crucial component in deciding what the best treatment is. Surgical options are open heart surgery or placement of a tube called stent. The cardiothoracic surgeon will assess which procedure is the most appropriate.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

As with other types of AAS, CAAD is often a surgical emergency. As such, consultation with an obstetrician and expedited delivery may be recommended. If the patient or a family member has a disorder that involves the aorta, consult the obstetrician before deciding to conceive.

PENATRATING AORTIC ULCER

WHAT IS THE ILLNESS?

Atherosclerosis or hardening of the arteries is a disease in which cholesterol and fat build up within the walls of the blood vessels called arteries. PAU is caused when a very severe plaque breaks through the aorta, causing a hole, or ulceration. Risk factors for PAU include advanced age, high blood pressure, high cholesterol, and smoking. Symptoms include chest and back pain, although some patients may have no symptoms.

Along with other forms of AAS, PAU is diagnosed by CT, TEE, or MRI.

HOW WILL THE PATIENT BE TREATED?

The doctor may recommend close monitoring with imaging studies, medications, or surgery.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF

BECOMING PREGNANT?

PAU is typically a disease that affects older people (more than 70 years of age). It is highly unlikely that it will occur during pregnancy.

TRAUMATIC AORTIC RUPTURE

WHAT IS THE ILLNESS?

TAR describes tearing of the aorta after a chest injury. It most commonly occurs after MVAs and bad falls.

TAR is a very dangerous condition and requires prompt medical attention. A mark across the skin of the chest due to a seat belt often is present when TAR is caused by an MVA. TAR is diagnosed using CT and TEE.

HOW WILL THE PATIENT BE TREATED?

Emergency surgery is the standard of care for TAR. The doctor may prescribe medications to lower HR and blood pressure if necessary; however, a cardiothoracic surgeon may be consulted as soon as possible. Treatment typically requires open heart surgery.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

Because TAR is a surgical emergency, consultation with an obstetrician for early delivery is crucial.

The surgeon may recommend delivery by cesarean section at the time of surgery to repair the broken aorta.

33

Edgar Argulian
Eyal Herzog

Pericardial Effusion and Tamponade

INTRODUCTION

Pericardial effusion is a relatively common finding in high-risk patients evaluated in the acute setting.[1] It should be considered in differential diagnosis for a variety of clinical presentations including chest pain, shortness of breath, and hypotension.[1] Pericardial effusion can be directly causal for patients' complaints (like in patients with pericardial tamponade) or be an incidental finding still carrying a prognostic significance (like in patients with pulmonary hypertension). The general approach to pericardial effusion once it is recognized includes establishing the cause of pericardial disease and assessing its hemodynamic significance.

RECOGNIZING THE PRESENCE OF PERICARDIAL EFFUSION

Pericardial effusion can be recognized on the basis of clinical suspicion or it can be an incidental finding on chest or cardiac imaging.[2] The following clinical settings may indicate the need to specifically evaluate for the presence of pericardial effusion[3]:

1. Cardiac arrest with pulseless electrical activity or asystole
2. Chest discomfort and/or any signs of hemodynamic instability in chest trauma, recent cardiac surgery, or percutaneous cardiac intervention
3. Any of the following when otherwise unexplained: chest pain, fever, dyspnea, and elevated cardiac biomarkers
4. Physical and electrocardiographic findings attributable to pericardial disease; the latter includes tachycardia, low voltage, and electrical alternans (**Figure 33.1**)
5. Enlarged cardiac silhouette or pleural effusions on chest X-ray
6. Any patient with ascending aortic dissection, severe pulmonary hypertension, renal failure, use of some medications, rheumatic diseases, malignancy, or other systemic conditions when pericardial effusion is thought to contribute to presentation or have prognostic significance[3]

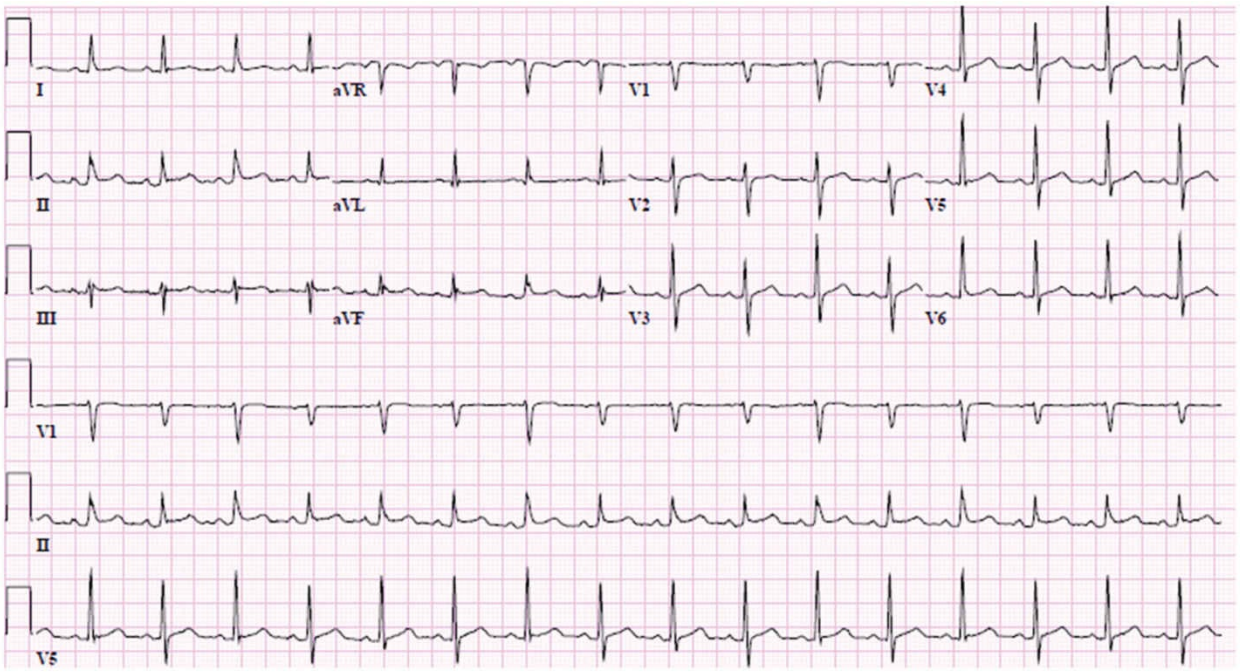

FIGURE 33.1 Electrocardiogram in a patient with large pericardial effusion. Electrical alternans is evident in multiple leads including V1and V5. ECG, electrocardiogram.

Echocardiography is the most commonly used modality to diagnose pericardial effusion: owing to its accuracy and portably, it can be easily used in any health care setting including bedside in an acutely ill patient. Other modalities (such as computed tomography [CT] scan or cardiac magnetic resonance) can be occasionally used to diagnose pericardial effusion, especially

when echocardiographic examination is limited or nondiagnostic.[4]

ESTABLISHING THE CAUSE OF PERICARDIAL EFFUSION

There is a long list of possible causes for pericardial effusion (**Table 33.1**), but a limited number of etiologies account for the majority of diagnoses.[5] A structured approach helps establish the cause of pericardial effusion in most cases.[6] A very aggressive approach, as is used in some studies, has a high diagnostic yield but low clinical relevance, especially for small effusions.[7,8] Routine sampling of pericardial fluid for diagnostic purposes is unnecessary.[3] History and physical examination often provide clues to the etiology of pericardial effusion. For example, the pericardium can be involved in patients with active systemic malignancy, and malignant effusion should be strongly considered in these patients. Active or recent infection, radiation therapy, rheumatic disease, and recent acute coronary syndrome, cardiac surgery, or percutaneous cardiac procedure, all provide relevant clues to etiology. A typical clinical presentation, physical findings, and electrocardiographic changes commonly confirm the diagnosis of acute idiopathic pericarditis.[9] In one study, the presence of "inflammatory" signs (characteristic chest pain, pericardial friction rub, fever, and/or diffuse ST-segment elevation) in patients with pericardial effusion was strongly associated with acute idiopathic pericarditis.[10]

TABLE 33.1	Causes of Pericardial Effusion
Aortic dissection	
Endocrine (hypothyroidism)	
Idiopathic	
Infectious (including viral, tuberculous, and purulent pericarditis)	
Medications	
Neoplastic (typically secondary)	
Perimyocardial infarction and postcardiotomy syndrome	
Pulmonary hypertension and right-sided heart failure	

Radiation
Renal failure
Rheumatic/autoimmune diseases
Traumatic (chest injury, procedure, surgery)

We use a parsimonious stepwise approach to laboratory testing and imaging in patients with pericardial effusion at our institution (**Figure 33.2**).[6] Transthoracic echocardiography is the standard test in establishing the presence of pericardial effusion, quantifying the size of the effusion and assessing its hemodynamic impact. The initial tier of testing includes complete blood count, complete metabolic panel, coagulation studies, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), cardiac biomarkers, thyroid stimulating hormone level, and chest X-ray. In appropriate clinical settings, human immunodeficiency virus (HIV) testing, autoantibodies, and blood cultures are obtained. Advanced chest imaging (CT scan, positron emission tomography, and magnetic resonance imaging) can be helpful in certain clinical situations, especially when malignancy is suspected. Besides, CT scan and cardiac magnetic resonance can be used as adjunct imaging modalities for assessing pericardial effusion in some patients.[4] They offer precise effusion localization, quantification, and tissue characterization, which are especially important for loculated and complex effusions. Tuberculosis testing should also be considered in the right epidemiologic and clinical settings. Viral cultures have little clinical significance and should not be routinely obtained, but they may be useful in some patients (eg, cytomegalovirus infection in transplant patients).[3] Transesophageal echocardiography can diagnose loculated effusion when transthoracic echocardiography is limited (eg, postoperative patients) and regional tamponade is considered. Our structured approach has yielded diagnosis by noninvasive targeted testing in 68% of patients, based on a retrospective review.[6]

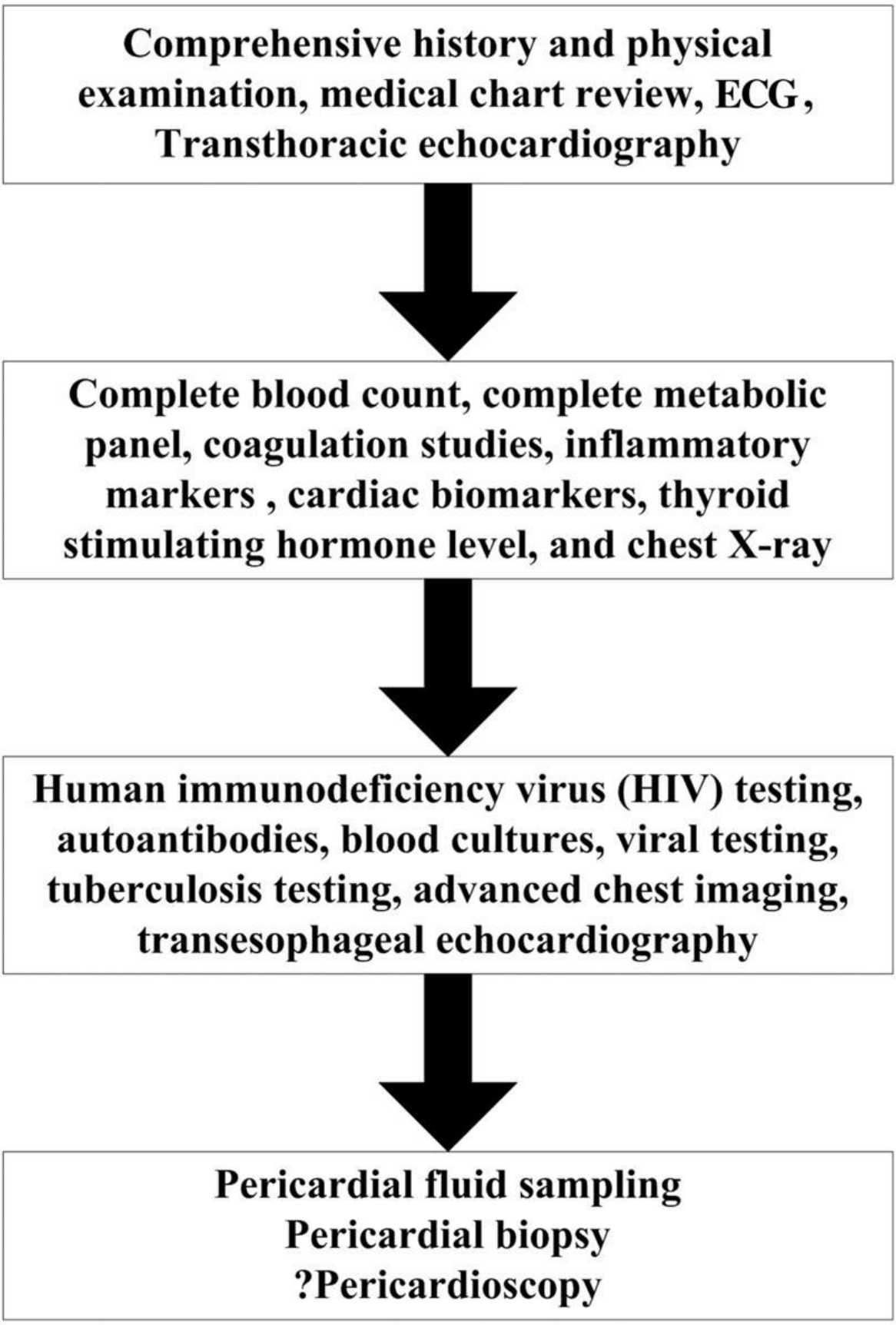
Comprehensive history and physical examination, medical chart review, ECG, Transthoracic echocardiography
Complete blood count, complete metabolic panel, coagulation studies, inflammatory markers , cardiac biomarkers, thyroid stimulating hormone level, and chest X-ray
Human immunodeficiency virus (HIV) testing, autoantibodies, blood cultures, viral testing, tuberculosis testing, advanced chest imaging, transesophageal echocardiography
Pericardial fluid sampling
Pericardial biopsy
?Pericardioscopy

FIGURE 33.2 Parsimonious stepwise approach to laboratory testing and imaging in patients with pericardial effusion. This systematic approach allows establishing diagnosis noninvasively in the majority of patients with moderate-to-large pericardial effusion. Question mark indicates optional and controversial.

Simple clinical assessment has also been shown to assist in establishing the diagnosis: large effusion without "inflammatory" signs or clinical signs of tamponade (jugular venous distension, hypotension, and/or pulsus paradoxus) commonly signifies chronic idiopathic pericardial effusion (likelihood ratio = 20, $P < .001$), whereas large effusions with clinical signs of tamponade and without "inflammatory" signs should raise the suspicion for malignancy (likelihood ratio = 2.9, $P < .001$).[10]

Pericardial effusion sampling for diagnostic purposes and occasionally for pericardial biopsy should be considered in the following settings:

1. Concern for purulent and tuberculous pericarditis
2. Clinical suspicion of neoplastic pericardial effusion
3. Moderate-to-large pericardial effusion in patients with advanced HIV and/or immune suppression
4. Moderate-to-large or progressive pericardial effusion in patients who are not responding to initial therapy or when the tiered workup is inconclusive

Pericardial fluid analysis can include Gram and acid-fast bacilli stains and cultures, polymerase chain reaction, tuberculosis-specific testing (eg, adenosine deaminase, lysozyme, and gamma-interferon), tumor markers, and cytology.[3] Contrary to common practice and unlike pleural effusion workup, cell count, lactate dehydrogenase, and protein and glucose levels have not been shown to be particularly useful in differential diagnosis and management of patients with pericardial effusion.[11] Pericardioscopy allows a targeted pericardial biopsy and it can potentially increase the diagnostic accuracy of sampling (eg, neoplastic pericardial effusion).

ASSESSING HEMODYNAMIC SIGNIFICANCE OF PERICARDIAL EFFUSION

When evaluating the hemodynamic impact of pericardial effusion one should take into account the acuity of presentation. Acute accumulation of fluid (within

minutes to hours) rapidly exceeds the pericardial stretch limit and commonly presents as cardiogenic shock.[12] This dramatic presentation is called acute or surgical tamponade and it requires immediate intervention. Chamber perforation during a percutaneous procedure is a good example of acute tamponade. Blunt chest trauma and ascending aortic dissection resulting in blood accumulation within the pericardium require prompt surgical intervention, and percutaneous pericardial effusion drainage is relatively contraindicated. When pericardial fluid accumulates slowly (within days to weeks), a large amount of fluid can be present without dramatic lowering of the cardiac output.[12] This can lead to subacute or medical tamponade, which requires careful assessment of both clinical and imaging data to establish the need for pericardial effusion drainage.[13] The following discussion elaborates the assessment for subacute (medical) tamponade.

HISTORY AND PHYSICAL EXAMINATION

Although many refer to pericardial tamponade as a "clinical diagnosis," the existing evidence suggests that subacute tamponade is a difficult diagnosis to make on mere clinical grounds.[13] Dyspnea is the cardinal symptom of subacute pericardial tamponade, but it is nonspecific. Other symptoms such as fever, cough, and chest pain can occur and typically reflect the underlying cause (ie, pericarditis) rather than pericardial fluid accumulation. Clinical findings of pericardial tamponade include tachycardia, jugular venous distension, pulsus paradoxus, and diminished heart sounds; and all lack both sensitivity and specificity.[14] Tachycardia is common in hospitalized patients for many reasons and it could be blunted by medications such as β-blockers. In a systematic review, the jugular venous distension had a pooled sensitivity of 76% for pericardial tamponade.[14] Assessment of jugular venous distension is limited by the experience of the observer; it can be difficult in some patients, even for experienced clinicians. Besides, jugular venous distension is associated with other conditions causing shortness of breath such as pulmonary hypertension and congestive heart failure. Although patients with acute (surgical) tamponade rapidly progress to cardiogenic shock, hypotension is rather uncommon in patients with subacute tamponade who accumulate pericardial effusion within days to weeks. On the contrary, many patients are hypertensive because of the high levels of circulating catecholamines in response to hemodynamic stress. In

studies of pericardial tamponade, the mean systolic blood pressure ranged from 127 to 144 mm Hg.[15] According to a recent review, hypertensive tamponade is seen in 27% to 43% of patients.[15] Systolic blood pressure commonly decreases in these patients after pericardial effusion drainage, and treating the hypertensive response without draining the effusion can be dangerous.

PULSUS PARADOXUS

Pulsus paradoxus is considered the cornerstone of the clinical diagnosis of pericardial tamponade.[12] Under normal conditions, the decrease in blood pressure is <10 mm Hg, and it is explained by phasic variation in the filling of the right- and left-sided cardiac chambers related to intrathoracic pressure changes with respiration. With tamponade, the accumulating pericardial effusion restricts cardiac filling and makes the respiratory variation in the right and left ventricular filling more pronounced and interdependent.[12] Pulsus paradoxus is measured by manual sphygmomanometer as the difference between intermittent and persistent Korotkoff sounds during normal respiration, not with deep breathing (**Figure 33.3**).[14] A wide variation in the incidence of pulsus paradoxus has been reported in patients with pericardial tamponade, ranging from 12% to 75%.[16] In patients with “low-pressure” tamponade, the incidence of pulsus paradoxus was reported as only 7%.[17] Besides limited sensitivity for pericardial tamponade, pulsus paradoxus is not very specific. A myriad of conditions have been reported to be associated with pulsus paradoxus; a short list includes asthma, right ventricular infarction, severe hypovolemia, constrictive pericarditis, restrictive cardiomyopathy, pneumothorax, chronic obstructive lung disease, and pulmonary embolism.[13] Some of these conditions can also cause jugular venous distension and tachycardia, common associated findings of pericardial tamponade.

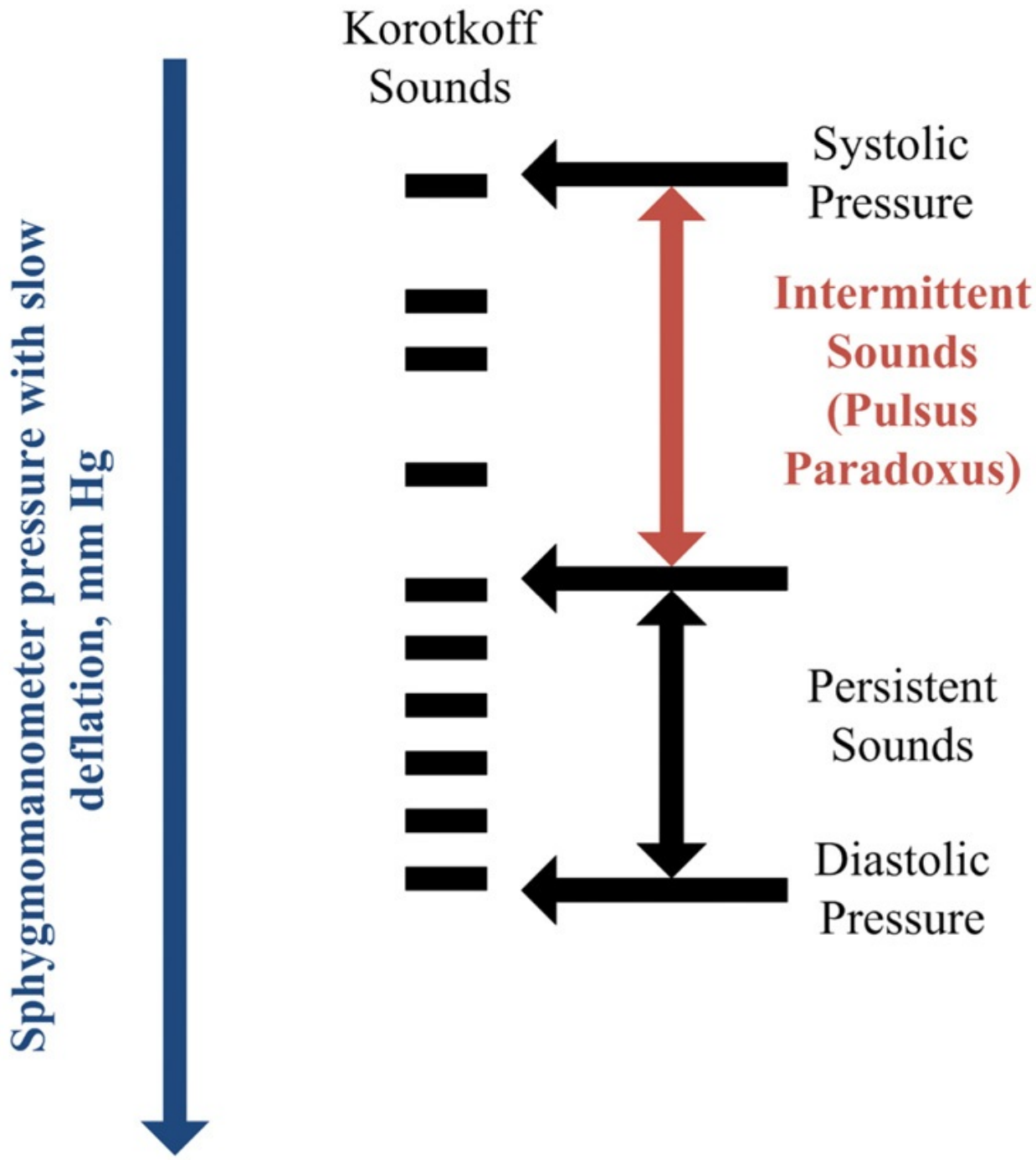

FIGURE 33.3 Assessing for pulsus paradoxus. Pulsus paradoxus is measured by manual sphygmomanometer as the difference between intermittent and persistent Korotkoff sounds during normal respiration.

INVASIVE AND IMAGING DATA

Before the widespread use of echocardiography, invasive data using cardiac

catheterization were commonly obtained to confirm the diagnosis of tamponade. Cardiac catheterization in tamponade demonstrates equilibration of diastolic intracardiac pressures and respiratory variation in right- and left-sided cardiac pressures corresponding to pulsus paradoxus.

Echocardiography is currently the cornerstone of hemodynamic evaluation of pericardial effusion.[4] Pericardial effusion is easily recognized during ultrasound examination as an echo-free space around the heart (**Figure 33.4**). Normally, intrapericardial pressure is lower than the central venous pressure. As pericardial fluid accumulates, the intrapericardial pressure equilibrates first with the right-sided filling pressures and then left-sided filling pressures.[14] During tamponade, intrapericardial pressure temporarily exceeds intracavitary pressure in various chambers during the cardiac cycle and results in chamber collapse (**Figure 33.5**).[4] Certain pitfalls should be kept in mind when interpreting echocardiographic findings. Transient buckling of the right atrium is commonly seen in patients with pericardial effusion and it is not specific. A more sustained collapse of the right atrium lasting at least one-third of the cardiac cycle appears to be more specific for pericardial tamponade.[18] Right ventricular early diastolic collapse is a less sensitive finding but has a high specificity. Left-sided chamber collapse is much less sensitive but highly specific for tamponade. Importantly, a study by Merce et al showed that 34% of patients with pericardial effusion but without clinical features of pericardial tamponade had at least one chamber collapse on echocardiography.[19] Therefore, in patients with pericardial effusion who have chamber collapse, one should carefully document respiratory flow variation across valves as a sign of ventricular interdependence (**Figure 33.6**) and interrogate the inferior vena cava size and collapsibility as a sign of elevated right-sided filling pressures.[20] The presence of respiratory variation in the inflow velocities is defined by consensus as >30% across the mitral valve and >60% for the tricuspid valve.[4] These echocardiographic signs, when present, increase the specificity of diagnosis. Finally, the size of the pericardial effusion seems to be an important but frequently underappreciated part of the echocardiographic assessment. In one study of hospitalized patients with pericardial effusion, the size of the effusion was the only independent predictor of adverse in-hospital outcomes in a multivariate model, but not chamber collapse or inferior vena cava plethora.[21]

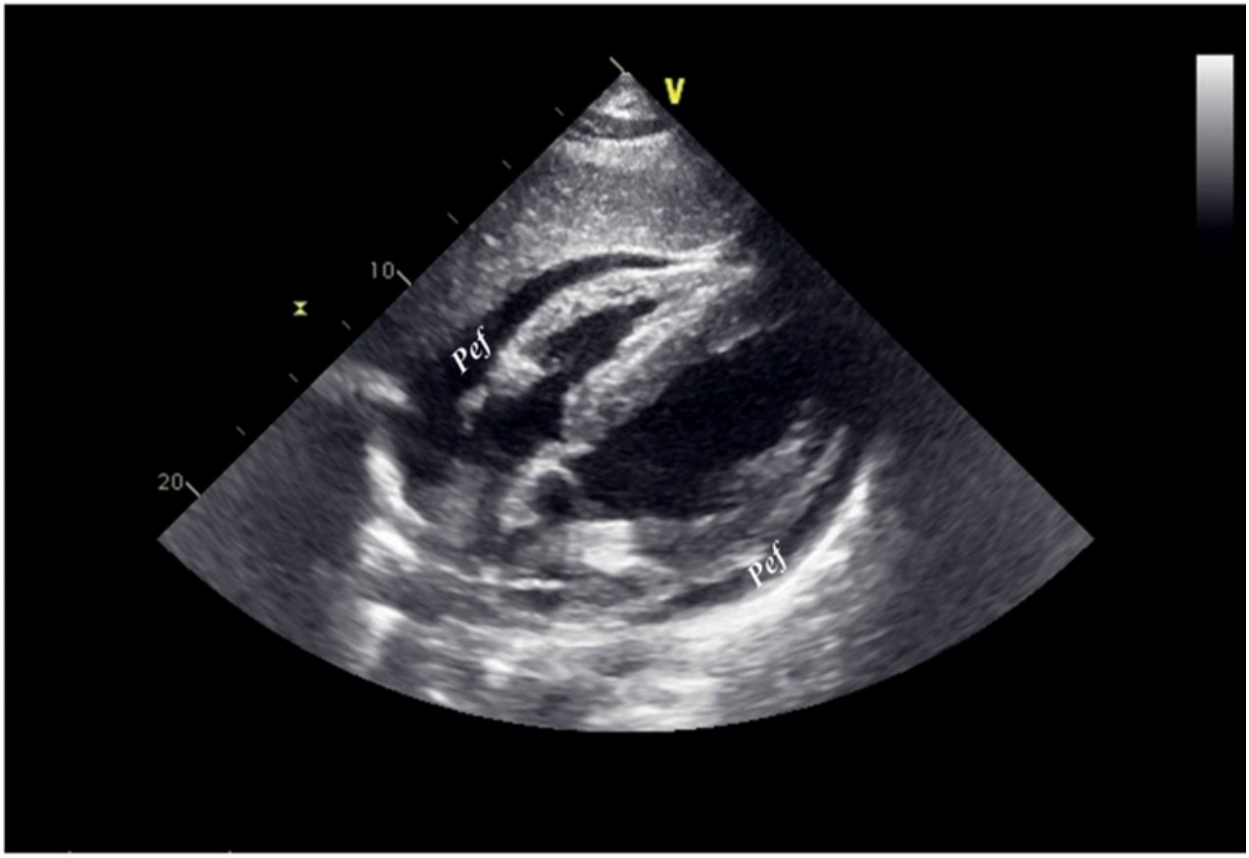

FIGURE 33.4 Pericardial effusion as seen with the ultrasound examination. Pericardial effusion (*Pef*) is easily recognized during ultrasound examination as an echo-free space around the heart.

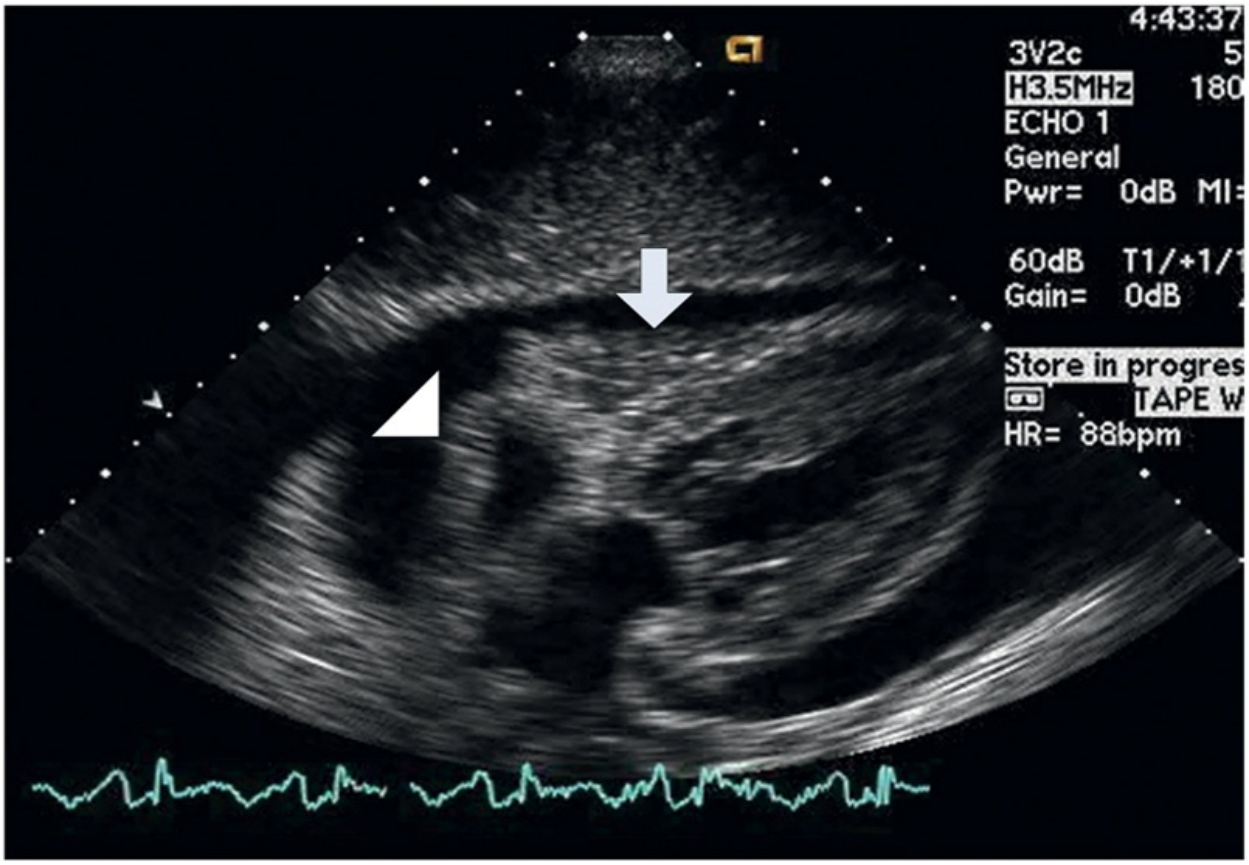

FIGURE 33.5 Chamber collapse with pericardial tamponade as seen with the ultrasound examination. There is evidence of right atrial collapse (arrowhead) as well as right ventricular compression by pericardial fluid (arrow).

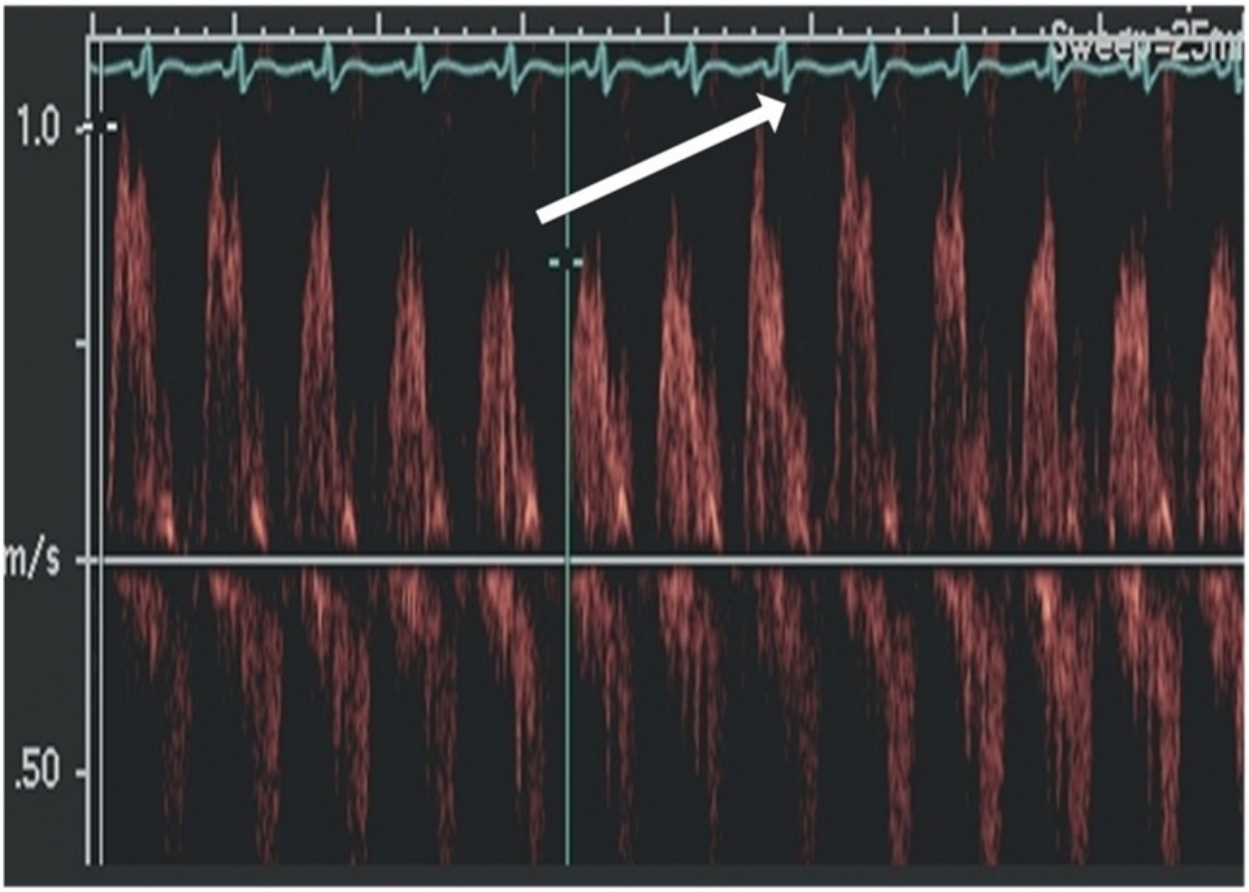

FIGURE 33.6 Doppler echocardiography in pericardial tamponade. Respiratory variation in the mitral inflow velocities (arrow) is seen.

The diagnosis of pericardial tamponade may be particularly difficult in patients with pulmonary hypertension and right ventricular failure because they commonly accumulate pericardial effusion. Pericardial effusion in these patients is a marker of adverse outcomes. Common clinical findings of pericardial tamponade such as tachycardia and jugular venous distension may not be helpful in differential diagnosis for shortness of breath and progressive right-sided heart failure. Collapse of the left-sided cardiac chambers has been described as an important echocardiographic clue to the presence of pericardial tamponade in these settings.[22] Conversely, more common findings of tamponade such as right atrial and ventricular collapse can be masked by elevated right-sided filling pressures. Poor outcomes have been reported with routine draining of pericardial effusion in these patients.

INTEGRATIVE APPROACH TO PERICARDIAL DRAINAGE

The diagnosis of subacute pericardial tamponade can be challenging because most patients are not hypotensive and can actually be hypertensive. An integrative approach that includes careful consideration of both clinical and imaging data helps clinicians assess the hemodynamic impact of pericardial effusion and the need for drainage.[13] The decision making should include the following factors:

1. Presence and timeline for symptoms (commonly dyspnea)
2. Supportive physical findings (jugular venous distension, tachycardia, and pulsus paradoxus)
3. Etiology of pericardial effusion and response to initial treatment
4. Size of pericardial effusion
5. Evidence of chamber collapse on echocardiography
6. Supporting signs for pericardial tamponade on echocardiography (respiratory variation in velocities and flows, engorgement of the inferior vena cava)

Percutaneous pericardiocentesis guided by echocardiography is the intervention of choice in many cases when pericardial drainage is desired. Emergency pericardiocentesis in acute (surgical) tamponade can be lifesaving. A study summarizing the 21-year experience from Mayo Clinic showed that echo-guided approach is rapid, safe, and effective with a major complication rate of 1.2%.[23] Extended catheter drainage has been used in certain scenarios, including neoplastic pericardial effusion when intrapericardial treatment is also occasionally employed. Stepwise drainage of pericardial effusion is reasonable in very large effusions and patients with pulmonary hypertension to avoid acute right ventricular dilation ("decompression syndrome").[3] Surgical drainage is generally preferred in traumatic pericardial effusion, aortic dissection, small effusions, recurrent effusions, and purulent pericarditis. In loculated (typically postsurgical) effusions, surgical approach or video-assisted thoracoscopic pericardiectomy can be used. Pericardial biopsy, when necessary, can be done using surgical procedure or pericardioscopy. Postdrainage echocardiography is important in assessing the efficacy of the procedure, possible complications and fluid reaccumulation, and diagnosing constriction physiology.[3]

SUPPORTIVE CARE

Promptly instituted treatment for presumed etiology of pericardial effusion (ie, anti-inflammatory therapy in acute pericarditis) can result in improvement and

defer the need for pericardial drainage. The response should be monitored by serial echocardiographic examinations. Endotracheal intubation with positive pressure ventilation requires great caution because it can markedly reduce cardiac preload and result in rapid hemodynamic deterioration.[24] Fluid resuscitation should also be used cautiously. In a hemodynamic study by Sagrista-Sauleda et al, 49 patients with pericardial tamponade were given 500 mL of intravenous normal saline before pericardiocentesis.[25] Increase in cardiac index > 10% from baseline was observed in 47% of patients. The improvement in cardiac index was modest, and only patients with systolic blood pressure < 100 mm Hg got the benefit. Actually, 31% of patients experienced a decrease in the cardiac output as the result of volume expansion. Intravenous saline infusion also consistently caused a significant increase in intrapericardial pressure, right atrial pressure, and left ventricular end-diastolic pressure.[25]

CONCLUSIONS

Pericardial disease is relatively common in acute settings and it requires prompt diagnosis. A structured approach to differential diagnosis of pericardial effusion and hemodynamic assessment is necessary in managing patients with pericardial effusion and suspected pericardial tamponade.

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Patient and Family Information for: PERICARDIAL EFFUSION AND TAMPONADE

Pericardial effusion refers to fluid accumulation in the double-membrane pericardial sack which surrounds the heart. Normally, there is a little amount of fluid that allows the heart to expand and receive blood. Abnormal fluid or blood accumulation in the pericardial sack can occasionally compress the heart and impair normal filling of heart chambers and therefore normal heart functioning. This is referred to as “tamponade,” a potentially life-threatening condition. Pericardial effusion can develop suddenly, for example, during a cardiac procedure when even a small amount of accumulated blood around the heart can cause compression; immediate intervention is necessary in that case to relieve the compression. Sometimes pericardial fluid accumulates slowly, over days and weeks as a result of infection, cancer spread, renal failure, or some other causes. In those cases, the symptoms are less dramatic but commonly include shortness of breath. Other symptoms may include tiredness, chest pain, and fever. Certain findings on physical examination and changes on electrocardiogram and chest X-ray can be suggestive of pericardial effusion. Ultrasound of the heart (also called echocardiogram) is the most commonly used diagnostic test to establish the presence of pericardial effusion and to assess the degree of heart compression. To establish the cause of pericardial effusion, the physician will typically order certain diagnostic tests which may include blood tests and occasionally advanced imaging tests (such as CT scan). Draining the pericardial fluid can be considered in some patients for two reasons: (1) establishing the diagnosis if the other tests are inconclusive and (2) relieving compression of the heart. It is performed either by a needle or surgery. During the former, a needle is introduced into the pericardial sack commonly under the guidance of ultrasound

or X-ray. The physician may decide to leave a tube (called a “drain”) in the pericardial sack for several days to avoid re-accumulation. The tube can be pulled out easily once the amount of drainage from the pericardial sack decreases significantly.

34

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Pathway for the Management of Pericardial Disease

Pericardial disease is a broad term that describes a wide range of pathologies. The clinical aspects of pericardial disease encompass acute pericarditis, pericardial tamponade, pericardial effusion, constrictive pericarditis, and effusive–constrictive pericarditis. These disorders differ not only in clinical presentation but also in the timeline of disease development; for example, pericardial tamponade is commonly an acute, life-threatening event, whereas constrictive pericarditis is a chronic process developing over months to years. Therefore, pericardial disease management is challenging for most clinicians. The evidence base in the field is relatively scarce compared with other disease entities in cardiology. The European Society of Cardiology released in 2015 its updated guidelines for the diagnosis and management of pericardial diseases.[1] Currently, there are no guidelines from American cardiology societies to help clinicians in managing pericardial disease. In this chapter we outline a unified, stepwise, pathway-based approach for the management of pericardial disease (**Figure 34.1**).[2]

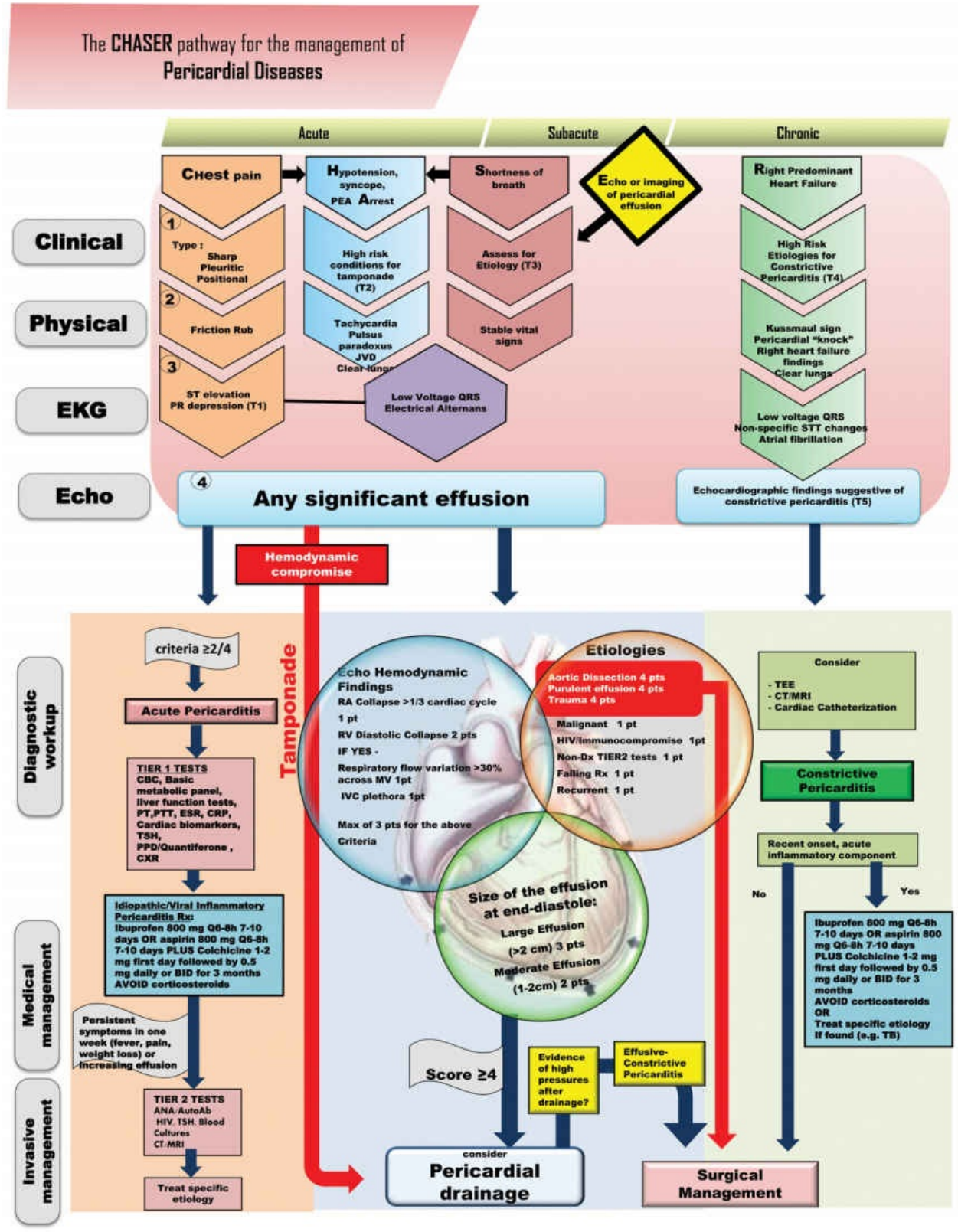

FIGURE 34.1 Novel "CHASER" pathway for the management of pericardial disease. The figure outlines a unified, stepwise pathway-based approach to pericardial disease management. ANA, antinuclear antibody;

CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IVC, inferior vena cava; JVD, jugular vein distension; MRI, magnetic resonance imaging; MV, mitral valve; PEA, pulseless electrical activity; PPD, purified protein derivative; PT, prothrombin time; PTT, partial thromboplastin time; RA, right atrium; RV, right ventricule; TB, tuberculosis; TEE, transesophageal echocardiography; TSH, thyroid-stimulating hormone. T1: Table 34.1, T2: Table 34.2, T3: Table 34.3, T4: Table 34.4, T5: Table 34.5

THE ADVANCED CARDIAC ADMISSION PROGRAM

The "Advanced Cardiac Admission Program (ACAP)" was launched in New York, in 2004. It consists of a series of projects that have been developed to bridge the gap between published guidelines and implementation during "real-world" patient care. The pericardial disease management pathway is the ninth project of the ACAP program.[2]

HOW TO USE THE PATHWAY

ENTERING THE PATHWAY

Despite the broad range of pericardial pathologies, there are a limited number of clinical presentations that would make a clinician suspect pericardial disease (**Figure 34.2**). We assigned each clinical presentation a certain pathway, which starts with patients' complaints and continues along the lines of further workup, diagnosis, and management. Typical clinical presentations in patients with pericardial disease include chest pain, hypotension/arrest, dyspnea, and right-predominant heart failure. Incidental finding of pericardial effusion during imaging study is also a common clinical scenario. **Figure 34.2** outlines the entry points into the pericardial disease management pathway. The timeline of symptom development is a continuum ranging from acute, immediate presentation to subacute and chronic symptoms. The recent European guideline[1] classified inflammatory pericardial syndromes as follows:

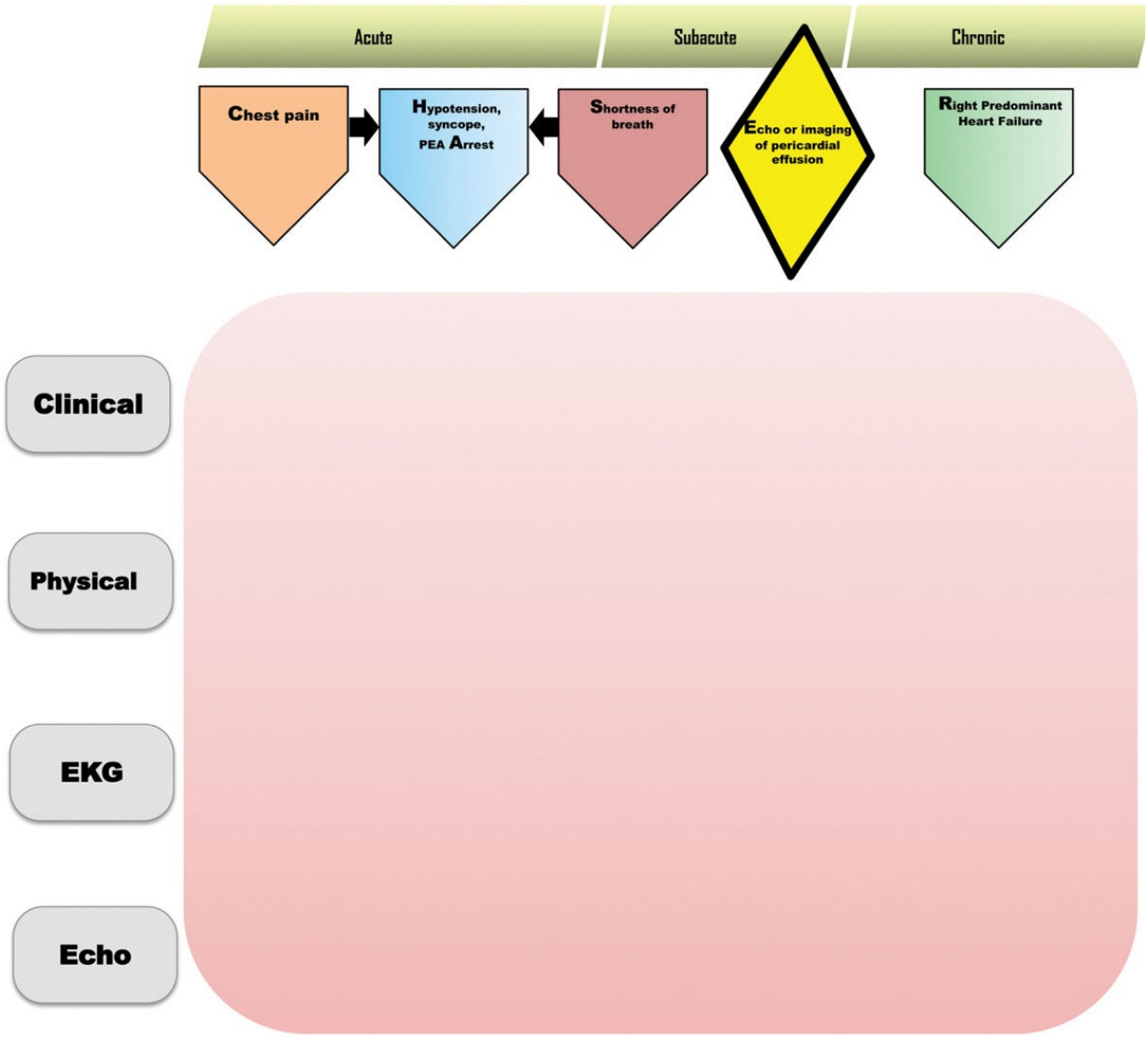

FIGURE 34.2 Entry points into the pericardial disease pathway. The entry points based on the initial clinical presentation form the "CHASER" acronym.

A. Acute pericarditis: new-onset pericarditis
B. Recurrent pericarditis: recurrence of symptoms after being symptom-free for 4 to 6 weeks
C. Incessant pericarditis: symptoms over 4 to 6 weeks
D. Chronic pericarditis: symptoms over 3 months

A systematic approach to patients with suspected pericardial disease starts with the chief presenting complaint and is followed by a history taking, physical examination, electrocardiogram (ECG), and echocardiography. Further

diagnostic testing is tailored to the initial findings.

The following are the five entry points:

1. Chest Pain

Acute pericarditis should be considered in the differential diagnosis of any patient presenting with chest pain along with other etiologies. The chest pain algorithm of the pathway is outlined in **Figure 34.3**. The diagnosis of acute pericarditis relies on the following four cardinal features: characteristic chest pain which is pleuritic and positional, friction rub on physical examination, characteristic evolving ECG changes (**Table 34.1**), and pericardial effusion demonstrated by echocardiography.[3–5] Presence of at least two of these features is usually diagnostic of acute pericarditis. Most cases of acute pericarditis in the Western world are idiopathic or viral, but other causes should also be considered.[6] Initial testing in all patients with acute pericarditis should include tier 1 testing (**Figure 34.3**).[7] Positive cardiac biomarkers indicate myocardial involvement and carry a worse prognosis. Inflammatory markers such as C-reactive protein can be followed sequentially to monitor disease progression and response to treatment. Typical treatment includes nonsteroidal anti-inflammatory agents at full doses for 7 to 10 days.[1] We recommend the following doses: ibuprofen 600 to 800 mg every 6 to 8 hours for 7 to 10 days or aspirin 800 mg every 6 to 8 hours for 7 to 10 days. In post–myocardial infarction pericarditis, aspirin is preferred. In patients without contraindications, colchicines at a dose of 1 to 2 mg first day followed by 0.5 mg daily or twice daily for 3 months should be given because it reduces the rate of recurrence substantially.[5,8]

TABLE 34.1 ECG Features of Acute Pericarditis

Stage 1: diffuse ST-segment elevation and PR-segment depression
Stage 2: normalization of ST-segment changes
Stage 3: diffuse T-wave inversion
Stage 4: normalization of T-wave changes

ECG, electrocardiogram.

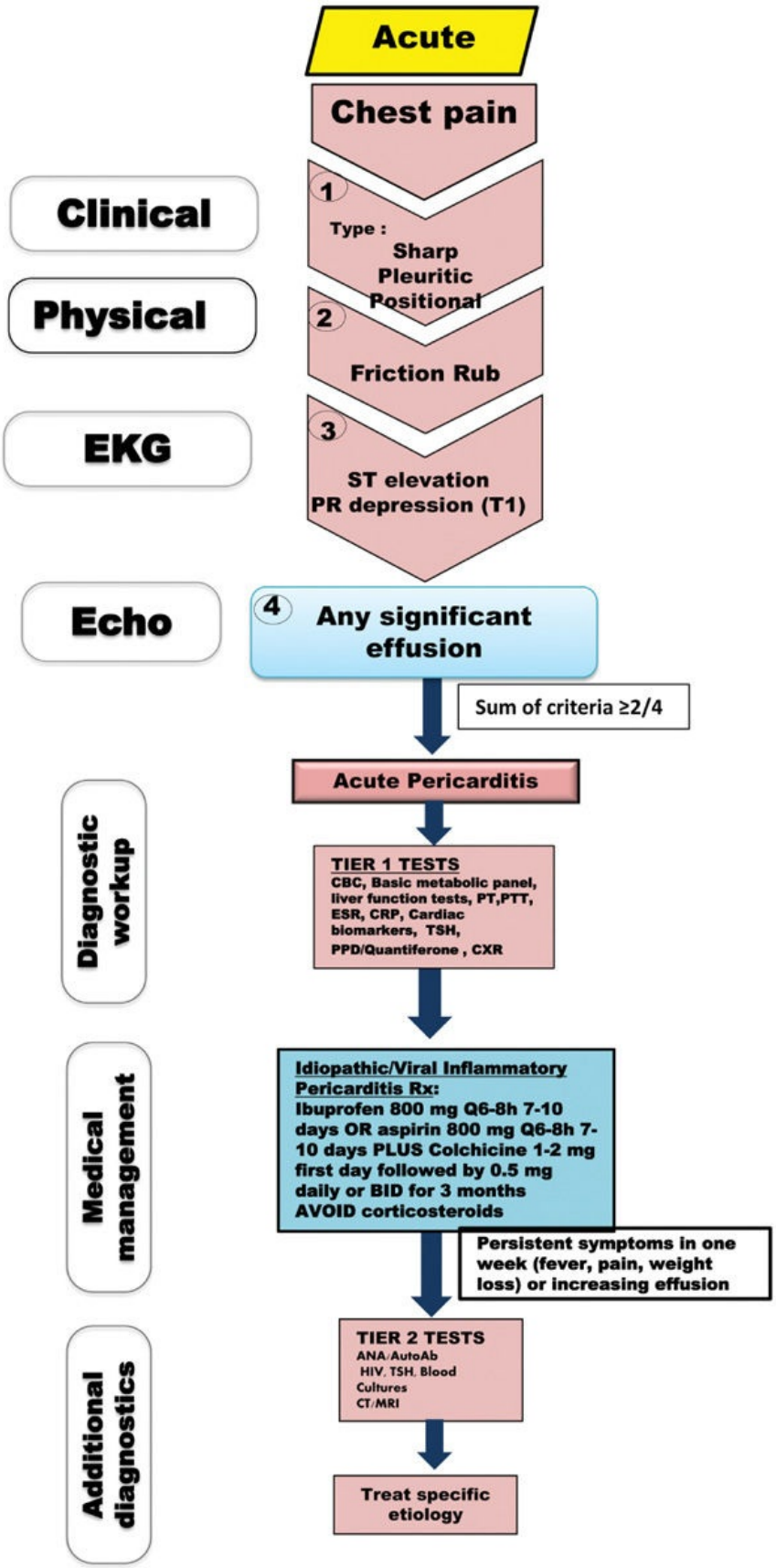
Acute
Chest pain
Clinical
1
Type :
Sharp
Pleuritic
Positional
Physical
2
Friction Rub
EKG
3
ST elevation
PR depression (T1)
Echo
4
Any significant effusion
Sum of criteria ≥2/4
Acute Pericarditis
Diagnostic workup
TIER 1 TESTS
CBC, Basic metabolic panel, liver function tests, PT,PTT, ESR, CRP, Cardiac biomarkers, TSH, PPD/Quantiferone , CXR
Medical management
Idiopathic/Viral Inflammatory Pericarditis Rx:
Ibuprofen 800 mg Q6-8h 7-10 days OR aspirin 800 mg Q6-8h 7-10 days PLUS Colchicine 1-2 mg first day followed by 0.5 mg daily or BID for 3 months
AVOID corticosteroids
Persistent symptoms in one week (fever, pain, weight loss) or increasing effusion
Additional diagnostics
TIER 2 TESTS
ANA/AutoAb
HIV, TSH, Blood Cultures
CT/MRI
Treat specific etiology

FIGURE 34.3 Evaluation of chest pain in patient with possible acute pericarditis. A stepwise algorithm outlines evaluation and management of chest pain patients suspected to have acute pericarditis. ANA, antinuclear antibody; CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; PPD, purified protein derivative; PT, prothrombin time; PTT, partial thromboplastin time; TSH, thyroid-stimulating hormone. T1: Table 34.1

Corticosteroids increase the likelihood of relapse and should be avoided unless specifically indicated (eg, in patients with connective tissue disease).[5,9] Patients with idiopathic or viral pericarditis usually respond promptly to treatment. Patients with persistent symptoms or with atypical clinical features are more likely to have other causes of pericarditis such as connective tissue disease and should undergo tier 2 testing, as seen in **Figure 34.3**.[10] Those tests include imaging studies such as computed tomography scan of the chest or magnetic resonance imaging.[1] Corticosteroids can be used as a last resort for those patients if no specific cause is found.[1]

2. Hypotension, Syncope, or Pulseless Electrical Activity Arrest

Patients with tamponade can have an acute, dramatic presentation as do patients with acute ascending aortic dissection involving the pericardial sac, or these patients can present with subacute symptoms of chest pain, dyspnea, and syncope as do patients with neoplastic pericarditis. Cardiac tamponade should be suspected in any patient with hypotension, collapse, and pulseless electrical activity arrest (**Figure 34.4**), and high-risk conditions commonly associated with tamponade should be specifically thought of (**Table 34.2**).[11] These include blunt chest trauma, recent procedure/intervention (eg, electrophysiology procedures and coronary interventions), chest surgery, and aortic dissection. Neoplastic pericardial effusion, tuberculous pericarditis, and, uncommonly, idiopathic pericarditis can progress to tamponade. Physical examination findings should focus on pulsus paradoxus, jugular vein pressure, and lung auscultation. ECG findings may include low-voltage QRS complex size and finding of pulsus alternans. Echocardiography is essential in diagnosing pericardial effusion and confirming tamponade by the echocardiographic signs of hemodynamic compromise (**Figure 34.5**). Echocardiography is also commonly used for guiding the intervention. Pericardiocentesis can be lifesaving in these patients.

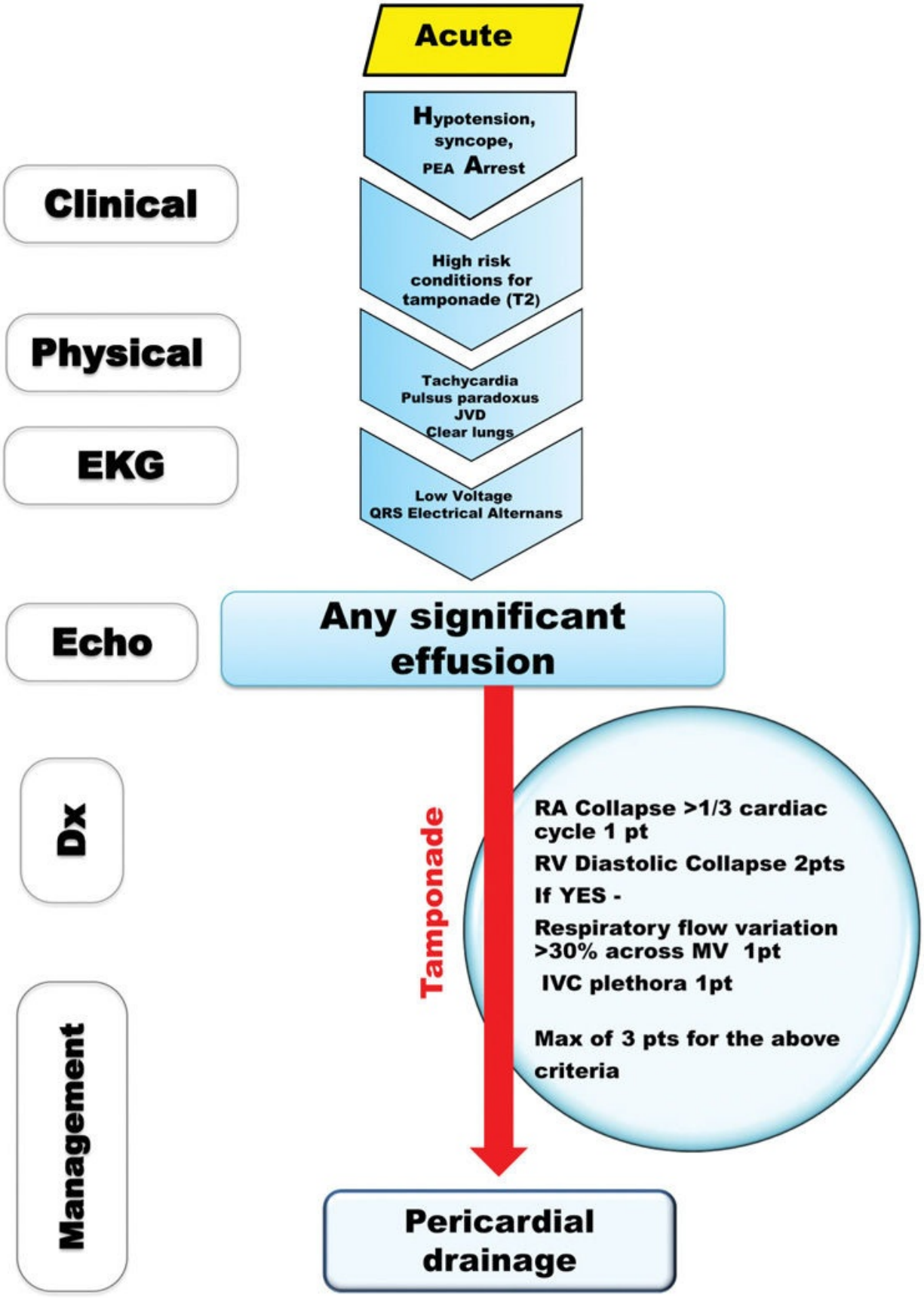
Acute
Clinical
Hypotension, syncope, PEA Arrest
Physical
High risk conditions for tamponade (T2)
Tachycardia
Pulsus paradoxus
JVD
Clear lungs
EKG
Low Voltage
QRS Electrical Alternans
Echo
Any significant effusion
Dx
Tamponade
RA Collapse >1/3 cardiac cycle 1 pt
RV Diastolic Collapse 2pts
If YES -
Respiratory flow variation >30% across MV 1pt
IVC plethora 1pt
Max of 3 pts for the above criteria
Management
Pericardial drainage

FIGURE 34.4 Approach to a patient with hypotension, syncope, or PEA arrest with possible pericardial tamponade. Initial clinical evaluation of patients suspected to have cardiac tamponade is outlined in the figure. JVD, jugular vein distension; MV, mitral valve; PEA, pulseless electrical activity; RA, right atrial; RV, right ventricular. T2: Table 34.2

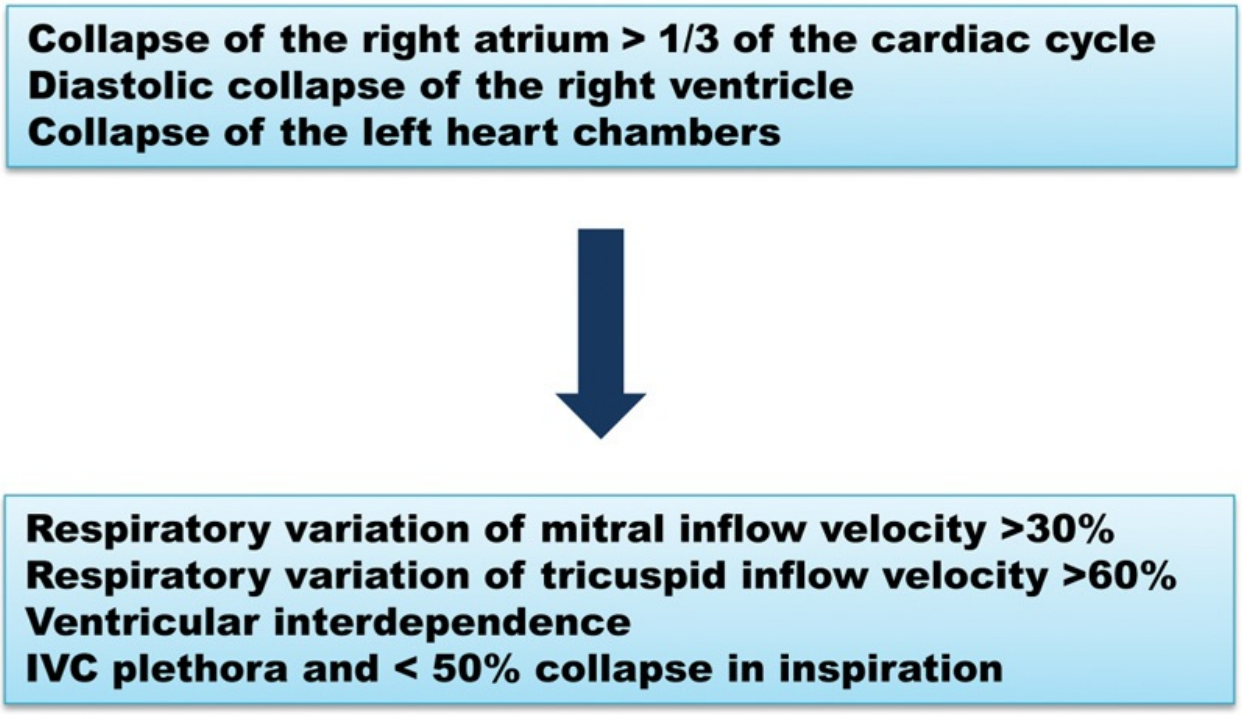

FIGURE 34.5 Echocardiographic signs of hemodynamic compromise. The findings of heart chamber collapse are presented in order of decreasing sensitivity and increasing specificity. Confirmatory signs include respiratory variation across the atrioventricular valves, ventricular interdependence, and IVC plethora. IVC, inferior vena cava.

TABLE 34.2	High-Risk Conditions for Tamponade
Advanced renal failure	
Aortic dissection	
Chest trauma	
Connective tissue disease	
Malignancy	
Purulent infection	
Recent acute coronary syndrome	
Surgery/intervention	
Suspected tuberculosis	

3. Dyspnea

Patients with significant pericardial effusion often present with dyspnea, poor exercise tolerance, chest discomfort, and fatigue. Although the differential

diagnosis of dyspnea is broad, it should include pericardial effusion (**Figure 34.6**). The pericardium can be the primary focus for the disease, as in most cases of acute pericarditis, or it can be involved in a systemic process such as malignancy, endocrine diseases, or rheumatic diseases. In every patient with suspected pericardial disease, a systematic approach and consideration of possible etiologies are important parts of clinical reasoning (**Table 34.3**). These patients are hemodynamically stable and have no clinical signs of tamponade. ECG characteristics commonly include low-voltage QRS complex size. Pulsus alternans is occasionally seen with large effusions without tamponade.[11] Echocardiography is an effective and inexpensive tool in diagnosing pericardial effusion.

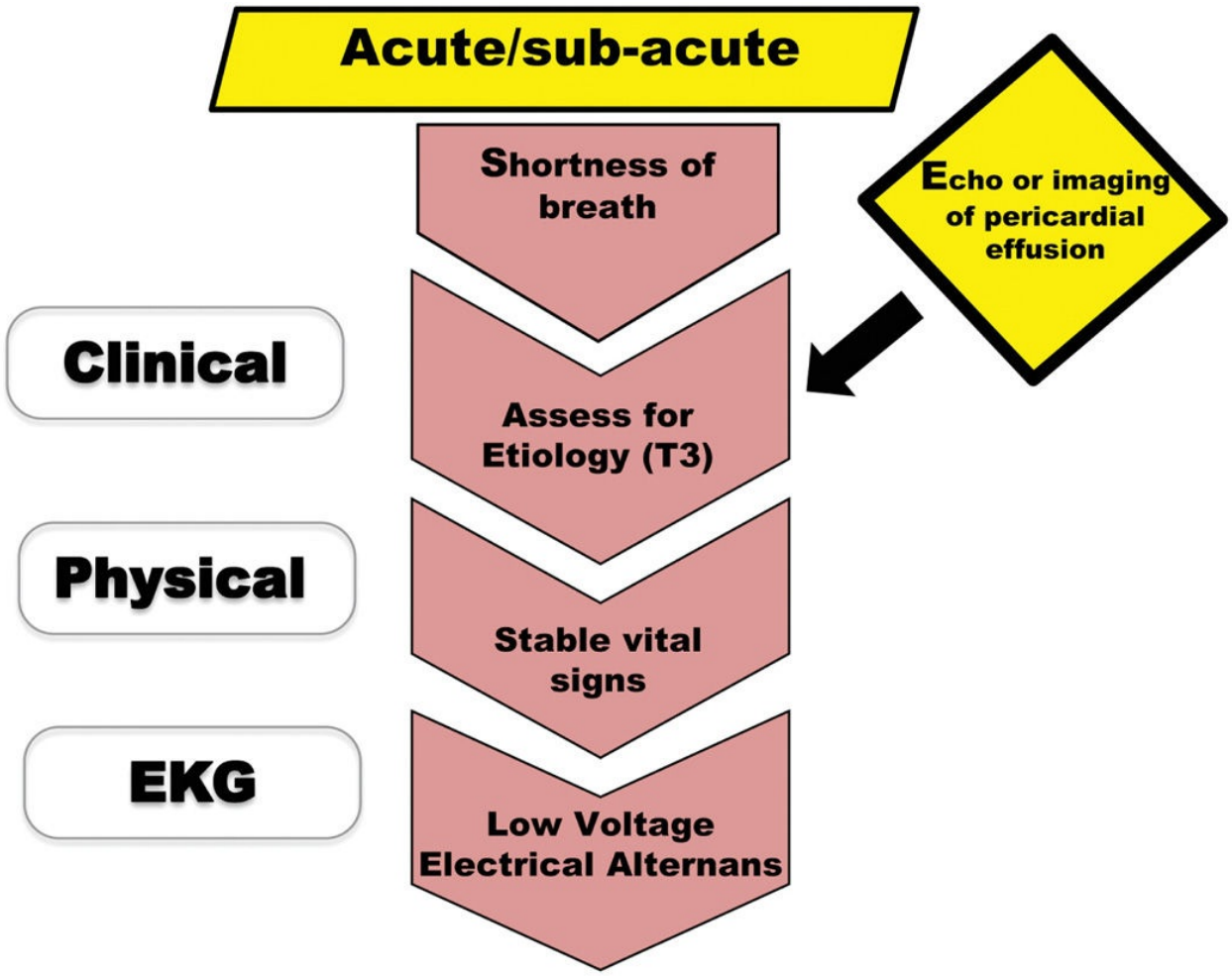

FIGURE 34.6 Approach to a patient with dyspnea and possible pericardial effusion. Initial clinical evaluation of patients suspected to have pericardial effusion is outlined in the figure. Some patients are diagnosed with incidental pericardial effusion during imaging study done for other indications. T3: Table 34.3

TABLE 34.3	Causes of Pericardial Disease

Endocrine
Hemopericardium (trauma, procedure, aortic dissection)
Idiopathic
Infectious (including viral, tuberculosis, and purulent)
Medications
Neoplastic
Perimyocardial infarction
Postcardiotomy syndrome
Radiation
Renal failure
Rheumatic/autoimmune diseases

4. Incidental Finding of Pericardial Effusion

Sometimes, pericardial effusion is found as an incidental finding in patients worked up for other causes. Although it is important to search systematically for possible etiologies of pericardial disease in each individual patient (**Table 34.3**), a substantial number of these cases remain unexplained.[12,13] In patients with moderate-to-large effusion, tier 1 and tier 2 testing seem reasonable.[12] If a specific cause is found, it should be addressed. In patients with no obvious clue to the cause of the effusion and no evidence of hemodynamic compromise, elevated inflammatory markers suggest acute idiopathic pericarditis and trial of nonsteroidal anti-inflammatory agents is justified. If inflammatory markers are within normal limits and there is no evidence of hemodynamic compromise, idiopathic pericardial effusion is high on the list of differential diagnoses.[12] Some patients with pericardial effusion have elevated right-sided pressures after pericardial drainage and they might have effusive–constrictive pericarditis.[14]

5. Right-Sided Heart Failure

Patients with constrictive pericarditis typically present with right-predominant heart failure (**Figure 34.7**). Careful review of medical history for high-risk conditions associated with constrictive pericarditis is necessary (**Table 34.4**).[15] Peripheral edema, hepatomegaly, jugular venous distension, and ascites are prominent findings on physical examination. The lungs are typically clear, although pleural effusion may be present. ECG findings, especially repolarization abnormalities, are nonspecific. Atrial fibrillation is present in over one-fifth of patients.[16] Echocardiography is essential in patients suspected to have constriction; these patients typically have normal left ventricular ejection fraction. Other echocardiographic findings include biatrial enlargement and

restrictive filling pattern on the mitral inflow Doppler recording (**Table 34.5**).[14] Further studies to confirm the diagnosis and differentiate it from restrictive cardiomyopathy include imaging studies (such as magnetic resonance imaging) and cardiac catheterization. Pericardial thickness as measured by transesophageal echocardiography may be helpful in making the diagnosis.[17] Early stages of pericardial constriction due to idiopathic pericarditis may have an inflammatory component and may respond to anti-inflammatory therapy.[18] Surgical therapy is otherwise the standard of care.

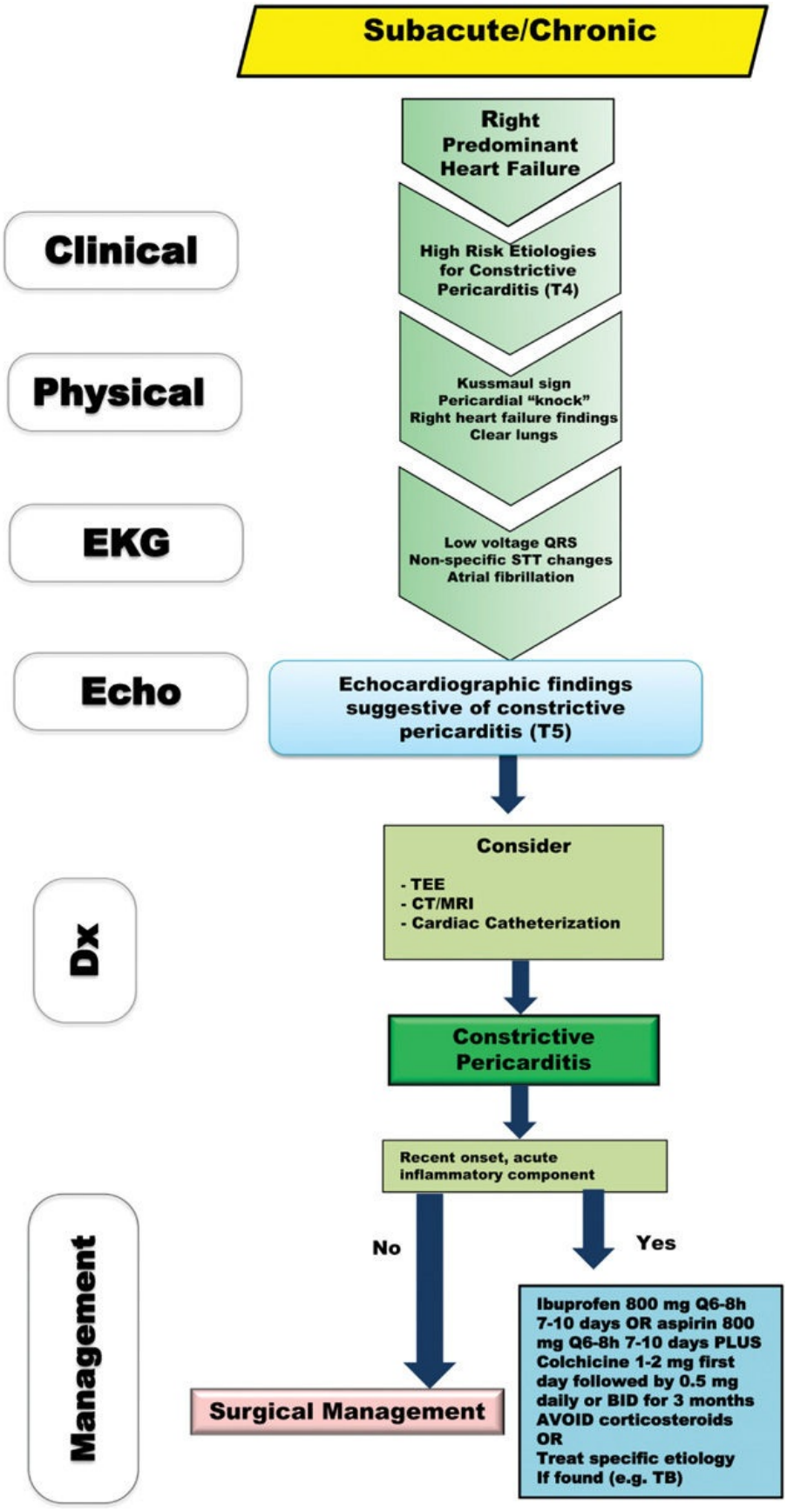
Subacute/Chronic
Clinical
Right Predominant Heart Failure
High Risk Etiologies for Constrictive Pericarditis (T4)
Physical
Kussmaul sign
Pericardial "knock"
Right heart failure findings
Clear lungs
EKG
Low voltage QRS
Non-specific STT changes
Atrial fibrillation
Echo
Echocardiographic findings suggestive of constrictive pericarditis (T5)
Dx
Consider
- TEE
- CT/MRI
- Cardiac Catheterization
Constrictive Pericarditis
Recent onset, acute inflammatory component
Management
No
Yes
Surgical Management
Ibuprofen 800 mg Q6-8h 7-10 days OR aspirin 800 mg Q6-8h 7-10 days PLUS Colchicine 1-2 mg first day followed by 0.5 mg daily or BID for 3 months
AVOID corticosteroids
OR
Treat specific etiology If found (e.g. TB)

FIGURE 34.7 Evaluation of right-predominant heart failure in a patient with possible constrictive pericarditis. A stepwise algorithm outlines evaluation and management of patients with right-predominant heart failure suspected to have constrictive pericarditis. CT, computed tomography; MRI, magnetic resonance imaging; TB, tuberculosis; TEE, transesophageal echocardiography. T4: Table 34.4, T5: Table 34.5

TABLE 34.4 High-Risk Conditions for Constrictive Pericarditis

Cardiac surgery
Connective tissue disease
HIV infection
Previous pericarditis
Radiation therapy to the chest
Tuberculosis

HIV, human immunodeficiency virus.

TABLE 34.5 Echocardiographic Findings of Constrictive Pericarditis

Normal left ventricular ejection fraction
Normal left ventricular wall thickness
Thickened pericardium (>2 mm) and/or pericardial calcifications
Restrictive filling pattern (E>>A wave, high E-wave velocity, short E-wave deceleration time)
Respiratory flow variations across atrioventricular valves
Displacement of interventricular septum
Rapid flow propagation (>100 cm/s)
Normal tissue Doppler findings (E′ > 8 cm/s)
Expiratory hepatic veins flow reversal

PERICARDIAL EFFUSION SCORE

Acute cardiac tamponade necessitates immediate pericardiocentesis. The decision to drain the pericardium in patients with slowly accumulating and subacute tamponade is often challenging. We proposed a score approach to decision making in clinically stable patients with pericardial effusion, as outlined in **Figure 34.8**. The score is composed of the following three major parameters: the etiology of the effusion, the size of the effusion, and the echocardiographic assessment of hemodynamic parameters. Etiologic factors favoring drainage of the effusion include traumatic effusion, aortic dissection, and purulent effusion. These effusions typically require surgical drainage as opposed to pericardiocentesis.[1] In malignant effusions, drainage should be considered to relieve symptoms and confirm neoplastic involvement of the pericardium.[19] Pericardial effusion in patients with advanced human immunodeficiency virus and immunosuppression, as well as unexplained and progressive effusion should

also be considered for drainage because some of the neoplastic and infectious causes in these patients are treatable.[20,21] The size of the pericardial effusion as assessed by echocardiography at the end of a diastole is a very important variable.[22] It should be viewed in the context of disease progression (the rate of fluid accumulation).

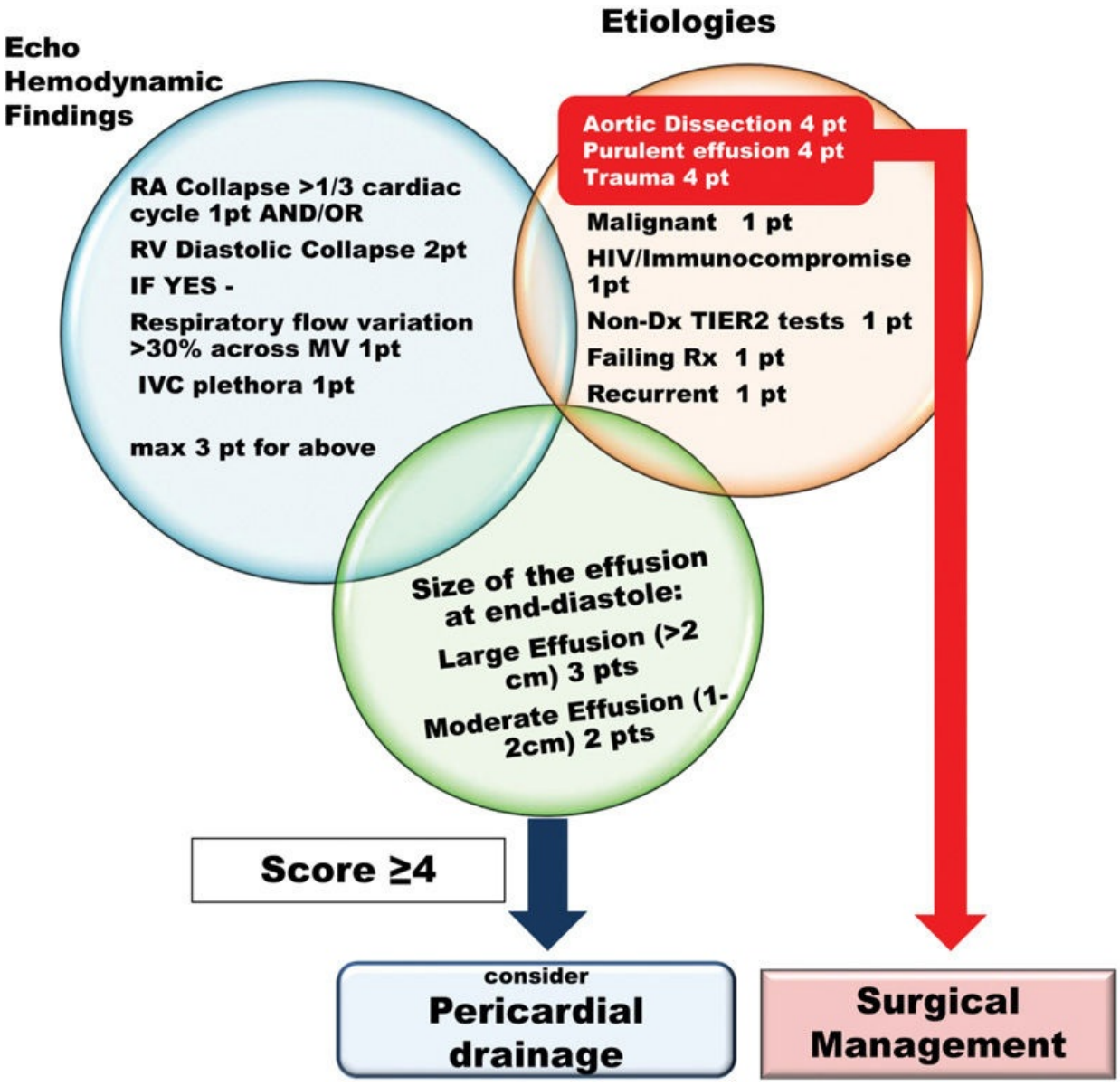

FIGURE 34.8 Pericardial effusion score. The pericardial effusion score, which has three components (etiology of the effusion, effusion size, and echocardiographic evidence of hemodynamic compromise), helps guide clinical decision making in clinically stable patients with pericardial effusion. HIV, human immunodeficiency virus; IVC, inferior vena cava; MV, mitral valve; RA, right atrial; RV, right ventricular.

Chronic large effusions present for more than 3 months are less likely to cause hemodynamic compromise as opposed to recent effusion (<1 month).[14] Echocardiographic signs of hemodynamic compromise provide important evidence in favor of drainage because they may indicate early or impending tamponade. Of note, right atrial collapse is the earliest sign of hemodynamic compromise but has a low specificity if only buckling is present. Right atrial collapse lasting more than one-third of the cardiac cycle seems to be both specific and sensitive.[23] Right ventricular diastolic collapse is a specific sign of hemodynamic compromise but is less sensitive than right atrial collapse.[24] In patients with significant pulmonary hypertension and right ventricular hypertrophy, the sensitivity of this finding is even lower. Left-sided chamber collapse is a late finding in tamponade, and therefore lacks sensitivity.[25] Confirmatory findings should be specifically looked for once a chamber collapse is present. These include respiratory variation in flow velocity across the atrioventricular valves (the mitral and the tricuspid valves), implying ventricular interdependence and engorgement of the inferior vena cava with reduced respiratory collapse. Any chamber collapse combined with a confirmatory finding has a very high sensitivity and specificity for tamponade.[26] In general, a score of 4 or more provides strong evidence in favor of draining the effusion. It should not be viewed as an absolute indication for drainage but rather as a qualitative measure to support decision making. Importantly, the score may change over time as the variables change. Patients with a borderline score may need frequent reassessment in terms of effusion size progression and echocardiographic evidence of hemodynamic compromise.

We conducted a case–control study in consecutive hospitalized patients with moderate-to-large pericardial effusion who had no evidence of hemodynamic compromise upon admission. Patients with pericardial effusion drained for diagnostic and/or therapeutic purpose served as cases, and patients who were not drained served as controls. Our conclusion was that the pericardial effusion scoring index obtained at the initial presentation in patients without immediate hemodynamic compromise showed a high accuracy in identifying patients who required pericardial effusion drainage downstream.[27]

PERICARDIAL DRAINAGE

In patients who need pericardial drainage, echocardiographically guided pericardiocentesis appears to be safe.[28] Depending on the pericardial fluid

accumulation pattern, parasternal, subxiphoid, and apical approaches are all acceptable. As mentioned, the surgical drainage of pericardial effusion is more appropriate in certain patient groups such as in patients with aortic dissection, traumatic hemopericardium, purulent pericarditis, and loculated effusions.[1]

CONCLUSIONS

A stepwise, pathway-based approach to the management of pericardial disease is intended to provide guidance for clinicians in decision making and a patient-tailored evidence-based approach to medical and surgical therapy for pericardial disease.

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35

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Alan F. Vainrib
Muhamed Saric

Aortic Valvular Disease in the Cardiac Care Unit

INTRODUCTION

The aortic valve normally consists of three semilunar leaflets. It is designed to allow unrestricted blood flow from the left ventricle into the ascending aorta during systole and to prevent backflow during diastole. A pathologic state is established whenever each of these two functions is compromised: either aortic stenosis (AS) or aortic regurgitation (AR).

In AS, blood cannot flow freely out of the left ventricle during systole; in AR, the blood flows back into the left ventricle during diastole. AS or AR can be primary causes of severe illness, or they can exacerbate concomitant diseases in critically ill patients presenting to cardiac care units (CCUs).

Because there is no effective medical therapy for these conditions, severe AS and AR ultimately require surgical or transcatheter aortic valve replacement (TAVR) to achieve clinical stability and alter their natural progression. Rapid diagnosis and supportive medical therapy are necessary until definitive treatment can be provided.

With the introduction of TAVR, a true revolution has occurred. Patients with severe AS who were previously deemed too high risk to undergo surgery are now able to be treated safely and effectively. In the early days of TAVR, the

procedure was done under general anesthesia and required postprocedural care with CCU observation. However, there has been a general trend to replace general anesthesia with moderate sedation, and CCU care is often shortened or even unnecessary.[1]

AORTIC STENOSIS

ETIOLOGY AND PATHOPHYSIOLOGY

In the adult CCU, the most common etiology of AS is calcific degeneration (**Figure 35.1)** of a previously normal trileaflet aortic valve (TAV) or a congenitally bicuspid aortic valve (BAV). Calcific TAV stenosis is typically encountered among the elderly and calcific BAV stenosis in middle-aged patients. It is estimated that moderate or severe AS is present in 0.4% of all Americans, and in 2.8% of people 75 years of age or older.[2]

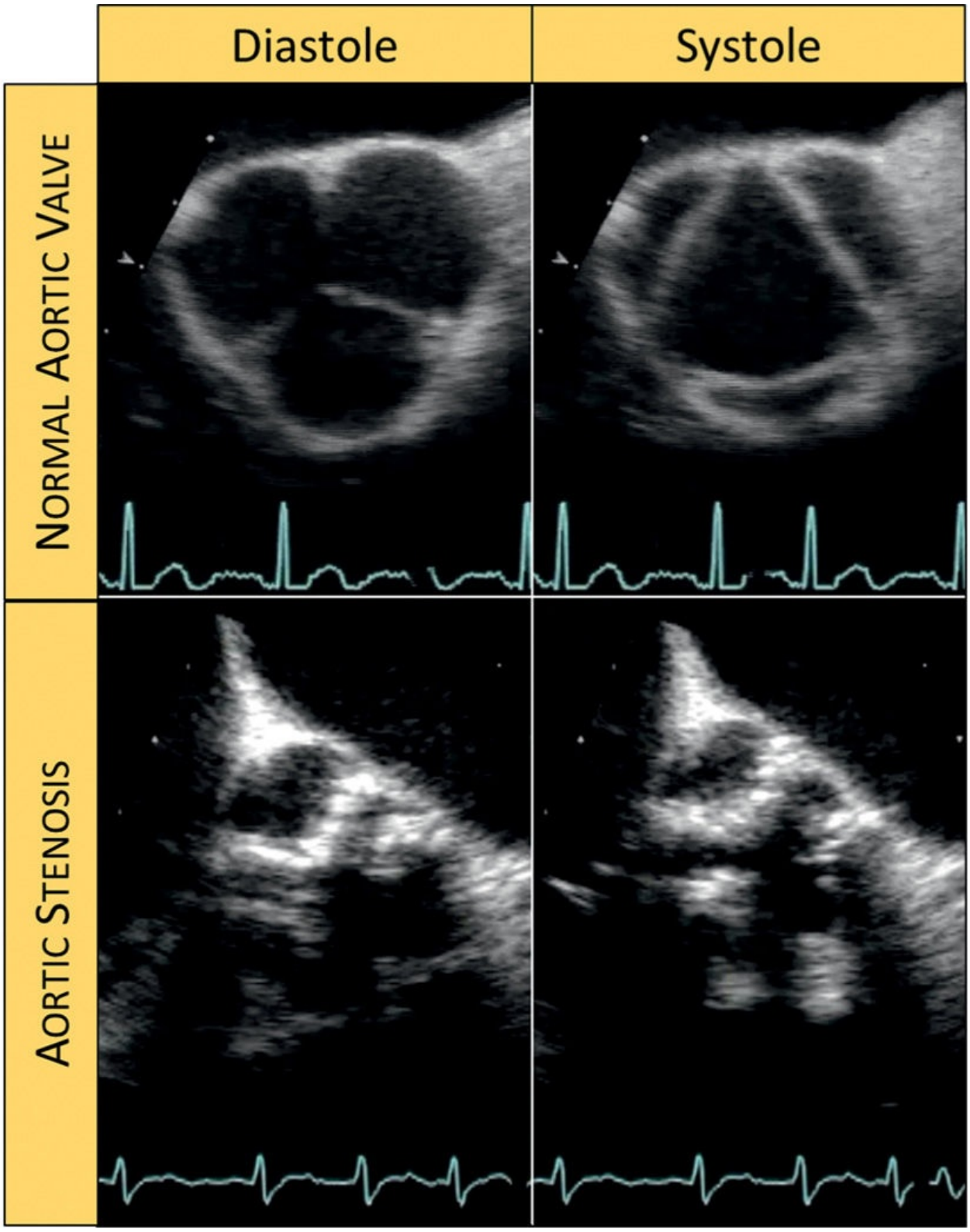

FIGURE 35.1 Aortic stenosis on echocardiography. Transesophageal echocardiogram (TEE) showing normal valve anatomy and a severely stenotic aortic valve, both in diastole and systole. Note how calcified and narrowed the stenotic valve appears.

Once thought to be the result of passive wear and tear, AS of a TAV is now understood to be a manifestation of generalized atherosclerosis, an active proliferative and inflammatory process.[3,4] Thus, this form of AS and atherosclerosis share risk factors such as smoking, hyperlipidemia, and hypertension.[5,6] In addition, disorders of calcium phosphate metabolism such as end-stage renal disease and Paget disease, as well as mediastinal radiation treatment, increase the risk for development of AS.[7]

BAV is the most common congenital heart defect, occurring in approximately 1% to 2% of all live births.[8] BAV may evolve into AS or AR and may be associated with diseases of the aorta such as aortic aneurysm, aortic dissection, and coarctation.[9]

The most important physiologic adaptation to the pressure overload from AS is left ventricular hypertrophy (LVH). This leads to concentric hypertrophy, a process in which the left ventricular (LV) chamber becomes smaller and its wall thicker; such changes decrease the wall stress and preserve left ventricular ejection fraction (LVEF) for very long periods. When LVEF starts to decrease, the underlying mechanism is an afterload-LVH mismatch (insufficient hypertrophy for the degree of AS) rather than true cardiomyopathy.

CLINICAL PRESENTATION

The classic triad of symptomatic severe AS consists of angina, syncope, and dyspnea from heart failure. AS is usually asymptomatic unless severe. The importance of recognizing the symptomatic stage of AS, as established by the seminal work by Ross and Braunwald, is the rapid rise in mortality once symptoms develop.[10] Following a latent asymptomatic period, patients who progress to severe symptomatic AS experience over 50% mortality in the next 2 to 3 years if no intervention is pursued.[11]

DIAGNOSIS

Although physical examination may establish the diagnosis, it is often unable to precisely grade AS severity. The typical findings in auscultation of AS include a systolic crescendo–decrescendo ejection murmur over the precordium that radiates to the neck, which becomes late peaking as the aortic valve becomes more stenotic. The prolonged ejection time leads to a single or, paradoxically, split second heart sound (S2), with occasional absence of S2 in severe cases.[12] Carotid upstroke is typically weak and delayed (*pulsus parvus et tardus*).

Electrocardiogram (ECG) often meets criteria for LVH and left atrial enlargement. Although chest X-ray (CXR) rarely provides direct evidence of AS, it occasionally shows aortic valve calcifications. In addition, pulmonary venous congestion is frequently seen in decompensated patients.

The primary means of diagnosing and grading AS is echocardiography, and aortic valve area (AVA) is the primary criterion of AS. When there is normal flow across the aortic valve, the magnitude of the peak and mean systolic gradient across the aortic valve is inversely related to AVA (**Table 35.1**). Additional echocardiographic findings in patients with significant AS include LVH, left atrial enlargement, and typically preserved LVEF.

TABLE 35.1 Aortic Valve Stenosis Criteria in Patient With Preserved Transvalvular Flow

	NONSTENOTIC AORTIC VALVE	MILD AS	MODERATE AS	SEVERE AS
Valve area (cm^2)	2.0–4.0	>1.5	1.0–1.5	<1.0
Valve area index (cm^2/m^2)				<0.6
Peak velocity (m/s)	<2.5	2.5–3.0	3.1–4.0	>4.0
Peak gradient (mm Hg)	<25	25–36	37–64	>64
Mean gradient (mm Hg)		<25	25–40	>40
ACC/AHA stage	A (at risk)	B (progressive)		C (asymptomatic) D (symptomatic)

ACC, American College of Cardiology; AHA, American Heart Association.

A low transvalvular gradient (mean gradient ≤30 mm Hg) does not exclude severe AS. In patients with low transaortic volume flow rate, peak and mean systolic gradients do not accurately reflect severity of AS. Low flow may occur for two separate reasons: (1) low stroke volume in the setting of small hypertrophied left ventricle with preserved LVEF and (2) low stroke volume in the setting of LV systolic dysfunction and low LVEF. Low flow is typically defined as a low LV stroke volume index of <35 mL/m^2.

In patients with low-flow, low-gradient severe AS with normal LVEF, echocardiography demonstrates small LV chamber size, abnormal diastolic

filling, and increased LV relative wall thickness. In contrast, in patients with systolic dysfunction and depressed LVEF, low transvalvular gradients are found for two reasons: either afterload-hypertrophy mismatch or concomitant cardiomyopathy (such as ischemic heart disease). Differentiating between these two groups is extremely important because the patients in the first group will benefit from aortic valve surgery, whereas those in the second group may not (**Figure 35.2**).[13]

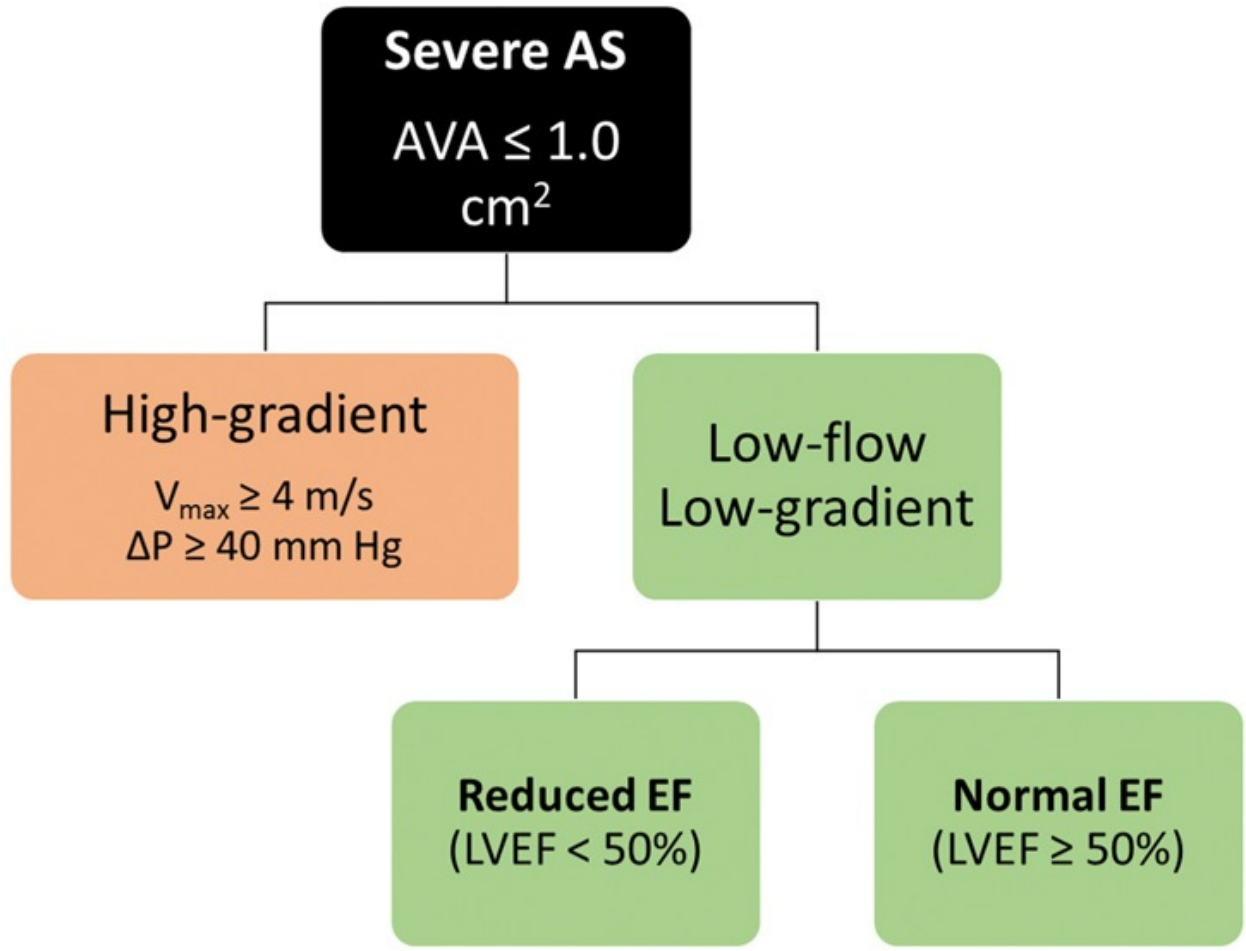

FIGURE 35.2 Three forms of AS. Flowsheet showing three different categories of severe aortic stenosis. Hemodynamic parameters (peak velocity and mean gradient) discriminate high-gradient from low-gradient severe AS. In low-gradient severe AS with reduced EF, dobutamine stress echocardiography is used to confirm true severe AS. In low-gradient severe AS with normal EF, low stroke volume, LV size and abnormal LV parameters are commonly present. AS, aortic stenosis; EF, ejection fraction; LV, left ventricular; LVEF, left ventricular ejection fraction.

To differentiate between these two groups, various LV and aortic valve parameters are assessed at rest and following intravenous infusion of increasing

amounts of dobutamine starting at 5 μg/kg/min and escalating up to 20 μg/kg/min.[14] These parameters are usually measured by echocardiography (modified dobutamine stress echocardiogram). However, these parameters may also be evaluated during cardiac catheterization.

In patients with low-gradient AS with reduced LVEF, changes in the following three parameters are measured during dobutamine stress testing: LV stroke volume, AVA, and mean gradient. If the stroke volume increases ≤20%, the patient likely has severe cardiomyopathy and is usually not a candidate for aortic valve surgery. On the other hand, if the stroke volume increases more than 20%, two scenarios are possible: (1) AVA remains essentially the same but the mean gradient increases above 30 mm Hg and (2) AVA increases by 0.2 cm^2 or more but the gradient remains essentially unchanged. In the first scenario, patients have true severe AS and will benefit from aortic valve surgery. In the second scenario, patients have pseudosevere AS due to LV cardiomyopathy; they are unlikely to benefit from aortic valve surgery (**Figure 35.3**).

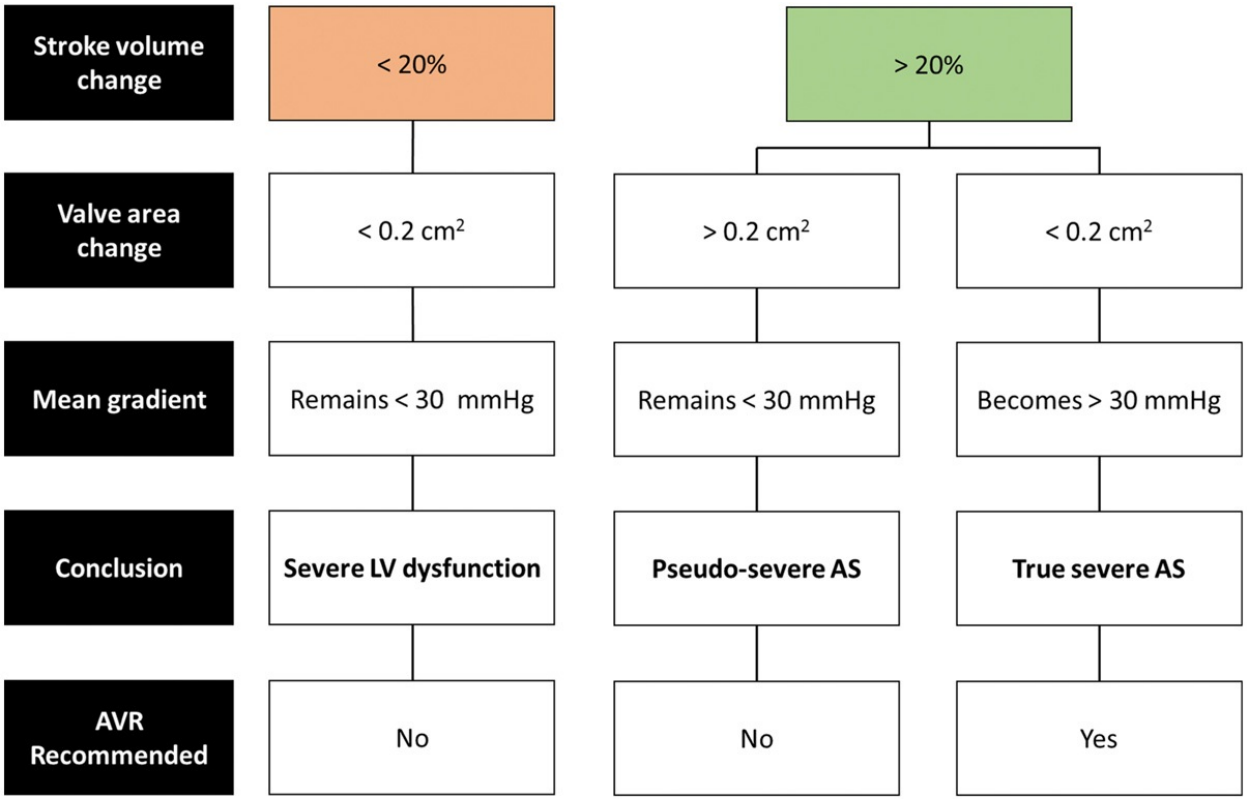

FIGURE 35.3 Dobutamine stress testing for severe low-gradient aortic stenosis with diminished LVEF. AS, aortic stenosis; AVR, aortic valve replacement.

Cardiac catheterization is usually unnecessary because echocardiography is the gold standard for diagnosis and quantification of AS. However, because coronary artery disease is common in patients with AS, coronary angiography is usually performed before surgical or percutaneous AVR. In this setting, aortic valve gradients may be evaluated using invasive hemodynamic measurements.

When comparing aortic gradients obtained by cardiac catheterization, it is the mean but not the peak aortic gradient that correlates with echocardiography. Cardiac catheterization and echocardiography measure two separate peak gradients (**Figure 35.4**).

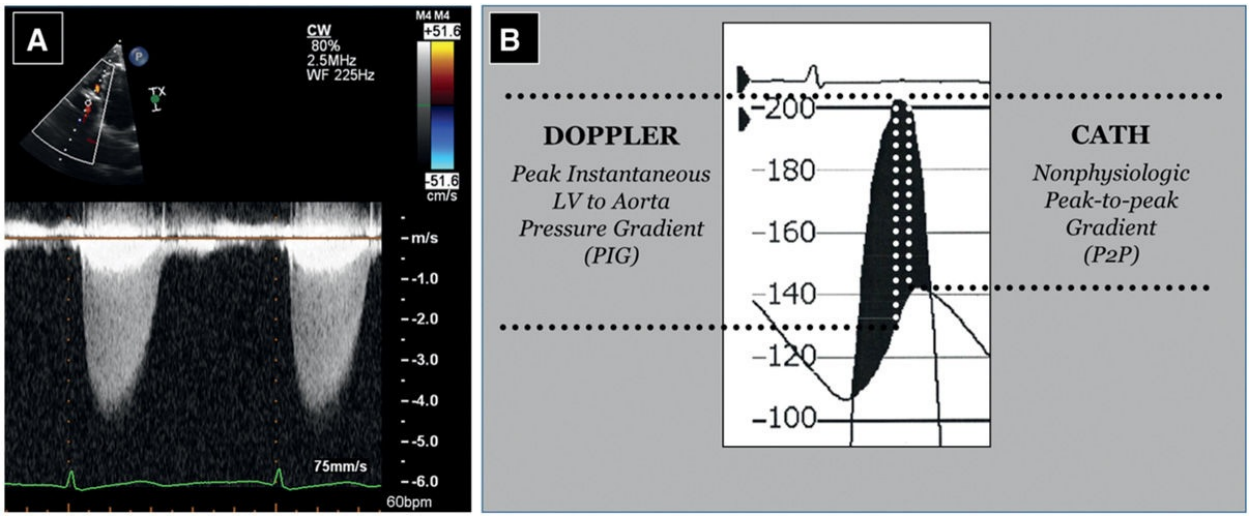

FIGURE 35.4 Aortic stenosis: echocardiography versus catheterization. Comparison between echocardiographic measurement of systolic aortic valve pressure gradient by peak velocity (A) and peak-to-peak gradient measured by cardiac catheterization (B). With simultaneous left ventricular and aortic pressure tracing, it becomes apparent that peak-to-peak gradient underestimates true maximum pressure gradient. Note the very high ventricular pressure in systole, and the delayed low-pressure peak in the aortic root (the hemodynamic basis for *pulsus parvus et tardus*). LV, left ventricular; PIG, peak instantaneous pressure gradient.

On catheterization, the so-called peak-to-peak (P2P) gradient is measured, which represents the pressure difference between the peak LV systolic pressure and the peak aortic systolic pressure. These two peaks do not occur simultaneously and are thus nonphysiologic; the more severe the AS, the greater the time difference between the two pressure peaks.

On echocardiography, the peak instantaneous pressure gradient (PIG) is measured instead; it represents the pressure difference between LV systolic and aortic pressure at the same time point. P2P is typically lower than PIG, largely due to the pressure recovery phenomenon (kinetic energy converted to potential

energy in the ascending aorta).[15]

MEDICAL THERAPY

There are no proven medical therapies for prevention or treatment of AS, and routine antibiotic prophylaxis of bacterial endocarditis in patients with AS is no longer recommended.[16]

Usually, patients with severe AS present to the CCU with clinical signs of heart failure. Pharmacologic therapy including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and digitalis may be used with caution. Although intravenous vasodilators used to be contraindicated in patients with severe AS, intravenous nitroprusside has been demonstrated to relieve symptoms of heart failure in patients with severe AS and severely reduced LV systolic function.[17] In that study, intravenous nitroprusside was started at a mean dose of 14 ± 10 μg/min, and the dose was increased to a mean of 103 ± 67 μg/min at 6 hours and 128 ± 96 μg/min at 24 hours.

Patients with severe AS may also present with other critical illnesses, such as septic shock. Management of these patients can be extremely challenging owing to the narrow balance between preload and afterload. Hemodynamic compromise is common. Hypotension from severe sepsis or septic shock may initiate a spiral of death, in which low aortic pressure leads to low coronary perfusion, with further ventricular impairment that fails to pump blood against a severely stenotic valve. This negative feedback rapidly leads to cardiac arrest and should be promptly recognized so that vasopressors are administered before such cascade takes place.

SURGICAL AND PERCUTANEOUS INTERVENTIONAL THERAPY

AS is a mechanical problem that requires a mechanical intervention. AVR is the preferred therapeutic choice in patients with AS to improve symptoms and increase survival. Major indications for AVR are listed in **Table 35.2**.

TABLE 35.2 Maior Indications for Aortic Valve Replacement in Patients With Aortic Stenosis

SYMPTOMS	RECOMMENDATION FOR AORTIC VALVE REPLACEMENT	ACC/AHA STAGE	COR	LOE
	Symptomatic high-gradient severe AS (by history or exercise testing)	D1	I	B

Symptomatic	Symptomatic low-flow/low-gradient severe AS with reduced EF (confirmed by dobutamine stress echocardiography)	D2	IIa	B
	Symptomatic low-flow/low-gradient severe AS with preserved EF (if valve obstruction is considered the cause of symptoms)	D3	IIa	B
	Severe AS undergoing other cardiac surgery	C or D	I	B
Asymptomatic	Asymptomatic high-gradient severe AS with LV dysfunction (EF <50%)	C	I	B
	Asymptomatic high-gradient very severe AS (V_{max} ≥5 m/s) and low surgical risk	C	IIa	B

ACC, American College of Cardiology; AHA, American Heart Association; AS, aortic stenosis; COR, class of recommendation; EF, ejection fraction; LOE, level of evidence; LV, left ventricular; V_{max}, peak velocity.
For a complete list, refer to the 2014 AHA/ACC Valvular Heart Disease Guideline. Note the lower class of recommendation for symptomatic patients with low-flow severe AS, both with reduced and preserved EF.

Surgical aortic valve replacement (SAVR) is the standard approach, indicated for patients with acceptable surgical risk who meet indications for AVR.[13] The technical aspects are beyond the scope of this chapter, but clinicians should be familiar with the decision process when choosing a surgical prosthesis. In addition to the appropriate size, such that there is no postoperative patient–prosthesis mismatch, the valve material has significant implications for the patient. Although a bioprosthesis is considered to be less durable than a mechanical valve, it offers the advantage of not requiring systemic anticoagulation. As such, in patients who are older or who have a contraindication for anticoagulation, a bioprosthetic implant is preferred. Conversely, in younger patients who have no contraindications for anticoagulation, a mechanical valve is reasonable. Above all, this should be a shared decision process between the surgeon and the patient.

Percutaneous interventions for AS include aortic valve balloon valvuloplasty and TAVR. Balloon valvuloplasty is an effective form of therapy for congenital AS. However, balloon valvuloplasty in calcific TAV or BAV AS is rather ineffective (valve area seldom increases above 1.0 cm^2 and there is a high rate of restenosis) and has significant morbidity and mortality.

Currently, typical indications for balloon valvuloplasty in calcific AS include short-term relief of AS in patients undergoing noncardiac surgery (such as hip replacement), in those with terminal illness (such as cancer), or as a temporizing measure in patients who are rapidly decompensating from severe AS in whom durable interventions are being entertained.

TAVR has changed the landscape of therapy for AS, allowing for patients who were previously too ill for surgery to receive lifesaving therapy. Since the first percutaneous replacement was performed by Alain Cribier in 2002, there have been over 200,000 TAVR procedures performed worldwide.[18] TAVR is now approved in patients with symptomatic severe AS who are inoperable, or are either high or intermediate risk for SAVR.

TAVR was considered experimental until 2010, when the first randomized trial showed a markedly improved survival in patients who were not surgical candidates.[19] These findings were subsequently confirmed in head-to-head trials comparing TAVR with SAVR in high-risk and intermediate-risk surgical patients.[20] In addition, TAVR is currently being investigated in low-risk patients.

Consequently, concerns regarding durability of transcatheter valves in comparison with surgical valves emerged, highlighted by the limited reliable data available on TAVR durability beyond five years.[21] Still, factors like lower rates of patient-prosthesis valve mismatch in TAVR compared with SAVR[22] might skew the durability data in favor of transcatheter prosthesis. There are currently two approved device types in the United States, a balloon-expandable (Edwards Sapien family of TAVR valves) and a self-expandable valve (Medtronic CoreValve family of TAVR valves), both of which been updated with new design features to reduce paravalvular AR (**Figure 35.5**).

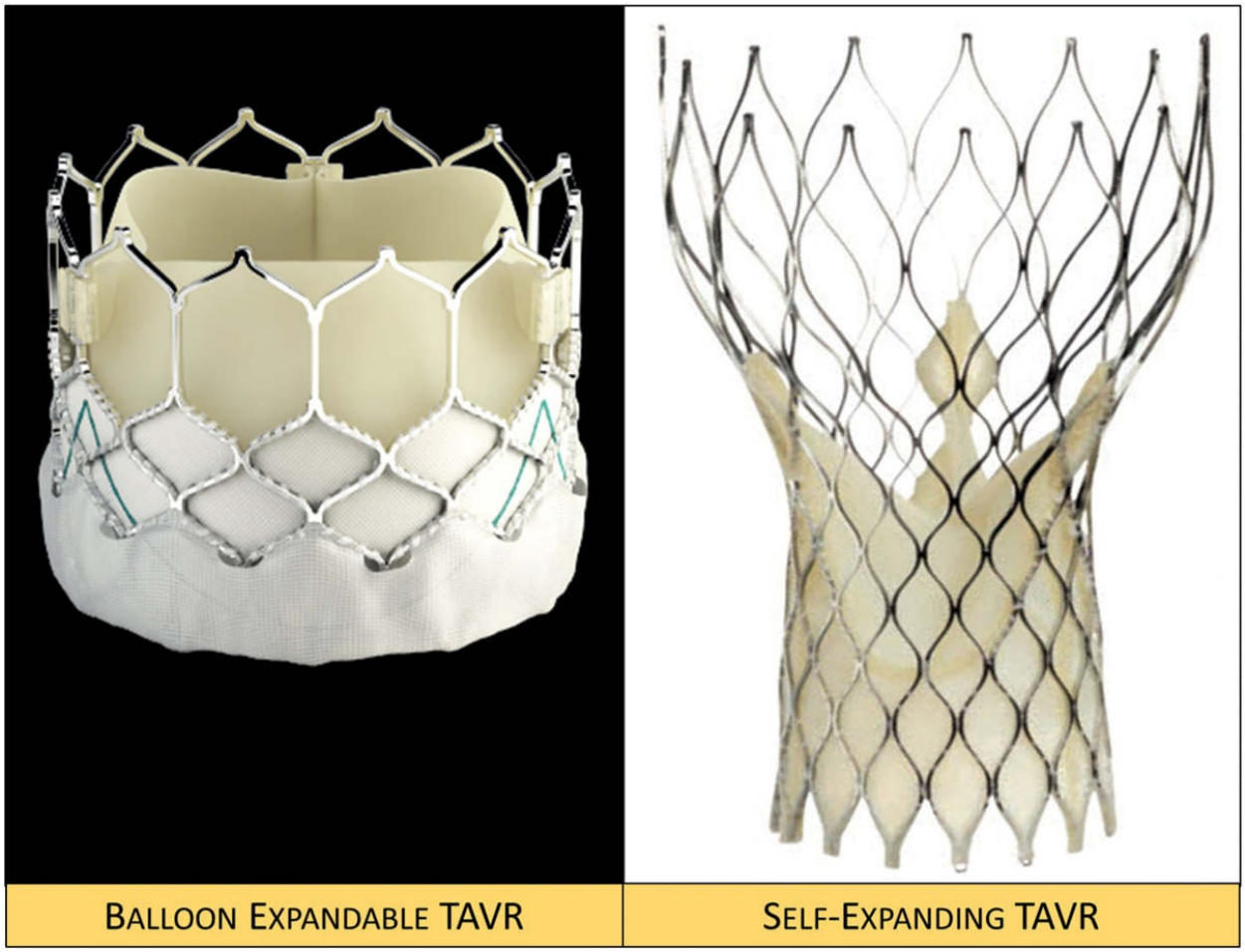

FIGURE 35.5 Transcatheter aortic valve replacement valves. Two major types of transcatheter implantable aortic valves. The balloon-expandable valve has a short and straight frame (left), whereas the self-expandable valve is longer and hourglass-shaped (right). These different metallic frames facilitate identification in routine chest radiography. TAVR, transcatheter aortic valve replacement. (Images available at the manufacturer's websites:www.tavrbyedwards.com and www.corevalve.com, respectively.)

POST-TRANSCATHETER AORTIC VALVE REPLACEMENT COMPLICATIONS

Patients who undergo TAVR are usually cared for in the CCU postprocedurally, so it is important to be familiar with the most common complications such as vascular access complications, neurologic events, conduction abnormalities, coronary artery obstruction, low cardiac output, annular rupture, and paravalvular AR.

Besides femoral access bleeding and vascular complications from the large sheaths used, patients should be closely monitored for neurologic changes given the risk of stroke from the large-profile devices advanced through the arterial system and crushing the calcified native valve.

Patients are also monitored for conduction abnormalities, specifically complete heart block from extrinsic compression of the conductions system following valve deployment. These patients routinely receive temporary venous pacemaker placement preprocedurally. Persistent heart block requiring permanent pacemaker is more common in patients with preexisting conduction system disease, especially right bundle branch block. Need for permanent pacing was previously more commonly seen in the self-expandable valve. However, with the latest generation of TAVR valve, the rate of permanent pacemaker implantation is similar between self-expanding and balloon-expandable TAVR valves.[23]

Periprocedural complications, usually diagnosed before transfer to CCU for monitoring, include coronary artery obstruction, low cardiac output, annular rupture, and paravalvular AR. Late complications include leaflet thrombosis, valvular degeneration, and infective endocarditis.

IMPACT OF SEVERE AORTIC STENOSIS ON PREGNANCY

Patients with calcific AS are seldom of child-bearing age. In patients of child-bearing age, AS is usually caused by noncalcific congenital abnormalities (such as unicuspid aortic valve). Young patients with moderate-to-severe AS should be advised against conception until AS is relieved. Those who nonetheless become pregnant may or may not develop severe symptoms. Pregnant patients with AS and mild symptoms may be managed conservatively during pregnancy with bed rest, oxygen, and β-blockers. Pregnant patients with severe symptoms may need percutaneous or surgical intervention. These procedures carry significant risk to both the mother and the unborn child.[24]

AORTIC REGURGITATION

ETIOLOGY AND PATHOPHYSIOLOGY

AR may be caused by disorders of the aortic root or the aortic valve leaflets. BAV, ascending aortic aneurysm, aortic dissection, and endocarditis are common causes of AR. Conditions predisposing the patient to aortopathies and AR include hypertension and connective tissue disorders (such as Marfan syndrome, Ehlers–Danlos syndrome, and ankylosing spondylitis). In less developed countries, rheumatic heart disease and tertiary syphilis remain important causes of AR.

In AR, the blood flows back into the ventricle through the aortic valve during diastole, joining the systemic volume that entered the left ventricle through the mitral valve. During the subsequent systole, both volumes leave the aortic valve together; the systemic volume continues into the aorta and its branches, whereas the regurgitant volume flows back into the ventricle. The cycle then repeats itself. Subsequent pathophysiology depends on whether AR is chronic or acute.

In chronic AR, the left ventricle progressively enlarges to accommodate the combined systemic stroke volume and the regurgitant volume. This remodeling often prevents significant elevation of left heart pressures. It may take years, if not decades, for patients with chronic AR to develop congestive heart failure owing to progressive LV systolic dysfunction. This adaptation contrasts with acute AR, in which there is sudden volume overload of a nondilated left ventricle, marked elevation of LV and left atrial pressures, life-threatening pulmonary edema, and even cardiogenic shock.

Patients with severe AR, whether acute or chronic, typically present to the CCU with signs and symptoms of heart failure. Although severe acute AR represents only a minority of AR cases, its often fulminant and life-threatening course necessitates CCU admission. The rest of the section on AR is devoted to severe acute AR.

CLINICAL PRESENTATION

The most common etiologies of severe acute AR are chest trauma, bacterial endocarditis, and dissection of the ascending aorta (Stanford type A aortic dissection). Less commonly, severe acute AR may result following balloon valvuloplasty for severe AS.

Patients with severe acute AR frequently present with fulminant pulmonary edema and cardiogenic shock. Patients with endocarditis will also have general signs and symptoms of a systemic bacterial illness. Patients with acute type A aortic dissection usually complain of severe chest pain, often in the setting of uncontrolled systemic hypertension.

DIAGNOSIS

In severe acute AR, there may be few or no auscultatory findings of AR; the diastolic murmur is often soft, short, or even absent because of the rapid equilibration of aortic and LV pressures during diastole. This is due to the acute nature of the disease, which precludes increased compliance of the left ventricle.

Therefore, the rapid rise in LV end-diastolic pressure limits the total regurgitant volume, explaining the underwhelming diastolic murmur and the lack of wide pulse pressure. There is, however, marked tachycardia and S3 gallop.

CXR in severe acute AR frequently reveals pulmonary congestion. ECG may show tachycardia; there may also be signs of myocardial ischemia (owing to high myocardial demand caused by very elevated LV pressures or when acute aortic dissection extends into the coronary artery ostia). When endocarditis leads to periaortic valve abscess, ECG may demonstrate varying degrees of atrioventricular conduction block.

Transthoracic and transesophageal echocardiography are the primary means of evaluating AR. Echocardiography may establish the etiology, mechanism, and severity of AR (**Figure 35.6**). The diagnostic criteria for grading the severity of AR are listed in **Table 35.3**.

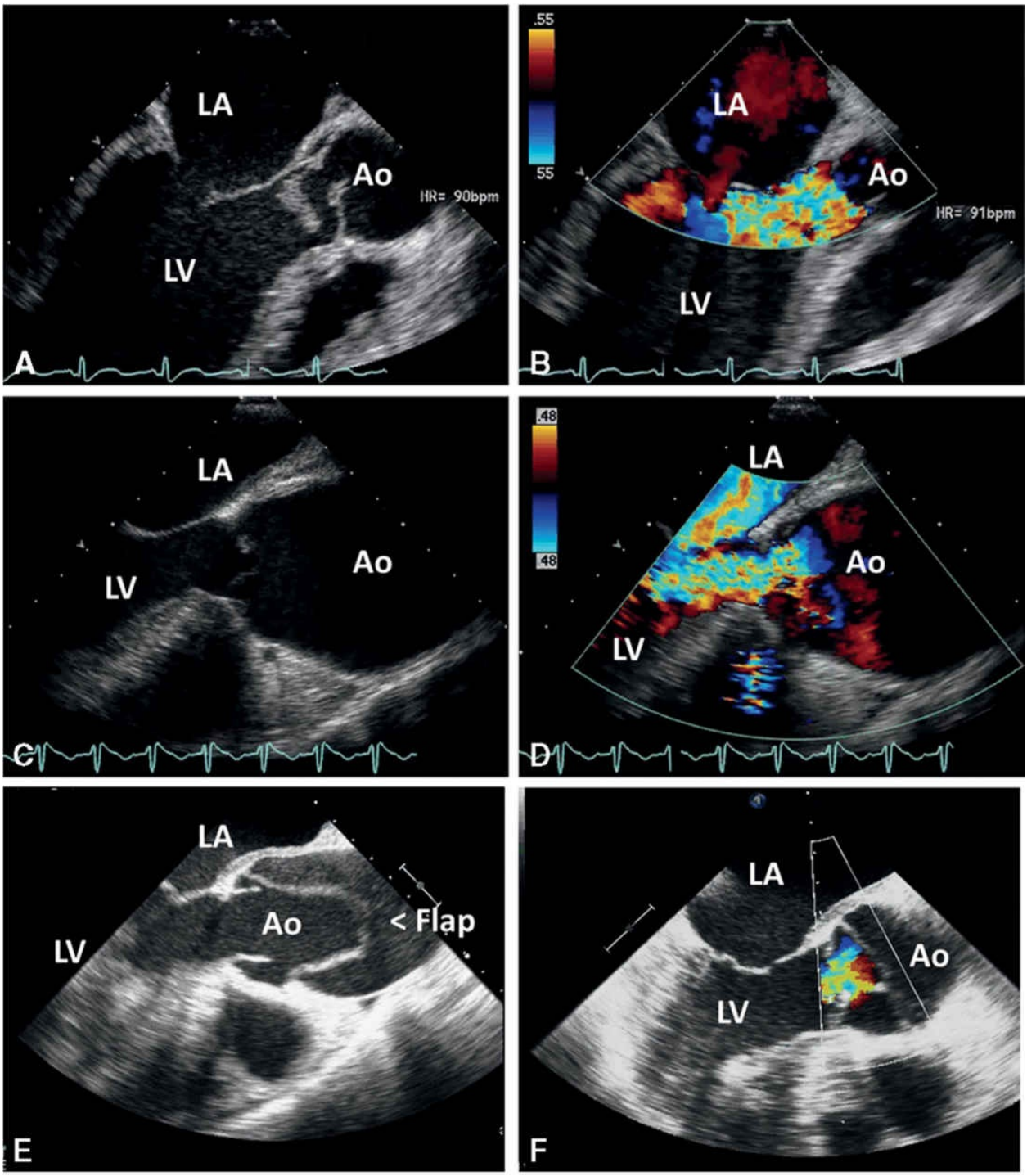

FIGURE 35.6 Aortic regurgitation on echocardiography. Causes of severe aortic regurgitation include aortic valve endocarditis (A and B), ascending aortic aneurysm (C and D), and type A aortic dissection (E and F). Ao, ascending aorta; LA, left atrium; LV, left ventricle.

TABLE 35.3 Grades of Aortic Regurgitation

	MILD	MODERATE	MODERATE–SEVERE

	AR	AR	AR	SEVERE AR
Grade	1+	2+	3+	4+
Regurgitant orifice area (cm^2)	<0.1	0.10–0.19	0.20–0.29	>0.3
Regurgitant fraction	<30%	30%–39%	40%–49%	>50%
Regurgitant volume (mL)	30	30–44	45–59	>60
Vena contracta (cm)	<0.3	0.3–0.6	>0.6	
ACC/AHA Stage	B (progressive)			C (asymptomatic) D (symptomatic)

ACC, American College of Cardiology; AHA, American Heart Association; AR, aortic regurgitation.
Note that stage A denotes a nonregurgitant aortic valve, which is at risk for aortic regurgitation (such as bicuspid aortic valve or ascending aortic aneurysm).

MEDICAL THERAPY

Severe acute AR is a life-threatening medical emergency that necessitates highest levels of CCU care. Diuretic therapy, positive end-expiratory pressure, and supplemental oxygen administration with endotracheal intubation are used to treat pulmonary edema. Afterload reduction may be achieved with the use of intravenous vasodilators (such as nitroprusside). Disease-specific therapies, if available, should also be administered (such as antibiotic therapy for endocarditis).

SURGICAL AND PERCUTANEOUS INTERVENTIONAL THERAPY

In severe acute AR, aortic valve surgery should be performed as soon as possible, especially in cases of type A aortic dissection and infective endocarditis. The standard procedure of choice is surgical AVR. At present, there is no approved percutaneous option for patients with pure AR.

Aortic valve sparing surgeries may be an alternative to surgical AVR in specialized centers. This surgery, known as the David procedure (after Tirone David, the Brazilian surgeon who conceived and first performed this technique), involves ascending aorta repair with a vascular graft, followed by coronary artery reimplantation, reconstruction of the aortic root, and reimplantation of the aortic valve.[25] This technique is better suited for young patients with genetic

syndromes associated with aortic root dilatation, and it is still not employed universally.

In-hospital and long-term survival is significantly improved in patients who promptly undergo SAVR or repair.[26] However, such intervention might be prohibitive in patients with severe embolic strokes or comorbid conditions that diminish the prospect of reasonable recovery.

Despite the excitement about transcatheter therapies in severe AS, use of TAVR in severe AR has been reported only anecdotally. A stenotic calcific aortic valve forms a solid structure for anchoring in transcatheter replacement, whereas a regurgitant aortic valve—often associated with a dilated aortic root—poses a great challenge in holding a transcatheter valve. Still, TAVR may represent a last resort in patients who present with severe symptomatic AR who are not surgical candidates.

Registry data from self-expanding TAVR (which have a larger anchoring profile than balloon-expandable valves) in patients with predominant AR show significantly increased mortality when compared with patients undergoing TAVR for severe AS (around 20%), particularly in patients in whom valvular calcification was absent.[27,28]

Furthermore, intra-aortic balloon pump (IABP) is absolutely contraindicated when significant AR is present. Diastolic counterpulsations—which are the hallmarks of IABP function—worsen AR. This, in turn, decreases effective stroke volume and cardiac output, worsening cardiogenic shock. In addition, it increases LV end-diastolic pressure and myocardial oxygen consumption, worsening pulmonary edema and myocardial ischemia. Therefore, in conditions that usually require IABP for medical stabilization (such as cardiogenic shock and refractory ischemia), use of counterpulsation is prohibitive with moderate or severe AR.

IMPACT ON PREGNANCY

The hemodynamic changes associated with pregnancy (increased cardiac output from increased heart rate and stroke volume) are more likely to decompensate patients with stenotic valvular diseases compared with those with insufficient valves, given the mechanical obstruction to blood flow in such conditions. Conversely, regurgitant lesions are better tolerated in pregnancy, and AR is generally tolerated unless it is severe.

Severe AR, whether acute or chronic, is one of the valvular heart lesions that

may be associated with high maternal and/or fetal risk during pregnancy. Pregnant women with AR who have New York Heart Association functional class III to IV symptoms, severe pulmonary hypertension (pulmonary pressure >75% of systemic pressures), and/or LV systolic dysfunction are at particular risk for maternal and fetal complications. The same is true for pregnant women having Marfan syndrome with or without AR.[24]

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Patient and Family Information for: AORTIC VALVULAR DISEASE IN THE CARDIAC CARE UNIT

GENERAL CONCEPTS OF AORTIC VALVULAR DISEASE

The heart is a muscular organ whose primary function is to pump blood in our body. To accomplish this goal, several valves are present in its different chambers to prevent backflow. The aortic valve is a valve composed of three thin leaflets, separating the aorta—the largest artery in the body from which all the blood pumped out of the heart flows—and the left ventricle—the chamber that pumps blood out of the heart to the rest of the body. When the aortic valve becomes too narrowed, doctors call it aortic stenosis. When it becomes leaky, it is called aortic insufficiency.

AORTIC STENOSIS

WHAT IS THE ILLNESS?

If the aortic valve becomes too narrow, pumping blood out of the heart becomes difficult. When patients feel symptoms from this valve narrowing (called stenosis), they usually report episodes of passing out, chest pain with exertion, and shortness of breath. Usually the cause of AS is wear and tear over many years, making it harder and less flexible with aging (the reason these patients are usually elderly). However, some patients are born with malfunctioning valves, and in these cases they develop valve narrowing at a younger age.

HOW WILL THE PATIENT BE TREATED?

There are no medicines that fix AS, so an invasive procedure is usually indicated in symptomatic patients. The standard procedure is to replace the valve with a prosthesis. In some patients this is done through open heart surgery, and in others the valve is replaced through catheters.

In patients with severe AS, the disease may progress rapidly and even cause death if not treated in time. Therefore, once diagnosed, planning for receiving a new valve should be undertaken.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

If there is severe narrowing of the aortic valve, pregnancy may need to be delayed until the narrowing is relieved—usually through the use of balloon catheter inserted through the groin, threaded to the heart, and blown up inside the valve to make it larger. If already pregnant and there are symptoms (such as shortness of breath or chest pain), the patient may need to take certain medications that are effective for her but not harmful to the child. If the symptoms during pregnancy are severe, the balloon catheter treatment or even open heart surgery may be needed. These procedures carry significant risk to both the mother and the unborn child.

AORTIC REGURGITATION

WHAT IS THE ILLNESS?

AR is the medical term to describe a leaky aortic valve, allowing blood to backflow into the heart after it is pumped to the aorta. When this happens, there is extra work for the heart to pump blood forward, and this backflow may cause breathing problems from water buildup in the lungs and other parts of the body.

One of the most common causes of AR in the United States is a dilated aorta, where the valve sits. When this artery becomes too big, the valve leaflets become too far apart from each other and blood leaks back into the heart. This enlargement may happen from wear and tear in older patients, or from a loose buildup in patients born with genetic predisposition to aortic enlargement.

Another common cause for AR is infection in the valve, causing destruction of the leaflets and, consequently, leakage. Wear and tear of the valve leaflets may also cause AR, not only in older patients but also in young patients born with a malfunctioning valve. Finally, in patients born outside of the United States, long-

standing syphilis and rheumatic fever may also lead to AR.

HOW WILL THE PATIENT BE TREATED?

In patients who develop AR in a short period of time, such that the heart does not have enough time to accommodate the leakage, quick medical stabilization in an intensive care unit is necessary. However, the ultimate treatment requires valve replacement with prosthesis.

Similar to AS, a severely leaky valve of AR may be replaced through open heart surgery. However, in contrast to AS, a severely leaky valve of AR cannot be replaced using catheters in most patients.

If the AR developed slowly, the heart eventually will become large and weak trying to accommodate the backflow of blood. However, in cases of rapidly developing severe AR, the disease may cause imminent death unless appropriate medicines and, eventually, surgery for valve replacement are employed.

WHAT IF THE PATIENT IS PREGNANT OR THINKING OF BECOMING PREGNANT?

Severe leakage of the aortic valve may not be well tolerated during pregnancy and the condition may harm the unborn child. Women with severe leakage who are considering pregnancy may need to delay it until the condition is treated. If already pregnant, significant heart problems may be experienced during the pregnancy.

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Mitral Valve Disease in the Cardiac Care Unit

INTRODUCTION

Severe mitral valve disease due to mitral stenosis or mitral regurgitation can lead to clinical decompensation requiring the care of a patient in the cardiac care unit setting. The backdrop of such decompensation may be chronic valve disease on which acute injury is superimposed.

MITRAL VALVE STENOSIS

ETIOLOGY AND PATHOPHYSIOLOGY OF MITRAL STENOSIS

The mitral valve is a left atrioventricular valve or bicuspid valve that lies in the annulus between the left atrium and the left ventricle. A competent mitral valve requires the coordination of all the components of the mitral valve: the valve leaflets, the chordal attachments, the annulus, the papillary muscles, and the supporting ventricular walls into which the apparatus inserts. Failure or malfunction of any component of the mitral valve apparatus with failure to open results in stenosis with difficulty of left atrial emptying into the left ventricle.

Mitral stenosis (MS) results in delayed emptying of blood from the left atrium

(LA) into the left ventricle (LV) during diastole. This can result in elevated pressures in the left atrium, pulmonary vasculature and eventually the right side of the heart, leading to pulmonary hypertension.

The Euro Heart Study Survey was specifically designed to study the management of patients with valvular heart disease and prospectively included 5001 patients from 92 centers in 25 European countries.[1,2] This survey does not represent the general population, but rather the type of valve disease seen in a European referral population for treatment of heart disease. The most common valvular etiology was degenerative disease, representing 63% of all cases of native heart disease (likely representing an aging population), with a mean age of >50 years among patients with aortic and mitral valve disease, followed by rheumatic heart disease (RHD) in 22% of all patients,[2] representing the distribution in industrialized countries.

The incidence of RHD has decreased in industrialized countries over the past 60 years, but still exists in elderly patients who were exposed to acute rheumatic fever during childhood. The incidence remains lowest in America and Western Europe (≤10 per 100,000 of the population per year), higher in Eastern Europe (>10 per 100,000), and approximated to have an incidence of 13 cases per 100,000 per year in sub-Saharan Africa.[3]

RHD is usually a consequence of rheumatic fever, caused by group A ***β***-hemolytic streptococci. As streptococcal proteins share antigenic properties with certain connective tissue proteins in the human host, the immune response that is mounted against the streptococci can lead to progressive and delayed valve damage. RHD causes mitral commissural adhesion; thickened, calcified, immobile mitral valve leaflets; and fibrosis, thickening, shortening, fusion, and calcification of the chordae tendineae (**Figures 36.1 and 36.2**). The male to female ratio for RHD is approximately 1:2. RHD remains prevalent in developing countries. Approximately 60% of patients with acute rheumatic fever will develop RHD.[3]

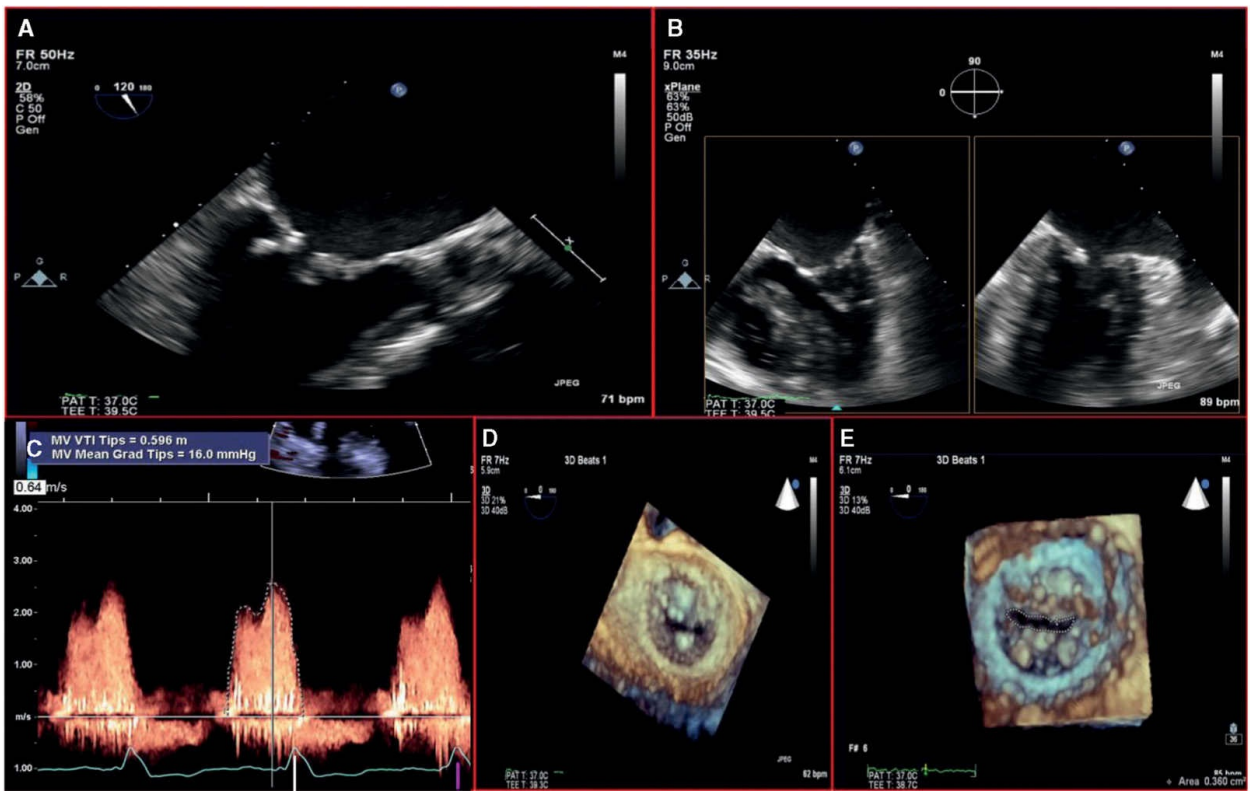

FIGURE 36.1 Severe mitral stenosis. A, A midesophageal view of the mitral valve via transesophageal echocardiogram (TEE). The mitral valve is thickened and shows restrictive leaflet motion. B, A biplane view on TEE of the mitral valve, again showing restricted leaflet motion. C, Demonstrates transmitral mean gradients are 16 mm Hg, consistent with very severe mitral stenosis. D and E, 3D images of severe mitral stenosis with severely restricted mitral valve motion. By planimetry, the mitral valve area was calculated to be about 0.4 cm^2.

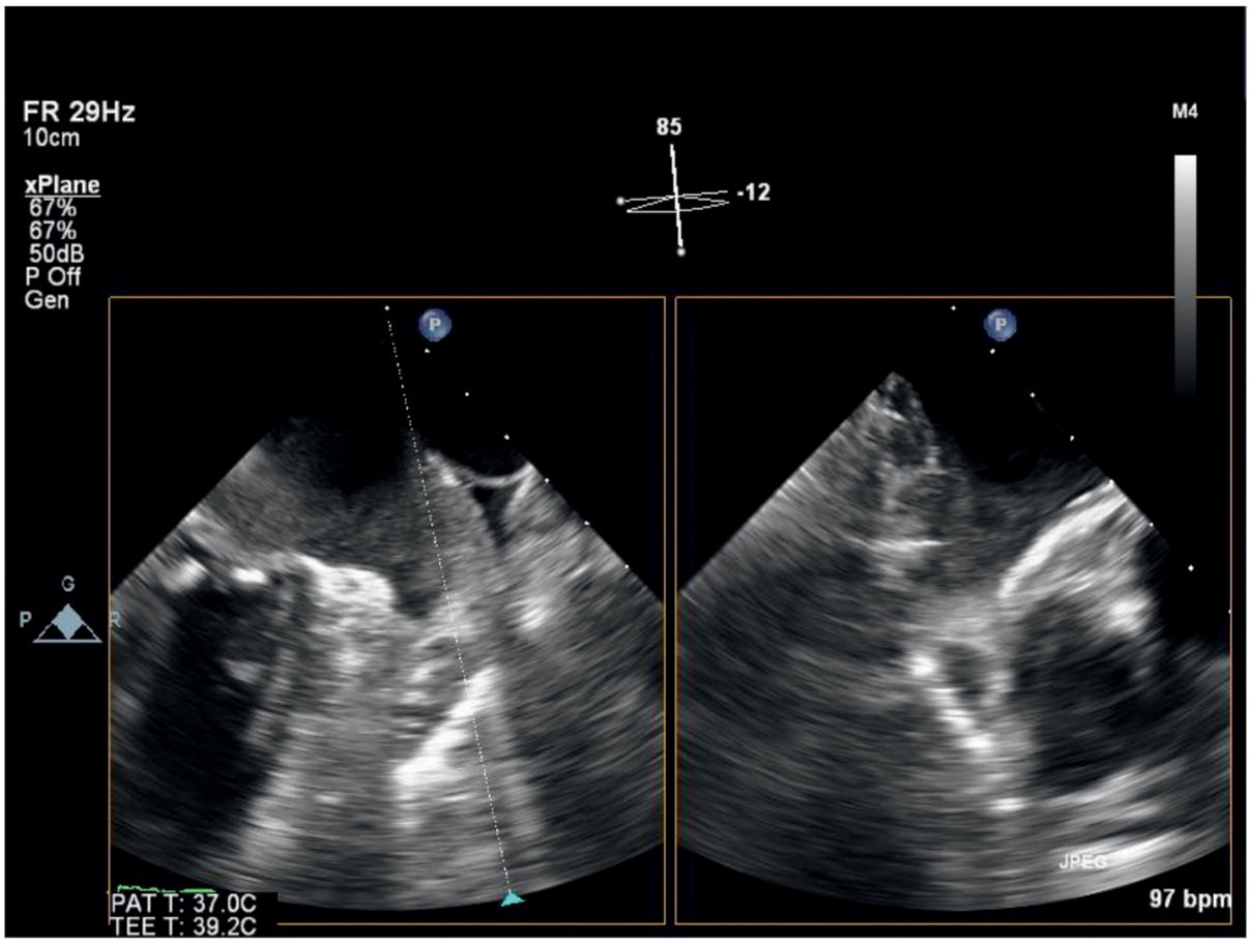

FIGURE 36.2 Severe mitral stenosis with fresh left atrial thrombus in the left atrial appendage, visible on a biplane view acquired by TEE in the midesophgeal view. Smoke is also visible in the dilated left atrium consistent with a low-flow state.

Etiologies, aside from degenerative valvular disease and RHD, include infective endocarditis, inflammatory disease, and congenital heart disease. These account for less than 10% of all cases of valvular heart disease.[1]

The normal mitral valve area in an adult measures approximately 4 to 6 cm^2. Patients may become symptomatic with shortness of breath as the valve area decreases over time. The diastolic gradient across the valve may increase, resulting in LA enlargement. Often, patients may have an acute event such as development of a rapid atrial arrhythmia (such as atrial fibrillation [AF]) that precipitates heart failure and decompensation of the patient requiring intensive medical care. Often, AF in the setting of MS is a highly prothrombotic state, marked by stasis of blood in the LA and left atrial appendage where thrombus can form. This puts the patient at risk for systemic thromboembolism.

Medical and interventional approaches to the management of patients with

valvular MS depend on accurate diagnosis of the cause and stage of the disease process.

CLINICAL PRESENTATION OF MITRAL STENOSIS

Patients with severe MS can have elevated LA and pulmonary pressure causing dyspnea and other signs and symptoms of congestive heart failure. The severity of symptoms is related to the transmitral gradient in diastole.[4–6] In turn, the magnitude of the mitral gradient is the result of interplay between the mitral valve area and the blood flow. Doubling the blood flow will quadruple the gradient. The heart's compensatory mechanisms such as left atrial enlargement may fail in the setting of rapid heart rates induced by exercise, pregnancy, hyperthyroid crisis, fever, or tachyarrhythmia (ie, AF).

DIAGNOSIS

Classic auscultatory findings of MS include loud first heart sound (S1), an opening snap (OS) after the second heart sound (S2), and a diastolic rumble. The duration of the S2–OS interval is inversely related to the severity of MS (a shorter interval suggests more severe MS). In patients with normal sinus rhythm, there is also an end-diastolic ("presystolic") accentuation of the rumble.

The electrocardiogram may demonstrate signs of LA enlargement characterized by wide, saddle-shaped P-wave in leads I and II (so-called P mitrale) as well as late, deep P-wave inversion in lead V1. AF is frequently present and there may be signs of right ventricular hypertrophy.

A transthoracic echocardiogram (TTE) is indicated in patients with signs and symptoms of MS. By TTE one can establish the diagnosis, determine the morphology of the mitral valve (to determine suitability for mitral commissurotomy), quantify hemodynamic severity (mean pressure gradient, mitral valve area, and pulmonary artery pressure), and assess concomitant valvular lesions.

Chest X-ray usually demonstrates LA enlargement with straightening of the left cardiac silhouette. Right ventricular enlargement, signs of pulmonary venous congestion, and mitral valve calcification are frequently observed.

Cardiac catheterization is not necessary for the diagnosis of MS in most instances because hemodynamic data can be acquired from a careful TTE, performed when the heart rates and blood pressures have been optimized, and there is optimal time for diastolic filling of the left ventricle.

GRADING OF MITRAL STENOSIS

The 2009 guidelines from the American Society of Echocardiography defined mitral stenosis with mean gradients of <5 mm Hg, MVA of >1.5 cm^2 as being mild mitral stenosis; mean gradient of 5 to 10 mm Hg, MVA 1.0 to 1.5 cm^2 as moderate stenosis; mean gradient of >10 mm Hg, MVA < 1.0 cm^2 as severe mitral stenosis.[7] The 2014 American Heart Association/American College of Cardiology (AHA/ACC) guideline for the management of patients with valvular heart disease took this even further, applying grading of valvular disease as stages across a clinical continuum: stage A for patients at risk of MS; stage B as patients with progressive MS with mitral valve area > 1.5 cm^2, possible mild to moderate left atrial enlargement; stage C as asymptomatic severe MS, with MVA ≤ 1.5 cm^2, often severe left atrial enlargement and elevated pulmonary artery pressures; stage D as symptomatic severe MS, with MVA ≤ 1.5 cm^2, severe left atrial enlargement, pulmonary hypertension, exertional dyspnea, and decreased exercise tolerance(**Table 36.1**).[5]

TABLE 36.1 Stages of MS Per the ACC/AHA Guidelines[5]

STAGE/DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
Stage A: at risk of MS	Mild valve doming during diastole	Normal transmitral flow velocity	None	None
Stage B: progressive MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA > 1.5 cm^2	Increased transmittal flow velocities MVA > 1.5 cm^2 Diastolic pressure half-time < 150 ms	Mild-to-moderate LA enlargement Normal pulmonary pressure at rest	None
Stage C: asymptomatic severe MS	Rheumatic valve changes with commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2 MVA ≤ 1.0 cm^2 with very severe MS	MVA ≤ 1.5 cm^2 (MVA ≤ 1.0 cm^2 with very severe MS) Diastolic pressure half-time ≥ 150 ms Diastolic pressure half-time ≥ 220 ms with very severe MS	Severe LA enlargement Elevated PASP > 30 mm Hg	None
	Rheumatic valve changes with	MVA ≤ 1.5 cm^2 MVA ≤ 1.0 cm^2 with		

Stage D: symptomatic severe MS	commissural fusion and diastolic doming of the mitral valve leaflets Planimetered MVA ≤ 1.5 cm^2	very severe MS Diastolic pressure half-time ≥ 150 ms Diastolic pressure half-time > 220 ms with very severe MS	Severe LA enlargement Elevated PASP > 30 mm Hg	Decreased exercise tolerance Exertional dyspnea

The transmitral mean pressure gradient should be obtained to further determine the hemodynamic effect of the MS and is usually >5 to 10 mm Hg in severe MS; however, due to the variability of the mean pressure gradient with heart rate and forward flow, it has not been included in the criteria for severity.
LA, left atrial; LV, left ventricular; MS, mitral stenosis; ms, milliseconds; MVA, mitral valve area; PASP, pulmonary artery systolic pressure.

The mean pressure gradient is highly dependent on the transvalvular flow and diastolic filling period and may vary greatly with change in heart rate. The diastolic pressure half-time depends on the degree of mitral obstruction and the compliance of the LV and LA and other measures of mitral valve area. Medical optimization and reevaluation in an intensive care setting may be necessary for a patient who presents with acute decompensation.

MEDICAL THERAPY FOR MITRAL STENOSIS

Patients with MS often present to the cardiac care unit (CCU) with clinical signs of heart failure, frequently in the setting of AF. Optimizing medical therapy can alleviate symptoms and prevent systemic thromboembolism. Congestion secondary to heart failure (HF) may need intravenous diuretic therapy. Heart rate control with ***β***-blockers, certain calcium channel blockers (such as verapamil and diltiazem), and digitalis can be beneficial in patients with MS and AF to control rapid ventricular response and to allow greater time for diastolic filling of the LV.

Anticoagulation is indicated in patients with MS who present with AF, whether it is paroxysmal, persistent, or permanent. This is particularly true in a patient with a prior embolic event who is at higher risk for a repeat thromboembolic event and certainly if the patient is diagnosed with a left atrial thrombus. Intravenous heparin may be indicated with bridging to a vitamin K antagonist such as warfarin. There is as of yet insufficient large-scale data to attest to the efficacy of non–vitamin K oral anticoagulants in preventing thromboembolism in valvular AF.

PERCUTANEOUS INTERVENTION FOR MITRAL STENOSIS

In the absence of LA thrombus or moderate-to-severe MR and favorable valve

morphology, percutaneous mitral balloon commissurotomy is recommended for the following: (1) symptomatic patients with severe MS; (2) symptomatic patients with mitral valve area > 1.5 cm^2 if there is evidence of hemodynamically significant MS based on pulmonary artery wedge pressure > 25 mm Hg or mean mitral valve gradient > 15 mm Hg during exercise; (3) asymptomatic patients with very severe MS (mitral valve area ≤ 1.0 cm^2, stage C); (4) asymptomatic patients with severe MS with new onset of AF. Percutaneous mitral balloon commissurotomy is also indicated in symptomatic patients (New York Heart Association [NYHA] class III to IV) with severe MS with suboptimal valve anatomy and are high-risk candidates for surgery.

Transthoracic echocardiography can help detect whether the valve has structural characteristics favorable for percutaneous mitral balloon commissurotomy. The Wilkins score captures the degree of leaflet deformity, scoring leaflet mobility, degree of thickening of the subvalvular chordal apparatus, leaflet thickening, and leaflet calcification on a score of 1 to 4. A summed score of 8 or less predicts a more favorable outcome with valvuloplasty than those with a higher score, although a high score does not preclude valvuloplasty (**Table 36.2**).[8]

TABLE 36.2 The Wilkins Score/Mitral Valvuloplasty Score[8]

GRADE	MOBILITY	SUBVALVULAR THICKENING	THICKENING	CALCIFICATION
1	Highly mobile valve with only leaflet tips restricted	Minimal thickening just below the mitral leaflets	Leaflets near normal in thickness (4–5 mm)	Single area of increased echo brightness
2	Leaflet mid and base portions have normal mobility	Thickening of chordal structures extending up to one-third of the chordal length	Mid leaflets normal, considering thickening of margins (5–8 mm)	Scattered areas of brightness confined to leaflet margins
3	Valve continues to move forward in diastole, mainly from the base	Thickening extending to the distal third of the chords	Thickening extending through the entire leaflet (5–8 mm)	Brightness extending into the mid portion of the leaflets
4	No or minimal forward movement of the leaflets in diastole	Extensive thickening and shortening of all chordal structures extending down to the papillary muscles	Considerable thickening of all leaflet tissue (>8–10 mm)	Extensive brightness throughout much of the leaflet tissue

Mitral valve score = leaflet mobility + valve thickening + calcification + subvalvular thickening. Each item is graded from 1 to 4 to yield a score from 4 to 16. A score of 8 or less predicts a more favorable outcome than those with a higher score, but

higher scores do not preclude mitral valvuloplasty.

Transesophageal echocardiography (TEE) should be performed on patients considered for percutaneous mitral balloon commissurotomy to better define the leaflet anatomy and to perform direct planimetry of the mitral valve. Three-dimensional (3D) imaging can be used to optimize the plane at which direct planimetry is performed. Detailed views of the LA and left atrial appendage can be obtained to assess for concomitant left atrial thrombus.

SURGICAL INTERVENTION FOR MITRAL STENOSIS

If percutaneous intervention is unavailable or the valve morphology is unfavorable for balloon valvuloplasty, appropriate patients are referred for surgical intervention.

As per the 2014 AHA guidelines, patients with very severe MS (MVA ≤ 1.0 cm^2), who are symptomatic (stage D), and have morphology unfavorable for percutaneous mitral balloon commissurotomy should be considered for mitral valve repair or replacement.[5]

If a patient with *severe* (mitral valve area ≤ 1.5 cm^2) or *moderate* (mitral valve area 1.6 to 2.0 cm^2) MS is undergoing a cardiac surgery for other operative indications (eg, aortic valve disease, coronary artery disease [CAD], tricuspid regurgitation [TR], aortic aneurysm), *concomitant* mitral valve surgery is recommended.

Mitral valve surgery and excision of the left atrial appendage may be considered for patients with severe MS who have had recurrent embolic events while receiving adequate anticoagulation.

PROGNOSIS OF MITRAL STENOSIS

AF, LA thrombus formation, and systemic thromboembolism (such as ischemic stroke) are important contributors to morbidity and mortality of MS.

IMPACT ON PREGNANCY

Often pregnancy is the first time that a patient with rheumatic MS becomes symptomatic due to a physiologic increase in intravascular volume, cardiac output, and heart rate. Percutaneous mitral balloon commissurotomy can be performed during pregnancy, but diagnosis and treatment before pregnancy is ideal.

MITRAL REGURGITATION

ETIOLOGY AND PATHOPHYSIOLOGY

Mitral regurgitation (MR), also known as mitral insufficiency or mitral incompetence, is one of the most common acquired valvular heart diseases. MR is a disorder where the mitral valve does not close properly during the systolic phase. Its onset may be acute or chronic, and the etiology can stem from any process that disturbs the architecture of the mitral valve apparatus.

Failure of any component of the mitral valve apparatus can result in failure of leaflet coaptation and regurgitation of blood during systole into the LA rather than being ejected out of the left ventricular outflow tract, across to the aortic valve into the systemic circulation to perfuse important organs.

Defining the etiology of MR is important because it influences the management and prognosis of such patients. Diseases that are primarily structural in origin are managed differently than those with primarily functional MR.

In MR, blood exits the LV both antegrade—through the left ventricular outflow tract (systemic stroke volume)—and retrograde—through the mitral valve (regurgitant volume). During diastole, the regurgitant volume meets in the LA with the systemic volume returning through the pulmonary veins. The combined volume then enters the LV through the mitral valve. This process leads to volume overload of the left heart.

CLINICAL PRESENTATION

In chronic MR, there is progressive enlargement of the LA and the LV to accommodate the combined systemic stroke volume and regurgitant volume. This remodeling often prevents significant elevation of left heart pressures; consequently, it may take years, if not decades, for the patient to develop congestive heart failure (due to progressive left ventricular systolic dysfunction) and AF (due to left atrial enlargement). In contrast, acute-on-chronic or acute MR can present with flash pulmonary edema requiring intensive care support and urgent intervention.

CHRONIC MITRAL REGURGITATION (PRIMARY VS SECONDARY)

In primary MR, a problem with one of the components of the valve, including the leaflets, chordae tendinae, or papillary muscles, causes valve incompetence

and regurgitation of blood from LV to LA during the systolic phase. Common causes of primary MR include mitral prolapse, due to myxomatous degeneration in a younger population or problems such as fibroelastic deficiency disease in older population, infective endocarditis or myxomatous degeneration. Other etiologies for primary MR include connective tissue disorder, rheumatic heart disease, cleft mitral valve, and radiation heart disease.

In contrast, *secondary (functional)* MR occurs where the mitral valve is normal but the supporting structures for the valve are abnormal. An abnormal or dilated LV can cause papillary muscle displacement and leaflet tethering. Annular displacement or dilatation as well as wall motion abnormalities due to myocardial ischemia or infarction can prevent leaflet coaptation. With secondary MR, restoration of mitral competence is not by itself curative.

ACUTE MITRAL REGURGITATION

It is estimated that there are approximately 2.5 million patients with moderate-to-severe or severe MR in the United States at present. Although acute MR represents only a minority of these cases, every health care professional working in the CCU setting should become proficient in diagnosing and managing this often life-threatening form of MR. In acute MR, there is sudden volume overload of nondilated left heart chambers leading to marked elevation of left atrial pressures, life-threatening pulmonary edema, and eventually cardiogenic shock.

The leading causes of acute MR are bacterial endocarditis (**Figures 36.3, 36.4, and 36.7**), papillary muscle rupture (traumatic or following myocardial infarction; **Figure 36.5**), and chordal rupture in the setting of preexisting myxomatous valve degeneration (**Figure 36.6**) and mitral valve prolapse.

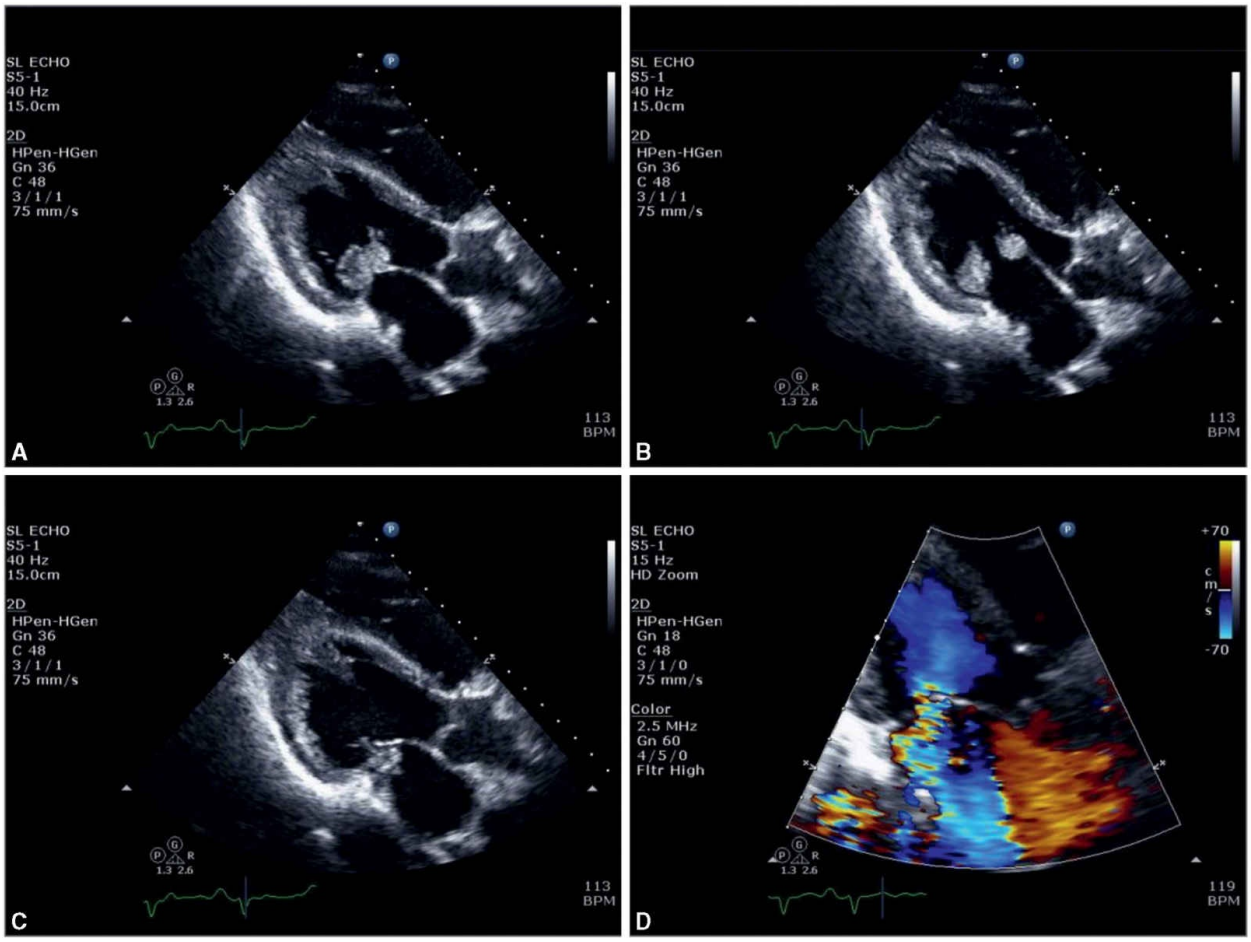

FIGURE 36.3 Large bileaflet mitral valve endocarditis with severe mitral regurgitation seen in the parasternal long-axis view on transthoracic echocardiogram TTE). A–C, Large mobile vegetations on both the anterior and posterior mitral valve leaflets, disrupting coaptation of the mitral valve and prolapsing into the left atrium. D, Resulting severe jet of eccentric mitral regurgitation.

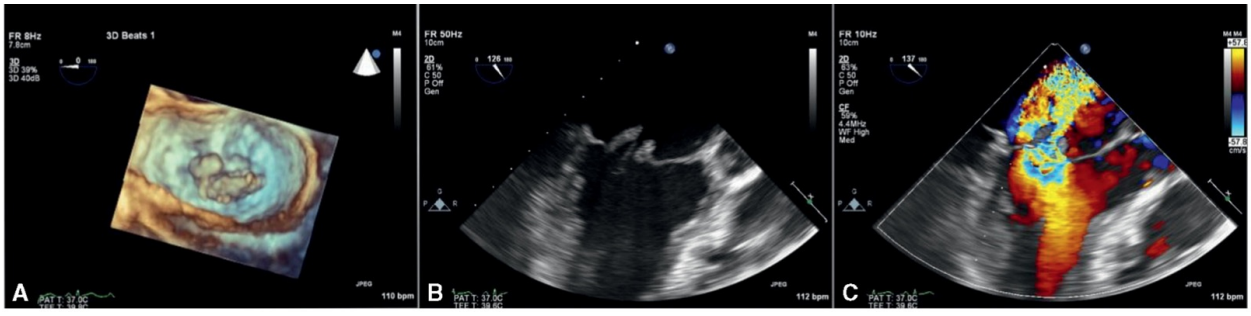

FIGURE 36.4 Bileaflet mitral valve endocarditis as seen on transesophageal echocardiogram (TEE). A TEE was obtained of the bileaflet vegetations seen in transthoracic echocardiogram in Figure 36.3. A, A 3D view of the mitral valve obtained on TEE in the midesophageal view, where the prolapse of the vegetations into the left atrium is visible at the coaptation plane. B, A 2D view of the mitral valve on TEE. C, Color Doppler of severe jet of eccentric mitral regurgitation.

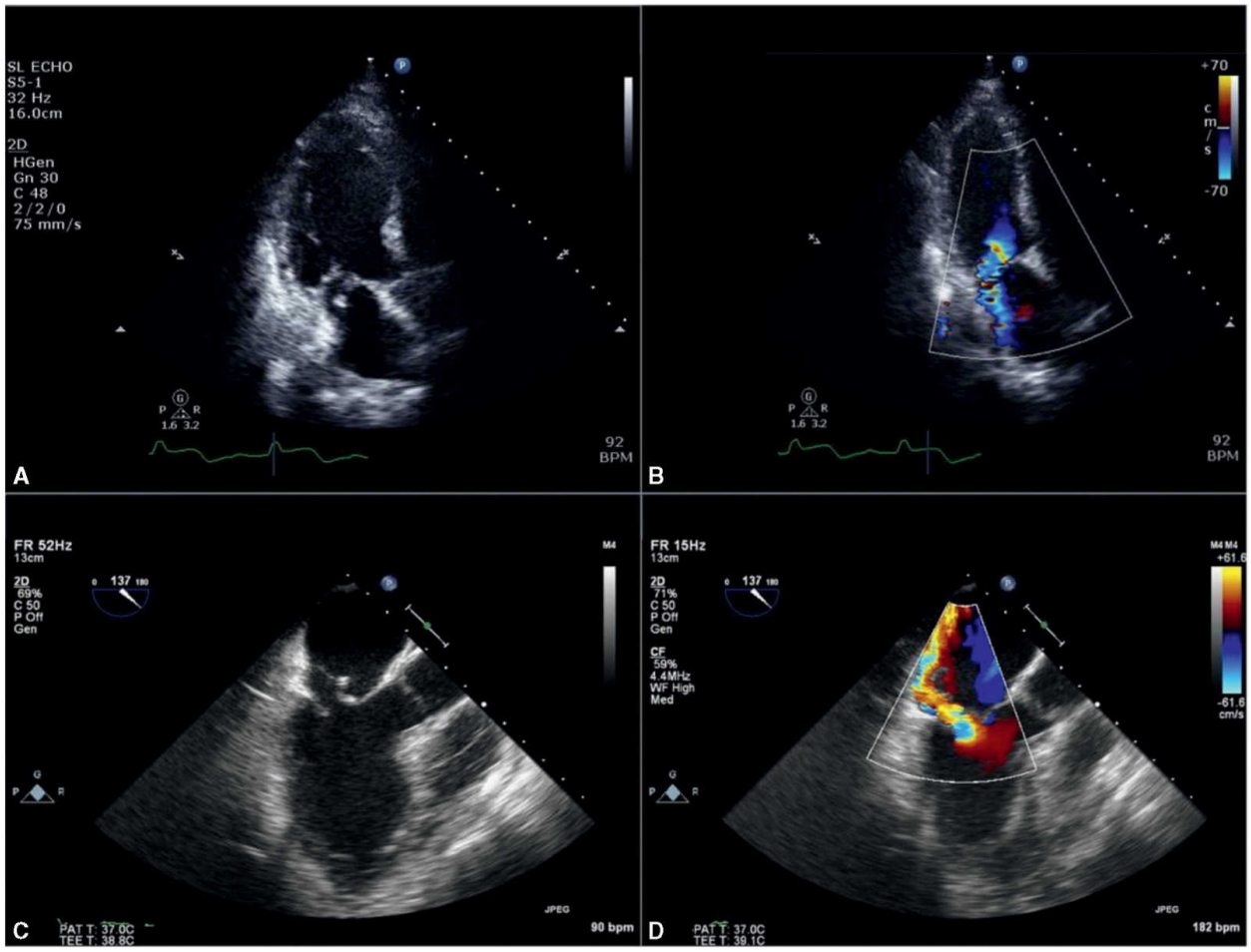

FIGURE 36.5 Flail mitral valve with papillary muscle rupture from inferior myocardial infarction (MI). A, A transthoracic echo image of the mitral valve in the apical five-chamber view. A density can be seen prolapsing into the left atrium, which was confirmed to be a papillary muscle during cardiac surgery. B, The same view with eccentric severe mitral regurgitation. C and D, Transesophageal echo images in the midesophageal view where the prolapse of the ruptured papillary muscle is evident.

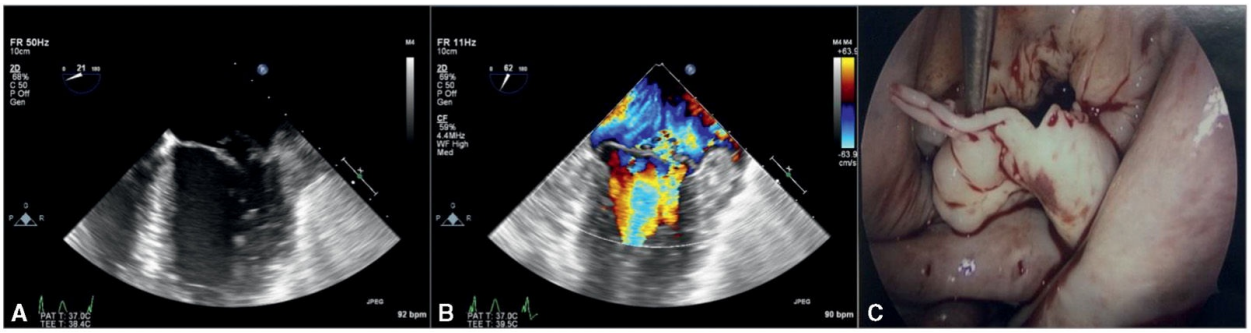

FIGURE 36.6 A and B, Midesophageal views on TEE. A myxomatous mitral valve can be seen with severe mitral regurgitation and flail posterior mitral valve (primarily P2). C, The flail leaflet as seen in the operating room during mitral valve surgery.

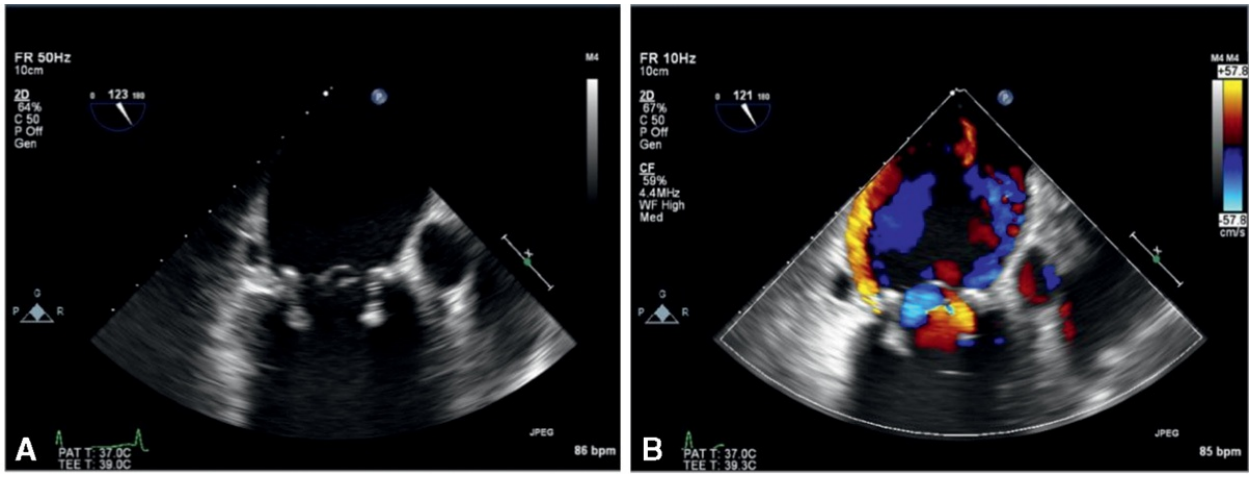

FIGURE 36.7 A, A transesophageal echo at the midesophageal position where a bioprosthetic mitral valve has a soft tissue echo density. This was prosthetic valve endocarditis. B, Associated moderate eccentric paravalvular mitral regurgitation that resulted from destruction of the valve.

Irrespective of the cause, patients with severe, acute MR frequently present with fulminant pulmonary edema and cardiogenic shock. Patients with endocarditis will present with general signs and symptoms of a systemic bacterial illness. Nontraumatic papillary muscle rupture is a mechanical complication that usually occurs 3 to 5 days after acute myocardial infarction (**Figure 36.5**).

Posteromedial papillary muscle (which usually has solitary blood supply from either the right coronary or the left circumflex artery) ruptures more frequently than the anterolateral one (which is usually supplied by both the left anterior descending and circumflex arteries).

SEVERITY OF MITRAL VALVE REGURGITATION

In addition to defining etiologic and anatomic mechanisms of MR, assessment of its severity and its hemodynamic impact on risk stratification determine the timing of intervention. The recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines to help grade the severity of MR are summarized in **Table 36.3**.

TABLE 36.3 Stages of MR Per the ACC/AHA Guidelines[5]

STAGE/DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS[a]	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
	Mild mitral valve	No MR jet or small		

Stage A: at risk of MR	prolapse with normal coaptation Mild valve thickening and leaflet restriction	central jet area < 20% LA on Doppler Small vena contracta < 0.3 cm	None	None
Stage B: progressive MR	Severe mitral valve prolapse with normal coaptation Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE	Central jet MR 20%–40% LA or late systolic eccentric jet MR Vena contracta < 0.7 cm Regurgitant volume < 60 mL Regurgitant fraction < 50% ERO < 0.40 cm^2 Angiographic grade 1–2+	Mild LA enlargement No LV enlargement Normal pulmonary pressure	None
Stage C: asymptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR > 40% LA or holosystolic eccentric jet MR Vena contracta ≥ 0.7 cm Regurgitant volume ≥ 60 mL Regurgitant fraction ≥ 50% ERO ≥ 0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension may be present at rest or with exercise C1: LVEF > 60% and LVESD < 40 mm C2: LVEF ≤ 60% and LVESD ≥ 40 mm	None
Stage D: symptomatic severe MR	Severe mitral valve prolapse with loss of coaptation or flail leaflet Rheumatic valve changes with leaflet restriction and loss of central coaptation Prior IE Thickening of leaflets with radiation heart disease	Central jet MR > 40% LA or holosystolic eccentric jet MR Vena contracta ≥ 0.7 cm Regurgitant volume ≥ 60 mL Regurgitant fraction ≥ 50% ERO ≥ 0.40 cm^2 Angiographic grade 3–4+	Moderate or severe LA enlargement LV enlargement Pulmonary hypertension present	Decreased exercise tolerance Exertional dyspnea

[a]Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category are present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.
ERO, effective regurgitant orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation.

DIAGNOSIS

In any patient with *chronic primary MR*, TTE is indicated for baseline structural

and functional evaluation of the heart. The mitral valve apparatus and leaflets can be visualized in detail, with color Doppler evaluation and hemodynamic assessment of MR.

Severe primary MR may be marked by a central jet of MR that is >40% LA or a holosystolic eccentric jet of MR, a vena contracta ≥ 0.7 cm, a regurgitant volume ≥ 60 mL or an effective regurgitant orifice (ERO) ≥ 0.4 cm^2.[5] TEE is also a helpful tool in primary MR to establish anatomic structures and guide valvular repair.

In any patient with chronic secondary MR, TTE is indicated to evaluate the extent and location of wall motion abnormalities and to assess global LV function, severity of MR, and magnitude of pulmonary hypertension. Severe secondary MR may be marked by an ERO ≥ 0.2 cm^2, as adverse outcomes are associated with a smaller calculated ERO as compared to primary MR, regurgitant volume ≥ 30 mL. The MR will likely progress due to associated progression of LV dysfunction and adverse remodeling. There is often underestimation of the ERO by 2D echo-derived flow convergence due to the often crescentic shape of the regurgitant orifice in secondary MR.[5]

In *severe acute MR*, there may be few or no auscultatory findings of MR per se; the systolic murmur is often soft, short, or even absent because there is rapid equilibration of left ventricular and left atrial pressures during systole. Other frequent findings include tachycardia and S3 gallop. Chest X-ray (CXR) in severe, acute MR routinely shows signs of pulmonary congestion. ECG may show tachycardia; there may also be signs of myocardial infarction when acute MR is caused by papillary muscle rupture. Transthoracic and transesophageal echocardiography are the primary means of evaluating MR. Echocardiography can establish the etiology, mechanism, and severity of MR.

ECHOCARDIOGRAPHY FINDINGS

Echocardiography has several important roles in MR: (1) Evaluation of the etiology of MR; (2) Grading the severity of MR; (3) Assessment of its impact on overall cardiac function, especially left ventricular function; (4) Guidance for further management, including timing of surgical intervention. TTE is the modality of choice for evaluation and follow-up of MR and global cardiac function. TEE plays an important role when differences exist between clinical assessment and TTE findings, or when mitral valve surgery is needed. Defining the etiology of MR is important because this influences management and

prognosis of such patients. Diseases that are primarily structural in origin are managed differently as compared with functional MR.

TREATMENT

There are different treatment options based on the MR type. As described earlier, *chronic primary MR* is mainly due to a dysfunctional valve. A prolonged and severe chronic primary MR will cause subsequent volume overload, myocardial damage, HF, and eventual death. Hence, correction of the MR in this group is "curative" and every effort should be made to repair the valve.

However, if it is the *chronic secondary type*, MR is secondary to myocardial disease (ie, ischemic, nonischemic, and idiopathic myocardial diseases; severe LV dysfunction, etc.). Hence, mitral valve repair by itself is not curative. Thus, efforts should be focused on treatment of the causes of chronic secondary MR such as revascularization or treating other underlying medical conditions as well as management of HF (ie, standard guideline-directed medical therapy for HF [including ACE inhibitors, ARBs, ***β***-blockers, and/or aldosterone antagonists as indicated], and cardiac resynchronization therapy with biventricular pacing for symptomatic patients who meet the indications for device therapy). Mitral valve surgery could be considered in patients with severe and chronic secondary MR who are undergoing other cardiac surgery like coronary artery bypass grafting (CABG) or aortic valve replacement (AVR), as well as severely symptomatic patients with persistent symptoms despite optimal guideline-directed medical therapy for HF.

Severe acute MR is a life-threatening medical emergency that requires the highest level of care in the CCU. Acute events such as an ST elevation myocardial infarction can lead to disruption of normal mitral valve anatomy, such as rupture of a mitral valve papillary muscle. Such a mechanical complication leads to an incompetent mitral valve, severe MR, heart failure, and possibly requirement of intubation to provide respiratory support and intravenous medications to provide intensive medical therapy.

Endotracheal intubation, oxygen administration, and diuretic therapy are used to treat pulmonary edema. Afterload reduction may be achieved with the use of intravenous vasodilators (such as nitroprusside). Disease-specific therapies, if available, should also be administered (such as coronary revascularization and anti-ischemic medical therapy).

CARPENTIER'S SURGICAL CLASSIFICATION OF MITRAL VALVE

PATHOLOGY

Carpentier's surgical classification of mitral valve pathology merits discussion as one works with cardiac surgery colleagues to characterize the mitral valve. Carpentier divided MR into three categories based on the opening and closing motions of both leaflets:

A. Type I, annular dilatation: Type I MR occurs despite normal leaflet motion. This can be due to annular dilatation seen in dilated cardiomyopathy.
B. Type II, excessive leaflet motion: Type II regurgitation refers to MR that occurs because of leaflet prolapse. This may be due to simple elongation of the leaflets, with prolapse into the LA.
C. Type IIIa refers to valvular and subvalvular thickening that can restrict mitral leaflet motion. Mitral annular calcification and thickening of the subvalvular apparatus are seen with increasing age, or as the sequelae of RHD.
D. Type IIIb, restricted leaflet motion: When leaflet motion is restricted, with displacement of the papillary muscles, this is referred to as Type IIIb MR. The most common culprit is dilated cardiomyopathy, where enlargement of left ventricular chamber is accompanied by elongation of papillary muscles and their displacement toward the apex, relative to the mitral valve leaflets.

PERCUTANEOUS INTERVENTIONAL THERAPY AND MITRAL VALVE SURGERY

Severe acute MR often requires percutaneous insertion of the intra-aortic balloon pump (IABP), which is threaded through the femoral artery into the descending thoracic aorta with its tip just distal to the origin of the left subclavian artery. Significant coexisting aortic regurgitation is a contraindication for IABP insertion. IABP and the medical therapies described in Chapters 17 and 19 are usually only palliative.

The patient may require urgent surgery to repair or replace the mitral valve. For the first time, the 2014 ACC/AHA Guidelines incorporated percutaneous mitral valve repair into their recommendations.[5] Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA Class III/IV) with chronic severe primary MR (stage D), who have a reasonable life expectancy but a prohibitive surgical risk because of severe comorbidities. The anatomy of the mitral valve, however, has to lend itself to a mitral valve clip.

IMPACT ON PREGNANCY

Severe MR, whether acute or chronic, is one of the valvular heart lesions that may be associated with high maternal and/or fetal risk during pregnancy. Pregnant women with MR who have NYHA functional class III–IV symptoms, severe pulmonary hypertension (pulmonary pressure > 75% of systemic pressures), and/or LV systolic dysfunction are at particular risk for maternal and fetal complications.

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Patient and Family Information for: MITRAL VALVE DISEASE IN THE CARDIAC CARE UNIT

GENERAL CONCEPTS OF MITRAL VALVE DISEASE

The mitral valve is an important valve through which blood flows from the left atrium (LA) into the left ventricle (LV). The LV is the main heart pump for the body. Mitral stenosis (MS) occurs when the valve does not open well, impeding blood flow. Mitral regurgitation (MR) occurs when the valve does not close well, resulting in backflow of blood into the LA.

MITRAL STENOSIS

WHAT IS MY ILLNESS?

If the mitral valve becomes too narrow, it takes a long time for blood to empty from the LA into the LV. There can be many reasons for this including simply advancing age and degeneration of the mitral valve. If you have had rheumatic fever as a child, that may result in thickening of the mitral valve later in life.

HOW WILL I BE TREATED?

Mild MS may be treated with medications to keep your heart rate from beating too rapidly because this gives time for blood to drain from the LA into the LV. If MS becomes severe, and you have symptoms such as severe shortness of breath or heart failure, you may be referred for mitral balloon commissurotomy (also referred to as a mitral valvuloplasty). In this procedure, a balloon on a catheter is used to open up the mitral valve further through your leg in the cardiac

catheterization laboratory. If your MS cannot be treated with mitral balloon commissurotomy, you may be referred for mitral valve surgery performed by a cardiac surgeon.

WHAT IF I AM PREGNANT OR THINKING OF BECOMING PREGNANT?

If you have mild MS, you may be able to work with your physician during your pregnancy. If, however, you have severe MS, the degree of volume overload that you experience during pregnancy may put you in danger of developing severe shortness of breath and heart failure. Management of your MS and seeing your cardiologist is prudent and you may have to delay pregnancy until the narrowing of your mitral valve is relieved.

MITRAL REGURGITATION

WHAT IS MY ILLNESS?

MR describes a leaky mitral valve that results in backflow of blood from the LV into the LA. In primary MR, there is a problem with the mitral valve. Common causes of primary MR include mitral prolapse due to myxomatous degeneration in a younger population or problems such as fibroelastic deficiency disease in older population, infective endocarditis, or myxomatous degeneration. Secondary MR occurs when the mitral valve is normal but its supporting structures are abnormal. Sudden MR can occur from complications of bacterial endocarditis, papillary muscle rupture (eg, after a heart attack), or chordal rupture from preexisting valve degeneration. In acute MR, there is sudden volume overload of nondilated left heart chambers leading to marked elevation of left atrial pressures, life-threatening pulmonary edema, and possibly even shock.

HOW WILL I BE TREATED?

In patients who develop MR over a short period of time, such that the heart does not have enough time to accommodate the leakage, medical stabilization in an intensive care setting may be necessary. Mitral valve surgery may be needed to repair or replace the mitral valve. New therapies are on the horizon for specific types of mitral valve disease such as percutaneous mitral valve clips.

WHAT IF I AM PREGNANT OR THINKING OF BECOMING PREGNANT?

Severe leakage of the mitral valve may not be well tolerated during pregnancy. Women with severe leakage who are considering pregnancy may wish to delay it until the condition is treated, and until a long discussion occurs with a cardiologist as to their options.

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Avinoam Shiran

Tricuspid and Pulmonic Valvular Disease in the Cardiac Care Unit

The tricuspid valve (TV) used to be called “the forgotten valve.” In recent years, the prevalence of TV disease and, in particular, tricuspid regurgitation (TR) has become apparent. Moderate or severe TR is present in 15% of patients referred to echocardiography, and it is strongly associated with heart failure and death.[1] This chapter focuses on TR, which is by far the most common lesion of right-sided valvular heart disease in the cardiac care unit (CCU) setting. In addition, we briefly discuss the pulmonic valve.

TRICUSPID REGURGITATION

ETIOLOGY AND PATHOPHYSIOLOGY

TR is most often functional, secondary to pulmonary hypertension (PHT), right ventricular (RV) remodeling, and tricuspid annular (TA) dilatation.[2]

PHT (usually >50 mm Hg) may be secondary to left heart failure, cor pulmonale, or pulmonary vascular disease. It results in elevated RV pressure, which may cause RV remodeling (both dilatation and distortion of the normal RV shape) and RV failure. RV remodeling causes papillary muscle displacement (similar to functional mitral regurgitation) and TA dilatation, TV leaflet tethering, and malcoaptation resulting in TR. TR in turn causes RV volume

overload, which combined with pressure overload causes further RV remodeling and TR progression, resulting heart failure, and if left unchecked, death. RV pressure and volume overload may also be caused by pulmonic valve disease.

TA dilatation may also be caused by right atrial dilatation secondary to atrial fibrillation, even in the absence of PHT. Worsening PHT and permanent atrial fibrillation are the most common cause of TR progression.[3]

Several disease processes directly affect the TV and may cause primary TR (**Table 37.1**). TV endocarditis is most often seen in IV drug abuse patients and may lead to destruction and perforation of the valve leaflets and chordal rupture, as well as septic pulmonary emboli. TR is common in rheumatic heart disease (prevalent now mainly in developing countries), especially in patients with mitral valve disease, and may appear years after successful mitral valve surgery (**Figure 37.1**).[2] In rheumatic patients TR is often functional, but may also be due to rheumatic involvement of the TV leaflets with leaflet thickening, restriction, and shortening. In Ebstein anomaly, the abnormal TV is displaced toward the RV apex, resulting in atrialization of the RV with a small dysfunctional RV, large right atrium (RA), and TR. In carcinoid syndrome, fibrous plaques may cause thickening and significant shortening of the TV leaflets resulting in severe TR.

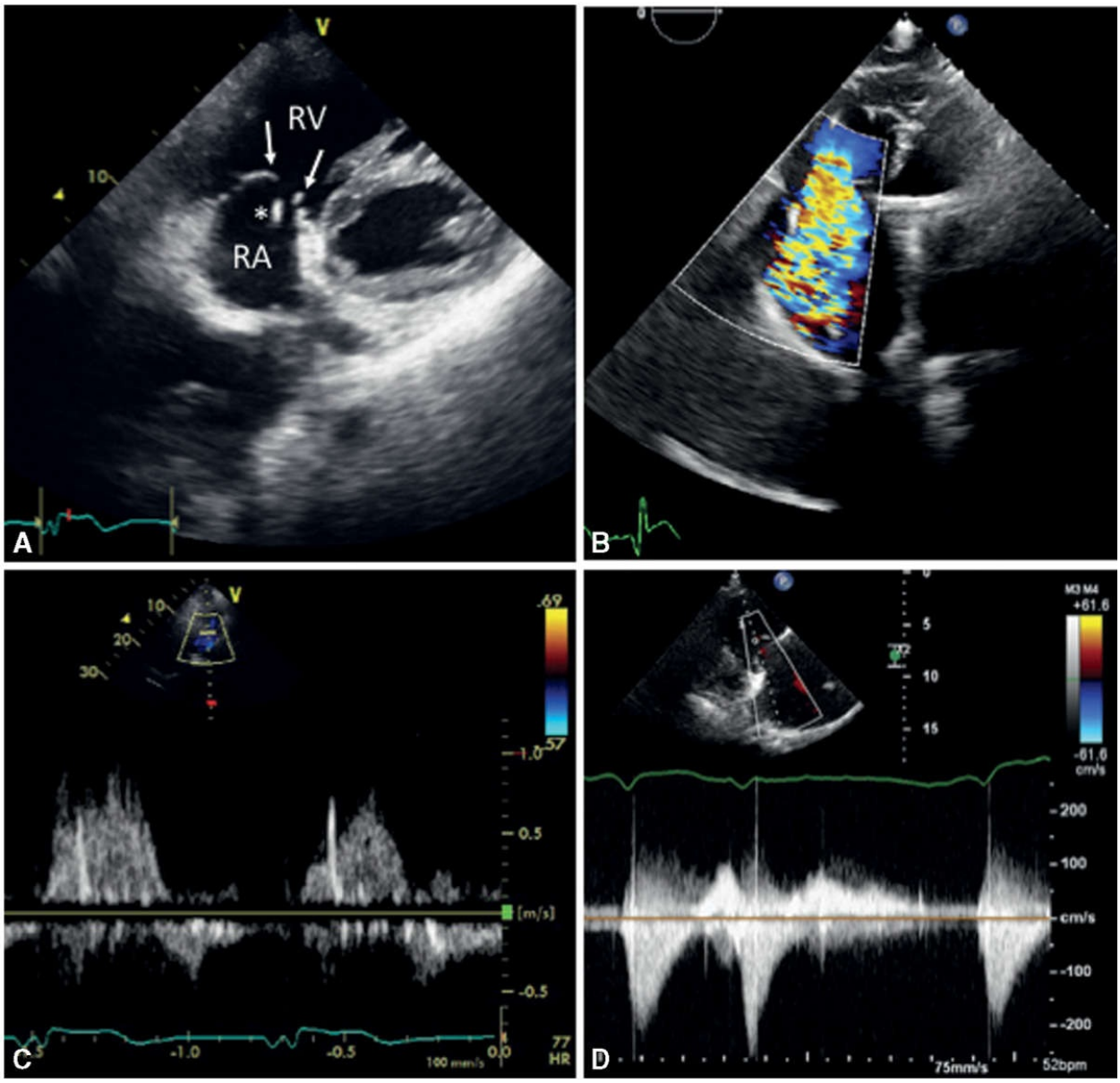

FIGURE 37.1 Tricuspid regurgitation. A, A 67-year-old woman with rheumatic heart disease and heart failure after mitral and aortic valve replacement. Parasternal short-axis view. TV leaflets *(arrows)* are thickened and restricted with severe malcoaptation. B, Modified four-chamber view showing severe TR on color Doppler. C, Pulsed wave Doppler of the hepatic veins (subcostal view) showing systolic flow reversal. D, Continuous wave Doppler (RV inflow view) showing a dense, triangular, low-velocity jet. RA, right atrium; RV, right ventricle; *, pacemaker electrode.

TABLE 37.1 Etiology of Tricuspid Regurgitation

Secondary (functional)
Primary
- Infective endocarditis (IV drug abuse)
- Rheumatic
- Pacemaker/ICD leads

Congenital (Ebstein anomaly)
Carcinoid
Myxomatous (prolapse, ruptured chords)
Trauma (blunt or penetrating)
Repeated endomyocardial biopsies in heart transplants
Prosthetic valve failure

Pacemaker and implantable cardioverter-defibrillator (ICD) leads are increasingly identified as a cause of TR, due to leaflet perforation, interference with TV closure, or with the subvalve apparatus (**Figure 37.2**).

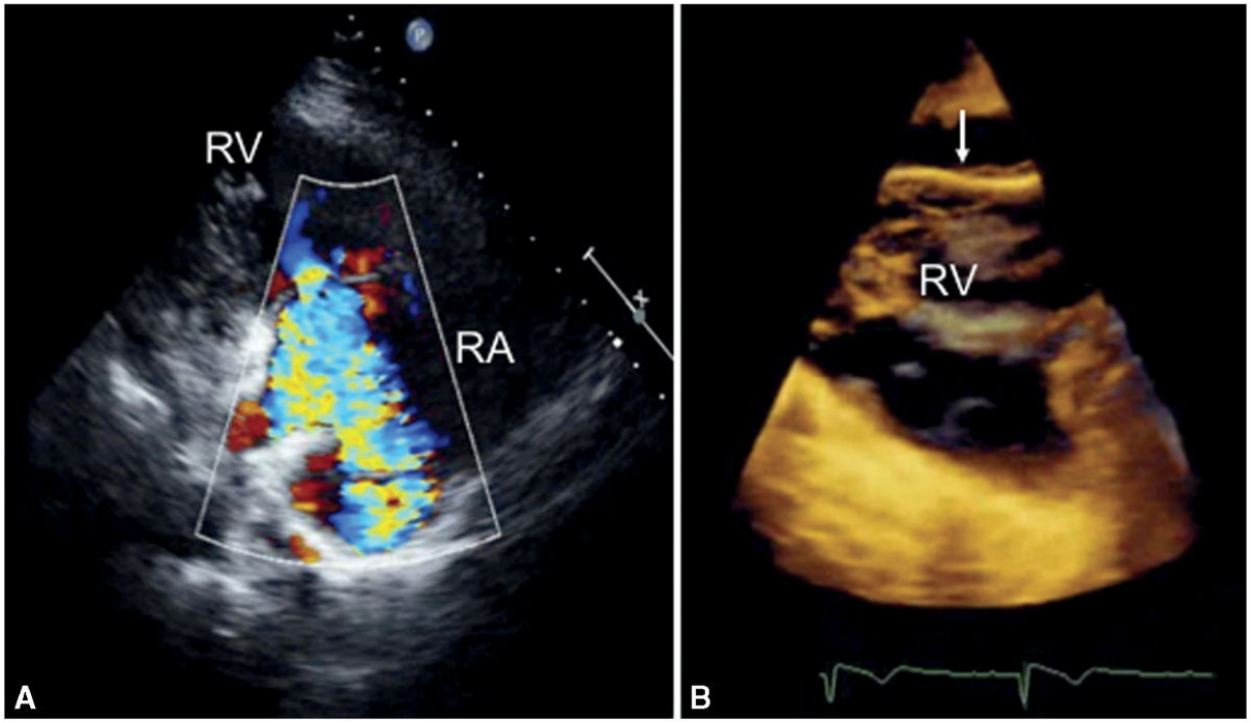

FIGURE 37.2 Tricuspid regurgitation after permanent pacemaker implantation. A, Severe symptomatic TR in a 48-year-old woman who had a pacemaker implantation with an RV lead after mitral valve replacement. RV inflow view. B, Transgastric 3D TEE showing the pacemaker electrode lodged in the subvalve apparatus. At surgery, the pacemaker electrode was found piercing and displacing the papillary muscle. TR resolved after repositioning of the electrode and TV annuloplasty. RA, right atrium; RV, right ventricle; arrow, pacemaker electrode; TEE, transesophageal echocardiography.

CLINICAL PRESENTATION

Patients with severe TR may be asymptomatic, especially when PHT and RV dysfunction are absent. With cor pulmonale or heart failure, dyspnea and fatigue are usually present. In the CCU setting, TR is most often seen in the setting of acute decompensated heart failure with dominant right heart failure, volume

overload, peripheral edema, and ascites. Right upper abdominal pain may be present secondary to a congested liver.

TR may sometimes complicate RV infarction. Such patients can present with a low-output state, hypotension, and right heart failure that can be resistant to inotropic therapy.[4]

In patients with right-sided endocarditis and TR, right heart failure may be absent initially if pulmonary pressure is normal, but may appear later as the RV eventually fails.

DIAGNOSIS

The clinical findings in severe TR are usually pathognomonic. Giant V waves are usually present in the jugular venous pulse, and are best seen in the sitting position. The liver may be distended, tender, and, most importantly, pulsatile. A right ventricular heave can be felt in the left parasternal area. When placing two hands, one on the left parasternal area and the other on the liver, a “seesaw” motion can be felt. In systole, the RV partially empties into the jugular and hepatic veins through the incompetent TV, producing a parasternal descent with jugular V waves and hepatic expansion. During diastole, the systemic veins empty into the RA and RV, producing RV parasternal lift and liver contraction. A left parasternal holosystolic murmur can sometimes be heard, which is typically augmented by inspiration (Carvallo sign).

Transthoracic echocardiography is key in the diagnostic workup of TR. In functional severe TR, there is usually RV dilatation, TA dilatation (>3.5 cm) and malcoaptation of the leaflets. Large TV vegetation and leaflet destruction are usually seen with TV endocarditis and TR. Color flow Doppler usually shows a large jet in the RA, with systolic flow reversal in the hepatic veins. In patients with wide-open TR, estimation of pulmonary artery systolic pressure using the TR jet velocity is inaccurate, due to equalization of systolic pressures in the RA and RV and difficulty in estimating RA pressure accurately. Spectral continuous-wave Doppler typically shows a low-velocity triangular TR flow (**Figure 37.1D**).

MEDICAL THERAPY

Patients with acute decompensated heart failure and secondary severe functional TR may respond well to heart failure therapy aimed to reduce PHT and eliminate volume overload. TR may regress considerably in such patients due to reverse

remodeling of the RV and the TA. Diuretics, angiotensin-converting enzyme inhibitors, and resynchronization therapy, when indicated, can reverse TR in patients with left ventricular failure. In patients with pulmonary arterial hypertension (PAH), RV failure, and functional TR, successful PAH therapy has been associated with improvement in TR severity and better outcome.[5]

Prolonged antibiotic therapy is indicated in TV endocarditis, but severe TR will usually not regress with medical treatment.

SURGICAL THERAPY

In patients with functional TR undergoing left heart surgery, and in particular mitral valve surgery, concomitant TV surgery should always be considered.[2] TR may persist and even progress years after mitral valve replacement, especially in patients with rheumatic heart disease. In such patients, concomitant TV repair with a ring annuloplasty should be considered when there is more than mild TR, with a dilated TA (≥3.5 cm) or with permanent atrial fibrillation.

TV surgery is more challenging with isolated TR, and surgical outcome in these patients used to be poor. In symptomatic patients with isolated severe TR, surgery (repair or replacement with a bioprosthetic valve) should be considered early when significant PHT is absent and RV function is still preserved.[6]

TV surgery is indicated in TV endocarditis and uncontrolled infection (persistent bacteremia despite antibiotic therapy >7 to 10 days or resistant organisms such as fungi). In such cases, all the infected tissue should be thoroughly excised, and the valve should be repaired, if possible. When the pulmonary pressure is normal, patients can tolerate severe TR after valve excision for several months or years, but eventually the RV will usually fail. IV drug addicts undergoing TV replacement are at high risk for recurrent endocarditis of the prosthetic valve if not successfully rehabilitated.

TRICUSPID STENOSIS

Tricuspid stenosis (TS) is rarely seen in the CCU. The etiology is almost always rheumatic, usually in conjunction with TR, mitral valve disease, and sometimes aortic valve disease as well. Patients may present with effort intolerance and fatigue due to a low-output state, but typically without dyspnea despite the accompanying mitral valve disease. In severe long-standing cases, cardiac

cirrhosis may also be present. On physical examination, neck veins are distended, the liver congested, and ascites, splenomegaly, and peripheral edema are usually present as well. Echocardiography typically shows thickened TV leaflets with restricted opening and turbulent diastolic flow on color flow Doppler (**Figure 37.3**). In significant TS, mean Doppler TV gradient is ≥5 mm Hg.[7] The RA and inferior vena cava are dilated, and inspiratory collapse of the inferior vena cava absent.

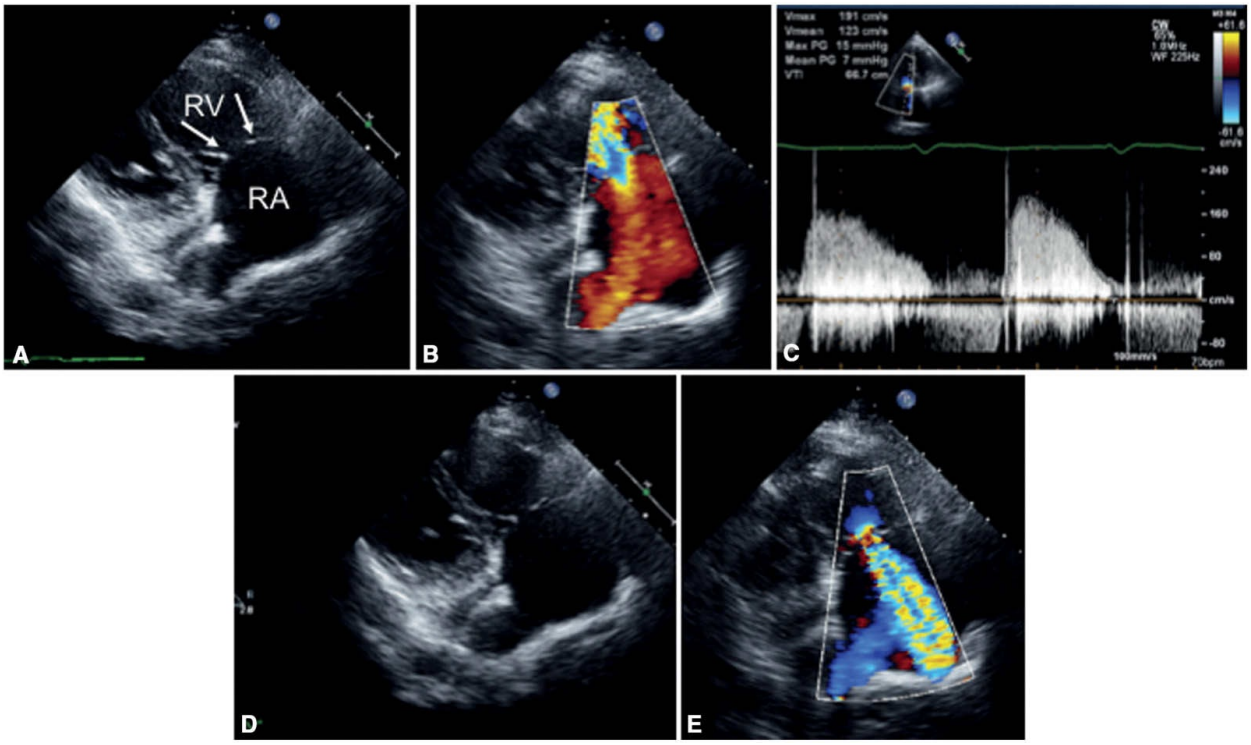

FIGURE 37.3 Tricuspid stenosis and regurgitation. A 47-year-old man with rheumatic TV disease, moderate TS, and severe TR. The patient had concomitant mitral and aortic disease. A, RV inflow view diastolic frame showing thickened restricted TV leaflets (arrows). B, Diastolic color Doppler frame showing a turbulent RV inflow. C, Continuous wave Doppler showing a mean diastolic tricuspid gradient of 7 mm Hg. D, RV inflow, systolic frame, showing severe malcoaptation of the TV leaflets. E, Color Doppler, systolic frame, showing severe TR. RA, right atrium; RV, right ventricle.

Sodium restriction and diuretics may reduce volume overload and improve liver function. In selected patients without significant TR, balloon valvuloplasty can be beneficial. In patients with significant symptomatic TS, TV commissurotomy or replacement with a bioprosthetic valve may be necessary, usually with concomitant mitral or aortic valve surgery.

PULMONIC STENOSIS

Pulmonic stenosis (PS) is rarely seen in the CCU setup. The etiology is usually congenital, and PS is usually mild in adults. Mild PS does not progress with time, but moderate PS can progress to severe PS in 20% of the patients due to calcification of the valve. Rarely, PS may be caused by carcinoid plaque deposition, with or without pulmonic regurgitation. Severe PS causes RV pressure overload and may result in effort intolerance, RV failure, and functional

TR. On auscultation, a pulmonic systolic ejection murmur is heard in the second left intercostal space. When the valve is pliable, an ejection click can be heard as well. P2 may be diminished when the valve is dysplastic or calcified.

The pulmonic valve (PV) can be visualized on echocardiography using the parasternal short-axis view or parasternal RV outflow view, or the subcostal short-axis view. When PS is caused by commissural fusion, the valve leaflets appear thin and systolic doming may be evident (**Figure 37.4**). With dysplastic valves, the leaflets are thickened and may calcify with time. The PV gradient can be estimated using continuous wave Doppler. Severe PS is defined as maximal PV jet velocity > 4 m/sec (peak gradient > 64 mm Hg).[7] When trying to estimate systolic pulmonary artery pressure in patients with PS, using TR velocity and the Bernoulli equation, one must remember to subtract the pulmonic gradient from the RV estimated systolic pressure.

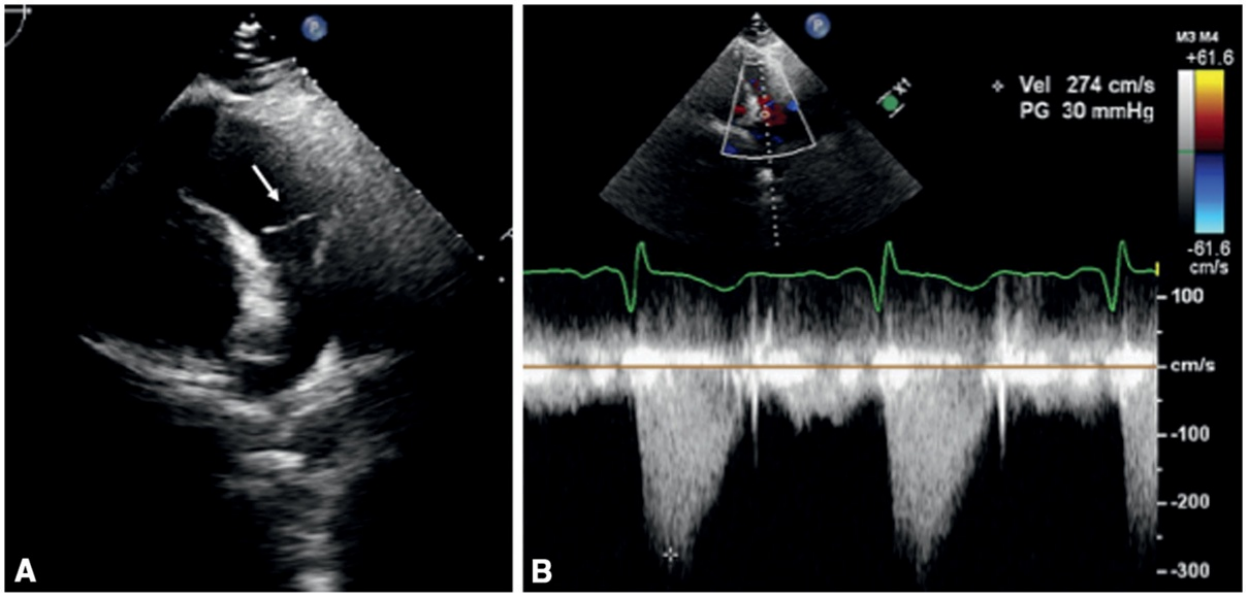

FIGURE 37.4 Pulmonic stenosis. A, Short-axis view, showing nonthickened pulmonic valve leaflets (arrow). B, Continuous wave Doppler showing increased pulmonic flow velocity and a peak pulmonic gradient of 30 mm Hg, corresponding to mild pulmonic stenosis. In this case, estimated peak systolic RV pressure, using TR velocity, was 43 mm Hg but pulmonary artery pressure was normal (43 – 30 = 13 mm Hg).

In young patients with symptomatic or severe PS and a pliable PV, balloon valvuloplasty may be beneficial. Percutaneous transcatheter PV implantation is indicated in patients with symptomatic PS (<65% expected exercise capacity) and maximal PV jet velocity > 3.5 m/sec, or in asymptomatic patients with peak

jet velocity > 4 m/sec or RV systolic pressure greater than two-thirds of systemic systolic pressure.

PULMONIC REGURGITATION

Pulmonic regurgitation (PR) is usually caused by PHT and secondary dilatation of the PV annulus or pulmonary artery and is usually nonsevere. Infective endocarditis can cause PR but it rarely affects the PV. Rarely PR can be caused by carcinoid plaques. Severe PR in adults is usually due to congenital heart disease, and seen mainly in patients with repaired tetralogy of Fallot or after PV valvuloplasty. Severe PR is usually well tolerated unless PHT is also present, which may then lead to RV failure and TR. On auscultation, a typical Graham Steell high-pitched decrescendo murmur is heard in the left 2 to 4 intercostal space in patients with concomitant PHT. Unlike in aortic regurgitation, the pulse pressure is not widened in PR. When pulmonary pressure is normal, the murmur is low pitched. The PR murmur is accentuated during inspiration, and the second heart sound may be widely split due to delayed RV emptying.

Echocardiography may show RV dilatation and diastolic flattening of the interventricular septum in patients with severe PR and RV volume overload. Color flow Doppler shows the regurgitant jet, which is wide in severe AR (**Figure 37.5**). Continuous wave Doppler of the PR jet can be used to estimate pulmonary artery diastolic pressure using the end diastolic PR velocity, similar to the way the TR jet is used to estimate pulmonary artery systolic pressure. With severe PR, the continuous wave diastolic Doppler signal is dense, with a steep deceleration reaching the baseline before the end of diastole.

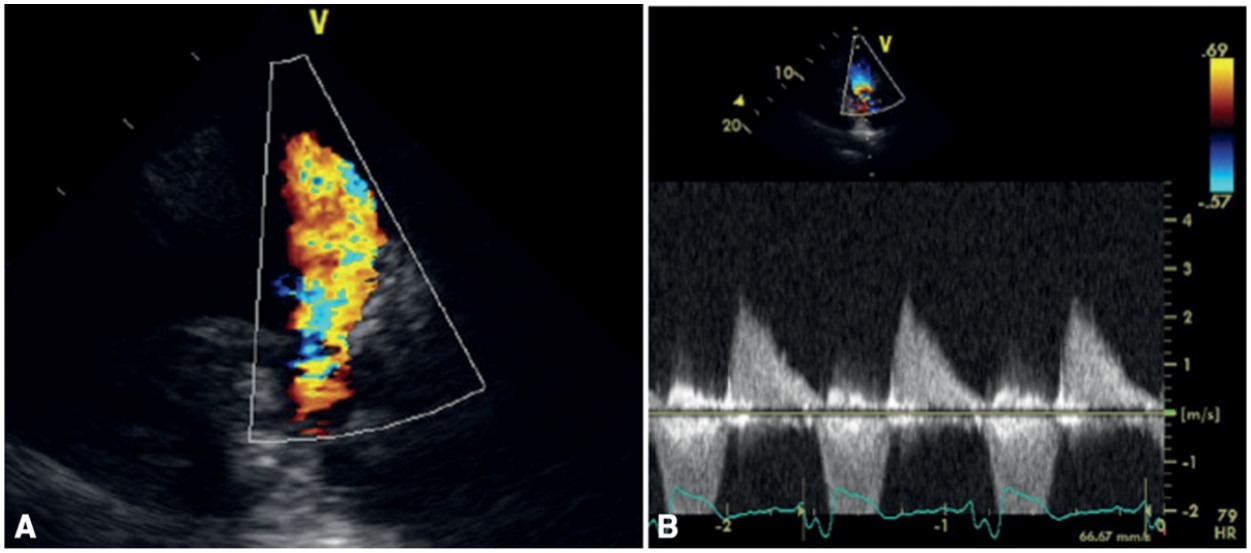

FIGURE 37.5 Pulmonic regurgitation. A 23-year-old patient with severe pulmonic regurgitation (PR) after repair of tetralogy of Fallot. A, Color Doppler short-axis view showing a wide PR jet. B, Continuous wave Doppler showing a dense diastolic signal with steep deceleration and a triangular shape. Moderate pulmonic stenosis was present in this case as well.

Percutaneous transcatheter PV implantation is indicated in patients with severe symptomatic PR, progressive RV dilatation or dysfunction, or with progressive TR.

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Patient and Family Information for: TRICUSPID AND PULMONIC VALVULAR DISEASE IN THE CARDIAC CARE UNIT

There are two valves on the right side of the heart. The tricuspid valve (TV) is located between the two chambers in the right heart—the right atrium, which receives unoxygenated blood from the veins in the body, and the right ventricle. The right atrium delivers the blood through the tricuspid valve to the right ventricle, which pumps the blood through the pulmonic valve, the second valve in the right heart, to the lungs. In the CCU, tricuspid regurgitation (TR), a leaky tricuspid valve, is the most common of all right heart valves conditions. We focus, therefore, on TR.

TRICUSPID REGURGITATION

WHAT IS MY ILLNESS?

One of your heart valves, the tricuspid valve (TV) is leaking. This condition is called “tricuspid regurgitation” or sometimes “tricuspid insufficiency.” This causes blood from the right heart pumping chamber, the right ventricle, to leak back into the right atrium and from there to the veins in your body, instead of going forward to the lungs.

Because of the leak, you may notice that the veins in your neck are dilated and pulsating with the heartbeat. You may also have a painful liver from the blood flowing back to it, under the rib cage on your right side. Your legs may be swollen from excess salt and water in your body.

The most common cause of your condition is failure of the left side of your

heart, which overloads the right side of the heart as well. Any condition that causes high pressure in the arteries of your lungs may cause overload of your right heart and TR. Another possible cause of TR is infection of the valve with germs from your bloodstream, which can damage the valves and cause it to leak. These germs can get into your bloodstream if you shoot drugs.

HOW WILL I BE TREATED?

Your doctors may choose to treat you with medications such as diuretics. These drugs can remove excess fluids from your body through the kidneys, which will cause the right ventricle to get smaller and the TR to reduce. Other heart failure medications and medications to lower the pressure in the lung arteries may help as well. If you have infection of the valve, you will be treated with antibiotics delivered through your veins.

Your doctors may decide to refer you to a surgeon for an open heart surgery to treat your leaky TV and other dysfunctional heart valves, if necessary. In this case, your valve may be repaired or replaced, usually with a bioprosthesis. A bioprosthetic valve is made from either pig or cow tissue. Unlike a metal prosthesis, it does not require medications to prevent clotting of the valve, but it may last for a shorter period. Nevertheless, a bioprosthetic TV usually lasts for 15 years and even more.

In any case, complete abstinence from illicit drugs is mandatory to prevent reinfection of your valve, which could be fatal.

WHAT IF I AM PREGNANT OR THINKING OF BECOMING PREGNANT?

If you have a leaky TV and normal pressure in your lung arteries, and you have good function of your left and right ventricles, then most likely your pregnancy will be well tolerated. Otherwise, you need to consult with your doctor about the risk for you and your baby during pregnancy.

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Ankit Chothani
Eyal Herzog
Edgar Argulian

Infective Endocarditis

Infective endocarditis (IE) refers to the infection of the endocardium or heart endothelium, which may include heart valve endocardium or mural wall endocardium. In the United States, 10 to 15 new cases of IE per 100,000 persons are reported annually.[1] There has been a steady increase in the incidence of IE over the last decade. Despite the recent advances in medical and surgical therapies, IE continues to be a life-threatening disease. A recent study reports 15% to 20% in-hospital mortality and about 40% 1-year mortality for patients diagnosed with IE.[2] Up to 20% to 50% patients have cardioembolic complications like stroke.[3]

ETIOLOGY

RISK FACTORS

Table 38.1 summarizes the common risk factors associated with IE. In general, preexisting native valve disease or prosthetic material can serve as a nidus for bacterial seeding. Conditions predisposing to transient bacteremia (like hemodialysis, poor dentition) and causing immune suppression (like diabetes mellitus) are also important identifiable risk factors. Patients with a prosthetic valve or prosthetic material, congenital heart disease, previous history of IE, and cardiac transplantation valvulopathy are at the highest risk of developing IE. As per current guidelines, routine antibiotic prophylaxis is recommended only for

this subgroup of patients.

TABLE 38.1	Risk Factors of Infective Endocarditis
Patient-Related Factors	
Age	Highest incidence for age > 60 years
Male gender[4]	2- to 3-fold higher prevalence in men
Comorbid Conditions	
Acquired valvular disease	Rheumatic heart disease (most commonly mitral valve), degenerative valve disease (aortic valve sclerosis or stenosis), mitral annular calcification, prior IE
Congenital heart disease	Mitral valve prolapse, bicuspid aortic valve, ventricular septal defect, tetralogy of Fallot
Prosthetic valves	Mechanical valves (especially in first 3 months of implantation), bioprosthetic valves
Cardiovascular implantable electronic device (CIED)[5,6]	Device/lead infection and endocarditis
Intravascular devices	Intravascular catheters and probes can cause bacteremia
Diabetes mellitus	Higher risk of IE and poor response to treatment
End-stage renal disease requiring hemodialysis	Calcific valvular disease, immune impairment, transient bacteremia with intravenous access
HIV infection	Higher risk of IE, occasionally unusual organisms like Salmonella
Others	
Intravenous drugs abuse	Common cause of right-sided IE (tricuspid valve) but can also cause left-sided IE
Poor dentition	IE caused by oral flora

IE, infective endocarditis.

MICROBIOLOGY

Staphylococcus aureus is the most common organism isolated from blood cultures of patients with IE. It is the most common cause of acute IE, nosocomial endocarditis, and endocarditis associated with intravenous drug abuse. Other common bacteria include *Streptococcus viridans* and coagulase-negative Staphylococci (usually found in normal skin flora). Enterococci and

Streptococcus bovis are usually associated with genitourinary and intestinal source, respectively. Gram-negative bacilli, HACEK organisms (*Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*), fungi, and polymicrobial infection account for a small number of IE cases. Occasionally, no organisms can be isolated in patients with established IE (culture-negative endocarditis).[7,8]

PATHOPHYSIOLOGY

The pathogenesis of endocarditis involves three steps.[9] First is transient bacteremia, which can be spontaneous, associated with invasive procedures that break mucosal or skin integrity, or caused by noncardiac infection. Next, the bacteria adhere to the endocardium. Bacterial deposition is facilitated by preexisting valve disease and platelet aggregates on the damaged endothelial surface and/or foreign/prosthetic material. Highly virulent bacteria (such as *Staphylococcus aureus*) have the ability to infect structurally normal valves. The third step involves bacterial proliferation and inflammation resulting in vegetation formation, valve destruction, and spread into the surrounding cardiac tissue. The latter can result in intracardiac fistula and abscess formation. Vegetations are typically friable resulting in embolization causing tissue infarction as well as metastatic infection. Ongoing intravascular infection also results in a high burden of circulating immune complexes that produce immunologic phenomena of IE (such as glomerulonephritis).

CLASSIFICATION

Based on clinical presentation, native valve endocarditis can be divided into acute and subacute IE.

Acute IE classically refers to rapidly progressive IE with acute clinical presentation. Distant metastatic infection is common. It is typically caused by highly virulent organisms such as *Staphylococcus aureus*. Acute IE can be fatal in days to weeks despite appropriate medical therapy.

Subacute IE usually has an indolent course, extending over weeks to months. It is typically caused by organisms with lower virulence like streptococci. Distant metastatic infection is less common.

Prosthetic valve endocarditis (PVE) and cardiovascular implantable electronic device (CIED) endocarditis are divided into early and late.[6]

Early PVE refers to endocarditis within the first 60 days of the prosthetic

valve or CIED implantation. The prosthetic material and tissue–suture interface are not endothelialized during this timeframe. They can get infected during implantation or get seeded during any transient bacteremia.

Late PVE refers to endocarditis more than 60 days after the prosthetic valve implantation. Late infection occurs as a result of hematogenous bacterial spread with pathogenesis resembling that of native valve endocarditis.

Health care associated IE (nosocomial IE) refers to IE diagnosed 48 hours after admission to hospital, with no signs of IE on presentation to the hospital, or associated with any procedure within last 4 weeks.

CLINICAL FEATURES

Symptoms

Fever is the most common symptom seen in > 90% of the patients. It can be low grade in the beginning of acute IE or in subacute IE. Other symptoms include chills, night sweats, weight loss, malaise, myalgia, abdominal pain, cough, shortness of breath, and pleuritic chest pain.

Signs

New cardiac murmur is the most common sign present in endocarditis. Cardiac murmurs are heard because blood regurgitates through a damaged or perforated valve.

Vascular lesions of IE typically present as petechiae on skin or mucosal surfaces and should be specifically looked for. Subungual, dark linear streaks (splinter hemorrhages) can be seen, likely representing an embolic phenomenon. Janeway lesions are nontender, erythematous macules on palms or soles. Histologically, they are microabscesses with neutrophil infiltration due to embolism.

Osler nodes are tender, subcutaneous, violaceous nodules on distal finger and toe pads.

Roth spots are exudative, edematous hemorrhagic lesions of the retina with a pale center.

Splenomegaly can be seen in patients with subacute IE.

The source of bacteremia should be identified and eradicated if possible. This

includes careful dental examination and diagnosis of ongoing periodontal disease.

ELECTROCARDIOGRAM (ECG) AND LABORATORY STUDIES

New conduction abnormalities (like atrioventricular block, bundle branch block, or complete heart block) can be seen on ECG due to bacterial invasion and involvement of the paravalvular area.[10] Uncommonly, coronary embolic phenomena can manifest as acute myocardial ischemia.

Routine laboratory findings are nonspecific for endocarditis but reflect an ongoing inflammation. These include leukocytosis, anemia, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), hypergammaglobulinemia, hypocomplementemia, and positive rheumatoid factor. Glomerular damage due to circulating immune complexes results in microscopic hematuria and proteinuria; occasionally, full-blown glomerulonephritis can be seen.

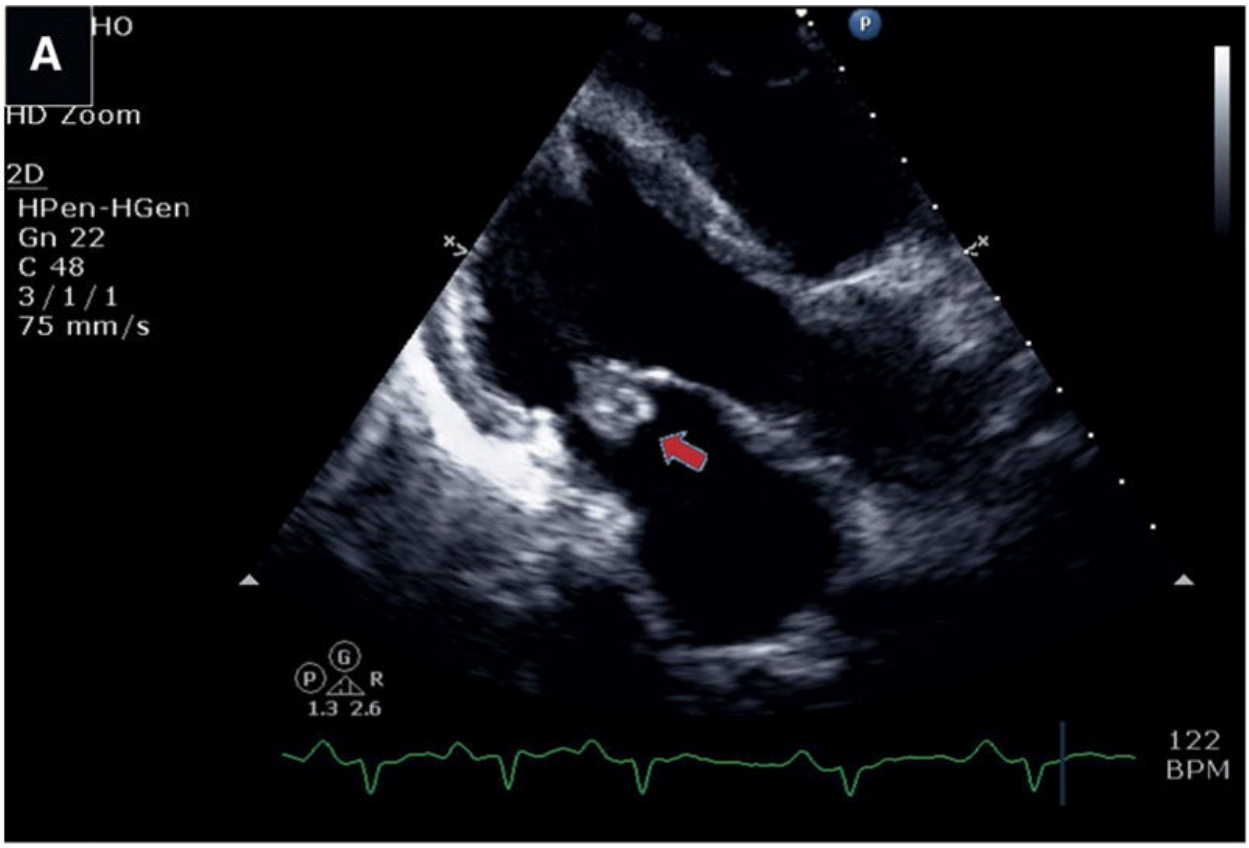
Noncardiac imaging studies such as X-rays, CT scans, and MRI can be useful in evaluating embolic phenomena due to IE (including strokes, abdominal organ infarcts, septic lung emboli, etc.) as well as exploring metastatic infection sites.

DIAGNOSIS

It is imperative to make an early diagnosis of IE because delayed initiation of treatment is associated with higher mortality and risk of embolic complications including stroke.[11] IE should be suspected in any patient with fever, bacteremia, and/or endocarditis risk factors.

In all patients suspected for IE, three sets of blood cultures should be drawn from different venipuncture sites with at least 1 hour between the first and the last sets. Transthoracic echocardiogram (TTE) should also be done as soon as possible to assess for the presence of vegetations, valvular regurgitation, and other complications of IE (**Figure 38.1**). Transesophageal echocardiogram (TEE) has a higher sensitivity for IE and its complications compared to TTE. It is recommended in all patients with suboptimal TTE images and in high-risk patients, even if TTE is negative. These include (but are not limited to) patients with suspected paravalvular involvement, prosthetic heart valves, CIED, and *Staphylococcus aureus* bacteremia without known source (**Figure 38.2**).[3,7,12]

Other cardiac imaging modalities for diagnosing IE (such as cardiac CT scan and nuclear techniques) are evolving and are supplemental at this stage.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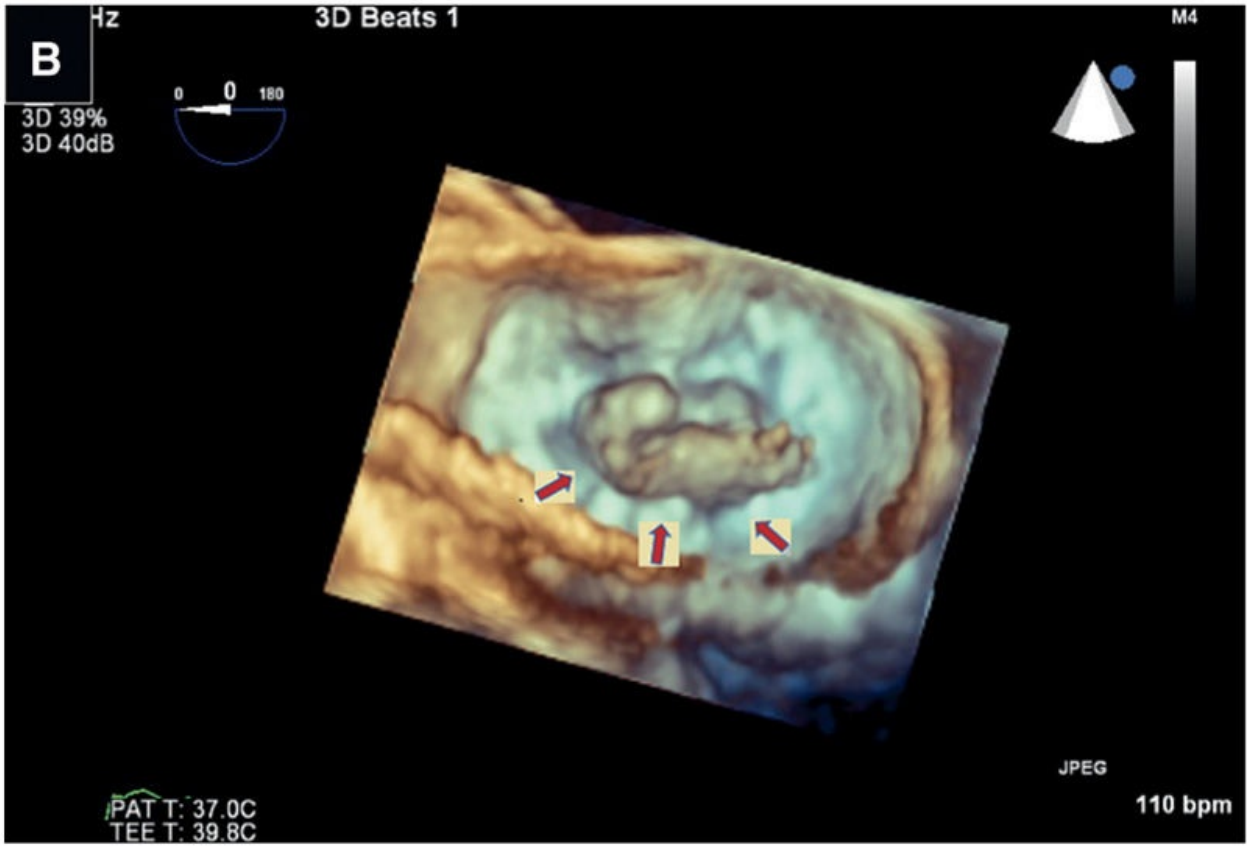
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FIGURE 38.1 A, Large vegetation (arrow) present on the mitral valve as seen on transthoracic echocardiogram. B, Three-dimensional transesophageal echocardiographic image of the same vegetation (arrows).

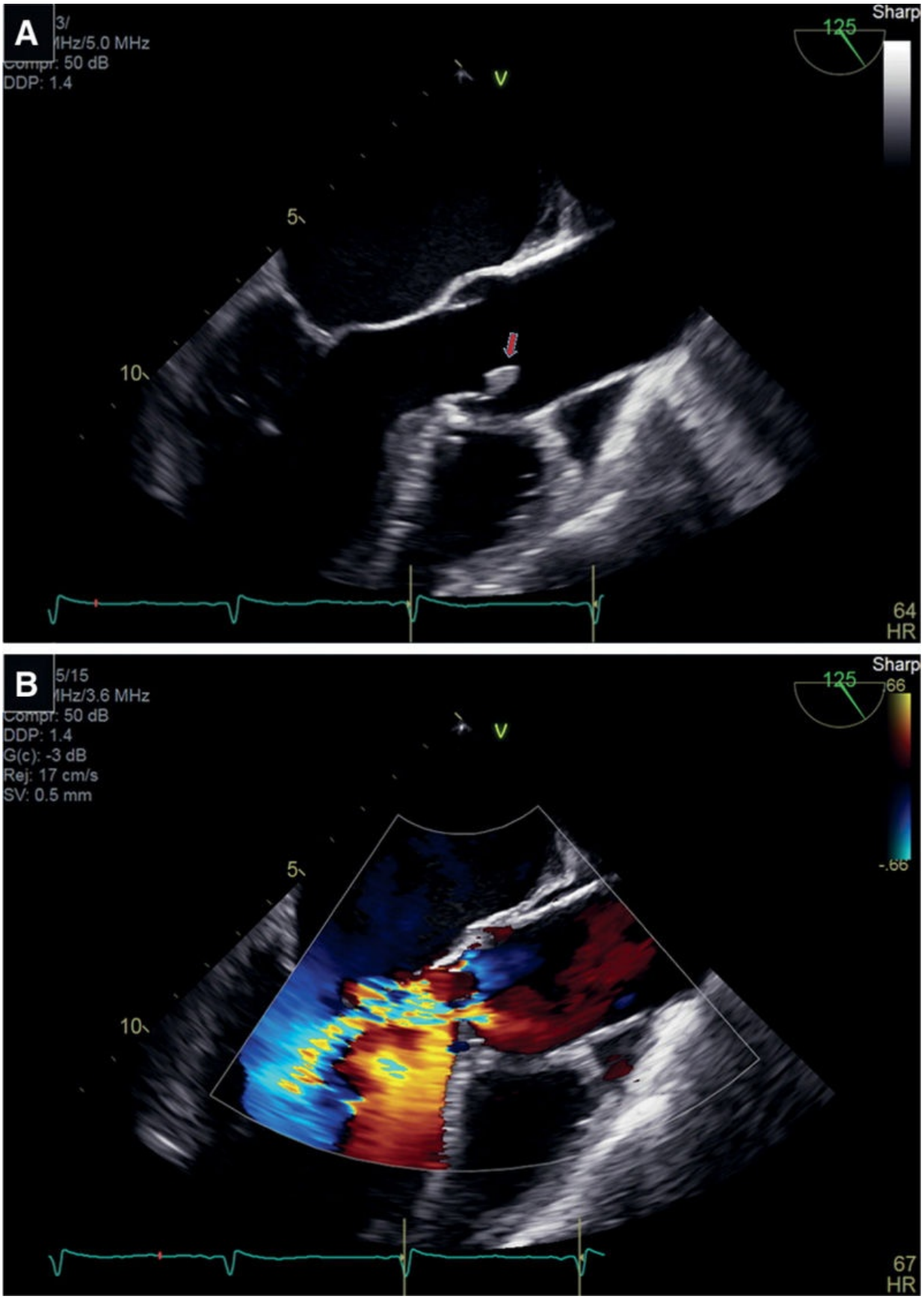
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FIGURE 38.2 A, Small round vegetation (arrow) present on aortic valve as seen on transesophageal echocardiogram. B, Color Doppler imaging shows an eccentric aortic regurgitation jet due to aortic valve damage.

MODIFIED DUKE CRITERIA

Modified Duke Criteria (see **Tables 38.2 and 38.3**)[13] use clinical, microbiologic, radiologic, and echocardiographic factors to stratify patients into definite IE, possible IE, and rejected categories. Current American Heart Association/American College of Cardiology (AHA/ACC) guidelines for IE support using Modified Duke Criteria in all patients with suspected IE.[7] These criteria have been extensively validated for left-sided native valve endocarditis. They likely have lower sensitivity for right-sided IE, prosthetic valve endocarditis, and CIED endocarditis.

TABLE 38.2 Modified Duke Criteria

Definite Infective Endocarditis

• Pathologic criteria:
  • Microorganisms demonstrated by culture or histologic examination of a vegetation that has embolized, or an intracardiac abscess specimen;
  • Pathologic lesions: vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis

• Clinical criteria:
  • 2 major criteria; or
  • 1 major criterion and 3 minor criteria; or
  • 5 minor criteria

Possible Infective Endocarditis
• 1 major criterion and 1 minor criterion; or 3 minor criteria
Rejected
• Firm alternative diagnosis; • Resolution of IE syndrome with antibiotic therapy for <4 days; • No pathologic evidence of IE at surgery or autopsy with antibiotic therapy for <4 days; • Criteria for possible IE are not met.

TABLE 38.3 Definition of Major and Minor Criteria

Major Criteria
Blood culture positive for IE

• Typical microorganisms consistent with IE from 2 separate blood cultures (*Streptococcus viridans*, *Streptococcus bovis*, HACEK group, *Staphylococcus aureus*, or community-acquired enterococci) or
• Persistently positive blood cultures defined as follows:
  • At least 2 positive cultures of blood samples drawn > 12 hours apart or
  • All 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least 1 hour apart)
  • Single positive blood culture for *Coxiella burnetii* or anti–phase I IgG antibody titer ≥ 1:800

Evidence of endocardial involvement Echocardiogram positive for IE, which is defined as follows: • Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • Abscess; or • New partial dehiscence of prosthetic valve; or • New valvular regurgitation.
Minor Criteria
Predisposition, predisposing heart condition, or intravenous drug use
Fever (temperature > 38°C)
Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor
Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with IE.

IE, infective endocarditis.

Complications of IE are common and have been shown to increase morbidity and mortality. **Table 38.4** summarizes potential IE complications.

TABLE 38.4 Complications Related to Infective Endocarditis

Cardiac • Heart failure • Conduction abnormalities • Perivalvular abscess • Pericarditis • Intracardiac fistulas • Coronary embolization	**CNS** • Embolic stroke • Mycotic aneurysm • Intracranial hemorrhage • Cerebral abscess • Meningitis
Pulmonary • Pulmonary embolism	**Renal** • Glomerulonephritis • Renal infarction
Musculoskeletal and Others • Limb ischemia • Septic arthritis • Splenic infarct	**Complications Related to Therapy** • Ototoxicity or nephrotoxicity from aminoglycoside antibiotics • Drug fever • Intravenous catheter thrombosis

CNS, central nervous system.

MANAGEMENT

Management of IE can be broadly divided into antimicrobial therapy and surgical therapy. However, given the complexity of this disease a multispecialty management approach is needed, which includes infectious disease specialist, cardiologist, cardiac surgeon, and cardiac anesthesiologist (if surgical therapy is planned).

ANTIMICROBIAL THERAPY

General Principles

It is essential that blood cultures are obtained before initiating antimicrobial therapy. Antimicrobial therapy should always be parenteral, bactericidal, and prolonged to ensure bacterial eradication. Synergistic antimicrobial agents should be used to increase the efficacy. In most cases, especially in patients who are clinically unstable, empirical, broad-spectrum antimicrobial regimen is recommended. Specific antimicrobial therapy should be substituted once the specific pathogen has been isolated from blood cultures. It is reasonable to obtain at least two sets of blood cultures every 24 to 48 hours until bloodstream infection has cleared to assess the response to the antimicrobial therapy. Duration of the therapy is usually up to 6 weeks. These days are counted from the first negative blood culture. Temporary discontinuation of anticoagulation is recommended for patients with IE, especially if complications like embolic stroke occur. It is also important to monitor patients' renal function and liver function during the treatment because antibiotic dosage needs to be adjusted according to creatinine clearance and hepatic impairment. Patients can finish their therapy as outpatients provided they are able to manage the intravenous access and follow up diligently.

Specific antimicrobial regimens have been suggested by recent 2015 American Heart Association (AHA)/Infectious Disease Society of America (IDSA) statement on IE management.[7] **Tables 38.5 and 38.6** show the recommended antibiotics regimen for the most common bacterial species —*Streptococcus viridans* or *Streptococcus bovis*, and *Staphylococcus aureus*.

Antibiotic therapy should be adjusted as necessary based on bacterial susceptibility.

TABLE 38.5 Antibiotic Regimen for Native Valve Endocarditis[7]

REGIMEN	MEDICINE	DOSAGE	DURATION	COMMENT
***Streptococcus viridans* or *Streptococcus bovis* (Highly Penicillin-Susceptible Organisms)**				
1	Penicillin G or	12–18 million units IV/day in 4 or 6 equally divided doses	4 weeks	
	Ceftriaxone	2 g/day IV/IM in 1 dose		
2	Penicillin G or	12–18 million units IV/day in 6 equally divided doses	2 weeks	
	Ceftriaxone plus	2 g/day IV/IM in 1 dose		
	Gentamicin	3 mg/kg/day IV/IM in 1 dose		
3	Vancomycin	Consider loading dose Load: 15–25 mg/kg or 25–30 mg/kg (severe infection) Maintenance: 15–20 mg/kg q8–12h (infuse each 1 g over at least 1 hour to avoid infusion-related red man syndrome)	4 weeks	Patient unable to tolerate ceftriaxone or penicillin Use actual body weight for dosing. Target trough Concentrations (before the 4th dose): >10 mg/L: always optimal to prevent resistance 15–20 mg/L: for IE dosing adjustment based on trough Nephrotoxicity and ototoxicity are rare without a concomitant offending agent.
Staphylococcus aureus				
1	Nafcillin or oxacillin	12 g/day IV in 4 or 6 equally divided in doses	6 weeks	Methicillin sensitive
2	Cefazolin	6 g/day IV in 3 equally divided doses	6 weeks	For nonanaphylactic penciling allergy
		Consider loading dose Load: 15–25 mg/kg or		Methicillin resistant Use actual body weight for dosing. Target trough Concentrations (before the 4th dose):

3	Vancomycin	25–30 mg/kg (severe infection) Maintenance: 15–20 mg/kg q8–12h (infuse each 1 g over at least 1 hour to avoid infusion related red man syndrome)	6 weeks	>10 mg/L: always optimal to prevent resistance 15–20 mg/L: for IE Dosing adjustment based on trough Nephrotoxicity and ototoxicity are rare without a concomitant offending agent.

TABLE 38.6 Antibiotic Regimen for Prosthetic Valve Endocarditis[7]

REGIMEN	MEDICINE	DOSAGE	DURATION	COMMENT
***Streptococcus viridans* or *Streptococcus bovis* (Highly Penicillin-Susceptible Organisms)**				
1	Penicillin G or	24 million units IV/day in 4–6 equally divided doses	6 weeks	
	Ceftriaxone With or without	2 g/day IV/IM in 1 dose		
	Gentamicin	3 mg/kg/day IV/IM in 1 dose	2 weeks	
2	Vancomycin	Same as above	6 weeks	Patients unable to tolerate ceftriaxone or penicillin
Staphylococcus aureus				
1	Nafcillin plus	12 g/day IV in 6 equally divided doses	≥6 weeks	Methicillin sensitive
	Rifampin plus	900 mg/day IV in 3 equally divided dose		
	Gentamicin	3 mg/kg/day IV/IM in 2–3 equally divided doses	2 weeks	
2	Vancomycin plus	Same as above	≥6 weeks	Methicillin resistant
	Rifampin plus	900 mg/day IV in 3 equally divided dose		
	Gentamicin	3 mg/kg/day IV/IM in 2–3 equally divided doses	2 weeks	

HACEK organisms are gram-negative fastidious bacilli that grow very slowly on standard blood culture media.[3] Patients with HACEK endocarditis should be treated with intravenous ceftriaxone, ampicillin, or ciprofloxacin for 4 weeks.

Fungal endocarditis is rare and most commonly due to *Candida* or *Aspergillus* species. Current guidelines recommend two-phase antimicrobial treatment with surgical management. The first phase involves intravenous antifungal therapy for 6 weeks followed by the second long-term suppressive period with oral antifungal medications.

SURGICAL THERAPY

The basic principle of surgical therapy is to debride infected and nonviable tissue, as well as to reconstruct the involved cardiac area and restore the competency of the damaged valve. Although randomized control data are limited, single-center observational studies show the decrease in in-hospital mortality and embolic complications with early surgery in selected patients with IE.

Early surgery (during initial hospitalization) is indicated in IE patients with signs or symptoms of heart failure due to valve dysfunction, endocarditis caused by highly resistant organisms such as fungi, and intracardiac complications of IE causing abscess or heart block. Persistent bacteremia despite appropriate antimicrobial treatment is also an indication for surgery. Surgery is considered with recurrent embolic events and persistent vegetations despite antimicrobial therapy and in patients with large mobile vegetations.[12,14]

Right-sided endocarditis carries better prognosis with antimicrobial therapy compared with left-sided endocarditis, but can also require surgical intervention. Valve replacement should be avoided in intravenous drug users given the risk of subsequent device infection with continued intravenous drug use. Valve repair rather than replacement should be performed when feasible for right-sided endocarditis.[7]

CIED endocarditis: In patients with CIED endocarditis, retained hardware (generator and leads) can lead to higher rate of infection relapse. Complete device and lead removal are recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis. Any patient with occult staphylococcal bacteremia or with persistent occult gram-negative bacteremia despite appropriate antibiotic therapy should also be considered for device explant. Current AHA/Heart Rhythm Society (HRS) guidelines recommend at least 14 days of antibiotics before reimplantation. Reimplantation of CIED should be done on the contralateral side.[6]

INFECTIVE ENDOCARDITIS PROPHYLAXIS

Revised 2007 AHA guidelines[15] recommend IE prophylaxis for patients with cardiac conditions associated with the highest risk of adverse events: patients with a prosthetic valve (including bioprosthetic valves); patients with previous history of IE; patients with unrepaired cyanotic congenital heart disease (including patients who underwent palliative procedures); patients with repaired congenital heart disease with residual defect at the site of prosthetic material; patients with completely repaired congenital heart disease with prosthetic material (first 6 months after the procedure); and cardiac transplant recipients with valvular disease.

Antibiotic prophylaxis is recommended only for dental procedures that involve manipulation of the gingival tissues, periapical region of teeth, or perforation of oral mucosa as well as procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue. Antibiotic prophylaxis is not recommended for genitourinary or gastrointestinal tract procedures unless there is an ongoing infection. Recommended prophylaxis regimens are listed in **Table 38.7**.

TABLE 38.7 Infective Endocarditis Prophylaxis Regimen[15]

SITUATION	MEDICATION	DOSE (SINGLE DOSE 30 TO 60 MIN BEFORE PROCEDURE)
Oral	Amoxicillin	2 g po
Unable to take oral medication	Ampicillin or	2 g IM/IV
	Cefazolin or ceftriaxone	1 g IM/IV
Allergic to penicillin—oral	Cephalexin or	2 g po
	Clindamycin or	600 mg po
	Azithromycin or clarithromycin	500 mg po
Allergic to penicillin—not able to take oral medication	Cefazolin or ceftriaxone or	1 g IM/IV
	Clindamycin	600 mg IM/IV

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Patient and Family Information for: INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) refers to infection of the inner lining of the heart or heart valves. IE, if not diagnosed and treated early, could lead to death and/or grave complications.

CAUSES AND RISK FACTORS

The highest incidence of IE has been noted in individuals over 60 years of age. IE is more common in patients with preexisting heart valve disease or structural heart disease. These could be congenital (present since birth) or acquired during the lifetime. Diabetes, HIV, or any low-immunity state decrease the body's ability to fight infection and are associated with increased IE risk. Poor dental hygiene, external catheters, frequent dialysis, and intravenous drug abuse can directly introduce bacteria to bloodstream, which can result in heart valve infection. At last, bacteria can easily attach to any foreign material in the body, like a prosthetic valve or pacemaker lead, and cause infection.

HOW DOES INFECTIVE ENDOCARDITIS DEVELOP?

Bacterial invasion to the bloodstream due to various reason, is usually the first step of the IE. Next, bacteria get attached to the damaged heart tissue, prosthetic valve, or pacemaker lead. Some aggressive strains of bacteria can infect structurally normal heart valves as well. Finally, bacteria grow and cause damage to the surrounding heart tissue. Bacterial growth leads to development of vegetation, an infected tissue attached to the inner lining of the heart, heart

valves, or foreign material (like a pacemaker lead). Further spread of the infection can lead to heart tissue destruction and pus accumulation (abscess).

SIGNS AND SYMPTOMS

Most common symptoms include fever, chills, night sweats, weight loss, shortness of breath, fatigue, or chest pain. The physician can hear a heart murmur due to blood leakage through the damaged valves. Vegetations that have developed due to IE can break off and obstruct the blood supply to other organs; stroke is a well-known complication of IE.

DIAGNOSIS

Blood culture and ultrasound imaging of the heart (echocardiogram) are the two most important tests for diagnosis of IE. Several blood cultures are collected from the patient and repeated after treatment is started to document clearance of the infection. Echocardiogram should be done as soon as possible if IE is suspected. Other imaging studies like CT scan or MRI of the head, chest, or abdomen may also be necessary to rule out other organ involvement or distant spread of infection.

COMPLICATIONS

Heart valve malfunction, congestive heart failure, and abscess formation are known complications of IE. IE can also cause a stroke. Infection can spread outside the heart causing pus collection in different organs including the spine.

TREATMENT

IE management usually needs a multi-pronged approach with the help of infectious disease specialists, cardiologists, and cardiac surgeons. Proper antibiotic therapy and surgery in appropriate cases are the key for successful management of IE. Antibiotics should be started early but typically after the

blood cultures are drawn. The antibiotic therapy is tailored to specific bacterial species cultured from the blood. Any primary source of infection and infected foreign material should be identified and treated. The antibiotic therapy is usually prolonged and intravenous.

Many patients with IE are considered for early surgical intervention. These include but are not limited to patients with heart valve damage causing heart failure or heart abscess formation. Damaged valves may need to be replaced during the surgery. Cardiac surgery is usually a high-risk procedure in this situation but provides the best chance for recovery. The infected pacemaker and leads should be removed.

PROPHYLAXIS

Prophylactic antibiotics are recommended for patients who are at the highest risk of developing IE, including patients with prior IE, some types of congenital heart disease, patients with a prosthetic heart valve, and heart transplant patients with valve disease. Only certain procedures require antibiotic prophylaxis (such as invasive dental procedures or procedures on infected skin). Typically, the prophylaxis consists of a single dose of oral antibiotic given 30 to 60 minutes before the procedure.

39

Chetan Huded
Samir Kapadia

Percutaneous Therapy for Valvular Heart Disease

INTRODUCTION

Patients with both acute and chronic presentations of severe valvular heart disease are frequently encountered in the intensive care setting due to heart failure and cardiogenic shock. In these patients, medical therapy can reduce symptoms of congestion and optimize their hemodynamic state, but an interventional or surgical approach to correct the valvular lesion is often required for a durable solution. Many intensive care patients are poor candidates for open heart surgery due to comorbidities. Some high-risk patients who are not surgical candidates may benefit from percutaneous interventions. Over the past decade, percutaneous interventions for valvular heart disease have rapidly expanded such that many patients can be successfully treated without an open surgical approach. Additionally, a minority of stable patients who undergo percutaneous valvular therapies on an elective basis will require intensive care in the immediate postprocedure period for monitoring and treatment of procedural complications. For these reasons, the practice of modern critical care cardiology requires an in-depth understanding of percutaneous therapies for valvular heart disease.

BALLOON AORTIC VALVULOPLASTY

Severe aortic stenosis (AS), defined as an aortic valve area < 1.0 cm^2 with mean aortic valve gradient > 40 mm Hg and peak aortic valve velocity > 4.0 m/s, manifests with symptoms of heart failure, syncope, and angina. Occasionally, severe AS results in cardiogenic shock. Medical therapy in patients with severe AS is challenging due to the balance necessary between adequate preload and afterload in the setting of a severe obstruction to left ventricular outflow. Patients treated with medicines alone without subsequent aortic valve replacement (AVR) have a very poor prognosis. In the Placement of Aortic Transcatheter Valves (PARTNER) trial, the 1-year survival of medically treated patients with severe AS was only 50%.[1] Interestingly, at 5 years all except one patient died on medical management including aortic valvuloplasty without aortic valve replacement.[2]

For over two decades, before availability of transcatheter aortic valve replacement (TAVR), balloon aortic valvuloplasty (BAV) was the only percutaneous therapy for severe AS. BAV was developed in the 1980s and initially suggested as an alternative to surgical aortic valve replacement (SAVR), but was quickly recognized as inadequate therapy due to inadequate increase in aortic valve area and almost certain restenosis within a few months.[3] BAV is performed by obtaining percutaneous femoral artery access and passing a wire retrograde across the aortic valve and into the left ventricle. A balloon advanced over the wire across the aortic valve is then inflated inside the aortic valve with the aim of disrupting calcific deposits within the valve and reducing the severity of AS. BAV can also be performed antegrade via femoral venous access and transseptal puncture across the interatrial septum in patients with insufficient iliofemoral arterial anatomy for the conventional retrograde approach. In most patients treated with BAV, the mean aortic valve gradient by transthoracic echocardiogram decreases by 50% and the aortic valve area significantly increases by 0.2 to 0.5 cm^2.[4] BAV can generally be performed with moderate rates of major complications. Procedural mortality ranges from 1% to 5% and is typically a result of aortic regurgitation while 30-day mortality ranges from 6% to 10% and is a consequence of heart failure among other comorbid conditions. Vascular complications occur in 1% to 2% of cases in modern practice. Despite favorable hemodynamic results in the early postprocedure period, many patients suffer from recurrent severe AS after BAV. Between 24% and 76% of patients

have been found to have restenosis of the aortic valve within 6 months after BAV, and some reports have shown restenosis as early as 2 hours after BAV.[5] Long-term outcomes after BAV without subsequent AVR are poor and similar to those of patients with severe AS treated medically. The probability of freedom from death or AVR at 1, 2, and 3 years after BAV is 40%, 19%, and 6%, respectively in a historical series.[6]

In the modern era of TAVR, BAV has been performed with increasing frequency as bridging therapy before TAVR. Between 1998 and 2010, the use of BAV increased by 158% corresponding to the advent of TAVR during that period.[7] However, even in the modern era the long-term outcomes after isolated BAV remain poor with high rates of recurrent AS and death in patients who are not treated with subsequent valve replacement. The survival of patients undergoing BAV alone remains significantly worse compared with patients who undergo BAV as a bridge to eventual TAVR. BAV may be considered as a bridging therapy in patients with severe AS admitted to the intensive care unit with heart failure, respiratory failure, or cardiogenic shock refractory to medical therapy. BAV is most useful in patients with a temporary contraindication to AVR (sepsis, multisystem organ failure, ventilator-dependent respiratory failure, coagulopathy, etc.) or in patients in whom the contribution of AS to their symptoms is uncertain. In these cases, BAV may offer a window to achieve cardiopulmonary stability or symptom improvement that may allow for bridging to subsequent AVR. BAV without plans for subsequent AVR is not a definitive therapy for severe AS and should be considered palliative.[4,8,9]

TRANSCATHETER AORTIC VALVE REPLACEMENT

In the past decade, TAVR has revolutionized the care of AS patients because it has become an established alternative to SAVR in patients with severe AS who are at more than low surgical risk (**Figure 39.1**).[10] “High risk” for SAVR is commonly defined as a Society of Thoracic Surgeons predicted risk of operative mortality (STS PROM risk score) of 8% to 15%, unsuitable anatomy for open surgery such as porcelain aorta or prior chest radiation, or significant frailty.[11] Most patients considered for TAVR are elderly with the mean age of participants in TAVR clinical trials being over 80 years of age.[1,12,13] Patients considered for TAVR often have multiple comorbidities that may have important implications

on prognosis. For this reason, patient selection is the most important aspect of a successful TAVR program. Careful clinical and geriatric risk assessment including frailty by a comprehensive heart valve team is the standard of care before TAVR in order to select patients with an anticipated benefit in terms of symptoms and longevity. The heart valve team approach to selecting patients for TAVR carries a class I indication in the most recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.[11] Clinical risk stratification is typically performed using risk scores designed for cardiac surgery populations (STS PROM risk score or Euroscore), but it is important to recognize that these risk scores do not assess certain factors unique to TAVR, such as aortic annulus sizing, iliofemoral vascular anatomy, and coronary ostia height, among others. Risk prediction tools specific for TAVR have been proposed but have not yet been widely adopted.[14,15] In general, TAVR should not be performed in patients with a life expectancy of <12 months due to a competing noncardiac condition. Attention to risk factors such as frailty, cognitive performance, and functional status is important to select patients with the greatest anticipated benefit from TAVR. Although TAVR has conventionally been applied to patients with degenerative calcific AS of a tricuspid aortic valve, it has been used effectively in carefully selected cases of severe bicuspid AS, aortic regurgitation, and within failed prior SAVR bioprosthesis as a so-called valve-in-valve TAVR.

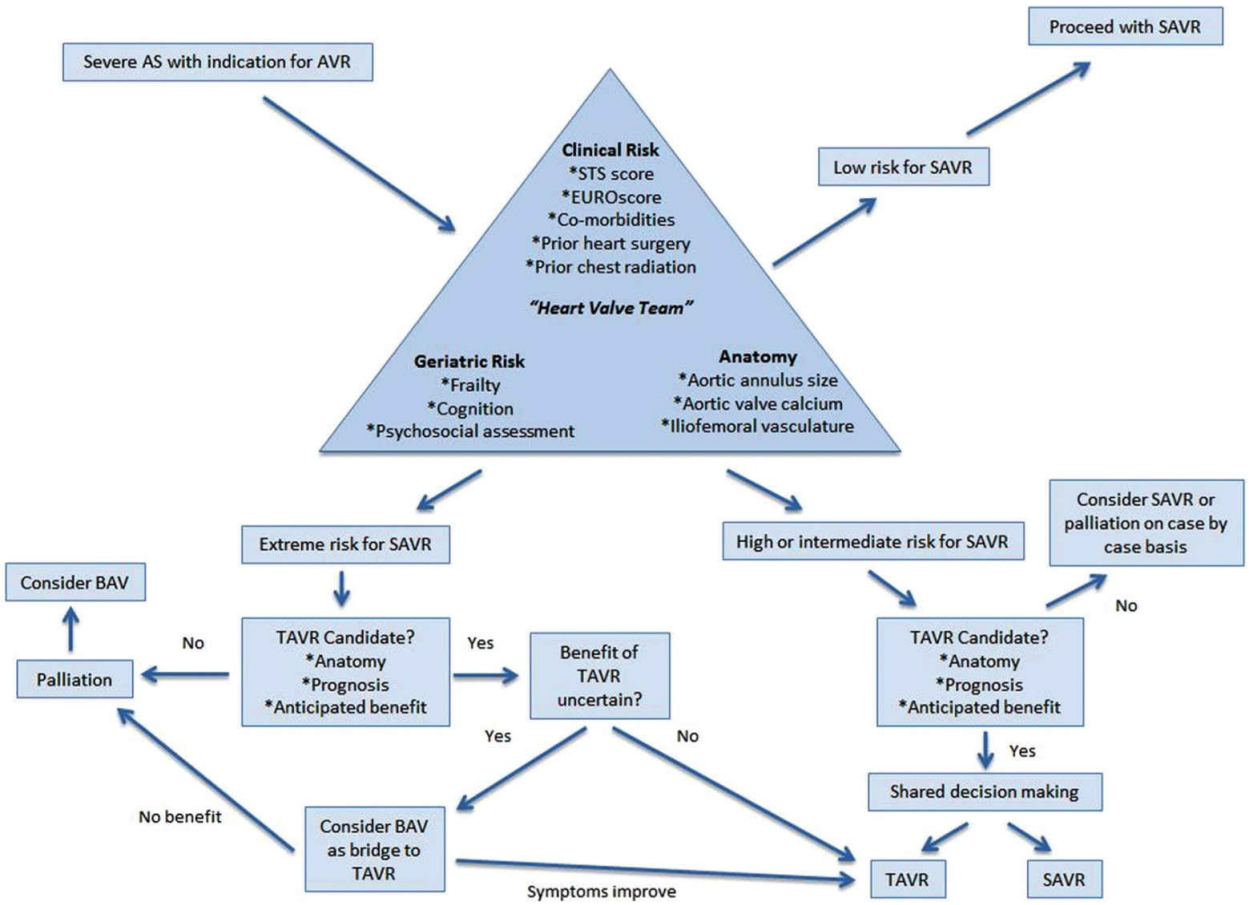

FIGURE 39.1 Decision algorithm for the interventional management of severe aortic stenosis. AS, aortic stenosis; AVR, aortic valve replacement; BAV, balloon aortic valvuloplasty; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

In the United States, there are two TAVR systems commercially approved by the Food and Drug Administration (FDA) and a number of other devices currently available in clinical trials. The Edwards Sapien 3 valve[1] (Edwards Lifesciences, Irvine, CA) and the Medtronic Evolut R[16] (Medtronic, Minneapolis, MN) are the predominant TAVR platforms used in contemporary practice. Both are FDA approved for use in patients with extreme risk or high risk for SAVR. The Edwards S3 and Sapien XT valves have recently gained FDA approval in intermediate risk patients as well. However, prior generations of these valves (the Edwards SAPIEN XT valve and the Medtronic CoreValve, respectively) have only limited applications in modern practice. During TAVR, a bioprosthetic stent-mounted valve is deployed through a transcatheter system within the native aortic valve annulus (**Figure 39.2**). Unlike SAVR in which the native aortic valve is excised and replaced, during TAVR the leaflets of the native aortic valve remain in situ and are pushed aside during valve deployment.

Edwards S3 valves are “balloon expandable” valves (BEV), which are bovine tissue valves deployed by inflation of a balloon mounted within the valve. The Medtronic system is a porcine tissue valve that is a “self-expandable” valve (SEV) that does not require balloon inflation. BEV and SEV have distinct advantages and disadvantages, but most TAVR centers have experience with both systems. BEV may be better suited for patients at risk for paravalvular leak (eccentric aortic valve annulus, heavy annular calcification, high left ventricular outflow tract to aorta angulation), whereas SEV may be better in patients at risk for coronary occlusion during TAVR due to low clearance of the coronary ostia.[10] Only one randomized controlled trial has directly compared outcomes of the Edwards SAPIEN XT valve and the Medtronic CoreValve.[17] In 241 patients randomized 1:1 to the Edwards SAPIEN XT and the Medtronic CoreValve, the Edwards SAPIEN XT valve group had a higher rate of successful device implantation, lower rate of aortic regurgitation, and lower rate of permanent pacemaker implantation. Despite these differences, mortality at 30 days was similar between the two groups.

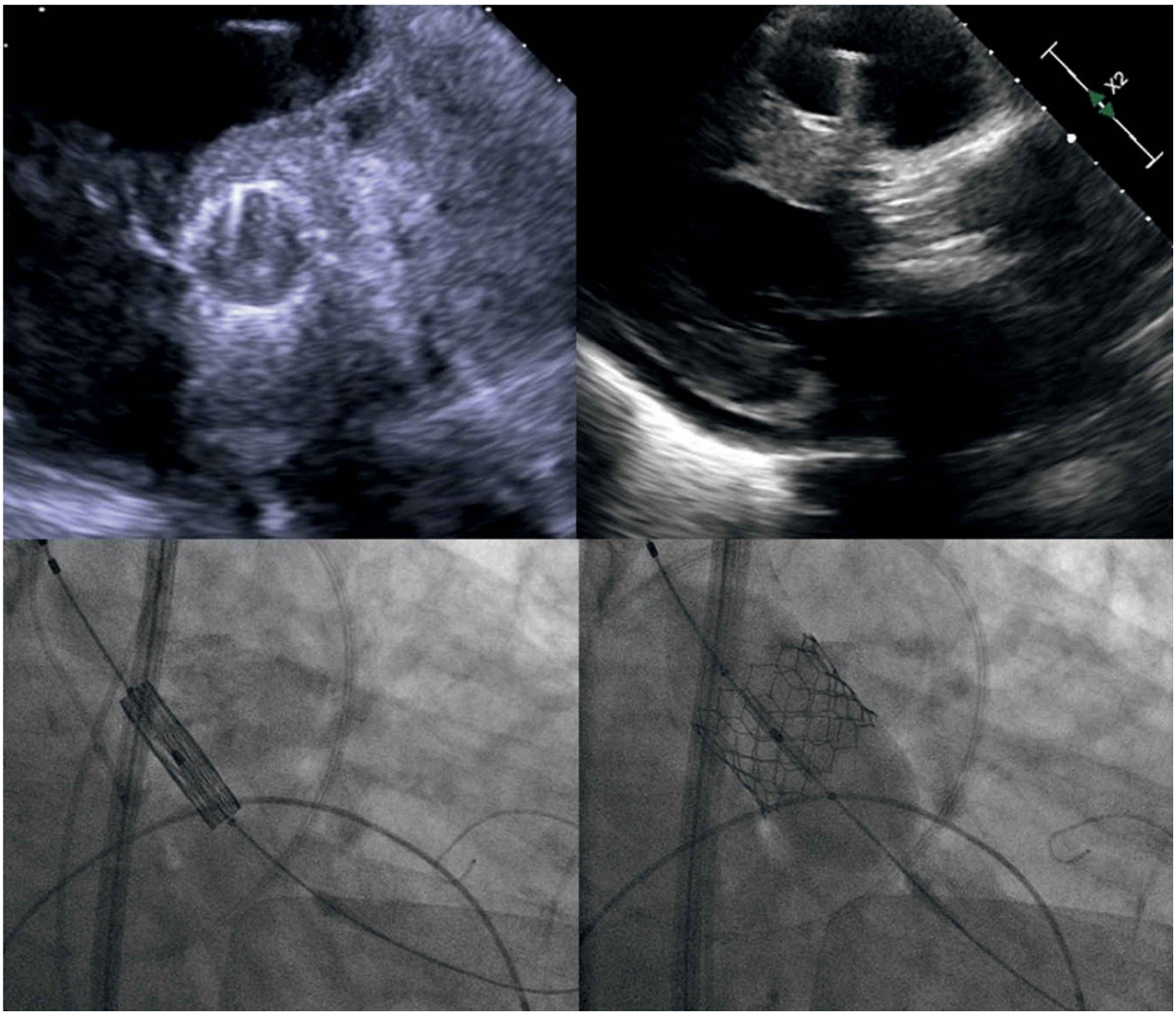

FIGURE 39.2 Echocardiography and fluoroscopy of the transcatheter aortic valve. Caval-aortic implantation of an Edwards transcatheter aortic valve for severe aortic stenosis. Top left—short-axis view of the Edwards valve by echo. Top right—long-axis view of the Edwards valve by echo. Bottom left—fluoroscopy of the Edwards valve before deployment. Bottom right—fluoroscopy of the Edwards valve during deployment with the balloon fully expanded.

Most TAVR procedures (almost 90%) are performed these days by percutaneous femoral artery access ("transfemoral TAVR"), which does not require routine surgical cut-down to expose or repair the femoral access site. However, in the minority of patients in whom the iliofemoral vessels are inadequate to accommodate a percutaneous TAVR (minimal lumen area < 6 mm^2), TAVR can be successfully performed using surgical access via the ascending aorta ("transaortic TAVR") or the left ventricular apex ("transapical TAVR"). Carotid artery and axillary/subclavian artery access for TAVR with a

surgical arterial exposure and repair have also been used with success. Rarely, TAVR can be performed by accessing the descending aorta via the adjacent inferior vena cava (“caval-aortic TAVR”) with percutaneous femoral vein access in patients in whom surgical access carries excessive risk and the iliofemoral arterial anatomy is inadequate to accommodate a transfemoral system. Surgical access for TAVR is associated with increased risk of adverse events, longer hospital stays, and increased short- and long-term mortality due to the more invasive nature of this procedure. Since the early days of TAVR, the proportion of cases performed by a transfemoral approach has increased substantially as the delivery sheaths have decreased from 24 French (8 mm external diameter) to 14 French (<5 mm diameter) over time.

It is critical to understand the complications of TAVR that may manifest intraprocedurally or during the index hospital stay. Intraprocedural complications such as aortic annular rupture, left ventricular perforation, valve embolization, bleeding, and vascular injury can be life threatening and require immediate attention by the procedural team including the interventional cardiologist and cardiac surgeon. However, a number of complications may develop in the immediate postprocedure period. Coronary ostia occlusion may not be immediately detected and can present as an acute myocardial infarction with chest pain, ischemic ECG changes, a major rise in cardiac biomarkers, and electrical or hemodynamic instability. Coronary occlusion is typically the consequence of the native aortic valve leaflet occluding the coronary ostia because it is pushed against the aortic annulus and aortic sinuses during deployment of the TAVR valve. However, myocardial infarction after TAVR due to underlying coronary artery disease (CAD) or coronary occlusion is exceedingly rare with rates < 0.5%.

Stroke is a feared complication after TAVR that occurs in 2% to 4% of cases. Most post-TAVR strokes occur within 5 days of TAVR and are related to manipulation of the native aortic valve, aortic arch, or aortic annulus. The risk of stroke after TAVR is similar between BEV and SEV and between femoral and nonfemoral access types.[18] Additionally, the rate of stroke after TAVR is similar to the rate of stroke in the SAVR arm of the PARTNER A trial and the SAVR arm of the CoreValve High Risk Study.[12,13] Embolic protection filter devices are currently under investigation as a way to mitigate the risk of stroke after TAVR, but these devices are not yet widely adopted for clinical use.

Paravalvular leak (PVL) after TAVR is a complication associated with increased long-term mortality. In a secondary analysis of the PARTNER trial,

patients with moderate/severe PVL after TAVR had a 35% mortality rate at 12 months compared with 22% mortality in patients with mild PVL and 16% mortality in patients with trace or no PVL (log-rank $P < 0.0001$).[19] In that study, moderate/severe PVL was an independent risk factor for all-cause 1-year mortality in a multivariate risk adjusted model. Risk factors for PVL include anatomic considerations that contribute to poor apposition of the TAVR valve with the aortic valve annulus (annulus geometry and calcification, left ventricular outflow tract–aorta angle), prosthesis undersizing, and poor valve position either too high or too low in the annulus. Although even moderate severity PVL is associated with increased mortality, the rate of significant PVL is now much less frequent with newer generation valves and increased operator experience (<5% with both the Edwards S3 valve and the Medtronic Evolut R).[20,21]

Conduction system disease is a common complication after TAVR due to the close proximity of the aortic valve annulus to the AV node and His bundle. Patients with high-grade AV block after TAVR often require critical care monitoring with a temporary pacemaker. New left bundle branch block is common after TAVR and is of uncertain clinical significance.[22] Conduction system disease requiring a new permanent pacemaker implantation within 30 days after TAVR occurs in 3% to 4% of patients treated with BEV and nearly 20% of patients treated with SEV in early trials.[1,12,16] However, pacemaker implantation rates are lower in next generation SEVs currently being tested in clinical trials.

Survival after TAVR is superior to survival among medically treated patients with severe AS and comparable to survival among SAVR in high-risk surgical patients. In large registries from the United States and Europe, mortality at 30 days after TAVR is 5% to 12% and 1-year survival is 76% to 85%.[10] TAVR valves appear to be durable without significant valve deterioration at follow-up intervals up to 5 years. Longer-term follow-up data are not widely available because of the relative youth of the procedure, although there is no evidence to date that TAVR valves are any less durable than SAVR bioprosthetic valves. This issue will merit careful scrutiny in the coming years as TAVR is tested in younger and lower-risk populations.

A recently recognized concern is the risk of leaflet thrombosis early after TAVR. During an ongoing clinical trial, a patient who suffered a post-TAVR stroke was noted to have reduced leaflet mobility of the TAVR valve by computed tomography (CT), which prompted concern that subclinical leaflet

thrombosis may be a risk factor for stroke after TAVR. In a subsequent retrospective analysis, reduced leaflet motion by CT was detected in up to 40% of patients after TAVR, although the clinical significance of this finding remains uncertain.[23] Interestingly, patients treated with therapeutic anticoagulation had return of normal leaflet motion suggesting that early anticoagulation after TAVR may reduce the risk of leaflet thrombosis. The role of anticoagulation in the post-TAVR setting is the topic of ongoing investigation in multiple clinical trials and registries.

BALLOON MITRAL VALVULOPLASTY

Severe mitral stenosis (MS) is characterized by mitral valve area < 1.5 cm^2, pressure half-time of ≥150 ms in diastole, a transmitral mean pressure gradient of > 5 to 10 mm Hg, and pulmonary hypertension by echocardiography.[11] The most common cause of hemodynamically significant MS is rheumatic heart disease. Calcific MS is increasingly recognized to be an import lesion in the United States.[24] In any event, MS is a far less common valvular lesion in the developed world compared with degenerative calcific AS. In the developing world, however, severe MS remains a prevalent cause of cardiovascular morbidity and mortality with over 15 million people affected with rheumatic heart disease annually.[25] Severe MS can be a challenging lesion to treat in the intensive care unit due to associated low cardiac output, pulmonary hypertension, pulmonary edema, and cardiogenic shock in severe cases. Additionally, patients with MS are often poorly tolerant of the increased chronotropy due to either endogenous catecholamine surge or pharmacologic therapy with chronotropic–inotropic medications. These patients often require correction of the valvular lesion to achieve cardiopulmonary stability.

Unlike BAV, percutaneous balloon mitral valvuloplasty (BMV), which was first introduced by Inoue in the 1980s, is effective and durable therapy for MS. BMV offers excellent long-term durability with survival free of cardiac death, repeat BMV, mitral valve surgery, or functional impairment of 69% at 7 years and 30% at 20 years.[26,27] Moreover, redo BMV can be performed with excellent safety and durability in patients with prior BMV who have restenosis of the mitral valve.[28,29] BMV can be safely performed with procedural mortality < 0.5% and severe mitral regurgitation in < 5% of cases.[25] In randomized

controlled trials, BMV has shown comparable rates of success and restenosis when compared with surgical commissurotomy.[30] Therefore, in the 2014 ACC/AHA guidelines on the management of valvular heart disease, BMV has a class I indication in patients with symptomatic severe MS and favorable valve morphology and a class IIa indication even in asymptomatic patients with very severe MS and favorable valve morphology for BMV.[11] These guidelines highlight the importance of patient selection by echocardiographic assessment of the mitral valve morphology. This assessment is typically performed using the Wilkins score, also termed the "splittability" score.[31] The Wilkins score incorporates echocardiographic assessment of four parameters (mitral valve leaflet mobility, leaflet thickness, leaflet calcification, and subvalvular chordal thickening), each graded on a scale of 1 to 4, creating an overall score ranging from 4 to 16. Patients with a Wilkins score ≤ 9 are most suitable for BMV, whereas those with a Wilkins score > 9 should be considered for mitral valve surgery. Contraindications for BMV include inadequate valve morphology for BMV, left atrial thrombus, severe mitral regurgitation (MR), or concomitant valvular disease or CAD that would favor open surgery over percutaneous therapy (severe tricuspid valve disease, severe aortic valve disease, or CAD necessitating bypass surgery).

During BMV, a 14 French venous sheath and a 5 French arterial sheath are placed in the femoral vessels. The procedure is performed via transseptal puncture across the interatrial septum, and the dumbbell-shaped Inoue balloon is advanced anterograde through the left atrium and across the mitral valve. The balloon is inflated from the distal (left ventricular) edge to the proximal (left atrial) edge with a designed waist in the middle portion with the aim of reducing the severity of MS by disrupting the mitral valve commissures.[30] A successful procedure is one in which the mitral valve area post-BMV is >1.5 cm^2 and the degree of MR is not more than mild.[32] Procedural complications of the BMV include cardiac perforation (up to 2%) and transient ischemic attack or stroke (2% to 3%).

PERCUTANEOUS MITRAL VALVE REPAIR

Mitral valve regurgitation is one of the most common valvular lesions encountered in the cardiac intensive care unit. The severity of MR is characterized by several echocardiographic parameters: it is considered severe in

the presence of a central MR jet > 40% of the left atrium, a holosystolic eccentric MR jet, a regurgitant volume of ≥ 60 mL, a regurgitant fraction ≥ 50%, a vena contracta ≥ 0.7 cm, and/or an effective regurgitant orifice of > 0.40 cm^2.[11] Degenerative MR (DMR), or "primary MR," is a lesion caused by valvular pathology (redundant and myxomatous leaflet tissue, endocarditis, rheumatic heart disease, and others) resulting in severe valvular regurgitation. In these patients, MR is often the primary cardiac pathology and symptoms of heart failure can be treated with successful valve repair or replacement. Additionally, observational data suggest improved survival with surgical repair compared with medical therapy in patients with severe symptomatic DMR. Contrary to DMR, functional MR (FMR) (also termed "secondary MR") is caused by failure of mitral valve leaflet coaptation due to annular dilatation or apical tethering of the subvalvular apparatus due to left ventricular enlargement. In these patients, MR is considered secondary to underlying myocardial dysfunction and treatments to improve cardiac symptoms require attention to both the MR and the underlying myocardial dysfunction. In FMR patients, surgery has not been shown to improve survival but has been used to palliate symptoms of heart failure in those who remain symptomatic despite optimal medical therapy. The role of mitral valve surgery in patients with FMR is controversial because it is not clear that the benefits of mitral valve surgery truly outweigh the risks.

Figure 39.3 depicts the decision algorithm for the interventional management of severe MR.

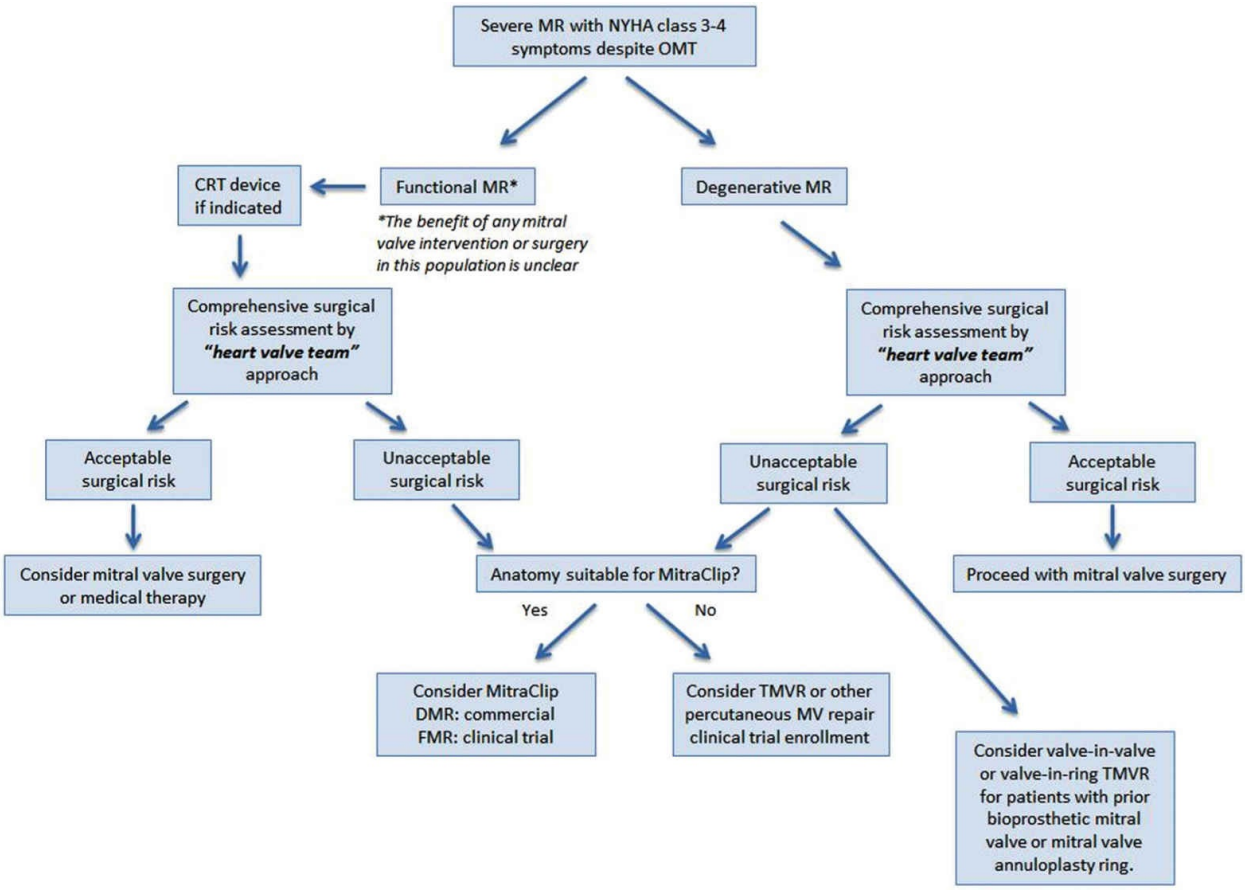

FIGURE 39.3 Decision algorithm for the interventional management of severe mitral regurgitation. CRT, cardiac resynchronization therapy; FMR, functional mitral regurgitation; MR, mitral regurgitation; NYHA, New York Heart Association; OMT, optimal medical therapy; TMVR, transcatheter mitral valve replacement.

A number of percutaneous devices for mitral valve repair have been or are currently under investigation, but the most widely adopted device is the MitraClip system (Abbott, Abbott Park, IL).[33] The MitraClip is a percutaneous approach that mimics the surgical Alfieri stitch first described in 1991. In the Alfieri stich procedure, a suture is placed between the medial scallops of the anterior and posterior mitral valve leaflets (A2 and P2 leaflets) creating a double-orifice mitral valve, which reduces the degree of MR. In the MitraClip procedure, a 24-French sheath is placed in the right femoral vein and the MitraClip device (cobalt–chromium metal alloy clip covered in polypropylene fabric) is advanced transseptally across the interatrial septum into the left atrium. Using transesophageal echocardiogram (TEE) guidance, the opened clip is positioned in the left ventricle and retracted to capture the mitral valve leaflets within the arms of the clip, and the clip is then closed (**Figure 39.4**). The degree

of MR and MS are assessed by TEE, and if the result is satisfactory the clip is released and left in place (**Figure 39.5**). The operator may reposition and regrasp the mitral valve leaflets up until the clip is released from the delivery system, but after the clip is released from the delivery system it cannot be repositioned. In about 40% of cases, two clips are needed to achieve a satisfactory result.[34]

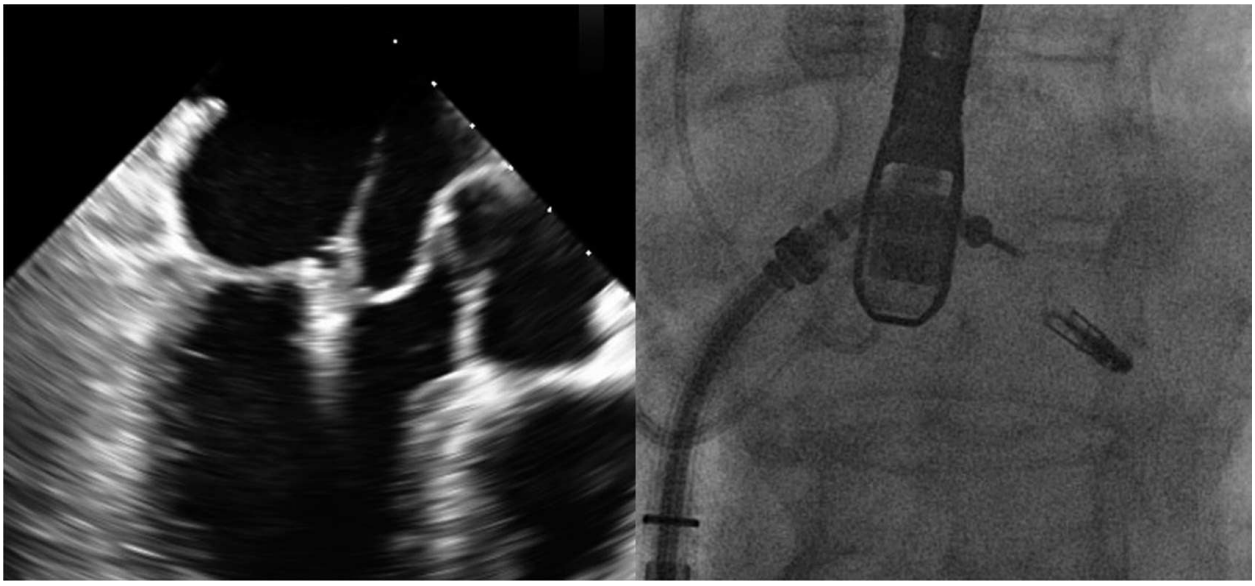

FIGURE 39.4 Echocardiography and fluoroscopy of the "MitraClip" percutaneous mitral valve repair device. Percutaneous mitral valve repair with the MitraClip device in the setting of heart failure due to severe mitral regurgitation from prolapse and flail of the posterior mitral valve leaflet. Left—Intraoperative transesophageal echo demonstrating the MitraClip device grasping the anterior and posterior leaflets of the mitral valve before deployment. Right—Fluoroscopy of the MitraClip device after deployment.

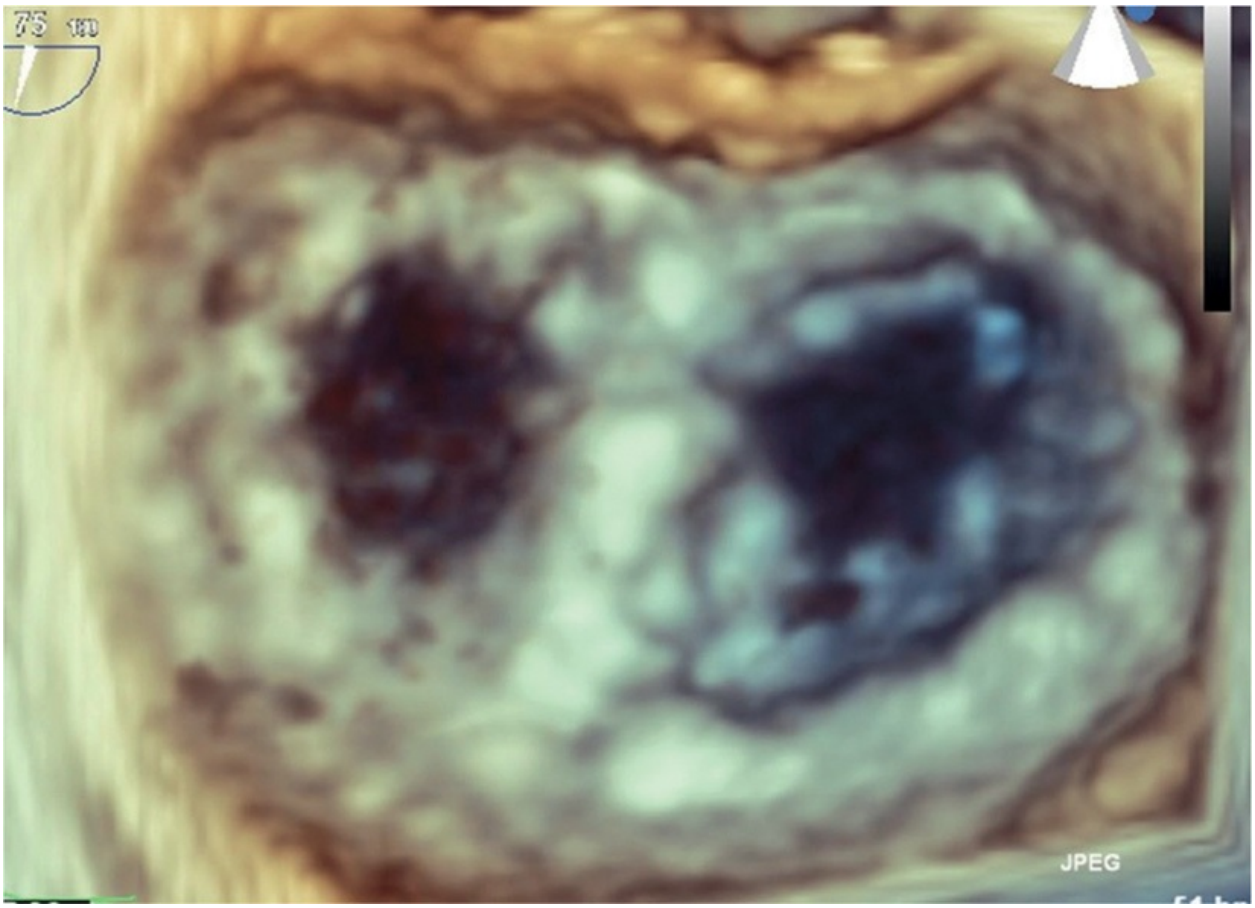

FIGURE 39.5 Three-dimensional echo of the mitral valve after percutaneous mitral valve repair with the MitraClip device. Intraoperative three-dimensional transesophageal echo of the mitral valve demonstrates the double orifice mitral valve resulting from successful percutaneous mitral valve repair with the MitraClip device.

The MitraClip is currently FDA approved in patients with severe symptomatic DMR who are deemed to have prohibitive risk to undergo mitral valve surgery. In the Endovascular Valve End-to-End Repair Study (EVEREST II), the MitraClip was compared to mitral valve surgery in 279 patients with a primary endpoint of death, mitral valve surgery, or 3+ or 4+ MR. All patients in that study were candidates for open heart surgery (inoperable patients were excluded) and most had DMR as opposed to FMR. The rate of the primary endpoint was 55% versus 73% ($P = 0.007$) at 12 months and 44% versus 64% ($P = 0.01$) in the MitraClip and surgery groups, respectively.[33,35] The difference in the primary endpoint was driven mainly by increased rates of mitral valve surgery in the MitraClip group, but mortality was comparable between arms and the rates of major adverse events were significantly lower in the MitraClip group at 12 months (15% vs 48%, $P < 0.001$). Importantly, the presence of the MitraClip did

not preclude future mitral valve surgery. The clip itself can be safely explanted during subsequent mitral valve surgery, and surgical mitral valve repair and replacement are options after MitraClip. Outcomes up to 4 years from the EVEREST II trial demonstrate equal survival in the MitraClip and surgery arms and equal rates of 3+ to 4+ MR in both arms.[36] Additionally, in the EVEREST II trial, successful MitraClip without significant residual MR was associated with improvements in quality of life and reductions in heart failure hospitalizations at 1-year follow-up in DMR patients.[37] Based on these data, the 2014 ACC/AHA guidelines give a class IIB recommendation that MitraClip may be considered in patients with severe symptomatic DMR who are not surgical candidates and have anatomy favorable for the MitraClip procedure.[11]

While the EVEREST II trial demonstrated the safety and efficacy of MitraClip in predominantly DMR patients with acceptable surgical risk, subsequent studies of the MitraClip in high-risk or inoperable patients including those with critical illness requiring inotrope therapy have demonstrated excellent procedural success rates, immediate hemodynamic improvements, and improvements in functional status.[25,38–43] Currently, the MitraClip is being compared to medical therapy in high-risk surgical patients with severe FMR and heart failure in both the Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical-Risk Patients (COAPT) trial and the Randomized Study of the MitraClip Device of Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF). As mentioned above, the role of mitral valve surgery is unclear in patients with severe FMR because there is no randomized controlled evidence of durable benefit from mitral valve surgery in these patients, and the ACC/AHA guidelines give only a class IIB recommendation that mitral valve surgery may be considered in this high-risk group.[11] The COAPT and RESHAPE-HF trials will offer important understanding of the potential benefit of mitral valve repair in high-risk surgical patients with heart failure and severe FMR.

Several other experimental percutaneous approaches to mitral valve repair are in development. Many of these other devices employ repair mechanisms distinct from the MitraClip system. For example, the Carillon device (Cardiac Dimensions, Kirkland, WA) uses an anchor mechanism placed in the coronary sinus to create an indirect percutaneous mitral valve annuloplasty while the Mitralign percutaneous annuloplasty system uses a retrograde approach across the aortic valve into the left ventricle to deliver an anchoring system directly into the mitral valve annulus from within the left ventricle. These and other devices

are currently being tested in clinical trials but have not been widely adopted in practice and remain beyond the scope of this chapter.[25,34,44]

TRANSCATHETER MITRAL VALVE REPLACEMENT

With the widespread adoption of TAVR over the past decade and its success in treating patients who were previously not candidates for AVR, there has been considerable interest in developing a transcatheter mitral valve replacement (TMVR) system. However, TMVR is far more technically challenging than TAVR for several reasons including higher-risk patient groups, larger and asymmetric valve annulus, complex subvalvular apparatus, and lack of annular calcium in many patients with severe MR that poses challenges for device anchoring. There are several TMVR devices currently in development, but these are only available in select centers on an experimental basis. Most devices were not attempted in humans until 2014 and the worldwide experience with these devices is very small to date.[25] While MitraClip and other transcatheter mitral valve repair devices can be successfully performed via a percutaneous approach, TMVR devices to date require a surgical approach with a transatrial or transapical exposure to the mitral valve. In highly selected cases of bioprosthetic mitral valve stenosis, there have been reports of placement of a TAVR device in the mitral position in a so-called valve-in-valve TMVR.[45] These valve-in-valve TMVRs have been performed with a percutaneous transseptal approach as well.[46]

TRANSCATHETER TRICUSPID VALVE INTERVENTION

Severe tricuspid regurgitation (TR) poses multiple therapeutic challenges. Most cases of severe TR are secondary to either primary right ventricular dysfunction or end-stage left-sided heart failure. Severe TR is a well-established independent risk factor for increased mortality, but the optimal treatment of severe TR remains a clinical conundrum. These patients are often quite ill and have manifestations of right-sided heart failure with peripheral edema, ascites, and congestive hepatopathy. Isolated surgical tricuspid valve repair or replacement is seldom performed due to very poor durability and outcomes in this population.[47]

There are several devices in development for transcatheter tricuspid valve

repair, but none of these is available outside of early clinical trials. A variety of mechanisms has been tested including annuloplasty systems like the aforementioned Mitralign device, direct anchor-based annuloplasty systems, and transvalvular spacing devices that anchor in the right ventricular apex. However, in-human experience with each of these devices is very small and no device appears to be close to widespread clinical use.[25,48]

Transcatheter tricuspid valve replacement has also been attempted, but most in-human experience with transcatheter tricuspid valve replacement involves valve-in-valve or valve-in-ring placement of a TAVR device or pulmonic valve device within a prior failed tricuspid bioprosthesis or tricuspid annuloplasty. Such valve-in-valve and valve-in-ring procedures are rare and only described in small case reports and series.[49–51] Transcatheter tricuspid valve replacement of a native tricuspid valve poses challenges given the ability of the tricuspid valve annulus to severely dilate under conditions of right ventricular failure. No such device is currently close to clinical use. Some centers have used "heterotropic" placement of a transcatheter valve (typically a TAVR device) in the superior and inferior vena cava to alleviate symptoms of severe TR as a palliative measure, but outcomes of this approach are limited to small observational series.[52,53]

TRANSCATHETER PULMONIC VALVE REPLACEMENT

Pulmonary valve disease is exceedingly rare in adult cardiology. Adult survivors of childhood congenital heart disease will occasionally present with pulmonic valve disease in adulthood. Those who have undergone a prior Ross procedure (replacement of the aortic valve with the patient's own pulmonary valve "autograft" and placement of a new pulmonary allograft valve) may present with a failing pulmonary bioprosthesis. Patients with repaired tetralogy of Fallot may present with stenosis or regurgitation of the reconstructed right ventricular outflow conduit. Infective endocarditis and rheumatic disease rarely affect the pulmonic valve. Other rare causes of pulmonary valve disease in adulthood include obstructive lesions due to cardiac masses or vegetation.[11]

In patients with a transpulmonary gradient > 50 mm Hg, balloon pulmonary valvuloplasty is indicated with serial balloon dilation of the pulmonic valve.[25] The maximum balloon to valve annulus ratio recommended is 1.4:1 to avoid subsequent pulmonic regurgitation. Unlike BAV, this procedure has durable efficacy with low rates of restenosis on long-term follow-up.[25,54] However, in

patients with stenotic pulmonary bioprostheses or prior conduits, pulmonic valve replacement is often required rather than balloon valvuloplasty because balloon valvuloplasty does not have durable efficacy in this setting as it does in native pulmonary valve stenosis. Cases of severe pulmonary regurgitation with right ventricular enlargement or dysfunction may also warrant pulmonary valve replacement.[25] Transcatheter pulmonary valve replacement can be performed safely and effectively with the balloon-expandable Melody pulmonary valve system or with an Edwards Sapien TAVR system.

FUTURE DIRECTION

Severe valvular heart disease is commonly encountered in the critical care setting, and the management of these patients often involves an interventional or surgical approach to achieve satisfactory long-term results. For over three decades, the only percutaneous option to treat valvular heart disease among inoperable patients was balloon valvuloplasty, but in modern practice the number of percutaneous therapies is rapidly expanding. Goals of the next generation of percutaneous devices include developing smaller profiles to expand treatment to more patients, and to reduce vascular and bleeding complications. Adjunctive therapies like embolic filter protection devices to mitigate the risk of stroke are also under ongoing clinical trial investigation. In the TAVR arena, novel devices are in development with anchoring mechanisms for patients with primary aortic regurgitation and little to no aortic annular calcium. Additionally, the adoption of TAVR in low- and intermediate-risk populations remains an area of active investigation and future promise. In the field of percutaneous mitral valve repair, the coming years will demonstrate whether this technology can improve outcomes among patients with congestive heart failure due to severe FMR. Moreover, the relatively young fields of tricuspid valve intervention and percutaneous mitral valve replacement promise substantial growth and maturation over the coming decade with several experimental devices in development in both these arenas.

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Patient and Family Information: PERCUTANEOUS THERAPY FOR VALVULAR HEART DISEASE

INTRODUCTION

The heart is a highly complex organ involving multiple systems that work together, such as the coronary arteries that supply blood flow to the heart muscle, the electrical system that coordinates each heartbeat, and the heart muscle that pumps the blood through the body. The valves of the heart are like doors between the chambers of the heart. There are four heart valves (tricuspid, pulmonic, mitral, and aortic) with two primary roles: (1) to allow blood to pass from one chamber to the next at the right time during the heartbeat; and (2) to prevent blood from flowing backward within the heart and lungs. Valvular heart disease occurs when either of these two roles of the heart valve is compromised. A valve that does not allow blood to flow forward is called “stenotic” or narrowed, whereas a valve that allows excessive amounts of blood to flow backward is called “regurgitant” or leaky. Valves with severe stenosis or regurgitation (or both) cause heart failure due to weakening of the heart muscle and fluid buildup within the heart and lungs.

SIGNS, SYMPTOMS, AND EVALUATION

Valvular heart disease can present differently in different patients. Some patients remain asymptomatic despite severe valvular heart disease, while other patients may have symptoms of chest pain, shortness of breath, passing out, or even shock. The severity of symptoms depends on how long the valvular heart disease

has been present and how well the body is able to compensate. Your doctor may find a heart murmur, engorged neck veins, fluid in the lungs, or swelling in the abdomen or legs. However, it is important to realize that some patients will have very few physical signs and symptoms of valvular heart disease and, on the contrary, not all patients with a heart murmur have severe valvular heart disease. An echocardiogram, which is an ultrasound study of the heart, is needed to study the heart valves in detail. The echocardiogram provides information on the severity of valve stenosis and regurgitation as well as the overall heart size and muscle function. In many patients, an invasive echocardiogram in which the ultrasound probe is passed into the esophagus (transesophageal echocardiogram or TEE) is needed to adequately study the heart valves. Since the ultrasound probe can be placed in closer proximity to your heart with this method, the images obtained will better elucidate the functionality of your heart valves as if having a closer look.

MEDICAL TREATMENT

Some patients with valvular heart disease can be successfully treated with medications alone. The usual goal of medical treatment is to reduce fluid buildup with diuretics (“water pills”). However, medicines cannot reverse or cure valvular heart disease in most cases. Treatment of high blood pressure and other underlying heart conditions such as CAD and arrhythmias can also help the heart valve function and to reduce symptoms because the various systems of the heart all work in concert with each other. In patients with severe valvular heart disease who have symptoms despite medications, a procedure to correct the valve problem may be needed.

HEART SURGERY

A cardiac surgeon can repair or replace a diseased heart valve in patients who can safely undergo the operation without excessive risk. In the hands of an experienced cardiac surgeon, valve repair and replacement can be performed safely and with outstanding long-term improvements in symptoms. When valve replacement is performed, either a tissue valve or a mechanical valve may be selected on the basis of a discussion between the patient and surgeon after

weighing the pros and cons in each case. In some forms of valvular heart disease, heart surgery is a lifesaving procedure. However, in other patients, heart surgery carries a very high risk of complications such as major bleeding, stroke, heart attack, or death. Risk factors for heart surgery complications include weak heart function, advanced age, prior heart or chest surgery, prior chest radiation, obesity, and severe disease of other organs such as the lungs, kidney, or liver. For patients in whom heart surgery carries an unacceptable risk of a major complication, the only option may be a less invasive procedure.

PERCUTANEOUS INTERVENTION

In select patients, a cardiologist and cardiac surgeon can perform a percutaneous valve procedure. Percutaneous means that the procedure can be performed through the blood vessels by a small puncture made through the skin, so open heart surgery is not needed. Not everyone is a candidate for this type of procedure due to certain factors related to each patient's anatomy and the valve involved. Your doctor may perform testing including echocardiogram, CT scan, MRI, or heart catheterization to determine whether a percutaneous intervention will be possible. In most centers, a heart valve team including imaging cardiologists, interventional cardiologists, cardiac surgeons, nurses, and coordinators will review each case to determine whether a percutaneous heart valve procedure is possible. Currently, percutaneous interventions are commonly used for AVR and mitral valve repair. In select centers, other valve procedures such as pulmonic valve replacement, mitral valve replacement, tricuspid valve repair, and tricuspid valve replacement may be possible. Additionally, balloon valvuloplasty, which is a procedure in which a stenotic valve is opened with a balloon but the valve is not repaired or replaced, is widely available in many centers and has been used for over three decades. Percutaneous valve procedures usually have a lower risk of major complications compared with heart surgery, and may be a better option for patients who cannot undergo heart surgery due to the risk of the procedure.

WHAT TO EXPECT

Percutaneous valve procedures are typically performed in an operating room or a

cardiac catheterization suite. Some percutaneous valve procedures require general anesthesia while others can be performed safely with mild sedation. A TEE may be used during the procedure to help the physician performing the procedure visualize the valve in real time. Most, but not all, percutaneous valve procedures are performed by puncture of the artery and/or vein in the groin area. The doctor will place a sheath, which is a tube through which equipment can be passed, in the groin vessels using a needle and a thin wire as a guide. The sheath can range anywhere from 5 mm in diameter to almost 9 mm in diameter. Multiple sheaths may be used for one procedure. Some valve procedures require the placement of a temporary pacemaker during and/or immediately after the procedure. These procedures usually take 1 to 2 hours. Most patients who do require general anesthesia can have the endotracheal breathing tube removed at the end of the procedure. The puncture site in the leg is repaired with sutures and several hours of bedrest are often needed immediately following the procedure to prevent bleeding complications at the puncture site. A 3- to 5-day hospital stay is common after a percutaneous procedure and varies depending on each patient’s unique needs. After a percutaneous aortic valve replacement, some patients require placement of a permanent pacemaker. A few patients, especially elderly adults, may require a short stay in rehabilitation after a valve procedure, but most patients are discharged home directly. Serious procedural complications include heart attack, stroke, death, or need for an emergency surgery. Each of these complications arise in typically < 5% of cases. More common complications include bleeding or injury to a blood vessel that may require a surgical repair afterward.

40

Joanna Chikwe
Henry Tannous

Contemporary Surgical Approach to Valvular Disease

AORTIC VALVE SURGERY

PATHOPHYSIOLOGY OF AORTIC STENOSIS

Morphology

Calcium is deposited in the collagen framework of abnormal leaflets due to the shear stresses occurring with each cardiac contraction. Eventually, the aortic valve becomes a lumpy, rigid structure with a tiny orifice, with calcification extending down the membranous septum and over the ventricular surface of the anterior mitral valve leaflet. Approximately 1% to 2% of people have a congenitally bicuspid aortic valve (right and left cusp fusion is present in more than 80% of patients with bicuspid valves).[1] Shear stresses in bicuspid valves are greater and they tend to calcify decades earlier than trileaflet valves. Rheumatic disease causes fibrous leaflet thickening, rolled leaflet edges, and fusion of commissures, and eventually also results in accelerated calcific changes.

Structural and Functional Changes

The average decrease in the stenotic aortic valve is 0.1 cm^2/y. This occurs faster in degenerative and bicuspid stenosis than in rheumatic stenosis.[1] Major

hemodynamic compromise does not occur until the valve is reduced to less than half the normal aortic valve area of 3 to 4 cm^2; beyond this, left ventricular (LV) outlet obstruction rapidly increases.[2] Turbulent flow in the ascending aorta may cause poststenotic dilatation. The left ventricle hypertrophies in response to outlet obstruction. The number of myocytes is fixed: hypertrophy is an increase in myofibrils, causing existing myocytes to become thicker. Concentric hypertrophy occurs in response to pressure overload seen in aortic stenosis (AS); and eccentric hypertrophy occurs in response to volume overload, for example, aortic insufficiency (AI). Concentric hypertrophy maintains ventricular volume. There is also an increase in interstitial collagen, but not much fibrosis. Initially hypertrophy (increase in LV mass from 150 g to up to 300 g) allows generation of the high interventricular pressures required to maintain LV ejection fraction and cardiac output through the stenotic lesion, despite gradients > 100 mm Hg: this is compensated AS. Eventually, hypertrophy cannot compensate for increased wall stress, and the left ventricle thins, dilates, and ejection fraction falls: this is low-gradient low-ejection fraction (also known as low-gradient low-flow) AS.

Systolic Function

In compensated AS, ejection fraction is preserved. Decompensated AS (low gradient, low flow) occurs when systolic function declines as a result of chronic afterload mismatch. The transvalvular gradient falls because cardiac output decreases, even though the valve stenosis is unchanged or worse.[2,3]

Diastolic Function

Diastole has an energy-dependent and a passive component. The passive component depends on normal compliance: this is often reduced in AS. The time required for the energy-dependent phase is greater because of impaired myocardial relaxation and decreased chamber compliance. LV end diastolic pressure is increased, eventually reducing diastolic coronary flow. Adequate LV filling is very dependent on the “atrial kick” supplied by synchronized atrial contraction and controlled heart rate.

Patients may exhibit symptoms of diastolic failure with paroxysmal nocturnal dyspnea, orthopnea, and pulmonary edema even with normal ejection fraction, and decompensate if they go into atrial fibrillation. Diastolic dysfunction may take months to years to improve after surgery and may not improve if patients

are left with a significant gradient across the prosthetic valve.[2,3]

Coronary Blood Flow

In AS, the myocardial oxygen supply–demand mismatch causes angina even in patients with normal coronary arteries. This is due to increased muscle mass, which results in increased myocardial oxygen demand. This eventually outpaces compensatory increase in blood flow resulting in lower coronary blood flow per 100 g of myocardium. The increased LV end diastolic pressure reduces coronary perfusion during diastole. Increased systolic time reduces diastolic filling time. Additionally coronary vasodilatory reserve results in decreased coronary flow in exercise.

Clinical Findings in Aortic Stenosis

Patients may be asymptomatic. Most present with any of the triad of angina, exertional syncope, and dyspnea. There is a 5% incidence of sudden death. Symptom onset is closely related to survival. Clinical findings include a slow, rising, low-amplitude pulse, occasionally with a thrill at the carotids; a sustained apex beat; a soft first heart sound, sometimes preceded by fourth heart sound; a single heart sound if valve is calcified; an ejection systolic murmur radiating from the aortic area to the right carotid; and a soft early diastolic murmur due to AI while leaflets become immobile.

PATHOPHYSIOLOGY OF AORTIC INSUFFICIENCY

Morphology

Pathology of any of the components of the aortic root can prevent leaflet coaptation leading to AI. In developing countries, rheumatic disease causes leaflet thickening and shortening. The main cause of AI in developed countries is annular dilatation, for example, annuloaortic ectasia caused by cystic medial dilatation associated with connective tissue disorders such as Marfan disease, or type A aortic dissection. AI may also be caused by endocarditis resulting in leaflet destruction, and calcification resulting in leaflet mobility.

Structural and Functional Changes

Acute Aortic Insufficiency

Acute AI is most commonly caused by endocarditis, aortic dissection, and

trauma. Acute severe AI is usually a surgical emergency. This is because there is no time for any of the adaptive changes that characterize chronic AI to develop and the sudden volume overload results in pulmonary edema while the filling pressure increases in a noncompliant ventricle. Reduced coronary blood flow, low cardiac output, and hypoxia due to acute pulmonary results in end-organ ischemia.[2]

Chronic Aortic Insufficiency

Chronic AI is better tolerated than acute partly because of the following adaptive and maladaptive changes. AI leads to both volume overload, because of the regurgitant fraction, and pressure overload, because of the increased volume of blood ejected. Volume overload causes eccentric hypertrophy and LV dilatation. Pressure overload results in concentric hypertrophy: the same increase in myofibrils and interstitial collagen described in AS occurs in AI. Ventricular enlargement produces a larger total stroke volume (up to 10 L/min), all of which enters the aorta during systole: this is compensated AI and the resultant increase in pulse pressure causes systemic hypertension and a large increase in LV afterload. LV compliance decreases and diastolic function is compromised as hypertrophy progresses. Eventually LV end diastolic pressures and left atrial pressures begin to increase: pulmonary hypertension and congestive cardiac failure is a feature of decompensated AI as well as acute AI. Finally, as myocytes are stretched beyond their limit of effective contraction, LV systolic function decreases, and the rate of increased LV end systolic diameter accelerates to about 7 mm/y. Coronary perfusion may be reduced for the same reasons as in AS.

Clinical Findings in Aortic Regurgitation

Acute AI is characterized by cardiovascular collapse and the symptoms of pulmonary edema. Chronic AI is usually asymptomatic until LV function is significantly impaired. Symptoms eventually include angina (because of myocardial oxygen supply–demand mismatch caused by the combination of increased oxygen consumption due to ventricular hypertrophy and contractility, and decreased coronary reserve caused by the fall in diastolic pressure gradient between the aorta and left ventricle), effort dyspnea, and the symptoms of congestive cardiac failure. Fatigue may predominate.

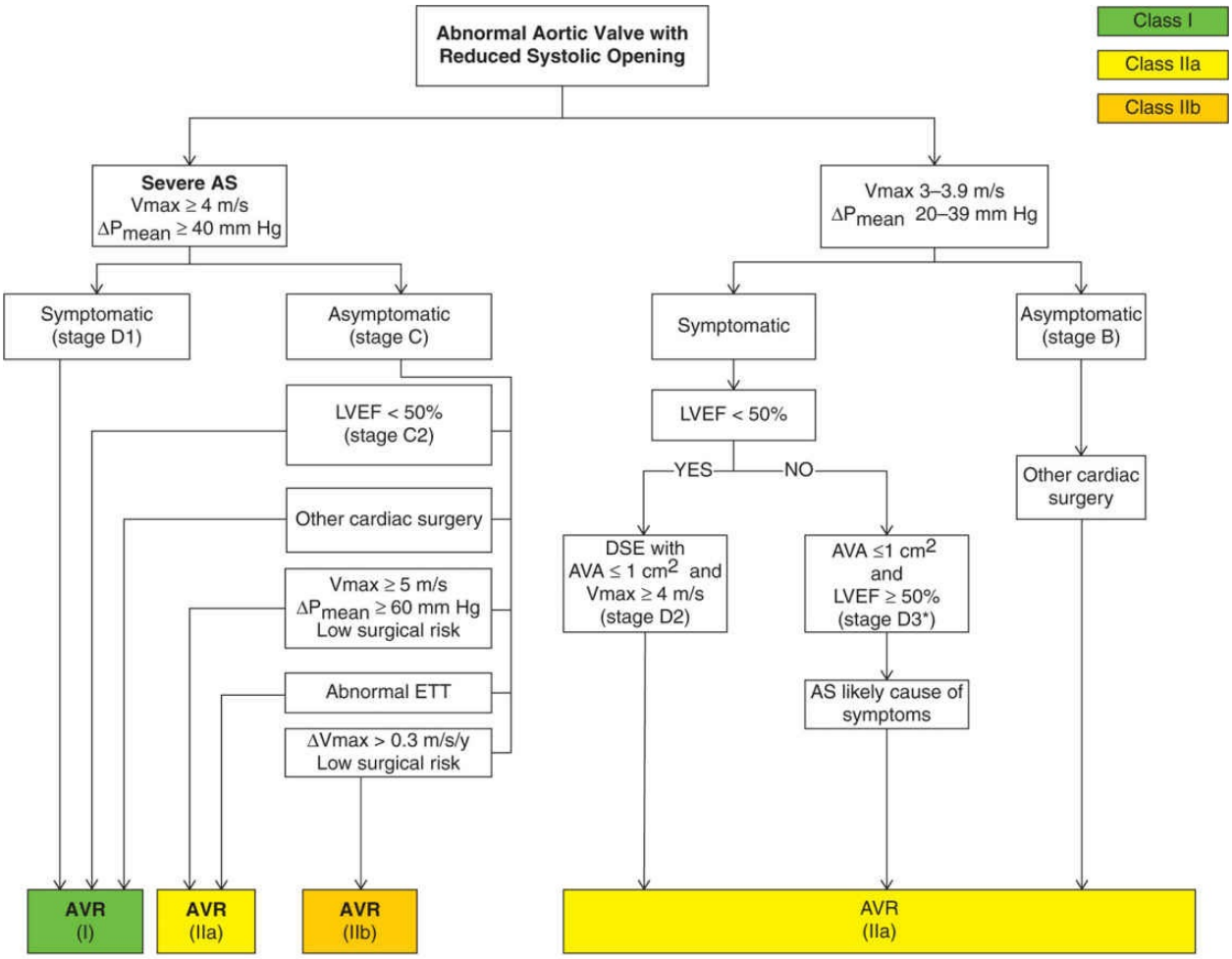
Clinical signs include a large-amplitude collapsing or “water-hammer” pulse

with a rapid upstroke; Quincke sign (capillary pulsation visible in the nail bed); Corrigan sign (visible pulsation in the neck); de Musset sign (head nodding as a result of arterial pulsation); Duroziez sign ("pistol-shot" femorals); a sustained, laterally displaced apex beat; a single second heart sound, with third heart sound; an early diastolic murmur maximal at lower left sternal edge radiating to the apex and axilla; an ejection systolic murmur may be present as well as a late diastolic murmur (Austin Flint) from fluttering of the anterior mitral leaflet as it is hit by the regurgitant jet.[2,3]

Indications for Aortic Valve Surgery

Severe AS may be defined as an aortic valve area < 1 cm^2. If the mean transvalvular gradient is over 40 mm Hg, then stenosis is severe, but severe AS may be present at lower gradients if the patient has poor LV function (see the above description of low-gradient low-flow AS).

The presence of symptoms or LV systolic dysfunction are both class I indications for aortic valve replacement in both AS and AI (**Figures 40.1 and 40.2**).



Arrow show the decision pathways that result in a recommendation for AVR. Periodic monitoring is indicated for all patients in whom AVR is not yet indicated, including those with asymptomatic AS (stage D or C) and those with low-gradients AS (stage D2 or D3) who do not meet the criteria for intervention.

*AVR should be considered with stage D3 As only if valve obstruction is the most likely cause of symptoms, stroke volume index <35 mL/m^2, indexed AVA is ≤0.6cm^2/m^2, and data are recorded when the patient is normotensive (systolic BP 140 mm Hg).

As indicates aortic stenosis; AVA; aortic valve area; AVR, aortic valve replacement by either surgical or transcatheter approach; BP, blood pressure; DSE, doubtamine stress echocardiography; ETT, exercise tredmill test; LVEF, left ventricular ejection fraction ΔP_{mean}, mean pressure gradient; and V_{max}, maximum velocity.

FIGURE 40.1 Indications for aortic valve replacement in aortic stenosis. AS, aortic stenosis; DP_{mean}, the mean pressure gradient across the valve; DV_{max}, change in maximum velocity across the valve on echocardiography. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488.)

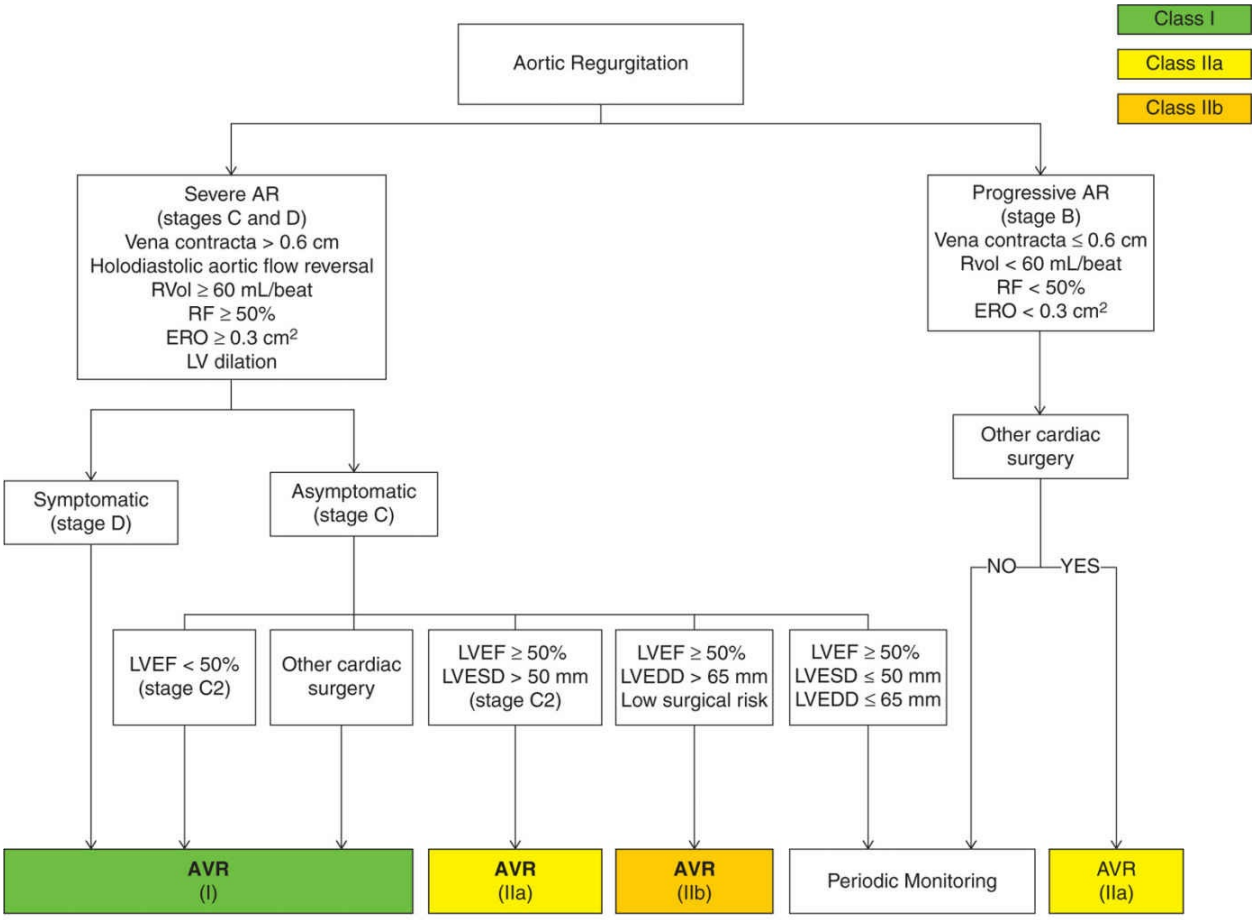


FIGURE 40.2 Indications for aortic valve replacement for aortic regurgitation. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488.)

Indications for Aortic Valve Surgery

Class I indications for aortic valve replacement in AS[1]:

- Symptomatic severe AS (aortic valve area < 1.0 cm^2 or mean gradient > 40 mm Hg);
- Patients with moderate AS undergoing other cardiac surgery;
- Asymptomatic patients with severe AS and LV systolic dysfunction.

Class IIb indications for aortic valve replacement in AS:

- Asymptomatic AS and abnormal response to exercise (eg, hypotension,

symptoms), or aortic valve area < 0.6 cm^2/mean gradient > 60 mm Hg if low surgical risk, or calcification/coronary disease implying rapid progression risk.

Class I indications for aortic valve replacement in AI:

- Acute severe AI, symptomatic severe AI;
- Severe AI undergoing coronary artery bypass grafting or other valve surgery;
- Severe asymptomatic AI and EF <50%

Class IIa indications for aortic valve replacement in AI:

- Severe AI and LV end systolic diameter > 50 mm or LV end diastolic diameter > 65 mm

Class IIb indications for aortic valve replacement in AI:

- Severe AI with normal ejection fraction and LV end systolic diameter > 50 mm or LV end diastolic diameter > 65 mm and progressive dilatation or declining exercise tolerance;
- Indications for aortic valve replacement in endocarditis;
- Endocarditis and severe AI or AS resulting in heart failure, heart block, annular abscess, destructive penetrating lesion (class I); recurrent emboli and vegetation despite appropriate antibiotics, fungal or other virulent organism (class IIa), or large, mobile vegetation > 10 mm (class IIb).

Symptomatic Aortic Stenosis

The onset of symptoms in patients with AS is a poor prognostic sign. There is a 5% incidence of sudden death per year. Symptoms are most likely because it is as if the aortic valve area is <1 cm^2 or the transvalvular mean gradient is >40 mm Hg, and symptom onset in these patients mandates prompt aortic valve replacement in all except very high-risk cases.[2,3]

Low-Gradient Low-Ejection Fraction (Low-Flow) Aortic Stenosis

There are three main subgroups of symptomatic AS patients with transvalvular gradients of <40 mm Hg. Dobutamine infusion during echo or cardiac catheterization can help stratify patients. If cardiac output and transvalvular gradient increase in response to dobutamine, it suggests there is a true flow-

limiting lesion in the setting of reversible ventricular dysfunction: surgery would be beneficial although at higher risk than in patients with normal LV function. In the irreversibly damaged left ventricle, there is little or no increase in transvalvular flow in response to inotropes, and lack of contractile reserve: these patients present with high postoperative mortality and worse survival. Finally, in patients with severe cardiomyopathy due to nonvalvular cause, with only moderate or mild AS, the aortic valve area increases during dobutamine stress testing. These patients derive minimal benefit from surgery.[2]

Asymptomatic Aortic Stenosis

Most asymptomatic patients with severe AS have near-normal life expectancy without aortic valve replacement. Their 1% to 2% incidence of sudden death is less than the mortality of aortic valve replacement (which is approximately 2% overall in the United States), making it crucial to select only those patients at high risk of sudden death without surgery. Two techniques are employed: echocardiography and exercise testing. Asymptomatic patients with a peak transvalvular gradient > 64 mm Hg have an 80% chance of becoming symptomatic within 2 years (hence surgery in these patients has an ACC/AHA IIb indication if surgery is likely to be low risk). Exercise testing is safe in asymptomatic patients, and can identify the presence of exercise-induced hemodynamic compromise, which is an ACC/AHA IIb indication for aortic valve replacement. The natural history of AS in asymptomatic patients with a positive exercise test is probably very similar to that of patients with exertional symptoms.

Aortic Insufficiency

Acute severe AI is a surgical emergency because of the potentially immediately life-threatening sequelae of pulmonary edema and coronary ischemia described earlier. In infective endocarditis with lesser degrees of AI, the indications for early operation are annular abscess formation, new heart block, or evidence of heart failure. In patients who develop chronic severe AI, it may be 10 years before symptoms become severe because of the adaptive changes described earlier. The prognosis during this period is good: severe chronic AI with preserved ejection fraction has an 80% 5-year survival. Surgery should take place before permanent LV dysfunction ensues: so surgery is often indicated in asymptomatic patients. Progressive LV enlargement or decreasing ejection

fraction usually precedes the onset of symptoms and decompensation. Aortic valve replacement should therefore be carried out before the LV ejection fraction falls below 50%, the LV end systolic diameter increases to >55 mm, or the LV end diastolic diameter increases to >70 mm.

Special Considerations

Elderly and High-Risk Patients

The life expectancy of octogenarians without significant comorbidity can be more than 10 years. Aortic valve replacement in selected octogenarians has <3% operative mortality and results in improved quality and length of life in patients with symptomatic AS. These patients, and younger patients adjudicated high risk, are increasingly seen as candidates for transcatheter aortic valve replacement, which in the United States is approved for use in patients with a Society of Thoracic Surgeons predicted operative mortality score of >3% (intermediate and high risk), with severe trileaflet, calcific AS.

Patient Prosthesis Mismatch

The postoperative gradient across a prosthetic aortic valve depends on the valve size and cardiac output: it is higher in small valves, large patients, anemia, fluid overload, tachycardia, and hyperdynamic left ventricles (which is why β-blockers are sometimes used to address high postoperative transvalvular gradients). Postoperative gradients 20 to 30 mm Hg are very common particularly with bioprosthetic valves, and common practice is to try to minimize a postoperative gradient by implanting the largest prosthesis that will fit in the patient's aortic annulus (AA), and not implanting a prosthesis "too small" for the patient's size. How small is "too small" is quantified by Patient Prosthesis Mismatch (PPM), defined as Indexed Effective Orifice Area (IEOA) < 0.85 cm^2/m^2.[4–8] There are, however, no strong data to show difference in survival or symptoms according to whether patients have PPM because the data are dominated by observational studies that are prone to selection bias, primarily because PPM tends to occur in patients with other risk factors for worse outcomes (females, obese, older patients).

There are several options to avoid a high transvalvular gradient after aortic valve replacement in a patient at risk for this because of a small aortic root. The theoretical long-term benefits of minimizing the residual transaortic gradient must be weighed against the incremental operative risks posed to the patient:

occlusion of either coronary ostia or annular rupture due to placing an oversized prosthesis is associated with very high morbidity and mortality. Aortic root enlargement is associated with an incremental 2% to 3% risk of operative mortality in observational series, and national mortality for aortic root replacement is 7% to 10%, compared with 2% for aortic valve replacement.[9,10]

Planning before surgery may identify the potential problem in advance, allowing other modalities to be considered. For example, an annular diameter < 20 mm on preoperative echo is likely to take only a 19-mm valve. If the patient is very active or large, has diastolic dysfunction, or low-gradient low-ejection fraction AS, a 19-mm aortic valve is unlikely to be suitable. Options include transcatheter aortic valve replacement, which allows a prosthesis with a larger effective orifice area to be placed. Sutureless valves also appear to have better characteristics in this regard. Alternatively, mechanical valves have superior hemodynamics for given size, which requires a careful discussion before surgery with the patient given the need for lifelong anticoagulation and incremental risk of stroke and major bleeding events. Surgical approaches in increasing order of complexity and operative risks include stentless valves, aortic root enlargement, and aortic root replacement.

Valve Sparing Procedures

There are a large number of procedures described for patients with morphologically normal aortic valves, but with aortic regurgitation caused by pathology affecting the sinotubular junction (STJ) or the aortic annulus (AA). In patients with severe AI, a normal STJ, and normal AA, a Dacron tube graft approximately 10% smaller than the diameter of the AA is scalloped into tailored flaps that are used to recreate the sinuses of Valsalva. It is necessary to reimplant the coronary arteries. Alternatively, tailored flaps are omitted and the valve is simply resuspended within the Dacron tube, restoring valvular competency. In patients with a normal AA but dilated STJ, which occurs in patients with chronic hypertension, poststenotic dilatation and type A dissection, a simple interposition style graft can be placed, with or without a band of PTFE (Polytetrafluoroethylene) for additional support at the level of the STJ. It is not necessary to reimplant the coronaries. In patients where both AA and STJ are enlarged due to annuloaortic ectasia that can be caused by connective tissue disorders such as Marfan syndrome, AI can be treated by valve-sparing root remodeling. A number of modifications to procedures originally separately described by Magdi Yacoub and Tirone David exist. The main principles of

valve-sparing surgery in Marfan disease involve implanting a Dacron graft at the annulus. The sinus aorta is attached to the inside of the Dacron graft, with reimplantation of the coronary ostia.

Surgical Approaches

Transcatheter aortic valve replacement is described in Chapter 39, and is increasingly the procedure of choice for intermediate and high-risk patients.[11] Surgical aortic valve replacement is most commonly performed via a sternotomy or an upper hemisternotomy, which allows the incision to be 6 to 7 cm in length. Occasionally anatomy is amenable to a minithoracotomy approach, which allows a 6-to-7-cm incision via an intercostal space. The aim of smaller incisions is to limit the impact of surgery on postoperative respiratory function, pain control, bleeding and transfusion requirement, and to improve cosmesis. Cannulation for cardiopulmonary bypass is usually performed via the ascending aorta and right atrium; however femoral cannulation may be used to facilitate smaller incisions. Retrograde flow from femoral arterial cannulation is associated with higher rates of stroke in elderly patients and those with atheromatous vasculature.

Results of Aortic Valve Surgery

Early Mortality

In an analysis of 141,905 isolated valve procedures in a U.S. national database, unadjusted mortality was 1.4% for patients adjudicated “low risk” with a Society of Thoracic Surgeons predicted operative mortality score (STS-PROM) score of <4%; 5.24% in patients adjudicated intermediate risk (STS PROMO score 4% to 8%) and 11.2% in patients adjudicated high risk with an STS PROM score > 8%.[12] The biggest risk factors for operative mortality are emergency presentation, advanced age, multiple valve surgery, coronary artery disease, aortic root pathology, and endocarditis. Results have improved over recent decades despite sicker patient profiles. Most early deaths are related to cardiogenic shock, stroke, and hemorrhage. The higher mortality observed in patients undergoing bioprosthetic compared with mechanical aortic valve replacement is related to their higher preoperative comorbidity, including greater age.

Late Mortality

Overall survival (including hospital deaths) after aortic valve replacement is

approximately 75% at 5 years, 60% at 10 years, and 40% at 15 years, depending on the patient's age and comorbid conditions. Type of prosthesis (mechanical versus bioprosthetic valve) has not been shown to have an impact on survival. Although patients with bioprosthetic valves have significantly worse unadjusted survival curves than patients with mechanical valves, as with early mortality, this reflects the greater age and comorbidity of this group at baseline. Survival can be described in terms of hazard phases: the early, rapidly declining hazard phase (short-term survival) is dominated by perioperative mortality. It gives way to a phase about 6 months after operation (intermediate-term survival) where the death rate remains steady at approximately 2% per annum. This begins to rise steadily after 5 years (late-term survival). Other risk factors for late mortality include advanced age at operation (30-day mortality 1% in patients aged 40 to 50 years compared with >3% in patients aged > 80 years). Additional risk factors for operative mortality include worse New York Heart Association (NYHA) class, LV enlargement, atrial fibrillation, the number of previous aortic valve replacements, coexisting coronary artery disease, aneurysm, or LV structural abnormality.

Complications of Aortic Valve Replacement

The complications of cardiac surgery in general include reexploration for bleeding or tamponade (2%), perioperative myocardial infarction (1%), deep sternal wound infection (1%), prolonged mechanical ventilation (2%), and organ dysfunction (5%). Complications particularly associated with aortic valve replacement are as follows:

COMPLETE HEART BLOCK

Permanent pacemakers are inserted for permanent complete heart block in about 5% of aortic valve replacement patients. Complete heart block results from trauma to the bundle of His after extensive debridement of calcium from the junction of the right and noncoronary cusp. Heart block characteristically worsens over postoperative days 1 to 3, and sometimes settles as edema improves.[13], [14]

STROKE

The overall risk of stroke is about 2% for isolated aortic valve replacement, increasing to 3% in combined aortic valve replacement with concomitant coronary bypass surgery.[15] Stroke following aortic valve replacement shares

many of the same risk factors as in other cardiac surgery, including prior stroke, carotid artery disease, aortic atheroma or calcification, endocarditis, and atrial fibrillation. Removal of all calcific debris from the operative field and thorough de-airing help prevent perioperative stroke.

Prosthetic Endocarditis

Mechanical valves are at slightly higher risk of endocarditis up to 3 months after surgery, the risks even out by 5 years. Homografts were once assumed to carry a lower risk of early endocarditis, but this has not been supported by data. The cumulative risk of prosthetic valve endocarditis is about 1% at 1 year and 3% at 5 years post aortic valve replacement. Early endocarditis (within 3 months of surgery) is usually hospital acquired: organisms are commonly staphylococci and gram-negative bacilli. Late prosthetic endocarditis usually results from a transient streptococcal bacteremia. The mortality is up to 60%.

Thromboembolism

The rate of valve thromboembolism is roughly 1% to 2% per year: the rate in adequately anticoagulated mechanical valves is slightly higher than that in bioprosthetic valves, which is one of the strong rationales for bioprosthetic valves.[16–20] Valve thrombosis is a rare emergency: cardiovascular collapse, venous congestion, and systemic embolization are usually acute, but may be insidious in onset. The management is intravenous heparin. If the thrombus is greater than 5 mm, thrombolysis or reoperative bioprosthetic aortic valve replacement is indicated.

Paraprosthetic Leak

Major paraprosthetic regurgitation occurs in 5% to 10% of transcatheter aortic valve replacements. It is uncommon with surgical aortic valve replacement, and is caused most commonly by prosthetic endocarditis (late), and less commonly by technical errors in insertion (early). Patients present with hemolytic anemia, and if severe, congestive heart failure. The treatment is surgery. If the area of dehiscence is small and there is no evidence of sepsis, one or two interrupted sutures may suffice. Occasionally, paravalvular regurgitation is amenable to percutaneous closure with an Amplatzer-type device. Where this is not possible, redo aortic valve replacement is indicated.[21]

Prosthesis Failure

Failure of mechanical valves is almost exclusive to strut failure of a particular

Bjork-Shiley tilting disc valve, withdrawn in 1986. Bioprosthetic aortic valve failure is age dependent: rates of failure are <10% at 10 years in the over 70s age group, but closer to 30% in the 40-to-50-year age group. Degenerative failure in cryopreserved homograft aortic valve replacement is between 5% and 10% at 10 years.

Reoperation for Any Reason

The risk of reoperation is highest in the first 6 months following aortic valve replacement due to prosthetic endocarditis and paravalvular leak. It falls to about 1% a year where it remains for mechanical valves.[13,14] The risk also falls initially in bioprosthetic valves, but begins to rise rapidly after 10 to 12 years due to structural degeneration.[15]

Failure to Improve Symptoms and Left Ventricular Function

90% of patients are NYHA class I or II, 5 to 10 years following aortic valve replacement, depending on their other comorbidities, and baseline LV function. Completely normal LV mass is rarely achieved, but where the LV end diastolic pressure was low preoperatively, and the transvalvular gradient is minimal, LV mass eventually returns to near-normal values.

MITRAL VALVE SURGERY

PATHOPHYSIOLOGY OF MITRAL REGURGITATION

Morphology

The mitral valve consists of the mitral valve annulus, leaflets, chordae tendineae, papillary muscles, and the left ventricle wall. Disease involving any of these structures may result in reduced leaflet coaptation leading to mitral regurgitation, described using a functional classification, description of etiology, and segmental valve nomenclature. Leaflet dysfunction is commonly described using Carpentier's classification of leaflet motion as either type I, which is normal leaflet motion; type II, which is excessive leaflet motion or prolapse; type III, which is restricted leaflet motion; and further subdivided into type IIIa, which is restricted leaflet opening; and type IIIb, which is restricted leaflet closure.

The functional classification can be supplemented with a description of the lesion causing the functional problem. Common lesions are chordal elongation or rupture, leaflet perforation, annular dilatation, and papillary muscle

displacement or rupture. Finally, the etiology underlying the lesion is described: common etiologies of mitral regurgitation include degenerative disease (which covers a range of overlapping pathology resulting in mitral valve prolapse including myxomatous disease, fibroelastic deficiency, and Barlow disease), ischemic disease (which can result in acute and chronic changes causing regurgitation), rheumatic disease, endocarditis, and dilated cardiomyopathy.

Etiology

Degenerative mitral valve disease is one of the commonest causes of mitral regurgitation in developed countries with an incidence of 1% to 2%. Typically degenerative disease causes prolapse (type II mitral regurgitation) due to chordal elongation or rupture, most commonly of the P2 segment. Histology shows myxomatous degeneration. Degenerative mitral valve disease encompasses a spectrum from single segment prolapse in small valves (fibroelastic deficiency) to multisegment prolapse in giant valves (Barlow).

Ischemic mitral regurgitation is usually due to chronic LV dysfunction and posterior displacement of papillary muscle (type IIIb) with normal leaflets. Acute papillary muscle rupture is a rare cause of acute type II mitral regurgitation after myocardial infarction. Dilated cardiomyopathy causes type I MR due to annular dilatation.

Endocarditis causes type I mitral regurgitation due to leaflet perforation and destruction, which may be extensive and involve the mitral annulus. Rheumatic disease results in type IIIa MR with restricted leaflet opening due to calcification and commissural fusion.

Less common causes of mitral regurgitation include abnormal systolic anterior motion, which results in mitral valve regurgitation and elevated LV outflow tract gradients, congenital causes such as cleft mitral valve, and connective tissue disease such as Marfan disease.

Structural and Functional Changes in Mitral Regurgitation

Chronic Mitral Regurgitation

The pathophysiologic changes associated with mitral regurgitation commonly progress through one or more of three stages: acute mitral regurgitation, chronic compensated mitral regurgitation, and chronic decompensated mitral regurgitation. Acute mitral regurgitation results in LV volume overload at end diastole, that is, increased preload and decreased afterload due to the regurgitant

pathway into the left atrium. The combination of increased preload and reduced afterload means that a larger volume of blood is ejected from the left ventricle.

Because a large volume of ejected blood enters the left atrium rather than the aorta, forward stroke volume, and hence cardiac output decreases. The increased blood volume in the left atrium raises the pressure from a normal left atrial pressure of 10 mm Hg to up to 25 mm Hg. The increased preload leads to eccentric hypertrophy and LV dilatation, increasing total stroke volume and forward stroke volume to near normal levels. Left atrial enlargement accommodates volume overload at lower filling pressures (15 mm Hg), but predisposes to atrial fibrillation and mural thrombi.

Chronic decompensated mitral regurgitation exists when systolic dysfunction prevents effective ventricular contraction; stroke volume and cardiac output are reduced as blood flows into the low-resistance regurgitant pathway, and left atrial and pulmonary pressures rise as a result. Untreated decompensated mitral regurgitation rapidly progresses to pulmonary edema and congestive cardiac failure. Symptoms, LV dysfunction, left atrial dilatation, atrial fibrillation, and pulmonary hypertension, are all associated with decreased long-term survival in the setting of chronic MR.

Clinical Findings in Mitral Regurgitation

The interval from diagnosis of mitral regurgitation to the onset of symptoms varies by etiology (it may be months in fibroelastic deficiency to many years in rheumatic or Barlow disease). LV ejection fraction remains normal despite even severe LV dysfunction because 50% of stroke volume ejects into low-pressure left atrium. While most deaths are related to heart failure, the incidence of sudden death suggests ventricular arrhythmias are an important feature of the disease process. Signs include atrial fibrillation, prominent sustained apex beat, systolic thrill, right parasternal heave reflecting right ventricular hypertrophy due to pulmonary artery hypertension, quiet first heart sound, third heart sound audible, and loud pansystolic murmur loudest at apex radiating to axilla.

Acute Mitral Regurgitation

Acute severe mitral regurgitation may be caused by chordal rupture, ischemic heart disease, or infective endocarditis, and it is an indication for urgent surgery. A sudden volume overload is imposed on the left ventricle, increasing preload and resulting in a small increase in total stroke volume. Without the compensatory left atrial and LV dilatation seen in chronic severe mitral

regurgitation, however, forward stroke volume is reduced, and congestive heart failure or even cardiogenic shock may result. The patient with acute severe mitral regurgitation is always symptomatic.

PATHOPHYSIOLOGY OF MITRAL STENOSIS

Morphology

The commonest cause of mitral stenosis is rheumatic fever: the disease process causes leaflet thickening and calcification and commissural and chordal fusion. Isolated mitral stenosis occurs in 40% of all patients presenting with rheumatic heart disease, and 60% of patients with mitral stenosis give a history of rheumatic fever. The ratio of female to male patients with this pathology is 2:1. Congenital malformation of the mitral valve occurs rarely.[2,3]

Structural and Functional Changes

The cross-sectional area of the normal mitral valve is 4.0 to 5.0 cm^2. Narrowing of this area to <2.5 cm^2 means that a pressure gradient must be generated across the mitral valve in diastole in order to expel blood from the left atrium into the left ventricle. This results in elevation of left atrial and pulmonary venous pressures. Left atrial enlargement, atrial fibrillation, and thrombus formation result from chronic left atrial pressure overload. Pulmonary hypertension results from passive transmission of elevated left atrial pressures, pulmonary vasoconstriction, and irreversible pulmonary vasculature remodeling. Pulmonary edema occurs when pulmonary venous pressure is greater than plasma oncotic pressure. At rest, mitral stenosis is usually asymptomatic, but any increase in transmitral flow rates (eg, due to hyperdynamic circulation) or reduction in the diastolic filling period, such as tachycardia or atrial fibrillation, will result in an increase in the pressure gradient, causing dyspnea. Severe mitral stenosis may have a low gradient in patients with a low cardiac output.

Clinical Findings in Mitral Stenosis

The first symptoms of dyspnea in patients with mitral stenosis are usually precipitated by physical exertion including exercise, sex, emotional stress, infection, pregnancy, or rapid atrial fibrillation because of the increase in the pressure gradient across the mitral valve described earlier. Recurrent chest infections are characteristic. In advanced cases, hemoptysis may be caused by

chest infections, pulmonary infarction, acute pulmonary edema, and rupture of small pulmonary vessels. Systemic embolism is frequent, particularly in atrial fibrillation.

Signs on clinical examination include a decreased amplitude pulse, atrial fibrillation, “tapping” apex beat, left parasternal heave due to right ventricular hypertrophy, thrill due to palpable opening snap, loud first heart sound, an opening snap loudest at lower left sternal edge, and a presystolic murmur, with a delayed mid-diastolic murmur.[2]

Indications for Mitral Valve Surgery

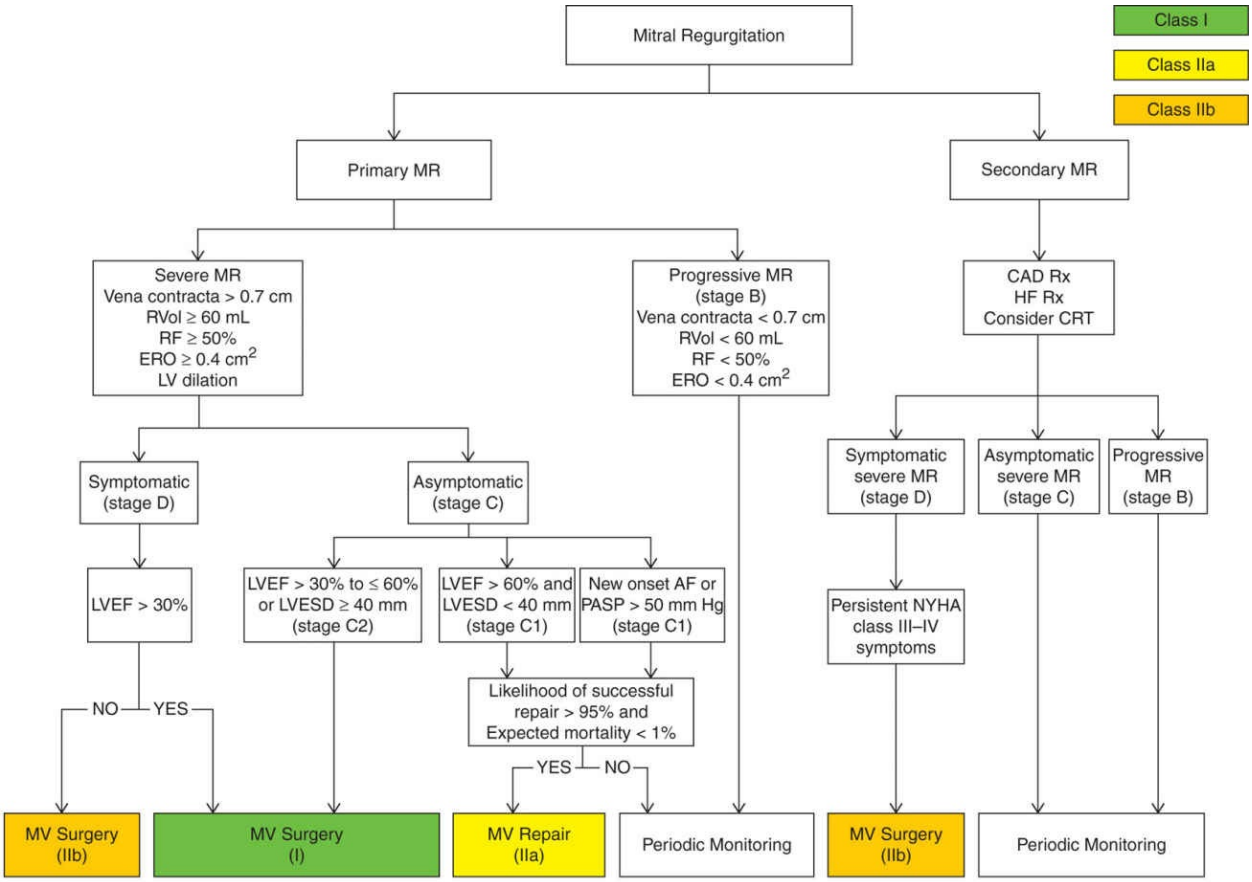
Chronic Mitral Regurgitation

The prognosis of chronic mitral regurgitation depends on both the etiology and severity of the lesion. In patients with severe symptomatic chronic mitral regurgitation of any etiology, the prognosis is poor. The average mortality rate is approximately 2% to 5% per year, and may be as high as 70% at 8 years. Patients with chronic mild to moderate mitral regurgitation are unlikely to require surgery, and therapy is aimed at treating the symptoms and preventing complications. American Heart Association (AHA) guidelines recommend that these patients are followed up on a yearly basis, with transthoracic echo if there are clinical grounds for suspecting a deterioration in LV or mitral valve function.[2,3]

In chronic ischemic mitral regurgitation, the valve itself is usually anatomically normal and the regurgitation is secondary to papillary muscle and LV dysfunction following infarction. The prognosis is poorer than in mitral regurgitation caused by nonischemic pathology. Coronary artery bypass may improve LV function and reduce mitral regurgitation. If LV dysfunction is very severe (LV end systolic diameter > 55 mm or LV ejection fraction < 30%), and repair/chordal preservation is unlikely, surgery does not extend life expectancy and is unlikely to provide symptomatic benefit.

Class I indications for mitral valve surgery therefore include chronic severe mitral regurgitation and NYHA class II to IV symptoms or mild to moderate LV dysfunction.[2,3] Additionally, class I indications include asymptomatic chronic severe mitral regurgitation with normal LV function if the likelihood of repair is more than 90%, or in the presence of new atrial fibrillation, pulmonary artery systolic pressures greater than 50 mm Hg at rest (or 60 mm Hg on exercise); or in the setting of NYHA III to IV symptoms with severe LV dysfunction if there

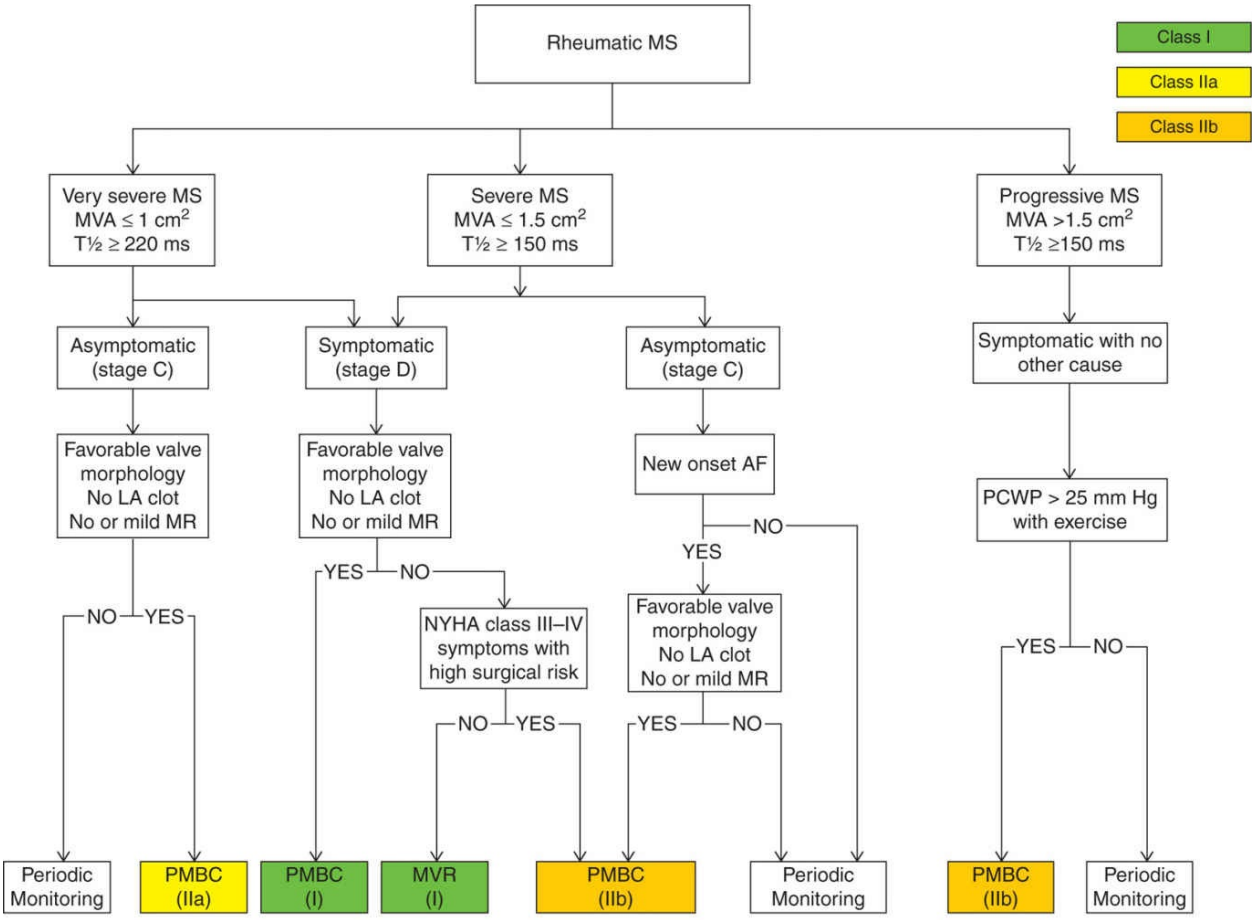
is a primary leaflet dysfunction (ie, not secondary or functional mitral regurgitation) and repair is likely. Class IIb indications for surgery include chronic severe mitral regurgitation due to severe LV dysfunction despite optimal medical therapy that may include biventricular pacing where appropriate (**Figures 40.3 and 40.4**).[2,3]



*Mitral valve repair is preferred over MVR when possible.

AF indicates atrial fibrillation; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ERO, effective regurgitant orifice; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation, MV, mitral valve; MVR, mitral valve replacement; NYHA, New York Hear Association; PASP, pulmonary artery systolic pressure; RF, regurgitant fraction; RVol, regurgitant volume; and Rx, therapy.

FIGURE 40.3 Indications for mitral valve repair or replacement for mitral regurgitation. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488.)



AF indicates atrial fibrillation; LA, left atrial; MR, mitral regurgitations; MS, mitral stenosis; MVA, mitral valve area; MVR, mitral valve surgery (repair or replacement); NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PMBC, percutaneous mitral balloon commissurotomy; and T½, pressure half-time.

FIGURE 40.4 Indications for intervention for mitral stenosis. (From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63:2438-2488.)

Acute Mitral Regurgitation

Acute severe mitral regurgitation is a class I indication for urgent surgery. There is no scope for compensatory changes: cardiac output falls, left atrial pressures increase, and pulmonary edema and cardiogenic shock ensue.

Mitral Stenosis

It may be as long as 20 to 40 years between the occurrence of rheumatic fever and the onset of symptomatic mitral stenosis. Once symptoms develop, it may take up to 10 years before these become disabling. In the minimally symptomatic patient, 10-year survival is 80%, which drops to 10% to 15% once

symptoms become limiting. Once there is severe pulmonary hypertension, mean survival drops to <3 years. The mortality of untreated mitral stenosis is due to heart failure in 60% to 70%, systemic embolism in 20% to 30%, pulmonary embolism in 10%, and infection in 1% to 5% of patients. Patients with a mitral valve area of <1.5 cm^2 and NYHA functional class III to IV symptoms should be referred for surgery if balloon valvotomy is not possible. There is good evidence that patients with NYHA functional class I to II symptoms and a mitral valve area <1.0 cm^2, and severe pulmonary artery hypertension (systolic pulmonary artery pressure > 60 to 80 mm Hg) benefit from surgery.[2]

Surgical Approaches

Mitral valve repair and replacement is most commonly performed via a sternotomy, and right (and very occasionally left) thoracotomy approach is very feasible. As in aortic valve surgery, the aim of smaller incisions is to limit the impact of surgery on postoperative respiratory function, pain control, bleeding and transfusion requirement, and to improve cosmesis. Cannulation for cardiopulmonary bypass is usually performed via the ascending aorta and Bicavally (Superior and Inferior Vena Cava); however, femoral cannulation may be used to facilitate smaller incisions. Retrograde flow from femoral arterial cannulation is associated with higher rates of stroke in elderly patients and those with atheromatous vasculature.

Mitral Valve Repair

Planning Mitral Valve Repair

In degenerative valve disease, mitral valve repair is associated with better early and late survival, and freedom from complications of prosthetic valve including stroke, recurrence of mitral regurgitation, and reoperation compared with mitral valve replacement. Therefore, mitral valve repair is preferable to replacement in patients with degenerative valve disease, particularly in young patients and asymptomatic patients where the sequelae of valve replacement are more serious.[2,3]

Mitral valve repair is not as reproducible as mitral valve replacement because it requires additional technical expertise primarily because mitral valve morphology is highly variable, and repair complexity depends on valve morphology. Consequently, in order to maximize the likelihood of a competent and durable mitral repair, it is important to match surgeon expertise to repair

complexity. Lesions associated with a more straightforward repair include type II mitral regurgitation from isolated P2 prolapse from degenerative disease, and type IIIb P3 from ischemic disease.

Lesions associated with more complex repair include multisegment or bileaflet prolapse, in Barlow disease, type IIIa lesion from rheumatic disease, lesions related to infective endocarditis, such as leaflet perforation and annular abscess, cleft mitral valve, primary abnormal systolic anterior leaflet motion, and previous failed mitral repair. Patients with these lesions should be seen by a surgeon with specific expertise in mitral valve repair.

Special Considerations

Concomitant Tricuspid Annuloplasty

Functional tricuspid regurgitation commonly occurs secondary to mitral valve lesions causing pulmonary hypertension and right ventricular dilatation. When right ventricular dilatation develops, the tricuspid annulus dilates because it is not supported by a fibrous skeleton. This is most pronounced in the posterior and anterior part of the annulus because the septal annulus is relatively fixed. Leaflet coaptation is reduced leading to tricuspid regurgitation. Observational data suggest that in patients with more than 2+ tricuspid regurgitation, annular dilatation, or pulmonary artery hypertension, functional tricuspid regurgitation may not resolve with correction of the left-sided lesion, and should be repaired to avoid late severe tricuspid regurgitation, which develops in a minority of patients and is associated with high morbidity and operative mortality. Tricuspid repair can be easily accomplished using tricuspid ring annuloplasty without significant incremental morbidity.[22]

Concomitant Atrial Ablation and Left Atrial Appendage Closure

Atrial fibrillation may be addressed at the time of mitral valve surgery with concomitant ablation using a variety of energy sources: cryoablation is used most commonly. Full-thickness lesions are created around the pulmonary veins, and may include more complete left and right atrial lesions sets. The freedom from atrial fibrillation at 1 year using this technique is 60% to 70%. Cut-and-sew maze procedures, where the lesions are created by resecting and resuturing the left and right atrium, offer much greater freedom from atrial fibrillation but at the expense of increased morbidity, particularly related to bleeding risk, and are not widely performed. In patients with atrial fibrillation, it is possible to ligate

the left atrial appendage either from inside the left atrium, which affords a more complete and durable closure if performed as a double layer rather than a single purse-string, or from outside using sutures or clips, which is faster but may not occlude the base of the appendage as reliably as a hand-sewn closure. The rationale is to reduce the risk of thromboembolic stroke, but there are little data to support the efficacy of any of the techniques, with some data showing increased stroke risk if there is residual blood flow after attempted surgical closure.

Mitral Valvotomy

Open mitral valvotomy is a historic procedure that used to be performed for mitral stenosis (usually rheumatic), before the wide availability of percutaneous balloon mitral valvotomy. It was one of the first cardiac surgical procedures performed, and the basic principles of the operation remained unchanged for three decades until the advent of cardiopulmonary bypass enabled the surgeon to work on the mitral valve under direct vision, in a still, bloodless field. Percutaneous balloon mitral valvotomy is performed using a transvenous approach with a transseptal puncture. The initial results of percutaneous versus surgical valvotomy are comparable, and both interventions have low rates of restenosis providing good functional outcomes up to 3 years. At 3 years, however, valve areas in the balloon mitral valvuloplasty group are greater than in the surgical ones. Additionally, procedural mortality is less than that associated with mitral valve replacement. In view of this, as well as the lower cost and morbidity of the percutaneous approach, percutaneous approach is recommended in patients without any contraindications. Contraindications to percutaneous balloon valvotomy include > 2+ mitral regurgitation, left atrial thrombus, Wilkins score ≥ 8 (range 4 to 16), or Cormier group 3, severely decreased leaflet mobility, prominent leaflet or subvalvar thickening, calcification especially commissures, and severe concomitant coronary artery disease or AS requiring surgery.

Results of Mitral Valve Surgery

Early Mortality

The mortality of isolated mitral valve repair, with or without tricuspid repair, for degenerative disease in patients without pulmonary hypertension is <1%. Higher operative mortality (2% to 5%) is seen in patients with pulmonary hypertension,

LV dysfunction, advanced age, ischemic mitral regurgitation, active endocarditis, and mitral replacement.

Late Mortality

Successful repair for degenerative mitral regurgitation restores life expectancy to that of an age-matched normal population. Ischemic mitral regurgitation is associated with much poorer survival: one-third of patients are dead within 5 years despite successful repair. LV end diastolic dimension greater than 65 mm is associated with worse survival with <50% of patients alive at 5 years. Rheumatic patients are usually younger, and have good long-term survival with around 80% to 90% still alive 10 years after surgery.[13]

Complications

The complications of cardiac surgery in general include reexploration for bleeding or tamponade (2%), perioperative myocardial infarction (1%), deep sternal wound infection (1%), prolonged mechanical ventilation (2%), and organ dysfunction (5%). Complications particularly associated with mitral valve surgery are as follows:

FAILURE OF REPAIR

A patient leaving the operating room with greater than 1+ mitral regurgitation is described as having residual mitral regurgitation, whereas recurrent mitral regurgitation refers to patients who initially had no mitral regurgitation after surgery, but developed mitral regurgitation later. Residual mitral regurgitation is usually due to a technical issue, such as incorrect choice of ring, failure to close cleft, inadequate treatment of prolapse, or advanced disease due to an etiology not amenable to repair (rheumatic mitral disease). Recurrent mitral regurgitation may occur early, and is also usually related to a technical problem, such as dehiscence of leaflet suture line, failure of chordal reconstruction, or very occasionally endocarditis. Late recurrent mitral regurgitation is usually due to progression of underlying disease. The late failure rate for degenerative disease is around 1% to 2% per year, and much lower than the failure rate for rheumatic and ischemic repair, reflecting the more progressive nature of the latter two etiologies.

COMPLETE HEART BLOCK

Permanent pacemakers are inserted for permanent complete heart block in about

1% to 2% of mitral valve replacement patients. Complete heart block results from trauma to the bundle of His. Heart block characteristically worsens over postoperative days 1 to 3, and sometimes settles as edema improves.

STROKE

The overall risk of stroke is about 1% for isolated mitral valve replacement, increasing to 3% in mitral valve replacement combined with concomitant aortic valve replacement or coronary bypass surgery. Stroke following mitral valve replacement shares many of the same risk factors as in other cardiac surgery, including prior stroke, carotid artery disease, aortic atheroma or calcification, endocarditis, and atrial fibrillation. Removal of all calcific debris from the operative field, and thorough de-airing help prevent perioperative stroke.

PROSTHETIC ENDOCARDITIS

Mechanical valves are at slightly higher risk of endocarditis up to 3 months after surgery, the risks even out by 5 years. Homografts were once assumed to carry a lower risk of early endocarditis, but this has not been supported by data. The cumulative risk of prosthetic valve endocarditis is about 1% at 1 year and 3% at 5 years post mitral valve replacement. Early endocarditis (within 3 months of surgery) is usually hospital acquired: organisms are commonly staphylococci and gram-negative bacilli. Late prosthetic endocarditis usually results from a transient streptococcal bacteremia. The mortality is up to 60%.

THROMBOEMBOLISM

The rate of valve thromboembolism is higher than in aortic prostheses because flow velocity across the valve is slower. It is roughly 2% per year, with adequate anticoagulation of mechanical valves, and 1% per year with bioprosthetic valves, and may present as stroke or systemic embolization.[16] The mainstay of management is intravenous heparin. Valve thrombosis is rare, and presents with acute onset of extreme dyspnea and orthopnea, but may be insidious. Fluoroscopy or echo is used to visualize if one or both leaflets are not moving. Acute thrombosis can be treated with thrombolytic therapy, but usually this is a chronic process with acute exacerbation that requires replacement (normally with a bioprosthesis to avoid a repeat episode). The thrombus is usually very organized and may be superimposed on pannus. Surgical thrombectomy may be tempting but is often ineffective because it is impossible to clear pannus and thrombus easily from ventricular aspect of prosthesis.

Paraprosthetic Leak

Paraprosthetic leak is uncommon after mitral valve replacement: immediate or early paraprosthetic leaks may be due to needle holes (tiny, and disappear after protamine), incomplete decalcification of annulus, annular tear, or suture positioning. Late new paraprosthetic leaks are more likely due to endocarditis. Narrow, high-velocity jets are high risk for hemolytic anemia that may be disabling (requiring multiple transfusions). Broader jets may be hemodynamically significant especially if mitral regurgitation was not present preoperatively. The decision to treat depends on balancing disadvantages of fixing the paravalvular leak (eg, reclamping diseased aorta, additional ischemic time in sick heart, severe mitral annular calcification making any improvement unlikely, high-risk resternotomy) against the disadvantages of leaving it. Prosthetic valve endocarditis is a strong indication for surgery in this context. In the absence of endocarditis, paravalvular regurgitation may be amenable to percutaneous closure with an Amplatzer-type device. Where this is not possible, redo mitral valve replacement may be indicated.

Prosthesis Failure

In the mitral position, the lifetime risk of reoperation for bioprosthetic failure is around 45% for a 50-year-old, and this falls by just over 10% for every additional 5 years of age at the time of implantation. At 20 years after surgery, around 10% to 15% of patients with mechanical valves will have required reoperative valve replacement for infective endocarditis, pannus, or valve thrombosis.[22]

Reoperation for Any Reason

The risk of reoperation is highest in the first 6 months following mitral valve replacement due to prosthetic endocarditis and paravalvular leak. It falls to about 1% a year where it remains for mechanical valves. The risk also falls initially in bioprosthetic valves, but begins to rise rapidly after 10 to 12 years due to structural degeneration.[22]

Failure to Improve Symptoms and LV Function

90% of patients are NYHA class I or II, 5 to 10 years following mitral valve replacement, depending on their other comorbidities and baseline LV function. Completely normal LV mass is rarely achieved, but where the LV end diastolic pressure was low preoperatively, and the transvalvular gradient is minimal, LV mass eventually returns to near normal values.

Atrial Fibrillation

Around 10% to 20% of patients undergoing mitral surgery have a history of preoperative atrial fibrillation and the incidence of postoperative atrial fibrillation is around 40%. Atrial fibrillation is associated with thromboembolic complications including stroke, heart failure, and decreased survival; so aggressive treatment of patients with a history of preoperative atrial fibrillation with intraoperative ablation is recommended. These patients are routinely anticoagulated for 3 months after surgery, may be at increased risk for thrombus formation in the early postoperative period, and are often pacemaker dependent for several days after surgery.

TRCIUSPID VALVE SURGERY

PATHOPHYSIOLOGY

Morphology

Functional tricuspid regurgitation commonly occurs secondary to left-sided valve lesions causing pulmonary hypertension and right ventricular dilatation. When right ventricular dilatation develops, the tricuspid annulus dilates because it is not supported by a fibrous skeleton. This is most pronounced in the posterior and anterior part of the annulus, since the septal annulus is relatively fixed. Leaflet coaptation is reduced leading to tricuspid regurgitation. Observational data suggest that in patients with more than 2+ tricuspid regurgitation, annular dilatation, or pulmonary artery hypertension, functional tricuspid regurgitation may not resolve with correction of the left-sided lesion, and should be repaired to avoid late severe tricuspid regurgitation, which develops in a few patients and is associated with high morbidity and operative mortality.

Acute tricuspid valve endocarditis is usually associated with sepsis from long-term indwelling venous catheters or intravenous drug use. Common causative organisms are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Rheumatic tricuspid valve may result in annular dilatation and functional tricuspid regurgitation secondary to severe mitral stenosis. The tricuspid leaflets are often characterized by mild restriction and leaflet thickening.

Transvenous pacing wires can lead to leaflet perforation, or more commonly scarring, causing tricuspid regurgitation. Traumatic tricuspid valve rupture is a rare sequela of severe nonpenetrating chest injury. Carcinoid valve disease results in severe leaflet thickening and immobility, causing regurgitation and

stenosis.

Clinical Findings

The symptoms and natural history are determined by the dominant left-sided heart lesion. Tricuspid stenosis causes increased systemic venous pressure, resulting in hepatomegaly, ascites, and peripheral edema. A mid-diastolic murmur may be present. In tricuspid regurgitation, the progression is slower than mitral regurgitation, and many patients are symptom free for decades. The predominant clinical features are those of raised venous pressure. A pansystolic murmur may be present. Patients usually have moderate to severe right ventricular failure by the time they present for surgery, as well as severe pulmonary hypertension, and moderate to severe liver dysfunction, which is why isolated tricuspid valve surgery has such high mortality (approximately 10% to 15%) with low cardiac output, respiratory failure, and sepsis being the major problems postoperatively.

Indications for Tricuspid Valve Surgery

Class I indications for tricuspid repair include severe tricuspid regurgitation in patients having mitral valve surgery. Tricuspid repair for mild tricuspid regurgitation and pulmonary artery hypertension or tricuspid annular dilatation are class IIb indications for tricuspid repair in patients having mitral valve surgery. Severe symptomatic primary tricuspid regurgitation is a class IIa indication for isolated tricuspid valve surgery.[2,3,23]

Surgical Approach

The tricuspid valve is easily approached via either a sternotomy or a right thoracotomy. The most common procedure is tricuspid annuloplasty, which may be performed using a rigid or flexible ring, or a running stitch around the annulus known as a De Vega suture annuloplasty that is less durable. The tricuspid annulus tissue offers little support and sutures need to be placed and tied carefully to avoid tears, correcting tricuspid regurgitation by reducing the posterior and anterior annulus that are most prone to dilatation. The atrioventricular node is avoided, leaving the area at the apex of the triangle of Koch free of sutures. Tricuspid valve replacement is usually performed for failed repairs, and in operations for endocarditis or carcinoid tricuspid pathologies. A bioprosthetic replacement is usually preferred over a mechanical valve

replacement, which will preclude future placement of transvalvular catheters or wires. The valve and subvalvular apparatus is excised, and the valve is inserted using horizontal everting mattress sutures with pledgets on the atrial side.

SURGERY FOR INFECTIVE ENDOCARDITIS

DIAGNOSIS

The Duke diagnostic criteria are 95% specific, with a 92% negative predictive value.

Duke criteria for infective endocarditis establish a definite diagnosis with two major or one major and three minor or five minor criteria. Possible endocarditis is defined by the presence of one major and one minor, or three minor criteria. The major Duke criteria include positive blood cultures (*Streptococcus viridans*, *Streptococcus bovis*, HACEK, *Staphylococcus aureus*, enterococci with no other primary focus from two separate cultures or persistent positive cultures more than 12 hours apart or all of three or majority of four separate cultures positive drawn over the space of >1 hour), and echo evidence including an oscillating intracardiac mass in the absence of alternative explanation, abscess or new regurgitant lesion, or new partial dehiscence of prosthetic valve. The minor Duke criteria include predisposition, fever > 38°C, emboli, or blood culture and echo signs that do not fulfill the definition of major Duke criteria.[2,3,24–30]

INDICATIONS FOR SURGERY

Surgery is indicated for structural valve lesions with evidence of hemodynamic compromise or abscess formation. The optimal time to operate after embolic stroke is 7 to 14 days if possible, but it is often necessary to operate sooner because of the patient's hemodynamic state. An accurate assessment of neurologic function is necessary before proceeding with surgery.

Acute endocarditis with stenosis or regurgitation and congestive heart failure is a class I indication for urgent surgery. Other class I indications for surgical intervention include fungal endocarditis; endocarditis complicated by heart block, annular or aortic abscess, or fistulae between right or left atrium or ventricle and sinus of Valsalva, or mitral leaflet perforation in aortic valve endocarditis; prosthetic valve endocarditis and dehiscence; or worsening valve function, heart failure, or abscess. Native valve endocarditis and recurrent emboli and persistent vegetations despite appropriate antibiotics, and the

presence of prosthetic valve endocarditis and bacteremia despite appropriate antibiotics are class IIa indications for surgery. Finally, the presence of mobile vegetations > 10 mm in size are class IIb indications for surgery.[2,3]

Choosing the right time to operate can be difficult: the surgeon must define "appropriate antibiotics," and balance the need to optimize major comorbidity, often including acute embolic stroke, with the fact that these patients are liable to deteriorate irreversibly. In most cases, early surgical intervention is preferable to late: in case of preoperative embolic stroke, delay surgery for 5 to 10 days if possible; if the patient has evidence of a hemorrhagic stroke, then several weeks are usually needed to minimize the risk of additional intracerebral bleeding while on cardiopulmonary bypass or postoperatively.

SURGICAL APPROACHES

The goals of surgery are to remove infected tissue and drain abscesses, reverse hemodynamic abnormalities, and to restore cardiac and vascular architecture. Transesophageal echocardiography is critical in planning surgery that may involve drainage of abscesses, debridement of necrotic tissue, closure of acquired defects, such as ventricular septal defect, annular abscess, fistulae, and aneurysms, in addition to valve repair and replacement. The most common approach is median sternotomy, which allows assessment and treatment of all valves in the event of more extensive involvement than identified preoperatively.

Aortic valve endocarditis is not usually amenable to valve repair, and is treated with complete excision and debridement of all infected tissue, with valve replacement if extensive annular involvement is not there. Extensive destruction of the annulus and sinuses requires treatment with aortic root replacement. There is no good evidence that homograft valve replacement versus bioprosthetic or mechanical valve root replacement reduces the risk of recurrent infective endocarditis. Aortic valve abscesses are most common posterior to the membranous part of the interventricular septum, and under the left coronary ostia.

Mitral and tricuspid calve endocarditis can often be treated effectively with surgical repair after resection and debridement of all infected tissues. Mitral valve abscesses are most common in the P2 portion of the annulus. For small abscesses, evacuation and debridement is relatively straightforward, but in extensive root abscesses involving the atrioventricular and ventriculoarterial junction, debridement may cause dehiscence and abscesses around the mitral valve should also be debrided with great regard for atrioventricular discontinuity.

In prosthetic valve endocarditis, extra care must be taken to debride all prosthetic material. Small vegetations can be debrided and perforations in the mitral valve may be repaired with autologous pericardium.

COMBINED VALVULAR PROCEDURES

PATHOPHYSIOLOGY OF COMBINED VALVE DISEASE

Rheumatic valve disease, infective endocarditis, and connective tissue disease are the most common causes of disease requiring surgical intervention on two or more valves. The pathophysiology is dictated by the dominant lesion. Aortic and mitral regurgitation impose a large volume overload on the left ventricle, which undergoes marked hypertrophy and eventual dilatation. Aortic and mitral stenosis result in a small, hypertrophied, noncompliant left ventricle, usually with well-preserved LV function. In patients with mitral stenosis and aortic regurgitation, the mitral stenosis is usually dominant. Mitral stenosis restricts LV, blunting the effect of AI on LV volume. Even in severe AI, hyperdynamic circulation and dilated left ventricle are absent. In AS and mitral regurgitation, the AS worsens the degree of mitral regurgitation. The mitral regurgitation causes difficulty in assessing the severity of the AS because of reduced forward flow. Patients can decompensate rapidly. In mitral stenosis or regurgitation and tricuspid regurgitation, pulmonary hypertension is usually present.

INDICATIONS FOR SURGERY IN MODERATE VALVE DISEASE

Although the nondominant lesion may be mild at the time of operation, these lesions are progressive. Rheumatic AS that was mild at the time of operation on concomitant rheumatic mitral lesion progresses to moderate to severe in one-third of patients within 5 years. The progression of AI is much slower and better tolerated, although distorting the aortic annulus by mitral annuloplasty ring or replacement may cause 2+ AI to become severe. Regurgitant combined lesions tend to progress faster, and the prognosis in combined stenotic lesions is worse than in isolated stenotic lesions. The temptation to operate on multiple valves to avoid later surgery needs to be balanced against increased perioperative mortality and long-term morbidity of valve replacement. It is sometimes reasonable to inspect the valve in question at the time of surgery to make a final decision.

PROSTHETIC VALVES

TYPES OF VALVE PROSTHESIS

Valve prostheses are either mechanical or bioprosthetic ("tissue").[31] Tissue valves are mounted on a metal frame (stented), or supported by pig aorta and cloth (stentless). Stented valves are the most commonly used bioprosthesis, and are usually either porcine aortic valves or bovine pericardium. Homografts are human cadaveric aortic roots, complete with aortic valves in situ. A pulmonary autograft is the patient's own excised pulmonary valve used in the Ross procedure.

Mechanical Valves

Over 50 models of mechanical valves exist underlying the fact that no single design meets all the criteria of the perfect prosthesis. Bileaflet valves provide the best hemodynamic profile and lowest thromboembolic risk, and so are the most widely used today. Commonly inserted models include CarboMedics (radiopaque titanium ring with carbon discs) and St Jude Medical (pyrolytic carbon, radiolucent). Tilting disc (or monoleaflet) valves have been largely superseded by bileaflet valves with better hemodynamic profile. Tilting disc valves include Metronic-Hall A770 carbon-coated disc in sewing ring and Bjork-Shiley carbon-coated disc with titanium struts. Ball-in-cage valves were the first prostheses with long-term durability, but are no longer manufactured. They are associated with higher thromboembolic rates and are bulky prostheses with Starr-Edwards the best known model.

Bioprosthetic Valves

There is a similar variety of choices of tissue valves. Discovery of glutaraldehyde fixation in the 1960s by Alain Carpentier, followed by antimineralization led to second- and third-generation tissue valves with improved durability. There are two main types: stented and stentless.[30] Stented valves are the most commonly implanted, as they are technically easier to implant. Porcine stented valves are made of pig aortic valves, usually with the porcine noncoronary cusp (which is smaller in the pig) replaced with a coronary cusp to make the valve symmetrical. Examples include Carpentier-Edwards 2625, Hancock (Medtronic), and the Hancock II with an anticalcification agent added to the fixative. Bovine stented valves are made of bovine pericardium

(equine occasionally used), such as the Perimount (CE 2700/CE Magna). Stentless valves are porcine valves supported by porcine aorta. The lack of a stent means the valves have a better hemodynamic profile, but are technically trickier to implant. The most commonly used include the Freestyle, which may be implanted in the subcoronary position as a valve replacement, as an inclusion root cylinder, or as a full aortic root replacement, and hence “Freestyle.”

Homografts

Homografts are aortic roots removed from cadaveric human hearts and implanted as root replacements: the graft does not express major histocompatibility complex antigen as viable endothelial cells disappear within hours of implantation and so allograft rejection does not occur. Valves are removed from disease-free cadaveric hearts, unsuitable for transplantation, of donors aged 6 months to 55 years, up to 12 hours after death. The donor heart is procured using aseptic technique, preserved in cold Ringer lactate solution, and packaged in sterile plastic bag that is buried in slush. Homograft preparation takes place in a clean not aseptic environment. The homograft block consists of all tissue between the base of the left ventricle containing the anterior leaflet of the mitral valve and the aortic annulus, to the innominate artery. The coronary ostia are preserved with a small rim of coronary artery. The annulus is sized and the length of aorta recorded. There are three main techniques for preservation, which aim to prevent bacterial colonization and preserve fibroblasts and endothelial cells. Cryopreservation has largely superseded antibiotic preservation. Homovital preservation is a recent development. After harvest, the homograft block is stored in a culture medium that contains a low concentration of broad-spectrum antibiotics and stored at 4°C for 24 hours. The culture medium is changed and the tissue stored for a further 24 hours at 4°C. It can either be used at this time as a homovital graft or frozen in 10% fetal calf serum and 10% dimethylsulfoxide (DMSO) with controlled rate freezing (fall of 1°C/min to a target temperature of −40°C) to achieve cryopreservation.

Where root replacement is indicated, homografts are more pliable than Dacron composite valve replacements, may be more resistant to infection (although there are little data to support this), and so are favored in surgery for aortic valve endocarditis requiring root replacement where tissue is very friable and reinfection a significant risk. However, homografts are not as durable as mechanical valves, and may not be as durable as porcine or bovine valve replacement. Homograft aortic root replacement is a technically demanding

operation and the results are very dependent on the surgeon, given the additional technical complexity of positioning the homograft in the correct anatomic position, dissecting out the coronary ostia and reimplanting them, and additional suture lines, all of which carry an increased risk of postoperative bleeding and prolong the time for which the patient is on bypass. The national mortality for aortic root replacement is approximately 7%,[9] compared with approximately 1% to 2% for subcoronary aortic valve replacement. There is a theoretical risk of transmitted infections: tuberculosis was transmitted in several cases before preservation and procurement protocols changed. Homografts depend on donor organ supply, which is falling. Homograft tissue is variable in quality, depending on the age of the donor, as well as the skill of the harvester: both the homograft aorta and the valve leaflets may be perforated or buttonholed, and the tissue can be very friable.

Pulmonary Autograft

Using the patient's own pulmonary valve to replace the aortic valve is known as the Ross procedure, after Donald Ross, the British surgeon who pioneered its use. The pulmonary valve is replaced with a pulmonary homograft, which has a life expectancy of 15 to 20 years. The patient's own pulmonary valve in the aortic position has better life expectancy than an aortic bioprosthesis, is resistant to infection, does not warrant formal anticoagulation, and most importantly "grows" with the patient.

Indications for the Ross procedure are controversial because of the additional mortality and morbidity associated with the operation and variable data on the freedom from need for reoperation. The use of the Ross procedure is least controversial in very young patients who will not be well served by implanting small prosthetic valves. Use of the Ross procedure in older patients with a predicted life expectancy of greater than 30 years, and in whom an active lifestyle requires good hemodynamic function and contraindicates warfarin, is thought by some clinicians to be reasonable if the surgeon can offer operative mortality of <2%, that is, comparable to isolated aortic valve replacement.

Contraindications to the Ross procedure include Marfan and other connective tissue disorders. Rheumatic valve disease is a viewed by some as a contraindication.

The drawbacks are primarily related to the technical difficulty of both procedure and reoperation, and many more surgeons have been discouraged by the steep learning curve and abandoned the operation than have managed to

successfully adopt it as part of their repertoire. Mortality in one metaanalysis ranged from 1% to 7%. Reoperation for autograft dilatation is reduced by modifications where Teflon felt is used to buttress the proximal suture line.

CHOICE OF VALVE PROSTHESIS

There are no strong data showing major long-term survival difference between mechanical versus tissue valve in either aortic or mitral position.[15,22,23–36] In a patient aged over 65 years, a bioprosthetic valve will likely last the patient's lifetime, does not require long-term anticoagulation, and carries an approximate 1% annual risk of thromboembolic stroke; but valve failure becomes an increasing risk from 10 to 15 years depending on position and patient age. Mechanical valves last decades but approximately 15% will need explanting by 15 years because of endocarditis, pannus, or thrombosis; they require lifelong anticoagulation and have 3% to 4% annual risk of stroke or hemorrhage.

Bioprosthetic Valve Deterioration

Freedom from structural valve deterioration at 12 years in older patients is over 90% with third-generation tissue valves such as the Carpentier-Edwards pericardial valves in the aortic position.[22,37] Tissue valves last longer in the elderly because the hemodynamic demands on the valve are less: the chances of bioprosthetic aortic valve failure at 12 years is approximately 40% in patients aged 18 to 39 years, at least 30% in patients aged 40 to 49 years, and at least 10% in patients aged over 70 years. Lifetime risk of reoperation is similar for each age group. Tissue valves last less well in the mitral position compared with the aortic position, and redo mitral valve replacement is associated with higher risk of mortality than redo aortic valve replacement. Calcification of bioprostheses occurs in areas of greatest stress: the commissural regions of porcine valves or the zone of flexion in porcine and pericardial valves, and leads eventually to prosthesis failure. This may happen earlier in patients with renal failure, but the disadvantages of managing anticoagulation in these patients and their shorter life expectancy means bioprostheses remain a reasonable choice in these patients.

Hemodynamic Profile

In smaller sizes (eg, #19, #21), bioprostheses cause more flow obstruction than same-size mechanical valves. Stented bioprostheses are more obstructive than

stentless, which are more obstructive than mechanical.

Thromboembolic and Hemorrhagic Events

Without anticoagulation, life-threatening thrombosis and thromboembolic events are inevitable. Even in an optimally anticoagulated patient (INR 2.5 to 3), the incidence of major thromboembolic events including stroke and hemorrhage is still 2% to 4% per year (and this number is higher in multiple valves and older patients).[21,38–43] Bleeding problems (pericardial effusion, late tamponade) are more common postoperatively, and valve thrombosis is a later risk in patients not therapeutically anticoagulated.

CHOICE OF VALVE PROSTHESIS IN SPECIAL GROUPS

Younger Patients

National analyses show a trend toward implanting more tissue valves in younger patients. This may reflect the lack of evidence for a long-term survival difference between mechanical and biologic valves[23,24]; greater awareness of the lifetime risk of stroke and bleeding rate and the inconvenience of lifelong anticoagulation; better durability of tissue valves; the fall in the mortality of reoperative surgery; and the increasing feasibility of transcatheter valve-in-valve replacement.[44–55]

Pregnancy

Pregnant women have increased risk of mechanical valve-related thromboembolism: anticoagulation is vital.[43–45] Warfarin, a teratogen, is contraindicated in the first trimester, and low molecular weight heparin or unfractionated heparin should be administered instead, from initial attempts to conceive up until the beginning of the second trimester or delivery. Consequently, bioprosthetic valves may be a reasonable choice for women of childbearing age, even though they will eventually need reoperative valve surgery.

Endocarditis

There are no data to suggest that choice of valve replacement affects recurrence of endocarditis. Homografts have not been shown to give increased resistance to endocarditis, and they are less durable than porcine valves: their main advantage

is that they are more forgiving to implant in very friable tissue.

Atrial Fibrillation

Atrial fibrillation is no longer an indication to implant a mechanical valve: concomitant ablation means 60% of patients will be in sinus rhythm at 1 year, obviating the need for anticoagulation altogether if a bioprosthesis is implanted.

PERIOPERATIVE CARE

Preoperative Management

All patients undergoing cardiac surgery should undergo a careful history and physical examination to first confirm the indication for surgery, identify possibly contraindications to surgery, and conditions that may increase surgical risk. An accurate description of severity, duration, and nature of symptoms; a cardiovascular history including prior cardiovascular interventions, risk factors, and medications; and a comprehensive cardiovascular examination are mandatory. Assessment of respiratory, renal, and neurologic dysfunctions is indicated based on clinical history, examination, and risk factors. A recent change in symptoms or clinical examination may be an important finding that may change the timing or type of surgery.

All patients should have a recent echocardiogram clearly identifying the severity of the lesion as well as left and right ventricular function, the presence of pulmonary hypertension, and other valvular lesions. Cardiac catheterization should be performed in most patients; in young patients with no risk factors for coronary disease, a CT coronary angiogram may be sufficient to show anatomy. In patients with bicuspid valve disease, a CT scan is useful to evaluate the ascending aorta for aneurysm. Older patients, those with a history of mediastinal radiation, evidence of aortic calcification on imaging, any pulmonary history, and those patients undergoing reoperative cardiac surgery should undergo a CT scan of the chest without contrast. Lung function testing should be performed in patients with pulmonary disease or smoking history.

Antiplatelet agents and anticoagulation should be stopped several days before surgery, with appropriate bridging therapy if indicated. It is common practice to stop angiotensin converting enzyme inhibitors for 24 hours preoperatively to reduce the risk of postoperative vasoplegia. A complete blood count, coagulation profile, blood chemistry, liver function tests, and blood cross match are part of the standard panel of tests. All patients should have a 12-lead ECG and a chest

X-ray. The patients must not eat or drink for 8 hours before induction of anesthesia. In diabetic patients, an insulin sliding scale may be needed.

Postoperative Management

Most patients follow the expected postoperative course, but particular vigilance is required to prevent and recognize potentially life-threatening complications including hemorrhage, cardiac tamponade, respiratory and renal failure, stroke, and arrhythmias and conduction block, which can arise unexpectedly particularly during the first 48 to 72 hours after surgery. Urinary, respiratory, and sternal wound infections are more common after postoperative day 4.

Patients arrive on the intensive care unit ventilated with a central venous line, radial arterial line, Foley catheter, and sometimes a pulmonary artery catheter in place. A chest X-ray, 12-lead ECG, complete blood count, coagulation profile, blood chemistry, liver function tests, and arterial blood gas are performed on arrival. The chest X-ray is checked to review the position of the endotracheal tube, the pulmonary artery catheter, and the presence of hemothorax or pneumothoraxes. The ventilator settings are adjusted accordingly. Inotropic support may increase but more commonly decreases during the first 6 hours, and is weaned according to hemodynamic parameters such as cardiac index and mixed venous and blood pressure. Temporary epicardial pacing may be required and it is important to understand how the pacing wires and box work, particularly in an emergency. Most patients wean from the ventilator and are extubated within 6 hours. A spontaneous diuresis of at least 1 mL/kg/h is expected. Mediastinal drainage should decrease steadily and should not be greater than 150 mL/h. Insulin requirements often increase. Prophylactic antibiotics are continued. Aspirin is given 81 mg orally or via the nasogastric tube. Preoperative antianginals are discontinued.

On postoperative day 1, the large chest drains are removed after 3 hours of consecutive zero drainage and a post drain removal chest X-ray is taken and checked for pneumothoraxes. The central line and arterial line are removed. The patient is transferred to the stepdown unit, and helped to mobilize. Routine oral medication is commenced (usually aspirin 81 mg qd, furosemide 40 mg qd, preoperative statin, paracetamol 1 g qid, lactulose 10 mL bid, senna two tablets, and low-molecular-weight heparin such as enoxaparin 40 mg qd s/c). Patients who require formal anticoagulation are started on warfarin. Patients should be sitting out of bed, and start eating and drinking.

Over the next 2 to 5 days, the Foley and any remaining central venous, arterial

lines, and chest tubes are removed. The patient should complete a satisfactory stairs assessment with a physiotherapist. All blood results and imaging should be returning to normal values. Adequate pain control should be possible with regular Tylenol and occasional oral opiate analgesia. Pacing wires are removed if there is no conduction block or coagulopathy on postoperative day 4 to 6. Most valve patients should have a routine postoperative transthoracic echocardiogram. The patient should have passed stool before being discharged home.

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Patient and Family Information for: CONTEMPORARY SURGICAL APPROACH TO VALVULAR DISEASE

WHAT THE PATIENT AND FAMILY NEED TO KNOW

The heart works by pumping blood though four one-way valves, and over time these valves may become too tight (stenosis) or leaky (regurgitation). This most commonly affects two valves on the left side of the heart—the aortic and mitral valves—and sometimes affects the first valve on the right side of the heart—the tricuspid valve. In all cases, this means that the heart has to work harder to accomplish its job of pumping 5 to 8 L of blood per minute around the body. If this happens slowly, then the heart can compensate by stretching and developing thicker muscle. But eventually the heart muscle reaches its limit, and heart failure can result. Before that, the effects of the extra work and compensation can be felt as chest pain, breathlessness, or dizziness with exercise. In advanced cases, fluids fill up in the lungs and patients may experience difficulty breathing even when lying down, and may have lower leg swelling.

Sometimes a murmur can be heard using a stethoscope, but usually the most accurate way to assess the problem is an echocardiogram, which is a type of ultrasound that measures the function and size of the chambers of the heart, and assesses the heart valves.

Mitral and tricuspid regurgitation can be repaired, which allows patients to keep their own valve tissue, with the advantage of not needing anticoagulation and less risk of needing repeat surgery in the future. Most stenotic valves cannot be repaired and need to be replaced: the options for replacement are either

mechanical valves or tissue valve (biologic). Mechanical valves are very durable, but need the recipient to take a blood thinner such as Coumadin for life. The risk of stroke and major bleeding is higher than with biologic valves, which do not need blood thinners. The disadvantage with tissue valves is that some patients will need repeat surgery as the valves eventually wear out over 10 to 15 years. For most people, a tissue valve is a good option.

Transcatheter aortic valve replacement is increasingly an option for treating aortic stenosis (AS), and for some people can replace a worn-out tissue valve. For most people, valve repair or replacement surgery is low risk, and the risk of major complications such as stroke is lower than the risk of dying or having a stroke if no treatment is carried out. Surgery usually takes 3 to 4 hours and is performed on the heart-lung machine, under a general anesthetic through a 2-to-5-inch incision usually in the front of the chest. Most patients are able to walk few days after surgery, and go home after 5 days.

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The Care of the Adult Patient With Congenital Heart Disease in the Cardiac Care Unit

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital lesion, estimated at 0.8% of newborns.[1–4] The medical and surgical revolution in the care of children with CHD over the recent decades has led to survival rates above 90% of children reaching adulthood. There are now more adults than children with CHD, with more than 1 million cases in the United States. Adults account for approximately 66% of the overall CHD population, and 60% of those with severe CHD.[5] A recent outcome study showed that survival of patients with adult congenital heart disease (ACHD) is increased when care is rendered in a center that has expertise in ACHD care.[6]

Care for the patient with ACHD in the cardiac care unit (CCU) is often challenging and requires meticulous investigation into the patient's past medical and surgical histories to understand complex pathophysiology. The patient and, commonly, the parents are an important source of information. One should enquire about the type of congenital defects and surgeries the patient underwent as well as the baseline vital signs, functional capacity, and known residual

lesions.

The physical examination may reveal and corroborate information. For example:

1. Left lateral thoracotomy scar may be a hint of a previous Blalock–Taussig (BT) shunt (communication between the subclavian and the pulmonary artery [PA] for lesions that obstruct pulmonary blood flow) or coarctation of the aorta (CoA) repair.
2. Blood pressure differences between the upper and lower extremities may suggest significant obstructive CoA.
3. Patients having Eisenmenger syndrome (ES) are cyanotic, have clubbing, an accentuated P2 component on cardiac auscultation, yet do not exhibit an impressive murmur of the original unrepaired shunt (eg, large ventricular septal defect [VSD]) because ventricular pressures have reached equilibrium.
4. Continuous murmur over the left upper chest with a wide pulse pressure may suggest a hemodynamically significant patent ductus arteriosus (PDA), aortic regurgitation (AR), or, in the relevant clinical setting, a sinus of Valsalva rupture.
5. Congenital pulmonary stenosis has a mid-systolic click on auscultation that decreases in intensity during inspiration (the only right-sided lesion that does not accentuate during inspiration).

To simplify the understanding of complex lesions and hemodynamics, the congenital clinical scenario could be deconstructed to basic components such as shunts and obstructive and regurgitant lesions. These are further incorporated to the common adult pathologies (eg, arrhythmia, heart failure [HF], ischemia, sepsis, hypovolemia, and pulmonary hypertension). A drawing of the heart with lesions may be useful.

Any evaluation of a change in the clinical status of a patient with ACHD warrants reevaluation of the anatomy using multimodality imaging (eg, transthoracic and transesophageal echocardiography [TTE, TEE], cardiac magnetic resonance imaging [MRI]) as well as a new hemodynamic assessment by a right-sided hemodynamic catheterization). Opacification of conduits, pathways, vascular structures, and baffles is often needed to further delineate the anatomy. In the setting of pulmonary hypertension, a vascular reactivity test with nitric oxide and oxygen may be useful to determine reversibility.

It is important to underscore the importance that ACHD cardiologists are to be

an integral part of the care team with congenital cases in the CCU. The ACHD team is a large collaboration between adult and pediatric clinical cardiologists, congenital imagers, and those in interventional cardiology, electrophysiology, intensive care, anesthesia, obstetrics, and genetics. Weekly complex case conferences with team members are encouraged.

The following sections detail specific congenital lesions followed by several fundamental topics.

SPECIFIC LESIONS

Shunt Lesions

In normal physiology, the pulmonary blood flow (Qp) and systemic blood flow (Qs) run in parallel and maintain an equivalent ratio of blood through both the circulations at any given time (Qp:Qs = 1:1). Any abnormal connection that allows oxygenated and deoxygenated blood to mix is called a shunt. Shunt calculations of Qp:Qs > 1 signify net left-to-right shunting, whereas Qp:Qs < 1 signifies net right-to-left shunting. Shunt lesions are further divided into pre-tricuspid lesion, such as atrial septal defects (ASDs) and partial anomalous pulmonary venous connection, and post-tricuspid lesions such as VSDs and PDAs. Pre-tricuspid lesions cause right-sided heart enlargement and post-tricuspid lesions cause left-sided heart enlargement. A Qp:Qs > 1.5 commonly denotes a significant shunt. The spectrum can vary from small ASDs or VSDs to near absence of delineation between the right and left heart, causing a single-ventricular mixing physiology. Commonly, shunt lesions with chamber enlargement are an indication for closure of the communication, unless there is evidence of irreversible pulmonary hypertension, which is the unfortunate sequela of chronic volume overload with or without pressure overload through the lung vasculature.[7]

CCU care of shunt lesions warrants delineation of the anatomy, shunt calculation (Qp/Qs, most accurate by cardiac magnetic resonance [MR] and cardiac catheterization), and assessment of the pulmonary pressures (by echocardiography and cardiac catheterization). The degree of shunting is influenced by the size of the shunt, compliance of the ventricles, and the downstream pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR). Altering each of these components would change the degree of shunting.

We discuss the most common congenital shunt lesions including ASD, VSD,

and PDA.

Atrial Septal Defect

ASDs are among the most common CHDs encountered in adulthood (**Figure 41.1**).[8] ASDs typically cause left-to-right shunting and right-sided heart structure enlargement. The direction of the shunting occurs because of greater compliance of the right ventricle and thus lower right atrial pressure. The timing of the interatrial shunt is typically in late systole, early diastole, and during atrial systole. In situations where the right ventricular (RV) compliance is decreased and right atrial pressure is increased, ASDs may shunt right-to-left and cause cyanosis. Qp:Qs > 1.5 and an ASD larger than 1 cm are associated with a significant shunt. The clinical concern with ASDs is the development of RV enlargement and dysfunction due to volume overload, arrhythmias, paradoxic emboli, and the development of pulmonary hypertension. Although rare, the pulmonary vascular disease may progress to a fixed state that would cause the shunt to reverse and cause cyanosis, which is referred to as ES.

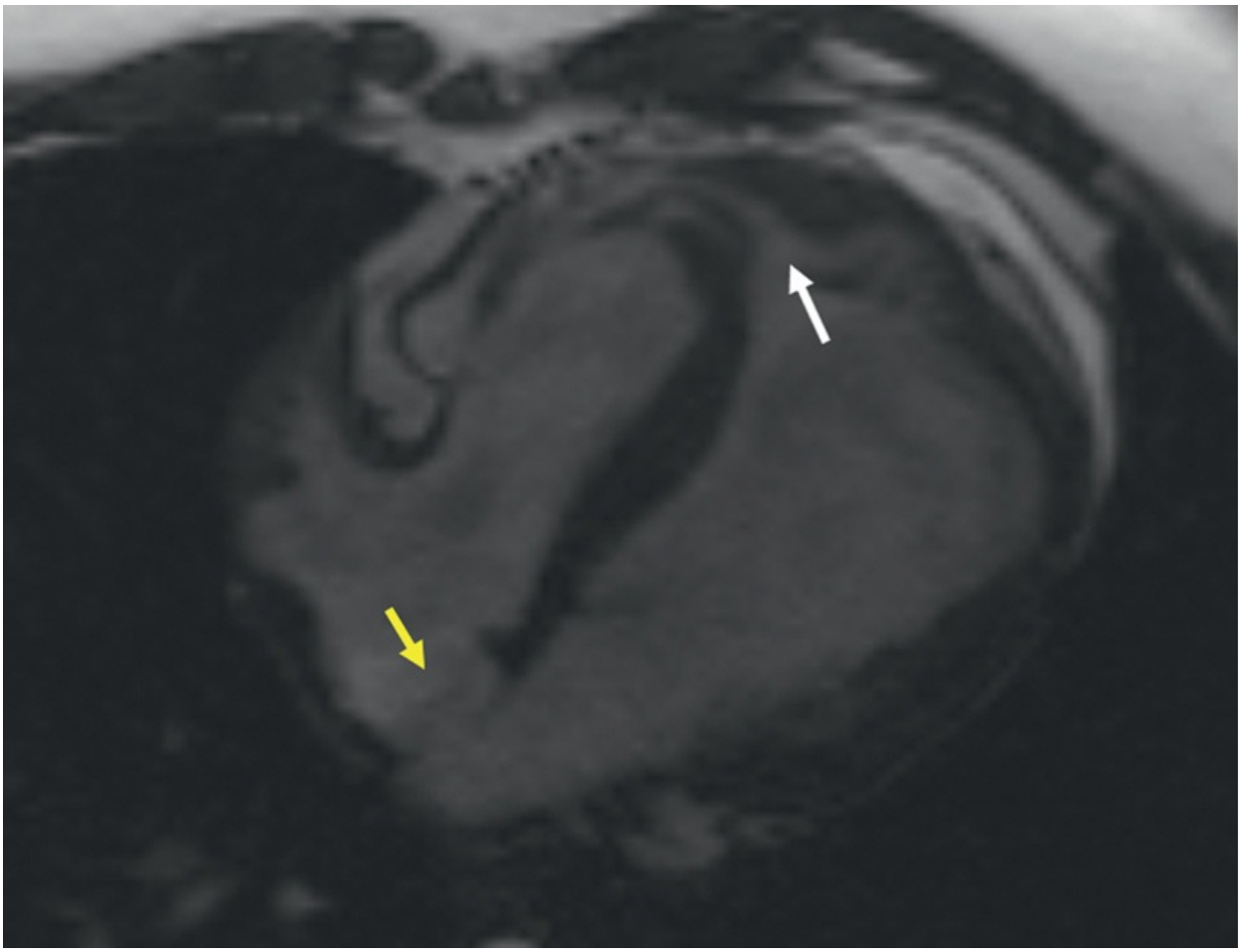

FIGURE 41.1 Shunts by CMR. Combination of a secundum atrial septal defect (*yellow arrow*) and an apical muscular ventricular septal defect (*white arrow*). The patient also has a relatively hypoplastic right ventricle compared to the left. CMR, cardiac magnetic resonance.

Clinically, the age and degree of symptoms vary according to the size of the shunt, direction of the shunt, and presence of other associated congenital malformations. The most common type of ASD is the secundum type, which is a deficiency of the septum primum, the major membrane forming the septum. The deficiency is located in the center of the interatrial septum. Other types include primum ASD, which is an inferior defect that is part of the endocardial cushions (junction between the atria and ventricles) and is associated with a cleft anterior mitral valve; sinus venosus defect is a deficiency in the tissue at the junction between the right atrium and the superior vena cava (SVC) or inferior vena cava (IVC) and is associated with anomalous pulmonary venous connections; and unroofed coronary sinus is a defect that opens between the coronary sinus (left-sided atrioventricular [AV] groove) into the left atrium and is associated with a persistent left SVC and could present with cyanosis.

Patients with ASDs commonly present by the fifth decade with exercise intolerance and/or arrhythmia. On physical examination, RV enlargement may cause an RV heave and on auscultation a wide and fixed splitting of S2 is characteristic of ASDs. Pulmonary hypertension will have a loud P2. Owing to the increased flow across the tricuspid valve (TV), a diastolic rumble that accentuates with inspiration may be heard. In primum ASD, which is associated with cleft mitral valve, murmur of mitral regurgitation can be appreciated. If a patient has ES, cyanosis and clubbing may also be present. Electrocardiogram (ECG) in secundum ASD shows right axis deviation, whereas in primum ASD it is left axis deviation; and the P waves in sinus venosus ASD are typically negative in the inferior leads. Otherwise, ECGs have rSr′ or rsR′ pattern due to RV hypertrophy, and the Crochetage pattern is a sensitive and specific sign of ASD described as a notch on the R wave in the inferior leads.

Echocardiogram is essential for diagnosis of an ASD and is helpful in identifying associated lesions. A TTE is also useful to evaluate the size and function of the right ventricle as well as direction of the shunt. Using Doppler echocardiography, pulmonary artery systolic pressure (PASP) and the ratio of Qp:Qs can also be estimated (however, these are not always accurate and are subject to errors). TTE is often adequate for diagnosis of secundum and primum ASDs. However, it is less sensitive for diagnosis of sinus venosus ASDs. Presence of right heart dilatation in the absence of an alternative etiology should always raise suspicion for an undiagnosed ASD on a TTE. TEE is typically needed for confirming diagnosis of sinus venosus ASD and unroofed coronary sinus. A TEE can identify anomalous pulmonary venous connection associated with sinus venosus ASD. A TEE is also helpful to evaluate the size of the ASD as well as to guide treatment options. Cardiac MRI is very useful for evaluating the degree of shunting (Qp:Qs), delineating the anatomy including identifying the pulmonary veins. In patients who cannot undergo a cardiac MRI, computed tomography (CT) may be considered. Lastly, once ASD repair is being considered, a cardiac catheterization is necessary to evaluate PA pressures as well as PVR and vascular reactivity because these factors impact the management of the ASD.

Indications for closure of ASDs are RV enlargement regardless of symptoms, paradoxic embolism, or orthodeoxiaplatypnea (dyspnea and cyanosis when sitting upright or standing). Secundum ASDs may be closed percutaneously with an ASD closure device, unless they are larger than 35 mm or have inadequate margins (<5 mm) and then surgical closure is warranted. Primum ASDs, sinus

venosus defects, and unroofed coronary sinus ASDs require surgical closure using a patch repair. Contraindications for ASD closure are evidence of irreversible pulmonary hypertension (ie, ES, PVR greater than two-thirds of SVR, or commonly PVR above 5 to 7 Woods units)

Patients with small, asymptomatic ASDs (typically <10 mm) with normal RV function and absence of pulmonary hypertension should be monitored.

Ventricular Septal Defect

VSDs are the most common CHD in children (**Figures 41.1** and **41.2**). VSDs are associated with left-sided heart enlargement and dysfunction and are more prone to cause pulmonary hypertension.[9]

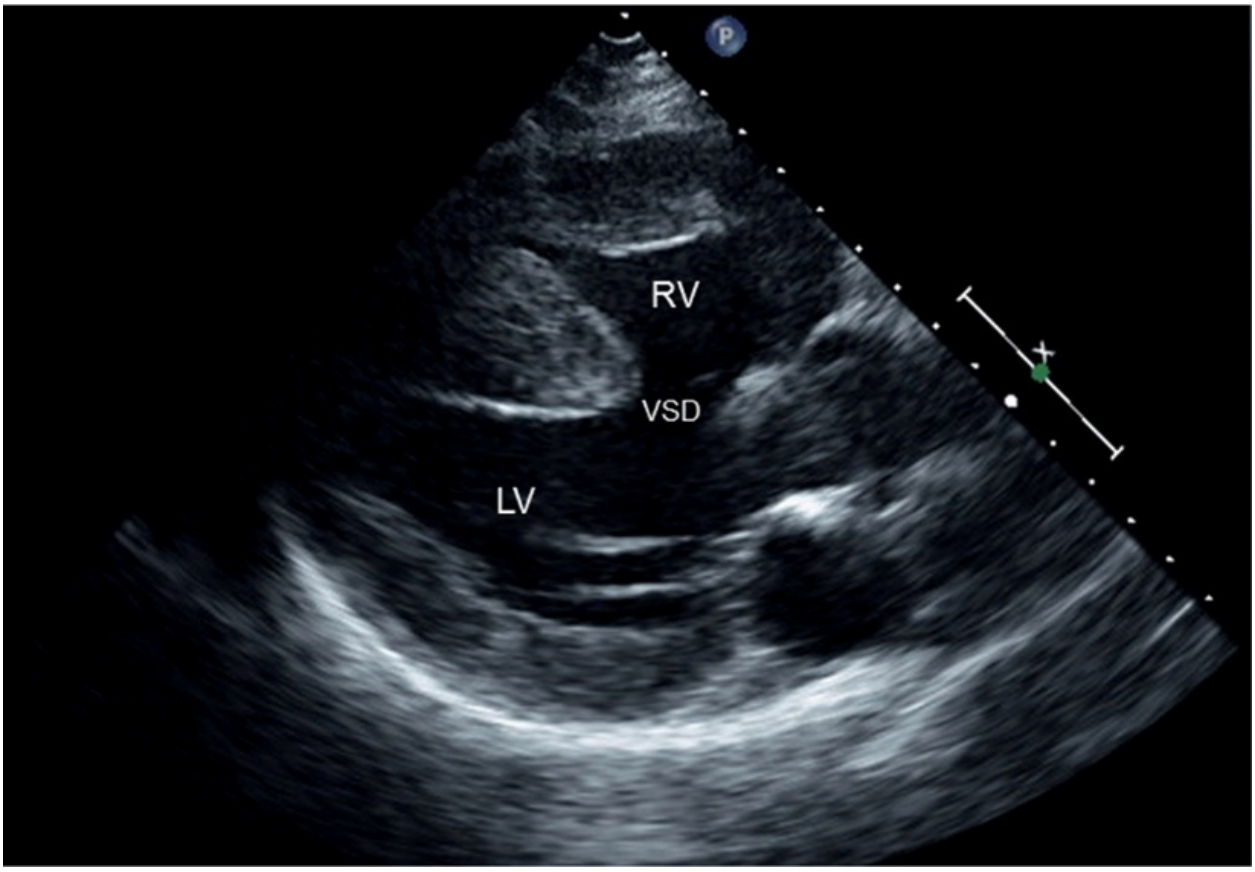

FIGURE 41.2 Large muscular VSD with Eisenmenger syndrome; transthoracic parasternal long-axis view echocardiography. The RV is severely hypertrophied. LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect.

The most common type is the membranous VSD, which is located next to the septal leaflet of the TV. Occasionally, it is associated within an aneurysm of the

TV-associated tissue and at times is occluded by the septal leaflet of the TV. Infundibular VSDs (also known as conal, supracristal, subpulmonary, subarterial, or doubly committed juxta-arterial) are common in the Asian population. These are typically located beneath the semilunar valves and are often associated with AR due to prolapse of the right coronary cusp of the aortic valve into the defect. Inlet VSD is a deficiency in the endocardial cushion (junction between the atria and ventricles) and is seen commonly in patients with trisomy 21. When associated with a primum ASD and a common AV valve, these constitute an atrioventricular canal defect (AVCD). Muscular VSDs (also called trabecular) are VSDs surrounded by muscle tissue and not infrequently are multiple. The types of VSDs that may close spontaneously in childhood (40% to 60% of VSDs) are the membranous and muscular types.

Clinically, the majority of patients in adulthood will not require any interventions, because isolated small VSDs remain asymptomatic. Moderate-sized VSDs already present with left-sided HF in childhood, and large VSDs present with HF in infancy or pulmonary hypertension in childhood. Interestingly, on physical examination the small VSDs present with a loud holosystolic murmur (large pressure gradient), whereas the large ones are minimally heard because there is equilibrium in pressure between the ventricles. As noted before, patients with ES would have cyanosis, clubbing, and signs of right-sided HF and an accentuated P2 on auscultation. Most patients with VSDs initially have relatively normal ECGs. Subsequently, as the left ventricle develops volume overload, signs of interventricular conduction delay and left ventricular (LV) enlargement may be noted. With the presence of Eisenmenger complex, signs of RV hypertrophy, right axis deviation may also be noted.

TTE is useful in visualizing the defect and assessing LV/RV size and function as well as pulmonary pressures. Cardiac MRI would provide supplemental visualization of the defect as well as more accurate shunt calculations. Cardiac catheterization is used to delineate anatomy and assess for pulmonary pressures as well as pulmonary vascular reactivity in the setting of pulmonary hypertension. A restrictive VSD is regarded as a small shunt with $Qp/Qs < 1.4$ and high-pressure gradients across the VSD. $Qp/Qs > 1.5$ denotes significant (moderate and above) shunt. LV enlargement with a $Qp/Qs \geq 2$ as well as symptoms or history of endocarditis without the presence of irreversible pulmonary hypertension are class I indications for VSD closure. Most VSDs require surgical patch repair; and if other concomitant lesions (such as aortic insufficiency) exist, they should be addressed as well. Percutaneous repair may

be considered for patients with an isolated uncomplicated muscular VSD and for membranous VSD bases on the anatomy. Asymptomatic patients with small VSDs can be followed up with serial imaging and follow-up. No endocarditis prophylaxis is warranted in patients with unrepaired VSDs.

Patients with ES are managed medically, which is discussed in a separate section.

Patent Ductus Arteriosus

PDA is a persistent communication between the aortic isthmus (junction between the aortic arch and descending aorta) and the main PA that causes a left-to-right shunt that may result in left-sided volume overload and pulmonary hypertension.[10] Usually, the ductus arteriosus, which is essential to the fetal circulation for blood flow from the heart to the lower part of the body, closes within 72 hours of birth. There is a female preponderance for PDA with a 2:1 ratio compared to male, and it is associated with congenital Rubella and birth at high altitudes as well as other congenital defects (ie, ASDs, VSDs, CoA). PDAs are primarily a clinical concern because of LV volume overload and dysfunction and a risk for endarteritis or endocarditis (commonly the pulmonary valve). The latter is estimated roughly as up to 1%/year.

The PDA shunt occurs continuously throughout the cardiac cycle in systole and diastole and sounds like “machinery” on auscultation. The direction of the shunt is from the aorta into the PA (left-to-right), and in the setting of a significant shunt, akin to AR, may cause a wide pulse pressure, low diastolic coronary filling pressures, and ischemia. With time, owing to the increased flow across the pulmonary bed, the PVR may rise, eventually leading to shunt reversal, right-to-left shunt, and Eisenmenger physiology. Because the shunt is connected between the PA and the aortic isthmus, the cyanosis only appears in the lower part of the body in the setting of ES, referred to as “differential cyanosis” (**Figure 41.3**).

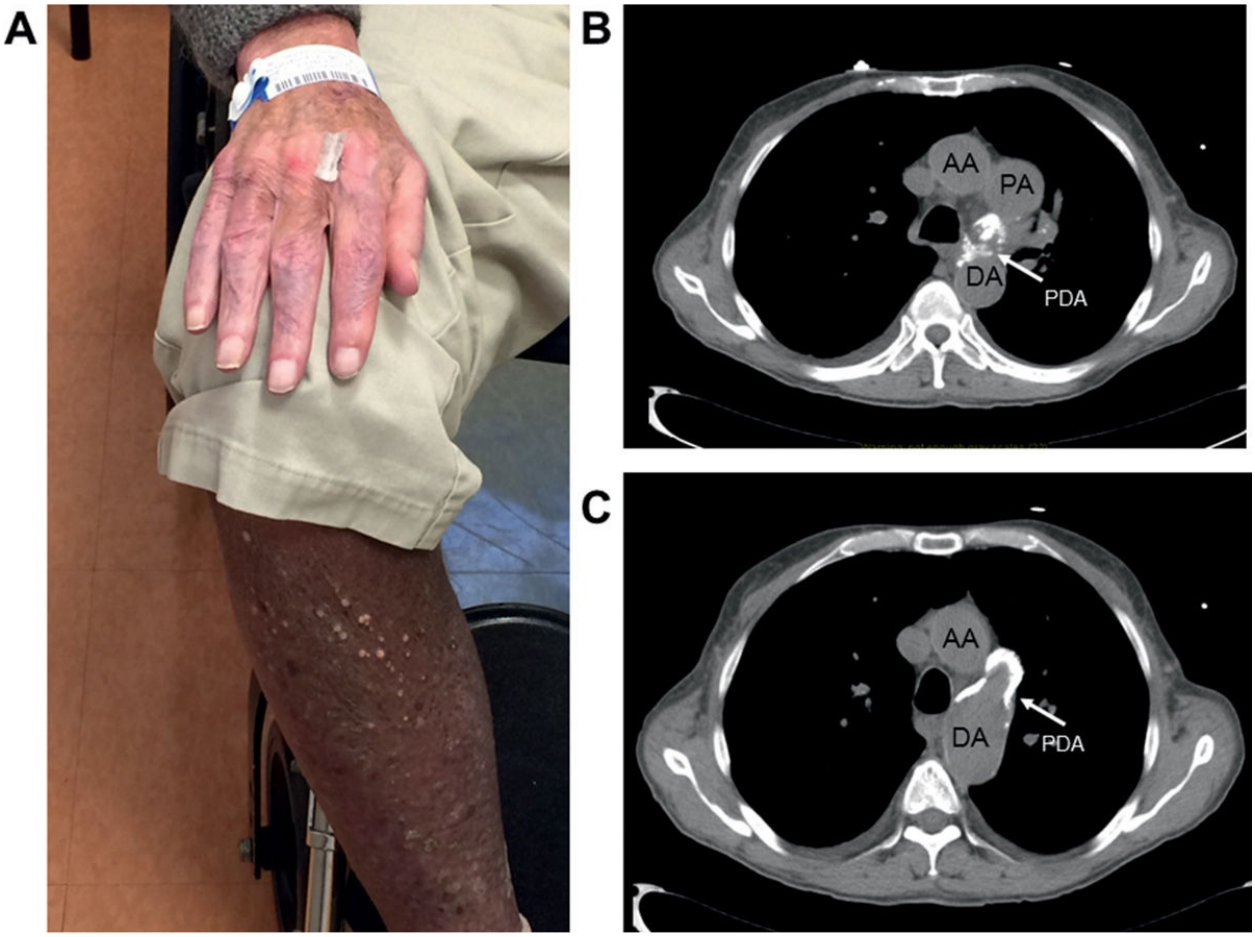

FIGURE 41.3 PDA complicated by Eisenmenger syndrome. A, "differential cyanosis," upper limbs proximal to the PDA are oxygenated and lower limbs beyond the PDA are deoxygenated, as pulmonary flow is shunting right-to-left through the PDA toward the lower body. B and C, two consecutive axial images of non–contrast-enhanced CT scan demonstrating a calcified large PDA *(arrow)* communicating between the DA and the PA. AA, ascending aorta; CT, computed tomography; DA, descending aorta; PA, pulmonary artery; PDA, patent ductus arteriosus.

The clinical presentation depends mainly on the size of the shunt and the presence of any concomitant lesions. Patients with small PDAs may remain asymptomatic and be incidentally diagnosed because of the presence of a murmur, whereas those with moderate-to-large PDAs typically present in early childhood and infancy, respectively, with signs of LV volume overload. Echocardiography is commonly the initial modality to make the diagnosis, and cardiac MR or CT angiography is supplemental for further delineation of the anatomy, Qp/Qs, and pulmonary pressure measurement in preparation for a catheter-based closure procedure.

Generally, any PDA that could be "heard" on auscultation during physical examination is designated for closure. According to guidelines, any PDA with

LV volume overload regardless of symptoms without irreversible pulmonary hypertension should be closed. Also, patients with a history of endocarditis should have their PDA closed. PDAs are occluded with coils or closure devices such as the Amplatzer ductal occluder.

BICUSPID AORTIC VALVE, COARCTATION, AND AORTOPATHIES

Bicuspid aortic valve (BAV) is a common congenital condition with an estimated incidence of 1% to 2% of the general population. The most common cusp fusion is between the right and left. Over time, BAVs can be either stenotic or regurgitant and may require aortic valve replacement in adulthood. BAV is associated with an aortopathy and increased frequency of ascending aortic aneurysms. Aortic root replacement is recommended when the aortic diameter exceeds 5.0 to 5.5 cm or if there is a rapid enlargement of the root (>5 mm/year).[11]

Frequently associated with BAV, CoA comprises a segmental narrowing of the aorta at the ligamentum arteriosum site adjacent to the left subclavian artery (**Figure 41.4**). Patients with significant CoA develop collateral vessels that mitigate the severity of the obstructive narrowing. More than half of patients with CoA have BAV, and about 10% of those with BAV, would be found to have CoA. Another association of CoA is Shone complex, which refers to multiple left heart obstructive lesions that include CoA, BAV, subaortic stenosis, parachute mitral valve, and supra-mitral valve ring.

FIGURE 41.4 Coarctation of the aorta by MR angiography. Three-dimensional reconstruction of the aorta demonstrating (*arrow*) a discrete coarctation of the aorta distal to the left subclavian artery and the area of the aortic isthmus. MR, magnetic resonance.

Patients with CoA commonly present with hypertension, exertional headaches, and leg claudication. CoA is an important diagnosis in the evaluation of systemic hypertension in the young. On physical examination, a significant CoA may cause an abnormally lower blood pressure measured in the lower limbs. However, a significant collateral network may mask these differences and a radial–femoral delay pulse check examination may be completely normal. In addition, carotid pulses may be hyperdynamic and a murmur or bruit may be present in the left interscapular area. Chest X-ray may show the “number 3” sign and rib notching. Patients with CoA are at risk for congestive HF, aortic rupture and dissection, endocarditis and endarteritis, intracerebral hemorrhage from associated brain aneurysms (5%), and myocardial infarction. Management of these patients includes consideration of percutaneous or surgical repair and medical therapy for hypertension. Blood pressure control in the setting of CoA may be challenging because excessive reduction of pressures beyond the coarctation may cause lower body hypotension, gut ischemia, and renal failure. By guidelines, intervention is recommended for patients who have a peak-to-peak gradient across the aortic narrowing as measured on cardiac catheterization greater than or equal to 20 mm Hg. Echocardiography measurements of the maximum instantaneous gradient across the area of coarctation commonly overestimate the peak-to-peak gradient measured in the catheterization laboratory. The mean gradient derived by TTE across the area of coarctation has been found to be more closely related to the peak-to-peak gradient. Cardiac MRI is very useful for delineation of the anatomy, collateral identification, and flow measurements in preparation for stent implantation, which is the preferred method of intervention in the adult patient. It should be noted that patients with CoA have accelerated atherosclerosis and ischemic heart disease, and these should be suspected in the relevant scenario.

TETRALOGY OF FALLOT

Tetralogy of Fallot (TOF) represents a spectrum of disease that is classically defined by four components: (1) subpulmonary infundibular/right ventricular outflow tract (RVOT) stenosis, (2) VSD (commonly membranous), (3) overriding aorta, and (4) RV hypertrophy. Frequently, these patients have small, stenotic pulmonary valves along with PA hypoplasia and stenosis, coronary anomalies, right aortic arch, as well as ASDs.

The embryonic pathophysiology is related to one single abnormal process—the anterior and cephalad deviation of the conal septum leading to right-sided obstruction with an aortic valve overriding the two ventricles. In the neonatal period, this disease causes lack of adequate pulmonary blood flow and cyanosis; and thus the initial treatment may include a shunt between the arterial and the pulmonary circulations (eg, BT shunt between the subclavian artery and the PA) followed by definite repair that includes surgical closure of the VSD and the relief of the RVOT obstruction, commonly using the transannular patch repair.

In the era of modern cardiac surgery, nearly all patients with TOF in the United States will have had reparative surgery early in life. Because the RVOT was resected and there is no functioning pulmonary valve, the major complication related to the TOF repair is chronic pulmonary regurgitation (PR) (**Figure 41.5**). Long-standing PR further begets RV dilatation and dysfunction, tricuspid regurgitation (TR), LV dysfunction related to RV/LV interactions (up to 30%) and tachyarrhythmias (intra-atrial reentrant tachycardia [IART], atrial fibrillation [AF], and VT). Other long-term complications include residual RVOT obstruction, residual VSD from a dehiscing patch, and patch-related TR. By clinical practice guidelines, pulmonary valve replacement (PVR) is warranted for severe PR in symptomatic patients with decreased exercise tolerance or clinical HF. In addition, it is generally agreed that PVR is also reasonable in asymptomatic patients with severe PR who exhibit moderate-to-severe RV enlargement (greater than indexed end-diastolic volume 150 cc/m^2, greater than indexed end-systolic volume of 80 cc/m^2) or dysfunction (right ventricular ejection fraction [RVEF] <47%), left ventricular dysfunction (left ventricular ejection fraction [LVEF] <55%), concomitant moderate and above TR, QRS >160 ms, severe AR, RVOT obstruction/aneurysm, or significant atrial or ventricular arrhythmias related to the right ventricle.[12] New native RVOT transcatheter pulmonary valves are in the investigational phase.

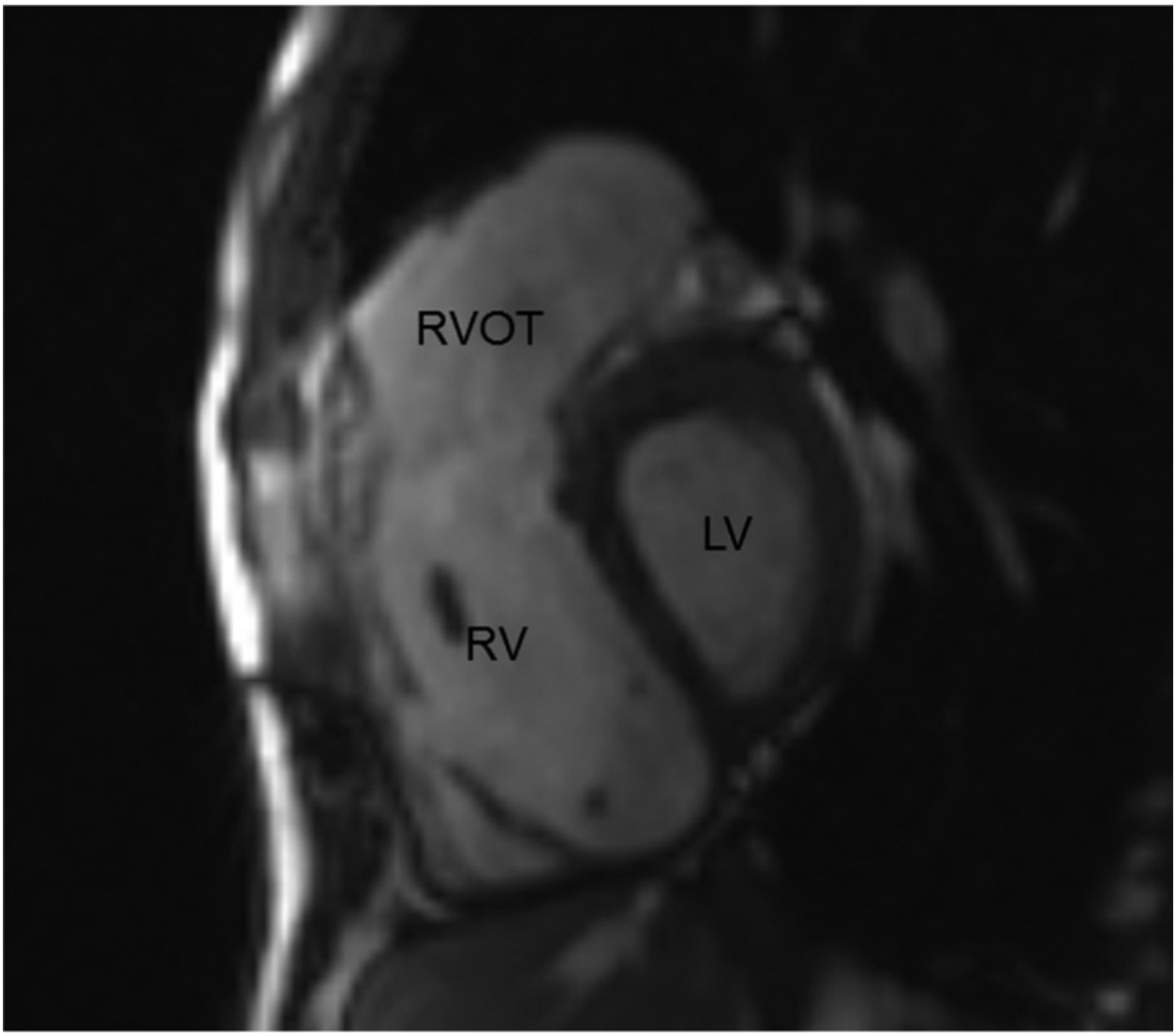

FIGURE 41.5 Repaired tetralogy of Fallot by CMR. Short-axis image demonstrating a severely dilated RV and an RVOT as well as free pulmonary regurgitation. There are no pulmonary valve leaflets identified. The septum is flat, suggesting RV volume overload compressing the LV. CMR, cardiac magnetic resonance; LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract.

Overall survival in repaired TOF is excellent, yet there is an increased risk of sudden cardiac death (SCD) later in life. Arrhythmias are related to surgical scar lines and dysfunctional right ventricle. SCD is estimated at 2% per decade in patients with repaired TOF, and overall arrhythmia frequency increases in the fifth decade. A QRS > 180 ms on ECG is a sensitive predictor of SCD in addition to morphologic findings such as RV hypertrophy and ventricular dysfunction. There is a direct relationship between the degree of RV enlargement/dysfunction and the degree of arrhythmias. Lastly, aortic root dilatation is also prevalent in patients with repaired TOF that could be explained

in part by the basic overriding aorta receiving an increased cardiac output and evidence of an intrinsic aortopathy.

Arrhythmia and HF related to RV and LV dysfunction are anticipated to be the diagnoses for admission to the CCU.

EBSTEIN ANOMALY OF THE TRICUSPID VALVE

Ebstein anomaly (EA) is a rare diagnosis and entails malformation of the TV in which there is failure of delamination (separation) of the septal and posterior tricuspid leaflets from the myocardium, causing the "functional" tricuspid annulus to be apically displaced[13] (**Figure 41.6**). The portion proximal to the annulus is dilated and the right ventricle proximal to the "functional" tricuspid annulus is similar in morphology to the atrium and thus is "atrialized." Because the posterior and septal TV leaflets are malformed, the anterior leaflet is often large and redundant; and, on physical examination, a systolic "snap" can be heard. This deformity leads to varying degrees of TR and rarely stenosis. EA is also associated with atrial communications (eg, patent foramen ovale [PFO], ASD), multiple accessory conduction pathways (ie, Wolf–Parkinson–White [WPW]), LV non-compaction, pulmonary valve abnormalities, PDA, and CoA. Clinical presentation varies and depends largely on the degree of malformation of the tricuspid leaflets, RV size and function, presence of associated cardiac lesions, and accessory pathways. For example, a first presentation to the CCU of a patient with EA may be collapse or SCD due to rapidly conducting AF in the setting of WPW. Others may present with exercise-induced cyanosis due to right-to-left shunting through an ASD or, more commonly, exercise intolerance due to RV dysfunction and severe TR. ECG shows "Himalayan" P waves, and the patient may have preexcitation with short PR interval and a very wide right bundle branch block. Echocardiographic diagnosis is based on apical displacement of the septal leaflet of the TV by more than 0.8 cm/m^2 from the true tricuspid annulus. TV repair of EA is surgically challenging and is warranted for decreased exercise tolerance, cyanosis, paradoxic embolism, and progressive RV enlargement and dysfunction. In the Cone procedure, the large anterior TV leaflet is manipulated to create a functional valve. If surgical repair is deemed impossible, a TV replacement is performed. In cases where the RV is considered too dysfunctional, a Glenn shunt (connection between the SVC and PA) may be performed to partially unload the right ventricle, that is, blood from

the upper part of the body would directly flow to the lungs bypassing the right ventricle. Lastly, accessory pathways should be ablated (see discussion in arrhythmia in adult congenital heart disease section).

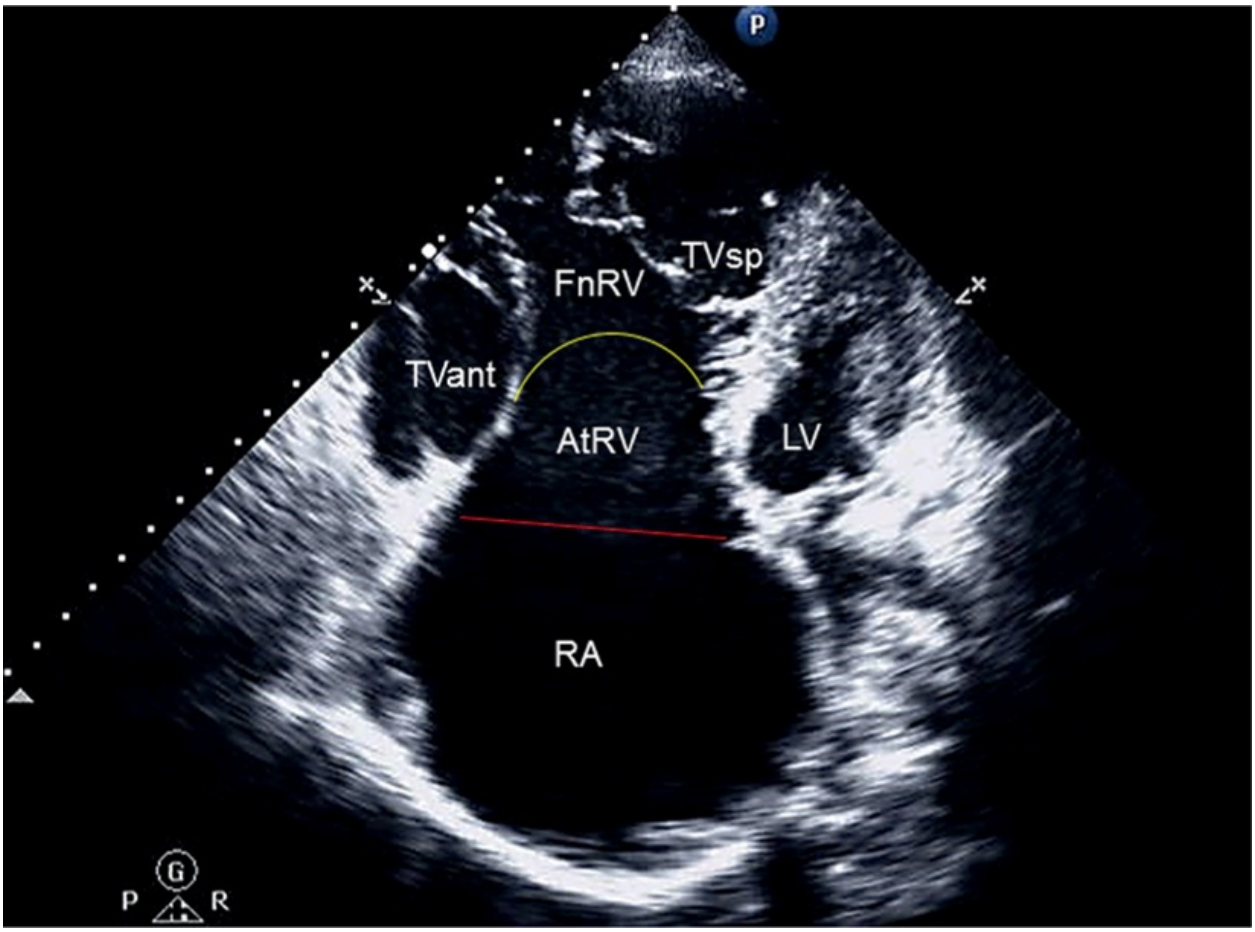

FIGURE 41.6 Transthoracic apical four-chamber view of Ebstein anomaly of the tricuspid valve demonstrating severe right ventricular dilatation, which is divided into a proximal atrialized portion (AtRV) and a distal function portion (FnRV) by the apicalized tricuspid annulus (curved yellow line). The apically displaced TVsp is diminutive in size and the TVant is large, redundant, and is connected to the anatomic tricuspid annulus (red line). The LV is small and compressed by the dilated right ventricle. Not seen in this figure, but the patient had severe tricuspid regurgitation. LV, left ventricle; AtRV, atrial right ventricle; FnRV, functional right ventricle; RA, right atrium; TVant, anterior leaflet of the tricuspid valve; TVsp, septal leaflet of the tricuspid valve.

PULMONARY ARTERIAL HYPERTENSION, CYANOSIS, AND EISENMENGER SYNDROME

Pulmonary arterial hypertension (PAH) occurs in approximately 5% to 10% of

ACHD. ES (**Figures 41.2 and 41.3**), which is the most extreme form of congenital PAH, is seen in about 1%.[14] The definition of PAH includes a mean PA pressure greater than or equal to 25 mm Hg with a normal capillary wedge pressure (<15 mm Hg). Congenital PAH is included in World Health Organization (WHO) group I category. ES typically occurs in patients with congenital defects that result in substantial unrestricted left-to-right shunting, most commonly VSD and AVCDs. Over time, the shunt causes detrimental hemodynamic effects with large increases in PVR (generally greater than 10 Wood units) that subsequently causes reversal or bidirectional flow across the existing shunt. Cyanosis and hemodynamic derangements depend on the degree of flow reversal across the shunt.

ES affects multiple organ systems because of the chronic cyanosis. The effects include secondary erythrocytosis with increased viscosity, iron deficiency anemia, thrombocytopenia, coagulopathy,[15] cerebral abscesses, microemboli, strokes, and renal dysfunction. Interestingly, the coronary arteries are ectatic with less atherosclerosis and calcifications.[16]

There are several unique management considerations for these patients including limitation of strenuous isometric exercise, dehydration, and chronic high altitude and warm environments. Active hydration is encouraged but may be challenging in the setting of chronic HF. Phlebotomy is offered for symptomatic patients with hyperviscosity symptoms such as severe headaches (commonly with hemoglobin >20 g%, hematocrit > 65%). Iron deficiency anemia is common and associated with increased frequency of strokes, yet careful correction is required because it increases the blood count further. Pregnancy is completely contraindicated because of the up to 50% maternal and fetal mortality, and termination of pregnancy should be counseled when possible.

Randomized controlled trials, the most notable being the BREATHE-5 (***B***osentan ***R***andomized Trial of ***E***ndothelin ***A***ntagonist ***THE***rapy-5), have demonstrated that patients with ES derive a clinical benefit from pulmonary vasodilator therapies (including prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors). Although these patients are at an elevated risk of PA thromboembolism, the role of anticoagulation is not entirely clear because they are prone to bleeding such as hemoptysis. Oxygen supplementation has limited support but could be offered. Lastly, for those with advanced disease, heart–lung transplantation can be offered for selected patients on a case-by-case basis.

CCU care depends on the inciting pathology, yet general care of the patient

with ES includes intravenous (IV) filters, oxygen support as needed, maintenance of SVR (use of vasopressors as needed) and reduction of PVR (nitric oxide inhalation, IV prostacyclin therapy), and correction of arrhythmia and iron deficiency anemia. Decision making in regard to diuresis depends on the degree of HF in the setting of limiting hypovolemia and hyperviscosity.

TRANSPOSITION OF THE GREAT ARTERIES AND SYSTEMIC RIGHT VENTRICLE

In d-transposition of the great arteries (d-TGA), the aorta originates from the right ventricle and the PA from the left ventricle.[17] The aorta is usually situated anteriorly and to the right of the PA. The immediate palliation at birth is the creation of an ASD with a balloon because the two parallel circulations are not compatible with life. The original surgical correction for d-TGA was the atrial switch operation (ie, Mustard or Senning procedures) in which the systemic venous circulation was baffled to the LV and the pulmonary venous circulation to the RV (**Figure 41.7**). Long-term complications include baffle obstruction (commonly at the SVC junction), baffle leak with paradoxic emboli, systemic RV dysfunction, TR, and tachyarrhythmia (mostly atrial that may degenerate to ventricular). CCU evaluation of the d-TGA post atrial switch should include imaging of the baffles for obstruction/leakage, correction of arrhythmia, and HF support. Baffle leaks and obstructions could be treated with stenting.

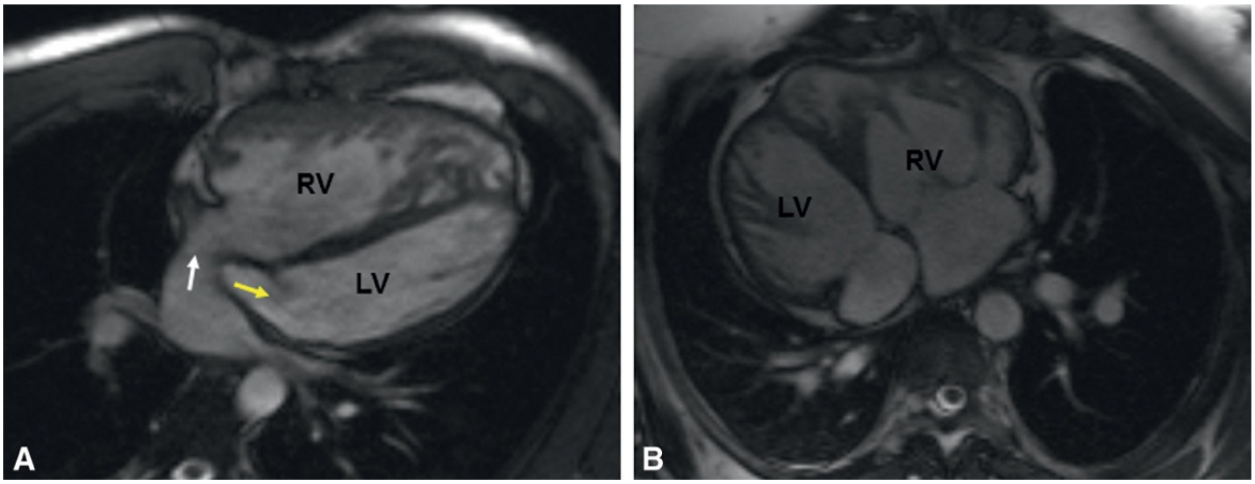

FIGURE 41.7 Transposition of the great arteries (TGA) with systemic right ventricles by CMR. A, d-TGA post atrial switch operation; white arrow denotes the pulmonary venous baffle and the yellow arrow denotes

the systemic venous baffle. B, Dextrocardia with congenitally corrected TGA (cc-TGA or levo-TGA [L-TGA]). CMR, cardiac magnetic resonance; LV, left ventricle; RV, right ventricle.

For the past 25 years, the arterial switch operation (ASO) or Jatene procedure has been the standard surgical approach to treatment of d-TGA. This procedure restores normal anatomy, yet has its own set of complications including coronary obstruction, aortic dilatation, and supra-pulmonary stenosis. A d-TGA post ASO should always raise suspicion of ischemia. Of note, the patient may have damaged cardiac innervation and not have classic complaint of angina.

In congenitally corrected transposition of the great arteries (cc-TGA or levo transposition of the great arteries [L-TGA]), the ventricles are inverted, and the morphologic right ventricle is situated on the left side and is connected to the aorta (so-called “double discordance”—AV and ventriculoarterial). The aorta is anterior and to the left of the PA. Long-term complications include TR (in 90%, the TV is abnormal), heart block (1% to 2%/year), outflow tract obstructions, and systemic RV dysfunction. Common surgeries for cc-TGA are TV repair, and at present children undergo double-switch operation with a simultaneous arterial switch and atrial switch for complete anatomic repair.

To reiterate, both d-TGA post atrial switch and cc-TGA share the same pathology of a systemic right ventricle (**Figure 41.7**). The systemic right ventricle, acting as the main pumping chamber to the aorta, is subjected to both increased pressure and volume load and thus develops HF. Interestingly, the TR seen in cc-TGA is primarily related to an abnormal TV and thus has the benefit of being corrected/replaced before worsening the systemic RV function (per guideline before RVEF of 40%); whereas in d-TGA post atrial switch, the TR seen is functional and related to systemic RV dilatation and dysfunction. Also, because the right coronary artery is still the main coronary providing blood to the chamber, ischemia may develop because of supply–demand mismatch. Potentially advanced HF therapies may be offered in the setting of intractable systemic HF (see Heart Failure in adult congenital heart disease section).

SINGLE VENTRICLE AND FONTAN PALLIATION

Single ventricle anatomy is one of the more challenging and complex ACHD pathologies (**Figure 41.8**). The term encompasses several different conditions including tricuspid atresia, mitral atresia, double-inlet left ventricle, and hypoplastic right or left ventricle. In caring for the patient with ACHD having

single ventricle anatomy, it is important to note that most of these patients have had several staged procedures early in life culminating in the Fontan operation.[18] Broadly, the Fontan operation is a palliative procedure in which systemic venous return is routed directly to the pulmonary arterial circulation. The systemic venous circulation flows passively into the lungs, now propelled by the negative intrathoracic pressure, skeletal muscles, and gravity of the blood from the upper part of the body. The hemodynamic consequence of the Fontan circulation is chronically elevated systemic venous pressures that eventually cause chronic liver congestion, ascites, leg varices, and promote lymphatic congestion that may cause protein-losing enteropathy (PLE)[19] and plastic bronchitis. Current Fontan surgery includes a total cavopulmonary connection that consists of an extracardiac conduit or lateral tunnel baffle (within the right atrium) connecting to the PA from the IVC and a Glenn shunt connecting the SVC to the PA from above. An older version of the Fontan palliation consisted of atriopulmonary connection (right atrium connected to the PA) that resulted in an extremely large right atrium that promoted arrhythmia and clot formation.

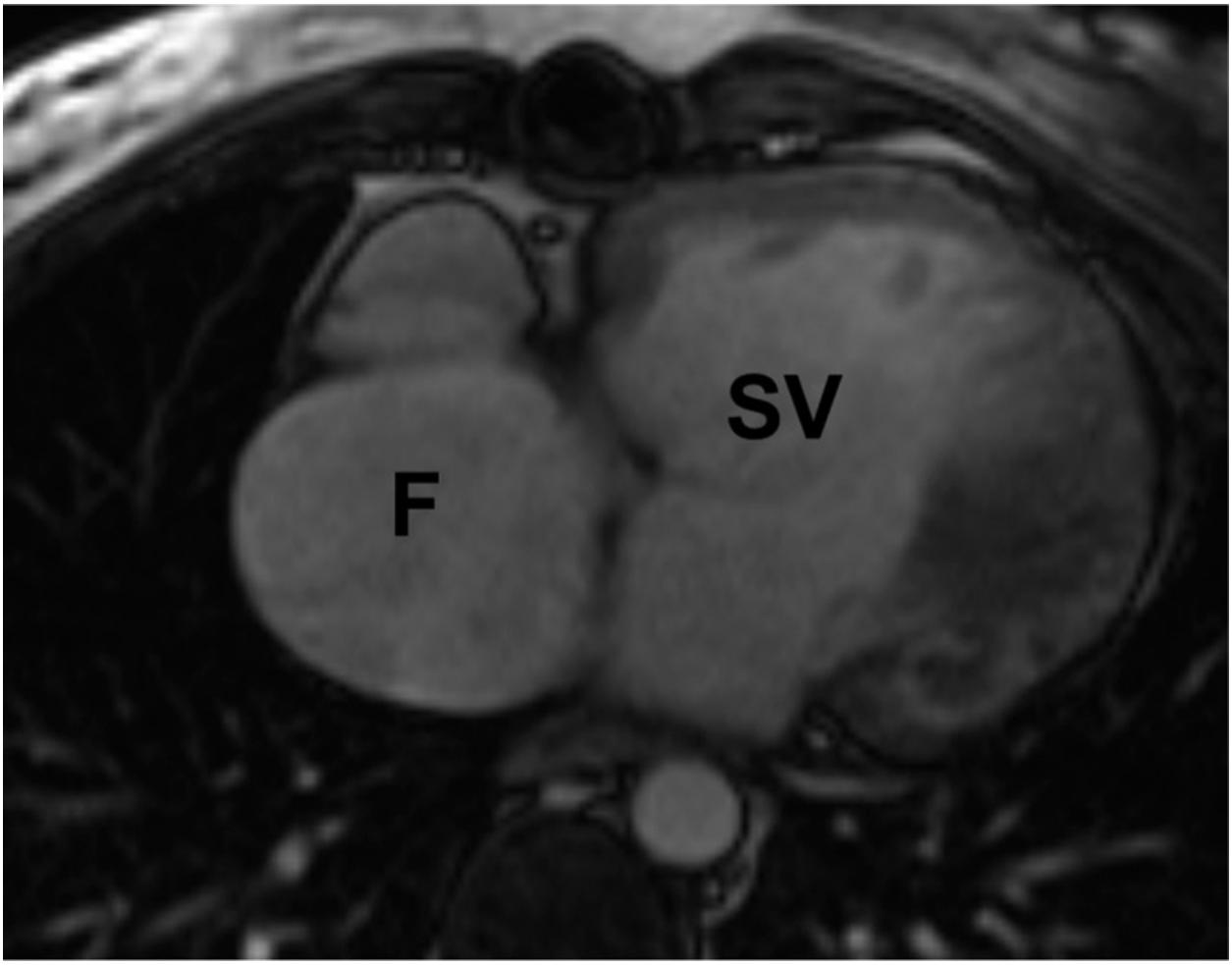

FIGURE 41.8 Fontan circulation by CMR. Baseline anatomy is double-inlet left ventricle with an atriopulmonary Fontan circulation. CMR, cardiac magnetic resonance; F, Fontan; SV, single ventricle.

The patients should be followed up closely by an ACHD specialist, particularly as several characteristic long-term issues arise including atrial arrhythmias, right atrial thrombus often necessitating systemic anticoagulation, single ventricular dysfunction, systemic AV valve regurgitation, cyanosis (due to veno-veno collaterals, pulmonary arteriovenous malformations, residual shunts, open fenestration, lung disease), hepatic congestion with deterioration of liver function from fibrosis to frank cirrhosis,[20–22] PLE, and plastic bronchitis. Although the 10-year survival after a Fontan is estimated to be 90%, many of these patients do require reoperation in adulthood and the long-term survival is protracted with SCD, thromboembolism, and HF being the most common causes of death.

CCU care for the patient with a Fontan circulation requires a thorough understanding of the limitation of having a passive pulmonary circulation. Any

increase in left atrial pressure (eg, LV dysfunction, AV valve regurgitation, LV outflow tract obstruction) or increase in PVR (eg, pulmonary baffle obstruction, pulmonary hypertension, pneumonia, pneumothorax, and obstructive sleep apnea) may hinder the passive flow and decrease the cardiac output. Arrhythmia is commonly supraventricular and not tolerated well, and therefore cardioversion is commonly the initial step in the treatment. A common caveat is that in such patients, a heart rate of 120 beats/min is commonly atrial flutter (IART). Furthermore, volume management is challenging because HF, cirrhosis, lymphatic obstruction, and chronic hypoalbuminemia contribute to chronic anasarca. End-stage patients require increasing dosages of diuretics and repeated paracentesis. Patients with atriopulmonary Fontan, which is the older version of the connection, may be offered a "Fontan conversion" in which the connection would be changed to an extracardiac version with plication of the right atrium and placement of a pacing system. The conversion reduces the frequency of arrhythmia and increases the efficiency of the circuit.

GENERAL TOPICS OF DIAGNOSIS AND MANAGEMENT IN ADULT CONGENITAL HEART DISEASE

ARRHYTHMIA IN ADULT CONGENITAL HEART DISEASE

Cardiac arrhythmias are a leading cause of morbidity and mortality in the ACHD population. The burden of arrhythmias increases with age, number of cardiac surgeries, and the complexity of the congenital lesion.[23,24]

Atrial Arrhythmias

The most common atrial arrhythmia in the ACHD population is IART. It may originate within the natural conduction channels (ie, the cavotricuspid isthmus) or iatrogenic conduction channels (suture lines or patches). IART commonly occurs in patients who have undergone surgical atrial manipulation (eg, atrial switch operations or Fontan procedure). Electrocardiographically, it will appear similar to atrial flutter, yet usually slower in rate (250 to 400 ms) and frequently conduct 2:1 to 1:1. Like in AF, these patients are at risk of thromboembolic complications. Hemodynamically unstable patients should be cardioverted emergently. Antiarrhythmic drugs may be considered for rate or rhythm control but have low efficacy. Therefore, these are typically treated with catheter ablation. The success of ablation procedures ranges from 55% to 90% depending

on the anatomy of the burden of fibrosis in the atrium. These arrhythmias may recur post ablation; and in select patients, surgical (intraoperative) ablation may be indicated.

AF is also a commonly encountered arrhythmia in ACHD and its frequency increases with age. Because AF arises from the left atrium, lesions affecting the left-sided structures are associated with AF; for example, mitral valve deformities and single ventricle or aortic stenosis. It should be noted that often times AF may occur in association with sinus node dysfunction with a slow ventricular response. Treatment strategies include class III antiarrhythmics and may warrant catheter or surgical pulmonary vein isolation. Anticoagulation should be prescribed in accordance with the AF guidelines to prevent thromboembolic complications.

Accessory pathways predispose patients with ACHD to tachyarrhythmias, and some may be life-threatening. WPW syndrome is commonly associated with EA (found in about 20% of patients), and congenitally corrected TGA with an Ebstenoid malformation of the left-sided TV. The location of the multiple accessory pathways is usually in the vicinity of the tricuspid annulus. The treatment typically includes catheter ablation of the pathway; however, it is often challenging because of the altered anatomy and the presence of multiple pathways.

Ventricular Tachycardias and Sudden Cardiac Death

The overall incidence of SCD in patients with ACHD is about 1% per decade but may be higher in more complex lesions and typically increases with age. The highest risk lesions include repaired TOF, EA, and congenital aortic stenosis. As in patients with HF, systemic ventricle dysfunction is the major risk factor for SCD. Any hemodynamic compromise or stress on the ventricles can increase the risk of malignant arrhythmias. In TOF, the risk of SCD is approximately 2% until adolescence, but acutely rises to 6% to 10% per decade in adulthood. RV enlargement and longer duration of the QRS width have also been correlated with SCD. Holter monitor and in select patients electrophysiologic (EP) study may be performed for risk stratification. Evidence of non-sustained ventricular tachycardia (VT) on Holter or inducible VT on EP study has been shown to predict risk of SCD in patients with TOF. In patients with congenital aortic stenosis or CoA, the risk of SCD directly correlates with the severity of the gradient across these lesions. VTs should be managed similarly to the general population, whereby hemodynamically unstable patients warrant emergent

defibrillation. Implantable cardioverter defibrillators (ICDs) are indicated for prevention of SCD. The indication for ICD implantation in patients with ACHD is largely similar to the general adult population. ICD implantation can often be challenging and have higher risk because of the distorted anatomy and prior surgeries. At times, epicardial ICDs may be implanted if venous access cannot be obtained. In select patients, subcutaneous ICDs are implanted. Patients with monomorphic VT can also be considered for VT ablations. Cardiac resynchronization therapy (CRT) is a primarily effective therapy for restoring electromechanical synchrony in the morphologic left ventricle. Owing to the altered anatomy, CRT is less effective in patients with ACHD with systemic right ventricles or single ventricles.[25]

Bradyarrhythmias

Sinus node dysfunction is common as a result of direct injury after a surgery. Rarely is the sinus node congenitally absent. Sinus node dysfunction is commonly seen after atrial switch operations (ie, Mustard and Senning) for d-TGA or after a Fontan operation. The bradycardia may predispose patients to higher incidence of atrial tachyarrhythmias. Because the AV node is embryologically a part of the AV canal, congenital anomalies including AV canal defects can lead to AV block. cc- TGA is also a common congenital cause of complete heart block as the AV node has an aberrant location. Similar to sinus node dysfunction, AV block can also occur post surgically (eg, post VSD or TOF repair). Treatment inevitably includes a pacemaker implantation. However, it should be noted that transvenous pacemaker implantation in the patient with ACHD is often challenging and requires thoughtful planning based on the anatomy, presence of intracardiac shunts, and patency of the venous system. Transvenous pacemakers are contraindicated in patients with atrial or ventricular shunts because of the risk of thromboembolism. In such cases, epicardial lead placement may be considered; however, this requires surgical access and is technically a more arduous procedure.

HEART FAILURE IN ADULT CONGENITAL HEART DISEASE

HF portends worse prognosis and increased mortality in patients with ACHD and is a major mode of death.[26,27] Of note, patients with ACHD may present with atypical symptoms compared to the general population; hence, a high index of suspicion must be maintained for the diagnosis. More commonly, patients

with ACHD develop heart failure with reduced ejection fraction (HFrEF), which can be due to pressure or volume overload, valvular dysfunction, alteration in the myocardial architecture (eg, non-compaction), ischemia, or arrhythmias.[28] However, heart failure with preserved ejection fraction (HFpEF) is probably under-recognized and has been implicated in patients with obstructive physiology (eg, Shone complex) or restrictive physiology. Presenting symptoms vary according to the affected ventricle. Involvement of the systemic ventricle regardless of morphology typically leads to symptoms of pulmonary congestion including shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, wheezing, and reduced exercise tolerance. If the sub-pulmonic ventricle is involved, the symptoms are typically that of "right-sided HF," which include fatigue, weight gain, increased abdominal girth, and bloating. A combination of the symptoms will occur in patients with biventricular failure. Patients with shunts may present with worsening cyanosis and, frequently, the first presentation is new onset of arrhythmia.

During the diagnostic investigation, laboratory testing, imaging, and, frequently, a new hemodynamic study (ie, right heart catheterization) is performed. Imaging is important to assess ventricular and valve function as well as conduit/baffle/pathway patency and functionality. Commonly, an echocardiogram is initially performed and cardiac MRI or CT (for pacemaker-dependent patients) is added for supplementation of data. Cardiopulmonary exercise test is helpful to determine the exercise capacity and the peak oxygen consumption (VO_2). Lower VO_2 values predict higher mortality and can help guide the need for advanced HF therapies, commonly peak VO_2 less than 14 cc/kg/min.[29]

When patients with ACHD have IV access, air filters should be placed on IV tubing to prevent paradoxic embolization of air and thrombus, because many patients will have residual shunts. In addition, establishment of arterial and central venous access can be difficult because the vascular anatomy may be altered and the patients frequently have occlusion of multiple arteries and central veins due to prior procedures. In patients with Glenn shunts (ie, communication between the SVC and PA), namely, most patients with Fontan circulation, the tracing in a central line represents the pulmonary pressures and not the right atrium.

B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are helpful for management and prognostication. BNP levels correlate with the functional class and degree of shunt severity. However, in asymptomatic

patients, there is no significant correlation between the degree of hypoxia and BNP levels. High BNP levels typically reflect elevated cardiac filling pressure, worsening valvular function, and chamber enlargement. In TOF patients, studies have found a correlation between BNP levels and the degree of RV dilatation as well as the severity of PR. In addition, the BNP levels decrease after pulmonary valve replacement. Rather than the absolute BNP value, the trend in BNP may be more helpful in evaluation of patients with HF. In addition, presence of anemia, liver/renal dysfunction, and hyponatremia portend a worse prognosis.

Limited data exists regarding the medical and surgical management of HF in patients with ACHD. However, understanding the underlying pathophysiology is key to tailoring the management in this patient population. For example, vasodilator therapy for HFrEF of the LV in a patient with right-to-left shunt will cause increase in shunt flow and should be used cautiously.

Medical management of HFrEF of the morphologic left ventricle is similar to the general management of HF, which includes diuretics, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and mineralocorticoid receptor antagonists. For HFrEF of a systemic RV (eg, cc-TGA, d-TGA post atrial switch) data are extremely limited. Symptomatic patients with signs of congestion may be treated similar to LV failure with diuretics, β-blockers, and neurohormonal blockade. However, in asymptomatic patients, the utility of β-blockers and neurohormonal blockade is not known and cannot be routinely recommended. In addition, in patients with d-TGA post atrial switch, venodilators that reduce preload may impair ventricular filling and cardiac output, and β-blockers should be used cautiously because sinus node dysfunction is common. Morphologic right ventricle in the subpulmonary position (normal anatomy) is commonly managed with diuretics, possibly digoxin, and in the setting of pulmonary hypertension with pulmonary vasodilators (ie, phosphodiesterase inhibitors, endothelin antagonists, or prostacyclins). Single ventricle post Fontan operation patients with HFrEF are commonly treated with diuretics and standard HF therapy as well as advanced PH therapies when applicable, yet data are scarce. In regard to HFpEF management, no medications have been found to improve survival in this group of patients with HF. For symptomatic relief of volume overload, diuretics should be used.

In critically sick patients with acute HF, extracorporeal membrane oxygenation and ventricular assist devices (VADs), right or left sided, may be considered. A VAD also has a role in bridge to transplant in patients with

advanced HF. A thorough evaluation of the vascular anatomy and patency should be conducted before deployment of these therapies.

Ultimately, patients with irreversible and medically refractory HF should undergo evaluation for heart transplant. A very detailed workup is performed to evaluate candidacy for heart transplant. Irreversible pulmonary hypertension should be ruled out before transplant to ensure favorable outcomes, or the patient should be considered for a heart–lung transplant.

Lastly, cardiopulmonary rehabilitation is recommended because limited data have demonstrated improved quality of life measures and safety.

PREGNANCY IN ADULT CONGENITAL HEART DISEASE

Medical care for these patients begins in the preconception period with careful planning that takes into account anticipated hemodynamic shifts and possible complications throughout pregnancy and labor orchestrated by a multidisciplinary team.[30] Although a detailed discussion of management strategies for specific congenital disorders is beyond the scope of this chapter, it is important to note that the normal hemodynamic changes in pregnancy may unmask previously undiagnosed CHD or exacerbate residual lesions. Several disease conditions have been designated as contraindicated to undergo pregnancy (according to the modified WHO classification), including PAH, severe systemic dysfunction (LVEF < 30%, NYHA class III to IV), severe mitral stenosis, severe symptomatic aortic stenosis, Marfan syndrome with dilated aorta >4.5 cm, BAV with aortic dilatation >5 cm, and severe CoA. As a general rule, with the increased blood volume and decreased SVR, regurgitant lesions tend to be tolerated (eg, PR in TOF, TR in EA), moderate and above stenotic lesions may become symptomatic and hemodynamically significant (eg, aortic stenosis), aortic dimensions enlarge (patients with connective tissue disease are most susceptible), systemic ventricular dysfunction may worsen, and the frequency of arrhythmia may increase. Fetal ultrasound is recommended at 18 weeks of gestation owing to the increased likelihood of CHD in the offspring of a patient with ACHD (from 0.8% in the general population to 3% to 6%) as well as genetic evaluation.

INFECTIVE ENDOCARDITIS IN ADULT CONGENITAL HEART DISEASE

Patients with ACHD have inherently the highest risk of contracting infective

endocarditis (IE) among the different cardiovascular populations owing to the abundant use of prosthetic material and the presence of shunts within their hearts.[31] In the CCU setting, any patient with ACHD who presents with clinical sepsis should immediately raise suspicion of IE, especially if the patient has had a recent dental procedure. Vegetations tend to develop on prosthetic material or in areas of turbulent flow that damage the endothelium (eg, septal leaflet of the TV from a membranous VSD jet or the pulmonary valve from a PDA jet). Treatment considerations are the same as those for the general population. Right-sided lesions such as pulmonary or TV endocarditis are usually well tolerated and the risk of systemic embolization depends on the presence of a concomitant shunt. Long-term follow-up of prosthetic conduits or graft endocarditis may be performed by serial positron emission tomography-fluorodeoxyglucose studies and inflammatory markers.

Primary prevention according to guidelines[32] currently recommends antibiotic prophylaxis for IE before dental procedures for ACHD with history of IE; prosthetic valves; uncorrected/palliated cyanotic CHD (including with shunts/conduits); completely repaired CHD (surgically or with a device) for the first 6 months and repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch/device that inhibits endothelization. In addition, the ACHD guidelines recommend IE prophylaxis before vaginal delivery in patients with prosthetic valves.[1]

COMORBID CONDITIONS

Noncardiac comorbidities are common in patients with ACHD. Renal dysfunction is present in up to 50% of young patients with ACHD, with up to 10% having moderate-to-severe dysfunction with a glomerular filtration rate <60 mL/min.[33] Similarly, restrictive lung disease is prevalent and results from prior sternotomies and thoracotomies, diaphragm dysfunction, parenchymal lung disease from perioperative insults, and cardiomegaly. These patients may also develop plastic bronchitis.[34] Patients with ACHD having chronic elevation in central venous pressure, such as patients with Fontan physiology or RV dysfunction, may have hepatic dysfunction and cirrhosis that may lead to abnormalities in coagulation, as well as to portal hypertension and esophageal varices.[20] Fontan patients are also at risk for the development of PLE.[19] In patients with cyanosis, hematologic abnormalities are common and include iron deficiency despite erythrocytosis, thrombocytopenia, platelet dysfunction, and

factor deficiencies.[15] Longitudinal studies of the neurocognitive development of patients with CHD have also revealed that neurodevelopmental and behavioral abnormalities are common in this population, as are abnormalities on brain MRI.[35] Presence of noncardiac abnormalities may significantly impact overall outcomes in patients with ACHD.

CONCLUSION

The majority of patients with CHD are reaching adulthood and require a new knowledge base and management considerations by the treating cardiologist. ACHD specialists are a valuable resource for the care of these fascinating and complicated patients.

ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Frank Cecchin for his valuable suggestions.

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V

INTENSIVE CRITICAL CARE

42

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Mechanical Ventilation in the Cardiac Care Unit

MECHANICAL VENTILATION

Mechanical ventilation is a life support method by which a device supports the partial or total transport of oxygen and carbon dioxide between the environment and the pulmonary capillary bed. Mechanical ventilation itself is not a treatment modality, but rather a supportive measure. The physiologic and clinical objectives are to restore homeostasis and support respiration as the underlying pathology is being treated (**Table 42.1**).

TABLE 42.1 Objectives of Mechanical Ventilation

- Improve pulmonary gas exchange by supporting alveolar ventilation and arterial oxygenation
  - Improve hypoxemia
  - Improve acute respiratory acidosis
- Decrease the metabolic cost of breathing by unloading the muscles of respiration
  - Ease respiratory distress and respiratory muscle fatigue
- Reduce systemic or myocardial oxygen consumption
- Prevent or improve atelectasis
- Reduce the risk of ventilator-associated lung injury

The causes of respiratory failure may be divided into hypoxemic and hypercapneic (**Table 42.2**). The majority of patients being admitted to a cardiac

care unit with respiratory failure falls into the category of hypoxemic respiratory failure due to cardiogenic pulmonary edema. Cardiogenic pulmonary edema causes decreased lung compliance, ventilation-perfusion mismatching, and diffusion impairment. Hypoxemia of mild-to-moderate severity can often be managed by the administration of oxygen through delivery systems ranging from nasal cannula to facemasks. However, it can be increasingly difficult to maintain adequate oxygenation and oxygen delivery with more severe hypoxemia, and these patients may require positive-pressure ventilation (PPV).

TABLE 42.2 Causes of Respiratory Failure

Hypercapnic respiratory failure

- Increased respiratory workload due to
  - Airway resistance (asthma, airway obstruction)
  - Elastic workload (pulmonary fibrosis, pneumonia, congestive heart failure)
  - Severe metabolic acidosis
  - Carbon dioxide production
  - Copious secretions in the airways
- Diminished central respiratory drive due to
  - Sedative or analgesic medications
  - Central nervous system injury
- Diminished respiratory muscle function due to
  - Mechanical disadvantage from
    - Chest wall deformities
    - Dynamic hyperinflation (COPD)
  - Respiratory muscle weakness from
    - Electrolyte abnormalities
    - Myopathies or neuropathies
    - Deconditioning

Hypoxemic respiratory failure

- Ventilation-perfusion mismatching
- Right-to-left shunt
- Alveolar hypoventilation
- Diffusion impairment
- Reduced inspired oxygen concentration

COPD, chronic obstructive pulmonary disease.

Physiologic derangements and clinical findings will determine the need for mechanical ventilation, which should be considered early in the course and not be delayed until the need becomes emergent. Patients suffering from cardiogenic shock will have an increased respiratory workload and reduced cardiac output delivered to the muscles of respiration. They are often described as “tiring out” or developing respiratory muscle fatigue and may show physical examination findings such as nasal flaring, use of accessory muscles of respiration (sternocleidomastoids or intercostals), paradoxic or asynchronous movements of

the rib cage and abdomen, and an increased pulsus paradoxus. If the mechanical workload progressively increases, the breathing demand at some point will exceed the respiratory pump capabilities. The patient will be unable to sustain adequate levels of ventilation to effectively eliminate carbon dioxide, and progressive hypercapnia will ensue. A substantial proportion of patients who require mechanical ventilation have relatively normal arterial blood gases, but show the other signs of respiratory failure mentioned. Therefore, the decision to place a patient on mechanical ventilation should not be determined by abnormalities of the arterial blood gas.

Increased respiratory work may markedly raise the oxygen cost of breathing, so that the respiratory muscles disproportionally consume oxygen at the expense of aerobic metabolism of other vital organs such as the heart, brain, and kidneys. Under these circumstances, mechanical ventilation decreases the work of breathing, decreases the oxygen cost of breathing, and redistributes oxygen delivery to the respiratory system and thereby improving oxygen delivery to other bodily organs.

If the underlying pathology is readily reversible and the clinician believes there is time, a trial of oxygen or noninvasive support can be initiated. However, those patients who are post cardiac arrest, are undergoing therapeutic hypothermia, experiencing ongoing cardiac ischemia, demonstrating cardiac or airway instability, exhibiting altered mental status, or having copious secretions are not candidates for noninvasive ventilation (NIV) and they require endotracheal intubation with PPV.

Working closely with the respiratory therapist is essential in decision making and implementation of respiratory support for critically ill patients.

HIGH-FLOW NASAL CANNULA

High-flow nasal cannula (HFNC) is emerging as a new mode of oxygen support for patients with acute hypoxemic respiratory failure with mild-to-moderate work of breathing.[1] Traditional nasal cannulas or masks can deliver flows up to 15 L/min. HFNC is a new form of oxygen support in which oxygen is delivered at very high flow (**Figure 42.1**). Humidified air is delivered at flows up to 60 L/min. In states of high patient workload, room air is entrained and there is dilution of the administered oxygen. With HFNC, the flow rate matches the patient's inspiratory flow and so there is less dilution of the administered oxygen. With HFNC, there is a small amount of positive pressure generated and an increase in lung volume. Compared with conventional oxygen therapy,

patients demonstrate a decrease in respiratory rate and greater synchrony. HFNC may be better tolerated than conventional oxygen or NIV.

FIGURE 42.1 High-flow nasal cannula.

Thus, HNFC may be effective in patients in the CCU with hypoxemia who are

able to sustain the work of breathing.

NONINVASIVE VENTILATION

NIV refers to a method of delivering ventilatory assistance through the use of a mask interface rather than through an invasive interface, such as an endotracheal tube (ETT) or tracheostomy. NIV may provide respiratory support to selected patients while avoiding complications of invasive mechanical ventilation.[2] Cardiogenic pulmonary edema and chronic obstructive pulmonary disease (COPD) exacerbation are two acute disorders for which NIV has proved beneficial.[2]

NIV reduces respiratory muscle work and facilitates a slower and deeper pattern of breathing, thus improving minute ventilation and alveolar ventilation. NIV has been shown to improve gas exchange, normalize arterial carbon dioxide, increase arterial oxygen, increase pH, increase tidal volume, and decrease respiratory muscle work in acute and chronic respiratory failure. Its use can also stabilize certain metabolic parameters such as heart rate, respiratory rate, and blood pressure.

The modes that are most commonly used in the critical care setting are PPV modes of continuous positive airway pressure (CPAP) and bilevel positive airway pressure (BPAP).

In acute cardiogenic pulmonary edema, both CPAP and BPAP have been shown to reduce the work of breathing and intubation rates.[3,4] CPAP has been shown to improve oxygenation, reduce respiratory rate, and reduce the rate of intubation compared to standard oxygen therapy. BPAP similarly has demonstrated lower intubation and complication rates compared to standard oxygen therapy. Although a trial comparing standard oxygen therapy with NIV (CPAP or BPAP) found no significant difference in 7- or 30-day mortality between either of the two groups, the NIV group did achieve more rapid improvement in respiratory distress and metabolic disturbances than did oxygen therapy alone.[5]

For patients with acute cardiogenic pulmonary edema who are hemodynamically stable and meet criteria for NIV, we recommend BPAP as the initial ventilatory mode.

PATIENT SELECTION

Successful application of NIV may obviate the need for endotracheal intubation in select patients. A trial of NIV is therefore worthwhile in most patients who do not require emergent intubation, assuming that they have no contraindications. Potential indicators of success with NIV use are listed in **Table 42.3**. The clinician must exclude patients in whom the use of NIV would be unsafe. Patients who are at risk of imminent respiratory or cardiac arrest or who have already sustained arrest should be promptly intubated. Patients with unstable conditions such as shock, myocardial ischemia, or life-threatening cardiac arrhythmias should not be managed with NIV. Patients who are comatose, agitated, or uncooperative also cannot undergo NIV. Patients being considered for NIV should be able to manage their secretions, and those with copious amounts should be considered for intubation. Facial surgery, trauma, or deformities that may prevent adequate fitting of the mask interface, and patients with gastric distension and vomiting are relative contraindications.

TABLE 42.3 Potential Indicators of Success with Noninvasive Ventilation

- Younger patient
- Lower severity of illness (APACHE score)
- Ability to cooperate, coordinate breathing with ventilator, less air leaking
- Moderate degree of hypercapnia ($Paco_2$ > 45 mm Hg, <92 mm Hg)
- Moderate degree of acidemia (pH > 7.1, <7.35)
- Improved gas exchange, heart rate, and respiratory rate within 2 h

APACHE, ***A***cute ***P***hysiologic ***A***ssessment and ***C***hronic ***H***ealth ***E***valuation.

INITIATION AND SETTINGS

Once the patient has been selected to receive a trial of NIV, it should be initiated as soon as possible. Any delay may result in further deterioration of the patient's condition and increase the likelihood of failure. The oronasal mask should be selected for most patients (**Figure 42.2**). This mask is secured to the patient's face by the use of adjustable Velcro straps. Parameters that need to be set with the BPAP mode of ventilation include inspiratory positive airway pressure (IPAP), expiratory positive airway pressure (EPAP), fraction of inspired oxygen (FIO_2), and a backup respiratory rate.

FIGURE 42.2 Oronasal noninvasive ventilation mask.

IPAP is used synonymously with the term *pressure support* and EPAP is regarded as *positive end-expiratory pressure (PEEP)*. Therefore, an IPAP of 15 cm water and an EPAP of 5 cm water are equivalent to a pressure support of 10 cm water and a PEEP of 5 cm water. The initial target IPAP and EPAP should be selected on the basis of bedside observation and determined primarily by patient tolerance. A minimum IPAP of 10 cm water and EPAP of 5 cm water is usually

appropriate, because giving the patient higher initial pressures may result in intolerance and early failure. The tidal volume delivered with this mode depends on the difference between IPAP and EPAP. For example, the tidal volume will be greater using an IPAP of 15 cm water and an EPAP of 5 cm water (difference of 10 cm water), than an IPAP of 10 cm water and EPAP 5 cm water (difference of 5 cm water). The goal tidal volume to be delivered in most patients is usually 6 to 8 mL/kg predicted body weight.

The BPAP machine is a pressure-limited device that supports a spontaneous mode of ventilation. That is, the breath will be delivered only if there is a recognized patient effort. If the physician wishes to add a mandatory minimum machine-directed breath, he can set a backup rate of 10 to 12 breaths/min. However, these forced breaths are commonly not synchronized with the patient's effort.

A practical approach is to set the initial F_{IO_2} to 100%. Arterial blood gas analysis should then be performed after 1 to 2 hours of initiation of BPAP, and the F_{IO_2} can be titrated down if the Pa_{O_2} is at an acceptable level. It is then reasonable to further titrate down the F_{IO_2} in small decrements based on the patient's oxygen saturation on pulse oximetry (usually to a goal greater than or equal to 90%). **Table 42.4** shows a protocol to guide the initiation of NIV. Adjustment of IPAP and EPAP may be necessary to achieve optimal tidal volumes and tolerance of NIV.

TABLE 42.4 Protocol for Initiation of NIV

1. Appropriately monitored location, with monitoring of pulse oximetry and vital signs
2. Patient in bed or chair at >30° angle
3. Connect all tubing, turn on ventilator, and select and fit mask interface
4. Start with low pressure with backup rate; 8 to 12 cm water IPAP; 3 to 5 cm water EPAP; back up rate of 12 breaths/min
5. Gradually increase IPAP (by 2 cm increments up to 10 to 20 cm water) as tolerated to achieve alleviation of dyspnea, decreased respiratory rate, increased tidal volume, and good patient–ventilator synchrony
6. Provide F_{IO_2} supplementation as needed to keep oxygen saturation >90%
7. Check for air leaks and readjust straps if needed
8. Monitor initial blood gas (1 to 2 h after initiation) and then as needed
9. Encouragement, reassurance, and frequent checks and adjustments as needed

EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation.

MONITORING AND TROUBLESHOOTING

Patients who are started on NIV for acute respiratory failure should be monitored

in the same way as patients who are mechanically ventilated through an ETT. Patients should be observed closely for the first 2 hours after initiation to troubleshoot, provide reassurance, and monitor for deterioration. If there is no stabilization or improvement over this time, NIV should be considered a failure and the patient should be promptly intubated. If the patient is clearly failing immediately after initiation, the clinician should not wait but should proceed to intubation. Clinical signs of failure include worsening gas exchange, worsening encephalopathy or agitation, inability to clear secretions, inability to tolerate any of the mask interfaces, persistent signs and symptoms of respiratory fatigue, and hemodynamic instability. Reductions in respiratory rate and accessory muscle use, coupled with improvement in thoracoabdominal synchrony and gas exchange, suggest a favorable response and good prognosis if seen within 2 hours.

Many patients do not tolerate BPAP, and this is usually due to patient–ventilator asynchrony (when the phases of inspiration and expiration do not match that of the patient). Waveform displays of breath-by-breath delivered flow, volume, and pressure are available on most intensive care unit (ICU) ventilators (**Figure 42.3**). If the alarms for these parameters are triggered (ie, low tidal volume or pressures), this is most likely due to a mask leak. Patients can often be satisfactorily ventilated despite such leakage because most pressure-limited ventilators are able to compensate for leaks by sustaining airflow to maintain mask pressure. If the leak is large enough to interfere with ventilatory support, readjusting the position of the mask on the face with tightening of the Velcro straps may help. Also, the mask size itself may have to be changed to ensure a proper fit. Air leaks may also be present if ventilator tubing becomes disconnected from the ventilator or facemask, or if nebulization ports remain open to the atmosphere.

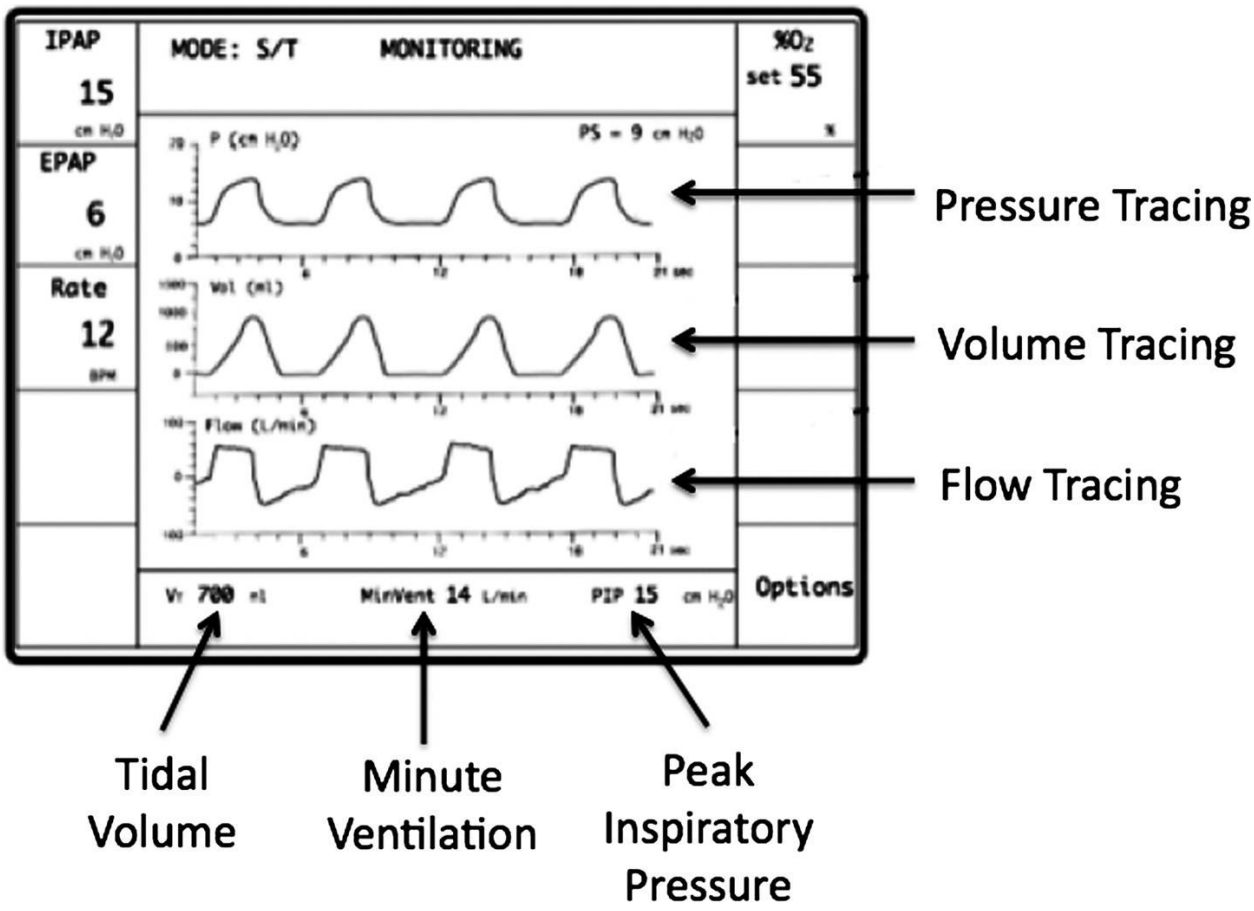

FIGURE 42.3 Waveform display in NIV. EPAP, expiratory positive airway pressure; IPAP, inspiratory positive airway pressure; NIV, noninvasive ventilation; PIP, peak inspiratory pressure. (Philips Respironics BiPAP Vision, Respironics Inc., Murrysville, PA.)

Some of the other problems that may be encountered with NIV are nasal congestion or dryness, nasal bridge redness or ulceration produced by excessive mask tension, irritation of the eyes causing conjunctivitis, and gastric insufflation leading to distension. Major complications such as aspiration, hypotension, and pneumothorax are seldom seen, and these events can be prevented by carefully selecting patients for NIV.

Patients With Do Not Intubate Order

NIV is frequently used in patients who have a directive for no intubation but have a potentially reversible cause of respiratory failure such as cardiogenic pulmonary edema. These patients may be good candidates for NIV because their short-term prognosis may be significantly improved. In contrast, NIV is also initiated in patients with advanced-stage diseases who have poor prognosis. It is

a life support measure and its use should be guided by the goals of care, because it may still offer benefits in alleviating respiratory distress or suffering. More information regarding this topic can be found in the chapter on *End-of-Life Care in the CCU*.

INVASIVE MECHANICAL VENTILATION

Invasive mechanical ventilation is usually initiated in the CCU for patients with acute respiratory failure, cardiogenic shock, and cardiac arrest. If a patient with pulmonary edema has a contraindication to or fails NIV, he/she should be promptly intubated.

UNDERSTANDING THE MECHANICAL VENTILATOR

The mechanical ventilator gives the patient each breath based on the settings selected by the clinician.[6] Understanding a few basic terms is helpful. The term *cycling or control* refers to the way the ventilator determines that the inspired breath is complete and signals to stop inspiration. This can be sensed either by volume (inspiration stops once the target volume is delivered), pressure (inspiration stops once the target pressure is reached), flow (when flow decreases to a given level, inspiration is terminated), or time (inspiration stops after a preset time interval). The term *limit* refers to a factor that limits the rate at which gas flows into the lungs and causes inspiration to end before cycling is complete. A limit can be pressure, volume, or flow. *Triggering* is the signal that opens the inspiratory valve, allowing air to flow into the patient. To initiate a breath, the ventilator must recognize that a set value has been reached. The trigger can be set to time, volume, pressure, or flow.

Breath types can be classified in several different ways. If the patient determines the beginning, duration, and end of a breath, the breath is termed *spontaneous*. If the ventilator controls for any of these aspects, the breath is considered to be either *assisted* or *mandatory (controlled)*.

Tidal volume (V_T) is the amount of air delivered with each breath. The normal V_T in a 70-kg person is roughly 500 mL. *Minute ventilation (MV_E)* is the product of tidal volume and the respiratory rate, and is the amount of air inhaled or exhaled in 1 minute. The normal MV_E is 5 to 8 L/min. *Fraction of inspired oxygen (Fio_2)* is the percentage of oxygen in the inspired air, and can range from

21% (room air) to 100%. *PEEP* is the pressure set on the ventilator to prevent expiratory alveolar collapse.

The selection of ventilator mode for a critically ill patient is generally based on the experience of the clinician and institutional preference. PPV can be either volume controlled or pressure controlled.[6] In *volume control (volume preset* or *volume cycled)* ventilation, the machine delivers a preset volume determined by the physician and, within limits, delivers that volume irrespective of the pressure generated within the system. The amount of pressure necessary to deliver this volume can fluctuate based on the resistance and compliance of the patient and ventilator circuit. If the tidal volume is set at 500 mL, the ventilator will continue to deliver gas until it reaches this goal. Upon completion of the inspired volume, the ventilator will open a valve allowing the patient to passively exhale.

In *pressure control (pressure preset* or *pressure cycled)* ventilation, the ventilator applies a predefined pressure target set by the physician. The ventilator will flow gas into the patient until this set pressure is reached. Upon reaching the preset pressure, the ventilator allows for passive exhalation. The resulting tidal volume will vary according to airway resistance and lung compliance.

The mode is also classified on the basis of how the breath is initiated—whether by the ventilator, the patient, or both. In *controlled mechanical ventilation (CMV)*, the MV_E is determined entirely by the set respiratory rate and the set control (volume or pressure control). The patient does not initiate additional MV_E above that set by the ventilator (ie, there is no ventilator triggering by the patient). For example, in volume-controlled CMV, if the set respiratory rate is 12 breaths/min and the preset tidal volume is 500 mL, the patient will be guaranteed an MV_E of 6 L/min (no lower and no higher). Patients are unable to alter their MV_E if the clinical situation changes such as hypoxemia or worsening acidosis, and acid–base maintenance is solely the responsibility of the physician. If placed on this mode, patients who are awake or spontaneously triggering may generate asynchronous respiratory efforts that may contribute to increased work of breathing, patient discomfort, and worsening gas exchange.

During assist-control (AC) *AC ventilation,* the physician determines the minimum MV_E by setting the respiratory rate and control (volume or pressure control). The patient can increase his own MV_E by triggering additional breaths (by flow or pressure) above the set respiratory rate. Each time the patient triggers, the ventilator will generate a fully supported breath according to the

volume or pressure preset. For example, in volume-controlled AC, if the respiratory rate is set to 12 breaths/min and the tidal volume to 500 mL, the minimum MV_E will be 6 L/min. If the patient triggers an additional 8 breaths/min, the MV_E then becomes 10 L/min. This mode is the most commonly used mode of ventilation in ICUs and is best suited for those who are awake or still have spontaneous respiratory efforts, and can even be used in those who do not generate any respiratory efforts.

Pressure-regulated volume control (PRVC) is a dual-control mode available on many ventilators. Its basic features are similar to those of AC ventilation, with the main difference being that the ventilator is able to auto-regulate the inspiratory time and flow to deliver the preset tidal volume at the lowest possible plateau airway pressure.

Pressure support ventilation (PSV) differs from the other modes of mechanical ventilation discussed in that it is a flow-cycled mode and is intended to support spontaneous respiratory efforts. The ventilator delivers inspiratory pressure until the inspiratory flow decreases to a predetermined percentage of its peak value (usually 25%). In this mode, the physician sets the pressure support level, PEEP, and FIO_2. The patient must trigger each breath because there is no set respiratory rate. Work of breathing is inversely proportional to pressure support level and inspiratory flow rate. Tidal volumes are therefore determined by a combination of PSV settings, the patient's effort, and underlying pulmonary mechanics. An adequate MV_E cannot be guaranteed and it cannot be used in patients who are heavily sedated, paralyzed, or who cannot generate spontaneous efforts.

CPAP is a mode of support that is also applied to spontaneously breathing patients. During the respiratory cycle, a constant pressure is applied to the airway throughout inspiration *and* expiration. The ventilator does not cycle during CPAP, and all breaths must be initiated by the patient. CPAP is commonly combined with PSV or may be used alone in patients weaning from mechanical ventilation.

Additional modes of ventilation (such as airway pressure release ventilation) are used mainly for patients with acute respiratory distress syndrome (ARDS) and are beyond the scope of this discussion.

ENDOTRACHEAL INTUBATION

Endotracheal intubation should only be performed by an experienced clinician or anesthesiologist. Patients are often intubated using an induction agent (ie,

propofol, etomidate) and in some instances undergo rapid sequence intubation with the addition of neuromuscular blocking agents. A specific neuromuscular blocking agent, succinylcholine, may cause a sudden release of potassium into the bloodstream and should be avoided in patients with renal failure or hyperkalemia because it may lead to sudden cardiac arrest. Induction agents have a common problem of causing peripheral vasodilation. This effect may become even more pronounced if there is significant dehydration, hypovolemia, or underlying acidosis. Critically ill patients in a state of compensated shock maintain their circulation by vasoconstriction and tachycardia. The use of a vasodilating induction agent can blunt this response and reduce systemic blood pressure by reducing peripheral vascular resistance.

When positive pressure is applied to the airway, there is an increase in intrathoracic pressure and a decrease in venous return to the heart causing reductions in ventricular filling pressures, stroke volume, and cardiac output. The effects of initiating PPV on blood pressure and cardiac output can usually be treated with the administration of saline boluses. Intravenous fluid preparations should always be prepared for the intubation process in anticipation of such adverse effects. If the effects of vasodilation caused by induction agents cannot be reversed with saline infusion, the temporary use of vasoconstrictor agents (ie, phenylephrine, norepinephrine) may be required. Complications of intubation include local trauma and aspiration of gastric contents.

Once the ETT is advanced through the vocal cords, the tube is secured and the cuff is inflated. Placement is clinically confirmed by the symmetric rise and fall of the chest wall, the presence of bilateral breath sounds, and end-tidal carbon dioxide measurement during manual ventilation. If placement is adequate and oxygen saturation is sufficient, the patient can then be attached to the mechanical ventilator. ETT cuff inflation pressure should not exceed 30 cm water to avoid complications such as tracheal rupture, pressure necrosis, or tracheo-innominate artery erosion and fistula. A chest radiograph should be obtained to ensure ideal location of the tip of the ETT, which should be between 3 and 5 cm above the carina.

PHYSIOLOGIC AND PATHOPHYSIOLOGIC CONSEQUENCES OF POSITIVE-PRESSURE VENTILATION

PPV can produce complex interactions in the patient's cardiopulmonary state.[7] PPV results in an increased mean intrathoracic pressure; the clinical effect on cardiac output is variable and depends on the patient's intravascular volume

status/ventricular filling pressures, underlying left ventricular compliance, and ejection fraction.

Increases in intrathoracic pressure can decrease venous return to the right heart. The amount of venous return is determined by the pressure gradient from the extrathoracic veins to the right atrium. The intrathoracic and right atrial pressures increase during PPV, which reduces the gradient for venous return. This effect may be overexaggerated by increases in PEEP or in those with intravascular volume depletion. Right ventricular output can also be reduced by increased alveolar inflation and compression of the pulmonary vascular bed, resulting in increased pulmonary artery pressures and pulmonary vascular resistance. In addition, left ventricular output may be compromised from shifting of the interventricular septum toward the left ventricle leading to impaired diastolic filling.

In contrast to these adverse effects, PPV can be beneficial in patients with left ventricular failure and pulmonary edema.[7] Transmyocardial pressures can be reduced by increases in intrathoracic pressure, resulting in a decreased left ventricular afterload and overall improved left ventricular performance. This effect is most likely to be seen when filling pressures are high and ventricular performance is poor.

Measurements of pressure, airflow, and volume can reveal basic physiologic properties of the respiratory system (**Figure 42.4**). *Peak inspiratory pressure (PIP)* is the maximal airway pressure recorded in the patient–ventilator circuit. It represents the total pressure needed to overcome resistance related to the ventilator tubing, ETT, and patient airways in addition to the elastic recoil of the lungs and chest wall.

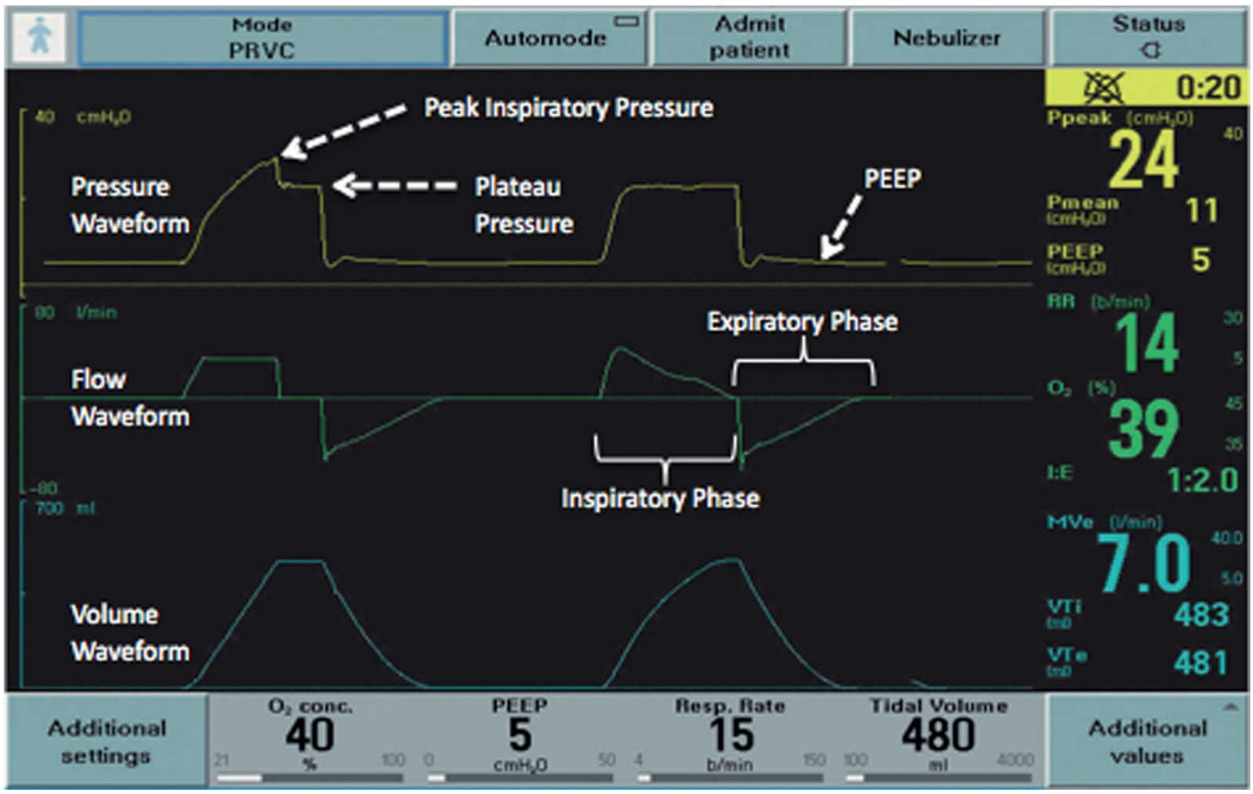

FIGURE 42.4 Waveform and pressure analysis on the invasive mechanical ventilator. PEEP, positive end-expiratory pressure; PRVC, pressure-regulated volume control. (SERVO-i, Maquet, Tastatt, Germany.)

The end-inspiratory pressure is measured by applying an inspiratory pause at the end of passive inflation; this will result in an immediate drop in airway opening pressure to a lower initial value, followed by a gradual decrement until a *plateau airway pressure* is reached. Because plateau pressure is measured when there is no airflow, it reflects the static compliance of the respiratory system. Increases in plateau pressures can be seen in patients with decreased lung compliance (ie, ARDS, congestive heart failure, multilobar pneumonia, severe atelectasis) or decreased chest wall compliance (ie, morbid obesity, kyphoscoliosis, abdominal distension, tension pneumothorax) (**Table 42.5**).

TABLE 42.5 Causes of Respiratory Distress in the Patient on Mechanical Ventilation

Ventilator issues
• Inadequate minute ventilation (tidal volume or respiratory rate), F_{IO_2}, inspiratory flow rate, PEEP, or trigger sensitivity
• Ventilator circuit leak
• Ventilator malfunction
Increased peak inspiratory pressures with unchanged plateau pressures

- Endotracheal tube problems
  Examples: patient biting, increased resistance in tubes by heat and moisture exchange, obstruction by secretions, blood, or foreign object
- Bronchospasm (asthma or COPD)
- Obstruction of lower airways (secretions, blood, or foreign object)
- Aspiration of oropharyngeal or gastric contents

Increased peak inspiratory pressures with increased plateau pressures
- Pneumonia
- Atelectasis
- ARDS and pulmonary edema
- Migration of ETT into a mainstem bronchus
- Pneumothorax
- Abdominal distension

Extrapulmonary issues
- Delirium, anxiety, or pain
- Acute neurologic event
- Sepsis

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ETT, endotracheal tube; PEEP, positive end-expiratory pressure.

Normally, a transpulmonary pressure of 35 cm water would inflate the lungs to near-total lung capacity. In patients with acute lung injury (ALI) or pulmonary edema, total lung capacity may be reduced because of alveolar collapse. Therefore, V_T delivered with each assisted breath may result in heterogeneous ventilation and over-distension of the more compliant regions of the lungs, and subsequent increased plateau/alveolar pressures. This may cause *volutrauma* to the alveoli as a result of the shear mechanical forces applied to the alveoli because they are repeatedly opened and closed. This damage is termed *ventilator-associated lung injury* and is often indistinguishable from other causes of ALI clinically and radiographically. Primary interventions to reduce this injury include preventing alveolar over-distension through the use of smaller V_T (6 mL/kg of predicted body weight) and keeping plateau pressures to a goal of less than 30 cm water.[8]

Pneumothorax, subcutaneous emphysema, pneumomediastinum, and other forms of extra-alveolar air are generally referred to as *barotrauma*. Barotrauma is usually the result of disruption of the pulmonary parenchyma and alveolar rupture from elevated airway pressures or volumes.

Extrinsic PEEP is generally added to prevent alveolar collapse, and increasing levels may be required depending on the clinical situation. In the setting of respiratory failure from ARDS or congestive heart failure, decreased lung compliance may lead to significant alveolar collapse and refractory hypoxemia

due to increased shunt fraction. In these settings, extrinsic PEEP has been used to prevent alveolar collapse, recruit alveoli, and improve oxygenation.

Intrinsic PEEP ($PEEP_i$*, auto-PEEP,* or *breath stacking)* is present when alveolar pressure exceeds atmospheric pressure at the end of expiration in the absence of a set ventilator PEEP level. When inspiration is initiated before expiratory flow from the preceding breath has ceased, air trapping will occur. Auto-PEEP can develop for numerous reasons including high minute volume (due to high V_T, respiratory rate, or high trigger sensitivity), prolonged inspiratory times (leading to obligatory decrease in expiratory time), and expiratory flow resistance or limitations (due to small-bore ETT or obstructive airways disease). Consequentially, it may potentiate the aforementioned hemodynamic effects of PPV by further increasing intrathoracic pressure. Auto-PEEP will also increase the risk of pulmonary barotrauma and the work of breathing by making it more difficult for the patient to trigger a ventilator-assisted breath. Treatment for auto-PEEP involves adjusting ventilator settings (decreasing inspiratory time, increasing inspiratory flow rate, decreased V_T, decreasing respiratory rate, decreasing trigger sensitivity), maintaining adequate anxiolysis and analgesia to reduce ventilatory demand, and reducing expiratory flow resistance (suctioning, bronchodilators).

Although supplemental oxygen is necessary and valuable in many clinical situations, inappropriate or excessive therapy can be detrimental. The effects of normobaric hyperoxia on the respiratory system have been extensively studied, showing effects ranging from mild tracheobronchitis to diffuse alveolar damage or ARDS. Hyperoxia appears to produce cellular injury through increased production of reactive oxygen species, which can ultimately result in cell death.[9] In general, attempts are made to decrease the FIO_2 to less than 60% to a goal Pao_2 of 60 to 65 mm Hg or Spo_2 greater than or equal to 90% as soon as patients are able to tolerate it. Optimal selection of PEEP may also help decrease oxygen requirements.

SETTINGS FOR MECHANICAL VENTILATION IN THE CCU

This section covers the basic initial settings for the volume-controlled AC mode. The settings that need to be considered with this mode include the V_T, respiratory rate, extrinsic PEEP, and FIO_2.

In principle, the ventilatory management of patients with cardiogenic shock

and pulmonary edema is similar to that of patients with noncardiogenic pulmonary edema (ARDS). In addition, patients in the CCU, especially those following cardiac arrest, may suffer ARDS due to aspiration at the time of the cardiac arrest. Many of the recommendations regarding ventilatory strategies for these groups of patients are based on avoiding the pulmonary complications of alveolar over-distension. These strategies are called *lung protective strategies*. Owing to the overwhelming evidence that inflating the lungs to near-total lung capacity or above can damage normal lung units in patients with ARDS and worsen mortality, the current recommendations for ARDS are to set the tidal volume to 6 mL/kg of predicted body weight.[8] It is reasonable to use V_T of 6 to 8 mL/kg predicted body weight in patients ventilated for reasons other than ARDS. Predicted body weight is based on height and gender, and so the height should be measured in all ventilated patients to set the proper tidal volume.

PEEP can potentially improve oxygenation by recruiting collapsed and flooded alveoli for gas exchange, diminishing intrapulmonary shunting of blood, improving ventilation-perfusion mismatching, and also redistributing intra-alveolar edema.

Initial Settings

Tidal volume V_T: 6 to 8 mL/kg predicted body weight.

Respiratory rate: at least 12/min. Higher rates may be required, for example, in patients with severe underlying acidosis or patients being ventilated for ARDS.

F_{IO_2}: set to 100% after intubation. The lowest possible F_{IO_2} necessary to meet oxygenation goals should be used. Arterial blood gas analysis should then be performed after 1 hour to ensure adequate oxygenation. F_{IO_2} should then be rapidly titrated down (by 10% to 20% every 30 minutes) to a goal Pa_{O_2} of 60 to 65 mm Hg or Sp_{O_2} greater than or equal to 90% to avoid complications of high inspired oxygen concentration.

PEEP: A typical initial PEEP of 5 cm of water is often applied to prevent atelectasis. Higher levels of PEEP may be required to recruit alveoli and improve gas exchange; however, attention must be paid to airway pressures to avoid complications of alveolar over-distension. PEEP above 20 cm water should rarely be used.

MONITORING PATIENTS ON INVASIVE MECHANICAL VENTILATION

Patient–ventilator asynchrony is commonly manifested as respiratory distress with “bucking” or “fighting” the ventilator. This happens when the phases of the breath delivered by the ventilator do not match that of the patient. Clinical signs include anxiety, agitation, tachypnea, tachycardia, use of accessory muscles of respiration, and uncoordinated thoracic wall and abdominal movements. Asynchrony can lead to dyspnea and increased work of breathing. Bedside observation and examination of ventilator waveforms can help detect the presence and identify the cause of asynchronous ventilation.

Asynchrony or respiratory distress may signify a life-threatening complication, and so rapid assessment is required. In addition to clinical examination, the clinician must monitor ventilator parameters such as tidal volume, respiratory rate, peak inspiratory pressure, plateau airway pressure, and auto-PEEP values. It should be noted that patient–ventilator asynchrony need not be present for possible pulmonary complications associated with mechanical ventilation to arise. In addition, extrapulmonary processes such as fever, pain, delirium, and anxiety may also increase respiratory drive and lead to patient–ventilator asynchrony. **Figure 42.5** offers an algorithmic approach to the mechanically ventilated patient in respiratory distress.

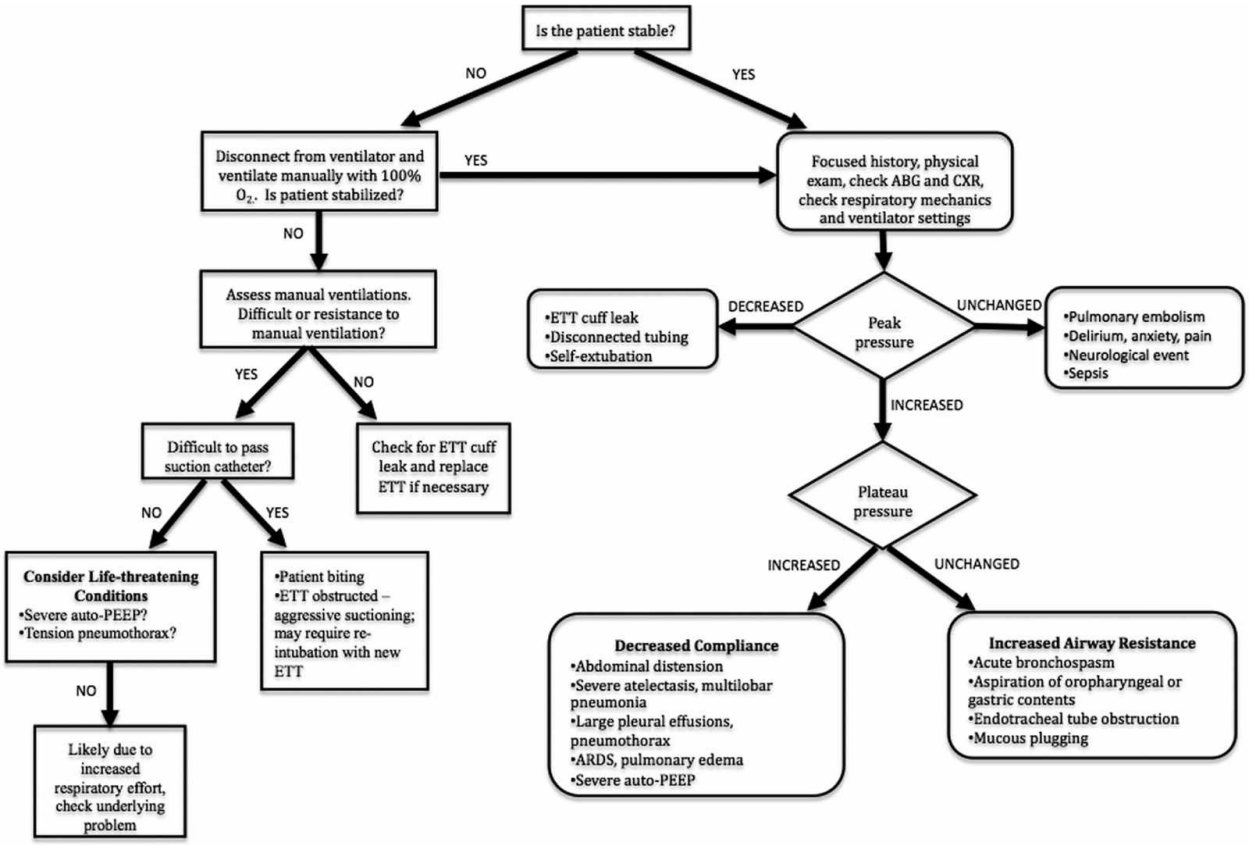

FIGURE 42.5 Approach to the mechanically ventilated patient in respiratory distress. ABG, arterial blood gas; ARDS, acute respiratory distress syndrome; CXR, chest X-ray; ETT, endotracheal tube; PEEP, positive end-expiratory pressure.

Chest radiographs should be followed to ensure proper positioning of the ETT (optimal 3 to 5 cm above the carina), because cephalad or caudad migration is very common.

Arterial blood gas analysis is usually performed at the initiation of mechanical ventilation and then periodically based on the disease process and ventilator changes. Acid–base disturbances may require adjustments of minute ventilation, because they can lead to significant and potentially life-threatening cellular dysfunction or hemodynamic consequences. F_{IO_2} will be adjusted to assure adequate oxygenation and avoid potential oxygen toxicity.

SEDATION IN THE MECHANICALLY VENTILATED PATIENT

The majority of mechanically ventilated patients will require sedation and/or analgesia to facilitate ventilator synchrony, and alleviate pain and discomfort from critical care procedures and treatments.[10] A number of different agents can

be used alone or in combination to achieve consistent sedation, anxiolysis, and analgesia. Common medication classes include benzodiazepines, opioid analgesics, and neuroleptic agents. A neuroleptic agent may be used if medication for delirium is indicated. Each class differs in the amount of anxiolysis, analgesia, amnesia, and hypnosis provided. Elimination half-life, volume of distribution, and drug clearance may be significantly altered in critically ill patients. No single agent is sufficiently superior to other agents to recommend its standard use in all patients. Selection must therefore be individualized according to the patient's distress, physiologic parameters, expected duration of therapy, and potential interactions with other medications. Careful attention should also be paid to the possible development of adverse reactions. Brief descriptions regarding drug classes, effects, and pharmacokinetics are presented in **Table 42.6**.

TABLE 42.6 Characteristics of Sedative Medications Commonly Used in the ICU Setting

DRUG	ONSET	DURATION	EFFECTS
Opioids • Morphine • Fentanyl	5–10 min <0.5 min	4 h 30–60 min	Potent sedative/analgesic effects, without causing anxiolysis, hypnosis, or amnesia
Benzodiazepines • Lorazepam • Midazolam • Diazepam	5–20 min 1–5 min 1 min	6–8 h 30 min 20–60 min	Sedative anxiolytic, hypnotic, and amnesic effects without analgesic effects
Neuroleptic • Haloperidol	30–60 min	0.5–6 h	Potent sedative anxiolytic with minimal hypnotic and amnesic effects; no analgesia provided
Anesthetic–sedative • Propofol	<1 min	3–10 min	Potent sedative hypnotic, with minimal amnesic effects; anxiolysis seen at low doses; no analgesia provided
Central α_2 agonist • Dexmedetomidine	5–10 min	1–2 h	Sedative sympatholytic with moderate anxiolysis and analgesia; no hypnosis or amnesia; no significant effect on respiratory drive

ICU, intensive care unit.

A goal depth of sedation should be determined before initiating sedative–

analgesic regimens and the goal should be individualized on the basis of the clinical situation.[10] Patients expected to have a shorter duration of mechanical ventilation may require lighter sedation or no sedation at all. On the other hand, patients being mechanically ventilated for severe hypoxemia or ARDS may require deeper sedation. The goal depth of sedation should be frequently assessed and titrated using validated and reliable scales for mechanically ventilated patients (eg, Richmond Agitation-Sedation Scale).

VENTILATOR-ASSOCIATED COMPLICATIONS

Critically ill patients requiring mechanical ventilation are at risk for clinically important upper gastrointestinal hemorrhage due to stress ulceration.[11] Histamine-2 receptor antagonists and proton pump inhibitors reduce the frequency of overt upper gastrointestinal hemorrhage in patients in the ICU when compared to no prophylaxis.

A ventilator-associated pneumonia (VAP) may complicate the course of patients requiring mechanical ventilation. The Centers for Disease Control has introduced the surveillance definition of a ventilator-associated event as worsening oxygenation for 2 days following a period of stability. On the basis of current definitions, a VAP requires sustained worsening oxygenation, along with fever, leukocytosis, need for antibiotics, purulent endotracheal secretions, and growth of a pathogenic organism. The most common cause of VAP is aerodigestive tract colonization, followed by aspiration of contaminated secretions into the lower airways. Proper specimens should be collected before beginning empiric antibiotic coverage. Steps to reduce the risk and prevent development of VAP should be employed routinely in mechanically ventilated patients.[12] These include semi-recumbent positioning, oral care, and compliance with strict hand washing and other infection control protocols.

WEANING AND EXTUBATION

Weaning refers to the process of liberating the patient from the mechanical ventilator. The use of weaning protocols, generally involving respiratory therapists and nurses, has been shown to reduce the duration of mechanical ventilation.[13] Readiness testing refers to the use of objective clinical criteria to determine whether a patient is ready to begin weaning. The reason for the patient’s respiratory failure should have been identified and the patient should have shown a favorable response to the treatment. Chest radiograph should

demonstrate improvement in pulmonary edema. Oxygenation should be satisfactory: Spo_2 greater than or equal to 90% while receiving less than or equal to 50% FIO_2 and PEEP less than or equal to 5 cm water. Patients should be hemodynamically stable with minimal or no need for vasopressor support, and without myocardial ischemia or unstable cardiac arrhythmias. Sedative drugs should be discontinued, and the patient should be awake and alert, or easily arousable, and be able to manage secretions. In addition, significant fluid, electrolyte, and metabolic disorders should be corrected before weaning attempts.

A once-daily spontaneous breathing trial should be initiated when the patient meets readiness criteria. A weaning trial can be performed using a T-piece or PSV.

A T-piece trial involves removing the ventilator with the ETT in situ connected to oxygen and monitoring spontaneous respirations. In a PSV trial, a pressure support level of approximately 5 cm water is added to the CPAP mode. We prefer using the PSV approach over the T-piece because PSV provides reassurance of ventilator alarm features and backup ventilatory assistance in case of apnea, extreme tachypnea, or inadequate minute ventilation. In addition, PSV overcomes the increased work of breathing from resistance of the ETT that may be seen with T-piece trials. A successful weaning trial meets the criteria outlined in **Table 42.7**. If the patient meets all of the weaning criteria, the patient may be extubated. If the patient fails to meet all of the criteria, ventilatory support should be resumed and another weaning trial should be attempted the following day. In the case of cardiogenic pulmonary edema, the administration of diuretics before extubation may be beneficial even if the patient is not in overt heart failure, because the cardiovascular effects of PPV discussed earlier will be reversed once positive pressure is removed.

TABLE 42.7 Criteria for a Successful Ventilator Weaning Trial

- Pressure support ≤ 8 cm water (ideally <5 cm water)
- PEEP ≤ 5 cm water
- Spo_2 > 92% while breathing ≤ 50% FIO_2
- Respiratory rate < 35 breaths/min
- Heart rate < 140 beats/min
- Systolic blood pressure <180 mm Hg but >90 mm Hg
- No diaphoresis or signs of respiratory fatigue
- Tolerated for at least 30 min to 2 h

PEEP, positive end-expiratory pressure.

For extubation, the patient should be placed in the upright position and the oropharynx and trachea via the ETT should be suctioned to remove secretions. The ETT cuff is then deflated and the ETT is removed. Immediately after removal, any secretions that are coughed up and present in the oropharynx should be promptly suctioned and supplemental oxygen should be provided. Physical examination including auscultation of the lungs to confirm bilateral air entry and the upper airway to exclude the presence of inspiratory stridor (which would suggest laryngeal edema) should be performed.

Respiratory distress following extubation may be due to airway disease, recurrent pulmonary edema, secretions, or laryngeal edema. In many cases, early and aggressive management with suctioning, bronchodilator therapy, diuresis, or NIV can prevent re-intubation. If laryngeal edema is present, the administration of intravenous glucocorticoids and inhaled racemic epinephrine may lessen the need for re-intubation. In patients with respiratory distress following extubation, NIV may prevent re-intubation if applied early.[14] If the patient fails a trial of NIV or meets any of the contraindications to the use of NIV discussed earlier in this chapter, he/she should be promptly re-intubated followed by a thorough evaluation and treatment of the cause of the post-extubation respiratory failure.

CONCLUSION

Mechanical ventilation provides life-saving support in the CCU. Clinicians must closely attend to the goals, ventilator settings, and patient–ventilator monitoring to utilize mechanical ventilation to the greatest benefit and prevent complications. Understanding and utilizing sedation goals and daily weaning assessments will assure that patients are promptly liberated from mechanical ventilation.

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Patient and Family Information For: MECHANICAL VENTILATION

A mechanical ventilator is a machine that helps patients breathe when they are not able to breathe enough on their own. It is commonly referred to as a *breathing machine or respirator*. Most patients who require help breathing with mechanical ventilators are cared for in the ICU or cardiac care unit. Many people think of mechanical ventilators as a way to treat breathing-related issues. However, patients are placed on ventilators to support their breathing function while giving time for treatments to improve their condition. Being on a respirator means the patient is critically ill—it is life support.

There is always a team taking care of the patient, including the physician, nurse and respiratory therapist.

WHY MECHANICAL VENTILATORS ARE USED

Mechanical ventilators help support the patient by pushing breaths with oxygen into the lungs, as well as removing carbon dioxide from the lungs. There are some patients who are in an ICU in whom breathing is difficult—they may feel short of breath and tired from the work that their breathing requires. This is called *respiratory failure* and is often due to the cardiac disease where poor pumping leads to fluid buildup in the lungs. Some patients also have pneumonia, COPD, or asthma, or too much mucus present in the windpipe or airways; and these conditions make it even more difficult to breathe. Mechanical ventilators can help ease the work of breathing for these people and prevent their condition from getting worse. If a patient does not get help early enough, the condition can worsen very quickly and ultimately cause the heart and lungs to stop.

Other patients may not be breathing at all because they are in a coma, have

brain damage or injury, very weak muscles, or because they suffered a cardiac arrest. In this case, a ventilator must be used to breathe for the patient.

HOW MECHANICAL VENTILATORS WORK

There are two basic types of ventilators that are available. The first is called a *noninvasive ventilator* or *BiPAP machine*. This device pushes air into the lungs through tubing that is connected to the patient by way of a mask, which covers the nose and mouth. It can help improve oxygen levels in the blood and lessen the amount of work that the muscles need to do to in order for the patient to breathe. Patients can sometimes still speak to their family and friends while on this machine, and some may also be able to eat provided it is safe to do so. This type of ventilator is commonly used in the cardiac care unit for patients suffering from shortness of breath due to heart failure.

Patients on BiPAP have to be monitored very closely. Even with the help of this device, some patients will continue to have a great deal of trouble breathing. If the patient has not improved within a few hours of this device being started, then this machine is not successful and the patient will need a second type of machine, called the *invasive mechanical ventilator*. Also, not all patients are good candidates for BiPAP and we may decide that it is more harmful than beneficial to use it.

The invasive mechanical ventilator is connected to the patient through a tube (called an ETT) that is placed in the mouth or nose and down into the windpipe. The process of placing the tube into the patient's windpipe is called *intubation*. The device blows air into the lungs and it can help a person by doing all of the breathing for them or just assisting their breaths. The difference between BiPAP and the invasive ventilator is that with the invasive ventilator the doctors have more control over a person's breathing and are able to completely rest the muscles used for breathing.

HOW PATIENTS FEEL WHILE ON INVASIVE MECHANICAL VENTILATORS

The ventilators themselves do not cause pain, but most people who require invasive ventilators do not like the feeling of having a tube in their mouth or

nose. They cannot talk because the tube passes through the voice box into the windpipe. They also cannot eat when the tube is in place, and so they need a temporary feeding tube from the mouth to the stomach until the breathing tube is removed. Some people will feel some discomfort as air from the machine is being pushed into the lungs and they will try to breathe out while the machine is trying to push air in. This is called *fighting* against the ventilator and makes it more difficult for the ventilator to help. In addition, people undergo many diagnostic tests and therapies that can cause physical discomfort or pain. For these reasons, patients are often given medications such as sedatives or painkillers to make them feel more comfortable.

HOW PATIENTS ARE MONITORED

Anyone on a ventilator will be hooked up to a monitor that measures heart rate, breathing rate, blood pressure, and oxygen levels at regular intervals. Other tests that may be done routinely include chest X-rays and blood tests that will measure the amount of acid, oxygen, and carbon dioxide in the blood. The doctors, nurses, and respiratory therapists use this information to gauge how well the patient is doing and to see if any adjustments need to be made to the ventilator.

RISKS OF MECHANICAL VENTILATION

Some risks of mechanical ventilation do exist. However, if the doctors feel that the patient needs to be on a ventilator, the benefits of placing the patient on one are always greater than these potential risks.

When a person is first placed on a respirator, he/she may experience a drop in blood pressure. This can usually be reversed with the use of intravenous fluids, but some patients may temporarily require medications to keep their blood pressure normal.

Sometimes, a part of the lung that is weak can become too inflated with air and start to leak. This leaked air collects in an empty space between the lungs and the chest wall. Because there is a limited amount of space in the chest, the leaked air starts to take up more space and the lung begins to collapse. This is called a *pneumothorax*. This air needs to be removed as soon as possible because

it can result in life-threatening complications. It is drained by a *chest tube*, which is likely to remain until the patient no longer requires the ventilator.

The pressure from the ventilator to put air into the lungs can also damage the lungs. Doctors try to keep this risk to a minimum using the lowest amount of pressure that is needed. In addition, very high levels of oxygen may be harmful to the lungs. Unfortunately, patients who already have damaged lungs may need very high levels of oxygen until the lungs start to heal, which makes it difficult to reduce this risk.

As mentioned, many patients on mechanical ventilation will need some level of sedation. Different patients will react to each medication differently. At times, sedation medications can build up and the patient may remain in a deep sleep for hours or days, even after the medication is stopped. The doctors and nurses try to adjust the medications so that the right amount is being delivered at all times.

The breathing tube can allow germs and bacteria from the mouth to get into the lungs more easily. This can cause an infection such as pneumonia, which can be a serious problem and could mean that the patient has to stay on the machine longer. People who are very sick can be more prone to infection than others. All members of the medical staff take maximum precautions to prevent this from happening; however, if an infection occurs, it can be treated with antibiotics.

HOW LONG ARE MECHANICAL VENTILATORS USED?

Ventilators can be lifesaving, but they do not fix the primary disease or injury. Ventilators help support a patient until other treatments become effective. The medical team will always try to help patients get off the ventilator at the earliest possible time, but will not do so until there has been an improvement or a reversal of the problem at hand.

Weaning refers to the process of getting the patient off the ventilator. Depending on the patient, this process may take a few hours up to a few days or longer. Specific criteria are used to decide whether a patient is ready to come off of the respirator including blood oxygen levels, chest X-ray results, and physical examination. Some patients will never improve enough to be taken off the ventilator completely and may require long-term ventilator support.

Not all patients improve just because they are on a ventilator, and patients can die even though they are on a respirator. It is hard to predict or know for sure whether a person will recover with treatment. Sometimes, doctors feel very sure

the ventilator will help and the patient will recover. Other times, the doctors only have a rough idea of the chances a person will survive. For patients who are very sick and at the end of life, mechanical ventilation sometimes only postpones death.

43

Matthew Durst
Hooman Poor

Pulmonary Embolism and Deep Vein Thrombosis

Pulmonary embolism (PE) and deep vein thrombosis (DVT) are two categories of a broader disease known as venous thromboembolism (VTE). VTE can have a wide range of clinical presentations ranging from an asymptomatic incidental finding to hemodynamic collapse and death. The incidence of VTE is estimated at approximately 200,000 new cases per year in the United States, with a slightly higher predominance of DVT compared to PE.[1]

Not only is VTE a fairly common disease but it is also a significant cause of mortality. Previous autopsy studies have demonstrated PE as a direct cause of, contributing to, or accompanying death in approximately 15% of hospitalized patients over the past 40 years.[1] In the International Cooperative Pulmonary Embolism Registry (ICOPER) study published in 1999, the 3-month mortality rate of all patients diagnosed with PE before autopsy was 15.3% and it increased to 58.3% in patients who presented with hemodynamic instability.[2]

PATHOGENESIS

While the exact cause of VTE is unknown, it has been associated with a number of factors and is likely dependent on the interplay between them. Three of these

factors, venous stasis, endothelial injury, and a hypercoagulable state, oftentimes referred to as Virchow triad, are all associated with the development of VTE.[1] The likelihood of developing VTE is significantly increased when multiple risk factors are present simultaneously.

Pulmonary emboli typically originate from thrombi present in the deep veins. The proximal veins of the lower extremities, specifically the iliac and femoral venous system, are believed to be the source of most diagnosed pulmonary emboli. Right heart, pelvic vein, renal vein, and upper extremity thrombi are also potential sources of pulmonary emboli. Patients with PE are also found to have clots in the right heart, otherwise known as emboli in transit, and are at high risk of mortality.[1]

PHYSIOLOGY OF THE RIGHT VENTRICLE AND THE PULMONARY VASCULATURE

The pulmonary circulation can be modeled similarly to electrical circuits using Ohm's law, which states that voltage difference (***V***) equals the current of electrons (***I***) multiplied by the resistance (***R***). The pressure difference between the pulmonary artery ($\boldsymbol{P}_{PA}$) and the left atrium ($\boldsymbol{P}_{LA}$) in the pulmonary circulation is analogous to the voltage difference in the electrical circuit. The cardiac output (CO), which is the flow of blood through the pulmonary artery (PA), is analogous to the current in the electrical circuit. And, the pulmonary vascular resistance (PVR) is analogous to the resistance in the electrical circuit (**Figure 43.1**).

Ohm's law: $V = I \times R$

Physiologic correlate for pulmonary circulation:

$P_{PA} - P_{LA} = CO \times PVR$ $\qquad$ $P_{PA} = (CO \times PVR) + P_{LA}$

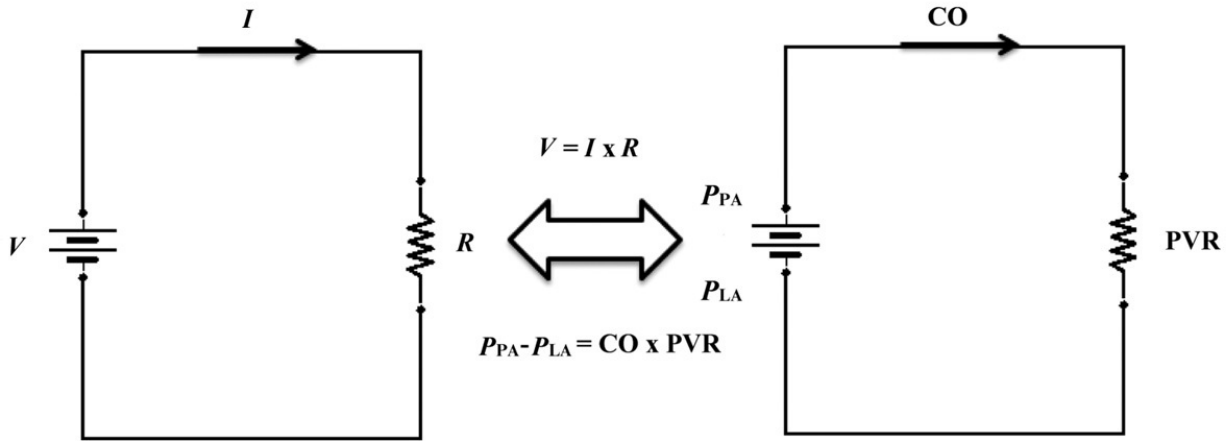


FIGURE 43.1 Circuit diagram of the pulmonary circulation. CO, cardiac output; I, current; PLA, left atrial pressure; PPA, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; R, resistance; V, voltage.

The normal pulmonary circulation is a low-pressure and low-resistance circuit due to differences in blood vessel structure compared to the systemic circulation. The structure and function of the right ventricle (RV) are different compared to that of the left ventricle (LV), because the RV does not have to generate nearly as much pressure to produce the same CO as the LV. The RV is crescentic and relies more heavily on longitudinal shortening for force generation, whereas the LV is concentrically shaped and relies more on circumferential constriction. Overall, the RV is a thinner walled, more compliant, and more energy-efficient chamber than the LV. However, the operating characteristics of the RV are heavily dependent upon the low-pressure nature of the pulmonary circulation, leaving the RV very susceptible and poorly equipped to handle acute increases in RV afterload.[3]

PATHOPHYSIOLOGY OF INCREASED PULMONARY

VASCULAR RESISTANCE

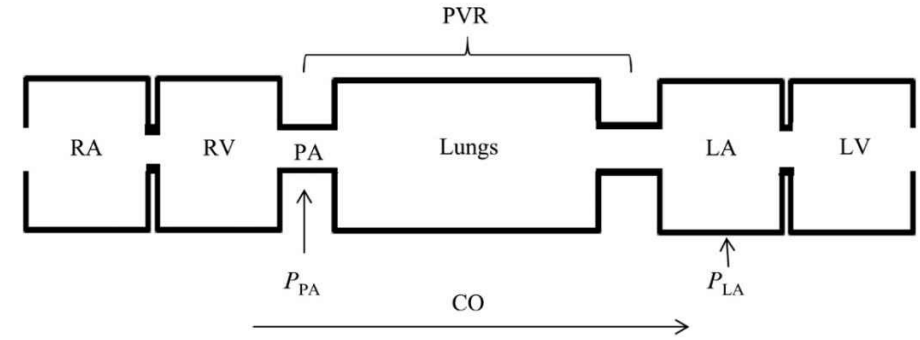
Emboli cause an increase in PVR through two mechanisms. The primary mechanism for the increase in PVR is mechanical obstruction of the vasculature. The relationship between clot burden and PVR is hyperbolic. At low levels of mechanical obstruction, blood is able to be diverted to regions of distensible vasculature, which minimizes the increase in PVR. However, with more significant clot burden, this compensatory mechanism is overwhelmed as the remaining vessels become over-distended, leading to rapid rises in PVR for small increases in obstruction. The second mechanism for increased PVR is the release of humoral factors, leading to vasoconstriction of the pulmonary vasculature.[4] The major humoral factors that have been associated with changes in PVR following PE are thromboxane-A_2, which is an end product of arachidonic acid metabolism, and serotonin.[5] Thromboxane-A_2 is both a systemic and pulmonary vasoconstrictor that is released by platelets with the purpose of causing vasoconstriction to achieve homeostasis. Platelets are also the likely source of serotonin release because serotonin plays an important role in platelet aggregation and is a very potent pulmonary vasoconstrictor despite causing systemic vasodilation. Because pulmonary emboli are composed primarily of fibrin and small amounts of platelets, it is unlikely that the embolus itself is the source of thromboxane-A_2 and serotonin release. Instead it is probable that fresh platelets that have amassed around the embolus are activated and release these vasoactive substances which then lead to significant pulmonary vasoconstriction. The roles that these two substances play in pulmonary vasoconstriction are supported by multiple animal studies looking at receptor antagonists that demonstrate significant attenuation to abolishment of the rise in PVR with blockade of the receptors.[5] The initial symptomatic relief resulting from treatment with heparin that is observed within hours likely stems from blockade of platelet activation and prevention of further release of humoral vasoconstrictors, not clot resolution, because not enough time has elapsed for significant fibrinolysis to have occurred.

EFFECTS ON HEMODYNAMICS

PE increases PVR both through mechanical obstruction as well as through

substrate-mediated pulmonary vasoconstriction. In non–hemodynamically significant PE, obstructing emboli and local vasoconstriction divert blood flow to unaffected regions of the vasculature, causing them to dilate and thus minimizing the overall increase in PVR. If enough of the vasculature is obstructed or constricted, PVR rises significantly and the RV afterload increases. To maintain CO, the RV must generate higher pressures. Although the RV is able to generate higher pressures to some degree, as discussed earlier, the RV in a healthy individual without prior cardiopulmonary disease is ill-equipped to deal with significant increases in afterload.

The maximal mean PA pressure that can be generated by a normal RV is approximately 40 mm Hg.[6] Increases in RV afterload beyond this point result in decreases in RV CO. The decreased RV CO leads to a drop in LV preload and subsequent LV CO. Increases in RV afterload lead to increased RV wall stress, which results in increased RV ischemia that can decrease RV CO. In addition, because of the compliance of the RV, increases in RV afterload result in RV dilation, which further exacerbates RV wall stress. As the RV dilates, the leaflets of the tricuspid valve are pulled apart, leading to poor coaptation and worsening tricuspid regurgitation, which leads to decreased RV output. Because the heart is encased in the pericardium, the free wall of the dilating RV cannot expand outward, and, instead, RV dilation leads to a leftward shift of the intraventricular septum, causing a decrease in the size of the LV cavity and a further decrement in LV preload. Notably, because of the drop in LV CO, there is a decrease in right coronary artery (RCA) perfusion, leading to further RV ischemia. These events continue to cascade in a downward spiral leading to further deterioration in RV function and resultant declines in CO, ultimately progressing to cardiogenic shock (**Figure 43.2**).[7,8] This vicious cycle can be exacerbated by additional factors. Excessive fluid loading will cause worsening RV dilation. Although sometimes unavoidable, intubation is especially dangerous because the sedatives used for induction can cause peripheral vasodilation, leading to decreased RCA perfusion pressure and RV ischemia. Furthermore, positive intrathoracic pressure from mechanical ventilation can lead to increased RV afterload because of the compression of pulmonary vessels.


PVR
RA
RV
PA
Lungs
LA
LV
P_{PA}
P_{LA}
CO

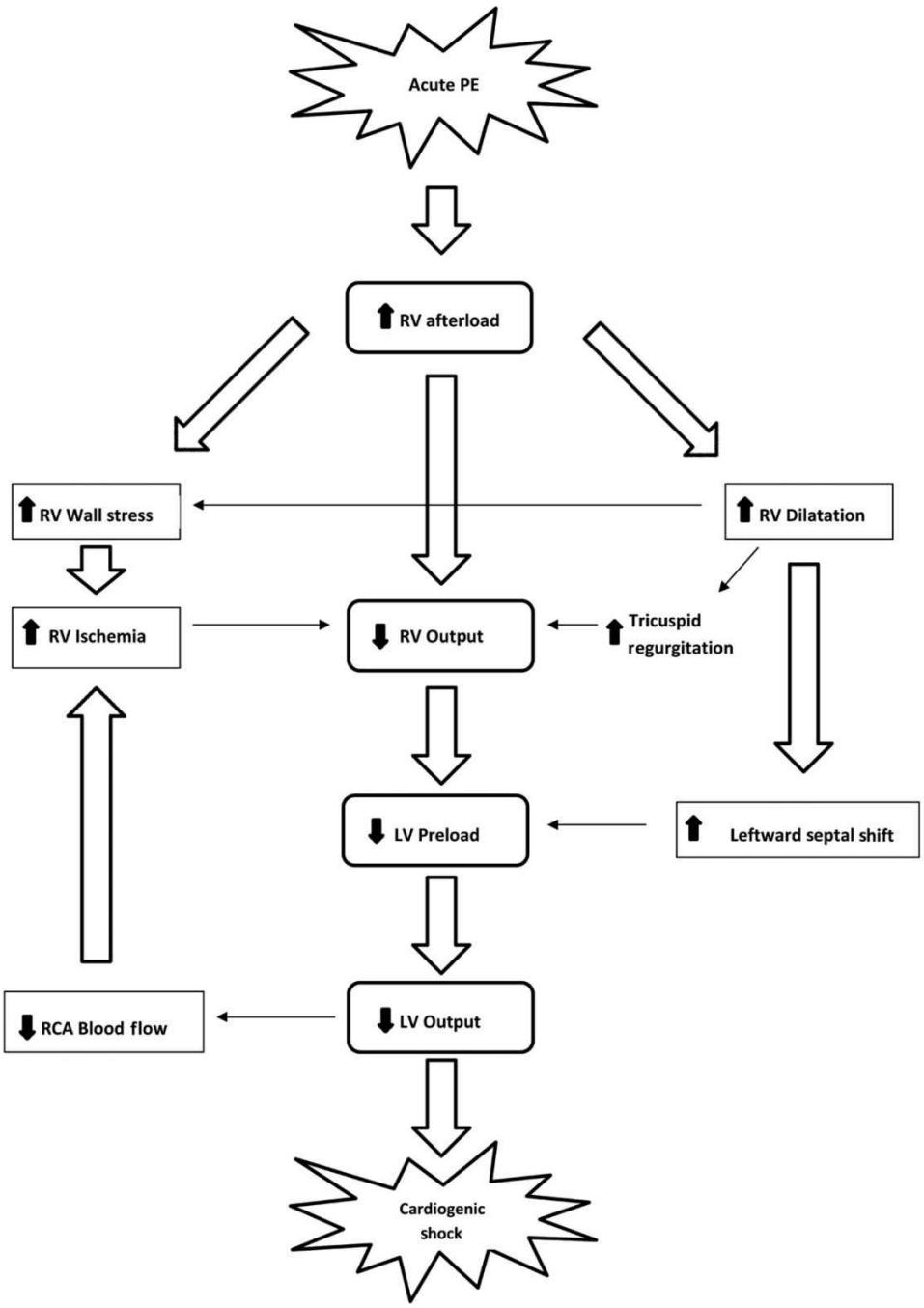

Acute PE
RV afterload
RV Wall stress
RV Dilatation
RV Ischemia
RV Output
Tricuspid regurgitation
LV Preload
Leftward septal shift
RCA Blood flow
LV Output
Cardiogenic shock

FIGURE 43.2 Vicious cycle of RV failure and cardiogenic shock following hemodynamically significant PE. CO, cardiac output, LA, left atrium; LV, left ventricle; PA, pulmonary artery; PE, pulmonary embolism; P_{LA}, left atrial pressure; P_{PA}, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RCA, right coronary artery; RV, right ventricle.

For patients with underlying chronic cardiopulmonary disease resulting in pulmonary hypertension, the RV has been chronically exposed to increased afterload, and thus has had time to adapt by undergoing hypertrophy, allowing it to generate pressures significantly higher than that which a normal RV can generate.[9] Nevertheless, patients with underlying cardiopulmonary disease are at increased risk for hemodynamic decompensation in the setting of a significant PE because of their baseline compromised state.

EFFECTS OF PULMONARY EMBOLISM ON GAS EXCHANGE

One of the major physiologic effects of PE is the creation of dead-space ventilation, which is defined as areas of the lung that receive ventilation but no perfusion. An increase in dead-space ventilation would normally result in hypercapnia because of a reduced ability to eliminate carbon dioxide from the blood stream; however, hypercapnia is not a common finding in PE because patients compensate by hyperventilating other areas of the lung that are participating in gas exchange. Typically, if the clot burden is severe enough to cause hypercapnia, the hemodynamic effects often prove fatal.[10]

Hypoxemia is a common finding in PE and is due to a combination of multiple factors. One factor is the development of an intrapulmonary shunt, defined as blood traversing areas of the lung that receive no ventilation. This lack of ventilation may occur because of effects from the embolism, which includes atelectasis, pulmonary infarction, and bronchoconstriction. Shunt physiology is also present in a small subset of patients who develop intracardiac shunting, typically through a patent foramen ovale that has opened because of increased right atrial pressure from RV failure. Low mixed venous saturations from decreased CO may contribute to hypoxemia because the venous blood starts at a lower oxygen saturation before traversing abnormal lungs. Hypoxemia is typically accompanied by an increased gradient between the alveolar oxygen concentration (Pa_{O_2}) and the arterial oxygen concentration (Pa_{O_2}). An increased

gradient may even be present in patients with a normal Pa_{O_2} because of the effects of hyperventilation on arterial CO_2 partial pressure.[10]

DIAGNOSIS OF DEEP VEIN THROMBOSIS

DVT, although not fatal by itself, has the potential to fragment and cause a fatal PE. On the other hand, inappropriate anticoagulation of patients exposes them to unnecessary risks, such as a potentially life-threatening hemorrhage. Therefore, it is important to make a proper diagnosis in patients suspected to have a DVT. The gold standard for diagnosis of DVT is venography, which involves the injection of iodinated contrast dye into a dorsal foot vein to outline the entire venous system of the lower extremity. Venography has been demonstrated to have a risk of approximately 1.2% for the development of symptomatic DVT or PE during 3 months of follow-up after a normal venogram. Venography is no longer commonly used to establish or rule out the diagnosis of DVT because of its invasive nature, associated risks, high cost, lack of availability at many centers, and the fact that it is contraindicated in some patients, such as those with renal dysfunction or severe allergies to the contrast material.[11]

Current practice typically uses combinations of clinical probability assessments, D-dimer assays (high sensitivity and moderate sensitivity), and imaging such as venous ultrasonography (US), computed tomography (CT) venography, or magnetic resonance imaging (MRI). The decision on the combination of tests used is dependent upon the pretest probability of the presence of DVT, the suspected location (lower vs upper extremity), and suspected first episode versus recurrence.[11]

Multiple clinical probability assessments for DVT exist. One of the more commonly used tools, known as the Wells score (**Table 43.1**), was developed by Wells et al.[12] and classifies the pretest probability of patients who are suspected of having DVT into three categories: low, moderate, or high probability. The scoring system consists of multiple questions with one point assigned for each question that is answered in the affirmative followed by a subtraction of two points if there is an alternative diagnosis to DVT that is at least equally as likely as the diagnosis of DVT. A score of less than 1 is considered low probability, 1 to 2 is considered moderate probability, and 3 or more is considered high probability of having a DVT. In the initial study of 593 patients, 3% in the low-

probability group, 17% of the moderate-probability group, and 75% of the high-probability group were ultimately diagnosed with DVT.[12] A modified version of the Wells score, which incorporates the presence of prior DVT and divides patients into either low- or high-probability groups, can also be used.[13]

TABLE 43.1 Wells Scores

DVT		PE	
Active cancer (treatment within 6 mo or palliative)	+1	Clinically suspected DVT	+3.0
Calf swelling ≥ 3 cm compared to asymptomatic calf (measured 10 cm below tibial tuberosity)	+1	Alternative diagnosis is less likely than PE	+3.0
Swollen unilateral superficial veins (nonvaricose, in symptomatic leg)	+1	Tachycardia (heart rate > 100)	+1.5
Unilateral pitting edema (in symptomatic leg)	+1	Immobilization (≥ 3 d) or surgery in previous 4 wk	+1.5
Previous documented DVT	+1	History of DVT or PE	+1.5
Swelling of the entire leg	+1	Hemoptysis	+1.0
Localized tenderness along the deep venous system	+1	Malignancy (treatment within 6 mo or palliative)	+1.0
Paralysis, paresis, or recent cast immobilization of lower extremities	+1		
Recently bedridden ≥ 3 d, or major surgery requiring regional or general anesthetic in the past 12 wk	+1		
Alternative diagnosis at least as likely	−2		
High probability	>2	High probability	>6.0
Moderate probability	1–2	Moderate probability	2.0–6.0
Low probability	<1	Low probability	<2.0

DVT, deep vein thrombosis; PE, pulmonary embolism.

The D-dimer, a degradation product of cross-linked fibrin, has a high sensitivity for the presence of VTE; however, it has a poor specificity because of

numerous conditions other than VTE that can cause an elevation in D-dimer levels. This makes the D-dimer assay a useful test in low-risk patients as a test to rule out the presence of DVT. Unfortunately, the test is much less useful in acutely ill or hospitalized patients because of the high occurrence of false-positive results.[11] Multiple versions of the test exist, each with its own sensitivity and specificity.[14]

Owing to its noninvasive nature, low cost, and lack of radiation or contrast dye, US is the most commonly used modality to diagnose DVT. The two types of US studies include proximal compression US and whole-leg US. In both cases, the US probe is used to assess for the presence of a clot within the vein by compression, a positive study defined as the inability to fully compress any segment of the vein under gentle pressure with the probe. The proximal study assesses the femoral and popliteal veins, but not the calf veins. Whole-leg US assesses the proximal veins as well as the calf veins.

For patients in whom US cannot be obtained, such as those who are in a cast, or in whom US is nondiagnostic, CT venography or MRI may be used to further evaluate for DVT. CT venography requires the injection of iodinated contrast, typically into an arm vein, with CT imaging timed for opacification of the deep veins. CT venography can be combined with computed tomography pulmonary angiography (CTPA) to evaluate for both PE and DVT. MRI may be used in a variety of ways to establish the diagnosis of DVT. Magnetic resonance venography can be done without contrast; however, the use of contrast agents such as gadolinium improves visualization of the vasculature. MRI can also be used to directly image thrombi using techniques to take advantage of the composition of clots. MRI is less frequently used because of higher costs and lack of availability for this purpose at most centers.[11]

DIAGNOSIS OF PULMONARY EMBOLISM

Combinations of clinical probability calculators, D-dimer assays, and imaging modalities such as pulmonary angiography, CT angiogram, lung scintigraphy (ventilation-perfusion [VQ] scan), and echocardiography are used to make the diagnosis of PE.[15]

Similar to how venography was the gold standard for the diagnosis of DVT, pulmonary angiography was previously the gold standard for the diagnosis of PE. It is done by performing a right heart catheterization and injecting contrast

dye into the pulmonary arteries. The vasculature is then examined for filling defects or amputation of a branch of the PA. One benefit of pulmonary angiography over CT angiography is the ability to simultaneously obtain invasive hemodynamic measurements. With the improvement in CT imaging, pulmonary angiography has fallen out of favor because of its invasive nature and cost.[15]

Multiple clinical prediction rules are available to determine the pretest probability of PE. The most frequently used scoring system was again developed by Wells et al.[12], which classifies patients into three groups: low likelihood, moderate likelihood, and high likelihood with rates of diagnosed PE of approximately 10%, 30%, and 65%, respectively (**Table 43.1**). A simplified version of the Wells score separates patients into two groups.[15]

CTPA is currently the diagnostic imaging modality choice for evaluation of patients with suspected PE. CTPA involves the injection of iodinated contrast, typically into an arm vein, with imaging timed for opacification of the pulmonary arterial circulation. This allows for adequate visualization of the pulmonary vasculature at least down to the level of the segmental pulmonary arteries, providing a sensitivity and specificity of 96% and 95%, respectively.[15] CTPA also allows for evaluation of the lung parenchyma that may reveal diagnoses other than PE that may be the cause of the respiratory problems.

VQ scans are another imaging modality that can be useful for the diagnosis of PE, particularly in patients who cannot undergo CTPA because of contrast allergies, renal insufficiency, or any other reason. The test involves the injection of technetium (Tc)-99m–labeled macroaggregated albumin particles that ultimately get lodged in the pulmonary capillaries and are viewable by scintigraphy, allowing for evaluation of pulmonary perfusion. The perfusion studies are then matched with ventilation studies, which require the inhalation of radio-labeled gas or microparticles that can be imaged to evaluate ventilation of the lungs. The matched scans are then examined, looking for areas of the lung with poor perfusion but preserved ventilation, which would signify a PE. VQ scans have the benefit of requiring significantly less radiation exposure when compared to CTPA. VQ scans are frequently classified into one of the following categories, considered diagnostic in most patients: normal or near normal, low probability, intermediate probability (nondiagnostic), and high probability.[15]

Echocardiography may also be helpful in making the diagnosis of PE and is a useful tool for prognostication. Signs such as RV dilatation and signs of RV pressure overload are highly suggestive of PE. McConnell sign, defined as a

decreased contractility of the RV free wall compared to the apex, can sometimes be seen in patients with PE. Mobile right heart thrombi seen on echocardiography essentially confirm the diagnosis of PE; however, they are a rare finding. Because the overall negative predictive value of echocardiography is low, it is a poor test to rule out PE.[15]

RISK STRATIFICATION FOR PATIENTS WITH PULMONARY EMBOLISM

To determine the optimal management of patients with PE, it is crucial to assess their risk of short-term decompensation. Patients with a higher risk of decompensation are likely to benefit more from aggressive therapies compared to patients with a lower risk profile.

The Pulmonary Embolism Severity Index (PESI) score is a tool that was developed to help risk stratify patients diagnosed with PE. The model utilizes 11 criteria to stratify patients into 5 classes of risk (PESI classes I to V), the lowest group having a 30-day mortality of 0% to 1.6% and the highest class having a 30-day mortality rate between 10% and 24.5%.[16] The PESI score is particularly useful for identifying low-risk patients (PESI I and II) who can be safely treated as outpatients.[17]

For patients in higher PESI classes, it is important to further stratify based on risk of short-term morbidity and mortality. On the basis of the Management Strategies and Determinants of Outcome in Acute Pulmonary Embolism Trial (MAPPET), hemodynamic status on presentation, specifically systolic blood pressure (SBP) <90 mm Hg, not clot burden, is the major determinant of short-term mortality. The trial included patients with PE and overt signs of impending right heart failure, noting in-hospital mortality rates of 8.1%, 25%, and 65% in patients with RV dysfunction but SBP > 90 mm Hg, cardiogenic shock, and those requiring cardiopulmonary resuscitation at presentation, respectively.[18] On the basis of this elevated risk of death, the American Heart Association defines massive PE as acute PE with sustained hypotension (SBP < 90 mm Hg for at least 15 minutes or requiring inotropes in the absence of another cause of hypotension), pulselessness, or persistent profound bradycardia (heart rate < 40 beats/min with signs or symptoms of shock) (**Figure 43.3**).[19] Owing to the high risk of early mortality in these patients, immediate intervention to restore

pulmonary perfusion is required.

PE CLASSIFICATIONS

Massive PE = Acute PE + one of the following:

1. Sustained Hypotension
   - SBP < 90 mmHg for at least 15 minutes or requiring inotropic support
   - Not due to another cause such as arrhythmia, hypovolemia, sepsis, or LV dysfunction
2. Pulselessness
3. Persistent Profound Bradycardia
   - Heart rate < 40 bpm with signs or symptoms of shock

Submassive PE = Acute PE without systemic hypotension (SBP ≥ 90 mmHg) + one of the following:

1. RV Dysfunction: defined as the presence of at least one of the following
   - RV dilation (echocardiography or CT)
   - Elevated BNP or NT-proBNP
   - EKG changes (new or incomplete RBBB, anteroseptal ST elevation or depression, or anteroseptal T-wave inversion)
2. Myocardial necrosis: defined as an elevation in troponin I or troponin T

FIGURE 43.3 PE classification from the scientific statement from the AHA. AHA, American Heart Association; PE, pulmonary embolism.

Normotensive patients with RV dysfunction and/or myocardial injury are at a slightly increased risk of deteriorating into a massive PE compared to those who

are low risk, and are thus classified as “submassive” PE.[19] Tests that can be used to determine whether a patient has RV dysfunction or myocardial injury include echocardiography, CT scans, electrocardiography, brain natriuretic peptide (BNP), N-terminal (NT)-proBNP, troponin I, and troponin T. Evidence of RV dysfunction on echocardiography includes RV free wall hypokinesis, RV dilatation, increased ratio of RV to LV diameter, and elevations in calculated RV systolic pressures. CT scans can also be used to evaluate for RV dilatation and increased ratio of RV to LV diameter. Electrocardiographic findings of sinus tachycardia, new-onset atrial arrhythmias, new right bundle branch block, Qr pattern in V1, an S1Q3T3 pattern, negative T waves in V1 to V4, and ST segment shift over V1 to V4 have been associated with higher short-term risk. BNP and NT-proBNP, which are released in states of RV pressure overload that lead to increased myocardial stretch, can also be useful tests because patients with normal BNP and NT-proBNP levels have a high negative predictive value for increased risk of poor outcome. Finally, troponin levels also have a good negative predictive value because patients without troponin elevations are at low risk for early adverse outcomes.[15,19] **Table 43.2** represents a risk stratification schematic.

TABLE 43.2 PE Risk Stratification for Early Mortality Risk

EARLY MORTALITY RISK	SHOCK OR HYPOTENSION	PESI CLASS III–V	RV DYSFUNCTION ON IMAGING	+ CARDIAC BIOMARKERS
High risk	+	N/A	+	N/A
Intermediate-high	−	+	+	+
Intermediate-low	−	+	Either one or neither +	
Low risk	−	−	Assessment unnecessary, both—if done	

PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RV, right ventricle.
Adapted from ESC Committee for Practice Guidelines (CPG), Endorsed by the European Respiratory Society (ERS), European Heart Journal. 2014; 35(43):3033-3073.

TREATMENT OF DEEP VEIN THROMBOSIS

Because DVT itself is not a fatal condition, the decision whether to treat a DVT and the choice of treatment involves weighing the risks of the progression to PE

and recurrence versus the risks of treatment. Factors involved in determining whether to treat include location of the thrombus, the presence or absence of a known provoking factor, any underlying hypercoagulable state, prior history of VTE, bleeding risk, and patient preference. Potential treatment options include monitoring, anticoagulation (**Table 43.3**) used to prevent further clots and promote passive reduction of thrombus size, thrombolysis which actively promotes clot breakdown, catheter-directed thrombolysis (CDT), inferior vena cava (IVC) filter placement, and thrombectomy.[20]

TABLE 43.3 Available Anticoagulants

ANTICOAGULANT	DOSE	ROUTE	RENAL ADJUSTMENT	REVERSAL AGENT
Apixaban	10 mg twice daily for 7 d, then 5 mg twice daily	Oral	Yes	No
Argatroban	2 µg/kg/min Titrate to aPTT goal	IV	No	No
Bivalrudin	0.15–0.2 mg/kg/h Titrate to aPTT goal	IV	No	No
Dabigatran	150 mg twice daily	Oral	Yes	Idraucizumab
Edoxaban	60 mg daily 30 mg daily if ≤ 60 kg	Oral	Yes	No
Fondaparinux	Weight based <50 kg = 5 mg daily 50–100 kg = 7.5 mg daily >100 kg = 10 mg daily	SubQ	Yes	No
LMWH	1 mg/kg every 12 h	SubQ	Yes	Protamine for partial neutralization
Rivaroxaban	15 mg twice daily for 21 d, then 20 mg daily	Oral	Yes	No
Unfractionated heparin	80 U/kg bolus, then 18 U/kg/h Titrate to aPTT goal	IV	No	Protamine
Warfarin	Individualized dosing Titrate to goal INR	Oral	No	Vitamin K

aPTT, activated partial thromboplastin time; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; SubQ, subcutaneous.

In the case of patients with a first occurrence of DVT, the location of the thrombus will play a significant role in the treatment decision. For patients with clots distal to the popliteal vein (isolated distal DVT) without severe symptoms or risk factors for extension such as positive D-dimer without an alternative reason, extensive thrombosis (>5 cm in length, involving multiple veins, or >7 mm in maximal diameter), close to proximal veins, no reversible provoking factor, active cancer, prior VTE, or inpatient status, monitoring with repeat US in 2 weeks is preferred to treatment with anticoagulation. If repeat US is unable to be performed or any risk factors are present, anticoagulation is preferred in patients with low-moderate bleeding risk. In patients with high bleeding risk, serial monitoring is preferred. If extension is seen on the repeat US, then anticoagulation should be initiated. For patients with proximal leg DVT, anticoagulation is recommended if tolerated and preferred over CDT. The use of an IVC filter in addition to anticoagulation is not recommended; however, an IVC filter should be used in patients who cannot tolerate anticoagulation due to bleeding, have a contraindication to anticoagulation, or have developed VTE despite being anticoagulated. For patients with proximal upper extremity DVT (axillary or more proximal veins), typically occurring in the setting of central venous catheter usage, treatment with anticoagulation is preferable to CDT and the catheter should be removed if still present. For patients with a recurrent episode of VTE while not on anticoagulation, initiation of anticoagulation is the preferred method of treatment.[20]

The initial choice of anticoagulation is based on multiple factors such as presence of active malignancy, presence of renal dysfunction, planned procedures, prior treatment failures, need for monitoring, and cost. For patients with active malignancy, low-molecular-weight heparin (LMWH) is the preferred agent. For patients without active malignancy, novel oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban are preferred to vitamin K antagonists (VKAs) such as warfarin, and VKAs are preferred to LMWH. For patients who have recurrent VTE despite anticoagulation, LMWH is recommended. If the recurrence occurs while the patient is compliant with LMWH treatment, the dose of the LMWH can be increased. In both cases of treatment failure, the presence of an underlying malignancy should be considered.[20]

The duration of anticoagulation is dependent upon whether the DVT was provoked by a known reversible factor, whether it is an initial clot or a recurrence, presence of active malignancy, presence of known hypercoagulable

state, and bleeding risk. For patients with a first occurrence with a known reversible risk factor such as surgery, pregnancy, leg injury, or a flight >8 hours, 3 months of therapy is the recommended duration. For patients who are low-moderate bleeding risk with unprovoked DVT, recurrent DVT while off anticoagulation, or who have an active malignancy, indefinite treatment with anticoagulation is preferred to 3 months of treatment. In patients with similar high bleeding risk, 3 months of treatment is recommended over indefinite treatment. Patient preferences should also be taken into account when deciding on treatment duration.[20]

TREATMENT OF PULMONARY EMBOLISM

Unlike in patients with DVT alone, patients with PE may present with hemodynamic instability and respiratory abnormalities such as hypoxemia. The initial step in management should be to provide adequate support to maintain organ perfusion and gas exchange. As discussed earlier, the etiology of hypotension and shock from PE is RV failure secondary to an increase in RV afterload. Aggressive volume expansion should be avoided because it may further exacerbate RV dilation and wall stress. Vasopressors such as norepinephrine should be used to maintain arterial pressure and inotropes such as dobutamine should be used to support RV contractility. The role of inhaled pulmonary vasodilators such as epoprostenol and nitric oxide is unclear, but may improve hemodynamics given the presence of pulmonary vasoconstriction from humoral factors. Hypoxemia should be treated with supplemental oxygen and mechanical ventilation should be initiated if required; however, if intubation and mechanical ventilation is required, special care should be taken because inducing agents and the use of positive-pressure ventilation can cause further hemodynamic compromise in these very unstable patients.

The mainstay of therapy for PE is anticoagulation, which prevents the formation of new thrombi and allows the patient’s endogenous fibrinolytic system to resolve the clots that are present. Because PE is a potentially life-threatening condition, empiric anticoagulation should be started in patients with intermediate-high clinical probability of PE during the diagnostic workup. In patients with a low probability of PE, anticoagulation can be withheld until a diagnosis of PE is confirmed. Recommended initial anticoagulation choices include subcutaneous LMWH, unfractionated heparin with monitoring of the

activated partial thromboplastin time, or subcutaneous fondaparinux. In cases where heparin products cannot be used, such as with heparin-induced thrombocytopenia, non–heparin-based anticoagulation should be used. Once the diagnosis of PE is confirmed, it is crucial to risk stratify patients to help decide the most appropriate treatment and level of monitoring. A sample algorithm is provided in **Figure 43.4**.

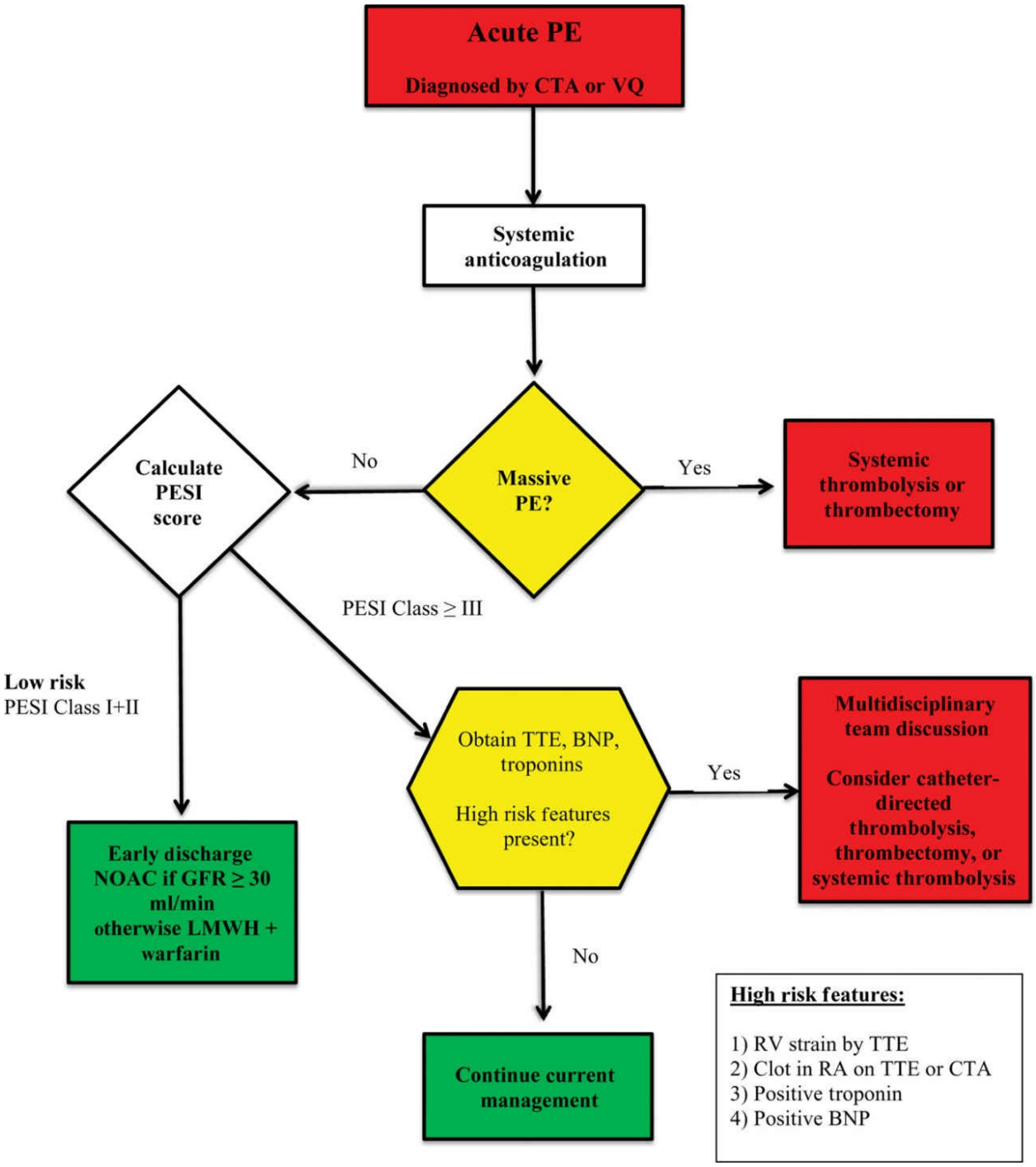


FIGURE 43.4 Sample PE treatment algorithm. BNP, brain natriuretic peptide; CTA, computed tomography angiogram; GFR, glomerular filtration rate; LMWH, low-molecular-weight heparin; NOAC, novel oral anticoagulant; PE, pulmonary embolism; PESI, Pulmonary Embolism Severity Index; RA, right atrium; RV, right ventricle; TTE, transthoracic echocardiogram; VQ, ventilation-perfusion.

For patients who are low risk (PESI I and II), no further workup for risk stratification is necessary, and these patients can be considered for early

discharge home with anticoagulation. As with DVT, the NOACs and VKAs are preferred to LMWH except for in-patients with active malignancy or recurrence while taking another form of anticoagulation. For patients at intermediate to high risk (PESI classes III to V), cardiac imaging and biomarkers should be obtained to evaluate for signs of RV dysfunction and/or myocardial necrosis.

For patients with massive PE, aggressive therapies to restore pulmonary perfusion should be undertaken given the high mortality risk. If there are no absolute contraindications, systemic thrombolysis is recommended (**Table 43.4**). Surgical embolectomy may also be considered in centers with experience with the procedure. Surgical embolectomy is also a good option in cases of clot in transit (right atrial or RV thrombus), which have a high risk of embolizing into the pulmonary vasculature.

TABLE 43.4 Contraindications to Systemic Thrombolysis

1. Prior intracranial hemorrhage
2. Structural intracranial cerebrovascular disease
3. Malignant intracranial neoplasm
4. Ischemic stroke within 3 mo
5. Suspected aortic dissection
6. Active bleeding or bleeding diathesis
7. Recent surgery encroaching on the spinal canal or the brain
8. Recent facial or closed-head trauma with evidence of bony fracture or brain injury

Adapted from 2014 AHA Statement.[19]

While the mortality rate for submassive PE is higher than that for low-risk PE, the role of thrombolysis in this population is controversial. Thrombolysis has been shown to reduce the rate of hemodynamic decompensation in patients with submassive PE; however, this benefit has not translated into a reduction in mortality, likely because of the increase in adverse events, particularly intracranial hemorrhage, which occurs in about 2% of patients receiving systemic thrombolysis. To reduce the bleeding risks of thrombolysis, lower doses can be administered. Ultrasound-assisted, catheter-directed, low-dose thrombolysis has been investigated as a potential treatment. The rationale of this therapy is to administer the thrombolytic directly at the clot while using high-frequency US to increase thrombus permeability to thrombolytic agents, allowing for use of even lower doses of thrombolytics and theoretically decreasing the risk of bleeding.[21]

Given the lack of clear consensus guidelines for the treatment of massive and submassive PEs, the use of multidisciplinary teams, often comprising physicians

from cardiology, pulmonology, critical care, interventional radiology, cardiothoracic surgery, and emergency medicine, can help determine the best treatment strategy and provide a multidisciplinary recommendation along with rapid mobilization of resources.

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Patient and Family Information for: PULMONARY EMBOLISM AND DEEP VEIN THROMBOSIS

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) are blood clots that occur in the blood vessels of the limbs, primarily the legs, and the lungs, respectively. They are part of a spectrum of disease known as Venous Thrombo-embolism (VTE). Typically, the body maintains a balance where blood remains fluid while inside the blood vessels, but clots whenever it exits the blood vessels. This mechanism is how the body stops bleeding after a cut occurs. DVTs occur when the blood clots inappropriately inside the body and can occur if the blood flow through those veins is sluggish, as can occur during prolonged surgery or very long periods of immobility such as a long plane flight. In other cases, patients may have a "hypercoagulable state," a condition where the blood is intrinsically more likely to form clots. Occasionally, pieces of these clots from the blood vessels of the limbs may break off and travel to the lungs and get lodged in the blood vessels of the lung, a process known as pulmonary embolism. The blood clots cause symptoms by blocking the blood flow in the blood vessels they reside.

The symptoms of blood clots are variable and depend on the location. For DVTs, the most common symptoms are swelling, pain, and redness near the location of the blood clot. Some patients may have no symptoms at all. Blood clots in the lung (PE) may cause shortness of breath, chest pain, a rapid pulse, and coughing up blood. Occasionally, some people with PE do not have any symptoms at all and the blood clots are found incidentally.

Of the two, PE is the more dangerous, life-threatening form of blood clot. In severe cases of PE, the blood clots can impair the ability of the flowing blood to take up oxygen and can also prevent blood from circulating through the lungs,

possibly leading to death. DVTs themselves do not cause these problems, but pieces can break off and result in PE.

If your doctor suspects that you have a PE or DVT, there are numerous tests that may be ordered to find the clot. These tests include imaging tests such as CT scans, VQ scans, and ultrasound of the limbs. A blood test, known as the D-dimer, which is often abnormally elevated in people with blood clots, can be helpful to rule out the presence of PE or DVT.

The treatment depends upon the severity of the clots. Simple blood clots are treated with blood thinners, otherwise known as anticoagulants, to prevent growth of current clots and also to prevent the formation of new blood clots. All patients with VTE are treated for at least 3 months, and treatment may be longer depending on the cause of the blood clot. In some patients who are unable to take blood thinners, such as people with recent bleeding or some recent surgeries, a device called an IVC filter may be placed in one of the veins in the abdomen to try to prevent blood clots that form in the lower limbs from reaching the lungs.

In very severe cases where patients have very low blood pressure, medications called thrombolytics may be given to try to dissolve the blood clots. In some cases, this may be determined to be unsafe and the person with the clot may have to undergo surgical removal of the blood clots.

44

Louis Brusco
Diana Anca

Sedation and Analgesia in the Cardiac Care Unit

INTRODUCTION

Patients in a cardiac care unit (CCU) experience pain, anxiety, stress and, at times, delirium, and altered mental status. Sedation and analgesia of these patients is not only a humane way to treat their discomfort but it also is an integral part of their therapy to allow them to tolerate the various other therapies, treatments, and instrumentations that they are subjected to in the critical care setting. It also is integral in reducing the metabolic response and oxygen demands of the critically ill cardiac patient.

Sedatives and analgesic medications carry with them hemodynamic, respiratory, neurologic, and other side effects, so that proper sedation is a balance between adequacy of sedation and minimizing these other effects. In addition, development of delirium in the cardiac care setting is a complication that dramatically impacts on the survival and quality of life of patients after they have recovered from their illness. Recently, the implication of the very choice of agent in the development of delirium has led to a reevaluation of the impact of all sedative/analgesic regimens in the context of their propensity to cause or help delirium.

The desired level of sedation in the cardiac care setting can vary widely

between the awake, alert, conversant, oriented and comfortable patient, and the patient who is in a drug-induced coma and therapeutically paralyzed. The precise level of sedation and the agents used are determined by the indications for sedation, whether they are anxiety, insomnia, agitation, coordination with a mechanical ventilator, prevention of removal of tubes or lines, protection against myocardial ischemia, or the need for amnesia during paralysis. Agents are chosen depending on the relative amounts of the different components of analgesia, anxiolysis, amnesia, sleep, and muscle relaxation that are needed.

Although use of pharmacologic agents is the main way to achieve these goals, it cannot be stressed enough that other measures that reduce the need for amounts or even the very need for sedation are tremendously beneficial to patients, their comfort, and the avoidance of confusion and delirium. Such measures include frequent reorientation, assurance, and communication from the nursing staff; proper environmental controls such as lighting, temperature, and noise control; assessment and management of sensations such as hunger, thirst, and need to void; providing a variety of stimuli, such as visitors and media; and maintenance of a diurnal variation, with, if possible, a window facing the outside.

EVALUATION OF LEVEL OF SEDATION

One goal of management of critically ill cardiac patients is maintaining an optimal level of pain control and sedation. Unfortunately, pain and anxiety are subjective and somewhat difficult to consistently measure from caregiver to caregiver. Over 50% of patients who were interviewed after their intensive care unit (ICU) stays rated their pain as moderate to severe, during rest as well as during procedures.[1–3] Thus, the assessment of pain and anxiety must be discussed first before moving on to the pharmacology of the agents.

Although patients in a CCU are being monitored with highly sophisticated equipment, technological methods of measuring pain and anxiety such as those using electroenphalography (EEG), cerebral function analyzing monitors, lower esophageal contractility, combinations of physiologic variables or serum concentrations of medications, among others, have all proved to be no more reliable and a lot more complicated and expensive as simple, clinically based scoring systems. Properly designed scoring systems can be used not only to assess and record pain and anxiety but also to allow bedside nurses to titrate

therapy in a more tightly defined window on their own, meeting regulatory requirements without needing repeated orders from a practitioner who is licensed to prescribe the medications.

The most basic of clinical methods of pain assessment is simply asking the patient to rate the pain on a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable. Although simple and widely used, and despite those instructions being given, the very fact that not infrequently some patients will answer “11” shows that when pain is being experienced acutely, the overall severity of the pain seems much greater than some historical control. One step up from a simple number scale is the use of a “Visual Analog Scale” (VAS)—which is simply a line that has the scale marked off in measured intervals. This scale is highly reliable and valid from patient to patient and caregiver to caregiver.[4] It can be further modified to have pictures of happy and unhappy patients or faces on the scale in varying degrees instead of numbers. Unfortunately, it is limited because it ignores qualitative aspects of pain, and many critically ill cardiac patients are not strong enough or awake enough to use such a system.

Measuring sedation and level of consciousness is similarly difficult, and requires the use of assessment of a practitioner observing the patient. The most basic method is to perform a mental status and neurologic examination and report the results. This is not practical on a repeated basis and does not allow the easy determination of changes that would allow titration of medications from time to time. The Glasgow Coma Scale (GCS) is widely used for the assessment of level of consciousness, but it was designed and validated for patients with neurologic deficits, and is not designed for assessment of sedation.

Sedation scales are subjective tools that, in general, measure the patient’s responsiveness to verbal, auditory, and or physical stimuli. The ideal scale would determine the degree of sedation and agitation, be applicable in a wide variety of patient situations, have a well-defined sedation goal, include behavioral descriptors, be easy to measure and score with minimal training, and be reproducible, reliable, and valid across caregivers. Proper use of such a scale can reduce the duration of mechanical ventilation and also reduce length of stay in both the CCU and the hospital.[5] However, even though this has been known for over 10 years, the clinical use of scoring systems still remains low.[6] It is therefore imperative that every patient care area or unit that sedates critically ill patients chooses a sedation scale that best fits its patients, trains the caregivers in its use, and develops procedures to use that information in the sedation of the

patients in the cardiac care area.

One of the most widespread of the currently used sedation scales is the Ramsay Sedation Scale (RSS), introduced in 1974 and modified slightly since then. The modified scale is shown in **Table 44.1**. As it was designed primarily for use during research into sedative agents, it was at the same time both groundbreaking but less than ideal for clinical use. Since its debut, many others have been developed for different reasons. Some of the more commonly referenced or clinically used ones include the Sedation Agitation Scale (SAS, **Table 44.2**),[7] the Motor Activity Assessment Scale,[8] the Vancouver Interactive and Calmness Scale (VICS),[9] the Richmond Agitation–Sedation Scale (RASS, **Table 44.3**),[10] the Adaptation to Intensive Care Environment (ATICE) instrument,[11] and the Minnesota Sedation Assessment Tool (MSAT).[12]

TABLE 44.1 Modified Ramsay Sedation Scale

SCORE	DEFINITION
1	Anxious and agitated or restless or both
2	Cooperative, oriented, and tranquil
3	Responds to commands only
4	Brisk response to a light glabellar tap or loud auditory stimulus
5	Sluggish response to a light glabellar tap or loud auditory stimulus
6	No response to a light glabellar tap or loud auditory stimulus

Performed using a series of steps: observation of behavior (score 1 or 2), followed (if necessary) by assessment of response to voice (score 3), followed (if necessary) by assessment of response to loud auditory stimulus or light glabellar tap (score 4 to 6).

TABLE 44.2 Sedation–Agitation Scale

SCORE	TERM	DESCRIPTOR
7	Dangerous agitation	Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Requiring Restraint and frequent verbal reminding of limits, biting ETT.
5	Agitated	Anxious or physically agitated, calms to verbal instructions.
	Calm and	

4	cooperative	Calm, easily arousable, follows command.
3	Sedated	Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again.
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously.
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow command.
Guidelines for SAS assessment		
1	Agitated patients are scored by their most severe degree of agitation as described.	
2	If patient is awake or awakens easily to voice (“awaken” means responds with voice or head shaking to a question or follows commands), that is a SAS 4 (same as calm and appropriate—might even be napping).	
3	If more stimuli such as shaking are required but patient eventually does awaken, that is a SAS 3.	
4	If patient arouses to stronger physical stimuli (may be noxious) but never awakens to the point of responding yes/no or following commands, that is a SAS 2.	
5	Little or no response to noxious physical stimuli represents a SAS 1.	

ET, endotracheal; SAS, Sedation–Agitation Scale.

TABLE 44.3 Richmond Agitation–Sedation Scale

SCORE	TERM	DESCRIPTION
14	Combative	Overtly combative or violent, immediate danger to staff
13	Very agitated	Pulls on or removes tube(s) or catheter(s) or exhibits aggressive behavior toward staff
12	Agitated	Frequent nonpurposeful movement or patient–ventilator dys-synchrony
11	Restless	Anxious or apprehensive, but movements not aggressive or vigorous
0	Alert and calm	
21	Drowsy	Not fully alert, but has sustained (.10 s) awakening, with eye contact, to voice
22	Light sedation	Briefly (,10 s) awakens with eye contact to voice
23	Moderate sedation	Any movement (but no eye contact) to voice
24	Deep sedation	No response to voice, but any movement to physical stimulation
25	Unarousable	No response to voice or physical stimulation

Performed using a series of steps: observation of behaviors (score 14 to 0), followed (if necessary) by assessment of response to voice (score 21 to 23), followed (if necessary) by assessment of response to physical stimulation such as shaking shoulder and then rubbing sternum if no response to shaking shoulder (score 24 to 25).

A thorough review and comparison of these scales can be found here.[13] The decision to use one scale or the other is many times a local, multidisciplinary decision. What is important is that a scale is indeed used and that it is performed in a standard and consistent manner.

ANALGESIC AND SEDATIVE AGENTS

Critically ill cardiac patients are often treated with continuous infusions of potent medications. Some, such as sedative-hypnotics, have sedation as a primary action; whereas others, such as opioids, have a sedative action that is a secondary effect to the primary analgesic effect. Patients require sedatives because of pain, anxiety, delirium, and the desire to keep them from remembering an uncomfortable time in their lives. Especially when patients are on mechanical ventilation, it is most often much easier to administer such medications via continuous infusion. Use of such agents via continuous infusion, however, is associated with prolonged mechanical ventilation and a longer stay in the CCU, whereas daily interruption of sedative treatment has been shown to reduce the duration of mechanical ventilation and CCU duration.[14] Thus, it is no longer considered acceptable to sedate patients to a deep, deep state but rather to move to a lighter plane of sedation. This is much more difficult and requires both the use of sedation scales as mentioned, sedation protocols, and the selection of agents that are somewhat easier to titrate and have somewhat shorter durations of action than in use previously. It has also been shown that a shift toward more of an analgesic-based sedation instead of a sedative-hypnotic–based regimen is beneficial.[15,16] We therefore now review the most commonly used agents in the CCU for sedation.

Some definitions are needed to help in the classification and description of the various agents. “Analgesic agents” have as their primary mode of action the reduction of patients’ pain. They usually will have as a side effect the sedation of patients, but the sedative effect and the analgesic effect may have different potencies and durations of action. Analgesics can be broadly divided into “opioids,” meaning morphine-like in action, and “nonopioids” which are medications such as nonsteroidal anti-inflammatory agents and acetaminophen.

"Sedative-hypnotics" are medications that have as their primary effect the reversible depression of the central nervous system, inducing sleep, allaying anxiety, and causing amnesia.

Other drugs used in sedation are such drugs as "psychotropic medications," such as haloperidol or risperidone; they are antipsychotic medications that interfere with neurotransmitters in the brain that affect the way the cerebral neurons interact with each other.

OPIOIDS

Opioids are the mainstay of analgesic therapy in the CCU patient. Opioid analgesics, such as morphine, have as their mechanism of action the means of acting selectively on neurons that transmit and modulate nociception, leaving other sensory modalities and motor functions intact. Opioid receptors are found in the brain, spinal cord, and peripheral tissues. When bound to receptors, opioids produce analgesia, drowsiness, changes in mood, and mental clouding. An important feature of opioid analgesia is that it is not associated with loss of consciousness except at extremely high doses.

All opioids depress respiratory drive in a dose-dependent manner, and this depression is increased when opioids are given in conjunction with sedative-hypnotic medications. In general, opioids have minimal hemodynamic effects when given to patients who are not volume depleted, but can cause hypotension in patients who are volume depleted because of veno-dilatation. The primary problems with long-term administration of opioids are tachyphylaxis and dependence and withdrawal symptoms with discontinuation of long-term continuous infusion. A dosing summary is contained in **Table 44.4**.

TABLE 44.4 Analgesics Used in the Cardiac Care Unit

DRUG	ELIMINATION HALF-LIFE	PEAK EFFECT (IV) (min)	STARTING DOSE
Morphine	2–4 h	10–30	1–4 mg bolus 1–5 mg/h infusion
Hydromorphone	2–4 h	10–20	0.2–1 mg bolus 0.5–2 mg/h infusion
Fentanyl	2–5 h	2–3	25–100 µg bolus 25–200 µg/h infusion
Remifentanil	4 min	1.5	6–9 µg/kg/h infusion

Methadone	12–24 h	30–60	5–50 mg every 6–12 h based on previous opioid dose

IV, intravenous.

Morphine

Morphine is the prototypical opioid. It was discovered in 1804 and is the most abundant alkaloid found in opium. It has been sold commercially for almost 200 years and remains a mainstay in the sedation of critically ill cardiac patients. This is primarily due to cost and familiarity factors, because other opioids lack some of the problems associated with morphine. The dose required to produce analgesia, as with most opioids, varies and is dependent on such factors as tolerance, tachyphylaxis, and metabolic and excretory ability. Although morphine is metabolized in the liver, 6% to 20% of the metabolites are morphine-6-glucoronide, a metabolite that is excreted by the kidneys;[17,18] and while the data is variable, it is anywhere from half as potent to 20 to 40 times more potent than morphine itself[18,19] and can accumulate in renal failure. For this reason, hydromorphone is the long-acting opioid that is preferred in renal failure. When given via bolus injection, morphine causes histamine release, but this is not a factor when used via infusion in patients in the CCU. However, when given by bolus, it was one of the classical treatments for cardiogenic pulmonary edema, because the vasodilation and preload reduction it causes, along with the analgesia and anxiolysis, made patients in cardiogenic pulmonary edema much more comfortable.

It is the most hydrophilic of the opioids and therefore has the slowest onset of action. A bolus dose of morphine will take effect in 5 to 10 minutes with peak analgesic effect in 90 minutes and lasting for 2 to 3 hours—after continuous infusion, it does not exhibit prolongations in half-life (known as “context-sensitive half-life”) such as happens with fentanyl and, to a lesser extent, with sufentanil and alfentanil.[20]

Usual doses to start morphine via infusion are 0.5 to 2 mg/h. Bolus doses of morphine can be given at 2 to 4 mg every 1 to 2 hours as a start, but doses can increase as tolerance develops. It is not unusual to see patients require morphine infusions of 15 mg/h or more.

Hydromorphone

Hydromorphone, the most common name for the drug actually called either

dihydromorphone or dimorphone, is a semi-synthetic derivative of morphine. It was synthesized and researched in the 1920s. It is slightly more lipophilic than morphine and thus exhibits superior fat solubility and speed of onset than morphine.[21] It is thought to be three to four times stronger than morphine but with a lower risk of chronic dependency. It lacks the renally excreted active metabolites of morphine. It also has a slightly longer duration of action than morphine—roughly 3 to 4 hours. Its duration of action makes it slightly more cumbersome to adjust via continuous infusion, but, because it does not exhibit the context-sensitive half-life prolongation of fentanyl, it is sometimes preferable to fentanyl via infusion for long durations of sedation.

Most clinicians will start with hydromorphone at 0.1 to 0.2 mg/h and titrate as needed. Bolus doses of 0.5 mg given every 2 to 4 hours can be a starting point for intermittent intravenous (IV) dosing.

Fentanyl

Fentanyl is a fully synthetic opioid that was first developed in 1960 and has served as the parent molecule to the synthetic opioids that have been developed since then—sufentanil, alfentanil, and remifentanil. It is far more potent than morphine—roughly 40 times more potent on an mg/mg basis. As with other opioids, it works by binding to opioid receptors in the brain, spinal cord, and periphery, but its highly lipophilic chemistry causes it to cross the blood–brain barrier very easily, giving it an extremely short onset of action. It does not cause histamine release, and, similar to other opioids, is neither an arterial vasodilator nor a negative inotrope.[22] It can, however, cause veno-dilatation and hypotension in a patient who is volume depleted. It is a potent blocker of endogenous catecholamines, which can be beneficial (in preventing a patient from becoming hypertensive and/or tachycardic with procedures) and detrimental (causing hypotension in patients whose hemodynamics are dependent on an elevated level of endogenous catecholamines).

Fentanyl is primarily metabolized in the liver to inactive metabolites, but its cessation of action is primarily through redistribution from the brain to the peripheral tissues rather than metabolism of active drug. Therefore, while a single or a few bolus doses have a shorter duration of action than morphine, on the order of 60 to 90 minutes, when given by infusion, even after 2 hours, the time to decrease by 50% concentration goes from 30 minutes for a bolus dose to 120 minutes with the infusion, and the time to decrease by 80% goes from 60 minutes with a bolus to over 600 minutes with the infusion.[20] This “context-

sensitive half-life" is due to slow release from the fatty compartments that fentanyl has such an affinity for, and causes a greatly prolonged effect for fentanyl when given by infusion—to an effective half-life much longer than morphine after a few hours of infusion.

Fentanyl also has a particular problem in many patients of having rapidly escalating dosing requirements.[23] It is not uncommon for patients to start out on one dose and 24 to 48 hours later be requiring four to five times as much as they were just a day or two earlier. This tolerance seems greater for many patients than with the longer acting opioids and, combined with the context-sensitive half-life prolongation, makes fentanyl a less than ideal medication to use for critically ill cardiac patients for any longer than 24 to 48 hours.

Fentanyl dosing usually starts at 50 to 100 μg for a bolus dose or 50 to 100 μg/h via infusion with titration—it is not uncommon to rapidly (over 24 to 72 hours) require 500 to 750 μg/h via infusion.

Sufentanil

Sufentanil is similar to fentanyl in every way except that it is more potent—roughly 10 times more potent than fentanyl and almost 400 times more potent than morphine. It does not exhibit quite the same context-sensitive half-life prolongation as fentanyl. It was synthesized in 1974. It is perhaps the most potent sympatholytic opioid in clinical practice. Its use in critically ill cardiac patients has been minimal because, until recently, it was under patent protection and was much more expensive than fentanyl when used for sedation in the CCU.

Remifentanil

Remifentanil is a potent ultrashort-acting synthetic opioid.[24] It is unique in that it has a rapid onset of action, and it has an ester linkage that undergoes rapid hydrolysis by nonspecific tissue and plasma esterases, which means that it has an organ-independent metabolism and does not accumulate in either renal or hepatic failure. Its context-sensitive half-life remains at a flat 4 minutes even after prolonged infusions.[25] It is fairly potent—roughly twice as potent as fentanyl and 100 times as potent as morphine. It is very hemodynamically stable but, unlike fentanyl, it does cause histamine release when given as a bolus; and many times an antihistamine such as diphenhydramine is given as an adjunct when it is used for sedation. It is a potent respiratory depressant, and practitioners familiar with its use commonly see patients who are awake but will

not breathe until it is fully worn off, which happens minutes later.

Remifentanil seems to have all the makings of an ideal sedative agent for critically ill cardiac patients. Although studies have been promising, review of a meta-analysis of studies in critically ill patients[26] shows that while remifentanil use is associated with a reduction in time to tracheal extubation, there was no reduction in mortality, duration of mechanical ventilation, length of ICU stay, or risk of agitation. The other reason it is not currently a viable analgesic for CCU use is that it is still on patent and extremely expensive—recent change in marketing arrangements for the drug have caused the price to double in the United States. Until the price significantly decreases, remifentanil remains a theoretical but not a practical answer to analgesic needs in the CCU.

Methadone

Almost polar opposite in pharmacology to remifenanil is methadone, among the longest acting of the opioids.[27] It is a synthetic opioid that is structurally unlike morphine but still acts on opioid receptors and produces many of the same effects. It was developed in 1937 and has been used commonly because of its long duration of action and low cost. High doses of methadone can block the euphoric effects of other opioids such as heroin and morphine, and it has become a mainstay in the treatment of patients addicted to opioid narcotics. Although that is its most common use, it does have other uses as well, and one of those is in the long-term critically ill patients. Methadone has an excellent oral bioavailability (80% to 90%), an elimination half-life of 12 to 24 hours, and is equipotent with morphine. It can be given via oral tablets or suspension, or intravenously.

Patients who are on long-term opioid infusions may suffer withdrawal symptoms on cessation—others, although not experiencing true withdrawal symptoms, simply need the medication slowly tapered off to allow the patient to gradually reach a state of no sedation. Frequently, this will take place when the patient is ready to leave a CCU but is prevented from leaving by the presence of a sedative infusion. Using methadone to transition a patient from a continuous IV infusion of opioid sometimes can be an ideal way to bridge this gap. Commonly, the patient will be given methadone at a dose of 0.5 to 0.75 mg/d of the equivalent amount of morphine the patient is on. The availability of methadone in an oral suspension makes it even easier to give to patients receiving tube feeds. It has been studied in pediatric patients, but the pharmacology is applicable to adult patients as well.[28]

One consideration in patients receiving methadone that does not exist with the other opioids is that methadone is associated with prolongation of the QTc interval in high doses, and has been implicated in progressing on to torsade de pointes. The mean daily dose in one study was over 350 mg/d, a very high dose; and in usual use it is easy to limit doses to below that, but especially in cardiac patients who may be more predisposed to arrhythmias and QT prolongation, this must be considered.[29]

SEDATIVE HYPNOTICS

In addition to opioids for analgesia, patients in cardiac care settings require sedation for anxiety, restlessness, agitation, and to decrease chances of remembering bad experiences in the CCU. Anxiety is best treated after pain is controlled with analgesics and reversible conditions such as hypoxia, infections, renal or hepatic failure, and metabolic abnormalities are corrected. Most sedative-hypnotics work by binding to the inhibitory gamma-aminobutyric acid (GABA) receptor, which counterbalances the action of excitatory neurotransmitters. By themselves, they have minimal respiratory depressant effect unless patients are made unresponsive to outside stimuli, but with even minimal doses of opioids the respiratory depression is significantly augmented. The clinical effects are very, very similar—so are the differences in pharmacokinetics, cost, and side effects of administration. A dosing summary is contained in **Table 44.5**.

TABLE 44.5 Sedatives Used in the Cardiac Care Unit

DRUG	ELIMINATION HALF-LIFE (h)	PEAK EFFECT (IV) (min)	STARTING DOSE
Midazaolam	3–5	1–2	1–2 mg bolus 0.5–10 mg/h infusion
Lorazepam	10–20	2–20	1–2 mg bolus 0.5–10 mg/h infusion
Propofol	20–30	1–2	20–70 mg bolus (sedation) 100–200 mg bolus (intubation) 25–100 µg/kg/min infusion
Halperidol	10–24	3–20	2–10 mg bolus 2–10 mg/h infusion

Dexmedetomidine	2	5–15	0.2–1.5 μg/kg/h

IV, intravenous.

Lorazepam

Lorazepam is a moderately slow-onset intermediate-acting benzodiazepine that is available to be given either via IV bolus or infusion or via the oral route. Its initial onset is in 5 to 10 minutes, but a wide therapeutic dosing range means that some patients will be fairly well sedated with a small initial dose and others will require multiple, higher doses.[30] For example, patients who are withdrawing from alcohol will sometimes require very high doses, whereas elderly patients will sometimes become heavily sedated with minute doses. Elderly patients may sometimes also "disinhibit" and become very agitated with all benzodiazepines, so they should be used with caution in the elderly.[31]

Lorazepam is metabolized in the liver to inactive metabolites; it has an elimination half-life of 10 to 20 hours, and an effective duration of action of 3 to 6 hours. It is glucuronidated in the liver, and because the glucuronidation system is less affected in liver dysfunction than in the oxidative system, lorazepam may not be as affected by hepatic dysfunction as are other medications, but it should still be used with caution in patients with liver dysfunction. It is not unusual for a patient to receive 24 hours of a moderate dose of lorazepam and take 5 to 7 days to wake up.

Like all members of this class of drugs, lorazepam will cause hypotension via arterial dilatation, and will cause a more pronounced hypotension via veno-dilatation in patients who are volume depleted. Lorazepam is diluted in propylene glycol, and with long-term high-volume infusions propylene glycol toxicity, causing acute tubular necrosis, lactic acidosis, and a hyperosmolar state, can occur.[32]

Initial bolus doses of lorazepam are typically from 0.5 to 2 mg, and infusion rates usually start at 0.5 to 1 mg/h and can go as high as 20 to 25 mg/h, with rates of over 100 mg/h not unheard of for patients in severe alcohol withdrawal.

Midazolam

Midazolam is a rapid-onset, short-acting benzodiazepine. It has the characteristic of causing anterograde amnesia (amnesia after administration) perhaps better than any other sedative. When given in small doses, it is not unusual to have patients arousable and talking and later have no recollection of those events. It

has a short onset of perhaps 1 to 2 minutes; and while the half-life is 1 to 4 hours, its duration of action after a single bolus dose is less than 15 minutes. It is water soluble in the bottle and becomes highly lipophilic at body pH. Its short duration of action is due to rapid equilibration and redistribution among the various bodily compartments. Owing to its lipophilic nature, it has a prolonged context-sensitive half-life due to a high volume of distribution in fatty compartments and also due to accumulation of an active metabolite, alpha1-hydroxymidazolam.[33] The half-life more than doubles, but, more importantly, because the short duration of action after bolus dose is due to redistribution, the effective duration of action after infusions of greater than 24 hours approaches that of lorazepam.

Midazolam is the drug of choice for short-term sedation in the non-intubated patient, especially for procedures. It has minimal respiratory depressant effects when given alone, but it highly potentiates the respiratory suppression of opioids. Dosing information is found in **Table 44.5**.

Propofol

Propofol is a rather unique drug that is not a benzodiazepine and has no other drugs in its class, as an alkylphenol. It is highly lipophilic and totally insoluble in water and is thus prepared in a 10% lipid emulsion at a concentration of 10 mg/mL. Similar to the benzodiazepines, it works on the GABA receptor, and it has excellent sedative and hypnotic properties, adequate amnestic properties, and has no analgesic properties. By itself, it has minimal respiratory depressant properties at lower doses but will suppress respiration at doses used for induction of general anesthesia, 1.5 to 2 mg/kg. Rapid equilibration across the blood–brain barrier is the reason for its extremely rapid onset of action.[34] Unlike benzodiazepines, in addition to vasodilatation it also is a myocardial depressant and thus can cause hypotension after large bolus dosing in hemodynamically unstable patients.

Propofol shows a short duration of action after less than 24 hours of infusion, and infusions of longer than 24 hours show only a slight prolongation of effect; after 24 hours, patients wake up much faster than they do with midazolam or lorazepam. It is metabolized in the liver, but there is extrahepatic metabolism as well,[35] so there is little or no prolongation of effect in renal or hepatic failure.[36]

Because of its formulation, a number of considerations must be mentioned. Because it is an emulsion in lipid, with high volumes of administration fat overload is a concern, especially in patients also receiving lipid formulations as

part of total parenteral nutrition. Nutritional lipids should be adjusted downward to compensate for the lipid administered with the propofol, and patients should be followed up for hypertriglyceridemia and, with longer infusions, for pancreatitis.[37] The lipid nature of the propofol emulsion makes it an excellent medium to grow bacteria, and to reduce the chances of bacterial overgrowth propofol in the United States has additives to act as bacteriostatic agents. Depending on the formulation, propofol will have either ethylenediaminetetraacetic acid, sodium metabisulfite, or alcohol. Patients who are sulfite allergic could have an adverse reaction to the propofol solution.[38]

Propofol has also been implicated in a sometimes fatal syndrome termed "propofol infusion syndrome" (PRIS).[39] Because propofol has properties similar to barbiturates such as sodium pentothal and pentobarbital in lowering cerebral metabolic rate for oxygen and decreasing intracranial pressure, it became popular to use it at fairly high doses for prolonged periods of time in patients with head injury and elevated intracranial pressure from cerebral edema. In 2001, the first series of cases of patients receiving propofol at doses over 5 mg/kg/h who developed progressive myocardial failure with dysrhythmias, metabolic acidosis, hyperkalemia, and evidence of muscle cell destruction.[40] Other studies have confirmed a dose-dependent connection, but there also have been some patients with some of the features of PRIS who received it at lower doses for only a few hours. Therefore, anyone receiving propofol infusion must be observed for the signs of PRIS, and most institutions have installed a cap of 5 mg/kg/h on dosage of propofol for durations over 24 hours.

Dexmedetomidine

Dexmedetomidine is another unique medication with a novel mechanism of action. It binds to the α_2 receptors in the brain as an agonist, and the location of the receptors determines the action of the medication. Dexmedetomidine binds to α_2 receptors in the locus ceruleus of the brain stem, giving it its sedative and anxiolytic effects, and in the dorsal horn of the spinal cord, releasing substance P and producing its analgesic effects.[41] It causes less hypotension than another medication that is also an α_2 receptor agonist, clonidine, and much more sedation and analgesia. The hallmark of dexmedetomidine therapy is mild sedation and induction of sleep, anxiolysis, analgesia with minimal respiratory depression, and reduction of stress response to surgery and other stimuli. The type of sleep is also important, because it comes closer than any other sedative to causing a sleep

that mimics normal rapid eye movement sleep. Patients sedated with dexmedetomidine appear tranquil and comfortable, yet being readily arousable and interactive and oriented when stimulated, only to fall right back to that tranquil, sleeping state when the stimulus is discontinued.[42]

The dosing of dexmedetomidine is also different from the other sedatives mentioned earlier. Bolus doses are poorly tolerated, do not have a good clinical effect, and are rarely used. A loading infusion may be used at the start of the therapy, with a dose of 1 μg/kg of actual body weight given as an infusion over 10 minutes (which translates into 6 μg/kg/h rate of infusion for 10 minutes). Alternatively, an infusion may just be started at the desired rate. Although in the United States, the approved dose range is from 0.2 to 0.7 μg/kg/h for up to 24 hours, doses higher than that for longer periods of time have been safely used.[43] Distribution half-life is 6 minutes, and elimination half-life is 2 hours, but effective duration of action is different—after a loading infusion, onset of sleep sensation starts during the loading and is at its peak 10 to 20 minutes after the load is complete. After cessation of therapy, there is a gradual return to baseline mental status—but because the sleep is so mild and so natural, plus other medications are usually being given, it is very difficult to indeed tell when the effect of the drug has lessened significantly.

The adverse effects of dexmedetomidine include paradoxical hypertension, especially during the bolus dose, followed by hypotension and bradycardia from the sympathetic inhibition. These can be beneficial, but they also may require the adjustment of other medications, such as beta-blockers or calcium channel blocker medications.

The biggest drawback to using dexmedetomidine is a practical one. The other sedatives used via infusion in a cardiac care setting can be given via bolus, and, when given via bolus or at high enough rates of infusion, reliably produce a patient who is essentially unresponsive to painful stimuli. This level of sedation is difficult, if not impossible, to attain with dexmedetomidine alone. Thus, other medications often need to be used for sudden breakthroughs of agitation and pain, and the need for those additional medications many times discourages caregivers from gaining extensive experience with dexmedetomidine.

Because of the more natural sleep pattern that is produced by dexmedetomidine, there has been hope that it will reduce the amount of delirium seen in critically ill patients. Delirium has become an important topic of discussion in critical care, as can be seen in the next section.

DELIRIUM

Over the past 10 years delirium in all types of critically ill patients has become an important area of concern. As medical knowledge and technology over time have improved survival of severely ill patients, many times their mental state after such recovery was less than optimal. Patients would recover from their multisystem organ dysfunction, only to be left with a delirious mental status that required long-term sedation, rehabilitation, or institutionalization in a skilled nursing facility. Elderly patients in particular seemed more susceptible to the onset of delirium, and it has been diagnosed in up to 60% to 80% of patients requiring mechanical ventilation.[44] Having delirium in a CCU is associated with a higher re-intubation rate, a higher mortality, and a longer length of stay. It also has a high rate of progression to permanent cognitive impairment. Thus, it is no longer a condition that can be expected to clear once the patient leaves the CCU.

Delirium is a disturbance of consciousness with inattention accompanied by a change in cognition or perceptual disturbance that develops acutely over a short period of time, from a few hours to a few days.[45] It can be further broken down into hyperactive and hypoactive forms.[46] The hyperactive form, commonly mislabeled “ICU psychosis” in the past, is characterized by agitation, restlessness, attempting to remove catheters and tubes, and emotional lability. It has a better long-term prognosis. The hypoactive form is characterized by withdrawal, lethargy, flat affect, apathy, and decreased responsiveness. It is sometimes erroneously termed ICU or critical care “encephalopathy.” Making the diagnosis of either type with precision is sometimes difficult, and can be done with one of two validated tools that can be found here.[44,47]

For the purposes of this chapter, it is important to recognize a number of aspects of delirium in critically ill cardiac patients. First is to diagnose it, and to rule out other organic causes of the condition. Second is to realize that sedative regimens that are used in the CCU have been implicated in the development of delirium. Sedatives and analgesics work by altering neurotransmitter levels and the exposure to benzodiazepines and/or opioids are involved in 98% of patients with delirium.[48] Some agents within a class have at times been shown to be more causative of delirium than others. Morphine,[49] fentanyl,[50] midazolam,[50] and lorazepam[51] have all been implicated in the development of delirium, with lorazepam probably being the most consistently implicated one. Conversely, the newer, more expensive agents, dexmedetomidine[52] and remifentanil,[53] may have

lower incidences of delirium. It has not yet been established, however, if the costs involved in using remifentanil or dexmedetomidine, among the other disadvantages, are worth the reduction in delirium.

Lastly, it is important to know what can be used to treat the hyperactive type of delirium and what else can be done to prevent delirium in the first place. As far as treatment of the delirium goes, in the past it was thought that patients needed to be "unscrambled" and so potent antipsychotic medications, such as haloperidol or risperidone, were used. Indeed, the very initiation of using a delirium assessment tool can increase the use of haloperidol dramatically.[54] Haloperidol is the only parenteral medication available to use in the patient with delirium, because benzodiazepines do not seem to be helpful.[55] Use of an atypical antipsychotic, quetiapine, seems to be the best studied and shows promise in treating patients with delirium in combination with haloperidol.[56] We are still in an early phase of this research, and much more work needs to be done.[57] Finally, it is important not to underestimate the importance of nonpharmacologic therapy. Such things as cognitive stimulation, reorientation prompts, a sleep protocol, visual and hearing aids, reminders to prevent volume depletion, and walking/exercise all reduced the incidence of delirium, and, while labor intensive, are absolutely essential in reducing and treating delirium in the CCU.[58]

SEDATION AND ANALGESIA IN DIAGNOSTIC AND THERAPEUTIC PROCEDURES IN THE CARDIAC CARE UNIT

Increasingly, diagnostic and therapeutic procedures are performed in the CCU at the bedside, both because of lack of timely access to the operating room (OR) and cost savings.

Both pain medications, sedatives and hypnotics, are used alone or in combination to facilitate the performing of bedside procedures. Concerns related to the patient physiology and to transport to the OR have made performing bedside procedures a more viable and safer option.

Care in the CCU setting is similar to the one in the OR from the point of view of both equipment and personnel. The monitors are nearly identical to the ones in the OR, and the ventilators have the same capabilities and more regarding

mechanical ventilation of patients, despite the lack of inhalational agents. CCU nurses are also similar to the ones in the OR with regard to many skills and capabilities.[59]

There are multiple diagnostic and therapeutic procedures done at the bedside in the CCUs for many different indications. Even though the concept and goal of sedation and analgesia is the same for all of them, there are small but important differences between each procedure. Some of these procedures are more or less specific to the CCU and the field of cardiology; others are common in other critical care settings and involve other subspecialties as well.

The following are common cardiovascular procedures in the CCU requiring sedation and/or analgesia.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) is an invaluable, semi-invasive, diagnostic modality that is increasingly used both in the CCU setting as well as in the OR for structural and functional study of the heart. Owing to its proximity to posterior cardiac structures, the TEE probe offers superior visualization of these posteriorly located structures; and because use of higher frequency probes is possible with this anatomical proximity, it offers better spatial resolution compared to transthoracic echocardiography (TTE). The indications are broad, including assessment of structure and function of native or prosthetic valves, infective endocarditis, cardiac sources of emboli, acute aortic syndrome, tumors, and congenital heart diseases.[60] When performed in the OR, patients are almost always under general anesthesia, but in the CCU setting, the patients are usually consciously sedated.

Patients undergoing TEE examination in the CCU tend to be more frail, with other comorbidities (cardiovascular, cerebrovascular, heart failure, and coronary or valvular heart disease) and usually have more acute clinical scenarios, making them at least intermediate risk for anesthesia most of the times.

TEE is generally regarded as a safe procedure. It involves the placement of the ultrasound probe via the oropharynx into the esophagus and down into the stomach, which might cause nausea, shortness of breath, agitation, and pain due to pharyngoesophageal intubation, symptoms that might be alleviated by use of local anesthetics and sedation.

There is significant variation with regard to sedation for TEE. Some centers use benzodiazepines alone, specifically midazolam, whereas others use a

combination of opiates, either as a bolus or infusion, in addition to midazolam.

Several studies have explored the use of different combinations of sedatives, alone or combined, and the use of local anesthetics to the oropharynx.[62,63]

The medications used, either alone or in combination, were propofol, midazolam, alfentanil, remifentanyl, and dexmedetomidine.[63–65]

Although TEE is regarded as a safe procedure and the complications are rare, they exist and mostly involve the gastrointestinal (GI), cardiovascular, and respiratory systems. These complications are mostly related to probe insertion, medications used for sedation, and operator experience.[61,66]

Given the potentially serious complications, especially in the particularly frail CCU patient population, careful pre-procedural evaluation and monitoring during the procedure should take place. These include careful assessment of medical history, particularly assessing history of esophageal and gastric pathology or history of bleeding disorders. Performing a thorough physical examination with particular emphasis on the examination of the airway, cervical spine mobility, and dentition is important. Fasting 6 to 8 hours before the procedure should be ascertained, and monitoring of vital signs at baseline and throughout the procedure should take place.

Supplemental oxygen should be administered and emergency airway equipment should be available.

Dentures should be removed when present, and bite guards should be placed on patients with full dentition.

After local anesthetic spraying of the oropharynx and/or sedation, the TEE probe is lubricated and then inserted, avoiding any resistance. Supplemental doses of the medications can be administered during the procedure to assure the patient’s comfort and optimal examination.

Obese patients pose a particular challenge both from the standpoint of safe sedation and analgesia and optimal examination. They have a higher incidence of coronary artery disease, hypertension, and sleep apnea; hence there is a higher potential for complications such as hypoxemia, especially in class III obesity.[67]

DIRECT CURRENT CARDIOVERSION

External electric cardioversion is used to treat abnormal heart rhythms to restore the normal sinus rhythm. Most non-emergent cardioversions in the CCU are performed to treat atrial fibrillation or atrial flutter. It is also performed on an emergent basis to correct dangerous rhythms when they are associated with

hypotension, chest pain, confusion, or shortness of breath. The procedure can be quite painful and requires sedation. Performing the procedure involves coordinating several teams: cardiology/electrophysiology, anesthesiology, and, when a prior TEE is required, the echocardiography team. This coordination can be sometimes difficult, because it could be needed at short notice. The ideal medication for sedation for cardioversion would have rapid onset and offset, cardiovascular stability, and no respiratory depression. Propofol has been the most widely used drug followed by etomidate and often a short-acting opiate.[68,70] The goal of sedation for cardioversion is a short period of deep sedation or general anesthesia using agents with a rapid recovery. Considering the potential risk of hypotension and respiratory depression associated with the procedure, the presence of an anesthesiologist to assure airway control is required. Supplemental oxygen and proper monitoring with blood pressure (invasive or noninvasive), pulse oximetry, electrocardiogram (ECG), and capnography are required.[69]

Because of the strong jolt associated with the electric shock and the resultant skeletal muscle contraction, lip and tongue laceration can occur despite sedation; it is therefore important to insert a soft bite block between the teeth right before induction of the sedation/anesthesia.

PERICARDIOCENTESIS

Pericardial effusion is accumulation of fluid around the heart, which in time can lead to pericardial tamponade and can be life threatening if not evacuated in a timely manner.

Pericardiocentesis is the aspiration of the fluid from the pericardial space and it can be lifesaving. Cardiac ultrasound is the gold standard for detection and assessment of the pericardial effusion.

Typically, the drainage of the pericardial fluid is performed by pericardiocentesis in the catheterization laboratory under fluoroscopic or echocardiographic guidance, or by establishing a pericardial window in the OR. When there are acute signs of pericardial tamponade, the pericardiocentesis can be performed at the bedside under echocardiographic guidance.[71] The procedure involves scanning with the ultrasound for the place where the effusion is the largest, sterile skin preparation, sterile drape cover, and requires local anesthetic injection and IV sedation, especially for anxious patients. If the decision is made for use of sedation, utmost care must be taken to use drugs with the least amount

of hemodynamic impairment, because these patients are already in a very frail hemodynamic state. Drugs such as midazolam and short-acting opiates are a good choice. If a deeper level of sedation is needed for a short period of time, etomidate and etamine are other good options.

INTRA-AORTIC BALLOON PUMP

Intra-aortic balloon pump (IABP) is a device that improves cardiac function by balancing the myocardial oxygen demand and supply. It inflates during diastole, increasing the coronary perfusion pressure and then deflates during systole leading to decreased afterload and left ventricular work. It is usually placed in the catheterization laboratory under fluoroscopy guidance but occasionally it is necessary to place the IABP in the CCU setting in unstable patients in cardiogenic shock, acute myocardial infarction, acute severe mitral regurgitation, or ischemic ventricular septal defect. IABP is placed percutaneously via the femoral artery using a Seldinger technique and rarely via the subclavian, axillary, or iliac artery. Considering the large lumen of the device, and the need for the patient to be still during insertion, local anesthetic and mild sedation might be necessary, with careful monitoring of the cardiovascular and respiratory status, especially because some patients might already be in pulmonary edema.

TEMPORARY TRANSVENOUS PACEMAKER

Emergent insertion of a temporary transvenous pacemaker is the treatment of choice for patients with different conduction abnormalities, such as Mobitz II, symptomatic bradycardia, complete heart block, and ischemic or nonischemic new-onset bifascicular block. It is usually used as a bridge to more permanent solutions for underlying conduction abnormality, such as treating the reversible underlying cause or insertion of a permanent pacemaker.[72]

Temporary transvenous pacing involves two components: obtaining central venous access and intracardiac placement of the pacing wire. The preferred route is the internal jugular vein, followed by the subclavian and femoral veins. The central venous access is obtained under ultrasound guidance and requires local anesthetic infiltration of the skin and sometimes mild sedation, especially because the procedure can be slightly prolonged by the need for proper positioning of the intracardiac wire, which is achieved by following the ECG waves.

MISCELLANEOUS PROCEDURES IN THE CARDIAC CARE UNIT

1. Upper GI endoscopy is sometimes performed at the bedside in patients in the CCU, to assess upper GI tract pathologies, such as bleeding or esophageal pathologies. The sedation and analgesia are similar to the ones for performing a TEE, because the procedure is quite similar and involves the same steps.
2. Placement of invasive monitoring or access lines, such as arterial and central venous lines, is a common procedure in patients in the CCU. Arterial line insertion involves placement of a catheter inside an artery (radial, brachial, femoral, or dorsalis pedis) for the purpose of continuous blood pressure monitoring on patients who are on inotropes or pressor infusions, or require multiple arterial blood sample drawings. The vast majority of times, the procedure only requires injection of a local anesthetic at the site, but on occasion, on very anxious or agitated patients, addition of other medication is required. Small, divided doses of benzodiazepines, opiates, or a combination of both are warranted in these settings with close monitoring of the patient's hemodynamic and respiratory status.

Because of necessity of patient positioning in a Trendelenburg position for central venous line placement with the head turned to the side and the need to cover the face with sterile drapes, and the slightly longer time for insertion, the central line placement poses more challenges than arterial placement; hence more frequent requirements for sedatives and analgesics in addition to the local anesthetic infiltration.

CONCLUSION

Patients in a cardiac care setting often need sedative or analgesic medications to help them through their course of CCU stay and while undergoing different therapeutic or diagnostic modalities. These medications have benefits but also side effects that need to be considered before administering the medications. The choice of medications may have long-lasting implications for patients in their recovery phase. Using a method of treating these patients that is balanced between personal professional experience and judgment and an evidence-based approach is the best way of properly choosing the optimal regimen.

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Patient and Family Information for: SEDATION AND ANALGESIA IN THE CARDIAC CARE UNIT

WHY PATIENTS NEED SLEEP OR PAIN MEDICATIONS IN THE CARDIAC CARE UNIT

Patients who are in a CCU can experience pain, anxiety, stress and, at times, an altered mental status. Quite simply, a CCU is a stressful and uncomfortable place to be in for any length of time. Many patients need some form of medication to help them cope with these conditions. Often, it is the most severely ill patients who require the most sedation.

Patients in a CCU will, at the very least, have attached to them a number of wires connecting them to the monitor, in addition to some sort of IV catheter. Patients who are more seriously and acutely ill may have IV catheters in their neck or chest, or larger tubes in their groin supporting their hearts. The most seriously ill patients will have a tube in their mouth, an endotracheal tube, to connect their lungs to an artificial respirator. Usually, the more support or monitoring an apparatus provides to the patient, the more uncomfortable it tends to be. The endotracheal tube, being hard plastic in contact with the main airway, is quite possibly the most irritating. Although some patients can tolerate an endotracheal tube without sedation, most patients need some sedation to tolerate the tube.

Treatments given to patients also tend to be, at best, uncomfortable, and, at worst, painful. Critically ill patients in a CCU do not tend to cough or breathe deeply enough and need help getting phlegm up from their lungs. Sometimes this is done by clapping on their backs, which can be uncomfortable. Sometimes, however, that maneuver is not enough, and a small tube needs to be placed into

the patient's nose or mouth and into their lungs to get the phlegm out before the patient develops pneumonia.

Increasingly, diagnostic and therapeutic procedures are performed in the CCU at the bedside, both because of lack of timely access to the OR and acuity of patients' condition. These procedures are often uncomfortable and sometimes painful, and patients need appropriate means to decrease their pain and suffering while undergoing a procedure.

In addition to being able to tolerate devices in the CCU, there is also the need for patients to get some sleep. It is very, very difficult to sleep in a CCU, because things are happening at all hours of the day and night, and it is difficult to make it dark enough for people to fall asleep. In addition, the monitors make noises, often with each heartbeat, and the attached cables and tubes frequently pull and wake patients up as they turn. The beds in a CCU are optimized for both durability and to keep from damaging the skin, but may not be the most comfortable for sleeping.

For these and other reasons, many times it is necessary to give patients either pain medications or sleep-inducing medications as part of their treatment in a CCU.

GOALS OF SEDATION AND PAIN MANAGEMENT IN THE CARDIAC CARE UNIT

Very often, family members do not have the same goals in mind as their caregivers when it comes to the treatment of pain or of the sedation of a loved one in the CCU. Some families think it is bad for the patient to be sedated, and want them to be more awake and interactive, going so far as to overstimulating the patient during visits. They get the mistaken impression that if the patient is not awake, he/she is in either an unintended or an induced coma which they perceive as a bad thing. They repeatedly ask for the sedation to be turned down. Other families are concerned that the patient is feeling too much discomfort or will remember too much of these traumatic events and want them more deeply sedated.

It is important to realize that sedation of patients in the CCU has become an important area of research and concern over the past 15 years. It was always known that patients needed sedation and pain medication in a CCU for them to not pull out their tubes or hurt themselves. It was also felt that sedating patients

fairly heavily was a good thing, to reduce the stress of being in the CCU, and, simply, to just be humane to the patient. Although there were always concerns that too much sedation was a bad thing, it was not until the year 2000 that research was published showing clearly that it was important not to over-sedate patients. That one study, and others following it, showed that waking patients up every day—even for a short period of time—and then reevaluating the need and dose of sedation leads to less time on the respirator, less time in the CCU, and an improved survival rate. But it is not an easy thing to do—there is a risk of patients getting too awake and hurting themselves, and so it must be done in the right patients at the right time and speed. It also has become clear through recent research that the type and amount of sedation can have a strong influence on the patients' mental state, long after they have recovered from their physical ailments and have left the CCU.

Usually, some type of rating scale that makes it very easy to tell if the patient is at the desired level of sedation or not is used. The scales are generally of two types. In the more basic scale, a patient is asked to rate the pain either on a number scale or by pointing at a line or chart, sometimes with happy or sad faces on it, sometimes with just a line or ruler on it. These are used primarily to rate the patient's pain, and will be used before and after every dose of pain medication to try to put a number rating to the pain a patient is feeling. In this way, the doctors caring for the patients can adjust the amount of medication by seeing what dose produces what response.

The other type of scale is one where the nurse evaluates a patient, and many times will do something like talk to a patient or touch a patient, to see the reaction, then gives the patient a number scale rating to determine their level of sedation. The physicians taking care of the patient, or the CCU nurse, will sedate the patient according to those ratings. Many sedation scales have been developed over the years.

It is important to have discussions with the physicians and nurses taking care of a family member about the precise goals of sedation. To be able to fully understand the sedation of a family member, ask to see the sedation scale in use in that particular CCU, discuss the desired level of sedation, and ask whether they perform a daily wake-up test. A family could also offer to help in the daily wake-up test, but that takes a skilled staff of the CCU and a family member who can avoid getting too emotional at the bedside, as the wake up may not be pleasant sometimes to watch. Once a family member understands the goals of sedation, then the member can try to help the staff in the CCU keep the patient at

the desired level of sedation.

NONSEDATIVE METHODS OF KEEPING PATIENTS COMFORTABLE

Using medications is not the only method we have to keep patients comfortable in the CCU. There are a number of other methods that are tried and true. The most important among these is to continually reorient the patient to the time, place, and, if necessary, names. The CCU is a very confusing place, and lack of sleep plays havoc with the patient's ability to keep track of time. It is not unusual for patients in a CCU to become confused and not know where they are, or what day it is, or to overestimate the amount of time that has passed since they have seen a family member. This is much more common with older patients, but younger patients can also be affected. Families tend to get very depressed and upset at such actions. Some even can get angry at their family member. It is important to remember that this happens all the time, and is not at all unusual. It also does not signify any permanent damage. This is probably where family members can be the most help to the staff in the CCU and to the patient. It may have to be done more than once on a visit. Another good thing for family members to do is to try to get patients to remember things from outside the CCU —bringing up events, people, foods, clothing, and so on. Bringing pictures to the CCU, especially with the patient in them with other people, is a very good way to aid in this process. Repeatedly reorienting patients, telling them the day, reminding them what day or what hour they last saw one or another family member can help the staff in the CCU use less sedating medications and ultimately help get the patient out of CCU faster and in better mental shape.

SEDATIVE AND PAIN MEDICATIONS IN THE CARDIAC CARE UNIT

It is helpful for the family to understand the different types of medications that are used in the CCU to promote sleep and treat pain. This is because some of them may have different meanings to the lay person, incorrect meanings that may have a negative connotation. For patients in the CCU, most of the time they get either strong pain relievers such as morphine, strong sleep medications such

as Ativan (lorazepam), or tranquilizers such as haloperidol. It is important for the family member to understand why each of those is used.

PAIN MEDICATIONS

Patients in the CCU have pain—if they are on the respirator, just the breathing tube alone causes a fair amount of discomfort and pain. Lying in bed for long periods of time is also uncomfortable. They may have surgical incisions, and many of the procedures that are done are painful. To treat those pains, most often patients are given medications such as morphine—others might receive Dilaudid (hydromorphone), fentanyl, or even methadone. This class of drugs is commonly called "opiates" or "narcotics." They are given via the IV line, either continuously all the time or intermittently. They differ primarily in how long they last, and some of the minor side effects. For example, morphine and hydromorphone may have more of a mind-altering quality to their effect than methadone or fentanyl. Fentanyl is the shortest acting, at about 45 minutes to an hour; then morphine which lasts 2 to 3 hours; hydromorphone, which lasts 3 to 4 hours, and, finally, methadone which can last 8 to 12 hours. Patients who are less ill may be able to receive pain medications by mouth—these generally last longer, from 6 to 24 hours each dose.

Pain medications such as these have a number of effects. First, they are used to reduce the amount of pain a patient feels. It is important to realize that these medications do not work like when something is taken for a headache—1 minute, there is pain; soon afterwards, the pain is totally gone. Most often, the patient will still feel the sensation that was painful, but it will not be as intense, they may not care that they feel it, they will be more comfortable; they may even say that the sensation is still there but it does not hurt. Second, these medications will have somewhat of a sleep-inducing effect, but this effect is shorter than the pain-relieving effect and if small enough doses are given may be minimal, if present at all. The most common side effects that are concerning about these medications is that they interfere with the patient's desire to breathe—so, if they go to sleep, they may not breathe, which is why they are monitored after they receive the medications. The other major side effect these medications have is that they can cause nausea and vomiting. So when these medications are given, physicians and nurses have to balance the desirable effects with the undesirable side effects.

When to give these medications is usually decided in a number of ways. If the patient is awake, it might only be given when they ask for them and at no other

times. Sometimes, a patient might be connected to a patient-controlled analgesia (PCA) pump where the patient gets small amounts of pain medication through the IV line whenever they push the button. The safety mechanism with both of these is that if the patient is too sleepy to either ask for the medication or push the button—they will not get too much and they will not make themselves too sleepy. This is why a nurse might be heard saying that the patients have to ask for the medication themselves, that they cannot give it just because family members want the patients to get more medication because they are grimacing or making a look on their face that looks like pain—it might be dangerous to give patients the pain medication in that state. For sicker patients, the nurse might be instructed by the physicians to use a pain scale such as described earlier to administer medications. Lastly, patients, especially those on mechanical ventilators, may be on a continuous amount of the medications so that they are getting a small amount every minute to provide constant comfort, and the rate at which they give the pain medication is determined by the scales mentioned earlier.

SEDATIVE (SLEEP) MEDICATIONS

In addition to medications to treat pain, to treat patients' anxiety and help them sleep, patients may also get sedative medications such as midazolam (Versed) or lorazepam (Ativan), which are more modern versions of a similar drug many people know about called diazepam (Valium). These medications have a wide range of effects that depend on dose, ranging from treating anxiety and making a patient feel calm, to inducing a comfortable sleep, to rendering a patient unconscious. Even low doses can cause amnesia, and the patient may not remember things that happen while under the influence of these medications. Although this may many times be a beneficial effect, because the CCU can be a scary place, it also can make it more difficult for the family to reorient the patient the way discussed earlier. Also, elderly patients can sometimes get wild and agitated with these medications and lose control of inhibitions—a side effect called "dis-inhibition." When combined with the pain medications described earlier, they can enhance the pain medications' ability to depress breathing, so they have to be used with caution when used together. Also, the combination of the deep sleep of the sedatives and the nausea and vomiting from the pain medications can be dangerous because patients can then have stomach contents go into the lungs and cause pneumonia. This is not at all to say that they cannot be used together, just that these are concerns that need to be watched for. Both

lorazepam and midazolam can be given either intermittently or continuously via the IV line. They differ only in that midazolam, when given once or twice, is very short acting, on the order of 15 to 30 minutes, whereas lorazepam can last for 2 to 4 hours. When given continuously, depending on what dose is required and how long the infusion is running for, can take a few hours to a few days to wear off.

Another medication that can be used continuously, usually in patients on mechanical ventilation, is called propofol. Propofol is easy to remember because it is a milky white liquid, sometimes nicknamed “milk of anesthesia.” It is a powerful sleep-inducing agent, and is usually not used to just treat anxiety, but, rather to go further and either makes patients very, very sleepy or even unconscious. Its ability to cause amnesia is not quite as great as for lorazepam or midazolam, so patients need to be more asleep with this medication if the goal is to keep them from remembering things. It is very, very short acting, which is why it usually is used only continuously. Similar to lorazepam or midazolam, it can cause blood pressure to drop; and when given with the narcotic pain relievers, it can cause a patient to stop breathing.

Still a different type of medication used in these settings is a relatively new drug called dexmedetomidine (Precedex). This drug causes a very natural and restful sleep, and does not work like other drugs to depress the patient’s drive to breathe. The sleep it causes is totally different from other medications—the patient will appear to be asleep, not responsive to verbal stimulation, yet, with gentle touch, will wake up and be totally coherent and appropriate, only to drift back to sleep when the stimulus is removed. It also has very nice pain-relieving qualities, and treats pain in a manner different from that of narcotics, so the combination of the two is a very effective way to treat pain. It does not have any amnesia effects, so it is not useful to make patients not remember their time in the CCU. It has a ceiling effect, so that it never will produce the deep sleep or near coma condition as midazolam, lorazepam, or propofol will produce, and it cannot be given intermittently, only continuously, and takes a while both to work and stop working, about 20 to 30 minutes on either end. It is most useful in combination with the other medications. Its main advantage is that it recently has been shown to cause less delirium in the CCU, as is discussed here.

DELIRIUM

When a patient is in the CCU and is subject to all the stresses of being there, the constant stimulation, the lights, the noise, the lack of natural sleep, and the administration of the medications, can all sometimes result in the patient developing a state of altered consciousness, called “delirium.” Delirium is an acute state of confusion. It is characterized by some combination of drowsiness, disorientation, hallucination, a sudden inability to focus attention, sleeplessness, and severe agitation and irritability. When it develops, it carries with it a longer time in the CCU and the hospital and a higher rate of complications such as infections and death. It is much more common in older patients, and one out of four elderly patients admitted to the hospital will suffer some form of delirium. Preventive measures include the daily wake up and lessening the use of sedatives mentioned, and the reorientation and helping the patient focus also help tremendously. Use of dexmedetomidine for sedation, with its more natural sleep tendencies, has been shown in some studies to decrease the incidence of delirium. Once it starts, it may require the use of tranquilizers that act on the chemicals in the brain that are out of balance and help straighten them out again. A number of tranquilizers can be used. If it is decided that the patient needs to get the medication fast, a medication called haloperidol (Haldol) can be given either via IV or into the muscle. If they are given orally, in addition to haloperidol, another common one is risperidone, and there are others as well. Tranquilizers such as these will cause a dazed and stunned look, and the patient will frequently be awake, answer questions in a rather flat toned voice, show little emotion, and have a very slow reaction to any stimuli. This is just a phase the patient will go through on the way to recovery, but it can last a while, sometimes days or weeks, until the patient is back to the usual state of mind.

ADDICTION

A very common reaction of families to hearing that their relative is getting these medications, some of them whose names they associate with drug abuse, is “Will they become addicted?” Strong pain killers such as morphine cause two types of dependence, commonly termed “addiction.” Patients may get chemically or physically dependent, where their bodies cannot tolerate a sudden withdrawal of the drug and it needs to be reduced slowly over time; otherwise the patient can get withdrawal symptoms. This is easily treated with slowly tapering off the medication over time, and the risk for it goes up depending on the dose and the

duration of medications the patient received in the CCU, which is another reason to give as little as possible. However, people mistake this for psychological dependency, in which the patient mentally craves for the drug and needs it from a mental standpoint. Only a minute fraction of patients receiving morphine-like drugs in the CCU ever become psychologically dependent on the medications, and the risk is considered small for the benefit most patients get from these important medications. The sedative drugs such as lorazepam are much less likely but still can cause a physical dependence.

ANESTHESIA AND PAIN CONTROL FOR BEDSIDE PROCEDURES IN THE CARDIAC CARE UNIT

Patients in the CCU oftentimes require certain procedures, either for diagnostic purposes or for therapeutic purposes.

Examples of different procedures done in the CCU include the following.

TRANSESOPHAGEAL ECHOCARDIOGRAPHY

TEE is a special form of echocardiogram, performed by esophageal placement of a probe with a transducer at its tip. It is very similar to the probe used by gastroenterologists to perform upper endoscopies. It is performed in patients who either await heart surgery to give the cardiac surgeon and anesthesiologist more information about the heart structures, confirm the success of the surgical repair or if additional repair is needed, or in patients who are treated in the CCU to assess and monitor medical treatment. It gives a very good image of the heart because the esophagus or swallowing tube is very close to the heart. An approximately 6- to 8-hour fasting is required before undergoing the procedure.

For the patient to tolerate this procedure, a combination of local anesthetic to the back of the throat and IV sedation are frequently used.

The local anesthetic is usually lidocaine spray or a solution to be gurgled to numb the oropharynx, and the tolerance of the procedure is enhanced by administering IV sedatives and analgesics. The combination of local anesthetics and IV sedatives and analgesics blocks the stress response, the laryngeal reflex to the TEE probe insertion, and the pain, and is very useful especially for very anxious patients or patients who are unable to cooperate.

The medications used are usually a combination of pain relievers such as

morphine and fentanyl, and sleeping medications such as midazolam or lorazepam. On occasion, a stronger sleeping medication might be used, such as propofol. The amount of medications used differs depending on the patient's weight, age, and how strong the heart is. Patients with weaker hearts might require less medication and it might take longer to achieve the desired effect. The same pattern is true for older patients.

Heavier patients might require more medication, although this pattern does not always stay true; however, the patients require more careful monitoring of their breathing, because they are prone to obstruct the air passage secondary to obstruction by the back of the tongue and might require additional maneuvers or equipment (such oral airways to lift the tongue and clear the throat to allow free air movement) to ensure safety.

CARDIOVERSIONS

If the heart has an irregular, abnormal rhythm or is beating too fast, a cardioversion might be necessary. The most commonly treated arrhythmias are atrial fibrillation and flutter.

Cardioversion is a procedure that includes applying an external electrical shock to the chest wall to restore the normal heart rhythm. The procedure involves placement of patches on the chest and back, in addition to the existing monitors already in place. Because the procedure can be painful, it requires deep sedation or general anesthesia. The shock lasts only a fraction of a second and it might need to be repeated. The whole procedure might last 20 to 30 minutes.

The sedatives will be administered via the IV catheter already in place, and the shock will be delivered through the patches on the patient's chest, once the patient is rendered unconscious. Sometimes more than one shock needs to be delivered to convert to the normal rhythm. Once the procedure is completed, the medication is stopped and the patient will wake up shortly. There are few potential complications that can occur with the cardioversion and they are related to the sedation used for the patient to tolerate the procedure, new arrhythmias, stroke, lip or tongue lacerations, or skin burns.

The deep sedation used to allow the delivery of the shock can result in aspiration of the stomach content into the lungs, which could lead to pneumonia. Also, the sedation can cause obstruction of breathing, especially in heavier patients or in those who have sleep apnea, so careful, divided administration of medication for sedation and careful monitoring of breathing has to take place.

The shock is timed with the heart beat so it does not produce dangerous

rhythms after cardioversion, but sometimes the heart is slow to go into the normal rhythm and a temporary pacemaker might be necessary to bridge this period.

Stroke can happen as a result of a preexisting, or a newly formed clot which can travel to the brain. The use of blood thinners before the cardioversion greatly reduces the risk of stroke.

An oxygen mask will be placed on the patient's face and a soft block will be placed between the teeth to avoid lip or tongue injury.

INSERTION OF CATHETERS AND DEVICES

Oftentimes the patients in the CCU require insertion of catheters for continuous monitoring of the blood pressure and access to frequent blood draws, such as arterial lines, which consists of placement of a small catheter into an artery, either at the wrist (most commonly), groin or foot (rarely).

Central venous catheters are inserted for both monitoring of pressures inside the heart and as the means of administering potent medications or blood if needed. They are typically placed in the veins in the neck (most frequently) or groin (rarely).

On occasion, a critically ill patient might require placement of a device called IABP to help with heart function and oxygen delivery to the heart. It is placed via one of the arteries in the groin and advanced all the way in the chest to the aorta, which is the main artery carrying blood out of the heart. It requires the patient to keep the leg straight afterwards, often being accomplished by placing a brace on the leg.

When patients have rhythm problems, the placement of a temporary transvenous pacemaker is required. It involves the placement of a catheter into one of the veins in the neck or in the groin and then advancing a wire into the heart.

The insertion of the central venous catheters or the IABP necessitates the patient to be still, on his/her back, in a "head down "position, sterile preparation of skin, and placement of sterile drapes which sometimes cover the patient's face, and can lead to significant anxiety.

The insertion of these catheters is facilitated by injecting the skin with local anesthetic, such as lidocaine, and most of the times is sufficient to assure the patient's comfort, especially for the small catheters (arterial lines, central venous catheters), but the larger catheters, such as IABP or temporary transvenous pacemakers, require the administration of sedatives, such as midazolam, and

analgesics, such as fentanyl.

PLACEMENT OF A BREATHING TUBE

Critically ill patients might need to be intubated, which involves deep sedation with drugs such as propofol or etomidate and placement of a breathing tube in the wind pipe, to adequately oxygenate them. After the intubation, to tolerate the breathing tube and the mechanical ventilation they will need continuous sedation with drugs such as midazolam, lorazepam, propofol, or etomidate. Sometimes pain medication such as opiates can also be added.

A careful balance has to be achieved by the CCU team between administering drugs for sedation and pain and maintaining stable blood pressure and breathing, and hence the need for multiple monitors.

CONCLUSION

It is important to understand the choice of medications and why each is used. The doctors and nurses must balance the need to treat pain and the need to reduce stress and anxiety with the very real side effects all of these medications can cause. By discussing with the doctors and nurses exactly what medications the patient is receiving, and what the goals of therapy are, helps understand better the treatment plan and also be more helpful to both the staff and to the patient, because the best calming effect usually is a calm family member being at the bedside working with the CCU staff to keep a patient oriented, calm, and tranquil. It will also allow the family member to endure the stay of the relative in the CCU with less stress to the member as well.

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Renal Failure in the Cardiac Care Unit

INTRODUCTION

Acute kidney injury (AKI), previously called acute renal failure, is a common problem in the cardiac care unit (CCU) and is characterized by an abrupt decline (over hours to weeks) in the glomerular filtration rate (GFR), leading to accumulation of nitrogenous waste products. AKI can result in uremia, oliguria, or anuria, and volume imbalance as well as electrolyte and acid base abnormalities. AKI is independently associated with an increased length of stay, increased morbidity, and short- and long-term mortality and imposes a heavy economic burden on the health care system.

There is substantial interaction between the heart and the kidneys that is now referred to as cardiorenal syndrome (CRS). In patients admitted to the CCU, AKI frequently complicates acute coronary syndromes, revascularization procedures, coronary artery bypass graft (CABG) surgery, decompensated heart failure, cardiogenic shock, and cardiac arrest. In critically ill patients, more often than not, AKI is multifactorial resulting from several insults occurring at once.

Early recognition, adequate hemodynamic support, and withdrawal of nephrotoxic agents are of paramount importance to help reduce the risks and the costs associated with AKI. AKI is associated with worsening outcomes,

particularly if occurring in critical illness and if severe enough to require renal replacement therapy (RRT). Hence, preventive measures should be part of appropriate management.

DEFINITIONS

AKI is diagnosed by an increase in serum creatinine (SCr) and blood urea nitrogen (BUN) on routine laboratory examination and/or by a decrease in urinary volume over a certain period of time. With the development of the RIFLE[1] classification and subsequently the acute kidney injury network (AKIN) criteria[2] (**Table 45.1**), the definition of AKI became more objective. Both criteria were very useful for quantitating renal function and for research purposes but less so for clinical practice.

TABLE 45.1 Summary of the RIFLE Classification, the AKIN Criteria, and the KDIGO Classification and Staging for AKI

RIFLE[1]				AKIN[2]			KDIGO[3]		
RIFLE Criteria	*SCr Increase*	*GFR Decrease*	*Urine Output*	*AKI Stage*	*SCr Increase*	*Urine Output*	*AKI Stage*	*Serum Creatinine*	*Urine Output*
Risk	1.5 × ULN	>25% decrease	<0.5 mL/kg/h for 6 h	Stage 1	1.5–2 × baseline	<0.5 mL/kg/h for 6 h	Stage1	SCr 1.5–1.9 times baseline OR > 0.3 mg/dL	<0.5 mL/kg/h for 6–12 h
Injury	2 × ULN	>50% decrease	<0.5 mL/kg/h for 12 h	Stage 2	2–3 × baseline	<0.5 mL/kg/h for 12 h	Stage 2	2.0–2.9 baseline	<0.5 mL/kg/h for >12 h
Failure	3 × ULN (or rise by 0.5 mg/dL if baseline SCr > 4 mg/dL)	>75% decrease	<0.3 mL/kg/h for 24 h OR anuria for 12 h	Stage 3	>3 × baseline (also if on RRT)	<0.3 mL/kg/h for 24 h OR anuria for 12 h	Stage 3	3.0 × baseline OR increase in SCr to >4 mg/dL OR initiation of renal replacement therapy	<0.3 mL/kg/h for >24 h OR Anuria for >12 h
Loss	Persistent acute kidney disease > 4 wk								
ESRD	End-stage renal disease (requiring dialysis > 3 mo)								

ESRD, end-stage renal disease; RRT, renal replacement therapy; SCr, serum creatinine; ULN, upper limit of normal.

More recently, building off the previous criteria, the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines[3] simplified the definition of AKI (**Table 45.1**); KDIGO defines AKI as any of the following:

1. An increase in SCr by at least 0.3 mg/dL within 48 hours; or
2. An increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
3. A decline in urine volume to <0.5 mL/kg/h for 6 hours.

A new terminology, CRS[4], has been proposed to define the spectrum of disorders secondary to the hemodynamic interdependence between the heart and the kidneys. It includes those disorders of the heart and kidneys where acute or chronic dysfunction in one organ induces acute or chronic dysfunction of the other. Five subtypes have been defined:

Type 1 acute CRS: Acute worsening of cardiac function leading to renal dysfunction;

Type 2 chronic CRS: Chronic cardiac dysfunction (ie, chronic heart failure) leading to renal dysfunction;

Type 3 acute renocardiac syndrome: Acute worsening of renal function (due, eg, to renal ischemia or glomerulonephritis) causing cardiac dysfunction (eg, heart failure);

Type 4 chronic renocardiac syndrome: Primary chronic abnormalities in renal function leading to cardiac disease (eg, coronary disease, heart failure, or arrhythmia);

Type 5 secondary CRS: Acute or chronic systemic conditions (eg, sepsis or diabetes mellitus) causing simultaneous dysfunction of the heart and kidney.

EPIDEMIOLOGY

Prior to the RIFLE criteria,[1] more than 30 different definitions of AKI were reported in the literature. Consequently, epidemiologic studies used various clinical and physiologic endpoints, yielding a discrepant incidence of AKI in different clinical settings ranging from 1% to 31% in hospitalized patients (with an average incidence of 5% to 7%)[5] and 35% to 40% in the critically ill.[6] The diagnosis of AKI independently increases the risk of mortality by 5.5- to 6.5-fold as compared to a similarly ill patient without AKI. The incidence of AKI requiring RRT was 5% in a large, multicenter study[7] with a 90-day mortality in the range of 50% to 60%.

RISK FACTORS

In a large tertiary center CCU, characteristics such as older age, African-American race, diabetes, hypertension, previous coronary disease, and heart failure were incrementally more common across increasing renal dysfunction patient strata.[7] Decompensated heart failure, cardiogenic shock, use of iodinated contrast media, aggressive diuresis, and use of nephrotoxic medications are common precipitants of AKI. Patients with underlying chronic kidney disease are also at higher risk of developing AKI, referred to as acute on chronic kidney injury.

RENAL NEUROHORMONAL REGULATION AND RESPONSE TO RENAL HYPOPERFUSION

The kidney plays a central role in maintenance of fluid balance and excretion of waste products. Renal hypoperfusion is initially compensated for by various systemic mechanisms in an attempt to restore tissue perfusion. Hypovolemia, of any cause, reduces release of atrial natriuretic peptide, increases production of antidiuretic hormone, and increases sympathetic (and decreases parasympathetic) activity through the baroreceptor reflex. In the kidney, the combination of hypotension and sympathetic activation leads to reduced perfusion pressure in the afferent arteriole and a decrease in the GFR. A decrease in tubular sodium chloride (due to slower transit and increased proximal reabsorption) is sensed by the macula densa in the distal convoluted tubule, and this causes the juxtaglomerular apparatus to release renin. Renin activates angiotensin, which is converted peripherally to angiotensin II. Apart from being a potent vasoconstrictor, angiotensin II also acts on the adrenal cortex to produce aldosterone, which increases salt and water reabsorption in the kidney. In addition to these mechanisms, the kidney possesses the ability to autoregulate, that is, to maintain its perfusion pressure despite changes in the mean blood pressure over a wide range of 80 to 180 mm Hg. As a consequence of this compensatory mechanism, the renal tubules remain intact despite renal hypoperfusion. When normal renal perfusion is restored, urine flow returns to normal.

A concept important to understanding the pathophysiology of AKI in the CCU is effective circulating volume (ECV). ECV is the arterial blood volume effectively perfusing tissue. ECV is a dynamic quantity and not a measurable distinct compartment, which normally varies directly with extracellular fluid (ECF). The ECV may not vary directly with the ECF volume in certain diseases, such as congestive heart failure (CHF) or hepatic cirrhosis; therefore, in these clinical settings, renal hypoperfusion may occur despite apparent volume excess.

In contrast to prerenal AKI, if the hypovolemia is severe or sustained, the renal tubules can become necrotic and lose their ability to conserve salt and water. Tubular obstruction by necrotic cells at the pars recta (where the proximal tubule narrows into the descending loop of Henle) leads to a rise in the intraluminal pressure, decreasing the glomerular tubular gradient. This reduction in GFR may persist even after restoration of normal hemodynamics.

Furthermore, injury to the tubular basement membrane can result in back leak of tubular fluid into the interstitial tissue. In this situation, urine flow may not be restored despite restoration of normal renal perfusion.

ETIOLOGIES OF ACUTE KIDNEY INJURY

Based on this pathophysiology of renal adaptation to injury, AKI is classically divided into three large pathophysiologic categories of prerenal, renal, and postrenal AKI (**Table 45.2**).

TABLE 45.2 Common Etiologies of AKI

Prerenal AKI

1. Hypovolemia, eg, renal (overly aggressive diuresis) or extrarenal fluid loss (bleeding, diarrhea, vomiting, sequestration)
2. Decreased renal perfusion: decreased forward flow secondary to low cardiac output, renal vasoconstriction, systemic vasodilatation, hepatorenal syndrome, impairment of renal autoregulation (NSAIDs, ACEIs, ARBs)

Renal AKI

1. Acute tubular necrosis
   a. Ischemic
   b. Toxic, eg, use of radiocontrast media, aminoglycosides, amphotericin B, calcineurin inhibitors, mannitol, hemolysis, rhabdomyolysis
   c. Infection, with or without sepsis
2. Glomerular diseases or vasculitis
   a. Glomerulonephritis, eg, as a complication of bacterial endocarditis, lupus nephritis
   b. Thrombotic microangiopathies, eg, malignant hypertension, scleroderma crisis
3. Interstitial nephritis commonly related to antibiotic use
4. Renovascular obstruction, eg, atheroembolic disease, arterial dissection

Postrenal AKI

Urinary retention owing to use of anticholinergic agents, obstruction, and compression by hematoma or mass

ACEIs, angiotensin converting enzyme inhibitors; AKI, acute kidney injury; ARBs, angiotensin receptor blockers; NSAIDS, nonsteroidal anti-inflammatory drugs.

Prerenal azotemia results from ineffective renal perfusion and is the most common cause of AKI in patients presenting to the emergency room. Renal or intrinsic AKI in the CCU most commonly results from ischemic or toxic acute tubular necrosis (ATN). The prerenal and intrinsic renal categories are not mutually exclusive but rather represent a continuum of renal injury where persistence of the ischemic insult may deteriorate into ATN.

A prerenal state also sensitizes the kidney to nephrotoxic insults, thus accounting for the increase in the incidence of AKI owing to nephrotoxic agents in hypovolemic states. Postrenal AKI due to obstruction in the urinary collecting system is an uncommon cause of AKI in the CCU but should always be ruled out promptly because of its reversibility. Nephrotoxicity can result from various drugs, such as aminoglycosides, amphotericin, calcineurin inhibitors, foscarnet, ifosfamide, cisplatin, and crystal-forming drugs. Additionally, conditions such as multiple myeloma and rhabdomyolysis can cause nephrotoxicity resulting in AKI. The pathophysiologic mechanism for renal injury differs among the agents and conditions.

CLINICAL EVAULATION

Either a rise in BUN and SCr or a drop in the urine output should alert the clinician to the presence of AKI. One of the earliest signs of AKI may be oliguria that is usually defined as decline in urine output to <0.5 mL/kg/h. However, a patient who is fluid overloaded or with a high catabolic rate may require a urine flow rate considerably higher than this minimum standard. A number of etiologies of AKI present with nonoliguric rises in the BUN and creatinine; therefore, absence of oliguria does not preclude an evaluation of renal injury.

The history should be focused on identification of risk factors of AKI, determination of baseline renal function to ascertain the presence of CKD if possible, careful assessment of symptoms and precipitants of volume depletion (careful review of the intake and output), careful review of vital signs to identify episodes of hypotension, and a thorough review of all home medications as well as all recently administered in-hospital medications to identify potential nephrotoxins. The history is essential in determining the etiology of AKI because it may help the clinician to prevent further exposure to ongoing nephrotoxic insults.

Another important historic feature is the temporal correlation between the possible nephrotoxic insult and the clinical course of AKI. The SCr rises rapidly (within 24 to 48 hours) in patients with AKI following renal ischemia and radiocontrast exposure. Peak SCr concentrations are usually seen after 3 to 5 days with contrast nephropathy and return to baseline after 5 to 7 days. In contrast, SCr concentrations usually peak later (7 to 10 days) in ATN and

sometimes even later in atheroembolic disease. The rise in SCr seen with many tubular epithelial cell toxins (eg, aminoglycosides) or in the setting of drug-induced acute interstitial nephritis usually happens 7 to 10 days after onset of therapy, although the latent period may be as short as 1 day after some antibiotics or as long as several months with nonsteroidal antiinflammatory drugs (NSAIDs).

Information from the physical examination is invaluable and must be integrated with the historic and laboratory data. The patient's volume status must be carefully assessed by examination of skin turgor, edema, jugular venous distension, orthostatic hypotension, and pulmonary vascular congestion. In addition, certain findings on physical examination can be diagnostic, for example, the presence of a distended bladder in a patient with urinary retention, a skin rash in suspected drug-induced interstitial nephritis, papilledema in malignant hypertension, or retinal cholesterol plaques in a patient with atheroembolic disease.

DIAGNOSTIC EVALUATION

Even with a careful history and examination, the determination of the etiology of AKI may be challenging. **Figure 45.1** is a clinical pathway that simplifies the diagnostic approach to AKI.

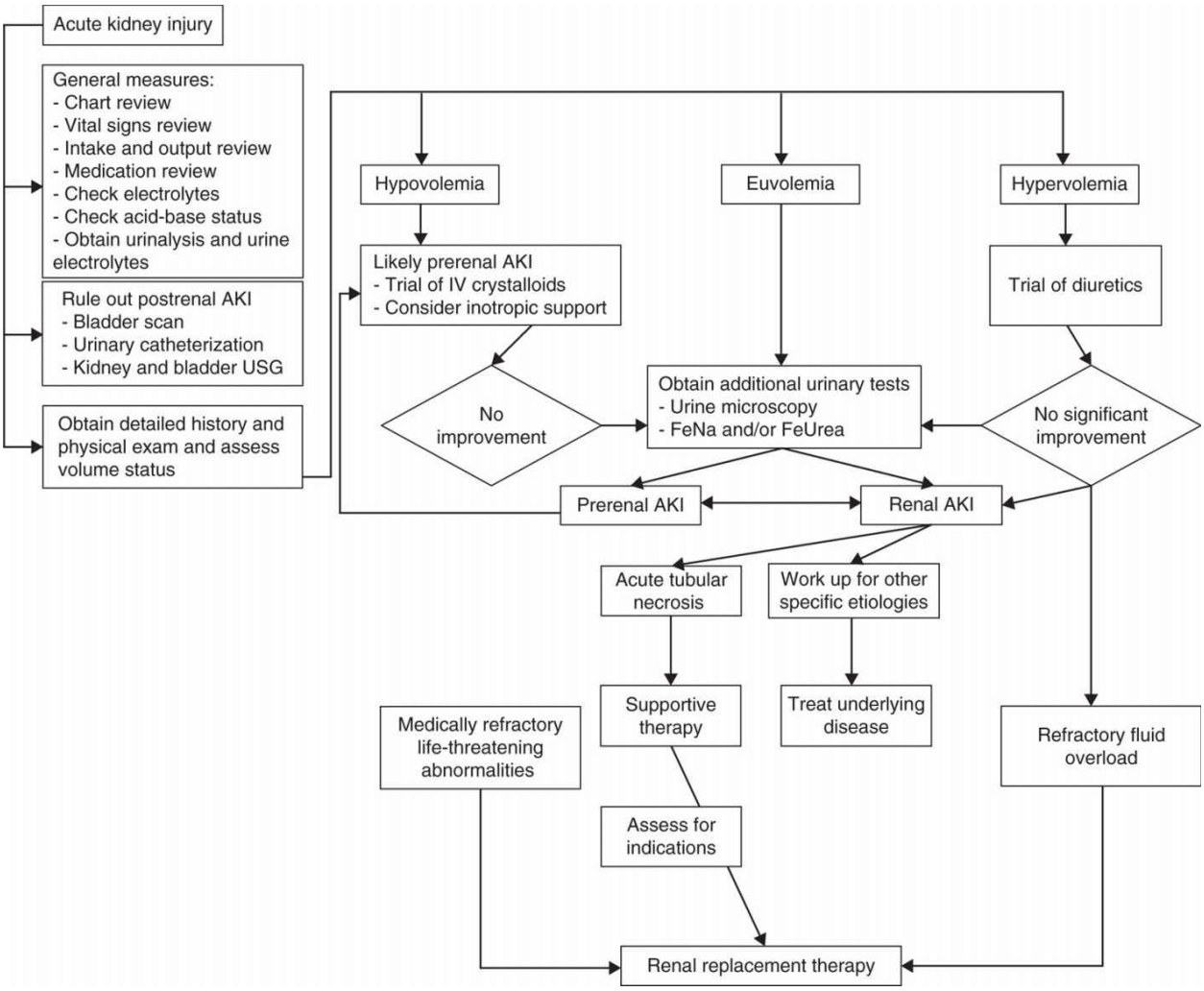

FIGURE 45.1 AKI pathway. AKI, acute kidney injury; FeNa, fractional excretion of sodium; FeUrea, fractional excretion of urea USG: Ultrasonogram.

Microscopic examination of the urine and urinary indices can be informative. Certain findings on urinalysis can point toward specific diagnoses as shown in **Table 45.3**. In prerenal or postrenal AKI, the urinalysis should be devoid of cells and protein. The absence of casts is usual in postrenal kidney injury but hyaline casts can be present in the setting of prerenal AKI.

TABLE 45.3 Urinalysis in Acute Kidney Injury

FINDING	SUGGESTED DIAGNOSIS
Muddy brown granular casts or epithelial cell casts	Acute tubular necrosis
RBC casts, dysmorphic RBCs	Acute glomerulonephritis

WBC casts, eosinophils	Acute interstitial nephritis
Large blood on dipstick with no RBCs	Hemoglobinuria or myoglobinuria
Specific crystals	Crystalline nephropathies, eg, Indinavir, Trimethoprim-sulfamethoxazole, or acyclovir associated, urate nephropathy

RBC, red blood cell; WBC, white blood cell.

Various urinary indices are commonly used to differentiate prerenal AKI from renal AKI. Urinary sodium concentration varies with the rate of water reabsorption. A patient who is in a prerenal state (both sodium and water avid) could have a decreased amount of sodium content in the urine but at a relatively high urine concentration (more than 20 to 40 mEq/L) due to a low urine volume in the setting of concurrent water avidity. Fractional excretion of sodium (FeNa) is a more reliable index since it does not vary with urine volume. FeNa measures the percentage of filtered sodium that is excreted in the urine. FeNa is calculated as follows:

$$\text{FeNa} = [(\text{urine sodium}/\text{plasma sodium})/(\text{urine creatinine}/\text{plasma creatinine})] \times 100.$$

A FeNa < 1% is indicative of a prerenal etiology. It is important to recognize that the FeNa value of 1% that distinguishes prerenal disease from acute tubular necrosis applies only in patients with a markedly reduced GFR. It is also important to remember that diuretics inhibit tubular sodium reabsorption so that in the CCU, patients receiving diuretics can have a FeNa > 1% despite intravascular volume depletion. A fractional excretion of urea nitrogen (FeUrea) and fractional excretion of uric acid (FeUric acid) may be more helpful in this setting. Similarly, the FeNa can be >1% despite volume depletion in patients with underlying CKD secondary to impaired tubular function at baseline. Also, prerenal states are not the only causes of low FeNa; it can also be low in acute glomerulonephritis, early obstructive nephropathy, liver failure, contrast nephropathy, pigment-induced nephropathy, and normal renal function. Some of the other diagnostic indices in this regard are listed in **Table 45.4**.

TABLE 45.4 Diagnostic Indices to Differentiate Prerenal and Renal Acute Kidney Injury

DIAGNOSTIC INDEX	PRERENAL AKI	RENAL AKI

Serum BUN to creatinine ratio	.20	,10–15
Urine Na (mEq/L)	,10	.20
Urine/serum creatinine ratio	.50	,20
Urine osmolality	.500	Variable
Urine specific gravity	.1.020	~1.010
FeNa (%)	,1	.1
FeUrea (%)	,35	.50
FeUric acid (%)	,12	.20

AKI, acute kidney injury; BUN, blood urea nitrogen; FeNa, fractional excretion of sodium; FeUrea, fractional excretion of urea; FeUric acid, fractional excretion of uric acid; Na, sodium.

Because the most commonly used marker of AKI, that is, SCr only rises 24 to 48 hours after the inciting injury, there is active research toward identifying newer serum and urine biomarkers for the early diagnosis of AKI. Some of the most promising markers are serum and urine neutrophil gelatinase-associated lipocalcin (NGAL),[8,9] interleukin 18 (IL-18),[10] kidney injury molecule-1 (KIM-1),[11] and cystatin C.[12] Further research is needed before these markers replace SCr as a marker of AKI in the clinical setting.[13]

Although glomerular diseases are an uncommon cause of AKI in the CCU, the finding of red blood cell casts or dysmorphic casts should prompt further evaluation. Estimation of urinary protein excretion is an important adjunct to further classify these patients. The use of random, spot urine protein/urine creatinine ratio as an estimate of 24-hour protein excretion has simplified this task by eliminating the need for cumbersome and often inaccurate 24-hour urine collections. A random urine protein/creatinine ratio >1 g protein/g of creatinine is usually seen in the presence of glomerular diseases. This ratio should be used only when kidney function is in steady state because the result may not be accurate in the setting of AKI. A number of serologic tests for secondary etiologies could help narrow the differential diagnosis; however, a definite diagnosis would require a kidney biopsy.

All patients with AKI should have periodic monitoring of serum electrolytes (sodium, potassium, magnesium, calcium, and phosphorus) and acid-base status because these are frequently abnormal and can become life threatening, for

example, severe hyperkalemia or severe metabolic acidosis.

Even though postrenal AKI is relatively uncommon in the CCU, a renal ultrasound should be obtained in all cases of unexplained AKI. A false negative study may be due to concomitant volume depletion or extrinsic compression, for example, secondary to a retroperitoneal hematoma. In the latter scenario, a noncontrast CT scan of the abdomen may be diagnostic.

DRUG DOSING

AKI affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (eg, absorption, drug distribution, and metabolism). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to estimated creatinine clearance. The most commonly used formulas are listed in **Table 45.5**. We recommend using the Cockcroft–Gault formula where creatinine clearance is estimated as a function of age, sex, and body weight. However, all those formulas were studied in patients with CKD with stable creatinine clearances and not in patients with AKI who have a day-to-day variation in the GFR. The actual GFR is much lower than the estimated GFR (often <10 mL/min in oliguric patients) for patients who are developing AKI and higher than the estimated GFR in patients who are in the recovery phase of AKI.

TABLE 45.5 Common Formulas Used to Estimate Glomerular Filtration Rate or Creatinine Clearance

NAME	FORMULA
MDRD formula, estimates GFR	eGFR (mL/min/1.73 m^2) 5 175 3 [serum creatinine (μmol/L) 3 0.0113]$^{-1.154}$ 3 age (years)$^{-0.203}$] (3 0.742 if female)
Cockcroft–Gault, estimates creatinine clearance (C_{Cr})	C_{Cr} 5 [(140 – age) 3 weight (kg)/(72 3 Cr)] (3 0.85 if female)
CKD-EPI, estimates GFR	eGFR 5 141 3 min (SCr/κ, 1)α 3 max(SCr/κ, 1)$^{-1.209}$ 3 0.993^{age} 3 1.018 [if female] 3 1.159 [if black]

κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1.
CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; MDRD,

modification of diet in renal disease; SCr, serum creatinine.

Loading doses of medications should not be decreased in patients with AKI or CKD. Recommended methods for maintenance of dosing adjustments are dose reductions, lengthening the dosing interval, or both. Physicians should be familiar with commonly used medications that require dose adjustments; however, it is impossible to be aware of all the subtle adjustments that are often needed. Before prescribing any new medication, dosing in AKI/CKD should be verified using any reliable print or electronic resource. Careful monitoring of drug levels, when available, can ensure therapeutic efficacy while minimizing toxicity.

In patients who are on RRT especially those on intermittent hemodialysis (IHD), the drug dosing for those drugs that are significantly dialyzed should be scheduled to be given post dialysis. Some of the common drugs used in the CCU that are likely to be significantly dialyzed include aspirin, dabigatran, atenolol, lisinopril, and antimicrobials like cefepime.

PREVENTION OF ACUTE KIDNEY INJURY

Because very few specific treatments are available for renal AKI, the key is prevention. This is especially true for patients who are at higher risk for developing AKI, for example, patients with advanced age, preexisting renal impairment, diabetes, hypertension, CHF, sepsis, or hypovolemia.

In addition to patients with prerenal azotemia, specific groups of patients may benefit from fluid administration to prevent AKI (ie, patients with early sepsis, rhabdomyolysis, and those receiving drugs such as amphotericin B and contrast media, or drugs associated with crystal deposition such as acyclovir and sulfonamides). Overaggressive fluid resuscitation should be avoided to prevent complications of fluid overload.

Maintenance of a mean arterial blood pressure > 65 mm Hg with optimization of volume status and use of vasoactive agents is critical to maintain optimal renal perfusion. In the setting of decompensated heart failure, the judicious use of inotropes can be necessary to prevent and treat AKI. Low-dose dopamine does increase renal plasma flow; however, clinical studies do not support the use of “renal dose” dopamine to prevent AKI or reduce the requirement of RRT.[14,15] The use of dopamine (or of fenoldopam,[16] a short-acting dopamine receptor-1

agonist) for this purpose is not recommended at present.

When using potentially nephrotoxic antimicrobials, attention to drug levels, adjusted dosing, and dose interval may minimize the risk of drug-induced nephrotoxicity. Furthermore, daily assessment of continued need for broad-spectrum antibiotics based on culture results is essential. Early identification of drug-induced AKI and discontinuation of the offending agent can prevent further renal injury.

ACUTE KIDNEY INJURY—SPECIAL SITUATIONS

CONTRAST-INDUCED NEPHROPATHY

Contrast-induced nephropathy (CIN) or contrast-induced acute kidney injury is generally defined as an increase in serum creatinine concentration of >0.5 mg/dL or 25% above baseline within 48 hours after contrast administration. Risk factors for CIN include advanced age, preexisting CKD, dehydration, hypotension, intra-aortic balloon pump, concomitant administration of nephrotoxic drugs, sepsis, diabetes mellitus, and CHF requiring active diuretic use. Various scoring systems are available to quantify this risk.[17] In patients with established AKI, avoiding the use of contrast media if possible until AKI has resolved should be considered.

Certain measures such as the following may be useful in minimizing the risk of CIN:

1. The use of low osmolar or isoosmolar contrast media and use of lowest possible volume (eg, avoiding left ventriculogram in patients at risk);
2. Optimization of volume status: Discontinuation of diuretics and use of isotonic saline starting 6 to 8 hours before contrast administration to ensure adequate hydration is a commonly used strategy.
3. Discontinuation of angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs) prior to contrast administration can sometimes be done but this strategy is not routinely recommended because data have shown conflicting results.
4. Isotonic sodium bicarbonate has been shown to be superior to isotonic saline in some studies but the evidence is equivocal.[18]
5. Another agent sometimes used is oral *N*-acetylcysteine (NAC). Evidence for the preventive efficacy of NAC is equivocal and cannot be routinely

recommended at this time.[19]

6. Recent data suggest a beneficial effect of statin administration although the quality of this data is weak.
7. All other potential nephrotoxins should be discontinued when possible.
8. Periprocedural hemodialysis has no role in the prevention of CIN.[20]

ACUTE KIDNEY INJURY POST CARDIAC SURGERY

AKI complicates up to 30% of cardiac surgery. The risk factors most commonly associated with AKI in this setting include female sex, left ventricular dysfunction, diabetes, peripheral vascular disease, chronic obstructive pulmonary disease, emergent surgery, use of intra-aortic balloon pump, prolonged cardiopulmonary bypass time, and, most importantly, preoperative elevations in SCr.[21] The avoidance of cardiopulmonary bypass has been shown to be associated with lower incidence of postoperative AKI[22] and should be considered whenever possible. Recently, nesiritide,[23] a recombinant human BNP and fenoldopam, a renal vasculature dilator, have shown mixed results in preventing postcardiac surgery AKI.

TREATMENT OF ACUTE KIDNEY INJURY

The treatment of AKI depends on its etiology. In postrenal AKI, rapid relief of obstruction will reverse the AKI. Prerenal AKI owing to hypovolemia should be managed with prompt restoration of the effective circulatory volume, usually by administration of crystalloid solutions. Hypovolemia can be caused by renal or extrarenal causes, and careful history and examination as outlined earlier is essential to determine absolute or effective hypovolemia. The adequacy of restoration of intravascular volume can be guided by periodic assessment of the central venous pressure (CVP). However, the possibility of right-sided heart failure, pulmonary arterial hypertension, or positive pressure ventilation can elevate CVP; this needs to be kept in mind while interpreting the results. The use of Swan-Ganz catheter guided therapy has fallen out of favor after the results of trials showed that use of these catheters increased anticipated adverse events and did not have any effect on overall mortality and hospitalization length.

In acute decompensated CHF, preload and afterload reduction with diuretics and vasodilators are the cornerstones of therapy. The judicious use of diuretics

with close monitoring of hemodynamics and renal parameters can increase cardiac output and lower renal venous hypertension, thereby improving renal perfusion. Appropriate use of inotropes may restore normal renal perfusion especially in patients with acute systolic heart failure or advanced left ventricular systolic dysfunction. The temporary discontinuation of ACEIs or ARBs and avoidance of NSAIDs may also help increase renal perfusion.

The management of intrinsic AKI depends on the underlying etiology. The management of individual diseases, especially that of glomerular diseases, is beyond the scope of this chapter.

We focus on the special considerations in patients with ATN, which is a common cause of renal AKI in the CCU. In case of any doubt regarding whether the patient has prerenal AKI or established ATN secondary to sustained renal hypoperfusion, an adequate trial of crystalloids and/or the use of vasoactive agents may be the only differentiating feature; rapid reversibility indicates a prerenal mechanism. While fluid resuscitation is ongoing, frequent monitoring of respiratory status in patients with heart failure is essential to avoid pulmonary edema. Withdrawal of all possible nephrotoxic agents to avoid further injury to the kidney should be done concurrently. Once ischemic or nephrotoxic ATN is established, there is no specific therapy. The main goal of treatment is to treat the complications of AKI and prevent further injury.

A number of drugs have been tried to reduce the requirement for RRT and to accelerate renal recovery in ATN but none has shown a conclusive benefit. Diuretics are commonly used in oliguric AKI; however, randomized controlled trials have failed to show a reduction in the need for RRT. Hence the role of diuretics in AKI is limited to management of volume overload and/or hyperkalemia in the setting of AKI. Similarly, the use of selective renal vasodilators such as dopamine or fenoldopam is not supported by current clinical evidence and thus is not recommended.[13]

RENAL REPLACEMENT THERAPY

Conventional indications for initiation of RRT include refractory fluid overload, intractable hyperkalemia and metabolic acidosis, and uremic syndrome. Other indications include uremic pericarditis, uremic encephalopathy, uremic neuropathy, and suspected drug/toxin overdose with a dialyzable substance. Traditional triggers for treatment were based on studies in CKD patients,

whereas patients with AKI who are critically ill may have a reduced tolerance of metabolic derangements.

Furthermore, the identification that iatrogenic fluid overload may play a role in perpetuating multiorgan dysfunction in critically ill patients has led to the belief that early initiation of RRT in this population may have beneficial effects on overall morbidity and mortality. However, timing of RRT initiation in critically ill patients remains unclear. Recently, a French multicenter trial showed no benefit of early versus late RRT initiation,[24] in discordance with another recent German single center trial that suggested that early initiation reduced mortality at 90 days as compared to late initiation.[25]

The available modalities for RRT include IHD, continuous renal replacement therapy (CRRT), hybrid therapies such as sustained low-efficiency dialysis and peritoneal dialysis. The choice of modality depends on institutional availability, physician preference, patient hemodynamic status, and the presence of other comorbidities. CRRT has been postulated to be more physiologic owing to its continuous nature. It is especially useful in the hemodynamically unstable patients with AKI where use of IHD could lead to further ischemic insult and delay in renal recovery. However, no randomized study has proven this theoretical benefit over conventional, intermittent dialysis.

One modality of CRRT, especially useful in the CCU, is slow continuous venovenous ultrafiltration that can allow removal of large amounts of fluid from the patient while minimizing the risk of hemodynamic instability. It can be considered as a therapeutic option in the management of a fluid overloaded patient with diuretic resistance even in the absence of AKI.

RECOVERY FROM ACUTE TUBULAR NECROSIS

Recovery from ATN is the rule rather than the exception. More than 90% of patients with ATN recover renal function sufficient to discontinue dialysis. The timing of this recovery varies among individual patients and can happen even after weeks of AKI. A post-ATN diuresis can commonly be seen in the recovery phase owing to osmotic diuresis. It is important to monitor these patients closely as they are often at the risk of developing new prerenal azotemia and electrolyte derangements if volume intake does not match urinary loss.

DEDICATION

This chapter is dedicated to the memory of Dr. James Jones who was a cherished colleague in the Division of Nephrology at Mount Sinai, St. Luke's and West. His untimely passing at the end of 2016 has left a void in our hearts and minds.

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Patient and Family Information for: Renal Failure in the Cardiac Care Unit

WHAT ARE THE KIDNEYS?

The kidneys are two bean-shaped organs located in the middle of the back, one on each side. Each measures about the size of a fist. These are vital organs and each is made up of about 1 million nephrons (filters) and tubules that process approximately 2 L of blood every 5 minutes.

WHAT ARE THE FUNCTIONS OF THE KIDNEY?

The human body consists of 60% to 70% water. This water also contains a variety of dissolved materials such as different salts (sodium chloride, potassium chloride, sodium bicarbonate, etc). All the water in the body is distributed between three spaces: the intracellular compartment (in the cells), interstitial spaces (between the cells), and intravascular (the blood). In an ideal setting, there is a perfect balance of water and salts between all these compartments. If any deregulation occurs, for instance if we get dehydrated (eg, diarrhea) or if we get fluid overloaded (eg, in patients with heart failure leading to lower extremity swelling and/or pulmonary edema), the kidneys jump into action to restore the equilibrium. Therefore, control of fluid and salt balance is an essential function of the kidneys.

Another important function of the kidneys is to excrete toxic wastes (such as urea, acid, etc) produced by the body on a daily basis. The kidney does this by filtering the blood that flows through it. In other words, the urine is actually a filtered form of blood that has all the waste material in it (urea, extra water, acid, salts, etc).

The third function of the kidney is to act as an endocrine organ. The main hormone that the kidneys produce is erythropoietin that is required by the body to produce red blood cells (that carry oxygen in the blood). In addition, the kidneys also activate other inactive products such as vitamin D (helps maintain healthy bones).

WHAT ARE THE TYPES OF KIDNEY DISEASE?

Depending on the duration of onset, kidney disease can be acute, chronic, or acute on chronic.

Acute: Such patients may have normal functioning kidneys at baseline. AKI is a potentially life-threatening condition and may require intensive care treatment. ATN is one of the most common subtypes of AKI in a critically ill patient. In ATN, the kidney tubules get damaged owing to various reasons (infections/pneumonia, low blood pressure resulting from heart failure/heart attack, etc). With time, and if the reason for damage is fixed, the tubules may start functioning again as before.

Chronic (when decrease in function takes place gradually over time): Common causes are hypertension and diabetes. Such patients may have CKD. Those who have had regular follow-up with their primary doctors may be aware of their underlying CKD. However, as kidney disease is usually painless, it is not uncommon for patients not to know of their underlying CKD until the disease is in an advanced stage.

Acute on chronic: Such patients have acute worsening of their CKD owing to critical illness, for example, pneumonia, heart attack, and heart failure.

WHAT ARE THE COMMON CAUSES OF ACUTE KIDNEY INJURY?

An injury to the kidneys is generally because of another disease process. Sometimes there may be more than one cause, and therefore it may be impossible to pinpoint the exact cause of AKI. Death is most common when AKI is caused by surgery, trauma, or severe infection in someone with heart disease, lung disease, or recent stroke. Old age, infection, loss of blood from the intestinal tract, and progression of kidney failure also increase the risk of death.

Some of the common causes of AKI are as follows:

Shock: Shock is a life-threatening condition that may accompany severe injury or illness, whereby the body suffers from insufficient blood flow to its vital organs. This can therefore result in decreased oxygen delivery to the organs (hypoxia) leading to organ failure, for example, kidney failure, heart attack (cardiac arrest), and so on. Shock may be of different type/causes: septic (owing to an infection in the body, pancreatitis, etc), hemorrhagic (owing to acute blood loss—as in a patient with bleeding from a stomach ulcer), cardiogenic (owing to heart failure from a weak heart or acute heart attack), and hypovolemic (eg, excess fluid loss from body after severe diarrhea or excessive use of diuretics).

Damage from medicine/dyes: Unfortunately, many of the medications used to treat patients may themselves cause kidney damage. People who have serious, long-term health problems are more likely than others to have such adverse effects. Some examples of such medications are as follows:

- Antibiotics used to treat life-threatening infections
- Pain medicines such as ibuprofen (and all other NSAIDs)
- Some blood pressure medicines and ACEIs (such as enalapril)
- The contrast/dyes used in imaging (CAT scan as discussed in the ensuing section)
- Some of the HIV medications, for example, tenofovir.

Urinary tract obstruction: This may happen in patients with a known history of kidney stones, benign prostate hypertrophy, or rarely in patients with cancers that invade or press on the urinary tract system.

WHAT ARE THE SIGNS AND SYMPTOMS OF KIDNEY FAILURE?

Kidney failure is almost always painless. In the setting of an intensive care unit, the following signs and symptoms may point toward a failing kidney:

Accumulation of fluid/water: Because the failing kidneys are unable to excrete water, accumulation of water in the body manifests as swelling of the feet, lower legs, face, and/or the hands. Sometimes when the kidneys fail, a lot of protein is lost in the urine, which can also cause worsening edema and labored breathing owing to accumulation of fluids in the lungs. If this is severe, the patient may

require intubation (whereby the patient is sedated and a breathing tube is inserted in the windpipe) and breathing support with the help of a machine (ventilator).

Irregular heart rate: Owing to the accumulation of toxins and electrolyte imbalance (hyperkalemia or high potassium), the heart rhythm may become irregular or dangerously slow, leading to cardiac arrest.

Symptoms resulting from accumulation of toxins/waste products such as urea: Loss of appetite, nausea, vomiting, weight loss, fatigue, sleepiness, itching, twitching, and a metallic taste in the mouth. They often indicate that the person is accumulating dangerous amounts of waste products (urea) because the kidneys are not working to excrete them.

Abnormal blood tests suggesting impaired kidney function: Sometimes the patient may be totally asymptomatic but the blood tests may suggest severe kidney failure, for example, hyperkalemia (high potassium), increased blood acidity, high creatinine, and BUN levels.

HOW TO DIAGNOSE KIDNEY FAILURE?

Nephrologists are specialists in kidney diseases. When a patient has evidence of kidney failure, the intensive care team will seek the help of nephrologists to manage it. The following tests will help to determine the severity and cause of kidney failure:

Blood test: In most cases, two parameters in the blood, namely the BUN and creatinine, can give a fair assessment as to the degree of kidney failure. Urea is a byproduct of protein breakdown, and creatinine is a byproduct of normal muscle functioning. In a normal person, the level of creatinine is 0.7 to 1.2 mg/dL and that of BUN is 12 to 24 mg/dL. In addition, blood levels of some important electrolytes such as potassium are also taken into consideration while treating a patient with kidney failure.

Urine tests: Microscopic analysis of patients' urine can give some indication as to the type of kidney failure (eg, AKI owing to ATN). Other urine tests such as urine protein concentration and urine electrolytes (sodium, creatinine) can also prove helpful in making the diagnosis: for example, a high protein and blood concentration in the urine with AKI may be suggestive of lupus nephritis (owing to autoimmune disease called systemic lupus nephritis).

Imaging tests: Noninvasive procedures such as ultrasound and CAT scan help in assessing the condition of the kidneys.

Ultrasound: It is a painless, harmless (uses sound waves that bounce off structures in the body and give images), and quick way to assess the size and texture of the kidneys. Kidneys are usually normal in size in patients with AKI unless the patient also has some underlying CKD. Ultrasound is also the procedure of choice to diagnose any obstruction of the urinary tract and it is important to rule this out as the cause of kidney injury in all patients.

Computed axial tomography scan: A CAT scan uses X rays to produce pictures in crosswise slices. CAT scans can detect kidney stones, blockage, tumors, cysts, and so on. In addition to the kidneys, an abdominal CAT scan can also be used to assess other abdominal organs. Sometimes CAT scans require using contrast dye, which itself carries the risk of causing kidney injury, especially in people who already have reduced kidney function.

Kidney biopsy: Very rarely would a nephrologist decide to do a kidney biopsy in a patient with AKI. He/she may decide on doing this if conventional analysis is unable to provide sufficient clues as to the underlying cause of AKI and/or if the treatment modality would require the exact diagnosis rather than the most probable cause of AKI. In kidney biopsy, a piece of kidney tissue is taken out under guidance of ultrasound or CAT scan. This tissue is then analyzed by experts to provide the exact cause of kidney failure. Kidney biopsy unfortunately carries a high risk of bleeding (10%) and even death in <1% of patients.

HOW TO MANAGE A PATIENT WITH KIDNEY FAILURE (HEMODIALYSIS)?

The most definitive treatment of kidney failure is to fix the underlying cause. For example, if the patient is having severe heart failure, the optimization of the heart failure will most likely help in resolving acute kidney failure. However, treating the underlying disease may take time, thus necessitating the initiation of renal replacement therapy (RRT). The decision to start RRT may be taken if the patient's serum potassium levels are dangerously high and/or if the patient has mental status changes, and/or if the patient has too much fluid, and/or if the patient develops pericarditis (inflammation of the heart covering owing to high urea). RRT basically implies the use of artificial methods (dialysis) to carry out the function of the kidneys. The commonly used technique for acute kidney failure is hemodialysis.

Hemodialysis is the most common intermittent method of artificial RRT,

wherein the blood is allowed to flow through a special filter that removes waste and extra fluids. The clean blood is then returned to the body. For hemodialysis, the patient needs to have a large bore catheter in one of the deep veins of the body (such as a nontunneled catheter that has to be typically changed after a few days of placement, and, a tunneled catheter that can be used for a longer period of time). It is therefore placed either in the neck or the groin. Each session of hemodialysis lasts for 3 to 4 hours and is done either daily or three times a week. However, the frequency may be adjusted based on the blood tests, degree of edema, and so on.

HOW LONG WILL THE PATIENT NEED HEMODIALYSIS?

Acute kidney failure is a potentially life-threatening condition and may require intensive care treatment. However, the kidneys usually start working again within several weeks to months after the underlying cause has been treated. Such patients may therefore require hemodialysis temporarily.

The recovery also depends on the baseline function of the kidneys, the underlying cause, and the severity of the AKI. In some cases, chronic kidney failure or end-stage kidney disease may develop, thus requiring hemodialysis lifelong.

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Elissa K. Fory
Stephan A. Mayer

Acute Neurologic Emergencies in the Cardiac Care Unit

Some of the most feared complications from acute cardiac disease are neurologic in nature. When acute brain injury occurs, significant morbidity and mortality may follow. A team-based approach that incorporates cardiology, neurology, and critical care expertise is desirable to maximize patient outcomes and address each patient's complexities. There are four common neurologic emergencies in the cardiac care unit (CCU): delirium, hypoxic ischemic encephalopathy (HIE), acute ischemic stroke, and intracranial hemorrhage (**Table 46.1**). This chapter is tailored to patients admitted to or being admitted to a CCU, and so a broader differential diagnosis is applicable to patients in other care environments (such as the emergency department or general medical floor).

TABLE 46.1 Common Acute Neurologic Emergencies in the CCU

Delirium
Hypoxic ischemic (anoxic) encephalopathy
Acute ischemic stroke
Intracranial hemorrhage

CCU, cardiac care unit.

DELIRIUM

Delirium is acute brain dysfunction characterized by a change in both the level and content of consciousness. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines delirium as a "disturbance in attention (ie reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)" that occurs over hours to days, often fluctuates (waxes and wanes), and is different from the patient's normal state of being. There may also be abnormalities of higher cognitive function or even focal neurologic deficits such as language difficulty, visuospatial changes, or changes in perception. In delirium, the symptoms are not due to an underlying or preexisting condition such as dementia. Finally, there needs to be evidence from the history, examination, or supporting data that the cause is due to a medical condition or is multifactorial. Synonyms for delirium include encephalopathy, acute brain failure, intensive care unit (ICU) psychosis, acute confusional state, and altered mental status. A diagnosis of delirium implies that there is no other underlying primary neurologic condition accounting for the patient's syndrome, such as a stroke causing aphasia or nonconvulsive status epilepticus.

RECOGNITION OF DELIRIUM

As with any medical problem, the diagnosis of delirium starts with a history and physical examination. With delirium, key questions include the following:

- How is the patient confused? Is he or she seeing objects, having difficulty speaking, or is he or she somnolent?
- When did the change start? Has this ever occurred before? Are the patient's symptoms coming and going or are they constant?
- Does the patient have pain?
- What are the vital signs?
    - Fever suggests infection. Tachycardia may be due to fever, dehydration, or atrial fibrillation. Severe hypertension should bring hypertensive encephalopathy into the differential diagnosis.
- What is the blood glucose?
    - Hypoglycemia can cause acute confusion and should be immediately treated with oral or intravenous glucose, as appropriate. Thiamine 100 mg intravenous (IV) should precede any IV dextrose administration whenever possible. Fingerstick glucose can be falsely normal or high from many factors, including sugars on uncleaned skin; a venous glucose or chemistry should be sent to the laboratory. To avoid prolonged profound hypoglycemia that can lead to permanent coma, thiamine and IV dextrose

should be given while awaiting the venous glucose result if there is *any* clinical suspicion for hypoglycemia as the cause of acute encephalopathy.

- What is the past medical history?
  - Patients with known dementia are at higher risk for delirium.
  - Patients with acute or chronic kidney or liver dysfunction are at risk for uremic or hepatic encephalopathy, respectively, as well as increased risk for medication toxicities if doses are not adjusted or organ function is changing rapidly over time.
- What is the patient's history regarding tobacco, alcohol, and substance abuse?
  - Delirium tremens should be considered in patients admitted to the hospital in the previous 12 to 72 hours.
  - Cocaine and amphetamine withdrawal can result in a somnolent, stuporous state.
  - Nicotine withdrawal can be prevented by prescribing a 21 mg nicotine transdermal patch for chronic smokers.
- Did the patient recently receive any medications (**Table 46.2**)?

TABLE 46.2 Common Medications in the CCU That Can Cause Delirium

Antibiotics: cefepime, flouroquinolones
Anticonvulsants: phenytoin, phenobarbital, levetiracetam, valproic acid
Antihistamines: diphenhydramine, dextromethorphan, famotidine
Benzodiazepines, zolpidem
Corticosteroids
Dopaminergic drugs: L-dopa, rotigotine
Digoxin
Lidocaine
Opiates

CCU, cardiac care unit.

  - Thoroughly review the patient's home medications, scheduled medications, and the medication administration record for one-time or as-needed doses.
  - If the patient received opiates and has other signs of opiate intoxication such as pinpoint pupils or hypoventilation, consider naloxone 0.4 mg IV.

BEDSIDE EXAMINATION IN DELIRIUM

Make a general assessment of the patient. Does he or she appear disheveled to suggest underlying psychiatric or dementing process? Is there nuchal rigidity? Auscultate heart and lungs to evaluate for tachypnea, rhonchi, or decreased

breath sounds, irregular rhythms, or cardiac valvular abnormalities. Make note of Janeway lesions, splinter hemorrhages, hepatomegaly, abnormal bowel sounds, or jaundice.

The neurologic examination starts when you first enter the room, in how the patient is able to (or unable to) give a history. Note the level of alertness. Using terms such as “lethargic” or “stuporous” can be nebulous and easily misinterpreted, making it difficult for another practitioner to later discern if the patient has had a change in his or her examination. Instead, consider describing how long the patient can sustain attention (for a few seconds, or a minute or 2), and what intensity of stimulus was required to awaken them (voice, nonnoxious tactile stimuli, noxious stimulus, or continuous noxious stimulation). For alert patients, the mental status examination starts with orientation questions. Simple tests of attention include counting backward from 20 to 1 and naming the days of the week or months of the year in reverse order. Formal language testing can include the naming of objects, repetition, and the ability to follow verbal commands (either simple such as “show me two fingers” or more complex like “touch your left ear with your right thumb”). Do not simultaneously demonstrate the verbal command, so that the request is testing receptive language and not the patient’s ability to mimic. Depending on the patient’s attention and ability to participate, further mental status testing might include a formal score such as the Montreal Cognitive Assessment (MoCA, available free at mocatest.org), Confusion Assessment Method for the ICU (CAM-ICU, icudelirium.org), or Intensive Care Delirium Screening Checklist (ICDSC).

The rest of the neurologic examination is focused on finding clues to a metabolic or systemic cause for delirium and identifying focality that would suggest a primary neurologic problem as opposed to delirium. Small pinpoint but reactive pupils suggest opiate effect. Eye motion abnormalities and nystagmus can be seen with Wernicke encephalopathy or with posterior fossa pathology. Facial movements should be assessed for symmetry. The precision of the motor exam will depend on the patient’s ability to participate. In a severely encephalopathic patient, strong and symmetrical withdrawal to pain in all extremities is reassuring that intracranial pathology is absent. With more cooperative patients, subtler signs of weakness such as pronator drift may be elicited. Additionally, arms should be held with elbows and wrists extended (“as if you are stopping traffic”) to test for asterixis—a sign of hepatic or uremic encephalopathy. Asterixis is also called negative myoclonus and manifests as a “quick release” or fast drop from a sustained posture with a return close to the

previous posture. Tremulousness can be seen with alcohol withdrawal. Tone can be tested in all patients. Deep tendon reflexes and Babinski signs should be checked. Sensory examination is almost always unreliable during a delirium evaluation and generally does not help narrow the diagnosis.

INITIAL LABORATORY AND IMAGING WORKUP FOR DELIRIUM

After evaluating the patient clinically and ensuring the fingerstick glucose is normal, the following tests should be considered:

- Chemistry, ammonia, complete blood count, therapeutic drug levels, urine toxicology:
  - Abnormalities of sodium, calcium, and glucose can cause encephalopathy and/or seizures. Profound uremia and hyperammonemia can cause metabolic encephalopathy.
- Urinalysis and urine culture; blood cultures;
- Arterial blood gas:
  - Acute respiratory acidosis or hypoxia can cause stupor. Respiratory alkalosis can suggest hyperventilation and tachypnea from sepsis. Hypoxia can be seen with pneumonia or pulmonary embolus.
- Chest X-ray should be ordered for any patient with fever, tachypnea, or hypoxia.
- Noncontrast head computed tomography (CT) should be considered for all patients and ordered emergently for any patient with a focal neurologic examination. If the patient has a new acute focal neurologic examination or an examination concerning for posterior fossa pathology, a CT angiogram (CTA) of the head and neck should be immediately and simultaneously acquired to rule out large vessel occlusion (LVO) causing stroke, which is treatable and reversible.
- Electroencephalograph (EEG) may give additional information. Triphasic waves suggest toxic or metabolic encephalopathy. Diffuse slowing of the background can be seen in either delirium or dementia. Epileptiform discharges do not diagnose seizures but may change one’s post-test probability for seizures as a cause of change in mental status.

TREATMENT OF DELIRIUM

Ultimately, the treatment of delirium requires diagnosis and correction of the underlying cause. If acute pain is the cause, pain medications should be given. If

agitation limits the ability to obtain initial studies, or if the patient is a threat to himself/herself or to others, then IV medications should be given with the goal of resolving the agitation (**Table 46.3**). Antipsychotics are first-line treatment for acute agitation.[1] Benzodiazepines are first line in the treatment of alcohol-withdrawal delirium, benzodiazepine-withdrawal associated delirium, or in acute hepatic failure.[2] Additionally, benzodiazepines may be considered as first-line treatment in patients with extreme or life-threatening prolongation of the QT interval. Overall, however, the total dose of benzodiazepines is associated with an increase in delirium, and so they should not be the initial treatment in a generalized patient population. Dexmedetomidine (Precedex) infusion may be used for patients who are intubated or spontaneously breathing. Dexmedetomidine has the advantages of being associated with a decreased prevalence of delirium and a decrease in ventilator days in intubated patients compared with benzodiazepines or morphine.[3] Side effects of dexmedetomidine include hypotension and bradycardia.

TABLE 46.3 Drugs for the Treatment of Acute Agitated Delirium

	INITIAL DOSE	SELECTED SIDE EFFECTS
Antipsychotics		
Haloperidol Olanzapine Quetiapine	1–10 mg IV/IM/po 5–10 mg po/IM 25–50 mg po	Prolonged QT, EPS Hyperglycemia
Benzodiazepines		
Lorazepam Midazolam	1–4 mg po/IV/IM 1–4 mg po/IV/IM	
Alpha 2 adrenergic agonists		
Dexmedetomidine	0.4 µg/kg/h IV infusion	Hypotension, bradycardia

IV, intravenous; IM, intramuscular. EPS, Extrapyramidal symptoms.

Nonpharmacologic treatments for delirium include frequent verbal redirection, ensuring comfort, and isolated hand restraints to prevent pulling of lines while allowing for freedom of movement. Wrist restraints and 4-point restraints may worsen agitated delirium. Treatment and prevention of delirium also include maintaining normal sleep-wake cycles: minimizing sleep interruptions at night,

decreasing light stimulus to the eyes at night (including televisions and smartphones or tablets), and increasing stimulation during the day including mobilization and physical therapy. Indwelling urinary catheters, nasogastric tubes, and multiple IV lines not only serve as a source of discomfort and potential infection, but also physically restrain patients; they should be discontinued or minimized as soon as they are no longer medically necessary. Finally, protocols and automatic order sets should avoid deliriogenic medications, such as diphenhydramine for sleep.[4]

HYPOXIC ISCHEMIC ENCEPHALOPATHY

The number one cause of morbidity and mortality post cardiac arrest is continued coma and persistent encephalopathy after resuscitation. Treating patients aggressively gives the best chance for neurologic recovery and prevents the self-fulfilling prophecy of a poor neurologic prognosis.

RECOGNITION OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

Any patient who is not awake and following commands after return of spontaneous circulation (ROSC) after cardiac arrest should be considered to have HIE. The initial neurologic examination should include pupil size and reactivity, corneal reflexes, oculocephalic reflexes (barring any concern for cervical spine injury), cough reflex, gag reflex, motor response, and verbal response. The Glasgow Coma Scale (**Table 46.4**) is a simple tool that communicates the level of coma and easily tracks changes in the neurologic examination. Note any extraneous movements such as myoclonus, nystagmus, flexor or extensor posturing, or shivering.

TABLE 46.4 Glasgow Coma Scale

EYE OPENING	BEST MOTOR RESPONSE	BEST VERBAL RESPONSE
4—eyes open spontaneously	6—follows commands	5—oriented
3—eyes open to voice	5—localizes to pain	4—disoriented
2—eyes open to pain	4—withdraws from pain	3—inappropriate words
1—none	3—flexor posturing to pain	2—incomprehensible sounds

	2—extension posturing to pain	1—none
	1—none	

It is extremely important to provide aggressive care to all patients on admission to the emergency department or hospital, regardless of their neurologic examination, to prevent the self-fulfilling prophecy of a poor neurologic outcome. Patients with coma shortly after ROSC, including those with some absence of cranial nerve function, can improve and even regain consciousness with aggressive medical care. Even if the patient meets criteria for brain death immediately after resuscitation or soon thereafter, aggressive critical care allows time for family discussions and for consideration of organ donation.

DIAGNOSTIC EVALUATION

Neuron-specific enolase (NSE) should be sent between 24 and 72 hours post arrest to assist with prognosis. Without hypothermia, an NSE of greater than 33 μg/L is associated with a poor prognosis. With hypothermia, patients may have a higher number (up to 80 to 100 μg/L have been reported) and still have a good outcome, although the higher the value, the less likely a good neurologic outcome.

Many centers perform noncontrast head CTs in the emergency department or directly after stabilization from cardiac arrest to rule out massive intracranial hemorrhage or acute hydrocephalus as the cause for cardiac arrest. This is a reasonable practice, but not one that is required if there is a known precipitant of cardiac arrest such as prolonged QT interval or a preceding period of hypoxia. Noncontrast head CTs have not been validated for use in neurologic prognostication, although the degree of changes can give the treating neurologist a flavor of the severity of the initial brain injury (**Figures 46.1–46.3**).

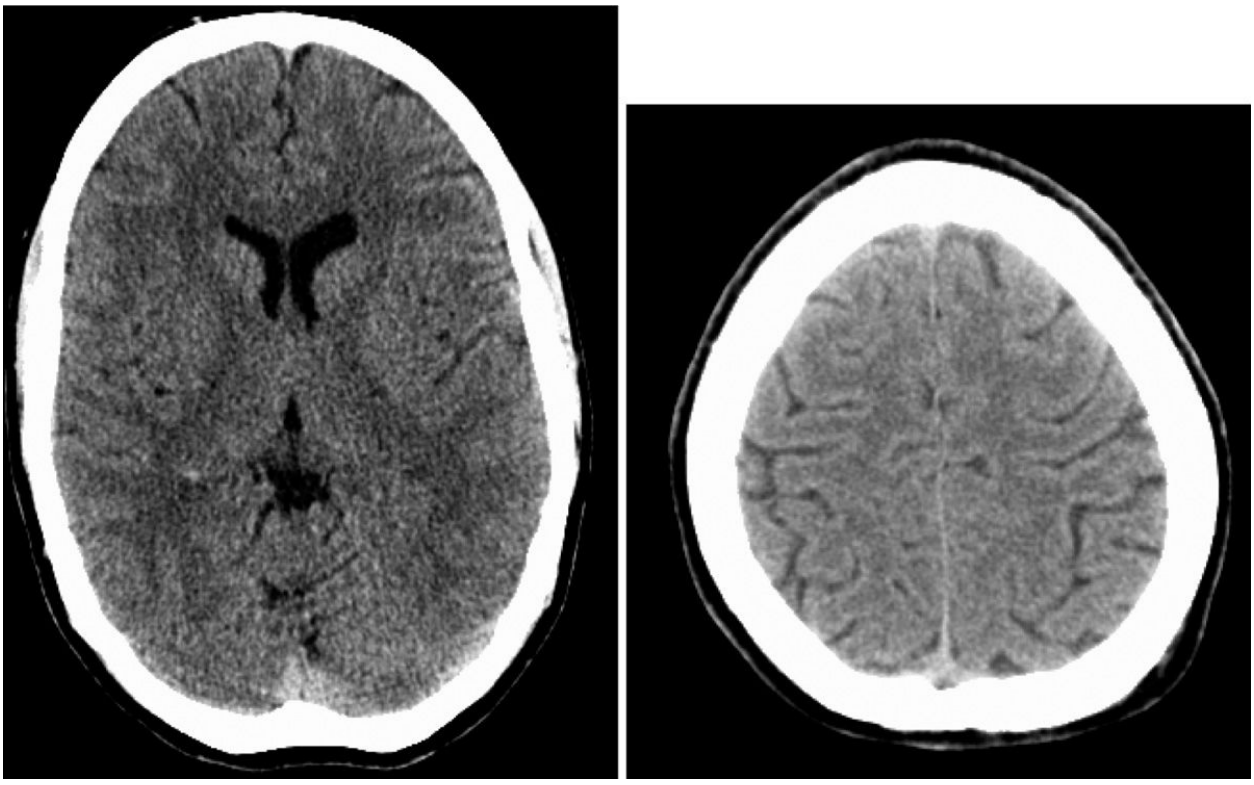

FIGURE 46.1 Two axial images from a normal noncontrast CT of the brain. CT, computed tomography.

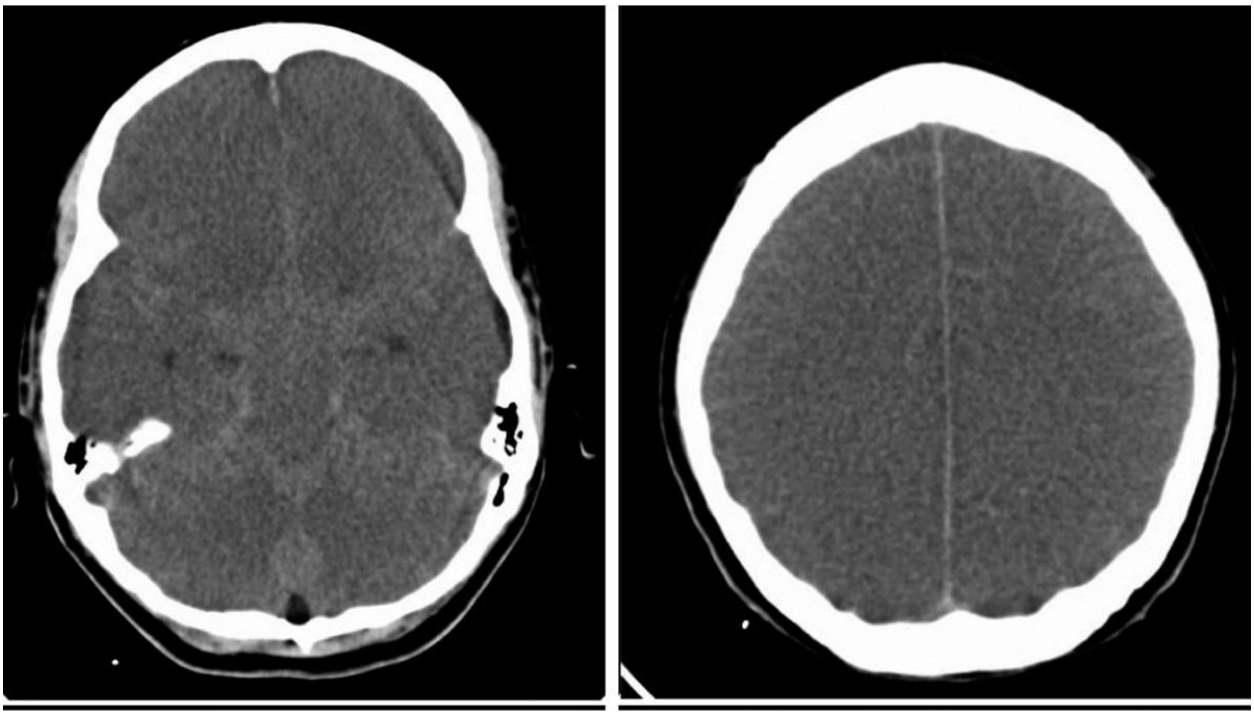

FIGURE 46.2 Noncontrasted CT scan of the head of a patient approximately 100 hours after an out-of-hospital asystolic cardiac arrest. The left panel shows pseudosubarachnoid hemorrhage and blurring of the

gray-white junction throughout all the structures of the brain. The right panel shows blurring of the gray-white junction with sulcal effacement. The patient's admission noncontrast CT scan of the brain was unremarkable. At this time, the patient had flexion posturing and nonreactive pupils. The patient expired on hospital day 7 after removal of life support. CT, computed tomography.

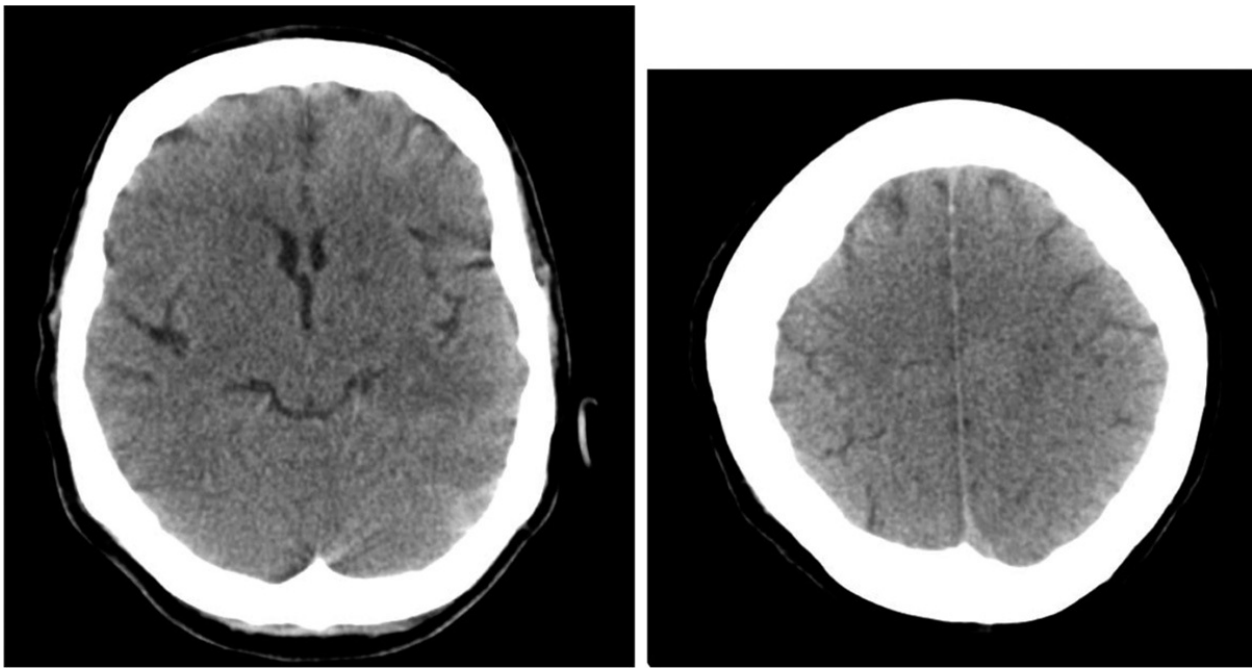

FIGURE 46.3 These two images are axial cuts of a noncontrasted head CT of a patient approximately 8 days after an out-of-hospital PEA cardiac arrest. There is loss of gray-white differentiation throughout the cerebral hemispheres, including loss of differentiation in both the basal ganglia and internal capsule (left panel), as well as the cortex. There is sulcal effacement especially at the vertex (right panel). These findings are consistent with diffuse anoxic injury. CT, computed tomography. PEA, pulseless electrical activity.

Magnetic resonance imaging (MRI) should not be ordered acutely after a cardiac arrest. However, noncontrasted MRI of the brain may be helpful in prognostication (**Figure 46.4**). The volume and intensity of Diffusion-Weighted Imaging (DWI) and Fluid-Attenuated Inversion Recover (FLAIR) signal changes in the cortex of the brain have prognostic value for neurologic recovery, when the MRI is performed between days 3 and 6 after the cardiac arrest. A greater amount of change prognosticates a poor neurologic outcome.[5]

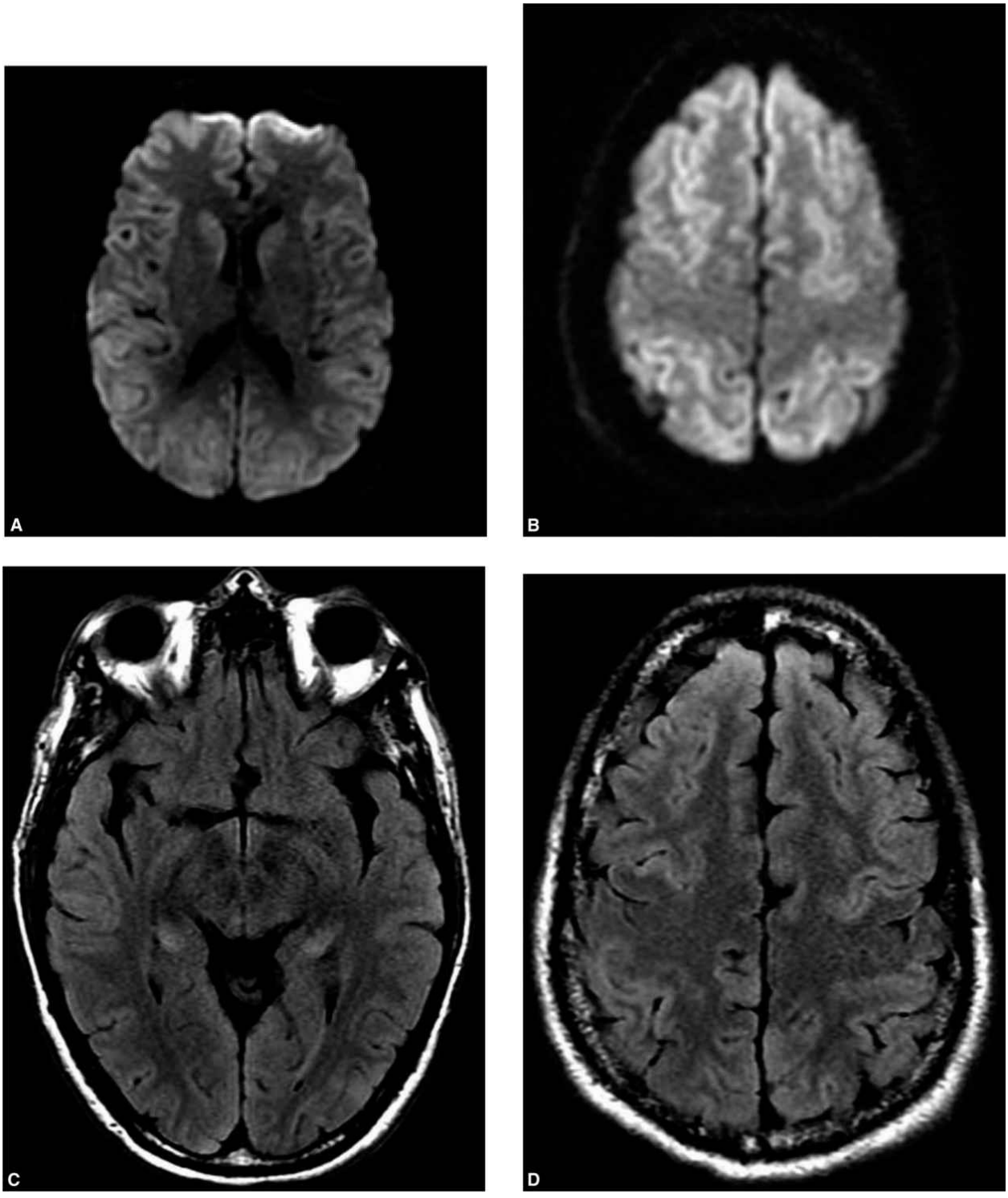

FIGURE 46.4 A, B, Axial diffusion-weighted images of the brain in a patient 5 days after an out-of-hospital asystolic cardiac arrest. There is restricted diffusion throughout the cortical ribbon. C, D, Axial FLAIR images of the brain. There is FLAIR signal hyperintensity throughout the cortical ribbon, and especially prominent in the lateral temporal lobes, occipital lobes, and frontal lobes. The total cortex score for this patient was 27, consistent with a poor neurologic prognosis.[5]

Seizures and nonconvulsive status epilepticus are common in the setting of HIE, occurring in approximately 20% of patients. Continuous EEG should be considered for all patients and started as soon as possible on any patient with myoclonus or suspicion for ongoing seizure.

Finally, somatosensory evoked potentials (SSEPs), where available, are a useful prognostic tool. Traditionally, absence of the N20 cortical responses bilaterally after median nerve stimulation prognosticates a poor neurologic outcome with a 0% false negative rate. The lack of bilateral cortical SSEP responses in patients after hypothermia continues to be highly predictive of a poor neurologic outcome. SSEPs can be performed as soon as 24 hours after cardiac arrest.[6]

TREATMENT

The only therapy shown to improve mortality and neurologic outcomes for patients with coma after cardiac arrest is targeted temperature management (TTM; hypothermia). The landmark hypothermia trials were published in the New England Journal of Medicine in 2002.[7] These studies evaluated patients after out-of-hospital ventricular fibrillation or ventricular tachycardia cardiac arrest. Hypothermia at a depth of 32°C to 34°C was started post arrest and maintained for 12 to 24 hours. The hypothermia group had a 20% absolute increase in survival and good neurologic outcome. However, in these studies, the patients in the standard therapy arm had fever to approximately 38°C. In 2013, the TTM study[8] demonstrated no differences in mortality or neurologic outcomes with the temperatures post cardiac arrest actively controlled at either 33°C or 36°C. The American Heart Association guidelines[9] now recommend using TTM for all cardiac arrest patients with coma after ROSC, at a constant temperature goal chosen between 32°C and 36°C, and maintained for at least 24 hours.

Only core temperatures should be used during hypothermia or TTM. Rectal, bladder (urinary catheter), or esophageal probes provide reliable and continuous temperature measurement. Temperature can be controlled in many ways. Simple methods include ice packs to the groin, axilla, and around the neck; rapid infusions of 4°C cold saline (useful for induction); cooling blankets; and fans. Most temperature-regulating technologies use feedback mechanisms that continuously measure the body’s core temperature and automatically adjust the amount of cooling by the device to maintain a consistent body temperature.

Examples include body-wrapping pads through which cold water circulates to cool the skin, central venous catheters through which cold water circulates in a closed loop and cools the surrounding venous blood as it passes, and esophageal probes with internally circulating cold water that cools the core via surrounding soft tissues.

There are no randomized controlled trial data on blood pressure management. Hypotension can worsen cerebral perfusion and observational data suggests worse outcomes with hypotension. Significant hypertension could be associated with cerebral edema if cerebral autoregulation is impaired. Overall, hypotension should be aggressively treated to maintain systolic blood pressure ≥90 mm Hg and mean arterial pressure ≥65–80 mm Hg.[9]

Any patient with suspicion for seizure should be treated with a stable continuous infusion of benzodiazepines (such as midazolam at a starting dose of 0.05 to 0.1 mg/kg/h) or propofol, and an EEG ordered as soon as feasible. Until the EEG interpretation is obtained, the goal of treatment should be suppression of the abnormal movements, including subtler movements such as nystagmus or eye or facial twitching. Whether or not to start a nonsedating antiepileptic drug such as levetiracetam, phenytoin, or valproic acid depends on the clinical suspicion for seizure and/or nonconvulsive status epilepticus as a cause for the abnormal movements. Seizure-like activity at ictus of the cardiac arrest is not necessarily indicative of ongoing seizure activity or of primary seizure as the cause of the arrest; it can occur due to cerebral ischemia during the no-flow or low-flow period.

Prognosis in Hypoxic Ischemic Encephalopathy

Prognostication of neurologic outcome is based on a collection of physical examination findings and diagnostic tests. In the prehypothermia era, and today in patients who have not received hypothermia, the physical examination can be used to guide prognosis between 24 and 72 hours. Patients who have received hypothermia may continue to have an improving motor response for up to 7 days post arrest. The reason may be related to increase in sedation given during the hypothermia protocol, slowed metabolism of sedation during hypothermia, and actual delay in the recovery of the brain due to slowed metabolic processes during hypothermia.

In patients who did not receive hypothermia, any one of the following findings traditionally predicts poor neurologic prognosis: lack of pupillary responses at days 1 to 3 post arrest, lack of corneal reflexes at days 1 to 3 post

arrest, NSE > 33 μg/L, lack of bilateral cortical responses on SSEPs on day 1 or later, myoclonic status epilepticus, or no motor response better than extension posturing at 3 days post arrest. The lack of these findings does not ensure a good prognosis but makes the prognosis indeterminate. A poor prognosis is defined as one of severe neurologic disability, where the patient has limited understanding or consciousness and requires long-term, full nursing care.[10]

In patients who did receive hypothermia, at least 7 days should be given for the motor examination to be used in prognostication.[6] The motor response in the neurologic examination is done without sedation or paralytics and is best described in terms of the Glasgow Coma Score. The arm movements are more reliable than the leg movements, as triple flexion in the legs can mimic withdrawal. The possible arm motor responses are as follows:

- No response/no movement;
- Extensor posturing (internal rotation of the arms with extension at the elbow, pronation of the forearm, and adduction at the shoulder, and may include extension and internal rotation of the legs simultaneously);
- Flexor posturing (a stereotyped movement of flexion at the elbows, wrists, and fingers, and may include extension and internal rotation of the legs simultaneously);
- Withdrawal (purposeful pulling away from noxious stimuli in a nonstereotyped manner);
- Localizing (reaching to a noxious stimuli at or across the midline, ie to take the examiner’s hand away from a sternal rub or endotracheal suctioning);
- Following commands.

A poor neurologic prognosis can be expected if the motor response is not better than extension 7 days post cardiac arrest. Take care not to attribute purposeful intent to stereotyped movements, because this may confuse both the care team and the family, and lead to additional difficulty with discussions regarding prognosis. As patients emerge from coma, movements are often small and difficult to classify. One approach is to undercall the examination so as not to build up false hope (in other words, if the movement is so small that one cannot distinguish between flexion posturing and withdrawal, call it flexion posturing initially). Serial neurologic examinations unobscured by sedation and tincture of time will clarify the true examination. The statement that any patient who has been comatose is now following commands should be taken with the

utmost seriousness; following commands implies that there is a clear and reproducible motor response to a verbal command. Generally, squeezing hands should be avoided as a command to follow due to potential confusion from a grasp reflex. Useful verbal commands for examining intubated and previously comatose patients include, “Close your eyes” followed by “Open your eyes,” “Stick out your tongue,” “Hold up two fingers,” “Hold up your thumb,” or “Wiggle your toes.”

Continuous EEG and noncontrast brain MRI are two modalities of current interest to assist in prognostication. EEG patterns associated with poor neurologic outcomes after cardiac arrest include spontaneous burst suppression, status epilepticus, and an EEG without change in the background to alerting maneuvers (also known as a “nonreactive” EEG background). MRI was previously discussed in this chapter.

Some patients will progress to brain death due to the severity of the initial hypoxic ischemic injury or from herniation due to cerebral edema. Clues that the patient may have progressed or be progressing to brain death include poikilothermia and diabetes insipidus (DI). Consider DI if the urine output is greater than 300 mL/h for more than 2 consecutive hours, or with high volume urine output with hypernatremia. It is important to continue aggressive critical care and maintain metabolic homeostasis as a brain-dead patient may be an organ donor candidate. Blood pressure should be supported, generally targeting a mean arterial pressure of 65 mm Hg or greater, using fluids or pressors as needed. If there is a high volume of urine output, consider desmopressin acetate IV or vasopressin infusion, titrating to a urine output of 75 to 150 mL/h. The goal is euvolemia. Hypernatremia should be corrected with half-normal saline or D5W, as appropriate. Warming blankets may be needed. Antibiotics for intercurrent infections should be continued.

ACUTE ISCHEMIC STROKE

Acute ischemic stroke can occur in patients already admitted to the CCU from a number of causes: atrial fibrillation, systolic heart failure with left ventricular thrombus, endocarditis, prosthetic cardiac valves, aortic dissection, ventricular assist devices, or postcardiac catheterization. Patients admitted to the CCU often have comorbid conditions that predispose them to stroke, such as diabetes, hypertension, hyperlipidemia, and atrial fibrillation. Other risk factors for in-

hospital strokes are vascular procedures or endovascular procedures (such as cardiac catheterization), active cancer causing hypercoagulable state, or withholding of anticoagulation.

RECOGNITION OF ACUTE ISCHEMIC STROKE

With in-hospital stroke, one major barrier to timely acute treatment is recognition by the staff of an acute stroke in the patient. Time to intravenous tissue plasminogen activator (IV tPA), the medical "clot-busting" therapy for acute stroke, with in-hospital patients has been shown to be significantly longer than for those patients admitted with acute ischemic stroke through the emergency room.[11] Reasons for this delay include lack of understanding regarding the urgency of the situation, personnel and treating teams not familiar with the protocol because it is not a part of their routine practice, retrieval of tPA itself from the inpatient pharmacy, and increased transport time to CT.

First, determine that the patient clinically seems to be having a stroke. Vital signs should be checked with particular attention to blood pressure; hypertension of greater than 185/110 mm Hg should be immediately treated with a short-acting intravenous medication to a goal of < 185/110 mm Hg. A fingerstick glucose should be obtained to rule out hypoglycemia or hyperglycemia as the cause for the neurologic deficit. Hypoxia with an oxygen saturation < 94% should be treated with supplemental oxygen. Labs should be drawn and sent stat for chemistry, complete blood count (CBC), prothrombin time (PT)/international normalized ratio (INR), partial thromboplastin time (PTT). A brief neurologic examination, often the National Institutes of Health Stroke Scale (NIHSS, **Table 46.5**), is then performed to define presence and extent of deficits. Always score what the patient *actually* does, not what you *think* they can do. An NIHSS ≥ 8 has a strong predictive value for LVO, which may be amenable to endovascular therapy.

TABLE 46.5 A Summary of the National Institutes of Health Stroke Scale (NIHSS)

ITEM	POINTS ON NIHSS			
1: Level of consciousness				
1A: Alertness	0—alert	1—not alert, arousable by minor	2—not alert, repeated stimulation to attend, or	3—only reflexive movements, or completely unresponsive

		stimuli	obtunded		
1B: Month and age	0—both questions correct	1—one correct	2—none correct		
1C: Simple commands: open and close eyes, make a fist and release	0—does both correctly, or mimics both correctly	1—follows one command	2—no commands		
2: Best gaze—look to both sides	0—normal	1—partial gaze palsy	2—forced deviation		
3: Visual fields	0—normal	1—partial hemianopia or extinction	2—complete hemianopia	3—blind	
4: Facial palsy	0—normal	1—minor paralysis	2—partial paralysis (upper motor neuron facial weakness pattern)	3—complete paralysis (lower motor neuron facial weakness pattern) on one or both sides	
5: Motor arm 5A: left 5B: right	0—no drift	1—drifts down in 10 s but does not hit bed	2—drifts down and hits bed within 10 s	3—no effort against gravity	4—no movement
6: Motor leg 6A: left 6B: right	0—no drift	1—drifts down in 5 s but does not hit bed	2—drifts down and hits bed within 5 s	3—no effort against gravity	4—no movement
7: Ataxia	0—absent	1—one limb	2—two limbs		
8: Sensory (pinprick testing)	0—normal	1—some sensory loss	2—severe or total sensory loss		
9: Language	0—normal	1—mild to moderate aphasia	2—severe aphasia	3—global aphasia or mute	
10: Dysarthria	0—normal	1—mild to moderate	2—severe or mute		
11: Extinction and Inattention: sensory or visual extinction	0—normal	1—extinction or inattention in 1 modality	2—profound hemi-inattention or deficits in more than 1 modality		

In order to determine if the patient is a candidate for IV tPA, the last known normal time must be clearly defined. This may be different from the time of discovery. For example, if the patient went to sleep and woke up with a hemiplegia, then the last known normal time is the time of sleep onset. IV tPA may be given in ischemic strokes where the last known normal time is within 3 hours,[12] or within 4.5 hours with additional contraindications.[13]

INITIAL WORKUP AND TREATMENT

After establishing that there is a new neurologic deficit, checking vital signs and glucose, and drawing appropriate labs, the patient should be taken emergently for a noncontrasted CT of the brain and a CTA of the head and neck (**Figures 46.5 and 46.6**). A CTA of the head and neck should be done with any patient with a NIHSS ≥ 8 or cortical signs or symptoms. In the setting of an acute stroke, CTA (which uses iodinated contrast) can and should be performed without regard to the patient's creatinine, because studies have shown the risk of acute kidney injury due to contrast in this setting to be small, and in some studies, no different than patients who did not receive a CTA.[14] A neurologist or neuroradiologist should immediately review and interpret the noncontrast head CT for contraindications for IV tPA therapy, and the CTA of the head and neck for indications that intraarterial (IA) therapy is indicated (mainly LVO).

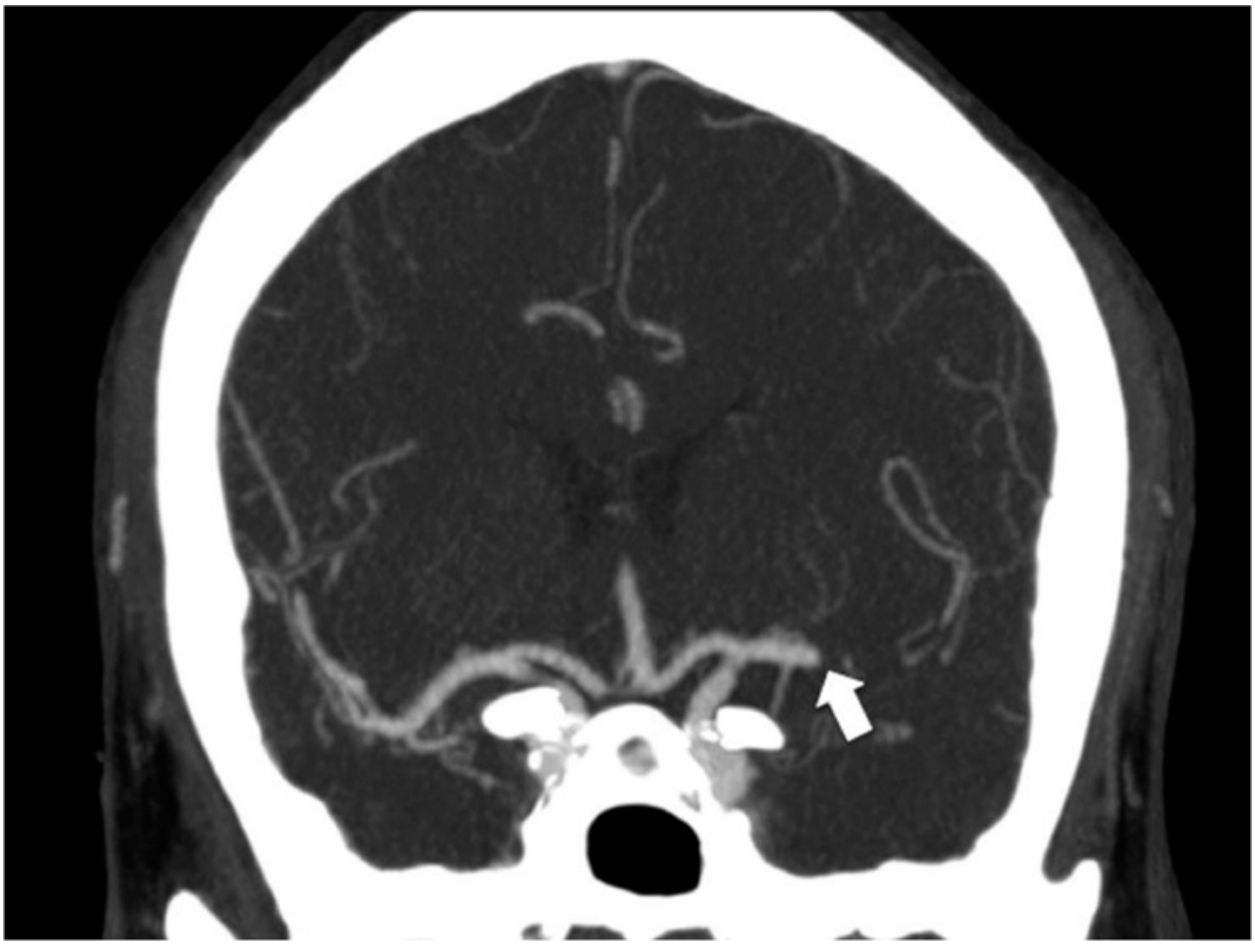

FIGURE 46.5 Coronal image of CTA of the head demonstrating an M1 segment occlusion of the left middle cerebral artery caused by thromboembolism. This type of lesion may be amenable to endovascular therapy. CTA, computed tomography angiogram

For patients with an acute ischemic stroke who qualify for IV tPA (**Tables 46.6 and 46.7**), it should be given as soon as possible, because there is an inverse relationship between benefit from tPA and time to administration. IV tPA is given at a dose of 0.9 mg/kg, with a maximum dose of 90 mg.[13] The first 10% is given as an IV bolus over 1 minute, and the additional 90% as an infusion over 1 hour. Blood pressure should be closely monitored and maintained at less than 185/110 mm Hg during the infusion. Neurologic checks should be performed to look for significant improvement or worsening. If the patient worsens during or after the infusion, any remaining tPA should be held and a stat noncontrast head CT obtained to rule out intracranial hemorrhage. Once tPA is given, generally no antiplatelet or anticoagulant therapy should be used for 24 hours. Blood pressures are maintained at less than 180/105 mm Hg. All patients are made nothing per oral at the time of an acute stroke, until they have a bedside swallow

evaluation or a formal speech therapy evaluation.

TABLE 46.6 IV tPA Inclusion Criteria

Acute ischemic stroke causing new significant neurologic deficits
Time within 3–4.5 hours of onset (last known normal time)
Blood pressure < 185/110 mm Hg

IV tPA, intravenous tissue plasminogen activator.

TABLE 46.7 Contraindications for IV tPA

CONTRAINDICATIONS FOR IV TPA WITHIN 3 H OF ONSET	ADDITIONAL CONTRAINDICATIONS FOR IV TPA WITHIN 3–4.5 H OF ONSET
Intracranial hemorrhage on noncontrast CT[a]	
CT with well-established acute or subacute infarctM[a]	
CT showing infarct greater than 1/3 the size of the MCA territory[a]	
Active bleeding or major acute trauma[a]	
Resolved neurologic symptoms[a]	
Rapidly improving neurologic symptoms	
Minor or nondisabling neurologic symptoms	
Suspected subarachnoid hemorrhage[a]	
Major head trauma or stroke within the last 3 mo	Age > 80 y
Myocardial infarction in the last 3 mo	Anticoagulant use, regardless of INR
Genitourinary or gastrointestinal hemorrhage in the last 21 d	NIHSS ≤ 25
Major surgery in the last 14 d	History of both previous stroke and diabetes
Arterial puncture at a noncompressible site or lumbar puncture in the last 7 d	
History of previous ICH	
If on oral anticoagulants, INR > 1.7	
If on heparin in the last 48 h, elevated PTT	
Receiving DOACs within 24–48 h	
Platelets < 100,000	
Blood glucose < 50 mg/dL	
Seizure at symptom onset	

[a]Absolute contraindications. CT, computed tomography; ICH, intracerebral hemorrhage; IV tPA, intravenous tissue plasminogen activator; INR, international normalized ratio; NIHSS, National Institutes of Health Strokes Scale. MCA, middle cerebral artery; DOACs, direct oral anticoagulants.

There has been a recent revolution in acute stroke treatment, as multiple randomized controlled trials published in the last 2 years have definitively proven the benefit of IA clot extraction techniques for acute strokes caused by LVOs. Pooled analysis of the six trials showed that good outcomes at 90 days increased in the intervention arm from 26% to 47% and mortality decreased from 18% to 8%.[15] Endovascular or IA therapy, combined with IV tPA when appropriate, is definitively superior to IV tPA alone for ischemic strokes due to

LVO. The fastest and least invasive way to diagnose an LVO is with a CTA of the head and neck (**Figures 46.5 and 46.6**). For this reason, all patients with suspected acute stroke should get a CTA of the head and neck at the time of the initial noncontrast head CT.

B

A

C

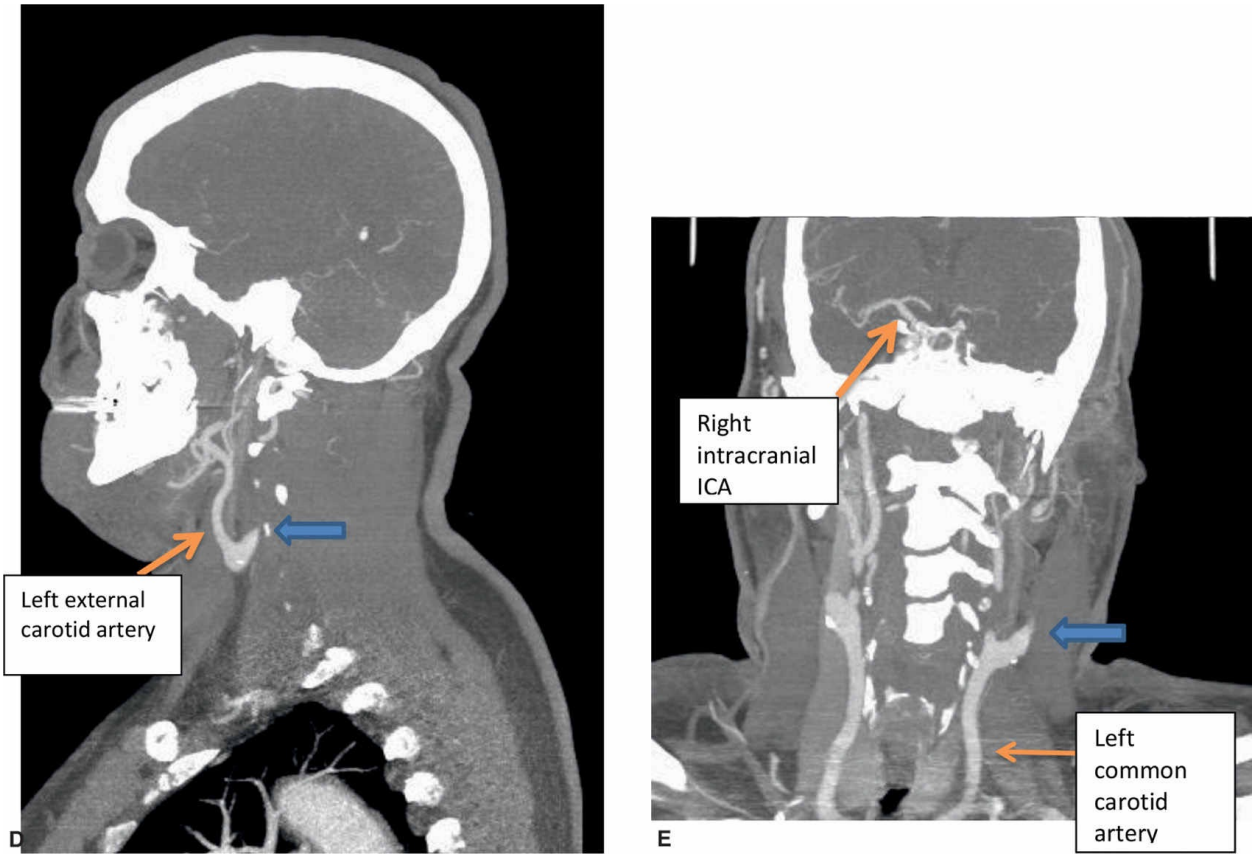

FIGURE 46.6 A-C, Initial, normal, non-contrasted head CT in a patient with an acute left internal carotid artery occlusion leading to a left middle cerebral artery syndrome (aphasia and right hemiplegia). The images were obtained 49 minutes after the onset of symptoms. D-E, MIPs from the CTA of the head and neck. Panel D is a sagittal MIP image at the level of the left internal carotid artery. There is no flow distally in the left internal carotid artery after this flame-shaped cutoff (large blue arrow). Panel E is a coronal MIP image showing occlusion of the cervical left internal carotid artery and the subsequent lack of opacification of the intracranial left internal carotid artery, middle cerebral artery, and anterior cerebral artery. The few vessels visualized in the left hemisphere appear to have been collateral flow from the anterior communicating artery or from meningeal collaterals. The patient was given IV tPA 153 minutes after the onset of symptoms. He underwent emergent revascularization of the left internal carotid and middle cerebral arteries. His initial NIHSS was 20; it improved to 5 by acute hospital discharge.

For most patients with acute stroke, 162 to 325 mg of aspirin is appropriate secondary stroke prevention in the acute setting. Aspirin can be started immediately if the patient is not an IV tPA candidate; it may be given per rectum or via nasogastric tube if the patient has dysphagia. Some patients will have indications for anticoagulation for secondary stroke prevention, the most common being atrial fibrillation. When the cohort of all ischemic stroke patients is analyzed, no benefit of IV heparin is seen acutely because the risk of serious harmful effects such as intracranial hemorrhage equals the benefit of additional decrease in thromboembolic events. Instead, patients who have an indication for

anticoagulation will often be bridged to warfarin with aspirin, or the initiation of new oral anticoagulants (NOACs) delayed until safe. The timing of anticoagulation initiation is an art dependent upon the size of the stroke, any hemorrhagic transformation, and the indication for anticoagulation. High dose statins should be used for all patients with low density lipoprotein (LDL) >100, unless a clear contraindications exists. Chemical deep vein thrombosis prophylaxis can be started 24 hours after tPA, or on admission if the patient did not receive tPA. Further workup and treatment of any particular stroke is beyond the scope of this chapter.

INTRACRANIAL HEMORRHAGE

Intracranial hemorrhage is classified based on the hemorrhage's location in relationship to the brain parenchyma: epidural hemorrhage is between the dura and inner table of the skull, subdural hemorrhage (SDH) is beneath the dura and above the arachnoid mater, subarachnoid hemorrhage is between the arachnoid mater and the pia mater, and intracerebral hemorrhage (ICH) is within the substance of the brain. In the absence of trauma, the common use of anticoagulants in the CCU predisposes patients to SDH or ICH.

ICH presents in a similar manner to acute ischemic stroke, with focal neurologic deficits. Headache is a common prominent symptom. If the hemorrhage is large and causing intracranial hypertension or intraventricular hemorrhage with hydrocephalus, there may also be hypertension, lethargy, nausea, or vomiting. The diagnosis of ICH is made by noncontrast head CT (**Figures 46.7 and 46.8**), where acute blood is hyperdense and seen inside the brain parenchyma. A CTA of the head and neck may still be appropriate in the initial workup, depending on the size, location, and clinical characteristics of the patient, to look for an underlying vascular malformation or the presence of a "spot sign," which can predict early hemorrhage expansion.

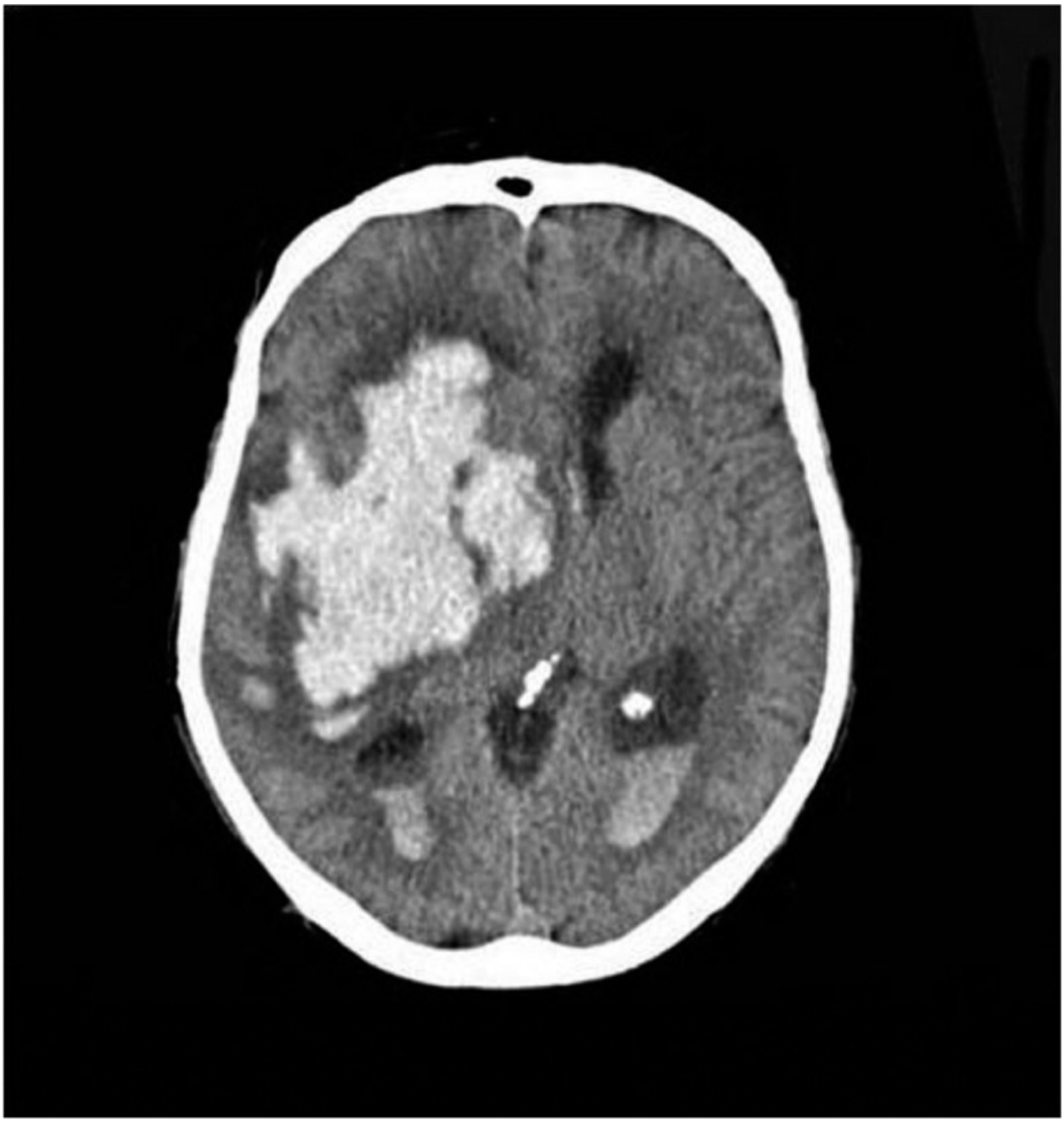

FIGURE 46.7 Large right basal ganglia intracerebral hemorrhage with intraventricular extension, hydrocephalus, and midline shift.

FIGURE 46.8 This axial noncontrasted head CT shows an acute right frontal intracerebral hemorrhage. CTA of the head was negative for any vascular pathology. The patient had uncontrolled hypertension and aspirin use as risk factors. He presented with acute left flaccid hemiplegia. CTA, computed tomography angiogram.

Initial workup and treatment for ICH parallels that of acute ischemic stroke.

Always remember to first evaluate the ABCs - airway, breathing, and circulation. A common cause of intubation in patients with acute neurologic injury is obtundation and inability to adequately maintain a patent airway and ventilation. Vital signs should be monitored every 5 to 15 minutes acutely, and once the patient is stabilized every 1 hour or as per ICU protocol. Generally in ICH, targeting the systolic blood pressure (SBP) to less than 140 mm Hg is thought to be safe and may improve functional outcomes.[16] Glucose should be normalized.

As in acute ischemic stroke, when the patient is being initially assessed, laboratory studies should be sent stat for chemistry, CBC, PT, and PTT. An arterial blood gas is indicated if the patient is obtunded or was recently intubated. Hypercarbia and hypoxia can exacerbate intracranial hypertension and so should be aggressively corrected.

The size and morphology of any intracranial hemorrhage is evaluated by noncontrast CT scan of the brain. For subdural hematomas, measure the maximum width of the hematoma, as well as any midline shift. For intraparenchymal hematomas, the size of the hemorrhage can be calculated by using measurements from the CT scan, using the ABC/2 formula:

$$\text{Volume of intraparenchymal hematoma (in cm}^3\text{ or mL)} = A \times B \times C/2$$

where A = maximum hematoma width in cm; B = maximum hematoma length perpendicular to A in cm; C = height in cm (number of [0.5 cm] CT cuts the hemorrhage is seen on)/2

Hematoma volume is directly related to outcome. Look for intraventricular hemorrhage, midline shift, uncal herniation, or crowding of the basal cisterns because these can cause rapid neurologic deterioration requiring life-saving interventions such as external ventricular drains (EVDs), emergency hematoma evacuation, or hyperosmotic therapy. The ICH score (**Table 46.8**) is a useful prognostic tool that may help in medical decision making.[17]

TABLE 46.8 The ICH Score

	POINTS
Glasgow Coma Score: 13–15 5–12 3–4	0 1 2
ICH volume: < 30 mL ≥ 30 mL	0 1

IVH: no Yes	0 1
Infratentorial location: no Yes	0 1
Age: < 80 y ≥ 80 y	0 1

The ICH score predicts historic mortality in ICH.
0 = 0%, 1 = 13%, 2 = 26%, 3 = 72%, 4 = 97%, 5 = 100%.
ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.

TREATMENT OF INTRACRANIAL HEMORRHAGE

Reversal of Coagulopathies

The most common coagulopathies in the CCU are from medications. Medications that can cause or contribute to pathologic bleeding include heparin, low-molecular-weight heparins such as enoxaparin, warfarin, NOACs, aspirin, and other antiplatelet agents. Other causes of coagulopathy should also be considered, such as uremia and failure of synthetic liver function. We now review the reversal of common medication-induced coagulopathies[18] (**Table 46.9**).

TABLE 46.9 Anticoagulants and Their Reversal Agents

Heparin	Protamine Maximum dose 50 mg, maximum infusion rate 5 mg/min Based on the units of heparin in the previous 2 to 3 h Time since heparin: 0 to 30 min: 1 mg protamine IV/100 units heparin 31 to 60 min: 0.75 mg protamine/100 units heparin 61 to 120 min: 0.5 mg protamine/100 units heparin >120 min: 0.4 mg protamine/100 units heparin	Immediate reversal Monitor for anaphylaxis, hypotension
Low-molecular-weight heparins	Protamine Time since enoxaparin: Less than 8 h: 1 mg protamine per 1 mg enoxaparin Greater than 8 h: 0.5 mg protamine per 1 mg enoxaparin Dalteparin: 1 mg protamine per each 100 units of dalteparin	Reverses 60%–75%
Warfarin	Vitamin K 10 mg IV PCCs OR fresh frozen plasma	May need repeated doses over hours to days
Dabigatran (Pradaxa)	Idarucizumab (Praxbind) 5 mg IV	
	PCC 50 IU/kg (Pending FDA Approval)	

Factor Xa inhibitors Rivaroxaban (Xarelto) Apixaban (Eliquis)	Andexanet IV bolus over 15–30 min, then 2 h infusion If factor Xa inhibitor taken > 7 h ago: 400 mg bolus, 480 mg infusion If factor Xa inhibitor taken ≤ 7 h ago, or unknown: 800 mg bolus, 960 mg infusion	Andexanet is pending FDA approval.
Antiplatelet agents	DDAVP 0.3 μg/kg IV once Platelet transfusion (one apheresis unit) only if neurosurgical intervention	

IV, intravenous; FDA, US food and drug administration; PCC, prothrombin complex concentrates.

Heparin is used for a wide variety of indications in the CCU, including acute myocardial infarction, stroke prevention in atrial fibrillation, deep vein thrombosis, and left ventricular thrombus. If a patient has sudden focal neurologic deficits, any anticoagulant drip or medication should be held and a stat PT/PTT drawn. A noncontrast head CT should be obtained emergently. If an ischemic stroke without hemorrhagic transformation is discovered, no emergency reversal is necessary: whether to continue heparin would be based on a patient's specific case. If the patient has an intracranial hemorrhage and the PTT is elevated from heparin, then protamine should be given. Protamine dosing is based on the amount of heparin given and the time since the last administration of heparin. Patients are monitored for hypotension or anaphylaxis, and epinephrine should be available. Low molecular weight heparins can be reversed 60% to 75% with protamine. The factor Xa inhibitor reversal agent (andexanet alfa) being developed may play a future role in reversal of low-molecular-weight heparins.

Patients receiving warfarin and with an elevated INR should be immediately reversed, because hematoma expansion can continue for up to 72 hours in patients with vitamin K antagonist use. There are three steps to reversal of warfarin: discontinuation of warfarin, administration of vitamin K, and immediate replacement of coagulation factors with prothrombin complex concentrates (PCCs) or fresh frozen plasma (FFP). Vitamin K should be given at a dose of 10 mg IV over 10 minutes. PCCs have come into favor over FFP for immediate coagulation factor replacement. PCCs have either three factors (II, IX, and X) or four factors (II, VII, IX, and X). The United States has three brands approved by the FDA: Bebulin, Profilnine SD, and Kcentra. PCCs have the following advantages over FFP: takes no time to thaw, short preparation time, significantly lower infusion volume, rapid INR reversal, and lower risk infection. Dosing is based on both body weight and INR (**Table 46.10**). The

PT/INR should be repeated 1 hour after the PCC dosing, and if it remains elevated, then PCC can be redosed. If PCC is not available, then FFP may be given at a dose of 15 mL/kg IV. Recombinant factor VIIa had previously been used and studied for the reversal of warfarin-associated coagulopathy, but it only replaces one of the factors depleted by warfarin use. With the approval of 4-factor PCC/Kcentra in the United States and high rate of thromboembolism, recombinant factor VIIa has fallen out of favor.[19]

TABLE 46.10 4-Factor Prothrombin Complex Concentrate (Kcentra) Dosing

PRETREATMENT INR	DOSE (units/kg)	MAXIMUM DOSE (units)
2–4	25	2500
4–6	35	3500
>6	50	5000

INR, international normalized ratio.

The only new oral anticoagulant agent currently with an antidote is the direct thrombin inhibitor dabigatran (Pradaxa). Idarucizumab (Praxbind) is a monoclonal antibody fragment that specifically binds dabigatran. A total of 5 mg IV is given in two doses of 2.5 mg IV no more than 15 minutes apart. Idarucizumab quickly and completely reverses the effects of dabigatran.[20] If dabigatran was taken in the preceding 2 hours, also give 50 g activated charcoal.

The oral factor Xa inhibitors currently approved by FDA in the United States and in common use are rivaroxaban (Xarelto) and apixaban (Eliquis). Andexanet alfa was developed as an antidote to the factor Xa inhibitors, and is currently pending FDA approval. With major bleeding, good or excellent clinical hemostasis is achieved in approximately 80% of patients. It should be noted that there is an 18% rate of thrombotic events at 30 days with patients who received the drug.[21] Until andexanet alfa is available, PCCs at a dose of 50 U/kg should be strongly considered because this reverses laboratory abnormalities from rivaroxaban in nonbleeding humans.[22] If a direct factor Xa inhibitor was ingested in the preceding 2 hours, then 50 g of activated charcoal should be given.

Finally, many patients in the CCU are on antiplatelet agents. Traditionally, patients on aspirin, clopidogrel, or other antiplatelet agents were given DDAVP

0.3 μg/kg IV once (maximum dose of 20 μg) and transfused with platelets, despite lack of evidence supporting transfusion. A recent randomized trial showed that platelet transfusion in the setting of spontaneous ICH was potentially harmful, with the group receiving platelets having a statistically significant higher rate of disability than the group who did not receive platelets, and a trend toward higher mortality.[23] This study excluded patients who required neurosurgical intervention. One randomized study of patients undergoing craniectomy for hematoma evacuation after ICH showed a benefit of platelet transfusion in postoperative hemorrhage rate and volume, and in mortality, in those patients who showed aspirin-sensitivity on a platelet aggregation test.[24] Patients with thrombocytopenia and intracranial hemorrhage should be transfused platelets for a goal of greater than 70,000.

An excellent and complete review of reversal of all antithrombotic agents in the setting of intracranial hemorrhage was published in Neurocritical Care in 2016.[18]

Blood Pressure Control

Uncontrolled hypertension is a risk factor for ICH itself and for greater hematoma expansion, neurologic deterioration, dependency, and death. Current 2015 American Heart Association/American Stroke Association guidelines recommend reducing the SBP to < 140 mm Hg if the initial SBP was 150 to 220 mm Hg. This seems to be a safe target blood pressure, and may improve functional outcomes.[16] If the SBP is higher than 220 mm Hg on presentation, the goal may be adjusted. No particular agent is advantageous, although short-acting and titratable agents such as labetalol, nicardipine, or clevidipine are useful. Nitroprusside should be avoided due to a theoretical risk of increasing intracranial pressure.

Neurosurgical Intervention

Some intracranial hemorrhages may need neurosurgical intervention. Generally, symptomatic acute SDHs with mass effect or shift are evacuated. For ICH, evacuation is considered if the hematoma is large (greater than 30 mL), cortical, cerebellar, or the patient is young. New minimally invasive clot removal techniques have shown great promise, and some have even shown improvement in neurologic outcomes over medical controls. Suboccipital craniectomy is a life-saving procedure with cerebellar hemorrhages that have mass effect onto the

brainstem or cause hydrocephalus. Finally, EVD placement may be needed if the patient has hydrocephalus or is somnolent, as a way to measure and treat intracranial pressure. Ultimately, an expert in neurology, stroke, or neurosurgery should be involved early in the care of patients with ICH to guide treatment, including invasive measures.

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Patient and Family Information for: STROKES

WHAT IS A STROKE?

A stroke occurs when there is sudden interruption of blood flow to a specific part of the brain. When this happens, those brain cells do not get enough blood. Blood carries oxygen. All cells need oxygen to live.

TYPES OF STROKE

There are two kinds of strokes: ischemic and hemorrhagic. An ***ischemic stroke*** is a “nonbleeding stroke” that happens when a blood vessel leading to the brain becomes blocked. This keeps the brain cells in that area from receiving blood and oxygen. A ***hemorrhagic stroke*** is a “bleeding stroke” that happens when a blood vessel in or near the brain bursts. The blood is released into the brain itself or into the space between the brain and the skull. The blood then presses on and irritates the surrounding brain and keeps the cells around it from working properly.

SYMPTOMS OF A STROKE

- Sudden numbness or weakness of the face, arm, or leg, especially on one side of the body;
- Sudden confusion, trouble speaking, or trouble understanding;
- Sudden trouble seeing in one or both eyes;
- Sudden trouble walking, dizziness, loss of balance, or loss of coordination;

- Sudden severe headache with no known cause.

If you experience any of these symptoms, **CALL 911 IMMEDIATELY.** Stroke is an emergency. Do not delay. Early treatment may be able to prevent or limit permanent disability or even death.

TESTS

These tests are done to see the location of the stroke and find out its type and cause:

- **CT scan:** This is a type of X ray that takes pictures of your brain. It shows if the stroke is ischemic or hemorrhagic.
- **CTA:** This is a special CT with dye given to light up the blood vessels going to the brain. The purpose is to show a blocked blood vessel that could possibly be opened up to make the stroke better. It can also show other abnormal blood vessels such as those that cause bleeding strokes.
- **MRI:** This test uses a giant magnet instead of X rays to take pictures of the brain. The pictures have more detail than a CT scan. Because the machine is narrow and loud, some patients get nervous and may need medicine to help relax. Patients with permanent pacemakers or implanted defibrillators often cannot have MRIs. Other metal in the body may or may not be safe for MRI. You will fill out a form to see if it is safe for you to have an MRI.
- **Magnetic resonance angiography (MRA):** This takes a picture of the blood vessels with the MRI. An MRA does not usually need dye.
- **Carotid Doppler:** This test uses sound waves (ultrasound) to make pictures of the blood vessels in the front of the neck that go to the brain.
- **Transesophageal echocardiogram (TEE):** For this test, the patient is given some medicine to help relax. The patient then swallows a small tube. The tube uses sound waves to make pictures of the heart and large blood vessels around the heart. This can show if there is a blood clot in the heart, a hole in the heart, or large plaque in the blood vessel just outside the heart. These types of problems can cause a stroke.

MEDICATIONS

Most people who have a stroke need several medicines. These medicines decrease the risk of having another stroke.

- Antiplatelet medications such as aspirin, clopidogrel (Plavix), and dipyridamole with aspirin (Aggrenox) are used to prevent new ischemic strokes in many patients.
- Anticoagulants are blood thinners. These are stronger than the antiplatelet drugs and are used to prevent new ischemic strokes from specific conditions like atrial fibrillation. There are now many anticoagulants, including warfarin (Coumadin), dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis). The choice of medicine is based on your body and the specific reason you need blood thinners.
- Statin medications such as simvastatin (Zocor) or atorvastatin (Lipitor) lower the cholesterol level. They can help cholesterol plaques to become smaller and smoother. This makes the plaque less likely to cause a stroke.
- Keeping a normal blood pressure with blood pressure medicines helps to prevent new strokes.

REHABILITATION

Patients usually need rehabilitation after a stroke. Rehabilitation or “rehab” involves physical therapy, occupational therapy, and/or speech therapy. There are several types of rehabilitation programs.

- **Acute rehabilitation:** This is an intensive inpatient program (in a hospital or rehab center). Every patient must be able to do at least 3 hours per day of therapy. A patient can stay here a few weeks to a few months before returning home.
- **Skilled nursing facility with rehabilitation:** In this type of program, a patient participates in therapy for 1 to 2 hours per day. The patient can stay at this facility for several months. The patient then returns home or goes to a long-term care facility.
- **Outpatient rehabilitation center:** Here, the patient comes from home for therapy. Usually it is about 1 hour of therapy, three times per week. The patient then goes back home.
- **Home rehabilitation:** This is for patients who are unable to go from their

homes to an outpatient rehabilitation center. Therapy is provided in the patient’s home 2 or 3 times per week.

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Gastrointestinal Emergencies in the Cardiac Care Unit

INTRODUCTION

Gastrointestinal (GI) consultation for patients in the Cardiac care unit (CCU) is common in modern inpatient medicine. GI bleeding, anemia, abdominal pain, abdominal distention, nausea and vomiting, and abnormal liver function tests all occur in patients with serious cardiac diseases.

Preparation for writing this chapter began with a review of cardiology textbooks, including old texts, plus the modern GI and cardiac literature. There is not a large literature on GI emergencies in the CCU. The older literature that exists largely focuses on surgery and the cardiologist's role. Little information is given about the nature of GI complications themselves, which confounds planning.

This chapter aims to review the general principles of evaluation and management of patients with serious cardiac disease from the GI perspective, as well as the common reasons for GI consultation, using case material from our institution. The impact of anticoagulation and antiplatelet therapies on management are analyzed in detail. The safety of GI procedures in cardiac patients is also discussed.

GENERAL PRINCIPLES

Charles Friedberg captured the essence of the gastroenterologists' and cardiologists' dilemmas in approaching a GI emergency in the CCU in his discussion of surgical procedures on the cardiac patient in his textbook *Diseases of the Heart.*[1] He wrote, "In general, it may be stated that the cogency of the surgical indication is more important than the cardiac status in determining whether an operation should be performed." The first task for the gastroenterologist is to assess the acuity of the presenting problem in relation to the acuity of the cardiac disease. Three examples should suffice.

Case 1: A 78-year-old female presented with 1 day of chest pain. She was found to have a ST-elevation myocardial infarction plus congestive heart failure (CHF). Evaluation revealed multivessel coronary artery disease (CAD) plus a right ventricular thrombus and a pericardial effusion, and she underwent emergency coronary artery bypass graft (CABG). She remained in cardiogenic shock after surgery, requiring multiple pressors, and developed renal failure. GI consultation was requested on postoperative day 10 because of a rapid rise in liver function tests, including hyperbilirubinemia, which was ascribed to shock liver. Absent bowel sounds and diffuse abdominal tenderness were noted on physical examination. Laboratory analysis revealed marked white blood cell (WBC) elevation plus persistent lactic acidosis. Noncontrast imaging studies were nondiagnostic. Because of a strong concern of bowel infarction, flexible sigmoidoscopy was performed and showed disruption of the bowel at the level of the sigmoid colon. Emergency laparotomy was performed and demonstrated infarction of the sigmoid colon and terminal ileum. The patient survived to leave the hospital 1 month later, though with very poor cardiac function.

Case 2: A 73-year-old man was transferred from another institution with hypotension and acute coronary syndrome. Cardiac catheterization revealed triple vessel disease. The patient had a history of ulcerative colitis. An intra-aortic balloon pump was placed to maintain cardiac output. The patient then developed bloody diarrhea without abdominal pain or increase in WBC count. Bowel sounds were audible. GI consultation was requested and the consultant opined that the patient had a flare of colitis rather than intestinal infarction or ischemic disease secondary to low cardiac output. Flexible sigmoidoscopy was performed while continuing ventricular assistance with the intra-aortic balloon pump, a diagnosis of active colitis was made, corticosteroids were given, the

patient responded promptly, and CABG was successfully performed 5 days later. Corticosteroids were tapered relatively rapidly and replaced by other antiinflammatory therapies after surgery to facilitate healing from the thoracotomy.

Case 3: A 60-year-old male presented with an acute coronary syndrome. Cardiac catheterization showed severe stenoses and the patient underwent coronary bypass grafting. He experienced bright red rectal bleeding on the second postoperative day. The bleeding was clinically mild, without hemodynamic changes or a fall in hematocrit. The patient had a history of prostate cancer, which had been treated with radiation. A presumptive diagnosis of radiation proctitis was made, the patient was treated with stool softeners without other evaluation until the day of discharge, when flexible sigmoidoscopy was performed and documented radiation proctitis. Plans for cauterization of the rectal lesions as an outpatient were made.

In the first case, the clinical impression of an abdominal catastrophe with a 100% morality rate, if untreated, mandated the performance of an endoscopic procedure without colonic preparation as well as emergency laparotomy, despite the patient's tenuous hemodynamic state. In the second case, the patient's history and the possible deleterious effect of a serious flare of ulcerative colitis on surgical outcomes also mandated the diagnostic procedure and treatment despite clear signs of hemodynamic instability, while the need to promote postoperative healing led to a more rapid tapering of the corticosteroids than is usually done. In the third case, the blood loss appeared trivial and not immediately threatening and the patient already had undergone cardiac operation; so the GI evaluation could be safely delayed until discharge. In some cases, evaluation can even be done after discharge. In all three cases, management was aided by repeated and effective communication and collaboration between the cardiologists and gastroenterologists.

Management of GI emergencies in the CCU has evolved greatly over the past generation. In the past, noncardiac evaluations and interventions were kept to an absolute minimum. The situation changed, at least from the gastroenterologist's point of view, when a publication in the GI literature more than 20 years ago demonstrated the safety and clinical efficacy of performing endoscopy in the presence of an acute coronary syndrome.[2] A second major development has been the widespread application of anticlotting therapies in cardiac patients, both anticoagulants and antiplatelet agents. This development has brought tremendous benefits in terms of decreasing morbidity and mortality from

thromboses and emboli. However, the therapies increase the risk of hemorrhage, especially in the GI tract.

The risks and benefits of anticlotting therapies follow a U-shaped curve. A greater degree of anticlotting therapy leads to a greater risk of bleeding but a lesser risk of thrombosis/embolism. Conversely, a lower degree of anticlotting therapy leads to a lesser risk of bleeding but a higher risk of thrombosis/embolism. The specific coefficients of increased or decreased risk are not entirely clear, especially with newer, short-acting agents. There are no data at all about combined antiplatelet/anticoagulant use, for example, in a patient with atrial fibrillation and an acute coronary syndrome. However, increased bleeding can be managed promptly by transfusion over the course of several hours, while thrombosis or embolism evolves over a much shorter time frame, which provides an advantage for anticlotting therapies. In addition, endoscopic or radiologic localization of a bleeding lesion may allow direct intervention for example, placing a hemostatic clip on a bleeding vessel or embolizing the bleeding vessel by interventional radiologists, which immediately reduces the risks of bleeding or rebleeding. For these reasons, gastroenterologists must learn to live with iatrogenic bleeding risks for patients in the CCU and those managing such patients must accept the attendant increased need for transfusions and invasive noncardiac therapies.

GASTROINTESTINAL BLEEDING

Gastrointestinal bleeding (GIB) potentially is a life-threatening condition affecting approximately 102 patients per 100,000 hospitalizations, with significant morbidity.[3,4] While the severity of GI hemorrhage varies greatly, anticoagulation or antiplatelet therapies complicate the situation. Around 2% of the world population is said to be on vitamin K antagonist therapy and there is increased use of direct oral anticoagulants (DOACs) inhibiting thrombin or factor Xa in the coagulation cascade.[5] Warfarin-related major hemorrhage (irrespective of the site) is around 1% to 9% per person year, the results for newer DOACs are similar or lower than for warfarin.[6–9] On the other hand, there was an overall incidence of GI bleeding after a percutaneous coronary intervention (PCI) of 1.04% over an 8-year period, with an underlying GI malignancy being a strong predictor of such events.[10]

Although the incidence of major bleeding is low in cardiac patients, several

factors are to be considered when GI bleeding is suspected: (a) the severity of bleeding; (b) antiplatelet therapy/anticoagulation type and its possible reversal; (c) potential sites and types of lesions; and (d) continuation or the timing of reintroduction of anticoagulants with careful and ongoing assessment of thrombotic risk. There are no specific guidelines on when to reverse anticoagulation effects and the optimal time for endoscopy if a lesion is suspected.

SEVERITY OF BLEEDING

Although the Glasgow-Blatchford and Rockall scoring systems, when negative, play a vital role in avoiding endoscopic intervention, the HAS-BLED scoring system attempts to estimate risk of major bleeding in patients with atrial fibrillation who are placed on anticoagulation. HAS-BLED, which includes risk factors of hypertension, abnormal renal or hepatic functional status, stroke, bleeding predilection, labile international normalized ratio (INR), age over 64 years, drugs and alcohol history, was first proposed in 2010, then introduced into guidelines. The risk stratification as low, moderate, and high risk (depending on the scores of 0, 1 to 2, and greater than 2, respectively) has been validated and found to be superior to other scoring systems ($HEMORR_2HAGES$, ATRIA, or CHA_2DS_2-VASc scores). Similarly, CRUSADE score (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines) has been used to stratify patients who undergo PCI in the setting of ST-elevation and non-ST elevation myocardial infarctions. The stratification is as follows: very low risk with score less than or equal to 20 has a 3.1% risk of major bleeding; low risk with score between 21 and 30 has a risk of 5.5%; moderate risk with score 31 to 40 has a bleeding risk of 8.5%; high risk defined as score of 41 to 50 has bleeding risk of 11.9%; and very high risk with scores above 50 has a bleeding risk of 19.5%.

While these scoring systems can help stratify some patients *prior to medical treatment*, they are, in fact, futile when a patient is in the cardiac intensive care unit with evidence of bleeding. These scoring systems do emphasize the importance of hemodynamics: blood pressure and heart rate. These two parameters can help guide medical care in patients with suspected bleeding for prompt resuscitation prior to any endoscopic intervention. Resting tachycardia, while difficult to interpret in patients with atrial fibrillation, implies mild to moderate hypovolemia, while any signs of hypotension suggest intravascular

volume loss greater than 15% (if orthostatic) and 40% (if supine). Fortunately, the latter situations are infrequently seen, particularly after starting anticoagulation or antiplatelet therapy.

ANTIPLATELET THERAPY/ANTICOAGULATION

A variety of anticoagulants are used for (a) treatment of venous thromboembolism (VTE); (b) stroke prevention in patients with atrial fibrillation; and (c) prosthetic heart valves. These medications include both vitamin K antagonists (warfarin) and DOACs (rivaroxaban, apixaban, dabigatran, and edoxaban). In the setting of GI hemorrhage, the question of when to reverse anticoagulation often is difficult to answer. No specific guidelines exist for when and how to reverse the effects of anticoagulation, particularly in hemodynamically stable patients with a complicated clinical picture requiring intensive care.

In a massive bleeding emergency, vitamin K based anticoagulation can be reversed during a clinical emergency with vitamin K, fresh frozen plasma, or protein complex concentrates (clotting factors II, VII, IX, and X). Postprocedure assessment can be done with laboratory tests to confirm restoration of normal anticoagulation. However, reversing the effects of DOACs is not as straightforward. The bleeding risk profile of DOACs as compared to warfarin was assessed in various studies: Randomized Evaluation of Long Term Anticoagulation Therapy (RELY); Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF), and Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE). Both dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily were associated with higher incidence of massive GI bleeding compared with warfarin, while apixaban had a similar bleeding risk as warfarin. Nevertheless, in several Meta analyses of randomized controlled trials, the relative risk of massive GI bleeding was higher with DOACs compared to warfarin.[11] While the initial studies seem to convey a bleak picture, international prospective registries provide evidence of more efficacy and safety, with one study showing half the bleeding complication rate of using rivaroxaban compared to the data presented in ROCKET-AF.[12] Protein complex concentrates have been shown to attenuate the effects of the newer DOAC regimens in small studies and animal models; however, the intended correction may overshoot the

“normal” target to confer a “procoagulant” environment while the additional clotting factors remain in the vasculature. Additionally, there is no laboratory support to confirm the reversal of the effects of DOACs. However, in dire life-threatening emergencies, these protein complex concentrates have been recommended as first-line agents. Nonetheless, specific drug therapies are being developed. Recently approved in the United States, idarucizumab, a monoclonal antibody therapy, binds specifically to dabigatran and rapidly neutralizes its effects in over 90% patients without any safety concerns.[13] Given the high costs, logistical issues, hospital protocols, and reimbursements, implementation is likely to lag. Additional reversal agents are in the pipeline, like andexanet alfa, for direct factor Xa inhibitors.

In the more likely scenario of nonemergent, non–life-threatening situations, DOACs fare better in reversal because they are short lived with normal restoration of coagulation profile within 12 to 24 hours after the last dose in patients without any renal compromise. Conversely, the effects of vitamin K antagonists are longer lasting and known to be effective for up to 3 days. However, the optimal timing for reversing anticoagulants’ effects in nonemergent settings is not known. Given the rapid clearance of DOAC in patients with normal drug clearance, the need to use reversing agents may be unnecessary, because the drug effects dissipate within hours.

To complicate matters further, many patients have CAD requiring vascular intervention and atrial fibrillation, necessitating the use of antiplatelet along with anticoagulation therapy in an attempt to reduce their risk of both ischemic heart disease *and* stroke. Overall, the benefits from reducing adverse events with these medications is not higher than the augmented risks of bleeding, and therefore these medications are not recommended.[14] However, the concomitant use of antiplatelet therapy in patients using anticoagulation increases the risk of GI bleeding over time, which is worse with dual antiplatelet therapy and in the elderly. The risk was assessed in the APPRAISE-2 trial, and additional trials are underway to assess the risk further with other DOACs.

Nonetheless, it is important to remember that most cases of GI hemorrhage are not life-threatening. In addition, many studies mentioned earlier (ie, RELY, ROCKET-AF) have looked at outcomes to assess morbidity and mortality (including but not limited to need for reversal use, use of blood products, death after bleeding), showing a noninferior profile of DOACs when compared to older vitamin K antagonists.

LOCALIZATION: UPPER VERSUS LOWER

Whether the source of bleeding is the upper or lower GI tract is a question often faced by the critical care team. By definition, any lesion seen above the ligament of Treitz (proximal to the jejunum) is considered an upper GIB, whereas a lesion in the rest of the GI tract is considered a lower GIB. While the definitions may be clear, the attempt to localize may yield no definite source, or multiple potential sources with possible ascertainment bias. Trends in population-based evidence show that there has been a significant increase in lower sources and a decreasing trend in upper sources of GIB.[15] This is likely due to more "gut surface area" distal to the ligament of Treitz, the fact that a negative upper endoscopy will automatically characterize a bleeding episode as a lower GIB, and to the widespread use of proton pump inhibitors.[9] Although the data for DOACs are sparse, data regarding the actual source of GIBs shows 18.9% of patients have peptic ulcer disease, of which 7.2% cases required endoscopic intervention, while 9.5% of the 57.1% patients who underwent colonoscopy had lower GI findings that needed intervention endoscopically.[16] It is important to reiterate that localizing a site of bleeding may allow direct intervention, such as placement of hemostatic clips, application of a heater probe, or vascular embolization by an interventional radiologist, with abrupt cessation of bleeding and the ability to restate anticlotting therapy. In many cases, endoscopy and other studies do not reveal the source of bleeding, which is then characterized as being obscure GIB.

TIMING OF ENDOSCOPY

No evidence or guidelines exist to determine when patients on anticoagulation should/can undergo endoscopy. However, the gastroenterologists' general practice tends to be based on the clinical situation and presenting symptoms. During active bleeding, particularly when hemodynamic instability is noted (tachycardia, hypotension, bloody emesis), prompt endoscopy within 12 hours usually is performed. The use of proton pump inhibitors may reduce the yield of high-risk lesions and the need for direct intervention during endoscopy. While medical management is as important as endoscopy, urgent endoscopy (within a few hours of presentation) has not shown to improve morbidity or mortality in the general population. To complicate matters further, with anticoagulation use, iatrogenic injury to the GI tract is a valid concern; so waiting for reversal of the medication effects prior to endoscopy may be prudent.

In all cases, endoscopy should be pursued in patients who are anticoagulated as long as hemodynamic stability has been achieved, though the critical care and the gastroenterology teams must be prepared to accept a negative upper endoscopy and a negative colonoscopy during a bleeding episode (which may have resolved at this point of the work up). Although the next logical step for the bleeding work up is capsule endoscopy to assess the small bowel (the largest area of the GI tract), the procedure often is not performed in an inpatient setting. Thus, resumption of anticoagulation is often discussed prior to the completion of GI evaluation.

RESTARTING ANTICOAGULANTS/ANTIPLATELET THERAPY

Resuming anticoagulation and antiplatelet therapy after a GIB episode involves balancing the benefits of the therapy and the risks of rebleeding. Expert guidelines generally recommend that anticoagulation therapy should be resumed for stroke/systemic embolism prevention as soon as possible after a bleeding site has been treated and "stable hemostasis" has been achieved. As one strategy, warfarin could be started the day of the procedure as the effects of anticoagulation reach therapeutic values in 72 hours, while one would have to wait 48 to 72 hours before resuming shorter-acting agents. However, the situation is more complicated if the source is obscure or resolves without any intervention. Therefore, the risks of rebleeding are not often fully known in many cases. Clinical experience indicates that bleeding from peptic ulcer disease typically occurs within 72 hours of the initial bleeding episode in the absence of definitive therapy, which guides the intensity of patient follow-up.[17] The variety of difficult situations that arise, particularly in the CCU, mandates evaluating and reevaluating the risks and benefits of therapy on a daily basis or even more frequently.

Case 1: A 50-year-old man with a past medical history of atrial fibrillation, on warfarin, and chronic heart failure presented to the hospital with signs of fluid overload and melena. He underwent diuresis and upper endoscopy revealed a clean-based ulcer that needed no endoscopic intervention (ie, hemostatic clip, epinephrine injections, or electrocautery).

Case 2: A 50-year-old man with a past medical history of atrial fibrillation, on warfarin, and chronic heart failure presented to the hospital with signs of fluid overload and melena. He underwent diuresis and upper endoscopy revealed an ulcer with a visible vessel that required a hemostatic clip (which was placed adequately).

Case 3: A 50-year-old man with a past medical history of atrial fibrillation, on warfarin, and chronic heart failure presented to the hospital with signs of fluid overload and melena. He underwent diuresis and upper endoscopy revealed an ulcer with a visible vessel that required a hemostatic clip (which was placed possibly inadequately).

Although the three cases present similarly, the outcome of endoscopy can help the critical care team decide to restart anticoagulation promptly (ie, the first two cases), whereas the third case required a brief delay in restarting anticoagulation therapy. Although the use of proton pump inhibitors reduces the need for endoscopic intervention on high-risk lesions during an acute event, there is no evidence of it preventing upper GI bleeding/rebleeding when used concomitantly with anticoagulation and antiplatelet therapy.

As it is impossible to delineate all the possible scenarios of GIB episodes in patients with anticoagulation, ongoing multidisciplinary discussions in these cases is imperative. A team-based approach to help address the risks and benefits on case-by-case basis will allow stratification of patients based on their hemodynamic stability, clinical presentation, anticoagulation status and possible reversal, the benefits of endoscopy, and possibly resumption of therapy around the time of the GIB episode.

ANTICOAGULATION IN CIRRHOSIS

Cirrhotics, particularly the decompensated patients, have a higher bleeding risk profile often complicated by bleeding esophageal varices. Anticoagulation in these patients may be considered for various reasons, including portal vein thrombosis and atrial fibrillation. It is important to remember that coagulopathy from liver disease is not equivalent to medication-induced anticoagulation. While current clinical management supports use of vitamin K antagonists and low molecular weight heparin in selected compensated patients (lack of ascites, bleeding varices, encephalopathy, and hepatorenal syndrome), the use of DOACs is unclear. Those patients were excluded from the pivotal trials.

In summary, most cases of GIB in anticoagulated patients are nonlethal and do not lead to long-term adverse effects. Endoscopy should be pursued in patients who are anticoagulated or on antiplatelet therapy at a time when hemodynamic stability has been achieved, knowing that no lesion may be found or no endoscopic intervention may be pursued.

The risks and benefits should be assessed daily and the decision to resume or restart antiplatelet/anticoagulation therapy should be a team-based decision.

ANEMIA WITHOUT GASTROINTESTINAL BLEEDING

A common scenario that cardiologists are faced with in the CCU is unexplained anemia, particularly in a patient on anticoagulation or antiplatelet therapy. Clinically occult GIB is high on the list in the differential diagnosis. Although this may be the case in certain situations, having a healthy differential is prudent, especially when no overt signs of bleeding have been noted (ie, melena, hematemesis, or hematochezia). Blood in the GI tract acts like a cathartic and often presents with multiple bowel movements rather than constipation. With no clinical signs of GIB, endoscopy may not be warranted. For example, retroperitoneal bleeding or a postcatheterization hematoma in the leg may be associated with a sudden fall in hematocrit as can sepsis and disseminated intravascular coagulation.

INTESTINAL ISCHEMIA

Intestinal ischemia is an uncommon disease, particularly in cardiac patients, and may be due either to embolic or atherosclerotic disease. Intestinal ischemia encompasses acute mesenteric ischemia, nonocclusive mesenteric ischemia, and chronic mesenteric ischemia. Similar to its varied presentation from acute or chronic, the progression also embodies a large spectrum from being reversible to fatal. For example, in the acute setting of mesenteric ischemia (from embolism originating from atrial fibrillation or thrombosis from atherosclerotic disease in the superior mesenteric artery), mortality in the absence of treatment can reach up to 93% while the nonocclusive mesenteric ischemia during low-flow states can be from 50% to 90%.[18] Risk factors include history of vascular disease from smoking, diabetes, hypertension, and hyperlipidemia (similar to the risks presented in patients with CAD), as well as history of cardiomyopathies, myocardial infarctions, cardiac arrhythmias including atrial fibrillation, hypotension, recent CABG, among others.

PATHOPHYSIOLOGY

Anatomically, three major vessels supply the vasculature of the intestines: arteries from the celiac axis (supplies stomach and duodenum), superior mesenteric artery (rest of small intestine up to the splenic flexure), and inferior mesenteric artery (splenic flexure to the rectum). Although extensive collaterals

help prevent ischemia in the gut, there are certain areas that are more vulnerable to injury, often labelled as watershed areas. These areas include classically the splenic flexure (Griffiths point) and the rectosigmoid region (Sudeck point).

DIAGNOSIS

Clinical presentation can vary and particularly in a cardiac patient, both acute and chronic abdominal pain should raise the possibility of “gut angina” to “gut ischemia” to “gut infarction” (similar to the workings of the heart). In textbooks, acute pain out of proportion that precedes voluminous diarrhea with or without blood noted subsequently is classic for an ischemic event. It can however present with abdominal distention (discussed later), nausea, and vomiting. Selective angiography is the most sensitive means of making a diagnosis of arterial disease and allows for the direct instillation of vasodilators.[19] Computed tomography (CT) angiography also has high sensitivity for the diagnosis of arterial disease but does not allow for therapeutic intervention. It is important to note that early diagnosis is imperative because it improves survival. If there are any signs of inflammation of the bowel wall or colitis noted on imaging, comprehensive work up to rule out infections like *Clostridium difficile* must be done.

MANAGEMENT

As with any bleeding or emergency, hemodynamic status needs to be optimized. Additionally, in intestinal ischemia, broad-spectrum antibiotics (eg, ciprofloxacin and metronidazole) need to be initiated to prevent bacterial translocation. All attempts to stop vasoactive drugs or vasoconstrictors should be made. While some data exists on use of thrombolytics on embolic events, it is not recommend given the increased risk of hemorrhage. Nonetheless, a prompt surgical consultation is necessary to remove the damaged bowel, particularly in acute mesenteric ischemia. Vasodilators like papaverine (a phosphodiesterase inhibitor) can be used particularly in nonocclusive mesenteric ischemia and chronic mesenteric ischemia. Colonoscopy can be safely done in stable patients with ischemic colitis to differentiate from other types of colitis of infectious and inflammatory origin.

ABNORMAL LIVER FUNCTION TESTS

Gastroenterologic or hepatologic consultation in the CCU may be related either to the condition that prompted CCU admission or to the same causes of liver dysfunction that might afflict anyone, such as acute or acute on chronic hepatitis, decompensated cirrhosis, cholecystitis, etc. In the latter instances, the presentation does not differ from that in the noncardiac patient and the major clinical problem is managing the disease in the face of cardiac dysfunction. In some cases, such as cholecystitis or perforation of a duodenal ulcer into the gastrohepatic ligament, the symptoms may mimic acute cardiac disease and may even cause ECG abnormalities. Drug-induced liver disease (DILI) may occur in cardiac patients, and may be caused by drugs used in the CCU. However, it is more common for GI consultation to involve circulatory failure.

CIRCULATORY FAILURE

Though the liver comprises 2.5% of body weight, it receives around 25% of cardiac output, two-thirds from the portal system and one-third from the hepatic artery. Within the liver, the pericentral areas (zone 3) are most prone to injury because of a low oxygen tension under normal circumstances. The liver is partially protected from ischemic injury because of its dual blood supply—arterial and portal venous. However, the biliary system is supplied only by the hepatic artery. Heart failure can lead to hepatic dysfunction via two mechanisms, hepatic congestion related to increased venous pressure or ischemic injury related to decreased blood flow (**Table 47.1**). Passive congestion from increased central venous pressure occurs as a result of right-sided heart failure and may be chronic or acute, the latter in the case of pulmonary embolism, especially a saddle embolus. Hepatic dysfunction from right-sided heart failure may result from constrictive pericarditis, severe pulmonary arterial hypertension, mitral stenosis, tricuspid regurgitation, cor pulmonale, or cardiomyopathy. Right ventricular dysfunction with increased hepatic venous pressure can lead to atrophy of hepatocytes and perisinusoidal edema. Chronic right-sided heart failure may lead to hepatic fibrosis, previously termed “nutmeg cirrhosis.” Rheumatic heart disease was a very common cause of nutmeg cirrhosis in the past. Mortality in this condition usually was related to the severity of the heart disease, rather than the liver disease. Although the condition is termed cirrhosis, portal hypertension typically is not seen.

TABLE 47.1 **Causes of Hepatic Ischemia**

Heart failure[a]
- Right-sided heart failure
  - Right-sided myocardial infarction
  - Pulmonary embolism
  - Pulmonary hypertension
- Left-sided heart failure
  - Myocardial infarction
  - Cardiomyopathy
  - Valvular disease

Hypovolemia
  - Hemorrhage
  - Dehydration

Hypoxemia
Sepsis
Heat stroke

This is not a complete list but rather conditions that one might encounter in a CCU.
[a]In the presence or absence of cardiogenic shock.
CCU, coronary care unit.

Right-sided heart failure in the absence of left-sided heart failure usually presents with edema, ascites, and hepatomegaly. Jaundice may be noted on physical examination. Rarely, patients can present with severe hepatomegaly and right upper quadrant pain, which is due to stretching of Glisson capsule. The liver may be pulsatile if there is tricuspid insufficiency. The liver edge typically is smooth, and hepatojugular reflux may be elicited. When present, ascites classically has elevated protein content (>2.5 g/L) and a low serum-to-ascites albumin gradient, which is different from cirrhosis secondary to alcoholic liver disease or chronic viral hepatitis. Left-sided heart failure usually does not present with these symptoms, but with symptoms of dyspnea. Mild elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase, and alkaline phosphatase (ALP) typically are seen in right-sided heart failure, with elevations of up to 2 to 3 times the upper limit of normal. Bilirubin typically remains below 3 mg/dL with an elevated unconjugated fraction, but may be higher in patients with chronic, severe CHF. The rise in transaminases is greater with more acute presentations and in the presence of systemic hypotension, and may resemble acute hepatitis.

Hepatic dysfunction also may arise from low cardiac output leading to decreased perfusion and the predisposing conditions are similar to those discussed earlier. While oxygen delivery to the liver is related to both blood flow and Pa_{O_2}, hypoxemia alone rarely is sufficient to cause tissue injury. If affected by hypoxemia, the areas around the central veins are most vulnerable, because oxygen tensions are lowest under normal circumstances. Virtually any cause of

hypotensive shock can result in hepatic injury, including hemorrhage, burns, heat stroke, toxic shock, sepsis, acute CHF, trauma, crush injuries, pulmonary embolism, etc. In addition to hepatic artery thrombosis and embolism, hepatic artery occlusion also may occur from sickle cell crisis, cocaine-induced arterial spasm, aortic dissection, vasculitis, hypercoagulable states, hepatic artery aneurysms, toxemia of pregnancy, embolism from tumor, endocarditis, and others (**Table 47.2**). The vulnerability of the liver to ischemic disease is greater in the presence of cirrhosis because of portosystemic shunting or portal vein thrombosis, and in CHF because of the inability of the heart to compensate for the decreased hepatic blood flow. The liver also is susceptible because of the relatively high metabolic activity of the hepatocytes. Furthermore, the liver may suffer from reperfusion injury with reactive oxygen species and lipid peroxidation as well as superoxides and hydrogen peroxide.

Hepatic injury usually is acute, but may be recognized well after the inciting event has occurred.

TABLE 47.2 Causes of Hepatic Infarction

Hepatic artery thrombosis
- Atherosclerosis
- Hypercoagulable states

Hepatic artery embolism
- Endocarditis
- Tumor emboli
- Therapeutic embolization

Hepatic artery aneurysm
Aortic dissection
Vasculitis involving the hepatic artery
Sickle cell disease
Vasospasm—cocaine ingestion

This is not a complete list but rather conditions that one might encounter in a CCU.
CCU, Cardiac care unit.

The diagnosis typically is made on clinical grounds. In severe episodes of hypotension, shock liver can occur in which there is a profound elevation in serum alanine aminotransferase and aspartate aminotransferase, and prolonged prothrombin time. The diagnosis of hepatic infarction can be made radiographically, with demonstration of a wedge-shaped or other defect, especially on a contrast CT study. Laboratory abnormalities in ischemic hepatitis usually peak after 1 to 3 days and normalize after 5 to 10 days. Diagnosis is typically clinical when liver tests are found to be abnormal 1 to 3 days after the episode of hypotension though the condition may mimic acute hepatitis,

especially if the inciting event was missed, for example, hypotension associated with a tachyarrhythmia in an outpatient setting. There may also be concomitant elevations in creatinine from acute tubular necrosis. In these episodes of severe hypotension leading to elevated liver tests, patients usually present with serum bilirubin elevations up to 20 mg/dL and AST more than 10 times the upper limit of normal. LDH typically rises and an ALT/LDH ratio of less than 1.5 can help differentiate ischemic liver damage from viral hepatitis. In addition, the transaminases tend to fall rapidly because of the acute, reversible inciting event, as opposed to viral hepatitis in which transaminase elevations are much more prolonged, lasting for a few weeks. Most cases resolve with supportive care, though hepatic decompensation may occur, especially in the presence of chronic liver disease. There is no specific therapy for ischemic injury.

The following case is an example of an acute ischemic injury to the liver.

A 36-year-old man presented to the emergency room with severe chest pain, with onset while returning from an overseas trip. CT angiogram showed no evidence of pulmonary embolism but did show aneurysmal dilatation of the ascending aorta. Transthoracic echocardiogram showed a flap in the ascending aorta plus severe aortic insufficiency. He underwent emergent aortic root replacement with reconstruction and reimplantation of coronary buttons and hemiarch replacement, with 16 minutes of circulatory arrest and a cross clamp time of 192 minutes. GI consultation was requested for marked transaminase elevations (AST, 9736 and ALT, 5731) on postoperative day 3, plus coagulopathy (INR, 3.3). Transfer to a liver transplantation center was sought but was denied due to the need for multiple pressors and other postoperative care. Continuous venovenous hemoperfusion followed by hemodialysis was started because of acute kidney injury. Doppler examination showed blood flow to both kidneys. The transaminases peaked on postoperative day 4, while the total bilirubin continued to rise until postoperative day 8. Renal recovery was noted on postoperative day 11. At discharge on postoperative day 15, both liver and kidney function tests were improving and the patient was no longer receiving hemodialysis.

DRUG-INDUCED LIVER INJURY

Medications are also a common cause of hepatic dysfunction, which may present as asymptomatic liver test elevations or even fulminant liver failure. DILI may be nonidiosyncratic or idiosyncratic. Acetaminophen is a classic nonidiosyncratic etiology of DILI because high doses of acetaminophen can lead

to DILI in anyone. However, many medications cause idiosyncratic DILI. In fact, it is estimated that 20 new cases of DILI per 100,000 persons occur each year and that idiosyncratic DILI causes 11% of the cases of acute liver failure in the United States. DILI is classified as hepatic, cholestatic, or mixed based on the abnormalities in alanine aminotransferases and ALP. It mostly presents within 6 months of drug exposure, but can occur within days or up to a year after starting the offending agent.

There are many medications used in the CCU that may contribute to elevated liver tests (**Table 47.3**). These include, but are not limited to, aspirin, amiodarone, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, clopidogrel, hydralazine, and diltiazem. Liver function abnormalities during statin therapy have been widely publicized but usually are not a problem in the CCU, though they could be present on admission in a patient recently started on high dose therapy, especially simvastatin or lovastatin, and in the presence of drug–drug interactions, with agents that are CYP3A4 inhibitors. Liver function abnormalities occur less frequently than muscle injury.

TABLE 47.3 Drug-induced Liver Injury

MEDICATIONS[a]	COMMENTS
ACE inhibitors	Associated with low rate of elevated serum aminotransferases (< 2%)
Alpha blockers	Associated with minimal rate of elevated serum aminotransferases (0.2%–2%)
Angiotensin II receptor antagonists	Associated with minimal rate of elevated serum aminotransferases (0.2%–2%)
Antiarrthymics	Amiodarone is associated with elevation of serum aminotransferases in 15%–50% on long-term therapy. It is recommended to have ALT and AST values checked at baseline and every 6 mo, with discontinuation of amiodarone if over twice the upper limit of normal. Using the medication intravenously may cause severe liver injury, including liver failure, with elevations in enzymes by 10–100 fold.
Hydralazine	Can cause delayed liver injury in a lupuslike syndrome or acute liver injury
Methyldopa	Chronic use is associated with mild elevation in serum aminotransferases in 5%–35% of patients. More rarely do patients present with acute liver injury.
Fibrates	Mild-to-moderate serum transaminase elevations
Niacin	Doses above 500 mg daily cause elevation >3 times ULN of transaminases. Sustained release forms may cause serious hepatotoxicity.

Statins	Associated with mild-to-moderate serum transaminase elevations. Very rarely causes acute liver failure.
Ezetimibe	Associated with transaminase elevations in 0.5%–1.5%
Aspirin	May cause elevated transaminase levels with high-dose therapy. Can have mild increase in alkaline phosphatase and bilirubin.
Clopidogrel	Associated with serum enzyme elevations in 1%–3% of patients
Prasugrel	Similar to clopidogrel
Ticlopidine	Associated with serum transaminase elevations in 4%
Dabigatran	Associated with moderate ALT elevations of >3 times ULN in 1.5%–3% in chronic use
Fondaparinux	Associated with enzyme elevation >3 times normal in 1%–3% patients
Rivaroxaban	Associated with ALT elevation of >3 times normal in 1.5%–3% patients
Apixaban	Associated with serum transaminase elevations >3 times normal in 1%–2% patients
Edoxaban	Associated with serum transaminase elevations >3 times normal in 2%–5% patients
Heparin	Associated with elevated serum transaminase 10%–60% patients
Beta-blockers	Rarely cause elevations in serum transaminase levels
Calcium channel blockers	Associated with elevated serum transaminase levels
Tolvaptan	Studies mixed: some demonstrate no hepatic damage; some show worsened outcomes in cirrhotic patients.
Sidenafil	Associated with hepatocellular and cholestatic injury
Endothelin receptor antagonists	Associated with serum transaminase elevations

[a]This is not a complete list but rather a list of medications that might be used in the CCU.
ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
From https://livertox.nih.gov/.

Diagnosis is usually made by careful medication history and by eliminating other etiologies of abnormal liver tests with laboratory testing for viral hepatitis, autoimmune hepatitis, etc, and imaging to rule out obstruction. The ultimate diagnosis can be made by liver biopsy, but is not required. Liver tests should

normalize with discontinuation of the offending agent. In some cases, the drug-induced injury is chronic. In these cases, improvement is slower, but clinical experience indicates that the transaminases will fall by at least 50% within 2 weeks of drug discontinuation.

INTESTINAL DISTENTION

Intestinal distention is a rather frequent cause of GI consultation for patients in the CCU, especially after open heart surgery. The causes may be mechanical (obstructive) or functional (nonobstructive). The major causes of mechanical obstruction are extrinsic compression, tumor, hernia, adhesion, stricture, volvulus (torsion), and intussusception, and usually are not related to the problems prompting CCU admission. In contrast, intestinal distention after cardiac surgery or myocardial infarction is more likely to be nonobstructive in nature, that is, ileus. The first task when seeing someone with intestinal distention is to differentiate obstruction from ileus. Ileus usually is reversible with treatment of the underlying causes/exacerbating factors, whereas obstruction may require surgery, sometimes on an urgent basis. The reason for this is that ischemia/infarction occurs when intraluminal and tissue pressures are higher than mean arterial pressure, and pressures are higher in obstruction than in ileus, so that strangulation with ischemia/infarction is more likely with obstruction.

PATHOPHYSIOLOGY

The pathophysiology of ileus is incompletely understood. Historically, ileus was felt to be related to paralysis from toxins, such as in patients with peritonitis. However, experimental studies demonstrated that removal of the distended bowel and rinsing with sterile solution allowed for peristalsis to return spontaneously. Thus, ileus began to be seen as inhibited motility. Toxic megacolon is a special circumstance associated with severe, transmural inflammation, associated with ulcerative colitis or infectious colitis, such as *C. difficile*-associated colitis, which includes systemic toxicity in addition to peritoneal irritation/inflammation.

The mechanisms controlling intestinal motility include neurogenic, myogenic, and humoral factors. Intestinal motility is stimulated by cholinergic impulses and inhibited by adrenergic impulses. Ileus is related either to increased inhibition,

decreased excitation, or both. Altered sympathetic/parasympathetic balance due to exaggerated sympathetic tone from retroperitoneal stimulation of thoracic sympathetic ganglia, for example, by blood products in or adjacent to the posterior peritoneum is felt to promote ileus in the small intestine (**Figure 47.1A**). The situation undoubtedly is more complicated because motility also is related to the presence of inflammatory cytokines, perhaps mediated through the activity of nitric oxide and prostaglandins.[20,21] The effects of inflammatory and other mediators are abetted by electrolyte imbalances, particularly calcium, magnesium, and phosphate, acid–base disorders, as well as by the pharmacologic effects of opiates, calcium channel blockers, and anticholinergics. Vomiting promotes loss of potassium and hydrogen ions. Intraluminal accumulation of fluid leads to losses from the intra- and extravascular compartments, while abdominal distention may limit respiration. Gaseous distention is caused, in large part, by swallowed air, which provides a rationale for nasogastric tube decompression.

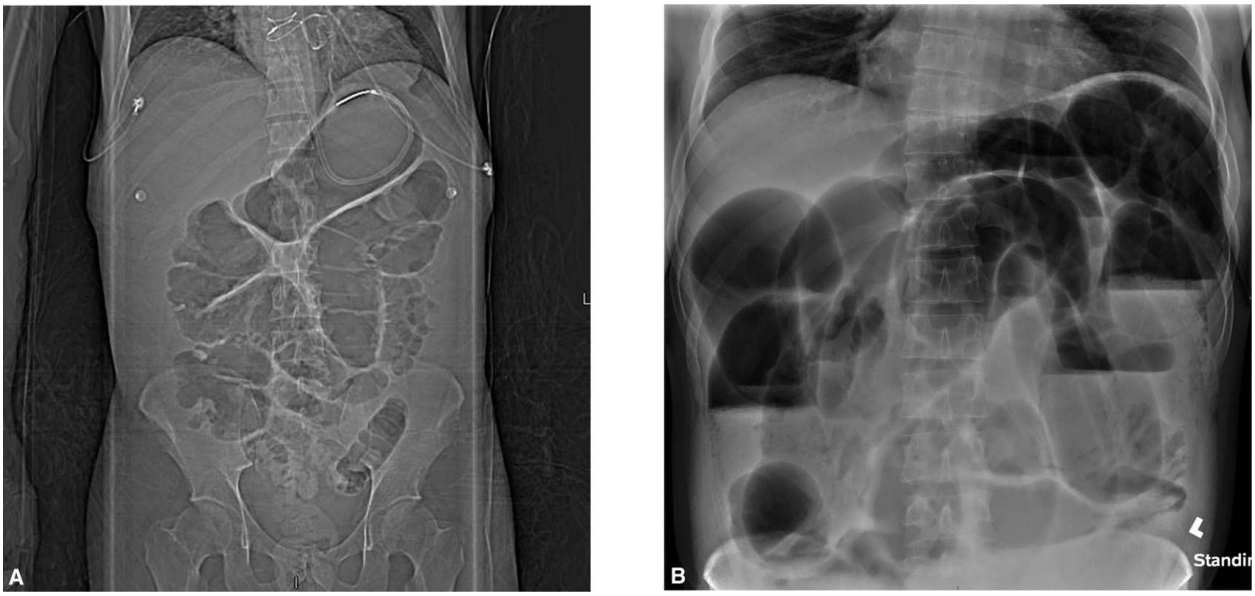

FIGURE 47.1 A, Supine abdominal film in a patient with ileus. Gaseous distention is limited to the small intestine. In this case, ileus was related to a mycotic aneurysm in a branch of the superior mesenteric artery in a patient with infective endocarditis. B, Upright plain film of the abdomen in a patient with organic obstruction, in this case volvulus associated with congenital malrotation. Note the air fluid is at different levels, which is typical for organic obstruction, as opposed to ileus.

Ileus may involve the small bowel or the colon, or both sites (**Table 47.4**). The small bowel is preferentially affected by retroperitoneal processes in the

thoracolumbar region, whereas the colon is preferentially affected by retroperitoneal processes in the sacral region. Of note, Ogilvie syndrome, or isolated colonic ileus, was originally related to retroperitoneal malignancies.

TABLE 47.4 Causes of Ileus

Infectious/inflammatory
- Severe sepsis
- Bacterial peritonitis
- Appendicitis
- Diverticulitis
- Cholecystitis
- Pancreatitis
- Pneumonia
- Pulmonary embolism
- Intraperitoneal hemorrhage

Ischemic
- Arterial thrombosis/embolism
- Venous thrombosis
- Nonobstructive mesenteric ischemia
- Mesenteric arteritis
- Strangulation/volvulus

Retroperitoneal processes
- Pyelonephritis
- Retroperitoneal hemorrhage
- Retroperitoneal abscess
- Retroperitoneal malignancy
- Ureteropelvic lithiasis

Drug-induced
- Opiates
- Anticholinergics
- Psychiatric medications

Metabolic
- Electrolyte imbalance—Sodium, potassium, calcium, magnesium, phosphate
- Uremia
- Acidosis

Other
- Laparotomy
- Perforated viscus
- Chronic obstructive pulmonary disease
- Sickle cell disease

This is not a complete list but rather conditions that one might encounter in a CCU.
CCU, Cardiac care unit.

DIAGNOSIS

A careful history, physical examination, and review of the medical records are important to uncover historical clues suggestive of obstructive disorders or ileus; prior abdominal surgery, prior episodes of obstruction, evidence of inguinal or abdominal hernias, prior intestinal cancer or polyps, prior radiation, inflammatory bowel diseases, gallstones, ulcers, and a history of gallstones all

raise the possibility of an obstructing lesion. On the other hand, a psychiatric history, certain medications (opiates, psychiatric medications, etc), and endocrine problems such as hypothyroidism may suggest ileus. Fever, rigors, leukocytosis, or hyperlactatemia suggest infection.

It is important to remember that mesenteric ischemia can mimic ileus radiologically as well as symptomatically. Mesenteric ischemia may be arterial or venous in origin and due to atherosclerosis, embolism, or vasculitis.[22] The colon is more vulnerable than the small intestine due to a less rich collateral circulation. Increasingly severe and steady pain in the presence of abdominal distention suggests intestinal infarction, but this is a late sign; a high index of suspicion is needed to lead to a correct diagnosis before infarction occurs. Elevations in serum amylase, ALP, creatine phosphokinase, ALT, AST, and lactate dehydrogenase suggest ischemia or infarction, with enzyme leakage from damaged cells.

Radiologic studies can suggest the etiology of intestinal distention as well as its severity. Air fluid at different levels on an upright film suggests organic obstruction (**Figure 47.1B**). A jejunal diameter of > 3.5 cm is considered worrisome. The diameter of the colon to be considered worrisome is uncertain. Classically, a diameter of > 12 cm is of concern, though patients with chronic distention, such as some patients on chronic psychiatric medications, have greater diameters and are asymptomatic. On the other hand, a rapid increase in diameter is worrisome no matter what the precise diameter is. Cross-sectional studies are helpful in detecting retroperitoneal pathology such as hemorrhage or infection, which may complicate thoracic as well as abdominal surgeries.

MANAGEMENT

For the treatment of organic obstruction, the reader is referred to GI or surgical texts. For the treatment of ileus, supportive care is key, with replacement of fluids and electrolytes as necessary, and the discontinuation of agents that inhibit motility. One should consider nasogastric decompression, especially in the presence of vomiting. One may consider colonic decompression for Ogilvie syndrome if it does not respond to conservative measures with placement of a rectal tube to maintain decompression. A cecostomy should be considered for recurrence of colonic ileus or failure of colonoscopic decompression. It should be emphasized that small intestinal ileus responds to conservative measures in most cases. Endoscopy rarely is needed in patients with ileus, though it may be helpful in patients with proximal obstruction of the small bowel or distal

obstruction of the large bowel. If endoscopy is performed, instilling as little air as possible is recommended so as not to exacerbate the situation and to use carbon dioxide for insufflation rather than room air, because it is resorbed much more rapidly.[23]

GASTROINTESTINAL COMPLICATIONS AFTER LEFT VENTRICULAR ASSIST DEVICE IMPLANTATION

GIB rate in patients with left ventricular assist device (LVAD) is frequent and estimated to be 18% to 44%.[24] The causes for GIB may be from use of antithrombotic agents, impaired platelet aggregation, acquired von Willebrand syndrome, and mostly commonly arteriovenous malformations (AVMs) or angiodysplasias in patients who suffer from chronic heart failure. Though the same lessons as described earlier apply to LVAD patients as well, additional precautions need to be taken with special attention to hemodynamics in this cohort. The possibility of obscure sources of GIB should be considered in these patients and a team-based approach is required to navigate these situations.

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Patient and Family Information for: GASTROINTESTINAL EMERGENCIES IN THE CARDIAC CARE UNIT

Being in the cardiac care unit can be an overwhelming time for both patients and their families. This can be escalated by other conditions and medical problems that present during a hospitalization. The key to understanding GI and liver diseases in a cardiac patient is to first understand that it involves interdisciplinary care and discussion among the cardiologists and gastroenterologists, with a plan individualized for each patient.

Gastro-Intestinal bleeding (GIB) can occur in any individual. This can be bleeding anywhere in the intestinal tract from the esophagus down to the rectum. Bleeding can be from the upper GI tract, which includes the esophagus, stomach, or first part of the intestines, or from the rest of the intestines, which is considered the lower GI tract. Patients may present with passing blood per rectum, black stools, or coffee-colored or bloody vomitus. If it is severe, it can cause shock with lowered blood pressure and a fast heart rate. Many different conditions can cause bleeding, ranging from an ulcer to a tear in the intestinal lining, hemorrhoids, a bleeding mass, irregular blood vessels called AVMs, to diverticulosis, which is an outpouching in the lining of the intestines. The treatment of the cause of bleed depends on the severity of the bleeding (ie, how much the blood counts drop, how much the blood pressure or heart rate changes, and how quickly blood is being lost). In some instances, it can be treated supportively with fluids, blood products, and certain medications to decrease acid secretion from the stomach. In other situations, patients may require direct visualization with endoscopy or colonoscopy, or CT studies to analyze the blood

vessels. In either case, direct treatments may be used to stop the bleeding.

Some patients are at higher risk for bleeding than others. These include sick patients in an intensive care setting, and patients on blood thinners such as most patients with cardiac conditions. Although the incidence of major bleed is low in cardiac patients, it can be life threatening. The gastroenterologists and cardiologists need to assess the severity of bleeding, the potential site that the patient is bleeding from, the type of blood thinners the patient is on, and whether blood thinners can be continued or not. It is a risk and benefit conversation that will have to be individualized based on the patient. If a bleed is severe enough to cause patients to be unstable, then regardless of their cardiac status they may require an invasive procedure. The biggest discussion will be held after the bleeding is controlled about the risks and benefits of using blood thinners in somebody with a recent bleed because blood thinners increase the risk of bleeding further. Again this will be individualized for each patient with discussions among the cardiologist, gastroenterologist, and the patient.

Another problem that arises in patients in the cardiac care unit is abnormal liver function tests. This can be for a few reasons. One is mainly caused by the fact that both the heart and liver work simultaneously to help blood flow throughout the body. Many patients in the cardiac care unit have heart failure. If you can imagine, this can present in two ways. If the heart is failing to pump out blood effectively enough, then there is a lack of blood flow to all organs, including the liver. This results in less oxygen being delivered to the liver and presents as damage to the liver. On the other hand, if the heart cannot fill properly with blood, the blood will back up to all of the organs, including the liver. The liver then becomes congested with blood and can become damaged. These conditions present with elevated liver function tests and should improve with improvement of the heart failure. If heart failure is long standing and not improving, there is a chance that it can lead to liver failure and cirrhosis.

Another situation is when patients have episodes of extremely low blood pressure and decreased blood flow from the heart, which causes less oxygen to be delivered to the liver, resulting in liver damage. The treatment for this is supportive with management of the blood pressure. It will slowly resolve over time and usually does not result in liver failure.

Certain medications, both cardiac and noncardiac medications, can cause elevations in liver tests as well. Usually this is diagnosed when the liver tests get elevated after starting certain medications and after elimination of all other types of liver disease, for example, viral hepatitis. It should resolve with stopping the

offending medication. The condition usually is not life threatening, but sometimes can cause chronic problems with the liver. In these instances with elevated liver tests, it is a matter of watching the laboratory values to see if they are improving and if not, patients may require a liver biopsy.

Many patients in the cardiac care unit also do not get out of bed and risk getting distension of the intestines. This differs from patients who have an actual obstruction (from a tumor, scar tissue, hernia, etc) and have a blockage in their intestines. If a patient gets distension of his or her intestines, basic radiologic workup will be done including an X-ray or a CT scan. After that, the treatment depends on whether or not the physicians believe there is an actual obstruction in the intestines. If so, the patient may require surgical intervention, because it can become life threatening. If not, the care is supportive with fluids, ensuring movement (which may be as simple as the nurse turning the patient, or walking), sometimes stopping medications that can induce distension (ie, opiate pain medications), and making sure the patient’s potassium and magnesium levels are normal.

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Line Access in the CCU

INTRODUCTION

Obtaining vascular access in the cardiac care unit (CCU) patient is a potentially lifesaving intervention and an important practical skill for physicians in training to acquire during their critical care rotations. Vascular access is essential for providing lifesaving medications, therapeutic interventions, and also hemodynamic monitoring. Determining the type of catheter needed, appropriate indications, contraindications, and the various considerations for the insertion, maintenance, and timely removal of arterial and venous catheters is important to prevent complications. Knowledge of vascular anatomy, familiarity with the equipment, and competency with the use of ultrasonography (US) are prerequisites for successful insertion of the catheter.

A central venous catheter (CVC) or central line (CL) is defined as a venous intravascular catheter that terminates at or close to the heart or in one of the great vessels. A CVC can be used to provide infusions of vasoactive and other medications, blood products, and also for hemodynamic monitoring. An arterial line (A-line) is an intraarterial catheter placed in a peripheral or central artery and is used for hemodynamic monitoring or for vascular access for procedures such as coronary angiography. The placement of CVCs and A-lines is routine CCU procedure, often performed at the bedside under sterile technique. Vascular

access devices (VAD) that may be encountered in the CCU patient include peripheral intravenous (PIV) catheters, triple lumen catheter (TLC), introducer catheter, tunneled and nontunneled hemodialysis catheters, peripherally inserted central catheter (PICC), Swan-Ganz or pulmonary artery catheter (PAC), A-lines, and venous and arterial sheaths.

Not every CCU patient requires a CVC or A-line. The decision to place a line and the choice of site of insertion should be based on a thoughtful assessment by the operator and the CCU team of the patient's anatomy, clinical status, and coagulation profile. All lines should be placed under aseptic technique using a "bundle" or "checklist" as per institutional policy. Real-time ultrasound guidance is recommended for CVC placement in sites such as internal jugular vein (IJV) or femoral vein (FV), as well as any difficult-to-access sites. Once a VAD has been placed, there should be a daily thoughtful assessment of the need for continued use of the catheter. The best way to avoid complications of VAD is to avoid unnecessary placement and remove them as soon as they are no longer necessary.[1]

Although the authors believe that there is no substitute for bedside hands-on learning, we hope this chapter serves as a fundamental quick reference guide for physicians, nurses, physician assistants, nurse practitioners, and other health care practitioners for "frequently asked questions" about VAD encountered in the CCU.

BASIC PRINCIPLES

MATERIAL

Most catheters in the CCU, including PIVs and CVCs, are polyurethane-based catheters, which provide some rigidity to the flexible catheter and prevent kinking. The main adverse effect of these catheters is the risk of vessel perforation, namely that of the superior vena cava (SVC) from a left-sided CVC. Silicone-based catheters are more pliable and have a lower risk of vessel injury, hence are placed for long-term venous access. These catheters need a sheath introducer or an inner dilator or stylet for percutaneous insertion. Examples of silicone-based catheters encountered in the CCU include PICC and some silicone-coated sheath introducers.

SIZE

Catheter size is classified in either gauge (G) or French (F) units. In general, needles or single lumen catheters are sized by gauge and multilumen catheters are measured by French size. Whereas French size and catheter diameter are directly related (the higher the French, the larger the diameter), gauge and size are inversely related (lower gauge indicates larger diameter). The size specifications are generally indicated on the outer packet or insert.[2]

FLOW RATES

A working knowledge of the relationship between catheter size, length, and flow rates is essential in choosing the appropriate catheter for the CCU patient. The rate of flow (***Q***) across a catheter is directly proportional to the pressure gradient (ΔP) and inversely proportional to the resistance (***R***) to flow:

$$Q = \Delta P \times \frac{1}{R} \qquad \text{(Eq. 1)}$$

Resistance is directly proportional to the length of the catheter and viscosity (μ) and inversely proportional to the radius (***r***): $R = 8\mu \times \text{length}/\pi r^4$. Hence the rate of flow is directly proportional to the inner radius of the catheter and the pressure gradient, and inversely proportional to the length of the catheter and the viscosity of the fluid or blood product being infused. This is based on Poiseuille's law:

$$Q = \frac{\pi r^4 \times \Delta P}{8\mu \times \text{length}} \qquad \text{(Eq. 2)}$$

This concept is important in the resuscitation of the CCU patient, whether it is for hypovolemia or hemorrhage. Flow rates improve exponentially (r^4) with larger radius catheters, pressure bag application, and with shorter catheters. A large bore catheter that is short is optimal for volume resuscitation. **Table 48.1** lists the flow rates achieved with various devices commonly used in the CCU. So if a patient in the CCU has a major bleeding complication (eg, from femoral arterial sheath removal or gastrointestinal bleeding from antithrombotic agents), a 16-gauge antecubital peripheral IV or an introducer catheter is preferred over a long triple lumen catheter (TLC) or PICC.[3]

TABLE 48.1 Flow Rates and Catheter Size

Catheter gauge and length	Flow Rate (mL/min)

24G × 0.75″	25
22G × 1.00″	35
20G × 1.00″	65
20G × 1.88″	55
18G × 1.16″	105
18G × 1.88″	95
16G × 1.16″	220
16G × 1.77″	205
TLC	98
16G distal lumen (brown)	52
18G medial lumen (blue)	22
18G proximal lumen (white)	24
PICC	
5F × 50 cm (single lumen)	29
5F × 50 cm (double lumen)	
18G distal lumen	9.6
20G proximal lumen	2.6
Sheath introducer	
8.5F × 10 cm	126
	333 (with pressure bag)

Source: www.BD.com, www.edwards.com, www.arrowintl.com.
PICC, peripherally inserted central catheter; TLC, triple lumen catheter.

PERIPHERAL VENOUS CATHETERS

Any patient admitted to the CCU would be considered a critically ill patient and hence needs at least one peripheral intravenous (IV) catheter. This can be

potentially lifesaving when the previously stable cardiac patient becomes unstable, whether it is from a bradyarrhythmia, tachyarrhythmia, or cardiac arrest. Infusates with a pH between 5 and 9 and osmolality < 600 mOsm/L can be delivered via a peripheral catheter. Even vasopressors can be administered emergently through a properly placed peripheral catheter until central venous access is obtained. Due to increased risk of phlebitis with catheter dwell time,[4] most institutions have policies requiring change of peripheral catheters every 72 to 96 hours.[1] A recent randomized controlled study from Australia however showed no difference in adverse outcomes such as phlebitis when peripheral catheters were changed only as clinically indicated.[5]

Most institutions have one of two types of catheters: an over-the-needle cannula (ie, angiocatheter or “angiocath”) or a winged catheter set (ie, butterfly) (**Figure 48.1A** and **B**). **Table 48.2** lists a step-by-step approach to placing a PIV. **Figure 48.2** illustrates the venous anatomy of the upper extremity. A proximal site is preferred if the patient is at risk for hemorrhage. In general, an 18G or 20G is preferable because it provides an adequate size for rapid infusion of medications or of contrast if the patient needs a computed tomography (CT) angiogram. Note that catheters in the antecubital fossa (eg, median cubital vein) may kink when the patient bends his or her arm, thus interfering with medication administration. If ultrasound guidance is used to cannulate the basilic or cephalic veins (**Figure 48.2**), a longer angiocatheter is preferred. Avoid sites that may appear injured or infected (ie, cellulitis). Complications include phlebitis (irritation), cellulitis, and bacteremia leading to sepsis. Hematoma, thrombus formation, and nerve injury can occur from multiple unsuccessful attempts. Infiltration of fluid around the IV site is not uncommon; however, extravasation of medications such as vasopressors and vesicants can lead to localized swelling and vascular compromise. Any early signs of minor or major complications should lead to removal of the catheter. Warm compresses and arm elevation can be used to treat phlebitis and extravasation.

FIGURE 48.1 A, Winged peripheral IV catheter system. B, Over-the-needle angiocatheter with retractable needle.

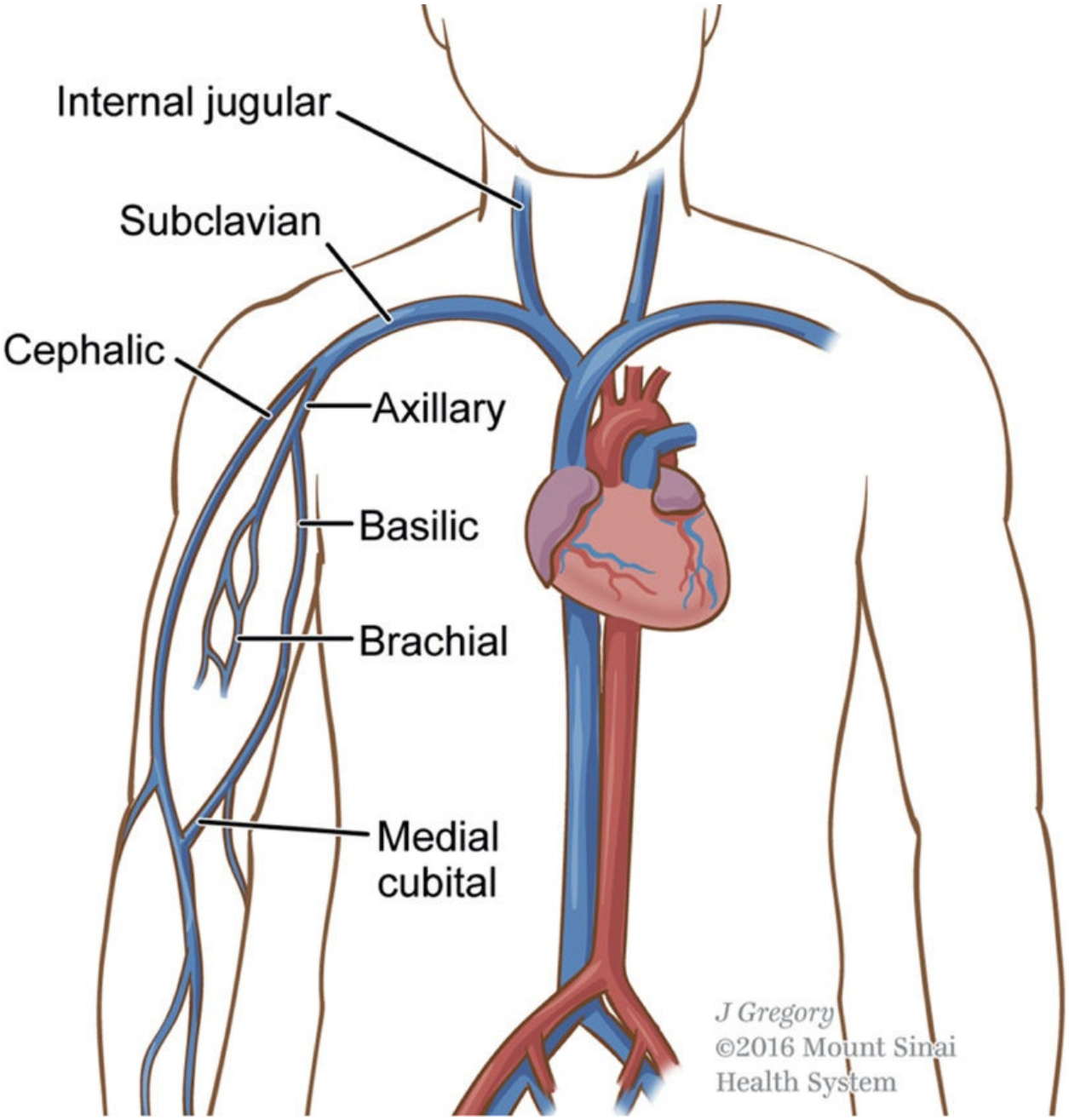


FIGURE 48.2 Venous anatomy of the neck and upper extremity.

TABLE 48.2 Peripheral IV Insertion Procedural Checklist

STEP	DESCRIPTION
1	Perform hand hygiene and organize equipment.
2	Explain procedure to patient.
3	Apply tourniquet on selected arm, 3 to 5 inches above the elbow.

4	Ask patient to open and close hand or hang arm to gravity.
5	Inspect arm for veins with largest diameter and fewest branch points.
6	Sterilize insertion site with chlorhexidine, alcohol, or povidone iodine.
7	Stabilize vein with nondominant hand by holding skin taut.
8	**Winged catheter system (butterfly)**
	a. Hold the system with thumb and forefinger on the finger grips.
	b. Access the vessel at a low 10 to 30 degrees angle.
	c. Visualize blood return along the catheter, then up the extension tube.
	d. Lower needle and advance the entire catheter and needle unit.
	e. Stabilize the system and pull back until the push-tab component releases from the device.
	f. Discard shielded needle into sharps container.
9	**Over-the-needle (angiocatheter)**
	a. Hold device by ribbed needle housing using dominant hand.
	b. Insert catheter using dominant hand with bevel up at 10 to 30 degrees angle in direction of vein.
	c. Observe for blood return through flashback chamber.
	d. Advance 2 to 3 mm and lower needle until flush with skin.
	e. Gently advance catheter into vein until hub rests at puncture site.
	f. Stabilize cannula and release tourniquet with nondominant hand.
	g. Use one finger to apply pressure over catheter tip to stop blood flow.
	h. Slide off needle or press safety button to retract needle.
	i. Dispose needle in sharps container.
10	Attach extension set and flush with normal saline.
11	Secure catheter with tape and transparent occlusive dressing.
12	Ensure that sterility is maintained throughout the procedure.

IV, intravenous.

CENTRAL VENOUS CATHETERS

OVERVIEW

A CVC is defined as a venous intravascular catheter that terminates at or close to the heart, in one of the great vessels. In the United States the Centers for Disease Control and Prevention (CDC) estimates that over 5 million CVCs are placed each year leading to 15 million central line days per year.[1] A CVC can be used for administration of select medications and blood products, central venous pressure (CVP) monitoring, and sampling of central venous blood. Additionally, in the CCU, an introducer catheter can allow introduction of a transvenous pacer (TVP) or a Swan-Ganz catheter. The vessels that are commonly cannulated for obtaining central venous access are the IJV, the subclavian vein (SCV) (**Figure 48.2**), and the FV. CVCs can also be used for hemodialysis, plasmapheresis, chemotherapy, and parenteral nutrition.

CVCs are available with antimicrobial impregnation (eg, chlorhexidine-silver sulfadiazine, minocycline-rifampin) and these are used when the anticipated use is over 5 days. Studies have shown a lower incidence of bacterial colonization and lower rate of central line-associated blood stream infection (CLABSI) when antimicrobial-coated CVCs are used.[6] A working knowledge of the indications and contraindications for CVC placement, as well as the principles for its insertion, maintenance, and removal is essential.

TYPES OF CENTRAL VENOUS CATHETERS

In the CCU, there are five main types of catheters that are used for central access. The most commonly used line is the TLC because it provides multiple lumens for infusion of medications and fluids (**Figure 48.3A and B**). Nontunneled hemodialysis catheters (**Figure 48.3C**) are often placed in the CCU for intermittent hemodialysis or continuous renal replacement therapy. Sheath introducers (**Figure 48.3D**) are usually single lumen and can be placed in the venous or arterial system. These can be used for insertion of a temporary pacemaker (venous circulation) and are also often left in place after left heart catheterization (arterial circulation). The Swan-Ganz catheter (**Figure 48.3E**) or PAC can be placed through a sheath introducer into the pulmonary artery. See Chapter 49 for a full discussion of invasive hemodynamic monitoring including CVP and pulmonary artery catheterization. PICC lines are often placed in the CCU patient for long-term vascular access for medications such as antibiotics. A

PICC line is considered a central line as the tip ends in the SVC. Intravascular cooling catheters (**Figure 48.3F**) may be used to induce therapeutic hypothermia in the CCU patient who is post cardiac arrest. Other central catheters one may encounter in the CCU patient include long-term VADs such as tunneled hemodialysis catheters, Hickman catheters, and Ports, which are not discussed in this chapter.

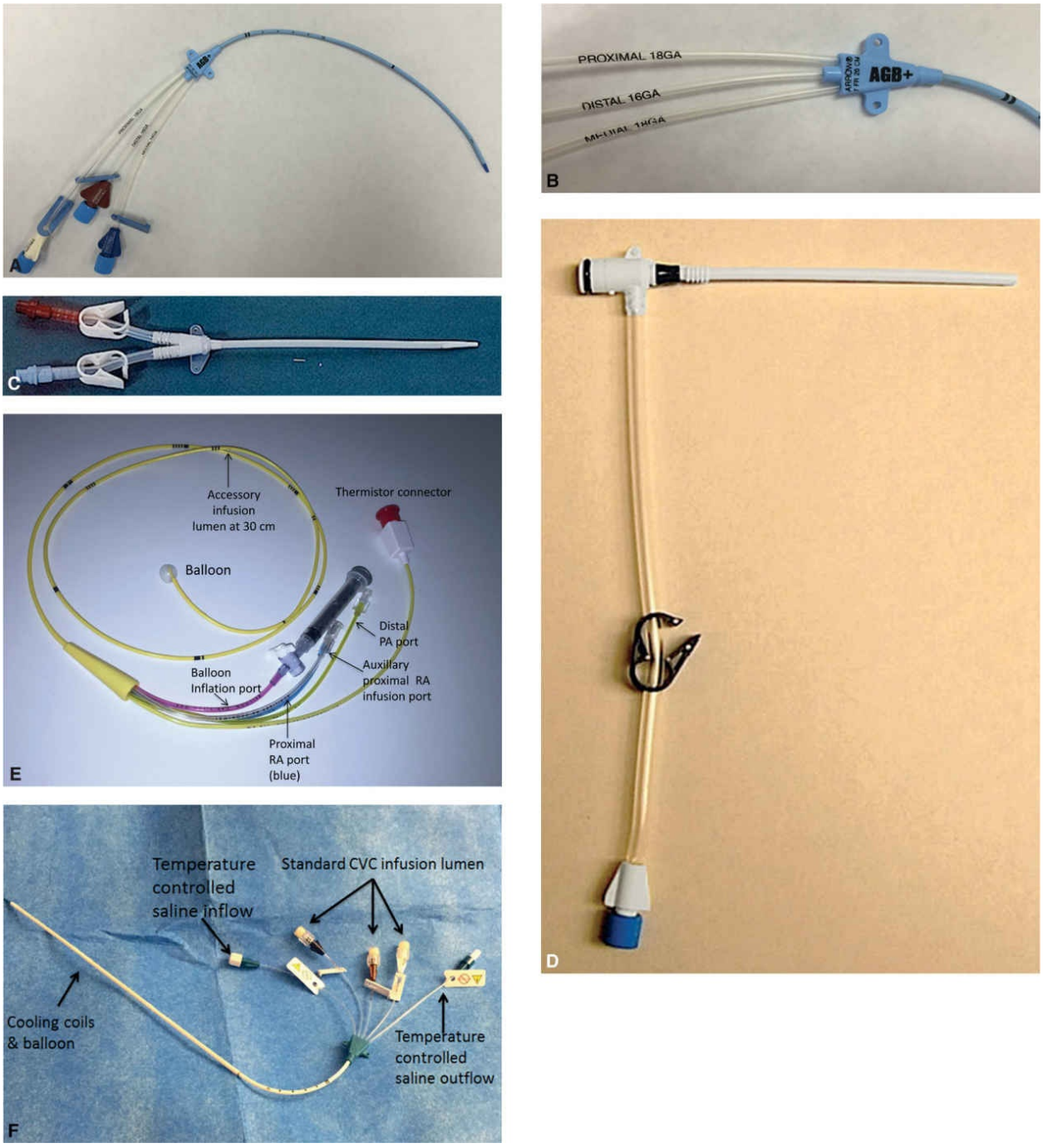


FIGURE 48.3 A, Triple lumen catheter. B, Three ports of the triple lumen catheter. C, Nontunneled hemodialysis catheter. D, Sheath introducer. E, Swan-Ganz or pulmonary artery catheter. F, Cooling catheter. CVC, central venous catheter. RA, Right atrium; PA, Pulmonary artery.

Triple Lumen Catheter

The TLC has three ports: proximal (white, 18G), medial (blue, 18G), and distal (brown, 16G) in relation to the site where the line enters the patient (**Figure**

48.3B). **Table 48.3** summarizes their basic characteristics. The catheter is easily inserted at the bedside either electively or during emergencies. It is sutured at an appropriate length based on the patient's height and insertion site (see section on technique). The catheter is typically made of polyurethane and is radiopaque so the tip can be easily visualized on a chest radiograph. The tip should be in the SVC, at the junction of the SVC, and the right atrium (RA). The three lumens allow infusion of multiple, even incompatible solutions, at the same time. The distal port (brown, 16G) has the fastest flow rate and is used for resuscitation fluids and blood products, as well as for monitoring CVP because it gives the most accurate waveform. The distal port should also be used for venous blood sampling such as measurement of central venous oxygen saturation ($Scvo_2$), as it has the fastest flow rate and is closest to the pulmonary artery. The $Scvo_2$ is a surrogate for mixed venous O_2 saturation (Svo_2). TLCs with continuous measurement of $Scvo_2$ are available as well (PreSep catheter, Edwards). If hyperalimentation or total parenteral nutrition (TPN) is anticipated, the medial lumen should be dedicated solely for this purpose in order to limit risk of infection.

TABLE 48.3 Port Characteristics of the Triple Lumen Catheter

LUMEN	COLOR	GAUGE	LOCATION	RECOMMENDED USES
Distal	Brown	16	Catheter tip	1. Central venous pressure monitoring
				2. Administration of viscous, high volume of fluids, or blood products
				3. Medication administration
				4. Blood sampling
Medial	Blue	18	2.2 cm from distal	1. TPN or cap for future TPN use
				2. Medication administration (if TPN is not anticipated)
Proximal	White	18	2.2 cm from medial	1. Medication administration
				2. Blood administration

The colors may vary depending on the manufacturer.
TPN, total parenteral nutrition.

Nontunneled Hemodialysis Catheter

These are double lumen catheters (**Figure 48.3C**) for hemodialysis access with internal diameter of approximately 12G to accommodate high flow rates needed for hemodialysis or plasmapheresis. The catheters typically have a brown port and a blue port. The blue is the distal port from which the wire appears. Blood is drawn from the brown port into the dialyzer machine and the dialyzed blood is returned via the blue port. The ports should be reserved only for hemodialysis, except in a life-threatening emergency. Hemodialysis catheters are placed in either the IJV or CFV; the SCV is avoided due to the risk of SCV stenosis or thrombosis, especially if arteriovenous fistula (AVF) creation is anticipated for long-term access.

Sheath Introducer

An introducer is an "L-shaped" single lumen, large bore (>8F) VAD with a port, which can be used to insert various devices and catheters (**Figure 48.3D**). The short length and large diameter make it an ideal catheter for large volume resuscitation. When an introducer is used with a pressurized system, liters of fluids and blood products can be infused within minutes. Since it has one lumen, additional incompatible medications cannot be infused through the same lumen. Double and triple lumen introducers are available and have the advantage of additional ports for medication infusion, however at the expense of a lower flow rate. Additionally, in an emergency, a TLC can be potentially inserted through an introducer for additional lumen, provided sterility is maintained. When placed in the venous system, it serves as a conduit for introduction of devices and catheters, like a TVP or PAC for right heart catheterization (RHC). When placed in the arterial system, introducers are used for procedures such as left heart catheterization. Accidental removal of sheath introducers, especially arterial sheaths, is potentially fatal. Only an experienced operator should remove arterial sheaths because it carries a high risk of hemorrhage and death.

Pulmonary Artery Catheter

The PAC or Swan-Ganz catheter is a long quadruple lumen thermodilution catheter used for invasive hemodynamic monitoring (**Figure 48.3E**). It is inserted through a sheath introducer under sterile technique and the balloon inflated before advancing into the pulmonary artery. It provides measurements of right atrial, right ventricular, pulmonary artery, and pulmonary artery occlusion

pressures (PAOP), and allows measurement of cardiac output and oxygenation (Svo_2). Although the PAC provides extremely useful information about the hemodynamic status of the patient, its role has diminished as studies show it does not change clinical outcomes. Nevertheless, the PAC does provide useful information and is still utilized in CCUs and cardiothoracic ICUs, both for diagnosis and monitoring of shock states, as well as postoperative management of the cardiac surgery patient. The PAC is reviewed in detail in Chapter 49.

Intravascular Cooling Catheter

With the advent of therapeutic hypothermia after cardiac arrest, targeted temperature management of post cardiac arrest patients is often performed in the CCU. Intravascular cooling catheters can have a built-in temperature sensor that allows for precise control. It controls the temperature of saline circulating through catheter balloons via remote sensing of the patient's temperature (Zoll IVTM Catheters, Chelmsford, MA). The catheters can come with additional lumens that can be used for vascular access. The patient is cooled or warmed as venous blood passes over each balloon, exchanging heat without infusing saline into the patient. This allows for cooling to targeted temperature for the induction of hypothermia and precise temperature control during the rewarming and maintenance phase of therapeutic hypothermia.

ECMO Catheter

Extracorporeal membrane oxygenation (ECMO) is being increasingly used for prolonged mechanical cardiopulmonary support and is often delivered in the CCU or cardiothoracic ICU. Venoarterial (VA) ECMO is used for patients with cardiac failure and venovenous (VV) ECMO is used for severe acute respiratory failure. ECMO catheters are much larger (13F to 31F) and usually placed percutaneously by surgeons, typically by a modified Seldinger technique, using serial dilators to accommodate the large size. The major complications to monitor for are bleeding and limb ischemia.

Peripherally Inserted Central Catheter and Midline Catheters

PICC lines are placed for long-term venous access for intravenous medications and other therapeutics. They are usually placed in the interventional radiology (IR) suite by the IR service or at the bedside by a PICC service or an intensivist. They are inserted using ultrasound guidance into the basilic, cephalic, or brachial

vein (**Figure 48.2**) through a small introducer. PICCs come with single, double, or even triple lumen and are sometimes placed in lieu of a TLC because they carry a lower risk of complications. Vasoactive agents, TPN, and caustic medications can be administered through a PICC; however, it is not an optimal line for resuscitation in a critically ill patient, especially if it is single lumen. In the CCU, they are inserted in patients with poor venous access or in patients who are being transferred to medical floor who need long-term vascular access (ie, antibiotics for endocarditis).

Midline catheters are long catheters (3 to 8 inches) that are placed in the brachial, basilic, or cephalic vein, however these are NOT considered central lines. These can remain in place for up to 30 days and often obviate the need for a central line. The infection risk with midline catheters is low and comparable to a peripheral IV.[7]

INDICATIONS FOR CENTRAL ACCESS IN THE CCU

Vascular access is crucial in the CCU patient and can often be challenging in the setting of difficult venous access, prior IV drug use, or in the context of a deteriorating patient or one in cardiac arrest. **Table 48.4** lists common indications for central access in the CCU patient. In general terms, cannulation of a central vein allows for five main scenarios:

1. Medication administration: Administration of medications contraindicated for peripheral access or when the latter is unobtainable (**Table 48.5**).
2. Hemodynamic monitoring: Measurement of parameters such as CVP and $scvo_2$. PAC allows for measurement of cardiac output and PAOP, which can be used to guide treatment.
3. Extracorporeal therapies: Central access is needed for hemodialysis and other forms of renal replacement therapy, plasmapheresis, and ECMO.
4. Introduction of catheters: An introducer is necessary for advanced procedures performed in the CCU such as pulmonary artery catheterization and transvenous cardiac pacing.
5. Volume loading: Although fluid resuscitation is not an indication for central access, large bore introducers are very helpful in massive resuscitation with fluids or multiple blood products. Patients often are in shock and need vasoactive agents as well; hence central access is preferred.

TABLE 48.4 Indications for Central Access in the CCU

THERAPEUTIC PURPOSES
Administration of vasoactive medications: vasopressors, inotropes
Administration of blood products
Aspiration for venous air embolism
Hemodialysis
Plasmapheresis
INVASIVE MONITORING
Hemodynamic monitoring
Central venous pressure monitoring
Central venous oxygen saturation ($Scvo_2$)
Pulmonary artery catheterization
Transvenous cardiac pacing
Intra-aortic balloon pump
Left ventricular assist device
MEDICATION ADMINISTRATION
Drugs with a pH < 5 and > 9
Venous irritants regardless of pH or concentration
Nutritional support (total parenteral nutrition)
VASCULAR ACCESS
Emergency venous access
Lack of peripheral access
Massive transfusion

CCU, cardiac care unit.

TABLE 48.5 Medications to be Infused Through a Central Line

DRUG	CLASS	COMMENT
Amiodarone (Cordarone)	Antiarrhythmic	Central line preferred if concentration >2 mg/mL
Calcium chloride	Electrolyte	Standard concentration (1 g/50 mL) contains three times more elemental calcium than calcium gluconate; at risk for precipitation, so CVC recommended except in case of cardiac arrest.
Dextrose in water	Nutrition/fluid	CVC preferred in high concentrations (>10%)
Dobutamine (Dobutrex)	Inotrope	Inotrope used to improve CO. Low fixed doses can be given temporarily via peripheral IV depending on institutional policy.
Dopamine (Intropin)	Adrenergic agent	Low fixed doses can be given via peripheral access depending on institutional policy.
Epinephrine (Adrenalin)	Adrenergic agent	Potent vasoconstrictor; concern for extravasation. Cardiac arrest dose (1 mg of 1:10,000) can be given peripherally.
Esmolol (Brevibloc)	Beta blocker	Short-acting beta blocker infusion; central access preferred but can be given peripherally.
Milrinone (Primacor)	Inotrope/vasodilator	Central access preferred but can be given peripherally.
Nicardipine (Cardene)	Calcium channel blocker	Venous irritant; can be infused through large peripheral IV but change site every 12 h.
Nitroglycerin	Vasodilator	Central access preferred but can be given peripherally.
Norepinephrine (Levophed)	Adrenergic agent	Potent alpha adrenergic agent, vasoconstrictor; concern for extravasation.
Phenylephrine (Neo-Synephrine)	Adrenergic agent	Works mainly on alpha adrenergic receptors. Low-dose boluses and low fixed-dose infusion can be given temporarily via peripheral access depending on institutional policy.
Potassium chloride (KC1)	Electrolyte	High concentrations (20 mEq/50 mL) infused via CVC
Sodium chloride (NaCl)	Electrolyte	Hypertonic solutions (≥ 3%) given via central line
Vasopressin (Pitressin)	Vasopressor	Vasoconstrictor; concern for extravasation

This is a limited list of medications that may be encountered in the CCU. Check your institutional policy for medications that have to be infused through a central line.

Exceptions may be made during emergencies.
CCU, cardiac care unit; CO, cardiac output; CVC, central venous catheter.

PRECAUTIONS AND CONTRAINDICATIONS

Once the patient meets criteria of appropriateness for central line placement, it is the clinician's duty to assess for contraindications specific to each potential site. As CCU patients are all critically ill, contraindications are all relative. The operator must balance the risks and benefits to truly assess the need for the CVC. **Tables 48.6 and 48.7** summarize some absolute and relative contraindications, as well as site-specific relative contraindications for central line placement. Absolute contraindications at a particular site include distorted anatomy or trauma, infected skin or soft tissue, thrombosis, existing lines or devices, and vascular injury at that site. Relative contraindications include coagulopathy and bleeding disorders; however, these patients may need emergent vascular access so the benefits must be weighed against the risks. Examples include the patient with thrombotic thrombocytopenic purpura who needs plasmapheresis or the patient on aspirin, clopidogrel, and warfarin presenting with cardiogenic shock. Efforts should be made to correct major coagulopathy; however, emergent central venous access can be potentially lifesaving and should not be delayed as a result.[8]

TABLE 48.6 Contraindications and Considerations for Central Line Placement

ABSOLUTE CONTRAINDICATIONS
Patient refuses
Uncooperative patient
Site specific:
• Skin or soft tissue infection
• Venous thrombosis
• Prior radiation or sclerosing agent
• Vascular injury
Superior vena cava or inferior vena cava injury or thrombosis
Expected risk outweighs any benefit

Presence of line, pacemaker, or defibrillator on the same side
Presence of fistula on the same side
RELATIVE CONTRAINDICATIONS
Moderate to severe thrombocytopenia
Uncorrected coagulopathy
Suspected stenosis of the target vein (hemodialysis patients)
Presence of arteriovenous Fistula
Multiple failed attempts (>2 attempts)
Patient cannot tolerate or has contraindication to Trendelenburg position (ie, stroke or intracranial hemorrhage with elevated intracranial pressure)
Mechanical ventilation on patient on high positive end-expiratory pressure (PEEP)
Hemothorax or pneumothorax on the contralateral side
Whole lung atelectasis or pneumonia in contralateral side
CONSIDERATIONS FOR AVOIDANCE OF CENTRAL ACCESS IN HOMONYMOUS SIDE
Anticipated need for limb alert in patient who will require long-term dialysis
Anticipated need for limb alert in patient who will require long-term implantable cardioverter defibrillator/permanent pacemaker
Lymphadenectomy in homonymous side after mastectomy or radiation therapy

TABLE 48.7 Site-specific Relative Contraindications for Central Line Placement

SUBCLAVIAN VEIN
Severe chronic obstructive pulmonary disease
Contralateral pneumothorax
Whole lung atelectasis or pneumonia in contralateral side
Mechanical ventilation with high positive end-expiratory pressure or oxygenation requirements
Morbid obesity or extreme cachexia

Major coagulopathy or bleeding risk—noncompressible site
Fracture of ipsilateral clavicle or anterior proximal ribs
Inability to lie in Trendelenburg position
Left bundle branch block—guide wire can potentially induce complete heart block
INTERNAL JUGULAR VEIN
Cervical spine immobilization
History of intravenous drug use
Inability to lie in Trendelenburg position
Whole lung atelectasis or pneumonia in contralateral side
Left bundle branch block—guide wire can potentially induce complete heart block
FEMORAL VEIN
Avoid site if possible, especially if patient is ambulatory
Ipsilateral deep vein thrombosis
Large pannus
Fungal skin infection

Laboratory results and use of US may alleviate some of these contraindications. The use of ultrasound imaging is an important tool for identifying preexisting thrombus formation and anatomic variations in the IJV location, and allows for a safer and more successful line placement.[9] Additionally, operator experience is a major factor with regard to overcoming relative contraindications and limiting risk of complications. Simulation-based training has been shown to improve success rates and decrease both infectious and mechanical complications rates among trainees.[10–12]

SITE SELECTION IN THE CCU PATIENT

The operator must have an individualized approach to the CCU patient, performing a thoughtful assessment to determine the safest location of insertion, the safest method, and the appropriate periprocedural care. This will depend

mostly on the experience and skill of the operator. **Figure 48.4** illustrates site-specific considerations when choosing the insertion site for central line placement. **Table 48.8** lists the anatomic landmarks to identify for each site and also the advantages, disadvantages, and complications associated with each site.

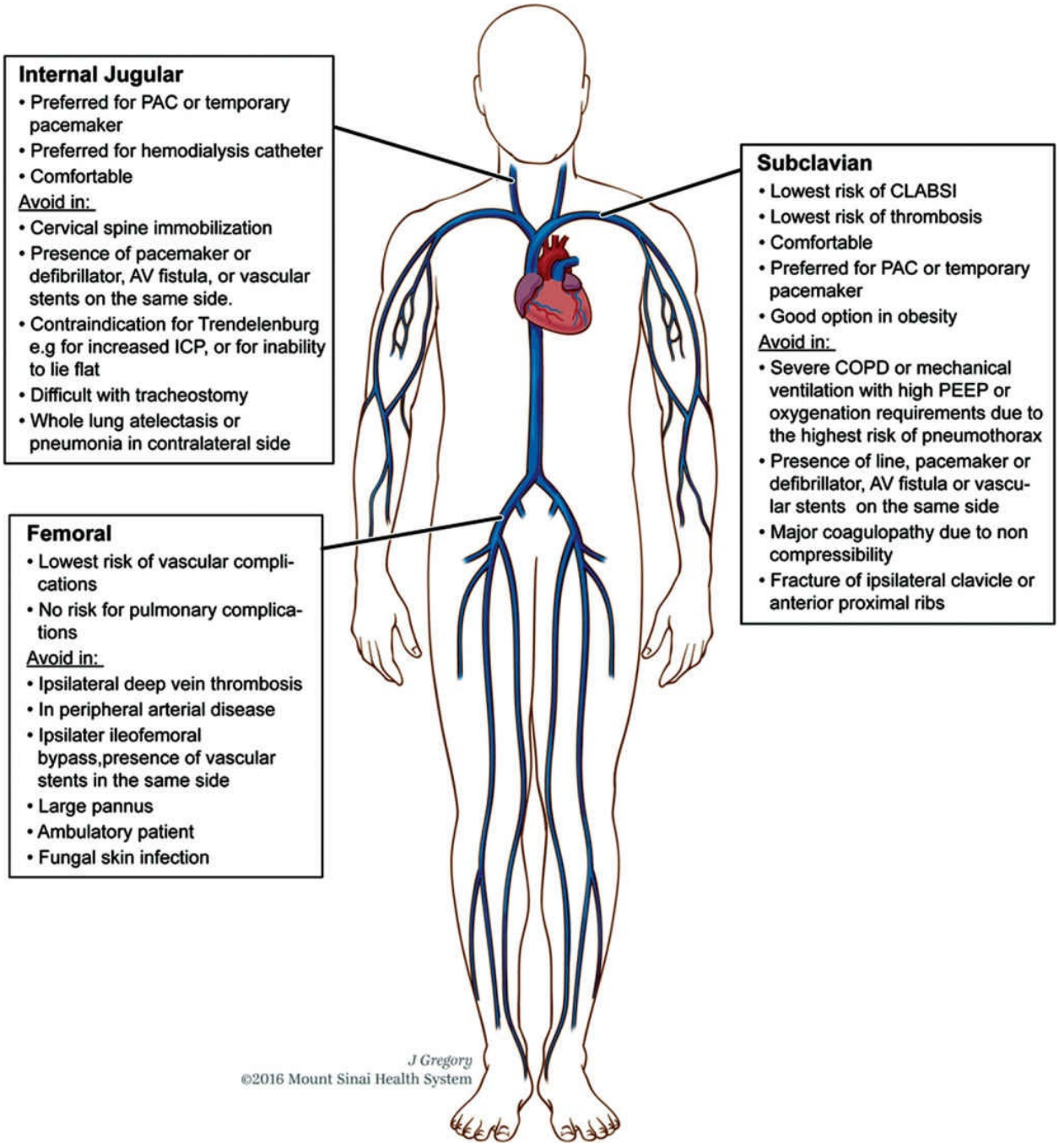


FIGURE 48.4 Site-specific considerations for central line placement. AV, arteriovenous; CLABSI, central line-associated blood stream infection; COPD, chronic obstructive pulmonary disease; ICP, intracranial pressure; PAC, pulmonary artery catheterization; PEEP, positive end-expiratory pressure.

TABLE 48.8 Site-specific Landmarks, Advantages, Disadvantages, and Complications

SITE	LANDMARKS	ADVANTAGES	DISADVANTAGES	COMPLICATIONS

Internal jugular vein	Mandibular angle Heads of sternocleidomastoid (SCM) Clavicle	Easy to locate, especially with US Straight path to superior vena cava Low complication rate Low maintenance from nursing standpoint Preferred site for pulmonary artery catheter (PAC) Low risk for malposition Lower risk of pneumothorax	Easily collapsible Proximity to: • Carotid artery • Lung apex • Thoracic duct • Phrenic/vagus nerve Higher infection rate Not preferred for short neck Difficult access during emergencies Need chest X-ray confirmation Dressings hard to maintain	Carotid puncture Infection Thrombosis Pneumothorax Arrhythmia Pleural effusion Chylothorax Brachial plexus injury Air embolism
Subclavian vein	Clavicle Suprasternal notch Manubriosternal junction 2 portions of SCM	Low infection rate Low risk for thrombosis Easily maintained Patient comfort Bony landmarks, even in obesity	Noncompressible site if bleeding Avoid in coagulopathy, cachexia, high PEEP Proximity to lung apex, thoracic duct High risk for malposition (crossing to contralateral subclavian or ipsilateral internal jugular vein) Need chest X-ray confirmation	Arterial puncture Pneumothorax Hemothorax Infection Thrombosis Arrhythmia Air embolism Chylothorax Pleural effusion Subclavian stenosis
Femoral vein	Inguinal ligament Laterally to pubic tubercle **VAN** (from medial to lateral: *vein, artery, nerve*)	Fast, easily accessed High success rate Can be used immediately Preferred for emergencies/cardiac arrest Preferred for patient in respiratory distress or on high PEEP	Highest risk for infection Highest risk for thrombosis Proximity to femoral artery No central venous pressure monitoring $scvo_2$ less reliable Prevents mobility	Infection Thrombosis Arterial puncture Retroperitoneal hematoma Arteriovenous fistula Pseudoaneurysm Inferior vena cava

	No risk of pneumothorax	Dressing changes take longer	filter dislodgement Air embolism

GENERAL RULES

As with any procedure, the operator should always weigh the risks and benefits of placing a central line at a particular site in order to avoid a high-risk complication. The operator should only attempt at a site where he or she is comfortable placing the CVC. With the popularity of US, many junior operators are very comfortable with US-guided CVC and may not feel as confident with SCV access. Always review the chest radiograph and attempt cannulation preferably on the same side as the lung pathology (ie, perform right IJV or subclavian CVC if the patient has pneumonia in the right lung). Causing a pneumothorax on the normal lung is potentially fatal. Always check a chest radiograph after unsuccessful attempts at IJV or subclavian CVC, prior to trying on the opposite side. Monitor for bleeding complications during and after CVC cannulation. A hematoma in the neck due to inadvertent puncture of the carotid artery can potentially lead to airway compromise by compressing the trachea. The subclavian site is noncompressible; so accidental cannulation of the subclavian artery may need intervention by a vascular surgeon. Similarly, bleeding in the FV or artery site can be very extensive before being recognized.

SITE-SPECIFIC CONSIDERATIONS

Subclavian Vein

The subclavian site is the most preferable site because it carries the lowest risk of CLABSI and thrombosis when compared to IJV or FV catheters; however, it has a higher risk of pneumothorax.[13] Additionally, once placed, it is a comfortable site for the patient and the catheter itself is tucked under the clavicle and less likely to be manipulated with patient movement. Accessing the SCV requires placement of the cannulation needle under the clavicle and near the apex of the lung, so it is not surprising that pneumothorax is a potential complication. Avoid SCV catheterization in patients with lung hyperinflation due to severe chronic obstructive pulmonary disease (COPD) or asthma, high F_{IO_2} and positive end-expiratory pressure while on mechanical ventilation, and patients with parenchymal lung disease and limited pulmonary reserve. Also avoid subclavian access in patients with chest wall deformities, cachexia, or

morbid obesity.

Internal Jugular Vein

This is a very popular site because it is easily accessed with ultrasonography.[9] The IJV is located under the sternocleidomastoid muscle (SCM) on either side of the neck. The right side of the neck is preferred because the vessels run a straight course to the RA. This side is preferred for PAC or temporary pacemaker placement, and hemodialysis catheter placement. IJV cannulation may be difficult in patients with tracheostomies because the tracheostomy holder often overlies the site. Additionally, oral and tracheal secretions from patients on mechanical ventilation often contaminate the IJV site, hence a transparent dressing is essential to secure the catheter and prevent CLABSI.

Femoral Vein

The FV site is associated with the fewest vascular and pulmonary complications; however it carries a higher infection rate and hence is discouraged by the CDC.[1] Interestingly, in a recent study comparing the three sites, there was no significant difference between the IJV and FV sites in rates of CLABSI; however, colonization rates were higher in the femoral site.[13] This site often limits the patient's ability to sit and walk, which can lead to deconditioning. Larger central catheters such as introducers and dialysis catheters are at risk for accidental displacement, which can potentially lead to massive hemorrhage. The FV is the choice of site for central venous catheterization during emergencies such as cardiac arrest (intraosseous access is another option) or in a patient who is in respiratory distress or agitated. It also has the added advantage in that placement does not have to be confirmed with a chest X-ray and so it can be used right away to administer lifesaving medications.

CATHETER-SPECIFIC CONSIDERATIONS

Introducer Catheter

An introducer for vascular access and resuscitation can be placed at any of three sites. If placing an introducer for insertion of PAC or temporary venous pacer in the CCU, right IJV access is preferred for direct access to the right heart. FV access for pulmonary artery catheterization is typically performed in the cardiac catheterization laboratory under fluoroscopic guidance.

Nontunneled Hemodialysis Catheter

A right IJV or FV catheter is preferred for central access for the initiation of hemodialysis in the CCU. The KDIGO guidelines for acute kidney injury (AKI) recommend (ungraded recommendation) in the order of preference: right IJV, followed by FV, then left IJV, and lastly, SCV with preference for the dominant side.[14] The subclavian and left IJV sites should ideally be avoided to limit risk of central venous stenosis. Although, the femoral site has been associated with increased risk of CLABSI, the CATHEDIA study demonstrated a lower catheter colonization rate in the FV site compared to IJV site in patients with body mass index (BMI) < 24.2 and a lower rate at the IJV site in patients with BMI > 28.4.[15]

CENTRAL VENOUS CATHETER PLACEMENT

Preparation and setup are key to successful CVC placement. Take time to optimize the setup by adjusting the height of the bed, procedure tray, and arrange the individual items in the order that they will be used. Always check the patient's platelet count, coagulation profile, and medication list (eg, anticoagulants, especially newer oral anticoagulants) prior to attempt.

STERILE TECHNIQUE

These catheters should be placed under the utmost sterile, operating room-like conditions. Always alert the CCU team including nursing and ancillary staff that a sterile procedure is going to be performed. Transit in and out of the room should be limited and anyone entering or leaving the room should wear a hat and a mask.

ULTRASOUND GUIDANCE

Numerous studies have shown that ultrasound guidance increases the first-attempt success rates and decreases mechanical and infectious complications.[9,11,16–18] The use of US for CVC placement is strongly advocated by various organizations such as the Agency for Health Care Research and Quality (AHRQ),[19] American Society of Anesthesiology,[20] American College of Surgeons,[21] American Society of Echocardiography, and Society of Cardiovascular Anesthesiologists.[22] Ultrasound guidance allows the operator to identify the target vessel and ensure that there is no thrombus within the vessel;

it allows for real-time visualization of the needle during the cannulation. Additionally, it allows confirmation of venous placement of the guide wire before dilation and placement of the catheter. Studies have shown significant variation in the size of the central vein and its position with respect to the artery (ie, deep to the artery or directly over the artery), allowing for the possibility of arterial puncture. Landmark methods lead to failure rates as high as 36%, even in experienced hands.[9,18]

US guidance is most useful for IJV and FV cannulation. Although US guidance can be used successfully for SCV access,[16] it has a steeper learning curve and should only be performed by experienced operators due to the risk of pneumothorax. Prior to inserting a central line using US guidance, the operator should perform a preprocedural scan. The portable US machine should be set to the "vascular" preset. A high-frequency linear array (ie, vascular) transducer or probe is used for this purpose because it images superficial structures well. The operator should hold the probe like a pencil with the hypothenar eminence steady on the patient's body. This allows for a steady image during the actual procedure. The marker on the transducer should always be "operator left" to match the marker on the upper left-hand corner of the screen of the US machine. Hence, the left side of the US probe corresponds to the left side of the screen. With this setup, in order to aim the needle left, one would advance the needle to the left, and vice versa. Ultrasound gel should be used as a medium to obtain the images. The depth should be adjusted such that the vessel of interest is in the center of the screen and the gain (brightness) should be optimized to ensure the image is not too bright and not too dark. Arteries have thick walls and are pulsatile, whereas veins have thin walls and are easily collapsible when pressure is applied over the vein. Bear in mind that in profound shock states, the artery may also be collapsible; however, it will still be pulsatile. Color Doppler or pulsed Doppler can be used to further confirm arterial versus venous flow.

In the short-axis or transverse plane, the vessels will appear as round circles (**Figure 48.5A**) as the ultrasound beam intersects the vessel in a cross section at a perpendicular angle.[23] In the long-axis or longitudinal view, the ultrasound beam is parallel to the vessels and the vessels will appear as long cylinders if the beam transects the vessel in the middle along its course (**Figure 48.5B**). Ensure the vein and artery are parallel to each other and not on top of each other. **Figure 48.6A and B** demonstrate examples of unsafe sites for cannulation as the carotid artery and IJV are not parallel to each other. Gentle side-to-side tilting of the transducer can often assist in optimizing the vessels such that they are parallel to

each other. Image the vein up and down in the transverse view to ensure patency. Do a compression maneuver by applying gentle pressure in at least three sites to ensure there is no thrombus (**Figure 48.7**). This is a leading cause of unsuccessful CVC placement; so avoid the site and order a comprehensive study through the radiology department. **Figure 48.8A and B** show examples of intraluminal thrombus detected prior to IJV CVC placement. This patient actually had left IJV thrombophlebitis due to *Fusobacterium necrophorum* sepsis with septic emboli to the lungs and other organs, also known as Lemierre syndrome. **Figure 48.9A and B** show the CT scan of the neck to correlate with the US findings. **Table 48.9** summarizes the steps for preprocedural ultrasound scan, which should always be done prior to US-guided line placement.

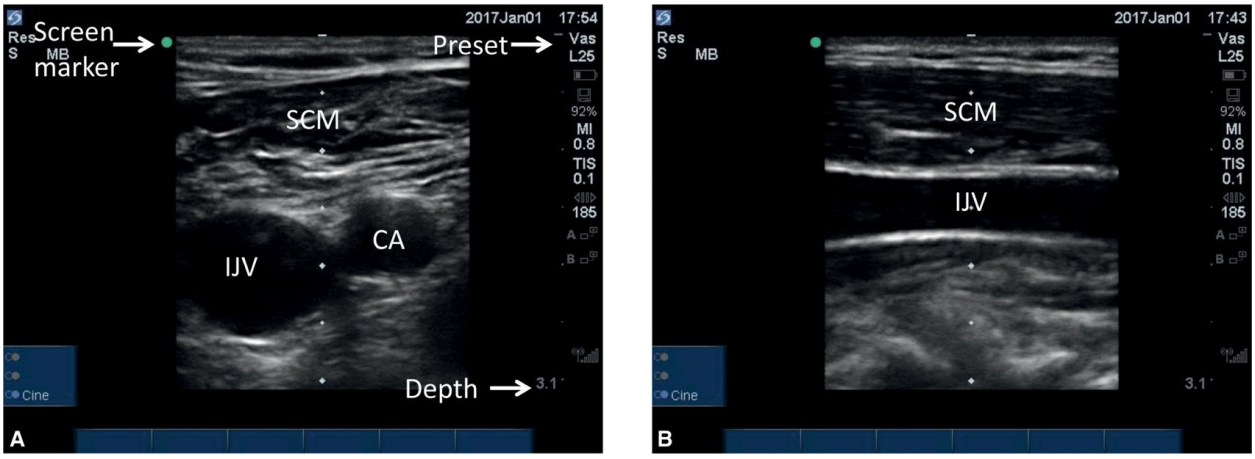


FIGURE 48.5 A, Short axis view of IJV. B, Longitudinal view of IJV. CA, carotid artery; IJV, internal jugular vein; SCM, sternocleidomastoid muscle.

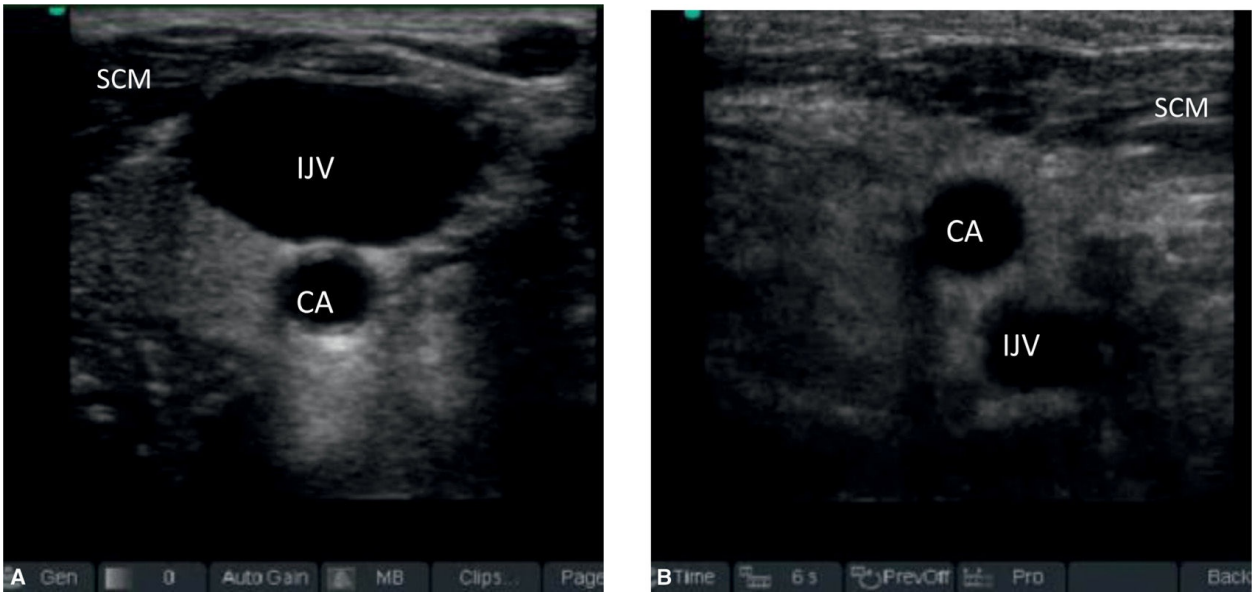
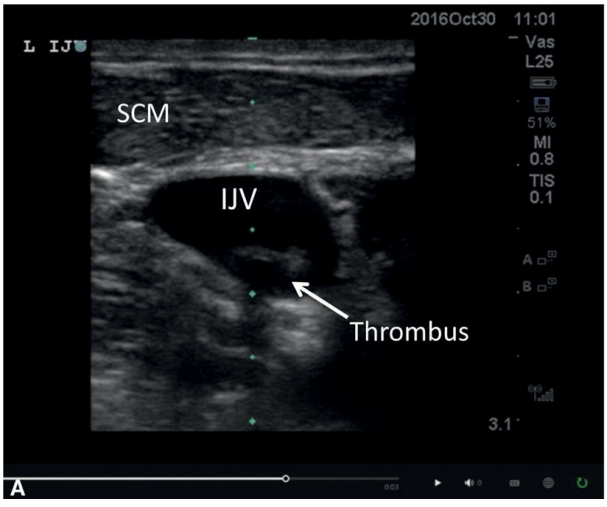


FIGURE 48.6 A, Unsafe site with carotid artery immediately beneath IJV. B, Unsafe site with carotid artery above IJV. CA, carotid artery; IJV, internal jugular vein; SCM, sternocleidomastoid muscle.

FIGURE 48.7 Image the entire length of the internal jugular vein and do a compression maneuver.



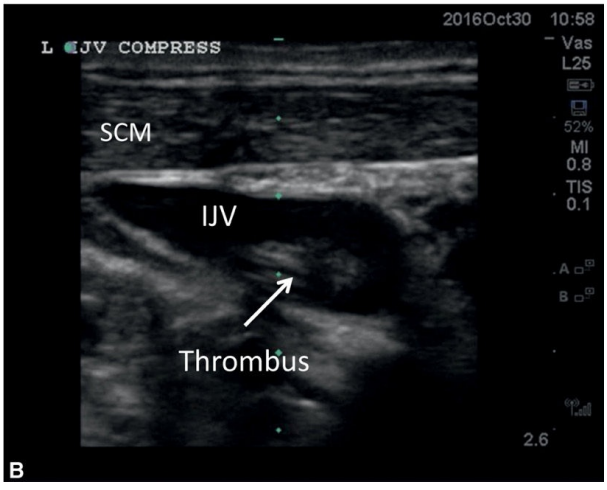


FIGURE 48.8 A, IJV intraluminal thrombus transverse view. B, IJV compression maneuver shows intraluminal thrombus with lack of compressibility.
CA, carotid artery; IJV, internal jugular vein; SCM, sternocleidomastoid muscle.

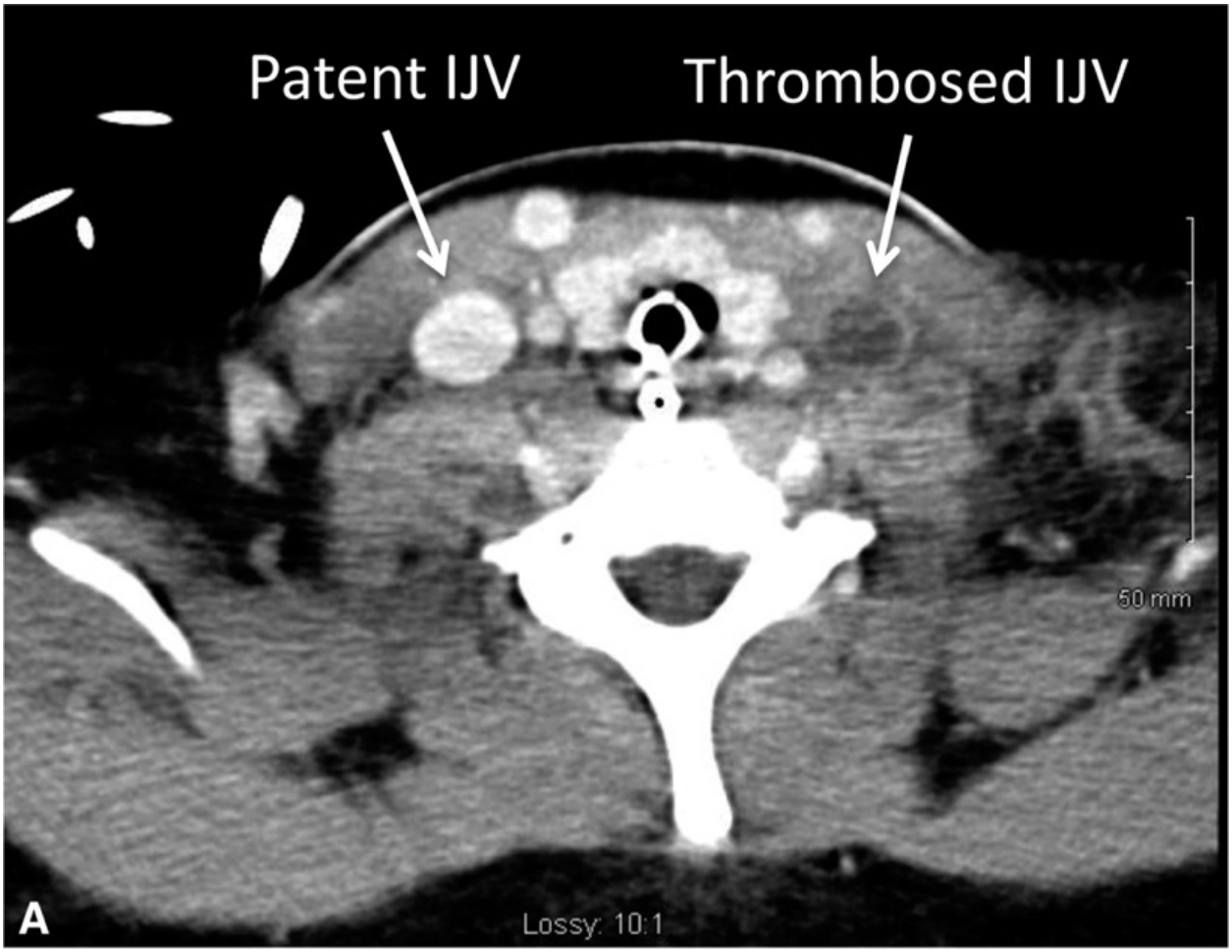


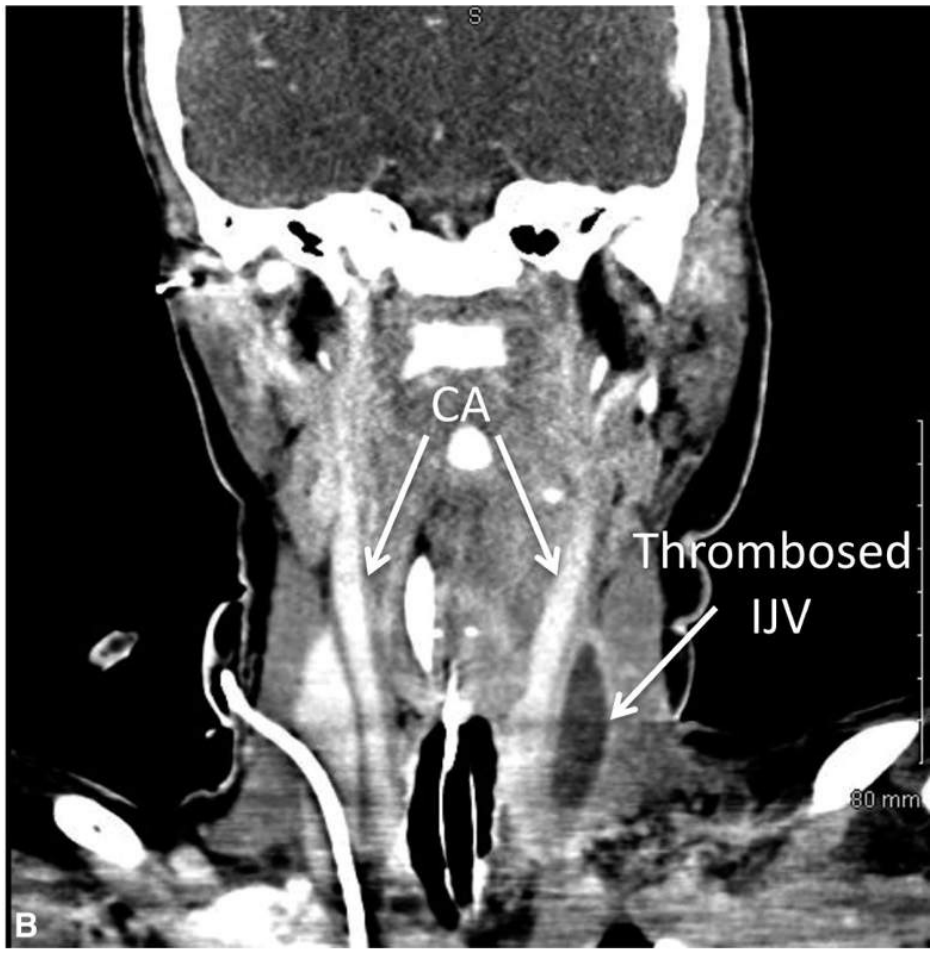
FIGURE 48.9 A, CT scan correlate of left IJV thrombosis (axial images). B, CT scan correlate of left IJV thrombosis (coronal images). CT, computed tomography; IJV, internal jugular vein.

TABLE 48.9 Steps for Line Placement: Preprocedural Ultrasound Scan

STEP	DESCRIPTION
1	Set ultrasound machine in “vascular” preset mode.
2	Hold vascular probe like a pencil with hand resting on patient.
3	Ensure probe marker is “operator left.”
4	Identify vein and artery.

5	Optimize gain and depth, ensuring vein is in center of screen.
6	Scan up and down the vessel to ensure patency.
7	Do a compression maneuver at three sites along the vessel to ensure no thrombus.
8	Ensure vein and artery are parallel to each other.
9	Image both sides for optimal site selection.
10	Identify safest site for cannulation.

Once a safe site is identified, cannulation should be performed with the thin-walled introducer needle with the needle inserted at a steep angle (70 to 90 degrees) and directly beneath the center marker of the probe. The US probe is held steadily with the nondominant hand and the needle advanced with the dominant hand. The needle and syringe apparatus may have to be jiggled gently because it is being advanced in order to appreciate the needle on the screen. Once there is good blood flow, the angle should be decreased prior to inserting the guide wire. Alternatively, a lower angle (30 to 60 degrees) can be used with the ultrasound probe being advanced as the needle is being advanced, with gentle back-and-forth sweeping of the probe to identify and follow the tip of the introducer needle directly into the vein (**Figure 48.10**). US can also be used for confirmation that the guide wire is in the vein and not the artery. Once the guide wire is inserted, the needle should be removed and the vein imaged in both the transverse and longitudinal planes. The guide wire should be visualized in the longitudinal plane within the thin-walled vein, which will be compressible with gentle pressure (**Figure 48.11). Be careful not to confuse this with the artery, which is immediately adjacent but will be thick walled, noncompressible, and pulsatile. A sterile probe cover should always be used in central venous catheterization. We recommend dynamic real-time use of ultrasound guidance over static US, where the skin overlying the central vein is marked due to higher success rates.**[18]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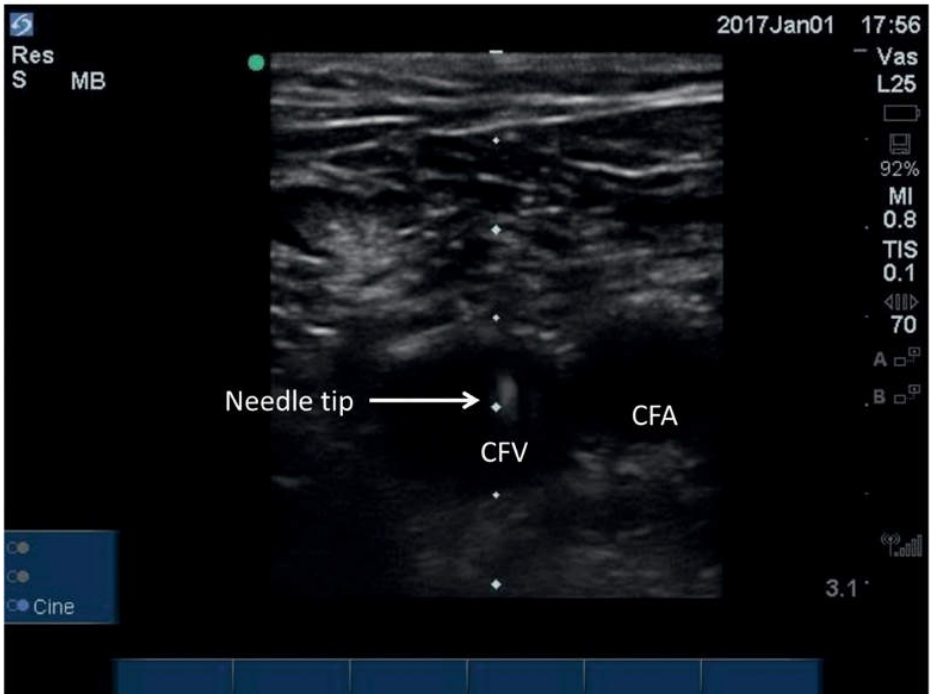
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TIS
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70
A
B
Needle tip
CFA
CFV
Cine
3.1

FIGURE 48.10 Echogenic needle tip visualized within common femoral vein. CFA, common femoral artery; CFV, common femoral vein.

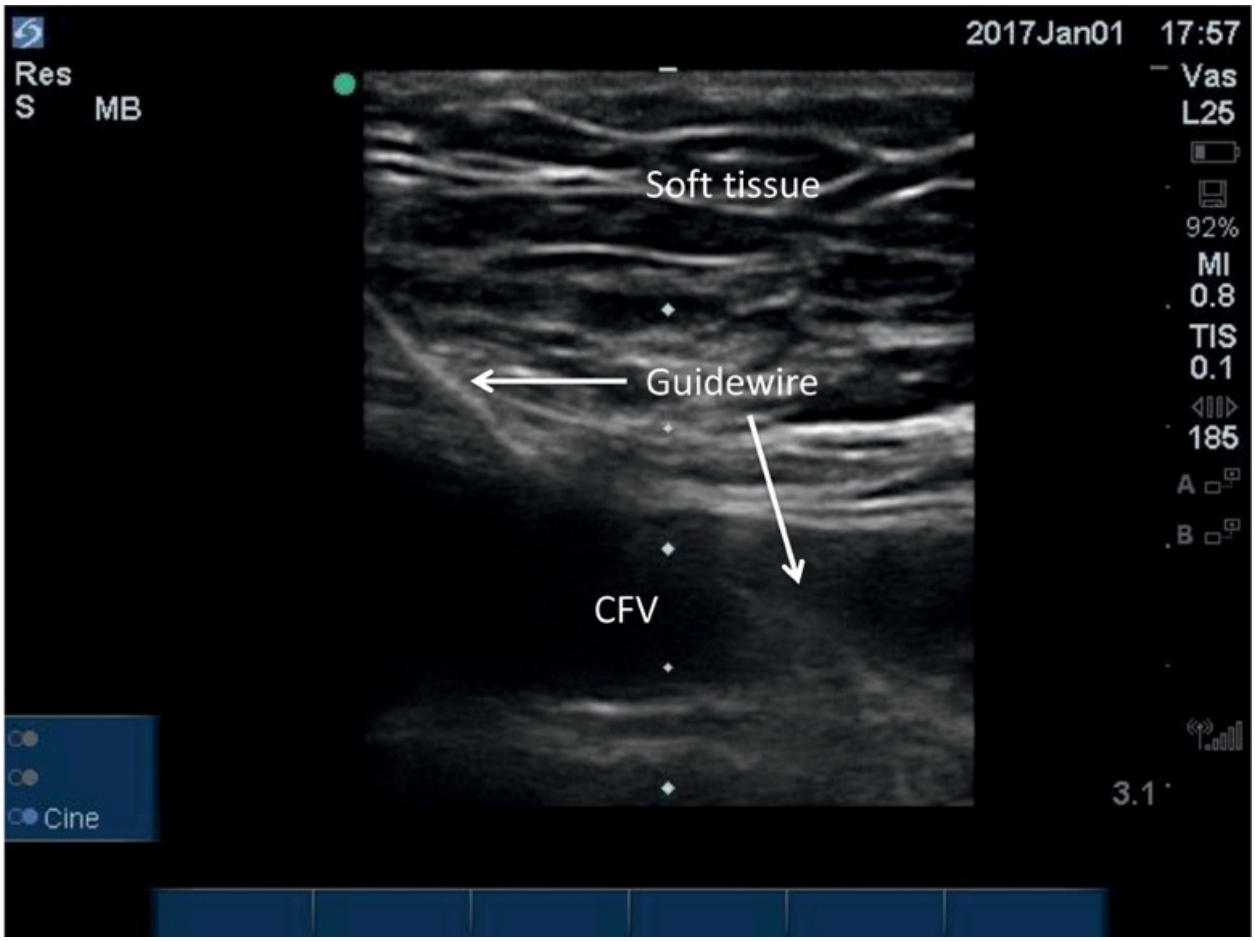

FIGURE 48.11 Echogenic guide wire visualized within common femoral vein. CFV, common femoral vein.

LINE PLACEMENT

The following instructions apply for all central venous access sites:

Step 1: Consent

Explain the necessity and benefits of the procedure in layman terms to the patient or surrogate, as well as the risks as described earlier; convey that this is a routine and frequently performed procedure in the CCU. Assure that you will provide local anesthesia to limit pain during the procedure and that the patient will need to be under a sterile drape for an approximate period of 20 to 30 minutes. In life-threatening situations, consent may be deferred if the procedure

is critical (eg, CVC placement for shock states) to treatment.

Step 2: Review Chart

It is imperative that the operator reviews the patient's laboratory data, medications, and chest radiograph to assess the safety of the procedure and for site selection. Consider platelet transfusion or reversing coagulopathy with fresh frozen plasma in the appropriate setting, if time allows.

Step 3: Prepare Equipment

Depending on the manufacturer, the central line kit will contain the basic items necessary to perform central venous catheterization (**Figure 48.12**). Many institutions have prepackaged customized procedure kits or a central line cart, which contains all the additional items necessary for CVC placement (**Figure 48.13**). Essential items to bring to the bedside include the central line kit, procedure pack or cart, ultrasound machine, ultrasound probe cover, and a bedside procedure table. **Table 48.10** contains a checklist of items necessary for central line placement.

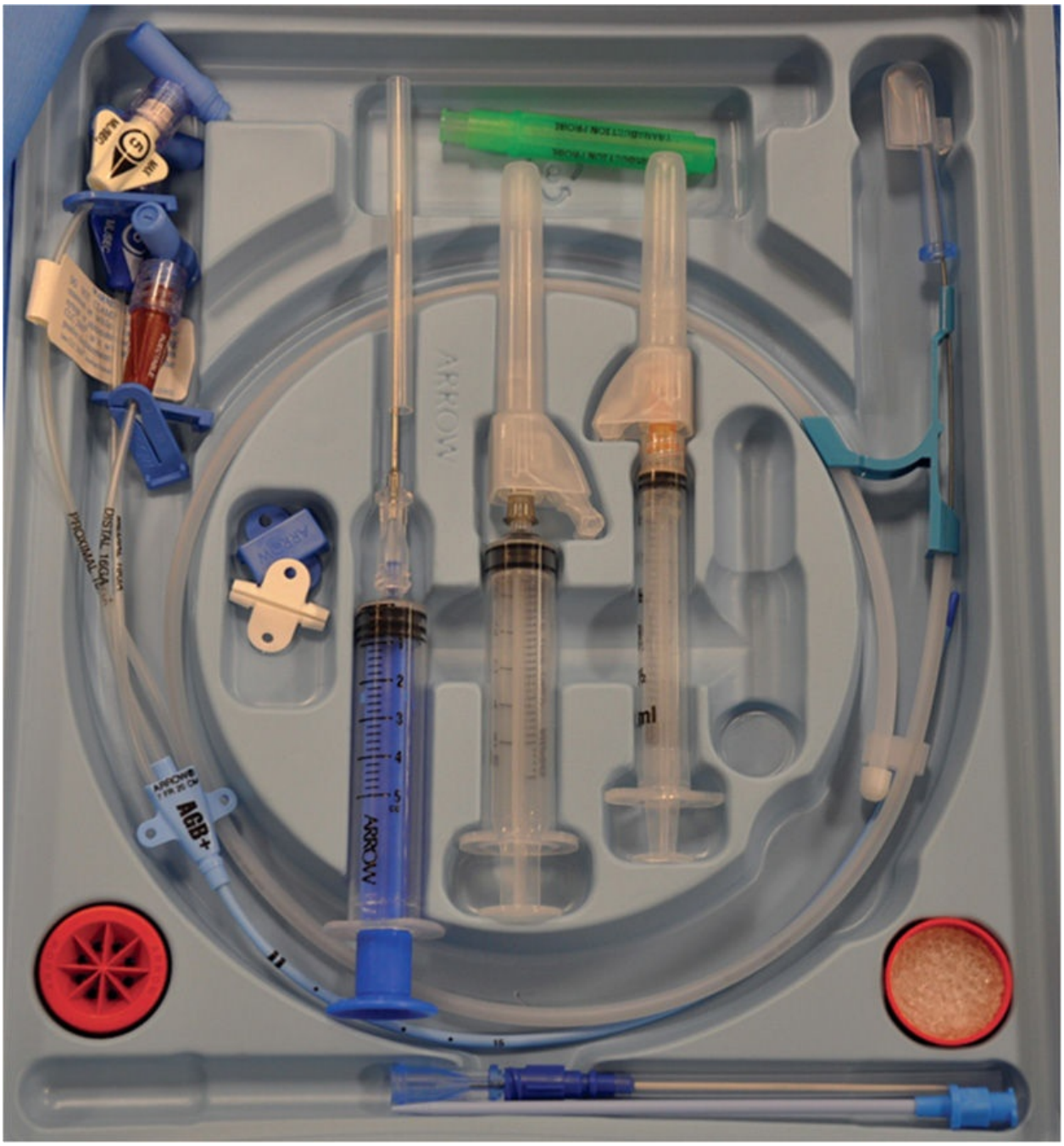

FIGURE 48.12 Central venous catheter kit.

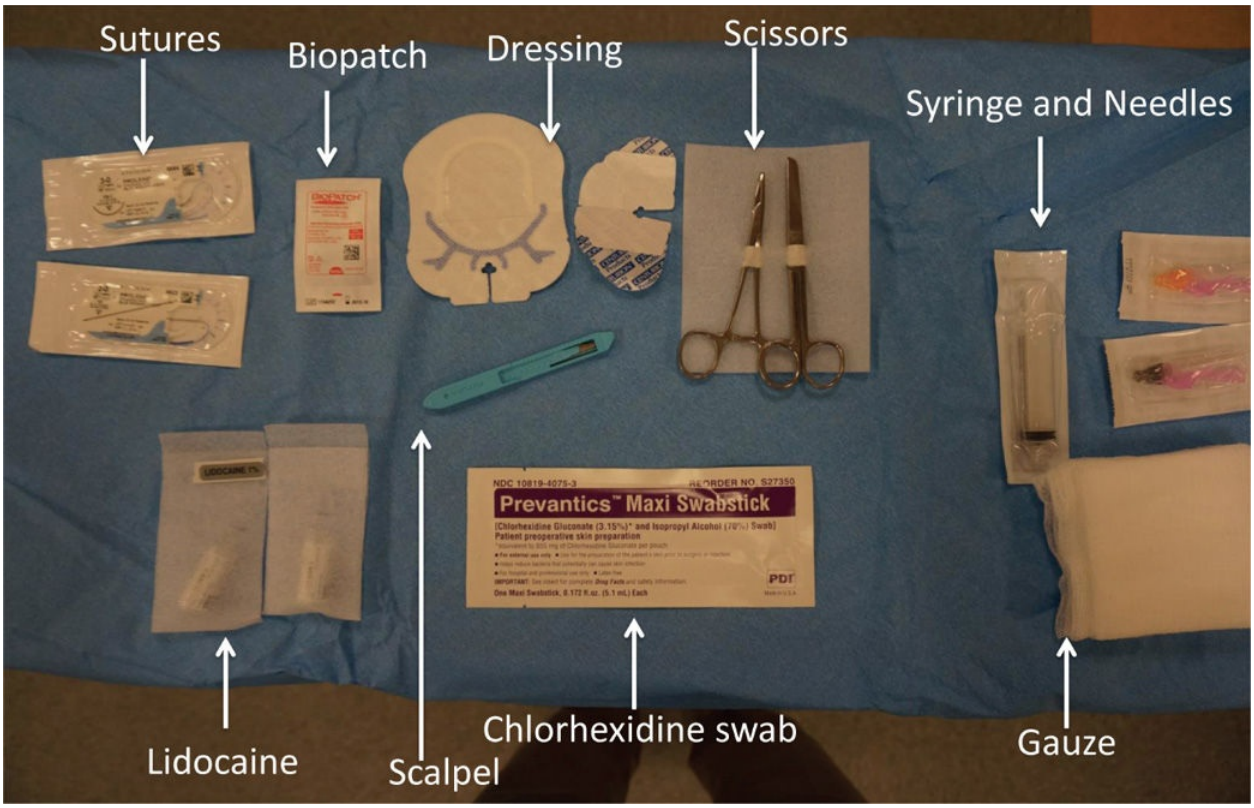

FIGURE 48.13 Additional items necessary for central line placement.

TABLE 48.10 Checklist of Items Necessary for Central Venous Catheterization

CENTRAL LINE KIT
Triple lumen catheter with Luer Lock caps
1% lidocaine 5 mL vial
25G × 1″ needle with 3 mL syringe for lidocaine administration
22G × 1.5″ “finder” needle with 5 mL syringe
18G × 2.5″ steel introducer needle with 5 mL Luer slip tip syringe
18G angiocatheter needle (in some kits)
GUIDE WIRE
Scalpel (#11)
Tissue dilator

Anchoring clips (clamp and fastener)
Needle holder
PROCEDURE CART OR PROCEDURE PACK ITEMS (IN ORDER OF USE)
2 surgical hair covers (one for assistant)
2 masks with eye shields (one for assistant)
Sterile gloves (for prepping) of appropriate size
2 chlorhexidine swabs/scrubs
Sterile gowns
Sterile gloves (for procedure) of appropriate size
Full-body fenestrated drape
3 sterile saline-filled syringes (or empty 10 mL syringe)
Medication label: 1% lidocaine
Sutures: 3.0 silk or nylon with curved or straight needle
Needle holder/driver for curved needle (if applicable)
Scissors (optional)
Gauze: 2″ × 2″ or 4″ × 4″ pads
Biopatch protective disk
Transparent, occlusive dressing
ADDITIONAL ITEMS
Portable ultrasound machine with linear array (vascular) probe
Sterile probe cover
Disposable underpad (blue Chux)

Step 4: Time-out

Prior to performing the actual procedure, it is important to engage the CCU nurse and any procedural assistants to conduct a preprocedural verification.

Perform and document a “Time-Out” as per your institution’s standardized protocol. All members should agree on the following:

1. Correct patient using two identifiers (name and date of birth or medical record number);
2. Correct procedure to be performed;
3. Correct site of insertion;
4. Ensure the procedural consent form is signed and dated.

Any concerns about procedural risks should be vocalized at this point. The assistant or any team member should be empowered to halt the procedure if inappropriate technique or break in sterility occurs.

Step 5: Patient Preparation

With an assistant’s help, optimize the position of the patient and the bed before sterile barrier precautions are in place. Once the site is prepped and draped, it is difficult and inconvenient to reposition the patient and optimize the procedural settings. Ensure the patient is on a monitor. Place the patient in Trendelenburg position, with the head of the bed tilted 15 degrees posteriorly. If US is being utilized, do a prescan of the venous anatomy on both sides and identify a safe site for venous access. A disposable underpad may be placed under the proposed insertion site to prevent blood contaminating the patient’s bed.

Internal Jugular Vein

Ensure the patient is in Trendelenburg position with the head slightly turned 45 degrees to the contralateral side from the intended insertion site. Anatomic landmarks for the IJV begin at the triangle formed by the heads of the SCMs and the clavicle (**Figure 48.14**). The surface projection of the IJV runs from the ear lobe to the medial clavicle, between the sternal and clavicular heads of the SCM. It increases in diameter as it descends to meet the SCV. Trendelenburg position and Valsava maneuver increase the size of the IJV. The IJV is easily collapsible and can often not be visualized due to excessive pressure by the ultrasound probe or the operator’s finger. Excessive head rotation can increase the overlap of the carotid artery over the IJV, increasing risk of arterial injury. Hence, US guidance is strongly recommended for IJV cannulation. The Trendelenburg position also minimizes risk and complications of venous air embolism. Caution is advised for patients with elevated intracranial pressure, congestive heart

failure, or other patients who cannot lay flat. These patients may be left in a comfortable position for most of the procedure (ie, prepping, draping) and then briefly placed in Trendelenburg position immediately before the cannulation portion.

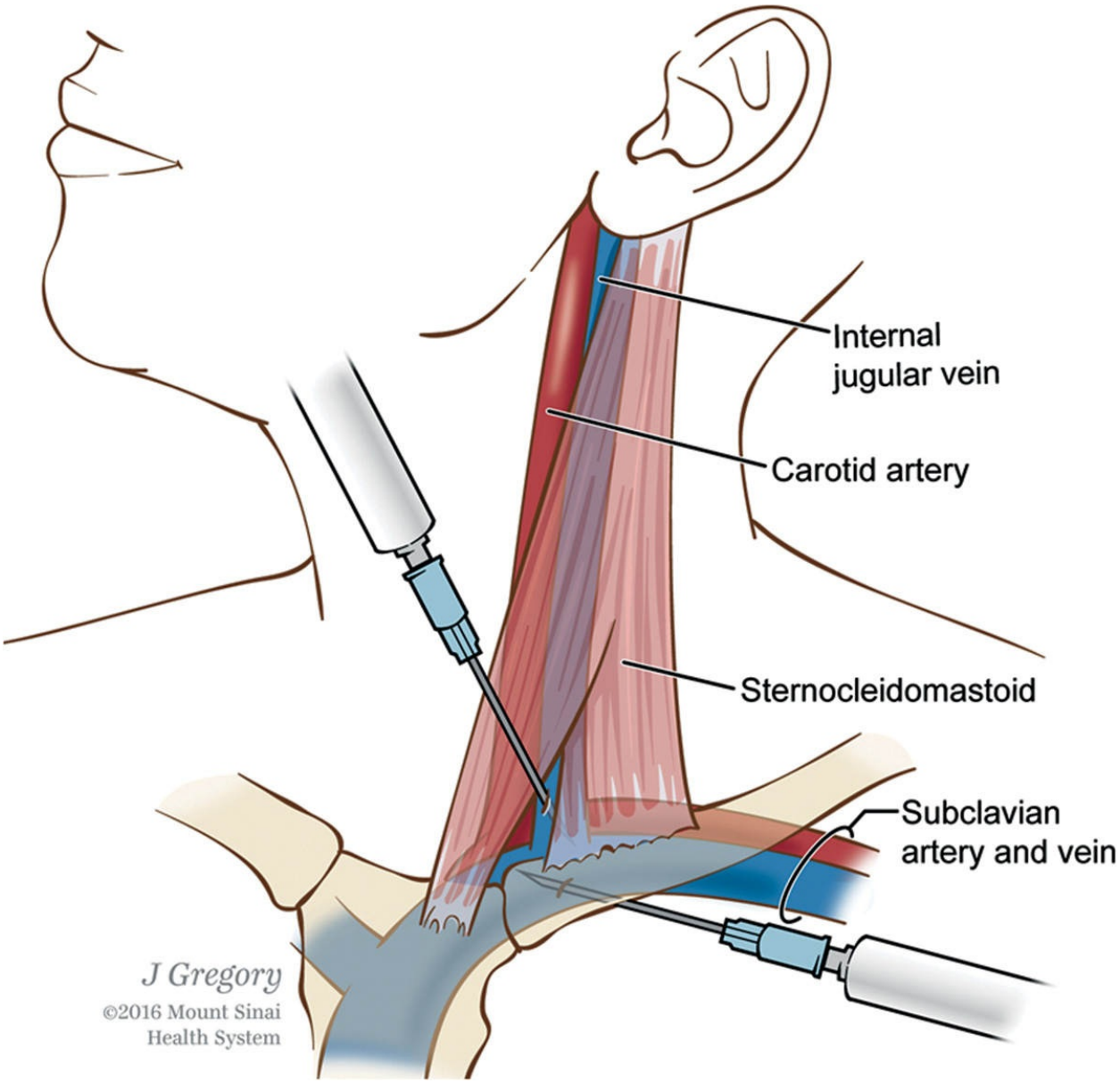

FIGURE 48.14 Internal jugular vein and subclavian vein anatomy.

Subclavian Vein

The SCV (**Figure 48.14**) is a continuation of the axillary vein and begins at the lateral edge of the first rib.[24] It courses anterior to the anterior scalene muscle, which separates it from the subclavian artery. It joins the IJV to form the brachiocephalic trunk. The pleural surface lies inferior and posterior to the SCV. The subclavian artery is immediately posterior to the vein. The SCV is usually not collapsible because it is tethered by fibrous connective tissue to the clavicle and first rib. This is especially helpful in the hypovolemic patient or during

cardiac arrest. The thoracic duct joins the left SCV at its junction with the IJV. Right SCV cannulation is preferred in order to avoid thoracic duct injury; however, it has also been shown to have higher mechanical complications such as malpositioning.[25]

Prior to cannulation, place the patient in a 15-degree Trendelenburg position and assess the anatomic landmarks, beginning with the middle third of the clavicle. Follow the clavicle laterally to the "bend" where it deviates superiorly from the proximal ribs. Just medial to this point, the SCV and IJV run inferior to the clavicle. The insertion site should be somewhat removed from the clavicle, so that the path of the needle stays parallel under the clavicle. The typical point is 2 cm lateral and 2 cm caudal to the middle third of the clavicle. Some operators place a rolled towel vertically under the spine to identify the external landmarks. Know that propping the shoulder or turning the head has been shown to decrease the size of veins. Although the traditional landmark approach is preferred by many, several articles suggest that US can increase the likelihood of success.[16,26]

Femoral Vein

For optimal exposure of the femoral region, place the patient in supine position, externally rotate and abduct the patient's leg away from midline.[27] The common FV lies medial to the common femoral artery as it runs distal to the inguinal ligament (**Figure 48.15**). The mnemonic "VAN" illustrates the contents of the femoral sheath (see **Figure 48.15**) from medial to lateral: femoral *v*ein, femoral *a*rtery, and femoral *n*erve. The femoral artery lies at the midpoint of a line connecting the pubic symphysis (PS) to the anterior superior iliac spine (ASIS). The FV lies 1 cm medial to the femoral artery. Localize the FV by palpating the artery or with US. The cannulation site must be inferior to the inguinal ligament. Reverse Trendelenburg position, with the feet tilted 15 degrees below the horizontal axis, can help engorge the FV and may aid in visualization.

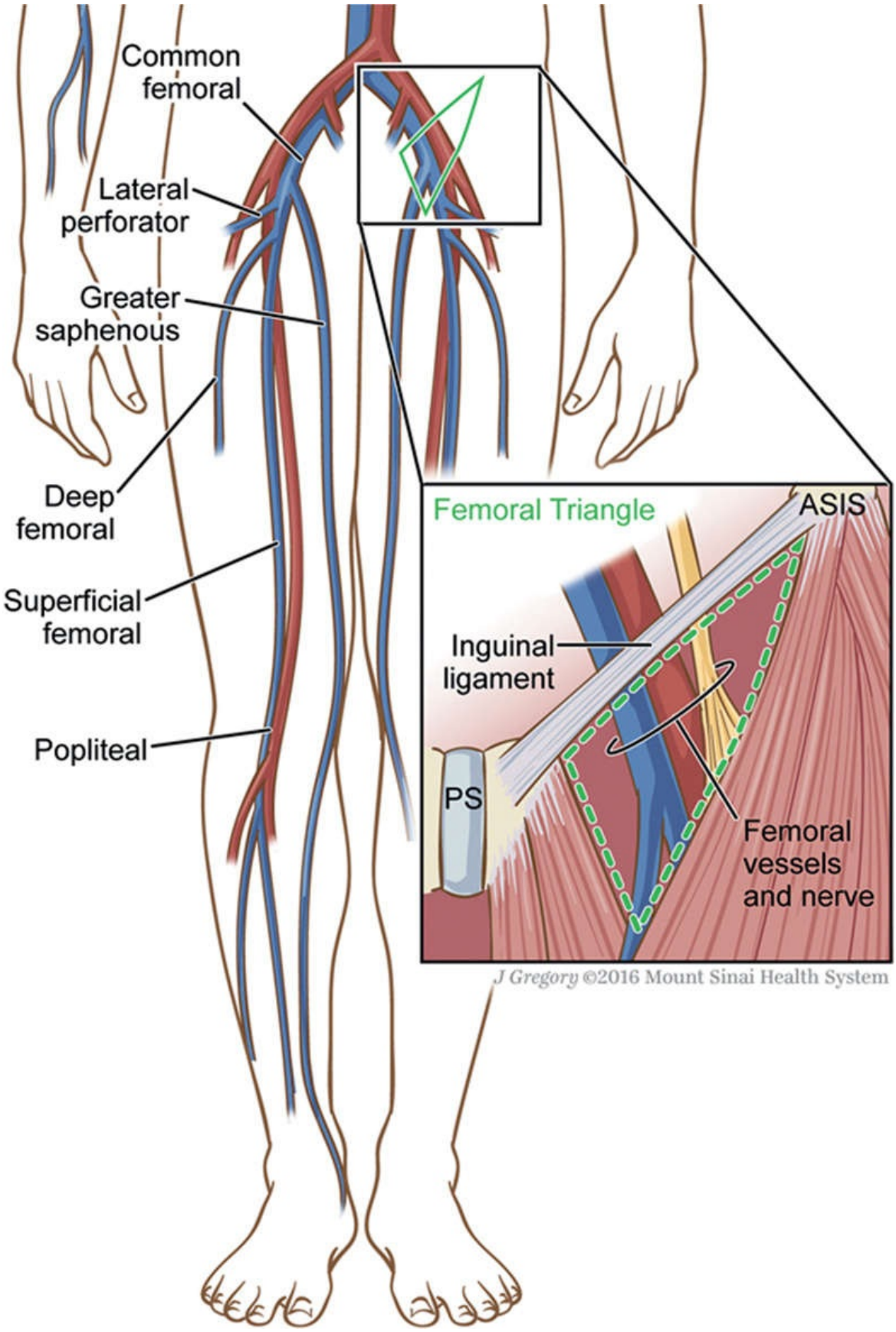

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FIGURE 48.15 Venous anatomy of femoral triangle and lower extremities. ASIS, anterior superior iliac spine.

Step 6: The Technique—The A to Z of Central Venous Catheterization

Dr. Seldinger developed the "Seldinger technique" in 1953.[28] More than 60 years later, the same technique is the gold standard for most vascular access procedures.[23,24] **Figure 48.16** illustrates the steps of the modified Seldinger technique where a needle is used to aspirate blood or fluid, a guide wire inserted through the needle, the tract dilated, and a catheter advanced into the vessel or desired space.

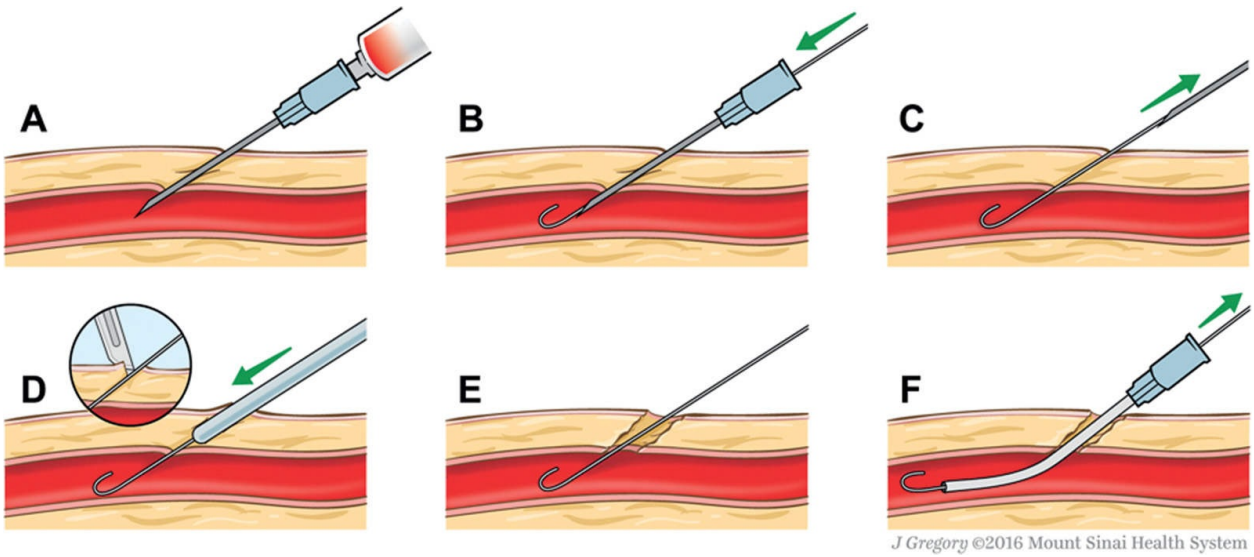


FIGURE 48.16 The Seldinger technique. A, Insert the needle into the vessel, advancing slowly until blood is aspirated. B, Stabilize the needle and insert the guide wire into the introducer needle. C, Remove the needle. D, Make a small skin incision and advance the dilator over the guide wire. E, Remove the dilator. F, Advance the catheter over the guide wire and then remove the guide wire.

The following is a list of steps for central venous catheterization using US guidance. Don a facemask with eye shield and a surgical hat ensuring all hair is tucked away. Jewelry or watches, which may be in the field, should be temporarily removed. Assistants and all personnel in the room should also wear a hat and mask.

A. Perform hand hygiene by washing hands for 30 seconds with soap and water or using an alcohol-based hand rub, taking care to cover areas such as the wrists, finger webs, and area under fingernails.

B. Don sterile gloves in sterile fashion. Open the wrapper widely, ensuring that

the sides of the wrapper do not fall back on the sterile gloves and contaminate it. Use care to touch only the inside of the glove with bare hands.

C. Prepare site using chlorhexidine-based swab or scrub with a back and forth motion for 30 seconds. Prepare a wide area and allow up to a minute for the solution to dry.

D. Deglove and perform hand hygiene once again.

E. Don sterile gown using correct technique. Put both hands into armholes and hold the gown away from the body allowing it to unfold completely. Minimize exposure of the hands outside the cuff. The assistant should pull the gown over the shoulder and tie the top portion and the inner belt of the gown, touching only the inside portion.

F. Don sterile gloves ensuring the cuffs of the gown are inside the sterile glove. Inspect the wrist to ensure that there is no exposed skin.

G. Grasp the belt card, wait, and hand it to the assistant. Make a counterclockwise turn and retrieve the outer belt from the assistant, who holds on to the belt card. Tie the outer belt firmly.

H. Hold the sterile full-body fenestrated drape and arrange it such that the head and feet match up with that of the patient. Remove the adhesive stickers and fold it gently like a book. Place the drape on the patient ensuring the fenestrated opening is directly on the insertion site. Pat down the drape to ensure it sticks to the body before opening. With one hand keeping the drape in place, gently open the sides of the drape like a book. The assistant can help extend the full-body drape by touching only the nonsterile edges of the drape. Be careful to avoid “drape creep,” whereby the drape is moved around, pulling material from the unprepped area to the sterile field.

I. The assistant should open the CVC kit and the operator should grasp the inside sterile cover and place the kit on the procedure table. Unfold the central line kit on the procedure table and position the contents at easy reach and in the order that you will use them. Take utmost care to ensure the contents do not get contaminated.

J. Prepare the TLC by placing Luer lock caps on the proximal (white) and medial (blue) ports, leaving the distal (brown) port open to allow exit of the guide wire. Flush the catheter lumens with sterile saline. If prepackaged sterile saline syringes are not available, three empty sterile syringes and a blunt needle can be used to aspirate sterile saline from a 50 mL saline bag with the assistant’s help. Alternatively, sterile saline can be spurted onto the

CVC kit from a prefilled 10 mL saline flush by the assistant. Prepare the guide wire by pulling back the J-shaped tip of the guide wire into the tapered hub.

K. Draw up 1% lidocaine local anesthetic using the 22G needle and syringe. Label the syringe with a lidocaine sticker. Note that the labeling is a requirement in the United States by the Joint Commission. This is done to ensure that the lidocaine is not confused with sterile saline and accidentally administered intravenously. Use a 25G needle for the initial injection over the skin.

L. If US is being utilized, drape the ultrasound probe with the sterile probe sheath. Hold the outside of the sterile cover and place sterile ultrasound gel (usually comes with the kit) inside the sheath. Have the assistant feed the nonsterile ultrasound probe into the inside of the sterile sheath, ensuring sterile gel is on the footprint of the probe. Grasp the sterile cover with the probe within and pull the sheath to cover the wire of the transducer. Do not touch the nonsterile probe or wire during this process. Place elastic bands or fasteners (comes with kit) to secure the outer cover so that it does not interfere with the procedure. Identify an area on the sterile field on which the probe can be placed when not in use. Be careful not to drag any uncovered parts of the wire into the sterile field.

M. Place gel onto the sterile probe and obtain a view where both the central vein and artery are visualized parallel to each other. The probe may need to be moved slightly up and down until the largest and safest site is identified. The assistant may need to further adjust the gain and depth to obtain an optimal view of the vein at the center of the screen.

N. Anesthetize the area over the insertion site, as well as the suture site, with 1% lidocaine. Make a wheal over the skin with the 25G needle and administer additional lidocaine in the soft tissue. Use the 22G needle if a longer needle is necessary, aspirating intermittently with the syringe to ensure a vessel is not entered. US guidance may be utilized to practice precise administration of the local anesthetic directly over the vein. Even in sedated patients, it may be wise to administer local anesthesia to ensure that they are not in pain and moving during the procedure.

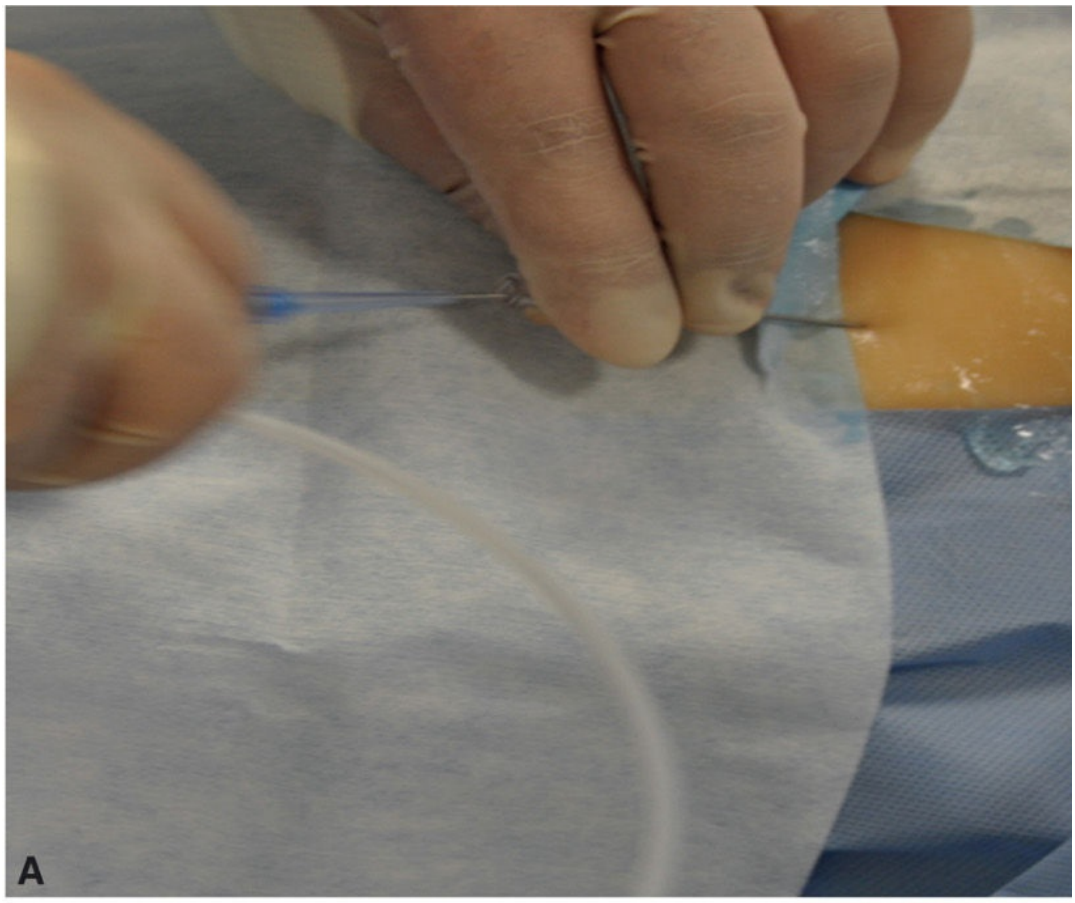
O. Prior to the actual central venous catheterization, arrange your equipment on the sterile procedure table in the order that you will use them: introducer needle, guide wire, gauze, scalpel, dilator, TLC, saline flushes. Scrambling to find these items during the procedure can often result in need for multiple

attempts.

P. Hold the ultrasound probe with your nondominant hand, steadying it by resting it on the patient. Obtain a transverse view and ensure the vein is at the center of the screen. Identify the distance to the vessel by looking at the distance scale on the right-hand side of the US monitor. A needle cap or the dilator can be used to apply pressure onto the skin to ensure the proposed insertion site is directly over the vein. With the dominant hand, insert the needle and slip-tip syringe (bevel up) immediately proximal to the probe at the center marker. Insert the needle using a steep angle (70 to 90 degrees) and advance the needle slowly into the vein, applying gentle negative pressure on the syringe (**Figure 48.17**). The skin may need to be made taut and a quick jab may be needed initially to pierce through the skin. The needle may need to be jiggled to identify it on the screen of the US machine. Alternatively, a lower angle (30 to 60 degrees) may be used with back and forth sweeping of the probe to follow the needle tip into the vein (**Figure 48.10**). Once the needle tip is directly over the vein, a quick jab may be needed to pierce through the vessel wall.

FIGURE 48.17 Needle position at center of linear array probe.

Q. When blood is aspirated, stop advancing and decrease the angle of the needle, ensuring good venous blood flow with negative pressure. Stabilize the needle by holding the needle with your thumb and index finger, steadying the needle by resting your hand on the body (**Figure 48.18A**). Remove the syringe from the needle making sure not to displace the needle from the vessel. Once you remove the syringe, nonpulsatile dark red blood is expected to flow gently. Pulsatile or bright red blood may indicate arterial cannulation. Remove needle and hold pressure if this occurs.


A

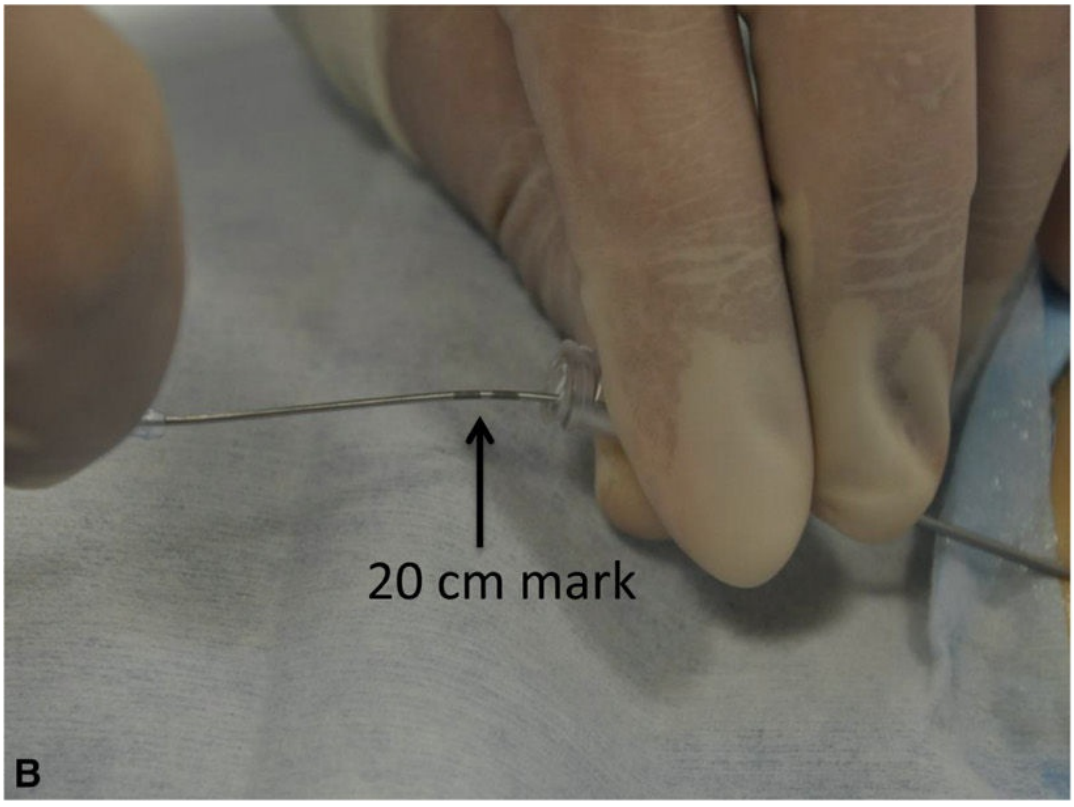

20 cm mark
B

FIGURE 48.18 A, Stabilization of the needle and insertion of the J-shaped guide wire. B, Advancement of the guide wire 20 to 25 cm.

R. Insert the guide wire into the introducer needle and advance it to 20 to 25 cm (**Figure 48.18A** and **B**). Each black mark on the guide wire indicates 10 cm. Monitor for arrhythmias if IJV or SCV is being cannulated. If you meet resistance, DO NOT force the guide wire. Resistance may indicate that the introducer needle may be against the vessel wall or intersection or may have come out of the vessel altogether. If this occurs, try withdrawing the guide wire, rotating it slightly, and decreasing the angle before readvancing it. If there is resistance still, remove the guide wire and confirm again your position into the vessel with US until blood is aspirated again into the syringe.

S. Once the guide wire is in, always keep a firm grip on it, especially after dilation. Now remove the needle and confirm the position of the guide wire with US by visualizing it in the vein in both the transverse and longitudinal views (**Figure 48.11**). In the transverse view, back-and-forth sweeping of the probe may be needed to visualize the guide wire entering the vein. In the longitudinal view, do not confuse the vein (compressible) and artery (pulsates when compressed).

T. Keeping the skin taut, make a small 1 to 2 mm nick with the number 11 blade at the insertion site with the scalpel (**Figure 48.19**). With the skin taut, advance the dilator over the wire in a twisting motion and dilate the skin and subcutaneous tissue only (**Figure 48.20**). Once the tract is dilated, remove the dilator and use gauze to control any bleeding that occurs after dilation. Keep hold of the guide wire at all times, particularly after dilation, to avoid inadvertent insertion into the vessel.

FIGURE 48.19 Skin incision with dull side of scalpel.

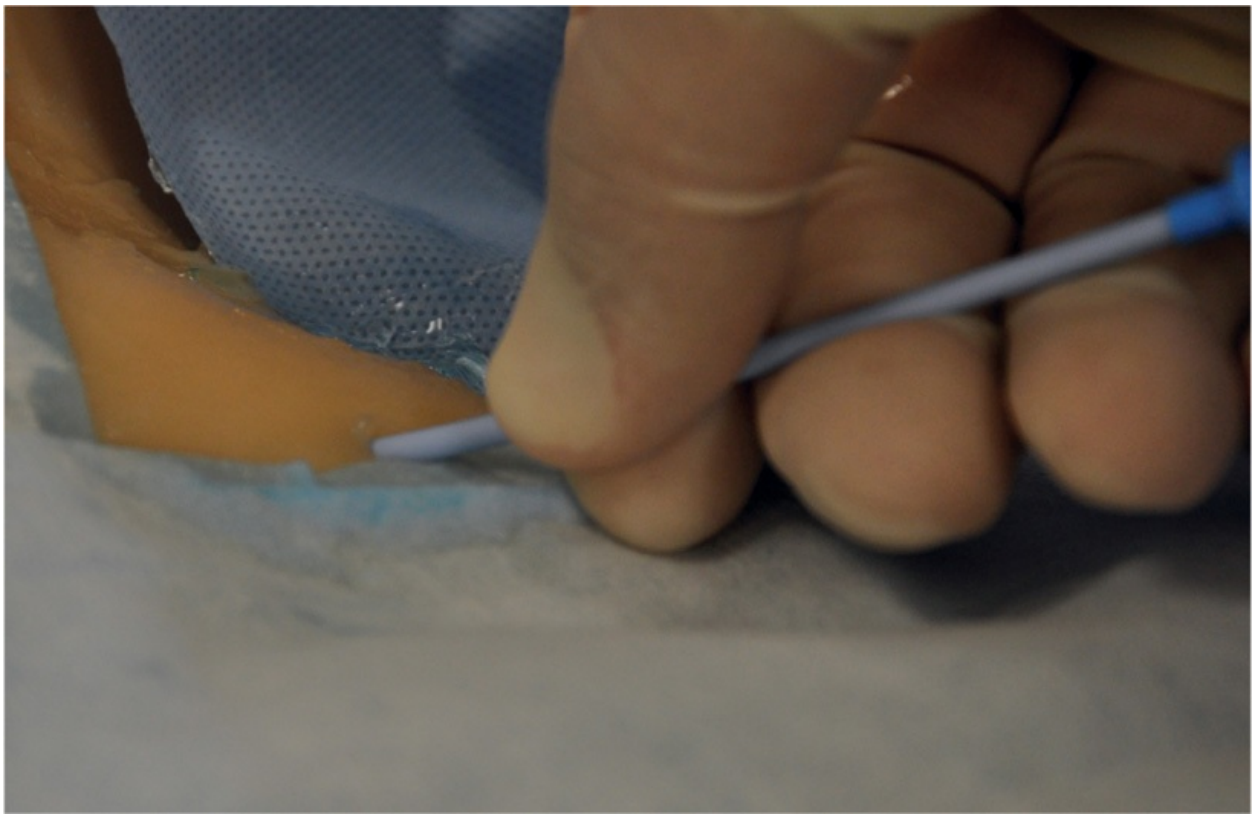


FIGURE 48.20 Dilation of the skin and soft tissue.

U. Thread the guide wire through the distal tip of the catheter until it comes out through the distal (brown) port of the TLC (**Figure 48.21A** and **B**). While holding the guide wire static with your nondominant hand, advance the catheter over the wire with your dominant hand to the desired depth (**Figure 48.21C**). Remove the guide wire and immediately cap the distal brown port. Confirm blood return from all ports and ensure all lumens flush without resistance. **Table 48.11** contains suggested depths to insert subclavian and IJV catheters. Depending on the height and gender of the patient, SCV and IJV CVCs can be advanced to the suggested depth. For IJV and SCV, the catheter tip should be in the SVC above its junction with the RA, with the distal tip parallel to the vessel wall. Femoral lines can generally be advanced all the way and secured.

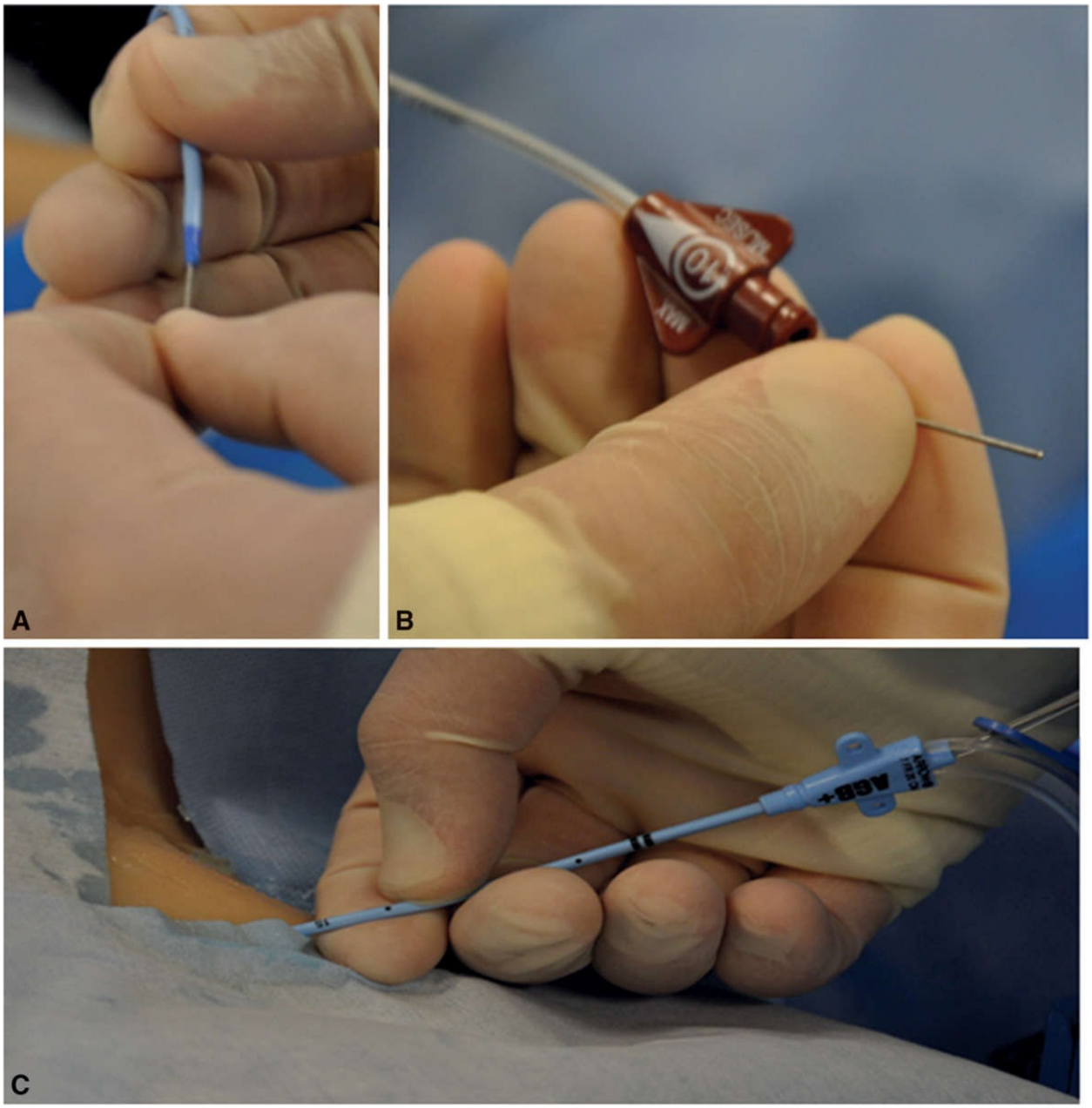


FIGURE 48.21 Advancement of the catheter over the guide wire. A, Insert the guide wire into the tip of the catheter. B, Thread the guide wire until it comes out through the distal port of the catheter and grasp the guide wire. C, Advance the catheter over the guide wire and then remove the guide wire.

TABLE 48.11 Depth of Central Venous Catheter Insertion

SITE	SUGGESTED DEPTH	FORMULA-BASED (HEIGHT IN CM)[a]
Right SCV	15–17 cm	(Height/10) – 2 cm
Right IJV	16–18 cm	Height/10

Left SCV	18–20 cm	(Height/10) + 2 cm
Left IJV	18–20 cm	(Height/10) + 4 cm

[a]There are no well-controlled studies of height-based formulas supporting their routine use.
IJV, internal jugular vein; SCV, superior vena cava.

V. Clean the site with alcohol or chlorhexidine and allow it to dry. Place the blue and white catheter anchoring clips over the catheter (SCV and IJV), and a Biopatch on the catheter at the insertion site (**Figure 48.22A**).

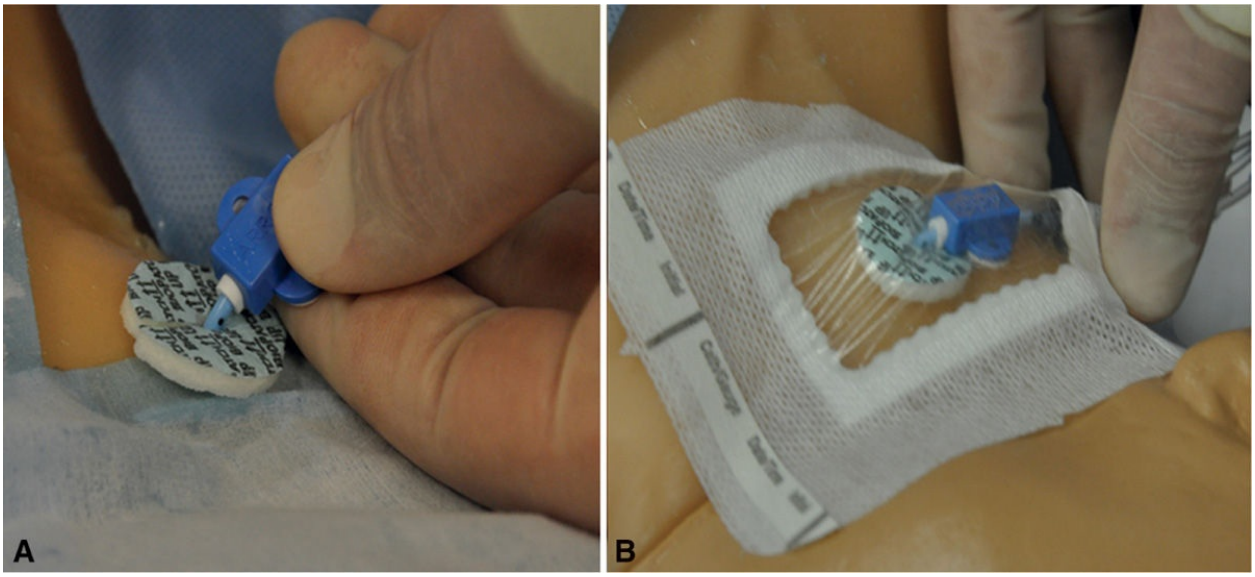


FIGURE 48.22 Securement of central venous catheter with anchoring clips, sutures, and transparent dressing.

W. Suture the line in place. Clean and apply a sterile, transparent, occlusive dressing (**Figure 48.22B**).

X. Uncover the patient, discard all the sharps in the sharps container and order a portable chest radiograph to confirm position.

Y. Write a procedure note.

Figure 48.23 delineates a step-by-step algorithm of central venous catheterization using the steps already described. Additional landmark approaches and site-specific techniques are described in later sections.

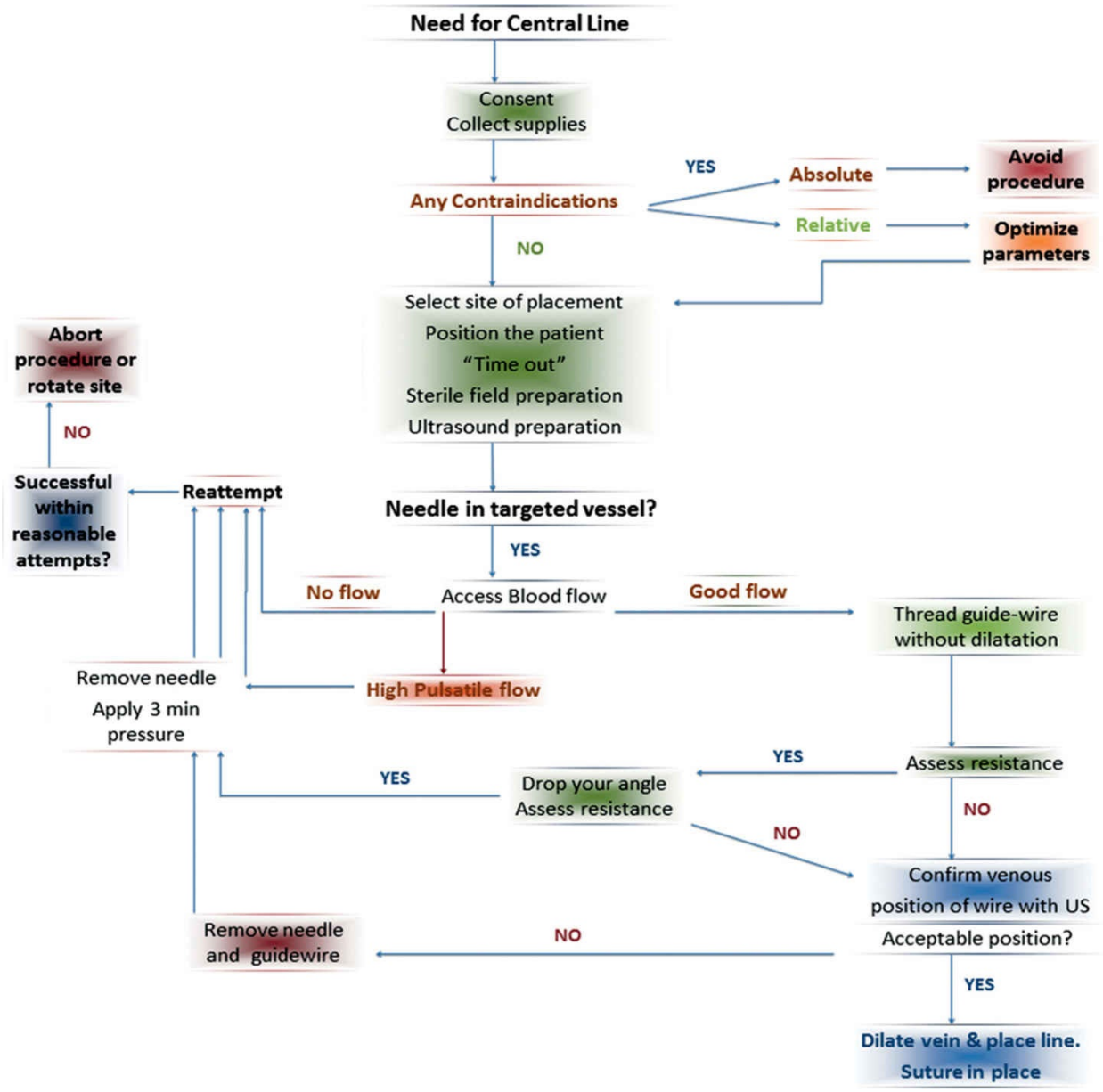


FIGURE 48.23 Central venous catheterization algorithm using Seldinger technique.

SITE-SPECIFIC LANDMARKS AND ULTRASOUND-GUIDED APPROACHES

Internal Jugular Vein

Anatomic landmarks for the central approach to IJV catheterization begin at the apex of the triangle formed by the sternal (medial) head and clavicular (lateral) head of the SCM and the clavicle (**Figure 48.14**). A confluence between the IJV and the brachiocephalic vein facilitates cannulation at this location. The head

should be rotated 45 degrees contralaterally, avoiding excessive rotation. With landmark approaches, a 21G or 22G “finder needle” attached to a 5 mL syringe is often used to locate the vein and estimate the distance and angle to the vein. The finder needle may be either removed or left in place for reference when the introducer needle is inserted.

Ultrasound-guided approach: This approach is the standard of care and preferred method to minimize mechanical and thrombotic complications. Do a preprocedural scan of the left and right IJV to select the best site. Place the ultrasound probe parallel and cephalad to the clavicle, at the apex of the triangle, with the probe marker “operator left.” Visualize the IJV and carotid artery in the transverse view. The carotid artery will be thick walled and pulsatile while the IJV will be thin walled and easily compressible (**Figure 48.5**). Identify a safe site for cannulation where the IJV is away from the carotid artery and not overlying it (**Figure 48.6**). Position the transducer and optimize the depth such that the vein is centered on the screen. Stay in the mid-neck and avoid the lower neck region above the clavicle, because there is a risk of puncturing the apex of the lung, even with US guidance. Use a high angle (70 to 90 degrees) and advance the needle into the IJV, maintaining negative pressure until the vein is punctured. Decrease the angle of the needle prior to feeding the guide wire.

Alternatively, a lower angle may be used but the operator must follow the tip of the needle into the vein using sweeping back-and-forth motions with the transducer to identify the needle tip as it is advanced into the IJV (**Figure 48.10**). Once the needle is inserted through the skin, slide or tilt the probe toward the needle tip until it is visualized on the screen. Be careful not to be confused by imaging the “shaft” of the needle, which will look similar to the tip. As the needle is advanced toward the vein, tilt the probe in the direction of the needle’s trajectory to ensure you can see the needle tip at all times. Periodically reposition the tip to confirm that it is directly above the vein. Make a small jab as the needle tip punctures the IJV and confirm good blood flow in the syringe prior to decreasing the angle and inserting the guide wire. Always confirm that the guide wire is in the vein prior to proceeding with the Seldinger technique (**Figure 48.24A** and **B**).

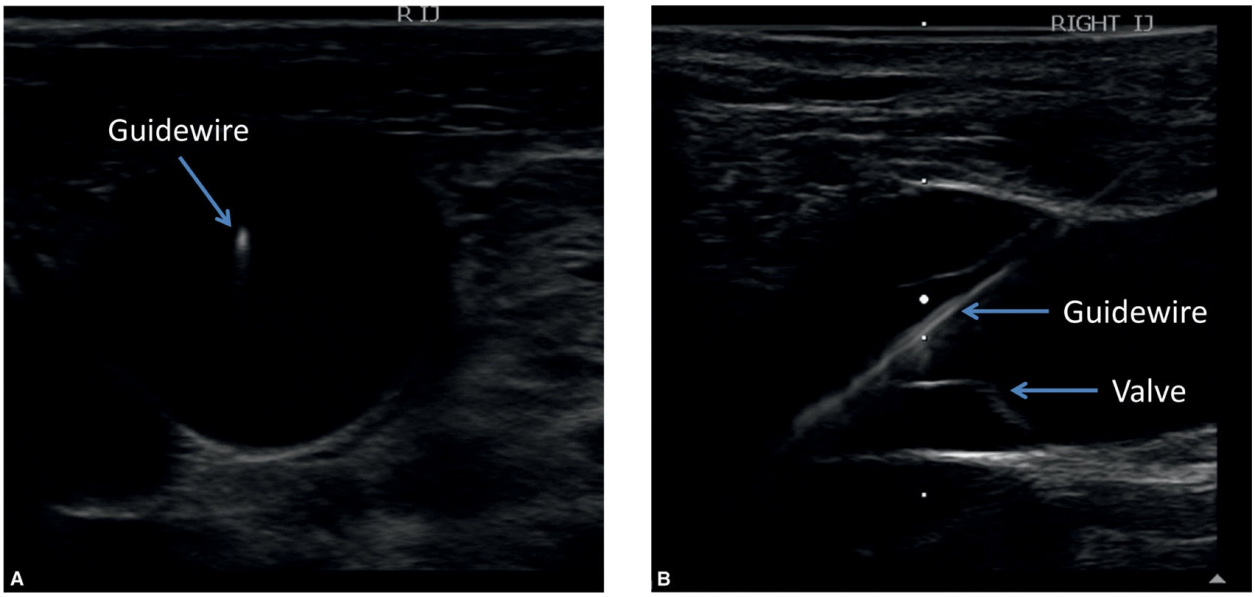


FIGURE 48.24 A, Guide wire in IJV. B, Longitudinal view of guide wire in internal jugular vein.

Landmark approach: The central approach is the most commonly used landmark approach. Place the index finger of the nondominant hand on the carotid artery pulse. Insert needle at apex of the triangle. The insertion point is just lateral to the carotid artery pulse. Use a 45 to 60 degrees angle and aim toward the ispsilateral nipple. The depth of the IJV using this technique is 3 to 5 cm. Sometimes the vessel will have been completely traversed by the needle with no blood return due to vessel collapse by hypovolemia or from pressure on the skin. Withdraw the needle to the subcutaneous plane and redirect the needle slightly medially.

Subclavian Vein

Landmark approach: The infraclavicular approach is most commonly used because it is quick and easy to perform, and obviates the need to set up the US machine. As part of setup, the clavicle should be divided into three parts: medial, middle, and lateral. Several different techniques and insertion sites are described in the literature:

- Insert the needle 2 cm caudal to the mid-clavicle.
- 2 cm lateral and caudal to the bend of the clavicle.
- 1 cm caudal to the junction of the medial and middle third of the clavicle.
- Inferior to the clavicle at the deltopectoral groove.

The needle should be inserted with the bevel facing the heart at a 10-degree angle toward the sternal notch. Matching up the numbers of the syringe with the bevel will allow you to know where the bevel is facing at all times. Starting 2 cm lateral to the bend of the clavicle and approximately 2 cm caudal (usually midclavicular), insert the catheterization needle through the skin and toward the sternal notch. Keep a low (<20 degrees) angle at all times. Once the needle is under the skin, keep the needle and syringe parallel and beneath the clavicle (**Figure 48.14**). Advance the needle toward the sternal notch until venous blood is aspirated.[24] Keep the middle finger of the nondominant hand on the sternal notch and use it as a landmark. Use the thumb of the nondominant hand to depress the soft tissue adjacent to the needle, so as to get beneath the clavicle and keep the needle flat at all times. Once blood is aspirated, advance the guide wire and follow the steps of the Seldinger technique(**Figure 48.16**).

Ultrasound-guided approach: Technically speaking, we are referring to US-guided axillary vein cannulation as the insertion point is lateral to the first rib. The brachial and basilic veins combine to form the axillary vein and the SCV is the anastomosis of the axillary and cephalic veins (**Figure 48.2**). Although US-guided SCV catheterization is safe, it requires expertise with vascular ultrasound. Using the linear array probe with the orientation marker left, scan along the inferior margin of the mid-clavicular region in a sagittal plane and slide the transducer laterally toward the axillary region. In the transverse or short-axis view, identify the axillary vein where it is most superficial and separate from the axillary artery. Stay within 4 cm of the mid-clavicle to avoid brachial plexus injury. Do a compression maneuver and use color Doppler to identify the vein from the artery. Identify the pleural line beneath the vessels. Now holding the base of the probe steady with the nondominant hand, turn the probe counterclockwise with the dominant hand and obtain a longitudinal view. Perform a compression maneuver and ensure the vessel is the vein and not the artery. While holding the probe steady with the nondominant hand resting on the body, insert the needle at the midpoint of the transducer at 45 to 70 degrees and follow the needle as it punctures the midpoint of the vein (**Figure 48.25**). Consider decreasing the angle to facilitate advancing the guide wire and the remaining steps.

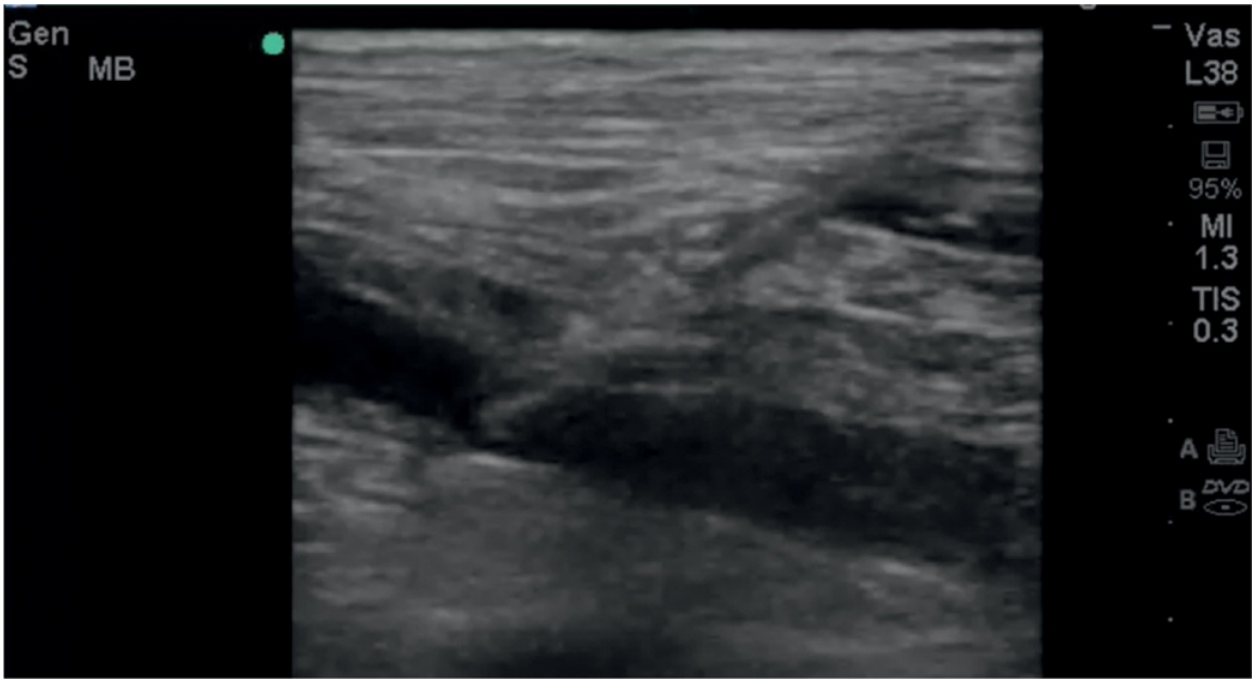


FIGURE 48.25 Ultrasound-guided cannulation using longitudinal approach.

Femoral Vein

Landmark approach: This is a useful approach during emergencies such as cardiac arrest. Externally rotate and abduct the patient's leg away from the midline. The FV lies caudal to the inguinal ligament and medial to the femoral artery in the femoral triangle (**Figure 48.15**). Palpate the femoral artery and insert the introducer needle 1 cm medial to this point at a 45 degree angle.[27] Advance the needle until there is a flash of venous blood. After stabilizing the needle, detach the syringe and advance the guide wire. Follow the remainder of the steps of the Seldinger technique. If the femoral artery is inadvertently punctured, hold compression for 5 to 10 minutes.

Ultrasound-guided approach: Using a linear array probe with the marker "operator left," identify the common FV and artery (**Figure 48.26**). As described previously, do a preprocedure scan to rule out deep vein thrombosis (**Table 48.9**). Identify the safest site for cannulation and holding the probe steady, insert the needle at a 45 to 70 degree angle into the vein. Once there is venous blood return, decrease the angle, ensuring there is still good blood flow. Holding the needle steady, detach the syringe and advance the guide wire. Use US to confirm that the guide wire is in the vein and not the artery. Follow the remaining steps for central venous cannulation.

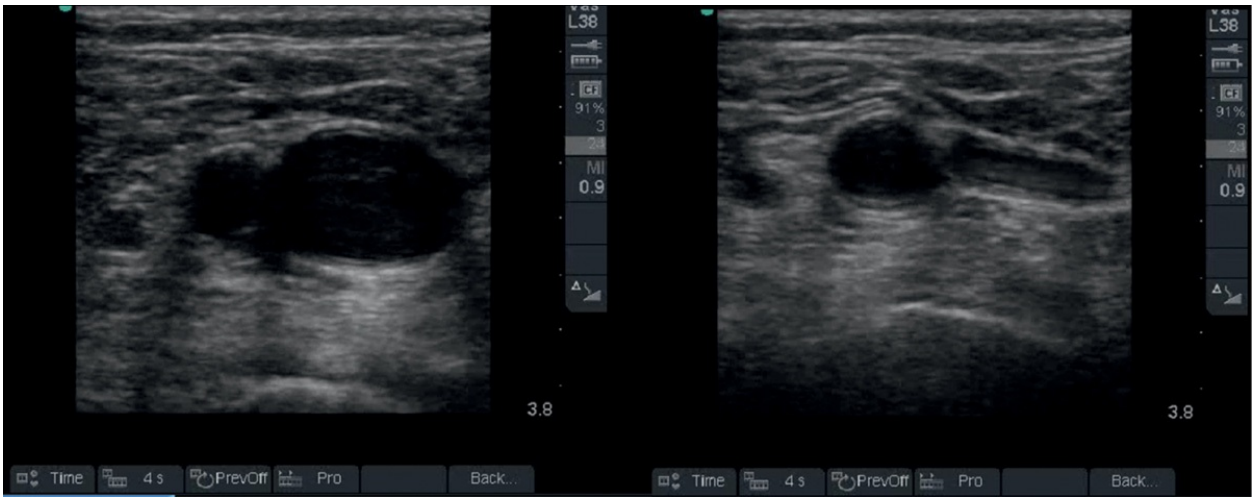


FIGURE 48.26 Common femoral vein with compression maneuver.

CENTRAL LINE VERIFICATION OF POSITION

The operator must ensure the catheter is placed in the central vein and not the artery. Arterial cannulation can lead to stroke, hemorrhage, and thrombosis. Ultrasound guidance can help with ensuring venous cannulation in IJV and FV CVC placement. The tip of the CVC must lie in the SVC or IVC and never in the RA. The catheter tip may potentially perforate the thin wall of the RA, resulting in hemorrhage and cardiac tamponade. A chest radiograph must be performed immediately after IJV and SCV CVC to confirm position and rule out complications.

For an ultrasound-guided placement of central line, confirmation of position is a multistep process. Initially, dark venous blood can be aspirated in the syringe. The operator must ensure that there is no pulsatile flow or bright red blood from the introducer needle, which may indicate cannulation of the artery. After insertion of the guide wire, the position can again be confirmed by visualizing the guide wire in the vein in the transverse and longitudinal views. This step precedes dilation of the vessel with the rigid dilator and ensures that the operator will not proceed if there is false cannulation of the carotid or femoral artery. In debatable situations, blood gas analysis is useful in differentiating arterial versus venous gas pattern. Additionally, the catheter can be connected to a pressure transducer to confirm venous waveform and pressure. With the introduction of US, this is not done routinely anymore. US is emerging as a tool to rule out malposition and pneumothorax but this is not the standard of care at this time.[29] Postprocedural chest radiography is necessary at the end of every internal jugular or subclavian venous cannulation to confirm the position of the distal tip

of the catheter and the absence of immediate complications like pneumothorax.

CORRECT POSITION

For any internal jugular or subclavian central line, the catheter tip is in correct position when it lies in the lower SVC or the cavoatrial junction. On a chest radiograph, this is at the level of the first anterior intercostal space above the carina (**Figure 48.27**). Placing an IJV or SCV catheter tip too deep can result in arrhythmias or even cardiac tamponade. A catheter can be repositioned by withdrawing it and resuturing, however it can never be advanced due to the risk of infection.

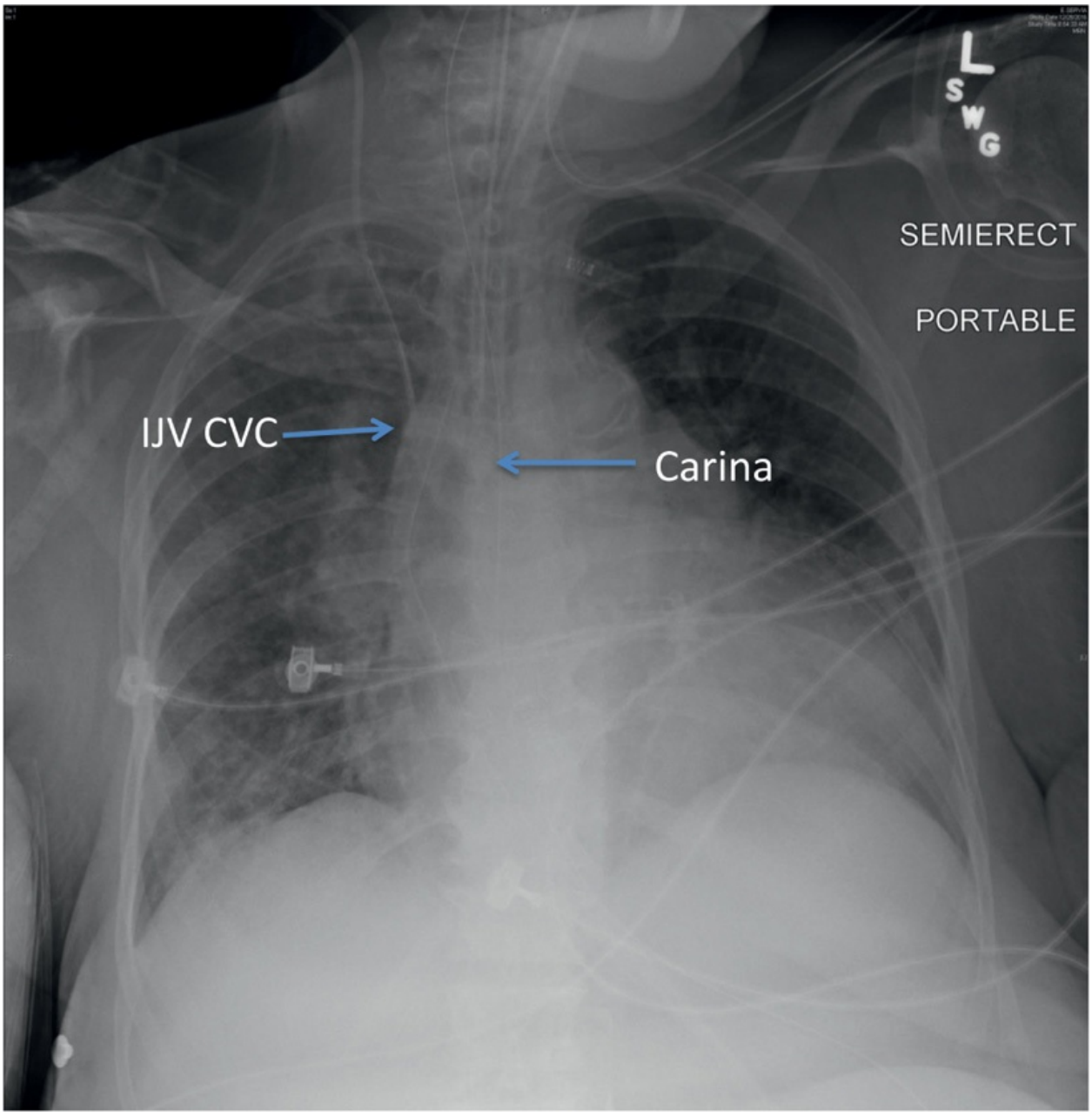


FIGURE 48.27 Central line position on chest radiograph. CVC, central venous catheter; IJV, internal jugular vein.

ROUTINE CATHETER CARE

Patency problems are common and include sluggish flow, no flashback of blood, or complete blockage. Possible causes for that would be clotted blood in the catheter or drug precipitation from infusate (eg, parenteral nutrition) or malpositioning of the catheter from initial placement. A rescue method to restore patency is by the use of a thrombolytic agent like alteplase (Cathflo or t-PA). See

Figure 48.28 for an algorithm to trouble shoot a nonfunctioning CVC.

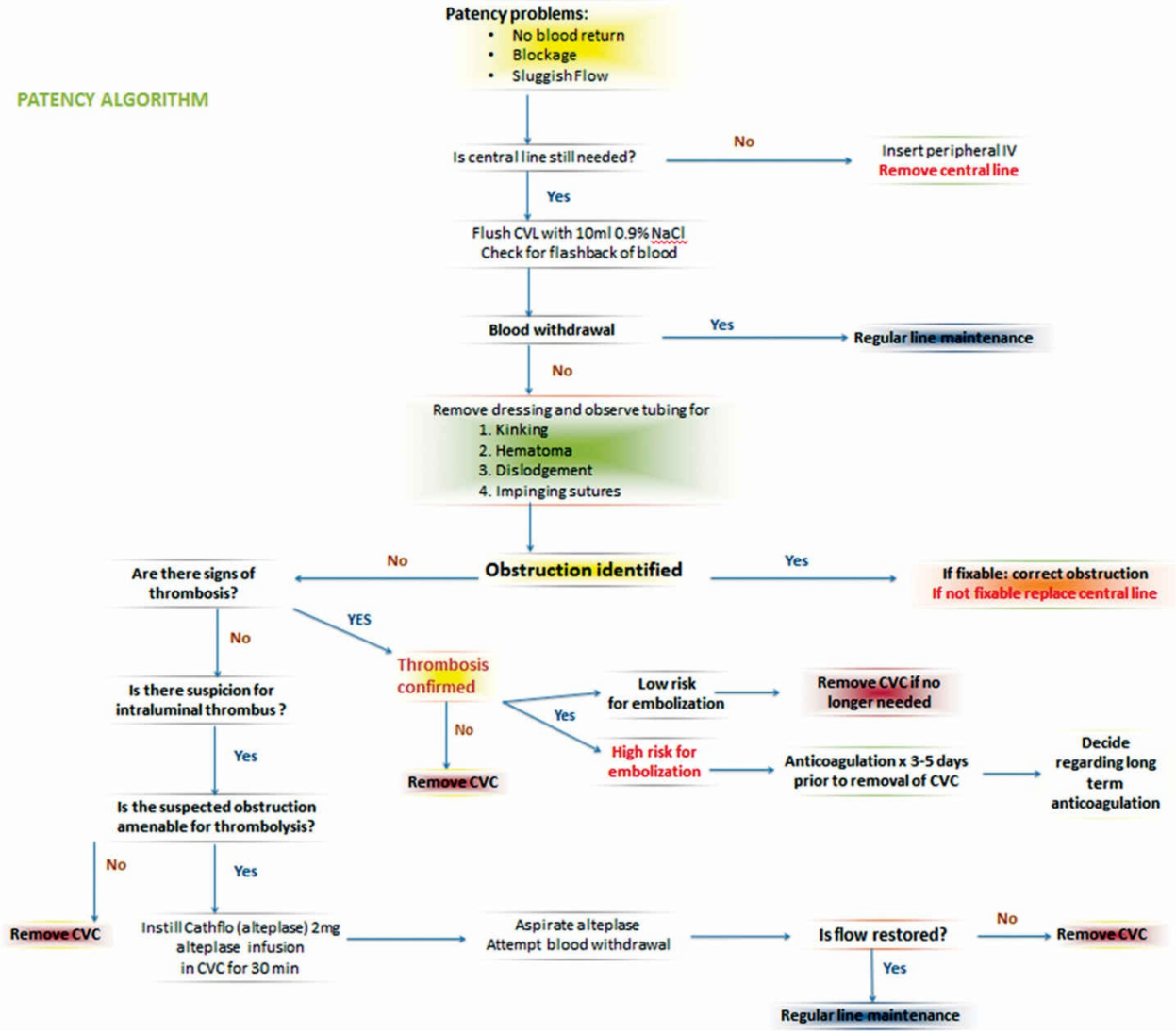


FIGURE 48.28 Central line occlusion trouble shooting algorithm.

COMPLICATIONS

Central line placement is an invasive procedure and it is not uncommon to have complications. General complications of placement of central lines are site specific and are summarized in **Table 48.12.**[30,31] The choice of site should be based on patient factors and operator's experience. In general, complication rates increase with increased number of attempts.[9,32] Simulation-based training has been shown to reduce the number of mechanical and infectious complications.[10,11,33]

TABLE 48.12 Complications of Central Venous Catheterization

MECHANICAL COMPLICATIONS	COMPLICATIONS	PREVENTATIVE MANAGEMENT
Internal Jugular CVC		
Immediate complications	Carotid puncture	Do not dilate; apply pressure.
	Pneumothorax	Insert chest tube if necessary.
	Bleeding	If severe, consider evacuation.
		Correct coagulopathy prior.
	Malposition	Correct position.
	Venous air embolism	Flush all ports with saline.
	Dysrhythmias	Retract guide wire.
	Submandibular hematoma	Watch for tracheal compression.
	Vagus nerve injury	
	Guide wire migration	Consult vascular surgery
	Thoracic duct injury (left side)	Keep NPO; requires TPN until healing; consult surgery.
Subclavian CVC		
Immediate complications	Subclavian arterial puncture	Do not dilate; apply pressure.
	Pneumothorax	Insert chest tube if necessary.
	Hematoma/hemothorax	If severe, consider surgical evacuation. Correct coagulopathy prior. Keep NPO; requires TPN until healing; consult surgery.
	Thoracic duct injury (left side)	
	Vagus nerve injury	
	Cardiac tamponade	Pericardiocentesis
	Malposition	Retract line; if needed, change.
	Venous air embolism	Flush all ports with saline.
	Dysrthymias	Retract guidewire.

	Guide wire migration	Consult vascular surgery.
Femoral CVC		
Immediate complications	Femoral artery puncture	Do not dilate; apply pressure.
	Femoral nerve puncture	Ultrasound use
	Retroperitoneal bleeding from external iliac artery puncture	Correct coagulopathy first. If severe, consider evacuation
	Venous air embolism	Flush all ports with saline.
	Guide wire migration	Might require vascular intervention.
	Punctured bladder	Urology consult
	Bowel perforation	If patient has femoral hernia
For all types of access	Bleeding	Apply pressure.
	Deep vein thrombosis (DVT)	DVT prophylaxis
	Thrombophlebitis	Prompt removal
	Infection	Early removal, antibiotics
	Extravasation	Manage as per vesicant
	Thrombosis	Consider thrombolytics.
	Nerve injury	

CVC, central venous catheter; TPN, total parenteral nutrition.

Infection

Observing standard infection control measures such as hand hygiene and using aseptic technique when placing CVC is paramount to preventing CLABSI.[1] The subclavian site carries the lowest risk of infection, however carries a higher pneumothorax risk and depends on operator experience.[13] The femoral site is associated with the highest risk of infectious complications. A central line bundle is essential for any CCU and includes hand hygiene, chlorhexidine skin antisepsis, and maximum barrier precautions during insertion, avoidance of the femoral site, a daily review of necessity of the CVC and removal when no longer necessary.[34] Interventions such as a daily goals sheet and simulation-based

training on sterile techniques have been shown to decrease CLABSI.[35] Any central line that is placed emergently or in a nonsterile fashion should be promptly removed. Routine catheter tip cultures, CVC changes, and guide wire exchanges are not recommended.

Pneumothorax

This is by far the most common complication of the subclavian site. There is no consensus as to whether all patients need chest tubes if a pneumothorax occurs. Stable patients with small pneumothoraces may be closely observed. Patients with large pneumothoraces or those who are on mechanical ventilation require chest tube placement to manage this complication and avoid tension pneumothorax, which is life threatening.

Arterial Puncture

Arterial puncture and even cannulation is not uncommon. If recognized early (ie, with introducer needle), 5 to 10 minutes of solid pressure on the site will resolve most bleeding issues without consequence. This is different, though, if the artery has been dilated or cannulated with a TLC or introducer sheath. If this occurs, leave the line in place and consult vascular surgery immediately.

Hematoma

Femoral artery puncture can lead to hematoma. Retroperitoneal hemorrhage is a feared complication and blood can flow freely into the retroperitoneum. The FV becomes the external iliac vein superior to the inguinal ligament and retroperitoneal hemorrhage can occur if the posterior wall is punctured multiple times above the inguinal ligament. This often occurs when the landmark approach is used during cardiac arrest or other emergencies. Occasionally, the FV is cannulated after the needle has traversed the femoral artery; so the bleeding will occur when the catheter is removed. Similarly, a hematoma from carotid artery puncture can compress the trachea and hence compromise the airway. US-guidance decreases the risk of all these mechanical complications.[11]

Air Embolism

This is a rarer occurrence but can be catastrophic. This can occur during CVC placement or during its removal.[36] The patient will quickly decompensate and become short of breath, altered, and hypotensive or have a cardiac arrest. If this

is suspected, place the patient in the left lateral decubitus or Trendelenburg position so as to trap the air in the right ventricle. Provide supportive care such as high-flow oxygen or mechanical ventilation, intravenous fluids, and vasopressors. The most useful technique to prevent air embolism is placing the patient in Trendelenburg when performing IJV or SCV catheterization or removal. Always cover the hub of the introducer needle or CVC once it is in the vein.

Guide Wire Embolization

Loss of a guide wire is possibly the most disturbing complication for the operator. This is a preventable complication and many institutions have policies of confirming that the guide wire was removed after the procedure. Always maintain control of the guide wire throughout the procedure and be all the more vigilant after the dilation of the vessel. If the operator does lose the guide wire, check to see if it is still in the lumen of the catheter. If so, then clamp the catheter and guide wire with a Kelly clamp or similar instrument and remove the entire apparatus, along with the guide wire. If the guide wire has embolized distally, consult vascular surgery or IR to help with retrieval. **Figure 48.29A** and **B** depict US images of guide wire embolization through the venous circulation into the RA.

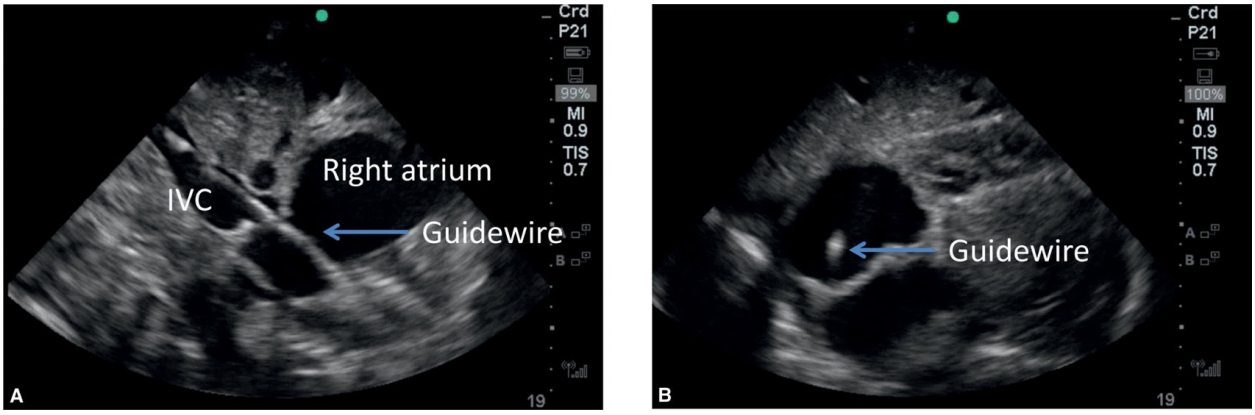


FIGURE 48.29 A, Guide wire embolization to inferior vena cava (IVC). B, Guide wire embolization to IVC/right atrium.

CENTRAL ACCESS REMOVAL

Any CVC should be removed as soon as it is no longer necessary. Central line removal is distinct from insertion, with its own set of potential complications.

Some complications of CVC removal include bleeding, air embolism, catheter fracture, and dislodgement of thrombus from the catheter tip. **Table 48.13** is a checklist of essential steps to follow during CVC removal. A working knowledge of potential complications and simulation-based training is essential for the CCU personnel removing lines. CVC removal should only be performed by professionals who have received adequate training and been assessed as competent in performing the procedure.[37]

TABLE 48.13 Checklist for Central Line Removal

CENTRAL LINE REMOVAL CHECKLIST
Place the patient in Trendelenburg position with the CVC exit site below the level of the heart.
Ensure that all CVC lumens are capped and/or clamped.
Cover the CVC exit site with gauze and apply gentle pressure while removing the catheter in a slow, constant motion.
Have the patient perform the Valsalva maneuver as the last portion of the CVC is removed.
Place pressure on the site for at least 5 min.
Apply a sterile occlusive dressing, such as gauze filled with petroleum jelly, and cover with a transparent film dressing.
Leave dressing in place for at least 24 h and change every 24 h until the exit site has healed.
Instruct the patient to remain lying flat for 30 min after removal of the catheter.

CVC, central venous catheter.

ARTERIAL LINE PLACEMENT

Arterial catheterization is indicated when continuous beat-to-beat blood pressure monitoring is needed. This applies for patients with circulatory shock, hypertensive emergencies, aortic syndromes, acute stroke, and multiorgan failure states. Arterial access is also required for diagnostic and therapeutic interventions like coronary angiography, aortic balloon pump, or left ventricular assisted devices, and ECMO. Indications for intraarterial line placement are summarized in **Table 48.14**. See Chapter 49 for a discussion on arterial blood pressure monitoring and its uses.

TABLE 48.14	Indications for Intra-arterial Lines in the CCU
INVASIVE MONITORING OR AGGRESSIVE HEMODYNAMIC RESUSCITATION INTERVENTIONS	
Hemodynamic monitoring: • Continuous blood pressure • Shock on vasoactive agents • Hypertensive emergency • Open heart surgery • Hemorrhagic stroke • Aortic syndromes • Cerebrovascular accident after thrombolysis • Blood pressure monitoring in obese patients, amputees, burn victims	
Cardiac output monitors (ie, Flotrac)	
Intra-aortic balloon pump	
Left ventricular assist device	
Arterial blood gas access	
Need for frequent arterial blood gases Acute respiratory distress syndrome or in severe metabolic derangements	

Like CVCs, intraarterial lines are interventions that require patient consent, cooperation, and sterile conditions as discussed earlier. A-lines are generally placed using the Seldinger technique (**Figure 48.16**). A-lines have a lower rate of infection, but the risk of infectious and thrombotic complications does exist; so they should be discontinued as soon as they are no longer indicated. No drugs should be injected via an A-line; the direct contact of a medication with the tissues can result in cell death, severe gangrene, and limb ischemia. **Table 48.15** contains a list of contraindications for A-line placement.[32,38]

TABLE 48.15	Contraindications for Intra-arterial Lines in the CCU
Thrombocytopenia	
Infection at insertion site	
Traumatic injury at insertion site	
Arteriovenous fistula	
Peripheral arterial insufficiency of intended limb	
Prior surgeries or radiation	

Raynaud syndrome
Thromboangiitis obliterans (Buerger disease)
Synthetic vascular graft

CCU, cardiac care unit.

Surgical and anatomic considerations are the influencing factors when choosing the site for arterial cannulation. The radial artery is the most common site for cannulation because it is thought to have a low rate of associated complications. This low rate of complications occurs as a result of extensive collateral circulation involving the ulnar artery and palmar arches with flow to the distal limb. The anatomic landmarks and advantages/disadvantages for each site are summarized in **Table 48.16.**[39] The most common complication is arterial thrombosis. Thrombotic risk factors include larger catheter size, hypotension, smaller arterial dimension, multiple arterial sticks, duration of cannulation, and administration of vasoactive agents. The cannulation site further potentiates thrombotic propensity.[40,41]

TABLE 48.16 Site-specific Characteristics of Arterial Line Placement

SITE	LANDMARKS	ADVANTAGES	DISADVANTAGES	COMPLICATIONS
Radial	Distal end of radius between tendons of brachioradialis and flexor carpi radialis	Easy to locate	Easily collapsible	Thrombosis risk
		Ease of placement	Prone to vasoconstriction if multiple attempts	Limb ischemia
		Most common site of cannulation	Difficult in profound shock	
		Presence of collateral flow (ulnar artery and palmar arch)	High thrombosis risk	
		Easily maintained		
			Frequent accidental removal	
	Below the inguinal	Easy cannulation especially with	Highest infection rate	Retroperitoneal

	ligament	ultrasound guidance		hemorrhage
Femoral artery	Palpated midway between the pubic symphysis and anterior iliac crest	Lower thrombosis risk	Compressible for bleeding control	
		Easily maintained	Avoid in peripheral arterial disease	
		Comfortable		
		Largest accessible arterial access		
Axillary artery	Palpated in the intramuscular groove between the coracobrachial and triceps muscles	Lower infection and thrombosis risk	Ultrasound guidance often needed	Brachial plexus compressive injury from hematoma
	Deep to pectoralis minor muscle	Maintains pulsation in profound shock due to proximity to aorta	High failure rate	Paresthesia
		Second largest after femoral artery	Proximity to pleural space, brachial plexus	Cannulation of left axillary is preferred compared to the right.
		Preferred in obese if radial access difficult	Right axillary line in continuity with right carotid⇒ risk for cerebral thromboembolism	
Brachial artery	Medial side of antecubital fossa	Easily accessed but lacks the anatomic benefit of collateral circulation	Highest likelihood for thrombosis and loss of radial pulsations	DO NOT USE
	Lateral border of brachial muscle			Any cannulation may lead to upper limb ischemia
				Median nerve injury

GENERAL RULES

Multiple failed attempts might lead to arterial vasoconstriction; therefore choice of radial artery requires a level of operator's comfort that he or she will be able

to place the line in with relatively low number of attempts. Prior to the procedure, the modified Allen test should be performed to assess for good collateral circulation from the ulnar artery. The modified Allen test is performed by asking the patient to make a fist. While the hand is clenched, the ulnar and radial arteries are occluded with digital pressure to obstruct blood flow to the hand. When the hand is unclenched, the pressure over the ulnar artery is released. In the presence of good circulation, the palm flushes in 5 to 10 seconds.[42] **Table 48.17** contains a list of basic items needed for arterial catheterization.

TABLE 48.17	Items Necessary for Arterial Line Placement
Arterial line kit	
Arterial catheter	
1% lidocaine 5 mL vial	
25G × 1″ needle for lidocaine administration	
22G × 1.5″ with 5 mL syringe for lidocaine administration	
20G steel introducer needle with 5 mL Luer slip syringe	
20G angiocatheter needle (in some kits)	
J-shaped guide wire	
Scalpel (#11)	
Thin dilator (not always used)	
Straight or curved needle with sutures	
Gauze: 2″ × 2″ or 4″ × 4″ pads	
Fenestrated drape	
Additional supplies	
Surgical caps	
Masks with eye shield	
Chlorhexidine swabs/scrubs	

Sterile gown
Sterile gloves
Biopatch protective disk
Transparent, occlusive dressing
A-line transducer setup with tubing connected to saline bag (supplied by registered nurse [RN])
Disposable underpad (blue Chux)
Additional items
Portable ultrasound machine with linear array (vascular) probe
Sterile probe cover

TECHNIQUE

If you are able to get arterial blood gas from radial artery, then you probably have already mastered the direct cannulation technique. Following are the basic steps of arterial catheterization. It is assumed that the operator will adhere to standard hospital policy of obtaining informed consent, performing a "time-out," and maintaining maximum barrier precautions throughout the procedure.

Catheter Over Needle Technique (Radial Artery Catheterization)

A. Palpate the radial artery and perform the modified Allen test. If you cannot feel it, aim as distally as possible, either rotate position or use US guidance to visualize the artery.
B. Once you identify the artery, position the patient with the wrist dorsiflexed using a rolled towel under the wrist and tape to maintain that position.
C. Adjust height of bed to ensure comfort during procedure.
D. Perform hand hygiene using an alcohol-based rub.
E. Don sterile gloves and prepare site using chlorhexidine swabs.
F. Don hat, mask, and sterile gown.
G. Identify the point of maximal pulsation of the radial artery and inject local lidocaine subcutaneously.
H. Hold the angiocatheter-covered needle with dominant hand while stabilizing the artery with the nondominant hand.
I. Puncture the skin at an angle of 30 to 45 degrees just distal to where the

artery is palpated. Once flashback of blood is seen, advance the needle 2 mm after flash to ensure catheter placement inside the lumen. Flatten the needle slightly and advance the catheter until flashback of blood is seen in the hub of the needle. Note that some catheters have a built-in guide wire that is advanced into the artery once there is flashback and then the catheter is advanced over the wire.

J. Withdraw the needle/wire from the catheter. There should be pulsatile flow of bright red blood coming out of the catheter. Press on the catheter proximal to the hub to control the bleeding.

K. Have an assistant hand you the transducer connecting tubing and connect it to the catheter hub. Be careful not to displace the catheter or pull it out mistakenly. Check for arterial waveform on the monitor.

L. Suture the catheter in place using a securing device and/or placing a suture around the proximal hub.

M. Clear the site and place a transparent dressing.

Catheter Over Guide Wire: Seldinger Technique (Femoral Arterial Catheterization)

A. Palpate the femoral artery in the femoral triangle, staying caudal to the inguinal ligament.

B. Perform hand hygiene; don hat, mask, and sterile drape.

C. Prepare, drape, and anesthetize the skin and soft tissue over the femoral artery.

D. Puncture the skin at an angle of 40 to 60 degrees with the introducer needle/syringe, distal to where the arterial pulse is palpated (note that a long introducer needle should be used).

E. Advance the needle until the artery is punctured and bright red blood is aspirated.

F. Decrease angle slightly ensuring good blood flow.

G. Stabilize needle and remove syringe from needle, confirming free pulsatile flow of bright red blood.

H. Pass the guide wire through the needle and withdraw the needle (**Figure 48.16**).

I. Advance the cannula over the guide wire while maintaining control of the guide wire at all times. Advance the guide wire into the lumen of the artery with rotational movements. Note a thin dilator is usually available in a vessel catheterization kit if needed.

J. Remove the guide wire and expect brisk high-pressure bright red blood flow from the catheter.

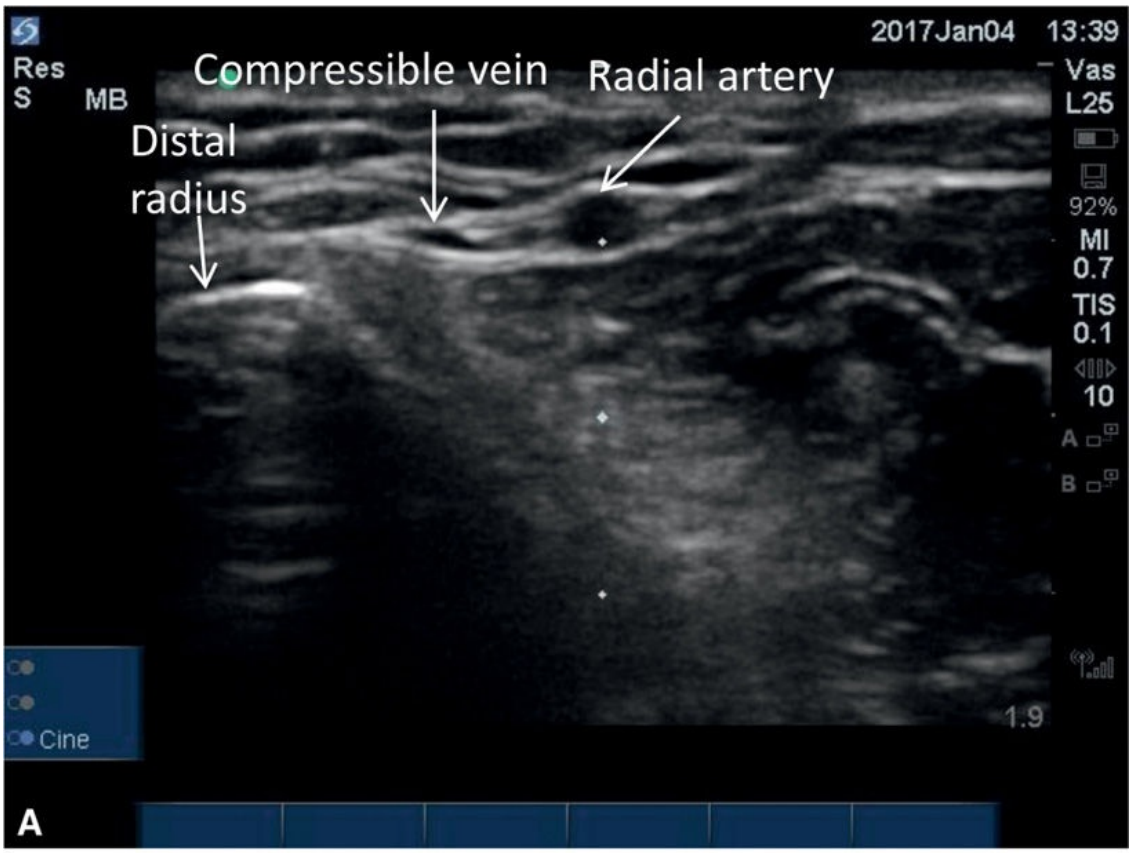
K. Attach the transducer connecting tubing to the catheter and look for a good A-line waveform on the monitor.

L. Secure the cannula with sutures and cover with a transparent dressing.

ULTRASOUND GUIDANCE

Ultrasound use is often helpful in arterial catheterization of the critically ill CCU patient. The insertion of the catheter by blind palpation can sometimes require multiple attempts and thus can cause patient discomfort and arterial vasospasm. This is particularly true in the CCU patient with profound shock. Ultrasound guidance is particularly helpful with axillary artery catheterization. The use of ultrasound guidance has been shown to increase first-pass success rate and reduce the number of attempts.[43,44]

Prior to the procedure, clean the ultrasound transducer with an antiseptic wipe. Perform a preprocedural scan with a high-frequency linear array transducer to identify the optimal site for cannulation. Ensure the transducer marker is "operator left" and the screen marker is also on the upper left hand corner. Identify the artery that will be cannulated and adjust the gain and depth to optimize the image such that the vessel of interest appears in the center of the screen. Arteries will appear round, thick walled, and are pulsatile with compression. Scan up and down in the transverse view to ensure there is no tortuosity or calcification. Locate a section with the largest diameter. The radial artery will be located adjacent to the styloid process of the radial bone (**Figure 48.30A**). The femoral artery is the pulsatile vessel located in the femoral triangle (**Figures 48.15 and 48.26**). For axillary artery cannulation, have the patient place his or her arm under his or her head and scan the axillary region until the vessels are identified. **Table 48.16** lists general anatomic landmarks and considerations for each potential site.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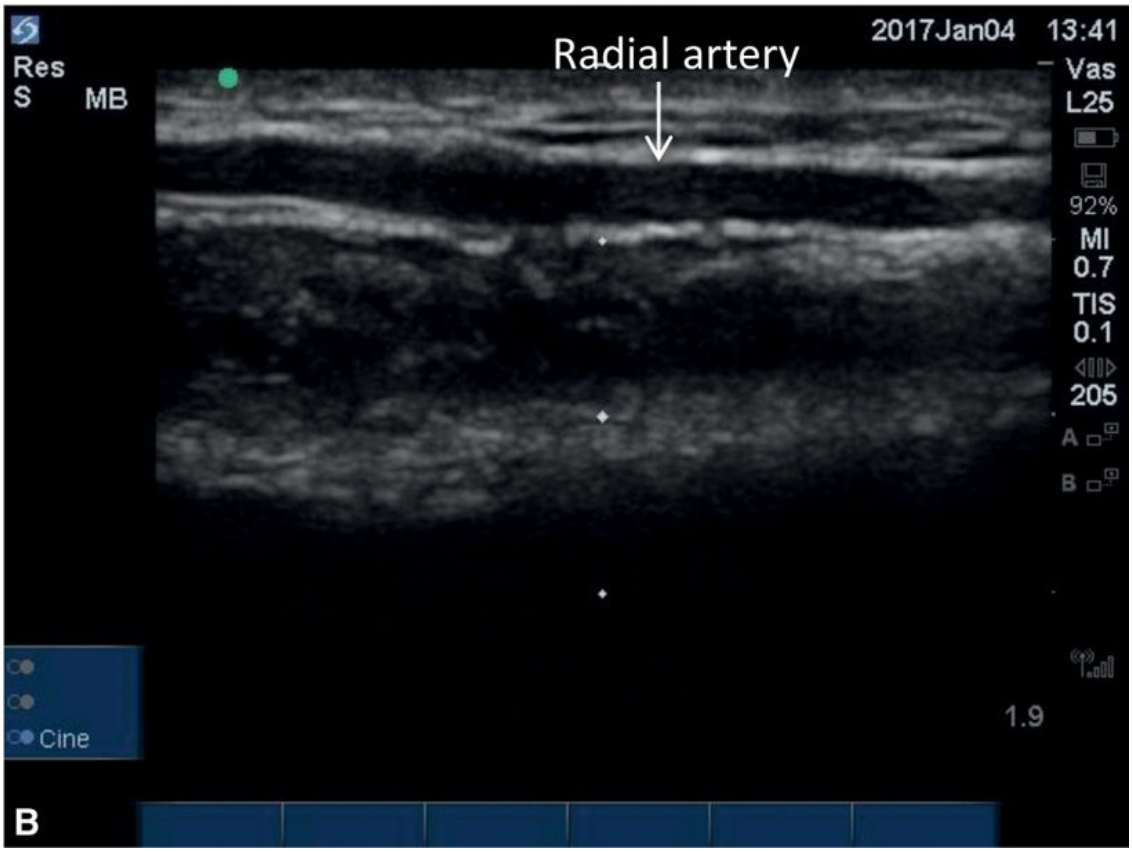
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FIGURE 48.30 A, Radial artery in transverse view. B, Radial artery in longitudinal view.

Transverse Approach

Arterial catheterization can be performed in either the transverse view or longitudinal view (**Figure 48.30A and B**).[40] It is assumed that the operator will maintain sterility throughout the procedure and will always use a sterile sheath to cover the ultrasound transducer. Sterile gel should be applied inside the sheath without contaminating the field or the operator's sterile gloves. After locating the artery, optimize the image and center the artery in the transverse view. Anesthetize the skin and insert the angiocatheter-covered needle at the midpoint of the transducer at a 45 to 60 degree angle. Slide or angle the probe up and down until the needle tip is visualized. Make sure you are imaging the tip and not the shaft of the needle. As the needle is advanced toward the artery, follow the tip of the needle by sliding the transducer back and forth. Adjust the position of the needle until it is directly over the artery and then puncture through the vessel wall into the lumen. Follow steps for either the catheter over needle/wire technique or the Seldinger technique described previously.

Longitudinal Approach

For the longitudinal view approach, first obtain a transverse view with the vessel in the center of the screen. Hold the base of the transducer steady, turn the transducer counterclockwise with the dominant hand, and obtain a longitudinal view (**Figure 48.30B**). Notice the thick-walled vessel that is pulsatile and noncompressible. While holding the transducer steady with the nondominant hand resting on the body, insert the needle at the midpoint of the transducer at a 30 to 45 degrees angle (**Figure 48.31**) and follow the needle as it punctures the midpoint of the artery. Follow steps for catheter over needle or Seldinger techniques described earlier. The longitudinal approach can be useful for radial artery cannulation, whereas the transverse approach is preferable for femoral artery and axillary artery catheterization.

FIGURE 48.31 Transducer hold for longitudinal approach for cannulation.

CONCLUSION

Line access is essential and allows for hemodynamic monitoring and administration of lifesaving medications in the CCU patient. A working knowledge of the types of catheters, indications, contraindications, and considerations for site selection is imperative. Knowledge of vascular anatomy, familiarity with the equipment, and competency in the procedure are prerequisites for successful insertion of the catheter. A daily assessment and early removal of the line as soon as it is no longer necessary reduces the risk of complications. Limiting the number of attempts at insertion drastically reduces both infectious and mechanical complications. Ultrasound guidance and simulation-based training are helpful in achieving competence and reducing complications.

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Patient and Family Information for:
LINE ACCESS IN THE CCU

During a patient's stay in the coronary care unit (CCU), various lines may be placed in the veins or arteries for close monitoring and for administering potent medications. Below are some of the lines that may be placed.

CENTRAL LINE

WHAT IS A CENTRAL LINE?

A central line, also known as a central venous catheter (CVC), is a long, thin, flexible tube that is inserted in one of the large veins in the neck, upper chest, or groin region and leads to the heart. It allows delivery of fluids and necessary medications and can stay in place much longer than a regular intravenous (IV) catheter. It can also be used to measure the pressures within the heart.

WHAT ARE THE TYPES OF CENTRAL LINES?

The most common central line is called a triple lumen catheter (TLC) because it has three ports, which all end in different openings within the catheter. It is inserted in a large vein in the neck, upper chest, or groin, with its tip residing near the heart. Dialysis catheters typically have two ports (dual lumen) and can be used on a short-term basis in order to perform dialysis while in the CCU.

A peripherally inserted central catheter (PICC line) is a really long catheter that is inserted into a vein in the upper arm and is threaded until it reaches the larger vein near the heart.

Long-term-use tunneled catheters, also known as perm-a-cath, is inserted usually in a large vein in the neck. This catheter can be used for long-term dialysis, if needed.

WHY YOU NEED A CENTRAL LINE?

Your doctor or nurse will explain the reason you need a central line.

Below are some common reasons why a patient in the CCU might require a central line.

- If the small veins in the arms are not easily found or it is difficult to place a regular IV line
- If the blood pressure is low and strong medications are needed to raise the blood pressure (These medications are too strong to be given through a regular IV.)
- If the intravenous medications that have to be given can potentially burn the smaller vessels or muscles
- If blood or other blood products need to be rapidly given
- If intravenous nutrition is needed for a number of days
- If you need to undergo dialysis or plasmapheresis, where the blood is purified

WHERE IS THE PROCEDURE PERFORMED?

The procedure is typically done at the bedside in the CCU. A PICC line or perm-a-cath may be performed in the interventional radiology (IR) department or in the operating room (OR).

WHAT IS THE CARE BEFORE AND AFTER THE PROCEDURE?

Before the procedure is done, your lab work will be checked to assess your risk of bleeding, especially if you are taking any blood-thinning medications. If your platelets are low or international normalization ratio (INR) is high, a transfusion of platelets, plasma, or vitamin K may be necessary before the procedure.

An ultrasound machine is often used to guide the procedure. The blood vessels are visualized with ultrasonography in order to decide where the central line will be placed and also to prevent placement of the catheter elsewhere.

The procedure is sterile. Your body and face will be covered with a sterile drape to minimize any risks for infection during the insertion. You will be able to talk with your doctors during the procedure. You may be placed in the Trendelenburg position, where the head is lowered and the legs are raised. This position ensures safety of the central line placement.

If the central line is placed in the neck or upper chest, a chest x-ray is performed afterward to confirm the position of the central line near the heart and also in order to make sure there is no pneumothorax, which is collapse of the

lung on the affected side.

IS THE PROCEDURE PAINFUL?

You will be awake and able to interact with the doctors performing the procedure. You will be given a numbing medication at the insertion area. After the initial injection of a local anesthetic, the procedure is pain free but you may experience pressure or discomfort. Your cooperation is of critical important during that time.

HOW LONG DOES IT TAKE?

No more than 30 to 45 minutes, accounting for the time of the procedure and preparation.

ARE THERE ANY POSSIBLE COMPLICATIONS?

All procedures carry some risk. This is a common procedure in CCUs and ICUs. A trained physician, physician assistant, or nurse practitioner usually places the line under sterile technique.

POSSIBLE COMPLICATIONS:

- Infection of the catheter
- Bleeding at the site or internally
- Puncture of the artery which is running next to the vein
- Pneumothorax or collapsed lung
- Heartbeat changes (arrhythmias)
- Blood clot in the vein where the line is placed
- Air bubbles entering the blood circulation

HOW TO CARE FOR THE CENTRAL LINE:

The catheter extends outside your body, allowing the nurses and doctors to access it to provide you medications, antibiotics, and fluids. The dressing will be getting changed at every nursing shift.

To avoid any infection, clotting, or other complications, meticulous care of the central line is important.

WHEN IS THE LINE REMOVED?

As soon as the central line is no longer needed, it should be removed. Gentle pressure should be applied on the area for 3 to 5 minutes.

The doctor will discuss with you if the line needs to be changed with a new one.

More Information:

1. American Thoracic Society (ATS): www.thoracic.org
2. Centers for Disease Control & Prevention: www.cdc.gov/

ARTERIAL LINE PLACEMENT

WHAT IS AN ARTERIAL LINE?

An arterial line is thin, flexible tube or catheter that is carefully inserted in the artery located in the wrist or groin. This catheter is connected through tubing to the monitor in the CCU, which will allow for beat-to-beat measurement of your blood pressure.

WHY YOU NEED AN ARTERIAL LINE?

Your doctor or nurse will explain the reason you need an arterial line.

Common Reasons for the Procedure:

- Low blood pressure (hypotension or shock) that requires medications in order to increase it
- High blood pressure (hypertension) requiring accurate measurements in order to control it with medications
- Lung problems or being on a ventilator, where the oxygen and carbon dioxide levels in the blood need to be checked frequently
- Severe respiratory or kidney problems that may require frequent checking of the acidity of the blood

WHERE IS THE PROCEDURE PERFORMED?

The procedure is typically performed at the bedside in the CCU.

WHAT IS THE CARE BEFORE AND AFTER THE PROCEDURE?

Before the procedure is performed, your lab work is checked to assess your risk

of bleeding. If your platelets are low or INR is high, you might need transfusion of platelets, plasma, or vitamin K in order to lower the risk of bleeding.

The radial artery is located in the wrist and femoral artery is located in the groin region. These arteries may be palpated to locate them or an ultrasound machine may be used to guide the procedure.

The procedure itself is sterile and hence your body will be covered with a sterile drape to minimize any risks for infection during the insertion.

You will be able to move and sit up with the catheter in place. Care must be taken to prevent kinking and accidental removal of the catheter, which can lead to profuse bleeding.

IS IT PAINFUL?

You will be given a local anesthetic or numbing medication at the site of insertion. After the initial injection of the local anesthetic, the procedure is pain free but you might experience pressure or discomfort. Your cooperation is of critical importance during this time.

HOW LONG DOES IT TAKE?

No more than 20 to 30 minutes.

ARE THERE ANY POSSIBLE COMPLICATIONS?

A trained physician, physician assistant, or nurse practitioner usually places the line under sterile technique and under safe and controlled settings. All procedures have a risk of potential complications.

POSSIBLE COMPLICATIONS:

- Pain at the insertion site
- Bleeding at the site or internally
- Infection of the catheter
- Clotting of the catheter and possible low blood flow to the arm or leg

WHAT IS THE CARE FOR THE ARTERIAL LINE?

To avoid any infection, clotting, or other complications, meticulous care of the

arterial line is important. Your CCU nurses and doctors will closely monitor the catheter and site.

WHEN IS THE LINE REMOVED?

As soon as the line is no longer needed, it gets removed. Gentle pressure will need to be applied on the area for 3 to 5 minutes. The site will be monitored for any further bleeding or swelling.

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Invasive Hemodynamic Assessment in the CCU

INTRODUCTION

Invasive hemodynamic monitoring is very often required in the care of a critically ill patient in the cardiac care unit (CCU) and is vital to the monitoring of the CCU patient, as well as dictating therapy. Various strategies of goal-directed fluid resuscitation utilizing dynamic measures of fluid responsiveness are available, which allow for monitoring and help direct therapy. A conservative fluid management strategy with judicious use of fluids along with monitoring of indices of tissue oxygenation is optimal in the CCU patient. Proper measurement and interpretation of the data is the key in ensuring adequate tissue perfusion and oxygen delivery, which is the goal.

PATHOPHYSIOLOGY OF HEMODYNAMICS IN A CRITICALLY ILL PATIENT IN THE CCU

It is important to understand oxygen delivery before we go into the various measures available for hemodynamic monitoring. Oxygenated blood is delivered to the tissues via the aorta, and deoxygenated blood returns to the right heart

from where it enters the lungs to get reoxygenated. Tissue extraction of oxygen occurs during this transit. The normal arterial oxygen saturation (SaO_2) is 96% to 99%. The normal mixed venous saturation ($S\bar{v}O_2$) in the pulmonary artery (PA) is 65% to 75%, which denotes tissue oxygen extraction to be roughly 25% to 35%.

Determinants of cardiac output (CO) are preload, afterload, and inotropic contractility. Many monitoring systems work to incorporate these measures to determine the adequacy of CO. A hemodynamically stable patient for the most part does not require invasive hemodynamic monitoring, whereas in the hemodynamically unstable patient, invasive monitoring is frequently warranted. Such patients invariably have an arterial line and a central venous catheter (CVC), which by themselves can provide useful hemodynamic parameters. When this is not sufficient, additional invasive devices such as PA catheters (PACs) and CO monitors are utilized.

Hemodynamic data can help classify the cause of shock. The measured data can be used to calculate variables such as CO, systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). The following equations are important to understand because they determine tissue perfusion and oxygenation:

$$CO = HR \times SV \quad \text{(Eq. 1)}$$

$$DO_2 = CO \times CaO_2 \quad \text{(Eq. 2)}$$

$$CaO_2 = 1.348 \times \text{Hemoglobin} \times SaO_2 + 0.003 \times PaO_2 \quad \text{(Eq. 3)}$$

where CO is cardiac output, HR is heart rate, SV is stroke volume, DO_2 is oxygen delivery, CaO_2 is oxygen content, SaO_2 is oxygen saturation, and PaO_2 is the partial pressure of oxygen.

HEART LUNG INTERACTIONS

Both spontaneous and mechanical ventilation induce cyclical changes in intrapleural or intrathoracic pressure and lung volume. Intermittent positive pressure ventilation induces cyclic changes in the loading conditions of the left and right ventricles. This can independently affect the key determinants of cardiovascular performance, which are preload or atrial filling, afterload, heart rate, and myocardial contractility.

Spontaneous inspiration produces a negative pleural pressure, and this

reduction in intrathoracic pressure is transmitted to the right atrium (RA). In contrast, intermittent positive pressure ventilation (tidal volume > 8 mL/kg ideal body weight) produces inspiratory increases in intrathoracic pressure and RA pressure decreasing venous return and right ventricular (RV) preload, and also increases RV afterload. This leads to a decrease in RV stroke volume, which is manifested as a decrease in left ventricular (LV) stroke volume, which is at its minimum during the expiratory period due to a phase lag of 2 to 3 beats (ie, pulmonary transit time). These cyclic changes are greater when patients are volume depleted and are on the steep rather than the flat portion of the Frank–Starling curve. This can lead to changes in pulse pressure (PP) variation, stroke volume variation, and inferior vena cava (IVC) size variation, indicating a patient who may be fluid responsive.[1] The biventricular dependence is confounded if the patient on a ventilator is also making spontaneous efforts or has an atrial arrhythmia. It is important to consider this while interpreting data.

ARTERIAL BLOOD PRESSURE

DEFINITION

Arterial blood pressure (ABP) is the pressure exerted by the circulating volume of blood upon the wall of the arteries. It is measured both at its peak (systolic blood pressure, SBP) and at its trough (diastolic blood pressure, DBP). The blood pressure in the aorta during systole is a clinical indicator of afterload (ie, the forces the left ventricle must overcome to eject blood).

The normal ranges in ABP are systolic 90 to 140 mm Hg and diastolic 60 to 90 mm Hg. PP is the difference between systolic and diastolic pressure. If BP is measured in the brachial artery, the average PP is approximately 40 mm Hg. Above 60 mm Hg, the risk of coronary events and all-cause mortality increases. The main determinant of PP is large artery compliance. The less compliant arteries are, the higher the PP, which is why PP increases with age, as elastin fibers of the arterial walls are weakened by years of stress.

ABP and PP can be affected by various factors as illustrated in **Tables 49.1 and 49.2**.

TABLE 49.1 Factors Affecting Arterial Blood Pressure

SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE

Stroke volume	
Left ventricular ejection velocity	Arterial wall distensibility
End diastolic volume	Systemic arterial resistance
Arterial wall distensibility	Blood viscosity
Systemic arterial resistance	Length of the cardiac cycle
Blood viscosity	

TABLE 49.2 Factors Affecting Pulse Pressure

INCREASED PULSE PRESSURE	DECREASED PULSE PRESSURE
Fever, exercise	Cardiac tamponade
Bradycardia	Hypovolemia
Aortic regurgitation	Shock
Anemia	Massive pulmonary embolism
Hyperthyroidism	Tension pneumothorax
	Aortic stenosis

Mean Arterial Pressure

Mean arterial pressure (MAP) is often used as a surrogate indicator of blood flow and a better indicator of tissue perfusion than SBP because it accounts for the fact that two-thirds of the cardiac cycle is spent in diastole. A MAP of 65 mm Hg or greater is needed to maintain adequate tissue perfusion.

Systemic MAP is defined as the mean perfusion pressure throughout the cardiac cycle and it can be calculated as follows:

$$MAP = SVR \times CO \qquad \text{(Eq. 4)}$$

A more practical estimate can be obtained by the following equation:

$$MAP = \frac{2}{3} DBP + \frac{1}{3} SBP \qquad \text{(Eq. 5)}$$

Intra-arterial Blood Pressure Monitoring

Intra-ABP is the direct measurement of arterial pressure and it involves inserting a catheter in a suitable artery. The catheter must be connected to a sterile, fluid-filled system, which is in turn connected to an electronic patient monitor.

CLINICAL UTILITY

ABP monitoring offers several advantages over noninvasive blood pressure (NIBP) monitoring. It allows continuous beat-to-beat pressure measurement and allows accurate blood pressure readings at very low pressures. It allows close monitoring of patients on vasopressors, inotropes, or vasodilators. It enables

ABP measurement in patients in whom NIBP monitoring is difficult and allows for frequent arterial sampling. The waveforms can also provide useful information about the patient's cardiovascular status.

MEASUREMENT

Most of the ABP measuring systems consist of a column of fluid directly connecting the arterial catheter to a pressure transducer. The pressure waveform of the arterial pulse is transmitted via the column of fluid to a pressure transducer where it is converted into an electrical signal. This electrical signal is then processed, amplified, and converted into a visual display by a microprocessor.

WAVEFORM

The arterial pressure wave is a complex wave generated by a series of pressure changes that occur during valve closure, systole, diastole, and by reflection waves caused by the impedance of blood flow as it traverses distally. The waveform seen in the transducer is the summation of all these waves resulting in a single waveform. Each component can be assigned to a specific point of the cardiac cycle and has hemodynamic significance. This can be appreciated by looking at the waveform in **Figure 49.1**. The systolic upstroke represents the pressure generated at the beginning of systole. The dicrotic notch represents the closure of the aortic valve and the subsequent downstroke represents the rapid decline during diastole. Due to the differences in the characteristics of the vascular tree, ejection velocities, and the length of the fluid column, arterial waveforms differ depending on the site of catheter insertion. The further the catheter is from the aorta, the higher the SBP, the further the dicrotic notch, and the wider the PP. The MAP, however, will remain constant and hence is relied on as the main hemodynamic parameter to assess perfusion.

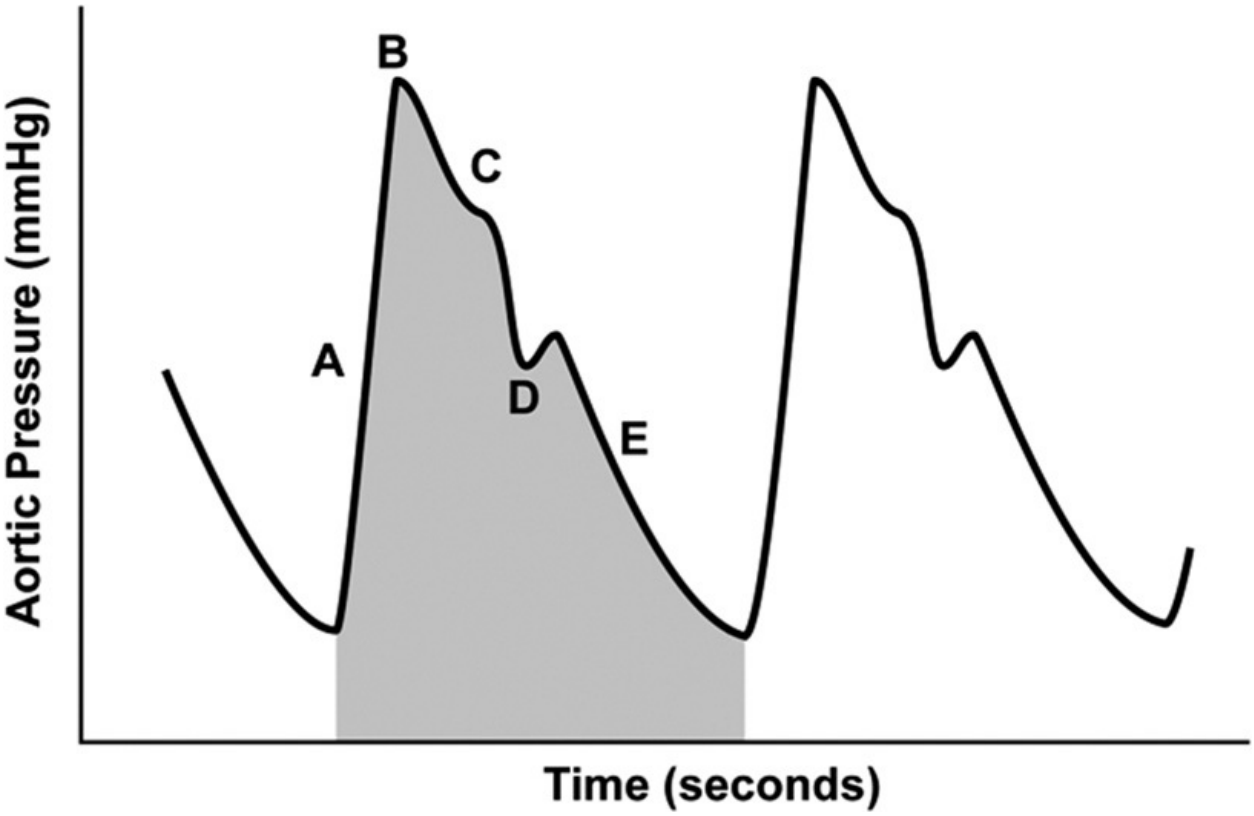


FIGURE 49.1 Arterial waveform. *A*, Systolic uptake. *B*, Peak systolic pressure. *C*, Systolic decline. *D*, Dicrotic notch. *E*, Diastolic runoff.

ACCURACY OF MEASUREMENTS

It is important that accuracy of the ABP measurements is maintained by reducing the length of tubing used and ensuring that there are no bubbles or clots in the system. The accuracy and interpretation of invasive pressure measurements depend on a number of physical principles of the systems used.

Damping

Anything that reduces energy in an oscillating system will reduce the amplitude of the oscillations. This is termed damping and measurements will be adversely affected if there is excessive (overdamping) or insufficient (underdamping) damping,

Factors that will cause overdamping include three-way stopcocks, bubbles, clots, long tubing, and kinks in the catheter or tubing. These may be a major source of error, causing an underreading of SBP and DBP, although the MAP is relatively unaffected.

Transducer position can be checked (ie, zeroed) by turning the stopcock off to

the patient and open to air, at the level of the heart. The monitor must be adjusted to display zero. Incorrect readings may be obtained if the transducer is not releveled with changes in position of the bed or patient.

Abnormal Arterial Line Waveforms

Under certain circumstances, it is possible to correlate the shape of an arterial waveform with a specific pathology. A steep systolic upstroke can be seen in hypertension or atherosclerosis due to noncompliance of the vessels. In aortic regurgitation, the PP is widened and a second peak, bisferient pulse can also be seen (**Figure 49.2**). Aortic stenosis can cause delaying of the upstroke slope and a low systolic peak due to limited outflow (**Figure 49.3**).

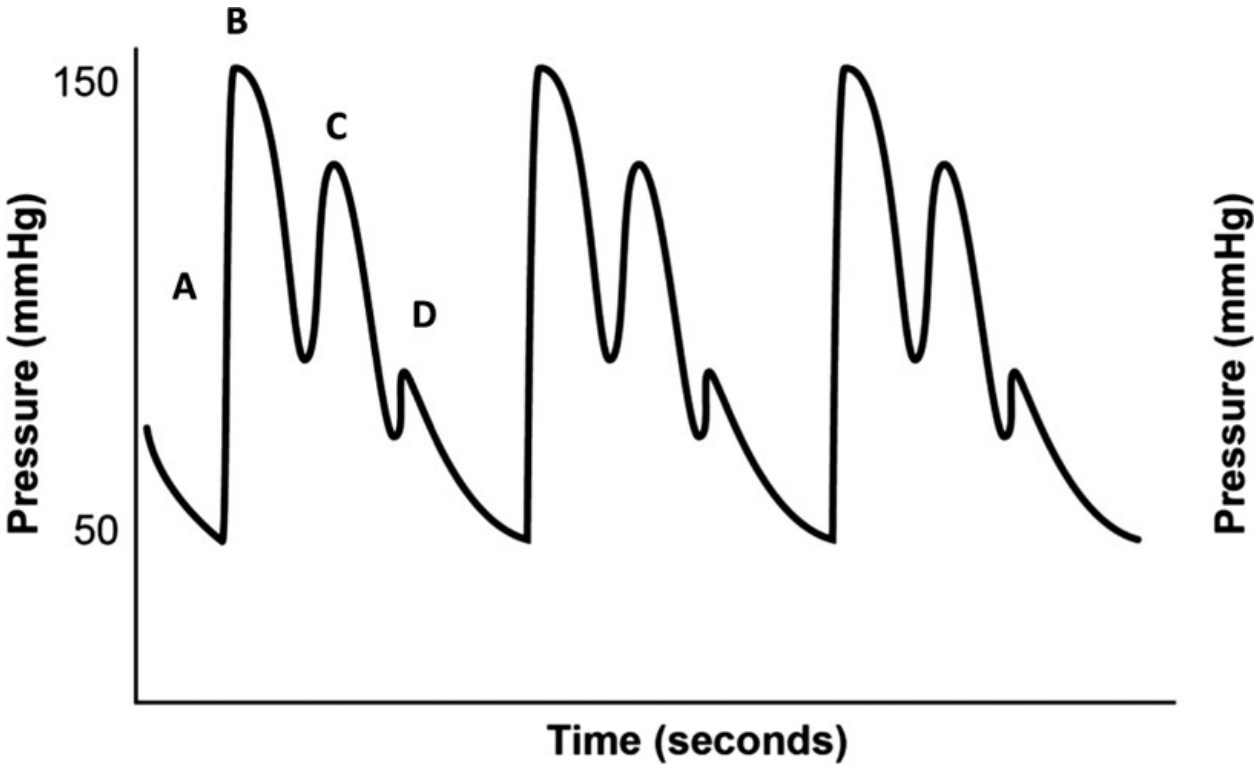


FIGURE 49.2 Arterial waveform in aortic regurgitation. *A*, Widened pulse pressure. *B* and *C*, Bisferiens pulse, peak C is a reflected wave. *D*, Dicrotic notch.

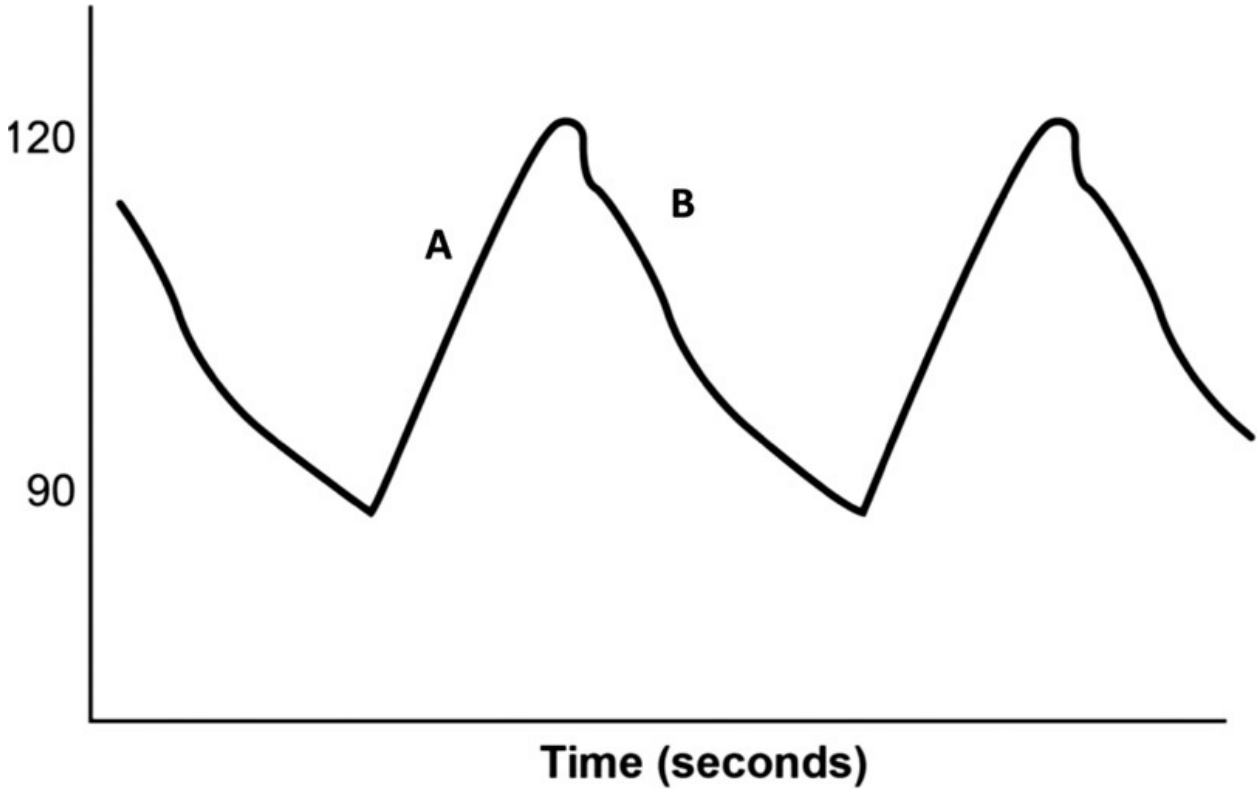


FIGURE 49.3 Arterial waveform in aortic stenosis. *A*, Slurred gradual systolic upstroke. *B*, Absent dicrotic notch.

CENTRAL VENOUS PRESSURE

DEFINITION

Central venous pressure (CVP) is the pressure measured in the lower third of the superior vena cava (SVC) and is considered a direct measurement of the pressure in the RA (ie, mean RA pressure). It is commonly used as an estimate of RV filling pressures or preload.

Some authors suggest the following equation to help health care providers:

CVP = Mean RA pressure = Right ventricular end diastolic pressure (RVEDP) = Preload.

The CVP value is determined both by the pressure of venous blood in the vena cava and the function of the right heart. The principal factors affecting CVP are shown in **Figure 49.4**. Venous return is in turn influenced by intravascular volume, compliance characteristics of the venous system (venous tone), PVR, and intrathoracic pressure. The changes in CVP are directly proportional to

volume changes and inversely proportional to venous compliance.

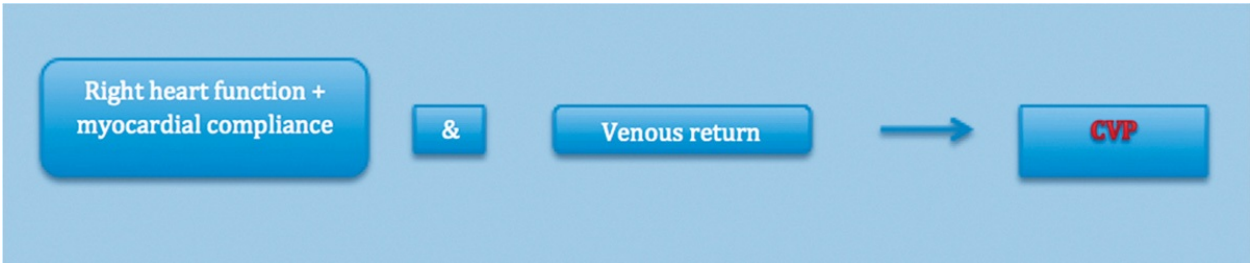


FIGURE 49.4 Factors affecting CVP. CVP, central venous pressure.

MEASUREMENT

CVP is acquired by inserting a CVC into any of several large veins. It is threaded so that the tip of the catheter rests in the lower third of the SVC. The pressure monitoring assembly is attached to the distal port of a multilumen CVC. The CVP can be measured manually (using a manometer) or electronically (using a transducer). Normal CVP is 2 to 6 mm Hg. The CVP must be set at zero at the level of the RA with the patient lying supine (the "phlebostatic axis"—usually 4th intercostal space in the midaxillary line). In the thorax, extravascular pressures should be close to zero at the end of expiration; hence, CVP is measured at end expiration and at end diastole.

CLINICAL UTILITY

Traditionally, CVP has been utilized to assess volume responsiveness, with a low CVP thought to predict fluid responsiveness whereas a patient with a high CVP is thought to be fluid replete. These concepts have been challenged based on meta analysis that have questioned the use of static measures of fluid responsiveness.[2]

CVP is elevated in conditions such as RV failure, tricuspid stenosis, or regurgitation, pericardial disorders, and mechanically ventilated patients on high positive end-expiratory pressure (PEEP) settings and does not reflect fluid status. For the last decade, the utility of CVP measurement to determine volume responsiveness has been questioned. Because of this debate, its use should be in association with information relating to other hemodynamic variables.

WAVEFORM

In sinus rhythm, the CVP waveform reflects changes in right atrial pressure during the cardiac cycle and contains five components:

- Two major positive deflections: *a* and *v* waves
- Two negative deflections: *x* and y descents
- A third positive wave: the *c* wave, which is not consistently observed

Figure 49.5 shows this anatomy of a CVP waveform in correlation with the cardiac cycle with the help of a simultaneous ECG tracing. The first peak is the *a* wave, which immediately follows the *P* wave of the ECG. This *a* wave (atrial) represents the pressure increase due to atrial systolic contraction. The *a* wave is followed by the *x* descent, which is the drop in atrial pressure during ventricular systole caused by atrial relaxation and the downward movement of the atrioventricular junction during early ventricular systole. The trough of the *x* descent is followed by the *v* wave, which represents the increase in pressure generated by the passive filling of the atria during ventricular systole. The *v* wave corresponds to the end of the *T* wave in the ECG. The *y* descent results from the drop in atrial pressure as the blood enters the ventricle during diastole. The *c* wave represents closure of the atrioventricular valves and is seen as a small positive wave early on in the interrupts the *x* descent. The waveform components and their timing in the cardiac cycle are listed in **Table 49.3**. Understanding the CVP waveform can help the clinician to interpret the various abnormalities that can be seen in certain clinical conditions. The waveform abnormalities and the conditions associated with them are listed in **Table 49.4**.

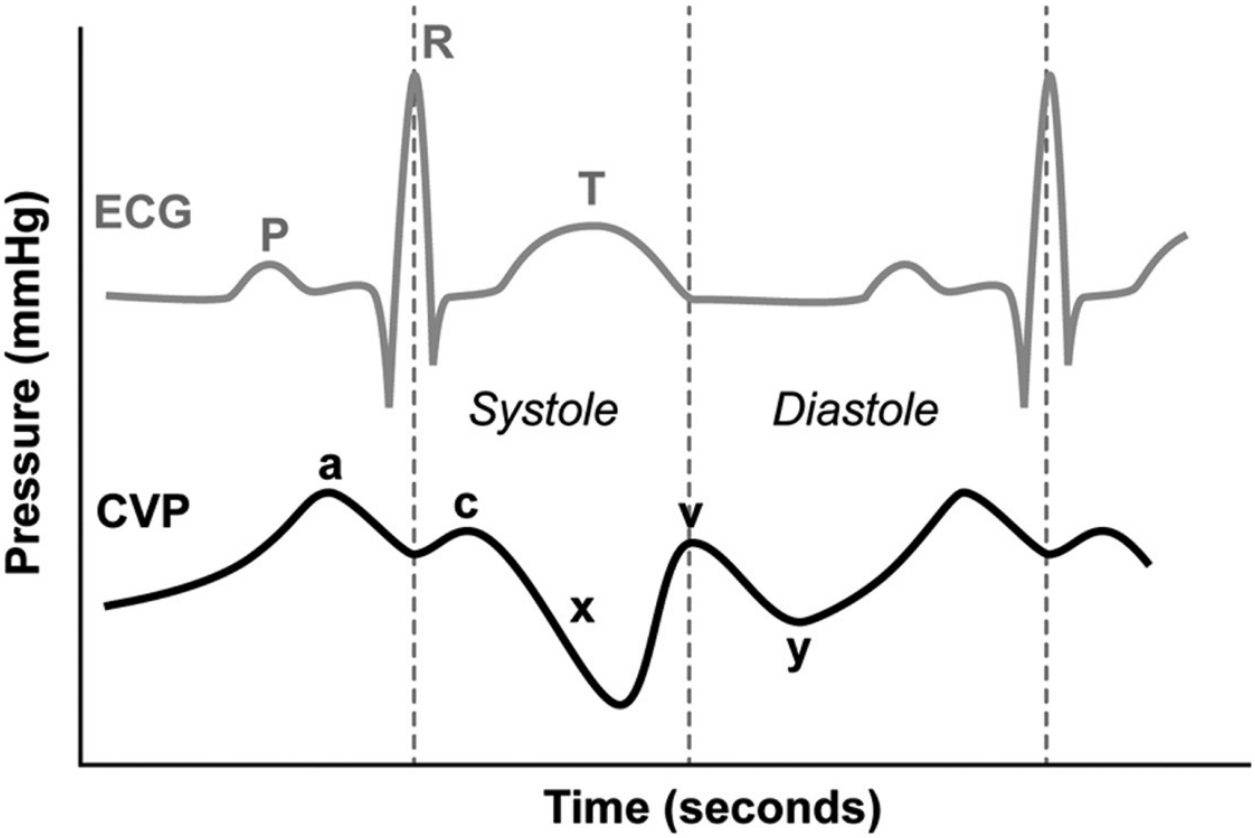


FIGURE 49.5 Anatomy of CVP waveform. CVP, central venous pressure.

TABLE 49.3	Components of the Central Venous Pressure Waveform	
WAVEFORM COMPONENT	**PHASE OF CARDIAC CYCLE**	**MECHANICAL EVENT**
a wave	End diastole	Atrial contraction
c wave	Early systole	Tricuspid bulging (inferior vena cava)
v wave	Late systole	Systolic atrial filling
x descent	Mid systole	Atrial relaxation
y descent	Early diastole	Early ventricular filling

TABLE 49.4	Abnormal Central Venous Pressure Waveforms
WAVEFORM ABNORMALITY	**CLINICAL CORRELATION**
Dominant *a* wave	Pulmonary hypertension Tricuspid stenosis Pulmonary stenosis

Canon *a* wave	Complete heart block Ventricular tachycardia with atrioventricular dissociation
Dominant *v* wave	Tricuspid regurgitation
Exaggerated *x* descent	Pericardial tamponade Constrictive pericarditis
Slow *y* descent	Tricuspid stenosis Atrial myxoma
Absent *y* descent	Tamponade
Prominent *x* and *y* descent	Constrictive pericarditis

CURRENT CONCEPTS

CVP AND ITS USEFULNESS IN GUIDING FLUID THERAPY

CVP is a static measure of right atrial pressures. Traditionally, clinicians have used the concept that a low CVP will be a measure of fluid responsiveness and a high CVP will predict someone who will not respond to a fluid challenge. This concept was promoted by the Surviving Sepsis Campaign (SSC) guidelines based on the Early Goal Directed Therapy trial by Rivers, which showed that using a target CVP goal of 8 to 12 mm Hg (12–15 mm Hg in mechanically ventilated patients) for fluid resuscitation, along with other early interventions, led to decreased mortality in patients with severe sepsis and septic shock.[3,4] However, this relationship between CVP and intravascular volume as well as its usefulness to predict fluid responsiveness has been questioned.[5] In 2008, Marik et al[2]. conducted a systematic review of the literature on this topic that included 24 studies and 805 patients. The studies analyzed demonstrated that patients with low CVPs may not be fluid responsive and patients with high CVPs may be fluid responsive. They found that there is a very poor correlation between CVP and blood volume as well as the inability of CVP or ΔCVP to predict the hemodynamic response to a fluid challenge. They concluded that CVP should not be used to make clinical decisions regarding fluid management.[2,6]

Overall, the methods for assessing fluid responsiveness have evolved over time from static parameters to dynamic measures based on either a passive leg raise (PLR) or a real fluid challenge, both of which have a higher degree of accuracy in predicting fluid responsiveness.[7] However, these dynamic measures

have not been fully incorporated into clinical practice. Although static measures of fluid responsiveness such as the CVP have fallen out of favor, extremes of CVP values still have clinical utility. Septic shock is associated with low CVP, high CO, and low SVR. In contrast, cardiogenic shock is associated with high CVP, low CO, and high SVR. A low CVP is useful because it suggests a low volume state whereas a high CVP is less useful because the patient may have fluid overload or have normal volume status with heart failure. A very high CVP in the absence of right-sided heart disease represents a patient who will likely not be fluid responsive. Although the CVP measurement has been heavily criticized in the literature, when measured correctly it is one of the few tools that is devoid of subjective interpretation by the end user. Additionally, it is a value that is easily obtained in the CCU patient and can be interpreted by various members of the health care team. A CVP should never be interpreted in isolation and should be used in context with one's physical examination, echocardiogram (ECG), and other dynamic measures of fluid responsiveness, which are described later in this chapter. For example, it should not be assumed that a patient is adequately fluid resuscitated if the CVP is normal. Similarly, a patient with right heart dysfunction with elevated CVP may be fluid responsive despite an elevated CVP. In summary, the CVP provides insight into the patient's hemodynamic status and is a useful adjunct when used in combination with other predictors of fluid responsiveness.

CENTRAL VENOUS OXYGEN SATURATION AND OXYGEN DELIVERY

The central venous oxygen saturation ($ScvO_2$) is obtained from a from a central line, preferably from an internal jugular or subclavian vein catheter, and serves as a surrogate of mixed venous oxygen saturation (SvO_2). It is estimated that the $ScvO_2$ is 3% to 5% higher than SvO_2. The femoral $ScvO_2$ is less reliable. $ScvO_2$, along with the CVP, can help guide further fluid management.

A low $ScvO_2$ serves as an indicator of poor oxygen delivery (ie, low CO, low hemoglobin or low SaO_2) or increased consumption by tissues (eg, fever, hyperthyroidism). A high $ScvO_2$ indicates poor extraction by tissues (eg, sepsis, hypothyroidism, cyanide poisoning) or arteriovenous shunting. The SSC sepsis guidelines recommend a target $ScvO_2$ of >70%[4] as a target for resuscitation for patients with severe sepsis and septic shock; however, these protocoled recommendations have since been challenged.[8–10]

THE PULMONARY ARTERY CATHETER

In 1970, Swan and his colleagues[11] described PAC with a balloon proximal to the tip, which could be directed to the branches of the PA. It permits measurement of intracardiac filling pressures. The catheter is inserted into the RA, RV, and when in position with the balloon inflated in the PA, a "wedge" pressure is obtained. This wedge pressure provides an indirect measure of LV filling pressure, which can guide the clinician in the management of fluid therapy in patients with shock and respiratory failure. CO measurements obtained by the thermodilution method and the derived SVR measurement can help distinguish mixed shock states and assist in titrating vasopressors and inotropic medications. The PAC can assist in the management of patients with acute myocardial infarctions, valvular dysfunction, intracardiac shunts, pericardial tamponade, and pulmonary hypertension. Additionally, it can help with the diagnosis and management of mechanical complications of myocardial infarction, such as ventricular septal rupture, papillary muscle rupture, and RV infarction. Contraindications to PAC include severe coagulopathy or thrombocytopenia, RV thrombus, tricuspid or pulmonic valve prosthesis, and right-sided endocarditis. In patients with left bundle branch block, passage of the catheter can induce complete heart block.

DESCRIPTION

A PAC or Swan-Ganz catheter is a flexible, balloon-tipped, flow-directed catheter that is guided through the right side of the heart and into a branch of the PA. Under sterile conditions, the catheter is generally inserted through the subclavian, internal jugular, or femoral, vein. The right internal jugular vein and left subclavian vein are ideal because the curvature of the PAC facilitates passage through the heart. The procedure, also known as right heart catheterization, may be performed with or without the use of fluoroscopy.[12]

The typical PAC is 110 cm long and has four lumens: the distal, proximal, thermistor, and inflation lumen. The distal lumen port is located at the tip of the catheter. This port allows monitoring of systolic, diastolic, and mean pressures in the PA and allows visualization of the waveform to guide proper placement. It can also be used for drawing mixed $S\bar{v}O_2$ samples. The proximal port, located approximately 30 cm from the tip of the catheter, is used to monitor RA pressure, CVP, and to inject the solution used to assess intermittent CO by thermodilution.

Additionally, there may be an accessory RA proximal port with its lumen at 30 cm from the catheter tip, which may be used for infusion of medications. **Figure 49.6** shows a standard PAC with the balloon inflated.

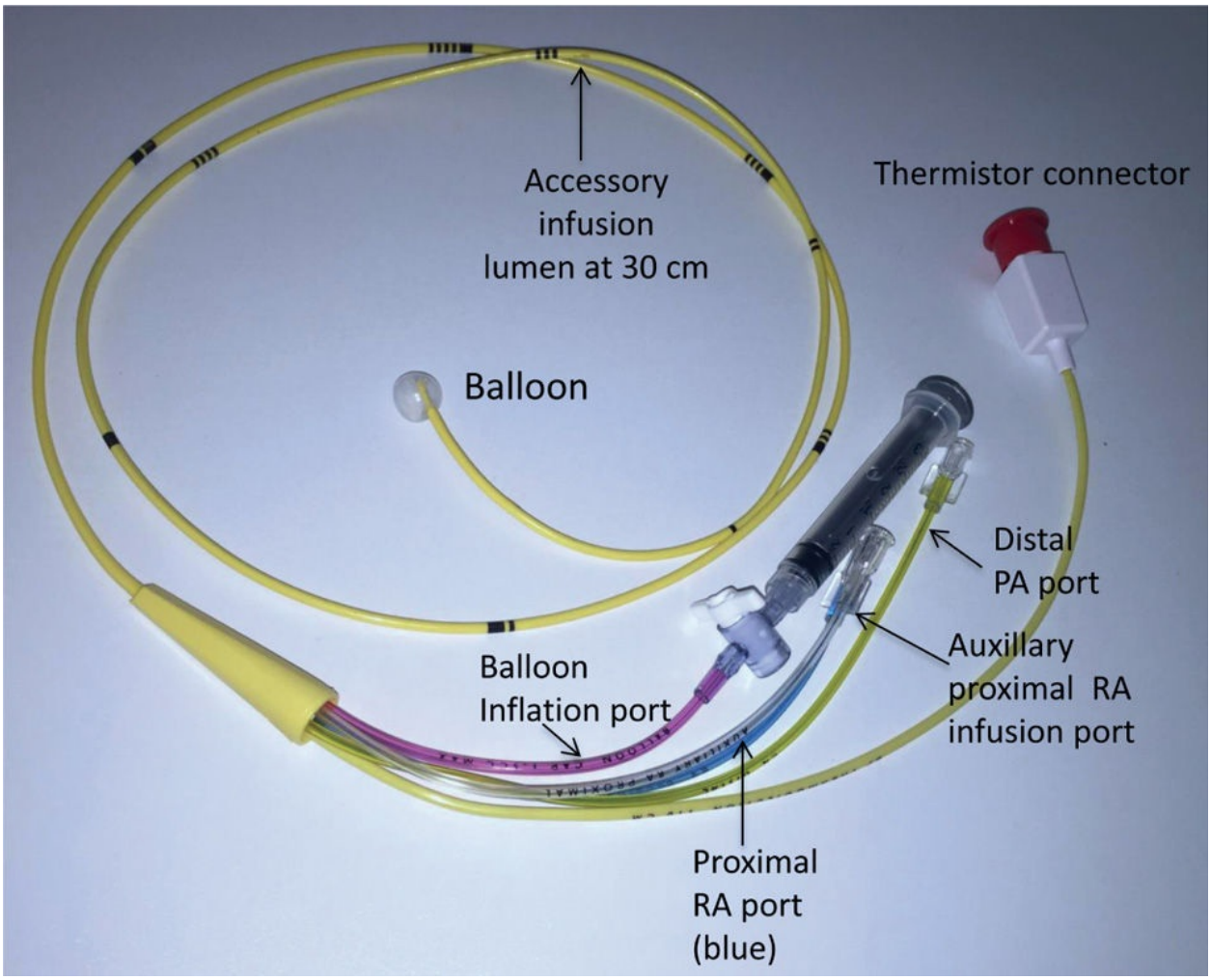


FIGURE 49.6 Standard pulmonary artery catheter.

Thermodilution involves injection of a known amount of solution with a known temperature rapidly into the RA lumen of the catheter. Usually cold fluid is injected into the proximal lumen and the temperature of the blood is measured downstream in the PA by a thermistor. This information is plotted on a time–temperature curve that represents the time it takes for the blood to change from a warmer baseline temperature to a cooler temperature after the injection and then back to the baseline temperature as the blood circulates. The rate of blood flow is inversely proportional to the change in temperature over time. When CO is

low, it takes longer for the blood temperature to return to baseline; when CO is high, the cooling fluid is carried faster through the heart, and the temperature returns to baseline faster.

The inflation lumen connects to a balloon that is located less than 1 cm from the catheter tip, which is inflated with 1.5 mL air to advance into the PA. The waveform is constantly observed on the monitor during advancement until a wedged position is obtained. It is important that on deflation of the balloon, a PA waveform is obtained so as to avoid over wedging. It is used to obtain PAWP, which is also called pulmonary artery occlusion pressure (PAOP) or pulmonary capillary wedge pressure (PCWP).

Once lodged in the PA, the inflated balloon serves as a continuous conduit from the catheter tip through the pulmonary vein, left atrium (LA), and open mitral valve into the left ventricle. This allows the distal lumen to indirectly measure LV pressure. The balloon should be deflated once PAOP measures are obtained. The pulmonary artery diastolic pressures (PADP) can also serve as a surrogate to PAOP. Newer catheters come with continuous cardiac output (CCO) and continuous S_{VO}^{2} monitoring. In order to measure CO continuously, thermal energy emitted by the filament located on the catheter is used to calculate CO using thermodilution principles.

INSERTION

Prior to PAC insertion, the system must be zeroed to ambient air pressure. The reference point for this is the midpoint of the LA, estimated at the fourth intercostal space in the midaxillary line with the patient lying in supine position. With the transducer at this height, the membrane is exposed to atmospheric pressure and the monitor is then adjusted to zero. The PAC should be checked for cracks and kinks. The balloon should be checked and all lumens flushed to remove air bubbles.

The catheter is inserted through an introducer catheter sheath and advanced using continuous pressure monitoring from the distal lumen (**Figure 49.7**). It is recommended to insert the catheter 15 cm so that the tip is outside of the sheath. The balloon is then inflated before advancing into the PA. **Figure 49.7** shows the various waveforms obtained during right heart catheterization. If an RV waveform is still present approximately 20 cm after the initial RV pattern appears, the catheter may be coiling in the RV. The catheter is withdrawn slowly and advanced again until the PA tracing is obtained and even further until a wedge tracing is obtained. Sometimes fluoroscopy is necessary in difficult cases.

Measure CO by connecting the thermistor to a computer and perform thermodilution. The assistant should note down the systolic, diastolic, and mean pressures in the right heart, including the PAOP at end expiration.

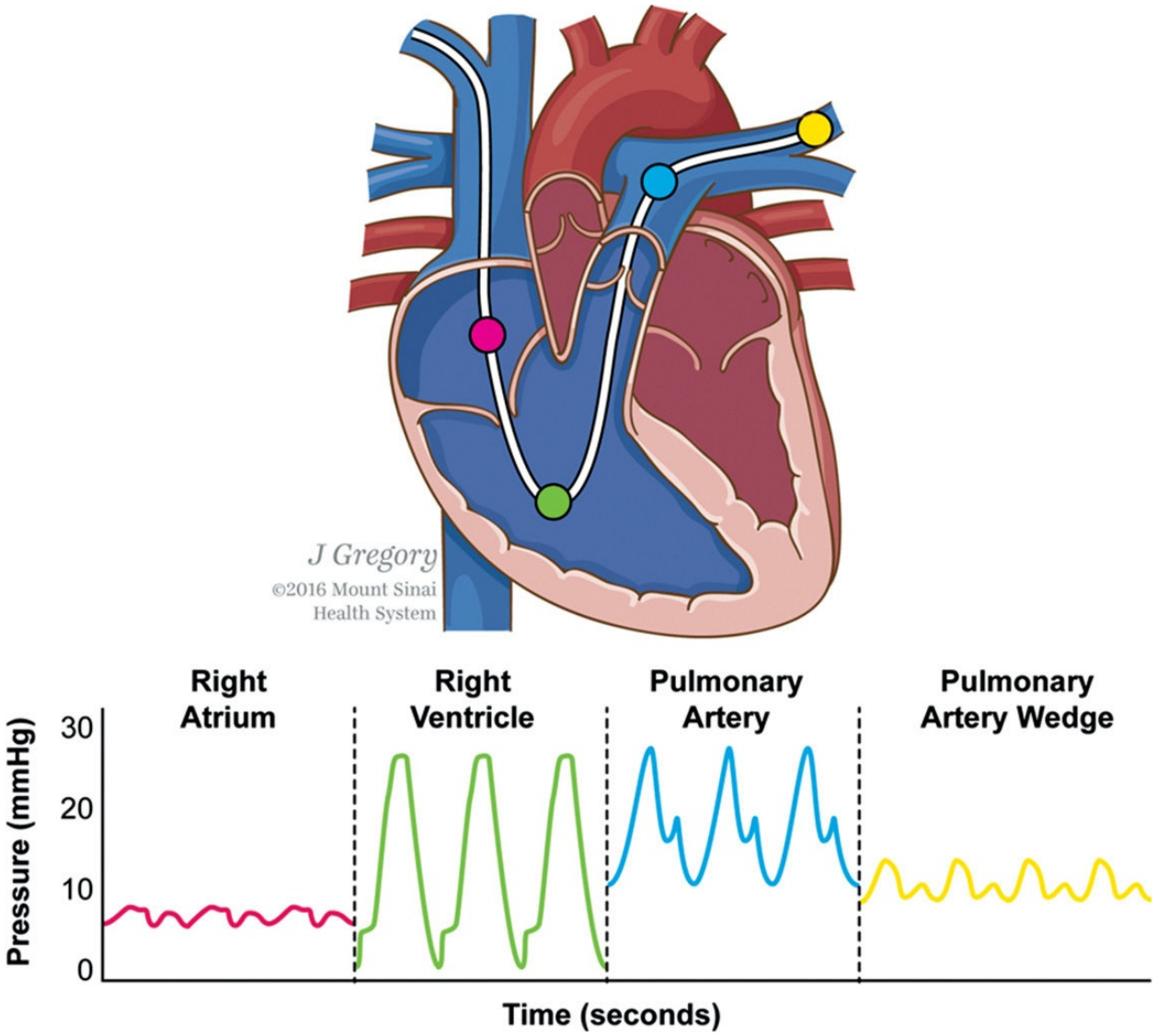


FIGURE 49.7 Waveforms during right heart catheterization.

An ideal positioning of the PAC is one which shows the PA tracing with the balloon deflated and a pulmonary occlusion tracing with the balloon inflated. It is important to deflate the balloon after acquiring readings and values. A chest X-ray is obtained to ensure proper placement preferably in West Zone 3, where the pulmonary capillary pressure exceeds the mean alveolar pressure.[13] This zone is located in the most dependent portion of the lung, where vascular pressures are the highest. If the PAOP is greater than the PA diastolic pressure or if there is marked respiratory variation, this may be a clue that the catheter has not migrated into Zone 3. The tip of the catheter should therefore be ideally positioned below the level of the LA. In a patient on a ventilator, high PEEP can

alter the baseline intrathoracic pressure. However if it is located in the right zone as mentioned earlier, the effects of PEEP on PAOP are usually small, and often do not affect clinical management.

The PAOP waveform is similar to the CVP waveform obtained from the proximal port, which reflects RA pressures. However, it is important to recognize that the PAOP waveform is shifted to the right by 80 to 120 ms in relation to the ECG because of the time delay in the waveform travelling through the pulmonary circuit.

As a review, let us contrast PAOP versus CVP. PAOP measures left atrial pressure, and approximates left ventricular end diastolic pressure (LVEDP) when the mitral valve functions properly.

Some authors simplify this concept by the following formula:

$$\text{PAOP} = \text{Mean LA pressure} = \text{LVEDP},$$

while

$$\text{CVP} = \text{Mean RA pressure} = \text{RVEDP} = \text{Preload}.$$

MEASUREMENTS

Direct measurements that can be obtained from an accurately placed PAC are the following:

- Central venous pressure
- Right atrial pressure (RAP)
- Right ventricular pressure (RVP)
- Pulmonary arterial pressure (PAP)
- Pulmonary artery occlusion pressure
- Cardiac output
- Mixed venous oxyhemoglobin saturation (SvO_2)

The PAC can also indirectly measure the following:

- Systemic vascular resistance
- Pulmonary vascular resistance
- Cardiac index (CI)
- Stroke volume index (SVI)
- Left ventricular stroke work index (LVSDI)

Right ventricular stroke work index (RVSI)
Oxygen delivery (DO_2)
Oxygen consumption (VO_2)

INTERPRETATION

Right ventricle: During catheter insertion using the distal tip, the peak RV systolic pressure and the RVEDP are measured from the RV pressure waveform. Normal RV systolic pressure varies from 15 to 30 mm Hg and normal RVEDP varies from 1 to 7 mm Hg. Elevations in RV pressure are associated with diseases that elevate the PAP, pulmonic valve disorders, and diseases that primarily affect the RV.

Pulmonary artery: Normal PA systolic pressures range from 15 to 25 mm Hg, whereas PA diastolic pressures range from 8 to 12 mm Hg. The mean PAP (mPAP) is typically 16 mm Hg (10 to 22 mm Hg). Pulmonary hypertension is defined as mPAP ≥ 25 mm Hg. The PA tracing is similar in appearance to the systemic arterial pressure tracing, except that the PAPs are normally much lower.

Pulmonary artery occlusion pressure: The PAOP or PCWP estimates the left atrial pressure. This is measured when the catheter tip is in the PA with the balloon inflated. Normal wedge pressures vary from 8 to 12 mm Hg, with a mean of 10 mm Hg. The PAOP usually estimates the LVEDP, which gives an idea of LV preload, assuming that there is no obstruction to flow between the LA and left ventricle and that the compliance of the left ventricle is normal. The PAOP may not reliably indicate LV preload when compliance of the left ventricle is abnormal (eg, LV hypertrophy, ischemia, or restrictive cardiomyopathy). Valvular pathology such as mitral stenosis, myxoma, or mitral regurgitation will overestimate PAOP, whereas PAOP will underestimate LVEDP in aortic regurgitation. **Table 49.5** outlines the conditions that cause abnormal PAOP values.

TABLE 49.5 Abnormal PAOP Values

Conditions that cause a high PAOP
Left ventricular systolic heart failure
Left ventricular diastolic heart failure
Mitral and aortic valve disease

Hypertrophic cardiomyopathy
Hypervolemia
Large right-to-left shunts
Cardiac tamponade
Constrictive and restrictive cardiomyopathies
Conditions that cause a low PAOP
Hypovolemia
Pulmonary venoocclusive disease
Obstructive shock due to pulmonary embolism

PAOP, pulmonary artery occlusion pressure.

ABNORMAL PAOP WAVEFORMS

Physiologically, the PAOP tracing has similar components to the RA with three positive and two negative deflections. The abnormal waveform seen in the PAOP tracing reflects changes on the left side of the heart. Electrocardiographic correlation is required for correct identification of these events. The PAOP waveform is delayed by >120 ms when compared with the ECG.

Large *a* waves: Increased amplitude of the *a* wave in the PAOP tracing can be seen with increased resistance to LV filling of any cause such as mitral stenosis or decreased LV compliance. Cannon *a* waves can also be seen with complete atrioventricular block due to atrial contraction against higher ventricular pressures.

Large *v* waves: The common cause of large *v* waves on a PAOP tracing is mitral regurgitation (MR). Other conditions such as ventricular septal defects can also cause large *v* waves due to increased atrial pressures. Giant *v* waves can be seen in cases of severe MR and often this may be mistaken for a PA tracing. This can be avoided by using the ECG tracing and understanding that the peak of the systolic PAP occurs within the *T* wave whereas the giant *v* wave occurs after it.

Conditions such as cardiac tamponade and constrictive pericarditis may present hemodynamic alterations prior to clinical manifestations. Whereas both conditions may produce equalization of diastolic pressures (RAP = RV diastolic pressure = PADP), waveform identification can assist in differentiating the two.

In cardiac tamponade, all right-sided pressures will be elevated and there is a prominent *x* descent and a loss of the *y* descent in a PAOP or RA tracing as a result of higher diastolic values. In constrictive pericarditis, there are exaggerated *y* descents from rapid diastolic filling as a result of the rigid pericardium.

Acute ventricular septal defect (VSD) can also produce low CO when the blood volume from the left ventricle shunts over to the right ventricle. This shunting causes a "step-up" of oxygen saturation from the right ventricle to the PA. By determining saturation values in the PA, a VSD can be detected. In severe cases, a resultant elevation in the *v* wave during a wedge recording may also be seen. This is due to the increase in blood volume from the left ventricle, which during atrial filling, records as an elevation in the *v* wave.

MEASURING THE PAOP

The correct reading of a PAOP waveform in relation to an ECG strip is shown in **Figure 49.8**. As opposed to a CVP tracing, there is a delay of two to three squares of the waveform in the PAOP tracing. The "*Z* point" (occlusion pressure at end diastole) is measured by any one of the following methods (see **Figure 49.8**):

1. The pre *c* wave location
2. Mean of the highest and lowest pressure of the *a* wave: $\text{PAOP} = \frac{a + x}{2}$
3. The *Z* point, a perpendicular line drawn two to three squares after the QRS complex

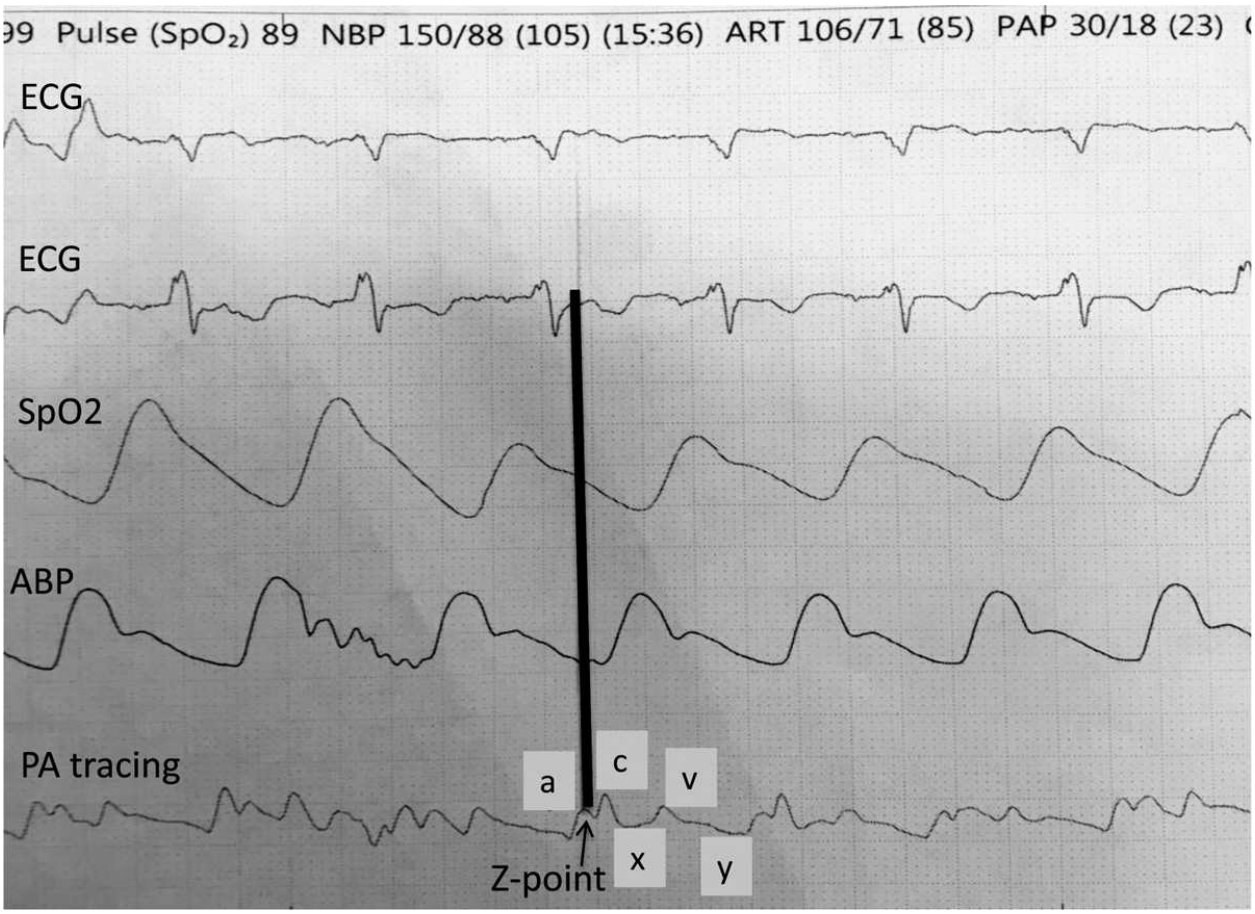


FIGURE 49.8 Pulmonary artery occlusion pressure waveform in relation to ECG. ECG, Electrocardiogram.

The abnormal waveform seen in the PAOP tracing reflects changes on the left side of the heart. The objective of placing a Swan-Ganz catheter is to obtain LVEDP, which is used to estimate LV end diastolic volume (LVEDV). The location of the end diastole period correlates to the point just before the *c* wave. If the *c* wave is not located, then the next approach would be to measure the mean of the highest and lowest pressures of the *a* wave. A third method is to find the *Z* point that correlates with the wedge pressure. This is located on the PAOP tracing by drawing a line, two to three boxes (0.08 to 0.12 seconds) after the QRS segment of the ECG tracing.

It must be remembered that respiratory efforts strongly affect the waveforms. Spontaneous ventilation tends to drop vascular pressures, whereas positive pressure ventilation raises the pressures in the inspiratory cycle. Pleural pressures become negative during inspiration in a spontaneously breathing patient and positive during the inspiratory cycle of a mechanically ventilated

patient. Since expiration is the longer and more stable phase, pressures are measured at the end of expiration, when pleural pressures are close to zero.

In summary, an ideal measurement of wedge pressure involves obtaining simultaneous tracings of ECG, respiration, and the PAOP tracing, then identifying the *Z* point using the ECG at the end of expiration, or measuring the average of the highest and lowest pressures of that *a* wave. Other interpretations of the waveforms are similar to what was mentioned in the CVP tracings except that they reflect left-sided function.

CALCULATION OF CARDIAC OUTPUT

Thermodilution Method

The thermodilution method has been well validated and is performed as specified earlier. Approximately 10 mL of cold or room temperature saline is injected into the proximal lumen and the temperature difference is sensed by the distal lumen. The bedside computer monitor integrates the time–temperature curve and calculates CO using the Stewart–Hamilton equation. The area under the temperature–time curve is inversely proportional to CO. Usually three CO measurements are performed in rapid succession and averaged.[14]

Clinicians should be aware of several important sources of error such as tricuspid regurgitation and intracardiac shunts. Tricuspid regurgitation leads to an underestimation of CO. Right-to-left and left-to-right intracardiac shunts can produce falsely elevated cardiac output measurements by the thermodilution technique. Variations in temperature (eg, after cardiopulmonary bypass) can also falsely affect the measurements. Accurate measurements also depend on calibration of transducers and a fluid-filled system that is devoid of air bubbles and blood clots. The CO can also be elevated physiologically. A high CO with or without heart failure can also be seen in a number of conditions such as sepsis, hyperthyroidism, anemia, Beriberi, renal disease, hepatic disease, and systemic arteriovenous malformation.

Fick Method

Fick's concept proposes that the uptake or release of a substance by an organ is the product of blood flow through that organ and the difference between arterial and venous values of that substance. Although the Fick method is considered the gold standard for CO measurement, it is not widely applied outside the cardiac

catheterization laboratory, because it has many limitations including a patient who is in steady state and the requirement of simultaneous expired air and blood samples.[14]

$$CO = \frac{\dot{V}o_2}{Cao_2 - Cvo_2} \qquad \text{(Eq. 6)}$$

where $V.O_2$ is oxygen consumption, CaO_2 is normal arterial oxygen content, and CvO_2 is normal venous oxygen content.

Oxygen consumption is either measured by exhaled breath analysis or estimated from a nomogram that is based on age, sex, height, and weight. The arteriovenous oxygen difference requires additional calculations:

$$Cao_2 - Cvo_2 = 1.34 \times Hgb \times (Sao_2 - S\bar{v}o_2) \times 10 \qquad \text{(Eq. 7)}$$

$$S\bar{v}o_2 = Sao_2 - \frac{\dot{V}O_2}{1.34 \times Hgb \times CO} \qquad \text{(Eq. 8)}$$

where Hgb is the hemoglobin, $S\bar{v}O_2$ is the mixed venous oxygen content and the SaO_2 is the arterial oxygen content.

DETECTION OF LEFT-TO-RIGHT SHUNTS

Arterial blood sampling from the RA, right ventricle, and PA provides helpful information when evaluating a suspected intracardiac (left to right) shunt. Detection of an oxygen saturation “step-up” in the right-sided chambers allows confirmation of the left-to-right shunt and determination of its location.

SYSTEMIC AND PULMONARY VASCULAR RESISTANCE

Once the CO has been determined, SVR and PVR can be estimated. Since the calculations of vascular resistance are based on direct measurements (ie, pressures) and indirect measurements (i.e., CO), each one can has its own intrinsic sources of error, giving rise to incorrect calculated values. Nonetheless, SVR can provide valuable information when distinguishing the classes of shock from each other and PVR is often useful when determining the prognosis of patients with pulmonary hypertension. **Table 49.6** lists the common formulas used for interpretation of Swan-Ganz values and **Table 49.7** lists the normal values. The derived values are illustrated in **Table 49.8**. Obtaining these values is very useful in creating a hemodynamic profile of the critically ill patient in the CCU. The commonly observed hemodynamic profile in the critically ill patient in various conditions is listed in **Table 49.9**.

TABLE 49.6 Formulas for Swan-Ganz Interpretation

FORMULAS
DO_2 (mL/min) = CO × CaO_2
CO (mL/min) = HR × SV
Ca_{O_2} (mL O_2/dL) = 1.34 × Hb × Sa_{O_2} + 0.003 × P_{O_2}
V_{O_2} (mL O_2/min) = CO × (CaO_2 − CvO_2)
SVR (dyne · s/cm^5) = $\frac{MAP - CVP}{CO} \times 80$
PVR (dyne · s/cm^5) = $\frac{MPAP - PAOP}{CO} \times 80$
CI (L/min/m^2) = $\frac{CO}{BSA}$
SVI (mL/m^2/beat)= $\frac{CI}{HR}$
LVSWI (g/m^2/beat)= (MAP − PAOP) × SVI × 0.136
RVSWI (g/m^2/beat)= (MPAP − CVP) × SVI × 0.136

BSA, body surface area; Ca_{O_2}, oxygen content; CI, cardiac index; CO, cardiac output; Cv_{O_2}, venous oxygen content; CVP, central venous pressure; DO_2, oxygen delivery; HR, heart rate; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance; RVSWI, right ventricular stroke work index; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; V_{O_2}, oxygen consumption.

TABLE 49.7 Normal Values

CO: 4–8 L/min
CI: 2.5–4 L/min
CVP: 2–6 mm Hg
PAWP: 8–12 mm Hg
PAP: 25/10 mm Hg
$S_{\bar{v}O_2}$: 0.65–0.70

CI, cardiac index; CO, cardiac output; CVP, central venous pressure; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure.

TABLE 49.8	Derived Values
USE OF FORMULA: CO = (MAP − CVP)/SVR	
SV:50–100 mL/beat	
SVI: 25–45 mL/beat/m^2	
SVR: 900–1300 dyne · s/cm^5	
SVRI: 1900–2400 dyne · s/cm^5	
PVR: 40–150 dyne · s/cm^5	
PVRI: 120–200 dyne · s/cm^5	

PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SV, stroke volume; SVI, stroke volume index; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index.

TABLE 49.9	Hemodynamic Profile in Common Critical Conditions				
CONDITION	**CVP**	**PAOP**	**CO**	**PVR**	**SVR**
Right heart failure	↑		↓	↑	
Left heart failure		↑	↓		↑
Pericardial tamponade	↑	↑	↓		↑
Hypovolemia	↓	↓	↓		↑
Cardiogenic shock	↑	↑	↓		↑
Distributive shock	↓	↓	↑		↓

CO, cardiac output; CVP, central venous pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

CONTROVERSIES ON THE MODERN USE OF THE PAC

PA catheterization is no longer routinely performed, perhaps due to a combination of overuse by inexperienced operators and lack of validity in various studies. Although it is an invasive and expensive technique, it remains a useful bedside tool in the management of select patients such as those with acute respiratory distress syndrome (ARDS) and sepsis, pulmonary hypertension, cardiogenic shock, or patients who have more than one condition.

Early studies showed that the PAC predicted hemodynamic profiles correctly in only 53% of critically ill patients; however in a subgroup analysis, PAC reduced mortality in patients with shock compared to those managed without a PAC.[15] Later studies showed that the PAC does not change clinical outcomes and that physicians had a poor understanding of how to interpret the hemodynamic data.[16] Gore et al[17] showed in a retrospective review of 3263 patients that patients managed with a PAC had a higher case fatality rate. An accompanying editorial called for a moratorium on the PAC.[18]

Additional studies in the 1990s, including the SUPPORT trial, showed that in critically ill patients, the PAC was associated with increased cost, length of stay, and mortality.[19] In patients with congestive heart failure, it was shown that management with a PAC increased anticipated adverse events and, in fact, did not affect overall mortality or hospitalization.[20] A large metaanalysis of 14 trials by Shah et al. further validated that the PAC neither decreased mortality nor hospital stay.[21] The PAC-Man study evaluated the effects of PAC-driven therapy in 65 British intensive care units (ICUs) and concluded that the PAC conferred neither benefit nor harm when used to manage critically ill patients.[22] The “nail in the coffin” was evidence from the U.S. National Institutes of Health sponsored FACTT trial, which showed that in patients with acute lung injury (ALI), PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy. These results, when considered with those of previous studies, suggested that the PAC should not be routinely used for the management of ALI.[23]

Overall, there has been a downward nationwide trend in the use of the PACs up to 65% between 1993 and 2004, most notably after acute myocardial infarction.[24] Nevertheless, PACs continue to be used in CCUs and cardiothoracic ICUs internationally, so one must still maintain a good understanding of its functionality. Although they are no longer used on a routine basis, they certainly provide valuable hemodynamic information in postoperative cardiac patients and in certain CCU patients who need close hemodynamic monitoring. One of the arguments in favor of ongoing management with PAC is that prior trials included broad populations of cardiac patients in shock states and acute respiratory failure and may not have identified the exact population who may benefit from PAC monitoring. Along with its overuse in the 1990s and a lack of proper understanding of the hemodynamic data, these factors likely contributed to the fallout of the PAC.

ESOPHAGEAL DOPPLER

Esophageal Doppler monitoring involves placement of a probe in the esophagus of the patient and measuring blood flow velocity in the descending aorta. By measuring aortic blood flow (ABF), esophageal Doppler monitoring allow a reliable estimation of CO.[25] This can be done with transesophageal echocardiography or with a commercially available device that can track changes in SV and CO after a volume challenge or vasoactive agents. Probes are inserted orally to a depth of 35 to 40 cm from the incisors or nasally to 40 to 45 cm. The probe is manipulated till the distinct descending aorta waveform shape is visualized. From the aortic Doppler waveform that is obtained, valuable information such as preload and SV can be obtained.

Application of esophageal Doppler may be used intraoperatively in the recovery room or the CCU. Generally speaking, a change in ABF of 10% or higher is considered to indicate that the patient is fluid responsive. An actual fluid challenge or a PLR can be performed to see if the SV increases and this can guide further fluid management.[26] In a study of mechanically ventilated patients in normal sinus rhythm, Monnet et al[27] showed that a respiratory variation in ABF before volume expansion of at least 18% predicted fluid responsiveness with a sensitivity of 90% and a specificity of 94%. Intraoperative esophageal Doppler-guided fluid management has been shown to improve postoperative outcomes, including length of stay, after abdominal surgery and orthopedic procedures.[28,29] Precise, goal-directed fluid management in the operating room has now become standard of care and a prerequisite by many insurance companies in the United States.

PULSE PRESSURE VARIATION AND STROKE VOLUME VARIATION

The principles underlying pulse pressure variation (PPV) and stroke volume variation (SVV) are based on simple physiology that intermittent positive pressure ventilation induces cyclic changes in the loading conditions of the left and right ventricles. Mechanical insufflation increases intrathoracic pressure, decreases preload, and increases afterload of the right ventricle. The inspiratory reduction in RV ejection fraction leads to a decrease in LV filling after a phase

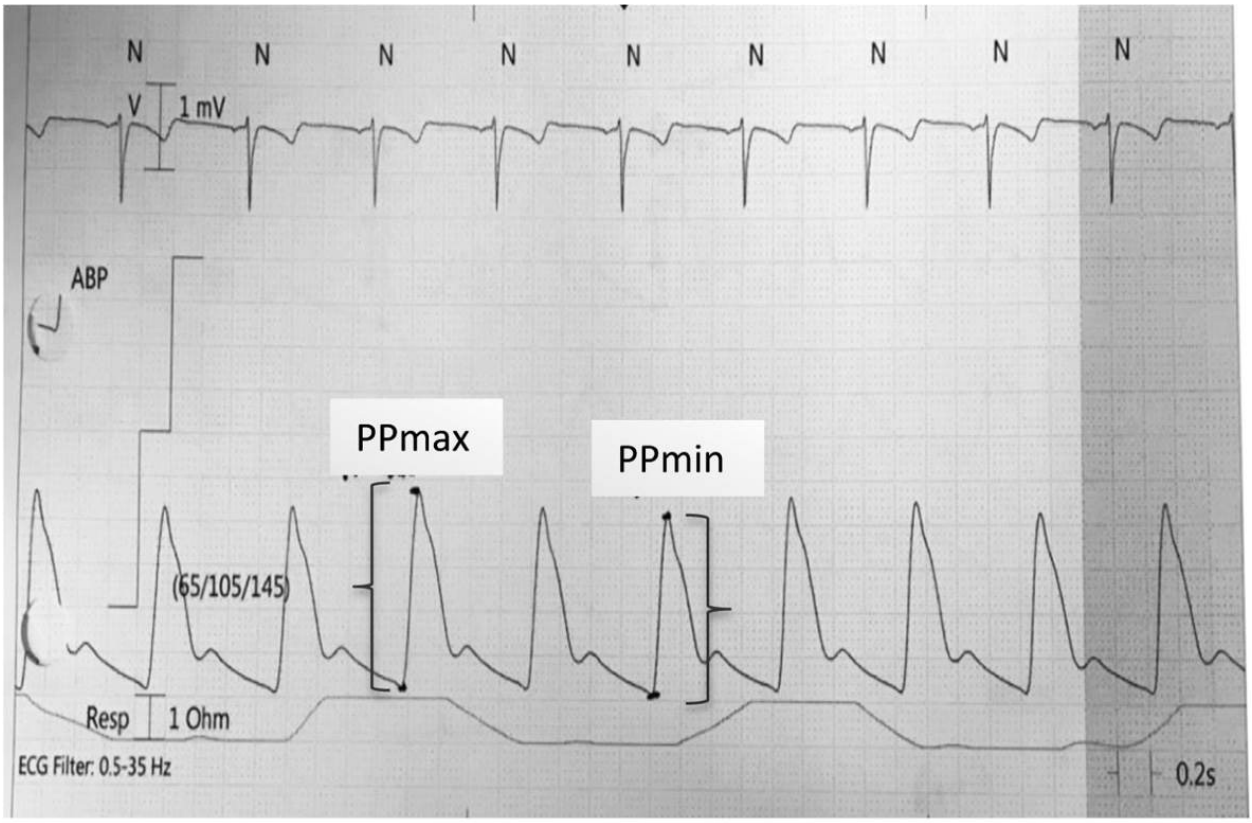
lag of two or three heart beats because of the long pulmonary transit time. Thus, the LV preload reduction may induce a decrease in LV stroke volume, which is at its minimum during the expiratory period. Therefore, the magnitude of the respiratory changes in LV stroke volume is an indicator of biventricular preload dependence

It should be appreciated that both arrhythmias, low tidal volumes (<8 mL/kg ideal body weight [IBW]), and spontaneous breathing activity, even on mechanical ventilation, will lead to misinterpretations of the respiratory variations in PPV and SVV.[26] Hence, when measuring PPV or SVV, the patient should be passive on the ventilator, on ≥ 8 mL/kg IBW tidal volume, and in normal sinus rhythm.

$$PPV\% = \frac{PPmax - PPmin}{PPavg} \times 100$$

Figure 49.9 shows PPV measurement.

Seminal studies by Michard and others have found that a PPV of > 12%, in the appropriate patient, predicts fluid responsiveness with a sensitivity of 94% and specificity of 96%.[30,31] Based on this data, the patient in **Figure 49.9** would be fluid responsive. Goal-directed fluid management in the operating room (OR), with minimizing of PPV, has been shown to improve postoperative outcomes and decrease length of stay in high-risk surgical patients.[32]



$$\text{PPV \%} = \frac{\text{PPmax} - \text{PPmin}}{\text{Mean of the 2 PP}} \times 100$$

FIGURE 49.9 Pulse pressure variation. PPV, pulse pressure variation.

NEWER HEMODYNAMIC MONITORING DEVICES

Various commercially available devices utilize the concepts described above in providing hemodynamic data.

FLOTRAC/VIGELEO

The FloTrac device (Edwards Lifesciences, Irvine, CA) is a CO monitor that uses pulse contour analysis to provide hemodynamic data. It requires a specialized sensor with a proprietary transducer attached to a radial or femoral arterial catheter. It analyzes the shape of the arterial pressure readings and calculates CO and other derived parameters such as SV, SVV, SVR, and CI. It updates key flow-based parameters such as CO, SV, and SVV every 20 seconds.

Although the variables themselves are not always exact, when compared to the PAC, variability and trends are helpful in the management of critically ill patients. Additionally, the autocalibration feature is advantageous and make it user-friendly for all CCU staff.

PICCO TECHNOLOGY

PiCCO (Maquet, Rastatt, Germany) is a CO monitor that combines pulse contour analysis and transpulmonary thermodilution technique. The pulse contour analysis provides continuous information while transpulmonary thermodilution provides static measurements. It requires a central venous line as well as the PiCCO arterial catheter, which has a thermistor on the end. For the transpulmonary thermodilution measurement, a defined bolus (eg, 10 mL cold 0.9% normal saline) is injected via a CVC. The cold bolus passes through the right heart, the lungs, and the left heart and is detected by the PiCCO catheter, commonly placed in the femoral artery. Using intermittent thermodilution and arterial pulse contour analysis, along with proprietary algorithms, various parameters such as CO, PPV, SVV, extravascular lung water, and global end diastolic volume can be obtained.

LITHIUM DILUTION CARDIAC OUTPUT (LIDCO)

LiDCO (LiDCO, London, UK) is another noninvasive method of CO measurement that utilizes thermodilution. A small dose of intravenous lithium is injected through a peripheral or central venous line, and subsequently the lithium concentration is measured by a lithium ion-sensitive electrode placed in a peripheral arterial line. A concentration–time curve is thus created, and from that curve, CO is calculated. This measurement is then used to calibrate the pulse contour analysis software. This initial calibration enables continuous subsequent CO measurement by analyzing the arterial pressure waveform. The LiDCOplus system also calculates the PPV and SVV during the respiratory cycle but uses different processing software from that used in PiCCO. This system has the advantage of not requiring a CVC but does require intermittent thermodilution.

These less-invasive hemodynamic devices have become more popular over the past decade. Data from a pooled analysis show that SVVs from these devices have a sensitivity of 82% and specificity of 86%.[31] These devices may also be useful in determining the hemodynamic response to a PLR. In this regard, an increase in CO by more than 10% in response to a PLR has been shown to

accurately predict volume responsiveness in mechanically ventilated patients with spontaneous breathing activity.[33]

CONCLUSION

Invasive hemodynamic monitoring is essential to the care of the critically ill patient. Clinicians should be aware of the various modalities available and their respective advantages and pitfalls. CVP has become controversial in fluid management. Although the PAC provides extremely useful information about the hemodynamic status of the patient, its role has diminished because studies show it does not change clinical outcomes. Heart–lung interactions can be utilized to look for dynamic changes in pulse pressure and stroke volume. No measurement should be used in isolation to make clinical decisions with regard to fluid management. Proper measurement and interpretation of the data is the key to ensuring adequate oxygen delivery and tissue perfusion, which is the goal of successful hemodynamic monitoring.

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Patient and Family Information for: Invasive Hemodynamic Assessment in the CCU

WHAT IS HEMODYNAMIC MONITORING?

Invasive hemodynamic monitoring allows doctors and nurses to closely monitor the patient's clinical status. Using catheters that are placed into veins and arteries, measurements can be made of the patient's blood pressure and the pressures within the chambers of the heart. These measurements can be used to guide the clinical team to determine fluid and medical therapy.

WHAT IS THE PREPARATION?

The clinical team will explain the type of invasive hemodynamic monitoring that is being planned, including its purpose, risks, and benefits. Most procedures in the cardiac care unit (CCU) that are performed for hemodynamic monitoring are done at the bedside. Occasionally, invasive procedures will be performed in the cardiac catheterization lab. Be sure to wear your hospital gown, as parts of your body may be uncovered to facilitate the exam. You may be asked to position yourself a certain way and lay still for the procedure. Local anesthesia or numbing medication will be administered to prevent pain. Sometimes, an intravenous antianxiety medication may be given to help facilitate the procedure.

HOW LONG DOES IT TAKE?

It can take anywhere from 15 to 30 minutes to insert catheters for invasive hemodynamic monitoring. Once the catheter is in place, it may be left in place for anywhere from 1-2 days to the entire stay in the CCU. The catheter will be removed as soon as it is no longer necessary.

WHAT IS THE PROCESS?

Measurements from invasive hemodynamic monitors will be displayed on the patient monitor in the room and also at the nursing station. These measurements will help your clinical team to guide your medical management.

WHAT ARE THE RISKS AND COMPLICATIONS?

Your clinical team will weigh the risks and benefits before proceeding with catheters for invasive hemodynamic monitoring. The main risks of any catheter placement are bleeding, infection, clotting of the catheter or vessel, and damage to the blood vessel or nearby structures. There may be risks of abnormal heart rhythms when the catheter is being placed and also risk of air entering the circulation. Your clinical team will take appropriate precautions to ensure that it is a safe procedure.

WHAT ARE SOME TYPES OF INVASIVE HEMODYNAMIC MONITORING?

1. CENTRAL VENOUS PRESSURE (CVP) MONITORING

A central venous catheter (CVC) or a central line is a sterile, flexible, small hollow tube inserted into the internal jugular vein in the neck or the subclavian vein in the upper chest. The tip of catheter rests within a vein connected to the heart called the superior vena cava. When this catheter is connected to additional tubing from the patient monitor, the CVP can be measured.

Normal CVP is between 8 to 12 cmH2O. A very low CVP can indicate that you may need additional intravenous (IV) fluids, and a very high CVP can mean that you do not need any additional IV fluids. Keep in mind that CVP monitoring has come under controversy recently, and hence your clinical team will interpret

the numbers in conjunction to their clinical exam and other available data to help guide your treatment.

2. ARTERIAL BLOOD PRESSURE (ABP) MONITORING

An arterial line (or A-line) is a small, sterile tube that is inserted into an artery, commonly either in the wrist (radial artery) or groin (femoral artery). When this catheter is connected to additional tubing from the patient monitor, it can obtain beat-to-beat measurements of the arterial blood pressure. These measurements are much more accurate that the regular blood pressure (BP) that is obtained from a standard BP cuff. These accurate measurements will help guide your doctors and nurses in adjusting your medications. In addition, A-lines can be used for obtaining frequent blood samples to assess the degree of acidity and levels of oxygen and carbon dioxide in the blood.

3. PULMONARY ARTERY CATHETERIZATION OR SWAN-GANZ CATHETERIZATION

A pulmonary artery catheter (PAC) is a thin tube or catheter that is placed into the right side of the heart and the artery leading to the lungs (pulmonary artery). An experienced physician, physician assistant, or nurse practitioner typically performs the procedure with local anesthesia and under sterile conditions. The catheter is generally inserted into one of three veins: the right internal jugular (RIJ) vein, located in the neck, which is the shortest, most direct path to the heart; the left subclavian vein, located under the clavicle or collar bone; or the femoral veins in the groin. During the procedure, your heartbeat and electrocardiogram will be closely monitored. A PAC measures how well the heart is functioning and monitors pressures within the heart and lungs. It is routinely used during heart surgery or when large amounts of certain heart support medications are needed. Occasionally, the catheter may damage the pulmonary artery or lung. It can also cause irregularity of the heart rhythm usually during insertion. Chest X-rays are routinely done to check for any complications.

The PAC travels through the right side of the heart and the tip rests in the pulmonary artery. Using the PAC, pressures can be obtained from the right-sided chambers of the heart and the pulmonary arteries. There is a balloon at the tip of the PAC, which can be inflated to obtain the pulmonary artery occlusion pressure (PAOP). This provides an estimate of the pressures in the left side of the heart.

These measurements can help guide your clinical team to make crucial decisions about your treatment. That said, the usefulness of the PAC has also come under controversy recently, and in light of the invasive nature of the procedure, this is no longer a routine procedure done in the CCU.

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Yuvrajsinh J. Parmar
Itzhak Kronzon

Noninvasive Hemodynamic Assessment in the CCU

Hemodynamic assessment using Doppler echocardiography in the evaluation of transvalvular gradients, valvular regurgitation, and certain clinically important variables such as pulmonary artery (PA) pressures is common among echocardiographers. In comparison, the use of echocardiography in measuring intracardiac pressures as it is done during cardiac catheterization is an underutilized tool. These measurements done by echocardiography can aid in the assessment and management of patients in the intensive care unit. This chapter focuses on the practical aspects of such an examination with the demonstration of a comprehensive hemodynamic evaluation in a patient. The information in this chapter is based on known and accepted hemodynamic and Doppler echocardiographic techniques. More data and references can be found in larger, more detailed textbooks.[1]

The simplified Bernoulli equation is the basis for the calculation of most intracardiac pressures.[2]

$$\Delta \boldsymbol{P} = 4\boldsymbol{V}^2$$

where $\Delta \boldsymbol{P}$ = pressure gradient in mm Hg and $\boldsymbol{V}$ = velocity in m/s.

EVALUATION OF RIGHT ATRIAL PRESSURE

The evaluation of the inferior vena cava provides information regarding right atrial pressures (RAPs). With the transducer in the subxiphoid position, the inferior vena cava can be evaluated as it travels through the liver into the right atrium. During its course, the inferior vena cava becomes perpendicular to the ultrasound interrogation beam, allowing for its size and changes in its diameter during the respiratory cycle to be recorded by M-mode echocardiography. The normal diameter of the inferior vena cava in adults is 1.5 to 2.5 cm measured just proximal to its entrance into the right atrium. Normally, with inspiration, there is a decrease of 50% or more in its diameter. Failure to collapse with respiration and a dilated inferior vena cava suggests elevated RAPs.[3,4] **Table 50.1** correlates inferior vena cava characteristics (diameter and respiratory changes) and RAP. **Figure 50.1** shows a two-dimensional image and M-mode echocardiogram of a patient with a markedly elevated RAP.

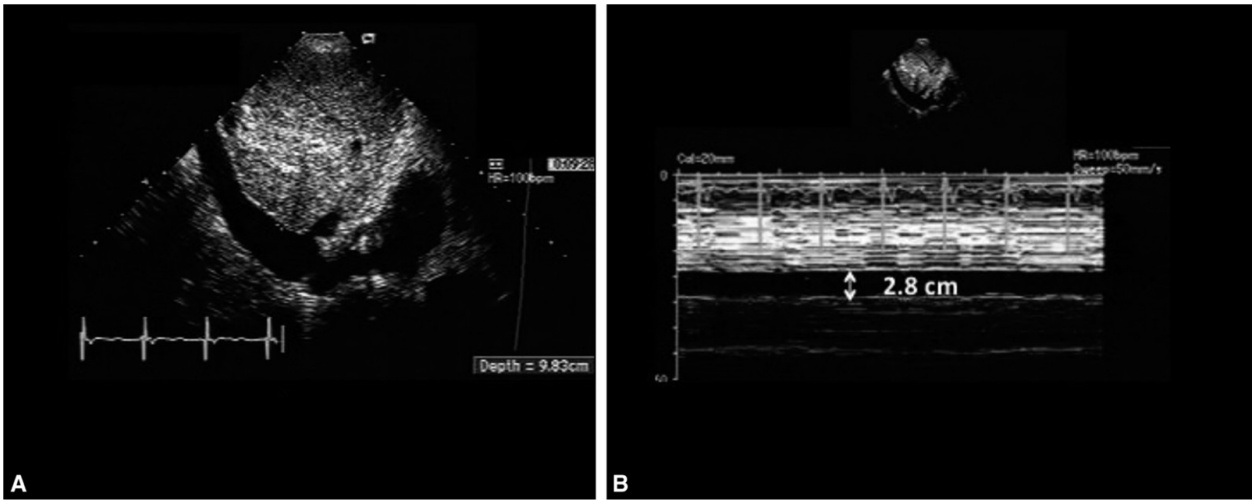

FIGURE 50.1 Assessment of right atrial pressure (RAP). A, The inferior vena cava (IVC) is markedly dilated at its entrance to the right atrium (2.8 cm). B, The M-mode recorded demonstrates lack of respiratory variations in diameter. RAP is estimated to be 15 to 20 mm Hg

TABLE 50.1 IVC Size and Respiratory Variation in the Evaluation of RA Pressure[3]

IVC (cm)	Δ WITH RESPIRATION (%)	RA PRESSURE (MM HG)
≤2.1	>50	0–5

≤2.1	<50	5–10
≥2.1	>50	10–15
≥2.1	<50	15–20

IVC, inferior vena cava; RA, right atrial.

EVALUATION OF RIGHT VENTRICULAR SYSTOLIC PRESSURE

Echocardiographic measurement of right ventricular systolic pressure (RVSP) is related to the velocity of flow across the tricuspid valve during systole. **Figure 50.2** shows the superimposed pressure curves of the right atrium and right ventricular and PA pressure. Under normal circumstances, there is a negligible gradient across the tricuspid valve during diastole and a negligible gradient across the pulmonic valve during systole. These gradients are so small that their measurement is beyond the sensitivity of cardiac catheterization. During systole, with the tricuspid valve closed, there is a pressure gradient between the right ventricle and the right atrium. Approximately 90% of normal adults have some degree (usually trace or mild) of tricuspid regurgitation. The velocity of the tricuspid regurgitant (TR) jet, as measured by continuous wave Doppler, is related to the pressure gradient between the right ventricle and right atrium. Using the simplified Bernoulli equation, the tricuspid regurgitation gradient can be calculated. The RVSP equals the TR gradient plus the RAP.

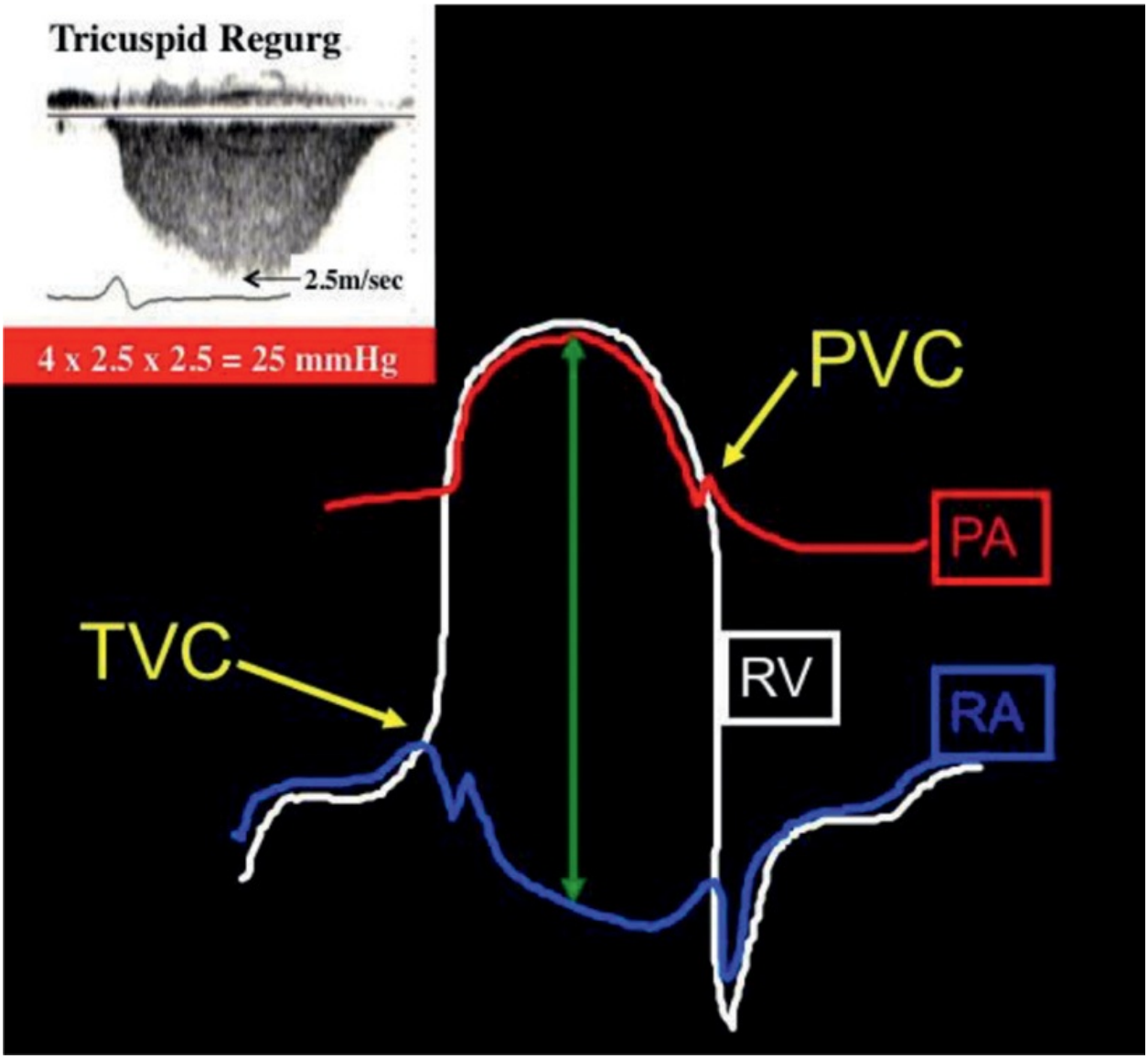

FIGURE 50.2 Assessment of RV systolic pressure (see text). The diagram shows normal right-sided pressures with no significant systolic gradient across the pulmonic valve and no significant diastolic gradient across the tricuspid valve. The gradient across the tricuspid valve in systole (green arrow) is responsible for the tricuspid regurgitation velocity seen in the upper left corner. With a peak regurgitant velocity of 2.5 m/s, the gradient between the right ventricle and right atrium is 25 mm Hg. PA, pulmonary artery pressure; PVC, pulmonic valve closure; RA, right atrial pressure; RV, right ventricular; TVC, tricuspid valve closure.

$$\text{RVSP} = \text{TR gradient} + \text{RAP}$$

Calculating RVSPs in patients who have a ventricular septal defect (VSD) with a left-to-right shunt requires measuring the gradient across the right and left ventricles. This gradient is related to the defect jet velocity between the ventricles. In the absence of aortic stenosis, the systolic pressure in the left

ventricle equals the systolic blood pressure (SBP) measured by a blood pressure cuff. Thus, the RVSP equals SBP minus the systolic ventricular septal defect (SVSD) gradient.

$$\text{RVSP} = \text{SBP} - \text{SVSD gradient}$$

The lower the SBP and the higher the RVSP, the smaller the interventricular gradient. VSDs that are associated with lower blood pressure and with high RVSP (as may be the case in VSD during acute myocardial infarction) will have a lower VSD systolic flow velocity and lower systolic VSD gradient. **Figure 50.3** shows an example of calculating RVSP in a patient after a myocardial infarction that developed a VSD with a left-to-right shunt.

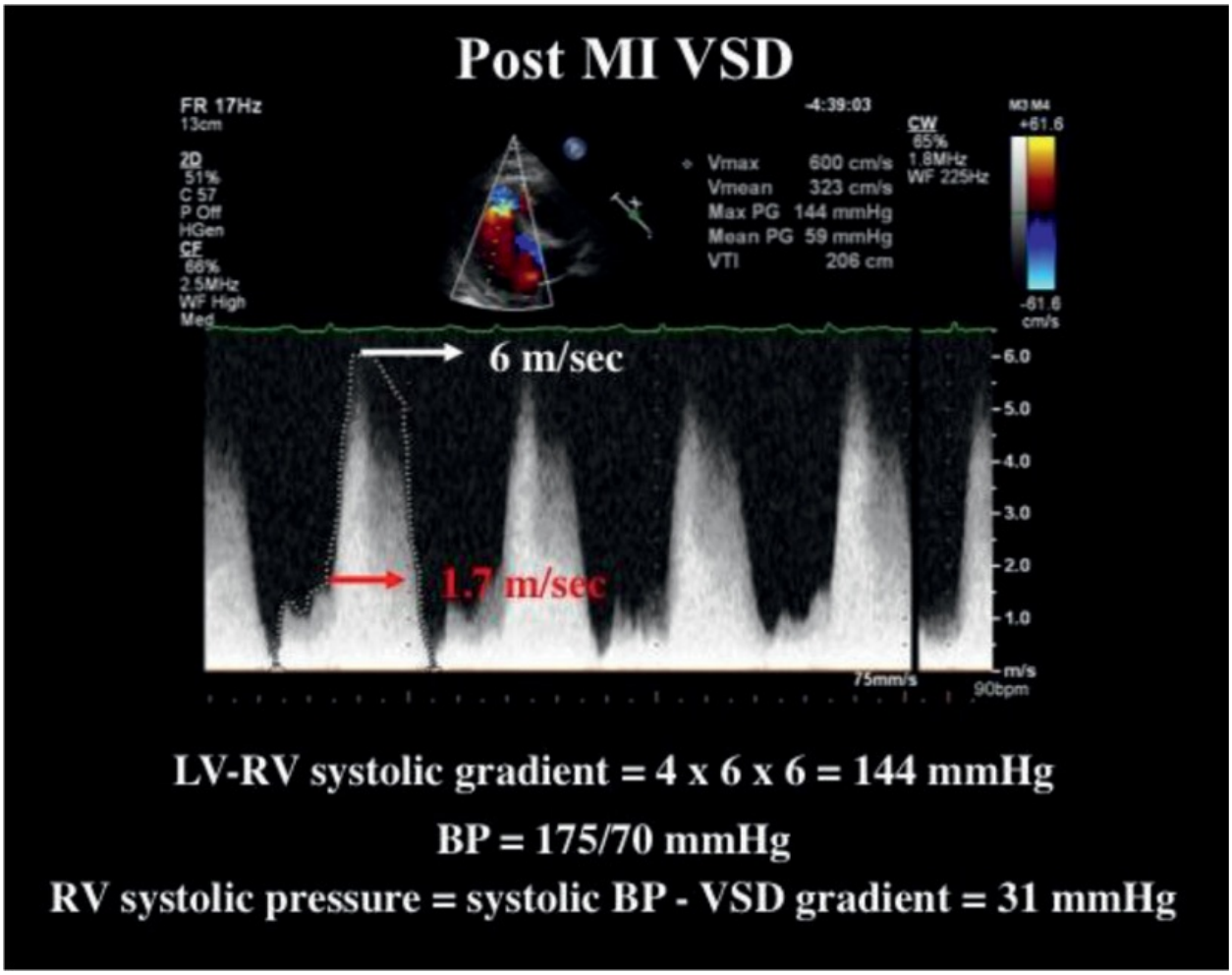

FIGURE 50.3 Assessment of right ventricular systolic pressure in a patient with a ventricular septal defect after myocardial infarction. Note that there is flow in both systole (white arrow) and diastole (red arrow). BP, blood pressure; LV, left ventricle; MI, myocardial infarction; RV, right ventricle; VSD, ventricular septal defect.

EVALUATION OF RIGHT VENTRICULAR DIASTOLIC PRESSURE

In the absence of tricuspid stenosis, there is a negligible gradient between the right atrial diastolic pressure and the right ventricular diastolic pressure (RVDP), and this gradient can therefore be ignored. As a result, it can be said that RVDP equals RAP.

$$RVDP = RAP$$

In the presence of VSDs with left-to-right shunt, the left ventricular diastolic pressure (LVDP) is usually higher than the RVDP. Therefore, there is flow between the left ventricle and right ventricle that continues throughout diastole. However, this velocity is significantly smaller when compared to the velocity of the jet across the VSD during systole (**Figure 50.3**). If the LVDP is known, then the RVDP can be calculated as the LVDP minus the diastolic ventricular septal defect (DVSD) gradient.

$$RVDP = LVDP - DVSD\ gradient$$

EVALUATION OF PULMONARY ARTERY SYSTOLIC PRESSURE

In the absence of pulmonic stenosis (PS), the pressure gradient between the right ventricle and the PA is negligible and can be ignored. It can be assumed that the pulmonary artery systolic pressure (PASP) equals the RVSP. Therefore, the PASP equals the tricuspid regurgitation (TR) gradient plus the RAP.

$$PASP = TR\ gradient + RAP$$

However, in the presence of PS, the gradient across the pulmonic valve must be accounted for. The flow velocity across the stenotic pulmonic valve can be evaluated and the PS gradient can be calculated. In these patients, the PASP equals the RVSP minus the PS gradient.

$$PASP = RVSP - PS\ gradient$$

EVALUATION OF PULMONARY ARTERY DIASTOLIC PRESSURE

The majority of patients normally have some degree (trace to mild) of pulmonic regurgitation (PR). The velocity of the PR is defined by the diastolic pressure gradient between the PA and the right ventricle. Thus, the pulmonary artery diastolic pressure (PADP) equals the pulmonary regurgitation gradient plus the RVDP.

$$\text{PADP} = \text{PR gradient} + \text{RVDP}$$

Because the RAP (in the absence of tricuspid stenosis) is approximately equal to the RVDP, this equation can be simplified to the PADP equaling the PR gradient plus RAP.

$$\text{PADP} = \text{PR gradient} + \text{RAP}$$

The ability to measure the PR velocity may be helpful in the evaluation of the PA pressure in patients who do not have tricuspid regurgitation. **Figure 50.4** shows a continuous wave Doppler tracing of pulmonic valve flow in a patient evaluated for significant pulmonary hypertension (HTN) who did not have tricuspid regurgitation. The end-diastolic velocity of the pulmonic regurgitant flow is 2.5 m/s, which indicates an end-diastolic gradient of 25 mm Hg across the pulmonic valve. Therefore, the diastolic pulmonary artery pressure is at least 25 mm Hg, a markedly elevated value.

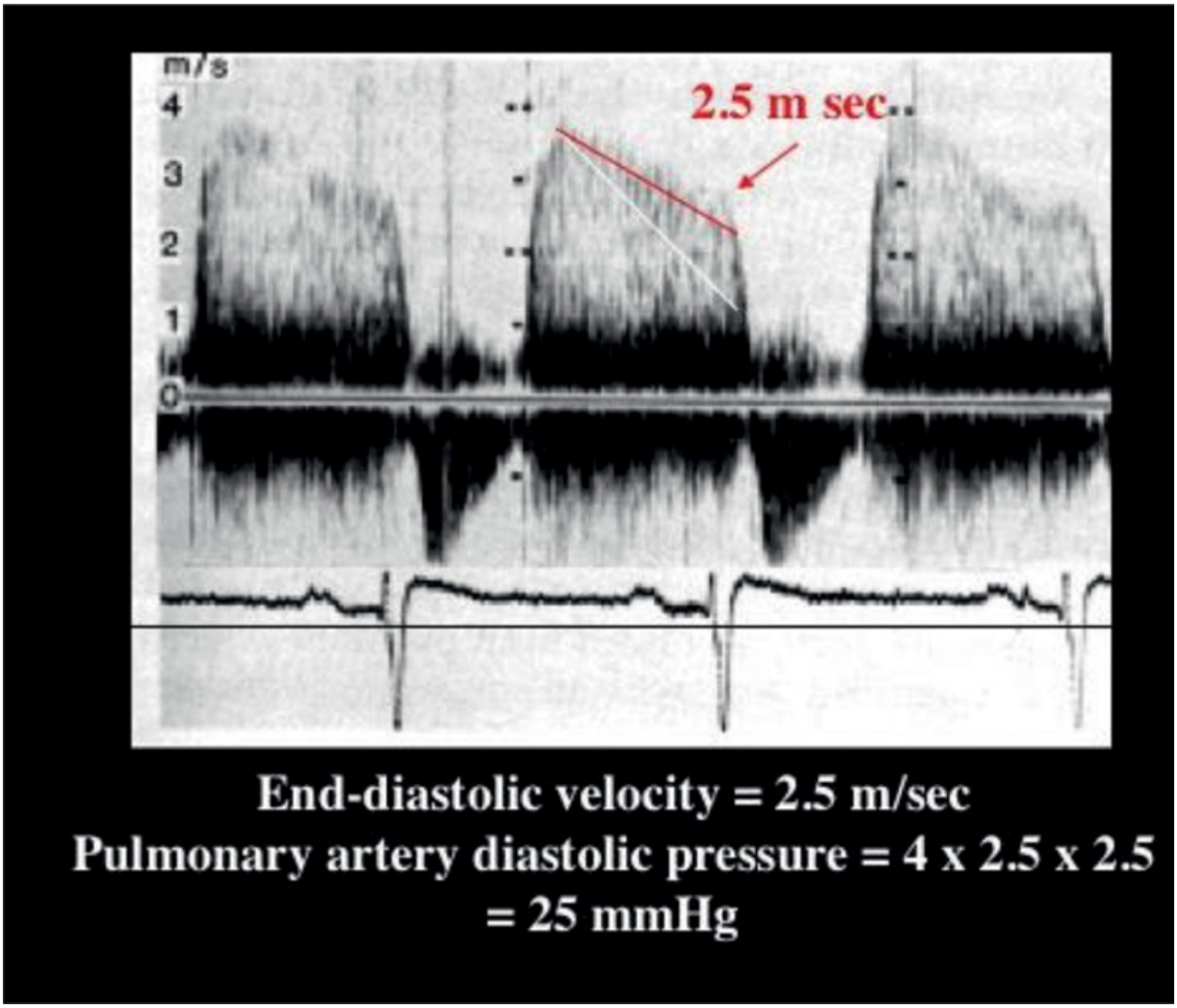

FIGURE 50.4 Assessment of pulmonary artery diastolic pressure in a patient with pulmonary hypertension. The continuous wave Doppler of the pulmonic valve shows an end-diastolic velocity of 2.5 m/s. This indicates an end-diastolic gradient of 25 mm Hg between the pulmonary artery and the right ventricle.

An estimation of PA pressures in the absence of tricuspid regurgitation or PR can be obtained with M-mode echocardiography and pulse wave Doppler. The characteristic M-mode pattern of the pulmonic valve in patients with severe pulmonary HTN (>70 mm Hg) includes absence of “a” deflection during atrial contraction (in spite of normal sinus rhythm), “flying W” appearance of the systolic opening, and lack of backward motion of the diastolic closure line (**Figure 50.5**). A more accurate estimation of mean PA pressures can be obtained by measuring the systolic acceleration time of the antegrade flow velocity measured by pulse wave Doppler just proximal to the pulmonic valve. The acceleration time is inversely proportional to the mean PA pressure.[5] The

equation used for this estimation is

$$PAMP = 79 - (0.45 \times AcT)$$

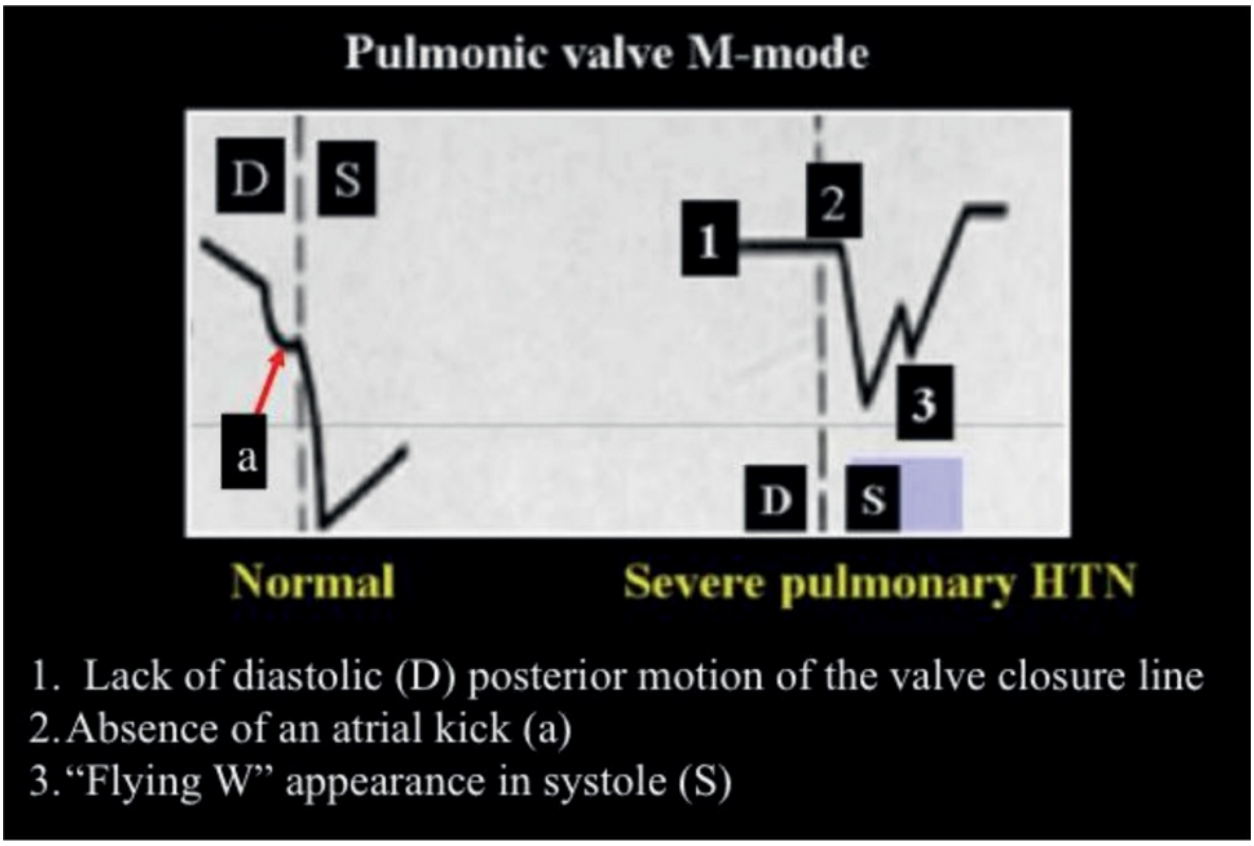

FIGURE 50.5 Comparison M-mode echocardiography of the pulmonic valve in individuals with and without severe pulmonary hypertension (HTN).

where PAMP is mean PA pressure in mm Hg and AcT is acceleration time in milliseconds.

A normal acceleration time is greater than 120 ms. Values less than 90 ms are associated with a PA mean pressure of 40 mm Hg or more.

EVALUATION OF LEFT VENTRICULAR SYSTOLIC PRESSURE

In patients without aortic valve or left ventricular outflow disease, the gradient between the left ventricle and the aorta during systole is negligible. Therefore, left ventricular systolic pressure (LVSP) is equal to the SBP.

$$LVSP = SBP$$

However, patients with aortic valve, subvalvular, or supravalvular stenosis have a gradient between the left ventricle and the ascending aorta. Because the systolic ascending aortic pressure equals the SBP, the LVSP equals the SBP plus the systolic pressure gradient across the aortic valve (or other subvalvular or supravalvular sites).

$$LVSP = SBP + \text{aortic stenosis gradient}$$

Gradients across the aortic valve can be measured using the Doppler examination. The maximal gradient that is recorded is the maximum instantaneous gradient (MIG), which differs from the peak-to-peak (P2P) gradient which is the gradient between peak aortic systolic pressure and peak LVSP. The P2P gradient is frequently measured and reported during cardiac catheterization. The value of the MIG is typically higher than that of the P2P gradient. In most cases of severe aortic stenosis, the P2P gradient is approximately 70% of the MIG. Both Doppler echocardiography and pressure measurement during invasive procedures are able to calculate a mean pressure gradient across the aortic valve (**Figure 50.6**). When using Doppler for the calculation of left ventricular pressure, the P2P gradient is estimated by taking 70% of the MIG and adding it to the SBP. Therefore,

$$LVSP = SBP + 70\% \text{ MIG}$$

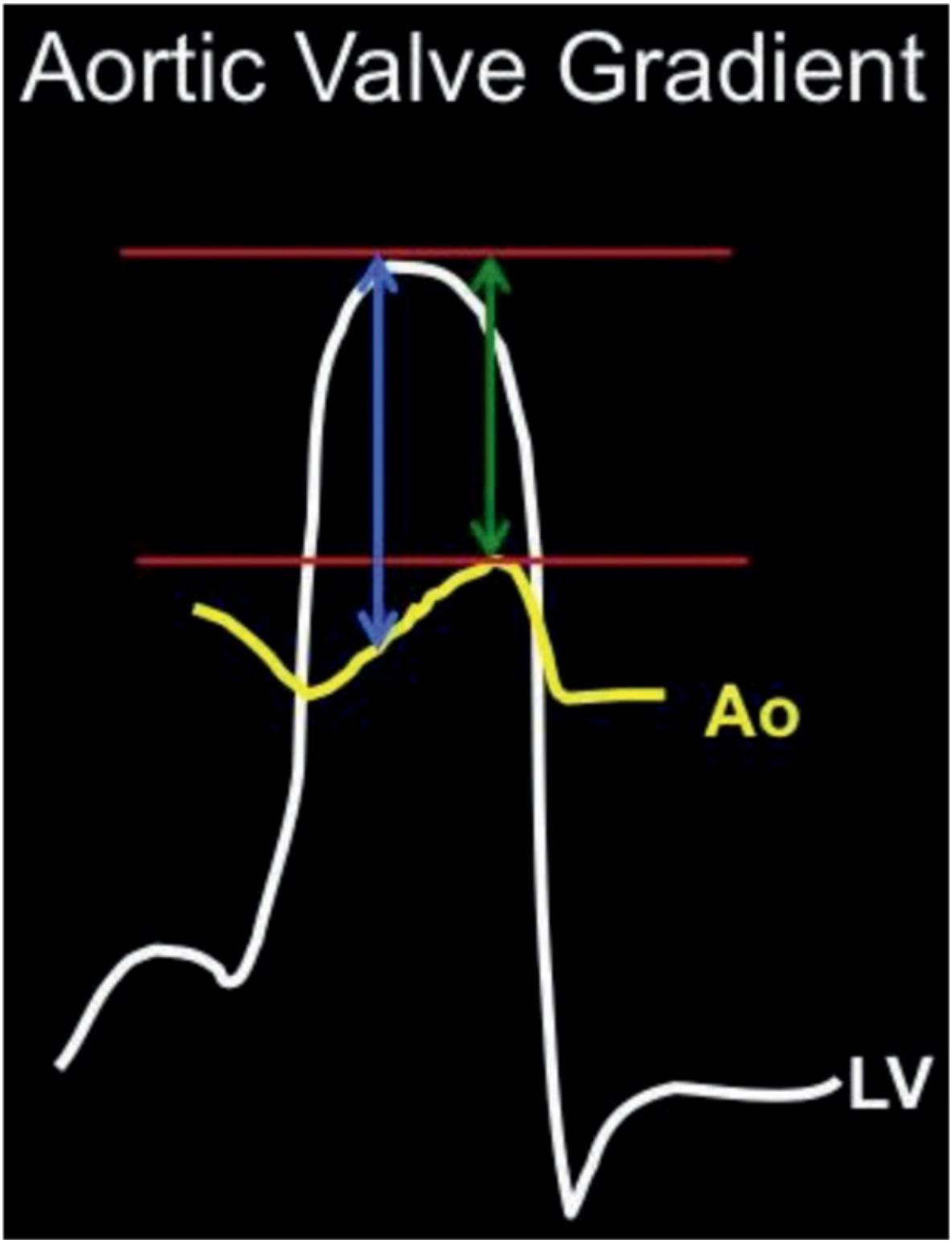

FIGURE 50.6 Left-sided pressure curves in aortic stenosis demonstrating maximum instantaneous gradient (blue arrow) and the peak-to-peak gradient (green arrow). Ao, aorta; LV, left ventricle.

EVALUATION OF LEFT VENTRICULAR DIASTOLIC PRESSURE

In the absence of mitral stenosis, the gradient between the left atrium and the left ventricle during diastole is small and can be ignored. Therefore, the left atrial pressure (LAP) is similar to the LVDP. The LAP can be estimated and will approximate left ventricular end-diastolic pressure (LVEDP).

$$\text{LVEDP} = \text{LAP}$$

In patients who have aortic regurgitation (AR), the regurgitant jet velocity is a function of the diastolic gradient between the aorta and the left ventricle. If the aortic diastolic pressure is known, then the LVEDP equals the diastolic blood pressure (DBP) minus the AR gradient at end diastole. In most patients, the aortic pressure equals the cuff pressure in the arm.

$$\text{LVEDP} = \text{DBP} - \text{end-diastolic AR gradient}$$

In patients with VSD with a left-to-right shunt, the LVEDP can be calculated if the RAP, which estimates RVDP (in the absence of tricuspid stenosis), is known. In these patients, the addition of the RAP and the VSD end-diastolic gradient equals the LVEDP.

$$\text{LVEDP} = \text{RAP} + \text{VSD end-diastolic gradient}$$

Figure 50.7 demonstrates a continuous wave Doppler tracing taken from a patient with both aortic stenosis and AR. The aortic stenosis peak velocity jet is 4 m/s and AR end-diastolic velocity is also 4 m/s. The blood pressure during the examination was 150/80 mm Hg. Therefore, the LVSP equals the SBP (150 mm Hg) plus 70% of the aortic systolic gradient. Because the maximum instantaneous aortic gradient is 64 mm Hg, the P2P gradient is 70% of 64 mm Hg, which is 45 mm Hg. The LVSP is therefore 150 + 45 = 195 mm Hg. The LVDP equals the DBP (80 mm Hg) minus the aortic diastolic gradient (64 mm Hg), which equals 16 mm Hg. Therefore, this patient’s left ventricular pressure is 195/16 mm Hg.

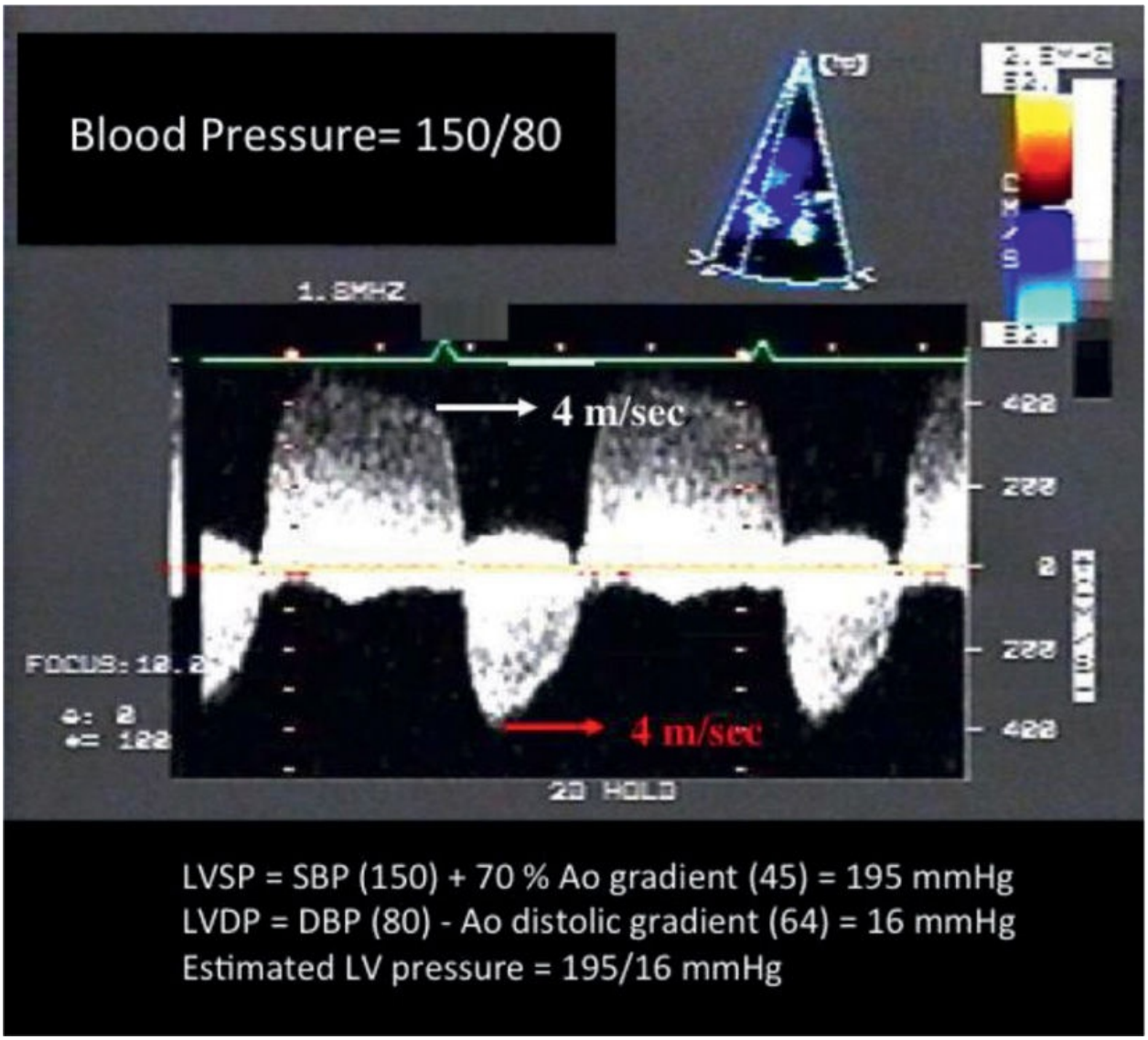

FIGURE 50.7 Continuous wave (CV) Doppler in the calculation of LV pressures in a patient with aortic stenosis and insufficiency (see text). Aortic stenosis peak velocity (red arrow) and aortic regurgitation end-diastolic velocity (white arrow) both measure to be 4 m/s. Ao, aorta; DBP, diastolic blood pressure; LV, left ventricular; LVDP, left ventricular diastolic pressure; LVSP, left ventricular systolic pressure; SBP, systolic blood pressure.

EVALUATION OF LEFT ATRIAL PRESSURE

Estimation of LAP by Doppler echocardiography can be performed in the absence of atrial fibrillation, ventricular pacing, left bundle branch block, left ventricular assist device, or mitral valve disease (mitral stenosis, moderate mitral annular calcification, more than moderate mitral regurgitation [MR], and mitral

valve repair or replacement). Pulsed Doppler of the transmitral and pulmonary venous flow, along with tissue Doppler of the lateral and septal mitral annulus allows for the estimation of LAP. Under normal flow patterns, the pressure in the left atrium is 6 to 12 mm Hg. Impaired relaxation results in a flow pattern with a low E-wave and high A-wave on pulse Doppler. This corresponds with a normal or minimally elevated LAP of 13 to 19 mm Hg. In pseudonormalization of transmitral flow, the LAP is elevated ranging from 20 to 24 mm Hg. Lastly, a restrictive pattern with a high E-wave, low A-wave, and rapid transmitral deceleration time (150 ms or less), the LAP is usually at least 25 mm Hg. A simpler alternative to calculating LAP uses the ratio of the transmitral flow ***E***-wave velocity and the tissue Doppler (***E′***). In general, as the LAP increases, ***E***-wave becomes higher and the ***E′*** becomes lower. An ***E/E′*** ratio of less than 9 is associated with normal LAPs, whereas a ratio of greater than 14 is highly specific for elevated LAPs (>14 mm Hg). An equation reported by Nagueh et al[6] describes the relation between LAP and ***E/E′***.

$$\text{LAP} = 1.24[(E/E') + 1.9]$$

A more simplified equation that may be used is

$$\text{LAP} = E/E' + 4 \text{ mm Hg}$$

PASPs can also be used to increase the accuracy of estimated LAP. **Table 50.2** provides estimations of LAP based on Doppler findings.[7] A more comprehensive analysis of diastolic dysfunction and estimation of LAP can be found by Nagueh et al.[8]

TABLE 50.2 Estimation of LAP Based on Doppler Findings

DOPPLER FINDING	MILD LAP ELEVATION (13–19 MM HG)	MODERATE LAP ELEVATION (20–24 MM HG)	SEVERE LAP ELEVATION (>25 MM HG)
E/A	0.8–1	1.2–1.5	>2
Deceleration time (ms)	N/A	N/A	<150
Average (*E*/*E*′)	9–12	13–18	>20
Estimated PASP (mm Hg)	35–40	45–55	>60

The predictive accuracy is enhanced with the presence of three to four of the above findings.[7]
LAP, left atrial pressure; PASP, pulmonary artery systolic pressure.

In patients with MR and without aortic stenosis, the LAP during ventricular systole (LAS) equals the SBP minus the MR gradient. In the absence of aortic stenosis, the LVSP equals the SBP.

$$\text{LAS} = \text{SBP} - \text{MR gradient}$$

In patients with mitral stenosis, the LAP during ventricular diastole (left anterior descending [LAD]) equals the LVEDP plus the mean transmitral gradient.

$$\text{LAD} = \text{LVEDP} + \text{transmitral gradient}$$

CALCULATION OF CARDIAC OUTPUT

Cardiac output (CO) can be calculated by measuring blood flow in either the left heart (systemic blood flow [SBF]) or right heart (pulmonary blood flow [PBF]). In the absence of shunts, the PBF is equal to the SBF. SBF is best calculated by evaluating the left ventricular outflow tract (LVOT). The cross-sectional area (CSA) of the LVOT can be calculated by measuring its diameter. The product of LVOT CSA and the velocity time integral (VTI) of the LVOT is the stroke volume (SV). Multiplying the SV with the heart rate (HR) provides the CO (**Figure 50.8**).

$$\text{SV} = \text{CSA}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}}$$

$$\text{CO} = \text{SV} \times \text{HR}$$

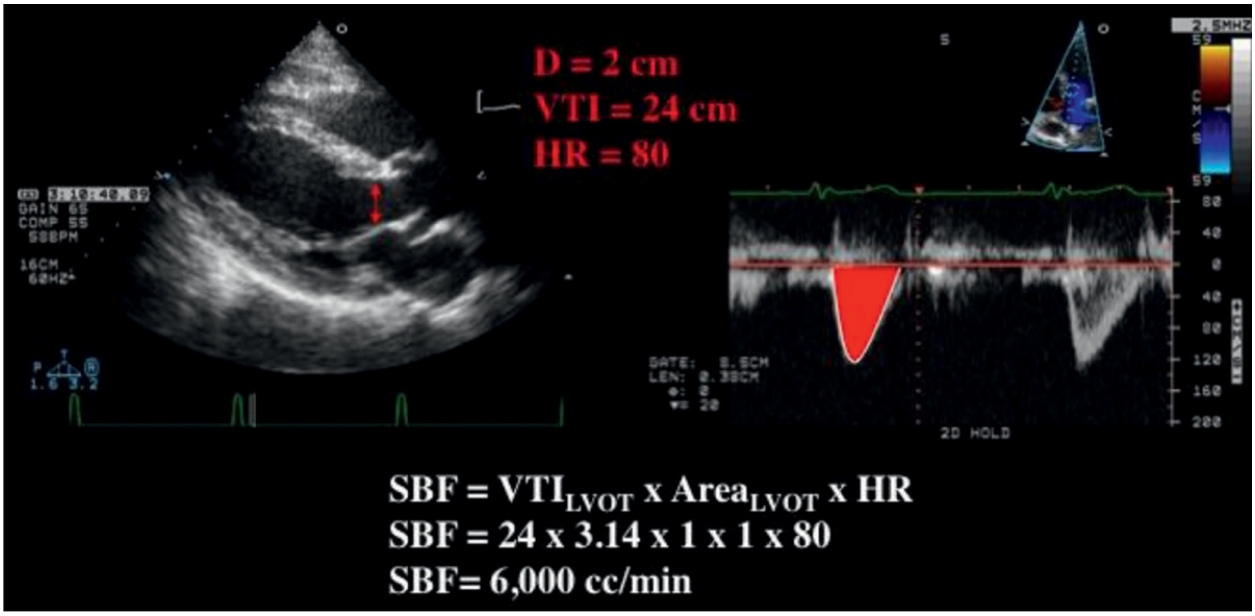

FIGURE 50.8 Calculation of systemic blood flow. The diameter (D) is measured at the LVOT in parasternal long axis view (left) and the VTI (right) is determined by pulse wave Doppler at the LVOT. HR, heart rate; LVOT, left ventricular outflow tract; SBF, systemic blood flow; VTI, velocity time integral.

Similarly, calculation of PBF can be done at the right ventricular outflow tract just proximal to the pulmonic valve.

CALCULATION OF SHUNT FLOW

The evaluation of shunt flow in patients with an atrial septal defect (ASD) or VSD with a left-to-right shunt can be performed by subtracting the SBF from the PBF.

$$\text{Shunt flow} = \text{PBF} - \text{SBF}$$

Alternatively, the product of the defect orifice area (DOA), the shunt VTI and HR equals the shunt flow across an ASD or VSD. **Figure 50.9** is an example of the calculation of ASD flow with a left-to-right shunt with an orifice area of 1.2 (radius of 0.6 cm), a VTI of 80 cm, and HR of 80 beats/minute. Using the equation given, the shunt flow is calculated.

$$\text{Shunt flow} = \text{DOA} \times \text{VTI}_{\text{shunt}} \times \text{HR}$$

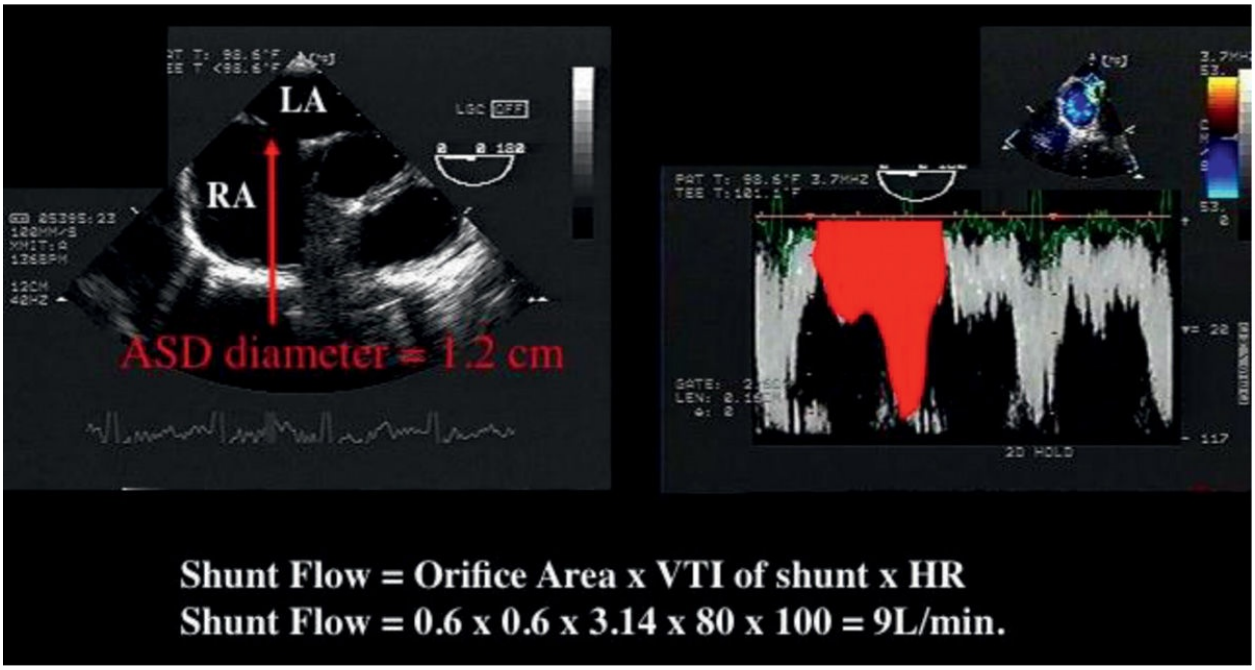

FIGURE 50.9 Calculation of ASD with left-to-right shunt flow. The red arrow marks the ASD orifice diameter (left). The VTI of the shunt flow is shown in the shaded red area (right). ASD, atrial septal defect; HR, heart rate; LA, left atrium; RA, right atrium; VTI, velocity time integral.

ESTIMATION OF PULMONARY VASCULAR RESISTANCE

Pulmonary vascular resistance (PVR) is defined as the ratio between the pressure gradient and the blood flow across the pulmonary vascular tree, measured in Wood's units. Invasively, PVR can be calculated using the following equation:

$$PVR = (PAMP - LAMP)/PBF$$

where PAMP is pulmonary artery mean pressure in mm Hg, LAMP is left atrial mean pressure in mm Hg, and PBF is the pulmonary blood flow in liters/minute. In patients with a normal PAMP (15 mm Hg), normal LAMP (5 mm Hg), and normal PBF (5 L/min), the calculated PVR is approximately 2 units.

The PVR is directly related to the PA pressure (and therefore to the maximal TR jet velocity) and inversely related to the SV in the RVOT (which can be measured noninvasively by pulsed Doppler, using the VTI at the RVOT, just proximal to the pulmonic valve). PVR can therefore be calculated by Doppler using the following equation[9]:

$$PVR = 10\ [(\text{peak TR velocity}/VTI_{RVOT}) + 0.16]$$

where PVR is expressed in Wood's units, TR = tricuspid regurgitation in m/s, and VTI_{RVOT} = velocity time integral at the right ventricular outflow tract in centimeters (**Figure 50.10**).

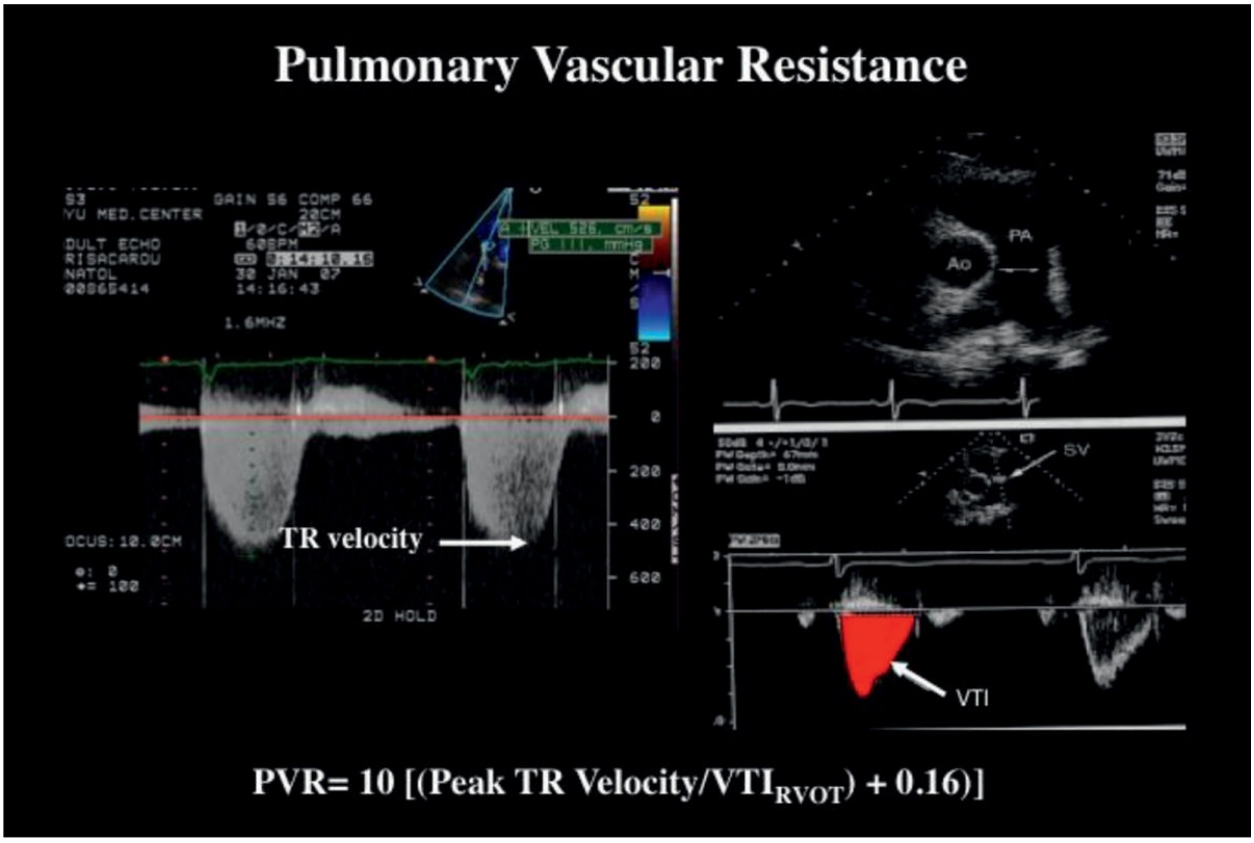

FIGURE 50.10 Noninvasive calculation of PVR in Wood's units using the peak TR velocity and VTI at the RVOT. PVR, pulmonary vascular resistance; RVOT, left ventricular outflow tract; TR, tricuspid regurgitant; VTI, velocity time integral.

CLINICAL CASE

COMPREHENSIVE HEMODYNAMIC EVALUATION

A complete echocardiographic examination can provide important information on a patient's hemodynamic profile. The information obtained may be comparable to invasive methods of hemodynamic evaluation and can guide therapy. The next few paragraphs evaluate the hemodynamic profile by means of echocardiography of a 63-year-old male with acute shortness of breath.

His vital signs during the evaluation showed a blood pressure of 100/55 mm

Hg and HR 70 beats/minute. His physical examination was notable for a regular HR, an apical diastolic rumble (mitral stenosis), apical holosystolic murmur (MR), a basal systolic ejection murmur radiating to the carotids (aortic stenosis), basal diastolic murmur (AR), and presence of jugular venous distension. **Figure 50.11** shows the hemodynamic information that was available at this stage. It is assumed that the aortic pressure was the same as the blood pressure measured by a blood pressure cuff.

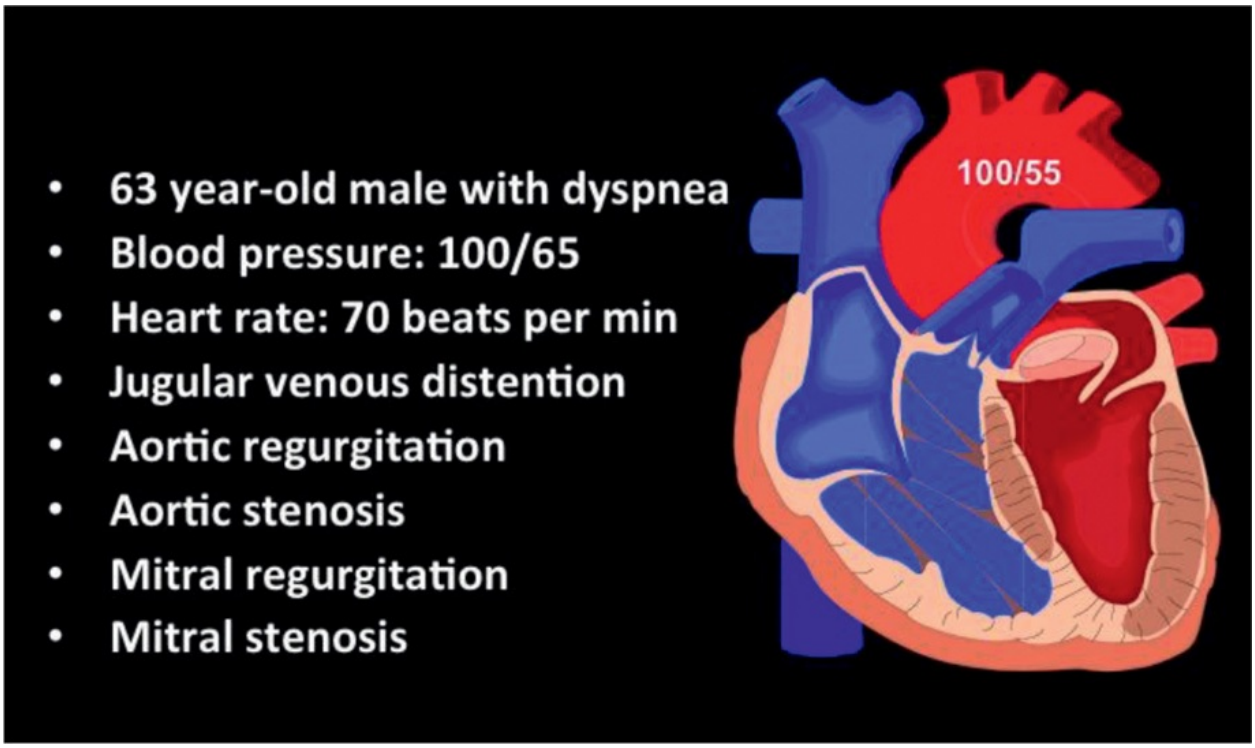

FIGURE 50.11 Initial hemodynamic profile and synopsis of history on presentation.

The evaluation begins with the inferior vena cava with subxiphoid echocardiography. As can be seen in **Figure 50.12A**, the inferior vena cava measured to be 2 cm and there was less than 50% respiratory collapse. Therefore, the inferior vena cava and the RAP (and also the superior vena cava) are slightly elevated (5 to 10 mm Hg); and for the sake of simplicity, a value of 10 mm Hg will be used. At this point, the known hemodynamic profile can be seen in **Figure 50.12B**.

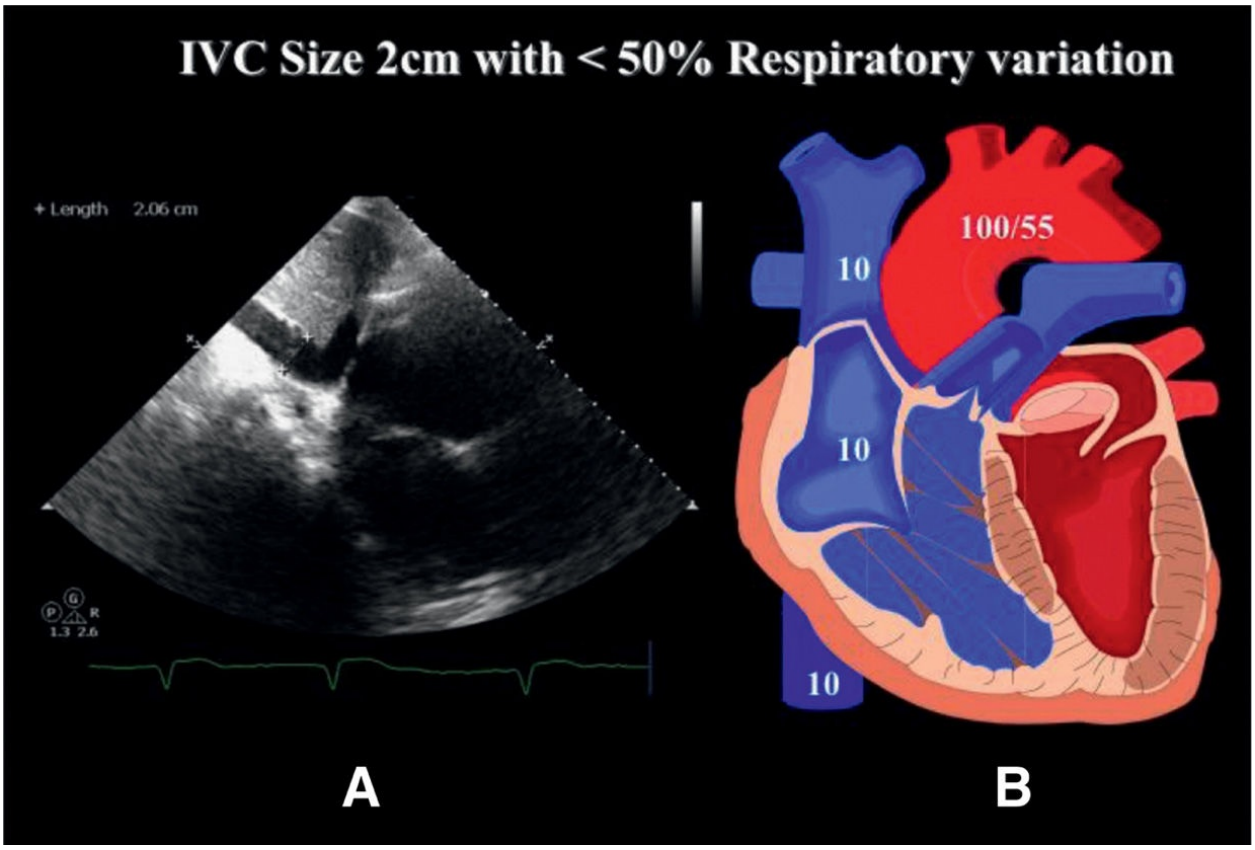

FIGURE 50.12 Calculation of right atrial pressure. A, IVC measuring 2 cm with less than 50% respiratory variation suggestive of slightly elevated right atrial pressure (5 to 10 mm Hg). B, The hemodynamic diagram shows a right atrial pressure of 10 mm Hg. IVC, inferior vena cava.

The right ventricular pressures can be estimated by evaluating flow across the tricuspid valve. The peak jet velocity of the tricuspid regurgitation (**Figure 50.13A**) is 3.7 m/s and, therefore, the gradient between the right ventricle and the right atrium is 56 mm Hg. The RVSP equals the RAP (10 mm Hg) plus the tricuspid regurgitation gradient (56 mm Hg), which equals 66 mm Hg. In the absence of tricuspid stenosis, the RVDP equals the RAP. Therefore, the pressure in the right ventricle is 66/10 mm Hg (**Figure 50.13B**).

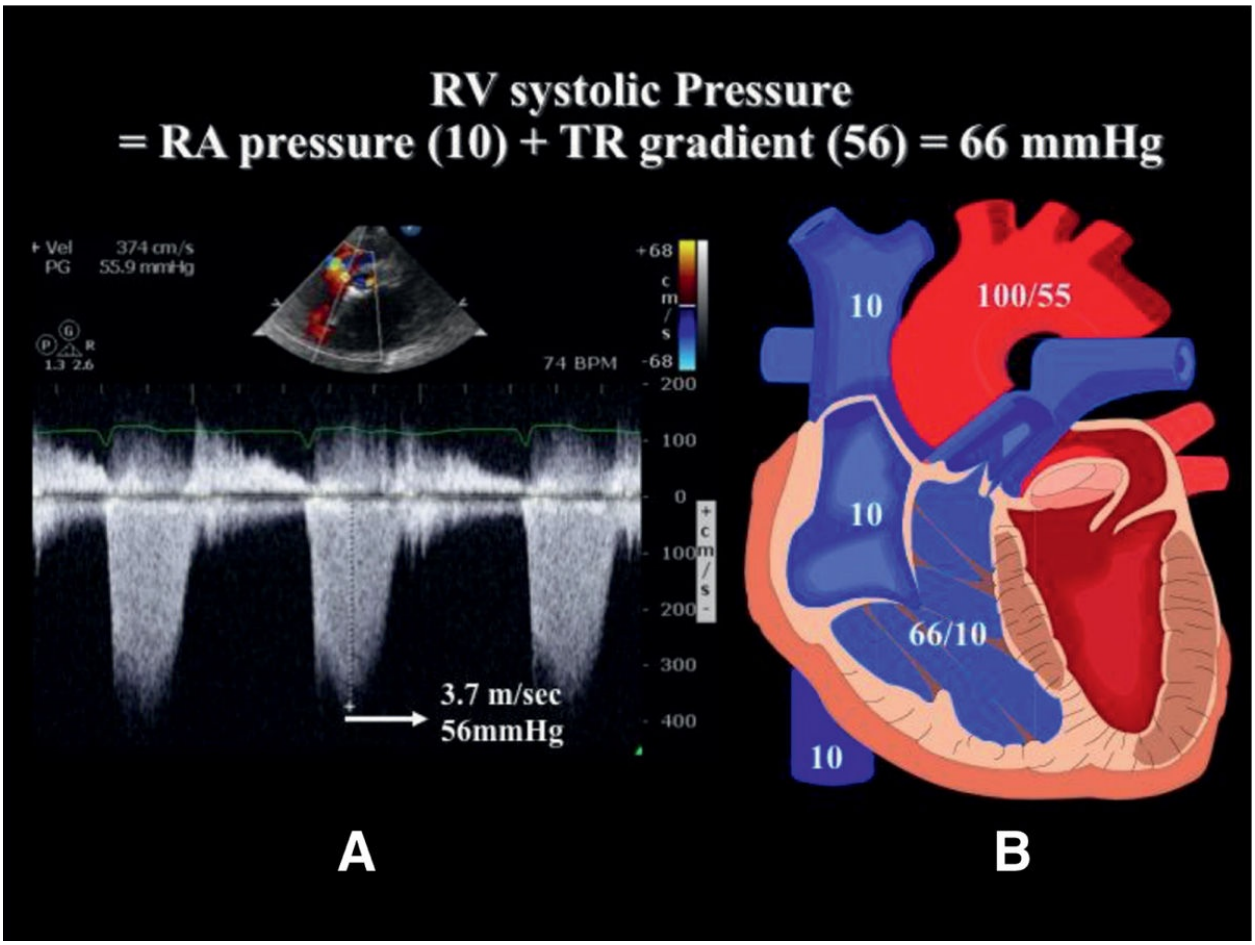

FIGURE 50.13 Calculation of right ventricular pressures. A, Tricuspid regurgitation velocity showing the gradient between the right ventricle and RA of 56 mm Hg. B, The hemodynamic diagram shows a right ventricular pressure of 66/10 mm Hg. RA, right atrium; RV, right ventricle; TR, tricuspid regurgitant.

The PA pressure can now be calculated. In the absence of PS, the RVSP (66 mm Hg) practically equals pulmonary arterial systolic pressure. As demonstrated in **Figure 50.14**, this patient has PR. The pulmonary diastolic pressure can be calculated by measuring the PR velocity at end diastole. The velocity of the PR jet is 2.2 m/s, which indicates a pulmonic regurgitant gradient of 20 mm Hg. The PADP is therefore the pulmonary regurgitation gradient (20 mm Hg) plus RAP (10 mm Hg), which equals 30 mm Hg.

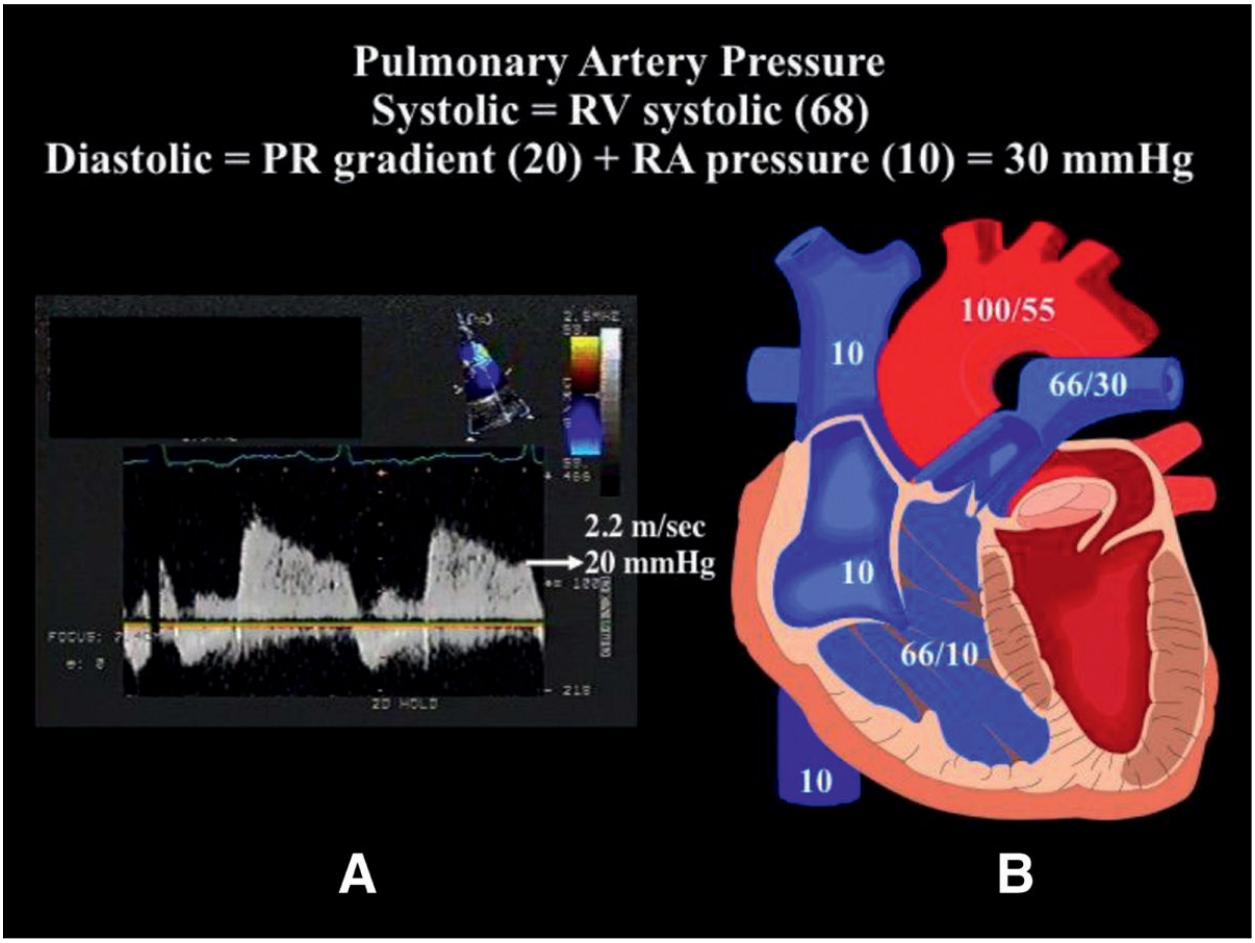

FIGURE 50.14 Calculation of pulmonary artery pressures. A, PR end-diastolic velocity of 2.2 m/s showing the gradient between the pulmonary artery and right ventricle of 20 mm Hg. B, The hemodynamic diagram shows a right pulmonary pressure of 66/30 mm Hg. RA, right atrium; RV, right ventricle; PR, pulmonic regurgitation.

Left ventricular pressures are calculated by evaluating flow across the aortic valve. The patient has AR (**Figure 50.15**). The end-diastolic velocity of the AR jet is 3 m/s and therefore the aortic end-diastolic gradient is 36 mm Hg. Therefore, the LVEDP equals the aortic diastolic pressure (55 mm Hg) minus the AR gradient (55 mm Hg), which equals 19 mm Hg. In addition, this patient has aortic stenosis (**Figure 50.16**) with a peak instantaneous aortic flow velocity of 4 m/s, which is equivalent to a MIG of 64 mm Hg. Because the P2P gradient is 70% of the MIG, the P2P equals 45 mm Hg. The LVSP is therefore the aortic systolic pressure (100 mm Hg) plus 70% of the MIG (45 mm Hg), which equals 145 mm Hg.

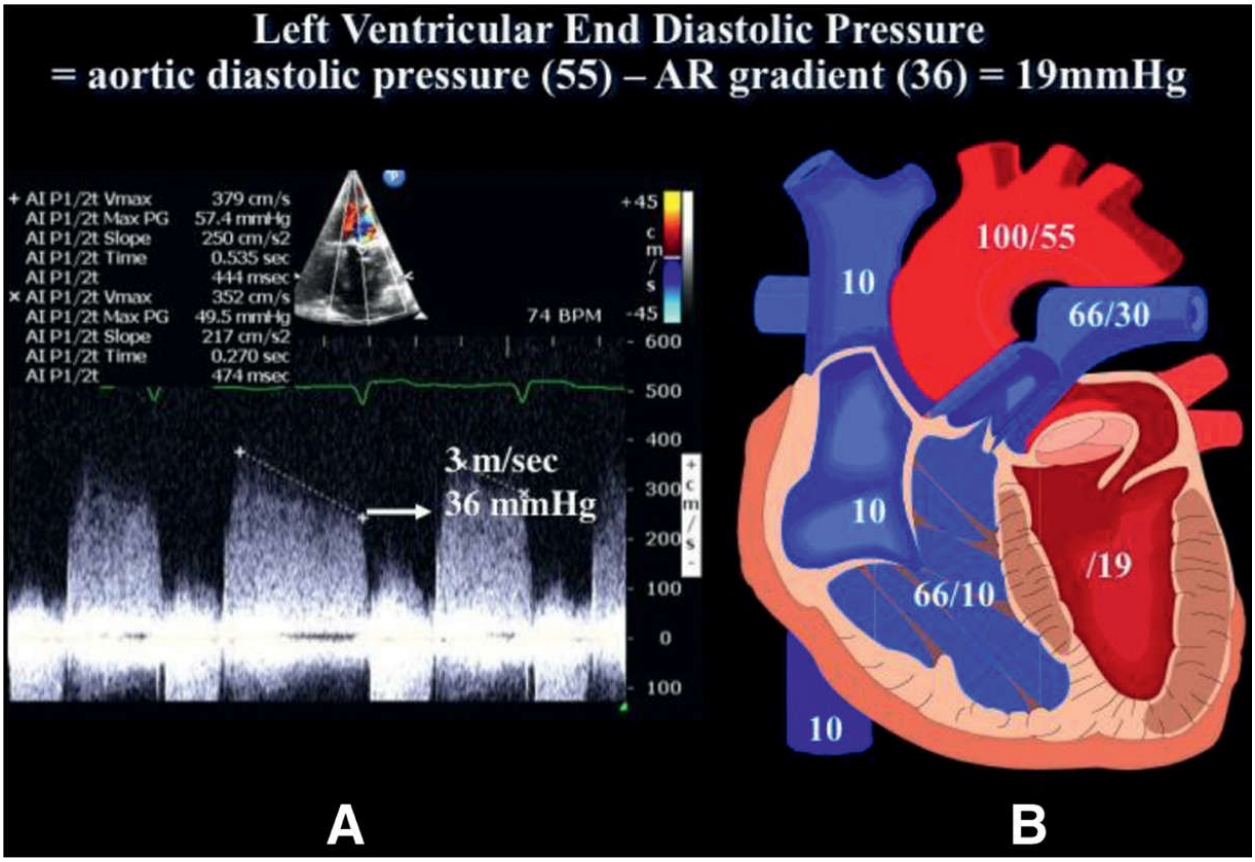

FIGURE 50.15 Calculation of left ventricular diastolic pressure. A, AR end-diastolic velocity of 3 m/s showing the gradient between the aorta and left ventricle of 36 mm Hg. B, The hemodynamic diagram shows a left ventricular diastolic pressure of 19 mm Hg. AR, aortic regurgitation.

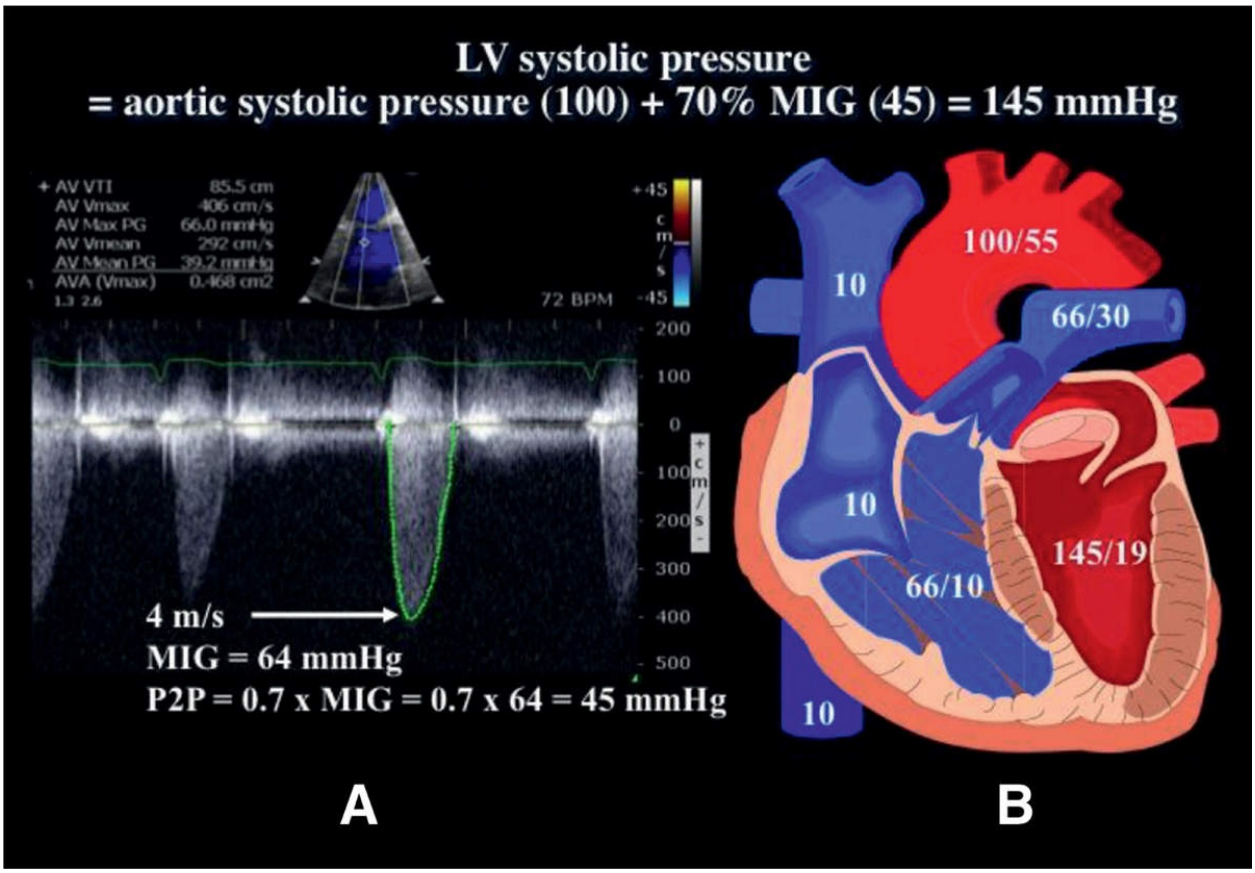

FIGURE 50.16 Calculation of LV systolic pressure. A, The peak instantaneous velocity of 4 m/s is used to calculate the MIG between the left ventricle and the aorta, which equals 64 mm Hg. Peak-to-peak (P2P) gradient, which is 70% of the MIG, equals 45 mm Hg. B, The hemodynamic diagram shows a left ventricular systolic pressure of 145 mm Hg. LV, left ventricular; MIG, maximum instantaneous gradient.

Finally, this patient has mitral stenosis (**Figure 50.17**). The mean mitral gradient was calculated to be 7 mm Hg. The LAP, therefore, equals the LVDP (19 mm Hg) plus the mitral valve mean gradient (7 mm Hg), which equals 26 mm Hg. Thus, with the use of echocardiography and without the use of invasive measures, the pressures in the cardiac chambers, the great arteries, and the veins can be calculated.

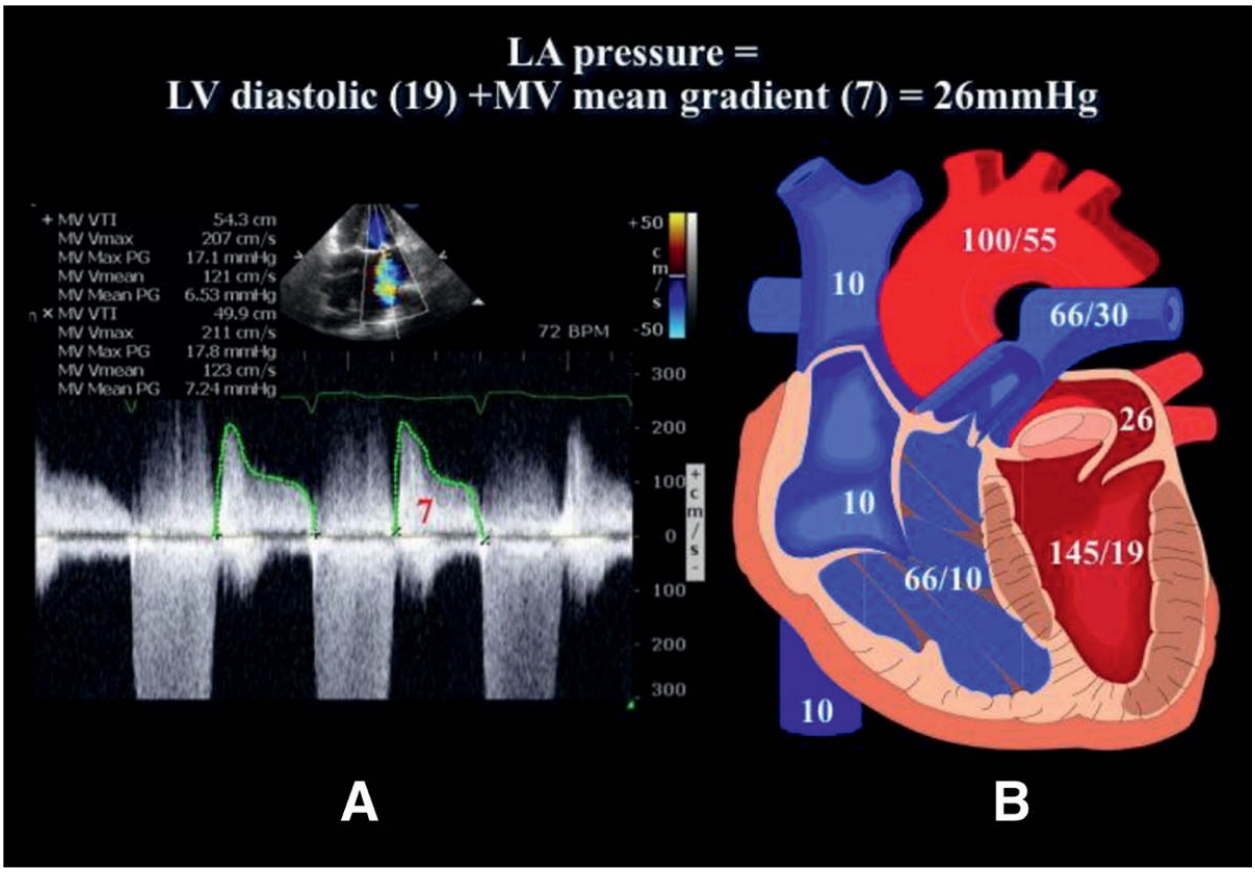

FIGURE 50.17 Calculation of LA pressure. A, Flow across the MV showing a mean mitral gradient of 7 mm Hg. B, The hemodynamic diagram shows an LA pressure of 26 mm Hg. LA, left atrial; LV, left ventricular; MV, mitral valve.

This hemodynamic evaluation provides an example of noninvasive pressure measurements in a patient with heart failure and valvular disease. Although these data are not available in all patients, some information is available in most. Invasive studies may be required when the clinical picture is not consistent with the echocardiography findings.

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Joseph P. Mathew

Noncardiac Point-of-Care Ultrasound in the CCU

INTRODUCTION

Goal-directed point-of-care ultrasound (POCUS) is real-time, organ-focused ultrasonography (USG) performed by a nonradiologist to answer a clinical question or guide a procedure. POCUS, also referred to as critical care ultrasonography (CCUS) or goal-directed USG, is performed and interpreted by clinicians at the point of clinical care.[1–3] Over the past decade, POCUS has become essential in the early diagnosis and treatment of critically ill patients. It allows for rapid, safe, and accurate assessment of a patient's condition and has great utility in guiding invasive bedside procedures. Safe application and interpretation of ultrasound (US) findings requires knowledge of the basic principles of USG and familiarity with the equipment and the modalities.

POCUS requires that all image acquisition, interpretation, and clinical application is performed by the clinician at the point of care, allowing for rapid integration of the results with the history and physical, laboratory, and imaging data to guide diagnosis and treatment.[4] When POCUS is performed with a focused clinical question and goal in mind, it serves as a valuable adjunct to the physical examination. We believe that POCUS is the most important contemporary innovation in critical care—an extension of the physical

examination or “visual stethoscope,” so to speak—and its adoption and incorporation into clinical care will certainly prove of value in the diagnosis and treatment of the patient in the cardiac care unit (CCU). We highlight the role of POCUS in making a rapid and acceptably accurate differential diagnosis of the patient in the CCU who is hypotensive, in respiratory distress, or in multiorgan failure.[5]

HISTORY

Although clinicians in these specialties such as radiology, cardiology, and obstetrics have been doing point-of-care bedside USG for the past several decades, bedside POCUS did not really advance until the 1990s, when more compact and affordable machines led to adoption by specialties such as emergency medicine (EM), anesthesiology, and pulmonary-critical care medicine. Early use of US in CCUs and intensive care units (ICUs) were driven by its success with improving the success and safety of central line placement.[6] Trauma surgeons and EM physicians started assessing patients with trauma using US, and the FAST (Focused Assessment with Sonography in Trauma) examination became fully integrated into Advanced Trauma Life Support (ATLS) guidelines.[7] US guidance is now standard of care for procedures such as thoracentesis and internal jugular vein central line placement.[8,9] Focused USG has now become part of nearly every specialty’s practice in some form.[5]

THE CASE FOR POINT-OF-CARE ULTRASONOGRAPHY

Traditionally, USG and echocardiography are performed by a technician and interpreted by a radiologist or cardiologist. Patients have to be transported for these examinations and the services are often only available during daytime hours on weekdays, thus leading to delays in performance, interpretation, and communication of the results. This is very limiting to units such as the CCU where questions need to be answered at all times of day or night and on weekends. POCUS is performed at the bedside by the treating clinician, interpreted right away, and the results applied right away in conjunction with the clinical presentation and laboratory data. POCUS by no means is a replacement for a comprehensive examination and consultation by radiology or cardiology

services.[4] Although POCUS is often limited to one organ system, multiple systems may have to be assessed for diagnostic purposes; but this can be done in a quick and efficient manner by the trained sonographer.[10] In addition, just like the physical examination, the sonographic examination can be repeated to reassess the patient.

The current evidence supporting the use of POCUS is overwhelming. Early studies by Lichtenstein and Axler[11] showed that focused sonography changed management in one out of every four patients in the ICU. In patients with trauma, the FAST examination has a sensitivity of 94% and specificity of 98% with a high negative predictive value for clinically significant intra-abdominal injury.[12] Multiorgan POCUS was shown to correlate accurately with the final diagnosis in patients in the emergency department (ED) with undifferentiated hypotension.[13] Lichtenstein's pioneering research showed that bedside USG could identify the correct diagnosis of acute respiratory failure, shock states, and even function as a noninvasive Swan Ganz catheter to guide fluid resuscitation.[10,14,15] Focused goal-directed echocardiography (GDE) can be helpful in the evaluation of shock states, and assessment of inferior vena cava (IVC) variability in mechanically ventilated patients has been used to accurately predict fluid responsiveness.[16,17] Work by Kory and Blaivas showed that non-radiologists could accurately detect deep vein thrombosis (DVT) at the point of care, saving time and expediting treatment.[18,19]

BASIC PRINCIPLES OF ULTRASONOGRAPHY

USs are sound waves with frequencies that exceed those perceived by the human ear (>20 kHz). Medical USG uses sound waves (2 to 10 MHz) created by a vibrating crystal within a ceramic probe (also called a transducer) that can both send and receive sound waves. Images are created on the basis of the piezoelectric principle, by which electric current causes crystals to vibrate and returning sound waves create electric current that the machine translates into real-time images. The strength or amplitude of the returning echo waves determines the brightness (ie, whiteness) of the echo pixel. Modern-day US machines generate B-mode or two-dimensional USG from an array of crystals (>128) across the footprint of the transducer.[5,20]

US waves travel through different tissue and are partly reflected at each tissue

interface. They penetrate well through solid organs and fluid; however, they do not penetrate air or bone, limiting the usefulness. Hence, the ribs are often an impediment when doing echocardiography and thoracic USG. Air is completely reflected back to the transducer. If air is in the way of sound waves, it generates "A-lines" or "air lines," which are a reverberation artifact. Bone typically has a white leading edge and then a black shadow due to near-total reflection of US waves.

Bright structures are referred to as *hyperechoic*. These "white" areas represent echogenic structures that transmit and reflect US waves. "Black" areas represent areas that are *anechoic*. This occurs when US waves encounter a structure that does not reflect any waves and no waves return to the transducer (eg, fluid). Sound waves propagate through fluid and thus fluid is a great window to see other nearby structures. US waves often lose energy after their interaction with a structure and return with a low amplitude. These low-amplitude waves are translated into shades of gray or *hypoechoic* regions. Lastly, lines occur at boundaries between two markedly different tissue reflectors, delineating the two structures. Soft tissue often has white, gray, and black planes and borders, representing different speeds of propagation and reflection of US waves.[20] **Table 51.1** lists examples of structures of different echogenicity. **Figure 51.1** shows the parasternal long-axis (PLAX) view of a patient with a posterior mediastinal mass presenting with rapid atrial fibrillation demonstrating the echogenicity of different structures in the thorax.

TABLE 51.1 Differences in Tissue Echogenicity

GRAY SCALE	TERMINOLOGY	STRUCTURE	EXAMPLE
	Anechoic	Pure fluid	Pleural or pericardial effusion Ascites Bladder Veins and arteries

Hypoechoic	Thick fluid Thrombosis Consolidation Tissue/organs	Hemothorax or hemoperitoneum DVT Pneumonia Liver, spleen, kidney, bowel Fat, lymph nodes, nerve
Hyperechoic	Bone/calculus Strong interface	Ribs; kidney or gallstones Pleura, pericardium Diaphragm, nerve, tendon

DVT, deep vein thrombosis.

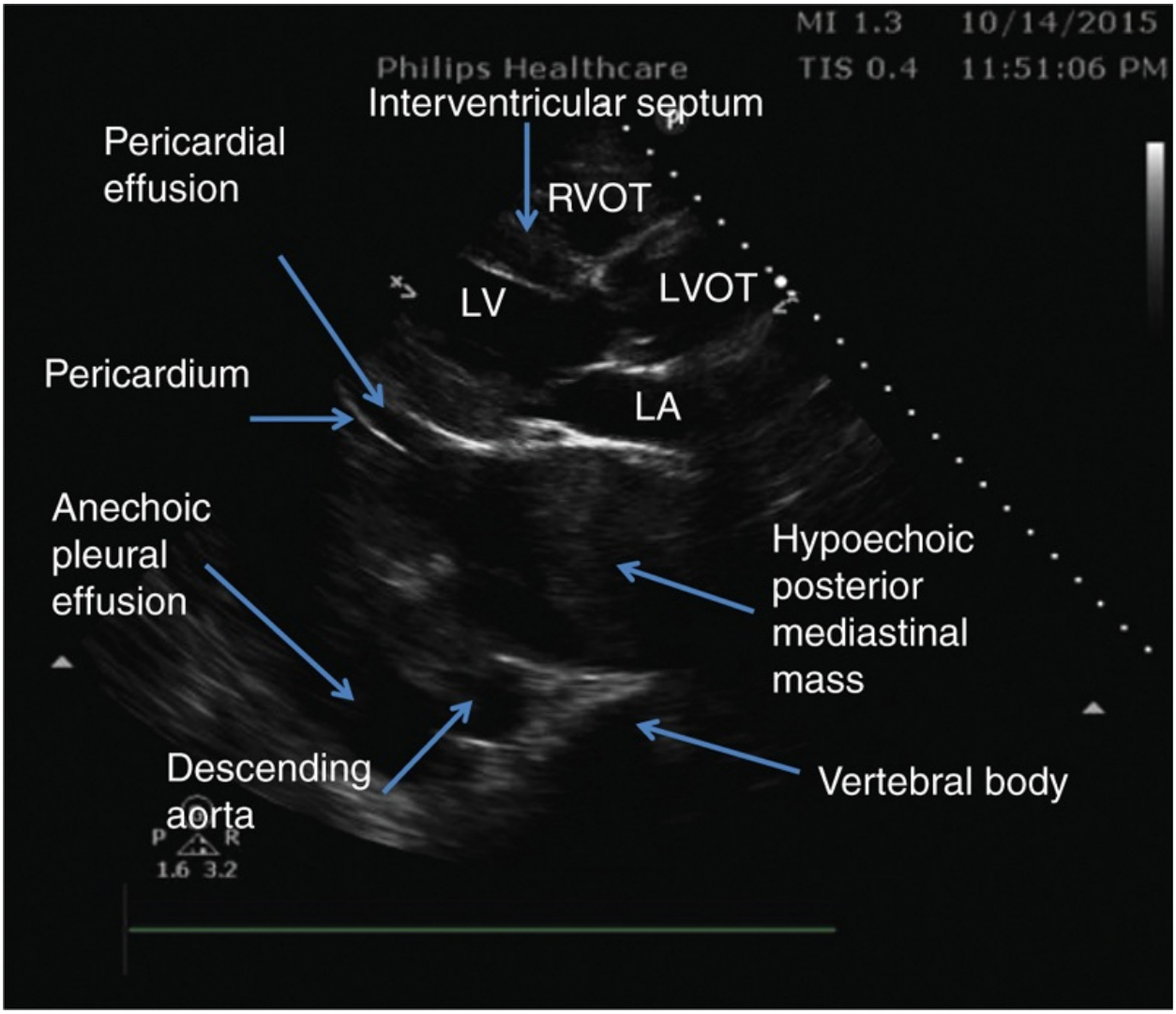


FIGURE 51.1 Differences in tissue echogenicity. LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract.

EQUIPMENT AND IMAGE ACQUISITION

Modern US machines are portable and consist of multiple transducers or probes (**Figure 51.2**). Linear array transducers emit high-frequency US waves at a frequency of 5 to 15 MHz and provide excellent resolution of superficial structures such as vascular structures. For POCUS, this transducer is mainly used for US guidance for vascular access and to assess for DVT. Because of its high resolution, it can be used to assess the pleura for pneumothorax. It has poor penetration and so is not used to image deeper structures. Phased array transducers are low-frequency transducers (1 to 5 MHz) and have good penetration; hence, they are used to image deeper structures. The small footprint of the transducer allows for image acquisition between the ribs, and is hence used for lung, pleural, and cardiac USG. This transducer can also be used for abdominal and pelvic imaging. The curvilinear transducer is a hybrid, multipurpose probe that images at lower frequencies ranging between 1 and 8 MHz. It has a larger footprint, which generates a beam that fans outward, resulting in a wide field of view. These probes are most often used for abdominal and pelvic applications and the FAST examination where the subcostal (SC) cardiac view can also be obtained. The microconvex probe has a small footprint that fits in between the rib interspace and can be used for thoracic imaging. **Table 51.2** summarizes the basic characteristics and uses of the different types of transducers.

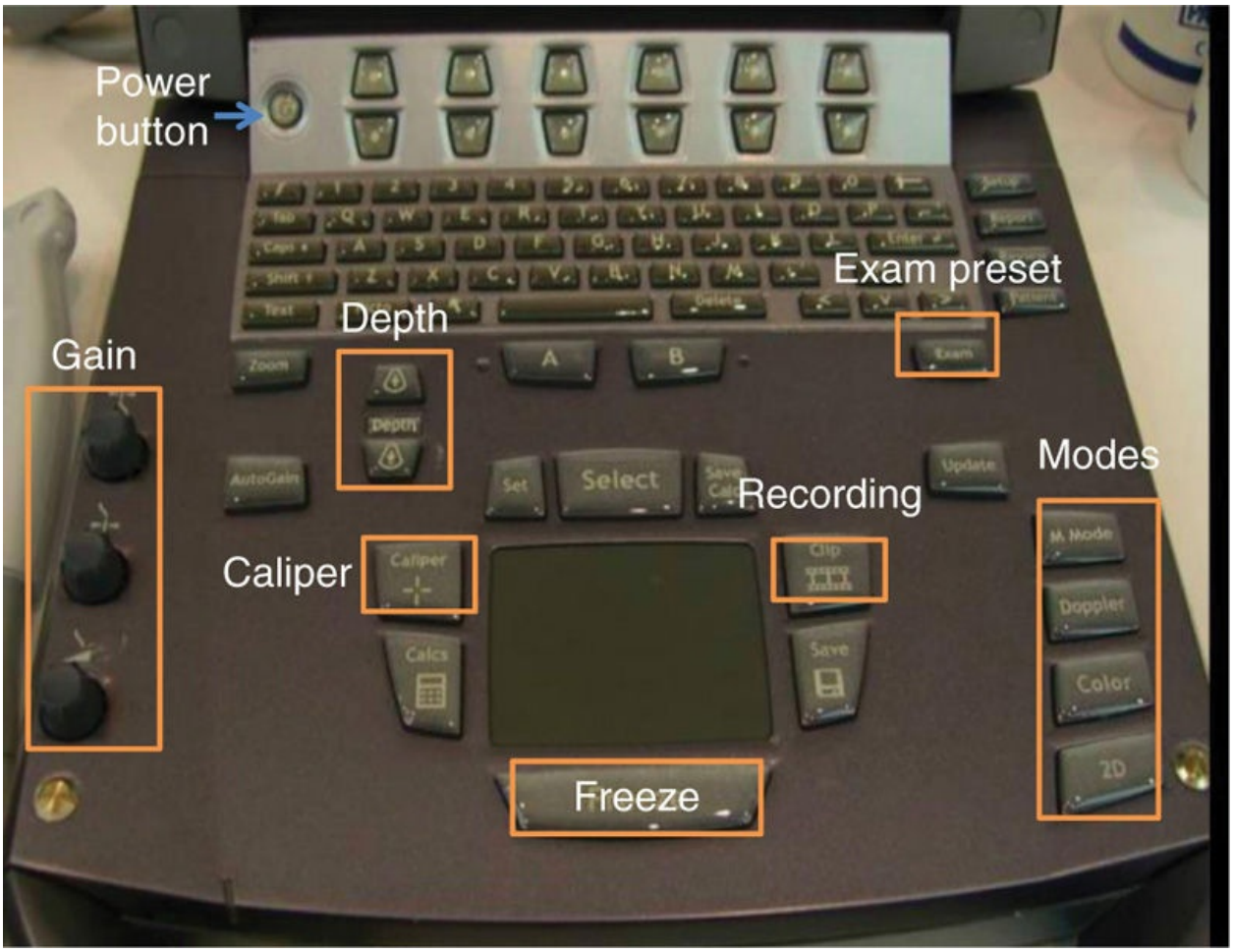


FIGURE 51.2 Portable ultrasound machine.

TABLE 51.2 Transducer Characteristics

TRANSDUCER	FREQUENCY	CHARACTERISTICS	USES
Linear array	5–15 MHz	High frequency Excellent resolution of superficial structures Loss of depth	Vascular access DVT study Pleural lines Soft tissue and musculoskeletal imaging

Phased array	1–5 MHz	Low frequency Small footprint Deep penetration	Cardiac Lung/pleural Abdomen
Microconvex	5–8 MHz	Small footprint Good resolution	Lung Abdomen Vascular Nerve
Curvilinear	1–8 MHz	Low frequency, low resolution Multipurpose Full depth of penetration	Abdominal/pelvic imaging FAST exam Lung/cardiac

DVT, deep vein thrombosis; FAST, focused assessment with sonography in trauma.

Transducer orientation and manipulation is of utmost importance in obtaining good images for diagnostic purposes or procedural guidance. The transducer should be held steady, as if holding a pencil (**Figure 51.3**). All US probes have a marker that correlates with the side of the marked screen. Structures adjacent to the probe marker will appear on the same side of the image as the screen marker, helping to orient the viewer and guide probe manipulations. The operator should always be aware of the orientation of the probe marker in relation to the marker on the monitor screen. Structures closest to the footprint of the transducer will appear on the top of the screen (near field) and those furthest away will appear on the bottom (far field). Portable US machines have preset examination settings (eg, abdomen versus cardiac) for each type of examination, which sets the resolution, frame rates, and the location of the screen marker.

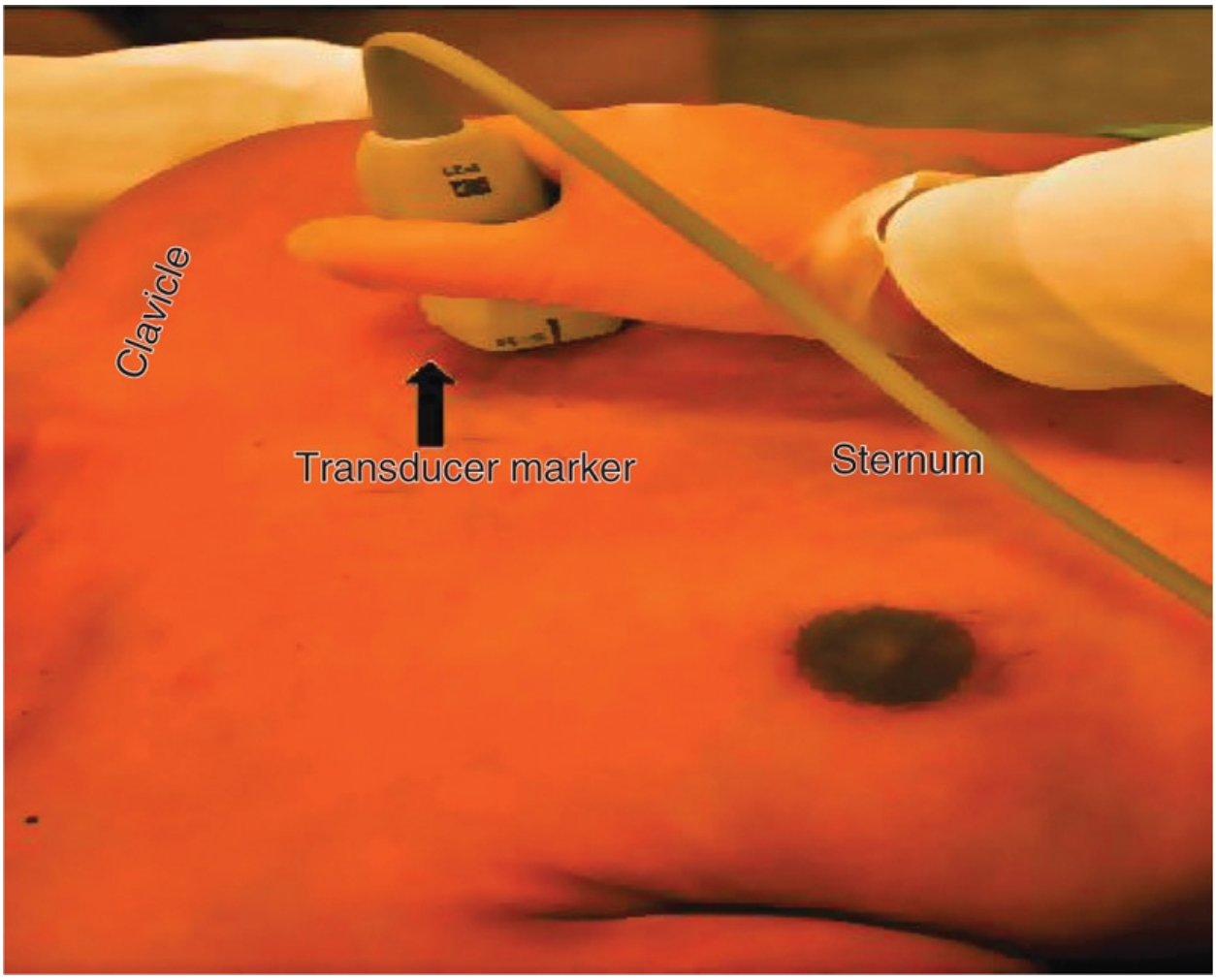


FIGURE 51.3 Transducer position for thoracic ultrasonography.

ULTRASOUND MANIPULATION

To obtain quality images, the gain and depth of imaging have to be optimized. *Depth* is manipulated on the console such that the structure of interest should always be in the center of the screen. The depth of interrogation is usually shown on a scale on the monitor. *Gain* adjusts the brightness of the entire image and should be adjusted such that there is maximal resolution between the different tissues that are imaged. Failure to adjust gain can lead to misinterpretation of image. Ensure that gain is uniform in both near (top half of screen) and far field (bottom half). The operator should be familiar with other features of the machine such as how to *freeze* and measure structures using the *caliper* button, how to *save* images and clips, and utilize features such as *M-mode* (motion mode) and

Doppler. The operator must always ensure that the portable US machine is in the appropriate exam preset. For example, the frame rates acquired in abdominal preset are not optimal for cardiac imaging and the screen marker on the opposite side will reverse all the cardiac images.

IMAGE MANIPULATION

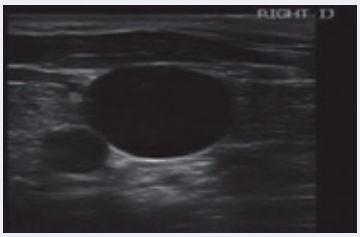
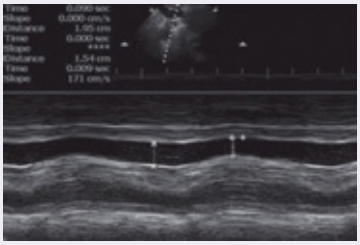
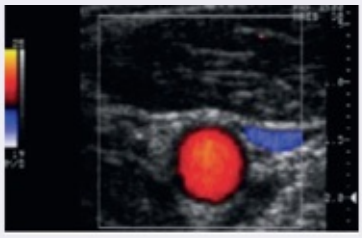
In general, the probe marker should be pointed to the operator's left side when imaging in the transverse (short-axis) plane or cephalad when imaging in the coronal or sagittal (long-axis) planes. Additional maneuvers that are used to optimize the views include *moving* the probe such that the entire transducer is moved on the body (eg, from one rib interspace to another). This maneuver helps find the optimal location and view to locate the structure of interest. *Sliding* the probe is a maneuver that slides the transducer along the course of the structure of interest (eg, blood vessel). *Compression* allows visualization of deeper structures and allows one to differentiate structures (eg, vein from artery and nerve) based on their compressibility. *Rocking* involves angling the transducer side to side and extends the plane of imaging. This is useful to center the image on the screen (eg, centering a central vein and separating it from the artery). *Rotation* is used to switch between short-axis and long-axis imaging. This is useful for vascular access procedures and for obtaining short-axis cardiac views. *Tilting* (also called *fanning* or *sweeping*) allows the operator to scan along the course of a structure along a narrow acoustic window that is used. The transducer is held in place on the skin and angled on the long axis of the transducer face to aim the US beam in different planes (eg, obtaining multiple short-axis views of the heart).

MODES

The standard mode used for POCUS is *B-mode* or 2D USG. *M-mode* is used to display and measure the movement of structures over time. This feature is used to assess variation in the IVC diameter, diaphragmatic excursion, and to assess the pleura in the evaluation of pneumothorax. *D-mode* or *Doppler* mode evaluates the characteristics of direction and speed of blood flow (and tissue motion) through a structure. This is presented in audible, color, or spectral display.[20] Color Doppler converts measurements into an array of colors to

visualize speed and direction. This is particularly useful in vascular imaging to distinguish arteries from veins. The conventional color code is such that flow toward the transducer is depicted as red and flow away from the transducer is blue ("BART": blue away, red toward). Spectral Doppler is used mainly in echocardiography and displays the movement of blood in a graph depicting flow velocities with respect to time. **Table 51.3** lists examples of the imaging modes used in POCUS.

Table 51.3 Modes of Ultrasonography

MODES		
B-mode	Brightness mode	
M-mode	Motion mode	
D-mode	Examines the characteristics of direction and speed of blood flow (and tissue motion) • Color Doppler • Spectral Doppler • Power Doppler • • • •	

PRACTICAL APPLICATION OF POINT-OF-CARE ULTRASONOGRAPHY IN THE CCU

The standard critical care US examination involves scanning the major regions that would answer the question about the presenting condition. The standard multiorgan POCUS examination generally includes four organ systems: thoracic (lung and pleural), cardiac, and limited abdominal and vascular imaging. The organ of interest is often scanned first (eg, heart in shock or lungs in respiratory failure), although a standardized multiorgan approach can be used for the critically ill patient in the CCU. Although a focused examination is often all that is needed, studies have shown that a multiorgan or whole-body approach leads to a more accurate diagnosis.[13,21] The US examination should always be performed in conjunction with the patient's clinical data. It should be repeated to reassess the patient and to see if certain therapeutic interventions were effective.

The most common indication for a point-of-care examination in the CCU is for cardiopulmonary failure. POCUS is indicated in the evaluation of the patient with undifferentiated shock and can help distinguish between obstructive, cardiogenic, hypovolemic, and distributive shock states.[4,13,21,22] Another major indication would be in the setting of acute respiratory failure. A focused US examination of the heart, lungs, and deep veins can be useful in diagnosing various causes of respiratory failure.[10] Overadministration of fluids in the patient in the CCU with limited cardiopulmonary reserve can be harmful and leads to increased days of ventilator support. Assessing IVC size and variation, as well as the heart and lungs, can help guide fluid resuscitation.[17] US is very helpful in the patient whose condition suddenly deteriorates. It can be used to quickly rule out pneumothorax, massive pulmonary embolism (PE), pericardial tamponade, valvular rupture, and intra-abdominal bleeding.

FUNDAMENTALS OF THORACIC ULTRASONOGRAPHY IN THE CCU

BASIC PRINCIPLES

The utility of bedside lung ultrasound (LUS) is gaining increasing popularity as an attractive alternative to chest radiography. Easily performed by the trained intensivist, it is safe, accurate, and cost-effective. Conventionally, thoracic US is limited to the evaluation of pleural effusions; however, more recently LUS has become an attractive new tool for assessing lung status in hypoxemic critically ill patients. A frontline intensivist, Dr Daniel Lichtenstein, has been largely

responsible for developing the field of critical care LUS, publishing a series of definitive reports in the 1990s that established the basis for the field.[23–26]

Traditionally, the lungs were not considered an organ amenable to USG, because US waves are not transmitted through air-filled structures. When air is displaced from the lung by a disease process, US findings change in a predictable manner. Because the lung parenchyma is normally filled with air, which is a near-total reflector, the healthy or "unhealthy" pleural line serves as the generator of reflecting signs, which can be interpreted. Lung disorders can be separated into dependent disorders and nondependent disorders, whereby fluid descends and air rises. The findings of LUS relate to the ratio of air to fluid within the lung. Most lung processes that are pertinent to the patient in the CCU (eg, pulmonary edema, pneumonia, pneumothorax, pleural effusion, and atelectasis) all extend to the lung periphery allowing the US machine's ability to distinguish air and water to produce artifacts. These artifacts are used to diagnose various disorders such as alveolar-interstitial syndrome and accurately assess lung aeration in patients with acute lung injury. LUS is therefore based on the clinical interpretation of a number of mostly dynamic artifacts.

THE LUNG EXAMINATION

To examine the thorax, a micro-convex (5 to 8 MHz) transducer is preferable or, alternatively, a low-frequency (1 to 5 MHz) phased array transducer can be used because it fits in the rib interspace (**Table 51.2**).[27] A high-frequency linear array transducer (5 to 15 MHz) can be used to visualize the superficial pleural line; however, it is limited by the depth of penetration and the linear trajectory of the US beam.

The scanning of the lung occurs in the intercostal spaces. The transducer is held in a longitudinal orientation and perpendicular to the skin surface, with the marker facing cephalad (**Figure 51.3**). Initial scanning should be performed at a maximum depth (around 16 cm) and then the gain and depth must be adjusted to optimize and center the image. By moving the transducer along a series of longitudinal scan lines while imaging through adjacent intercostal spaces, the examiner can perform a complete lung examination and construct a 3D image of the thorax. The thorax can be divided into three zones: anterior, lateral, and posterior zones and then further into upper and lower zones (**Figure 51.4**).[27] Thus, a complete examination consists of 12 imaging regions, 6 in each hemithorax.

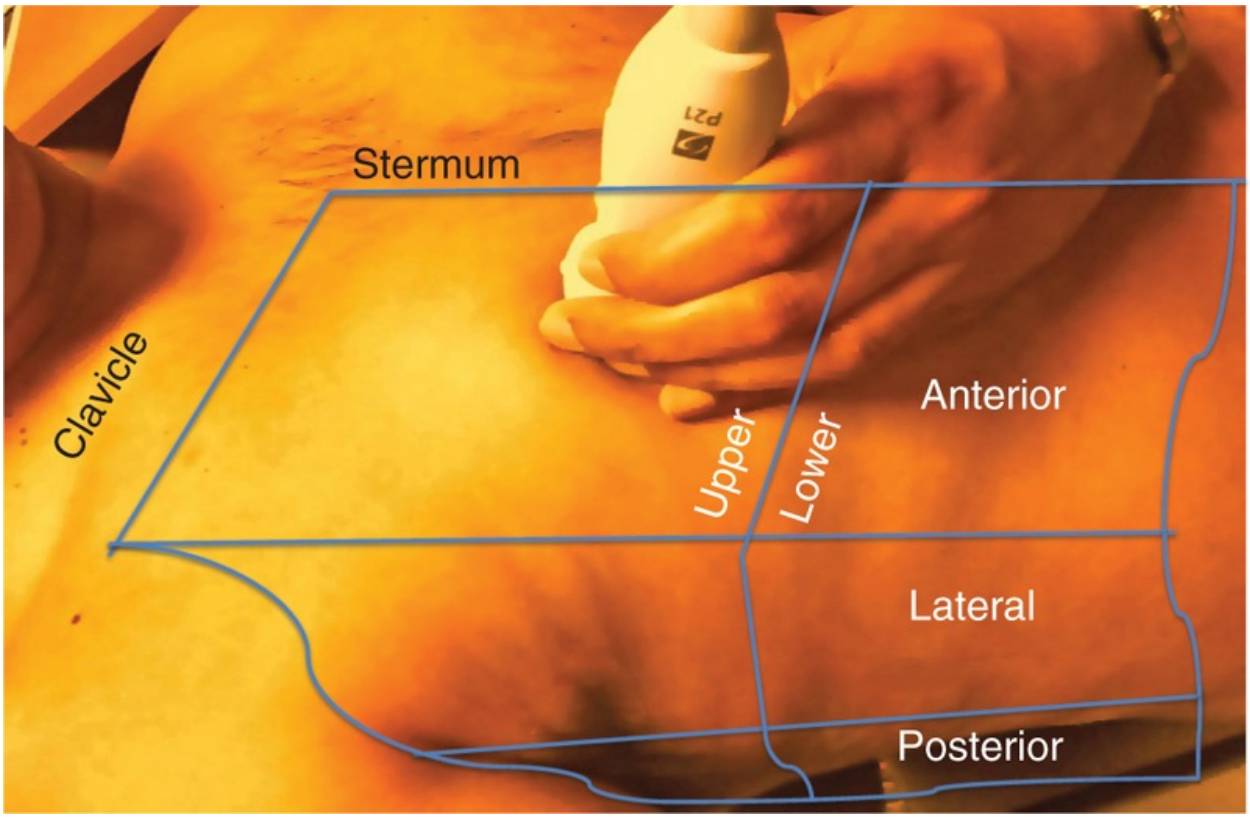


FIGURE 51.4 Lung zones for thoracic ultrasonography.

The sternum and the anterior axillary line border the *anterior lung zone*, whereas the *lateral zone* lies between the anterior and posterior axillary lines. The *posterior lung zone* lies behind the posterior axillary line. The anterior lung zone is assessed for alveolar-interstitial syndromes, lung consolidation, and pneumothorax. When examining the lateral zone, it is important to identify the hemi-diaphragm, which appears as a hyperechoic structure that separates the lungs from abdominal contents. Pleural effusions, atelectasis, and consolidation can often be seen above the hemi-diaphragm in this region. The posterior lung zone is a forgotten region where dependent pleural effusions and lung consolidation may be seen, so it is important to turn the critically ill patient to assess this area. Alternatively, Lichtenstein describes four points that can be quickly assessed as part of the BLUE (bedside lung ultrasound in emergency) protocol (**Figure 51.5**), a goal-directed LUS examination that can be performed in <3 minutes.[10]

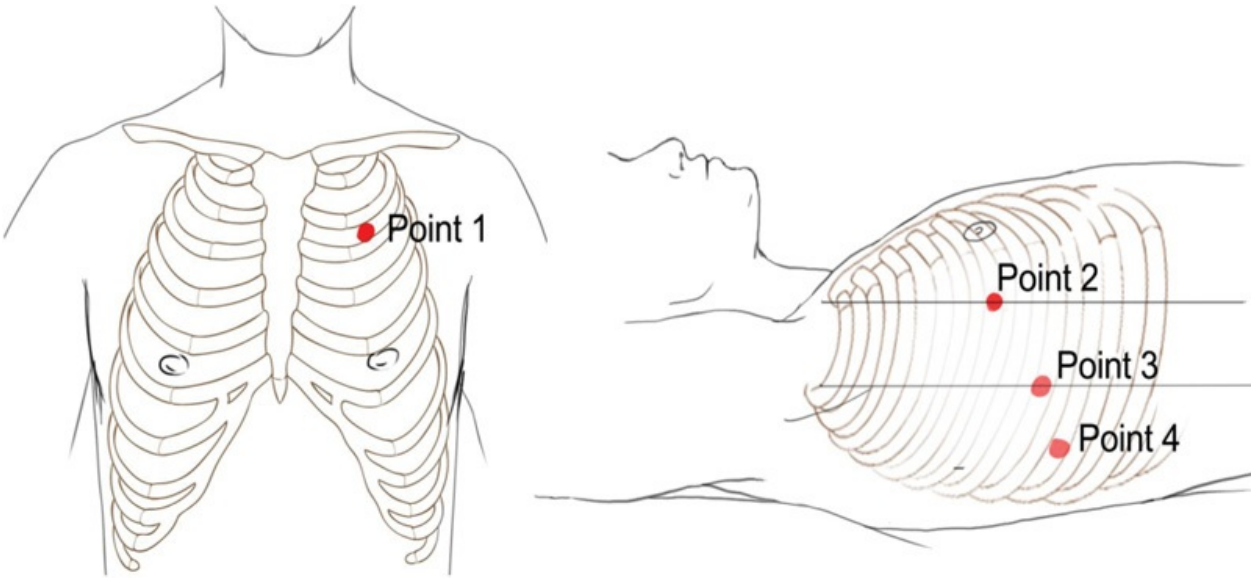


FIGURE 51.5 Bedside lung ultrasound in emergency (BLUE) protocol.

LUNG SIGNS

There are five cardinal lung signs to look for when performing thoracic USG. **Table 51.4** describes these and additional signs that are described in LUS and pleural USG. **Table 51.5** summarizes common LUS patterns seen in common disease processes that may be encountered in the CCU.

TABLE 51.4 Normal and Abnormal Signs in Lung Ultrasonography

SIGN	LUNG ULTRASOUND PATTERN	CLINICAL SIGNIFICANCE
A-line	Horizontal reflections or reverberations of pleural line Hyperechoic and equal in distance from skin to pleural line	Present in normal lung, "air" line indicates air in lung or pleural space
B-lines	"Comet tail" or "lung rockets"—vertical hyperechoic reverberation artifacts that arise from the pleural line and extend to the bottom of the screen Move synchronously with lung sliding and efface A-lines; implies fluid-filled subpleural interlobular septa	>3 B-lines = interstitial pathology Multiple diffuse B-lines indicate interstitial syndrome Focal B-line can be seen in pneumonia, infarct, and cancer
Lung sliding	Sliding or shimmering of the pleural line that occurs with respiration Indicates intact visceral and parietal pleura	Present in normal lung Absent in pneumothorax, apnea, fibrosis, ARDS, and pleurodesis

Lung pulse	Subtle rhythmic movement of the visceral upon the parietal pleural with cardiac oscillations	Present in normal lung Rules out pneumothorax
Seashore sign	Normal M-mode image with lines above echogenic pleura and speckled pattern deep to it, indicating normal lung sliding	Normal aeration pattern No pneumothorax
Bar code or stratosphere sign	Abnormal M-mode image showing a linear pattern above and below the pleura	Signifies absence of lung sliding; can be seen with pneumothorax
Lung point	Transition point where visceral and parietal pleura separate—image changes from the intermittent presence and then absence of lung sliding	Pathognomonic sign for pneumothorax
Lung hepatization/consolidation	Loss of aeration of lung leads to a hyperechoic appearance of lung; alveoli are filled with fluid or inflammatory cells or are atelectatic	Can be seen with atelectasis or pneumonia
Dynamic air bronchograms	Dynamic echogenic foci within consolidated lung that fluctuate with the respiratory cycle	Seen with pneumonia
Static air bronchograms	Hyperechoic foci that do not move with respiration	Seen with atelectasis
Shred sign	Border between consolidated and aerated lung	Seen with consolidation but not translobar consolidation
Curtain sign	Intermittent obscuration of underlying organs by intervening air-filled lung	Can be normal finding
Hematocrit sign	Effusion is separated into different echogenicity with a layering effect	Seen in hemothorax or highly cellular effusions (eg, malignant effusion)
Flapping lung (jellyfish sign)	Floating movement of collapsed lung within a pleural effusion	Atelectatic lung in effusion
Sinusoid sign	In a pleural effusion, M-mode appearance of the pleura moving toward and away from the parietal pleura	Can be used to distinguish pleural thickening from effusion
Plankton sign	Particulate matter in lung effusion	Complex effusion

ARDS, acute respiratory distress syndrome.

TABLE 51.5 Lung Ultrasound Patterns

LUNG ULTRASOUND PATTERN	CLINICAL SIGNIFICANCE
A-lines with lung sliding	Normal aeration pattern

A-lines without lung sliding and +lung point	Pneumothorax
B-7 lines	Interlobular septal pathology
B-3 lines	Alveolar-interstitial syndrome
Focal absence of B-lines	Pulmonary embolus, cancer
Lung hepatization + dynamic air bronchograms	Pneumonia
Lung hepatization ± static air bronchograms	Atelectasis
Anechoic collection without septations	Simple pleural effusion
Echogenic fluid with septations	Complicated effusion

Lung Sliding

This is a subtle shimmering of the hyperechoic pleural line (**Figure 51.6**). It represents movement of visceral pleura past the parietal pleura during respiration. It must be present at multiple sites and will be present more often at the lung base. The presence of lung sliding rules out pneumothorax with 100% certainty at that particular site on the thorax.[26,27] The presence of lung sliding strongly suggests that two conditions are met: the pleural surfaces are adjacent (ie, no pneumothorax) and that the lung volume is changing. The examiner can also use a high-resolution linear array transducer because it images the pleura well. A similar analogous sign can be from *lung pulse*, which is produced when cardiac motion causes pulsations of the pleural line. Air in the pleural space (ie, pneumothorax) will cause absence of lung sliding and lung pulse. Other conditions can also cause lack of lung sliding, including apnea or hypoventilation (eg, contralateral bronchial intubation), pleurodesis, and dense lung consolidation.

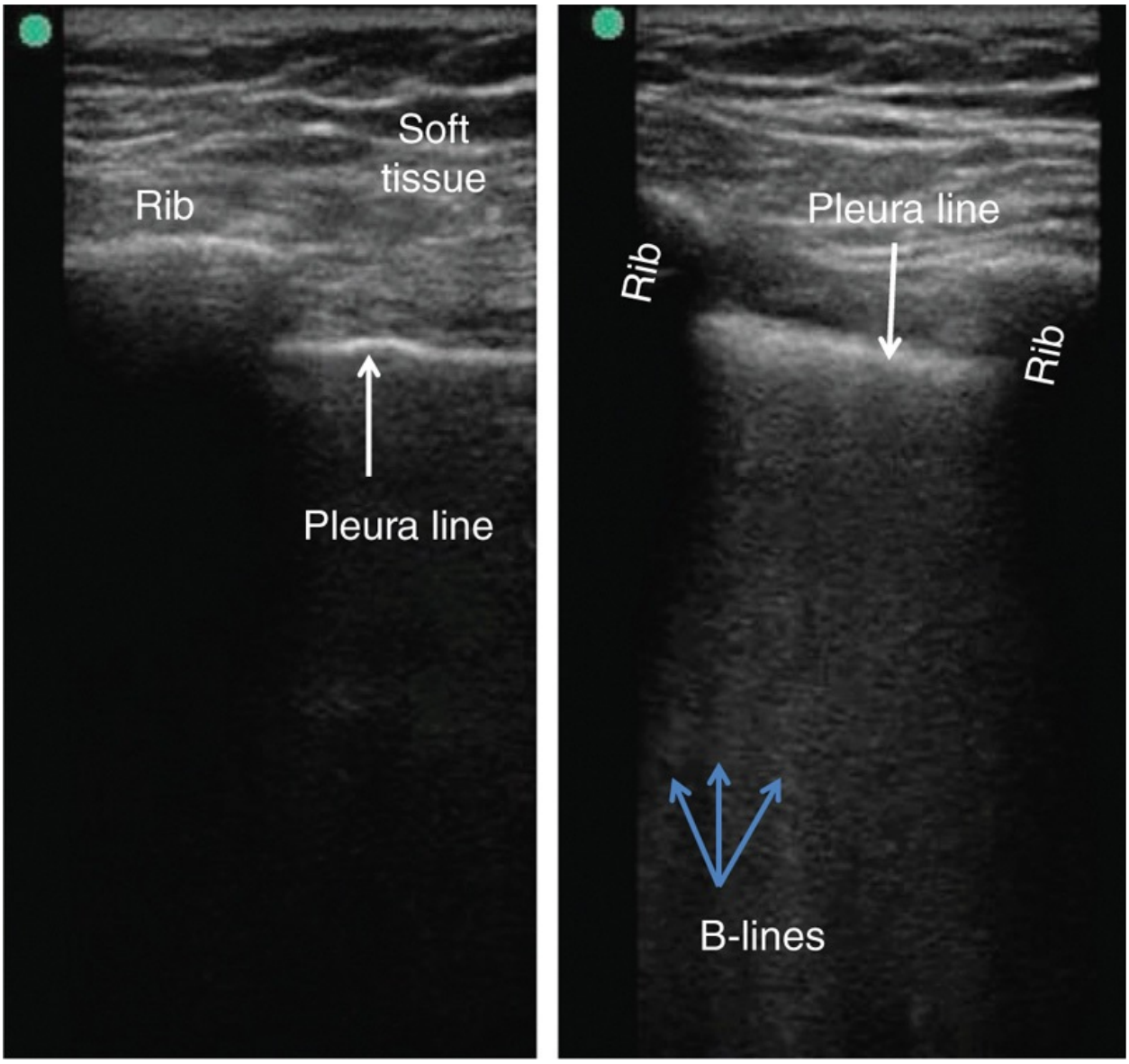


FIGURE 51.6 Normal pleural line with lung sliding imaged with linear array transducer.

A-Lines

Sonographic A-lines are visualized as hyperechoic lines perpendicular to the US beam (**Figure 51.7**). They are reverberation artifacts that arise when the US beam reflects off the pleura; therefore, these lines are below the pleural line. There is equal distance between the transducer, pleural line, and each subsequent A-line. A-lines can be thought of as “air” lines, but the air can be either in the pleural space or in the lung parenchyma. The presence of sliding lung determines that the air is in the lung parenchyma and its absence indicates that the air may be in the pleural space (ie, pneumothorax). Hence, the presence of

A-lines and sliding lung means the lungs are normal at that particular site. The standard view of the upper rib, pleural line, and lower rib has the appearance of a bat flying out of the screen, and hence is called a *batwing sign* (**Figures 51.6 and 51.7**).[10,28]

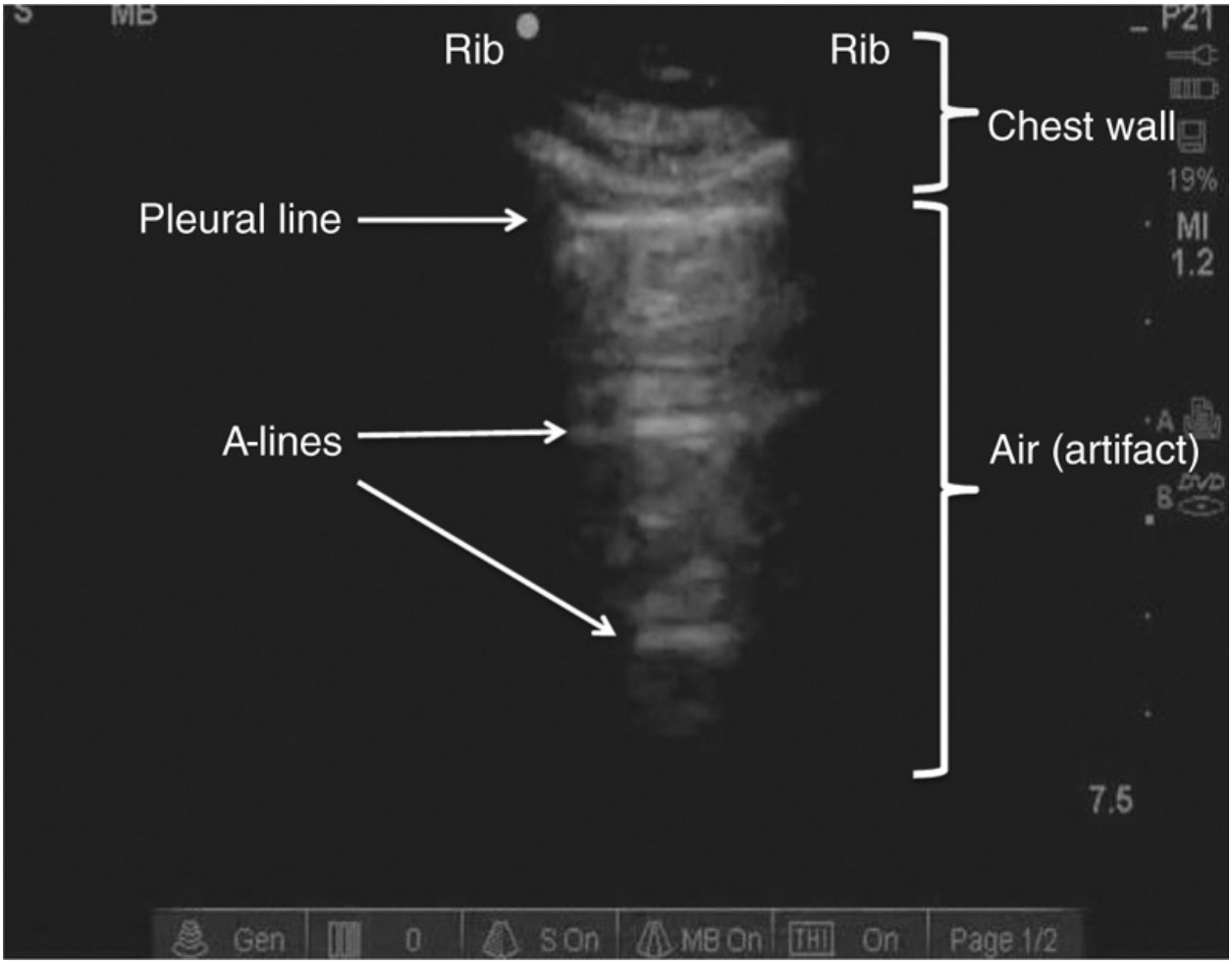


FIGURE 51.7 Standard view of A-line from anterior lung zone imaged with phased array transducer.

B-Lines

B-lines are vertical raylike projections that start from the pleural line and continue to the bottom of the screen (**Figure 51.8**). They are also known as comet tails or lung rockets because of their sonographic similarity with comets and rockets. B-lines follow the motion of the lung sliding and efface the normal A-lines at the point of their intersection. B-lines are generated when the interlobular septa become abnormally thickened with fluid or when the alveoli become abnormally filled with fluid, blood, or purulent material. Although

isolated B-lines in any given region may be a normal finding, seeing more than three lines is considered abnormal. It is not uncommon to find B-lines at the lung bases in the hospitalized patient; however, the presence of >3 B-lines in the anterior lung zones is abnormal. The focal location of B-lines may be suggestive of local infiltration (eg, focal pneumonia). A generalized B-line pattern represents an interstitial syndrome such as pulmonary edema, pneumonia, acute respiratory distress syndrome (ARDS), or interstitial lung disease.[10,23,24]

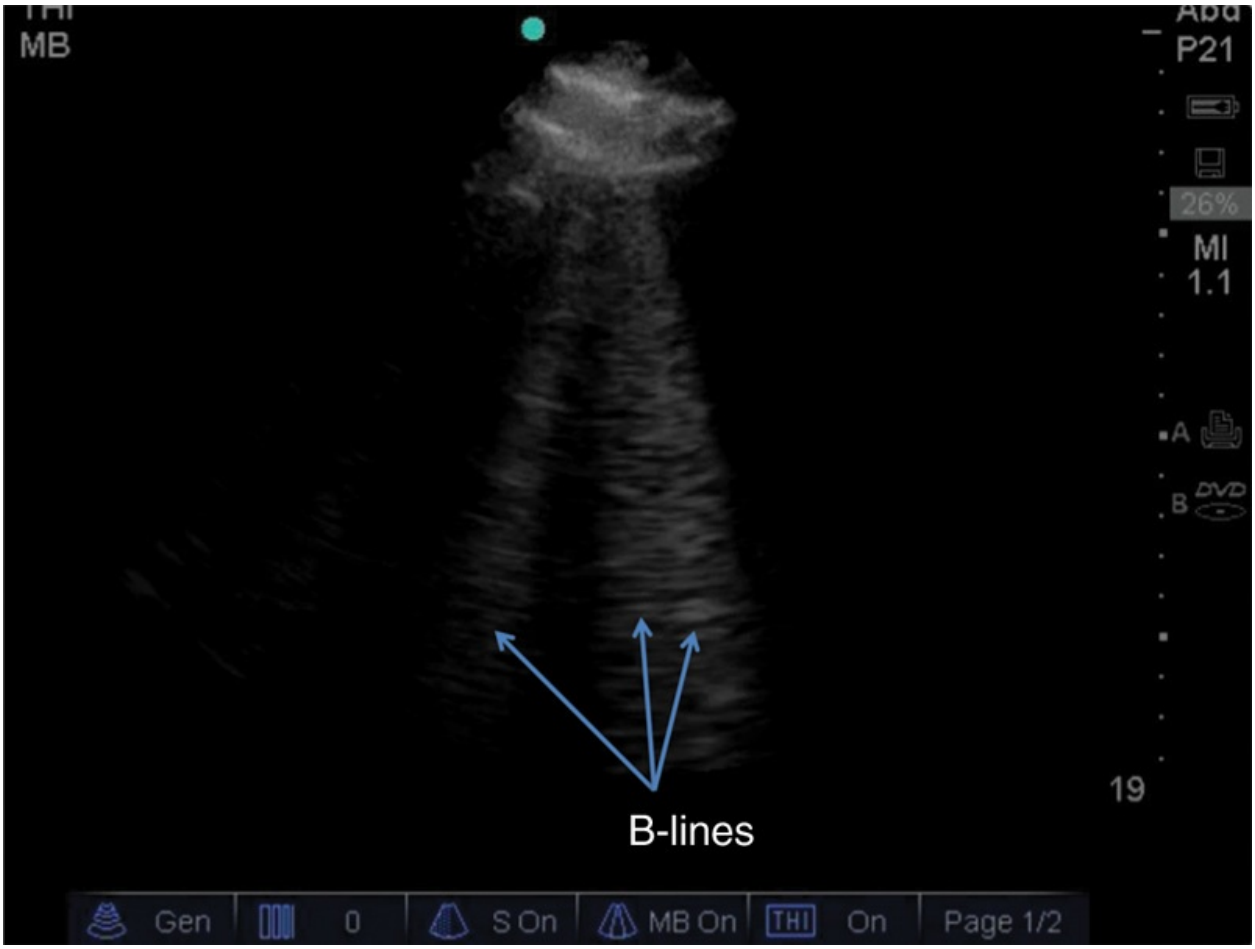


FIGURE 51.8 B-line pattern.

Alveolar Consolidation

When the alveoli become devoid of air and are filled with pus, fluid, or blood, the lungs develop echogenicity. Consolidated lung adjacent to the pleura will permit the transmission of US waves. In the circumstance of lung consolidation, the lung appears sonographically similar to the liver; therefore, the term “lung

hepatization" has been descriptively utilized.[10,27] In addition, sonographic air bronchograms or punctate hyperechoic foci within the consolidated lung may be visualized, which indicates that air still remains in the bronchioles. The presence of mobile or dynamic air bronchograms has high specificity (94%) for the diagnosis of pneumonia, as compared to static air bronchograms, which is seen in resorptive atelectasis.[29] **Figure 51.9** shows an example of a patient with lung consolidation as a result of severe pneumonia with parapneumonic effusion.

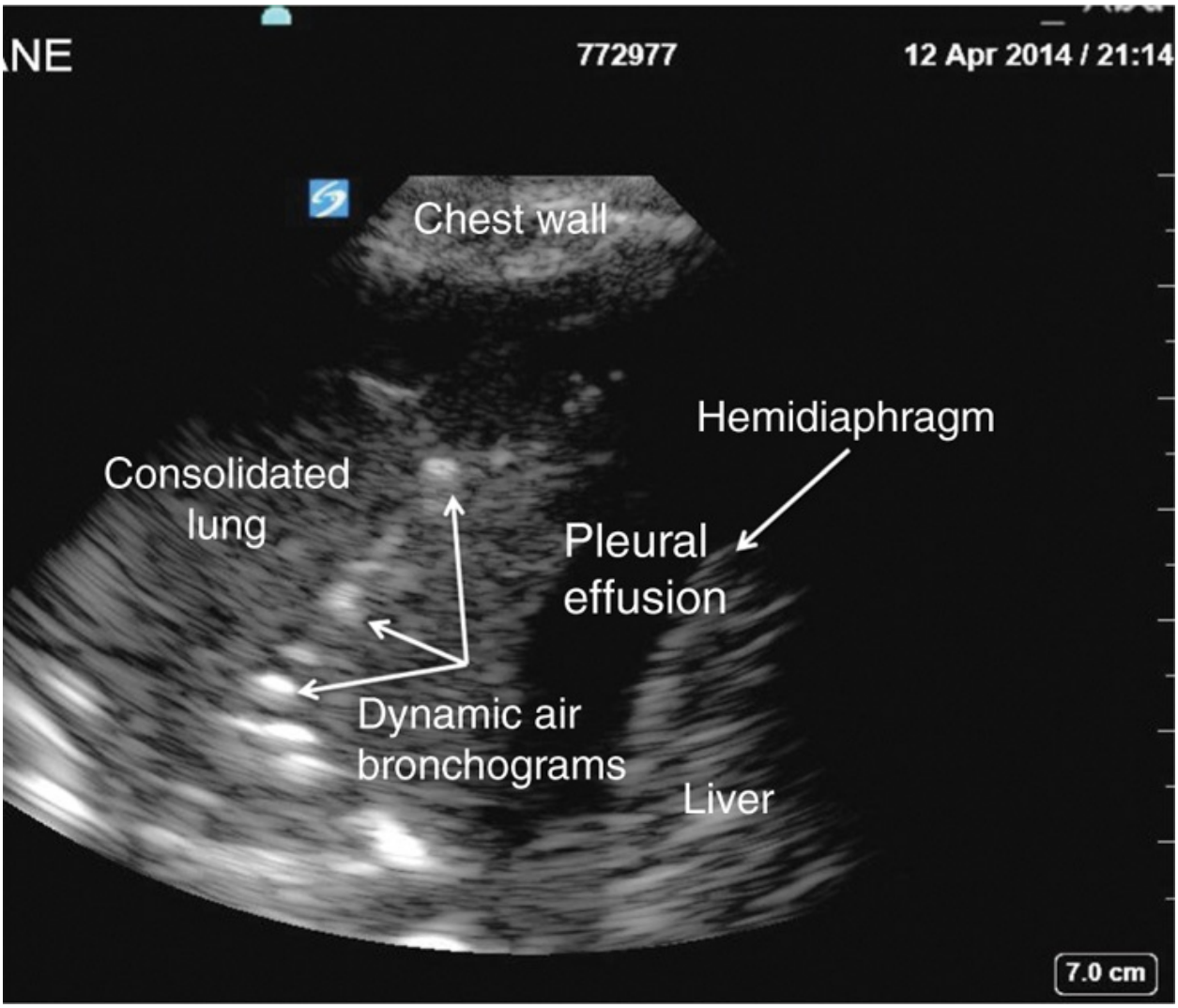


FIGURE 51.9 Lung consolidation with sonographic air bronchograms.

Pleural Effusion

One of the most important uses of US in thoracic pathology is the ability to detect, quantify, and characterize pleural effusion. Pleural USG is superior to

standard upright chest radiography and supine chest radiography for detecting pleural effusions.[30] On a portable chest radiograph in the patient in the CCU, both lung consolidation and pleural effusion will appear “white.” POCUS is particularly helpful in these patients, because it will help differentiate the two. Pleural fluid is typically anechoic, whereas consolidated or atelectatic lung is echogenic. It is important to also distinguish pleural effusion from pericardial effusion in such patients. In the PLAX view, pleural effusions lie posterior to the descending aorta and pericardial effusions anterior and within the pericardium. In addition, scanning the lateral or posterior lung zone (**Figure 51.4**) further helps differentiate the two effusions. The use of US also allows for the identification of a safe puncture site to perform thoracentesis, even in mechanically ventilated patients in the CCU.[8] Before thoracentesis, ensure the three cardinal features of a pleural effusion: an anechoic space; anatomic boundaries of chest wall, diaphragm and lung; and dynamic changes of the atelectatic lung and diaphragm related to respiration and cardiac motion.[28]

Pleural USG can further help characterize the pleural effusion and can even identify septations within it. Simple anechoic fluid suggests a noncomplicated pleural effusion, which may or may not be a transudate. The *flapping lung* or *jellyfish sign* is the oscillating movement of a collapsed lung in a pleural effusion (**Figure 51.10**). Strands of echogenic floating matter suggest complex fluid; this is called the *plankton sign*.[31] Septated or loculated effusions imply complicated effusions that require sampling of the fluid and usually warrant a chest tube placement or surgical drainage. **Figure 51.11A** demonstrates the multiple septations within the pleural fluid of a patient with pneumonia and empyema. This patient was a poor surgical candidate, and so was treated with a small-bore chest tube and intrapleural alteplase and deoxyribonuclease (DNase). Similarly, pleural effusions can demonstrate the *hematocrit sign*, where an echogenic or highly cellular effusion (ie, blood) has gravity-dependent fading of echogenicity.[31] **Figure 51.11B** is that of a patient with trauma who presented with a hemothorax.

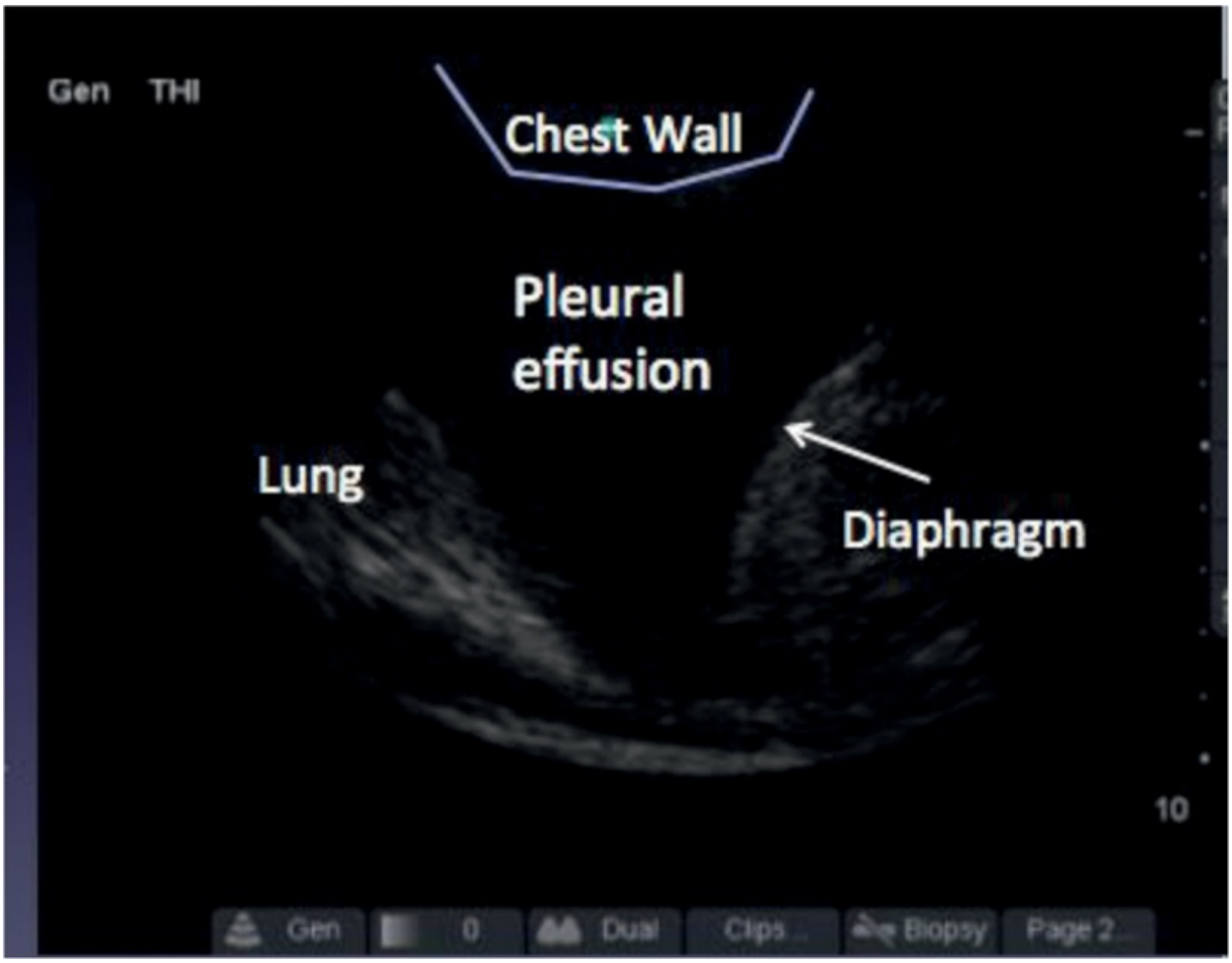


FIGURE 51.10 Moderate pleural effusion with flapping lung.

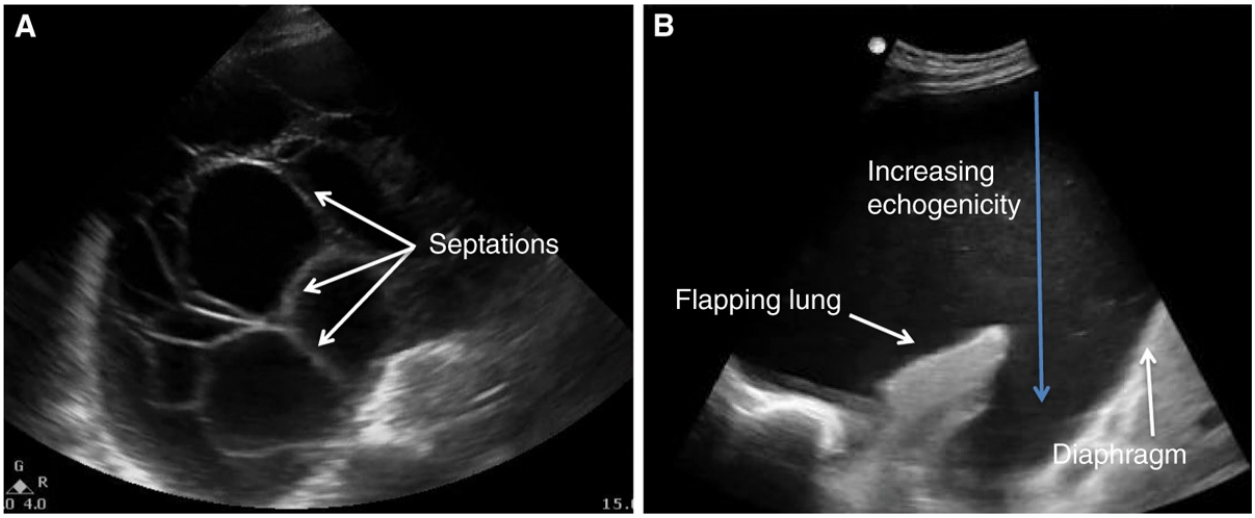


FIGURE 51.11 A, Empyema with thickened pleura and multiple septations within pleural effusion. B, Hemothorax with increasing echogenicity of fluid in the pleural space.

CLINICAL SCENARIOS ENCOUNTERED IN THE CCU

Detection of Pneumothorax

Pneumothorax can occur spontaneously in the CCU and is potentially fatal. Patients on mechanical ventilation with underlying emphysema or those undergoing central line placement are at risk for pneumothorax. Lung ultrasonography carries a >95% sensitivity in the detection of pneumothorax.[32] The examination requires, on an average, 2 to 3 minutes. The transducer is placed longitudinally in the mid-clavicular line at the level of the second to third intercostal space. Sequential movement of the transducer inferior and lateral across multiple rib interspaces will allow for a comprehensive examination of the pleural space.[27] The presence of lung sliding is characteristic of normal visceral and parietal pleural layers and carries a 100% negative predictive value in the diagnosis of pneumothorax.[26] In contrast to normal lung, when air is trapped between the visceral and parietal pleural layers, lung sliding will not be detected. Nevertheless, absence of lung sliding may not always be due to the presence of pneumothorax because it has also been observed in massive atelectasis, ARDS, pleural adhesions, and severe lung fibrosis. The presence of B-lines or lung pulse also rules out pneumothorax.[24,33]

In the occasion that lung sliding is difficult to visualize, additional information is obtained with the assistance of M-mode analysis. Characteristically, M-mode analysis of normal lung tissue demonstrates the *seashore sign*, a characteristic linear wave pattern representing the motionless chest wall, and below the pleural line a granular pattern represents normal lung motion (**Figure 51.12**A). If present, it confirms the presence of lung sliding and therefore the absence of pneumothorax. When there is air in the pleural space, this morphology is replaced on M-mode imaging by parallel linear lines called the *stratosphere sign* or *bar code sign* (**Figure 51.12**B*)*.[32] The visualization of the *lung point* may also be used in the diagnosis of pneumothorax, having a specificity of 100%. The lung point represents the transition point between normal lung sliding and to an area of absent lung sliding (**Figure 51.13**).[25] Lung point is helpful to also quantify how large a pneumothorax is and helps with procedural guidance for chest tube placement. One approach during central line placement would be to check for lung sliding before and after line placement to quickly rule out a pneumothorax. These concepts can be applied within seconds to the patient in the CCU who is quickly decompensating to rule out pneumothorax.

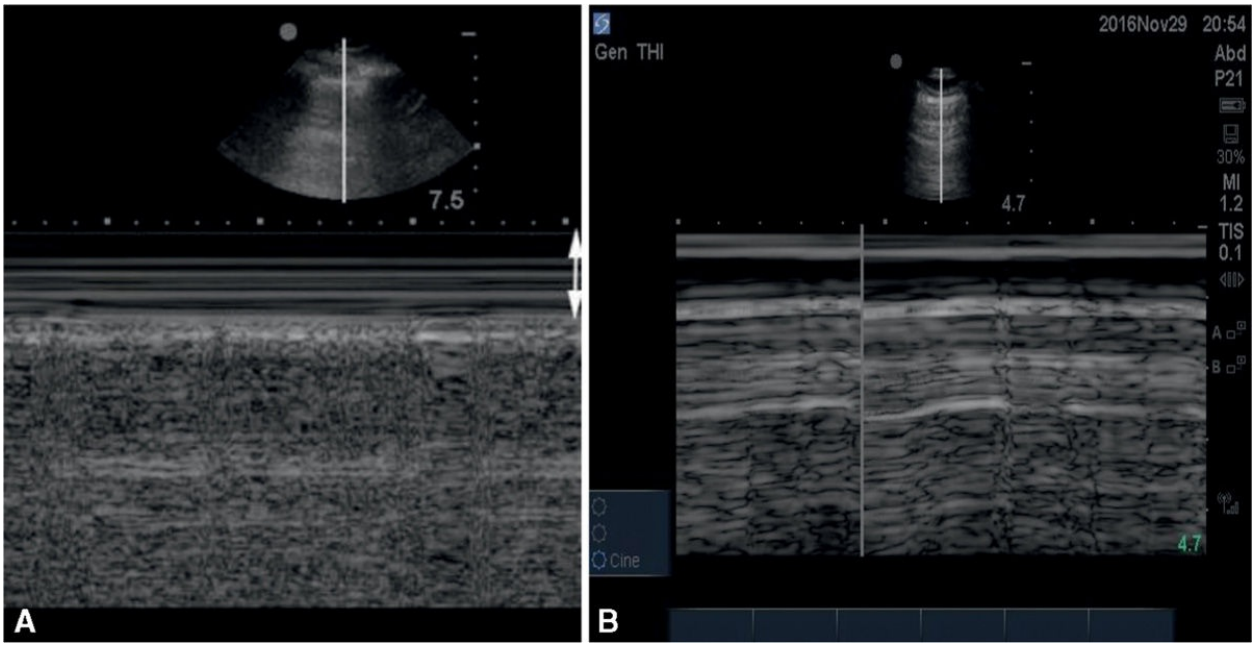


FIGURE 51.12 A, Seashore sign. B, Stratosphere or bar code sign.

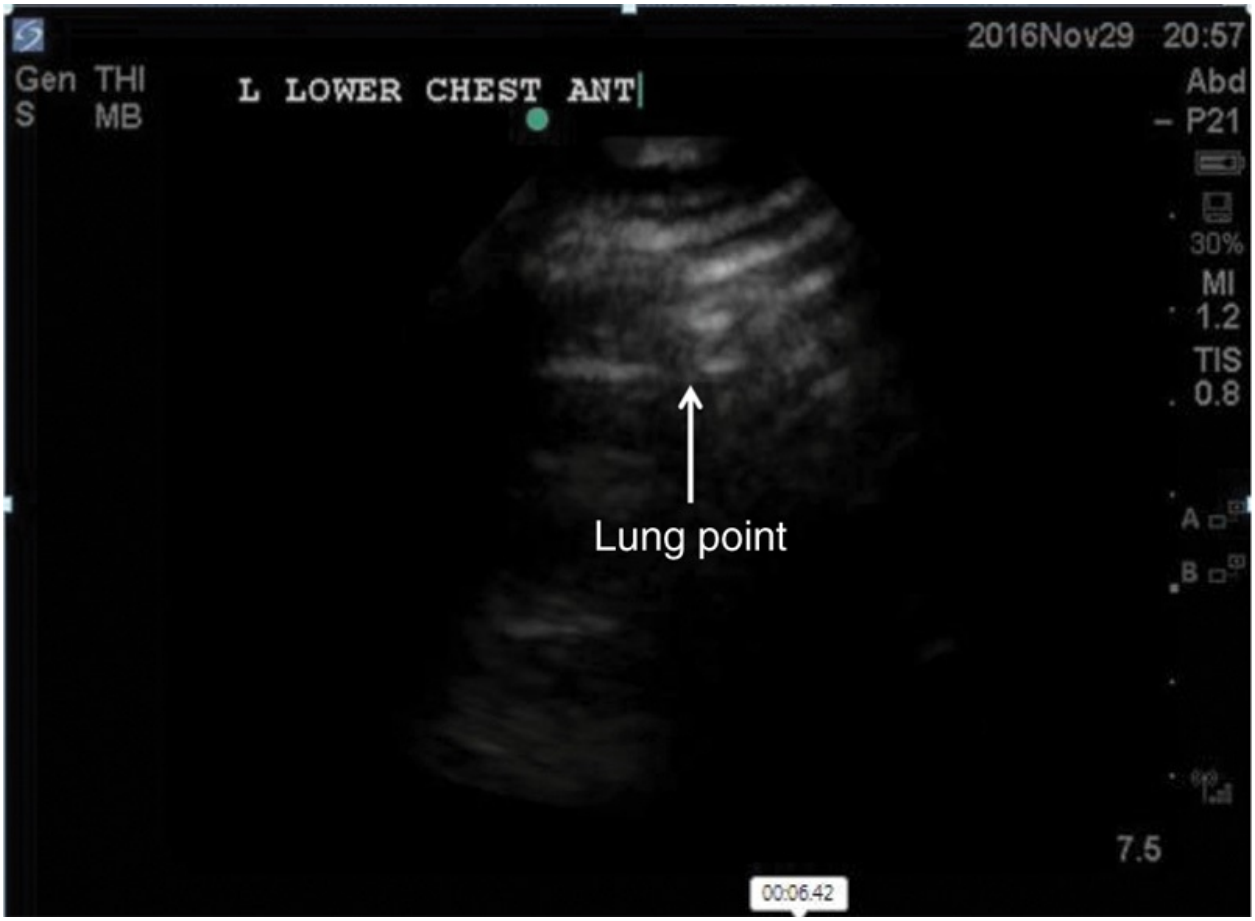


FIGURE 51.13 Lung point.

Detection of Lung Alveolar-Interstitial Syndrome

Alveolar-interstitial syndrome is a common entity in the CCU, caused by a variety of conditions, including acute pulmonary edema, ARDS, and interstitial pneumonias. B-lines 7 mm apart, called *B-7 lines*, correspond to edematous or thickened interlobular septa and extravascular lung volume (similar to Kerley B-lines on a chest radiograph). Lichtenstein also described *B-3 lines*, which are B-lines that are 3 mm apart and more confluent, indicating alveolar edema or an alveolar process such as pneumonia. The more B-lines that are present anteriorly, the lower the air to fluid and the more severe the lung pathology.

LUS is very sensitive in detecting early pulmonary vascular congestion, much more than a chest X-ray. In an acutely dyspneic patient, the detection of diffuse B-lines allows the intensivist to immediately differentiate acute pulmonary edema from chronic obstructive pulmonary disease (COPD).[23] Even while administering fluids in the CCU, the appearance of new B-lines corresponds to early pulmonary edema and correlates to elevated pulmonary artery occlusion pressures (>18 mm Hg).[14] Similarly, while administering diuretics in patients with acute pulmonary edema, one can assess for reduction in the number of B-lines and also reduction in the volume of pleural effusions.

Differentiating Between Types of Lung Alveolar-Interstitial Syndrome

Diffuse B-lines suggest an interstitial pattern, and the presence of a diffuse B-line pattern in both lungs suggests a diffuse alveolar interstitial syndrome such as pulmonary edema, pulmonary fibrosis, or ARDS. The presence of a smooth pleural line may be seen in pulmonary edema, whereas with lung fibrosis, an irregular or "lumpy bumpy" pleural line may be visualized with a high-frequency linear array transducer. In ARDS, subpleural consolidation may be visualized below the pleural line with sparing of certain areas.[28] **Table 51.6** summarizes the main characteristics that can be used to distinguish these entities.

TABLE 51.6 Differentiating causes of the interstitial syndrome

	ACUTE PULMONARY EDEMA	CHRONIC HEART FAILURE	ARDS	PULMONARY FIBROSIS
Clinical setting	Acute	Chronic	Acute	Chronic

B-lines number	++++	+/++/+++	++++	+/++/+++
B-lines distribution	Multiple, diffuse, bilateral	Multiple, diffuse, bilateral following dependent regions	Non-homogenous distribution, spared areas	More frequently posterior at lung bases
Other Lung US signs	Small bilateral pleural effusions	Bilateral pleural effusions	Subpleural consolidations, possible effusion	Irregular pleural line
Echo	Abnormal	Abnormal	Likely normal	Likely normal

Assessing Diaphragmatic Function

The diaphragm is hyperechoic and easily visualized by USG. Diaphragmatic function can be quickly assessed in the patient in the CCU or the patient post cardiac surgery with acute respiratory failure or inability to wean from mechanical ventilation, obviating the need for fluoroscopy. The technique involves scanning the lateral lung zone, along the anterior or mid-axillary line, and identifying the liver or spleen. M-mode imaging can be utilized to obtain a quantitative measure of diaphragmatic excursion. Normal diaphragmatic excursion for a male in quiet breathing is 1.8 and 7.5 cm during deep breathing. Sonographically detected diaphragmatic dysfunction, defined as <10 mm or paradoxical motion, can identify patients who are difficult to wean. **Figure 51.14** represents 2D and M-mode imaging of the left hemidiaphragm in a patient with amyotrophic lateral sclerosis who presented with Takotsubo cardiomyopathy and acute respiratory failure.

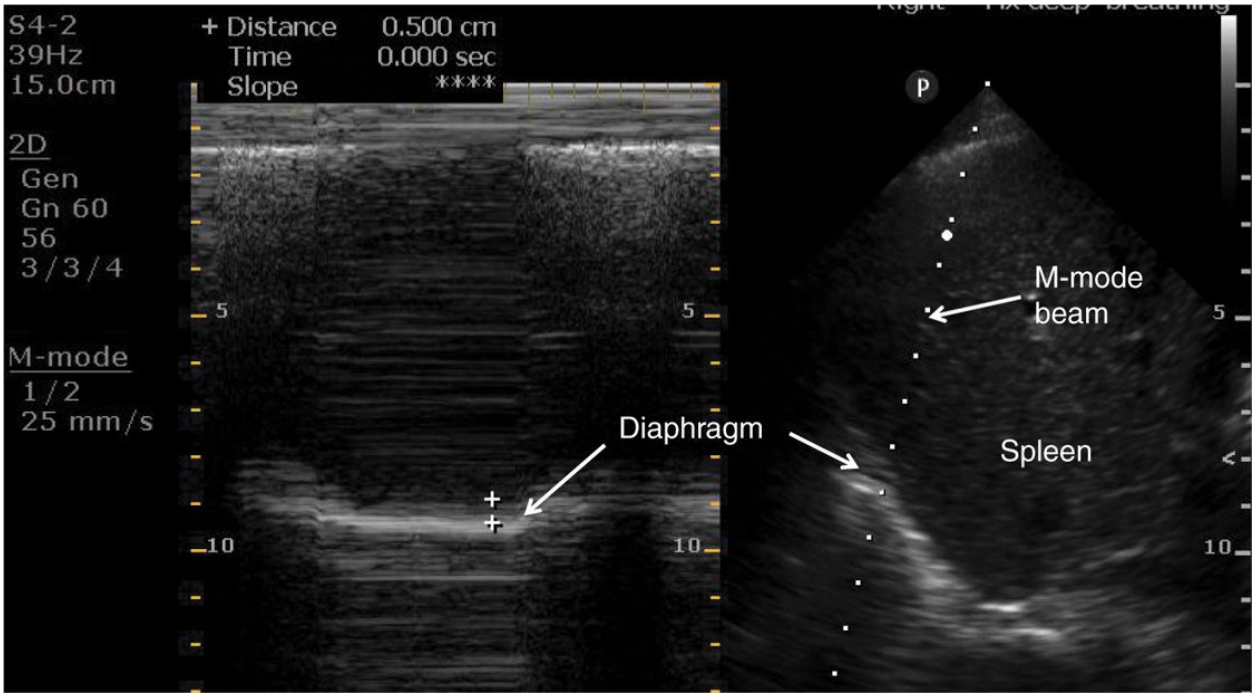


FIGURE 51.14 Decreased diaphragmatic excursion on M-mode.

Rapid Assessment of the Acutely Decompensating Patient in the CCU

Using the concepts described in this section, the CCU practitioner can rapidly assess the patient with acute respiratory failure and find the etiology of the decompensation. If there is an A-line pattern and absence of lung sliding, then pneumothorax has to be ruled out. Presence of diffuse B-lines and pleural effusions bilaterally detected on POCUS points to a pulmonary edema picture. Unilateral B-lines or a consolidation pattern can be seen with pneumonia. If lung sliding is present with a normal A-line pattern in all the lung zones, then the etiology of the respiratory decompensation has to be either due to airways disease (ie, asthma/COPD) or pulmonary vascular disease (ie, PE). Combining thoracic US with GDE can detect findings such as right ventricular (RV) strain or clot-in-transit, leading to a diagnosis of acute PE.[34]

Lichtenstein summarized these concepts in what he called the BLUE protocol, a simple, goal-directed LUS examination combined with a DVT study for acute respiratory failure. Blinded investigators scanned the four BLUE points (**Figure 51.5**) and performed compression US of the lower extremities, following a standardized algorithm (**Figure 51.15**). They were able to rapidly make an accurate diagnosis in 90% of the cases. In addition, the profiles described had very good sensitivity and excellent specificity to diagnose the conditions

correlating with each profile.[10] The concepts of thoracic USG can be easily learned by house staff and other clinicians and utilized to make accurate diagnosis in patients presenting with dyspnea.[35]

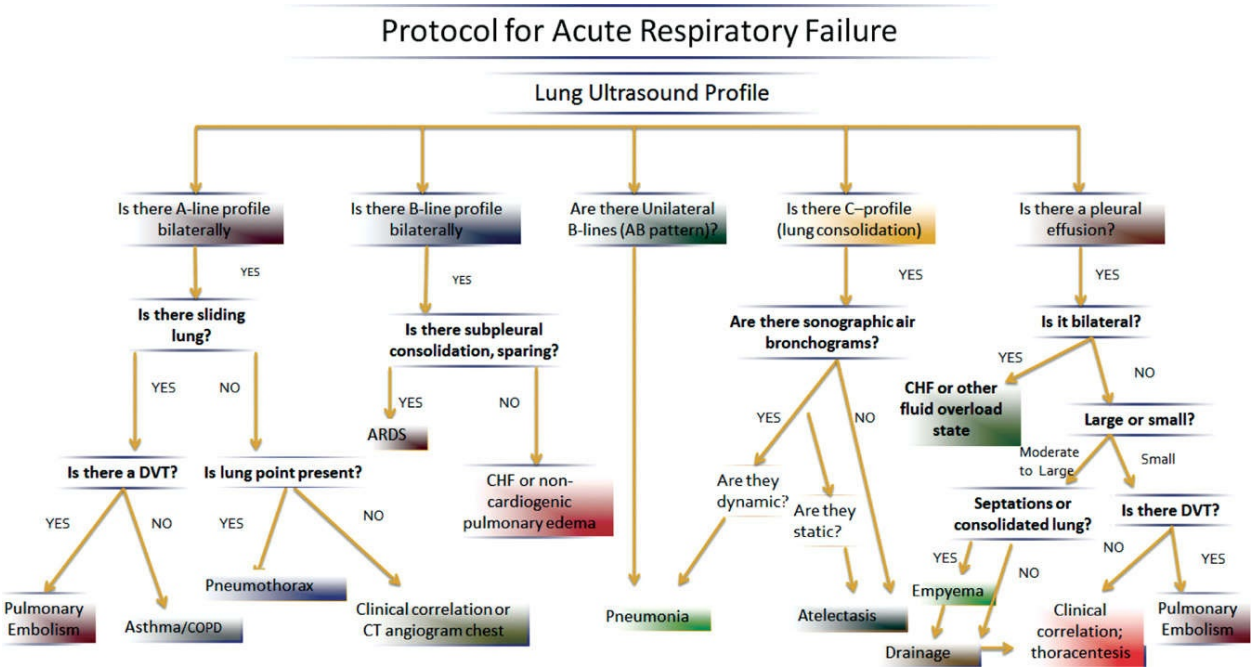


FIGURE 51.15 Lung ultrasound profiles and algorithm for the evaluation of acute respiratory failure. ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DVT, deep vein thrombosis. (Modified from Lichenstein D. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest*. 2008;134: 117-125.)

FUNDAMENTALS OF ULTRASONOGRAPHY IN UNDIFFERENTIATED SHOCK: MULTIORGAN POINT-OF-CARE ULTRASONOGRAPHY

Shock is a commonly encountered condition in the CCU but is not always associated with cardiac causes. Physical examination and laboratory parameters, along with multiorgan POCUS, guide the evaluation and management. POCUS techniques involving the heart, lungs, abdomen, and vasculature are performed on the basis of the appropriate clinical setting in an attempt to identify the cause of hypotension and optimize management. The goal-directed evaluation of a new, unexpected, or unexplained shock state in a patient in the CCU requires a

structured approach that will diagnose or rule out reversible causes such as cardiac tamponade, tension pneumothorax, pulmonary embolus, ruptured aortic aneurysm, and intra-abdominal hemorrhage.

GDE allows the intensivist to assess for RV or left ventricular (LV) failure, pericardial effusion, major valvular failure, and fluid responsiveness. The statement on training in CCUS makes the recommendation that training in critical care includes training in basic critical care echocardiography.[1–3] GDE can be learned and performed well by non-cardiologists with adequate training.[36–38] Combining GDE with sonography of other organs (multiorgan or whole-body USG) adds to the diagnostic yield when evaluating the patient in shock.[4,13] One can perform a goal-directed multiorgan POCUS examination in an efficient and systematic way to discern the etiology of shock:

1. Basic critical care echocardiography to evaluate LV and RV function; rule out tamponade and valvular failure
   a. PLAX, parasternal short-axis (PSAX), apical four-chamber, and SC views
2. IVC imaging to assess volume status in the setting of hypovolemia or sepsis
3. Thoracic US to rule out pneumothorax, hemothorax
4. Limited abdominal examination
   a. Right and left flank to rule out hemoperitoneum
   b. Abdominal aorta to evaluate for dissection
   c. Kidneys and bladder to rule out hydronephrosis in the setting of sepsis or renal failure
5. Compression US of lower extremities to evaluate for DVT

A systematic approach to the patient with shock in the CCU also employs the following questions while performing POCUS[22]:

1. Is there an imminently life-threatening cause of shock?
2. Is there evidence of pump failure: LV or RV failure?
3. Is the shock state likely to be fluid responsive?
4. Is there more than one cause for the shock state?
5. Is it noncardiac in origin?
6. Is there evidence of life-threatening hemorrhage?

Figure 51.16 illustrates an algorithmic approach to the patient in the CCU who is hypotensive. Many POCUS protocols exist for the evaluation of shock.

Essentially, they all incorporate multiorgan POCUS to evaluate the etiology of shock. **Table 51.7** summarizes a few of these protocols and the organs that are assessed.[39–41] Further discussions on cardiac etiologies of shock are found in other sections of this textbook.

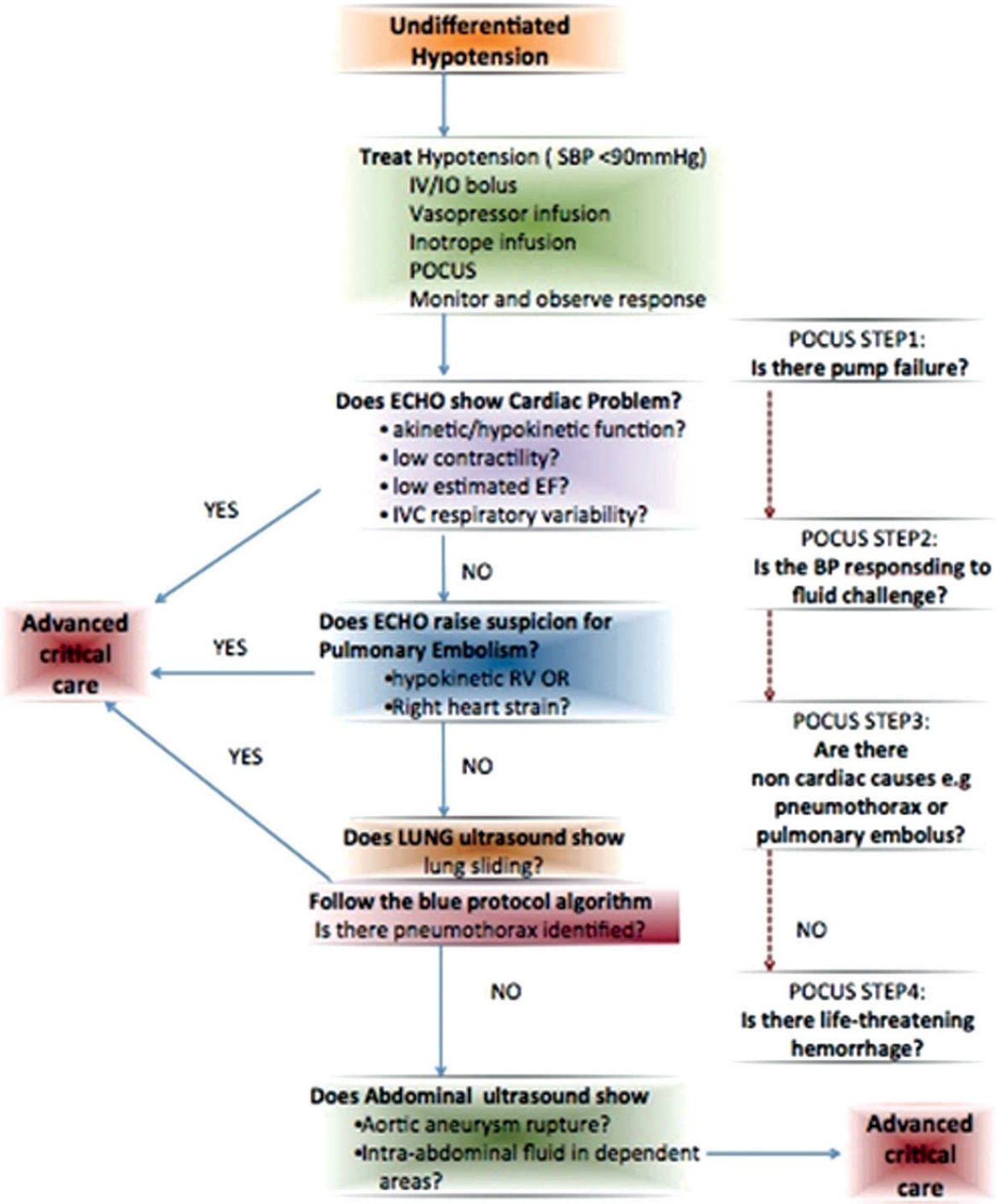


FIGURE 51.16 Approach to undifferentiated shock. BP, blood pressure; EF, ejection fraction; IO, intraosseous; IV, intravenous; IVC, inferior vena cava; POCUS, point-of-care ultrasonogaphy; RV, right ventricle; SBP, systolic blood pressure.

TABLE 51.7 Standardized POCUS Protocols in the Evaluation of Shock

NAME	PROBE LANDMARKS	VIEWS/STRUCTURES	EVALUATION GOALS
RUSH examination *R*apid *U*ltrasound in *SH*ock	PLAX/PSAX A4C/SC views SC Neck Right flank/RUQ Left flank/LUQ Suprapubic Anterior chest Chest/abdomen Femoral, popliteal veins	LV, RV, valves, pericardium IVC IJV Hepatorenal, splenorenal recess Splenorenal recess pelvis (FAST) Lung/pleura Aortic slide view Limited DVT study	**"Pump"**—LV failure, RV strain from PE, tamponade **"Tank"**—IVC and IJV collapsibility to evaluate volume status Hemoperitoneum, hemothorax, ascites Pneumothorax and pulmonary edema **"Pipes"**—ruptured aortic aneurysm, DVT/PE DVT/PE
EFAST examination *E*xtended *F*ocused *A*ssessment of *S*onography in *T*rauma	Anterior chest Subxiphoid Right flank/RUQ Left flank/LUQ Suprapubic	Lung/pleura SC cardiac Hepatorenal, splenorenal recess Pleural space Retrovesicular	Pneumothorax, pulmonary edema Pericardial tamponade Hemoperitoneum Splenic rupture Hemothorax Free fluid/pelvic hemorrhage
FALLS *F*luid *A*dministration *L*imited by *L*ung *S*onography	PLAX/PSAX/A4C/SC Lung US (BLUE protocol)	Basic cardiac views Lung/pleura	Rules out tamponade and PE Rules out pneumothorax Determine A-line vs B-line profile A-line profile—gives fluids until improvement or B-line appears (points to septic or distributive shock) B-line profile—suggests cardiogenic shock

A4C, apical four chamber; BLUE, bedside lung ultrasound in emergency; DVT, deep vein thromobosis;, EFAST, Extended Focused Assessment with Sonography in Trauma; FAST, Focused Assessment with Sonography in Trauma; IVC, inferior vena cava; IJV, internal jugular vein; LUQ, left upper quadrant; LV, left ventricle; PE, pulmonary embolism; POCUS, point-of-care ultrasonography; PLAX, parasternal long axis; PSAX, parasternal short axis; RUQ; right upper quadrant; RV, right ventricle; SC, subcostal; US, ultrasound.

INFERIOR VENA CAVA IMAGING: EVALUATING FLUID STATUS AND FLUID RESPONSIVENESS IN SHOCK

The IVC caliber is altered by respiration, blood volume, and right heart failure. The IVC can be used to assess intravascular volume status. Fluid responsiveness is by definition an increase in cardiac output (generally >15%) after an adequate volume challenge. Interpretation of IVC size and variability is dependent on whether a patient is spontaneously breathing or on mechanical ventilation. In the

spontaneously breathing patient, IVC imaging helps estimate right atrium (RA) pressures (ie, as a “noninvasive” central venous pressure [CVP] reading). In the patient on mechanical ventilation in the CCU, respiratory variation of the IVC can predict fluid responsiveness, in the appropriate settings.

TECHNIQUE

Multiple ways have been described to image the IVC. With the patient in supine position (and knees bent if possible), the IVC can be visualized from the SC cardiac view by placing the phased array transducer in the SC space with the marker facing the patient’s head. Alternatively, obtain an SC four-chamber view by positioning the probe flat just below the xiphoid, with the probe marker facing the patient’s left side (**Figure 51.17**). Identify the RA at the top of the screen and track it while turning the probe counterclockwise and slightly perpendicular to the body such that the marker is facing the patient’s head. The IVC will appear within the liver with a hepatic vein joining it and emptying into the RA. **Table 51.8** delineates basic characteristics used to identify the IVC and differentiate it from the aorta, which runs alongside the IVC. The IVC can be measured using 2D imaging or via M-mode imaging using the caliper feature. The “sniff” maneuver can be used in spontaneously breathing patients to estimate RA pressures. In patients on mechanical ventilation, the maximal and minimal diameter can be calculated to assess for respiratory variability.

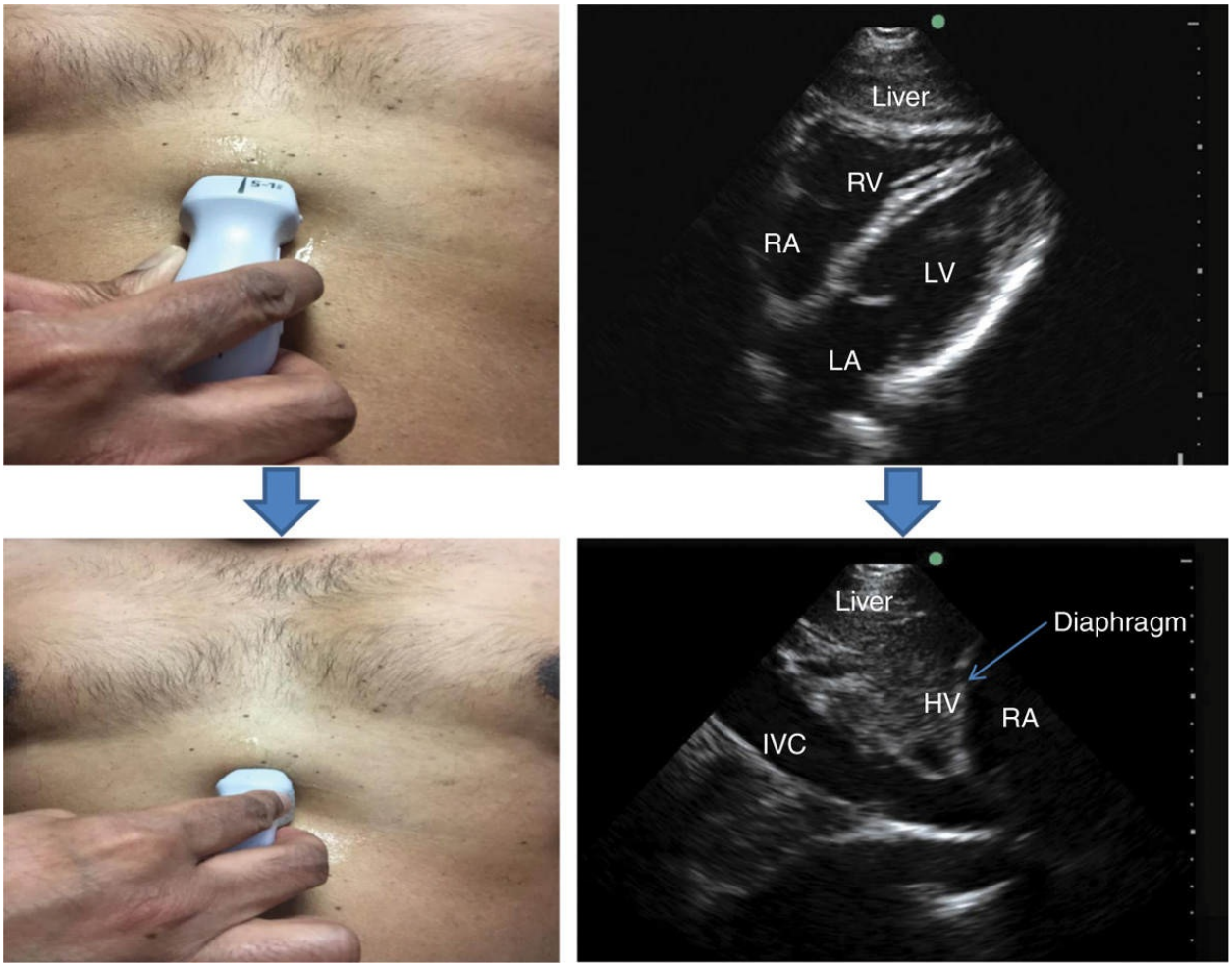


FIGURE 51.17 Technique for IVC image acquisition. HV, hepatic vein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

TABLE 51.8 Distinguishing IVC from Aorta

	IVC	AORTA
Direction	Goes through the liver	Goes through the liver
Relation to heart	Merges with right atrium	Continues down the heart
Flow	Continuous, changes with respiration	Pulsatile
Walls	Thin-walled, may not be visible	Thick-walled, hyperechoic
Respiratory variations	May be present	No
Collateral vessels	Sub-hepatic veins merge with the IVC	Not visible from this approach

IVC, inferior vena cava.

SPONTANEOUSLY BREATHING PATIENT

In the spontaneously breathing patient, IVC size and the degree of collapse correlate to CVP. An IVC >2 cm in diameter, with inspiratory collapse <50% approximates a CVP of 15 cm H_2O. When the IVC is narrow (<1.5 cm) and collapses a large amount (>50%), the CVP will be low and a hypovolemic (dehydration, hemorrhage) or distributive (sepsis, anaphylaxis) cause of shock is likely (**Table 51.9**).[42] When the IVC is dilated (>3 cm) and non-collapsing, it usually indicates volume unresponsiveness unless the patient has right heart strain. On the other hand, when the IVC is extremely small or a "virtual IVC," it likely indicates that the patient is fluid depleted (**Table 51.10**).

TABLE 51.9 IVC Size, Collapsibility, and Estimation of CVP in Spontaneously Breathing Patients

IVC DIAMETER (cm)	INSPIRATORY COLLAPSE (%)	CVP (mm Hg)
Normal: <2.1	>50	0–5 (mean 3)
IVC findings other	±	5–10 (mean 8)
High: >2.1	<50	10–20 (mean 15)

CVP, central venous pressure; IVC, inferior vena cava.

TABLE 51.10 IVC Variability and Fluid Responsiveness in Critically Ill Patients

EVALUATING FLUID STATUS VIA INFERIOR VENA CAVA SIZE AND VARIABILITY
Fluid responsiveness: clinically relevant increase in cardiac output (>15%) after a volume challenge

Spontaneously breathing patients
• Measure IVC size 2–3 cm from the right atrium using M-mode:
• Static:
  • <1 cm → likely volume depleted
  • >3 cm → sufficient volume status

Patients on mechanical ventilation (criteria) • On mechanical ventilation • Tidal volume >8 mL/kg ideal body weight • Passive on ventilator support (no spontaneous breaths) • Normal sinus rhythm
Patient is fluid responsive if: • (Maximum diameter–minimum diameter)/minimum diameter >18% OR

- (Maximum diameter–minimum diameter)/average diameter >12%

IVC, inferior vena cava.

MECHANICALLY VENTILATED PATIENT

Studies have shown that dynamic measures of fluid responsiveness (eg, IVC variation) are more reliable than static measures (eg, CVP).[43] During mechanical ventilation of a sedated or paralyzed patient, pleural and juxtacardiac pressures increase during inspiration, causing RA pressures to rise and decreasing filling of the right heart. This causes a reduction in RV stroke volume (SV) and less filling of the left ventricle, thus reducing LV SV several cardiac cycles later. These respiratory changes are exaggerated in the hypovolemic patient and these variations in SV can be used to predict fluid responsiveness.[22] Respiratory variation of the IVC diameter has been shown to accurately predict fluid responsiveness.[17,44] **Tables 51.9** and **51.10** summarize interpretation of IVC size and variation. **Figure 51.18** shows examples of measurement of IVC diameter and respiratory variability using M-mode. **Figure 51.19** show examples of small and dilated IVCs.

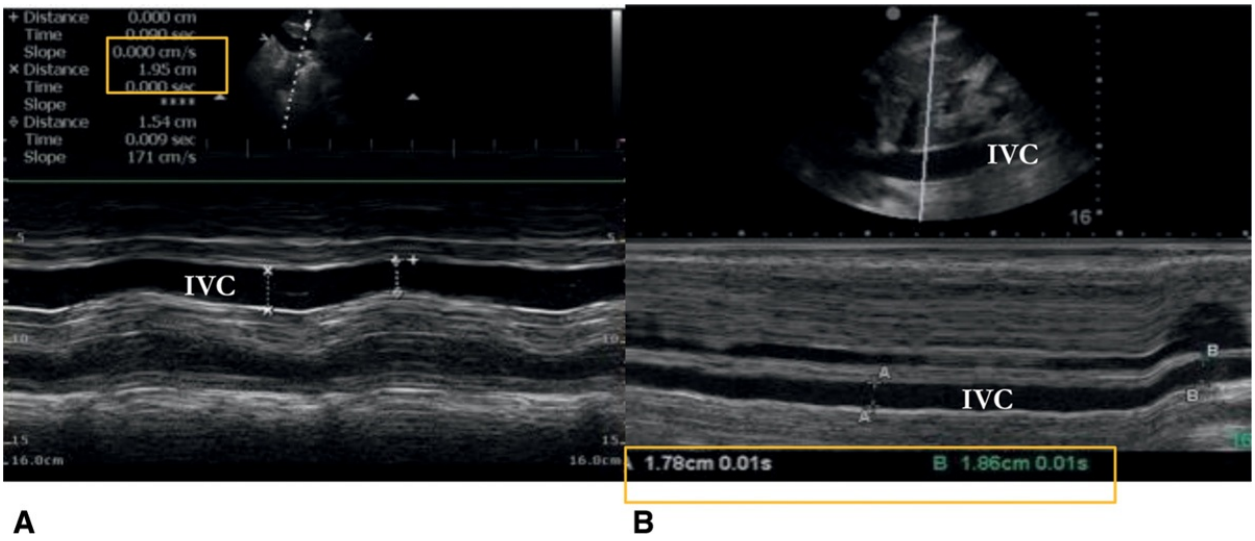


FIGURE 51.18 A, M-mode image showing respiratory variation of the IVC. B, M-mode image showing lack of respiratory variability of the IVC. IVC, inferior vena cava.

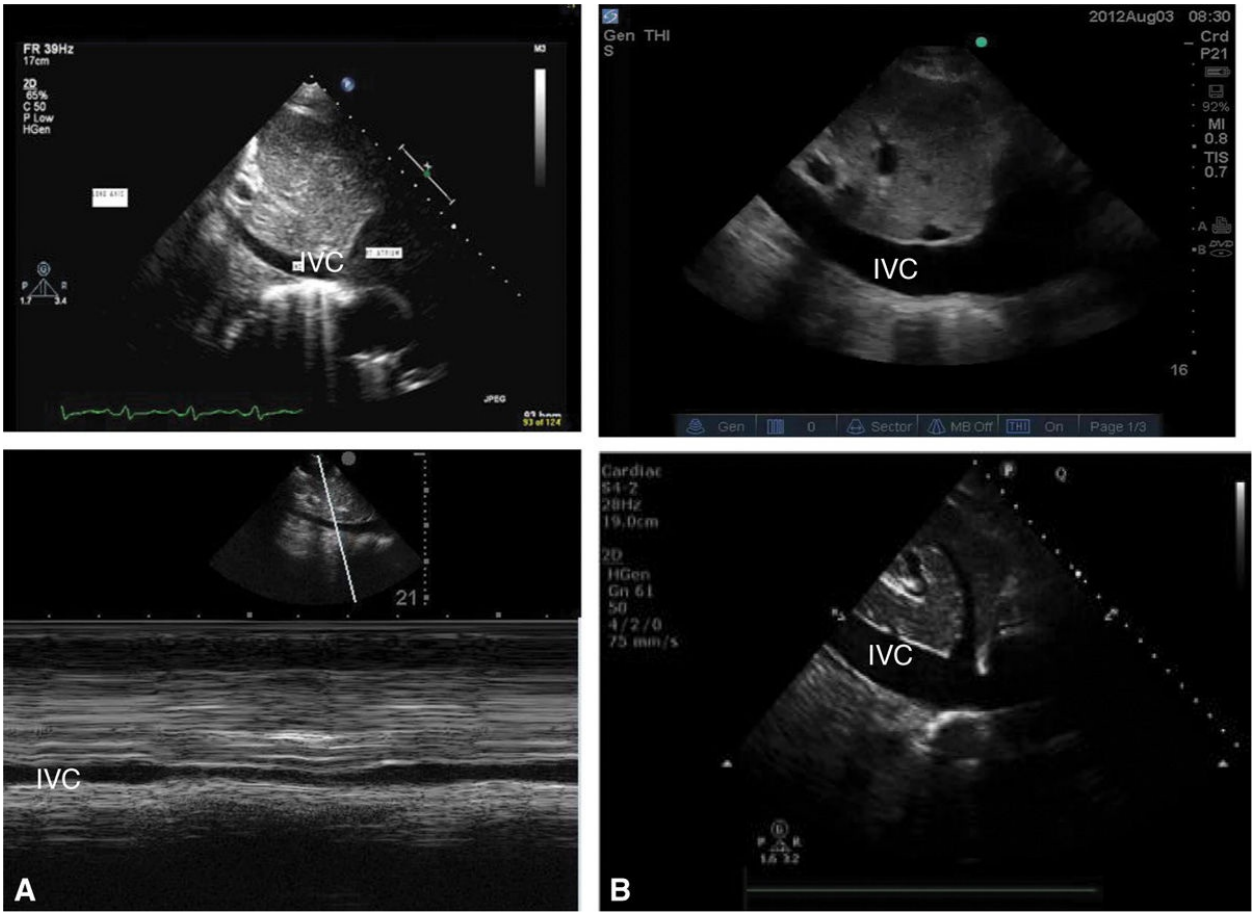


FIGURE 51.19 A, Small IVC. B, Dilated IVC. IVC, inferior vena cava.

FUNDAMENTALS OF ABDOMINAL ULTRASOUND IN CRITICAL ILLNESS

Abdominal USG has several applications in the evaluation of the critically ill patient in the CCU. Intraperitoneal or retroperitoneal bleeding may be the etiology of hemorrhagic shock in a patient who recently underwent a cardiac catheterization, an intra-aortic balloon pump placement, or an intravascular cooling catheter placement. Not uncommonly, patients get subjected to invasive procedures involving femoral venous or arterial sheath placement and are at risk for hemorrhage both during insertion and after removal. In addition, patients in the CCU are frequently on dual antiplatelet agents and anticoagulation, and are at high risk for intra-abdominal bleeding.

FOCUSED ASSESSMENT WITH SONOGRAPHY IN TRAUMA

EXAMINATION

The FAST examination has been demonstrated to have 90% sensitivity in the detection of intra-peritoneal free fluid.[12] An approximate volume of at least 200 mL of free fluid is required for the test to have high sensitivity. In other words, a smaller volume of free blood may not be demonstrated on initial FAST examination; therefore, repeat testing may be warranted.[7]

A curvilinear transducer or, alternatively, a low-frequency phased array transducer is used for the FAST examination. The duration of the examination averages <3 minutes and is best performed in the supine position. These windows used serve to conduct the sound wave to the three most dependent areas of the peritoneal cavity in the supine patient as well as to the costophrenic angles bilaterally. The fourth view provides a view of the heart and pericardium, typically obtained from the subxiphoid region. The order of obtaining these views is not as important as systematically evaluating each quadrant for pathology.

For the right-sided evaluation, the probe is placed in the right mid-axillary line at the level of the xiphoid process in the longitudinal view (probe marker pointing cephalad and slightly posterior). This obtains a coronal view of the right hemidiaphragm, liver, and kidney. Morrison's pouch or the hepatorenal space is a site where free fluid can be detected very early (**Figure 51.20A**). Scan above the diaphragm to evaluate for a pleural fluid collection as well. For the left-sided evaluation**,** the probe is placed in the posterior axillary line at the level of the xiphoid process, in the longitudinal view. The left hemidiaphragm, spleen, kidney, and splenorenal space can all be identified from this view. The suprapubic region should be scanned for free fluid in the pelvis by placing the transducer in the midline of the pubic symphysis and tilting down (**Figure 51.20B**). A transverse (probe marker pointing to patient's right) and longitudinal view (probe marker facing cephalad) should be obtained to assess for free fluid in the pelvis. An SC echocardiographic view should be obtained to evaluate for pericardial fluid. The extended FAST examination also includes an examination of the anterior lung zone to rule out pneumothorax (**Table 51.7**). **Figure 51.21A** and **B** shows examples of hemoperitoneum where blood is seen as layering with increasing echogenicity, and echogenic material in the retroperitoneum (hematoma). USG does not have high sensitivity to detect retroperitoneal bleeding; hence, a computed tomography of the abdomen should be performed.

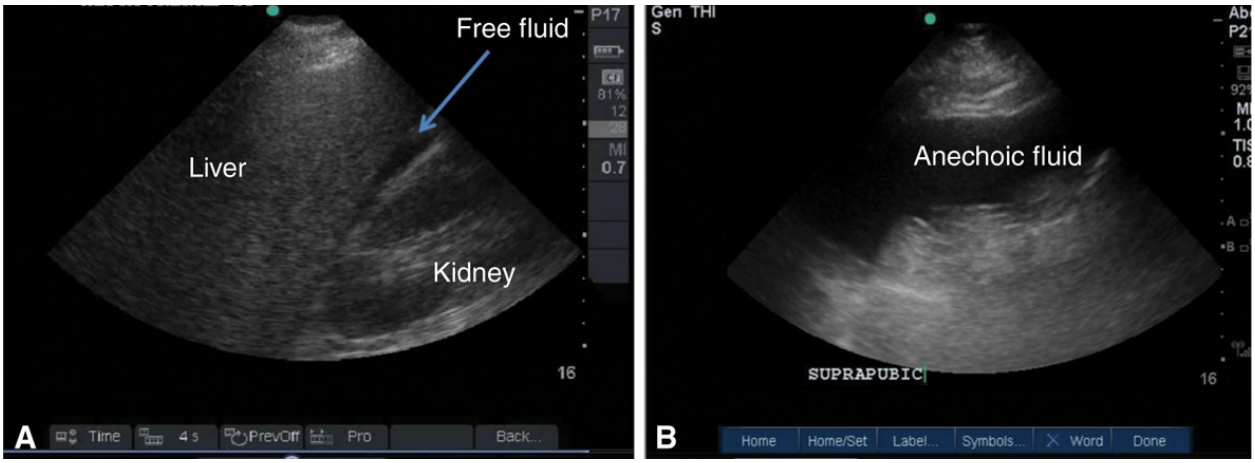


FIGURE 51.20 A, Early ascites—fluid in hepatorenal recess. B, Ascites—simple anechoic fluid in pelvis.

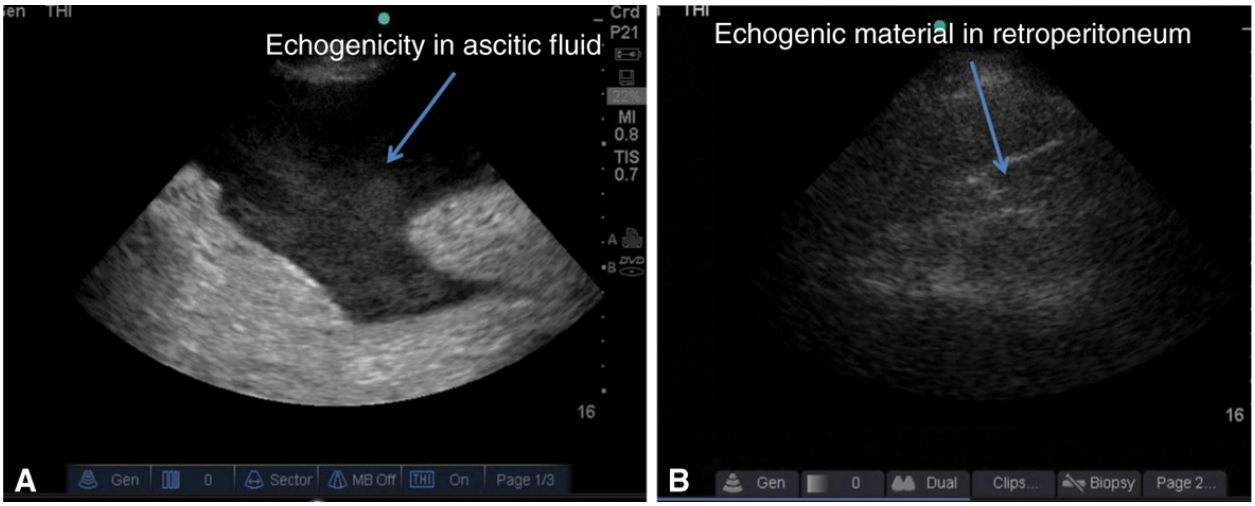


FIGURE 51.21 A, Hemoperitoneum. B, Retroperitoneal hematoma.

ABDOMINAL AORTIC ULTRASONOGRAPHY

Aortic sonography allows for detection of aortic syndromes such as thrombosis, dissection, or rupture. Abdominal USG serves as a rapid noninvasive test that provides important clinical information without the need for radiation or intravenous contrast. Conventionally, an abdominal aortic aneurysm (AAA) is diagnosed when the diameter of the aorta exceeds 4 cm. The risk of rupture at this level is <4% within a year, but it exponentially increases for AAA of larger diameter (>5 cm). The presence or absence of AAA can be evaluated with POCUS with high sensitivity and specificity; however, it has poor sensitivity for extraluminal blood. Nevertheless, in one ED study it was shown to improved diagnosis of ruptured AAA in the appropriate clinical setting and resulted in the

correct decision to perform surgery.[45]

Sonographic visualization of the abdominal aorta is achieved through a transabdominal approach. The proximal aorta can be visualized with a curvilinear transducer. Ideal conditions for scanning are a thin body habitus and a non–gas-filled transverse colon. Scanning of the aorta is done between the xiphoid process and the umbilicus, because these two areas correspond to the 12th thoracic and 4th lumbar vertebral bodies where the aorta enters the abdominal cavity and bifurcates to the iliac arteries. This area below the diaphragm within a distance of 1 cm is where the aorta gives rise to its three major branches: the celiac trunk (immediately below the diaphragm) giving rise to the common hepatic artery and splenic artery (called *seagull sign*), the superior mesenteric artery, and the renal arteries. The majority (>90%) of all aortic aneurysms occur distal to the point of the renal arteries. **Figure 51.22** shows examples of the appearance of the aorta at different branch points in the abdominal aorta.

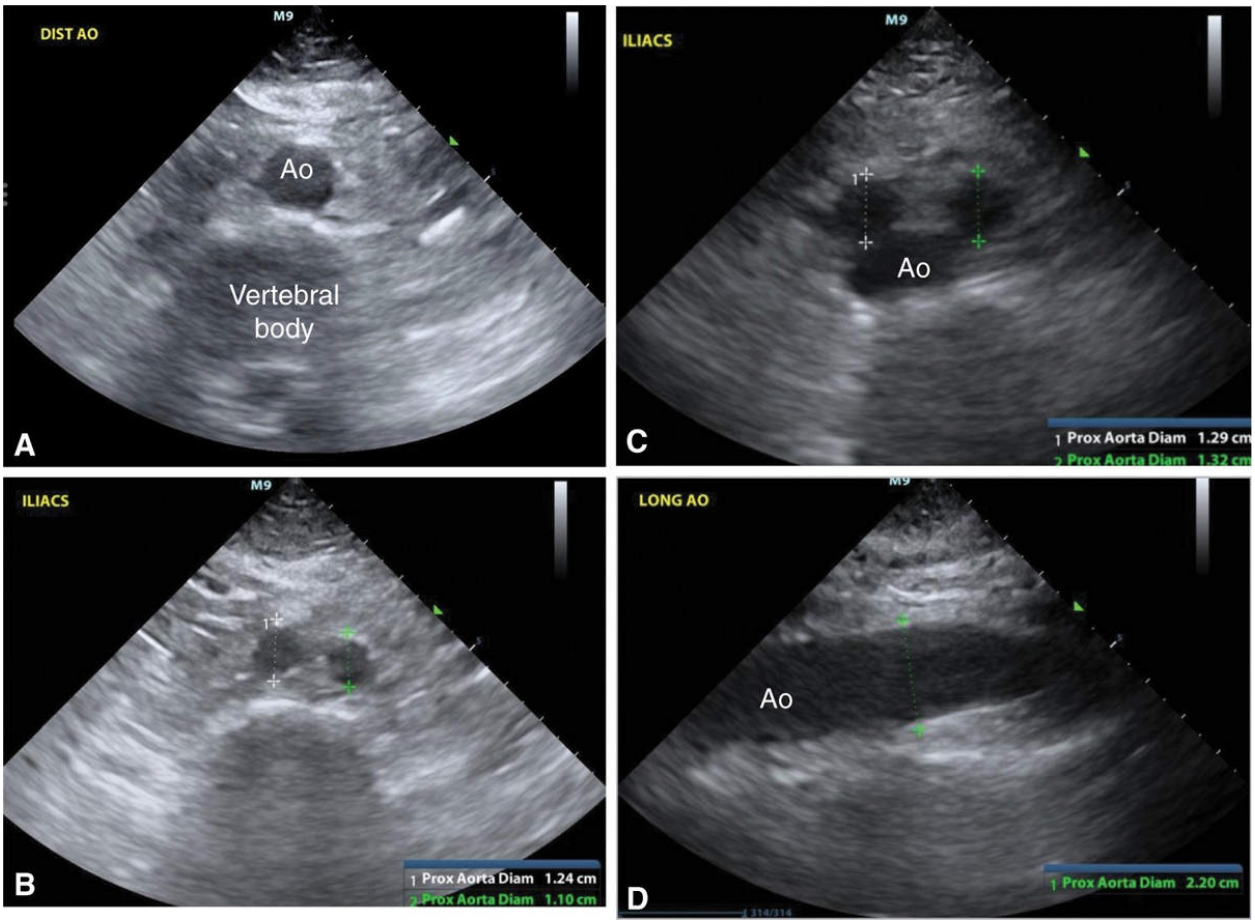


FIGURE 51.22 A, Distal aorta. B, Aorta bifurcating in iliacs. C, Aorta at the level of bifurcation to the common iliac arteries. D, Proximal aorta; longitudinal view. Ao, aorta.

ASCITES

Bedside USG is an easy way to assess for ascites in the patient with cirrhosis or right heart failure. US also facilitate paracentesis by assisting in selection of the best pocket for sampling and by avoiding nearby structures such as bowel and vasculature. US guidance has shown to lead to successful paracentesis with up to a 95% success rate in one study as compared to traditional methods (61% success rate).[46] Similarly, simulation-based training on US guidance using a paracentesis trainer has been shown to improve procedural competence of medical residents.[47]

KIDNEY AND BLADDER

In the patient with acute renal failure or abdominal pain in the CCU, bedside POCUS can serve to quickly eliminate a post-obstructive etiology. The normal kidney has a hyperechoic medulla and a relatively hypoechoic cortex. With increasing obstruction, the collecting system will become dilated and extend to the major and minor calyces and eventually thin the cortex of the kidney. Fluid is anechoic; so if the center of the kidney becomes dilated with anechoic fluid, suspect hydronephrosis. Similarly, in a post-obstructive state, one can visualize a dilated, fluid-filled (anechoic) bladder (**Figure 51.23A** and **B).** It is not uncommon to see a Foley balloon in a dilated anechoic bladder, indicating the catheter itself is obstructed.

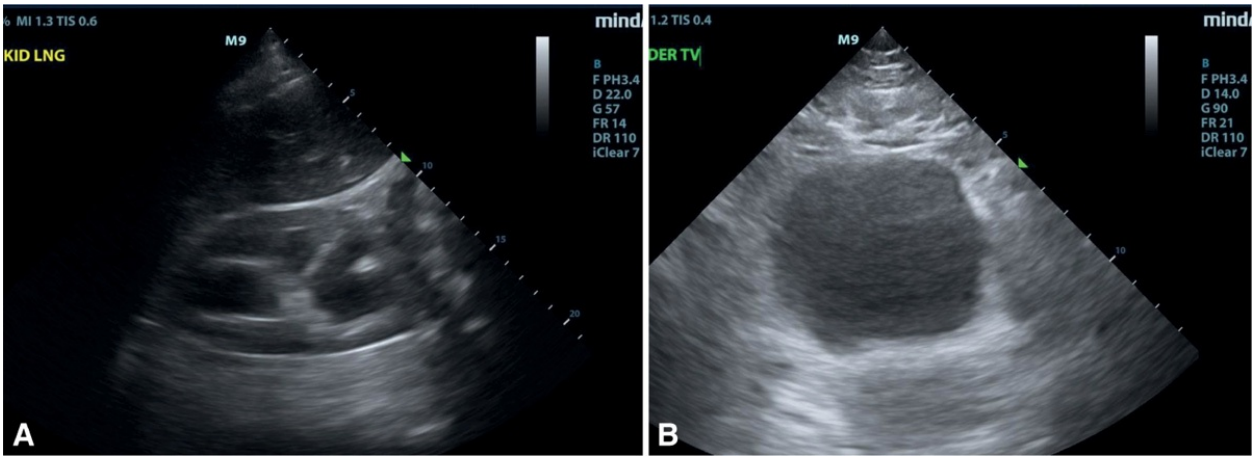


FIGURE 51.23 A, Hydronephrosis. B, Full bladder.

Using a low-frequency phased array or curvilinear probe, obtain transverse

and longitudinal views of the kidneys and bladder. The landmarks for scanning are the same as those for the FAST examination, described earlier. Fan the probe anteriorly and posteriorly through each kidney, assessing for any dilation of the collecting system. Color Doppler can be used to ensure that an anechoic duct is not a blood vessel. Rotate the probe 90° counter clockwise and fan the probe superior to inferior to scan through the entire kidney. Place the transducer over the pubic symphysis and evaluate the bladder in the transverse and longitudinal views.[48]

DIAGNOSTIC VASCULAR ULTRASOUND

DEEP VENOUS THROMBOSIS

Critically ill patients are at higher risk for development of venous thromboembolism due to risk factors such as immobility, indwelling central venous catheters, cardiac failure, dehydration, and inflammatory states. The examination for lower extremity DVT is performed with a high-frequency linear transducer. US evaluation of venous thrombosis consists of verifying vein patency or the lack thereof. The gold standard for venous patency is the ability of a vein to collapse completely under pressure, with the lumen disappearing entirely under direct visualization with US. The diagnosis is confirmed when echogenic thrombus is observed in the vascular lumen or when the vein is not completely collapsible during compression.

To allow for better visualization of the vessels, the patient is supine, with the leg externally rotated and with the knee slightly bent. Once the common femoral vein (CFV) is identified, compressions should begin above the inguinal ligament at the proximal portion of the external iliac vein. Downward pressure should be applied to the transducer and the vein should collapse completely. The operator should then compress every 1 to 2 cm while moving distally along the CFV, the greater saphenous vein, over the lateral perforator-CFV junction until the CFV is seen branching into the superficial and deep branches (**Figure 51.24**). The examination then moves to the popliteal region. The knee is flexed 45 degrees and externally rotated, with the transducer placed transversely over the mid-fossa. The popliteal vein is identified overlying the artery. Even minimal pressure can compress the popliteal vein. Sequential compression at approximately 1-cm intervals should occur while moving distally to the trifurcation of the popliteal vein. Color Doppler and pulse-wave Doppler give

the traditional venous US examination its name, “duplex.” Studies have shown that using compression US alone, nonradiologists such as EM physicians and intensivists can accurately diagnose DVT with 95% accuracy and reducing the time to diagnosis.[18,19]

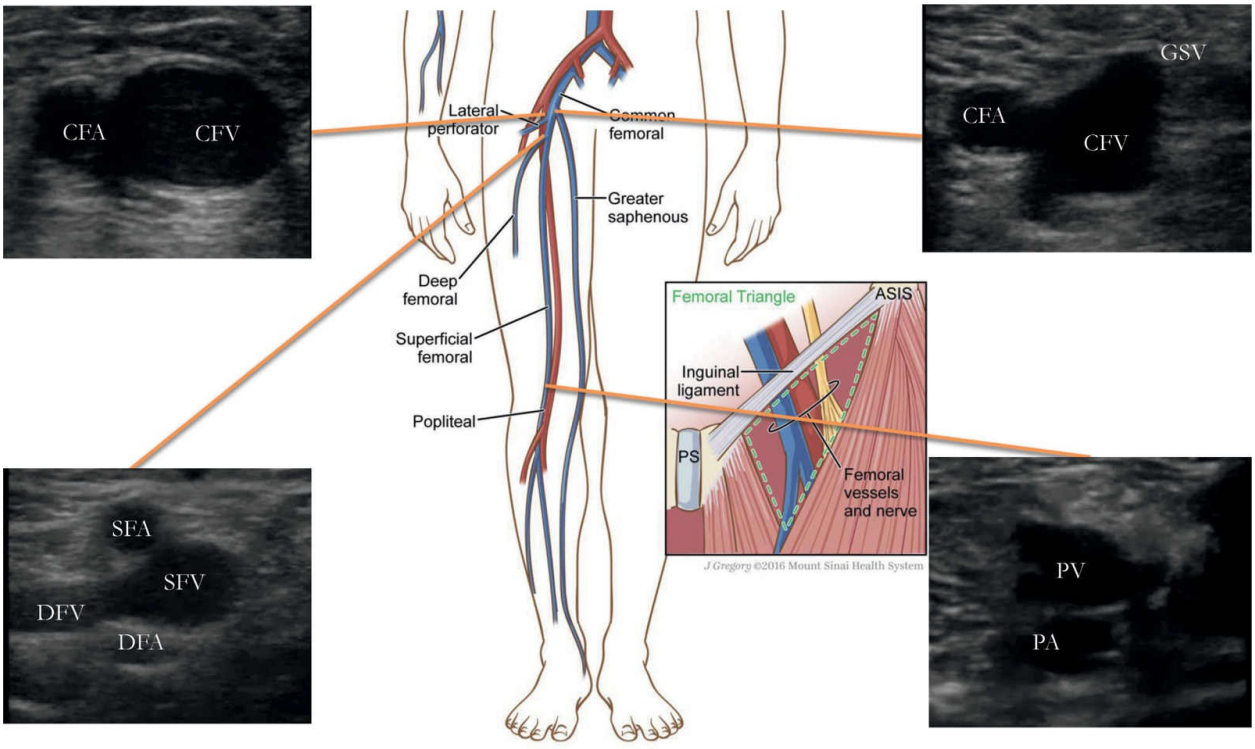


FIGURE 51.24 Compression ultrasonography to assess for DVT. ASIS, anterior superior iliac spine; CFA, common femoral artery; CFV, common femoral vein; DFA, deep femoral artery; DFV, deep femoral vein; DVT, deep vein thrombosis; GSV, great saphenous vein; SFA, superficial femoral artery; SFV, superficial femoral vein; PA, pulmonary artery; PS, pubic symphysis; PV, pulmonary vein.

PROCEDURAL GUIDANCE FOR VASCULAR ACCESS

This is one of the highest utilization indications for POCUS in the CCU. The topic is discussed in detail with regard to both CVC placement and arterial line placement in Chapter 48 of this volume from the same authors.

LIMITATIONS OF POINT-OF-CARE ULTRASONOGRAPHY

USG has developed as an irreplaceable tool in for the critical care physician in the management of a critically ill patient. Patient factors such as obesity, body habitus, rib shadows, artifacts, the presence of edema, subcutaneous emphysema, or suboptimal patient position can be a limitation. It is also operator dependent, so adequate training and a proper certification process is required.

EDUCATION IN POINT-OF-CARE ULTRASONOGRAPHY

Studies have shown that bedside sonography can be taught to both early and advanced learners. With the popularity of POCUS, many medical schools are now adopting US education into undergraduate medication education, as early as in first year anatomy courses to fourth year electives.[49,50] Basic cardiac echocardiography, which may seem intimidating to the novice, can be easily learned with proper training and supervision. Resident physicians, after 12 hours of didactic teaching and image interpretation, were able to accurately identify LV failure, RV dilatation, pericardial effusion, and IVC dilatation.[38] Similarly, intensivists were able to successfully obtain and interpret images after 10 1-hour tutorial sessions by cardiologists.[36] Large 3-day hands-on educational courses led by Dr Paul Mayo and the American College of Chest Physicians, in which the authors have been course faculty (GN, JM), have trained thousands of physicians (eg, pulmonologists, intensivists, cardiologists, anesthesiologists, hospitalists, critical care fellows, advance care practitioners, etc) since its inception in 2007. This multiday format has been shown to be an effective way to train a large group of clinicians in POCUS with excellent performance in image acquisition, interpretation, and subject knowledge.[51]

CONCLUSIONS

POCUS has evolved into an invaluable tool in facilitating the diagnosis and treatment of acutely ill patients. With the advent of portable US machines, POCUS has revolutionized the way that patients are managed and has drastically improved the safety of procedures. Goal-directed USG readily answers clinical questions in the management of critically ill patients in the CCU with conditions such as shock, acute respiratory failure, and multiorgan failure. With proper training and supervision, POCUS is easily learned both by early and advanced learners. Challenges that remain in further dissemination of the use of POCUS include appropriate training, credentialing, and reimbursement. As medical societies make inroads into these hurdles, POCUS will continue to diffuse into medical education and daily practice.

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Janet M. Shapiro

End-of-Life Care in the CCU

Patients in the cardiac care unit undergo intensive and heroic treatments intended to save and prolong life. The cardiac care unit has evolved over the past several decades such that the current CCU provides care to patients with advanced age and increasing cardiac and noncardiovascular critical illness, including sepsis, acute renal injury, and acute respiratory failure.[1] Patients in the CCU are frequently managed with life support measures including mechanical ventilation, cardiovascular support, and renal replacement therapy. Thus, the CCU clinician is faced with critically ill patients on life support measures, some of whom may be at the end of life. The major cardiology societies encourage provision of supportive and palliative care in cardiac patients at the end of life. The goal of this chapter is to provide practical information about end-of-life decision making and the process of withdrawal of life-sustaining treatments in the CCU.

Decision making about end-of-life care in the CCU is challenging for several reasons. Many patients do not have an advance directive. Even in cardiac patients with advanced interventions, including implantable electronic devices, discussions about advance directives are uncommon.[2] Clinicians face difficulty in prognostication for critically ill patients in general. In patients with heart failure, variability in the course makes identifying the end of life especially complicated. The guidelines of the Heart Failure Society of America and the American College of Cardiology/American Heart Association promote consideration of end-of-life care in patients with advanced heart failure,

including decisions about inactivation of implantable defibrillators.[3,4] Aggressive and invasive treatments are often initiated for patients in the CCU in the hope of restoring life, and this initial aggressive support is construed by the family as the optimistic expectation that the patient will recover. This is especially true for patients following cardiac arrest, in whom therapeutic hypothermia is initiated. The hope from this treatment must be tempered with the reality that the majority of patients still suffer neurologic injury. The need for sedation and the post-arrest state require time for neurologic prognostication. During this time, communication with the family about uncertain prognosis and the possibility of anoxic encephalopathy is important. A multidisciplinary team approach must include the neurologist for prognostication and decision making.

GOALS OF CARE

As clinicians, our goals for patients are to save lives, return to health or an acceptable existence, alleviate suffering, and provide the dying with a peaceful death. The transition of the goal from curative treatment to comfort care is one of the most challenging aspects of critical care. It is possible to combine a palliative approach even when life-sustaining treatments are in place, so that clinicians may still focus on alleviation of symptoms and overall goals of care.

The goals of palliative care can be applied to many patients, even those receiving aggressive interventions: control of symptoms such as pain, dyspnea, and discomfort; effective communication about appropriate goals of treatment and concordance of treatment with patient preferences; and enhancing quality of life. The role of palliative care in the CCU includes providing guidance and support, so that care will be consistent with the patient's values.[5]

Effective communication is the means to achieving patient preferences in end-of-life care. The landmark SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) revealed that the wishes of dying patients were often unexplored by physicians and those patients received potentially undesired treatments at the end of life.[6] Clinicians must also recognize that their own wishes may not coincide with those of their patients, because physicians and nurses may be less likely to desire life support than patients and families. Decision making that is shared between the patient/family and the clinicians is the model process supported by American and European critical care societies.[7,8] The evolution of critical care decision making from a

paternalistic model to the current standard of shared decision making is predicated on respect for patient autonomy and values. In the cardiac care unit, the majority of patients may be unable to participate in decisions owing to the severe illness, need for life support, and sedative medications. Therefore, the legally recognized appropriate surrogate often assumes the decision-making role to represent the patient's values and preferences. The family-centered approach respects the patient's values, and also acknowledges that many patients would want their family members to participate in decision making.

ETHICAL PRINCIPLES IN END-OF-LIFE DECISION MAKING

Patient *autonomy* is a foundation ethical principle for patient care. U.S. Supreme Court cases such as the Quinlan and Cruzan cases established that patients have a right to determine which medical treatments to accept or refuse, even when refusal leads to death.[9] Often, in the critical care unit, the patient is incapable of participating in the decision making. However, the patient may have left guidance in the form of an advance directive, such as a proxy, living will, or oral statements articulating his or her wishes concerning life support at the end of life. The patient may have assigned a health care proxy to make decisions if he or she becomes unable to do so. If no proxy has been assigned, the surrogate decision maker is chosen from the patient's close relatives or friends based on a priority order. In this way, the patient's values and preferences can still guide the decision-making process when decision-making capacity is lost.

The principle of *beneficence* maintains that physicians will work to provide the best course of treatment for the patient. Physicians see the goal of preserving life, but beneficence also means the support of the patient's informed decision even when refusal of therapy may lead to death. *Nonmaleficence* means not inflicting harm. This principle instructs the physician to weigh potential harms of treatments against potential benefits and not provide interventions that will not benefit the patient.

Conflict may arise when the patient, family, and clinician disagree about the appropriateness of an intervention. Nonabandonment is an important principle that obliges the physician to help the family understand the situation and support the family's decision. Physicians are not obligated to disregard their own beliefs and so, if the physician disagrees with the patient and family decision, the

principle of nonabandonment requires the physician to try to transfer care to another physician who will pursue the desired plan of care. The hospital administration or ethics committee may be involved to assist in resolution of these complicated situations.

ADVANCE DIRECTIVES

As stated, patient autonomy is the strongest ethical principle driving medical decision making, so that patients have the right to make decisions for themselves; and when conscious capacity is lost, this right remains protected. Advance directives, such as the health care proxy and living will, provide for decision making based on patient values and preferences when the patient loses decision-making capacity. Respect for patient autonomy underlies the federal Patient Self-Determination Act of 1990, which requires hospital personnel to ask patients whether they have an advance directive and inform patients of their right to accept or refuse medical treatments and to create an advance directive.[10] A Do Not Resuscitate (DNR) order is one kind of advance directive that addresses interventions in the setting of a cardiopulmonary arrest. A DNR order means that if the patient suffers a cardiopulmonary arrest, the interventions of intubation, cardiopulmonary resuscitation (CPR), and advanced cardiac life support will be withheld. A DNR order is often issued for patients at the end of life, and in patients with chronic or terminal illnesses. In some patients with DNR orders, the patient may be expected to benefit from and will receive intensive care interventions, but CPR will be withheld in the event of cardiac arrest. A DNR order is often a first step in the family's decision-making process.

COMMUNICATION

Achieving appropriate decision making is based on effective communication, family comprehension of the information, and sharing of the patient's values. It should not be assumed that families grasp the severity of their relative's illness or the ramifications of life support measures. Family understanding of critical illness and intensive care treatments has been shown to be inadequate. Knowledge about CPR is especially poor, with a prevalent unrealistic expectation of survival among patients with serious medical illness and their

families.[11] Accordingly, assessing family members' understanding of the patient condition is vital and will be part of the communication strategy in a family meeting.

FAMILY MEETING

Communication with the family occurs in several venues: bedside discussions, conversations with the nurse, telephone updates, as well as a formal family meeting. The contributions of the entire team are invaluable. The bedside nurse usually has important insight into the patient's condition and the family understanding of the patient's condition. A family meeting is an opportunity to present and review the situation and treatments, provide information on short-term and long-term prognoses, answer questions, explore patient and family values and wishes, and assess the family's understanding of the patient's condition. Investigators have examined family meetings and found missed opportunities in time allotted for family speech, articulating a prognosis, emphasizing the process of surrogate decision making, supporting the decision, and assuring nonabandonment. Family satisfaction with the meeting was associated with increased time for family speech; presumably this is their opportunity to make the patient and his values known.[12] Prognostication is important for family members, but the meetings often lacked discussion of prognosis for survival. Although families may doubt the accuracy of the prognosis given by physicians, that prognostic information is desired and important in the family's understanding and deliberation.[13]

Here, we can make some points about the family meeting.

- The medical team should prepare for the family meeting. The clinicians should discuss the goals of the family meeting, review the patient's condition, and achieve consensus concerning prognosis and treatments to be administered. The team should be aware of specific issues or problems related to the family situation. The bedside nurse may have great insight into the patient's condition and family situation and should be included in the meeting. It may be helpful to include team members such as the neurologist, and primary cardiologist, if applicable.
- The physician will lead the discussion in a private, quiet place. All participants should be introduced. The family should be asked their understanding of the condition and treatments. The physician should provide information about the illness, treatments including life support measures, and prognosis in a

meaningful and compassionate manner, avoiding excessive medical jargon. The clinicians should explain surrogate and shared decision making.

- The clinicians should allow time for the family to speak about the patient's values and preferences, to demonstrate their understanding of the situation, and to ask questions.
- The physician leader should judge how the family has understood the information and whether they are ready to discuss goals and end-of-life decisions. For some meetings, it is sufficient to provide the medical information and it may be better to discuss end-of-life decisions in a subsequent meeting.
- Often, the family members report that they never discussed end of life with the patient. Some ways to elucidate patient wishes include asking whether they ever had a conversation about the patient's own wishes, in the setting of another family member's illness or even related to a topic in the news; how the patient lived life, what it may mean to be dependent in all aspects of care; and what they think the patient might say about life support measures if he or she were in this meeting. The leader may ask the family what they believe is a meaningful and acceptable quality of life for the patient.
- If withdrawal of life support is discussed, the clinicians should emphasize that this does not mean withdrawal of *care* and that supportive and comfort care will be provided.
- The staff should offer support for the decision of the family, whether the decision is to withdraw or not withdraw life support. The team should assure the family that the patient will not be abandoned and all measures will be taken to prevent suffering.
- The family cannot be rushed to make a decision. The clinicians should understand that the family may not yet accept the expressed prognosis.
- The meeting may conclude with a plan to reconvene in the following days to review the situation.

It is important that clinicians do not relinquish medical decisions to the family. The physicians must give information, prognosis, and advice on how to proceed. The family provides information about the values and preferences of the patient. The transition from aggressive CCU care to comfort care is often made quickly by clinicians who have the benefit of medical knowledge of disease and prognosis, but families may need time for this adjustment and should not be rushed to make a decision. Planning a follow-up conversation within a specified

time period allows the clinicians to further assess the patient's trajectory and permits the family time to grasp the information and condition. Families need ongoing contact and communication. Families need assurances that all efforts will be made to maintain comfort. Involving the palliative care service may be beneficial in optimizing the medical and nursing treatments for palliation.

Cultural values and beliefs may exert a profound influence on decision making. Domains affecting decisions include attitudes about truth telling concerning illness and prognosis, religious and spiritual beliefs, historical and political context, perception of illness, and the decision-making process in the group. The not uncommon clinician impression that the family is not accepting a dire diagnosis and prognosis may therefore at times be explained by cultural factors.[14] Recognizing the influence of cultural factors may lead to enhanced understanding and compassionate and effective communication.

Conflicts may develop between family and physicians, within families, as well as among the health care team. Given physicians' inability to be certain of the outcome, the family may be reluctant to accept a poor prognosis. The CCU team may involve other disciplines such as the patient's primary care physician, other involved subspecialties, palliative care, pastoral care, and social work. For conflicts that reveal marked differences in desires among the patient, family, and physicians, the hospital ethics committee may be involved. Ethics committee consultations may be beneficial in resolving conflicts, establishing desired care, and limiting non-beneficial life support measures. In addition, legal affairs involvement may be required in rare, complicated situations.

WITHDRAWAL OF LIFE SUPPORT

Ethical principles described previously support the decision to withdraw or withhold life-sustaining treatments. The U.S. Supreme Court cases confirmed that patients or surrogates can refuse life-sustaining therapies.[9] The decision to withdraw life support is based on patient values and preferences as articulated by the patient or his proxy or surrogate. Withdrawal of life support would be allowing the patient to die from the underlying disease. Withholding and withdrawing life support are considered equivalent, although clinicians may be more uncomfortable with the withdrawal of treatment.

Decisions to withhold or withdraw life support are common among critically ill patients, and frequently precede intensive care unit (ICU) deaths. All forms of

life support may be withheld or withdrawn, including mechanical ventilation, vasopressors, antibiotics, blood product transfusions, hydration, and nutrition. Sometimes all treatments are discontinued at once, sometimes in a stepwise manner. With the exception of the withdrawal of mechanical ventilation, withdrawing these other treatments does not often lead to an evident clinical change. The decision to withdraw mechanical ventilation may be a more difficult decision for families as well as for clinicians. With the assurance that withdrawal would be the patient's wish and that medications will be provided for comfort, withdrawal of mechanical ventilation is often desired at the end of life.

At the time of withdrawal of life support, there should be written documentation of the prognosis, discussion, and decision making with the patient/surrogate, goals of care and plan, including orders to discontinue specific therapies. In particular, an order for removal of mechanical ventilation or deactivation of an implantable device should be entered.

The process of withdrawal of life support is delineated in **Table 52.1**. This process involves the actual withdrawal of life support measures as well as the palliative medications that may be required.

TABLE 52.1 Withdrawal of Life Support: Process of Withdrawal of Mechanical Ventilation in the Cardiac Care Unit

Ask if family wishes to be present for extubation. Explain the process. May request chaplain presence, palliative care, and hospice services
Do Not Resuscitate Order is placed. Documentation in the medical record should reflect the discussions and decision to withdraw life support
If patient has an ICD, discuss inactivation of device
Discontinue previous orders for routine vital signs, routine laboratory tests, and radiographs
Discontinue enteral tube feedings several hours before extubation
Discontinue nonessential medications Continue only palliative medications and necessary medications (such as anticonvulsants)
Change ventilator setting to spontaneous breathing mode (such as pressure support 5 cm H_2O) to assess palliative medication needs. Adjust palliative medications to goal of comfort and unlabored breathing. Consider opiates for dyspnea, benzodiazepines for seizures, anticholinergics for secretions, acetaminophen for fever, and antipsychotic medications for delirium.
Optimize the environment: • Remove unnecessary equipment, provide space for family • Discontinue monitor alarms • Discontinue inappropriate television

Extubate patient with respiratory therapist assistance
Room air or 2–4 L of oxygen by nasal cannula if this improves comfort

ICD, implantable cardioverter defibrillator.

ORGAN DONATION

A minority of deaths in the CCU is determined by brain death criteria. Most deaths in CCU are expected and are due to progression of the cardiac and other organ failures.

Patients in the CCU may be candidates for organ donation based on brain death criteria or donation after cardiac death.[15] Institutions have policies for determination of brain death, organ donation following brain death, and organ donation after cardiac death. Patients who are admitted following cardiac arrest who suffered anoxic encephalopathy may progress to brain death. Patients should be referred to the organ procurement organization if they meet specific triggers. The actual brain death determination is performed by a qualified attending physician. In patients who have undergone therapeutic hypothermia following cardiac arrest, additional vigilance is recommended in initiating the brain death determination.

For patients who have a nonrecoverable neurologic injury but not brain death, the family may make the decision to withdraw life support. These patients may be candidates for organ donation following cardiac death. Institutional policies address the referral, process, and management of patients. The cardiac team will generally involve specialists including intensivists and neurologists to confirm the neurologic prognosis. Only after the decision to withdraw life support will the organ donor network approach the family concerning organ donation.

WITHDRAWAL OF MECHANICAL VENTILATION

Communication with the family about the process of withdrawing ventilation and what to expect is essential. Although it is difficult to be certain, the physician should provide an estimation of duration of survival following extubation. The family may want to be present and may desire pastoral care to be present for support. All nonbeneficial treatments, including vasoactive medications, should be discontinued, and alarms should be silenced. Palliative medications should be adjusted before extubation while the patient is on a spontaneous breathing mode. The endotracheal tube is removed and the family

should remain with the patient for as long as desired.

WITHDRAWAL OF CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICE THERAPY

Implantable defibrillation and pacing devices provide life support that can be declined or withdrawn based on patient values and preferences.[16] The dying patient or surrogate may request inactivation, if the device effectiveness is outweighed by burdens experienced by the patient: prolonging the dying process, preventing a natural death, and suffering the loss of dignity and quality of life. The Heart Rhythm Society published a consensus statement on the management of cardiovascular implantable electronic devices in patients nearing the end of life.[16] This document sets out the ethical principles, concerns, and practical management of withdrawal of cardiovascular implantable electronic device therapy. Deactivation may prevent uncomfortable shocks in dying patients. In pacemaker-dependent patients, the device sustains life and may, like other life-sustaining treatments such as mechanical ventilation, be discontinued on the basis of the patient's right to decline therapy. If cardiac resynchronization is aiding cardiac function, then inactivation may lead to increased symptom burden. So each therapy must be addressed in light of the overall goals. The Heart Rhythm Society consensus statement offers practical advice for communication, assessing patient understanding of the device, and utilizing the overall care goals to guide management of the cardiac device. The patient's cardiologist and electrophysiologist should be involved in these discussions about deactivation.

NONINVASIVE VENTILATION

Many physicians use noninvasive ventilation for respiratory failure near the end of life.[17] Its use should be guided by the goals of care. A patient who declines mechanical ventilation may receive noninvasive ventilation with the goal of survival: in patients with heart failure, noninvasive ventilation may successfully prevent intubation and the patient may survive the episode. In patients at the end of life, noninvasive ventilation has been used for palliation of dyspnea as well as a means to give more time for family to arrive and communicate with the patient. However, if noninvasive ventilation becomes uncomfortable or burdensome, it should be removed. Noninvasive ventilation should be addressed with the patient and family as a life support measure that can be continued or

discontinued based on the goals of care. Use of high-flow nasal cannula may be a good choice for patients who require O_2 support for comfort and have high ventilatory requirements.

SYMPTOM MANAGEMENT

Most critically ill patients experience pain and discomfort related to procedures and nursing care in the ICU. The possibility of pain in patients unable to report their symptoms is a great concern for families and clinicians. Dyspnea is a common symptom in critically ill patients. When withdrawal of mechanical ventilation is being discussed, a frequent concern of the family is that the patient will experience respiratory distress. The clinicians should assess the patient with input from the bedside nurse and family.

Management is individualized, based on the patient's level of consciousness, underlying disease, and reason for respiratory failure. The patient's prior use of and response to opiates is important in dosing this medication. Route of administration and dosages must be adjusted, often with the assistance of the critical care pharmacist and palliative care specialist. **Table 52.2** shows common medications used during withdrawal of life support in the critical care unit. The intravenous route of administration is often used for these patients; however, enteral, sublingual, subcutaneous, rectal, and transdermal routes can also be used for medications. **Table 52.2 s**hows initial doses. Patients with severe dyspnea or pain at the end of life may require much higher dosages and infusion rates. It is important to provide these medications, even at high rates, for the goal of comfort. Goals are relief of dyspnea, resolution of tachypnea and tachycardia, and lack of indication of pain by verbal response or clinical appearance.

TABLE 52.2 Withdrawal of Mechanical Ventilation: Initiation of Palliative Medications

PAIN OR DYSPNEA[a]	
Morphine 1–4 mg intravenous every hour as needed Continuous infusion start at 2 mg/h	If requiring continued hourly dosing, change to continuous infusion For continued symptoms, administer bolus doses of 2x hourly rate, increase infusion (range: 2–30 mg/h)
Hydromorphone 0.5–1 mg intravenous every 3 h as needed	If requiring continued dosing, change to standing or continuous infusion For continued symptoms, increase infusion to 3 mg/h

Continuous infusion 0.5–1 mg/h
ANXIETY OR AGITATION
Lorazepam 0.5–1 mg intravenous every hour as needed Continuous infusion start at 2 mg/h Haloperidol 0.5–1 mg intravenous every 4 h as needed
TERMINAL SECRETIONS
Scopolamine patch 1.5–3 mg every 3 d Glycopyrrolate 0.2 mg subcutaneously every 4–6 h

[a]If patient is comfortable on stable doses of opioid, continue current dose when starting withdrawal of ventilation. If the patient is not already receiving these medications, consider starting before extubation.

Opioid analgesia is a basic medication class for patients at the end of life. The desired effects are analgesia and sedation, but there is also a respiratory depressant effect on the medullary respiratory center. Opioid medications are useful in management of the symptoms and signs of respiratory distress. Morphine is often chosen for management of pain or dyspnea. In patients with renal failure, there may be accumulation of active metabolite. In these patients, hydromorphone is often used. It is important to remember that hydromorphone is 5 to 10 times as potent as morphine. These medications are given at the dosages necessary to relieve symptoms.

The concern about hastening a patient's death by administering opiate analgesia is overridden by the intention of providing comfort and relieving suffering. Studies have demonstrated that the use of palliative medications at the end of life does not hasten death.[18,19] In fact, adequate pain management may mitigate the systemic effects of severe pain. In addition to respiratory depression, attention must be directed to several effects of opioid analgesia: inhibition of peristalsis with constipation, nausea and vomiting; and myoclonus and seizures.

Benzodiazepine medications provide sedation and anxiolysis. These medications do not provide analgesia but may be useful in combination with an opioid to prevent the anxiety related to pain. Side effects also include depressed level of consciousness and respiratory depression. Delirium, in the form of either an agitated or a calm state, is a common symptom in dying patients in the ICU. Although haloperidol is the standard medication for the management of delirium, the team should implement nonpharmacologic measures such as removing restraints, reducing activity and noise, and having family members at

the bedside to calm and orient the patient.

AT THE TIME OF DEATH

Notification to the family, optimally in person, using unambiguous language that the patient died is the initial duty. A minority of deaths is determined by brain death criteria and selected patients undergoing withdrawal of life support may be candidates for organ donation following cardiac death. This process requires a specialized protocol for the withdrawal of life support and management in collaboration with the organ donor organization. The staff may assist the family by providing information about the next steps, including autopsy, funeral, and bereavement services.

The critical care unit staff can also benefit from a debriefing about the patient's course, the end-of-life care, and the death. Physicians and nurses have different perspectives on end-of-life decision making, intensity of interventions, symptom management, and the quality of death and dying.[20] The burdens experienced by ICU nursing staff may lead to burnout, moral distress, and post-traumatic stress disorder. Communication to improve collaboration and the ethical climate may improve the environment for clinicians as well as the care of dying patients.

CONCLUSION

Patients and their families should expect excellence in all treatments in the cardiac care unit, including care at the end of life. Patients deserve humanity, compassion, and respect for autonomy. End-of-life care in the cardiac care unit requires expertise on many levels: assessing prognosis, communicating information, understanding patient values and preferences for life support, and implementing a patient's end-of-life decision. The CCU team can utilize the expertise of consultants, including palliative care specialists, in optimizing end-of-life care. Clinicians' management will be rewarded by alleviating a patient's suffering, facilitating a peaceful and dignified death, and providing peace and satisfaction for the patient's family.

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Patient and Family Information for: END-OF-LIFE CARE IN THE CCU

The doctors, nurses, and the entire CCU team treat patients with the goal of curing disease, prolonging life, and making the patient better. The team also works to relieve pain and suffering. Even with all the medical care, technology, and life support machines, patients may not get better or survive. Sometimes, the patient has an incurable illness, such as advanced heart disease, which has led to damage to all the vital organs and also led to coma. These patients are in a terminal condition and the use of life support may only postpone death. For patients and families, it is very important to communicate with the cardiac care unit team to understand the illness and outlook (prognosis) and to make decisions so that the patient's wishes and values are respected.

HOW ARE END-OF-LIFE DECISIONS MADE?

Decisions in the cardiac care unit are based on shared decision making between the physicians and the patient and family. Communication is the key to decision making for a critically ill patient. The wishes of the patient are most important. If the patient does not want life-sustaining measures, they can be stopped. This is respect for the patient's autonomy, which means control over his/her own body. The law states that the patient has a right to agree to or refuse treatments, including life support.

The decision to limit or stop life support measures is based on the wishes of the patient, as well as the patient's best interest if the exact wishes are unknown. Often, patients in a critical condition cannot communicate or participate in making decisions and trust their closest relatives to make the decisions. The patient may have prepared for this by appointing a health care proxy to make

medical decisions if the patient is unable to speak. A surrogate is a close relative or friend who will make decisions if a proxy has not been appointed and the patient is unable to make decisions. If the patient has not assigned a proxy, a surrogate is chosen from the patient's close relatives or close friends based on a priority order. Some patients have filled out a proxy or living will; these documents can spell out the care or treatment that the patient wants or does not want in the case of a terminal illness or condition.

Remember that decisions about life support are made on the basis of careful, thorough discussions with doctors, patient, and family/proxy/surrogate. Patients and family members should be sure that the doctors and nurses are aware of wishes concerning the end-of-life care.

FAMILY MEETING

The CCU team will provide information to the patient and family about the patient's condition and treatment. Often, the patient is very ill and unable to understand or participate, and so the physicians will speak with the family and health care proxy. A family meeting is often convened to talk about the patient's condition, treatments, and obtain information about the patient's wishes and values. It is often very difficult to be sure of the patient's outcome (prognosis); however, the physicians should give some information about whether the patient is expected to survive and what the function might be if he/she survives. If one member of the family becomes the contact person for the CCU staff, this will help the communication process.

WHAT IS LIFE SUPPORT?

Life support measures are treatments or procedures that support or replace body functions that are failing. When patients have curable or treatable conditions, life support is temporary until the organ function improves. With advanced illness and advanced age, certain diseases lead to a continued decline in function of the organs and of the entire person. Sometimes, the body never recovers and the patient would not be able to survive without life support.

It is important to understand the benefits and burdens of life support treatments. A treatment may be beneficial if it restores functioning, improves quality of life, and relieves suffering. The same treatment could be a burden if it causes pain, prolongs the dying process, or decreases the quality of life. The

decision about whether a treatment is a benefit or a burden is a personal decision based on the patient's preferences and values. If the patient is able to tell the doctors, his/her decision will be respected. If the patient is unable to express his/her wishes, the doctors will meet with the family and proxy/surrogate to learn the patient's preferences and values.

WHAT ARE LIFE SUPPORT MEASURES?

CPR (Cardiopulmonary Resuscitation) is a set of treatments given when a patient's heart and breathing stop in order to restart the heart and breathing. It involves breathing for the patient using a mask or tube placed into the patient's airway. The team will compress the chest and may apply electric shocks to get the heart beating again.

In certain conditions, CPR can be very effective, for example, if a patient has a sudden heart attack. However, in patients at the late stages of a terminal illness who are at the end of life, CPR is usually not successful. Even if the heart does start beating, often the patient remains in a coma or dies within a short period of time. Making a decision about whether the patient should go through CPR is an important decision. In patients at the end of life, when the heart stops, this would be a natural death. A DNR (Do Not Resuscitate) order means that if the heart stops, CPR will not be done and the patient would die a natural death.

Mechanical ventilation is the use of a *ventilator* to support the breathing function of the lungs. Ventilator and *respirator* both mean the same machine. A tube is inserted through the mouth into the trachea (windpipe) and this tube is connected to a ventilator that gives the breaths to the patient. Patients on a ventilator are not able to speak, sometimes are awake enough to communicate, and often require sedation so that they are not anxious or uncomfortable. Mechanical ventilation may be used for a short period, such as in heart failure or pneumonia, and can also be used for a long time in patients with neurologic disorders, who may still be satisfied with the quality of their life. However, in a dying patient, mechanical ventilation will not improve the condition or the quality of life. In a patient who is dying, being on a respirator may prolong the dying process.

Noninvasive mechanical ventilation is the use of a ventilator machine that is attached to a special face mask. The ventilator will force air through the mask so the patient will feel some pressure of air moving in. Some patients can work well

with the mask and even speak; for others, it is uncomfortable. This is a kind of life support that can be used if helpful; if it becomes uncomfortable and is not beneficial, it can be stopped.

Hemodialysis is used to replace the function of failed kidneys, which will clean the blood of wastes that normally accumulate. Dialysis requires placement of a large catheter and long periods on the dialysis machine. Some patients with kidney failure can live for years while receiving dialysis treatments several times each week. For patients at the end of life, dialysis cannot be expected to restore health.

Artificial nutrition and hydration can be given by a feeding tube placed into the stomach, which replaces normal eating and drinking. Artificial feeding may be necessary in some patients undergoing a prolonged illness until their bodies recover. In patients at the end of life, artificial nutrition and hydration still cannot restore health.

WHAT HAPPENS IF THE DECISION IS MADE TO WITHDRAW LIFE SUPPORT?

The decision to withdraw life support is made after careful discussion of the prognosis and patient preferences and values. All forms of life support can be withdrawn. The doctors may suggest placing an order for no CPR—a DNR order and not administering certain medications.

The mechanical ventilator can be removed, based on patient desires and values. The physician and nurse will assure that the patient is comfortable. The family can be present during this process if they wish.

HOW WILL THE DYING PATIENT BE TREATED?

The goal of the health care team is to provide the desired and beneficial care. In a dying patient, p*ain management and comfort care* will always be provided. Pain and discomfort can be managed by medications and also by working on the environment, such as having family present. Certain medications such as morphine are used to relieve pain and can also make the patient sleepy. All medications and treatments have other effects, so the overall goal of comfort must be a priority. The physicians and nurses will monitor the patient and also

rely on the family to tell the staff whether the patient is comfortable.

There are clinicians who specialize in palliative care who may be consulted to assist the team with care. Patients and families may want the services of pastoral care.

The overall goal is for the cardiac team to work with the patient and his/her family, health care proxy, and surrogate to provide care that is beneficial and desired. Comfort and respect are priorities. It is important that there is communication and understanding in the shared responsibility for decision making and care for each patient.

VI

RISK FACTORS: FROM THE ACUTE SETTING TO CHRONIC MANAGEMENT

53

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Hypertension in the Cardiac Care Unit

The Committee on Public Health Priorities to Reduce and Control Hypertension in the U.S. Population concluded that "the Centers for Disease Control (CDC)'s cardiovascular disease program in general, and the HTN program in particular, are dramatically under-funded relative to the preventable burden of disease."[1] The global burden of hypertension (HTN) is tremendous. HTN is a risk factor for essentially every medical condition that would warrant admission to a hospital's cardiac care unit (CCU); in fact, the CCU is where the most severe forms of the HTN burden can be seen. HTN can be defined as a sustained rise in blood pressure (BP) that increases the risk of cerebral, cardiac, and renal events. In industrialized countries, the risk of becoming hypertensive during a lifetime exceeds 90%. The clinical spectrum of HTN ranges from mild elevations in BP to hypertensive emergencies requiring immediate therapy. Patients may be asymptomatic despite marked elevation in systemic BP, yet the resultant end-organ damage is a major cause of morbidity and mortality; hence the designation of HTN as the "silent killer."

At our institute, we have created a pathway for the management of in-hospital HTN, with a particular focus on the management of HTN in the CCU (**Figure 53.1**).

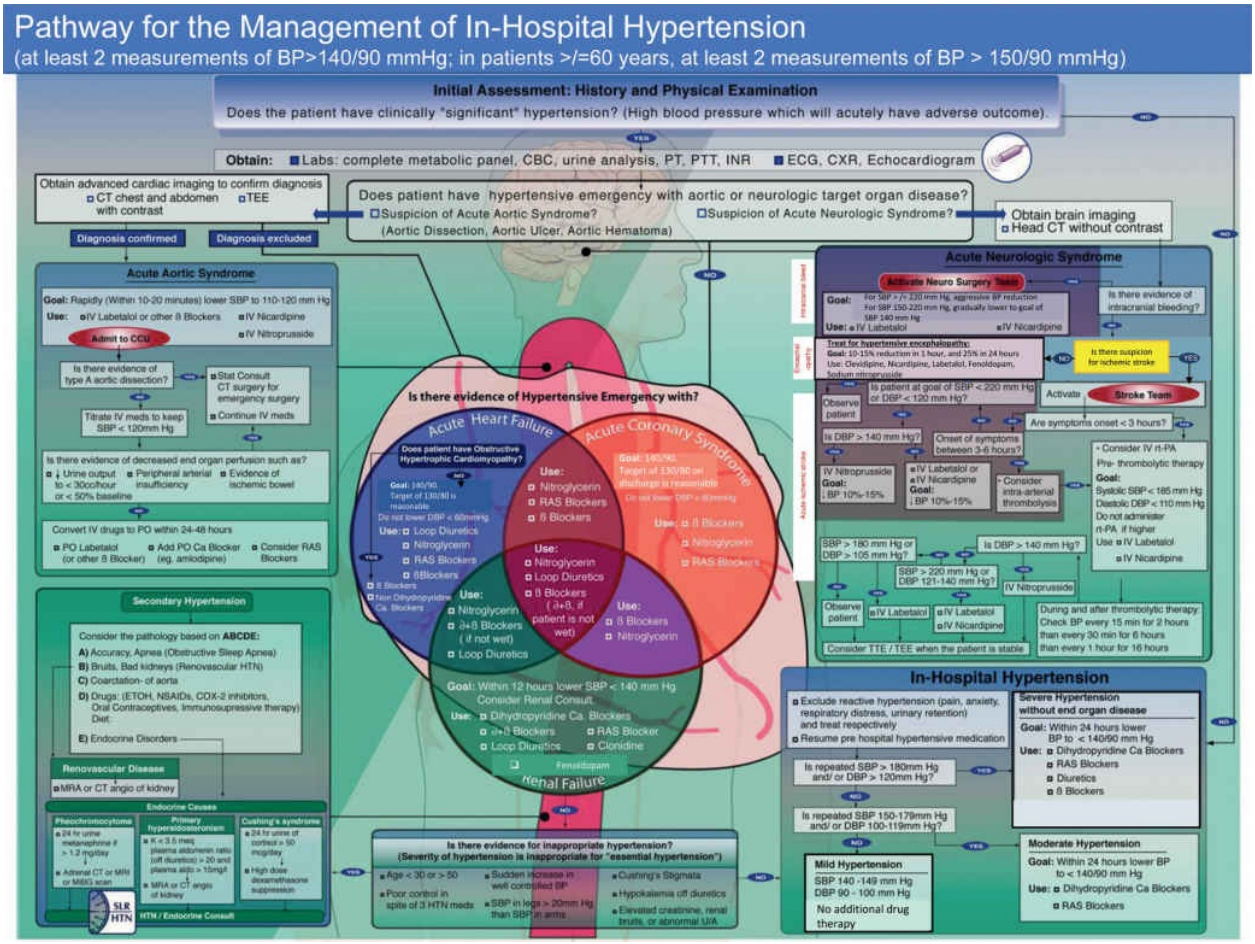

FIGURE 53.1 Pathway for the management of in-hospital hypertension. BP, Blood pressure; CBC, complete blood count; CCU, cardiac care unit; COX-2, Cyclooxygenase-2; CT, computed tomography; CXR, chest X-ray; DBP, diastolic blood pressure; ECG, electrocardiogram; ETOH, ethanol; HTN, hypertension; INR, international normalized ratio; MIBG, metaiodobenzylguanidine; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; NSAIDS, non-steroidal anti-inflammatory drugs; PT, prothrombin time; PTT, partial thromboplastin time; PO, Per Os (Oral); RAS, renin–angiotensin system; SBP, systolic blood pressure; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

HYPERTENSION: DEFINITION AND PATHOPHYSIOLOGY

The 2014 Guidelines of the Eighth Joint National Committee (JNC 8) and the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) define hypertension in a non-elderly (<60-year-old) patient without diabetes and chronic kidney disease (CKD) as BP of ≥140/90 mm Hg.[2,3] JNC 8 recommends initiating treatment beyond this threshold and aiming for goals of systolic blood pressure (SBP) <140 mm Hg and diastolic blood pressure (DBP)

<90 mm Hg. Although the recommendations of JNC 8 are largely based on consensus expert opinions, high-quality evidence from several randomized control trial supports their recommendation to initiate treatment for HTN in patients ≥60 years when BP is only ≥150/90 mm Hg. Additional recommendations of JNC 8, in terms of thresholds for initiating treatment and BP goals, include initiating treatment for HTN in patients <60 years with CKD or diabetes mellitus (DM) when BP ≥140/90 mm Hg, aiming for SBP <140 mm Hg and DBP <90 mm Hg. In the diabetic population, the recommendation is based largely on the results of the ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes–Blood Pressure) trial, which found that aiming for lower BP goals did not reduce the risk of nonfatal and fatal major adverse cardiovascular events.[4] The more recent SPRINT (*S*ystolic Blood *PR*essure *INT*ervention) trial suggests that intensive treatment to a lower BP goal may improve cardiovascular outcomes and reduce mortality in elderly patients with increased cardiovascular risk; it may be noted, however, that the trial excluded patients with diabetes and prior strokes, including a large proportion of patients with increased cardiovascular risk.[5]

HTN is a frequent reason for admission to the CCU. More commonly, however, a patient is admitted to the CCU for a condition related secondarily to HTN, with high BP being a critical target of therapy and of future risk reduction. For example, although the patient with acute coronary syndrome (ACS) or heart failure (HF) is not admitted primarily for HTN, HTN is one of the mediators of the ongoing myocardial oxygen supply–demand imbalance in ACS, and of pump failure in HF, and thus is a critical target of therapy.

BP is determined by the product of heart rate, stroke volume, and systemic vascular resistance. Heart rate is determined largely by sympathetic activity. Stroke volume depends on cardiac preload and afterload, which in turn depend on multiple variables affecting vascular tone, as well as on myocardial contractility that is determined, among other things, by sympathetic activity. It follows that BP can be reduced by reducing heart rate, stroke volume, and/or vascular resistance.

HTN can be essential or secondary. Secondary HTN is due to a discernible cause, such as renal or endocrine disease, whereas essential HTN, which is responsible for the majority of cases, is not. HTN can also be thought of as an elevation of BP due to one or more abnormalities in cardiac function, vascular function, renal function, and/or neuroendocrine function.

Cardiac: A hyperkinetic circulation due to excessive sympathoadrenal activity

or increased sensitivity of the heart to baseline neurohormonal regulators increases cardiac output and causes HTN with normal systemic vascular resistance, often in younger patients.

Vascular: Elevated vascular resistance, more common in the elderly, due to abnormal blood vessel responsiveness to sympathetic outflow, endothelial damage that disrupts vasodilatory/vasoconstrictor balance, and ion channel defects will raise BP.

Renal: Renovascular disease leads to increased production of angiotensin II and aldosterone, which increase vasomotor tone and sodium/water retention leading to increased cardiac output and systemic vascular resistance.

Neuroendocrine: Neuroendocrine dysfunction as in pheochromocytoma and primary hyperaldosteronism can alter cardiac, vascular, and renal function to cause HTN via a number of mechanisms.

GENERAL PRINCIPLES ABOUT THE PHARMACOLOGIC MANAGEMENT OF HYPERTENSION

The fundamental concept of HTN treatment is that BP can be decreased by reducing heart rate, stroke volume, and/or systemic vascular resistance. These factors are interrelated, and many pharmacologic agents affect more than one of these determinants of BP. The drugs used to treat HTN are many, but when grouped into classes they are surprisingly few. It is important to remember that it is degree of BP reduction and control that is the major determinant of prevention of major adverse cardiovascular outcomes, and not class of antihypertensive drug; this fact has been accepted by major societies such as the ESH and ESC.[3] The armamentarium of drugs used to treat systemic HTN includes those that reduce intravascular volume (diuretics), downregulate sympathetic tone (β-blockers, α-blockers, and central sympatholytics), modulate vascular smooth muscle tone (calcium channel blockers [CCBs] and potassium channel openers), and inhibit the neurohormonal regulators of the circulatory system (angiotensin-converting enzyme inhibitors [ACEIs] and angiotensin receptor blockers [ARBs]). These drug classes make up the bulk of medications used to treat not only HTN but also the most common disease processes that warrant a CCU admission. β-Blockers, for example, are antihypertensives fundamentally important for reasons that go beyond their antihypertensive effects, in the treatment of HF, ACS, acute neurologic syndrome, and acute aortic syndrome. It

is useful to organize drugs in classes and by mechanism of action because an understanding of how the drug class works helps one understand why it is effective for a disease process.

DIURETICS

Diuretics, which function to reduce intravascular volume and vasodilate, increase renal excretion of sodium and water. Diuretics include thiazide (thiazide-type and thiazide-like) diuretics and loop diuretics. Thiazide diuretics (thiazide-like—chlorthalidone, indapamide; thiazide-type diuretics—hydrochlorthiazide) have a long duration of action and moderate intensity of diuresis, making them more suitable for chronic HTN treatment than for short-term aggressive diuresis. After the publication of the ALLHAT (Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack) trial in 2002, thiazides became the initial antihypertensive monotherapy of choice.[6] However, recent evidence has challenged that notion; the ACCOMPLISH (*A*voiding *C*ardiovascular Events in *COM*bination Therapy in *P*atients *LI*ving with *S*ystolic *H*ypertension) trial in 2008 showed that the combination of benazepril and amlodipine was superior to the combination of benazepril and hydrochlorthiazide in reducing cardiovascular outcomes in hypertensive patients with increased cardiovascular risk.[7] Despite this, thiazides are still among the four main classes of antihypertensive drugs recommended for initial monotherapy (in addition to ACEI, ARBs, and dihydropyridine CCBs), as recommended by the expert panel of JNC 8.[2] If a thiazide is to be used, it is always preferable to use chlorthalidone, which is more potent and longer acting than hydrochlorthiazide (despite increased risk of glucose intolerance, hyperuricemia, and hypokalemia).

Loop diuretics (eg, furosemide) have a relatively short duration of action (4 to 6 hours) and are useful more for brisk diuresis than antihypertensive efficacy, making them critical in the treatment of HF exacerbations. However, in patients with CKD and glomerular filtration rate (GFR) of less than 30 mL/min, thiazides are less effective. In such patients, loop diuretics are much more effective as antihypertensives. In patients with a low GFR, their volume status is a major determinant of BP; as such, loop diuretics play a major role in BP management by rapidly modulating volume status. Interestingly, when HTN persists even at high doses of loop diuretic, a thiazide (such as chlorthalidone, hydrochrothiazide, or metolazone) can enhance diuresis. Although ACEI forms

the most important therapy for patients with CKD with proteinuria, in the absence of proteinuria or in the presence of edema, loop diuretics form an initial component of initial therapy for BP management in such patients.

Another diuretic, spironolactone, has recently gained attention after the publication of the PATHWAY-2 (*P*revention *A*nd *T*reatment of *H*ypertension *W*ith *A*lgorithm-based therap*Y*) trial.[8] Spironolactone has been shown to be the most effective add-on drug for the treatment of resistant HTN, defined as suboptimal BP control despite treatment with at least three blood-lowering drugs. This effectiveness of spironolactone in the treatment of HTN supports sodium retention as an underlying pathophysiologic cause of resistant HTN. It is important to monitor electrolytes and renal function during initiation of spironolactone.

ADRENERGIC BLOCKADE: α- AND β-BLOCKERS

β_1 Receptors found on myocardial cells, when activated, increase heart rate (chronotropy) and contractility (inotropy). α_1 Receptors found on vascular smooth muscle promote contraction and thus vasoconstriction.

β-Adrenergic antagonists or β-blockers (eg, metoprolol) have negative chronotropic and negative inotropic effects as well as effects on resistance vessels. In addition, they protect against the cardiac remodeling imposed by adrenergic stimulation and have shown long-term benefit in coronary artery disease (CAD) and HF. α-Blockers (eg, doxazosin), on the other hand, promote peripheral vasodilation, leading to a decrease in peripheral vascular resistance. Some β-blockers (labetalol, carvedilol) block α- and β-receptors, thus mediating vasodilatation (α-blockade) and decreased reflex tachycardia, along with decreased heart rate and decreased cardiac contractility. However, decades ago, the MRC (Medical Research Council) Study in the United Kingdom showed that β-blockers were less effective than other agents as antihypertensives.[9] This has been shown again by several systematic reviews and meta-analyses,[10–12] and none of the major professional societies support the use of β-blockers as initial monotherapy for HTN. Further, in the ALLHAT trial, the doxazosin arm had to be stopped early because of adverse cardiovascular outcomes.[6] α-Blockers are never used for HTN monotherapy, except to concomitantly treat an enlarged prostate.

CALCIUM CHANNEL BLOCKERS

Calcium ions are major mediators of vascular smooth muscle cell contraction as well as inotropic and chronotropic function of the heart. Calcium enters vascular smooth muscle cells, cardiomyocytes, and pacemaker cells via voltage-dependent calcium channels. CCBs, by inhibiting calcium entry into the vascular myocytes, promote myocyte relaxation, thus leading to vasodilation. In a similar way, by inhibiting calcium entry into the cardiac myocyte, they have negative chronotropic and negative dromotropic effects.

CCBs are recommended by the expert panel of JNC 8 as agents that can be used as initial monotherapy for HTN.[2] In general, dihydropyridine CCBs (eg, amlodipine, nifedipine, felodopine, isradipine) are the preferred agents; they are highly selective for arterial tissues, including the coronary arteries, where they cause vasodilation. Intravenous (IV) nicardipine has strong antihypertensive activity; intra-arterially, it decreases vasospasm in subarachnoid hemorrhage, and it is a recommended agent for HTN after acute ischemic stroke and intracerebral hemorrhage (ICH).[13] Clevidipine, a new third-generation IV dihydropyridine CCB, has a high vascular selectivity with a fast onset and offset of BP-lowering effect, thus making it easily and rapidly titratable and an especially attractive drug for acute HTN. In perioperative patients requiring HTN treatment, clevidipine compared favorably to nitroglycerin (NTG), nitroprusside, and nicardipine in terms of BP-reducing efficacy and 30-day outcomes (death, myocardial infarction [MI], stroke, renal failure).[14]

The non-dihydropyridine CCBs (diltiazem, verapamil) bind to different sites and are less selective for vascular smooth muscle; they have negative chronotropic and dromotropic effects on sinoatrial (SA) and atrioventricular (AV) nodal conducting tissue and negative inotropic effects on cardiomyocytes, making them useful heart-rate–controlling agents as in atrial fibrillation with rapid ventricular rate. Non-dihydropyridine CCBs should be used with caution in patients with impaired systolic function or conduction system disease because these agents can exacerbate HF and SA or AV node dysfunction, especially in patients already on β-blocker therapy. As such, dihydropyridine CCBs are preferred agents for HTN monotherapy. Still, diltiazem and verapamil may be useful for HTN, when used concomitantly for some other indication, such as atrial fibrillation. Further more, they are preferred second-line agents in patients with CKD, because they help in reducing proteinuria.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS

ACEIs prevent the ACE-mediated conversion of angiotensin I to angiotensin II, leading to decreased circulating angiotensin II and aldosterone (angiotensin II stimulates the release of aldosterone from the adrenal glands). Angiotensin II elevates BP by causing peripheral vasoconstriction and also through sodium and water reabsorption in the distal tubules. In the long term, it promotes HTN by promoting atherosclerosis; this occurs through various mechanisms such as direct effects of angiotensin II on constriction and remodeling of resistance vessels, aldosterone synthesis and release, enhancement of sympathetic outflow from the brain, and facilitation of catecholamine release from the adrenals and peripheral sympathetic nerve terminals. In the heart, angiotensin can cause adverse tissue remodeling. It is an important trigger of several genomic and non-genomic pathways that play a role in pathogenesis of myocardial hypertrophy and fibrosis. Angiotensin II is an upregulator of intracellular genomic pathways that lead to the activation of a hypertrophic gene transcription program and the development of myocardial hypertrophy.[15] It is also one of the stimulators of fibroblasts to myofibroblast transformation, a crucial step in pathogenesis of cardiac fibrosis. Angiotensin also stimulates release of chymase from the cardiac mast cells, which additionally upregulates fibrosis by stimulating collagen production within the fibroblasts.[16]

ACEIs decrease levels of vasoconstricting angiotensin II. By reducing aldosterone production, they also promote natriuresis and reduction of intravascular volume. By decreasing bradykinin breakdown, ACEIs promote vasodilatation. They may be nephroprotective because reducing angtiotensin II levels reduces renal efferent arteriole constriction, thus reducing intraglomerular pressures and limiting glomerular damage over time. For all these reasons, these drugs are particularly useful in patients with hypertensive diabetes and HF. ARBs, by blocking angiotensin receptors, promote vasodilation and reduction in aldosterone levels, thus aiding natriuresis. However, they do not affect the levels of bradykinin.

For HTN, ACEIs are recommended as initial monotherapy by JNC 8 for the general nonblack population. For the black population, irrespective of their diabetic status, thiazides and CCBs are preferred as initial monotherapy.[2] This is based on the findings of the ALLHAT trial, which found these classes of drugs to be superior to ACEIs in the black patient population. However, for patients with CKD having proteinuria, irrespective of their race or their diabetic status, ACEIs form the first-line monotherapy. In the absence of proteinuria, ACEIs still can be used as initial monotherapy in the patient with CKD, although diuretics should

be favored when there is edema. The recommendations for ARBs are similar.

NITRATES

Organic nitrates are chemically reduced to release nitric oxide (NO), an endogenous signaling molecule that causes vascular smooth muscle relaxation. Although NO can dilate both arteries and veins, venous dilation predominates at therapeutic doses. NO-induced venodilation increases venous capacitance, leading to a decrease in the return of blood to the right side of the heart, and subsequently decreased right ventricular and left ventricular (LV) end-diastolic pressure and volume. This decrease in preload reduces myocardial oxygen demand. At higher concentrations, nitrates may cause arterial vasodilation. In the coronary circulation, NTG preferentially dilates large epicardial arteries rather than smaller coronary arterioles, thus preventing coronary steal phenomenon, encountered with such agents as dipyridamole. It is unclear to what extent nitrates' effects on coronary vasodilation benefit the patient with angina because the chronic oxygen deficit in patients with CAD causes maximal dilation of coronary arteries and because atherosclerotic coronary arteries may remain noncompliant even in the face of coronary artery vasodilators. Furthermore, doses of nitrates sufficient to vasodilate epicardial arteries can induce peripheral vasodilation, hypotension, and reflex tachycardia, which harm the delicate supply-demand balance. In patients with HF, however, reflex tachycardia is rare; the venodilation and decreased end-diastolic pressure effects of nitrates make them acceptable at certain doses for decreasing pulmonary congestion in the patient with hypertensive emergency and congestive HF. Side effects related to hypotension include dizziness and syncope; nitrates are contraindicated in hypotension, and not advised in diastolic dysfunction and hypertrophic obstructive cardiomyopathy, two disease states for which adequate preload are critical to sustain cardiac output. Also, nitrates should not be taken by patients taking phosphodiesterase inhibitors (ie, sildenafil [Viagra]).

Sodium nitroprusside is a nitrate that, like NTG, liberates NO but does so nonenzymatically; as a result, nitroprusside does not target specific vessels and consequently dilates both arteries and veins. With rapid onset of action and high efficacy, nitroprusside is useful in hypertensive emergencies, but must be infused with continuous BP monitoring. Sodium nitroprusside is metabolized to products that are potentially toxic if they accumulate excessively: cyanide (acid–base disturbance, cardiac arrythmia) is converted to thiocyanate (psychosis, spasms, convulsions).

HYPERTENSION AND THE CCU

HTN is a risk factor and target of therapy (both short term and long term) for virtually every condition that warrants a CCU admission. We review the most common CCU disease states in terms of pathophysiology, diagnosis, and management in relation to HTN. **Figure 53.2** outlines the initial assessment of a patient with HTN in the hospital who may require care in the CCU. **Figure 53.3** outlines our working group's assessment of a hypertensive emergency.

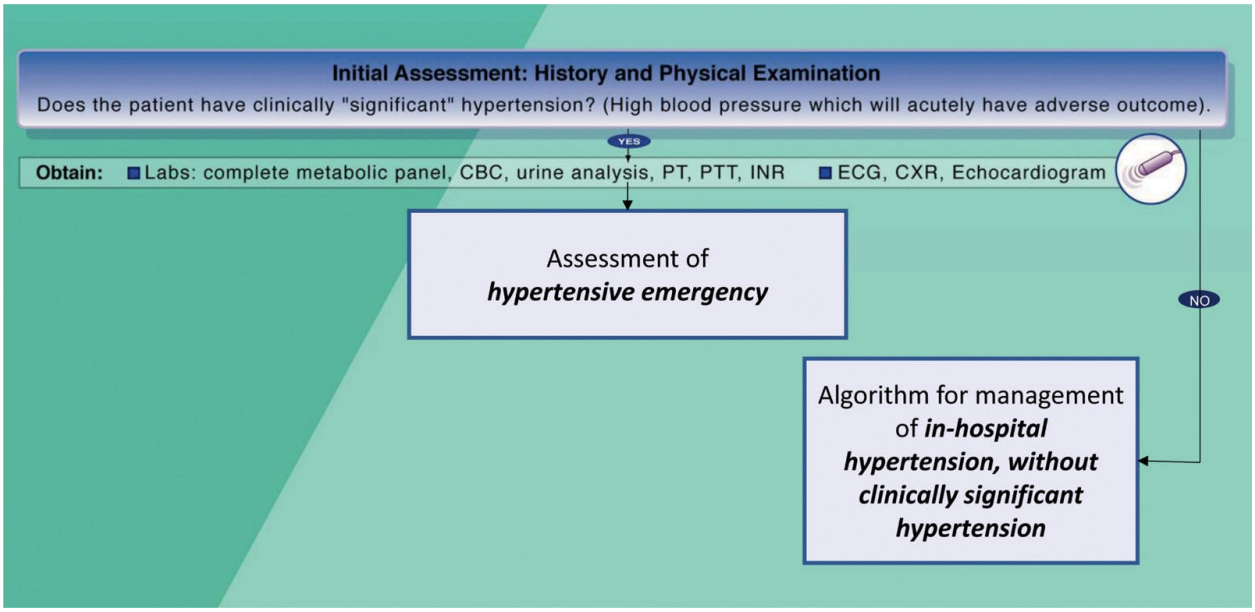

FIGURE 53.2 Initial assessment of a patient with in-hospital hypertension, which might require cardiac care unit (CCU) level of care. CBC, complete blood count; CXR, chest X-ray; ECG, electrocardiogram; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time.

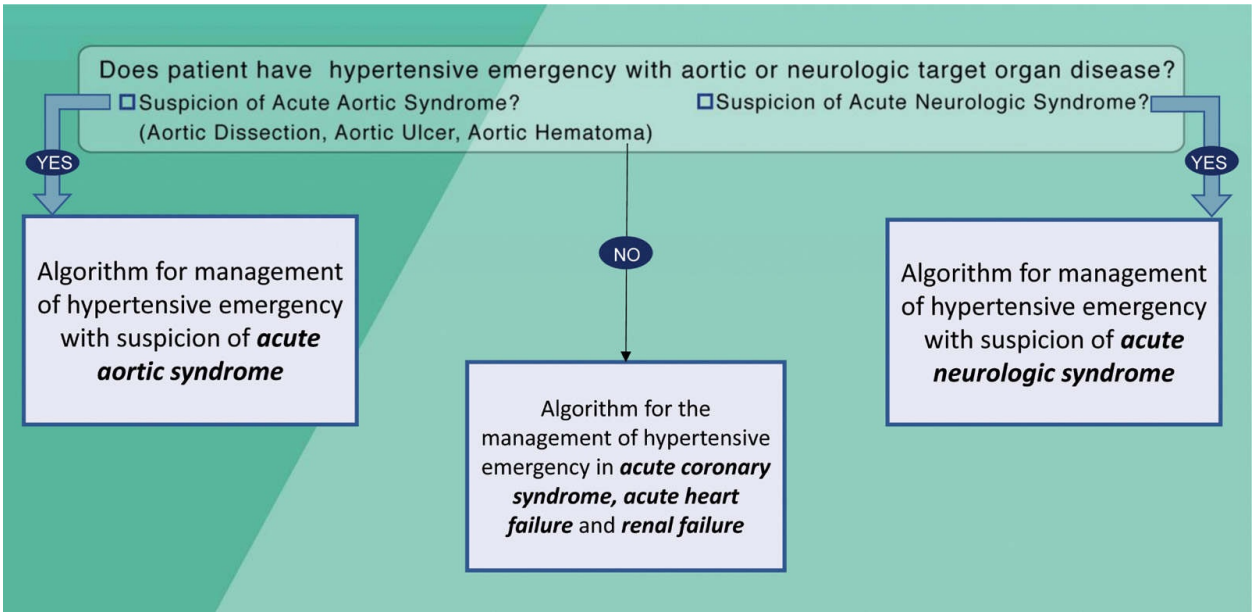

FIGURE 53.3 Assessment of hypertensive emergency.

HYPERTENSION AND DISEASES OF THE AORTA

Diseases of the aorta include aortic atheroma, aneurysm, arteritis, and acute aortic syndromes (aortic dissection, intramural hematoma, penetrating ulcer). These diseases tend to follow an indolent asymptomatic progressive course until they culminate in an acute life-threatening clinical presentation. The most common of these processes is aortic dissection.

Aortic dissection is characterized by an intimal tear and formation of a false lumen within the media of the artery. Repetitive hemodynamic forces produced by the blood ejected into the aorta with each cardiac cycle contribute to the weakening of the aortic intima and to medial degeneration. Sustained HTN intensifies these forces. Acute elevations in heart rate and BP can lead to catastrophic acute worsening of the disease process. The false lumen, as it extends, can obstruct the true lumen, leading to such complications as acute MI, acute renal failure, and stroke. Many patients with aortic dissection have undermining of the elastic or muscular components of the media, which is quantitatively and qualitatively more severe than expected from aging, as seen in Marfan and Ehlers–Danlos syndromes, and congenital bicuspid aortic valve.

Patients with aortic syndrome present with acute onset of severe chest pain that typically radiates through to the back. The pain is at its most severe at onset, unlike the typically crescendo pain of ACS. Although clearly not diagnostic, terms such as “tearing,” “ripping,” and “stabbed me in the chest and back”

should alert the caregiver to the possibility of dissection. Presentations can vary, and thus aortic disease must be considered in any patient presenting with chest pain, especially because some treatments for ACS (thrombolysis and antithrombotic therapy) can worsen acute aortic syndrome.

Therapy for aortic dissection aims to halt progression; lethal complications arise not due to the tear itself but due to the extension of the tear such that occlusion or rupture occurs. Untreated, aortic dissection will result in death in 25% of patients in 24 hours, 50% in 1 week, and over 90% in 1 year. As the major etiologic component of the development and progression of aortic dissection, BP is the major target of treatment. Heart rate is also a major target of treatment because BP and heart rate together create a hemodynamic force that favors extension of the dissection.

Pathway Management

Figure 53.4 outlines the management of a hypertensive emergency with suspicion for an acute aortic syndrome.

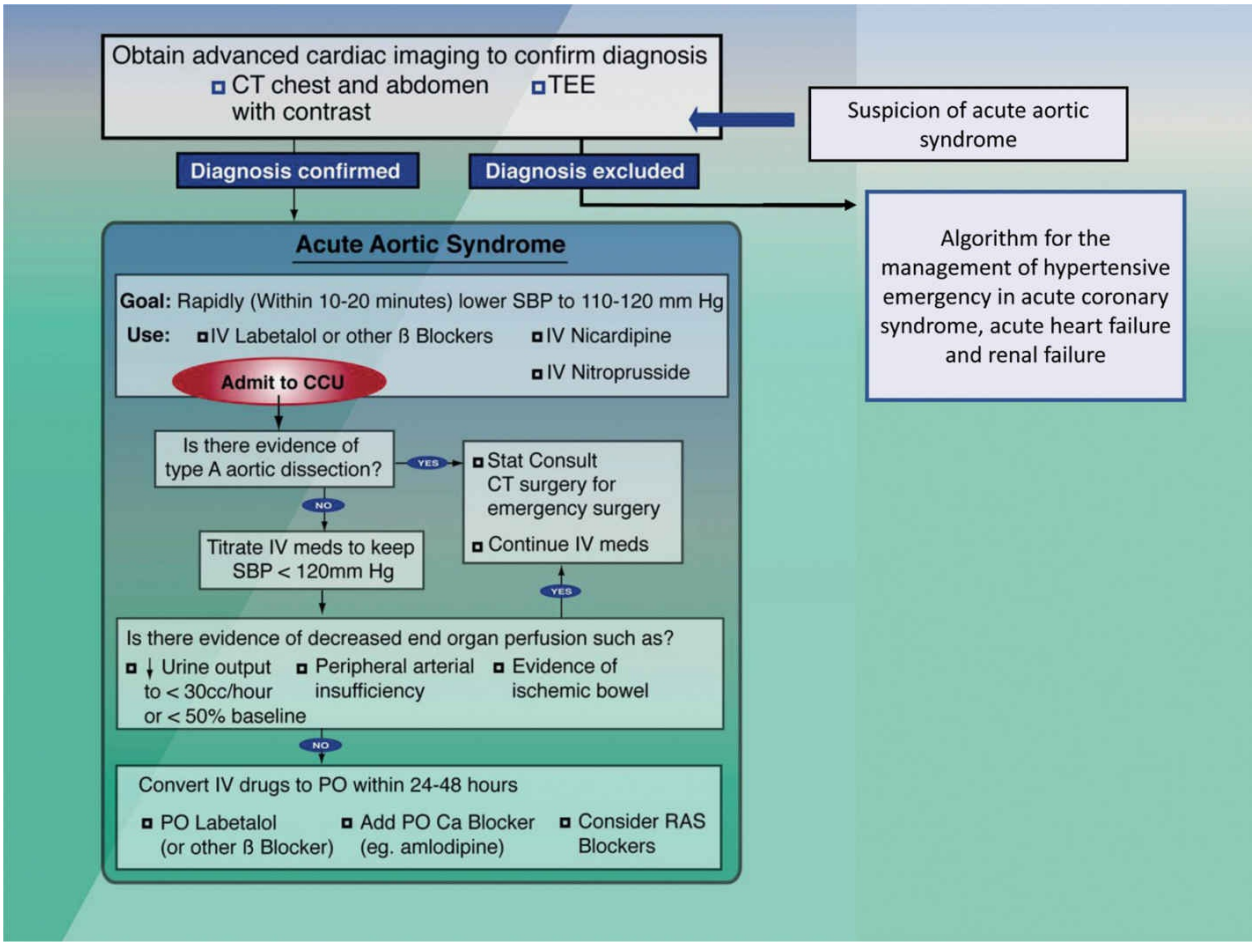

FIGURE 53.4 Management of a hypertensive emergency with suspicion of an acute aortic syndrome. CT, computed tomography; IV, intravenous; RAS, renin–angiotensin system; SBP, systolic blood pressure; TEE, transesophageal echocardiogram.

The modalities available for the diagnosis of aortic dissection include computed tomography (CT), magnetic resonance imaging (MRI), transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE), and aortography. The goals of imaging are to establish the diagnosis, determine location of the dissection (ascending, type A dissections are considered surgical emergencies), and determine extent of disease (eg, coronary or cerebral artery involvement). The choice of modality may be influenced by clinical presentation. The patient with suspected aortic dissection who also presents with physical examination findings suspicious for pericardial effusion or aortic regurgitation may benefit more from a TEE than CT, for example.

When the dissection involves the ascending aorta, the focus is surgical management. However, whether the dissection is ascending or descending, medical management to reduce BP and heart rate are critical and urgent.

Labetalol, which has α_1 and β_1 and β_2 adrenergic receptor inhibitory action, is an ideal drug because it reduces BP and heart rate, and can be given intravenously for immediate onset of action and titration. We recommend lowering BP within 10 to 20 minutes to an SBP level of 110 to 120 mm Hg. Esmolol, with its short half-life and β_1 receptor selectivity, may be a good alternative for those with reactive airway disease. The CCB nicardipine is an alternative as well. Once the patient is stabilized, whether surgically for ascending or medically for descending dissection, oral forms of the same medications (β-blocker, CCB, ACEI) are used for long-term BP control, which is crucial for secondary risk reduction.

HYPERTENSION AND ACUTE NEUROLOGIC SYNDROME

Stroke results from either ischemic or hemorrhagic causes. Ischemic stroke can be categorized by presumed mechanism of ischemia into coagulopathies (protein C deficiency, antiphospholipid antibody), small vessel-lacunar (vasculitis, embolic), large vessel-intracranial (dissection, atherosclerosis), large vessel-extracranial (Takayasu, atherosclerotic), and cardioembolic (atrial fibrillation, ventricular thrombus, infectious endocarditis). Some strokes are cryptogenic, or of undetermined cause. Hemorrhagic stroke can be categorized as intracerebral (bleeding into brain parenchyma, further classified as primary and unrelated to a brain lesion, or secondary and related to a congenital or acquired brain lesion or abnormality), subarachnoid, or intraventricular. HTN is a major risk factor for both ischemic (especially small vessel-lacunar) and hemorrhagic stroke, and thus there is little doubt that treating BP for stroke prevention (both primary and secondary prevention) is justified and very important. However, it is in the treatment of HTN for the patient in the acute phase of a stroke that there has been much controversy and ambiguity; recent data are shedding more light on this important issue.

Stroke is a major cause of morbidity and mortality; in 2014, it was the fifth leading cause of death in the United States, behind heart disease, cancer, chronic lower respiratory illnesses, and unintentional injuries.[17] Perhaps more devastating is the morbidity in survivors; stroke is the leading cause of long-term disability in adults. A total of 15% to 30% of stroke survivors are permanently disabled, and 20% require institutional care by 3 months.

Timely diagnosis of stroke, greatly dependent on history and physical examination, is critical because early implementation of treatment can improve

prognosis; some treatments for ischemic stroke, for example, are only implementable within 3 (IV recombinant tissue plasminogen activator [rtPA]) to 6 hours (intra-arterial thrombolysis) from onset of event. For this reason, the most important piece of history is time of symptom onset. Findings such as focal neurologic deficit, persistent neurologic deficit, acute onset of symptoms, and no history of head trauma favor the diagnosis of stroke; the presence of all four of these findings makes a stroke likely. Symptoms also enable the experienced clinician to determine the vascular distribution (eg, anterior or posterior) of a stroke. Once stroke is suspected, severity can be assessed with the NIH (National Institutes of Health) Stroke Scale, the diagnosis can be further pursued with imaging studies, and tests can be obtained to exclude conditions that mimic strokes (tumor, hypertensive encephalopathy, seizure, migraine variant).

The first imaging test to obtain in the acute stroke patient is a noncontrast CT scan of the brain, because this will identify most intracranial hemorrhage (ICH) and help exclude stroke mimickers such as neoplasms. Importantly, CT will not reliably diagnose ischemic stroke when early in its evolution; MRI, on the other hand, will. MRI with diffusion-weighted and perfusion-weighted imaging has a high sensitivity and specificity for ischemic lesions, even within minutes of symptom onset, and can identify brain tissue that is ischemic but not yet infarcted and therefore amenable to being rescued if successfully revascularized. CT angiogram provides maps of cerebral blood flow, thus possibly revealing occlusion or stenosis.

An elevated BP is often detected in the first few hours after stroke. BP is usually higher for acute stroke patients with a history of HTN than in those without premorbid HTN. For ischemic strokes, the elevated BP may be a protective response of the body to maintain perfusion of partially ischemic areas. Still, for every 10 mm Hg increase above 180 mm Hg, the risk of neurologic deterioration increases by 40%, and the risk of poor outcome increases by 23% in the case of ischemic strokes. Despite this association between elevated BP and poor outcomes, the management of arterial HTN in ischemic stroke has been controversial. Investigators found a U-shaped relationship between death and admission BP; both elevated and low admission levels were associated with high rates of early and late death from stroke.[18] Elevations in mean BP during the first few days after stroke had an unfavorable effect on outcomes; death due to brain injury and brain edema correlated with high initial BP. Theoretical reasons for lowering BP include reducing brain edema, reducing risk of hemorrhagic transformation, and preventing further vascular damage. Conversely, it has been

theorized that overly aggressive BP reduction may lead to neurologic worsening.[19] Furthermore, the majority of patients experience a drop in BP within the first hour of stroke without any medical treatment. Recommendations for BP control vary depending on whether it is the acute post-stroke phase or the chronic phase, and whether thrombolysis is being pursued or not; this has been discussed subsequently. In the case of hemorrhagic strokes, the issue is complex as well. Although elevated BP maintains perfusion of jeopardized brain tissues, it serves as a continued driving force for bleeding. However, rapid decrease in BP can impair perfusion and cause ischemia. Recommendations for management are discussed here.

Pathway Management

Figure 53.5 outlines the management of a hypertensive emergency with suspicion for an acute neurologic syndrome.

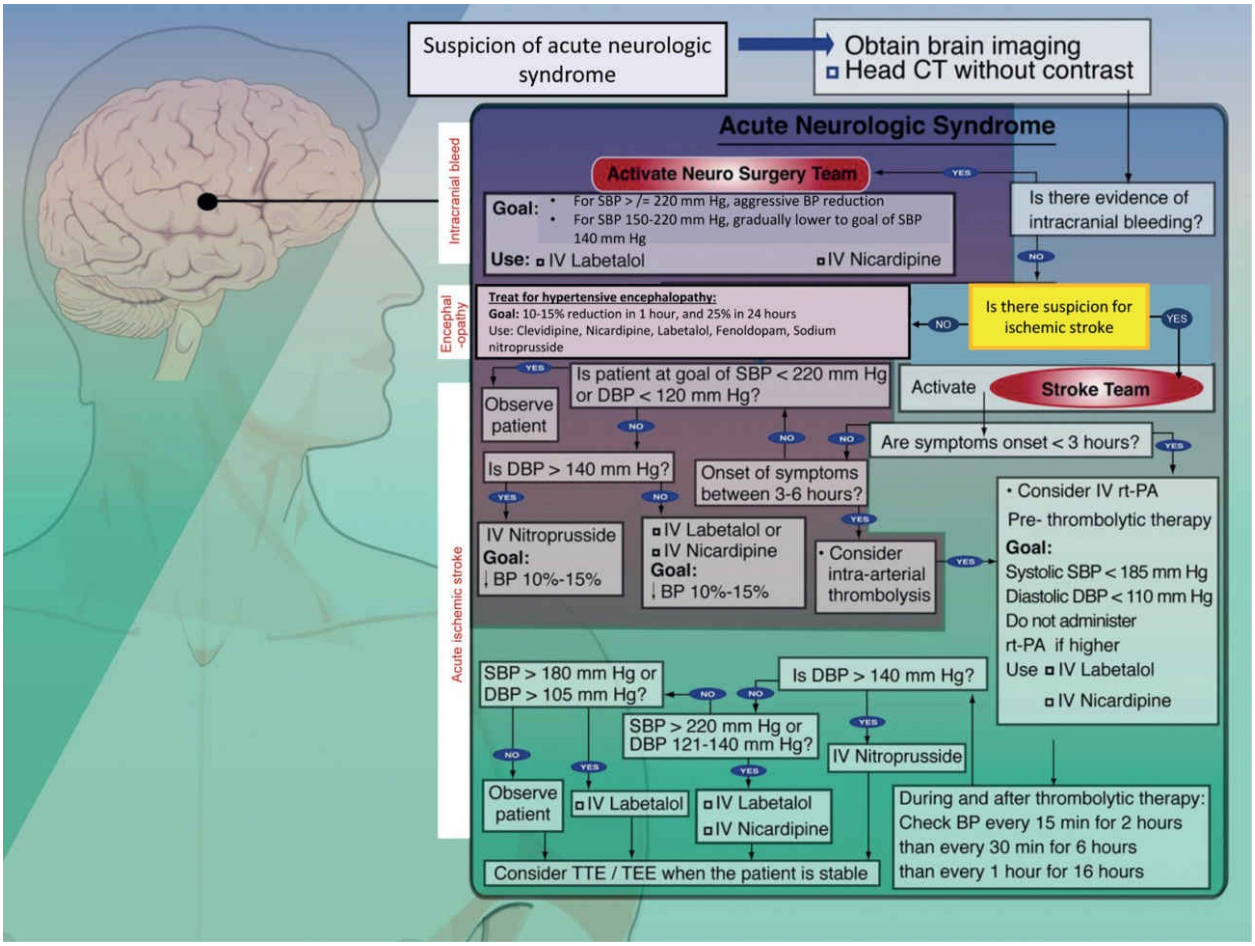

FIGURE 53.5 Management of a hypertensive emergency with suspicion of an acute neurologic syndrome. BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; IV, intravenous; rtPA, recombinant tissue plasminogen activator; SBP, systolic blood pressure; TEE, transesophageal echocardiogram; TTE, transthoracic echocardiogram.

Our group subdivides the management of a hypertensive emergency with the suspicion of an acute neurologic syndrome into the management of three distinct clinical scenarios:

a. ICH: With respect to patients with ICH, controversy persists regarding the appropriate goal for BP management. Some studies have shown no benefit in terms of mortality and disability for aggressive BP management,[20,21] whereas others have shown reduction in hematoma size with aggressive BP control.[22] At the moment, guidelines recommend that for SBP > 220 mm Hg, rapid reduction of BP with IV agents is necessary, whereas for SBP between 150 and 220 mm Hg, targeting an SBP of 140 mm Hg should be pursued.[23]

b. Ischemic stroke: For ischemic strokes, the management and guidelines for BP

control are somewhat different. For symptoms less than 3 hours old, IV rtPA is recommended for selected patients without contraindications (eg, history of previous ICH); for symptoms 3 to 6 hours old, intra-arterial thrombolysis may be used. However, BP over 185/110 mm Hg is a contraindication to IV rtPA. In this setting, labetalol and nicardipine may be used to rapidly lower BP. During and after thrombolytic therapy, nitroprusside, labetalol, or nicardipine should be used, depending on how high the BP is, to maintain BP below 180/105 mm Hg.[24]

c. Hypertensive encephalopathy: For hypertensive encephalopathy, on the other hand, the baseline BP must be considered to avoid excessive BP lowering and prevent cerebral ischemia. Lowering the mean arterial pressure by 10% to 15% in the first hour and by 25% in the first 24 hours usually is a safe maneuver because of the pressure autoregulatory cerebral blood flow range.

Patients who were taking antihypertensive medications before their stroke or are found to have sustained HTN after their stroke will need long-term antihypertensive treatment. Historically, there was a belief in the medical community that permissive HTN in the long term was protective for patients after an ischemic stroke. In fact, in patients followed up from the time of a first ischemic stroke to the time of a second stroke in the same territory, risk was increased rather than decreased with higher BP, a finding driven mainly by SBP elevations above 160 mm Hg.[25] The same facts are valid for ICH. Control of the SBP is the cornerstone of secondary prevention of recurrent ICH.[26] The timing of the reinstitution of treatment and the selection of medications will depend on the patient's neurologic status, the underlying stroke mechanism, the patient's ability to swallow medications, and the presence of concomitant disease. Presumably, most patients with mild-to-moderate stroke who are not at high risk for increased intracranial pressure may have their prestroke antihypertensive medications restarted 24 hours after their vascular event.[24]

Figure 53.6 outlines the management of a hypertensive emergency with acute HF, ACS, or renal failure.

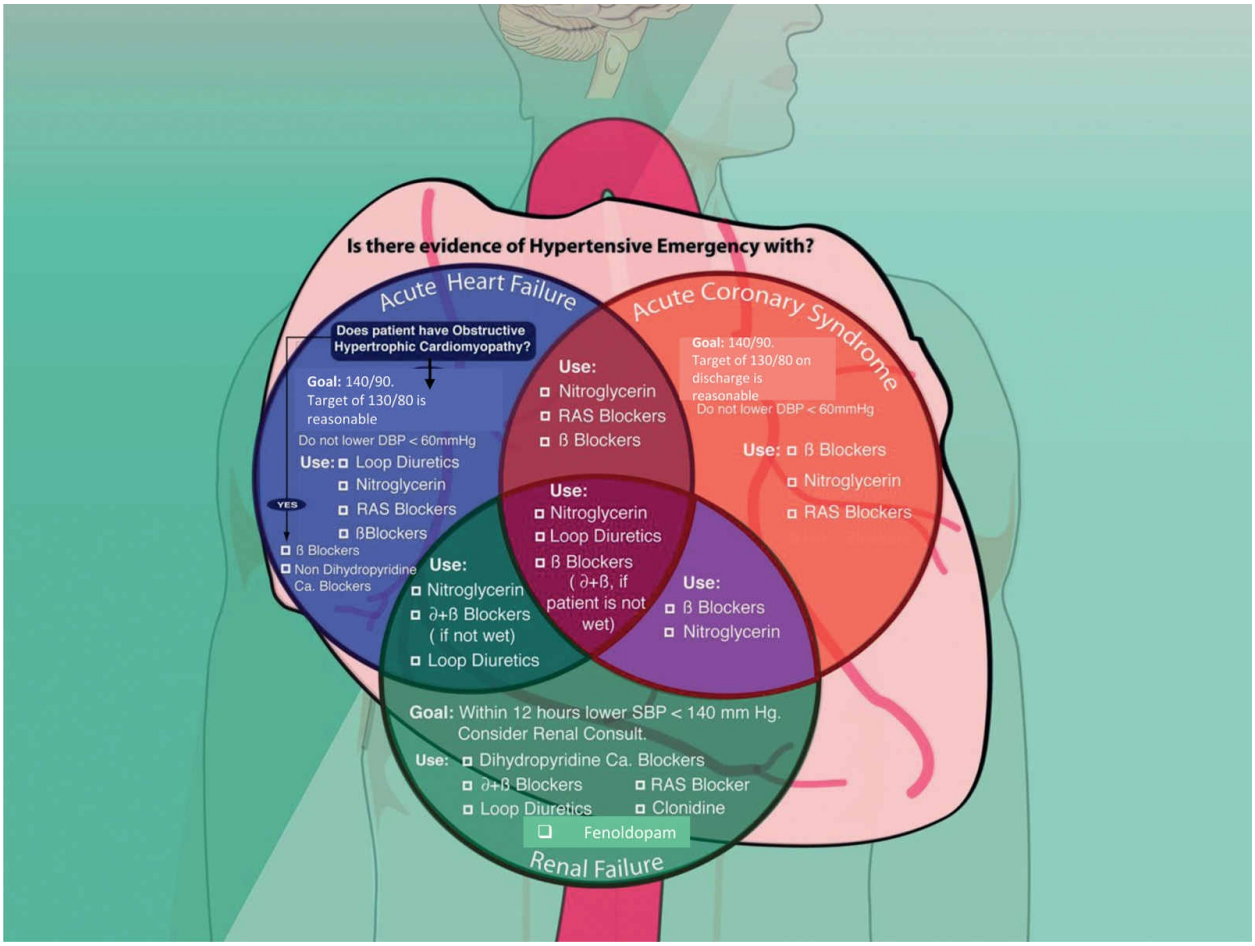

FIGURE 53.6 Management of a hypertensive emergency in acute coronary syndrome, acute heart failure, or renal failure. BP, blood pressure; DBP, diastolic blood pressure; RAA, renin–angiotensin system; SBP, systolic blood pressure.

HYPERTENSION AND ACUTE CORONARY SYNDROME

ACS refers to a spectrum of diseases that range from unstable angina and non–ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI).

ACS is perhaps best explained in terms of the delicate balance between myocardial oxygen supply and demand. When this balance is disrupted by a disease process that affects coronary blood flow, myocardial ischemia may induce contractile dysfunction, precipitating a vicious cycle that includes tachycardia and hypotension, which may further worsen the supply–demand imbalance.

Myocardial oxygen demand is largely dependent on heart rate, myocardial wall stress (systolic pressure), and LV contractility. Myocardial oxygen supply

depends on the coronary circulation. In contrast to most other vascular beds, myocardial oxygen extraction is near maximal (75% of arterial oxygen content) at rest.[27] Consequently, demand for increased myocardial oxygen consumption must be met primarily by increased oxygen delivery. A 2-fold increase in any of the determinants of oxygen consumption requires an approximately 50% increase in coronary flow.

HTN increases demand: it increases myocardial wall stress and thus requirements of coronary flow. HTN may also limit supply: it is a risk factor for vascular remodeling and atherosclerosis, the disease process that limits coronary blood flow. Even at an early age, increased vascular wall tension in people with high BP leads to thinning, fragmentation, and fracture of elastin fibers, as well as increased collagen deposition in arteries, which results in decreased compliance of these vessels. In addition to these structural abnormalities, the HTN-mediated functional abnormality of increased arterial rigidity due to endothelial dysfunction develops over time because of aging and HTN and contributes to systolic HTN.[28]

Many of the mechanisms that initiate and maintain HTN (increased sympathetic nervous system and renin–angiotensin–aldosterone system [RAAS] activity; deficiencies in release and/or activity of vasodilators, structural and functional abnormalities in conductance and resistance arteries) are also those that mediate damage to target organs, including the coronary vessels and the myocardium.[29] This may be why antihypertensive drugs exert at least some of their beneficial effects on the vasculature by actions that are independent of BP lowering alone.

The medications used to treat ACS can be understood within the framework of the supply/demand balance. β-Blockers work to decrease BP and heart rate, two major determinants of myocardial oxygen demand. Nitrates decrease preload, and thus ventricular filling pressures and wall stress (demand). Nitrates also cause coronary vessel dilatation (supply). Morphine decreases pain and thereby heart rate, while also decreasing venous return and filling pressures (demand). Often, the patient with ACS will need a cardiac catheterization whether for diagnostic or treatment purposes. Cardiac catheterization is the gold standard for diagnosis of coronary vessel disease, and angioplasty and coronary stenting can relieve the stenosis or occlusion (supply) in a way no medication can.

Pathway Management

Detailed guidelines exist for HTN in ACS.[30] In an ACS, β-blockers are the first line of treatment based on their ability to reduce both heart rate and BP and thus myocardial oxygen demand **(Figure 53.6)**. In the case of hypertensive emergences, an IV β-blocker may be needed. NTG has been a cornerstone of therapy for decades in ACS, and in the hypertensive patient, IV NTG is effective in the reduction of BP and symptoms. Patients need to be monitored for potential adverse effects, particularly profound hypotension, which can exacerbate ischemia. Caution should be used if there is right heart dysfunction. If β-blockers are contraindicated, a non-dihydropyridine CCB (diltiazem or verapamil) may be used, assuming there is no LV dysfunction. An ACEI or an ARB can also be considered for the management of HTN in patients with ACS, and must be added when there is LV dysfunction, anterior wall MI, diabetes, and if HTN persists. In persistent HTN even after optimization with β-blockers and ACEI/ARB, a long-acting dihydropyridine CCB (especially if there is persistent angina) or a thiazide may be used. In patients with MI and LV dysfunction, in whom HTN persists despite β-blocker and ACEI, an aldosterone antagonist may be considered. When there is symptomatic HF or CKD with GFR <30 mL/min, a loop diuretic can be used. In patients with ACS, guidelines recommend lowering BP to <140/90 mm Hg in patients who are hemodynamically stable. Targeting BP of <130/80 mm Hg at discharge is reasonable, lowering diastolic pressure <60 mm Hg should be avoided.

HYPERTENSION AND HEART FAILURE

HF can be due to a decrease in cardiac output such that end-organ perfusion is compromised (systolic dysfunction), or due to maintenance of cardiac output at the expense of increased left atrial filling pressures (diastolic dysfunction), or due to both. Both systolic and diastolic dysfunction can be understood in terms of the determinants of cardiac performance.

The determinants of cardiac performance are preload, afterload, contractility, and heart rate. As the ability of the myocardium to maintain normal forward output fails, compensatory mechanisms are activated to preserve circulatory function. Preload increases to increase stroke volume (Frank–Starling mechanism). Hemodynamic stress that cannot be compensated initiates structural changes at the cellular levels, referred to as myocardial remodeling. If the Frank–Starling and remodeling mechanisms are unable to reestablish cardiac output, neurohormonal systems are also activated. Although each of these mechanisms may contribute to maintenance of circulatory function, each may

also contribute to development and progression of pump dysfunction.

HTN is intricately linked to both systolic and diastolic dysfunction by affecting each of these mechanisms. The renin–angiotensin system (RAS) that is so fundamentally linked to HTN and that recruits intravascular volume to sustain end-diastolic filling pressures may elevate preload to the point of putting a patient on the flat or descending portion of the Frank–Starling curve. HTN induces cardiac remodeling and LV hypertrophy; to decrease LV wall stress, contractile proteins are added to myocytes in parallel, thus increasing wall thickness and decreasing cavity size. Increasing thickness and decreasing cavity size relieves the increase in wall stress, but at the expense of LV remodeling and hypertrophy. Finally, the sympathetic activation that increases vascular tone also increases myocardial oxygen demand and eventually results in downregulation of β-adrenergic receptors, further impairing the ability of the system to maintain forward output.

The staples of HF treatment are diuretics, β-blockers, and ACEIs. Diuretics, specifically loop diuretics, combat the increased total body volume that is central to the pathophysiology of HF. β-Blockers and ACEIs/ARBs combat the cardiac remodeling and neurohormonal activation. Aldosterone antagonists are particularly important when there is LV dysfunction, by countering neurohormonal-mediated remodeling. The CCB amlodipine, although not first line, appears to be safe if needed for the treatment of HTN (or angina) in the patient with LV dysfunction.[31]

Pathway Management

Careful guidelines exist for the management of HTN in HF, both systolic and diastolic HF **(Figure 53.6)**.[30,32] β-Blockers and ACEIs, which show benefit in systolic HF, should form first-line therapy. Diuretics are important for volume control and BP; although thiazides can be used, loop diuretics are key in severe HF (New York Heart Association [NYHA] Class III and IV) and in CKD when GFR is <30 mL/min. In persistent HTN in patients with LV dysfunction, aldosterone antagonists may be used. In African Americans, with LV systolic dysfunction, hydralazine and isosorbide dinitrate should be added to standard therapy. In hypertensive emergencies or in patients with severe pulmonary edema, parenteral nitrates play an important role. Although few guidelines exist for management of diastolic dysfunction, BP management—both SBP and DBP—is paramount. In addition, therapy may be directed toward management of pulmonary edema and toward rate control in atrial fibrillation. One caveat in the

management of HTN in the setting of acute HF is the exclusion of hypertrophic cardiomyopathy. In patients with hypertrophic cardiomyopathy, guidelines recommend the exclusive use of a β-blocker or a non-dihydropyridine CCB (in patients with a contraindication to β-blockers) and avoidance of diuretics or NTG.

HYPERTENSION AND RENAL FAILURE

Renal failure tends not to be the primary reason for CCU admission but rather a complication or comorbidity of some other disease process requiring CCU care, such as hypertensive emergency or acute decompensated heart failure (ADHF). Nonetheless, because renal failure is associated with poor outcomes, preserving or improving the CCU patient's renal function must be a primary objective.

Severe and/or long-standing HTN induces renal microvascular damage. Mechanical stress and endothelial injury lead to increased vascular permeability, activation of the coagulation cascade and platelets, and deposition of fibrin. This fibrinoid necrosis narrows the vessel lumen, which causes renal hypoperfusion and triggers massive renin release, generating a vicious cycle of ongoing injury. RAS activation involves production of angiotensin II and release of aldosterone; this in turn leads to further vasoconstriction and sodium reabsorption, worsening HTN. Angiotensin II, acting on the efferent arteriole of the nephron, leads to pressure natriuresis, which can lead to end-organ hypoperfusion, ischemia, and dysfunction. HTN begets renal damage that begets more HTN, which if severe enough causes acute end-organ damage (hypertensive emergency).

Renal failure in the setting of acute HF is a complex issue, and an understanding of the concept of cardiorenal syndrome is essential. HF decreases renal perfusion and predisposes to renal failure. Further more, vascular congestion and increased intra-abdominal pressure in acute HF may also be implicated.[33] With worsening renal failure, there is increased fluid retention and volume overload that can worsen HF. Further more, renal failure makes diuretic dose requirements for HF higher; if HF is hemodynamically significant such that renal perfusion is compromised, inotropes or dialysis may be the only effective options. Diuretics increase solute delivery to distal segments of the nephron, resulting in epithelial cell hypertrophy and hyperplasia, which increases the solute resorptive capacity of the kidney. Reduction in renal extracellular fluid volume also leads to an increase in solute and fluid reabsorption, specifically in the proximal tubule. These mechanisms result in a state in which HF and renal failure worsen each other and make difficult the treatment of both. Although

these patients may be hypotensive initially, they often eventually become hypertensive. The elevated BP may augment renal perfusion, whereas the continued venous congestion causes renal failure to persist, and the rising BP worsens HF. As such, BP management and efficient diuresis is key.

Pathway Management

For the hypertensive emergency patient in acute renal failure, the recommendation is a goal of lowering SBP to 140 mm Hg within 12 hours and considering consultation by a nephrologist (**Figure 53.6**). A recommended strategy is for a 10% to 20% reduction in mean arterial pressure during the first 1 to 2 hours, and then a further 10% to 15% reduction during the next 6 to 12 hours.

Early on, parenteral agents may be needed. Some physicians advocate the use of fenoldopam, which is unique among the parenteral BP agents because it mediates peripheral vasodilation by acting on peripheral dopamine-1 receptors, and thus, despite lowering systemic BP, by acting on these receptors in the renal vessels, it promotes renal perfusion. Thus, fenoldopam improves creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function.[34] Fenoldopam has onset of action within 5 minutes, peak action by 15 minutes, and duration of action from 30 to 60 minutes. No adverse effects have been reported.

The recommended sequence of add-on parenteral drugs is dihydropyridine CCB (nicardipine: onset 5 to 15 minutes, duration 4 to 6 hours, and increases stroke volume and reduces both cardiac and cerebral ischemia; clevidipine may also be used) and then α- + β-blocker (labetalol: liver metabolism, onset in 2 to 5 minutes, peak at 5 to 15 minutes, duration 2 to 4 hours, maintains cardiac output because of α-blocking effect). In addition, the ultimate therapy includes loop diuretics, RAS blocker, and clonidine. Loop diuretics are essential, especially in acute glomerular diseases, to reduce volume and pressure. ACEIs improve renal blood flow and reduce ischemia; they are essential in acute vascular forms of renal failure, such as scleroderma renal crisis.

Regarding long-term management, it is important to note that patients with CKD die from heart disease more than anything else. CKD is a risk factor for CAD, valvular heart disease, and other causes of heart disease. HTN control is critical to reduce the rate of development of these cardiovascular processes. If HTN is controlled, CKD progresses more slowly. Because the mechanism of HTN in the patient with CKD is RAAS activation, ACE inhibitors and ARBs are

particularly valuable agents. The choice of agents often is dictated by the presence or absence of proteinuria (for which an ACEI or ARB is essential) or if edema is present (for which a diuretic is needed). In patients with proteinuric CKD, ACEI and ARB are first-line agents, irrespective of race.[2] Second-line agents include diuretics and non-dihydropyridine CCB (as they reduce proteinuria), although a diuretic is preferred in the setting of edema. In the absence of proteinuria, diuretics are preferred first-line agents, and these can be followed by dihydropyridine CCB and angiotensin blockers in patients with edema; in the absence of edema, ACEI/ARB or CCB can be used first.[7]

PLAN FOR DISCHARGE THERAPY

Once discharged from the CCU, the patient must take seriously the importance of secondary prevention, of which BP control is an important component.

Lifestyle modifications that have been associated with favorable results in hypertensive patients include weight loss, increased physical activity, smoking cessation, and a low-fat, low-sodium diet. Tightly controlled dietary modification, as in the Dietary Approaches to Stop Hypertension (DASH) study, for example, can reduce mean SBP by 3.0, 6.2, and 6.8 mm Hg in subjects on a low-, intermediate-, and high-sodium-intake diet, respectively. Weight loss, reduced sodium intake, moderation of alcohol consumption, exercise, and an overall healthy dietary pattern are entirely appropriate for patients aiming to control HTN.

Oftentimes, pharmacologic treatment is necessary to control BP, especially for patients discharged from the CCU. The most important question to ask when selecting the initial drug treatment is, which class of drug will deliver the most effective BP lowering for this patient? As mentioned, certain medications have beneficial effects for certain disease states that go beyond the medication's BP-lowering effects (β-blockers for HF). However, it must be emphasized that BP lowering is in itself a driver of benefit. In other words, regardless of the drug used, the goal should be to, lower BP. The response to different classes of drugs is similar when compared head-to-head in heterogeneous populations. However, individual responses can differ strikingly.

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Patient and Family Information for: HYPERTENSION IN THE CARDIAC CARE UNIT

CARDIOVASCULAR SYSTEM AND HYPERTENSION

The cardiovascular system serves to propel and transport blood, which carries the elements necessary for healthy functioning of all the organs of the body. Oxygen, glucose, electrolytes, immune cells, clotting cells, and a variety of other blood components must travel to every part of the body.

The cardiovascular system is sometimes compared to a water system with a pump and water pipes. It is a closed system, in that the system is self-contained; there are no openings to the outside. All the blood that starts in the heart returns to the heart (unless, of course, there is damage to the system, as in a tear to a vessel that results in internal or external bleeding). The pipes that leave the pump are largest because they must bear the greatest volumes and pressures. The pipes let off more and more branches as they get farther from the source and therefore get smaller and thinner. The vessels that leave the heart are arteries that feed capillaries before the blood makes its way back to the heart in veins.

BP is an index of the force per unit area inside the arteries. Factors that influence BP are the rate of blood flow through the vessel and the flexibility of the blood vessel wall. The rate of blood flow ejected from the heart through the arteries and veins per minute (cardiac output) depends on the number of heart beats per minute (heart rate) and the amount of blood ejected per beat (stroke volume). The flexibility or resistance of blood vessel walls depends on many factors including age, the nervous system, and hormones. In summary, the heart pump and its cardiac output along with the blood vessels and their resistance are what determine a person’s BP. This is important because it serves as the basis for

understanding how such factors as age, medications, and lifestyle influence our BP.

The medical term for high BP is HTN. HTN is defined as a BP of 140/90 mm Hg or above. The first number represents the SBP; the second is the DBP. As mentioned, the heart beats to propel blood, and does so, on average, between 60 and 80 times/min. When the heart ejects blood, the pressure in the arteries goes up because the pressure generated in the heart's largest chamber is transmitted throughout the closed cardiovascular system and there is a surge in the rate of blood flow through the arteries; this yields the SBP. After the heart muscle contracts, it must relax to prepare for the next contraction and in so doing allows for blood, which returns through veins, to refill the chambers of the heart. This yields the DBP: the pressure in the arteries during the heart muscle's relaxation phase.

CCU AND HYPERTENSION

The CCU is where patients go when they are too sick to be adequately managed on a general hospital floor. The patient in the CCU needs more specialized care and to this end is managed by nurses and doctors with specialized training in critical care and cardiovascular medicine. The nurses are responsible for fewer patients than on a general floor, and thus are able to dedicate a greater level of attention to each patient. The team of doctors assigned to the CCU remains in that unit throughout the day, rather than moving throughout the hospital.

Patients can be admitted to the CCU for a variety of conditions, such as heart attack, HF, tears in the aorta (the major artery that leaves the heart), and very high BP. BP is an important component of every disease condition that warrants a CCU admission. In some cases, BP can be dangerously high; in others dangerously low. In some cases, aberration in BP (too high or too low) is the source of the problem (hypertensive emergency causing HF), whereas in others it is the result of the problem (heart attack causing dangerously low BP). Regardless, BP is something the CCU doctor must manage for every patient, and something the patient must be educated about and take seriously, both for the short term and for the long term.

DRUGS

Surely, patients and their families have heard doctors use an overwhelming number of names of drugs. Not only are there a seemingly endless number of medications but also every medication has at least two names, a generic name and a brand name (ie, metoprolol is also Lopressor and Toprol). It makes things simpler to think of drugs in terms of drug classes. This is how doctors think, and for good reason. Drugs that make up a drug class perform a similar function via a similar mechanism. β-Blockers, for example, help block activity of the β-receptor, found on the surface of many cells, including those of the heart and blood vessels. β-Blockers are very important in the treatment of HF and HTN (among other things). Furthermore, most drugs in a class have a similar-sounding generic name. β-Blockers, for example, end in "lol" (ie, metoprolol, carvedilol, atenolol). So, for example, one remembers the β-blockers as the "-lol" drugs, which are used to treat HF. ACEIs are the "-pril" drugs (ie, lisinopril, captopril, enalapril) most commonly used to treat HTN, HF, and kidney disease. A drug class that is similar to the ACEIs is the ARB family, or "-artan" drugs (ie, irbesartan, candesartan, losartan). These drugs have clinical indications similar to those of the ACE inhibitors, and have the benefit of a lesser likelihood of causing cough as an adverse effect. The CCBs can be subdivided into the dihydropyridne and non-dihydropyridines. The dihydropyridine CCBs are commonly used BP medicines, and can be remembered as the "-dipine" drugs (ie, amlodipine, nicardipine, nifedipine). The α-blocker medicines mediate their BP-reducing effects by blocking a receptor on blood vessels responsible for vessel constriction (as the vessel diameter gets smaller, the pressure within the vessel increases). These "-osin" (ie, tamsulosin, terazosin, doxazosin) medicines have a second use in relieving the symptoms of urinary frequency, hesitancy, and urgency associated with benign prostatic hyperplasia, or BPH. Thinking in terms of classes of medicines, which conveniently tend to have similar-sounding and thus easier-to-remember names, is much easier and more intuitive than remembering individual drugs.

HYPERTENSION AND ITS ROLE IN THE COMMON CCU DISEASE PROCESSES

As mentioned, patients are admitted to the CCU for a variety of conditions, most, if not all, of which have HTN as a significant consideration, either as cause, effect, or important comorbidity.

HYPERTENSION AND DISEASES OF THE AORTA

The aorta is the largest artery of the body. Because it is the first vessel that blood travels through once it leaves the heart, within it travels all of the blood that leaves the heart. All other vessels are branches of a larger vessel and therefore will only receive a fraction of the cardiac output (blood leaving the heart per minute), whereas the aorta must withstand the volume and pressure of the entire cardiac output. It is no surprise, then, that the aorta is the largest, thickest-walled blood vessel in the body. One can imagine that diseases of the aorta are potentially catastrophic; for example, a ruptured vessel in the finger will cause that vessel to spill its fraction of cardiac output, whereas a rupture of the aorta will lead to rapid loss of a huge proportion of the body's blood. Motor vehicle accidents, for example, in which the passenger is propelled forward, and then held back by a seat belt, can cause the aorta to tear, leading to immediate death.

Patients admitted to the CCU for disease of the aorta often have an acute aortic syndrome, subdivided into three conditions: aortic dissection, intramural hematoma, and aortic ulcer. An aortic dissection is a tear in the innermost lining of the aorta; an intramural hematoma is a pooling of blood in the wall of the aorta without any tear in the lining of the vessel; an aortic ulcer occurs when a plaque in the inner lining of the vessel leads to erosion of the inner part of the vessel wall and swelling of the vessel contained by the outermost lining of the wall. Patients with any of the acute aortic syndromes will usually feel sudden onset, severe, "ripping" or "tearing" pain that often feels like it goes through the chest and into the back.

Aortic dissection is a tear in the innermost lining of the aorta such that blood begins infiltrating the wall of the vessel. The problem is that this infiltrating blood pushes the inner lining into the pathway of oncoming blood, leading to obstruction to flow and an expansion of the tear. If the tear is in the first "ascending" part of the aorta, the patient needs surgery; if the tear is in the "descending" aorta, the management is medical and not surgical. Aortic dissection may be a consideration for a patient who presents with chest pain, especially patients who smoke and/or have HTN. Aortic dissection can easily be confused with heart attack; this is important because not only are the treatments different but certain treatments for heart attack, for example, clot breaking medication, can be harmful for a patient with aortic dissection.

High BP is the major risk factor for both types of aortic dissection, and BP is also the major target of medical treatment. Precipitous reductions in BP can sometimes be dangerous in other conditions such as ischemic stroke, but in the

case of acute aortic dissection, the physician can and should be aggressive in lowering BP. BP reduction helps prevent extension of the tear, which could lead to stroke, cardiac tamponade, or other major complications. Every time the heart beats, a surge of blood exerts a force against the vessel wall, forcing blood into the tear and potentially causing the tear to enlarge and extend. β-Blockers, the "-lol" drugs, are often used because they lower not only BP but also the heart rate. IV β-Blockers such as labetalol are used for rapid BP and heart rate reduction to a target of under 120 mm Hg BP and under 60 beats/min heart rate, or as low as tolerated by the patient (lowering heart rate or BP too much can lead to such symptoms as dizziness). The patient is sent to the CCU to continuously monitor heart rate and BP in response to IV medication and also to monitor electrocardiogram readings in case the dissection leads to complications. Once BP is controlled, the patient can be switched to oral medications. The patient must understand the importance of compliance with medical and lifestyle recommendations to prevent future complications of aortic dissection.

HYPERTENSION AND ACUTE NEUROLOGIC SYNDROME

Patients may often be admitted to the CCU for stroke or hypertensive encephalopathy. Stroke, or cerebrovascular accident, is due to decreased oxygenated blood supply to the brain. A heart attack is death of heart muscle due to decreased blood flow to the heart, whereas stroke is death of brain cells due to impaired blood flow to the brain. If blood flow is restored before cell death occurs, brain function may recover completely; this condition is referred to as a TIA or transient ischemic attack. Stroke can be thought of as coming in two forms: stroke due to a blockage (ischemic stroke) versus bleeding (hemorrhagic stroke) of an artery supplying the brain. The end result, brain cell death, is similar for both. In addition, stroke may increase pressure in the skull and thus cause compression of surrounding healthy brain tissue because of edema or swelling in ischemic stroke and accumulation of blood in hemorrhagic stroke. In hypertensive encephalopathy, on the other hand, severe HTN causes not localized brain ischemia but rather global brain dysfunction with its associated symptoms. As a result, patients suffering from stroke often have focal neurologic deficits (weakness in a limb, slurring of speech, facial drooping), whereas patients with hypertensive encephalopathy lack focal symptoms and present instead with nausea, blurry vision, headache, and/or altered consciousness.

The first step in the assessment of a patient with suspected neurologic syndrome is a head CT scan to evaluate for bleeding in the skull. CT scans are

effective for detecting blood, and although not necessarily helpful in the diagnosis of hypertensive encephalopathy or early ischemic stroke, a CT scan is the first test because an intracranial bleed, if found, might require immediate neurosurgery.

HTN is a major risk factor for acute neurologic syndrome, and a major target of therapy. For hemorrhagic stroke, BP must be lowered promptly but not to such an extent that arterial pressure becomes inadequate to sufficiently overcome intracranial pressure; cerebral perfusion pressure, or the net BP gradient responsible for blood flow to healthy brain tissue, depends on adequate arterial pressure. Generally, the BP goal is 140 mm Hg for SBP. For ischemic stroke, it has been commonly accepted in the medical community that aggressive lowering of BP may do more harm than good. On the other hand, high BP increases the risk of expansion of edema and/or conversion of an ischemic stroke into a hemorrhagic one. Many patients have spontaneous declines in BP during the first 24 hours of stroke onset. In general, the BP goals for patients with ischemic strokes are different depending on whether interventions involving “clot busters” called “thrombolytics” are undertaken to reestablish blood flow in the blocked artery. When thrombolytic therapy is undertaken, lower BP targets are aimed for during and after the procedure (around 180/105 mm Hg). When thrombolytics are not used, no treatment is required when BP is less than 220/120 mm Hg. In 2013, an expert panel reiterated these recommendations.

For hypertensive encephalopathy, the baseline BP must be taken into consideration to avoid excessive BP lowering and to prevent cerebral ischemia. Lowering the mean pressure by 10% to 15% in the first hour and by 25% over 1 day is usually safe.

HYPERTENSION AND ACUTE CORONARY SYNDROME

An ACS is a decreased blood supply to the heart (myocardial cell ischemia) that may or may not result in myocardial cell injury or death and that is due to CAD. The three forms of ACS are unstable angina, non-STEMI, and STEMI. These three entities are manifestations of the same disease process and were extensively discussed in Section A of this book.

The heart is thought of as the organ that supplies blood to the rest of the body; in fact, the heart supplies blood to the rest of the body and to itself. It does so through vessels known as coronary arteries, which come off the aorta immediately after the blood leaves the heart. There are three large coronary arteries that travel along the surface of the heart before diving deep to feed all

the cells of the heart muscle. A blockage to flow in any of the coronary arteries can cut off supply enough to starve cells and lead to their death. If cells of a certain portion of the heart fail to beat adequately, the heart may not generate enough force to sustain cardiac output. A heart attack, or MI, may cause the heart to stop beating effectively (HF), or stop beating altogether (sudden cardiac death). HTN is considered a major risk factor for CAD, and thus for MI and HF.

The key concept to understand regarding coronary blood supply is that of supply and demand. The heart is unique in that it is responsible for both its supply and demand. As the heart beats harder, it supplies more blood flow, but it also demands more blood flow. HTN affects demand: higher BP forces the heart to beat harder, thus increasing the heart's demand for blood. A 70% blockage may still allow the necessary blood supply to the normotensive patient's heart, but for the hypertensive patient's more demanding heart, a 70% blockage may result in chest pain or, worse, myocardial cell damage. HTN also affects supply: higher BP leads to the development of the blockages themselves. Through mechanisms, many still to be completely understood, HTN promotes atherogenesis, or the development of plaques within the inner lining of arteries such as the coronary arteries. Not only do plaques make passageways for blood flow narrower over time but they can also rupture, releasing contents that can immediately clot and completely block blood flow. This plaque rupture is what usually causes devastating MIs.

Initial therapy of HTN in patients presenting to the CCU with an ACS should use medications that improve myocardial supply, lessen demand, or both. β-Blockers, for example, not only lower BP but they also lower the heart rate, and thus lessen the amount of energy the heart expends and the amount of blood flow it demands. Nitrates lower BP, but they also lessen the amount of blood returning to the heart, thus lessening the volume of blood the heart must pump per beat, which also lessens demand. Nitrates and β-blockers are often first-line BP medications in patients with ACS. One exception is in the patient whose heart is so damaged that lowering the heart rate may further lessen cardiac output; in this situation, β-blockers should not be used. ACEIs and ARBs can also be used to lower BP.

Target BP is 140/90 mm Hg. DBP should not be lowered too significantly because it is the diastolic pressure that provides the force to send blood through the coronary arteries; too low a DBP may be harmful.

Upon discharge, the patient who has suffered a heart attack should be on a β-blocker and ACEI if possible. These medications lower BP and help the heart

preserve or even regain function.

HYPERTENSION AND HEART FAILURE

The heart, as described, is a pump that allows for blood to be propelled throughout the cardiovascular system of blood vessels. To effectively perform this task, the heart must fill with an adequate volume of blood, pass this blood between each of its four chambers, and have sufficient muscle strength to eject blood against a significant resistance in the aorta to the entire body.

Chambers divide the heart into a right (right atrium and right ventricle) and left (left atrium and left ventricle) side. When blood returns to the heart through veins, it passes through the right atrium and ventricle before passing through the lungs to pick up oxygen and then passes to the left atrium and ventricle, where sufficient pressure is generated to propel blood to the entire body. The left ventricle is the heart's strongest and largest chamber.

HF is failure of the heart to propel blood, whether because the muscle is weak or because the heart does not fill adequately, such that either cardiac output is insufficient to meet the demands of the body's tissues or these demands are met at the expense of blood "backing up" in the direction of the lungs. In other words, HF can be due to poor forward flow or adequate forward flow but with concomitant inappropriate backward flow.

HF can be due to a multitude of abnormalities: ischemia such as in the form of a heart attack; damaged valves; drugs such as alcohol or certain chemotherapies; and, of course, HTN are among the many possible causes of HF.

HTN forces the heart to pump harder to overcome the greater resistance to forward flow, and over time the heart muscle starts to fail; it may become stiff or weak or both, resulting in forward and/or backward flow failure.

Acute HF is one of the most common reasons for admission to the CCU. A patient may have already been diagnosed with HF, and for some reason (not taking medications, not adhering to a dietary regimen, an irregular heart rhythm, a heart attack, uncontrolled BP) suffer an insult that disrupts the delicate balance and throws the patient into acutely symptomatic HF. It is also possible that a patient admitted to the CCU with HF never had any symptoms of HF. A previously adequately functioning heart may go into failure because of a heart attack, or severe damage to a heart valve, or severe HTN. A heart that is accustomed to beating against a BP of 120/80 mm Hg may fail to overcome a sudden burden of 220/120 mm Hg, or a heart that is forced to beat against a pressure of 150/100 mm Hg for years and years may do well in the beginning

but with time, stretch and thicken and eventually decompensate. Regardless of the scenario, to treat HTN is to relieve the burden against which the failing heart is struggling to pump.

HTN is a common cause of HF; about 75% of patients admitted with HF have HTN. HTN is also a major target of therapy for HF. In fact, the medications that treat HF—β-blockers ("-lol" meds), ACEIs ("pril" meds), ARBs ("-artan" meds), and diuretics or water pills—also have effects on BP.

The initial urgent step is to stabilize the patient. A doctor will aim to reduce BP, ultimately to 140/90 mm Hg or lower, although not too quickly as to potentially starve certain tissues of adequate blood supply. Once the patient is stabilized, tight BP control becomes a fundamental component of long-term care. The patient with HF can easily decompensate again if he or she has a drinking binge, or salty-food binge, or skips a couple of days' doses of medicines. Managing HTN must be emphasized as crucial for preventing future decompensations and giving the heart the best chance of recovering over time.

HYPERTENSION AND RENAL FAILURE

The kidneys filter blood; they excrete much of what is not needed and retain much of what is needed. They also help maintain total body water and electrolyte (sodium, potassium, calcium, etc.) concentrations within a rather narrow healthy range. When a person becomes dehydrated, the kidneys are able to retain fluid and reduce urine output dramatically; if a person were to drink excessively, the kidneys could excrete liters and liters of free water daily. The elegant and delicate mechanism that allows such regulation involves an intricate series of blood vessels and kidney tubules and electrolyte channels; this delicate structure can be disrupted when forced to withstand the forces of high BP over many years.

Renal failure can be acute or chronic; in other words, it can develop over hours to days often with obvious symptoms, or it can develop slowly often without symptoms for several years after kidney damage first begins. HTN can cause both acute and chronic kidney damage. In fact, HTN is the second leading cause of CKD, after diabetes. Renal failure can be a reason for admission to the CCU (when due to hypertensive emergency), but more likely, it is a common complication of another disease process that warrants admission to the CCU.

Hypertensive emergency is defined as BP high enough (often DBP above 120 mm Hg) to cause end-organ damage. "End organs" most commonly affected by extremely high BP are the brain, heart, and kidneys. The high BP damages the

delicate system of arteries feeding the kidney and disrupts the filtering mechanism, leading to such symptoms as decreased urine output, nausea, swelling in the legs, and generalized malaise. The goal in management of acute renal failure due to severe HTN is to limit further renal damage through BP control. The choice of optimal drug therapy is controversial. Although nitroprusside is the drug with the longest track record, it does have potential cyanide and thiocyanate toxicity, especially with prolonged infusions of high doses of nitroprusside. Fenoldopam is another useful IV agent. Other antihypertensive drugs that preserve renal blood flow are CCBs and adrenergic blocking agents.

It is worth mentioning that kidney damage is not only a consequence of HTN but also a cause of HTN. Patients with CKD, especially those on dialysis, are at very high risk for having HTN.

As mentioned, although kidney disease due to hypertensive emergency is a cause for CCU admission, more commonly a patient in the CCU for some other reason (heart attack, HF) develops renal failure concomitantly because the heart attack or HF, for example, led to decreased blood supply to the kidneys. The renal failure makes more complicated the treatment of heart disease and becomes in itself an important target of treatment. For example, diuretics, often referred to as “water pills,” are critical for HF treatment. A patient in the CCU with HF is often “volume-overloaded,” sometimes as much as 20 or 30 pounds heavier than usual because of water retention. The goal is to remove this water, but (1) this fluid removal can damage the kidneys, and (2) kidney damage coupled with the low output state of HF can make the fluid removal difficult. The kidney damage, at least partly brought on by the HF and/or its treatment, has made treatment of the HF more difficult. In recent years, some doctors have used the term “cardiorenal syndrome” precisely to emphasize how strongly linked are the kidney and the heart, in that function and treatment of one very often affects function and treatment of the other.

In summary, kidney damage can be a reason for CCU admission, as in the case of hypertensive emergency, but more often, kidney damage is related secondarily to, and complicates treatment of, the primary disease process that necessitated CCU admission. Good management of HTN can help preserve both kidney and cardiovascular health. When the patient with kidney damage recovers and leaves the hospital, BP control is of paramount importance.

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Diabetes Mellitus in the Cardiac Care Unit

INTRODUCTION

Diabetes mellitus (DM) is a complex chronic condition, with heterogeneous clinical presentation and disease progression, depending on the type of diabetes and its underlying pathophysiology. However, the defining feature of diabetes is an inappropriate elevation of blood glucose (BG), known as hyperglycemia, regardless of the underlying pathophysiologic disorder. Persistent chronic hyperglycemia leads to tissue injury resulting in micro- and macrovascular complications, such as neuropathy, retinopathy, nephropathy, and cardiovascular diseases (CVDs).

In the initial part of this chapter, we discuss the diagnostic and classification criteria of DM and general principles of care in patients with diabetes; in the latter part we focus on diabetes management in the CCU setting and discuss epidemiologic studies of patients admitted to the CCU with diabetes, outcomes in patients with hyperglycemia admitted to the CCU, and an overview of strategies for hyperglycemia management in the CCU.

DIABETES MELLITUS: GENERAL PRINCIPLES

WHAT IS DIABETES MELLITUS? DIAGNOSIS AND CLASSIFICATION

The defining feature of DM is an inappropriate elevation of BG—hyperglycemia. This could be due to excessive glucose production, impaired glucose clearance, or both. Sustained, chronic hyperglycemia, over several years, leads to tissue injury resulting in chronic micro- and macrovascular complications such as diabetic neuropathy, retinopathy, and nephropathy and atherothrombotic vascular diseases. "Inappropriate" hyperglycemia has been defined by experts as the level which, if chronically sustained, will lead to the development of diabetic complications.

The current criteria used to make the diagnosis of DM are listed in **Table 54.1**. According to the American Diabetes Association (ADA) 2011 criteria, either random plasma glucose, fasting plasma glucose, an oral glucose tolerance test, or a hemoglobin A_{1C} (% glycosylated hemoglobin, A_{1C}) can be used to diagnose diabetes.[1]

TABLE 54.1 Diagnosis of Diabetes Mellitus

CRITERIA FOR THE DIAGNOSIS OF DIABETES

1. $A_{1C} \geq 6.5\%$. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay (http://www.ngsp.org, accessed January 2, 2017)[a]
   OR
2. FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h[a]
   OR
3. Two-hour plasma glucose ≥ 200 mg/dL (11. 1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water[a]
   OR
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11. 1 mmol/L)

CATEGORIES OF INCREASED RISK FOR DIABETES (PREDIABETES)[b]

1. FPG 100–125 mg/dL (5.6–6.9 mmol/L) [IFG]
2. Two-hour plasma glucose in the 75-g OGTT 140–199 mg/dL (7.8–11.0 mmol/L) [IGT]
3. A_{1C} 5.7%–6.4%

[a]In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.
[b]For all three tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.
Adapted from American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes 2017. Diabetes Care 2017;40(Suppl. 1):S11–S24.
NGSP: National Glycohemoglobin Standardization Program, DCCT: Diabetes Control and Complications Trial, FPG:

Fasting plasma glucose, OGTT: Oral glucose tolerance test
IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

DM is currently classified by etiology as type 1, type 2, gestational, or other specified types (**Table 54.2**). Type 1 diabetes is characterized by an absolute or severe insulin deficiency and is immune mediated. Type 2 diabetes is a complex polygenic disease characterized by both insulin resistance and relative insulin deficiency, that is, insulin levels and secretion are inappropriate to the levels of insulin resistance and out of proportion to the glucose stimuli (dual defect).[2] Gestational DM is characterized by onset during pregnancy owing to increased insulin resistance generated by the hormonal milieu. Typically, it resolves at the end of pregnancy; however, women with gestational diabetes are at higher risk for developing type 2 diabetes later in life.[3] Other specific types of diabetes listed by etiology are a result of genetic defects in β-cell function and/or insulin action (monogenic diabetes), exocrine pancreatic disease, some endocrinopathies, drug or chemically induced (exogenous corticosteroid administration, etc.), or other rare forms (infections, immune mediated, etc.). These specific forms could manifest clinically in a manner similar to either type 1 or type 2 diabetes.

TABLE 54.2 Classification of Diabetes Mellitus

Type 1 Diabetes
• Due to autoimmune β-cell destruction, usually leading to absolute insulin deficiency
Type 2 Diabetes
• Due to a progressive loss of β-cell insulin secretion frequently on the background of insulin resistance
Gestational Diabetes
• Diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation.
Other Specific Types
• Monogenic diabetes syndromes • Neonatal diabetes • Maturity-onset diabetes of the young (MODY) • Diseases of the exocrine pancreas (cystic fibrosis, etc.) • Drug- or chemical-induced diabetes (treatment of HIV/AIDS, glucocorticoids, treatment after organ transplantation)

Adapted from: American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In Standards of Medical Care in Diabetes 2017. Diabetes Care 2017;40(Suppl. 1):S11–S24

Type 1 Diabetes

Certain clinical aspects of diabetes presentation are characteristic of type 1 diabetes: diabetic ketoacidosis (DKA); signs of insulin deficiency such as weight loss and/or BG level above 250 mg/dL accompanied by non–fasting positive urine ketones; acute onset in a child or young adult; triggered by recent infection or viral illness; onset during puberty or association with other autoimmune diseases (thyroiditis, Graves disease, pernicious anemia, celiac, and Addison disease).

Type 2 Diabetes

The pathogenesis of type 2 diabetes is very different from that of type 1 diabetes. As opposed to type 1 diabetes, in type 2, insulin resistance is almost universally present, and the defect in insulin secretion is milder—just secretion is not high enough to overcome the resistance (β-cell dysfunction).

Prediabetes and Screening for Diabetes Mellitus

Type 2 diabetes is often preceded by a condition called prediabetes characterized by either abnormal fasting glucose levels (impaired fasting glucose or IFG) and/or impaired glucose tolerance (IGT, abnormal postprandial glucose), which leads to increased levels of A_{1C} (**Table 54.1**). During the prediabetes stage, there is a gradual increase in insulin resistance as a result of various causes (aging, obesity, physical inactivity, or genetics) which, when not accompanied by an increase in insulin secretion, will eventually result in elevated BG levels in the diabetic range (**Figure 54.1**). Prediabetes can be identified through the same tests used to diagnose diabetes (**Table 54.1**). It is now recommended that individuals at risk be screened for the presence of type 2 diabetes (**Table 54.3**).[1] During this screening, normal glucose tolerance, prediabetes, or full-blown diabetes can be identified. The screening is very important because (a) preventive measures such as weight loss and/or increased physical activity and sometimes pharmacologic measures could prevent or delay the development of type 2 diabetes in the individuals with prediabetes and (b) early diagnosis and treatment of the clinical manifestation of type 2 diabetes could prevent chronic complications and improve chances of survival.

TABLE 54.3 Criteria for Testing for Diabetes in Asymptomatic Adult Individuals

1. Testing should be considered in all adults who are overweight (BMI ≥25 kg/m2 or ≥23 kg/m2 in Asian Americans) adults who have one or more of the following risk factors:
   A1C≥5.7% (39 mmol/mol), IGT, or IFG on previous testing Physical inactivity
   First-degree relative with diabetes mellitus
   Members of a high-risk race/ethnicity (eg, African American, Latino, Native American, Asian American, Pacific Islander)
   Women who delivered a baby weighing >9 lb or were diagnosed with Gestational Diabetes Mellitus (GDM)
   Hypertension (140/90 mm Hg or on therapy for hypertension)
   HDL cholesterol level 250 mg/dL (2.82 mmol/L)
   Women with polycystic ovary syndrome (PCOS)
   Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosisnigricans)
   History of CVD
2. In the absence of the above mentioned criteria, testing for diabetes should begin at age 45 y
3. If results are normal, testing should be repeated at least at 3-y intervals, with consideration for more frequent testing depending on initial results and risk status

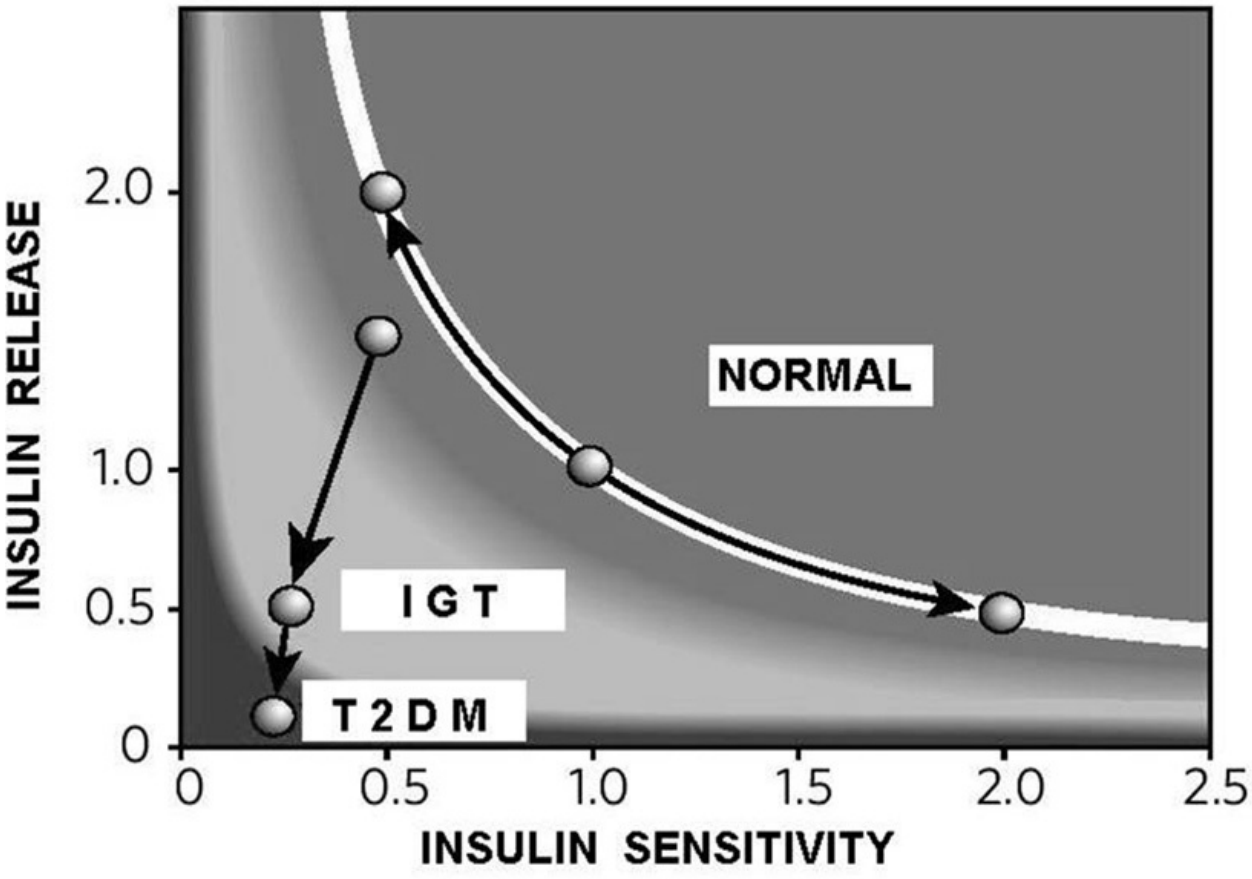

FIGURE 54.1 Relationship between insulin sensitivity and insulin release. DM, diabetes mellitus; IGT, impaired glucose tolerance.

Metabolic Syndrome

Prediabetes and insulin resistance are integral parts of the so-called metabolic syndrome, which is defined as a clustering of risk factors that predict the

development of both type 2 diabetes and CVD. More than 80% of patients with type 2 diabetes have metabolic syndrome and clustering of risk factors for CVD, which include hypertension, dyslipidemia, and associated inflammation and hypercoagulable state.[4] The clustering of these risk factors predicts the development of CVD independent of the degree of hyperglycemia. The treatment of the risk factors and the underlying pathophysiologic causes could prevent both diabetes and CVD. The most prominent underlying modifiable pathophysiologic causes are abdominal obesity and insulin resistance.[5] Inflammation and hypercoagulable states are also important factors to be addressed. The comprehensive treatment of the metabolic syndrome includes smoking cessation, assessment of diabetes risk and implementation of diabetes prevention strategies, control of blood pressure, control of glucose if type 2 diabetes is present, reduction of abdominal obesity, increase in physical activity to at least 30 minutes of activity daily (above usual), decrease in saturated fats to less than 7% of total calories, elimination of trans fat, addressing lipid levels such as low-density lipoprotein, triglycerides, and high-density lipoprotein cholesterol according to the 10-year calculated Framingham risk and eating five servings of fruits and vegetables per day.[6]

CLINICAL MANIFESTATIONS AND COMPLICATIONS OF DIABETES MELLITUS

Clinical manifestations of DM could be acute (DKA or hyperosmolar hyperglycemic state [HHS]) or chronic. The chronic complications manifest as microvascular (retinopathy, neuropathy, nephropathy) or macrovascular (cerebrovascular disease, coronary artery disease [CAD], peripheral vascular disease) disease. Other complications are susceptibility to infections and connective tissue disorders. Positive correlations were found between glycemic control (as measured by the A_{1C} level) and prevalence and incidence of diabetic microvascular complications. Prospective randomized trials have shown that intensive control of BG significantly reduces the risk of microvascular complications in both type 1 and type 2 diabetes. The effect of tight glucose control on macrovascular complications in the absence of intensified control of other risk factors for macrovascular disease is presently controversial. It is known, however, that tight control of other CVD risk factors such as hypertension and elevated lipids does significantly reduce risk of fatal and nonfatal macrovascular events in both type 1 and type 2 diabetes patients. This

reduction in risk was reported to be 20% to 50% with blood pressure control, 25% to 55% with lipid control, but only 10% to 20% with tight glucose control.[7] A comprehensive approach including tight glucose control and control of other CVD risk factors was reported to lower both micro- and macrovascular complications by 35%.[8] Unintended consequences and adverse effects of tight glucose control could be hypoglycemia, weight gain, and possible short-term worsening of proliferative retinopathy, especially and mostly when the patients require insulin, such as patients with type 1 or long-standing type 2 disease. Of particular concern is the effect of hypoglycemia on macrovascular event rates and outcomes.[7]

PHARMACOLOGIC TREATMENT OF HYPERGLYCEMIA: GENERAL PRINCIPLES IN THE OUTPATIENT SETTING

INSULIN: Patients with type 1 diabetes are always treated with insulin. In fact, one of the reasons it is very important to make the differentiation between type 1 and type 2 diabetes is to determine if there is a need for insulin at all times to avoid DKA. Patients with type 2 diabetes may also be requiring insulin for control of BG, although lack of insulin will not produce DKA except in rare cases. Insulin is used in type 2 patients when it is not possible to achieve glucose level goals with oral agents alone. Insulin treatment should be physiologic and anticipatory. That is, it should include long-acting (basal) insulin to suppress glucose production overnight and normalize fasting glucose and rapid-acting (prandial) insulin to cover meal-related glucose excursions. This physiologic concept is called the basal-bolus concept (**Figure 54.2**). Examples of different types of insulin and their peak action time and duration of action are shown in **Table 54.4**. Insulin delivered with a prefilled insulin pen, rather than from a bottle with a syringe and needle, is easier to accurately dose (**Figure 54.3A**). Similar principles, as described earlier, are used for continuous subcutaneous (SQ) insulin delivery systems utilizing an insulin pump (**Figure 54.3B**).

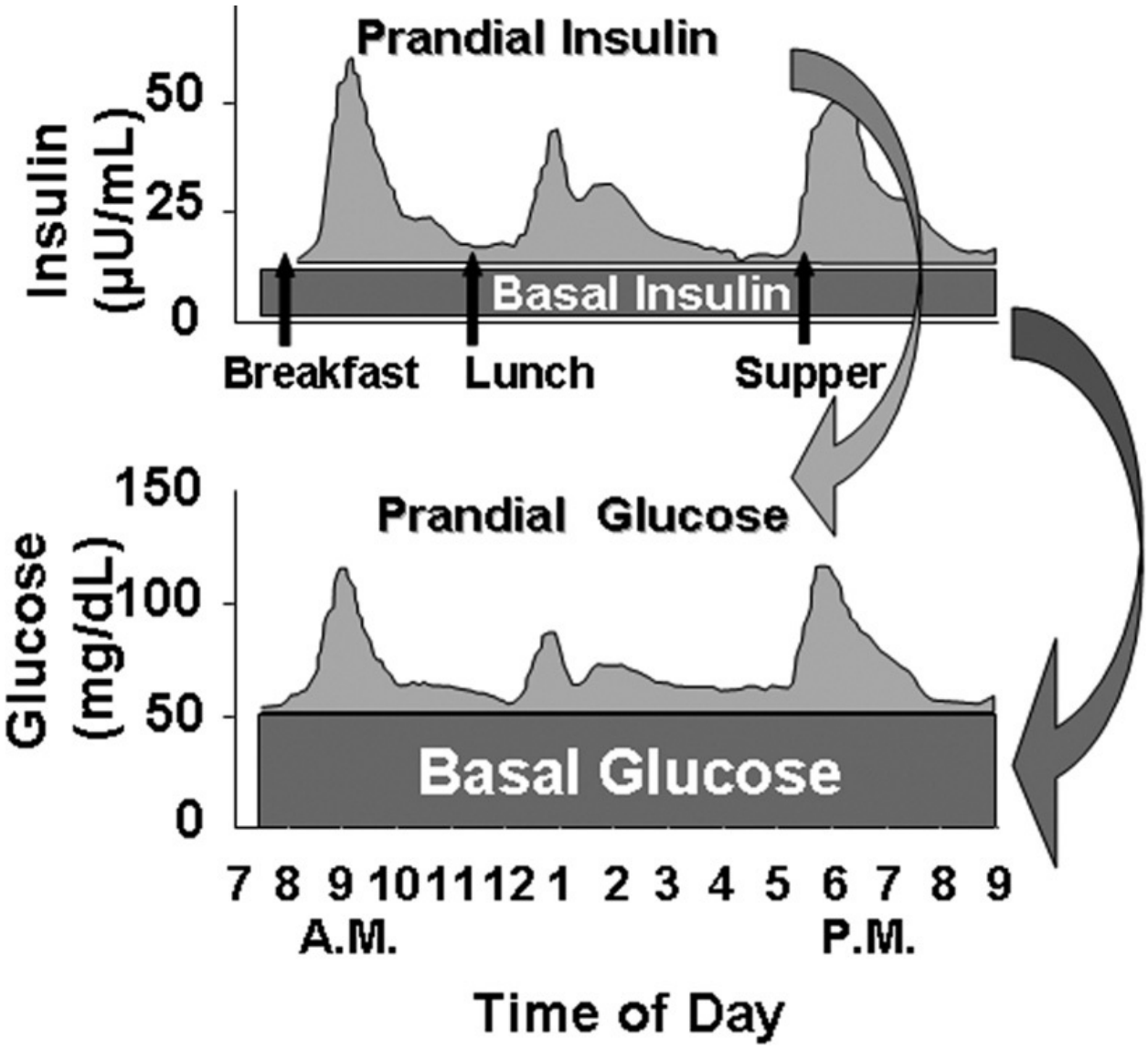

FIGURE 54.2 Physiologic insulin administration: the basal-bolus concept. The prandial insulin is 50% of the total daily dose administered before each meal to cover the prandial glucose excursions. The basal insulin is 50% of the total daily dose and controls fasting glucose by suppressing glucose production between meals and overnight. (Adapted from the Society for Hospital Medicine Glycemic Control Task Force presentation at www.hospitalmedicine.org.)

TABLE 54.4 Insulin Preparations by Subcutaneous Administration: Onset, Peak, and Duration of Action

INSULIN, GENERIC NAME (BRAND)	ONSET	PEAK	EFFECTIVE (h)
Rapid-acting (prandial or correction insulin)			
Aspart (Novolog), lispro (Humalog), glulisine (Apidra)	5–15"	30–90"	<5

Short acting (prandial or correction insulin)			
Insulin regular (Novolin/Humulin)	30–60"	2–3 h	5–8
Intermediate (basal insulin q12h)			
Insulin NPH (Novolin or Humulin) (OK in pregnancy)	2–4 h	4–10 h	10–16
Long-acting (basal insulin q24h or q12h)			
Insulin glargine (Lantus) (avoid in pregnancy)	2–4 h	No peak	20–24
Insulin detemir (Levemir) (avoid in pregnancy)	3–8 h	No peak	6–23
Premixed (basal and prandial mixed)			
75% Lispro prot. susp./25% lispro (Humalog mix 75/25)	5–15"	DUAL	10–16
50% Lispro prot. susp./50% lispro (Humalog mix 50/50)	5–15"	DUAL	10–16
70% Aspart prot. susp./30% aspart (Novolog mix 70/30)	5–15"	DUAL	10–16
70% NPH/30% regular (Novolin or Humulin 70/30)	30–60"	DUAL	10–16

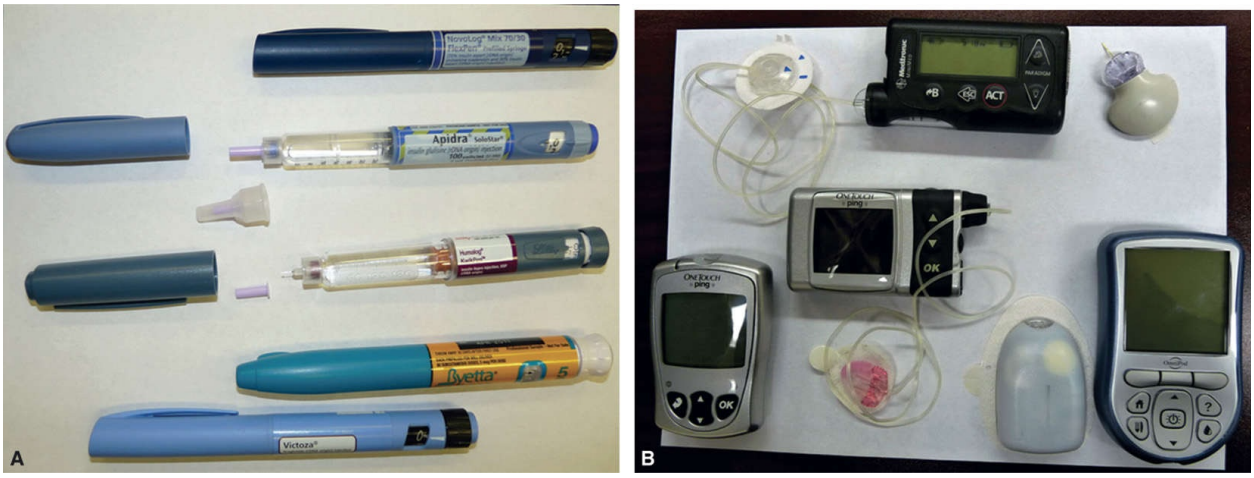

FIGURE 54.3 A, Insulin injection devices: insulin pens (short-acting, long-acting, and mixed insulins) and pens used to deliver GLP-1 analogs (Byetta and Victoza). Insulin pens are easier to use than syringes, improve patients' attitude and adherence towards the injectable treatment, and have accurate dosing mechanisms when used as prescribed. B, Insulin pumps and CGMS devices. Insulin pumps deliver insulin through a plastic catheter inserted subcutaneously; they can communicate wirelessly with a glucometer. CGMS devices measure glucose continuously through a sensor inserted subcutaneously. The hope is that in the near future, CGMS devices and insulin pumps could be combined to form an artificial pancreas. CGMS, continuous glucose monitoring system.

Oral Hypoglycemic Agents

These drugs lower glucose by several mechanisms: improve insulin resistance (sensitizers), improve insulin secretion (secretagogues), improve insulin secretion but also decrease glucagon and gastric emptying through modulation of incretin and gut hormone levels, and those which lower glucose by decreasing absorption in the gut or increase its excretion in the urine. The agents that improve insulin resistance are either biguanides (eg, metformin) or thiazolidinedione. They work through increasing insulin sensitivity in the liver, muscle, and adipose tissue. The secretagogues work directly on the β-cells (sulfonylureas, amino acid derivatives, and meglitinides). α-Glucosidase inhibitors decrease glucose absorption in the gut. Sodium-glucose co-transporter 2 inhibitors, the most recent class of oral hypoglycemic agents, reduce BG levels by increasing urinary glucose excretion. The drugs that work through modulating incretin levels (glucagon-like peptide or GLP-1 and others) are analogs of GLP-1 and dipeptidyl peptidase (DPP-4) inhibitors. DPP-4 inhibitors (eg, sitagliptin) enhance the effects of endogenous incretins by preventing their breakdown by DPP-4 as well as through other mechanisms. All these oral agents have potential side effects and have to be used with caution in hospitalized patients particularly when renal and hepatic failure are present, because they increase the risk of hypoglycemia. Combination treatments of different oral drug classes work well and are often used. Such combinations should be tried before insulin treatment is initiated. Insulin should be initiated early, however, if there is evidence of severe β-cell dysfunction, such as rapid weight loss or very high A_{1C} > 9%, despite sustained efforts at diet and exercise and multiple oral agent combinations.

GLP-1 Analogs and Amylin

Amylin is a hormone that is co-secreted from the pancreas together with insulin. Amylin was shown to play a role in synchronizing the emptying of nutrients from the stomach with the secretion of insulin through acting in the brain to slow gastric emptying, lower gluconeogenesis, and decrease food intake. In type 1 diabetes, amylin levels are low, and its replacement leads to less dramatic fluctuations of BG. GLP-1 analogs, which produce GLP 1 effects, that is, decrease in glucagon and increase in insulin and amylin secretions, have also been developed. These are drugs that need to be administered through an SQ injection, and increase GLP-1 to levels greater than those observed after

administration of DPP-4 inhibitors. GLP-1 analogs promote decrease in food intake and weight loss in a large number of overweight and obese patients who take them and are frequently prescribed to obese patients with type 2 diabetes. Their development in user-friendly pens enhances their excellent results (**Figure 54.3A**). Unfortunately, some patients may not be able to tolerate them because of nausea. More severe but infrequent side effects include acute pancreatitis and renal failure. These drugs are not indicated for use during hospitalizations.

Glycemic Targets in Outpatient Settings

It is currently recommended to aim for tight glucose control as early as possible in the course of diabetes treatment (**Table 54.5**).[1] The target A_{1C} level recommended by the ADA is less than 7% or as close to normal as is safely possible to achieve in most nonpregnant adults.[1] More stringent goals (such as 6.5%) could be sought if achieved without significant hypoglycemia or other adverse effects of treatment. This stringent goal could be recommended in patients with recent-onset diabetes, those treated with lifestyle or metformin only, those with long life expectancy, and/or no significant CVD. Less stringent goals (A_{1C} of 8% or less) are recommended for patients with a history of severe hypoglycemia, limited life expectancy, extensive complications and/or comorbid conditions, or those with long-standing diabetes in whom the goal is difficult to achieve despite appropriate education, monitoring, and appropriate use of multiple glucose-lowering agents including insulin.

TABLE 54.5 Recommendations for Glycemic Control during Chronic Outpatient Management

A_{1C} < 7.0%	
Preprandial capillary plasma glucose	90–130 mg/dL
Peak postprandial capillary plasma glucose[a]	180 mg/dL
Key concepts in setting glycemic goals are as follows: • A_{1C} is the primary target for glycemic control • Goals should be individualized based on	
Duration of diabetes	Known CVD or advanced microvascular complications
Age/life expectancy	Comorbid conditions

Hypoglycemia unawareness	Individual patient considerations
	• Certain populations (children, pregnant women, and elderly) require special considerations • More stringent goals (A_{1C} < 6.5%) if able to achieve without significant hypoglycemia or polypharmacy for individual patients: short diabetes duration, on lifestyle or metformin only, long life expectancy, no significant CVD • Less stringent goals (A_{1C} < 8%) for patients: with history of severe hypoglycemia, advanced diabetes complications, extensive comorbid conditions, limited life expectancy, long-standing diabetes where goal is difficult to achieve despite optimal treatment • Postprandial glucose may be targeted if A_{1C} goals are not met despite reaching preprandial goals

[a]Postprandial glucose measurements should be made 1to 2 hours after the beginning of the meal.
CVD, cardiovascular disease.

The A_{1C} should be tested every 6 months if the value is at target or every 3 months when not at target or when treatment changes. Levels of A_{1C} together with the prevalence of hypoglycemia will dictate the management of glucose control. Correlation of A_{1C} with average glucose level is seen in **Table 54.6**. If A_{1C} is less than 7% and the hypoglycemia is not frequent and/or severe, then the treatment can be maintained at the current level. If A_{1C} is between 7% and 8%, this is likely due to 2-hour postprandial elevations, the following need to be reviewed: meal and activity plans, glucose monitoring techniques and frequency, compliance with medication administration and schedule, and sick day management. If A_{1C} is more than 8%, in addition to previous recommendations, goal setting, assessment of psychosocial issues, DSME (diabetes self-management education workshops) referral and medication adjustments are likely all needed (**Table 54.5**).

TABLE 54.6 Correlation of A_{1C} With Average Glucose

	MEAN PLASMA GLUCOSE	
A_{1C}(%)	***mg/dL***	***mmol/L***
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4

11	269	14.9
12	298	16.5

These estimates are based on ADAG data of approximately 2,700 glucose measurements over 3 months per A_{1C} measurement in 507 adults with type 1, type 2, and no diabetes. The correlation between A_{1C} and average glucose was 0.92. A calculator for converting A_{1C} results into estimated average glucose (eAG), in either mg/dL or mmol/L, is available in http://professional.diabetes.org/eAG.

Hypoglycemia Management

The correct management of hypoglycemia is crucially important in all patients with diabetes who receive insulin or insulin secretagogue medications but especially in those with CVD or advanced complications. The hypoglycemia should be correctly evaluated and treated. It is defined as mild to moderate when levels of BG range from 50 to 70 mg/dL and/or patients can treat it themselves. It can be treated with oral, simple, easily absorbable carbohydrate, such as glucose tablets or gel, orange juice, or soft drinks containing 15 to 20 g of glucose. Glucose levels should be checked again in 15 minutes, and patients must be instructed to carry glucose with them at all times. Severe hypoglycemia is usually when glucose is less than 50 mg/dL, it is accompanied by altered consciousness, and patients need assistance. They need to take 20 to 30 g of simple glucose by mouth (if able), be given glucagon by intramuscular (IM) injection, or be rescued by emergency medical personnel with intravenous (IV) glucose administration. If any severe hypoglycemia episodes occur, then precipitating causes should be assessed, patients should be referred to DSME, use of glucagon IM injections should be taught to family members or care takers, and BG goals should be revised. If patients have frequent severe hypoglycemia or have hypoglycemia unawareness, then support of families and friends is absolutely needed, patients should wear identifying bracelets, and driving is not recommended.

IDENTIFYING AND TREATING COMPLICATIONS OF DIABETES

The treatment of chronic diabetes complications should be conducted according to published standards of care to ensure early diagnosis and prevent progression. These standards of care are published yearly by the ADA.[1] For microvascular disease, retinopathy, nephropathy, and neuropathy are targeted.

Retinopathy

Retinopathy is one of the ophthalmic complications of DM. It could be background or proliferative and could lead to retinal detachment, vitreous bleeding, and blindness if not treated. Early laser treatment could prevent blindness. Diabetes is also a risk factor for development of cataracts and glaucoma. Patients should have annual dilated eye examinations after 3 years from onset of type 1 diabetes and at onset of type 2 diabetes. Prevention of background or proliferative retinopathy occurrence or worsening is not only through continuing tight control of BG but also by smoking cessation and control of blood pressure and lipids.

Nephropathy

Diabetic nephropathy manifests itself as proteinuria, glomerulosclerosis, and renal failure. Nephropathy should be screened for annually with a urinary microalbumin/albumin determination. Goal is <30 mg/g creatinine, which corresponds roughly to 30 mg protein per 24 hours. In addition, glomerular filtration rate (GFR) and creatinine level need to be monitored at least annually. The prevention of nephropathy should be done through tight glucose and blood pressure control and through administration of agents that lower proteinuria, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Treatment of nephropathy presenting with hematuria and nephrotic-range proteinuria include dietary protein reduction, blood pressure lowering to less than 125/75 mm Hg and revised glucose management for reduced GFR as well as a nephrology consult. If GFR < 30 mL/min, chronic kidney disease (CKD) management principles apply. Oral hypoglycemic agents' safety should be reassessed with worsening GFR.

Neuropathy

Diabetic neuropathy could be peripheral or autonomic and could lead to diabetic foot ulcer, diabetic arthropathy, and deformities with pathologic fractures, cellulitis, osteomyelitis, and amputations. The annual screening of feet for diabetes includes a complete assessment of sensation. Inspection of feet should be done at every visit; feet at high risk should be referred to podiatric care and for orthotics.

OTHER ASPECTS OF DIABETES MANAGEMENT

For all newly diagnosed diabetics, essential care should also address the

following: (a) diabetes self-management education and nutrition education; (b) psychosocial screening; (c) pregnancy, contraception, and osteoporosis in women, and erectile dysfunction in men; and (d) dental care and vaccinations. A minimum amount of diabetes education (survival skills) should be taught in the hospital before discharge, and patients should be referred to an outpatient ADA-certified diabetes self-management education program. In such programs, there is an initial workshop that follows a core curriculum so core knowledge reaches all patients. Usually this is completed in about 6 hours. Self-knowledge assessment tests are given before and after the teaching sessions. Patients should attend a refresher course each year for up to 4 hours/year. Diabetes self-management nutrition education addresses diet and energy balance: weight loss issues if needed, need for carbohydrate counting in insulin-requiring patients, risk of low BG with decreased energy intake, increase in physical activity, increase in dietary fiber (14 g/1,000 kcal) and alcohol intake (maximum one drink per day for women and two drinks per day for men). Physical activity is recommended to be of both aerobic and resistance-type training and should be done in combination. Aerobic activity should be at least 150 min/week and it should be of moderate intensity, 50% to 70% of maximum heart rate (220-age). Resistance exercise should be done 3 times a week if there are no contraindications, such as the presence of proliferative diabetic retinopathy. A screening is needed to assess the literacy level that is essential for diabetes self-management education of glucose monitoring and medication adherence. Mood disorders such as depression and anxiety must be addressed because they can influence diabetes control as well as coping. Social barriers (family and economic issues) and physical barriers (blindness, amputations, etc.) are all likely to affect diabetes management and should be addressed accordingly.

DIABETES MELLITUS IN THE CARDIAC CARE UNIT

HYPERGLYCEMIA AND DIABETES IN THE CCU

Hyperglycemia is a common condition among hospitalized patients with and without diagnosed diabetes. Hyperglycemia on admission can affect up to 50% to 60% of patients admitted with acute coronary syndrome (ACS) and acute decompensated heart failure (HF), which varies based on the definition applied. More importantly, it has been reported that 14% to 50% of those presenting with ACS and hyperglycemia on admission were never diagnosed with diabetes.[9]

Hyperglycemia in patients admitted to the cardiac care unit (CCU) can be seen in three main scenarios: (1) those with previously known diagnosis of DM (of any type), (2) those with undiagnosed DM but meeting criteria for diagnosis during admission, and (3) those with stress hyperglycemia. Patients with previously diagnosed diabetes will commonly have worsening of their glycemic status—partly due to stress hyperglycemia, as explained here. Hyperglycemia in hospitalized patients with ACS has been associated with increased morbidity, mortality, and poor hospital-related outcomes, regardless of their previous status.[10]

INPATIENT HYPERGLYCEMIA AND STRESS HYPERGLYCEMIA—BRIEF DEFINITION

In the general hospitalized population, acute—or inpatient—hyperglycemia was traditionally considered as an admission or random BG ranging from >110 to >200 mg/dL in several studies.[10] Subsequently, the ADA, the AACE and the Endocrine Society defined inpatient hyperglycemia as a BG ≥ 140 mg/dL on admission or at any time during the hospitalization, or an admission HgA_{1C} > 6.5%, in patients with or without diabetes.[11]

In hospitalized patients with ACS, the American Heart Association, in the scientific statement on "Hyperglycemia and Acute Coronary Syndrome" similarly defined inpatient hyperglycemia as an admission BG > 140 mg/dL during an admission, and recommended intensive glucose control in patients with BG > 180 mg/dL, regardless of their prior diabetes status. These recommendations are supported by several observational studies demonstrating that admission, mean 24-hour or mean in-hospital BG > 140 mg/dL is associated with increased mortality in the ACS population, and that lowering glucose to <140 mg/dL is associated with improved survival.[12]

Stress hyperglycemia refers to a transient elevation of BG occurring during acute illnesses, which resolves spontaneously after the acute insult dissipates. This disorder can occur in patients with or without diabetes, and has been associated with higher risk of complications and mortality compared to patients with previously diagnosed DM.[13] Trauma, infection, and surgery result in remarkable metabolic stress on the human body. Stress associated with critical illness is characterized by the activation of inflammatory cellular mediators and the hypothalamic pituitary-adrenal axis. In addition, the level of insulin is decreased, along with associated insulin resistance, at least partially from stress

hormones in acutely ill patients.

In patients with ACS and “isolated” stress hyperglycemia (without previously known diabetes), the risk of mortality increases as the BG levels go above 120 to 140 mg/dL; whereas in patients with known DM and ACS, the risk of mortality starts to increase when the BG is >200 mg/dL.[14] These patients are also at increased risk of developing diabetes in the future. Greci et al. demonstrated that up to 60% of patients with stress hyperglycemia may be diagnosed with DM at 1 year[15]; therefore, screening and follow up after discharge are essential in these patients.

INCIDENCE AND PREVALENCE OF HYPERGLYCEMIA AND DIABETES IN THE CCU

According to the International Diabetes Federation, there were over 415 million people worldwide with DM in 2015 (http://www.diabetesatlas.org, accessed January 1, 2017). From 1980 to 2014 in the United States, the number of people with diabetes has increased by 4-fold, from 5.5 million to 22.0 million (https://www.cdc.gov/diabetes/statistics, accessed January 1, 2017).

There is a direct relationship between the increased prevalence of obesity and DM2 in the United States over the past two to three decades, escalating to epidemic numbers. Patients with metabolic syndrome usually have visceral obesity and insulin resistance, and are at risk for developing DM2 and CVD. Patients with DM2 and those with associated metabolic syndrome, in particular, are at high risk for CAD, cerebrovascular events, nonischemic cardiomyopathy, peripheral vascular disease, and death.[16]

The overall prevalence of hyperglycemia among hospitalized patients ranges from 32% to 42% in critically ill patients to 20% to 35% in non–critically ill patients.[11] Hospitalized patients with CVDs may have a higher burden of diabetes. In the CRUSADE study, up to 36.3% of patients with non-ST segment elevation myocardial infarction had known diabetes.[17]

In patients with ACS, hyperglycemia (with or without previously recognized diabetes) ranges from 25% to >50%, depending on the definition used by the different studies (> 110 vs 140 vs >180 mg/dL).[12] Unfortunately, the higher burden of diabetes may commonly be unrecognized by patients already presenting to the hospital with diabetes-related complications such as CVDs. In several large studies, the scenario of unrecognized diabetes has been reported in 10% to 50% of those presenting with ACS and hyperglycemia.[18]

Hyperglycemia in patients admitted for HF is also common. It has been reported that the prevalence of hyperglycemia in this population is about 42% in patients without diabetes and up to 40% to 50% in patients with diabetes.[19]

HYPERGLYCEMIA AND OUTCOMES IN HOSPITALIZED PATIENTS WITH DIFFERENT CARDIAC DISORDERS

Hyperglycemia in hospitalized patients has been associated with increased mortality and adverse outcomes. Paradoxically, patients admitted with hyperglycemia without a prior diagnosis of DM have been shown to have worse outcomes compared to those with previously diagnosed DM.[10]

Hyperglycemia and Acute Coronary Syndromes

In patients with known diabetes admitted with ACS, several studies have demonstrated that admission hyperglycemia is associated with increased risk of hospital mortality and hospital-related complications. A meta-analysis of patients with diabetes admitted with ACS reported that admission BG ≥ 180 mg/dL was associated with a 70% relative risk increase in hospital mortality, compared with normoglycemic patients on admission.[10]

Whether hyperglycemia on admission predisposes the patient to myocardial injury or is just a marker of disease severity is unclear. Hyperglycemia on admission is well accepted to be an independent predictor for poor outcomes in patients with and without diagnosed diabetes presenting with ACS. However, admission BG only represents a very specific time in the hospitalization. Persistent hyperglycemia during a hospitalization for ACS was found to be a better predictor of mortality than admission BG. Thus, some authors advocate the use of mean hospital glucose as the most accurate and practical glucometric tool in this population.[10]

In patients admitted with ACS and unrecognized DM, a meta-analysis reported that mortality increases as BG increases above 110 mg/dL, compared with normoglycemic patients.[10] Similarly, the HI-5 study showed that the 6-month mortality rate was higher in patients with BG > 144 mg/dL.[20]

Hyperglycemia and Heart Failure

With regard to patients admitted with acute HF, several studies reported an increased risk of in-hospital and overall mortality in patients with hyperglycemia.[21,22] A recent report from the “Swedish National Diabetes

Registry" reported that patients with type 1 diabetes have 4-fold increased risk for HF hospitalizations, whereas poor glycemic control and albuminuria were considered strong risk factors.[22]

Hyperglycemia and Atrial Fibrillation

Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia, and its prevalence is directly related to advancing age. The prevalence of DM2 is about 7% to 16% in patients with AF. A recent meta-analysis of patients with DM2 reported a 40% increased risk of AF, compared to unaffected patients. DM2 has also been found to be an independent risk factor for AF hospitalization.[23]

Hyperglycemia and Outcomes of Coronary Artery Bypass Grafting

Diabetes can affect up to 30% to 40% of patients undergoing coronary artery bypass graft (CABG) surgery. In a retrospective study at the Mayo Clinic, patients with intraoperative hyperglycemia were found to have a higher rate of mortality and complications, such as AF, sternal wound infections, prolonged mechanical ventilation, urinary tract infection, delirium, and strokes, following CABG surgery, regardless of whether they had previously recognized diabetes or not.[24] In the recent GLUCO-CABG trial, Umpierrez et al. randomized patients with inpatient hyperglycemia (BG > 140 mg/dL) to receive an intensive glycemic control; aiming BG targets between 100 and 140 mg/dL, versus a more conservative target of 141 to 180 mg/dL. The authors found similar results regarding a composite of outcomes, including mortality, wound infection, pneumonia, bacteremia, acute kidney injury, and major adverse cardiovascular events (42% vs 52%, $P = 0.08$). However, patients without known diabetes, so-called stress hyperglycemia, had a significantly lower rate of complications (34% vs 55%, $P = 0.008$).[25]

Hyperglycemia and Outcomes of Heart Transplant Surgery

Heart transplant recipients will sometimes be cared for by the CCU staff. Pre-transplant DM is a common comorbidity, presenting in up to 25% of patients undergoing heart or lung transplantation. Lang et al.[26] reported similar rates of acute rejections, graft vasculopathy, and infections in recipients with pre-transplant DM, whereas others reported higher rates of infections and posttransplant CAD/graft vasculopathy.[27]

HYPOGLYCEMIA AND OUTCOMES IN PATIENTS HOSPITALIZED WITH CARDIAC CONDITIONS

Several professional societies recommended glucose control in hospitalized patients admitted to critical settings, including those admitted with ACS. However, hypoglycemia is an inevitable consequence of glycemic management and has been associated with increased morbidity and mortality.[28]

Extensive literature has shown that hypoglycemia is a common event in the hospitalized patient. Patients with acute CVDs are very vulnerable to the deleterious effects of hypoglycemia. Hypoglycemia is associated with increased risk of arrhythmias, ranging from bradycardia to ventricular ectopic beats and QT prolongation, mostly because of sympathetic and adrenal activation.[29] The relationship between mortality and glycemic control in hospitalized patients with ACS follows a U-shape curve.[30]

However, several studies have shown that spontaneous hypoglycemia is associated with worse outcomes and mortality than iatrogenic hypoglycemia in hospitalized patients. These results suggest that spontaneous inpatient hypoglycemia may be a marker of disease severity.

INTRODUCTION TO THE MANAGEMENT OF HYPERGLYCEMIA IN THE CCU

The negative impact of hyperglycemia and hypoglycemia in patients admitted to the CCU merits a comprehensive and multidisciplinary management plan. This plan may include dietary modifications, glucose monitoring, personalized glycemic targets to improve hyperglycemia while preventing hypoglycemia, a safe transitioning plan from the CCU to the regular medicine floors and/or home, and proper outpatient follow-up.

GLUCOSE MONITORING IN THE CCU

Given the negative impact of both inpatient hyperglycemia and hypoglycemia, it is necessary to closely monitor the BG levels in all patients admitted to the CCU. Current guidelines recommend glucose monitoring every 1 to 2 hours in critically ill patients. An international consensus meeting recommended against relying solely on the use of capillary BG for monitoring, given the poor reliability in critically ill patients. In patients with permanent vascular access (arterial and/or venous), all samples should be taken from this site following standard safety precautions. Arterial catheters may be preferred in patients with

shock, severe peripheral edema, and/or on vasopressor therapy. In patients without arterial or venous catheters, capillary BG can be used. The samples should be analyzed in the blood gas analyzer machines within the intensive care unit (ICU) or CCU, because results can be rapidly available compared to hospitals' central laboratory.[31]

Novel technologies, such as the continuous glucose monitoring (CGM) system, have shown promising results in the area of glucose monitoring in the hospital. Previous studies raised concern for inaccurate BG readings in critically ill patients; however, recent prospective randomized trials have demonstrated better accuracy and safety in patients in the CCU.[32] Closed-loop insulin delivering system is a novel technology that could aid in the management of inpatient and peri-operative hyperglycemia. Closed-loop systems are composed of an insulin pump allowing appropriate insulin doses and a glucose sensor for CGM. Landmark studies in ambulatory patients and a few pilot studies in the hospital have shown that these systems may improve glycemic control, decrease hypoglycemia, and the burden of diabetes care. However, these initial pilot studies are awaiting larger multicenter studies for efficacy and safety validation. Their main limitations at this time are high cost, lack of training among providers and patients, time needed for implementation, and lack of outcome data at this time.[33]

GLYCEMIC TARGETS IN CRITICALLY ILL PATIENTS ADMITTED TO THE CCU

The benefits of a proactive management of inpatient hyperglycemia are well known in the general hospitalized population with or without known diabetes. For critically ill patients, the American Association of Clinical Endocrinologists (AACE) and the ADA recommend starting an IV insulin infusion and frequent glucose monitoring for patients with BG ≥ 180 mg/dL, targeting a BG of 140 to 180 mg/dL, with lower targets of 110 to 140 mg/dL only in selected patients.[11] The Society of Critical Care similarly recommends an insulin infusion for BG > 150 mg/dL and to maintain BG below that target, but absolutely <180 mg/dL.[28]

In patients with ACS, a scientific statement from the American Heart Association Diabetes Committee in 2008, recommended starting intensive insulin therapy in patients with hyperglycemia >180 mg/dL, regardless of their prior history of diabetes. They recommended using a validated and efficient IV insulin protocol with close BG monitoring. Similarly, the European Society of

Cardiology in 2012 recommended maintaining BG between 90 and <200 mg/dL in patients with ST segment elevation myocardial infarction, but absolutely avoiding hypoglycemia. Insulin therapy should be decreased and/or adjusted if BG < 70 mg/dL and should be reassessed if BG < 100 mg/dL.[12,34]

For non–critically ill patients, the Endocrine Society and AACE/ADA guidelines recommended a target premeal BG of <140 mg/dL and random BG < 180 mg/dL, with subcutaneous (SQ) basal-bolus regimen preferred.[11]

GLYCEMIC TREATMENT: INSULIN THERAPY IN THE CCU

The LEUVEN study was a landmark study performed by Van den Bergh et al. in Leuven, Belgium in 2001. This study opened an interesting area of investigation in glucose control in surgical critically ill patients and outcomes. Initially, this single-center study showed a mortality benefit in patients treated with insulin to an "intense glycemic target," BG between 80 and 100 mg/dL, compared to a less strict goal of BG between 180 and 200 mg/dL. Notably, there were more severe hypoglycemic episodes in the intervention arm. However, these results were not replicated by several other prospective studies, including the van den Bergh group.[35,36]

The subsequent study by the van der Bergh group in Leuven, including patients in the medical intensive care unit (MICU) this time, showed no difference in mortality. This study also found higher rates of hypoglycemia, presumably because of changes in the nutrition management between the two patient populations, in the intense glycemic group.[37] The largest trial of intense glucose control in the ICU to date is the "Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR)" trial. This trial randomly assigned patients in the MICU and surgical intensive care unit (SICU) to an intensive BG target (BG between 81 and 108 mg/dL) versus a conventional/less strict glucose target (BG < 180 mg/dL). Conversely, this study showed that the intensive glycemic control group had a higher 90-day mortality and incidence of hypoglycemic episodes.[36]

Some small studies have yielded small but significant differences in mortality when goals are less stringent, but comparison is hard and hampered because of the heterogeneity of different studies. The DIGAMI and HI-5 trials are the two landmarks studies of glucose control in the ACS patient population. The first DIGAMI trial studied the effects of intensive in-hospital insulin treatment (insulin-glucose infusion for at least 24 hours followed by multidose SQ insulin

regimen) versus usual care in 620 patients with acute myocardial infarction with or without diabetes and an admission glucose of 200 mg/dL. Patients with myocardial infarction were randomized to receive insulin infusion to maintain BG 126 to 180 mg/dL versus standard of care without an insulin infusion. Better glycemic control was achieved in the intensive insulin therapy arm (mean 24-hour posttreatment BG of 173 vs 210 mg/dL in the control group). A significant 28% mortality reduction benefit was seen in the intervention arm after long-term follow up of 3.4 years.[38] The DIGAMI 2 trial attempted to compare three different treatment regimens (acute insulin-glucose infusion followed by insulin-based long-term glucose control; insulin-glucose infusion followed by standard glucose control on discharge; and routine metabolic management in both inpatient and outpatient settings) and found no difference in outcomes between the three regimens.[39] Moreover, the subsequent HI-5 trial was the first randomized trial that included patients with hyperglycemia without a diagnosis of diabetes. Patients were assigned to an intensive insulin infusion arm (BG goal of 72 to 180) and a conventional arm that was treated with their usual diabetes medication including SQ insulin. There was no difference in mortality rates among the groups during hospitalization or at 3 or 6 months. There were, however, significant reductions in post–myocardial infarction HF during the hospitalization (10% absolute risk reduction) and in reinfarction at 3 months.[20]

This brief description of some of the landmark studies regarding hyperglycemia in critically ill patients with ACS was intended to show the conflicting results of intensive glycemic targets in this population. These controversial results may probably be due to heterogeneity in patient characteristics and study protocols. We advise the readers to exercise some caution with extrapolation of the data from general MICU and SICU patients, or combined trials into the CCU practice. Nevertheless, hyperglycemia management targeting less stringent goals has become part of the standard of care in hospitalized patients, as endorsed by several national organizations.[11,12,28,34]

INSULIN INTRAVENOUS INFUSION THERAPY (“DRIP”) IN THE CCU

The preferred approach to manage medical or surgical critically ill patients is using an insulin infusion protocol with regular human insulin.[28] There are several validated infusion protocols, some nurse-driven or computer-generated algorithms, that have been validated for their safety and efficacy.[40] Oral

hypoglycemic agents are generally not recommended for the critically ill and non–critically ill hospitalized patients, and should be discontinued upon admission to the CCU.[25]

In brief, most insulin infusion protocols include instructions on how much insulin to start infusing based on the initial BG. Then, the insulin rate per hour is adjusted on the basis of the rate of BG change. In addition, the protocol will instruct on how to correct hypoglycemia, and adjust the infusion rate to prevent it again. It has been shown that BG targets are usually achieved within approximately 4 to 8 hours in most patients. The onset of regular insulin after IV administration is within 15 minutes, with a half-life of 9 minutes, a maximal effect within 15 to 30 minutes, and a duration of 30 to 60 minutes. Thus, this safely ensures a rapid up- or down-titration of the doses in anticipated (ie, rapid decline of BG, use of vasopressors) or unanticipated (ie, acute clinical status deteriorations, hypoglycemia) situations.[28]

Several centers use nurse-driven computer-based algorithms, whereas others use paper-based protocols. The Glucommander is an example of a computer-driven insulin infusion software, developed since 1984. After entering a bedside BG into the system, the Glucommander calculated the initial insulin infusion rate (ie, BG − 60 mg/dL × 0.02 = insulin dose/h). The system will notify the nurse or provider when the next bedside BG is needed. The system continues making adjustment recommendations of the insulin infusion until it is stopped by the provider. The pilot studies by Davidson et al. showed that the system can maintain BG within target range, without significant hypoglycemia, and run by nonspecialized staff.[40]

Peri-operative patients may require additional considerations. Oral hypoglycemic agents and non–insulin injectable agents should be held on the day of the surgery. For patients with DM2 who will be fasting (NPO) for at least 8 hours before surgery, basal insulin should be adjusted to 75% to 100% of the regular home dose the night before surgery, depending on the patient’s glycemic curve. Because the patient is fasting, prandial insulin is, by definition, not required. However, correctional sliding-scale insulin every 4 to 6 hours should be used for correction of residual hyperglycemia, while NPO. For patients using neutral protamine Hagedorn (NPH) insulin, because of the increased risk of hypoglycemia compared with basal insulin analogs—glargine or detemir—it is recommended to give about 75% of the usual dose the day before surgery and 50% to 75% on the surgical day. IV insulin infusion protocols can allow for rapid insulin adjustments based on BG in these scenarios of rapid glucose shifts.

Close glucose monitoring every 1 to 2 hours is usually recommended for monitoring. For short-duration (approximately <4 hours) and small or simple surgical procedures, SQ insulin can be used. For longer and more complicated procedures (>4 hours) IV insulin infusion is the recommended approach.[41,42]

In our institution, we have created a pathway for management of hyperglycemia in cardiac patients, which is depicted in **Figure 54.4**.[43]

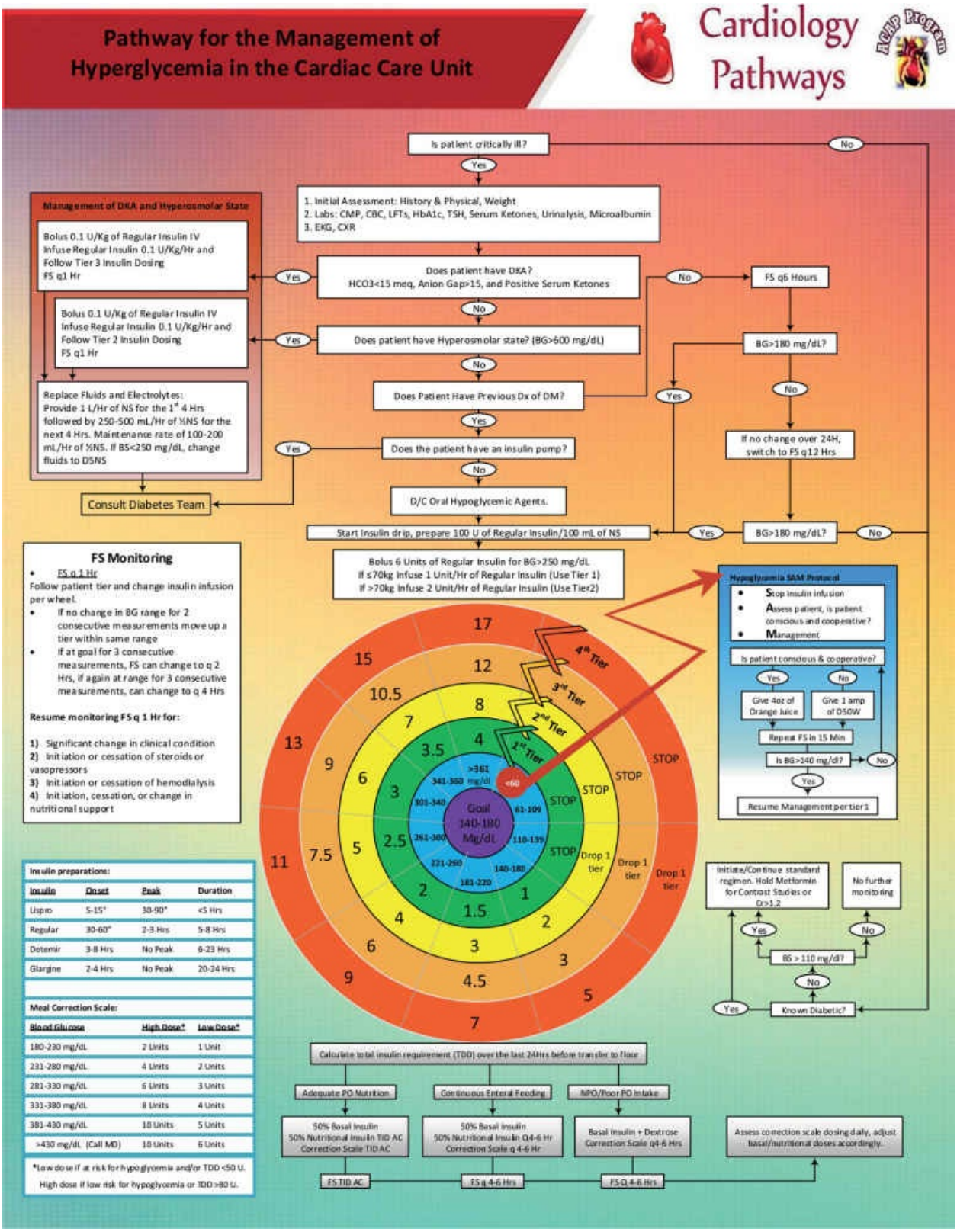

FIGURE 54.4 Pathway for the management of hyperglycemia in the cardiac care unit. BG, blood glucose; CBC, complete blood count; CMP, comprehensive metabolic panel; CXR, chest X-ray; ECG, electrocardio

gram; DKA, diabetic ketoacidosis; FS, fasting sugar; LFT, liver function test; NS, normal saline; TDD, total daily dose; TSH, thyroid-stimulating hormone

Pathway for the Management of Hyperglycemia in the Cardiac Care Unit

The main goal of this pathway is to provide glycemic control for critically ill patients. Initial assessment of the former group of patients should include history, physical examination, and recording of weight. We have also defined a basic laboratory test panel required for all patients (**Figure 54.5**). We included patients with DKA and patients with hyperosmolar state and provided guidelines for their management (**Figure 54.6**). These patients might not necessarily be treated in the cardiac care unit depending on their associated cardiovascular morbidities. Patients managed in this protocol have a diagnosis of DM. If a patient is not known to have DM, capillary BG determinations every 6 hours will be required. A BG of 180 mg/dL qualifies patients for enrollment into our pathway of insulin infusion protocol (**Figure 54.7**).

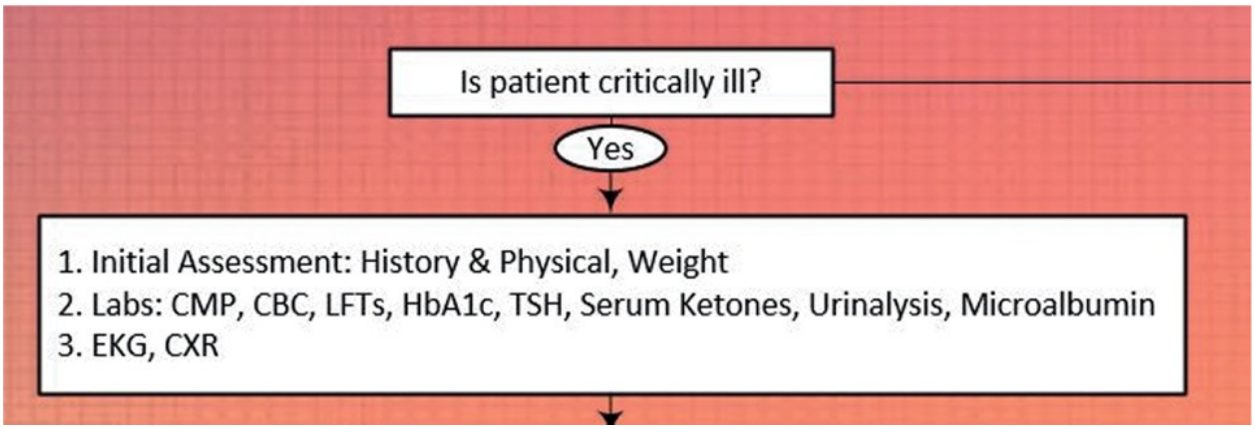

FIGURE 54.5 Initial assessment of patients with hyperglycemia who are screened to a cardiac care unit. CBC, complete blood count; CMP, comprehensive metabolic panel; CXR, chest X-ray; ECG, electrocardiogram; LFT, liver function test; TSH, thyroid-stimulating hormone.

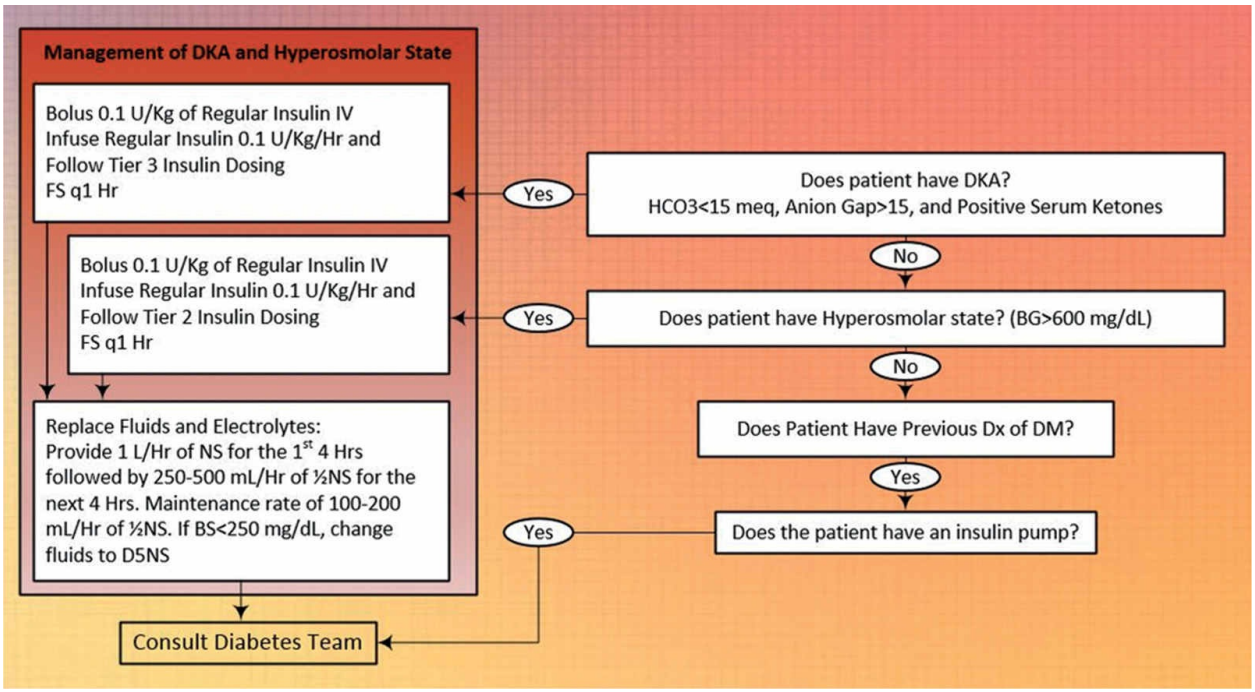

FIGURE 54.6 Management of DKA and hyperosmolar state and activation of diabetes team. DKA, diabetes ketoacidosis; DM, diabetes mellitus; IV, intravenous.

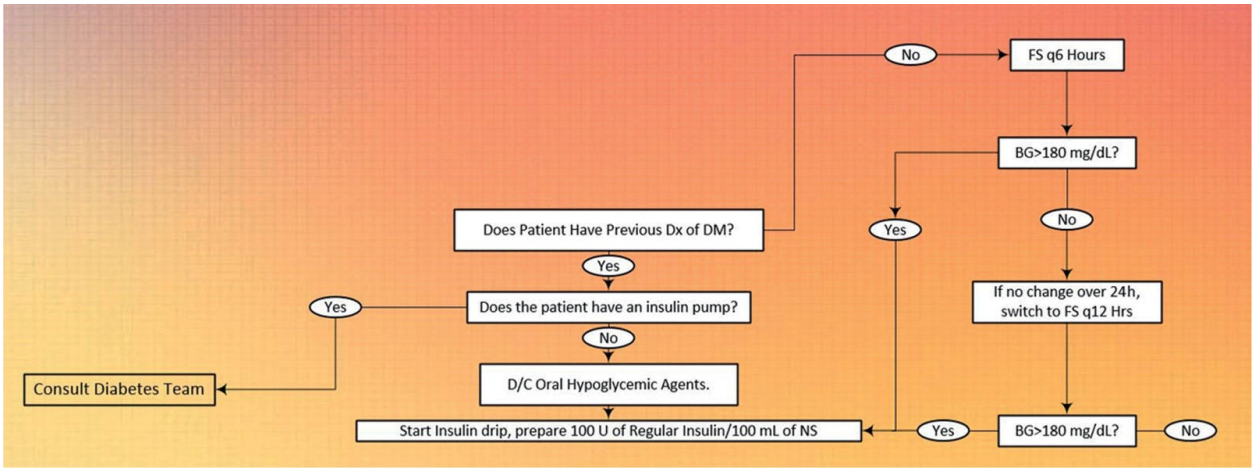

FIGURE 54.7 Blood glucose determination for enrollment into the hyperglycemia pathway. DM, diabetes mellitus; NS, normal saline.

Initiation of the insulin infusion is achieved by providing a bolus of 6 units of regular insulin for patients with a BG of 250 mg/dL or more and starting an infusion protocol that is based on weight. If the initial BG value is above 180 but below 250 mg/dL, the patient will not need the bolus insulin and will be started on weight-based insulin drip only (**Figure 54.8**).

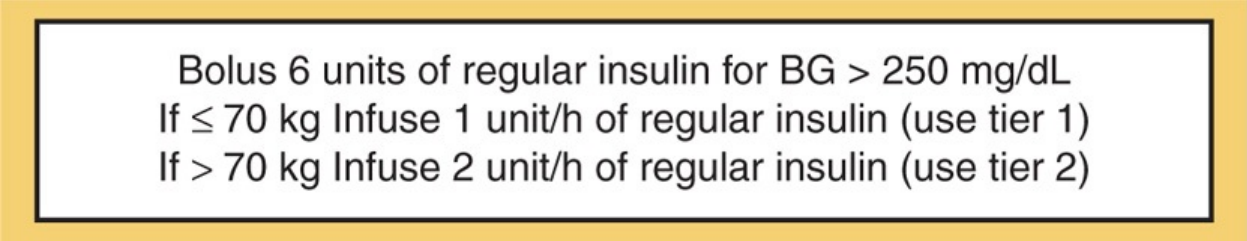

FIGURE 54.8 Initiation of insulin infusion protocol. BG, blood glucose; DM, diabetes mellitus; NS, normal saline.

The key element of this pathway is the "wheel" that provides treatment instruction for insulin administration (**Figure 54.9**). This wheel is made up of six circles. The core circle shows the acceptable glycemic range for all the patients and the inner circle represents the measured BG ranges. The four outer circles represent four different rates of insulin infusion, also known as "tiers." For patients who are less than 70 kg, the insulin infusion rate should be calculated on the basis of tier 1. For patients who weigh more than 70 kg, the infusion rate is based on tier 2. BG monitoring is performed every 1 hour. The infusion rate is then adjusted according to the instructions corresponding to the BG of the same tier: "dialing up and down the wheel within the tier." If there is *no* decrease in BG range for two consecutive measurements, the health care provider moves up a tier at the same glucose range.

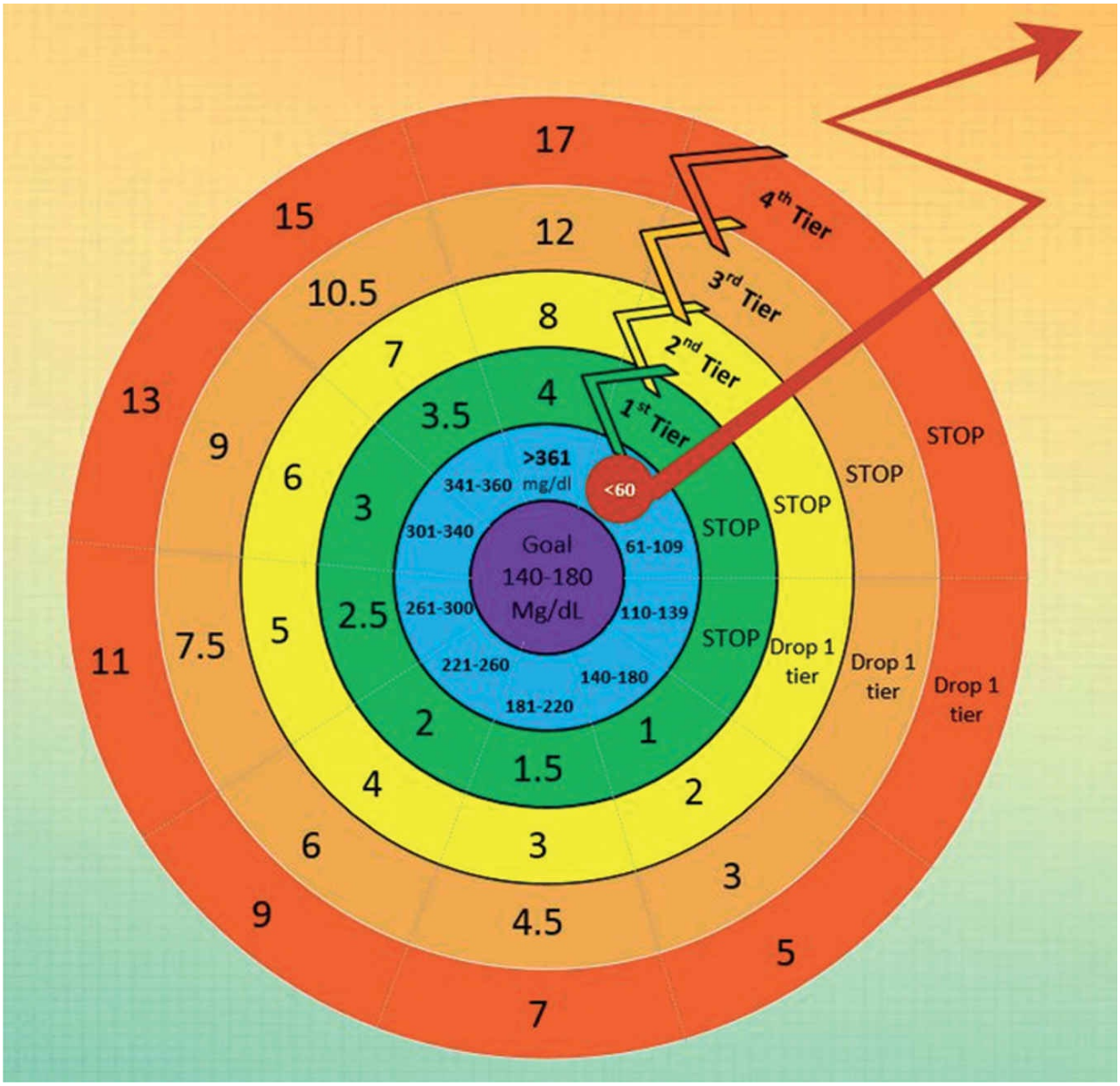

FIGURE 54.9 The "wheel" as a tool for insulin infusion.

A major goal in the management of hyperglycemia is the prevention of hypoglycemia. If a patient is found to be hypoglycemic (defined as BG of 60 mg/dL or less), a protocol for management is provided, as seen in **Figure 54.10**. We named this protocol SAM to reflect the key components of treatment: *S*top insulin infusion, *A*ssess the patient for consciousness and cooperation, and *M*anage the patient (with orange juice or D50%W infusion). If a patient's BG exceeds 140 mg/dL, the management using the "wheel" is resumed with the initial insulin infusion rate based on tier 1 and the corresponding BG.

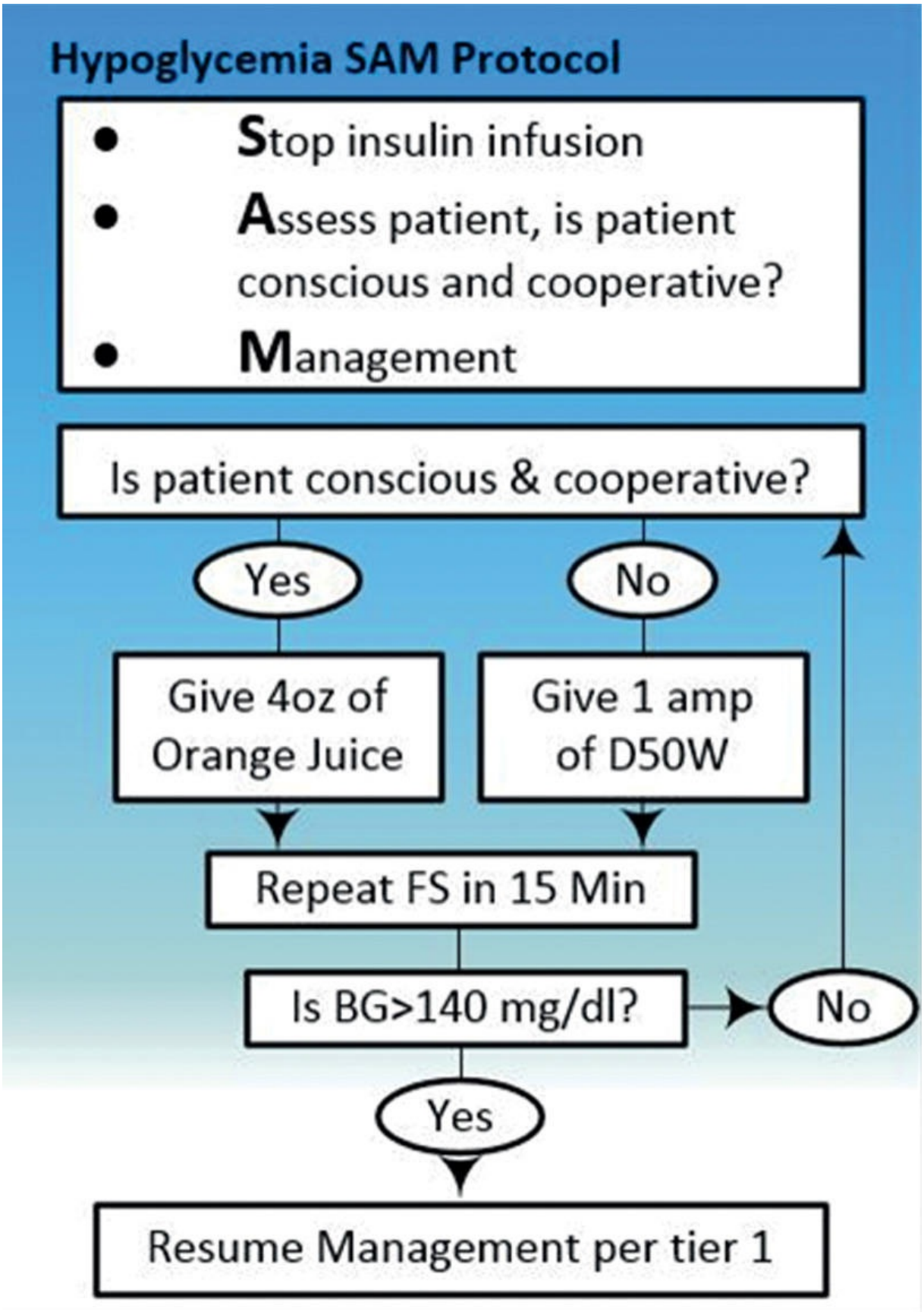
Hypoglycemia SAM Protocol
Stop insulin infusion
Assess patient, is patient conscious and cooperative?
Management
Is patient conscious & cooperative?
Yes
No
Give 4oz of Orange Juice
Give 1 amp of D50W
Repeat FS in 15 Min
Is BG>140 mg/dl?
No
Yes
Resume Management per tier 1

FIGURE 54.10 Management of hypoglycemia. BG, blood glucose; FS, fasting sugar.

Instructions for frequency of BG monitoring are provided to the health care provider. Initially, all monitoring is performed every 1 hour. If BG results are at goal for three consecutive readings, then the frequency of monitoring is decreased to every 2 hours and, again, if there is no change for three consecutive readings, it is decreased to every 4 hours. Return to frequent monitoring (BG every 1 hour) is required for the following conditions: significant change in clinical condition; initiation or cessation of corticosteroids or vasopressors; initiation or cessation of hemodialysis and/or initiation, cessation, or change in nutritional support (**Figure 54.11**).

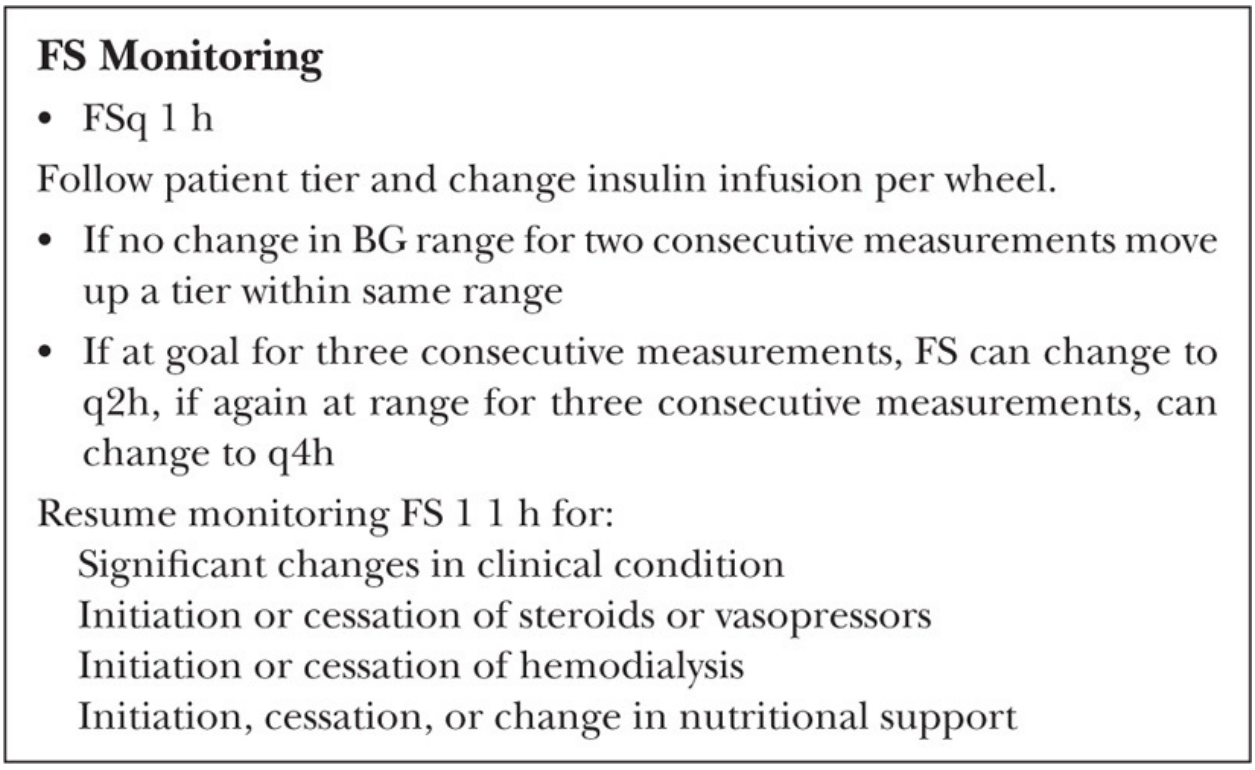

FIGURE 54.11 Guidelines for finger stick monitoring for patients with hyperglycemia. BG, blood glucose; FS, fasting sugar.

A protocol was developed to convert from the insulin infusion to SQ insulin injection without sacrificing diabetes control. First, the health care provider calculates the total insulin requirement (total daily dose [TDD]) over the last 24-hour period in the cardiac care unit. The patients are then divided into the following three groups based on their nutritional status.

Group I: Patients With Adequate PO Intake

This group of patients receives a combination of long-acting insulin (50% of the TDD)—usually glargine—at bedtime and the rapid-acting insulin lispro in three equal doses before every meal. They will also receive correctional scale insulin before every meal (to be added to the standing nutritional insulin dose) based on glucose monitoring before each meal (**Figure 54.12**).

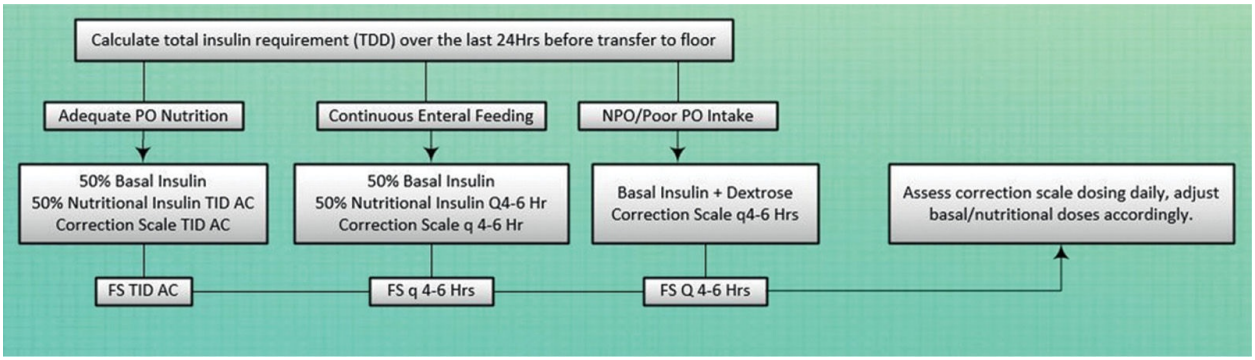

FIGURE 54.12 A protocol for conversion from insulin infusion to subcutaneous insulin injection. FS, fasting sugar; TDD, total daily dose.

Group II: Patients on Continuous Enteral Feeding

Patients on continuous enteral feeding, just like those with adequate PO intake, will receive 50% of their TDD as long-acting insulin at bedtime and will also receive the rest of the TDD in three divided doses of nutritional insulin. The only difference will be in the timing of this nutritional and correctional insulin. Because these patients are receiving continuous enteral feeding, there is no specific meal time during the day to be the base of measurements and administration of insulin. In these patients, both BG measurements and insulin administration will happen every 4 to 6 hours to give them a smoother glycemic range during the day (**Figure 54.12**).

Group III: Patients Who Are NPO or Those With Inadequate PO Intake

Because these patients do not have any reliable source of nutrition, they will not receive nutritional insulin. They will still need basal insulin (specifically if they are type 1 diabetic). To receive basal insulin without hypoglycemia, these patients need to be on dextrose infusion. They will also benefit from BG measurements every 4 to 6 hours and will need correctional scale insulin if these values are high.

In all of these patients, the 24-hour insulin requirements should be checked frequently and the basal and nutritional doses should be adjusted accordingly to minimize the amount of correctional insulin needed (**Figure 54.12**).

Correctional Insulin Scale

We provide two doses for meal correctional insulin in our pathway, the high-dose and the low-dose scale (**Figure 54.13**). The health care provider can also pick the value in between that will represent the medium dose scale of correctional insulin. Use of either of the dosing values is mainly based on clinically estimated risk of hyper- or hypoglycemia.

Insulin preparations:			
Insulin	**Onset**	**Peak**	**Duration (h)**
Lispro	5–15”	30–90”	<5
Regular	30–60”	2–3 h	5–8
Detemir	3–8 h	No Peak	6–23
Glargine	2–4 h	No Peak	20–24
Meal Correction Scale:			
Blood Glucose		**High Dose* (units)**	**Low Dose* (units)**
180–230 mg/dL		2	1 Unit
231–280 mg/dL		4	2
281–330 mg/dL		6	3
331–380 mg/dL		8	4
381–430 mg/dL		10	5
>430 mg/dL (Call MD)		10	6
*Low dose if at risk for hypoglycemia and/or TDD < 50 U. High dose if low risk for hypoglycemia or TDD> 80 U.			

FIGURE 54.13 Correctional sliding scale and characteristics of different insulin preparations. TDD, total daily dose.

Medium- or high-dose scale is used mostly in patients who are obese, or have acute, severe illness or infection or those on some medications including steroids, vasopressors, certain antipsychotics, or any other medication that causes a rise in BG level. Low-dose scale is used in patients who are NPO or those who suffer from malnutrition, low body weight, lean type 1 DM, or poor PO intake. This scale is also appropriate to use in those with renal insufficiency, hepatic disease, HF, shock, adrenal failure, burns, alcoholism, malignancy, or those with a history of severe or recurrent hypoglycemia.

Another approach to decide regarding the dosage of the correctional scale is based on patients’ total daily insulin intake with low dose used in those with TDD < 50 units, medium dose in those with TDD 51 to 80 units, and high dose in those with TDD > 81 units.

We also provide pharmacologic characteristics of different types of insulin

preparation that are used most commonly in the cardiac care unit (**Figure 54.13**).

Non–Critically Ill Patients in the Cardiac Care Unit

Non–critically ill patients will not benefit from aggressive control of their BG using insulin infusion. These patients will need a standard regimen for management of their DM while they are in the hospital. Those with known diabetes who are on established and effective diabetic regimen should be kept on their respective regimens while in the hospital. The only exception will be to hold the metformin if they are about to undergo contrast studies. Other patients without a history of diabetes who fulfill the criteria for DM diagnosis should be assessed and started on a guideline-based regimen to control their DM. The remainder of the patients who do not fulfill diagnostic criteria of DM will not benefit from frequent BG measurements (**Figure 54.14**).

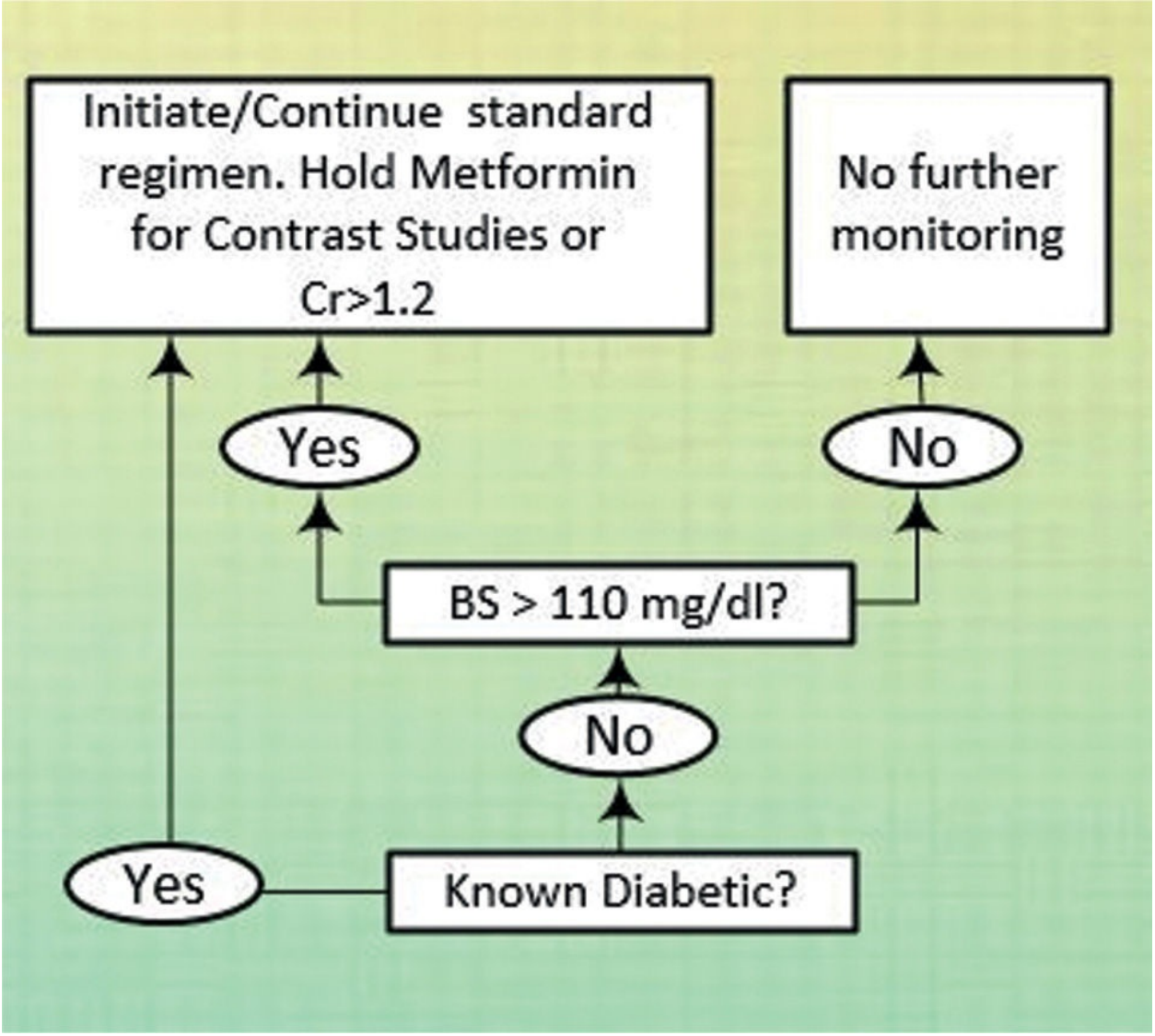

FIGURE 54.14 Management of hyperglycemia in non–critically ill patients. BS, Blood sugar..

This comprehensive pathway provides a detailed algorithm for management of hyperglycemia in cardiac care units. It introduces the novel concepts of the "wheel," which is the primary tool permitting rapid restoration of euglycemia and is the focus of this pathway.

TRANSITION OF CARE—FROM THE CCU TO MEDICINE WARD, FROM HOSPITAL WARDS TO HOME

Patients may be transitioned to a SQ insulin regimen once clinically stable, when restarted on oral diet, and/or when transferred out of the CCU. Several factors should be considered during the "transition period," including insulin

requirements while on the insulin infusion, current or planned nutrition, and/or concurrent infections or medications, such as steroids. Several randomized controlled trials using SQ basal-bolus insulin regimens have reported better glycemic control and reduction of complications compared to sliding-scale insulin in patients with type 2 diabetes.[44] Insulin sliding scales as a sole management approach is strongly discouraged in patients transitioned from the CCU to the general wards. Sliding-scale insulin regimens treat hyperglycemia after it has already occurred, instead of "proactively" preventing the occurrence of hyperglycemia with scheduled insulin doses. This "reactive" approach can lead to rapid changes in BG levels, exacerbating both hyperglycemia and hypoglycemia. The recent Basal-Plus study, a randomized controlled trial consisting of basal insulin plus correctional premeal doses of rapid-acting insulin per sliding scale, showed that this approach may be an alternative in some situations, such as in patients not eating full meals, or with nausea, or with very mild hyperglycemia.[45]

Communication between the multidisciplinary team members, including CCU nurses, diabetes team members, and primary medicine team, is key for a safe transition. The involvement of several members will ensure appropriate glucose monitoring, insulin dose adjustments, and close communication. Before transitioning the patient to the SQ basal-bolus insulin regimen, some clinical characteristics should be evaluated. The patient should have reached clinical stability, have stable glycemic control for several hours, and not continue to require critical medical or nursing care. Some authors suggest a period ranging from 6 to 24 hours of glycemic control with minimal variability in IV insulin rates. Patients should ideally be without vasopressors or inotropic agents and have a stable nutrition plan or should be tolerating PO diet. In patients admitted with DKA, the anion gap and acidosis should have normalized before considering transitioning to SQ insulin. Postoperative stress, pain, variable oral intake, infection, and underlying insulin resistance are all factors that affect insulin requirements. Given the short half-life of IV regular insulin, SQ insulin should be given before stopping the infusion, to avoid rebound hyperglycemia or acidosis. Consideration should also be given to the time to onset of each type of SQ insulin. For instance, glargine should be given at least 2 hours in advance before stopping the IV insulin.[46]

The insulin infusion requirements are usually high during the first few hours of treatment of patients with DKA or HHS, progressing into a highly variable infusion rate, before finally settling down to a more stable pattern. Similarly,

patients with stress hyperglycemia have markedly increased insulin infusion utilization within the first 48 to 72 hours post surgery. Using these variable insulin rates (ie, change greater than two units per hour), especially the initial extremely high rates, in the 24-hour SQ total insulin calculation will yield a result that potentially overestimates the patient's requirements once clinically stable and off the insulin infusion.[46] For this reason, it is recommended to use the hourly insulin rate from a previous period when BG was stable and within target range; in other words, the rate was reasonable and stable for some time. One can then look at the infusion rates during this stable period of time, ideally 6 to 8 hours in duration, to calculate the average insulin rate per hour required. This hourly insulin rate is multiplied by 24 to extrapolate these data to a 24-hour time period and the total 24-hour insulin requirements is calculated. Some authors suggest utilizing 50% to 60% of this 24-hour insulin dose in patients with stress hyperglycemia and no previous diagnosis of diabetes, whereas up to 60% to 80% can be used in patients with DM2 and high insulin requirements. The total insulin dose is then divided into 50% basal and 50% bolus insulin.[46]

In hospital settings, basal insulin analogs, such as glargine or detemir, are generally preferred over NPH or mixed insulin because they have been associated with less glycemic variability and less severe hypoglycemia.[47] Renal dysfunction is common in hospitalized patients, increasing the risk of insulin and non–insulin-related hypoglycemia. Baldwin et al. studied two basal-bolus (glargine-glulisine) insulin-dosing regimens in patients hospitalized with DM and CKD (eGFR < 45 mL/min). The authors found that a weight-based insulin regimen of 0.25 units/kg/d was associated with 50% less hypoglycemia (15.8% vs 30%, $P = 0.08$).[48]

It is important to establish institutional protocol for transition from the inpatient to the outpatient settings. In general, length of stay for patients with diabetes, although longer than for those without, has been gradually decreasing just as for all inpatient stays being on average 5 to 6 days. Therefore, the discharge plan for patients with diabetes has to be set from the admission. In established diabetes, it is important to determine the goals for the patient's level of glycemic control. A recent prospective study recommended using the admission HbA_{1C} to determine the diabetes plan.[49] In patients with stress hyperglycemia, it is important to coordinate appropriate follow-up to assess for the development of diabetes later.

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Patient and Family Information for: DIABETES MELLITUS IN THE CARDIAC CARE UNIT

DIABETES MELLITUS: GENERAL PRINCIPLES

WHAT IS DIABETES MELLITUS AND HOW IS IT DIAGNOSED?

Diabetes Mellitus (DM) is a condition in which the level of glucose or sugar in the blood is higher than normal (also called hyperglycemia). A higher level of glucose in the system over a long period of time leads to injury to different organs in the body, generally affecting the nerves, eyes, and possibly the arteries as well. According to the American Diabetes Association (ADA) criteria, a number of measurements can be used to make the diagnosis of DM, such as the following:

1. Randomly measured levels of glucose in the blood
2. The measurement of glucose while fasting
3. The measurement of blood sugar after a standardized glucose intake is given to the patient orally
4. By measuring the amount of glucose particles attached to blood hemoglobin (A_{1C}), which represents average blood glucose (BG) level over a 3-month period and is a very consistent indicator of risk for diabetes complications

Some of these measurements need to be repeated to confirm the final diagnosis of diabetes.

WHAT CAUSES DIABETES?

DM has various types including type 1, type 2, gestational (associated with pregnancy), or other specified and less common types. Insulin is the hormone mainly responsible for titration of blood sugar level and is secreted from pancreas (an organ in the abdomen that is closely associated with intestinal tract). Type 1 diabetes means that the pancreas is not producing enough, or any, insulin to maintain the blood sugar in the normal range. Type 2 diabetes is not only characterized by resistance to the action of insulin for multiple reasons but also by a relative decrease in the body's ability to secrete insulin (insulin is produced but not in sufficient quantities or in an appropriate pattern to overcome the insulin resistance). Increased resistance to insulin, owing to greater quantities of different hormones in the blood that occur during pregnancy, is the basis for gestational diabetes. The resistance to insulin usually resolves after the patient gives birth but the presence of gestational diabetes constitutes a high-risk factor of developing type 2 diabetes later in the patient's life and therefore these patient's require close follow-up. Other less common types of diabetes could be because of genetic defects affecting insulin's action, pancreatic disease with decreased insulin production, various endocrine dysfunctions, various drugs, rare infections, immune-mediated reactions, and so on. The overall clinical manifestation of these other types are similar to either type 1 or type 2 diabetes.

Type 1 diabetes: Insulin therapy is essential in patients with type 1 diabetes because they do not produce any. DKA is a known complication of type 1 diabetes in patients not receiving insulin injections. This is a very dangerous condition characterized by dehydration, nausea, and vomiting and is so severe that it can lead to coma and even death if left untreated. It is completely reversible with the appropriate administration of insulin and glucose.

Type 2 diabetes: Basically it means a resistance to insulin and the body's inability to compensate by producing more from the pancreas. Type 2 diabetes is always preceded by a condition called prediabetes. Prediabetes is defined by high levels of fasting glucose, unusual rise in blood sugar in response to the higher amounts of glucose intake, and higher levels of A_{1C} but not to the degree seen in full-blown diabetes. A gradual increase in resistance to insulin's action (insulin resistance) occurs with aging, obesity, physical inactivity, and genetic factors. If the insulin resistance is not overcome by producing more insulin then, this will lead to increased glucose in the blood and finally frank DM. It is important to understand that obesity, especially "male-type" abdominal obesity is the central component in developing prediabetes and type 2 diabetes.

Prediabetes can be detected through the same tests as full-blown diabetes.

Individuals considered “at risk” should be screened for both prediabetes and type 2 diabetes. Early detection not only allows an early implementation of preventive measures aimed at reducing insulin resistance (weight loss, increased physical activity, etc.) but can also prevent chronic complications and can improve longevity and chances of complication-free survival.

ELEVATED BLOOD GLUCOSE WHILE HOSPITALIZED (INPATIENT HYPERGLYCEMIA)

Sometimes acutely ill patients who are not known to have had diabetes or prediabetes of any kind may develop high BG while admitted to the hospital because the stress on the body from illness causes a state of insulin resistance. This can also happen in patients who have latent diabetes, prediabetes, or just are at risk for diabetes development but are normally glucose tolerant when not sick. It is unclear how frequently this leads to persistent diabetes after hospitalization, but inpatient elevations of BG have been linked to worse outcomes in the critical care units. If the patient survives the critical event but shows signs of impaired glucose tolerance (IGT) (prediabetes), this can be an indication for the future development of diabetes, and it should be addressed by the physician caring for the patient in the outpatient setting.

CLINICAL MANIFESTATION OF DIABETES MELLITUS

Clinical manifestations of DM could be acute (such as diabetic ketoacidosis (DKA) or chronic. The chronic complications may affect the small blood vessels (microvascular) or large blood vessels (macrovascular) in the body. Microvascular complications include worsening vision, nerve dysfunction (neuropathy), and damage to the kidneys. Macrovascular complications include effects on the brain, heart, and other peripheral blood vessels (atherosclerosis and clotting). Other complications include an increased risk of infections and disorders of the skin, joints, and muscles.

TREATING ELEVATED BLOOD GLUCOSE TO ACHIEVE TARGET (OUTPATIENT MANAGEMENT)

Currently it is recommended to aim for tight glucose control early in the course of diabetes. There are several ways to assess glucose control in DM. One can frequently test BG throughout the day with a glucometer (a handheld machine for bedside or home BG measurements), measure A_{1C}, or measure BG

continuously through a subcutaneous catheter (inserted under the skin), which is called continuous glucose monitoring. Glucose monitoring is essential for the patients to achieve the glucose targets. A_{1C} reflects mean glucose over a 2- to 3-month period. Beyond the desirable range, it is a marker for risk of complications. The target level of A_{1C} recommended by the ADA is <7% or as close to normal as safely possible to achieve. It should be tested every 6 months if the value is at target or every 3 months when not on target, or when treatment changes. Other glucose targets for tight control have been defined for fasting BG and for glucose checked 2 hours after consumption of a meal (postprandial). The fasting glucose target has been defined by the ADA as 90 to 130 mg/dL, whereas 2-hour postprandial glucose target has been defined as <180 mg/dL peak value. Glucose monitoring is best demonstrated by a diabetes educator, who can also best determine the devices that should be used and how often to test. The glucose should be monitored at least 3 times/day, before each of the main meals, for patients on insulin injections to guide dosing. Those not on insulin could use self-monitoring as a guide to success.

MANAGEMENT OF LOW BLOOD GLUCOSE (HYPOGLYCEMIA)

The correct management of low levels of BG is crucial in all diabetics but especially in those with cardiac disease, vascular disease, or advanced complications. The low BG levels should be correctly evaluated and treated immediately. The severity of low glucose levels is considered mild to moderate when levels of BG range from 50 to 70 mg/dL and/or patients can treat it themselves. It can be treated with simple, and easily absorbable oral sources of carbohydrate such as glucose tablets/gel, orange juice, or soft drinks containing 15 to 20 g glucose. Glucose levels should be checked again in 15 minutes and patients must be educated to carry a source of glucose with them at all times. Extremely low BG levels of <50 mg/dL, when accompanied by altered consciousness and requiring the patients to need assistance, is considered to be very severe. The patient needs to take 20 to 30 g of simple glucose orally if able to or be given glucagon (a hormone produced by the pancreas, which counteracts insulin) by intramuscular injection. If the patient is not responsive to the previous methods, then 911 should be called for IV glucose to be administered. If severe hypoglycemia is consistently present, patients should be referred for a diabetes self-management education workshop, where the use of glucagon injection should be taught to family members or caretakers. In addition, BG

goals have to be revised. If patients have frequent episodes of low BG or are unaware of the symptoms that usually accompany these low levels, they need support from family members or friends to prevent them from harm. These at-risk patients should wear identifying bracelets and it is not recommended that they drive.

IDENTIFYING AND TREATING COMPLICATIONS OF DIABETES

The treatment of chronic complications of diabetes should be conducted according to published standards of care to ensure early diagnosis and to prevent progression. These standards of care are published yearly by the ADA. Retinopathy, nephropathy, and neuropathy are the targeted complications. Retinopathy is one of the eye complications of DM. It can lead to blindness if not treated early with laser or other methods. Diabetes is also a risk factor for the development of cataracts and glaucoma. Patients should have annual dilated eye examinations after 3 years from the onset of type 1 diabetes and immediately at the time of diagnosis for type 2 diabetes. Prevention of retinopathy is through tight control of BG and also by smoking cessation along with control of blood pressure and blood lipids (cholesterol and triglycerides). Diabetic nephropathy (kidney injury) manifests itself as protein leaking into the urine, which eventually can lead to kidney failure requiring dialysis. The amount of protein leaking into the urine should be checked annually with a random spot urine test. Also, the kidney function needs to be monitored at least annually. The prevention of kidney failure should be done through tight glucose and blood pressure control and through administration of agents that lower leakage of protein in the urine. When severe protein leakage is present, there may be swelling of the legs, and the treatment should include dietary protein reduction, blood pressure lowering to <125/75 mm Hg, and revised glucose management goals. Diabetic neuropathy or nerve damage can affect the “peripheral” nerves (those going to the feet and legs, hands, etc.) or the nerves that go to the internal organs. The former can lead to diabetic foot ulcers, damage to the joints, and deformities of the feet with fractures and infections and, ultimately, even amputations. Inspection of the feet should be done at every visit; feet identified to be at high risk should be referred for podiatric care and for orthotics. Patients should have diabetes self-management education including foot care training.

DIABETES MELLITUS IN THE CARDIAC CARE UNIT

HIGH PREVALENCE OF DIABETES MELLITUS AND HYPERGLYCEMIA IN THE ACUTE CORONARY SYNDROME

Patients with type 2 diabetes have a very high incidence of obesity and the so-called metabolic syndrome. Obesity, particularly abdominal obesity, predisposes the body to become more resistant to the effects of insulin. Metabolic syndrome is a constellation of insulin resistance with resultant metabolic derangements that puts the patient at particularly high risk for DM as well as CVD. Other associated metabolic abnormalities of this syndrome that include inflammation, abnormal lipid levels in the blood and a tendency to have blood clots in the vascular system are also associated with acute complications of CVD such as CAD which can lead to coronary syndrome (ACS). or heart attack. Numerous studies have shown that there is a very high prevalence of diabetes in patients admitted to the CCU with acute coronary syndrome (ACS). In addition to being frequently present in ACS, diabetes also predicts unfavorable outcomes in those who have ACS. Patients afflicted with both conditions (diabetes and ACS) have more frequent high blood pressure, high cholesterol, and kidney failure. This is regardless of whether the diabetes is new onset or established. High blood sugar affects ACS outcomes even if diabetes was not present before the event and is diagnosed in the hospital.

STRATEGIES FOR IMPROVING OUTCOMES IN ACUTE CORONARY SYMPTOM COMPLICATED BY DIABETES AND/OR HIGH BLOOD GLUCOSE

To counteract complications from cardiac events in type 2 diabetes, various blood-thinning medications and early strategies to unblock blood vessels are done as early as possible. In addition to these important lifesaving therapies that are similar to those utilized in non–diabetic patients, glucose-lowering therapies and aggressive use of secondary prevention therapies for control of high blood pressure, cholesterol, and inflammation are also utilized. Currently, the consensus is that high BG should be lowered in patients with diabetes and ACS, but the level to be obtained will be dependent on how safe it is to get there without causing hypoglycemia. Both hyperglycemia and hypoglycemia are harmful and should be avoided in the CCU. Many patients with diabetes might need round-the-clock infusions of insulin intravenously to keep their BG level in the appropriate range. The rate at which this infusion enters the body is calculated and adjusted by frequent monitoring of BG levels via glucometers.

TRANSITION TO OUTPATIENT CARE

As soon as the patient's condition is stable and he/she is able to eat, the IV infusion of insulin can be safely switched to SQ (under the skin) injections in preparation for transfer to a general medical floor outside the CCU and eventually home. While in critical conditions, the body's insulin requirements are usually higher and as the acute critical condition improves, the insulin requirements usually go back to their baseline.

OTHER ASPECTS OF DIABETES MANAGEMENT

It is important to assess the goals of diabetes management before the hospital discharge and to follow up with primary care providers outside the hospital to make sure these goals are reached successfully. For anyone with a newly diagnosed DM, essential care also includes diabetes self-management education and nutrition education. If diabetes is diagnosed for the first time while the patient is in hospital, a minimum amount of diabetes education (survival skills) will be taught in the hospital before discharge and patients will be referred to an outpatient, ADA-certified, diabetes self-management education program. Diabetes self-management nutrition education addresses diet and energy balance, weight loss issues if needed, need for carbohydrate (sugar intake) counting in insulin-requiring patients, risk of low BG with decreased calorie intake, increase in physical activity, increase in dietary fiber (14 g/1,000 kcal), and alcohol intake (maximum one drink per day for women and two drinks per day for men).

Physical activity is recommended to be of both aerobic and resistance-type training and should be done in combination. Aerobic activity should be at least 150 minutes per week and it should be of moderate intensity, 50% to 70% of maximum heart rate (220-age). Resistance exercise should be done 3 times a week if there are no contraindications, such as the presence of advanced diabetic retinopathy. Blood pressure targets are lower for diabetics compared to general population (130/80 mm Hg in diabetics and125/75 mm Hg in diabetics with advanced kidney disease). Cholesterol levels also need particular attention in diabetics. Compliance with dietary recommendations and also regular physical activity not only improves the BG but will also significantly improve the cholesterol and triglyceride levels. The doctor might also prescribe cholesterol-lowering medications to help decrease risk of heart and vascular disease. Mood disorders such as depression and anxiety as well as social (family and economic issues) or physical (blindness, amputations, etc.) barriers can affect diabetes

management. Inform the doctor about any possible barrier to an optimum diabetes management plan.

In those with inpatient hyperglycemia but without prior history of diabetes, it is important to arrange for regular follow-up after discharge to determine whether the hyperglycemia persists, and if not whether the patient is at risk of developing diabetes.

For more information about diabetes and treatments, visit the ADA website at http://www.diabetes.org/.

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Barak Zafrir

Lipid Management in the Cardiac Care Unit

LIPIDS, ATHEROSCLEROSIS, AND CARDIOVASCULAR RISK

Elevated plasma lipoproteins are among the most important risk factors for coronary heart disease and are the driving force of atherogenesis. This strong link has been consistently demonstrated over the past decades in pathologic, epidemiologic, genetic, and interventional clinical studies, establishing causality between low-density lipoprotein cholesterol (LDL-C) and atherosclerosis.

Lipoprotein particles accumulate in the intima of arteries in hypercholesterolemic states and undergo oxidative and other modifications that are accelerated during endothelial dysfunction, leading to the uptake of LDL-C by macrophages and generation of foam cells evolving into fatty streaks.[1] This process initiates smooth muscle proliferation and the formation of a fibrous cap, covering the lipid core filled with macrophages. The concept of “response to retention” provides a mechanistic link between accumulation of lipoprotein particles, proinflammatory effects, and the initiation and progression of the atherosclerotic plaque.[2]

Epidemiologic studies have firmly established a direct relationship between serum cholesterol levels and the prevalence of atherosclerotic cardiovascular

disease (CVD). Many large randomized controlled trials in the statin era have documented that lowering total cholesterol and LDL-C reduces the risk for both coronary heart disease and stroke, largely irrespective of the initial lipid profile, in a wide range of individuals, including those at relatively low risk for vascular events, and in direct relationship to the intensity of the statin regimen.[3–5] Epidemiologic data have also shown that the concentration of high-density lipoprotein cholesterol (HDL-C) is an independent, inverse predictor for CVD and is important in global risk assessment. However, there is a lack of convincing evidence that raising HDL-C by pharmacologic interventions reduces the risk for CVD, and therefore currently low HDL-C concentration is not a primary target of drug therapy. A renewed interest driven by epidemiologic and genetic data supports triglyceride-rich lipoproteins and their cholesterol content (remnant cholesterol) as an additional contributor to CVD and cardiovascular mortality. However, conclusive evidence as to whether lowering high triglycerides levels reduces the risk of CVD is lacking.

Interindividual variability in blood lipids concentration is derived from both lifestyle and inherited factors. Single-gene mutations in LDL receptor pathway are strongly associated with high cholesterol levels and predispose to familial hypercholesterolemia and premature CVD.[6] In contrast, low cholesterol levels from birth caused by proprotein convertase subtilisin/kexin type 9 (PCSK9) loss-of-function gene mutations confer protection from atherosclerotic disease.[7] Genetic studies further show that genetic variants causing lifetime low LDL-C levels are associated with very low rates of coronary heart disease.[8] Polymorphisms (SNPs) from several genes that are associated with modulation of cholesterol levels were also demonstrated to be an independent risk factor for CVD. In contrast to the causal relationship between LDL-C and CVD, genetic mechanisms that raise plasma HDL-C were not reported to be related to lower risk of myocardial infarction. This challenges the concept that raising plasma HDL-C will uniformly translate into reduction in the risk of coronary heart disease.[9] Research now focuses on assessment of HDL functionality as a marker for atherosclerotic risk and a better target for therapeutic intervention than HDL-C.

PLASMA LIPID PROFILE

Routine lipid profile in most clinical biochemistry laboratories includes direct

measurement of total cholesterol, HDL-C, and triglycerides. LDL-C is usually measured indirectly, calculated by the Friedewald equation: LDL-C = Total cholesterol minus HDL-C minus triglycerides/5 (with values in mg/dL). Friedewald equation underestimates LDL-C levels when triglycerides are elevated, and therefore LDL-C is not calculated indirectly when triglycerides are above 300–400 mg/dL, depending on specific institute laboratory. Direct measurement of LDL-C when triglyceride concentrations are high is feasible, but not available routinely at all institutions. Accordingly, calculation of non–HDL-C from standard lipid panel as total cholesterol minus HDL-C is recommended in hypertriglyceridemic states, and expresses the cholesterol content of all atherogenic apolipoprotein B (apoB)–containing particles. Non–HDL-C does not require additional charge, appears to be a more accurate marker of cardiovascular risk than LDL-C, and should be considered an alternative risk marker and a secondary treatment target, especially in hypertriglyceridemic states such as in metabolic syndrome, diabetes, and chronic kidney disease. The specific target for non–HDL-C should be about 30 mg/dL higher than the corresponding LDL-C target. To improve patient compliance with lipid testing, a recent consensus panel advocated the routine use of nonfasting lipid profiles, whereas fasting sampling should be considered when nonfasting triglycerides are signifcantly elevated.[10]

Early studies indicated that cholesterol levels (both LDL-C and HDL-C) start to decline 24 hours after acute myocardial infarction because of an acute-phase response, reach the nadir on approximately day 7, and normalize within 2 months after acute coronary syndrome (ACS). These changes in lipid levels should be taken into account when making clinical decisions in treating hyperlipidemia after ACS, and efforts should be made to take blood samples for lipid profile early in the course of ACS.

LIPOPROTEIN *(a)*

Lipoprotein(a) [Lp(a)] is a genetic, causal risk factor for CVD, showing an independent and continuous association with cardiovascular risk, including myocardial infarction, stroke, peripheral arterial disease, and calcific aortic valve stenosis.[11,12] Lp(a) is composed of a single molecule of apoB100 covalently linked to apo(a), which contains a unique region that is structurally homologous to plasminogen. It is suggested that Lp(a) induces both prothrombotic activity because of competitively antagonizing plasminogen binding and potential atherogenic effect secondary to arterial deposition of oxidized phospholipids by

apoB. Candidates for Lp(a) screening include patients with a strong family history of premature CVD, patients with hypercholesterolemia in which Lp(a) has synergistic effects with elevated LDL-C levels, and patients with ACS and recurrent cardiovascular events despite maximal statin therapy. Niacin is the only medication that has consistently shown a dose-dependent lowering effect on Lp(a), reducing levels up to 30% in clinical trials. Lipoprotein apheresis is an effective therapeutic option reserved for severe cases of progressive coronary disease despite optimal drug therapy.[12] Although Lp(a) is a major causal cardiovascular risk factor in both genetic and population studies, there are no controlled trials that have shown that lowering Lp(a) through pharmacotherapy significantly reduces risk. Novel therapies such as PCSK9 inhibitors reduce 25% to 30% of Lp(a) concentration, and recent promising phase I studies in humans demonstrated a more significant reduction of Lp(a) levels by antisense oligonucleotides (ASOs) that inhibit apo(a) mRNA translation.

ADVANCED LIPOPROTEIN TESTING

Advanced lipoprotein analysis, including testing of lipoprotein subfractions, LDL particle number, and apoB concentration, has been proposed as a more accurate measure to assess the risk attributable to atherogenic lipoproteins and as a potential means to reduce residual cardiovascular risk. The cholesterol content of LDL particles varies substantially between individuals, and subjects with the same LDL-C level may have discordant numbers of LDL particles. Many patients with high cardiometabolic risk or diabetes have relatively normal levels of LDL-C that poorly characterize the excess concentration and risk of small dense LDL particles. The discordance between LDL-C and LDL particle number was shown to impact cardiovascular risk in the Framingham and Multi-Ethnic Study of Atherosclerosis (MESA)studies.[13,14] Therefore, measurements of LDL particle number or apoB rather than the cholesterol content of LDL may be more adequate to assess the residual risk for coronary disease in high cardiometabolic risk subjects who achieve “optimal” LDL-C levels. However, the clinical utility of advanced lipoprotein analysis is still debated, and this test is not routinely in use in clinical medicine.

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is a common monogenic disorder of lipoprotein metabolism, associated with high concentrations of LDL-C,

predisposing affected individuals and their families to premature coronary heart disease.[6] FH is prevalent globally, reaching 1:300 in the general population in its heterozygous form because of principally autosomal dominant inheritance. Nevertheless, FH is vastly underdiagnosed and undertreated in most countries. Patients with FH are often unrecognized despite typical presentation with premature coronary heart disease and severely elevated LDL-C levels. Cardiovascular risk is driven by the presence of concomitant risk factors and the cumulative LDL-C burden throughout life, which is a function of age of initiation of drug therapy and compliance with treatment. LDL-C ≥ 190 mg/dL in adults and ≥ 160 mg/dL in children raises the likelihood of the presence of monogenic disorder. However, in the setting of the general population, customary LDL-C cutoffs of 190 mg/dL in children, 220 mg/dL between ages 20 and 29 years, and 240 mg/dL in adults ≥ 30 years are associated with an 80% probability of FH (MEDPED criteria). Secondary causes of severe hypercholesterolemia should be excluded (**Table 55.1**). Family history of hypercholesterolemia and coronary disease at young age in relatives, as well as physical stigmata such as tendon xanthomas and arcus cornea, which are seen in about 30% to 40% of patients and are correlated with severity and duration of hypercholesterolemia, are aditional diagnostic criteria.

TABLE 55.1 Secondary Causes of Hyperlipidemia

DISORDERS AFFECTING LIPIDS	MEDICATIONS AFFECTING LIPIDS
Hypercholesterolemia *Nephrotic syndrome* *Hypothyroidism* *Cholestatic liver disease* *Cushing syndrome* *Anorexia nervosa* *Pregnancy* *Autoimmune disorders* • Lupus; Rheumatoid arthritis *Immunoglobulin excess* • Gammopathies Hypertriglyceridemia *Diabetes mellitus* *Obesity* *Metabolic syndrome and PCOS*[a] *Hypothyroidism* *Chronic kidney disease* *Pregnancy* *Excessive alcohol consumption* *Diet high in simple carbohydrates* *Lipodystrophies*	Antihypertensives *β-Blockers* *Thiazides* Steroid hormones *Combined oral contraceptives* *Estrogen replacement therapy* *Anabolic steroids (testosterone)* *Glucocorticoids* Antiretroviral therapy *Protease inhibitors* Psychotropic medications *Clozapine; Olanzapine; Risperidone* Antidepressants *Tricyclics; Mirtazapine* *SSRIs*[a] *(Sertraline and Paroxetine)* Retinoic-acid derivatives (isotretinoin) Immunosuppressant agents *Cyclosporine; Tacrolimus* Anticonvulsants *Valproic acid*

[a]PCOS, polycystic ovary syndrome; SSRI, selective serotonin reuptake inhibitors.

Identification of FH patients is important, because early intensive treatment and cascade screening of families may further reduce cardiovascular event rates. Although direct detection of causative gene mutations is available and molecular genetics for screening family relatives is carried out successfully in several countries, genetic testing is still costly and is not systematically feasible in most places. Cardiovascular divisions such as the cardiac care unit may provide ideal locations to promote identification and treatment of high-risk patients with FH.

LIPID MANAGEMENT IN ACS

STATINS

Statins are the cornerstone of pharmacologic therapy in the prevention of atherosclerotic CVD. Statins inhibit HMG-CoA reductase, the rate-limiting step of cholesterol synthesis, subsequently upregulating LDL receptors on the surface of hepatocytes. Statins are targeted mainly for significant reduction of LDL-C levels, up to 55%, but improve, to some extent, all components of the lipid profile. Large-scale, randomized, controlled statin trials of both primary and secondary prevention in humans have shown repeatedly that LDL-C reduction by statins correlates linearly with CVD, reducing myocardial infarction, stroke, and cardiovascular death.[4,5] These trials have demonstrated that the beneficial effects of statins are preserved also in subjects with low baseline LDL-C< 100 mg/dL and in patients with diabetes. Furthermore, intensive lipid lowering with a more potent or higher dose statin resulted in further reduction of both LDL-C levels and major cardiovascular events compared with a less intensive regimen, in both stable and acute coronary artery disease populations. Patients with a history of atherosclerotic vascular disease, including ischemic stroke or peripheral artery disease, are considered coronary heart disease risk equivalents, and, as such, are targeted for high-intensity statin therapy to reduce cardiovascular events.

EFFECTS OF EARLY STATIN TREATMENT ON CLINICAL OUTCOMES AFTER ACS

Early initiation of statin treatment has become a guideline-directed standard of care after ACS because of several landmark randomized prospective trials

presented during the years 2001 to 2004. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study was the first large study investigating the potential clinical benefit of the early use of statins in ACS.[15] Initiation of high-dose atorvastatin (80 mg/d) early (24–96 hours) after ACS reduced cardiovascular adverse events during the first 4 months after starting therapy, especially new hospitalizations for recurrent ischemia. In the A-to -Z trial, patients admitted for ACS and treated with an early intensive statin therapy (simvastatin 40 mg/d for 1 month followed by 80 mg/d) had lower mortality risk compared to less intensive treatment (placebo for 4 months followed by simvastatin 20 mg/d) that was started later.[16] However, the study failed to show an improvement in overall cardiovascular outcomes. The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial compared a standard statin regime (pravastatin 40 mg/d) to intensive treatment (atorvastatin 80 mg/d), within 10 days of hospital admission for ACS, confirming that high-intensity statin therapy provided greater protection, reducing the rate of cardiovascular adverse events in 16% during a mean follow-up of 24 months, as well as 30-day clinical outcomes.[17] Additional substudy later confirmed the results in the subset of patients who performed percutaneous coronary intervention (PCI) for the acute coronary event, and showed reduced target vessel revascularization in the patients randomized for high-intensity statin.

Although the results of these studies seem to support the protective role of high-intensity statin therapy in the early period after ACS, it should be noted that several meta-analyses summarizing the evidence on early statin therapy for ACS showed favorable but nonsignificant reduction in death or myocardial infarction in the short term, but significant reduction in the occurrence of unstable angina at 4 months following ACS.[18,19] Past ACC/AHA guidelines recommended (Level of Evidence 1A) the use of statin therapy before hospital discharge for all patients with ACS regardless of the baseline LDL-C. The most recent ACC/AHA 2013 guidelines on the treatment of blood cholesterol state that high-intensity statin therapy (atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg) should be initiated or continued as first-line therapy in all patients ≤75 years of age that have clinical atherosclerotic CVD but do not relate specifically to the early phase post-ACS.[20]

STATIN-ASSOCIATED BENEFITS IN PATIENTS UNDERGOING PCI

Several studies have reported that short-term preprocedural administration of

statins might reduce the incidence of adverse effects after PCI. The Atorvastatin for Reduction of Myocardial Damage during Angioplasty—Acute Coronary Syndromes (ARMYDA-ACS) trial evaluated the loading dose of high-intensity atorvastatin before PCI in NSTEMI ACS, showing a reduced incidence of cardiovascular events in the first month after PCI.[21] A meta-analysis addressing the impact of timing of statin administration given before or after PCI on clinical outcomes reported that administration of statins before PCI reduces the odds of myocardial infarction at 30 days to a greater extent compared with a post-PCI administration, and that the earlier the statin administration, the lower the risk of early major adverse cardiovascular events.[22]

BENEFICIAL MECHANISMS OF EARLY STATIN INITIATION

The mechanisms underlying the protective actions of early statin administration may be independent of LDL-C reduction. Statins have been shown to modulate several mechanisms involved in the pathogenesis of ACS, including inflammation, oxidative stress, and vascular smooth muscle proliferation. Beneficial effects on platelet aggregation and endothelial function were also reported. Intravascular ultrasound (IVUS) studies have shown that statins significantly decrease plaque volume after ACS,[23] and cumulative data support the effectiveness of statin treatment in promoting plaque stabilization and regression, especially after ACS and with the use of high-intensity statins.[24]

STATINS AND THE PREVENTION OF CONTRAST-INDUCED ACUTE KIDNEY INJURY

Patients with ACS have a 3-fold higher risk of developing contrast-induced acute kidney injury, which is associated with prolonged hospitalization and increased morbidity and mortality. The Atorvastatin for Reduction of Myocardial Damage during Angioplasty—Contrast-Induced Nephropathy (ARMYDA-CIN) trial has shown that short-term pretreatment with high-dose atorvastatin decreases the incidence of contrast-induced nephropathy in statin-naïve patients with ACS undergoing early PCI.[25] More recently, the Protective Effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome (PRATO-ACS) study has similarly demonstrated that preprocedural high-dose rosuvastatin given on admission to statin-naïve patients with ACS, who were scheduled for an early invasive procedure, can prevent contrast-induced acute

kidney injury and improve short-term clinical outcomes.[26] More effective kidney protection was demonstrated in ACS subjects with higher baseline high-sensitivity C-reactive protein (hs-CRP) levels.

STATIN INTOLERANCE AND ADVERSE EFFECTS

Statin therapy is generally considered to be safe. However, muscular symptoms are common in clinical practice, may reduce patients' adherence to therapy, and can be a barrier in maximizing cardiovascular risk reduction, especially in secondary prevention of CVD, of which high-intensity statins are now indicated. The clinical spectrum of statin-induced myotoxicity includes myalgia (reaching 1%–3% in randomized-controlled trials, but 10%–20% in observational and epidemiologic studies), less commonly myositis with significant elevated creatine kinase levels, and, very rarely, rhabdomyolysis. Asymptomatic rise in creatine kinase concentration is also observed. Factors that increase the risk of statin-induced myopathy include patient-related factors such as advanced-age, female gender, lower weight, excess of alcohol and strenuous exercise, as well as hypothyroidism, vitamin D deficiency, statin–drugs interactions, high statin dose, Asian ancestry, and genetic predisposition. In addition to ruling out possible conditions that may increase the risk of muscle symptoms, the management options include reduction in statin dose, alternate day regimens of statins with longer half-life (atorvastatin and rosuvastatin), transient cessation of therapy, and usage of an alternative statin or other lipid-lowering agent. In cases where muscle symptoms are progressive or creatine kinase is more than X10 the upper limit of normal (ULN), the statin treatment should be stopped. In rare cases of necrotizing autoimmune myopathy, steroids and immunosuppression may be needed. There is no clear evidence that Co-enzyme Q10 treatment is beneficial in statin-induced myotoxicity, because small randomized trials displayed equivocal results.

Mild elevations of hepatocellular liver enzymes are commonly seen in clinical practice. However, liver failure in statin users is rare and is similar to that in the overall population. In cases where hepatic aminotransferase levels are >3 times the ULN values, it is recommended to withhold statin treatment, reassess liver tests, and consider other causes of liver damage. Nevertheless, routine periodic monitoring of liver function tests in patients taking statins is no longer recommended, because it does not appear to be effective for detecting or preventing serious liver injury.

Randomized trials, including recent meta-analyses, have demonstrated a

consistent relationship between statins, elevation of blood glucose level, and a modest increase in the risk of incident diabetes.[27] This association seems to be dependent on the dose and potency of the statin. Individuals prone to statin-induced diabetes were shown to have major risk factors for diabetes that were similar to those in the general population, including multiple components of the metabolic syndrome and impaired fasting glucose. The benefits of statins in reducing cardiovascular events outweigh the potential risk for developing new-onset diabetes in patients who are at moderate or high risk for cardiovascular events and in secondary prevention.

Although some patients in observational data and small randomized trials were reported to experience ill-defined memory loss and confusion, recent large meta-analyses and systematic reviews have shown no evidence of increase in the risk of cognitive impairment.

NONSTATIN LIPID-LOWERING THERAPIES

Ezetimibe selectively inhibits cholesterol absorption from the intestine by blocking the transport protein Niemann–Pick C1-Like 1 transporter (NPC1L1) in the brush border of enterocytes, lowering plasma LDL-C levels by 15% to 20%. Ezetimibe is usually used in combination with statins, enhancing LDL-C lowering effect, with a good safety profile. The recently published IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) showed that when added to simvastatin therapy, ezetimibe resulted in incremental lowering of LDL-C levels and improved cardiovascular outcomes after ACS, demonstrating that lowering LDL-C to levels below previous targets provided additional benefit.[28] This landmark study is the first to show a cardiovascular benefit in adding a nonstatin lipid-modifying agent to statin therapy, reaffirming the LDL hypothesis suggesting that the reduction of LDL-C levels reduces the rate of CVD.

Medications for lowering triglycerides include fibrates, omega-3 polyunsaturated fatty acids (fish oil supplements) in pharmacologic dosages (DHA/EPA 2 to 4 g a day), and niacin. These medications have the ability to reduce 20% to 50% of triglyceride levels in blood and are indicated when levels are above 500 to 1,000 mg/dL in order to prevent acute pancreatitis. However, randomized trials showing the cardiovascular benefit of triglyceride reduction are scarce, and trials assessing fibrates and niacin as an add-on therapy against a background of statin treatment failed to show cardiovascular risk reduction. Therefore, in the statin era the routine use of fibrates and niacin is limited.

Nevertheless, subgroup analysis of outcome trials with the major fibrates showed significant relative risk reduction of cardiovascular events in patients with atherogenic dyslipidemia manifested by elevated triglyceride levels (>200 mg/dL) and low HDL-C (<35 mg/dL). Accordingly, fibrates might be considered in high-risk patients with atherogenic dyslipidemia, especially in diabetes and metabolic syndrome, as an add-on treatment to statins in order to reduce the risk for atherosclerotic CVD. Large-scale trials are awaited to provide conclusive evidence as to whether lowering triglycerides reduces the risk of CVD.

PCSK9 inhibitors are a new class of lipid-lowering medications. Binding of PCSK9 to the LDL receptor targets the receptor for lysosomal degradation. The recognition that inhibition of PCSK9 increases LDL receptor activity and the discovery of gene mutations affecting PCSK9 with clinical effects on cardiovascular risk have led to the development of human monoclonal antibodies against PCSK9, self-administered by subcutaneous injections. The PCSK9 inhibitors, approved by the U.S. Food and Drug Administration (FDA) in mid-2015 (evolocumab and alirocumab), when evaluated in numerous phase 3 trials, were found to reduce LDL-C levels up to 65% independent of background statin therapy and with a good safety profile, at least for the short term. However, information on whether PCSK9 inhibitors affect cardiovascular events or mortality is not yet available, and long-term outcome and safety studies are ongoing. Therefore, PCSK9 inhibitors are currently approved for use, in addition to maximally tolerated statin therapy, in patients with FH or clinical atherosclerotic CVD, who require additional lowering of LDL-C to achieve treatment goals.

DIET AND LIFESTYLE INTERVENTIONS

Nonpharmacologic, therapeutic lifestyle interventions are an essential part of the treatment of lipid disorders in both primary and secondary prevention of atherosclerotic CVD. This includes physical activity with an emphasis on aerobic exercise, weight loss, smoking cessation, moderation of alcohol intake, and adjustment of dietary patterns and nutrient intake (discussed separately). Patients with the metabolic syndrome, characterized by central obesity, impaired fasting glucose and insulin resistance, as well as hypertension and atherogenic dyslipidemia (hypertriglyceridemia, low HDL-C and small dense LDL particles), may benefit in particular from lifestyle interventions that were shown to significantly delay conversion to diabetes and its cardiovascular complications. The setting of hospitalization may serve as an ideal opportunity for initial dietary

and lifestyle counseling of high-risk patients. In addition, attention should be given to severe hypertriglyceridemia during hospitalization, because it may precipitate acute pancreatitis. Secondary causes of hypertriglyceridemia should be searched for and targeted; these include high carbohydrate intake (especially fructose) and calorie excess, ethanol consumption, central obesity, poor glycemic control, and medications such as systemic glucocorticoids (**Table 55.1**).

GUIDELINES FOR THE TREATMENT OF DYSLIPIDEMIA

Guidelines provide consistency in care, aiming to incorporate new evidence and guide clinical decision making. In 2013, after more than a decade, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a set of guidelines on the control of blood cholesterol to reduce atherosclerotic CVD risk.[20] The AHA/ACC guidelines differed from previous widely adopted national and international guidelines, and thus have been a subject of controversy. Major changes included the abandonment of numerical LDL-C treatment targets, focusing instead on the intensity of statin therapy (**Table 55.2**), and the formation of a newly developed *Pooled Cohort Equations* calculator for estimating 10-year atherosclerotic CVD risk. In addition, in comparison to the previous Adult Treatment Panel III (ATP III) lipid guidelines, the risk threshold for considering statins in the primary prevention setting was lowered to a 10-year absolute atherosclerotic CVD risk of 7.5%. **Table 55.3** compares the similarities and differences in treatment recommendations between the ACC/AHA 2013 guidelines and the most recent European guideline for the management of dyslipidemias.[29] Recently, an ACC expert consensus panel attempted to provide practical guidance for clinicians and patients regarding the use of nonstatin therapies as an add-on to statins, to further reduce CVD risk in situations not covered by the guidelines.[30] An algorithm for the management of lipids in ACS is provided in **Figure 55.1**.

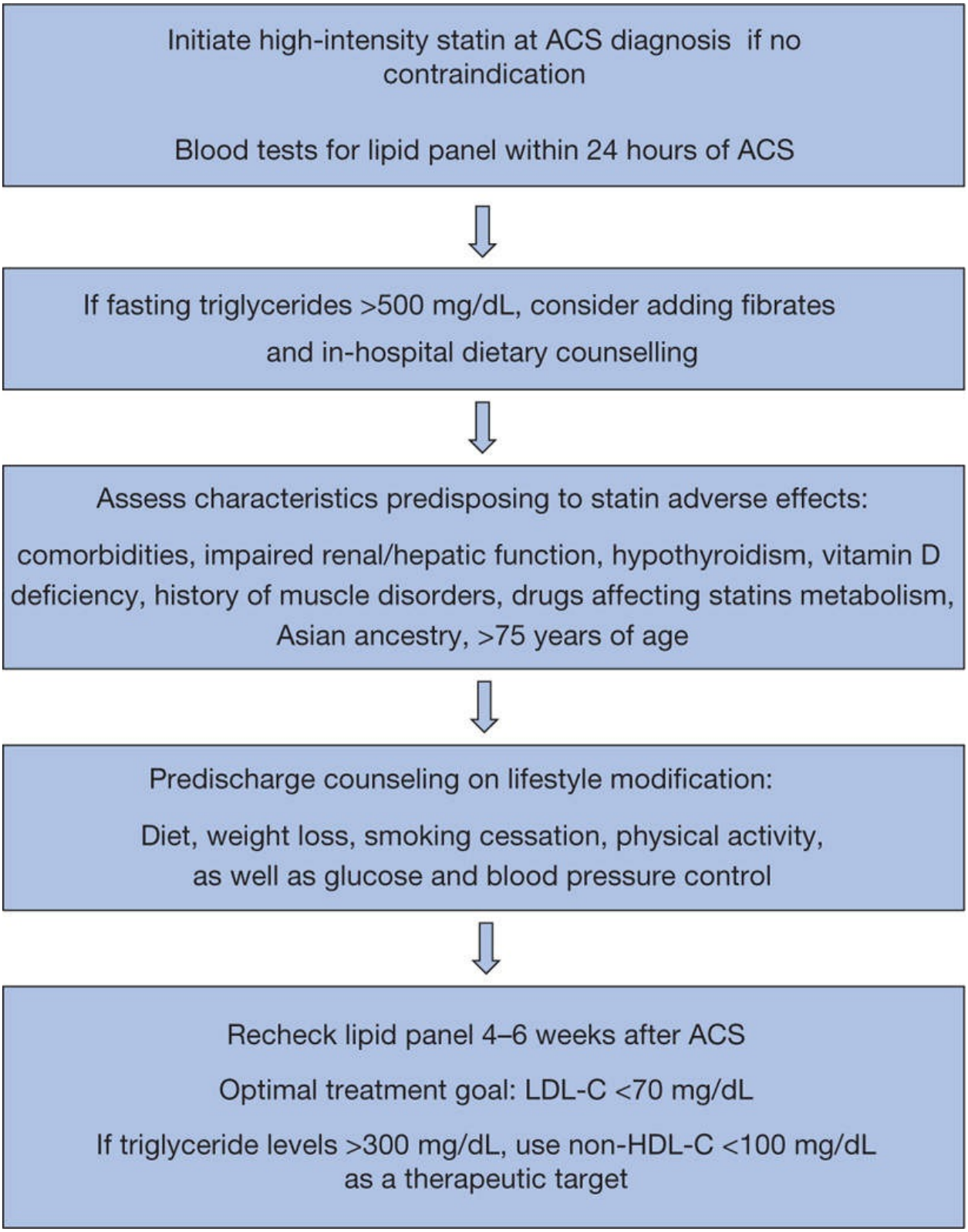

FIGURE 55.1 Algorithm for the management of hyperlipidemia in acute coronary syndrome (ACS). HDL-

C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TABLE 55.2 Statin Therapy Intensity and LDL-C Reduction

STATIN INTENSITY	HIGH INTENSITY	MODERATE INTENSITY	LOW INTENSITY
LDL-C lowering (daily dose)	≥50%	30%–50%	<30%
Drugs	Atorvastatin 40–80 mg Rosuvastatin 20–40 mg	Atorvastatin 10–20 mg Rosuvastatin 5–10 mg Simvastatin 20–40 mg Pravastatin 40–80 mg Lovastatin 40 mg Fluvastatin 80 mg Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

TABLE 55.3 Comparison Between Lipid Treatment Guidelines

ACC/AHA (2013) GUIDELINE ON THE TREATMENT OF BLOOD CHOLESTEROL TO REDUCE ASCVD RISK		ESC/EAS (2011) GUIDELINES FOR THE MANAGEMENT OF DYSLIPIDEMIAS	
RISK CATEGORIES	**TREATMENT**	**RISK CATEGORIES**	**TREATMENT**
Clinical ASCVD[a]	High-intensity[b] statin Age > 75 or safety concern: Moderate-intensity[b] statin	**Cardiovascular disease[a]**	LDL-C < 70 mg/dL and/or ≥50% reduction.
Diabetes: Type I or II Age 40–75 LDL-C 70–189 mg/dL	*High-risk*: (10-y ASCVD risk ≥7.5%): High-intensity statin *Low-risk*: Moderate-intensity statin	**Diabetes (type II or type I with target organ damage) or moderate to severe CKD (GFR ≤ 60 mL/min/1.73 m^2)**	LDL-C < 70 mg/dL and/or ≥50% reduction. Second goals: non-HDL-C< 100 mg/dL and apoB < 80 mg/dL.
Primary LDL-C ≥190 mg/dL	High-intensity statin Achieve>50% LDL-C reduction	**Familial dyslipidemia**	LDL-C < 100 mg/dL or maximal reduction with drug combinations and LDL apheresis.
None of the above (primary prevention; age 40–75): (a) 10-y ASCVD	(a) Moderate-to high-intensity	**None of the above: 10-y risk estimate of First fatal atherosclerotic CV**	(a) Very high risk: LDL-C < 70 mg/dL

risk ≥ 7.5% (b) 10-y ASCVD risk 5%–7.5% **(risk calculator based on the pooled cohort equations)**	statin (b) Consider moderate-intensity statin	**event:** (a) **SCORE > 10%** (b) **SCORE 5%–10%** (c) **SCORE 1%–5%**	(b) High risk: LDL-C < 100 mg/dL (c) Moderate risk: LDL-C < 115 mg/dL
If risk-based assessment uncertain, consider: • **Family history premature CVD** • **hsCRP ≥ 2.0 mg/L** • **CAC score ≥ 300 Agatston unit** • **ABI < 0.9** • **LDL-C ≥ 160 mg/dL** • **Lifetime ASCVD risk**		**Additional data modifying risk:** • **Elevated triglycerides** • **Social deprivation** • **Central obesity** • **Familial hypercholesterolemia** • **High lipoprotein (a) levels** • **Subclinical atherosclerosis** • **Chronic kidney disease** • **Family history of premature CVD** • **Low HDL-C**	
Additional recommendations: (a) Encourage lifestyle modifications. (b) Guidelines do not consider data on the use of lipid fractions other than LDL-C. (c) Statins are not routinely recommended for NYHA II–IV heart failure patients and those receiving hemodialysis. (d) Do not routinely measure and monitor ALT or CK, unless symptomatic.		Additional recommendations: (a) Encourage lifestyle modifications (b) Non-HDL-C and apoB should be considered an alternative risk marker and second treatment target in metabolic syndrome and diabetes (class IIa indication). (c) Statins are not indicated in patients with moderate or severe heart failure. Statins are indicated in moderate to severe CKD (LDL-C<70 mg/dL). (d) ALT should be measured before treatment, 8 weeks after starting treatment or dose increase, and annually thereafter. CK should be measured before starting treatment, but not necessary for monitoring.	

ABI, ankle-brachial index; ALT, alanine transaminase; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; CK, creatine kinase; LDL-C, low-density lipoprotein cholesterol.

[a]ACC/AHA clinical ASCVD definition includes acute coronary syndromes, previous myocardial infarction, stable/unstable angina, arterial revascularizations, ischemic stroke or transient ischemic attack, and peripheral arterial disease presumed to be of atherosclerotic origin. ESC/EAS Cardiovascular disease definition includes, in addition, preclinical evidence for atherosclerotic disease on the basis of any imaging modality.

[b]High-intensity statin: daily dose lowers LDL-C by ≥50% (rosuvastatin 20 mg [40 mg]; atorvastatin 40/80 mg). Moderate-intensity: daily dose lowers LDL-C by 30% to 50%.

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Patient and Family Information for: LIPID MANAGEMENT IN THE CARDIAC CARE UNIT

HYPERLIPIDEMIA

Increased level of lipids (fats) in the blood is termed hyperlipidemia and includes both elevated cholesterol and triglycerides. Hyperlipidemia is a major cause of atherosclerosis, a term that refers to the buildup of fats and other substances in the walls of the arteries in the body, leading to the formation of plaques that can restrict blood flow. Hyperlipidemia significantly increases the risk of developing CVD, damaging the blood vessels supplying the heart, causing coronary artery disease and heart attacks. It may similarly lead to vascular disease in the limbs (peripheral vascular disease) and in the arteries supplying the brain (cerebrovascular disease).

LIPID PROFILE

BLOOD CHOLESTEROL

Cholesterol is a substance found in lipid particles in cells and body fluids, which is important to the cell structure and function and is a precursor to various metabolic pathways. High blood cholesterol is a major risk factor for developing heart disease. Low-density lipoprotein (LDL) particles are the main transporters of cholesterol throughout the body. The retention of LDL cholesterol in the walls of the arteries and the buildup of atherosclerotic plaque may narrow the coronary arteries supplying blood to the heart and cause symptoms such as effort-induced chest pain. Rupture or erosion of plaque in the coronary arteries may precipitate

thrombi formation that obstructs the blood vessel and causes heart attack.

Many people are unaware that their cholesterol levels are high. A common genetic disease named “familial hypercholesterolemia” is associated with markedly elevated cholesterol levels and premature heart attack and stroke. Because this genetic disorder may pass to half of first degree relatives, it is important to measure the lipid profile in the blood at a young age in individuals with a family history of high blood cholesterol or premature heart disease, and in everyone at the age of 20. Lowering the cholesterol levels lessens the risk for developing heart disease.

Total Cholesterol Levels

- Desirable: <200 mg/dL
- Borderline high: 200 to 239 mg/dL
- High: ≥ 240 mg/dL

LDL Cholesterol Levels

LDL cholesterol, often called the “bad cholesterol,” is directly associated with the risk of developing heart disease, and is therefore the primary target for drug therapy in individuals at risk.

- Optimal: <100 mg/dL
- Mean levels: 100 to 129 mg/dL
- Borderline high: 130 to 159 mg/dL
- High: 160 to 189 mg/dL
- Very high: ≥190 mg/dL

TRIGLYCERIDES

Triglycerides are a form of fat used as an energy source by the body and usually stored in fat cells. High triglyceride levels are often associated with obesity and diabetes and are a risk factor for developing heart disease. Triglyceride-rich lipoprotein particles are broken down by enzymes to smaller particles termed “remnant cholesterol,” which are rich in cholesterol and are also atherogenic. Triglycerides should be measured after prolonged fasting of 12 hours.

Triglyceride Levels

- Normal: less than 150 mg/dL
- Borderline high: 150 to 199 mg/dL

- High: 200 to 499 mg/dL
- Very high: 500 mg/dL and above

Triglycerides above 500 mg/dL are a risk factor for developing pancreatitis, which may cause abdominal pain and multiple health complications. Therefore, very high triglyceride levels are an indication for making aggressive lifestyle changes and taking medical treatment.

HDL CHOLESTEROL

HDL cholesterol is the cholesterol carried in particles called high-density lipoproteins (HDL), known as the "good cholesterol," with protective antiatherogenic properties, carrying harmful cholesterol away from the vessel wall back to the liver for metabolism and clearance, a process termed reverse cholesterol transport. Desirable HDL cholesterol levels in blood are above 40 mg/dL in men and 50 mg/dL in women. Low HDL cholesterol is often associated with high triglyceride levels, and both are features of the metabolic syndrome, characterized also by elevated blood pressure, large waist circumference (central obesity), and high glucose levels. Likewise, smoking is associated with reduced HDL cholesterol level and function.

NON-HDL CHOLESTEROL

Non-HDL cholesterol is simply calculated as total cholesterol minus HDL cholesterol. The measurement of non-HDL cholesterol does not require fasting. Non-HDL cholesterol is a good predictor of cardiovascular risk, especially in metabolic syndrome and diabetes. Desirable levels of non-HDL cholesterols and goals for therapy are 30 mg/dL above the LDL cholesterol goals.

CALCULATING RISK FOR DEVELOPING HEART DISEASE

In addition to lipid disorders, major risk factors associated with atherosclerosis and developing heart attack include age, cigarette smoking, high blood pressure, and diabetes. Obesity, physical inactivity, and family history of early heart disease and stroke are also conditions associated with greater risk. Moreover, disorders associated with chronic inflammatory states, such as rheumatoid arthritis and psoriasis, may aggravate atherosclerosis if severe and untreated at an early stage.

Several cardiovascular risk calculators were developed over the years on the basis of large epidemiologic and population studies. These calculators are based on age and common risk factors and aim to predict the 10-year risk for developing atherosclerotic CVD and/or cardiovascular death. The goal of risk calculators is to support clinicians in optimizing individual cardiovascular risk reduction and to make an informed decision about the necessity of drug treatment for prevention of CVD. The most commonly utilized risk calculators are the atherosclerotic cardiovascular disease risk estimator (ASCVD), by American heart societies, and SCORE risk charts, by the European Society of Cardiology. Both risk calculators have a web-based interactive interface available for use online.

MANAGEMENT OF LIPID DISORDERS

WHEN AND WHOM TO TREAT?

The decision to start lipid-lowering treatment is a function of lipid levels, presence of concomitant risk factors, and diagnosis of CVD. Studies have demonstrated that lipid lowering is beneficial in coronary heart disease and significantly reduces the risk of recurrent cardiovascular events. Accordingly, it is common practice today to start cholesterol-lowering medications (ie, statins) in all people with coronary heart disease. Moreover, studies have shown the additional benefit of initiation of high-intensity statin while in the hospital, during the acute coronary event, and preferably before performing cardiac catheterization. In individuals with coronary artery disease, the positive effects of statins are regardless of the baseline LDL cholesterol levels. People with vascular disease of atherosclerotic origin in other arterial blood vessels, such as the carotid arteries and brain (ischemic stroke) and peripheral artery disease, are considered coronary disease equivalent and are therefore eligible for lipid-lowering therapy with statins for secondary prevention of CVD, similar to patients with coronary heart disease. In addition to treating all patients with atherosclerotic CVD with high-intensity statins, international guidelines recommend achieving a target LDL cholesterol level below 100 mg/dL and even less than 70 mg/dL in very high-risk individuals.

In people without a history of CVD, the benefit from lipid-lowering therapy depends on the global risk of developing CVD. People with diabetes or chronic kidney disease are at high risk for heart disease and are entitled to primary

prevention therapy with statins. In addition, individuals without diagnosed CVD but with a high predicted risk of developing heart attack according to risk calculators are recommended for initiating statin therapy (eg, a 7.5% risk of developing CVD over 10 years is the threshold suggested for initiating statin therapy for primary prevention in the ASCVD calculator). Additional groups that are recommended for statin therapy regardless of other risk factors are those with very high LDL cholesterol levels, > 190 mg/dL, without apparent secondary reversible cause.

Very high triglyceride levels are also an indication for making aggressive lifestyle changes and taking medical treatment to prevent pancreatitis. Although high triglyceride levels are not the primary treatment target for preventing CVD, in some situations health care providers may recommend specific treatment for this indication, such as in high-risk diabetic patients with increased triglycerides and low HDL cholesterol under statin therapy.

MANAGEMENT OF HIGH CHOLESTEROL

Lifestyle changes are important in the treatment of high cholesterol levels. Losing weight, performing regular physical activity, and diet alterations, including reduction in saturated fats and cholesterol intake, may help reduce blood cholesterol levels. In addition, enrichment of nutrition with soluble dietary fibers is beneficial. Plant stanols and sterols are compounds naturally found in plants and available commercially as food products and dietary supplements, which may further reduce blood cholesterol by 10% to 15%. However, there are no significant data demonstrating a reduced risk of heart disease in people who consume plant sterols and stanols.

Decision making regarding initiation of medications for lowering cholesterol is carried out in accordance with the degree of risk of developing heart attacks or death from heart disease.

Drugs available for cholesterol lowering:

- **Statins:** a powerful group of drugs that are able to reduce LDL cholesterol levels by 30% to 55%. Statins work by inhibiting the production of cholesterol in liver cells and consequently increasing the expression of LDL receptors on the cells' surface, which causes the liver to remove more cholesterol from the blood to disassemble in the liver. Numerous studies in a wide range of populations at various cardiovascular risks have demonstrated over the years the ability of statins to significantly reduce heart attacks, stroke, and cardiovascular death. Accordingly, statins are the drugs of choice in the

treatment of high cholesterol levels.

Some side effects of statins are possible and vary from person to person. The more common side effects include muscle pain or cramps, constipation, and stomach pain. In addition, statin therapy may result in elevation in liver function tests, muscle enzymes, and glucose levels in blood, which are usually mild without clinical implication. Overall, statins have a good safety profile, and serious side effects are very rare.

- **Ezetimibe**: reduces blood cholesterol levels by 15% to 20%, by inhibiting dietary cholesterol absorption in the small intestine. Ezetimibe is most often used in combination with a statin drug.
- **PCSK9 inhibitors**: a novel class of injectable drugs that inhibit PCSK9, an enzyme that is a regulator of the LDL receptor and helps the liver to absorb more cholesterol from the blood when inhibited. Both evolocumab (Repatha) and alirocumab (Praluent) are human monoclonal antibodies against PCSK9 that were recently approved by the FDA for use in people with very high levels of cholesterol, and in people with a history of coronary disease or who are intolerant to statin therapy and cannot attain lipids treatment goals. These new drugs are very efficient, reducing LDL cholesterol levels by 60% when injected subcutaneously twice a month. Clinical trials with PCSK9 inhibitors are ongoing, to evaluate long-term safety and the ability to improve cardiovascular outcomes.
- **Additional drugs**: bile acid sequestrants, which lower cholesterol indirectly by binding to bile acids, and niacin (nicotinic acid), which has a positive effect on all lipid components, are less commonly used today because they are less potent than statins and have more significant adverse effects.

HDL cholesterol levels are inversely associated with CVD, and low HDL cholesterol is a marker of increased cardiovascular risk. Lifestyle changes may help in raising HDL cholesterol. This includes aerobic exercise most days of the week, smoking cessation, weight loss with maintaining healthy body weight, and diet with alteration of intake of carbohydrates and fats (decreasing refined carbohydrates, avoiding sugary beverages, reducing trans fat, and consuming unsaturated fats). Although some medications such as niacin may increase HDL cholesterol levels, in the statin era, there is no good evidence that raising HDL cholesterol levels pharmacologically on top of statin therapy is beneficial in reducing heart disease.

MANAGEMENT OF HYPERTRIGLYCERIDEMIA

Healthy lifestyle choices have the ability to significantly lower triglycerides:

- **Diet**: dietary changes associated with reduction in triglycerides levels include: (a) reducing saturated fats and trans fats, (b) eating less processed and fast food, (c) increasing fiber intake by consuming more vegetables and whole grains, (d) limiting refined carbohydrates, fruit juices, sugars, and sweets, (e) increasing omega-3 intake, such as in fish like salmon and tuna, and (f) reducing alcohol intake.
- **Exercise**: increasing occupational and leisure-time physical activity; minimum of 150 minutes per week, on most days, preferably aerobic activities.
- **Weight loss**: losing weight by adoption of healthy diet and regular exercise. Even 5% to 7% reduction in weight may significantly improve triglyceride levels and glucose balance.

Drugs available for triglycerides lowering:

Prescription medications aimed at reducing triglyceride levels include fibrates (such as fenofibrate) and niacin. In addition, high-dose fish oil supplements significantly lower triglyceride levels. High blood sugars and uncontrolled diabetes are common precipitators of high triglycerides and should be treated accordingly.

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Mary O'Sullivan
Diandra Fortune

Smoking Cessation in the Cardiac Patient

INTRODUCTION

For patients with coronary heart disease, quitting smoking is associated with a 36% reduction in all-cause mortality,[1] yet 1 year post–acute myocardial infarction (AMI), two-thirds of patients given low-intensity counseling have resumed smoking.[2] The decline of cardiovascular mortality in the United States is attributed largely to the reduction in smoking prevalence from about half of US men and a third of US women to 20.5% and 15.3%, respectively.[3,4] Because the benefit is of immediate onset, and because there are effective tools available, smoking cessation for the cardiac patient is an essential component of care.[5] Quitting smoking reduces the risk of coronary events to that of a nonsmoker within 3 years and reduces mortality by half after a heart attack over 3 to 5 years.[6,7] For patients with left ventricular (LV) dysfunction after myocardial infarction (MI), smoking cessation is associated with a 40% lower hazard of all-cause mortality over a median follow-up of 42 months.[8] Smoking post-MI is a powerful independent risk factor for reinfarction and death.[1,9,10] Those who quit have the same risk of sudden death as those who have never smoked.[9] The impact of smoking cessation in this population is therefore of at least the same

magnitude as that of angiotensin converting enzyme (ACE) inhibitors (19% relative risk decrease), β-blockers (23% relative risk decrease), and aldosterone antagonists (15% relative risk decrease).[10–12] It is vital that this information be imparted to the Cardiac Care Unit (CCU) patient who has been a smoker.

The effects of smoking on heart rate, blood pressure, cardiovascular blood flow, myocardial oxygen demand, and thrombosis are largely reversible. In this chapter, we review how cigarettes induce cardiac disease, the role of nicotine in this process, the pharmacologic tools available, their safety profile in the cardiac patient, and the basics of behavioral modification for the smoking addiction. Helping patients quit smoking is certainly more challenging than simply ordering a medication. Understanding the biology involved assists us in helping our patients break this notoriously severe addiction.

HOW DOES SMOKING CAUSE HEART DISEASE?

Although the entry portal for cigarette smoke is the lung, where the chemicals present in the smoke are quickly and easily absorbed, the resulting inflammatory cascade has a profound effect that extends well beyond the confines of the lung (**Figure 56.1**). The systemic effects of cigarette smoking include a variety of complicated processes that induce, in the genetically susceptible individual, vascular and hematologic abnormalities that can result in accelerated atherosclerosis as well as the acute events of MI and sudden death.

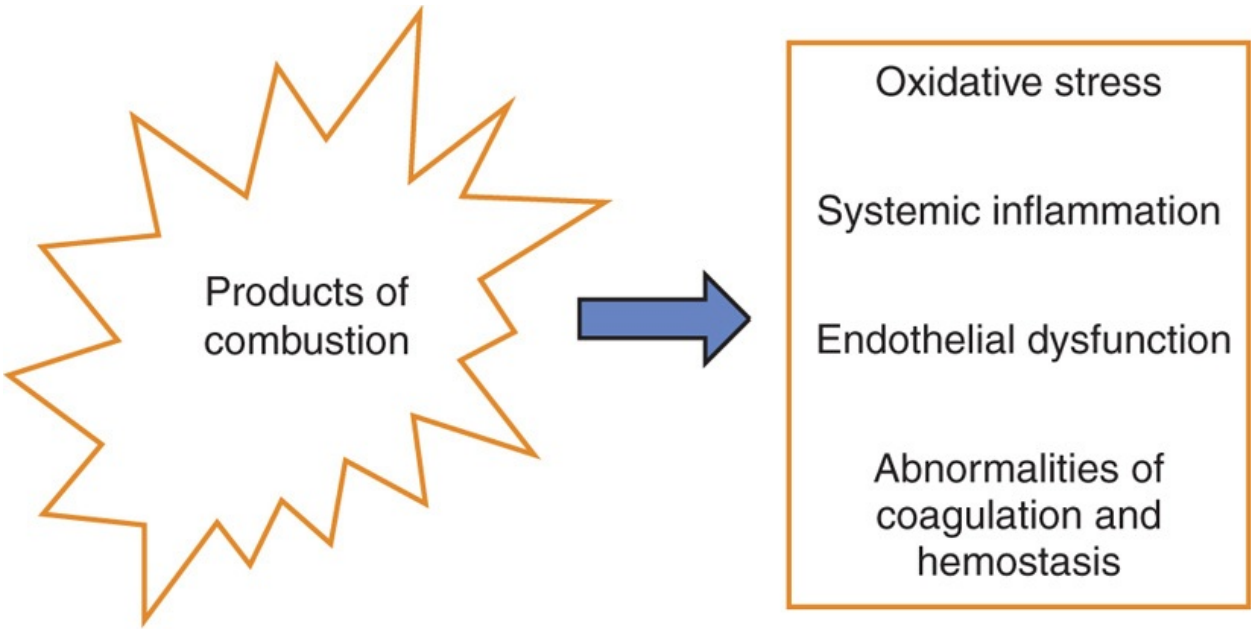

FIGURE 56.1 How smoking causes heart disease.

The main responsible constituents are combustion products that are inhaled and induce (1) oxidative stress, increasing free radicals and lipid peroxidation; (2) systemic inflammation with activation and release of both inflammatory cells and inflammatory mediators; (3) endothelial dysfunction; and (4) abnormalities of coagulation and hemostasis.[13–15]

1. *Oxidative stress*. The particulate (tar) phase of cigarette smoke contains over 10^{17} free radicals/gram, and the gas phase contains over 10^{15} free radicals/puff. Many of the damaging effects of smoking are induced by these molecules. The sustained release of reactive free radicals from the tar and gas phases of smoke imposes an oxidant stress, inducing a variety of chemical injuries, including the formation of proatherogenic oxidized particles, specifically oxidized low-density lipoprotein cholesterol. Also, the inhaled oxidant molecules significantly deplete the body's antioxidant defense system.[13,14]
2. *Systemic inflammation.* Long-term cigarette smoking increases total white blood cell (WBC) counts. There is an increased early bone marrow release of polymorphonuclear leukocytes (PMNs) and platelets into the circulation. These activated inflammatory cells then produce a variety of inflammatory mediators, acute phase proteins, and cytokines, among them C-reactive protein (CRP), fibrinogen, IL-6, and tumor necrosis factor. Some of the

inflammatory mediators and hematologic effects of smoking decline rapidly after smoking cessation. However, CRP can remain elevated for 10 to 19 years.[10] These mediators may not be just markers of disease but may be actively involved in the proinflammatory and proatherogenic effects of chronic smoke exposure.

3. *Endothelial dysfunction.* Smoking induces endothelial dysfunction though a variety of biochemical, physiologic, and metabolic factors. Both oxidizing chemicals that are the products of combustion present in cigarette smoke and nicotine appear to be involved. Vasoregulation and changes in endothelial and platelet function affect the microcirculation. Decreased production or availability of NO results in impaired vasodilatory function at the macrovascular level (eg, coronary arteries) as well as at the microvascular level.[16,17] NO is also affected by cigarette smoke via the changes induced on low-density lipoprotein (LDL). In cigarette smokers, LDL gets oxidatively modified by the inhaled oxidant molecules. The modified LDL then interferes with the protective effect of NO on the arterial wall. The result is increased inflammatory cell entry into the arterial wall. The oxidatively modified LDL is taken up by the macrophages that enter the arterial wall; cholesterol esters are deposited and foam cells form.
4. *Abnormalities of coagulation and hemostasis.* Smoking cigarettes induces a hypercoagulable state that is a major factor in acute vascular events in smokers. Viscosity is increased, with increased levels of fibrinogen, lipoproteins, and hematocrit. Antithrombotic and prothrombotic factors and platelet function are affected. There is impaired release of the tissue plasminogen activator (t-PA), the main fibrinolytic activator resulting in impaired fibrinolysis. Hypercoagulability is responsible for 25% to 50% of the link between smoking and coronary artery disease (CAD)[9] and is especially involved in acute cardiac events. This is borne out in multiple clinical situations:
    - Smoking increases the risk of MI and sudden death much more than it increases the risk of angina, reflecting the importance of acute thrombus formation.[18]
    - Similarly, the prognosis after thrombolysis is better in smokers than in nonsmokers. This reflects the greater part that clots play in the disease process.[19]
    - Sudden cardiac death is correlated with the presence of acute thrombosis and not the level of plaque burden.[18]

- Smokers who continue to smoke after thrombolysis or angioplasty have a substantially increased risk of reinfarction or reocclusion.[20,21]
- At least a part of the thrombotic effects of smoking are induced by even passive smoke.[22,23] The remarkable sensitivity of the coagulation system to the effect of cigarette smoke[24] mandates that the cardiac patient must cease all smoking, not just curtail their habit.[25] Patients should be taught the seriousness of this issue.

Although some of the effects of smoking on inflammatory markers may persist for years, a great portion of these effects are reversible by stopping smoking.

WHAT IS THE ROLE OF CO IN THIS PROCESS?

CO acutely poisons the oxygen delivery system, placing the patient at risk for arrhythmia and MI.[18] In patients with CAD, CO induces ischemia at lower levels of work.

HOW DOES NICOTINE PARTICIPATE IN THIS PROCESS?

The major cardiovascular effects of nicotine are mediated through sympathetic neural stimulation as well as the enhanced release of various neurotransmitters. Smoking produces a transient rise in blood pressure and an increase in myocardial work. In patients with coronary disease, smoking constricts epicardial coronary arteries and reduces coronary blood flow.

NICOTINE ADDICTION

After inhalation, nicotine rapidly reaches the nicotinic cholinergic receptors, found in both the peripheral and central nervous systems, resulting in the release of a variety of neurotransmitters, including dopamine, glutamate, γ–aminobutyric acid, norepinephrine, acetylcholine, serotonin, and endorphins, which may contribute to the effects of nicotine on blood vessels but also play an important role in the development of addiction in the susceptible individual. The pleasure derived from the dopamine release contributes to the addictive process.

It is important for the provider to discuss with the patient that nicotine dependence is highly heritable and metabolically driven.[26] Over 50% of the vulnerability to nicotine dependence is in large part a genetically determined

phenomenon based on the type of nicotine receptors that the patient has. The type of nicotine receptors the patient has determines its pleasurable effects, its rate of metabolism, its withdrawal syndrome, and the susceptibility to neural plasticity that causes the learned behaviors that become triggers. One of the primary genes involved is the *CYP2A* gene, which is a controller of the rate of metabolism of nicotine, vulnerability to tobacco dependence, and response to smoking treatment and is involved with lung cancer risk. The α3β4 nicotinic acetylcholine receptor is believed to mediate the cardiovascular effects of nicotine.[27] Thus, depending on the type of nicotine receptors they have, for some patients it is easy to quit, whereas for others it is incredibly difficult. For those who are smoking with known cardiovascular disease, the level of addiction is intense. Understanding that this is a biologically driven process and that, very much like diabetes, it is a chronic illness needing long-term lifestyle modification and medication for support is vitally important. Addressing the interplay of physical addiction and learned behavior is a key feature of therapy (**Figure 56.2**).

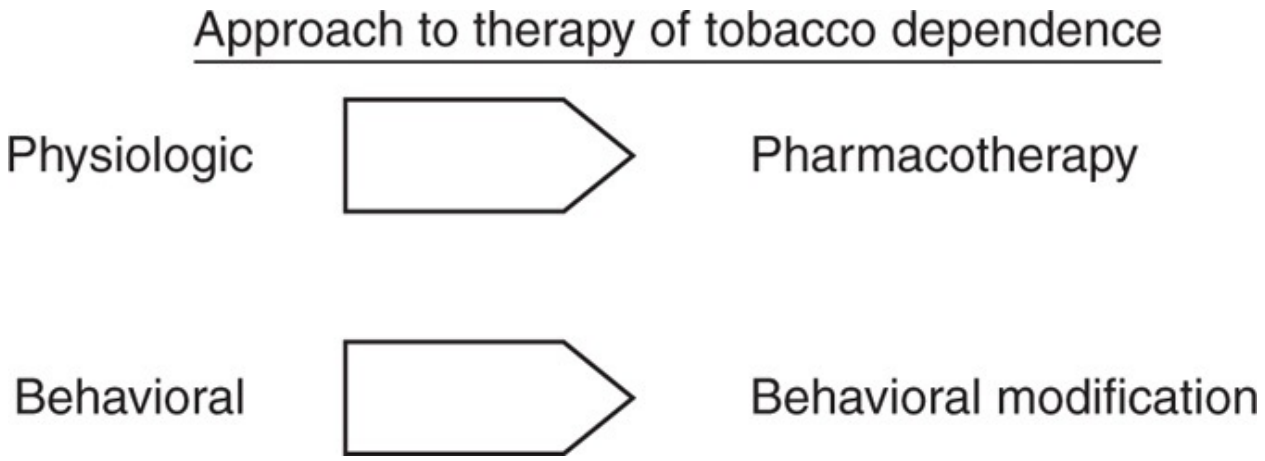

FIGURE 56.2 Approach to therapy of tobacco dependence.

With repeated exposure, nicotine tolerance develops via a desensitization of the receptors to the effect of nicotine and an increase in the number of nicotine receptors. Nicotine withdrawal is a complex process, not unlike that of withdrawal from alcohol, cocaine, opiates, and cannabinoids, that results in a state of anxiety, stress, generalized discomfort, inability to concentrate, and depressed mood.[27]

Thus, smokers learn to use the cigarette’s nicotine as a modulator of anxiety,

concentration, depressive symptoms, and pleasure as a major tool for handling life's stresses. In addition, those who are genetically susceptible to the addiction, after a relatively short period of use, become trapped by an inability to function without the satisfaction of the increased number of less responsive nicotine receptors. Not only does smoking relieve the intense discomfort of withdrawal within 10 seconds, but the relief is also accompanied by significant pleasure and ability to cope.

With time, the smoker associates certain situations with smoking: after a meal, drinks with friends, coffee, stress, etc. This association is learned and contributes significantly to the activity of the nicotine receptors and the expectation of immediate relief. These conditioned responses, also called neural plasticity, play a significant role in maintaining the addiction and become a significant impediment to the process of quitting. These triggers are to be avoided, and understanding the biology elucidates the importance of the behavioral component of smoking cessation.[27] As we will see from the studies on smoking cessation in the cardiac patient, the behavioral component of therapy is as important as the pharmacologic component (**Figure 56.2**). The permanence of the receptors, and the persistence of the learned behavior, makes the incidence of relapse very high; thus the importance of "learning" new sources of pleasure, stress management, concentration, and mood regulation.

WHAT IS THE ROLE OF NICOTINE IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASE?

Sympathetic overactivity is a significant factor by which smoking, and at least in part nicotine, induces cardiovascular disease.[18] Nicotine releases catecholamines, increases heart rate and cardiac contractility, constricts cutaneous and coronary blood vessels, and transiently increases blood pressure.[28] There is an increase in myocardial work and oxygen consumption through an increase in blood pressure, heart rate, and myocardial contractility.[29] Nicotine also reduces sensitivity to insulin and may contribute to endothelial dysfunction.[30,31] How much of the sympathetic overactivity induced by smoking is due to the effect of nicotine in the cigarette is unclear, but this is of obvious concern when we are considering using nicotine replacement therapy (NRT) in the cardiac patient. Interestingly, the effect of nicotine on autonomic ganglia is

dose dependent and biphasic. Small doses stimulate all autonomic ganglia. With larger doses, initial stimulation is followed by blockade of catecholamine release and increased splanchnic nerve stimulation, thus resulting in nausea. The dose response curve for the cardiovascular effects, such as heart rate acceleration or the release of catecholamines, is flat, and, consequently, even adding nicotine medication to smoking produces no further effect.[29]

Pharmacologic therapy is strongly recommended. The 2008 U.S. Clinical Practice Guidelines for Treating Tobacco Use and Dependence recommends counseling and medications to help all hospitalized tobacco users maintain abstinence and treat withdrawal symptoms. Three forms of medication are available: nicotine replacement, bupropion, and varenicline. Each medication has advantages and disadvantages, and the choice should be tailored to the patient's individual clinical profile. Although not widely available now, in the future, identifying slow nicotine metabolizers will predict those who respond best to NRT versus bupropion or varenicline. Resistance to the use of medication is not uncommon but, as we have discussed, for the cardiac patient the stakes are too high to risk failure. Medication use doubles the success rate.

IS THE USE OF NRT SAFE?

After initial concerns regarding the safety of NRT, studies have shown the safety of NRT even as a high-dose patch, with combination NRT and concurrent smoking.[32–34] In a 2010 meta-analysis of adverse events associated with the use of NRT among 177,390 participants, Mills et al.[35] found that NRT is associated with an increased risk of GI complaints and insomnia. There was an observed risk of skin irritation and, with orally administered NRT, oropharyngeal complaints. Although NRT was associated with an increased risk of heart palpitations and chest pain, there was no increased incidence of heart attack or death. Their conclusion was that NRT is associated with adverse effects that may be discomforting for the patient but are not life-threatening. Again, in a more recent meta-analysis that was largely limited to smokers without preexisting heart disease, nicotine replacement therapies had a statistically significant risk of cardiovascular disease events that was driven primarily by less serious effects such as tachycardia. When analysis was limited to major cardiovascular disease events, there was no evidence of harm with NRT.[36] When their review was limited to high-risk patients, the trend toward having an increased risk of overall cardiac events (including tachycardia) remained, but the relative risk decreased

and the confidence intervals became wider, not reaching statistical significance.[36]

NICOTINE REPLACEMENT THERAPY

When recommending NRT to a patient, especially one with cardiac disease, multiple questions arise, shown later with responses (**Figure 56.3**).

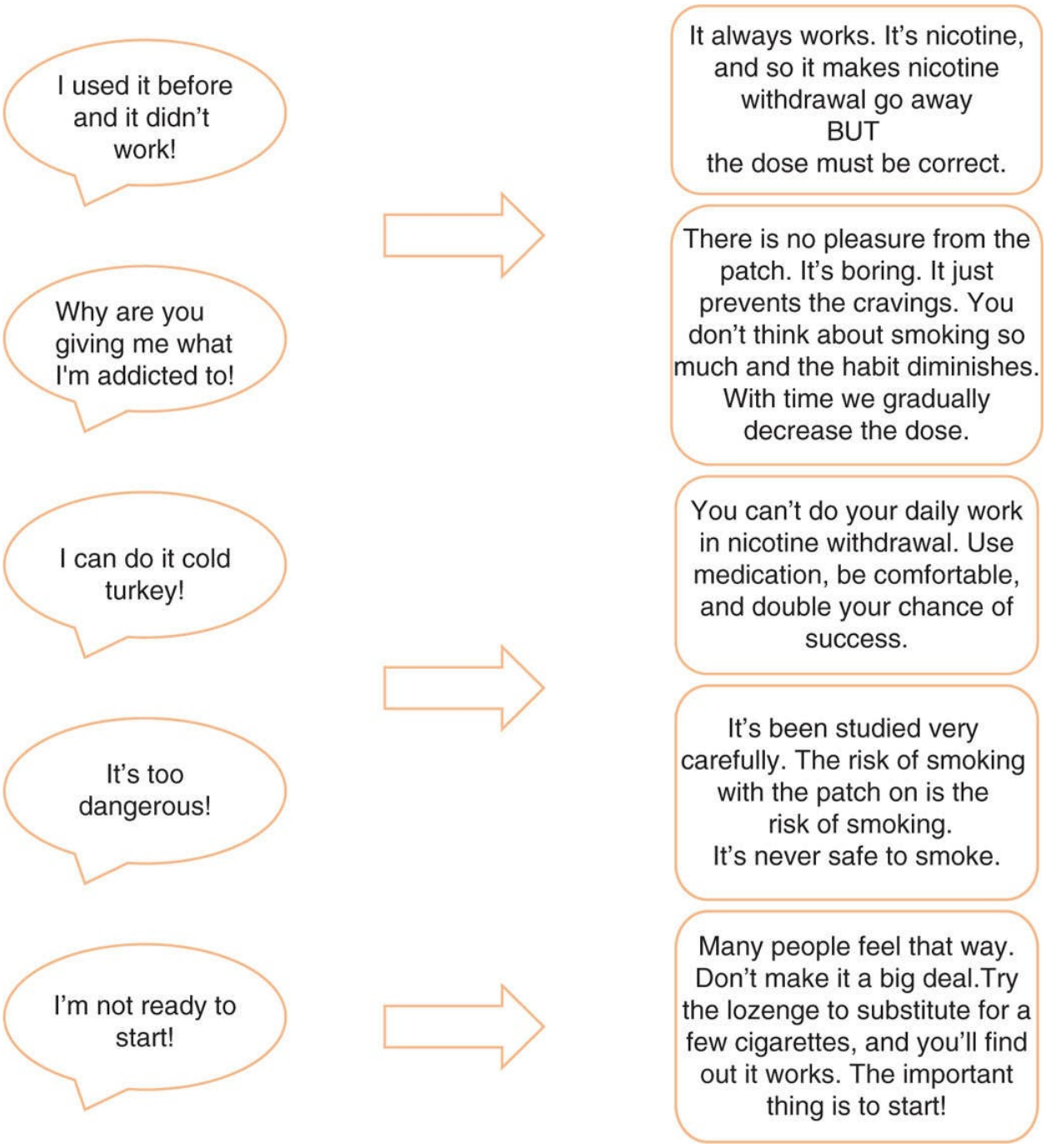

FIGURE 56.3 Common patient concerns regarding use of NRT and answers to these concerns.

Nicotine Replacement Comes in a Variety of Delivery Systems

Nicotine Patch

The nicotine patch comes in three strengths—21, 14, and 7 mg—and is equivalent to a full pack a day, half a pack a day, and a third of a pack a day.

Variations in the intensity of smoking and differing metabolic rates of nicotine among individuals may necessitate dosing adjustment from these guidelines. If the patch is too strong, the patient experiences nausea, dizziness, and headache. If it is too weak, there are cravings. Adjust the dose to comfort. The patch takes an hour to reach level, which is still well below the level of arterial spike achieved by the cigarette. The gradual delivery allows the body to equilibrate with its effects, contributing to its safety profile. It is applied in the morning and removed at bedtime to avoid potential nightmares. Adjust the dose to comfort. Change the location daily. Some patients are allergic to the adhesive and are unable to use it because they develop blisters.

Nicotine Gum

The delivery system of the gum is meant to allow a controlled release of nicotine. If it is chewed, it delivers too much nicotine too fast, resulting in nausea, hiccups, and vomiting. Only crack the coating open: it comes in 2- and 4-mg pieces and can be used every hour if needed. The patient can “bite and park,” placing it in the cheek and waiting. This is a much faster delivery system compared to the patch, and the patient is aware of a “hit.” It is very useful in combination with the patch for craving relief, especially in the morning before the patch has begun to work (**Figure 56.4**).

FIGURE 56.4 Nicotine gum.

Nicotine Lozenge

This is similar to the gum in delivery. Allow it to slowly dissolve on the tongue. It can be used alone or in combination with the patch.

Nicotine Inhaler

Puffing on this device delivers straight nicotine to the oral mucosa. It is not meant to be inhaled, but only puffed into the mouth. It can satisfy some of the ritual the smokers may desire. The patient may use six cartridges per day if needed, and each cartridge lasts 30 minutes.

NRT Safety Profile

The use of NRT has presented long-standing safety concerns although the blood level of nicotine achieved with a NRT does not approach the rapid arterial bolus achieved with the cigarette. Multiple studies have shown the safety of NRT even as a high-dose patch, combination patch and gum therapy, and patch and concurrent smoking (10 to 12 Mills and Thornland) (**Figure 56.5**).

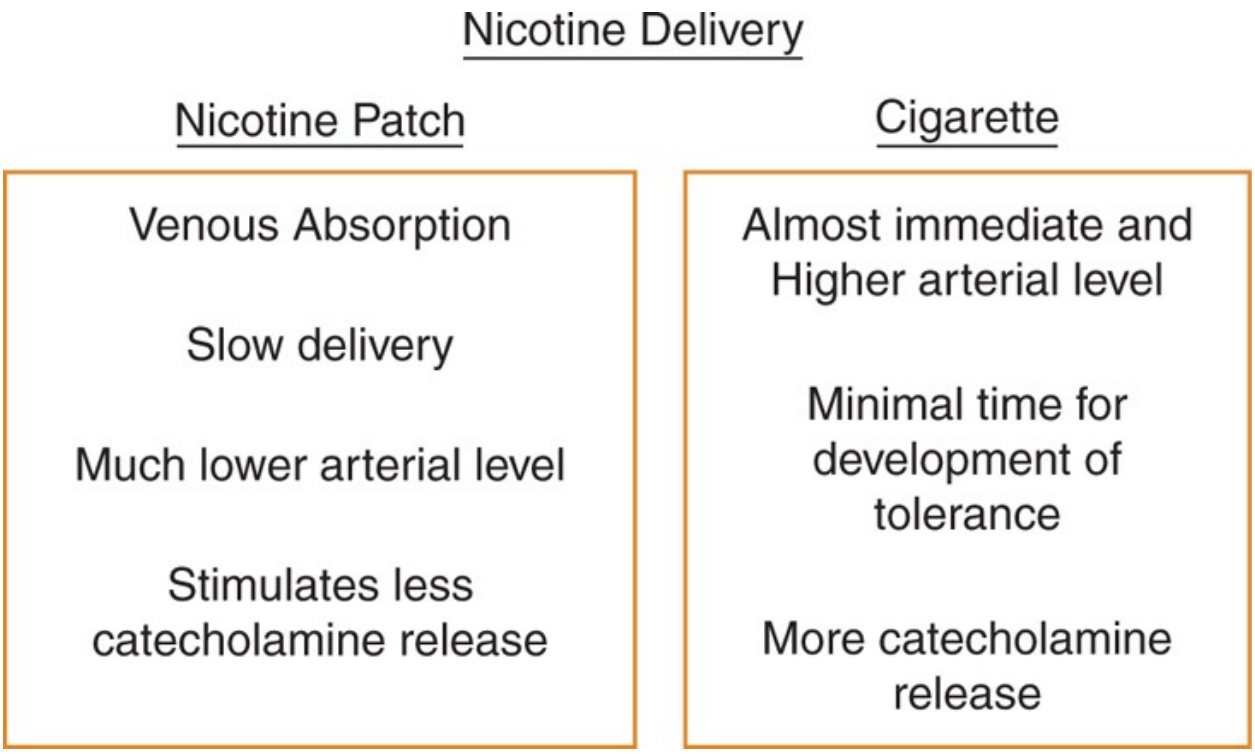

FIGURE 56.5 Nicotine delivery in patch vs. cigarette.

In a 2010 meta-analysis of adverse events associated with the use of NRT among 177,390 participants, Mills et al.[35] found that NRT is associated with increased risk of gastrointestinal (GI) complaints, reflecting the previously noted splanchnic nerve stimulation, along with insomnia. There was an observed risk of skin irritation and, with orally administered NRT, oropharyngeal complaints. Although NRT was associated with an increased risk of heart palpitations and chest pain, there was no increased incidence of heart attack or death. Their conclusion was that NRT is associated with adverse effects that may be discomforting for the patient, but are not life-threatening.

In a more recent meta-analysis that was largely limited to smokers without preexisting heart disease, Mills et al analyzed the data for evidence of cardiac toxicity from NRT. They subdivided the cardiac events into two categories: (1) all cardiac events and (2) major cardiovascular events (MACEs) defined as cardiovascular death, nonfatal MIs, or nonfatal stroke. Although they identified a significant increase in minor events such as tachycardia, there was no increase in MACEs (Mills and Thorlund). This remained true for a subgroup analysis of high-risk patients, although the numbers were small.

IS THE USE OF NRT IN THE CARDIAC PATIENT SAFE?

Early case reports suggested cardiovascular risk associated with use of NRT, especially if the patient smoked while using nicotine replacement. Data are now available[18,32,37–41] from randomized controlled trials, efficacy studies, observational data, and physiologic studies, supporting the safety of NRT used in the stable cardiac patient. There was no increased risk of angina, MI, stroke, arrhythmia, or death. These studies looked at patients with stable cardiovascular disease who had no cardiac event requiring an intervention in the prior 2 weeks.

Although NRT is cautiously prescribed for relief of withdrawal symptoms for cardiac patients in the CCU, there is a lack of randomized evidence to support its safety in the early period after an MI. As previously discussed, nicotine increases heart rate, BP, and myocardial contractility, and has the potential to cause endothelial dysfunction and coronary vasoconstriction. There is only one study[42] that looks at use of NRT among patients who were admitted for acute coronary syndromes (ACS) and who received transdermal NRT during that hospitalization. In this retrospective propensity analysis from Duke University, patients who had undergone a cardiac catheterization for an ACS and received NRT were retrospectively compared with comparable patients from their

database. After a propensity-matched analysis, they found no difference in short- or long-term mortality in patients who did or did not receive the patch. There was no significant difference between the groups in the need for undergoing coronary artery bypass graft surgery (CABG) or percutaneous transluminal angioplasty. Nonetheless, nicotine does have hemodynamic effects that could contribute to acute cardiovascular events.

There are two troubling retrospective reports regarding the use of nicotine replacement in critically ill patients. One is among medical intensive care unit patients[43] and the other among patients undergoing CABG.[44] In each study, the use of NRT was associated with an increased mortality. Unfortunately, because of the retrospective nature of the studies and their small size, they could not control for associated comorbidities, thus limiting the weight that we can place on them. However, they most definitely indicate the need for further studies and raise a need for caution.

As far as the e-cigarette is concerned, there is insufficient literature available to address its use in the cardiac patient. There is literature on exposure to both the aerosol and the particulate components that they generate.[45] Using 20 e-cigarette refill solutions from five manufacturers in cultured rat cardiac myoblasts, the aerosols from three solutions were found to be cytotoxic to the cardiac myoblasts. Although tests on e-cigarettes show much lower levels of most toxicants, they do not show reduced levels of particulate matter when compared with that of conventional cigarettes. The distribution of particulate matter generated by the e-cigarette is similar to that of the traditional cigarette. They are small enough to reach deep into the lung and cross into the systemic circulation. Toxicity thresholds are not known, but we know that exposure to ultrafine particles from tobacco smoke or air pollution turns on systemic inflammatory processes and increases the risk of cardiovascular death.[46–48] Overall, although the e-cigarette is likely to be less toxic than the cigarette, the products are unregulated, contain toxic chemicals, and have not been proven as cessation devices. Should the patient insist on e-cigarette use, they should be urged to set a quit date and not plan on using it indefinitely.[45]

Overall, the clinically relevant hemodynamic effects of NRT appear to be very mild, and its use in the stable cardiac patient appears to be quite safe. Clinical trials have not examined the efficacy of NRT in the AMI patient population. However, given the significant health consequences of smoking after MI, and analyzing current data, Benowitz and Prochaska have suggested an approach including, in addition to intensive counseling and follow-up, a personalized

prescription of medication that may include NRT to relieve withdrawal symptoms and provide an effective transition from inpatient to outpatient smoking cessation.[49]

BUPROPION FOR SMOKERS WITH CARDIOVASCULAR DISEASE

Bupropion, an atypical antidepressant with a structure related to amphetamine, has, like nicotine replacement, been shown to be an effective smoking cessation tool. After approximately 10 days on treatment, the desire to smoke diminishes significantly. In addition, it prevents the depression that not uncommonly surfaces in patients who stop smoking. The contraindications include a seizure history, alcoholism, bipolar disorder, bulimia nervosa, and panic attacks. The side effects include dry mouth, headache, agitation, and insomnia. Hypertension has been described, especially in patients taking both bupropion and the nicotine replacement. The treatment is usually begun at bupropion 150 mg sustained release (SR) and can subsequently be increased to 150 mg SR twice a day. The side effects are dose dependent, and some patients may obtain an adequate therapeutic benefit with the 150-mg-daily dose. The drug is metabolized in the liver, so dose adjustment is advised with significant liver disease. The drug inhibits the activity of CYP2D6 isoenzyme, which metabolizes β-blockers, antiarrhythmics, certain antidepressants, SSRIs, and antipsychotics.

Bupropion approximately doubles quit rates in otherwise healthy smokers and patients with stable cardiovascular disease.[2] There have been a number of case reports of death and severe adverse cardiovascular reactions occurring in patients taking bupropion,[50] but in the meta-analysis of Mills and Thorlund[35] in a high-risk population (cardiac disease and COPD), bupropion was safe with a MACE relative risk approaching 1. A 2008 clinical practice guideline issued by the U.S. Department of Health and Human Services suggests that bupropion can be safely used in the acute post-MI period.[51]

Although the safety data are encouraging, in the meta-analysis of Mills and Thorlund,[35] efficacy was questioned. Three trials of bupropion therapy that had begun in the CCU did not support significant efficacy at 1 year, with only a 5% improvement in quit rate versus placebo at 1 year.[2,52,53] However, Benowitz and Prochaska point out in their editorial[49] that the 12-month quit rate difference of

5% that was achieved with bupropion over placebo would have a meaningful public health impact for a group at such high risk for ongoing cardiovascular events. There is one randomized trial for smoking cessation comparing bupropion SR 150 mg BID with placebo in outpatients with stable cardiovascular disease,[54] demonstrating improved 1-year quit rates. At 1 year, the quit rates were 27% for the bupropion arm versus 11% for the placebo arm. Safety profile was once again validated.

Duration of therapy with bupropion appears to be a significant factor that needs to be considered in the acute cardiac patient for whom relapse has a particularly high risk. In a five-hospital, double-blind placebo-controlled trial, patients who were admitted with acute cardiovascular disease were randomized to receive either bupropion SR 150 mg BID and intensive counseling or placebo and intensive counseling for 3 months. Bupropion's safety profile was supported for smokers hospitalized with acute cardiovascular disease. The bupropion group did have improved short-term quit rates (37.1% vs 26.8%) but not improved long-term quit rates (25% vs 21.3%) over intensive counseling. After 30 days off the drug, there was a borderline significant increase in cardiac events, and 75% of the subjects were smoking before the event. The patients enrolled in the study were significantly addicted, and 40% of them had been smoking with known CAD before admission, making them a highly addicted group. In addition to supporting the safety of the use of bupropion in the CCU patient, this study raises the question of a need for longer-term therapy with bupropion to help maintain the abstinence advantage seen at 3 months.[53]

In studies of bupropion SR being used as an antidepressant in patients with cardiac disease, few cardiac adverse effects were seen. There was occasional hypertension, but no effect on cardiac conduction or ejection fraction. A black box warning remains on bupropion regarding suicide risk.

Despite the concern raised by case reports, current evidence suggests that bupropion SR is a safe and possibly efficacious treatment for smoking cessation for patients with cardiovascular disease. Full evaluation of bupropion SR in patients with cardiac disease is needed. Bupropion may be used in combination with nicotine replacement. The success rate of this combination has not been shown to be statistically superior[55,56] and has not been evaluated in the cardiac patient. It is suggested that while on combined therapy, blood pressure should be monitored.

WHAT IS THE ROLE OF VARENICLINE FOR THE CARDIAC PATIENT?

Varenicline is a highly effective smoking cessation medication that is both a partial nicotine agonist and an antagonist. After taking this drug for a week, the patient experiences little to no cravings, and if they do smoke they derive no pleasure. Common side effects include insomnia (19%), nausea (16%), abnormal dreams (9%), and constipation (5%). Seizure disorder is a contraindication. Although this drug has had the highest quit rates among healthy individuals, postmarketing data raised concerns regarding the risk of depression, aggressive behavior, suicidal ideation, and suicide. It is well known that depression may surface in patients attempting to quit smoking. Many patients use the nicotine in cigarettes to treat a full-blown or borderline depression, and when they stop smoking, depression may be uncovered. Subsequent studies of varenicline and the risk of depression and suicidal ideation have not substantiated this risk; however, it remains a subject of ongoing research.

More recent studies have validated the use of varenicline in combination with NRT, with a significantly improved quit rate at 24 weeks.[58] In addition, the drug has now been approved for 6 months of therapy. Furthermore, recognizing that gradual reduction may be preferred by some smokers, varenicline has been used in a graduated smoking reduction plan versus placebo with quit rates of 27% versus 9.9% at 1 year.

For the cardiac patient considering use of varenicline, two questions arise. First, is there any excess cardiovascular risk? Second, what is the risk of depression? This is of special concern in this often depressed population.[57]

Theoretically, varenicline should have little to no cardiovascular effects. The sympathomimetic cardiovascular effects of nicotine are mediated primarily by binding to α3β4 nicotinic acetylcholine receptors. Because varenicline binds to a different nicotinic receptor, α4β2, it was theorized not to have cardiovascular effects. In 2010, Rigotti et al.[59] published a multicenter randomized, double-blind placebo-controlled trial comparing the efficacy of 12 weeks of varenicline with counseling versus counseling alone in 714 smokers with stable cardiovascular disease. At the end of a year, the quit rate was 19.2% for the varenicline group versus 7.2% for placebo. Although the trial was small, there was no increase in cardiovascular events or mortality. For this study, patients had to be otherwise well, including no psychiatric history. Mood was not

systematically assessed, but there was no difference in spontaneously reported psychiatric symptoms in the varenicline versus placebo group.

Although a meta-analysis by Singh[60] raised concern over the cardiovascular safety of varenicline, other meta-analyses[35,61,62] did not find an increased risk of cardiovascular events. However, in 2011 the FDA issued a safety alert regarding a numerically but not statistically greater rate of adverse cardiovascular events with varenicline compared with placebo. A more recent large retrospective cohort study found no increased risk of cardiovascular events, depression, or self-harm.[63] It appears that varenicline has a small, nonsignificant cardiovascular risk, if any. Similarly, psychiatric concerns have not been supported in the current literature, although the black box warnings persist and change of mood should be taken seriously.

The use of varenicline in the CCU in the acute AMI setting has been studied in the EVITA (Evaluation of Varenicline in Smoking Cessation for Patients Post–Acute Coronary Syndrome) trial, suggesting that 12 weeks of varenicline is both safe and effective in patients with ACS.[64] At 24 weeks, there was a 14.8% absolute difference in point prevalence abstinence for those in the varenicline (47.3%) versus the placebo group (32.5%). Less than a third of those receiving placebo were abstinent at 24 weeks.

Varenicline is our most effective pharmacotherapy for smoking cessation to date. Even though further work is needed to shed more light on the psychiatric risk and to ensure the cardiac safety profile, the risk benefit ratio weighs strongly on the side of this tool. The data provide a strong evidence base to support the safety and effectiveness of varenicline for cardiac patients, both those with stable cardiovascular disease and those in the acute setting of ACS. Questions that need clarification, beyond issues of safety, are the role of more extended courses or even long-term therapy for this chronic severe addiction and the role of integrating intensive behavioral therapy into the varenicline treatment plan.

WHAT IS THE APPROACH TO THE PHARMACOTHERAPY?

In the patient with ACS in the CCU, clinical judgment needs to guide the approach. Given the significant health consequences of smoking after MI, and based on the available current data, Benowitz and Prochaska have emphasized the importance of a personalized plan including behavioral modification along with the prescription of medication to relieve withdrawal symptoms and provide an effective transition from inpatient to outpatient smoking cessation.[49] NRT has

no safety data in the acute setting but abundant safety data for the stable cardiac patient. It has the advantage of immediate relief of withdrawal symptoms. The disadvantage of the delayed onset of action of both bupropion and varenicline is counterbalanced by substantial safety data in the acute setting. The improved effectiveness of varenicline along with its safety data gives support to its use in this group of patients. The ongoing, although decreasing, concern regarding psychiatric comorbidities remains. Until we have better randomized long-term control trials, the approach needs to be guided by informed clinical judgment.

Even when we have devised a plan, some patients may be unwilling to stop abruptly. Recent investigations have shown that gradual reduction may be effective, although in the cardiac patient this is not ideal.[65]

BEHAVIORAL MODIFICATION

Although 30% to 45% of smokers who suffer an initial cardiac event stop smoking,[66] 60% to 70% of them relapse within a year. No matter which pharmacologic therapy one uses to stop smoking, there is a 50% relapse rate. The problem is that nicotine addiction is permanent. The patient who smokes immediately on waking or who is uncomfortable in places where they cannot smoke for any length of time is very addicted. The faster and stronger the craving, the more addicted the patient. Other patients are able to wait hours before their first cigarette. They are less affected by the decreased nicotine level that occurs over a night without smoking. They have fewer or no cravings. They have a larger behavioral component to their habit and are less in need of medication to quit.

As previously noted, patients who are highly addicted need more than medication to have sustained success. They need to learn behavioral techniques to allow them to remain smoke free through a lifetime. We know that smoking cessation programs that do not include postdischarge counseling and that do not provide follow-up for more than a month are ineffective.[67–70] Follow-up of at least 3 months is indicated.[50,71] Cardiologists should attend to these simple techniques and the importance of lifestyle modification on an ongoing basis.[72,73]

WHAT ARE THE PRINCIPLES INVOLVED?

- Most importantly, convince the patient that he or she can succeed and that you are confident that they will. Put the patient on a positive footing. Identify areas of accomplishment. A cardiac patient who is smoking is often tremendously guilt-ridden. You, as their health care provider, will support them through the process. Medications and behavioral techniques will help control the withdrawal and the cravings.
- Allow them to lead the conversation regarding what aspect of smoking is of concern to them. Address their concerns, whether they are financial, social, or health related, to get the conversation going. Identify why they use the cigarette: for pleasure, relief of depression, boredom, anxiety, or stress; improved concentration, relief from cravings, or all of these? Together, consider alternative approaches to each of those problems, which requires identifying other pleasures, as well as addressing depression,[43] stress and anger management techniques, exercise, being otherwise occupied, and avoiding the situations that lead to the urge to smoke.
- Have the patient make a concrete plan for what he or she will do to cope with cravings (eg, gum, water, or deep breathing).
- Identify and plan for avoidance of triggers such as coffee, alcohol, friends who smoke.
- Identify substitutes that the patient likes and can look forward to, for example, movies, museums, friends who do not smoke, or magazines.
- Encourage the patient to be as busy as possible, especially immediately after meals.
- Most importantly, discuss with the patient the permanence of the addiction and the need to be on guard even years later, especially in situations of stress. Unfortunately, the thought of picking up another cigarette recurs for a very long time, and one puff can lead to full relapse.
- Patients should never allow others to smoke around them or endanger their sobriety. As their cardiologist, you are giving them the license to be an inconvenience to others who want to smoke around them, because of their cardiac health. Their success is so important that nothing should be allowed to endanger it.
- Web-based interventions are available. The http://www.smokefree.gov website of the National Cancer Institute (NCI) combines evidence-based guidelines tailored to readiness to quit with available professional assistance via instant messaging and quitline (1-877-44U-QUIT).
- Texting interventions show borderline results.

- Social media (Twitter and Facebook) have potential benefit, utilizing buddy groups.
- Monetary incentives have shown only short-term benefit.

Smoking cessation in the cardiac patient covers a spectrum of therapy from simple behavioral modification to complex decisions involving pharmacotherapeutic options. We have ample data indicating that the approach must be a combination of techniques, with months of ongoing support. Still, the relapse rate remains unacceptably high. As we have reviewed, the risks of ongoing smoking are high, as are the benefits from quitting. Clearly, we need more physician participation in this process, and who could be more effective in guiding the patient to success than their own cardiologist?

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Patient and Family Information for: SMOKING CESSATION FOR THE CARDIAC PATIENT

As a cardiac patient who smokes, you have an urgent need to understand not only how much cigarettes endanger your survival, but also how rapidly and thoroughly stopping smoking will improve your health and outcome. For patients with coronary heart disease, quitting smoking produces a 36% reduction in death from any cause. As you well know, cigarette addiction can be very intense for many people. But despite the intensity of this addiction, with your own determination and a little help from medication and behavioral techniques, you really will succeed.

HOW DOES IT BEGIN?

You most likely began smoking as a teenager, when you were very vulnerable to the addictive properties of nicotine. You tried a cigarette and found that it gave you a certain degree of confidence and pleasure. That feeling came from a substance called dopamine, which the nicotine in cigarette smoke causes to be released in the brain. Quickly, as you developed tolerance to nicotine, you found that in order to get the same effect you needed two cigarettes. Eventually, you found that you needed a cigarette to get going in the morning. Nowadays, it is hard to function without that morning cigarette and maybe a cup of coffee. The discomfort before that first cigarette in the morning is called withdrawal, and when you first felt it you were hooked.

WHY CAN SOME PEOPLE STOP “COLD TURKEY” AND I

CANNOT?

The level of addiction varies from person to person. It is determined genetically, by how your body handles nicotine, the addicting substance in the cigarette. Some people can be “social” smokers and just have an occasional cigarette. They experience the harmful effects of the cigarette, but they are not addicted. Their bodies handle nicotine differently. They do not have the genetic makeup that causes them to be susceptible to the addictive properties of nicotine. Why is this important to understand? Accepting that your smoking is an addiction is a heavy burden, but it is important for you and your loved ones to understand it, accept it, and look forward to getting you the help that you need to quit.

HOW DO YOU KNOW IF YOU ARE ADDICTED?

The easiest way to know if you are addicted to cigarettes is to ask yourself how soon after you wake up you have your first cigarette. If it is within minutes, you are very addicted and quitting may be tough for you. We therefore suggest that for you, quitting will be most successful if you combine medication with behavioral changes. Participating in a program with ongoing support, such as a smoking cessation clinic, is likely to be a major help.

WHAT IS NICOTINE WITHDRAWAL?

Nicotine withdrawal is a real physical brain dysfunction. You cannot do your day’s work. You get irritable, unable to concentrate. And what makes cigarettes so addicting is that within 10 seconds of smoking, not only is that uncomfortable feeling gone, but you experience real pleasure.

IS IT TOO LATE TO QUIT?

Absolutely not! Much of the effect of smoking on the heart and circulation is reversible and, within 3 years of quitting, the risk of recurrent coronary events becomes that of someone who never smoked. The benefits begin immediately.

Within hours of quitting smoking, the carbon monoxide that poisons your oxygen delivery system and the chemically induced tightening of your blood vessels dissipate.

An important part of what happens when a person has a heart attack is caused by the development of clots in the coronary arteries. That is why your doctor is giving you medicines like aspirin and other anticoagulants to thin your blood. Smoking, however, causes your blood to clot, and that effect is not blocked by aspirin. The clotting system is so sensitive to the effect of smoking that even one cigarette causes it to be disrupted. It is therefore very important to understand that it is not enough to cut down on your smoking. You must quit entirely. Even one cigarette endangers your survival. The good news is that your clotting system renews itself very well and fairly rapidly, so the benefits of quitting begin almost immediately.

Smoking also contributes to vascular damage over the years; damage not just to your coronary arteries, but to all the vessels in your body. If you are also diabetic, this effect is further enhanced with an increased risk of blindness, kidney damage, stroke, and loss of limb.

HOW DO I STOP?

There are two parts to this process: medication, for the physical withdrawal, and behavioral change for the habit. You may be disturbed by the idea of taking another medication and believe that you can do this without pharmacologic support. The truth is, if you are addicted, you double your chance of success with treatment, and stopping smoking is as important for your cardiac health as taking some of your cardiac medications, ACE inhibitors, or β-blockers.

MEDICATION

Your doctor will speak with you about using medication to help with nicotine withdrawal. It may be a nicotine patch or gum or even an inhaler, a medication called bupropion, which can be used with or without nicotine replacement or varenicline, which is used alone.

If you have been a heavy smoker and are using nicotine replacement therapy, you will need higher doses of nicotine replacement or possibly a combination of

medications such as the patch and gum. If you used nicotine replacement before and felt that it did not help, be aware that the dose must be just right for you. Also, it may seem strange to take nicotine to quit smoking when it is nicotine that you are trying to get away from. The reason this works is that the patch satisfies your need for nicotine without giving you any pleasure. It also breaks the ritual of the smoking habit, doubling your chance of success. As you become comfortable not smoking, the dose of nicotine is gradually reduced and finally stopped.

Your doctor may prescribe bupropion, which helps with the desire to smoke, cravings, as well as with depression. If you have been depressed, it is important to let your doctor know, because bupropion may be very helpful.

There is also a newer, highly effective medicine for stopping smoking called varenicline. It may cause nausea and strange dreams, but after taking it for 7 days you will not feel like smoking. You continue to take varenicline for several months. Unfortunately, some people can become very depressed and even suicidal while taking it. Your doctor may ask a family member to be aware of this and monitor you for any change of mood. If you do experience any change of mood, you need to stop varenicline immediately and speak with your doctor. Although warnings of mood change and depression are concerning, the effectiveness of this drug is very real. You and your doctor need to discuss this option in light of previous quit attempts, level of addiction, and the vulnerability of your cardiac status.

No matter which pharmacotherapy you use, a year later the relapse rate is the same. Something more is needed to remain smoke free, and this is called behavioral therapy: learning new life skills to cope with the issues that made you want to smoke in the first place.

WHAT IS THE BEHAVIORAL PART OF MY TREATMENT?

In addition to dealing with the nicotine withdrawal, you must have a plan for handling the behavioral part of your addiction. Do you use cigarettes for stress, boredom, anger, pleasure, socializing? It is important to look at the reasons for your smoking in order to plan a lifetime change, not just while you are taking medication, but a whole new approach to handling those situations that make you want to smoke.

Develop a clear plan for limiting your stress, avoiding situations that upset

you. Exercise regularly, giving yourself real rewards. Put relaxation into your day. Develop hobbies that you can substitute for the pleasure that you derived from cigarettes. Bring a magazine to work for what used to be your smoking break. Have a game on your cell phone to play when you are waiting for the bus. Music, reading, meditation, yoga, sketching, deep breathing, whatever gives you pleasure.

Some tips:

- Develop a list of activities that you can use to keep yourself busy, happy, and relaxed.
- Do not let anyone interfere with or endanger your success. No one can smoke around you!
- Avoid alcohol: it is the strongest trigger.
- For some, coffee is a trigger. Get a substitute, tea or juice or chocolate, at least for the first few days, to change your routine and make it easier to quit.
- Purchase healthy snacks and keep them on hand to relieve the cravings and avoid weight gain.

Pick a quit day and have all your tools ready to go. Choose a busy, nonstressful day; have no cigarettes in the house; throw out all your ashtrays. Keep very busy and go to bed early. If this thought is overwhelming, you are not alone. Some need to begin in a more stepwise fashion. Try using the nicotine lozenge to substitute for a few cigarettes for a few days to get started. Discuss this with your doctor. For the cardiac patient, this is not ideal because all cigarettes are dangerous, but the important message is to start.

Cigarette addiction can be overcome, but it never goes away completely, even as your body becomes much healthier. If you do have a relapse, get back to your plan immediately. Relapse is very common, but it is best to think of it as a learning opportunity—how you could handle that situation differently in the future. It is all part of the process of becoming smoke free.

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May Bakir
Eyal Herzog

Women's Heart Disease in the Cardiac Care Setting

Case Presentation

A 44-year-old woman presents to the emergency room complaining of chest pain. The patient began to experience chest discomfort during lunch and initially thought it was heartburn. The patient was awoken from recurrent chest pain later that evening around 4 pm and called emergency medical services. In the emergency room, the patient was found to have <1 mm ST elevations in leads aVR, V1, and V2. The patient's initial troponin level was 0.12 ng/mL. Blood pressure and heart rate were within normal limits. Bedside echocardiogram demonstrated left ventricular ejection fraction (LVEF) of 50% and no overt segmental wall motion abnormalities. The patient was admitted to the telemetry floor.

The following morning, the patient's troponin level was <0.03 ng/mL, and the patient was scheduled to have a stress echocardiography. During the stress test, the patient began to experience chest pain and had ST elevations in leads aVR, V1, and V2. Echocardiogram showed new segmental wall motion abnormalities during stress in the basal anterior, anteroseptal, and septal regions. Chest pain and ST elevations resolved quickly with the termination of the stress test. The patient was transferred to the cardiac intensive care unit.

She remained hemodynamically stable and was scheduled for cardiac angiography that evening.

Cardiac catheterization was completed and did not demonstrate significant angiographic stenosis. Nitrate medication was initiated, and the patient was scheduled to follow up with a cardiologist as an outpatient.

This case broaches the question “why were there ST elevations and normal coronary anatomy?”

INTRODUCTION

Women with signs and symptoms of cardiac ischemia will undergo cardiac angiography. Many of these patients are found to have normal-appearing coronary arteries. Several studies have demonstrated that up to 40% of patients who undergo cardiac catheterization will not have angiographically significant coronary stenosis.[1] Historically, these patients were said to have cardiac syndrome X. Cardiovascular disease accounts for about 1 in 3 female deaths. For women presenting for evaluation of suspected ischemic symptoms, a diagnosis of normal coronary arteries is 5 times more common than for men.[2] A substantial percentage of these patients have coronary microvascular dysfunction (CMD). In the past two decades, in part because the National Heart, Lung and Blood Institute initiated the Women’s Ischemia Syndrome Evaluation in 1996, an extensive amount of research has focused on coronary microvasculature. CMD is now acknowledged as a cause of cardiac ischemia and can occur alone or along with macrovascular coronary artery disease (CAD). Patients with CMD have a significantly higher rate of hospitalization, heart failure, sudden cardiac death, and myocardial infarction (MI).[3] CMD can affect the cardiac vasculature in a number of ways that essentially disrupt the coronary arteries’ vasodilatory ability and therefore hinders coronary blood flow (CBF), causing ischemia.[4]

MYOCARDIAL ISCHEMIA IN WOMEN IN THE CRITICAL CARE SETTING

All patients with acute coronary syndrome (ACS) are evaluated for placement in the cardiac care unit (CCU). Patients who are believed to have high-risk lesions,

such as left main coronary disease, will be appropriately monitored in the CCU until further diagnostic procedures can be obtained. As with the patient in the case presentation, because of the ST elevations in leads aVR, V1, and V2 and concordant echocardiographically demonstrated wall motion abnormalities during exercise stress, it was thought that there was a high likelihood of left main coronary disease. Optimal medical therapy for women experiencing ACS does not differ from that for men. In the absence of absolute contraindications, aggressive therapy should be initiated with antiplatelet therapy with aspirin, a platelet $P2Y_{12}$ receptor blocker, anticoagulation therapy, β-blockade, and lipid-lowering medication. Cardiac angiography would be the next diagnostic approach to assess the coronary arteries. It is well known that about 50% of patients who undergo clinically indicated coronary angiography will not have obstructive CAD. Of the patients without obstructive CAD, more than half are believed to have CMD. The importance of the diagnosis of CMD lies in its poor prognosis.

PROGNOSIS

In women who present with ACS, it is not uncommon for the angiogram to demonstrate nonobstructive CAD. National data have shown that the odds for obstructive CAD in the ACS setting are 50% lower in women when compared with men.[5] However, in the setting of ACS, nonobstructive coronary anatomy does not carry a benign prognosis. Studies have shown that women with signs and symptoms of ischemia and no obstructive CAD have elevated major adverse cardiac event (MACE) rates, including MI and cardiac death. In some patients, the worse prognosis is attributed to advanced age and comorbidities, but younger women in particular do worse. This may be due to underutilization of lifesaving therapies and medications.[6] CMD can occur secondary to either endothelial-dependent or non–endothelial-dependent regulatory systems. Endothelial-dependent CMD is defined as impaired vasomotor response to acetylcholine. Endothelial-dependent CMD has been shown to be an independent risk factor for MACE.[7] Non–endothelial-dependent CMD is diagnosed when there is reduced coronary flow reserve (<2.36), and it is significantly associated with MACE in 5-year follow-up from initial diagnosis.[3]

TAKOTSUBO CARDIOMYOPATHY

Stress cardiomyopathy, also known as Takotsubo cardiomyopathy or broken heart syndrome, is a syndrome characterized by regional systolic dysfunction of the left ventricle (LV) where the presentation mimics troponin-positive ACS or ST-elevation MI, but lacking obstructive disease on cardiac angiography.[8] There are several forms of Takotsubo cardiomyopathy, the most common presentation being apical ballooning of LV apex, with hypokinesis of the mid-and apical segments and hyperkinesis of the basal segments of the LV[9] (**Figure 57.1**). This syndrome is more common in women, and the pathogenesis, although not fully understood, is postulated to be secondary to catecholamine release, coronary spasm, or microvascular dysfunction. These patients, although lacking obstructive CAD, demonstrate abnormal myocardial perfusion.[10] Several findings argue that Takotsubo cardiomyopathy is consistent with CMD, including abnormal coronary flow reserve (CFR) measured by echocardiography and improvement of LV function with the administration of adenosine.[11,12]

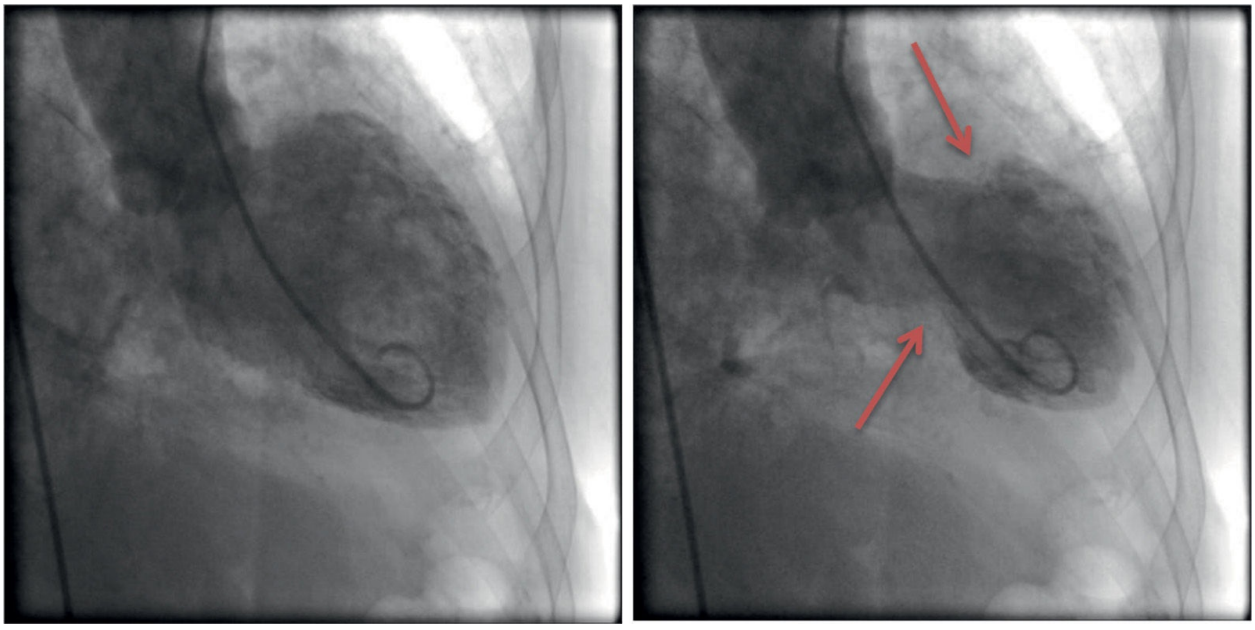

FIGURE 57.1 Takotsubo cardiomyopathy on cardiac angiography. Arrows indicate the hinge points between hyperdynamic basal segments and akinetic mid- and apical segments.

DIAGNOSIS

STRESS TESTING

Exercise stress testing is commonly used to assess CAD. However, stress testing is not very sensitive or specific in detecting heart disease in women. Currently, there are no methods to directly visualize the coronary microvasculature. Indirect assessment of the coronary microvasculature is made through functional testing. CFR is one method that provides vasodilator response to adenosine. CFR is calculated as the ratio of the CBF at maximal dilation to the CBF at rest and can be obtained through various imaging modalities. There is not an absolute cutoff for the CFR in defining CMD; however, most are considered to have CMD if the CFR is <1.5.[13]

POSITRON EMISSION TOMOGRAPHY

Cardiac positron emission tomography (PET) scanning is used for myocardial perfusion scanning as a technique to identify perfusion defects, which in turn reflect CAD. In nonobstructive CAD, perfusion defects reflect microvascular ischemia along distribution of the three main coronary arteries.[14]

CONTRAST ECHOCARDIOGRAPHY

Assessing the coronary arteries with cardiac angiography can be challenging in a critically ill patient. Contrast echocardiography can be safely used at the bedside.[15] Features of ACS are commonly seen in critically ill patients, including ECG changes, troponin elevation, and angina. These features of ACS are frequently seen in conditions other than obstructive CAD, such as Takotsubo cardiomyopathy and CMD. Cardiac microvasculature in the endocardial regional has the lowest flow reserve and is more susceptible to ischemia than the epicardium possibly because of the larger epicardially placed coronary arteries.[16] Therefore, in CMD there may be a reduction in the blood flow in the endocardial myocardium to a greater extent than in the epicardial myocardium (**Figure 57.2**), which can be seen with reduced perfusion during contrast echocardiography.[15]

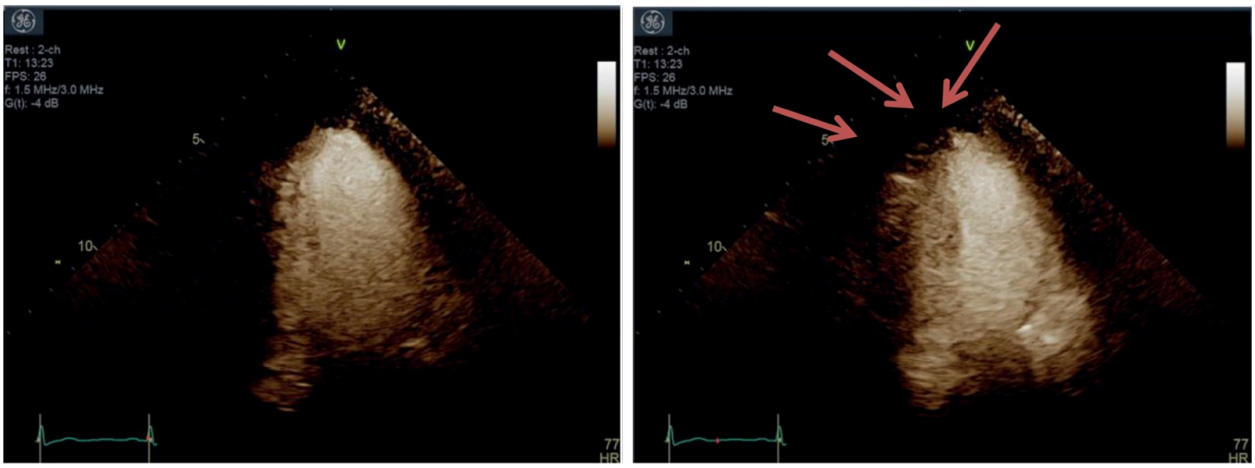

FIGURE 57.2 Contrast echocardiography demonstrating decreased circulation at the apical segment (arrows).

CARDIAC MAGNETIC RESONANCE IMAGING

Myocardial scar can be detected by cardiac magnetic resonance imaging (CMRI) late gadolinium enhancement (LGE) and is a known predictor of MACE. Women with signs and symptoms of ischemia and no obstructive CAD have been shown to have a prevalence of myocardial scar detected by CMRI LGE, with a predominant traditional MI pattern (**Figure 57.3**) indicative of CMD. The amount of ischemia can be assessed on the basis of the intensity of gadolinium that is perfused in the myocardium.[17] The use of CMRI has confirmed that many of these women can have irreversible myocardial injury, which appears to be clinically underdiagnosed.[18]

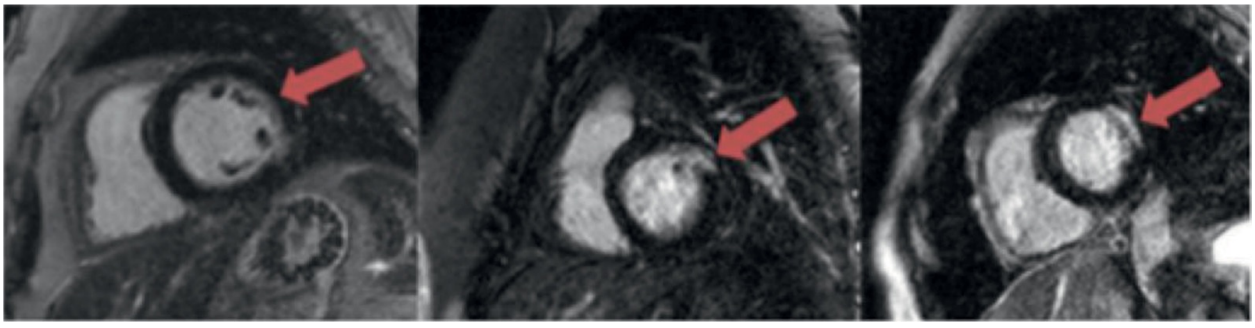

FIGURE 57.3 Cardiac magnetic resonance imaging with late gadolinium enhancement (arrows): Typical infarction pattern along the coronary arteries seen in coronary microvascular dysfunction.

CORONARY REACTIVITY TESTING

The gold standard for diagnosing CMD is through coronary reactivity testing.

This is done while the patient is having a cardiac angiography. Adenosine is used to assess endothelial-independent dysfunction, and acetylcholine is used to assess endothelial-dependent dysfunction. Coronary flow is quantified before the adenosine injection and again after administration. In non–endothelial-dependent dysfunction, the CFR, in response to adenosine, will be ≤2.5.[19] Endothelial-dependent dysfunction is seen when there is less than 50% increase in coronary blood flow after the bolus of acetylcholine.[20] Coronary spasm can also be assessed with acetylcholine if the patient has chest pain in addition to ECG changes and if the change in the coronary artery diameter is less than 90%.[21]

TREATMENT

Currently, there are no guidelines to treat CMD. Treating CMD begins with risk factor control and lifestyle modification. Treatment should be aimed at reducing ischemic disease to reduce the risk of adverse cardiac events, ameliorating symptoms to improve quality of life and to decrease the morbidity from unnecessary and repeated cardiac catheterization.

Patients with endothelial dysfunction should be counseled on smoking cessation, which is known to improve endothelial dysfunction and therefore CMD.[22] Adrenergic modulation seems to play an important role, and therefore exercise should also be encouraged in this population. Angiotensin-converting enzyme inhibitors and statin medications improve endothelial dysfunction and should be used as first-line therapy. Statins lower cholesterol and have anti-inflammatory properties that have been shown to increase CFR.[23]

Patients with non–endothelial-dependent CMD benefit from β-blocker and nitrate medications. Nitrates help with angina by decreasing preload with venous dilation. β-Blockers are beneficial in that they decrease myocardial oxygen demand and increase diastolic filling time.

Ranolazine is a medication that is used to treat angina with varying results. Ranolazine inhibits the late sodium channels and reduces intracellular calcium, leading to improved ventricular relaxation.[24] Patients who have refractory angina despite being on maximal medical therapy should have a trial of Ranolazine to see if their symptoms improve.

CONCLUSION

Myocardial ischemia has specific sex differences. Despite having a lower prevalence of obstructive CAD, women have a higher prevalence of symptoms, ischemia, and mortality relative to men. Diagnostic testing can be used to accurately assess for myocardial ischemia in symptomatic women, in addition to providing important prognostic information. Women who are critically ill because of unstable angina or ACS and who do not have obstructive CAD should not be dismissed from care without further workup. Many of these women have been shown to have CMD that has been proven to be associated with high mortality, and, therefore, CMD is important to consider when diagnosing and treating these patients.

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Patient and Family Information for: WOMEN'S HEART DISEASE IN THE CARDIAC CARE SETTING

Coronary microvascular disease (CMD) is a disease that affects the small vessels of the heart that branch off from the larger coronary arteries. Patients often have signs and symptoms that are consistent with a blockage of the larger coronary arteries, but after cardiac angiography are not seen to have blockage. CMD is defined as damage to the inner walls of the blood vessels that can lead to spasms and decreased blood flow to the heart muscle. CMD affects more women than men. Despite not having obstructive disease of the large vessels of the heart, patients with CMD have a high risk of recurrent hospitalization, chronic chest pain, heart attack, and sudden cardiac death.

Stress-induced cardiomyopathy, also known as Takotsubo cardiomyopathy, is thought to be partially secondary to CMD. Patients who have experienced stressful situations, which could include anything from the loss of a family member to an illness or any general life hardship, can be affected by this type of cardiomyopathy. The pump function of the heart decreases in stress-induced cardiomyopathy because the apex of the heart will not contract as it should. Most often, this cardiomyopathy is reversible if treated properly.

The diagnosis of CMD has been evolving over the past two decades. There are noninvasive imaging modalities that can be used, such as positron emission tomography, echocardiography, and cardiac magnetic resonance imaging. Invasive testing can be done during cardiac angiography to see how the small vessels respond to certain medications to determine if there is a dysfunction within the lining of the blood vessels.

There are no specific guidelines on the treatment of CMD. All patients with CMD should undergo risk adjustment with lifestyle modification. Smoking

cessation is essential because cigarette smoke affects the lining of the small blood vessels and exacerbates the symptoms of CMD. Exercise should be encouraged because it increases blood flow throughout the body, including to the small vessels. Medications that increase blood flow to the small vessels should be considered. These include angiotensin receptor blockers, β-blockers, nitrates, and Ranolazine, each having their respective mechanism of action. Cholesterol-lowering medications should be started because they both lower cholesterol and have anti-inflammatory properties, which are thought to aid in the treatment of symptomatology.

To conclude, women with chest pain should have a thorough workup done by a cardiologist. Women who have been admitted to the hospital for an acute coronary syndrome but have not been found to have obstructive coronary disease of the large vessels should not go without follow-up because if they do have CMD and go undiagnosed and untreated, the prognosis is often poor.

58

Alan Rozanski
Randy Cohen

Lifestyle Management after the Diagnosis of Heart Disease

As the 20th century approached, pneumonia, tuberculosis, and diarrhea/enteritis were the leading causes of death in the United States. However, marked advances in our understanding of the determinants and transmission of diseases were beginning to reduce the mortality risk from acute illnesses. These included such measures as sanitation, chlorination, the introduction of measures to ensure a safer food supply, and the development of vaccines against acute illnesses, which by 1900 included vaccines against cholera, tetanus, typhoid fever, and bubonic plague. By the 1920s, chronic diseases were replacing acute illnesses as the major causes of mortality, with cardiovascular disease (CVD) as the leading cause of death. Thus, a “war” against CVD was initiated by the American medical community.

Initial success was slow because of a limited understanding of the disease and its risk factors. CVD increased in epidemic proportion before peaking in its incidence in the late 1960s. Since then, the reversal of disease has been remarkable. In the late 1960s, heart disease dwarfed cancer as a cause of death, and strokes were all too common. Since 1970, however, the mortality rates from cardiac disease and stroke have fallen by 70%, and the death rates from heart disease and cancer are now comparable (**Figure 58.1**).[1]

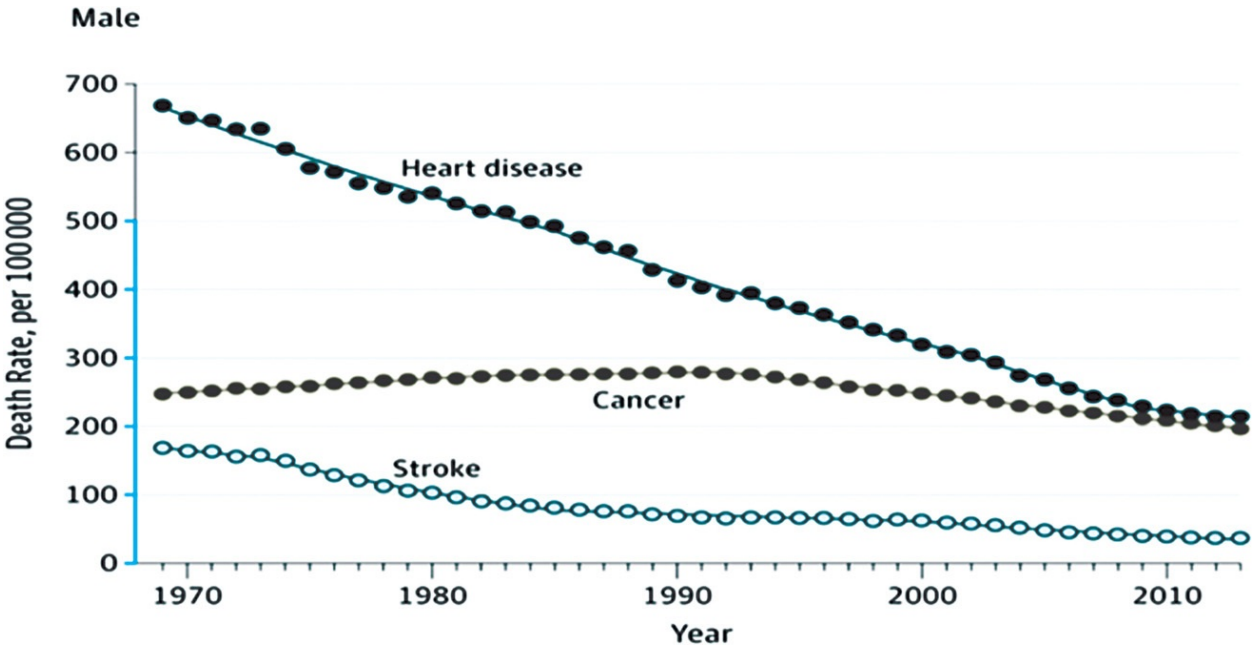

FIGURE 58.1 Temporal decline in death rates from heart disease, cancer, and stroke since 1969. (From Ma J, Ward EM, Siegel RL, Jemal A. Temporal trends in mortality in the United States, 1969–2013. *JAMA*. 2015;314:1731-1739.)

Two broad factors have accounted for this success: remarkable improvements in the treatments for heart disease and important advances in CVD prevention. Each of these factors is estimated to account for approximately 50% of the decline in heart disease.[2]

The medical advances have been broad based, including the initiation of cardiac care units, introduction of stress testing, development of cardiac bypass surgery and percutaneous coronary interventions, echocardiography, radionuclide stress testing, defibrillators, pacemakers, ablation procedures for arrhythmias, cardiac transplant, and the development of many effective classes of cardiac medications. The increasing sophistication of treatment has led to the development of many cardiac subspecialties, such as in cardiac imaging, electrophysiology, interventional cardiology, heart failure, and preventive cardiology. In each of these arenas, there have been continual advances that have improved care and survival. For instance, in the early introduction of angioplasty, reocclusion was a common problem. Improvement came with the development of bare metal stents, but in-stent restenosis remained a problem. The subsequent introduction of drug-eluting stents reduced the incidence of in-stent stenosis and allowed the performance of more complex procedures. Now fully bioabsorbable stents have been approved for use and will be tested for their

added efficacy. Similarly, the treatment of heart failure has been revolutionized by ever safer ventricular assist devices and resynchronization devices. Cardiac imaging has expanded to include cardiac MRI, coronary artery calcium scanning and coronary CT angiography, as well as continued advances in echo and nuclear cardiology. Other important recent advances include the expanding use of trans-aortic valvular replacement (TAVR), hypothermia for cardiac arrest, and many new drug therapies, such as those used to treat diabetes, the introduction of PCSK 9 inhibitors for hyperlipidemia, and novel anticoagulants.

The improvements in CVD prevention have also been broad based and impressive. An important advance in this regard was the initiation of the famous Framingham Study in 1948, which was dedicated to determining what risk factors accounted for heart disease in the town of Framingham, Massachusetts. By the early 1960s, the study had revealed that high cholesterol, hypertension, smoking, and diabetes were all important risk factors for CVD. At that time, nearly 45% of Americans smoked, often with great frequency, and many others were subject to secondhand smoke. The greatest single advance in cardiac prevention that has occurred since that time has been the dramatic drop in smoking rates (**Figure 58.2**),[3] aided by societal measures to prevent individuals from being exposed to secondhand smoking. Second, dietary guidelines and change in eating habits, such as the reduction in animal lard use and trans fats, have helped reduce serum cholesterol levels (which began even before the statin era) (**Figure 58.3**).[4] In addition, the advent of statins to treat dyslipidemia and powerful medications to control hypertension and diabetes has markedly improved our ability to prevent CVD.

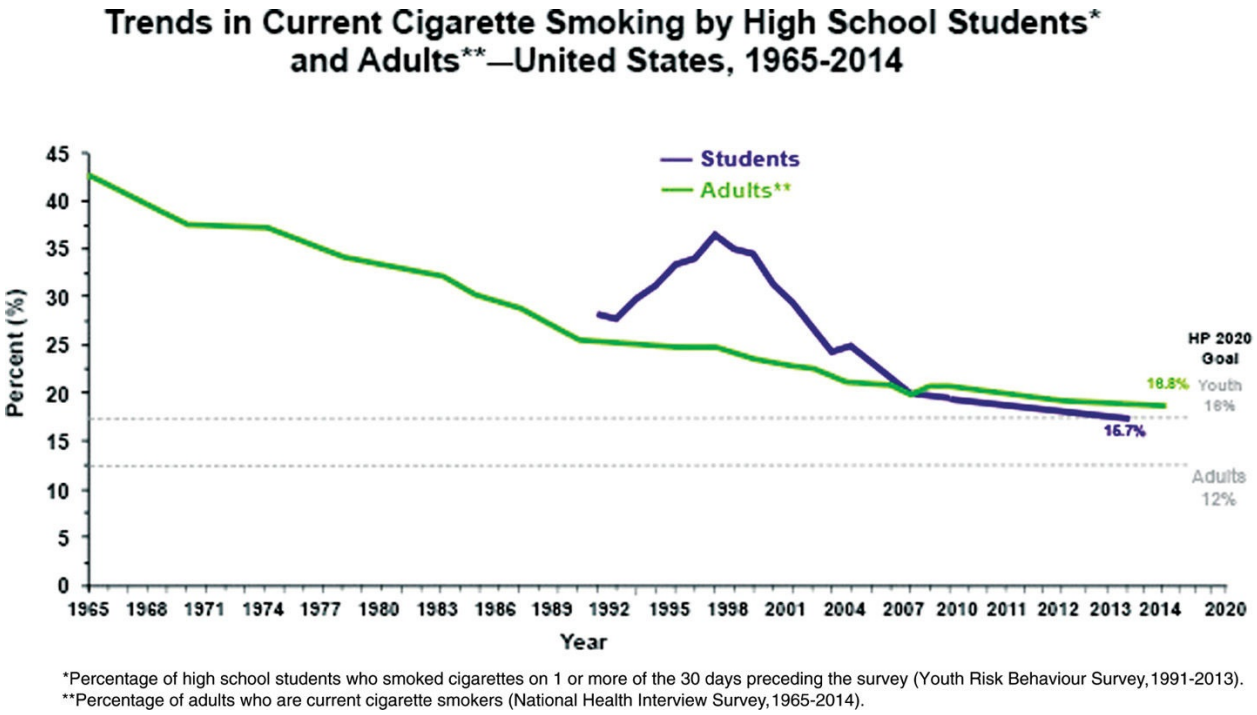

FIGURE 58.2 Temporal decline in the prevalence of smoking in the United States since 1965 for adults (green line) and students (blue line). (From Trends in current cigarette smoking among high school students and adults, United States, 1965–2014. Atlanta, GA: Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion; March 2016.)

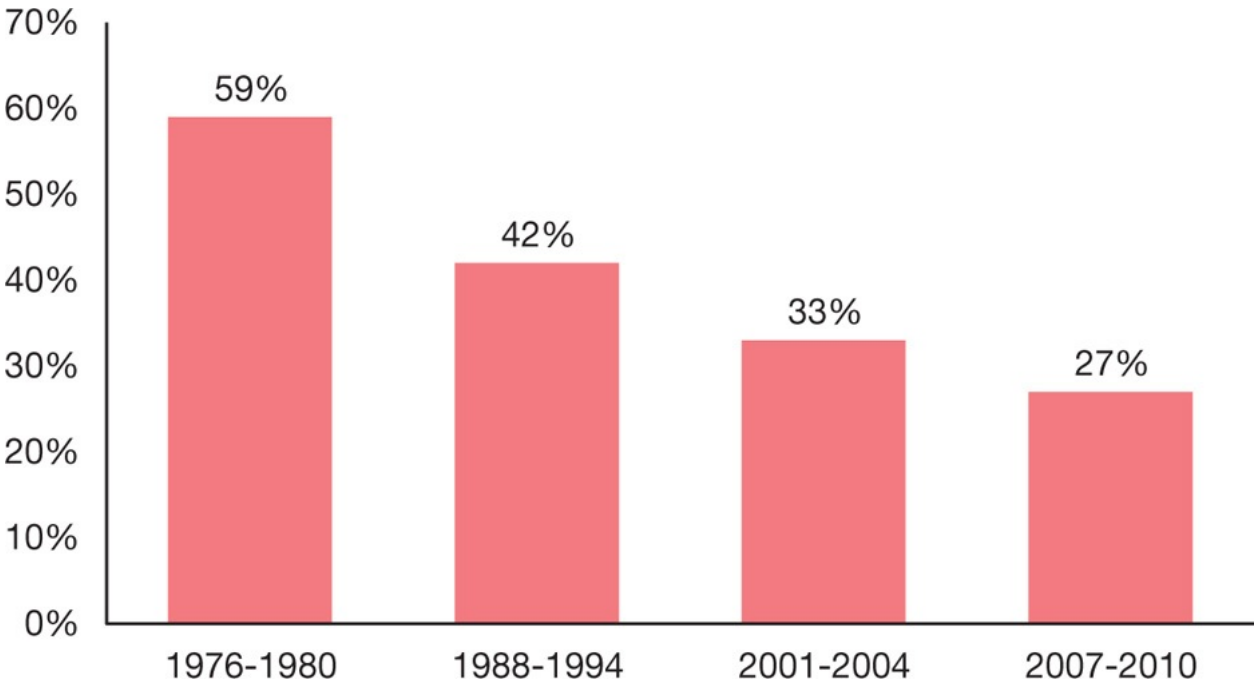

FIGURE 58.3 Temporal decline in the prevalence of high LDL cholesterol levels in the United States as assessed over four temporal periods. (From Kuklina EV, Carroll MD, Shaw KM, Hirsch R. Trends in high

LDL cholesterol, cholesterol-lowering medication use, and dietary saturated-fat intake: United States, 1976–2010. Atlanta, GA: National Center for Health Statistics Brief No. 117; March 2013.)

Because of these remarkable advances in prevention, there has been a marked decline in sudden cardiac death, and both the frequency and magnitude of myocardial infarction have declined.[5,6] So too has the incidence of peripheral vascular disease.[7] There has also been a marked decline in the frequency of inducible myocardial ischemia among patients presenting to stress labs for the workup of suspected CVD (**Figure 58.4**).[8] In sum, heart disease today is not only less frequent but also milder than yesteryear.

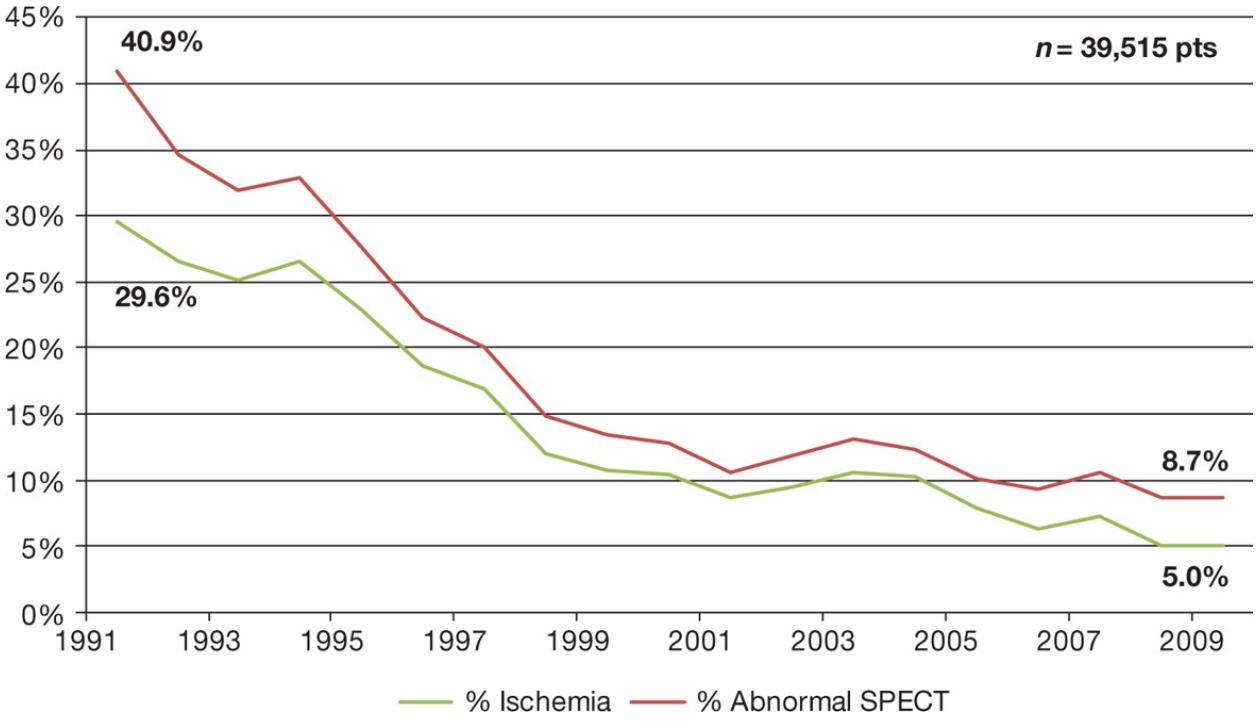

FIGURE 58.4 Temporal decline in the frequency of abnormal stress-rest myocardial perfusion SPECT studies (red line) and frequency of inducible ischemia (green line) between 1991 and 2009 among 39,515 patients referred for testing at a single medical center because of suspected CAD. (From Rozanski A, Gransar H, Hayes SW, et al. Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009. *J Am Coll Cardiol*. 2013;61:1054-1065.)

Nevertheless, despite all of this progress, CVD remains the number one cause of death in the United States, among both men and women.[9] Further progress will depend on addressing two interrelated problems. First, although the medical advances cited earlier have remarkably altered the course of CVD, they have also markedly increased the cost of cardiovascular health care, which has been

projected to triple between 2010 and 2030 (**Figure 58.5**).[9] Thus, efforts to reduce CVD costs have become an important driving force in health care policy. Second, although some risk factors for CVD have declined, three important risk factors have increased in frequency: obesity, sedentary behavior, and diabetes.

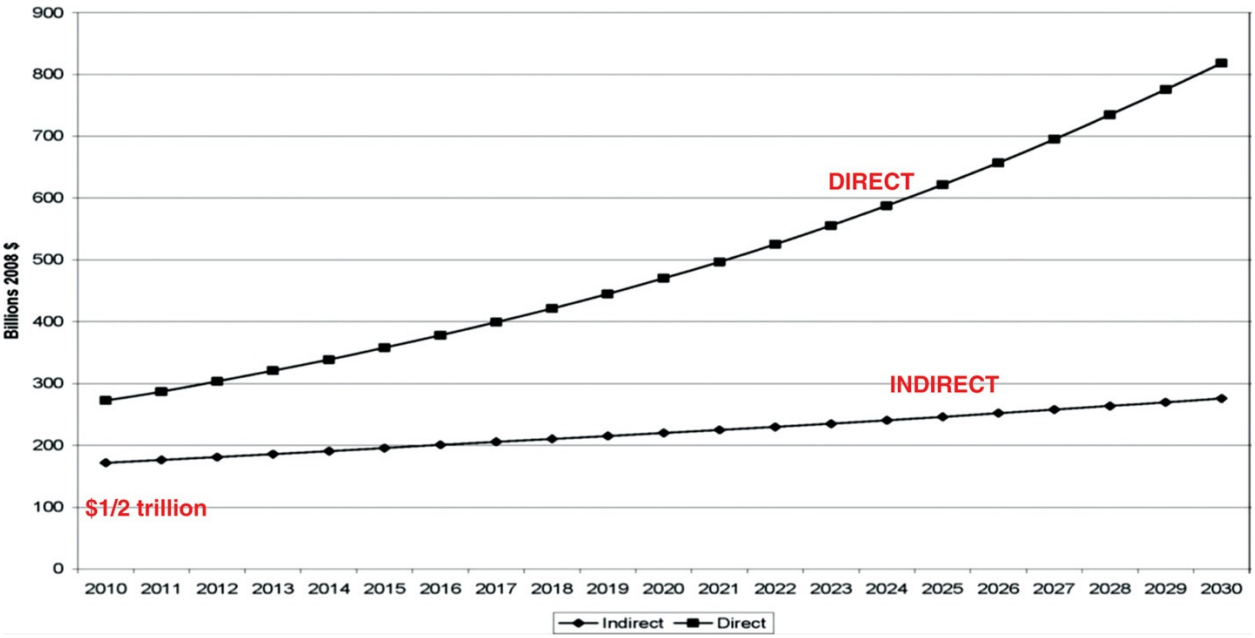

FIGURE 58.5 Projected direct and indirect medical costs for cardiovascular care in the United States between 2010 and 2030, according to an American Heart Association analysis. (From Heidenreich PA, Trogdon IG, Khaugov OA, et al. Forecasting the future of cardiovascular disease in the United States. A policy statement from the American Heart Association. *Circulation*. 2011;123:933-944.)

Since the 1980s, obesity has increased around the world in epidemic fashion. To exemplify the problem, the Centers for Disease Control and Prevention (CDC) maps the prevalence of obesity by state on a yearly basis. For instance, **Figures 58.6** and **58.7** show the U.S. obesity maps for 1990 and 2010. In 1990, not one state had a prevalence of obesity that was >15%.[10] By contrast, in 2010, a mere 20 years later, approximately one-quarter of states had obesity rates >30%. Today, approximately 30% of Americans are overweight and >30% are obese. It is widely recognized that this sudden rise in obesity is not due to genetic change, but rather to societal and environmental changes that have occurred since the 1980s, including such factors as eating more refined grains, changes in how food is processed, advertising of unhealthy foods, increasingly sedentary behavior, growth of convenience stores, increasing size of food portions, and decreasing sleep patterns. The poor diet of Americans is a large

part of this story. The American Heart Association has identified seven components of “ideal” cardiovascular health, on the basis of diet, physical activity, body mass index, abstinence from tobacco use, blood pressure, cholesterol, and blood glucose levels.[11] Of these factors, Americans’ poor diet is a particularly challenging one, with the vast majority of Americans scoring poorly on their diet metric.

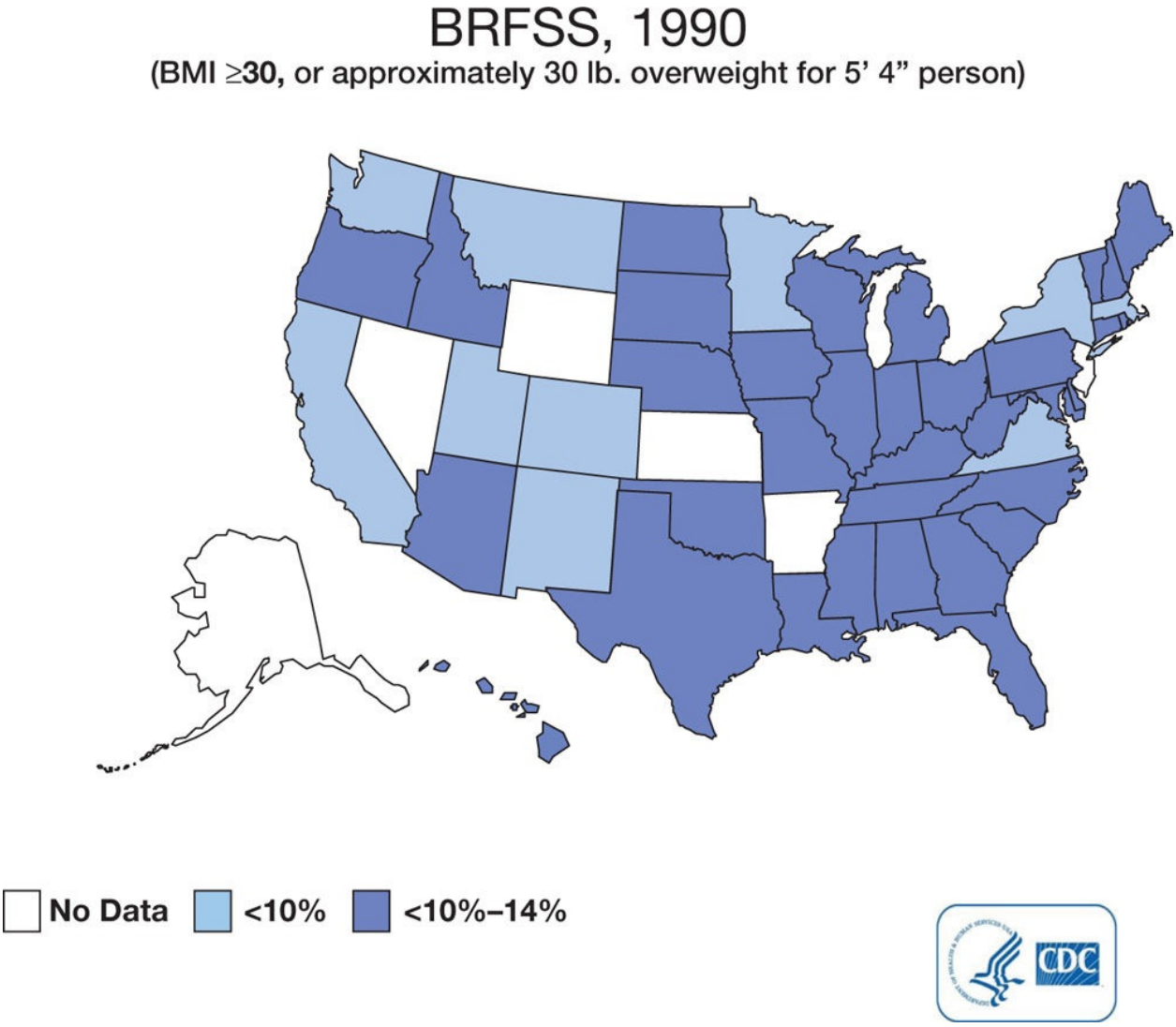

FIGURE 58.6 Prevalence of obesity in the United States, by state, according to a Behavioral Risk Factor Surveillance System (BRFSS) analysis in 1990. As shown on the color maps, no state exceeded a 15% prevalence of obesity.

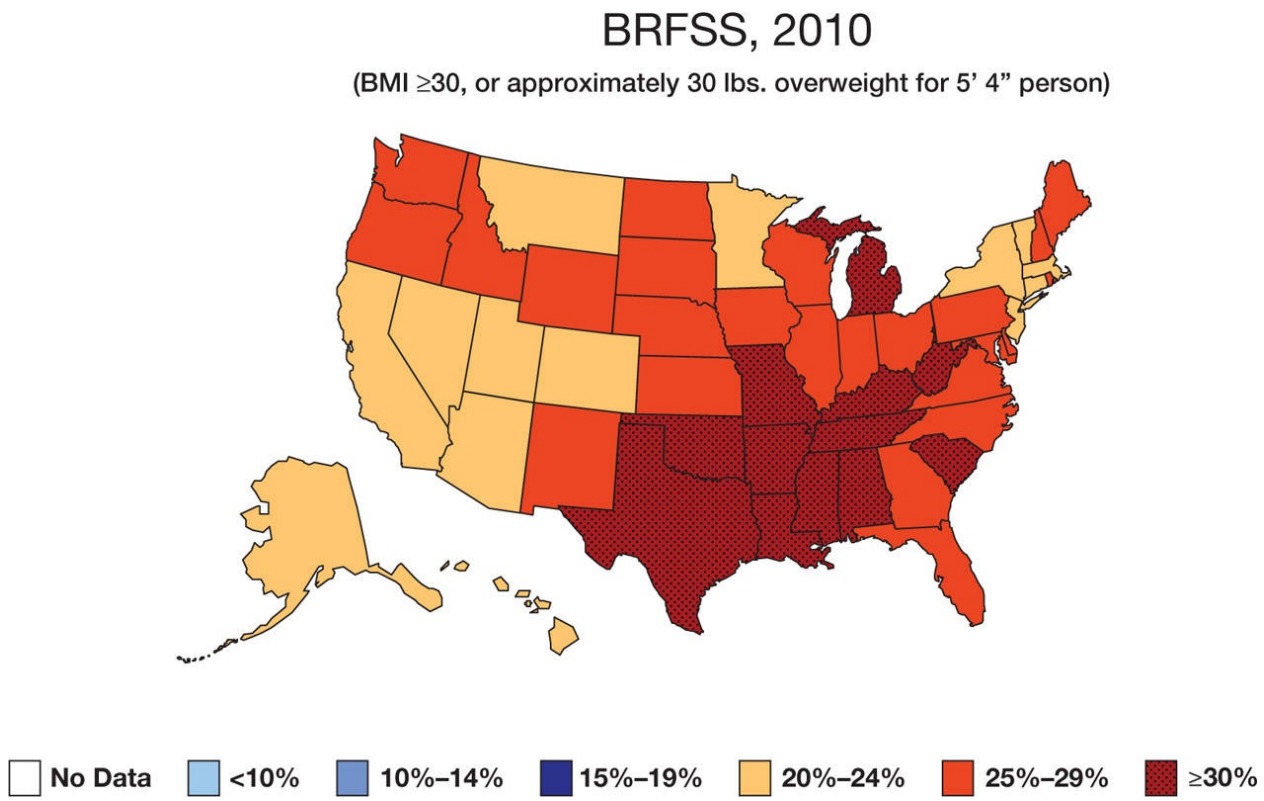

FIGURE 58.7 Prevalence of obesity in the United States, by state, according to a Behavioral Risk Factor Surveillance System (BRFSS) analysis in 2010. As shown on the color maps, 12 states exceeded a 29% prevalence of obesity.

Sedentary behavior has become normative in our society and may be increasing because of various societal trends. Excessive TV watching, increasing screen time, sedentary pastimes (eg, video games), a shift to more sedentary jobs,[12] convenience devices that have led to less physical activity at home (**Figure 58.8**),[13] less maternal time spent engaged in physical activity (**Figure 58.9**),[13] and a drop in physical activity among teenagers (**Figure 58.10**),[14] a time when physical activity habits are being set, are among the reasons for too little physical activity in today's society. Today's society has also become more fast paced and time pressed, resulting in greater difficulty for finding time to exercise among many people.

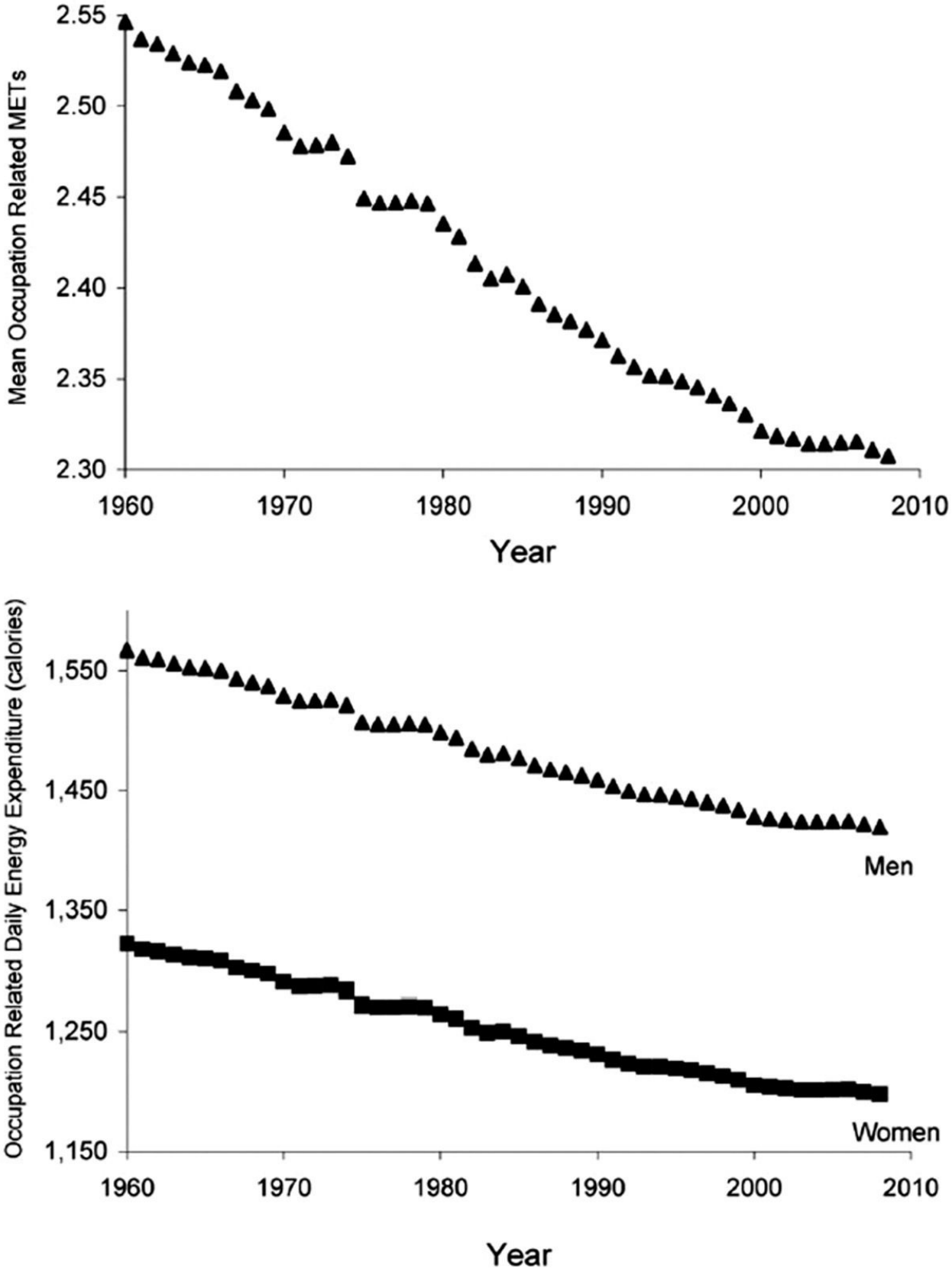

FIGURE 58.8 Decline in household levels of energy expenditure over a 45-year period. (From Archer E,

Lavie CJ, McDonald SM, et al. Maternal inactivity: 45-year trends in mothers' use of time. *Mayo Clin Proc*. 2013;88[12]:1368-1377.)

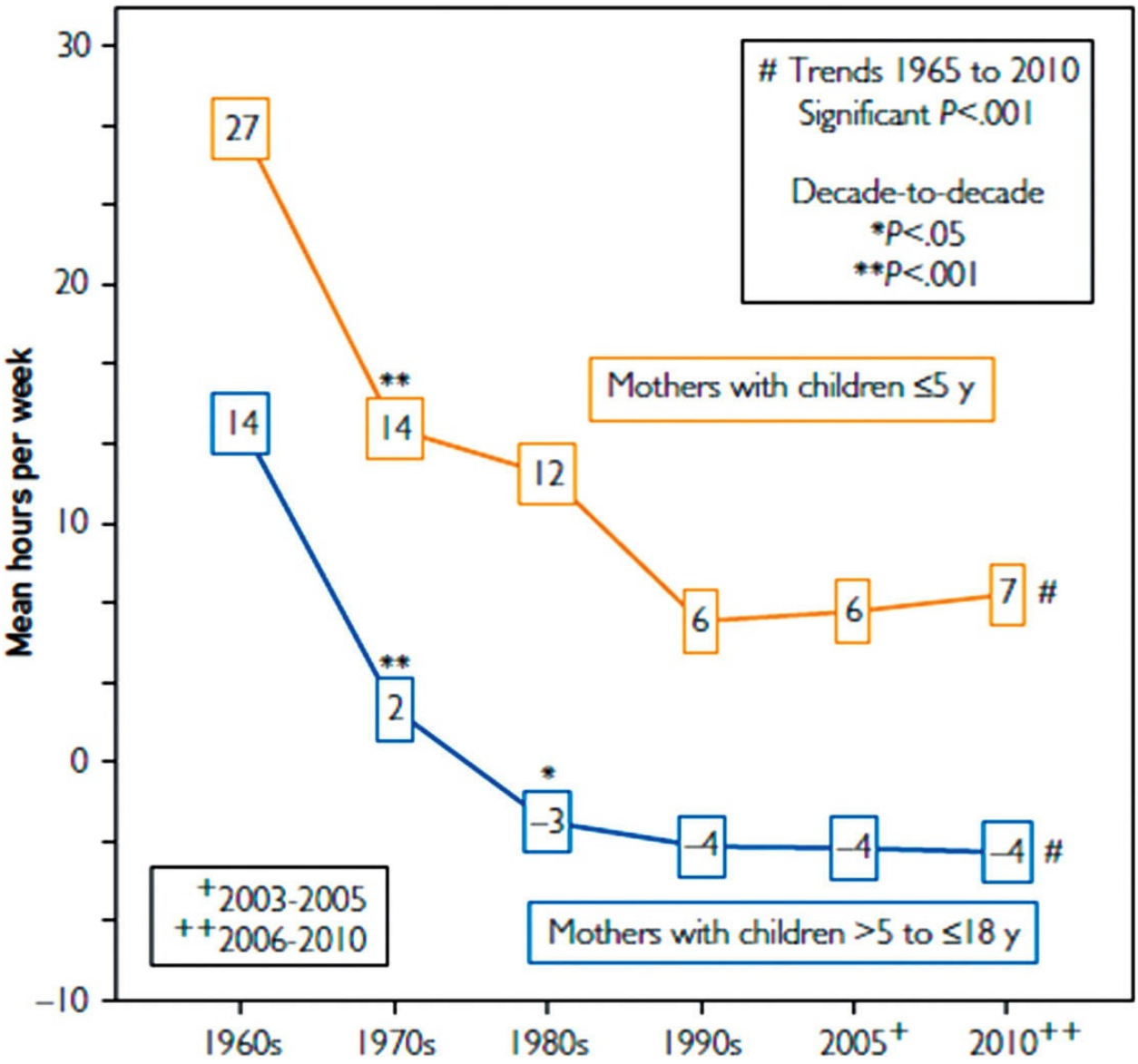

FIGURE 58.9 Time reallocation (mean hours per week spent in physically active behaviors minus hours per week spent in sedentary behaviors; numbers rounded to the nearest whole number) in US mothers, 1965–2010. Negative values denote more time spent in sedentary than in physically active behaviors. (From Archer E, Lavie CJ, McDonald SM, et al. Maternal inactivity 45-year trends in mothers' use of time. *Mayo Clin Proc*. 2013;88[12]:136-1377.)

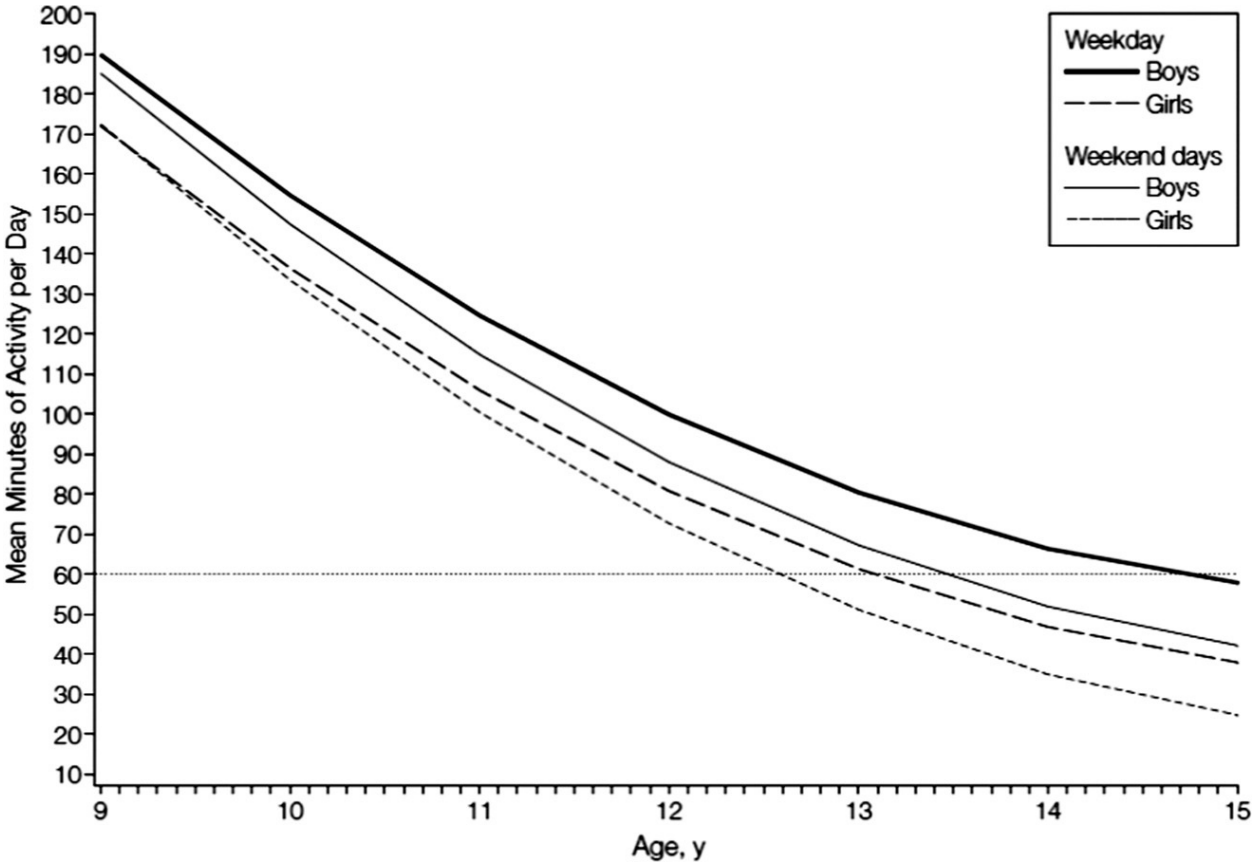

FIGURE 58.10 Daily minutes of physical activity for children between the ages of 9 and 15, for boys and girls, including weekdays and weekends. Note the marked decline in physical activity during the teenage years. (From Nader PR, Bradley RH, Houts RM, McRitchie SL, O'Brien M. Moderate-to-vigorous physical activity from ages 9 to 15 years. *JAMA*. 2008;300[3]:295-305.)

The result of poor nutritional habits, the rise of obesity, and the decline in physical activity have fueled an epidemic rise in diabetes (**Figure 58.11**), which now affects nearly 30 million Americans (approximately 9.3% of the population), and nearly 85 million Americans over the age of 20 are also considered prediabetic.[15] The presence of these three risk factors has helped to sustain our continued high rate of CVD, and these risk factors also lead to many other chronic medical conditions, as shown for obesity in **Figure 58.12**. It is estimated that the majority of chronic diseases could be obviated if people would adopt healthy lifestyle habits.[16,17] For this reason, increasing emphasis now needs to be placed on the promotion of healthy nutrition, exercise, and successful weight management.

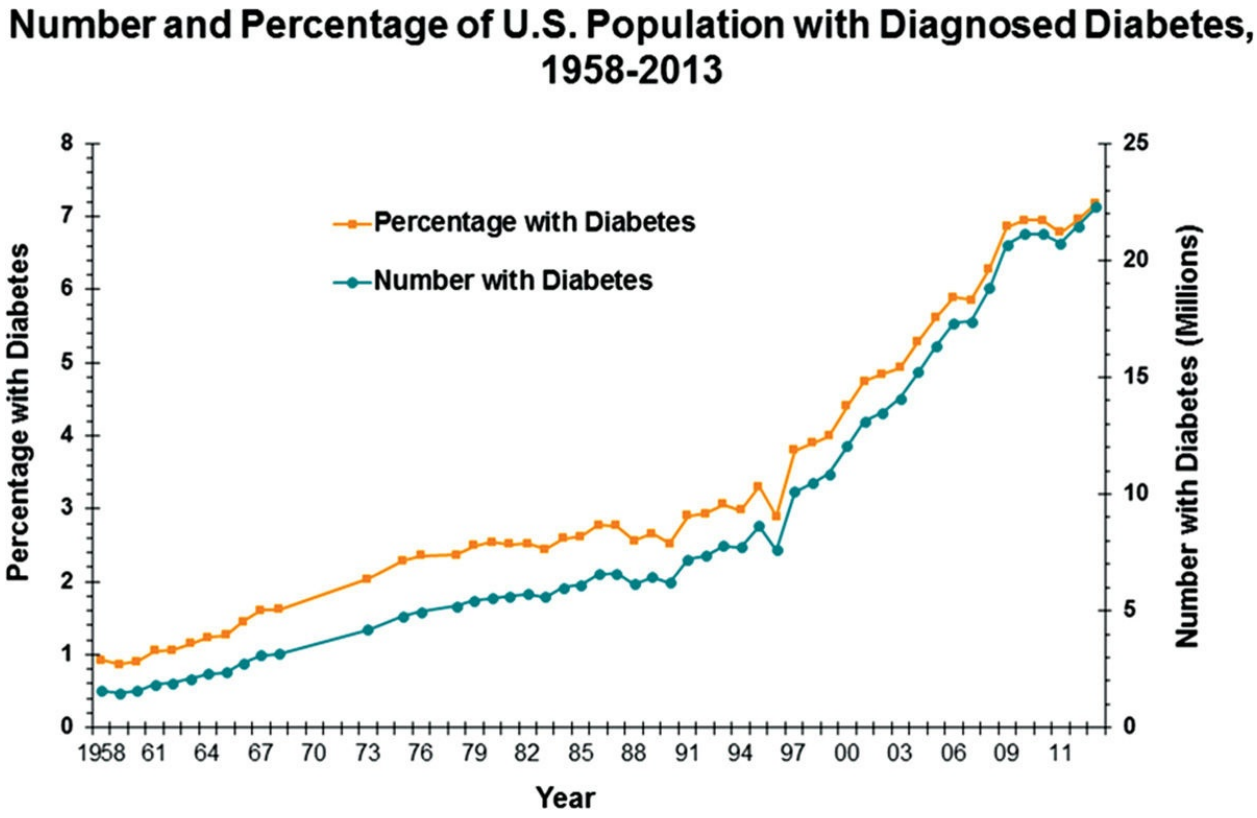

FIGURE 58.11 The number (blue) and percentage (gold) of Americans with diagnosed diabetes between 1958 and 2013. (From Centers for Disease Control and Prevention. National diabetes statistics report: estimates of diabetes and its burden in the U.S., 2014. Atlanta, GA: U.S. Department of Health and Human Services; 2014.)

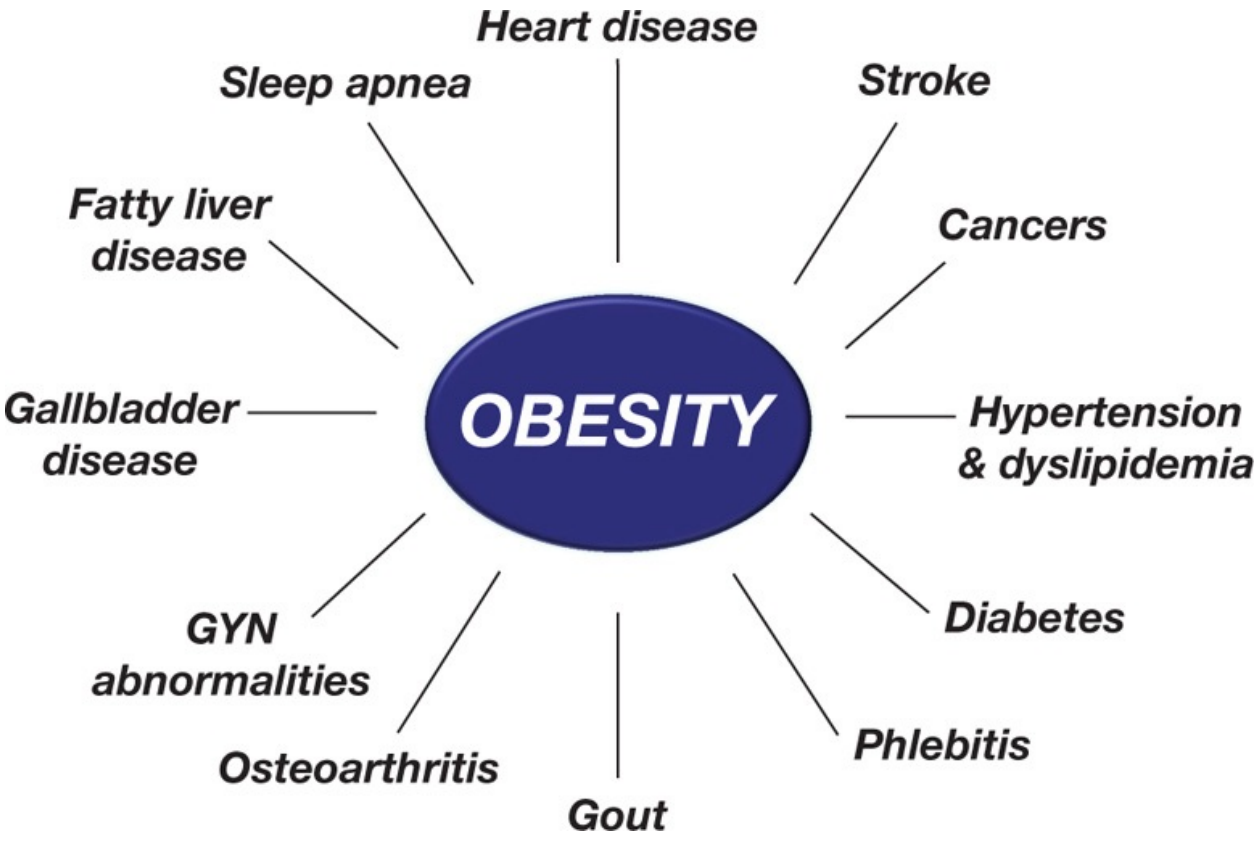

FIGURE 58.12 Medical conditions that are increased in frequency because of obesity.

However, changing negative health habits is not simple. Even adherence to medication change is often difficult for patients. Thus, a new field of behavioral cardiology has emerged, which is dedicated to studying the behavioral and psychosocial determinants of cardiac disease and the behavioral approaches to modifying negative health habits.[18,19] This field has made rapid strides in recent decades.[20] The field is based on a psychosocial model of health that recognizes that psychosocial factors both contribute to negative health habits and help cause disease directly through various pathophysiologic mechanisms. The field is also dedicated to the application of psychological principles for aiding patients to change their negative lifestyle behaviors.

To illustrate the development of behavioral cardiology and its application to patients following myocardial infarction, we present the story of David, a patient recovering from myocardial infarction, in the next three chapters. The first chapter deals with David's dietary management based on a new body of scientific literature that has identified which foods and dietary patterns are associated with better health and a reduced risk of CVD.[21] The second chapter focuses on the growing science of exercise physiology and epidemiology and

how it might apply to a patient like David.[22] The third chapter focuses on a dramatic growth in the field of behavioral cardiology: identification of the psychosocial risk factors that help contribute to the development of CVD and the increasing application of psychological principles for the management of negative health habits and psychosocial risk factors for CVD.[23] Together, these three chapters provide growing insights into the application of behavioral cardiology for the betterment of patients' lifestyles following the occurrence of cardiac events.

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59

Randy Cohen
Alan Rozanski

Nutrition and Weight Management in Cardiac Patients

David is a 52-year-old male who until recently felt well. One day, however, he developed sudden chest pain, prompting him to go to the local hospital. Much to his surprise, he was diagnosed with a heart attack and needed a coronary stent placed to open up a blocked artery. Although David had been told by his doctor for years to lose weight, change his diet, and start exercising in order to avoid developing medical conditions that can predispose to heart disease, he just didn't have the necessary time to commit to these lifestyle changes. Having three teenage children and a working wife, David had a very demanding job that required long hours, a long commute, and expectations to work from home. In David's mind, it was more important to work hard and provide for his family than to tend to these lifestyle changes, which he mentally thought of as something one does after retirement.

David's heart attack was real and life changing. As he sat recuperating in his hospital bed, he thought about all the things he could have done differently to avoid this major medical event that, for better or worse, has now affected his life and put a burden on his family, coworkers, and friends. Thankfully, David's hospitalization was unremarkable, and he was given an excellent prognosis. As he was being discharged to his home, David felt a deep sense of responsibility to himself and his family to make all the important lifestyle

changes necessary to regain his sense of health and vitality. The only problem was he didn't know where to start. As a first step, he established care with a local cardiologist and began asking questions: "How can I change my diet and poor eating habits? What is the most safe and effective way to lose weight? How do I initiate an exercise program? What is the best way to manage the stress in my life?"

David's first visit with the cardiologist started out with a general assessment of his health. Although he felt well, during the hospitalization David found out that he had mild hypertension and high cholesterol, both of which required medical therapy for adequate control. He was also told that he was overweight with a body mass index of 28 and was prediabetic with a fasting blood glucose of 110 mg/dL and a HbA1C of 6.2%. His blood pressure was controlled on medication, and his physical exam and ECG were unremarkable. David expressed his reluctance to take medications and asked if he could manage his heart condition with only diet and exercise. His cardiologist explained that the medications were essential to stabilizing his condition after the heart attack and preventing recurrent problems from developing in the future. In fact, research indicates that many of the medications David was taking can lower his risk of a recurrent heart event by 20% to 30%. That being said, however, his cardiologist went on to explain that medications can only do so much and that changing his lifestyle would be the only way to achieve and maintain health and vitality.

After a prolonged discussion, David and his cardiologist agreed to focus first on diet and nutrition. He was referred to a local dietitian, who sent him a primer on nutrition before his first visit, with copies of articles that had been extracted for those who wanted to delve more closely into nutrition.

THE DIET CONUNDRUM

David took on his nutrition packet as a homework assignment. He quickly became aware of how vast the topic of nutrition is and how much information is out there. In an age when dietary advice is dispensed through so many sources, it should be easy for patients to know what constitutes a good diet. However, the easy access to information is also often a hindrance: much contradictory information is often provided. For years, diet information was based on scant data or poorly designed nutritional studies. But over the last 15 to 20 years, a

new evidence-based science of nutrition has emerged. In addition, an evidence-based set of principles have also emerged that help guide patients on the psychological barriers and approaches that can be used to implement a new diet.

WHY FOCUS ON NUTRITION?

At the beginning of his first session with the dietitian, she asked David why he was interested in meeting with her. David told her he had been frightened by his heart attack and wanted to do everything he could to improve his health. To reinforce the issue, the dietitian asked David what the potential health benefits of a good diet were. David answered that they included rising good cholesterol, decreasing bad cholesterol, preventing heart disease, and preventing obesity.

"Very good" responded the dietitian. "That is all correct. But the effects of diet on our physiology are actually even more extensive than that." She then showed him a diagram (**Figure 59.1**) that revealed the many ways in which the food we eat can affect our physiology. Besides the factors that David mentioned, these include effects upon our blood pressure, increase or decrease in systemic microinflammation, endothelial health of our blood vessels, and many other factors. She explained that people do not sufficiently realize that so much of what we can eat can affect our health either for the better or for the worse. Over time, the effects can be powerful. Intrigued, David asked her to explain more.

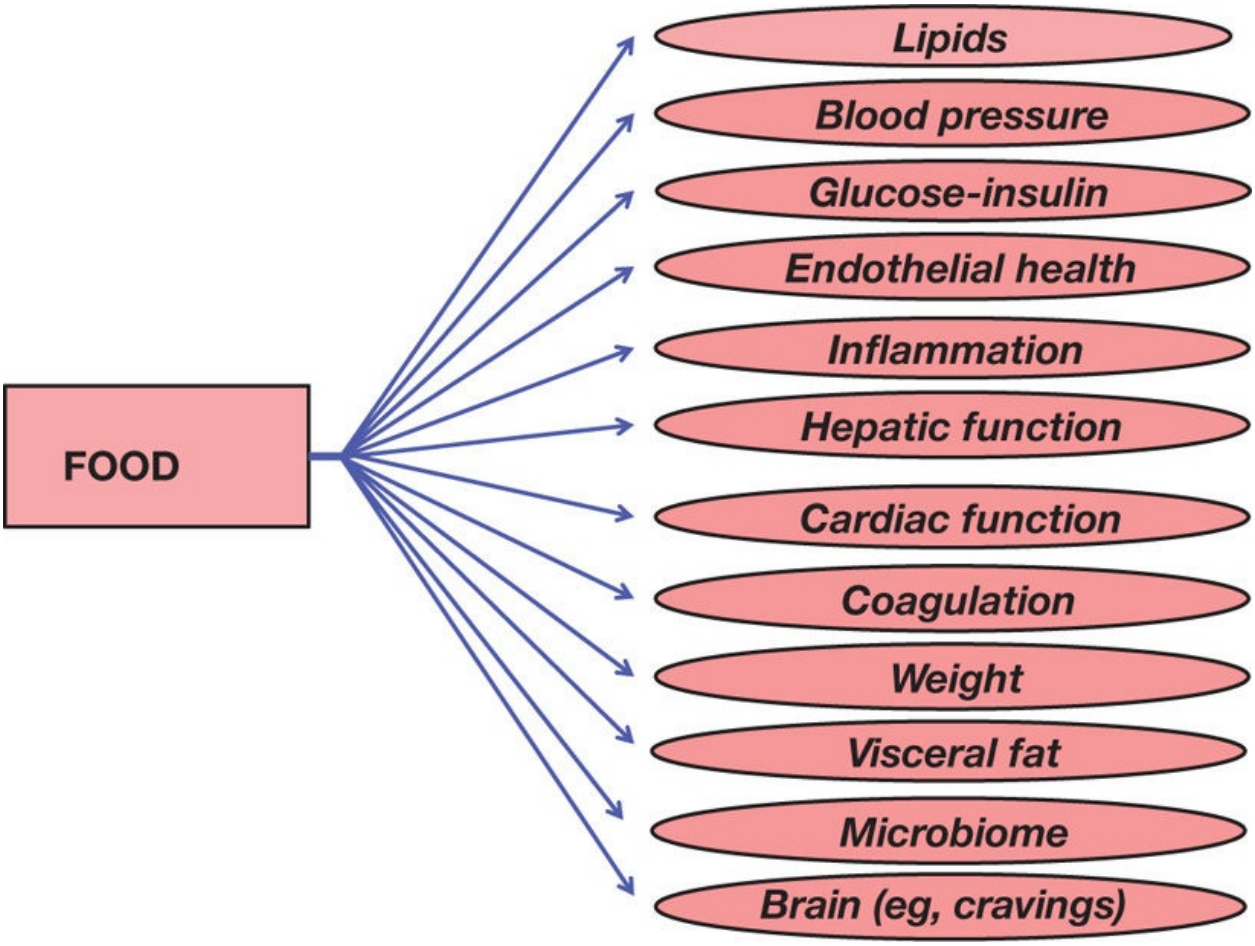

FIGURE 59.1 Illustration of how the food we eat impacts diverse bodily functions.

UNDERSTANDING THE BASICS OF NUTRITION

The dietitian then asked David if she could review with him some basic facts about nutrition. She understood that David did not have a science background, but there were a few central principles that she thought David and everyone should understand. She first discussed the concept of calories. She explained that our body requires a certain amount of energy each day to perform all of its basic functions—eating, working, playing, and even breathing. Energy for these basic activities is expressed in the form of "calories." She told David that in his case, on the basis of his age, height, and weight, he required about 2,000 calories per day in order to maintain his weight. If he consumed more than this (ie, more energy than his body needs to perform his daily activities), this would place him in "positive energy balance" and he would gain weight. If he consumed less than

this (ie, less energy than his body needs to perform his daily activities), he would be in “negative energy balance” and would begin to lose weight. She explained that food (in any form) represents energy (calories).

UNDERSTANDING THE MAJOR DIETARY COMPONENTS

She then introduced the topic of major dietary components, or what we term *macronutrients*and *micronutrients*. She explained that most people go straight to asking what diet or dietary pattern they should be on, but she felt understanding this first was essential.

There are three main macronutrients: fat, carbohydrate, and protein. The “typical” American diet is comprised of about 20% protein, 30% to 35% fat, and 45% to 50% carbohydrate. Of note, whereas the protein content of various diets remains relatively fixed, the fat and carbohydrate content can fluctuate greatly. In fact, it is the variation in fat and carbohydrate that often differentiates various popular diet patterns, as shown in **Table 59.1**. The dietitian then began to explain these macronutrients in more detail, beginning with fats.

TABLE 59.1 Types of Diets

	LOW-/VERY LOW–FAT DIETS (eg, ORNISH)	MODERATE-FAT DIETS (eg, MEDITERRANEAN, DASH)	HIGH-FAT DIETS (eg, ATKINS)
Fat	11%–19%	20%–40%	50%–55%
Carbohydrate	>65%	55%–60%	<25%
Protein	10%–20%	15%–20%	25%–30%

DIETARY FATS

The dietitian explained that there are three basic types of fat, which can be distinguished biochemically, according to the number of carbon–carbon double bonds that are present in their chemical structure. Saturated fats have zero double bonds, monounsaturated fats have one double bond, and polyunsaturated fats have two or more double bonds. Polyunsaturated fats are broadly categorized as either omega-6 or omega-3 fatty acids. Another type of fat, trans fat, is formed by taking a polyunsaturated fat and converting it through a process called hydrogenation into hydrogenated fat.

All fats contain 9 calories of energy per gram of fat consumed. By comparison, carbohydrates and proteins contain only 4 calories of energy per gram. Thus, fat represents the most energy-dense form of food.

The dietitian then showed David a chart that contained examples of saturated, monounsaturated, and polyunsaturated fats **(Table 59.2)**.

TABLE 59.2 Types of Fat

SATURATED FATS	MONOUNSATURATED FATS	POLYUNSATURATED FATS
Palmitic (palm oil, meat)	Oleic and palmitoleic (nuts, olives, avocado)	Omega-6 Linoleic (soybean, corn, and safflower oils)
Myristic (dairy foods)		Arachidonic (meats)
Lauric (coconut oil, palm kernel oil)		Omega-3 Alpha linolenic (soybean and canola oils, nuts, and flaxseed)
Stearic (meat, cocoa butter)		DHA/EPA (fatty cold water fish—trout, herring, salmon, sardines)

With this knowledge in hand, the dietitian then explained that on the basis of considerable scientific study, we now make a distinction between fats that are healthy, neutral, and unhealthy. The healthiest fats are polyunsaturated fats. Lipids have been most studied over the years for their effect on serum lipid values (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and triglycerides), but the analysis of lipids is only one important effect of lipids. For example, not only do foods high in polyunsaturated fats lower LDL cholesterol and triglycerides and raise HDL, but they can also lead to improvement in blood pressure and endothelial function and reduce inflammatory biomarkers in the body. Monounsaturated fats also have beneficial effects on health. These fats have a neutral or even lowering effect upon total and LDL cholesterol, while having a lowering effect on triglycerides and a raising effect on HDL. At the other end of the spectrum are the trans fats, which are particularly atherogenic. Trans fats are known to raise total and LDL cholesterol as well as promote oxidation of lipids, a key step in atherosclerosis. These fats have strong and consistent associations with cardiovascular disease (CVD). Although recently banned by the Food and Drug Administration (FDA), trans fats have historically been present in packaged and processed foods including frozen pizza, pastries, deep-fried foods, and stick margarine.

After asking David if he had any further questions about fat, the dietitian then turned to the second major macronutrient: carbohydrates.

CARBOHYDRATES

Carbohydrates in their most basic form are sugars. Carbohydrates come in various forms ranging from simple sugars such as sucrose (table sugar), lactose (milk sugar), and fructose (fruit sugar), to more complex forms such as starch and fiber. As with fats, the quality of carbohydrates in one's diet is related to one's overall health. A complete understanding of what constitutes healthy carbohydrates centers around a variety of factors, including the glycemic response to digestion, the degree to which the carbohydrate is processed, and its fiber content.

The Glycemic Response to Digestion

The ease with which carbohydrates are broken down by the body into simple sugars often determines how it will affect blood sugar levels. For example, refined starches (eg, white bread, white rice, potatoes) can be quickly broken down to sugar, which can lead to spikes in blood sugar levels. Alternatively, unrefined carbohydrates rich in fiber (eg, whole-grain breads, brown/multigrain rice) take much longer to break down, thus leading to a slow and steady rise in blood sugar **(Figure 59.2)**.

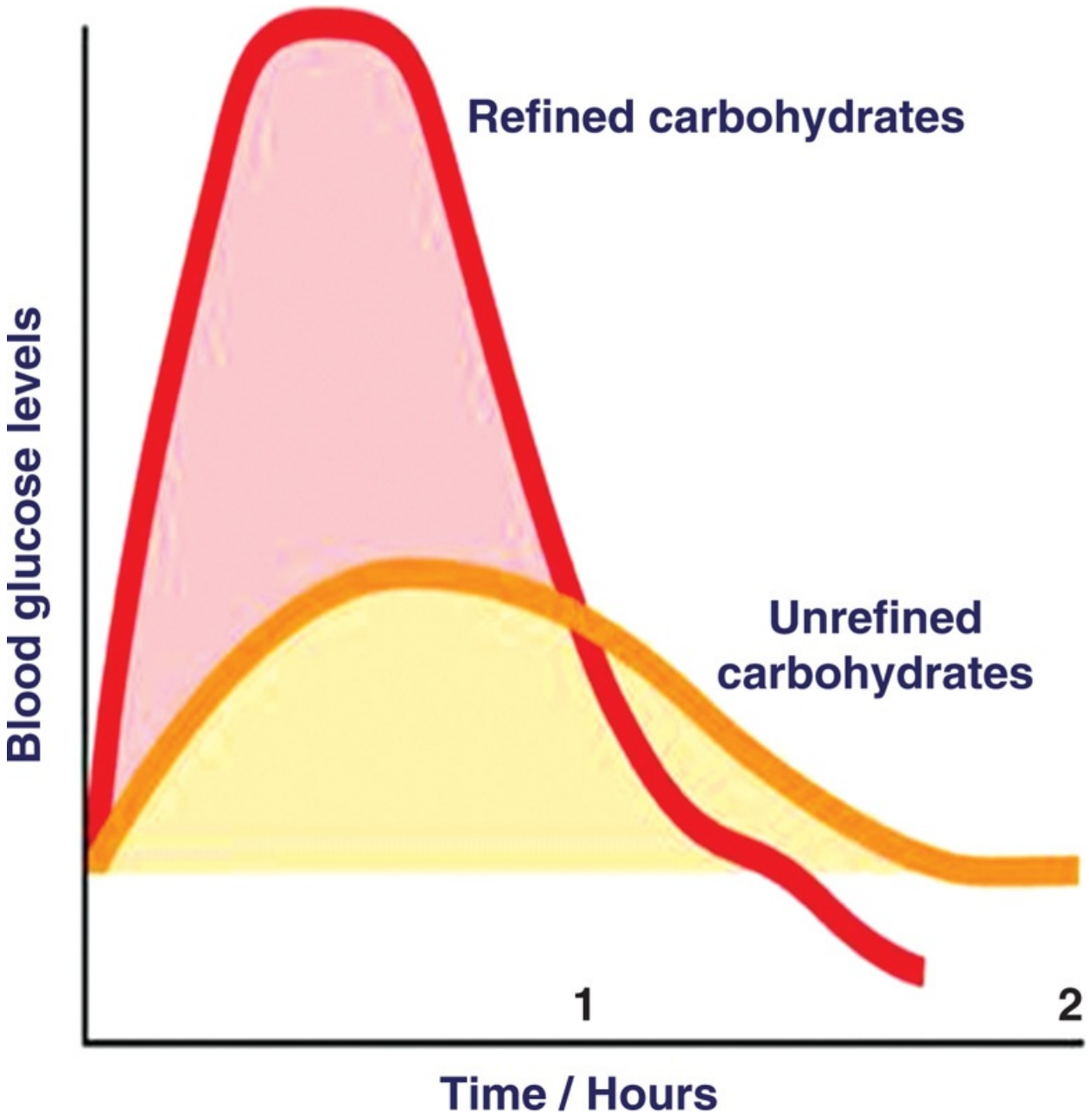

FIGURE 59.2 Impact of carbohydrate quality on blood glucose levels. Highly refined carbohydrates cause large spikes in blood glucose levels over a short period of time, often leading to periods of relative hypoglycemia. Unrefined carbohydrates, however, cause a slow and steady rise of blood glucose levels followed by a gradual decline to baseline. GI, glycemic index.

Among the dietary sugars, it is important to distinguish between those sugars consumed in their natural form, such as lactose or fructose, and those that are added to food during cooking, processing, or packaging. Sugars such as lactose and fructose, in moderation, can be a healthy part of one's diet. Milk contains not only lactose, but also protein, calcium, and vitamin D. Similarly, fruits

contains not only fructose, but also important vitamins, minerals, and fiber. On the other hand, added sugars, which are sugars that are added to foods to enhance flavor (eg, pastries, candy, soda, fruit juice, or other sugary drinks), have been consistently linked to weight gain, diabetes, and even CVD.

The Degree to Which the Carbohydrate is Processed

Similar to the differences between added sugars and natural sugars, there are important differences in how grains are prepared for consumption. Although wheat is among the more popular types of grains, there are, in fact, many other types of grains (**Table 59.3**). In its most basic, natural form, a grain of wheat is composed of the bran, endosperm, and germ (**Figure 59.3**).

Table 59.3	Examples of Whole Grains
Barley	Quinoa
Buckwheat	Rye
Corn	Spelt
Farro	Wheat
Millet	Wild rice
Oats	

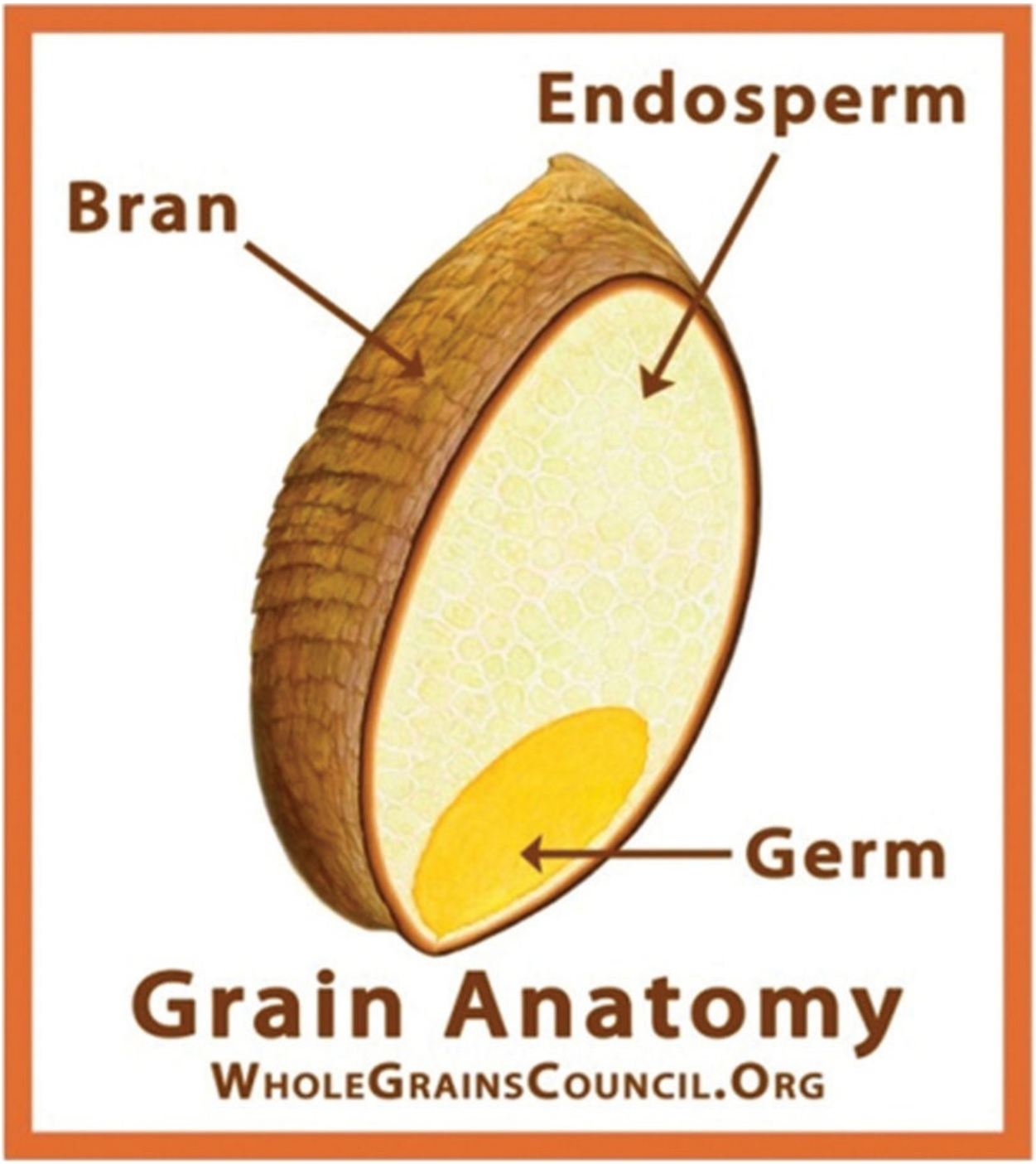

FIGURE 59.3 Anatomy of a grain with an outer coating of bran, a middle endosperm, and the germ at the core.

Diets containing excessive refined grains have been linked to diabetes, high triglycerides, metabolic syndrome, weight gain, and CVD.

When a food product contains whole-grain wheat, for example, it refers to the entire grain (bran, endosperm, and germ). Food products containing whole

grains (unrefined grains) are always preferred because they contain fiber (bran), starch (endosperm), and vitamins, protein, and fat (germ). Unfortunately, over the years whole grains have undergone extensive processing to promote mass production and prolonged shelf life. During the refinement process, whole grains are often stripped of the fiber-rich bran, and sometimes the germ, bleached to achieve a more visually appealing white color, and enriched with artificial forms of fiber, vitamins, and minerals. These refined grains are very easily digested, often leading to spikes in blood sugar.

Fiber Content

Diets rich in fiber can help lower cholesterol, blood sugar, and blood pressure, while helping increase satiety. It is recommended that most individuals consume diets with at least 25 g of fiber per day. Unfortunately, the “typical” American diet falls quite short of this recommendation. Good sources of fiber include (but are not limited to) whole grains such as whole wheat, brown/multigrain rice and quinoa, vegetables, fruit with the skin, nuts, and legumes.

In summary, although there is no single parameter that best characterizes carbohydrate content, attempting to minimize refined grains, added sugars, and starchy foods, such as russet or white potatoes, is highly recommended. Each of these foods produces a sharp rise in blood glucose and insulin, leading to multiple adverse effects, including a craving for more food.

Another useful index of carbohydrate quality is the total carbohydrate-to-fiber ratio (gram/serving). The lower the ratio, the healthier the carbohydrate. Generally, a ratio of <10:1 is preferable. **Figure 59.4** illustrates the important differences in fiber content (and the carbohydrate-to-fiber ratio) between two similar honey-flavored cereals.

Nutrition Facts
Serving Size 3/4 Cup (32g)

Amount Per Serving
Calories 120 Calories from Fat 15

	% Daily Value*
Total Fat 1.5g	2%
Saturated Fat 0g	0%
Trans Fat 0g	
Polyunsaturated Fat 0.5g	
Monounsaturated Fat 0.5g	
Cholesterol 0mg	0%
Sodium 85mg	4%
Potassium 90mg	3%
Total Carbohydrate 26g	9%
Dietary Fiber 4g	15%
Soluble Fiber less than 1g	
Insoluble Fiber 3g	
Sugars 5g	
Protein 3g	

Vitamin A 0% • Vitamin C 0%
Calcium 0% • Iron 4%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs:

	Calories	2,000	2,500
Total Fat	Less than	65g	80g
Sat. Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Potassium		3,500mg	3,500mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Nutrition Facts
Serving Size: 3/4 cup (28g)

Amount Per Serving
Calories 110 Calories from Fat 14

	% Daily Value*
Total Fat 1.5 g	2%
Saturated Fat 0 g	0%
Trans Fat 0 g	
Cholesterol 0 mg	0%
Sodium 190.12 mg	8%
Potassium 115.08 mg	3%
Total Carbohydrate 21.65 g	7%
Dietary Fiber 1.99 g	8%
Sugars 9 g	
Sugar Alcohols	
Protein 3 g	
Vitamin A 500.08 IU	10%
Vitamin C 5.99 mg	10%
Calcium 99.96 mg	10%
Iron 4.5 mg	25%

FIGURE 59.4 Nutrition fact sheets for two different brands of honey-flavored cereal. Although very similar products, note the differences in carbohydrate quality as demonstrated by the varying fiber content and the total carbohydrate-to-fiber ratio.

PROTEIN

Protein is an essential component of our diets, required for normal growth, development, and metabolism. In broad terms, protein can originate from either plant or animal sources, as shown in **Table 59.4**. Although animal meat is a good source of protein, important differences in health outcomes exist. For example, poultry has a relatively health-neutral effect, whereas processed meats are consistently associated with negative cardiovascular outcomes. Unprocessed red meat, however, is more controversial. Some studies have found similar health-damaging effects as processed meat (albeit less damaging), whereas other studies have found relatively neutral effects.

TABLE 59.4	Sources of Protein
PLANT SOURCES	**ANIMAL**
Nuts	Meat (eg, beef, poultry, pork)
Whole grains	Dairy (eg, cheese, milk, yogurt)
Legumes	Fish
	Eggs

MINOR DIETARY COMPONENTS: MICRONUTRIENTS

After this discussion, David felt like he had a basic understanding of macronutrients. He then asked, “What about things like salt, vitamins, and minerals, and where do they fit in?” To save time, the dietitian focused only on a few key points in response to David’s question. She stated that vitamins, minerals, and trace elements are considered minor dietary elements (ie, micronutrients), which are essential components of any diet, but present in small quantities. Among them, sodium is a mineral of considerable importance because it is required for normal cellular function throughout the body. Abundant in the food supply, sodium is found mainly in the form of sodium chloride (salt). According to national surveys, the average American consumes about 3,400 mg of sodium each day. By contrast, the American Heart Association recommends consuming 1,500 mg of sodium each day. Although most people think of salt as a seasoning, which is sprinkled on to foods after cooking to enhance flavor, by far the more common source of salt is in prepacked and processed foods, as well as fast food and chain restaurant foods. Although there is some controversy in the medical literature as to whether or not too much dietary salt can cause high blood pressure, there is universal agreement that the typical American diet contains excessive salt. Among individuals with high blood pressure, or other cardiac conditions, excessive dietary salt can lead to elevations in blood pressure, retention of water, and even congestive heart failure.

Besides her comments on salt, the dietitian raised the issue of supplements. These represent a broad category of substances that are taken to enhance one’s usual dietary intake and promote health and wellness. Examples include

vitamins, minerals, trace elements, herbs, and other substances. In general, it is always better to consume vitamins, minerals, and trace elements as a part of a healthy balanced diet, rather than supplements. Should additional supplementation be necessary for medical reasons, a health care professional should be consulted. If one is interested in taking supplements to promote health and wellness, it is still useful to consult with a health care professional first to ensure it is appropriate and will not interact with other medications.

A HISTORIC CHANGE IN OUR UNDERSTANDING OF NUTRITION

After completing their session, the dietitian told David to review his notes before the next session and come back with any questions. She said she would ask him to summarize his understanding at the beginning of the next session. When they next met, David remarked that not only he, but also his family and friends had presumed that too much fat was not good. In fact, many of his friends were currently on a high-carbohydrate/low-fat diet. Why were the recommendations so different now?

The dietitian explained. In the 1940s and 1950s, researchers working with the Framingham Heart Study discovered an association between various health conditions and heart disease. Among these "risk factors" were conditions such as high blood pressure, smoking, and high blood cholesterol. Later in the 1960s, work by Drs. Keys and Hegsted established a link between dietary saturated fat and high blood cholesterol. Subsequent to this, there were a number of large-population studies that confirmed the relationship between dietary saturated fat, high blood cholesterol, and heart disease–related events. It was this groundbreaking series of work that led to large-population–level public health campaigns against diets high in total and saturated fat.

Over the next 30 to 40 years, dietary fat became a major target for the primary and secondary prevention of CVD. In response to public and private sector efforts to promote lower-fat diets, the U.S. population effectively lowered its consumption of total and saturated fat. The lower U.S. consumption of fat was balanced by an increased consumption of carbohydrates (**Figure 59.5**). Over the same general period that the U.S. population was lowering their consumption of saturated fat and increasing their consumption of carbohydrates, epidemiologic studies indicated a rising prevalence of obesity (**Figure 59.6**) and diabetes

mellitus. Further examination of these trends revealed a higher consumption of refined grains and lower consumption of fiber (**Figure 59.7**).

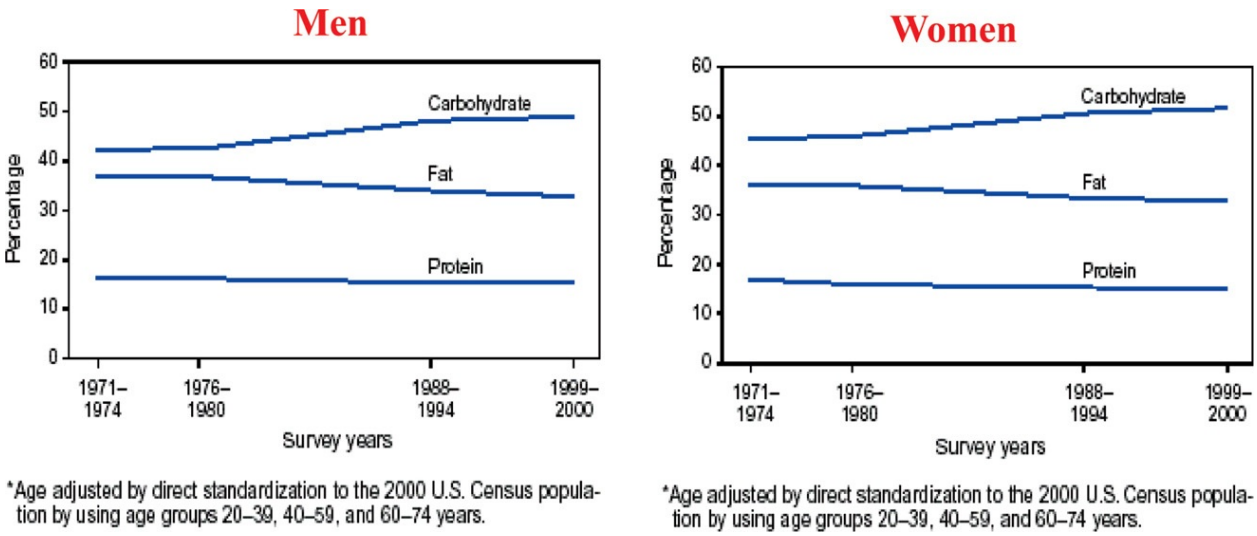

FIGURE 59.5 Survey data illustrating how the average fat content of the U.S. population declined over time, however, at the expense of a greater proportion of carbohydrates.

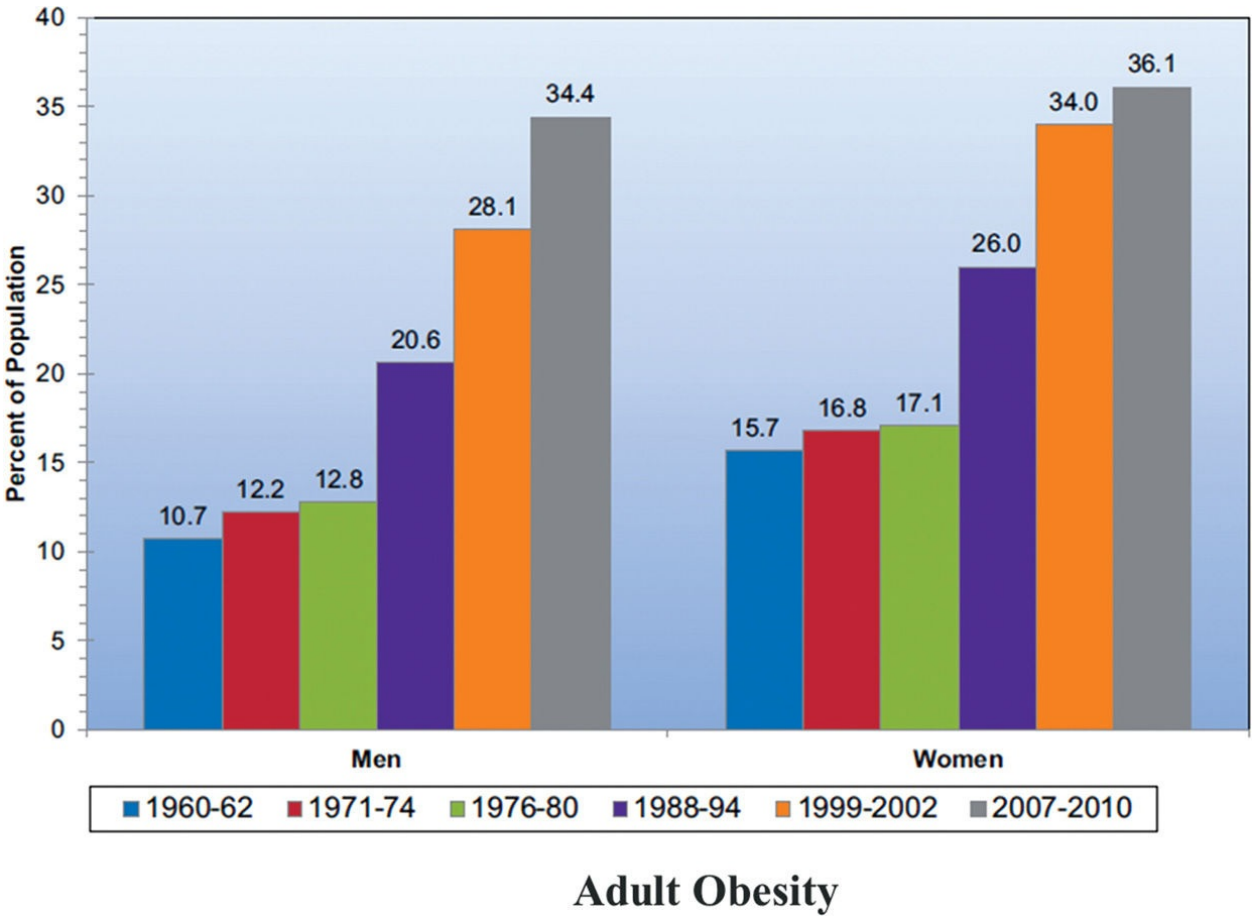

FIGURE 59.6 Survey data illustrating how the U.S. population has become more obese over time.

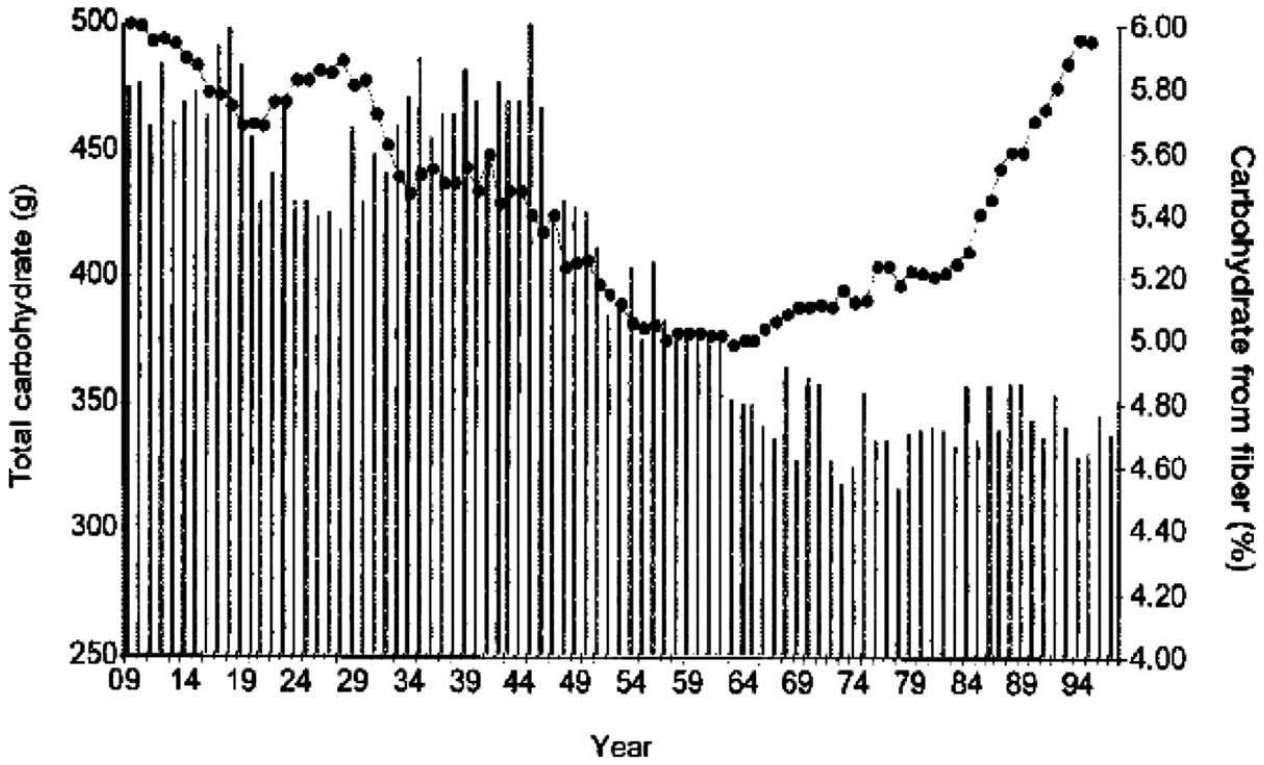

FIGURE 59.7 Survey data illustrating how the carbohydrate quality of the U.S. diet has changed over time. Although carbohydrate consumption was high in the early 1900s, most of it was high-quality carbohydrates rich in fiber. From the 1960s to 1990s, carbohydrate consumption was on the rise, but fiber consumption remained low, indicating that Americans were consuming poorer quality carbohydrates.

Thus, in our efforts to lower our collective risk of heart disease by reducing our intake of dietary saturated fat, we increased our consumption of highly processed, refined (poor-quality) grains, with the net effect of higher rates of obesity, diabetes mellitus, and the metabolic syndrome.

Subsequently, more authoritative studies revealed that there was no significant association between saturated fat and important health outcomes.[1] In related work,[2] investigators examined not only the CV effects of a reduced saturated fat diet, but also what macronutrient was being substituted for the fat. This was amplified by a study examining over 120,000 patients over 24 years, in which CVD risk was assessed according to the macronutrient that was being substituted for dietary fat.[3] The studies were concordant for observing the following:

- When dietary saturated fat was replaced with refined grains, CVD risk either remained similar to or was increased compared with that of saturated fat.
- If dietary saturated fat was replaced with whole grains or high-quality fats (ie, polyunsaturated fat), CVD risk was reduced.

Thus, simply reducing the saturated fat content of our diets is not sufficient,

the dietitian said. Rather, we must replace this fat with higher quality fats and/or higher quality carbohydrates to effectively reduce our risk of CVD.

At this point, the dietitian introduced a diagram summarizing what she had covered with David (**Figure 59.8**). Foods can be categorized as healthy to unhealthy on the basis of hard scientific evidence finding consumption of individual foods to cause heart disease, diabetes, stroke, and other adverse outcomes. The healthiest foods include fruits, vegetables, whole grains, and legumes. The unhealthiest foods include processed meat, refined grains, and added sugars. The neutral zone foods are to be consumed in moderation. These include milk, cheese, eggs, poultry, butter, and red meat (unprocessed).

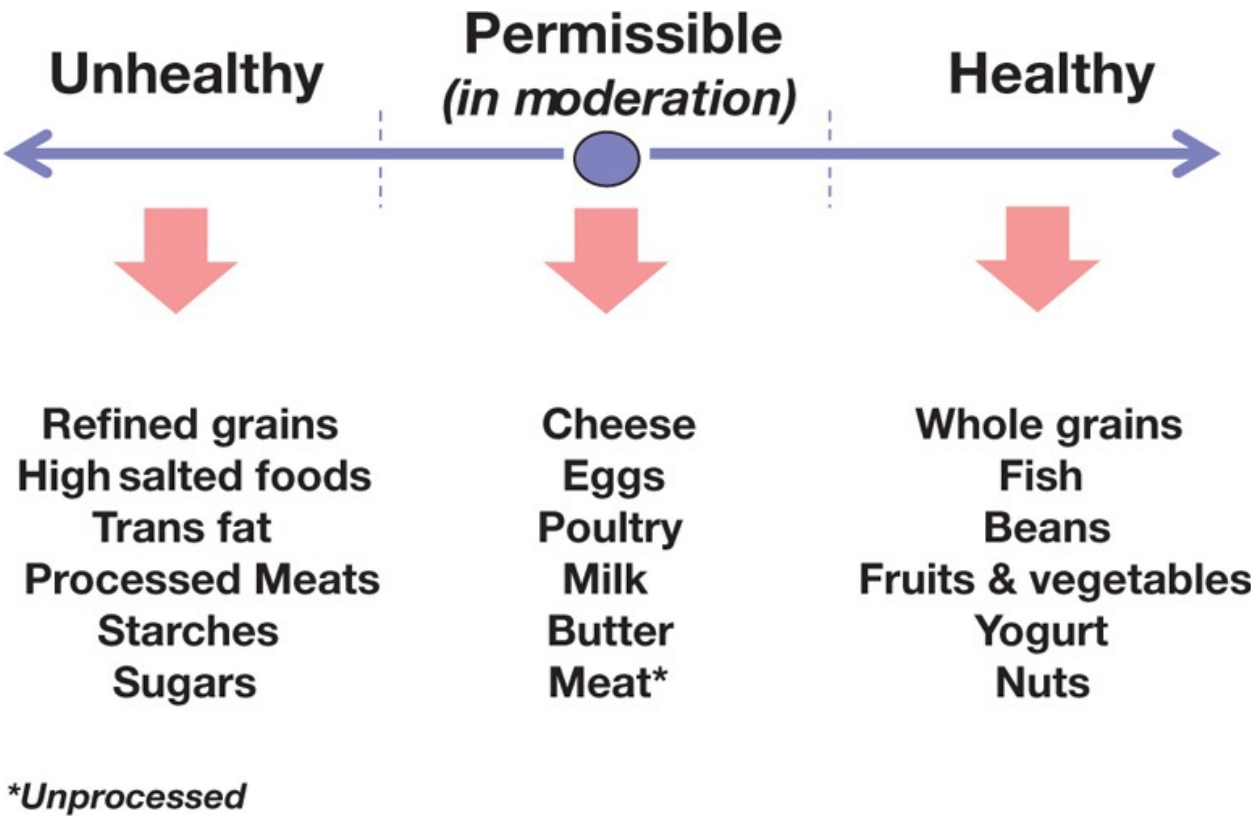

FIGURE 59.8 Illustration of how the food we eat lies along a spectrum from unhealthy to healthy. Dietary intake should be focused on those foods at the far right, with moderate consumption of foods in the middle and little consumption of foods at the far left.

FOCUSING ON DIETARY PATTERNS RATHER THAN SPECIFIC NUTRIENTS

At this point, the dietitian felt ready to establish a specific diet plan with David. She had just covered with him what foods are known to increase and decrease health risk. However, her training had taught her that most individuals follow a dietary pattern rather than focusing on any particular food group. She now decided to broach this subject with David.

She explained to David that the study of what constitutes healthy diet patterns has been an important breakthrough in nutritional science. Important insights have come from the use of food questionnaires, which inquire about the frequency and quantity of different foods (anywhere from 50 to 150 different foods) consumed over the prior week to month. Using a statistical method called principal components analysis, investigators have been able to ascertain which foods are consumed in high versus low quantities by a given population of subjects. This then allows for different dietary patterns that can be extrapolated and correlated with various clinical outcomes (eg, biomarkers, CVD, mortality).

The consistent finding from these epidemiologic cohort studies is that diets rich in fruits, vegetables, whole grains, legumes, high fiber, fish, lean meats, moderate alcohol, and low-fat dairy are consistently associated with a reduced risk for CVD.

Conversely, diets high in red and processed meat, refined grains, processed foods, soda, and other added sugars are associated with an increased risk for CVD.

Further study revealed that the “heart healthy” dietary pattern previously noted is most consistent with the diet consumed in most parts of the Mediterranean region—hence the term*Mediterranean diet*.

Importantly, a number of studies have since confirmed the beneficial effects of a Mediterranean-style diet, including a lower risk of heart disease, diabetes, cancer, and all-cause mortality.[4–6] **Figure 59.9** is an example of one of the landmark studies showing the reduction in cardiovascular events with a Mediterranean diet. As a result of this consistent body of literature, the FDA now recommends a similar (Mediterranean-style) diet pattern in the 2015 Dietary Guidelines for Americans.[7] It is important to remember, however, that these recommendations are only a guide, the foundation of which can be applied to individual tastes as well as cultural, ethnic, and religious preferences.

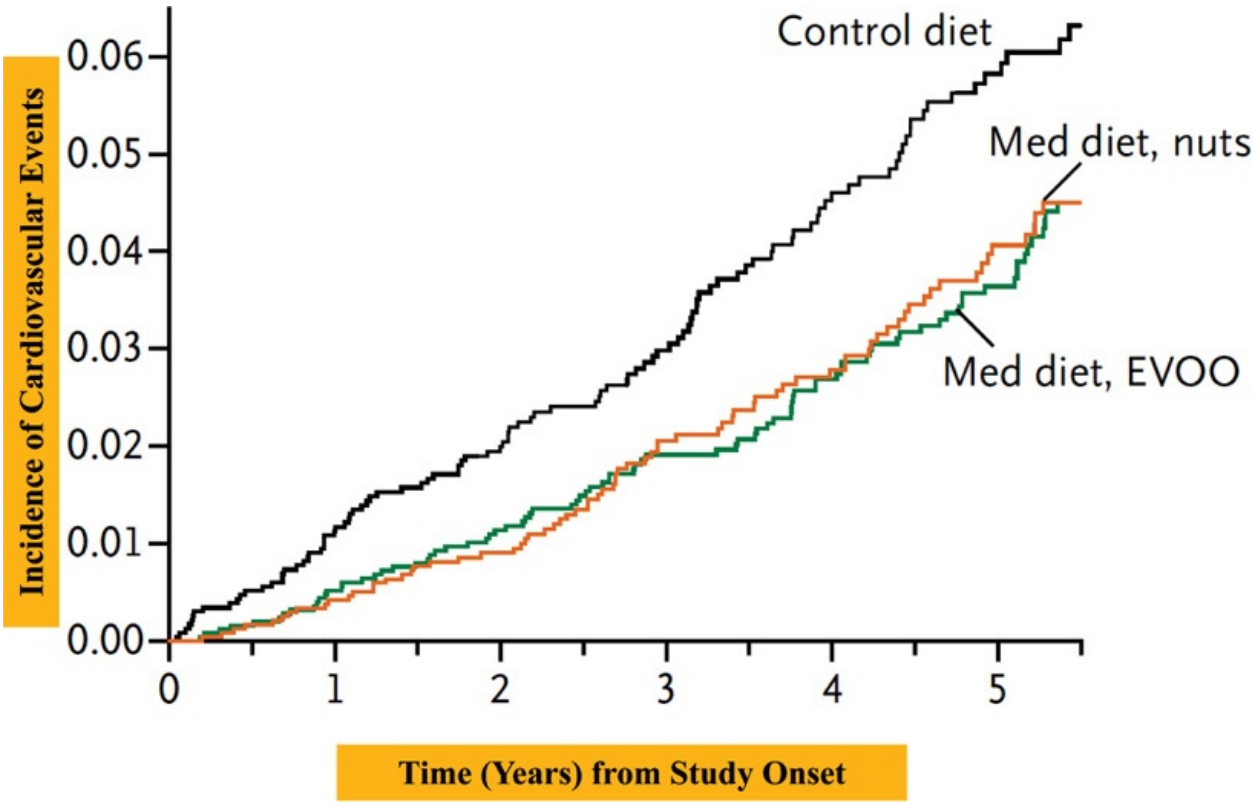

FIGURE 59.9 The PREDIMED study was a landmark clinical trial that demonstrated how consuming a Mediterranean diet (Med diet + nuts or Med diet with extra-virgin olive oil) was associated with a significant reduction in cardiovascular events relative to a low-fat diet. EVOO, extra virgin olive oil.

EATING AND SHOPPING HABITS

After discussing macro/micronutrients and diet patterns, the dietitian briefly turned to David's eating habits. In particular, she wanted to know which foods he liked and disliked, how much he liked to eat (calories per day), how he usually ate (distracted, mindless eating), where he usually ate (in front of the television or computer), why he ate (stress eating, social eating, food addictions), and when he typically ate (late-night meals, skipping meals). Furthermore, she inquired about participation in food shopping and meal preparation. Each one of these factors plays a crucial role in shaping one's dietary habits. On the basis of David's responses, she recommended that David take on a Mediterranean-style diet, focusing on foods that are rich in mono- and polyunsaturated fats, high-quality carbohydrates rich in fiber (found in whole grains), lean sources of protein (eg, fish, poultry), nuts, low-fat dairy, fruits, vegetables, legumes, and olive oil.

In conjunction with this recommendation, the dietitian wanted to make sure that David was sufficiently savvy in reading food labels. She explained that almost all foods have labels outlining the exact macronutrients, micronutrients, and ingredients they contain and that he could use this information to make more informed decisions about his food purchases. Much like reading a menu at a restaurant, it is important to read food labels to gain a deeper understanding of what is in the food (ie, key ingredients) and the nutritional value of the food. Some time ago, the FDA required labeling of all food products sold in stores and many chain restaurants. This has allowed consumers to become more aware of the nutritional value of individual foods, compare foods within similar categories, and make more informed decisions. Two examples of a nutrition fact sheet are shown in **Figure 59.4**. Although both foods are honey-flavored cereals, there are important differences in the nutritional content.

Whole Wheat Flour, **Unbleached Enriched Wheat Flour** (Flour, Malted Barley Flour, Reduced Iron, Niacin, Thiamin Mononitrate [Vitamin B_1], Riboflavin [Vitamin B_2], Folic Acid), Water, Sugar, Sunflower Seeds, Wheat Gluten, Wheat, Rye, Cellulose Fiber, Oats, Yeast, Soybean Oil, Ground Corn, Salt, Molasses, Buckwheat, Brown Rice, Calcium Propionate (Preservative), Monoglycerides, Triticale, Barley, Flaxseed, Millet, Calcium Sulfate, Datem, Grain Vinegar, Calcium Carbonate, Citric Acid, Soy Lecithin, Nuts (Walnuts and/or Hazelnuts and/or Almonds), Whey, Soy Flour, Nonfat Milk.

Whole Wheat Flour, Water, **High Fructose Corn Syrup**, Wheat Gluten, Sugar, Yeast, Contains 2% or less of each of the following: Soybean Oil, Calcium Sulfate, Salt, Dough Conditioners (May Contain One or More of the Following: Mono- and Diglycerides, Ethoxylated Mono- and Diglycerides, Sodium Stearoyl Lactylate, Calcium Peroxide, Datem, Ascorbic Acid, Azodicarbonamide, Enzymes), Wheat Bran, Guar Gum, Distilled Vinegar, Calcium Propionate (Preservative), Yeast Nutrients (Monocalcium Phosphate, Calcium Phosphate, Ammonium Phosphate), Corn Starch, Vitamin D3, Soy Lecithin, Milk, Soy Flour.

FIGURE 59.10 Examples of ingredient lists from two types of commercial breads. Although the products appear similar, important differences in wheat quality and sugar exist.

Of similar importance to reading nutrition fact sheets is reading ingredient lists for foods. Gaining a deeper understanding of the actual ingredients that make up the food is a necessary step to making better food choices. In most instances, the ingredient in highest proportion appears first, with the remaining ingredients in descending order of proportion. Examples of two ingredient lists are shown in **Figure 59.10**. Although both products are bread, important differences exist.

The dietitian suggested that David go food shopping this coming week, analyze food labels, and come into their next scheduled session with any questions that he experienced while reviewing the labels. David was very excited by the idea.

At their next session, David and the dietitian reviewed his success in following his new Mediterranean-style diet, his trip to the grocery store, and his

questions about food labels. David was pleased that he was now able to incorporate foods into his diet, such as eggs and cheese, that he had previously thought he had to avoid as a heart patient.

The dietitian concluded by imparting some additional advice on the basis of her previous screening of David's eating habits. Her suggestions included eating smaller, more frequent meals during the day, avoiding late-night meals or meal skipping, as well as adopting healthy mealtime habits—for example, eating to satiety and nondistracted, mindful eating. David thanked the dietitian for her counsel and left enthused with his newly acquired knowledge base and commitment to eating according to a healthy dietary plan.

WEIGHT LOSS AND WEIGHT MANAGEMENT

David had a follow-up visit with his cardiologist 2 weeks later. At this point, David was maintaining his new diet, but he had not lost any weight. The cardiologist had not set weight loss as an initial goal because he first wanted David to get on a healthy diet plan. He now explained to David that while specific foods and diet patterns have been shown to favorably impact blood pressure, cholesterol, and blood glucose levels, modest weight loss has also been associated with favorable changes in these risk factors. For example, he explains, in the Look AHEAD (Action for Health in Diabetes) study that involved over 5,000 men and women with a mean baseline weight of 100 ± 19 kg, weight loss of 5% to 10% was associated with significant improvements in blood glucose, blood pressure, high-density cholesterol (HDL), and triglyceride levels at 1 year.[8] Encouraged by this research, David asked for specific suggestions to modify his diet program to achieve weight loss. Although he was encouraged to follow up with the dietitian for more specifics, he was offered the following explanation by his physician.

A number of diet strategies exist to facilitate weight loss and weight maintenance, including fad diets (eg, Paleo), commercial weight-loss programs (eg, Weight Watchers), variable macronutrient composition diets (eg, low-fat diets), and dietary patterns (eg, Mediterranean diet). Although considerable public opinion exists as to which diet strategy is superior for achieving and maintaining weight loss, research suggests that calorie restriction is the common underlying mechanism responsible for the success of these diet programs rather than any particular food, macronutrient, or diet pattern. In a landmark study by

Williamson et al., 811 overweight adults were randomized to one of four diet plans varying in macronutrient composition.[9] On 2-year follow-up, there was no significant difference in achieved weight loss among the different macronutrient composition diets. Participants in all four diet programs achieved similar weight loss, which averaged 4 kg at 2 years. Of note, successful weight loss was also associated with greater participation in group counseling sessions.

His cardiologist emphasized that a gradual reduction in weight should be sought, with a goal of losing 2 to 4 pounds per month. To this end, he suggested that David attempt to reduce his daily caloric intake by about 250 to 500 calories per day, if possible. Both agreed that he should see the dietitian for further follow-up concerning his weight-loss goals. His physician also recommended that David begin an exercise program, both for overall health promotion and for facilitating his pursuit of successful weight loss and maintenance of weight loss. This program is the subject of the next chapter.

CONCLUSION

Reflecting on his journey over the past few months, David admits to undergoing a significant transformation. What started out as years of denial and misinformation has now evolved to a deep understanding of health and wellness. He has committed not only to obtaining the necessary information to make informed decisions about his health, but also to the process of lifestyle modification as it relates to diet, nutrition, and successful weight loss. David notes that his sense of self-esteem and vitality have both increased since he started his diet. While his initial heart attack was frightening to him, he now realizes that this event was a blessing in disguise. David now feels far more energetic than he did before his heart attack, as well as knowing that he is on a path to better health.

WHAT PATIENTS AND FAMILY NEED TO KNOW

1. Learn to become an educated consumer of food.
- Read food labels and nutrition fact sheets on food products.
- Participate in food shopping and meal preparation to promote healthier eating.

- Consider taking a healthy cooking class or subscribing to healthy eating magazines.

2. If you are overweight or obese, or have known or suspected heart disease, consider consulting with a dietitian to gain a deeper understanding of your dietary habits and how to make healthier choices to promote better health.
3. Consider adopting a Mediterranean-style diet as this type of dietary pattern has been consistently shown to be associated with a reduced risk of heart disease, diabetes, and cancer and improved longevity.
4. Foods with saturated fats can be eaten in moderation.
5. Sugars, refined grains, processed meats, and high-sodium foods should be avoided because of their harmful health effects.
6. As discussed later in the chapter on exercise, regular physical activity is an important part of lifestyle modification for high blood pressure, high blood cholesterol, and high blood sugar, as well as effective weight loss and weight maintenance.

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Randy Cohen
Alan Rozanski

Exercise and Physical Activity in Cardiac Patients

Six months after the initial hospitalization for a heart attack, David visited his cardiologist for a routine follow-up visit. David had not experienced any chest pain since his initial event, and reported success in maintaining a Mediterranean-style diet after his visits to a dietician. This had resulted in a nearly 10-pound weight loss, which David was proud of. All of David's laboratory work and his blood pressure, on medications, were now within normal limits. However, David had not taken up his physician's request to initiate an exercise program, citing the heavy workload at his job.

David's cardiologist, however, had gotten to know David well by now and felt that he was ready to add exercise to his routine. He suspected that David was not yet sufficiently motivated to start exercising because he did not realize the medical importance of being physically active. Further, David could probably benefit from formal instruction and supervision as to how to exercise. The cardiologist's institution offered two options for patients like David. One was a formal cardiac rehabilitation program that people like David could join. The other was a hybrid gym-based program, which involved initial supervision by a physical therapist who worked with their Rehabilitation unit. The Rehab facility offered an introductory lecture given by a physiatrist that met monthly. The next lecture was taking place in a few days. David's cardiologist

suggested that David attend this introductory lecture and then either call him or make an appointment for a follow-up visit a week afterward. David was more than eager to do so.

At the start of the lecture, the physiatrist asked each participant to write down on a piece of paper their daily work and physical activity routine, with as much detail as possible. David wrote that he did not currently engage in any planned physical activity. Although he had tried to engage in regular physical activity at various points over his life, he always seemed to find excuses not to go to the gym. In fact, David wrote, he found himself becoming increasingly sedentary with each passing year. David described his daily routine as one characterized by a great deal of sitting time with long periods of inactivity. Specifically, David spent an hour commuting to work each day, then worked at a desk job, sitting at his computer for most of the time during his 8 to 10 hour workday, and then commuting another hour back home. Once at home, David sat to eat dinner with his family and then either worked further using his home computer or relaxed, watching TV with his wife and children. As he wrote this down, David was surprised to realize just how much time he sat during the day. He decided he was going to pay keen attention to the lecture.

THE BIRTH OF EXERCISE EPIDEMIOLOGY

The physiatrist first remarked that the modern study of exercise was spurred, in part, by a landmark study conducted by Morris and colleagues in the 1950s.[1] In a classic study, these investigators followed drivers and conductors of double-decker buses among London's Transport Workers, comparing bus drivers (sedentary occupation) with conductors (active occupation). The bus drivers had a classically sedentary job, whereas the conductors were constantly standing, going between the first and second levels of the bus. During the follow-up period, the conductors were observed to have a significantly lower incidence of cardiac events. In subsequent work, these investigators also followed sedentary clerical workers versus postmen in the British civil service. Again, the more active group (ie, the postmen) developed less heart disease during follow-up.

Many subsequent epidemiologic studies have shown how important leisure-time physical activity is. For instance, in 1986 Paffenbarger et al. published their findings on the assessment of leisure-time physical activity levels in over 16,000

Harvard alumni who had been followed for 16 years (**Figure 60.1**).[2] As a result of the groundbreaking work by Morris, and those who followed, the field of exercise science was born.

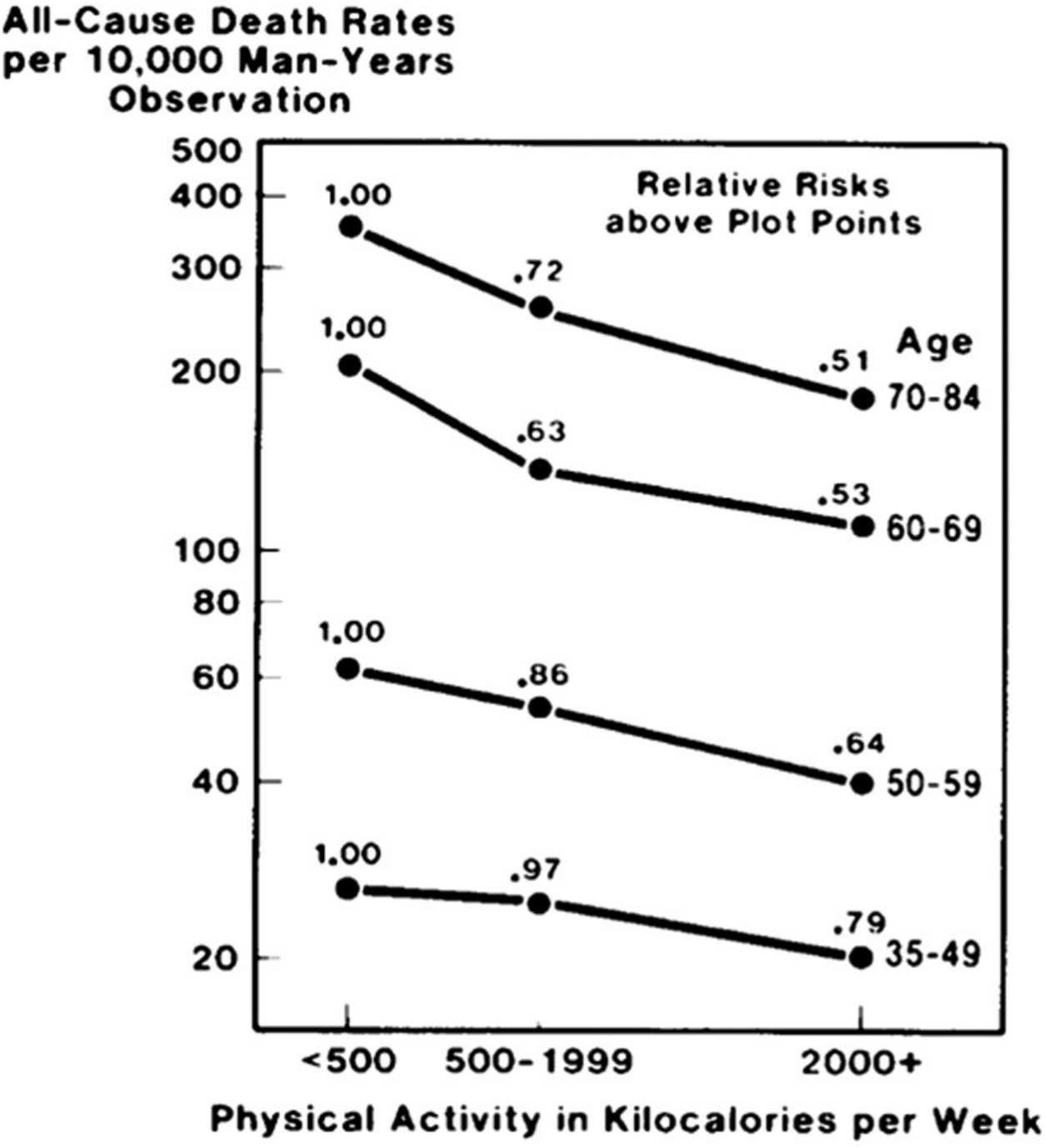

FIGURE 60.1 Decline in all-cause mortality with increasing physical activity, stratified by age groups.

ASSESSING EXERCISE ABILITY IN THE STRESS LABORATORY

The physiatrist then noted that at first, cardiologists had no formal ability to quantify an individual's exercise capacity in their offices. The first formalized approach was developed by Dr. Arthur Masters in the 1920s. His initial approach involved having patients step up and down two steps as fast as they could for 90 seconds (later extended to 3 minutes). The longer it took, the greater was the patient's risk of heart disease. Initially, this task was performed without electrocardiographic monitoring, but as this technology developed, postexercise ECG and then, eventually, ECG monitoring both during and following exercise were added to the evolving stress test.

A major advance was the development of the motorized treadmill, which allowed the performance of progressively higher levels of exercise while patients were electrocardiographically monitored. In 1963, Dr. Robert Bruce validated what has subsequently been called the Bruce protocol: a progressive graded exercise test, increased by two degrees of incline and by increasing speed during each 3 minutes of exercise.[3] Today, the Bruce treadmill exercise protocol is still the standard for performing exercise ECG testing in cardiac practice.

Exercise electrocardiography permits the assessment of ischemia (how much ST-segment deviation is elicited during exercise), patients' clinical response to exercise (ie, whether chest pain was elicited during stress testing), and the assessment of patients' overall exercise functional capacity (eg, how many minutes patients were able to exercise). Hundreds of outcome studies have shown that all three of these parameters are prognostically useful, but the most potent parameter is patients' functional exercise capacity. For example, Myers et al. followed 6,213 individuals for 6.2 years after exercise ECG testing, including a group with and without known cardiovascular disease (CVD).[4] In both groups, after adjusting for age, the mean exercise capacity, measured in metabolic equivalents (METs), was the strongest predictor of outcome. For each 1-MET increase in exercise capacity, there was a 12% improvement in survival.

In another particularly large study, Gupta et al. reported on the follow-up of 66,371 individuals without preexisting heart disease who underwent exercise ECG testing as part of the Cooper Center Longitudinal Study between 1970 and 2006. All subjects were followed for CVD mortality.[5] The presence of traditional risk factors, such as hypertension, diabetes, and smoking, was associated with an

increased risk of CVD events during follow-up (**Figure 60.2**). However, consideration of exercise capacity was quite important. After adjusting for the presence of these risk factors, each quintile of increasing exercise fitness was associated with a progressively greater decrease in the risk of CVD mortality.

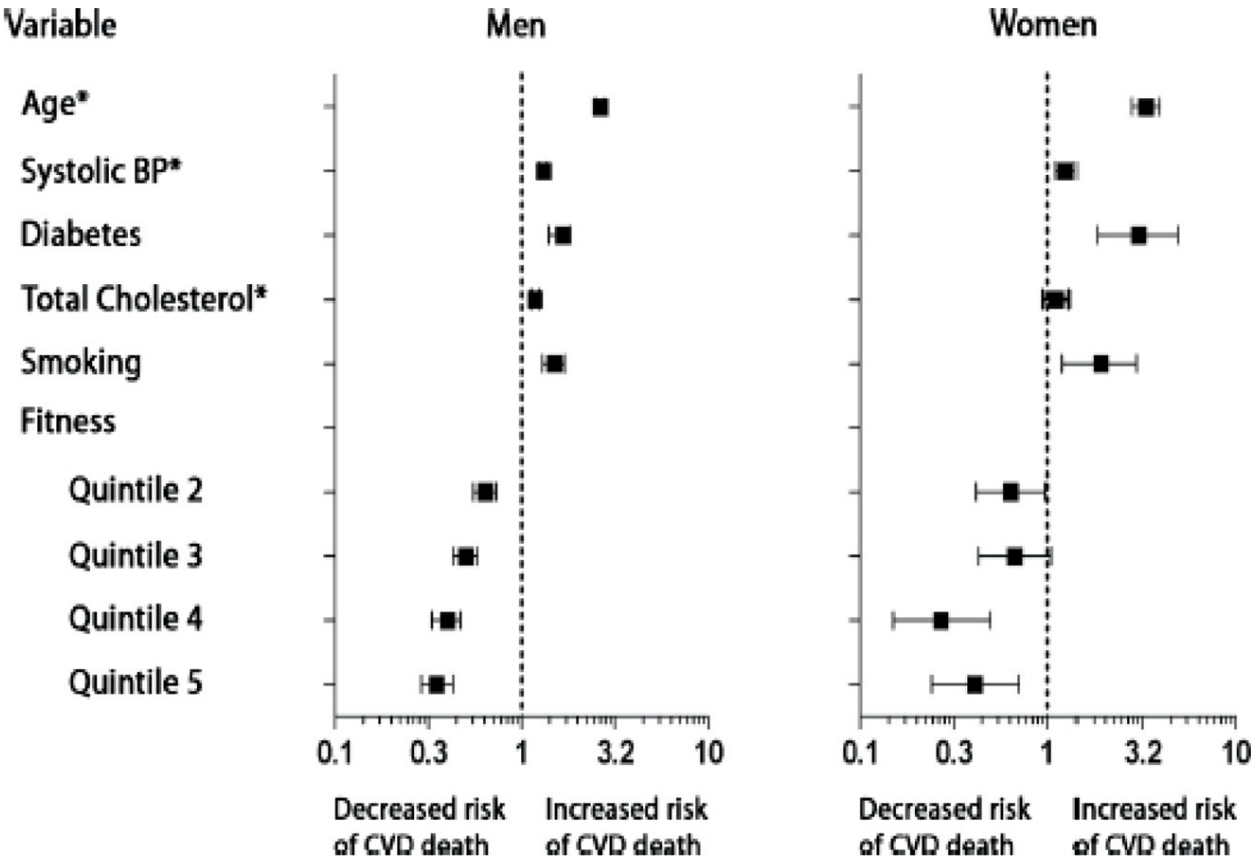

FIGURE 60.2 Lower risk of cardiovascular death (CVD) with increasing quintiles of cardiorespiratory fitness. Even in the lowest quintile (Q2) of fitness, there is a reduced risk of cardiovascular death.
*Hazard ratios are per 1 SD (per 10 years for age, per 14 mm Hg for systolic blood pressure and per 40 mg/dL for total cholesterol).

THE PHYSIOLOGIC BENEFITS OF EXERCISE

The physiatrist then turned his attention to the principal mechanisms by which physical activity and exercise promote better health. The beneficial physiologic effects are shown in **Table 60.1**. Among these is a favorable reduction in blood pressure. Although acute bouts of exercise cause transient elevations in heart rate

and blood pressure, the hours immediately following exercise are characterized by consistently lower systolic and diastolic blood pressure readings and a lower pulse. In a review of 14 studies by Thompson et al., the mean change in systolic and diastolic blood pressure after acute dynamic exercise was −2.1 mm Hg and −0.3 mm Hg, respectively.[6] In contrast, regular physical activity and cardiorespiratory fitness have been consistently associated with −3.4 to −10.5 mm Hg and −2.4 to −7.6 mm Hg reductions in systolic and diastolic blood pressure, respectively.[7] Although these reductions in blood pressure may not seem clinically important, epidemiologic data inform us that a 2-mm Hg reduction in systolic and diastolic blood pressure translate into a 14% and 17% reduction in stroke, and a 9% and 6% reduction in coronary artery disease.[8]

TABLE 60.1 Beneficial Physiologic Effects of Exercise

- Reduced blood pressure
- Increases serum high-density lipoprotein level; minimal lowering of serum low-density lipoprotein levels
- Lowering of triglyceride levels
- Improved glucose metabolism
- Increased insulin sensitivity
- Decrease in inflammatory markers
- Improved autonomic function
- Enhanced endurance and muscle strength
- Promotes bone and joint health
- Promotes positive vascular remodeling
- Improves endothelial function
- Aids weight management
- Promotes cognitive function and reduces dementia risk
- Promotes better moods

Another favorable effect of exercise is its influence on serum lipids, including a rise in serum high-density lipoprotein (HDL) cholesterol, and reduction in serum triglycerides. But extensive research has shown that even chronic, high-intensity aerobic exercise leads to only modest improvements in total and low-density lipoprotein (LDL) cholesterol. Thus, exercise is not a primary tool used to lower serum LDL cholesterol.

Exercise has many other effects, including an enhancement in glucose metabolism and insulin sensitivity; decrease in negative inflammatory markers; better autonomic function (ie, increased vagal tone); increased endurance and muscle strength; and greater bone strength and joint health.

In addition, exercise helps promote better vascular health through a number of mechanisms. Vascular function, which is a measure of how well the arteries expand and contract in response to every heartbeat, is known to be significantly

better among individuals with versus without cardiorespiratory fitness. The mechanism behind improved vascular function is thought to be related to exercise-induced reduction in oxidative stress and chronic inflammation, as well as enhanced production of nitric oxide, a potent vasodilator. In addition, exercise promotes favorable vascular remodeling, including enlargement of the coronary vessels, and it improves the endothelial function of blood vessels, thus making them less susceptible to negative pathophysiologic changes, such as the buildup of plaque.

Regular physical activity is also an important component of weight loss as well as the prevention of weight gain after successful weight loss. Even among obese individuals unable to successfully achieve meaningful weight loss, regular physical activity and cardiorespiratory fitness are important goals to achieve. As shown by Barry et al. in a meta-analysis of 10 studies, all-cause mortality rates were similar among those individuals demonstrating cardiorespiratory fitness, regardless of their body mass index (normal weight or obese).[9]

Finally, exercise has important psychological benefits. Exercise can help reduce feelings of stress, anxiety, and depression. In fact, randomized controlled studies have found exercise to be comparable to antidepressant medications for reducing depression symptoms in those studies.[10]

THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND CHRONIC DISEASE

After reviewing the physiologic benefits of exercise, the physiatrist reviewed the particular benefits of exercise with respect to disease prevention. He pointed out that given the diverse benefits of regular physical activity on various bodily functions (eg, cardiovascular, metabolic, bone health) that he had just discussed, it is not surprising that physical activity has been found to significantly reduce the risk of many chronic diseases. For example, in a large prospective cohort study, Wen et al. assessed leisure-time physical activity in over 400,000 individuals and then followed them for an average of 8 years.[11] Relative to the inactive group, those in the low, medium, high, or very high activity levels had significant reductions in all-cause as well as cancer- and cardiovascular-related mortality (**Figure 60.3**). Of note, even among those able to engage in only 15 minutes of leisure-time physical activity per day, a 14% reduction in all-cause mortality and a 3-year longer life expectancy was observed. In related work,

Blair and colleagues examined how changes in fitness over time impacted mortality.[12] As expected, those who were found to be fit by treadmill testing at both baseline and follow-up visits had the lowest all-cause and cardiovascular mortality. However, among those who improved their fitness level (unfit at baseline → fit on follow-up), a 44% reduction in mortality was observed. This association was maintained even after correcting for age, health status, and other factors associated with premature mortality. These findings underscore the importance of establishing a regular physical activity program, even if one is not healthy or fit at baseline.

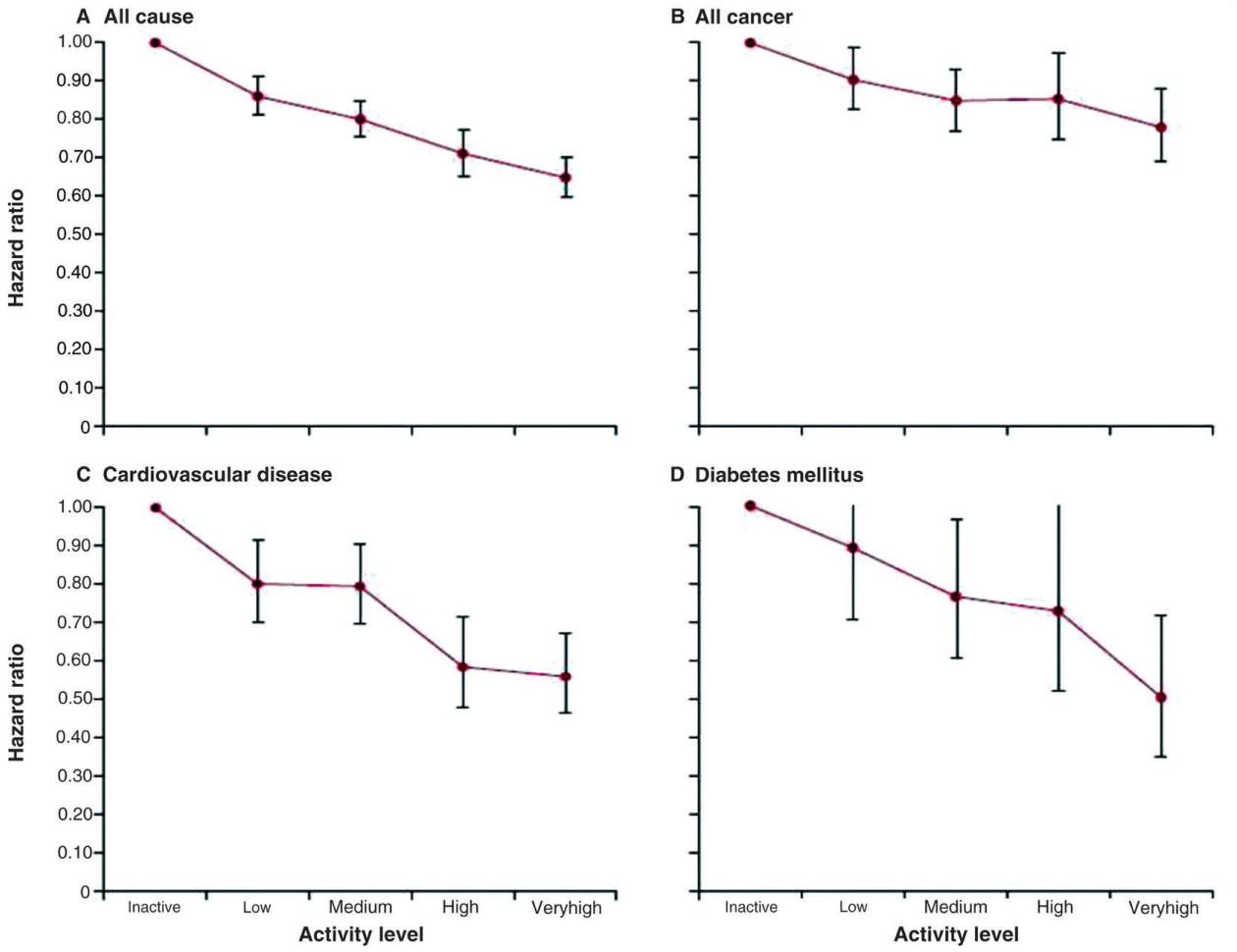

FIGURE 60.3 Decline in all-cause mortality, cancer, cardiovascular disease, and diabetes with increasing levels of leisure-time physical activity.

In related work, Moore et al. examined the association between leisure-time physical activity and 26 different types of cancer in over 1.4 million subjects.[13] After 15+ years of follow-up, regular leisure-time physical activity was associated with substantial reductions in many cancers, including lung, kidney, endometrial, colon, rectal, myeloid leukemia, and bladder.

Regular physical activity, as well as physical activity that is part of a comprehensive lifestyle modification program, has also been shown to substantially reduce the risk of developing diabetes mellitus. In a review of 10 studies involving over 300,000 participants, brisk walking (≥2.5 hours/week) was associated with a 30% reduction in new onset diabetes mellitus.[14] In the landmark Diabetes Prevention Program trial, involving over 3,000 patients, regular physical activity along with healthy eating and modest weight loss

reduced the incidence of diabetes mellitus by 58%.[15]

Another beneficial effect of exercise is its role in maintaining bone health and muscle strength during the aging process. For instance, regular physical activity has been shown to be of critical importance in preventing osteoporosis and frailty. In a review by Hendricks et al., regular exercise reduced the risk of developing osteoporosis and subsequent injuries by promoting bone strength as well as strengthening muscle groups that contribute to balance, coordination, and gait stability.[16] In recent years, frailty has emerged as an important threat to successful aging and has been associated with a number of poor health outcomes.[17,18] Specifically, frailty is defined as a clinical syndrome involving any three of the following characteristics: unintentional weight loss, low physical activity, weakness, fatigue or exercise intolerance, and slowed motor performance.[19] In a recent review by de Labra et al., exercise was found to be an effective intervention for older adults exhibiting signs of frailty, although the exact type and duration of exercise remain unclear.[20]

Another important and exciting area of exercise science relates to cognitive function. In a recent review by Bherer et al., regular physical activity was shown to have a significant and positive impact on cognitive function among a variety of individuals, ranging from asymptomatic elderly adults to those with established cognitive impairment.[21] In related work, Erickson and colleagues concluded that physical activity can induce important, dynamic changes in cognitive function that can slow or delay the onset of cognitive decline.[22] In particular, physical activity can promote brain plasticity and enhance the growth of the prefrontal and hippocampal regions, which are involved in memory function.

THE CURRENT RISE OF PHYSICAL INACTIVITY

At this point of his presentation, the physiatrist paused to summarize the physiologic and medical benefits of exercise. He then moved on to an interesting aspect of his presentation: how societal trends were leading to decreasing, rather than increasing, levels of physical activity. He began this section by citing many recent studies that have documented population-level declines in physical activity. For example, Church et al. identified a significant decline in occupational physical activity over a 50-year time frame (**Figure 60.4**).[23] Similar declines in physical activity have been observed across the globe (**Figure**

60.5),[24] as well as in different demographic groups.[25]

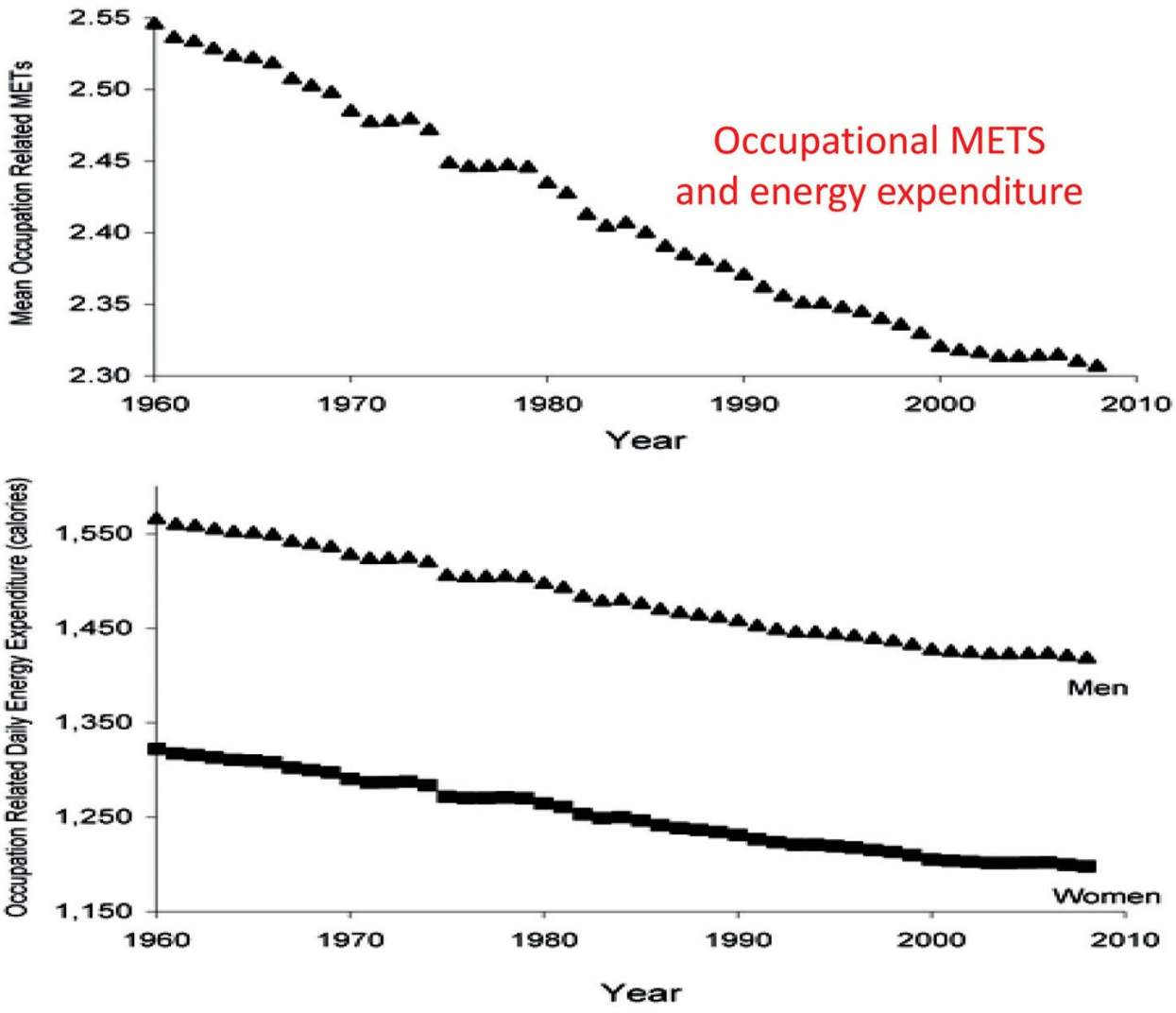

FIGURE 60.4 Progressive decline in occupational physical activity (METs) and energy expenditure (calories) over a 50-year period.

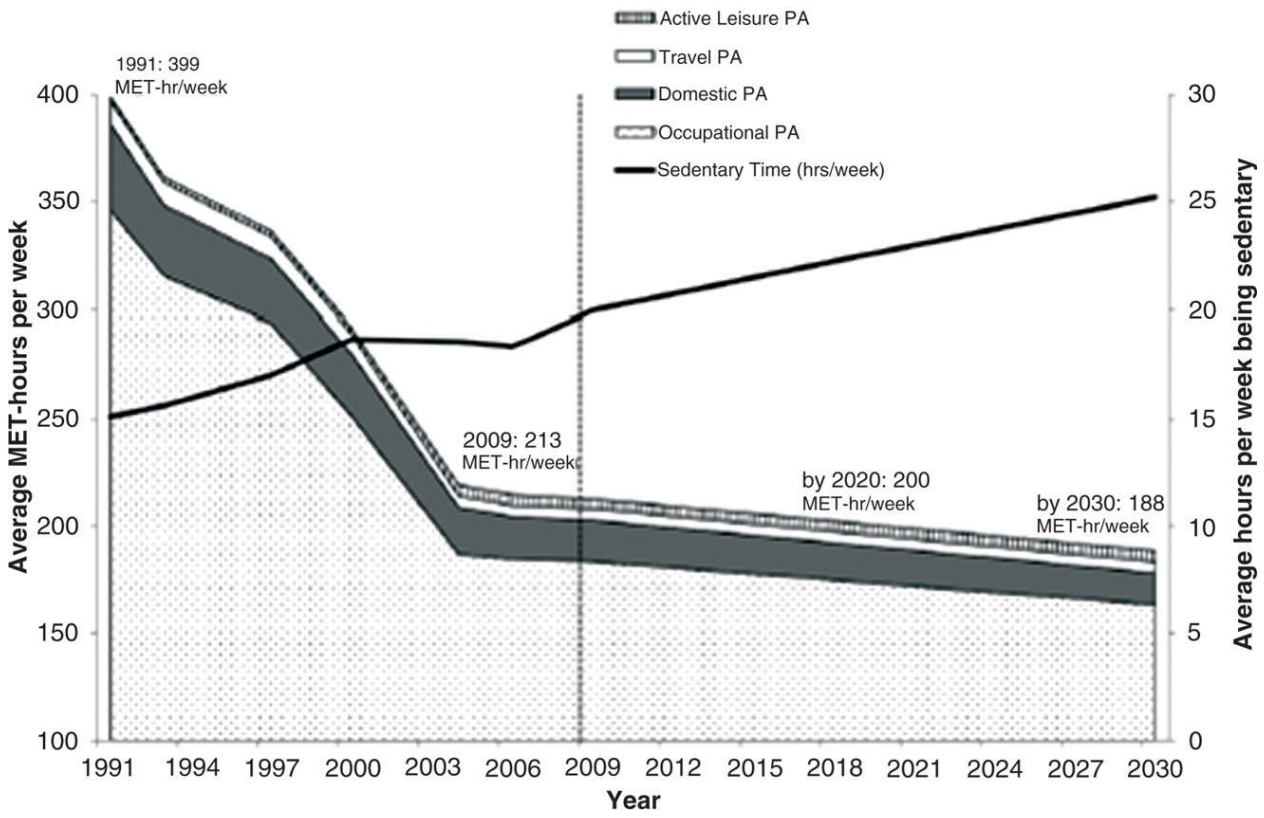

FIGURE 60.5 Progressive decline in all types of physical activity, and increasing sedentary time, over a 25-year period in China.

Another trend causing concern is the amount of screen time (TV, computer/tablets, phone) individuals engage in each day. According to the U.S. Bureau of Labor Statistic's Time Use Survey for 2015, at least 56% of all daily leisure-time activity involves screen time (**Figure 60.6**). This has had a particularly detrimental effect on youth, and significant declines in leisure-time physical activity have been documented in children and adolescents.[26,27]

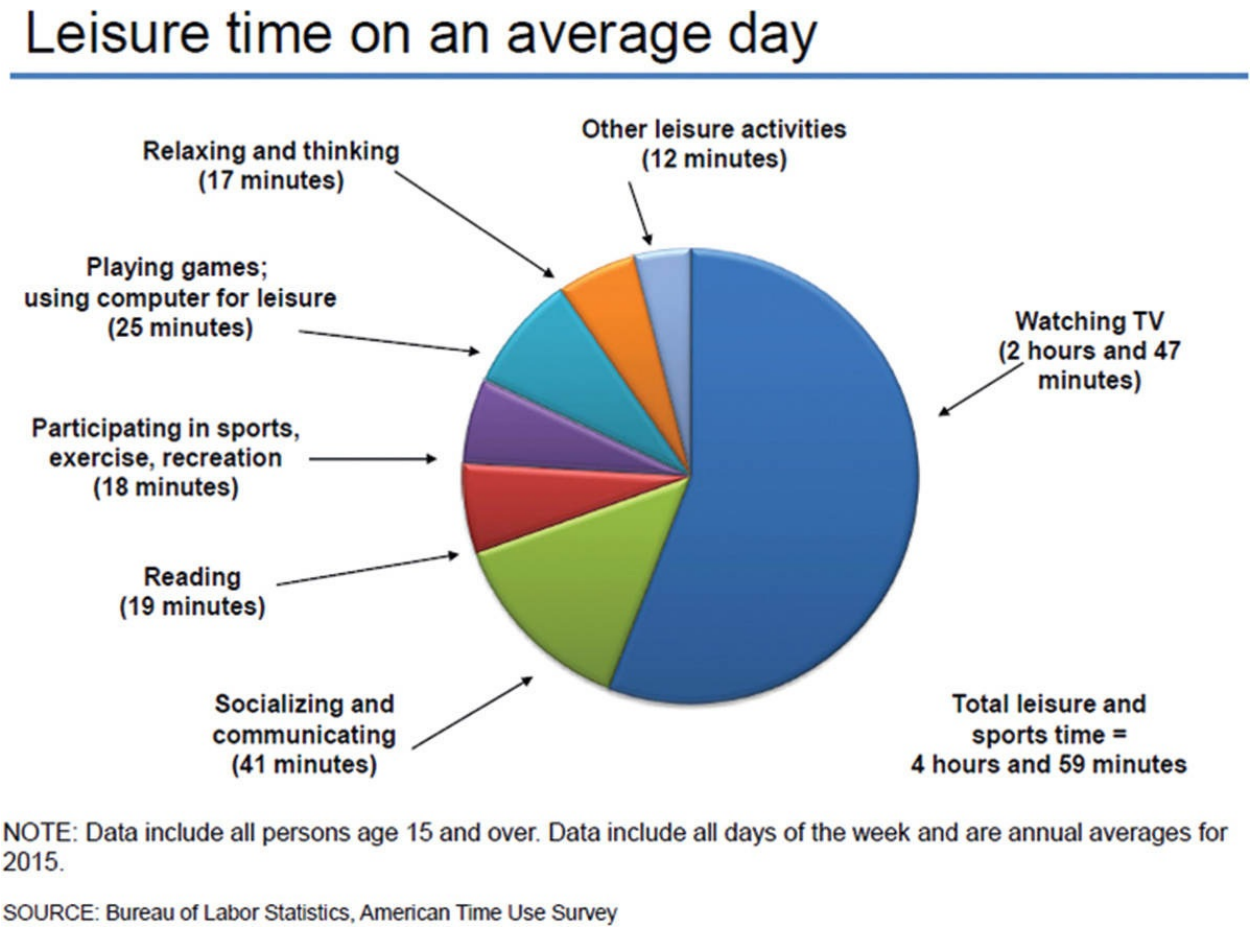

FIGURE 60.6 Time spent in various leisure-time activities, according to the U.S. Bureau of Labor Statistics. Note the significant amount of time per day spent on screen-related activities (eg, computers, video games, television).

Relatedly, there has been increasing research into the health detriments posed by excessive sitting. Although often necessary for occupational, transportation, and recreational needs, excessive sitting time (often related to excessive screen time—computers, TV, video games) has now been linked to a variety of negative health outcomes, including obesity, diabetes, CVD, cancer, and all-cause mortality (**Figure 60.7**).[28–31] Although initial studies linking sitting time with health outcomes were often based on subjective questionnaires, more recent studies involving objectively measured sitting time using accelerometers yielded similar results. A recent study involving over 5,000 individuals examined the interaction between objectively measured (via accelerometer) sedentary time and moderate to vigorous physical activity (MVPA).[32] Although both outcomes (sedentary time and MVPA) were independently associated with all-cause

mortality, interestingly, among those above the median level of MVPA, sedentary time was no longer associated with mortality. What this suggests is that, among those who are perhaps committed to prolonged sitting time (eg, occupational or transportation-related sitting), those who are able to engage in MVPA are somewhat protected from the deleterious effects of excessive sitting. To combat excessive sitting, health professionals recommend standing/walking breaks every 30 to 60 minutes. In fact, pointed out the physiatrist, a recent study found that standing > 2 hours per day (vs < 2 hours per day) was associated with a 10% reduction in all-cause mortality.[33]

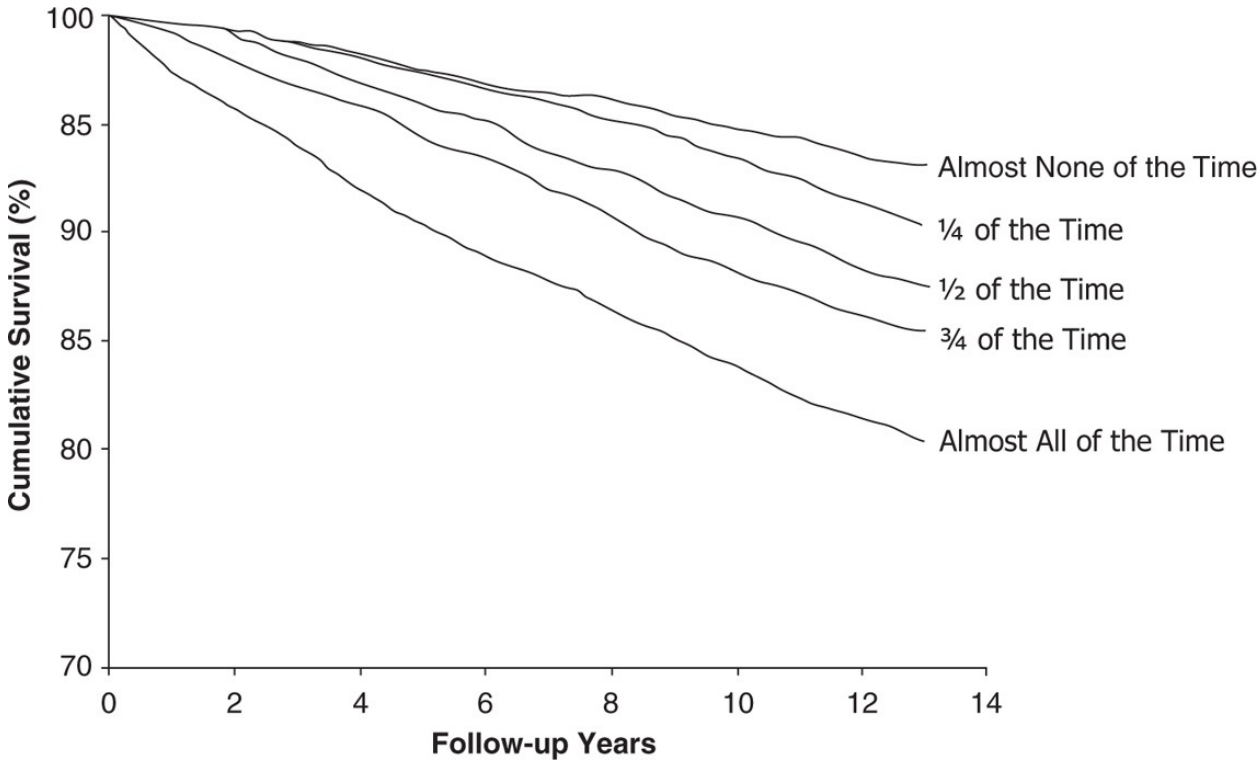

FIGURE 60.7 Daily sitting time and its association with all-cause mortality, cardiovascular disease, and cancer.

EXERCISE ACTIVITIES

At this point, the physiatrist turned his attention toward a general discussion of exercise activities. Aware that many individuals in the audience were people like

David, with different forms of cardiac conditions, the physiatrist emphasized that the initiation of exercise among cardiac patients should be done only under medical supervision. He thus said that although he would cover general points about exercise, patients should check with their doctors before initiating a specific exercise program. The physiatrist covered three general forms of activity:

AEROBIC EXERCISE

According to the U.S. physical activity guidelines,[34] adults should work toward achieving 150 minutes of moderate-intensity aerobic exercise per week. Alternatively, individuals can engage in 75 minutes of vigorous-intensity exercise per week for similar health benefits. Examples of moderate and vigorous exercise activities are listed in **Table 60.2**. It should be emphasized that although substantial health benefits are achieved with these levels of physical activity, research indicates that any amount of regular physical activity can promote cardiovascular health and wellness. As for patients, many of whom have been completely sedentary, transitioning from sedentary behavior to aerobic physical activity can be quite daunting, and should be taken up with a graduated program that minimizes the risk of physical injury.

TABLE 60.2 Examples of Moderate- and Vigorous-Intensity Physical Activities

MODERATE INTENSITY (3.0–5.9 METs)	VIGOROUS INTENSITY (≥ 6.0 METs)
Brisk walking	Running or jogging (10-min mile or faster)
Bicycle riding on level ground	Bicycle riding at brisk pace/up hills
Doubles tennis	Singles tennis
Mowing the lawn (push mower)	Shoveling/carrying heavy loads
Washing windows/vacuuming/mopping	Basketball
Water aerobics	Lap swimming
Ballroom dancing	Soccer
	Aerobic classes (Zumba, spinning, etc.)

One tool that has been shown to be effective in promoting the initiation and maintenance of exercise activities is pedometers. These portable electronic devices are capable of monitoring one's daily steps, thus tracking physical activity. More advanced devices are even able to track sitting time and issue alarms when the user has exceeded a predetermined amount of sitting (eg, 1 hour). Pedometers have become so prevalent and technologically advanced that most smartphones and smart watches now have them built in. A useful way to start using a pedometer is to simply wear the device (from first thing in the morning till bedtime) every day for 1 week. Do not worry about monitoring step counts, sitting time, etc.; just wear the device and carry on with your usual weekly activities. At the end of 1 week, review the recorded data for total daily step count and calculate the average number of steps per day (eg, 3,000 steps/day). This will now serve as your baseline level of physical activity from which you can start to add steps.

It is worth noting that time recommendations can be achieved in a variety of ways. For example, for moderate-intensity activities, 30 minutes/day, 5 days/week will fulfill the 150-minute/week goal. The 30 minutes/day can even be divided into three 10-minute bouts of activity throughout the day.

STRENGTH (RESISTANCE) TRAINING

Although not well known, strength training is an equally important component of any exercise routine, and should be performed at least 2 times/week (in addition to the aerobic exercise recommendations). As noted earlier, strength training is important for maintaining muscle tone and strength, which are essential for successful aging and the prevention of injuries. Examples of strength (resistance) training exercises are listed in **Table 60.3**. In general, strength training can include the use of weights or, alternatively, resistance from body weight (eg, push-ups) or elastic bands. For optimal results, strength training should include as many large muscle groups as possible, including hips, back, legs, arms, chest, abdomen, and shoulders. Although no fixed rule exists, in general, strength (resistance) training exercises should be performed in 1 to 3 sets of 8 to 12 repetitions each.

TABLE 60.3 Examples of Strength (Resistance) Training Exercises

Light free or machine weights
Push-ups/sit-ups/pull-ups

Yoga
Pilates
Fitness bands

BALANCE TRAINING

Older adults, and those at increased risk for falls, should engage in balance training in addition to aerobic and strength exercises. Numerous studies have noted benefits from balance training relating to overall strength, coordination, and prevention of falls and fall-related injuries among older adults. Established balance exercises include backward and sideways walking, heel walking, toe walking, and repeated standing from a sitting position (**Table 60.4**). Tai chi is also an accepted form of balance training, many exercises of which can also be used for strength training.

TABLE 60.4	Examples of Activities for Promoting Balance
Walking backward	
Walking sideways	
Walking on heels	
Walking on toes	
Repeated standing from sitting position	
Tai chi	

THE QUESTION-AND-ANSWER SESSION

After completing his general presentation, the physiatrist asked the audience to write down any questions they had and to hand them to his assistant. He briefly reviewed these questions and then chose the following questions to discuss with the entire audience:

HOW DO I KNOW IF I AM GETTING ENOUGH EXERCISE?

The official recommendations for leisure-time physical activity are 150 minutes of moderate-intensity exercise each week or, alternatively, 75 minutes of vigorous-intensity exercise each week. This time requirement, regardless of whether it is moderate or vigorous, can be divided into different blocks throughout the day or week. For example, one can engage in 30 minutes of moderate-intensity exercise daily for 5 days, 25 minutes of vigorous-intensity exercise daily for 3 days, or any combination of moderate and/or vigorous activity to achieve the weekly recommendation. However, for those individuals just starting with exercise activities, these recommendations may be too demanding to achieve at first. Rather, one should start by committing to walking or another similar activity for a few minutes per day. After achieving some degree of success, and developing a new habit of regular exercise, one can work toward achieving progressively higher levels of exercise activity.

WHAT ARE METs AND VO_2 MAX, AND DO I NEED TO KNOW THESE TO START MY EXERCISE PROGRAM?

METs are metabolic equivalents and represent energy expenditure by the body during various physical activities. 1 MET is the amount of energy expended by the body at rest. Thus, various physical activities represent multiples of the baseline energy expenditure. For example, if resting quietly is equal to 1 MET, a brisk walk might be 3 to 4 METs, and jogging might be 6 to 7 METs.

VO_2 max represents the maximal amount of oxygen an individual can use during high-intensity exercise. Although typically used to help train high-level athletes, it is also used to guide the evaluation and management of patients with advanced heart and lung disease.

If the goal is to initiate and maintain a physical activity program for the purposes of health and wellness, it is not necessary to learn and use METs or VO_2 max. Rather, it would be more useful to understand which activities are generally classified as being of moderate versus vigorous intensity to help identify the types of activities and the time duration needed to meet official recommendations (Table 60.2).

WHAT IS THE DIFFERENCE BETWEEN PHYSICAL ACTIVITY AND PHYSICAL FITNESS?

Physical activity simply refers to the act of engaging in coordinated movements of the body for the purpose of achieving health (eg, walking, jogging, sports).

Fitness, on the other hand, refers to the ability of the heart and lungs to adequately supply oxygen to the muscles during regular sustained exercise activity. Cardiorespiratory fitness is a more specific form of fitness that integrates not only physical and aerobic capacity, but other factors as well, including age, gender, and ethnicity. Thus, it is no surprise that cardiorespiratory fitness is the most potent measure of fitness and correlates the most with various health outcomes. In fact, cardiorespiratory fitness has been found to be as strong a predictor of all-cause mortality as other commonly accepted risk factors, including smoking, diabetes mellitus, high blood pressure, and high cholesterol. In general, cardiorespiratory fitness levels < 5 METs are associated with a higher risk of mortality, whereas levels > 8 METs are associated with increased survival.[35] Another important distinction is that physical activity, and even fitness, can be assessed by detailed questionnaires, whereas cardiorespiratory fitness can be assessed only by actual exercise testing.

IS THERE SUCH A THING AS TOO MUCH EXERCISE?

One can think of exercise in terms of both volume (duration of time spent) and intensity (low or moderate or vigorous). In terms of volume, as we noted earlier in this chapter, even the lowest level of activity (eg, standing for > 2 hours per day vs < 2 hours per day) is associated with better health outcomes. As shown by Powell et al., progressively larger volumes of exercise are associated with greater reductions in CVD, with no apparent upper limit beyond which benefit is lost (**Figure 60.8**).[36] Of note, the greatest reductions in cardiovascular risk appear to be when transitioning from sedentary to low or moderate activity. With respect to exercise intensity, no upper limit of low- or moderate-intensity exercise exists beyond which benefit is lost. In terms of vigorous-intensity exercise, some data suggest an upper limit of benefit (11 MET-hours/week); however, there is no consistent evidence of actual harm.[37]

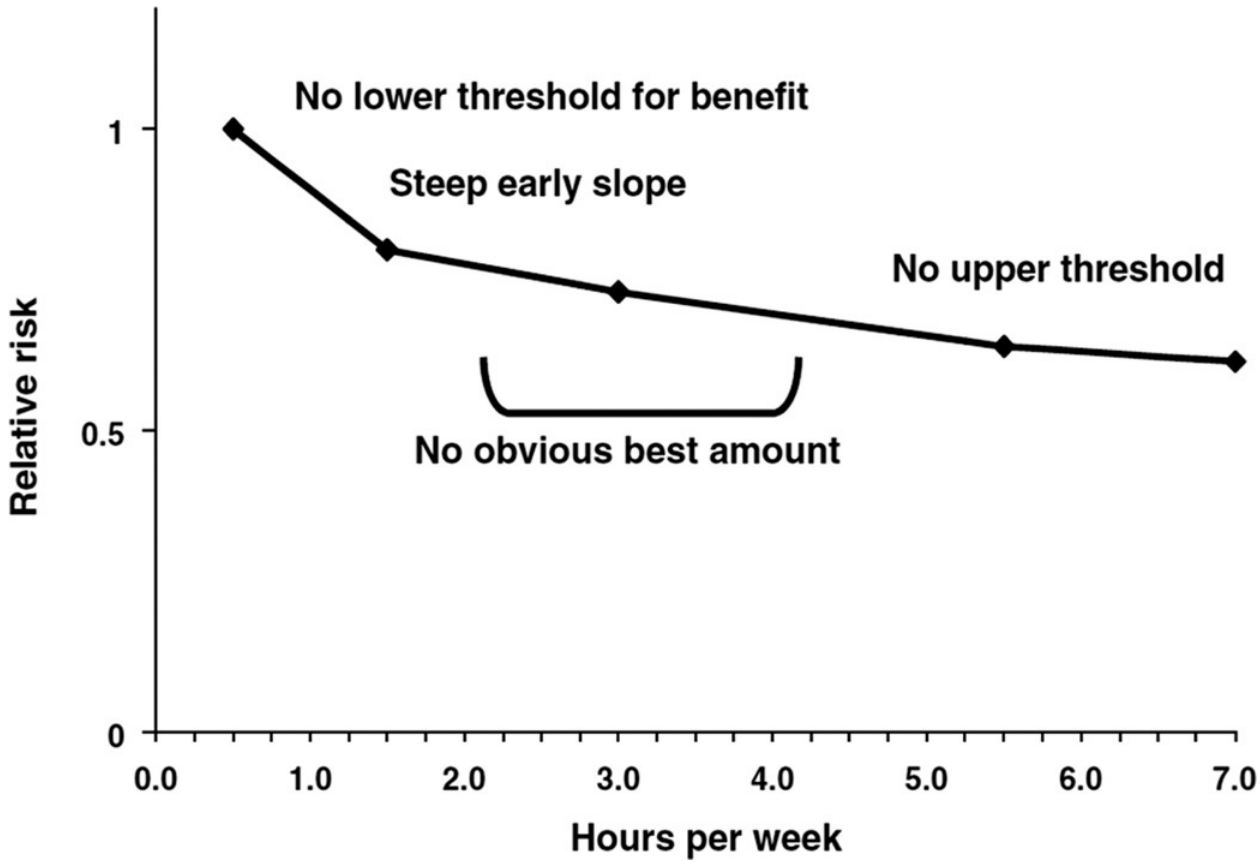

FIGURE 60.8 Risk of all-cause mortality according to hours per week of moderate to vigorous physical activity (MVPA). Note the lack of an upper or lower threshold above or below which benefit of MVPA is lost.

THE PHYSIATRIST'S SUMMARY

The physiatrist concluded by reiterating the value of making regular physical activity an important part of one's daily routine. He reminded the audience that there is now an overwhelming amount of scientific research that associates physical activity with a reduced likelihood of many chronic diseases. Furthermore, physical activity can even be used as a successful treatment of various diseases and in some cases lead to the regression of disease (eg, type II diabetes mellitus). Another compelling reason to engage in regular physical activity is to promote one's sense of wellness and vitality. He told the audience that as the U.S. population ages, those who are hitting social security age (age 65) can expect to now live, on average, another 20 years. Unfortunately, too

many elderly adults find themselves living with chronic debilitating diseases (eg, arthritis, obesity) in older age. This can greatly impair one's sense of wellness and vitality, decreasing one's ability to enjoy and contribute to all that life has to offer. The goal, therefore, should be to defer chronic disease and disability to the last *few years* of one's life, not the last *few decades*. This concept is referred to as the "compression of morbidity" and is tightly linked to maintaining health, wellness, and a sense of vitality for as many years as possible before illness and disability set in.[38]

If deferring illness and disability to the latter years of one's life is not sufficient reason to engage in physical activity, perhaps saving money will be another, as shown by a recent study in which higher fitness in middle age was associated with less health costs in later life (**Figure 60.9**).[39] As we learned earlier in this presentation, said the physiatrist, physical inactivity has been directly associated with an increased risk of obesity, diabetes mellitus, cardiovascular disease, and cancer, and can greatly impair cognitive function and promote musculoskeletal dysfunction and injury, as well as overall unsuccessful aging. At an economic level, physical inactivity has been estimated to contribute to over $53 billion in worldwide health care costs, creating a substantial economic burden on the public and private sectors, as well as individual households.[40] In the United States alone, physical inactivity has been estimated to contribute to approximately 11% of aggregate health care expenditures.[41]

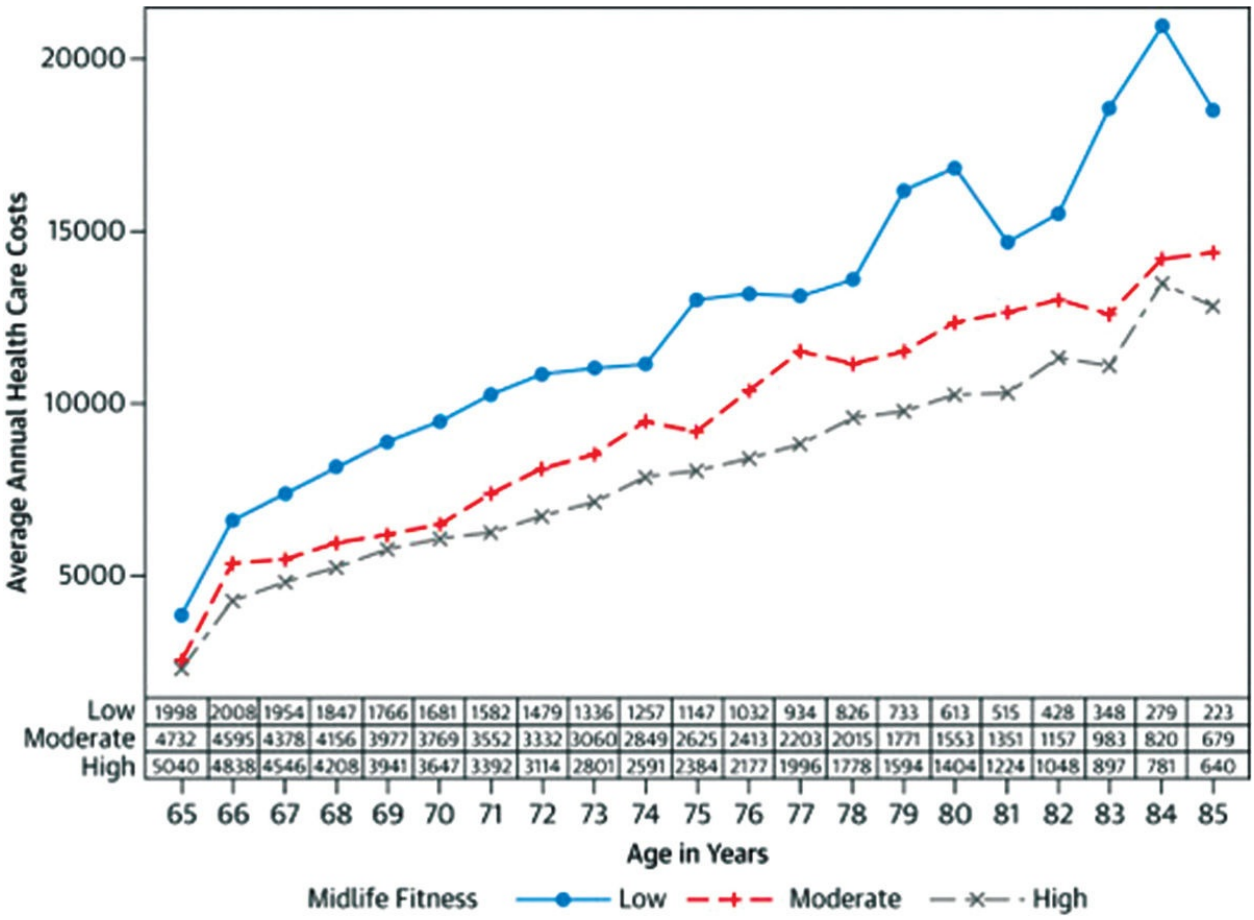

FIGURE 60.9 Health care–associated costs later in life according to cardiorespiratory fitness level in middle age.

David's Follow-Up Visit With His Cardiologist

David scheduled a return visit to his cardiologist, as suggested, a week after the lecture. It was clear that David had been very inspired by the lecture and was motivated to start adding an exercise program to his health regimen. Knowing that inspiration is fleeting, his cardiologist decided to get David to commit to a specific exercise plan before he left the office. He first suggested a formal cardiac rehabilitation program that David was eligible for, which involved group exercise under medical supervision, including electrocardiographic monitoring. However, the Rehabilitation Center was located 40 minutes away from David's work, and he was afraid the time involved in traveling would make the program prohibitive. However, the cardiologist was aware of this type of problem and knew of alternative options

within the community. He suggested that David join a general gym that also sponsored a cardiac patient program three nights per week between 6 and 7 pm and that was also conducted by members of the Hospital's Rehabilitation team. David indicated that option would work fine. The cardiologist wrote down the name of the gym and the contact person for David and asked him when he would make the call to join. David promised to do so that very afternoon.

His cardiologist then suggested that David also purchase a pedometer and gave him a sheet with various options.

Finally, he asked David if there was anything else he planned to do. David mentioned that he was particularly impressed about the discussion regarding the hazards of sitting and that he had already gone ahead and ordered a standing desk. His cardiologist was very impressed. He saw that David had not only been inspired to be more physically active, but had now taken important steps to anchor this motivation into a plan that would promote David's health for years to come.

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61

Alan Rozanski
Randy Cohen

Applying Psychological Principles for the Lifestyle Management of Cardiac Patients

Fifteen months after sustaining his heart attack, David is scheduled for a routine follow-up with his cardiologist. Now 53 years old, David's preexisting hypertension and high cholesterol are presently well controlled on his current medical regimen and dietary changes. David had also been noted to have a high HgbA1C after his heart attack (6.2%), signaling a prediabetic state, but this value has now decreased to 5.7%. At his 3, 6, and 9-month follow-up visits, David had sustained his new health habits, including a strict adherence to a restricted-calorie (1,800 calories) Mediterranean diet, and an exercise regimen that he had adopted after his three-month visit, including joining a health club, which he attended for 45 to 60 minutes 3 times/week. During this time, he had also bought a standing desk and purchased a pedometer, which he wore every day.

However, 5 months before his current visit, David began to experience more stress at his law firm, which had recently expanded its operations. As one of the senior associates, David was traveling more and cutting back on some of his sleep. Feeling quite time pressed, he decided he would defer his exercise program for a week or 2, and he allowed himself permission to eat an extra

snack or 2 during the day. Without thinking about it, David had resumed a prior pattern of night eating, and once he stopped exercising, he did not restart his exercise program. By the time he saw his cardiologist, he had regained 8 of the 14 lb he had previously lost during the first 9 months following his heart attack. David was pleased that his risk factors were under control, but he was quite discouraged by his failure to maintain his new health habits.

However, David's cardiologist was not perturbed by the setback. Instead, he praised David for his initial success and said that this proved he could do it again. He then mentioned to David that he knew a health psychologist, Dr. Jones, who helped coach patients who were having trouble adopting new health behaviors and maintaining them for the long term. He mentioned that Dr. Jones gave a monthly lecture on stress and heart disease at the hospital and suggested that David attend the lecture.

David was very eager to do so. At the lecture, Dr. Jones explained that his presentation was divided into three parts. First, he would discuss the scope of psychological factors that are related to heart disease. Second, he would describe psychological principles related to the management of health behaviors and stress management. Third, he would provide the participants with a self-reflective exercise that could guide their future self-management of their health goals.

PSYCHOSOCIAL RISK FACTORS FOR HEART DISEASE

Dr. Jones began the first portion of his lecture by showing a slide that listed the psychological domains that he would discuss (**Table 61.1**). He then spent a few minutes discussing the following essentials regarding each psychological domain that was listed on the slide.

TABLE 61.1 Psychosocial Risk Factors for Cardiovascular Disease

1. Depression
2. Anxiety syndromes
   - Elevated anxiety symptoms
   - Phobias
   - Generalized anxiety disorder
   - Posttraumatic stress disorder
3. Pessimism
4. Hostility/anger

5. Loneliness and poor social support
6. Lack of life purpose
7. Chronic stress
   - Work stress
   - Marital stress
   - Caregiver stress
   - Effects of trauma and abuse
   - Chronic illness
8. Fatigue states
   - Vital exhaustion
   - Burnout
   - Lack of sleep

DEPRESSION

Depression is a common psychological symptom that can range from very mild symptoms to those that are very severe. Severe or “major depression” is said to be present when patients experience a markedly depressed mood or the lack of interest in nearly all of their activities in life for at least 2 consecutive weeks, in conjunction with other psychological symptoms, including either loss or increase in appetite, insomnia, fatigue, difficulty concentrating, and feelings of guilt.

The systemic pathophysiologic effects of depression are profound. When depression is chronic, it can result in persistent activation of the hypothalamic pituitary adrenal axis and dysregulation of the sympathetic nervous system, leading to a rise in serum cortisol levels and elevated norepinephrine levels. This in turn can lead to profound systemic effects affecting many physiologic functions and organ systems, as shown in **Figure 61.1**.[1] For instance, people suffering from depression have a higher frequency of insulin resistance and elevated risk for diabetes. They are also more prone to develop abdominal obesity and elevation in inflammatory proteins, as well as pathology in the inner lining of blood vessels (“endothelial dysfunction”). Depression also leads to platelet abnormalities in the blood. All of these changes combine to accelerate the development and progression of atherosclerosis in the coronary vessels.

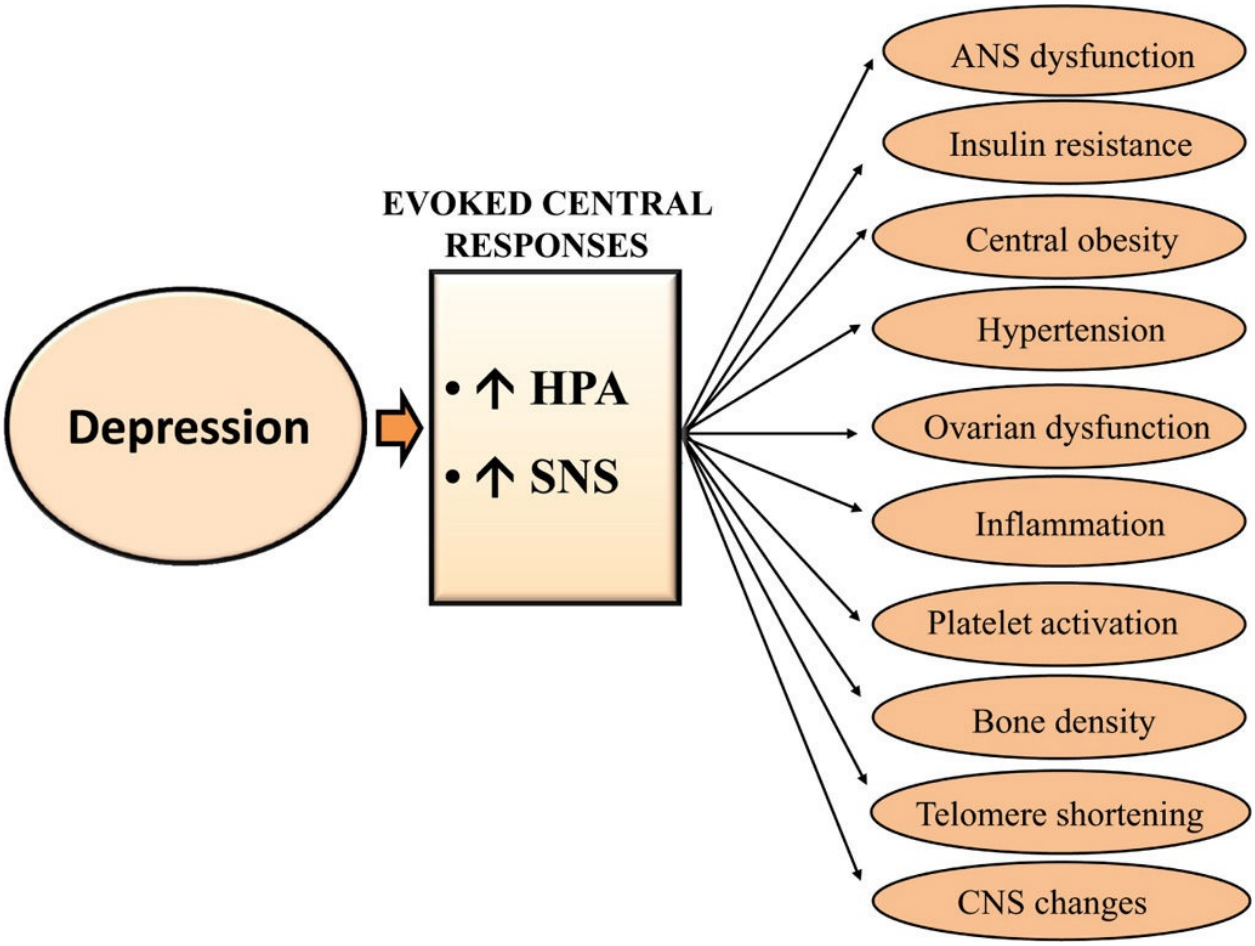

FIGURE 61.1 In the presence of chronic depression, there is persistent stimulation of the sympathetic nervous system and the hypothalamic pituitary axis (HPA). The result is diverse pathophysiologic effects, as shown. ANS, autonomic nervous system. (Modified from Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. *J Am Coll Cardiol*. 2005;45:637-651.)

Secondly, depression also has an important negative effect on the health habits of individuals. People who are depressed are more likely to eat poorly, be sedentary, smoke, and be less proactive about their health in general. Moreover, once depression sets in, people find it harder to comply with recommended behavioral changes, such as suggestions for exercise, or even with their prescription medications.

Epidemiologic study indicates that chronic depression is a particularly potent factor for promoting heart disease. In a large meta-analysis of 54 epidemiologic studies, the adjusted risk for developing adverse cardiac events among individuals who were depressed was increased nearly 2-fold among depressed versus nondepressed subjects in both community cohorts as well as in patients

with prior cardiovascular disease (CVD) (**Figure 61.2**).[2]

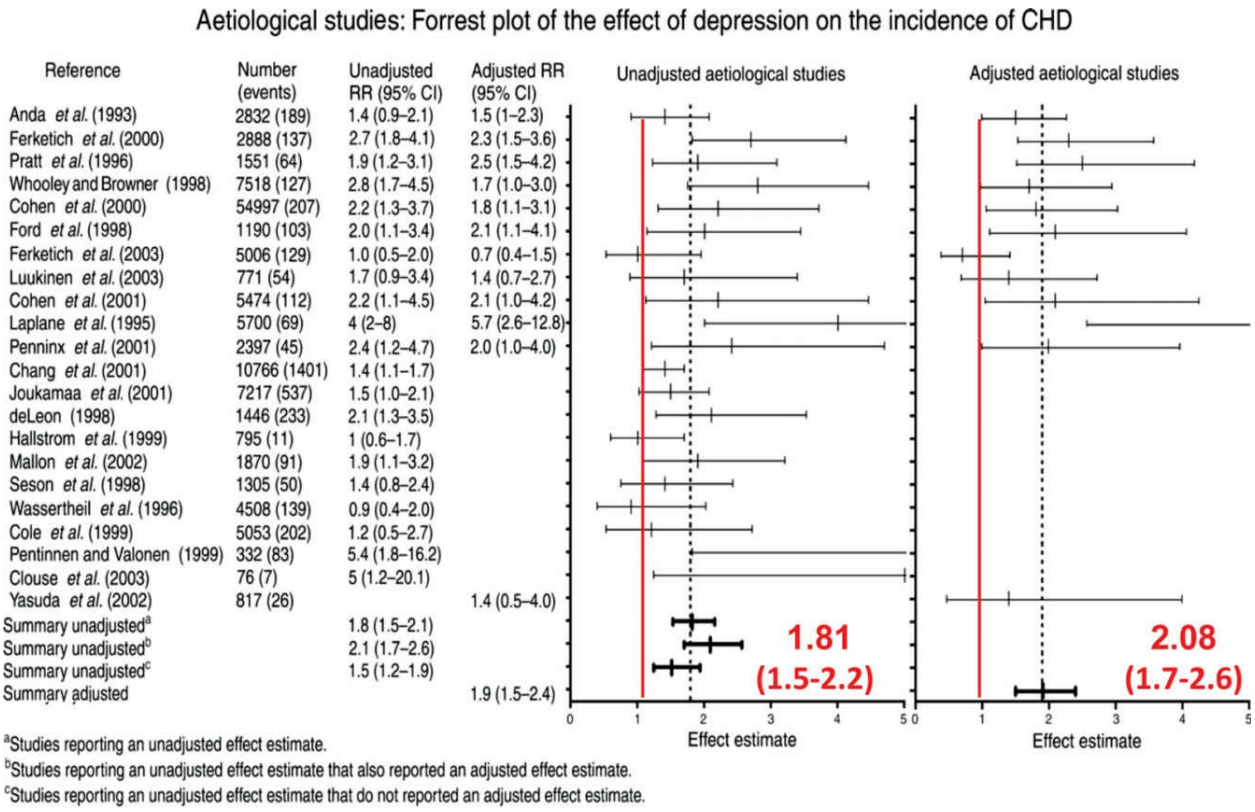

FIGURE 61.2 Relative risks (RR) are shown for the occurrence of coronary disease events (cardiac death or myocardial infarction) in association with depression among community cohorts, according to both unadjusted and adjusted data. A substantial elevation in risk is noted. RR, risk ratio; CHD, coronary heart disease; CI, confidence interval. (From Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6,362 events among 146,538 participants in 54 observational studies. *Eur Heart J*. 2006;27:2763-2774.)

Investigators have also found a graded relationship between the degree of depressive symptoms and the likelihood of adverse cardiac events. For example, Lesperance et al.[3] conducted a follow-up study in 896 patients who had sustained a myocardial infarction. All patients filled out a questionnaire (the Beck Depression Inventory) to assess their degree of depressive symptoms at baseline, and were then followed for 5 years (**Figure 61.3**). The risk of cardiac mortality during the follow-up period increased in direct proportion to the magnitude of depressive symptoms. Notably, even mild depressive symptoms increased risk somewhat in comparison with patients who had no signs of depressive symptoms.

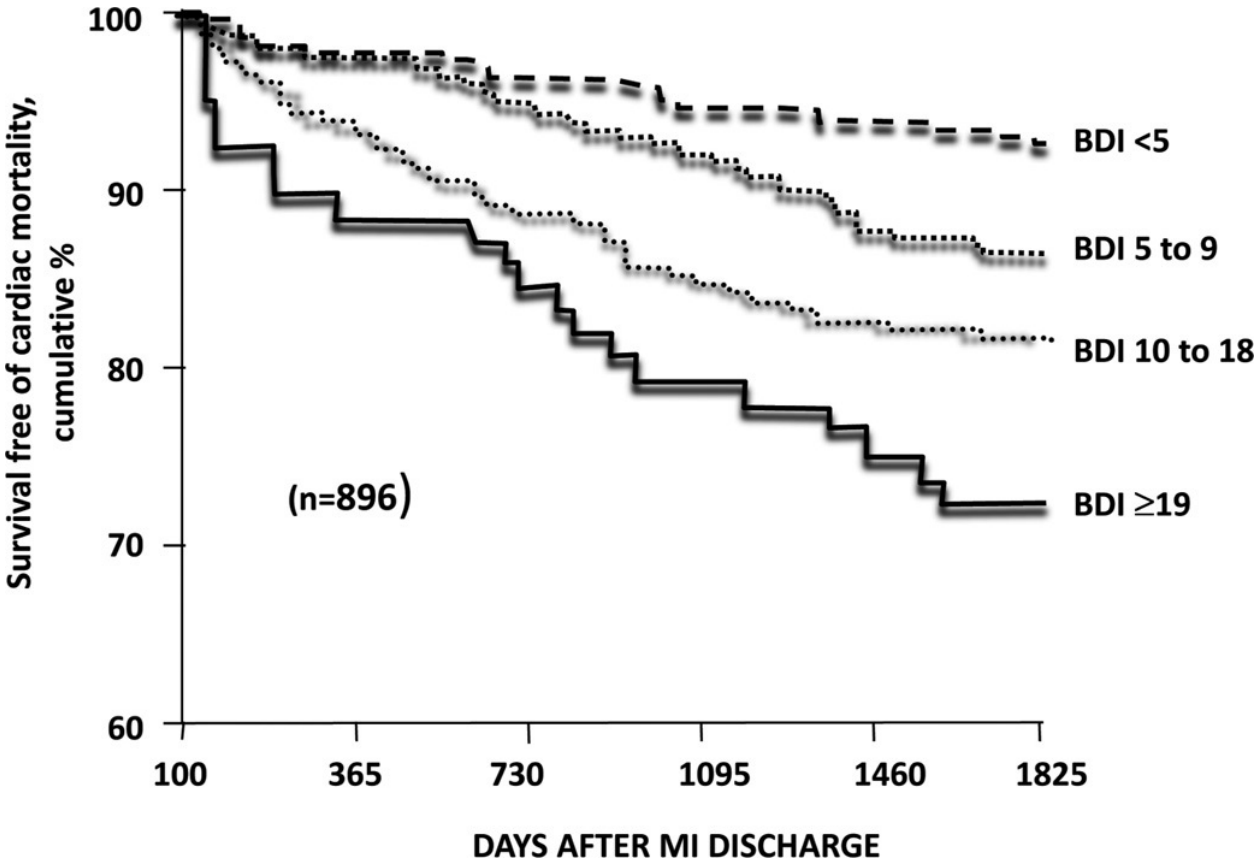

FIGURE 61.3 A 5-year follow-up of 896 post–myocardial infarction (MI) patients who were assessed according to their degree of depressive symptoms according to the Beck Depression Inventory (BDI), ranging from no depressive symptoms (BDI < 5) to moderate to severe depressive symptoms (BDI ≥ 19). There was a gradient relationship between the magnitude of depressive symptoms and the frequency of subsequent deaths. (From Lesperance F, Frasure-Smith N, Talajiv M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation*. 2002;105:1049-1053.)

Notably, the prevalence of depression is substantial among cardiac patients. The 1-month community-based prevalence of major depression is approximately 4% to 5%. By contrast, this prevalence is approximately 2-fold higher in cardiac populations.[4] In addition, depressive symptoms of a milder degree than major depression are found in another 15% of cardiac patients.[4] The high prevalence typifies a reciprocal relationship: depression is a risk factor for heart disease, but in addition, the development of heart disease can lead to depressive symptoms in some patients.

ANXIETY

Anxiety symptoms are also common in society and increase in prevalence

among patients with heart disease and other chronic medical symptoms. As with depression, symptoms may range from mild symptoms to severe psychiatric conditions, including phobias, panic disorder, generalized anxiety disorder, and posttraumatic stress disorder (PTSD). The relationship between anxiety and cardiac disease was recently assessed in a very large meta-analysis of 46 studies, involving 2,017,276 participants and 222,253 subjects with anxiety.[5] Anxiety was associated with a moderately elevated risk for cardiac disease, cardiac death, stroke, and heart failure, as shown in **Figures 61.4 and 61.5**.

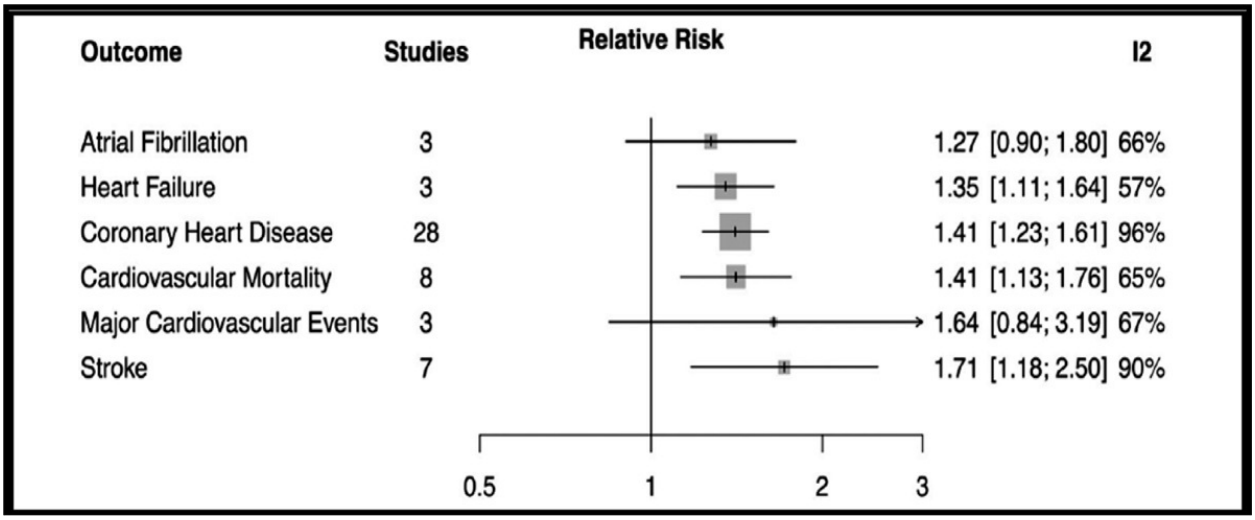

FIGURE 61.4 The relative risk posed by anxiety in association with various cardiac conditions. (From Emdin CA, Odutayo A, Wong CX, et al. Meta-analysis of anxiety as a risk factor for cardiovascular disease. *Am J Cardiol*. 2016;118:511-519.)

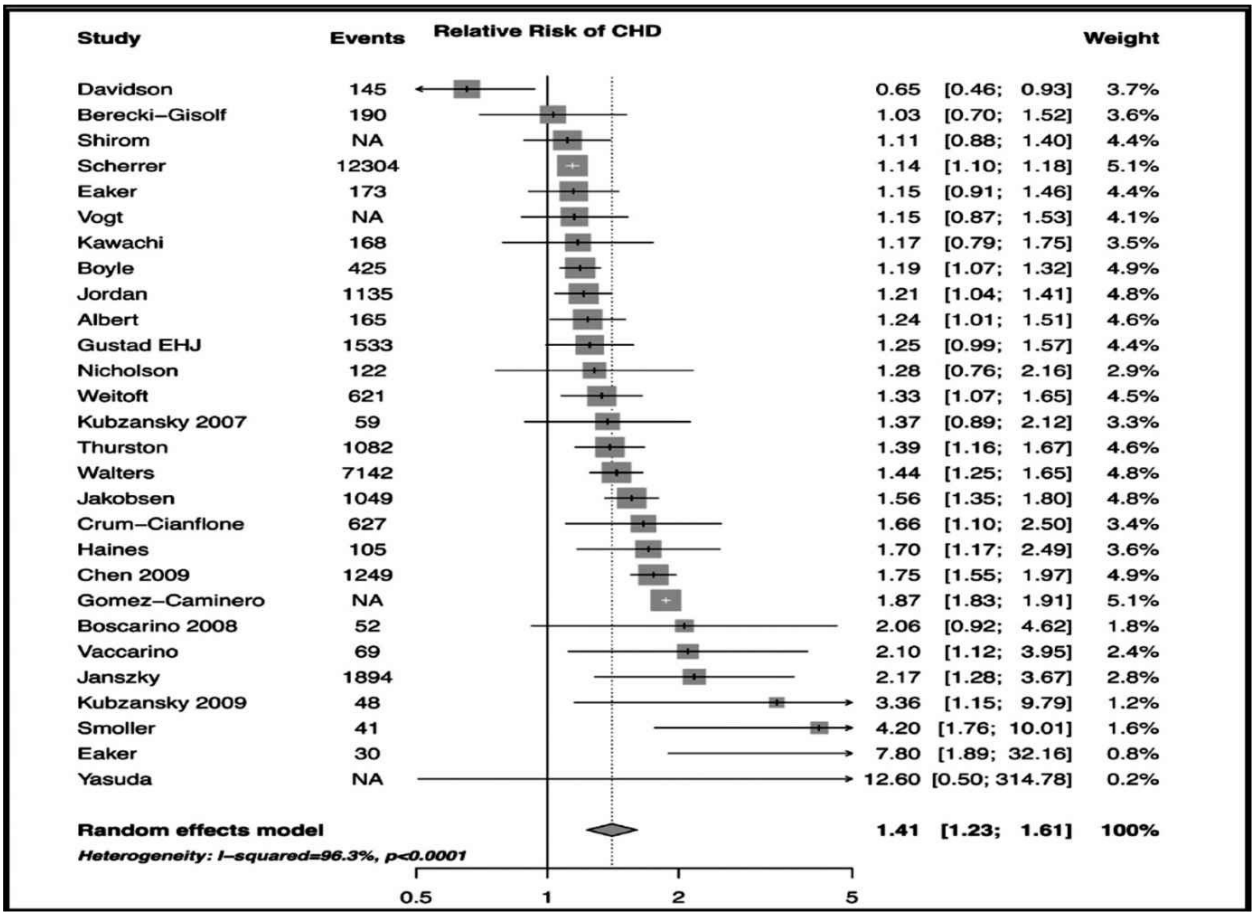

FIGURE 61.5 The relative risk of developing coronary heart disease (CHD) is shown for each of 28 studies included in this meta-analysis. (From Emdin CA, Odutayo A, Wong CX, et al. Meta-analysis of anxiety as a risk factor for cardiovascular disease. *Am J Cardiol*. 2016;118:511-519.)

Psychiatric-level anxiety syndromes are associated with even further cardiac risk.[6–9] For instance, an interesting study concerning PTSD was conducted in 562 twins in whom only one of the two twins had suffered from PTSD. The twins were followed for a mean of 13 years.[10] The presence of PTSD in one of the twins was associated with a more than 2-fold increase in cardiac disease.

PESSIMISM

It has been demonstrated that optimism is a general life asset, associated with greater likelihood of successful goal achievement in life and an enhanced sense of resilience. Pessimism, by contrast, can diminish coping skills and self-confidence, and it is associated with an increased risk of depression. Studies on the specific effects of pessimism versus optimism as a cardiac risk factor, however, have only been recent.

Pessimism is generally characterized as a personality disposition toward expecting negative outcomes in the future. Optimists, on the other hand, tend toward expecting positive outcomes. Another way psychologists have assessed optimism versus pessimism in the past is by examining people's "explanatory style." Pessimists tend to evoke an explanatory style of self-blame when negative events occur, and they tend to expect that these events will be persistent and affect many aspects of their lives. Optimists, on the other hand, tend to avoid self-blame for negative events, and view these events as transient and limited in scope.

Both dispositional and explanatory pessimism have been linked to negative health outcomes. The results, in fact, have been quite consistent. Pessimism is associated with reduced longevity and increased risk of cardiovascular events and stroke.[11–15] Optimism has the opposite effect. As with most psychological risk factors, a graded relationship has been noted between the level of pessimism or optimism and the occurrence of these negative events. Recent data from the Nurses' Health Study (NHS) have also demonstrated important effects of optimism on reduction of other health outcomes, including cancer, respiratory disease, and infection.[16]

As with other psychological risk factors, the impact of optimism versus pessimism on health appears to be related to both biologic and behavioral mechanisms. Biologic mechanisms include a positive effect of optimism on immune function, better autonomic function, and, pending further study, potentially slower rates of telomere shortening over time. In addition, optimists tend to exhibit a higher likelihood of engaging in exercise, eating a healthy diet, and a lower likelihood of smoking and other negative behaviors.

HOSTILITY

Hostility is a broad construct that encompasses the traits of anger, cynicism, and mistrust. The study of hostility has been an outgrowth of initial work by Friedman and Rosenman to study a personality complex that they termed "Type A behavior pattern," based on three features: the presence of easily provoked hostility, a competitive drive, and a sense of time urgency and impatience. Over time, epidemiologic data did not confirm initial positive findings concerning Type A behavior pattern as a cardiac risk factor, but the hostility component has been shown to demonstrate a modest relationship to heart disease. This construct is hard to study because many patients with hostility tend to have some degree of

self-denial or lack of self-awareness about their anger and hostility. Nevertheless, a large meta-analysis found that individuals with a pattern of anger/hostility have about a 20% to 25% elevated risk for heart disease compared to individuals without hostility.[17]

LONELINESS AND POOR SOCIAL SUPPORT

Individuals have a basic need to be socially connected to others. Here, we can make a distinction between being alone and feeling lonely. People vary in the depth of their need for connectivity to others, but unmet social needs and/or a feeling of loneliness is not only painful, but often health damaging. One of the first studies to examine the relationship between social factors and adverse outcomes was the "Alameda County study."[18] This study asked individuals to characterize how many people were in their social network and then followed them for a number of years. The investigators found that as the size of one's "social network" decreased, the risk of all-cause mortality increased (**Figure 61.6**). Since then, this finding has been reproduced in many studies. Similarly, other studies have demonstrated that a variety of social factors are related to health, including the size, structure, and frequency of contacts within one's social network, and the quality of either functional and/or emotional support that one receives from others. A recent meta-analysis of 148 studies found that individuals who scored high on a measure of social integration had an approximately 2-fold increase in survival compared to individuals who were less socially integrated.[19] Such an increase in survival is a substantial health benefit when compared to other clinical parameters that can affect health.

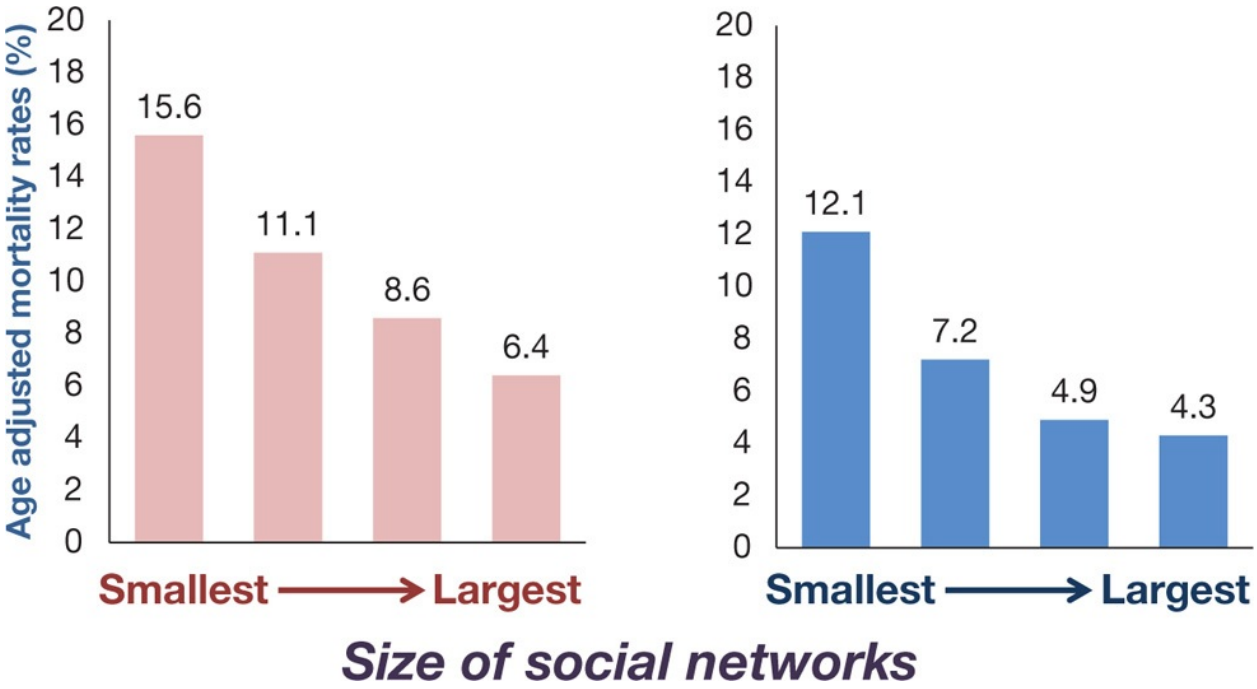

FIGURE 61.6 The age-adjusted mortality results are shown for men and women who were characterized at baseline according to the size of their social network size in the Alameda County study. Mortality rates were highest in those with small social networks and lowest in those with high social networks. (From Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda county residents. *Am J Epidemiol*. 1979;109:186-204.)

PURPOSE IN LIFE

Living with intentionality and goal directedness provides individuals with a strong sense of life purpose. By contrast, a lack of life purpose is associated with boredom and increases the risk of future depression. Over the last decade, a series of studies have studied the relationship between one's sense of life purpose and important clinical outcomes, such as heart disease, dementia, and longevity. In one recent meta-analysis of 10 prospective studies that involved over 136,000 subjects, investigators found that a high sense of life purpose was associated with a reduced risk ratio for cardiac events and for all-cause mortality (**Figure 61.7**).[20] The results were highly consistent among the individual studies constituting this meta-analysis. A higher sense of purpose has also been linked to a reduced risk of stroke, future physical disability, and dementia. Prospective study is needed to study the mechanisms by which this occurs, but preliminary data suggest that people who live with a high sense of life purpose tend to maintain more positive health behaviors and have a greater sense of psychological well-being. In addition, purpose in life may be associated with greater resilience, as suggested by a meta-analysis of 70 studies that found that

purpose in life was associated with a greater sense of competence, stronger social integration, and more positive affect.[21]

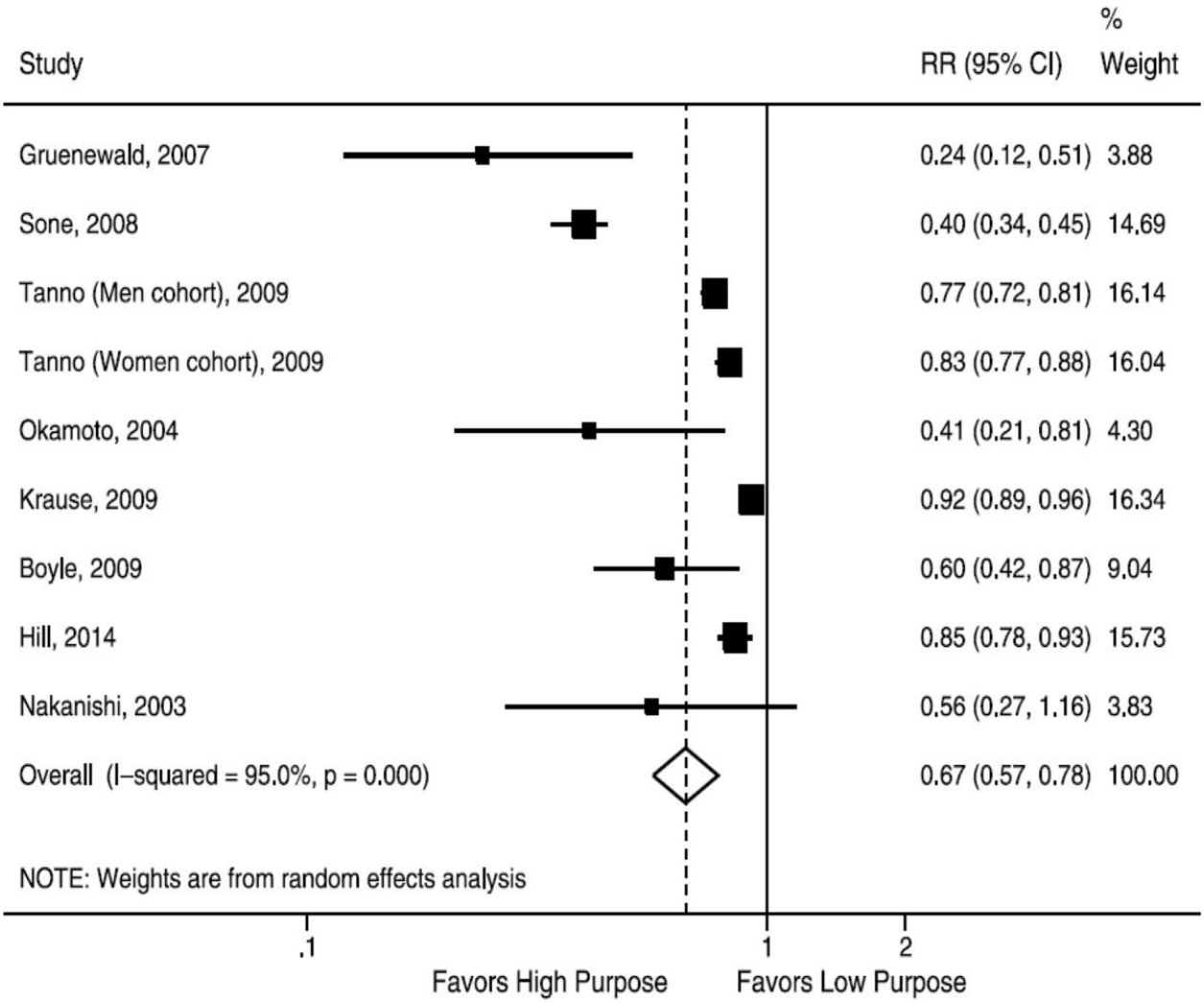

FIGURE 61.7 Meta-analysis of the risk ratio for having adverse cardiac outcomes according to the presence of having a high versus low sense of life purpose. The presence of high purpose was associated with a diminished risk of cardiac events. CI, confidence interval; RR, risk ratio. (From Cohen R, Bavishi C, Rozanski A. Purpose in life and its relationship to all-cause mortality and cardiovascular events: a meta-analysis. *Psychosom Med*. 2016;78:122-133.)

CHRONIC STRESS

Another psychological factor associated with heart disease is chronic stress. More distinctively, it is “toxic” stress, or a chronic sense of distress, that seems to be associated with adverse medical outcomes. That is, not all stress is bad. Rather, individuals, as part of their desire to live a life of purpose, like to take on life challenges. Successful coping with life stress can provide both life satisfaction and an increased sense of self-esteem.

As with depression, chronic distress can lead to stimulation of the hypothalamic–pituitary–adrenocortical axis and the sympathetic nervous system,

leading to many similar effects on physiologic functions and organ systems. Of note, people under chronic distress are also more likely to become physiologic "hyper-reactors," meaning that there is a tendency for heart rate and blood pressure responses to rise higher and recover more slowly following acute stimulations compared to people who are not under distress. Other studies indicate that chronic distress can lead to signs of accelerated aging, as measured by DNA evidence.[1,22] Finally, chronic distress can result in adverse changes in the brain's plasticity, including increase in the size of the amygdala, which is the brain's fear center, and reduction in the size of the hippocampus and prefrontal cortex.[23]

There are various types of distress that have been linked to a higher risk of heart disease, including work stress and marital strain. In addition, acute and chronic illnesses can also produce a stress response among some patients. For instance, Edmonsdon et al.[24] found that among patients presenting with acute coronary syndrome (ACS) patients, 12% developed symptoms of PTSD. Other common negative chronic stressors include caregiving strain and the enduring effects of childhood abuse or trauma. For instance, in the NHS II, involving a 16-year follow-up of 66,798 women, a history of childhood abuse was associated with an approximately 1.5-fold increase in the onset of cardiovascular events by middle age.[25] The investigators found that adult risk factors such as smoking, diabetes, and increased body mass index, as well as the presence of other psychosocial factors, such as depression, accounted for the majority of this elevated risk.

NEGATIVE FATIGUE STATES

Another negative psychological risk factor is the presence of negatively charged fatigue states (ie, a feeling of tiredness that is intermixed with negative emotions or a sense of tension). This is in contrast to calm-tiredness, which may occur after a long day of satisfying work. The latter is regenerative, whereas a state of "tense-tiredness" can induce negative moods and a need for quick fix behaviors.[26,27] When individuals are in sync in terms of physical health, social well-being, and a sense of purpose, they have a greater sense of vitality. The presence of vitality promotes an overall sense of well-being and provides people with energy for successful coping and emotional regulation. On the other end of the spectrum is the presence of "vital exhaustion," a condition of excessive fatigue, feelings of demoralization, and increased irritability, which has been

postulated to be a result of prolonged distress.[28] Epidemiologic study has consistently linked vital exhaustion to an increased risk of cardiac events and/or all-cause mortality. For instance, vital exhaustion was recently compared to other CVD risk factors in a follow-up of 8,882 individuals who were initially free from CVD in the Copenhagen City Heart Study.[29] Vital exhaustion was found to be a strong independent risk factor for the development of CVD in both genders, with manifestation of a strong risk-adjusted gradient relationship. Another negative fatigue state is the presence of burnout, which is characterized by a sense of exhaustion, depersonalization, and diminished efficacy at work. Preliminary study also suggests that burnout can increase the risk for heart disease.[30-31] In addition, chronic poor sleep, including insomnia, represents another risk factor for heart disease.[32,33]

"CLUSTERING" OF PSYCHOSOCIAL RISK FACTORS

Although psychosocial stresses are often studied in isolation, in life they often tend to cluster together. For example, people with poor social support are also more likely to feel life stress. When such negative psychosocial risk factors cluster, they tend to magnify the potential pathophysiologic effects of these factors. For example, in a study of post–MI patients, the presence of high levels of life stress and social isolation were both found to be associated with an approximately 2-fold increase in subsequent clinical events.[34] But overall clinical risk was increased 4-fold among post–MI patients reporting both social isolation and life stress. Similarly, clinical risk is magnified among patients who report both anxiety and depression.[35] Notably, psychosocial factors also interact synergistically with physical risk factors to increase overall clinical risk. For example, depressed patients who are physically inactive are at increased risk for future cardiac events (**Figure 61.8**).[36] Such data emphasize the need to treat any and all risk factors as best as one can to reduce the overall clinical risk among patients.

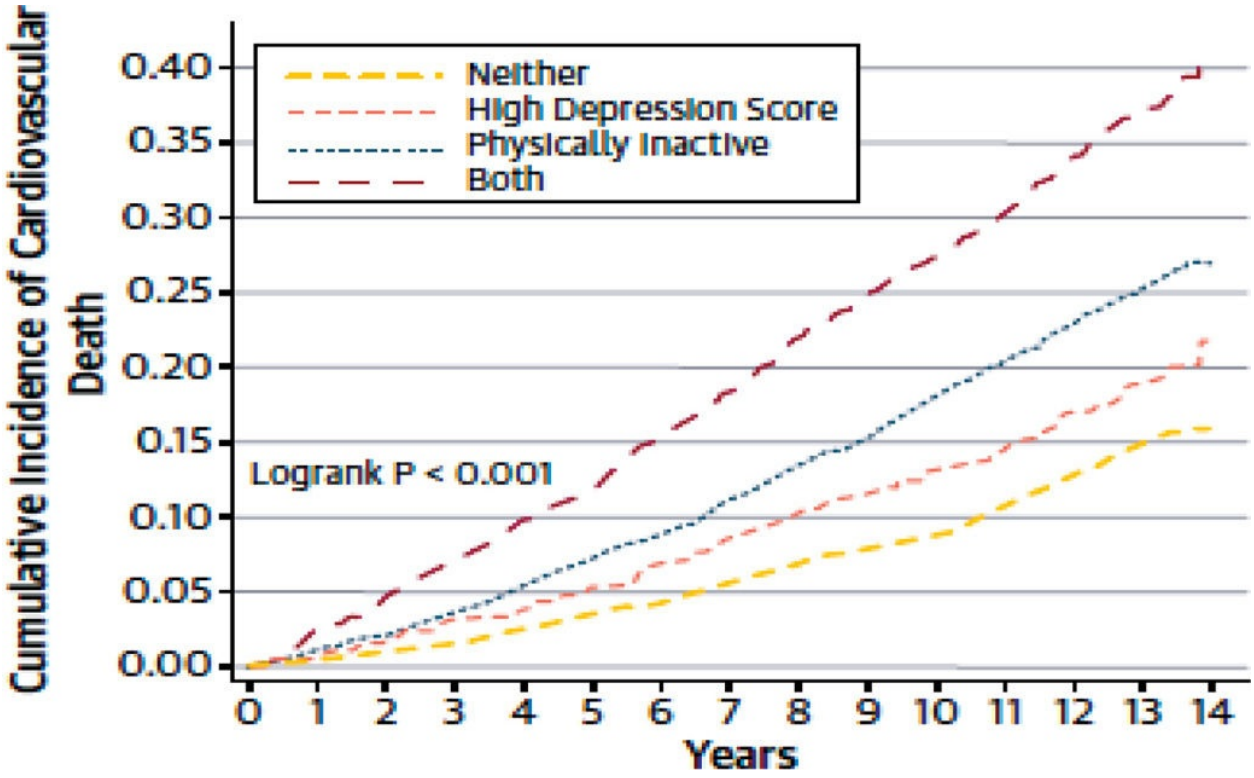

FIGURE 61.8 The cumulative incidence of cardiovascular death among patients divided into four groups according to being physically active or inactive and according to having a high versus low depression score in the Cardiovascular Health Study. (From Win S, Parakh K, Eze-Nliam CM, et al. Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. *Heart*. 2011;97:500-505.)

MANAGING HEALTH BEHAVIORS AND LIFE STRESS

After providing the audience with this overview, Dr. Jones asked if there were any questions and then began the second portion of his lecture. He mentioned that any health goal, like goals in general, could be broken down into three phases, as illustrated in another slide he showed them (**Figure 61.9**). These three phases included: (1) motivation; (2) goal execution; and (3) goal maintenance. Under each category, Dr. Jones listed a number of representative tools and techniques that could be used by individuals to foster that phase of goal pursuit. To save time, Dr. Jones chose to address just a few of these tools in his lecture, as follows:

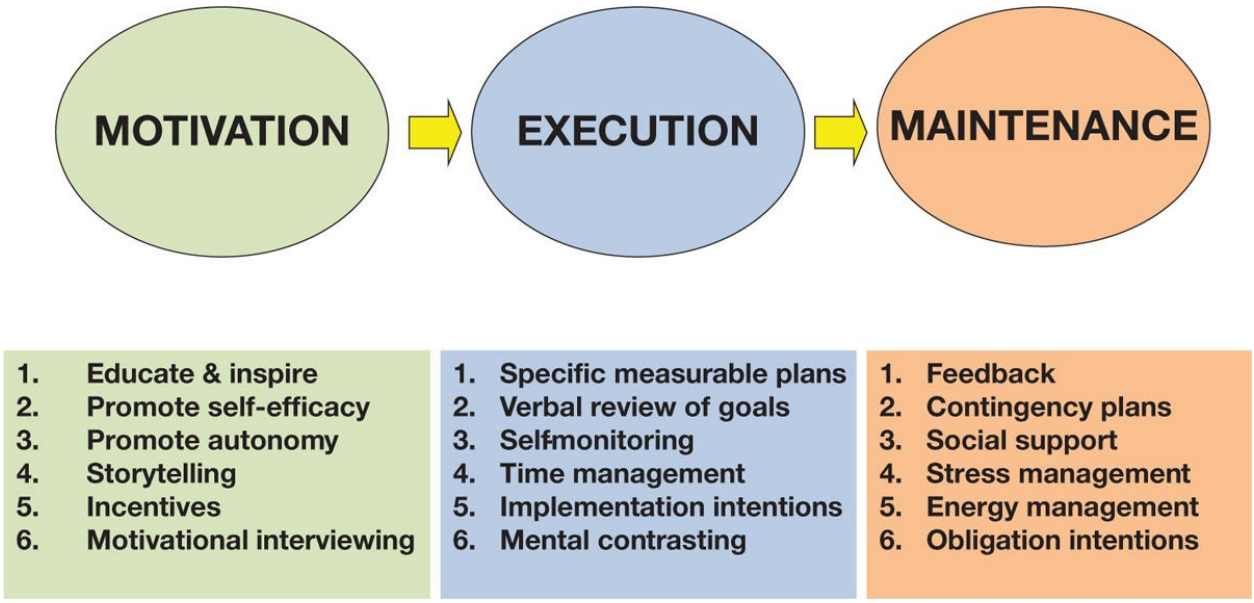

FIGURE 61.9 The pursuit of goals can be divided into three components, as shown. Techniques that can be used to foster motivation, execution, and maintenance in each group are shown. (From Rozanski A. Behavioral cardiology: current advances and future directions. *J Am Coll Cardiol*. 2014;64:100-110.)

AUTONOMY

Motivation can be classified as either "intrinsic" or "extrinsic" in origin. Examples of extrinsic motivation include warning, provision of incentives, or the provision of case managers. When motivation comes from within, this is termed internal motivation. Patients, as with all people, are more likely to stick with a goal that is derived from internal motivation. The desire to choose a goal based on your own volition rather than being told by someone else what to do is termed "autonomy." For instance, whereas physicians can provide patients with compelling health reasons for exercise, diet, and so forth, a schooled physician will also look for other angles by which to foster internal motivation in patients. For instance, a patient may want to start a diet to feel good or to please a spouse or merely to please his or her physician. The more compelling the personal reason is, the more likely the patient will follow through. In addition, merely asking patients to verbalize their own personal reasons helps patients to take more ownership of their health goals. Various studies have found that when patients leave their doctors' office with a sense of autonomy regarding a suggested health goal, they are more likely to adhere to their health goals over time.

SELF-EFFICACY

The setting of unrealistic goals is a prescription for failure. By contrast, the more someone believes that a certain goal can be accomplished (ie, the greater the sense of "self-efficacy"), the more the person will be willing to try. For instance, health organizations recommend that individuals get at least 20 to 30 minutes of moderate physical exercise on most days of the week. Although this is a reasonable goal for people who are generally fit, this is generally too hard for a completely sedentary person. It is more important that sedentary people first establish a goal that is compatible with their individual sense of "self-efficacy," even if this means a very minimal goal at first, such as walking 5 to 10 minutes/day. Once patients have tasted some success in a new health domain, goals can then be increased incrementally.

SPECIFIC ACTION PLANS

Vague action plans are another prescription for failure. Rather, the more specific the action plan, the greater the likelihood of patient adherence. For instance, establishing a goal to get more exercise is a vague goal. Deciding to join a gym is more specific. Even better is committing to which days of the week one may go to the gym and for how long. Writing down one's goals helps build one's sense of commitment.

SELF-MONITORING

Self-monitoring helps to anchor health goals by providing a mechanism for daily self-awareness and personal feedback. The most obvious example of self-monitoring is using a scale to weigh oneself daily. Studies indicate that overweight individuals who weigh themselves daily are more successful in maintaining weight loss compared to individuals who do not. More recently, the use of pedometers as a means of self-monitoring one's physical activity has become increasingly promulgated. For example, a review of medical studies found that the use of pedometers was associated with a 27% increase in physical activity compared to physical activity before initiating pedometer use.[37] The use of pedometers has a number of potential advantages: it is a way of becoming more cognizant of one's physical activity; it can be motivational for some to monitor their steps and try to increase them; and the information can also represent a form of feedback to patients as they learn to monitor and track their daily steps.

There are different potential walking goals that can be established with the use

of a pedometer. Some providers have popularized a goal of achieving 10,000 steps/day, but caution needs to be employed, because such a goal may not be practical initially for many older adults, those with chronic illnesses, or those who are significantly deconditioned. Rather, an incremental approach in terms of increasing pedometer steps based on one's baseline level of activity is preferred for those who are initially sedentary. For instance, after determining baseline step counts based on a week of observation, patients may begin by seeking to increase their physical activity by a mere 100 to 200 steps/day, with progressive increases according to an individual's sense of self-efficacy during subsequent weeks.

IMPLEMENTATION INTENTIONS

When a patient commits to a new health goal, the new practice is highly vulnerable because of the pressures of daily life. A new practice must be repeated continually before it becomes a habit. To strengthen habit formation, a group of investigators, Gollwitzer and colleagues, have developed a technique called "implementation intentions."[38] An implementation intention involves the use of an external stimulus to cue a specific behavior ("X"), followed by a specific action ("Y") that will be initiated when that cue occurs. The cue can be a stimulus in time, place, or situation. Gollwitzter et al. suggest that the formulation should always be stated as follows:

> **"When it is X, I will do Y," where "X" is the cue, and "Y" is the behavior.**

Although this technique might seem simple, a large meta-analysis of many studies involving the use of implementation intentions has found that implementation intentions are associated with a moderate to large effect in stimulating successful goal achievement.[39] One such example comes from a study of women who were being encouraged to perform breast self-examination (BSE) to promote early detection of breast cancer.[40] In the study, all women received a lecture on the importance of BSE, but half of the women were also asked to perform an implementation intention around how and when they would perform this task (eg, *"On the first evening of each new month, I will perform my breast self-examination."*). Notably, the women who were asked to form an implementation intention concerning BSE manifested a substantially higher rate of adherence to this health practice during follow-up.[40] Similar findings were

noted in a study concerning implementation intentions and physical activity (**Figure 61.10**).[41]

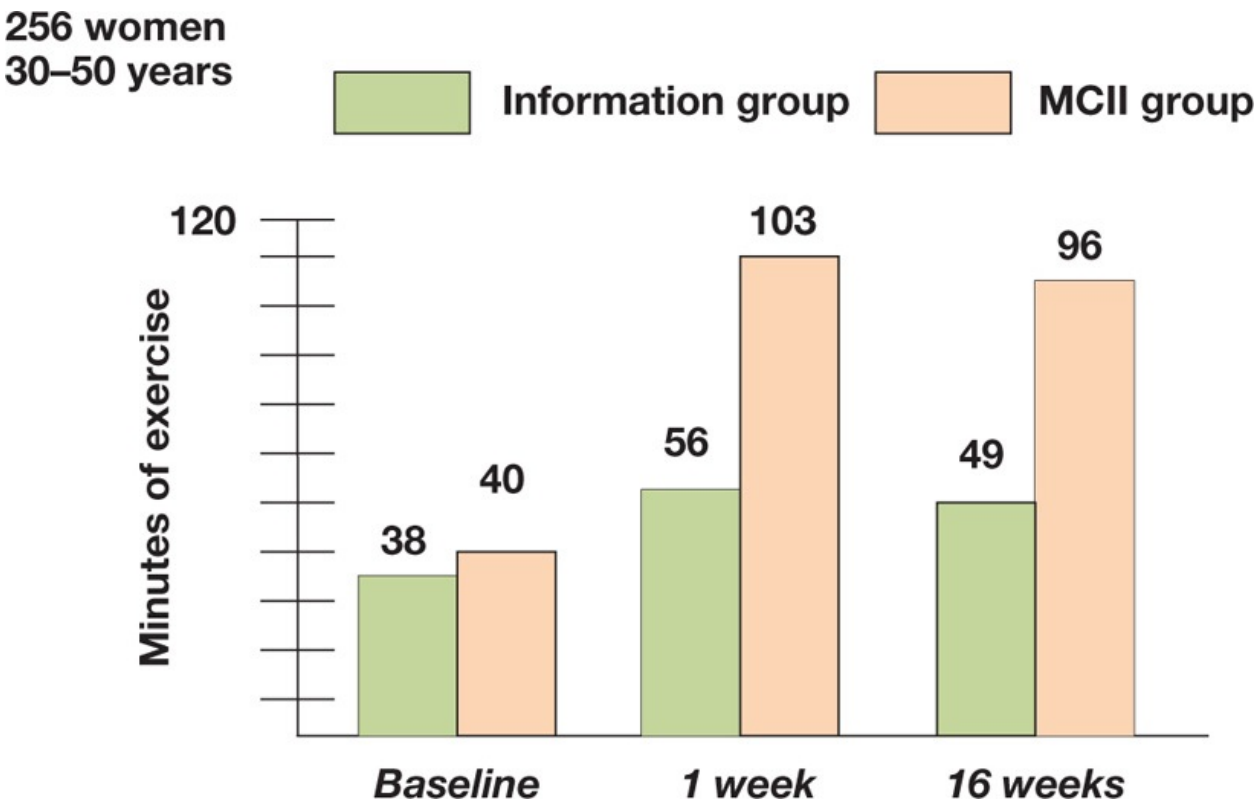

FIGURE 61.10 Minutes of moderate to vigorous physical activity per week among two groups of women, randomized to either an information group about exercise or to a group that were also asked to perform mental contrasting and make an implementation intention about exercise (MCII). The MCII group had nearly double the amount of physical activity at both one week and four months. (From Stadler G, Oettingen G, Gollwitzer PM. Physical activity in women: effects of a self-regulation intervention. *Am J Prev Med*. 2009;36:29-34.).

CONTINGENCY PLANS

Developing contingency plans around new goals is an important step in fostering long-term goal maintenance. Stressful life events, boredom, new competing priorities, and many other factors frequently intervene to challenge a patient's ability to stick with a new health goal. The key thing during such times is to not let the desired goal activity go down to zero, since the complete cessation of activity increases the risk that the health goal will not be reinstituted. A contingency plan represents a certain floor of minimal activity that will be maintained during times of stress. For example, if a patient has committed to exercising at the gym five times per week, the contingency plan may be a

temporary reduction to exercising only 2 times/week.

SOCIAL SUPPORT

Having social support can provide both renewable motivation and coping help to maintain new health goals. Medical studies reveal that when social support is lacking, patients are less likely to adhere to their physicians' health recommendations.[42] Building appropriate social support is highly personal and depends on many factors, such as one's personal need for social support, the availability of friends, social opportunities in one's community, and time constraints.

FEEDBACK

Feedback represents a specific form of tangible support, combining components of the aforementioned tools. Knowing that feedback will be provided by one's health provider tends to increase one's sense of accountability. Feedback may also help people gain insights into the natural blind spots that they experience when pursuing difficult goals. Feedback also provides a sense of social support and a sense of teamwork—"we're in this thing together."

STRESS MANAGEMENT

One of the common reasons why patients fail to maintain new health habits over the long term is their difficulty in balancing this new commitment with other life priorities. Many patients can benefit from enhanced stress management skills. One useful approach that may be particularly relevant for cardiac patients is to consider stress from the perspective of one's sense of energy and sense of tension. This was the focus of research by Dr. Robert Thayer years ago.[26,27] Through his work, he developed his model of tension and energy, as shown in **Figure 61.11**. He observed that when people are both tense and tired, they tend to be more moody and more likely to resort to "quick fix" behaviors that will reduce their tension or increase their energy. Very often, these quick fixes are counterproductive and health damaging, such as the use of cigarette smoking to reduce tension or frequent ingestion of candy bars to mollify stress or increase energy.

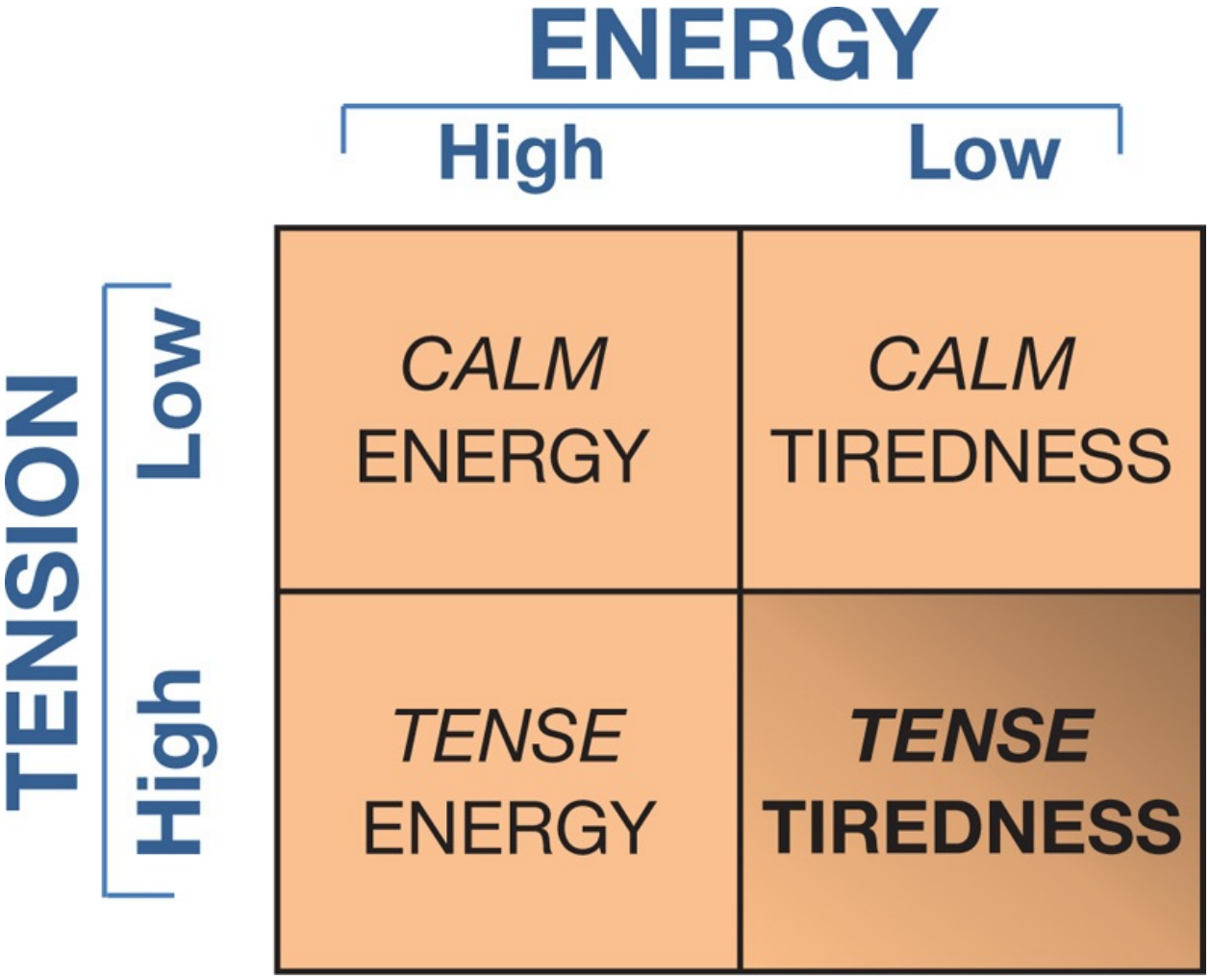

FIGURE 61.11 Per work developed by Thayer et al., personal states can be characterized by one's level of energy and tension, as shown. Periods of tense-tiredness tend to be characterized by a higher frequency of low moods and quick-fix behaviors.

Either increasing energy and/or reducing stress can be used to decrease the frequency of tense-tiredness that a person may feel. The best way to reduce chronic stress is to reduce the source of the tension. However, even when this is not possible, the breakup of continuous tension can be quite beneficial. Tension-busters include breathing exercises, guided meditation exercises, engaging in interests that one finds stimulating or relaxing, and social diversions. In addition, individuals may turn to specific forms of stress-reducing physical activities such as yoga and tai-chi.

Alternatively, individuals can attempt to reduce tense-tiredness by taking steps to increase their general energy level. Importantly, research shows that people tolerate their stress better when they feel energetic. Taking on positive health

behaviors, such as exercise, adequate sleep, and a healthy diet plan all help in this regard. In addition, if a person realizes that there is a point in the day at which they are particularly prone to feeling tired, they can build an energy plan around that, such as taking a short nap, or developing the habit of taking out a 10- to 15-minute physical or mental breather that is restorative of energy during energetically low points of the day.

When one feels that their stress is unmanageable, seeking the advice of trained coaches may be useful for isolated problems, such as poor time management skills, and/or the consideration of mental health counseling, particularly if there is also an overlay of anxiety, depressive symptoms, increasing pessimism, sleeping problems, an inability to relax physically or mentally, or feelings of social alienation.

AN EXERCISE IN LIFESTYLE MANAGEMENT

After completing the second phase of his lecture, Dr. Jones explained that life stress and psychological challenges are commonplace, and can frequently be exaggerated by acute or chronic illnesses. He then mentioned that there is no specific formula for dealing with life stress, because of the highly varied differences in individuals' "life settings" (eg, income, social circumstances), personalities, coping skills, level of conflicting priorities, and many other factors, intrinsic talents, upbringing to them. To illustrate some of the points of his lecture, Dr. Jones gave the audience participants the following assignment:

First, he asked the people to identify all negative health habits and psychological problems that were relevant to them on the basis of his lecture presentation. David thought about this. He certainly did not feel depressed, unduly anxious, or hostile toward anyone. He was quite dissatisfied with his failure to exercise and to maintain his new diet. In addition, he recognized that he was overdoing it at work and that he had to work on his time management skills He was also not getting enough sleep. David realized that he had a lot on his plate.

Dr. Jones then asked each individual to identify one problem that they would like to work on over the next 3 months. This did not preclude working on other problems, but he explained that strong success in one area often breeds energy to succeed in other arenas. David was fascinated by the question. He decided to take on the issue of restarting an exercise program. He recalled how good he had

felt when he was getting more physically fit and how that had helped him to maintain his health diet during that time.

Dr. Jones then asked each participant to form a specific health goal to address a chosen problem, with the greatest specificity possible. David realized that the only time he was likely to exercise was when he left work. He got to work too early to consider exercise, and exercising during the day was not an option. Once he got home at night, he was either too distracted or tired to go out to the gym again. Thus, the only practical option was to exercise after leaving the office, before he got home. As to the frequency, David figured he would try to exercise daily after work, so that he could make this more habitual. He further decided to devote a total of 1 hour at the gym per session, which would include time to change into and out of his gym gear and a 30-minute workout.

Dr. Jones then asked the audience to form an implementation intention around their new health goal. David had really enjoyed that part of the lecture and he quickly formulated his intention (**Figure 61.12**):

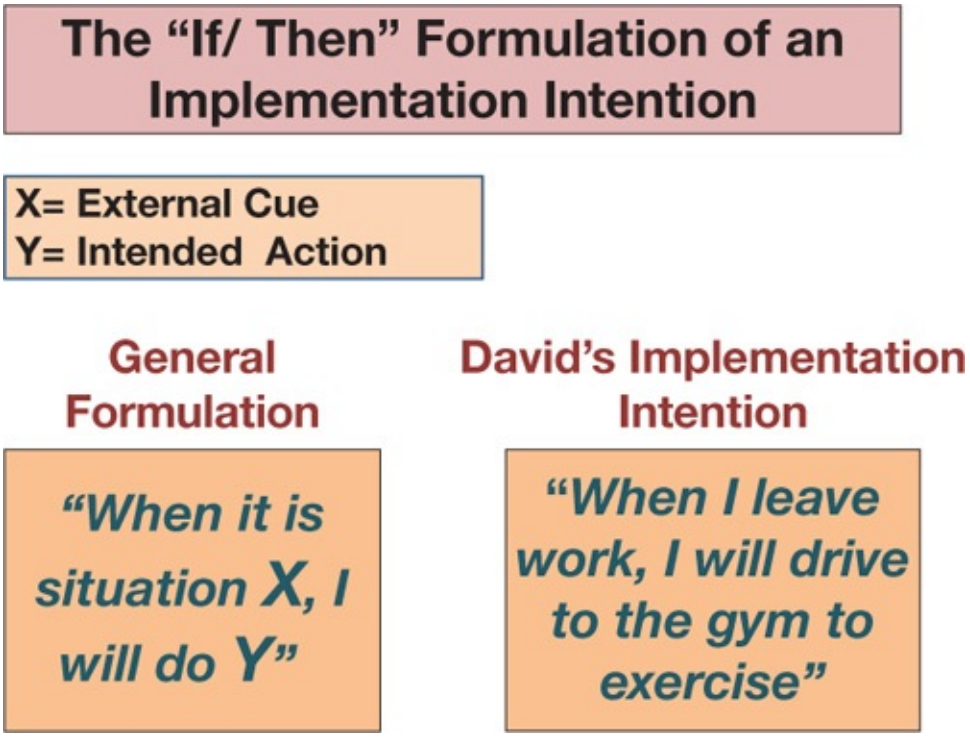

FIGURE 61.12 General formulation of an Implementation Intention and the specific Implementation Intention formulated by David. "X" is the external cue, which may be a specific time, place, or situational cue. "Y" is the intended action.

"When I leave the office on Monday through Friday, I will drive

directly to the gym to work out for 30 minutes."

Leaving work was David's cue to engage in his health behavior. Working out at the gym was the specific behavior.

Finally, Dr. Jones suggested that each individual formulate a contingency plan for their new goal. For David, this amounted to going to the gym on Fridays, for one half-hour of exercise, with a second makeup session on the weekends.

Dr. Jones then asked the participants to write down their implementation intention and share it with someone who could hold them accountable. He also suggested that the participants calendar their intended program, if possible, in their daily planners.

David left the lecture feeling very pleased with what he learned. Over the course of the next 3 months, David found himself exercising nearly every day during the week. At first, it was very difficult. As he drove to the gym, he found himself having all sorts of complaints, such as "I am too tired tonight" or "I have too much to do" or "I am hungry." But he stuck with the plan and was now realizing that the goal was taking root as a new habit. In fact, he was beginning to feel uncomfortable on the days that he did not go to the gym. During this time, David had also begun to eat better again and had lost 4 lb. He was excited to make his next follow-up meeting with his cardiologist. David shared with him his success, the life skills he felt he had learned in the process, and his overall sense of feeling quite energetic. At the end of the visit, David thanked his physician for being attuned to the psychological dimensions of health care and left the office with a sense of confidence about his health and his future.

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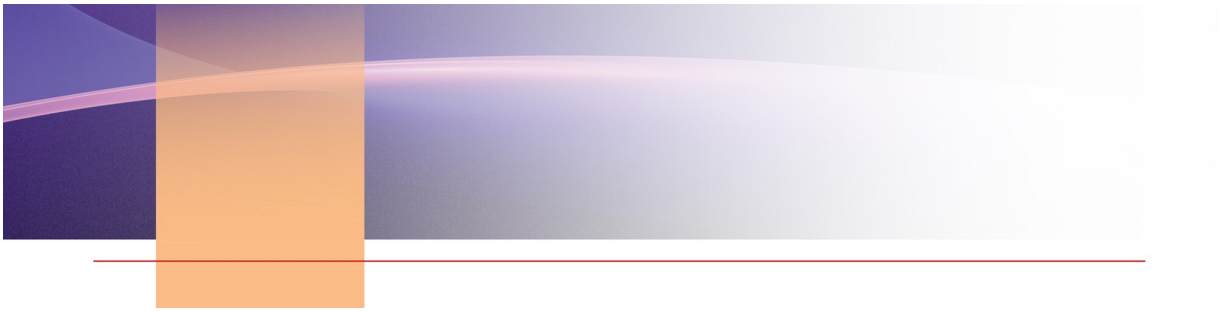

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Cardiovascular Medicine

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Acquisitions Editor: Julie Goolsby
Product Manager: Leanne Vandetty
Vendor Manager: Alicia Jackson
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Production Service: Integra Software Services

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Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
LWW.com

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Second Edition © 2004 by Lippincott Williams & Wilkins
First Edition © 2000 by Lippincott Williams & Wilkins

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Printed in People's Republic of China

Library of Congress Cataloging-in-Publication Data

Manual of cardiovascular medicine/editor, Brian P. Griffin; associate editors, Thomas D. Callahan, Venu Menon; guest editors, Willis M. Wu, Clay A. Cauthen, Justin M. Dunn. -- 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4511-3160-4 -- ISBN 1-4511-3160-7
I. Griffin, Brian P., 1956-
[DNLM: 1. Heart Diseases--diagnosis. 2. Cardiac Surgical Procedures--methods. 3. Heart Diseases--therapy. WG 141]
616.1'2--dc23

2012007462

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To our families and to the fellows and staff of the Department of Cardiovascular Medicine, Cleveland Clinic
—BG, VM, TC, WW, CC, JD

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PREFACE

The 4th edition of the *Manual of Cardiovascular Medicine* has been extensively updated and revised. New chapters on diabetes and the heart, pulmonary hypertension, cardiovascular manifestations of systemic disease, percutaneous management of structural heart disease, and troubleshooting ventricular assist devices have been added. Examples of key electrocardiographic tracings have been added as has a quick reference list of often needed formulae. Our aim has been to make this an easy-to-use, up-to-date, portable reference for all those involved in the management of cardiovascular disease. We have included current guidelines from the American Heart Association/American College of Cardiology and other national and international cardiovascular societies where appropriate. We appreciate the feedback we have received concerning prior editions and suggestions as to how to improve the book.

This manual has been written by the current and past fellows and staff of the Department of Cardiovascular Medicine, Cleveland Clinic. I wish to thank all those who contributed to this and previous editions, especially Eric Topol, coeditor in prior editions and now at Scripps, San Diego, and Steve Marso now at Mid America Heart Center, Kansas City, coeditor of the 1st edition. I wish to recognize the associate editors of this edition, Venu Menon and Tom Callahan, who are associate directors of the Cardiovascular Disease Training Program at Cleveland Clinic and who have done a superb job in helping edit the manual and keeping it topical. The guest editors, Willis M. Wu, Clay A. Cauthen, and Justin M. Dunn, are or have been Chief Fellows in the Cardiovascular Training Program at Cleveland Clinic and have done a fine job of ensuring that the contributions were on time and comprehensive. The section editors, Leslie Cho, Esther S.H. Kim, Richard A. Krasuski, and W.H. Wilson Tang, have done a great job in ensuring the quality and topicality of their sections.

I wish to thank Lois Adamski, the educational coordinator of the Cardiovascular Disease Training Program at Cleveland Clinic, for having anchored the program over many years. Fran DeStefano, Leanne Vandetty, and everyone at Wolters Kluwer have been wonderful to work with. I remain deeply indebted to John and Rosemary Brown for endowing a Chair in Cardiovascular Medicine that supports my academic activity and for their wonderful friendship. I have learned much over the years from my colleagues and fellows at the Department of Cardiovascular Medicine at Cleveland Clinic and from my surgical colleagues in the Heart and Vascular Institute, Cleveland Clinic, and I thank all of them for their collegiality and kindness. Finally, I wish to express my immense gratitude to my family: to my parents for instilling in me a thirst for knowledge and to my wife Mary without whose support, patience, and fortitude this and all other endeavors would have been impossible.

Brian P. Griffin, MD

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SECTION I

Ischemic Heart Disease

EDITOR

Venu Menon

CHAPTER 1

Christopher M. Huff

Acute Myocardial Infarction

I. EPIDEMIOLOGY. Acute myocardial infarction (MI) is the leading cause of death in North America and Europe. Each year, an estimated 785,000 Americans will sustain a new MI, and another 470,00 will have a recurrent MI. An American has an acute MI every 25 seconds, and someone dies of an MI every minute. In 2007, coronary heart disease caused one out of every six deaths. The incidence and mortality with acute MI have declined dramatically over the last 30 years, with the advent of the coronary care unit, fibrinolytic therapy, catheter-based reperfusion, and statin therapy. The aging of the population in advanced economies, as well as the global increased incidence of diabetes and obesity, will however, increase the sequelae of atherosclerotic coronary artery disease in the future (1).

II. PATHOPHYSIOLOGY. In most patients, coronary plaque rupture is the initiating event of acute MI. Rupture of the fibrous cap of a coronary atheroma exposes the underlying subendothelial matrix to formed elements of circulating blood, leading to activation of platelets, thrombin generation, and thrombus formation. Erosion of a coronary plaque without rupture can also lead to thrombus formation and is estimated to cause up to 25% of MIs. Acute coronary syndrome (ACS) is a dynamic process that involves cyclical transitioning among complete vessel occlusion, partial vessel occlusion, and reperfusion. Occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI). The pathophysiology of STEMI and non–ST-segment elevation myocardial infarction (NSTEMI) is similar, and this explains the substantial overlap in ACSs with regard to ultimate outcome, extent of necrosis, and mortality rates. The recognition of ST-segment elevation is particularly important because it generally mandates the need for emergent reperfusion therapy.

III. DEFINITION. A 2007 expert consensus document (2) redefined acute MI as the detection of a rise and/or fall in cardiac troponin with at least one value above the 99th percentile of the upper reference limit (URL) utilizing an assay with < 10% coefficient of variation at the level of detection, together with evidence of ischemia. Ischemia was defined as any symptom of ischemia, electrocardiographic changes suggestive of new ischemia, development of pathologic Q waves on electrocardiogram (ECG), or imaging evidence of infarction. Included in the definition were sudden cardiac death (SCD) with evidence of myocardial ischemia (new ST elevation, left bundle branch block [LBBB], or coronary thrombus) and biomarker elevation > 3× URL for post–percutaneous coronary intervention (PCI) patients or > 5× URL for post–coronary artery bypass grafting (post-CABG) patients. Documented stent thrombosis was recognized in this new definition as well (Table 1.1). Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q waves on serial ECGs, imaging evidence of MI, or pathologic findings of healed or healing MI.

TABLE 1.1 Clinical Classification of Different Types of Myocardial Infarction

Type 1	Spontaneous MI related to ischemia from a coronary plaque rupture or dissection
Type 2	MI due to ischemia resulting from increased oxygen demand or decreased supply
Type 3	Sudden cardiac death with symptoms of ischemia, new ST elevation, or LBBB or coronary thrombus
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 5	MI associated with CABG

CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Adapted from Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol.* 2007;50:2173–2175.

IV. CLINICAL DIAGNOSIS. In any patient with a clinical history of chest pain suspected to be of cardiac origin, an ECG should be obtained within 10 minutes of presentation and interpreted promptly to determine eligibility for reperfusion therapy. If the **ECG demonstrates acute ST-segment elevation or new LBBB, emergent reperfusion treatment with primary PCI or fibrinolysis is indicated**. During this evaluation period, a targeted medical history and physical examination should be performed. If the patient's history is compatible with cardiac ischemia and the ECG does not meet the criteria for reperfusion therapy, the patient may have unstable angina or NSTEMI. These syndromes are discussed in Chapter 2.

A. Signs and symptoms

1. The classic symptoms are severe, **crushing substernal chest pain** described as a squeezing or constricting sensation with frequent radiation to the left arm, often associated with an impending sense of doom. The discomfort is similar to that of angina pectoris, but it is typically more severe, of longer duration (usually > 20 minutes), and is not relieved with rest or nitroglycerin. Peak intensity is usually not instantaneous, as it would be with pulmonary embolism or aortic dissection.
   a. The chest discomfort may radiate to the neck, jaw, back, shoulder, right arm, and epigastrium. Pain in any of these locations without chest pain is possible. Myocardial ischemic pain localized to the epigastrium is often misdiagnosed as indigestion. Acute MI can occur without chest pain, especially among postoperative patients, the elderly, and those with diabetes mellitus.
   b. If the pain is sudden, radiates to the back, and is described as tearing or knife-like, aortic dissection should be considered.
2. Associated symptoms may include diaphoresis, dyspnea, fatigue, light-headedness, palpitations, acute confusion, indigestion, nausea, or vomiting. Gastrointestinal symptoms are especially common with inferior infarction.

B. Physical examination. In general, the physical examination does not add much to the diagnosis of acute MI. However, the examination is extremely important in excluding other diagnoses that may mimic acute MI, in risk stratification, in the diagnosis of impending heart failure, and in serving as a baseline examination to monitor for mechanical complications of acute MI that may develop.

1. **Risk stratification**, which aids in treatment decisions and counseling patients and families, is based in part on age, heart rate, and blood pressure and on the presence or absence of pulmonary edema and a third heart sound.
2. The **mechanical complications** of mitral regurgitation and ventricular septal defect are often heralded by a new systolic murmur (see Chapter 3). Early diagnosis of these complications relies on well-documented examination findings at baseline and during the hospital course.

V. DIFFERENTIAL DIAGNOSIS. The differential diagnosis of ST elevation includes conditions with comorbid ischemia such as acute aortic dissection involving the root, conditions with ST elevation but no ischemia such as left ventricular (LV) hypertrophy or early repolarization abnormality, and conditions with chest pain but no ischemia such as myopericarditis (Table 1.2). The most common differential diagnostic considerations are discussed in the following text.

A. Pericarditis. Chest pain that is worse when the person is supine and improves when the person is sitting upright or slightly forward is typical of pericarditis. Care must be taken in excluding acute MI, however, because pericarditis can complicate acute MI. The electrocardiographic abnormalities of acute pericarditis may also be confused with acute MI. Diffuse ST-segment elevation is the hallmark of acute pericarditis, but this finding may be seen in acute MI that involves the left main coronary artery or a large "wraparound" left anterior descending artery. PR-segment depression, peaked T waves, or electrocardiographic abnormalities out of proportion to the clinical scenario may favor the diagnosis of pericarditis. The ST-segment elevations in pericarditis are often concave, whereas the ST-segment elevations in acute MI are usually convex. Reciprocal ST depression does not occur in pericarditis, except in leads aVR and V_1. Early T-wave inversion is not a feature of acute pericarditis. Echocardiography may be useful, not in evaluating pericardial effusion, which may occur in either condition, but in documenting the lack of wall motion abnormalities in the setting of ongoing pain and ST elevation.

B. Myocarditis. As with pericarditis, the symptoms and electrocardiographic findings of myocarditis may be similar to those of acute MI. Echocardiography is less useful in differentiating this syndrome from acute MI, because segmental LV dysfunction may be encountered in either condition. A complete history often reveals a more insidious onset and associated viral syndrome with myocarditis.

TABLE 1.2 Differential Diagnostic Considerations for ST-Segment Elevation Myocardial Infarction

Comorbid ischemia	ST elevation but no ischemia	Chest pain but no ischemia
Aortic dissection	Early repolarization	Aortic dissection
Systemic arterial embolism	Left ventricular hypertrophy	Myopericarditis
Hypertensive crisis	Left bundle branch block	Pleuritis
Aortic stenosis	Hyperkalemia	Pulmonary embolism
Cocaine use	Brugada syndrome	Costochondritis
Arteritis		Gastrointestinal disorders

Adapted from Christofferson RD. Acute ST-elevation myocardial infarction. In: Shishehbor MH, Wang TH, Askari AT, et al., eds. *Management of the Patient in the Coronary Care Unit.* New York: Lippincott Williams & Wilkins; 2008.

C. **Acute aortic dissection.** Sharp, tearing chest pain that radiates through the chest to the back is typical of aortic dissection (see Chapter 26). This type of radiation pattern should be investigated thoroughly before administration of antithrombotic, antiplatelet, or fibrinolytic therapy. Proximal extension of the dissection into either coronary ostium can account for acute MI. A chest radiograph may reveal a widened mediastinum. Transthoracic echocardiography may reveal a dissection flap in the proximal ascending aorta. If it does not, a more definitive diagnosis should be obtained with transesophageal echocardiography (TEE), computerized tomography (CT), or magnetic resonance imaging (MRI).

D. **Pulmonary embolism.** Shortness of breath associated with pleuritic chest pain but without evidence of pulmonary edema suggests pulmonary embolism. Echocardiography helps to rule out wall motion abnormalities and may identify right ventricular (RV) dilatation and dysfunction in the setting of pulmonary embolism.

E. **Esophageal disorders.** Gastroesophageal reflux disease, esophageal motility disorders, and esophageal hyperalgesia can cause chest pain, the character of which is very similar to cardiac ischemic pain. These disorders can often coexist in patients with coronary disease, thereby complicating the diagnosis. A workup for coronary disease should precede evaluation of esophageal disorders. Symptoms that may be suggestive but not diagnostic of chest pain of an esophageal origin include postprandial symptoms, relief with antacids, and lack of radiation of pain.

F. **Acute cholecystitis** can mimic the symptoms and ECG findings of inferior acute MI, although the two can coexist. Tenderness in the right upper quadrant, fever, and an elevated leukocyte count favor cholecystitis, which can be diagnosed by means of hepatobiliary iminodiacetic acid (HIDA) scanning.

VI. LABORATORY EXAMINATION (Fig. 1.1)

A. **Troponins.** Troponin T and troponin I assays are particularly useful in the diagnosis and management of unstable angina and NSTEMI because of their high sensitivity, ability to be used and interpreted rapidly at bedside, and nearly universal availability. Currently, the lag time between occlusion and detectable elevations in serum levels limits their usefulness in the diagnosis of acute STEMI; however, the development of high-sensitivity troponin T assays may allow for more rapid detection of myocardial necrosis. Also, data have suggested that a single troponin T concentration measured 72 hours after acute MI may be predictive of MI size, independent of reperfusion (3). Troponin elevation in the absence of ischemic heart disease can be found in congestive heart failure (CHF), aortic dissection, hypertrophic cardiomyopathy, pulmonary embolism, acute neurologic disease, cardiac contusion, or drug toxicity.

B. **Creatine kinase (CK).** An elevated level of CK is rarely helpful in making the diagnosis of acute MI for a patient with ST-segment elevation. Because it usually takes 4 to 6 hours to see an appreciable rise in CK levels, an initial normal value does not exclude recent complete occlusion. CK and CK-MB (creatine kinase myocardial band) levels can be elevated in the presence of pericarditis and myocarditis, which may cause diffuse ST-segment elevation. CK levels are more helpful in gauging the size and timing of acute MI than in making the diagnosis. CK levels peak at 24 hours, but the peak CK level is believed to occur earlier among patients who undergo successful reperfusion. False-positive results of CK elevation occur in a variety of settings, including skeletal muscle disease or trauma (e.g., rhabdomyolysis).

C. **Myoglobin.** Damaged cardiac myocytes rapidly release this protein into the bloodstream. Peak levels occur between 1 and 4 hours, allowing for early diagnosis of acute MI. However, myoglobin lacks cardiac specificity, thereby limiting its clinical utility. Studies have indicated that it might play a role in risk stratification after reperfusion therapy (4).

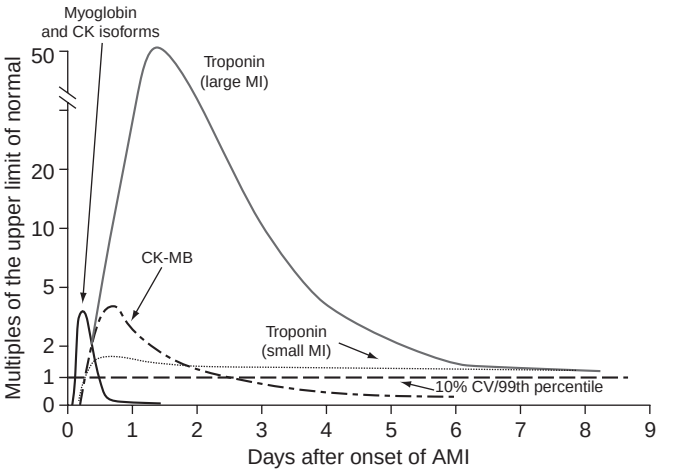


FIGURE 1.1 Timing of biomarker release after acute myocardial infarction. AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CV, coefficient of variation. (Reprinted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol.* 2007;50:652–726, with permission from Elsevier.)

VII. DIAGNOSTIC TESTING

A. Electrocardiography

1. **Definitive electrocardiographic diagnosis** of acute MI requires ST elevation of 1 mm or more in two or more contiguous leads, often with reciprocal ST depression in the contralateral leads. In leads V_2–V_3, 2 mm of ST elevation in men and 1.5 mm in women are required for accurate diagnosis.
2. **ECG subsets.** ST-segment elevations can be divided into subgroups that may be correlated with the infarction-related artery and risk of death. These five subgroups are listed in Table 1.3 and illustrated in Figure 1.2.
3. **Left bundle branch block**
   a. **New LBBB in the setting of symptoms consistent with acute MI** may indicate a large, anterior wall acute MI involving the proximal left anterior descending coronary artery and should be managed as acute STEMI.
   b. **In the absence of an old ECG or in the presence of LBBB at baseline**, the diagnosis of acute STEMI can be made with > 90% specificity on the basis of the criteria listed in Table 1.4 and illustrated in Figure 1.3.
   c. **Right bundle branch block (RBBB) may** complicate interpretation of ST elevation in leads V_1 through V_3. RBBB does not, however, obscure ST-segment elevation.

B. Echocardiography may be helpful in the evaluation of LBBB of undetermined duration in that the lack of regional wall motion abnormality in the presence of continuing symptoms makes the diagnosis of acute MI unlikely. It is worth noting that abnormal septal motion is often observed in the setting of LBBB even in the absence of ischemia.

TABLE 1.3 Acute Myocardial Infarction: Electrocardiogram Subsets and Correlated Infarct-Related Artery and Mortality

Category	Anatomy of occlusion	ECG findings	30-Day mortality rate (%)[a]	1-Year mortality rate (%)
1. Proximal LAD	Proximal to first septal perforator	ST↑ V_1–V_6, I, aVL and fascicular or bundle branch block	19.6	25.6
2. Mid-LAD	Proximal to large diagonal but distal to first septal perforator	ST↑ V_1–V_6, I, aVL	9.2	12.4
3. Distal LAD or diagonal	Distal to large diagonal or diagonal itself	ST↑ V_1–V_4, or I, aVL, V_5, V_6	6.8	10.2
4. Moderate to large inferior (posterior, lateral, right ventricular)	Proximal RCA or left circumflex	ST↑ II, III, aVF, and any of the following: (a) V_1, V_3R, V_4R (b) V_5, V_6 (c) R > S in V_1, V_2	6.4	8.4
5. Small inferior	Distal RCA or left circumflex branch	ST↑ II, III, aVF only	4.5	6.7

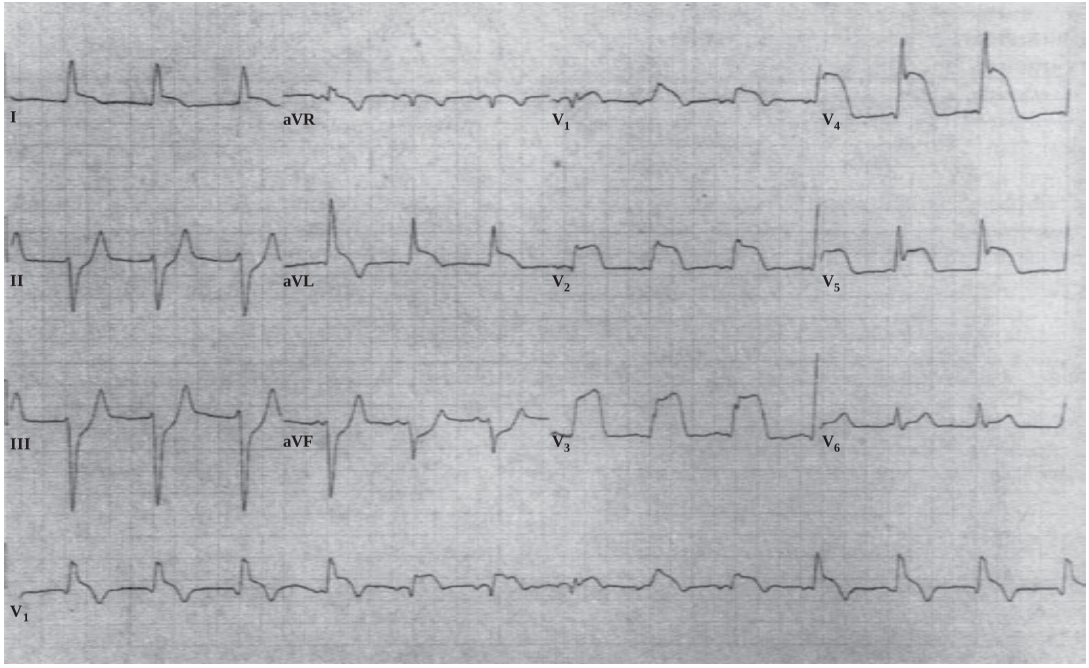
ECG, electrocardiogram; LAD, left anterior descending (coronary artery); ↑, increased; RCA, right coronary artery.

[a]Mortality rate based on GUSTO I cohort population in each of the 5 year categories, all receiving reperfusion therapy.

From Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 1998, with permission.

VIII. RISK STRATIFICATION. It is possible and useful to estimate the risk of death of a patient with acute MI. The estimate can aid in making treatment decisions and recommendations and in counseling patients and families. Five simple baseline parameters have been reported to account for > 90% of the prognostic information for 30-day mortality. These characteristics are given in descending order of importance: age, systolic blood pressure, Killip classification (Table 1.5), heart rate, and location of MI (Table 1.3, Fig. 1.2) (5). In addition, various risk models have been created to improve risk prediction.

A. The Thrombolysis in Myocardial Infarction (TIMI) risk score incorporates eight variables obtained from the history, physical examination, and ECG (Table 1.6). In patients treated with fibrinolysis, a TIMI score of 9 or greater predicts a 30-day mortality of approximately 35%. In patients with a TIMI score of 0 or 1, the 30-day mortality rate is < 2%. The strongest predictor of poor prognosis is advanced age (where age ≥ 75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables that predict a poor prognosis include hypotension, Killip class II–IV at presentation, tachycardia, history of diabetes or hypertension, anterior ST elevation (also complete LBBB), low body weight, and a time to treatment of > 4 hours.



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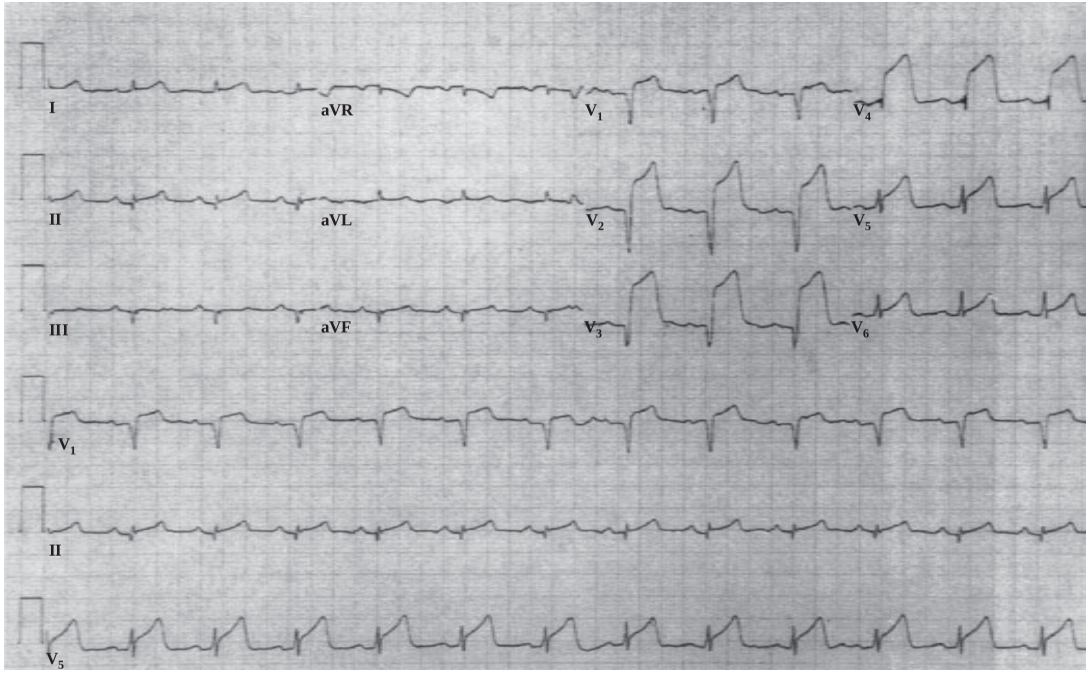

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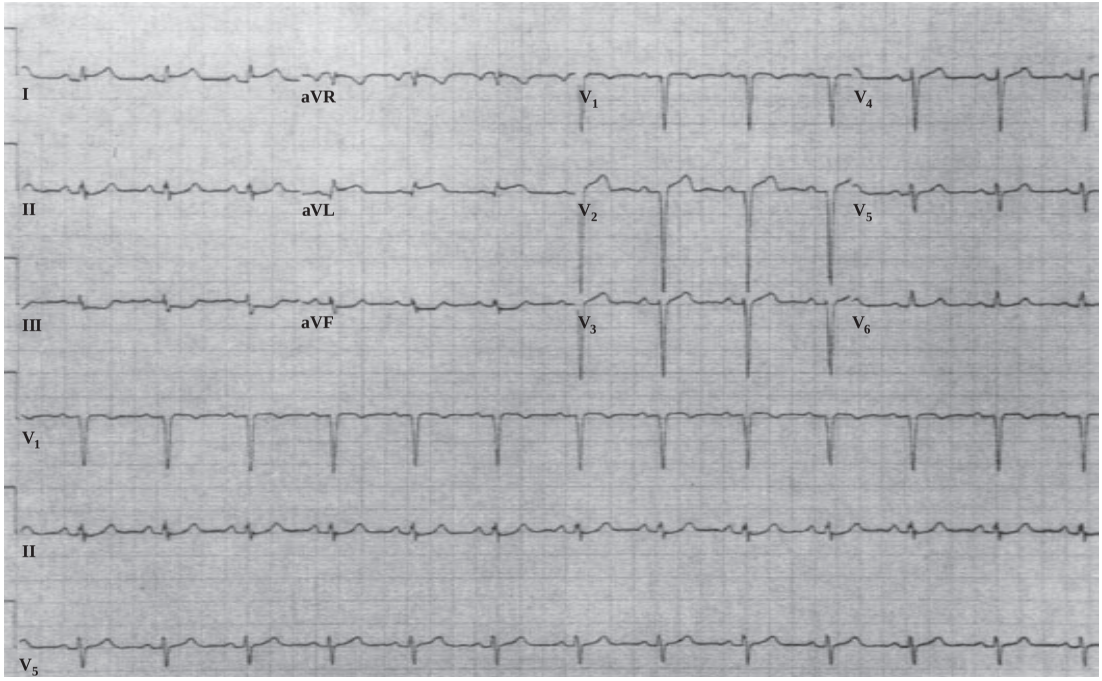

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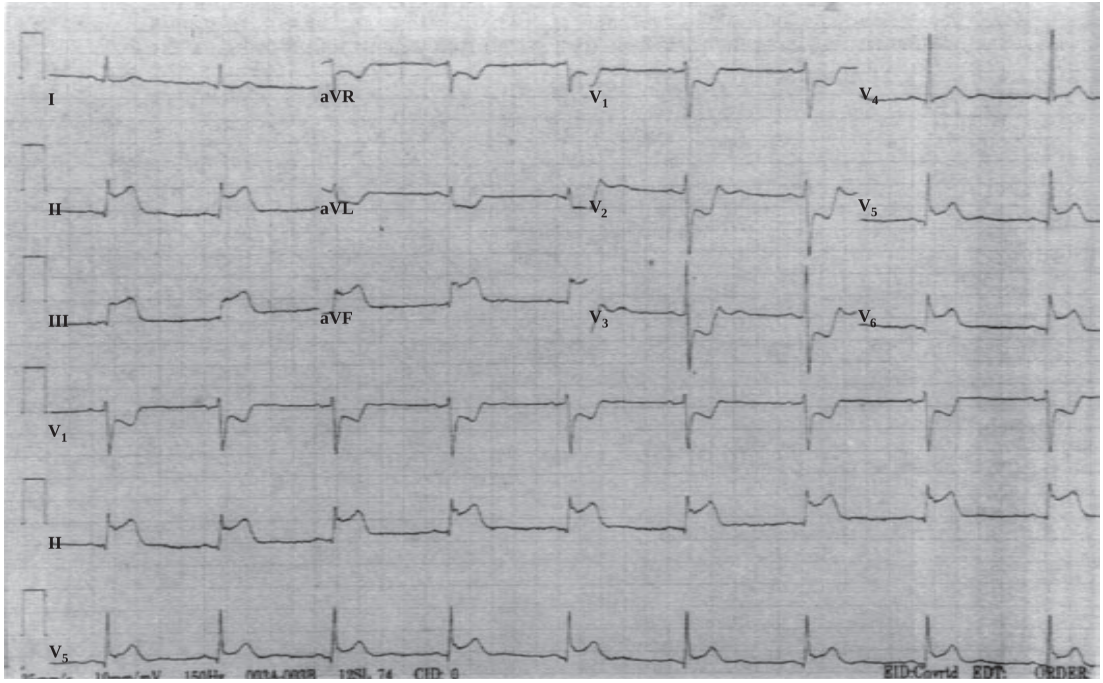

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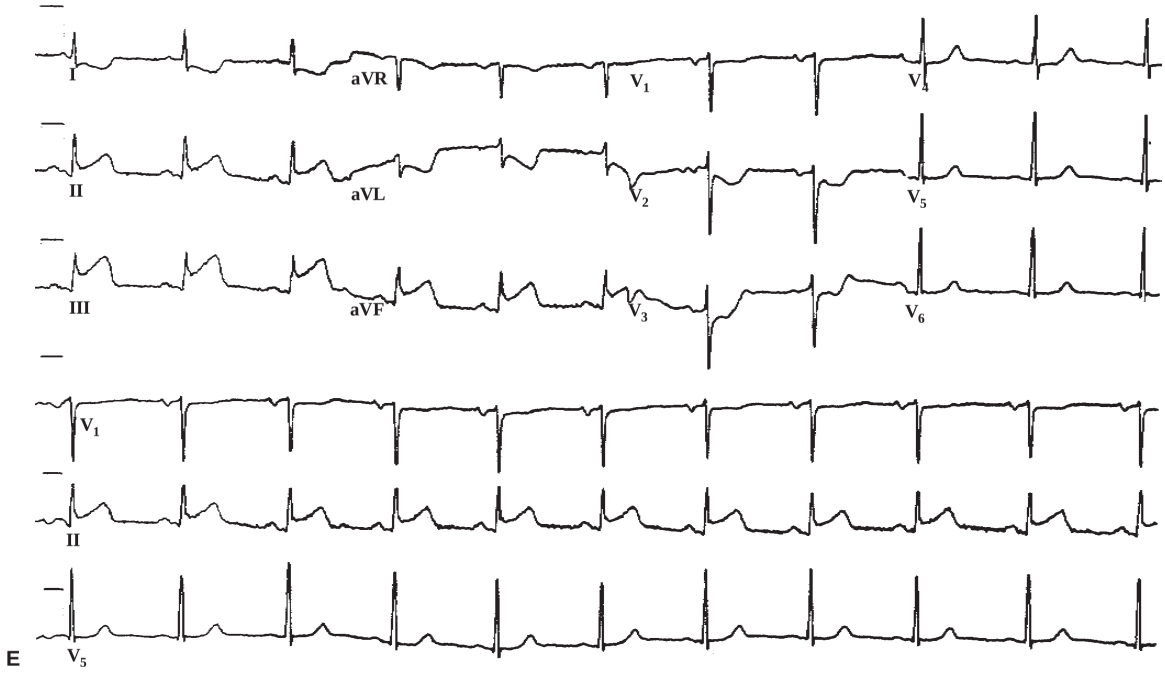

FIGURE 1.2 Electrocardiographic subsets of acute myocardial infarction (MI). **A:** Large anterior MI with conduction disturbance (proximal left anterior descending [LAD] coronary artery). **B:** Anterior MI without conduction disturbance (mid-LAD). **C:** Lateral MI (distal LAD, diagonal branch, or left circumflex branch). **D:** Large inferior MI with reciprocal changes (proximal right coronary artery [RCA]). **E:** Small inferior MI (distal RCA). (From Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 2002, with permission.)".

TABLE 1.4 Electrocardiographic Criteria for the Diagnosis of Acute Myocardial Infarction in the Presence of Left Bundle Branch Block

Criterion	Score[a]
ST-segment elevation ≥ 1 mm concordant with QRS	5
ST-segment depression ≥ 1 mm in leads V_1, V_2, or V_3	3
ST-segment elevation ≥ 5 mm discordant with QRS	2

[a]Point scores for each criterion met are added. Total point score of 3 yields ≥ 90% specificity and an 88% positive predictive value.

Adapted from Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med.* 1996;334:481–487.

B. The Global Registry of Acute Coronary Events (GRACE) score is used to predict in-hospital mortality in patients with ACS. Risk is calculated based on Killip class, heart rate, systolic blood pressure, creatinine level, age, presence or absence of cardiac arrest at admission, presence or absence of cardiac biomarkers, and ST-segment deviation. Patients with a score of ≤ 60 have a ≤ 0.2% probability of in-hospital mortality, whereas patients with a score of ≥ 250 have a ≥ 52% probability of in-hospital mortality.

IX. THERAPY

A. Prior to reperfusion

1. **Aspirin.** Immediate administration of aspirin is indicated for all patients with acute MI, unless there is a clear history of true aspirin allergy (not intolerance). Aspirin therapy conveys as much mortality benefit as streptokinase (SK), and the combination provides additive benefit (6). The dose should be four 81 mg chewable tablets (for more rapid absorption) or one 325 mg nonchewable tablet. If oral administration is not possible, a rectal suppository can be given. If true aspirin allergy is present, clopidogrel monotherapy is the best alternative. In STEMI patients who undergo PCI, aspirin should be continued indefinitely. According to the 2011 ACCF/AHA/SCAI PCI guidelines, after PCI it is reasonable to use 81 mg of aspirin as opposed to higher maintenance doses (16).
2. **Oxygen.** Supplemental oxygen by means of nasal cannula should be given to all patients with suspected MI. Administration through a face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.
3. **Nitroglycerin.** It is worthwhile to give sublingual nitroglycerin (0.4 mg) to determine whether the ST-segment elevation represents coronary artery spasm while arrangements for reperfusion therapy are being initiated. Patients should be questioned about recent use of a phosphodiesterase inhibitor (PDE) because administration of nitroglycerin within 24 hours of a PDE may cause life-threatening hypotension. A meta-analysis performed before the age of routine reperfusion suggested a mortality benefit with intravenous nitroglycerin (8), although routine use of oral nitrates after MI had no benefit in two large randomized trials in the modern era. Nitroglycerin can be useful in the management of acute MI complicated by CHF, ongoing symptoms, or hypertension. A 30% reduction in systolic blood pressure can be expected with appropriately

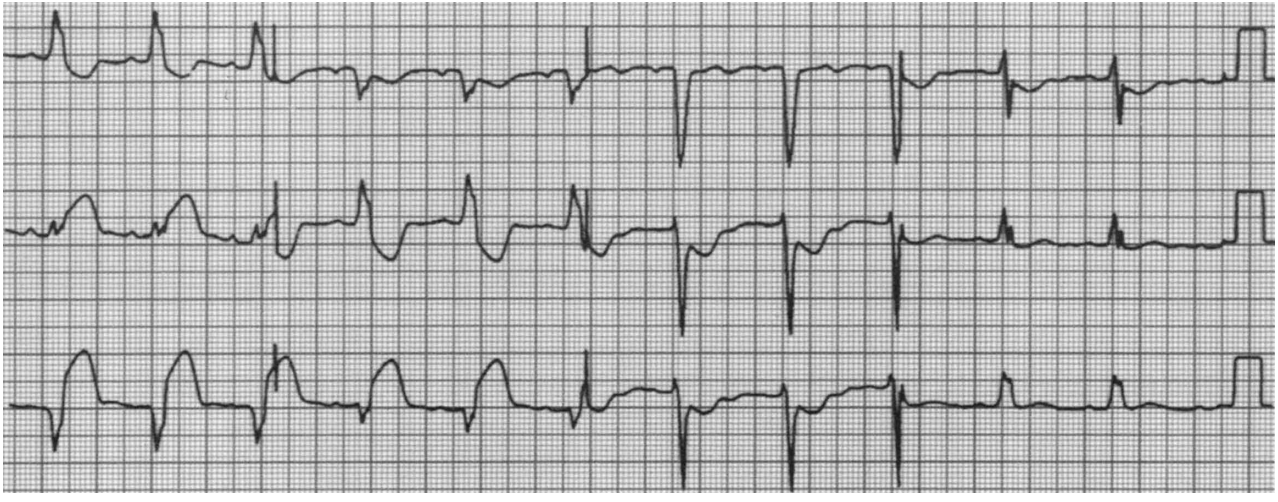

FIGURE 1.3 Electrocardiogram displays all of the criteria for the diagnosis of acute myocardial infarction (MI) in the setting of left bundle branch block (LBBB): ST-segment elevation > 1 mm, concordant with QRS in lead II (5 points); ST-segment depression > 1 mm in leads V_2 and V_3 (3 points); and ST-segment elevation > 5 mm, discordant with QRS in leads III and VF (2 points). A score of 10 points indicates an extremely high likelihood of inferior MI. (From Sgarbossa EB, Wagner G, 1997, with permission.)

TABLE 1.5 30-Day Mortality Based on Hemodynamic (Killip) Class

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5.1
II	Rales, ↑ JVD, or S_3	13	13.6
III	Pulmonary edema	1	32.2
IV	Cardiogenic shock	1	57.8

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention; S_3, third heart sound.

Adapted from Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation.* 1995;91:1659-1668.

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in ST-Segment Elevation Myocardial Infarction Patients

History	
Age 65–74 years	2 points
Age ≥ 75 years	3 points
Angina or DM/HTN	1 point
Physical examination	
HR > 100 bpm	2 points
SBP < 100 mm Hg	3 points
Killip class II–IV	2 points
Weight < 67 kg	1 point
Presentation	
Anterior ST elevation or LBBB	1 point
Time to treatment > 4 h	1 point
TIMI risk score = total points (0–14)	

DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LBBB, left bundle branch block; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

Adapted from Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation.* 2000;102:2031-2037.

aggressive dosing (10 to 20 μg/min with 5 to 10 μg/min increases every 5 to 10 minutes). Intravenous therapy can be continued for 24 to 48 hours, after which time patients with heart failure or residual ischemia can transition to oral or topical therapy with an appropriate nitrate-free interval to avoid tachyphylaxis.

4. **Platelet $P2Y_{12}$ receptor antagonists** should be used routinely in all patients with STEMI regardless of whether or not PCI is performed (9). Currently, the three agents recommended for treatment of STEMI are clopidogrel, prasugrel, and ticagrelor. Clopidogrel and prasugrel are thienopyridines that irreversibly inhibit the platelet adenosine diphosphate $P2Y_{12}$ receptor, and Ticagrelor is a reversible direct inhibitor of this same receptor. In patients in whom PCI is planned, a loading dose should be given prior to or at the time of PCI. The recommended loading dose of clopidogrel is 600 mg. This is largely based on results of a meta-analysis that included more than 25,000 patients undergoing PCI. The meta-analysis demonstrated that when compared to 300 mg, a 600 mg clopidogrel loading dose reduces MACE without an increase in major bleeding. (10). The recommended loading dose of prasugrel is 60 mg (9). Prasugrel is considered to be superior to clopidogrel in onset of action and potency of platelet inhibition; in addition, its metabolism is not influenced by cytochrome P450 genetic polymorphisms. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) investigators compared efficacy and safety of prasugrel versus clopidogrel in patients with moderate- to high-risk ACS undergoing PCI. The primary end point was a composite of death due to cardiovascular causes, nonfatal MI, or nonfatal stroke. Patients who received prasugrel had a significant reduction in the primary end point compared with patients who received clopidogrel (9.9% vs. 12.1%; hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.73 to 0.90; $p < 0.001$). This difference was primarily driven by a reduction in nonfatal MI (7.3% for prasugrel vs. 9.5% for clopidogrel; HR 0.76; 95% CI, 0.67 to 0.85; $p < 0.001$). The risk of TIMI major bleeding was higher with the use of prasugrel (2.4% vs. 1.8%; HR 1.32; 95% CI, 1.03 to 1.68; $p = 0.03$), though the net clinical benefit end point, which included all-cause mortality, ischemic events, and major bleeding events, still favored the use of prasugrel (11). Based on subgroup analysis, diabetics derived a greater benefit with prasugrel as compared with clopidogrel, whereas post hoc analysis showed that patients 75 years of age or older or patients with a body weight of < 60 kg derived no net clinical benefit from prasugrel. Post hoc analysis also showed net harm in patients treated with prasugrel who had a history of a transient ischemic attack or stroke, and therefore prasugrel should be avoided in these patients (11). Ticagrelor is given as a 180 mg loading dose. Platelet inhibition with ticagrelor occurs faster and is more potent than clopidogrel. The efficacy and safety of ticagrelor was compared to clopidogrel in the PLATO (Platelet Inhibition And Patient Outcomes)trial. At one year, patients who received ticagrelor had a significant reduction in the composite endpoint of death from vascular causes, MI, or stroke, without an increase in major bleeding. Of note, patients who receive ticagrelor should not be treated with high dose aspirin, which has been associated with worse outcomes in these patients (12). Currently, guidelines do not endorse one agent over another except in patients who have received fibrinolysis. In these patients, clopidogrel is the thienopyridine of choice, at a loading dose of 300 mg if fibrinolysis was performed within 24 hours of administration (13). This is based on results of the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction) trial, which showed pretreatment with clopidogrel to be safe and effective without increased bleeding among patients treated with fibrinolytic therapy, with many receiving subsequent PCI (-57%). The composite end point of cardiovascular death, reinfarction or revascularization, was reduced from 14.1% to 11.6% ($p = 0.03$) by clopidogrel pretreatment (9,13). In patients receiving a stent (BMS or drug-eluting stent [DES]), thienopyridine therapy should be continued for at least 1 year (9).

The maintenance dose of clopidogrel and prasugrel is 75 mg daily and 10 mg daily, respectively. The maintenance dose for prasugrel is 90 mg twice a day. An important consideration is the increased risk of major bleeding during surgery. It is currently recommended that clopidogrel and ticagrelor be held for 5 days and prasugrel be held for 7 days prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding (9).

5. **Parenteral anticoagulants.** Unless there is a contraindication, all STEMI patients should receive antithrombotic therapy. Traditionally, this has been accomplished with unfractionated heparin (UFH). The dose of UFH is 60 U/kg as a bolus (maximum 4,000 U), followed by 12 U/kg/h infusion (maximum 1,000 U/h) to achieve a partial thromboplastin time of 45 to 65 seconds (7). Based on the GUSTO I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, heparin should be given as an adjunct to patients who receive thrombolysis with alteplase, but should not be given to patients who receive streptokinase unless the patient has recurrent ischemia or there is another indication for anticoagulant therapy (14). The use of UFH as adjunctive therapy with reteplase and tenecteplase (TNK) has been validated in GUSTO III and ASSENT 2 (Assessment of the Safety and Efficacy of a New Thrombolytic), respectively. Low-molecular-weight heparin (LMWH) is an alternative to UFH and should be preferred in patients undergoing fibrinolysis. The ASSENT 3 trial tested the efficacy of various antithrombotic regimens in conjunction with weight-based TNK. TNK plus enoxaparin was superior to TNK plus UFH in reducing the composite end point of death, in-hospital reinfarction, or in-hospital refractory ischemia (15). Similarly, the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment - Thrombolysis in Myocardial Infarction) trial randomized STEMI patients undergoing fibrinolysis to either enoxaparin throughout the index hospitalization or UFH for 48 hours. The primary end point was death or nonfatal MI at 30 days. The enoxaparin group had a significant reduction in the primary end point, most of which was due to a significant reduction in the rate of reinfarction (3.0% vs. 4.5%). The enoxaparin group was also less likely to undergo urgent revascularization (2.1% vs. 2.8%). It is worth noting that duration of therapy differed between the two groups. Although UFH was only administered for 48 hours, LMWH therapy was continued for a mean of 7 days (16). Patients undergoing PCI after treatment with LMWH may need additional dosing in the cardiac catheterization laboratory, depending on the time at which the last dose was administered. If the last dose was within 8 hours, no additional enoxaparin should be given. If the last dose was given 8 to 12 hours earlier, an intravenous dose of 0.3 mg/kg should be given. If it has been > 12 hours since that last dose, an additional 1 mg/kg dose should be administered subcutaneously. LMWH should be avoided in patients > 75 years old or in patients with significant renal insufficiency (22). The 2009 focused update of the ACC/AHA STEMI guidelines added bivalirudin as an acceptable anticoagulant in patients undergoing primary PCI (9). The 2011 ACCF/AHA/SCAI PCI guideline confirmed this with a class I recommendation for bivalirudin during PCI (17). This is primarily based on results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. The HORIZONS-AMI trial randomized 3,600 patients to either bivalirudin and provisional glycoprotein (GP) IIb/IIIa inhibitor or UFH and planned GP IIb/IIIa inhibitor prior to primary PCI. The primary end point was the 30-day rate of the combined outcome of net adverse clinical events, including major bleeding, death, reinfarction, target vessel revascularization (TVR), and stroke. Patients in the bivalirudin group

had a significant reduction in the primary end point (9.2% vs. 12.1%; relative risk [RR] 0.76; 95% CI, 0.63 to 0.92; $p = 0.005$) primarily due to decreased major bleeding (4.9% vs. 8.3%; $p = 0.001$). The benefit was maintained at 1 year (18). Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor that has also been studied in acute MI. The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial evaluated fondaparinux with fibrinolytics and appeared to demonstrate benefit versus placebo/UFH in terms of death and reinfarction at 30 days (9.7% vs. 11.2%; HR – 0.86; 95% CI, 0.77 to 0.98; p = 0.008) without an increased risk of bleeding (19). However, in the primary PCI subset, there was no benefit and a significant increase in guiding catheter thrombosis, which has limited its widespread use. Accordingly, current ACC/AHA guidelines recommend that patients treated with fondaparinux receive additional anticoagulation with an anti-IIa agent prior to proceeding with PCI.

B. Reperfusion therapy. The primary goal in the management of acute MI is to institute reperfusion therapy as quickly as possible. All patients with ST-segment elevation or new LBBB MI who seek treatment within 12 to 24 hours from onset of continuous symptoms should be considered for immediate reperfusion therapy. Persistent ischemic symptoms after 12 hours may indicate a stuttering course of occlusion, spontaneous reperfusion, and reocclusion and may indicate potential continued benefit for early therapy.

1. **Benefit.** The benefit of reperfusion therapy has been well documented in the management of acute MI, regardless of age, gender, and most baseline characteristics. However, the patients who derive the most benefit are those treated earliest and those at highest risk, such as those with anterior MI.
2. **Time to treatment is paramount.** Patients treated in the first hour have the highest mortality benefit. **There is an inverse relationship between time to treatment and survival benefit**. This relationship appears more consistent with fibrinolytic therapy than with direct PCI. After 12 hours of continuous symptoms, there is little net benefit to pharmacologic reperfusion with fibrinolytics. The therapeutic window for PCI extends beyond that of fibrinolysis, but is not infinite (20,21). The Occluded Artery Trial (OAT) suggests that stenting of an occluded infarct-related artery > 72 hours after the initial event is not associated with benefit and may be harmful (21). Currently, the AHA recommends against PCI of an occluded infarct-related artery > 24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia (22).
3. **Fibrinolysis versus direct PCI.** After it has been determined that a patient is a candidate for reperfusion therapy, the decision to use fibrinolytic or direct PCI therapy must be made quickly.
   a. If facilities for immediate coronary angiography and PCI are available within 90 minutes of first medical contact, this is the preferred therapy. Pooled data from several large trials show a significant (22%) reduction in short-term mortality for patients treated with primary angioplasty (23). This benefit was durable because there were significant reductions in the incidence of death, nonfatal MI, and recurrent ischemia at long-term follow-up. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage compared with fibrinolytic therapy.
   b. If facilities for immediate coronary angiography and direct PCI are not available, fibrinolytic therapy, unless contraindicated, should be instituted within 30 minutes of first medical contact. There is some controversy regarding the use of primary PCI with prolonged transfer times. Several trials, including the DANAMI-2 (Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction) (24), the Air-PAMI (Air-Primary Angioplasty in

Myocardial Infarction) (25), and the PRAGUE (Primary Angioplasty in Patients Transferred from a General Community Hospital to Specialized PTCA Units) (26), have investigated the benefit of on-site fibrinolysis compared with transfer to tertiary centers for direct PCI. These studies have found improved outcomes in patients randomized to a transfer strategy and direct PCI even after taking into account the increased time for patient transfer. For example, patients in DANAMI-2 randomized to transfer for PCI had a significantly lower 30-day incidence of death, MI, or stroke (8.5% vs. 14.3%; $p = 0.002$) despite a median time from randomization to balloon inflation of 112 minutes. According to current guidelines, if a patient presents with STEMI at a PCI-capable facility and can undergo PCI within 90 minutes of first medical contact, this is the preferred approach. Conversely, if the patient presents to a hospital without PCI capability and cannot receive PCI within 120 minutes of first medical contact, fibrinolytics should be administered within 30 minutes of hospital presentation (17,22). This assumes that there are no contraindications to fibrinolysis (Table 1.7).

c. If a contraindication to fibrinolytic therapy exists or there is some question of the diagnosis, arrangements should be made for transfer to a PCI facility.

TABLE 1.7 Contraindications and Cautions for Use of Thrombolytic Agents to Manage Myocardial Infarction

Absolute contraindications
Previous hemorrhagic stroke at any time; ischemic stroke within 3 mo
Known intracranial neoplasm, structural cerebral vascular lesion, or closed head injury within 3 mo
Active bleeding or bleeding diathesis (excluding menses)
Suspected aortic dissection
Relative contraindications
Severe, uncontrolled hypertension at presentation (blood pressure > 180/110 mm Hg) or history of chronic severe hypertension
History of ischemic stroke > 3 mo, dementia, or known intracerebral pathologic condition not covered in contraindications
Current use of anticoagulants, the risk increases with increasing INR
Traumatic or prolonged (> 10 min) CPR or major surgery (< 3 wk)
Noncompressible vascular punctures
Recent (within 2–4 wk) internal bleeding
For streptokinase or anistreplase: prior exposure (> 5 d prior) or prior allergic reaction
Pregnancy
Active peptic ulcer

CPR, cardiopulmonary resuscitation; INR, international normalized ratio.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004;44:E1–E211.

d. Because of the relative lack of efficacy of lytic therapy among patients with cardiogenic shock or prior bypass operations, such patients are especially well suited for primary PCI.

4. Primary PCI. Once the decision has been made to perform reperfusion with primary PCI, the patient should be moved to the cardiac catheterization laboratory and undergo angiography as rapidly as possible. After the culprit lesion has been identified, reperfusion should be achieved with standard PCI techniques (see Chapter 65).

a. Platelet GP IIb/IIIa inhibitors. Several clinical trials, including RAPPORT (ReoPro and Primary PTCA Organization and Randomized Trial) and ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up), have documented the benefits of abciximab in improving clinical outcomes after primary PCI with or without stenting in patients with STEMI (27,28). Despite these trials, the emergence of potent platelet ADP $P2Y_{12}$ receptor inhibtors has sparked controversy regarding the benefit of GP IIb/IIIa treatment in STEMI patients receiving dual, oral antiplatelet therapy. Three major trials have evaluated the efficacy of GP IIb/IIIa therapy in STEMI patients receiving dual, oral antiplatelet therapy. The Bavarian Reperfusion AlternatiVes Evaluation-3 (BRAVE-3) study looked at 800 STEMI patients who received aspirin plus 600 mg of clopidogrel and either abciximab or placebo during PCI. The primary end point was infarct size measured by single photon emission computed tomography prior to hospital discharge. The study also compared 30-day major adverse cardiovascular events (MACE) between the two groups. Compared with placebo, abciximab offered no additional benefit in terms of reducing infarct size or MACE (28,29). On-TIME 2 was a randomized control trial in Europe that compared outcomes in STEMI patients undergoing PCI who were treated with aspirin and 600 mg of clopidogrel plus either high-dose tirofiban or placebo. Patients in the high-dose tirofiban group had improved ST-segment resolution at 1 hour, but there was no significant difference in TIMI grade 3 flow or 30-day MACE (30). Lastly, in the HORIZONS-AMI trial, patients undergoing primary PCI for STEMI were randomized to either UFH plus a GP IIb/IIIa or bivalirudin with provisional GP IIb/IIIa therapy. All patients received aspirin and thienopyridine therapy prior to PCI. At 30 days, net adverse clinical events were higher in patients treated with a GP IIb/IIIa, primarily due to increased bleeding (18).

The timing of GP IIb/IIIa therapy has also been questioned. The FINESSE (Facilitated Intervention with Enhanced Speed to Stop Events) trial compared half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI) in patients undergoing PCI for STEMI. Although more patients with fibrinolytic plus GP IIb/IIIa therapy had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; p = NS), suggesting no benefit to upstream GP IIb/IIIa therapy (31). In addition, bleeding rates were higher with half-dose fibrinolytic + GP IIb/IIIa inhibitor (31).

Meta-analyses have been performed to compare the efficacy of small molecule GP IIb/IIIa inhibitors with abciximab in STEMI patients undergoing PCI. Results show no statistically significant difference in 30-day mortality, reinfarction, major bleeding, TIMI grade 3 flow, or ST-segment resolution between eptifibatide, tirofiban, and abciximab (32,33).

Based on all available data, if a patient has no contraindication to dual, oral antiplatelet therapy, it is reasonable to reserve the use of GP IIb/IIIa

therapy until coronary anatomy has been defined. Current ACC/AHA guidelines reflect this practice, as GP IIb/IIIa administration during PCI carries a class IIa recommendation, while upstream use is classified as class III (17). Also according to current guidelines, abciximab, tirofiban, and eptifibatide are considered equivalent options for GP IIb/IIIa therapy in patients undergoing PCI for STEMI (9).

b. **Thrombus aspiration.** The use of aspiration catheters has been shown to improve ST-segment resolution and myocardial blush and more recently has been associated with improved clinical outcomes. TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) was a single-center, randomized, clinical trial that compared manual thrombus aspiration before PCI with conventional balloon angioplasty and stenting in patients with STEMI (34). Unless contraindicated, all patients were treated with aspirin, 600 mg of clopidogrel, UFH, and abciximab. Complete resolution of ST-segment elevation occurred in significantly more patients who received aspiration thrombectomy when compared with patients who underwent conventional balloon angioplasty and PCI (56.6% vs. 44.2%; $p < 0.001$). In addition, a TIMI myocardial blush grade of 0 or 1 occurred in 17.1% of patients who received aspiration thrombectomy compared with 26.3% of patients who received conventional PCI ($p < 0.001$) (34). Although death, reinfarction, and TVR rates did not differ at 30 days, at 1 year there was a significant reduction in the rates of cardiac death (3.6% vs. 6.7%; $p = 0.02$) and cardiac death or nonfatal reinfarction (5.6% vs. 9.9%; $p = 0.009$) in the thrombus aspiration group (34,35). Based on current guidelines, thrombus aspiration is considered reasonable during PCI in patients with STEMI who have a high clot burden and short ischemic times (9).

c. **Distal embolic protection devices (EPDs)** have failed to show any benefit in multiple trials and may in fact increase infarct size. The major criticism of these trials is the exclusion of patients with large thrombus burden. Regardless of this caveat, these devices are not routinely recommended for acute PCI of native coronary arteries. If the culprit vessel is a saphenous vein bypass graft, an EPD should be used, as it has been shown to reduce a 30-day composite outcome of death, MI, emergency CABG, and target-lesion revascularization (TLR).

d. **Coronary stenting.** The early benefit of angioplasty over thrombolytic therapy is attenuated with more extended follow-up. In the GUSTO IIb expanded previously trial in which use of accelerated tissue plasminogen activator (tPA) was compared with angioplasty alone (percutaneous transluminal coronary angioplasty, PTCA), the reduction in rates of death and nonfatal MI at 30 days (13.7% tPA vs. 9.6% PTCA) dwindled, and by 6 months, the difference (16.1% for tPA vs. 14.1% for PTCA) had lost statistical significance (36). This loss of effect may be at least partially caused by restenosis of the target lesion that was managed directly with angioplasty. Although coronary stents are known to reduce rates of restenosis during elective PCI, it was once believed that stents should not be placed in thrombus-laden lesions, such as those associated with acute MI, because of risk of in-stent thrombosis. However, clinical trials with adequate antiplatelet therapy have shown stenting to be safe. The STENT-PAMI (STENT-Primary Angioplasty in Myocardial Infarction) (37) study found that coronary stenting significantly reduced the need for TVR at 6 months (7.7% vs. 17.0%; $p < 0.001$). These findings were confirmed in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (38) trial, which found that coronary stenting significantly reduced the incidence of restenosis at 6 months (40.8% vs. 22.2%; $p < 0.0001$),

independent of abciximab use. Based on several meta-analyses, there does not appear to be a difference between DES and BMS in terms of mortality, MI, or risk of stent thrombosis (39–41). There is, however, a reduction in TVR with DES (39–41). This was also seen in the HORIZONS-AMI trial, which randomized > 3,000 patients to DES or BMS in a 3:1 ratio. At 12 months, there was no difference in the composite end point of death, reinfarction, stroke, or stent thrombosis; however, DES patients had a decreased rate of ischemia-driven TVR and TLR (5.8% vs. 8.7% and 4.5% vs. 7.5%, respectively) (18,42). Accordingly, patients with the highest risk of in-stent restenosis such as diabetics and patients with long, smaller diameter coronary lesions derive the greatest benefit from DES. In 2009, the ACC/AHA guidelines were updated to include DES as an alternative to BMS in patients undergoing primary PCI for STEMI (9). As mentioned by the ACC/AHA writing group members, the greatest challenge in determining if a STEMI patient is a candidate for DES is deciding in an emergent situation if the patient is a candidate for prolonged dual-antiplatelet therapy. The ideal candidate for a DES should not have social or financial barriers to prolonged dual-antiplatelet therapy, should have no surgical procedures scheduled within the next year, and should be at low risk for bleeding complications (9).

5. **Fibrinolytic therapy.** The lifesaving capability of early fibrinolytic therapy has been well established, beginning with the GISSI 1 (Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico) trial (43) in 1986. Pooled data show a relative reduction in mortality of 18% and an absolute reduction of nearly 2%. Even more dramatic long-term mortality benefit may be the result of preservation of normal LV function.
   a. **Contraindications.** As discussed previously (Table 1.7), the only **absolute contraindications to fibrinolytic therapies are recent cerebrovascular accident (CVA), hemorrhagic CVA, intracranial neoplasm, active internal bleeding, and suspected aortic dissection**. The presence of one of these or one or more of the relative contraindications would favor PCI, even if it meant delaying reperfusion.
   b. **Choice of agent**
      (1) **Alteplase (tPA).** The GUSTO I previously expanded trial showed that use of accelerated alteplase significantly reduced 30-day mortality rate by 15% relative to SK plus subcutaneous or intravenous heparin (14). This mortality reduction correlated with significantly higher rates of TIMI 3 flow at 90 minutes compared with SK (54% vs. 31%; $p < 0.001$). The benefit was initially challenged because of the high cost of alteplase (approximately US $2,200 per episode of MI) compared with SK (approximately US $300). For alteplase, this corresponds to a cost of US $32,678 per year of life saved, less than that of the well-accepted standard of hemodialysis for end-stage renal disease (44). The benefit was seen across all subgroups, although the patients at highest risk derived the most benefit. The accelerated protocol consisted of an intravenous bolus dose of 15 mg followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg over 60 minutes. Alteplase is considered a fibrin-specific agent because of its relative selectivity for clot-bound fibrin.
      (2) **Reteplase.** The first of the third-generation fibrinolytic agents approved for use in the United States, reteplase, is a less fibrin-specific mutation of alteplase. Reteplase has a longer half-life than alteplase and can be administered in a double bolus (10 mg each, 30 minutes apart). The GUSTO III trial (45) showed no mortality benefit of reteplase over alteplase, but its ease of use may help to reduce time to administration.

(3) **Tenecteplase**, another third-generation fibrinolytic, is characterized by its improved fibrin specificity, enhanced resistance to plasminogen activator inhibitor 1, and decreased plasma clearance. These properties allow it to be administered as a single bolus. The ASSENT 2 trial found no mortality difference between TNK and tPA at 30 days (46). However, TNK was associated with significantly less noncerebral bleeding and improved mortality in patients treated for > 4 hours after symptom onset. The weight-adjusted dose of TNK is 30 to 40 mg (ASSENT 1).

(4) **Streptokinase.** This first-generation nonfibrin-specific lytic is a reasonable alternative to second- or third-generation agents if newer agents are not available or cannot be used because of limited financial resources. Because of the possible development of antibodies, SK should not be administered to a patient who has received it in the past. Because the overall rate of intracerebral hemorrhage is lower with SK (0.5%) than with tPA (0.7%), some cardiologists advocate its use in the care of high-risk patients, such as elderly patients with a history of a cerebrovascular event or severe hypertension. SK is a nonfibrin-specific agent capable of lysing circulating and clot-bound plasminogen to plasmin. This process results in substantial systemic fibrinogenolysis, fibrinogenemia, and elevation in fibrin degradation products.

c. **Bleeding complications after fibrinolysis.** The most serious **complication** of fibrinolytic therapy is **intracerebral hemorrhage, which occurs in approximately 0.5% to 0.7% of patients receiving such therapy. The major risk factors for intracranial hemorrhage include age (> 75 years), hypertension, low body weight, female gender, and coagulopathy** (e.g., prior Coumadin use). The diagnosis must be considered if a patient has severe headache, visual disturbances, new neurologic deficit, acute confusional state, or seizure. If the clinical suspicion is high, fibrinolytic, antithrombin, and antiplatelet therapy should be interrupted while emergency CT or MRI is performed and neurosurgical consultation is obtained. Surgical evacuation may be lifesaving. Even with prompt recognition and treatment, the mortality rate is higher than 60%; elderly patients (> 75 years) have a mortality rate higher than 90%. There is controversy regarding the risk of fibrinolytic therapy in elderly patients. An observational study (47) from the Medicare database found that patients older than 75 years had an increased risk of death at 30 days with fibrinolytic therapy (RR = 1.38; 95% CI, 1.12 to 1.71; $p = 0.003$). However, an updated meta-analysis of nine randomized trials (48,49) found that the risk reduction with fibrinolysis in patients older than 75 years was 16% (odds ratio = 0.84; 95% CI, 0.72 to 0.98; $p < 0.05$). There appears to be a decreasing relative benefit with fibrinolysis in the elderly, but an absolute gain in lives saved. The only randomized trial to specifically study management of STEMI in the elderly found that patients treated with PCI had significantly lower 30-day and 1-year mortality rates than patients treated with fibrinolysis (49). However, the ExTRACT-TIMI 25 study more recently indicates that fibrinolytic therapy may be safe in the elderly if a reduced dose of enoxaparin is used (16). Gastrointestinal, retroperitoneal, and access site bleeding may complicate fibrinolytic therapy but are usually not life-threatening if promptly recognized and managed. In any case, the best treatment of acute STEMI in elderly patients appears to be primary PCI.

d. **Prehospital fibrinolysis.** Early administration of fibrinolytic therapy by emergency services has been shown to potentially reduce infarct size but lacks solid randomized trial data advocating its routine use. It has also been found to reduce time to treatment (50,51), but this did not translate

into a reduction in mortality. Although a meta-analysis (52) of prehospital fibrinolytic trials did find a 17% reduction of in-hospital mortality, it remains to be seen whether this strategy can improve long-term outcomes in clinical practice.

6. **Combination fibrinolytic therapy with GP IIb/IIIa inhibitors (without PCI)**
   a. **Rationale.** Sustained tissue-level reperfusion occurs in only 25% of patients treated with fibrinolytic therapy. Platelets have paradoxically increased activity after fibrinolysis and are important mediators in the tendency for vessel reocclusion. Aspirin is pathway specific and, therefore, a relatively weak antiplatelet agent. GP IIb/IIIa inhibitors, however, are potent antiplatelet agents that block the final common pathway of platelet aggregation, and for this reason, they have been studied in combination with half-dose fibrinolysis.
   b. **Clinical trials.** GUSTO V found that the addition of abciximab to half-dose reteplase did not reduce mortality at 30 days or 1 year compared with full-dose reteplase, but it did reduce reinfarctions and complications after MI (53). ASSENT 3 also found comparable reductions in reinfarction with the combination of half-dose TNK and abciximab (15).
   c. **Contraindications.** GUSTO V found that the rate of intracranial hemorrhage in elderly patients (> 75 years) treated with combination therapy was almost twice that of standard lytic therapy (2.1% vs. 1.1%; $p = 0.07$). ASSENT 3 confirmed this finding. Age older than 75 years is, therefore, an additional contraindication for combination lytic therapy. No increase in intracranial hemorrhage was seen in younger patients.
7. **Rescue percutaneous revascularization** is defined as the use of PCI when fibrinolytic therapy has proved unsuccessful. Despite the proven mortality benefit, > 30% of patients who received lytic therapy have TIMI 0 to 1 flow at 90 minutes, whereas patency at 90 minutes has been shown to correlate with long-term survival (54). If reperfusion is not clearly evident 90 minutes after initiation of lytic therapy, particularly among patients with large acute MI, the decision to perform emergency angiography and mechanical reperfusion should be made promptly. Patients in cardiogenic shock, with severe CHF, or with compromising arrhythmias after lytic therapy should undergo immediate coronary angiography and should not await clinical assessment of reperfusion.
   a. **Clinical determination of successful reperfusion.** It can be difficult to determine clinically whether a patient has successful reperfusion with fibrinolytic therapy. Resolution of chest pain is an inaccurate measure of reperfusion, because the pain may be blunted by narcotic analgesia or the partial denervation that is known to occur among some patients with MI. Serial assessment of 12-lead ECGs is a more reliable indicator of reperfusion, although it is also suboptimal. An accelerated idioventricular rhythm (AIVR) is fairly specific for reperfusion, but arrhythmias other than AIVRs are not reliable indicators because a variety of ventricular and supraventricular arrhythmias may be observed in patients with nonreperfused infarction-related artery. The complete resolution of chest pain and electrocardiographic changes (defined as > 70% resolution of ST-segment elevation), accompanied by a run of AIVR, is highly specific for successful reperfusion, but it occurs in < 10% of patients receiving lytic therapy. Resolution of ST-segment elevation by > 70% is correlated with effective tissue-level reperfusion, and this finding has been correlated with better clinical outcomes and angiographic reperfusion.
   b. **Benefit.** It has been shown in the RESCUE (Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints) trial (55) that patients with anterior MI who have unsuccessful thrombolysis (TIMI 0 or

1 flow) have a significant benefit from rescue angioplasty. In addition, the Rapid Early Action for Coronary Treatment (REACT) trial demonstrated that among patients with failed reperfusion with lytics, treatment with rescue angioplasty with or without PCI is associated with an ~50% reduction in death, reinfarction, stroke, and severe heart failure (56). The Grupo de Análisis de la Cardiopatía Isquémica Aguda I (GRACIA I) trial evaluated an early invasive strategy (within 24 hours) versus an ischemia-guided approach among patients with STEMI treated with fibrinolytic therapy. This trial primarily demonstrated a reduction in revascularization events with the early invasive approach, although a trend was seen toward fewer deaths and reinfarcts. Based on the above data, an early angiography strategy (within 24 hours) may also be considered a reasonable approach in all patients who receive lytic therapy. However, this approach should be differentiated from the facilitated PCI strategy described later.

8. **Facilitated PCI** refers to the use of an initial pharmacologic regimen to improve vessel patency rates prior to planned PCI. This method has been proposed as a way to manage patients with acute MI who present to hospitals without 24-hour catheterization laboratory facilities. Various facilitated PCI strategies have been proposed, including high-dose heparin, early GP IIb/IIIa inhibitors, full-dose or reduced-dose fibrinolytics, and combination fibrinolytics and GP IIb/IIIa inhibitors. Theoretical advantages include earlier time to reperfusion, improved hemodynamic stability, smaller infarct size, greater procedural success, and improved survival, albeit at increased risk for bleeding complications. The ASSENT 4 PCI previously expanded trial was the largest study to evaluate full-dose fibrinolytic therapy (TNK) plus PCI versus primary PCI alone. The trial was terminated prematurely because of higher in-hospital mortality rates (6% vs. 3%; $p = 0.01$) and higher primary composite end points (death, shock, and heart failure within 90 days) with full-dose fibrinolytics plus PCI versus primary PCI alone (18.6% vs. 13.4%; $p = 0.0045$) (57). As discussed previously, the FINESSE trial randomized STEMI patients undergoing PCI to half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI). Although more patients with fibrinolytic plus GP IIb/IIIa inhibitor had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; p = NS), the bleeding rates being higher with the half-dose fibrinolytic plus GP IIb/IIIa inhibitor. Finally, a large meta-analysis of multiple smaller trials confirmed that primary PCI is superior to facilitated PCI (58).
9. **Pharmacoinvasive Strategy.** Though it is clear that routine fibrinolysis prior to transfer for PCI in all patients who present with AMI (facilitated PCI) results in worse outcomes, fibrinolysis is still necessary to achieve early reperfusion in some patients who present to non-PCI-capable facilities. More recent data suggest that high risk patients (Table 1.8) who receive fibrinolytic therapy benefit from immediate transfer for PCI. The CARESS-in-AMI (Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction) trial (59) randomized patients presenting to a non-PCI-capable facility, who received half-dose fibrinolytics and abciximab, to either immediate transfer for PCI or rescue PCI. Patients who were transferred immediately for PCI had a significant reduction in the primary endpoint of death, reinfarction, or refractory ischemia at 30 days (59). In addition, the TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study showed that high-risk patients benefit from this pharmacoinvasive strategy. This trial looked at 1,059 high-risk patients with STEMI who presented to a non–PCI-capable facility within 12 hours of symptom onset (60). All patients

received fibrinolysis with TNK and were then randomized to immediate transfer for PCI or rescue PCI dictated by continued chest pain, < 50% resolution of ST elevation, or hemodynamic instability. The primary end point was 30-day composite of the first occurrence of death, MI, recurrent ischemia, new or worsening heart failure, and cardiogenic shock. The primary end point was significantly less common in the pharmacoinvasive group compared with the group who received rescue PCI (11% vs. 17.2%; RR 0.64; 95% CI, 0.47 to 0.87; $p = 0.004$) (60). Based on the CARESS-in-AMI and TRANSFER-AMI trials, the ACC/AHA now recommends abandoning the use of the terms "facilitated" and "rescue" and rather decide on transfer for PCI based on the patient's level of risk (9). High-risk patients (Table 1.8) who receive fibrinolysis as the primary reperfusion strategy should be transferred to a PCI-capable facility as soon as possible. PCI can then be performed immediately or as needed. For low-risk patients, this management strategy is a class IIb recommendation (9).

10. **The late open artery hypothesis** postulates that benefit in terms of improved ventricular function, increased electrical stability, and provision of collaterals can be gained by late patency of occluded infarct arteries. However, OAT failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI (21). Criticism of this trial includes exclusion of high-risk patients with New

TABLE 1.8 ACC/AHA Definition of High-Risk Patients with Acute Myocardial Infarction

Defined in CARESS-in-AMI

(1) STEMI patients with one or more of the following:
- – Extensive ST-segment elevation
- – Previous MI
- – New-onset LBBB
- – Killip class > II or EF ≤ 35% for inferior MI

(2) Anterior MI with ≥ 2 mm or more ST elevation in two or more leads

Defined in TRANSFER-AMI

(1) ≥ 2 mm ST elevation in two anterior leads or ST elevation ≥ 1 mm in inferior leads with at least
- – SBP < 100 mm Hg
- – HR > 100 bpm
- – Killip class II–III
- – ≥ 2 mm ST-segment depression in anterior leads
- – ≥ 1 mm of ST elevation in right-sided lead V_4 indicative of RV infarct

EF, ejection fraction; HR, heart rate; LBBB, left bundle branch block; MI, myocardial infarction; RV, right ventricular; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

Adapted from Kushner FG, Hand M, King SB, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). *J Am Coll Cardiol.* 2009;54:2205–2241.

York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three-vessel disease), or severe inducible ischemia on stress testing. Regardless of these concerns, this study has led to a new **class III recommendation against PCI of a totally occluded artery > 24 hours after STEMI in asymptomatic patients without the previously noted high-risk criteria** (22).

11. **Emergency coronary bypass surgery** may be the treatment of choice for patients in whom the intent is to perform direct or rescue percutaneous mechanical reperfusion but who are found to have a critical left main stem lesion or severe three-vessel disease unapproachable with percutaneous revascularization. Studies of this strategy are fairly encouraging, especially when patients can be taken to the operating room early in the course of infarction, before severe myocardial necrosis has occurred. RV infarction is a relative contraindication to bypass surgery because it complicates the discontinuation of cardiopulmonary support.
12. **PCI in hospitals without surgical backup.** The C-PORT (Atlantic Cardiovascular Patient Outcomes Research Team) trial (61) found a reduced 6-month composite outcome of death, MI, and stroke in patients with acute MI randomized to primary PCI versus fibrinolytic therapy (12.4% vs. 19.9%; $p = 0.03$), even when PCI was performed in hospitals without surgical backup. All the community hospitals involved in this study underwent a formal "PCI development program." Based on current PCI guidelines, it is reasonable to perform primary PCI at a facility that does not have surgical backup if there is a proven plan in place for rapid transfer to another hospital capable of performing cardiac surgery. This plan must involve the ability to use hemodynamic support if needed during transfer.

C. Adjuvant therapy

1. **β-Blockers.** Extensive data from the era before reperfusion established the usefulness of β-blockers in reducing recurrent ischemia, arrhythmias, and mortality. Several small randomized trials performed in the fibrinolytic reperfusion era confirmed the anti-ischemic and antiarrhythmic benefits, although short-term mortality was not affected. As a result, prior recommendations have stated that β-blockers should be administered to all patients within the first 24 hours of acute MI, unless contraindicated by severe reactive airway disease, hypotension, bradycardia, or cardiogenic shock. However, more recent data from the PCI era have shown no difference in mortality and no difference in the composite end point of death, reinfarction, or ventricular fibrillation arrest (62). The COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) trial, a large ($n = 22{,}929$) randomized controlled trial found that the metoprolol group had more ventricular fibrillation arrest (2.5% vs. 3.0%; $p = 0.001$) and shock (5.0% vs. 3.9%; $p < 0.001$). The incidence of shock was most notable in patients with Killip class II and III heart failure. This has led to a change in guidelines recommending more judicious use of early (< 24 hours) β-blockers, avoiding use in patients with significant signs of heart failure, low cardiac output, risk of cardiogenic shock, or other relative contraindications to their use (22).
    a. **For ongoing ischemia with tachycardia or hypertension**, after rapid evaluation of ventricular function, intravenous metoprolol can be given (5 mg every 5 minutes until the desired blood pressure and pulse are achieved). Patients who tolerate the intravenous loading can begin moderate oral doses (12.5 to 50 mg of metoprolol, two to four times daily). The dose should be subsequently titrated upward to the maximally tolerated dose (200 mg of sustained-release metoprolol, once daily). Use of β-blockers should be avoided in patients with tachycardia of unclear origin, as these

agents can decompensate heart failure in patients with compensatory tachycardia.

2. **Angiotensin-converting enzyme (ACE) inhibitors** can be started orally in the first 24 hours for all patients without hypotension, acute renal failure, or other contraindications. These medications were shown to reduce mortality in the GISSI 3 (62) and ISIS 4 (International Study of Infarct Survival) (63) trials. ACE inhibitors should be continued indefinitely in patients with LV dysfunction or clinical CHF, because these patients have been shown to derive a mortality benefit. In addition, the Heart Outcomes Prevention Evaluation (HOPE) study (64) found that high-risk patients, including those with prior MI but normal LV function, still had long-term benefit from ramipril. Intravenous formulations of these agents should not be used because they have not demonstrated benefit and may increase mortality. Rather, a graded oral regimen is advised. Angiotensin-receptor blockers remain a viable option for ACE inhibitor–intolerant patients.
3. **Calcium channel blockers.** Evidence for a potential increase in mortality has limited the use of calcium channel blockers in the care of patients with acute MI. They are indicated for the management of supraventricular tachyarrhythmia, cocaine-induced MI, or relief of postinfarction angina unresponsive to β-blockade. Otherwise, these agents should be avoided. Short-acting agents, such as nifedipine, are contraindicated because of their reflex sympathetic activation. Verapamil and diltiazem should be avoided in patients with LV dysfunction or CHF. Amlodipine is an effective antianginal agent and appears safe to use for this indication in patients with CHF.
4. **Magnesium.** There was once considerable enthusiasm for the routine use of intravenous magnesium in patients with MI, based on the findings of LIMIT 2 (Leicester Intravenous Magnesium Intervention Trial), which observed a 24% reduction in mortality compared with placebo. The larger ISIS 4 and MAGIC (Magnesium in Coronaries) trials failed to duplicate this benefit, however, and enthusiasm has waned. Some have speculated that the lack of effect in ISIS 4 was because of delayed administration or low control group mortality. In the modern era, magnesium is not routinely used other than to replete serum magnesium levels that are lower than 2.0 μg/dL or for the management of *torsade de pointes* (1 to 2 g over 5 minutes).
5. **Aldosterone antagonists.** The use of aldosterone-blocking agents has been shown to be beneficial in post-MI patients. RALES (Randomized Aldactone Evaluation Study) found a reduction in all-cause mortality with the use of aldactone in patients with ischemic cardiomyopathy and NYHA class III or IV heart failure. However, the only randomized trial to address the use of such agents among patients with ventricular dysfunction after STEMI is EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), where eplerenone was found to reduce death, cardiovascular death, and hospitalization for heart failure.
6. **Diabetes control.** The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study found a significantly lower mortality rate at 1 year compared with standard therapy (8.6% vs. 18.0%; $p = 0.020$) in diabetic patients treated with aggressive blood glucose reduction with an insulin infusion during hospitalization, followed by multidose subcutaneous insulin injections. However, a small trial (OASIS-6 GIK) and a large (> 20,000 patients) randomized trial (CREATE-ELCA) failed to show any benefit to glucose–insulin–potassium (GIK) infusions. As a result, it appears prudent to institute sound glucose control, but it is not necessary to aggressively pursue glucose control with GIK infusions. Current guidelines suggest insulin therapy

to achieve and maintain blood glucose levels < 180 mg/dL while avoiding hypoglycemia (9).

7. **Antiarrhythmics.** The use of lidocaine or other antiarrhythmic agents is not warranted for the prophylactic suppression of ventricular tachycardia (VT) and fibrillation. Although lidocaine may decrease tachyarrhythmias, there is no survival benefit. There is also evidence to suggest an increase in mortality related to an increased incidence of bradycardia and asystole. In addition, there is evidence that "high-dose" amiodarone may actually increase mortality. Antiarrhythmic therapies are discussed in more detail in Chapter 21.
8. **Intraaortic balloon pump (IABP).** In the treatment of patients with cardiogenic shock, IABP counterpulsation is the preferred means of augmenting systolic pressure because use of an IABP decreases afterload and oxygen requirements while increasing diastolic coronary flow. IABP is contraindicated in the care of patients with marked aortic regurgitation, because it may worsen the regurgitation and cause rapid hemodynamic deterioration (see Chapter 63).
9. **Inotropic agents.** In general, these agents should be avoided whenever possible because of their tendency to increase myocardial oxygen demand and their associated risk of tachycardia and arrhythmias. If IABP counterpulsation proves insufficient, intravenous inotropic support may be warranted, but its use should be guided by means of pulmonary arterial catheter monitoring whenever possible.
   a. **Patients with hypotension accompanied by a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg** should be managed with rapid infusion of boluses of normal saline solution, as should patients with inferior MI who have concomitant RV infarction.
   b. **After intravascular volume has been repleted** and the PCWP is > 15 mm Hg, dopamine may be indicated at doses up to 20 μg/kg/min if hypotension or signs of heart failure persist. Norepinephrine may be used as second-line therapy. The benefits of improved cerebral and systemic perfusion pressure by an increase in inotropy usually come at the cost of increased afterload and myocardial oxygen demand from vasoconstriction.
   c. **Dobutamine** can be useful when PCWP is > 18 mm Hg in the setting of mild to moderate hypotension (70 to 90 mm Hg) or when nitroglycerin or nitroprusside is contraindicated because of the risk of inducing hypotension. Use of PDEs such as milrinone, which have combined vasodilating and inotropic actions, is problematic because of their arrhythmogenicity and their tendency to increase myocardial oxygen consumption. Use of these drugs to maintain adequate systemic pressure and forward output is acceptable if the other therapies have failed. The main goal, however, should be to avoid these agents or reduce the need for them in terms of absolute dose and duration.
10. **Implantable cardioverter–defibrillators (ICDs).** Posited to reduce the risk of sudden death following acute MI, ICDs were routinely implanted an average of 18 days following the index MI event in patients with reduced ventricular function and autonomic dysfunction (DINAMIT trial) (65). Although there was a decrease in cardiovascular death, this study failed to demonstrate any reduction in all-cause mortality. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) evaluated the benefit of delayed ICD insertion in patients with prior MI (66). The trial enrolled 1,232 patients with a history of MI at least 1 month prior to enrollment (90 days if bypass surgery was performed) and a left ventricular ejection fraction (LVEF) of ≤ 30%. Patients were randomized to prophylactic ICD insertion or standard medical therapy. At an average follow-up of 20 months, prophylactic insertion of an ICD significantly reduced all-cause

mortality (14.2% vs. 19.8% for standard therapy; HR 0.69; 95% CI, 0.51 to 0.93; $p = 0.016$) (66). According to current ACC/AHA guidelines, an ICD should be inserted in patients with ventricular fibrillation or hemodynamically significant sustained VT that occurs 48 hours after acute MI, assuming there is no recurrent ischemia or MI (67). Patients with an EF ≤ 35% and NYHA class II or III heart failure secondary to an MI that occurred at least 40 days prior should also receive an ICD (67). In addition, patients who are 40 days post-MI with NYHA class I heart failure and an EF ≤ 30% are candidates for ICD insertion (67). Lastly, any patient with a prior MI, nonsustained VT, EF ≤ 40%, and inducible ventricular fibrillation or sustained VT during an electrophysiological study should receive an ICD (67). Patients who have received CABG should have their LVEF and NYHA functional class reassessed 90 days after the procedure to determine ICD candidacy.

11. **Wearable cardioverter–defibrillators.** Patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after CABG, can be given the option of a wearable cardiac defibrillator as a bridge to ICD implantation or recovery of LVEF. The efficacy of wearable cardioverter–defibrillators was evaluated by a two-component trial consisting of the WEARIT and BIROAD studies (68). The WEARIT study enrolled 177 patients with an LVEF < 30% and NYHA class III or IV heart failure. The BIROAD study enrolled 112 patients with a recent MI or CABG who were considered high risk for SCD but did not meet criteria for or refused ICD implantation. During the 901 patient-month observation period, there were six successful and two unsuccessful defibrillations (68). Both unsuccessful defibrillation attempts were due to the device being worn incorrectly (68). During the study, there were six instances of SCD. Five cases were secondary to the device not being worn and in one case the device was being worn incorrectly (68). While wearable cardioverter–defibrillators are currently not recognized in the ACC/AHA guidelines, there appears to be a benefit in select patients.
12. **Anticoagulation for large anterior wall MIs.** Historical teaching (not based on randomized data) has advocated anticoagulating patients for 6 weeks after a large anterior wall MI, with the goal of preventing LV thrombus development. However, in the era of primary PCI with coronary stenting, this recommendation would necessitate treatment with aspirin, clopidogrel, and coumadin, placing patients at fairly high risk for bleeding. Some clinicians recommend anticoagulation only if there is objective evidence of LV thrombus by echocardiography. Others still recommend empiric anticoagulation, but with a slightly lower target international normalized ratio (1.5 to 2.0).

X. ACUTE MI ASSOCIATED WITH COCAINE ABUSE.

The pathophysiologic process and management of acute MI associated with cocaine use differ from those of classic MI.

A. Pathophysiology

1. **The underlying pathophysiologic factor** in acute MI associated with cocaine abuse is believed to be coronary spasm or thrombus formation caused by α-adrenergic stimulation. This can occur in a normal segment of artery or be superimposed on mild to moderate atherosclerosis. Atherosclerosis is accelerated by chronic cocaine use.
2. **Increased oxygen demand** caused by β-adrenergic stimulation of heart rate and contractility also contributes to the onset of ischemia.

B. Clinical presentation.

Chest pain caused by infarction after cocaine ingestion typically occurs within 3 hours, although it can vary from minutes to days, and depends on the route of administration (median of 30 minutes with intravenous cocaine,

90 minutes with crack smoking, and 135 minutes with nasal inhalation). More than 80% of persons with infarction are also cigarette smokers. Studies with animals have demonstrated a synergistic effect between cigarette smoking and cocaine use.

C. Therapy

1. The **initial management** of ST-segment elevation associated with cocaine use includes the routine administration of aspirin, oxygen, and heparin. Aggressive use of sublingual and intravenous nitroglycerin or intravenous calcium channel blockers is advised in an effort to relieve coronary spasm. Intravenous benzodiazepines should also be given, as they not only relieve cocaine induced chest pain but also improve cardiac hemodynamics (69).
2. **β-Blockers are contraindicated in patients with cocaine-induced acute MI.** Although they block undesirable β-adrenergic effects, these agents allow unopposed α-adrenergic stimulation and have been associated with increased mortality in nonrandomized analyses.
3. **Reperfusion therapy must be considered if vasodilator therapy is unsuccessful** in relieving symptoms and ST-segment changes.
4. **Immediate angiography and mechanical revascularization as appropriate** may be even more beneficial in cocaine-induced MI patients. Many patients who use cocaine have contraindications to thrombolysis, such as severe hypertension or persistent vasospasm without thrombosis, which is not amenable to thrombolytic therapy.

XI. POSTOPERATIVE ACUTE MI

A. Etiology and pathophysiology. Acute MI following noncardiac operations most commonly occurs on the third or fourth postoperative day. Conventional theory was that MI was caused by a combination of increased oxygen demand and arterial shear stress associated with the increased adrenergic drive that accompanies pain and ambulation in the postoperative period. Intravascular volume shifts caused by redistribution of fluids, intravenous administration of fluids, and decreased enteral intake all contribute to the risk of postoperative MI. It is apparent that there is a postoperative inflammatory state associated with hypercoagulability, marked by an increase in fibrinogen and other acute-phase reactants. Recent data would indicate that perioperative management of patients with DESs may be problematic, as risk of stent thrombosis may be speculated to be increased in this milieu, whereas antiplatelet therapies are discontinued to reduce bleeding risks.

B. Therapy. Management is complicated by limitations on the use of fibrinolytic agents and anticoagulant therapies. Therapy relies more heavily on the intravenous use of β-blockers and urgent angiography and mechanical reperfusion. The optimal antiplatelet or anticoagulation regimen for recent (< 1 year) DES patients undergoing noncardiac surgery is not known.

XII. SIMPLIFIED REPERFUSION STRATEGY.

The wealth of data regarding reperfusion strategies and adjunctive therapies in acute MI detailed previously may lead to confusion regarding the optimal approach. Based on guideline recommendations, a simplification of the STEMI management strategy can be achieved.

A. For patients presenting with acute MI where primary PCI is available, a reasonable strategy would involve prehospital administration of aspirin, parenteral anticoagulation, and a platelet $P2Y_{12}$ receptor inhibitor, as well as nitrates and β-blocker therapy if not contraindicated, and immediate transfer to the catheterization laboratory. The decision for GP IIb/IIIa therapy and whether coronary stenting should be performed with BMS or DES should be left at the discretion of the interventional cardiologist. If the patient does not have decompensated heart failure or renal failure, assessment of ventricular function should be performed, allowing risk stratification

and initiation of additional adjunctive therapies such as statins, ACE inhibitors, and aldosterone antagonists.

B. For patients presenting to a hospital where primary PCI is not available, but immediate transfer (medical contact to balloon time < 120 minutes) to a PCI facility is available, a similar strategy is employed, with initiation of aspirin, platelet $P2Y_{12}$ receptor antagonist, anticoagulation, nitrates, and β-blockers prior to transfer, although patients at high risk with potentially longer transfer times may benefit from the addition of GP IIb/IIIa inhibitor or half-dose fibrinolytics plus GP IIb/IIIa inhibitor prior to transfer.

C. If anticipated transfer times will exceed the medical contact-to-PCI time of 120 minutes, then fibrinolytic therapy should be instituted in eligible patients within 30 minutes of medical contact. The choice of UFH or enoxaparin remains operator dependent, with either option reasonable. Among patients receiving fibrinolytics, immediate transfer to a PCI facility is preferable, and early angiography (< 24 hours) is recommended. Full-dose fibrinolytics followed by immediate transfer for coronary angiography should be performed in any patient with cardiogenic shock, severe CHF, or ventricular arrhythmia causing hemodynamic compromise, provided that the patient is a suitable candidate for revascularization.

ACKNOWLEDGMENTS: *The author thanks Drs. Deepak P. Vivekananthan, Michael A. Lauer, and Ryan D. Christofferson for their contributions to earlier editions of this chapter.*

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KEY REVIEWS

Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol*. 2004;44:E1–E211.
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RELEVANT BOOK CHAPTERS

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CHAPTER 2

James E. Harvey

Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

I. INTRODUCTION. **Unstable angina (UA)** and **non–ST-segment elevation myocardial infarction (NSTEMI)** remain leading causes of morbidity and mortality in the United States, accounting for more than 1.5 million hospital admissions in the year 2004 alone. These conditions are part of a continuum of acute coronary syndromes (ACSs) that range from UA and NSTEMI to ST-segment elevation myocardial infarction (STEMI). **The clinical presentation of non–ST-elevation acute coronary syndrome (NSTE-ACS) can be variable**, ranging from **progressive exertional angina** to **postinfarction angina**. Because **NSTEMI is distinguished from UA by the presence of elevated serum levels of cardiac biomarkers**, serial measurements in patients presenting with ACS should be performed. With improvements in the diagnosis and risk stratification of patients with UA and NSTEMI, therapeutic approaches to NSTE-ACS have continued to evolve.

II. CLINICAL PRESENTATION

A. Risk factors

1. **Clinical characteristics indicative of high risk.** Symptoms may include an **acceleration of ischemic symptoms within the preceding 48 hours, angina at rest (> 20 minutes), congestive heart failure (S_3 gallop, pulmonary edema, and rales), known reduced left ventricular (LV) function, hypotension, new or worsening mitral regurgitation murmur, age > 75 years, diffuse ST-segment changes on an electrocardiogram (ECG, ≥ 0.5 to 1 mm), and the presence of elevated serum cardiac biomarkers (typically creatine kinase myocardial band [CK-MB], troponin T, or troponin I)**. Patients at intermediate or low risk have angina of short duration, have no ischemic ST-segment changes on ECG, are negative for cardiac biomarkers, and are hemodynamically stable (Table 2.1).
2. **Electrocardiogram.** The initial ECG can help risk-stratify patients with UA. Ideally, this should be performed within 10 minutes of arrival to the emergency department (ED). Patients with ST-segment deviation (i.e., ST-depression or transient ST-elevation) ≥ 0.5 mm or with pre-existing left bundle branch block (LBBB) are at increased risk for death or myocardial infarction (MI) at 1 year after presentation. ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel coronary artery disease (CAD). **T-wave inversions alone are generally not predictive of adverse ischemic events**.
3. **NSTEMI.** NSTEMI predicts a poorer prognosis among patients with NSTE-ACS. Multivariate predictors of NSTEMI in patients with ACS include **prolonged chest pain** (> 60 minutes), **ST-segment deviations** (depression or transient elevation), and **new or recent onset of angina** (in the past month). Elevations in the levels of troponin I or troponin T, contractile proteins released

TABLE 2.1 Risk Stratification of Patients with Unstable Angina

High risk[a]	Intermediate risk	Low risk
One of the following must be present:	No high-risk feature but must have one of the following:	No high- or intermediate-risk features present
Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease	
Prolonged ongoing rest pain (> 20 min): moderate or high likelihood of CAD	Prolonged rest pain (> 20 min) that resolves	Increased frequency or duration of angina
Pulmonary edema: most likely caused by ischemia	Rest angina (> 20 min or relieved with rest or sublingual NTG)	Angina provoked by less exertion
Rest angina with dynamic ST changes ≥ 0.5 mm	Nocturnal angina	New-onset angina (within 2 wk to 2 mo)
New or worsening rales, S_3, or MR murmur	New-onset, severe angina within 2 wk with moderate or high likelihood of CAD	
Hypotension, bradycardia, tachycardia		
Bundle branch block, new or presumed new	T-wave changes	Normal or unchanged ECG
Sustained ventricular tachycardia	Pathologic Q waves or resting ST depression (< 1 mm) in multiple lead groups	
Positive serum cardiac biomarkers	Slightly elevated CK-MB, troponin T, troponin I (e.g., troponin T 0.01 ng/mL but < 0.1 ng/mL)	Normal cardiac markers
	Age older than 70 y	

CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerin.

[a]Risk stratification involves considering clinical characteristics and ECG findings to make early triage decisions.

from necrotic cardiac myocytes, are independently predictive of morbidity and mortality among patients with UA (discussed later). According to the European Society of Cardiology/American College of Cardiology (ESC/ACC), troponin elevations in this clinical setting are, by definition, NSTEMI.

4. **Clinical risk classification systems.** Numerous scores have been derived to facilitate risk assessment and guide medical therapy in patients with NSTE-ACS. It is important to note that these scores can also be used to determine which patients may benefit most from early invasive therapy as opposed to a more conservative approach. The **Braunwald classification system** risk-stratifies patients with UA at presentation (Table 2.2). Braunwald defined UA according to the **characteristics of anginal pain** and the **underlying cause**. Patients with

TABLE 2.2 Braunwald Classification of Unstable Angina

Class	Characteristics[a]
I	**Exertional angina**
	New onset, severe, or accelerated
	Angina of < 2 mo duration
	More frequent angina
	Angina precipitated by less exertion
	No rest angina in the last 2 mo
II	**Rest angina, subacute**
	Rest angina within the last month but none within 48 h of presentation
III	**Rest angina, acute**
	Rest angina within 48 h of presentation
	Clinical circumstances
A	**Secondary unstable angina**
	Caused by a noncardiac condition, such as anemia, infection, thyrotoxicosis, or hypoxemia
B	**Primary unstable angina**
C	**Postinfarction unstable angina**
	Within 2 wk of documented myocardial infarction

[a]This classification can be used for risk stratification. Clinical characteristics at presentation and severity of angina are considered.

increasing Braunwald class have been shown to have increasing risk of recurrent ischemia and death at 6 months. Vital clinical characteristics not included in this classification were age, the presence of comorbid conditions (e.g., diabetes mellitus and renal insufficiency), electrocardiographic criteria, and the presence of positive cardiac markers.

The thrombolysis in myocardial infarction (TIMI) UA risk score, based on the TIMI IIB and ESSENCE trials, incorporates **the combination of age, clinical characteristics, ECG changes, and cardiac markers for risk stratification** (Table 2.3). A higher risk score correlated with an increase in the incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization. The GRACE prediction score, which incorporates nine clinical variables derived from the medical history and clinical findings on initial presentation and during hospitalization, can be used to estimate the in-hospital and 6-month outcomes for patients hospitalized with any form of ACS. Other risk stratification scores based on the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial and the GUSTO IV–ACS trial (Table 2.4) have also been described. Together, these various clinical risk stratification systems help identify high-risk patients likely to benefit most from more aggressive therapy.

TABLE 2.3 Thrombolysis in Myocardial Infarction Risk Score

Score	Incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

Scoring system

One point when risk factor is present, zero points if absent (a total of seven points are possible): Age > 65 y

- Presence of more than three risk factors for coronary artery disease
- Prior coronary stenosis ≥ 50%
- Presence of ST-segment deviation on admission electrocardiogram
- More than two episodes of angina within the past 24 h
- Prior use of aspirin in past 7 d
- Elevated cardiac markers

B. Demographics. Compared with STEMI, patients with **UA/NSTEMI** tend to be **older** and have a higher incidence of **cardiac risk factors or comorbid conditions (e.g., diabetes, hypertension, and hypercholesterolemia)** and a greater likelihood of **prior MI and revascularization procedures** (i.e., percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]).

C. Signs and symptoms. Chest pain due to UA may be rest pain or may be triggered with minimal exertion and can be new onset or increased in severity and frequency or precipitated with less effort than prior angina. Compared with stable angina, **chest pain in UA** is usually more **severe and protracted**, often requiring several doses of sublingual nitroglycerin or extended periods of rest for relief. UA or NSTEMI cannot be differentiated on the basis of chest pain characteristics or ECG abnormalities alone. **The only way this determination can be made is with evidence of myocardial necrosis by measurement of cardiac biomarkers**.

D. Differential diagnosis. It is vitally important to determine the probability that the chest pain or presenting symptom(s) are caused by ACS resulting from obstructive CAD. The exclusion of other diagnoses that mimic angina such as costochondritis, pneumonia, or pericarditis, as well as other life-threatening conditions such as aortic dissection, pneumothorax, and pulmonary embolus, is essential. Hypertensive urgency or emergency, thyrotoxicosis, systemic infection, anemia due to blood loss, and other precipitating causes of myocardial ischemia and secondary UA should also be sought.

TABLE 2.4 GUSTO Risk Score

Risk score	30-Day mortality rate (%)
0–5	0.4
6–10	2.8
11–15	8.7
16–19	25.0
20–22	41.7

Scoring system	
Points are assigned based on the following criteria:	
Age (y)	Points
50–59	2
60–69	4
70–79	6
80+	8
Clinical history	
Prior heart failure	2
Prior stroke/TIA	2
Prior MI/revasc./chronic angina	1
Vitals and laboratory values	
Heart rate ≥ 90 beats/min	3
Elevated troponin and CK-MB	3
Creatinine > 1.4 mg/dL	2
CRP (μg/L) > 20	2
10–20	1
Anemia	1

CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; GUSTO, Global Utilization of Strategies to Open Occluded Arteries; MI, myocardial infarction; revasc., revascularization; TIA, transient ischemic attack.

E. Physical findings. Physical examination alone is insufficient for the diagnosis of UA. **Signs of heart failure** (elevated jugular venous pressure, S_3), impaired myocardial performance (S_4), or peripheral vascular disease (i.e., bruits over major vessels) may be present. These findings predict a higher likelihood of significant CAD.

III. PATHOPHYSIOLOGY. The pathophysiology of ACS encompasses a complex interplay of plaque erosion or rupture, platelet activation and aggregation leading to thrombus formation, endothelial dysfunction, vasospasm, and vascular remodeling.

A. Plaque rupture. UA, NSTEMI, and STEMI share a common initiating event: atheromatous plaque fissure or rupture. Plaque rupture exposes thrombogenic components stimulating platelet deposition, activation, and aggregation at the site

of injury, followed by activation of the coagulation cascade and thrombus formation. Factors contributing to plaque instability include lymphocyte and macrophage activation and increased inflammation. Ruptured plaques or culprit lesions in patients, even when medically stabilized, tend to progress in comparison with stable lesions. Follow-up angiography of 85 patients with UA who were medically stabilized 8 months after initial presentation revealed that 25% of culprit lesions progressed in disease severity (usually to complete occlusion), compared with 7% of nonculprit lesions. This progression of disease correlated with future cardiac events.

B. Thrombus formation. Exposure of circulating platelets to subendothelial contents results in platelet adhesion, aggregation, and, ultimately, thrombus formation. With platelet activation, the glycoprotein (GP) IIb/IIIa receptor on the platelet surface undergoes a conformational change, facilitating further platelet activation and aggregation. This markedly increases thrombin production, further expanding and stabilizing the thrombus.

C. Vasospasm can be induced by the local production of vasoactive substances released from the subendothelial matrix or propagating thrombus or it can occur as a primary phenomenon. Severe localized spasm of a coronary artery segment (i.e., Prinzmetal's angina) may also result in ACS. This vasospasm frequently occurs at sites of unstable plaque and is thought to contribute to thrombus formation. Even angiographically normal coronary arteries with underlying endothelial dysfunction may be subject to vasospasm.

D. Multiple lesions. Although a single culprit lesion is often found at angiography, multiple culprit lesions are not uncommon in patients presenting with UA/NSTEMI, attesting to the global nature of the disease. In a substudy of patients with NSTEMI, **multiple apparent culprit lesions were found in 14% of patients**, whereas a single culprit lesion was found in 49%. An intravascular ultrasound study of patients with NSTEMI undergoing angiography and possible PCI revealed an average of 2.1 plaque ruptures per patient, with 79% of patients having a lesion in a location different from that of the culprit lesion.

E. Secondary causes. UA can also result from a supply–demand mismatch of oxygen delivery to the myocardium. With stable obstructive coronary lesions, precipitants of UA include **increased myocardial oxygen demand** (i.e., tachycardia, severe hypertension, cocaine use, hyperthyroidism, fever, or sepsis) and **decreased oxygen supply** (i.e., anemia or hypoxemia).

IV. INITIAL EVALUATION AND MANAGEMENT

A. Initial triage and clinical assessment recommendations

1. Patients with symptoms suggestive of ACS should be instructed to call 911 immediately. It is recommended that the patient be transported to the hospital by ambulance rather than by friends or relatives.
2. Prehospital emergency service providers should give 162 to 325 mg of aspirin to patients who have symptoms suggestive of ACS, unless it is contraindicated. The patient should be instructed to chew the aspirin rather than swallow it whole so as to facilitate rapid absorption.
3. Patients who have been prescribed nitroglycerin should be instructed to take only one dose in response to chest pain. If the symptoms have not improved or are worsening within 5 minutes, then the patient should call 911 immediately before taking additional nitroglycerin. If the patient is known to have chronic stable angina and the chest pain is significantly improving after taking a dose of nitroglycerin, it is appropriate to instruct the patient to take additional doses of nitroglycerin every 5 minutes for a total of three doses and then call 911 if symptoms have not completely resolved.

4. Patients with suspected ACS who have had anginal symptoms at rest for greater than 20 minutes, hemodynamic instability, or recent syncope should be referred immediately to the ED.

B. Early risk stratification recommendations

1. Patients who present with suspected ACS should be quickly assessed and should undergo early risk stratification for adverse cardiovascular events. This should include a history and physical examination focused on high-risk features of ACS (prolonged chest pain at rest, syncope, signs of CHF, etc.), an ECG, and laboratory biomarkers of cardiac injury, preferably troponin I or T.
2. **A 12-lead ECG should be performed immediately upon arrival at the ED, with the standard being within 10 minutes of arrival for patients with symptoms suggestive of ACS.**

   Common ECG findings in UA/NSTEMI include ST-segment depression, transient ST-segment elevation, and T-wave inversion. However, approximately 20% of patients with an NSTEMI confirmed by cardiac enzymes have no ischemic ECG changes. Moreover, a "normal" ECG pattern is not sufficient to rule out ACS in patients with chest pain (> 4% of patients presenting with chest pain and normal ECG patterns are diagnosed with UA). Persistent ST-segment elevation of ≥ 1 mm in two or more contiguous leads or new LBBB suggests acute STEMI and should be considered for emergency reperfusion therapy (see Chapter 1). As previously mentioned, ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. T-wave inversions are the least specific of ECG changes in ACS. However, new, deep, symmetric T-wave inversions of ≥ 2 mm across the precordium in patients presenting with UA (Wellens' syndrome) often correspond to acute ischemia, usually related to a severe proximal left anterior descending artery stenosis. In this setting, revascularization often results in improved ventricular function and normalization of the ECG.
   a. Older classification systems recognized NSTEMI as non–Q-wave MI because myocardial necrosis occurs without ECG evidence of transmural injury. Because of the inability to determine the transmural extent of myocardial injury based on the presence or absence of ST-segment elevation, NSTEMI has become the preferred terminology.
   b. Analysis of 1,473 UA or NSTEMI patients in the **TIMI III trial** revealed transient ST-segment elevation in 10%, ST-segment depression in 33%, T-wave inversion in 46%, and no ischemic ECG changes in 9%.
3. **In patients in whom the initial ECG is not diagnostic** but the anginal symptoms persist, serial ECGs should be performed in 15- to 30-minute intervals. This is done in order to detect the development of ST-segment depression or elevation. Posterior circulation ischemia/infarction should be suspected and the use of posterior ECG leads and echo imaging should be considered.
4. Cardiac biomarkers should be measured in all patients presenting with symptoms suggestive of ACS. The preferred and recommended biomarker is a cardiac-specific troponin (troponin I or T). Patients with negative cardiac biomarkers within 6 hours of symptom onset should have the biomarkers remeasured at 8 to 12 hours after the onset of symptoms.
   a. **Troponins.** Cardiac troponin I and T are contractile proteins found only in cardiac myocytes and are the preferred assays to document the presence of cardiac necrosis. Many clinical trials have used troponin levels for diagnosis and prognosis in ACS. Serum levels of troponins I and T typically rise within 3 to 12 hours after myocardial necrosis and remain elevated afterward for much longer than creatine kinase (CK; 10 to 14 days). Although troponins are more sensitive and specific for myocardial injury than CK and CK-MB, elevated troponin levels can be seen in other nonischemic cardiac conditions

(advanced heart failure and acute pericarditis) and in the setting of renal insufficiency. In the setting of NSTE-ACS, troponins have important prognostic significance beyond that specified by clinical criteria, with elevated levels portending a worse prognosis. In the **GUSTO IIb** trial of patients with UA, the 30-day mortality rate for patients with an elevated troponin T level (> 0.1 ng/mL) was 11.8%, compared with 3.9% for patients with normal troponin levels. Elevated troponin levels in the setting of NSTE-ACS have also been associated with increased likelihood of multivessel disease, high-risk culprit lesions, and intracoronary thrombus visible at the time of angiography.

b. Creatine kinase. Among the most commonly used biochemical markers for the evaluation of patients with suspected ACS are CK and the MB isoenzyme of CK, measured serially every 6 to 8 hours for the first 24 hours. Total CK levels **peak at 12 to 24 hours** after the onset of symptoms, and **CK-MB levels peak at 10 to 18 hours** after the onset of symptoms. The CK-MB isoenzyme is more specific and more sensitive than the total CK measurement for documenting myocardial necrosis. Although a low level of CK and CK-MB is usually found in normal patients, values above the upper limit of normal for a given laboratory suggest the presence of myocardial necrosis. **Many nonischemic conditions, such as pericarditis, skeletal muscle injury, and renal failure**, can cause elevations of total CK levels or, less likely, an increase in CK-MB.

5. The initial evaluation should include consideration and appropriate evaluation of noncoronary causes of the unexplained symptoms (see Section **II.D**).

C. Recommendations for immediate management and triage. The initial management of patients with suspected ACS is dependent on the predicted risk of adverse cardiovascular outcomes. Patients can be initially categorized as low, intermediate, or high risk depending on the historical and clinical findings (Table 2.1). The use of risk stratification models such as the TIMI (Table 2.3), GRACE, and PURSUIT risk scores can also assist in determining which patients are at increased risk.

Patients with probable or possible ACS whose initial 12-lead ECG and cardiac biomarker levels are normal should be monitored on telemetry. Repeat ECGs and repeat cardiac biomarker measurements should be performed at scheduled intervals 6 to 8 hours apart.

1. In **low- and intermediate-risk patients** (Table 2.1) whose serial ECGs and cardiac biomarkers are normal, a conservative strategy may be considered and a **cardiac stress test** should be performed in the ED or monitoring facility. For low-risk patients, it is also appropriate to consider performing the stress test as an outpatient within 72 hours. The optimal time for testing may be determined at the discretion of the physician and in consideration of the patient's wishes. For such patients who are referred for outpatient stress testing, the initiation of antiplatelet and anti-ischemic pharmacotherapy (nitroglycerin and β-blockers) should be strongly considered.

2. **High-risk patients** (Table 2.1) and low-risk patients who have a positive stress test with high-risk features should be admitted to the hospital for inpatient management. Patients with active ongoing ischemia or hemodynamic or electrical instability should be admitted to the intensive care unit.

3. **Noninvasive stress testing.** Stress testing has been thought to be contraindicated in the evaluation of patients with UA because of the concern for acute occlusion with increased cardiac workloads in the presence of unstable plaques. However, patients at low or even intermediate risk who remain pain free for at least 12 to 24 hours and without any symptoms of heart failure can safely undergo functional testing. Intermediate-risk patients include those with age > 70 years; slightly elevated cardiac biomarkers (e.g., troponin T > 0.01 ng/mL but

< 0.1 ng/mL); T-wave changes; pathologic QS; minimal resting ST-depression (< 1 mm) on ECG; rest angina or present with atypical symptoms; and prior history of MI, CABG, peripheral or cerebrovascular disease, or aspirin use.

a. Patients who have **normal myocardial perfusion scan** without fixed or reversible perfusion defects can be safely **discharged** from the hospital and followed up on an outpatient basis. However, **cardiac catheterization** should be considered for patients found to have high-risk features on stress testing because they are at increased risk for adverse ischemic events.

b. If patients are unable to exercise, **pharmacologic stress testing** can be performed instead with dobutamine or a vasodilator such as adenosine or regadenoson. However, no large-scale studies using these modalities for stress testing have been performed in this patient population.

V. EARLY HOSPITAL CARE. The mainstay of treatment for ACS is directed at anti-ischemic therapy and antithrombotic (antiplatelet and anticoagulation) therapy. In clinical practice, the choice of specific antithrombotic therapy is partly determined by whether an initial conservative or an initial invasive approach is planned.

A. Anti-ischemic therapy. All patients admitted to the hospital with ACS should have their activity limited to bed or chair rest to help maintain minimal myocardial demand. Continuous ECG monitoring (telemetry) is recommended, and supplemental oxygen should be provided for patients who are in respiratory distress or have an oxygen saturation < 90%. The following anti-ischemic medications should also be considered.

1. **Nitrates.** Despite a lack of randomized clinical trial data, nitrates remain the mainstay of treatment for patients with UA with chest pain or spontaneous ischemia.

   a. **Dosing.** Sublingual nitroglycerin or nitroglycerin spray (0.4 mg) should be administered immediately and repeated every 5 minutes (three times) to relieve anginal discomfort. If angina persists, intravenous nitroglycerin may be started (at 10 to 20 μg/min). Intravenous nitroglycerin can be quickly titrated (5 to 10 μg/min increases every 5 to 10 minutes) to relieve angina. Caution must be exercised as it may cause profound hypotension. Topical (nitroglycerin transdermal patch, 0.2 to 0.6 mg/h, or nitropaste, 1 to 2", replaced every 6 hours) or oral (isosorbide dinitrate, 10 to 40 mg orally three times daily, or isosorbide mononitrate, 30 to 120 mg orally each day) nitrates can also be used in patients to prevent recurrent anginal symptoms. Tolerance to nitrates is dose and interval dependent and can occur within 24 hours of initiation, requiring higher doses of nitrates. After symptoms are controlled, changing from intravenous to topical or oral formulations with nitrate-free intervals can limit this phenomenon.

   b. **Contraindications.** Contraindications are known **hypersensitivity to nitrates and hypotension. Sildenafil (Viagra) use** within the prior 24 hours has been associated with hypotension, MI, and death.

2. **β-Blockers.** β-Blockers may relieve myocardial ischemia by lowering myocardial oxygen demand through its effects on blood pressure, heart rate, and contractility. A meta-analysis of 4,700 patients with UA and impending MI showed that β-blockers reduced the risk of MI, but no clear effect on mortality was seen. The goals of therapy are a resting heart rate of usually 50 to 60 beats/min and relief of angina. Cardioselective β-blockers (e.g., metoprolol and atenolol) are typically used to minimize side effects.

   a. **Dosing.** Patients with ongoing anginal pain or persistent hypertension can initially be treated with intravenous β-blockers. Intravenous metoprolol can be given in 5-mg increments every 5 to 10 minutes until the desired heart rate and blood pressure response is achieved. Oral metoprolol therapy can

then be started at a dose of 25 to 50 mg every 6 to 12 hours and can be subsequently titrated as necessary.

b. **Contraindications.** Contraindications to β-blocker therapy include **advanced atrioventricular block, active bronchospasm, cardiogenic shock, hypotension, baseline bradycardia,** and **congestive heart failure**.

3. **Calcium channel blockers.** Calcium channel blockers have diverse physiologic effects, including vasodilation, decreased or slowed atrioventricular conduction, and negative inotropy and chronotropy. A meta-analysis of calcium channel blocker trials in the management of UA showed no effect on death or nonfatal MI. However, short-acting nifedipine increased the risk of MI or recurrent angina compared with metoprolol. Diltiazem may reduce adverse events among patients with UA with normal LV function. However, patients with LV dysfunction or pulmonary congestion on physical examination are reported to have worse outcomes when treated with diltiazem.

   a. **Indications.** Calcium channel blockers are recommended for patients with UA, but **only in patients with contraindications to β-blockers or when β-blockers and nitrates fail to fully relieve symptoms of ischemia**. Calcium channel blockers are preferred in patients with variant angina or cocaine-induced vasospasm.

   b. **Contraindications.** Contraindications to calcium channel blockers include LV dysfunction or signs and symptoms of congestive heart failure, hypotension, or atrioventricular conduction abnormalities.

4. **Angiotensin-converting enzyme (ACE) inhibitors.** In patients with LV dysfunction, ACE inhibitors improve survival and ventricular remodeling. The effects of ACE inhibitors in the care of patients with UA or NSTEMI are less well defined. However, **if patients have LV dysfunction, ACE inhibitors should be added to existing medical therapy**. Moreover, in the long term, ACE inhibitors should be considered in every patient with UA/NSTEMI, especially given the overall favorable data for their use in patients with CAD.

B. **Initial conservative versus initial invasive strategy.** Two approaches to managing patients with NSTE-ACS have evolved. Based on a host of factors, including an overall assessment of patient risk, a decision to pursue either an early invasive strategy or an initial conservative strategy needs to be made early in the management of NSTE-ACS (Table 2.5). Overall, patients selected to have early invasive therapy will have coronary angiography performed within 24 hours of admission, or sooner, depending on the clinical situation. Those patients elected to a conservative strategy are managed with optimal medical therapy and undergo angiography only in select circumstances such as development of recurrent symptoms or objective evidence of ischemia while on appropriate medical therapy. There have been several studies comparing these two strategies. Bavry et al. performed a contemporary meta-analysis of seven randomized trials evaluating an early invasive versus a conservative approach in the management of patients with NSTE-ACS. In this pooled analysis of 8,375 patients, there was a 25% relative reduction in all-cause mortality at 2 years with use of early invasive as compared with conservative therapy (4.9% vs. 6.5%, $p = 0.001$). Early invasive therapy also reduced the incidence of nonfatal MI and rehospitalization for UA by 17% and 31%, respectively.

1. The 2011 UA/NSTEMI ACC/AHA guidelines provide specific treatment strategies for the following patient populations:

   a. Patients who have **refractory angina despite medical therapy, hemodynamic instability, or electrical instability** are recommended to undergo an **early invasive strategy**.

   b. For patients who are **initially stabilized but are at high risk for adverse events**, it is reasonable to undergo an **early invasive strategy *or* an initially**

TABLE 2.5 Initial Management Strategy in NSTE-ACS: Early Invasive versus Conservative (Selective Invasive) Approach

Early invasive	Conservative
Hemodynamic instability	Low risk score (e.g., TIMI, GRACE, and PURSUIT)
Arrhythmia instability	Physician or patient preference in low- to intermediate-risk patient
High risk score (e.g., TIMI, GRACE, and PURSUIT)	
Elevated troponin T or I	
Refractory angina despite aggressive medical therapy	
Prior PCI within 6 mo or prior CABG	
Signs or symptoms of congestive heart failure	
New or worsening mitral regurgitation	
Left ventricular function < 40%	

CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; TIMI, thrombolysis in myocardial infarction.

conservative strategy. This includes patients who are troponin positive. The decision of which strategy to employ should be based upon both physician and patient preference.

c. For patients who are **not at high risk**, it is reasonable to proceed with a **delayed invasive approach**.

d. **Women with low-risk features** are recommended to proceed with a **conservative strategy**.

e. For patients with **extensive comorbid conditions** (e.g., cancer and liver or pulmonary failure), **an early invasive strategy is not recommended**. This is particularly true when the risks of revascularization are likely to outweigh the benefits.

f. It is **not recommended to proceed with an early invasive strategy** in patients with **acute chest pain and a low likelihood of ACS**.

g. Patients who are **not willing to undergo coronary revascularization should not undergo an early invasive strategy**.

2. **Randomized trials.** The following is a summary of the randomized trials that have compared an early invasive versus an early conservative approach in different patient populations.

a. Two earlier trials performed prior to the current era of antiplatelet therapy and coronary stenting were the **TIMI IIIB** and **VANQWISH** trials. Both of these trials showed similar long-term outcomes (death or MI) between early invasive and conservative treatment strategies; however, there was an increase in early mortality associated with invasive therapy in the VANQWISH study,

and these two trials were excluded from the recent meta-analysis, since both are noncontemporary.

b. In the **FRISC II** trial, patients with UA/NSTEMI were randomized in a factorial design to an early invasive or conservative strategy and to dalteparin or placebo. An early invasive strategy was associated with a reduction in the rate of death or MI at 6 months (9.4% vs. 12.1%, $p = 0.031$) and reduced symptoms of angina and rehospitalization, regardless of treatment with dalteparin.

c. In the **TACTICS-TIMI 18** trial, patients with UA/NSTEMI treated with aspirin, heparin, and tirofiban were randomized to an early invasive or a conservative strategy. Patients assigned to an **early invasive approach underwent catheterization within 4 to 48 hours**, with revascularization as appropriate. Patients assigned to the conservative arm underwent cardiac catheterization only if there was objective evidence of recurrent ischemia or abnormal stress test. An early invasive strategy was associated with a reduction in the composite of death, nonfatal MI, or rehospitalization for ACS at 6 months (15.9% vs. 19.4%, $p = 0.025$), as well as a reduction in the incidence of death or nonfatal MI at 6 months (7.3% vs. 9.5%, $p < 0.05$).

d. In the **RITA 3** trial, an early invasive strategy for moderate-risk patients with UA/NSTEMI was associated with a decreased rate of death, MI, or refractory angina compared with conservative therapy at 4 months (9.6% vs. 14.5%, $p = 0.001$). This was caused primarily by a reduction in refractory angina. These results suggest that even in moderate-risk patients, an early invasive strategy may be preferred. The RITA 3 investigators also reported a meta-analysis of trials comparing an early invasive versus a conservative approach, with an association between the early invasive approach and a decreased incidence of death or nonfatal MI at 1 year (relative risk [RR] = 0.88, 95% confidence interval [CI]: 0.78 to 0.99).

e. In the **ISAR-COOL** trial, patients with UA/NSTEMI treated with intensive medical therapy (aspirin, heparin, clopidogrel [600-mg loading dose], and tirofiban) were randomized to immediate invasive therapy (median time of 2.4 hours) versus delayed invasive therapy after a "cooling off" period (median time of 86 hours). Those who had early intervention had a significant reduction in death or MI at 30 days compared with those who had a "cooling off" period (5.9% vs. 11.6%, $p = 0.04$).

f. In the **ICTUS** trial, 1,200 patients with NSTE-ACS with elevated troponins were randomized to either early invasive therapy (angiography within 24 to 48 hours) or initial conservative strategy with selective invasive therapy. There was no difference in the primary composite end point of death, MI, or rehospitalization for ACS at 1 year between the two groups (22.7% vs. 21.2%, $p = 0.33$). The aggressive medical therapies and high rates of revascularization (47%) in the initial conservative strategy group are two among many potential explanations for the findings of this trial.

g. In the **TIMACS** trial, patients with NSTEMI presenting within 24 hours of onset of symptoms were randomized to undergo angiography as soon as possible (within 24 hours) or after a minimum delay of 36 hours. These patients received contemporary medical therapy including acetylsalicylic acid (ASA), clopidogrel (>80%), heparin or fondaparinux, and GP IIb/IIIa inhibitors (23%). Overall, there was a nonsignificant trend toward a reduction in death, new MI, or stroke at 6 months for patients who received an early invasive strategy (11.3% for delayed angiography vs. 9.6% in the early intervention, $p = 0.15$). However, there was a significant reduction in the secondary end point of death, MI, or refractory ischemia for patients randomized to an early invasive strategy (12.9% vs. 9.5%, $p = 0.003$) that was primarily driven

by a decrease in refractory ischemia. Interestingly, patients who were in the highest tertile of risk according to the GRACE score were the most likely to benefit from an early invasive strategy. Overall, this study supports an early invasive strategy for patients presenting with UA/NSTEMI, particularly for those among the highest tertile of risk according to the GRACE scale.

h. The **ABOARD** trial assessed whether a very aggressive strategy of emergent intervention (analogous to primary PCI for STEMI) would benefit patients presenting with UA/NSTEMI versus delayed angiography and intervention. Immediate angiography and intervention did not decrease the rate of the primary outcome of median troponin I release (2.1 ng/mL for the invasive strategy vs. 1.7 ng/mL for the delayed strategy) nor did it show a trend toward improved outcomes in the secondary end point of death, MI, or urgent revascularization at 1 month (13.7% for early invasive management vs. 10.2% for the conservative approach, $p = 0.31$).

C. Antiplatelet and anticoagulant therapies. There are many different antiplatelet and antithrombotic agents currently available for the treatment of ACS. As such, the decision of which combination of medications to use and when to administer them can be challenging. In general, the decision of which agents to use depends on (1) whether an early invasive strategy is used and (2) what post-angiography management strategy is employed. Regardless of which strategy is chosen, all patients presenting with ACS should receive a loading dose of aspirin (162 to 325 mg) to be chewed and swallowed; if the patient is aspirin intolerant, then a loading dose of clopidogrel (300 to 600 mg) should be given. The antiplatelet and anticoagulant therapies available for each of the following strategies are listed below. The specific doses, adverse effects, and pharmacokinetics of these agents are then listed separately.

1. **Initial conservative strategy.** After receiving aspirin, patients who undergo an initial conservative strategy should receive an **anticoagulant** and be started on **clopidogrel** therapy. Enoxaparin and fondaparinux are the anticoagulants of choice; unfractionated heparin (UFH) is an acceptable alternative. Of note, if fondaparinux is used and an invasive strategy is ultimately employed, then another anticoagulant with factor IIa activity (UFH) must be coadministered to prevent catheterization-associated thrombosis.
2. **Initial invasive strategy.** After receiving aspirin, patients who undergo an initial invasive strategy should receive **anticoagulation with enoxaparin, UFH, or bivalirudin**. Before proceeding with catheterization, it is recommended to administer a **second antiplatelet agent**. These agents include clopidogrel or ticagrelor. Prasugrel may also be utilized after angiographic definition. A GP IIb/IIIa inhibitor such as eptifibatide or tirofiban may be considered.
3. **Once angiography is performed, the appropriate subsequent therapy depends on the management plan.**
   - **a.** For patients undergoing **CABG surgery**, it is recommended to **continue aspirin therapy**. If clopidogrel therapy has been started, it should be discontinued 5 days prior to CABG. GP IIb/IIIa inhibitors should be discontinued 4 hours prior to CABG. Although ticagrelor is a reversible $P2Y_{12}$ inhibitor, bleeding rates were similar to clopidogrel following CABG when discontinued 5 days prior to surgery. Bleeding rates following CABG were greater with prior exposure to prasugrel compared with clopidogrel in the TRITON–TIMI 38 trial and the risk persisted for up to 7 days from last drug exposure. UFH can be continued until CABG; however, enoxaparin should be discontinued 12 to 24 hours prior to CABG and bivalirudin should be discontinued 3 hours prior to CABG.
   - **b. Percutaneous coronary intervention.** All patients undergoing PCI should be on dual antiplatelet therapy. Routine GP IIb/IIIa inhibitor prior to PCI is not warranted and may be used adjunctive to PCI in selective cases.

c. **Medical therapy.** If the catheterization reveals no significant obstructive CAD, then the antiplatelet and anticoagulant therapy is to be continued at the discretion of the physician. If catheterization reveals significant CAD that is to be medically managed, then it is recommended to continue aspirin therapy and to load with clopidogrel therapy if not done so prior to catheterization. GP IIb/IIIa therapy should be discontinued. UFH should be continued for 48 hours; enoxaparin or fondaparinux should be continued for the duration of the hospitalization. Bivalirudin should be continued for 72 hours.

4. **Aspirin.** Despite being a relatively weak inhibitor of platelet aggregation, aspirin has a significant effect on mortality in UA. There are several pathways that lead to platelet activation, of which aspirin blocks only the cyclooxygenase-derived thromboxane A_2 pathway. Aspirin therapy for UA/NSTEMI has been studied in five major clinical trials at doses ranging from 75 to 325 mg/d. Overall, treatment with aspirin reduced the combined end point of death or nonfatal MI by 50%.
   a. **Pharmacokinetics.** The onset of aspirin's antiplatelet effect is quite rapid, with substantial inhibition of thromboxane A_2 production within 15 minutes, translating into measurable platelet inhibition within 60 minutes. It should be given as soon as patients present with ACS. Because aspirin's inhibition of cyclooxygenase is irreversible, its antiplatelet effect is durable, lasting 7 to 10 days.
   b. **Dosing.** Unless contraindicated (e.g., active bleeding and documented hypersensitivity to aspirin), an initial dose of 162 to 325 mg of nonenteric-coated aspirin (chewed and swallowed) should be given to all patients with suspected UA. Those patients allergic or intolerant to aspirin should receive clopidogrel as soon as possible. For patients who undergo PCI, aspirin at 162 to 325 mg/d is recommended for at least 1 month after bare-metal stent (BMS), 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation followed by 81 to 162 mg/d indefinitely thereafter. Subsequent daily aspirin doses can be reduced, with the preferred dose for secondary prevention being 81 to 162 mg daily; this should be continued indefinitely.
5. **Ticlopidine.** Ticlopidine was the first commercially available thienopyridine. Ticlopidine and the other thienopyridines inhibit adenosine diphosphate–induced platelet aggregation. Compared with placebo, ticlopidine reduced rates of death or MI at 6 months among patients with UA to a degree similar to that of aspirin. Ticlopidine is associated with a 1% to 5% increase in neutropenia and is thus no longer recommended as a first-line thienopyridine in patients who present with UA/NSTEMI. It is now reserved for patients in whom clopidogrel or prasugrel is not tolerated or contraindicated.
   a. **Pharmacokinetics.** Ticlopidine's onset of action is delayed, usually taking 2 to 3 days for maximum antiplatelet effect.
   b. **Side effects.** Ticlopidine can cause neutropenia (1% to 5% of patients) and is rarely associated with thrombotic thrombocytopenic purpura (TTP).
   c. **Dosing.** Ticlopidine is given as a loading dose of 500 mg followed by 250 mg twice daily.
6. **Clopidogrel.** Clopidogrel was the second commercially available thienopyridine and is the most extensively studied member of this group. In the CURE trial, patients with UA or NSTEMI had a lower rate of cardiovascular death, nonfatal MI, or stroke when treated with aspirin and clopidogrel versus aspirin alone (9.3% vs. 11.4%, $p < 0.001$). Patients treated with this combination experienced lower rates of refractory ischemia, heart failure, or revascularization. However, an increased rate of major bleeding (3.7% vs. 2.7% for aspirin) was seen in

patients receiving clopidogrel, predominantly in those undergoing CABG. In a substudy of the CURE trial, PCI-CURE, pretreatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization at 30 days (4.5% vs. 6.4%) in patients with UA/NSTEMI undergoing PCI. Long-term treatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or revascularization, without a significant increase in major bleeding. The benefit of clopidogrel pretreatment in PCI was further confirmed in the CREDO trial in which patients receiving a 300-mg loading dose plus 1 year of 75 mg daily maintenance therapy of clopidogrel had a 26.9% relative reduction in death, nonfatal MI, or stroke at 1 year compared with those receiving only 1 month of maintenance therapy without any loading dose of clopidogrel.

a. **Pharmacokinetics.** Clopidogrel is a prodrug that is metabolized to a pharmacologically active metabolite. Clopidogrel has a shorter onset of action than ticlopidine when 300 mg is given, with antiplatelet activity being detected within 2 hours after administration. Loading with 600 mg has been shown to have an even more rapid onset of action.
b. **Side effects.** Clopidogrel is generally well tolerated. Rarely, it can cause an allergic reaction typically resulting in diffuse urticaria. There have also been case reports of TTP with clopidogrel therapy.
c. **Dosing.** The conventional loading dose for clopidogrel has been 300 mg; however, recent evidence demonstrates a more rapid and heightened platelet inhibitory response, resulting in decreased ischemic events after PCI with use of a 600-mg loading dose of clopidogrel. The CURRENT OASIS-7 trial found that patients presenting with ACS who ultimately undergo PCI have a lower rate of cardiovascular death, MI, and stroke when loaded with 600 mg versus 300 mg. This decrease in ischemic end points came at the cost of an increase in major bleeding. Clopidogrel maintenance therapy is 75 mg daily.

7. **Prasugrel.** Prasugrel is the most recently commercially available thienopyridine. In preclinical studies, prasugrel has been shown to have a more potent antiplatelet effect than clopidogrel. The TRITON–TIMI 38 trial evaluated the efficacy of prasugrel versus clopidogrel in patients presenting with ACS with planned PCI. In this study of 13,608 patients, use of prasugrel as compared with clopidogrel resulted in a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%, $p < 0.001$). However, the salutary benefits in reduction of ischemic events with prasugrel came at the expense of an increase in late bleeding events, including a significant increase in rates of both major bleeding (2.4% vs. 1.1%, $p = 0.03$) and fatal bleeding (0.4% vs. 0.1%, $p = 0.002$). It is an absolute contraindication to use prasugrel in patients with a history of transient ischemic attack or stroke and a relative contraindication in patients ≥ 75 years of age or < 60 kg due to the absence of a net favorable benefit or even a harmful effect in these patient subgroups.

a. **Pharmacodynamics.** Like clopidogrel, prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. After a 60-mg loading dose of prasugrel is given, 90% of patients achieve ≥ 50% inhibition of platelet aggregation within 1 hour, with maximum achieved platelet inhibition being approximately 80%. The mean steady-state inhibition of platelet aggregation with prasugrel is 70% after 3 to 5 days of treatment. Platelet aggregation returns to baseline 5 to 9 days after discontinuation of therapy.
b. **Side effects.** Similar to clopidogrel, prasugrel is generally well tolerated. Allergic reactions to prasugrel are rare; however, bleeding-related complications such as epistaxis or easy bruising are not uncommon.

c. **Dosing.** The loading dose for prasugrel is 60 mg followed by a maintenance dose of 10 mg/d.

8. **Ticagrelor.** Ticagrelor is a recently FDA-approved reversible non-thienopyridine $P2Y_{12}$ receptor antagonist. Unlike clopidogrel and prasugrel, ticagrelor is not a prodrug and does not require bioactivation. In the PLATO trial involving patients presenting with ACS, there was a significant 1.9% reduction in major adverse cardiac events and a significant 1.4% reduction in death for patients who were randomized to receive ticagrelor versus clopidogrel. This came at the cost of an increase in nonprocedural bleeding in patients who were randomized to ticagrelor. In addition, dyspnea was noted in 14% of patients taking ticagrelor.
   a. **Dosing.** The loading dose of ticagrelor is 180 mg followed by a maintenance dose of 80 mg twice daily. Ticagrelor was not FDA approved at the time of the 2011 UA/NSTEMI guidelines, and so it is not currently included in the recommendations.
9. **Heparin.** UFH in combination with aspirin reduces the incidence of ischemic events in patients with UA. A meta-analysis of six trials in patients with UA demonstrated that treatment with aspirin plus UFH reduced the incidence of death or nonfatal MI by 33% compared with treatment with aspirin alone, although this difference did not quite reach statistical significance. The treatment effect of heparin may also wane after therapy is discontinued.
   a. **Duration of therapy.** Although the optimal length of therapy with UFH is unknown, studies have suggested that therapy must be continued for at least 3 to 7 days to achieve clinical benefit. Currently, heparin is discontinued after angiography and PCI are performed.
   b. **Rebound ischemia.** Rebound ischemia is thought to result from the accumulation of thrombin during UFH administration and the ensuing platelet aggregation. Studies have shown that this rebound ischemia can be attenuated with the concomitant use of aspirin.
   c. **Recommendations.** Intravenous UFH can be used for anticoagulant therapy in patients with NSTE-ACS undergoing either an invasive or conservative treatment strategy unless contraindicated (e.g., active bleeding, known hypersensitivity, and history of heparin-associated thrombocytopenia).
   d. **Dosing.** Initially, heparin should be given as a weight-adjusted bolus (60 U/kg), followed with an infusion (15 U/kg/h). The activated partial thromboplastin time (aPTT) should be monitored every 6 hours until it stabilizes between 50 and 70 seconds and monitored subsequently every 12 to 24 hours thereafter. Standardized heparin nomograms have simplified and streamlined the initial orders for UFH and the subsequent adjustment of dosing based on aPTT levels.
10. **Low-molecular-weight heparin (LMWH).** The advantages of LMWH compared with UFH include increased bioavailability, a fixed dosing regimen, more effective thrombin inhibition, lower rates of heparin-induced thrombocytopenia, and cost savings because serial aPTT levels do not have to be monitored.
   a. **Comparison with heparin.** A meta-analysis of 12 trials involving 17,157 patients with UA/NSTEMI that compared the use of several different LMWHs with UFH found no significant benefit with LMWHs compared with UFH (odds ratio [OR] = 0.88, 95% CI: 0.69 to 1.12, $p = 0.34$). In the **ESSENCE** trial, however, patients with UA/NSTEMI had a lower rate of death, MI, or recurrent angina at 30 days when treated with the LMWH, enoxaparin, than with UFH (19.8% vs. 23.3%, $p = 0.016$). Patients treated with enoxaparin also underwent fewer revascularization procedures and experienced similar rates of major bleeding. Similarly, in the **TIMI IIB** study, patients with UA/NSTEMI treated with enoxaparin had a lower rate of death, MI, or urgent revascularization at 43 days compared with those treated

with UFH (17.3% vs. 19.7%, $p = 0.048$). Enoxaparin has been shown to be superior to UFH in this patient population and may be used instead of UFH, unless CABG is anticipated within 24 hours. In the **SYNERGY** trial of 9,978 high-risk patients with NSTE-ACS treated with an invasive therapeutic approach, enoxaparin was found to be noninferior but not superior to UFH. The rate of death or MI at 30 days was 14% in the enoxaparin group and 14.5% in the UFH group ($p = 0.396$). There was an increase in major bleeding per the TIMI criteria in those patients randomized to enoxaparin as compared with UFH (9.1% vs. 7.6%, $p = 0.008$). Post hoc analysis suggested that crossover from enoxaparin to UFH may have partly been the reason for this excess bleeding risk associated with enoxaparin.

b. **Dosing. Enoxaparin** is administered as a 1 mg/kg dose given subcutaneously (SQ) every 12 hours. No routine laboratory values have to be followed. However, in certain clinical settings (e.g., renal insufficiency and severe obesity), an anti-Xa level can be measured. The therapeutic anti-Xa level has yet to be determined in patients with UA/NSTEMI or in patients undergoing PCI, but the commonly accepted therapeutic range is 0.5 to 1.0 anti-Xa units/mL.

c. **Recommendations.** In patients with NSTE-ACS who may undergo either a conservative or an early invasive therapy, enoxaparin is an acceptable agent for anticoagulation.

11. **Direct thrombin inhibitors (DTIs).** DTIs inhibit clot-bound thrombin more effectively than UFH and are not inactivated by plasma proteins or platelet factor 4. Hirudin is an older generation DTI that is no longer used clinically and has been supplanted by its synthetic derivative, bivalirudin.

    a. **Bivalirudin (previously Hirulog).** Bivalirudin is a synthetic derivative of hirudin, with a shorter half-life, that reversibly inhibits thrombin. In the **ACUITY** trial of 13,819 patients with UA/NSTEMI, the clinical efficacy of bivalirudin plus GP IIb/IIIa inhibition was noninferior to heparin plus GP IIb/IIIa inhibition, with 30-day rates of ischemia of 7.7% versus 7.3%, respectively.

        (1) **Recommendations.** Current guidelines recommend bivalirudin as a possible choice for anticoagulant therapy in conjunction with GP IIb/IIIa inhibition or a thienopyridine prior to angiography in patients presenting with NSTE-ACS with a planned invasive therapeutic approach. Bivalirudin is not recommended in those patients determined to undergo an initial conservative approach with medical therapy.

12. **Factor Xa inhibitors.** Fondaparinux is a heparin pentasaccharide analog that selectively inhibits factor Xa in the coagulation cascade. In comparison with UFH, fondaparinux has decreased binding to plasma proteins along with dose-independent clearance with a longer half-life. These properties translate into more predictable and sustained anticoagulation, which permits fixed-dose, once-daily administration.

    a. **Comparison with enoxaparin.** The **OASIS-5** trial evaluated the efficacy of fondaparinux versus enoxaparin in 20,078 patients with UA/NSTEMI. Patients receiving fondaparinux (2.5 mg SQ once daily) had a similar rate of the combined end point of death, MI, or refractory ischemia at 9 days as those randomized to enoxaparin (1.0 mg/kg SQ twice daily). The use of fondaparinux was associated with a lower rate of major bleeding at 9 days as compared with enoxaparin (2.2% vs. 4.1%, $p < 0.001$). However, in this trial, there was an increased incidence of catheter-associated thrombus noted, and the trial protocol was changed to allow for use of open-label UFH, which initially was not allowed during PCI.

    b. **Dosing.** The dosing of fondaparinux for UA/NSTEMI is 2.5 mg SQ once daily. Fondaparinux is renally cleared and its use is contraindicated in those patients with a creatinine clearance (CrCl) < 30 mL/min.

c. **Recommendations.** Fondaparinux can be used for anticoagulant therapy in those patients selected to undergo a conservative medical approach. It is the preferred therapy in patients with increased risk of bleeding being managed with medical therapy. For patients who undergo angiography and PCI, adjuvant UFH is recommended, given the increased rates of catheter-associated thrombus with fondaparinux in the **OASIS-5** trial.

13. GP IIb/IIIa inhibitors

Background. Platelet aggregation requires the activation of GP IIb/IIIa receptors on the platelet surface. The GP IIb/IIIa receptors of adjacent platelets bind fibrinogen molecules that allow cross-linking of the platelets, which subsequently initiates thrombus formation. Blocking the GP IIb/IIIa receptor inhibits platelet aggregation and reduces thrombus formation. **Abciximab**, the Fab fragment of a murine monoclonal antibody to the human GP IIb/IIIa receptor, binds this receptor tightly and inhibits platelet aggregation for days after the drug infusion is discontinued. In addition to its affinity for the GP IIb/IIIa receptor, abciximab inhibits other receptors, including the vitronectin receptor on endothelial cells and the MAC-1 receptor on leukocytes. **Eptifibatide** is a cyclic peptide inhibitor derived from snake venom, with rapid onset and a short half-life. Because of its short half-life, continuous drug infusion is required to sustain maximal inhibition of platelet aggregation. **Tirofiban** may also be utilized.

Use in UA during PCI. Abciximab and eptifibatide have been approved by the FDA for use as adjunctive therapy during PCI. Tirofiban has been approved for the treatment of UA, with continuation of its use into the catheterization laboratory.

a. **Abciximab** was studied in patients with UA undergoing high-risk percutaneous transluminal coronary angioplasty (PTCA) in the Evaluation of 7E3 for the Prevention of Ischemic Complications (**EPIC**) trial. In 489 patients, abciximab lowered major ischemic event rates (12.8% for placebo vs. 4.8% for abciximab, $p = 0.012$) at 30 days, primarily because of a reduced rate of death or MI. This benefit was maintained at long-term follow-up (3 years). In the Evaluation in PTCA to Improve Long-term Outcome with abciximab Glycoprotein IIb/IIIa blockade (**EPILOG**) trial, treatment with abciximab in addition to heparin was associated with a significant reduction in the rate of death, MI, or urgent revascularization at 30 days (11.7% vs. 5.2% in the low-dose heparin group, $p < 0.001$), expanding the benefit to low- and intermediate-risk patients undergoing PCI. In the EPILOG trial, a lower, weight-adjusted dosing algorithm of heparin resulted in similar major and minor bleeding rates between abciximab and placebo. In the c7E3 Fab Antiplatelet Therapy for Unstable Refractory Angina (**CAPTURE**) study, abciximab given 18 to 24 hours before PCI reduced the rate of death, MI, and urgent intervention (10.8% vs. 15.4%, $p = 0.017$). Patients treated with abciximab also had a higher rate of thrombus resolution and improved procedural success. Results from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (**EPISTENT**) trial demonstrated that when **stents and abciximab** are used together, the rate of adverse ischemic events and long-term (1-year) mortality is lower than that with stents alone. Abciximab (bolus of 0.25 mg/kg abciximab is followed by 12-hour infusion at 10 μg/min) is commonly used during PCI in patients with ACS.

b. **Tirofiban.** In the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (**RESTORE**) trial, patients presenting with ACS who underwent PCI within 72 hours of presentation were treated with heparin and aspirin with the addition of tirofiban or placebo. Treatment with tirofiban resulted in a reduction in the short-term rate of death, MI, or revascularization for failed PTCA or recurrent ischemia without an increase in major bleeding. In the Platelet Receptor Inhibition in Ischemic Syndrome

Management (**PRISM**) trial, treatment with tirofiban (the dose used was a 0.6 μg/kg/min bolus for 30 minutes, followed by an infusion of 0.15 μg/kg/min) in patients with UA resulted in a 32% decrease in the rate of death, MI, or refractory ischemia at 48 hours (3.8% vs. 5.6%, $p = 0.01$). The composite end point, however, was not significantly different at 30 days, although the mortality was reduced (3.6% vs. 2.3%). Notably, very few patients underwent PCI during the treatment period (1.9%). In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (**PRISM-PLUS**) trial, tirofiban in addition to heparin was associated with a decreased rate of death, MI, or refractory ischemia compared with heparin alone at 7 days (12.9% vs. 17.9%, $p = 0.004$), at 30 days (18.5% vs. 22.3%, $p = 0.03$), and at 6 months (27.7% vs. 32.1%, $p = 0.02$).

c. **Eptifibatide** was evaluated in the **PURSUIT** trial. Eptifibatide treatment (180 μg/kg bolus followed by an infusion of 1.3 or 2.0 μg/kg/min) in patients with UA/NSTEMI was associated with a decreased rate of death or nonfatal MI at 30 days compared with placebo (14.2% vs. 15.7%, $p = 0.04$), although with an increased rate of bleeding.

d. **Use independently of PCI.** Eptifibatide and tirofiban have been approved for use in the care of patients with UA as a primary medical therapy whether PCI is performed or not. A pooled analysis of the **CAPTURE**, **PURSUIT**, and **PRISM-PLUS** trials revealed that during the study medication infusion, treatment with a GP IIb/IIIa inhibitor resulted in a reduction of death or nonfatal MI of 34% in patients with UA/NSTEMI, suggesting an early benefit during medical treatment that may be independent of its effect during PCI. However, in the **GUSTO IV–ACS** trial, patients with UA/NSTEMI treated with abciximab bolus and infusion for 24 or 48 hours received no benefit in addition to conventional therapy with aspirin and heparin, with the 30-day incidence of death or MI being similar across groups (8.0% placebo, 8.2% for 24-hour infusion, and 9.1% for 48-hour infusion). Medical management was encouraged during the first 48 hours, and only 1.6% of patients underwent PCI while on the study drug. In patients not likely to be treated with an early invasive strategy, abciximab has shown no benefit using the dosing protocol described in that trial.

e. **Recommendations. The benefit of GP IIb/IIIa inhibitors is predominantly in patients who subsequently undergo PCI.** However, in the contemporary era with newer anticoagulant therapies and use of higher loading doses of clopidogrel (600 mg), there is less clarity regarding the utility of adjuvant GP IIb/IIIa inhibition with PCI. The **ISAR-REACT 2** trial randomized 2,022 patients with NSTE-ACS undergoing PCI to abciximab or placebo in addition to pretreatment with a 600-mg loading dose of clopidogrel. Overall, there was a 25% reduction in death, MI, or urgent target-vessel revascularization noted in those patients who received abciximab. However, this benefit was observed solely in those patients with elevated troponin levels. Also, the **ACUITY** trial suggests that GP IIb/IIIa inhibition is unnecessary in those patients who have received bivalirudin plus clopidogrel pretreatment with a loading dose of at least 300 mg at least 6 hours prior to angiography. For patients with UA/NSTEMI undergoing an **early invasive strategy**, the ACC/American Heart Association (AHA) guidelines state that either a GP IIb/IIIa inhibitor or clopidogrel can be used upstream in lower risk patients, whereas combination therapy with both is favorable in patients with high-risk features, with early recurrent ischemic discomfort, or having a delay to angiography. If PCI is likely to be performed and there is no expected delay to angiography, then abciximab can be used upstream for

GP IIb/IIIa inhibition. Otherwise, eptifibatide or tirofiban is the preferred GP IIb/IIIa inhibitor of choice.

f. Subgroups that benefit from GP IIb/IIIa inhibitors

(1) Troponin-positive status. Several studies have shown that the benefit of these agents resides primarily with patients presenting with elevated cardiac troponins. In the **CAPTURE** trial, patients with UA with an elevated troponin T level had a greater reduction in the rate of death or nonfatal MI with abciximab therapy than patients with a normal troponin T level. This continues to be true in the contemporary era of dual antiplatelet therapy with aspirin and clopidogrel, as discussed earlier with the results of the **ISAR-REACT 2** trial. Therefore, elevated troponin levels continue to identify patients at higher risk for adverse cardiac events who may benefit particularly from therapy with GP IIb/IIIa inhibitors.

(2) Diabetics. In a meta-analysis of diabetic patients with ACS, the use of GP IIb/IIIa inhibitors was associated with decreased mortality at 30 days (6.2% vs. 4.6%, $p = 0.007$). In diabetic patients with ACS undergoing PCI, treatment with GP IIb/IIIa inhibitors was associated with a more marked benefit (mortality rate: 4.0% vs. 1.2%, $p = 0.002$). In this same analysis, GP IIb/IIIa inhibitors did not confer the same improvement in mortality to nondiabetic patients (3.0% vs. 3.0%). These data suggest that diabetic patients, in particular, benefit from the use of these agents, when undergoing PCI during the initial hospitalization.

g. Oral GP IIb/IIIa inhibitors. Oral GP IIb/IIIa inhibitors have not been shown to be beneficial and may increase mortality. The reason for this dichotomy between the benefit seen with intravenous GP IIb/IIIa inhibitors and the detriment seen with oral inhibitors is not entirely clear. One possible explanation is that the oral agents, in contrast to the intravenous GP IIb/IIIa inhibitors, have partial agonist activity, which actually leads to an increase in fibrinogen binding and platelet aggregation on administration.

14. Fibrinolytic agents. Although fibrinolytic therapy has decreased mortality and improved LV function among patients with STEMI, the use of these agents is associated with worse outcomes in patients with UA and NSTEMI. A meta-analysis of fibrinolytic therapy in the management of UA demonstrated an increase in death or nonfatal MI in patients receiving fibrinolytics (9.8% for fibrinolytics vs. 6.9% for placebo). The lack of efficacy of fibrinolytic agents in these patients may result from the prothrombotic milieu induced by exposure of clot-bound thrombin after fibrin cleavage. Plasmin generation increases, and platelets are activated, perpetuating this prothrombotic state. Fibrinolytic agents would not be expected to dramatically improve coronary blood flow in UA because of the nonocclusive nature of thrombi in these patients.

VI. HOSPITAL DISCHARGE AND POSTDISCHARGE CARE. The risk of progression to MI or the development of recurrent MI or death is highest during the first two months after UA/NSTEMI. Thus, although patients with UA usually receive definitive therapy during hospitalization, close follow-up care after hospital discharge is imperative. There are no guidelines regarding noninvasive stress testing of patients without symptoms who have undergone percutaneous or surgical revascularization for UA. If anginal symptoms recur after hospital discharge, stress testing or cardiac catheterization can be performed, depending on the clinical presentation. Follow-up must include lifestyle alteration, risk factor modification, and secondary prevention. An exercise regimen in stable patients, smoking cessation efforts, and dietary changes have all been shown to improve outcomes. Hypertension, dyslipidemia, and diabetes mellitus must be diagnosed and aggressively treated. Antianginals (i.e., nitrates, β-blockers, and possibly calcium antagonists) should be used for symptom relief. Patients must be reassured and educated about their

acceptable level of activity. **The long-term use of aspirin, clopidogrel, β-blockers, statins/cholesterol-lowering regimens, and/or ACE inhibitors should not be neglected**. Specific recommendations regarding a secondary prevention postdischarge medication regimen are listed below:

A. **Anti-ischemic medications** that were required to control symptoms during the hospitalization should be continued after discharge in patients who did not undergo coronary revascularization, had an unsuccessful revascularization, or had recurrent angina after revascularization. This will often require additional titration of the antiischemic medications (see Section **VI.A**). All patients should be given clear instructions about what symptoms to look for that are suggestive of worsening myocardial ischemia. In addition, all patients should be given **sublingual or spray nitroglycerin** and instructions on how to use it.

B. **Aspirin 75 to 162 mg daily should be continued indefinitely for all patients who have had UA/NSTEMI**. Patients who have undergone PCI with a BMS should be given ASA 162 to 325 mg daily for at least 1 month after stent implantation. Patients who have undergone PCI with a drug-eluting stent (DES) should be given ASA 162 to 325 mg daily for at least 3 months after sirolimus-eluting stent implantation and at least 6 months after paclitaxel-eluting stent implantation, after which daily ASA at 75 to 162 mg should be continued indefinitely. For post-PCI patients in whom there is concern for a risk of bleeding, an initial lower dose of ASA at 75 to 162 mg/d is acceptable. For patients in whom ASA is contraindicated or not tolerated, clopidogrel 75 mg daily (preferred) or ticlopidine (if not contraindicated) should be given indefinitely.

C. **Thienopyridine therapy.** In patients with UA/NSTEMI who underwent PCI with a DES or BMS, clopidogrel, ticagrelor, or prasugrel therapy should be continued for at least 12 months and further continuation beyond 15 months may be considered. In patients in whom the risk of bleeding outweighs the expected benefits of prolonged thienopyridine therapy, early discontinuation can be considered, especially in patients who have received a BMS. UA/NSTEMI patients who were treated medically without PCI should be given clopidogrel 75 mg daily for at least 1 month, and ideally up to 1 year. Although there are currently no data proving that performing **platelet function testing** on patients on thienopyridine therapy results in improved outcomes, it is considered reasonable to do so if the results of testing would alter management.

D. **β-Blockers** should be given indefinitely to all UA/NSTEMI patients unless contraindicated. Patients recovering from UA/NSTEMI with moderate or severe LV dysfunction should be gradually titrated onto adequate β-blocker therapy. **Calcium channel blockers** (other than short-acting dihydropyridine calcium channel blockers) are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or are not tolerated.

E. **ACE inhibitors** should be given indefinitely to all patients with UA/NSTEMI and heart failure, left ventricular ejection fraction (LVEF) < 40%, hypertension, or diabetes mellitus unless contraindicated. An ACE inhibitor is also reasonable in UA/NSTEMI patients in the absence of these conditions. **Angiotensin receptor blockers** should be given to patients who are intolerant of ACE inhibitors and have heart failure with an LVEF < 40%.

F. **Aldosterone receptor antagonists** should be given to post-UA/NSTEMI patients who do not have significant renal dysfunction (CrCl > 30 mL/min), do not have hyperkalemia (K ≤ 5 mEq/L), are already on an adequate dose of ACE inhibitor, and have heart failure or diabetes mellitus with an LVEF < 40%. In the **EPHESUS** trial, 6,642 patients post-MI (3 to 14 days) with an LVEF ≤ 40% along with either symptomatic heart failure or diabetes mellitus were randomized to oral eplerenone (starting dose of 25 mg, titrated to maximum of 50 mg/d) or placebo in addition to optimal medical therapy. In those individuals randomized to eplerenone as compared with placebo, there was a significant reduction in overall mortality (14.4% vs. 16.7%,

$p = 0.008$), cardiovascular mortality (12.3% vs. 14.6%, $p = 0.005$), and cardiovascular mortality or hospitalization for cardiovascular events (26.7% vs. 30%, $p = 0.002$) at mean follow-up of 16 months. There is an increased risk of hyperkalemia with use of this agent, particularly in those patients with abnormal renal function. In the **EPHESUS** study, there was a significant increase in the risk of serious hyperkalemia (serum potassium ≥ 6.0 mmol/L) in patients using eplerenone as compared with those in the placebo group (5.5% vs. 3.9%, $p = 0.002$). Eplerenone should not be used in those patients with severe renal insufficiency.

G. Statin therapy should be given to all patients with UA/NSTEMI, regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels. LDL-C levels should be lowered to ≤ 100 mg/dL and to levels ≤ 70 mg/dL if feasible.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., **statins**) have been shown to be integral in primary and secondary prevention of CAD. Early initiation of statin therapy has beneficial effects in patients with NSTE-ACS as well. In the **MIRACL** study involving 3,086 patients with UA/NSTEMI, treatment with atorvastatin 24 to 96 hours after presentation was associated with a decreased rate of death, nonfatal MI, cardiac arrest, or recurrent ischemia at 16 weeks (14.8% vs. 17.4%, RR = 0.84, 95% CI: 0.70 to 1.00, $p = 0.048$), primarily because of reduced recurrent symptomatic ischemia requiring hospitalization. The **PROVE IT–TIMI 22** trial demonstrated the salutary effects of aggressive lipid-lowering therapy in patients with ACS. In this study, 4,162 patients with ACS were randomized to pravastatin 40 mg daily (standard therapy) or atorvastatin 80 mg daily (intensive therapy) and followed for a mean of 24 months. There was a significant 16% reduction in the rate of death, MI, UA requiring rehospitalization, revascularization, and stroke at 2 years in those randomized to more intensive lipid-lowering therapy compared with standard lipid therapy (22.4% vs. 26.3%, $p = 0.005$). Further analysis from this trial demonstrated an early clinical benefit, which correlated with concomitant reductions in C-reactive protein levels, at 30 days with use of intensive lipid-lowering therapy. These early benefits from statin therapy are likely caused by the "pleiotropic" or nonlipid-lowering effects of statins such as their anti-inflammatory, antioxidant, and antithrombotic properties. Statins' anti-inflammatory effects are likely responsible for beneficial effects in the periprocedural MI reduction seen in patients with NSTE-ACS treated with PCI. In the **ARMYDA-ACS** study of patients with NSTE-ACS undergoing PCI, pretreatment (12 hours prior to PCI) with atorvastatin 80 mg as compared with placebo resulted in a significant reduction in death, MI, or unplanned revascularization at 30 days (5% vs. 17%, $p = 0.01$), which was driven entirely by the reduction in periprocedural MI rates (5% vs. 15%, $p = 0.04$).

ACKNOWLEDGMENTS: *The author thanks Drs. Telly Meadows, David S. Lee, and Matthew T. Roe for their contributions to earlier editions of this chapter.*

SUGGESTED READING

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CHAPTER 3

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Complications of Acute Myocardial Infarction

I. INTRODUCTION. **In-hospital mortality after acute myocardial infarction (MI) is primarily caused by circulatory failure from severe left ventricular (LV) dysfunction and/or other acute complications of MI.** These complications can be broadly classified as **mechanical, arrhythmic, embolic, and inflammatory (e.g., pericarditis)**.

II. MECHANICAL COMPLICATIONS. Mechanical complications of acute MI include ventricular septal rupture (VSR), acute mitral regurgitation (MR), ventricular free wall rupture, ventricular pseudoaneurysm, and ventricular aneurysm.

A. Ventricular septal rupture

1. **Clinical presentation.** VSR occurred in 1% to 2% of patients after acute MI in the prethrombolytic era and accounted for 5% of the periinfarction mortality. The incidence has dramatically decreased in the postthrombolytic era. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial, the incidence of VSR was approximately 0.2%, occurring with equal frequency in anterior and non-anterior locations. VSR is more likely to occur in patients who are **older, female, and hypertensive and have no prior history of smoking.** It commonly occurs in the setting of a **first MI, in the background of delayed or absent reperfusion therapy.** Angiography usually reveals an **absence of collateral circulation to the infarct zone**. VSR may develop as early as 24 hours after MI but is usually seen 2 to 5 days after MI. Fibrinolytic therapy is not associated with increased risk of VSR but may accelerate rupture in vulnerable subjects, accounting for the "early hazard" observed with treatment over placebo in randomized clinical trials.
   a. **Signs and symptoms.** Patients with post-MI VSR may appear relatively comfortable early in the disease course. Recurrence of angina, pulmonary edema, hypotension, and shock may develop abruptly later in the course. Alternatively, precipitous onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new murmur may be the initial manifestation.
   b. **Physical findings.** The diagnosis should be suspected when a new **pansystolic murmur** develops, especially in the setting of worsening hemodynamic profile and biventricular failure. For this reason, it is important that **all patients with MI have a well-documented cardiac examination** at presentation and frequent evaluations thereafter. This assumes critical importance as systems struggle to achieve optimal door-to-balloon times.
      (1) The murmur is usually best heard at the **lower left sternal border**; it is accompanied by a **thrill in 50% of the cases**. In patients with a large

TABLE 3.1 Differential Diagnosis of a New Systolic Murmur after Acute Myocardial Infarction

Differentiating features	Ventricular septal rupture	Acute mitral regurgitation
Location of MI	Anterior = nonanterior	Inferoposterior > anterior
Location of murmur	Lower left sternal border	Cardiac apex
Intensity	Loud	Variable; may be faint
Thrill	50% of patients	Rare
RV failure	More likely	Less likely
Pulmonary edema	Less likely	More likely
V waves in PCWP	Present or absent	Almost always present
V waves in PA tracing	Absent	Present
O_2 step-up in PA	Almost always present	Present or absent

MI, myocardial infarction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

VSR and severe heart failure or cardiogenic shock, the murmur may be of low intensity or inaudible, but **the absence of a murmur does not rule out VSR**.

(2) Several features differentiate the murmur of VSR from that of acute MR (Table 3.1). The murmur may radiate to the base and the apex of the heart. A third heart sound (S_3), loud P_2, and signs of tricuspid regurgitation may be present.

2. **Histopathology.** The defect usually occurs at the myocardial infarct border zone, located in the **apical septum with anterior MI** and in the **basal posterior septum with inferior MI**. A VSR almost always occurs in the setting of a transmural MI. The defect may not always be a single large defect; a meshwork of serpiginous channels can be identified in 30% to 40% of patients. Multiple fenestrations are especially common with inferior MIs.
3. **Diagnostic testing**
   a. **An electrocardiogram** (ECG) may show atrioventricular (AV) node or infranodal conduction abnormalities in approximately 40% of patients.
   b. **Echocardiography**
      (1) **Transthoracic echocardiography is the test of choice** for the diagnosis of VSR. It is important for the clinician to interrogate the area of interest with color Doppler ultrasound. Lowering the Nyquist limit will enable definition and help define the size of the defect. The echocardiogram will also provide insight into the feasibility of utilizing temporizing percutaneous closure devices in this setting.
         (a) **Basal VSR** is best visualized in the parasternal long axis with medial angulation, the apical long axis, and the subcostal long axis.
         (b) **Apical VSR** is best visualized in the apical four-chamber view.
      (2) In some cases, **transesophageal echocardiography** may help in determining the extent of the defect and assessing suitability for potential percutaneous closure.
      (3) Echocardiography may help determine the size of the defect and the magnitude of the left-to-right shunt by comparing flow across the pulmonary valve with flow across the aortic valve.

(4) An assessment of right ventricular (RV) and LV function is key to prognostication and management as they remain important determinants of mortality.

c. **Right heart catheterization.** Pulmonary artery (PA) catheterization with oximetry measurement can help diagnose VSR by demonstrating an oxygen saturation step-up in the RV and PA. The **location of the increase is significant** because there have been case reports of enhanced oxygen saturation in the peripheral PA due to acute MR. Diagnosis involves fluoroscopically guided measurement of the oxygen saturation in the superior and inferior venae cavae; high, mid, and low right atrium (RA); base, mid, and apical levels of the RV; and the PA.

(1) Normal oxygen saturations for these chambers are 64% to 66% in the superior vena cava (SVC), 69% to 71% in the inferior vena cava (IVC), 64% to 67% in the RA, 64% to 67% in the RV, and 64% to 67% in the PA.

(2) An oxygen step-up at the level of the RV is characteristically seen with VSR. A left-to-right shunt across the ventricular septum typically results in a **5% or greater** increase in oxygen saturation between the RA and the RV or PA.

(3) **Shunt fraction is calculated as follows:**

$$Q_p/Q_s = (Sa{O_2} - Mv{O_2})/(Pv{O_2} - Pa{O_2})$$

In this equation, Q_p is pulmonary flow; Q_s is systemic flow; $Sa{O_2}$ is peripheral arterial oxygen saturation; $Mv{O_2}$ is mixed venous oxygen saturation; $Pv{O_2}$ is pulmonary venous oxygen saturation; and $Pa{O_2}$ is pulmonary arterial oxygen saturation. $Mv{O_2}$ is calculated by multiplying the SVC oxygen saturation by three, adding the IVC oxygen saturation, and then dividing the sum by four. $Pv{O_2}$ is generally assumed to be equal to the peripheral oxygen saturation. **Qp/Qs ≥ 2 suggests the presence of a considerable shunt. In the acute MI setting, any VSR should be considered for urgent surgical repair, regardless of the shunt fraction**.

(4) For a patient with an intracardiac shunt, **cardiac output measured by means of the thermodilution technique is inaccurate; the Fick method should be used**. The key to measurement of accurate systemic flow in the presence of a shunt is that the oxygen content measured in the PA will be abnormally elevated and must be measured in the chamber immediately **proximal** to the shunt (i.e., the RA or the SVC and IVC in the case of VSR). The Fick equation is normally calculated as follows:

$$\text{Cardiac output} = O_2 \text{ consumption}/([Sa{O_2} - Pa{O_2}] \times Hgb \times 1.34 \times 10)$$

d. **Left heart catheterization.** Ventriculography performed after angiography or percutaneous intervention (PCI) may reveal VSR if the suspicion is high. Visualization is best in the left anterior oblique projection with cranial angulation.

e. **Cardiac MRI and CT** are additional imaging modalities that can be utilized. However, the studies are more difficult to perform in hemodynamically unstable patients and do not play a significant role in this setting.

4. **Therapy**

a. **Priority of therapy.** Urgent surgical closure is the treatment of choice (AHA/ACC class I recommendation), especially when the patient's condition is stable because hemodynamic deterioration in this setting is unpredictable. Although initial reports suggested that delaying surgery to allow healing of friable tissue improved surgical mortality, it was likely that lower mortality

was simply a result of selection bias. The mortality rate for patients with VSR treated medically is 24% at 72 hours and 75% at 3 weeks.

b. Vasodilators can decrease left-to-right shunt and increase systemic flow by means of reducing systemic vascular resistance (SVR); however, a greater decrease in pulmonary vascular resistance may actually increase shunting. The vasodilator of choice is **intravenous nitroprusside**, which is started at 0.5 to 0.8 μg/kg/min and titrated to a mean arterial pressure (MAP) of 70 to 80 mm Hg.

c. An **intraaortic balloon pump (IABP)** should be inserted as early as possible as a bridge to a surgical procedure, unless there is marked aortic regurgitation. IABP counterpulsation decreases SVR, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP, vasodilators can be tailored with hemodynamic monitoring.

d. Surgical therapy

(1) Cardiogenic shock and multisystem failure are associated with high surgical mortality, further supporting earlier operations on these patients before complications develop. Mortality in patients with cardiogenic shock and VSR was 81% in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK?) trial registry (1).

(2) Surgical mortality is high among patients with **basal septal rupture associated with inferior MI** (70% compared with 30% in patients with anterior infarcts) because of the greater technical difficulty and the need for concomitant mitral valve repair in these patients, who often have coexisting MR. RV dysfunction due to infarction and/or pressure and volume overload further increases the risk profile of these subjects.

e. Percutaneous therapy. Although surgical closure remains the treatment of choice for VSR, emerging data suggest that **percutaneous closure** may be a viable treatment for high-risk surgical patients and patients in whom surgical closure has failed. In a series of 29 patients treated with percutaneous VSR closure at a median time of 1 day after MI, mortality at 30 days in patients treated with successful device placement was 36% and 86% without and with cardiogenic shock, respectively. At a median follow-up of 730 days, mortality was 36% and 93%, respectively. In our institution, a percutaneous approach is utilized for temporary palliation and as a bridge to surgical repair only in patients considered too high risk to undergo surgery.

B. Acute MR. The incidence of acute MR after MI was 13% to 39% in large registries such as GUSTO-1 and SHOCK. Fibrinolytic agents decrease the overall incidence, but rupture may occur earlier in the post-MI period. MR, even if clinically silent, is a predictor of poor prognosis in MI. Multiple mechanisms may account for acute MR. These include dilation of the mitral valve annulus as a result of LV dilation; papillary muscle dysfunction with a concomitant ischemic regional wall motion abnormality near the insertion of the posterior papillary muscle; and partial or complete rupture of the chordae or papillary muscle. Severe MR caused by papillary muscle rupture is a life-threatening complication of acute MI. Historical reports indicate that papillary muscle rupture occurs between days 2 and 7. However, the SHOCK registry revealed a median time to papillary muscle rupture of 13 hours. Acute severe MR accounted for 7% of the cases of cardiogenic shock and 5% of mortality after acute MI in the SHOCK registry.

1. Clinical presentation

a. Signs and symptoms. These are variable and depend on the anatomy of the papillary muscle involved, the mechanism of valvular dysfunction, and the extent of injury. Complete transection of the papillary muscle is rare and usually results in immediate cardiogenic shock and death. Patients with partial or complete rupture of one or more heads of the papillary muscle lose

significant leaflet support. The resultant torrential MR can result in pulmonary edema and severe respiratory distress.

b. **Physical findings.** A new **pansystolic murmur that is audible at the cardiac apex with radiation to the axilla or the base of the heart suggests acute MR**. In posterior papillary muscle rupture, the murmur radiates to the left sternal border and may be confused with the murmur of VSR or aortic stenosis. The intensity of the murmur does not predict the severity of the MR. The **murmur may often be quiet, soft, or absent** in patients with poor cardiac output or in persons with elevated left atrial pressure due to the rapid equilibration of pressures. Resting tachycardia and mechanical ventilation can also make murmur recognition challenging.

2. **Pathophysiology.** Papillary muscle rupture is **more common with an inferior MI** because the posteromedial papillary muscle receives blood supply from the posterior descending artery, whereas the anterolateral papillary muscle has dual blood supply from the left anterior descending (LAD) and circumflex arteries. Papillary muscle rupture is more likely to occur in patients with a **first MI**, and in many patients the **infarct size may be relatively small. The discordance between the degree of hemodynamic instability and the extent of myocardium in jeopardy is often a clue to the underlying condition**.

3. **Diagnostic testing**
   a. An **ECG** usually shows evidence of recent inferior or posterior MI.
   b. A **chest radiograph** may demonstrate pulmonary edema. In some patients, focal pulmonary edema may be seen in the right upper lobe because of flow directed at the right pulmonary veins.
   c. **Transthoracic echocardiography** with Doppler and color flow imaging is the diagnostic modality of choice.
      (1) The **mitral valve leaflet is usually flail** with severe MR.
      (2) Color Doppler imaging is useful in differentiating papillary muscle rupture with severe MR from VSR after MI.
   d. **Transesophageal echocardiography. Transthoracic echo may underestimate the degree of acute MR**. Rapid equalization of pressure, resting tachycardia, and poor acoustic windows may contribute to this finding. An eccentric jet in this setting should lead to the performance of **transesophageal echocardiography** to quantify the severity and elucidate the mechanism of MR.
   e. **PA catheterization.** Hemodynamic monitoring with a PA catheter may reveal large V waves in the pulmonary capillary wedge pressure (PCWP) tracing. However, patients with VSR may also have large V waves because of increased pulmonary venous return in a normal-sized and normally compliant left atrium. Among patients with severe MR and reflected V waves in the PA tracing, **oxygen saturation in the PA may be higher** than that in the RA, complicating differentiation from VSR. There are two methods for differentiating MR from VSR:
      (1) Prominent V waves in the PA tracing before the incisura are almost always associated with acute severe MR (Fig. 3.1).
      (2) Blood for oximetry is obtained with fluoroscopy to ensure sampling from the main PA rather than distal branches.

4. **Therapy**
   a. **Priority of therapy.** Papillary muscle rupture should be identified early. Patients should receive **aggressive medical therapy** and consideration for **emergent surgical repair**.
   b. **Vasodilator therapy** is beneficial in the treatment of patients with acute MR. **Intravenous nitroprusside** decreases SVR, reduces regurgitant fraction, and increases stroke volume and cardiac output. Nitroprusside is started at 0.5 to 0.8 μg/kg/min and is titrated to an MAP of 70 to 80 mm Hg.

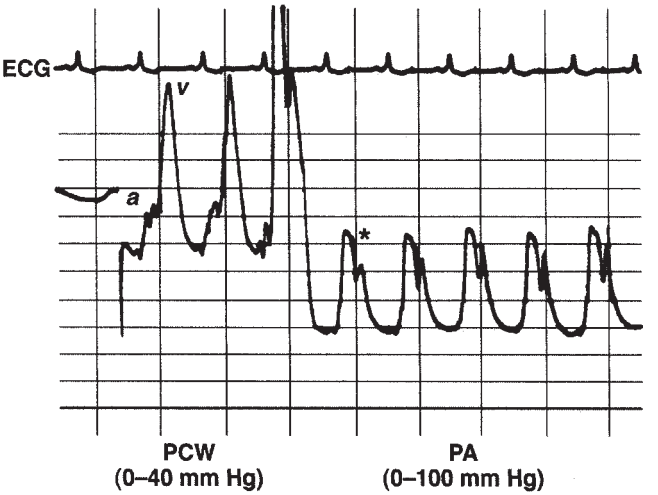

FIGURE 3.1 Giant V waves on the pulmonary capillary wedge (PCW) tracing can be transmitted to the pulmonary artery (PA) pressure, producing a notch (*asterisk*) on the PA downslope. (Adapted from Kern M. *The Cardiac Catheterization Handbook.* 2nd ed. St. Louis, MO: Mosby-Year Book; 1991.)

c. **Intraaortic balloon pump.** Vasodilator therapy is contraindicated in patients with significant **hypotension** and an IABP should be inserted promptly. An IABP decreases LV afterload, improves coronary perfusion, and increases forward cardiac output. Patients with hypotension can often be given vasodilators after insertion of an IABP to improve hemodynamic values.

d. **Percutaneous therapy.** Improvement in hemodynamic values and reduction in MR has been reported after PCI in patients with severe MR caused by papillary muscle ischemia rather than rupture. However, this is a relatively rare clinical presentation. **PCIs have no role in true papillary muscle rupture**.

e. **Surgical therapy should be considered immediately for patients with papillary muscle rupture.**

(1) The prognosis is very poor among patients treated medically. Even though perioperative mortality (20% to 25%) is higher than that for elective surgical treatment, surgical therapy should be considered for every patient.

(2) **Coronary angiography** should be performed before surgical correction, because revascularization is associated with improved short- and long-term mortality.

C. **Ventricular free wall rupture**

1. **Clinical presentation.** The incidence of ventricular free wall rupture after MI in the reperfusion era is < 1%. However, ventricular free wall rupture accounts for approximately **10% of mortality after MI**. In the SHOCK registry, in-hospital mortality associated with ventricular rupture was > 60%. Rupture occurs in the

first 5 days in 50% of patients and within 2 weeks in 90% of patients. Ventricular free wall rupture occurs in the setting of a transmural MI. Risk factors include advanced age, female sex, first MI, and poor coronary collateral vessels.

a. Signs and symptoms

(1) Acute course. With acute rupture, patients develop tamponade, electromechanical dissociation, and sudden death. Sudden onset of chest pain with straining or coughing may suggest the onset of myocardial rupture.

(2) Subacute course. Some patients may have a contained rupture and present subacutely with pain suggestive of pericarditis, nausea, and hypotension. In a large retrospective analysis of post-MI patients, 2.6% of patients were found to have sustained subacute ventricular free wall rupture. Immediate bedside echocardiography may reveal localized pericardial effusion or pseudoaneurysm.

b. Physical findings. Jugular venous distention, pulsus paradoxus, diminished heart sounds, and a pericardial rub suggest subacute rupture. New to-and-fro murmurs may be heard in patients with subacute rupture or pseudoaneurysm.

2. Pathophysiology

a. Ventricular free wall rupture constitutes part of the "early hazard" of thrombolytic therapy. Mortality among patients who receive thrombolytic agents is higher for the first 24 hours and is partially attributable to ventricular rupture. Nevertheless, the overall incidence of ventricular free wall rupture is not greater in patients treated with thrombolytics. The incidence of ventricular free wall rupture is lower in patients treated with primary angioplasty compared with thrombolytics. Rupture most commonly occurs at the anterior or lateral wall, although any wall may be involved.

b. There are **three distinct types of ventricular free wall rupture** (Fig. 3.2):

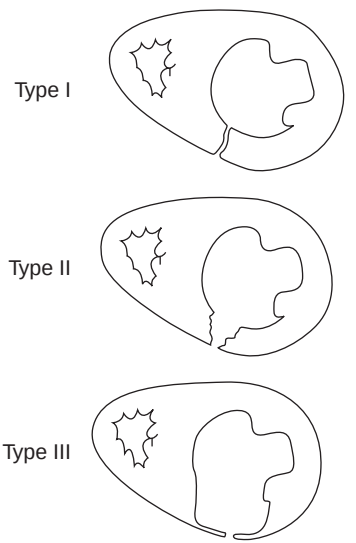

FIGURE 3.2 Morphologic classification of ventricular free wall rupture. (Reprinted with permission from Becker AE, van Mantgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol.* 1975;3:349-358.)

(1) **Type I** generally occurs within the first 24 hours and is a slitlike full-thickness rupture characterized by abrupt onset of symptoms (this rupture type increases with thrombolytics).
(2) **Type II** occurs as a result of erosion of the myocardium at the site of infarction. The rupture progresses more slowly and symptoms may be subacute.
(3) **Type III** occurs late and is characterized by expansion of the infarct zone with marked wall thinning and then rupture through the subsequent aneurysmal segment. It has been postulated that type III rupture occurs as a result of dynamic left ventricular outflow tract (LVOT) obstruction and the resultant increased wall stress. Type III rupture occurs less frequently in patients treated with thrombolytics.

3. **Diagnostic testing.** There may not be time for diagnostic testing in the treatment of patients with acute ventricular free wall rupture.
   a. In addition to evidence for new MI, an **ECG** may show junctional or idioventricular rhythm, low-voltage complexes, and tall precordial T waves. A large proportion of patients have transient bradycardia immediately preceding rupture.
   b. **Transthoracic echocardiography** reveals findings of **cardiac tamponade** in patients with a subacute course: RA and RV diastolic collapse, dilated IVC (i.e., IVC plethora), and marked respiratory variation in mitral (> 25%) and tricuspid (> 40%) inflow. Visualization of ventricular free wall rupture may be improved with echocardiographic contrast agents.
   c. **Cardiac catheterization.** Hemodynamic evaluation with a PA catheter may reveal **equalization of the RA pressure, RV diastolic pressure, PA diastolic pressure, and PCWP** consistent with pericardial tamponade. During left heart catheterization, analysis of the arterial waveform may reveal significant **respiratory variations in the systolic blood pressure (pulsus paradoxus)**. Ventriculography performed in the right anterior or left anterior oblique orientation may allow visualization of the rupture.
   d. **Cardiac MRI and CT** can be utilized in hemodynamically stable patients but are usually not available for critical decision making.
4. **Therapy.** Reperfusion therapy has reduced the overall incidence of cardiac rupture.
   a. **Priority of therapy.** The goal is to rapidly identify the problem and perform emergency surgical treatment.
   b. **Medical therapy** has little role in the treatment of these patients, except for aggressive supportive care in anticipation of surgical correction.
   c. **Percutaneous therapy**
      (1) **In the setting of hemodynamic extremis, immediate pericardiocentesis** should be performed in patients with tamponade as soon as the diagnosis is made and while arrangements are being made for transport to the operating room.
      (2) If the index of suspicion is high and the patient's condition is unstable, pericardiocentesis should be attempted without waiting for diagnostic test results.
      (3) An indwelling catheter should be clamped and left in the pericardial cavity and connected to a drainage bag during transfer to the operating room so that continued decompression of the pericardial cavity with recurrent hemodynamic compromise can be achieved.
   d. **Surgical therapy.** Emergency thoracotomy with surgical repair is the definitive therapy and is the **only chance for survival among patients with acute ventricular free wall rupture**.

D. Ventricular pseudoaneurysm (i.e., contained rupture)

1. **Clinical presentation.** Ventricular pseudoaneurysm is **more likely to occur with inferior MI than with anterior MI** (2).
   a. **Signs and symptoms.** Pseudoaneurysms may remain clinically silent and be discovered during routine investigation. However, patients may present with chest pain, dyspnea, recurrent tachyarrhythmia, and sudden cardiac death.
   b. **Physical findings.** Systolic, diastolic, or to-and-fro murmurs related to flow of blood across the narrow neck of the pseudoaneurysm during systole and diastole may be appreciated.
2. **Pathophysiology.** Ventricular pseudoaneurysm is caused by contained rupture of the LV free wall.
   a. The **outer walls of a true ventricular aneurysm are formed by infarcted myocardium and scar**, whereas the **outer walls of a pseudoaneurysm are formed by the pericardium and mural thrombus**. A pseudoaneurysm may remain small or undergo progressive enlargement.
   b. Ventricular pseudoaneurysms communicate with the body of the ventricle through a **narrow neck, the diameter of which is < 50% of the diameter of the fundus**.
3. **Diagnostic testing**
   a. A **chest radiograph** may show cardiomegaly with an abnormal bulge on the cardiac border.
   b. An **ECG** may demonstrate persistent ST-segment elevation, as with true aneurysms.
   c. **Ventriculography is the most reliable method of diagnosis**.
   d. **Echocardiography, cardiac MRI, and cardiac CT** may be utilized in evaluation as well. Echocardiographic contrast agents may increase the diagnostic accuracy.
4. **Therapy.** Spontaneous rupture may occur without warning in approximately one-third of patients with a pseudoaneurysm. **Surgical resection is recommended for patients with or without symptoms, regardless of the size of the pseudoaneurysm, to minimize the risk of death**.

E. Ventricular aneurysm

1. **Clinical presentation.** The incidence of ventricular aneurysm after MI in the reperfusion era is approximately 15% and occurs **more commonly with anterior MI than with inferior or posterior MI**.
   a. **Signs and symptoms**
      (1) **Acute aneurysm.** Acute development of a large ventricular aneurysm can result in severe LV dysfunction and cardiogenic shock. Patients with an acute MI that involves the apex of the LV, particularly those with transmural anteroapical infarcts, are at greatest risk. Acute aneurysms expand during systole. This expansion wastes contractile energy generated by normal myocardium and puts the entire ventricle at a mechanical disadvantage.
      (2) **Chronic aneurysms** persist > 6 weeks after MI, are less compliant than acute aneurysms, and rarely expand during systole. Patients with chronic aneurysms may experience heart failure, ventricular arrhythmias, mural thrombus, and systemic embolism, but they frequently have no symptoms.
   b. **Physical findings.** A dyskinetic segment of the ventricle may be apparent during inspection or may be felt during palpation. The apical impulse may be displaced to the left of the midclavicular line due to cardiac enlargement. An S_3 or S_4 gallop may be appreciated due to LV dilation and stiffening. A systolic murmur of MR may occur due to changes in LV geometry.
2. **Pathophysiology.** Infarct expansion and progressive LV dilation are consequences of absent or ineffective coronary reperfusion. The aneurysmal segment initially consists of necrotic tissue and is later replaced by fibrous scar tissue.

3. **Diagnostic testing**
   a. **ECG**
      (1) **Acute aneurysm.** The ECG reveals evidence of ST-segment elevation MI, which may persist despite evidence of reperfusion.
      (2) **Chronic aneurysm.** ST-segment elevation that persists > 6 weeks occurs in patients with chronic ventricular aneurysms.
   b. **Chest radiography** may reveal a localized bulge in the cardiac silhouette.
   c. **Transthoracic echocardiography** is the diagnostic **test of choice** and accurately depicts the aneurysmal segment. It may also reveal the presence of a mural thrombus. Echocardiography is useful in differentiating a true aneurysm from a pseudoaneurysm. True aneurysms have a wide neck, whereas pseudoaneurysms have a narrow neck in relation to the diameter of the aneurysm.
   d. Cardiac **MRI and CT** may also be utilized to characterize ventricular aneurysm.
4. **Therapy**
   a. **Medical therapy**
      (1) **Acute aneurysm.** LV failure caused by acute aneurysm is managed with **intravenous vasodilators** and **IABP** therapy. **Angiotensin-converting enzyme (ACE) inhibitors** have been shown to reduce infarct expansion and progressive LV remodeling. Because infarct expansion starts early, ACE inhibitors should be initiated within the first 24 hours of the onset of acute MI if blood pressure allows.
      (2) **Chronic aneurysm.** Heart failure associated with chronic aneurysm formation is managed with afterload reduction, namely with ACE inhibitors.
      (3) **Anticoagulation**
         (a) Anticoagulation with **warfarin sodium** should be prescribed (AHA/ACC class I indication) to patients found to have a LV mural thrombus or embolic phenomenon. Patients are initially treated with intravenous heparin with a target partial thromboplastin time (PTT) of 50 to 65 seconds. Warfarin is started simultaneously. Patients should be treated with warfarin to a target international normalized ratio (INR) of 2 to 3 for at least 3 months and then indefinitely if the risk of bleeding is not excessive. Novel oral anticoagulants such as dabigatran etexilate and rivaroxaban have not been approved for this indication at this time.
         (b) It is reasonable (AHA/ACC class IIa indication) to prescribe prophylactic anticoagulation to patients with LV dysfunction and extensive regional wall motion abnormalities that do not have a mural thrombus.
         (c) Patients with MI requiring dual antiplatelet therapy because of PCI need to have the benefits of anticoagulation weighed against an **increase in bleeding risk with triple therapy**.
   b. **Surgical therapy.** Patients with refractory heart failure and/or refractory ventricular arrhythmias should be considered for aneurysmectomy. Surgical resection may be followed by conventional closure or newer techniques (e.g., inverted T closure and endocardial patch) to maintain LV geometry.

F. **LV failure and cardiogenic shock.** Please refer to Chapter 4 for further discussion.

G. **RV failure.** Mild RV dysfunction is common after **MI of the inferior or inferoposterior wall**; however, hemodynamically significant RV impairment occurs in only 10% of patients. The **proximal right coronary artery** (RCA) is commonly involved. Extensive, irreversible RV damage is unusual because the RV has lower oxygen requirements due to its smaller muscle mass, is perfused during systole and

diastole, and often receives extensive left to right collateral blood flow. Most patients with RV infarction who survive the acute phase spontaneously improve after 48 to 72 hours.

1. **Clinical presentation**
   a. **Signs and symptoms.** The triad of **hypotension, jugular venous distention, and clear lung fields** is highly specific (but has poor sensitivity) for RV infarction. Patients with severe RV failure have symptoms of a low cardiac output state, including diaphoresis; cool, clammy extremities; and altered mental status. Patients often are hypotensive and oliguric. The use of **nitrates or β-blockers during routine MI treatment may precipitate profound hypotension** and provide the first clue of RV involvement. Table 3.2 lists causes of hypotension among patients with inferior wall MI.
   b. **Physical findings.** Patients with RV failure without concomitant LV failure may have elevated jugular venous pressure (JVP) and a RV S_3 with clear lungs. The combination of JVP > 8 cm H_2O and **Kussmaul's sign** (i.e., failure of JVP to decrease with inspiration) is sensitive and specific for severe RV failure. Elevated right-sided pressures can occasionally result in **right-to-left shunting** through a patent foramen ovale. This should be considered in patients with RV infarction and hypoxia. Table 3.3 lists the clinical findings associated with an RV infarction.
2. **Pathophysiology.** RV involvement depends on the location of the RCA occlusion. Marked dysfunction occurs only if occlusion is proximal to the acute marginal branch. The degree of RV involvement also depends on the presence of left to right collateralization and the extent of diastolic reverse perfusion through the thebesian veins.
3. **Diagnostic testing**
   a. An **ECG** usually shows **inferior ST-segment elevation**. ST-segment elevation in **V_4R** in the setting of suspected RV infarction has a positive predictive value of 80%. RV infarction is also suggested by ST-segment elevation that is greater in lead III than lead II. ST-segment elevation exceeding 1 mm may be seen in V_1 and occasionally in V_2 and V_3 (Fig. 3.3).
   b. A **chest radiograph** is usually normal and there is no evidence of pulmonary congestion.
   c. **Transthoracic echocardiography** is the diagnostic **study of choice** for RV infarction. It may demonstrate RV dilation and severe RV dysfunction and usually shows LV inferior wall dysfunction. It is also useful in

TABLE 3.2 Causes of Hypotension in Patients Presenting with Inferior Myocardial Infarction

Right ventricular infarction
Left ventricular failure
Bradyarrhythmia
Acute severe mitral regurgitation
Ventricular septal rupture
Bezold-Jarisch reflex

TABLE 3.3 Clinical Findings Associated with Right Ventricular Infarction

Hypotension
Elevated jugular venous pressure
Kussmaul's sign
Abnormal jugular venous pressure pattern (y ≥ x descent)
Tricuspid regurgitation
Right-sided S_3 and S_4
Pulsus paradoxus
High-grade atrioventricular block

differentiating RV infarction from other syndromes that can mimic it, such as cardiac tamponade.

d. Pulmonary artery catheterization. Hemodynamic monitoring with a PA catheter usually reveals **high RA pressures with low PCWP**. Acute RV failure results in underfilling of the LV and a low cardiac output state. The PCWP is usually low unless concomitant, severe LV dysfunction is present. In some patients, RV dilation can cause decreased LV performance resulting from ventricular interdependence. As the RV dilates, the septum flattens or bows into the LV and restricts ventricular filling. RA pressure > 10 mm Hg and RA pressure to PCWP ratio ≥ 0.8 strongly suggests RV infarction.

4. Therapy

a. Medical therapy

(1) Fluid administration. Management of RV infarction involves volume loading to increase preload and cardiac output. Some patients may require several liters in 1 hour. **Hemodynamic monitoring is crucial** because overzealous fluid administration in a patient with severe RV dilation can further decrease LV preload and cardiac output. Excessive fluid administration can cause the ventricular septum to shift toward the LV and impede LV filling. The target central venous pressure is approximately 15 mm Hg.

(2) Inotropes. When volume loading fails to increase cardiac output, the use of inotropes is indicated. Administration of **dobutamine** increases cardiac index and RV ejection fraction and is superior to afterload reduction with nitroprusside.

b. Percutaneous therapy

(1) Patients who undergo successful **reperfusion** of the RV have improved RV function and decreased 30-day mortality rates.

(2) AV sequential pacing may markedly improve the condition of a patient with RV infarction and bradyarrhythmia or loss of sinus rhythm. **A longer AV delay of approximately 200 milliseconds and a heart rate of 80 to 90 beats per minute are usually optimal for these patients.**

(3) An IABP may be beneficial, especially in cases of concomitant LV dysfunction.

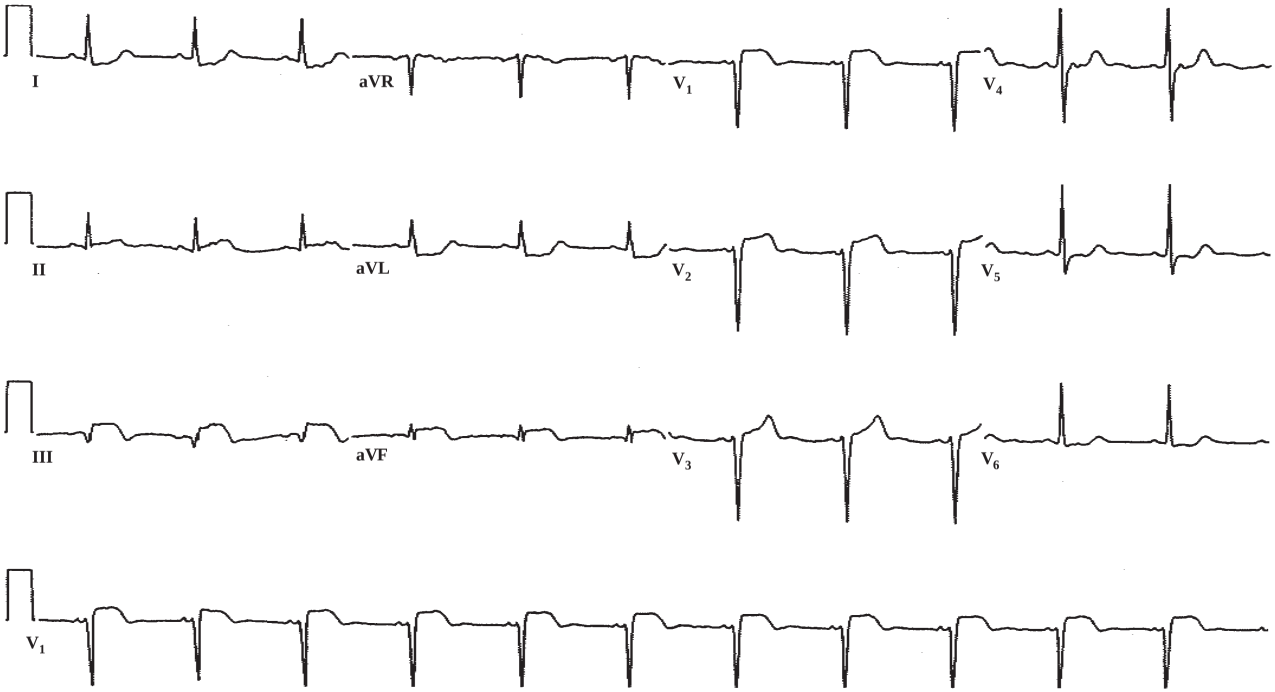

FIGURE 3.3 Electrocardiogram demonstrating acute inferior myocardial infarction with right ventricular involvement.

c. **Surgical therapy**
   (1) **Pericardiectomy** may be considered in the care of patients with refractory shock as it reverses the septal impingement on LV filling.
   (2) An **RV assist device** is indicated in the care of patients who remain in cardiogenic shock despite the foregoing measures.

H. Dynamic LVOT obstruction. Dynamic LVOT obstruction is an **uncommon complication** of acute anterior MI. Although this complication has been cited only in case reports, it may be an underappreciated and underreported complication.

1. **Clinical presentation**
   a. **Signs and symptoms.** Patients may have respiratory distress, diaphoresis, and cool, clammy extremities in addition to the typical signs and symptoms of acute MI. Patients with severe obstruction may appear to be in cardiogenic shock, with severe orthopnea, dyspnea, and oliguria in addition to altered mental status from cerebral hypoperfusion.
   b. **Physical findings** frequently include a new systolic ejection murmur heard best at the left upper sternal border with radiation to the neck. A new systolic murmur can be heard at the apex with radiation to the axilla, as a result of systolic anterior motion (SAM) of the mitral leaflet. An S_3 gallop, pulmonary rales, hypotension, and tachycardia may also occur.
2. **Pathophysiology.** The dynamic LVOT obstruction that may occur as a complication of acute anterior MI is related to compensatory hyperkinesis of the basal and mid segments of the LV. The increased contractile force of these regions decreases the cross-sectional area of the LVOT. The resultant increase in velocity of blood through the outflow tract can produce decreased pressure below the mitral valve and cause anterior mitral valve leaflet displacement toward the septum (i.e., Venturi effect). This results in further outflow tract obstruction and MR. It has been postulated that this complication can play a role in ventricular free wall rupture. LVOT obstruction leads to increased end-systolic intraventricular pressure, which leads to increased stress of the weakened, necrotic infarcted zone.
3. **Diagnostic testing. Transthoracic echocardiography** is the diagnostic test of choice and helps evaluate the hyperkinetic segments, the LVOT obstruction, and the presence of systolic SAM of the mitral leaflet.
4. **Medical therapy** is focused on decreasing myocardial contractility and heart rate while expanding intravascular volume and increasing afterload modestly.
   a. **β-Blockers** should be added slowly and with careful monitoring of the heart rate, blood pressure, and cardiac output.
   b. **Intravenous hydration** should be initiated with several small (250 mL) boluses of normal saline to increase preload and decrease LVOT obstruction and SAM. The patient's hemodynamic and respiratory status should be monitored closely during this therapeutic intervention.

III. ARRHYTHMIC COMPLICATIONS. Arrhythmias are a common complication after acute MI and are associated with significant mortality. Please refer to Chapters 21 through 25 and 41 for further discussion.

IV. EMBOLIC COMPLICATIONS. The contemporary incidence of LV mural thrombus after acute MI is approximately 5% and the incidence of systemic embolism in patients with LV mural thrombus is approximately 13%. The incidence of mural thrombus in patients with a **large anterior wall MI** is approximately 10%. Other factors associated with LV mural thrombus include **decreased LV ejection fraction, wall motion abnormalities, and LV aneurysm**.

A. **Clinical presentation**
   1. **Signs and symptoms.** The most common clinical presentation of an embolic complication is stroke, although patients may have limb ischemia, renal infarction, and intestinal ischemia. Most episodes of systemic embolization occur in the first 2 weeks after acute MI.
   2. **Physical findings.** The physical findings depend on the site of embolism.
      a. Patients with stroke present with neurologic deficits.
      b. Embolism to the peripheral circulation results in limb ischemia and cold, pulseless, and painful extremities.
      c. Renal infarctions may cause hematuria and flank pain.
      d. Mesenteric ischemia causes abdominal pain and bloody diarrhea.
   3. **Diagnostic testing**
      a. **Transthoracic echocardiography** is the initial diagnostic test of choice to evaluate for LV mural thrombus. Echocardiographic contrast agents may increase the diagnostic accuracy.
      b. **Cardiac MRI** has similar specificity but may be more sensitive than echocardiography in the detection of an LV mural thrombus.

B. **Therapy** with anticoagulation is outlined above in the management of ventricular aneurysm.

V. INFLAMMATORY COMPLICATIONS

A. **Early pericarditis.** The incidence of early pericarditis after acute MI is approximately 10%. The inflammation usually develops 24 to 96 hours after MI.
   1. **Clinical presentation.** Early pericarditis occurs in patients with transmural MI. A transient pericardial friction rub may be audible in some patients before symptoms become prominent.
      a. **Signs and symptoms**
         (1) Patients report progressive, severe chest pain that lasts for hours. The **pain is postural**: worse when the patient is supine and alleviated if the patient sits up and leans forward. The pain is usually pleuritic in nature and is worsened with deep inspiration, coughing, and swallowing.
         (2) **Radiation of pain to the trapezius ridge** is nearly pathognomonic for acute pericarditis and does not occur in patients with ischemic pain. The pain may also radiate to the neck and less frequently to the arm or back.
      b. **Physical findings.** The presence of a pericardial friction rub is pathognomonic for acute pericarditis; however, it can be evanescent.
         (1) The rub is best heard at the left lower sternal edge with the diaphragm of the stethoscope.
         (2) The rub has three components: one component each in atrial systole, ventricular systole, and ventricular diastole. In about 30% of patients, the rub is biphasic, and in 10% it is uniphasic.
         (3) The development of pericardial effusion may cause fluctuations in the intensity of the rub, although the rub may still be heard despite substantial pericardial effusion.
   2. **Etiology and pathophysiology.** Pericarditis typically results from an area of localized pericardial inflammation overlying the infarcted myocardium. The inflammation is fibrinous in nature. The development of an evanescent pericardial rub correlates with a larger infarct and hemodynamic derangements.

3. **Diagnostic testing**
   a. An **ECG** is the most useful test in the diagnosis of pericarditis; however, evolving electrocardiographic changes may make the diagnosis difficult for patients who have had MI. Unlike ischemia, in which the changes are limited to a particular territory, pericarditis produces generalized electrocardiographic changes.
      (1) The ST-segment elevation seen with pericarditis is a concave upward or saddle-shaped curve.
      (2) In pericarditis, T waves become inverted after the ST segment becomes isoelectric, whereas in acute MI, T waves may become inverted when the ST segment is still elevated.
      (3) Four phases of electrocardiographic abnormality have been described in association with pericarditis (Table 3.4).
   b. **Chest radiography** is of limited value in the diagnosis of pericarditis.
   c. **Echocardiography** may reveal pericardial effusion, which strongly suggests pericarditis, although the absence of effusion does not rule out the diagnosis.
4. **Therapy**
   a. **Aspirin** is used to manage post-MI pericarditis and doses as high as 650 mg every 4 to 6 hours may be needed.
   b. **Nonsteroidal antiinflammatory agents and corticosteroids should not be used to treat these patients**. These agents may interfere with myocardial healing and contribute to infarct expansion.
   c. **Colchicine** may be beneficial. Colchicine 0.6 mg every 12 hours plus conventional therapy with aspirin decreases symptom recurrence in patients with idiopathic pericarditis.

B. **Late pericarditis (i.e., Dressler's syndrome).** The incidence of Dressler's syndrome is between 1% and 3%. The syndrome occurs 1 to 8 weeks after MI. The pathogenesis is unknown, but an autoimmune mechanism has been suggested.
1. **Clinical presentation.** Patients may present with chest discomfort that suggests pericarditis, pleuritic pain, arthralgia, malaise, fever, pericardial friction rub, elevated leukocyte count, and an elevated sedimentation rate. Echocardiography may reveal a pericardial effusion.
2. **Therapy** is similar to that for early post-MI pericarditis: aspirin, colchicine, and avoidance of nonsteroidal antiinflammatory drugs and corticosteroids. However, if > 4 weeks have elapsed since the MI, nonsteroidal antiinflammatory agents and corticosteroids may be indicated for severe symptoms.

TABLE 3.4 Electrocardiographic Changes of Pericarditis

Stage I	ST elevation, upright T waves
Stage II	ST elevation resolves, upright to flat T waves
Stage III	ST isoelectric, inverted T waves
Stage IV	ST isoelectric, upright T waves

ACKNOWLEDGMENTS: *The authors would like to thank Dr. David Tschopp, Dr. John Galla, and Dr. Debabrata Mukherjee for their contributions to earlier editions of this chapter.*

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CHAPTER 4

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Venu Menon

Cardiogenic Shock Complicating Acute Myocardial Infarction

I. INTRODUCTION. Left ventricular (LV) dysfunction is common after acute myocardial infarction (MI), and the severity of dysfunction correlates with the extent of myocardial injury. Cardiogenic shock is estimated to **complicate 3% to 8% of cases of acute MI** (1–3). **The mortality associated with cardiogenic shock in patients with acute MI had historically approached 80%** (1,4). Despite advancements in coronary reperfusion, **the contemporary mortality associated with MI complicated by cardiogenic shock remains at 40% to 70%** (3,5,6). **Prior MI, older age, female sex, diabetes, and anterior infarction** are risk factors for the development of cardiogenic shock after MI.

II. CLINICAL PRESENTATION. Cardiogenic shock is a clinical condition in which **inadequate tissue perfusion is the consequence of cardiac dysfunction**. It is characterized by a **reduction in cardiac output despite adequate filling pressures**. Criteria typically used to define cardiogenic shock include **systolic blood pressure < 90 mm Hg** for at least 30 minutes or need for vasopressor or intra-aortic balloon support to maintain systolic blood pressure > 90 mm Hg, **pulmonary capillary wedge pressure (PCWP) > 15 mm Hg, and cardiac index < 2.2 L/min/kg/m^2**.

- **A. Symptoms.** Patients in cardiogenic shock from LV failure typically present with **respiratory distress**. **Confusion** may occur due to inadequate tissue perfusion.
- **B. Physical findings**
  1. **Hypotension, tachycardia, confusion, diminished urine output (<30 mL/h), and cool, mottled, and cyanotic extremities** typically characterize the clinical presentation of cardiogenic shock. Peripheral pulses are often diminished in cardiogenic shock due to decreased pulse pressure **(pulsus parvus)**. In a failing left ventricle the strength of every other beat may alternate, a phenomenon known as **pulsus alternans**. A **dyskinetic segment of the ventricle** may be apparent during inspection or may be felt during palpation. An **S_3 gallop** may be heard in patients with poor LV function.
  2. Patients with acute mechanical complications of MI such as ventricular septal rupture, acute mitral regurgitation, ventricular free wall rupture, ventricular pseudoaneurysm, ventricular aneurysm, right ventricular failure, and dynamic outflow tract obstruction may present with additional physical findings as discussed in Chapter 3.
  3. Cardiogenic shock due to LV failure may cause pulmonary congestion and inspiratory rales. However, **a significant proportion of patients in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK?) registry had no pulmonary congestion** (7). Neither auscultation nor chest radiograph detected pulmonary edema in 28% of the patients.
  4. A select group of patients may exhibit **preshock**. This clinical entity is characterized by signs of hypoperfusion with resting tachycardia but not frank hypotension due to a compensatory increase in systemic vascular resistance. On right heart catheterization, these patients have an ineffective cardiac index and are at high risk for in-hospital mortality.

III. RISK STRATIFICATION

- **A.** In the prereperfusion era, **Killip and Kimball** classified **four subsets of patients on the basis of clinical presentation and physical findings** at the onset of MI (4). They reported an 81% in-hospital mortality in patients with cardiogenic shock (Killip class IV). In the fibrinolytic era, the 30-day mortality rate for patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial that presented with cardiogenic shock was 58% (Table 4.1) (8). The presence of resting tachycardia and pulmonary congestion identifies patients at highest risk even in the current reperfusion era.
- **B.** In a classic study performed in the prereperfusion era, **Forrester** classified **four hemodynamic subsets of patients on the basis of PCWP and cardiac index** (Table 4.2) and determined the associated mortality in acute MI (9).
- **C.** Right heart catheterization hemodynamic parameters including stroke volume, cardiac output, and cardiac index are strong predictors of in-hospital mortality in patients presenting with MI complicated by cardiogenic shock. In the SHOCK registry, the **cardiac power index** (mean arterial pressure × cardiac index/451) in W/m^2 was the strongest independent hemodynamic correlate of in-hospital mortality (10).
- **D.** The SHOCK trial investigators have also published a **severity scoring system** to predict in-hospital mortality in patients with acute MI complicated by cardiogenic

TABLE 4.1 30-Day Mortality Based on Hemodynamic (Killip) Class in the GUSTO-1 Trial

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5
II	Rales, ↑ JVD, or S_3	13	14
III	Pulmonary edema	1	32
IV	Cardiogenic shock	1	58

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention.

Adapted from Fox AC, Glassman E, Isom OW. Surgically remediable complications of myocardial infarction. *Prog Cardiovasc Dis.* 1979;107:852-855.

shock (11). Age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, systolic blood pressure, prior coronary artery bypass grafting, anterior MI location, and creatinine > 1.9 mg/dL are the risk factors utilized in a multivariable model. In patients with hemodynamic monitoring, age, end-organ hypoperfusion, anoxic brain damage, stroke work, and left ventricular ejection fraction < 28% are the variables considered.

IV. ETIOLOGY. Table 4.3 outlines the various etiologies of cardiogenic shock complicating acute MI. Patients with acute MI and cardiogenic shock typically have significant **left main** and **severe three-vessel coronary artery disease** and commonly have substantial involvement of the **left anterior descending artery** (12). Autopsy studies have revealed that at least 40% of the LV is affected in most patients presenting with cardiogenic shock complicating acute MI (13). Forty percent of patients have a history of prior MI. If the previous MI was large, even a small, acute MI in a nonanterior location may cause shock. **In the SHOCK registry, LV failure (79%), severe mitral regurgitation (7%), ventricular septal rupture (4%), right ventricular failure (3%), and ventricular free wall rupture (1%) were the leading causes of cardiogenic shock in acute MI** (6). **Bradyarrhythmias and tachyarrhythmias** related to acute MI can also cause cardiogenic shock. **Medications** administered for acute MI such as β-blockers, angiotensin-converting enzyme inhibitors, and morphine can cause iatrogenic shock by inducing hypotension.

TABLE 4.2 Forrester Classification

Subset	PCWP	Cardiac index	Mortality rate
I	<18	>2.2	3
II	>18	>2.2	9
III	<18	<2.2	23
IV	>18	<2.2	51

PCWP, pulmonary capillary wedge pressure.

TABLE 4.3 Causes of Cardiogenic Shock Complicating Acute Myocardial Infarction

Left ventricular failure
Right ventricular failure
Ventricular septal rupture
Acute mitral regurgitation
Ventricular aneurysm
Ventricular free wall rupture
Cardiac tamponade
Dynamic left ventricular outflow tract obstruction
Arrhythmia
Iatrogenic (e.g., β-blocker related)

In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), early β-blocker use was associated with an increased risk of developing cardiogenic shock, especially when used within the first day of admission (14). **Occult bleeding** resulting from antiplatelet and anticoagulation therapies in acute MI can also result in hypotension and circulatory collapse.

V. PATHOPHYSIOLOGY. Ineffective cardiac output in the setting of cardiogenic shock results in hypotension and tachycardia. A compensatory increase in systemic vascular resistance may occur through peripheral vasoconstriction in an effort to maintain blood pressure and tissue perfusion. However, this classic paradigm has been challenged. Data from the SHOCK registry revealed that many patients with cardiogenic shock instead had low systemic resistance, similar to patients with septic shock (15). It has been postulated that a systemic inflammatory response-like syndrome with a low systemic vascular resistance may be encountered in up to one-fifth of patients with acute MI complicated by cardiogenic shock (16). Figure 4.1 provides an overview of the pathophysiology of cardiogenic shock caused by acute MI and the expansion of the paradigm to include the contribution of inflammatory mediators.

VI. LABORATORY EXAMINATION. Decreased mixed venous oxygen saturation, lactic acidosis, and elevated creatinine and liver transaminase levels are common.

VII. DIAGNOSTIC STUDIES

A. Electrocardiogram. Patients with cardiogenic shock resulting from LV failure usually have extensive electrocardiographic abnormalities consistent with massive infarction, severe diffuse ischemia, or evidence of a large, prior MI. Extensive ST-segment deviations are common. Both ST-elevation MI and non–ST-elevation MI can manifest as cardiogenic shock.

B. Chest radiography may reveal pulmonary congestion.

C. Hemodynamic monitoring with an **arterial line** and **pulmonary artery (PA) catheter** is helpful in monitoring the patient's hemodynamic status and may also identify complications of acute MI, including right ventricular infarction, acute mitral regurgitation, and ventricular septal rupture. In GUSTO-1, mortality among patients ($n = 995$) presenting with acute MI and cardiogenic shock that were managed with

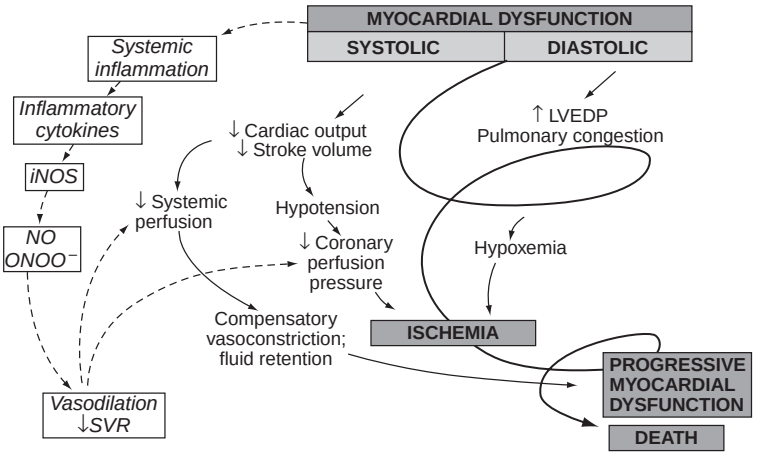

FIGURE 4.1 Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. LVEDP, left ventricular end diastolic pressure; NO, nitric oxide; iNOS, inducible nitric oxide synthase; $ONOO^-$, peroxynitrite; SVR, systemic vascular resistance. (Reprinted with permission from Hochman JS, Ohman EM. Pathophysiology. In: *Cardiogenic Shock*. Oxford: Wiley-Blackwell; 2009.)

PA catheters (45.2%) was less than among those (n = 1,406) that were not managed with PA catheters (63.4%) (17). However, the difference in part may be attributable to survivor bias as well as confounding.

D. Transthoracic echocardiography may help determine the etiology of shock as well as the extent of myocardial injury. It can identify the complications of acute MI that contribute to cardiogenic shock. It may also draw attention to additional causes of cardiogenic shock such as aortic dissection, cardiac tamponade, or pulmonary embolism.

VIII. THERAPY

A. Priority of therapy. Early revascularization is critically important in the management of patients presenting with acute MI and cardiogenic shock. The benefits of this strategy were proven in the SHOCK trial (18). Early revascularization saved 13 lives per 100 treated at 1 year compared with a strategy of medical stabilization and delayed revascularization. This strategy should be strongly considered in all patients aged < 75 years in the absence of contraindications; select older patients with good premorbid functional status also derived a similar benefit from this approach. Consequently, patients with acute MI complicated by cardiogenic shock should undergo prompt angiography for defining coronary anatomy. Subsequent revascularization should be guided by clinical presentation, extent of disease, and concomitant valvular function.

B. Percutaneous coronary intervention (PCI) of the infarct-related artery should be attempted emergently in this population. With the adoption of PCI, there has been a marked decline in the mortality of patients with acute MI complicated by cardiogenic shock. Persistence of shock following successful PCI of the infarct-related artery may be an indication to consider multivessel intervention, especially when remote ischemia in noninfarct distributions is suspected.

C. Coronary artery bypass grafting. Emergency surgical revascularization should be considered in the care of patients with severe multivessel disease or substantial left main coronary artery stenosis. It is also indicated when there is a significant concomitant valvular disease that is contributing to hemodynamic instability. Despite sicker patients with more extensive coronary artery disease being referred for coronary artery bypass grafting, mortality due to surgery in the SHOCK Trial and Registry was comparable to that of PCI. However, at many centers, there is reluctance to operate on patients in cardiogenic shock and early reperfusion is generally performed utilizing PCI.

D. Adjunctive support

1. An **intra-aortic balloon pump** (IABP) should be inserted as soon as possible in a patient with cardiogenic shock to ensure hemodynamic stability and protect end-organ perfusion. IABP support reduces afterload, improves cardiac output, and decreases the myocardial oxygen requirement by means of reduction in wall stress. An IABP is also beneficial in MI because diastolic augmentation may increase coronary perfusion in vessels that do not have a flow-limiting stenosis. Contraindications to placement include the presence of significant peripheral vascular disease, aortic dissection, and more than moderate aortic insufficiency. There are no randomized controlled trials to support the placement of an IABP in this setting. One must, however, remember that the IABP was an integral component of the early revascularization strategy observed in the SHOCK trial.
2. **Transvenous pacing.** Patients with inadequate heart rate due to bradyarrhythmia or chronotropic incompetence may require temporary pacing to increase the heart rate and augment cardiac output. **Atrial pacing** maintains atrioventricular synchrony and normal LV contraction and is preferable to ventricular pacing if atrioventricular conduction is intact.

E. Medical therapy

1. **Vasopressors.** Patients may need vasopressors to maintain an effective mean arterial pressure. **Dopamine** is started at 3 μg/kg/min and titrated to a maximal dose of 20 μg/kg/min. **Norepinephrine** is started at 2 μg/min and titrated to a maximal dose of 30 μg/min. Dopamine may be associated with higher mortality in cardiogenic shock than norepinephrine when titrated to maintain an effective mean arterial pressure (19).
2. **Inotropic agents.** Patients with severe LV failure and cardiogenic shock may require temporary support with an inotropic agent.
   a. **Dobutamine** has a positive inotropic action comparable to that of dopamine and may decrease afterload. Dobutamine is started at a dose of 2.5 μg/kg/min and increased to a maximal dose of 40 μg/kg/min.
   b. **Milrinone**, a phosphodiesterase inhibitor with inotropic and vasodilator action, may be beneficial in some patients, especially those with right ventricular dysfunction. Milrinone is given as a 50-μg/kg bolus over 10 minutes, followed by an infusion of 0.375 to 0.75 μg/kg/min. The bolus may be omitted in the care of patients with low blood pressure. Patients without adequate blood pressure may not tolerate milrinone.
   c. **Levosimendan** is an intravenous agent that increases inotropy by binding cardiac troponin C and sensitizing myofilaments to calcium. It is currently approved for use in some countries in Europe and South America but is not available for use in the United States.
3. **Vasodilators** such as **nitroglycerin** and **sodium nitroprusside** can play an important role in the management of post-MI LV failure by means of preload and afterload reduction. However, in the setting of cardiogenic shock, their use may be limited by refractory hypotension.
4. Table 4.4 summarizes the hemodynamic effects of medications used in the management of cardiogenic shock.

TABLE 4.4 Hemodynamic Effects of Medications Used to Manage Cardiogenic Shock

Medication	Preload	Afterload	Inotropy	Chronotropy
Dopamine (3–10 μg/kg/min)	0	–	++++	++
Dopamine (>10 μg/kg/min)	0	+++	+++	+++
Norepinephrine (2–300 μg/min)	0	++++	+	++
Epinephrine (0.05–1 μg/kg/min)	0	+++	+++	+++
Phenylephrine (0.5–15 μg/kg/min)	0	++++	0	–
Dobutamine (2.5–25 μg/kg/min)	–	–	++++	+++
Milrinone (0.375–0.75 μg/kg/min)	– –	– –	+++	+
Nitroglycerin (2.5–300 μg/min)	– – –	–	0	+
Nitroprusside (0.3–10 μg/kg/min)	– – –	– – –	0	+

0, no effect; –, decrease; +, increase.

IX. MANAGEMENT OF REFRACTORY SHOCK AFTER CORONARY REVASCULARIZATION

A. Triage. Patients that remain in cardiogenic shock despite coronary revascularization are best served by transfer to a facility that can provide additional adjunctive hemodynamic therapies. In addition, the facility should have an active cardiac transplant program and full-time availability of interventional cardiology, electrophysiology, cardiothoracic surgery, and neurology services.

B. Decision making. The prognosis for patients that remain in cardiogenic shock after coronary revascularization is extremely poor. However, there are patients that do ultimately recover their LV function and survive. It is often impossible to predict which patients will do well and which patients will succumb to their illness. In our institution, we often consider additional adjunctive hemodynamic therapies as a bridge to decision making.

C. Additional adjunctive hemodynamic support

1. **Percutaneous ventricular assist device (pVAD).** Traditional mechanical circulatory support from an IABP may prove insufficient in certain patients, and consideration may be given to more aggressive support with a percutaneous assist device, especially if shock persists after coronary revascularization.
   - **(a)** The **TandemHeart** (Fig. 4.2) device provides left atrial to femoral artery bypass flow at rates of up to 5.0 L/min with percutaneous access and can serve as a bridge to recovery or more definitive therapy. Limited case series from isolated centers suggest that the TandemHeart device is able to rapidly reverse the terminal hemodynamic compromise seen in patients with severe cardiogenic shock refractory to IABP and/or high-dose vasopressor support (20).
   - **(b)** The **Impella** intracardiac axial flow ventricular assist device can provide either 2.5 or 5.0 L/min support. Our experience has been that the Impella 2.5 L/min device does not provide much additional benefit beyond that of an IABP, whereas the 5.0 L/min device provides substantial adjunctive support. Currently, the Impella 5.0 L/min device requires surgical cut-down for vascular access.

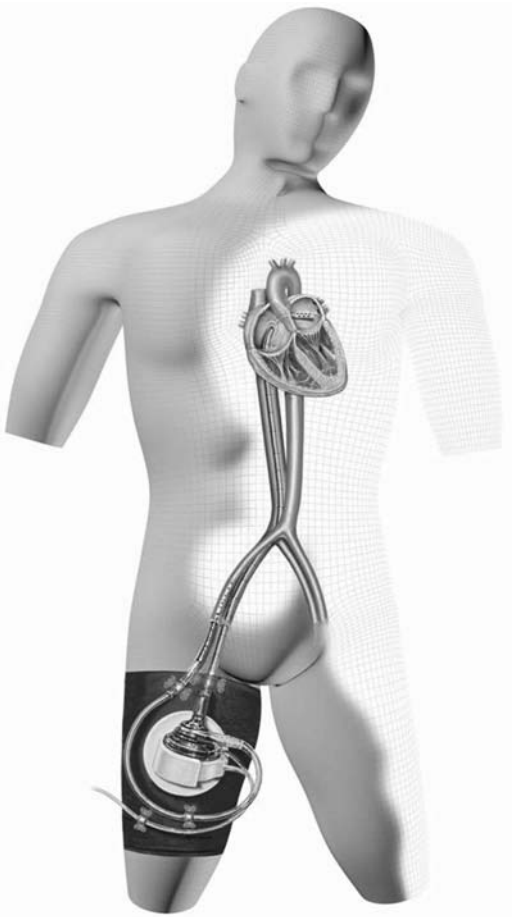

FIGURE 4.2 The TandemHeart percutaneous left ventricular assist device. (Reprinted with permission from CardiacAssist, Inc.)

2. **Extracorporeal membrane oxygenation (ECMO).** ECMO is an established therapy that can be implemented expeditiously in experienced hands. It provides hemodynamic support and as an additional advantage can support oxygenation if the lung function is compromised. We often use ECMO in our institution as a bridge in deciding whether to use more long-term therapy such as an implanted left ventricular assist device (LVAD).
3. **Left ventricular assist device.** Surgical LVAD therapy is often utilized in advanced LV failure as a destination therapy or as a bridge to transplant. In patients presenting with acute MI complicated by cardiogenic shock, LVAD therapy is a consideration. However, other temporizing measures such as pVAD or ECMO are often considered first.

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CHAPTER 5

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Post–Myocardial Infarction Risk Stratification and Management

I. INTRODUCTION. More than 1.5 million patients will have an acute coronary syndrome (ACS) in the United States each year. At least 1 million will have evidence of myocardial infarction (MI), for which mortality and morbidity remain considerable. Although patient outcomes have improved, well-documented therapies are still often underprescribed. Besides identifying patients with MI, the goals of the physician must be to successfully stratify patients according to risk, implement medical interventions, and initiate risk factor modification during the initial hospitalization.

II. RISK STRATIFICATION. Post-MI risk stratification identifies patients at high risk for subsequent cardiovascular events who will benefit from revascularization.

A. Age is the most important predictor of mortality after MI. The average age of patients with first MI is approximately 65 years. Although older patients are at greatest risk and may benefit most, they receive less aggressive treatment compared with younger patients, who have the lowest overall mortality.

B. Assessment of left ventricular (LV) function

1. **LV function** is the second most important predictor of mortality after MI. An inverse relation exists between left ventricular ejection fraction (LVEF) and mortality. Mortality is greatest for patients with an LVEF < 40%.
2. Assessment of LV function is indicated for all patients diagnosed with MI. Echocardiography is often utilized to assess LV function because it is readily available, is relatively inexpensive, and can assess concomitant valvular function as well as mechanical complications of MI. Left ventriculography performed during diagnostic catheterization, or ascertained by radionuclide ventriculography, and cardiac magnetic resonance may also be utilized to evaluate LV function. Availability, local expertise, and cost are important considerations when deciding which procedure to use.

C. Other indicators. Biomarkers are useful in further risk-stratifying patients after MI. **Cardiac troponin** elevation identifies high-risk patients and incremental increases in troponin levels predict higher mortality in patients with ACS. Elevated serum levels of high-sensitivity **C-reactive protein** and **B-type natriuretic peptide may also provide prognostic information**. New **ST-segment changes**, both elevation and depression, portend higher risk of death, heart failure, recurrent ischemia, and severe coronary artery disease (CAD). **Electrical instability**, such as ventricular arrhythmias and atrial fibrillation, are associated with increased risk. Anterior MI, renal insufficiency, poor glycemic control, and anemia are also associated with worse outcomes.

D. Risk models. Various models utilize a combination of the aforementioned risk factors to quantitate a predictive score of patient risk for subsequent cardiac events

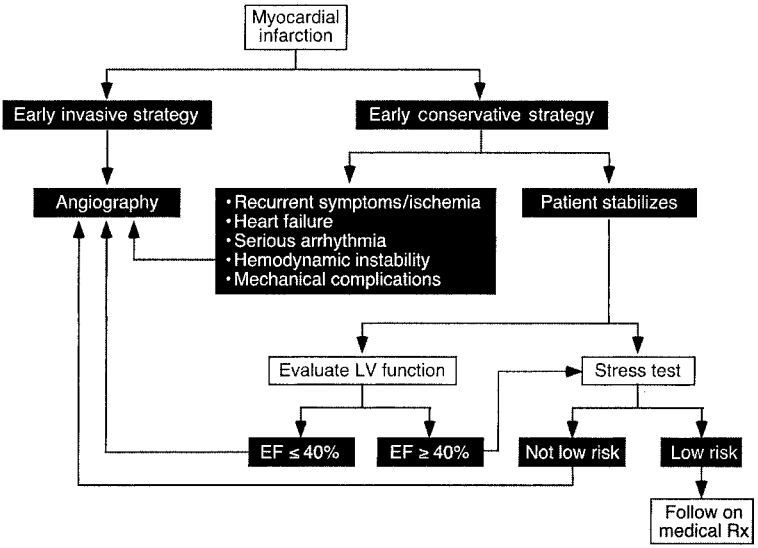

FIGURE 5.1 Post–myocardial infarction risk stratification. LV, left ventricular; EF, ejection fraction.

and mortality. Examples include Thrombolysis in Myocardial Infarction (TIMI), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI), and the Global Registry of Acute Coronary Events (GRACE).

E. Assessment of residual ischemia (Fig. 5.1). The extent of CAD and the presence of residual ischemia are two strong predictors of mortality among patients who have had an MI. For this reason, post-MI patients who have not undergone angiography should undergo stress testing before discharge or shortly thereafter (preferably within 3 to 7 days post-MI). Non–ST-elevation ACS patients at low or intermediate risk who do not have ongoing ischemia or heart failure for at least 12 to 24 hours are also candidates for submaximal stress testing. Because of increasing availability of percutaneous revascularization and growing implementation of a pharmaco-invasive strategy for ST-elevation MI (STEMI) patients who receive thrombolytics, most patients with STEMI undergo angiographic definition. Stable STEMI patients who have not undergone catheterization should undergo stress testing to assess for ischemia 2 to 3 days after the index event.

1. **Submaximal exercise stress testing is optimal for noninvasive risk stratification.** This test provides considerable prognostic information, assesses functional capacity and efficacy of medical therapy, and can guide cardiac rehabilitation after discharge. Patients who achieve at least 3 metabolic equivalents (METs) of the task have a good prognosis. Inability to achieve 3 METs, hypotension during exercise, or marked ST-segment depression or elevation is an indication for coronary angiography.
2. **Stress imaging with echocardiography** or **radionuclide imaging is** recommended in patients who have uninterpretable electrocardiograms (e.g., baseline ST-T changes, LV hypertrophy, intraventricular conduction delays, paced rhythm, or digoxin-related effects). Addition of either imaging modality increases both the sensitivity and specificity of detecting CAD. Patients with

severe resting or exercise-induced LV dysfunction or evidence of extensive ischemia (large perfusion defect, multiple moderate perfusion defects, wall motion abnormalities at low-dose dobutamine or low heart rate, and stress-induced LV dilation) are considered high risk and should undergo coronary angiography.

3. **Dobutamine, adenosine, and dipyridamole** are pharmacologic agents used safely in conjunction with imaging for post-MI stress testing if a patient cannot exercise (see Chapter 6).

III. THERAPY AFTER MI

A. Coronary angiography

1. **Indications**
   - **a.** Coronary angiography is indicated in patients with STEMI as well as in those with non-STEMI who are at high risk for clinical events, recurrent angina or ischemia on medical therapy, or high-risk findings on noninvasive stress testing.
   - **b.** An **"early invasive strategy" utilizing coronary angiography** is the preferred approach for patients at high risk for clinical events, including a high-risk score, elevated troponin, congestive heart failure, mechanical complications, and electrical or hemodynamic instability.
   - **c. Patients with a history of prior revascularization,** either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), should generally be referred for angiography.
   - **d.** Coronary angiography to identify potential bypass targets is generally preferred prior to open heart surgery if a patient has surgical anatomy or has a mechanical complication post-MI requiring surgical intervention. Such complications of MI include ventricular septal rupture, LV aneurysm, and acute mitral regurgitation due to papillary muscle rupture. In rare instances when hemodynamic instability precludes angiography, the surgeon may bypass all or selected coronary arteries.
2. **Contraindications.** Catheterization should not be performed on patients who are ineligible for surgical or percutaneous revascularization because of severe comorbid conditions or who do not consent to angiography because of personal preference.
3. **Controversy.** Low-risk, asymptomatic patients who have sustained an uncomplicated MI generally have a good long-term prognosis and may not need to undergo angiography. These patients presumably are those without high-risk features on noninvasive stress testing who will receive aggressive medical therapy and risk factor modification.
4. **PCI.** A new era of PCI therapy that includes novel anticoagulants, antiplatelet agents, and newer generation drug-eluting stents continues to significantly enhance the options and outcomes for post-MI patients undergoing revascularization.

B. CABG after MI can be divided into two categories: emergent and elective.

1. **Emergent CABG.** The indications and management considerations for emergent CABG are discussed in Chapter 1.
2. **Elective CABG.** CABG has been shown to provide a survival benefit for patients with left main (> 50% stenosis) or extensive three-vessel CAD. Surgical revascularization remains preferable for patients with severe LV dysfunction, diabetes, or two-vessel disease with proximal left anterior descending involvement and either high-risk noninvasive stress test results or LV dysfunction. However, the Arterial Revascularization Therapies Study (ARTS) demonstrated no significant difference in mortality, MI, or stroke among patients with multivessel disease and normal to moderately decreased LV function randomized to CABG versus PCI. The Synergy between Percutaneous Coronary Intervention with Taxus and

Cardiac Surgery (SYNTAX) trial evaluated PCI versus CABG for three-vessel or left main disease and nearly 30% of the patients had ACS. This trial demonstrated equivalent cumulative rates of major adverse cardiac or cerebrovascular events in the low (0 to 22) and intermediate (22–32) SYNTAX score patients, though there was a higher rate of adverse events in the high (≥33) SYNTAX score patients who underwent PCI. Target vessel revascularization was higher in the PCI group but stroke rate was higher in the CABG group.

3. **Operative risk.** No prospective, randomized trials have been performed to determine the optimal timing of elective CABG after MI. Most data suggest that CABG 3 to 7 days after MI is associated with a low operative mortality similar to that of elective bypass in patients without recent infarction. **Operative risk increases** among patients with LV dysfunction, advanced age, and multiple comorbid conditions (e.g., diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal insufficiency). Emergent CABG and reoperations on patients with prior open heart surgery are associated with a higher operative mortality. If initiated previously, **clopidogrel** should be held for at least **5 days** prior to surgery and **prasugrel** for at least **7 days** prior to decrease perioperative bleeding risk. Ticagrelor is a reversible inhibitor of the adenosine diphosphate (ADP) receptor $P2Y_{12}$ that is more rapid acting and potent than clopidogrel. There was initial hope that the use of ticagrelor in patients with ACS undergoing urgent bypass surgery could reduce the time from cessation of antiplatelet agents to the time of surgery to just 2 or 3 days, given the more rapid reversal of platelet inhibition. However, results from the Study of Platelet Inhibition and Patient Outcomes (PLATO) demonstrated no difference in TIMI major bleeding or transfusion rates in patients with ACS who stopped clopidogrel 5 days prior to CABG compared with those who stopped ticagrelor 24 to 72 hours before surgery. Bleeding rates were equivalent even when surgery occurred 1 to 3 days after discontinuation of antiplatelets. Therefore, current ACC/AHA guidelines recommend **withholding ticagrelor for at least 5 days** prior to elective open heart surgery.

IV. SECONDARY PREVENTION

A. Smoking cessation is mandatory. Smoking doubles the rate of reinfarction and death after MI, causes coronary artery spasm, and reduces the effectiveness of β-blocker therapy. The risk reduction attributed to smoking cessation is rapid and nearly equals that of post-MI patients who never smoked in only 3 years. Half of all patients who stop smoking after MI will begin smoking again within 6 to 12 months. Many approaches to smoking cessation have been attempted, including pharmacologic therapy, formal smoking cessation programs, hypnosis, and abstinence.

1. **Nicotine substitutes** can be delivered by a variety of vehicles, including transdermal patches, chewing gum, nasal spray, and inhalers. These systems can deliver 30% to 60% of the nicotine of cigarettes. Although nicotine substitutes are not recommended for the acute phase of MI, use of these agents is safe in later phases. Patients who start smoking again should discontinue the use of nicotine substitutes.
2. **Pharmacotherapy. Bupropion** appears to be an effective aid in smoking cessation. The dose is doubled after 3 days and it is then taken twice daily for 7 to 12 weeks. Patients set a goal to stop smoking 1 to 2 weeks into therapy. **Varenicline**, a partial agonist of nicotine receptors, provides nicotine stimulation while blocking cigarette nicotine effects. In a head-to-head trial, varenicline was more effective than bupropion at the 12-week time period, but data suggest no significant difference in rates of abstinence at 1 year. In addition, the FDA issued a communication in 2011 warning that varenicline may increase the risk of cardiovascular events.

3. **Recommendations.** Physicians can aid patients in their effort to stop smoking by using a stepped approach with education and a firm recommendation to quit smoking, devising a plan, and reinforcing the need to quit. Patients who are likely to relapse are older, less educated, or heavy smokers. Formal smoking cessation programs have been shown to have high rates of patient abstinence. Coinhabitants should also stop smoking to increase the likelihood of success.

B. Lipid management

1. **Low-density lipoprotein (LDL).** Most patients with acute MI have abnormal lipid profiles. Several large, secondary prevention trials have demonstrated that lowering of lipids can reduce the incidence of future mortality, reinfarction, and stroke.
   a. **Diagnostic testing.** All patients who have had an MI should have a complete lipid panel (e.g., total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) determined during hospitalization.
   b. **Diet.** Current ACC/AHA guidelines recommend that all patients should start the AHA step II diet (< 7% of total calories as saturated fat and < 200 mg/d cholesterol). However, adherence to step II diet is low.
   c. **Therapy.** The National Cholesterol Education Program III **(NCEP III)** recommends a target LDL cholesterol level < 100 mg/dL, with a goal of < 70 mg/dL in very high risk patients (e.g., post-MI). Given the results of the Heart Protection Study (HPS), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, or **statin, should be initiated in all patients irrespective of LDL levels,** owing to potential benefits in addition to lipid lowering, including anti-inflammatory and antithrombotic effects. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials demonstrate that **early initiation of aggressive lipid-lowering statin therapy** during an ACS is associated with a **reduction in major cardiovascular events, including death**. Long-term compliance with statins is improved by in-hospital initiation of therapy (77% vs. 40%). Other therapies include bile acid sequestrants, niacin, gemfibrozil, moderate alcohol consumption (particularly red wine), and exercise. These may be used in conjunction with statin therapy.
2. **HDL.** Low HDL cholesterol level is an independent risk factor for MI. The NCEP III recommends an HDL level of at least 40 mg/dL. Consideration can be given to therapy with exercise, niacin, or gemfibrozil. An earlier trial, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE), compared the use of a cholesteryl ester transfer protein (CETP) inhibitor torcetrapib plus statin versus statin alone and demonstrated increased HDL levels but significantly more adverse cardiovascular events and death from all causes in the torcetrapib group. A more recent trial with a newer drug anacetrapib, the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study, has corroborated the beneficial effect on HDL and LDL but without an increase in cardiovascular side effects. Randomized clinical trials are currently evaluating the role of CETP inhibitors in event reduction.
3. **Triglycerides.** Hypertriglyceridemia may be an independent risk factor for CAD, commonly accompanied by low HDL levels or diabetes. Patients with TG levels above 200 mg/dL should be counseled to achieve non-HDL levels below 130 mg/dL. Fenofibrate or gemfibrozil can be added when TG levels exceed 200 mg/dL, particularly if a low HDL level is concurrent. Fibrates and high doses of statins can increase the risk of myopathy and should be avoided if possible. Omega-3 fatty acids may also be beneficial. Niacin can also be

considered for treatment of hypertriglyceridemia, but results from the recent Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial challenge the efficacy of extended-release niacin in preventing cardiovascular events. In this trial, even though extended-release niacin, when added to statin therapy, was able to decrease TG levels from 164 to 122 mg/dL, decrease LDL from 74 to 62 mg/dL, and raise HDL from 35 to 42 mg/dL, there was no difference in the primary end point (mean follow-up period of 3 years) consisting of a composite of cardiovascular outcomes.

C. Diabetes management. The American Diabetes Association recommends treating glucose levels with the goal of lowering the hemoglobin A1c to below or around 7% with the intent of decreasing micro- and macrovascular events. However, the concept of "intensive" glucose control has been challenged recently by trials demonstrating adverse events associated with this strategy in both the inpatient and outpatient settings. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial enrolled critically ill patients in an ICU setting and demonstrated increased mortality in the group randomly assigned to maintaining target glucose levels between 81 and 108 mg/dL versus a target glucose level of 180 mg/dL or less in the comparison group. Likewise, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a large randomized study of over 10,000 outpatients, was discontinued due to excess mortality in the intensive therapy group assigned to achieve a hemoglobin A1c < 6% compared with the standard therapy group whose target A1c was between 7% and 7.9%.

D. Antiplatelet therapy

1. All patients who have had an MI should take **aspirin** upon presentation and continue indefinitely unless there are absolute contraindications. Aspirin therapy after MI results in a mortality reduction of 25 lives per 1,000 patients treated. Aspirin reduces the rates of vascular mortality, nonfatal stroke, and nonfatal MI. Doses of at least 75 to 162 mg daily are recommended for all patients presenting with ACS. Patients receiving dual antiplatelet therapy (e.g., aspirin plus thienopyridines) have fewer side effects, such as bleeding, at lower aspirin doses.
2. **Thienopyridines** (i.e., ticlopidine, clopidogrel, prasugrel, and ticagrelor) inhibit platelets via adenosine diphosphate antagonism. Clopidogrel is favored over ticlopidine because of a greater incidence of hematologic dyscrasia associated with ticlopidine. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the combination of clopidogrel and aspirin was given early for ACS without ST-segment elevation, thereby reducing cardiovascular death, MI, stroke, in-hospital ischemia, and revascularization, with benefit seen at 1 year of therapy. The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) demonstrated the benefit of clopidogrel in patients with ST-elevation MI with reperfusion via lytics or PCI. Prasugrel is a more potent and more rapid inhibitor of ADP than clopidogrel, and the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI) 38 trial demonstrated a reduction in the composite end point of death from all causes, nonfatal MI, or urgent target vessel revascularization with use of prasugrel compared with clopidogrel. Absolute contraindications to prasugrel use include prior stroke or transient ischemic attack. Patients with elevated risk of bleeding with prasugrel include those above age 75 years and those who weigh < 60 kg, and caution should be taken before prescribing this drug to these patients. Ticagrelor is the first reversible inhibitor of the $P2Y_{12}$ receptor and its action is more rapid and potent than that of clopidogrel. The PLATO trial demonstrated the superiority of ticagrelor over clopidogrel in reducing a composite of death from vascular causes, MI, or stroke in patients with ACS. It was also able

to demonstrate a greater reduction in the secondary end point of death from any cause using ticagrelor versus clopidogrel. Opinions vary as to whether to withhold thienopyridine loading prior to arrival in the catheterization lab in patients who are likely to require CABG because of an increased risk of bleeding and possible delay in surgery. If a patient requires urgent surgery, then clopidogrel and ticagrelor should be held for at least 24 hours to reduce the risk of major bleeding.

3. **Adding other medications,** such as sulfinpyrazone and dipyridamole, has not been shown to be more efficacious than aspirin alone and is not recommended for patients who have had an MI.

E. Warfarin sodium

1. **Patients** with a large anterior MI and LV thrombus treated with warfarin are at decreased risk for embolic stroke. Randomized trials do not exist, but many physicians recommend 6 weeks of warfarin therapy for this group of patients. This may assist in stabilization and endothelialization of the thrombus.
2. Data for the routine use of warfarin in conjunction with aspirin for secondary prevention of reinfarction are conflicting. The Combination Hemotherapy and Mortality Prevention (CHAMP) study and the Coumadin Aspirin Reinfarction Study (CARS) trial found no benefit from the addition of warfarin to standard aspirin therapy. However, combination therapy with aspirin and warfarin decreased infarct-related artery reocclusion and recurrent events in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT 2) trial. The routine use of warfarin after MI is currently not recommended except for other established indications for anticoagulation, such as atrial fibrillation or prosthetic heart valves. Patients with concomitant use of dual antiplatelet agents for coronary disease are at significant risk for bleeding and hence this therapy should be used judiciously in these patients.

F. β-Blockers

1. **Indications.** β-Blockers are anti-ischemic, antihypertensive, and antiarrhythmic and they reduce LV wall stress. Mortality reduction results from decreased risk of sudden death, non–sudden cardiac death (SCD), and nonfatal infarction. Overall, the use of β-blockers reduces post-MI events by approximately 20%.
   a. **The beneficial effects of β-blockers are greatest among patients who are at high risk,** such as patients with anterior infarction, complex ventricular ectopy, advanced age, and LV dysfunction. In the COMMIT trial, metoprolol given at presentation significantly reduced reinfarction and ventricular fibrillation in patients with acute MI who were hemodynamically stable; mortality benefit was not significant and this was probably the result of a net hazard during days 0 to 1 for patients presenting with New York Heart Association (NYHA) class III or IV heart failure. Several studies have found that only 50% of patients who sustain an MI actually receive β-blockers. **β-Blockers should be started as soon as possible in hemodynamically stable patients with MI** and should be continued indefinitely. Moderate LV dysfunction and compensated congested heart failure are not contraindications to β-blocker treatment.
   b. **β-Blockers** without intrinsic sympathomimetic activity, such as carvedilol, metoprolol, propranolol, timolol, and atenolol, appear to have the greatest benefit. Reduction in heart rate seems to be important in achieving a mortality benefit.
2. **Contraindications.** Relative contraindications include second- or third-degree heart block, severe asthma, severe chronic obstructive pulmonary disease, severe or decompensated congestive heart failure, heart rate < 60 beats/min, hypotension with systolic blood pressure < 120 mm Hg, or other signs of a low-output state. In patients with heart rate > 100 beats/min, cardiogenic shock should be

ruled out by history and examination before administering β-blockers. Diabetes is not an absolute contraindication; however, the dose of the β-blocker may have to be reduced or discontinued if hypoglycemic episodes are frequent or severe.

G. Angiotensin-converting enzyme (ACE) inhibitors

1. **Indications.** Ventricular remodeling can be attenuated by ACE inhibitors, reducing ventricular dilation and development of congestive heart failure. During infarction, the expression of ACE increases within the myocardium. Several large randomized clinical trials have demonstrated that ACE inhibitors reduce mortality. These trials include Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), and Trandolapril Cardiac Evaluation (TRACE). The greatest benefit was found among patients with large areas of infarction, anterior infarction, and infarction that impaired LV function. **ACE inhibitor therapy should be considered in all patients after an acute MI** in the absence of contraindications. Therapy should be continued indefinitely in the setting of LV dysfunction (ejection fraction [EF] < 40%), heart failure, hypertension, or diabetes, although the ACC/AHA guidelines give class IIa recommendation for indefinite therapy in all patients after MI regardless of LV function or comorbidities. Angiotensin receptor blockers (ARBs) may be substituted if ACE inhibitors are not tolerated. The Valsartan in Acute Myocardial Infarction (VALIANT) trial evaluated post-MI patients with clinical signs of heart failure and low EF (< 35% by echo or angiography or < 40% by radionuclide ventriculography). Even though this study did not support superiority of valsartan therapy, it demonstrated noninferior mortality outcomes between groups treated with valsartan, captopril, or the two combined. However, adverse events including hypotension and medication dose reductions due to renal causes were more frequent in the valsartan and valsartan plus captopril groups. Cough, rash, and taste disturbances were more commonly reported in the captopril group.
2. **Side effects** include cough, worsening renal function, hypotension, and angioedema. Adverse events, especially renal impairment and hypotension, may be worse when ACE inhibitors and ARBs are used concomitantly, as was shown in the Ongoing Telmisartan Alone and in Combination with Rampril Global End Point Trial (ON TARGET) and VALIANT trials.

H. Aldosterone antagonists

1. **Indications.** The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that eplerenone, when added to optimal medical therapy in post-MI patients with an EF of 40% or less, reduced the risk of death from any cause as well as the risk for a combination of death from cardiovascular causes and hospitalization for cardiovascular events. Optimal medical therapy included ACE inhibitors, ARBs, β-blockers, and coronary reperfusion.
2. **Contraindications.** Because of its diuretic property and effect on the renin–angiotensin–aldosterone neurohormonal system, eplerenone should not be used in patients with renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (serum potassium > 5.0 mmol/L).

I. Calcium channel blockers. The preferred agent after ACS is a β-blocker unless truly contraindicated. Calcium channel blockers are reserved for patients with **refractory angina** and not recommended for routine use after MI by the ACC/AHA guidelines. Longer acting preparations should be used if necessary, whereas short-acting dihydropyridine antagonists should be avoided.

1. **Indications.** The use of calcium channel blockers should be limited to patients with refractory angina or rapid atrial arrhythmias or to patients with clear contraindications to the use of β-blockers.
2. **Contraindications.** Calcium channel blockers should be avoided in patients with congestive heart failure or high-degree atrioventricular block after an MI.

Short-acting dihydropyridine antagonists, such as nifedipine, may increase the risk of death or infarction after MI. Short-acting nifedipine may be especially harmful to patients with hypotension or tachycardia and can induce coronary steal or reflex sympathetic activation, which increases myocardial oxygen demand. Verapamil and diltiazem are contraindicated in the care of patients with LV dysfunction or congestive heart failure after MI. These agents may be useful in patients with contraindications to β-blockers who do not have LV dysfunction or congestive heart failure. Few data are available for the effect of the second-generation agents, amlodipine and felodipine, on survival after MI.

J. Estrogen replacement therapy. The Heart and Estrogen/Progestin Replacement Study (HERS) found no benefit from hormone replacement therapy as secondary prevention for coronary disease, as the therapy was associated with an early increase in death and MI. The Women's Health Initiative (WHI) also observed an increased risk of cardiovascular events and breast cancer with hormone replacement therapy. Initiation of estrogen for primary and secondary prevention of cardiovascular disease is not recommended and should be discontinued at the time of MI.

K. Antioxidants. Previous epidemiologic studies suggested that vitamin E, vitamin C, and β-carotene were associated with a lower incidence of CAD, but more recent studies failed to corroborate these findings. The HPS did not demonstrate a mortality or cardiovascular benefit from antioxidant therapy. Several other large randomized trials have failed to show either primary or secondary benefit for other similar vitamin supplementation strategies. The ACC/AHA guidelines, therefore, do not support the use of vitamin C or vitamin E, β-carotene, or folate with or without B_6 and B_{12}, for primary or secondary prevention.

V. PREVENTION OF SCD AFTER MI

A. Risk stratification for SCD

1. **All patients are at risk** for SCD after MI, with the greatest risk encountered during the first year (3% to 5%), most commonly due to ventricular arrhythmias.
2. **Reduced LV function (< 40%)** remains the best predictor of mortality. Measurement of LV function soon after MI may reflect myocardial stunning, so echocardiography should be re-measured again at the time of possible implantable cardioverter defibrillator (ICD) implantation, usually 40 days after MI for primary prevention or 3 months if reperfused after MI, via either PCI or CABG.
3. Many studies have found that patients who have more than six premature ventricular contractions per hour have a 60% relative increased risk for SCD. Patients with ventricular fibrillation or sustained ventricular tachycardia more than 48 hours after MI also are at increased risk. Monomorphic ventricular tachycardia is a manifestation of scar-related reentrant ventricular tachycardia.
4. Various techniques have been tested to identify patients at increased risk for SCD, but none is sensitive enough to be recommended for routine use. Signal-averaged ECG, heart rate variability, QT-interval dispersion, and baroreflex sensitivity are noninvasive tests, with each test having a low (< 30%) positive predictive value. Repolarization alternans (T-wave alternans) appears to have a higher sensitivity and specificity for inducible ventricular arrhythmia during electrophysiologic testing. Still invasive electrophysiologic testing has a low predictive value for future cardiac events. Consequently, **these modalities are not recommended for routine post-MI risk stratification**.

B. Therapy

1. The only medications proven to reduce risk for SCD are **β-blockers**. All patients should receive β-blockers after an MI unless absolutely contraindicated.
2. **Other medications. Amiodarone** has multiple antiarrhythmic effects, but is primarily classified as a class III agent. Trials of amiodarone in the care of

patients who have had an MI with LVEF < 40% have shown conflicting results, although a significant reduction in mortality has not been demonstrated. Amiodarone is still the preferred antiarrhythmic therapy for symptomatic or sustained ventricular arrhythmias in post-MI patients. Lidocaine is sometimes used as an alternative to amiodarone, but it should not be administered without documented ventricular tachycardia. Likewise, the prophylactic use of sotalol after MI has been associated with increased mortality. The use of type IC antiarrhythmic agents (i.e., encainide, flecainide, and propafenone) after MI is contraindicated.

3. **Implantable cardioverter-defibrillator. Early implantation of an ICD after MI has not been shown to be beneficial.** The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) found no mortality benefit despite a reduction in arrhythmogenic death when ICDs were implanted within 40 days after MI despite LVEF < 35%. The Immediate Risk-Stratification Improves Survival (IRIS) trial enrolled patients at increased risk for sudden death within 31 days of an MI. Such patients were those with an EF = 40% and a heart rate > 90 beats/min or those with evidence of nonsustained ventricular tachycardia on ECG or holter monitor, or both. Overall mortality was not reduced in those in whom an ICD was implanted compared with the group treated with medical therapy. On the contrary, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) investigators and others demonstrated a survival benefit in patients with LV dysfunction and previous MI receiving a prophylactic ICD (see Chapter 23). The Multicenter Unsustained Tachycardia (MUST) trial noted improved survival with ICD implantation in patients who had inducible ventricular arrhythmias with electrophysiologic (EP) study. Therefore, class I indications for ICD therapy post-MI include patients with ischemic cardiomyopathy EF < 35% with NYHA class II or III symptoms at least 40 days post-MI, ischemic cardiomyopathy EF < 30% with NYHA class I symptoms at least 40 days post-MI, and ischemic cardiomyopathy EF < 40% with inducible ventricular fibrillation or sustained ventricular tachycardia on EP study. Patients who undergo either percutaneous or surgical revascularization after MI should have an assessment of LV function after 3 months to help determine the appropriateness of ICD implantation.

VI. THERAPY AND PREVENTION AFTER HOSPITAL TREATMENT

A. Cardiac rehabilitation programs seek to improve the biopsychosocial aspects of patients after MI by addressing the benefits of exercise, weight loss, proper diet, smoking cessation, and good mental health. Both randomized data and meta-analyses have demonstrated a mortality benefit associated with cardiac rehab in patients after MI.

1. Formal rehabilitation programs use **exercise and patient education** to help patients modify their lifestyles. The benefits of cardiac rehabilitation include improvement in a patient's commitment to treatment, increased functional capacity, and reduced likelihood of readmission for recurrent ischemia. The **social support** offered is associated with a 25% reduction in both cardiac and all-cause mortality. Depression after MI is common, and patients must be screened during follow-up. Depression is also an independent risk factor for mortality, possibly by decreasing commitment to therapy and exercise. There are limited data regarding the safety and efficacy of antidepressant medications in the post-MI setting. In a small study, sertraline was found to be safe and efficacious for the treatment of major depressive disorder after ACS.
2. **Home programs and family care.** Although cardiac rehabilitation has been shown to have many benefits, less than one-half of patients who have had an MI participate in formal programs. Home programs may be helpful, but they do not provide the social network found in group rehabilitation programs. Because most cardiac arrests after MI occur within 18 months after discharge, family members should be encouraged to learn basic cardiopulmonary resuscitation.

B. Soon after receiving the diagnosis of MI, patients should be counseled regarding **lifestyle modification** to improve weight control, diet, exercise, lipid control, blood pressure, and smoking cessation.

1. Optimal control of hypertension and diabetes should be achieved. The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) determined the need for strict glucose control of insulin and non–insulin-dependent diabetes. Improvement in serum glucose levels decreases the progression of microvascular complications. In both trials, a trend toward decreased microvascular events among the groups that received aggressive treatment was observed.
2. **Weight reduction.** Among adults in the United States, approximately two-thirds of the population, or nearly 130 million persons, are overweight (i.e., body mass index > 25 kg/m^2). Patients should be encouraged to achieve (or maintain) an ideal body weight. All patients should begin an AHA step II diet to achieve lipid goals. Fewer than 50% of patients comply with step II diet, and many patients will need additional pharmacologic therapy to manage hyperlipidemia.
3. **Resumption of daily activities**
   a. At discharge, all patients who have had an MI should receive information regarding resumption of sexual activity, driving, work, and exercise.
   b. **Sexual activity** can be resumed within a week for most patients. Oral phosphodiesterase inhibitors **are absolutely contraindicated in patients on concomitant nitrate therapy. Nitrates should not be used** within 24 hours of sildenafil and 48 hours of tadalafil. Vardenafil has a similar half-life as sildenafil and thus similar precautions should be taken. **Driving** can also be resumed within a week. Most patients who have had an MI who do not have symptoms can **return to work** within 2 weeks.
   c. A patient's performance on an **exercise test** can be used to generate an activity prescription. Patients who can perform at least 5 METs on a submaximal exercise test without marked ST-segment depression or development of angina have a good long-term prognosis.
   d. Because of the lowered oxygen tension in most commercial aircraft (pressurized to 7,500 to 8,000 feet), only patients in stable condition should **travel by plane** within the first 2 weeks after MI. They should carry sublingual nitroglycerin and request a wheelchair for transportation.

ACKNOWLEDGMENTS: *The authors thank Drs. Shaun Senter, Mehdi Shishehbor, John H. Chiu, and Elaine K. Moen for their contributions to earlier editions of this chapter.*

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CHAPTER 6

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Stable Angina

I. INTRODUCTION. Angina pectoris, derived from the Greek "ankhon" (strangling) and the Latin "pectus" (chest), is the term used to describe the syndrome of chest discomfort resulting from myocardial ischemia. Angina is characterized as stable or unstable on the basis of symptom pattern.

A. Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque and decreased clinical risk.

B. Angina is said to be unstable when the symptom pattern worsens abruptly (increase in frequency and duration) without an obvious cause of increased myocardial oxygen consumption. Similarly, the onset of rest angina in a patient for whom angina was previously provoked by some degree of exertion may signal an unstable syndrome.

C. For some patients with new-onset angina that has been stable over a few weeks, clear distinction between stable and unstable angina is not possible. These patients can be considered to be in an intermediate stage between unstable and stable angina.

II. CLINICAL PRESENTATION. For most patients with chest pain, the diagnosis of angina pectoris can be made with careful history taking. The presence of risk factors for coronary artery disease (CAD), such as hypertension, diabetes mellitus, smoking, family history, hyperlipidemia, claudication, and advanced age, increases the likelihood that the chest pain is being caused by myocardial ischemia.

A. Signs and symptoms. The constellation of symptoms characteristic of angina pectoris includes the following four cardinal features.

1. **Location.** Discomfort is commonly located in the retrosternal area with radiation to the neck, shoulders, arms, jaws, epigastrium, or back. In some instances, it involves these areas without affecting the retrosternal area.
2. **Relation to a trigger.** Symptoms are typically triggered by physical activity, emotional stress, exposure to cold, consumption of a heavy meal, or smoking.
   a. Some patients will experience the resolution of angina despite continued exertion, which is known as the walk-through phenomenon. Others may experience the warm-up phenomenon, in which an initial exertion produces angina but a similar second exertion does not reproduce anginal symptoms. These circumstances probably result from the recruitment of collateral coronary flow during the initial episode of ischemia.
   b. Decubitus angina, which is a less common manifestation, occurs with a change in posture and is believed to be caused by a shift in blood volume. Nocturnal angina, which occurs at night, is frequently associated with nightmares and tachyarrhythmias.
3. **Character.** Most patients describe angina as a vague chest discomfort. They describe it as a squeezing, burning, tight, choking, heavy, and occasionally hot or cold sensation. Many patients do not perceive angina as pain per se. Some patients may experience dyspnea, profound fatigue, weakness, lightheadedness, nausea, diaphoresis, altered mental status, or syncope in the absence of any chest discomfort. These symptoms are often referred to as anginal equivalents. Noncardiac causes of chest pain (gastrointestinal, respiratory, musculoskeletal, etc.) may be indicated by fleeting chest pain, unrelenting chest pain not affected by activity, antecedent chest trauma, association with food intake, location inferior to the umbilicus, pleurisy, etc.
4. **Duration.** The chest pain associated with ischemia typically lasts 3 to 5 minutes. Ischemic pain usually does not last more than 30 minutes without causing myocardial infarction (MI). Chest pain triggered by emotional distress tends to last longer than that triggered by exercise. Chest pain that lasts < 1 minute is unlikely to be of cardiac origin, especially when it is not associated with other typical symptoms or findings.
5. It should be stressed that women may present with symptom constellations that may be atypical in location or quality in comparison to the symptoms described by men or manifest as anginal equivalents such as nausea or dyspnea.
6. Chest pain is defined as "typical angina" if it consists of characteristic substernal discomfort, is provoked by stress, and is relieved by rest or nitroglycerin. It is considered "atypical" if it involves two or less of the previously mentioned criteria.
7. **Classification.** Various classifications are available to assess the severity and to predict the outcome among patients with angina. The Canadian Cardiovascular Society classification is the most popular one (Table 6.1). Other classification systems include the Specific Activity Scale, the Duke Activity Status Index, and the Braunwald classification.

B. Physical findings. For patients with a history of chest pain, physical examination helps identify risk factors for CAD and occult cardiac abnormalities.

1. **The signs associated with a high risk for CAD** include elevated blood pressure or manifestations of hypertensive vascular disease such as retinal arteriopathy, signs of hyperlipidemic conditions including corneal arcus or xanthelasma, and evidence of carotid or other peripheral vascular disease.

TABLE 6.1 Classification of Angina

CCS class	Definition	Comment
I	Ordinary physical activity does not cause angina	Angina only with extraordinary exertion at work or recreation
II	Slight limitation of ordinary activity	Angina with walking more than two blocks on a level surface or climbing more than one flight of stairs at a normal pace
III	Marked limitation of ordinary physical activity	Walking one to two blocks on a level surface or climbing one flight of stairs at a normal pace
IV	Inability to carry on any activity without discomfort	Angina at rest or with minimal activity or stress

CCS, Canadian Cardiovascular Society.

2. **Physical examination** performed during an episode of chest pain may reveal rales, an S_3 or S_4 gallop, or a systolic murmur from ischemic mitral regurgitation, all of which generally disappear with resolution of symptoms.

C. **Baseline electrocardiogram (ECG)**

1. A baseline ECG is **useful for the initial screening** of CAD, although about 60% of patients with chest pain have a normal ECG. Presence of a Q wave or persistent ST depression is associated with an unfavorable outcome. The ECG can also demonstrate other abnormalities, such as left ventricular (LV) hypertrophy, bundle branch block, and preexcitation syndromes.
2. Information obtained from the ECG is **useful in the assessment of chest pain** and helps to stratify patients who are at risk for an adverse event.
3. ECG at the time of chest pain can also **help identify the cause of the chest pain**. Transient changes in the T-wave, ST-segment, or conduction patterns point toward a cardiac source of the chest pain. A normal ECG does not exclude ischemia as being the etiology of chest pain.

III. DIAGNOSTIC TESTING. For a patient with stable CAD, investigations are aimed at risk stratification and management of symptoms and unfavorable outcomes.

A. Stress testing. The basic principle of stress testing is to provoke ischemia or produce coronary vasodilation, followed by functional assessment with different systems to detect ischemia. Stress tests can be categorized according to the methods used to provoke and detect myocardial ischemia. The sensitivity and specificity of each test to identify coronary stenosis vary according to the study population, definition of disease, definition of a positive test result, protocol used for the stress testing, and experience of the interpreter. The following is a brief overview of noninvasive cardiac testing. **For a thorough discussion on noninvasive imaging and stress modalities, please refer to the specific chapters**.

1. **Methods to induce ischemia.** Exercise is the most physiologically sound and useful method for inducing ischemia. An exercise test is considered adequate if 85% or more of age-predicted maximum heart rate (220 – age) is achieved. Exercise testing provides an objective assessment of functional capacity, which provides useful prognostic information. Pharmacologic testing, with dobutamine or adenosine/adenosine derivatives (i.e., dipyridamole), can be used for patients who cannot exercise adequately.

2. **Methods to assess ischemia**
   a. **Stress ECG.** Exercise ECG provides useful diagnostic information about the patients with normal baseline ECGs who are at intermediate risk for CAD. Stress ECG is also used to create an exercise prescription in patients with stable angina. The sensitivity and specificity of stress ECG are poor among patients with an abnormal baseline ECG, LV hypertrophy, ventricular pacing, left bundle branch block (LBBB), or intraventricular conduction disturbance and among patients taking digitalis or other medications that affect conduction and depolarization. Electrocardiographic changes during dipyridamole or adenosine infusion have high specificity but poor sensitivity. Electrocardiographic changes during dobutamine infusion have sensitivity and specificity similar to those of exercise ECG.
   b. **Echocardiographic imaging.** Stress echocardiography is an economical test with good specificity for identifying the location and extent of ischemic territories. This is assessed by the induction of regional wall motion abnormalities with stress or dilation of the left LV cavity with stress (which may indicate global ischemia). If the patient is unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Augmentation of contractility in hypokinetic segments may indicate the presence of hibernating myocardium in a specific coronary distribution. At some medical centers, dipyridamole and adenosine stress tests are performed with echocardiographic imaging. This method is less sensitive in detecting underlying CAD. Results of stress echocardiography are difficult to interpret in some patients with a hypertensive response to exercise and in some patients with severe mitral or aortic regurgitation. Preexisting wall motion abnormalities may further complicate image interpretation.
   c. **Radionuclide imaging.** Single-positron emission computed tomography (SPECT) can be performed after injection with thallium 201 or technetium (Tc) 99m–labeled radiopharmaceuticals. Positron emission tomography (PET) can be performed utilizing rubidium 82 or 13N ammonia tracers. PET imaging provides greater spatial resolution and diagnostic accuracy in comparison with SPECT imaging. Injection of fluorine 18–labeled deoxyglucose (FDG) allows assessment of myocardial viability in patients with resting perfusion defects. The sensitivity and specificity of nuclear testing are decreased among patients with severe obesity, balanced three-vessel disease, and LBBB.

B. **Echocardiography** provides useful information in the overall assessment of suspected stable angina.
   1. Regional wall motion abnormalities involving the left ventricle are commonly caused by CAD and may represent resting ischemia or prior MI. Any impairment in LV systolic function, LV hypertrophy, and presence of substantial mitral regurgitation are associated with heightened clinical risk and poor outcome. LV systolic function may guide the choice of medical therapy versus revascularization.
   2. Echocardiography is the test of choice to quantify aortic stenosis or the presence of hypertrophic cardiomyopathy.

C. **Magnetic resonance imaging (MRI)**
   1. Ischemic evaluation using pharmacologic stress (dobutamine or adenosine) and cardiovascular magnetic resonance can also be utilized to evaluate myocardium in jeopardy. MRI uses gadolinium as a contrast medium to evaluate regional wall motion abnormalities and ejection fraction, as well as segmental myocardial perfusion (when using adenosine). MRI can also provide direct visualization of the

coronary arteries, although computed tomography (CT) angiography is much better for this application.

2. Delayed-phase gadolinium imaging also provides information on the location and transmurality of myocardial scar.
3. The weaknesses include increased cost, lack of portability, and unsuitability for use in the growing population of patients with pacemakers and defibrillators.

D. Electron beam computed tomography (EBCT)

1. EBCT is a noninvasive method of obtaining cross-sectional images of the heart and allows quantification of coronary artery calcification. The test is rapid and provides a "calcium score." This test does not provide sufficient detail to accurately quantify and grade stenosis due to atherosclerotic lesions. An increasing calcium score correlates strongly with heightened risk of cardiovascular events and abnormal findings should lead to further risk factor modification and cardiovascular risk assessment.

E. Multidetector computed tomography

1. **Strengths.** Coronary computed tomography angiography (CCTA) allows for the evaluation of the epicardial coronary tree using a noninvasive approach. The sensitivity of CCTA for assessing coronary stenosis approaches 97% with a specificity of 86% when using a 64-slice technology. With technologic advances allowing a greater number of slices to be acquired in current practice, the accuracy of this study is expected to increase. Importantly, the negative predictive value of CCTA is 99%, with an optimal study and appropriate patient selection. Severe coronary artery calcification or previous coronary stent placement may significantly detract from image quality, rendering the evaluation of specific coronary segments uninterpretable. Larger stents may be grossly evaluated for patency but accurate quantification for in-stent restenosis in anatomical locations distal to the left main coronary artery (LMCA) is not always feasible.

F. Coronary angiography

1. **Strengths.** Coronary angiography is the standard for anatomic assessment of coronary arterial stenosis and provides important prognostic information.
   a. Patients with > 75% stenosis involving at least one coronary artery have a lower survival rate than patients with 25% to 50% or < 25% stenosis. Even for mild stenosis, risk for MI is markedly higher than for no stenosis.
   b. The severity of lesions demonstrated with angiography is not predictive of plaque stability; two-thirds of patients with acute MI have stenosis of > 50% diameter at the site of plaque rupture before MI. It is possible, however, to assess plaque instability on the basis of angiographic characteristics or morphologic features of the lesion.
      (1) Eccentric lesions with narrow necks, overhanging edges, or scalloped borders (type II plaques) are more unstable than concentric lesions with smooth borders (type I plaques).
      (2) Lesion roughness (i.e., irregular borders) is predictive of plaque instability and heightens the risk of future infarction.
      (3) The morphologic characteristics of the plaque help in judging the feasibility and risk of percutaneous or surgical intervention.
   c. Ventriculography performed at the time of selective coronary angiography adds an important dimension to risk stratification by providing an index of LV systolic function and regional wall motion characteristics as well as the presence and degree of mitral regurgitation.
2. **Indications.** In the management of stable angina, use of angiography is variable. An American College of Cardiology and American Heart Association (ACC/AHA) task force classified the indications for coronary angiography into three categories. The relevant indications in the context of stable angina are presented in Table 6.2.

TABLE 6.2 Indications for Coronary Angiography in Stable Angina

Class I (general agreement among cardiologists)
Severe anginal symptoms (CCS class III or IV) with optimal medical therapy
Stress testing indicators of high-risk coronary disease
Survivors of sudden cardiac arrest
Symptoms of congestive heart failure with angina
Clinical predictors of severe CAD
Class II (frequently used but controversial)
Symptoms of angina and positive stress test
Inadequate information from noninvasive testing
Severe angina that improves to mild/moderate angina with medical therapy
Anginal symptoms and intolerance of medical therapy
Asymptomatic patients with positive stress test
Patients who are unable to be evaluated noninvasively
Patients with an occupation that involves an unusual degree of risk
Patients suspected of ischemic symptoms caused by nonatherosclerotic coronary disease (i.e., vasculitis and radiation coronary disease)
Suspicion of coronary vasospasm with the need for provocative testing
Suspicion of left main or three-vessel coronary disease
Recurrent hospitalization for chest pain and need for definitive coronary evaluation
Patients with intermediate or high probability of CAD and a desire for definitive diagnosis
Class III (unjustified use of angiography)
Mild symptoms that resolve with medical therapy
Patients who would not undergo revascularization
Patients with low probability of CAD and a desire for definitive diagnosis

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society.

3. **Limitations.** Coronary angiography underestimates plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease. Coronary angiography does not depict intraluminal plaque burden and does not show coronary flow reserve. Adjunctive use of intravascular ultrasonography (IVUS) greatly facilitates the investigation of hazy areas on coronary angiograms, which may be caused by calcium, thrombus, severe eccentric lesion, or dissection. The IVUS can also assess positive and negative remodeling, which has been shown to correlate with stable and unstable syndromes.

G. Intravascular ultrasonography allows visualization of the cross-sectional image of coronary arteries. This modality helps to quantitate plaque area, artery size, and luminal stenosis; assess hazy areas on coronary angiograms, questionable areas of stenosis, and extent of stenosis; and sometimes determine the calcium content of a plaque. Hypodense areas in a plaque may correlate with high lipid content, which may indicate fast-growing or potentially unstable plaque. This information can help

assess the need for and options of therapy. This modality does not, however, have a role in routine evaluation of patients with stable angina, due to the invasive nature of the test.

H. Optical coherence tomography (OCT) is a relatively new intracoronary imaging modality that has better resolution than IVUS but provides less depth. It has been used, thus far, almost exclusively as a research tool, but a number of studies are currently ongoing to establish its clinical utility. Potential contributions of OCT include characterization of plaque, better understanding of stent characteristics (degree of apposition and stent endothelialization, etc.), and arterial remodeling. This technique requires injection of contrast medium during imaging (usually totaling 12 to 20 cc per run) and so may be of limited use in patients with chronic kidney disease.

I. Invasive functional assessment. Invasive assessment of the functional significance of an intermediate stenosis can be made by means of coronary blood flow measurement with intracoronary Doppler ultrasound and direct measurement of a pressure gradient across a stenosis.

1. With the help of a small transducer mounted on a guidewire, coronary blood flow can be measured by means of a fixed sample volume and pulsed Doppler.
   - **a.** In the left coronary artery, most coronary flow occurs during diastole. In normal arteries, a ratio of proximal-to-distal flow velocity approaching 1 is considered normal. In the presence of coronary stenosis, coronary blood flow becomes mainly systolic because the diastolic component of the flow is jeopardized first.
   - **b.** Three indices can help identify physiologically important stenoses:
     - **(1)** Diastolic-to-systolic average peak coronary flow velocity ratio of < 1.8 distal to the obstruction
     - **(2)** A proximal-to-distal average peak coronary flow velocity ratio of > 1.7
     - **(3)** Coronary flow reserve (i.e., increase in coronary flow with adenosine, which is administered after intracoronary nitroglycerin) with a less than twofold increase in peak velocity
2. **Direct measurement of pressure gradients** can be accomplished with a transducer mounted on a catheter. Ratio of mean pressure distal and proximal to the lesion after maximum vasodilation (fraction flow reserve or FFR) of < 0.75 to 0.80 indicates a hemodynamically significant lesion. These techniques supplement angiography in determining the functional significance of an intermediate (30% to 70%) angiographic stenosis. In a group of patients with angiographically intermediate stenosis, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) investigators were able to demonstrate lower rates of mortality and MI (8.4% vs. 23.9%, $p = 0.02$) with less stent placement when a strategy of FFR-guided (vs. angiography-guided alone) percutaneous coronary intervention (PCI) was pursued.

J. Holter monitoring

1. After MI, increased ventricular ectopy is predictive of increased cardiovascular morbidity and mortality. This association is less important among patients with stable angina without prior MI, and routine Holter testing for risk stratification is not indicated. No medical treatment aimed at suppressing ventricular ectopy has been shown to improve outcome.

IV. THERAPY.

The goals of therapy are to prevent cardiovascular morbidity and mortality and to improve quality of life.

A. Therapeutic options. Medical therapy, PCI, and coronary artery bypass grafting (CABG) have all been shown to control symptoms and improve exercise time to ischemia. In an era of rudimentary medical therapy, CABG has been proven to decrease cardiovascular mortality in specific patient subsets. Although PCI has been shown to improve stable anginal symptoms and improve quality of life, a decrease in mortality has not been proven in randomized controlled trials (RCTs).

B. Pharmacologic therapy

1. Platelet inhibitors

a. The Antiplatelet Trialists' Collaboration was a meta-analysis that included approximately 100,000 patients from 174 trials involving antiplatelet therapy. This data set showed that aspirin (acetylsalicylic acid, ASA) reduced the rate of stroke, MI, and death among high-risk patients, including those with stable angina without previous MI. A recent systematic review confirms that, while optimal dosing is controversial, there is general support in the literature for limiting the dose of ASA to 75 to 81 mg daily. Approximately 5% to 10% of patients with CAD have aspirin resistance, defined as a lack of decrease in platelet function associated with aspirin use. Aspirin resistance has been shown to result in higher thrombotic events in people with peripheral vascular disease. Patients who demonstrate increased platelet reactivity despite aspirin therapy have increased risks for stroke, MI, and vascular death compared with aspirin responders.

b. Among patients with true allergy or intolerance to aspirin, clopidogrel has been shown to decrease the frequency of fatal and nonfatal vascular events in peripheral, cerebral, and coronary vessel diseases.

(1) Clopidogrel is a second-line therapy in patients unable to tolerate aspirin. In high-risk patients with prior cardiac surgery or ischemic events, the use of clopidogrel as monotherapy, or in addition to aspirin, is beneficial. In patients receiving bare-metal stenting (BMS) for stable coronary disease, at least 1 month of dual antiplatelet therapy (DAPT; aspirin 81 mg plus clopidogrel 75 mg daily) is recommended. The use and duration of DAPT with clopidogrel and aspirin in the setting of drug-eluting stent (DES) implantation are currently under intense review, with concerns of very late stent thrombosis (ST) on one hand and studies questioning the benefit of extended duration DAP on the other. The most recent ACC/AHA PCI guidelines recommend 12 months of DAPT in patients undergoing DES, though longer duration may be considered (class IIb) in specific high-risk patient/stent subsets. Clopidogrel is usually well tolerated and has few side effects.

(2) In the initial analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, performed on a large group of patients included with either prior cardiovascular events or multiple cardiovascular risk factors, there was no benefit from the use of DAPT over aspirin alone in preventing MI or death. A prespecified analysis of higher risk patients only (such as those with prior MI) did show a decrease in cardiovascular events for the group receiving clopidogrel in addition to aspirin. This suggests that an appropriate group of patients may benefit from prolonged DAPT.

2. Lipid-lowering agents. Among patients with established CAD, secondary prevention with lipid-lowering therapy, specifically statins, has demonstrated marked reduction in risk for subsequent cardiovascular events. Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoA reductase). They are the most effective medical therapy for lowering levels of low-density lipoprotein (LDL) and have also been shown to upregulate nitric oxide (NO) synthase, decrease expression of endothelin-1 mRNA, improve platelet function, and decrease production of detrimental free radicals; all of these promote normal endothelial function.

a. Indications. The Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS) trials have provided convincing evidence that in patients with evidence of cardiovascular

disease with normal or elevated cholesterol levels, statins decrease mortality, the rate of MI and stroke, and the need for CABG.

b. Effectiveness. Recent studies have shown that in patients with stable CAD (treating to new targets [TNT]) or post-acute coronary syndrome (ACS) (PROVE IT-TIMI-22), aggressive lipid lowering to an LDL goal of 70 mg/dL decreases the risks of cardiovascular death, MI, and stroke compared with patients treated to an LDL goal of 100 mg/dL. There is also a suggestion that aggressive statin therapy retards and even results in a mild degree of plaque regression as measured by IVUS.

c. Choice of agents. Statins should be the first line of therapy in patients with CAD. The quantification of lipoprotein(a) [Lp(a)], fibrinogen, apolipoprotein (apo A), and apolipoprotein B_{100} (apo B_{100}) is investigational. Bile acid sequestrants primarily reduce LDL cholesterol and should not be used in patients with triglyceride levels higher than 300 mg/dL, because these agents may exacerbate hypertriglyceridemia. Nicotinic acid reduces LDL and triglyceride levels and is the most effective of the available lipid-lowering medications at increasing high-density lipoprotein (HDL) level. It is also the only agent that lowers Lp(a). Fibric acid derivatives are most effective against hypertriglyceridemia; they raise HDL level modestly and have little effect on LDL. They are the first line of treatment in patients with triglyceride levels higher than 400 mg/dL. ω-3 Fatty acids may also be used to treat hypertriglyceridemia that is refractory to niacin and fibric acid therapy. Agents to raise HDL cholesterol, cholesteryl ester transfer protein inhibitors, are currently undergoing intensive clinical evaluation in RCTs and may provide a beneficial treatment adjunct to statin therapy in the future.

(1) Current evidence supports aggressive lowering of LDL cholesterol levels in patients with established coronary disease, or CAD equivalents, to a goal of 70 mg/dL (class IIa). A level of HDL cholesterol > 45 mg/dL and triglycerides < 150 mg/dL are secondary goals of dietary, lifestyle, and pharmacologic therapies.

(2) The side effects of statin therapy, including myositis and hepatitis, are quite rare. The package inserts recommend liver function test evaluation prior to initiation of therapy (or increase in dose) and 3 months thereafter. Blood tests are not necessary for routine follow-up of patients who are stable on these medications and should only be measured based upon clinical suspicion of an untoward effect.

3. Nitrates (Table 6.3)

a. Mechanism of action. Nitrates decrease cardiac workload and oxygen demand by means of reducing preload and afterload of the left ventricle. They also redistribute blood flow to the ischemic subendocardium by means of decreasing LV end-diastolic pressure, vasodilation of epicardial vessels, and improvement of collateral blood flow to ischemic tissue. In an adjuvant role, nitrates may also be weak inhibitors of platelet aggregation.

b. Evidence for effectiveness. Nitrates can decrease exercise-induced myocardial ischemia, alleviate symptoms, and increase exercise tolerance in patients with stable angina.

(1) Adding nitrates to an optimal β-blocker regimen does not improve frequency of anginal episodes, glyceryl trinitrate consumption, exercise duration, or duration of silent ischemia.

(2) In some small studies, the efficacy of nitrates in reducing anginal episodes was increased with concomitant use of angiotensin-converting enzyme (ACE) inhibitors.

(3) No study has shown survival benefit with the use of nitrates to treat patients with chronic stable angina.

TABLE 6.3 Nitrates

Medication	Route of administration	Each dose	Frequency
Nitroglycerin (glyceryl trinitrate, Nitro-Bid, Nitrostat, and Nitro-Dur)	Sublingual tablet	0.15–0.6 mg	As needed
	Sublingual spray	0.4 mg	As needed
	Sustained-release capsule	2.5–9.0 mg	Every 6–12 h
	Ointment (topical)	0.5–2″ (1.25–5 cm)	Every 4–8 h
	Disk (patch)	1 disk (2.5–15 mg)	Every 24 h
	Intravenous	5–400 μg/min	Continuous
	Buccal tablet	1 mg	Every 3–5 h
Isosorbide dinitrate (Isordil, Sorbitrate, and Dilatrate SR)	Sublingual tablet	2.5–10 mg	Every 2–3 h
	Chewable tablet	5–10 mg	Every 2–3 h
	Oral tablet	10–40 mg	Every 6 h
	Sustained-release tablet	40–80 mg	Every 8–12 h
Isosorbide-5-mononitrate (Imdur and Ismo)	Sublingual tablet	10–40 mg	Every 12 h
	Sustained release	60 mg	Every 24 h
Erythrityl tetranitrate (Cardilate)	Sublingual tablet	5–10 mg	As needed
	Tablet	10 mg	Every 8 h

c. Selection of preparations. Because nitrates have a fast onset of action, a sublingual tablet or oral spray offers immediate relief of an anginal episode.

(1) For short-term prophylaxis (up to 30 minutes), nitroglycerin tablets can be used when activities known to precipitate angina are anticipated. Timing and frequency of the doses can be individualized according to the diurnal rhythm of anginal episodes. A nitrate-free interval of about 8 hours is adequate for preventing tolerance.

(2) Use of long-acting medications and transcutaneous delivery systems improves compliance but still necessitates a nitrate-free interval.

d. Side effects. Oral nitrates should be taken with meals to prevent heartburn.

(1) Headache is common and can be severe. Severity usually decreases with continued use and often can be controlled by decreasing the dose.

(2) Transient episodes of flushing, dizziness, weakness, and postural hypotension can occur, but these effects are usually abrogated by positioning and by other procedures that facilitate venous return.

e. Drug interactions

(1) Hypotension can occur with the use of other vasodilators, such as ACE inhibitors, hydralazine, or calcium channel blockers. **Concurrent use of PDE5 inhibitors like sildenafil (Viagra) and nitrates can lead to severe hypotension and, therefore, is *absolutely contraindicated*.**

f. Controversies

(1) Tolerance. Sustained therapy attenuates the vascular and antiplatelet effects of nitrates. Although the basis for this phenomenon of nitrate tolerance is not completely understood, sulfhydryl depletion, neurohormonal activation, and increased plasma volume are likely involved.

Administration of *N*-acetylcysteine, ACE inhibitors, or diuretics does not consistently prevent nitrate tolerance. Intermittent nitrate therapy is the only way to avoid nitrate tolerance.

(2) **Rebound.** Intermittent use of nitrates is not associated with serious rebound of angina among patients taking maintenance therapy with β-blockers. Dosing to allow for a longer nitrate-free interval is also not associated with rebound.

4. **β-Blockers** (Table 6.4)
   a. **Mechanism of action.** Blocking the β_1-adrenergic receptors in the heart decreases the rate–pressure product and oxygen demand. Decreased tension in the LV wall allows favorable redistribution of blood flow from the epicardium to the endocardium.
      (1) Coronary vasospasm is rare from the β_2-receptor blocking effect, but use of β-blockers should be avoided among patients with known, active vasospasm.
      (2) β-Blockers have a variable degree of membrane-stabilizing effect.
   b. **Evidence for effectiveness.** β-Blockers decrease mortality after MI. The mortality benefit is not proven among patients with stable angina without prior MI, although symptomatic improvement is well documented.
   c. **Side effects.** The most important side effects are related to blockade of β_2-receptors. However, data show that some of the side effects may occur less frequently than previously believed, and potentially lifesaving therapy should be offered to those at greatest risk for adverse events.
      (1) Bronchoconstriction, masking of symptoms caused by hypoglycemic reaction among patients with diabetes, exacerbation of symptoms of peripheral vascular disease, and central nervous system (CNS) side effects such as somnolence, lethargy, depression, and vivid dreaming are well documented. The CNS side effects are thought to be related to the lipid solubility of these compounds.
      (2) Symptomatic bradycardia and precipitation of heart failure are concerns for patients with a diseased conduction system and preexisting heart failure, respectively.
      (3) Decreased libido, impotence, and reversible alopecia can be a problem for some patients.
      (4) β-Blockers adversely alter lipid profile by increasing LDL cholesterol and decreasing HDL cholesterol.
   d. **Drug interactions.** Severe bradycardia and hypotension can occur with concomitant use of some calcium channel blockers.
   e. **Selection of preparations.** Cardioselectivity, lipid solubility, mode of excretion, and frequency of dosing are the main considerations when selecting a particular agent. The major cardiospecific agents (i.e., β1 blockade) include metoprolol, atenolol, bisoprolol, and nebivolol. Of note, nebivolol also induces the endothelial NO pathway and contributes to vasodilation. Intrinsic sympathomimetic activity is not a clinically important factor in the choice of a medication, although benefits in patients with CAD have been decreased with agents having intrinsic sympathomimetic activity.
   f. **Effect on lipids.** The clinical significance of lipid abnormalities associated with β-blockers is unclear. β-Blockers have been associated with a decline in HDL level and a rise in triglycerides level. β-Blockers can improve survival among patients in New York Heart Association (NYHA) class I or II heart failure and angina. The condition of a patient with NYHA class III or IV disease should be stabilized before β-blocker therapy is instituted.
5. **Calcium channel blockers** (Table 6.5)

TABLE 6.4 β-Blockers

Compound	Daily dose (mg)	Frequency	Excretion	Lipid solubility	Intrinsic sympathomimetic activity	Membrane stabilization
Selective β-blockers						
Metoprolol						
Short-acting	50–400	Every 12 h	Liver	Moderate		
Long-acting		Every 24 h			None	Possible
Atenolol	25–200	Every 24 h	Kidney	None	None	None
Acebutolol	200–600	Every 12 h	Kidney	Moderate	Low	Low
Nebivolol	5–40	Every 24 h	Kidney	High	None	
Betaxolol	20–40	Every 24 h	Kidney		Low	
Nonselective β ($\beta_1 + \beta_2$)-blockers						
Propranolol	80–320	Every 4–6 h	Liver			
Long-acting		Every 12 h		High	None	Moderate
Nadolol	80–240	Every 24 h	Kidney	Low	None	None
Timolol	15–45	Every 12 h	Liver	Moderate	None	None
Pindolol	15–45	Every 8–12 h	Kidney	Moderate	Moderate	Possible
Labetalol[a]	600–2,400	Every 6–8 h	Liver	None	None	Possible
Carvedilol[a]						
Short-acting	25–50	Every 12 h	Liver	Moderate	None	Possible
Long-acting	10–80	Every 24 h				

[a]Also a potent α_1-antagonist.

TABLE 6.5 Calcium Channel Blockers

Compound	Each dose (mg)	Frequency	Vasodilation	Sinoatrial node inhibition	Atrioventricular node inhibition	Negative inotrope
Nifedipine	30–120	Every 8 h	5	1	0	1
Nifedipine (Procardia XL)	30–180	Every 24 h				
Diltiazem	30–90	Every 6–8 h	3	5	4	2
Diltiazem (Cardizem CD)	120–300	Every 24 h				
Verapamil	40–120	Every 6–8 h	4	5	5	4
Verapamil (Calan SR and Isoptin SR)	120–240	Every 12 h				
Amlodipine (Norvasc)	2.5–10	Every 24 h	4	1	0	1
Felodipine (Plendil)	5–20	Every 24 h	5	1	0	0
Bepridil (Vascor)	200–400	Every 24 h	4	4	4	5
Isradipine (DynaCirc)	2.5–10	Every 24 h	4	4	0	0
Nicardipine (Cardene)	10–20	Every 8 h	5	1	0	0

0, no activity; 5, most potent effect. Intermediate numbers suggest intermediate potency of effects.

a. **Mechanism of action.** These agents block calcium entry into vascular smooth muscle cells and cardiac cells by inhibiting calcium channels, but they do not affect the regulation of intracellular calcium release. The result is decreased contraction of muscle cells.
   (1) The four types of calcium channels are L, T, N, and P.
   (2) The T-type calcium channels are located in the atria and sinoatrial node and affect the phase I of depolarization.
   (3) The L-type channels contribute to entrance of calcium into the cell during phase III of the action potential.
   (4) The N and P types of channels are present mainly in the nervous system.
   (5) The three main groups of calcium channel blockers are dihydropyridines (e.g., nifedipine), benzothiazepines (e.g., diltiazem), and phenylalkylamines (e.g., verapamil).
   (6) The dihydropyridines bind to the extracellular portion of the L channels at a specific site. They do not bind to the T channels and do not have a negative chronotropic effect. Because of their extracellular site of action, dihydropyridines do not inhibit receptor-induced intracellular calcium release.
   (7) Verapamil binds to the intracellular part of the L channel and inhibits the T channel. Intracellular calcium release is inhibited by verapamil because of its intracellular binding site and reflex sympathetic activation is less effective. Use dependence occurs with verapamil because open channels are needed for transport of the drug into the intracellular binding site. In stable angina, verapamil helps by improving rate–pressure product and by increasing oxygen delivery from coronary vasodilation.

b. **Evidence of effectiveness.** Numerous placebo-controlled, double-blind trials have shown that calcium channel blockers decrease the number of anginal attacks and attenuate exercise-induced depression of ST segments.
   (1) Studies comparing the efficacy of β-blockers and calcium channel blockers in the management of stable angina in which death, infarction, and unstable angina were used as end points showed calcium channel blockers to be as effective as β-blockers.
   (2) Increased mortality caused by short-acting nifedipine among patients with CAD was demonstrated in a retrospective study and meta-analysis. If the use of nifedipine is contemplated, a long-acting preparation in conjunction with β-blocker therapy is the safer approach. The mechanism of increased mortality is unclear, but reflex tachycardia and coronary steal phenomenon are potential explanations.

c. **Side effects.** The most common side effects are hypotension, flushing, dizziness, and headache. Because a negative inotropic effect can precipitate heart failure, the use of calcium channel blockers to treat patients with impaired LV function is relatively contraindicated. Conduction disturbances and symptomatic bradycardia occur with the use of compounds that have a marked inhibitory effect on the sinoatrial and atrioventricular nodes. Bepridil is known to prolong QTc, and QT monitoring is necessary when this medication is used. Lower extremity edema is often seen with the use of dihydropyridine calcium channel blockers and this may necessitate lowering the dose or discontinuation of the medication. The non–dihydropyridine calcium channel blockers are also known to cause constipation.

d. **Drug interactions.** Digitalis levels are increased by the non–dihydropyridine calcium channel blockers verapamil and diltiazem. The use of these drugs is contraindicated in the presence of digitalis toxicity.

e. **Selection of preparations.** Calcium channel blockers have a variable negative inotropic effect.

(1) Amlodipine is most likely to be tolerated by patients with compensated heart failure. In decompensated heart failure, all calcium channel blockers should be avoided. Amlodipine is the only calcium channel blocker approved for angina by the US Food and Drug Administration (FDA).

(2) Patients with conduction disturbances should take agents with minimal effects on the conduction system. Longer acting preparations minimize the risk for precipitation of angina caused by reflex tachycardia.

6. **ACE inhibitors.** The rationale for using ACE inhibitors to manage chronic stable angina comes from post-MI and heart failure trials that demonstrated a significant reduction in ischemic events with the use of ACE inhibitors.
   a. It is possible that ACE inhibitors, by decreasing mainly the preload and, to some extent, afterload, decrease myocardial oxygen demand and help in the management of chronic stable angina. The Heart Outcomes Prevention Evaluation (HOPE) trial in high-risk patients with CAD, stroke, diabetes, and peripheral vascular disease showed that ramipril was associated with a significant reduction in death, MI, and stroke in this population. A recent meta-analysis found that ACE inhibitors reduce the risk of these outcomes even in patients with atherosclerosis who do not have evidence of systolic dysfunction. It is notable that the randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) study evaluating the use of trandolapril in patients with preserved LV function did not find a benefit with respect to death, MI, angina, revascularization, or stroke. Numerous hypotheses to explain these divergent results, including dose effects, difference in medication effects, and the risk level of enrolled patients, have been postulated. Nevertheless, the use of ACE inhibitors is recommended (class I) for patients with abnormal LV function and considered reasonable (class IIa) for patients with normal LV function.
   b. The relative efficacy of different ACE inhibitors for relieving ischemia has not been well studied.
   c. Serious side effects of ACE inhibitors include cough, hyperkalemia, and decreased glomerular filtration rate. They are contraindicated in the care of patients with hereditary angioedema or bilateral renal artery stenosis.
7. **Hormone replacement therapy (HRT).** The lipid profiles of women change unfavorably after menopause. LDL, total cholesterol, and triglyceride levels increase and HDL level decreases. All these changes have an adverse effect on cardiovascular morbidity and mortality. Several large case-controlled and prospective cohort studies suggested that the postmenopausal use of estrogen alone or in combination with medroxyprogesterone acetate has a favorable effect on lipid profile and cardiovascular events. However, both the Women's Health Initiative (WHI) study on primary prevention and the Heart and Estrogen/progestin Replacement Study (HERS) on secondary prevention showed an increased risk of cardiovascular and cerebrovascular events in postmenopausal women receiving HRT. Another randomized trial quantifying coronary atherosclerosis angiographically showed negative results with respect to estrogen use. As a result, it has been postulated that the previously shown benefits might have been caused by the "healthy user" effect, and the use of HRT for primary prophylaxis against cardiovascular events is not recommended.
   a. **Benefits of use.** Although the use of estrogen has shown an increase in cardiovascular events, it is associated with some specific favorable findings. The positive effects of estrogen use include maintenance of normal endothelial function, reduction in levels of oxidized LDL, alteration in vascular tone, maintenance of normal hemostatic profile, a favorable effect on plasma glucose levels, reduction of osteoporotic fractures, and a reduction in menopausal symptoms.

b. **Side effects** include bleeding, nausea, and water retention. Because doses of estrogen are small, these side effects are uncommon. For patients with an intact uterus, routine gynecologic examination is mandatory for cancer surveillance. The risk of breast cancer is also increased with the use of HRT, and routine screening is beneficial.

8. **Antioxidants.** The role of vitamins A, C, and E is unclear in patients with CAD.
   a. The initial observational studies on the role of daily vitamin E supplementation in reducing the risk of cardiovascular events among patients with proven atherosclerotic heart disease appeared promising. However, when vitamin E was tested in a randomized fashion, no benefit in its use was proved. There are also data suggesting that vitamin E may attenuate the effect of statins. Vitamins A, C, and E are not recommended for the secondary prevention of cardiovascular events.
   b. Data are lacking about vitamins A and C. Most of the available information suggests no benefit in taking supranormal doses of these vitamins. Vitamin A does not prevent LDL oxidation, even though it binds to LDL molecules. Because it is water soluble, vitamin C does not bind to the LDL molecule. These two vitamins are not recommended for the prevention of progression of atherosclerosis.
9. **Ranolazine**
   a. Ranolazine has recently been shown to work by inhibiting the late sodium channel in myocytes, which can otherwise remain open in pathologic states such as ischemia and heart failure. By reducing the late sodium entry into myocytes, ranolazine causes reduced sodium-dependent calcium entry into the cytosol. This downstream reduction in intracellular calcium levels is thought to reduce diastolic stiffness, thereby improving diastolic blood flow and reducing ischemia and angina. Earlier studies had suggested that effects of ranolazine were primarily through its impact on fatty acid metabolism; however, the weight of evidence now suggests that late sodium channel inhibition is its primary mechanism.
   b. Numerous randomized studies of ranolazine, with or without background antianginal therapy, have shown a benefit in patients with stable angina with respect to frequency of anginal attacks, exercise duration, time to ST-segment depression on treadmill testing, and use of sublingual nitroglycerin.
   c. **Side effects.** Dizziness, headache, and GI intolerance are the most common side effects noted. Prolongation of the QT interval has been reported, especially in patients with hepatic or liver dysfunction due to decreased metabolism. **Prolonged QT interval** at baseline or during treatment follow-up **is a contraindication** to its use.
   d. **Drug interactions.** Inhibitors of CYP3A4, such as azole antifungals, non–dihydropyridine calcium channel blockers, macrolide antibiotics, protease inhibitors, and grapefruit juice, should not be used concomitantly due to inhibition of ranolazine metabolism.
10. **Newer pharmacologic approaches**
   a. Therapy with direct infusion of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor proteins has been shown to increase collateral blood flow in animal models. Studies are underway to investigate the role of these agents in improving collateral blood flow to the ischemic myocardium of patients with angina. Although early results are encouraging, long-term risks and benefits of such therapy remain largely unknown.
   b. Approaches involving the use of gene therapy to cause overexpression of these endogenous growth factors to control the development of collateral blood vessels have been proposed. These approaches are under investigation.

11. **Enhanced external counterpulsation (EECP)** has become a treatment option for patients with stable angina.
    a. EECP involves the intermittent compression of the lower extremities in an effort to increase diastolic pressure and augment coronary blood flow. Three sets of balloons are wrapped around the lower legs, lower thighs, and upper thighs, with precise cuff inflation and deflation gated with the ECG. The lower cuffs are inflated at the start of diastole, as represented by the beginning of the T wave, and simultaneous deflation of all three chambers is triggered just before systole at the onset of the P wave.
    b. In patients with refractory angina, clinical trials have demonstrated improvements in exercise tolerance, reduction in anginal symptoms, decreased use of nitroglycerin, and improvements in objective measures of ischemia as measured by thallium scintigraphy. These benefits are maintained at 2 years of follow-up.

C. **Percutaneous coronary intervention.** The effectiveness of PCI to control symptoms in chronic stable angina and to prevent death or MI has been compared with medical management and CABG.
    1. **Compared with medical treatment**
        a. The Angioplasty Compared with Medicine (ACME) trial compared PCI with medical therapy in approximately 200 patients with single-vessel and multivessel CADs. Patients with single-vessel CAD showed better symptomatic relief at 6 months with PCI but no difference in mortality or MI. Patients with two-vessel CAD had no significant differences in symptoms, mortality, or MI.
        b. The Medicine, Angioplasty, or Surgery Study (MASS) randomized approximately 200 patients with proximal left anterior descending (LAD) artery disease to medical therapy, PCI, or CABG. This study demonstrated no difference in the primary end point (i.e., death, MI, or refractory angina necessitating revascularization). Patients randomized to CABG had a lower incidence of events compared with the other two groups, driven by a decrease in repeat revascularization procedures.
        c. The Randomized Intervention Treatment of Angina-2 (RITA-2) trial randomized more than 1,000 patients with stable angina to medical therapy or PCI. After 2.7 years of follow-up, the primary end point (i.e., death or MI) was lower in the medically treated group. There was an improvement in angina, exercise capacity, and perceived quality of life in patients who underwent PCI. There was also a higher incidence of revascularization in the medically treated group.
        d. The study on Optimal Medical Therapy (OMT) with or without PCI for Stable Coronary Disease (by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] Trial Research group) evaluated patients with severe angiographic disease of one or more vessels, and either classic symptoms or documented ischemia on provocative testing. Compared with aggressive medical therapy, an initial strategy of PCI with BMS did not reduce the primary endpoint of death or major adverse cardiovascular events including symptom relief. Notable limitations to the interpretation of this study include the fact that the OMT group had stringent follow-up to achieve the high rates of medical adherence, one-thirds of patients in the medical therapy group crossed over to PCI (but were included in the OMT group as intention-to-treat analysis), and almost 80% of patients had no or minimal angina. Furthermore, it should be stressed that all patients were enrolled after angiography had been performed.
        e. In a substudy of patients enrolled in COURAGE on the basis of positive stress imaging, investigators found that PCI in addition to OMT was

superior in reducing ischemia than OMT alone. Furthermore, the degree of residual ischemia was related to future risk of death or MI. The adequately powered ISCHEMIA trial has been funded by the National Heart, Lung, and Blood Institute to address this issue.

f. The Occluded Artery Trial (OAT) tested the hypothesis that routine PCI of totally occluded arteries 3 to 28 days after MI in high-risk but asymptomatic patients would improve outcomes. In the 2,166 patients studied, there was no statistically significant difference in long-term cardiac events between the PCI and the medical therapy groups, although the PCI group had more rapid relief of angina.

g. The use of DES in comparison to BMS has significantly decreased the risk of in-stent restenosis and the need for target vessel revascularization, thereby improving quality of life, providing freedom from angina, and reducing the risk of repeat procedures. Acknowledging the slightly greater risk of ST with DES compared with BMS, the absolute risk of ST even with DES is quite low. Therefore, their use in appropriate situations is still highly considered in patients without bleeding issues, upcoming surgery, or financial constraints to long-term antiplatelet therapy.

2. Compared with CABG

a. The Emory Angioplasty versus Surgery Trial (EAST) randomized approximately 400 patients with multivessel disease to PCI or CABG. After 8 years of follow-up, there was no difference in the combined end point of mortality, Q-wave MI, and large thallium perfusion defect. In patients with proximal LAD artery disease or diabetes, there was a nonsignificant trend toward improved survival with CABG.

b. The Bypass Angioplasty Revascularization Investigators (BARI) conducted the largest trial comparing PCI with CABG in the management of multivessel disease. In this trial, there was no difference in survival between patients randomized to PCI or CABG at 7 years of follow-up, although the subgroup of patients with diabetes had a better survival rate with CABG than with PCI (76.4% vs. 55.7%).

c. The Arterial Revascularization Therapies Study (ARTS) randomized 1,200 patients with multivessel disease to CABG or BMS placement. After 1 and 5 years of follow-up, there was no difference in mortality, MI, or stroke. Outcomes were similar for patients with stable and unstable angina. Among diabetic patients, however, mortality was greater for those who received PCI. There was a greater incidence of repeat revascularization in the PCI group, although the use of DES in ARTS 2 (compared with the historic CABG group from ARTS 1) shows a similar 1-year rate of revascularization between PCI and CABG groups.

d. The surgery or stenting (SoS) study compared almost 1,000 patients with multivessel disease in the setting of ACS or non-ACS presentation. There was an increased mortality and need for repeat revascularization in the PCI group, which could not be attributed to a diabetic population.

e. In the BARI 2 Diabetes (BARI 2D) trial published more recently, investigators compared prompt revascularization (PCI or CABG as deemed appropriate) and OMT in a group of patients with type 2 diabetes mellitus and CAD. The primary outcome of death was not significantly different in the two groups, nor was the rate of major cardiovascular events (the major secondary end point including death, MI, and stroke). When stratified by revascularization strategy, patients in the CABG group had greater freedom from major cardiovascular events (77.6% vs. 69.5%, $p = 0.01$); this finding was not significant in patients undergoing PCI. Notably, however, this trial was not designed to compare CABG and PCI as revascularization strategies.

f. The recently reported SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) was a pivotal trial randomizing patients with three-vessel disease or left main trunk (LMT) stenosis to multivessel PCI versus CABG. The primary end point of death, stroke, MI, and repeat revascularization favored CABG (12.3% vs. 17.6%, $p = 0.002$). The secondary end point which included death, stroke, and MI was not different between the two groups (7.7% vs. 7.6%, $p = 0.98$). The primary end point favoring CABG was therefore driven primarily by increased rates of repeat revascularization in the PCI group (13.5% vs. 5.9%, $p < 0.001$), though notably the rate of stroke was also significantly lower in the PCI group (2.2% vs. 0.6%, $p = 0.003$).

g. The other major take-home point of the SYNTAX trial was the formulation of the SYNTAX score, which received a class I indication for evaluation of LMT or multivessel disease in the most recent ACC/AHA PCI guidelines. The SYNTAX score grades coronary anatomy on the basis of lesion location, complexity, and functional impact and is a helpful tool for assessing patients at the individual level when discussing options of CABG versus PCI. In the trial, outcomes were assessed by SYNTAX score tertile: patients with a low (0 to 22) or intermediate (23 to 32) score had no difference between the two modes of revascularization for the primary outcome. In patients with a score > 32, however, CABG was favored for the primary outcome (10.9% vs. 23.4%, $p < 0.001$).

h. In patients with LMT stenosis, guidelines had long recommended CABG as the treatment of choice. However, in the modern era of stent placement, PCI of "unprotected" LMT stenosis has gained favor. The 2011 ACC/AHA PCI Guidelines revised the previous class III recommendation for unprotected LMT PCI to class IIa.

Small studies have shown that the mortality difference between PCI and CABG in similarly matched groups of patients is negligible. Furthermore, recent studies comparing the experience of DES implantation in LMT with BMS placement have shown a marked decrease in the need for repeat revascularization.

i. In the prespecified subgroup of patients undergoing unprotected LMT PCI versus CABG in the SYNTAX trial, the primary outcome was similar between the two groups. As in the main study population, stroke was higher in the CABG group (2.7 vs. 0.3%, $p = 0.009$) and repeat revascularization was higher in the PCI group (11.8 vs. 6.5%, $p = 0.02$). Given the clinical equipoise that surrounds unprotected LMT revascularization, the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial is currently underway. The investigators plan to randomize 2,500 patients with LMT stenosis and a SYNTAX score < 32 to PCI versus CABG.

j. At present, strong consideration is given to CABG in the group of patients with multivessel disease and diabetes, LV dysfunction, or LMT disease who are able to undergo open heart surgery. In the general population with multivessel or LMT disease, however, there is a paucity of evidence showing a survival advantage to CABG over PCI, and recent trials with modern treatment practices (including DES implantation, aggressive antiplatelet therapy, off-pump coronary artery bypass procedures, and use of arterial grafts) have shown favorable comparisons between the two treatment strategies. For patients who are able to undergo either of the treatments, an educated decision should be made by the patient, the cardiologist, and a cardiac surgeon.

3. Revascularization methods. For details of PCI strategy and equipment, please refer **Chapter 65**.

D. Coronary artery bypass grafting

1. **Compared with medical treatment.** Compared with medical treatment, CABG improves the survival rate among patients with high-risk stable angina. The benefit is most profound in patients with three-vessel CAD, impaired LV function, or substantial LMCA stenosis.
   a. This information is derived from the Coronary Artery Surgery Study (CASS), European Coronary Surgery Study (ECSS), and Veterans Administration Cooperative Study (VACS). These trials were completed before generalized awareness grew regarding the benefits of medical management with β-blockers, ACE inhibitors, antiplatelet agents, or lipid-lowering medications.
   b. Surgical techniques have also changed significantly, with greater use of arterial conduits including internal mammary artery (IMA) grafts, minimally invasive surgery, and improved techniques of cardiac tissue preservation and anesthesia.
2. **Venous or arterial grafts.** There are different techniques of CABG. The use of minimally invasive bypass surgery involving the left internal mammary artery (LIMA) in patients with isolated LAD artery stenosis has not shown any difference in the rate of mortality, MI, or stroke in comparison to PCI but has shown a decrease in the need for repeat revascularization. With open sternotomy, in which the use of LIMA is well studied, mammary arterial grafting has better long-term outcome compared with vein graft conduits. Given the success of the (LIMA) graft, other arterial conduits have been used, such as the right internal mammary artery (RIMA), the radial artery, and the right gastroepiploic artery.
   a. Twenty percent of venous grafts are nonfunctional at 5 years and only 60% to 70% are functional after 10 years. In contrast, > 90% of LIMA to LAD artery grafts are patent 20 years after the operation.
   b. **Internal mammary artery** grafts have a better patency rate at 10 years when used for LAD lesions (95%) than for circumflex (88%) or right coronary artery (76%) lesions. The patency rates are higher for LIMA compared with RIMA and for in situ grafts compared with free grafts.
   c. Patient survival is better with an IMA graft than when only saphenous venous grafts are used. This survival benefit persists for up to 20 years.
   d. The use of bilateral IMA grafts appears promising, with evidence that the use of RIMA in addition to LIMA improves survival in comparison to LIMA plus saphenous vein grafting. The use of RIMA is technically difficult, however, and has, therefore, not been widespread.
   e. The radial artery graft was introduced into clinical practice around the year 1970 and initially had mixed results. However, at approximately 1 year, 92% of the grafts are patent and at 5 years 80% to 85% of grafts are open. The right gastroepiploic arterial graft has been in use for approximately 15 years, and a 5-year angiographic patency rates of 92% has been reported.
3. **Previous CABG.** Little information is available on the treatment of patients who have already undergone bypass surgery and have stable angina. Although another bypass operation may be offered to these patients, direct comparison with medical treatment in this patient population has not been made. The use of multiple arterial grafts at the time of first CABG reduces the need for reoperation.
4. **Compared with PCI.** This is discussed in Section **IV.C**.

E. Other forms of revascularization

Percutaneous and intraoperative transmyocardial revascularization are potential treatments for patients with coronary disease not amenable to PCI or CABG. Some reports suggest improvement in symptoms, a decrease in perfusion defects, and improvement in contractile function after these procedures but no survival benefit

has been reported. This procedure should be reserved as palliation for patients with medically refractory angina and no other revascularization option, but it has generally fallen out of favor in recent years.

Promotion of ancillary blood vessels by means of injection of blood vessel–promoting agents such as VEGF at the time of surgical or percutaneous coronary revascularization is currently under investigation. So far, the results of this form of intervention have been mixed. Smaller studies targeting improvement in perfusion and exercise tolerance suggest some benefit in the active treatment group. However, two, somewhat larger, studies have recently been terminated early due to lack of benefit at interim analysis.

F. Lifestyle modification

1. **Exercise**
   a. **Rationale.** Exercise conditions the skeletal muscles, which decreases total body oxygen consumption for the same amount of workload. Exercise training also lowers heart rate for any level of exertion, which decreases the oxygen demand on the myocardium for any workload. Some evidence shows that higher physical activity and exercise can decrease cardiovascular morbidity and mortality.
   b. **Recommendation.** For secondary prevention, aerobic and isotonic exercises with a goal of achieving a sustained heart rate of approximately 70% to 85% of the maximum predicted heart rate at least 3 or 4 times per week has been shown to improve survival. For beginners, a supervised exercise or rehabilitative program, in which 50% to 70% of maximal predicted heart rate is achieved, is also helpful. Isometric exercises are not recommended because they increase myocardial oxygen demand substantially.
2. **Diet.** A low-fat diet that includes cereals and grains, skimmed dairy products, fruits and vegetables, fish, and lean meats should be recommended and this is effective in providing cardiovascular risk reduction in patients with CAD. These are also integral components of the "Mediterranean Diet," which has been shown to reduce cardiovascular risk. A multidisciplinary approach to the care of patients with CAD that includes a nutritionist/dietician can be quite helpful in personalizing patients' eating habits.
3. **Smoking cessation.** Cigarette smoking is associated with progression of atherosclerosis, increased myocardial demand due to an α-adrenergic increase in coronary tone, and adverse effects on hemostatic values, all of which can lead to worsening of stable angina. Smoking cessation decreases cardiovascular risk among patients with established CAD, including patients who have undergone CABG. Physician counseling is the best approach to achieve this goal and adjunctive therapies include nicotine replacement patches, gum, or sprays, or medications such as bupropion and varenicline.
4. **Psychological factors.** Anger, hostility, depression, and stress are shown to adversely affect CAD. Results of small, nonrandomized trials show that biofeedback and various relaxation techniques can help modify these factors.

V. RECOMMENDED APPROACH TO STABLE ANGINA

A. The following approach is suggested for the treatment of patients with stable angina.

1. It is reasonable to risk stratify patients with stable angina using stress testing with imaging, such as nuclear isotope imaging or echocardiography.
   a. LV systolic function should be assessed with echocardiography to guide therapy and to identify patients with moderate LV systolic dysfunction.
   b. Patients with small perfusion defects or small wall–motion abnormalities, high threshold for ischemia, normal LV systolic function, and clear symptoms should be treated with medication.

2. If symptoms continue after medical therapy is maximized, angiography should be planned. Coronary angiography should also be performed for patients with evidence of impaired perfusion involving multiple territories, a low threshold for ischemia, and moderate LV systolic dysfunction.
3. **Single-vessel disease.** If a patient has single-vessel CAD that does not involve the LMT or supply a large myocardial territory, medical management with risk factor modification is the appropriate first step.
   a. If patients cannot tolerate medical treatment or have symptoms despite maximum medical therapy, revascularization therapy should be offered.
4. Among patients with **multivessel CAD**, medical treatment remains an alternative for patients who have normal LV systolic function, mild symptoms, and relatively smaller areas of myocardium at risk.
   a. The decision for multivessel PCI versus CABG in this group of patients should be made on an individual basis, taking into consideration the angiographic anatomy, LV function, patient comorbidities, surgical risk, and patient preference.
   b. Any doubt regarding viability of the myocardium at risk should be addressed with appropriate diagnostic studies before revascularization.
5. In patients with "unprotected" LMT stenosis, the previous recommendations of CABG in all patients who are able to undergo surgery have recently been revised. PCI for severe LMT disease may be appropriate in select patients.
6. Regardless of treatment strategy, aggressive risk factor modification, including use of lipid-lowering agents, lifestyle modification, and aspirin therapy, is an essential component of management.

ACKNOWLEDGMENT: *The authors thank Dr. Keith Ellis for his contributions to earlier editions of this chapter.*

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CHAPTER 7

Gus Theodos

Other Ischemic Syndromes: Silent Ischemia and Syndrome X

SILENT ISCHEMIA

I. INTRODUCTION. Silent ischemia represents an underappreciated manifestation of coronary artery disease (CAD), occurring in up to 20% to 40% of patients with stable and unstable coronary syndromes. It is estimated that 195,000 silent first myocardial infarctions (MIs) occur each year, which assumes that 21% of MIs are silent. By definition, patients are asymptomatic, lacking typical or atypical anginal symptoms. Silent ischemia may be documented by a variety of diagnostic modalities, including resting electrocardiogram (ECG), ambulatory ECG (AECG), nuclear scintigraphy, and echocardiography.

II. CLINICAL PRESENTATION. Patients may be loosely categorized into three groups, collectively representing a continuum of silent ischemia.

A. Type I have **asymptomatic** ischemia with no known CAD history with **asymptomatic** MI patterns. Clinicians may discover evidence of subclinical MI from a resting ECG or a preoperative stress test. In the Framingham study, 12.5% of patients with MI had an unrecognized "silent" infarction. Patients may also present with arrhythmias or sudden death from subsequent scar. These patients are considered to have an ineffective "anginal warning system."

In addition, a subset of this group includes patients with **asymptomatic** ischemia without a history of infarction. Silent ischemia is often discovered by stress tests after referral for aggressive primary screening. This type of screening may occur in patients with diabetes, strong family histories, or a high-risk electron beam computed tomography (EBCT) result. Given the increasingly technological nature of medical culture, the prevalence of these patients is likely to rise. AECG is rarely used as a primary screening modality. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines consider the use of AECG for ischemia monitoring in asymptomatic individuals as a class III recommendation.

B. Type II have **symptomatic** MIs but subsequent **asymptomatic** ischemic syndromes. Ischemia is often missed because of a lack of symptoms. Patients in this category are most often encountered after a positive stress test or the rarely ordered AECG. Type II patients may have an abnormal **pain threshold.**

C. Type III encompass the largest patient population with silent ischemia. These patients with known CAD have both **symptomatic** and **asymptomatic** ischemia. Between 20% and 40% of patients with chronic anginal symptoms have silent ischemia. About 75% of ischemic episodes are silent and only 25% are symptomatic.

III. DIAGNOSTIC TESTING. Most patients with silent ischemia are either never identified or identified retrospectively. In the Asymptomatic Cardiac Ischemic Pilot (ACIP) study, patients with frequent silent ischemic events were found to be at increased risk for advanced

coronary disease, including high-risk coronary anatomy such as three-vessel disease. Currently, testing to detect ischemia in asymptomatic patients is controversial. The ACC/AHA guidelines consider the use of exercise ECG testing (without imaging) in asymptomatic patients with possible myocardial ischemia on AECG or severe coronary calcification on EBCT as a *class IIb recommendation*. The use of exercise plus imaging stress testing (echo and nuclear) in asymptomatic patients with a low-risk Duke treadmill score on exercise ECG testing is a *class III recommendation*. In patients with an intermediate- or high-risk Duke treadmill score, it is a *class IIb recommendation.* In *asymptomatic* patients with prior revascularization with high-risk features, periodic stress testing is a *class IIb recommendation*.

IV. MECHANISMS

A. The exact explanation for a lack of symptoms in the face of unequivocal ischemia remains **unknown**. It likely represents abnormal modulation of cardiac **pain perception at different levels in the afferent pathway of the heart**.

B. The association between diabetes and silent ischemia and painless infarction has been attributed to **autonomic neuropathy**. A higher threshold for pain has been related to increased baseline plasma β-endorphin levels and increased age. A potential connection exists between baroreceptor function and pain perception. This may explain the relationships among increased systolic blood pressure, reduced sensitivity to ischemic pain, and the demonstration of anginal relief with carotid sinus stimulation. Results of one study suggested that the gating of afferent signals at the thalamic level is a potential mechanism for silent ischemia. Patients with symptoms had activation of basal frontal, anterior, and ventral cingulate cortices and the left temporal pole. **Cortical activation was limited to the right frontal region in patients with silent ischemia**. It also has been proposed that, among type III patients, asymptomatic ischemia may represent shorter and less severe episodes compared with symptomatic episodes.

V. MANAGEMENT

A. Medications effective in preventing symptomatic ischemia (i.e., nitrates, calcium antagonists, and β-blockers) and in decreasing myocardial O_2 demand are also effective in reducing or eliminating episodes of silent ischemia. In one randomized study, metoprolol was found to be better than diltiazem in reducing the mean number and duration of ischemic episodes. However, the combination of calcium antagonists and β-blockers was more effective than either agent alone. Lipid-lowering therapy has also shown a reduction of ischemia on AECG. The ACC/AHA guidelines currently regard the use of ASA (aspirin), β-blockers, angiotensin-converting enzyme inhibitors, and statins as class I recommendations in asymptomatic patients with evidence of previous MI and class IIa recommendations in patients without history of previous MI. It has also been postulated that ranolazine may also reduce ischemia before symptoms become present.

B. The goal of therapy remains controversial. It is not clear whether therapy should be guided by ischemia or angina. The ACIP study revealed no difference in benefit from either of these approaches. However, 2-year follow-up data from this study demonstrated improved prognosis with initial revascularization compared with angina- or ischemia-guided medical therapy. The Swiss Interventional Study on Silent Ischemia type I (SWISSI I) randomized 54 type I subset patients to treatment with antianginal medications and aspirin versus risk factor modification only. Their findings showed that treatment with the combination of antianginal drug therapy and aspirin appeared to significantly reduce cardiac events, including cardiac death, nonfatal MI, or acute coronary syndrome. In addition, these patients had consistently lower rates of exercise-induced ischemia during follow-up. The SWISSI II study randomized 201 patients with type II silent ischemia to percutaneous coronary intervention (PCI) versus ongoing anti-ischemic medical therapy. The results showed a significant decrease in rates of cardiac death, nonfatal MI, and subsequent

need for revascularization in patients in the PCI group over a 10-year follow-up period. Similarly, in patients with type I silent ischemia, with an ineffective "anginal warning system," it has been suggested that it may be reasonable to treat silent ischemia in a manner equivalent to that for symptomatic ischemia in the general population in terms of revascularization and medical therapy.

VI. PROGNOSIS. Myocardial ischemia, whether symptomatic or asymptomatic, is associated with poorer outcomes among patients with CAD. Patients with frequent and accelerating episodes of ST-segment depression on AECG monitoring are at higher risk for subsequent cardiac events than patients with few or no such episodes. The Copenhagen Holter study examined the significance of ischemic changes on AECG in asymptomatic, healthy individuals between the ages of 55 and 75 years (type I subset). They found that patients with silent ischemia had a threefold higher risk of subsequent cardiac events over a 5-year follow-up period. Circadian effects of asymptomatic ST depression on AECG have been noted with changes being more common in the morning hours; however, nocturnal ST-segment changes have been associated with multivessel CAD or left main narrowing. It has not been proven conclusively, however, that detection of silent ischemia is an independent risk factor for future cardiac events.

VII. CONTROVERSIES

A. Patients with silent ischemia on AECG monitoring represent heterogeneous populations. This may be a marker of unstable, complex coronary plaque or microvascular dysfunction. Results of the angiographic substudy of the ACIP study suggested that most patients with silent ischemia have proximal coronary lesions or complex coronary plaques. This hypothesis has not been tested in a larger population and continues to be investigated.

B. The potential role of **AECG monitoring** for ischemia still needs to be determined to assess its utility compared with more commonly used tests, such as exercise testing with thallium imaging. Different populations should be carefully examined at specific times after their events to answer these questions. Currently, the exercise ECG test remains the most useful and validated screening test for significant CAD.

C. **Medical therapy** should be used to decrease or eliminate ischemia; however, the relative role of medical therapy compared with revascularization in asymptomatic patients with demonstrable ischemia remains unclear.

D. **Coronary artery calcium** scanning to screen asymptomatic patients for CAD is now a *class IIa indication* in those patients with an intermediate (10% to 20%) 10-year risk of cardiac events based on the Framingham risk score or other global risk algorithm and for asymptomatic patients aged 40 years and older with diabetes mellitus.

SYNDROME X

I. INTRODUCTION. Syndrome X is defined as the constellation of effort-induced **anginalike discomfort** in the setting of **angiographically normal coronary arteries** (without inducible spasm on ergonovine provocation testing). This chest pain is usually indistinguishable from traditional ischemic angina caused by obstructive coronary disease and is, therefore, considered a diagnosis of exclusion.

II. PRESENTATION. In the clinical setting, syndrome X is a diagnosis given to patients with persistent **anginal symptoms**, often with abnormal stress testing despite a **normal angiogram** and **negative workup** for noncardiac chest pain. Up to 25% of all coronary angiograms performed in the United States for symptoms of chest pain are normal; yet, most cardiologists do not routinely use ergonovine provocation or intravascular ultrasound to evaluate for variant angina or angiographically silent coronary atherosclerosis in this subset of patients. When intravascular ultrasonography studies have been performed

in these patients, a spectrum of findings ranging from normal vessels to intimal thickening to nonobstructive atheromatous plaque has been reported. Syndrome X has an increased occurrence in women (3:1 preponderance), both premenopausal and postmenopausal. Of note, abnormal cardiac physical examination findings and left ventricular (LV) dysfunction on stress testing are both uncommon in syndrome X.

III. ETIOLOGY AND PATHOPHYSIOLOGY. Syndrome X represents a heterogeneous population and may represent multiple processes with varying causes. **Endothelial dysfunction, microvascular ischemia, and abnormal pain perception have all been implicated in the genesis of this disorder**. Endothelial dysfunction as demonstrated by abnormal coronary flow reserve (CFR), single positron emission computed tomography stress, and positron emission tomography stress testing is common in these patients. In addition, behavioral and psychiatric conditions often coexist. Specific treatment aimed at managing behavioral issues may lead to symptomatic improvement in chest pain in some patients.

IV. DIAGNOSTIC TESTING. Because syndrome X is a **diagnosis of exclusion**, both traditional obstructive coronary atherosclerosis and causes of noncardiac chest pain must be ruled out before a final diagnosis can be made. Multislice computed tomography angiography may play an increasingly important role in avoiding invasive angiography in some of these patients. Laboratory testing for endothelial dysfunction is not widely utilized in the clinical setting. Abnormal CFR in the catheterization laboratory can help confirm abnormalities in microcirculatory control, often accompanied by endothelial dysfunction in patients with syndrome X. C-reactive protein (high-sensitivity CRP) has been shown to correlate with the severity of symptoms and ECG changes in this population.

V. THERAPY. The **primary goal** of the therapy should be **aggressive cardiac risk factor modification,** including lifestyle changes and lipid treatment, although the **ideal treatment regimen is unknown**. β-Blockers have been shown to be very effective in controlling anginal symptoms in this population and are considered superior to calcium channel blockers and nitrates. Other treatments that have provided benefit include tricyclic antidepressants (imipramine), oral aminophylline, and estrogen in postmenopausal women. Given the recent data on estrogens, caution should be exercised when considering estrogen therapy in patients with suspected syndrome X.

VI. PROGNOSIS. The prognosis for patients with angina and normal coronary arteriograms is generally favorable with good long-term outcomes shown in multiple studies. However, subsets of these patients such as patients with persistent anginal symptoms and/or evidence of significant myocardial ischemia on stress testing seem to be at higher risk and have significantly higher event rates, including premature death, MI, and stroke, than the baseline population. These subsets of patients should be treated aggressively with risk factor modification and counseled regarding lifestyle modification.

VII. OTHER. Although not clearly related to syndrome X, **Takotsubo syndrome** (aka LV apical ballooning syndrome and stress-induced cardiomyopathy) is a condition that has been receiving increasing attention. Clinical features include sudden onset of chest pain, ECG changes (often ST elevation) mimicking an acute MI, usually in the setting of severe emotional distress and catecholamine surge. The angiogram shows normal coronary arteries, and diagnosis is made on the typical appearance seen on LV ventriculogram or echocardiogram with basal hyperkinesis and severe apical systolic wall motion abnormality. Most patients recover LV function and require only hemodynamic and pharmacologic support.

ACKNOWLEDGMENTS: *The author and editors would like to thank Apur R. Kamdar, Tim Williams, and Marc S. Penn for their contributions to the previous version of this chapter.*

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SECTION II

Heart Failure and Transplant

EDITOR

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CHAPTER 8

Michael A. Samara
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Heart Failure with Systolic Dysfunction

I. INTRODUCTION

A. Heart failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive maladaptive neurohormonal activation of the cardiovascular and renal systems leading to circulatory insufficiency and congestion. Currently, acute heart failure syndromes (AHFS) constitute the most common indication for hospitalization in adults over age 65. With the increasing age of the population, improved survival of patients with acute coronary syndromes, and reduced mortality from other diseases, the incidence and attendant cost of managing patients with heart failure will inevitably increase.

B. Terminology

1. Based on the hemodynamic model, **systolic heart failure** has been defined by the presence of impaired contractility of the left ventricle, most commonly conveyed in an ejection fraction (EF) of < 40% to 50%. This drop in contractility may be associated with chamber dilation and a decreased stroke volume (Fig. 8.1). There is a growing appreciation for the limitations of this classification. The threshold for systolic dysfunction is arbitrary and it is now clear that patients with heart failure with preserved EF suffer similar morbidity and mortality. There is substantial variability in EF determinations made by different imaging modalities. Most importantly, EF correlates poorly with symptoms, cardiac indices, and potential response to pharmacotherapy.
2. In practice, heart failure is a bedside diagnosis that is defined by clinical assessment. Patients may have cardiac dysfunction without symptoms, often referred to as **asymptomatic left ventricular (LV) dysfunction**. Others may have preserved LV systolic function with typical signs and symptoms of heart failure, best referred to as **heart failure with preserved EF** (see Chapter 9).
3. The major pathophysiologic process in the progression of heart failure is **cardiac remodeling**, in the form of progressive chamber enlargement with an obligatory reduction in EF. Histopathologically, this is associated with myocyte hypertrophy, apoptosis, and necrosis. Molecular alterations including reexpression of a fetal gene program and alterations in excitation–contraction coupling and regulatory proteins occur.
4. In some cases, **myocardial recovery** or **reverse remodeling** is possible with pharmacologic and device therapy.
5. The term **congestive heart failure** is overused and nonspecific, often being applied to states of hypervolemia unrelated to cardiac dysfunction. Conversely, not all patients with heart failure have signs and symptoms of congestion.
6. The term **right heart failure** is used to describe patients with predominantly peripheral signs and symptoms of heart failure with a relative paucity of pulmonary congestion.
7. **Acute decompensated heart failure** or **AHFS** refer to episodes of acute or subacute deterioration of heart failure due to a wide range of precipitants. The vast majority of these events are marked by systemic and pulmonary congestion.

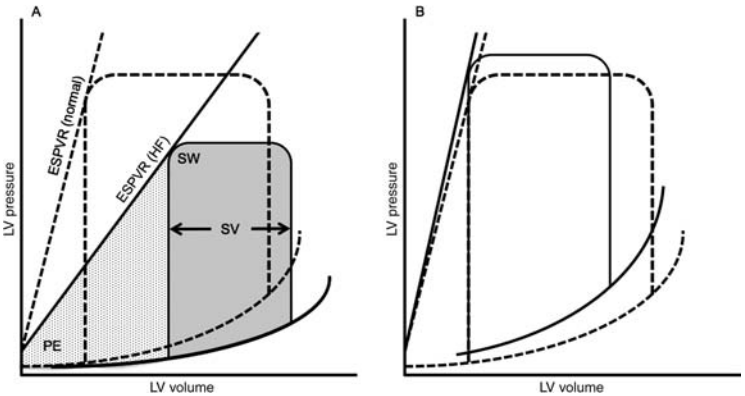

FIGURE 8.1 Pressure–volume loops in normal (dashed line) and heart failure (HF; solid line) patients. **A:** Pressure–volume loops in HF with impaired ejection fraction typically demonstrate a reduction in the end-systolic pressure–volume relationship (ESPVR; i.e., the end-systolic elastance), a representation of contractility. This is typically accompanied by an increase in end-diastolic volume and a reduction in stroke volume (SV) and stroke work (SW; shaded area). At a given ESPVR, a reduction in end-systolic pressure results in an increased SV and reduction in the left ventricular (LV) elastic potential energy (PE; speckled area). **B:** In contrast, patients with HF with preserved ejection fraction have a normal or elevated ESPVR with a left and upward shift in the end-diastolic pressure–volume relationship reflecting decreased myocardial compliance.

II. PATHOGENESIS

A. Heart failure is a progressive disorder initiated by some form of myocardial injury. This injury may range from acute disruptions in myocardial function (myocardial infarction or myocarditis) to one of a number of chronic derangements including familial and metabolic cardiomyopathies or chronic volume or pressure loading related to valvulopathies, intracardiac shunts, or systemic hypertension. Regardless of the initial insult, the compensatory mechanisms that may be beneficial acutely ultimately become maladaptive in the chronic phase.

B. Neurohormonal activation

1. **Activation of the sympathetic nervous system.** Chronic activation of the sympathetic nervous system ultimately results in decreased β-adrenergic receptor responsiveness and decreased norepinephrine stores and sympathetic innervation of the myocardium. Chronically, these changes contribute to myocyte hypertrophy, fibrosis, and necrosis. Extracardiac effects include increased tubular reabsorption of sodium, activation of the renin–angiotensin system (RAS), neurogenic vasoconstriction, and vascular hypertrophy.
2. **Activation of the RAS.** As heart failure progresses, renal hypoperfusion and sympathetic stimulation of the kidneys result in increased production of renin by the juxtaglomerular apparatus. Renin cleaves circulating angiotensinogen into the biologically inactive angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to the biologically active angiotensin II. Importantly, angiotensin II can be generated in renin and ACE-independent pathways as well. In addition to direct cardiovascular effects, angiotensin II stimulates aldosterone production by the zona glomerulosa of the adrenal cortex, which in turn promotes reabsorption of sodium in exchange for

potassium in the distal nephron. Chronically, aldosterone results in the promotion of hypertrophy and fibrosis in the vasculature and myocardium, endothelial dysfunction, and inhibition of norepinephrine uptake.

3. **Other neurohormonal derangements.** Inappropriate production of arginine vasopressin has an antidiuretic effect contributing and worsens vasoconstriction. Endothelin, neuropeptide Y, and other peripheral vasoconstrictors further enhance vascular tone.

III. CLASSIFICATION

A. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines currently classify heart failure on the basis of the evolution of the disease across a continuum:

1. **Stage A:** patients at high risk for developing heart failure without structural heart disease or symptomatic heart failure.
2. **Stage B:** patients with structural heart disease who have not yet developed symptoms of heart failure.
3. **Stage C:** patients with structural heart disease with prior or current symptoms of heart failure.
4. **Stage D:** patients with refractory end-stage heart failure who require specialized advanced treatment.

B. The **New York Heart Association (NYHA) functional classification**, although subjective and vague, remains the most commonly used standard by which the severity of functional impairment is graded (Table 8.1).

C. The **Killip classification** grades the severity of signs of decompensated heart failure in the post-acute coronary syndrome setting and is highly predictive of 30-day mortality.

VI. ETIOLOGY.

It is essential to make every effort to identify the specific etiology of heart failure as it may have implications for management and prognosis. While ischemic cardiomyopathy is by far the most common cause of systolic heart failure, a diverse array of disease states can culminate in this phenotype (Table 8.2).

TABLE 8.1 New York Heart Association Functional Classification

Class	Description
I	Patients have cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in an inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

TABLE 8.2 Etiologies of Heart Failure

- Dilated cardiomyopathy
  - Idiopathic
  - Familial
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy
- Unclassified cardiomyopathies
  - Fibroelastosis
  - Mitochondrial cardiomyopathy
  - Left ventricular noncompaction
- Specific cardiomyopathies
  - Ischemic cardiomyopathy
  - Stress-induced cardiomyopathy
  - Valvular obstruction or insufficiency
  - Hypertensive
  - Inflammatory (lymphocytic, eosinophilic, giant cell myocarditis)
  - Infectious (Chagas disease, Lyme disease, HIV, enterovirus, adenovirus, CMV, bacterial or fungal infections)
- Metabolic
  - Endocrine (thyroid diseases, adrenal insufficiency, pheochromocytoma, acromegaly, diabetes mellitus)
  - Familial storage disease (hemochromatosis, glycogen storage disease, Hurler's syndrome, Anderson-Fabry disease)
  - Electrolyte deficiency syndromes (hypokalemia, hypomagnesemia)
  - Nutritional deficiencies (kwashiorkor, anemia, beriberi, carnitine and selenium deficiency)
  - Amyloid
  - Familial Mediterranean fever
- Systemic diseases
  - Connective tissue disorders (SLE, polyarteritis nodosa, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis, sarcoidosis)
  - Muscular dystrophies (Duchenne's, Becker's, myotonic, limb girdle)
  - Neuromuscular (Friedreich's ataxia, Noonan's disease)
  - Toxins (alcohol, catecholamines, cocaine, anthracyclines and other chemotherapeutics, radiation)

CMV, cytomegalovirus; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.
Modified from WHO Classification.

A. Ischemic cardiomyopathy is the cause of 60% to 75% of cases of systolic heart failure in industrialized countries. It is defined as **cardiomyopathy in the presence of prior extensive myocardial infarction, hibernating myocardium, or severe coronary artery disease**. However, the mere ***presence of obstructive coronary artery disease does not equal ischemic cardiomyopathy as it is possible to have coronary artery disease superimposed with a nonischemic etiology of heart failure***. A careful assessment of the coronary anatomy, the burden of ischemia, and the presence of infarcted and viable myocardium must be made and an assessment of the proportionality of these findings to the degree of myocardial dysfunction should be made. The risks and benefits of percutaneous or surgical revascularization should be assessed in all patients with ischemic cardiomyopathy. Extensive observational data have suggested a benefit for coronary artery bypass grafting (CABG) compared with medical therapy alone in moderate to severe LV systolic dysfunction. Registry data suggest that CABG is superior to percutaneous coronary intervention in patients with reduced EF. However, recently released 5-year data from the Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated no difference in 5-year mortality for patients with left ventricular ejection fraction (LVEF) < 35% undergoing CABG in addition to optimal medical therapy versus optimal medical therapy alone. Furthermore, a substudy of STICH demonstrated that preoperative viability testing did not effectively predict whether patients derived benefit from CABG. Notably, patients with left main trunk disease and severe angina were excluded from the study and these patients should continue to be treated aggressively with revascularization.

B. Dilated cardiomyopathy. In 20% to 30% of cases of heart failure with systolic dysfunction, the precise etiology is not established and a diagnosis of nonischemic, dilated, or idiopathic cardiomyopathy is made. Patients with **dilated cardiomyopathy typically have a better prognosis than their ischemic counterparts**.

1. Dilated cardiomyopathy is frequently attributed to the residual effects of **subclinical viral myocarditis**. Reverse transcription polymerase chain reaction analysis of endomyocardial biopsies from patients with dilated cardiomyopathy demonstrates amplification of viral genomes in approximately two-thirds of cases. Any virus can cause myocarditis, but, owing to its ubiquity, coxsackie B virus is the most epidemiologically important.
2. **Familial dilated cardiomyopathy.** It is now recognized that 25% to 50% of cases of dilated cardiomyopathy may have a genetic basis. Conditions are typically autosomal dominant and show variable penetrance. A detailed three-generation family history is essential at the time of initial evaluation. If the family history suggests a genetic predisposition, clinical screening of family members is appropriate and genetic testing can be performed following referral to a genetic counselor. Importantly, only 15% to 25% of presumed familial dilated cardiomyopathies have identifiable genetic alterations.

C. Hypertensive and diabetic cardiomyopathy are seldom considered as stand-alone diagnoses. Progression from LV hypertrophy to overt dysfunction in hypertensive patients (the so-called burnt-out hypertensive heart) most likely results from progressive microvascular ischemia. Hypertension and diabetes also contribute significantly to the development of coronary artery disease and ischemic cardiomyopathy.

D. Cardiotoxic agents. The list of toxins that can produce cardiomyopathy is extensive. Identification of the toxin and removal of the offending agent may halt the progression of or even reverse LV dysfunction.

1. **Chemotherapeutic agents. Anthracycline** toxicity can cause myocyte destruction and cardiomyopathy. Patients who receive a cumulative doxorubicin equivalent dose of < 400 mg/m^2 are at low risk for this syndrome, while those receiving a cumulative dose > 700 mg/m^2 have an approximately 20% lifetime risk of developing cardiomyopathy. Other cardiotoxic drugs that require careful cardiac monitoring include **cyclophosphamide** and **trastuzumab**. Trastuzumab

(Herceptin) is now frequently used in the treatment of human epidermal growth factor receptor 2 positive breast cancer and has been associated with a reversible cardiomyopathy in 2% to 7% of patients undergoing treatment. Antiangiogenic drugs such as sunitinib can also cause cardiotoxicity and uncontrolled hypertension.

2. **Alcohol** consumption is thought to represent a common cause of toxin-mediated cardiomyopathy; however, there is limited observational data on the actual incidence of the cardiomyopathy or the volume of alcohol consumption necessary to induce it. Total abstinence from alcohol may result in complete resolution, whereas continued use is associated with a 3- to 6-year mortality exceeding 50%.
3. **Stimulant drugs** including cocaine and methamphetamine may result in the development of heart failure via multiple derangements including progressive concentric hypertrophy and recurrent myocardial infarction.
4. **Toxin exposures** including lead, arsenic, and cobalt can result in progressive myocardial dysfunction.

E. Inflammatory cardiomyopathy (i.e., myocarditis) is discussed in detail in Chapter 11.

F. Tachyarrhythmia-induced cardiomyopathy can complicate the course of atrial fibrillation, atrial flutter, ectopic atrial tachycardia, and even occult sustained ventricular tachycardia and frequent premature ventricular contractions (> 20% to 30% of beats). In general, it is thought that persistent tachycardia in excess of 110 bpm is required to induce LV dysfunction. This is a critical diagnosis to make, as treatment of the underlying tachyarrhythmia generally results in complete resolution of the cardiomyopathy.

G. Peripartum cardiomyopathy is defined as a dilated cardiomyopathy occurring between the last month of pregnancy and up to 5 months postpartum. The majority of peripartum cardiomyopathy patients improve with standard heart failure pharmacotherapy, with over 50% of patients experiencing complete normalization of cardiac function.

H. Valvular disorders are common causes of heart failure. Aortic regurgitation and mitral regurgitation (MR) result in chronic volume overload and ultimately culminate in dilated cardiomyopathy. Severe aortic stenosis and outflow tract obstruction commonly lead to progressive LV dysfunction (see Chapters 14 and 15). Surgical correction is the preferred management of severe valvular lesions.

I. Miscellaneous disorders

1. **Thyroid disorders**
   a. **Hypothyroidism** is common in patients with heart failure. Severe hypothyroidism (i.e., myxedema) may cause decreased cardiac output and heart failure. Bradycardia and pericardial effusion can develop in extreme cases of hypothyroidism.
   b. Heart failure may complicate **hyperthyroidism**, especially in elderly patients with low ventricular reserve. Atrial fibrillation is a common accompanying arrhythmia, occurring in 9% to 22% of patients with thyrotoxicosis. Nonspecific symptoms such as fatigue, weight loss, and insomnia predominate. Previously stable angina may become unstable. Patients treated with amiodarone may develop a wide range of thyroid disorders ranging from abnormal thyroid function tests to overt amiodarone-induced thyrotoxicosis or hypothyroidism. Both conditions can occur in otherwise normal thyroid glands.
2. **Thiamine deficiency (beriberi).** Although rare in industrialized countries, thiamine deficiency is still prevalent in the developing world. It can also occur in alcoholics or individuals observing fad diets. Wet beriberi includes features of **high-output cardiac failure such as marked edema, peripheral vasodilatation, and pulmonary congestion**. The signs and symptoms of dry beriberi include glossitis, hyperkeratosis, and peripheral neuropathy. The laboratory diagnosis is made using decreased RBC transketolase and 24-hour urine thiamine

levels. Severe cases can present with lactic acidosis. Intravenous therapy with 100 mg of thiamine followed by daily oral supplementation can result in dramatic clinical improvement. Chronic use of high-dose diuretics may be complicated by subclinical thiamine deficiency of unknown significance.

3. **Other nutritional deficiencies.** Carnitine and selenium deficiency may result in dilated cardiomyopathy complicating chronic parenteral nutrition.
4. **High-output heart failure from anemia.** Acute anemia caused by rapid blood loss is associated with decreased cardiac output due by hypovolemic shock. In contrast, chronic anemia can be associated with symptoms of heart failure due to compensatory mechanisms. These include fluid retention, increased cardiac output, decreased vascular resistance, and increased 2,3-diphosphoglycerate with a resultant rightward shift in the oxyhemoglobin dissociation curve. Moderate degrees of chronic anemia (hemoglobin < 9 g/dL) typically only result in heart failure symptoms in patients with preexisting cardiac disease. Chronic anemia of severe proportions (hemoglobin < 7 g/dL) may result in high-output heart failure even in individuals with normal hearts. Evaluation and management of the underlying cause and supportive care are advised. Thresholds for transfusion depend on the clinical context and rapidity of blood loss. Iron repletion should be considered in iron-deficient patients and in inpatients is most readily achieved with the daily administration of intravenous ferric gluconate 125 mg for 8 to 10 days.
5. While early in its course **hemochromatosis** may present with restrictive cardiomyopathy, it typically progresses to a mixed or dilated form. Treatment with chelating agents or phlebotomy may improve cardiac function in both primary and secondary forms.
6. **Inherited myopathies** such as Becker's and Duchenne's muscular dystrophies, limb girdle dystrophy, and myotonic dystrophy are associated with dilated cardiomyopathy. Friedreich's ataxia is most commonly associated with hypertrophic cardiomyopathy, but in rare instances can present with a dilated phenotype. Mitochondrial cardiomyopathies may also present with dilated cardiomyopathy.
7. **Cardiac sarcoidosis** can present with LV dysfunction with regional hypokinesis or aneurysmal dilatation. It is frequently associated with conduction abnormalities and ventricular tachyarrhythmias. The diagnosis can be supported with stereotypical findings on cardiac MRI and positron emission tomography (PET). The diagnosis is rare in the absence of extracardiac manifestations.
8. **Chagas disease** caused by the flagellate protozoan *Trypanosoma cruzi* remains a common cause of heart failure in patients from Latin America. In the chronic symptomatic phase, patients typically present with a syndrome of ventricular dysfunction with regional wall motion abnormalities in the absence of obstructive coronary artery disease. This pattern should prompt *T. cruzi* titers in patients from endemic regions.

V. SIGNS AND SYMPTOMS

A. There is a wide spectrum of signs and symptoms in heart failure patients. Subjective changes in signs and symptoms are often difficult to elicit and frequently leave insufficient time lag for therapeutic interventions prior to hospitalization.

1. The most common and earliest presenting symptom is **dyspnea**, typically with exertion. **Orthopnea** is typical with more advanced disease. It is amongst the most sensitive (90%) and specific (90%) signs of decompensated heart failure. As further decompensation occurs, **paroxysmal nocturnal dyspnea** and **Cheyne-Stokes respiratory patterns** may occur.
2. **Fatigue** and **exercise intolerance** are common complaints in patients with heart failure and may reflect diminished cardiac output. Seldom considered but highly prevalent symptoms include **nocturnal cough, insomnia, and depressed mood**.

3. **Palpitations** and **syncope** may occur in patients with underlying arrhythmia and require prompt evaluation.
4. **Anorexia** and **abdominal pain** are common in advanced right heart failure.

B. Physical examination of patients with significant but well-compensated systolic heart failure may reveal no abnormalities. Physical signs vary according to the degree of compensation, the chronicity, and the chamber involvement.

1. **Volume overload** is the hallmark of heart failure. Typical signs of volume overload include the following:
   a. **Weight gain** is a sensitive indicator of congestion.
   b. **Pulmonary rales** due to accumulation of fluid in the pulmonary interstitium and alveoli secondary to high left atrial pressure are commonly referred to as **acute cardiogenic pulmonary edema**. Importantly, rales may be absent in patients with chronic systolic heart failure who develop compensatory perivascular and lymphatic changes.
   c. **Jugular venous distention or elevated jugular venous pressure (JVP)** while not directly reflecting left-sided filling pressures can track these with a reasonable sensitivity (70%) and specificity (79%). JVP should be assessed at a 45° incline with the neck fully exposed. In cases of extreme JVP elevation, the patient may need to be seated upright in order to properly visualize. Five centimeters of water should be added to the vertical distance from the sternal angle to the meniscus of the JVP to account for the distance to the midpoint of the right atrium. Compression of the right upper quadrant and a resultant positive **hepatojugular reflex** (defined as a sustained increase in JVP of ≥4 cm) increase the sensitivity of the JVP for detecting congestion.
   d. **Pedal edema** by some estimates is only present in 30% of patients with decompensated heart failure and is somewhat nonspecific, as it may reflect venous insufficiency, nephrotic syndrome, cirrhosis, or concomitant treatment with calcium channel blockers or thiazolidinediones.
   e. **Ascites and hepatomegaly** may occur. When accompanied by a palpably pulsatile liver, hepatomegaly suggests severe tricuspid regurgitation.
   f. A holosystolic murmur of **MR** is often present in the setting of LV dilatation.
   g. **A third heart sound** (S_3 gallop) is best heard with the bell of the stethoscope in the left lateral position and signifies increased LV end-diastolic pressure.
2. Often neglected are the subtle signs of **peripheral hypoperfusion**.
   a. **Pulsus alternans** or a low-amplitude pulse in the absence of alternative explanations reflects severely impaired cardiac output.
   b. Tachycardia and narrow pulse pressure also suggest diminished cardiac output.
   c. Lethargy, pallor, mottled skin, cool extremities, and poor capillary refill are typical signs.
   d. **Hypotension** itself may be one of the most important clinical findings in heart failure. Several studies have demonstrated that a systolic blood pressure < 90 mm Hg is a strong predictor of morbidity and mortality.

VI. DIAGNOSTIC EVALUATION

A. Laboratory work is used to diagnose potentially reversible causes, identify comorbidities, monitor and correct abnormalities before or during treatment, and assess the disease severity.

1. A **comprehensive metabolic panel** should be assessed on initial evaluation and then subsequently based on clinical judgment. Particular attention should be paid to the presence of hyponatremia, which portends a worse prognosis. Hypokalemia is common in the setting of ongoing diuretic therapy. Hyperkalemia can be seen in the context of overaggressive potassium repletion and ongoing treatment with ACE or aldosterone inhibitors or in diabetic patients with

associated type IV renal tubular acidosis. Aside from the pragmatic considerations, many real-world registries have identified elevated blood urea nitrogen (BUN) and creatinine as powerful predictors of outcome. Renal function must also be taken into account when considering therapy with renally excreted drugs. Transaminitis and in some cases a cholestatic pattern of liver function test abnormalities may be seen in the context of right heart failure.

2. **Anemia** is present in up to 40% of heart failure patients and is associated with increased mortality and functional impairment. While frequently due to anemia of chronic disease, a thorough diagnostic evaluation should be performed.
3. The natriuretic peptides **B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP)** are released in the setting of increased ventricular dilation or wall stress. Normal ranges (BNP < 100 pg/mL; NT-proBNP < 125 pg/mL if age < 75 years and < 450 pg/mL if age ≥75 years) must be interpreted in the context of associated conditions known to alter levels. Increasing age and worsening renal function are associated with increased levels. There is an inverse relationship between natriuretic peptides and body mass index.
   a. **Screening for heart failure.** Although cardiac dysfunction has been associated with elevated natriuretic peptide levels, the sensitivity is relatively low in asymptomatic patients and is highly dependent on the cut-off levels chosen. In general, routine assessment of BNP is not recommended as a screening test for structural heart disease in asymptomatic patients.
   b. **Diagnosing heart failure.** The primary use of natriuretic peptides remains the diagnosis of heart failure in symptomatic patients particularly when the diagnosis is unclear. The high negative predictive value (up to 90%) in this setting allows BNP testing to be useful to rule out a cardiac cause of symptoms. With the growing epidemic of obesity, it is important to remember that ***normal natriuretic peptide levels may be present in morbidly obese patients with decompensated heart failure.***
   c. **Management of heart failure.** While still controversial, there is emerging evidence that serial measurements of natriuretic peptides may be beneficial in guiding outpatient heart failure management and may result in decreased heart failure–related mortality versus usual care.
   d. **Determining prognosis of heart failure.** Data now suggest that natriuretic peptide levels are closely correlated with morbidity and mortality in patients with both established heart failure and other cardiovascular diagnoses (e.g., stable coronary artery disease, acute coronary syndromes, pulmonary hypertension, and atrial fibrillation).
4. **Other biomarkers.** A growing list of biomarkers assessing systemic inflammation, oxidative stress, extracellular matrix remodeling, and myocyte injury is commercially available or in development. While some of these provide useful prognostic information, it is not clear how to best integrate them into the diagnosis and management of heart failure.
5. **Thyroid function testing** is warranted for all patients with a new diagnosis of heart failure.
6. Iron studies including ferritin, serum iron, and total iron binding capacity (with calculation of percent transferrin saturation) should be performed to screen for hemochromatosis and occult iron deficiency.
7. Standard laboratory screening for **modifiable cardiovascular risk factors** including fasting lipid panel and serum glucose should be obtained.

B. **The electrocardiogram (ECG)** may provide important information pertaining to the cause and management of heart failure and is a recommended component of the evaluation of any patient with a clinical diagnosis of heart failure.
   1. It is important to look for evidence of prior myocardial infarction, chamber enlargement and hypertrophy, conduction disease, and supraventricular or ventricular arrhythmias.

2. Specific diagnoses can be suggested in the ECG. Cardiac amyloidosis classically presents with low voltages and a pseudoinfarction pattern in the anterior leads in stark contrast to echocardiographically thickened walls. Arrhythmogenic right ventricular (RV) cardiomyopathy may present with epsilon waves or localized prolongation (> 110 milliseconds) of the QRS complex in the right precordial leads.
3. The ECG is an important means of assessing **dyssynchrony**. Marked first-degree atrioventricular (AV) block or very short AV delays in the presence of paced rhythms may contribute to AV dyssynchrony. The presence of QRS prolongation > 120 milliseconds (particularly left bundle branch block morphologies with QRS > 130 milliseconds) suggests interventricular dyssynchrony and remains the most important predictor of response to cardiac resynchronization therapy.
4. **Holter or event monitors** are often useful in identifying occult arrhythmia and arrhythmia burden.

C. Examination of the **chest radiograph** should include an assessment of the heart size and the condition of the pulmonary parenchyma. Determinations of cardiac size are best restricted to standard posteroanterior projections, as "portable" anteroposterior projections will magnify the cardiac silhouette. Lateral projections are useful to assess for RV enlargement, with associated filling of the retrosternal space. A normal cardiac silhouette does not exclude systolic or diastolic dysfunction. The lung field abnormalities may range from mild engorgement of the perihilar vessels to bilateral pleural effusions, Kerley B lines, and frank pulmonary edema.

D. Echocardiography is perhaps the most useful diagnostic test in the evaluation of patients with heart failure. It can provide useful information pertaining to the etiology and prognosis of heart failure. As described in later sections, echocardiography also plays a key role in guiding heart failure therapy.

1. **Etiology of heart failure.** Regional wall motion abnormalities occurring in an anatomic coronary artery distribution are suggestive of ischemic cardiomyopathy. However, regional wall motion abnormalities can also be seen in the context of nonischemic dilated cardiomyopathy, stress-induced cardiomyopathy, and infiltrative cardiomyopathies (with inferobasal wall motion abnormalities classically seen in the setting of cardiac sarcoidosis). The presence and severity of valvular stenosis or insufficiency can be assessed as can the relative dysfunction of the right and left ventricles.
2. **Prognosis in heart failure.** The following parameters are useful in assessing the risk of heart failure–associated morbidity and mortality.
   a. **EF and LV dimensions.** While correlating poorly with heart failure symptoms, exercise capacity, and oxygen consumption, the EF provides valuable prognostic information with morbidity and mortality closely linked to EF and LV volumes. The American Society of Echocardiography recommends that assessment of EF and LV volumes be made using the biplane Simpson's method of disks.
   b. **LV mass.** Remodeling in the failing heart results in increased LV mass due to eccentric hypertrophy, which worsens prognosis. Eccentric hypertrophy is defined echocardiographically as an LV mass > 95 g/m^2 in women and > 115 g/m^2 in men with a regional wall thickness (2 × posterior wall thickness/LV end-diastolic dimension) of ≤0.42.
   c. **The myocardial performance index (Tei index).** The Tei index provides a useful assessment of systolic and diastolic function and is equal to (the isovolumic contraction time + the isovolumic relaxation time)/the ejection time. All dimensions are obtained via pulse wave or tissue Doppler. A Tei index of > 0.77 in patients with dilated cardiomyopathy is highly predictive of cardiovascular morbidity and mortality.
   d. **Measures of diastolic dysfunction.** Many of the measures of diastolic dysfunction detailed in Chapter 9 have powerful prognostic ability in patients

with systolic heart failure. The presence of a restrictive filling pattern ($E/A > 2$, deceleration time < 115 to 150 milliseconds) persisting despite Valsalva maneuver is a particularly ominous finding.

E. Other imaging modalities

1. **Cardiac magnetic resonance (CMR) imaging** (Chapter 51). CMR offers unparalleled myocardial tissue characterization and allows for myocardial viability assessment. As such, it is an increasingly useful tool in the diagnosis of specific cardiomyopathies (e.g., LV noncompaction and cardiac sarcoidosis). The distribution of late gadolinium hyperenhancement representing scar can effectively discriminate between ischemic and nonischemic causes of fibrosis. Cine MRI provides accurate assessments of chamber volumes and LV and RV systolic function that can be performed in arbitrary tomographic views. Major limitations are incompatibility with most implanted electronic cardiovascular devices and the potential for nephrogenic sclerosing fibrosis with the use of gadolinium-based contrast agents in patients with preexisting renal insufficiency (see Chapter 51).
2. **Nuclear imaging.** Single photon emission computed tomography (SPECT) and PET imaging are primarily of use in ruling out myocardial ischemia and/or viability. **Viability assessment** (i.e., discriminating between scarred and hibernating myocardium) is critical in the assessment of patients with heart failure and coronary artery disease and the potential for myocardial recovery with revascularization. This can be achieved with PET using concomitant flow and metabolism tracers (typically [^{18}F]fluorodeoxyglucose) or thallium 201 SPECT redistribution imaging (see Chapter 50). There is growing evidence that PET is superior to SPECT in patients with systolic dysfunction, and when available it should be used preferentially in patients with an LVEF < 35%. Dobutamine stress echocardiography and CMR are alternative means of assessing viability. Radionuclide ventriculography using multiple-gated acquisition scanning has long served as the gold standard for precise serial measurements of the LVEF (classically in the evaluation of patients receiving cardiotoxic chemotherapeutics). Increasingly, however, it is being surpassed by CMR and three-dimensional echocardiography.

F. Right heart catheterization (see Chapter 60). Invasive hemodynamic monitoring is often helpful in the diagnosis and inpatient management of heart failure. Right heart catheterization can be combined with exercise testing or infusions of inotropic or vasodilatory agents to study their hemodynamic effects. Reasonable indications for right heart catheterization include short-term management of acute cardiogenic shock, evaluation of patients for cardiac transplantation or mechanical circulatory support, clarification of hemodynamics in the context-specific comorbidities (e.g., suspected RV infarction or mechanical complications of myocardial infarction), adjustment of therapy in patients with recurrent or refractory symptoms, and optimization of medical therapy in order to facilitate weaning from inotropes.

1. **Cardiac output/index** is one of the important measurements provided by right heart catheterization. It can be determined using the thermodilution technique or the Fick method using an estimated or derived oxygen consumption and a directly measured mixed venous oxygen saturation (MVO_2).
2. **Pulmonary capillary wedge pressure (PCWP)** should be measured in all cases. An inability to normalize the PCWP (< 16 mm Hg) with pharmacotherapy was shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial to confer a twofold increased risk of mortality.
3. **Right atrial pressure** is an important indicator of volume status and right heart function. An elevated central venous pressure has been shown to be the most important predictor of worsening renal function during hospitalizations for acute decompensated heart failure.

G. Coronary angiography (see Chapter 64). There are many approaches to determining which patients with systolic heart failure warrant evaluation by coronary angiography. The Heart Failure Society of America recommends performing coronary angiography in patients with a high pretest probability of underlying ischemic cardiomyopathy and who are candidates for percutaneous or surgical revascularization. At a minimum, patients meeting this description should undergo some form of noninvasive stress testing. Some centers advocate for a baseline coronary angiogram in all patients with newly established systolic heart failure regardless of risk factors or presentation.

H. Endomyocardial biopsy (see Chapter 61) is indicated only when a specific primary myocardial disease is suspected and other causes of decompensation have been ruled out. A recent AHA/ACC/ESC writing group identified 14 clinical scenarios in which there is an incremental diagnostic, prognostic (e.g., amyloidosis), or therapeutic (e.g., giant cell myocarditis) value to biopsy that can be weighed against the procedural risk.

I. Cardiopulmonary exercise testing (metabolic stress testing) while not recommended as part of the routine evaluation of patients with heart failure should be considered in the context of symptoms out of proportion with objective measures of disease severity, discriminating between cardiac and pulmonary etiologies of dyspnea, or assessing candidacy for cardiac transplantation or mechanical circulatory support. Several routinely measured parameters are highly predictive of prognosis in patients with established heart failure.

1. **Peak oxygen consumption (Vo_2)** is perhaps the most important parameter in objectively describing functional capacity and prognosticating. Normal values based on age and sex are indexed to body weight, with a normal value being > 84% predicted. Patients being considered for heart transplantation undergo risk stratification with a metabolic stress test. Patients with a peak Vo_2 < 14 mL/kg/min or < 50% predicted are at increased risk for adverse cardiovascular events and if the limitation is deemed to be cardiac should be considered for transplantation. Interpretation of the peak Vo_2 is highly dependent on the adequacy of effort as assessed by the respiratory exchange ratio (RER). The RER is the ratio of Vco_2/Vo_2 and is at steady state an estimate of the respiratory quotient. It signifies the conversion to anaerobic metabolism and the sudden rise in co_2 production occurring with the onset of metabolic acidosis. Failure to achieve an RER > 1.05 suggests insufficient effort or premature termination of the study. Up to 50% of heart failure patients are incapable of achieving an adequate RER, with a modified Bruce treadmill protocol necessitating the use of alternative protocols.
2. **Ventilatory anaerobic threshold** is another means of assessing the adequacy of effort and represents the point at which minute ventilation (V_E) increases out of proportion with Vo_2 (typically occurring at 60% to 70% of peak Vo_2).
3. **V_E/Vco_2 slope** is a dimensionless ratio indicating the relationship between minute ventilation and CO_2 production. The slope is elevated in most patients with heart failure and is inversely related to cardiac output at peak exercise. A slope > 35 identifies higher risk individuals independently of peak Vo_2.

J. Sleep study. Obstructive sleep apnea and central sleep apnea are common comorbidities contributing adversely to the pathogenesis and prognosis of patients with heart failure. There should be a low threshold for appropriate testing.

VII. TREATMENT.

The effective management of heart failure relies on appreciating the distinction between acute and chronic therapies.

A. Acute heart failure syndromes. In the United States, AHFS continue to constitute the most common indication for hospital admission in adults over age 65 years. These hospitalizations represent an inflection point in the course and prognosis of the chronic disease, with 90-day and 1-year postdischarge mortality as high as 14%

TABLE 8.3 Precipitants of Acute Decompensated Heart Failure

Medication nonadherence
Myocardial ischemia, infarction
Arrhythmias (tachyarrhythmias, bradycardia)
Infection
Anemia
Alcohol consumption
Pregnancy
Worsening hypertension
Acute valvular insufficiency
Drugs that can acutely worsen HF symptoms
Calcium channel antagonists
β-Blockers
Nonsteroidal anti-inflammatory drugs
Thiazolidinediones
Antiarrhythmic agents (all class I agents, sotalol)

and 37%, respectively. Only 20% of AHFS represent patients with de novo heart failure. The majority are patients with worsening chronic heart failure. The initial management goals include symptom improvement, decongestion, and hemodynamic stabilization with optimization of tissue perfusion. It is important to attempt to identify and correct any precipitating factors (Table 8.3).

1. **Invasive hemodynamic monitoring**
   a. **Pulmonary artery catheter.** The **ESCAPE** trial demonstrated that the routine use of a pulmonary artery catheter in the management of patients with AHFS did not result in a reduction in subsequent hospitalizations or mortality but did result in an increase in anticipated complications. The use of a pulmonary artery catheter should therefore be restricted to the scenarios detailed above where there is need for clarification of cardiac indices or filling pressures and in critically ill patients failing to respond to standard therapies. When available, a PCWP of > 18 mm Hg suggests cardiogenic pulmonary edema and a cardiac index of < 2.0 L/min/m^2 is consistent with cardiogenic shock.
   b. **Arterial catheter.** Continuous blood pressure monitoring with an arterial catheter can be useful in cases with marginal blood pressure and allows for optimal titration of intravenous vasodilators.
2. **Maximizing oxygenation** is vital. All patients with acute cardiogenic pulmonary edema should be positioned upright and receive supplemental oxygen. **Noninvasive positive pressure ventilation (NIPPV)** should be considered in those with ongoing increased work of breathing, respiratory acidosis, or persistent hypoxemia. The Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema (**3CPOE**) trial demonstrated that NIPPV results in more rapid resolution of symptoms and metabolic derangements than continuous positive airway pressure (CPAP) ventilation or standard oxygen therapy. While there was no evidence of a reduction in short-term mortality, this can be an invaluable tool

often forestalling intubation. Patients who fail to respond to NIPPV should be promptly intubated. The use of positive end-expiratory pressure (PEEP) can be effective in improving oxygenation, but high levels of PEEP come at the cost of reduced systemic venous return and cardiac output, which may be problematic in patients in shock.

3. **Vasodilators.** In the absence of symptomatic hypotension, intravenous vasodilators are the first-line therapy for the management of cardiogenic pulmonary edema.
   a. **Nitroglycerin** reduces LV filling pressures via venodilation and to a lesser extent via systemic afterload reduction. It may be given rapidly in the emergency setting (0.4 to 0.8 mg, given sublingually every 3 to 5 minutes) and by means of intravenous infusion in the subacute setting (starting dosage of 0.2 to 0.4 μg/kg/min), with titration every 5 minutes on the basis of symptoms or mean arterial pressure (MAP). While there is no maximal dose, increasing beyond 300 to 400 μg/min likely yields no additional benefit and should prompt the addition of another vasodilator. Tachyphylaxis can occur with high-dose infusions. Headache is the most common side effect, and use is contraindicated in the setting of recent use of phosphodiesterase-5 (PDE-5) inhibitors.
   c. **Sodium nitroprusside** is a potent vasodilator with balanced venous and arteriolar effects. It requires careful hemodynamic monitoring (typically by arterial line). A starting dosage of 0.1 to 0.2 μg/kg/min is used and titrated every 5 minutes to achieve a clinical response while maintaining an MAP > 65 mm Hg. Nitroprusside is particularly useful in instances where a rapid and large reduction in afterload is desired (e.g., cardiogenic shock and acute severe aortic regurgitation or MR). While cyanide and thiocyanate toxicity is exceedingly rare with short durations of therapy, nitroprusside should be used with caution in patients with severe renal dysfunction. Long-term, high-dose infusions should be avoided. In patients with myocardial ischemia, nitroglycerin or a combination of nitroglycerine and nitroprusside is preferred to avoid the theoretical risk of coronary steal.
   d. **Nesiritide** is an intravenous vasodilator that gained popularity in the acute care setting because of its ease of use in the absence of invasive hemodynamic monitoring. Typical dosing starts with 2 mg/kg delivered by intravenous bolus followed by an infusion at a rate of 0.01 mg/kg/min for up to 48 hours. The recently published Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (**ASCEND-HF**) trial demonstrated that nesiritide had no effect on death or rehospitalization for heart failure at 30 days when compared with conventional therapy. While providing some reassurance regarding previous safety concerns, these results have led most experts to discourage its use on the basis of lack of efficacy.
4. **Diuretics.** In addition to their ability to gradually reduce intravascular volume, diuretics have an immediate vasodilatory effect, which may be responsible for their prompt symptom relief. Reductions in filling pressures may be associated with augmented forward flow due to optimization of LV and RV mechanics and interventricular interaction. Because many patients with acute cardiogenic pulmonary edema do not have total body salt and water excess, the judicious use of diuretics is recommended. Often, filling pressures normalize with the use of vasodilators alone. Patients without chronic exposure to loop diuretics usually respond to 20 to 40 mg of intravenous furosemide. Patients undergoing long-term furosemide therapy typically need an intravenous bolus dose at least equivalent to their oral dose. Rather than an arbitrary therapeutic goal of net fluid balance or an estimated dry weight, frequent clinical assessments of volume status should

guide therapy and define the point at which conversion to an oral maintenance regimen should occur. Nevertheless, up to 30% of patients with AHFS continue to have symptoms of congestion at the time of discharge. Important adverse effects include hypotension, hypokalemia, hypomagnesemia, and hypocalcemia. There is also extensive evidence suggesting that intravenous diuretics may result in at least transient neurohormonal activation which is theoretically disadvantageous. Electrolyte repletion is best achieved with scheduled doses of potassium and magnesium supplements to prevent severe deficits. Results of the recently published Diuretic Optimization Strategies Evaluation (**DOSE**) trial demonstrate no benefit of continuous or bolus dose intravenous diuretic administration and no detriment from high doses (an intravenous dose 2.5 times the patients' chronic oral dose of furosemide). If a continuous diuretic infusion is opted for, it should be preceded by a bolus dose, as should any subsequent titration in the continuous rate. Diuretic resistance can be addressed with escalating doses of loop diuretics and subsequently with the addition of a thiazide diuretic (hydrochlorothiazide, metolazone, or chlorothiazide). Some degree of worsening renal function must often be tolerated in order to achieve adequate decongestion. However, if progressive renal failure occurs despite persistent congestion, ultrafiltration or the addition of an intravenous vasodilator or inotrope needs to be considered.

5. **Inotropic therapy.** When signs and symptoms of decompensated heart failure persist despite administration of vasodilators and diuretics, intravenous inotropes may be considered. Their use should be restricted to patients with clear clinical or direct hemodynamic evidence of refractory elevated filling pressures and reduced cardiac output. For patients without significant hypotension, the intravenous inodilators dobutamine or milrinone can be used to augment cardiac output. Both drugs are associated with increased myocardial oxygen demand and cardiac arrhythmias and should be used with extreme caution in patients with ischemia and preexisting arrhythmias. Both drugs may cause hypotension, although this is more common with loading doses of milrinone. ***There is no evidence to support benefit with the use of chronic or intermittent infusion of inotropic agents, and in fact, there is extensive observational data suggesting a trend toward increased postdischarge mortality.*** Use is typically confined to the acute care setting and as a bridge to transplant/mechanical circulatory support or palliation in patients who are not candidates for advanced therapies. In cases of severe hypotension (especially as a result of administration of vasodilators or β-blockers), temporary use of vasopressors such as dopamine, norepinephrine, and phenylephrine may be necessary. In contrast to the conventional wisdom, recent prospective data suggest that norepinephrine is not inferior to dopamine in the setting of cardiogenic shock.
   a. **Dobutamine** acts on β-1 and to a lesser extent on β-2 and α-1 adrenergic receptors. It has a shorter half-life than milrinone and usually is the drug of choice in the acute setting. Infusions are usually started at 2.5 to 5.0 μg/kg/min. On the basis of hemodynamic response, it may be titrated by 1 to 2 μg/kg/min every 30 minutes until the desired effect or a dosage of 10 μg/kg/min is reached.
   b. **Milrinone** is a PDE inhibitor that increases myocardial inotropy by inhibiting the degradation of cyclic adenosine monophosphate. It is a potent systemic and pulmonary vasodilator due to its effects on vascular PDE. For patients who need an immediate inotropic response, a loading dose of 50 μg/kg over 10 minutes is followed by an infusion of 0.125 to 0.75 μg/kg/min. Because it does not target β-receptors, milrinone may be more effective than dobutamine in the setting of recent or ongoing β-blocker therapy.
6. **Ultrafiltration** has been used as an alternative to pharmacologic diuresis in acute decompensated heart failure. The Ultrafiltration vs. Intravenous Diuretics

for patients hospitalized for Acute Decompensated Congestive Heart Failure (**UNLOAD**) study demonstrated that ultrafiltration was safe and resulted in a reduced need for intravenous diuretics and inotropes. Whether ultrafiltration should be considered a first-line alternative to standard intravenous diuretics will depend on the outcome of future trials assessing the relative safety, efficacy, and cost-effectiveness. Currently the use of ultrafiltration is reserved for patients refractory to intravenous diuretic therapy or with diuresis complicated by worsening renal function.

7. **Vasopressin antagonists.** The oral vasopressin receptor 2 antagonist tolvaptan was shown to be safe and results in short-term symptom improvement in patients hospitalized with acute decompensated heart failure in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (**EVEREST**) trial. This occurred without a reduction in long-term heart failure morbidity or mortality. Tolvaptan and the nonselective intravenous vasopressin receptor inhibitor conivaptan are both approved for the management of hypervolemic or euvolemic hyponatremia that can accompany decompensated heart failure.
8. **Temporary mechanical circulatory support.** The use of temporary and permanent mechanical circulatory support is described in detail in Chapter 12. Patients with refractory cardiogenic shock and cardiogenic pulmonary edema may benefit from the temporary use of intraaortic balloon counterpulsation or an alternative temporary means of mechanical circulatory support (i.e., veno-arterial extracorporeal membrane oxygenation, Impella, or TandemHeart) may facilitate bridging to stabilization or further decision making.
9. Diagnosis and management of atrial and ventricular tachyarrhythmias is critical to the care of patients with acute decompensated heart failure, as these frequently precipitate exacerbations and alter the disease course. Their management is discussed in detail in Chapter 21.
10. **Transition to chronic pharmacotherapy** is implemented once clinical stability is achieved. Generally, vasodilators (ACE inhibitors, angiotensin II receptor blockers [ARBs], or hydralazine/isosorbide dinitrate) are reintroduced first in concert with weaning of intravenous vasodilators. If β-blockers were held due to cardiogenic shock, they can be cautiously reintroduced in stable, euvolemic patients.

B. Chronic medical therapies. The goals of chronic medical therapy are to prolong survival and to improve symptoms and functional status. While there have been few recent major advancements in pharmacotherapy, the evolution of therapies with profound survival benefit for patients with heart failure represents a triumph of modern medicine.

1. **ACE inhibitors** have been shown to reduce morbidity and mortality among patients with systolic heart failure. The mechanism of long-term benefit is related to attenuation of the RAS. In addition, ACE inhibitors improve symptoms, clinical status, and exercise capacity.
   a. **Use of an ACE inhibitor is the first-line therapy for asymptomatic and symptomatic LV dysfunction.** The dose of the ACE inhibitor should be increased to the target doses demonstrating clinical benefits in trials (Table 8.4). Although there are theoretical benefits of using "tissue" ACE inhibitors (e.g., quinapril and ramipril), there are no data to support their preferential use. Relative contraindications include hyperkalemia (potassium > 5.5 mEq/L), renal insufficiency (creatinine > 3.0 mg/dL), and hypotension (systolic blood pressure < 90 mm Hg) and should be gauged on a case-by-case basis. It is not advisable to stop ACE inhibitors in patients with systolic heart failure, even when there is complete resolution of symptoms.

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

Drug	Start (mg)	Target (mg)	Max (mg)
ACE inhibitors			
Captopril (Capoten)	6.25–12.5 tid	50 tid	100 tid
Enalapril (Vasotec)	2.5–5 bid	10 bid	20 bid
Lisinopril (Prinivil, Zestril)	2.5–5 qd	20 qd	40 qd
Ramipril (Altace)	1.25–2.5 bid	5 bid	10 bid
Quinapril (Accupril)	5 bid	20 bid	20 bid
Fosinopril (Monopril)	2.5 or 5 bid	20 bid	20 bid
Benazepril (Lotensin)[a]	2.5 or 5 bid	20 bid	20 bid
Moexipril (Univasc)[a]	7.5 qd	30 qd	30 qd
Trandolapril (Mavik)	1 qd	4 qd	4 qd
Angiotensin receptor blockers			
Candesartan (Atacand)	16 qd	32 qd	32 qd
Valsartan (Diovan)	80 qd	160 qd	320 qd
Losartan (Cozaar)[a]	12.5–25 qd	50 qd	100 qd
Irbesartan (Avapro)[a]	150 qd	300 qd	300 qd
Telmisartan (Micardis)[a]	40 qd	80 qd	80 qd
Hydralazine/isosorbide dinitrate			
Hydralazine	25 qid	50–75 qid	100 qid
Isosorbide dinitrate	10–20 tid	20–80 tid	80 tid
Hydralazine–isosorbide dinitrate (BiDil)	25/37.5 tid	50/75 tid	50/75 tid
Aldosterone antagonists			
Spironolactone (Aldactone)	12.5–25 qd	25 qd	50 bid
Eplerenone (Inspra)	25 qd	50 qd	100 qd
Diuretics[b]			
Furosemide (Lasix)	10 qd (IV) 20 qd (po)	As required	1,000 qd (IV) 240 bid (po)
Bumetanide (Bumex)	1 qd	As required	10 qd
Torsemide (Demadex)	10 qd	As required	200 qd
Ethacrynic acid (Edecrin)	50 qd	As required	200 bid
Hydrochlorothiazide (HCTZ)	25 qd	As required	50 qd
Triamterene (Maxzide)	50 qd	As required	100 bid
Metolazone (Zaroxolyn)	2.5 qd	As required	10 qd

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure (*Continued*)

Drug	Start (mg)	Target (mg)	Max (mg)
β-Blockers			
Carvedilol (Coreg)	3.125 bid	25 bid	50 bid
Carvedilol phosphate (Coreg CR)	10 qd	40 qd	80 qd
Metoprolol succinate (Toprol XL)	25 qd	150–200 qd	200 qd
Bisoprolol (Zebeta)[a]	1.25 qd	10 qd	20 qd

ACE, angiotensin-converting enzyme.

[a]Not yet approved by the FDA for management of heart failure.

[b]Oral to IV conversion for furosemide is approximately 2:1. Oral to IV conversion for all other loop diuretics is 1:1.

b. After initiation, close monitoring for **hyperkalemia** and **renal insufficiency** is warranted.

(1) Hypotension is common, especially with first dose in a volume-depleted patient (e.g., after aggressive diuresis). This may require downtitration of diuretic doses and other vasodilator therapy. Due to its short half-life, captopril is usually used in the acute setting (e.g., after myocardial infarction).

(2) Renal insufficiency and **hyperkalemia** may occur when ACE inhibitors are given in the setting of volume depletion. **It is crucial to discontinue other nephrotoxic agents (e.g., nonsteroidal anti-inflammatory agents)** and ensure adequate kidney perfusion. **If BUN or creatinine levels increase by < 50%, ACE inhibitors can be continued safely; if they increase by > 50%, the ACE inhibitor dose should be halved; if they increase by > 100%, the ACE inhibitor should be held and switched to hydralazine and isosorbide dinitrate**. In the case of hyperkalemia, discontinuation of potassium supplementation and reducing the ACE inhibitor dose is usually effective.

c. Unique side effects of ACE inhibitors are cough and angioedema.

(1) The **cough** associated with ACE inhibitors is related to increased levels of bradykinin. It tends to be nonproductive and involuntary, rarely resolving with altering the dose or specific agent. All attempts should be made to identify an alternative cause of cough before discontinuing ACE inhibitors.

(2) Angioedema is a rare complication of ACE inhibitors (0.4%). It involves soft tissue edema of the lips, face, tongue, and, occasionally, the oropharynx and epiglottis. Angioedema typically begins within 2 weeks of initiation of ACE inhibitor therapy, but some patients present with this complication months to years after starting therapy. **Angioedema is an absolute contraindication to the use of any type of ACE inhibitor**.

2. Angiotensin II receptor blockers are specific receptor antagonists to the angiotensin II type 1 receptors. Although they theoretically provide more complete inhibition of the deleterious effects of angiotensin II than do ACE inhibitors, clinical trials have not demonstrated superiority in patients with heart failure. In general, ARBs are used and monitored in the same manner as ACE inhibitors. These drugs are reserved for patients who are ACE inhibitor intolerant, although in practice, they are used extensively. ARBs have a similar side-effect profile to ACE inhibitors (e.g., hypotension, renal insufficiency, and hyperkalemia). There appears to be a < 10% incidence of cross-reactivity for ACE inhibitor–associated

angioedema in patients receiving ARBs. However, consideration for the use of these agents must be weighed against the life-threatening nature of this complication. Whether ARBs can produce additional benefit when added to ACE inhibitors is still being debated. While the addition of an ARB is reasonable in patients on maximal medical therapy including target doses of ACE inhibitors and β-blockers with persistent symptoms, it is preferable to add an aldosterone antagonist in this setting. ARBs should not be added to an ACE inhibitor in the postmyocardial infarction period. Valsartan and candesartan are the best studied ARBs in patients with heart failure and should be used preferentially.

3. The combination of **hydralazine** and **isosorbide dinitrate** may provide a reduction in morbidity and mortality in selected heart failure patients. A fixed dose combination of hydralazine and isosorbide dinitrate (BiDil) demonstrated a substantial reduction in mortality when added to African American patients on optimal medical therapy including ACE inhibitors and β-blockers in the African-American Heart Failure Trial (A-HeFT). This combination is also indicated in patients intolerant of ACE inhibitors or ARBs. Side effects of hydralazine may include reflex tachycardia and rarely drug-induced lupus erythematosus.
4. **β-Adrenergic blockers (β-blockers).** Once considered to be contraindicated in patients with heart failure, β-blockers are now considered **first-line therapy for symptomatic patients with heart failure (NYHA class II, III, or stable class IV)** because of their consistent mortality benefits.
   a. It is often customary to start ACE inhibitors before β-blockers. This in part reflects the fact that all major β-blocker trials demonstrated their benefit on a background of therapy with ACE inhibition. Furthermore, while ACE inhibitors provide immediate beneficial hemodynamic effects, β-blockers may acutely result in diminished LVEF and cardiac output, which may be poorly tolerated in decompensated patients. In some instances (e.g., postmyocardial infarction and comorbid tachyarrhythmias), β-blockers may be particularly beneficial and should be started before or concurrently with ACE inhibitors. β-Blockers should generally not be initiated or titrated in the setting of acutely decompensated heart failure whether due to congestion or severely impaired cardiac output.
   b. Only carvedilol, bisoprolol, and metoprolol succinate have been approved for the medical treatment of chronic heart failure. Although atenolol and metoprolol tartrate are widely available and relatively inexpensive, there is no evidence to support their use in this population. β-Blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) in particular should be avoided.
   c. Relative contraindications to β-blocker therapy are a heart rate < 60 bpm, symptomatic hypotension, more than minimal pulmonary or systemic congestion, signs of peripheral hypoperfusion, a PR interval > 0.24 seconds, second- or third-degree AV block, a history of severe reactive airway disease, and peripheral arterial disease with resting limb ischemia. It is important to note that these are relative contraindications and particularly in the setting of reactive airway disease and peripheral arterial disease, the risks of β-blocker therapy must be weighed against their known benefits.
   d. Current recommendations are to start β-blockers in those who are clinically euvolemic. The general principle is to "start low and go slow." The initial dose is **slowly up-titrated every 2 to 4 weeks over 3 to 4 months to achieve target doses**, provided that the patient can tolerate side effects. It is imperative to maintain contact with the patient and adjust vasodilator or diuretic therapy during titration. It is not advisable to stop β-blockers in patients with a history of heart failure, even if there is complete resolution of symptoms and LV dysfunction.

e. Every effort should be made to achieve target doses, but it is clear that even low doses of these drugs provide benefit. While the degree of β-blockade appears to be the best predictor of long-term response, there is no evidence to support titration to a given resting heart rate.

f. Side effects are common when using β-blockers. Patients should understand that these drugs are used to prolong survival and often do not improve symptoms.

(1) Dizziness and **light-headedness** are common and may be related to hypotension or heart block. **Significant bradycardia** mandates dose reduction of β-blockers and other rate-lowering agents such as digoxin and amiodarone. **Advanced heart block** is a contraindication to β-blockers unless a permanent pacemaker is present. **Hypotension** can be managed by staggering the timing of drug administration. In practice, carvedilol (with its nonselective, α_1-blocking vasodilator effects) may have greater blood pressure lowering than selective β_1 agents such as metoprolol succinate. Both drugs are well tolerated in up to 70% of heart failure patients in our clinics.

(2) Worsening heart failure is still an important adverse effect of β-blockers. Intensification of diuretic therapy and dose reduction or slower titration may be necessary.

5. Aldosterone receptor antagonists have long been used as weak, potassium-sparing diuretics in patients with heart failure. The concept of incomplete blockade of the RAS by ACE inhibitors led to studies demonstrating significant pleiotropic effects of aldosterone antagonism in patients with advanced heart failure including antifibrotic effects and a reduction in sudden cardiac death. Results from the Randomized Aldactone Evaluation Study (**RALES**), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (**EPHESUS**), and now Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (**EMPHASIS-HF**) trial have demonstrated substantial mortality benefit in all stages of heart failure.

a. Aldosterone inhibitors are indicated in patients with NYHA class II symptoms and an LVEF ≤ 30% or NYHA class III or IV patients with an LVEF ≤ 35% already treated with ACE inhibitors and β-blockers and without significant renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (potassium > 5 mEq/L). Their use is also indicated in patients with postinfarction LV dysfunction (LVEF ≤ 40%) with any heart failure symptoms or diabetes mellitus.

b. In most cases, potassium supplementation should be reduced or discontinued. A basic metabolic panel should be checked within 1 week after initiation and monitored at regular intervals.

c. The most common and life-threatening side effect of aldosterone antagonists is **hyperkalemia**, which is particularly problematic in patients with concomitant **renal insufficiency** and diabetes mellitus (type IV renal tubular acidosis). **Painful gynecomastia** and **galactorrhea** may occur when using spironolactone.

d. While studies were typically performed with either spironolactone (RALES) or eplerenone (EPHESUS and EMPHASIS-HF), most experts believe that aldosterone inhibitors work via a class effect. Our approach is to initiate treatment with spironolactone due to its low cost and to transition to eplerenone only in the setting of significant gynecomastia.

6. Diuretics are used to maintain euvolemia and to improve symptoms, but their overuse can result in volume contraction, hypotension, and renal dysfunction.

a. An effective and inexpensive initial regimen includes 20 to 120 mg of furosemide taken orally each day. If furosemide doses higher than 120 mg/d are

needed, a second evening dose is typically prescribed. If this regimen fails, a daily dose of a thiazide diuretic such as metolazone or hydrochlorothiazide can be added 30 minutes prior to furosemide dosing.

   b. More expensive loop diuretics (e.g., torsemide and bumetanide) may have superior bioavailability and may be more effective in diuretic-resistant patients. Torsemide in particular may have unique benefits in the form of antifibrotic effects and minimization of the postdiuretic sodium retention that complicates the use of loop diuretics with shorter half-lives.

   c. The concept of **diuretic resistance** is evolving. Very often, this is contributed to by a failure to adhere to a low-sodium (< 2,000 mg/d) diet.

   d. The goal of chronic diuretic therapy is maintenance of euvolemia. This is most reliably achieved in patients who record daily weights and make physician-supported changes in diuretic dosing on an as-needed basis.

7. **Digoxin** is reasonable to use in patients with persistent heart failure symptoms despite appropriate medical therapy including ACE inhibitors and β-blockers and in patients with atrial fibrillation to control ventricular rate.

   a. Despite a fairly narrow therapeutic window, digoxin is safe and significantly reduces heart failure hospitalizations. A typical starting dose of 0.125 mg of digoxin daily is appropriate in patients with normal renal function.

   b. While the **Digitalis Investigation Group (DIG) trial** demonstrated the best clinical outcomes in patients with a serum digoxin concentration of 0.5 to 0.8 ng/mL, routine measurement of levels is not recommended in the absence of concern for toxicity.

8. **Other drugs of importance. Statins** should be used in the secondary prevention of atherosclerotic cardiovascular disease without regard to the presence of heart failure. There is no evidence of benefit in heart failure patients without coronary artery disease. While **aspirin** clearly prevents reinfarction and other vascular events in patients with known coronary artery disease, there is growing evidence from observational and randomized studies that it may worsen outcomes in heart failure patients via inhibition of prostaglandin synthesis and the resultant adverse hemodynamic and renal effects. This remains a controversial subject and the decision of whether to use aspirin or not should be made on a case-by-case basis. It should likely be avoided in patients without coronary disease who have refractory heart failure symptoms.

9. **Electrolyte supplementation** is among the most important and least emphasized areas in chronic heart failure management. Potassium depletion is common with diuretic therapy, whereas hyperkalemia can be caused by ACE inhibitors, spironolactone, or worsening renal insufficiency. In general, oral potassium supplementation is necessary to maintain serum potassium level in the ideal range of 4.0 to 5.0 mEq/L. Magnesium, thiamine, and calcium depletion are also common with long-standing diuretic therapy.

10. **Device therapy.** Chapters 55 and 56 provide detailed coverage of the indications, contraindications, and clinical issues related to implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT-D).

11. **Device monitoring.** Currently implanted electrical cardiovascular devices including ICD and CRT-Ds have the capability to remotely monitor a variety of electrophysiologic (e.g., heart rate variability, atrial arrhythmia burden and rate, ventricular tachycardia, % biventricular pacing, and average heart rate) and physiologic (e.g., patient activity and intrathoracic impedance) parameters with prognostic value. Several implantable hemodynamic monitors are under development for use in patients with advanced heart failure. How to best integrate device monitoring into a comprehensive approach to heart failure disease management remains to be established.

12. **Novel therapies**
    a. **ω-3 polyunsaturated fatty acids (PUFA)** have demonstrated an ability to reduce heart failure–associated morbidity and mortality and are now considered a reasonable intervention in patients with NYHA functional class II–IV symptoms by the Heart Failure Society of America. The **Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF)** trial demonstrated that 1 g/d of PUFAs resulted in a reduction in all-cause mortality. Recent data suggest that higher doses of PUFAs used in patients with milder heart failure symptoms due to nonischemic cardiomyopathy may result in a dramatic reduction in heart failure hospitalizations. The formulation of PUFA used is important, as there does appear to be a dose–response effect. Formulations containing at least 1 g of eicosapentaenoic acid and docosahexaenoic acid appear to be required for benefit.

C. Chronic nonmedical therapies

1. **Patient education and disease management programs** remain the most effective treatment strategy for patients with systolic heart failure. Sodium restriction (< 2,000 mg daily) and medication compliance are crucial to reducing hospitalizations. Control of blood pressure, serum glucose, and lipid levels should be emphasized. Some highly motivated patients can perform self-monitoring (i.e., daily weights and symptom assessment) and care (i.e., titration of diuretics) analogous to the chronic management of diabetes.
2. **Exercise training.** There is a clear body of evidence supporting the fact that exercise training improves endothelial function and functional capacity in patients with chronic heart failure. A supervised cardiac rehabilitation program should be advised when available.

D. Advanced therapies. Mechanical circulatory support and orthotopic heart transplantation are therapies currently reserved for patients with ACC/AHA stage D heart failure refractory to other therapies. These are described in detail in Chapters 12 and 13, respectively.

VIII. PROGNOSIS. Heart failure is associated with high rates of morbidity and mortality. In the Framingham Heart study, patients with heart failure had mortality rates four to eight times those of age-matched controls. A patient with NYHA class IV heart failure has a 1-year survival between 30% and 50%—a mortality rate comparable to that of advanced malignancies. Several risk scores have been developed to characterize the risk of heart failure hospitalization and mortality. The Seattle Heart Failure Model is perhaps the most widely used of these and incorporates demographic, clinical, pharmacologic, and laboratory data to provide accurate 1-, 2-, and 3-year survival estimates. Table 8.5 lists some common clinical predictors of poor survival in systolic heart failure.

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure

- Increased age
- Male gender
- Increased New York Heart Association functional class
- Severely reduced LV ejection fraction (< 25%), extensive cardiac remodeling (LVIDd > 65 mm), or reduced cardiac index (< 2.5)
- Concomitant diastolic dysfunction (particularly irreversible restrictive filling, stage IV diastolic dysfunction)
- Reduced right ventricular function

(Continued)

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure (*Continued*)

- Atrial fibrillation, elevated average heart rate, and reduced heart rate variability
- Low peak Vo_2 with maximal exercise (14 mL/min/kg), low heart rate response to exercise, increased peripheral chemosensitivity (ventilatory response to hypoxia), and high V_E/Vco_2
- High plasma BNP and N-terminal proBNP levels
- High levels of other cardiac and neurohormonal biomarkers including norepinephrine, renin, arginine vasopressin, aldosterone, endothelin-1, tumor necrosis factor, cardiac troponin T and I, and C-reactive protein
- Anemia
- Markers of reduced tissue perfusion:
  - Low mean arterial pressure
  - Renal insufficiency (creatinine clearance < 60 mL/min)
  - Attenuated response to diuretics and lack of hemodynamic and structural improvement (reverse remodeling) with medical therapy
  - Persistent signs of congestion and fluid retention or failure to normalize filling pressures (PCWP < 16 mm Hg, CVP < 8 mm Hg) with medical therapy
  - Serum sodium < 135 mg/dL
- Cardiac dyssynchrony (QRS > 130 milliseconds, left bundle branch block)
- Depression
- Nocturnal Cheyne-Stokes respiration and obstructive sleep apnea

BNP, B-type natriuretic peptide; CVP, central venous pressure; LV, left ventricular; LVIDd, left ventricular internal dimension at diastole; PCWP, pulmonary capillary wedge pressure.

ACKNOWLEDGMENTS: *The authors would like to thank Dr. Brian Hardaway for his contributions to earlier editions of this chapter.*

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USEFUL WEB SITES

Seattle Heart Failure Model: http://depts.washington.edu/shfm/
HFSA Heart Failure Guidelines: http://www.heartfailureguidelines.org/

CHAPTER 9

Evan Lau
W.H. Wilson Tang

Heart Failure with Preserved Ejection Fraction and Restrictive Cardiomyopathy

I. INTRODUCTION

A. Epidemiologic studies suggest that nearly one-half of patients with heart failure have a normal ejection fraction; the proportion in those hospitalized has been reported to range from 24% to 55%. The survival of patients with heart failure and preserved ejection fraction was once thought to be better than those with a decreased ejection fraction, but recent evidence suggests similar mortality rates.

Heart failure with preserved ejection fraction (HFpEF) has become the preferred term in the literature. This clinical entity has also been referred to as diastolic heart failure and heart failure with preserved ejection fraction. In this chapter, we focus on HFpEF and provide a brief discussion of the restrictive cardiomyopathies, which are important differential diagnoses in patients presenting with heart failure and a normal ejection fraction.

B. Definition. In the latest consensus document (by the European Working Group), HFpEF is defined as **(1) signs *and* symptoms of congestive heart failure; (2) left ventricular ejection fraction (LVEF) > 50% and a nondilated left ventricle (< 97 mL/m^2); (3) and evidence of elevated left ventricular (LV) filling pressures (Table 9.1)**. The last criterion is fulfilled in one of three ways: (1) invasive hemodynamics (pulmonary capillary wedge pressure [PCWP] > 12 mm Hg or left ventricular end-diastolic pressure [LVEDP] > 16 mm Hg), (2) unequivocal echocardiographic evidence of elevated LV filling pressure (E/e' > 15), or (3) equivocal echocardiographic evidence (E/e' > 8 but < 15) **and** a positive β-natriuretic peptide (BNP) (NT-BNP > 220 pg/mL or BNP > 200 pg/mL).

C. Pathophysiology. Most pathophysiologic abnormalities in patients with HFpEF are related to diastolic function. There are two major determinants of diastolic function: LV relaxation and LV stiffness. LV relaxation relates to the cellular mechanisms involved with actin–myosin crossbridge detachment. This requires intracellular calcium uptake into the sarcoplasmic reticulum, an energy- or adenosine triphosphate (ATP)-dependent process. Thus, ischemia, which would decrease intracellular availability of ATP, would prolong the time required for ventricular relaxation. LV stiffness relates to the compliance of the myocardial tissue. One determinant of this is the extracellular matrix. For example, increase in fibrosis and collage deposition, as in patients with hypertensive heart disease, leads to an increase in LV stiffness. Restrictive cardiomyopathies share a similar pathophysiology, with increased LV stiffness; however, these differ in the pathology underlying the change in ventricular compliance: extracellular amyloid deposition (cardiac amyloidosis); endocardial fibrosis from eosinophilic injury (Loeffler's endocarditis and endomyocardial fibrosis); intracellular lysosomal engorgement with sphingolipids (Fabry's disease); and others.

TABLE 9.1 Diagnostic Criteria for Heart Failure with Preserved Ejection Fraction

Clinical	Signs and symptoms of CHF
Left ventricular size and function	Nondilated (< 97 mL/m^2), EF > 50%
Hemodynamics (one of the following conditions must be met)	1. LVEDP > 16 mm Hg or PCWP > 12 mm Hg 2. E/e' > 15 3. If E/e' > 8 but < 15, then BNP must be elevated (NT-BNP > 220 pg/mL or BNP > 200 pg/mL)

CHF, congestive heart failure; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; BNP, β-natriuretic peptide.

A number of other pathophysiologic mechanisms have been implicated in patients with HFpEF. These include arterial stiffness, the relationship between arterial and ventricular stiffness, and chronotropic incompetence. The implications and relative importance of these mechanisms are still unclear.

II. CLINICAL PRESENTATION

A. Demographics. When compared with patients with systolic dysfunction, those with HFpEF tend to be older and are more likely to be female. Associated comorbidities include hypertension, diabetes, obesity, and chronic kidney disease.

B. Symptoms. Analogous to systolic dysfunction, diastolic dysfunction spans the spectrum of asymptomatic or subclinical disease to those with an established clinical syndrome of congestive heart failure. The symptoms of diastolic heart failure are indistinguishable from those of systolic heart failure. It may present with only exertional fatigue or dyspnea symptoms. Other patients will have more overt symptoms of left-sided (dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) and right-sided (edema and abdominal bloating) heart failure.

C. Signs. The signs of HFpEF are similar to those for systolic heart failure. One should look for the typical signs of right-sided (elevated jugular venous pressure, hepatic congestion, ascites, and lower extremity edema) and left-sided (rales) congestion. The presence of an S4 usually signifies a stiff left ventricle. As opposed to those patients with dilated cardiomyopathies, the location of the apical impulse is usually close to the midclavicular line, signifying a normal-sized ventricle. One should also pay attention to the strength of the impulse; in patients who do not have thick chest walls, a hypertrophied ventricle will often have a stronger impulse than the one without left ventricular hypertrophy (LVH). In patients with exertional symptoms alone, the above signs may not be present as the manifestation of their diastolic dysfunction may occur only during exercise.

In patients who present with impressive right-sided heart failure features, particularly ascites and hepatic congestion, restrictive cardiomyopathy or constrictive pericarditis or a combination should be considered. In these patients, clinical findings of multiorgan disease may indicate specific etiologies of restrictive cardiomyopathy. The cardiac examination may demonstrate more specific findings, including Kussmaul's sign: a paradoxical elevation in the mean jugular venous pressure during inspiration. This is classically described in constrictive pericarditis but can be seen in patients with restrictive cardiomyopathy as well as other pathologies (severe right ventricular failure and tricuspid regurgitation).

III. LABORATORY EXAMINATION AND BASIC INVESTIGATIONS

A. Electrocardiogram (ECG). ECG is an insensitive test for HFpEF. In this scenario, the most important finding is the amplitude of QRS voltage. The presence of elevated voltages and other criteria for LVH would support this as a possible cause of HFpEF. Conversely, in a patient who has increased wall thickness (typically by echocardiography) but has low voltage or infarction patterns on ECG (in this case, "pseudoinfarction"), infiltrative or restrictive cardiomyopathy should be considered.

B. Chest radiograph. The chest x-ray has few specific findings for HFpEF. In a posterior–anterior film, a normal-sized heart (lateral heart width < 2/3 of a hemithorax) may be a clue to a normal-sized left ventricle. Otherwise, the findings are the same as in systolic dysfunction: fluffy alveolar opacities (alveolar pulmonary edema), increased interstitial markings (increased interstitial fluid), pulmonary vascular redistribution (increased pulmonary venous pressures), and pleural effusions.

C. Specific laboratory investigations. BNP can be helpful in establishing the diagnosis of HFpEF (as stated above). When compared with patients with systolic heart failure, the elevation in BNP is generally lower. In patients with undifferentiated dyspnea, a normal BNP would argue against the presence of any heart failure syndrome.

IV. DIFFERENTIAL DIAGNOSIS.

For the purposes of our discussion, there are two clinical presentations to consider: exertional dyspnea (without findings of heart failure) and congestive heart failure. In a patient presenting primarily with exercise intolerance or exertional dyspnea, HFpEF should be considered, in addition to silent coronary artery disease, primary lung disease, anemia, etc.

In a patient who has an established clinical syndrome of heart failure, the differential diagnosis is typically narrowed following echocardiography. In a patient with preserved ejection fraction and a normal-sized left ventricle, HFpEF is the most likely cause. Other entities to consider include restrictive cardiomyopathies, hypertrophic cardiomyopathy (HCM), valvular heart disease, and constrictive pericarditis. Here, we primarily discuss HFpEF and restrictive cardiomyopathies.

A. HFpEF. Heart failure without another obvious cause, particularly in the context of advanced age, hypertension, obesity, chronic kidney disease, and diabetes, should lead to an early consideration for HFpEF. In such patients, myocardial ischemia may play some role in the manifestation of heart failure. This is particularly true for patients presenting with acute heart failure or flash pulmonary edema. In the absence of dynamic valvular regurgitation, ischemia leading to pulmonary edema usually denotes a large amount of myocardium at risk. This type of presentation certainly warrants aggressive investigation for obstructive coronary disease and when applicable, revascularization. Whether or not ischemia plays a role in patients with more subacute or chronic heart failure presentations is debatable.

B. Hypertrophic cardiomyopathy. The diagnosis of HCM is usually made in the presence of LVH, without concomitant hypertension or aortic stenosis. There are many manifestations of HCM, one of which is a "restrictive" phenotype that presents predominantly with diastolic heart failure. Distinction between HCM and other restrictive cardiomyopathies is not always clear, but it should be considered in certain scenarios: examples of this would include family members with HCM (particularly with an identified gene mutation), the typical reverse curve morphology of the interventricular septum, predilection for sudden death or ventricular tachyarrhythmia, and/or the presence of LV outflow tract obstruction.

C. Restrictive cardiomyopathies. Restrictive cardiomyopathies represent a group of disorders in which ventricular stiffness is increased by mechanisms/pathologies other than those related to the more garden-variety HFpEF patients. This may be a result of infiltrative, inflammatory, or metabolic diseases. The most common etiology of restrictive cardiomyopathy is cardiac amyloidosis.

1. **Cardiac amyloidosis.** Amyloidosis refers to the deposition of amyloid, or an abnormal protein, in organ tissue. There are several causes, and the following are the most important ones that manifest with cardiac involvement.
   a. Primary amyloidosis is caused by a primary hematologic malignancy. Monoclonal plasma cells produce a light-chain immunoglobulin; deposition into cardiac tissue is variable. Early stages show subclinical diastolic dysfunction (usually seen on echocardiography); later stages show severe restrictive cardiomyopathy. Traditionally, patients presenting with heart failure are felt to have a very poor prognosis with limited treatment options. However, anecdotal experience suggests that achieving remission of the malignancy with chemotherapeutics may positively impact patient's heart failure symptoms.
   b. Familial amyloidosis involves the inheritance of a gene that produces a mutant form of transthyretin, a serum protein carrier of thyroxine and retinol. The protein is produced in the liver and is deposited in the kidneys, the heart, and the nerves. Some centers may offer cardiac transplantation to selected patients.
   c. Senile amyloidosis is similar to familial amyloidosis in that it is related to the deposition of a pathologic variant of transthyretin. This usually occurs in older men.
2. **Endomyocardial fibrosis.** Endomyocardial fibrosis occurs in areas close to the equator, such as equatorial Africa, South America, and Asia. It usually affects children and young adults. Histologically it is characterized by granulation tissue, collagen, and extensive connective tissue lining the endocardium. It affects both ventricles (50%), left ventricle (40%), or isolated right (10%) ventricle and is associated with a 2-year mortality rate of up to 50%. Atrial fibrillation, mitral regurgitation, and thromboembolism are common. The response to medical treatment is poor. Endocardial decortication may be beneficial for those with New York Heart Association (NYHA) class III or IV symptoms. This technique has high operative mortality (15% to 20%), but when successful, reduces symptoms and may favorably affect the survival.
3. **Loeffler's (eosinophilic) endocarditis.** Loeffler's endocarditis is more commonly seen in temperate climates and generally occurs as part of the idiopathic hypereosinophilic syndrome. It typically manifests in middle age. Features include eosinophilia, restrictive cardiomyopathy, and nervous system and marrow involvement. Left ventricular mural thrombus frequently occurs. Aside from conventional heart failure medications (including anticoagulation), corticosteroids and hydroxyurea are useful treatment options. Surgery may be required for advanced fibrotic disease.
4. **Idiopathic restrictive cardiomyopathy.** Idiopathic restrictive cardiomyopathy is a diagnosis of exclusion. It usually occurs sporadically, but may be inherited with an autosomal dominant pattern in association with distal skeletal myopathy and occasionally a heart block. Echocardiography reveals near-normal LV dimensions and function, biatrial enlargement, and variable hypertrophy. Endomyocardial biopsy is unremarkable or shows nonspecific changes. The condition may manifest at any age throughout childhood or adult life. Survival time varies, with a mean survival of 9 years. Cardiac transplantation may be indicated in selected patients.
5. **Sarcoidosis.** Cardiac sarcoidosis can present with restrictive cardiomyopathy, but much more commonly it produces a dilated cardiomyopathy phenotype. Associated cardiac manifestations include conduction disease and ventricular tachyarrhythmia.
6. **Radiation carditis.** Radiation heart disease affects almost all components of the heart. Direct myocardial involvement, usually in the form of diastolic dysfunction, can be underappreciated, particularly when there is concomitant valvular, coronary, and/or pericardial disease. Separating the relative contributions of multiple pathophysiologic mechanisms in a given radiation patient is extraordinarily challenging. This is particularly evident when these patients go to surgery for

correction of valvular, coronary, and/or pericardial disease; suboptimal outcomes despite these corrections may be related to residual myocardial disease.

7. **Metabolic storage diseases** are characterized by intracellular deposition of substances within the myocyte, resulting in increased myocardial stiffness.
   a. **Hemochromatosis**, or iron overload, is listed as a storage disorder that can cause restrictive cardiomyopathy. However, when cardiac manifestations occur, the phenotype is usually a dilated cardiomyopathy.
   b. **Glycogen storage diseases.** Types II, III, IV, and V glycogen storage diseases may present with cardiac manifestations, usually as asymptomatic increase in LV thickness.
   c. **Gaucher's disease.** Gaucher's disease is caused by a deficiency in β-glucosidase, which leads to cerebroside deposition into multiple organs (spleen, liver, brain, bone marrow, lymph nodes, and heart). In the heart, this can cause increased ventricular thickness with diastolic dysfunction, LV systolic dysfunction, pericardial effusion, and valvular disease. This can be treated with enzyme replacement.
   d. **Fabry's disease** is a lysosomal storage disease caused by a deficiency in α-galactosidase (X-linked, recessive trait). This leads to glycosphingolipid accumulation in the kidney, the skin, and the heart. Cardiac manifestations include increased LV thickness, diastolic dysfunction, AV block, and mitral regurgitation. This can be treated with enzyme replacement.

V. DIAGNOSTIC TESTING

A. Echocardiography is the primary modality in evaluating a patient with a clinical syndrome of congestive heart failure. It is the modality of choice when evaluating LV diastolic function (Fig. 9.1). The most commonly used parameter in clinical practice is the Doppler interrogation of the transmitral flow pattern and tissue Doppler evaluation of annular velocity to determine the E/e' ratio. There are numerous other 2D and Doppler findings that are critical to diagnosis, including chamber size and wall thickness.

1. **Transmitral flow pattern.** In sinus rhythm, using pulsed wave Doppler across the mitral inflow tract generates two waves: the early E wave, corresponding to rapid ventricular filling as the mitral valve opens, and the A wave, which reflects atrial contraction. In healthy people younger than 50 years, E is larger than A (i.e., E/A ratio > 1). The E-wave deceleration time is the time from peak E inflow

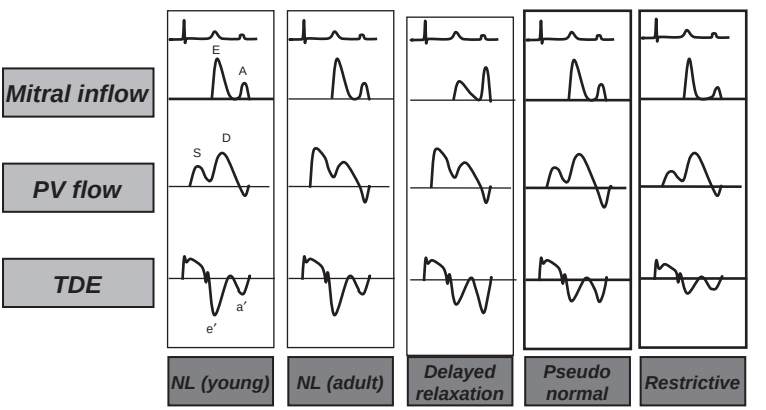

FIGURE 9.1 Patterns of diastolic function. PV flow, pulmonary vein flow; TDE, tissue Doppler (mitral annulus); NL, normal.

velocity to decay to zero. With age, hypertension, or ischemia, the viscoelastic properties of the ventricle decrease, and the E wave decreases in amplitude, has a gentler slope, and has a longer deceleration time. The atrial kick is proportionately greater, and E–A reversal occurs, with an E/A ratio < 1 (grade 1 diastolic dysfunction). With progression of diastolic dysfunction, left atrial (LA) pressure rises further to compensate, and the E wave becomes more prominent than the A wave (i.e., pseudonormalization or grade 2 diastolic dysfunction). As diastolic dysfunction progresses, the LV stiffness increases and the deceleration time shortens, reflecting rapid equilibration of LA/LV pressures during early diastole. When the deceleration time is < 160 milliseconds and the E/A ratio is > 2, the patient is considered to have grade 3 diastolic dysfunction.

Although the transmitral flow pattern is one of the primary ways of evaluating diastolic function, it has several limitations. It can be difficult to differentiate normal diastolic function from the "pseudonormal" pattern of grade 2 diastolic dysfunction, as they both have E/A ratios > 1. Because of this, American Society of Echocardiography guidelines have assigned stronger weight to other findings, including tissue Doppler imaging (TDI) and LA chamber size. Also, the transmitral flow pattern can often be difficult to interpret or uninterpretable in common scenarios, including atrial fibrillation, tachycardia (fusion of E and A waves), and mitral valve disease (MR ≥ 3+, mitral stenosis, and mitral prosthesis).

2. **Tissue Doppler imaging (TDI) of the mitral annular velocity.** In the evaluation of LV diastolic function, TDI is used to measure the velocity of movement of the septal and lateral aspects of the mitral annulus. The myocardial velocities have three main components: systolic wave (S'), early diastolic wave (e'), and the late diastolic wave (a'). In the earliest stages of diastolic dysfunction, the diastolic velocities of annular motion decrease. Normally, the lateral annulus tends to have higher velocities than the septal mitral annulus. Septal e' < 8 cm/s and/or a lateral e' < 10 cm/s suggests the presence of diastolic dysfunction.

   Unlike the transmitral flow pattern, there is no "pseudonormalization" pattern with annular velocity, making it easier to differentiate normal from abnormal diastolic function. The mitral annular TDI should be used with caution when other conditions coexist that may affect annular velocity independent of ventricular relaxation such as infarction of the septum or lateral wall or constriction with pericardial adhesion of the lateral wall.

3. **E/e'.** The ratio of the E velocity (obtained from the transmitral flow pattern) and the e' (obtained from TDI primarily of the lateral mitral annulus) can be used to estimate filling pressure, as there is a rough correlation with invasive hemodynamics (PCWP). This correlation is better with patients with depressed ejection fraction but is reasonable in patients with normal ejection fraction. Extreme values are most helpful. E/e' < 8 correlates with normal LV filling pressures. E/e' > 15 correlates with PCWP > 12 mm Hg; higher values are more specific for this. Unfortunately, there are many patients that fall into the intermediate zone, where E/e' > 8 but < 15. For these patients, the presence of elevated filling pressure cannot be determined by this method alone. Echocardiographic guidelines suggest using the presence of LA enlargement (LA volume index > 34 mL/m^2). Plasma BNP may be helpful in equivocal cases to determine whether or not there is corroborating evidence for elevated pressures.

   In patients with predominantly **exertional** symptoms, it may be useful to perform exercise echocardiography to determine the presence of diastolic dysfunction during exertion, particularly when this is not evident at rest. The sonographer should obtain LV images in multiple views following stress. Once the 2D information has been acquired, Doppler studies, including the transmitral flow pattern and the TDI of the septal and lateral mitral annulus, should be recorded. The diastolic abnormalities usually persist after tachycardia subsides, so

it is recommended that the data are recorded for a period of time following stress to reduce the likelihood of E- and A-wave fusion, which would make the E-wave velocity difficult to interpret. The most important parameter is E/e' following stress; if it is > 15, exertional increase in LV filling pressures is likely.

B. Invasive hemodynamic assessment. Invasive hemodynamic assessment is not routinely performed but is indicated when it is unclear whether elevated filling pressures are present on noninvasive studies. The PCWP (> 12 mm Hg) or LVEDP (> 16 mm Hg) should be measured. Other diastolic parameters, including Tau (τ), the time constant of isovolumic relaxation, are rarely measured in clinical practice.

When restrictive cardiomyopathy is considered, detailed hemodynamics may be of greatest value in directing management but are often less helpful in differentiating between possible diagnoses. Findings such as elevated and equalized diastolic pressures in four chambers (within 5 mm Hg), M pattern of the right atrial pressure waveform, "dip and plateau" of the ventricular diastolic pressures, equalization of LVEDP/RVEDP, and Kussmaul's sign occur in a number of pathologies, including restrictive cardiomyopathy, constrictive pericarditis, severe right ventricular failure, and severe tricuspid regurgitation.

C. Magnetic resonance imaging (MRI). In most patients with a diagnosis of HFpEF, cardiac MRI is rarely needed. It is useful to measure ventricular function, mass, and volumes when echocardiography is not diagnostic. It is also helpful in establishing or excluding specific conditions such as constrictive pericarditis, sarcoidosis, amyloidosis, or hemachromatosis (see Chapter 51).

D. Endomyocardial biopsy. Endomyocardial biopsy is used in selected circumstances, particularly when there is a high suspicion of a disorder whose diagnosis will profoundly impact management and prognosis. The most common indication is when cardiac amyloidosis is suspected. Biopsy in this setting can determine the presence of amyloid as well as differentiate between the different types of amyloid. The yield of endomyocardial biopsy for patchy diseases, such as sarcoidosis, is low.

VI. THERAPY. A handful of trials have attempted to look at the role of a variety of agents, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and β-blockers in patients with HFpEF. Unfortunately, **none of these trials have shown mortality benefit**. There has been variable effect of these medications on morbidity end points, including heart failure hospitalizations, symptoms, and LVH regression. The relevance of some of these trials is in question, as their entry criteria included patients with LV dilation and LVEF < 50%, likely a population quite different from our current conception of HFpEF patients. As the literature currently stands, no specific treatment has clearly demonstrated mortality benefit in patients with HFpEF. Treatment of hypertension should be in accordance with JNC VII guidelines (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Otherwise, treatment should be aimed toward symptomatic relief. The current ACC/AHA 2009 guidelines are listed in Table 9.2.

A. Salt restriction. Patients should be placed on a salt-restricted diet, usually 2,000 mg of sodium daily.

B. Diuretics. Diuretics should be used for symptomatic treatment of edema and pulmonary congestion. Chronic use of loop diuretics may lead to diuretic resistance; in this scenario, a thiazide- or potassium-sparing diuretic may be used to augment diuresis. For this indication, hydrochlorothiazide (usually 50 mg dosage, given once or intermittently) is effective within the first day. In extreme cases, patients may have significant bowel edema, rendering diuretics with poor oral absorption ineffective. In these patients, torsemide, which has a better oral absorption profile, is a reasonable option. Diuresis is often limited by the occurrence of prerenal azotemia. This is particularly common in those HFpEF or restrictive cardiomyopathy patients with

TABLE 9.2 Guidelines Adapted from ACC/AHA 2009 Update

Class I guidelines	
Control systolic and diastolic hypertension	Physicians should control hypertension in accordance with published guidelines (level of evidence: A)
Diuretics	Physicians should use diuretics to control pulmonary congestion and peripheral edema (level of evidence: C)
Ventricular rate should be controlled in the presence of AF	Physicians should control ventricular rate in AF (level of evidence: C)
Class IIa guidelines	
Coronary revascularization	In patients with CAD in whom ischemia is having an adverse effect on cardiac function (level of evidence: C)
Class IIb guidelines	
Restoration and maintenance of sinus rhythm	May be useful in improving symptoms (level of evidence: C)
Digoxin	Usefulness in reducing symptoms is not well established (level of evidence: C)
β-Blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists and controlled hypertension	Might be effective in minimizing symptoms (level of evidence: C)

AF, atrial fibrillation; CAD, coronary artery disease.

systemic disorders that have concomitant effects on the kidney, including hypertension, diabetes, or amyloidosis. In these cases, balancing congestive symptoms and azotemia can be challenging. On occasion, the patient may only achieve symptomatic relief after aggressive diuresis, even to the point where the blood urea nitrogen and/or creatinine are at levels higher than baseline values.

C. Angiotensin receptor blockers. Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme (CHARM-P) and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are two trials that evaluated the use of ARBs in the HFpEF population. I-PRESERVE is arguably the most relevant trial, as it enrolled patients with LVEF ≥ 45% and randomized patients to irbesartan versus placebo. This trial showed no difference in the primary end point of mortality and heart failure hospitalizations between the active and placebo groups. CHARM-P, which randomized candesartan versus placebo also failed to show a difference in a similar primary end point; the secondary end point of heart failure hospitalizations did seem to be reduced in the candesartan arm.

D. ACE inhibitors. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized patients with LVEF > 40% to perindopril versus placebo. The primary end point was not met, but after 1 year, there appeared to be a statistically significant decrease in heart failure hospitalizations in the active treatment arm.

E. Beta-blockers. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial randomized

nebivolol versus placebo in all-comers with congestive heart failure. Thirty-five percent of the patients had LVEF > 35%. In the overall trial, the nebivolol group demonstrated a significant decrease in the primary end point of mortality and heart failure mortality. In the subgroup analysis, the improvement appeared to hold in the group with LVEF > 35%.

F. Digoxin. The Digitalis Investigation Group (DIG) trial evaluated the use of digoxin in patients with heart failure. A subgroup of that trial examined patients with LVEF > 45%. There was no significant difference in mortality in this subgroup. There was a nonsignificant trend toward decreased heart failure hospitalizations but an increased trend toward unstable angina hospitalizations in those treated with digoxin.

G. Spironolactone. In patients with depressed ejection fraction, aldosterone antagonists have been demonstrated to have beneficial effects, likely working through antifibrotic mechanisms. There are two ongoing pivotal trials, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) and Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF), designed to evaluate the use of spironolactone in patients with HFpEF.

H. Sildenafil. Currently, there is no indication for phosphodiesterase 5 inhibitors in HFpEF, and mechanistic studies are ongoing.

VII. PRACTICAL APPROACH TO HFpEF AND RESTRICTIVE CARDIOMYOPATHIES

A. Exertional dyspnea only. In these patients, HFpEF should be on the differential diagnosis. Resting echocardiogram should be performed, with particular attention paid toward the presence of resting diastolic dysfunction. If this is absent, one can consider exercise echocardiography to determine exercise-induced diastolic dysfunction. Even in the presence of this diagnosis, specific treatment or change in management is uncertain.

B. Congestive heart failure. For patients presenting with overt signs of congestive heart failure, echocardiography should be used to narrow the differential diagnosis. In the absence of findings to support LV systolic dysfunction, valvular disease, or constrictive pericarditis, one should consider HFpEF as the diagnosis if there is evidence of diastolic dysfunction and elevated LV filling pressures. This is determined by unequivocal echocardiographic evidence ($E/e' > 15$); equivocal echocardiographic evidence ($E/e' > 8$ and < 15) + elevated BNP (NT-BNP > 200 pg/mL or BNP > 200 pg/mL); or invasive hemodynamics (PCWP > 12 mm Hg, LVEDP > 16 mm Hg). If the above findings are met and the patient fits the appropriate demographic (elderly, female, hypertension, chronic kidney disease, diabetes, and obese), then HFpEF is a reasonable diagnosis.

Restrictive cardiomyopathy should be entertained when patients present with significant right-sided heart failure symptoms (ascites, hepatic congestion, and severe edema), have multiorgan presentations (amyloidosis—orthostasis and renal failure; Fabry's—renal and skin involvement), or do not fit the typical demographic for HFpEF (young and no hypertension). In these patients, additional, focused testing should be performed to establish the etiologic diagnosis. This may include cardiac MRI and, in selected circumstances, endomyocardial biopsy.

C. Treatment. To date, there has been no class of medications that has been clearly established to have mortality benefit for patients with HFpEF. As it is believed that hypertension is the underlying etiology in most patients with HFpEF, blood pressure in these should be treated according to the established guidelines. However, particular agents do not have a priority as they do in patients with depressed ejection fraction, because they have not yet been demonstrated to have the same mortality and morbidity benefits. Otherwise, diuretics should be used for symptomatic benefit. The importance of concomitant obstructive coronary artery disease is debatable in asymptomatic patients. Likewise, revascularization should be reserved for patients in which ischemia is thought to play a major, adverse role in cardiac function (Table 9.2).

For those patients with restrictive cardiomyopathy, treatment should be directed toward the specific etiology. Oftentimes, there are no therapies that can reverse the severity of the restrictive cardiomyopathy, and the presence of congestive heart failure portends a poor prognosis. In these patients, diuretics are used for symptomatic relief. In selected candidates, cardiac transplantation may be entertained.

VIII. PROGNOSIS. HFpEF was once thought to confer a better prognosis than systolic dysfunction. Recent evidence demonstrates that the survival rates in both cases are similar. Twenty-two percent to 29% of patients with HFpEF die within 1 year of being discharged from their first hospitalization; 65% die within 5 years. Unlike patients with systolic dysfunction, no effective treatment has been found to improve this dismal outcome. The two groups have also been found to have similar rates of readmission for heart failure.

ACKNOWLEDGMENTS: *The authors thank Drs. Ryan P. Daly, John G. Peterson, and W.H. Wilson Tang for their contributions to earlier editions of this chapter. Special thanks to Dr. Allan Klein for his contributions to the figures of this chapter.*

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CHAPTER 10

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Hypertrophic Cardiomyopathy

I. INTRODUCTION. The generally accepted definition of hypertrophic cardiomyopathy (HCM) is left ventricular (LV) hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself could produce such hypertrophy. There are many causes of LV wall thickening (Table 10.1), including long-standing hypertension, aortic stenosis, and infiltrative cardiomyopathies. However, these diseases can typically be identified by noninvasive markers, such as a history of significant hypertension and severe aortic stenosis. Other diseases will be identified by multisystem organ involvement (e.g., skeletal muscle weakness in Danon disease). HCM can be identified by a constellation of abnormalities, including gene mutations, marked LV thickness (> 25 mm), the presence of left ventricular outflow tract (LVOT) obstruction, and/or the presence of systolic anterior motion (SAM).

While there are many alternative names for HCM, including *idiopathic hypertrophic subaortic stenosis, hypertrophic obstructive cardiomyopathy, and muscular subaortic stenosis*, the World Health Organization (WHO) recommends that HCM should be used. It is the preferred term because it does not imply that obstruction (present in only approximately 25% of cases) is an invariable component of the disease.

II. CLINICAL PRESENTATION

A. Natural history

1. The **histological features** of HCM are disarray of cell-to-cell arrangement, disorganization of cellular architecture, and fibrosis. The most common sites of ventricular involvement are, in decreasing order, the septum, apex, and midventricle. One-third of patients have wall thickening limited to one segment. These morphologic and histological features, which vary in phenotypic and clinical expression, give rise to the characteristically unpredictable natural history of HCM.
2. The **prevalence** of HCM is approximately 1 in 500, and the condition appears to be familial in origin. This makes HCM one of the most common genetically transmitted cardiovascular diseases. It is found among 0.5% of unselected patients referred for echocardiographic examination and is a leading cause of sudden death among athletes younger than 35 years.

B. Signs and symptoms

1. **Heart failure.** Symptoms, which include dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, and fatigue, are largely a consequence of two processes: elevated LV diastolic pressure caused by diastolic dysfunction and dynamic LV outflow obstruction.
   a. Events that accelerate heart rate, decrease preload, shorten diastolic filling time, increase LV outflow obstruction (i.e., exercise and tachyarrhythmias), or worsen compliance (i.e., ischemia) exacerbate these symptoms.

TABLE 10.1 Differential Diagnosis of Left Ventricular Wall Thickening

Long-standing hypertension
Athlete's heart
Aortic stenosis
Amyloidosis
Mitochondrial disease
Fabry disease
Friedreich's ataxia
Danon disease
Noonan syndrome
Pompe disease

   b. Between 5% and 10% of patients with HCM progress to severe LV systolic dysfunction, characterized by progressive LV wall thinning and cavity enlargement.

2. **Myocardial ischemia.** Myocardial ischemia occurs in obstructive and nonobstructive HCM.
   a. The **clinical and electrocardiographic** presentation is similar to that of ischemic syndromes in persons without HCM. Ischemia has been demonstrated with thallium perfusion studies, elevated myocardial lactate levels during rapid atrial pacing, and positron emission tomography.
   b. While epicardial artery obstruction is less common, **mismatch of supply and demand** due to thickened vessels and small vessel disease from increased collagen deposition in the intima and media are the most likely pathophysiologies of ischemia. Contributing factors include the following:
      (1) Small vessel coronary disease with decreased vasodilator capacity
      (2) Elevated myocardial wall tension as a consequence of delayed diastolic relaxation time and obstruction to LV outflow
      (3) Decreased capillary-to-myocardial fiber ratio
      (4) Decreased coronary perfusion pressure
3. **Syncope and presyncope** are usually a consequence of diminished cerebral perfusion caused by inadequate cardiac output. These episodes are commonly associated with exertion or cardiac arrhythmia.
4. **Sudden death.** The annual mortality rate for HCM is **1%**. Most deaths are sudden or unexpected.
   a. Not all patients with HCM are at equal **risk for sudden death**. Twenty-two percent of patients with sudden death have no symptoms. **Sudden death appears to be most common among older children and young adults**; it is rare in the first decade of life. Approximately 60% of deaths occur during periods of inactivity; the remaining deaths occur after vigorous physical exertion.
   b. **Arrhythmogenic and ischemic mechanisms** can initiate a clinical spiral of hypotension, decreased diastolic filling time, and increased outflow obstruction that often culminates in death.

III. PHYSICAL EXAMINATION

A. Inspection of the jugular venous system may reveal a prominent *a* wave that indicates hypertrophy and lack of compliance of the right ventricle. A precordial heave, representing right ventricular (RV) strain, can be found in persons with concomitant pulmonary hypertension.

B. Palpation

1. The **apical precordial pulse is usually laterally displaced and diffuse**. LV hypertrophy may cause a presystolic apical impulse or palpable fourth heart sound (S_4). A three-component apical impulse may occur, with the third impulse resulting from a late systolic bulge of the left ventricle.
2. The carotid pulse has been classically described as bifid. This **rapid carotid upstroke followed by a second peak** is caused by a hyperdynamic left ventricle. This is in contrast to the *parvus et tardus* pulse of fixed aortic or subvalvular aortic stenosis, which is a carotid pulse characterized by a delayed amplitude and upstroke.

C. Auscultation

1. S_1 (first heart sound) is usually normal and is preceded by S_4.
2. S_2 (second heart sound) can be normal or paradoxically split as the result of the prolonged ejection time of patients with severe outflow obstruction.
3. The **harsh, crescendo–decrescendo systolic murmur** associated with HCM is best heard at the left sternal border. It radiates to the lower sternal border but not to the neck vessels or axilla.
   a. An important aspect of the murmur is its **variation in intensity and duration** with ventricular loading conditions. During periods of increased venous return, the murmur is of shorter duration and is less intense. In the underfilled ventricle and during periods of increased contractility, the murmur is harsh and of a longer duration.
      (1) The **concomitant murmur of mitral insufficiency** can be differentiated because of its holosystolic, blowing quality that radiates to the axilla.
      (2) A soft, early, decrescendo, **diastolic murmur of aortic insufficiency** is found in approximately 10% of patients with HCM.
   b. **Maneuvers that affect preload and afterload** can be helpful in diagnosing HCM and differentiating it from other systolic murmurs (Table 10.2).

TABLE 10.2 Effects of Maneuvers or Pharmacologic Intervention to Differentiate Murmur of Hypertrophic Cardiomyopathy from Aortic Stenosis

Maneuver	Physiologic effect	HCM	AS	MR
Valsalva and standing	Decreases VR, SVR, and CO	↑	↓	↓
Squat and handgrip	Increases VR, SVR, and CO	↓	↑	↑
Amyl nitrite	Increases VR Decreases SVR and LV volume	↑	↑	↓
Phenylephrine	Increases SVR and VR	↓	↑	↑
Extrasystole	Decreased LV volume	↑	↓	No change
Post-Valsalva release	Increased LV volume	↓	↑	No change

AS, aortic stenosis; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; SVR, systemic vascular resistance; VR, venous return; ↓, decrease; ↑, increase.

TABLE 10.3 Molecular Genetics of Hypertrophic Cardiomyopathy

Gene symbol	Protein name	% of HCM caused by mutations in this gene
MYH7	Myosin heavy chain	40
MYBPC3	Myosin-binding protein C	40
TNNT2	Troponin T	5
TNNI3	Troponin I	5
TPM1	Tropomyosin 1	2
ACTC1	Actin, α	Unknown
MYL2	Myosin regulatory light chain 2	Unknown
MYL3	Myosin light polypeptide 3	1

HCM, hypertrophic cardiomyopathy.

IV. GENETIC ASPECTS OF HCM. Familial HCM is caused by mutation in one of the genes currently known to encode different components of sarcomere proteins or sarcomere-associated proteins that are inherited in an autosomal dominant manner (see Chapter 42). To date, familial HCM is known to be caused by over 1,400 different mutations in at least 8 genes (Table 10.3). Multiple analyses suggest that these common genetic subtypes are essentially phenotypically indistinguishable.

HCM genotype does not necessarily imply that subjects will have the phenotypic traits of HCM as variable penetrance exists, and environmental factors as well as modifier genes affect whether a particular subject will manifest HCM phenotypically.

Patients with an **identified pathogenic mutation** are at an increased risk for cardiovascular death, nonfatal stroke, or progression to NYHA functional class III or IV compared with patients with no identified mutations.

V. DIAGNOSTIC TESTING

A. Electrocardiogram (ECG). Although most patients have electrocardiographic evidence of disease, no changes are pathognomonic for HCM. Common electrocardiographic findings in HCM are listed in Table 10.4. These abnormalities do not correlate with disease severity or pattern of hypertrophy.

B. Echocardiography is the preferred diagnostic method because of its high sensitivity and low risk profile. It also allows characterization of the site of obstruction. Careful

TABLE 10.4 Electrocardiographic Findings in Hypertrophic Cardiomyopathy

Evidence of right and left atrial enlargement
Q waves in the inferolateral leads
Voltage criteria for large negative precordial T waves (associated with Japanese variant)
Left-axis deviation
Short PR interval with slurred upstroke

TABLE 10.5 Two-Dimensional, M-Mode, and Doppler Echocardiographic Findings in Hypertrophic Cardiomyopathy

Asymmetric septal hypertrophy (> 13 mm)
Systolic anterior motion of the mitral valve
Small left ventricular cavity
Septal immobility
Premature closure of the aortic valve
Resting gradients > 30 mm Hg
Provocable gradients > 50 mm Hg
Normal or increased motion of the posterior wall
Reduced rate of closure of the mitral valve in mid-diastole
Mitral valve prolapse with regurgitation
Maximal left ventricular diastolic wall thickness > 15 mm

assessment for conditions that can also cause secondary hypertrophy (aortic or subaortic stenosis, hypertension, infiltrative diseases, etc.) should also be done.

1. **M-mode and two-dimensional** echocardiographic findings in HCM are listed in Table 10.5. Close evaluation of the extent of hypertrophy should be done given the role of septal thickness in risk stratification for sudden cardiac death (SCD).
2. **Doppler echocardiography** enables recognition and quantification of dynamic LVOT obstruction as well as the response to various maneuvers.
   - **a.** Approximately one-fourth of patients with HCM have a resting pressure gradient between the body and LVOT; others have only provocable gradients.
   - **b.** The **diagnosis of HCM with obstruction** is based on resting peak instantaneous gradient > 30 mm Hg. These gradients correlate directly with the time of onset and duration of contact between the mitral leaflet and the septum, as occurs during SAM of the mitral leaflet. The earlier and longer the contact occurs, the higher the pressure gradient.
     - **(1)** Inducing obstruction and, therefore, gradients, in patients believed to have latent obstruction, can be accomplished with substances (e.g., amyl nitrite, isoproterenol, and dobutamine) or maneuvers (e.g., Valsalva maneuver and exercise) that decrease LV preload or increase contractility.
     - **(2)** Although the **clinical relevance of outflow obstruction has been debated, relief by means of surgical or pharmacologic technique is associated with clinical improvement** among many patients. Echocardiographic recognition of HCM and of HCM with outflow obstruction is, therefore, important.
   - **c. Recognition of mitral regurgitation (MR).** Echocardiographic evaluation of MR and the detection of valve anomalies may have a considerable effect on medical and surgical strategies in the care of patients with HCM.
     - **(1)** Approximately **60% of patients with HCM have structural abnormalities of the mitral valve**, including increased leaflet area, elongation of leaflets, and anomalous insertion of papillary muscles directly into the anterior mitral leaflet.

(2) When there is no leaflet abnormality, the degree of MR is directly related to the severity of obstruction and lack of leaflet coaptation.

C. Magnetic resonance imaging (MRI). Advantages of MRI in the evaluation of HCM include excellent resolution, lack of radiation, inherent contrast, three-dimensional imaging, and tissue characterization. Disadvantages are cost, length of study, and exclusion of patients with contraindications to exposure to magnetism, such as patients with implantable cardioverter–defibrillators (ICDs) or pacemakers.

1. MRI can detect **LV hypertrophy** missed by echocardiography, specifically in the anterolateral and basal LV free walls.
2. **Myocardial scar**, often found in patients with HCM, can be detected as **delayed hyperenhancement with gadolinium-contrast MRI**. Some small studies have suggested that the amount of hyperenhancement may be a predictor of SCD in this patient population.
3. Improved identification of MR, SAM, abnormal papillary muscles, and diastolic dysfunction.
4. Differentiate from alternative causes of LV thickening such as Fabry disease and amyloidosis.

D. Cardiac catheterization is used primarily for defining coronary anatomy before myectomy or a mitral valve operation and evaluation of ischemic symptoms. The characteristic findings of HCM during hemodynamic assessment are listed in Table 10.6 and illustrated in Figure 10.1.

1. Patients with normal coronary arteries may have **typical ischemic symptoms**. These symptoms may indicate myocardial bridges, phasic narrowing during systole, reduced coronary flow reserve, or systolic reversal of flow in the epicardial vessels.
2. **Left ventriculography** usually reveals a hypertrophied ventricle, prominent septal bulge, nearly complete obliteration of the ventricular cavity during systole, SAM, and MR. The **spadelike** appearance of the ventricular cavity is confined to ventricles with **apical involvement**.

VI. MANAGEMENT STRATEGIES

A. Priority of therapy. Effective therapy must include pathways for the **prevention and management of heart failure** caused by diastolic and systolic dysfunction, arrhythmias, ischemia, and failed medical therapy and the **prevention of sudden death**. The specific strategies for patients with HCM can be as heterogeneous as the clinical presentation and evolution. See Figure 10.2 for a simplified treatment algorithm.

TABLE 10.6 Hemodynamic Findings during Cardiac Catheterization

Subaortic or mid-ventricular outflow gradient on catheter pullback
Spike-and-dome pattern of aortic pressure tracing[a]
Elevated right and left ventricular end-diastolic pressures
Elevated pulmonary capillary wedge pressure
Increased V wave on wedge tracing[b]
Elevated pulmonary arterial pressure

[a]A consequence of outlet obstruction.
[b]May result from either mitral regurgitation or elevated left atrial pressure.

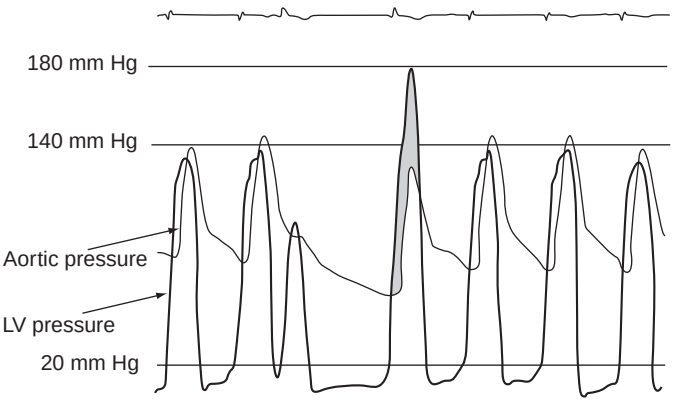

FIGURE 10.1 Severe increase in the left ventricular (LV) aortic gradient in the beat after a premature ventricular contraction (PVC) (Brockenbrough-Braunwald-Morrow sign) due to an increase in contractility and decrease in afterload during the post-PVC beat.

B. Medical therapy. Although never proven to reduce mortality in clinical trials, **β-blockers are the first-line therapy** for HCM, regardless of the presence of LV outflow obstruction.

1. **β-Blockers** improve symptoms and exercise tolerance. β-Blockers with additional α-blocking properties, such as carvedilol and labetalol, should probably not be used as first-line agents because of their additional vasodilatory properties.
   a. The mechanism of action of β-blockers is inhibition of sympathetic stimulation brought about by the negative inotropic and chronotropic properties of the drugs. β-Blockers diminish myocardial oxygen requirements and augment diastolic filling, which mitigate angina and the detrimental effects of LV outflow obstruction, respectively.
2. **Calcium channel blockers (CCBs)** are considered to be second-line agents that are also effective in reducing the common symptoms of HCM in patients who are intolerant of or have undergone unsuccessful treatment with β-blockers.
   a. **CCBs** have a negative inotropic effect and reduce the heart rate and blood pressure. They may also have beneficial effects on diastolic function by improving rapid diastolic filling, although possibly at the expense of higher LV end-diastolic pressures. The beneficial effects seem to be limited to the nondihydropyridines **verapamil** and **diltiazem** (Table 10.7). Conversely, dihydropyridine CCBs may be contraindicated (see below).
   b. Because of the unpredictable hemodynamic effects of their vasodilator properties, CCBs should be administered cautiously to patients with considerable outlet obstruction and elevated pulmonary pressures.
3. **Disopyramide**, a class 1a antiarrhythmic agent, may be an effective alternative or adjunct to β-blocker and CCB therapy. Its strong negative inotropic qualities coupled with its ability to suppress ventricular and supraventricular arrhythmias make it an effective treatment when marked outflow obstruction or arrhythmias are manifested. Potential disadvantages are anticholinergic properties, accumulation in patients with hepatic or renal dysfunction, the possibility of augmenting atrioventricular (AV) nodal conduction in the presence of atrial fibrillation, and

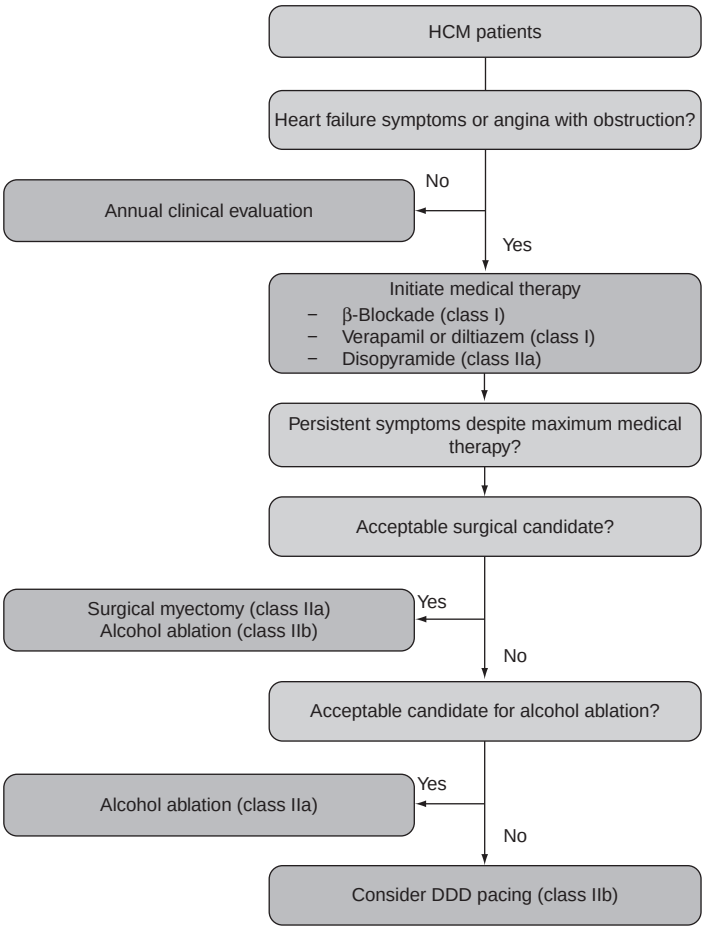

FIGURE 10.2 Management algorithm for hypertrophy cardiomyopathy. DDD, dual pacing for both chambers, dual chamber activity sensing, and dual response; HCM, hypertrophic cardiomyopathy. (Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831)

waning hemodynamic effects with time. It is because of these significant side effects that disopyramide is typically used in a very symptomatic patient when a more definitive procedure is being planned, such as surgical myectomy or alcohol septal ablation. It is not considered to be a long-term treatment for HCM.

4. **Dihydropyridine CCBs** (e.g., nifedipine and amlodipine), **angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers** should be avoided because they cause peripheral vasodilation, which may result in decreased LV filling and worsening of outflow tract obstruction.

TABLE 10.7 Pharmacologic Therapy for Hypertrophic Cardiomyopathy

Drug	Standard dose[a] (mg/d)
β-Blockers	
Metoprolol	50–200
Atenolol	50–100
Calcium channel antagonists	
Verapamil	120–360
Diltiazem	120–360
Antiarrhythmics	
Disopyramide	400–1,200
Amiodarone	200–400
Sotalol	160–320

[a]Doses can be increased to treat patients with persistent symptoms who have no evidence of an adverse response.

5. **Diuretics** should be used cautiously as high filling pressures are often necessary due to the stiff ventricle, and overdiuresis may reduce LV size and increase obstruction.
6. **Digoxin** should be avoided due to potential worsening of the LVOT obstruction secondary to the positive inotropic effect.
7. **Phenylephrine**, a pure α-agonist that causes vasoconstriction, can be considered in cases of refractory hypotension unresponsive to IV fluids. Pressors with positive inotropic effects, such as norepinephrine, dopamine, and dobutamine, can provoke LVOT obstruction and should be avoided.

C. **Nonpharmacologic treatment** is typically reserved for those patients with symptoms despite optimal medical therapy (Table 10.8). With severe symptomatic, nonobstructive HCM, cardiac transplantation remains the only option. However, persons with symptomatic obstruction and resting or latent gradient of 50 mm Hg or more despite optimal medical treatment are candidates for septal myectomy or alcohol septal ablation. Younger patients with gradients > 75 mm Hg and low surgical risk should be considered for septal myectomy even in the absence of symptoms.

1. **Septal myectomy** of HCM has been performed for more than 50 years and is the **procedure of choice for patients with progressive, drug-refractory functional limitation due to LVOT obstruction.**
   a. When performed by an experienced surgeon, septal myectomy is considered the most definitive treatment and is associated with a mortality rate of < 1% to 2%. It is effective in abolishing resting gradients in > 90% of patients, and most patients have long-lasting symptomatic relief. Enlargement of the LVOT has been found to reduce SAM, MR, LV systolic and end-diastolic pressures, left atrial pressure, and resting gradients. A retrospective study by Ommen et al. (1) from the Mayo Clinic published in 2005 demonstrated that patients who underwent myectomy had significantly longer survival and less incidence of SCD as compared with patients with obstruction who did not undergo surgery. In fact, after myectomy, survival was no different as compared with HCM patients who did not have obstruction at baseline.

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Invasive therapies—recommendations

Class I

Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.

Class IIa

Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: C)*

Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: B)*

Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction (> 50 mm Hg) for whom standard medical therapy has failed. *(Level of Evidence: C)*

When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional class III or IV). *(Level of Evidence: B)*

Class IIb

Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. *(Level of Evidence: B)*

The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (i.e., > 30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. *(Level of Evidence: C)*

Selection of patients for ICD

Class I

The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision making. *(Level of Evidence: C)*

ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. *(Level of Evidence: C)*

Class IIa

It is reasonable to recommend an ICD for patients with HCM with

1. Sudden death presumably caused by HCM in one or more first-degree relatives. *(Level of Evidence: C)*
2. A maximum LV wall thickness ≥ 30 mm. *(Level of Evidence: C)*
3. One or more recent, unexplained syncopal episodes. *(Level of Evidence: C)*

(Continued)

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy (*Continued*)

An ICD can be useful in select patients with NSVT (particularly those < 30 years of age) in the presence of other SCD risk factors or modifiers. *(Level of Evidence: C)*

An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers. *(Level of Evidence: C)*

It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation. *(Level of Evidence: C)*

Class IIb

The usefulness of an ICD is uncertain in patients with HCM with isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers. *(Level of Evidence: C)*

The usefulness of an ICD is uncertain in patients with HCM with an abnormal blood pressure response with exercise when in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction. *(Level of Evidence: C)*

Participation in competitive or recreational sports and physical activity

Class IIa

It is reasonable for patients with HCM to participate in low-intensity competitive sports (e.g., golf and bowling). *(Level of Evidence: C)*

Management of AF

Class I

Anticoagulation with vitamin K antagonists (i.e., warfarin, to an INR of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM. *(Level of Evidence: C)*

Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of β-antagonists and nondihydropyridine calcium channel blockers. *(Level of Evidence: C)*

Class IIa

Disopyramide (with ventricular rate-controlling agents) and amiodarone are reasonable antiarrhythmic agents for AF in patients with HCM. *(Level of Evidence: C)*

Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs. *(Level of Evidence: B)*

Maze procedure with closure of LA appendage is reasonable in patients with HCM with a history of AF, either during septal myectomy or as an isolated procedure in selected patients. *(Level of Evidence: C)*

Class IIb

Sotalol, dofetilide, and dronedarone might be considered alternative antiarrhythmic agents in patients with HCM, especially in those with an ICD, but clinical experience is limited. *(Level of Evidence: C)*

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; INR, international normalized ratio; LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow tract ; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia. From Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831.

2. **Alcohol septal ablation**—essentially a controlled infarction of the septum—is an alternative to septal myectomy. Because it has a greater risk than myectomy of complications including complete heart block and extensive myocardial infarction, it is **generally used in patients who are not candidates for surgical myectomy**. There are no randomized trials comparing myectomy and septal ablation.
   a. **Technique.** In the cardiac catheterization laboratory, a guidewire is advanced through the left main trunk to probe the first or second septal perforator, or both. An angioplasty catheter is placed in the proximal portion of the septal branch for vessel isolation. Ultrasonic contrast agents are infused in the cannulated perforator to define the area at risk for infarction. Infusion of 1 to 4 mL of absolute alcohol causes infarction in the zone of septal myocardium served by the cannulated septal branch. In most centers, a temporary ventricular pacing catheter is placed into the RV apex before performing the ablation, in order to manage any transient conduction abnormalities.
   b. **Results.** In the majority of patients, there is a marked immediate decrease in the LVOT gradient. This gradient response is thought to be triphasic: immediate reduction (due to stunning), early reappearance, and sustained fall by 3 months after the procedure (due to remodeling). Within this initial period, most patients attain good symptomatic relief. Risks of the procedure include high-grade AV block, coronary dissection, large anterior wall myocardial infarction, pericarditis, and electrical instability of the scar that forms as a result of the infarction. In a Scandinavian study by Jensen et al. of 313 alcohol septal ablation procedures performed in 279 patients, mortality was low at 0.6%, but 20% of patients required implantation of a pacemaker (2).
3. **Dual-chamber pacing** has been previously used in hopes of alleviating symptoms by altering the timing of septal contraction, but studies have not confirmed any long-term benefit. Dual-chamber pacing should only be considered in patients with medically refractory symptoms who are not candidates for septal reduction therapy.
4. **Special management considerations**
   a. **Atrial fibrillation**, which occurs in up to a third of patients with HCM, can have devastating consequences. Atrial fibrillation decreases diastolic filling time and causes the loss of atrial systole. These changes can lead to acute hemodynamic decompensation and pulmonary edema given the stiff left ventricle of patients with HCM. Because of the increased risk of thromboembolism, all patients with HCM-associated atrial fibrillation (be it paroxysmal or permanent) should be strongly considered for anticoagulation therapy. Aggressive efforts should be made to maintain sinus rhythm given the increased morbidity and mortality associated with atrial fibrillation in patients with HCM.
      (1) **Acute paroxysms** of atrial fibrillation are best managed with prompt cardioversion with transesophageal echocardiogram (TEE). Data concerning the prevention of recurrence are lacking, but the 2006 ACC/AHA Guidelines for the Management of Patients with Atrial Fibrillation suggest disopyramide or amiodarone as possible agents. Other class III agents, such as dofetilide, sotalol, and dronedarone, should be reserved for use in patients with an ICD given the paucity of safety data.
      (2) **Chronic atrial fibrillation** may be well tolerated if the heart rate is controlled with β-blockers or calcium channel antagonists.
      (3) **Maze or radiofrequency ablation.** For patients who do not tolerate atrial fibrillation and cannot be maintained in sinus rhythm, AV nodal ablation and implantation of a dual-chamber pacemaker may be an option. Other options including catheter ablation or combined surgical myectomy–maze can be considered.

b. Risk stratification for sudden death remains one of the more challenging aspects for the management of HCM, especially for primary prevention. Table 10.9 lists the established factors for risk stratification. Additional risk factors (e.g., scar burden as determined by late gadolinium contrast on MRI) continue to be evaluated. Currently, the only effective means of preventing SCD is an ICD.

(1) Placement of an ICD carries several potential complications, including but not limited to infection, inappropriate firing, lead fracture, and generator depletion. The **decision to implant an ICD is highly individualized** and should take into consideration that younger patients will be subject to a higher risk of device-related complications due to the longer time the device will be present.

(2) Patients who survive an episode that might have ended in sudden death, have sustained ventricular arrhythmias, or have multiple risk factors for sudden death should be strongly considered for an ICD.

(3) Selection of patients for ICD implantation as primary prevention is difficult. A retrospective multicenter study from the Minneapolis Heart Institute Foundation (3) evaluated the incidence of appropriate ICD interventions in patients with HCM who previously received a device for one of four SCD risk factors: history of HCM-related SCD in a relative younger than 50 years, "massive" LV hypertrophy, nonsustained ventricular tachycardia on Holter monitoring, and prior unexplained syncope (nonneurocardiogenic). The study concluded that one risk factor may be enough for consideration of ICD implantation. Of note, there was no control group in this study.

VII. SPECIAL CONSIDERATIONS

A. Athlete's heart

1. Differentiating HCM from hypertrophy of athletes. Failure to diagnose HCM places an athlete at undue risk for sudden death while incorrect labeling of HCM often leads to irrational treatments, unnecessary fears, and inappropriate recommendations concerning exercise. Diagnostic uncertainty is greatest when maximal diastolic LV wall thickness exceeds the upper limit of normal (12 mm) but is less than the defined lower limit of expected hypertrophy (15 mm) for HCM and in the absence of SAM and LV outflow obstruction.

a. Characteristics that **substantiate the diagnosis of HCM** include unusual patterns of hypertrophy, an LV end-diastolic diameter of < 45 mm, septal thickening > 15 mm, left atrial enlargement, abnormal diastolic function, family history of HCM, and abnormal LV filling.

TABLE 10.9 Risk Factors for Sudden Cardiac Death

Previous cardiac arrest
Sustained ventricular tachycardia
Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor
Left ventricular wall thickness > 30 mm
Family history of SCD
No change or a decrease in blood pressure with exercise
Syncope or near-syncope

SCD, sudden cardiac death.

b. Findings more consistent with the **hypertrophied heart of an athlete** are LV end-diastolic diameter > 45 mm, septal thickening < 15 mm, left atrial size < 4 cm, LV end-diastolic diameter > 45 mm, and a decrease in LV thickness with deconditioning.

Should differentiation not be possible, the patient should stop training: after several months, ventricular hypertrophy will typically regress in the athlete but will persist in a patient with HCM.

2. Participation in sports. HCM is the most common cause of sudden death in young athletes. It appears that intense exercise, with its resulting rapid changes in hemodynamics, can increase the risk of death as well. The European Society of Cardiology recommends prohibiting athletes with HCM from participating in competitive high school and college sports. These recommendations remain in force after medical or surgical intervention.

a. Athletes with HCM with or without obstruction who are younger than 30 years should **not** participate in competitive, aerobically demanding sports.

b. Participation in recreational sports should take into consideration the intensity of the activity (with the resulting fluctuations in hemodynamics) and the danger to the individual should impaired consciousness occur. For instance, activities such as rock climbing and weightlifting carry a higher risk of morbidity and mortality than activities such as golf and bowling.

B. Infective endocarditis (IE)

1. Predisposing factors. Gastrointestinal and genitourinary tract surgical procedures place patients at increased risk for bacteremia. It is unclear if dental procedures place patients with HCM at risk.

2. Pathophysiology. Bacterial seeding of endomyocardial lesions is caused by repeated trauma associated with hemodynamic and intrinsic valvular abnormalities.

3. Prophylaxis. Guidelines on the prevention of IE published by the AHA in 2007 question the practice of treating patients with HCM with antibiotics prior to dental procedures and recommend against it except in the setting of prior endocarditis. However, there are no large, prospective, randomized double-blind trials testing the efficacy of IE prophylaxis. Given the catastrophic consequences of endocarditis in patients with HCM, routine antimicrobial prophylaxis for IE should be weighed on an individual basis.

C. Yamaguchi's or Apical HCM

1. Clinical presentation. Patients experience chest pain, dyspnea, fatigue, and, in rare instances, sudden death.

2. Prevalence. Within Japan, apical HCM constitutes 25% of all cases of HCM. Outside Japan, only 1% to 2% of cases are associated with isolated apical hypertrophy.

3. Diagnostic testing

a. An **ECG** reveals giant negative T waves in the precordial leads and LV hypertrophy (Fig. 10.3).

b. Echocardiographic findings include the following:

(1) Localized hypertrophy in the distal left ventricle beyond the origin of the chordae tendineae

(2) Wall thickness in the apical region of at least 15 mm or a ratio of maximal apical to posterobasal thickness > 1.5

(3) Exclusion of hypertrophy in other parts of the ventricular wall

(4) No LVOT obstruction or gradient

c. MRI demonstrates localized hypertrophy to the cardiac apex. MRI is useful in the care of patients with poor echocardiographic windows.

d. Cardiac catheterization reveals a spadelike configuration of the LV cavity at end diastole and apical end-systolic LV cavity obliteration.

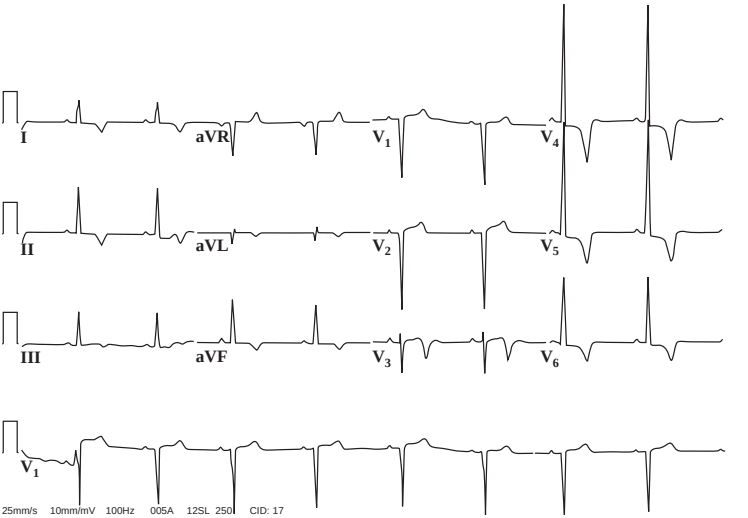

FIGURE 10.3 Electrocardiogram (ECG) in an apical hypertrophic cardiomyopathy (HCM, Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions.

4. **Prognosis** is favorable compared with that associated with other forms of HCM.
5. **Therapy.** Therapeutic efforts are limited to management of diastolic dysfunction with β-blockers and calcium channel antagonists.

D. HCM among the elderly

1. **Clinical presentation.** In addition to the signs and symptoms of other forms of HCM, hypertension is more common with HCM in the elderly population.
2. **Incidence.** Although the incidence is unknown, HCM among the elderly is probably more common than expected.
3. **Genetic aspects.** Reports have suggested that the delayed expression of mutations in the gene for cardiac myosin-binding protein C may play an important role in HCM in the elderly.
4. **Echocardiographic findings** for elderly patients (65 years or older) are compared with findings for young patients (40 years or younger) as follows:
   a. **Common findings**
      (1) LVOT gradient, both provocable and at rest
      (2) Asymmetric hypertrophy
      (3) SAM of the mitral valve
   b. **Differences pertaining to the elderly**
      (1) Less hypertrophy
      (2) Less RV involvement
      (3) Ovoid versus crescentic left ventricle
      (4) Prominent septal bulge (i.e., sigmoid septum)
      (5) More acute angle between the aorta and septum as the aorta uncoils with age
      (6) Management of HCM in the elderly is similar to that of other forms of HCM.
      (7) The **prognosis** is favorable compared with that for forms of HCM that occur at a younger age.

E. Screening of family members. With familial HCM, the dominant pattern of inheritance imparts a 50% chance of disease transmission to offspring.

- **a.** Serial 12-lead ECG and transthoracic echocardiogram are recommended **every 12 to 18 months in first-degree relatives** of HCM patients starting at age 12 during adolescence due to the propensity of HCM to worsen during growth spurts.
- **b.** Because of the possibility of late-onset phenotypic expression, **screening of first-degree relatives should continue into middle age**, but the frequency of screening can be scaled back to a minimum of every 5 years once full growth has been obtained.
- **c.** If genetic testing reveals a mutant HCM gene in the offspring, the high penetrance of the mutation imparts a > 95% lifetime risk of developing clinical and/or phenotypic evidence of disease. These gene-positive offspring should continue with serial examinations.
- **d.** First-degree relatives that are mutation negative have no risk of developing HCM and do not need further screening.

ACKNOWLEDGMENTS: *The author acknowledges the contributions of Eiran Gordeski, MD; Mark Robbins, MD; and A. Thomas McRae III, MD, to prior editions of this chapter.*

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CHAPTER 11

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Myocarditis

I. INTRODUCTION. Myocarditis is defined as an inflammatory infiltration of the myocardium with associated necrosis or degeneration, or both. The disease is also known as **inflammatory cardiomyopathy** (or myocarditis with cardiac dysfunction in the World Health Organization 1995 classification for cardiomyopathy). The incidence and prevalence of myocarditis are unclear; the syndrome is underdiagnosed because of the large number of asymptomatic cases. Myocarditis usually affects younger individuals; the median age of patients with lymphocytic myocarditis is 42 years.

A. Clinicopathologic classification of myocarditis is clinically oriented but not widely used.

1. **Fulminant myocarditis** (17%) usually has a distinct onset. It can result in either complete, spontaneous resolution or rapidly progressive deterioration and death due to severe cardiac compromise. Usually there are multiple active foci of inflammatory infiltrate on histology with complete resolution.
2. **Acute myocarditis** (65% of myocarditis cases) has an indistinct onset, with moderate cardiovascular compromise and incomplete recovery, often resulting in cardiac dysfunction or subsequent death. Histologically, there are active or borderline inflammatory infiltrates that resolve completely over time.
3. **Chronic active myocarditis** (11% of myocarditis cases) has a presentation similar to that of acute myocarditis, but the chronic form usually progresses to only mild or moderate cardiac dysfunction, occasionally with restrictive physiology. Histologic examination often shows ongoing fibrosis, suggesting chronic inflammatory changes.
4. **Chronic persistent myocarditis** (7% of myocarditis cases) has an indistinct onset, with nonresolving active or borderline inflammatory infiltrates seen on histologic examination. Usually, there is no cardiovascular compromise.

B. Histologic classification of myocarditis, also called the Dallas classification (1986)

1. Initial biopsy
   - **a.** Myocarditis: myocardial necrosis or degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrates or fibrosis, or both
   - **b.** Borderline myocarditis: inflammatory infiltrates too sparse or myocyte damage not apparent
   - **c.** No myocarditis: no inflammatory infiltrates or myocyte damage
2. Subsequent biopsy
   - **a.** Ongoing (persistent) myocarditis or fibrosis, or both
   - **b.** Resolving (healing) myocarditis or fibrosis, or both
   - **c.** Resolved (healed) myocarditis or fibrosis, or both

C. World Health Organization (Marburg Criteria, 1996). A minimum of 14 infiltrating leukocytes per mm (1), preferably T lymphocytes, and up to 4 macrophages may be included.

II. CLINICAL PRESENTATION

A. Signs and symptoms

1. Myocarditis can be **totally asymptomatic** or can manifest with **chest pain syndromes** ranging from mild persistent chest pain of acute myopericarditis (35% of cases) to severe symptoms that mimic acute myocardial infarction. Chest pain associated with coronary artery vasospasm may rarely occur in patients with myocarditis. Alternatively, chest pain may be more typical for pericarditis, suggesting pericardial involvement.
2. About 60% of patients may have antecedent arthralgias, malaise, fever, sweats, or chills consistent with viral infections (e.g., pharyngitis, tonsillitis, and upper respiratory tract infection) 1 to 2 weeks before onset.
3. The hallmark symptoms are those of **heart failure** (e.g., dyspnea, fatigue, and edema). In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis can progress rapidly and result in acute myocardial failure and cardiogenic shock. The diagnosis is usually presumptive, based on patient demographics and the clinical course (i.e., spontaneous recovery after supportive care).
4. In some instances, patients may present with **arrhythmia** in the form of syncope, palpitations caused by heart block (i.e., Stokes-Adams attack), ventricular tachyarrhythmia, or even sudden cardiac death. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias. Palpitations secondary to premature atrial or ventricular extrasystoles are common.

B. Physical findings. Patients often present with signs of **acute decompensated heart failure**, including an S_3 (third heart sound) gallop, central and peripheral edema, jugular venous distention, and tachycardia (see Chapter 8). An audible pericardial friction rub may accompany concomitant myopericarditis. Specific findings in special cases are as follows:

1. **Sarcoid myocarditis:** lymphadenopathy, also with arrhythmias, and sarcoid involvement in other organs (up to 70%)
2. **Acute rheumatic fever** (usually affects heart in 50% to 90%)**:** associated signs such as erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules **(i.e., Jones criteria)**
3. **Hypersensitive or eosinophilic myocarditis:** pruritic maculopapular rash and history of onset temporally related to initiation of potential culprit medications
4. **Giant cell myocarditis (GCM):** sustained ventricular tachycardia in rapidly progressive heart failure
5. **Peripartum cardiomyopathy:** heart failure developing in the last month of pregnancy or within 5 months after delivery (see Chapter 38)

III. LABORATORY EVALUATION

A. Inflammatory markers of myocarditis

1. **Complete blood count.** Leukocytosis is common (often lymphocytic), although the presence of eosinophilia may suggest hypersensitive (eosinophilic) myocarditis.
2. **Elevated acute phase reactants** such as erythrocyte sedimentation rates or ultrasensitive C-reactive protein are good monitors of clinical progression or response to therapy, but they have **low specificity** for myocarditis. Novel inflammatory markers under investigation include tumor necrosis factor-α, interleukins, interferon-γ, serum-soluble Fas, and soluble Fas ligand levels. Elevation of these markers portends a worse prognosis.
3. **Serum viral antibody titers** are usually increased fourfold or more acutely and gradually fall during convalescence. However, measurement of viral antibody titers is rarely indicated.
4. **Anticardiac antibody titers.** Because of their low specificity, measurement of anticardiac antibody titers (against sarcolemma, myosin, laminin, ADP/ATP

translocator, or β-adrenergic receptors) is not indicated (only 62% of myocarditis cases have titers ≥1:40).

B. Rheumatologic screening. Screening of antinuclear antibodies and rheumatoid factor is often indicated. Disease-specific testing is indicated if the following conditions are suspected:

1. Systemic lupus erythematosus: anti-dsDNA (reported positive anti-Ro/SSA and anti-La/SSB in lupus carditis in children)
2. Polymyositis: anti-Jo_1
3. Wegener's granulomatosis: c-ANCA (antineutrophil cytoplasmic antibody)
4. Scleroderma: anti-Scl_{70}

C. Serum cardiac enzymes (markers of myonecrosis)**:** creatinine kinase (myoglobin subfraction) is elevated in only 7.5% of patients with biopsy-proven myocarditis, whereas the cardiac **troponin I or T is elevated in at least 50% of patients** with biopsy-proven myocarditis (89% to 94% specificity and 34% to 53% sensitivity).

IV. DIAGNOSTIC TESTING

A. Electrocardiogram. The electrocardiogram often reveals sinus tachycardia, although the presence of nonspecific ST-segment and T-wave abnormalities may represent focal or global ischemia. Occasionally, the changes in electrocardiogram are suggestive of an acute myocardial infarction and may include ST-segment elevation. Pericarditis can accompany myocarditis and is often manifested in pericarditislike changes seen in electrocardiography. The sensitivity of the electrocardiogram for myocarditis is low (47%). In some cases, fascicular block or atrioventricular conduction disturbances and ventricular tachyarrhythmia may be hemodynamically significant.

B. Echocardiogram. A complete echocardiogram is standard procedure for patients with suspected myocarditis to exclude alternative causes of heart failure, detect the presence of intracardiac thrombi and associated valvular disease, and quantify the degree of left ventricular (LV) dysfunction to monitor response to therapy.

1. Occasionally, focal wall motion abnormalities and presence of pericardial fluid may prompt further workup or intervention.
2. Fulminant myocarditis is often characterized by near-normal diastolic dimensions and increased septal wall thickness, whereas acute myocarditis often has increased diastolic dimensions but normal septal wall thickness.
3. In a series of 23 patients with biopsy-proven myocarditis, significant reduction in right ventricular function was a powerful predictor of death or the need for cardiac transplantation.

C. Other imaging modalities

1. **Antimyosin scintigraphy (indium III monoclonal antimyosin antibody)** provides identification of myocardial inflammation, with a high sensitivity (91% to 100%) and negative predictive value (93% to 100%) but low specificity (28% to 33%).
2. **Gallium scanning** identifies severe myocardial cellular infiltration with high specificity (98%) but low sensitivity (36%).
3. **Gadolinium-enhanced magnetic resonance imaging (MRI)** is being used more frequently for diagnosis based on several small observational studies that have found up to 100% sensitivity and specificity depending on the protocol. In one study, MRI was also used for guiding biopsy to areas of focal increased uptake of gadolinium in patients with clinically suspected myocarditis with significantly higher diagnostic yield compared with those who did not have enhancing areas with which to guide the bioptome.

D. Coronary angiography. Cardiac angiography is often indicated to rule out coronary artery disease as the cause of new-onset heart failure, as the clinical presentation of myocarditis may mimic myocardial infarction (i.e., pseudoinfarct pattern), especially if there are focal wall motion abnormalities and localizing electrocardiographic changes.

V. ETIOLOGY. Up to 50% of all cases may not have a clear underlying cause (i.e., idiopathic cases).

A. Infective causes (Table 11.1)

1. Viral myocarditis. Cardiotropic viruses such as enteroviruses (specifically the coxsackie group B and echoviruses) may cause direct cardiotoxic injuries, cytokine activation, cytoskeletal damage, and autoimmune responses. However, data suggest that the incidence of myocarditis after infection is lower than previously projected. Viral myocarditis is often considered when accompanied with a clinical

TABLE 11.1 Causes of Myocarditis

Cause	Examples
Infectious causes	
Viruses	Enteroviruses, coxsackievirus A and B, echovirus, influenza virus, poliovirus, herpesviruses, adenovirus, mumps, rubella, rubeola, hepatitis B or C virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19
Rickettsia	Rocky Mountain spotted fever
Fungi	Cryptococcosis, aspergillosis, coccidioidomycosis, and histoplasmosis
Protozoa	*Trypanosoma cruzi* (Chagas disease) and *Toxoplasmosis gondii*
Helminths	Trichinosis and schistosomiasis
Bacteria	*Legionella*, *Clostridium*, streptococci, staphylococci, *Salmonella*, and *Shigella*
Spirochetes	*Borrelia burgdorferi* (Lyme disease)
Noninfectious causes	
Hypersensitive reaction	Eosinophilic myocarditis
Cardiotoxic drugs	Catecholamines, amphetamines, cocaine, chemotherapeutic drugs (e.g., anthracyclines, fluorouracil, streptomycin, cyclophosphamide, interleukin-2, trastuzumab [Herceptin]), and small pox vaccine
Collagen vascular diseases	Systemic lupus erythematosus (i.e., lupus carditis), Wegener's granulomatosis or Churg-Strauss syndrome, dermatomyositis or polymyositis, and scleroderma
Systemic illnesses	Sarcoidosis, giant cell myocarditis, Kawasaki disease, large-vessel vasculitis (e.g., polyarteritis nodosa and Takayasu arteritis), and inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease)
Acute rheumatic fever	
Bites and stings	Venoms of scorpions, snakes, wasps, and black widow spiders
Chemicals	Hydrocarbons, carbon monoxide, thallium, lead, arsenic, and cobalt
Physical injury	Irradiation, heatstroke, and hypothermia
Childbirth	Peripartum cardiomyopathy
Alloantigens	Posttransplantation cellular rejection

picture of recent febrile illness, often with prominent myalgias, followed by rapid onset of cardiac symptoms. However, direct proof is lacking (and often unnecessary), and many cases of idiopathic dilated cardiomyopathies have been attributed to antecedent viral myocarditis. Antiviral therapies have not proved to be useful.

2. **Chagas disease.** Cardiomyopathy caused by *Trypanosoma cruzi* in South and Central America, particularly in persons aged 30 to 50 years. It is estimated that 16 to 18 million persons are infected with *T. cruzi* in Latin America. Cardiac involvement usually appears decades after initial treatment and is the leading cause of death of persons aged 30 to 50 years in the endemic areas.
   a. **Diagnosis**
      (1) Serologic test results should be positive for at least two types of tests (i.e., indirect immunofluorescence, indirect hemagglutination, complement fixation, immunoenzymatic, and radioimmune assays).
      (2) Cardiac lesions diagnosed by in situ polymerase chain reaction methods of analyzing biopsies.
      (3) Typical electrocardiographic changes include right bundle branch block with left anterior hemiblock, premature ventricular complexes, T-wave inversions, abnormal Q waves, variable atrioventricular blocks, low QRS voltage, and sick sinus syndrome.
      (4) Echocardiographic findings include LV aneurysm with or without thrombi, posterior basal akinesis or hypokinesis with preserved septal contraction, and diastolic dysfunction.
   b. **Clinical presentation**
      (1) The acute and subacute phases (i.e., 4 to 8 weeks of acute inflammation) consist for the most part of local inflammation at the parasite entry site and flulike symptoms. Occasionally hepatosplenomegaly and lymphadenopathy occur, but concomitant meningoencephalitis is rare. These manifestations often result from pathogen-induced cytotoxicity and inflammatory responses. More than 90% of cases resolve in 4 to 8 weeks without therapy.
      (2) The chronic phase (up to 10 to 30 years after acute infection) manifests with symptoms of palpitations, syncope, chest pain, and, subsequently, heart failure. Approximately 5% to 10% of affected patients may develop direct acute-to-chronic progression.
         (a) Heart failure (predominantly right sided in advanced stages) may develop in 25% to 30% of those affected.
         (b) Cerebral or pulmonary thromboembolism may occur in 10% to 15% of those affected.
         (c) Concomitant megaesophagus or megacolon may develop.
         (d) Apical LV aneurysm and apical fibrosis may develop.
      (3) Chagas disease is highly arrhythmogenic.
         (a) Frequent, complex ectopic beats and ventricular tachyarrhythmia occur in 40% to 90% of affected patients, with sudden cardiac death occurring in 55% to 65%.
         (b) Bundle branch block occurs in 50% of affected patients, and bradyarrhythmia with high-grade atrioventricular block occurs in 7% to 8%.
         (c) Atrial fibrillation develops in 7% to 10% of affected patients.
   c. Antibiotic therapy aims to reduce parasitemia and prevent complications.
      (1) Benznidazole (5 to 10 mg/kg/d q12h for 60 days) or
      (2) Nifurtimox (8 to 10 mg/kg po q24h for 90 to 120 days)
3. **Human immunodeficiency virus (HIV)–related cardiomyopathy.** HIV disease has been recognized as an important cause of dilated cardiomyopathy, with an estimated incidence of 1.6%. HIV type 1 (HIV-1) virions appear to infect myocardial cells in patchy distributions, leading to cytokine activation and progressive tissue damage. Cardiac autoimmunity, nutritional deficiencies, and drug

toxicities (i.e., mitochondrial damage from zidovudine and vasculitis or coronary artery disease associated with highly active antiretroviral therapy regimens) are possible contributing causes. In addition, other known viral pathogens, including cytomegalovirus, Epstein-Barr virus, and coxsackievirus B, have been isolated from endomyocardial biopsy (EMB) specimens of HIV-positive patients with myocarditis in conjunction with HIV nucleic acid sequences, suggesting that opportunistic viral infections may play an important role in the pathogenesis of this type of cardiomyopathy.

B. Peripartum cardiomyopathy (see Chapter 38)

C. Giant cell myocarditis (i.e., pernicious myocarditis, Fiedler's myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis): This is a rare disorder with an unclear origin. The **hallmark feature is the presence of fused, multinucleated (> 20 nuclei) epithelioid giant cells of histocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes**.

1. GCM often presents with an **aggressive clinical course**, with progression over days to weeks. Rapidly progressive heart failure is the presentation in 75% of affected patients. Sustained ventricular tachyarrhythmia occurs in 29% of patients with GCM and atrioventricular block occurs in 50%.
2. The prognosis is **dismal without therapy**, but the disease is often refractory to standard medical therapy, with a 1-year mortality rate of up to 80% (median survival of 3 to 5 months from symptom onset).
3. Small observational series have suggested potential benefits of immunosuppressive therapy, and a randomized, prospective multicenter study is ongoing. Consideration for **early cardiac transplantation** is appropriate (71% 5-year survival after successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. A 20% to 25% rate of histologic recurrence in surveillance EMBs has been observed after transplantation.

D. Hypersensitive reaction (i.e., eosinophilic myocarditis). Eosinophilic endomyocardial disease (i.e., Loeffler's endomyocardial fibrosis, see Chapter 9) occurs as a major complication of idiopathic hypereosinophilic syndrome as a result of direct toxic damage caused by eosinophil granule proteins within the heart. Drug-induced eosinophilic myocarditis is independent of cumulative dose and duration of therapy.

The absence of peripheral eosinophilia does not rule out eosinophilic myocarditis. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent when known.

1. Medications that may cause eosinophilic myocarditis include the following:
   a. Antibiotics (e.g., ampicillin, chloramphenicol, tetracycline, and sulfisoxazole)
   b. Diuretics (e.g., hydrochlorothiazide and spironolactone)
   c. Anticonvulsants (e.g., phenytoin and carbamazepine)
   d. Other drugs (e.g., lithium, clozapine, and indomethacin)
   e. Tetanus toxoid
2. Collagen vascular diseases such as Wegener's granulomatosis or Churg-Strauss syndrome (i.e., allergic granulomatosis and vasculitis) may also lead to eosinophilic myocarditis.
3. Other causes include parasitic infection, drug hypersensitivity, and cellular rejection after cardiac transplantation, as well as postvaccinia myocarditis after small pox vaccination.

E. Systemic autoimmune disorders with myocarditis. Although the histologic appearance of myocarditis occurring as part of sarcoidosis, systemic lupus erythematosus, or polymyositis is similar to that seen in isolated myocarditis, the natural history is different. **Systemic causes of myocarditis often respond poorly to medical therapy and cardiac transplantation**, and their prognoses are often unfavorable. However, small retrospective surveys and case series have identified a significant decrease in mortality and improved clinical course among cardiac sarcoid patients treated with corticosteroids and other immunosuppression strategies.

VI. PROGNOSIS. On the basis of population studies, adults with myocarditis may present with few symptoms or with an acute toxic state of cardiogenic shock or frank heart failure (i.e., fulminant myocarditis). However, adults may present with heart failure years after the initial index event of myocarditis (up to 12.8% of patients with idiopathic dilated cardiomyopathy had presumed prior myocarditis in one case series).

A. Natural history and sequelae of myocarditis. The outlook is poor in the acute phase, regardless of clinicopathologic classification, but those surviving the acute phase have a more favorable prognosis (except for those with chronic active myocarditis).

1. Many patients may have **full spontaneous clinical recovery**, even after weeks of mechanical support (e.g., intra-aortic balloon counterpulsation and mechanical assist devices).
2. In the Myocarditis Treatment Trial, the 1-year mortality rate was 20% and the 4-year mortality rate was 56%.
3. In-hospital case series point to an 11-year survival rate of 93% for patients with fulminant myocarditis and 45% for nonfulminant myocarditis.
4. Evolution to dilated cardiomyopathy
   a. Up to one-half of patients with myocarditis develop subsequent cardiomyopathy over a range of 3 months to 13 years.
   b. Histologic evidence of myocarditis is seen in 4% to 10% of EMBs of patients with idiopathic dilated cardiomyopathy.
5. Severe heart block requiring permanent pacemaker placement occurs in 1% of patients.

B. Predictors for morbidity and mortality

1. Unfavorable factors for survival include extremes of **age** (i.e., very old or very young), **electrocardiographic abnormalities** (e.g., QRS alterations, atrial fibrillation, and low voltages), **syncope**, and **specific diagnoses** (e.g., peripartum cardiomyopathy and GCM).
2. Favorable factors for survival include normal ventricular function, shorter clinical history, and fulminant presentation at onset.

VII. TREATMENT

A. Heart failure management

1. Patients who present with myocarditis with acute dilated cardiomyopathy should be treated according to the current American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Heart Failure Society of America (HFSA) guidelines. Standard heart failure therapy consists of diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone antagonists. Studies have not been done to determine when and how to discontinue standard heart failure therapy in patients who recover LV function.
2. Because of its proarrhythmic properties in animal models, digoxin should be avoided.
3. Anticoagulation to prevent thromboembolic events is usually recommended in patients with apical aneurysm with thrombus (e.g., Chagas disease, atrial fibrillation, and prior embolic episodes).
4. Inotropic therapy is reserved for severe hemodynamic compromise, particularly in fulminant myocarditis.
5. Aggressive support with mechanical and surgical intervention is often indicated (see Chapters 8 and 12).
   a. Intra-aortic balloon counterpulsation for hemodynamic support and afterload reduction
   b. Mechanical assistive devices (left ventricular assist device)
   c. Extracorporeal membrane oxygenation

6. Early consideration for cardiac transplantation should be given, especially for patients with progressive, biopsy-proven GCM or peripartum cardiomyopathy. However, patients with myocarditis have increased rates of rejection and reduced survival after heart transplantation compared with those without myocarditis, and recurrent disease may affect the allograft.

B. Exercise restriction

1. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death, as shown in animal models.
2. Patients are usually advised to abstain from vigorous exercise for up to 6 months or longer after the onset of symptoms. The length of activity restriction can be based on recovery of LV function.

C. Arrhythmia management

1. Antiarrhythmics provide the first-line treatment using standard therapy such as β-blockers, amiodarone, and sotalol.
2. Implantable cardioverter–defibrillators are used for patients stabilized in the chronic phase with persistently low ejection fraction (EF) and for those with malignant arryhythmias that are refractory to medical therapy.
3. Permanent pacemakers are used for heart block or bradyarrhythmia.

D. Follow-up

1. Clinical follow-up should be close because persistent chronic inflammation may lead to dilated cardiomyopathy. Initially, 1- to 3-month intervals are used for drug and physical activity titration.
2. Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment after myocarditis.

E. Immunosuppressive therapy is reserved for refractory disease or biopsy-proven GCM. No benefits have been established for antiviral regimens or nonsteroidal antiinflammatory agents (see Section **VIII.B**). The most recent HFSA guidelines do not recommend routine use of immunosuppressive therapy in patients with myocarditis. More work is needed to identify patient cohorts who will benefit from tailored antiviral and immunosuppressive therapy.

VIII. CONTROVERSIES IN MYOCARDITIS

A. Endomyocardial biopsy

1. **Routine EMB confirmation of myocarditis is unnecessary.**
   a. EMB can be considered in those patients with a **rapid deterioration in cardiac function** of unknown etiology who do not respond to standard medical therapy.
   b. Incidence of biopsy-proven myocarditis in recent-onset, unexplained heart failure can be as low as 8% to 10%. Concerns have emerged that this is caused by low sensitivity of the Dallas criteria, and several recent trials of immunosuppressive therapy have utilized supplemental pathologic criteria to assess myocarditis, including upregulation of human leukocyte antigen, presence of virus, and anticardiac antibodies.
   c. **False-negative rates are high** (50% even in four or five biopsies) because of the small number of lymphocytes and difficulties in distinguishing cell types, with wide interobserver variability.
2. However, EMB may be considered in patients with the following conditions in which a diagnostic biopsy may provide information on prognosis and/or therapeutic possibilities (see Table 11.2):
   a. Rapidly progressive heart failure symptoms despite conventional therapy or new-onset frequent ventricular tachyarrhythmia or conduction disturbances
   b. Suspected specific causes of myocarditis (e.g., GCM, eosinophilic myocarditis, cardiac sarcoidosis, and vaccinia myocarditis)

TABLE 11.2 Relevant ACC/AHA Recommendations for the Role of Endomyocardial Biopsy

Scenario	Class of recommendation
New-onset heart failure of < 2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	I
Heart failure of > 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	IIa
Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia	IIa
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 weeks	IIb
Heart failure of > 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 wk	IIb
Unexplained ventricular arrhythmias	IIb

Adapted from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. *Circulation 2007;* 116: 2216–2233.

3. Although specificity is high (98%), sensitivity has been found in some series to be as low as 10% to 22%. It increases with multiple biopsies, but postmortem examinations have found that more than 17 specimens were needed to make the diagnosis with 80% sensitivity in proven myocarditis cases.
4. **Biopsy** for staging of myocarditis:
   a. Cell types include lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed.
   b. Amount of cells: none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3).
   c. Distribution: focal (i.e., outside of vessel lumen), confluent, diffuse, and reparative (i.e., in fibrotic areas).
   5. Other tests:
   a. Immunohistochemical staining to examine upregulation of major histocompatibility complex antigens and quantify inflammation, although rates of correlation with biopsy-proven myocarditis have not been consistent between studies.
   b. Approximately 12% to 50% of patients with acute or chronic myocarditis have persistent viral mRNA detected in biopsy samples.

B. Immunosuppressive therapy in acute myocarditis

1. Routine immunosuppressive therapy is not recommended because of the neutral findings from multiple trials, including the Myocarditis Treatment Trial and the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study. There is no Food and Drug Administration (FDA)–approved regimen for the treatment of acute or chronic myocarditis.

2. Considerations are reserved for patients with new-onset, rapidly deteriorating, advanced heart failure with suspicion of the following conditions:
   a. GCM is treated with combination therapy (Table 11.3).
   b. Eosinophilic or sarcoid myocarditis is treated with high-dose steroids.
   c. Specific therapy is used for underlying collagen vascular diseases, if present.

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study[a]

Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV × 2 d

Giant Cell Myocarditis study[b]

Cyclosporine: 25 mg po bid, increase by 25 mg increments to target level:

Monoclonal whole-blood immunoassay: 200–300 ng/mL

High-performance liquid chromatography assay: 150–250 ng/mL

Fluorescence polarization immunoassay serum-based polyclonal assay: 100–150 ng/mL

Dose reduction if renal dysfunction develops

Muromonab-CD3 (OKT-3): 5 mg IV qd × 10 d

Dose reduction if hypotension develops

Corticosteroid: methylprednisolone, 10 mg/kg IV qd × 3 d, followed by prednisone, 1–1.25 mg/kg with extended taper

Azathioprine: 200 mg po qd

Myocarditis Treatment Trial[c]

Corticosteroid/cyclosporine versus corticosteroid/azathioprine versus placebo (biopsy-proven myocarditis, LVEF < 45%, NYHA ≥ class II)

Oral prednisone: 1.25 mg/kg/d in divided doses × 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is 0.33 mg/kg/d at week 12; maintain oral dose until week 20 and then reduce dose by 0.08 mg/kg/wk until week 24; then off.

Oral cyclosporine: 5 mg/kg bid to achieve level of 200–300 ng/mL × 1 wk; adjust oral dose to achieve level of 100–200 ng/mL from weeks 2 to 4; adjust oral dose to achieve level of 60–150 ng/mL from weeks 4 to 24.

Immunosuppressive therapy for active lymphocytic myocarditis[d]

Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association.

[a]McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation.* 2001;103:2254–2259.

[b]Rosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. *Semin Arthritis Rheum.* 2000;30:1–16.

[c]Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med.* 1995;333:269–275.

[d]Frustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation.* 2003;107:857–863.

3. Studies are ongoing in an attempt to identify markers to predict favorable response to immunosuppressive regimens. A study of 112 patients with histopathologic acute lymphocytic myocarditis who failed to improve with conventional therapy and subsequently received prednisone and azathioprine found that one-half of the treated group improved, with EF rising from 26% to 47% and improvement in biopsy findings. Of those who failed conventional therapy, those patients who responded to immunosuppression were significantly more likely to have positive cardiac antibodies (90% vs. 0%) and less likely to have viral persistence when compared with nonresponders (14% vs. 85%).

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CHAPTER 12

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Nontransplantation Surgical Treatment for Chronic Heart Failure

I. INTRODUCTION. Even with optimal medical therapy, the morbidity and mortality associated with chronic heart failure (CHF) is significant. Fortunately, there are multiple possible surgical interventions available for these patients that may help to avoid or postpone the need for advanced salvage therapies and transplantation. Despite the improvement in surgical techniques and an enhanced understanding of the role of reconstructing structural abnormalities of the failing heart, safety and efficacy data are still limited for many of these procedures. Elective and planned procedures for advanced heart failure (e.g., revascularization, valvular surgery, left ventricular [LV] reconstructive surgery, and cardiomyoplasty) and urgent or bridging procedures (e.g., circulatory support devices and total artificial heart [TAH]) are discussed in this chapter. Surgical approaches to the management of heart failure must be accompanied by continued aggressive pharmacologic therapy.

II. SURGICAL REVASCULARIZATION FOR ISCHEMIC CARDIOMYOPATHY

A. Pathophysiology

1. Loss of coronary flow reserve in severe coronary artery disease leads to reduction in myocardial perfusion, tissue hypoxia, and myocardial dysfunction.
2. Myocardial infarction results in necrosis, scarring, and loss of contractile function. Sites distal to infarction undergo increased mechanical stress and adverse remodeling over time. Progressive ventricular dilation and impairment of systolic and diastolic function occur.
3. Chronic ischemia can decrease perfusion, leading to hibernation, repeated episodes of stunning, and recurrent infarction. The cardiomyocytes may shift metabolic states to hibernation. Thus, revascularization may help retain viability and recover function. Stunning and hibernation may be detected by various imaging modalities (see Chapter 50).
   a. **Stunning** is the loss of contractile function caused by a momentary total occlusion of blood flow with subsequent restoration of flow.
   b. **Hibernation** is the downregulation of myocardial function to match the chronic reduced blood flow. Hibernating cardiomyocytes manifest sustained glucose extraction, decreased glycogen content, and decreased contractile proteins and function.

B. Clinical significance

1. Heart failure, rather than angina or an acute coronary syndrome, is a common presentation of myocardial ischemia in patients with underlying cardiac dysfunction.
2. At least two-thirds of patients with cardiac dysfunction have evidence of epicardial coronary artery disease as the primary etiology. Coronary angiography is indicated when the suspicion of an ischemic cause for cardiomyopathy is high.

3. Some patients may have epicardial coronary artery disease superimposed on an underlying dilated cardiomyopathy. In this scenario, the presence of epicardial coronary artery disease may not necessarily explain the "degree" of depressed myocardial contractility. The role of revascularization remains unclear for these patients.

C. Recommendations

1. Most recently, the Surgical Treatment for Ischemic Heart Failure (STICH) trial reported that in patients with coronary artery disease amenable to coronary artery bypass grafting (CABG) and left ventricular ejection fraction (LVEF) < 35%, there was no difference in the trial's primary end point of all-cause mortality when treated with optimal medical therapy versus CABG. However, benefit was seen in the CABG group with respect to the secondary end point of cardiovascular death at follow-up. There were several limitations to this study: 30-day mortality was high in the CABG group and significant crossover occurred, both of which may have diminished the benefits of CABG in the primary intention to treat analysis.
2. Primary CABG should still be considered for patients with an LVEF > 15%, LV end-diastolic dimensions < 65 mm, distal vessels suitable for grafting, and evidence of a significant amount of ischemic or hibernating myocardium. These guidelines are arbitrary and many centers consider patients with more severe diseases.
3. Patients with hibernating myocardium and severe LV dysfunction who undergo CABG may achieve survival advantage comparable to those receiving cardiac transplantation (about 80% survival in 3 years).
   a. The potential for significant improvement in LV function and symptoms is assumed to be great enough to recommend revascularization when there are four or more viable segments of myocardium, representing approximately 31% of the left ventricle.
   b. Surgical revascularization of the patient with severe heart failure should generally be considered as part of a multifaceted approach, including evaluation for valve repair, ventricular reconstructive surgery, cryoablation for ventricular arrhythmias, and maze procedure or pulmonary vein isolation procedures for atrial dysrhythmias. To maximize the therapeutic benefit from this approach, aggressive complementary pharmacologic approaches are indicated postoperatively.

III. MITRAL VALVE SURGERY

A. Pathophysiology

1. As the ventricle fails, progressive dilation leads to abnormal geometry of the left ventricle, giving rise to mitral regurgitation (MR). MR results in progressive increase in volume overload of the left ventricle, progressive LV dilation, and further worsening of MR.
2. Other alterations of the annular–ventricular apparatus and ventricular geometry contribute to the pathogenesis of MR: papillary muscle ischemia or infarction, myocardial thinning and dilation, blunting of the aortomitral angle, widening of the interpapillary distance, and increased leaflet tethering leading to loss of the zone of coaptation.

B. Clinical significance and recommendations

1. Restoration of zone of coaptation by inserting an "undersized" annuloplasty ring may correct the MR and improve the LV geometry and cardiac output. However, mitral valve repair in ischemic cardiomyopathy ("ischemic MR") is less successful than in degenerative MR.
2. Subvalvular apparatus should be kept intact when possible.

3. In some patients, mitral valve surgery results in improved symptoms and measures of LV function and remodeling but not necessarily in improved survival.
4. In some patients, mitral valve repair with a figure-of-eight stitch (i.e., Alfieri approach) or the "edge-to-edge" technique may be used in addition to annuloplasty to secure the repair.
5. Mitral valve replacement is required in a minority of patients and may be associated with a significantly worse outcome.

IV. LV RECONSTRUCTIVE PROCEDURES

A. Pathophysiology

1. Laplace's law dictates that as the failing heart dilates, the intracavity radius increases and thus wall stress increases. The result is increased myocardial oxygen consumption and stimulation of adverse remodeling.
2. Surgical remodeling helps to decrease ventricular size and wall stress. Endoventricular circular patch plasty (EVCPP, also called the Dor procedure) is performed in patients with ischemic cardiomyopathy and significant areas of LV akinesis or dyskinesis. Partial LV resection, also called the Batista procedure, was performed in the past on patients with dilated, nonischemic cardiomyopathy. This was abandoned because of poor intermediate results and increased mortality, despite promising short-term outcomes.

B. Endoventricular circular patch plasty

1. Acute myocardial infarction leads to tissue necrosis, scar formation, followed by LV remodeling, leading to dilation and heart failure. The Dor procedure is suitable for patients with a left anterior descending artery territory scar or aneurysm with relatively preserved lateral and posterior LV wall function.
   a. It involves opening of the akinetic or dyskinetic scar and placement of a purse-string suture at the neck of the aneurysm. The residual opening may be closed with a Dacron patch, after which the ventriculotomy is closed by running sutures.
   b. This procedure is accompanied by CABG in >90% of cases. Additional valve and ablative surgical procedures are commonly performed.
2. Good candidates for EVCPP include patients with LV aneurysm (or large akinetic area), an increased LV end-systolic index, absence of scar in the circumflex territory, as well as good target tissue and viability for concomitant CABG. Assessment of the severity of MR is needed at the time of surgery, and mitral valve repair is performed in 30% to 50% of patients undergoing EVCPP.
3. EVCPP results in improved LVEF, end-diastolic and end-systolic volume indices for LV volumes, and improvement in New York Heart Association (NYHA) functional class.
   a. In a series of patients with advanced heart failure, the event-free survival rate was 98% at 1 year, 95.8% at 2 years, and 82.1% at 5 years.
   b. Independent predictors of mortality include higher preoperative NYHA class, lower LVEF (< 30%), higher end-systolic volume index, and remote asynergy.
   c. Interestingly, the STICH trial demonstrated that despite the reduced LV volume, there was no difference in symptoms, exercise tolerance, hospitalization, and death in patients who received CABG with surgical ventricular reconstruction versus CABG alone. On the basis of this trial, surgical ventricular reconstruction may not add any benefit to HF patients with documented ischemia who are on optimal medical management.

C. Partial LV resection (i.e., **Batista procedure**) involves the resection of myocardium at the posterolateral wall between the anterolateral and the posteromedial papillary

muscles in nonischemic cardiomyopathy, with or without mitral annuloplasty or mitral valve replacement. For the reasons previously stated, this procedure is no longer performed.

D. Dynamic cardiomyoplasty

1. The procedure involves the mobilization of the entire latissimus dorsi muscle to be used as a pedicle graft. The muscle is passed into the thoracic cavity through a window created by removing the left second rib. The muscle is wrapped around the heart and anchored posteriorly, adjacent to the right atrium and pulmonary artery, and anteriorly around the right ventricle.
   a. Sensing electrodes are placed epicardially on the right ventricle, and intramuscular stimulator electrodes are placed in the latissimus muscle.
   b. The muscle conditioning process takes place 2 weeks after surgery and involves the delivery of a single pulse with every other cardiac cycle for 2 weeks. The signal is then incrementally increased every 1 to 2 weeks for 12 weeks.
2. Cardiomyoplasty is believed to work by systolic augmentation of the failing left ventricle and the girdling effect of the muscle acting as an elastic constraint. This prevents LV dilation and improves symptoms, but has no proven survival advantages. Indeed, early mortality is high, especially in those with NYHA class IV status. This procedure is rarely performed now, and data are lacking on its long-term efficacy.
3. Approximately 80% to 85% of surviving patients show NYHA class improvement (mean 1.4 classes). A phase II multicenter FDA study demonstrated significant improvement in LVEF, LV stroke work, and stroke index.
4. Mortality of surgery for class III patients has been < 10%.
5. Hypertrophic obstructive cardiomyopathy is considered to be a relative contraindication.

V. CIRCULATORY SUPPORT DEVICES (I.E., MECHANICAL ASSIST DEVICES)

A. Background

1. Mechanical circulatory assistance is necessary for patients with hemodynamic compromise that are unlikely to survive without a transplant or advanced salvage therapies. Mechanical circulatory support devices may help bridge the patients to recovery or transplantation.
2. The types of devices include the following: intra-aortic balloon counterpulsation pump (IABP), extracorporeal membrane oxygenation (ECMO), univentricular and biventricular nonpulsatile and pulsatile ventricular assist devices (VADs), and the TAH.
3. The decision about which device to use is based on the predicted duration of use, the reversibility of the underlying condition that caused cardiogenic shock, need for single-chamber versus dual-chamber support, and the patient's size.

B. Patient selection

1. Mechanical support is generally indicated in patients who have an inability to maintain hemodynamic stability despite maximal pharmacologic support and who usually must meet criteria as candidates for cardiac transplantation:
   a. Systolic blood pressure < 75 to 80 mm Hg
   b. Cardiac index of < 1.5 to 1.8 L/min/m^2
   c. Pulmonary venous saturation < 50%
2. Indications for short-term circulatory support devices include the following:
   a. Cardiogenic shock after cardiac surgery
   b. Acute myocardial infarction with cardiogenic shock
   c. Acute (fulminant) myocarditis
   d. Cardiac arrest as a complication of interventional cardiac procedures (associated with high mortality and poor survival rates)

3. The 2006 International Society for Heart and Lung Transplantation (ISHLT) guidelines for cardiac transplant candidates:
   a. The most recent ISHLT recommendations give a class I recommendation to thoroughly evaluate other clinical risk factors prior to device implantation. For instance, an inverse relationship between outcome and age > 60 to 65 years has been reported. However, age by itself should not be a contraindication to implantation.
   b. Patients with serum creatinine > 3.0 mg/dL are at higher risk but may be considered candidates for implantation if renal failure is acute and recovery is likely (class I).
   c. Pulsatile intracorporeal devices should only be implanted in patients with body surface area (BSA) > 1.5 m^2.
   d. In patients with abnormal liver function tests secondary to right ventricular (RV) failure, biventricular support should be considered. In addition, biventricular support should be considered in those with irreversible pulmonary hypertension, RV failure, or multiorgan dysfunction.
   e. Active infection should be identified and treated before implantation.
4. If recovery is anticipated, the best option is to use the least traumatic, least complicated device for the individual patient. If recovery of ventricular function is not expected, patients should be considered for the use of a long-term implantable device.

C. Short-term devices

1. Intra-aortic balloon counterpulsation pump

   a. IABP should be placed percutaneously under fluoroscopy so that the tip is about 2 cm below the left subclavian. Height of the patient will determine the size of the IABP (40 cc balloon for the average-sized male). Swan-Ganz catheter and arterial line are encouraged and typically required for hemodynamic monitoring.
   b. IABP enhances coronary blood flow during inflation and decreases oxygen demand by reducing systolic pressure and LV wall stress during deflation. As a result, myocardial consumption and cardiac work are decreased while cardiac output is increased.
   c. Indications: Cardiogenic shock, severe mitral stenosis, decompensated critical aortic stenosis, ventricular septal defect/rupture, refractory ischemia, ischemia ventricular tachycardia, and bridge to definitive therapy.
   d. Contraindications: Hemodynamically significant aortic insufficiency (≥3+), abdominal or thoracic aortic aneurysm/dissections, severe coagulopathy, and sepsis.

2. Extracorporeal membrane oxygenation

   a. ECMO is an extracorporeal system that uses a centrifugal pump to drive blood from the patient to a membrane oxygenator system for carbon dioxide and oxygen exchange.
   b. The femoral artery and vein are cannulated for peripheral access, but the aorta and right atrium can be used as well. The blood is driven from the venous system to the pump and oxygenator and then back into the arterial system.
   c. The device requires systemic anticoagulation and may cause substantial trauma to blood components.
   d. ECMO has the advantage of providing oxygenation in the presence of severe pulmonary dysfunction resulting in hypoxemia. It can also unload both the right ventricle and left ventricle.
   e. The large number of possible complications makes ECMO suitable only for short-term use. It is generally used as a bridge to transplantation, VAD implantation, or other types of definitive therapy.

3. **Percutaneous LV support devices** (TandemHeart, Reitan Catheter Pump, and Impella Recover) are indicated only for short-term use (up to 5 days) and are similar to an IABP with respect to decreasing afterload and myocardial oxygen consumption. Unlike an IABP, these devices completely unload the ventricle rather than simply augmenting it.
   a. The Impella (LP2.5 and LP5.0) is a catheter-based system inserted through the femoral artery that provides hemodynamic support by an axial pump. Blood is pumped directly from the left ventricle to the ascending aorta.
   b. The Impella LP2.5 and LP5.0 can provide cardiac output support of up to 2.5 and 4.5 L/min, respectively, depending on the maximum speed of the rotor.
   c. The TandemHeart system is an extracorporeal continuous-flow centrifugal assist device that provides hemodynamic support via a left atrial-to-femoral bypass with up to a maximum cardiac output of 5.0 L/min. Oxygenated blood is withdrawn from the left atrium via a transseptal cannula and pumped into the femoral artery.
   d. Both systems require anticoagulation with heparin, prolonged supervision, and bed rest.
   e. Hemodynamic support from the Impella and TandemHeart can be continued for up to 5 days.
   f. These devices can potentially be used to support patients with acute MI with cardiogenic shock, patients with decompensated heart failure with myocarditis, and during high-risk percutaneous coronary intervention or valvuloplasty. The TandemHeart can be used for RV support if the catheters are placed so as to pump from the right atrium to the pulmonary artery.
   g. Recent trials for the Impella 2.5, namely, PROTECT I, ISAR-SHOCK (vs. IABP), AMC-MACH2 (vs. IABP), PROTECT II (vs. IABP), RECOVER II (vs. IABP), and EUROPELLA, demonstrated more favorable hemodynamics, reduction in infarct size, as well as reduction in 30-day major adverse cardiac event.
   h. There is a paucity of data regarding clinical outcomes and safety of patients with TandemHeart despite this being commercially available since 2004.
   i. See Table 12.1 for contraindications and potential adverse events.

TABLE 12.1 Contraindications to and Cautions with Percutaneous Left Ventricular Support Devices

Devices	Contraindications	Potential adverse events
Impella	Mural thrombus in the left ventricle, mechanical aortic valve, constrictive heart device, severe peripheral arterial disease, moderate to severe aortic stenosis (≥2+) and regurgitation (≥2+), severe aortic tortuosity, and calcification	Aortic regurgitation, aortic valve injury, arrhythmias, bleeding, tamponade, infection, stroke/transient ischemic attack, hemolysis, limb ischemia
TandemHeart	Moderate to severe aortic stenosis (≥2+) and regurgitation (≥2+), severe peripheral vascular disease	Bleeding, a femoral arteriovenous fistula, thromboembolic events, atrial septal defect, limb ischemia, wound infection, lymphocele, hypothermia

4. **Centrifugal pumps** such as the BioMedicus Biopump are extracorporeal and are commonly used for biventricular support for small patients (BSA ≤ 1.5 m^2) and also with ECMO.
   a. The nonpulsatile pump uses a spinning chamber to generate blood flow through rotating cones or by an impeller mechanism.
   b. The cannulation site for inflow into the pump is the femoral vein, right atrium, or ventricle, and the outflow cannula is placed in the femoral artery, axillary artery, or aorta. The lines are typically left between an unclosed sternum with only skin closure. This necessitates continuous supervision by trained staff and limits the devices to short-term use only.
   c. Heparin anticoagulation is needed.
5. **Pulsatile pumps** are extracorporeal, asynchronous pumps (e.g., Abiomed BVS5000) that are commonly used for right, left, or biventricular support.
   a. There are atrial and arterial cannulas. The atrial cannula is put into the right or left atrium, and the arterial cannula is in the aorta. The advantage over centrifugal systems is that subcostal lines allow sternal closure.
   b. The pump has an upper chamber and a lower chamber. The upper chamber is filled passively by continuous blood flow from the atrium. The lower chamber has two trileaflet polyurethane valves (i.e., inflow and outflow valves) and is designed to eject a stroke volume of approximately 80 mL.
   c. The pump is pneumatically driven by compressed room air and provides 4 to 5 L/min of pulsatile flow.
   d. Anticoagulation is recommended with heparin or warfarin sodium to lower the rate of thromboembolism.
   e. The disadvantages of this system are the lack of mobility and the lower flow rates achieved compared with the chronically implanted devices. A decision is made after 5 to 7 days of support, and if further mechanical support is needed, the Abiomed is removed and a chronic device is implanted.
   f. In small retrospective studies, outcomes in terms of successful bridge to transplantation, pre- and posttransplant mortality, and hospital discharge have not been shown to be significantly different between pulsatile and nonpulsatile devices.
6. **Axial flow pumps**
   a. Nonpulsatile rotary pumps are similar to centrifugal flow devices, but these generate the energy for acceleration of blood by deflecting the flow in the circumferential direction using impellers.
   b. They are smaller and less noisy than other devices, making them a good option for patients with a smaller BSA, as well as potentially decreasing the risk of infection due to smaller pocket size.
   c. Major complications include an increased tendency for pump thrombus, thus mandating anticoagulation and hemolysis.

D. Longer term implantable devices

1. Pulsatile implantable devices: Thoratec paracorporeal system, the CardioWest TAH, Novacor, and HeartMate XVE are currently used.
   a. Thoratec is a paracorporeal system that can be used for left, right, or biventricular support. Because the system is outside the body, it can be used in patients with BSA ≤ 1.5 m^2. However, this does limit mobility and flow rates (maximum stroke volume is 65 mL and flow rates can reach 7.2 L/min). Systemic anticoagulation is required.
   b. The CardioWest TAH is implanted after removal of the native heart and provides complete support. To accommodate the sizable device, patients must have a BSA > 1.7 m^2 and anteroposterior distance of the chest of > 10 cm. Systemic anticoagulation is required. This device has been approved for use as a bridge to transplantation. Another TAH, the Abiocor, is in the

investigational stages of development. This device is smaller and provides more mobility.

c. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized patients with end-stage heart failure who required ionotropic therapy but were ineligible for cardiac transplantation to a vented electric LVAD or optimal medical therapy. There was a 48% relative reduction in risk of death from any cause in the group that received LVAD compared with the medically treated group. The probability of device failure was 35% at 24 months, and 10 patients had the device replaced. The LVAD group had significant improvement in the quality of life over the trial, but the survival rates with permanent VAD are still far inferior to those for cardiac transplantation. This trial led to the approval of the HeartMate LVAD as a destination therapy in selected patients not eligible for transplant. The follow-up of outcomes in 42 patients who were implanted with destination therapy HeartMate LVAD since the REMATCH trial reveals improved survival rates at 1 month and 1 year and decreased rates of infection and adverse events compared with those found in the trial patients. Occasionally, patients who are implanted with the intent of destination therapy have improvement in conditions such as renal impairment or pulmonary hypertension that had precluded them from eligibility for transplantation earlier in their course and thus are suitable to be reevaluated for transplantation.

2. Axial flow pumps: Jarvik 2000, HeartMate II, and the MicroMed DeBakey.
   a. Produce continuous nonpulsatile blood flow using a small pump with rotor blades. Bearings of the rotor are in direct contact with the blood.
   b. MicroMed and HeartMate II have inflow cannulas that insert in the LV apex. The MicroMed and HeartMate II require a sternotomy and are implanted into a small abdominal pocket. The outflow cannula is attached to the descending aorta.
   c. Jarvik is intraventricular, which eliminates the need for an inlet cannula and eliminates inlet graft kinking, thrombosis, pannus formation in the inlet graft, and inlet obstruction by the septum or lateral wall of the heart. The outflow cannula is attached to the descending aorta. The small size allows the Jarvik to be surgically implanted through a left thoracotomy, with or without cardiopulmonary bypass, and it can be implanted in smaller adults or children.
   d. Axial flow pump is a true LVAD because it augments LV function. Optimal pump speeds are between 8,000 and 12,000 rpm. Native left ventricle is allowed to eject through the aortic valve, giving some pulsatility to the blood flow.
   e. Axial flow pumps can generate flows up to 5 to 7 L/min.
   f. Major complications are thromboembolic events due to inadequate blood flow in the ascending aorta giving rise to thrombus formation and the potential for embolic stroke.
   g. HeartMate II is the best studied LVAD and in turn has become the standard of care in VADs. Miller and colleagues demonstrated the safety and efficacy of the HeartMate II device when used as a bridge to transplantation. Further studies have demonstrated improved quality of life, functional status, and incidence of end-organ failure. Slaughter and colleagues reported a significant improvement in the quality of life and survival free from stroke and device failure with implantation of a continuous-flow LVAD when compared with a pulsatile-flow device for destination therapy.
   h. Data describing experience with the Jarvik 2000 showed that the cardiac index increased by 43%, capillary wedge pressure decreased by 52%, and

80% of the patients improved from NYHA class IV to I. No device thrombosis was reported.

E. Contraindications to VADs

1. Uncontrolled sepsis.
2. Aortic valve incompetence needs to be corrected before implantation of the VAD because it might lead to regurgitation of blood from the outflow cannula back into the left ventricle. Severe mitral stenosis should also be treated to avoid limiting the device output due to decreased native ventricular filling.
3. Preexisting mechanical prosthetic valves may need to be changed to bioprosthetic valves to obviate the need for anticoagulation before implanting the VAD.
4. Hypercoagulable states may preclude the placement of VADs not requiring anticoagulation.
5. Aortic aneurysm or dissection may affect the optimal placement of the outflow cannula in the ascending aorta.
6. Bleeding diathesis.
7. Patent foramen ovale or atrial septal defects need to be closed before implantation of VADs to prevent right to left shunting of blood and paradoxical emboli as the left side of the heart is decompressed.
8. Recent or evolving cerebrovascular accident.
9. Multiorgan failure.
10. Metastatic tumors are an absolute contraindication.

F. Predictors of poor outcomes after implantation of LVADs

1. Age
2. RV failure
3. Urine output < 30 mL/h
4. Central venous pressure > 16 mm Hg
5. Receiving mechanical ventilation
6. Prothrombin time is > 16 seconds; vitamin K is usually given in high doses preoperatively to patients being considered for VAD
7. Reoperation
8. Cachexia syndrome

G. Echo-Doppler assessment of VAD dysfunction. After the implantation of LVAD, intraoperative transesophageal echocardiography is used to assess the following factors:

1. Position of the inflow cannula at the LV apex. If the cannula is angulated toward the interventricular septum, inflow obstruction may result. The velocity of the flow across the inflow cannula is affected by multiple factors, including the flow generated by the device. However, if this velocity is > 2 m/s, then obstruction of the cannula should be considered and thrombus or another mechanical cause of obstruction should be sought.
2. Adequacy of LV decompression.
3. Aortic valve. If the flow rate through the LVAD is adequate, the aortic valve should not open. If there is significant aortic regurgitation, the aortic valve may have to be replaced.
4. Doppler interrogation of the inflow and outflow cannulas is done to exclude inflow and outflow valve dysfunction. Usually, the valves are unable to open, resulting in increased forward flow velocities.
5. Periodic follow-up echocardiographic evaluation is performed to exclude thrombus formation, inflow cannula valve dysfunction, or endocarditis and to evaluate LV systolic function.

H. Right ventricular assist device (RVAD)

1. Decisions for RVAD support (needed by 20% of patients) are based on hemodynamics after LVAD placement. However, implantation of long-term RVAD

devices is more labor intensive and requires long bypass times for placement, which carries higher morbidity.

2. Univariate predictors of RVAD use are small BSAs, female gender, preoperative circulatory support, preoperative mechanical ventilation, and high total bilirubin and aspartate transferase values. Preoperatively, hemodynamic indices of a low mean or diastolic pulmonary artery pressure or a low RV stroke work index (RVSWI < 400 mm Hg · mL/m^2) may indicate the necessity for RVAD after LVAD insertion.
3. Inotropic agents, volume infusions, and vasodilators are used to optimize pulmonary pressures and LVAD flows, with right heart hemodynamic values used as a guide. Aggressive diuresis is often necessary. If VAD flow remains < 2 L/min/m^2, an RVAD system may be placed with the inflow from the right atrium and outflow to the pulmonary artery.
4. Inhaled nitric oxide has gained popularity as a potential alternative to RVAD implantation. In one center, it reduced the need for RVAD support from 7% to 0%.
5. However, the RVAD use is associated with higher incidence of repeat sternotomy for bleeding, and the survival to transplantation is poor at 17%. It may be prudent for patients with risk factors for RV dysfunction to receive a biventricular assist device or a TAH from the start.

I. Complications of VADs

1. **Perioperative bleeding** increases with prolonged cardiopulmonary bypass times and causes excess fibrinolysis and platelet consumption. The degree of bleeding is intimately associated with RV failure and RVAD support. Transfusion is associated with infection and human leukocyte antigen immunization, which can increase the risk of hyperacute humoral rejection for a patient who goes on to transplantation. The use of LVADs increases this risk from 4% to 25% because of the need for perioperative transfusions. Leukocyte-poor blood products should be used to minimize this risk as much as possible.
2. **Gastroinstestinal bleeding** appears to be increased in continuous-flow LVADs in comparison with pulsatile ones, which is thought to be related to decreased levels of large multimers of von Willebrand factor and decreased platelet aggregation. Additional studies have also demonstrated increased incidence of arteriovenous malformations.
3. **Malignant arrhythmias.** There is a high incidence of malignant cardiac arrhythmia after device implantation. Causes include cardiomyopathy, ischemia, chamber dilation, use of inotropic agents, and focal abnormalities at the sewing ring.
4. **Infection.** Antibiotic prophylaxis should be administered to prevent infection. In the long term, there is a 25% to 45% rate of infection, which temporarily removes 20% of patients from the active transplantation list. The most serious infection is VAD endocarditis, which carries a 50% mortality rate and necessitates removal or replacement of the device.
5. **Embolic complications.** Thromboembolism still occurs at a high rate despite appropriate anticoagulation. The Thoratec device carries a 22% risk for cerebrovascular embolic events; the Novacor, 10%; and the HeartMate, 3% to 5% over a 1-year period.
6. **Aortic valve fusion and aortic insufficiency** may develop in patients with continuous-flow LVAD. In a small series of patients who received LVADs for bridge to transplant, examination of the explanted hearts demonstrated some degree of commissural fusion. Echocardiograms of those patients prior to explant demonstrated an increased incidence of aortic insufficiency during LVAD therapy. It is thought that the combination of valve fusion and continuous high pressure on the valve may contribute to the development of aortic insufficiency.

7. **RV failure** is responsible for significant morbidity and mortality after the institution of LVAD therapy. The complex pathophysiology resulting in RV failure includes RV myocardial dysfunction, changes in RV afterload, and interventricular dependence. Risks for the development include biochemical signs of congestions (elevated total bilirubin and aspartate aminotransferase/alanine aminotransferase), decreased RVSWI, increased pulmonary vascular resistance, female gender, smaller patients, and pre-LVAD support. Therapies include inotropic support as well as right-sided mechanical support.

J. Bridging to transplantation. Patients presenting with severe, refractory low cardiac output states need mechanical support as a bridge to transplantation. However, it has been recognized that major end-organ dysfunction affects the survival after transplantation. Mechanical support of the failing heart using short-term circulatory support devices can permit time to assess the reversibility of major organ dysfunction and allow a full workup for the suitability of cardiac transplantation. If the patient meets the selection criteria found in Table 12.2, full LVAD support can be implemented, and if the major organ dysfunction normalizes, a successful bridge to transplantation can be expected. It is expected that 70% to 80% of patients with an LVAD can be successfully bridged to transplantation, compared with 36% of patients managed on inotropic agents with or without an IABP, and 80% of these transplant patients will survive to be discharged from hospital. The percentage of transplant patients requiring mechanical support has increased steadily from 3% in 1990 to > 28% in 2004. Most LVAD implantations (75%) are performed with the strategy of bridge to transplantation. For those with biventricular failure that necessitates mechanical support, the options are combined RVAD and LVAD therapy or support with a TAH. The CardioWest TAH has been approved as a bridge to transplantation therapy.

TABLE 12.2 Patient Selection Criteria for Ventricular Assist Device Support as a Bridge to Cardiac Transplantation

1. Upper age consistent with successful cardiac transplantation, usually about age 70 y
2. Lower age limit determined by patient size large enough to accommodate a device
3. Suitable candidate for cardiac transplantation
4. Imminent risk of death before donor heart availability, usually with evidence of deterioration on maximal appropriate inotropic support and/or intra-aortic balloon support
5. General hemodynamic guidelines:
   a. Cardiac index < 1.8 L/min/m^2
   b. Systolic arterial blood pressure < 90 mm Hg
   c. Pulmonary arterial capillary wedge pressure > 20 mm Hg despite appropriate pharmacologic management
6. Adequate psychological criteria and external psychosocial support for transplantation and potentially prolonged LVAD support
7. Informed consent of patient or family
8. Absence of fixed pulmonary hypertension (pulmonary vascular resistance > 6 Wood units)
9. Absence of irreversible renal or hepatic failure (LVAD support not expected to reverse existing renal or hepatic dysfunction)

LVAD, left ventricular assist device.

Adapted from Kirklin JK, McGriffin D, Young JB. *Heart Transplantation.* New York, NY: Churchill Livingstone; 2002.

K. Bridging to recovery. Clinical recovery sufficient to allow mechanical support device removal has been reported in small numbers at a few institutions. In theory, chronic mechanical unloading may permit reverse remodeling with downregulation of collagen production and hypertrophy and decrease in circulating inflammatory cytokines. Likelihood of successful recovery is greater in those with acute nonischemic cardiomyopathy and much less likely in those with chronic dilated cardiomyopathy. Currently, approximately 5% of LVAD implantations are performed with the strategy of bridge to recovery.

ACKNOWLEDGMENTS: *The authors thank Drs. Bethany Austin, Kenneth Ng, and James O'Neill for their contributions to earlier editions of this chapter.*

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CHAPTER 13

Peter Zimbwa

Cardiac Transplantation

I. INTRODUCTION. Christiaan Barnard performed the first cardiac transplant in Cape Town in 1967. Since then, cardiac transplantation has become a well-established therapeutic option for a select group of patients with end-stage heart disease. It offers these patients, who have no other alternatives, a chance for extended survival and improved quality of life. Cardiac transplantation, however, should not be perceived as a curative procedure. Although the patient's primary problem of heart failure is alleviated by a successful transplantation, a new set of potential long-term complications arises primarily owing to the secondary effects of chronic immunosuppression.

Almost 89,000 heart transplants have been reported worldwide to the International Society for Heart and Lung Transplantation (ISHLT) registry since 1983 (1). As reporting to the ISHLT is voluntary, this number underestimates the actual number of cardiac transplants. There has, however, been a reduction in the number of annual heart transplants from a peak of > 4,000 in the mid-1990s to > 3,000 now. With an estimated additional 2,000 heart transplants per year not reported to the ISHLT, the total number of cardiac transplants likely exceeds 5,000 per year worldwide.

In the United States, the United Network for Organ Sharing (UNOS) reports a 10% reduction in cardiac transplantations over the same time period. UNOS is a national organization which, along with local organ procurement agencies, maintains organ transplantation waiting lists, initiates the evaluation of potential organ donors, allocates organs when a donor is identified, and compiles statistics annually on all aspects of the transplant process, including survival. Since 1990, the number of patients listed and waiting for a cardiac transplant in the United States has more than doubled. There is a shortage of donors, and each year 1.5 to 3 times as many patients are listed for cardiac transplantation as there are donors, so this problem is only going to escalate as the population gets older unless there is a significant increase in organ donation. The annual mortality rate while on the waiting list in 2001 was 15%, which has declined continually over the last decade, probably because of improved medical therapy for end-stage congestive heart failure and increased use of implantable cardioverter–defibrillator. As the annual number of cardiac transplantations has declined, wait times have continued to lengthen. The national median waiting time by UNOS status at listing from 2003 to 2004 data is as follows: 49 days for status 1A, 77 days for status 1B, and 308 days for status 2 patients. However, this can be misleading, as patients with different blood types such as blood type O wait significantly longer than other blood types such as blood type AB on average. A blood type O, status 2 patient could easily wait for > 2 years for a cardiac transplantation.

In the last 5 years (January 2005 to June 2009), the primary indication for adult cardiac transplantation has been nonischemic cardiomyopathies (53%), followed by ischemic cardiomyopathies (38%). Valvular heart disease (3%), adult congenital disease (3%), and retransplantation (3%) and miscellaneous causes (< 1%) account for the remainder (1). The average cardiac transplant recipient is male (77.1%), with an average age of 54 years, which reflects the demographics of the patients on the waiting list. The average donor age is 33 years, and donors > 50 years of age, which were rarely reported before 1986, now account for > 12% of all donors. Outcomes of transplantation continue to improve despite transplants performed on older, sicker patients. Recent data show that 44.5% of recipients were on intravenous inotropic support compared with 34% of recipients 10 years ago. Mechanical circulatory support is also more common, with > 31% of patients on some form of mechanical circulatory support at the time of transplantation, including 20.1% with a left ventricular assist device (LVAD) compared with only 15% on mechanical circulatory support (11% with an LVAD) 10 years ago (1). Survival rates post cardiac transplantation have improved from a median of 8.3 years in the 1980s to 13 years for those surviving to 1 year (1). The risk of death is highest in the first 6 months posttransplantation. Pretransplant factors associated with higher risk of mortality in the first posttransplant year include requiring mechanical circulatory support bridging to transplantation, congenital heart disease, and ischemic cardiomyopathy. Other risk factors include hemodialysis, mechanical ventilation, prior blood transfusion, and infection (1).

Because of the scarcity of donor organs and growing transplant waiting lists, it is crucial that cardiac transplant programs adequately screen and properly select potential transplant recipients. Effective use of this limited resource is essential to avoid "wasting" organs that become available for suboptimal recipients.

II. INDICATIONS FOR CARDIAC TRANSPLANTATION

A. Patients should be on optimal medical therapy for congestive heart failure, as recommended by the American College of Cardiology/American Heart Association guidelines, including angiotensin-converting enzyme (ACE) inhibitor, digoxin, diuretic, β-blocker, and spironolactone. If a patient is intolerant to an ACE inhibitor, she or he should be on an angiotensin receptor blocker.

B. Medically reversible causes of decompensated congestive heart failure should be excluded, including hypothyroidism, tachycardia-mediated cardiomyopathy, alcohol abuse, obstructive sleep apnea, hypertension, and medical noncompliance.

C. Surgically reversible causes of decompensated congestive heart failure should be excluded, including valvular heart disease, unrevascularized coronary artery disease with large territories of ischemia or viability, hypertrophic obstructive cardiomyopathy, and LV (left ventricular) aneurysm for which resection would improve overall cardiac hemodynamics.

D. Patients should be too ill or not candidates for cardiac resynchronization therapy. Alternatively, cardiac resynchronization therapy might have failed to improve symptoms or to halt progression of the underlying pathology.

E. If the previous criteria are met, indications for a cardiac transplant evaluation are as follows:

1. Cardiogenic shock requiring mechanical support (i.e., LVAD or intraaortic balloon pump counterpulsation)
2. Cardiogenic shock requiring continuous intravenous inotropic therapy for hemodynamic stabilization
3. New York Heart Association (NYHA) class III or IV congestive heart failure symptoms, particularly if progressively worsening
4. Recurrent life-threatening LV arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic drug therapy (usually amiodarone), or attempted catheter-based ablation, if appropriate
5. End-stage complex congenital heart disease without pulmonary hypertension
6. Refractory angina without potential medical or surgical therapeutic options

III. COMPONENTS OF A CARDIAC TRANSPLANT EVALUATION AND CONTRAINDICATIONS.

The purpose of a cardiac transplant evaluation is to exclude patients with medical and psychosocial comorbidities and to quantify the severity of a patient's cardiac functional impairment. Recommended investigations prior to a transplantation are summarized in Table 13.1 and exclusion criteria for cardiac transplantation are summarized in Table 13.2.

A. **Blood work.** A standard blood work includes a complete blood cell count; a complete metabolic panel, including hepatic enzymes and thyroid function tests; and blood typing and antibody screening. A serologic assessment should also be performed to determine a potential recipient's presensitization to cytomegalovirus (CMV), toxoplasmosis, hepatitis B and C viruses, and human immunodeficiency virus (HIV).

1. Patients who are anemic should have a thorough evaluation, including iron studies and a colon examination. Esophagogastroduodenoscopy and a hematologic evaluation, including a bone marrow biopsy, may also be necessary. Some patients may benefit from erythropoietin treatment to increase red blood cell counts without the need for transfusions that may expose the patient to further antigens.
2. Patients found to have an elevated serum creatinine level should undergo further evaluation to determine its relationship with low renal perfusion. A normal urinalysis result suggests the absence of renal parenchymal disease. This should include an assessment of cardiac hemodynamics and a renal ultrasound to assess renal parenchymal size and the presence of two kidneys without evidence of obstruction.
3. Patients found to have elevated hepatic enzymes should undergo further evaluation to determine the right-sided filling pressures and they should undergo a hepatic ultrasound scan. All patients should have their hepatitis B and C viral serologies assessed.
4. The patient's serum should be screened for antibodies against human leukocyte antigen (HLA) of B and T lymphocytes, drawn from community volunteers representative of the major HLA allotypes. These antibodies are collectively referred to as panel reactive antibodies (PRAs) and are often elevated in multiparous women and patients with multiple transfusions (often perioperatively in the past). Elevated PRA levels (> 10%) necessitate a pretransplant donor HLA crossmatch

TABLE 13.1 Recommended Evaluation prior to Transplantation

Complete history and physical examination
Laboratory investigations:
- Complete blood count with differential and complete metabolic panel
- Thyroid function studies (thyroid-stimulating hormone)
- Liver function panel, creatinine clearance
- Lipid profile, hemoglobin A1c, and urinalysis

Immunologic data:
- Blood type and antibody screen
- Human leukocyte antigen typing
- Panel reactive antibodies' screen

Serology for infectious diseases:
- Hepatitis (HBsAg, HBsAb, HBcAb, and HepCAb)
- Herpes group virus
- Human immunodeficiency virus
- Cytomegalovirus IgG antibody
- Toxoplasmosis
- Varicella and rubella titers
- Epstein-Barr virus IgG and IgM antibodies
- Venereal Disease Research Laboratory or Rapid Plasma Reagin

Cardiovascular investigations:
- Electrocardiogram, chest X-ray, and echocardiogram
- Exercise test with oxygen consumption
- Right and left heart catheterization
- Myocardial biopsy (if indicated, e.g., to rule out infiltrative process such as amyloidosis)

Vascular assessment:
- Carotid Doppler
- Peripheral vascular assessment (ankle–brachial index and/or duplex ultrasound)
- Abdominal ultrasound
- Ophthalmology examination (if indicated, e.g., to rule out diabetic retinopathy)

Cancer screening:
- Prostate-specific antigen (in men if indicated)
- Papanicolaou smear and mammography (in women if indicated)
- Colonoscopy (if indicated)

Psychosocial evaluation:
- Support system
- Substance abuse history (alcohol, tobacco, and drug use)
- Psychiatric history

Baseline investigations:
- Dental examination
- Bone density scan
- Pulmonary function tests

TABLE 13.2 Exclusion Criteria for Cardiac Transplantation

Irreversible pulmonary parenchymal disease
Renal dysfunction with Cr > 2.0–2.5 or CrCl < 30–50 mL/min (unless for combined heart-kidney transplant)
Irreversible hepatic dysfunction (unless for combined heart–liver transplant)
Severe peripheral and cerebrovascular obstructive diseases
Insulin-dependent diabetes with end-organ damage
Acute pulmonary embolism
Irreversible pulmonary hypertension (PVR > 4.0 Wood units after vasodilators)
Psychosocial instability or substance abuse
History of malignancy with probability of recurrence
Advanced age (> 70 y)
Severe obesity
Active infection
Severe osteoporosis

PVR, pulmonary vascular resistance.

and increase the likelihood of it being positive, making waiting times longer and transplantation more difficult. If a patient has elevated PRA levels, an attempt to reduce them before transplantation with intravenous immunoglobulin, plasmapheresis, mycophenolate mofetil (MMF), or cyclophosphamide, alone or in combination, may be considered. Traditionally, each potential recipient would undergo a thorough HLA tissue typing analysis, including a cytotoxicity assay for assistance in matching donor hearts. In this assay, random donor lymphocytes are incubated with recipient sera. Complement-dependent antibody-mediated cytolysis identifies potential donor-specific antibodies present in that recipient. Currently, most programs use flow cytometry to assess preformed antibodies, rather than cytotoxic assays. This allows for the detection of weaker interactions and provides a wider, more efficient screening process.

B. Imaging

1. All patients should undergo coronary angiography or a functional assessment for ischemia and viability. If ischemia or viability can be demonstrated, consideration should be given to percutaneous or surgical revascularization.
2. Bilateral carotid ultrasound scans should be performed in patients with risk factors for atherosclerosis. Select patients with carotid stenoses, who would otherwise be cardiac transplant candidates, may undergo pretransplantation percutaneous or surgical intervention, thereby eliminating this contraindication.
3. Occasionally, an abdominal aortic ultrasound is obtained to rule out an aneurysm, particularly in patients being considered for mechanical support.

C. Functional assessment

1. Metabolic stress testing is performed to assess the severity of cardiac functional impairment. Patients with compensated congestive heart failure and a peak oxygen consumption of < 14 mL/kg/min or < 50% predicted are considered sufficiently impaired for transplantation (2). Adequate patient effort during the stress test can be assessed by the respiratory exchange ratio, which should be > 1.1, indicating the onset of anaerobic metabolism.

2. Generally, a right heart catheterization is performed to assess cardiac hemodynamics and to optimize a patient's medical therapy. Fixed, severe pulmonary hypertension, defined as a pulmonary vascular resistance (PVR) > 4 Wood units, is a contraindication to cardiac transplantation. In this setting, the donor right ventricle will likely immediately fail after implantation because it is not accustomed to high pulmonary pressures. An attempt should be made to medically decrease the pulmonary hypertension with inotropic agents, nitrates, or nitroprusside. Sometimes an LVAD is required to sufficiently decompress the left ventricle to reverse the pulmonary hypertension. Rarely, endomyocardial biopsy (EMB) is performed, except when an infiltrative cardiomyopathy is suspected.
3. Pulmonary function tests are performed to exclude patients with significant chronic obstructive or restrictive pulmonary disease.
4. Peripheral vascular studies may be obtained to exclude patients with significant peripheral arteriosclerosis obliterans.

D. Comorbidities and implications of heart transplant listing. Advanced age, cancer, and obesity are the three common comorbidities that remain somewhat controversial with respect to their impact on whether an individual program will list a patient for heart transplantation.

1. Age criteria for eligibility were initially quite rigorous; however, it has become apparent that **chronologic and physiologic age are often discrepant**. Most centers do not have a fixed upper age limit, but generally patients > 65 years of age are very carefully screened to rule out comorbidities. ISHLT recommends considering patients for cardiac transplantation if they are ≤70 years of age (3). Patients > 70 years of age may be considered for cardiac transplantation at the discretion of the transplant program and should theoretically be in excellent health except for heart disease. An alternate type of program has been proposed for these patients, whereby older donor hearts would be utilized in this population (3).
2. Active **malignancy** other than skin cancer is an absolute contraindication to cardiac transplantation due to limited survival rates. Chronic immunosuppression is associated with a higher than average incidence of malignancy and is associated with increased recurrence of prior malignancy. Patients with cancers that have been in remission for ≥5 years and patients with low-grade cancers such as prostate cancer are generally accepted for transplant evaluation. Preexisting malignancies are heterogeneous in nature and some are readily treatable with chemotherapy. Thus an individualized approach to these patients is required, and consultation with an oncologist regarding prognosis is often very helpful.
3. Traditionally, centers have been cautious when considering **obese** patients for transplantation. Most currently available data indicate that patients with a pretransplant body mass index (BMI) > 30 kg/m^2 have poor outcomes following cardiac transplantation, with increased rates of infection and higher mortality rates. However, this area remains controversial and some recent data presented in abstract form only demonstrate no significant mortality differences between obese (BMI, 30 to 34.99) transplant recipients and overweight (BMI, 25 to 29.99) transplant recipients. Despite this controversy, the current ISHLT recommendations are that patients achieve a BMI < 30 kg/m^2 or a percent ideal body weight < 140% prior to being listed for cardiac transplantation (3). This cutoff will vary from center to center, but generally a BMI > 35 kg/m^2 will preclude listing for cardiac transplantation.

E. Consultations

1. A **psychosocial assessment** is a crucial component of every cardiac transplant evaluation. Accepted psychosocial contraindications for cardiac transplantations include active smoking; active substance abuse, including alcohol; medical noncompliance; and significant untreated psychologic or psychiatric diagnoses.

Relative psychosocial contraindications to cardiac transplantation include posttraumatic stress disorder and lack of an adequate support structure.

2. For **diabetic patients, an ophthalmology consultation** is obtained for an assessment of retinal end-organ damage related to the diabetes.

IV. UNOS AND THE RECIPIENT LIST. After a patient is accepted as a potential cardiac transplant recipient by a UNOS-certified transplant program, the patient's name is entered on a national list compiled by UNOS. The patient is given a status level based on predefined clinical criteria (Table 13.3), which can be adjusted as the patient's clinical situation evolves. A patient's priority on the UNOS list depends on his or her status level and the duration of time on the list. **Highest priority is given to patients with status 1A and those who have been waiting the longest**. A critical patient initially listed as status 1A immediately has a higher priority than a patient with a status 1B, regardless of the duration of time spent as status 1B. Whether a patient is hospitalized or not does not affect priority on the list, other than the fact that hospitalized patients are more likely to be receiving hemodynamic support (mechanical or inotropic) and are

TABLE 13.3 Description of Status Levels in the United Network of Organ Sharing List

Status	Description
1A	Must be an inpatient
	Life expectancy < 7 d
	LVAD and/or RVAD (maximum 30 d)
	VAD-related thromboembolism
	VAD-related infection (including the pocket and the driveline)
	Mechanical failure of VAD
	Total artificial heart
	Extracorporeal membrane oxygenation
	Intraaortic balloon pump with inotropic criteria
	Life-threatening refractory arrhythmias with or without a VAD
	Mechanical ventilation
	High-dose single intravenous inotrope (see doses below) or multiple intravenous inotropes, in addition to Swan-Ganz catheter
1B	Inotrope-dependent
	VAD not meeting criteria for 1A status
2	Not inotrope-dependent
7	Inactive on list because of improved clinical status or short-term contraindications to cardiac transplantation (e.g., active infection)
Inotrope criteria for status 1a	
1.	Two or more inotropes, regardless of dose
2.	Intravenous milrinone, at least 0.5 μg/kg/min by continuous infusion
3.	Intravenous dobutamine, at least 7.5 μg/kg/min by continuous infusion

LVAD, left ventricular assist device; RVAD, right ventricular assist device; VAD, ventricular assist device.

at a higher status level. A hospitalized patient on continuous inotropic therapy has the same status as a similar patient on home continuous inotropic therapy. Patients on home continuous inotropic therapy awaiting cardiac transplantation are generally thought to have an increased mortality related to the proarrhythmic effect of inotropic therapy, and most programs require implantation of an intracardiac defibrillator as a prerequisite for discharge.

V. WORKUP OF A POTENTIAL CARDIAC DONOR. Potential cardiac donors are patients who are declared brain dead but otherwise have viable internal organs. Generally, these are patients with lethal head injuries or catastrophic central nervous system events (i.e., intracranial hemorrhage, stroke, or cerebral anoxia).

A. Declaration of brain death. A neurologist or a neurosurgeon usually declares the brain death of a potential organ donor. Usually, this declaration is made after a period of observation (about 12 hours) during which no neurologic improvement is seen. Physicians involved in the care of potential transplant recipients are not involved in this decision to avoid conflicts of interest. Criteria for the determination of brain death are very specific. Absence of any one of the following criteria makes the patient ineligible for organ donation.

(1) A known cause of death
(2) Absence of hypotension, hypothermia, hypoxemia, and metabolic perturbations
(3) Absence of medical or recreational drugs known to depress the central nervous system
(4) Absence of cerebral cortical function
(5) No response to painful stimuli
(6) Absence of brainstem reflexes
  (a) Pupillary constriction to light
  (b) Corneal reflex
  (c) Vestibular ocular reflexes (i.e., doll's eyes or cold caloric testing)
  (d) Gag reflex
  (e) Cough reflex
(7) Positive apnea test: no spontaneous respiration despite arterial $P_{CO_2} > 60$ mm Hg for at least 10 minutes after disconnection from the ventilator
(8) An electroencephalogram (EEG) is not required but may be performed at the discretion of the examining physician. The EEG should demonstrate electrical silence.

B. Potential donor screening. After a patient is declared brain dead, a local organ procurement organization (OPO), under the auspices of UNOS, performs the initial evaluation of a potential donor. This evaluation includes a thorough patient and family history, focusing specifically on cardiac risk factors and potentially transmittable diseases (i.e., malignancy and infection). Preliminary blood tests are done, including determinations of cardiac enzymes; serologies for hepatitis B and C viruses, HIV, toxoplasmosis, and CMV; ABO blood group typing; and HLA antigen typing. An echocardiogram is routinely performed to assess the cardiac function and to rule out congenital anomalies and valvular disease. At the request of the potential recipient's physician, a coronary angiogram may be obtained if a donor has significant cardiac risk factors, has positive cardiac enzymes, or is relatively advanced in age. Cardiac donor selection criteria are summarized in Table 13.4.

If the potential recipient also has elevated PRA levels, a prospective complement-dependent antibody-mediated lymphocytotoxic crossmatch is usually performed, in which the recipient's serum is incubated with donor lymphocytes to identify potential donor–recipient HLA incompatibility. Many centers today perform a "virtual crossmatch" for patients with elevated PRA levels to improve donor availability. With the HLA technologies available today, the exact antigen specificity of the recipients' anti-HLA antibodies is known. If the HLA tissue typing of the potential donor

TABLE 13.4 Cardiac Donor Selection Criteria

Must meet legal requirements for brain death
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Normal ECG
Normal cardiac angiogram, performed if indicated by donor age (male > 45 y or female > 50 y) and history
Negative HBsAg, hepatitis C virus, and human immunodeficiency virus serologies
Systolic blood pressure > 100 mm Hg or mean arterial pressure > 60 mm Hg
Central venous pressure 8–12 mm Hg
Inotropic support < 10 μg/kg/min dopamine or dobutamine
Age < 55 y preferred

ECG, electrocardiogram.

does not include the antigens against which the recipient is sensitized, it is assumed that the actual crossmatch will be negative (i.e., a "virtual" negative crossmatch). If a prospective crossmatch is not performed, a retrospective crossmatch (by lymphocytotoxic assay or by flow cytometry) is performed using donor lymphocytes obtained from donor aortic lymph nodes retrieved at the time of harvest.

C. Donor–recipient matching. UNOS maintains a computerized list of all patients listed and waiting for cardiac transplantation. A list of potential recipients with compatible blood types is generated for each potential donor organ and is made available to the OPO. In this list, priority is given to local patients (defined as within the OPO's territory) with the highest status level who have been waiting the longest. Recent changes to the UNOS donor net criteria mean that a local status 2 patient is no longer higher on the list than a status 1A patient from outside the OPO's territory.

Transplant physicians of the potential recipient may also reject a potential organ because of a positive prospective crossmatch, donor–recipient size mismatch, or a prolonged projected ischemic time (usually related to long-distance travel). Matching donor and recipient size is important, because an oversized donor organ may not allow closure of the chest without compression of the organ and an undersized donor organ may not be able to pump a sufficient quantity of blood. **Current guidelines suggest that the recipient's weight should range between 70% and 130% of a potential donor's weight** (4).

VI. SURGICAL ISSUES RELATED TO CARDIAC TRANSPLANTATION. Most surgical issues related to cardiac transplantation are beyond the scope of this chapter and are mainly of interest to the cardiac surgeon. The main surgical issue of interest to the transplant cardiologist is related to the anastomosis of the right atrium. The surgeon may suture the donor atrium to the recipient atrium (i.e., **biatrial anastomosis**) or suture the donor superior vena cava to the recipient superior vena cava and the donor inferior vena cava to the recipient inferior vena cava (i.e., **bicaval anastomosis**). The bicaval anastomosis approach is more time consuming but reduces the incidence of atrial arrhythmias (including sinus

node dysfunction), reduces the incidence of posttransplant tricuspid regurgitation, and improves right atrial hemodynamics. The bicaval anastomosis approach does, however, provide some potential difficulties to the cardiologist trying to perform surveillance EMBs, because these anastomoses have a tendency to scar and narrow the central lumen over time. Currently, most centers employ the bicaval anastomosis approach, although no survival advantage has been conclusively demonstrated with this approach.

VII. POSTOPERATIVE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

A. Surgical complications. The most common surgical complication is the development of a **pericardial effusion** with or without tamponade. Pericardial effusions are very common because of the large potential space left behind as the dilated and dysfunctional recipient left ventricle is replaced with a more appropriately sized donor left ventricle. Rarely, pericardial tamponade develops, necessitating percutaneous or surgical evacuation of the pericardium. Other surgical complications are much less common but can be catastrophic and usually result from a problem either at a site of anastomosis or at a site of cannulation.

B. Early graft dysfunction

1. **LV systolic dysfunction.** It is common for transplant recipients to require inotropic support as they come off cardiopulmonary bypass. The most commonly used inotropic agents in this setting are dobutamine, milrinone, and isoproterenol, used alone or in combination. It is also common for transplant recipients to require peripheral vasoconstrictors such as epinephrine, norepinephrine, and dopamine in the early postoperative period, because most are on large quantities of oral or intravenous vasodilators before transplantation. Most patients can be weaned off inotropic therapy and peripheral vasoconstrictors within the first 48 hours.
2. **LV diastolic dysfunction** is very common soon after cardiac transplantation. It usually results from reversible ischemia or reperfusion injury to the donor organ and normally resolves over a period of days to weeks. If the ischemia or reperfusion injury is sufficiently severe to induce significant contraction band necrosis or myocardial fibrosis, as seen on EMB, chronic diastolic dysfunction can ensue. Another potential cause of diastolic dysfunction is donor–recipient mismatch, particularly with a small donor organ or acute rejection.
3. **Right ventricular dysfunction** is much more common than LV dysfunction after cardiac transplantation, especially in patients with preexisting pulmonary hypertension. The right ventricle is subjected to similar ischemic or reperfusion injury risks as the left ventricle. Right ventricular dysfunction is usually accompanied by right ventricular dilation and the failure of coaptation of the tricuspid valve leaflets, leading to severe tricuspid regurgitation. The treatment for perioperative right ventricular dysfunction is usually intravenous milrinone and nitrates to increase cardiac output and lower the PVR. In patients with refractory pulmonary hypertension, other agents to be considered include nitroprusside, nesiritide, isoproterenol, or rarely, inhaled nitric oxide. Usually, the pulmonary hypertension and right ventricular dysfunction improve over a period of days to weeks.

C. Cardiac arrhythmias. Most transplant recipients require perioperative temporary atrioventricular pacing. Sinus node dysfunction is very common, probably because of a combination of surgical trauma, ischemia or reperfusion injury, and denervation. The incidence of sinus node dysfunction is believed to be reduced by the bicaval anastomosis technique compared with the biatrial anastomosis technique. With time, the sinus node usually recovers, and a permanent pacemaker is unnecessary. Preoperative use of amiodarone increases the likelihood of bradycardia after transplantation. Other cardiac arrhythmias are rare, especially off inotropic therapy, and may signify acute rejection.

D. Renal dysfunction. Preoperatively, many transplant recipients have some degree of impaired renal function. There is a risk of worsening renal function perioperatively.

This risk is compounded by the fact that the major immunosuppressive agents (i.e., cyclosporine and tacrolimus) are nephrotoxic. If renal function does worsen postoperatively, induction therapy is begun to delay initiation of cyclosporine or tacrolimus. Most centers no longer use OKT3 for induction therapy but rather use interleukin-2 (IL-2) receptor blockers or thymoglobulin for induction therapy.

VIII. SYSTEMIC IMMUNOSUPPRESSION. Much of the success in cardiac transplantation today is attributed to advances in immunosuppression. However, balancing the risk of allograft rejection against the inherent risk of immunosuppression remains a challenge in transplant medicine. Immunosuppressant protocols during and after cardiac transplantation vary greatly from program to program and even from patient to patient within a program. Triple therapy, which constitutes the cornerstone of modern immunosuppressive regimens in cardiac transplantation, including a calcineurin inhibitor (such as cyclosporine or tacrolimus), a cell cycle–modulating or antiproliferative agent (such as MMF or azathioprine), and a corticosteroid (4), is increasingly being challenged. Recently, the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial prospectively randomized 150 cardiac transplant patients in an open fashion to receive either tacrolimus monotherapy or tacrolimus and MMF. Corticosteroids were used in all patients but were successfully discontinued over 8 to 9 weeks. The addition of MMF to tacrolimus did not provide an advantage over tacrolimus alone in terms of primary end point of rejection over the first 6 months, the secondary end points of allograft vasculopathy, and 3-year survival (5). The trial has, however, been criticized for being underpowered to demonstrate true differences in the primary and secondary end points, its use of an unvalidated biopsy grading scale, inconsistent timing of intravascular ultrasound (IVUS), use of higher and potentially nephrotoxic levels of tacrolimus, and the lack of a control arm of routine triple drug immunosuppression for comparison with the two study arms (6). Controversy remains about the advisability of using cytolytic or induction therapy in the nonpresensitized recipient without renal failure (Table 13.5).

A. Steroids. The mechanism by which steroids serve as immunosuppressants is complex and incompletely understood. Steroids bind to nuclear receptors, thereby preventing gene expression of various cytokines important for B-cell and T-cell activation and proliferation, the most important of which is IL-2. Steroids also have important anti-inflammatory properties and suppress macrophage activity. Important side effects of steroids include diabetes, hypertension, weight gain, osteoporosis, and avascular necrosis of the femoral head.

Steroid-dosing protocols vary tremendously from one institution to another. A dose of 500 to 1,000 mg of intravenous Solu-Medrol is usually given to the patient before being brought to the operating room and then 125 to 150 mg is usually repeated every 8 hours for a total of three more doses. At that point, if the patient is extubated, oral prednisone is begun. Some centers start at a divided dose of 1 mg/kg/d and wean by 5 mg daily, whereas others start immediately at only 20 mg daily. The dose of steroid is slowly tapered, provided the patient continues to have a clean biopsy record. The trend in clinical practice is to wean most patients completely off steroids. Some centers continue to advocate the indefinite use of low-dose prednisone (2.5 to 5 mg daily). If a decision is made to withdraw steroids completely, it should be done approximately 1 month before the next scheduled biopsy to ensure continued lack of acute cellular rejection.

Steroids are also given in "pulses" to treat episodes of acute cellular rejection. If a patient has acute cellular rejection associated with hemodynamic compromise, she or he is admitted for 1 g of intravenous Solu-Medrol daily for 3 days and may be given cytolytic therapy or plasmapheresis, or both. If no hemodynamic compromise is associated with the episode of rejection, a daily dose of 100 mg oral prednisone for 3 days is usually sufficient, followed by repeat biopsy, at most 2 weeks later to ensure resolution.

TABLE 13.5 Common Immunosuppressants

	Steroids	Calcineurin inhibitors	MMF	AZA	TOR inhibitors	OKT3	Polyclonal antilymphocyte antibodies	IL-2 receptor blockers
Drugs	Prednisone (P) (po) Solu-Medrol (S) (IV)	Neoral (N) Tacrolimus (T)	—	—	Rapamycin (R) Everolimus (E)	—	Atgam (A) Thymoglobulin (T)	Basiliximab (B) Daclizumab (T)
Indication	Chronic IM, acute rejection	Chronic IM	Chronic IM, skin cancer with AZA	Chronic IM	Chronic IM, vasculopathy	Induction, acute rejection	Induction, acute rejection	Induction
Dosing								
Initial	IV 125–150 mg q8h	N: 100 mg bid T: 2 mg bid	1.5 g bid	1–2 mg/kg/d	R: 2–5 mg qd E: 1.5–3 mg qd	—	—	—
Induction	—	—	—	—	—	5 mg qd × 5–15 d	A: 15 mg/kg/d T: 1.5 mg/kg/d × 5–15 d	B: 20 mg on days 1 and 4 D: 1 mg/kg q1-2wk × 5 doses
Maintenance	Weaned off	Adjusted to levels	1.5 g bid	1–2 mg/kg/d	Adjusted to levels	—	—	—
Acute rejection	P: 100 mg qd × 3 S: 1g IV qd × 3	Consider change from CsA to tacrolimus	—	—	—	As above	As above	—

Target levels	—	See Tables 12.3 and 12.4	2–4 ng/mL, 12-h trough, WBC > 4.0	WBC > 3.0	R: 4–12 ng/mL, 18-h trough	CD3 count < 20 cells/mL	CD3 count < 20 cells/mL	—
Common side effects	Diabetes, osteoporosis, weight gain, hypertension, and adrenal insufficiency	Nephrotoxicity, hypertension, tremors, and gingival hyperplasia	Diarrhea, nausea, and myelosuppression	Myelosuppression, skin cancer	Hypertriglyceridemia and thrombocytopenia	Cytokine release, hypotension, capillary leak syndrome, PTLD, and CMV superinfection	Thrombocytopenia, fevers, chills, PTLD, and CMV superinfection	—
Common drug interactions	—	Erythromycin, diltiazem, verapamil, rapamycin, anticonvulsants, rifampin, and statins	Cholestyramine and probenecid	Allopurinol	Cyclosporine	—	—	—

AZA, azathioprine; CMV, cytomegalovirus; CsA, cyclosporin A; IL, interleukin; IM, immunosuppression; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; TOR, target of rapamycin.

B. Calcineurin inhibitors. Calcineurin is a phosphatase enzyme that triggers transcription of new messenger RNA after activation of the T-cell receptor by an appropriate antigen, leading to increased gene expression of IL-2 and other important cytokines. Calcineurin antagonists inhibit this phosphatase activity, thereby preventing the synthesis of these cytokines, which prevent B-cell and T-cell proliferation.

1. **Cyclosporine** (Neoral, Gengraf, and Sandimmune) is a calcineurin antagonist with a highly variable pattern of bioavailability, depending on the oral formulation taken. Bioavailability of the original soft gelatin capsule (Sandimmune) was low and depended on emulsification by bile salts. The newer microemulsion formulation (Neoral) does not depend on bile salts for emulsification and has a more consistent bioavailability. Nevertheless, there remain tremendous interpatient differences in bioavailability, and dosing of Neoral is primarily based on serum drug trough levels. Because of the narrow therapeutic range of cyclosporine, drug trough levels are also important to prevent toxicity. Nephrotoxicity is the most important side effect of cyclosporine therapy and is related to renal afferent arteriolar vasoconstriction and the resultant reduced renal perfusion. Other side effects include systemic hypertension, gingival hyperplasia, and tremors. Calcium channel blockers, particularly diltiazem, reduce hepatic metabolism of cyclosporine, thereby increasing serum drug levels. This drug interaction is frequently used clinically to reduce the oral dose of cyclosporine required to achieve a given serum drug concentration, thereby minimizing the cost of immunosuppression.

   Postoperatively, once the patient is hemodynamically stable with good urine output, cyclosporine is initiated via continuous infusion at 1 mg/h. When the patient is able to take oral medicines, Neoral is begun at a dose of 100 mg twice daily, with adjustments in the dose based on serum trough levels (Table 13.6). The dose of Neoral is gradually reduced over a period of 1 year if the patient has a clean biopsy record.

2. **Tacrolimus** (Prograf), previously known as FK506, is another calcineurin inhibitor that has low oral bioavailability. Tacrolimus has never been prospectively shown to be superior to cyclosporine in the prevention of acute cellular rejection. However, it has become a standard practice to change cyclosporine in a patient's immunosuppressive regimen to tacrolimus in the setting of recurrent or persistent acute cellular rejection with adequate cyclosporine levels. Some programs empirically use tacrolimus for all female patients because a common side effect of cyclosporine is hirsutism. The major side effects of tacrolimus are nephrotoxicity and neurotoxicity (most commonly tremor).

   Like cyclosporine, tacrolimus is initiated postoperatively once the patient is hemodynamically and renally stable. A dose of 0.01 mg/kg/d of tacrolimus is administered by continuous infusion. Unfortunately, intravenous tacrolimus is seemingly more nephrotoxic than cyclosporine. Tacrolimus can be given sublingually using an oral to sublingual dose ratio of 1:1. After the patient starts taking

TABLE 13.6 Target Serum Cyclosporin A Levels

Time	Target level (12-h trough)
0–3 mo	250–350 ng/mL
3–12 mo	200–250 ng/mL
>12 mo	150–175 ng/mL

TABLE 13.7 Target Serum Tacrolimus (FK506) Levels

Time	Target level (12-h trough)
0–30 d	12–20 ng/mL
1–6 mo	8–15 ng/mL
6–18 mo	5–15 ng/mL
>18 mo	5–10 ng/mL

medicines orally, the dosage of tacrolimus is changed to 0.5 to 2 mg twice daily, with dose adjustment based on serum FK506 levels (Table 13.7).

C. Mycophenolate mofetil (CellCept). MMF inhibits DNA synthesis by inhibiting de novo purine synthesis. Because human lymphocytes depend on the de novo synthesis of purines for DNA replication, MMF has the unique ability to inhibit B-lymphocyte and T-lymphocyte proliferation without affecting DNA synthesis in other cell lines, which can obtain purines through the parallel and unaffected purine salvage pathway. MMF has become the preferred immunosuppressant over azathioprine at most transplant centers because of a reduced mortality rate at 1 year (6.2% vs. 11.4%; $p = 0.03$), especially among patients with treated biopsy-proven rejection and severe hemodynamic compromise (32% vs. 0%). Although there is a trend toward a reduced incidence of grade 3A (now 2R) rejection in MMF-treated patients compared with azathioprine-treated patients, it did not reach statistical significance (45% vs. 52.9%; $p = 0.055$). The main disadvantage of MMF over azathioprine is the increased cost (almost 10-fold) and the potential increased risk of opportunistic viral infections. Toxicities of MMF include gastrointestinal symptoms (nausea, vomiting, and diarrhea) and myelosuppression. Some patients on MMF develop clinically significant leukopenia, necessitating dose reduction or discontinuation of the drug. The incidence of these adverse events is higher in patients receiving > 3 g/d of MMF. Most symptoms will resolve with the reduction of dose.

MMF is given intravenously or orally. Because of the high bioavailability (> 90%), the initial dose of MMF is 1 g taken twice daily, regardless of the route of administration. The initial dose is given within the first 12 hours after transplantation. Few centers monitor the serum levels of mycophenolic acid (MPA), the active metabolite of MMF. The serum levels of MPA are higher when MMF is administered with tacrolimus compared with cyclosporine; therefore, it may be advisable to empirically reduce the dosage of MMF when switching from cyclosporine to tacrolimus. Although there is no consensus on dose adjustment of MMF, at the Cleveland Clinic, the dose is adjusted to maintain MPA 12-hour trough concentrations in the range of 2 to 4 µg/mL.

D. Azathioprine (Imuran) is a purine analog that impairs DNA synthesis, thereby preventing B-lymphocyte and T-lymphocyte proliferation in response to antigen stimulation. Azathioprine has largely been replaced by MMF as the antiproliferative agent of choice in the triple immunosuppressant cocktails of today. Because there is no drug level assay available, azathioprine dosing is usually fixed between 1 and 2 mg/kg/d. The major side effect of azathioprine is myelosuppression, and the dose of azathioprine is usually adjusted to maintain a white blood cell count of > 3,000/mL. Azathioprine is metabolized by xanthine oxidase, and xanthine oxidase inhibitors such as allopurinol can lead to the accumulation of toxic levels of azathioprine and profound and prolonged myelosuppression.

E. Inhibitors of the target of rapamycin (TOR) enzyme: sirolimus (Rapamune) and everolimus (Certican, previously known as RAD). Immunosuppressants have been developed that inhibit the enzyme TOR. TOR is activated after IL-2 stimulation of the T-cell IL-2 receptor and is critical for lymphocyte growth and proliferation. In contrast to calcineurin inhibitors, inhibitors of TOR do not block cytokine production (e.g., IL-2) but rather block the cellular response to these cytokines. TOR inhibitors also inhibit vascular smooth muscle cell growth and proliferation in response to various growth factors. It is hoped that this property of TOR inhibitors will help reduce the rate of progression of chronic transplant coronary vasculopathy. Unlike calcineurin inhibitors, TOR inhibitors are not nephrotoxic. When used in combination with cyclosporine, TOR inhibitors appear to act synergistically with regard to immunosuppression. However, worsening of renal function is common but can be prevented by lowering the cyclosporine dose without worsening of immunosuppression. The main side effects of this class of compounds are significant hypertriglyceridemia and thrombocytopenia.

Sirolimus and everolimus are both TOR inhibitors. They are structurally similar, but everolimus has a much higher bioavailability than sirolimus. The appropriate dosing of these agents remains unclear, but for sirolimus, it is probably 1 to 5 mg/d, and for everolimus, it is probably 1.5 to 3 mg/d. Sirolimus appears to lower the incidence of acute cellular rejection in humans (7) and to slow the progression of transplant vasculopathy (8). Preliminary human studies using intravascular coronary ultrasonography have also shown a reduction in neointimal proliferation with both sirolimus and everolimus.

It remains unclear where TOR inhibitors will fit in with current immunosuppressive protocols. The most likely scenario is their use in combination with a calcineurin inhibitor and prednisone, in place of MMF or azathioprine. Alternatively, they could be used in place of calcineurin inhibitors and in combination with MMF or azathioprine and prednisone, particularly in patients with either preexisting or worsening renal dysfunction.

F. Induction therapy and therapy for steroid-resistant acute rejection. The purpose of induction therapy is to deplete T lymphocytes or to prevent lymphocyte proliferation during the most immunoreactive phase, which occurs immediately after transplantation. Induction therapy has continued to be a subject of controversy in heart transplantation for more than 20 years. Induction therapy is not routinely used in posttransplant patients because of a lack of evidence of improved survival or less acute rejection. The two clear indications to use induction therapy are as follows: (1) in patients who have severe renal dysfunction, which precludes the introduction of calcineurin inhibitors within the first 2 days following transplantation and (2) in patients who have acute graft failure secondary to an immune mechanism such as with hyperacute rejection or humoral rejection. The two scenarios in which induction therapy is often used are in patients with preexisting significant renal dysfunction and in significantly presensitized patients.

The principle behind the treatment of steroid-resistant acute rejection is similar, in that the depletion of activated T lymphocytes presumably prevents further clonal expansion of the antigen-activated offending lymphocyte population.

1. **OKT3** (Muromonab-CD3) is a murine-based monoclonal anti-CD3 antibody. The CD3 antigen is part of the T-cell receptor complex present on activated, circulating T lymphocytes. OKT3 binds to the CD3 antigen and produces cell death by multiple mechanisms or T-cell receptor internalization, thereby inactivating the lymphocyte.

   The dose of OKT3 is 5 mg/d, for a total of 5 to 10 days. After a course of OKT3, there is an immediate and well-recognized rebound in CD3-positive (activated) T-lymphocyte counts that can lead to acute cellular or humoral rejection. Cytokine release syndrome frequently occurs and typically begins 30 to 60 minutes after administration of a dose of OKT3 and may persist for

several hours. Premedication with acetaminophen, steroids, and antihistamines may help minimize symptoms. CD3+ T cells are generally undetectable during OKT3 therapy; however, within 12 to 24 hours after cessation of OKT3, CD3+ T cells reappear in circulation, unlike after treatment with antithymocyte globulin (ATG) preparations, with which the lymphocyte depletion is present for weeks. Therefore, many programs prophylactically increase the steroid dose during withdrawal from OKT3. Since OKT3 is a murine-based monoclonal antibody, patients may develop antibodies toward the mouse component of the antibody that may limit the effectiveness of future courses of OKT3. Patients treated with OKT3 have had an increased incidence of posttransplant lymphoproliferative disorder (PTLD) and lymphoma with a cumulative dose of > 75 mg. Opportunistic viral infections are also more common after OKT3 therapy.

2. **Polyclonal antilymphocyte antibodies** are produced by injecting animals with human lymphocytes or thymocytes and then collecting the animal's serum. Two commercially available formulations are antithymocyte globulin (Atgam), which is horse-based, and Thymoglobulin, which is rabbit-based. The antibodies produced in this manner are directed against a variety of targets on the surface of B and T cells and induce complement-mediated lymphocytolysis. The recommended doses of Atgam and Thymoglobulin are 15 mg/kg/d and 1.5 mg/kg/d, respectively, for a total of 7 to 10 days. Adequate lymphocyte depletion can be ensured by quantifying the CD2-positive lymphocytes, a marker present on all lymphocytes. Similar to OKT3, immunity may develop to the animal component of these antibodies, rendering them ineffective if further courses of therapy are necessary. An increased incidence of PTLD, lymphoma, and opportunistic viral infections has also been observed. Patients receiving either formulation are often prophylactically treated with ganciclovir to prevent CMV infection.
3. **IL-2 receptor blockers** are competitive fully humanized monoclonal anti-CD25 antibodies. CD25 antigen is the IL-2 receptor and is only present on the cell surface of activated T lymphocytes. In contrast to OKT3, there is no initial receptor agonist phase and no cytokine release syndrome.

   For the two commercially available IL-2 receptor blockers, basiliximab (Simulect) and daclizumab (Zenapax), there are data to support the use of daclizumab only for induction therapy after cardiac transplantation, particularly in patients with preexisting renal dysfunction in whom calcineurin inhibitor avoidance is preferable in the early postoperative period. Fewer patients treated with daclizumab, in addition to standard triple immunosuppressant therapy, developed acute rejection compared with controls (9). Patients treated with daclizumab also had a lower severity and frequency of acute rejection during the first 3 months and had a longer time to the first episode of rejection. In contrast to other agents used for induction therapy, daclizumab does not appear to increase the risk of lymphoma, PTLD, or opportunistic viral infections. The serum half-life of daclizumab is 21 days, and dosing strategies call for a dose of 1 mg/kg every 1 to 2 weeks after transplantation, for a total of five doses (including the initial dose). There is no indication for either basiliximab or daclizumab as therapy for steroid-resistant persistent acute rejection. Given the virtual absence of side effects from IL-2 receptor blockade, the critical issue that needs to be addressed for these agents to become widely used clinically is whether the reduction in early acute rejection episodes translates into improved long-term survival and a reduction in transplant coronary vasculopathy.

IX. REJECTION. In the ISHLT registry, 30% of the cardiac allograft recipients between January 2003 and June 2008 experienced rejection during the first year. Females and young patients were at higher risk than males and older patients, respectively. Allograft rejection involves both the cellular and humoral arms of the adaptive response. An ideal immune monitoring strategy has been described as the one that would be noninvasive,

TABLE 13.8 Grading Scale (2004) for Endomyocardial Biopsies

Grade	Severity of cellular rejection	Histologic findings
1R[a]	Mild	Interstitial and/or perivascular infiltrate with up to 1 focus of necrosis
2R	Moderate	≥2 foci of infiltrate with associated necrosis
3R	Severe	Diffuse infiltrate with multifocal necrosis ± edema ± hemorrhage ± vasculitis

[a]R = revised.

would reliably distinguish between the presence and absence of rejection, and would detect overimmunosuppression (10). Such a strategy does not, however, exist. The immunologic status of a transplant recipient is currently monitored by immunosuppressant drug levels, echocardiographic assessment of allograft function, and EMB. Noninvasive monitoring therapies have been tested in the hope of overcoming these limitations. Gene expression profiling (GEP) test, which is also known as the AlloMap test, and cardiac magnetic resonance (CMR) imaging are examples of promising alternatives that are being evaluated.

A. Endomyocardial biopsy. The current gold standard of rejection surveillance after cardiac transplantation is EMB. However, EMB is invasive, inconvenient, expensive, and subject to sampling error and interobserver variability. Rejection of the cardiac allograft is usually clinically silent unless it is accompanied by significant hemodynamic compromise (i.e., congestive heart failure). As a result, EMBs are routinely performed for rejection surveillance (see Chapter 63). To mitigate the interobserver variability, the ISHLT revised and simplified the grading criteria for acute cellular rejection (Table 13.8) (11). Because the likelihood of acute rejection is highest early after transplantation, the frequency of biopsies is high during this period and then gradually tapers off, depending on the results (Table 13.9).

B. Surrogate markers of rejection

1. **Peripheral biomarkers.** While high levels of circulating pretransplant, donor-specific antibodies to HLAs have been demonstrated to predict greater risk of severe

TABLE 13.9 Endomyocardial Biopsy Schedule

Weeks after transplantation	Biopsy frequency
1–4	Weekly
5–12	Every 2 wk
13–24	Monthly
25–52	Every 2 mo
Year 2	Every 3–4 mo
Years 3–4	Every 6 mo
>4 y	Only if clinically indicated
After biopsy with acute rejection	2 wk after initial biopsy

rejection, no peripheral markers have been shown to reliably correlate with allograft rejection posttransplantation among those evaluated, including cytokine levels, markers of myocardial necrosis (CK-MB and troponin), complement fragments, prothrombin, P-selectin fragments, CD69 membrane protein, soluble CD30, endothelin, serum nitrate, thromboxane A_2, matrix metalloproteinase-1 in brain, vascular endothelial growth factor, natriuretic peptide, and C-reactive protein (12).

2. **Echocardiography.** Echocardiography is ubiquitous in cardiac transplant centers, drawing investigative attention to it as a noninvasive surveillance alternative to EMB for cardiac allograft rejection. For it to be a useful screening tool, however, echocardiography must identify graft rejection before global LV systolic dysfunction ensues. The challenge has been to identify such sentinel markers. Myocardial performance index, pressure halftime, intraventricular relaxation time, and acoustic quantification of cardiac filling volumes have not shown consistency. Changes > 10% in serial measurements of pulsed wave tissue Doppler measurements of early diastolic basal posterior wall motion velocity were able to exclude clinically relevant rejection with positive predictive value and negative predictive value of 92% and 95%, respectively. Technical limitations with this technique in the cardiac transplant population together with inconsistent observer interpretation have meant that echocardiography is neither sufficiently sensitive nor specific to supplant routine EMB (12).
3. **Gene expression profiling.** GEP is a new modality for surveillance of cardiac allograft rejection. **This test uses microarray and quantitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells to measure the expression of 20 genes** (11 informative, 9 control and normalization) (13). A score ranging from 0 to 40 is generated by a multigene algorithm. It has been shown to correlate strongly with histologically diagnosed cellular allograft rejection. In the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study, scores of < 34 were associated with a negative predictive value of > 99% for grade ≥3A/2R rejection. Several factors influence AlloMap score, including time posttransplantation, peripheral alloimmune activity, corticosteroid dose, and CMV. Transplant vasculopathy has been shown to be associated with increased AlloMap GEP score. GEP testing can be used in clinically stable cardiac transplant recipients who are > 15 years of age and 6 months or more posttransplantation. It is used to identify patients at low risk for moderate/severe (≥3A original ISHLT grade or ≥2R revised ISHLT grade) cellular rejection (8). In the Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial, 602 patients who had undergone cardiac transplantation at least 6 months previously were randomly assigned to the AlloMap test or EMB. The composite primary outcome of the study was allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with GEP and 15.3% with EMB. The AlloMap test was thus not inferior to EMB in detecting allograft rejection. However, wholesale embrace of the IMAGE trial is tempered by the limitations of the trial, including the enrolment of only 20% of potentially eligible patients and of patients at lower risk for rejection. The noninferiority margin chosen was wide and included events that would not be associated with rejection since not all cases of graft dysfunction, death, or retransplantation are due to rejection (14).

   The frequency of rejection surveillance using the GEP or AlloMap testing should be individualized to the patient's rejection history, immunosuppression regimen, time posttransplantation, and transplant center protocol. GEP is a cost-effective and less expensive alternative to EMB for monitoring allograft rejection in cardiac transplant patients. It has demonstrated great clinical promise in these early studies and may one day surpass EMB as the gold standard for rejection surveillance after cardiac transplantation.

4. **Cardiac magnetic resonance.** CMR is able to evaluate both the myocardial tissue composition, including edema and necrosis, and the allograft function, which makes it an attractive modality for assessing cardiac allograft rejection. Studies to date have, however, not demonstrated consistent results in human populations (15). Marie et al. (16) demonstrated a 97% negative predictive value and a 35% positive predictive value of elevated T2 relaxation times in a series of 123 scans in 68 heart transplant recipients, 82% of whom were within 1 year of transplantation. Relaxation time of at least 56 milliseconds measured with a black-blood sequence predicted moderate or greater biopsy-proven rejection with 89% sensitivity and 70% specificity, and treatment of rejection episodes resulted in normalized relaxation times. Subgroup analysis showed a correlation between positive results in conjunction with a negative biopsy and subsequent rejection episodes in the following 3 months (16). In another study, Taylor et al. (17) compared the performance of CMR with EMB in assessing acute cardiac allograft rejection in 50 patients, 802 ± 224 days posttransplantation. Acute rejection was confirmed by EMB in 11 cases and presumed in 8 cases with a recent fall in left ventricular ejection fraction (LVEF) not attributable to coronary allograft vasculopathy. CMR evaluated myocardial function, edema, and early and late post-gadolinium-DTPA contrast enhancement. With rejection defined as increased early contrast enhancement or myocardial edema, the sensitivity and specificity of CMR compared with EMB were 100% and 73%, respectively. Eight patients with presumed rejection had significantly elevated early myocardial contrast enhancement compared with controls, which reduced along with improvement in LVEF following increased immunosuppression. The drawback of CMR, however, is that it is expensive, time consuming, nonspecific, and not universally available. Moreover, it cannot be used in claustrophobic patients or those with significantly reduced renal function (i.e., those with acute kidney injury or chronic kidney disease with a glomerular filtration rate < 30 mL/min/1.73m^2) in whom the use of gadolinium has the attendant risk of nephrogenic systemic fibrosis.

A. Types of rejection

1. **Hyperacute rejection** is usually fatal and is the result of allograft rejection by preformed antibodies. It can occur immediately on surgical reperfusion. The incidence of hyperacute rejection is thankfully rare in the era of PRAs and prospective crossmatches.
2. **Cell-mediated rejection** is characterized by infiltration of mononuclear inflammatory cells that are predominantly T cells directed against the allograft. Variability in the interpretation of histologic grading of cellular rejection of EMB by pathologists led to the revision of the grading system in 2004 (11). Biopsy grades of ≥2R warrant accentuation of immunosuppression. If there is no hemodynamic compromise, then patients are routinely treated as outpatients with 100 mg of prednisone taken orally for 3 days. If there is a hemodynamic compromise or persistent or recurrent severe rejection (at least grade 2R), then many therapeutic options are available, including 1 g of intravenous Solu-Medrol for 3 days, conversion from cyclosporine to tacrolimus, OKT3, Atgam, Thymoglobulin, plasmapheresis, photopheresis, and total lymphoid irradiation (4).

Grade 0R: no acute cellular rejection.
Grade 1R: mild, low-grade, acute cellular rejection.
Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage.
Grade 2R: Moderate, intermediate-grade, acute cellular rejection.
Two or more foci of infiltrate with associated myocyte damage.
Grade 3R: Severe, high-grade, acute cellular rejection.

Diffuse infiltrate with multifocal myocyte damage ± edema ± hemorrhage ± vasculitis.

3. **Antibody-mediated rejection (AMR)** occurs due to preformed or de novo alloantibody (immunoglobulin G or M) against donor antigens. Such antibodies and complements are deposited in the donor coronary microvasculature and are demonstrable by immunofluorescence or by immunohistochemistry staining against CD68, C4d, or C3d complement fragments that mediate vascular injury and, ultimately, allograft failure. There has, however, been no consensus on its diagnosis. The ISHLT has recently proposed a framework for reporting AMR (18):

pAMR 0: negative for pathologic AMR.
Both histologic and immunopathologic studies are negative.
pAMR 1 (H+): histopathologic AMR alone.
Histologic findings are present and immunopathologic findings are negative.
pAMR1 (I+): immunopathologic AMR alone.
Histologic findings are negative and immunopathologic findings are positive.
pAMR 2: pathologic AMR.
Both histologic and immunopathologic findings are present.
pAMR 3: severe pathologic AMR.

This category recognizes the rare cases of severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, and marked edema. The reported experience of the group was that these cases are associated with profound allograft dysfunction and poor clinical outcomes.

AMR is not routinely screened for in EMBs unless suspected clinically because of allograft dysfunction or hemodynamic compromise. Treatment options for patients with vascular rejection include intravenous or oral steroids, plasmapheresis, or immunoadsorption (4).

X. INFECTIOUS DISEASE AFTER TRANSPLANTATION. The risk of infection is highest in the first year post cardiac transplantation, accounting for 29% of deaths. Thereafter, the risk falls but remains > 10%. In the first month post transplantation, nosocomial infections predominate. The therapeutic immunosuppression consequent upon transplantation leaves cardiac allograft recipients vulnerable to opportunistic infections or reactivation of latent infection, particularly between 1 and 6 months. Infections after 6 months are usually community-acquired. An infectious disease specialist with an interest in transplantation is an invaluable resource to any transplant program. The two pathogens of particular interest in the transplant patient are CMV and pneumocystis jiroveci pneumonia (PJP), formerly called pneumocystis carinii pneumonia, but there are several potential pathogens including *Mycobacterium*, *Nocardia*, *Listeria*, *Candida*, *Aspergillus*, and *Strongyloides* (1,4).

A. Cytomegalovirus. Primary CMV infection occurs when a CMV-negative recipient receives a CMV-positive donor organ or is infected de novo from another source. Secondary CMV infection occurs when a CMV-positive recipient has reactivation of quiescent CMV infection with viremia after immunosuppression, particularly with induction therapy or bolus immunosuppression prescribed for a rejection episode. Active CMV disease may manifest as fevers, myalgias, gastritis, colitis, pneumonitis, retinitis, or leukopenia and thrombocytopenia. The most sensitive and specific test for diagnosing CMV is quantitative PCR. PCR detects CMV DNA in plasma and quantifies the CMV viral load. Although CMV DNA replication may be detected by PCR, most patients do not have the clinical syndrome of CMV disease. The issues of whether a detectable CMV viral load will progress to the clinical syndrome and whether to treat patients with CMV detection in the absence of symptoms remain controversial.

Prophylaxis against CMV disease is considered to be the standard of care for CMV-positive recipients (regardless of the CMV status of the donor) and CMV-negative patients with a CMV-positive donor. There is no consensus on the duration

of ganciclovir therapy in these patients. Most patients are initially treated with intravenous ganciclovir, followed by a variable course of oral valganciclovir or acyclovir. Periodic monitoring of the CMV viral load may assist in guiding the duration of therapy in these patients.

Passive immunization with CMV immunoglobulin (CytoGam) may be considered in patients deemed at risk for CMV disease, particularly if they have low levels of serum immunoglobulins (< 500 mg/dL). Patients undergoing induction therapy, polyclonal or monoclonal antibody therapy for steroid-resistant rejection, or increased immunosuppressive therapy for acute rejection should be deemed at risk for reactivation of CMV disease.

The duration of therapy with valganciclovir for active CMV disease is usually 3 to 6 weeks. An undetectable CMV viral load should be demonstrated in such patients before consideration is given for antiviral therapy discontinuation (4).

B. *Pneumocystis jiroveci* pneumonia. Transplant recipients are at increased risk for the development of PJP because of their immunocompromised state. PJP is rare if appropriate prophylaxis with trimethoprim–sulfamethoxazole (TMP–SMX) is provided. Patients intolerant to TMP–SMX may be treated with inhaled pentamidine or dapsone. PJP is rarely seen at maintenance immunosuppressant doses in transplant patients. TMP–SMX may be discontinued at 6 to 12 months after transplantation in most patients (4).

XI. CARDIAC ALLOGRAFT VASCULOPATHY (CAV).

CAV is a progressive, neointimal proliferative process in the epicardial coronary vasculature and in the microcirculation. It is common, with an incidence of 20%, 30%, and > 50% at 3, 5, and 10 years after transplantation. CAV is a significant cause of mortality beyond the first year after transplantation, accounting for 30% to 50% of deaths at 5 years. The pathophysiology of CAV is not completely understood. **Initially CAV was thought to be an accelerated form of atherosclerosis; however, it is now clear that both immunologic and nonimmunologic factors are involved in the process**. Chronic, subclinical, and immune-mediated injury at the level of the donor coronary endothelium creates a chronic inflammatory milieu. The exact mediator of the endothelial injury remains controversial, but it is probably multifactorial, including chronic humoral and cellular rejection, ischemic and reperfusion injury at the time of transplantation, and chronic CMV infection of endothelial cells. Table 13.10 lists risk factors for the development of CAV, of which older donor age and hyperlipidemia are well-established risk factors, whereas the others are potential risk factors.

Because donor hearts are denervated at explantation, **the transplant recipient typically will not experience cardiac angina from advanced CAV.** The clinical presentation of CAV previously unrecognized in a patient may include symptomatic or asymptomatic LV dysfunction, myocardial infarction, or cardiac arrhythmia, including ventricular arrhythmias, heart block, syncope, or sudden cardiac death. Owing to the usually asymptomatic nature of CAV, transplant recipients require frequent surveillance studies to detect significant vasculopathy, including coronary angiography with or without IVUS, cardiac perfusion magnetic resonance imaging, and dobutamine echocardiography. The frequency and method of surveillance are center-specific. Although coronary angiography is useful for the diagnosis of nontransplant coronary artery disease, its sensitivity is considerably less in CAV because of the diffuse nature of this disease. Coronary IVUS imaging provides useful tomographic perspective to study the development and progression of CAV and is now considered by many to be the gold standard modality for diagnosing CAV. However, not all centers have access to routine IVUS imaging and thus its use will vary greatly from center to center. The nomenclature of CAV has not been standardized until recently (19). The recommended nomenclature for CAV is as follows:

CAV0 (not significant): no detectable angiographic lesion.

ISHLT CAV1 (mild): angiographic left main (LM) < 50%, primary vessel with maximum lesion of < 70%, or any branch stenosis < 70% (including diffuse narrowing) without allograft dysfunction.

TABLE 13.10 Risk Factors for the Development of Cardiac Allograft Vasculopathy

Older donor age
Hyperlipidemia
Donor brain death secondary to spontaneous intracranial hemorrhage
Cytomegalovirus infection
Increased C-reactive protein levels (> 1.66 mg/L)
Recurrent cellular rejection
Humoral (vascular) rejection
HLA antigen mismatch
Donor hepatitis B and C
Female donor
Peritransplant myocardial ischemia
Pretransplant coronary atherosclerotic disease
Conventional atherosclerosis risk factors (diabetes, hypertension, and smoking)

HLA, human leukocyte antigen.

ISHLT CAV2 (moderate): angiographic LM < 50%, a single primary vessel ≥ 70%, or isolated branch stenosis ≥ 70% in branches of two systems, without allograft dysfunction.

ISHLT CAV3 (severe): angiographic LM ≥ 50%, two or more primary vessels ≥ 70% stenosis, or isolated branch stenosis ≥ 70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤ 45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific).

Definitions

(a) A "primary vessel" denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus, and the dominant or codominant right coronary artery with the posterior descending and posterolateral branches.

(b) A "secondary branch vessel" includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches, or any portion of a nondominant right coronary artery.

(c) Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 milliseconds), shortened deceleration time (< 150 milliseconds), or restrictive hemodynamic values (right atrial pressure > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, and cardiac index < 2 L/min/m^2).

The detection of significant CAV should prompt aggressive percutaneous or more rarely surgical revascularization. Because of its relationship with chronic rejection, advancement of the immunosuppressant regimen has also been advocated. Statins have been shown prospectively to decrease the incidence of transplant vasculopathy and improve survival, regardless of the patient's lipid profile (20). Preliminary studies investigating the antiproliferative effects of TOR inhibitors (sirolimus and everolimus) suggest a significant reduction in coronary neointimal proliferation and, therefore, transplant coronary vasculopathy. In the future, the development of transplant vasculopathy may prompt a switch to a TOR inhibitor–based immunosuppressant regimen if the initial suggestion of attenuation of progression, and perhaps regression, of transplant vasculopathy is confirmed in larger, prospective clinical trials. In severe, advanced CAV, frequently the only viable option is repeat transplantation (1,4).

XII. MALIGNANCY

A. Malignancy is a common and devastating complication of cardiac transplantation. In immunocompetent people, the cellular arm of the immune system actively defends against a variety of neoplastic processes. With the initiation of immunosuppression after transplantation, this defense mechanism is rendered feeble and previously undeclared neoplastic foci may proliferate. Because up to 38% of patients undergo cardiac transplantation for ischemic cardiomyopathy, a significant proportion of which is smoking-related, lung cancers can occur. Other common tumors include lymphomas, skin cancers, colon cancers, and breast cancers. Skin cancers are particularly common in patients on azathioprine, and they usually prompt a substitution of MMF for azathioprine. Posttransplantation malignancies are particularly common in patients who have received cytolytic or induction therapy with OKT3, Atgam, or Thymoglobulin, and the risk correlates with cumulative dosing of immunosuppression. The risk of developing a malignancy as a result of immunosuppression is enhanced by the inability to adequately assess for overimmunosuppression. Underimmunosuppression is readily detected because of the development of acute rejection, whereas there is no clinical finding to suggest overimmunosuppression.

PTLD is an Epstein-Barr virus–related clonal expansion of B lymphocytes. PTLD may develop in any location but most commonly affects the gastrointestinal tract, lungs, and central nervous system. The primary treatment for PTLD is a reduction in immunosuppression (by about 50%), which can frequently be curative. Surgical debulking, systemic chemotherapy, and antiviral therapy may also be indicated in selected patients (1,4).

XIII. HYPERTENSION

Arterial hypertension commonly develops after cardiac transplantation secondary to the untoward effects of immunosuppression. **Hypertension developing after cardiac transplantation occurs in most cyclosporine-treated and tacrolimus-treated patients**. Three mechanisms proposed are as follows:

(1) direct sympathetic activation,
(2) increased responsiveness to direct circulating neurohormones, and
(3) direct vascular effects.

A common end point of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention and an elevated plasma volume. Corticosteroids play a minor role in the pathogenesis of cardiac transplant hypertension, which is described as a salt-sensitive type. Abnormal cardiorenal reflexes secondary to cardiac denervation may also contribute to salt-sensitive hypertension and fluid retention.

Patients with blood pressure consistently > 140/90 mm Hg should be treated. Titrated monotherapy with either ACE inhibitors or calcium channel blockers is usually effective in about 50% of the patients. Some patients will be prone to hyperkalemia secondary to the combined effect of cyclosporine and ACE inhibition on the kidney. The use of diltiazem, verapamil, or amlodipine necessitates the use of lower doses of cyclosporine and initially more frequent cyclosporine level monitoring because these drugs are competitive antagonists of cyclosporine at the cytochrome P450 level. Combination therapy with both an ACE inhibitor and a calcium channel blocker is a commonly employed strategy. Problematic hypertensives requiring multiple agents often require diuretics as part of their regimen. Hypertension in some patients is inadequately controlled despite maximally tolerated doses of both calcium channel blockers and ACE inhibitors. The final tier of management would be to add a β-blocker such as clonidine or doxazosin in refractory cases. β-Blockers traditionally have been avoided due to their known tendency to reduce exercise performance and because of concerns about excessive bradycardia. Some transplant cardiologists, however, routinely use β-blockers to manage hypertension in their transplant patients. Thus, β-blockers are not contraindicated but rather may be used with due caution (1,4).

XIV. OUTCOMES AFTER CARDIAC TRANSPLANTATION. Survival outcomes after cardiac transplantation continue to improve on a yearly basis despite what is generally accepted as a population of transplant recipients at greater risk, primarily because of advancing recipient age and increasing severity of heart failure. The 1-year survival rate after cardiac transplantation is 84% nationwide, but it is frequently > 90% at large transplant centers. The mortality in the first year after transplantation primarily results from postoperative complications, including multiorgan failure, primary graft failure, and systemic infection. Those surviving the first year posttransplantation have a median survival of 13 years. It is unlikely that any major improvements in early posttransplant survival will occur in light of these excellent results. However, a 10-year survival rate after cardiac transplantation is only 50%. Mortality in the long term primarily results from transplant coronary vasculopathy, malignancy, and renal failure. It is hoped that a major impact can be made on long-term survival with newer immunosuppressive drug regimens that may be less nephrotoxic and more effective at preventing transplant coronary vasculopathy (1).

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RELEVANT WEB SITES

International Society for Heart and Lung Transplantation (ISHLT) (www.ishlt.org).
Scientific registry of solid-organ transplant recipients in the United States (www.ustransplants.org).

CHAPTER 14

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Pulmonary Hypertension

I. INTRODUCTION. Pulmonary hypertension (PH) is a routinely made diagnosis in contemporary cardiology and pulmonary clinics. It is essential for the specialist as well as the internist to have a high index of clinical suspicion for this devastating disease, as early diagnosis and referral may affect the survival. Substantial advances are being made in the management of pulmonary arterial hypertension (PAH), which is more rapidly available at centers specializing in PH.

A. Terminology/definitions. PH is defined as mean pulmonary artery pressure (mPAP) > 25 mm Hg. PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The terms PH, which is a hemodynamic and pathophysiologic condition, and PAH, a clinical condition, are different terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly employed in PH include the following:

1. **Trans-pulmonary gradient (TPG)** is defined as the pressure difference between mean left atrial pressure (LAP) (more commonly pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP.
2. **Pulmonary vascular resistance (PVR)** is defined as TPG divided by the cardiac output (PVR = TPG/CO in Wood units).
3. **PAH** is hemodynamically defined as PH (i.e., mPAP ≥ 25 mm Hg) with increased PVR (more than 3 Wood units) and normal wedge pressure (< 15 mm Hg). It is a clinical condition characterized by precapillary PH and pathologic changes in the lung microcirculation.
4. **Pulmonary venous hypertension is characterized by mPAP ≥ 25 mm Hg, PVR > 3** Wood unit**, and elevated wedge pressure (PCWP ≥ 15 mm Hg).**

B. Classification. The World Health Organization has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics. The most recent classification derived from the world symposium on PH held in Dana Point, California, in 2008 is listed in Table 14.1.

C. Epidemiology. The total PH burden of the disease is substantial as it represents an end stage of multiple disease processes such as left-sided heart disease, chronic lung diseases, as well as PAH which is very rare. Most of the patients who are diagnosed with PH on routine testing (echocardiogram with pulmonary arterial systolic pressure [PASP] > 40 mm Hg) will end up having left heart disease (nearly 80%), some with lung disease and hypoxia (10%), and only a small minority (4%) will have PAH.

Data from registries estimate the prevalence at around 15 to 50 cases/million adults and its incidence at around 2.4 cases/million adults/year. Idiopathic PAH (IPAH) and familial PAH (previously known as "primary PH") are rare diseases with a prevalence of around 6 cases/million. **Familial cases account for 5% to 10% of all PAH cases. Mutations in the *bone morphogenetic protein receptor-II* (BMPR2)**

TABLE 14.1 Dana Point Classification of Pulmonary Hypertension (Simplified)

	Type	Subtype
1	Pulmonary arterial hypertension	Idiopathic Heritable Drugs and toxins induced Associated with CTD, HIV, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia Persistent PH of newborn
1′	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	
2	PH due to left heart disease	Systolic Diastolic Valvular
3	PH due to lung disease and/or hypoxia	COPD ILD Mixed obstructive and restrictive lung disease Sleep-disordered breathing Alveolar hypoventilation syndromes, etc.
4	Chronic thromboembolic PH	
5	PH with unclear and/or multifactorial mechanisms	Hematologic Systemic such as sarcoid and vasculitis

PH, pulmonary hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

gene have been identified in about 70% of patients with familial PAH and 10% to 40% of patients with sporadic IPAH. Hence, relatives of patients with familial IPAH should be advised about the availability of genetic testing and counseling in addition to echocardiographic screening.

PAH has been associated with environmental factors such as the use of drugs and toxins. **Anorexigens** (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) have been associated with PAH, with agents such as aminorex fumarate and (dex) fenfluramine. Select patient populations at an increased risk of developing PAH are discussed below.

1. **Patients with connective tissue diseases** (CTDs), especially the **limited cutaneous form of systemic sclerosis (formerly referred to as the CREST syndrome)**. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 10%. In other CTDs, such as systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome, PAH is observed less frequently.
2. **Human immunodeficiency virus (HIV) infection** is associated with approximately 0.5% incidence of PAH. However, because of this low incidence, routine screening is not recommended.
3. Patients with **cirrhosis and portal hypertension** are at an increased incidence of PH (5% of patients were referred for liver transplantation).

4. **Congenital heart disease** may lead to PAH when the underlying systemic-to-pulmonary shunt is not corrected. Most commonly, it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (e.g., ventricular septal defect and patent ductus arteriosus). However, high blood flow alone, as in atrial septal defect, may be sufficient. Once PVR approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to desaturation and cyanosis (Eisenmenger syndrome).

II. SIGNS AND SYMPTOMS

A. Symptoms. The symptoms of PH are nonspecific and are gradual in onset; therefore, there is a lag time of about 2 years (from symptom onset to diagnosis) in 90% of patients with PAH. These symptoms may include dyspnea on exertion, fatigue, weakness, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Symptoms at rest occur only at late stages of the disease and portend poor prognosis.

Some patient populations are at an increased risk for developing PH and should be carefully screened by clinicians by careful history taking, examination, and laboratory tests. These populations include patients with known, or relatives of those with, BMPR2 mutations, CTD, HIV infection, portal hypertension, prior appetite suppressant use, congenital heart disease with shunt, recent acute pulmonary embolism, left heart disease, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea.

It is advisable to perform annual screening with echocardiography in select high-risk groups, such as

(1) those with known BMPR2 mutation;
(2) first-degree relative of the patient with BMPR2 mutation or within pedigree of two or more patients with PAH;
(3) those with systemic sclerosis; and
(4) those with sickle cell disease.

B. Physical examination. Physical examination may provide clues as to the cause of PH. Findings of telangiectasia, digital ulceration, and sclerodactyly suggest scleroderma, while inspiratory crackles may point toward interstitial lung disease. Patients should be carefully screened for the presence of stigmata of liver disease, such as spider naevi, testicular atrophy, and palmar erythema. The presence of clubbing suggests congenital heart disease or pulmonary veno-occlusive disease. Cardiovascular examination of patients with PH may reveal a left parasternal lift, a loud P_2 at the apex, a pansystolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a right ventricular (RV) S_3. Lung sounds are usually normal (except for those with class 3 PH). Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are ominous signs suggestive of advanced stages with right-sided heart failure.

III. LABORATORY EVALUATION

A. Blood work

1. Routine biochemistry, hematology, and thyroid function tests.
2. **Serologic testing** is important to detect the underlying CTDs, HIV (mandatory screening), thrombophilia (in chronic thromboembolic pulmonary hypertension [CTEPH]), and hepatitis (in patients with suspected liver disease). More than a third of patients with IPAH have low-titer elevation in antinuclear antibodies. Systemic sclerosis is the most important CTD to exclude because of high prevalence of PAH in this syndrome. Anti-centromere antibodies are usually positive in limited scleroderma as are other antinuclear antibodies, including dsDNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP. In the diffuse variety of scleroderma, U3-RNP is positive. In patients with systemic lupus erythematosus, anticardiolipin antibodies may be found.

3. **Biomarkers.** Several circulating biomarkers have prognostic implications in patients with PAH, but their value in everyday clinical practice is still not established. Uric acid levels are shown to be increased in patients with IPAH, and elevated plasma troponin T levels (> 150 pg/mg) have been associated with worse outcomes in patients with CTEPH and PAH. BNP levels have also been used to monitor response to therapy or clinical course, as those with persistently elevated levels have worse outcomes. Similarly, NT-proBNP below cutoff levels < 1,400 pg/mL has been associated with better outcomes. BNP/NT-proBNP plasma levels should be checked for the initial risk stratification and may be considered for monitoring the effects of treatment, in view of their prognostic implications. Low and stable or decreasing BNP/NT-proBNP may be a marker of successful disease control in PAH.

B. The electrocardiogram (ECG). In typical cases of PH, the ECG shows right atrial (RA) dilatation, RV hypertrophy with strain, and a right axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occurs, leading to further clinical deterioration.

C. Chest radiograph. Initial chest x-rays are abnormal in majority (90%) of patients with IPAH at the time of diagnosis. There is often central pulmonary arterial (PA) dilatation with "pruning" (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. The chest x-ray may also point to lung abnormalities and show features suggestive of left heart disease.

D. Echocardiography. If PH is suspected based on history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. By using the Doppler technique, peak velocity of the tricuspid regurgitation jet can be measured. From this measured velocity, the pressure difference between right ventricle and right atrium can be estimated by employing the simplified Bernoulli equation ($\Delta P = 4v^2$). On condition that there is no pulmonic valve stenosis, PASP = 4 × (tricuspid regurgitant jet velocity)^2 + right atrial pressure (RAP). RAP can be estimated on the basis of inferior vena cava (IVC) characteristics. If the IVC is plethoric and there is clinical evidence of Jugular venous distension (JVD), RAP is presumed to be 10 to15 mm Hg, whereas if findings are normal, it is usually calculated as 5 mm Hg.

Other echocardiographic characteristics may raise the suspicion of PH, such as RA or RV dilatation, flattening of the interventricular septum with D-shaped left ventricle, increased RV wall thickness, dilatation of the pulmonary artery, and the presence of pericardial effusion. These features tend to occur later in the course of the disease.

Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with severe tricuspid regurgitation and overestimate PASP in non-PH patients. Ultimate confirmation requires RHC.

E. Right heart catheterization. RHC is required to ***confirm the diagnosis of PH, to assess the etiology and severity, and to test for vasoreactivity of the pulmonary circulation***. At experienced centers, morbidity (1.1%) and mortality (0.055%) rates are low. Consecutively, RAP, right ventricular pressure (RVP), PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter (Table 14.2). Cardiac output can be determined using the thermodilution method and/or the Fick method (measurement of mixed venous saturation SvO_2 needed). The PCWP is taken as a surrogate measure of LAP and, in the absence of mitral stenosis, left ventricular end-diastolic pressure (LVEDP). This measurement is very important because it helps differentiate PH associated with left heart disease from other conditions. However, it is subject to error in measurement and interpretation. Occasionally, it may be necessary to perform a left heart catheterization for direct measurement of LVEDP.

TABLE 14.2 Normal Values of Pressures and Measurements Derived from a Right Heart Catheterization

Measured characteristic	Normal value
Right atrial pressure	Mean 1–10 mm Hg
RVSP/RVDP	15–30/1–10 mm Hg
PASP/PADP	15–30/5–10 mm Hg (mean < 20 mm Hg)
PCWP	Mean 5–12 mm Hg
LVEDP	5–12 mm Hg
Cardiac output Cardiac index	5–7.5 L/min 2.5–4.0 L/min/m^2
PVR	0.25–1.6 Wood units
TPG	4–6 mm Hg

RVSP/RVDP, right ventricular systolic and diastolic pressures; PASP/PADP, pulmonary artery systolic and diastolic pressures; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

Temporal evolution of the hemodynamic variables with progression of PAH is depicted in Figure 14.1. As the disease progresses, the right ventricle starts to fail, leading to reduction in CO. As a result, PAP may decrease again. This decrease may give a false impression of hemodynamic improvement or suggest that there is mild to moderate disease. Therefore, it is imperative to measure PVR, which will be high in this situation. Usually, the RAP and PCWP also increase, implying RV failure and left ventricular (LV) diastolic dysfunction, respectively. The latter is the consequence of ventricular interdependence and abnormal compliance of the left ventricle produced by an enlarged right ventricle.

Vasoreactivity testing in PAH: In PAH, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers

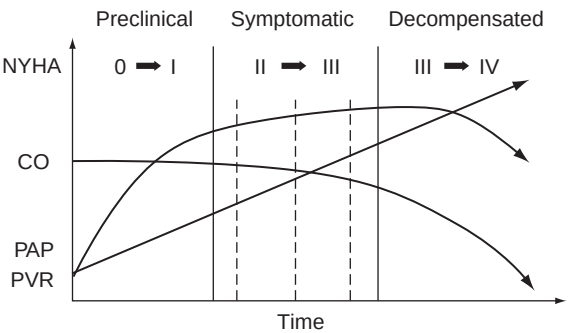

FIGURE 14.1 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (From Galie N, Manes A, Palazzi M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J.* 2007; 9:H68-H74, with permission.)

(CCBs). The agent most often used to test this is inhaled NO, with (i.v.) epoprostenol and (i.v.) adenosine as alternatives.

A positive acute response is defined as a > 10 mm Hg decrease in mPAP to reach an absolute value of mPAP < 40 mm Hg with an increased or unchanged CO and without significant drop in systemic blood pressure.

In patients with IPAH, about 10% to15% are acute responders and nearly half of these will prove to be long-term responders with a more favorable prognosis. This concept is less clear in other forms of PAH, although vasoreactivity testing is still recommended but controversial in congenital heart disease. It is not useful in other forms of PH (groups 1', 2, 3, 4, and 5). In veno-occlusive disease and left heart disease, it can even provoke pulmonary edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.

It is important to understand the difference between PAH vasoreactivity testing and the assessment of PH reversibility in left-sided heart failure. In PAH, vasodilator response testing is performed to select patients who may respond favorably to CCBs as the first agent versus those who will likely not. In left-sided heart failure and PH, vasodilatory drugs that affect the LV afterload, such as sodium nitroprusside, are given with an intention to reduce LV filling pressure and, evaluate for reversible pulmonary hypertension. Those who have persistent elevation in TPG and PVR to high levels (such as when TPG remains elevated to > 15 mm Hg and/or PVR is > 3 Wood units despite the reduction of PCWP to < 15 mm Hg) are at high risk for transplant failure, as the transplanted heart may not withstand persistently elevated PAPs , which results in right heart failure.

F. Pulmonary testing and arterial blood gas (ABG). Pulmonary function tests and ABGs are used to identify underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the range of 40% to 80% predicted) and mild to moderate reduction in lung volumes. Arterial oxygen partial pressure is normal or only slightly lower than normal at rest and arterial carbon dioxide partial pressure is decreased because of alveolar hyperventilation. The severity of emphysema and of interstitial lung disease can be diagnosed using high-resolution computed tomography (CT). If clinically suspected, screening overnight polysomnography may diagnose significant obstructive sleep apnea.

G. Six-minute walk distance. The 6-minute walk test (6MWT) is the most commonly employed measure of exercise capacity in patients with PH, both in clinical assessment and in research settings. In addition to the distance walked, the degree of dyspnea (Borg score) and oxygen saturation are also measured. **A 6-minute walk distance of < 332 m and a drop in oxygen saturation by > 10% are suggestive of poor prognosis**. It is also measured on routine follow-ups and can be indicative of clinical deterioration. It may also be used to assess the response to therapy.

H. Other tests. Chest CT and ventilation–perfusion (V/Q) scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding thromboembolic disease, V/Q scan is the preferred screening test. A normal or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%, while a high-probability scan warrants further evaluation with a pulmonary angiogram. Pulmonary angioscopy may be considered at specialized centers in cases of CTEPH to determine surgical candidacy.

IV. PATHOGENESIS

A. Hemodynamically, PH is a disease state with increased pulmonary pressures. Applying Ohm's law to the pulmonary circulation

TPG or pressure difference (mPAP – PCWP) = flow (CO) × resistance (PVR).

Thus, elevated mPAP may be a consequence of ***elevation in PCWP, increase in flow, or increase in PVR***. However, pulmonary vessels are highly compliant and capable of recruitment with progressive reduction in PVR for the increment in flow. These low-pressure, low-resistance, and high-compliance characteristics of the pulmonary vascular bed are regulated by a balance between vasodilators and vasoconstrictors and between cell proliferation and apoptosis. Genetic and environmental factors may disturb this balance, resulting in excessive vasoconstriction, vascular remodeling, and micro-thrombosis, which leads to pulmonary (arterial) hypertension. This leads to elevated PVR and an increase in RV afterload, ultimately resulting in RV dilatation and hypertrophy. This may progress to RV failure with further dilatation, thinning of the wall and tricuspid regurgitation, and worsening outcome.

B. Histologically, PAH is a panvasculopathy predominantly affecting the small pulmonary arteries. The initial lesions seem to be intimal hyperplasia and medial hypertrophy followed by more irreversible lesions such as intimal fibrosis, thrombosis in situ, inflammation, and plexiform arteriopathy. These lesions may be present in various distributions, local or diffuse, in a patient.

C. Molecular and endothelial abnormalities. Various vasoactive molecules play an important role in the pathologic evolution of PAH. Our understanding of these factors and various pathologic forces is limited, but some pathways have been elucidated mainly due to their therapeutic potential (Fig. 14.2).

1. **Prostacyclin/thromboxane A_2:** Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin has potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 has the opposite effect. In PAH, the balance is shifted toward thromboxane A_2 in small and medium-sized pulmonary arteries.
2. **Endothelin-1 (ET-1):** ET-1 is produced by endothelial cells and exerts its effect on the smooth muscle cells through two receptors: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of ET_B on the endothelial cells causes vasodilatation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are increased and ET-A receptors are abundant.
3. **Nitric Oxide:** NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of NO synthases (NOSs). It is a potent vasodilator and an inhibitor of platelet activation and of vascular smooth muscle cell proliferation. Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in patients with PAH.
4. **Others:** Various molecules such as serotonin, vasoactive intestinal peptide, and angiopoietin-1, and various inflammatory cells have been associated with PAH.

V. TREATMENT. The treatment of group 1 PH (or PAH) is primarily in the form of pulmonary-specific vasodilator therapy, whereas treatment in groups 2, 3, and 4 PH is mainly oriented toward treating the underlying condition (such as left heart disease and chronic lung disease).

A. General measures. A few general measures apply to all the PH groups:

(1) Mild physical activity, possibly via exercise rehabilitation, is beneficial.

(2) Routine influenza and pneumococcal vaccinations are recommended.

(3) Contraception should be discussed with females of child-bearing age, as pregnancy carries a 30% to 50% mortality risk and is contraindicated.

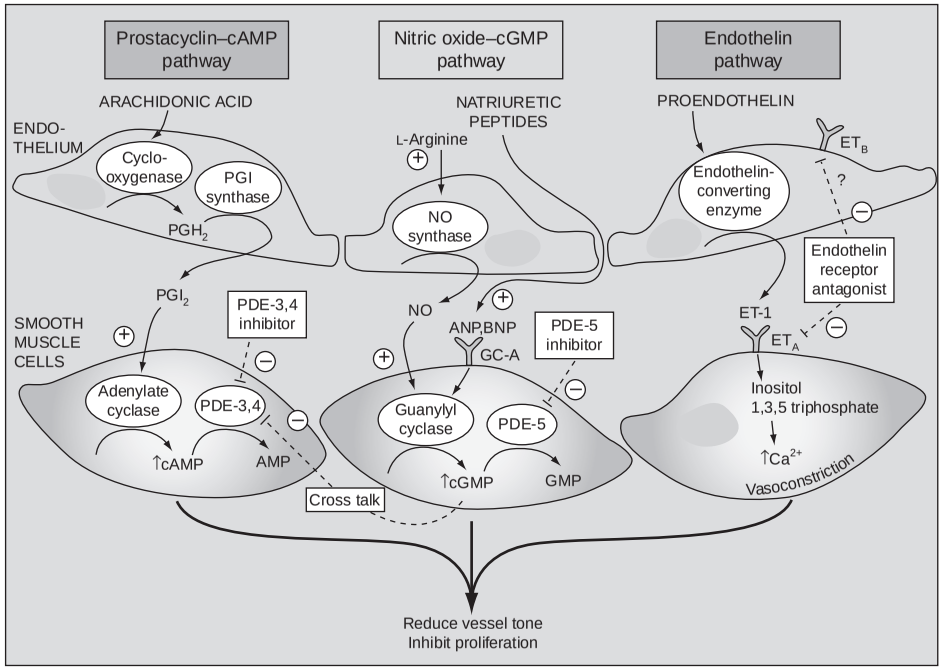

FIGURE 14.2 Therapeutic targets in pulmonary hypertension. cAMP, cyclin adenosine monophosphate; cGMP, cyclin guanosine monophosphate; PGI_2, prostacyclin; PGH_2, prostaglandin H_2; PDE, phosphodiesterase; NO, nitric oxide; ET, endothelin. (Reprinted from Benza RL, Park MH, Keogh A, et al. Management of pulmonary arterial hypertension with a focus on combination therapies. *J Heart Lung Transplant*. 2007;26(5):437–446, with permission from Elsevier.)

(4) Oxygen supplementation is advised to maintain saturation above 90%.
(5) Exposure to high altitude should be avoided. If flying, supplemental oxygen should be used if the patient's preflight saturation is less than 92%.
(6) Diuretic therapy is indicated to manage RV failure with volume overload.
(7) Digoxin may be considered in the case of atrial tachyarrhythmias.
(8) Oral anticoagulation is recommended in CTEPH, in IPAH, and in advanced diseases (e.g., continuous i.v. therapy). In PAH, a low therapeutic value of international normalized ratio (between 1.5 and 2) is generally targeted; however, this has not been evaluated in a randomized controlled trial (RCT).

B. Pulmonary vasodilators. The initial treatment choice in PAH is guided by vasoreactivity testing. For the responders (about 10% to 15% of the IPAH population), CCBs are the first line of treatment. Careful reassessment for safety and efficacy is mandatory, because only half of these patients will prove to be long-term responders and many will need additional vasodilators. The current treatment algorithm for PAH as suggested by the 2009 ACCF/AHA expert consensus document is shown in Figure 14.3.

1. **Prostacyclin analogs:** Prostacyclin is a potent endogenous vasodilator and an inhibitor of platelet aggregation and also appears to have antiproliferative activity. This may explain why *epoprostenol* (Flolan) can be used to acutely lower PAPs (as used in vasoreactivity testing) as well as to achieve long-term hemodynamic improvement in patients with PH who are nonresponders. In RCTs, epoprostenol has been shown to improve the functional class, exercise tolerance, hemodynamics, and survival in patients with IPAH. Epoprostenol has to be administered in a continuous i.v. infusion, and early titration often results in unbearable side effects of nausea, headache, flushing, jaw and leg pain, and diarrhea. Adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. *Treprostinil* (Remodulin) is another prostacyclin analog that can be administered by inhalation, orally, or via continuous subcutaneous pump. It has been shown to improve the exercise

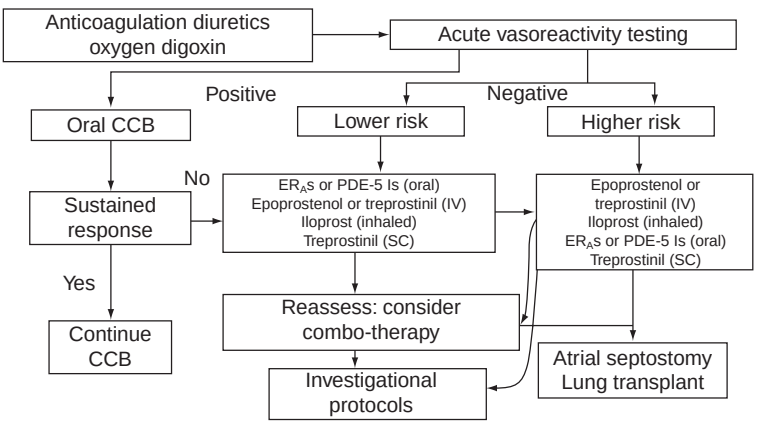

FIGURE 14.3 PAH treatment algorithm. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 Is, phosphodiesterase type 5 inhibitors. (Reprinted from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. *J Am Coll Cardiol*. 2009;53(17):1573–619, with permission from Elsevier.)

capacity, hemodynamics, and symptoms. Infusion site pain is the most common side effect. *Iloprost* (Ventavis) is available as an aerosol administration and has a proven beneficial effect in patients with PAH and CTEPH.

2. **Endothelin receptor antagonists (ERAs):** *Bosentan* (Tracleer) is an oral active dual ET_A/ET_B receptor antagonist that has been shown to improve the exercise capacity, functional class, hemodynamics, and cardiac performance as measured by echocardiography and clinical outcomes. *Sitaxsentan* and *ambrisentan* are more selective ET_A receptor antagonists with similar benefits as bosentan. Liver injury and teratogenicity are major concerns and require monthly monitoring.
3. **PDE-5 inhibitors:** Orally active PDE-5 inhibitors prevent the degradation of cGMP, causing vasorelaxation. *Sildenafil* (Revatio) has favorable effects on exercise capacity, symptoms, and hemodynamics. Tadalafil (Adcirca) has the same effects, although it also delays the time to clinical worsening. Headache, flushing, dyspepsia, and epistaxis are the usual side effects.

In low-risk patients, oral therapy with ET receptor antagonists or PDE-5 inhibitors is the first choice, whereas i.v. epoprostenol is reserved for the high-risk population. Combination therapy is being routinely employed if treatment goals are not achieved with one compound ("goal-directed therapy"). The rationale is based on attacking different pathologic processes with different agents.

C. Treatment of non-group 1 PAH. Many pulmonary vasodilators have been evaluated for various non-PAH groups such as left-sided heart disease and lung disease. The following recommendations are based on current evidence:

1. **Group 2 PH (left-sided heart disease):** prostanoids and ERAs are associated with an increased event rate in patients with LV dysfunction and are contraindicated. There is some evidence of improvement in the quality of life, exercise performance, and hemodynamics with sildenafil in patients with left heart disease and in patients bridged to transplantation with a left ventricular assist device.
2. **Group 3 PH (lung disease of hypoxia):** pulmonary vasodilators are not recommended.
3. **Group 4 PH (CTEPH):** prostanoids, ERAs, or PDE-5 inhibitors may be used prior to surgery to improve hemodynamics. It may be used in patients with predominant peripheral disease or in those with persistent PH after surgery.

D. Surgical therapies. In CTEPH, surgery (pulmonary endarterectomy) is potentially curative in patients with accessible (proximal) disease. It is recommended that surgical evaluation and procedure be performed at high volume centers. Balloon atrial septostomy is rarely performed for palliation in patients with advanced PAH with recurrent syncope and/or right heart failure who have failed all available medical treatments. RV assist devices have emerged as a therapy in postoperative RV failure in the presence of PH. Heart–lung transplantation should be considered in a subset of eligible patients who remain in New York Heart Association functional class III or IV or in those who cannot achieve a significant exercise and hemodynamic improvement after 3 months of epoprostenol therapy.

VI. CONTROVERSIES.

Several controversies exist in the clinical and research arenas regarding PH, leading to frequent difference of opinions among referring internists, pulmonologists, and cardiologists. It is therefore important to identify such areas of concern. This may help target future research and identify these patients who would benefit from management at a specialized center where a multidisciplinary approach may be provided.

A. Most therapies (except epoprostenol) in PAH have not shown mortality benefits. Most therapeutic trials are small randomized clinical trials with soft end points such as 6MWT, exercise tolerance, and improvement in dyspnea scoring. While this raises

valid concerns regarding the long-term benefit of many expensive drugs, it is interesting that the overall survival in this patient population is improving.

B. Pulmonary vasodilators have generally been ineffective or harmful in patients with left-sided heart failure. However, PDE-5 inhibitors are an exception, as there have been multiple small studies that suggest improvement in exercise parameters and hemodynamics. One study, PhosphodiesteRasE-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure Study (RELAX), is currently enrolling participants to study the effect of sildenafil in patients with diastolic heart failure.

C. In "out-of-proportion" PH, many patients with left-sided heart failure may have only modest increase in PCWP (< 22 to 25 mm Hg) but very high PAP (systolic PAP > 60 mm Hg) with high TPG (> 18 mm Hg). This usually happens in patients who have developed a "fixed" PH, as opposed to a very few who have both left-sided heart failure and PAH.

D. Pulmonary vasoreactivity is often used in heart transplant candidates with "out-of-proportion" PH by administering sodium nitroprusside or nitroglycerin in the cardiac catheterization laboratory and assessing hemodynamics with reduction in PCWP. Those who have reduction in PAP and TPG may be able to undergo transplantation without right heart failure.

E. The treatment for "out-of-proportion" PH is primarily focused on treating the underlying left-sided failure.

VII. PROGNOSIS AND FOLLOW-UP

A. Prognosis. Survival in patients with PH differs between PH groups and also within each group depending on the etiology. For example, the prognosis in patients with severe aortic stenosis with PH will be different from that of patients with diastolic heart failure and PH. Similarly, it is quite different between idiopathic and scleroderma-related PH. Evaluating disease severity and predicting survival is important because it may guide clinical management. Best data regarding prognosis are available for the IPAH subset population. The natural history of this group shows survival rates of 68%, 48%, and 34% after 1, 3, and 5 years, respectively. There is registry level evidence that prognosis has improved with pulmonary vasodilator therapies. Table 14.3 outlines clinical, echocardiographic, and hemodynamic features that may

TABLE 14.3 Prognostic Variables in Pulmonary Hypertension

Lower	Determinants of risk	Higher
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (> 400 m)	6-Min walk distance	Shorter (< 300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion Significant RV dysfunction
Normal/near-normal RAP and CI	Hemodynamics	High RAP, low CI

RV, right ventricular; BNP, brain natriuretic peptide; RAP, right atrial pressure; CI, cardiac index.

Adapted from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension*: ACCP evidence-based clinical practice guidelines *Chest*. 2004;126:78s–92s.

predict the prognosis in patients with PAH. Again, these data are mainly derived from the IPAH population, and it is unknown whether these data are transferable to other P(A)H populations.

B. Follow-up

1. **Frequency**: Longitudinal follow-up of patients with PAH should be done at a center that specializes in PAH management with a sizeable patient population. Such centers have nurses, physicians, and ancillary support who are experienced in managing the disease and its complications. The frequency of follow-up depends on the clinical course. Those who have stable clinical course (i.e., with no evidence of heart failure, normal RV size/function, functional class I–II, 6MWT > 400 m, normal/near-normal hemodynamics, and stable BNP levels, and those maintained on oral therapy) should have clinical visits every 3 to 6 months. Unstable patients—those with sign of right heart failure, 6MWT < 300 m, abnormal hemodynamics, increasing BNP, and on i.v. therapy or combination therapy—should be evaluated every 1 to 3 months.
2. **Routine evaluation:** Assessment at each visit should include physical examination, assessment of functional class, 6MWT at each visit, and echocardiogram at 6 to 12 months, and blood work including biomarkers are usually performed at each visit or with change in clinical status or therapy; RHC is performed every 6 to 12 months in unstable patients and in stable patients it is performed when there is clinical deterioration or change in therapy.

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SECTION III

Valvular Heart Disease

EDITOR

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CHAPTER 15

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Brian P. Griffin

Aortic Valve Disease

I. AORTIC STENOSIS

A. Introduction. Aortic stenosis (AS) causes progressive obstruction of the left ventricular outflow tract (LVOT), resulting in pressure hypertrophy of the left ventricle and the classic symptoms of heart failure, syncope, and angina pectoris. Stenosis most commonly occurs at the level of the valve (AS); however, subaortic and supravalvular stenoses are also well-defined entities. Untreated AS is associated with significant morbidity and mortality. As prompt recognition and treatment are associated with normalized life expectancy in those patients with symptomatic severe AS, careful evaluation and management can have significant impact on survival.

B. Etiology

1. Valvular AS has several causes, including congenital, rheumatic, bicuspid, and most commonly inflammation with resultant calcification.

a. The most common cause of AS in the United States is calcific degeneration. Although initially thought to be the result of normal "wear and tear" of the valve leaflets, there is now ample evidence that suggests that the progression of stenosis is related to an active process of inflammation involving the renin–angiotensin system, lipid accumulation, and resultant calcification. Several inflammatory pathways are implicated, including those that utilize osteopontin, bone morphogetic proteins, and receptor activator of nuclear factor-κB ligand.

Aortic sclerosis is caused by calcification and thickening of the aortic valve without the increased gradients as seen in AS. Both aortic sclerosis and calcific aortic stenosis have been associated with traditional risk factors for atherosclerosis, such as smoking, hypertension, and hyperlipidemia. Aortic sclerosis is associated with an increased risk of cardiovascular death and myocardial infarction and can progress to AS. Other conditions associated with calcific AS include Paget's disease and end-stage renal disease.

b. Bicuspid valves are present in 1% to 2% of the population, are predominant in men, and occur in **9% of first-degree family members** of those afflicted. The most common anatomic abnormality seen in a bicuspid valve is the fusion of the right and left coronary cusps. Concurrent **coarctation, aortic root dilation, and a propensity for aortic dissection are seen** in a minority of patients. Severe stenosis typically develops by the fifth or sixth decade; however, earlier and later presentations are not uncommon. Unicuspid valves open only at one commissure, are uncommon, and are usually severely stenotic at an early age.

The most recent American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines (2006) highlight the importance of evaluating the aorta and valve in bicuspid aortic valve with echocardiography or, if this is inadequate, with other imaging modalities such as magnetic resonance imaging or computed tomography. In some instances, the aorta may require surgical intervention before the valve. The guidelines recommend that patients with an aortic diameter > 4 cm and bicuspid valve should have

yearly follow-up of aorta size and should have **surgical intervention if the aorta is > 5 cm or increases by > 0.5 cm in a year**, irrespective of the valve lesion severity. **If the valve requires surgery, then aorta replacement is recommended if the aorta is > 4.5 cm at the time of surgery**. β-Blockers should be considered in bicuspid aortic valve patients in the presence of ascending aorta enlargement.

c. **Rheumatic AS** often coexists with aortic regurgitation (AR) and mitral valve lesions. It is a rare cause of isolated severe AS in the industrialized world. Fusion of the commissures occurs leaving a small central orifice.

2. **Subvalvular AS.** This is a congenital condition, although it may not be apparent at birth. Typically, a circumferential **fibromuscular membrane involving the anterior mitral valve leaflet is present in the LVOT below the aortic valve.** In more extreme cases, a tunnel-like obstruction may be present, rather than a discrete membrane. The pathogenesis of this condition is not perfectly understood but is thought to represent a maladaptive response to abnormal flow dynamics in the LVOT. It may exist with other left-sided obstructive lesions, such as coarctation as part of Shone's syndrome. The condition may recur even after successful membrane resection. Subvalvular AS may be difficult to distinguish from hypertrophic cardiomyopathy, especially when secondary left ventricular hypertrophy (LVH) is pronounced.
3. **Supravalvular AS** is uncommon. It may occur as part of a congenital syndrome such as Williams syndrome caused by a mutation in the elastin gene (i.e., associated hypercalcemia, elfin facies, developmental delay, small stature, and multiple stenoses in the aorta and peripheral arteries) or be caused by lipid deposits in severe forms of familial hypercholesterolemia. Obstruction occurs above the valve in the ascending aorta.

C. Pathophysiology

1. **Pressure overload.** All forms of AS are characterized by progressive narrowing of the LVOT. To maintain cardiac output in the face of increased afterload, the left ventricle must generate higher systolic pressures, which increases LV wall stress. In response to the pressure overload and increased wall stress, the left ventricle undergoes compensatory, concentric hypertrophy. The increase in LV wall thickness allows the wall stress to normalize according to Laplace's law: wall stress = (pressure × radius)/(2 × thickness).
2. **Diastolic dysfunction.** LV diastolic function is determined by LV relaxation properties and LV compliance (i.e., change in volume with change in pressure [dV/dP]). Increased afterload and LVH lead to a reduction in LV compliance. Furthermore, there are changes in strain and torsion characteristics of the left ventricle in AS. Passive early diastolic filling is reduced, and maintenance of an adequate LV preload becomes more dependent on active left atrial contraction.
3. **Supply–demand mismatch.** Myocardial oxygen demand is determined by heart rate, cardiac contractility, and myocardial wall stress. Over time, LVH is unable to compensate for the increase in wall stress imposed on the left ventricle by progressive pressure overload. As the AS becomes more severe, wall stress and myocardial oxygen demand increase in parallel. Concurrently, AS is associated with a decrease in myocardial oxygen supply. Progressive LVH and diastolic dysfunction lead to an elevation in left ventricular end-diastolic pressure (LVEDP). Elevated LVEDP leads to decreased perfusion pressure across the coronary bed and causes endocardial compression of small intramyocardial arteries, impairing coronary flow reserve. The imbalance between myocardial oxygen supply and demand can precipitate ischemia during exertion.

D. Natural history. The classic survival curve for patients with untreated AS, as described by Ross and Braunwald (1), is shown in Figure 15.1.

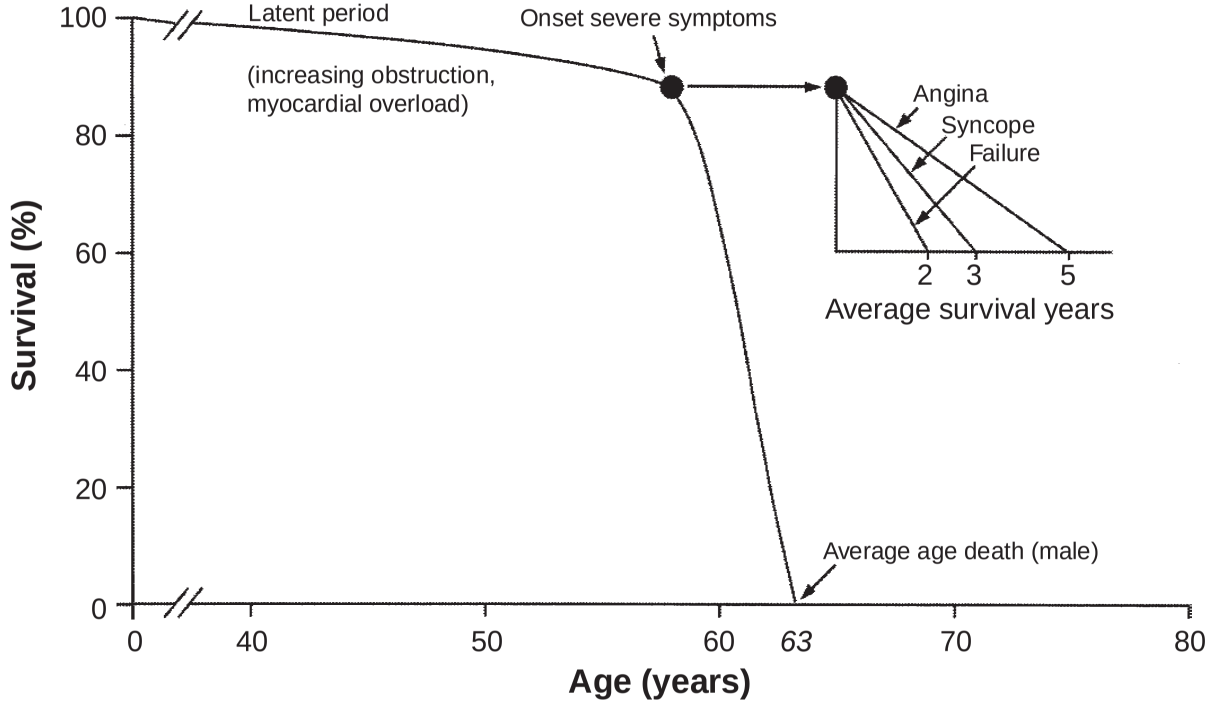

FIGURE 15.1 Patient survival in aortic stenosis.

1. **Asymptomatic patients**
   a. The disease process of AS is characterized by a long latent phase, during which the patient has no symptoms. This period is associated with near-normal survival. The risk of sudden cardiac death in asymptomatic patients with critical AS is < 2% per year.
   b. Although the underlying cause helps predict the age of symptom onset, there is marked individual variability in the length of the latent period and the subsequent rate of progression of disease. In general, among asymptomatic valvular AS patients, the mean aortic valve gradient rises by 7 mm Hg/y and the aortic valve area (AVA) decreases by 0.1 cm^2/y.
   c. Because of the variable rate of disease progression, all patients with AS should be advised to report the onset of any symptoms to their physician and should be followed clinically and with Doppler echocardiography with increasing frequency as the lesion progresses.
   d. Once the **valve becomes severely narrow**, as evidenced by a peak **Doppler velocity of 4 m/s across it, the likelihood of developing symptoms or requiring surgical intervention over the following 2 years is very high.** This likelihood is increased if the valve is heavily calcified.
2. **Symptomatic patients.** When symptoms of AS develop, the survival rate decreases markedly, unless aortic valve replacement (AVR) is performed.
   a. Patients with **angina** have a 50%, 5-year survival rate without surgical intervention. Those with **syncope** have a 50%, 3-year survival rate without surgical intervention. Patients with **heart failure** have a mean survival time of < 2 years if treated medically.
   b. In patients with severe, symptomatic AS, sudden cardiac death can occur in the setting of hypotension or arrhythmia due to ischemia, LVH, or impaired LV function.
   c. Signs and symptoms of severe AS might be subtle in some patients. Information concerning activity levels from family members may be useful in this situation, as may a symptom-limited stress echocardiogram. Exercise stress testing is absolutely contraindicated in the setting of definite symptoms.

E. **Clinical manifestations**
1. **Signs and symptoms.** The onset of symptoms usually indicates progression to severe AS and heralds the need for surgical evaluation.
   a. **Angina.** Patients with severe AS can experience ischemia from myocardial supply–demand mismatch due to high LV diastolic pressures, decreased myocardial perfusion, and increased wall stress. Angina can also result from underlying coronary artery disease (CAD). CAD is common among patients with severe AS. It occurs in 40% to 80% of patients with angina and in 25% of patients without angina.
   b. **Syncope.** Because of fixed LVOT obstruction, patients with severe AS are unable to augment their cardiac output under conditions of low systemic vascular resistance (SVR) (i.e., induced by certain medications or vasovagal reactions). The ensuing hypotension can cause presyncope, syncope, or even cardiovascular collapse and death. Syncope can also result from atrial or ventricular arrhythmias, abnormal baroreceptor function, or abnormal vasodepressor responses induced by LV pressure overload.
   c. **Heart failure** symptoms, such as exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea, and fatigue can result from LV systolic or diastolic dysfunction.
2. **Physical findings**
   a. **Arterial examination.** A hallmark finding in AS is a diminished and delayed carotid upstroke, pulsus parvus et tardus. However, elderly patients

with noncompliant vessels or patients with concomitant AR may often maintain a normal carotid pulsation, despite severe AS. These findings are rare with obstruction above or below the valve. It is classically thought that severe AS is not associated with hypertension, as the narrowed valve limits the flow into the arterial system and thus gives rise to a narrowed pulse pressure and relative hypotension. In fact, in the elderly, hypertension and severe AS may often coexist, likely as a result of impaired elasticity of the aortic walls, and the finding of arterial hypertension does not preclude significant associated AS.

b. Palpation. With LVH and normal LV cavity dimensions, the apical impulse is usually nondisplaced, diffuse, and sustained. However, the apical impulse may later be displaced when there is LV systolic dysfunction. A double apical impulse represents a palpable *a* wave or S_4, caused by a noncompliant left ventricle. A systolic thrill may be palpable in the second right intercostal space.

c. Auscultation. The main auscultatory findings are shown in Figure 15.2.

(1) The typical murmur of AS is a systolic ejection murmur heard at the right upper sternal border that radiates to the neck. With a mobile bicuspid valve, an aortic opening sound may precede the murmur. As the severity of stenosis increases, the murmur becomes longer and peaks later in systole. The intensity of the murmur does not necessarily correspond to the severity of AS. S_1 is usually normal in AS. As the AS becomes more severe, the aortic component of S_2 diminishes and eventually disappears, resulting in a soft, single S_2. Often, with severe AS, S_2 is paradoxically split because of the prolonged ejection duration through the severely narrowed valve. S_3 is indicative of poor LV systolic function. An S_4 is common because of reduced LV compliance.

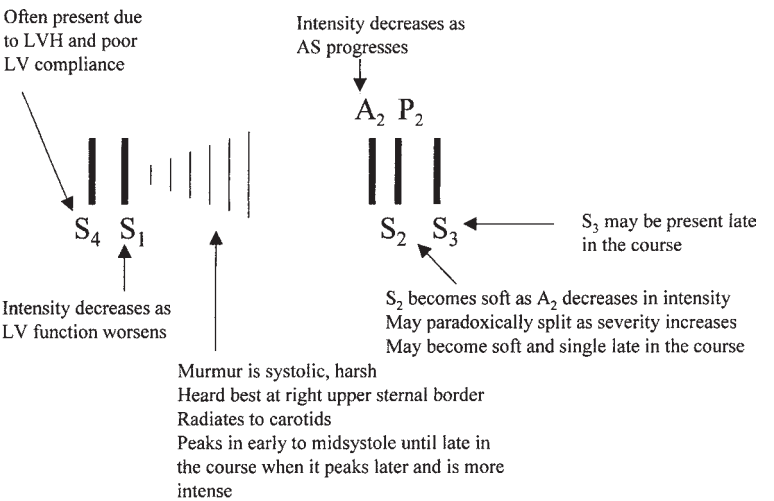

FIGURE 15.2 Auscultatory findings in aortic stenosis. LVH, left ventricular hypertrophy; LV, left ventricular.

TABLE 15.1 Physical Findings and Maneuvers Useful in Distinguishing Various Forms of Left Ventricle Outflow Tract Obstruction

Maneuver finding	Valvular	Supravalvular	Subvalvular	Hypertrophic cardiomyopathy
Pulse volume after PVC	Increases	Increases	Increases	Decreases
Valsalva effect on systolic murmur	Decreases	Decreases	Decreases	Increases
AR	Common	Rare	Common	Rare
S_4	Common	Uncommon	Uncommon	Common
Carotid pulse	Normal to anacrotic (parvus et tardus)	Unequal	Normal to anacrotic	Rapid jerky upstroke

AR, aortic regurgitation; PVC, premature ventricular contraction

(2) Careful examination for other murmurs should be performed. AS is often accompanied by AR. Maneuvers performed during the physical examination can help differentiate different types of LV outflow obstruction, whether this is at, below, or above the valve. These are summarized in Table 15.1.

3. **Diagnostic testing**
   a. The typical **electrocardiogram (ECG)** of a patient with isolated severe AS usually demonstrates left atrial abnormality (80% of cases) and LVH (85% of cases).
   b. **Chest radiography** can be entirely normal, even in patients with critical AS. The cardiac silhouette may become boot-shaped because of concentric LVH. Cardiomegaly may be identified if there is LV dysfunction or coexisting AR. Aortic valve and root calcification can be seen in adults with severe calcific, degenerative AS. Poststenotic dilation of the ascending aorta may be evident.
4. **Severity of AS**. The severity of AS is currently graded by ACC/AHA valve guidelines as follows:

Mild: valve area > **1.5 cm**^{2}, mean gradient < 25 mm Hg, or jet velocity < 3.0 m/s
Moderate: valve area **1.0 to 1.5 cm**^{2}, mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m/s
Severe: valve area < **1.0 cm**^{2}, mean gradient > 40 mm Hg, or jet velocity > 4.0 m/s

The normal aortic valve opens to 3 to 4 cm^2.

5. **Echocardiography**
   a. **Transthoracic Doppler echocardiography** is the test of choice per ACC/AHA guidelines to establish the diagnosis of AS, to determine the cause and location, and to assess its severity. It should be performed when the diagnosis of AS is first suspected and information such as LV wall thickness, size, and function should also be obtained. After the diagnosis is established, patients should have frequent, regular clinical follow-up examinations to look for the development of symptoms. Echocardiographic follow-up can be tailored to the severity of disease: at least annually for severe AS and more frequently

as the severity increases. Development of new symptoms and signs should quickly prompt a repeat evaluation.

(1) The parasternal long-axis views, two dimensional and M-mode, provide valuable information for determining the mechanism and severity of AS. In this view, the coaptation line of the aortic valve is normally centered within the LVOT in a trileaflet valve. The leaflets of a bicuspid valve often have an eccentric closure line, typically posterior to the midline. Systolic leaflet doming can be seen in congenital AS and rheumatic AS. The degree of LVH, LV chamber enlargement, or left atrial enlargement can be quantitated using two-dimensional and M-mode imaging. The LVOT diameter used in the continuity equation is measured in the two-dimensional, parasternal long-axis view.

Subaortic stenosis and supravalvular AS may also be detected in this view. Subaortic stenosis may be evident as a membrane below the aortic valve with normal motion of the valve. Pulsed Doppler may indicate that the obstruction is occurring below the valve and 2 dimensional echocardiogram often shows AR due to the turbulent jet hitting aortic valve leaflets and causing leaflet scarring and impaired coaptation. In supravalvular AS, narrowing above the valve is evident on imaging and with Doppler.

(2) The parasternal short-axis view is the most useful view for establishing the cause of congenital AS. The number of commissures and the shape of the valve orifice should be assessed (Fig. 15.3). Trileaflet valves open

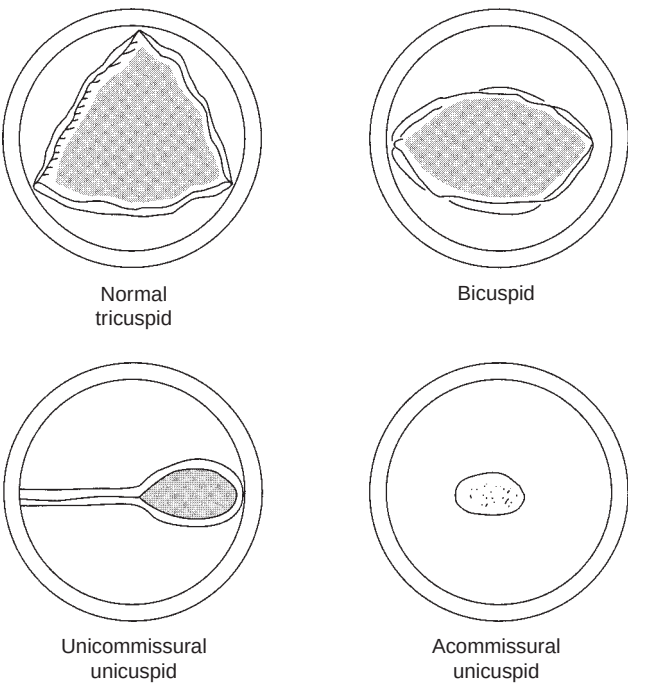

FIGURE 15.3 A schematic representation of parasternal short axis of a congenitally abnormal aortic valve.

as a triangle, whereas an elliptical opening suggests a bicuspid valve. In a unicuspid valve, the opening is elliptical but occurs across a radius rather than the diameter of the valve.

(3) The apical five-chamber and three-chamber views are well aligned with flow through the aortic valve. Continuous wave Doppler recordings across the aortic valve and pulsed wave Doppler flow in the LVOT proximal to the aortic valve are recorded in these views for the continuity equation.

(4) Continuous wave Doppler should be performed at multiple sites, including the suprasternal notch and the right sternal border, to ensure that the maximal velocity across the aortic valve is recorded. The dimensions of the ascending aorta should be measured, and coarctation in the descending aorta should be sought, especially in those with bicuspid aortic valves.

b. **Transesophageal echocardiography (TEE).** Planimetry of the aortic valve orifice is often possible with TEE and relates well to that measured by cardiac catheterization. Planimetry is difficult when the valve is extremely calcified. In bicuspid valve, the smallest area should be sought carefully, as the valve opening is not planar but rather forms a cone due to the doming of the valve as it opens. TEE is particularly useful for determining the morphologic features of the valve in congenital AS. TEE is often necessary to confirm the diagnosis of subaortic membrane and to differentiate it from hypertrophic cardiomyopathy or valvular AS.

c. **Dobutamine echocardiography and stress echocardiography.** Exercise testing in patients with asymptomatic AS may provide useful information such as exercise-induced symptoms or abnormal blood pressure response (ACC/AHA class IIb indication). Exercise testing is contraindicated (ACC/AHA class III indication) in symptomatic patients with AS. Dobutamine echocardiography may be useful in evaluating low-flow/low-gradient AS in patients with LV dysfunction (see Chapter 51 for further discussion).

6. **Hemodynamic calculations**

a. **Doppler echocardiography** is the standard modality used for the assessment of transvalvular pressure gradient and AVA.

(1) **Simplified Bernoulli equation ($\Delta P = 4v^2$)**, in which P is pressure and v is peak velocity of flow across the aortic valve, is used to estimate the peak instantaneous gradient. The mean gradient across the valve can be measured by calculating the area under the Doppler envelope. The peak velocity of flow across the aortic valve should be measured in three areas: the LV apex, the right sternal border, and the suprasternal notch. The highest measured velocity is used to calculate the peak transvalvular gradient. When stenosis is present at two levels (i.e., in LVOT and at the valve), the gradient across the LVOT reflects the integrated effects of the obstruction at both levels. It is usually impossible with Doppler to precisely differentiate the contribution of each level of obstruction to the total. This may be inferred by the analysis of the images, by TEE, or by direct measurement at cardiac catheterization.

(2) Calculation of AVA is based on the **continuity principle**, which states that the flow of an incompressible fluid in a closed system must remain constant. Flow in a vessel is the product of the cross-sectional area (A) of the vessel and the velocity (V). Area is calculated as πR^2 or $\pi \cdot D^2/4 = 0.785D^2$, where R is the radius of the vessel and D is the diameter. A schematic representation of the variables for calculating AVA is shown in Figure 15.4. The continuity equation for the aortic valve is as follows:

$$\text{Area}_{\text{aortic valve}} = \text{diameter}_{\text{LVOT}}{}^2 \times 0.785 \times \text{VTI}_{\text{LVOT}}/\text{VTI}_{\text{aortic valve}}.$$

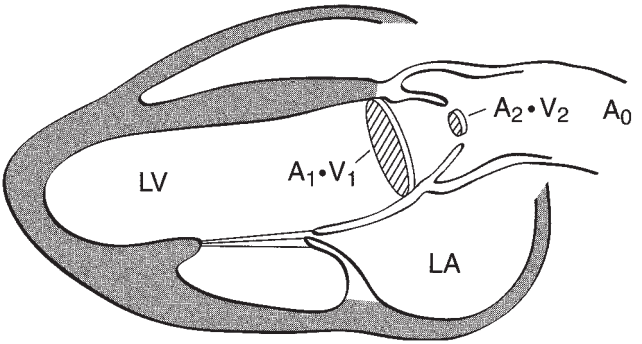

FIGURE 15.4 A schematic representation of parasternal long-axis view and the continuity principle. LV, left ventricle; LA, left atrium.

In the above equation, VTI is the time–velocity integral. The continuity equation is valid only for valvular AS. It cannot be used to assess valve area when there are stenoses in series such as valvular and subvalvular narrowing occurring simultaneously.

(3) Care should be taken to avoid measuring postextrasystolic beats. If the patient is in atrial fibrillation, 10 consecutive beats should be measured and averaged for both velocity measurements.

(4) During evaluation of an aortic valve prosthesis, the standard continuity equation cannot be used. Instead, the velocity ratio or **dimensionless index** is used to estimate the severity of prosthetic stenosis. It is calculated by dividing the peak velocity in the LVOT by the peak velocity through the aortic valve. **A dimensionless index of < 0.25 is generally accepted to represent severe stenosis**. This is also useful if the LVOT diameter is difficult to ascertain.

b. Cardiac catheterization was once considered the gold standard for the quantification of AS but is now contraindicated (ACC/AHA class III indication) in the routine evaluation of a patient when echo-Doppler studies are adequate and congruent with clinical findings.

(1) Preoperative catheterization. Patients > 50 years of age, patients with angina, and patients with significant risk factors for CAD should undergo coronary cineangiography before aortic valve operations (ACC/AHA class I indication).

(2) Catheter-derived hemodynamic data are indicated (ACC/AHA class I indication) to further evaluate the severity of AS when the clinical and echocardiographic findings diverge. Because cardiac catheterization findings often differ from those of echocardiography, it is important to understand the differences in what is being measured. The mean gradients obtained during catheterization should be equivalent to the mean gradients obtained by echocardiography. These correlate well when performed expertly and simultaneously. The peak gradient measured during catheterization is the peak-to-peak gradient, which is lower than the peak instantaneous gradient obtained with echocardiography (Fig. 15.5). In the setting of reduced cardiac output of any cause, the aortic gradient may be much lower and may be < 20 mm Hg in severe LV dysfunction despite critical AS.

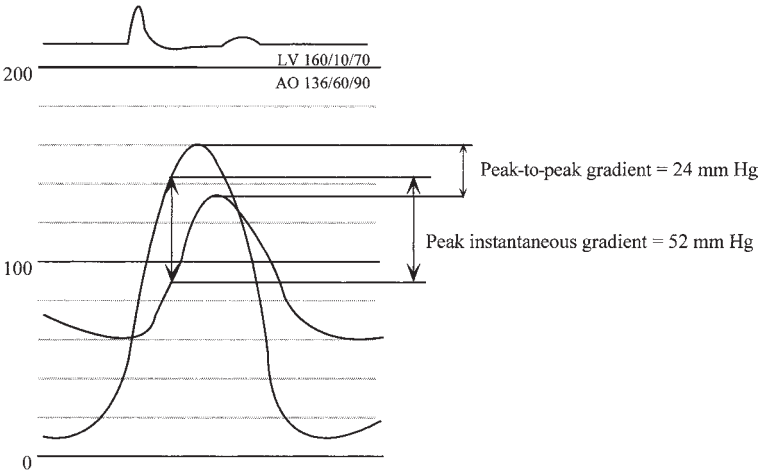

FIGURE 15.5 Simultaneous recording of LV and aortic pressures. LV, left ventricle; AO, aorta.

(3) The most precise measurement of transaortic valvular gradient is made with two different catheters (one in the LV cavity and the other in the ascending aorta) or with a double-lumen pigtail catheter. Because the two-catheter technique requires cannulation of both femoral arteries, another acceptable method of measuring the peak-to-peak gradient is catheter pullback from the left ventricle to the ascending aorta. A typical pressure tracing of simultaneous LV and aortic pressures is shown in Figure 15.5.

(4) Catheterization of the patient with severe AS should be performed with low-osmolar, nonionic contrast agents. These cause less hypotension due to peripheral arterial vasodilation, less bradycardia, less transient myocardial dysfunction, and less osmotic diuresis after the procedure. Left ventriculography should be avoided.

(5) The Gorlin formula is used to estimate AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/(44.3 \times \text{heart rate} \times \text{SEP} \times \sqrt{\text{MVG}}).$$

In the above equation, SEP is the systolic ejection period, defined as the time from aortic valve opening to closing (in seconds), and MVG is the mean valvular gradient (mm Hg). The **Gorlin** formula measures the **true anatomic area** of the aortic valve, as it has a correction factor (the discharge coefficient) to account for the difference of flow across the true anatomic valve versus the flow at the level of the vena contracta. **Continuity equation** measures the **physiologic area** (vena contracta) and as such is smaller than that measured by Gorlin.

An alternative measurement can be made by Hakki equation, which is a simplification of Gorlin formula, where the observation of heart rate × SEP approximates 1,000. This then simplifies the estimation of AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/\sqrt{\text{MVG}}.$$

F. Therapy

1. **Medical therapy.** The mainstay of therapy for severe AS is surgical replacement of the aortic valve. Onset of symptoms in patients with severe AS is associated with a marked reduction in lifespan when treated medically, rather than surgically. Medical therapy alone is ineffective for severe symptomatic valvular AS.
   a. **Antibiotic prophylaxis.** The updated 2007 AHA guideline on prevention of infective endocarditis has been extensively modified. Unless the patient has a valve prosthesis or prior history of infective endocarditis, antibiotic prophylaxis prior to dental procedures is no longer recommended in patients with valvular pathology.
   b. **Medical therapy in asymptomatic patients.** During the asymptomatic phase, therapy is directed at primary prevention of CAD, maintenance of sinus rhythm, and blood pressure control.
   c. **Medical therapy in symptomatic patients.** Medical therapies may be necessary in symptomatic patients with severe AS who are awaiting surgery or who are considered inoperable and require palliation. Therapy for heart failure is directed at relief of pulmonary congestion. This is usually achieved with cautious use of diuretics. Overly aggressive diuresis can cause hypotension if hypovolemia significantly impairs cardiac output by diminishing preload. Nitrates can also cause hypotension and syncope by reducing preload and should be avoided or used with extreme caution. Thus, the management of symptomatic patients with AS and CAD is difficult, and urgent surgery is the optimal treatment where feasible. Digoxin is used for symptom relief in the setting of impaired LV systolic function and volume overload, particularly if atrial fibrillation develops.
   d. **Vasodilator therapy** has been relatively contraindicated in patients with AS, because lowering SVR in the setting of a fixed cardiac output may cause syncope, especially in the ambulatory setting. However, patients with severe heart failure and LV dysfunction with severe AS may benefit from the careful titration of intravenous nitroprusside in the intensive care unit with concomitant invasive arterial and pulmonary artery monitoring. One study suggests an improvement in hemodynamic indices with this approach. This therapy is used only as a bridge to definitive surgical therapy. Intraaortic balloon counterpulsation is another strategy that can be used while patients with LV dysfunction and severe AS in cardiogenic shock are worked up toward urgent surgery.
   e. **Treatment of hyperlipidemia.** The association between AS and risk factors for atherosclerosis has prompted trials with statins to retard the progression of AS. Several studies suggested that when statin therapy is indicated based on current guidelines for hyperlipidemia it is associated with a modest effect in slowing the rate of progression of AS. However, in more recent randomized controlled trials of patients with calcific AS, where statin therapy was not otherwise mandated, statins had no effect on AS progression. As such, there is currently no indication for statin use specific to AS, although in hyperlipidemic patients with AS, aggressive lowering of LDL level with statins appears warranted. In patients with supravalvular AS due to severe familial hyperlipidemia, improvement in the obstruction may occur after low-density lipoprotein apheresis.
2. **Percutaneous aortic balloon valvuloplasty (PABV) and percutaneous valve replacement**
   a. In pediatric congenital, noncalcific AS, PABV is a safe and effective therapy, comparable to surgical repair or replacement. The goal of PABV in congenital AS is to achieve a 60% to 70% reduction in the measured peak-to-peak transvalvular gradient. Redilatation or AVR becomes necessary within 10 years of

the initial PABV in > 50% of children. AR is well recognized as a potential early or late complication of PABV, although moderate-to-severe AR occurs in a minority of cases.

b. In adults, PABV is not an effective long-term therapy for AS compared with surgical AVR. Although PABV initially achieves effective relief of LVOT obstruction (up to 50% improvement in AVA), nearly 50% of patients have restenosis within 6 months. Moreover, PABV does not prolong survival in adults with AS. For these reasons, PABV is mainly used for palliation of symptoms or as a bridge to AVR (ACC/AHA class IIb indication). PABV is generally not recommended in asymptomatic patients with severe AS who are undergoing urgent noncardiac surgery. It is recommended that these patients undergo vigilant monitoring with careful hemodynamic monitoring.

c. Percutaneous replacement of the aortic valve. An exciting strategy currently in development is the placement of a stented bioprosthetic valve over the native aortic valve, either percutaneously from an arterial site (usually in the femoral or iliac artery) or transapically from an incision made at the LV apex on the chest wall (transcatheter aortic valve replacement [TAVR]). The native valve is initially dilated with a balloon. The stented valve is deployed during rapid pacing to allow adequate time for successful placement. Currently, two percutaneous valves are available in the U.S. (Edwards Sapien and CoreValve). Of these, Edwards Sapien valve has gained approval from FDA in 2011 as it has been shown to improve survival in inoperable patients compared to medical therapy. Trials for both valves are currently ongoing. As an option to treat patients who are otherwise not candidates for open surgical replacement, TAVR provides a viable alternative over medical or surgical management. However, the technology is still developing. Paravalvular leak is still common following valve deployment, and the technique has considerable morbidity, not least as it has been used up to now in very ill patients (see Chapter 66).

3. Surgical therapy. AVR is the surgical treatment of choice. It is preferred over repair because debridement of aortic valve calcification often results in early postoperative AR from leaflet fibrosis and retraction, a process that progresses over time.

a. Recommendations for the use of AVR in patients with AS according to the modified 2006 ACC/AHA guidelines are given in Table 15.2. The major indications are for severe AS with symptoms or where other cardiac surgery is needed or when LV dysfunction develops as a result of severe AS.

b. Surgical mortality rate varies among patients with AS depending on age and other comorbidities including concomitant CAD. In an otherwise healthy individual, mortality rate for isolated AVR in experienced centers should be < 1%. When this is the case, the 2006 ACC/AHA guidelines suggest that prophylactic surgical intervention may be considered in severe AS, even in the absence of symptoms, especially if the valve is calcified and therefore the disease is likely to progress rapidly (ACC/AHA class IIb indication).

Successful AVR is feasible and normalizes life expectancy, even in very elderly patients without multiple comorbidities. Surgical options include pulmonary valve autograft (i.e., Ross procedure), aortic valve homograft conduit, a pericardial or porcine bioprosthesis, or a mechanical valve. The relative advantages, disadvantages, and indications for use of the different prostheses are outlined in Chapter 18.

(1) In the Ross procedure, the pulmonary valve and main pulmonary artery are removed as a unit and placed in the aortic position with reimplantation of the coronary arteries. A pulmonary homograft is placed in the pulmonic position. This procedure is best suited for pediatric and adolescent patients

TABLE 15.2 Recommendations for Aortic Valve Replacement in Patients with Aortic Stenosis

Class I

1. AVR is indicated for symptomatic patients with severe AS
2. AVR is indicated for patients with severe AS undergoing CABG or surgery on the aorta or other heart valves
3. AVR is recommended for patients with severe AS and LV systolic dysfunction (ejection fraction < 0.50)

Class IIa

AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves

Class IIb

1. AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension)
2. AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset
3. AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate-to-severe valve calcification, that progression may be rapid
4. AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area < 0.6 cm^2, mean gradient > 60 mm Hg, and jet velocity > 5.0 m/s) when the patient's expected operative mortality is 1.0% or less

Class III

AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIa/IIb recommendations

AVR, aortic valve replacement; AS, aortic stenosis; CABG, coronary artery bypass grafting; LV, left ventricular; CAD, coronary artery disease.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2006;48: 598–675, with permission from Elsevier.

with growth potential, because the autograft is capable of growth, does not require anticoagulants, and has an excellent hemodynamic profile. The procedure, however, is long and technically difficult and subsequently turns a single-valve problem into a double-valve problem. Problems with pulmonary homograft are common in adults who underwent this operation.

Aortic valve homografts have been used to treat younger patients, especially those who wish to avoid anticoagulation, in the hope that greater durability of this valve might result than with a bioprosthesis. Unfortunately, more recent data suggest that any durability advantage of a homograft over a bioprosthesis in middle-aged patients is slight. Moreover, the homograft tends to calcify and is often difficult to remove at subsequent reoperations. Therefore, enthusiasm for homografts has waned, except in the setting of endocarditis of native or prosthetic valves with pyogenic complications such as abscess or fistula or when the LVOT is small, in which case homografts maximize the flow area and minimize the pressure gradient.

(2) **Bioprostheses** include porcine heterografts and bovine pericardial prostheses. These valves are most often used to treat patients older than 60 years because structural deterioration is much slower in this age group compared with younger patients. These valves have a low risk for thromboembolism and do not necessitate long-term anticoagulation. Because of the sewing ring and struts, all prostheses, both mechanical and biologic, have a pressure gradient across them, even with normal function. The largest possible valve should be inserted to minimize this pressure gradient. The threshold to insert bioprostheses at a younger age continues to decline given the excellent quality of life these afford.

(3) **Mechanical valves.** The most commonly used mechanical prostheses include the St. Jude, Medtronic-Hall, and CarboMedics prostheses. These all require anticoagulants to minimize the risk of valve thrombosis and thromboembolism. These valves are durable if anticoagulation is maintained and careful antibiotic prophylaxis is used over the years. Mechanical valves are used with caution in older patients (> 65 years) given the substantial increase in anticoagulation-related hemorrhage and resultant mortality in this population.

G. Special considerations

1. Management of asymptomatic patients with severe AS

a. High-risk patients. Most asymptomatic AS patients have low mortality and morbidity rates. A minority of asymptomatic patients, however, may die suddenly or have rapid progression of disease. These patients may benefit from AVR in the absence of symptoms. Accurate identification of such patients has been difficult. A transaortic flow velocity of > 4 m/s predicts a 70% likelihood of needing an AVR within the subsequent 2 years, whereas a velocity of < 3 m/s corresponds to a low likelihood (< 15%) of needing an AVR in the subsequent 5 years. Patients with highly calcified valves and a rapid increase in the pressure gradient may be considered for elective AVR if the transaortic flow velocity is > 4 m/s. Other reasonable indications for AVR in patients with severe asymptomatic AS include LV dysfunction attributable to AS, exercise-induced hypotension, pulmonary hypertension (> 60 mm Hg), a high likelihood of rapid progression, and before pregnancy.

b. Coronary artery bypass grafting (CABG) in moderate AS. Is there a need for AVR? Studies suggest a benefit of concomitant AVR in patients undergoing CABG who have an AVA of < 1.5 cm^2. Although concomitant AVR increases the risk of the initial surgery, the need for reoperation is significantly lower in these patients, and this may provide a survival benefit. Patients with mild AS who have evidence of moderate/severe calcification with a high likelihood of rapid progression may also undergo AVR during CABG.

2. Patients with AS and severely reduced ejection fraction.

LV dysfunction in patients with AS can result from the afterload stress imposed on the left ventricle by the stenotic valve or from primary contractile dysfunction (e.g., result of other causes of cardiomyopathy). When LV dysfunction results primarily from afterload mismatch, surgical correction of AS often results in improvement or normalization of LV function. In contrast, patients with primary contractile dysfunction have an overall poor prognosis and are unlikely to benefit from AVR. It is important to determine the cause of LV dysfunction in patients with severe AS for prognostic and therapeutic purposes. These patients should be considered in three major groups: those with high transvalvular gradients (mean gradient > 40 mm Hg), those with low transvalvular gradients (mean gradient < 30 mm Hg), and those with aortic pseudostenosis.

a. High transvalvular gradient. A high transvalvular gradient is a surrogate measure of high afterload mismatch. When the transvalvular gradient is

substantial (e.g., mean gradient > 40 mm Hg), surgical correction of AS can result in normalization of LV function.

b. **Low transvalvular gradient.** Patients with true anatomically severe AS (AVA < 1.0 cm^2) and low transvalvular gradients (mean gradient < 30 mm Hg) have a very poor prognosis without surgery. Despite a substantial operative mortality, survival appears improved in those treated surgically, especially if they demonstrate **contractile reserve** when challenged with dobutamine. Contractile reserve is defined as the ability to increase transvalvular flow by > 20% from baseline. Dobutamine infusion may help identify the subset of patients with low-gradient AS who benefit from AVR.

c. **Aortic pseudostenosis.** Patients with primary contractile dysfunction and mild AS can have a falsely small calculated valve area, mimicking severe AS. This phenomenon, called aortic pseudostenosis, occurs principally because the force generated by the weakened left ventricle is not sufficient to open a mildly stenotic valve. Differentiating low-gradient, anatomically severe AS from aortic pseudostenosis is usually accomplished by one of two methods: increasing the cardiac output with dobutamine or decreasing the total peripheral resistance with vasodilators such as nitroprusside. Patients with truly severe AS experience a parallel increase in cardiac output and in the transvalvular pressure gradient after dobutamine infusion (in the echocardiography or catheterization laboratory). The calculated valve area, therefore, does not increase. In contrast, dobutamine infusion in patients with aortic pseudostenosis results in an increase in cardiac output without a significant increase in the transvalvular pressure gradient (the mildly stenotic valve is able to accommodate the increase in blood flow). As a result, the calculated AVA increases significantly (≥0.3 cm^2). Nitroprusside infusion can also be used to differentiate true stenosis from pseudostenosis by lowering SVR. In true severe AS, the transvalvular gradient increases in response to vasodilators, but the fixed LV outflow obstruction does not allow cardiac output to increase concomitantly. In pseudostenosis, the valve resistance is small, and a decrease in SVR is accompanied by a significant increase in cardiac output and a decrease in the transvalvular gradient. The calculated valve area, therefore, remains the same or decreases in true stenosis and increases in pseudostenosis. The differentiation of true severe AS from aortic pseudostenosis is important because patients with aortic pseudostenosis have primary contractile dysfunction and are unlikely to benefit from AVR alone.

3. **Severe AS with low gradients and preserved left ventricular ejection fraction (LVEF).** Several patients present with severe AS with seemingly normal left ventricular function and paradoxically low gradients. This population appears to be composed of two groups: one with low flow and relatively high afterload and the other in whom the discrepancy between gradients and area may be due to errors in measurement. There is evidence that those with true low flow and severe AS are more likely to be women with small ventricles, significant LVH, and hypertension. In this group, outcome is worse than expected, as surgery may be delayed based on the discrepancy between AVA and gradients even in the presence of symptoms. It is important to be aware of this group and to ensure that those who have severe AS and low flow are considered for early surgery once symptoms occur.
4. **Subaortic stenosis.** Surgical removal of the membrane leading to subaortic obstruction is indicated for symptomatic patients, for asymptomatic patients with a pressure gradient greater than 50 mm Hg, and if there is evidence of concomitant moderate or greater AR as a result of damage to the aortic valve leaflets from the turbulent subvalvular jet.

TABLE 15.3 Major Causes of Chronic Aortic Regurgitation

Leaflet abnormalities	Aortic root or ascending aorta abnormalities
Rheumatic fever	Age-related aortic dilation
Infective endocarditis	Annuloaortic ectasia
Trauma Myxomatous degeneration	Cystic medial necrosis of the aorta (isolated biscuspid aortic valve or Marfan's syndrome)
Congenital aortic regurgitation	Systemic hypertension
Systemic lupus erythematosus	Aortitis (syphilis and giant cell arteritis)
Rheumatoid arthritis	Reiter's syndrome
Ankylosing spondylitis	Ankylosing spondylitis
Takayasu's arteritis	Behçet's syndrome
Whipple's disease	Psoriatic arthritis
Crohn's disease	Osteogenesis imperfecta
Drug-induced valvulopathy	Relapsing polychondritis
	Ehlers-Danlos syndrome

II. AORTIC REGURGITATION

A. Introduction. AR can develop from primary disease of the valve leaflets or from abnormalities of the aortic root or ascending aorta. The chronic and acute forms of AR are distinct disease entities, with different causes, clinical presentations, natural histories, and treatment strategies.

B. Etiology

1. **Chronic AR.** Disease of the valve leaflets can cause AR by inadequate leaflet coaptation, leaflet perforation, or leaflet prolapse. The most common causes of leaflet abnormalities and aortic root abnormalities that lead to the gradual development of AR are given in Table 15.3. Subaortic stenosis can also cause AR due to a high-velocity jet of blood that is a result of the outflow obstruction hitting the aortic valve, causing damage to the leaflets. Perimembranous ventricular septal defects are associated with AR as well. In addition to disease of native valve leaflets, structural deterioration of bioprosthetic valve leaflets is an important cause of chronic AR.
2. **Acute AR.** Acute AR can also result from abnormalities in the valve leaflets or in the aortic root. The causes of acute AR are limited (Table 15.4).

TABLE 15.4 Major Causes of Acute Aortic Regurgitation

Leaflet abnormalities	Aortic root or ascending aorta abnormalities
Traumatic rupture	Acute aortic dissection
Acute infective endocarditis	Perivalvular leak or dehiscence of prosthetic valves
Acute prosthetic valve dysfunction	
Post aortic balloon valvuloplasty	

C. Pathophysiology

1. **Chronic AR.** AR results in diastolic regurgitation of LV stroke volume. This produces an increase in LV end-diastolic volume, thereby raising wall tension (i.e., Laplace's law). The ventricle responds to added wall tension by compensatory eccentric hypertrophy of myocytes. As a result, during the chronic compensated phase of AR, the left ventricle is able to adapt to an increase in diastolic volume without a significant increase in end-diastolic pressure. The left ventricle produces a larger total stroke volume with each contraction, preserving normal effective forward stroke volume. Over time, however, progressive interstitial fibrosis reduces LV compliance, leading to the chronic decompensated phase. Chronic volume overload results in impaired LV emptying, an increase in LV end-systolic volume and end-diastolic pressure, further cardiac dilation, and a fall in the ejection fraction and forward cardiac output.
2. **Acute AR.** Acute AR is usually a hemodynamic emergency because the left ventricle does not have sufficient time to adapt to the rapid increase in LV volume. The effective forward stroke volume and cardiac output fall acutely, potentially resulting in hypotension and cardiogenic shock. The sudden increase in LV diastolic pressure initially causes preclosure of the mitral valve in early diastole, protecting the pulmonary vasculature from elevated diastolic pressure. However, further LV decompensation leads to diastolic mitral regurgitation (MR), which allows transmission of elevated diastolic pressure to the pulmonary vascular bed, resulting in pulmonary edema. The tachycardia that accompanies cardiac deterioration helps shorten the diastolic-filling period during which the mitral valve is open.

D. History and clinical presentation

1. **Chronic AR** is usually asymptomatic for a long time. After the development of LV dysfunction, patients gradually experience symptoms related to pulmonary congestion, including increased dyspnea with exertion, orthopnea, and paroxysmal nocturnal dyspnea. LV enlargement frequently produces an uncomfortable sensation in the chest that is exaggerated after premature ventricular contractions and in the supine position. Although angina is uncommon, it can be produced by latent CAD, decreased diastolic coronary perfusion pressure, nocturnal bradycardia and fall in arterial diastolic pressure, marked LVH, and subendocardial ischemia.
2. **Acute AR.** Patients with acute, severe AR usually present with signs of sudden hemodynamic deterioration such as weakness, altered mental status, severe shortness of breath, or syncope. If left untreated, these patients quickly progress to total cardiovascular collapse. When severe chest pain is part of the initial clinical presentation, aortic dissection must be strongly suspected.

E. Physical findings

1. **Chronic AR.** Patients with chronic AR can have a wide array of physical findings, especially during examination of the peripheral pulses and cardiac auscultation. The physical examination may yield clues about the cause of AR. Patients with AR should be examined for the peripheral manifestations of infective endocarditis, signs of Marfan's syndrome, evidence of chronic aortic dissection, and signs of collagen vascular disorders.
   a. **Peripheral pulse examination.** The increased total stroke volume in chronic AR leads to an abrupt increase in arterial pressure during systole, followed by a rapid fall in arterial pressure during diastole. The widened pulse pressure accounts for a number of physical findings associated with chronic AR (Table 15.5). Patients with chronic AR may exhibit a bisferiens pulse, characterized by double systolic peaks with increased amplitude. The signs of hyperdynamic circulation are not specific to AR and can be seen in conditions that cause high-output heart failure, including sepsis, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula.

TABLE 15.5 Physical Signs Associated with Hyperdynamic Pulse in Chronic Aortic Regurgitation

Physical sign	Description
Water hammer or Corrigan's pulse	Rapid upstroke followed by quick collapse
de Musset's sign	Head bob with each heartbeat
Traube's sign	Pistol shot sounds heard over the femoral arteries in both systole and diastole
Müller's sign	Systolic pulsation of the uvula
Duroziez's sign	Systolic murmur over the femoral artery when compressed proximally and diastolic murmur when compressed distally or systolic–diastolic murmur with increasing compression over femoral artery
Quincke's sign	Capillary pulsations visible in the lunula of the nail bed
Hill's sign	Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by > 60 mm Hg
Becker's sign	Arterial pulsations visible in the retinal arteries and pupils

b. Palpation. With severe AR, the apical impulse is typically enlarged and displaced lateral to the midclavicular line in the fifth intercostal space because of LV enlargement. The impulse may be sustained and hyperdynamic. A diastolic thrill may be palpable in the second left intercostal space, as may a systolic thrill caused by increased aortic flow.

c. Auscultation. The main auscultatory findings are outlined in Figure 15.6.

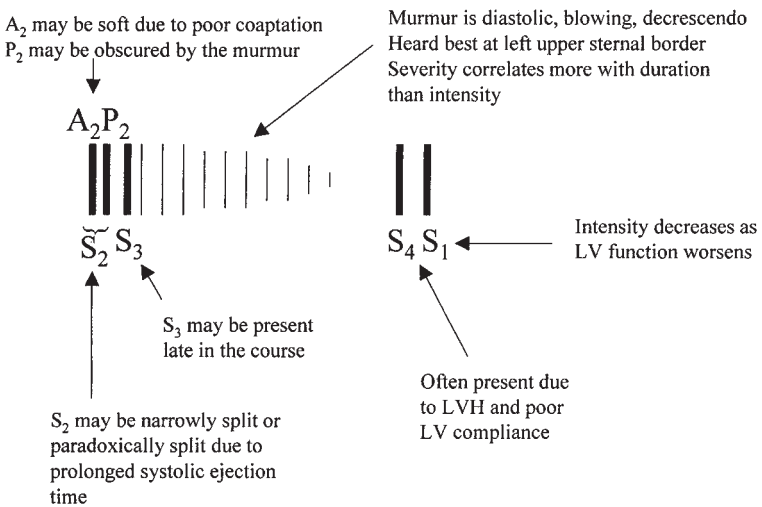

FIGURE 15.6 Physical findings in aortic regurgitation. LV, left ventricular; LVH, left ventricular hypertrophy.

(1) **Heart sounds.** S_1 may be diminished in the presence of PR-interval prolongation, LV dysfunction, or preclosure of the mitral valve. S_2 may be soft, singly split (P_2 obscured by the diastolic murmur) or paradoxically split. An S_3 may be heard with severe LV dysfunction. An S_4 is often present and represents left atrial contraction into a poorly compliant left ventricle.

(2) **Diastolic murmur.** The hallmark murmur of AR is a blowing, diastolic, decrescendo murmur that starts immediately after A_2 and is best heard in the left upper sternal border with the patient sitting up and leaning forward slightly in full expiration. In general, the severity of AR correlates with the duration of the murmur more than with its intensity. Early in the course of disease, the murmur is typically short. As the disease progresses, the murmur may become pandiastolic. In the end stages of AR, the murmur may shorten again because of rapid equilibration of pressures in the aorta and left ventricle from an elevated LVEDP. In this situation, other signs of severe AR are usually present.

(3) A **second diastolic murmur** may be audible at the apex in severe AR. The Austin Flint murmur is a middle-to-late diastolic rumble that is believed to be caused by vibration of the anterior mitral leaflet as it is struck by the regurgitant jet or by turbulence in the mitral inflow from partial closure of the mitral valve by the regurgitant jet. Unlike the murmur of true valvular mitral stenosis, the Austin Flint murmur is not associated with a loud S_1 or with an opening snap.

(4) A short **midsystolic ejection murmur** may be audible at the base of the heart, radiating to the neck. It reflects the increased ejection rate and large stroke volume traversing the aortic valve.

2. **Acute AR.** The physical examination of patients with acute AR differs considerably from that of patients with chronic AR. The physical examination may be most notable for signs of hemodynamic compromise, such as hypotension, tachycardia, pallor, cyanosis, diaphoresis, cool extremities, and pulmonary congestion.

   a. **Peripheral examination.** The signs of hyperdynamic circulation that characterize chronic AR are often absent in acute AR. The pulse pressure may be normal or only slightly widened. The heart size is often normal, and the point of maximal intensity is not displaced laterally. When aortic dissection is suspected, blood pressures should be taken in all extremities to detect the differences.

   b. **Heart sounds.** S_1 may be diminished due to preclosure of the mitral valve. Pulmonary hypertension may manifest as an increased P_2 component of the second heart sound. An S_3 often accompanies cardiac decompensation.

   c. **Murmurs.** The early diastolic murmur of acute AR is shorter and lower in pitch than the murmur of chronic AR. In severe, acute AR, the murmur may not be audible when the diastolic pressure in the left ventricle and aorta equilibrates. The systolic murmur reflecting increased flow across the aortic valve may be heard but is usually not loud. The Austin Flint murmur, if present, is short.

F. Laboratory evaluation

1. **ECG.** The typical ECG in chronic AR shows LVH, left-axis deviation, and left atrial abnormality. Conduction abnormalities are unusual but can occur after the development of LV dysfunction. Premature atrial and ventricular beats are common. Sustained supraventricular or ventricular tachyarrhythmias are uncommon in the absence of LV dysfunction or concomitant mitral valve disease. In acute AR, the ECG is usually notable only for nonspecific ST-T–wave abnormalities.

2. **Chest radiograph.** In chronic AR, the chest radiograph may reveal marked cardiomegaly, with the heart being displaced inferiorly and leftward. Dilation of the aortic knob and root may be seen. In acute AR, the LV and left atrial dimensions are usually normal. Aortic dissection can lead to a widened mediastinum and/or a widened cardiac silhouette due to pericardial effusion. The chest radiograph is notable for signs of pulmonary congestion.
3. **Echocardiography.** Two-dimensional and M-mode echocardiography are useful in determining the cause of AR, evaluating the aortic root, and assessing the overall LV size and function. Doppler echocardiography is useful for detecting AR and estimating severity. There are several different methods of estimating the severity of AR with color Doppler, pulsed wave Doppler, and continuous wave Doppler ultrasonography.
   a. **Two-dimensional and M-mode echocardiography.** The cause of AR can be assessed using two-dimensional echocardiography. Rheumatic AR typically causes thickening and retraction of the leaflet tips, leading to failure of cusp apposition. Bacterial endocarditis, which can cause leaflet fibrosis and retraction, leaflet perforation, or flail of the valve cusp, should be suspected if a vegetation is detected. Prolapse of the aortic valve cusps can occur in many conditions, including infective endocarditis, bicuspid aortic valve, myxomatous degeneration, and Marfan's syndrome. Aortic root abnormalities are also well visualized in the parasternal long-axis view. Aortic root dilation is most often idiopathic, although Marfan's syndrome, Ehlers-Danlos syndrome, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, syphilis, and giant cell arteritis are other potential causes. Symmetric dilation of the aortic root produces a central jet of AR, and focal dilation causes an eccentric jet. In the parasternal long axis, the transducer should be moved up one interspace to assess the ascending aorta. Infective destruction of the aortic wall and proximal aortic dissection flaps may occasionally be visualized on transthoracic images. M-mode echocardiography may reveal **premature closure of the mitral valve in severe, acute AR**. In acute AR and chronic AR, the regurgitant jet can strike the anterior mitral valve leaflet, causing it to reverberate or "flutter" in diastole. Reversed doming of the anterior mitral leaflet may be seen on two-dimensional imaging and generally indicates grade 3 to 4+ AR.
   b. **Doppler and color flow imaging.** Doppler and color flow echocardiography is used to detect AR and to assess its severity. AR is identified by Doppler imaging as high-velocity pandiastolic flow originating immediately under the aortic valve. Color flow imaging allows the assessment of jet origin, size, and direction. Continuous wave Doppler provides measurement of jet velocity and timing of flow. The maximum length of the AR jet correlates poorly with severity of regurgitation when assessed angiographically. Several other Doppler measures are used to estimate the severity of AR (Table 15.6). The ratio of the jet width to LVOT diameter is measured in the parasternal long-axis view and correlates well with the angiographic severity of AR. The pressure half-time of the aortic regurgitant velocity is defined as the time required for the pressure gradient across the aortic valve to fall to half of its initial value. The pressure half-times of patients with mild, moderate, and severe AR have demonstrated considerable overlap. In general, shorter pressure half-times are associated with increased severity of AR, and a pressure half-time of < 200 milliseconds is nearly always associated with severe AR. Quantitation of regurgitant volume and regurgitant fraction provides the most direct correlation with quantitative angiographic estimates of AR severity. Regurgitant volume is the difference between the stroke volume across the LVOT (representing the sum of forward flow and regurgitant flow) and

TABLE 15.6 Echo-Doppler Assessment of Aortic Regurgitation Severity

	Aortic regurgitation		
	Mild	**Moderate**	**Severe**
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	Central jet, width < 25% of LVOT	➢ Mild but no signs of severe AR	Central jet, width > 65% LVOT
Doppler vena contracta width (cm)	< 0.3	0.3–0.6	> 0.6
Quantitative (cath or echo)			
Regurgitant volume (mL/beat)	< 30	30–59	≥60
Regurgitant fraction (%)	< 30	30–49	≥50
Regurgitant orifice area (cm^2)	< 0.10	0.10–0.29	≥0.30
Additional essential criteria			
Left ventricular size			Increased

AR, aortic regurgitation; LVOT, left ventricular outflow tract.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol.* 2006;48:598–675, with permission from Elsevier.

that across the mitral valve inflow (representing forward flow), provided there is no significant MR. The regurgitant fraction is the ratio of the regurgitant volume divided by the LVOT stroke volume. The proximal isovelocity surface area (PISA) method is also used for estimating AR severity. The PISA method is used to calculate the effective regurgitant orifice (ERO) area. An ERO area ≥ 0.30 cm^2 is indicative of severe AR. The presence of a proximal convergence area on transthoracic echocardiogram at the aortic valve is indicative of at least moderate AR. Pulsed wave Doppler echocardiography should be performed in the proximal descending aorta to establish the presence of diastolic flow reversal. Some degree of flow reversal is normally seen early in diastole due to reflux of blood into the coronary vasculature, but if this is > 40 cm/s and continues throughout diastole, then severe AR is likely, especially if this persists in the abdominal aorta. Flow reversal may also be seen with other conditions that cause blood to leak out of the arterial system such as patent ductus arteriosus or sizeable arteriovenous fistula.

c. TEE is used to rule out vegetation or aortic valve ring abscess in patients who may have bacterial endocarditis. In pure AR, vegetation typically occurs on the LV side of the aortic valve. TEE is also used to visualize congenital valvular abnormalities (e.g., bicuspid valve) and to exclude aortic dissection.

d. Stress echocardiography is useful for assessing the ability to exercise. However, a fall in LVEF on exercise is less predictive of occult contractile dysfunction in severe AR than it is in MR. In AR, afterload often increases substantially on exercise, precipitating a fall in ejection fraction. A fall in LVEF on stress echocardiography alone is not a primary indication for valve surgery.

4. **Cardiac catheterization.** Cardiac catheterization is not necessary for all patients with chronic AR unless there are concerns about AR severity, hemodynamic abnormalities, or LV function, despite noninvasive testing and the physical examination. All patients older than 50 years with severe AR should undergo coronary cineangiography before any definitive surgical procedure on the valve to detect CAD. The decision to perform cardiac catheterization in younger patients should be made on an individual basis after assessment of the patient's cardiac risk profile. Catheter manipulation in patients with AR may be difficult because of dilation of the ascending aorta. Caution should be exercised when manipulating catheters in patients with Marfan's syndrome or cystic medial necrosis of the aortic wall to minimize the risk of vascular trauma. In addition to conventional coronary cineangiography, aortography should be performed to evaluate the degree of AR. The grading of AR by angiography is given in Table 15.7. Right heart catheterization may be helpful in certain circumstances, such as new-onset heart failure or combined AR and AS.

G. Natural history. Moderate-to-severe AR may have a good prognosis for many years, provided the patient is asymptomatic and does not exhibit signs of LV dysfunction or severe dilation. Asymptomatic patients with normal LV function require AVR at a rate of only 4% per year. Ninety percent of such patients remain asymptomatic at 3 years, 81% at 5 years, and 75% at 7 years after the diagnosis is made. Patients with mild-to-moderate AR have had a 10-year survival rate of 85% to 95%. Patients with moderate-to-severe AR treated with medical therapy have a 5-year survival rate of 75% and a 10-year survival rate of 50%. After the development of LV dysfunction, progression to symptoms is greatly accelerated, with rates approaching 25% per year. When symptoms develop, there is a rapid decline in functional status. Without surgical intervention, symptomatic patients usually die within 4 years of the onset of angina and within 2 years of the onset of heart failure. Sudden death may occur among patients with severe, symptomatic AR. Sudden cardiac death is frequently the result of ventricular arrhythmias that are primary (in the context of LVH or dysfunction) or secondary, resulting from myocardial ischemia. It has become clear that the various dimensions used to guide surgery in AR are relative and should be interpreted in the context of patient size and gender.

H. Therapy

1. **Medical therapy**
   a. **Chronic AR**
      (1) **Medical therapy.** Vasodilators, such as hydralazine, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers, have been used in the treatment of chronic AR to reduce the severity of regurgitation and help delay surgical intervention. There is conflicting evidence of their value (Table 15.8). Current ACC/AHA guidelines contraindicate their use (ACC/AHA class III indication) as an alternative to surgery when surgical intervention is indicated in a patient with acceptable surgical risk.

TABLE 15.7 Angiographic Grading of Aortic Regurgitation

Degree of aortic regurgitation	Left ventricular opacification	Rate of clearing
Mild (1+)	Faint, incomplete	Rapid
Moderate (2+)	Faint, complete	Rapid
Moderate to severe (3+)	Equal to aortic opacification	Intermediate
Severe (4+)	Greater than aortic opacification	Slow

TABLE 15.8 Indications for Vasodilator Therapy in Chronic Severe Aortic Regurgitation

Indication	Class
Chronic therapy in patients with severe regurgitation who have symptoms and/or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors	I
Short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction prior to proceeding with AVR	IIa
Long-term therapy in asymptomatic patients with severe regurgitation who have LV dilation but normal systolic function	IIb
Not indicated for long-term therapy in asymptomatic patients with mild-to-moderate AR and normal LV systolic function	III
Not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for valve replacement	III
Not indicated for long-term therapy in symptomatic patients with either normal LV function or mild-to-moderate LV systolic dysfunction who are otherwise candidates for valve replacement	III

AR, aortic regurgitation; AVR, aortic valve replacement; LV, left ventricular.

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Vasodilators are recommended in nonsurgical candidates with severe, chronic AR who develop symptoms or LV dysfunction (ACC/AHA class I indication). Vasodilators may also be reasonable for short-term therapy, improving the hemodynamics in patients with severe heart failure and LV systolic dysfunction prior to AVR. In asymptomatic patients, long-term vasodilator therapy may be considered for those with severe AR and normal LV systolic function who begin to demonstrate LV dilation. Long-term vasodilator therapy is not recommended for asymptomatic patients with mild-to-moderate AR and normal systolic function. These patients have a good prognosis and do not appear to benefit from vasodilator therapy. Although asymptomatic patients with LV systolic dysfunction or symptomatic patients may be treated with vasodilators in the short term, appropriate surgical candidates should be referred for AVR, and vasodilators should be continued on a long-term basis only if LV systolic dysfunction persists after AVR. The evidence for the use of specific vasodilator agents has been variable. Hydralazine was found to improve LV systolic function and to reduce LV chamber dimensions in some studies. Nifedipine was found to reduce LV volume and increase LVEF in a group of asymptomatic patients who were followed for 1 year. When compared with digoxin, nifedipine slowed the progression of LV dysfunction and delayed the time to surgical treatment in an unblinded, randomized study over a 5-year period. ACE inhibitors have been shown to decrease LV volume in some studies. However, the benefits of ACE inhibitor therapy were seen only when blood pressure was effectively lowered.

(2) In patients with significant aortic root dilation as a result of cystic medial necrosis or related conditions, treatment with a β-blocker should be considered to slow the rate at which the aortic root enlarges. This has been proved to be beneficial in Marfan's syndrome and is also indicated in patients with bicuspid AV and dilated aortic roots without moderate or severe AR. Angiotensin receptor blockers have also been associated with reduction in progression of aortic disease and should be considered in patients with Marfan-related syndromes. When aortic root dilation is larger than 5 cm in severe AR (lower in Marfan's syndrome), aortic valve surgery and root replacement are indicated.

b. Acute AR

(1) The goal of **medical therapy** in acute AR is hemodynamic stabilization before proceeding with surgical correction. For patients presenting with cardiogenic shock, intravenous vasodilators are used to reduce the afterload stress on the left ventricle, to lower LVEDP, and to augment forward cardiac output. In severe cases, intravenous inotropic agents may be required for temporary hemodynamic support. β-Blockers may be used with caution when acute AR is caused by an aortic dissection. β-Blockers help reduce arterial dP/dt, which reflects the transmission of force from LV ejection to the arterial wall. Although this is an essential component of the treatment of acute aortic dissection, β-blockers increase the length of diastole by slowing the heart rate, which can exacerbate acute AR and contribute to cardiovascular collapse.

(2) A **surgical evaluation** should be performed immediately for a patient with AR caused by aortic dissection or chest trauma. The goal of medical therapy in this setting is to maximize forward cardiac output and minimize propagation of aortic dissection if present.

(3) If acute AR is associated with **endocarditis**, antibiotic therapy should be instituted as soon as all culture specimens are obtained.

2. Percutaneous therapy. ***Insertion of an intraaortic balloon counterpulsation device in patients with more than moderate AR or in the presence of aortic dissection is contraindicated.*** Patients with combined AS and AR are poor candidates for PABV because the degree of AR is likely to increase after the procedure.

3. Surgical therapy

a. Chronic AR. The ACC/AHA guidelines on the indications for AVR in patients with chronic AR are given in Table 15.9.

(1) **Symptomatic patients.** The updated ACC/AHA guidelines state that AVR is recommended for symptomatic patients with severe AR regardless of the ejection fraction.

(2) The indications for AVR in **asymptomatic patients** remain controversial. AVR is recommended when patients with chronic severe AR are undergoing any other open heart surgery. Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (ejection fraction < 50%) are at high risk for the development of symptomatic heart failure within 2 to 3 years and, therefore, should be considered for elective surgical intervention. Asymptomatic patients with normal LV systolic function at rest and evidence of severe LV dilation (LV end-diastolic dimension > 75 mm and end-systolic dimension > 55 mm) have an increased risk of sudden cardiac death. Their prognosis after AVR, however, is excellent, and they should be referred for valve replacement. When patients with severe LV dilation develop symptoms or LV systolic dysfunction, the perioperative mortality rate increases significantly. AVR is not recommended in asymptomatic patients with normal systolic function at rest and normal or mildly abnormal LV dimensions (end-diastolic

TABLE 15.9 Indications for Aortic Valve Replacement in Severe Aortic Regurgitation

Indication	Class
Symptomatic patients with severe AR irrespective of LV systolic function	I
Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (EF < 50%) at rest	I
Patients with chronic, severe AR undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	I
Asymptomatic patients with severe AR and EF > 50%, but with severe LV dilation (EDD > 75 mm or ESD > 55 mm[a])	IIa
Patients with moderate AS while undergoing surgery on the ascending aorta or coronary artery bypass grafting surgery	IIb
Asymptomatic patients with severe AR and normal LV systolic function (EF > 50%) when the EDD > 70 mm or ESD > 50 mm, when there is evidence of progressive LV dilation[a], declining exercise tolerance or abnormal hemodynamic responses to exercise	IIb
AVR not indicated for asymptomatic patients with mild, moderate, or severe AR and normal LV systolic function at rest (EF > 50%) and when degree of dilation is not severe (EDD < 70 mm and ESD < 50 mm)	III

AR, aortic regurgitation; LV, left ventricular; EF, ejection fraction; EDD, end-diastolic dimension; ESD, end-systolic dimension; AS, aortic stenosis.

[a]Consider lower threshold values for patients of small stature of either gender.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol.* 2006;48:598–675, with permission from Elsevier.

dimension < 70 mm and end-systolic dimension < 50 mm). However, in practice, few physicians wait until the LV end-diastolic dimension is 75 mm or the end-systolic dimension is 55 mm to consider surgical intervention even if the patient remains asymptomatic. Most physicians weigh up the benefit and risk to the individual patient and err on sending the asymptomatic patient to surgery at a lower end-systolic dimension (usually 50 mm) and may opt to intervene even earlier in patients of smaller body size and height.

(3) The **surgical alternatives** are discussed in **Section** I. **Many patients with prolapse of bicuspid valve as the cause of AR may be candidates for surgical repair of the aortic valve.** Some patients with leaflet perforation caused by infectious endocarditis may be candidates for repair in which a pericardial patch is sewn over the defect.

(4) Postoperatively, patients with severe AR may show initial worsening in LV function despite relative normalization of LV size. This is likely due to the hemodynamic changes produced by eradicating the regurgitation. Slow improvement with normalization or at least stabilization of function at about 6 months is common in these patients. Afterload reduction is indicated postoperatively in patients with impaired LV systolic function at least until there is normalization of LV systolic function.

4. **Follow-up care.** Patients with chronic AR should be observed closely for the development of LV systolic dysfunction. Follow-up evaluation is typically conducted with serial echocardiography. When signs of LV systolic dysfunction manifest, consideration should be given to surgical therapy, even if the patient has no symptoms. Routine postoperative care is appropriate after AVR or repair is completed.
5. **Key suggestions**
   a. Acute, severe AR is usually a surgical emergency. Signs of congestive heart failure and mitral valve preclosure are ominous in acute AR.
   b. Valve replacement can be performed without infection of the prosthesis in active endocarditis, even when antibiotics have only recently been started. An aortic valve homograft is the preferred prosthesis in the setting of endocarditis.
   c. Aortic dissection should be suspected in any patient with chest pain and AR.
   d. If LV systolic dysfunction is present for < 18 months, LV function is likely to improve postoperatively.
   e. Heart rate is usually normal until late in the course of disease, when a low effective stroke volume is compensated with tachycardia to maintain cardiac output.
   f. Rapid atrial or ventricular pacing may be used as a temporary measure to manage acute AR caused by endocarditis or trauma to improve cardiac output. The diastolic-filling phase is shorter at higher heart rates; therefore, there is less time for valvular regurgitation.

ACKNOWLEDGMENTS: *The authors would like to thank Dr. Anne Kanderian and Dr. Anjli Maroo for their work in the previous editions.*

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CHAPTER 16

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Brian P. Griffin

Mitral Valve Disease

I. INTRODUCTION

A. The **mitral valvular apparatus** consists of the anterior and posterior leaflets, the mitral annulus, the chordae tendineae, and the papillary muscles (PMs).

1. Normal function of the apparatus brings both leaflets together in systole, creating the coaptation zone.

2. The anterior portion of the mitral annulus is in continuity with the fibrous skeleton of the heart, making it less prone to dilation than the posterior annulus.

3. The coaptation line of the anterior and posterior leaflets is located in the posterior one-third of the valve orifice.

4. The middle scallop of the posterior leaflet is designated P_2, with the lateral scallop designated P_1 and medial scallop designated P_3. The corresponding areas of the anterior leaflet are designated A_1, A_2, and A_3.

5. The mitral valve leaflets are attached via the chordae tendineae to the PMs, which are part of the left ventricle.

B. Mitral regurgitation (MR) can occur as a result of malfunction of any of these components.

C. Mitral valve prolapse (MVP) exists when one or both mitral leaflets extend beyond the plane of the mitral valve annulus into the left atrium during systole.

D. Mitral stenosis (MS) is usually valvular and is caused more rarely by the fusion of subvalvular components.

II. MITRAL REGURGITATION

A. Clinical presentation

1. Signs and symptoms

a. With **acute, severe de novo MR**, an abrupt rise in pulmonary capillary wedge pressure (PCWP) causes pulmonary edema. The symptoms include rest dyspnea, orthopnea, and possibly signs of diminished forward flow, including cardiogenic shock.

b. Chronic MR is usually **asymptomatic** for years. The most common presentation is an asymptomatic murmur. **When symptoms develop**, exercise intolerance and exertional dyspnea usually occur first. Orthopnea and paroxysmal nocturnal dyspnea may develop as MR progresses. Fatigue is caused by diminished forward cardiac output. With the development of left ventricular (LV) dysfunction, further symptoms of congestive heart failure (CHF) are manifest. **Long-standing severe MR** may cause **pulmonary hypertension**, with symptoms of right ventricular (RV) failure. Atrial fibrillation commonly occurs as a consequence of left atrial (LA) dilation.

2. Physical findings

a. Inspection and palpation. When LV function is preserved, carotid upstrokes are sharp, and the cardiac apical impulse is brisk and hyperdynamic. An early diastolic LV filling wave may be palpable because of the

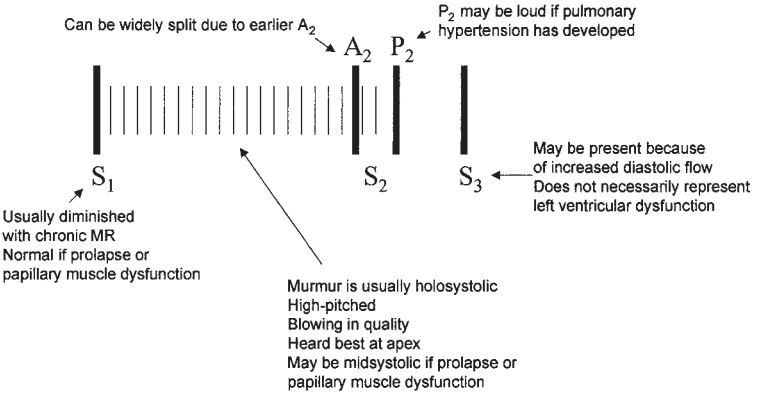

FIGURE 16.1 Auscultatory findings in mitral regurgitation.

large volume of blood traversing from the left atrium to the left ventricle. A late systolic thrust may be present in the parasternal location because of systolic expansion of the left atrium (which may be difficult to differentiate from an RV lift). With the development of LV dilation, the apical impulse is displaced laterally. An RV heave and a palpable P_2 are present if pulmonary hypertension has developed. An elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema indicate secondary RV dysfunction.

b. Auscultation. The main auscultatory findings are shown in Figure 16.1. A loud S_4 (not illustrated) can be heard sometimes, particularly with acute MR. In acute, severe MR, the systolic driving pressure across the mitral valve is reduced due to a high LA pressure and, as a result, the murmur is short and relatively soft. If the LA pressure is markedly elevated, the murmur of acute MR may be inaudible. With decompensated systolic heart failure, fine inspiratory pulmonary crackles may be evident.

3. The **differential diagnosis of holosystolic murmurs** includes MR, tricuspid regurgitation, and ventricular septal defect (VSD). All are high pitched, but the murmur of a VSD is often harsh in quality, unlike the blowing murmurs of MR and tricuspid regurgitation.
   - **a.** The murmur of **MR** is best heard in the apical position and often radiates to the axilla (although possibly to the base with anteriorly directed jets); those of tricuspid regurgitation and VSD typically do not. The murmur of posteriorly directed MR radiates to the back.
   - **b.** Tricuspid regurgitation is best heard at the left lower sternal border and radiates to the right of the sternum and left midclavicular line. Like all right-sided murmurs, tricuspid regurgitation is accentuated by inspiration.
   - **c.** A **VSD** murmur is heard at the left sternal border and often radiates throughout the precordium.

B. Etiology and pathophysiology. MR is more commonly myxomatous or ischemic, rather than rheumatic, in etiology. The causes of MR are summarized in Table 16.1.

1. In **acute MR**, the regurgitant volume that returns from the left atrium causes a **sudden increase in LV end-diastolic volume.** The left ventricle compensates for this by means of the Frank-Starling mechanism: increased sarcomere length (preload) enhances LV contraction (inotropy). This occurs at the cost of

TABLE 16.1 Causes of Mitral Regurgitation

Leaflet abnormalities
Myxomatous degeneration of leaflets with excessive motion (most common)
Rheumatic disease: scarring and contraction lead to the loss of leaflet tissue
Endocarditis: can cause leaflet perforations and retraction in the healing phase
Aneurysms: usually from aortic valve endocarditis; aortic insufficiency produces jet lesion on the mitral valve
Congenital:
- Cleft mitral valve: isolated or with ostium primum atrial septal defect
- Double-orifice mitral valve

Hypertrophic cardiomyopathy: systolic anterior motion of the mitral valve

Mitral annular abnormalities
Annular dilation
- From left ventricular dilation: dilated cardiomyopathy, ischemic disease, hypertension
- Normal 10 cm in circumference
- With sufficient dilation, loss of adequate leaflet coaptation
- Tethering of leaflet and chordae can occur and produce relative restriction of leaflet motion

Mitral annular calcification
- Degenerative disorder, most commonly seen in the elderly
- Accelerated by hypertension or diabetes
- Also seen in renal failure with dystrophic calcification
- Also seen with rheumatic heart disease
- Marfan syndrome and Hurler syndrome
- Mitral regurgitation results from immobility of the annulus and loss of sphincter activity

Chordal abnormalities
Chordal rupture (most severe form is flail leaflet) results in loss of leaflet support usually with myxomatous degeneration
Rheumatic heart disease (chordal fibrosis and calcification)

Papillary muscle abnormalities
Rupture with myocardial infarction
- Complete rupture typically not survived
- Partial rupture more typically encountered

Dysfunctional papillary muscle
- Ischemia
  - Posteromedial papillary muscle, single blood supply through posterior descending artery
  - Anterolateral papillary muscle, supplied by left anterior descending artery and left circumflex artery

Infiltrative processes: amyloid and sarcoid
Congenital: malposition, parachute mitral valve

increasing LV filling pressure and may cause symptoms of pulmonary congestion. LV wall stress (afterload) is reduced because blood is ejected into the lower pressure left atrium as well as into the systemic circulation. Increased inotropy and reduced afterload cause more complete LV emptying and hyperdynamic function. Forward cardiac output declines, however, because much of the flow is directed to the left atrium. If the acute hemodynamic insult is tolerated, the patient's condition **may progress to a chronic compensated state**.

2. In **chronic compensated MR**, there is **dilation of the left ventricle with eccentric hypertrophy**.
   a. Wall stress is normalized with the development of hypertrophy. Afterload reduction by the low-resistance left atrium is not as significant as it is in the acute phase. Preload remains elevated by the same mechanism as in acute MR. LA dilation helps to accommodate the increased preload at lower filling pressures. LV function is not as hyperdynamic as in the acute state but is in the high-normal range.
   b. Patients may stay in this asymptomatic or minimally symptomatic phase for years; however, **contractile dysfunction may develop insidiously** during this phase. Increased preload, normal or decreased afterload, and increased sympathetically mediated contractility all continue to augment the ejection fraction (EF). However, as the regurgitant volume ejected back into the left atrium diminishes the actual forward stroke volume (SV), the EF may overrepresent cardiac output.
3. In **chronic decompensated MR**, there is LV dysfunction along with progressive enlargement of the LV chamber with increased wall stress. LV dysfunction and enlargement increase the severity of MR, further contributing to the cycle of deterioration. **Irreversible LV contractile dysfunction** may be present by the time overt symptoms develop and this confers higher rates of postoperative heart failure and increased mortality.

C. Laboratory examination

1. The **electrocardiographic** findings are **nonspecific**. The principal features are LA enlargement and atrial fibrillation. LV hypertrophy and RV hypertrophy may also be seen in patients with severe MR.
2. Chest radiography. Cardiomegaly with LA and LV enlargement may be seen in chronic MR. Interstitial edema, manifest as Kerley B lines, followed by alveolar edema may develop in acute cases or with progressive LV failure. Calcification of the mitral annulus may be visualized as a C-shaped opacity in the lateral projection.

D. Diagnostic testing

1. Echocardiography plays a pivotal role in the evaluation of MR. It is useful in **diagnosing MR and in determining its severity and cause**. MR **severity is graded semiquantitatively as follows**: 1+ for mild, 2+ for moderate, 3+ for moderately severe, and 4+ for severe regurgitation. Increasingly, **MR is quantified where feasible**. This is accomplished most often using the proximal convergence method (see below). Quantification provides prognostically powerful information that is less affected by the ongoing loading conditions.

   The American College of Cardiology/American Heart Association (ACC/AHA) class I recommendation is for the use of Doppler echocardiography to determine the mechanism and severity of MR, to assess the LA and LV size and function over time, to assess the pulmonary artery (PA) pressures, and to reevaluate periodically if more than mild, and after mitral valve surgery. The current ACC/AHA classification of MR severity by Doppler echocardiography is summarized in Table 16.2.
   a. Color Doppler echocardiography allows the diagnosis of MR by means of visualization of the regurgitant jet or jets entering the left atrium and allows the assessment of severity.
      (1) Jet length and area are used in this assessment. These measurements are **reliable with central jets**, but underestimation of MR may occur with eccentric jets. Because a jet directed against the atrial wall appears smaller than a free jet of the same regurgitant volume (Coanda effect), it is common practice to upgrade the estimated severity of MR by at least one grade in this situation. The direction of the MR jet can also aid in assessing the

TABLE 16.2 Assessment of Severity of Mitral Regurgitation

	Mild	Moderate	Severe[a]
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (< 4 cm^2 or < 20% LA area)	Signs of MR > mild present, but no criteria for severe MR	Vena contracta width > 0.7 cm with large central MR jet (area > 40% of LA area) or with a wall-impinging jet of any size
Doppler vena contracta width (cm)	< 0.3	0.3–0.69	≥0.70
Quantitative (cath or echo)			
Regurgitant volume (mL/beat)	< 30	30–59	≥60
Regurgitant fraction (%)	< 30	30–49	≥50
Regurgitant orifice area (cm^2)	< 0.20	0.2–0.39	≥0.40

[a]In severe MR, evidence of LA and LV dilation is essential.

MR, mitral regurgitation; LA, left atrium; LV, left ventricle.

Adapted from 2006 Valve Disease ACC/AHA Guidelines.

cause of MR (Table 16.3). Regurgitation caused by prolapse or flail (excessive leaflet motion) results in a jet direction opposite to the affected leaflet (i.e., posterior jet with anterior leaflet prolapse). MR caused by leaflet restriction (rheumatic and ischemic) is directed toward the affected leaflet.

(a) Caveats

i. MR is assessed with **transesophageal echocardiography (TEE)**. Patients often receive sedation before TEE, and the sedation may reduce systemic blood pressure (afterload). This could make the MR appear less severe than it is under normal physiologic circumstances. This effect of sedation may be mitigated to some extent by increasing the afterload by handgrip or by the cautious administration of phenylephrine.

ii. In the evaluation of MR in the **intraoperative setting**, there may be fluctuations in afterload and preload.

(b) Multiple factors, such as hemodynamic considerations, geometric factors (constraint imposed by the LA wall), and instrumentation, may affect color Doppler measurements. This has led to the development of other measurements to quantify MR.

(2) The width of the vena contracta, which is the narrowest portion of the proximal regurgitant jet downstream from the orifice, is a **reliable indicator of the severity of MR**. A width **≥0.70 cm suggests severe MR**. High-resolution and zoom images must be used for an accurate

TABLE 16.3 Mechanisms, Direction of Color Jet, and Surgical Management of Mitral Regurgitation

Jet direction	Leaflet motion	Likely cause	Surgical method
Anterior	Excessive	Posterior leaflet prolapse	Quadrilateral resection Annuloplasty Chordal shortening Shortening of papillary muscle
	Restricted	Anterior leaflet restriction	Debridement
Posterior	Excessive	Anterior leaflet prolapse	Chordal transfer or shortening
		Posterior leaflet resection to move coaptation apically	
	Restricted	Posterior leaflet restriction	Debridement, annuloplasty
	Normal	Ventricular dilation	Annuloplasty
Central	Excessive	Bileaflet prolapse	Resection, chordal transfer
	Restricted	Bileaflet restriction	Debridement
	Normal	Ventricular dilation	Annuloplasty
Commissural	Papillary muscle dysfunction		Reattach or fold papillary muscle
	Eccentric	Perforation or cleft	Pericardial patch

From Stewart WJ. Intraoperative echocardiography. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine.* Philadelphia, PA: Lippincott–Raven Publishers; 1998, with permission.

assessment of the vena contracta or else TEE may be needed. There is some tendency for overestimation of the width of the vena contracta because of limited lateral resolution.

b. Pulsed-wave Doppler echocardiography of pulmonary venous flow may be useful in the assessment of the severity of MR (Fig. 16.2). Sampling of the pulmonary veins results in three distinct waves: a systolic antegrade wave, a smaller diastolic antegrade wave, and a small negative wave that represents atrial reversal during atrial contraction. With increasing MR, there is a progressive decrease in the systolic wave of pulmonary inflow with eventual reversal. **Blunting of the systolic component** of pulmonary venous flow in the presence of normal LV function suggests at least moderately severe MR. **Systolic flow reversal** suggests severe MR. Blunted pulmonary venous flow is a less reliable indicator of substantial MR in the setting of atrial fibrillation or severe LV dysfunction, since these conditions also can cause systolic blunting.

c. **Pulsed-wave Doppler echocardiography of mitral inflow.** SV across the regurgitant mitral valve can be estimated and compared with the SV derived from pulsed-wave Doppler imaging across a competent valve (such as the aortic or pulmonary valve). The excess flow at the mitral valve over that

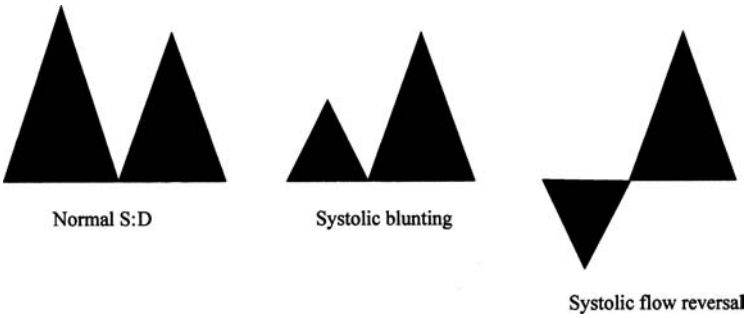

FIGURE 16.2 Patterns of pulmonary venous flow. *First triangle* in each panel represents flow during systole. *Second triangle* represents flow during diastole. The three potential patterns are displayed: normal flow ratio, blunted systolic flow, and reversed systolic flow.

derived at the aortic valve is **the regurgitant volume**. These methods are both tedious and technically difficult.

d. The **proximal isovelocity surface area (PISA)** or flow convergence method provides a quantitative assessment of MR (see Fig. 16.3 and Chapter 67). Peak mitral flow rate is derived as follows:

$$QFC = 2\pi r^2 V$$

where r is the radius of the shell and V is the aliasing velocity at that shell. **Regurgitant orifice area (ROA)**, a relatively load-independent measure of regurgitation, is derived from peak flow rate by dividing this by peak flow velocity (maximal MR continuous-wave velocity, ***Vmr***):

$$ROA = 2\ \pi\pi r^2\ V/\ Vmr$$

The **regurgitant volume** (RV) may be further calculated by the equation ROA × VTI*mr*, where VTI*mr* is the velocity–time integral of the regurgitant jet.

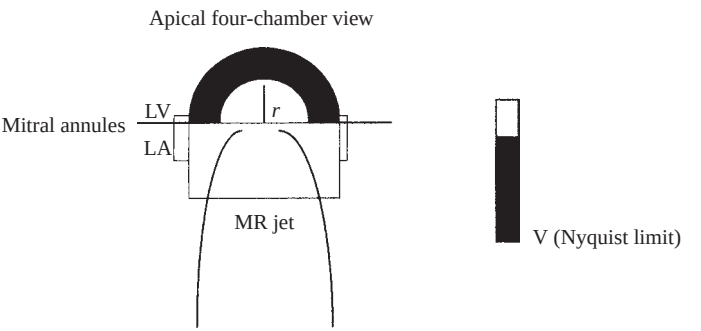

FIGURE 16.3 The proximal isovelocity surface area method for determining severity of mitral regurgitation (MR). LV, left ventricle; LA, left atrium.

If the forward SV is known, then the **regurgitant fraction** (RF%) may be derived as follows:

$$RF = RV/RV + SV$$

SV may be estimated in the LV outflow tract as area × VTI, as performed in the continuity equation (see Chapter 15).

ROA has been shown to be prognostically powerful in MR of ischemic or degenerative origin. **An ROA of 0.4 cm^2** or greater is indicative of severe MR.

(1) Simplified proximal convergence method. The preceding calculation may be simplified to allow the ROA to be estimated with only one measurement. Using this method, MR velocity is assumed to be 5 m/s and the aliasing velocity is set at 40 cm/s. The ROA may be calculated as $r^2/2$. **Higher ROA indicates an increased severity of MR.**

(2) Inaccuracies in using proximal convergence method occur when the orifice is nonspherical, multiple jets are present, or the flow convergence zone is constrained as occurs with eccentric jets. The latter situation occurs with a flail leaflet, as regurgitant flow and ROA are typically overestimated by the use of the PISA method; accuracy may be improved by the use of angle-correction formulas.

2. Cardiac catheterization

a. The **amplitude of the v waves** on hemodynamic tracings (which are a reflection of LA filling from the pulmonary veins during ventricular systole) can provide clues to the severity of MR, particularly in acute MR.

(1) Amplitudes of *v* wave more than two to three times mean LA pressure suggest severe MR. However, in slowly developing MR, an abnormal *v* wave may not be seen. The *v* waves are also diminished by afterload reduction. The **absence of v waves does not exclude severe MR.**

(2) Other conditions that may produce prominent *v* waves are LV dysfunction with a dilated noncompliant left atrium, postinfarction VSD, and other situations in which there is increased pulmonary blood flow.

b. Left ventriculography allows the visual assessment of the severity of MR. It is affected by multiple factors such as the adequacy of the contrast injection to fill the ventricle, the placement of the catheter, and ventricular arrhythmia during injection. The grading system is as follows:

1. **1+ (mild):** clears with each beat; entire left atrium is never opacified.
2. **2+ (moderate):** does not clear with a single beat; may faintly opacify the entire left atrium.
3. **3+ (moderate to severe):** fills entire left atrium over 2 or 3 beats; complete opacification of the left atrium, equal in intensity to the left ventricle.
4. **4+ (severe):** complete opacification of the left atrium in 1 beat; contrast material refluxes into the pulmonary veins.

c. Coronary angiography is useful to detect **concomitant coronary artery disease** (CAD) in these patients. Those being considered for surgery to correct MR undergo coronary angiography, even in the absence of symptoms, if they are older than 50 years or have multiple risk factors.

E. Therapy. An understanding of the pathophysiologic mechanism of MR is essential to management.

1. Acute MR

a. Medical therapy. If there is adequate mean arterial pressure, pharmacologic therapy with **afterload reducing agents** may reduce the acute MR. Intravenous nitroprusside and nitroglycerin may reduce pulmonary pressures and maximize forward flow. If surgery is not immediately indicated a switch to oral agents may be made. Angiotensin-converting enzyme (ACE) inhibitors

(ACE-I) and direct-acting vasodilators (such as hydralazine) help maximize forward output and reduce regurgitant fraction.

b. Percutaneous therapy. The large sudden volume overload on an left ventricle that is not dilated or hypertrophied causes symptoms of pulmonary congestion and even cardiogenic shock. For such patients with acute hemodynamically significant MR, especially from postinfarction PM rupture, placement of an intraaortic balloon pump (IABP) may serve as a temporary stabilizing measure until surgical repair can be undertaken.

c. Surgical therapy. Patients with acute, severe MR usually require urgent surgical intervention.

2 Chronic MR

a. Choosing the appropriate therapy (see Table 16.4 for a summary of the current ACC/AHA guidelines)

(1) Most patients who have **moderately severe to severe MR** and are **symptomatic** should be considered for elective surgical treatment. Decisions need to be individualized based on the age of the patient, the likelihood of valve repair, comorbidities, LV function, and the likelihood that surgical intervention will improve symptoms and/or survival. Generally, **intervention for symptoms is indicated for severe MR if the cause of the MR is primary to the valve** (i.e., prolapse, rheumatic, or congenital in origin). When the **valve lesion is secondary to ventricular dysfunction,** either from ischemic heart disease or from dilated cardiomyopathy, **aggressive medical management of heart failure** (see subsequent text) is indicated first.

(3) In **severe MR due to dilated cardiomyopathy associated with severe symptoms** and refractory to medical management and cardiac resynchronization therapy (CRT) where indicated, mitral valve repair may lead to symptomatic improvement, but a survival benefit has not yet been demonstrated.

(4) Management of patients with **minimal or no symptoms but severe MR** is more complex. **The key is to identify patients before contractile dysfunction of the left ventricle becomes irreversible.** Watchful waiting until serious symptoms develop carries a risk for the development of severe LV dysfunction and a poor prognosis. The feasibility of mitral valve repair with improved postoperative survival and EF (see later) has been another incentive in the push for earlier surgical intervention. If the valve repair is not feasible, one may choose to wait longer before proceeding to surgical treatment. The 2006 valve guidelines **lowered the threshold to intervene in asymptomatic patients with repairable valves** when repair is performed in an experienced center where the likelihood of repair exceeds 90% (Table 16.4).

b. Timing of surgery. A variety of clinical, echocardiographic, and invasively derived values appear to be predictive of the development of postoperative LV dysfunction, decompensated heart failure, and death among patients with significant but asymptomatic MR. The timing of mitral valve surgery is a **decision that must be individualized** and depends on several variables, including clinical signs and symptoms, echocardiographic findings, catheterization data, hemodynamic data, operative risk, and repairability of the mitral valve. Generally, the variables to be considered in patients whose MR is asymptomatic are (a) LV size and function; (b) exercise capacity and LV size and function at peak exercise; (c) repairability of the valve; (d) severity of MR, including the presence of flail leaflet; (e) pulmonary artery pressures; (f) atrial fibrillation; and (g) age and other comorbidities.

TABLE 16.4 Indications for Mitral Valve Surgery in Mitral Regurgitation

Class I

- **(a)** MV surgery is recommended for the symptomatic patient with acute severe MR
- **(b)** MV surgery is of benefit for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction < 0.30) and/or end-systolic dimension > 55 mm
- **(c)** MV surgery is of benefit for asymptomatic patients with chronic severe MR and mild to moderate LV dysfunction, ejection fraction 0.30–0.60, and/or end-systolic dimension ≥ 40 mm
- **(d)** MV repair is indicated over MV replacement in most patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair

Class IIa

- **(a)** MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR with preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom the likelihood of successful repair without residual MR is > 90%
- **(b)** MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new-onset atrial fibrillation.
- **(c)** MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension (pulmonary artery, systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise)
- **(d)** MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction < 0.30 and/or end-systolic dimension > 55 mm) in whom MV repair is highly likely

Class IIb

MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction < 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing

Class III

- **(a)** MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom significant doubt about the feasibility of repair exists
- **(b)** Isolated MV surgery is not indicated for patients with mild or moderate MR

MV, mitral valve; MR, mitral regurgitation; NYHA, New York Heart Association; LV, left ventricular.
Adapted from 2006 Valve Disease ACC/AHA Valve Disease Guidelines.

(1) LV size and function. As noted previously, contractile impairment is often occult in severe MR when conventional indices of LV function are used. Elastance measured at the time of cardiac catheterization is the best load-independent measure of true contractile function in MR. However, as it requires the construction of a series of pressure–volume loops for its calculation, it is rarely performed outside research laboratories. Fortunately, conventional indices of LV size and function do

provide useful information in MR. Newer noninvasive techniques, such as two-dimensional (2D) strain imaging, are of interest because of their ability to detect subtle changes in LV function that precede reductions in EF. **In severe primary MR with preserved contractile function, left ventricular ejection fraction (LVEF) should be in the high-normal range. Studies have indicated that once the LVEF is < 60%, the likelihood of impaired survival and permanent LV dysfunction postoperatively is high**. Therefore, consideration should be given to surgical intervention before the LVEF drops to below 60%. Increased LV size and volume in end systole (more load-independent than end diastole) is also an indicator of increased likelihood of impaired survival and LV dysfunction postoperatively. When **LV end-systolic diameter is > 4.0 cm, surgical intervention should be considered**.

(2) We have found that **exercise echocardiography** is very helpful in determining the likelihood of latent LV contractile dysfunction. **The ability of the left ventricle to cope with exercise is an indication of its contractile reserve**. In addition, **poor functional capacity** may indicate an adaptive response to MR (the patient was not truly asymptomatic) and may influence the decision to proceed with surgical treatment. We have found that a **failure to *increase* LVEF, or for end-systolic volume to *decrease* with stress, is predictive of postoperative LV dysfunction** and is a superior predictor of this eventuality than resting LVEF. In patients with severe asymptomatic MR, we perform stress echocardiography at 6-month intervals and recommend mitral valve surgery once end-systolic volume fails to decrease significantly at peak exercise or if LVEF fails to increase. This is particularly helpful in patients who wish to postpone surgical intervention as long as possible.

(3) The **feasibility of repair** depends on the cause of MR. This can be determined during the preoperative evaluation by echocardiography. **Repair in an experienced center is usually likely in MVP unless chordae to both leaflets are severed, severe damage from endocarditis has occurred, or there is extensive leaflet calcification**. Repair is usually feasible for a cleft valve and in less extreme forms of endocarditis such as leaflet perforation without chordal disruption, as well as in many cases of secondary MR (ischemic or dilated cardiomyopathy). Repair is more difficult to achieve in rheumatic involvement and when the valve leaflets or chordae are severely disrupted from any cause. **The threshold to intervene surgically is lower if repair appears feasible because of the lower surgical and long-term mortality and morbidity associated with repair compared with replacement**.

(4) The more severe the MR, the greater the volume load on the left ventricle usually, and the more likely that LV dysfunction will develop. One caveat here is that MR is not always holosystolic. Occasionally, apparently severe MR is seen without evidence of significant LV enlargement because the MR is occurring only in the latter part of systole.

The threshold to intervene surgically is lower as MR severity increases. In situations where MR severity is in doubt, a TEE should be performed and the quantitative assessment used as described previously. A flail leaflet usually (but not always) implies severe MR. A retrospective study suggested that earlier surgical intervention was associated with better long-term survival in patients with a flail leaflet, even if the condition was asymptomatic, with flail being considered a surrogate for severe MR. More recent quantitative studies suggest that once ROA is ≥ 0.4 cm^2, survival is better in those treated surgically, even in the absence of symptoms.

(5) Pulmonary pressures > 50 mm Hg at rest or > 60 mm Hg at peak exercise in the absence of another likely cause are an indication of severe MR and impaired survival and these **are considered ACC/AHA class IIa indications for surgical intervention**. These can be assessed noninvasively from the tricuspid regurgitant velocity at stress echocardiography.

(6) The occurrence of **atrial fibrillation** or flutter in the setting of severe MR is considered an indication (IIa) for surgical intervention. A concomitant maze or more usually now a modified maze procedure (pulmonary vein and great vein isolation) may be performed with mitral valve repair, especially if atrial fibrillation has become persistent or frequent.

(7) Age and other comorbidities. Patients > 75 years, those with concomitant CAD, or those with renal dysfunction have worse outcomes after surgical treatment. Patients with ischemic MR have a worse prognosis than those with regurgitation from other causes.

c. Medical therapy

(1) The role of medical therapy for **asymptomatic, chronic MR caused by primary valve disease** is not well established. There is no evidence that pharmacologic agents delay progression of the disease or prevent ventricular dysfunction. Patients with severe MR should be evaluated semiannually with echocardiography and stress echocardiography, if indicated. Patients with moderate MR should be evaluated annually.

(a) The success of afterload reducers in acute MR has led to trials of vasodilators, such as **ACE-I and hydralazine**, in chronic MR. However, existing small trials have been largely negative. As a result, the ACC/AHA and European Society of Cardiology guidelines recommend against the use of pharmacological vasodilatation in chronic MR with preserved EF, although this is not necessarily reflected in common practice.

(b) Sympathetic overstimulation appears to be a key element of progression to LV failure in MR, and there is limited evidence for the experimental use of β-blockers in MR but no clinical evidence of utility of postponement of surgical intervention.

(c) MR secondary to LV dysfunction is managed with standard heart failure therapy, including ACE-I and β-blockers.

(d) Diuretics and nitrates have a role in the management of pulmonary congestion.

(e) Ventricular rate-controlling agents and antiarrhythmics are used for atrial fibrillation. **Digitalis and β-blockers** are the mainstay of therapy for rate control. In severe MR with atrial fibrillation, maintenance of sinus rhythm is unlikely if the regurgitation remains uncorrected.

(2) **In accordance with recent AHA guidelines**, endocarditis prophylaxis is not routinely indicated in patients with MR. These new guidelines recommend that prophylaxis be used only in patients with underlying cardiac conditions associated with the highest adverse outcome from infective endocarditis, including prosthetic heart valves or prior repair surgery, previous infective endocarditis, certain classes of congenital heart disease, and in valvulopathy occurring post cardiac transplantation.

d. Surgical therapy

(1) Mitral valve replacement with transection of the subvalvular apparatus was once the only approach used in the surgical management of MR. Postoperative reduction of LV function and decompensated heart failure were common sequelae. Chordal preservation by leaving the subvalvular structures intact has been shown to reduce LV volumes and wall stress postoperatively and is now the technique of choice.

(2) The increasing success of **mitral valve repair** has greatly reduced the morbidity and mortality associated with severe MR. Mitral valve repair almost always involves placement of an undersized annuloplasty ring, which reduces annular diameter, improves leaflet coaptation, and significantly decreases MR. Additional components may include a pericardial patch at the site of leaflet perforation, chordal shortening or transposition, leaflet resection, and sliding valvuloplasty of the posterior leaflet to reposition the coaptation line. Artificial chordae are increasingly used in the repair of anterior leaflet prolapse.

(3) Although no randomized trials have compared repair with replacement, **comparative data suggest better postoperative LV function and survival with repair** (which in part reflects the selection of patients who are able to undergo repair). Long-term risk of thromboembolism and endocarditis is reduced with repair versus replacement, and the need for reoperation is similar. Excellent 20-year outcomes following repair have been reported from multiple large volume centers, with the estimated risk of reoperation approximating 10%.

(4) **Minimally invasive** video-assisted approaches employing hemi-lower sternotomy and right thoracotomy incisions may be options in experienced centers and selected patients. In the latter, cardiopulmonary bypass is usually achieved via femoral artery and vein cannulation. These approaches have the benefit of smaller incisions, resulting in more rapid postoperative recovery but require considerable expertise. Introduction of robotic surgical instrumentation and high-definition three-dimensional (3D) imaging allows mitral valve repair through portlike incisions, with further reduction in procedural invasiveness. **Robotically assisted valve repair** has shown good results in a few centers, although there are currently no data for superior outcomes. Complex surgeries, particularly if they require concomitant coronary artery bypass grafting (CABG) or multivalvular repair, are likely better handled with a standard operative approach at this point. These techniques may enjoy broader application in the future.

(5) **Mitral valve replacement** is indicated when repair is not technically possible. The choice of **mechanical or bioprosthetic** valve replacement depends on weighing the risk of chronic anticoagulation required with mechanical valves, against the reduced longevity of the bioprosthetic valves. Structural degeneration of bioprosthetic mitral valves typically affects 20% to 40% patients at 10 years and over 60% at 15 years.

(6) Intraoperative echocardiography helps in the **assessment of complications** of valve repair or replacement.

- (a) Residual MR is the most common problem after a pump run. If further repair is feasible, a second pump run should be considered to correct residual MR (if 1+ or greater). If further repair is not possible, valve replacement may be needed. A second pump run does not appear to increase in-hospital mortality.
- (b) **Dynamic LV outflow obstruction** is an important potential complication of mitral valve repair. This is now uncommon in experienced centers. It is caused by anterior displacement of mitral leaflet coaptation point when the posterior leaflet is redundant (typically > 1.5 cm in height). The result is systolic motion of the mitral leaflet into the outflow tract, creating a pressure gradient across the outflow tract and the development of MR. This may be apparent immediately after surgery in the operating room, with intraoperative echo or later in the course. It is exacerbated by increased inotropy and small LV size. Many instances resolve with cessation of the use of

sympathomimetic agents and volume repletion. In the operating room, if these efforts fail to correct the condition, more surgery to reduce the height of the posterior mitral leaflet (sliding annuloplasty) or, rarely, mitral valve replacement may be necessary. In the postoperative patient, volume repletion and judicious use of β-blockade are often all that is necessary, although occasionally surgical revision of the repair is needed. The development of a new apical systolic murmur in the patient who has undergone mitral valve repair should prompt an echocardiogram to exclude this complication.

e. Postsurgical follow-up care

(1) Baseline echocardiography should be performed postoperatively. This is ideally scheduled 4 to 6 weeks after the operation, but for the sake of convenience it is often done before hospital discharge (within 3 to 4 days).

(2) MR can recur because of failure of the repair or because of progression of the disease that caused MR. Patients should undergo clinical evaluations at least once a year. **Yearly echocardiography** after the operation to assess for MR and LV function is reasonable.

f. Resynchronization therapy. LV wall motion abnormalities are often the major pathology in secondary (functional) MR, and CRT has demonstrated symptomatic benefit in carefully selected patients.

g. Percutaneous mitral valve repair. Percutaneous mitral valve repair is a developing catheter-based treatment option in which improved coaptation of the mitral leaflets is attempted using an implantable device. Current techniques emulate the existing surgical procedures, with the devices currently under investigation being classified into two functional approaches.

(1) A **clip** can be used to approximate the center of the mitral valve leaflets, thus giving a double-orifice valve in an approach that models the surgical Alfieri edge-to-edge repair. To date, this is the best studied percutaneous option, with the Endovascular Valve Edge-to-Edge Repair Study II recently reporting the 12-month results of 279 patients with 3 to 4+ MR randomized to MitraClip (Abbott Vascular, Menlo Park, CA, USA) versus surgical mitral valve repair/replacement. The primary composite end point for efficacy was freedom from death, from mitral valve surgery, and from 3 or 4+ MR. About 55% of subjects in the percutaneous repair group met the end point at 1 year compared with 73% in the surgery group. All-cause mortality was equivalent in the percutaneous and surgical groups. There were significantly fewer adverse events in the percutaneous group, although significance was lost when blood transfusion was excluded as a complication. Implantation of the MitraClip is currently performed in the United States as part of a continued access registry.

(2) A **flexible ring** can be deployed and tightened in the coronary sinus (CS) in order to effectively reduce the mitral annulus area. Concerns regarding this procedure include the variable relationship between the CS and mitral annulus, as well as the proximity to the circumflex artery. Devices under investigation include two stents deployed into the CS, with the connecting coil bridge being tightened over time called the Monarc (Edwards Lifesciences, Irvine, CA, USA); a fixed length, double-anchor CS device called the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA, USA); and a CS anchor that is attached to the interatrial septum via a cord under tension called the Percutaneous Septal Shortening System (Ample Medical, Foster City, CA, USA).

The clip may be more appropriate for repair of MVP, whereas annular remodeling is felt to be better suited for the repair of functional regurgitation.

III. ISCHEMIC MR (IMR)

A. Clinical presentation. IMR may present either acutely in the setting of active ischemia or infarction or chronically with long-standing CAD. Among patients with CAD, the presence of MR portends a worse prognosis. Acute severe IMR presents with cardiogenic shock and hemodynamic instability, with symptoms and signs consistent with those previously described for acute MR. The clinical presentation of chronic IMR also parallels that of other etiologies of chronic MR; in addition, a history of known CAD or cardiovascular risk factors should be sought.

B. Etiology and pathology

1. Ischemia or infarction may give rise to one or more of the following mechanisms of IMR. Those common in the acute setting include the following:
   a. PM rupture or chordal avulsion;
   b. altered LV geometry, causing PM displacement; and
   c. elongation of the infarcted PM and exaggerated contraction of the noninfarcted PM.
2. Mechanisms common in the chronic IMR setting include
   a. PM necrosis causing leaflet tethering and poor coaptation;
   b. decreased mitral valve closing forces because of LV systolic dysfunction; and
   c. LV cavity dilation causing mitral valve annular dilation.
3. The anterolateral PM receives its blood supply from the left anterior descending and circumflex circulations; the posteromedial PM is supplied by the right coronary or left circumflex artery depending on the coronary dominance.
4. Of note, acute IMR is more frequently a result of geometric changes due to regional LV dysfunction (especially of the inferolateral wall) that induce leaflet tethering and prolapse, rather than ischemia of the PM itself.

C. Laboratory examination and diagnostic testing

1. **Echocardiography.** The most important determinations are the assessment of valvular anatomy, quantification of regurgitation, and evaluation of LV structure and function. Echocardiography can often reveal the mechanism of IMR by evaluating for PM rupture, leaflet restriction, mitral valve tethering, and relevant regional wall motion abnormalities. As previously described, the degree of regurgitation is quantified using color flow and Doppler techniques. Urgent transthoracic echocardiography and/or TEE is the investigation of choice in a patient with acute pulmonary edema where IMR is being considered as an etiology.
2. **Electrocardiogram (ECG).** In acute IMR, ECG is key in evaluating for the presence of active ischemia or infarction. As described above, branches from the left or right coronary systems can supply the PMs. However, it is in the setting of inferior or inferolateral MIs that acute IMR is most commonly seen. In chronic IMR, LA abnormalities, atrial fibrillation, and nonspecific ST-T changes may be seen.
3. **Chest radiography.** In acute IMR, findings of pulmonary edema may be present. Cardiomegaly with LA and LV enlargement may be seen in chronic IMR.
4. **Cardiac catheterization.** Evaluation of the patient with IMR will include angiography to assess the location, extent, and revascularization options of the CAD. In some cases, invasive hemodynamics may provide useful additional data regarding MR severity.

D. Therapy.

1. Intravenous afterload reduction with nitroprusside and nitroglycerin +/– IABP insertion is often required when managing cardiogenic shock secondary to acute IMR. This scenario is associated with a **very poor prognosis**, and surgical intervention with coronary artery bypass and valve repair or replacement is usually the only hope for survival.
2. The medical management of chronic IMR with preserved EF remains controversial, as described above. If LV dysfunction is present, the use of a heart failure medical regimen is essential.

3. Patients with significant IMR will likely require surgery for revascularization and valve repair or replacement. However, studies to date **have not demonstrated any long-term benefit from the addition of valvular surgery to CABG** in this setting. The success rate and durability of valve repair in IMR are significantly lower than those of degenerative mitral valve disease.

IV. MITRAL VALVE PROLAPSE

A. Clinical presentation. Prolapse exists when either or both of the mitral leaflets protrude > 2 mm beyond the annulus into the left atrium during systole, and the coaptation point of the leaflets lies superior to the plane of the annulus. A wide spectrum of pathologic changes and clinical symptoms have been observed, from mild degrees of prolapse diagnosed with echocardiography only to clinically evident severe MR. MVP is the most common cause of MR in the United States. **It affects approximately 2% of the population. Recent studies have suggested an equal prevalence among males and females**. **Males and older patients (age > 45 years) are disproportionately more likely to require surgical intervention** and to develop other major complications such as endocarditis.

1. **Signs and symptoms**
   - **a.** Most patients with MVP have **no symptoms,** and the diagnosis is made by means of routine examination or echocardiography performed for other indications.
   - **b.** Although in the past many symptoms were attributed to MVP, including chest pain, panic attacks, and autonomic instability, more recent studies suggest that these occur no more frequently in patients with MVP than in control populations. Most symptoms associated with adverse prognostic implications occur when significant MR is present.
   - **c.** Arrhythmias are more common with MVP, even in the absence of MR. These include **supraventricular tachyarrhythmias, ventricular tachyarrhythmias, and bradyarrhythmias**. Sudden cardiac death is a rare complication in MVP, occurring in < 2% patients over long-term follow-up. It is more common in the setting of severe MR and/or flail valve leaflet and is likely due to ventricular arrhythmias.
   - **d.** Transient ischemic attack or stroke has been reported in MVP. The most recent studies in this area suggest no excess risk of cerebrovascular events among young patients with MVP.
   - **e.** When prolapse causes MR, symptoms referable to the valvular insufficiency may be present.
2. **Physical findings**
   - **a. Inspection.** There is a higher than expected incidence of **pectus excavatum** among patients with mitral valve. Straight back and scoliosis are also found. Patients often have low body weight and relative hypotension.
   - **b.** The main **auscultatory** findings are shown in Figure 16.4. The **midsystolic click** is the classic finding in prolapse. A systolic murmur is heard if MR is present.
   - **c.** Dynamic changes are elicited by **conditions that decrease LV size** (decreased venous return, increased contractility, or decreased systemic volume), which lead to earlier occurrence of prolapse, an earlier click, and increased duration of the murmur. These conditions include standing, the Valsalva maneuver, dehydration, and exposure to amyl nitrite.
   - **d.** Maneuvers that **increase LV size** by increasing venous return, decreasing contractility, or increasing systemic volume move the click and murmur later into systole. Examples include squatting and infusion of phenylephrine. The presence of a **click that responds to provocative maneuvers is sufficient**

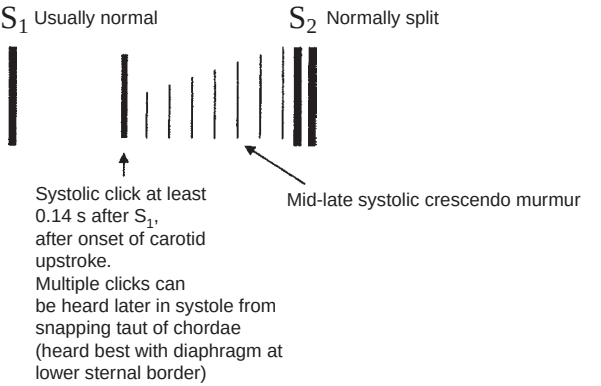

FIGURE 16.4 Auscultatory findings in mitral valve prolapse.

for the diagnosis of prolapse, even if an echocardiogram is not diagnostic (see **Section III.D.1**).

e. The **intensity of the murmur typically decreases with conditions that result in a later click and murmur**. An exception is exposure to amyl nitrite, which also reduces LV systolic pressure and the gradient that drives regurgitant flow. As such, the murmur is of lower intensity, although it occurs earlier in systole.

f. Aortic and pulmonic ejection sounds can produce systolic clicks. These occur earlier in systole than the click of mitral prolapse and may be differentiated on the basis of timing in conjunction with the carotid upstroke. Other causes of midsystolic clicks include septal and free wall aneurysms and mobile tumors such as myxoma. Clicks produced by these conditions do not change with maneuvers that alter LV volume.

B. Etiology and pathology. Prolapse may exist as a result of valvular abnormalities, deemed primary prolapse, or occur in the setting of normal leaflets (secondary prolapse).

1. Primary prolapse results from **myxomatous proliferation of the leaflets**.

Myxomatous mitral valve disease describes thickening of the leaflets and chordae tendineae due to abnormal accumulation of **mucopolysaccharides**, with prominence of the spongiosa layer of the leaflets. Impaired tensile strength is more marked in the chordae than in the leaflets. Chordal elongation results in prolapse and loss of leaflet coaptation and may cause MR. **Thickening of the leaflets ≥5 mm is considered "classic" MVP** and is associated with greater future complications.

a. Within the pathological spectrum of myxomatous mitral valve disease, there are two subtypes of diseases. **Barlow disease** is seen in younger patients, shows greater annular dilation, and has more marked leaflet redundancy and prolapse that may involve multiple segments. Conversely, **fibroelastic deficiency** occurs in older patients, is typically confined to the posterior middle scallop (P_2), and is associated with thinning and rupture of chordae.

b. Primary prolapse appears to have a genetic predisposition. There is a higher prevalence of MVP among family members of those affected, and an **autosomal dominant** mode of inheritance with variable penetrance has been postulated. Recent linkage studies suggest a site on chromosome 16 in some families

with MVP. In addition, MVP is seen as part of disorders with more generalized abnormalities of the connective tissue, such as Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and myotonic dystrophy.

c. Most **complications** of prolapse, particularly severe MR, are associated with primary prolapse. Men in their sixth decade of life represent the most common demographic group with such a presentation.

2. In **secondary prolapse**, there is relatively **normal valvular structure**. A disproportion between leaflet size and LV cavity size produces mechanical forces that may lead to leaflet prolapse. This form of prolapse particularly affects **younger women**. It may also occur with atrial septal defect, hyperthyroidism, emphysema, and hypertrophic cardiomyopathy. Normalization of the relative disproportion between leaflet size and cavity size often occurs with ageing among women, so the incidence decreases with age. **Secondary prolapse is usually of little clinical significance and is not usually associated with significant MR**.

C. Laboratory examination and diagnostic testing

1. **Echocardiography.** M-mode demonstrates late or holosystolic bowing of the mitral valve leaflet 3 mm or more below the C–D line. In 2D echocardiography, prolapse is defined as **>2-mm displacement of one or both mitral leaflets into the left atrium during systole in the parasternal or apical long-axis views**. Caution must be used in making the diagnosis with the apical four-chamber view because normal valve leaflets may appear to prolapse in this view owing to the saddle shape of the mitral annulus. With primary causes of prolapse, increased leaflet thickness (≥5 mm) and redundant leaflets and chordae are seen. Doppler echocardiography is used to assess the presence and severity of MR. Annual echocardiography is advised for those patients with moderate to severe MR.
2. **Electrocardiogram.** If there is severe MR, the findings described earlier are present. Otherwise, the ECG usually is normal or has nonspecific ST-T changes.
3. **Chest radiography.** Pectus excavatum or scoliosis can be present in some cases. If severe MR is present, the typical findings described earlier are seen. Otherwise, the **chest radiograph is usually normal.**

D. Therapy. For most patients, MVP carries a benign prognosis, and **periodic clinical follow-up examinations and reassurance** are all that is needed.

1. Endocarditis prophylaxis is not routinely indicated in patients with MVP.
2. Approximately 10% to 15% of patients, particularly those with redundant and thickened leaflets, eventually develop progressive MR. Chordal rupture is a contributing factor among these patients. **Management of MR** is outlined in **Section II.E.** Patients with evidence of primary MVP should avoid situations that might increase the stress on the chordae, such as sudden heavy lifting.
3. For patients with a history of **transient ischemic attacks, antiplatelet therapy with aspirin** (80 to 325 mg/d) is indicated. The ACC/AHA guidelines also recommend aspirin for poststroke patients with MVP who have no evidence of MR, atrial fibrillation, LA thrombus, or echocardiographic evidence of thickening (≥5 mm) or redundancy of the valve leaflets. However, long-term **anticoagulation therapy with warfarin** is recommended if any of these higher risk features are present, and in MVP patients with recurrent transient ischemic attacks while taking aspirin (international normalized ratio [INR]: 2.0 to 3.0). Aspirin is sufficient for patients with MVP and atrial fibrillation who are < 65 years, have no MR, and have no history of stroke, hypertension, or heart failure.
4. Patients who experience palpitations should be advised to abstain from caffeine, alcohol, and tobacco use. **β-Blockers** are useful in the management of premature atrial or ventricular contractions and often alleviate symptoms. **Ambulatory electrocardiographic monitoring** is recommended for persistent palpitations. Ventricular tachycardia is an indication for **electrophysiologic testing** to assess the risk of sudden death and the possible need for **implantation of a defibrillator device.**

V. MITRAL STENOSIS. Although declining in incidence in the United States, rheumatic disease remains the predominant cause of MS. Other etiologic factors are listed in Table 16.5. In general, once symptoms begin to develop, there follows a period of about 10 years before they become debilitating. Once significant limiting symptoms develop, the 10-year survival rate is < 15%.

A. Clinical presentation

1. Signs and symptoms

a. There is often a **long asymptomatic course**, consisting of a couple of decades.

b. When symptoms do develop, **dyspnea** is common. Predominant symptoms are exertional dyspnea initially, followed by paroxysmal nocturnal dyspnea and orthopnea, which reflect elevated pulmonary venous pressure.

c. Precipitating factors, such as exercise, emotional stress, pregnancy, infection, or atrial fibrillation with a rapid ventricular response, can produce or dramatically worsen symptoms by generating increased transvalvular gradients and LA pressure. **Atrial fibrillation with rapid ventricular response is a classic exacerbating factor** and may produce pulmonary edema, even in those with mild MS. The LA dilation is a predisposing factor for the development of atrial fibrillation.

d. Hemoptysis can occur and likely represents rupture of small bronchial veins from elevated LA pressure.

e. Hoarseness occurs when the dilated left atrium impinges on the recurrent laryngeal nerve (Ortner syndrome).

f. LA dilation and stasis, particularly in the context of atrial fibrillation (persistent or paroxysmal), may cause thrombus formation and embolic events. **Cerebrovascular events, coronary embolization, and renal emboli and infarction** are all possible sequelae. The malformed valve is predisposed to the development of **endocarditis**.

g. Fatigue is common because of reduced cardiac output.

h. With long-standing MS and elevated pulmonary pressure, symptoms of **RV failure** may develop.

i. Patients with elevated pulmonary pressures may have **angina-like chest pain**, as a reflection of increased RV oxygen demand.

TABLE 16.5 Causes of Mitral Stenosis

Rheumatic: most common cause
Congenital
Parachute mitral valve: single papillary muscle to which chordae to both leaflets attach; results in mitral stenosis or mitral regurgitation
Supravalvular mitral ring
Systemic diseases: can cause valvular fibrosis
Carcinoid
Systemic lupus erythematosus
Rheumatoid arthritis
Mucopolysaccharidosis
Healed endocarditis
Prior anorectic drug use
Severe mitral annular calcification

2. **Physical findings**
   a. **Inspection and palpation.** Patients may have a **malar facial flush**. The jugular venous pulse can demonstrate a **prominent** a **wave** if there is elevated pulmonary vascular resistance and the patient is still in sinus rhythm. **Jugular venous pressure is elevated with RV failure**. In advanced cases with low cardiac output, **peripheral cyanosis** occurs. The **carotid upstrokes are usually normal** but are of low amplitude if there is diminished cardiac output. The apex beat is not displaced and the impulse can have a tapping quality due to a palpable first heart sound. An apical diastolic **thrill** may be felt in the lateral decubitus position and has a quality that simulates a purring cat. If there is pulmonary hypertension, a **parasternal RV lift with a palpable P_2** is present.
   b. **Auscultation.** The main auscultatory findings are shown in Figure 16.5.
      (1) The **opening snap** is the most characteristic auscultatory hallmark of MS. However, as the mitral valve becomes more calcified and immobile, the opening snap may be lost (just as S_1 becomes softer).
      (2) The **murmur** of MS is typically a low-pitched rumbling mid-diastolic murmur, heard best with the bell of the stethoscope with the patient in the left lateral decubitus position. Presystolic accentuation can be present whether or not the patient is in sinus rhythm (exact mechanism is unknown). Auscultation after a **brief period of exercise may accentuate the murmur** of MS as the increased output and heart rate increase the transvalvular gradient. The length of the murmur correlates better with the severity of MS than the loudness. **The longer the murmur and the shorter the time interval from S_2** to the opening snap, the more severe the MS.
      (3) Concomitant **conditions that result in decreased flow across the valve**, such as CHF, pulmonary hypertension, and aortic stenosis, may **reduce the diastolic murmur**. The presence of a loud S_1 may be the only clue to the presence of MS in these cases, particularly if pulmonary hypertension exists.
      (4) Auscultation of the lungs may reveal fine inspiratory crackles. However, it is remarkable that some patients with severe MS have clear lung fields, possibly due to lymphatic hyperfunction clearing the transudated alveolar fluid that would be expected from the elevated LA pressure.

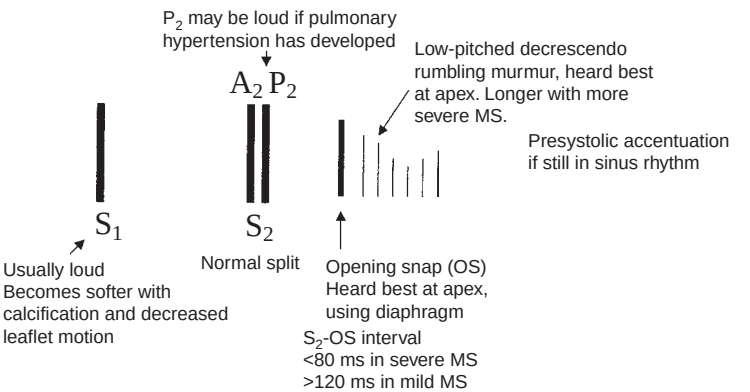

FIGURE 16.5 Auscultatory findings in mitral stenosis.

(5) Other **conditions that mimic** the clinical presentation of MS include LA myxoma and cor triatriatum. The tumor plop of myxoma may be mistaken for an opening snap, and tumor obstruction of the valve leads to a diastolic murmur. However, in this condition, the physical findings will vary with changes in position and from examination to examination. Other conditions in which a diastolic rumble may be present include atrial septal defect or VSD, the Austin-Flint murmur of aortic regurgitation (the murmur lessens with decreased afterload and is preceded by an S_3, and the S_1 is normal), and tricuspid stenosis (the murmur is heard at the left sternal border and typically increases with inspiration, known as Carvallo's sign).

B. Etiology (Table 16.5)

1. In **rheumatic MS**, up to 50% of patients are not aware of a history of rheumatic fever. Rheumatic fever is now rare in developed nations, although it is unclear whether this is due to improvements in living conditions or a change in the virulence or immunogenicity of *Streptococcus pyogenes*.
   a. In **acute** rheumatic fever, MR often predominates. Stenosis usually develops anywhere from 2 to 20 years later, and symptoms may not develop for many years thereafter. Although the incidence of rheumatic fever is roughly equal between men and women, rheumatic MS develops two to three times more frequently in women.
   b. Thickening of leaflets with **fibrous obliteration** is a characteristic finding. Commissural and chordal fusion and chordal shortening contribute to the development of stenosis. Calcium deposition occurs on leaflets, chordae, and annulus, further restricting valvular function. These changes collectively produce a funnel-shaped mitral valve with a fish-mouth orifice.
2. Nonrheumatic MS causes include congenital malformation, extensive annular calcification in the elderly, radiation heart disease, and restrictive mitral valve repair for MR.

C. Pathophysiology

1. The normal area of the mitral orifice is 4 to 6 cm^2. When the valve area is < 2 cm^2, a **pressure gradient between the left atrium and the left ventricle in diastole occurs**. As orifice area declines, both the transmitral pressure gradient and the LA pressure increase, but these are also affected by the flow through the valve. **Although the transmitral pressure is a useful indicator of MS severity, it is critically affected by the cardiac output at any moment**. The **cross-sectional area of the mitral valve orifice is, for the most part, independent of flow considerations and thus is a more robust measure of the severity of MS**.

   Typical findings indicative of the **severity of stenosis** as defined by the American Society of Echocardiography and endorsed by the recent ACC/AHA valve disease guidelines are as follows:
   a. **Severe** stenosis is associated with a **mean** transvalvular gradient **> 10 mm Hg**, PA pressures > 50 mm Hg, and a valve **area < 1.0 cm^2**.
   b. **Moderate** stenosis is associated with a **mean** transvalvular gradient of **5 to 10 mm Hg**, PA pressures of 30 to 50 mm Hg, and a valve area of **1.0 to 1.5 cm^2**.
   c. **Mild** stenosis is associated with a **mean** transvalvular gradient of **< 5 mm Hg**, PA pressures < 30 mm Hg, and a valve area **> 1.5 cm^2**.

   The severity of the stenosis needs to be assessed in terms of not only the valve area but also symptomatology and exercise capacity. Mixed MS and MR is often associated with greater symptomatic impairment than might be predicted from the severity of either lesion alone.
2. The **increased LA pressure is transmitted to the pulmonary vasculature**, resulting in symptoms of pulmonary congestion. The passive increase in pulmonary venous pressure may elevate pulmonary vascular resistance (reactive pulmonary hypertension). This condition is usually reversible if the stenosis is

relieved. However, in long-standing, severe MS, obliterative changes in pulmonary vasculature may occur. Severe pulmonary hypertension can in turn lead to right-heart failure.

3. Up to 30% of patients have a **depressed LVEF**. This appears to result from decreased preload (decreased inflow into the left ventricle) or a rheumatic myocarditis. The former will normalize after a corrective mitral valve procedure, the latter will not.
4. In severe MS, there may be sufficiently low cardiac output to cause **symptoms of poor perfusion**. Chronically depressed cardiac output causes a reflex increase in systemic vascular resistance and increased afterload. This may further diminish LV performance.

D. Laboratory examination and diagnostic testing

1. Echocardiography has several critical roles in the evaluation of MS (all endorsed by ACC/AHA recommendations): initial diagnosis, determination of severity, evaluation of suitability for percutaneous balloon mitral valvuloplasty, and identification of concomitant valve lesions.
   a. M-mode findings include dense echoes on the mitral valve and decreased excursion of the mitral valve. **Poor leaflet separation in diastole, anterior motion of the posterior leaflet, and decreased E–F slope on the anterior leaflet** are M-mode hallmarks of MS.
   b. Two-dimensional findings include restricted motion and diastolic doming of leaflets (hockey stick sign) (Fig. 16.6). The leaflets and chordae are thickened and are often calcified in older patients.
   c. Doppler echocardiography is **essential** in the assessment of stenosis severity.
      (1) A **transmitral peak velocity** > 1 m/s suggests MS. However, this is not specific because tachycardia, increased inotropy, MR, and VSD may cause increased flow in the absence of MS.

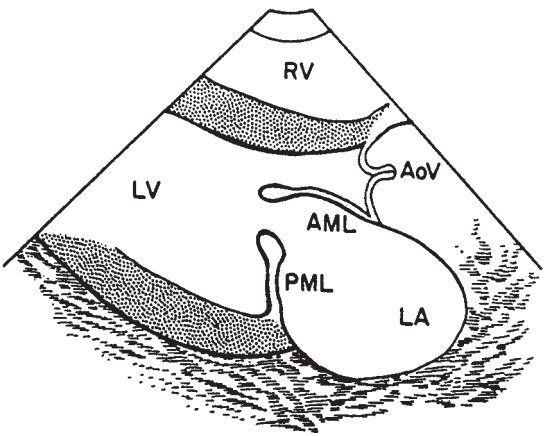

FIGURE 16.6 Two-dimensional echocardiographic scan in parallel long-axis view shows findings of mitral stenosis. Doming of leaflets is present. LV, left ventricle; RV, right ventricle; AML, anterior mitral leaflet; PML, posterior mitral leaflet; LA, left atrium; *AoV*, aortic valve. (Reproduced from Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J.* 1988;60:299–308, with permission from BMJ Publishing Group Ltd.)

(2) The **transvalvular mean gradient** (assessed by means of tracing mitral inflow) provides an estimate of the severity of stenosis. A mean gradient < 5 mm Hg is typical in mild stenosis. Moderate stenosis is associated with a mean gradient between 5 and 12 mm Hg. A gradient > 12 mm Hg suggests severe MS.

d. Echocardiography is used to estimate the **mitral valve area**.

(1) Direct planimetry of the orifice can be performed in the parasternal short-axis view.

(i) Optimal positioning is done by first obtaining a parasternal long-axis view and placing the mitral valve orifice in the center of the scan plane. The transducer is then rotated 90° to obtain the short-axis view. Measurements are obtained at the tips of the mitral leaflets.

(ii) Poor-quality 2D images and a thick, calcified subvalvular apparatus can make it difficult to obtain accurate measurements. Improper orientation of the scanning plane can produce oblique cuts across the valve and lead to overestimation of valve area. Scanning up and down until the typical fish-mouth appearance is seen helps in this regard. Dense fibrosis or calcification at the margins of the valve orifice can lead to underestimation of the valve area. Low-gain settings can cause dropout at the edges of the valve and overestimation of the valve area. High-gain settings can lead to underestimation. Planimetry is more difficult if commissurotomy has been performed, but remains the preferred method to assess the mitral valve area by means of echocardiography. With the advent of **3D imaging via transthoracic echocardiography**, more accurate orifice mapping for planimetry is now possible (see below).

(2) Pressure half-time method. Impedance to LA emptying prolongs the decline in transvalvular pressure gradient. This prolongs pressure half-time (time that it takes for pressure to fall to one-half the starting value, which equates with the time for the velocity to decrease to 70% of peak velocity). The mitral inflow E wave is used in the calculation.

(i) Empiric pressure half-time has been shown to correlate with valve area:

$$\text{Mitral valve area (in cm}^2\text{)} = 220/\text{pressure half-time}$$

(ii) If a software package to perform the calculations is not available, pressure half-time can be calculated by multiplying the deceleration time by 0.29. If atrial fibrillation is present, 5 to 10 consecutive beats are obtained and averaged.

(iii) It is important to have the Doppler beam parallel to the direction of blood flow.

(iv) The pressure half-time method **is inaccurate if there are rapid changes in LA hemodynamics**, such as immediately after balloon valvuloplasty.

(v) Obtaining a pressure half-time may be very difficult if sinus tachycardia is present (E–A fusion). Severe aortic insufficiency also fills the left ventricle in diastole, decreases pressure half-time, and leads to overestimation of the mitral valve area.

e. Stress echocardiography is useful in the evaluation of patients with symptoms when the **resting study is discrepant with symptoms or clinical findings** (ACC/AHA class I). Gradients can be assessed during (supine bicycle) or immediately after (treadmill) exercise. Measurement of tricuspid regurgitation velocity is used to estimate pulmonary pressures with stress.

f. **TEE** is indicated to exclude LA thrombus and assess MR prior to valvuloplasty, or if the TTE data are suboptimal (ACC/AHA class I), but is not indicated routinely if TTE data are adequate (ACC/AHA class III).

g. **Three-dimensional echocardiography (3DE)** can provide a 3D data set to determine the mitral valve area. This method can avoid error in measurement related to correct alignment of the cut-plane with the level of the mitral valve tips and speeds up the time required for optimal planimetry. Using real-time 3D transesophageal technology, visualization of the mitral valve en face from the left atrium or left ventricle is possible at the time of percutaneous balloon mitral valvuloplasty. The main advantage of preoperative transesophageal 3DE is that it replicates the surgical view of the mitral valve that will be seen upon opening the left atrium.

2. **Cardiac catheterization.** Hemodynamic measurements obtained in a cardiac catheterization laboratory are used to **assess the severity of stenosis**. Simultaneous measurement of LV end-diastolic pressure, LA pressure (either directly or more commonly with PCWP as a surrogate), cardiac output (Fick method or thermodilution), heart rate, and diastolic filling period (seconds per beat) is required. LV pressure and PCWP (or LA pressure) tracings are made simultaneously (Fig. 16.7). A mean transmitral gradient is derived from the preceding measurements (planimeter area between the left ventricle and PCWPs during diastole; this area is multiplied by the scale factor of the tracing in millimeters of mercury per centimeter to obtain the gradient). The PCWP tracing ideally should be realigned by 50 to 70 milliseconds to the left (with tracing paper) to account for the time delay in transmission of LA pressure to the pulmonary venous beds.

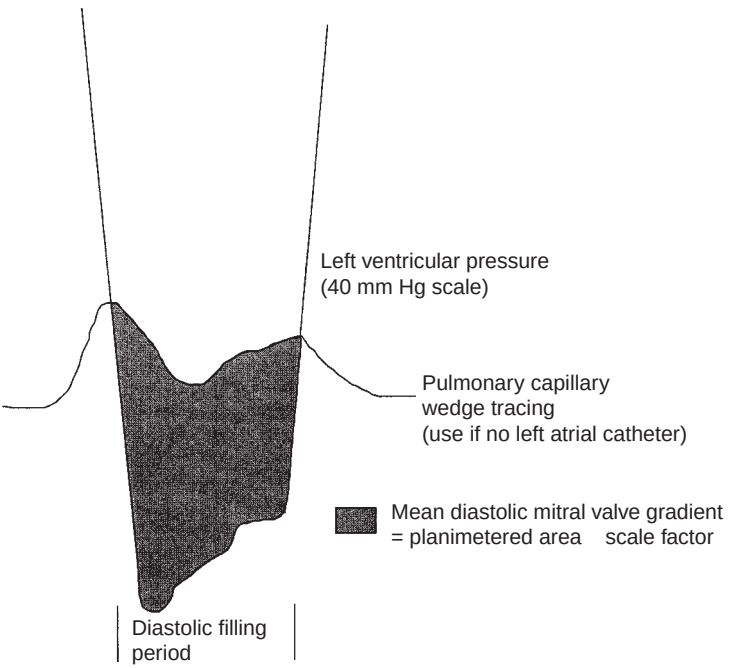

FIGURE 16.7 Simultaneous left ventricular and pulmonary capillary wedge pressure tracings used to measure mean gradient across mitral valve during diastole.

a. The **Gorlin formula:**

$$\text{Area} = \frac{\text{Cardiac output/diastolic filling period} \times \text{heart rate}}{37.7 \times \sqrt{(\text{mean transmitral pressure gradient})}}$$

Gorlin derived the empirical constant of 37.7, which is the Gorlin constant (44.3) multiplied by 0.85 (the correction factor for the mitral valve).

b. A **simplified version of the Gorlin formula** proposed by Hakki et al. has been validated and provides a reasonable approximation of the valve area:

$$\text{MVA} = \frac{\text{cardiac output}}{\sqrt{(\text{mean mitral gradient})}}$$

c. Pitfalls. PCWP cannot be used if the patient has pulmonary venous occlusive disease or cor triatriatum. The catheter must be properly wedged. In addition, **thermodilution cardiac output is less accurate** if there is severe tricuspid regurgitation or low cardiac output. **Immediately after valvuloplasty** MR or atrial septal defect, flow may lead to inaccurate estimations of mitral flow.

d. Cardiac catheterization is indicated in the evaluation of patients when echo-Doppler and clinical findings are discrepant (ACC/AHA class I) or when echo findings are internally discordant (class IIa) or if pulmonary hypertension is disproportionate to MS severity as assessed by echo (class IIa).

3. ECG. LA enlargement (P mitrale) is usually present when sinus rhythm persists. Signs of RV hypertrophy are seen with pulmonary hypertension. Atrial fibrillation is common and the fibrillatory waves are usually coarse.

4. Chest radiography. LA enlargement is apparent with a **double density** along the right heart border. A convexity can be apparent below the pulmonary artery, representing the LA appendage. Radiographic splaying of the carina with elevation of the left main bronchus and posterior displacement of the esophagus at barium swallow examination reflect LA enlargement. Kerley B lines may be present from increased pulmonary venous pressure. RV enlargement (decreased retrosternal air space on the lateral radiograph) may be present. Evidence of mitral valve calcification, or rarely LA calcification (McCallum's patch), may be present.

E. Therapy. The overall management approach to the individual with MS should integrate symptomatic status, degree of stenosis, and suitability of the valve for percutaneous balloon mitral valvuloplasty.

1. Medical therapy

a. Patients **without symptoms** who have mild MS (valve area > 1.5 cm^2 and mean gradient < 5 mm Hg) need no specific treatment and, **in accordance with current AHA guidelines, do not require endocarditis prophylaxis**. In patients with rheumatic valve disease, guidelines for the **prevention of rheumatic fever** should be applied. Annual reevaluation is recommended, but a yearly echocardiogram is not indicated unless there is a change in clinical status.

b. Patients with only **mild symptoms of exertional dyspnea** can be treated with **diuretics** and salt restriction to lower LA pressure. **β-Blockers** blunt the chronotropic response to exercise and may improve exercise capacity. **Arterial vasodilators should be avoided**.

c. Atrial fibrillation can clearly exacerbate symptoms, and **cardioversion or rate control measures** are important to maintain diastolic filling time. **Embolism** is a much feared complication of MS and occurs in up to 20% of patients; risk is increased with advancing age and atrial fibrillation.

(1) Digitalis and **β-blockers** are the preferred agents to achieve rate control.
(2) **Anticoagulation** with warfarin **is imperative** for patients with paroxysmal, persistent, or chronic **atrial fibrillation and MS** because they are at **high risk for thromboembolism** and this is also **indicated** in those with a history of **prior embolism or known LA thrombus** (ACC/AHA class I). Newer less emphatic recommendations (ACC/AHA class IIb) have been made for anticoagulation in MS patients with large atrial diameter (≥ 55 mm) or those with severe MS and enlarged LA size and evidence of spontaneous contrast on echocardiogram. The targeted INR is typically between 2.5 and 3.5.
(3) Antiarrhythmic drug therapy may be used in an attempt to restore sinus rhythm, but long-term efficacy may depend on correction of the MS.
(4) The role of percutaneous balloon mitral valvuloplasty in patients with new-onset atrial fibrillation and moderate to severe MS who are otherwise asymptomatic is controversial.

TABLE 16.6 ACC/AHA Indications for Percutaneous Mitral Balloon Valvotomy

Class I

1. PMV is effective for symptomatic patients (NYHA functional class II, III, or IV), with moderate or severe MS and valve morphology favorable for PMV in the absence of left atrial thrombus or moderate to severe MR
2. PMV is effective for asymptomatic patients with moderate or severe MS and valve morphology that is favorable for PMV, who have pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR

Class IIa

PMV is reasonable for patients with moderate or severe MS who have a nonpliable calcified valve, are in NYHA functional class III–IV, and are either not candidates for surgery or at high risk for surgery

Class IIb

1. PMV may be considered for asymptomatic patients with moderate or severe MS and valve morphology favorable for PMV who have new-onset atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR
2. PMV may be considered for symptomatic patients (NYHA functional class II, III, or IV) with MV area > 1.5 cm^2 if there is evidence of hemodynamically significant MS based on PA systolic pressure > 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient > 15 mm Hg during exercise
3. PMV may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA class III–IV

Class III

1. PMV is not indicated for patients with mild MS
2. PMV should not be performed in patients with moderate to severe MR or left atrial thrombus

PMV, percutaneous mitral valvotomy; NYHA, New York Heart Association; MS, mitral stenosis; MR, mitral regurgitation; MV, mitral valve.

2. **Percutaneous or surgical therapy** (Table 16.6). **If more than mild symptoms** (New York Heart Association [NYHA] class II or greater) are present due to MS, the patient should be referred for surgical or percutaneous therapy. An asymptomatic patient, with moderate to severe MS and evidence of pulmonary hypertension at rest or with exercise, should also be referred for percutaneous therapy if the valve is suitable. Mortality increases substantially as symptoms progress. Results of natural history studies, conducted before valvotomy procedures were developed, indicate that young symptomatic patients have about 40% mortality at 10 years and almost 80% at 20 years. Elderly patients have 60% to 70% mortality at 10 years. Marked **pulmonary hypertension** (pulmonary arterial systolic pressure > 60 mm Hg) is an indication for mechanical treatment, even in the absence of symptoms in moderate to severe MS. Rarely, for **patients with asymptomatic MS** who do not have pulmonary hypertension, surgical or balloon intervention may be warranted. Instances where this is indicated include **women with severe MS contemplating to become pregnant**, those with severe MS who will need a major surgical procedure with massive fluid shifts, or those with repeated embolism despite anticoagulation. In the last instance, surgical intervention is usually indicated, and LA appendage ligation is performed simultaneously.
   a. **Percutaneous balloon mitral valvuloplasty is considered the treatment of choice for symptomatic patients with moderate to severe MS who have favorable valve morphology**. The technique involves placement of a balloon-tipped catheter into the left atrium through a transseptal puncture and then across the mitral valve. The hourglass-shaped balloon (Inoue balloon) is inflated and deflated to increasingly larger diameters until the desired result is obtained.
      (1) Typically, there is an increment in valve area of 1 cm^2, mainly as a result of splitting of the fused commissures. The mean valve area usually doubles with a 50% to 60% reduction in transmitral gradient.
      (2) This procedure is **generally contraindicated in patients with > 3+ MR** (the procedure normally increases MR by one grade) **or in whom there is an LA or appendage thrombus** (risk of procedural embolism). Severe tricuspid regurgitation (does not improve substantially) and severe pulmonary hypertension (if pulmonary artery pressures do not fall, then substantial risk of right-to-left shunt across procedural atrial septal defect) are relative contraindications to the procedure.
      (3) An **echocardiographic score** has been developed to help select patients who may be candidates for percutaneous valvuloplasty. There are four parts to the assessment (mobility, leaflet thickening, subvalvular thickening, and calcification) (Table 16.7). In general, extensive subvalvular disease results in a poorer outcome with valvuloplasty. Patients with extensive fluoroscopically visible mitral valve calcification also have a worse outcome after percutaneous therapy.
         (a) A total echocardiographic score (adding the four components) **higher than 11** is associated with a poorer outcome and a suboptimal increase in valve area, a higher incidence of heart failure and restenosis, and higher mortality. Patients with high scores **should not undergo valvuloplasty** unless surgical treatment is impossible.
         (b) Echocardiographic scores of **9 to 11** represent a **gray zone** in which some patients have good results with valvuloplasty. Others have suboptimal results.
         (c) Optimal results of balloon valvuloplasty are usually achieved when the echocardiographic score is **8 or less**.
      (4) TEE plays a critical role during valvuloplasty. The most immediate concern is to **rule out LA and appendage thrombi**. If thrombosis

TABLE 16.7 Echo Score Assessment for Percutaneous Valvuloplasty in the Management of Mitral Stenosis

Mobility (grade 0–4, 0 being normal)
1. Highly mobile with only leaflet tips restricted
2. Mild leaflet restriction; base portions have normal mobility
3. Valve moves forward in diastole, mainly from base
4. No or minimal diastolic movement of valve

Subvalvular thickening (grade 0–4, 0 being normal)
1. Minimal thickening below leaflets
2. Chordal thickening up to one-third of chordal length
3. Thickening extending to distal one-third of chords
4. Extensive thickening to papillary muscles

Thickening of leaflets (grade 0–4, 0 being normal)
1. Near normal (4–5 mm)
2. Marginal thickening (5–8 mm) with normal thickness of midleaflets
3. Thickening of entire leaflet (5–8 mm)
4. Extensive thickening of all leaflet tissues (> 8–10 mm)

Calcification (grade 0–4, 0 being normal)
1. Single area of echo brightness
2. Scattered areas of increased brightness along leaflet margins
3. Brightness extending to the midportion of leaflets
4. Extensive brightness throughout the leaflet tissue

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is present, anticoagulation for at least 1 month is undertaken with repeat TEE to confirm resolution before valvuloplasty. TEE can also help guide balloon positioning; after each inflation, the degree of MR and the gradient can be assessed. The degree of residual MS can be estimated with planimetry of the valve orifice before and after inflation. The pressure half-time method is unreliable until 24 to 48 hours after the procedure.

(5) Echocardiography is useful in the determination of immediate **postprocedural complications** (Table 16.8). Among these is MR with an incidence estimated at 3% to 8%, depending on the series. The echocardiographic score is less predictive of the severity of postprocedural MR.

TABLE 16.8 Complications of Balloon Valvuloplasty

Mitral regurgitation

Cardiac perforation: incidence as high as 2–4%

Embolization: incidence 2% in the National Heart, Lung, and Blood Institute registry

Residual atrial septal defect: most close within 6 mo; can persist long term among as many as 10% of patients; generally small and well tolerated

(6) The frequency of **restenosis of the valve** is variable, depending on the age of the patient and the immediate procedural increment in valve area. Data from the National Heart, Lung, and Blood Institute registry of all functional classes of patients show an 84% survival rate 4 years after treatment. Advanced age, high NYHA functional class, presence of atrial fibrillation, smaller initial mitral valve area, higher pulmonary arterial pressure, and substantial tricuspid regurgitation are **associated with poorer long-term results**. These variables identify a population with more serious illness that frequently necessitates intervention and should not preclude valvuloplasty. More postprocedural MR and lower postprocedural mitral valve area are associated with poorer long-term results.

b. Surgical treatment. Closed **commissurotomy** was the earliest surgical approach used. This was performed through a thoracotomy (without cardiopulmonary bypass) and atriotomy with a valve dilator. This procedure is rarely used in the United States since the development of the percutaneous approach and improvements in open-heart surgery. **Open mitral valvotomy** involves direct visualization of the mitral valve (with cardiopulmonary bypass), debridement of calcium, and splitting of fused commissures and chordae.

(1) Severe subvalvular disease or valvular calcification often leads to the choice of **surgical intervention over valvuloplasty**. Coexistent disease in other valves (e.g., aortic stenosis or aortic regurgitation) that necessitates treatment also favors surgical intervention.

(2) Mitral valve replacement. Valve replacement is often required, especially when there is **extensive fibrosis and calcification or concomitant MR**.

(3) Mitral valve repair is more difficult but can be performed in selected cases with commissurotomy when there is mixed MS/MR.

(4) For patients with long-standing **atrial fibrillation**, a combined maze procedure (either surgical or using an intraoperative ablation catheter) can be performed in conjunction with the valve operation. LA appendage ligation may also be added to reduce future cardioembolic risk.

c. Comparison of balloon valvuloplasty and open commissurotomy. Studies in ideal patients for balloon valvuloplasty and commissurotomy suggest equal improvement in valve area and symptoms immediately postprocedure and in medium-term follow-up.

d. Postprocedural follow-up care. Patients who have undergone balloon valvuloplasty or operations for MS should undergo baseline echocardiography, preferably > 72 hours after the procedure. In patients with a history of atrial fibrillation, warfarin should be restarted 2 to 3 days after the procedure. **Clinical follow-up examination** should be performed at least once a year and more often if symptoms develop. It has become common practice at many centers for patients to undergo **follow-up echocardiography on a once-a-year basis**, although no firm guidelines have been developed for this.

ACKNOWLEDGMENTS: *The authors wish to thank Carmel Halley, MD, and Maran Thamilarasan, MD, for their contributions to earlier editions of this chapter.*

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CHAPTER 17

Shikhar Agarwal
Brian P. Griffin

Tricuspid Valve Disease, Pulmonary Valve Disease, and Drug-Induced Valve Disease

TRICUSPID VALVE DISEASE

I. INTRODUCTION. The **tricuspid valve (TV) apparatus** consists of three valve leaflets—septal, anterior, and posterior—along with the tricuspid annulus, the chordae tendineae, and the papillary muscles. Normally, the TV has an orifice area of 5 to 7 cm^2. The normal TV annulus is an elliptical and nonplanar structure, lying somewhat inferiorly and anterolaterally compared with the mitral valve (MV) annulus. The noncircularity and the nonplanarity of the TV have important mechanistic and therapeutic implications for correction of TV anomalies. Both tricuspid stenosis (TS) and tricuspid regurgitation (TR) can produce typical symptoms of right-sided congestive heart failure in their advanced stages. TV dysfunction can occur in both anatomically normal and abnormal valves.

II. TRICUSPID STENOSIS (TS). TS is rare as an isolated entity and is most commonly part of a multivalvular process. TS is usually organic in nature and is commonly encountered in conjunction with TR.

A. Etiology. Table 17.1 lists the causes of TS.

1. **Rheumatic heart disease (RHD)** by far is the most common cause of TS, accounting for > 90% of cases. Isolated TS is uncommon in these patients, and most patients have a combination of TS and TR. A large majority of patients with rheumatic TS have concurrent MV and aortic valve involvement. Clinically significant TV anomaly is present in only 5% of patients with RHD. Rheumatic TS is characterized by thickening and fibrosis of the valve leaflets, eventually culminating in marked leaflet contracture and commissural fusion.
2. **Carcinoid heart disease** is encountered in the setting of primary intestinal carcinoid tumors with secondary metastatic spread to the liver. Once metastatic to the liver, this neuroendocrine malignancy secretes numerous vasoactive substances (e.g., serotonin, histamine, and bradykinin), which directly affect the right-sided heart valves. Carcinoid valvular disease is characterized by thickened, retracted, shortened, and even fixed tricuspid leaflets, causing a mixed picture of regurgitation and stenosis. The pulmonic valve may also be involved. Unless there is a significant right-to-left shunt (via an atrial septal defect or patent foramen ovale), the left-sided heart valves are usually spared, owing to the clearance of vasoactive substances by the lungs.

B. Pathophysiology

1. TS produces a **diastolic pressure gradient** between the right atrium and the right ventricle, which is augmented when transvalvular flow increases. Therefore, the pressure gradient increases during inspiration or exercise and decreases during expiration. This typically occurs once the valve area falls below 1.5 cm^2.
2. A modest elevation of mean diastolic pressure gradient (i.e., ≥5 mm Hg) can raise right atrial pressure (RAP) (i.e., > 10 mm Hg) sufficiently to produce signs of **systemic venous congestion**, including hepatomegaly, ascites, and edema.
3. The right atrial *a wave* may be very prominent and may approach the level of the right ventricular systolic pressure (RVSP).
4. Resting cardiac output may be markedly reduced and may fail to augment with exercise, due to limited right ventricular preload.
5. Development of atrial fibrillation may result in higher RAPs due to the absence of organized atrial contraction and emptying.

C. Clinical presentation

1. **Signs and symptoms.** The presentation of TS varies depending on the **severity of stenosis**, the presence of **concomitant cardiac lesions**, and the **etiology of the valvular disease**.
   a. **Fatigue** is common and related to low and relatively fixed cardiac output.

TABLE 17.1 Causes of Tricuspid Stenosis

Disease entity
Congenital
Rheumatic
Infective endocarditis
Prosthetic valve failure
Carcinoid syndrome
Malignancy (e.g., myxoma and metastases)
Whipple's disease
Fabry's disease

b. **Right upper quadrant pain** can result from high systemic venous pressure and concomitant hepatomegaly, ascites, and abdominal distention.
c. Occasionally, patients will experience a **fluttering discomfort** in the neck, caused by the giant *a waves* transmitted to the jugular veins.
d. Severe TS may mask the typical symptoms of other coexisting valvular lesions, such as mitral stenosis (MS). In the case of MS, the flow limitation across the TV can minimize the pulmonary congestion, orthopnea, and paroxysmal nocturnal dyspnea usually associated with MS.

2. **Physical findings.** The diagnosis of TS is often missed without a high index of suspicion. Clues that should raise suspicion of TS include the presence of **elevated jugular venous pressure** and **accentuation of a diastolic murmur along the left sternal border with inspiration** (not present in MS).
a. Elevated central venous pressure may lead to marked hepatomegaly, ascites, and peripheral edema. In sinus rhythm, a giant *a* wave in the jugular venous pulse at the first heart sound (S_1) results from impaired right atrial diastolic filling during atrial systole.
b. **Diastolic murmur.** The murmur of TS is **low pitched**, **diastolic**, and best heard along the left lower sternal border in the third to fourth intercostal space or over the xiphoid process. If the rhythm is sinus, the murmur is prominent at end diastole (presystole). The low-pitched diastolic murmur may be obscured by the usually associated MS murmur. Accentuation of the murmur **intensity with inspiration** (Rivero-Carvallo sign) or other preload augmenting maneuvers (e.g., leg raising and squatting) may serve to differentiate the two murmurs or at least identify a component of TS in the setting of concurrent MS.
c. An **opening snap** (OS) may be heard at the left lower sternal border; however, this can be difficult to auscultate due to the commonly coexistent mitral OS.
d. Despite elevated neck veins and venous congestion, the patient may be comfortable lying flat due to the absence of pulmonary congestion. This apparent discrepancy between the severity of peripheral edema and the paucity of pulmonary congestion can help discriminate and identify TS from other valvular lesions.
e. Respiratory variation in splitting of the second heart sound (S_2) may be absent in patients with TS due to the relatively fixed diastolic filling of the right ventricle despite respiration.
f. In patients with the carcinoid syndrome, symptoms related to neurohormonal release, such as flushing and diarrhea, are typically more common than symptoms attributable to TS.

D. **Diagnostic testing.** The hemodynamic expression of TS is a pressure gradient across the TV in diastole. A mean diastolic pressure gradient of 2 mm Hg across the TV establishes the diagnosis of TS during catheterization. Nowadays, hemodynamic diagnosis is rarely required, as the diagnosis is usually apparent on Doppler echocardiography.

1. **Electrocardiogram (ECG).** TS is suggested by the presence of right atrial enlargement on the ECG (P-wave amplitude > 2.5 mV in lead II). Because of the common coexistence of MS, biatrial enlargement may be seen.
2. **Two-dimensional** (2D) **echocardiography**. The **echocardiogram is the most useful tool** in identifying TS. Typical findings **include reduction in the diameter of the TV orifice** and **thickening and diastolic doming of the tricuspid leaflets** (especially the anterior leaflet). Doppler interrogation of the TV will reveal increased transvalvular velocity; a mean pressure **gradient > 5 mm Hg using continuous-wave (CW) Doppler** is generally diagnostic of TS. Although it is possible to estimate the TV area by pressure half-time or planimetry, such measurements have limited utility in practice, as the severity of TS is more commonly described by the tricuspid diastolic pressure gradient. **Transesophageal echocardiogram (TEE)** is generally less useful than transthoracic echocardiogram (TTE) for assessing transvalvular gradients in TS, given that the TV is an anterior structure.

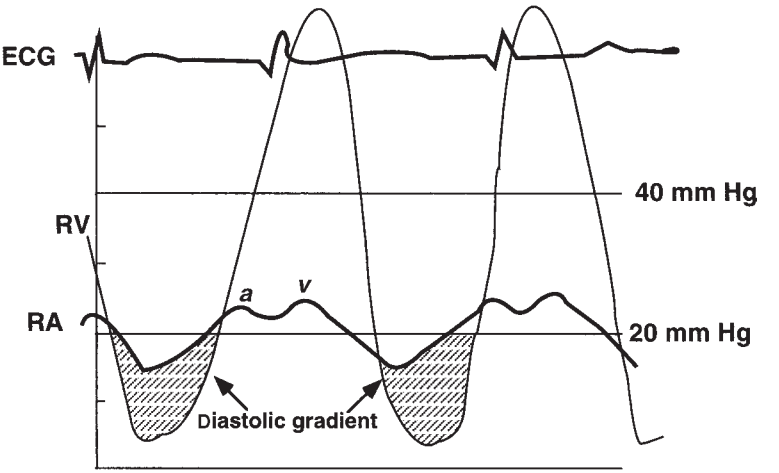

FIGURE 17.1 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid stenosis.

3. **Three-dimensional (3D) echocardiography.** Given the complex 3D structure of the TV, 3D echocardiography (transthoracic or transesophageal) may prove to be a useful adjunct to standard 2D echocardiography. Using this modality, all TV leaflets can be simultaneously imaged, potentially allowing for more accurate calculation of TV area and precise visualization of leaflet motion.
4. Given the accuracy of modern echocardiographic techniques, cardiac catheterization can often be bypassed. **Right heart catheterization can be used to confirm the diagnosis** already suggested by Doppler echocardiography and can serve as a prelude to therapeutic balloon valvuloplasty. Cardiac output is typically low. The RAP is elevated and the *a wave* may be very tall, sometimes approaching the RVSP in magnitude. Simultaneous measurement of the right atrial and right ventricular pressures with dual catheters (or a dual-lumen catheter) enables the calculation of the diastolic pressure gradient (Fig. 17.1). The measured gradient is highly dependent on cardiac output and heart rate. Maneuvers such as lifting the legs or administration of atropine may accentuate the gradient.

E. Therapy

1. **Medical therapy** consists of intensive sodium restriction and diuretics.
2. **Defining coexisting valvular lesions** is critical to properly managing TS. For instance, in patients with combined TS and MS, the former should not be corrected alone, as this may produce pulmonary congestion. If other valvular surgery is planned, concomitant treatment of TS should be considered if the gradient exceeds 5 mm Hg or the TV orifice area is < 2.0 cm^2.
3. **Severe stenosis requires balloon valvuloplasty or TV replacement.** The indications for surgery or balloon valvuloplasty are usually determined by the severity of concomitant mitral or aortic valve disease. Limiting symptoms due to predominant TS are considered an indication for valvuloplasty or surgery. Balloon valvuloplasty appears to be successful from both a symptomatic and a hemodynamic standpoint, but can result in significant TR, potentially necessitating valve replacement.

4. **Bioprostheses are favored** when valve replacement is necessary at the tricuspid position, as **mechanical prostheses are more prone to thrombosis** at this location. Combined severe stenosis and regurgitation, as occurs with carcinoid disease, usually necessitates a surgical approach.

III. TRICUSPID REGURGITATION

A. Etiology and pathophysiology. Any disease process that causes derangement of the TV apparatus (annulus, leaflets, chordae, and papillary muscles) can lead to TR. The most common cause of TR is not intrinsic valvular disease but rather dilation of the right ventricle, causing secondary (functional) TR. Table 17.2 lists the causes of TR.

1. The most commonly encountered type is the **functional or secondary TR**. Functional TR refers to the TR secondary to the left or the right heart pathology in the face of **normal TV leaflet morphology**. Functional TR is a dynamic entity that is regulated by several factors, including annular dilation, annular shape, pulmonary hypertension, ventricular dysfunction, and leaflet tethering.
2. TR with an **anatomically abnormal valve (i.e., primary TR)** may be a manifestation of congenital heart disease (e.g., Ebstein's anomaly, atrioventricular canal defects, and ventricular septal defect [VSD]). In addition, a variety of conditions such as RHD, myxomatous degeneration, carcinoid heart disease, radiation, endomyocardial fibrosis, and the hypereosinophilic syndrome may cause scarring/thickening of the TV apparatus, resulting in poor leaflet coaptation and TR.

B. Clinical presentation

1. **Signs and symptoms.** The spectrum of symptoms of TR is wide and depends on its etiology and chronicity. **Isolated TR is usually well tolerated**. When TR and pulmonary hypertension coexist, cardiac output declines and patients

TABLE 17.2 Causes of Tricuspid Regurgitation

Primary causes

Rheumatic
Ebstein's anomaly
Carcinoid
Connective tissue disease (e.g., Marfan's syndrome)
Tricuspid valve prolapse
Trauma
—*Blunt/penetrating injuries*
—*Iatrogenic secondary to pacemaker lead insertions*
Tumors (myxoma, tumors of tricuspid valve leaflet)
Infective or marantic endocarditis
Papillary muscle dysfunction
Radiation injury
Toxic secondary to phen-phen or methysergide valvulopathy

Secondary (functional) causes

Right ventricular dilation (dilated annulus)
Pulmonary hypertension
Right ventricular dysfunction
—*Global: cardiomyopathy, myocarditis, infarction*
—*Segmental: ischemia, infarction, fibrosis, arrhythmogenic right ventricular dysplasia*

may manifest symptoms of right heart failure. Patients may present with painful **hepatic congestion and substantial peripheral edema. Fatigue** from reduced cardiac output is another common presentation. Patients may notice **pulsations in their neck** due to the prominent *cv wave* in the jugular venous pulse. TR often coexists with MV disease; in these patients, the symptoms associated with MV disease usually predominate.

2. **Physical findings**
   a. On general examination, patients with severe TR may have signs of weight loss, cachexia, and jaundice related to congestive hepatopathy and bowel edema.
   b. The neck veins will show loss of the usual *x* wave and a prominent systolic wave, usually referred to as a *cv* wave, followed by a rapid *y* descent. The characteristics of the large *cv* wave in the jugular venous pulse are dependent on TR severity. With significant TR, the prominent *cv* wave has maximal height at S_2, and the rapid *y* descent is most prominent on inspiration. A venous systolic thrill and murmur in the neck may be present in severe TR. The right ventricular impulse is often hyperdynamic.
   c. TR typically produces a **pansystolic murmur** at the third to fourth intercostal space along the left sternal border. The TR **murmur increases with inspiration (Carvallo sign)**.
   d. A TR murmur that develops **in the presence of pulmonary hypertension is usually high pitched** and pansystolic, whereas a TR **murmur of primary etiology** (from endocarditis or trauma) is **short** (limited to first half of systole) **and low pitched**.
   e. TR causes an increase in diastolic flow across the TV. This may be heard as an **early diastolic rumble** (short and low-pitched) along the left sternal border.
   f. With **severe, long-standing TR**, there is **ventricularization of the right atrium** (the pressure gradient across the TV is minimized), and the TR **may be barely audible or absent**.
   g. **Other findings.** A **right-sided third or fourth heart sound (S_3 or S_4) is often present along the left sternal border, which augments with inspiration. If pulmonary hypertension coexists, P_2** is accentuated. **Systolic pulsation** of the liver is often an associated physical finding, although this may be diminished once congestive cirrhosis develops.

C. **Diagnostic testing**
1. **Electrocardiography.** The findings are usually nonspecific. Incomplete right bundle branch block may be seen. Atrial fibrillation is commonly found in association with severe TR.
2. **Echocardiography.** The most common views used for the detection of TR are the parasternal right ventricular inflow, basal short axis, and the apical four-chamber views.
   a. **Physiologic TR.** A small degree of TR is observed in about 70% of patients with structurally normal hearts, and the prevalence increases with age. Physiologic TR is usually represented by a small jet that does not extend > 1 cm into the atrium.
   b. **Two-dimensional echocardiography**
      (1) Leaflet thickening may be seen in TR due to rheumatic or carcinoid disease. In functional TR, the leaflets usually appear normal. Tricuspid prolapse often occurs in patients with MV prolapse and may cause significant TR. In Ebstein's anomaly, the septal leaflet of the TV is displaced apically. Vegetations are evident with endocarditis, and a flail valve leaflet may be seen with iatrogenic damage (e.g., after endomyocardial biopsy) or following papillary muscle rupture with right ventricular infarction.
      (2) With moderate to severe TR, a **right ventricular volume overload pattern** is seen, characterized by right ventricular enlargement, ventricular septal flattening or shift to the left in diastole, and paradoxical motion in

systole. There is often associated dilation of the right atrium and inferior vena cava (IVC).

c. Doppler analysis. Assessment of TR involves incorporation of all of the Doppler information obtainable: size of the color jet, presence or absence of a proximal convergence zone (on the right atrial side of the valve), velocity profile, and eccentricity of the TR jet. Eccentric, wall-hugging jets should be typically upgraded by one grade, as is done for mitral regurgitation, because these are generally not visualized fully by echocardiography.

(1) TR direction and severity are assessed with color-flow Doppler. The severity of TR is estimated in several ways, including

(a) Jet area—This measure is highly dependent on echocardiographic settings, particularly the pulse repetition frequency, and the direction and eccentricity of the jet.

(b) Vena contracta width—The narrowest portion of the jet just downstream from the valve orifice gives a rough estimate of the effective orifice area. A jet width of > 0.7 cm suggests severe TR.

(c) Proximal flow convergence (see Chapter 16).

(d) CW Doppler—The signal intensity and contour of the TR jet on CW Doppler can help define TR severity. Severe TR produces a dense spectral recording along with a triangular, early peaking velocity.

(e) Hepatic vein flow—Systolic flow reversal in the IVC or hepatic veins is consistent with severe TR.

(2) The RVSP is estimated using the modified Bernoulli equation after measuring the peak TR jet velocity by CW Doppler. In the absence of pulmonic stenosis, the pulmonary artery systolic pressure (PASP) can then be estimated as PASP = RVSP + RAP.

3. Cardiac catheterization. In the presence of moderate to severe TR, right heart catheterization will show a dominant *v* wave in the RAP curve (Fig. 17.2), an RAP curve resembling that of the right ventricle, increased right ventricular end-diastolic pressure, and low cardiac output by thermodilution and Fick techniques. **Angiocardiography** involves injecting contrast into the right

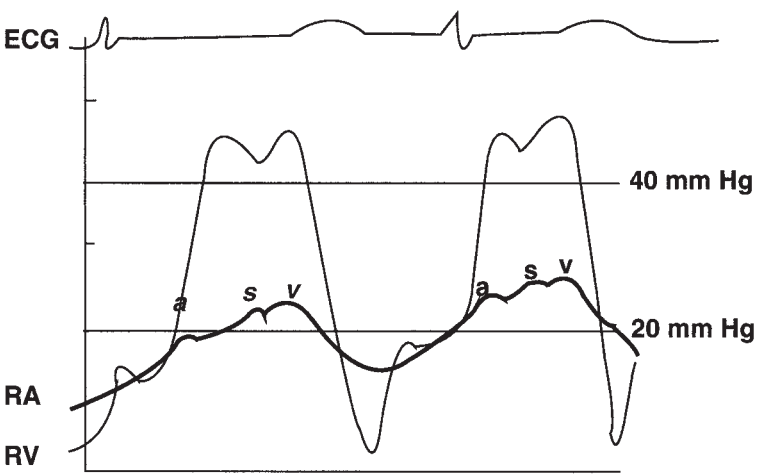

FIGURE 17.2 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid regurgitation.

ventricle while viewing the right anterior oblique projection. This method allows for visualization and semiquantification of the TR jet but is rarely performed, as echocardiographic techniques are more reliable.

D. Therapy

1. In the absence of pulmonary hypertension, mild to moderate degrees of TR can be well tolerated for many years, and surgery is not recommended (American College of Cardiology/American Heart Association [ACC/AHA] class III). If right ventricular failure develops, **medical therapy** should be targeted at diuretic therapy and afterload reduction, as in other heart failure states.
2. **Surgical therapy.** When there is an **organic cause** of moderate to severe TR, **surgical repair or replacement** may be necessary depending on the symptoms and the degree of leaflet destruction/damage. Currently, there is a lack of a clear consensus regarding indications for surgical repair of mild to moderate functional TR. ACC/AHA recommends surgical repair of severe TR in the setting of multivalvular disease (class I). Several studies have demonstrated a significant improvement in the functional status among individuals undergoing concomitant TV repair with MV or AV surgery in comparison to those undergoing left heart valvular surgery alone. In addition to multivalvular disease, tricuspid annuloplasty is recommended in patients undergoing MV surgery when there is pulmonary hypertension or significant TV annular dilation (class I). Most commonly, surgery for TR is considered in combination with left heart valvular surgery. In patients with MS and TR, a decision to repair the TV should be based on the severity of the TR, as well as the duration and severity of pulmonary hypertension (i.e., TR in the setting of long-standing pulmonary hypertension and MS is unlikely to improve with MV surgery alone). Usually tricuspid repair or annuloplasty is favored over prosthetic implantation where this is feasible. The other situations where TV repair may be considered include severe TR with deteriorating exercise capacity (ACC/AHA class I), severe TR with atrial fibrillation (ACC/AHA class IIa), and progressive enlargement of an already dilated right ventricle (ACC/AHA class IIb).

PULMONARY VALVE DISEASE

I. INTRODUCTION. The pulmonary valve is a trileaflet valve that separates the right ventricle from the pulmonary vasculature. Dysfunction of the valve can have adverse effects on the right ventricle by producing pressure and/or volume overload. A small degree of pulmonic regurgitation (PR) may be a common finding in healthy adults. Acquired pulmonary valve disease is rare in comparison with other valvular disorders.

II. VALVULAR PULMONARY STENOSIS (PS)

A. Etiology

1. **Congenital** PS is the most common pulmonary valve problem, occurring in approximately 10% to 12% of all adult patients with congenital heart disease. Valvular PS is typically an isolated abnormality, but it may occur in conjunction with VSD.
2. **RHD** can affect the pulmonary valve, although this is uncommon and usually occurs in the setting of multivalvular involvement. This can result in thickening and fusion of the valve leaflets, resulting in PS.
3. As with the TV, **carcinoid heart disease** (see Section **II.A.2**) can affect the pulmonary valve, causing formation of typical "carcinoid plaques." The plaques may result in constriction of the pulmonic valve ring, retraction and fusion of the cusps, and usually a combination of PS and PR.
4. Rarely, pseudopulmonary valve stenosis can occur as a result of **right ventricular outflow obstruction** from cardiac tumors or from an aneurysm of the sinus of Valsalva.
5. Although most cases of isolated PS are valvular, **obstruction may occur below the valve in the right ventricular outflow tract or above the valve at the junction with the main pulmonary artery**. Congenital PS is most frequently

caused by a dysplastic valve and less frequently a bicuspid valve. Right ventricular hypertrophy from the pressure overload of the PS on the right ventricle may cause concomitant right ventricular outflow tract obstruction, which usually reverses following successful dilation of the valvular stenosis.

B. Clinical presentation

1. **Signs and symptoms.** Patients with isolated PS present most commonly in the fourth or fifth decade of life with signs and symptoms of right heart failure and dyspnea on exertion. Of note, many patients with moderate PS remain asymptomatic. When the stenosis is severe, patients may occasionally have retrosternal chest pain or syncope with exertion. If the foramen ovale is patent, right-to-left shunting may occur, producing cyanosis and clubbing.
2. **Physical findings**
   a. PS causes a systolic crescendo–decrescendo murmur, heard best in the third and fourth intercostal spaces, with delayed peaking of the murmur in severe cases. The murmur typically increases with inspiration. A thrill may be felt in the suprasternal notch and at the left upper sternal border. S_2 is often split widely, and the degree of the splitting increases with worsening stenosis due to delay in P_2. The intensity of P_2 may be increased in mild stenosis but is usually diminished with severe stenosis. An ejection click can sometimes be heard along the left sternal border, and it may vary with respiration. As severity of PS increases, the click will move closer to S_1.
   b. The right ventricular impulse may be palpated at the left sternal border and be hyperdynamic.
   c. The jugular venous pressure can be normal. However, in patients with reduced right ventricular compliance, a prominent *a* wave may be seen in the venous pulse. A right-sided fourth heart sound (RV S_4) may be heard at the left lower sternal border.
   d. In advanced cases, evidence of right-sided heart failure may be present, including hepatic congestion and peripheral edema.

C. Diagnostic testing

1. **Electrocardiogram.** In patients with moderate to severe PS, the ECG may show right-axis deviation and right ventricular hypertrophy.
2. Chest radiography may reveal **poststenotic dilation** of the main pulmonary artery and diminished pulmonary vascular markings.
3. **Echocardiography** is useful in diagnosing pulmonary valve stenosis and for quantifying the severity of the obstruction. The best images of the pulmonary valve are obtained from the short-axis view at the level of the base from the parasternal and subcostal windows. Transesophageal echocardiography is useful when the TTE images are suboptimal.
   a. **Leaflets.** In adults, the leaflets can appear thickened and calcified with restricted motion. In children with congenital PS, the leaflets are noncalcified with doming of the valve.
   b. **Right ventricle.** The right ventricle may be normal, especially in children. Right ventricular dilation and hypertrophy may be seen in adults, depending on the severity and the duration of this disease.
4. **Doppler echocardiography** is the preferred method for grading the severity of PS. This method of quantifying the degree of stenosis is well correlated with the direct measurement obtained during cardiac catheterization. The peak gradient is measured across the pulmonary valve by using CW Doppler with the modified Bernoulli equation. The following levels of severity have been defined in the 2006 ACC/AHA guidelines on the management of valvular heart disease:
   (a) Severe stenosis: a peak jet velocity of > 4 m/s (peak gradient > 60 mm Hg).
   (b) Moderate stenosis: peak jet velocity of 3 to 4 m/s (peak gradient 36 to 60 mm Hg).
   (c) Mild stenosis: peak jet velocity of < 3 m/s (peak gradient < 36 mm Hg).

D. Therapy

1. Mild to moderate PS generally has a good prognosis, and intervention is rarely necessary. Survival is excellent among patients with mild PS, with 94% patients alive as long as 20 years after diagnosis.
2. Patients with severe PS usually warrant a therapeutic intervention for relief of stenosis. The treatment of choice is **balloon valvuloplasty**, usually leading to a 75% decrement in the transvalvular gradient after a successful procedure. The procedure is usually successful if the valve is mobile and pliable. Prognosis and morbidity subsequent to the procedure are largely based on right ventricular function at the time of the procedure. The hypertrophic subpulmonary stenosis that may accompany valvular stenosis usually regresses after successful valvuloplasty. Valve replacement may be necessary if the valve is severely calcified or if there is severe concomitant TR.
3. The **ACC/AHA guidelines for intervention** in congenital PS are as follows:
   Class I: Balloon valvuloplasty is indicated in symptomatic patients with > 30 mm Hg gradient (peak–peak) across the pulmonary valve at cardiac catheterization and in asymptomatic patients when this gradient is > 40 mm Hg.
   Class II: Balloon valvuloplasty may be reasonable if the gradient across the pulmonary valve is 30 to 39 mm Hg by cardiac catheterization in an asymptomatic adolescent or young adult.
   Class III: Balloon valvuloplasty is not indicated in asymptomatic patients whose pulmonary valve gradient is < 30 mm Hg at catheterization.
4. PS secondary to **carcinoid syndrome** has a very poor prognosis (with a median survival of 1.6 years), and the valve often does not respond to balloon valvuloplasty. **Valve replacement** is often necessary.

III. VALVULAR PULMONARY REGURGITATION (PR)

A. Etiology. PR is most commonly produced secondary to dilation of the valve ring due to pulmonary hypertension or dilation of the pulmonary artery.

1. **PR may occur secondary to rare congenital causes**, such as an absent, malformed, or fenestrated leaflet. In the setting of repaired tetralogy of Fallot, PR is a common and difficult problem, often contributing to progressive right ventricular dilation and dysfunction.
2. Acquired causes of pathologic PR are much more common. **The most common acquired cause is pulmonary artery hypertension**, followed by infective endocarditis. Both carcinoid syndrome and RHD may cause PR but they are more likely to cause PS. Marfan's syndrome may cause PR secondary to dilation of the pulmonary artery. Iatrogenic PR may be caused by placement of a pulmonary artery catheter.

B. Clinical presentation

1. **Signs and symptoms.** Like TR, PR causes volume overload of the right ventricle. However, in the absence of significant pulmonary hypertension, it may be tolerated well for many years. Once symptomatic, the patients with PR present with the signs and symptoms of **right heart failure and exertional dyspnea**. In the setting of PR caused by infective endocarditis, patients may present with fever and hypoxia due to septic pulmonary emboli.
2. **Physical findings**
   a. The murmur of PR is a relatively brief **low-pitched, diamond-shaped, diastolic murmur**, heard best in the third and fourth left intercostal spaces with a widening of S_2. The murmur increases with inspiration, and **P_2 is accentuated** in the presence of pulmonary artery hypertension.
   b. The **Graham Steell murmur** is a high-pitched, blowing decrescendo diastolic murmur starting immediately after P_2, which is accentuated by inspiration.

This characteristic murmur occurs when PASP exceeds 70 mm Hg in the presence of PR.

c. A right ventricular S_3 and S_4 may be audible in the fourth intercostal space and will be augmented by inspiration. Depending on the severity and duration of the regurgitant valve, signs and symptoms of right heart failure may also be present on examination.

C. Diagnostic testing

The pulmonary valve is best evaluated with **echocardiography**, using the left ventricle short-axis view from the parasternal and subcostal windows. Minor degrees of PR are seen in 40% to 78% of normal individuals. Pathologic PR is relatively infrequent and should be diagnosed in the context of other structural abnormalities.

1. **Anatomic assessment.** The right ventricular outflow tract and pulmonary valve should be interrogated for abnormalities such as leaflet hypoplasia, increased cusp number, and abnormal valve motion (i.e., doming).
2. **Right ventricle.** The size and function of the right ventricle can provide an indicator of the severity of PR (i.e., long-standing severe PR should be associated with right ventricular dilation and/or hypertrophy).
3. Color-flow Doppler will reveal a regurgitant jet toward the right ventricle during diastole. Jet length is determined primarily by the pressure difference between the pulmonary artery and right ventricle and, therefore, is an unreliable indicator of PR severity. The **vena contracta** is probably a better measure of PR severity.
4. CW Doppler will show a dense spectral signal and rapid equilibration of diastolic pressures in severe PR. Maintenance of the regurgitant velocity during diastole suggests that **pulmonary hypertension** is the cause of valve incompetence. Furthermore, increasing pulmonary artery pressures correlate with decreasing acceleration times of pulmonary artery flow. Pulmonary artery pressures can be obtained using Doppler flow measurements and the following equation. Pulmonary artery diastolic pressure (PADP) is only obtainable in the setting of PR:

$$\text{PADP} = 4(V_{\text{PR-E}})^2 + \text{RA}_{\text{pressure}}$$

where $V_{\text{PR-E}}$ is the end-diastolic PR velocity.

D. Therapy

1. **Primary pulmonary valve regurgitation.** The prognosis is very good; rarely is correction of the defect necessary, except in cases of intractable right heart failure.
2. **Secondary pulmonary valve regurgitation.** The prognosis due to endocarditis, carcinoid, or pulmonary artery hypertension is dependent upon the prognosis and treatment of the primary disease. Treatment of the primary condition (e.g., repairing MV in the setting of pulmonary hypertension) often ameliorates the PR. Besides this, vasodilating therapies for pulmonary hypertension can reduce secondary PR. When a treatment is absolutely necessary, **the preferred approach is valve replacement with a bioprosthesis or a pulmonary allograft**. Percutaneous deployment of a prosthetic valve has been successfully accomplished in this setting and is under active investigation currently. Annulus repair is ideal in patients with coexisting left-sided valvular lesions.

DRUG-INDUCED VALVE DISEASE

I. INTRODUCTION. Most common forms of valve disease are inherited or acquired in response to a specific disease process. Over the last three decades, however, it has become clear that several pharmacologic agents may produce a cardiac valvulopathy, which mimics other etiologies of valvular disease.

II. DRUGS KNOWN TO CAUSE VALVE DISEASE

A. Ergot alkaloid derivatives (ergotamine and methysergide) used for migraine prophylaxis have been reported to cause valvulopathy since the early 1990s.

B. In 1997, Connolly et al. reported that both **fenfluramine** and **dexfenfluramine**, the constituents of popular diet pills, were associated with valvular heart disease with a typical histologic appearance (described in subsequent text). This led to the withdrawal of a number of common diet drugs from the market. At their peak usage, about 14 million prescriptions had been written for these medications.

C. More recently, valvular heart disease was reported in 24% to 28% of patients undergoing treatment of Parkinson's disease with **ergot-derived dopamine agonists (pergolide and cabergoline)**.

D. There is an increased risk of valvulopathy in individuals with heavy and frequent use of the recreational drug, **3,4-methylenedioxymethamphetamine (MDMA)**. This drug, popularly known as *ecstasy*, has become one of the most frequently used party drugs in Western Europe and the United States over the last two decades.

E. Thus far, there has been no convincing evidence of valvular heart disease with the use of other serotonergic drugs (e.g., selective serotonin reuptake inhibitors).

III. PATHOLOGY AND PATHOGENESIS

A. Valves that are surgically removed from patients using these drugs are described as having a white, glistening appearance, with histologic evidence of a plaquelike process extending along the leaflet and encasing the chordae tendineae. These findings are **very similar to the findings seen in patients with valvular disease due to carcinoid tumors**, which also secrete vasoactive amines.

B. Subsequent research has indicated that valvulopathic drugs may act via their ability to stimulate the serotonergic receptors, particularly the 5-hydroxytryptamine $(5\text{-HT})_{2B}$ serotonin receptor. This receptor is plentiful in normal heart valves and appears to be essential for normal cardiac development. Stimulation of the 5-HT_{2B} receptor appears to cause mitogenic stimulation of normally quiescent valve cells, causing an "overgrowth" valvulopathy.

IV. PREVALENCE. Estimates of the prevalence of drug-induced valvular disease have varied widely. Initial studies based on case series suggested a prevalence of valve disease as high as 20% to 30% in the setting of fenfluramine exposure, but larger population-based studies suggest a much lower prevalence of around 10% to 12% (vs. 5% to 6% in control group). **Factors that appear to be associated with a greater prevalence of valvular disease include duration of treatment, use of combination agents, and shorter time from cessation of drug treatment to evaluation**. The prevalence of disease is highest in those who have been on a valvulopathic medication for **> 6 months**.

V. CLINICAL PRESENTATION. Most commonly, patients seek advice based on a history of taking ergot-derived medications or diet drugs, given the media attention associated with this condition and the legal action that has been mounted against the drug manufacturers. Patients may also present with symptoms of valve disease, such as dyspnea and fatigue. **The predominant findings on examination in patients with significant valve disease involve regurgitation of the AV, the MV, or the TV**. Although the right-sided valves are usually involved, the ergot derivatives may also affect the left-sided valves and cause valvular regurgitation. Aortic regurgitation is reported with increased frequency in those with anorexient abuse than regurgitation at other valve locations.

VI. EVALUATION. Patients suspected of having valve lesions on examination or those in whom a cardiac examination is somewhat limited by obesity and who have been exposed to diet drugs should undergo echocardiography. The echocardiographic features simulate both rheumatic disease and carcinoid disease with **leaflet thickening and doming of the MV and thickening of the AV or the TV leaflets**. Despite the apparent restriction of motion of the leaflets, clinically significant **stenosis is rare**. Regurgitation, when present, may be of any grade or severity, although it is generally

mild. However, severe regurgitation requiring surgery has been reported with diet drug–induced valve disease.

VII. TREATMENT. Once drug-induced valve disease is suspected, the offending drug should be discontinued immediately. In the case of anorexient-induced valve lesions, **mild improvement in the severity of the valvular regurgitation has been reported on medium-term follow-up after drug discontinuation**. Progression in the severity of valvular disease following drug discontinuation is relatively uncommon. Indications for the surgical intervention in drug-induced valvulopathy are similar to those of other disease processes. However, watchful waiting is a prudent approach in these patients, given the potential for some reversibility of the valve lesions upon drug discontinuation. Endocarditis prophylaxis is not indicated in those with evidence of drug-induced valve disease, per the most recent ACC/AHA guidelines.

VIII. FOLLOW-UP. Patients with valve disease should be evaluated both clinically and with echocardiography initially every 6 months. In those with mild stable lesions, yearly evaluation is appropriate.

ACKNOWLEDGMENTS: *The authors thank Drs. Amy P. Scally, Deepu Nair, and Marc Penn for their contributions to earlier editions of this chapter.*

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CHAPTER 18

João L. Cavalcante

Prosthetic Heart Valves

Prosthetic valve replacement still represents the treatment of choice for severe native valve dysfunction, especially for rheumatic disease, which remains the most frequent cause of replacement worldwide. This chapter discusses the types of prosthetic valves, indications, and prosthetic valve choices and provides a brief overview of the recent developments in transcatheter aortic valve replacement (TAVR).

I. INDICATIONS FOR IMPLANTATION

A. Types of prosthetic valves. Prosthetic valves are classified into two major categories: mechanical and bioprosthetic. Each model differs in its durability, thrombogenicity, and hemodynamic performance. Various mechanical and bioprosthetic valves are shown in Figure 18.1.

1. Bioprosthetic valves. These resemble native valves but have a slightly less optimal hemodynamic performance, owing to the reduction in flow profile by interposed stents and the sewing ring.

a. Heterografts

(1) Carpentier-Edwards valves are made of either bovine pericardium (aortic position), which have greater durability, or porcine leaflets mounted on a cloth-covered annular ring and supported by steel alloy flexible stents at each of the commissures.

(2) The Hancock II stented porcine valve (Medtronic) has been considered as the porcine bioprosthetic valve with the best hemodynamics and longevity available. The supraannular prosthetic sewing ring improves hemodynamic performance; and modern preservation techniques using low-pressure fixation and treatment with sodium dodecyl sulfate increase longevity by delaying calcification. The durability of bioprosthetic bovine pericardial versus porcine valves is controversial, although many consider that the pericardial valves may have some durability advantage in younger patients.

(3) For the **stentless porcine bioprostheses** (Medtronic Freestyle or St. Jude Medical), there are three different methods for implantation, with the subcoronary valve replacement being the most common. Although the stentless valves offer a better hemodynamic profile owing to the larger effective orifice area (EOA), convincing advantages in terms of mortality, left ventricular (LV) mass regression, and durability (when compared with pericardial and not porcine valves) have yet to be demonstrated.

(4) Since the first-in-man **TAVR** done by Cribier in 2002, more than 40,000 patients have undergone TAVR worldwide (see Chapter 66). The technology has evolved tremendously and is now transforming the management of patients with critical aortic stenosis who are high-risk surgical candidates. The ground-breaking Placement of AoRtic TraNscathetER Valves (PARTNER) trial changed the paradigm. It randomly assigned

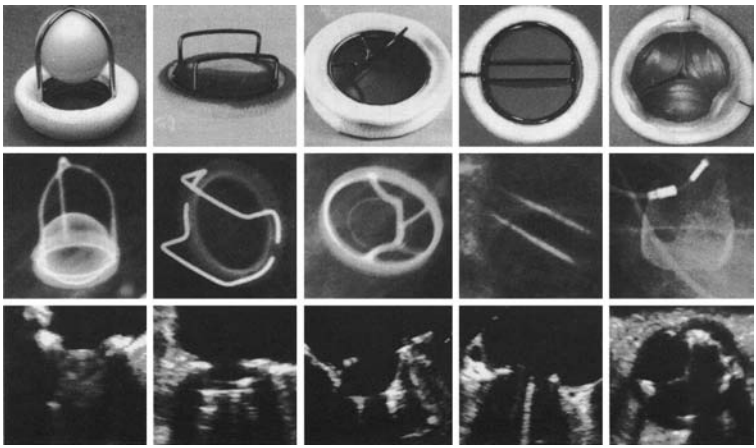


FIGURE 18.1 Photographic and radiographic appearance of different prosthetic heart valves. From left to right: Starr-Edwards caged ball, Kay-Suzuki caged disk, Björk-Shiley single-tilting disk, St. Jude's bileaflet tilting disk mechanical valves, and Carpentier-Edwards xenograft. (From Garcia M. Principles of imaging. In: Topol EJ, ed. *Comprehensive Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven Publishers; 1998:610.)

patients ($n = 358$) with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery, to standard therapy (including balloon aortic valvuloplasty) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve. The primary end point was the rate of death from any cause.

The results showed that this approach was associated with a significant reduced 1-year mortality for patients with severe aortic stenosis who are not surgical candidates due to advanced comorbidities (50.7% for medical treatment vs. 30.7% in the TAVR group; hazard ratio with TAVR, 0.55; 95% confidence interval [CI], 0.40 to 0.74; $p < 0.001$). The valve tested was Edwards SAPIEN heart valve system (Edwards Lifesciences) that consisted of a trileaflet bovine pericardial valve and a balloon-expandable, stainless steel support frame (Fig. 18.2).

The second largest experience, mostly European, is with the self-expanding Medtronic CoreValve ReValving system. It uses a porcine pericardial valve in a larger and self-expandable nitinol frame, which covers both the left ventricular outflow tract (LVOT) and the aortic root. It has also demonstrated similar trends in outcome, although with slightly higher incidence (up to 25%) of atrioventricular block requiring pacemaker implantation.

The long-term durability of these valves has been addressed only in small studies. Theoretically, and according to the manufacturer's wear test, both transcatheter valve systems are designed to last ≥10 years. All published studies suggest good durability and preserved hemodynamic function, with EOAs over 1.5 cm^2 at 3 years. Paravalvular leak has been a concern with these valves, but this is generally mild and does not usually progress significantly at least over medium-term follow-up.

A

B

FIGURE 18.2 Transcatheter aortic valve prosthesis currently available for clinical use (*). **A:** Balloon-expandable Edwards SAPIEN XT valve (Edwards Lifescience, Irvine, CA). **B:** Self-expanding CoreValve ReValving System (Medtronic, Minneapolis, MN). (*) The CoreValve system is currently not approved yet by FDA for clinical use in the USA.

b. Aortic homografts are cryopreserved cadaveric human aortic valves. These are typically implanted stentless, with a short segment of the donor's aortic root for support. The coronary arteries require reimplantation. The hemodynamic profile of the homograft is similar to that of the native valve. Availability of homografts is a limiting factor.

c. Autograft. An autograft is a procedure in which the patient's own valve is moved from its normal anatomical position to another site. Typically, this is done with the pulmonary valve in patients with significant aortic valve disease. A pulmonary homograft is placed at the native pulmonary position. This operation is called the Ross procedure, after the surgeon who popularized it. This procedure has the advantage of putting a native valve at the hemodynamically most important position. It has been advocated for younger patients, and some reports suggest that the autograft may grow with the patient, which is advantageous in the adolescent age group. However,

the initial enthusiasm with this procedure has been tempered by suboptimal outcomes in many adult patients, particularly with regard to the pulmonary homograft. Additionally, progressive root enlargement may ensue in patients with bicuspid valve and ascending aortic dilatation, leading to autograft failure. The decision to proceed to autograft implantation in adults should be considered very carefully and in consultation with a surgeon with extensive experience of this procedure.

2. **Mechanical valves**
   a. **Single-leaflet tilting disk.** This valve (e.g., Björk-Shiley, Medtronic-Hall, and Omniscience) consists of a metallic sewing ring attached to a tilting disk made of pyrolytic carbon that rotates about an off-centered pivot axis, with a range of about 60° to 85° from the occluded to the open position. When open, the prosthesis has two orifices separated by the occluder. The major orifice is formed as the disk swings downstream to the open position. The disk on the other side of the pivot axis swings proximally, forming the minor orifice.
   b. **Bileaflet tilting disk.** The St. Jude and CarboMedics valves have two semicircular pyrolytic carbon disks that rotate freely through 75° to 90°. Two large lateral orifices and a small central rectangular space are created in the open position. A built-in leakage volume is designed to reduce thrombus formation on disks.
   c. **Caged ball.** The Starr-Edwards valve consists of a silicone ball within a cage attached to a metallic alloy ring. The ball is free to travel along the cage over a distance of 1 to 2 cm. Flow across the prosthesis is directed circumferentially around the ball. The hemodynamic profile is less favorable than that of the tilting disk prosthesis. This is the valve with the greatest durability, with a 30-year follow-up in some studies.

B. **Selection of valves.** Table 18.1 summarizes the clinical factors that favor selection of a bioprosthetic versus a mechanical valve. The choice is largely dependent upon the age of the patient at the time of prosthetic valve implantation and on which complication the patient wants to avoid: specifically, anticoagulation therapy and its complications with the mechanical valve and structural valve deterioration with a bioprosthesis.

The recommendation to use tissue valves in older patients and mechanical valves in younger patients is based on information obtained from older trials. There have

TABLE 18.1 Clinical Factors Leading to Selection of a Bioprosthetic versus a Mechanical Valve

Factors favoring bioprosthesis	Factors favoring aortic homograft	Factors favoring mechanical prosthesis
Age > 70 y	Endocarditis	Age < 50 y
Bleeding diathesis	Small aortic annulus in older patients	Combined multivalvular placement
High risk of trauma		Other indications for chronic anticoagulation
Poor compliance		Completed childbearing in younger woman
Young woman considering pregnancy		

TABLE 18.2 Characteristics Favoring Valve Repair versus Replacement

Favoring valve replacement	Favoring valve repair
Rheumatic valve disease	Mitral valve prolapse
Endocarditis	Excessive leaflet mobility
Inexperienced surgeon	Ischemic mitral valve regurgitation
Complex mitral valve morphology	Bicuspid aortic valve with prolapse
Calcified and fibrosed valve	Annular dilatation with normal leaflets
Extensive leaflet destruction	

been no randomized controlled trials after 1982 comparing mechanical with bioprosthetic valves, which makes the decision difficult, as newer bioprosthetic valves may be more durable than older ones. There has been a shift toward using bioprosthetic valves in younger patients over the last decade.

1. **Valve repair.** The feasibility of native valve repair instead of replacement should always be considered prior to surgery (Table 18.2). Currently, the greatest experience is with mitral valve repair. If feasible, mitral valve repair offers several potential advantages over replacement, including **preservation of LV function via conservation of the subvalvular apparatus, lower operative mortality, higher long-term survival rate, and freedom from anticoagulation**. Mitral valve repair may be considered for asymptomatic patients with severe mitral regurgitation if there is a high chance of repair at high-volume centers.

   An aortic valve with predominant regurgitation due to prolapse, but without severe stenosis or calcification, can also be repaired. Intraoperative transesophageal echocardiography (TEE) appears to have a role determining the quality of the repair and predicting the long-term durability.
2. **Bioprosthetic valves** are indicated in patients with **a contraindication to chronic anticoagulation** and are preferred for **patients ≥65 years (70 years in the mitral position)** due to reasonable durability, favorable hemodynamic profile, and freedom from chronic anticoagulation. Approximately 30% of heterograft bioprostheses fail within 10 to 15 years of implantation, although the incidence of bioprosthesis failure is age dependent (Table 18.3). Overall complication rates for aortic bioprosthetic and mechanical valves are similar at 12 years, with a higher rate of reoperation for bioprosthetic valves and a higher rate of hemorrhage with mechanical valves. The advent of newer low-profile bioprostheses and the apparent improved durability of later models have led to an increase in their use, especially in patients who wish to avoid anticoagulation.
3. **Transcatheter aortic valve replacement**, as mentioned before, is now indicated in patients with severe aortic stenosis who are considered inoperable or high risk for conventional open heart surgery due to advanced comorbidities. A comprehensive evaluation for procedural eligibility and candidacy is required including coronary angiography to exclude significant coronary artery disease. If significant coronary lesions are present, they should be revascularized percutaneously and the TAVR procedure is usually deferred for ≥1 month. Computed tomography (CT) angiography with three-dimensional vessel reconstruction is also required to determine the suitability of the iliofemoral access. Dedicated imaging, in particular of the infrarenal aortic segment to the femoral arteries, is needed for sizing of the arterial access (preferably > 6 mm in diameter), vessel tortuosity, and calcification of the iliac arteries. Lastly, TEE, both preprocedural and intraprocedural,

TABLE 18.3 Heterograft Valve Failure Rate 10 Years after Valve Replacement Relative to the Patient's Age

Patient's age (years)	Failure rate at 10 years (%)
< 40	40
40–49	30
50–59	20
60–69	15
≥70	10

Modified from Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med.* 1996;335:412, by permission of the Massachusetts Medical Society.

is important in the evaluation of the aortic annulus size, aortic valve morphology, and calcification of the aortic root and aortic valve leaflets. It can enhance procedural success in determining appropriate valve and device sizing selection in addition to continuous monitoring for procedural complications.

The transapical approach requires a small left thoracotomy to allow direct puncture and sheath introduction into the left ventricle for antegrade delivery of the TAVR system. Patients who require this approach have a higher incidence of peripheral vascular disease, which is a marker of worse long-term outcome. Nonetheless, in patients who require AVR but have aortic atheroma or peripheral vascular disease that limits their candidacy for retrograde transcatheter AVR, the transapical approach should be considered.

4. **Homografts.** The homograft is the **valve of choice in aortic valve endocarditis** and has the lowest valvular gradient among the bioprosthetic valves. Durability was thought to be superior to that of heterografts, but recent studies throw some doubt on this. Only 10% are still functioning after 20 years. The primary operation is more difficult with homografts, as the coronary arteries require implantation. Reoperation is also more complex, as the homograft frequently calcifies and is difficult to remove and replace. The main current indication for an aortic homograft is complex endocarditis involving a native valve, especially in prosthetic valve endocarditis and abscess where the risk of reinfection of a new prosthesis is high. Another indication is in older patients with small aortic root and LVOT in order to maximize hemodynamics and minimize the transaortic gradient.
5. **Mechanical valves.** Mechanical valves are **more durable than bioprosthetic valves**; some can last > 20 years. Mechanical prostheses are generally recommended for **patients < 50 years** because of greater durability and for **patients already on permanent anticoagulation** for previous stroke or arrhythmia. The stroke risk of about 1% per annum for patients with a mechanical valve receiving appropriate anticoagulation management is similar to that for a bioprosthetic valve without anticoagulation. In **younger patients requiring combined aortic and mitral valve replacement**, mechanical valves are preferred, given the more rapid rate of prosthesis deterioration in the mitral position. **Pregnancy should be discouraged in patients with mechanical prostheses** because of the high risk to the mother and the fetus (see Chapter 38). Given their lower profile, mechanical prostheses may be preferred in **patients with small ventricles**. Issues of **compliance with anticoagulation and risks of trauma** should be integrated into the selection of a mechanical valve.

a. St. Jude Medical and Medtronic-Hall valves are the most popular prosthetic valves because of their favorable hemodynamic performance, longevity, and low rates of complications. Loss of structural integrity has been reported in a small percentage of patients with St. Jude valves, whereas the primary concern with the Medtronic-Hall valve is the potential for occluder impingement during placement.

b. Starr-Edwards valves are the most durable of all the prosthetic valves. However, they are less popular today because of their thrombogenicity and suboptimal hemodynamic performance in comparison with tilting disk valves.

c. Manufacture of the Björk-Shiley valve was discontinued in 1986 following published reports of complications with **strut fracture**.

6. The decision with regard to the optimal valve type should be made in consultation with the cardiothoracic surgeon and patient and should not solely be based on age. Lifestyle, compliance, other medical issues, and consideration of pregnancy all have an impact on the decision.

C. Follow-up after valve surgery. There is a **wide spectrum of clinical practices** in the follow-up of the asymptomatic patient after valve surgery. A **Doppler** study should be performed between 1 and 6 weeks following surgery as a baseline for future reference. For **mechanical valves, anticoagulation** should be monitored regularly for life. **Endocarditis prophylaxis** is imperative for prosthetic valves, and patients should receive appropriate education. Annual or biannual echocardiography seems prudent **after the fifth postoperative year** for valve repair and replacement.

D. Anticoagulation. Table 18.4 summarizes the recommended targets for anticoagulation therapy in patients with prosthetic heart valves. The **embolic event rate is greater for mitral than for aortic** prostheses.

1. **Immediate postoperative period**

a. **Mechanical valves.** The approach to **postoperative anticoagulation** for mechanical prostheses varies widely. Early anticoagulation increases the risk of bleeding and tamponade. One approach is **warfarin, but not heparin, 3 to 4 days following surgery** when the epicardial wires are removed. Other centers recommend **low-dose intravenous heparin**, targeted for upper normal limits of activated partial thromboplastin time within 6 to 12 hours after valve replacement, and **full-dose intravenous heparin once the chest tubes are removed**. **Warfarin** is initiated within 24 to 48 hours following valve replacement. **Chronic anticoagulation for mechanical valves is associated with rates** of minor hemorrhage of 2% to 4% per year, major hemorrhage of

TABLE 18.4 Recommended Anticoagulation Therapy for Patients with Mechanical Prosthetic Valves

Level of risk	Prosthesis type	Recommended INR
Low	Single-tilting disk	3.0–4.0
	Double-tilting disk	2.5–3.0
High[a]	Caged disk	3.0–4.5
	Caged ball	3.0–4.5
	Multiple prostheses	3.0–4.5

INR, international normalized ratio.
[a]Patients with atrial fibrillation, left atrial thrombus, severe left ventricular dysfunction, or previous embolic events.

1% to 2% per year, and death of 0.2% to 0.5% per year. The bleeding risk is 5% to 6% in patients aged ≥70 years. The target international normalized ratio (INR) is between 2.0 and 3.0 for mechanical valves (tilting disk and bileaflet) in the aortic position and 2.5 and 3.5 for mechanical valves in the mitral position. Patient-related risk factors for thromboembolism are older age, atrial fibrillation, and LV dysfunction.

b. **Bioprosthetic valves.** The **need for anticoagulation** in bioprosthetic valves is **controversial and is not evidence based**. The risk of embolism is greatest in the early postoperative period, declines after 3 months, and is greater for mitral (7%) than for aortic valves (3%). A reasonable approach is to anticoagulate patients with a **mitral** bioprosthesis for 3 months and then change to aspirin, 325 mg daily. Patients with **aortic prostheses** should receive aspirin, 81 mg daily, for at least 3 months unless there is another reason for anticoagulation. **Patients with prior embolic events, atrial fibrillation, or LV dysfunction should be anticoagulated for the long term**.

2. **Management of anticoagulation in patients with prosthetic valves undergoing noncardiac surgery.** Although the risk of thromboembolism increases when anticoagulant therapy is briefly discontinued, the decision to suspend therapy should be individualized.

   a. For **major procedures** in which substantial blood loss is expected, **warfarin should be discontinued at least 3 days prior to the procedure** to achieve an INR of 1.6 or less. Hospital admission for **intravenous heparin administration** is often recommended for patients with **caged ball prosthetic valves, atrial fibrillation, left atrial thrombus, severe LV dysfunction, or previous embolization. Postoperatively**, intravenous heparin therapy should be **resumed when it is considered safe and continued until therapeutic anticoagulation is achieved with warfarin. Low-molecular-weight heparin (LMWH) may be considered for patients with prosthetic valves as bridge therapy**.

   b. For **minor procedures** (e.g., dental extraction) where blood loss is minimal, anticoagulation can be continued.

3. **Pregnancy** (see Chapter 38). Pregnant women have an increased incidence of thromboembolic complications. The use of warfarin through the entire course of pregnancy is associated with warfarin embryopathy in as many as 6.4% of live births. Given its teratogenic effects, **warfarin should be discontinued (at least between 6 and 12 weeks of the pregnancy) when pregnancy is considered or detected during the first trimester. Subcutaneous heparin** 17,500 to 20,000 U every 12 hours with a target-activated partial thromboplastin time of 1.5 to 2.0 times the control 6 hours after injection should be administered until at least between 6 and 12 weeks of pregnancy, at which time warfarin may be resumed and continued until the middle third trimester. Subcutaneous heparin 5,000 U is then administered twice a day until delivery. Low-dose aspirin can be used in conjunction with anticoagulant therapy for women at higher risk for thromboembolism. LMWH or unfractionated heparin may be considered as an alternative for the entire course of the pregnancy. With LMWH, the anti-Xa levels should be monitored to ensure therapeutic efficacy.

II. ASSESSMENT OF PROSTHETIC VALVES

A. **Clinical presentation.** The clinical presentations of prosthetic valve dysfunction can vary substantially. A discussion of the various entities is detailed in Section **III**.

1. **History.** This should include a thorough cardiovascular review in addition to questions pertinent to the function of the prosthesis.

   a. The **indication** for placement of valve prosthesis, **position** of implantation, **type** of prosthesis, and the **year of implantation** should be elicited. The

model and size of the prosthesis can be verified by the identification card provided by the manufacturer.

b. Other important questions involve **compliance with the anticoagulation** regimen, previous **endocarditis, thromboembolism, fever**, and perceived **change in the quality of the valvular click**.

2. Physical findings

a. The physical examination may be remarkable for a **new murmur, muffled prosthetic valve sounds, or evidence of embolic events**.

b. Prosthetic valves are associated with **distinct auscultatory events caused by prosthesis motion or altered flow patterns**. The prosthesis sounds may mask the normal heart sounds; significant valvular dysfunction may occur without audible changes. However, familiarity with the normal auscultatory findings in the prosthetic valve examination can provide valuable clues on prosthesis dysfunction prior to the more definitive imaging examination. Figure 18.3 summarizes the acoustic characteristics of common valve prostheses.

B. Laboratory examination and diagnostic testing. The diagnosis of structural valve degeneration relies predominantly on echocardiographic findings, which can often identify degeneration prior to the onset of symptoms.

1. Two-dimensional echocardiography. Echocardiography of prosthetic heart valves is more demanding, both to perform and to interpret, compared with the assessment of native valves. By their design, almost all replacement valves are obstructive compared with normal native valves. The degree of obstruction varies with the type and size of the valve. Thus, it may be difficult to differentiate obstructive hemodynamics due to valve design from those of mild obstruction observed with pathologic changes and from prosthesis–patient mismatch. Most

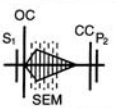
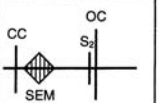
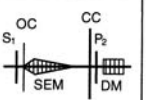
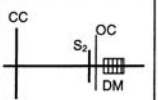
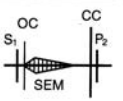
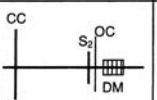
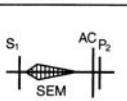
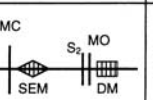
Type of valve	Aortic Prosthesis		Mitral Prosthesis	
	Normal findings	Abnormal findings	Normal findings	Abnormal findings
Caged ball (Starr-Edwards)		Aortic diastolic murmur Decreased intensity of opening or closing click		Low-frequency apical diastolic murmur High-frequency holosystolic murmur
Single tilting disk (Björk-Shiley or Medtronic-Hall)		Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Bileaflet tilting disk (St. Jude Medical)		Aortic diastolic murmur Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Heterograft bioprosthesis (Hancock or Carpentier-Edwards)		Aortic diastolic murmur		High-frequency holosystolic murmur

FIGURE 18.3 Acoustic characteristics of various mechanical and bioprosthetic valves. (From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med.* 1996;335:410, with permission from the Massachusetts Medical Society.)

mechanical valves and many biologic valves are associated with trivial or mild transprosthetic regurgitation. The pattern of this "physiologic" regurgitation varies with the design of the replacement valve. Last, because of shielding and artifacts, insonation of the valve, particularly of regurgitant jets associated with the valve, may be difficult.

The interrogation of the prosthetic valve requires a thorough evaluation of the native structures and a systematic approach to the following: prosthetic apparatus, peak and mean gradient, and regurgitant flow. Typically, **TEE** is performed to evaluate **patients whose disease is symptomatic or who are suspected of having endocarditis**. The two-dimensional assessment of prosthetic valves is similar to that of the native valve but is **limited by reverberation artifacts and acoustic shadowing**. In general, echocardiographic evaluation should be done to assess the following:

a. **Occluders and leaflets.** Failure of the leaflet or occluder to open or coapt properly may result from pannus ingrowth (see Section **III.H**), **thrombus formation** (see Section **III.E**), **or calcification of bioprosthetic leaflets**. Imaging of leaflets and occluders may be suboptimal with transthoracic echocardiography (TTE). Multiplane TEE provides higher temporal and spatial resolution of the prosthesis than TTE and may allow measurement of valve area and mobility. Furthermore, use of real-time biplane imaging can enhance the diagnostic accuracy by providing simultaneous orthogonal imaging planes. Although the aortic prosthesis is less well visualized relative to the mitral prosthesis, TEE still provides a better visual inspection of the posterior aspect of the prosthesis and perivalvular structures than TTE. From 0° to 90° in the lower esophageal position, various aspects of the **mitral prosthesis** can be visualized. The mitral prosthesis can be imaged in cross-sectional view from the transgastric window. Mechanical valve leaflets in the aortic position can be challenging to assess, especially when there are two mechanical valves.

b. **Sewing ring.** The orientation of the prosthetic valve in the annulus can be variable; however, **excessive motion** ("rocking") of the sewing ring is consistent with **dehiscence of the prosthesis**. Concomitant paravalvular regurgitation can be commonly identified with the use of color Doppler mapping. **Furthermore, adjacent echolucent structures** identified in the evaluation of endocarditis may represent abscess, fistula, or pseudoaneurysm. In general, **flow into an adjacent echolucent space is pathologic**. This may involve any portion of the annulus or the mitral–aortic intervalvular fibrosa.

c. **Three-dimensional echocardiography.** Three-dimensional echocardiography is increasingly useful in the evaluation of prosthetic valves, as it allows improved display of the complex structures involved especially when used with TEE. Occluder motion and the sewing ring are often well evaluated, and the precise location of an abnormality relative to the sewing ring may be optimally demonstrated.

2. **Doppler evaluation.** Doppler evaluation complements the two-dimensional examination and provides a **reliable indirect assessment of the prosthetic valve performance**. Color Doppler is useful in assessing regions of high velocity, proximal flow convergence, and regurgitant jets, whether they are valvular or perivalvular. Pulsed-wave and continuous-wave Doppler are used to assess transvalvular gradients, from which effective valve areas can be derived.

   a. **Imaging planes for TTE.** Prosthetic mitral and aortic regurgitation can be visualized in the **parasternal long- and short-axis views**. Acoustic shadowing from the aortic and mitral prosthesis can interfere with the color Doppler display in the proximal portion of the aortic and mitral regurgitant jets. The apical views allow assessment of transvalvular pressure gradients but may

underestimate the size of the mitral regurgitant jets due to acoustic shadowing. Pulmonary vein flows may not be available for the same reason. **Prosthetic aortic regurgitation** can be characterized from the **apical window**.

b. Imaging planes for TEE. At 40° from the upper esophageal position (cross-sectional view), the origin of the aortic regurgitant jet (intravalvular or perivalvular) can be identified. The extent of the aortic regurgitant jet into the LV cavity with color Doppler can be visualized at 120°. Advancing the probe to the lower esophagus at 0° brings forth the four-chamber view, which allows unimpeded visualization of the mitral regurgitant jet and measurement of transmitral gradients. Color Doppler interrogation of the medial and lateral aspects of the mitral prosthesis can be performed by increasing the array toward 90° while rotating and advancing or pulling back the probe. Continuous-wave Doppler is used to measure the peak velocity across the prosthesis.

(1) Continuous-wave Doppler evaluation of the **aortic valve** may be performed at the lower esophageal level using the pinch maneuver (simultaneous ante- and right lateral flexion of the probe). Inserting the probe into the stomach at 5° to 10° with the probe anteflexed allows visualization of the origin of the mitral regurgitant jet. At 90° to 110°, continuous-wave Doppler evaluation of the aortic valve may be performed by left lateral flexion of the probe. Advancing the probe further to the deep transgastric view at 0° with anteflexion also brings the aortic valve in line for Doppler interrogation.

(2) Continuous-wave Doppler can also be used to assess **mechanical prosthetic regurgitation**. Advantages of continuous-wave Doppler include excellent temporal resolution to allow identification of specific periods in the cardiac cycle and the ability to indicate the severity of a regurgitant jet by its signal intensity. Using two-dimensional or color-flow imaging to guide, continuous-wave Doppler allows interrogation of different parts of the prosthesis and can help to detect eccentric jets. Color Doppler is useful if a view can be obtained where the ultrasound beam can enter the chamber receiving the regurgitant flow without traversing the prosthetic valve.

C. Normal Doppler findings

1. **Prosthetic valve clicks.** The opening and closure of mechanical valve leaflets create a brief intense Doppler signal that appears as a narrow band on the spectral display.
2. **Prosthetic valve velocities/pressure gradients.** The systolic spectral Doppler contour is frequently triangular, with an earlier systolic peak velocity and a higher peak gradient than that of the mean gradient. The expected normal velocities and pressure gradients for commonly used prosthetic valves are shown in Table 18.5. However, there is a large variability in these numbers depending on flow and other factors. Therefore, a postoperative baseline study, usually before hospital discharge, is indicated for patients with prosthetic valves.
3. **Physiologic prosthetic valve regurgitation.** Many prosthetic valves have regurgitant flow characterized by a uniform color without aliasing. For a mechanical prosthesis, the physiologic prosthetic regurgitant flow typically has a regurgitant jet area of < 2 cm^2 and jet length of < 2.5 cm in the mitral position and a jet area of < 1 cm^2 and jet length of < 1.5 cm in the aortic position. **Most tissue valves exhibit minor regurgitant flow (closure volume) early after implantation**.
4. **Assessment of prosthetic valve dysfunction.** Loss of prosthetic valve clicks is a sensitive marker for prosthesis dysfunction.
   a. Prosthetic valve stenosis

TABLE 18.5 Normal Doppler Values of Prosthetic Valves

Prosthetic valve	Peak velocity (m/s)	Mean gradient (mm Hg)
Aortic position		
Starr-Edwards	3.1 ± 0.5	24 ± 4
Björk-Shiley	2.5 ± 0.6	14 ± 5
St. Jude	3.0 ± 0.8	11 ± 6
Medtronic-Hall	2.6 ± 0.3	12 ± 3
Aortic homograft	0.8 ± 0.4	7 ± 3
Hancock	2.4 ± 0.4	11 ± 2
Carpentier-Edwards	2.4 ± 0.5	14 ± 6
Mitral position		
Starr-Edwards	1.8 ± 0.4	5 ± 2
Björk-Shiley	1.6 ± 0.3	5 ± 2
St. Jude	1.6 ± 0.3	5 ± 2
Medtronic-Hall	1.7 ± 0.3	3 ± 1
Hancock	1.5 ± 0.3	4 ± 2
Carpentier-Edwards	1.8 ± 0.2	7 ± 2

Modified from Nottestad SY, Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM, ed. *The Practice of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1997:803.

(1) **Transvalvular gradients.** Assessment of transvalvular gradients is the mainstay of the Doppler evaluation. **Each prosthetic valve is inherently stenotic and thus has a higher than normal peak velocity across it.** The continuous-wave Doppler gradient across the prosthesis obtained within weeks following implantation serves as a control for subsequent evaluations. High gradients may also be obtained in nonobstructive situations, such as high-output states, tachycardia, anemia, severe prosthetic leaks, or the pressure recovery phenomenon. Pressure recovery occurs secondary to flow acceleration through a narrowed orifice, especially with the mechanical bileaflet prosthesis in the aortic position. With this, the highest pressure measured through the prosthesis by Doppler overestimates the true pressure gradient by approximately one-third. With **prosthetic valve stenosis, pressure recovery becomes less evident.**

(2) **Valve area calculations.** Calculation of orifice area in prosthetic valves is difficult given the complexity of the orifice (struts/disks and so forth), especially in mechanical prostheses. The following methods have been used to approximate orifice area:

(a) **Continuity equation.** The continuity equation can be used to estimate the functional orifice area of prosthetic aortic and mitral valves. For calculation of the prosthetic valve area in the aortic position,

$$\text{Area}_{\text{aortic prosthesis}} = (\text{diameter}_{\text{sewing ring}})^2 \times 0.785\ \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{aortic prosthesis}}$$

where TVI is time–velocity integral and LVOT is left ventricular outflow tract.

The LVOT diameter is replaced by the sewing ring inner diameter in the equation. The aortic prosthesis TVI is determined from continuous-wave Doppler velocity through the prosthesis. LVOT TVI is determined by pulsed-wave Doppler. Mitral valve prosthesis TVI is determined from continuous-wave Doppler. For the mitral position,

$$\text{Area} = (\text{LVOT diameter})^2 \times 0.785 \times \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{mitral prosthesis}}$$

(3) Pressure half-time (PHT). For a mitral valve prosthesis, the PHT method is useful for assessing prosthetic valvular stenosis. The empirical constant of 220 provides a reasonable approximation for mechanical prosthetic mitral valve area. The PHT method can also determine whether increased velocity is secondary to increased flow or to obstruction. If the peak velocity is increased but the PHT is not prolonged, then the increased velocity is most likely due to increased forward flow. However, PHT may overestimate the area of the mitral prosthesis. Also if there is concomitant more than mild aortic regurgitation, estimation of prosthetic mitral valve area will not be accurate by PHT method.

(4) Dimensionless index. The LVOT and aortic valve prosthesis velocity ratio is possibly the most helpful index for the evaluation of prosthetic valve stenosis, particularly when the valve size is not known. The higher the index, the larger the EOA, and vice versa. A value ≤0.25 suggests prosthesis stenosis:

$$\text{Dimensionless index} = \text{velocity}_{\text{LVOT}}/\text{velocity}_{\text{aortic prosthesis}}$$

(b) Pathologic prosthetic valve regurgitation. The pathologic flow disturbance is **larger and wider than that seen with physiologic regurgitation**. Its **severity can be reliably quantified by TEE**, which can best identify periprosthetic regurgitation. Pathologic regurgitation may be related to a scarred/calcified annulus, with disruption of the sutures securing the valve or a perivalvular abscess with adjacent tissue destruction. Single or multiple jets may be present.

(1) Severe mitral prosthetic regurgitation is suggested by increased peak early diastolic velocity (≥2.5 m/s) and normal mitral inflow PHT (≤150 m/s) (see Chapter 16).

(2) Severe aortic regurgitation is usually present when the PHT ≤250 milliseconds or when flow reversal is detected in the descending aorta (see Chapter 15).

5. Cinefluoroscopy. Cinefluoroscopy is useful for assessing **mechanical prosthetic valves**. The image intensifier is moved to a position with x-rays parallel to the valve ring plane to determine the occluder's excursions in a caged valve. Despite the radiolucency of pyrolytic carbon disk valves, the opening angle can be measured from positioning the image intensifier parallel to the plane of the open leaflets. **The mitral prosthesis is best visualized from the right anterior oblique (RAO) cranial projections. The aortic prosthesis can be viewed from RAO caudal or left anterior oblique cranial projection**.

a. Diminished motion of the disks suggests valve obstruction, whereas excessive rocking of the base ring (i.e., 7° for aortic prosthesis and 11° for mitral prosthesis) suggests partial dehiscence of the valve.

b. In the setting of **suspected strut fracture in a Björk-Shiley valve**, cinefluoroscopy evaluation of the prosthesis is best performed with the tunnel view

profile. Increased incidence of strut fracture has been noted in patients with an opening angle of 70° or more.

6. **Cardiac catheterization**
   a. **Invasive assessment** of the left ventricle can be performed safely in patients with bioprosthetic aortic valves. However, catheter-based evaluation of the mechanical aortic valve must be performed with a transseptal technique in patients with a mechanical prosthesis. It may be necessary for accurate measurement of the prosthetic mitral valve gradient, as catheter-based assessment overestimates the mitral valve gradient because of a dampening of the pressure contour and intrinsic delay in the pulmonary capillary wedge tracing.
   b. **Never cross the following prosthetic valves:**
      (1) Single or bileaflet tilting disk prosthesis
      (2) Caged disk prosthesis
      (3) Caged ball prosthesis
7. **Magnetic resonance imaging** can be performed safely in patients with most prosthetic valves, as they are not ferromagnetic. It can identify **prosthetic regurgitation, periprosthetic fistulas, and abscess**. Prosthetic valves cause **imaging artifacts**, which preclude assessment of the leaflets of the prosthetic valve; however, dedicated sequences can provide information about **blood flow velocities** and **regurgitant jets**.
8. **Multislice** gated cardiac CT with retrospective image acquisition also allows adequate evaluation of leaflet motion in mechanical valves using multiplanar reformatting and reconstruction to view the valve motion in any selected plane. The utility of this method over conventional fluoroscopy remains to be evaluated. One particular limitation compared with cinefluoroscopy is the lower temporal and spatial resolution of CT as well as the need for potentially higher doses of ionizing radiation. However, it can be particularly useful in patients with more than one mechanical valve prosthesis, in which echocardiography can be difficult due to artifacts.

III. VALVE DYSFUNCTION AND COMPLICATIONS RELATED TO PROSTHETIC VALVES

A. Atrial fibrillation. Up to 50% of patients undergoing valve surgery experience postoperative atrial fibrillation. Management of atrial fibrillation is discussed in Chapter 24.

1. In **patients without a previous history** of atrial fibrillation, the **arrhythmia is often self-limited**.
2. For patients with **persistent atrial fibrillation beyond 24 hours, anticoagulation, direct current cardioversion, and a short course of antiarrhythmic therapy** are warranted.
3. β-Blockade or amiodarone prophylaxis has been found to reduce the incidence of postsurgical atrial fibrillation.

B. Conduction disturbances. High-grade heart block requiring permanent pacemaker implantation has been described in 2% to 3% of patients after valve replacement and 8% following repeat valve surgery. It is caused by trauma to the bundle of His or from postoperative edema of the periannular tissue. Aortic or mitral annular calcification, preoperative conduction disturbance, advanced age, infectious endocarditis, and tricuspid valve surgery are associated with higher rates of postoperative conduction abnormalities, leading to permanent pacemaker implantation. As mentioned before, the higher profile of Medtronic's self-expandable CoreValve ReValving system has been associated with higher rates (up to 25%) of complete heart block requiring permanent pacemaker implant.

C. Endocarditis. Approximately 3% to 6% of patients with prosthetic heart valves will experience prosthetic valve endocarditis. Prosthetic valve endocarditis is typically

associated with large vegetations, since microorganisms are sheltered from the host defense mechanisms.

1. Early prosthetic valve endocarditis (< 60 days following implantation) is typically caused by *Staphylococcus epidermidis.* The clinical course is often fulminant, with high mortality rates ranging from 20% to 70%.
2. Late prosthetic valve endocarditis occurs most commonly in patients with multiple prostheses and bioprosthetic valves, especially in the aortic position. Its clinical course resembles that of native valve endocarditis. Streptococci are the most common infectious agents, followed by gram-negative bacteria, enterococci, and *S. epidermidis.*
3. TEE is the imaging modality of choice, with sensitivity of 95% and specificity of 90% in diagnosis. It is also useful in detecting complications including abscess, tissue invasion, dehiscence, and fistula formation and monitoring the efficacy of medical therapy.
4. **Therapy.** The mortality of patients managed with antibiotics alone is 61% versus 38% for those having valve replacement. (See Chapter 19 for more information on diagnosis, management, and antibiotic prophylaxis for endocarditis.)
   a. **Medical therapy.** Medical cure of prosthetic valve endocarditis caused by **staphylococci, gram-negative organisms, or fungi is rare. Streptococcal** prosthetic valve endocarditis responds to medical therapy alone in **50% of cases**. Patients with mechanical prosthetic valve endocarditis should **continue to receive anticoagulation**. In the absence of anticoagulation, prosthetic valve endocarditis is associated with up to 50% incidence of stroke. Continuing anticoagulation for patients with prosthetic valve endocarditis is associated with a 10% incidence of cerebral embolization. There is no conclusive evidence for increased hemorrhage with warfarin in patients with prosthetic valve endocarditis. Careful surveillance of medically managed patients with prosthetic endocarditis is essential and should involve an infectious diseases consultant, multiple repeat cultures after the cessation of antibiotic treatment, and follow-up with TEE when needed. A high index of suspicion should be maintained for the presence of residual infection, and surgical reevaluation should be considered if medical treatment fails.
   b. **Surgical therapy.** Valve replacement surgery is indicated in the setting of
      (1) persistent bacteremia despite intravenous antibiotics
      (2) tissue invasion or fistula formation
      (3) recurrent embolization
      (4) fungal infection
      (5) prosthesis dehiscence or obstruction
      (6) new or worsening heart block
      (7) **new-onset or worsening** congestive heart failure

D. Hemolysis. Subclinical hemolysis is present in many patients with mechanical valves but **rarely results in significant anemia**.

1. **Pathophysiology and etiology.** Clinical hemolysis occurs in 6% to 15% of patients with **caged ball valves** but is uncommon with normal bioprosthetic or tilting disk valves. Clinical hemolysis is also associated with **multiple prosthetic valves, small prostheses, periprosthetic leaks, and prosthetic valve endocarditis**. Mechanisms involved in the generation of hemolysis include high shear stress or turbulence across the prosthesis, interaction with foreign surfaces such as cloth, and rapid deceleration of erythrocytes following collision with adjoining structures (e.g., struts or cardiac walls).
2. **Laboratory examination and diagnostic testing**
   a. Diagnosis is made by **elevated lactate dehydrogenase, reticulocyte count, unconjugated bilirubin, urinary haptoglobin**, and presence of **schistocytes on blood smear**.

b. Echocardiographic findings consistent with mechanical hemolysis include **abnormal rocking of the prosthesis or regurgitant jets of high shear stress** (e.g., eccentric or periprosthetic regurgitant jets or those impacting a solid surface such as the left atrial appendage or sewing ring).

3. Therapy

a. Medical therapy. Mild hemolytic anemia can be managed with **iron, folic acid supplement, erythropoietin stimulants and, if needed, blood transfusion. β-Blockade and blood pressure control** may reduce the severity of hemolysis. Paradoxically, treatment of the anemia may reduce the degree of hemolysis by limiting the need for high flow through the defective valve.

b. Surgical therapy. Repair of perivalvular leaks or valve replacement is indicated in **patients with severe hemolysis requiring repeated transfusions or in those with congestive heart failure**. Increasingly, however, it is possible to reduce focal paravalvular leaks percutaneously with the use of coils or other occluders. Percutaneous approaches are not feasible with extensive dehiscence or where there is active infection.

E. Thrombosis. The annual incidence of mechanical prosthetic valve thrombosis is 0.2% to 1.8%. The incidence is highest in the tricuspid position, followed by the mitral and then the aortic position. Thrombus is suspected in patients with **acute onset of symptoms, embolic event, or inadequate anticoagulation**. Thrombosis at bioprostheses is uncommon but may occur in low-flow or prothrombotic states.

1. Laboratory examination and diagnostic testing. TEE is the most widely used diagnostic technique, although cinefluoroscopy can be used to document restriction in occluder mobility. Three-dimensional TEE may be of particular value in some instances in outlining the nature of the obstruction. No imaging modality, however, can clearly differentiate thrombus from pannus (see Section **III.H**). Frequently they coexist. Comparison with previous studies is crucial to determine temporal changes. Although sometimes differentiation of thrombus versus pannus can be difficult, a few things argue more in favor of pannus such as location (aortic > mitral valve), duration since valve implantation, subacute/chronic course, symmetrical involvement, location of thickening (pannus is usually annular, whereas thrombus is most of the times attached to the valve ring). Subtherapeutic anticoagulation over an extended period increases the likelihood of thrombus. Echocardiographic features suggestive of thrombus include soft, irregular, or mobile mass.

2. Therapy. The valve type or suspected duration of valve thrombosis does not influence the indications for treatment, although location of prosthetic valve does.

a. Priority of therapy

(1) Heparin is typically initiated early in the course of evaluation.

(2) Warfarin is continued unless surgery is planned.

(3) TTE, TEE, or cinefluoroscopy should be performed at 24 hours and, if the thrombus is still present, should be repeated serially.

b. Medical therapy

(1) Fibrinolytic therapy is considered the treatment of choice for **right-sided prosthetic valve thrombosis** because the consequences of distal embolization are less severe than in left-sided prosthesis. Streptokinase and urokinase are the most commonly used agents. Fibrinolytic therapy has an initial success rate of 82%, overall thromboembolism rate of 12%, and a 5% incidence of major bleeding episodes. For left-sided valves, there is a similarly high success rate (82%) with fibrinolytic therapy; however, the associated risks of death (10%) or systemic embolism (12.5%) are high. Thrombolysis should be considered for left-sided valves in patients with contraindications to surgery. Thrombolysis may be a reasonable alternative

to surgery for mitral or aortic prosthetic valve thrombosis in patients with a small thrombus burden, particularly if there is hemodynamic compromise and/or multiple comorbidities increasing the surgical risk.

(a) The classical regimen for **streptokinase** is a 500,000 IU bolus given over 20 minutes, followed by an infusion of 1.5 million IU infused over 10 hours.

(b) rtPA (recombinant tissue plasminogen activator) 10 mg bolus followed by 90 mg an hour for 9 hours.

(c) Thrombolysis should be stopped if there is no hemodynamic improvement after 24 to 72 hours. TEE is useful in assessment of progress.

(d) Following successful thrombolysis, close **follow-up of anticoagulation along with serial Doppler echocardiography** on an individual basis is recommended.

(2) Anticoagulation with heparin and warfarin is generally recommended for **small thrombus** (≤5 mm). The regimen consists of intravenous heparin followed by subcutaneous heparin 17,000 U twice a day and warfarin (INR 2.5 to 3.5) for up to 3 months.

c. Surgical approach. The lowest surgical mortality reported has been approximately 5%. The risk profile of the individual patient must be balanced against the expertise and experience at each center.

(1) Valve replacement and debridement are generally performed for **left-sided prosthetic valve thrombosis**, unless the thrombus is small or the patient has a prohibitive surgical risk.

(2) Surgery is also indicated in the case of **unsuccessful thrombolysis** 24 hours following discontinuation of the infusion.

F. Dehiscence. Detachment of the sewing ring from the annulus may occur in the early postoperative period because of poor surgical techniques, excessive annular calcification, chronic steroid use, fragility of the annular tissue (particularly following prior valve operations), or infection. Late dehiscence occurs mainly from infectious endocarditis. **Abnormal rocking of the prosthesis** on echocardiography or cinefluoroscopy is an **indication for urgent surgery**. Some rocking of a mitral prosthesis may occur normally with preservation of the mitral valve apparatus.

G. Patient–prosthesis mismatch. All prosthetic valves, with the exception of stentless aortic homografts, have effective orifices that are smaller than those of native valves. There is an **inherent pressure gradient and relative stenosis with each prosthesis**. Occasionally, when an inappropriately small prosthesis is placed, the **ensuing low output may cause symptoms**. Patient–prosthesis mismatch should be considered mild if indexed valve EOA is < 0.85 cm^2/m^2, moderate if > 0.65 cm^2/m^2 but ≤ 0.85 cm^2/m^2, or severe if ≥ 0.65 cm^2/m^2. The impact and prevalence of patient–prosthesis mismatch are controversial. Depending on the definition and surgical series used, this mismatch may occur between 20% and 70% of cases after aortic valve replacement. It has been shown in some series to be associated with worse hemodynamic function, less regression of LV hypertrophy, more cardiac events, and lower survival, although others question its importance. Unlike most of the other risk factors, patient–prosthesis mismatch can be avoided or its severity can be more or less reduced by putting in place a prevention strategy at the time of the operation. **It is rare that patient–prosthesis mismatch occurs to a degree that surgical explantation is necessary**.

Some important points to consider:

1. The projected indexed EOA should be systematically calculated at the time of the operation to estimate the risk of patient–prosthesis mismatch.
2. In a patient with a **small annulus, a hemodynamically favorable prosthesis** like a stentless bioprosthesis, aortic homograft, or a tilting disk valve is preferred. Alternatively, the aortic annulus may be enlarged surgically in order to accommodate a prosthesis of acceptable size.

3. Aortic prostheses < 21 mm in diameter are not recommended for a large or physically active patient.
4. Young patients in particular, as well as those with poor LV function and/or severe LV hypertrophy, are more vulnerable to patient–prosthesis mismatch.

H. Pannus formation. Valve obstruction occurs in up to 5% of mechanical valves per year. Valve thrombosis and pannus formation are responsible for the majority of mechanical prosthesis obstructions. Frequently, thrombus coexists with pannus. **Little is known about the causes** of fibroblastic proliferation in pannus formation. Foreign body reactions to the prosthesis, inadequate anticoagulation, endocarditis, and blood flow turbulence in the mitral position have been implicated as potential causes. Pannus formation begins around the annulus of the valve and is more common in aortic than in mitral valve prostheses. A subacute presentation of fatigue or dyspnea in a patient who is well anticoagulated can suggest pannus formation. **TEE and/or cinefluoroscopy is generally required** to identify the cause of prosthetic valve obstruction.

I. Embolic stroke. Following an embolic stroke, the risk of recurrent stroke is approximately 1% per day for the first 2 weeks.

1. If no evidence of hemorrhage is detected on CT scan at 24 to 48 hours, **intravenous heparin** should be administered after a small to moderate embolic stroke. **Maintaining anticoagulation** reduces the risk of recurrent stroke to one-third but **carries an increased risk of hemorrhagic transformation** of 8% to 24%, particularly during the first 48 hours.
2. In patients with **larger infarcts, anticoagulation should be withheld for 5 to 7 days**.
3. Anticoagulation is withheld for 1 to 2 weeks in the setting of **hemorrhagic transformation**.
4. **Aspirin or clopidogrel** may be needed in the event of recurrent strokes, despite adequate anticoagulation.
5. Rarely, **reoperation with placement of a tissue valve** is needed for recurrent embolization.

J. Mechanical failure

1. Failure of **bioprostheses** is expected as the valves age. This may manifest as stenosis, regurgitation, or a combination and is usually due to the deposition of calcium on the leaflets. The onset of mechanical failure is usually gradual. Leaflet tears may produce a sudden clinical deterioration with the onset of severe regurgitation. Bioprosthetic deterioration is managed expectantly with increasing frequency of evaluation as the valve ages and deterioration becomes more evident clinically and on echo. Indications for reoperation are similar to those for native valve lesions, although the threshold to reoperate is somewhat higher, given the greater mortality and morbidity associated with reoperation.
2. Failure of the current generation of **mechanical prostheses** is rare but may precipitate catastrophic hemodynamic compromise. Catastrophic failure occurs when a strut holding the occluder breaks, allowing the occluder to embolize, resulting in overwhelming regurgitation. Strut failure has been reported most commonly with the Björk-Shiley valve and results from fatigue of a metal weld in valves of specific sizes (larger) and valves with year of manufacture 1981 to 1982, especially, in those younger than 50 years at time of implantation. Explantation of those at highest risk has been recommended; in evaluating patients with Björk-Shiley valves, the risk/benefit of explantation versus strut fracture should be determined, based on the excellent published literature on the topic.
3. In older ball-in-cage prostheses, ball **variance**, a structural deterioration of the occluder, can occur, giving rise to impaired occluder motion, sticking, and thromboembolism. This is rarely seen nowadays with improved prosthetic materials.

ACKNOWLEDGMENTS: *The author thanks Drs. Ron Jacob and Richard Troughton for their previous contributions to this chapter.*

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CHAPTER 19

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Infective Endocarditis

I. INTRODUCTION

A. Infective endocarditis (IE) is **an infection of the cardiac endothelium**, macroscopically seen as vegetations. Despite modern medical and surgical therapy, IE is a serious and life-threatening condition. Mortality rates are 20% to 30% for both native and prosthetic valve endocarditis (PVE) and may be as high as 70% in certain high-risk patients. The clinical diagnosis is based on multiple elements, and **IE is best managed via multidisciplinary collaboration among cardiologists, cardiothoracic surgeons, and infectious disease specialists**.

B. The incidence of IE has remained constant over the last 30 years, accounting for 1 case per 1,000 hospital admissions. An estimated 10,000 to 15,000 new cases of IE are diagnosed each year in the United States, and the incidence has increased in the elderly and in illicit injection drug users. There has also been an increase in the number of acute cases, prosthetic valve infections, and cases due to gram-negative, rickettsial, chlamydial, fungal, and fastidious organisms.

C. Risk factors associated with infection include underlying cardiac structural abnormalities, immunosuppressed status, underlying conditions that predispose patients to pacemaker-related infections, prolonged surgery, reoperation, catheter-related bacteremia, and sternal wound infection.

II. CLINICAL PRESENTATION

A. Signs and symptoms. The clinical manifestations of IE are highly variable, ranging from subtle symptoms to fulminant congestive heart failure (CHF) with severe valvular regurgitation. **Acute IE** presents as marked toxicity and progresses to valvular destruction and metastatic infection over several days to weeks. **Subacute IE** evolves over several weeks to months with mild or modest toxicity and rarely causes metastatic infection. The rate of progression depends upon the virulence of the causative organism, the age and underlying health of the patient, and the nature and extent of the underlying valvular disease.

1. The **hallmarks of IE are fever and a new murmur** (> 85%); however, fever may be absent in patients who are elderly, uremic, or immunosuppressed. Murmurs may be absent with right-sided or mural infection or intracardiac device infections.
2. The patient often has nonspecific symptoms of fatigue, weight loss, malaise, chills, night sweats, and/or musculoskeletal aches.

B. Physical findings. A new murmur remains an important finding.

1. CHF occurs in up to 55% of cases and tends to be more common in those with aortic valve disease (75%) than in those with mitral (50%) or tricuspid (20%) valve involvement.
2. Neurologic findings may include clinically apparent cerebral emboli (20%), encephalopathy (10%), mycotic aneurysm leak (< 5%), meningitis, or brain abscess (< 5%).

3. Additional physical findings reflecting **embolic or immune complex phenomena** include mucosal **petechiae** (20% to 40%), **splinter hemorrhages** (subungual dark linear streaks: 10% to 30%), **Osler's nodes** (painful, tender erythematous nodules on the pads of fingers or toes: 10% to 25%), **Janeway lesions** (erythematous, macular, nontender lesions on the fingers, palms, or soles: < 5%), **clubbing** (10% to 20%), **arterial embolism** (peripherally or centrally), **splenomegaly** (30% to 50%), and **Roth's spots** (retinal hemorrhages: < 5%). These classic physical findings are **neither sensitive nor specific** for the diagnosis of IE, and their frequency is continuing to diminish due to a decrease in *Streptococcus* viridans IE and an increase in *Staphylococcus aureus* IE.
4. A formal **fundoscopic examination** should be routine in all patients with suspected or documented IE. It may reveal **chorioretinitis or endophthalmitis**.
5. **Systemic** embolization occurs in 25% to 50% of cases of IE and may mimic acute coronary syndrome (coronary artery emboli), peritonitis (embolization to the spleen, kidney, or bowel), acute stroke (cerebral emboli), and pulmonary embolism (from right-sided IE) or cause a cold extremity with reduced or absent pulse. Septic emboli also cause Janeway lesions.

III. ETIOLOGY

Table 19.1 presents the various etiologic factors.

A. Seventy percent to 75% of patients with IE have preexisting cardiac abnormalities. Mitral valve prolapse with regurgitation is the leading condition underlying IE in adults. Rheumatic heart disease as a substrate for IE is decreasing, with congenital heart disease underlying 10% to 20% of IE cases.

B. The source of infection can only be identified occasionally (e.g., dental procedures, an infected vascular catheter, or an infected skin lesion). In many patients, there is no history of an antecedent localized infection.

C. Native valve endocarditis

1. The most common microorganisms that cause native valve IE in adults are streptococcal and staphylococcal organisms (80%). Other important causes

TABLE 19.1 Frequency of Organisms Causing Infective Endocarditis

Organism	NVE (%)	IDU (%)	Early PVE (%)	Late PVE (%)
Streptococci	60	15–25	5	35
Viridans *Streptococcus*	30–40	5–10	< 5	25
S. bovis	10	< 5	< 5	< 5
Enterococci	10	10	< 5	< 5
Staphylococci	25	50	50	30
Coagulase positive	23	50	20	10
Coagulase negative	< 5	<5	30	20
Gram-negative (aerobes)	< 5	5	20	10
Fungi	< 5	< 5	10	5
Culture negative	5–10	< 5	< 5	< 5

IDU, intravenous drug use; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

Adapted from Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's the Heart*. 11th ed. New York, NY: McGraw Hill; 2004.

include *Streptococcus bovis*, *Enterococcus*, and the HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) group organisms. The HACEK group, accounting for roughly 3% of cases, includes fastidious gram-negative organisms that are normal flora in the upper respiratory tract. *S. bovis* IE is often associated with colonic polyps and colon cancer; as such, a colonoscopy is recommended for these patients.

2. Right-sided IE in injection drug users is usually due to *S. aureus* (60%), with a predilection for normal as well as abnormal cardiac valves. Despite the virulence of this organism, the disease tends to be **less severe** (mortality rates of 2% to 6%) than with left-sided IE. The valve most commonly affected in injection drug users is the tricuspid valve (60% to 70% of cases), followed by the mitral (30% to 40%) and the aortic valves (5% to 10%). More than one valve is involved in 20% of these patients. Septic pulmonary emboli occur in up to 75% of injection drug users with tricuspid IE.
3. IE from *Pseudomonas aeruginosa* is both **destructive and poorly responsive to antibiotic therapy and thus often necessitates surgical intervention**.
4. Enterococcal IE is increasing in prevalence. The diagnosis must be considered in patients who have undergone recent genitourinary or obstetric procedures; these patients may not have underlying heart disease.
5. Other members of the Enterobacteriaceae (*Escherichia coli, Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, *Citrobacter*, *Shigella*, and *Yersinia*) are occasionally implicated in IE.
6. *Streptococcus pneumoniae* accounts for 1% to 3% of native valve IE, and it may present as part of the **"Osler triad,"** which also includes pneumococcal pneumonia and meningitis. Alcoholics are typically affected, and the mortality rate is high (30% to 50%).
7. The most common congenital heart anomalies predisposing to IE are bicuspid aortic valve, patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, and tetralogy of Fallot. There is **no evidence** that secundum atrial septal defects increase the risk of IE.
8. *Staphylococcus lugdunensis* is a rare but destructive cause of IE. This organism is a coagulase-negative *Staphyloccus*; however, it differs from other coagulase-negative staphylococci in its aggressive nature and predilection for native valves. *S. lugdunensis* IE portends a high complication and mortality rate without surgical intervention.

D. PVE accounts for about 10% to 20% of all cases of IE. The greatest risk of infection is in the first 6 months after valve implantation and appears to be **similar in mechanical and bioprosthetic valves**. Recent studies have suggested that infection occurs with similar frequencies at the mitral and aortic positions.

1. PVE occurring within 2 months of surgery (early PVE) is commonly associated with intraoperative contamination and nosocomial infection and this usually implicates **coagulase-negative staphylococci** (30% of cases). The second most common pathogen in early PVE is *S. aureus* (20% of cases).
2. The microbiology of PVE with an onset of more than 2 months after surgery (late PVE) reflects the pathogens of native valve IE and is most commonly caused by streptococcal species, *S. aureus*, and *Enterococcus*. Coagulase-negative staphylococci cause < 20% of infections in this period. Fungi account for 10% to 15% of late PVE cases and are associated with a higher mortality rate. Among 270 cases of fungal endocarditis reported from 1965 to 1995, 135 (50%) occurred on prosthetic valves. These patients generally lacked an identifiable portal of entry for fungemia. Establishing the diagnosis of fungal PVE can be difficult due to the low yield from blood cultures. Despite aggressive antifungal therapy, these patients remain at risk for the development of PVE months or years later. *Corynebacterium* species and other coryneform bacteria, often called

diphtheroids, are also an important cause of PVE during the first year after surgery (5%). Although they are often blood culture contaminants, diphtheroids in multiple cultures should not be ignored.

E. Pacemaker/defibrillator endocarditis is increasing in frequency in clinical practice with the burgeoning number of devices being implanted. The incidence of endocarditis following device therapy ranges from 0.2% to 7%. The infection may involve the generator or defibrillator pocket, the electrodes, and valvular or nonvalvular endocardium.

1. Pacemaker/defibrillator endocarditis occurring within 1 to 2 months of surgery is likely caused by direct intraoperative microbial seeding. Late infection in the pocket produces a thinning of the overlying tissue and ultimately device erosion. The infection may eventually involve the electrodes and ultimately the endocardium. Hematogenous dissemination from distant sites of infection appears to be relatively rare, with the exception of *S. aureus* bacteremia.

2. The majority of infections in PVE are caused by staphylococci: *S. aureus* and coagulase-negative staphylococci. More than 90% of early infections are caused by coagulase-negative staphylococci, whereas late infections are caused by both *S. aureus* (50%) and coagulase-negative staphylococci (50%). Infection by gram-negative bacilli, enterococci, or fungi is rare.

F. The incidence of **culture-negative endocarditis** may be as high as 10%. Blood culture–negative endocarditis is defined as endocarditis without positive cultures after inoculation of three blood samples. Cultures can be negative in IE when there is infection with a fastidious bacteria or fungus, the microbiological techniques are inadequate, or there had been administration of antibiotic therapy prior to obtaining blood cultures. The latter reason is the most common cause of culture-negative IE, and the most common causative agents are *Streptococcus* or fastidious organisms such as fungi, HACEK organisms, anaerobes, *Legionella*, *Chlamydia psittaci*, *Coxiella*, *Brucella*, *Bartonella*, *Tropheryma whipplei*, and nutritionally deficient streptococci. *Bartonella henselae* infection is a rare cause of subacute IE, which is associated with exposure to cats. *Coxiella burnetii* causes Q fever and often infects previously damaged valves or prosthetic valves. *T. whipplei* is the cause of Whipple's disease, and this organism can be identified using periodic acid-Schiff staining of macrophages or polymerase chain reaction (PCR). **Nonbacterial endocarditis** (Libman-Sachs, marantic, and antiphospholipid syndrome) should also be considered in cases of culture-negative IE.

G. Fungal endocarditis (*Candida* and *Aspergillus*) usually occurs in association with **prosthetic valves, indwelling intravascular hardware, immunosuppression, or injection drug use. The most common cause is** Candida **species, but other causes include *Histoplasma* and *Aspergillus*. Fungal IE usually presents with large vegetations that extend into the perivalvular apparatus and embolize into large vessels and therefore requires surgical intervention**.

IV. PATHOPHYSIOLOGY.

The first step in the pathogenesis of vegetation is the formation of a **nonbacterial thrombotic endocarditis (NBTE)**, which usually results from endothelial injury followed by focal adherence of platelets and fibrin. Microorganisms circulating in the bloodstream in turn infect this sterile platelet–fibrin nidus.

A. Vegetations classically occur along the line of closure of the valve leaflet. The endothelium may be injured by regurgitant jets, leading to vegetation formation on the atrial surface of incompetent atrioventricular valves or the ventricular surface of incompetent semilunar valves. The foreign body, such as an intracardiac device, is not endothelialized initially and acts as a formation site for platelet–fibrin thrombi.

B. Bacteremia is the event that converts NBTE to IE when host defenses fail. The foreign material also impairs host defenses, rendering them more difficult to treat.

C. Vegetations often further impair valvular coaptation or cause perforation or chordal rupture, leading to worsening of regurgitation and CHF. Furthermore, the vegetations may dislodge, causing peripheral septic–nonseptic embolization.

D. The infection may extend to the surrounding structures, such as the valve ring, the cardiac conduction system, the adjacent myocardium, or the mitral–aortic intravalvular fibrosa. Consequently, conduction defects, abscesses, diverticula, aneurysms, or fistula may develop. Infections involving prosthetic valves commonly invade paravalvular tissue, resulting in abscess formation or valve dehiscence.

V. LABORATORY EXAMINATION

A. Blood tests

1. Laboratory findings often reflect nonspecific acute inflammatory response, manifest as a **modest leukocytosis**, a **normochromic normocytic anemia**, and a slightly increased or decreased **platelet count**. Other laboratory abnormalities may include an **elevated erythrocyte sedimentation rate**, C-reactive protein, rheumatoid factor, and/or a hypergammaglobulinemia. IE may also cause false-positive Venereal Disease Research Laboratory (VDRL) test and Lyme serologic test.

2. Decreased complement and an elevated blood urea nitrogen or creatinine may implicate renal dysfunction from an immune complex glomerulonephritis or drug toxicity.

3. Blood cultures are critical in the diagnosis and management of IE. However, if a patient is acutely ill, **therapy should not be delayed for more than 2 to 3 hours**, as a fulminant infection may be rapidly fatal. In recent reports, cultures were negative in 2% to 7% of cases with established IE, despite the best modern methods.

a. If the clinical condition allows, three sets of cultures should be drawn at three different venipuncture sites before empiric antimicrobial therapy is started. Each set should include two flasks, one containing an aerobic medium and the other an anaerobic medium, into which at least **20 cm^3** (per tube) of blood should be placed. The HACEK group bacteria are cultured routinely. Fungal cultures should be included when fungal infection is suspected, such as in immunocompromised hosts.

b. Intravascular infection leads to constant bacteremia originating from vegetations. Therefore, **it is unnecessary to await the arrival of a fever spike or chills to obtain blood cultures**.

c. The laboratory should be alerted if a **culture-negative IE or a fastidious infectious agent** is suspected, as it may be necessary to enhance the culture medium or prolong the incubation period. For example, the HACEK group (see Section **III.C.1**) needs prolonged incubation of up to 21 days. The most common culture-negative IE organisms are *C. burnetii*, *Bartonella* sp., *T. whipplei*, HACEK group bacteria, *Brucella* sp., *Legionella* sp., *Mycoplasma* sp., *Mycobacterium*, and fungi. Serology for *Brucella*, *Legionella*, *Coxiella*, or *Psittacosis* may be revealing. Fastidious organisms can also be identified using PCR in valvular specimens. This technique does not require a culture medium; however, it does require excised valvular tissue. PCR has been shown to have a sensitivity of 41% and a specificity of 100% in recent studies, and thus it may provide important information about the causes of IE that could not be identified by culture. This information may help guide future empiric treatment plans in certain patient populations.

d. Special attention should be paid to cultures positive for coagulase-negative staphylococci. *S. lugdunensis* is a coagulase-negative Staphylococcus that rarely causes IE. Unlike other coagulase-negative staphylococci it often affects native valves, is destructive, frequently causes abscesses, and is associated with high mortality without surgical intervention. Thus, in the setting of

high suspicion for IE, cultures positive for coagulase-negative staphylocccci should not be disregarded as a contaminant and should be further speciated.

B. Histologic evaluation. Histopathology of resected valvular tissues remains the gold standard for the diagnosis of IE. It may demonstrate valvular inflammation, vegetations, and/or specific organisms. Detection of an etiologic agent in the vegetation using special stains or immunohistology can guide the choice of antimicrobial treatment. This is particularly useful in culture-negative IE, such as Q fever, *Bartonella* spp., or *T. whipplei* (Whipple's disease bacillus). **Good communication among cardiologists, surgeons, pathologists, and microbiologists helps ensure accurate diagnosis**.

C. Urinalysis. Microhematuria with or without proteinuria may be seen.

D. Electrocardiography. All patients with suspected IE should undergo baseline and follow-up electrocardiogram (ECG).

1. ECG may reveal **conduction disturbances** reflecting intramyocardial extension of infection, ranging from a prolonged PR interval to complete heart block (especially with PVE). A **new atrioventricular block** carries a 77% positive predictive value for abscess formation with 42% sensitivity.
2. Myocardial infarction due to embolization of vegetations occurs rarely.

E. Chest x-ray may reveal **CHF or pleural effusions.** Right-sided IE may cause **nonspecific infiltrates** due to multiple septic pulmonary emboli.

VI. DIAGNOSTIC IMAGING TECHNIQUES

A. Echocardiography has a key role in both diagnosis and management of IE. The primary objective is to identify, localize, and characterize valvular vegetations and their effects on cardiac function. Vegetations may occur at intracardiac locations other than valves, such as the site of impact of a high-velocity jet or shunt. A limitation of echocardiography is that vegetations cannot always be distinguished from other noninfectious masses.

1. All patients in whom IE is suspected should undergo baseline transthoracic echocardiography (TTE) to define underlying cardiac abnormalities, to determine the size and location of vegetations, and to explore the possibility of complications (e.g., aortic annular ring abscess). TTE has a low sensitivity for vegetations in IE (29% to 63%) but has close to 100% specificity. However, the finding of morphologically and functionally normal valves on TTE decreases the likelihood of IE. In one series, 96% of patients with normal valves on TTE also had a negative transesophageal echocardiography (TEE).
2. TEE has increased the diagnostic accuracy of IE. If IE is strongly suspected and the TTE is negative, then TEE should be performed because it is more sensitive in detecting vegetations, especially if TTE imaging is difficult. TEE is particularly useful for assessing posterior structures, abscesses, fistulae, perivalvular leaks, small vegetations, right-sided heart structures, masses on intracardiac devices, leaflet perforations, and prosthetic valves. The ability to detect paravalvular abscesses, fistulae, and paraprosthetic leaks has a major impact on management strategy. Intraoperative TEE can be used to evaluate the success of surgical interventions and the need for potential modification of reparative cardiac surgical procedures. A postoperative TTE should also be done as a baseline measure of cardiac anatomy/function for long-term follow-up. Although in most cases a TTE should be the first diagnostic test of choice, in certain circumstances TEE may be the optimal initial test to rule out IE. These include cases that involve *S. aureus* bacteremia, prosthetic valves, prior IE, limited echo windows, and bacteremia due to an organism that is known to commonly cause IE.
   a. A negative result on TEE indicates a low likelihood of IE (provided adequate images are available). However, it does not completely rule out the diagnosis. The negative predictive value is > 90%, but false negatives may occur early

in endocarditis or if vegetations are small. Repeat TEE should be considered if clinical suspicion is high. Of note, a negative TEE should never override strong clinical evidence of endocarditis in the diagnosis of PVE.

b. Myocardial abscesses are more reliably detected with TEE (87% sensitive) than with TTE (28% sensitive). Detection of a perivalvular abscess is essential, as an abscess is a serious complication and a strong indication for surgical intervention.

c. In the setting of PVE, TEE is superior (82% sensitive) to TTE (36% sensitive) in the detection of vegetations due to acoustic shadowing of prosthetic valves, especially in the mitral and aortic positions. **TEE should be performed if PVE or pacemaker endocarditis is suspected but is not evident on TTE**.

3. Fungal endocarditis tends to cause larger vegetations than bacterial infections, whereas in Q fever vegetations are often absent. Care should be taken to differentiate bacterial vegetations from myxomas, papillary fibroelastomas, rheumatoid nodules, inflammation involving degenerative valvular lesions, Lambl's excrescences, and nonbacterial endocarditis. **It is essential to interpret images in conjunction with clinical data**.

4. One meta-analysis showed that the **risk of embolization in patients with large vegetations (> 10 mm) was nearly three times higher than in patients with no detectable vegetations** or small vegetations. Prolapsing vegetations and involvement of extravalvular structures increase the overall risk of heart failure, embolization, and need for valve replacement. Vegetations that increase in size, despite appropriate therapy, are also more likely to be associated with adverse events requiring surgery.

5. TEE is indicated in patients with suspected pacemaker or defibrillator endocarditis. The sensitivity of TTE for detecting valvular or lead vegetations is 30%, compared with 90% with TEE.

B. Cardiac catheterization. Left heart catheterization with selective coronary angiography is indicated prior to surgical intervention if there is a suspicion of obstructive coronary disease. The abnormal rocking motion of a dehisced prosthetic valve may be noted on fluoroscopy. Care should be taken to avoid unnecessary coronary angiography or cardiac catheterization in aortic valve endocarditis because of the risk of embolization of vegetations.

C. Central nervous system (CNS) imaging. Computerized tomography (CT), magnetic resonance imaging (MRI), or cerebral angiography should be considered in any patient who has sustained a CNS complication, such as an embolic infarct, intracranial bleed, or mycotic aneurysm, or in the patient with persistent headaches.

D. Body imaging. CT or MRI may be useful in the detection of metastatic infection. The value of CT may increase in the future as spatial resolution improves. **MRI** does not currently have a significant role in assessing cardiac manifestations of IE, owing to intrinsic problems related to temporal resolution.

VII. DUKE CRITERIA. Given the complexity of IE, the diagnosis requires a high index of suspicion. The Duke schema is currently the most sensitive and specific diagnostic set of criteria available. It is particularly useful in diagnosing endocarditis in patients with *S. aureus* bacteremia, those with right-sided endocarditis, and those with negative blood culture results. However, these criteria have not been validated in PVE.

A. The criteria are divided into **definite** (pathologic or clinical), **possible**, and **rejected** diagnostic groups.

B. For a **definite pathologic diagnosis**, either (A or B) of the pathologic findings listed in Table 19.2A is sufficient.

C. For a **definite clinical diagnosis** (Table 19.2B), two major criteria, or one major and three minor, or five minor criteria are needed.

TABLE 19.2A Duke Criteria: Definite Pathologic Diagnosis

A. Microorganisms, as demonstrated by culture or histology in vegetation

Vegetation that has embolized

Intracardiac abscess

B. Pathologic lesions

Vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation.* 2005;111:394–434.

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis

Major clinical criteria

1. Positive blood culture results for infective endocarditis
   A. Typical microorganisms (in two or more cultures)
      - Viridans *Streptococcus*
      - *S. bovis*
      - HACEK group
      - *S. aureus*
      - Community-acquired enterococci, in the absence of a primary focus

   B. Persistently positive blood culture
      - Recovery of a microorganism consistent with IE from two blood cultures drawn more than 12 h apart

      or

      - Recovery of a microorganism consistent with IE from all of three or a majority of four or more separate blood cultures, with the first and last draw at least 1 h apart

      or

      - Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer > 1:800

2. Evidence of endocardial involvement
   A. Positive echocardiogram
      - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or on implanted material, in the absence of an alternative anatomic explanation

      or

      - Abscess

      or

      - New partial dehiscence of prosthetic valve

or

   B. New valvular regurgitation (increase or change in preexisting murmur not sufficient)

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis (*Continued*)

Minor clinical criteria

1. Predisposition:
   - Predisposing heart condition
   - Injection drug use
2. Fever > 38.0° C (100.4° F)
3. Vascular phenomena
   - Major arterial emboli
   - Septic pulmonary infarcts
   - Mycotic aneurysm
   - Intracranial hemorrhage
   - Conjunctival hemorrhages
   - Janeway lesions
4. Immunologic phenomena
   - Glomerulonephritis
   - Osler's nodes
   - Roth's spots
   - Rheumatoid factor
5. Microbiologic evidence
   - Positive blood culture but not meeting major criteria as noted above
   - Serologic evidence of active infection with organism consistent with infective endocarditis

HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella;* IE, infective endocarditis.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation.* 2005;111:394–434.

D. The **possible diagnostic** group has findings consistent with IE, including one major criteria and one minor criteria or three minor criteria.

E. For a **rejected diagnosis**, there is a firm alternative diagnosis for clinical manifestations or resolution of clinical manifestations, with antibiotics for 4 days or less, or no pathologic evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days or less.

VIII. THERAPY. Due to the complexity of IE, a team approach (cardiologist, cardiothoracic surgeon, infectious diseases specialist, and pathologist) in the diagnosis and management of this disease cannot be overemphasized. Effective therapy requires identification of the microbial cause, determination of a bactericidal regimen of proven efficacy, an understanding of the intracardiac pathology of IE and its implications for surgery, and effective management of extracardiac complications.

A. Medical therapy

1. **Principles of therapy.** Antibiotic regimens should be bactericidal and chosen in consultation with an infectious diseases specialist. **Measures of antibiotic effectiveness** include the minimum inhibitory concentration (MIC) of antibiotic required to inhibit growth, the minimum bactericidal concentration (MBC) of an antibiotic required to kill an organism, and the serum bactericidal titer (SBT), which is the highest dilution of a patient's serum that kills 99.9% of an inoculum. The SBT is especially helpful when treating unusual organisms, when using unusual antibiotic regimens, or when treatment is failing. The MIC and MBC are not routinely measured, but currently recommended antimicrobial regimens for specific organisms are based on these values.
   a. Combination therapy using a β-lactam agent such as penicillin with an aminoglycoside has a synergistic bactericidal effect in streptococcal IE and is also somewhat effective in a subset of patients with staphylococcal IE. However, aminoglycoside resistance represents the most common and grave obstacle to optimal therapy for enterococcal endocarditis.
   b. A multidrug regimen is recommended for optimal management of staphylococcal PVE. Rifampin has a unique ability to kill staphylococci. However, staphylococci have a relatively high intrinsic mutation rate for the gene controlling the site of rifampin action. Therefore, when large populations of staphylococci are exposed to rifampin, selection of rifampin-resistant organisms is common. Often, antistaphylococcal agent(s) may be administered for 3 to 5 days to reduce the total number of staphylococci before the commencement of rifampin. A multidrug approach (two antibiotics that are known to be active against the staphylococcal isolate in addition to rifampin) may reduce the probability of developing rifampin-resistant subpopulations.
   c. Renal function is an important consideration when using **aminoglycosides or vancomycin**. These antibiotics should be dosed according to estimated creatinine clearance. The following doses outlined are for normal renal function. A vancomycin dose should not exceed 2 g per 24 hours unless serum levels are monitored.
   d. Anticoagulation does not prevent embolization related to IE. In fact, **simultaneous treatment with penicillin and heparin increases the risk** of fatal intracerebral hemorrhage. Warfarin may be given safely during the treatment of patients with PVE.
2. Empiric therapy for IE is often started and continued until the etiologic organism is identified and the antibiotic sensitivities are known, especially in cases with hemodynamic compromise. Occasionally, empiric therapy is administered as a therapeutic trial to help confirm a diagnosis. Empiric therapy should cover the most likely pathogens, including staphylococci (both methicillin-sensitive and methicillin-resistant strains), streptococci, and enterococci. Vancomycin plus gentamicin is the recommended empiric regimen in native valve endocarditis, with the addition of rifampin in PVE. Once an etiologic agent is identified, therapy should be narrowed (see Tables 19.3A–F). Unless clinical or epidemiologic clues suggest an etiologic factor, treatment for culture-negative IE is the same.
3. It is important to point out that when initiating therapy for coagulase-negative staphylococcal PVE, the organism should be assumed to be methicillin-resistant until the laboratory definitively excludes this.
4. Antibiotic therapy **after surgery** is discussed in **VIII.B**.
5. Medical therapies for **specific organisms** are summarized in Tables 19.3A–F.
6. **Uncommon causes of IE.** *C. burnetii* IE is treated with doxycycline and rifampin, trimethoprim–sulfamethoxazole, or fluoroquinolones for at least 3 years and requires surgical intervention in cases of prosthetic valve involvement, CHF, or

TABLE 19.3A Therapies for Native Valve Infective Endocarditis due to Penicillin-Susceptible Viridans *Streptococcus* or *S. bovis*

Medication	Dosage	Duration of therapy (wk)
Penicillin G	12–18 million U per 24 h continuously IV or in 4–6 divided doses	4
or		
Ceftriaxone	2 g once daily IV or IM	4
or		
Penicillin G	12–18 million U per 24 h continuously IV or in 6 divided doses	2[a]
or		
Ceftriaxone *plus*	2 g once daily IV or IM	2
Gentamicin *or* if penicillin allergic	3 mg/kg once daily IV or IM	2
Vancomycin	30 mg per 24 h in 2 divided doses	4

IM, intramuscular; IV, intravenous.

[a]For relatively resistant viridans *Streptococcus* or *S. bovis*, or known cardiac or extracardiac abscess, or for those with creatinine clearance < 20 mL/min, penicillin G dosing is extended to 4 weeks.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3B Standard Therapies for Susceptible Enterococci, for Resistant and Nutritionally Variant Viridans *Streptococcus* Infective Endocarditis, and for Prosthetic Valve Endocarditis due to Viridans *Streptococcus* or *S. bovis*

Medication	Dosage	Duration of therapy (wk)
Penicillin G	24 million U per 24 h continuously IV or in 4–6 divided doses	6
or		
Ceftriaxone	2 g once daily IV or IM	6
with or without		
Gentamicin	3 mg/kg once daily IV or IM	2–6[a]
or		
if penicillin allergic, vancomycin	30 mg/kg IV per 24 h in 2 divided doses	6

IM, intramuscular; IV, intravenous.

[a]If penicillin-susceptible strain (minimum inhibitory concentration ≤ 0.12 μg/mL), duration of gentamicin in combination with ceftriaxone is 2 weeks; if penicillin relatively resistant or fully resistant strain (minimum inhibitory concentration > 0.12 μg/mL), duration of gentamicin is extended to 6 weeks.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3C Therapies for Infective Endocarditis due to Methicillin-Sensitive *Staphylococcus* in the Absence of Prosthetic Material

Medication	Dosage	Duration of therapy
Nafcillin or oxacillin	2 g IV every 4 h	6 wk
plus		
optional gentamicin	1 mg/kg IV or IM every 8 h	3–5 d
or		
Cefazolin	2 g IV every 8 h	6 wk
plus		
optional gentamicin	1 mg/kg IV or IM every 8 h	3–5 d
or		
if penicillin allergic,		
vancomycin[a]	30 mg/kg per 24 h in 2 divided doses	6 wk

IM, intramuscular; IV, intravenous.

[a]Recommended for methicillin-resistant *Staphylococcus.*

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation.* 2005;111:394–434.

TABLE 19.3D Therapy for Infective Endocarditis due to Methicillin-Sensitive *Staphylococcus* in the Presence of Prosthetic Material

Medication	Dosage	Duration of therapy (wk)
Nafcillin[a] or oxacillin	2 g IV every 4 h	> 6
plus rifampin	300 mg orally every 8 h	> 6
plus gentamicin	1 mg/kg IV or IM every 8 h	2

IM, intramuscular; IV, intravenous.

[a]For methicillin-resistant *Staphylococcus* or for the penicillin-allergic patient, vancomycin, 30 mg/kg per 24 h IV in two divided doses, is substituted for nafcillin.

refractory infection. *Brucella* IE usually requires surgical intervention in combination with doxycycline and either streptomycin or gentamicin for 8 weeks to 10 months after surgery. *Pseudomonas* IE should be treated with high doses of piperacillin and tobramycin and requires surgical intervention in cases of left-sided infection.

7. **Fungal IE.** When fungal IE is diagnosed, the standard of care involves a **combined medical/surgical approach**.
   a. The mainstay of antifungal drug therapy is **amphotericin B** with or without **flucytosine** (a synergistic effect).

TABLE 19.3E Therapy for Infective Endocarditis due to HACEK (*Haemophilus, Actinobacillus, Cardiobacterium, Eikenella, and Kingella)* Microorganisms

Medication	Dosage	Duration of therapy
Ceftriaxone[a]	2 g once daily IV or IM	4
or		
Ampicillin–sulbactam[a]	3 g IV every 6 h	4
or		
Ciprofloxacin	1,000 mg orally once daily *or* 400 mg IV every 12 h	4

IM, intramuscular; IV, intravenous.
[a]The third-generation cephalosporins or ampicillin–sulbactam therapy should be considered the drugs of choice. Length of therapy for prosthetic valve infective endocarditis should be 6 weeks. A fluoroquinolone should be considered as an alternative agent for patients unable to tolerate β-lactam therapy.
Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation.* 2005;111:394–434.

TABLE 19.3F Therapy for *Pseudomonas aeruginosa* and Other Gram-Negative Bacilli (Enterobacteriaceae)[a]

Extended-spectrum penicillin (ticarcillin or piperacillin)
or
third-generation cephalosporin
or
imipenem
plus aminoglycoside

[a]Combination therapy is recommended. The final choice of antibiotic therapy is to be made after sensitivity results are available.

(1) Amphotericin B is infused in 5% dextrose over 2 to 4 hours at a dose of 0.7 to 1.0 mg/kg daily. Larger doses (1 to 1.5 mg/kg daily) are recommended for the management of PVE caused by *Aspergillus* spp.
(2) The major toxicity of amphotericin B is **renal dysfunction**. Liposomal preparations may be less nephrotoxic.
(3) The primary toxicity of flucytosine is **bone marrow suppression**; for this reason, flucytosine blood levels may be useful during therapy.

b. After 1 to 2 weeks of full-dose amphotericin B therapy, surgery should be performed because effective penetration of the medicine into vegetations is unlikely. Valve replacement becomes necessary in almost all cases of fungal IE.

c. Long-term oral suppressive therapy with antifungal agents such as fluconazole or itraconazole is commonly recommended to prevent relapse.

B. Surgical therapy (Table 19.4). Surgery is indicated in approximately 25% to 30% of cases during the acute phase of infection and in another 20% to 40% in subsequent or secondary phases. Antibiotic therapy combined with valve replacement and cardiac reconstruction results in higher survival rates and fewer relapses or rehospitalizations and lower late endocarditis–related mortality than do antibiotics alone in patients with complicated IE.

1. The **fundamental principles** of operative procedures for IE involve debridement of infected tissue, removal of all nonviable tissue, reconstruction of the involved area, and restoration of valve competence. There is general consensus for surgical intervention in any of the following situations: refractory CHF due to significant valve dysfunction, native and PVE caused by *S. aureus*, uncontrolled infection, failed antimicrobial therapy with perivalvular extension of infection, most cases of PVE, most cases of fungal IE, and established abscess. Controversial indications include the presence of more than one serious systemic embolic event or one embolus with a large residual vegetation. These indications are not absolute and must be implemented with a careful risk–benefit analysis (see the American College of Cardiology/American Heart Association [ACC/AHA] guidelines for surgical intervention in Table 19.4).
2. CHF (New York Heart Association class III or IV) is the strongest indication for surgery in IE, as 90% of all deaths result from CHF. It should be noted

TABLE 19.4 ACC/AHA Guidelines: Surgical Intervention for Infective Endocarditis

Class I

1. Acute native valve IE presenting with valve stenosis or regurgitation that results in heart failure
2. Acute native valve IE presenting with AR or MR with hemodynamic evidence of elevated LVEDP or LAP
3. Native valve IE caused by fungal or other highly resistant organisms
4. Native valve IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions
5. Prosthetic valve IE presenting with heart failure
6. Prosthetic valve IE presenting with dehiscence confirmed by fluoroscopy or echocardiography
7. Prosthetic valve IE presenting with increasing obstruction or worsening regurgitation
8. Prosthetic valve IE presenting with complications such as abscess formation

Class IIa

1. Native valve IE presenting with mobile vegetations > 10 mm with or without emboli
2. Prosthetic valve IE presenting with persistent bacteremia or recurrent emboli despite appropriate antibiotic therapy
3. Prosthetic valve IE presenting with relapsing infection

IE, infective endocarditis; AR, aortic regurgitation; MR, mitral regurgitation; LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure

Adapted from the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease. JACC 2006.

that the benefit of surgery persists even in the presence of comorbidities, such as acute renal failure, and surgery should not be delayed in the setting of life-threatening heart failure or cardiogenic shock if the patient is likely to recover after surgery.

3. PVE usually requires a combined medical/surgical approach.
4. **Patients with CNS infarcts or bleeds.** Special attention must be paid to the presurgical candidate who may have had a CNS infarct or bleed, since large doses of heparin are required for cardiopulmonary bypass. Several studies report a significant risk of postoperative neurologic deterioration or even death in patients with recent CNS complications of IE. The best management in the scenario of hemodynamic instability and new-onset embolic stroke has not been addressed in randomized clinical studies. When possible, cardiac surgery is delayed for at least 4 days, ideally 10 days postinfarction in those with a CNS embolic infarct, and for 21 days following an intracranial hemorrhage. However, some patients may need early surgery despite a recent stroke if they are at high risk for recurrent emboli. **If a mycotic aneurysm is found, the timing of surgery should be reconsidered, and any prosthesis that requires postoperative anticoagulation should be avoided.** A ruptured mycotic aneurysm should be resected, clipped, or embolized **before** cardiac operation.
5. Metastatic infection, usually attributed to *S. aureus*, should be drained if accessible.
6. The optimal duration of **antibiotic therapy after surgery** for IE is not known.
   a. For **native valve IE** caused by an antibiotic-resistant organism with subsequent negative cultures, preoperative plus postoperative antibiotic therapy should consist of a full course of recommended treatment.
   b. For patients with **positive intraoperative cultures**, a full course of therapy should be given postoperatively.
   c. Patients with prosthetic valves who are undergoing surgery for IE should receive a full course of antibiotics postoperatively when organisms are discovered in resected material.

C. The optimal management of **pacer or defibrillator endocarditis** has been controversial in the literature, especially regarding the necessity for device removal.

1. The success rate without removal of the entire device is low because typically the entire device is infected. Most studies suggest that the complete explantation of all hardware combined with antibiotic therapy is the optimal management.
2. The optimal route or duration of antibiotics remains unclear in the literature. Experience suggests that a prolonged course of intravenous antibiotics is needed.
3. The timing of device reimplantation is another important issue. It is prudent to provide sufficient duration of antibiotic therapy to eradicate bacteremia and to suppress or eradicate endocardial infection prior to reimplantation in order to minimize the risk of reinfection of the new device. Studies have shown that reimplantation is successfully performed at a median of 7 days (5 to 25 days) after explantation.

IX. COMPLICATIONS

A. Table 19.5 lists the complications of IE.

B. Valve ring abscess is a noteworthy complication of PVE, seen with mechanical and bioprosthetic valves and also occasionally seen in severe infection of native valves. Infection of the sutures used to secure the sewing ring to the periannular tissue may result in dehiscence of the valve. The clinical finding of a new perivalvular leak in a patient with PVE is worrisome. Risk factors for abscess formation include persistent fever, CHF, a history of intravenous drug use, infection with a virulent organism, and PVE.

TABLE 19.5 Complications

Cardiac complications
Congestive heart failure (leading cause of death)
Abscess (pericardial, aortic annular, or myocardial)
Conduction abnormalities (due to invasive disease)
Coronary embolism
Mycotic aneurysm (often clinically silent)
Valvular regurgitation (cusp/leaflet flail or perforation)
Valvular stenosis
Prosthetic dehiscence
Septal perforation (ventricular septal defect)
Extracardiac complications
Systemic embolism (stroke, renal infarct, splenic infarct, or ischemic limb)
Mycotic aneurysm
Abscess
Immune complex deposition (glomerulonephritis)

X. RESPONSE TO THERAPY. Although a reduction in the size of vegetations during antimicrobial therapy suggests therapeutic success, vegetations may persist unchanged despite microbiologic cure. Significant enlargement of a vegetation during treatment indicates possible treatment failure and constitutes a relative indication for surgery.

- **A.** Blood cultures should be obtained during therapy for IE to ensure eradication of the organism (see Section **V.A.3**).
- **B.** Defervescence usually follows 3 to 7 days of successful antimicrobial therapy. **Persistent or recurrent fever may represent therapeutic failure, drug fever, a secondary nosocomial infection, or intracardiac or extracardiac abscess formation**. Generally, if fever persists for more than 7 days or if blood cultures are positive beyond the first week of antibiotic therapy, the treatment is considered a failure.
- **C.** Relapses, should they occur, usually manifest clinically within 4 weeks and can be confirmed by blood cultures. With a combined medical and surgical approach, recurrent PVE occurs in 6% to 15% of patients.
- **D.** **The frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy,** and the risk is considered to be greatest in the setting of large vegetations (> 10 mm in diameter) and specific infections (*S. aureus* and *Candida*).
- **E.** Medical management is successful in many patients with IE; however, surgery is required in approximately 25% to 33% of cases.

XI. PROGNOSIS. The prognosis depends on **the virulence of the causative organism, the underlying health of the patient, the valvular structures, the duration of the infection, and the presence or absence of CHF**. The overall mortality of IE is around 20% to 30%. Notably, the mortality rates in early PVE (40% to 80%) are much higher than in late PVE (20% to 40%). Five-year survival rates after surgery for PVE have ranged from 54% to 87%. In *S. aureus* IE, mortality has decreased from 50% to 60% to 15% to 30% in recent years. The presence of the factors listed in Table 19.6 should trigger an early and aggressive management plan.

TABLE 19.6 Factors and Complications That Predispose to a Poor Outcome

Congestive heart failure (leading adverse prognostic factor)
Nonstreptococcal disease
Aortic valve involvement
Infection of a prosthetic valve
Older age
Abscess formation
HIV with CD4 count < 200 cells/mm^3
Delayed diagnosis
CNS or coronary embolization
Recurrent infective endocarditis

CNS, central nervous system; HIV, human immunodeficiency virus.

A. There has been an increasing demand to develop an endocarditis risk score for predicting mortality and surgical outcomes in IE. One barrier to the development of this model is inconsistencies in the prognostic value of individual parameters in the published data. These differences may in part be due to time dependencies of various risk factors. One study evaluated risk factors in a time-dependent manner in order to derive a validated risk score for the prognostic evaluation of IE in patients before and during early hospitalization. Factors that contributed to increased mortality included older age, CHF, lower platelet count, higher creatinine, and severe embolic events, consistent with previous studies. A recent study used the Society of Thoracic Surgery database to develop a surgical mortality risk scoring system. Although several studies have attempted to evaluate the most significant predictors of risk, a standardized risk scoring model has yet to be established.

XII. PROPHYLAXIS. Revised IE prophylaxis guidelines from the AHA concluded that **only those patients at highest risk for adverse outcomes from IE require prophylaxis** prior to certain dental or surgical procedures (Tables 19.7A and 19.7B). This is based on studies suggesting that IE is more likely to occur from everyday activities such as flossing or brushing teeth than from dental procedures, and that an extremely small number of cases of IE might be prevented by antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures. It is a standard practice (AHA guidelines) that at-risk individuals be counseled and advised to carry a card with current prophylaxis recommendations. Failure to adhere to this practice may invite litigation. A recent study suggests that an echocardiographic report, stating the endocarditis risk and need for prophylaxis, improves compliance with AHA recommendations.

A. In deciding the need for antibiotic prophylaxis, two factors must be considered: the risk associated with the specific valvular lesion (Table 19.7A) and the type of procedure to be performed (Table 19.7B). Patients for whom antibiotic prophylaxis for IE is recommended include those with **prosthetic heart valves, prior IE, postcardiac transplantation valvulopathy, and certain patients with congenital heart disease** (Table 19.7A). Routine IE prophylaxis is no longer recommended in most cardiac conditions, including mitral valve prolapse, rheumatic heart disease, bicuspid aortic valve, calcific aortic stenosis, atrial septal defect, and ventricular septal defect.

TABLE 19.7A Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Infective Endocarditis

Prophylaxis for endocarditis recommended
Prosthetic heart valves
Previous infective endocarditis
CHD
Unrepaired cyanotic CHD (including palliative shunts or conduits)
Repaired CHD with residual defect at, or adjacent to, the site of repair
During the first 6 mo after repair of congenital heart defects using prosthetic material or device
Cardiac transplantation recipients who develop cardiac valvulopathy

CHD, congenital heart disease.

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation.* 2007;115:1–19.

TABLE 19.7B Recommendations for Prophylaxis in Dental or Surgical Procedures

Prophylaxis recommended only in patients at highest risk of adverse outcome from infective endocarditis (Table 19.7A)
Oropharyngeal procedures
Dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa
Tonsillectomy and/or adenoidectomy
Respiratory procedures
Invasive procedures involving incision
Miscellaneous
Procedures on infected skin or musculoskeletal tissue

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation.* 2007;115:1–19.

B. Endocarditis prophylaxis following **dental or oral procedures** is directed primarily against viridans *Streptococcus*; following **genitourinary and gastrointestinal surgery** it is directed primarily against *Enterococcus* organisms.

C. **Routine antibiotic prophylaxis solely to prevent IE is no longer advised prior to gastrointestinal or genitourinary procedures.** This is based upon an increasing frequency of antimicrobial-resistant strains of enterococci and a lack of evidence conclusively linking these procedures to IE.

D. Available evidence supports a shift in emphasis away from dental procedures and antibiotic prophylaxis toward a greater **emphasis on maintaining good oral hygiene** and improved access to dental care in patients at risk for IE.

TABLE 19.7C Prophylactic Regimens

Clinical situation	Antibiotic	Dose
Standard prophylaxis	Amoxicillin	2 g PO 1 h before procedure
Unable to take oral medications	Ampicillin *or*	2 g IV or IM within 30 min before procedure
	Cefazolin or ceftriaxone	1 g IV or IM within 30 min before procedure
Penicillin allergy	Clindamycin *or*	600 mg PO 1 h before procedure
	Cephalexin *or*	2 g PO 1 h before procedure
	Azithromycin *or* clarithromycin	500 mg 1 h before procedure

IM, intramuscular; IV, intravenous; PO, per oral.

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation.* 2007;115:1–19.

E. Prophylaxis against viridans *Streptococcus* is advised in patients at highest risk of IE who undergo **invasive procedures of the respiratory tract** that involve incision or biopsy (i.e., tonsillectomy or adenoidectomy). Routine endocarditis prophylaxis prior to **vaginal delivery** or hysterectomy is not recommended.

F. Incision and drainage or other procedures involving infected tissue may result in bacteremia. For nonoral soft-tissue infections, an antistaphylococcal penicillin or first-generation cephalosporin is an appropriate choice of prophylaxis.

G. Prophylaxis regimens are listed in Table 19.7C. **Cardiac surgical patients** who undergo placement of prosthetic heart valves or other prosthetic material should receive antibiotic prophylaxis, primarily directed against *S. aureus.* A first-generation cephalosporin is commonly used, but the choice of antibiotic should be influenced by the antibiotic susceptibility pattern at each hospital. Prophylaxis should be started immediately before the procedure, repeated during prolonged procedures, and continued for no more than 48 hours. **A careful preoperative dental evaluation** is recommended so that, whenever possible, required dental treatment can be completed before cardiac valve surgery.

H. **Patients after cardiac transplantation** are at moderate risk for endocarditis because of continuous immunosuppression and the tendency for acquired valvular dysfunction (tricuspid regurgitation from endomyocardial biopsy or rejection).

I. Pneumococcal vaccination is recommended for all patients with prosthetic heart valves.

XIII. CONTROVERSIES

A. Therapy

1. Short courses of antibiotics (2 weeks) have shown some efficacy in the injection drug user population, as have oral antibiotics in the same population. However, intravenous antibiotics are indicated until conclusive data concerning attentive regimens are available. At least 5 to 7 days of inpatient therapy is advocated before considering outpatient treatment.

2. Correct timing of surgery is often the most difficult and critical decision in the management of IE. It is important to balance the need for medical stabilization

with timely surgery. Kiefer et al. (1) conducted a large multicenter randomized trial of over 4,000 patients with IE and heart failure and showed that surgical intervention during initial hospitalization was associated with decreased inhospital and 1-year mortality rates. In patients with large mitral or aortic valve vegetations (> 10 mm), early surgery has been found to be associated with decreased mortality and embolic events when compared with conventional medical therapy (3% vs. 23%) in the recently published Early Surgery Versus Conventional Treatment in Infective Endocarditis (EASE) trial. In this trial, patients who had surgery within 48 hours had a decreased rate of all-cause death.

3. Valve repair is a reasonable option for mitral, tricuspid, and, less often, aortic IE in which the infection has been controlled. The choice among mechanical, bioprosthetic, and biologic devices may be made according to the usual criteria. However, in the setting of aortic prosthetic endocarditis, a homograft or an autograft is less likely to become infected than either a xenograft or a mechanical valve and is considered the optimal valve substitute.

ACKNOWLEDGMENTS: *The authors thank Drs. Mateen Akhtar, Xiao-Fang Xu, and Mark Murphy for their contributions to earlier editions of this chapter.*

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CHAPTER 20

Chetan Vagesh Hampole

Rheumatic Fever

I. INTRODUCTION. Rheumatic fever (RF) is a systemic autoimmune disorder related to prior streptococcal infection and is the leading cause of heart disease in those under the age of 40 years living in developing nations.

A. The incidence of RF and prevalence of rheumatic heart disease **vary substantially among countries**. In many developing countries, the incidence of acute RF approaches or exceeds 200 per 100,000, whereas in the Unites States, it is estimated to be less than 1 per 100,000. Since the first half of this century, there has been a

gradual decline in the incidence of RF in the United States, Japan, and most European countries. This is due to improved public health and living conditions, the development of modern antibiotics, as well as a shift in the endemic strains of group A streptococcus (GAS). Localized outbreaks of RF have occurred in the United States as recently as the mid-1980s.

B. RF is more common among populations at high risk for streptococcal pharyngitis, such as military recruits, those in close contact with school-aged children, and persons of low socioeconomic status. It most commonly occurs between the ages of 5 and 18 years. RF affects both sexes equally, except for Sydenham's chorea, which is more prevalent in females after puberty.

II. CLINICAL PRESENTATION. The clinical manifestations of RF **develop 3 weeks after a GAS tonsillopharyngitis**. It is important to note that one-third of patients with RF do not remember having had a sore throat. Patients with RF present initially with a sudden onset of constitutional symptoms, including fever (101°C to 104°C), malaise, weight loss, and pallor. An exudative and proliferative inflammatory process involving collagen fibrils characterizes the acute phase of RF. **Multiple organ systems**, such as the dermis, central nervous system, synovium, and heart, may be involved. In addition, manifestations may include serositis and involvement of the lungs, kidneys, and central nervous system.

A. Diagnostic criteria

1. The **Jones criteria** are designed to aid in the diagnosis of the first episode of RF. It can be diagnosed when a **previous upper airway infection with GAS is detected in conjunction either with two major manifestations or with one major and two minor manifestations**. Major manifestations include arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Minor manifestations include fever, arthralgias, high C-reactive protein (CRP) level or high erythrocyte sedimentation rate (ESR), and a prolonged PR interval on electrocardiogram (ECG) (Table 20.1).
2. In some circumstances, the **diagnosis of RF can be made without strict adherence to Jones criteria**, as in cases of indolent or recurrent carditis or isolated cases of chorea when other causes have been excluded.

B. Major manifestations (Table 20.1)

1. **Carditis.** This is the most serious and is often regarded as the most specific manifestation of RF, affecting 41% to 83% of patients. It may manifest

TABLE 20.1 Diagnosis of Rheumatic Fever[a]

GAS infection	Major Jones criteria	Minor Jones criteria
Culture	Carditis	Fever
ASO titers	Arthritis	Arthralgia
Anti-DNase B	Sydenham's chorea	High ESR or CRP
Other antistreptococcal antibodies	Subcutaneous nodules	Prolonged PR
Streptococcal antigens	Erythema marginatum	

ASO, antistreptolysin *O*; anti-DNase, antideoxyribonuclease B; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcus.

[a]The diagnosis of rheumatic fever requires confirmation of a previous ***GAS infection*** with at least one of the methods listed above together with either ***two major criteria or one major criterion and two minor criteria***.

as pancarditis affecting the endocardium, myocardium, and pericardium simultaneously.

- **a.** Cardiac involvement ranges from an asymptomatic presentation to progressive congestive heart failure and death.
- **b.** The most typical manifestations include **increased heart rate, rhythm disturbances, new murmurs or pericardial friction rub, cardiomegaly, and heart failure**.
- **c.** Heart failure is rare in the acute phase; if present, it is usually the result of myocarditis.
- **d.** The most characteristic component of rheumatic carditis is a valvulitis (endocarditis) involving the mitral and aortic valves.
  - **(1)** Mitral insufficiency is the hallmark of rheumatic carditis. Aortic insufficiency is less common and is almost always associated with mitral insufficiency. As a rule of thumb, patients under the age of 30 years tend to present with isolated mitral regurgitation, whereas patients develop mitral stenosis during the third decade, with mixed mitral valve disease predominating thereafter.
  - **(2)** Acute mitral valve regurgitation produces an apical systolic murmur that may be accompanied by a mid-diastolic Carey Coombs murmur of relative mitral stenosis (a high-pitched early diastolic murmur that varies from day to day). Right-sided valves are rarely involved.
  - **(3)** Those valvular lesions that are diagnosed by echocardiogram but are clinically silent usually heal without scarring and have a good prognosis. Controversy exists whether echocardiographic findings of mitral regurgitation or aortic insufficiency constitute subclinical rheumatic carditis sufficient to meet the Jones criteria.
- **e.** Pericarditis may cause chest pain, friction rubs, and distant heart sounds but is often clinically silent.

2. **Arthritis.** This is the **most common manifestation of RF but is the least specific**. It occurs in 80% of patients and is described as **painful, asymmetric, migratory, and transient. It involves large joints**, such as the knees, ankles, elbows, wrists, and shoulders. It is **more common in older patients and improves markedly with the use of salicylates** within 48 hours of treatment. Monoarthritis, oligoarthritis, and involvement of small joints of the extremities are less common. However, arthritis of the first metatarsophalangeal joint, enthesopathy, and axial involvement, especially of the cervical spine, have also been reported. **Arthritis of RF is benign and self-limiting** (lasting 2 to 3 weeks) and does not result in permanent sequelae. Inflammatory changes without signs of infection are seen in the joint fluid.
3. **Sydenham's chorea.** Also known as Saint Vitus' dance or chorea minor, this **extrapyramidal disorder is characterized by purposeless and involuntary movements** of face and limbs, muscular hypotonia, and emotional lability.
   - **a.** Initial manifestations include difficulty in writing, talking, or walking. Handwriting may deteriorate; speech may change to an explosive and halting tone; and the patient may become uncoordinated and easily frustrated.
   - **b.** Symptoms tend to be more evident when the patient is under stress or awake and usually disappear during sleep.
   - **c.** Sydenham's chorea is a **delayed manifestation of RF**, usually appearing 3 months or more after an upper airway infection; it is often the sole manifestation of acute RF. Chorea has been reported in up to 30% of the patients. Most cases tend to follow a benign course, with complete resolution of symptoms in 2 to 3 months, although cases in which symptoms persisted for > 2 years have been reported.

d. It is important to **differentiate the symptoms of Sydenham's chorea from tics, athetosis, conversion reactions, hyperkinesia, and behavioral abnormalities**.

4. **Subcutaneous nodules.** These usually measure 0.5 to 2 cm and are **firm, painless, and freely mobile nodules that can be isolated or found in clusters** over the **extensor surfaces** of joints (knees, elbows, and wrists), bony prominences, tendons, dorsum of foot, occipital region, and cervical processes. They are seen in up to 20% of patients with RF and last for a few days. The skin overlying the nodules is freely mobile and shows no signs of discoloration or inflammation.
5. **Erythema marginatum.** This is an **evanescent erythematous macular rash** with a pale center of irregular shape. It is **usually nonpruritic and tends to disappear after a few days**. It is highly specific, occurring in < 5% of patients, and is obvious only in fair-skinned individuals. The lesions vary in size and affect mainly the trunk, abdomen, and inner aspect of arms and thighs, but not the face. The rash may be induced by application of heat. Its presence is **suggestive of coexisting carditis**.

C. **Minor manifestations.** Fever and arthralgias are common, but nonspecific findings of RF that can be used to support the diagnosis of RF when only a single major manifestation is present (Table 20.1).

1. Fever is encountered during the acute phase of the disease and does not follow a specific pattern.
2. Arthralgia is defined as pain in one or more large joints without objective findings of inflammation on physical examination.
3. Other clinical manifestations of RF include **abdominal pain, epistaxis, acute glomerulonephritis, rheumatic pneumonitis, hematuria, and encephalitis**. These are not included as diagnostic criteria for the diagnosis of RF.

III. ETIOLOGY AND PATHOPHYSIOLOGY

A. The association between tonsillopharyngitis–scarlet fever epidemics and acute RF in the 1930s, the findings of high levels of antistreptolysin *O* (ASO) in sera of patients with RF, and the confirmation of antibiotics as an efficient mode of prophylaxis of RF provide **strong evidence that GAS is the agent causing initial and recurrent attacks of RF**.

1. Acute RF might not be caused directly by the bacteria but rather through an immunologic mechanism. Specifically, it appears that patients who develop RF demonstrate a hyperimmune response to GAS, and the level of the immune response correlates with the severity of the RF manifestations. Supporting evidence includes onset approximately 3 weeks following an upper respiratory tract infection, rarity before the age of 5 years when the immune system is still immature, and cross-reactivity between streptococcal cellular antigens and proteins present in human connective tissue.
   a. The most important antigenic structures (M, T, and R proteins) are localized in the external layer of the bacterial cell wall.
   b. The M protein not only is responsible for type-specific immunity but also has a powerful antiphagocytic action and is classically regarded as a marker of streptococcal rheumatogenic potential. Patients with acute RF possess high levels of antibodies targeted against this protein. Specific M serotypes of GAS have long been recognized as strong stimulators of a robust immune response and are associated with an increased risk of developing RF. Those M serotypes associated with impetigo or pyoderma may cause glomerulonephritis but are not associated with RF.
2. In epidemics of streptococcal pharyngitis, it is estimated that approximately **3% of untreated individuals will go on to develop RF**. However, recurrence of

RF is seen in about 50% of patients with a history of RF. For endemic GAS pharyngeal infections, the incidence of RF is much less common.

B. Numerous epidemiologic studies favor a **familial and even genetic predisposition**. A monoclonal antibody to B-cell alloantigen (D8/17) is almost universally detected in patients with RF, whereas this antibody is present in < 14% of the general population. In addition, susceptibility to RF has also been linked with D-related human leukocyte antigen 1, 2, 3, and 4 haplotypes. These genetic markers may be useful in the future to identify individuals susceptible to acute RF.

IV. LABORATORY EXAMINATION AND DIAGNOSTIC TESTING. RF is a clinical diagnosis because there is no single laboratory study that is diagnostic of RF.

A. Supporting evidence of antecedent GAS infection can be obtained through cultures, antigen test, or serum antistreptococcal antibody test.

1. Although no consensus exists regarding which tests to order at what time, commonly ASO titers and cultures are initially obtained when RF is suspected. Other tests as detailed in the subsequent text are useful only under certain conditions.
2. A negative throat culture is usually sufficient to withhold antibiotic treatment in most cases, especially if clinical suspicion of RF is low.
3. Elevated or rising ASO titers provide solid evidence for recent GAS infection. **A greater than twofold rise in ASO titers compared with convalescent titers is diagnostic**.
4. The probability of detecting a previous GAS infection can be increased by obtaining repeated ASO tests or by looking for antibodies to other streptococcal antigens, such as **antideoxyribonuclease B**.
5. A slide agglutination test is commercially available, which measures antibodies to several streptococcal antigens. Although this test is simple to perform, it is **not well standardized and is not very reproducible**. Therefore, it is **not recommended** as a definitive test for prior GAS infection.

B. Biopsies

1. Aschoff's nodules, a form of granulomatous inflammation, can be seen in the proliferative stage and are considered pathognomonic for rheumatic carditis. They are encountered in 30% to 40% of biopsies from patients with primary or recurrent episodes of RF. Such nodules are most often found in the interventricular septum, the wall of the left ventricle, or the left atrial appendage.
2. The histologic findings of endocarditis include edema and cellular infiltration of valvular tissue. Hyaline degeneration of the affected valve results in the formation of verrucae at its edge, preventing the normal leaflet coaptation. If the inflammatory process persists, fibrosis and calcification develop, leading to valvular stenosis.
3. Endomyocardial biopsy does not help in diagnosing first attacks of rheumatic carditis. It is **useful in distinguishing chronic inactive rheumatic heart disease from acute rheumatic carditis**. As such, it is rarely indicated except in cases where recurrent carditis is suspected but cannot be confirmed otherwise.

C. Other blood tests

1. As in any inflammatory process, **leukocytosis, thrombocytosis, or hypochromic or normochromic anemia** may be noted.
2. The favored tests to measure acute phase response are ESR and CRP. Although these tests are nonspecific, they may be helpful in monitoring the inflammatory activity of the disease. These levels are **almost always elevated during the acute phase of RF in patients with arthritis and polyarthritis and are usually normal in patients with chorea**.

D. Radiography. Chest radiography may identify increased cardiac size, increased pulmonary vasculature, or pulmonary edema.

E. Electrocardiography and echocardiography. In patients in whom **carditis is subtle and signs of valvular involvement may be mild or transient, a baseline echocardiogram and ECG** may help provide evidence of carditis.

1. The most common finding in the **ECG** is the presence of **PR prolongation and sinus tachycardia**. Myocarditis may prolong the QT interval. In cases of pericarditis, low-voltage QRS complexes and ST-segment changes in the precordial leads can be observed.
2. Echocardiography is likely to show mitral regurgitation or aortic insufficiency. Calcifications of the leaflets and subvalvular apparatus are present in the chronic, not acute, phase of rheumatic heart disease.

V. THERAPY.

It is generally recommended that **patients with suspected RF be admitted for close observation and workup**.

A. Carditis

1. Secondary prophylaxis with penicillin has been shown to reduce not only streptococcal infections but recurrent attacks of acute RF as well. Patients with mild carditis should receive secondary prophylaxis for 10 years after the most recent attack or at least until the age of 25 years, whichever is longer. More severe valvular damage necessitates lifelong secondary prophylaxis.
2. Congestive heart failure should be managed with standard therapy (Chapters 8 and 9).
3. In patients with significant cardiac involvement, corticosteroids are preferred over salicylates. The recommended dose of corticosteroid is 1 to 2 mg/kg/d (maximum of 60 mg/d). Salicylate or steroid therapy does not affect the course of the disease; therefore, the duration of anti-inflammatory therapy is somewhat arbitrary and is guided by the severity of disease and the response to therapy. Commonly, therapy is needed for 1 month in patients with relatively mild cardiac involvement. Therapy should be continued until there is sufficient clinical and laboratory evidence of disease inactivity.
4. After cessation of anti-inflammatory agents, relapse with mild symptoms may occur. **A gradual reduction in steroid dosing is necessary to avoid relapses**. If **symptoms are mild, they usually subside without specific treatment**. For **severe symptoms, treatment with salicylates** should be tried before restarting corticosteroids. Administering salicylate therapy (75 mg/kg/d) while tapering corticosteroids may reduce the likelihood of a relapse.
5. Corticosteroids, despite relieving symptoms or carditis, do not prevent valvular damage.

VI. PREVENTION.

See Table 20.2.

A. Primary prevention. The most important step in the management of RF is the eradication of GAS infection, which prevents chronic and repetitive exposure of antigenic streptococcal components to the host immune system. However, **no treatment can eradicate GAS completely in all patients because of high colonization rates**.

1. Early therapy is advisable because it reduces both morbidity and the period of infectivity. Studies have shown that antimicrobial therapy, even when started 9 days after the onset of acute streptococcal pharyngitis, is still effective in preventing primary attacks of RF.
2. Penicillin is the agent of choice primarily for its narrow spectrum of activity, long-standing proven efficacy, and low cost.
   a. Best results are achieved with a **single intramuscular dose of penicillin G benzathine**. An intramuscular regimen is preferred in patients unlikely to complete a 10-day course of oral therapy or in patients with personal or

TABLE 20.2 Prevention of Rheumatic Fever

Drug	Dosage	Route	Duration
Primary prevention			
Benzathine (penicillin G)	600,000 U (≤ 27 kg) 1.2 million U (≥ 27 kg)	IM	Once
	or		
Penicillin V (children)	250 mg (2–3 times/d)	Oral	10 d
Penicillin V (adolescents and adults)	500 mg (2–3 times/d)	Oral	10 d
Penicillin-allergic patients			
Erythromycin ethyl succinate	40 mg/kg/d (2–4 times/d up to 1 g/d)	Oral	10 d
Erythromycin estolate	20–40 mg/kg/d (2–4 times/d up to 1 g/d)	Oral	10 d
Secondary prevention			
Benzathine (penicillin G)	1.2 million U	IM	q3-4wk
or			
Penicillin V	250 mg	Oral	bid
or			
Sulfadiazine	0.5 g (≤ 27 kg) 1.0 g (> 27 kg)	Oral	qd
Penicillin- and sulfadiazine-allergic patients			
Erythromycin	250 mg	Oral	bid

bid, twice a day; IM, intramuscular; qd, every day.
Adapted from Dajani AS. Rheumatic fever. In: Braunwald E, ed. *Heart Disease*: *A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 1997:1769–1775.

family history of RF or rheumatic heart disease. This preparation is painful; **preparations that contain procaine penicillin are less painful**.

b. In comparison with the intramuscular regimen, the oral regimen has several disadvantages, such as lower compliance due to its longer duration, more complicated dosing schedules, drug interactions, and, more importantly, socioeconomic factors. The oral antibiotic of choice is penicillin V (phenoxymethylpenicillin) (see Table 20.2 for dosage information). A broader spectrum penicillin, such as amoxicillin, offers no microbiologic advantage over penicillin.

3. Patients allergic to penicillin:
   a. Oral erythromycin can be used. The recommended dosage is erythromycin estolate or erythromycin ethyl succinate for 10 days. The maximum dose of erythromycin is 1 g/d.
   b. Although uncommon in the United States, **strains resistant to erythromycin** have been found in some areas of the world and have caused treatment failures. The newer **macrolides, such as azithromycin**, have the advantage of a short treatment duration (5 days) and few gastrointestinal side effects. These can be used as second-line therapy for patients 16 years or older with GAS pharyngitis. The recommended dosage is 500 mg as a single dose on the first day followed by 250 mg once daily for 4 days.
   c. Another alternative regimen for penicillin-allergic patients is a **10-day course with an oral cephalosporin**. A first-generation cephalosporin with a narrower spectrum of action (cefadroxil or cephalexin) is preferable to the broader spectrum antibiotics such as cefaclor, cefuroxime, cefixime, and cefpodoxime. Several reports support the evidence that a 10-day course with oral cephalosporin is superior to a 10-day course with oral penicillin and a 5-day course with selected oral cephalosporins is comparable to a 10-day course with oral penicillin for the eradication of GAS.
   d. Sulfa-derived antibiotics **(sulfonamides and trimethoprim) do not eradicate GAS** in patients with pharyngitis, and **tetracycline should be avoided** because of the high prevalence of resistant strains.

B. **Secondary prevention.** Prophylaxis for preventing recurrences should **start as soon as RF or rheumatic heart disease is diagnosed**, as recurrences can sometimes be asymptomatic.
   1. Penicillin in doses of 600,000 IU (patient's weight < 27 kg) to 1.2 million IU (patient's weight > 27 kg) every 4 weeks is the recommended regimen in most circumstances. The interval is reduced to 3 weeks for individuals at high risk for developing acute RF or living in endemic areas.
   2. The duration of prophylaxis depends on the individual situation. Table 20.3 provides additional information.
      a. Prophylaxis for **recurrent RF in patients without cardiac manifestations** should be continued for 5 years after the last RF attack or up to the age of 21 years, whichever is longer.

TABLE 20.3 Duration of Therapy for Secondary Prevention of Rheumatic Fever

Disease state	Duration of therapy
RF + carditis + residual valvular disease	At least 10 y postepisode and at least until the age of 40 y. Lifelong prophylaxis may be required
RF + carditis without valvular disease	10 y or beyond adulthood, whichever is longer
RF without carditis	5 y or until the age of 21 y, whichever is longer

RF, rheumatic fever.

Adapted from Dajani AS. Rheumatic fever. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 1997:1769–1775.

b. For **patients with RF and carditis but no residual valvular disease**, prophylaxis should extend for a period of 10 years or well into adulthood.
c. Indefinite antibiotic prophylaxis is recommended in **patients with valvular heart disease**.

3. The success of **oral prophylaxis** depends on the patient's understanding and adherence to the prescribed regimen. Oral agents are **more appropriate for patients at lower risk for rheumatic recurrences**. Some favor switching patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of rheumatic attacks for at least 5 years.
a. The preferred oral medication is penicillin V.
b. For **patients with true or suspected allergy to penicillin, sulfadiazine** can be used (Table 20.2). **Erythromycin** is an alternative.
c. It is important to keep in mind that even with optimal patient adherence, the **risk of recurrence is higher with an oral than with an intramuscular prophylactic regimen**.

C. Endocarditis prophylaxis. Updated guidelines from the American Heart Association published in 2007 recommend against routine prophylaxis for endocarditis in patients with rheumatic valvular disease undergoing dental or other procedures. Antibiotic prophylaxis is recommended only for patients with prosthetic valves, previous endocarditis, and certain forms of congenital heart disease and for heart transplant patients with vasculopathy (see Chapter 19).

D. Vaccines targeted against GAS. Several multivalent vaccines against GAS are currently in clinical trials. The M protein is the most promising target, but vaccine development has been complicated because there are multiple M-protein subtypes that are rheumatogenic. The use of a vaccine may prevent pharyngeal colonization, thereby removing population reservoirs, which allow for endemic disease.

VII. SCREENING

A. Screening in endemic areas. Given the significant burden of rheumatic heart disease, screening children and young adults has proven useful for those in endemic areas.

1. Screening generally involves three components: (1) eliciting a history of acute RF, (2) physical examination, and (3) echocardiography. Two screening approaches have been described in high-risk populations. First, physical examination including auscultation for murmur is followed by echocardiographic confirmation in those found to have a murmur. Alternatively, portable echocardiography is used for all followed by clinical examination of abnormal cases. Because auscultation has been shown to be clinician dependent and crude in detecting valve pathology, many cases of rheumatic heart disease go unidentified, favoring the echocardiographic approach to screening.

ACKNOWLEDGMENTS: *The author thanks Drs. Stephen Gimple, Simone Nader, and Mohammed Nasir Khan for their contributions to earlier editions of this chapter.*

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SECTION IV

Arrhythmias

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CHAPTER 21

Omeed Zardkoohi

Tachyarrhythmias

I. INTRODUCTION. Tachyarrhythmias have been classically categorized by their location and mechanism. Tachyarrhythmias can originate from ventricular tissue (ventricular tachycardia) or, alternatively can originate from or involve supraventricular tissue (supraventricular tachycardia). The three mechanisms of tachyarrhythmias include abnormal automaticity, triggered activity, and reentry.

A. Abnormal automaticity. Automaticity refers to the ability of cardiac tissue to spontaneously generate pacemaker activity. There are both normal and abnormal sources of automaticity.

1. An example of **normal** accelerated automaticity is the rapid firing rates of a normal pacemaker focus, such as the sinus node (SN), atrioventricular (AV) node, or Purkinje system due to ischemia, metabolic disturbance, exercise, or pharmacologic manipulation. A clinical example would be accelerated **sinus tachycardia** or **junctional rhythm**.
2. Abnormal automaticity refers to tissues that under normal circumstances do not demonstrate automaticity, but can become automatic in the setting of ischemia, metabolic disturbance, or pharmacologic manipulation. Overall, abnormal automaticity is responsible for < 10% of tachyarrhythmias. These latent or ectopic loci of cells generate automatic, spontaneous impulses that usurp control of the cardiac rhythm. These usually have a warm-up and cool-down period and cannot be induced by programmed electrical stimulation. A clinical example would be **accelerated idioventricular** rhythm (see Section IV.C.1) or **multifocal atrial tachycardia** (see Section **II.F**).

B. Triggered activity refers to pacemaker activity that is dependent on afterdepolarizations from a prior impulse or series of impulses. Afterdepolarizations are oscillations in the membrane potential. If these reach the critical threshold for depolarization of the surrounding cardiac tissue, they may trigger an action potential, thereby precipitating further afterdepolarizations and perpetuating the pacemaker activity. The two categories of afterdepolarizations are early and delayed.

1. Early afterdepolarizations (EADs) occur before repolarization of the cardiac tissue is completed (during phase 3 of the action potential) and may be the mechanism responsible for the ventricular arrhythmias of the **long QT syndromes (LQTSs)**, as well as **torsade de pointes** ("twisting of the points") produced by class I and class III antiarrhythmics, sympathetic discharge, and hypoxia. Antibiotics such as macrolides, certain azole antifungal agents, some psychotropic medications such as haloperidol, and several nonsedating antihistamines have been shown to produce EADs. Rapid heart rates and the administration of magnesium have been shown to suppress EADs.
2. Delayed afterdepolarizations (DADs) occur after the repolarization of the surrounding tissue is complete (during phase 4 of the action potential) and are thought to be the mechanism of triggered atrial tachycardia, arrhythmias of **digitalis toxicity**, and rare ventricular tachycardias (VTs) responsive to calcium channel blockers. These have been demonstrated in various cardiac issues, including

parts of the conducting system, myocardial cells, and valve tissues. Increases in intracellular calcium are associated with DADs, such as those caused by digitalis preparations or excessive sympathetic stimulation. Drugs that block the influx of calcium (such as calcium channel blockers and β-blockers) and drugs that decrease the sodium current (such as lidocaine and phenytoin) suppress the occurrence of DADs, whereas rapid heart rates augment DADs.

C. Reentry. **Reentry is the most common cause of tachyarrhythmias**. In order for reentry to occur, **three conditions** must be met:

1. Two functionally distinct conducting pathways must connect to form a circuit.
2. Unidirectional conduction block occurs in one of the pathways due to differences in refractory periods (block occurs in pathway with the longer refractory period).
3. Slow conduction occurs down the unblocked pathway (which has the shorter refractory period), allowing the blocked pathway time to recover excitability and sustain the arrhythmia.

Reentrant circuits can occur in the sinus node, the atrium, the AV node, between the atrium and ventricle via bypass tracts, and within the ventricle itself. The typical substrate for malignant reentry in the ventricle is **scar or ischemia**, which can produce regions in the heart that **depolarize and repolarize heterogenously**. Therefore, the impulse can spread to an area that has already repolarized after being previously depolarized. This can set up a circular movement of the impulse resulting in sustained tachyarrhythmias such as VT. Reentry can typically be induced by premature electrical stimulation during electrophysiologic testing.

Elucidation of the mechanisms of tachyarrhythmias has led to the development of catheter-based treatment strategies and more advanced medical therapy.

II. SUPRAVENTRICULAR TACHYARRHYTHMIAS

A. Sinus tachycardia

1. **Clinical presentation.** Sinus tachycardia manifests as sinus rhythm with a rate above 100 beats/min. Although the rate may be as high as 200 beats/min in younger individuals, it is generally **150 beats/min or less in older individuals**.
2. **Pathophysiology**
   - **a.** The SN is an epicardial structure that is located laterally near the junction between the superior vena cava and the right atrium. Under normal circumstances, the rate of SN discharge is governed by sympathetic and vagal stimulation.
   - **b.** Sinus tachycardia generally reflects **an underlying process, metabolic state, or effect of medication**. Fever, hypovolemia, shock, congestive heart failure (CHF), anxiety, pulmonary disease including pulmonary embolism, anemia, thyrotoxicosis, caffeine, nicotine, atropine, catecholamines, or withdrawal from alcohol or drugs (both therapeutic and illicit) can cause sinus tachycardia.
   - **c.** Sinus tachycardia can be appropriate, where it represents a normal physiologic response, **or inappropriate**, as in defects in vagal or sympathetic tone or an intrinsic problem with the SN itself.
   - **d.** The **clinical consequences of sinus tachycardia vary** based on the presence or absence of underlying heart disease. Patients with significant coronary artery disease (CAD), left ventricular (LV) dysfunction, or valve disease may not tolerate sinus tachycardia. Patients with inappropriate sinus tachycardia may experience significant symptoms such as palpitations, dyspnea, and/or chest pain.
3. **Diagnostic testing.** Electrocardiography is the primary diagnostic test. The main differential is between sinus tachycardia, sinus node reentry tachycardia (SNRT) (see Section **II.B**), and inappropriate sinus tachycardia. Inappropriate sinus tachycardia is characterized by the following features: **(a) heart rate > 100 beats/min, (b) P-wave axis and morphology during tachycardia similar or identical to that during sinus rhythm, (c) exclusion of secondary causes**

of sinus tachycardia, (d) exclusion of atrial tachycardias, and (e) symptoms clearly documented to be related to resting or easily provoked sinus tachycardia.

4. Therapy is generally directed at the elimination of the underlying cause whenever possible.
   a. If withdrawal from a therapeutic medication is suspected, then reinstitution or slow tapering of this medication can be attempted, if clinically appropriate.
   b. In the case of **inappropriate sinus tachycardia, β-blockers and calcium channel blockers** may be necessary to control the heart rate.
   c. In **medically refractory cases, catheter ablation for sinoatrial nodal modification** may have to be considered.

B. SNRT accounts for 5% to 10% of all supraventricular tachyarrhythmias.

1. **Clinical presentation.** SNRT is most frequently seen in patients with structural heart disease or CAD, especially in inferior myocardial infarctions (MIs). The rate varies from 80 to 200 beats/min. SNRT's characteristic abrupt onset and termination (paroxysmal nature) along with its ability to be induced and terminated by pacing imply that the underlying mechanism is reentry and distinguish it from sinus tachycardia and inappropriate sinus tachycardia.
2. **Pathophysiology.** Reentry occurs within or adjacent to the SN and then conducts via the normal conduction pathway to the rest of the heart. The morphology of the P wave is identical to the underlying sinus morphology. Block at the AV node may occur, but it does not slow the tachycardia. In fact, a Wenckebach-type block often occurs with this rhythm. The development of a bundle branch block does not affect the cycle length or the PR interval.
3. **Therapy.** Vagal maneuvers or adenosine may successfully terminate this arrhythmia. **Rapid atrial pacing** can be used to induce and terminate this tachycardia. Various agents such as β-blockers, calcium channel blockers, and digoxin may help prevent recurrences. SN ablation or modification is rarely necessary.

C. Atrial fibrillation (AF) is the most common sustained arrhythmia, occurring in up to 1% of the general population. The prevalence of AF increases with age, affecting up to 10% of the population older than 80 years (see Chapter 24).

D. Atrial flutter. Atrial flutter is the **second most common of the atrial tachyarrhythmias**. Its reported incidence varies from 0.4% to 1.2% in hospital reports of electrocardiogram (ECG). The **clinical significance of atrial flutter is generally due to its association with AF** (with all of the attendant risks of AF) and/or its association with rapid rates of ventricular response.

1. **Clinical presentation.** The clinical presentation may vary widely depending on the presence of underlying heart disease, the ventricular rate, and the overall condition of the patient. It is **occasionally reported to persist for days** and, less commonly, for weeks or longer. Careful examination of the jugular venous pulse may reveal **frequent, regular a waves** that correspond to the atrial flutter rate. Like AF, it is **commonly seen after open heart surgery, as well as with other conditions commonly associated with AF**, such as pulmonary disease, thyrotoxicosis, atrial enlargement due to any cause including mitral/tricuspid valve disease, and SN dysfunction.
2. **Pathophysiology.** "Typical" atrial flutter is the **result of a macroreentrant circuit in the right atrium**. Atypical atrial flutter generally involves other macroreentrant circuits around scar tissue or surgical incisions.
   a. **In a typical atrial flutter, the reentrant circuit most commonly travels in a counterclockwise rotation** down the right atrial anterolateral free wall across the cavotricuspid isthmus (area of slow conduction) and up the interatrial septum. Clockwise rotation of this circuit may also be seen.

b. Atrial flutter has been classified into type I and type II based on the following characteristics:

(1) Type I atrial flutter can be terminated with rapid atrial pacing and typically has an atrial rate in the range of 240 to 340 beats/min in the absence of drug therapy.

(2) Type II atrial flutter cannot be terminated with rapid atrial pacing and typically has an atrial rate in the range of 340 to 440 beats/min in the absence of drug therapy.

(3) Types I and II are not synonymous with typical and atypical atrial flutters. Type I atrial flutter can include typical and atypical atrial flutters. Type II atrial flutter is less well characterized than type I with respect to etiology and therapy; therefore, **we refer to type I atrial flutter throughout this discussion**.

3. Laboratory examination

a. The **diagnosis can be difficult when the AV conduction is 2:1**, as the flutter waves may be superimposed on the QRS complex and/or the T waves. When the diagnosis is uncertain, one should **consider maneuvers or medications to slow the ventricular response**, thus revealing the atrial flutter complexes.

(1) Vagal maneuvers include carotid sinus massage and Valsalva maneuver. **Caution must be exercised** when attempting carotid sinus massage **in patients with known or suspected carotid disease** or vagal maneuvers in **patients with CAD who are at risk for ischemia**.

(2) Adenosine can be administered, 6 mg rapid intravenous push, followed by 12 mg if there is no response (a second 12-mg dose can be given if there is no response). The half-life of this medication is very short, approximately 9 seconds. This causes transient (lasting seconds), complete AV block. Alternative agents include the intravenous calcium channel blocking agents **verapamil and diltiazem** and the intravenous β-blockers **esmolol and metoprolol**. Patients should be connected to a transcutaneous pacing device during the administration of this medication for reasons of safety.

(3) The clinician can place and record from a **transesophageal electrode** or record from a **temporary atrial epicardial pacing wire** (placed at open heart surgery). This results in an ECG with clearer atrial complexes and thus simplifies diagnosis. This strategy also allows a method of delivering rapid atrial pacing in an attempt to terminate the atrial flutter.

b. On the surface ECG, typical counterclockwise atrial flutter shows the **classic negatively directed "sawtooth" waveform** in the inferior leads (II, III, and aVF) (Fig. 21.1). Conversely, the atrial depolarizations are positive in these leads in clockwise atrial flutter (Fig. 21.2).

c. The **atrial rate** in the absence of drug therapy is **240 to 340 beats/min**.

d. The **QRS complex should be the same as that seen during sinus rhythm** although aberrant conduction may occur, and the QRS may be slightly distorted by the atrial flutter waves.

e. The **ventricular response** can be irregularly irregular, due to varying degrees of block (2:1, 4:1, and so on), but is more **typically regular as a fixed ratio of the flutter rate**.

4. Therapy

a. Medical therapy differs very little from that for AF (see Chapter 24).

(1) Control of the ventricular response rate with a β-blocker, a calcium channel blocker, or digoxin is critical prior to initiating therapy with agents such as the class IA or IC agents. The class IA or IC agents either enhance AV nodal conduction through their vagolytic effects, thereby enabling 1:1 (AV) conduction, or slow the atrial rate to a point where 1:1 conduction is facilitated.

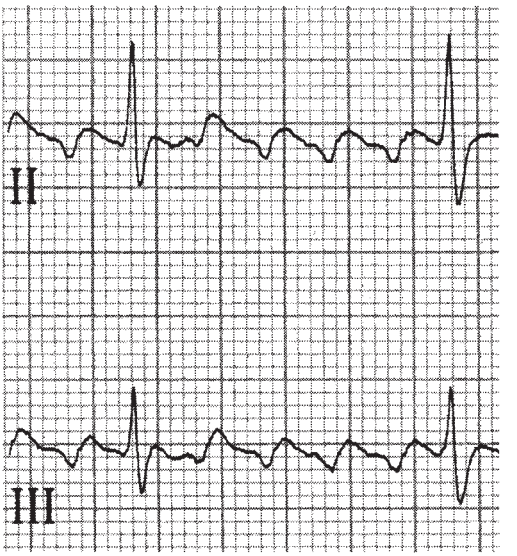


FIGURE 21.1 "Typical" atrial flutter, leads II and III.

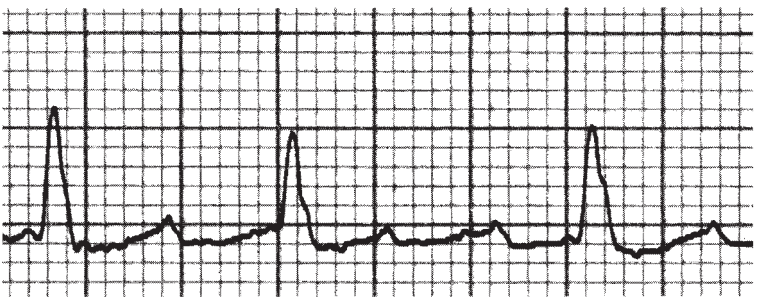


FIGURE 21.2 "Atypical" atrial flutter, lead II.

(2) The conversion from atrial flutter to AF after cardioversion is substantially reduced by the administration of antiarrhythmic drugs prior to direct current cardioversion (DCC), thereby increasing the chance of converting to sinus rhythm.

(3) **Anticoagulation.** There are no prospective data looking at the incidence of thromboembolic events with atrial flutter. However, retrospective data suggest an increased incidence of thromboembolic events. Recent ACCP (2004) and ACC/AHA/ESC (2006) guidelines recommend managing anticoagulation in atrial flutter in a manner similar to that for AF, including cardioversions. Optimal management is unclear and often needs to be individualized with the patients' profile for thromboembolic risk dictating the type and duration of therapy. We treat atrial flutter in a manner similar to that used for AF with regard to anticoagulation.

b. Direct current cardioversion

(1) DCC is the preferred and most effective therapy for most patients. The procedure is detailed in Chapter 59. A starting energy as low as 25 to 50 J is often effective. Because DCC may result in conversion from atrial flutter to AF, a second shock is sometimes necessary to convert AF to sinus rhythm.

(2) Rapid atrial pacing should be considered as the **first line of therapy for all patients who have epicardial atrial pacing wires in place after open heart surgery**. It may be considered via a transesophageal pacing lead or via a transvenously placed pacing lead in patients for whom DCC fails or who are not candidates for DCC. **Before attempting to rapidly pace the atria, it must be confirmed that ventricular capture is not inadvertently occurring** by first pacing at a relatively slow rate while observing for such a phenomenon. Once this is confirmed, the atrium is paced at a rate of 10 to 20 beats/min faster than the underlying atrial flutter rate. Once atrial capture is attained, the rate is increased steadily until the hallmark negative-sawtooth waveform converts to a positive waveform. The pacing is then either halted abruptly or slowed rapidly to an acceptable atrial pacing rate. In cases that require extremely rapid rates of pacing (> 400 beats/min) or high amplitudes of pacing stimulus strength (> 20 mA), there is an increased tendency for the atrial flutter to convert to AF. **When pacing via a transesophageal lead, a higher stimulus strength (up to 30 mA) may be necessary**. **Because this type of pacing can be quite painful**, a sufficient energy to convert the atrial flutter should be used initially to minimize the conversion attempts.

(3) Percutaneous therapy. Radiofrequency ablation (RFA) of the cavotricuspid isthmus is often curative, with an efficacy > 90% for the long-term elimination of atrial flutter. Despite the high success rate of catheter-based therapy, a significant number of patients may subsequently develop AF.

E. Atrial tachycardias. This term encompasses a number of different types of tachycardias that originate in the atria. These tachycardias account for between10% and 15% of the tachycardias seen in older patients, usually in the setting of structural or ischemic heart disease, chronic obstructive pulmonary disease, electrolyte imbalances, or drug toxicity (particularly digitalis).

1. Clinical presentation. These tachycardias are **infrequently seen in younger, healthy patients without underlying heart disease**. They are **typically paroxysmal**, but if incessant they can lead to a tachycardia-induced cardiomyopathy.

2. Diagnostic testing

a. ECG

(1) The **P-wave axis** or morphology is usually different from that of sinus rhythm. One exception is atrial tachycardias originating from the right superior pulmonary vein, which is anatomically close to SN. The axis can be used to predict the origin of the atrial tachycardia.

(2) Atrial rhythm is regular, except with automatic atrial tachycardia, which displays a warm-up period (see Section **II.E.3.b**).

(3) A **QRS complex that is generally identical to sinus rhythm** (QRS can be wide if aberrant conduction occurs) follows each P wave.

(4) PR interval is within normal limits or prolonged.

(5) Nonspecific ST-T–wave changes may be present.

(6) When an AV block is present, there is an **isoelectric baseline** between P waves in all leads.

b. Electrophysiologic study has become critical in determining the underlying mechanism of these tachycardias, as the clinical differences are subtle and overlapping.

3. **Subclassifications.** The current subclassifications are **based on mechanisms** and include automatic atrial tachycardia, triggered atrial tachycardia, and intra-atrial reentry.
   a. Intra-atrial reentry is usually a disorder **seen in those with underlying heart disease or history of atrial arrhythmia**, such as AF or atrial flutter. The mechanism is not well understood. The ventricular rate is typically 90 to 120 beats/min due to the frequent occurrence of 2:1 AV block, such that hemodynamic effects are generally minimal. This rhythm can be difficult to distinguish from other supraventricular tachyarrhythmias. One clue is that despite any AV conduction block, the rhythm continues. The ability to terminate with adenosine and β-blockers is variable. **RFA may be effective**, with success rates **>** 75%. **Antiarrhythmics** (the same drugs as for AF and atrial flutter) **have been disappointing in the prevention of recurrence**.
   b. Automatic atrial tachycardia appears to be generated by an ectopic atrial focus, which usually arises from regions around the crista terminalis in the right atrium and around the base of the pulmonary veins in the left atrium. The mechanism is not well understood. Automatic atrial tachycardia is **seen more often in younger patients**, displays a **warm-up phenomenon** (the supraventricular tachyarrhythmia accelerates after its initiation), **does not respond to vagal maneuvers, and is more likely to be incessant**. Automatic atrial tachycardia can be induced with treadmill testing or with administration of isoproterenol. Atrial stimulation during electrophysiologic study has no effect on either initiating or terminating this arrhythmia. **Propranolol** has been used successfully to suppress automatic atrial tachycardia. **Catheter ablation is the preferred therapy when the tachycardia is incessant**. Although adenosine may transiently slow automatic atrial tachycardia, it is unlikely to terminate it. Likewise, verapamil has been used without success.
   c. Triggered atrial tachycardia is the least common of the atrial tachycardias and is virtually never incessant. It is more likely to appear in **older individuals**. It can be induced with rapid atrial pacing and is cycle length–dependent. The mechanism of triggered atrial tachycardia is thought to be due to DADs (see Section **I.A.2**) secondary to digitalis toxicity or sympathetic discharge. Catecholamines may play a role in the initiation of this arrhythmia, and thus exercise testing and isoproterenol may provoke it. Verapamil and adenosine have been shown to terminate triggered atrial tachycardia. β-Blockers have been less effective. **RFA** is preferred when the tachycardia is very symptomatic and not responsive to medication.

F. Multifocal atrial tachycardia

1. **Clinical presentation.** This atrial arrhythmia is uncommon and estimated to occur in 0.37% of hospitalized patients. The atrial rate is generally 100 to 130 beats/min. It occurs most often in elderly, critically ill patients and is frequently **associated with concurrent pulmonary disease, particularly chronic obstructive pulmonary disease**. It may also be seen in CHF and can degenerate into AF.
2. **Pathogenesis and diagnostic tests.** The mechanism appears to be abnormal automaticity or triggered activity arising from distinct atrial sites. The diagnosis requires the following criteria: (1) atrial rate > 100 beats/min, (2) P waves with three or more different morphologies, (3) varying P-P, P-R, and R-R intervals, and (4) the P waves separated by isoelectric intervals. Loss of AV conduction of each P wave is uncommon, making it possible to distinguish multifocal atrial tachycardia from AF.
3. **Therapy is directed at the underlying illness, with little role for antiarrhythmics.** Calcium channel blockers in high doses may be useful, or amiodarone when antiarrhythmic therapy is deemed necessary. Maintenance of electrolyte balance, particularly potassium and magnesium, may suppress the occurrence of multifocal atrial tachycardia.

G. Atrioventricular nodal reentrant tachycardia (AVNRT)

1. **Clinical presentation.** AVNRT usually has a narrow QRS complex with a ventricular rate typically in the range of 150 to 250 beats/min, although faster rates are infrequently observed. AVNRT is generally seen in patients without underlying heart disease. Palpitations and dyspnea are common presenting complaints. Angina, CHF, and rarely shock may be seen in those with a history of underlying heart disease. Syncope may occur due to rapid ventricular rates or due to asystole or bradycardia seen occasionally when this tachycardia terminates.
2. **Pathophysiology.** The mechanism in AVNRT appears to be a reentrant circuit composed of separate fast and slow atrial pathways involving the AV node. In 50% to 90% of patients with "typical" AVNRT, the antegrade conduction to the ventricles travels over the slow pathway and the retrograde conduction to the atria occurs over the fast pathway. The initiating event may be either a premature atrial complex (PAC) or a premature ventricular complex (PVC). The PAC blocks the fast pathway antegradely and conducts down the slow pathway, then backs up the fast pathway after it has repolarized. Less commonly, a PVC conducts retrogradely to the atria via the fast pathway and then returns to the ventricles via the slow pathway. In the remaining 5% to 10% of patients, with atypical AVNRT, the antegrade conduction is down the fast pathway and retrograde via the slow pathway. The cycle length is thus dependent on the conduction velocity of the slow pathway, since the fast pathway generally has rapid conduction. Termination of the tachycardia is often the result of a block in the slow pathway. AV dissociation may develop during the tachycardia because the ventricles are not involved in the reentry circuit. This does not affect the rate of tachycardia nor does the development of bundle branch block.
3. **Laboratory features and diagnosis.** P waves are generally hidden within the QRS complex or at the terminal portion of the QRS in typical AVNRT. This may be visible as a small pseudo-R′ in lead V_1 or small negative deflections in the inferior leads, as depolarization of the atria occurs simultaneously with ventricular depolarization. The RP segment is generally < 100 milliseconds. AVNRT is often induced abruptly by a PAC and its termination, which also tends to be abrupt, is often followed by a retrograde P wave. The termination may be followed by a brief period of asystole or bradycardia before the SN recovers from its tachycardia-induced suppression. The cycle length may vary, especially at the beginning and at the end of the tachycardia. This variation reflects the variable antegrade AV nodal conduction time. Vagal maneuvers may slow or terminate this tachycardia.
4. **Therapy.** Presently, the success and safety of percutaneous catheter ablation have allowed this approach to be considered equally with medical therapy as first-line therapy for long-term management of AVNRT. The decision about treatment approach should be individualized according to the characteristics of each patient and his or her arrhythmic patterns.
   a. RFA has the advantage of curing the arrhythmia in the majority of instances and eliminating the need for long-term suppressive therapy with medications. Cure rates with catheter ablation for AVNRT are in excess of 95%.
   b. **Medical therapy.** Medications that suppress AV nodal conduction such as β-blockers, calcium channel blockers, digoxin, and adenosine all slow or block conduction in the antegrade slow pathway, whereas class IA and class IC antiarrhythmic drugs slow the conduction in the retrograde fast pathway. Adenosine may be considered as first-line drug therapy for acute termination of AVNRT. This medication is available in an intravenous form only and has a very short half-life of about 9 seconds. The use of intravenous or oral β-blockers or calcium channel blockers is an alternative if adenosine is unsuccessful. The onset of action of digoxin limits its usefulness in terminating these arrhythmias, although it may be useful to prevent recurrences. Recurrences may be prevented in patients

with frequent sustained episodes with any of the above-mentioned agents except adenosine. Antiarrhythmic drug therapy is not routinely necessary or desirable for AVNRT, given the high success rates and low complication rates for catheter ablation.

c. DCC should be considered for patients whose disease is unstable or highly symptomatic. Low energies of 10 to 50 J are usually sufficient to terminate AVNRT.

H. Atrioventricular reentrant tachycardia (AVRT)

1. **Clinical presentation.** Similar to AVNRT, this is another example of an AV nodal–dependent supraventricular tachycardia (SVT). AVRT usually has a narrow QRS with ventricular rates similar to those of AVNRT, although it more often tends to have a ventricular rate > 200 beats/minute. The clinical features are very similar to those of AVNRT but are distinct on an electrophysiologic basis.
2. **Pathophysiology.** The mechanism in AVRT relies on the presence of an accessory pathway as one portion of the circuit and the AV node as the other portion. The atrium and the ventricle on the same side as the accessory pathway are necessary components of the circuit. AVRT may be orthodromic or antidromic. Orthodromic AVRT usually has a narrow complex that uses the AV node as the antegrade limb and the accessory pathway as the retrograde limb of the circuit. Antidromic AVRT has a wide complex that is the opposite of the orthodromic variety, such that the accessory pathway serves as the antegrade limb and the AV node as the retrograde limb of the circuit. AVRT is most often of the orthodromic type. Accessory pathways may be "concealed" (inapparent by ECG) because of having only retrograde (V to A) conduction properties or "manifest" (apparent on ECG as delta waves, i.e., Wolff-Parkinson-White [WPW] pattern). **Unlike AVNRT, the AVRT circuit must involve one of the ventricles; therefore, the development of bundle branch block on the side ipsilateral to the accessory pathway can prolong the ventricular to atrial conduction time and often the cycle length of the tachycardia**. Bundle branch block, particularly left bundle branch block (LBBB), occurs more commonly in AVRT than in AVNRT. AVRT can be distinguished from AVNRT by electrophysiologic study. The presence of AV or ventriculoatrial (VA) block with continuation of the tachycardia should exclude the presence of an accessory AV pathway.
3. **Laboratory features and diagnosis.** The P waves of AVRT are frequently inscribed on the ST segment or T wave, as the atrial depolarization and ventricular depolarization are in series rather than in parallel. The RP segment is generally > 100 milliseconds. Orthodromic AVRT is more common, accounting for about 95% of all AVRTs, whereas antidromic AVRT accounts for only about 5%. Orthodromic AVRT is usually characterized by a narrow QRS complex as opposed to antidromic AVRT, which is characterized by a wide QRS complex.
4. **Therapy.** See the discussion of therapy for WPW syndrome (Section **I.4**).

I. Preexcitation syndromes. Preexcitation was originally used to describe the premature activation of ventricle in patients with WPW. The term has broadened to include all conditions in which antegrade ventricular activation or retrograde atrial activation occurs partially or totally via an anomalous pathway distinct from the normal cardiac conduction system. The incidence of preexcitation on ECG is approximately 1.5 per 1,000 cases, most of which occur in otherwise healthy subjects without organic heart disease. About 7% to 10% of these patients have associated Ebstein's anomaly and are thus more likely to have multiple accessory pathways. There is a higher rate of preexcitation in males, with the **prevalence** decreasing with age, although the **frequency** of paroxysmal tachycardia increases with age.

1. **Clinical presentation.** Approximately 50% to 60% of patients with preexcitation report symptoms such as **palpitations, anxiety, dyspnea, chest pain or tightness, and syncope**. In approximately 25% of the cases, the disease will

become asymptomatic over time. Those patients older than 40 years whose disease has been asymptomatic are likely to remain symptom free. The absence of preexcitation on ECG despite the discovery of accessory pathways in patients with asymptomatic disease likely identifies a group of patients at low risk for developing symptoms.

2. **Pathophysiology.** Patients with preexcitation generally have an accessory pathway(s) that alters the conduction between the atria and the ventricles. These accessory pathways are likely congenital, as relatives of subjects with preexcitation have an increased incidence of preexcitation. AVRT is the most common mechanism associated with preexcitation (80% to 85%), with permanent junctional reciprocating tachycardia, Mahaim fiber tachycardia, and Lown-Ganong-Levine (LGL) syndrome accounting for the remainder.
   a. **WPW syndrome.** The basic abnormality lies in the existence of an accessory pathway of conducting tissue, outside of the normal conducting system, which connects the atria and the ventricles. This accessory pathway permits the atrial impulse to bypass the normal pathway through the AV node to the ventricles. In the past, these accessory pathways have been referred to as "bundles of Kent." An impulse from the atria can be conducted down both the accessory pathway and the AV node, arriving at the ventricle at nearly the same time. This results in preexcitation of the ventricle, which is really a fusion beat, as a portion of the ventricle is activated via the accessory pathway (giving rise to the delta wave; Fig. 21.3) and the remainder of the ventricle is activated by the normal activation pathway. If antegrade conduction occurs exclusively via the accessory pathway, the resultant QRS is maximally preexcited and is a wide complex. These accessory pathways may conduct rapidly, but frequently have longer refractory periods than the AV node. The inciting event for AVRT is frequently a PAC that is blocked in the accessory pathway and that conducts to the ventricles via the AV node, which has recovered more rapidly. The resultant QRS complex in this instance is normal in appearance. After the QRS complex, the accessory pathway has had sufficient time to recover excitability, and the impulse thus conducts retrogradely to the atria. A small but significant percentage (5% to 10%) of patients have multiple accessory pathways.
   b. Permanent junctional reciprocating tachycardia is a variant of AVRT. It is often an incessant supraventricular tachyarrhythmia with an unusual accessory pathway. Here, the accessory pathway behaves like the AV node in that it displays decremental retrograde conduction properties. Thus, the faster the stimulation of such an accessory pathway, the slower the conduction through the pathway. The accessory pathway is most often located in the posteroseptal region and acts as the retrograde limb of the reentrant circuit. The VA conduction is slowed by the decremental nature of the accessory pathway. Due to the incessant nature of this tachycardia, a tachycardia-induced cardiomyopathy may result.
   c. **Mahaim fiber tachycardias are another variant of reentrant tachycardia.** The two most common varieties that are recognized are **atriofascicular and fasciculoventricular.** In the former, the accessory pathway is located within a few centimeters of the AV node and inserts into the right bundle branch. The reentrant tachycardia conducts antegrade via the accessory pathway, resulting in an LBBB morphology with left-axis deviation. The retrograde circuit is via the AV node. In the second form of Mahaim reentry, the accessory pathway arises in the His-Purkinje fibers and allows bypass of the distal conducting system.
   d. LGL syndrome is diagnosed by the presence of a short PR interval and a normal QRS complex on the surface ECG. LGL syndrome likely represents one

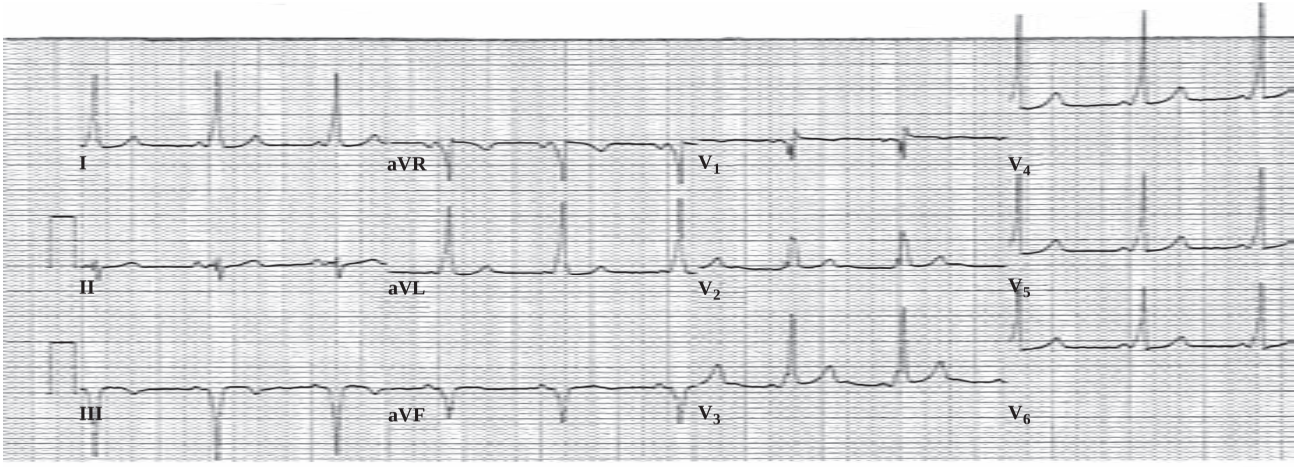


FIGURE 21.3 Wolff-Parkinson-White syndrome, with widespread delta waves seen at the upstroke of the QRS complexes.

end (enhanced) of the normal spectrum of AV nodal conduction properties, but in some cases it is impossible to exclude a distinct perinodal accessory pathway or an abnormality in conduction characteristics of the AV node. It is uncertain if this abnormality in AV conduction is itself associated with arrhythmias.

3. Diagnostic testing

a. The following electrocardiographic criteria are suggestive of an accessory pathway consistent with a WPW pattern. The WPW syndrome occurs in the setting of the WPW pattern and SVT.

(1) The PR interval is short, typically < 120 milliseconds.

(2) The QRS complex exceeds 120 milliseconds, with some leads showing the characteristic slurred upstroke known as a delta wave (Fig. 21.3) and a normal terminal QRS portion.

(3) The ST-T segment is directed opposite to the major delta and QRS vectors.

b. The most commonly seen tachycardia in WPW syndrome is characterized by a normal QRS with a regular rate of 150 to 250 beats/min. Onset and termination are abrupt.

c. Localization of accessory pathway. The **surface ECG** may provide information that allows localization of the accessory pathway. The simplest classification is that of type A or type B. **Type A** has a large R wave in lead V_1. It is due to a left-sided accessory pathway, which permits preexcitation to the posterobasilar segment of the left ventricle. **Type B** has an S or QS in lead V_1 and is due to a right-sided accessory pathway. When present, the morphology of a retrograde P wave can be helpful in predicting the location of the accessory pathway. More elaborate algorithms for localization are available. The **most precise localization method is electrophysiologic study** with ventricular pacing or during orthodromic AVRT (the latter condition is especially helpful as there is VA conduction purely through the accessory pathway, and fusion with VA conduction through the AV node is, therefore, avoided). A positive P wave in lead V_1 during supraventricular tachyarrhythmia suggests a left free wall pathway, whereas a negative P wave suggests a right-sided pathway.

d. Risk stratification should be considered for patients with WPW pattern or ventricular preexcitation according to ECG findings. The appearance or disappearance of preexcitation on **serial ECGs is of no predictive value**. However, **the intermittent loss or appearance of preexcitation on a beat-to-beat basis is indicative of lower risk**. This may be assessed with ambulatory Holter monitoring during usual activities or with formal exercise stress testing. Such intermittent preexcitation suggests a pathway without the ability for rapid AV conduction and, therefore, lower risk of sudden cardiac death (SCD). However, the reverse is not necessarily true in that most patients with persistent preexcitation may still be at low risk for SCD, but these patients cannot be distinguished from those at risk. As the greatest danger to patients with preexcitation may be the development of AF, **the induction of AF may be most useful in risk stratification**. This can be done via transesophageal pacing; however, electrophysiologic study is the procedure of choice for risk stratification in patients with persistent ventricular preexcitation.

4. Therapy

a. Emergency management of acute tachycardia episodes. A patient ***demonstrating hemodynamic instability or extreme symptomatology should be cardioverted rapidly***. Stable patients may be treated medically.

(1) Normal QRS width. Both types of AVRT (orthodromic and antidromic) are AV node–dependent and thus respond to AV nodal blocking therapies. Although it is reasonable to use vagal maneuvers and AV nodal

blocking medications acutely in patients presenting with a narrow QRS (immediate synchronized DCC should be available should the rhythm degenerate), it is not safe in patients when they present with a wide QRS. Atrial pacing, either transvenous or transesophageal, is also quite efficacious for terminating these types of tachycardias. Adenosine, although effective in treating orthodromic and antidromic AVRTs, may induce AF in up to 15% of cases and should, therefore, be used with caution. In patients with WPW syndrome, AF is a potentially life-threatening arrhythmia, especially when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction.

(2) **Wide QRS width.** Patients with accessory pathways can present with wide QRS complex resulting from **(1)** orthodromic AVRT with aberrant conduction; **(2)** antidromic AVRT; or, **most importantly**, **(3)** atrial arrhythmias (atrial tachycardia/atrial flutter/atrial fibrillation) with antegrade conduction down an accessory pathway. Since it is often initially impossible to determine the mechanism of a wide QRS complex in patients with an accessory pathway, they should be treated with agents that slow conduction in the accessory pathways (procainamide, flecainide, sotalol, or amiodarone). Because atrial arrhythmias with antegrade accessory pathway conduction are **not** AV node–dependent, AV nodal blocking therapies are ineffective and potentially very dangerous. β-Blockers, calcium channel blockers, digoxin, and adenosine should be avoided in patients presenting with wide complex tachycardias (WCTs), as they may encourage preferential conduction down accessory pathways and accelerate ventricular rates, precipitating ventricular fibrillation (VF). **If the tachycardia persists, synchronized DCC** is the treatment of choice. Energies of at least 200 J are likely to be required.

(3) If the patient develops AF, it has been observed that **definitive therapy for the AV reentrant circuit, such as ablation of the accessory pathway, often results in the prevention of future episodes of AF**.

b. Long-term management

(1) **Priority of therapy.** Patients whose disease is asymptomatic at diagnosis are at low risk for sudden death. As such, it may not be justified to pursue medical or ablative therapy in these patients unless there is a family history of sudden death or the patients are competitive athletes or are in a high-risk occupation. Patients whose disease is symptomatic or who have a history of AF or aborted sudden death may be at higher risk, and such patients warrant further study.

(2) **Medical therapy.** Medical therapy may be **appropriate for those with increased risk but no prior symptoms, those with accessory pathways located near the normal conduction pathway that might develop AV block with RFA**, or those at increased risk from invasive procedures. Single-drug therapy may be attempted with **amiodarone, sotalol, flecainide, or propafenone**. These drugs work to slow conduction in both the accessory pathway and the AV node. **Combination therapy** can be accomplished with drugs that work on the AV node (calcium channel blockers, β-blockers) and with drugs that work exclusively on the accessory pathway (class IA antiarrhythmics).

(3) **Percutaneous therapy.** RFA is effective 85% to 98% of the time, depending on the location of the accessory pathway. Recurrence rates are approximately 5% to 8%. Catheter ablation should be considered for any patient at high risk, patients with symptoms or tachycardias refractory to medical therapy, those who have intolerance to medical therapy, and those with high-risk occupations such as pilots.

J. Atrial premature depolarizations (APDs). APDs are premature depolarizations that arise from a region other than the SN. The P-wave morphology and PR interval may be different from the sinus P wave and normal P interval, depending on the location and timing of the APD.

1. **Clinical presentation.** APDs are usually asymptomatic and in isolation are considered to be benign. Some patients may feel palpitations or skipped beats. If there is atrial bigeminy with each APD causing AV block, patients may develop symptoms of bradycardia. APDs may trigger SVT (AVNRT, AVRT, and atrial tachycardia) or AF in patients with the electrical and structural substrate for these arrhythmias. APDs increase in frequency as patients age and may be more frequent in patients with mitral valve disease, LV dysfunction, hypertrophic cardiomyopathy (HCM), mitral stenosis, pulmonary disease, and renal failure. Stress, alcohol and caffeine consumption, and smoking can promote APDs. However, APDs also occur in healthy individuals with structurally normal hearts and without significant external exposures (caffeine, alcohol, and stress). Although one study showed a correlation between the frequency of APDs within a 24-hour period and the risk of stroke in men, it is unclear what percentage of these men developed AF. Furthermore, in the ARIC (Atherosclerosis Risk in Communities) study which followed patients with APDs and ventricular premature depolarizations (VPDs), patients with APDs only did not have increased incidence of SCD.
2. **Pathophysiology.** APDs may be caused by a variety of mechanisms, including reentry, triggered activity, and increased automaticity. Reentry is thought to be the most common mechanism.
3. **Therapy.** Asymptomatic individuals do not need treatment for APDs. For symptomatic patients, β-blockers and class IA, class IC, and class III antiarrhythmic drugs may be considered, although no randomized controlled trials have been performed in this patient population.

III. VENTRICULAR TACHYARRHYTHMIAS.

Ventricular tachyarrhythmias, including monomorphic VT, polymorphic VT, and VF, account for up to 80% of SCD.

A. Ventricular tachycardia. VT is defined as three or more consecutive QRS complexes of ventricular origin at a rate exceeding 100 beats/min. The various types of VTs and their course of disease are discussed in Section **IV**.

1. **Clinical presentation.** The presentation is variable and depends on the clinical setting, the heart rate, the presence of underlying heart disease, and other medical conditions. Some patients have no or minimal symptoms, whereas others may present with syncope or sudden death. The loss of normal AV synchrony may cause symptoms in patients with decreased cardiac function at baseline. Heart rates < 150 beats/min are surprisingly well tolerated in the short-term, even in the most compromised individuals. Exposure to these rates for more than a few hours is likely to be associated with heart failure in patients with poor ventricular function, whereas those with normal ventricular function may tolerate prolonged periods at such rates. The range of 150 to 200 beats/min is tolerated variably, according to the factors noted previously. Once the rate reaches and exceeds 200 beats/min, there are symptoms in virtually all patients. **Nonsustained ventricular tachycardia** (NSVT) is generally defined as a VT of duration < 30 seconds. VT is **generally regular in rate and appearance**, although it can be polymorphic in appearance, slightly irregular with respect to rate, and may have capture and/or fusion beats within it.
2. **Differential diagnosis.** VT needs to be distinguished from **supraventricular tachyarrhythmia with aberrant intraventricular conduction, bundle branch block, and morphologic changes of the QRS complex secondary to metabolic derangement or pacing**.

a. **Brugada criteria.** Distinguishing VT from **supraventricular tachyarrhythmia with aberrancy** can be challenging. Various criteria have been proposed. A good rule of thumb **is that any WCT in a patient with ischemic heart disease is VT until proven otherwise**. Some have reported that > 80% of WCTs in such patients are VTs. The **algorithm proposed by Brugada may be helpful in making this distinction, and the algorithm is both sensitive** (99%) **and specific** (96.5%) in patients without a preexisting bundle branch block. As shown in Figure 21.4, a stepwise approach is applied. In the first step, the precordial leads are examined for the presence or absence of an RS complex. If an RS is uniformly absent, VT is established. If an RS is present in at least one precordial lead, one moves to the second step, which is measuring the interval from the onset of the QRS complex to the nadir of the S wave. If this distance is > 100 milliseconds in at least one precordial lead, then the diagnosis of VT is made. If there is no RS interval > 100 milliseconds, the third step is used. In the third step, one looks for evidence of AV dissociation. If there are more QRS complexes than P waves, then the diagnosis is VT. If not, then one moves to the fourth step, which involves examining the morphology of the QRS in the precordial leads V_1 and V_6. If the morphology criteria for VT (Fig. 21.5) are present in these leads, then the diagnosis of VT is established. If not, the diagnosis is supraventricular tachyarrhythmia with aberrant intraventricular conduction.

b. The Brugada criteria have been further refined to distinguish between VT and supraventricular tachyarrhythmia with antegrade conduction over an accessory pathway. After applying the preceding criteria, a second stepwise algorithm is applied (Fig. 21.6). This **second algorithm has a sensitivity of 75% and a specificity of 100% to diagnose VT and exclude preexcited tachycardia**. In the first step, leads V_4 to V_6 are examined to see if the QRS is predominantly negative. If so, then VT is favored. If not, then the second step, examining leads V_2 to V_6 for the presence of a QR complex in one or more of these leads, is applied. If there is a QR complex in any of these leads, then the diagnosis is VT. The third criterion, presence of AV dissociation, is 100% specific for VT. If there is no AV dissociation, then supraventricular tachyarrhythmia with antegrade accessory pathway conduction is favored.

c. A new criterion for differentiating VT from SVT was published in 2008 by Vereckei et al. (1), which boasts a > 90% accuracy in their cohort (Fig. 21.7). The rationale to use the new method was to simplify the approach by using one electrocardiographic lead (aVR) in a four-step, tree-like model. The method starts with identifying the presence of an initial R wave in aVR. If present, VT is diagnosed. If not, then the next step is to assess the presence of an initial R or Q wave > 40 milliseconds, and if present, is VT. If this criterion is not satisfied, then the presence of a notch on the descending limb of a negative onset and predominantly negative QRS gives the diagnosis of VT. If this is not present, then one should compare the voltage of the initial 40 milliseconds (V_i) with the voltage of the terminal 40 milliseconds (V_t) of the QRS complex. If $V_i/V_t \leq 1$, then it is VT. If none of these criteria are satisfied, then SVT is diagnosed.

3. **Therapy**

a. **General management.** The treatment of VT may involve DCC, discontinuation of offending proarrhythmic drugs, specific antiarrhythmic therapy with drugs, correction of electrolyte imbalances, implantable devices, ablation, revascularization, and surgery. The appropriate selection of the preceding therapies is aided by the assessment of the patient, an understanding of the etiology and mechanism of the VT, knowledge of any exacerbating medical conditions contributing to the VT, and the risk-to-benefit ratio of the available therapies.

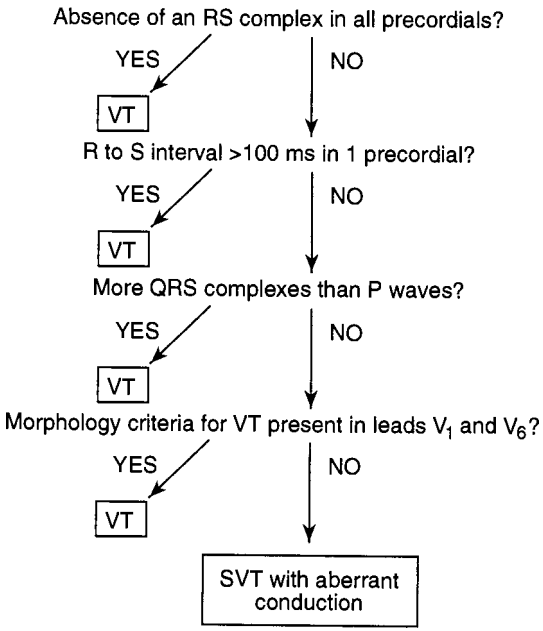
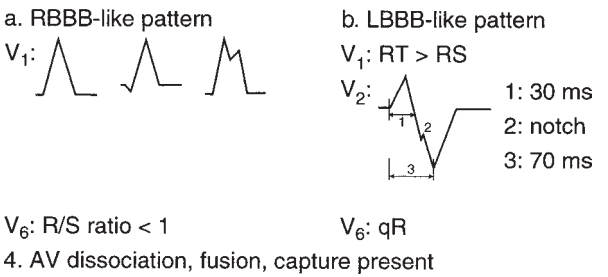


FIGURE 21.4 Brugada criteria for differentiating ventricular tachycardia from supraventricular tachycardia with aberrant intraventricular conduction. VT, ventricular tachycardia; SVT, supraventricular tachycardia.

b. Priority of therapy. A patient who has no hemodynamic compromise can be treated medically, at least initially. As with most types of tachyarrhythmias, **the treatment of any unstable patient with VT is rapid DCC**. The treatment for pulseless VT is asynchronous DCC with a starting energy of 200 to 360 J. If the patient is conscious but has unstable vital signs or is extremely symptomatic, **synchronized DCC** is recommended. Current 2011 Advanced Cardiac Life Support (ACLS) guidelines (AHA) currently emphasize the delivery of high-quality cardiopulmonary resuscitation (CPR): effective chest compressions (100/min and compression depth of at least 2″) with minimal interruptions, rescue breaths given over 1 second with visible chest rise while avoiding hyperventilation (30:2 ratio before an advanced airway and 8 to 10 asynchronous breaths/min after airway is secured), and a **single** shock to attempt to defibrillate pulseless VT patients (as opposed to three-stacked shocks) followed by immediate continuation of CPR. (See Section **IV.F.3** for treatment of pulseless VT/VF patients.)

c. Acute medical therapy. Intravenous amiodarone, lidocaine, procainamide, β-blockers, and other oral agents may be given initially depending on the clinical scenario. Amiodarone is the agent of choice for resistant VT causing repeated episodes and also for pulseless VT/cardiac arrest. Amiodarone and lidocaine are the preferred agents in patients with LV dysfunction (left ventricular ejection fraction [LVEF] < 40%). Lidocaine is effective when VT is thought to be ischemic in nature. Procainamide is reasonable as the initial treatment in patients with stable monomorphic VT, as it more effectively provides early rate slowing and conversion than amiodarone. β-Blockers may be preferred for acute coronary syndrome, especially if not already being

1. QRS width > 0.14 s
2. Superior QRS axis
3. Morphology in precordial leads:



4. AV dissociation, fusion, capture present

FIGURE 21.5 Classic morphology criteria for ventricular tachycardia.

taken by the patient. Whenever possible, a **reversible cause for VT** should be sought. Elimination of **ischemia** and correction of **electrolyte abnormalities** are recommended. **Bradycardia** may cause frequent premature ventricular contractions or VT. Maneuvers and agents that increase heart rate should be employed for these bradycardias. **Hypotension** should be promptly corrected. Therapy for CHF should be optimized with the agents

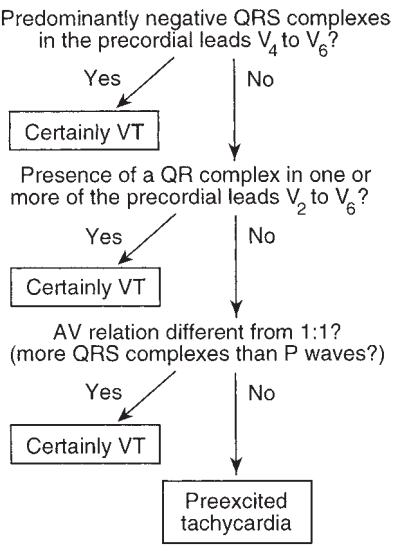


FIGURE 21.6 Brugada criteria for differentiating ventricular tachycardia from antidromic tachycardia over an accessory pathway. VT, ventricular tachycardia; AV, atrioventricular.

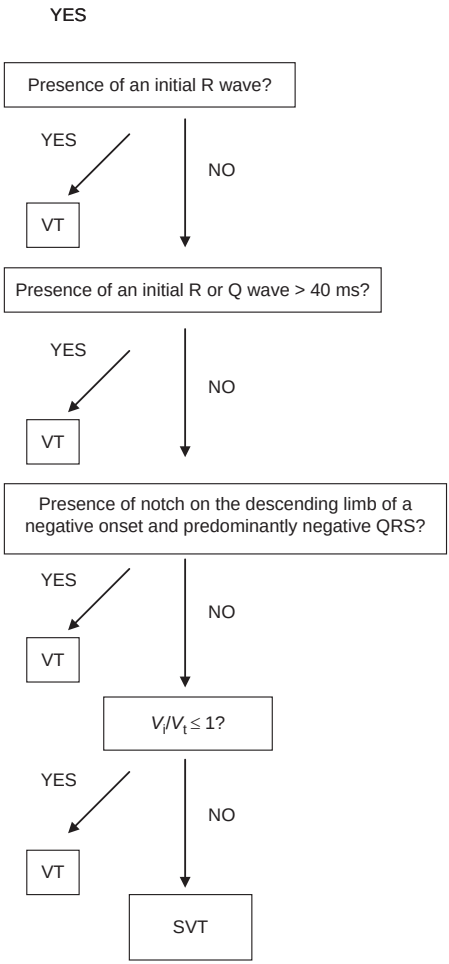


FIGURE 21.7 aVR criteria for diagnosing ventricular tachycardia. Vi = vertical excursion (mV) during initial (V_i) and terminal (V_t) 40 milliseconds of the QRS complex. VT, ventricular tachycardia; SVT, supraventricular tachycardia.

known to promote survival in this disorder. **Offending agents** should be stopped whenever possible, and **antidotes** should be administered in the case of overdosage and poisoning.

4. **Prevention and prophylactic treatment.** All antiarrhythmic agents to date, except β-blockers, have not been shown in randomized clinical trials to be effective as the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of SCD. Since the Cardiac Arrhythmia Suppression Trial (CAST) data have become available, there has been a shift

away from the use of class I agents and toward the **use of class III agents and β-blockers for prophylactic maintenance therapy** of VT. The development of **curative catheter-based therapies and surgical procedures** has somewhat reduced the role of antiarrhythmics in the prevention of recurrence, especially for VT occurring in normal hearts, which has very high cure rates with catheter ablation **(see Section IV.A)**. However, antiarrhythmic drug therapy remains the first-line treatment for VT, particularly for patients with cardiomyopathy. The greatest impact on survival in sudden death has been made by the implantable **cardioverter–defibrillator (ICD)**. Data from the Multicenter Unsustained Tachycardia Trial (MUSTT) investigations have shown that **patients with CAD, an EF < 40% and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT.

a. Medical therapy

(1) Although drug therapy continues to have a role in the prevention of VT and sudden death, this role has become more limited as there has been no decrease in mortality with the use of antiarrhythmic drugs. The Electrophysiologic Studies Versus Electrocardiographic Monitoring (ESVEM) trial studied the efficacy of seven antiarrhythmics (imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine, and sotalol) in preventing the recurrence of sustained VT. Sotalol was seen to be the most effective, although even with sotalol the recurrence rate was disappointing. The European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) investigations were designed to study the effectiveness of empiric amiodarone for the prevention of VT after MI. Although both of these trials showed a decrease in arrhythmic deaths, no survival benefit was recorded.

(2) Combination therapy. Drug therapy is becoming **an adjunct to ICD therapy** in this high-risk population. At present, fully half of those with ICDs remain on antiarrhythmic therapy. The rationale for this combined therapy includes preventing atrial tachyarrhythmias and reducing the frequency of VT and thus the frequency of ICD discharge.

(3) Calcium channel blockers are used primarily in the management of supraventricular tachyarrhythmia. However, some of the idiopathic monomorphic VTs, described in Section **IV.A** (the VTs originating in the right ventricular outflow tract [RVOT]), fascicular VT, and the VTs of digitalis toxicity are responsive to calcium channel blocking agents such as verapamil and diltiazem (due to the underlying mechanism of calcium-dependent triggered activity). RFA is potentially curative for idiopathic VTs and should be considered despite effective termination with calcium channel blockers.

(4) β-Blockers may be effective, particularly for outflow tract VT. Idiopathic left VT may respond to calcium channel blockers.

b. Percutaneous therapy

(1) ICDs. Two large trials comparing ICDs with amiodarone in high-risk patients with prior infarction, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, have been completed. High risk implies either an EF of 35% or less or the presence of inducible sustained VT at electrophysiologic study. Both trials showed a **decided advantage for ICDs**, with 30% to 50% reductions in mortality with ICDs. In fact, the AVID trial found no survival benefit from amiodarone, β-blockers, or any other antiarrhythmic agent. Newer ICDs often have antitachycardia pacing (ATP) capabilities, can recognize monomorphic ventricular

rhythms with rates < 200 beats/min, and can rapidly pace the ventricles to restore sinus rhythm, aborting the need for countershock (see Chapter 23). In the Primary Prevention Parameters Evaluation (PREPARE) study which evaluated the effects of ICD programming in a patient population receiving ICDs for primary prevention, using ATP as first-line therapy for fast VT (≥ 182 and < 250 beats/min), including a monitoring zone at 167 beats/min, and applying SVT versus VT discriminators for rates < 200 beats/min helped in reducing shocks without negatively affecting the mortality. Data from MADIT II have shown that in patients with a prior MI and an EF < 30%, the implantation of a defibrillator is associated with a significant improvement in survival.

(2) Catheter-based therapy. RFA may be effective for reducing the incidence of VT. The success rate depends on the type of VT, with the highest success rates (> 90%) in structurally normal hearts. VT associated with underlying cardiomyopathy has lower success rates with ablation, particularly those with arrhythmogenic RV cardiomyopathy and ischemic cardiomyopathy. However, catheter ablation still remains an effective and feasible approach, even for these types of VTs. Presently, catheter ablation of VT does not obviate the need for an ICD in a patient with an indication for one.

IV. DIAGNOSTIC EVALUATION OF A PATIENT WITH VT. Once the diagnosis of VT has been established and the patient has been acutely managed with either DCC or medical therapy, further management depends on the underlying cardiac pathology. In broad terms, the substrate can be divided into two categories: the structurally normal heart and the structurally abnormal heart. Various modalities are available to determine the cardiac structure and function, which include electrocardiography, cardiac catheterization, echocardiography, nuclear imaging, and magnetic resonance imaging.

A. VT in a structurally normal heart. About 10% of VT in the United States occurs in structurally normal hearts, the so-called idiopathic VT. These patients have no significant CAD, no family history of arrhythmia or sudden death, and normal surface ECGs. They can be focal VTs or reentry VTs. Focal VTs are a result of triggered activity, abnormal automaticity, or reentry within the Purkinje fibers.

1. Focal VT

a. Mechanism. Focal VTs most commonly arise from the RVOT and account for up to 70% of idiopathic VTs. They may be caused by cAMP-mediated EADs. Of particular importance in the diagnosis of a patient who presents with LBBB VT is to be cognizant of the possibility of arrhythmogenic right ventricular dysplasia (ARVD), which falls into the category of VT/PVCs in the structurally abnormal heart. The clinician should investigate for RV structural abnormalities (fatty infiltration), ask about a family history of ARVD, and review the electrogram for the presence of T-wave inversion across the right precordial leads, and/or epsilon waves (Fig. 21.10). A cardiac MRI or cardiac PET scan may also be useful to rule out the presence of cardiac sarcoidosis, which also would fall into the category of the structurally abnormal heart.

b. ECG. The surface ECG usually demonstrates an LBBB and inferior axis with very positive QRS voltage in inferior leads. Other locations of focal VTs may include the LV outflow tract, aortic cusps, pulmonary artery, mitral and tricuspid annuli, papillary muscles, and epicardium.

c. Treatment. In general focal VTs are benign, carrying a very low risk of SCD. Therefore, the treatment is predominantly guided by symptoms. Given the role of cAMP in inducing this form of VT, adenosine may be effective at acute termination. For longer term therapy in the symptomatic patient,

β-blockers are typically the first-line agents and can be effective in up to 50% of patients. The nondihydropyridine calcium channel blockers may also be effective in 25% to 50% of patients. Very effective medications are sotalol and amiodarone, with up to 90% success rate in eliminating symptoms, but potential side effects may limit their use. Patients who wish to potentially avoid lifelong medications or who are refractory to medical therapy can be considered for ablation, which has variable success rate depending on the location. RVOT VT ablation success rate may be as high as 90%. Ablation procedures, while generally safe, may be associated with infrequent but life-threatening complications, including cardiac perforation and tamponade.

2. **Fascicular VTs.** Fascicular VT involves reentry using the tissue of the LV septum as the antegrade limb and usually the posterior fascicle in the retrograde limb.
   a. **ECG.** This typically produced a right bundle branch block (RBBB) with left-axis deviation pattern. Less commonly, the QRS pattern is an RBBB with right-axis deviation (left anterior fascicular VT).
   b. **Treatment.** This subtype of VT may be verapamil-sensitive, but catheter ablation can be attempted in patients who want to avoid long-term medication or in whom medical therapy is ineffective.

B. VT/VF associated with channelopathies. Various cardiac ion channel disturbances can predispose to ventricular arrhythmias. Patients with these channelopathies have no overt structural heart disease. They are genetically heterogeneous and have variable penetrance. They include LQTS, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT.

1. **Long QT syndrome**
   a. **Pathology and presentation**

This channelopathy is characterized by prolonged cellular repolarization resulting in an increase of the QT interval. Clinical presentation includes syncope or sudden death as a result of torsade de pointes, and usually an autosomal dominant transmission pattern.

While at least 12 mutations have been identified, the most common subtypes of LQTS are LQT1, LQT2, and LQT3, which are characterized by mutations in the I_{Ks}, I_{Kr}, and I_{Na} channels, respectively. Interestingly, a minority of patients with the genetic mutation may actually have "normal" QT intervals. LQT1 and LQT2 mutations result in decreased outward potassium current, while LQT3 mutation results in increased inward sodium current, both of which result in prolonged cellular repolarization. The Jervell and Lange-Nielsen, a clinical syndrome with a constellation of a prolonged QT and sensorineural deafness, is transmitted in an autosomal recessive pattern, and thus far has been localized to the LQT1 or LQT5 mutations.

LQT1 patients typically have broad-based T waves and exercise-induced arrhythmias, especially during swimming. LQT2 syndrome is characterized by low-amplitude or notched T waves and auditory triggers such as sudden loud sounds like alarm clocks or strong emotion, and LQT3 is characterized by a long isoelectric ST segment and arrhythmias during sleep.

   b. **Treatment**

In patients with LQTS, risk stratification involves assessment of age, gender, clinical history, and possibly the QT interval and genetic mutation. While β-blockers have a variable efficacy depending on the type of LQT mutation, typically high doses of propranolol or nadolol are used to prevent clinical symptoms. For the LQT3 patients, there may be a role for flecainide given its effects on the sodium channel inhibition, but this is experimental and has not reached guideline recommendations yet. Patients should be advised against high-intensity sports and should be educated regarding avoidance of QT prolonging drugs. Patient with syncope, history of aborted

sudden death, or torsade de pointes despite β-blocker therapy should undergo ICD implantation. Certain high-risk subgroups such as patients with LQT3 in whom β-blockers may be less effective, patients with QTc > 550 milliseconds, or female LQT2 patients with QTc > 500 milliseconds may benefit from ICD implantation. Left cardiac sympathetic denervation can be used as an adjunctive therapy to reduce recurrence of arrhythmias.

2. **Short QT syndrome.** This syndrome is characterized by gain-of-function mutations in the I_{Ks}, I_{Kr}, and I_{K1} potassium channels or CACNA1 and CACNB2 L-type calcium channel mutations. ICD therapy is the primary treatment modality. However, particular attention needs to be given to the prevention of inappropriate shocks, as patients may have T-wave oversensing (tall T waves) and a high incidence of AF.
3. **Brugada syndrome.** Brugada syndrome is a condition associated with SCD in the setting of a structurally normal heart, characterized by an electrocardiographic pattern of RBBB and ST-segment elevation in leads V_1 to V_3 (Fig. 21.8). It is inherited in an autosomal dominant pattern with a male predominance. It is a genetically heterogeneous disease with many mutations linked to the gene *SCN5A*, which encodes for a cardiac sodium channel, leading to unopposed I_{to} potassium current in the RV epicardium. The diagnosis can be difficult because of the variable expression of the ECGs at baseline, changes in the ECG over time induced by a host of factors (temperature, heart rate, autonomic tone, and medications), and the wide range of clinical manifestations. The diagnosis should be considered in patients who have documented VF, self-terminating polymorphic VT, family members with ST-segment elevation, syncope, or family history of sudden death in the setting of the electrocardiographic findings noted previously. Currently, no medication has proved effective in preventing SCD in these patients, but quinidine, which blocks the I_{to} channel, may be used as an adjunctive therapy to reduce the likelihood of arrhythmias. ICDs are currently the only available treatment and are recommended in patients with previous cardiac arrest (class I), syncope with spontaneous ECG pattern (class IIa), and documented VT that has not resulted in cardiac arrest (class IIa). It is generally recommended to implant an ICD in **symptomatic** patients and clinically follow **asymptomatic** patients with an abnormal ECG only on pharmacologic provocation and no inducible ventricular arrhythmias.
4. **Catecholaminergic polymorphic VT.** This arrhythmia is more common in adolescents and children and may present with SCD or stress-induced syncope. While usually familial, it can also occur due to de novo mutations. Triggers often include emotional or physical stress, and the arrhythmia can be polymorphic, bidirectional, and less commonly, VF. Two culprit genes have been identified thus far: calsequestrin 2 (autosomal recessive pattern) and cardiac ryanodine receptor (autosomal dominant pattern). ICDs are indicated in patients with this syndrome and syncope and/or VT. β-Blockers can reduce the incidence of arrhythmias as well. Flecainide and sympathetic denervation have been used in some patients who are refractory to β-blocker therapy.

C. VT in the structurally abnormal heart

1. **Ischemic VT. Patients with ischemic VT may have acute ischemia leading to MI or a history of ischemic heart disease with scar.** Patients who have VF/VT within 48 hours of an acute MI have a relatively high inhospital and 30-day mortality compared with patients who do not have VF/VT.
   a. **Etiology and pathophysiology.** At the cellular level, ischemia may alter action potentials, prolong refractoriness of cells, and uncouple the cell-to-cell propagation of depolarization. The biochemical milieu in which the cells exist with respect to ion concentrations, acid–base balance, and so forth can be altered. Also, the myocardial damage as a result of infarction is structurally

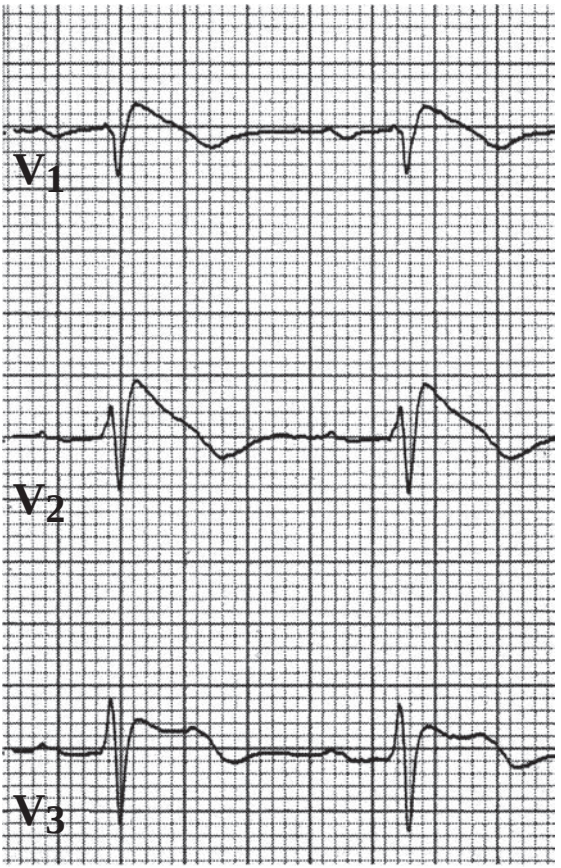


FIGURE 21.8 Leads V_1 through V_3, demonstrating Type 1 Brugada pattern.

heterogeneous. Therefore, scar tissue and healthy tissue are admixed in the region of the infarction. As described before, a reentrant circuit requires two functionally distinct pathways with unidirectional block in one pathway and slowed conduction down a second pathway. The changes associated with ischemia provide the anatomic substrate for reentry. The VT in the setting of ischemia tends to be **polymorphic**, while VT in the setting of established myocardial scar tends to be **monomorphic**. Ischemia has been shown to prolong the QT interval in some subjects, often with associated T-wave inversion. The **QT interval in ischemic-mediated polymorphic VT is not as prolonged** as that in torsade de pointes, another polymorphic VT. Ischemia is by far the **most common cause of polymorphic VT with normal QT interval**.

b. Predictors of VT. As might be expected, **larger infarcts with greater resultant impairment of LV systolic function** are more likely to be associated with VT. In fact, LV systolic function is the single most important predictor of sudden death due to arrhythmia. Similarly, the presence of an **open artery**

appears to reduce the occurrence of VT and other arrhythmias. Other proposed predictors include syncope, abnormal signal-averaged electrocardiogram (SAECG) result, NSVT, absence of heart rate variability, abnormal electrophysiologic study outcome, and T-wave alternans (TWA); however, currently, the LVEF remains the most accurate predictor of sudden death.

c. **Laboratory examination and diagnostic testing.** The various tests for risk stratification (electrophysiologic study, SAECG, heart rate variability, TWA, and so forth) have shown poor specificity and positive predictive value for VT **and thus should not be used alone to guide therapy but in combination with the rest of the clinical information**.

d. **Role for ICD.** In patients who present with a VF/VT arrest in the setting of an acute MI (within 24 to 48 hours of infarction), revascularization should be the primary initial treatment. Given the fact that acute ischemia is considered a "transient or potentially correctable cause" of VF/VT, and such patients were excluded from the AVID trial, based on currently guidelines, an ICD would be indicated 90 days after revascularization if the LVEF is ≤ 35% or after 40 days if no revascularization was performed, but treatment should be guided on a patient-to-patient basis. Of note, patients in the AVID registry who were excluded from the AVID trial due a "transient or potentially correctable cause" had a high mortality risk in follow-up. Of the 278 patients studied, 183 patients were determined to have ischemic causes. Of these, 161 were categorized as new myocardial infarction and 22 were categorized as transient ischemia. Other causes included electrolyte abnormalities, antiarrhythmic drug interaction, and "other (illicit drug use, sepsis, hypoxia, electrocution, drowning)". For patients who are post-MI and are deemed to be at high risk for SCD during the waiting period of 40 to 90 days, a wearable cardioverter–defibrillator (WCD) may provide protection against cardiac arrest, but no randomized clinical trials comparing WCDs with medical therapy in this post-MI period have been completed to date. Patients with late VT/VF (i.e., > 48 hours after acute MI) are deemed to be particularly high risk for recurrent VT/VF and therefore typically receive ICDs before hospital discharge. These patients are considered to meet secondary prevention indications for ICDs.

e. Accelerated idioventricular rhythm (Fig. 21.9) is a form of VT seen almost exclusively in ischemic heart disease, particularly during an MI and especially after reperfusion of an occluded territory. It may be seen with digitalis toxicity, but can also be present in healthy adults and children with no structural heart disease.

   (a) The electrocardiographic features include regular or slightly irregular ventricular rhythm, rate of 60 to 110 beats/min, a QRS morphology resembling that of PVCs, and, often, AV dissociation as well as fusion beats and capture beats.

   (b) **Pathophysiology.** The ectopic ventricular pacing focus competes with the SN and takes control of the ventricular rate when the sinus rate slows or when sinoatrial or AV block occurs. Enhanced automaticity is the likely underlying mechanism.

   (c) Accelerating the sinus rhythm with atropine or atrial pacing can be useful to suppress the accelerated idioventricular rhythm. **Therapy is rarely necessary, unless** the loss of AV synchrony results in hemodynamic compromise, a more rapid VT intervenes, the accelerated idioventricular rhythm falls on the T wave of the preceding beat (R on T phenomenon), the ventricular rate is rapid enough to produce symptoms, or VF occurs.

2. **Dilated cardiomyopathy (DCM).** Risk stratification is particularly difficult in patients with DCM as SAECG, microvolt TWA, and an electrophysiologic study are not reliable predictors in this population, and asymptomatic ventricular arrhythmias are common. The **Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation** (DEFINITE) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have influenced the current guidelines for implanting ICDs in patients with DCM. ICDs are recommended for patients

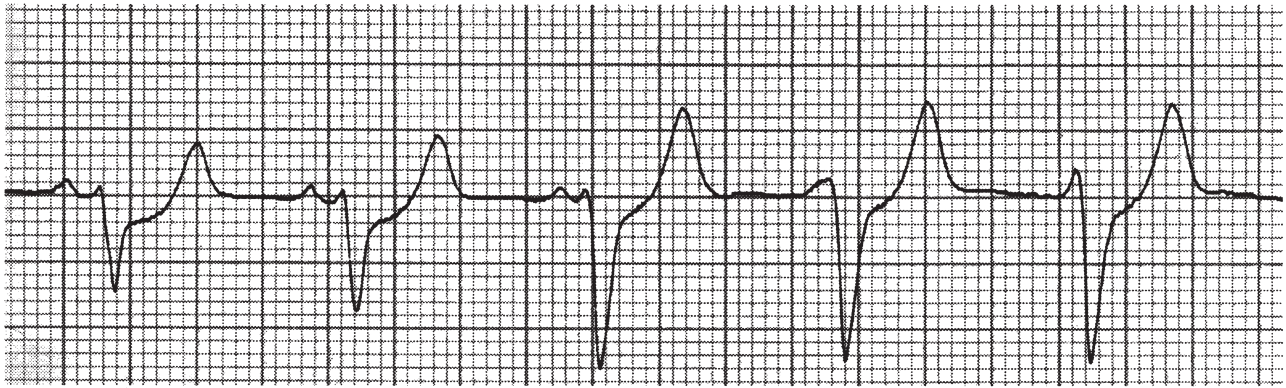


FIGURE 21.9 Accelerated idioventricular rhythm (beats 3 through 5), interspersed with normal sinus rhythm (beats 1 and 2), lead IV.

who manifest life-threatening arrhythmias or syncope and for primary prevention in patients who have an LVEF < 35% and are New York Heart Association (NYHA) classes I–III (less evidence exists for class I). All patients should be receiving chronic optimal medical therapy and have a life expectancy > 1 year. Bundle branch reentrant tachycardia occurs most commonly in patients with DCM for which electrophysiologic testing is helpful in diagnosing and guiding ablative treatment. Although ablation may be curative if bundle branch reentry is the mechanism, such patients should still be considered for ICD implantation.

3. **Hypertrophic cardiomyopathy.** Supraventricular tachyarrhythmia and AF are particularly poorly tolerated by these patients, as is ischemia, and may lead to VT. No prospective randomized trials regarding ICD therapy have been carried out to date in this patient population. Consequently, the precise risk stratification is debated. ICDs are recommended for patients who have sustained VT or VF, or both, and for primary prevention in patients who have either one of the preceding life-threatening arrhythmias or one or more of other major risk factors for SCD (nonsustained spontaneous VT, family history of premature SCD, unexplained syncope, LV thickness ≥ 30 mm, or abnormal exercise blood pressure). Again, all patients should be receiving chronic optimal medical therapy and have a life expectancy > 1 year. Electrophysiologic study may be helpful in stratifying risk for VT and sudden death. Patients at low risk for HCM include those with infrequent or brief episodes that are asymptomatic or mildly symptomatic. Although **amiodarone** may be beneficial in this population, an ICD is increasingly used in those considered to be at high risk.
4. **Muscular dystrophies**, particularly Duchenne's muscular dystrophy and myotonic dystrophy, have been associated with frequent defects in the conduction system. Heart block and bundle branch block as well as sudden death due to ventricular tachyarrhythmias are well-recognized complications of these muscular disorders.
5. **Congenital heart disease.** Structural abnormalities such as **repaired tetralogy of Fallot and mitral valve prolapse** have been associated with increased risk of VT and sudden death. In tetralogy of Fallot, the VT often originates in the RVOT, at the site of a previous repair. Risk of VT and sudden death in this population has been associated with QRS width (and rate of QRS width increase) as well as severity of pulmonary insufficiency. Mitral valve prolapse has been uncommonly linked to sudden death, although ventricular arrhythmias are not uncommon. **The prognosis with respect to VT is quite good in mitral valve prolapse**.
6. **Arrhythmogenic right ventricular cardiomyopathy** is a cardiomyopathy that begins in the right ventricle and often progresses to involve the left ventricle. It results in RV dilation with resultant poor contractile function. The RV muscle becomes increasingly replaced by adipose and fibrous tissues as the disease progresses. VT arising in the right ventricle is often an early manifestation of this disorder. The **VT is a reentrant type and has an LBBB morphology**, although in sinus rhythm there is often inversion of the T waves in the anterior precordial leads and a slurring of the terminal portion of the QRS complex, known as an epsilon wave (Fig. 21.10). These patients frequently have a positive SAECG for late potentials. The combination of the scarring and the late potentials provides the anatomic substrate for reentry. During electrophysiologic study, it may be possible to elicit VT of varying morphologies, due to the prolific scarring of the myocardium. The **risk of VT correlates with the extent of myocardial involvement**. Therapy with sotalol or high-dose amiodarone may be somewhat successful. Ablation via catheters is often successful, but only temporizing, as the generalized involvement tends to give rise to arrhythmias at a different locus later in the disease course. ICDs are often the only reliable therapy to prevent sudden

death in this disorder. Patients are advised against intense exercise, as this may promote the incidence and progression of arrhythmias.

7. Several inflammatory or infectious conditions have been associated with VT.
   a. Sarcoidosis is frequently cited as a cause of heart block and may also cause VT and VF. **Amiodarone** and **sotalol** are the most efficacious agents in this disorder, although an ICD may be necessary in addition to the drug therapy.
   b. Acute myocarditis has been associated with both polymorphic and monomorphic VTs. It may be intractable in giant cell myocarditis. **Antiarrhythmic therapy and anti-inflammatory therapy** are generally combined in the treatment of these patients.
   c. Chagas disease, caused by the parasite *Trypanosoma cruzi*, is a well-known cause of cardiomyopathy, particularly in South and Central America. VT and other arrhythmias due to conduction system involvement are common complications. Therapy involves antiparasitic treatment, standard therapy for CHF, antiarrhythmics, and pacemaker or ICD implantation, as appropriate. Some patients require catheter ablation of refractory VT, which sometimes must be performed epicardially.
8. **Coronary anomalies.** Anomalous aortic origin of the coronary artery is recognized as a cause of sudden death and/or exercise-induced death in young individuals. In an autopsy study of over 200 patients conducted by the Armed Forces Institute of Pathology, the most common coronary anomalies included the right coronary artery and left main coronary artery arising from the left sinus, the left main and right coronary arteries arising from the right sinus, single coronary artery from the aorta, and the left main or left anterior descending artery arising from the pulmonary artery. Patients whose coronary arteries take an interarterial course (between the pulmonary artery and the aorta) may develop exercise-induced ischemia and/or sudden death. Surgical revascularization in patients with symptomatic coronary anomalies has been well described. Surgical treatment for patients with high-risk coronary anomalies who are asymptomatic is controversial.

D. Drug-induced VT. Drugs are a well-known cause of VT, both polymorphic and monomorphic VTs. This is particularly true in ischemic or infarcted hearts. Phenothiazines, tricyclic antidepressants, digitalis, epinephrine, cocaine, nicotine,

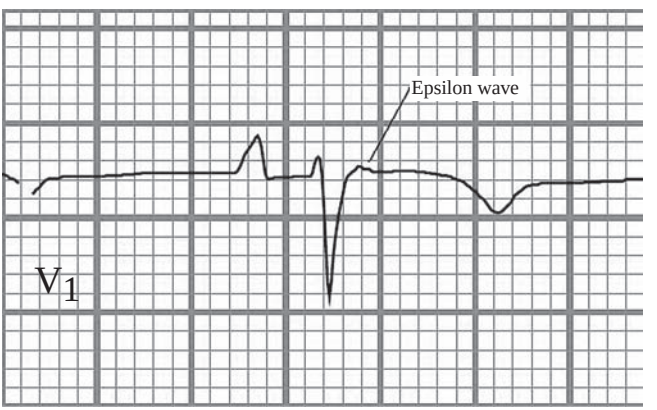


FIGURE 21.10 Epsilon wave in a patient with arrhythmogenic right ventricular dysplasia.

alcohol, and glue (inhaled) are some of the wide variety of drugs that have been implicated in the development of monomorphic VT. The CAST and other trials of the late 1980s showed an increase in mortality resulting from the use of class I antiarrhythmic agents employed to suppress asymptomatic ventricular ectopy after MI. NSVT and depressed LV function remain risk factors for sudden death, and the agents studied in CAST did decrease the occurrence of ventricular ectopy; however, it is believed that these drugs (flecainide, encainide, and moricizine) generated VT, causing sudden death in recipients. These agents all have in common their sodium channel blocking activities. Other drugs in this class, including procainamide, quinidine, disopyramide, lidocaine, tocainide, and mexiletine, have all been shown either experimentally or clinically to be associated with increased mortality compared with controls in the periinfarction period. The results of CAST caused a major shift away from the sodium channel blocking agents (class I antiarrhythmics) in the periinfarction period.

1. The generation of torsade de pointes due to effects on the QT interval is discussed in Section **IV.D.2**.
2. Digitalis toxicity can propagate DADs, which generate action potentials, leading to VT. The VT of digitalis toxicity is typically monomorphic and often responds to calcium channel blockers. Rarely, digitalis toxicity manifests as a bidirectional VT, meaning that it has a regular rhythm with an axis that alternates from −60 to −90° to +120 to +130°, with a ventricular rate from 140 to 200 beats/min. Because digitalis toxicity may have a narrow QRS complex and may respond to calcium channel blockers, it may be confused with supraventricular tachyarrhythmia. This type of VT is best managed by removing the offending agent, digoxin, with its binding antibody. The treatment for digitalis toxicity is the same in the face of bidirectional VT.
   a. Torsade de pointes is a type of polymorphic VT associated with delayed myocardial repolarization, most often manifested as a prolonged QT interval. Although the duration of torsade de pointes is typically brief (< 20 seconds), it can be sustained and can degenerate into VF. It generally has an irregular ventricular rate (> 200 beats/min) and displays a polymorphic structure with an undulating appearance. The QRS complexes appear to twist around an isoelectric axis. Characteristics that distinguish torsade de pointes from other forms of VT include (1) prolonged QT interval, (2) initiation with a short–long–short sequence, and (3) typical "twisting of the points" appearance of the VT.
      (1) **Etiology.** QT prolongation can be congenital or acquired.
         (a) The **congenital** forms are seen in the LQTS, discussed in Chapter 23.
         (b) The **acquired forms are most often drug induced**, although polymorphic VT with a prolonged QT can be caused by electrolyte abnormalities, hypothyroidism, cerebrovascular events, MI or ischemia, starvation diets, organophosphate poisoning, myocarditis, severe CHF, and mitral valve prolapse.

      The **most commonly implicated drugs have been the class IA drugs**, although less frequent occurrences have been reported with all subclasses of class I antiarrhythmics. The class III drugs, such as sotalol, dofetilide, and, less commonly, amiodarone, have been implicated. The incidence of torsade de pointes with sotalol is in the range of 2% to 5% and with dofetilide it is < 1%. Ibutilide is an antiarrhythmic agent for supraventricular tachyarrhythmias that is associated with an incidence of torsade de pointes at least as high as that of sotalol. Other drugs implicated include the phenothiazines, haloperidol, and the tricyclic antidepressants. Antibiotics, including erythromycin and other macrolides, as well as trimethoprim–sulfamethoxazole combinations, have been implicated. The macrolides are particularly prone to cause torsade de pointes when combined with certain antihistamines such

as astemizole and terfenadine. These antihistamines have also been found to cause torsade de pointes when combined with certain azole antifungal agents such as ketoconazole. Ionic contrast and promotility agents such as cisapride have also been associated with torsade de pointes. Medications associated with increasing QT interval are listed on the following website: www.torsades.org. It is maintained by the University of Arizona Center for Education and Research on Therapeutics.

Bradycardia can promote torsade de pointes in patients with prolonged QT intervals, although it is not clear if bradycardia by itself predisposes to torsade de pointes. Specifically, pause-dependent VT occurs in the setting of bradycardia and a prolonged QT interval. Usually a long RR interval followed by a short RR interval followed by another long RR interval initiates the VT.

Electrolyte disorders. **Hypokalemia** is the electrolyte disorder most reliably linked to torsade de pointes. **Hypomagnesemia** has been proposed as a logical cause, as the administration of magnesium frequently terminates torsade de pointes. However, there is scant evidence to confirm this. Likewise, although **hypocalcemia** is associated with prolongation of the QT interval, there are only rare reports of torsade de pointes associated with hypocalcemia.

Short coupled VT. Polymorphic VT is initiated < 400 milliseconds following the preceding QRS complex.

R-on-T phenomenon occurs when a defibrillation or pacing current or spike is delivered simultaneously with occurrence of the electrocardiographic T wave resulting in polymorphic VT.

A variety of **cerebrovascular events** have been associated with torsade de pointes, most notably subarachnoid hemorrhage. The prolongation of the QT interval sometimes seen with intracranial bleeding is usually transient, resolving within weeks.

(2) Therapy. Acute management is aimed at terminating the arrhythmia.

(a) If torsade de pointes is sustained or associated with hemodynamic compromise, prompt DCC should be carried out. Starting voltages are generally 50 to 100 J and can be advanced to 360 J if necessary.

(b) Correction of hypokalemia, hypomagnesemia, and hypocalcemia should be undertaken promptly. Magnesium can be given in a bolus form at a dose of 1 to 2 g, with a total dose of 2 to 4 g given over 10 to 15 minutes. This successfully terminates torsade de pointes within 5 minutes in up to 75% of patients and within 15 minutes in virtually all patients.

(c) Bradycardia can be corrected with either isoproterenol infusion or temporary transvenous pacing. Pacing may be preferable when readily available, due to the potential complications of isoproterenol therapy (worsened ischemia and hypertension). Offending agents should be discontinued.

E. Miscellaneous

Commotio cordis. Commotio cordis is the sudden ventricular arrhythmia occurring as a result of a blunt, nonpenetrating impact to the precordial region, which is most commonly observed in young healthy persons during participation in sports. The blow likely falls within a small 10- to 30-millisecond window of ventricular vulnerability just prior to the peak of the T wave that results in polymorphic VT and sudden death. A 2002 case series of 128 individuals showed that only 16% of patients survived an episode of commotio cordis, with most returning to a baseline level of function. Prompt CPR/defibrillation was the only identifiable factor associated with a favorable outcome.

F. Ventricular fibrillation

1. VF is a **chaotic ventricular rhythm that reflects no organized electrical activity and hence no cardiac output** from the ventricle. It is devoid of the distinct elements that makeup the usual electrical complex of ventricular activity. It is a **rapidly fatal rhythm, and if resuscitation is not begun within 5 to 7 minutes, death is virtually certain**. VF is often preceded by VT. Virtually all of the risk factors and conditions discussed for VT are applicable to VF. It may arise without any inciting cardiac rhythm or event.
2. **Course of disease.** Of patients who experience an out-of-hospital cardiac arrest, 75% have VF as their initial cardiac rhythm. Of those successfully resuscitated, 75% have significant CAD and 20% to 30% have a transmural infarction. Patients without an ischemic etiology have an increased risk of further episodes of sudden death, whereas those who have an MI associated with sudden death have a 1-year recurrence rate of 2%. Anterior MI complicated by VF represents a subgroup at high risk for recurrence of sudden death. Predictors of SCD include evidence of ischemia, decreased LV systolic function, 10 or more PVCs per hour on telemetry, inducible or spontaneous VT, hypertension and LV hypertrophy, smoking, male sex, obesity, elevated cholesterol, advanced age, and excessive alcohol use.
3. **Therapy.** As noted previously, VF is a rapidly fatal rhythm, which virtually never terminates spontaneously. CPR must be initiated promptly and rapid, asynchronous DCC performed as soon as possible. A **single** shock of 200 to 360 J (biphasic devices, 200 J; monophasic devices, 360 J) should be given initially followed by immediate resumption of CPR for 2 minutes before checking for a pulse. If VF/pulseless VT persists, an immediate **second** shock (biphasic devices, ≥ 200 J; monophasic devices, 360 J) should be given followed by a vasopressor (1 mg of epinephrine every 3 to 5 minutes; single dose of 40 units of vasopressin may replace first or second dose of epinephrine). If VF/pulseless VT persists after two or three shocks, CPR, and a vasopressor, administration of an antiarrhythmic should be considered (amiodarone is preferred and lidocaine as an alternative). The emphasis should be on performing high-quality CPR with interruptions in chest compressions **only** for ventilation (until an advanced airway is established), rhythm checks (pulse checks only if an organized rhythm is observed), and shocks.

   See Chapter 23 for a discussion about the long-term treatment of survivors of VF.

G. Ventricular premature depolarizations and nonsustained ventricular tachycardia.

1. **VPDs** are common in patients with both structurally normal and structurally abnormal hearts. They are usually not hemodynamically significant, except in patients with depressed EF or in patients with frequent VPDs and/or bradycardia. Whether or not VPDs increase risk of subsequent cardiovascular events depends on the study. In the ARIC study, after controlling for cardiovascular risk factors, patients with a single VPD on a 2-minute Holter had over a two-fold incidence of dying of CAD over a 10-year follow-up period compared with patients who had no VPDs. However, in the Baltimore Longitudinal Study on Aging which evaluated ambulatory ECGs on apparently healthy subjects ≥ 60 years of age, VPDs on ambulatory ECG monitoring did not predict the development of coronary events. One main difference between the ARIC study and the Baltimore Longitudinal Study was that in the latter, inclusion criteria were more strict, requiring a normal exercise stress test, and therefore, likely had less patients with subclinical CAD.

   Although patients post-MI with VPDs have a higher mortality than patients post-MI without VPDs, suppression of VPDs with antiarrhythmic medication is associated with increased mortality. For patients with symptomatic VPDs, β-blockers or calcium channel blockers should be the first-line agent. If this fails and the patient has no structural heart disease, class IC

agents may be effective; however, potential risks and benefits of the antiarrhythmic drug should be explained to the patient. Sotalol has been shown to reduce the frequency of VPDs by 70% to 80%. In CAMIAT, amiodarone reduced VPDs and arrhythmic deaths, but did not reduce overall mortality. **A very high burden of VPDs (> 20,000/d) may be associated with reduced** EF**, although it may be difficult to determine if the VPDs caused the cardiomyopathy or vice versa**. However, in some patients with a high burden of VPDs and idiopathic DCM, treating the VPDs either with medication or with catheter ablation may improve the LVEF. Ablation can be an alternative approach to treatment in patients with very symptomatic VPDs refractory to medical therapy and/or patients with reduced EF thought to be a result of the VPDs.

2. **NSVT** is defined as VT of duration < 30 seconds. It can occur in up to 4% of healthy adults and increases in frequency as people age, and NSVT during exercise is not associated with a poor cardiovascular prognosis. The approach to NSVT is based on the cardiac substrate. However, patients with frequent polymorphic NSVT should undergo an evaluation for LQTS and catecholaminergic VT (Sections **IV.B.1** and **IV.B.4**, respectively). One should also be mindful of repetitive monomorphic NSVT that may be of LBBB morphology in patients who have a family history of arrhythmias or sudden death, which may suggest ARVD. Monomorphic NSVT may also be a part of the spectrum of the outflow tract VTs (Section **IV.A.1**).
   a. In patients in whom structural heart disease has been excluded, NSVT does not carry prognostic significance. Treatment should therefore only be guided by symptoms. A similar approach to NSVT with regard to medication choices is used as with symptomatic VPDs (Section **IV.G.1.**)
   b. Structural heart disease. In patients with MI, NSVT within the first 24 to 48 hours has little prognostic significance. However, NSVT > 48 hours after acute MI may increase the risk of sudden death by almost twofold, and the risk is even higher in patients with reduced LV function. **Patients with CAD, an EF < 40%, and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT. In patients with HCM, NSVT on Holter monitoring is one of the major risk factors of SCD. Patients with mitral valve prolapse and aortic stenosis who have NSVT are not at increased risk for SCD compared with those without NSVT. In patients with nonischemic DCM, NSVT is not an independent predictor of sudden death.

ACKNOWLEDGMENTS: *The author thanks Drs. Ross Downey, Keith Ellis, and Thomas Dresing for their contributions to earlier editions of this chapter.*

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CHAPTER 22

Santosh S. Oommen

Bradyarrhythmias, Atrioventricular Block, Asystole, and Pulseless Electrical Activity

I. INTRODUCTION.

Bradyarrhythmias and **conduction blocks** are common electrocardiographic findings. Many of these arrhythmias are asymptomatic and do not require specific therapy, whereas others can be life threatening, requiring rapid intervention. **Myocardial ischemia** is an important cause of acute and potentially dangerous bradyarrhythmia.

II. ANATOMY

A. Sinoatrial node.

The sinus beat originates in the **sinoatrial (SA) node**, a focus of automatic cells near the junction of the superior vena cava and right atrium.

1. The blood supply to the SA node is from the **sinus node artery**, which arises from the proximal **right coronary artery** in 55% of the population (Fig. 22.1) and from the **circumflex artery** in 35%. The SA node receives a dual supply of blood from both the right coronary artery and the circumflex artery in 10% of the population.
2. The automaticity of the SA node is affected by both the parasympathetic and sympathetic nervous systems. If the SA node fails to generate an impulse, other foci in the atrium, atrioventricular (AV) node, or ventricle can act as "backup" pacemaker sites.

B. AV node.

The AV node is located in the anteromedial portion of the right atrium just anterior to the coronary sinus.

1. The impulse generated by the SA node progresses through the atrium to the AV node. The AV node is also innervated by both the parasympathetic and sympathetic nervous systems.
2. The AV node receives its blood supply from the AV node artery, which arises from the posterior descending artery in 80% of the population (Fig. 22.1), from the circumflex artery in 10%, and from both arteries in 10%.
3. Collateral blood supply from the left anterior descending artery makes the AV node somewhat less prone to ischemic damage than the SA node.

C. His bundle and bundle branches

1. After a delay of < 200 milliseconds in the AV node, the electrical impulse is propagated down the His bundle to the right and left bundle branches. The **left bundle branch splits further into anterior and posterior fascicles**. The autonomic nervous system does not have a major effect on conduction below the AV node.
2. The **His bundle and right bundle branch** receive their blood supply from the AV nodal artery and from septal penetrating branches of the left anterior descending artery. The anterior fascicle of the **left bundle branch** receives blood from the septal perforating branches of the left anterior descending

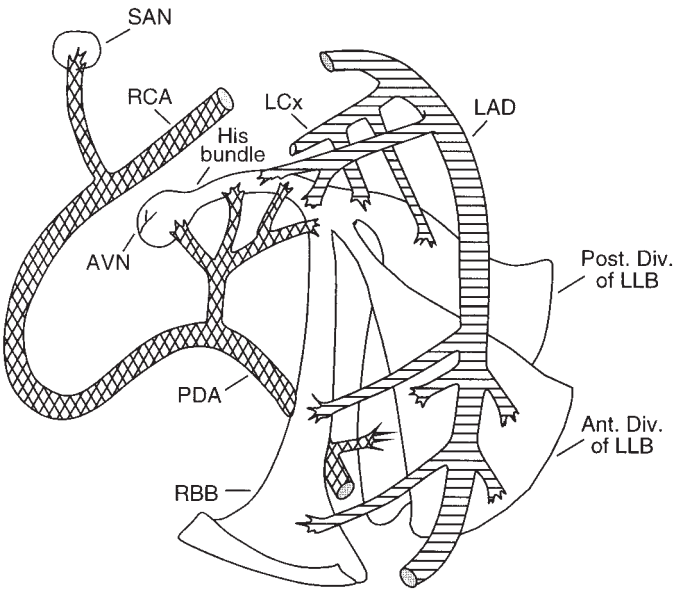

FIGURE 22.1 Diagrammatic representation of the conduction system and its blood supply. SAN, sinoatrial node; RCA, right coronary artery; AVN, atrioventricular node; PDA, patent ductus arteriosus; RBB, right bundle branch; LCx, left circumflex artery; LAD, left anterior descending; LLB, left lateral branch.

artery. The posterior fascicle has a dual blood supply: from the septal perforating branches of the left anterior descending artery and branches of the posterior descending artery.

III. SINUS NODE DYSFUNCTION. Sinus node dysfunction encompasses any dysfunction of the sinus node and includes **inappropriate sinus bradycardia**, SA **exit block**, SA **arrest, and tachycardia–bradycardia syndrome**.

A. Clinical presentation. There is a wide range of presentations, and some patients' disease may be asymptomatic.

1. Syncope and **presyncope** are the most dramatic presenting symptoms. **Fatigue, angina, and shortness of breath** are more subtle consequences of sinus node dysfunction.
2. In the tachycardia–bradycardia syndrome, the primary complaint may be palpitation. Documentation of the arrhythmia may be difficult because of the sporadic and fleeting nature of the problem.

B. Etiology. The intrinsic and extrinsic causes of sinus node dysfunction are listed in Table 22.1. **Idiopathic degenerative disease** is the most common cause of intrinsic sinus node dysfunction, and the incidence increases with age. **Acute coronary syndromes** are a common cause of bradyarrhythmias, occurring in 25% to 30% of patients with myocardial infarction (MI) (Table 22.2).

C. Electrocardiographic findings

1. Inappropriate sinus bradycardia, also known as "chronotropic incompetence," is defined as a sinus rate of < 60 beats/min that does not increase appropriately

TABLE 22.1 Etiologies of Sinus Node Dysfunction

Intrinsic causes
Idiopathic degenerative disease
Coronary artery disease
Cardiomyopathy
Hypertension
Infiltrative disorders (amyloidosis, hemochromatosis, and tumors)
Collagen vascular disease (scleroderma and systemic lupus erythematosus)
Inflammatory processes (myocarditis and pericarditis)
Surgical trauma (valve surgery and transplantation)
Musculoskeletal disorders (myotonic dystrophy and Friedreich's ataxia)
Congenital heart disease (postoperative or in the absence of surgical correction)
Extrinsic causes
Drug effects
β-Blocking agents
Calcium channel blocking agents
Digoxin
Sympatholytic antihypertensives (clonidine, methyldopa, and reserpine)
Antiarrhythmic drugs
Type IA (quinidine, procainamide, and disopyramide)
Type IC (flecainide and propafenone)
Type III (sotalol and amiodarone)
Others (lithium, cimetidine, amitriptyline, and phenytoin)
Autonomic influences
Excessive vagal tone
Carotid sinus syndrome
Vasovagal syncope
Well-trained athletes (normal variant and not dysfunction)
Electrolyte abnormalities
Hyperkalemia
Hypercarbia
Endocrine disorders—hypothyroidism
Increased intracranial pressure
Hypothermia
Sepsis

From Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott–Raven; 1998, with permission.

TABLE 22.2 Incidence of Bradyarrhythmia in the Setting of Acute Myocardial Infarction

Rhythm	Incidence (%)
Sinus bradycardia	25
Junctional escape rhythm	20
Idioventricular escape rhythm	15
First-degree AV block	15
Second-degree, Mobitz type I AV block	12
Second-degree, Mobitz type II AV block	4
Third-degree AV block	15
Right bundle branch block	7
Left bundle branch block	5
Left anterior fascicular block	8
Left posterior fascicular block	0.5

AV, atrioventricular.

with exercise. Inappropriate sinus bradycardia must be differentiated from a low resting heart rate, which may be normal in athletes and sleeping individuals.

2. Sinus arrest, or sinus pause, occurs when the sinus node fails to depolarize on time. Pauses of < 3 seconds may be seen on Holter monitoring in up to 11% of normal adults (especially athletes) and are not a cause for concern. However, **pauses lasting longer than 3 seconds are generally considered abnormal and are suggestive of underlying pathology**, especially if the patient is awake when they occur.
3. SA exit block, although similar to sinus arrest on the electrocardiographic tracing, may be distinguished by the fact that the **duration of the pause is a multiple of the sinus PP** interval. High-grade SA exit block cannot be differentiated from prolonged sinus arrest and is treated in the same manner.
4. Tachycardia–bradycardia syndrome, also referred to as "sick sinus syndrome," is characterized by episodes of sinus or junctional bradycardia interspersed with an atrial tachycardia, usually paroxysmal atrial fibrillation.

D. Diagnostic testing. Invasive testing is used when noninvasive methods have failed to yield a diagnosis and sinus node dysfunction is still strongly suspected.

1. **Noninvasive testing**
   a. **Electrocardiogram (ECG).** In evaluating sinus node dysfunction, the initial workup should include a 12-lead ECG, followed by a 24-hour to 48-hour ambulatory ECG monitoring, if necessary. Use of a diary during the recording period can help correlate symptoms with the cardiac rhythm. For less frequent events, a loop recorder or an event recorder may be used to assess symptoms over a 2-week to 4-week period. Stress testing can help document the severity of chronotropic incompetence.
   b. Autonomic testing includes physical maneuvers, such as carotid sinus massage and tilt table testing, as well as pharmacologic interventions to test the autonomic reflexes.
      (1) Carotid sinus massage distinguishes intrinsic sinus pause/sinus arrest from a pause due to **carotid sinus hypersensitivity**, which is a 3-second

or longer pause and/or a ≥ 50 mm Hg or greater drop in blood pressure that occurs with massage of the carotid sinus (firm pressure applied to one carotid sinus at a time for 5 seconds). **Carotid sinus massage should not normally precipitate sinus pause/sinus arrest**, although it will decrease the rate of depolarization of the SA node and slow conduction in the AV node.

(2) Tilt table testing may help differentiate between syncope caused by sinus node dysfunction and that due to autonomic dysfunction. **Bradycardic episodes precipitated by tilt table testing are usually caused by autonomic dysfunction and not by sinus node dysfunction**.

(3) Pharmacologic testing may be used to differentiate between sinus node dysfunction and autonomic dysfunction. Total autonomic blockade is achieved after administration of atropine 0.04 mg/kg and propranolol 0.2 mg/kg. The resulting intrinsic heart rate represents the sinus node rate, devoid of autonomic influences. Assuming that the normal intrinsic heart rate (in beats/min) is defined by the formula

$$\text{Intrinsic heart rate} = 118.1 - (0.57 \times \text{age})$$

then an intrinsic heart rate lower than predicted using this formula is consistent with sinus node dysfunction; an intrinsic heart rate close to the predicted rate in a patient with a clinical presentation of sinus node dysfunction is suggestive of an autonomic dysfunction as a cause of the bradyarrhythmia.

2. Invasive testing. The two most common tests use indirect measurements of SA node function. Direct measurement of SA node function is laborious and rarely performed.

a. Sinus node recovery time (SNRT) is the time it takes the SA node to recover following paced overdrive suppression of the node.

(1) A delay of longer than 1,400 milliseconds is considered abnormal. This measurement may be corrected by subtracting the intrinsic sinus cycle length (in milliseconds) from the recovery time. **A corrected SNRT > 550 milliseconds is suggestive of sinus node dysfunction**.

(2) The limitations of this test are as follows:

(a) It is an indirect measurement of SA node function and reflects both sinoatrial node conduction time(SACT) and automaticity.

(b) It may be falsely shortened by an SA node entrance block during atrial pacing (due to failure of the paced impulse to reset the sinus node) or falsely prolonged by an SA node exit block (the sinus node is normal but the impulse cannot leave the node), which affects its specificity.

(c) The SNRT is not prolonged in all patients with sinus node dysfunction, which affects its sensitivity.

b. Sinoatrial node conduction time

(1) The steady-state atrial rate is determined (A_1–A_1 interval or the time between P waves). Then premature atrial **extra stimuli** (A_2) are introduced by pacing high in the right atrium, starting in late diastole at progressively shorter intervals until atrial refractoriness is found (i.e., A_2 does not result in a P wave). The duration before the next spontaneous atrial impulse (A_3) is measured and the baseline rate is subtracted.

$$\text{SACT} = (A_2 - A_3 \text{ interval}) - (A_1 - A_1 \text{ interval})$$

(2) The test assumes that SA node automaticity is not affected by pacing, that conduction time into the node is equal to conduction time out of the node, and that there is no shift in the principal pacemaker site.

E. Therapy. Treatment for symptomatic sinus node dysfunction may be pharmacologic, pacing, or a combination of both.

1. Indications for pacing in sinus node dysfunction are determined by symptoms (e.g., correlation with a documented arrhythmia; Table 22.3). Another common indication is when drug therapy that causes sinus node dysfunction cannot be stopped or changed.
2. Medications that suppress sinus node automaticity should be stopped if possible. If this is not possible, it may be necessary to place a temporary or permanent pacemaker (Table 22.3).
3. For patients with **tachycardia–bradycardia syndrome**, a pacemaker is often placed for management of the bradyarrhythmia, and antiarrhythmic drugs are added for treatment of the tachycardia episodes.
4. Acute treatment for patients with **symptomatic sinus node dysfunction** includes the following:
   (a) Atropine (0.04 mg/kg intravenous bolus)
   (b) Temporary pacing for patients whose conditions fail to respond to drug therapy
   (c) Isoproterenol (starting at 1 μg/min intravenously), which may be used as a bridge to pacemaker placement. Isoproterenol is not indicated in most patients with cardiac arrest

IV. AV CONDUCTION DISTURBANCES. These disturbances are classified as first-degree, second-degree, or third-degree block, depending on the severity of the conduction abnormality.

A. Classification

1. First-degree AV block is characterized by the prolongation of the PR interval beyond 200 milliseconds. This finding may occur as a normal variant in 0.5% of asymptomatic young adults without overt heart disease. In older individuals, it is most often caused by idiopathic degenerative disease of the conducting system.
2. **Second-degree** AV **block**
   a. Second-degree AV block is characterized by **a failure of one or more, but not all, atrial impulses to conduct to the ventricles**. The block may be at any level of the AV conduction system.
   b. When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes (for three P waves preceding each QRS complex, 3:1 second-degree AV block is present).
      (1) Lesser degrees of AV block (i.e., 4:3 or 3:2) with a prolonging PR interval prior to a nonconducted atrial impulse are described as **Mobitz type I AV block** (also known as Wenckebach block).
         (a) The conducted impulse of a **Mobitz type I block** will generally be narrow, and the site of block is often in the AV node above the His bundle.
         (b) A Mobitz type I block with a bundle branch block is still likely to be above the His bundle, but a His bundle ECG is needed to confirm the level of block.
      (2) High-grade AV block (3:1, 4:1, or greater) is typically described as **Mobitz type II AV block**. The conducted impulses will generally be preceded by constant PR intervals and have a wide QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] pattern). The site of block is often below the AV node. A **Mobitz type II block** is usually intra-Hisian or infra-Hisian and has a greater propensity for progressing to third-degree AV block.
      (3) Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II, and if diagnostic maneuvers (such as exercise) are not able to elucidate one type of second-degree block versus the other, an electrophysiology study may be warranted.

TABLE 22.3 Indications for Permanent Pacing

Indication	Class I	Class II	Class III
SND	1. SND documented in association with symptomatic bradycardia and due to factors that are irreversible or due to essential drug therapy 2. Symptomatic chronotropic incompetence	IIa. No clear association between SND with heart rate < 40 beats/min and symptoms can be documented IIb. In minimally symptomatic patients, chronic heart rate < 40 beats/min while awake	1. SND with marked sinus bradycardia or pauses but no associated symptoms including that due to long-term drug therapy 2. SND in patients with symptoms suggestive of bradycardia that are clearly documented as *not* associated with a slow heart rate 3. SND with symptomatic bradycardia due to nonessential drug therapy
Acquired AV block	1. Third-degree AV block at any anatomic level, associated with any one of the following conditions: a. Bradycardia with symptoms presumed to be due to AV block b. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia c. Documented periods of asystole ≥ 3.0 s, or an escape rhythm below the AV node, or any escape rate < 40 beats/min in awake, symptom-free individuals in sinus rhythm d. Documented pauses > 5 s in awake, symptom-free patients who are in atrial fibrillation	IIa. 1. Asymptomatic third-degree AV block at any anatomic site with average awake ventricular rates ≥ 40 beats/min 2. Asymptomatic type II second-degree AV block. Of note, when type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a class I recommendation 3. Asymptomatic type I second-degree AV block at intra-His or infra-His levels found incidentally at EP study performed for other indications	1. Asymptomatic one-degree AV block 2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or not known to be intra-Hisian or infra-Hisian 3. AV block expected to resolve and unlikely to recur (e.g., drug toxicity and Lyme disease)

Indication	Class I	Class II	Class III
	e. After catheter ablation of the AV junction f. Postoperative AV block that is not expected to resolve g. Neuromuscular diseases with AV block such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb's dystrophy (limb girdle), and peroneal muscular dystrophy h. Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 beats/min or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node. i. Permanent pacemaker implantation is indicated for second-degree or third-degree AV block during exercise in the absence of myocardial ischemia 2. Second-degree AV block regardless of type or site of block, with associated symptomatic bradycardia	4. First-degree AV block with symptoms suggestive of pacemaker syndrome and documented alleviation of symptoms with temporary AV pacing	
Post–myocardial infarction	1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree AV block within or below the His-Purkinje system after acute myocardial infarction	IIa. None IIb. 1. Persistent second-degree or third-degree AV block at the AV node level, even in the absence of symptoms	1. Transient AV block without intraventricular conduction defect 2. Transient AV block in the presence of isolated left anterior fascicular block

(Continued)

TABLE 22.3 Indications for Permanent Pacing (*Continued*)

Indication	Class I	Class II	Class III
	2. Transient advanced (second-degree or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an EP study may be necessary 3. Persistent and symptomatic second-degree or third-degree AV block		3. Acquired left anterior fascicular block in the absence of AV block 4. Persistent first-degree AV block in the presence of bundle branch block that is old or age indeterminate
Chronic bifascicular and trifascicular blocks	1. Intermittent third-degree AV block 2. Type II second-degree AV block 3. Alternating bundle branch block	IIa. 1. Syncope not proved to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia 2. HV interval > 100 milliseconds 3. Pacing-induced block below the His that is not physiologic	1. Fascicular block without AV block or symptoms 2. Fascicular block with first-degree AV block without symptoms
Carotid sinus hypersensitivity (carotid sinus irritability) and neurally mediated syncope	1. Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of > 3 s duration in the absence of any medication that depresses the sinus node or AV conduction	IIb. None IIa. 1. Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response 2. Syncope of unexplained origin when major abnormalities of sinus node function or AV conduction are discovered or provoked in EP studies	1. A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms 2. A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms A hyperactive cardioinhibitory response to carotid sinus stimulation in the presence of vague symptoms such as dizziness, light-headedness, or both

Indication	Class I	Class II	Class III
		IIb. 1. Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt with or without isoproterenol and other provocative maneuvers	3. Recurrent syncope, light-headedness, or dizziness in the absence of a hyperactive cardioinhibitory response 4. Situational vasovagal syncope in which avoidance behavior is effective

Class I: conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.
Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of pacing.
Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: usefulness/efficacy is less well established by evidence/opinion.
Class III: conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.
SND, sinus node dysfunction; AV, atrioventricular; LV, left ventricular; EP, electrophysiologic; HV, half-value.

Adapted from Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices). *J Am Coll Cardiol*. 2008; 51:2085-2105.

3. Third-degree AV block, or **complete heart block**, may be acquired or congenital.
   a. Of patients with **congenital complete heart block**, 60% are female. Of children with congenital complete heart block, 30% to 50% of their mothers have connective tissue disease, usually systemic lupus erythematosus.
   b. Acquired AV block occurs most frequently in the seventh decade and more commonly affects males.

B. Clinical presentation

1. **Signs and symptoms**
   a. First-degree AV block is generally not a cause of symptoms.
   b. Second-degree AV block sometimes results in symptoms; however, high-grade second-degree AV block may progress to third-degree AV block, which can frequently cause symptoms.
   c. Depending on the ventricular escape rate, patients with **third-degree** AV **block** may experience **fatigue** or **syncope**.
2. **Physical findings.** The amplitude of the arterial pulse and venous waveform varies, depending on the timing of atrial filling of the ventricles.
   a. Second-degree AV block is associated with a periodic change in amplitude. In patients with **third-degree AV block**, amplitude is constantly changing, for example, periodic appearance of cannon *a* waves (large-amplitude waves in the venous pulsations seen in the neck when the atria contracts against a closed tricuspid valve).
   b. Heart sounds are similarly affected by the change in filling duration of the ventricles.
      (1) **The first heart sound** (S_1) becomes softer as the PR interval is prolonged, resulting in a soft S_1 in first-degree AV block, a progressive softening of S_1 in type I second-degree AV block, and a constantly changing S_1 in third-degree AV block.
      (2) Third-degree AV block may also result in a functional systolic ejection murmur.

C. Etiology. The causes of AV block are listed in Table 22.4; the most common cause is **idiopathic fibrosis. Acute MI** results in AV block in 14% of patients with inferior infarction and 2% of those with anterior infarction, usually within the first 24 hours.

D. Diagnostic testing

1. **First-degree AV block.** Measuring a PR interval longer than 200 milliseconds in adults and 180 milliseconds in children makes up the diagnosis. A P wave precedes each QRS, and both the P and the QRS are morphologically normal.
2. **Second-degree AV block**
   a. The diagnosis of **Mobitz type I** is made when the following criteria are met on the ECG:
      (1) Sequential and gradual prolongation of the PR interval terminated by a nonconducted P wave
      (2) Prolongation of the PR interval occurring in progressively shorter increments in "typical" Wenckebach, which results in progressive shortening of the RR intervals prior to the nonconducted atrial impulse
      (3) Duration of the pause following the nonconducted P wave is less than the sum of any two consecutively conducted beats
      (4) Decreased PR interval following the pause when compared with the prepause PR interval
      (5) "Grouped beating," a pattern of repeated groups of QRS complexes characteristic of Wenckebach block
   b. Mobitz type II second-degree AV block is less common than type I.
      (1) The PR interval is constant with a sudden nonconducted P wave (Fig. 22.2), in contrast to nonconducted premature atrial contractions that have a varying PR interval.

TABLE 22.4 Causes of Atrioventricular Block

- Drug effects
  - Digoxin
  - β-Blockers
  - Certain calcium channel blockers (nondihydropyridines)
  - Membrane-active antiarrhythmic drugs
- Ischemic heart disease
  - Acute myocardial infarction
  - Chronic coronary artery disease
- Idiopathic fibrosis of the conduction system
  - Lenegre's disease
  - Lev's disease
- Congenital heart disease
  - Congenital complete heart block
  - Ostium primum atrial septal defect
  - Transposition of the great vessels
  - Maternal systemic lupus erythematosus
- Calcific valvular disease
- Cardiomyopathy
- Infiltrative disease
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
- Infectious/inflammatory diseases
  - Endocarditis
  - Myocarditis (Chagas disease, Lyme disease, rheumatic fever, tuberculosis, measles, and mumps)
- Collagen vascular diseases (scleroderma, rheumatoid arthritis, Reiter's syndrome, systemic lupus erythematosus, ankylosing spondylitis, and polymyositis)
- Metabolic
  - Hyperkalemia
  - Hypermagnesemia
- Endocrine—Addison's disease
- Trauma
  - Cardiac surgery
  - Radiation
  - Catheter trauma
  - Catheter ablation
- Tumors
  - Mesothelioma
  - Hodgkin's disease
  - Malignant melanoma
  - Rhabdomyosarcoma
- Neurally mediated
  - Carotid sinus syndrome
  - Vasovagal syncope
- Neuromyopathic disorders
  - Myotonic muscular dystrophy
  - Slowly progressive X-linked muscular dystrophy

From Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott–Raven; 1998, with permission.

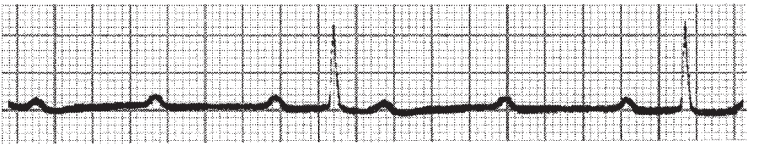

FIGURE 22.2 Mobitz type II second-degree atrioventricular block with 3:1 conduction.

(2) Each QRS complex may have multiple P waves, which are designated by the number of P waves before each conducted QRS (3:1, 4:1, etc.). The QRS complex is typically not narrow (a narrow QRS complex is suggestive of a Mobitz type I block).

3. **Third-degree AV block** (Fig. 22.3)
   a. Third-degree AV block is characterized by the identification of **complete dissociation of the atrial and ventricular electrical activities** (no temporal relationship exists between the P waves and the QRS complexes), with atrial activity more rapid than ventricular activity. Using calipers, it is possible to march out the progression of the P waves to determine the atrial rate.
   b. Third-degree AV block is only one cause of AV dissociation; **not all AV dissociation is third-degree AV block.** For example, conditions where the ventricles are depolarizing faster than the atria—such as accelerated junctional rhythm or ventricular tachycardia—also result in AV dissociation if there is a lack of retrograde conduction over the AV node.

E. **Therapy.** Patients with first-degree AV block and Mobitz type I AV block usually do not require therapy. Permanent pacing is indicated for Mobitz type II AV block and third-degree AV block. (See Table 22.3 for complete indications for pacing.)

1. Medical therapy may be used as a bridge to pacing but it has no role in long-term treatment.
   a. The principal drug used as a bridge to pacing is **atropine**,
      (1) which reduces heart block due to hypervagotonia but not due to AV nodal ischemia;
      (2) which is more useful for AV block in inferior MI than anterior MI;
      (3) which does not increase infranodal conduction (will not improve second-degree or third-degree AV block that is below the AV node);
      (4) which is ineffective in the denervated hearts of transplant patients;
      (5) which is used with caution (if at all) in Mobitz type II AV block due to a possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases, and a 2:1 block with an atrial rate of 80 beats/min and a ventricular rate of 40 beats/min may be converted to a 3:1 block with an atrial rate of 90 beats/min and a ventricular rate of 30 beats/min).
   b. Digoxin-specific Fab fragments may be used to treat patients with symptomatic AV blocks related to the use of digitalis. The number of vials = weight (kg) × digoxin serum concentration (ng/mL)/100.
2. **Pacing**
   a. Third-degree AV block as a complication of inferior MI is usually temporary and thus usually only requires **temporary pacing**.
   b. However, complete heart block as a result of anterior MI often requires **permanent pacing** (Table 22.3).
   c. Acquired third-degree AV block usually requires pacing, but patients with congenital third-degree AV block often have a sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.

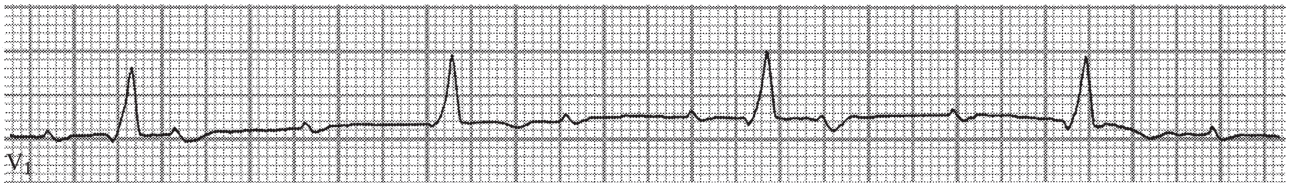

FIGURE 22.3 Third-degree atrioventricular block with sinus tachycardia and right bundle branch block.

V. JUNCTIONAL RHYTHMS. Junctional rhythms arise from the area surrounding the AV node, including the approaches to the node, the node itself, and the bundle of His. This area has an intrinsic rate of 30 to 60 beats/min and serves as an escape mechanism to prevent ventricular asystole in case of complete AV block. Junctional rhythm that is faster than the sinus rhythm is referred to as **accelerated junctional rhythm**.

A. Clinical presentation. Patients usually do not develop symptoms that are directly attributable to accelerated junctional rhythm. The **physical findings of AV dissociation may be noted** and are the same as those seen in third-degree AV block.

B. Etiology

1. Accelerated junctional rhythm is seen in approximately **10% of patients with acute MI**. More than one-half of these patients have inferior MI and about one-third have anterior infarctions.
2. Digitalis toxicity by itself does not seem to cause accelerated junctional rhythm, as evidenced in persons with normal hearts who take accidental overdoses of digoxin. **Concomitant heart disease** is required to develop accelerated junctional rhythm.
3. Other causes of accelerated junctional rhythm are valve surgery, acute rheumatic fever, direct current cardioversion, cardiac catheterization, serious infection, chronic obstructive pulmonary disease, systemic amyloidosis, and uremia with hyperkalemia.

C. ECG findings

1. **Accelerated junctional rhythm**
   a. **Unless the junctional rhythm causes retrograde activation of the atria**, the P wave is normal in morphologic characteristics. The QRS complex has a normal duration, unless there is concomitant bundle branch block. The distinguishing characteristic of accelerated junctional rhythm is the AV dissociation and changing PR interval (Fig. 22.4).
   b. **The difference between accelerated junctional rhythm and third-degree AV block is the fact that the ventricular rate is faster than the atrial rate in accelerated junctional rhythm and slower than the atrial rate in third-degree AV block**.
2. **Junctional rhythm.** In the absence of a sinus beat, the AV node can act as a backup pacemaker. The ECG findings are an absence of P waves (or retrograde P waves immediately before or after the QRS complex), a narrow QRS complex, and a rate of 30 to 60 beats/min.

D. Therapy

1. Therapy for junctional rhythm secondary to SA node failure or AV block is as previously outlined for AV conduction disturbances.
2. Patients with accelerated junctional rhythm do not usually require therapy for the arrhythmia, although management of the underlying cause is indicated.
3. Suppression of accelerated junctional rhythm may be achieved by **increasing the atrial rate with drugs** (e.g., atropine and adrenergics) or **pacing**.
4. Digoxin-induced accelerated junctional rhythm is an indication to stop digoxin but it does not usually require administration of digoxin-specific Fab fragments.

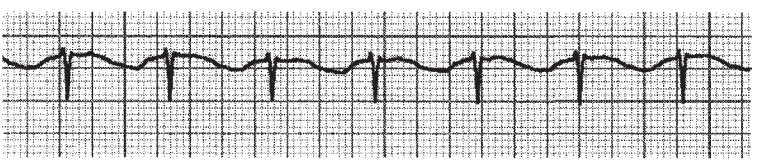

FIGURE 22.4 Accelerated junctional rhythm.

VI. INTRAVENTRICULAR CONDUCTION DISTURBANCES. Conduction disturbances due to blockage below the AV node are classified on the basis of the intraventricular conduction system. An intraventricular conduction disturbance (IVCD) does not itself cause bradyarrhythmia, but it may be associated with any of the other rhythms that cause bradycardia. When associated with an acute MI, an IVCD predicts a worse outcome.

A. Etiology

1. The causes of IVCDs are similar to those that cause AV block (Table 22.4); **idiopathic degenerative conduction disease** and **acute ischemic syndromes** are the most common causes.
2. IVCDs increase with age and affect up to 2% of individuals older than 60 years.
3. The incidence of IVCDs is increased in persons with structural heart disease, especially those with coronary artery disease.

B. ECG findings

1. The ECG findings of IVCDs are summarized in Table 22.5 and examples are presented in Figures 22.5 to 22.8. As shown, **IVCDs may be further classified by the number of fascicles they affect**.
2. **Fascicular blocks**
   a. Unifascicular blocks affect only one of the three fascicles. Examples are RBBB, left anterior fascicular block, and left posterior fascicular block (LPFB).
   b. Bifascicular block is present when conduction disturbances affect two of the fascicles, most commonly the right bundle branch and the left anterior fascicle. Approximately, 6% of these patients progress to complete heart block. RBBB with LPFB is less common, but the progression to complete heart block is more common.
   c. "Trifascicular block" is said to be present when there is a combination of bifascicular block and first-degree AV block (Fig. 22.8).

C. Therapy. Pacing is indicated in patients with bifascicular block who have intermittent symptomatic complete heart block and in patients with bifascicular or trifascicular block with asymptomatic intermittent Mobitz type II AV block (Table 22.3).

TABLE 22.5 Electrocardiographic Features for the Fascicular and Bifascicular Blocks

ECG finding	LBBB	LAFB	LPFB	RBBB	RBBB and LAFB	RBBB and LPFB
QRS axis		≥ – 45°	+90° to +120°		–60° to –120°	≥ +120°
QRS duration Leads I/aVL	≥ 120 milliseconds broad monophasic R	Normal qR	Normal rS	≥ 120 milliseconds qRS with wide terminal S	≥ 120 milliseconds qR	≥ 120 milliseconds rS
Leads II, III, and aVF		rS	qR		rS	qR
Leads V_1 and V_2	rS or QS			rsR′ or rSR′	rsR′ or rSR′	rsR′ or rSR′
Leads V_5 and V_6		S	no Q's	qRS		

ECG, electrocardiogram; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.

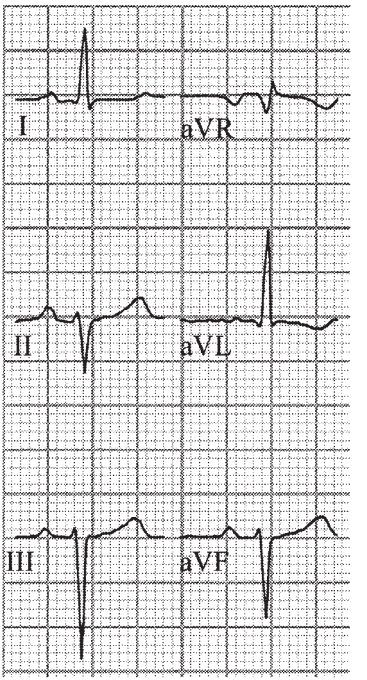

FIGURE 22.5 Left anterior hemiblock.

VII. POSTSURGICAL BRADYARRHYTHMIAS

A. Etiology. Bradyarrhythmias following cardiac surgery are common.

1. Valvular surgery and septal myectomy can cause mechanical damage to the conduction system, leading to AV blocks and IVCDs. For example, there is an approximately 7% incidence of postoperative permanent pacemaker implantation for high-grade AV block after conventional aortic valve replacement in patients with severe calcific aortic stenosis (this may be partly due to a higher prevalence of infranodal conduction system disease at baseline). Also, there is a high incidence of LBBB after septal myectomy, due to the presence of the left bundle branch in the myocardium being excised.
2. Prolonged ischemic time during cardiac transplantation can lead to sinus node damage.

B. Therapy. Because postsurgical bradyarrhythmias may be only temporary, the decision to proceed to **permanent pacing** should be made after 5 to 7 days. The same criteria listed in Table 22.3 are used to determine the need for a pacemaker. Permanent pacing is required in 2% to 3% of patients following valve surgery (when considering all types) and in upward of 10% of transplant patients.

VIII. PULSELESS ELECTRICAL ACTIVITY.

Pulseless electrical activity is defined as the absence of a pulse or blood pressure measured by usual methods, with the continued presence of electrical activity of the heart.

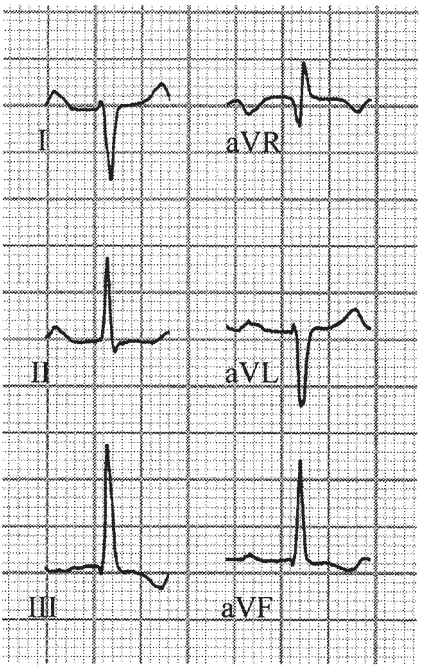

FIGURE 22.6 Left posterior hemiblock.

A. Etiology

1. Pulseless electrical activity may result from a variety of **rhythm disturbances**, such as electrical–mechanical dissociation, idioventricular rhythms, and ventricular tachycardias. When the electrical activity is organized and within the physiologic range, the term **electrical–mechanical dissociation** is used.
2. A variety of clinical situations are also associated with pulseless electrical activity, a potentially manageable condition if certain actions are undertaken rapidly (Table 22.6).

B. Therapy

1. Specific management of the underlying cause is most likely to result in a successful outcome (Table 22.6).
2. Emergency intervention should be initiated at once, including the following:
   - **(a)** Effective cardiopulmonary resuscitation (CPR) and airway management
   - **(b)** Epinephrine, 1 mg intravenous push every 3 to 5 minutes
   - **(c)** A one-time intravenous push of 40 IU of vasopressin may be considered as an alternative to epinephrine during the first or second round of advanced cardiac life support
   - **(d)** Atropine is no longer recommended for routine administration during advanced cardiac life support for pulseless electrical activity, as per 2010 ACC/AHA guidelines.
   - **(e)** Discovery and correction of the underlying reason for the pulseless electrical activity (see Table 22.6) remains the paramount concern along with performing

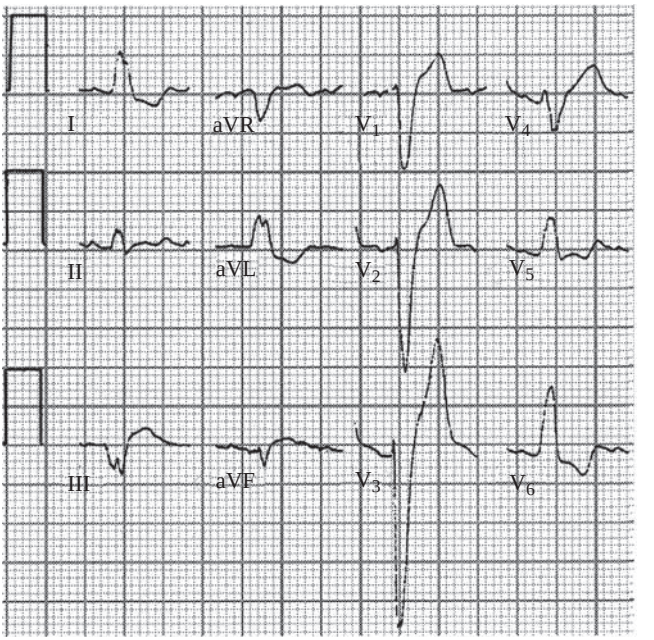

FIGURE 22.7 Left bundle branch block.

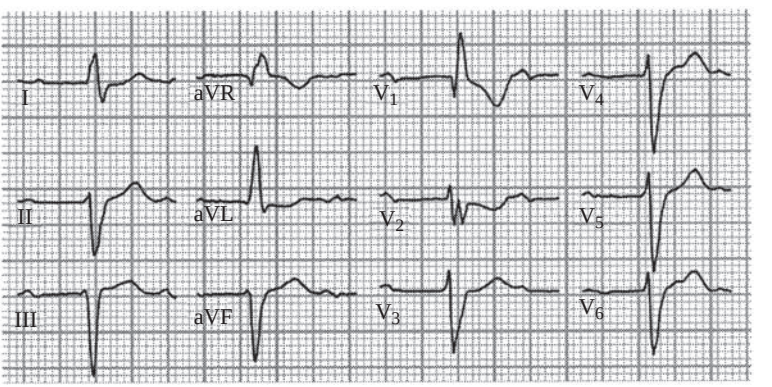

FIGURE 22.8 First-degree atrioventricular block with right bundle branch block and left anterior hemiblock.

effective CPR. The "H's and T's" of hypoxia, hypovolemia, hypothermia, hyperkalemia, acidosis ("hyper-H+"), tension pneumothorax, thrombosis (coronary or pulmonary), tamponade, and toxins must be considered and addressed as soon as possible.

TABLE 22.6 Conditions That Cause Pulseless Electrical Activity

Condition	Clues	Management
Hypovolemia	History and flat neck veins	Volume infusion
Hypoxia	Cyanosis, blood gases, and airway problems	Ventilation
Cardiac tamponade	History (trauma, renal failure, and malignancy), no pulse with CPR, vein distention; impending tamponade—tachycardia, hypotension, and low pulse pressure	Pericardiocentesis
Tension pneumothorax	History (asthma, ventilator, chronic obstructive pulmonary disease, and trauma), no pulse with CPR, neck vein distention, and tracheal deviation	Needle decompression
Hypothermia	History of exposure to cold, central body temperature, and ECG	Gradual warming
Massive pulmonary embolism	History and no pulse felt with CPR	Pulmonary arteriogram, surgical embolectomy, and thrombolytics
Drug overdose (tricyclics, digoxin, β-blockers, and calcium channel blockers)	Bradycardia, history of ingestion, empty bottles at the scene, pupils, and neurologic examination	Drug screens, intubation, lavage, activated charcoal, and lactulose per local protocols
Hyperkalemia	History of renal failure, diabetes, recent dialysis, medications, and ECG	Calcium chloride (immediate); then combination of insulin, glucose, and sodium bicarbonate; then sodium polystyrene sulfonate/sorbitol; and dialysis (long term)
Preexisting acidosis	Renal failure	Sodium bicarbonate and hyperventilation
Acute massive MI	History, ECG and enzymes	Treatment for cardiogenic shock

CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; MI, myocardial infarction.

IX. ASYSTOLE

A. Clinical presentation. Asystole is defined as the absence of myocardial electrical activity. *It should be confirmed by switching between several leads or changing the position of the defibrillation paddles.*

1. Most patients with asystole present in a code situation. Persons outside of the hospital who are found to have asystole by the initial responding team usually have it as a result of **profound myocardial ischemia**. The possibility of a successful outcome in this situation is extremely small.

2. Hospital inpatients monitored by telemetry, on the other hand, may have a favorable outcome.

B. Etiology. Asystole may be due to profound parasympathetic suppression of both atrial and ventricular activities, stunning of the myocardium due to electrical defibrillation, complete heart block, or prolonged myocardial ischemia. Also, many of the causes of pulseless electrical activity may also lead to asystole, and the same search for obvious and immediately reversible causes is warranted (Table 22.6).

C. Therapy. Management consists of effective **CPR, airway protection**, and **a similar management algorithm to** pulseless electrical activity.

1. Routine shocking is strongly discouraged. Electrical shocks have not been demonstrated to have any benefit in the management of asystole and may in fact produce a stunned myocardium, leading to a delay in the return of a rhythm.
2. Pacing for asystole is controversial. If pacing is to have any effect, it must be initiated early. Patients with asystole due to myocardial ischemia are unlikely to respond to pacing, but those with asystole due to other causes might respond.
3. As with the 2010 revised guidelines for management of pulseless electrical activity, atropine is no longer recommended for routine use in the resuscitation of the asystolic patient.

X. CAROTID SINUS HYPERSENSITIVITY. Carotid sinus hypersensitivity, defined as a sinus pause of 3 seconds or more and/or a drop in blood pressure of 50 mm Hg or more with carotid sinus massage, is common, affecting up to one-third of older men with coronary artery disease. Carotid sinus hypersensitivity may be purely cardioinhibitory, purely vasodepressive, or a combination of both. **Carotid sinus syndrome** is present when carotid sinus hypersensitivity is accompanied by syncope or near syncope.

A. Etiology and pathophysiology

1. The **cause of carotid sinus hypersensitivity and carotid sinus syndrome is unknown**. It is more common in older individuals, particularly those with atherosclerotic disease. Carotid sinus syndrome may be precipitated by the patient stretching his or her neck (such as with shaving or turning the head) or wearing a tight collar, but often a precipitating event cannot be found.
2. Sites of potential lesions causing carotid sinus hypersensitivity are the sternocleidomastoid muscle, the central nervous system, and the feedback loops between the cardiovascular and the central nervous systems.
3. It has been demonstrated that the **carotid sinus function is intact** and the sinus is not hypersensitive in the true sense. Some investigators have suggested that carotid sinus syndrome be renamed carotid sinus irritability to better reflect its pathophysiology.

B. Diagnostic testing. A patient with suspected carotid sinus hypersensitivity/carotid sinus syndrome should be tested lying down with ECG and blood pressure monitoring.

1. Carotid sinus massage is performed by placing firm manual pressure over the carotid sinus located at the bifurcation of the carotid artery for not more than 5 seconds. Only one sinus at a time is compressed, and the temporal artery should be lightly palpated to ensure that complete occlusion of the artery does not occur.
2. Potential risks of carotid sinus massage are transient ischemic attack and stroke. This test should not be performed if a carotid bruit is present. Tilting the patient to an upright position will increase the diagnostic yield of the test but it may also result in false-positive outcomes.

C. Therapy

1. Carotid sinus hypersensitivity by itself generally does not require treatment. However, therapy is warranted if carotid sinus hypersensitivity is demonstrated to be the cause of syncope or near syncope.

2. For purely cardioinhibitory or the mixed type of carotid sinus syndrome, the therapy of choice is pacing (Table 22.3).
3. Management of vasodepressive carotid sinus syndrome is more difficult, and pacing is generally ineffective.

ACKNOWLEDGMENTS: *The author thanks Drs. Christopher Cole, Gregory Bashian, and Oussama Wazni for their significant contributions to earlier editions of this chapter.*

LANDMARK ARTICLES

Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices). *J Am Coll Cardiol*. 2008;51:2085–2105

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CHAPTER 23

Edmond M. Cronin

Sudden Cardiac Death

I. DEFINITION AND EPIDEMIOLOGY. Sudden cardiac death (SCD) is defined as death following cardiac arrest in a patient with or without known preexisting heart disease in whom the mode and time of death are unexpected (1). The generally accepted timeframe between the onset of symptoms and loss of consciousness is 1 hour, although some patients who receive medical interventions may live for much longer after the initiating event before expiring. If the patient survives the event, due to defibrillation or spontaneous recovery, it is labeled sudden cardiac arrest (SCA). The incidence of SCD in the United States is estimated at 460,000 cases per annum, accounting for 10% to 15% of all deaths from natural causes and about 50% of all cardiac deaths. SCD exhibits a bimodal age distribution with peaks between birth and 6 months of age and then rises steadily from age 30. A male preponderance is observed in all age groups, narrowing after age 65, and is attributable to an increased incidence of coronary artery disease (CAD). While the absolute risk of SCD is greater among high-risk populations, most SCDs occur in patients who have not been identified as being at risk, being the first presentation of cardiovascular disease in approximately 25% of patients.

It is likely that ventricular fibrillation (VF) or ventricular tachycardia (VT) is the initiating rhythm in most cases of SCA. As the time from onset and rhythm identification increases, the proportion of VF decreases. This suggests that asystole and pulseless electrical activity (PEA) are frequently the result of prolonged VF and resultant ischemia and hypoxia. However, a significant proportion of SCA is due to bradyarrhythmias and pump failure. The proportion of these deaths is slightly higher in patients with advanced heart failure, although tachyarrhythmias still predominate.

II. CAUSES OF SCD

A. Coronary artery disease accounts for 80% or more of episodes of SCD in Western societies, and SCD is the first presentation of CAD in 20% to 25% of patients. However, the extent to which acute ischemia plays a role in initiating a trigger for SCD is unclear. Autopsy data have demonstrated a recent occlusive thrombus in only about 15% to 20% of patients, while evidence of a remote infarct is identified in 40% to 70% of cases. The majority (80%) of SCD episodes in patients with CAD are considered to be primary (i.e., no precipitating factor can be identified), whereas secondary causes like myocardial ischemia/infarction, drug toxicity or proarrhythmia, decompensated heart failure, or electrolyte imbalance can be identified in the minority. Patients with reduced left ventricular ejection fraction (LVEF) and frequent premature ventricular contractions (PVCs) are identified as a particularly high-risk subgroup. A study of patients implanted with a loop recorder with recent myocardial infarction (MI) and ejection fraction (EF) ≤ 40% found that the terminal rhythm was VF in 86% of sudden deaths, and 50% of all deaths, with bradyarrhythmias in the remaining 50%.

B. Cardiomyopathies

1. **Dilated cardiomyopathy (DCM).** Patients with DCM represent the second largest group of patients who experience SCD, accounting for approximately 10% of cases. The annual mortality from DCM is 11% to 15%, with SCD accounting for about 30% of all deaths in this population. The presence of reduced LVEF and syncope are markers of a high risk of SCD in these patients. There is also a higher incidence of sudden deaths related to bradyarrhythmias and PEA in patients with advanced disease.
2. **Hypertrophic cardiomyopathy (HCM).** The incidence of SCD in patients with *HCM* is 2% to 4% per year in adults and 4% to 6% per year in children and adolescents. Risk factors that identify a high-risk population in patients with HCM include prior SCA, family history of SCD, sustained or nonsustained VT (NSVT), syncope, a drop in blood pressure with exercise, and septal hypertrophy ≥ 30 mm. Myocardial scar, detected by late gadolinium enhancement on magnetic resonance imaging (MRI), is also emerging as a predictor of risk. SCD usually results from ventricular arrhythmias, but occasionally it may be precipitated by atrial fibrillation, bradyarrhythmias, or myocardial ischemia.
3. **Arrhythmogenic right ventricular dysplasia (ARVD).** *ARVD* is a rare genetic disorder characterized by heart failure, ventricular arrhythmias, and SCD. Mutations involving the desmosome are manifested by fibrofatty infiltration of the right ventricle. The incidence of SCD is approximately 2% per year and is mainly due to ventricular tachyarrhythmia. Patients are identifiable by right bundle branch block (RBBB), T-wave inversion in V_1 through V_3 and epsilon waves on the electrocardiogram (ECG), regional right ventricular akinesia, dyskinesia, or aneurysm on echo or MRI, and findings on endomyocardial biopsy.

C. The channelopathies

1. **The congenital long QT syndrome (LQTS).** *LQTS* is a familial disease with a prevalence of about 1:2,000, characterized by an abnormally long QT interval, leading to the development of early afterdepolarizations and torsades de pointes.

The two variants of the syndrome include the more common autosomal dominant form (Romano-Ward syndrome) and the less common recessive form (Jervell and Lange-Nielsen syndrome), which is associated with congenital deafness. To date, mutations at 12 different LQTS susceptibility genes have been identified. The most common, accounting for over 50% of cases, is a mutation in *KCNQ1*, which encodes the α-subunit of the potassium channel conducting the slow delayed rectifier current (I_{Ks}). This mutation produces LQT1, which is characterized clinically by broad-based T waves and exercise-induced arrhythmic events (especially swimming). LQT2 (35% to 40% of cases) is caused by mutations in the *KCNH2* gene encoding the HERG protein (I_{Kr} current) and presents with low-amplitude, notched T waves and auditory arrhythmogenic triggers. LQT3 is caused by a gain-of-function mutation in the sodium channel gene *SCN5A* and manifests a long, isoelectric ST segment and SCD events during sleep.

The mortality rate for LQTS is estimated to be about 1% per year. High-risk patients include those with a corrected QT interval > 500 milliseconds, a history of syncope or SCA, male sex in children and female sex in adults (especially after menopause), and the LQT2 or LQT3 genotype. It has been postulated that 11% to 13% of sudden infant death syndrome cases could be caused by LQTS. All patients are treated with β-blocker therapy; however, genotype-specific and individualized therapies are evolving. Symptomatic patients who are either refractory to or intolerant of medical therapy, or who have other high-risk markers for SCD, should be considered for implantable cardioverter–defibrillator (ICD) implantation and left cardiac sympathetic denervation. It seems increasingly likely that many patients who suffer cardiac events due to drug-induced or other acquired QT prolongation have a *forme fruste* of LQTS.

The very rare *short QT syndrome* is caused by mutations in genes encoding the potassium channel, resulting in shortening of the action potential duration and vulnerability to VF.

2. **Brugada syndrome.** The *Brugada syndrome* is an autosomal dominant arrhythmogenic disorder caused by mutations in the *SCN5A* gene encoding the cardiac sodium channel, which predisposes patients to develop polymorphic VT or VF. The arrhythmias commonly occur at rest or during sleep, and the risk of SCA is up to 30% at 3 years in untreated symptomatic patients. Incomplete RBBB with coved ST elevation in the right precordial leads is diagnostic and, although often transient, may be elicited by a drug challenge. Atrial fibrillation and conduction abnormalities are frequently associated. Symptomatic patients (syncope or SCA) should undergo ICD implantation; risk stratification for asymptomatic patients is controversial.
3. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** is due to mutations in the ryanodine receptor and calsequestrin and results in a malignant phenotype of bidirectional VT during emotional or physical stress. Treatment is with β-blockers and ICD, and recent evidence suggests an emerging role for flecainide.

D. Others. The risk of SCD is also higher in patients with *Wolff-Parkinson-White (WPW) syndrome*, especially if they have rapidly conducting accessory pathways, when atrial fibrillation can be associated with very rapid ventricular rates and degeneration to VF. An RR interval ≤ 220 milliseconds during spontaneous AF indicates a higher risk. The incidence of SCD is 0.05% to 0.1% per year and is higher in males in their second and third decades, but the phenomenon is easily identifiable and manageable. When no cause of SCA can be found, the label *idiopathic VF* is applied. In some cases, VF is triggered by a PVC which is amenable to catheter ablation. Recent evidence suggests that *early repolarization* on ECG denotes a higher risk of SCD in the presence of proarrhythmic triggers, and the clinical implications of this are still being clarified. Some of the other cardiac and noncardiac causes of SCD are presented in Table 23.1.

TABLE 23.1 Some Other Conditions with an Increased Risk of Sudden Cardiac Death

Cardiac	Noncardiac
Cardiac vascular	Neurologic
Coronary artery anomalies	Epilepsy
Coronary artery embolism	Hereditary muscular dystrophies
Coronary arteritis (polyarteritis nodosa and Kawasaki syndrome)	Friedreich's ataxia
Coronary artery dissection	Central nervous system injury
Coronary spasm	Respiratory
Myocardial bridging	Asthma
Valvular and great vessels	Obstructive sleep apnea
Severe aortic stenosis	Massive pulmonary embolism
Severe mitral regurgitation	Pulmonary hypertension
Prosthetic valvular obstruction or dehiscence	Endocrine and metabolic
Ruptured sinus of Valsalva aneurysm	Diabetes mellitus
Aortic dissection	Acromegaly
Electrophysiologic	Electrolyte disturbances
Progressive cardiac conduction disease (Lev-Lenegre disease)	Acid–base disturbances
Myocardial	Renal
Left ventricular hypertrophy	Chronic kidney disease
Infiltrative disease (sarcoid and amyloid)	Hemodialysis
Apical ballooning syndrome	Psychiatric/psychological
Myocarditis	Depression
Congenital	Anxiety
Eisenmenger physiology	Anorexia nervosa
Late after surgical repair, especially of tetralogy of Fallot	Intense emotion
Trauma	Situational
Cardiac tamponade	Intense exercise and athletes
Commotio cordis	Drugs
	Antiarrhythmic drugs
	Typical and atypical antipsychotics
	Other QT-prolonging drugs
	Drug–drug interactions
	Cigarette smoking
	Cocaine

III. DIAGNOSTIC AND PROGNOSTIC TESTING. Survivors of SCA should have a detailed cardiovascular evaluation. Reversible precipitating factors must be identified and corrected. Underlying diseases must be identified and managed, and the risk of recurrent SCD must be determined. Diagnostic and prognostic testing appropriate for the survivor of SCA includes the following:

A. ECG for the evidence of MI or ischemia, intraventricular conduction delay, accessory pathway (WPW syndrome), prolonged QT interval, epsilon waves, Brugada pattern, and left ventricular hypertrophy.

B. Laboratory data to rule out reversible causes, such as cardiac biomarkers (creatine kinase–myocardial band, troponin T, and troponin I), abnormal electrolytes, antiarrhythmic drug levels for toxicity, and urine screening for illicit drugs such as cocaine.

C. ECG monitoring to assess frequency, duration, and symptomatology of arrhythmias.

D. **Twenty-four-hour ambulatory electrocardiography** during normal activities can be useful in predicting the risk of recurrent SCA.

E. **Echocardiography** for the assessment of left ventricular function, valvular disease, cardiomyopathy, and hypertrophy. Nuclear or angiographic determinations of left ventricular function may be used but do not provide as much information as echocardiography. The LVEF continues to be the most potent predictor of SCD, behaving as a continuous variable with markedly increased risk < 40%. However, nonsudden death also increases with declining EF, meaning that the likely mode of death cannot be predicted. LVEF is also limited by poor sensitivity—from 22% to 59% in studies in the last decade.

F. **Coronary angiography** for the assessment of CAD or coronary anomalies.

G. **Exercise or pharmacologic stress testing** with radionuclide imaging or echocardiography if CAD is present and myocardial ischemia and/or viability is in question.

H. **Electrophysiologic (EP) testing** has a limited role in assessing the survivor of SCA. Given its low sensitivity, a negative test does not exclude recurrent SCA, and almost all patients who survive SCA are in any case candidates for an ICD. Although EP testing can be performed to guide programming of the ICD, this is rarely done in practice. Voltage mapping has been used to corroborate a diagnosis of ARVD, and mapping and ablation are essential in the management of patients with WPW and selected patients with cardiomyopathy and VT. Emerging applications of ablation in ARVD and Brugada syndrome deserve further study.

I. **Cardiac MRI.** Particularly for the patient with normal left ventricular function, cardiac MRI may be useful to evaluate for arrhythmogenic right ventricular cardiomyopathy and to investigate left ventricular hypertrophy.

J. Drug challenge with flecainide, procainamide, or ajmaline to provoke the Brugada pattern should be considered in all SCA survivors where the above tests do not reveal a cause. Epinephrine infusion or exercise testing has been used to diagnose LQT1 and CPVT.

K. Genetic testing for the channelopathies, HCM, and ARVD is becoming increasingly comprehensive; however, many as yet unidentified mutations are postulated to exist. At present, only 21% of patients with Brugada syndrome and 52% with ARVD have an identifiable causative mutation. Testing in cases where a clear phenotype has not been established, or is not suggestive of a genetic disorder, is discouraged, as many variants are of uncertain significance. A positive genetic test is useful and facilitates family screening, but a negative test is not.

IV. THERAPY

A. Acute therapy for SCA

1. **Cardiopulmonary resuscitation (CPR).** Early response is crucial. The two most critical components of out-of-hospital cardiac resuscitation are the availability of a rapid response system and citizen bystander CPR. Survivors of SCA are more likely to be discharged from the hospital if the arrest is witnessed and they receive early CPR from bystanders. There is an increasing drive to train police personnel, students, and the general public in resuscitation techniques, focusing on high-quality, uninterrupted chest compressions.
2. **Automated external defibrillator (AED) and public access defibrillation.** An AED is designed to be used by emergency personnel and lay rescuers with minimal or no training, particularly for victims of out-of-hospital SCA. The device monitors the patient's ECG via self-adhesive defibrillation electrode pads applied to the chest wall and is programmed with a VF detection algorithm. When the device detects VF, an alarm is emitted, followed by delivery of a defibrillation shock or an indicator for the rescuer to press a button to deliver the shock. Availability of these devices results in more rapid delivery of defibrillation and improved survival to hospital discharge in several large trials. Provision of AEDs for public access defibrillation in airports, sporting facilities, and shopping

malls has the potential to have a significant impact on survival of out-of-hospital SCA. Home AEDs have not been shown to increase survival.

3. **Advanced cardiac life support (ACLS).** Unlike AEDs, incorporation of ACLS techniques into prehospital care has not been shown to improve survival in out-of-hospital SCA. Continuous refinements in ACLS algorithms continue to be made, including an emphasis on high-quality CPR with minimal interruption.
4. **Post–cardiac arrest hospital care.** Initial management is focused on establishing and maintaining hemodynamic stability and supportive care. Amiodarone or lidocaine (especially if ischemia is suspected as the trigger) is often used to prevent further ventricular tachyarrhythmias. Therapeutic hypothermia for patients who remain unconscious after resuscitation confers a modest improvement in neurologic outcome. Immediate coronary angiography, with revascularization if indicated, may improve survival in patients in whom an ischemic etiology is suspected. Further diagnostic testing is described above.

B. Primary prevention of SCD

1. **Identifying individuals at risk for SCD.** No single factor has been identified that accurately predicts the occurrence of SCD, although combinations of factors have been more useful. In general, the specificity and positive predictive value of these tests are poor, whereas the negative predictive value is much better (particularly for combinations of tests). Overall, the most potent predictor of survival continues to be LVEF, but other factors may aid prognostication and guide subsequent therapy. Other tools for predicting the risk of SCD, such as EP testing, ambulatory electrocardiography, signal-averaged electrocardiography (SAECG), baroreflex sensitivity, heart rate variability (HRV), and T-wave alternans, have been used to identify high-risk groups, but none have been shown to be of convincing value. Although a combination of different tests can improve sensitivity and specificity, the positive predictive value remains modest.
2. **Pharmacologic agents and surgical/percutaneous revascularization.** Because the majority of episodes of SCD occur in patients with CAD, agents that reduce myocardial ischemia (β-blockers), prevent or limit the extent of MI, and alter ventricular remodeling after MI (ACE inhibitors and aldosterone antagonists) have all been shown to reduce the incidence of SCD. Although there is no direct evidence of a role for antiplatelets or statins in reducing SCD, such an effect is likely, given the reduction in mortality in several broad populations. Early studies of surgical myocardial revascularization showed a reduction in SCD for patients with triple-vessel CAD and left ventricular dysfunction compared with those patients treated medically. Fibrinolysis and percutaneous coronary intervention also reduce SCD in patients with MI. Catheter ablation of VT has a role in select patient populations, particularly in patients with incessant arrhythmias, despite antiarrhythmic drug and/or implantable device therapy.

   More than 40 years ago, complex ventricular ectopy in survivors of MI was recognized as a risk factor for SCD. Suppression of ventricular ectopy with antiarrhythmic drugs in such patients was, therefore, thought to be beneficial. However, the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that the proarrhythmic effects of class Ic antiarrhythmic drugs are greater than the benefit achieved through ectopy suppression in the post-MI population, resulting in a 2.6-fold increased mortality. Excess mortality was also demonstrated in survivors of MI with poor left ventricular function taking the class II/III agent sotalol in the Survival With Oral *d*-Sotalol (SWORD) study and with mexiletine.

   To date, of all the antiarrhythmic drugs only amiodarone has been shown to reduce SCD in some populations. Initial small trials of amiodarone therapy for survivors of MI, and meta-analyses of these trials, suggested reduced SCD mortality and the larger but unblinded Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) study appeared to corroborate

this finding. However, several prospective, placebo-controlled trials did not. The Survival Trial of Amiodarone in Patients with Congestive Heart Failure (CHF-STAT) failed to demonstrate a significant reduction in either SCD or all-cause mortality in a largely male population with heart failure, EF ≤ 40%, and frequent PVCs. Although the European Myocardial Infarct Amiodarone Trial (EMIAT) demonstrated a 35% reduction in arrhythmic deaths in a population with recent MI, there was no difference in all-cause mortality. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) similarly reported a reduction in resuscitated VF or arrhythmic death in survivors of MI with frequent ventricular ectopy, but no difference in all-cause mortality. Lastly, there was no difference in the primary end point of all-cause mortality between amiodarone and placebo in the medical treatment arm of the large Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The newer benzofuran derivative, dronedarone, also reduced SCD in the pivotal ATHENA trial of patients with atrial fibrillation and additional risk factors, but increased all-cause mortality in patients with severe heart failure in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA). Mexiletine showed a trend toward increased mortality, and dofetilide and azimilide had no effect on all-cause mortality or SCD in patients with recent MI in large controlled studies.

In summary, amiodarone reduces SCD but not all-cause mortality in patients with heart failure or recent MI, and several other antiarrhythmics, including class Ic agents, mexiletine, dronedarone, and sotalol, may increase mortality in this population.

3. **Implantable devices.** In light of the inefficacy and even hazards of antiarrhythmic drugs for the prevention of SCD, attention has shifted to the ICD. Since its introduction by Mirowski in 1980, technical refinements have paralleled a series of clinical trials which extended indications to primary prevention in select populations. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated a 54% relative risk reduction in all-cause death versus usual care in 196 patients with prior MI, New York Heart Association (NYHA) class I–III heart failure, EF ≤ 35%, NSVT, and inducible, nonsuppressible, ventricular arrhythmia during EP study (EPS). The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with coronary artery disease, EF ≤ 40%, NSVT, and inducible VT/VF to receive EP-guided antiarrhythmic drug therapy, with or without an ICD, or no therapy. The 27% reduction in arrhythmic death or cardiac arrest in the EP-guided drug therapy arm was entirely driven by a 76% reduction in patients with ICDs, with no difference between drug therapy and no therapy. Given the modest predictive value of EPS, MADIT II dispensed with inducible VT as an inclusion criterion and enrolled patients with prior MI on the basis of an EF ≤ 30%. This randomized comparison of ICD with usual care demonstrated a 31% relative risk reduction in all-cause mortality over an average follow-up of 20 months. MADIT, MUSTT, and MADIT II all enrolled patients with prior MI. While the underpowered Amiodarone Versus Implantable Cardioverter-Defibrillator (AMIOVIRT) and Cardiomyopathy Trial (CAT) failed to show a benefit of ICDs over medical therapy in patients with nonischemic cardiomyopathy (NICM), the results of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial extended primary prevention ICD therapy to these patients. In patients with NICM, heart failure, EF ≤ 35%, and NSVT or frequent PVCs, a nonsignificant reduction in all-cause mortality was observed, with a significant reduction in SCD. The larger SCD-HeFT randomized 2,521 patients with ischemic cardiomyopathy (52%) or NICM (48%), EF ≤ 35%, and NYHA functional class II or III heart failure to receive conventional therapy plus placebo,

amiodarone, or a single lead ICD. ICD therapy reduced all-cause mortality by 23% compared with placebo, whereas amiodarone was not associated with any benefit. These trials, and SCD-HeFT in particular, ushered in the current era of primary prevention ICDs for patients risk-stratified largely on the basis of EF.

The limitations of ICDs have also been defined by clinical trials. The Coronary Artery Bypass Graft (CABG) Patch Trial demonstrated that primary prevention ICD implantation at the time of CABG in patients with preoperative left ventricular dysfunction (EF ≤ 35%) and an abnormal SAECG did not improve the overall survival, despite reducing arrhythmic deaths. The lower event rates in the CABG Patch Trial were consistent with earlier evidence that CABG reduces the risk of SCD in this population, negating the protective effect of the ICD.

MADIT, MUSTT, and MADIT II studied patients with remote (> 3 weeks) ischemic events. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) assessed whether the benefits of ICD therapy would also be seen early after MI. The trial enrolled patients 6 to 40 days post-MI with EF < 35% and impaired HRV or elevated average 24-hour heart rate and randomized them to receive an ICD or no ICD. Although ICD therapy reduced arrhythmic death, this was offset by an increase in nonarrhythmic death in the ICD group, so there was no difference in all-cause mortality over 30 months of follow-up. These results were confirmed by the larger Immediate Risk Stratification Improves Survival (IRIS) trial, which enrolled a similar population. Taken together, IRIS and DINAMIT suggest that while ICDs prevent SCD in high-risk patients early post-MI, this merely changes the mode of death to nonsudden death, without affecting the overall survival. This is supported by a secondary analysis of DINAMIT, which showed that the risk of nonsudden death in the ICD group was 4.8-fold higher in those who had received an appropriate shock. The above findings have been incorporated into the Centers for Medicare and Medicaid Services (CMS) coverage determination for ICDs, which excludes patients with MI within 40 days and surgical or percutaneous revascularization within 3 months of ICD implantation. A wearable defibrillator is available for temporary use, while diagnostic testing is ongoing, or during periods of transient elevated risk.

4. **Cardiac resynchronization therapy (CRT).** Approximately 30% of patients with advanced heart failure (EF ≤ 35%) have an associated ventricular conduction delay resulting in a QRS duration ≥ 120 milliseconds and are candidates for CRT. Biventricular pacing has been shown to improve survival, quality of life, exercise capacity, and EF in patients with advanced CHF. Extended follow-up data from the Cardiac Resynchronization in Heart Failure (CARE-HF) trial also reported a significant 46% reduction in SCD in patients with CRT without a defibrillator when compared with no CRT. However, a significant number of SCDs occurred in the CRT group, some of which might conceivably have been prevented by a defibrillator. The only large randomized trial comparing CRT with a defibrillator (CRT-D), CRT without (CRT-P), and no device was the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. While not powered to detect a difference between CRT-D and CRT-P, a nonsignificant 50% decrease in SCD was seen with CRT-D in patients with NYHA class III or IV CHF, EF ≤ 35%, and a QRS duration ≥ 120 milliseconds. These data suggest that CRT-D should be considered for most patients eligible for biventricular pacing.

C. Secondary prevention

1. **Pharmacologic agents.** As with primary prevention of SCD, the disappointing efficacy and safety of class I antiarrhythmic drugs shifted attention to other antiarrhythmic drugs for the secondary prevention of SCD. In the Cardiac Arrest in Seattle Conventional Versus Amiodarone Drug Evaluation (CASCADE) study,

amiodarone reduced cardiac death, arrest, and ICD shocks compared with conventional class I antiarrhythmic drugs in a secondary prevention population. In addition, the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial demonstrated that the class II/III antiarrhythmic drug sotalol was superior to six class I agents guided by EP testing or Holter monitoring in preventing all-cause, cardiac, and arrhythmic mortality in patients with a history of VT/VF, SCA, or syncope. However, emergence of the ICD led to randomized trials comparing the efficacy of best medical therapy and ICDs for the secondary prevention of SCD.

2. **Implantable devices.** The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial studied the efficacy of ICD therapy versus the antiarrhythmic drugs amiodarone or sotalol for the secondary prevention of SCD in patients with resuscitated VF or sustained VT plus either syncope or EF ≤ 40% and hemodynamic compromise during VT. Inducible arrhythmias were not required for inclusion, and only sotalol therapy was guided by EP testing (only 2.6% of patients randomized to antiarrhythmic drug therapy were discharged on sotalol). ICDs reduced all-cause mortality by 31% at 3 years of follow-up.

   Two other large trials of ICDs for secondary prevention of SCD that ran concurrently with AVID reported similar results. The Cardiac Arrest Study Hamburg (CASH) found that ICDs conferred a nonsignificant 23% reduction in all-cause mortality when compared with amiodarone or metoprolol in patients with resuscitated cardiac arrest due to documented VT/VF. The propafenone arm of the study was terminated early after an interim analysis showed excess mortality compared with the ICD group. The Canadian Implantable Defibrillator Study (CIDS) enrolled a similar population as the AVID trial randomizing patients with resuscitated VF, sustained VT with syncope or hemodynamic compromise and EF ≤ 35%, or unmonitored syncope with subsequent spontaneous or induced VT to ICD or amiodarone therapy. Over a mean follow-up period of 3 years, a nonsignificant 19.7% relative risk reduction in all-cause mortality was observed, as well as a nonsignificant 32.8% reduction in SCD. Each of the above studies excluded patients with a transient or reversible cause of ventricular arrhythmias, such as MI within 72 hours, or electrolyte imbalances. A meta-analysis of these three trials confirmed a significant 28% reduction in the relative risk of death with the ICD, which was due largely to a 50% reduction in SCD.

   Of considerable interest is evidence that patients screened for the AVID trial but thought to have a transient or reversible cause of SCA, and who were not entered in the trial but followed in a registry, had poor long-term survival similar to those patients who were also ineligible for the trial but known to be at high risk for SCD. These data emphasize the need for meticulous evaluation of every SCA survivor and careful consideration of whether SCA was due to a cause that was not only transient and reversible but also preventable in the future.

D. Summary: antiarrhythmic drugs versus ICDs. Current guidelines for ICD therapy are summarized in Table 23.2. From the available data, there is good evidence that many antiarrhythmic drugs are not efficacious and may be harmful in the primary prevention of SCD, and antiarrhythmic drugs (apart from β-blockers) are not indicated for this purpose. ICD therapy has been proven to be highly effective in the termination of malignant ventricular arrhythmias and is more effective than antiarrhythmic medications for the prevention of SCD in patients with ischemic or nonischemic heart failure and an EF ≤ 35%. Patients with prolonged QRS duration, especially with LBBB, should also be considered for CRT. The most powerful predictor of SCD risk in this population remains LVEF, and other methods such as EP testing and SAECG may give additional information but are neither sensitive nor specific enough to select patients for ICD therapy. Specific antiarrhythmics may have niche uses in high-risk patients with genetic diseases predisposing

TABLE 23.2 Indications for Implantable Cardioverter–Defibrillator Therapy

Class I

1. Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced during electrophysiologic study
4. LVEF ≤ 35% due to prior MI, at least 40 d post-MI, and NYHA class II or III
5. Nonischemic DCM, LVEF ≤ 35%, and NYHA class II or III
6. LV dysfunction due to prior MI, at least 40 d post-MI, LVEF ≤ 30%, and NYHA class I
7. Nonsustained VT due to prior MI, LVEF ≤ 40%, and inducible VF or sustained VT during electrophysiologic study
8. Symptomatic sustained VT in association with congenital heart disease after hemodynamic and electrophysiologic evaluation

Class IIa

1. Unexplained syncope, significant LV dysfunction, and nonischemic DCM
2. Sustained VT and normal or near-normal ventricular function
3. Hypertrophic cardiomyopathy with one or more major risk factors for SCD
4. ARVD/C with one or more risk factors for SCD
5. Long QT syndrome with syncope and/or VT while receiving β-blockers
6. Nonhospitalized patients awaiting heart transplantation
7. Brugada syndrome with syncope
8. Brugada syndrome with documented VT that has not resulted in cardiac arrest
9. Catecholaminergic polymorphic VT with syncope and/or documented sustained VT while receiving β-blockers
10. Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease
11. Congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias during electrophysiologic study

Class IIb

1. Nonischemic heart disease, LVEF ≤ 35%, and NYHA class I
2. Long QT syndrome with risk factors for SCD
3. Syncope and advanced structural heart disease where thorough invasive and noninvasive investigations have failed to define a cause
4. Familial cardiomyopathy associated with sudden death
5. LV noncompaction

TABLE 23.2 Indications for Implantable Cardioverter–Defibrillator Therapy (Continued)

6. Recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause

Class III

1. Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 y
2. Incessant VT or VF
3. Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up
4. NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D
5. Syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease
6. VF or VT that is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease)
7. Ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma)

VF, ventricular fibrillation; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; DCM, Dilated cardiomyopathy; SCD, sudden cardiac death; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; CRT-D, cardiac resynchronization therapy with a defibrillator; RV, right ventricle; LV, left ventricle.

Adapted from the 2008 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.

to SCD, such as HCM, ARVD, Brugada syndrome, and LQTS, and an ICD is also indicated in select patients. The bradyarrhythmias respond well to pacemaker therapy. Radiofrequency catheter ablation is the therapy of first choice in patients with WPW syndrome and is an effective synergistic therapy in patients with VT who have recurrent ICD shocks.

Evidence from several recent randomized trials demonstrates the superiority of the ICD over antiarrhythmic drugs for the population requiring secondary prophylaxis. Antiarrhythmic drugs such as amiodarone, sotalol, and mexiletine may be of use in those patients who experience frequent ICD shocks.

V. PROGNOSIS

A. VF and pulseless VT ("shockable rhythms") are the initial rhythm in approximately one-quarter of SCA victims and are associated with more favorable outcomes than asystole or PEA. VT/VF incidence declines by ~10% with each minute since the onset of SCA; therefore, witnessed SCA and prompt recognition and defibrillation are associated with improved survival. Only one-third of SCA victims receive bystander CPR. A recent large study of cardiac arrest incidence and outcomes in North America found that of the 58% of patients in whom resuscitation was attempted, 7.6% survived to hospital discharge, with wide regional

variation. This proportion rose to 21% if the initial rhythm was VF. A number of factors have been identified to aid prognostication post arrest, including preexisting comorbidities, absent pupillary and corneal reflexes, extensor or no motor response to pain on day 3, and myoclonus status epilepticus; however, none are definitive.

VI. FUTURE. Large population studies are needed to better define the incidence of SCD across ethnic/racial groups and elucidate the mechanisms. Discovery of risk markers of SCD in the general population, such as clinical, molecular, and genetic factors, will facilitate targeting of evaluation and therapy to those who need it. Coronary artery disease and its consequences account for 80% of SCD, often occurring as the first presentation of CAD. Given the difficulty in identifying those with subclinical disease who are ostensibly at low risk, focus has recently moved to primordial prevention—the prevention of the development of risk factors for CAD. This will likely have the most impact on SCD at the population level, but its effects are difficult to measure. In those at established risk, improved risk markers that refine the current LVEF-based approach will allow better targeting of ICD therapy.

ACKNOWLEDGMENTS: *The author thanks Drs. Bryan Baranowski, Mandeep Bhargava, and Robert A. Schweikert for their contributions to earlier editions of this chapter.*

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CHAPTER 24

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Atrial Fibrillation

I. INTRODUCTION. Atrial fibrillation (AF) is the most common sustained tachyarrhythmia and is associated with increased cardiovascular morbidity, mortality, and preventable stroke, accounting for approximately one-third of cardiac hospitalizations for cardiac rhythm disturbances. The incidence and prevalence of AF increase with age, with a prevalence of 0.4% to 1% in the general population and as high as 8% in patients older than 80 years. In addition, the age-adjusted incidence in the Framingham study has increased significantly from the 1960s to the present. It is estimated that 3 million people in America and 6 million people in Europe have either paroxysmal AF or persistent AF. AF is associated with increased risk of stroke, heart failure exacerbation, and all-cause mortality, especially in women. The mortality rate in patients with AF is about twice that of patients with normal sinus rhythm (NSR).

A. Classification. AF may be classified as lone, idiopathic, first detected, recurrent, paroxysmal, persistent, long-standing persistent, and permanent. **Lone AF** is used to describe patients experiencing AF without clinical or echocardiographic evidence of cardiopulmonary disease. **Idiopathic AF** refers to the uncertainty of AF origin without considering age or underlying cardiovascular pathology. During a patient's first detected episode of AF, it should be noted whether it is self-limited or the patient symptomatic with the arrhythmia. When a person has experienced two or more episodes of AF it is considered **recurrent**, and once recurrent AF is terminated it is referred to as **paroxysmal**. Paroxysmal episodes are usually self-terminating and, at least initially, do not usually require direct current cardioversion (DCC). **Persistent AF** usually lasts longer than 7 days and requires cardioversion for its termination. **Long-standing persistent** is when AF has lasted for > 1 year. AF becomes **permanent** once cardioversion, either electrical or chemical, is unsuccessful and presence of arrhythmia is accepted by the patient and physician and hence rhythm control interventions are not pursued.

B. Clinical presentation. As with all arrhythmias, the clinical presentation of AF can vary widely and **patients may be asymptomatic**, despite rapid rates of ventricular response. Common symptoms include **palpitations, fatigue, dyspnea and/or shortness of breath, dizziness, and diaphoresis**. Less commonly, patients may present with extreme manifestations of hemodynamic compromise, such as **chest pain, pulmonary edema, and syncope**. AF is often noted in patients presenting with a new thromboembolic stroke, with reported rates of 10% to 40%.

C. Differential diagnosis. AF needs to be distinguished from multifocal atrial tachycardia (MAT), frequent premature atrial contractions, and automatic atrial tachycardias.

D. Etiology. AF is most commonly associated with advanced age, hypertension, valvular heart disease, congestive heart failure (CHF), and coronary artery disease (CAD). The pathophysiology is dependent on the interaction between atrial anatomic and physiologic factors that favor the initiation and maintenance of the arrhythmia. Pathophysiologically, these entities result in left atrial fibrosis, pulmonary vein dilation, and reduced atrial contractility, which in turn result at a cellular

level in abnormal intracellular calcium handling, atrial myolysis, connexin down-regulation, and altered sympathetic innervation. Structural remodeling results in electrical dissociation between muscle bundles and local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical substrate permits multiple small reentrant circuits that can stabilize the arrhythmia and lead to the establishment of AF.

AF has been associated with physiologic stress, drugs, pulmonary embolism, chronic lung disease, hyperthyroidism, caffeine, infectious processes, and various metabolic disturbances. AF has also been linked with obesity and likely underlying sleep-disordered breathing. This phenomenon seems to be mediated by left atrial dilation. Other less common cardiac associations include Wolff-Parkinson-White (WPW) syndrome, pericarditis, and cardiomyopathy. Surgery, particularly **cardiac surgery, is associated with a high risk of postoperative AF** that depends on the type of cardiac surgery and is highest for mitral valve surgery, which may reach 35% to 50%. Persistence of AF has been correlated with elevated C-reactive protein levels, which raises the question of a role for inflammation in this condition, and atrial natriuretic peptide has been found to be elevated in people with acute AF. This hormone, which is released by myocardial tissue in response to increased wall stress, promotes diuresis and vasodilation. However, with long-standing AF, atrial natriuretic peptide levels remain within the normal range and patients do not experience its useful hemodynamic effects.

E. Pathophysiology

1. The role of the pulmonary veins as a source of triggers and/or drivers in AF is increasingly appreciated. A previous model proposed by Moe et al. in 1962 had described multiple reentrant wavelets within the atrial tissue (substrate) that contributed to the maintenance of AF. Recent data support **a focal mechanism involving both increased automaticity and multiple reentrant wavelets, occurring predominantly in the left atrium around the pulmonary veins**. A new model incorporates these mechanisms of initiators/drivers of AF and atrial substrate conditions for AF maintenance. This in turn may be affected by various modulating factors, such as autonomic tone, medications, atrial pressure, and catecholamine levels. AF is a very complex arrhythmia, and this mechanistic model simply serves to provide a conceptual framework from which to gain insight into it.
2. Paroxysmal, persistent, or chronic AF presents a **considerable risk for thromboembolism;** lone AF is presently thought to also increase the risk, but to a lesser extent. **The risk of stroke becomes more pronounced with increased age.** An increased risk of stroke has been shown to be associated with AF in the presence of any of the following: **age > 65 years, history of diabetes, history of hypertension, history of CHF, history of prior stroke, or transient ischemic attacks (TIAs)**. Left ventricular (LV) systolic dysfunction predicts ischemic stroke in patients with AF who do not receive antithrombotic therapy.

F. Laboratory examination and diagnostic testing. The initial evaluation of a patient with new-onset AF includes at a minimum a detailed history including enquiry about family history of AF and physical examination to define the clinical type of AF—frequency, duration, and precipitating factors—and to delineate the presence and nature of symptoms associated with AF. In addition, evaluation should include the following:

1. **A 12-lead electrocardiogram** (ECG) to identify the rhythm (that is to verify AF), underlying LV hypertrophy, and presence of preexcitation, and to diagnose the existence of CAD and any other atrial arrhythmias. A 12-lead ECG may also be used to measure and follow PR, QRS, and QT intervals during the treatment with antiarrhythmic agents. In AF the P waves are absent. Atrial activity is chaotic and fibrillatory **(F) waves are present**. The baseline of the ECG is often

undulating and may occasionally have coarse, irregular activity that can resemble atrial flutter, but it is not as stereotypical from wave to wave as atrial flutter. AF is distinguished from MAT by the presence in MAT of at least three different morphologic types of P waves. **Ventricular rhythm is usually irregularly irregular, and if AF is suspected with a regular ventricular response, then heart block with a junctional or ventricular escape should be considered**. The **atrial rate** is generally in the **range of 400 to 700 beats/min,** while the ventricular response is generally in the range of 120 to 180 beats/min in the absence of drug therapy. Ventricular response may be 180 beats/min or greater in the presence of an accessory pathway.

2. **Transthoracic echocardiogram** is usually performed to identify the presence of valvular heart disease, to assess atrial and ventricular size and function, and to document coexistent pulmonary hypertension. Echocardiography is also used as a prognostic tool to predict the development of systemic complications from AF and to help in the decision to initiate antithrombotic therapy. **Echocardiographic predictors of increased thromboembolic risk include mitral stenosis, left atrial enlargement, reduced LV systolic function, decreased left atrial appendage emptying velocities, and evidence of spontaneous contrast ("smoke") or thrombus in the left atrium or left atrial appendage**.
3. **Tests of thyroid, renal, and hepatic function.** Hyperthyroidism should always be considered, especially when the ventricular rate is difficult to control.
4. Additional investigation in selected patients with AF may include ambulatory ECG monitoring (e.g., Holter), or a 6-minute treadmill walk test to document heart rate response to exercise and an evaluation of sleep-disordered breathing should be considered especially in obese patients.

G. Therapy. The therapy of choice in any unstable patient where AF is recent in onset and contributing to the instability is immediate DCC. The term "unstable" should include the patient who is highly symptomatic (e.g., chest pain and pulmonary edema), as well as the patient who is hemodynamically unstable. **General management of AF centers on three areas: control of the ventricular response, minimization of the thromboembolic risk, and restoration and maintenance of sinus rhythm**.

1. **Control of the ventricular response.** The ventricular response is generally **controlled through drugs** that slow conduction through the atrioventricular (AV) node. AF that presents in the setting of WPW syndrome usually has evidence of preexcitation on ECG and is treated differently from AF conducting down the AV node alone. As noted previously, **intravenous calcium channel blockers, β-blockers, adenosine, and lidocaine are contraindicated in patients with AF and WPW syndrome associated with preexcitation because they facilitate conduction down the accessory pathway, causing acceleration of the ventricular rate, hypotension, and ventricular fibrillation**. In the hemodynamically stable patient, class I antiarrhythmic medications such as procainamide may be administered intravenously, which diminishes antegrade conduction down the accessory pathway and decreases the degree of preexcitation and may convert the AF. For patients without evidence of preexcitation, the following agents are available to control the ventricular rate.
   a. β-Blockers have a **rapid onset of action,** as well as **short half-lives in both the oral and intravenous forms.** These medications should be used cautiously in patients who have known decreased systolic function or evidence of heart failure. Intravenous preparations of metoprolol, esmolol, and propranolol have their onset of action in approximately 5 minutes. Orally available β-blockers of varying durations of action can be used for rate control. These include metoprolol and propranolol, as well as atenolol, nadolol, and a number of less commonly used agents. Amiodarone is an antiarrhythmic

medication with β-blocking properties and can be used for both rate and rhythm control in the acute setting. Sotalol is another class III antiarrhythmic medication with β-blocking properties, which can be used for both rate and rhythm control; however, this medication is available in oral form only and is more proarrhythmic than amiodarone.

b. Calcium channel blockers such as diltiazem and verapamil are available in both intravenous and oral forms. The intravenous forms are rapidly effective and have a short duration of effect. **In appropriate patients, they provide rapid control of the ventricular response**. Both oral diltiazem and verapamil are available in short-acting and sustained-release preparations.

c. Digitalis has long been used for rate control. Given its relatively long onset of action, **digoxin is ideally used in patients with decreased LV function or where a contraindication exists to the use of β-blockers or calcium channel blockers** (e.g., bronchospastic airway disease, asthma, or hemodynamic instability). It may be used as an adjunct to β-blockers or calcium channel blockers in patients in whom these medicines alone do not provide sufficient control of the heart rate. Digoxin is usually **effective at controlling the resting heart rate;** however, it is **less effective at lowering the ventricular response to activity**. Because of this it is recommended that if digoxin alone is used in rate control, the patient should undergo monitored exercise and the exertional heart rate verified to be < 110 beats/min.

Digoxin can be administered intravenously or orally. The **onset of action of digoxin is slow** (1 to 4 hours). Initially dosing of digoxin is 0.25 mg intravenously every 6 hours for a total of 1 mg every 24 hours. Then a maintenance dose is given, which is based on the patient's renal function. Digoxin is **generally well tolerated, although it is associated with adverse effects**, such as gastrointestinal toxicity and neurotoxicity, and because of its long half-life (38 to 48 hours) is more likely to be associated with symptomatic bradycardia requiring intervention such as temporary pacing.

d. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists may decrease the incidence of AF by decreasing left atrial pressure and by reducing the frequency of atrial premature beats. These medications may also reduce atrial fibrosis and decrease the recurrence of AF. Withdrawal from ACE inhibitors is associated with postoperative AF in patients undergoing coronary artery bypass grafting (CABG) surgery, and concurrent therapy with ACE inhibitors and antiarrhythmic agents enhances the maintenance of sinus rhythm.

e. HMG-CoA reductase inhibitors: statin drugs decrease the risk of AF recurrence following cardioversion. The mechanisms underlying this are poorly understood but probably include an inhibitory effect on the progression of coronary disease as well as their pleiotropic anti-inflammatory and antioxidant properties.

f. Antiarrhythmic agents such as dofetilide and ibutilide are effective for conversion of atrial flutter and AF but are not effective for the control of ventricular rate alone. Propafenone, which is a class IC antiarrhythmic drug, exerts additional mild β-blocking effects and may slow conduction across the AV node, although this is seldom sufficient to control the rate in patients with AF and may paradoxically cause an increase in AV nodal conduction and accelerate the ventricular rate response. Flecainide is another class IC agent that is very effective in converting AF in structurally normal hearts but like propafenone requires concomitant AV nodal blockage.

2. Thromboembolic risk management

a. Current recommendations regarding the use of antithrombotic therapy to prevent the development of thromboembolism in patients with AF are to

use antithrombotic therapy in all patients with AF except those with lone AF or with contraindications to antithrombotic agents. **Lone AF is defined as that occurring in a structurally normal heart, in a patient younger than 65 years.** The American Heart Association (AHA) recommends that the individualized selection of appropriate antithrombotic agents **associated with the highest risk of stroke in patients with AF include a history of prior thromboembolism (stroke, TIA, and systemic embolism) and rheumatic mitral stenosis.** Moderate risk factors for stroke include age older than 65 years, CAD, CHF, female gender, hypertension, diabetes mellitus, and renal insufficiency. Presence of more than one moderate risk factor suggests the use of a vitamin K antagonist with a goal international normalized ratio (INR) of 2.0 to 3.0 or or alternative anticoagulation with dabigatran, rivaroxaban or apixaban. Aspirin in doses of 81 to 325 mg daily is recommended as an alternative to vitamin K antagonism in low-risk patients or in those with contraindications to oral anticoagulation, and more recent evidence suggests that combination of aspirin and clopidogrel is superior to the use of either agent alone in patients who are unable to tolerate warfarin therapy. The guidelines also suggest similar use of antithrombotic therapy in patients with atrial flutter. Table 24.1 outlines one method of selecting the appropriate antithrombotic therapy for any given patient.

Based on the multivariate analysis from randomized controlled trials (RCTs), there have been several clinical scores developed to stratify the risk of systemic complications. The most well known of these is called the **CHADS** (*C*ardiac Failure, *H*ypertension, *A*ge, *D*iabetes, and *S*troke) risk index, which is a point system and assigns two points for history of TIA or stroke and one point for

TABLE 24.1 Selection of Appropriate Antithrombotic Therapy

Risk category	Recommended therapy	
No risk factors	Aspirin, 81–325 mg daily	
One moderate risk factor	Aspirin, 81–325 mg daily or warfarin (INR 2.0–3.0, target 2.5)	
Any high risk factor or more than one moderate risk factor	Warfarin (INR 2.0–3.0, target 2.5)[a]	
Less validated or weaker risk factors	**Moderate risk factors**	**High risk factors**
Gender (female)	Age ≥ 75 y	Previous stroke, TIA, or embolism
Age (65–74 y)	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve[b]
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

[a]If mechanical valve, target INR > 2.5.
[b]Mechanical prosethetic heart valve especially if in the mitral position to replace "prosthetic heart valve"
INR, international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.
Adapted from ACC/AHA practice guidelines.

each of the following risk factors: age older than 75 years, hypertension, diabetes, or recent heart failure. This risk factor index was evaluated retrospectively in patients older than 65 years and with nonvalvular AF, and the stroke risk varied from 1.8% per year in the lowest risk group with a CHADS score of 0, to 18.2% per year for those with an index score of 6. Another thromboembolic risk factor scoring system is the CHA2DS2-VASc, which assigns two points for age > 75 years and prior history of TIA or stroke and one point for each of the *following* risk factors: CHF, hypertension, diabetes, stroke, vascular disease, age 65 to 74 years, and female gender. Thus, this risk stratification scheme extends the CHADS2 scheme by considering additional stroke risk factors that may influence the decision on whether or not to anticoagulate with a threshold for therapy that is similar to the CHADS scheme. An assessment of bleeding risk is an integral part of patient evaluation prior to initiating anticoagulation. A simple bleeding risk score (HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [age > 65 years], drugs/alcohol concomitantly) has been used to assess the risk of bleeding while on anticoagulant therapy. A score of ≥ 3 indicates higher risk and suggests caution and regular review of the patient following the initiation of anticoagulant therapy.

Following cardioversion, therapeutic anticoagulation should be continued until sinus rhythm has been maintained for at least 4 weeks to allow for recovery of the atrial transport mechanism and for the recurrence of AF. The decision to anticoagulate beyond 4 weeks will be dependent on the CHADS2 score of the patient with long-term anticoagulation being recommended for all patients with a CHADS2 score ≥ 2. For patients with a CHADS2 score of 1, the physician and patient should discuss the merits and risks of long-term anticoagulation versus the use of aspirin alone. **If cardioversion cannot be postponed for 3 weeks and the AF has been present for > 48 hours, patients should be anticoagulated (Table 24.2) with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin as a bridge to therapeutic INR or alternatively dabigatran, rivaroxaban or apixaban could be used and the patient should undergo transesophageal echocardiography (TEE)** to rule out atrial thrombus; **then anticoagulation should be** used for at least 4 weeks after cardioversion.

b. A number of major trials have attempted to compare the benefits of aspirin and warfarin in minimizing the stroke risk in patients with AF. Overall, warfarin has shown an annual average reduction of 68% in relative risk for stroke, with aspirin showing a reduction anywhere from 0% to 44% (mean, ~30%). A recent trial has shown that clopidogrel reduces the risk of embolic stroke similar to that of aspirin and the combination of aspirin and clopidogrel is superior to either agent alone but inferior to warfarin therapy.

The decision to anticoagulate patients with AF depends on both the risk of thromboembolic complications and the risk of bleeding. In younger patients at low risk for stroke (younger than 65 years, without other risk factors), and who generally lead active lifestyles that place them at increased risk for bleeding, **aspirin** may be an acceptable alternative to warfarin. **Older patients at greater risk for stroke (age 65 and older, with or without other risk factors)** should be anticoagulated with **warfarin to maintain an INR of 2 to 3 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban. The risk of thromboembolism increases rapidly at INR levels even slightly < 2, and the risk of bleeding increases at INR levels > 3**. Studies of fixed low-dose warfarin and aspirin have shown ineffective protection from thromboembolic risk as compared with anticoagulation with warfarin to maintain an INR of 2 to 3, and thus are not recommended. **Patients who have contraindications to warfarin** therapy should be treated with **aspirin or the combination of aspirin and clopidogrel should be considered if the patients can tolerate it**.

TABLE 24.2 Anticoagulation Strategies in Patients Who Require Cardioversion

Length of time in atrial fibrillation	Elective cardioversion?	Timing and anticoagulation strategy
< 48 h	Yes	Depends on the presence of risk factors for thromboembolism
< 48 h	No	Immediate DCC may be performed without delay or need to start anticoagulation
> 48 h or unknown	Yes	A goal INR 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban for at least 3 weeks prior to and 4 weeks following DCC
> 48 h or unknown	Yes	A TEE can be performed while the patient is on IV heparin with a goal aPTT ratio of 1.5–2.0, and if no identifiable thrombus is present, DCC can safely be performed, followed by 4 weeks of oral coumadin with goal INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban
> 48 h or unknown	Yes	If the TEE demonstrates a thrombus, then anticoagulation with coumadin with a goal INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban for a period of 3 weeks prior to a repeat TEE to assess for thrombus resolution. If no identifiable thrombus is visible on repeat TEE, then DCC should be followed by at least 4 weeks of anticoagulation with INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban post DCC

DCC, direct current cardioversion; INR, international normalized ratio; TEE, transesophageal echocardiography; IV, intravenous.

The **risk of thromboembolism increases with longer duration of AF. Current guidelines recommend that patients who have been in AF for longer than 48 hours should be systemically anticoagulated** whenever possible. This can be accomplished quickly with intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or oral dabigatran, rivaroxaban or apixaban. Cardioversion should be delayed in patients with AF of > 48 hours duration who have not been anticoagulated as described in the AHA guidelines discussed previously unless a patient is sufficiently unstable that more rapid cardioversion is necessary, in which case screening of the atria for the presence of thrombus with TEE is appropriate.

c. TEE is highly effective in the detection of thrombus in the atria and in the left atrial appendage and is more sensitive in this regard than transthoracic echocardiography. The Assessment of Cardioversion using Transesophageal

Echocardiogram (ACUTE) study compared the use of TEE screening of patients with AF prior to cardioversion with a conventional approach based on 3 weeks of anticoagulation therapy. In the TEE group, those patients without thrombus on TEE underwent immediate cardioversion after therapeutic anticoagulation had been initiated and without waiting for 3 weeks. Patients were continued on warfarin for 4 weeks after the cardioversion as in the conventional group. No significant difference was noted in the embolic event rate or in the likelihood of maintenance of normal rhythm. TEE cardioversion is now considered an acceptable alternative when the conventional approach is not possible.

d. Cardiac output may be decreased after cardioversion in up to one-third of patients, and this can persist for as long as a week. Rarely, this leads to pulmonary edema as soon as 3 hours after cardioversion. Atrial function also declines immediately after cardioversion, even after that occurring spontaneously or pharmacologically. Cardiac output should return to baseline within 4 weeks. The risk of thromboembolism is thus still increased during this time period, and that is why systemic anticoagulation is recommended for a minimum of 4 weeks after cardioversion.

e. After 4 weeks of therapy, the decision to continue anticoagulation is based on each patient's individual risk for recurrence of AF. **Patients who cannot be successfully cardioverted should be anticoagulated long-term**, as should patients with frequent recurrences/paroxysms.

f. In addition to the expanding number of pharmacologic options for anticoagulation, there are now nonpharmacologic methods for reducing thromboembolic risk. In the Embolic Protection in Patients with Atrial Fibrillation Trial (PROTECT trial), the WATCHMAN left atrial appendage occlusion system was noninferior to anticoagulation with warfarin in terms of thromboembolic outcomes. More data are needed on the long term safety and efficacy of this device.

3. Rate control during AF. Patients with AF may have controlled heart rates at rest, but they accelerate even with mild exercise. Hence, it is useful in patients with chronic AF to evaluate the heart rate response to submaximal or maximal exercise or to monitor the heart rate over an extended period (such as a 24-hour Holter monitor). The traditional criteria defining that adequate rate control varies with age but usually involves achieving a ventricular rate between 60 and 80 beats/min at rest and between 90 and 110 beats/min during moderate exercise have not been shown to be beneficial over a more lenient approach to achieve a resting heart rate of < 110 beats/min in patients with persistent or continuous AF and stable LV systolic function.

4. Restoration and maintenance of sinus rhythm. There is debate whether restoration to sinus rhythm is beneficial for patients whose disease is asymptomatic as compared with a combined strategy of simply controlling the ventricular response and minimizing the thromboembolic risk. Data from nonrandomized trials show an increase in mortality in patients on long-term antiarrhythmic therapy for AF. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial compared two treatment strategies in patients with asymptomatic or tolerable AF. One group was treated with antiarrhythmic drugs and cardioversion as necessary to maintain sinus rhythm. The other group was allowed to remain in AF and the ventricular rate alone was controlled. Both groups received anticoagulation therapy. There was no difference in survival or embolic event rate between the two groups.

a. Direct current cardioversion. When restoration of sinus rhythm is deemed necessary, this is most effectively carried out with DCC. **DCC is successful at least 80% of the time**, whereas pharmacologic rates of successful cardioversion are lower and depend on the antiarrhythmic drug used and the clinical scenario. Whenever possible, **DCC should be carried out under sedation, with appropriate cardiac and hemodynamic monitoring, and**

in the presence of personnel skilled in airway control/management. See Chapter 59 for details of DCC, including sedation and methods.

b. Pharmacologic cardioversion

(1) The "drugs first" approach may promote more successful DCC and/or maintenance of sinus rhythm after DCC, if the attempt at pharmacologic cardioversion is unsuccessful. Similarly, it is reasonable to **attempt chemical cardioversion on any patient who fails DCC**, especially before repeated attempts at DCC.

(2) Table 24.3 shows the currently available intravenous agents available for the pharmacologic cardioversion of AF to sinus rhythm.

(i) Procainamide is a class IA antiarrhythmic drug that is often considered **the first line of therapy** for the pharmacologic conversion of AF occurring in the postoperative period after cardiac surgery.

TABLE 24.3 Intravenous Medications Used for the Cardioversion of Atrial Fibrillation

Drug name	Vaughan Williams class	Dose	Adverse side effects
Amiodarone	III	5–7 mg/kg over 30–60 min, followed by 1.2–1.8 g/d until 10 g, then 200–400 mg daily for maintenance	Hypotension, bradycardia, hyperthyroidism, hepatitis, skin discoloration, and phlebitis
Ibutilide	III	1 mg over 10 min, repeat as needed	Torsade de pointes, increased QTc
Propafenone	IC	1.5–2.0 mg/kg over 20 min	Hypotension and atrial flutter with RVR
Flecainide	IC	1.5–3.0 mg/kg over 10–20 min	Hypotension and atrial flutter with RVR
Vernakalant (approved in Europe but not yet in United States)	III	3 mg/kg IV infusion over 10 min. Second infusion of 2 mg/kg IV over 10 min after 15 min of rest	Vernakalant is contraindicated in patients with systolic blood pressure < 100 mm Hg, severe aortic stenosis, heart failure (NYHA classes III and IV), ACS within the previous 30 d, or QT interval prolongation. Before its use, the patients should be adequately hydrated. ECG and hemodynamic monitoring should be used, and the infusion can be followed by DCC if necessary. The drug is not contraindicated in patients with stable coronary artery disease, hypertensive heart disease, or mild heart failure

RVR, rapid ventricular response; ACS, acute coronary syndrome; ECG, electrocardiogram; DCC, direct current cardioversion.

(ii) Amiodarone is considered a class III antiarrhythmic drug, although it has properties of all of the four Vaughan Williams classes. Like procainamide, amiodarone is commonly used intravenously in the postoperative period for AF after cardiac surgery, particularly for those patients with renal insufficiency or failure who are not candidates for procainamide.

(iii) Ibutilide is an agent approved for the pharmacologic conversion of AF. The incidence of torsade de pointes is at least 1% to 2% with ibutilide, which is higher than that seen with procainamide or amiodarone. Ibutilide is available only in the intravenous form and is, therefore, not an option for long-term maintenance of sinus rhythm.

(iv) Vernakalant is an agent that was recently approved in Europe for chemical cardioversion but has not yet been approved by the US Food and Drug Administration (FDA). It is more effective than amiodarone for conversion of AF to sinus rhythm. Vernakalant is contraindicated in patients with systolic blood pressure < 100 mm Hg, severe aortic stenosis, heart failure (NYHA classes III and IV), acute coronary syndrome (ACS) within the previous 30 days, or QT interval prolongation. Before its use, patients should be adequately hydrated. ECG and hemodynamic monitoring are mandatory, and the infusion can be followed by DCC if necessary. The drug is not contraindicated in patients with stable CAD, hypertensive heart disease, or mild heart failure. The clinical positioning of this drug has not yet been determined, but it is likely to be used for acute termination of recent-onset AF in patients with lone AF or AF associated with hypertension, CAD, or mild to moderate (NYHA classes I and II) heart failure.

(3) A number of **oral agents** are available for the pharmacologic cardioversion of AF. **In appropriate patients the class IC agents, such as flecainide and propafenone, may be particularly effective for pharmacologic cardioversion**. In the text to follow are mentioned some other agents that may be used in the long-term for maintenance of sinus rhythm in patients with AF. It should be kept in mind that initiation or upward dose titration of antiarrhythmic drugs should be done with caution and, in many instances, should be performed in a hospital setting with a cardiac monitor. This is particularly true for the class III agents sotalol and dofetilide. On the other hand, in patients without structural heart disease, the class IC agents flecainide and propafenone may be considered for initiation on an outpatient basis. Table 24.4 outlines the presently available orally acting medications to treat AF.

(i) Class IA agents. These agents have seen a decline in their use, primarily due to a high incidence of intolerance because of side effects but also due to evidence of possible increased mortality for those patients with structural heart disease.

- **Procainamide.** This medication has not been used as frequently now for long-term treatment of AF, especially due to the potential for gastrointestinal, hematologic, and immunologic (e.g., lupus-like syndrome) side effects. An active metabolite of this drug, *n*-acetylprocainamide (NAPA), is cleared renally and has class III antiarrhythmic properties. Blood levels of both procainamide and NAPA need to be monitored to prevent toxicity, especially in the setting of renal and/or hepatic insufficiency.
- **Quinidine** is another class IA drug that has not been used as frequently in recent years, again primarily due to a relatively high

TABLE 24.4 Oral Agents Available for Rhythm Control in Atrial Fibrillation

Drug name	Vaughan Williams class	Cardioversion dose		Daily maintenance dose
Amiodarone	III	400–800 tid dosing daily until 10 g, then		200–400 mg
Dofetilide	III	Based on CrCl (mL/min):	Dose: (μg bid)	Same. Dosing also adjusted for adjusted QTc
		> 60 mL/min	500	
		40–60	250	
		20–40	125	
		< 20	Contraindicated	
Propafenone	IC	600 mg		450–900 mg
Flecainide	IC	200–300 mg		Same
Sotalol	III	160–320 mg		Same
Dronedarone	III		Contraindicated if CrCl < 30 and patient with class IV heart failure, admission for CHF in preceding 4 weeks especially if EF < 35%	400 mg bid

CHF, congestive heart failure; EF, ejection fraction; IV, intravenous.

incidence of gastrointestinal, hematologic, and neurologic side effects. In addition, quinidine interacts with several cardiac and noncardiac medications.

- **Disopyramide.** This antiarrhythmic medication may have a "niche" for the treatment of vagally mediated AF or AF that occurs in the setting of hypertrophic cardiomyopathy. However, its **negative inotropic effects** are greater than those of other class IA drugs, and it is associated with **greater anticholinergic effects** such as constipation and urinary retention.

(ii) Class IC agents. This group has become the preferred antiarrhythmic drugs for the management of AF in patients without structural heart disease, especially those patients with "lone" AF. These medications should not be used in patients with structural heart disease, especially patients with known or suspected ischemic heart disease. **Flecainide** was shown in the Cardiac Arrhythmia Suppression Trial (CAST) to be associated with increased mortality when used for suppression of ventricular arrhythmias in patients with LV dysfunction

following myocardial infarction (MI). This has led to much concern over the use of the class IC agents in any patient with CAD and even in other types of structural heart disease.

- **Flecainide.** This is a well-tolerated medication that has a low incidence of neurologic side effects. This medication is approved in both oral and intravenous forms for the acute cardioversion of AF. Randomized trials with this drug show that it converts 60% to 70% of patients with new-onset AF at 4 hours and close to 90% at 8 hours. Oral administration and intravenous administration were equally efficacious, but the average response to the intravenous loading is seen within 1 hour, whereas it is 3 hours with the oral loading dose.
- **Propafenone.** This is also a well-tolerated medication. Its β-blocking properties limit its use in patients intolerant of such medications. Like sotalol, this property allows for its use as a single agent for AF suppression and ventricular rate control.

(iii) Class III agents. This group has become the preferred treatment for AF in patients with structural heart disease.

- Sotalol also has β-blocking properties, which makes it useful as a **single-agent therapy** for AF suppression and ventricular rate control. However, these properties are also responsible for the intolerance seen with this drug and may contribute to exacerbation of heart failure in some patients. **The dose must be reduced with renal insufficiency**.
- **Dofetilide.** This is the latest antiarrhythmic drug to be approved by the FDA for management of AF. This drug is generally well tolerated and has been shown to be safe for patients with structural heart disease, in particular those patients who have had an MI and those with CHF. **This drug has been associated with proarrhythmia, especially in the setting of renal dysfunction. The prescription of the drug is tightly controlled, and only those certified in its use may prescribe it**.
- **Amiodarone.** This is a unique medication in that it has properties of all four Vaughan Williams classes. It is also unique with regard to its very long elimination half-life (up to 120 days). Amiodarone is effective for the management of AF but is generally reserved for patients in whom other antiarrhythmic drugs have been ineffective or poorly tolerated, due to the important potential organ toxicities that may occur, predominantly in the liver, lungs, thyroid, and eyes. It is recommended that patients treated with amiodarone have baseline and then regular screening tests such as ophthalmologic examination, pulmonary function study, chest x-ray, and blood tests for liver and thyroid function.
- **Dronedarone** is a multichannel blocker that inhibits the sodium, potassium, and calcium channels and has noncompetitive antiadrenergic activity. It is **similar to amiodarone with a much better side-effect profile, though it is less effective than amiodarone**. Contraindicated in NYHA classes III and IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, powerful CYP3A4 inhibitors, and creatinine clearance < 30 mg/mL. There is potential for serious liver toxicity with dronedarone and liver function tests have to be monitored closely when patients are on this medication.
- **Azimilide.** New class III antiarrhythmic drug that is not yet FDA approved for the management of AF.

(4) Figure 24.1, adapted from American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) guidelines, outlines strategies used in the maintenance of sinus rhythm.

c. AV nodal ablation in conjunction with permanent pacemaker.

(1) Symptomatic refractory AF, especially when the ventricular rate is uncontrollable or such control is limited by underlying bradycardia, may be amenable to ablation of the AV node and implantation of a **rate-responsive single-chamber permanent pacemaker**. These patients still require systemic anticoagulation. A recent meta-analysis of 21 studies that included 1,100 patients who underwent AV nodal ablation for highly symptomatic AF concluded that AV nodal ablation and subsequent pacemaker implantation significantly improved the quality of life, exercise capacity, and LV function and decreased symptoms of AF. In a small subset of 56 patients who had impaired LV function (an ejection fraction < 40%) and AV nodal ablation, permanent pacemaker implantation caused an average improvement in ejection fraction of 8% and complete normalization of the ejection fraction in one-third of the patients. The remaining patients with persistent LV dysfunction after AV nodal ablation had a 5-year survival rate of <40%. The 1-year mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3%, which includes a high 2% risk of sudden cardiac death (SCD), which is thought to be related to early post pacemaker implantation R-on-T phenomenon caused by pacemaker-induced bradycardia. For this reason, it has been suggested, without a great deal of support in the published literature, that pacemakers be programmed with a minimum heart rate of 90 beats/min for the first month after the AV nodal ablation procedure.

(2) Indications for permanent pacemaker for AF. A permanent pacemaker may be needed in patients who develop symptomatic bradycardia, which may be exacerbated by therapy for AF. This may occur because of an underlying sinus node dysfunction or perhaps poor AV conduction leading to slow ventricular rates during AF. Modern pacemakers have **"mode switching"** capabilities, so that the pacing mode changes from dual-chamber to single-chamber ventricular pacing at the onset of AF to avoid rapid ventricular pacing rates due to the pacemaker responding to the atrial activity.

(3) Limitations. Although, as mentioned earlier, AV nodal ablation has been shown to cause symptomatic improvement in patients with refractory and very symptomatic AF, its limitations include the potential lifelong need for anticoagulation, the loss of AV synchrony, and the lifelong pacemaker dependence with its attendant risks.

Several recent pacemaker trials have shown worsening hemodynamic effects of right ventricular (RV) apical pacing compared with biventricular pacing. The Post AV Nodal Ablation Evaluation (PAVE) trial randomized patients to RV apical pacing versus biventricular pacing following AV nodal ablation for permanent AF. At an average follow-up of 6 months, the biventricular-paced group had longer 6-minute walk times and increased peak oxygen consumption and reported improved quality of life. Although LV ejection fraction did not differ between the groups at baseline, at follow-up, the ejection fraction in the biventricular pacing group stabilized, whereas the ejection fraction in the RV apically paced group had declined significantly.

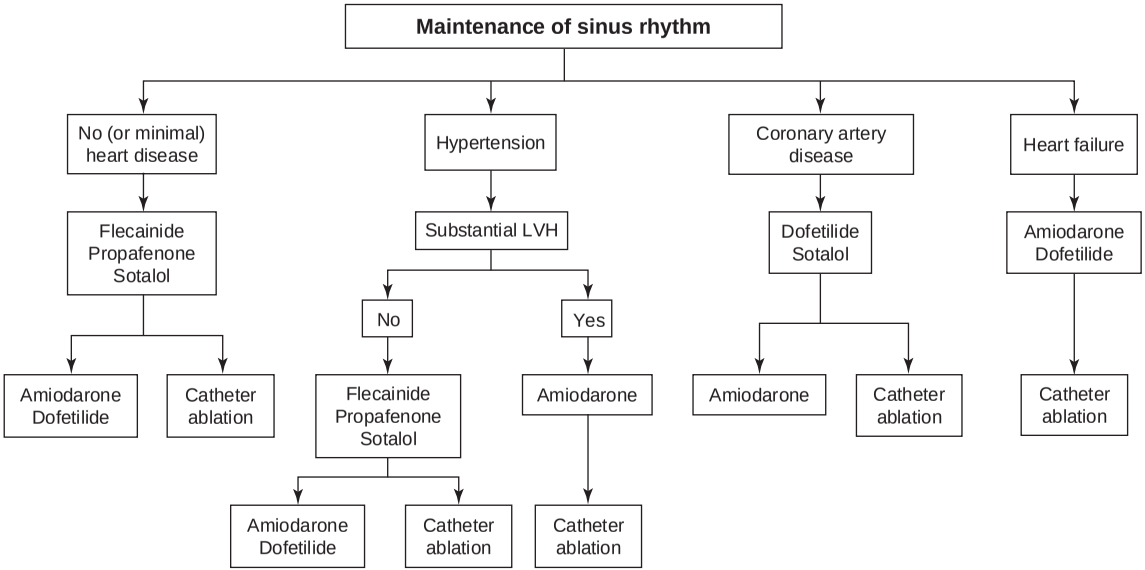

FIGURE 24.1 Therapeutic approach to the maintenance of sinus rhythm. Adapted from American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines. LVH, left ventricular hypertrophy.

Current recommendations regarding the choice of pacemaker following AV nodal ablation suggest the use of RV pacing devices in patients with normal LV function or in those thought to have reversible LV dysfunction secondary to AF with poor rate control. In patients with impaired LV function not caused by AF, a biventricular pacemaker with or without defibrillator capability should be considered. In patients who have undergone AV nodal ablation and developed heart failure symptoms following RV apical pacing, an upgrade from an RV apical system to biventricular system should be considered.

d. Implantable devices with treatment and suppressive strategies for AF are now available for selected patients. Some devices may terminate AF with a rapid atrial burst pacing or a cardioversion shock. Pacemakers that have pacing algorithms aimed at preventing AF episodes have become available. The use of such pacemakers in patients without an indication for pacing is still under investigation. A difficulty in their implementation is the frequency of episodes of AF in patients requiring device activation and the discomfort associated with shock delivery.

e. Invasive curative therapies. There are two major interventional approaches for the management or cure of AF, one based on a percutaneous approach and the other on a surgical approach. These approaches are not yet first-line therapy, but in recent years have become a much more attractive option for patients with troublesome AF in whom antiarrhythmic treatment has been ineffective or poorly tolerated.

(1) Catheter ablation of AF with pulmonary vein isolation (PVI). In 1998, Haissaguerre and colleagues described the presence of isolated foci in the left atrium and pulmonary veins and their role in the initiation of AF. They were also able to demonstrate that ablation of these foci could successfully terminate AF. Based on this early work, the field of AF ablation was born. Initial experiences with AF ablation attempted to mimic the surgical Maze procedure. Since that time, ablation has undergone various changes in both philosophy and technique.

Approaches to AF ablation can vary widely. Purely anatomic approaches may focus on the creation of linear lesions around the pulmonary veins and may not require demonstration of entrance or exit block. Other techniques focus on ablation of sites of autonomic ganglia or areas of complex fractionated electrograms. Electrogram-based approaches make use of a mapping catheter to help identify electrograms in areas targeted for isolation but may vary in the scope of the area targeted for isolation. Anatomic ablation techniques use recently developed three-dimensional (3D) mapping systems to demonstrate the anatomy of the left atrium and the pulmonary veins. Various anatomic techniques including the isolation of each of the four veins, individually or via isolation of two veins at a time, have been developed. In addition, anatomic lines extended to the mitral isthmus or involving the room of the left atrium have been utilized. Exit block is often used as an end point in the anatomic approach.

Electrogram-based techniques require the use of a second (ring) mapping catheter. After circumferential isolation, the mapping catheter is used to evaluate for the presence of gaps in the ablation line and these gaps are then ablated. There have also been experiences using electrogram-based approaches to perform additional ablation points in other areas of the heart, including the coronary sinus, the superior vena cava, and the right atrium, after performing PVI. Additionally, drug testing with adenosine and isoproterenol to provoke AF and thereby identify potential triggers for ablation is sometimes used.

Advances in techniques have improved the efficacy and safety of the procedure. One major advance has been the development of protocols that ablate outside the ostia of the pulmonary veins to help reduce the incidence of postprocedure pulmonary vein stenosis. Catheter ablation is now considered a reasonable alternative to pharmacologic therapy to prevent recurrent AF in symptomatic patients with little or no left atrium enlargement with a class I recommendation in the most recent guideline update. In addition, catheter ablation performed in experienced centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.

Patient preparation and procedural considerations. Prior to ablation, considerations including access, conscious sedation, and choice of anticoagulation regimen should be made on an individual patient basis. The presence of multiple catheters in the left atrium requires patients to be given full anticoagulation. Prior to the procedure, some centers require patients to be therapeutic on warfarin for 4 to 6 weeks. Patients not anticoagulated prior to the procedure should undergo transesophageal echocardiogram to exclude the presence of left atrial thrombus. Regardless of preprocedural anticoagulation status, patients are fully anticoagulated with unfractionated heparin during the procedure to achieve a prespecified targeted activated clotting time.

Catheters are placed in the right atrium and coronary sinus, typically via sheaths in the right and left femoral veins, and an additional sheath is often needed if intracardiac echo is used. The left atrium is accessed via transeptal puncture. Great care is needed, using fluoroscopic guidance to assure successful transeptal puncture, and many centers use intracardiac echo to assist in safely achieving transeptal puncture. After placement in the left atrium, circular "lasso" mapping and ablation catheters are used to approach the pulmonary veins. If used, intracardiac echo can assist 3D mapping techniques in identifying the pulmonary vein ostia.

End point for ablation differs depending on the technique used. On completion of electrogram-based ablation, success is demonstrated by the development of entry block in the antrum of the pulmonary veins. However, anatomic-based procedures do not require the demonstration of block.

Centers performing ablation should have backup available of physicians experienced in pericardiocentesis and cardiothoracic surgery, secondary to the development of hemorrhagic pericardial effusion or atrial appendage rupture.

The identification of the pulmonary veins as the predominant source of ectopic foci that trigger AF has led to catheter-based ablation strategies to electrically isolate the pulmonary veins by delivering radiofrequency energy at their ostium. In the initial series, foci of increased automaticity within the pulmonary veins were targeted and ablated. In one early series of 45 patients with AF, 62% became free of symptomatic AF over a mean follow-up of 8 months. However 70% of the patients required multiple procedures. In a subsequent study using the same approach, the success rate (defined as the absence of return of symptomatic AF) was 86% over a 6-month follow-up.

Continued research into the substrate for AF has demonstrated that there are many potentials that can contribute to the initiation and maintenance of AF and that these may arise in multiple areas of the right and left atria. Thus, catheter ablation procedures have been developed to

incorporate linear lesions in the roof of the left atrium and mitral valve isthmus ablation to account for these. Using this approach in a series of 70 patients with symptomatic AF, 70% of the patients were found to be free from AF following PVI without antiarrhythmic medications at 4 months of follow-up. The procedure continued to advance with the development of the circular mapping catheter, which allowed for more accurate mapping and isolation of the pulmonary veins.

At the time of this writing, the accumulated published experience in PVI suggests an approximately 70% to 90% success rate in patients with paroxysmal AF and 40% to 80% success rate in patients with persistent AF. It must be noted that the success rates in patients with depressed ejection fraction are much lower than that in patients with normal systolic function.

A newer approach to radiofrequency catheter ablation of AF involves the ablation of complex fractionated electrograms, which has a 91% efficacy reported at 1 year. This study also showed that restoration of sinus rhythm following catheter-based ablation of AF caused a significant improvement in exercise capacity, quality of life, and LV systolic function.

Presently, the long-term efficacy of catheter-based ablation is not known and requires further study. Long-term follow-ups from RCTs are presently either lacking in patient numbers or marred by high crossover rates or by antiarrhythmic use. The current ACC/AHA/HRS guidelines allow for the use of PVI in the treatment of symptomatic AF following intolerance to, depending on the substrate, at least one drug and as many as three antiarrhythmic drugs.

Complications. Major complications from catheter-based ablation have been reported in about 2% to 3% of patients and include pulmonary vein stenosis, systemic thromboembolism, atrial esophageal fistula, and the development of atypical left atrial flutter.

The incidence of **pulmonary vein stenosis** has diminished by the judicious use of radiofrequency ablation energy to target areas just outside the pulmonary veins so as to isolate the ostia of the pulmonary veins from the remainder of the left atrium. The use of intracardiac echocardiography to detect microbubble formation as a means to measure the magnitude of radiofrequency energy delivered has been reported to reduce the instance of pulmonary vein stenosis. This complication often presents as dyspnea and breathlessness in the weeks to months following catheter-based ablation, with radiographic evidence of asymmetric pulmonary edema or pulmonary emboli, as it results in obstructive venous outflow from a single pulmonary lobe. This diagnosis is best made by the use of computed tomography venography, but it can also be made through the use of TEE with the finding of high-velocity flow in the affected pulmonary vein.

Systemic embolic events, including embolic stroke, are among the most serious complications of catheter-based ablation of AF, and the reported incidence varies from 0% to 5%. A trial comparing heparin-dosing regimens found that increasing the intensity of anticoagulation reduces the probability of forming left atrial thrombi from 11% to 3%, when the activated clotting time was increased from 250 to > 3 00 seconds.

Atrial esophageal fistula is a relatively rare complication of PVI, and it is more likely to occur when extensive ablation occurs over the posterior left atrial wall where it abuts the esophagus. Typical symptoms include nausea, vomiting, fever, and sudden neurologic deterioration

(from systemic embolization), which occur in the days to weeks following ablation. Successful treatment of this condition requires prompt recognition of its clinical signs, as delay in the treatment often leads to death.

The development of **atypical left atrial flutter** is thought to be related to the development of scar in the left atrium, which creates the substrate for reentry required for this arrhythmia. The most important predictor of the development of left atrial flutter is the presence of an incomplete line of ablation, and it has been found that extending the ablation line to the mitral valve annulus may reduce the frequency of this complication. This arrhythmia, as is the case with right atrial flutter, is amenable to further catheter-based ablation.

(2) Cox-Maze procedure is a surgical approach that has been developed over the last 25 years and that tested the original hypothesis that reentry is the predominant mechanism for the development and maintenance of AF. It has undergone multiple revisions through the years, and now it has evolved to include techniques that surgically isolate the pulmonary veins and connect these dividing lines to the mitral valve annulus. The surgical procedure uses atrial incisions in critical locations to create barriers to the propagating wavelets that are responsible for the initiation and maintenance of AF and that consequently eliminate the macroreentrant circuits in the atrium necessary to maintain AF.

The Maze procedure has changed over the last two decades, and present techniques use transmural lesions to isolate the pulmonary veins and to connect these dividing lines to the mitral valve annulus, as well as lesions to create barriers in the right atrium. The reported success of the combined three developmental stages of the Cox-Maze procedure is 93% in patients with symptomatic AF who were intolerant of antiarrhythmic drugs. This long-term report included 178 patients, and there was a 2.2% risk of periprocedure death and a 6% risk of pacemaker requirement in the patients undergoing a Cox-Maze I procedure. Other, more current studies have reported lower success rate of around 70%. This procedure maintains the atrial transport function, and especially when allied with left atrial appendage ligation substantially reduces the risk of postoperative thromboembolic events.

Procedure risks include **death** risk, which is dependent on the patient's comorbidities but is usually estimated to be < 1% as an isolated procedure, the need for a **pacemaker**, **impaired atrial transport function**, and delayed **atrial arrhythmias** including atrial flutter.

The Maze procedure has not had widespread acceptance as a means of treatment for AF, except in patients undergoing open heart surgery. Even in these patients, the additional intraoperative time and complexity of the procedure have limited its widespread surgical application. Currently under development are less invasive approaches, including thoracoscopic and catheter-based epicardial techniques.

The Maze procedure is often associated with significant edema formation, probably due to atrial natriuretic peptide derangements. This is effectively mitigated by the use of aldosterone antagonists such as spironolactone for the first 4 to 6 weeks postoperatively. All procedures used to restore NSR in patients with AF have had a variable effect on the restoration of atrial transport function, depending on the duration of fibrillation before the procedure and the rhythm maintained following the procedure. The need for long-term anticoagulation therapy following these procedures is generally assessed on an individual basis.

II. SPECIAL CONSIDERATIONS

A. Postoperative AF. AF is common postoperatively. The incidence of AF postoperatively varies with the type of surgery and is highest following open heart surgery, during which time it ranges between 20% and 50%. It usually occurs in the first 5 days. Risk factors for perioperative AF include age, a history of AF, chronic obstructive pulmonary disease (COPD), valvular heart disease (especially mitral valve disease), atrial enlargement, perioperative heart failure, and withdrawal from a β-blocker or an ACE inhibitor. Postoperative AF is a major determinant of length of stay and thus of cost. It is associated with all the risks associated with AF in the nonpostoperative setting including hemodynamic compromise and thromboembolism.

1. **Therapy.** Postoperative AF is usually self-limited, and DCC is usually not needed. There are a variety of antiarrhythmic agents available for cardioversion in postoperative patients. In a small trial, ibutilide was found to be more effective than placebo for the treatment of postoperative AF. Sotalol is particularly acutely effective in patients with preserved LV systolic function, because the risk of proarrhythmic toxicity is small and also because its β-blocker action contributes to slowing the ventricular rate.

   AF carries an increased risk of stroke in post-CABG patients, and so anticoagulation with heparin followed by oral anticoagulants is recommended if AF persists for longer than 48 hours. The choice of antiarrhythmic therapy, choice of AV nodal blocking agents, and the use of either heparin and/or oral anticoagulants depend on the individual patient, the time from surgery, and the specific type of surgery.

2. **Prevention.** There is evidence supporting the prophylactic administration of β-blocker medications in patients undergoing cardiac surgery to prevent the development of AF. Sotalol has also been studied, but there is at present conflicting evidence regarding its effectiveness. Amiodarone, when given either prophylactically before cardiac surgery or following open heart surgery, has been found to significantly reduce the incidence of postoperative AF. In the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Began Early After Revascularization (PAPABEAR) trial, oral amiodarone, dosed at 10 mg/kg beginning 6 days before and continuing for 6 days after surgery, decreased the incidence of postoperative AF by 50%. This efficacy was present in patients irrespective of whether CABG, valve surgery, or a combination was performed. Preoperative treatment with procainamide has yielded inconsistent results, as has treatment with either digoxin or verapamil.

   At present there are limited data supporting the use of atrial overdrive pacing as opposed to single-chamber pacing in the prevention of postoperative AF. In a randomized trial involving 132 patients undergoing CABG, postoperative biatrial pacing significantly reduced incidence of AF by 12.5% compared with left atrial pacing, right atrial pacing, or no pacing. A meta-analysis of 10 randomized trials also concluded that biatrial pacing, atrial pacing, and right atrial pacing reduced the incidence of AF after CABG surgery.

B. AF in acute MI. The incidence of AF following acute MI varies depending on the population sampled as well as the type of MI but ranges between 10% and 20% at 30 days. AF is more commonly associated with acute MI in older patients as well as those with a higher Killip class and more severe LV dysfunction. Patients with AF in the setting of an acute MI have a worse outcome at 30 days than those in sinus rhythm (29.3% with AF vs. 19% with NSR). Stroke rates are also increased in patients with post-MI AF.

The guidelines presently recommend urgent DCC in patients with acute MI who present with AF, especially if in rapid ventricular response with intractable ischemia or evidence of hemodynamic instability including CHF. Intravenous β-blockade is indicated for rate control to reduce myocardial oxygen consumption and demand, and digoxin is an alternative in patients with severe left surgical dysfunction and

heart failure. Anticoagulation is recommended in patients with large anterior MIs and those in which the AF becomes persistent. Post-MI ACE inhibitors seem to reduce the incidence of AF in patients with significant LV dysfunction. Post-MI use of carvedilol also seems to diminish the incidence of AF and atrial flutter.

C. AF and WPW syndrome. The most feared complication of the WPW syndrome is the development of ventricular fibrillation and SCD secondary to antegrade conduction of the AF into the ventricles. The incidence of SCD in patients with a WPW syndrome is around 0.6% per year, and risk factors for SCD include having a short antegrade bypass tract refractory period (< 250 milliseconds), short RR intervals during preexcited AF, and the presence of multiple accessory pathways.

It is important to avoid AV nodal blocking agents in a patient who presents with a preexcited tachycardia, as this has the potential to increase the refractory period of the AV node and facilitate conduction down the accessory pathway. Administration of AV nodal blocking agents such as verapamil, diltiazem, and digoxin is contraindicated in this setting. Intravenous β-blockers are ineffective in this setting and may have adverse hemodynamic consequences.

Flecainide, a class IC antiarrhythmic agent, can be used to slow the ventricular rate in patients who have AF with rapid ventricular rates associated with preexcitation by shortening the shortest preexcited cycle length during AF.

Patients with WPW syndrome and syncope or with a short antegrade bypass tract refractory period require immediate DCC followed by catheter-based ablation of the accessory pathway as the preferred therapy. Ablation of the bypass tract does not necessarily prevent recurrence of the AF, but it should be noted that following this ablation the management of AF is similar to that of patients without preexcitation.

D. AF in pregnancy. AF occurs infrequently during pregnancy and when it does it usually has an identifiable cause, such as mitral valve disease, thyroid disease, or pulmonary processes. The ventricular rate can be controlled with digoxin, β-blockers, or a nondihydropyridine calcium channel blocker. Currently available antiarrhythmic medications cross the placenta and are excreted in breast milk and should be avoided if possible in the pregnant and lactating individuals, but amiodarone, sotalol, and flecainide have all been used successfully during pregnancy in selected instances. Quinidine has the longest safety record of any antiarrhythmic agent in pregnancy and remains the agent of choice for pharmacologic conversion of AF. In the hemodynamically unstable patient, DCC can be performed without any concerns of fetal damage.

Anticoagulation should also be given high priority during pregnancy, given the risk of thromboembolic disease during pregnancy, and only those patients with lone AF at low risk for thromboembolic complications do not require anticoagulants.

The oral anticoagulant warfarin is generally avoided during the first trimester of pregnancy because of teratogenic effects and also during the last month of pregnancy because of bleeding concerns during delivery. Administration of unfractionated heparin either by continuous intravenous infusion in a dose sufficient to increase the activated partial thromboplastin time (aPTT) to 1.5 to 2 times control or by intermittent subcutaneous injection of 10,000 to 20,000 units every 12 hours adjusted to prolong the midinterval aPTT to 1.5 times control is appropriate. Low-molecular-weight heparin may also be considered during the first trimester and last month of pregnancy, although there are limited data on clinical outcomes with its use.

E. AF and hypertrophic obstructive cardiomyopathy (HOCM). Patients with AF and HOCM have a high risk of systemic embolic events. For this reason, it is recommended to maintain oral anticoagulation therapy in the range of an INR of 2.0 to 3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban in patients with HOCM and AF regardless of what the CHADS2 score is. Antiarrhythmic medications can be used to prevent recurrent episodes of AF, and although there are insufficient data comparing the various antiarrhythmics, anecdotal evidence seems to support the use of disopyramide in combination with a β-blocker or a nondihydropyridine calcium channel blocker.

F. AF and pulmonary disease. AF commonly develops in patients with COPD exacerbations. General recommendations include the treatment of the underlying lung process, correction of hypoxia, and of the acid–base imbalances. Medications commonly used to treat bronchospastic airway disease such as theophylline and β-adrenergic agonists can precipitate AF and decrease the ability of medications to control the ventricular rate. Antiarrhythmic medications with β-blocking properties such as sotalol, propafenone, and adenosine can worsen bronchospasm and are contraindicated in patients with severe bronchospastic airway disease. Ventricular rate control is usually achieved with nondihydropyridine calcium channel blockers such as verapamil and diltiazem.

ACKNOWLEDGMENTS: *The authors acknowledge the contribution of Dr. Carlos Alves to an earlier edition of this chapter.*

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SECTION V

Vascular and Pericardial Disease

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CHAPTER 25

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Venous Thromboembolism and Hypercoagulable States

I. VENOUS THROMBOEMBOLISM AND HYPERCOAGULABLE STATES

A. Venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) represent different manifestations of the same clinical entity referred to as venous thromboembolism (VTE). It is a common, lethal disease that affects hospitalized and nonhospitalized patients, recurs frequently, is often overlooked, and can result in long-term complications, including chronic thromboembolic pulmonary hypertension (CTPH) and the postthrombotic syndrome (PTS). Although PE is the third most common cause of hospital-related death in the United States, less than half of all hospitalized patients at risk for VTE receive adequate prophylactic treatment. Most hospitalized patients have at least one or more risk factors for VTE, and **without prophylaxis, the incidence of hospital-acquired DVT is 10% to 20% among medical patients and even higher among surgical patients (15% to 40%)**.

1. **Deep vein thrombosis.** The lower extremities are the most common sites for DVT, but other affected sites include the upper extremities and the mesenteric and pelvic veins. The main goal in the management of DVT is the prevention of PE and PTS. Proximal lower extremity DVTs (popliteal vein and above) have an estimated risk of PE of 50% if not treated. Approximately 25% of calf vein thrombi propagate (in the absence of treatment) to involve the popliteal vein or above.
2. **Pathogenesis and risk factors.** Virchow's triad still forms the best framework for understanding the pathogenesis of VTE. **The triad includes *stasis, hypercoagulability,* and *injury to the vessel wall.*** There are both inherited and acquired risk factors for hypercoagulability. The most common **inherited** risk factors include **factor V Leiden** (FVL) and **prothrombin gene mutation (G20210A)**; deficiency of the natural **anticoagulant protein C (PC), protein S (PS)**, and **antithrombin (AT)**; **hyperhomocysteinemia**; and **elevated factor VIII** levels. Acquired risk factors include **immobilization, surgery**, **trauma**, **pregnancy**, use of oral **contraceptives** (OCPs) or **hormone replacement** therapy (HRT), **malignancy**, **antiphospholipid syndrome** (lupus anticoagulant and/or anticardiolipin antibodies), **heparin-induced thrombocytopenia** (HIT), **myeloproliferative** disorders, **smoking**, **obesity** (body mass index [BMI] > 30), **inflammatory bowel disease**, **central venous catheters** or **pacemakers**, and **the nephrotic syndrome**.
3. **Clinical manifestations.** Typical symptoms of DVT in the upper and lower extremities include pain and swelling. Signs of DVT on physical examination may include increased warmth, tenderness, edema, the presence of dilated veins (collaterals), erythema, and, in extreme situations, cyanosis or gangrene. Various signs such as Homans' sign (dorsiflexion of the ankle with the knee at 30° flexion causing calf pain), Louvel's sign (worsening of pain with coughing or sneezing), and Lowenberg's sign (more pain on the affected leg after inflation of a sphygmomanometer around each calf) have been described, but these are

neither sensitive nor specific for the diagnosis. A limb-threatening manifestation of DVT, **phlegmasia cerulea dolens**, occurs most often in the setting of malignancy, HIT, or other hypercoagulable conditions in which the thrombus completely occludes venous outflow, causing massive limb swelling, hypertension in the capillary bed, and eventually ischemia and necrosis. Phlegmasia cerulea dolens is a vascular emergency requiring leg elevation, anticoagulation, and, in select cases, thrombolysis or surgical or catheter-based thrombectomy. Fasciotomy may also be required to relieve associated compartmental syndromes.

4. **Diagnosis**
   a. **Clinical examination** is unreliable in the diagnosis of DVT, as symptoms and signs are often insensitive and nonspecific. Pretest probability scores improve the utility of further testing. For example, using the Wells score (Table 25.1), patients in the low pretest probability category have a 96% negative predictive value for DVT (99% if the D-dimer is negative as well), but the positive predictive value in patients with a high pretest probability is < 75%, supporting the need for further diagnostic testing to identify patients with thrombosis.

TABLE 25.1 Pretest Probability of Deep Vein Thrombosis (Wells Score)

Clinical feature[a]	Score
Active cancer (treatment ongoing or within previous 6 mo of palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 d or major surgery, within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of DVT	–2
Score	
High	3 or greater
Moderate	1 or 2
Low	0 or less
Modified score (adds one point if there is a previously documented DVT)	
Likely	2 or more
Unlikely	1 or less

DVT, deep vein thrombosis.
[a]In patients with symptoms in both legs, the more symptomatic leg is used.

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b. Venography has been the gold standard test for the diagnosis of DVT in the past. The presence of an intraluminal filling defect is diagnostic, although abrupt cutoffs, nonfilling of the deep venous system, and/or demonstration of collateral flow may also serve as evidence for the presence of DVT. However, because venography is invasive and requires the use of potentially harmful contrast agents, it has largely been replaced by noninvasive tests such as duplex ultrasonography.

c. Duplex ultrasonography has a sensitivity and specificity of about 95% and 98%, respectively, for the detection of proximal DVT in symptomatic patients; however, it is operator dependent and is less sensitive in asymptomatic individuals and for thrombi located in the calf veins. **An inability to compress the vein with the ultrasound transducer is diagnostic for DVT**. Other findings suggestive, but not diagnostic, of an acute DVT include venous distention or absent or decreased spontaneous flow. Diagnosis of recurrent DVT is more challenging, given the high incidence of persistently noncompressible veins after an initial event. Other limitations of compression ultrasonography include difficulty in detecting isolated thrombi in the iliac veins or femoral veins within the abductor canal. False positives may occur when pelvic masses result in isolated noncompressibility of the common femoral veins.

d. D-Dimer. The sensitivity and negative predictive value of this test are high. The combination of a **low pretest probability and a negative D-dimer has an extremely high negative predictive value for VTE (approximately 99%)**. A positive D-dimer, however, is nonspecific, and other diagnostic testing should be performed.

e. Other diagnostic tests less frequently used to detect DVT include magnetic resonance venous imaging and computed tomography (CT). These tests are mainly helpful in the diagnosis of DVT in the pelvic veins, inferior vena cava (IVC), or mesenteric veins.

5. Treatment

a. The main goals of treatment for DVT include relief of symptoms and prevention of PE, CTPH, PTS, and recurrent VTE. Once the diagnosis of DVT is confirmed, **anticoagulation should be started immediately unless there is a contraindication**. Initial therapy should include heparin, low-molecular-weight heparin (LMWH), or fondaparinux followed by an oral anticoagulant (vitamin K antagonist or VKA). LMWH and fondaparinux are renally cleared, and although the LMWHs can be given in patients with renal insufficiency after dose adjustment, both are contraindicated in patients requiring dialysis.

Weight-based dosing of unfractionated heparin (UFH) (80 U/kg bolus followed by 18 U/kg/h intravenous [IV] infusion) has been shown to achieve a therapeutic activated partial thromboplastin time (aPTT) more rapidly than fixed-dose regimens. The target aPTT has traditionally been 1.5 to 2.5 times the control aPTT; however, the actual therapeutic aPTT range varies among laboratories because of their use of different aPTT reagents. The American College of Chest Physicians (ACCP) and the College of American Pathologists now advocate the use of an anti-factor Xa assay to establish a heparin dose–response curve for the aPTT ratio (of each laboratory), using concentrations that correlate to therapeutic heparin levels of 0.3 to 0.7 IU/mL determined by factor Xa inhibition. The aPTT should not be followed in patients with an abnormal baseline aPTT (e.g., in patients with lupus anticoagulant) and in patients who require unusually high doses of heparin such as in AT deficiency. In these situations, the anti-factor Xa assay should be used. UFH can also be administered subcutaneously as an alternative to IV administration, and several dosing nomograms have been recommended. One approach is to give an initial IV bolus of 5,000 U followed by a subcutaneous dose of 17,500 U twice daily on the first day. Blood for an aPTT is drawn 6 hours after

the initiation dose, and subsequent doses are adjusted accordingly to achieve an aPTT 1.5 to 2.5 times the control. Another fixed-dose nomogram recommends a subcutaneous loading dose of 333 U/kg followed by fixed doses of 250 U/kg subcutaneously every 12 hours without the need for aPTT monitoring.

LMWH is administered as a weight-based subcutaneous injection. Enoxaparin, the most commonly used agent in the United States, is given either as a once-daily injection (1.5 mg/kg/d) or twice per day (1 mg/kg every 12 hours). No monitoring is required except in obese, pediatric, or pregnant patients or patients with renal insufficiency. The anti-Xa level using LMWH as a reference standard should be measured 4 hours after an injection. The therapeutic range is 0.5 to 1.0 IU/mL for the 12-hour regimen and ≥ 1.0 IU/mL for the daily dose.

Once anticoagulation with UFH or LMWH is begun, a VKA may be initiated. The overlap should be continued for a minimum of 4 to 5 days and until the international normalized ratio (INR) is within the target range of 2.0 to 3.0 for two consecutive days to permit adequate depletion of vitamin K–dependent coagulation factors.

Fondaparinux, an indirect factor Xa inhibitor, is approved by the US Food and Drug Administration (FDA) for use as DVT prophylaxis in patients undergoing orthopedic procedures (total hip and knee arthroplasty) and abdominal surgery. It is also approved as treatment for acute DVT and PE when used in combination with a VKA. Its efficacy and safety in comparison with LMWH for the treatment of acute DVT and in comparison with IV UFH for the treatment of PE have been shown in large randomized controlled trials. Fondaparinux is administered as a once-daily subcutaneous injection of 2.5 mg for DVT prophylaxis and 5, 7.5, or 10 mg based on body weight (< 50, 50 to 100, and > 100 kg, respectively) for the treatment of DVT or PE. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and bacterial endocarditis. When used as DVT prophylaxis, fondaparinux is also contraindicated in patients with body weight < 50 kg who are undergoing hip fracture, hip replacement or knee replacement surgery, and abdominal surgery.

Thrombolytic therapy for DVT may be beneficial in select individuals and is preferably administered locally via a catheter-directed approach. Systemic lysis is also an option if a catheter-directed approach is not available. Both routes carry an increased risk of systemic hemorrhage compared with standard anticoagulation alone. Although it has been suggested that the use of thrombolytics promotes early recanalization and minimizes the incidence of PTS, their role in DVT treatment in the absence of a threatened limb is still unclear. The current ACCP guidelines recommend against their routine use in patients with DVT, except for those patients (without contraindication) with an extensive acute proximal DVT (ileofemoral DVT) or individuals at risk for limb gangrene secondary to venous occlusion.

Damage to the venous valves from lower extremity DVT and venous hypertension can lead to the development of PTS, a condition characterized by leg edema, skin changes such as hyperpigmentation and lipodermatosclerosis, pain, and, in severe cases, stasis ulceration. The incidence of this complication is drastically reduced with the use of **compression stockings**, and current guidelines recommend the use of stockings at a pressure of 30 to 40 mm Hg at the ankle for 2 years after an episode of DVT. In addition, early ambulation as tolerated after diagnosis is encouraged, as mobile patients with DVT do not require bed rest.

b. Vena caval interruption. Current guidelines recommend against the routine insertion of IVC filters for the treatment of DVT. **Indications for placement of IVC filters are as follows: a contraindication to anticoagulation,**

a complication from anticoagulation, or recurrent thromboembolization despite adequate anticoagulant therapy. Relative indications for IVC filters are massive PE, iliocaval DVT, free floating proximal DVT, cardiac or pulmonary insufficiency, high risk of complications from anticoagulation (frequent falls and ataxia), or poor compliance. **Retrievable** filters can be considered for situations in which anticoagulation is temporarily contraindicated or there is a short duration of PE risk. **IVC filter alone is not an effective therapy** for DVT, and resumption of anticoagulation as soon as risk of bleed is acceptable is recommended.

c. **Duration of treatment.** The **duration** of treatment following the diagnosis of DVT is **dependent on the risk of recurrence**. Risk factors for recurrence include an idiopathic DVT, underlying hypercoagulable states (listed in subsequent text), and malignancy. In addition, placement of a permanent IVC filter, elevated D-dimer levels, advanced age, male sex, and increased BMI also place individuals at a higher risk for recurrence. The risk of recurrence is low while patients are on anticoagulation; however, clinicians must weigh the risk of bleeding against the risk of new thrombosis.

Current guidelines **recommend 3 months of anticoagulation** with a VKA targeting **an INR of 2 to 3** for patients with a **first episode of DVT secondary to a transient cause**. Anticoagulation with a VKA for at least **6 to 12 months** with a target **INR of 2 to 3** is recommended for patients with a **first episode of idiopathic DVT**, although consideration should also be given for indefinite anticoagulation in this situation. Patients with the antiphospholipid syndrome, homozygous for FVL, or doubly heterozygous for FVL and prothrombin gene mutation should be considered for **indefinite anticoagulation**. Long-term (indefinite) anticoagulation is also recommended in patients with malignancy for as long as the cancer remains active, and in patients who have unexplained recurrent DVTs.

6. **Calf vein thrombosis.** Anticoagulation is generally indicated for symptomatic calf vein DVT or when there is propagation into the **popliteal vein or more proximally**. Current guidelines recommend 3 months of treatment with a VKA targeting an INR of 2 to 3 for patients with a first episode of symptomatic DVT confined to the calf veins secondary to a transient cause. Monitoring calf vein thrombosis for propagation into the proximal veins with serial ultrasonography (once or twice weekly for 2 to 3 weeks) without anticoagulation represents an alternative approach to treatment for individuals with high risk of bleeding.
7. **Superficial venous thrombosis** frequently occurs as a complication of an IV line in an upper extremity, but may occur spontaneously in the upper or lower extremities. Anticoagulation is generally not required due to the lower risk of PE, unless the thrombosis propagates into the deep venous system or if the event is spontaneous. Guidelines recommend intermediate doses of heparin or LMWH for at least 4 weeks for spontaneous superficial thrombophlebitis. Alternatively, a VKA can be used for 4 weeks. A recent study showed that daily fondaparinux at a dose of 2.5 mg for 45 days was effective in the treatment of lower extremity symptomatic superficial thrombophlebitis without serious side effects.
8. **Upper extremity DVT.** Upper extremity DVT is most often related to central venous catheter placement and/or pacemaker devices. Other less common causes include thoracic outlet syndrome, Paget-von Schröetter syndrome (also referred to as effort thrombosis), and hypercoagulable conditions including malignancy. Patients may be asymptomatic but more frequently complain of arm swelling and pain. Anticoagulation is indicated if there are no contraindications. Thrombolysis should be considered in younger patients with effort thrombosis, who have a low risk of bleeding and symptoms of acute onset. Determination of the length of anticoagulation with a VKA should be decided using the same processes described for acute lower extremity DVTs.

B. PE. It is difficult to approximate the true incidence of PE, but there are estimates that as many as 300,000 Americans have a fatal PE each year and as many as 34% of affected individuals present with sudden death. **The majority of patients die because of a failure in diagnosis rather than inadequate therapy**. In fact, the mortality rate for PE without treatment is approximately 30%, whereas it is only 2% to 8% with adequate treatment. PE remains the most common preventable cause of hospital death in the United States.

1. **Pathophysiology and symptoms.** Hemodynamic collapse related to PE results from a combination of vascular obstruction from thrombus and vasoconstriction caused by inflammatory mediators and hypoxia. Elevated pulmonary vascular resistance results in decreased right ventricular outflow, leading to a decrease in preload and cardiac output resulting in hypotension. To overcome an obstruction of 75% and maintain pulmonary perfusion, the right ventricle must generate a systolic pressure in excess of 50 mm Hg and a mean pulmonary artery pressure > 40 mm Hg. The normal right ventricle is unable to generate these pressures, and right heart failure and cardiac collapse ensue. In addition, elevated right ventricular wall tension can lead to decreased right coronary artery flow and ischemia. Cardiopulmonary collapse from PE is more common in patients with coexisting coronary artery disease (CAD) or underlying cardiopulmonary disease.

   PE may present as one of the following three syndromes: (a) **acute cor pulmonale**, (b) **pulmonary infarction**, or (c) **dyspnea**. Patients presenting with acute cor pulmonale, as manifested by the sudden development of dyspnea, cyanosis, shock, or syncope, usually have a massive PE leading to cardiovascular collapse. Patients with pulmonary infarction usually present with pleuritic chest pain, dyspnea, and hemoptysis, and an audible friction rub may be heard. The majority of patients present with generalized symptoms of chest pain, dyspnea, and malaise.

2. **Diagnosis**
   a. Several pretest probability scores have also been developed for the diagnosis of PE similar to those for the diagnosis of DVT. In a validation study of the Wells clinical decision rule, only 0.5% of patients who were unlikely to have PE and had a negative D-dimer had subsequent nonfatal VTE.
   b. **Troponin.** Cardiac troponins have been evaluated in the setting of acute PE, and elevated levels correlate with electrocardiographic and echocardiographic findings of right ventricular pressure overload. Elevations in this marker can be seen in patients with and without CAD, but the overall mortality and inhospital complications are higher in patients with acute PE and elevated cardiac troponin than in patients without elevated cardiac troponin.
   c. **Brain natriuretic peptide** elevation in the absence of renal dysfunction is also a marker of right ventricular dysfunction in patients with PE. Like elevated troponin levels, these elevated levels have also been shown to be predictors of adverse outcome in patients with acute PE.
   d. **Arterial blood gas.** PE can result in significant hypoxia, but in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 26% of patients with angiographically proven PE had Pa_{O_2} > 80 mm Hg. Similarly, a **normal alveolar–arterial gradient does not preclude the diagnosis of PE**. Therefore, a normal Pa_{O_2} cannot rule out PE; however, hypoxia in the absence of cardiopulmonary disease should raise the suspicion for this diagnosis. In patients with cardiopulmonary collapse, a normal Pa_{O_2} suggests that PE is an unlikely cause.
   e. **Chest radiography** may be more helpful in establishing other diagnoses. When present, findings are nonspecific and include pleural effusion, atelectasis, and consolidation. The classic signs, including the Westermark sign (regional oligemia), Hampton's hump (pleural-based, wedge-shaped shadow), and Palla's sign (enlarged right inferior pulmonary artery), are uncommon.

f. **Electrocardiography.** Like chest radiography, the major utility of the electrocardiogram (ECG) in the diagnosis of PE is to rule out other major diagnoses, such as acute myocardial infarction (MI). The most specific finding on an ECG is the classic $S_1Q_3T_3$ pattern, but the most common findings are nonspecific ST-segment and T-wave changes. Other commonly reported findings include sinus tachycardia, atrial fibrillation, and right bundle branch block.

g. **Echocardiography.** More than 50% of hemodynamically stable patients with PE will not have evidence of right ventricular dysfunction on transthoracic echocardiography (TTE). Patients with **hemodynamic collapse, however, will generally have severe right ventricle dysfunction**, and TTE can provide rapid bedside assessment in these critically ill patients. TTE findings include right ventricular dilation, right ventricular hypokinesis, tricuspid regurgitation, septal flattening, paradoxical septal motion, diastolic left ventricular impairment secondary to septal displacement, pulmonary artery hypertension, lack of inspiratory collapse of the IVC, and, rarely, direct visualization of the thrombus. In patients with large PE, it has been observed that despite moderate or severe right ventricular free wall hypokinesis there is relative sparing of the apex. This finding is referred to as **McConnell's sign** and has a specificity of 94% and a positive predictive value of 71% for PE. McConnell's sign may be useful in discriminating right ventricular dysfunction due to PE versus other causes.

h. **Ventilation–perfusion (V/Q) scanning. V/Q** scanning is now considered a second-line imaging method for the diagnosis of PE. **V/Q** scans are helpful in patients who have normal chest radiography or who are unable to have CT scanning, such as those with renal insufficiency, contrast allergy, or pregnancy. The results of PIOPED suggest that **V/Q** scanning is helpful if the scan is normal or at high probability for PE (87% of patients with high-probability scans had PE, but only 4% of patients with normal scans had PE). Intermediate-probability or low-probability scans are the most common finding, however, occurring in approximately 70% of patients in the PIOPED study. In addition, patients who had a high or intermediate clinical suspicion for PE but a low-probability scan still had a 40% and 16% rate, respectively, of PE diagnosed by pulmonary angiography. Hence, it is currently advised that **patients with a high or intermediate clinical suspicion for PE but a low-probability V/Q scan have additional tests to confirm or refute the diagnosis**.

i. **Computed tomography pulmonary angiography (CTPA).** Because of its wide availability and the ability to directly visualize thrombus, **CT imaging has become the standard imaging technique for the diagnosis of acute PE**. CTPA not only allows direct visualization of the thrombus but also has great value in excluding other diseases, including aortic dissection, pneumonia, or malignancy. It is especially useful in evaluating central PE (thrombus is seen as an intraluminal filling defect), and although the diagnostic yield for peripheral or subsegmental PE was low initially, the use of multidetector CTPA has greatly increased its sensitivity and specificity for the diagnosis of small peripheral or subsegmental PEs. CT venography of the abdomen and pelvis can also allow direct evaluation of the IVC and pelvic veins. This may be of value in selected cases as recent studies have shown that the routine use of CT venography of the pelvis during CTPA does not significantly improve the detection of VTE and therefore should not be performed routinely in all patients being evaluated for PE. The major disadvantages of CT are radiation exposure, higher cost, and the possibility of contrast-induced nephrotoxicity. A meta-analysis of 23 studies including 4,657 patients who were suspected of having PE but had normal CT scans found that only 1.4% developed VTE and 0.51% developed fatal PE by 3 months. These rates are similar to those in other studies involving patients who had suspected PE but were found to have normal pulmonary angiograms.

j. **Pulmonary angiography** remains the gold standard diagnostic test for PE, but it is used infrequently due to the advent of CT scanning. Four injections with four views (right and left anteroposterior and right and left oblique) are performed. In some situations where a lung scan shows perfusion abnormalities and is nondiagnostic for PE, selective angiography of the abnormal area may be considered so as to limit the amount of contrast needed. In experienced centers, associated morbidity and mortality are low.

k. **Magnetic resonance angiography** (MRA) may be an alternative to CT for the diagnosis of PE in patients who have contrast allergy or for whom avoidance of radiation exposure is desired. In PIOPED III, MRA had insufficient sensitivity and a high rate of technically inadequate images. Addition of magnetic resonance venography (MRV) to MRA improves sensitivity; however, 52% of patients in the study had a technically inadequate study. At the current time, an MRA/MRV should be considered only at those centers with experience with this modality and only for patients for whom standard tests are contraindicated.

3. **Treatment.** Anticoagulation with heparin, LMWH, and fondaparinux followed by the addition of a VKA and supportive care has remained the standard of care in the management of acute PE. **Current guidelines recommend initial treatment with anticoagulants for patients with a high clinical suspicion for PE while awaiting the results of diagnostic testing.** For patients with nonmassive PE, subcutaneous LMWH, IV UFH, or fondaparinux are recommended as initial treatment. In patients with acute nonmassive PE, LMWH is recommended over UFH. A VKA may be initiated together with IV UFH, LMWH, or fondaparinux and should be continued for a minimum of 4 to 5 days and until the INR is stable and ≥ 2.0.

   a. **Thrombolysis** for the treatment of acute PE is highly individualized, as there have been no clearly established short-term mortality effects. Because of favorable outcomes with prompt recognition and anticoagulation for PE, **thrombolysis should be reserved for hemodynamically unstable patients with acute massive PE and a low risk of bleeding**. It is unclear whether there is any benefit for thrombolytic therapy in patients who are hemodynamically stable but who have echocardiographic evidence of right ventricle dysfunction. Streptokinase, urokinase (no longer available in the United States), and tissue plasminogen activator are the current agents approved by the FDA. Current guidelines recommend the use of systemic thrombolytic therapy in patients who are hemodynamically unstable. Local administration of thombolytic therapy via a catheter is not suggested, owing to the risk of hemorrhage at the insertion site.

   b. Pulmonary embolectomy was the first definitive therapy to be performed for PE. There have been no randomized trials evaluating embolectomy, and the primary use of this procedure is in patients with shock and a contraindication to thrombolysis. Other investigational therapies include catheter-based embolectomy procedures that utilize aspiration, fragmentation, or rheolytic therapy. As of yet, there are currently no guidelines for the use of these therapies.

4. **New oral anticoagulants.** Until recently, warfarin was the only available oral anticoagulant for the treatment of VTE. Multiple new oral agents, with different mechanisms of action, have been evaluated in phase III clinical trials and have become available in markets outside the United States. These medications have the potential to revolutionize management of VTE. The agents that are most advanced in their development are the oral direct thrombin inhibitor (DTI), dabigatran etexilate, and oral direct factor Xa inhibitors (such as apixaban and rivaroxaban).

   These new oral anticoagulants in general have a more rapid onset of action, which may obviate the need for parenteral anticoagulation in the initial treatment

of VTE. Additionally, because these agents have stable pharmacodynamics (unlike warfarin), routine monitoring is not required. This makes them more favorable for use as long-term anticoagulants. A major disadvantage of these medications, however, is the current lack of an antidote in case of bleeding complications.

a. Oral direct thrombin inhibitors. Ximelagatran was the first oral DTI to complete phase III clinical trials; however, because of the high incidence of hepatotoxicity, it was withdrawn from the market.

Dabigatran etexilate—a prodrug—has been shown in a randomized, double-blind, noninferiority trial (RE-COVER) to be as effective as warfarin for the treatment of acute VTE with a similar safety profile. Dabigatran was given in a fixed dose without the need for laboratory monitoring. Dabigatran was also not inferior to subcutaneous enoxaparin in the prevention of VTE after total knee or total hip arthroplasty with similar bleeding risks. Dabigatran is not approved yet by the FDA for the prevention and treatment of VTE; however, it has been approved recently for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation based on the data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. It requires dose adjustments for patients with a creatinine clearance of 15 to 30 mL/min and is not recommended if the creatinine clearance is ≤ 15 mL/min.

b. Oral direct factor Xa inhibitors. Rivaroxaban is an oral direct factor Xa inhibitor with a relatively short half-life of 5 to 9 hours and rapid onset of action of 2.5 to 4 hours.

Oral rivaroxaban given alone was not inferior to subcutaneous enoxaparin followed by warfarin for the treatment of acute symptomatic DVT, with a similar safety profile (EINSTEIN-DVT trial).

Rivaroxaban has also been shown to be superior to enoxaparin for the prevention of VTE following knee and hip replacement surgery, with a similar safety profile in the RECORD trials. It was recently approved by the FDA for the prevention of VTE in adults following hip and knee arthroplasty.

Rivaroxaban was also approved recently for the prevention of stroke and systemic embolization in patients with nonvalvular atrial fibrillation based on the results of ROCKET-AF trial. It should not be used in patients with severe renal insufficiency or significant hepatic impairment.

Apixaban is another oral direct factor Xa inhibitor with promising data. Apixaban was found to be comparable to warfarin in a small phase II trial for the treatment of DVT. Apixaban was superior to enoxaparin when given using the European regimen (40 mg daily starting on the evening before surgery) in preventing VTE after knee and hip replacement. However, in another study, apixaban failed to meet the noninferiority standards for the prevention of VTE after knee replacement when compared with enoxaparin (given in the North American regimen of 30 mg every 12 hours starting 12 to 24 hours after surgery). Abixaban has been approved in Europe for the prevention of VTE in adults following hip and knee arthroplasty but is not yet approved in the United States. Similar to dabigatran and rivaroxaban, abixaban will likely also to be approved soon in the United States for the prevention of stroke in nonvalvular atrial fibrillation based on the data from ARISTOTLE trial.

C. VTE prophylaxis. Thromboprophylaxis should be provided to all hospitalized patients. Unfortunately, studies show that less than half of hospitalized patients receive appropriate VTE prophylaxis. Individuals who are considered at greatest risk are those over 40 years and patients who are immobilized or who have an underlying medical conditions (MI, stroke, congestive heart failure, and pneumonia), suffered trauma, or have undergone recent surgical procedures (especially hip fracture, total knee or hip replacement, or neurosurgical procedures). There are two major forms of prophylaxis, **mechanical and pharmacologic**. Those who cannot receive prophylactic anticoagulation should be prescribed mechanical modalities such as intermittent pneumatic

compression devices. Pharmacologic prophylaxis can be achieved by a number of agents, including UFH, LMWH, fondaparinux, a VKA, and rivaroxaban, which has been approved recently for VTE prophylaxis after hip and knee replacement surgery. Other new oral anticoagulant agents (dabigatran and apixaban) are available outside the United States for prophylaxis and will likely be available sometime in the near future in the United States. In high-risk populations such as those with hip or knee replacement, a combination of mechanical and pharmacologic therapies should be considered. In select surgical procedures, extended prophylaxis is recommended. For example, extended prophylaxis for up to 28 to 35 days is recommended for patients who have had a hip fracture or who undergo total hip replacement surgery.

II. HYPERCOAGULABLE CONDITIONS. Conditions that predispose persons to an increased risk of thrombosis are referred to as hypercoagulable states or thrombophilia. These conditions are being identified more frequently and may be classified as inherited or acquired. Hypercoagulability testing should be considered in individuals with idiopathic VTE, family history of clotting, a first thrombotic event before the age of 50 years, thrombosis at unusual locations, resistance to anticoagulation, and those with recurrent thromboses.

A. FVL and prothrombin gene mutation. Activated PC inactivates factors Va and VIIIa and is one of the mechanisms by which the balance between clotting and bleeding is maintained. The autosomal dominant acquisition of a single-point mutation (FVL) in the factor V gene renders the protein factor V resistant to inactivation by activated PC. Both homozygous and heterozygous states are at an increased risk of venous thrombosis, with a 50-fold to 100-fold increase in the homozygous state and a 3-fold to 7-fold increase in the heterozygous state. The FVL mutation is more prevalent in persons of European and Scandinavian ancestry.

The prothrombin gene mutation G20210A (PT G20210A) is also inherited as an autosomal dominant mutation and may lead to a higher plasma level of prothrombin. It is also more common in those of Caucasian ancestry and confers a 2.8-fold increased risk of VTE. The role of FVL and PT G20210A mutations in arterial thrombosis is unclear. There is only a modest association between inherited thrombophilias and major arterial thromboses such as MI, stroke, or peripheral arterial disease. Therefore, routine screening for these mutations is not warranted in most patients with arterial thrombosis. In young persons who develop arterial events, however, abnormalities in hemostasis may play a role, particularly in the presence of other risk factors such as smoking and OCP use, and additional testing may be warranted. FVL and PT G20210A are associated with VTE during pregnancy, OCP use, and HRT. For example, the annual risk of DVT is 3 per 10,000 in women without FVL who use OCPs, 5.7 per 10,000 in women with FVL who do not use OCPs, and 28.5 per 10,000 in women with FVL who use OCPs. FVL can be identified by evaluating for activated PC resistance in plasma or by gene analysis using polymerase chain reaction. The prothrombin gene mutation is also identified by genetic analysis. There are no clear evidence-based guidelines for managing patients with thrombosis in the setting of these thrombophilias. In general, acute thrombosis should be managed in a standard fashion, but the duration of therapy is less clear, and the benefits of long-term anticoagulation must be weighed against the risks of bleeding. Current guidelines recommend **long-term therapy for patients who are homozygous for FVL or who are doubly heterozygous for FVL and PT G20210A,** as well as individuals with the **antiphospholipid syndrome**. Asymptomatic gene carriers should receive prophylaxis in high-risk situations.

B. Defects in the natural anticoagulants (PC, PS, and AT). Deficiency of any of the three natural anticoagulants is associated with an increased risk of venous thrombosis. All are inherited as autosomal dominant defects and are further subclassified based on reduction in their levels or defective quality of the protein. PS acts as a cofactor in the inactivation of factors Va and VIIIa by activated PC. It is bound to C4-binding protein (an acute phase reactant) in the plasma. Levels of PS and PC are lower in conditions such as disseminated intravascular coagulation (DIC), inflammatory states,

nephrotic syndrome, acute thrombosis, and liver disease. Pregnancy and OCP use can also decrease the levels of PS. Both PC and PS levels are lowered by warfarin therapy, and, therefore, these tests should not be assayed in patients who are receiving VKAs. Similarly, initiation of warfarin therapy without concomitant anticoagulation in the setting of acute VTE may lead to warfarin-induced skin necrosis (manifested as painful necrosis of the skin, primarily in fatty areas including the breast, buttocks, and thighs). Treatment includes stopping warfarin, administering vitamin K and fresh frozen plasma to replete levels, and using an alternative anticoagulant. AT is produced by the liver and endothelial cells and functions by inactivating thrombin and factors Xa, IXa, XIa, and XIIa. Homozygous states are incompatible with life. Levels are also low in the following: those with DIC, sepsis, liver disease, nephrotic syndrome; with the use of OCPs; and during pregnancy. As previously discussed, patients with AT deficiency may have resistance to heparin because it exerts its anticoagulant effect through AT. AT concentrates are available and can be used temporarily to correct this deficiency.

C. Homocysteine. Hyperhomocysteinemia is a risk factor for venous and arterial thromboses. It may be inherited, and genetic defects causing a deficiency of cystathionine β-synthase or a mutation in methylenetetrahydrofolate reductase have been reported. Acquired causes include deficiencies in vitamin B_{12}, B_6, or folate; smoking; and liver or renal failure. Treatment with folate in doses between 0.5 and 5 mg is usually effective in reducing the levels of homocysteine; however, this does not reduce the risk of major cardiovascular events, symptomatic venous thrombosis, or recurrent venous thrombosis.

D. Heparin-induced thrombocytopenia. HIT is a common, underrecognized but potentially devastating condition in patients who receive heparin or LMWH. The reported incidence is between 3% and 5% in patients exposed to UFH and lower (< 1%) in patients exposed to LMWH. The pathogenesis of HIT involves the formation of antibodies (usually immunoglobulin G [IgG]) against a heparin–platelet factor 4 (PF4) complex. The HIT antibodies then trigger procoagulant effects through platelet and endothelial cell activation, as well as thrombin generation leading to both microvascular and macrovascular thromboses. The clinical spectrum of HIT ranges from isolated thrombocytopenia without thrombosis (referred to as isolated HIT) to HIT(T), which is associated with both arterial and venous thromboses. Other manifestations of HIT may include hypotension from adrenal hemorrhage secondary to adrenal vein thrombosis and ensuing infarction, skin necrosis at injection sites, or venous limb gangrene. HIT should be suspected in any patient who develops thrombocytopenia while receiving heparin or LMWH; any patient who develops a < 50% decline in platelet count after the initiation of either anticoagulant; or any patient who develops new thrombosis or extension of an existing thrombosis while receiving either of these agents. In patients with HIT and de novo exposure to heparin, thrombocytopenia (platelet count < 150,000 per μL) usually occurs between days 5 and 14 (with day of heparin exposure being day 0). In patients with a recent exposure to either agent (generally within the last 100 days), HIT may develop sooner and is referred to as rapid-onset HIT. This complication may also develop 9 to 40 days after heparin or LMWH has been discontinued and is known as delayed-onset HIT. Laboratory tests to aid in the diagnosis of HIT include functional assays (detection of heparin-dependent platelet activation in the presence of UFH or LMWH), such as heparin-induced platelet aggregation and serotonin release assays (SRA), and antigen assays (immunoassays), which detect IgG, IgM, or IgA antibodies that bind UFH to PF4. The SRA has the highest sensitivity and specificity for the diagnosis of HIT. The first step in the treatment of HIT is the prompt discontinuation of all sources of heparin or LMWH, including heparin flushes, heparin-coated catheters, any intermittent use of heparin during dialysis, and total parenteral nutrition or angiography. However, approximately 20% to 53% of patients with HIT will develop thrombosis (many within the first month) when treated only with discontinuation of heparin or LWMH alone. Therefore, the

initiation of an alternative anticoagulant, unless contraindicated, is recommended. **DTIs**, including lepirudin and argatroban (both approved by the FDA), may be used initially. Lepirudin has a longer half-life and is metabolized primarily by the kidney. The aPTT can be used to monitor therapy with a target range of 1.5 to 2.5 times the baseline level measured 4 to 6 hours after dose adjustments. Argatroban has a shorter half-life than lepirudin and is primary metabolized in the liver. The goal for aPTT is 1.5 to 3.0 times the baseline level. There are no agents available that reverse the effects of either drug; therefore, if bleeding develops, prompt discontinuation should be considered. Once platelet counts are more than 100,000 to 150,000 mm^3, warfarin may be started at a low dose (2.5 to 5 mg preferred). Early introduction or higher doses of warfarin may lead to venous limb gangrene or warfarin-induced skin necrosis. Overlapping the DTI with the VKA should be continued for at least 5 days and not discontinued until the INR is therapeutic for two consecutive days. Argatroban falsely elevates the INR; therefore, it should not be discontinued until INR > 4, as recommended by the manufacturer. After cessation of argatroban, the INR should be rechecked within a few hours to confirm that it is between 2 and 3. The duration of anticoagulation for patients with HIT is generally determined by the location and type of thrombosis. In patients without thrombosis (isolated HIT), the duration of anticoagulation is less clear, but given the high incidence of thrombosis within the first month, it is reasonable to continue anticoagulation for at least a month in the absence of contraindications.

E. Antiphospholipid antibodies are a heterogeneous group of autoantibodies that, if present in a patient with thrombosis, lead to the antiphospholipid syndrome. Antiphospholipid antibodies can be divided into three groups: (a) anticardiolipin antibodies, (b) lupus anticoagulants, and (c) β_2 glycoproteins. They are often associated with other autoimmune conditions and can cause recurrent pregnancy loss, as well as arterial or venous thrombosis. Thrombocytopenia is also an occasional feature of this syndrome. Anticardiolipin antibodies are detected and quantified using an enzyme-linked immunosorbent assay and may be IgG, IgM, or IgA. IgG titers have been correlated more often with thrombosis. Lupus anticoagulants prolong phospholipid-dependent blood clotting times, and it has been reported that there is about a fivefold increased risk of thrombosis in patients with this finding. Once a thrombotic event occurs, long-term therapy with warfarin must be considered. A higher target INR had been considered necessary in the past (approximately ≥ 3.0), but is no longer considered necessary as data have suggested that most patients can be maintained with a target INR of 2.0 to 3.0. In those individuals that are suspected of failing adequate therapy, one strategy is to correlate the INR to factor II and factor X levels (of ≤ 20% to 30%) to ensure adequate anticoagulation. Patients with recurrent miscarriages should receive aspirin and LMWH during pregnancy.

F. Malignancy. Many malignancies induce a hypercoagulable state, and in patients with idiopathic VTE, a search for age- and gender-specific malignancies may be necessary. LMWH as monotherapy for the first 3 months before bridging to Coumadin has been shown to decrease the risk of venous thrombosis recurrence or anticoagulation failure.

G. Other conditions. Elevated factor VIII levels and the dysfibrinogenemias have also been associated with thrombosis; however, the role of deficiencies of plasminogen, tissue plasminogen activator (of the fibrinolytic system), and factor XIII polymorphisms as emerging risk factors for hypercoagulability is less clear.

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Dr. Vijay Nambi and Dr. John Bartholomew to earlier editions of this chapter.*

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CHAPTER 26

Matthew C. Bunte
Maran Thamilarasan

Aortic Aneurysm and Aortic Dissection

I. INTRODUCTION

A. Aorta. The aorta is the **principal conductance vessel** in the body and is divided into the ascending, arch, descending thoracic, and abdominal components.

1. The **ascending aorta** includes the aortic root, which contains the sinuses of Valsalva. The left and right coronary arteries arise from the left and right coronary sinuses, respectively.
2. The **aortic arch** gives rise to the great vessels of the head and arms. These include the brachiocephalic (innominate), the left common carotid, and the left subclavian arteries.
3. The **descending thoracic aorta** provides the intercostal vessels as it courses through the posterior mediastinum. The vascular supply to the anterior spinal artery is included among these vessels.
4. The **abdominal aorta** begins just after the aorta crosses the diaphragm. It provides the splanchnic and renal arteries before bifurcating to become the common iliac arteries.

B. Histology. The aorta comprises **three layers**: the intima, the media, and the adventitia.

1. The **intima** is the internal lining layer of the aorta and is easily damaged.
2. The **media** is the main structural layer of the aorta. It consists primarily of laminar layers of elastic tissue and smooth muscle in varying amounts. This structure allows for the high tensile strength and elasticity required to withstand the pressure changes of each heartbeat throughout the life of the individual.
3. The **adventitia** is the thin outer layer that anchors the aorta within the body, in addition to providing nourishment to the outer half of the wall through the vasa vasorum.

C. Physiology

1. The **elasticity of the aortic wall allows it to distend** under the pressure created during ventricular systole. In this way, the kinetic energy that was developed during ventricular systole is stored as potential energy in the distended aortic wall. Then, during ventricular diastole, the potential energy is converted back to kinetic energy by elastic recoil of the wall. Therefore, forward blood flow is maintained throughout the cardiac cycle.
2. The aorta aids in the control of **systemic vascular resistance (SVR)**. Pressure receptors in the ascending aorta and aortic arch signal the vasomotor centers of the brain via the vagus nerve. When blood pressure is elevated, the reflex response is to lower heart rate and decrease SVR. The converse is true when blood pressure is decreased.

D. Acute aortic syndromes including aortic dissection, aortic intramural hematoma (IMH), and penetrating atherosclerotic ulcer (PAU) are life-threatening disorders that require prompt diagnosis and treatment.

E. The 2010 ACC/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease is the principal source of information discussed in this chapter. Where appropriate and unless otherwise indicated, class I guideline recommendations from this document are embedded in italics within this chapter. The level of evidence following the corresponding recommendation is provided in parenthesis.

II. AORTIC DISSECTION

A. The International Registry of Acute Aortic Dissections (IRAD). Since 1996, the IRAD has built a consortium of 24 referral centers in 12 countries dedicated to the study of acute aortic dissection that now includes over 1,600 patients. This research collaborative has provided considerable insight into and improvement in the management and outcomes of acute aortic dissection. More information about IRAD can be found at www.iradonline.org.

B. Etiology and pathology

1. **Aortic dissection classically occurs when a tear in the intima results in separation of the intima from the media (90% of cases), forming a false lumen within the aortic wall. Less commonly, rupture of the vasa vasorum within the aortic wall may result in separation of the intima and media, thereby causing dissection. In either case, acute aortic dissection results from a pathologic weakening of the aortic wall due to medial necrosis, atherosclerosis, or inflammation**. There are many risk factors for aortic dissection, although the most common is a history of systemic hypertension as evidenced in over 70% of cases. Younger patients suffering aortic dissection are more likely to have a genetic or morphologic risk factor, such as genetic syndromes associated with aortopathy, bicuspid aortic valve (BAV), or prior aortic surgery. The following list includes the most common conditions associated with aortic dissection:
   a. Increased age and uncontrolled hypertension are the two most common risk factors.
   b. Tobacco use, dyslipidemia, and cocaine use are important risk factors.
   c. Genetic diseases, especially Marfan, Loeys-Dietz, and vascular-type Ehlers-Danlos syndromes, are associated with aortic aneurysm and dissection.
   d. Familial thoracic aortic aneurysm (TAA) and dissection syndrome and other congenital anomalies associated with aortic aneurysm and dissection, including BAV and Turner syndrome.
   e. Inflammatory vasculitides, including Takayasu arteritis, Giant cell arteritis, and Behçet arteritis.
   f. Infections involving the periaortic tissue, as seen in prosthetic aortic valve endocarditis.

g. Aortic trauma, particularly with deceleration and torsional injuries, although may occur with direct endoluminal trauma during arterial catheterization or with cardiothoracic surgery.
h. Pregnancy.

2. **Genetic syndromes associated with aortic aneurysm and dissection.** Marfan, Ehlers-Danlos, and Loeys-Dietz syndromes are associated with an increased risk of aortic dissection. **These patients require comprehensive aortic imaging at diagnosis and heightened surveillance to follow aortic diameter owing to the increased risk of complications related to aortic disease.** *Aortic imaging is recommended for first-degree relatives with TAA and/or dissection to identify those with asymptomatic disease (Level of Evidence: B).*
   a. **Marfan syndrome.** Marfan syndrome is a genetic disorder with high penetrance and variable expression affecting connective tissue. Marfan syndrome is associated with mutations of the *FBN1* gene, which encodes fibrillin-1, a large glycoprotein that contributes to the structure of the extracellular matrix and serves as a regulator of transforming growth factor-beta (TGF-β). The principal features of Marfan syndrome involve the cardiovascular, ocular, and skeletal systems, with patients at exceedingly high risk for aortic disease. In fact, nearly all patients with Marfan syndrome demonstrate some form of aortic disease during their lifetime.
   b. **Loeys-Dietz syndrome.** An autosomal dominant disorder associated with a triad of arterial tortuosity and aneurysm, hypertelorism, and bifid uvula, Loeys-Dietz syndrome results from mutations in either TGF-β receptor type 1 or 2 (*TGFBR1* or *TGFBR2*). Vascular disease among these patients is highly prevalent, with 98% demonstrating aortic root aneurysms, and portends a grim prognosis. Early reports of Loeys-Dietz syndrome suggested a particularly aggressive disease process with arterial complications occurring at a mean age of 26 years. However, subsequent data have revealed less aggressive phenotypes with later presentations, and a mean age of death closer to the fifth decade among less severe phenotypes. Repair of the aortic root is recommended at lesser aorta diameters (< 5.0 cm) due to the aggressive nature of this condition.
   c. **Ehlers-Danlos syndrome, type IV (vascular form).** The vascular form of Ehlers-Danlos syndrome is characterized by an autosomal dominant inheritance of the *COL3A1* gene mutation that encodes type III procollagen. Clinical features include easy bruising and rupture of the uterus, intestines, and arteries. Median survival is 48 years and often no aneurysms are documented. Gravid women with this condition have a particularly poor prognosis during childbirth due to the high risk of arterial and uterine rupture.

3. **Hereditary conditions and congenital anomalies** such as BAV and coarctation of the aorta are also established risk factors for aortic dissection. Turner syndrome is associated with BAV (10% to 25%), aortic coarctation (8%), and dilatation of the ascending aorta. Although patients with Turner syndrome require screening for aortic disease at diagnosis, requirements of surveillance for aortic dilatation follow those of other patients with BAV. *All patients with BAV should have both the aortic root and ascending aorta evaluated for evidence of aortic dilatation (Level of Evidence: B). First-degree relatives of patients with a BAV, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of TAA or dissection should be evaluated for the presence of a BAV and asymptomatic thoracic aortic disease (Level of Evidence: C).*
4. **Vasculitides** associated with large vessel inflammation and aortitis contribute to medial degeneration of the aortic wall and may increase the risk of aortic dissection. Examples of these inflammatory disorders include giant cell arteritis, Takayasu arteritis, syphilis, and Behçet disease.

5. **Aortic dissection exhibits a strong association with pregnancy**. Among cases of aortic dissection in women < 40 years of age, up to half may present during the third trimester or early in the postpartum period. **Gravid women with Marfan syndrome and preexisting aortic root dilatation are at especially high risk for aortic dissection**.
6. **Direct aortic trauma is associated with aortic dissection**. Blunt chest trauma, such as that occurring in a motor vehicle accident, may cause aortic transection or mural hematoma. Intravascular instrumentation as during arterial catheterization, insertion of an intraaortic balloon pump, or aortic cannulation, cross-clamping, and graft insertion may also serve as a source of intimal damage and dissection.

C. Epidemiology. The incidence of aortic dissection has been estimated from 2 to 3.5 cases per 10,000 person-years, corresponding to 6,000 to 10,000 cases per year in the United States. The male-to-female ratio approaches 3:1, with the peak incidence in the sixth and seventh decades of life. The mortality for untreated acute aortic dissection is largely determined by the location of the dissection, but overall mortality is approximately 1% per hour within the first 48 hours if surgery is not performed. Approximately 65% of dissections originate in the ascending aorta (just above the right or noncoronary sinus), 20% in the descending thoracic aorta, 10% in the aortic arch, and the remainder in the abdominal aorta.

D. Classification schemes

1. **Anatomic classification schemes** used to commonly describe aortic dissection include the DeBakey and Stanford systems (see Table 26.1 and Fig. 26.1 for a description of the DeBakey and Stanford classifications). Anatomic classification refers to the portion(s) of aorta involved. The Stanford classification will be used throughout this chapter.
2. Dissections are further classified according to chronicity: acute (< 2 weeks from onset) or chronic (> 2 weeks from onset).
3. Anatomic involvement and chronicity of dissection influence the recommended treatment approach and indicate prognosis.
   a. **Type A dissection.** Predictors of death are age 70 years or older, abnormal electrocardiogram (ECG), pulse deficit, acute renal failure, and the composite of hypotension, shock, or tamponade.
   b. **Type B dissection.** Predictors of death are branch vessel involvement, absence of chest or back pain, and hypotension/shock. Continued patency of the false lumen predicts a worse outcome in type B aortic dissection. The highest survival benefit is among those with complete thrombosis of the false lumen.

TABLE 26.1 Aortic Dissection Classification Systems

Classification	Pathologic description
Stanford	
Type A	Any dissection involving the ascending aorta
Type B	Any dissections *not* involving the ascending aorta
DeBakey	
Type I	Entry point in the ascending aorta, extends to the aortic arch and often beyond
Type II	Confined entirely to the ascending aorta
Type III	Entry in the descending aorta (distal to left subclavian); extends distally (usually) or proximally (rarely)

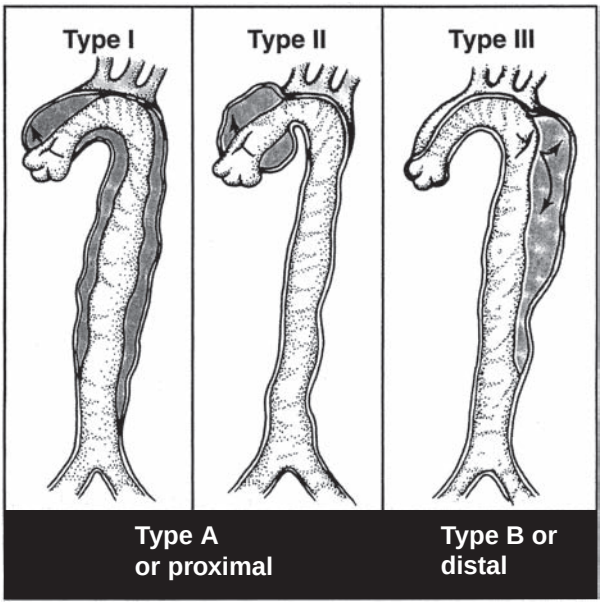

FIGURE 26.1 Anatomic appearance of three different aortic dissection classifications.

E. Atypical variants of aortic dissection

1. **IMH** represents a focal hemorrhage of the aortic wall caused by rupture of the vasa vasorum within the aortic wall and may cause secondary dissection. The natural history of IMH is similar to that of classic aortic dissection. In fact, in 4% to 10% of dissections, an intimal tear is not found. Therefore, *it is reasonable to treat IMH similar to de facto aortic dissection including surgery if located in the ascending aorta or aggressive medical therapy if in the descending aorta (Level of Evidence: C).*
2. **PAU** is a focal defect in the endoluminal surface of the aortic wall produced by atherosclerotic erosion through the intima with ulceration into the media. Risk factors for PAU include older age, extensive atherosclerosis, and uncontrolled hypertension. PAU may manifest as subtle asymptomatic erosions noted incidentally on radiography to symptomatic IMH with eccentric or saccular aneurysms of the aorta. In either case, PAU may progress to aortic dissection or aortic perforation, although the natural history of this condition remains uncertain. Nevertheless, surgery is often recommended for patients exhibiting unstable symptoms or lesions involving the ascending aorta. Otherwise, medical management and frequent radiologic follow-up for signs of progression is recommended.

F. Clinical presentation

1. **Signs and symptoms**
   a. Aortic dissection may present with a wide range of clinical manifestations. Proximal dissections are most commonly characterized by a sudden onset of chest pain (80%) that is severe in intensity and ripping, tearing, stabbing, or sharp in quality. Pain may radiate to the interscapular region of the back (47%) or abdomen (21%). Among descending aortic dissections, back pain (64%), chest pain (63%), and abdominal pain (43%) are most common. **Typical symptoms are less common in the elderly**.

b. Presenting clinical findings may include the murmur of severe aortic insufficiency (AI) (45%) associated with proximal aortic dissection and contributing to acute heart failure (5% to 6%), hypotension (14%) or shock (13%) associated with cardiac tamponade (5% to 10%), syncope (13%), myocardial infarction (MI) (7% to 19%) with retrograde dissection into the ostia of the coronary arteries, cardiovascular accident (CVA) (8%) with cephalad carotid extension, paraplegia (2%) with extension into the intercostal and spinal arteries, or cardiac arrest. Dissections involving the arterial supply to the limbs may contribute to pulse deficits (26%), acute limb ischemia (10%) with distal extension, and neuropathy.

G. Diagnostic testing

1. **Evaluation.** Figure 26.2 provides an algorithm to aid in diagnosis. Key characteristics important in defining the extent of aortic dissection and clinical management include ascending versus descending aortic involvement, site of the intimal tear, presence or absence of AI, presence of pericardial effusion and/or tamponade, coronary involvement, and involvement of visceral arterial supply. Computed tomography (CT), magnetic resonance imaging (MRI), transesophageal echocardiography (TEE), and invasive aortography are common imaging modalities useful in the diagnosis of acute aortic dissection. The relative advantages and disadvantages of the four modalities are outlined in Table 26.2. **Selection of the specific imaging modality for identification or exclusion of aortic dissection should be based on clinical variables, local expertise, and clinical availability to facilitate rapid diagnosis (Level of Evidence: C)**.
2. *An ECG should be performed in all patients with suspected aortic dissection (Level of Evidence: B).* Most frequently, ECG is useful to exclude an acute coronary syndrome presenting atypically as symptoms of aortic dissection. *Because dissection-related acute MI is infrequent, ST-segment elevation on ECG should be treated as an independent coronary event without delay for aortic imaging unless the patient is at high risk for aortic dissection (Level of Evidence: B).*

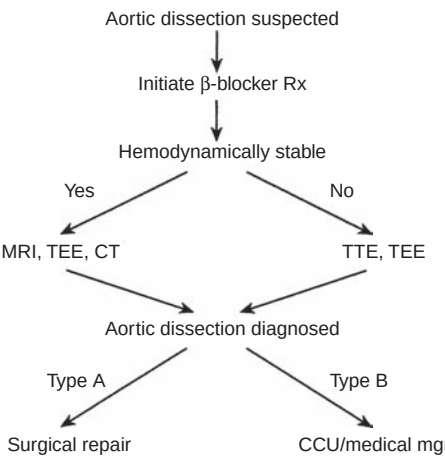

FIGURE 26.2 Aortic dissection diagnostic/therapeutic algorithm. CCU, coronary care unit; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

TABLE 26.2 Comparison of Imaging Modalities in Aortic Dissection

Factor	Angiography	CT	MRI	TEE
Intimal tear definition	++	+++	+++	++
False lumen thrombus +/–	+++	+++	+++	+
Involvement of branch vessels	+++	++	++	+
Pericardial effusion	–	+++	+++	+++
Coronary involvement	+++	–	–	++
AI presence	+++	–	+	+++
Overall sensitivity (%)	88	100	98	98
Overall specificity (%)	95	98	98	95

AI, aortic insufficiency; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography.

Modified from Isselbacher EM, Eagle RA, DeSanctis RW. Diseases of the aorta. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 5th ed. Philadelphia, PA: WB Saunders, 1997:1546–1581.

3. Chest radiography may occasionally detect findings suggestive of dissection, although it is inadequately sensitive to definitively exclude the presence of acute aortic dissection. *A negative chest x-ray should not delay definitive aortic imaging in patients determined to be high risk for aortic dissection by initial screening (class III recommendation, Level of Evidence: C).*

H. Selected imaging modalities for diagnosis of acute aortic dissection

1. **Computed tomography.** Contrast-enhanced, cardiac-gated multidetector CT is a widely available and the most commonly used imaging modality for the detection of aortic dissection, with excellent sensitivity and specificity approaching 100%. This modality has many advantages, including rapid scan and interpretation times. Disadvantages include iodinated contrast and radiation exposure.
2. **MRI and magnetic resonance angiography (MRA).** Like CT, MRI provides multiplanar imaging of the thoracic aorta with high sensitivity and specificity that is very accurate for diagnosis of acute aortic disease. MRA offers unique gadolinium-enhanced and black blood imaging techniques to evaluate aortic anatomy and morphology that prove particularly useful in assessing the aortic wall. Advantages of MRI include the ability to identify anatomic variants, such as IMH or penetrating aortic ulcer, assess branch arterial involvement, and provide useful information on aortic valvular and left ventricular systolic function while avoiding exposure to iodinated contrast or radiation. MRI is well suited for chronic follow-up of aortic syndromes since ionizing radiation is not necessary. Use of MRI is limited by availability, prolonged acquisition time, and incompatibility with implanted ferromagnetic devices. MRI is not an appropriate test for patients that are hemodynamically unstable.
3. **Transthoracic echocardiography (TTE) and TEE.** TTE allows for a rapid noninvasive evaluation, primarily of the proximal aorta with overall limited sensitivity and specificity. Visualization of the proximal aorta and other critical structures using TTE may be limited by factors that reduce image quality, such as emphysema, mechanical ventilation, and obesity. With an esophageal approach, TEE overcomes many of the challenges with improved sensitivity and specificity while offering a safe and rapid assessment of acute aortic disease. A major limitation of either TTE or TEE includes the appearance of ultrasound artifacts that may mimic a dissection flap, such as that of reverberation artifact.

4. **Invasive aortography.** Aortography offers accurate information about the location of dissection, providing visualization of the false lumen or intimal flap, branch vessel involvement, and communication between true and false lumens. Invasive aortography is useful in evaluating PAU, as it is characterized by endovascular aortic contrast protruding into an atherosclerotic plaque. False negatives can occur with thrombosis of the false lumen, IMH, or equal filling of the false lumen. Disadvantages or aortography include a low sensitivity, risks associated with any invasive procedure, contrast administration, and availability of experienced operators to perform the study.
5. **Recommendations for aortic imaging techniques to determine the presence and progression of thoracic aortic disease**
   a. *Measurements of aortic diameter should be taken at reproducible anatomic landmarks, perpendicular to the axis of blood flow, and reported in a clear and consistent format (Level of Evidence: C).*
   b. *For measurements taken by CT imaging or MRI, the external diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*
   c. *For measurements taken by echocardiography, the internal diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*
   d. *Abnormalities of aortic morphology should be recognized and reported separately even when aortic diameters are within normal limits (Level of Evidence: C).*
   e. *The finding of aortic dissection, aneurysm, traumatic injury and/or aortic rupture should be immediately communicated to the referring physician (Level of Evidence: C).*
   f. *Techniques to minimize episodic and cumulative radiation exposure should be utilized whenever possible (Level of Evidence: B).*

I. Therapy. Death in aortic dissection results from vascular compromise, tamponade, or aortic rupture. ***Management of proximal (type A) thoracic aortic dissection requires immediate surgical treatment to resect the entire aneurysmal aortic segment and the proximal extent of dissection (Level of Evidence: C).*** Surgery greatly improves outcomes and avoids the risks associated with progression of dissection. One- and three-year survival after surgery for type A dissection is excellent, with survival rates of 96.1% and 90.5%, respectively. Survival rates at 1 and 3 years are 88.6% and 68.7%, respectively, among those who do not receive surgery for type A dissection. ***Patients with distal (type B) thoracic and abdominal aortic dissections should be managed medically unless life-threatening complications, such as malperfusion syndromes, progression of dissection, aortic enlargement, or refractory hypertension, develop (Level of Evidence: B).*** **Percutaneous endovascular aortic repair (EVAR)** is a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection, although it has not been approved by the Food and Drug Administration (FDA) for this indication. Table 26.3 recommends the course of treatment for various types of dissections. The 5-year survival rate for patients leaving the hospital with appropriate treatment (medical or surgical) for type B dissection ranges from 75% to 82%.

1. **Priority of therapy.** The initial management of patients with suspected aortic dissection is directed at **reducing aortic wall stress. Aortic wall stress is affected by the velocity of ventricular contraction (dP/dt), the rate of ventricular contraction, and blood pressure. Medical stabilization of acute aortic dissection should target the reduction of heart rate followed by lowering of blood pressure**. Invasive hemodynamic monitoring and sufficient intravenous access for volume replacement should be established simultaneously. An

TABLE 26.3 Surgical versus Medical Therapy for Aortic Dissection

Medical therapy	Surgical therapy	Endovascular therapy
Uncomplicated type B dissection	Acute, type A dissection	Malperfusion syndrome associated with type B dissection
Stable, lone arch dissection	Acute, complicated type B dissection	Possibly as an alternative to surgical therapy for complicated type B dissection
Stable, chronic type B dissection (> 2 wk after onset of symptoms)	End-organ dysfunction	Possibly as an alternative to medical treatment for uncomplicated type B dissection
	Rupture/impending rupture Aortic insufficiency Associated with Marfan syndrome Retrograde extension into the ascending aorta	

initial and aggressive treatment approach to reduce d*P*/d*t* applies to all patients regardless of the location of dissection or whether the eventual management strategy is medical or surgical.

2. **Medical therapy** (see Table 26.4)
   a. ***With suspicion of acute aortic dissection, β-blockers should be initiated immediately and titrated to target heart rate of < 60 beats per minute***

TABLE 26.4 Intravenous Dosing for Acute Medical Management of Acute Aortic Syndromes

Drugs	Loading dose	Maintenance dose
First-line agents		
Propranolol	1 mg IV q3-5min (max. 6.15 mg/kg)	2–6 mg IV q4-6h
Labetalol	10 mg IV over 2 min, then 20–80 mg q10-15min (max 300 mg)	2 mg/min IV drip titrate to 5–20 mg/min
Esmolol	500 μg/kg IV bolus	50–200 μg/kg/min IV continuous
Metoprolol	5 mg IV q5min to effect	5–10 mg IV q4-6h to effect
Second-line agents in patients with contraindications for β-blockers		
Enalaprilat	0.625 mg IV	0.625 mg IV q4-6h
Diltiazem	0.25 mg/kg IV over 2 min; 0.35 mg/kg IV after 15 min if no effect	5 mg/h titrate by 2.5 to 5 mg/h increments; max 15 mg/h
Verapamil	0.075–0.1 mg/kg to 2.5–5 mg/kg over 2 min	5 to 15 mg/h IV drip

IV, intravenous.

(Level of Evidence: C). In patients who are intolerant of β-blockers, nondihydropyridine calcium channel blockers may serve as an acceptable alternative to control heart rate (see Table 26.4) (*Level of Evidence: C). In the setting of acute aortic regurgitation, use of rate-controlling agents, such as β-blockers, should be used with caution since they block compensatory tachycardia (Level of Evidence: C).*

b. *Once the heart rate goal has been achieved, systolic blood pressure should be targeted to < 120 mm Hg with the use of angiotensin-converting enzyme inhibitors or vasodilators to reduce blood pressure while maintaining adequate end-organ perfusion* (*Level of Evidence: C)*. With a goal of heart rate and blood pressure control, β-blockers with α-effect, such as labetalol, may be particularly advantageous. Sodium nitroprusside is a particularly useful vasodilator, given a rapid onset and easy titration as an intravenous infusion. Close monitoring for reflex tachycardia should be done with use of vasodilators—*vasodilator therapy should not be initiated prior to heart rate control since reflex tachycardia may increase aortic wall stress and risk of propagation or expansion of dissection (class III, Level of Evidence: C).*

3. Managing complications of acute aortic dissection

a. Hypotension and shock. Aortic wall rupture or hemorrhage into the pericardial space with cardiac tamponade may manifest as shock. In either event, **aggressive volume replacement should be initiated and the patient taken to the operating room promptly**. Pericardiocentesis is generally not recommended. If pericardiocentesis becomes an absolute requirement to get the patient to the operating room, enough pericardial fluid should be removed to raise the blood pressure to an acceptable level, but no more. **If vasopressors are required for hemodynamic stabilization, norepinephrine and phenylephrine are the drugs of choice, as neither has a demonstrable effect on d*P*/d*t*. Epinephrine and dopamine should be avoided.**

b. Acute MI. Coronary thromboembolism and retrograde progression of the aortic dissection flap into the coronary ostia are infrequent complications of proximal aortic dissection. In this setting, **thrombolysis is contraindicated**. Coronary arteriography and percutaneous intervention are not generally recommended since these procedures will **delay surgical repair of the dissection while exposing it to mechanical complications related to angiography in an already compromised aorta**.

c. Refractory hypertension. Sufficient blood pressure reduction can be difficult to obtain, with many patients requiring several antihypertensive drugs of different classes. Adequate analgesia is essential to reduce pain-related increases in sympathetic tone and blood pressure associated with acute aortic dissection. Following initial stabilization, use of β-blockers should be continued with consideration for angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists that may slow pathologic aortic dilatation.

4. Surgical management of acute aortic dissection

a. *Patients with a proximal (type A) thoracic aortic dissection should receive emergent surgery. A partially dissected aortic root with a normal aortic valve may be repaired with supracommissural aortic valve resuspension. In the event that the aortic valve cannot be repaired or resuspended, a Bentall procedure may be performed with a prosthetic valve sewn onto a Dacron graft and used to replace the native valve with reimplantation of the coronary arteries into the graft (Level of Evidence: C).*

b. *Patients with type B dissection who have evidence of rupture or end-organ involvement should receive surgical repair with replacement of the entire segment of dissected aorta (Level of Evidence: C).* Reattachment of the visceral arteries and T_8 to L_2 intercostal/lumbar arteries are implanted into the graft conduit.

c. Perioperative risk. Compared with unstable patients with aortic dissection, those demonstrating preoperative stability have an improved prognosis.

Nevertheless, stable patients still carry a substantial surgical mortality of 17%. When patients have features of instability—such as cardiac tamponade, shock, congestive heart failure (CHF), cerebrovascular accident, coma, MI, acute renal failure, or mesenteric ischemia—surgical mortality rates rise to approximately 31%. Surgical mortality increases with age. However, the relative benefits of surgery outweigh risks of nonoperated type A dissection until at least the age of 80 years. Therefore, the benefits of surgery should be measured against surgical risks of all age groups, with consideration for complexity of repair, preoperative medical comorbidities, and anticipated quality of life after surgery.

d. Postsurgical complications of open thoracic surgical repair include respiratory failure (5% to 15%), stroke (2% to 8%), bleeding requiring reoperation (1% to 6%), infection (1% to 5%), MI (1% to 5%), heart failure (1% to 5%), ventricular arrhythmias (1% to 5%), acute postoperative renal failure, paraplegia (2% to 10%), and mesenteric ischemia.

(1) *A brain-protective strategy to prevent stroke and preserve cognitive function should be a key element of the surgical, anesthetic, and perfusion techniques used to accomplish repairs of the ascending aorta and aortic arch (Level of Evidence: B).*

(2) Paraplegia stands among the most feared complications of descending thoracic and thoracoabdominal aortic repairs, occurring in 2% to 4% and 3% to 10% of cases, respectively. Paraplegia results from the disruption of blood flow to the anterior spinal artery via the intercostal arteries. *Cerebrospinal fluid drainage is recommended as a spinal-protective strategy in open and endovascular thoracic aortic repair for patients at high risk for spinal cord ischemic injury (Level of Evidence: B).*

5. Percutaneous EVAR for type B aortic dissection. EVAR represents a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection, although it has not received FDA approval for this indication and such use is considered "off-label." Nevertheless, stent-grafting for conditions other than abdominal aortic aneurysm (AAA) is an area of active study, with proposed uses for EVAR in stable type B aortic dissection, IMH, PAU, acute traumatic aortic transection, and pseudoaneurysm.

a. Potential advantages of EVAR over conventional surgery include the absence of thoracotomy, avoiding cardiopulmonary bypass and clamping of the aorta, lower hospital morbidity rates, and shorter length of hospital stays. A mortality advantage of endovascular therapy was suggested in early trial reports, although it has largely been lost with longer-term follow-up from these studies.

b. Comparing EVAR with optimal medical management (OMM). Although OMM remains the mainstay for acute treatment of uncomplicated type B dissection, long-term morbidity and mortality of chronic dissection remain substantial. Data on EVAR for use in descending aortic dissection are limited. Results from a meta-analysis of 609 cases suggest that mortality rates are higher with EVAR (5.3%) compared with open surgical correction (2.5%), although the risk of major complications with either treatment is similar. Two prospective randomized trials have compared endovascular repair with OMM.

(1) The prospective INvestigation of STEnt grafts in patients with type B Aortic Dissection (INSTEAD) trial provided the first randomized evaluation of elective stent-graft placement in 140 patients with subacute or chronic uncomplicated type B aortic dissection. INSTEAD did not show a 2-year survival advantage or difference in adverse event rates with EVAR compared with optimal medical therapy.

(2) The optimal timing of EVAR for aortic dissection remains to be defined. The Acute Dissection Stent-grafting OR Best Medical Treatment

(ADSORB) trial is an ongoing study poised to compare EVAR with OMM for *acute* uncomplicated type B aortic dissection. Target enrollment is 250 patients with 3-year follow-up. Study completion is anticipated in 2015.

6. **Postoperative surveillance after thoracic aortic repair or monitoring of chronic descending aortic dissection**
   - **a.** *CT or MRI of the thoracic aorta is reasonable after type A or type B aortic dissection or after prophylactic repair of the aortic root/ascending aorta (class IIa, Level of Evidence: C).*
   - **b.** *CT or MRI of the aorta is reasonable at 1, 3, 6, and 12 months after dissection, then annually thereafter if clinically stable (class IIa, Level of Evidence: C).* In about 30% of cases, late deaths are caused by rupture of a secondary aneurysm or recurrence of the dissection. A majority of these secondary aneurysms will develop within 2 years of the initial treatment.
   - **c.** *For patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, open repair is recommended* (*Level of Evidence: B).*
   - **d.** *Long-term, aggressive cardiovascular risk factor management is critical before and after thoracic aortic surgery and includes aggressive heart rate and blood pressure control to reduce dP/dt, lipid profile optimization, and smoking cessation (Level of Evidence: C).* In the event of medical treatment failure, including end-organ damage related to complications of aortic disease, aortic leak, or escalating visceral pain, patients with chronic descending aortic dissection should be considered for surgical treatment.

III. AORTIC ANEURYSM. An aortic aneurysm is a pathologic dilatation of the aorta to > 1.5 times its normal diameter. Aneurysms are classified based on involvement of the anatomic aortic segment, including AAA and TAA. The etiology, natural history, and treatments differ somewhat for aneurysms of each location.

A. Abdominal aortic aneurysm. Aneurysms of the aorta located below the diaphragmatic crura and above the bifurcation of the common iliac arteries are classified as AAA.

1. **Etiology and pathology of aortic aneurysm**
   - **a. Aneurysms of the aorta are caused by degenerative disease within the aortic wall, leading to inflammation, weakening of the aortic tissues, loss of elasticity, and dilatation of the aorta.** Atherosclerosis has traditionally been linked with development of AAA, although the pathogenesis is likely multifactorial, involving immunologic, genetic, environmental, and hemodynamic factors. Matrix metalloproteinases and other proteases produced locally by smooth muscle cells may degrade elastin and collagen and lead to aneurysm formation.
   - **b. Genealogic studies demonstrate a strong familial component to developing AAA**, with up to 28% of patients having a first-degree relative with an abdominal aneurysm. First-degree male relatives of patients with AAA have a 12 times greater risk of having an aneurysm.
   - **c. Risk factors for the development of AAA** include current or past history of tobacco use, male gender, advanced age, first-degree relative with AAA, hypertension, hyperlipidemia, and atherosclerosis in other vascular beds. Less common causes include infection (*Salmonella* and *Staphylococcus aureus*), *vasculitis*, and trauma.
   - **d. Rate of enlargement is dependent on aneurysmal diameter.**
     - **(1)** Rate of enlargement can range from 0.2 cm/y to > 3 cm/y. The majority of aneurysms enlarge at a rate of 2.6 mm/y. **The larger the aneurysm grows, the faster it will continue to expand.**

(2) Laplace's law defines the parameters for growth of aneurysms.

Wall tension = transmural pressure (TP) × radius (*r*)

(1) Therefore, with luminal dilatation (increased *r*), the wall tension will increase at a given blood pressure (TP). This leads to a further increase in radius and to a self-perpetuating cycle of growth of the aneurysm.

e. Characteristics of aneurysmal rupture:

(1) *Risk is proportional to aneurysm size*. Aneurysms > 6.0 cm have > 20% per year risk of rupture, whereas those between 5 and 6 cm have approximately 6% risk of rupture per year.

(2) Rupture usually occurs into the left retroperitoneal space (80%). Rupture in this location may initially be contained, although it will ultimately extend, causing shock and death if untreated.

(3) AAA can also rupture into the inferior vena cava (causing aortovenous fistula formation). Fistulous connection between an enlarging aortic aneurysm and the gastrointestinal tract may create an aortoenteric fistula that may present as a life-threatening emergency requiring prompt surgical intervention. A **gastrointestinal bleed with known AAA or history of AAA repair should prompt consideration for an aortoenteric fistula**.

(4) **Rupture of an AAA is associated with high mortality**. One-quarter of patients with rupture die before reaching the hospital and 50% die prior to undergoing surgery. Among those who survive to undergo surgery, the operative mortality approaches 50%.

2. Epidemiology

a. AAA is much more common than TAA, as nearly 75% of aneurysms involve the abdominal aorta.

b. AAA affects men more commonly than women. Among patients over age 65 years, the prevalence of AAA among men and women is 5% and 1.0% to 2.2%, respectively. The incidence of AAA increases after age 55 years in men and 70 years in women. Most cases (95%) involve the infrarenal aorta.

3. Clinical presentation. The majority of AAAs are discovered incidentally on physical examination or during radiologic evaluation of the abdomen.

a. Signs and symptoms. Most patients are asymptomatic; therefore, the diagnosis of AAA should be considered in patients with an appropriate risk profile and family history.

(1) Rapid enlargement of the aneurysm may be associated with severe back or flank pain and herald impending rupture. Pain associated with an expanding AAA is described as sudden in onset, constant, and not affected by movement or position. Occasionally, there is radiation to the legs, buttocks, or groin.

(2) Findings consistent with shock (hypotension, pallor, diaphoresis, oliguria, and obtundation) can develop rapidly with a ruptured aneurysm.

b. Physical findings

(1) A palpable, pulsatile mass may be felt on abdominal examination and may extend variably from the xiphoid process to below the umbilicus, although accurate sizing is nearly impossible on physical examination. Palpation should be gentle or potentially avoided, especially if the aneurysm is tender, as tenderness can be an indication of impending rupture.

(2) Associated vascular disease is common among those with AAA and may be represented by abdominal or femoral bruits or decreased pulses in the extremities.

(3) Examination findings of distal thromboembolism may be noted in the distal extremities and represent atheromatous material or mural

thrombus with embolism. Other related findings may include livedo reticularis, painful blue toes, hypertension, and acute kidney injury.

4. **Diagnostic testing**
   a. **Abdominal ultrasound** is the most commonly used screening tool for AAA. Aortic ultrasound has the capacity to obtain both longitudinal and transverse images of the aneurysm and has been validated to accurately measure size to within ±0.3 cm. **Major advantages of ultrasound include its wide availability, cost-effectiveness as a diagnostic and screening imaging technique, and avoidance of ionizing radiation exposure**. If imaging is adequate, ultrasound is an effective option when monitoring aneurysm growth serially. Disadvantages of abdominal ultrasound include poor definition of branch vessels; therefore, ultrasound is insufficient for preoperative evaluation.
   b. **CT aortography** with cardiac gating allows for accurate evaluation of the aneurysm shape, and volumetric acquisition provides detailed three-dimensional analysis of spatial relations to branch vessels and diagnosis of associated acute aortopathies including PAU. CT measurements have been validated to within ±0.2 cm. CT offers an advantage of evaluating for extravasated blood in acute or subacute rupture. The major disadvantages of CT include the requirement for ionizing radiation and intravenous contrast, which limit its utility in follow-up of chronic aortic dissection (see Chapter 52).
   c. **MRI** provides excellent definition of aneurysm size as well as suprarenal and iliofemoral extension. MRA allows for improved visualization of compromised flow to branch vessels, although it lacks sensitivity to absolutely define obstruction in the renal vessels. MRI is disadvantaged by cost and limited availability.
   d. **Aortography** effectively defines both suprarenal and iliofemoral involvement as well as branch vessel impingement, although it tends to underestimate the size, especially when mural thrombus is present. Compared with other techniques, aortography is invasive and requires the use of intravenous contrast and ionizing radiation. Aortography is now generally reserved for planning endografting in some centers and is less useful as an initial diagnostic modality.

5. **Therapy**
   a. **Medical therapy**
      (1) β-Blockers have been shown to decrease the rate of enlargement and risk of rupture in at least one clinical trial (Gadowski et al., *J Vasc Surg.* 1994), although other studies have not confirmed this effect.
      (2) Aggressive risk factor modification with control of hypertension and hypercholesterolemia is **imperative to prevent adverse events from atherosclerotic disease in other vascular beds. Smoking cessation should be strongly advocated**.
      (3) Serial ultrasound or CT scanning is indicated in patients without symptoms that have aortic diameters of 2.5 cm or greater. Studies should be obtained yearly when the aortic diameter reaches 3.0 cm, every 6 months for dimensions between 4 and 5 cm, and every 3 to 6 months for aneurysms between 5.0 and 5.5 cm not surgically repaired. Ultrasound is generally preferred for surveillance of small AAAs, owing to lack of radiation exposure.
   b. **Endovascular aortic repair.** Percutaneous aortic stent-grafting has been FDA-approved for use in descending thoracic aortic or infrarenal AAA. Endovascular grafting is a less invasive option for the repair of AAA and is especially appealing for elderly patients or those with substantial cardiac, pulmonary, and renal dysfunction.
      (1) **The EVAR procedure.** Under fluoroscopic guidance, the proximal and distal ends of the stent-graft are affixed to normal segments of the aorta above and below the aneurysmal portion, thereby sealing off the

aneurysm. **Suitable anatomy is necessary for stent-grafting.** Favorable characteristics for EVAR include normal diameter of aorta distal to the renal arteries and proximal to the aneurysmal segment, minimal angulation, freedom from severe obstructive lesions, and patency of side branches and distal iliac vessels. Only 30% to 60% of patients will have anatomy suitable for endovascular repair.

(2) **Comparing EVAR with open surgical repair.** Several randomized trials have compared endovascular repair with open surgical repair, including the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, the Endovascular Aneurysm Repair 1 (EVAR-1) trial, and the Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative trial, among others. Six years after randomization, patients in the DREAM trial received no survival benefit after EVAR compared with those undergoing conventional surgery. Similarly, patients followed to a median of 6 years in the EVAR-1 trial enjoyed a lower operative mortality with endovascular repair over open repair, although no differences were seen in total mortality or aneurysm-related mortality in the long term. As techniques improve, so too may postoperative outcomes among patients randomized to endovascular versus open AAA repair. An interim report from the most contemporary OVER Veterans Affairs Cooperative trial has concluded that early operative advantages of EVAR have not yet been offset by increased morbidity and mortality in the first 2 years after aortic repair. Further comparisons of outcome data from this and other ongoing trials will continue to provide appraisal of the long-term clinical benefits and cost-effectiveness of this technique compared with conventional therapy.

(3) **EVAR among unsuitable surgical candidates.** Compassionate use of EVAR among patients for whom open repair is deemed too high risk because of medical comorbidities was studied in the Endovascular Aneurysm Repair 2 (EVAR-2) trial. This study failed to show any survival benefit with endovascular repair—a disappointing finding as the clearest indication for endovascular repair was traditionally thought to be for those at high risk for open repair.

(4) **Endoleak as a complication of EVAR.** One of the common complications of endovascular repair is endoleak (Table 26.5). Endoleak represents a failure of the stent-graft to completely exclude the aneurysm and

TABLE 26.5 Classification of Endoleaks

Endoleak type	Cause of leak about graft
I	Inadequate seal at proximal and/or distal graft attachment
II	Retrograde arterial flow into the aneurysm sac from an aortic arterial branch within the stented segment
III	Structural failure of the graft material (e.g., graft tear or hole, stent fracture)
IV	Stent-graft porosity
V	Aneurysmal expansion without demonstrable endoleak ("endotension")

Modified from Hiratzka, LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol.* 2010;55(14):e27–e129.

results in persistent flow into the aneurysm, thereby increasing the risk of aneurysm expansion and rupture. Endoleaks occur in 10% to 20% of cases and are associated with more frequent reinterventions than open repair and the requirement of lifelong periodic follow-up imaging.

(5) **Other complications related to EVAR** include endograft migration, prosthesis infection, vascular access site-related infections, bleeding, thromboembolism, and spinal cord ischemia with paraplegia.

(6) *Periodic long-term surveillance imaging should be performed to monitor for endoleak, confirm graft position, document shrinkage or stability of the excluded aneurysm sac, and determine the need for further intervention in patients who have undergone endovascular repair of infrarenal aortic and/or iliac aneurysms (Level of Evidence: A).*

c. **Surgical therapy.** Surgical repair generally requires resection of the aneurysmal segment, with replacement using a Dacron tube graft inserted in place of the diseased aorta. The major branches are then reimplanted to the graft.

(1) **Preoperative evaluation.** Given the strong association of coronary artery disease with AAA and high operative mortality with untreated severe coronary artery disease, **all patients being considered for surgical repair of AAA require preoperative cardiac risk assessment**. Perioperative mortality in elective procedures is 4% to 6% (< 2% in low-risk patients).

(2) **Repair of AAAs < 5.0 cm in diameter provides no long-term survival benefit.** Controversy remains regarding medical versus surgical management of aneurysms between 5.0 and 5.5 cm and so should be managed on a case-by-case basis. **Surgery is indicated for an aneurysm with diameter measuring 5.5 cm or if rapidly expanding (> 1 cm/y)**. Women have a higher overall risk of rupture and tend to rupture at smaller aortic diameters compared with males. Therefore, it is the recommendation of some vascular societies that women should undergo elective repair at aortic diameters 4.5 to 5.0 cm. Symptomatic patients should also be referred for repair.

B. Thoracic aortic aneurysm. Thoracic aneurysms include those that involve the aorta from the level of the aortic root to the diaphragmatic crura. Extension of a descending thoracic aneurysm below the diaphragm creates a thoracoabdominal aneurysm.

1. **Clinical presentation.** Most patients with thoracic aneurysm are asymptomatic at the time of diagnosis, and the condition is often discovered as an incidental finding on imaging done for other reasons.

a. **Signs and symptoms**

(1) **Vascular complications of the aneurysm** include AI with left ventricular dilatation and CHF, myocardial ischemia due to coronary artery compression, sinus of Valsalva rupture into the right atrium/ventricle with left-to-right shunt and CHF, or thromboembolic phenomena.

(2) **Compression of external structures by the aneurysm** causes superior vena cava syndrome, dysphagia from esophageal compression, or hoarseness from recurrent laryngeal nerve compression. In addition, compression of the trachea or mainstem bronchus can lead to wheezing, dyspnea, tracheal shift, cough, or hemoptysis. Chest or back pain from compression and bony involvement is described as constant, boring, and deep.

(3) **Rupture** presents with sudden, severe, sharp chest or back pain. In order of decreasing frequency, TAAs rupture into the left pleural space, the pericardium (presenting as tamponade), and the esophagus (presenting as hematemesis).

(4) **Aortic dissection.** See Section III.

b. Physical examination. Specific physical findings directly attributable to TAA **are usually absent**.

(1) Cardiac. The diastolic murmur of AI (classically right lower sternal border) and a laterally displaced point of maximum impulse are sometimes noted with chronic ascending aortic dilatation. Signs of CHF can be seen in these circumstances. Unilateral jugular venous distention can be seen in patients with venous compression.

(2) Vascular. Rarely, a pulsatile mass can be palpated in the suprasternal notch. Differential pulses in the extremities can sometimes be found. Evidence of thromboembolic events can be seen upon examination of the digits. If the aneurysm compresses the venous return, evidence of superior vena cava syndrome or lower extremity edema may be found.

(3) Pulmonary. If the aneurysm compresses part of the bronchial tree, decreased air movement or stridor is auscultated.

2. Etiology

a. Table 26.6 gives the various classifications of TAAs as well as the segment involved and pathophysiology. The most common cause of TAA formation is medial necrosis, characterized by loss of elastic fibers and smooth muscle within the aortic media with replacement of tissue with interstitial cysts of basophilic ground substance leading to a cystic appearance.

b. Approximately 5% to 10% of patients undergoing surgery for AI are secondary to **annuloaortic ectasia**, which is a variant of cystic medial necrosis. Annuloaortic ectasia is a clinicopathologic diagnosis in which the aortic root, ascending aorta, and aortic annulus dilate, resulting in AI. This is more common in men and is typically seen in the fourth, fifth, and sixth decades of life.

3. Clinical course and surgical recommendations for asymptomatic TAA

a. Onset of symptoms usually heralds a more rapid course, as do larger dimensions at baseline. *Patients with symptoms suggestive of expansion of a TAA should be evaluated for prompt surgical intervention unless life expectancy from comorbid conditions is limited or quality of life is substantially impaired (Level of Evidence: C).*

b. Rupture is the most common cause of death in these patients. Data from the Yale group found that median size at rupture for an ascending aortic aneurysm was 6.0 cm and for a descending aortic aneurysm it was 7.2 cm. ***Asymptomatic patients should be evaluated for surgical repair*** *who have degenerative TAA, IMH, PAU, mycotic aneurysm, or pseudoaneurysm, who are otherwise suitable candidates and* ***for whom the ascending aorta or diameter of the aortic sinuses is 5.5 cm or greater*** *(Level of Evidence: C).*

c. TAAs tend to grow more rapidly as they increase in size and thereby increase the risk of acute rupture or dissection. Aneurysms < 5.0 cm at baseline have a mean growth rate of 0.17 cm/y, whereas those > 5.0 cm grew at a mean rate of 0.79 cm/y. ***Patients with a growth rate > 0.5 cm/y in an aorta that is < 5.5 cm in diameter should be considered for operation*** *(Level of Evidence: C).*

d. *Patients undergoing aortic valve repair or replacement who also have an ascending aorta or aortic root diameter > 4.5 cm should be considered for concomitant repair of the aortic root or replacement of the ascending aorta (Level of Evidence: C).*

e. *Patients with Marfan, Loeys-Dietz, or vascular-type Ehlers-Danlos syndrome or other genetically mediated disorders (BAV, Turner syndrome, and familial TAA and dissection) should undergo elective operation at smaller diameters (4.0 to 5.0 cm depending on the condition) to avoid acute dissection or rupture (Level of Evidence: C).* Among patients with Marfan syndrome and BAV, the ratio of maximal aortic cross-sectional area in square centimeters to the patient's height in meters with a result of > 10 has been proposed as

TABLE 26.6 Causes of Thoracic Aortic Aneurysm

Etiology	Aortic segment involved	Pathophysiology
Cystic medial degeneration	Ascending aorta, aortic arch	De novo cystic medial degeneration
Marfan syndrome	Ascending aorta and root, aortic arch	Defective fibrillin; secondary cystic medial degeneration
Loeys-Dietz syndrome	Aortic root aneurysms (98%) and arterial tortuosity, especially of the head and neck vessels	Autosomal dominant; defective transforming growth factor receptor type I or II genes
Ehlers-Danlos syndrome, type IV	Ascending aorta, predominantly aortic arch	Defective collagen; secondary cystic medial degeneration
Bicuspid aortic valve	Ascending aorta and root	Inadequate production of fibrillin; cystic medial degeneration
Familial thoracic aortic aneurysm syndrome	Ascending aorta	Autosomal dominant, 3p24.2-25, 5q13-15, 11q23.2-q24
Turner syndrome	Ascending aorta and root	Cystic medial degeneration
Advanced age		Cystic medial degeneration
Atherosclerotic	Descending aorta	Atherosclerotic plaques, weakening vessel walls
Traumatic	Aortic isthmus, proximal descending aorta	Damaged vessel wall, intramural hematoma
Inflammatory	Variable	Takayasu arteritis, giant cell arteritis, HLA-B27–associated spondyloarthropathies, others
Infectious	Aortic root (syphilis), variable (mycotic)	Cystic medial degeneration (syphilis), inflammatory changes (mycotic)
Poststenotic	Ascending (aortic stenosis), descending (coarctation)	Hemodynamic insult
Postsurgical	Aortic valve replacement, status post–aortic anastomosis	Weakening of the anastomotic walls
Chronic aortic dissection	Variable	Weakening of false lumen over time

an indication for surgical intervention, particularly since patients with this finding may be at greater risk for spontaneous dissection.

4. **Diagnostic testing.** Unique advantages and disadvantages of each radiographic technique are described in detail in preceding sections. The specific attributes of each technique when evaluating TAA are reviewed below.
   a. The **chest radiograph** frequently shows widening of the mediastinum, unusual aortic contours, or displacement of the trachea or bronchi in the presence of a large TAA.

b. Both computed tomography angiography (CTA) and MRA provide excellent assessment of size and extent of aneurysmal involvement. CTA is the preferred modality for serial follow-up after surgical or endovascular repair, whereas MRA is the preferred modality when visualization of the aortic root is necessary.

c. TTE and TEE. TTE is of limited use in evaluating the thoracic aorta, except for the aortic root and proximal ascending portion. TEE can be used to visualize the entire thoracic aorta, but given the availability of noninvasive imaging to diagnose TAA, TEE is not routinely used for this purpose.

d. MRI and MRA are also useful for detecting and defining the extent of aneurysmal involvement. They allow for evaluation of the entire aorta, branch vessels, aortic valve, and pericardium.

e. Aortography allows for evaluation of the segment involved by the aneurysm as well as the branch vessels off the aorta. This procedure is currently reserved for preoperative evaluation to establish branch vessel patency.

5. Therapy

a. Medical therapy. Long-term data on medical management for TAA are lacking. Based on one small prospective trial of patients with Marfan syndrome, patients treated with propranolol enjoyed a slower rate of aortic dilatation. *β-Blockers are generally recommended for all patients with TAA, but particularly those with Marfan syndrome to reduce the risk of aortic dilatation (Level of Evidence: B). Antihypertensive therapy should be administered to hypertensive patients with TAA to achieve a goal blood pressure < 140/90 mm Hg, or < 130/80 mm Hg among patients with concurrent diabetes mellitus or chronic kidney disease (Level of Evidence: B). The angiotensin receptor blocker losartan may be particularly beneficial to slow aneurysm growth in patients with Marfan syndrome (class IIa, Level of Evidence: B).* Losartan has been shown in animal models of Marfan syndrome to slow the rate of dilatation of the aorta and human studies are underway.

b. Endovascular therapy. Use of percutaneous aortic stent-grafts has been reported in aortic arch and descending thoracic aneurysms. Contemporary studies, including the Talent VALOR and Zenith TX2 trials, have suggested that endovascular therapy represents a safe and effective strategy and an alternative to open surgery in patients with TAA. However, these studies have also exposed limitations of EVAR including restricted applicability due to a need for careful patient selection with anatomy appropriate for endovascular techniques, vascular access and device implantation issues, and need for concomitant subclavian and less commonly carotid artery bypass grafting, among others. Larger studies and longer follow-up must be presented before widespread use of this technology can be encouraged. Currently, EVAR is reserved for TAA among patients at high risk for open repair among those with ideal aortic anatomy having the procedure performed in centers with a qualified team to perform open aortic surgery.

c. Preoperative evaluation for TAA

(1) *In preparation for surgery, imaging studies adequate to establish the extent of disease and the potential limits of the planned procedure are recommended (Level of Evidence: C).*

(2) *Patients with thoracic aortic disease requiring a surgical or catheter-based intervention who have symptoms of myocardial ischemia should undergo additional studies to determine the presence of significant coronary artery disease (Level of Evidence: C). Patients with unstable coronary syndromes and significant coronary artery disease should undergo preoperative revascularization or concomitant coronary artery bypass graft surgery (Level of Evidence: C).*

d. Surgical therapy for TAA. The technical details of repair are beyond the scope of this text. However, the basic premise is for a Dacron tube graft to be inserted in place of the diseased aorta. The main branches are reimplanted to the graft (coronary arteries, great vessels, mesenteric, and T_8 to L_2 intercostals/lumbricals). When the aortic valve is involved with aortic root dilatation, a modified **Bentall procedure** (composite prosthetic aortic valve with Dacron graft) or **aortic valve homograft** is performed. The aortic valve homograft is a cryopreserved cadaveric aortic valve with a portion of the original ascending aorta intact. Aneurysms involving both the ascending and descending aorta can be treated by a two-staged approach, with an **elephant trunk** procedure. With this, the ascending aorta and arch are replaced initially and the distal portion of the graft is suspended into the proximal portion of the descending thoracic aorta for subsequent union with a descending aorta graft placed either by open surgical procedure or percutaneously. Overall perioperative survival is reported to be 90% to 95% for elective repair (ascending aorta) in most institutions.

(1) *Patients with Marfan, Loeys-Dietz, and Ehlers-Danlos syndromes and other patients with dilatation of the aortic root and sinuses of Valsalva should undergo excision of the sinuses in combination with a modified valve-sparing root reimplantation (David) operation if technically feasible or, if not, root replacement with valved graft conduit (Level of Evidence: B).*

(2) *For patients with degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent-grafting should be strongly considered if feasible (Level of Evidence: B).*

(3) *For patients with thoracoabdominal aneurysms, in whom endovascular stent-graft options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or less if a connective tissue disorder such as Marfan or Loeys-Dietz syndrome is present (Level of Evidence: C).*

(4) *For patients with thoracoabdominal aneurysms and with end-organ ischemia or significant stenosis from atherosclerotic visceral artery disease, an additional revascularization procedure is recommended (Level of Evidence: B).*

e. Complications after TAA repair. These include MI (7.2%), CVA (4.8%), acute renal failure (2.4%), perioperative hemorrhage (7.2%), and paraplegia (6.0%) due to perioperative ischemia of the anterior spinal cord. Procedural adjuncts, including epidural cooling, distal aortic perfusion to support collateral circulation to the spinal cord during surgery, and motor-evoked potential monitoring, have been used to reduce the rate of paraplegia.

(1) Factors associated with increased surgical risk include emergent surgery, greater age, prolonged cross-clamp time, diabetes, previous aortic surgery, and intraoperative hypotension.

IV. CONTROVERSIES AND FUTURE RESEARCH DIRECTIONS

A. Screening for AAA. The U.S. Preventive Services Task Force (USPSTF) currently recommends one-time screening for AAA by ultrasound in men aged 65 to 70 years who have ever smoked, although it makes no recommendation for screening of men that have never smoked. What's more, the USPSTF recommends against routine screening for AAA in women. These recommendations are based on a systematic review of four large randomized trials of screening for AAA, with ultrasound beneficial among ever-smoking men aged 65 to 79 years alone. Further investigation is needed to refine the concept of screening for AAA, particularly in women.

B. Risks and Benefits of Imaging Technologies. Compared with acute coronary syndromes, acute aortic syndromes are less common, although several features of

each disease overlap. When acute aortic disease is suspected, rapid and accurate assessment is required so as to avoid delays in treatment of acute coronary syndromes, as suggested by ECG. What's more, imaging techniques used for aortic disease requiring longitudinal follow-up must be cost-effective and avoid unnecessary radiation exposure. Clinical studies exploring cost-effectiveness and safety of various screening protocols are needed.

C. Clinical Therapeutic Trials for Aortic Syndromes. The National Heart, Lung, and Blood Institute has recommended an Aortic Aneurysm Clinical Trials Network be developed to test medical and surgical treatments among patients with TAA. Significant interest and efforts are underway to develop novel therapeutic targets and biomarkers for acute aortic dissection using animal models. Gene-based models that describe mechanisms of aortic disease based on specific mutations have contributed greatly to our understanding of Marfan, Loeys-Dietz, and other familial syndromes. Further collaborative efforts and expansion of existing registries are likely to improve understanding and provide more effective treatments for diseases of the aorta.

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CHAPTER 27

Femi Philip

Peripheral Arterial Disease

I. INTRODUCTION. Peripheral arterial disease (PAD) describes the pathologic states that lead to stenoses and aneurysms in the noncoronary arterial circulation. This chapter focuses on the diseases of the **arterial supply to the extremities** and the **renal vasculature** (disease states involving the aorta and cerebral vasculature are discussed elsewhere in this volume). PAD can be classified as occlusive or aneurysmal. **Atherosclerosis is the most common cause of PAD**. In **aneurysmal** states, weakening of the arterial media results in focal dilatation of the artery to at least 1.5 times the normal diameter. These aneurysmal segments can subsequently dissect, rupture, or thrombose, with catastrophic consequences. In addition to atherosclerosis, there are several less common pathologies that can cause PAD, including vasculitis, arterial injury, entrapment syndromes, and cystic adventitial disease. These disorders are beyond the scope of this chapter.

II. LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

A. Etiology and natural history. Atherosclerosis is the most common cause of lower extremity PAD. Traditional risk factors include age, smoking history, diabetes mellitus, hyperlipidemia, and hypertension. Emerging risk factors include elevated

markers of inflammation such as C-reactive protein, fibrinogen, and interleukin 6; chronic kidney disease; hypercoagulable states such as hyperhomocysteinemia; and possibly a genetic predisposition to PAD. African Americans have a twofold increase in risk of developing PAD. The prevalence of PAD increases significantly with age, such that the prevalence is 2% to 3% in persons aged ≤ 50 years and up to 20% in persons aged > 70 years. **Fibromuscular dysplasia (FMD)**, a noninflammatory and nonatherosclerotic process, can also affect the lower extremities by causing hyperplastic cell growth and luminal narrowing, although it predominantly affects the renal and carotid arteries. Patients with lower extremity PAD may present with leg symptoms or may be entirely asymptomatic. Approximately 50% of patients > 55 years old with PAD, with or without claudication symptoms, when followed for 5 years will remain stable or improve with exercise and lifestyle modifications. The remaining 50% will have progressive worsening of symptoms, and approximately 4% will require major amputation if they do not undergo revascularization. The highest risk of amputation occurs in those patients who are diabetic and continue to smoke. **Cardiac disease accounts for the majority of deaths in patients with PAD, in whom the relative risk of death from cardiac causes is increased more than sixfold. Approximately one-third to one-half of all patients with PAD will have concomitant coronary disease depending on the diagnostic criteria utilized, and thus PAD is considered a coronary artery disease risk equivalent**.

B. Clinical manifestations

1. **Signs and symptoms.** Rest perfusion of the lower extremities may be adequate; however, if the arterial stenosis is severe, then exercise may precipitate ischemia and **claudication**. Symptoms may include pain, discomfort, or fatigue of the buttock, thigh, or calf musculature and are usually gradual in onset. The amount of exercise required to precipitate pain is roughly related to the severity of the stenosis. Pain is usually manifested one segment below the area of severe stenosis (Table 27.1), and the most frequently involved artery in intermittent claudication is the superficial femoral artery. The symptoms are usually promptly relieved with rest or standing. More severe stenosis or more distal atherosclerotic lesions may result in **limb-threatening ischemia with foot pain at rest, tissue ulceration, or gangrene**. There are two terms frequently used to describe this condition that should be differentiated: critical limb ischemia and acute limb ischemia. **Critical limb ischemia** is resting limb pain that results from severe atherosclerotic disease that compromises distal blood flow of the involved limb. This term is typically used to describe chronic lesions such as ischemic rest pain, ischemic ulcers, or gangrene and is caused by a slow progression of atherosclerotic disease. **Acute limb ischemia** occurs abruptly and threatens the viability of the involved tissue. Acute limb ischemia is usually the result of an embolic event or arterial thrombosis.
2. **Physical examination.** Characterization of **femoral, popliteal, dorsalis pedis, and posterior tibial pulses**; **auscultation for bruits** in the abdomen and

TABLE 27.1 Localization of Peripheral Arterial Disease

Location of pain	Likely involved segment
Buttock and thigh	Aortoiliac
Thigh	Aortoiliac, common and/or profunda femoral artery
Calf	Superficial femoral or popliteal artery[a]
Foot	Tibial or peroneal arteries

[a]Most commonly involved artery.

bilateral groins; and palpation for **aneurysm** in the abdomen and over the popliteal arteries are all part of a comprehensive lower extremity vascular examination. A complete cardiac examination and auscultation of carotid arteries should also be performed to assess for concurrent abnormalities, given the common atherosclerotic pathogenesis of cerebral, myocardial, and peripheral arterial disease. Signs of lower extremity arterial insufficiency can include coolness, dry skin and scaling, pallor that is worsened with leg elevation, and ulcerations. Rarely muscular atrophy can be seen. The evaluation of a patient with possible acute limb ischemia should include the "5 P's": pain, pallor, pulselessness, paresthesias, and paralysis. These clinical features have prognostic value in acute limb ischemia (Table 27.2).

C. Diagnostic evaluation (Fig. 27.1)

1. **Ankle–brachial index (ABI).** The ABI is a measurement of lower extremity perfusion, which compares the blood pressure in a pedal artery with the higher of two brachial artery blood pressures. The ABI cannot localize stenosis, but is a simple and accurate measure of disease severity (Table 27.3). In general, ABI value correlates poorly with symptoms, and two patients with the same ABI may have remarkably different complaints. **Symptoms at rest rarely occur, unless the ABI is < 0.4 (i.e., critical limb ischemia)**. The ABI has limited use in noncompressible, calcified vessels. In patients with noncompressible ankle vessels (ABI > 1.4) the toe–brachial index can be used in conjunction with pulse-volume recordings (PVRs) to document PAD. Measuring the ABIs before and after exercise can help diagnose PAD when the resting ABI is normal but there is a high clinical suspicion for PAD. It can also help differentiate between true claudication and nonarterial leg pain (pseudoclaudication).
2. **Pulse-volume recordings.** PVRs detect changes in the volume (arterial flow) of the limb during the cardiac cycle. Blood pressure cuffs are placed at the thigh (one or two cuffs), calf, ankle, midfoot, and toe. The change in volume of the respective cuff during the cardiac cycle identifies the presence of arterial stenosis by reduction in the pulsatile flow as detected by changes in pulse contour and amplitude at that cuff, as documented by the PVR waveform (Fig. 27.2). Segmental blood pressure measurements may be taken along the leg with the segmental PVR tracings for localization of disease. Unlike ABIs, arterial

TABLE 27.2 Categorizing Acute Limb Ischemia

Category	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler signal	Venous Doppler signal
Viable	Not immediately threatened	None	None	Audible	Audible
Threatened marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Often inaudible	Audible
Threatened immediately	Salvageable with immediate revascularization	More than toes, rest pain	Mild, moderate	Usually inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage	Profound anesthesia	Profound paralysis	Inaudible	Inaudible

Adapted from Katzen BT. Clinical diagnosis and prognosis of acute limb ischemia. *Rev Cardiovasc Med.* 2002;3(suppl 2):S2–S6.

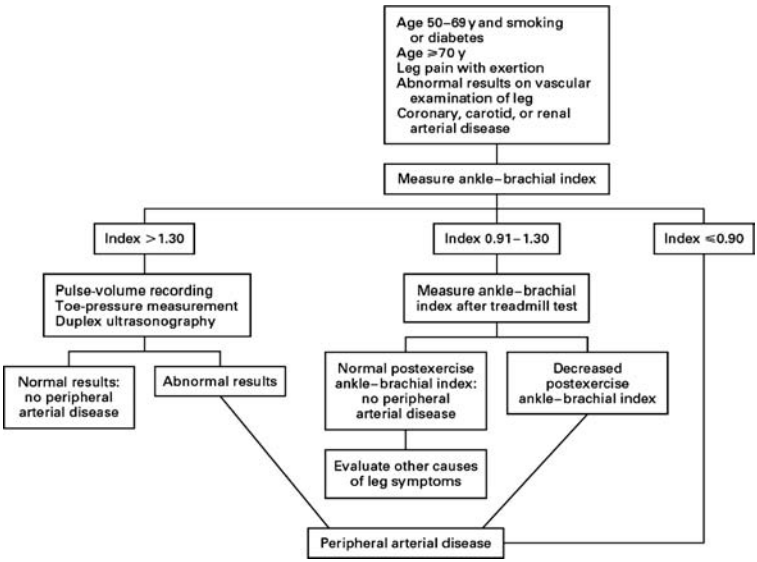

FIGURE 27.1 Evaluation of patients in whom peripheral arterial disease is suspected. (Reproduced from Hiaat WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608, with permission.)

calcification does not effect PVR tracings, and PVR can often be helpful in the diabetic patient with a foot ulcer and suspected arterial calcification.

3. **Duplex ultrasound.** Arterial duplex renders an anatomic assessment of the arterial system using a combination of B-mode ultrasound imaging and Doppler frequency spectral analysis. Doppler complements the standard qualitative ultrasound imaging by allowing waveform analysis and assessment of Doppler velocities. Using the concept that velocity of blood flow increases as it flows through a stenotic lesion, peak systolic and end-diastolic velocities are measured and used to estimate the severity of a stenosis. This modality is useful for anatomic visualization of lesions and for surveillance after stenting or bypass grafting.

TABLE 27.3 Evaluating Disease Severity with the Ankle–Brachial Index

ABI	Interpretation
1.3	Noncompressible vessel
1.0–1.29	Normal
0.91–0.99	Equivocal
0.4–0.90	Mild to moderate PAD
< 0.4	Severe PAD

ABI, ankle–brachial index.

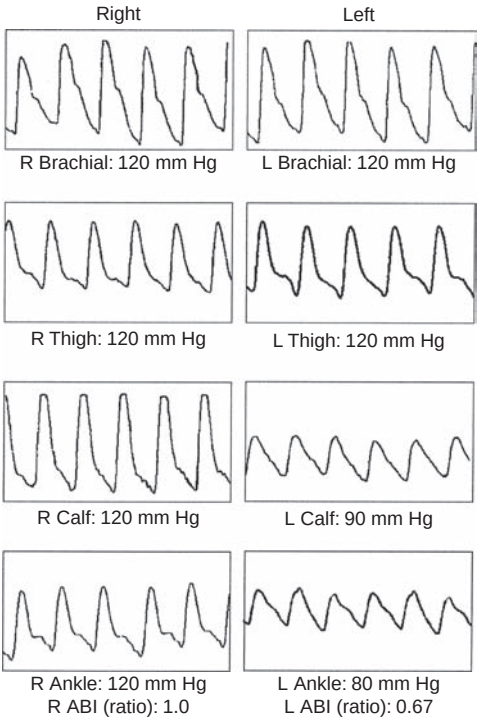

FIGURE 27.2 Pulse-volume recording (PVR) of the lower extremities. This PVR was obtained from a 42-year-old man with a history of diabetes mellitus and tobacco use who developed new left calf cramping with exertion. It demonstrates moderate disease (ankle–brachial index [ABI] = 0.66) of left femoropopliteal segment and a normal recording on the right lower extremity. He was advised to begin both a tobacco cessation program and a walking regimen.

4. **Magnetic resonance angiography (MRA).** The MRA signal is a reflection of the velocity and flow patterns of protons within the artery. The noninvasive nature of MRA and its ability to generate three-dimensional (3D) reconstructions are the main advantages of MRA over conventional angiography. Its limitations include a tendency to overestimate lesion severity secondary to flow turbulence, imaging artifact with metal clips or stents, and its association with nephrogenic systemic fibrosis (2.5% to 5.0%) in patients with a glomerular filtration rate < 30 mL/min. Despite these limitations, MRA still has a class I indication to diagnose the anatomic location and severity of stenosis in patients with PAD.
5. **Computed tomographic angiography (CTA).** CTA is a rapidly progressing technology that uses an intravenous contrast agent and a multidetector scanner to obtain images that are of similar quality to those of conventional angiography. A total of 64 detector scanners allow the simultaneous acquisition of 64 cross-sectional image slices; this has dramatically reduced radiation and contrast doses required to obtain adequate images. CTA has the advantage of being capable of reconstructing 3D images in virtually any oblique projection to help evaluate

eccentric stenoses. Other advantages of CTA include better visualization of collaterals to distal vessels, identification of aneurysms, and cystic adventitial disease, which may not be picked up by conventional angiography. CTA also has several disadvantages when compared with catheter-based angiography: CTA has lower spatial resolution than digital subtraction, venous opacification can interfere with visualization of arterial filling, asymmetric leg filling may miss the arterial phase in some vessels, and the enormous quantity of data obtained (up to 2,000 images) may be difficult for workstations to process and store. Several recent studies have shown the accuracy of CTA for the diagnosis of stenoses > 50%, and CTA is quickly becoming an important imaging modality for the diagnosis of PAD. Currently, the American College of Cardiology/American Heart Association (ACC/AHA) PAD guidelines give a class IIb indication for CTA in the diagnosis of the anatomic location and severity of stenosis in patients with PAD.

6. **Catheter-based angiography.** Long considered the gold standard for the diagnosis of arterial disease, this invasive procedure requires intraarterial vascular access and contrast (often nonionic dye, although gadolinium or carbon dioxide can be used). It is recommended for the evaluation of patients for whom revascularization procedures are planned (those with lifestyle-limiting claudication, rest pain, ischemic ulceration, or gangrene) or for whom noninvasive techniques are inconclusive. Because contrast angiography demonstrates only the arterial lumen, it can underestimate lesion severity. Contrast angiography (Ia) with digital subtraction (Ib) has a class I indication for patients with PAD when revascularization is considered.

D. Treatment. The two main goals of therapy for patients with PAD are to relieve symptoms and improve survival from related cardiovascular diseases. Options for treatment of intermittent claudication include surgical revascularization ("bypass"), percutaneous revascularization, pharmacotherapy, and exercise. Aggressive risk factor modification is the primary therapy for the prevention of cardiovascular events. Therefore, the mainstay of treatment for many patients with mild to moderate claudication is to **"stop smoking and start walking."** Accordingly, a trial of supervised exercise therapy is given a class I recommendation as the initial therapy of choice for claudication in the ACC/AHA PAD guidelines. Supervised exercise therapy ("PAD rehab") has been reported to increase walking distance by up to 130% to 180% among patients with claudication.

1. **Antiplatelet therapy**

Aspirin/clopidogrel. Current guidelines recommend that all PAD patients should be on aspirin (75 to 325 mg) therapy unless contraindicated (class I). Clopidogrel can be used in the setting of aspirin allergy (class I). In a subset analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, clopidogrel reduced composite major adverse events by 23.8% compared with aspirin in a large cohort of 19,185 patients with atherosclerotic vascular disease, of whom 6,452 had symptomatic PAD. In terms of dual antiplatelet therapy, the Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial failed to show a significant additive reduction in composite cardiovascular events with dual antiplatelet therapy in patients with asymptomatic cardiovascular disease or multiple cardiovascular disease risk factors but did show a reduction in myocardial infarction and hospitalization in a subset of PAD patients, albeit at the cost of higher rates of bleeding.

Since the publication of the guidelines, several recent trials have triggered some debate about the efficacy of aspirin for prevention of cardiovascular events in patient with PAD. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial comprising 1,276 patients with diabetes and ABI ≤ 0.99 showed that aspirin failed to prevent the composite cardiovascular end point when compared with placebo (hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.76 to

1.26). The Aspirin for Asymptomatic Atherosclerosis (AAA) trial comprising 3,350 patients with ABI ≤ 0.95 and no known cardiovascular disease also showed a failure of aspirin to decrease rates of composite cardiovascular events when compared with placebo (HR 1.03; 95% CI 0.84 to 1.27). A meta-analysis of randomized controlled trials including 18 trials and 5,269 patients showed that while there is a trend for aspirin to prevent cardiovascular events, the difference is not statistically significant (risk ratio [RR] 0.88; 95% CI 0.76 to 1.04). In light of these recent trial data, recommendations from updated PAD guidelines are eagerly anticipated.

2. **Risk factor modification.** PAD is a coronary risk equivalent and as such aggressive risk factor modification is warranted.
   a. Cigarette **smoking** has been associated with progression of atherosclerosis. Physician counseling is essential, as **tobacco cessation can reduce the 5-year amputation risk and decrease the 5-year mortality rate by 50%**. The importance of this intervention cannot be underestimated. Whenever possible, extensive counseling and referral to formal smoking cessation programs should be offered (class I). In addition, several pharmacologic therapies are available (bupropion, nicotine replacement, and varenicline) and should be prescribed when indicated.
   b. Current guidelines recommend treatment of **hypertension** to goal blood pressure < 140/90 mm Hg in patients with PAD and < 130/80 mm Hg in patients with PAD and diabetes or chronic kidney disease to prevent the development of future cardiovascular adverse events. The use of β-blockers as antihypertensive agents in patients with PAD is *not* contraindicated. Given the findings of the Heart Outcomes Prevention Evaluation Study, which included patients with PAD, it is reasonable to treat patients with symptomatic PAD, irrespective of diabetes, with an angiotensin-converting enzyme (ACE) inhibitor to reduce cardiovascular events (class IIa).
   c. Aggressive treatment of **hyperlipidemia** should include therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) whenever possible to achieve a low-density lipoprotein (LDL) goal of < 100 mg/dL in patients with PAD (class I). For patients at especially high risk for ischemic events, an LDL goal of < 70 mg/dL may be desirable (class IIa). Patients with normal LDL cholesterol, low high-density lipoprotein (HDL) cholesterol, and elevated triglycerides may derive benefit from a fibric acid derivative (class IIa).
   d. The management of **diabetes** in patients with PAD is important, given their increased risk of amputation (overall 20%) and increased mortality (estimated to be 50% at 5 years). Current recommendations advocate daily assessment of the feet to aid in the early identification of complications of ischemia, such as foot ulcers (class I). The recommended target HbA1c is < 7.0% (class IIa). Aggressive risk factor modification is a critical component of management for diabetic patients with PAD, and these patients should be treated with antiplatelet therapy, lipid-lowering agents, and ACE inhibitors in the absence of contraindication.
3. **Treatment of claudication**
   a. **Exercise is an inexpensive, low-risk option in comparison with invasive therapies and pharmacotherapies for intermittent claudication.** Potential mechanisms by which exercise improves symptoms include augmentation of collateral flow, improved rheologic characteristics of blood, decreased reliance on anaerobic metabolism, and greater extraction of oxygen. Supervised exercise programs have been shown to improve pain-free walking distance up to 180% from resting values. For patients with symptomatic claudication, current guidelines recommend a supervised exercise program for 30 to 45 minutes three times a week for at least 12 weeks (class I). For patients who do not have a supervised exercise program available to them, a self-directed structured walking program should be encouraged.

b. **Cilostazol** is a type 3 phosphodiesterase inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator. Cilostazol also beneficially increases HDL, decreases triglycerides, and inhibits vascular cell adhesion molecule-1 expression, thereby decreasing vascular smooth cell proliferation. Randomized controlled trials of patients with moderate to severe claudication have demonstrated 40% to 60% increases in maximal walking distances with 12 to 24 weeks of therapy with cilostazol 100 mg twice daily. A trial of cilostazol, 100 mg twice daily, is recommended in all patients with PAD and intermittent claudication to relieve symptoms and improve walking distance (class I). Cilostazol is contraindicated in patients with congestive heart failure, owing to an increased risk of sudden death associated with related phosphodiesterase inhibitors. Common side effects associated with cilostazol include diarrhea, palpitations, and headaches.

c. **Pentoxifylline.** Oral pentoxifylline, 400 mg three times daily, can be considered as a second-line alternative to cilostazol in patients with symptomatic claudication (class IIb). Pentoxifylline is a methylxanthine derivative that functions as a vasodilator and an antiplatelet agent, reduces blood viscosity, and improves deformability of erythrocytes and leukocytes to exert its effects. Trials have been divergent on the efficacy of pentoxifylline and is felt to result in only marginal improvements in maximal walking distance and symptoms.

4. **Revascularization.** Revascularization is indicated for "lifestyle-limiting" claudication (after failed medical therapy), rest pain, ischemic ulceration, or gangrene. It may be **performed surgically or percutaneously**.

a. **Percutaneous therapy.** In carefully selected patients, catheter-based revascularization is an attractive alternative to conventional surgical management. Percutaneous revascularization has a class I indication for individuals with lifestyle-limiting claudication when there is a reasonable likelihood of procedural success and there has been an inadequate response to conservative therapy. Percutaneous revascularization is recommended according to the TransAtlantic Inter-Society Consensus II (TASC II) guidelines, which divide lesion anatomy according to location, distribution, length, and likelihood of procedural success. TASC type A lesions are those in which endovascular therapy is recommended, and type B lesions are those in which endovascular therapy is preferred in most cases. For instance, TASC type A disease in the aortoiliac system is defined as unilateral or bilateral disease in the common iliac or external iliac arteries of short length (< 3 cm). In the femoral popliteal region, a type A lesion is defined as a single stenosis ≤ 10 cm in length or a single occlusion ≤ 5 cm in length. Translesional pressure gradients (criteria: threshold peak systolic difference 5 to 10 mm Hg prevasodilation and 10 to 15 mm Hg postvasodilation) should be obtained for angiographic lesions that appear moderately stenotic (e.g., 50% to 75%) prior to intervention (class I). The treatment of choice for focal aortoiliac disease is angioplasty with or without stenting. This approach has a technical success rate of 90%, 2 year patency rate of 73% to 84%, a complication rate of < 10% (usually related to the arterial access site), and periprocedural mortality rate of < 1%. For femoropopliteal disease, patency rates with percutaneous therapies are lower than those in iliac disease; therefore, angioplasty is utilized to manage focal disease after failure of medical therapy. Direct stenting as a primary therapy is not recommended for femoral, popliteal, or tibial arteries; however, stenting may be effective as salvage therapy after suboptimal or failed balloon angioplasty (class I).

b. **Surgical.** Similarly, surgical revascularization also has a class I indication for individuals with lifestyle-limiting claudication when there is a reasonable likelihood of procedural success and there has been an inadequate response to conservative therapy. Surgery is used to bypass long segments of diffuse disease

(particularly involving the femoropopliteal segment) or when endovascular therapy fails. Various conduits, such as reversed or in situ saphenous vein grafts, Dacron grafts, and polytetrafluoroethylene grafts, can be used. For severe disease below the popliteal artery, both percutaneous and surgical revascularization approaches have marginal outcomes with regard to limb salvage. In patients younger than 50 years, the efficacy of surgical intervention for symptomatic claudication is not well established due to the aggressive nature of their atherosclerosis and limited graft durability (class IIb). Given the coincidence of coronary artery disease in these patients, a thorough preoperative assessment of cardiac risk should be performed prior to vascular surgery.

III. LOWER EXTREMITY ANEURYSMS. Aneurysms of the peripheral arteries, as in the aorta, are most commonly due to atherosclerotic disruption of the arterial media. Up to 70% of lower extremity aneurysms involve the popliteal arteries. The incidence of bilateral involvement in lower extremity aneurysm is high (45% to 68%). The majority of patients (62%) with popliteal aneurysms have been reported to have concomitant abdominal aortic aneurysms (AAAs), and this coprevalence increases to 85% in patients with femoral artery aneurysms. Accordingly, patients diagnosed with peripheral arterial aneurysms, especially femoral or popliteal, should be screened with ultrasound for AAA and for the presence of contralateral lower extremity disease (class I). The greatest concern with lower extremity aneurysms is thrombosis and thromboembolism. Lower extremity aneurysms infrequently rupture (7% to 12%), but up to 60% will have an ischemic complication; therefore, acute limb ischemia is the most common presenting symptom. As an aneurysm increases in size, it can compress adjacent venous and lymphatic structures causing lower extremity edema. Given the risk of thrombosis, it is recommended that popliteal aneurysms > 2.0 cm (class I) and femoral artery aneurysms > 3.0 cm be repaired. Unless symptomatic, aneurysms of smaller caliber should be followed by annual arterial duplex ultrasound examinations (class IIa).

IV. UPPER EXTREMITY ARTERIAL DISEASE. In addition to atherosclerosis, the most common cause of upper extremity PAD, other pathologic states can result in stenosis of the upper extremity arteries. These disorders include vasculitis (particularly Takayasu and giant cell arteritis), FMD, thoracic outlet syndrome, ionizing radiation, and repetitive injury. Associated clinical symptoms include arm and hand claudication, digital ulceration, and neurologic symptoms caused by vertebral–subclavian steal. The diagnostic modalities are similar to those in lower extremity arterial disease. The simple clinical maneuver of checking blood pressure measurements in both arms is an excellent screening test for significant upper extremity PAD. Risk factor modification and revascularization (for symptomatic patients) are the mainstays of therapy. Finally, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.

V. RENAL ARTERY DISEASE

A. Clinical manifestations. Renal artery stenosis (RAS) is commonly associated with two clinical syndromes: hypertension and ischemic nephropathy. Clues to the presence of RAS include the following: **abrupt onset of hypertension** (before age 30 years, often due to FMD, or after age 55 years, often due to atherosclerotic disease); **previously well-controlled essential hypertension that becomes resistant to medical therapy** (three-drug regimen including a diuretic); **azotemia**, which is unexplained or induced by ACE inhibitor administration; and **recurrent flash pulmonary edema**, often with normal left ventricular function (due to renin-angiotensin–mediated volume overload and peripheral vasoconstriction). Physical examination in RAS may reveal hypertension, epigastric bruits, and evidence of atherosclerosis in other vascular beds (e.g., carotid or femoral bruits and diminished pedal pulses). Renal imaging can reveal an atrophic kidney or a size discrepancy between the two kidneys.

B. Etiology and natural history. The most common causes of RAS are atherosclerosis and FMD. Atherosclerosis accounts for 90% of RAS and usually involves the ostium and proximal third of the main renal artery. The prevalence of atherosclerotic RAS increases with age, particularly in patients with diabetes, aortoiliac disease, coronary artery disease, or hypertension. Studies have suggested that the prevalence of RAS in patients with PAD may be as high as 59%. It is the most common cause of secondary hypertension, may account for 1% to 5% of all cases of hypertension, and may be the cause of end-stage renal failure in up to 20% of new dialysis patients. RAS is an independent risk factor of mortality in patients with other vascular diseases. Moreover, end-stage renal disease due to RAS is associated with the highest mortality (median survival of 2.7 years) among all dialysis-dependent patients. FMD accounts for < 10% of cases of RAS, but should be suspected in younger patients without atherosclerotic risk factors who present with RAS. It more frequently affects the distal two-thirds of the main renal artery and its branches, and in the most common type of FMD, medial fibroplasia, there is a characteristic "string of beads" appearance on angiography. The cause of FMD is unknown. Rarer causes of RAS include vasculitis, neurofibromatosis, congenital bands, extrinsic compression, and ionizing radiation.

C. Diagnostic evaluation

1. **Laboratory studies.** Blood urea nitrogen and serum creatinine are readily available and are often used in practice as screening tools. Although azotemia and increased serum creatinine are neither sensitive nor specific for RAS, they may be the first clue to the disease. Urinalysis in RAS usually reveals proteinuria and a bland sediment. Because of the advent of sensitive and specific noninvasive imaging modalities, plasma renin activity and selective renal vein renin measurements are not recommended as screening tests to diagnose RAS (class III).
2. **Duplex ultrasonography (DUS).** Arterial duplex uses a combination of B-mode ultrasound imaging and Doppler frequency spectral analysis. Elevated peak systolic velocities, the renal-to-aortic ratio, and the presence of color and spectral turbulence are criteria used to determine the presence of significant RAS. In addition, DUS allows for calculation of the renal resistive index (renal parenchymal peak systolic velocity minus end-diastolic velocity divided by the peak systolic velocity), which is a potential marker of renal parenchymal disease. Some data suggest that patients with an elevated resistive index may not improve after revascularization. DUS is inexpensive, widely available, and highly sensitive and specific for RAS when compared with angiography (reported sensitivities between 84% and 98% and reported specificities between 62% and 99%). It is also highly useful for surveillance of renal arteries after stenting, as flow through a stent can be easily detected, in contrast to MRA, which is limited by metal artifact. DUS for RAS must be performed in experienced centers. The test may be limited by difficulty in obtaining measurements due to excess bowel gas or obesity. It also has lower sensitivity (64%) for identifying accessory renal arteries, narrowing of which could also lead to the signs of RAS.
3. **Renal scintigraphy.** Radionuclide renal imaging is used to assess differential renal blood flow and has been used in conjunction with captopril renography to attempt to diagnose RAS. Captopril renography precipitates an ACE inhibitor–mediated fall in glomerular filtration to amplify differences in renal perfusion consistent with RAS. Due to a relative lack of sensitivity (74%) and specificity (59%) compared with catheter-based angiography, captopril renography is no longer recommended for the screening of RAS (class III).
4. **Magnetic resonance angiography.** MRA now has a class I indication as a test for the diagnosis of RAS, with reported sensitivity and specificity from 90% to 100% and 76% to 94%, respectively, when compared with angiography. MRA is noninvasive and has the ability to generate 3D reconstructions. Its limitations include expense, limited availability, lack of resolution in the setting of high-grade

stenosis (often appearing as an occlusion or loss of signal), a tendency to overestimate lesion severity, and difficulty with post–stent imaging due to artifact. It is also less sensitive for the detection of FMD, given that the typical arterial beading may be subtle and resolution of MRA is still limited, particularly of the distal renal vasculature. In addition, in patients with advanced renal insufficiency or renal failure, gadolinium-containing contrast agents have been linked to nephrogenic systemic fibrosis in 2% to 3% of patients (see Chapter 51). This has complicated the use of contrast-enhanced MRI in patients with RAS and renal insufficiency.

5. **Computed tomographic angiography.** Like MRA, CTA has the capability of producing excellent 3D images of the renal arteries as well as the aorta and other visceral vessels. CTA has a sensitivity and specificity for detecting significant RAS ranging from 59% to 96% and 82% to 99%, respectively. Contrast administration (100 to 150 mL) and radiation dose remain limitations of CTA. Unlike MRA, CTA does not have significant imaging artifact with metal clips or stents and, therefore, can be used to detect in-stent restenosis.
6. **Renal arteriography.** This is the gold standard for the diagnosis of RAS. It allows for excellent visualization of the main renal and accessory renal arteries and their branches. Arteriography allows for assessment of the degree of stenosis visually and adds the ability to obtain hemodynamic measurements (gradients) across the stenotic lesions. Disadvantages include the requirement for intraarterial access and nephrotoxic radiocontrast.

D. Treatment. Despite antihypertensive therapy, RAS tends to progress and may be associated with renal ischemia and loss of renal function (i.e., renal insufficiency). Atherosclerotic nephropathy is complex and not simply related to stenosis of the renal artery. Examination of renal histology in patients with atherosclerotic nephropathy reveals other potential mechanisms for loss of function, including small-vessel occlusion from atheroemboli, intrarenal arterial stenoses, and preexisting hypertensive nephrosclerosis. Importantly, as with other peripheral vascular disease processes, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.

1. **Medical therapy.** Aggressive antihypertensive therapy using multiple agents remains the mainstay of RAS therapy and is often the control arm of randomized trials of interventional approaches to RAS. ACE inhibitors, angiotensin receptor blockers, diuretics, β-blockers, calcium channel blockers, and various other antihypertensives have been shown to be effective in treating hypertension associated with RAS. ACE inhibitors and angiotensin receptor blockers should not be used in patients with bilateral RAS or a solitary kidney with RAS. However, these agents can be highly effective in the management of hypertension in patients with unilateral RAS (class I). Patients with RAS should be treated to achieve blood pressure targets consistent with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension. Aggressive atherosclerotic disease risk factor modification should be part of a comprehensive treatment plan.
2. **Percutaneous revascularization.** The principle behind revascularization is that early restoration of renal artery patency in patients with atherosclerotic RAS may improve hypertension management and minimize progressive renal dysfunction; however, there is a paucity of data from controlled clinical trials to show that revascularization for RAS improves hypertension or delays renal dysfunction. Two small randomized trials demonstrated that patients treated with percutaneous renal artery angioplasty had improved systolic blood pressure and/or blood pressure control (as measured by a reduction in the number or dose of antihypertensive agents used) compared with patients treated with antihypertensive therapy alone. Response to percutaneous intervention is better among patients with FMD than those with atherosclerotic RAS, a finding that may be expected given the pathology that is seen at multiple levels in renal vasculature with atherosclerotic RAS. Congestive

heart failure and chronic obstructive pulmonary disease have been shown to be independent predictors of increased mortality in patients undergoing renal artery stenting; however, baseline azotemia remains the strongest predictor of long-term mortality (70% 5-year mortality rate with serum creatinine > 2.5 mg/dL).

Revascularization for RAS has been shown to stabilize or improve renal function in patients with symptomatic RAS up to 1 year after intervention. In the ACC/AHA PAD guidelines, the only class I indication for percutaneous renal artery revascularization is hemodynamically significant RAS in patients with recurrent unexplained pulmonary edema or congestive heart failure. Other clinical scenarios in which percutaneous renal artery revascularization for hemodynamically significant RAS can be considered (class IIa) are uncontrolled/malignant hypertension, progressive chronic kidney disease with bilateral RAS, RAS in a solitary functioning kidney, or unstable angina with RAS. A hemodynamically significant lesion in RAS is defined as any lesion with > 70% stenosis or a lesion that has 50% to 70% stenosis with a translesional pressure gradient > 20 mm Hg or mean gradient > 10 mm Hg. In terms of revascularization technique, renal artery stent placement has a class I indication for ostial atherosclerotic RAS. Stenting is also recommended as bailout therapy following failed angioplasty in renal FMD, although angioplasty alone is generally successful in this disorder. Predictors of poor outcomes with RAS interventions include significant proteinuria (> 1 g/d), renal atrophy, parenchymal renal disease, and diffuse renal arterial disease.

3. **Surgical revascularization.** Vascular surgery approaches to RAS include surgical bypass (aortorenal, celiac-renal, or mesenteric-renal) and endarterectomy. Perioperative mortality rates range from 1% to 5%. The comparable procedural success with percutaneous approaches and fewer major complications have led to a decline in the number of vascular surgeries for RAS. In the setting of RAS and aortic disease (either aneurysmal or occlusive), surgical revascularization with renal artery bypass grafting is the preferred approach (class I). Surgical revascularization is also recommended for patients with significant atherosclerotic RAS and clinical indications for intervention with multiple renal arteries or early branching main renal artery (class I). In patients with FMD, surgical revascularization is recommended for RAS associated with macroaneurysms or complex disease involving segmental renal arteries (class I).
4. **Controversies.** Among existing revascularization procedures for peripheral vascular disorders, renal artery stenting is possibly the most widely applied and poorly tested. To date, there are no published randomized controlled trials demonstrating the superiority of renal artery stenting over optimal medical therapy (risk factor modification, aggressive antihypertensive therapy, lipid reduction therapy, and aspirin) for RAS. In addition, the ability of renal artery stenting to decrease mortality or progression to dialysis or to provide prolonged benefits in blood pressure control remains uncertain. The National Institutes of Health (NIH)–sponsored Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial is the first large randomized controlled trial comparing medical therapy with medical therapy plus renal artery stenting for the treatment of patients with systolic hypertension and RAS, and its findings are awaited with interest.

ACKNOWLEDGMENTS: *The author thanks Dr. Frank J. Zidar and Dr. Thomas Helton for their contributions to earlier editions of this chapter.*

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HELPFUL WEB SITES

http://www.acc.org/clinical/**guidelines**/pad/index.pdf
www.tasc-2-pad.org/
http://www.padcoalition.org/wp
http://www.aboutpad.org
http://www.coralclinicaltrial.org
http://www.vdf.org

CHAPTER 28

Hemal Gada

Carotid Artery Disease

I. EPIDEMIOLOGY AND ETIOLOGY OF STROKE

A. Annually, there are nearly 800,000 strokes in the United States and 15 million strokes worldwide. Stroke is the **third leading cause of death** in Western societies and the leading cause of long-term disability in the United States.

B. Ischemic stroke accounts for approximately 85% of all strokes and can be classified into two broad categories.

1. **Embolic:** May be arterial (e.g., aortic atheroma or large vessel atherosclerosis in the carotid, vertebral, or basilar arteries) or cardiac (e.g., left ventricular thrombus postmyocardial infarction [post-MI], atrial fibrillation, valvular disorders, and cardiac tumors) in origin and most often occurs suddenly, with deficits indicating focal loss of brain function.
2. **Thrombotic:** May be caused by stenosis of smaller intracerebral arteries, a hypercoagulable state, or a systemic inflammatory condition causing vasculitis, with symptoms that may fluctuate in presence and intensity.

II. NORMAL CAROTID ANATOMY

A. The aortic arch normally gives rise to the innominate artery (aka brachiocephalic artery), the left common carotid artery (CCA), and the left subclavian artery (Fig. 28.1). The innominate artery bifurcates into the right CCA and the right subclavian artery. The **left common carotid arises from the aortic arch in 70% of people and from the innominate artery in 20% ("bovine arch" variant)**.

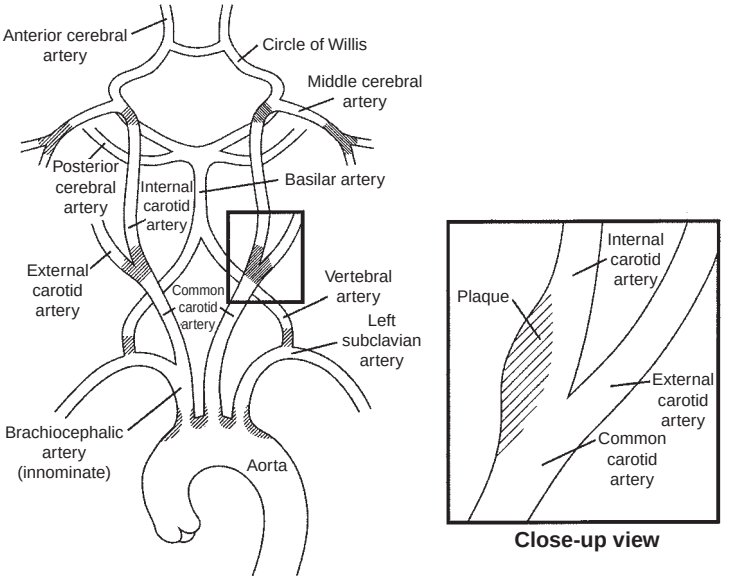

FIGURE 28.1 Normal anatomy of the aortic arch, great vessels, and circle of Willis. The *shaded regions* depict the areas most prone for the development of atherosclerosis.

B. The aortic arch can be classified into three types based on the distance of the origin of the great vessels from the top of the arch (Fig. 28.2). The widest diameter of the left common carotid is used as a reference unit. If all the great vessels originate **within an arc of the aortic arch subtended by a line parallel to a horizontal reference line at the top of the arch and separated from the top reference line by the reference unit**, it is classified as a **type I arch**. In a **type II arch**, all the great vessels originate within an arc **within two reference units** from the top of the arch, and in a **type III** arch the great vessels **originate within an arc beyond two reference units** from the top of the arch. Type III arches are harder to access during percutaneous intervention than type I arches.

C. The CCAs divide into the internal and external carotids at the C4-5 level in 50% of the patients. In approximately 40% of patients, the bifurcation is higher, and it is lower in the remaining 10%.

D. The external carotid artery provides flow to the facial muscles, scalp, and thyroid. It has a complex system of collaterals, and symptoms from stenosis are rare.

E. The circle of Willis provides collateral flow between the left and right hemispheres of the brain and connects the anterior and posterior circulation.

III. RISK FACTORS FOR CAROTID ATHEROSCLEROSIS

A. **Smoking and age** are the two most important risk factors for developing carotid atherosclerosis. The others, in order of importance, are **hypertension, diabetes, gender (men more than women if younger than 75 years; women more than men if older than 75 years), and hyperlipidemia**. As with coronary artery disease (CAD), inflammation likely plays a major role in carotid disease. African American men and Hispanic Americans appear to have a higher incidence of carotid atherosclerosis. Some data suggest a role for chronic infection in the development of carotid disease.

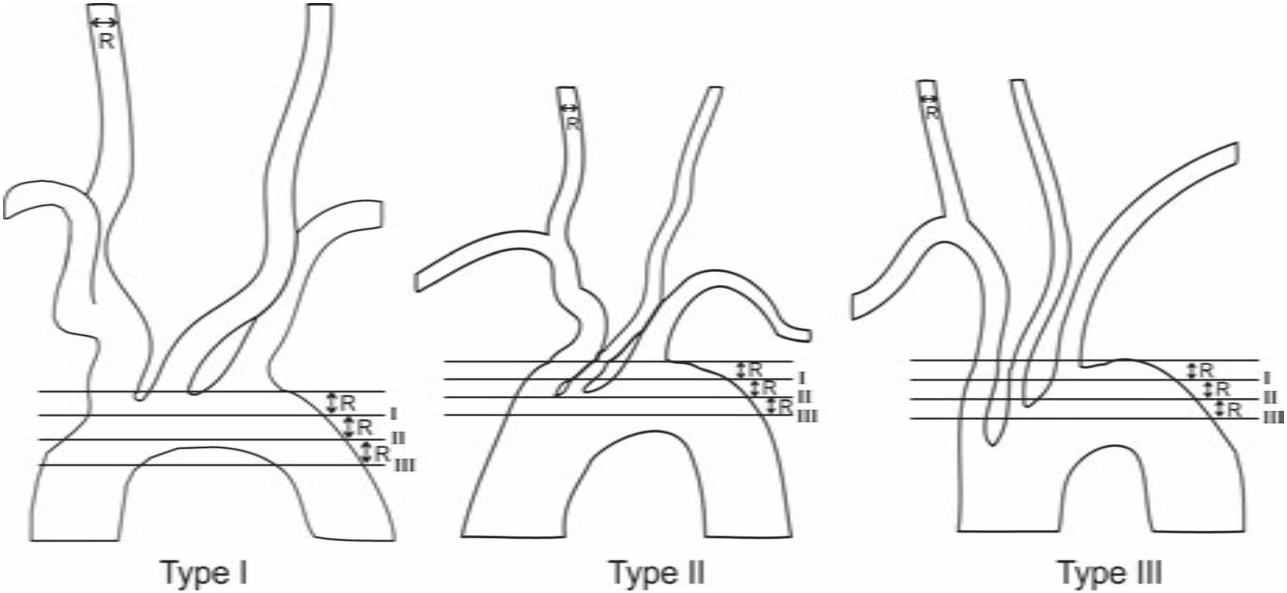

FIGURE 28.2 Aortic arch classification. The classification system is based on the distance of the origin of the great vessels from the top of the arch.

B. Elevated serum lipoprotein(a) has been associated with intracranial, extracranial, and aortic large artery occlusive disease.

C. Between 30% and 60% of patients with peripheral arterial disease have carotid disease, and approximately 50% to 60% of patients with carotid disease have severe CAD. However, only 10% of patients with CAD have severe carotid disease.

IV. PATHOPHYSIOLOGY

A. As with coronary disease, atherosclerotic carotid disease usually develops at branch points and bends, especially at the bifurcation of the CCA and origin of the internal carotid artery (ICA) (Fig. 28.1).

B. Plaque is most often localized at the carotid bifurcation and tends to extend from the outer wall of the carotid bulb into the ICA origin (Fig. 28.1).

C. The reasons that carotid stenoses become symptomatic are not completely understood, but there is a linear increase in the risk of stroke as the stenosis increases to > 70%. Two hypotheses explain how carotid disease can cause stroke.

1. **Carotid plaque is highly vascularized.** Rupture of this vasculature or rupture of the plaque can result in plaque hemorrhage or ulceration, with subsequent in situ thrombus formation. This can lead to complete vessel obstruction or distal atherothromboembolism. This mechanism accounts for most cerebrovascular events caused by carotid disease.
2. Larger plaques can result in high-grade carotid stenosis or obstruction, with subsequent ischemic stroke due to a reduction in cerebral flow, in the setting of inadequate or absent collateral circulation.

V. DIAGNOSIS

A. History and physical examination

1. **Careful history can aid in the localization of neurologic symptoms. Hemispheric symptoms include unilateral weakness, numbness, difficulty with speech, and visual field defects, whereas vertebrobasilar symptoms can include cerebellar disturbances such as ataxia or brain stem symptoms including syncope, dysphagia, dysarthria, or diplopia. Amaurosis fugax is transient, unilateral vision loss ipsilateral to a carotid lesion.**
2. **An assessment for the presence of a cervical bruit is an important part of the physical examination but should not be relied on as the sole marker for the presence of carotid disease.** In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the presence of a cervical bruit had an approximately 60% sensitivity and specificity for high-grade carotid stenosis. In the Framingham study, the presence of a carotid bruit in asymptomatic patients doubled the risk of stroke, but most of these strokes occurred in vascular beds different from those of the carotid bruit. The presence of a bruit may be a general marker for patients at higher risk for cerebrovascular and cardiovascular events.
3. **In addition to auscultation for carotid bruits, a complete evaluation in a patient with symptoms includes a focused neurologic examination to correlate symptoms with neurologic territory, a funduscopic examination to detect retinal embolization, and a cardiac examination to rule out potential cardioembolic sources for symptoms.**
4. All patients should have an evaluation of the carotid arteries after a stroke or a transient ischemic attack (TIA). The risk of a second stroke is elevated for several years after the first stroke or TIA. Symptomatic patients with 70% or more stenosis have an 8% risk of stroke at 30 days and a 13% annual incidence of stroke. The risk of stroke in asymptomatic patients increases as the degree of carotid stenosis increases. Asymptomatic patients with 60% or more stenosis have a stroke risk of approximately 2% per year. Asymptomatic patients with 80% or more stenosis have a risk of approximately 5% per year.

B. Duplex ultrasound

1. Although carotid angiography is the gold standard, duplex ultrasound is the most widely used method for the detection and quantification of carotid artery disease. It has a sensitivity and specificity of > 80% among patients with 70% to 99% stenoses and sensitivity and specificity of > 95% among patients with complete carotid occlusion. Due to its high sensitivity and specificity in severe carotid disease and its noninvasive nature, duplex ultrasound should be the first study performed to assess for carotid disease.
2. The ultrasound diagnosis of carotid stenosis is based largely on peak systolic and end-diastolic velocities in the ICA. Duplex ultrasound criteria for carotid stenosis vary by institution, and each vascular laboratory must assess the accuracy of its criteria for stenosis in a quality assurance program. Compared with angiography, duplex ultrasound is noninvasive, less expensive, and can be done at the bedside. Limitations include the inability to image intracranial disease, limited ability to assess collateral flow, occasional inaccuracy in distinguishing high-grade stenoses ("string sign") from complete obstructions, and the need for an experienced sonographer. Conditions that may elevate intravascular flow velocities, such as common carotid disease, vessel tortuosity, contralateral carotid disease, or presence of a carotid stent, may result in an artificially high estimate of ICA stenosis. The ability of ultrasound to assess the posterior carotid circulation is limited.

C. Computed tomography angiography (CTA)

1. CTA offers high sensitivity and specificity for the identification of severe (> 70%) carotid artery disease (sensitivity 75% to 100%, specificity 63% to 95%, negative predictive value up to 100%). CTA allows for visualization of the carotid artery lumen as well as adjacent bony and soft tissue structures. Advantages include high sensitivity (particularly for carotid artery occlusion), reproducibility, and the ability to visualize the entire carotid artery including the extracranial and intracranial portions. Disadvantages include cost and the need for contrast injection, which may be unsuitable for patients with chronic kidney disease or volume overload.

D. Magnetic resonance angiography

1. Contrast-enhanced magnetic resonance angiography (CEMRA) is rapidly gaining acceptance as a sensitive (91% to 95%) and specific (88% to 92%) test for severe carotid disease. Advantages include high sensitivity, reproducibility, and the ability to visualize the entire carotid artery including the extracranial and intracranial portions. The use of a paramagnetic agent as a vascular contrast confers higher quality images less prone to artifact. Disadvantages include high cost and the inability to study critically ill patients, claustrophobic patients, or patients with ferromagnetic implants such as pacemakers.
2. The combination of CEMRA and Doppler ultrasound results in a lower number of misclassifications and higher sensitivity and specificity for the diagnosis of severe ICA stenosis. When there is concern regarding the accuracy of one study, it is justifiable to perform both.

E. Contrast angiography

1. Contrast angiography with digital subtraction angiography (DSA) is the gold standard for assessment of carotid atherosclerosis. It allows the simultaneous assessment of the aortic arch, subclavian arteries, vertebral arteries, and intracranial circulation. Angiography enables the accurate assessment of collateral circulation. This is important because the presence of collateral circulation in medically treated patients with high-grade stenosis reduces the risk of ipsilateral stroke.
2. The risk of neurologic events during carotid angiography has historically been cited from as low as 0.5% for major events to as high as 4% for all events. In the hands of an experienced interventional cardiologist, the risk of stroke in one study was found to be approximately 0.5%. In our institution, 1 stroke was

observed in 580 consecutive diagnostic carotid catheterizations. Nonetheless, the risk–benefit ratio of performing carotid angiography must be carefully evaluated for each patient.

3. Two criteria are used to quantify carotid stenosis angiographically: the NASCET criteria and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria (Fig. 28.3). According to the NASCET criteria, the normal reference internal carotid diameter is the maximum diameter of the ICA distal to the lesion and distal to the carotid bulb. According to the ECST criteria, however, the normal reference diameter is determined by the estimated position of the external wall of the carotid bulb. The same lesion has a higher percentage of stenosis using the NASCET criteria compared with the ECST criteria. In addition, the NASCET criteria are difficult to apply in subtotal occlusions with collapse of the distal ICA due to underfilling. However, the NASCET criteria inherently have less variability and are now recommended as the standard for reporting of angiographic carotid stenosis in Medicare physician quality initiatives.
4. **Technique**
   a. Complete cerebral angiography involves angiography of the aortic arch and carotid arteries, intracerebral angiography, and angiography of the vertebral arteries and posterior circulation.
   b. A low-osmolar or iso-osmolar, nonionic, heparinized contrast agent should be used. In the absence of contraindications, the patient should be anticoagulated with 50 U/kg of intravenous heparin. The patient's head is often put in a holder or immobilizer to prevent inadvertent movement, and the patient is advised to look at the ceiling or keep his or her eyes closed. DSA should be used, if available, to improve resolution and minimize the amount of contrast needed. Before obtaining each cine angiogram, the patient should be instructed not to move, breathe, or swallow during image acquisition.
   c. Aortic arch angiography is performed using an angled pigtail catheter. Using a 0.035″ guidewire, the pigtail catheter is positioned in the mid-portion of the ascending aorta, and a cine angiogram of the aortic arch is obtained in a left anterior oblique projection (approximately 45°).
   d. Carotid angiography can be safely performed using a Judkins right (JR4) or a Headhunter catheter. Alternatively, a Vitek catheter can be used with

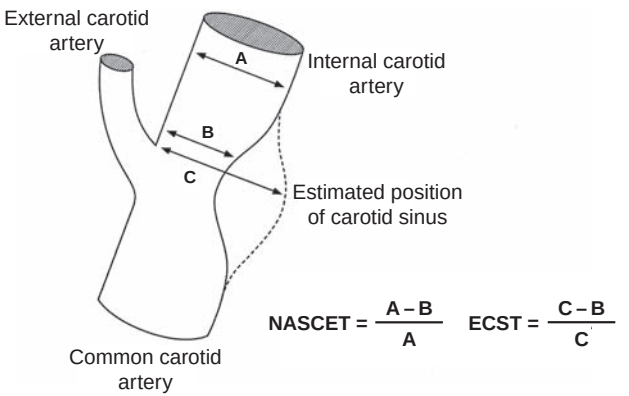

FIGURE 28.3 The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria for determining the degree of carotid stenosis.

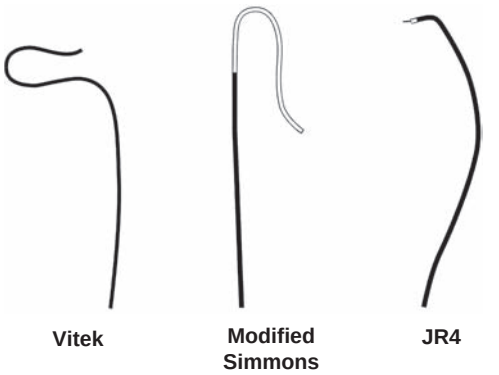

FIGURE 28.4 The three most common types of catheters used for carotid angiography.

bovine anatomy or type II or III arch. The Simmons catheter is useful in cases of severe tortuosity but requires reshaping in the aortic arch, which can lead to higher complication rates (Fig. 28.4). In the left anterior oblique projection, the JR4 catheter is positioned in the superior portion of the ascending aorta and rotated counterclockwise until it is positioned in the innominate artery. Nonselective cine angiography of the innominate, right subclavian, right carotid, and right vertebral arteries can then be performed with the image train in the right anterior oblique projection. In the right anterior oblique projection, a 0.035″ wire (e.g., Stiff-Angled Glide, Magic Torque, and Wholey) is used to advance the JR4 catheter to selectively engage the right common carotid. Two basic views should be obtained for each carotid: an ipsilateral oblique view (30° to 45°) and a cross-table lateral view. The table should be positioned so that the carotid bifurcation is in the middle of the screen, and shutters and filters should be used to optimize image quality.

e. For cerebral angiography, the patient's head is positioned in the center of the screen. Cine angiography is performed in the posteroanterior and lateral projections. It is important to continue the cine until the venous runoff has been captured to assess for intracranial arterial venous malformations and anomalous venous drainage. To selectively engage the left carotid, the catheter is positioned in the innominate artery so that the tip is pointing superiorly. The catheter is slowly pulled back, ensuring that the tip remains pointed superiorly, until the catheter tip exits the innominate and engages the left common carotid. The same views can then be obtained for the left carotid.

VI. MANAGEMENT OF CAROTID DISEASE

A. Medical management

1. Risk factor modification. Aggressive cardiovascular risk factor modification is recommended to reduce the risk of stroke and prevent the progression of existing disease, regardless of whether or not revascularization is indicated. Smoking cessation, blood pressure control to levels recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines (< 140/90 mm Hg and more aggressive control in patients with atherosclerotic cardiovascular disease,

chronic kidney disease, or diabetes), control of diabetes (HbA1c < 7%), and lipid management (goal low-density lipoprotein [LDL] < 100 mg/dL, < 70 mg/dL if high CAD risk) are important treatment goals for which to strive in any patient with carotid disease.

2. **Antiplatelet therapy**
   a. The Antiplatelet Trialists' meta-analysis including 73,247 high-risk patients found that antiplatelet therapy as secondary prevention resulted in a 27% (25% attributed to aspirin) relative reduction in the combined end point of vascular death, MI, and stroke.
   b. **Aspirin** is the most extensively studied antiplatelet drug for the prevention of stroke and other cardiovascular events and should be initiated in all patients with evidence of carotid atherosclerosis. Men whose 10-year risk for the development of stroke or MI is ≥ 10% or greater should be started on low-dose (75 to 160 mg/day) aspirin for primary prevention. Women ≥ 65 years or older should be started on aspirin therapy (75 to 325 mg/day) for the primary prevention of MI and stroke. Aspirin therapy is also recommended in women younger than 65 years for the prevention of stroke when the benefits of ischemic stroke prevention outweigh the adverse effects of aspirin therapy.
   c. The **Clopidogrel** versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial demonstrated a decrease in the combined end point of vascular death, stroke, and MI with clopidogrel therapy compared with aspirin (5.32% vs. 5.83%) among patients with a history of stroke, MI, or symptomatic peripheral vascular disease. These data represented an 8.7% relative risk reduction ($p = 0.043$). Currently, there is no consensus on the use of clopidogrel for the primary prevention of stroke. Clopidogrel may be an option for the primary prevention of stroke in patients with moderate carotid stenosis who cannot tolerate aspirin.
   d. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) study, which evaluated dual antiplatelet therapy with aspirin and clopidogrel versus clopidogrel alone in stroke patients with concomitant cardiovascular disease, patients who suffered a stroke while on a single antiplatelet agent, and patients with severe aortic arch disease, demonstrated an insignificant trend toward improved efficacy with dual antiplatelet therapy; however, there was a highly significant increase in life-threatening bleeding events.
   e. In contrast to MATCH, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial evaluated aspirin plus clopidogrel versus aspirin alone in patients with symptomatic cardiovascular disease or a constellation of cardiovascular risk factors. In this patient population, the combination of aspirin and clopidogrel was not more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes. Dual antiplatelet therapy did improve rates of all-cause stroke (2.4% vs. 1.9%, $p = 0.05$), and subgroup analyses showed a significant 12.5% relative reduction in the risk of primary events in patients with established cardiovascular disease. As will all subgroup analyses, however, these results should be interpreted with caution.
   f. Low-dose aspirin (25 mg twice daily) plus dipyridamole (200 mg twice daily) has been found to be more beneficial than aspirin alone or dipyridamole alone for the secondary prevention of stroke in the European Stroke Prevention Study 2 (ESPS 2). Similarly, in the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), extended-release dipyridamole administered with aspirin was superior to aspirin alone in the prevention of MI, stroke, or vascular death.

g. The Prevention Regimen for Effectively avoiding Second Strokes (PRoFESS) trial, which enrolled over 20,000 patients with noncardioembolic ischemic stroke, showed that clopidogrel monotherapy and aspirin plus extended-release dipyridamole have similar risks and benefits for secondary stroke prevention. There was no difference between treatment with aspirin plus extended-release dipyridamole or clopidogrel for the primary outcome of recurrent stroke or the composite secondary outcome of stroke, MI, or vascular death. However, despite the nearly identical event rates, the trial failed to meet the prespecified noninferiority criteria for treatment with aspirin and extended-release dipyridamole.

h. According to the American Heart Association (AHA)/American Stroke Association (ASA) Guidelines for the Prevention of Stroke in Patients with Ischemic Stroke or TIA, the accepted treatment strategies for the secondary prevention of noncardioembolic stroke include one of the following:
(1) Aspirin (50 to 100 mg daily)
(2) Aspirin (25 mg) and extended-release dipyridamole (200 mg twice daily)
(3) Clopidogrel (75 mg daily), especially for patients with aspirin allergy or resistance

3. Antihyperlipidemic agents

a. Epidemiologic data have shown higher stroke rates among patients with high LDL and low high-density lipoprotein cholesterol levels. Several studies have consistently shown carotid plaque regression in patients treated with statins, and clinical trials have shown a reduction in stroke among patients treated with statins. In the Scandinavian Simvastatin Survival Study (4S), nonembolic strokes were significantly reduced in the statin arm. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) study demonstrated a 16% relative risk reduction in stroke with statin therapy in 4,731 patients with prior stroke or TIA randomized to atorvastatin versus placebo. In a meta-analysis of randomized trials that included a total of 165,792 patients with hyperlipidemia, each 39 mg/dL reduction in LDL cholesterol equates to a reduction in relative risk of stroke of 21.1%.

b. The beneficial effects of statins in reducing strokes are highest among patients at the highest risk for stroke. For primary prevention, all high-risk patients (e.g., diabetes, peripheral vascular disease, and CAD) should be treated with statins. For secondary prevention, all patients with a history of MI, TIA, and stroke should be on statin therapy.

4. Antihypertensive agents

a. Hypertension is the single most modifiable risk factor in the prevention of stroke, and epidemiologic data suggest that approximately 60% of all strokes are attributable to hypertension. Several randomized controlled trials have shown benefit of a variety of antihypertensive agents, ACE inhibitors, and diuretics in particular. The Heart Outcomes Prevention Evaluation (HOPE) study showed a relative risk reduction of 32% for stroke in patients with known risk or at high risk for cardiovascular disease treated with ramipril versus placebo. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) showed a 43% reduction in stroke in patients with prior strokes with the use of perindopril versus placebo. The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALL-HAT) showed that thiazide diuretics were superior to lisinopril for prevention of stroke in patients with hypertension and one other coronary heart disease risk factor (risk of stroke: risk ratio [RR] 1.15, 95% confidence interval [CI] 1.02 to 1.30). In the Losartan Intervention for Endpoint Reduction (LIFE) study, the angiotensin receptor blocker losartan was associated with a 40% reduction in stroke compared with atenolol.

b. The JNC7 guidelines recommend that all patients with prehypertension (systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg) undergo lifestyle modifications to lower blood pressure. Furthermore, all patients with blood pressure > 140/90 mm Hg (or > 130/80 mm Hg with diabetes or chronic kidney disease) should receive antihypertensive drug therapy to achieve their blood pressure goal. ACE inhibitors and diuretic agents remain first-line therapy in patients with cerebrovascular disease.

5. Anticoagulation

a. There are no data specifically addressing the use of warfarin for primary stroke prevention in patients with documented carotid stenosis. However, one study has suggested that **low-dose warfarin may attenuate carotid plaque progression** in men. The use of warfarin for the secondary prevention of noncardioembolic strokes (including patients with carotid stenosis) is controversial. There was no clear benefit for low- and medium-dose oral warfarin therapy (international normalized ratio [INR] 2.0 to 3.0) for the secondary prevention of noncardioembolic stroke in the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial and a significant increase in adverse effects, including death, major hemorrhage, and MI, with warfarin use. High-dose warfarin (INR 3.0 to 4.5) for the secondary prevention of noncardioembolic stroke results in a high rate of bleeding complications, including hemorrhagic stroke, and should not be used.

B. Surgical management: carotid endarterectomy (CEA)

CEA is the standard of care for the reduction of stroke or TIA in patients with high-grade symptomatic or asymptomatic carotid stenosis. Several trials have firmly established the utility of CEA in preventing stroke in the presence of severe carotid stenosis as compared with medical therapy. It is important to keep in mind that high-risk patients were not enrolled in these trials. Because the risk of surgery among such patients probably would be higher than reported in these trials, extrapolation of these data to high-risk patients must be done with caution.

1. Major trials

a. Asymptomatic, low-risk patients

(1) Asymptomatic Carotid Atherosclerosis Study (ACAS)

(a) A total of 1,662 patients with asymptomatic carotid stenosis of 60% or more were randomized to CEA or medical therapy. All patients were treated with aspirin (325 mg daily).

(b) At a median of 2.7 years of follow-up, the estimated 5-year risk of stroke or death was 5.1% in the surgical arm and 11% in the medically treated arm ($p = 0.004$). The annual risk of stroke among patients in the medical arm was 2.3%. The perioperative stroke or death rate was 2.3%.

(2) Veterans Affairs Asymptomatic Carotid Stenosis Study

(a) In this study, 444 men with 50% or more carotid stenosis were randomized to CEA or to medical therapy with aspirin.

(b) The incidence of ipsilateral stroke was 4.7% in the surgical group versus 9.4% in the medical group, but there were no significant differences between the surgical and medical groups for all strokes and deaths (surgical 41.2% vs. medical 44.2%; RR 0.92, 95% CI 0.68 to 1.22).

(3) Asymptomatic Carotid Surgery Trial

(a) In this trial, 3,120 patients with > 60% carotid stenosis were randomized to immediate CEA plus medical treatment versus medical treatment and deferred CEA.

(b) The risk of perioperative stroke or death within 30 days of CEA was 3.1%. The estimated 5-year risks of stroke were 6.4% versus 11.8%, $p < 0.001$, for immediate CEA versus deferred CEA.

b. Symptomatic, low-risk patients

(1) The NASCET randomized 2,926 patients with symptomatic carotid stenosis (30% to 99%) to either medical therapy or medical therapy plus CEA. Recruitment of patients with severe carotid stenosis (70% to 99%) was stopped after 659 patients due to highly beneficial effect of CEA.

(a) A total of 659 patients with severe carotid stenosis (70% to 99%), ipsilateral hemispheric or retinal TIA, amaurosis fugax, or nondisabling stroke within 120 days were randomized to CEA or medical therapy.

(b) For those with severe (70% to 99%) carotid stenosis, the 30-day risk of stroke or death was 3.3% in the medical group and 5.8% in the surgical group. Two-year risk of any stroke was 26% in the medical group and 9% in the surgical group ($p < 0.001$), and the risk of major stroke or death was 18.1% in the medical group and 8% in the surgical group ($p < 0.001$). Patients with the most severe stenoses had the most benefit.

(c) A total of 2,267 patients with 30% to 69% stenosis, ipsilateral hemispheric or retinal TIA, or nondisabling stroke within 120 days were randomized to CEA or medical therapy. Patients with 50% to 69% stenosis had a 5-year stroke rate of 22.2% in the medical group and 15.7% in the surgical group ($p = 0.045$). Patients with 30% to 49% stenosis had a 5-year stroke rate of 18.7% in the medical group and 14.9% in the surgical group ($p = 0.16$).

(2) Veterans Affairs Cooperative Study

(a) In the Veterans Affairs Cooperative Study, 189 men with > 50% internal carotid stenosis with ipsilateral symptoms were randomized within 120 days of a neurologic event to CEA or medical therapy.

(b) At a mean of 11.9 months' follow-up, the incidence of stroke or TIA was 19.4% in the medical arm and 7.7% in the surgical arm ($p = 0.011$). The 30-day stroke or death rate was 6.6% in the surgical group and 2.2% in the medical group.

(3) The ECST Collaborative Group

(a) A total of 2,518 patients with symptomatic carotid stenosis were randomized to CEA or medical therapy. Patients ($n = 374$) with mild stenosis (0% to 29%) had low rates of ipsilateral stroke overall, and 3-year benefits of surgery were small and outweighed by operative risk. The ipsilateral stroke rate at 3 years of follow-up for patients with stenoses between 70% and 99% ($n = 778$) was 16.8% in the medical arm and 10.3% in the surgical arm.

2. Complications and management of patients after CEA

a. Major complications of CEA include MI, stroke, and death. Other complications include bleeding and wound hematoma, cranial nerve injury, wound infection, bradycardia, hyper- or hypotension, and, rarely, seizures and intracerebral hemorrhage.

b. After CEA and in the absence of contraindications, all patients should be treated with antiplatelet therapy.

3. The ASA/American College of Cardiology Foundation (ACCF)/AHA recommendations for CEA

a. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral ICA is reduced > 70% as documented by noninvasive imaging or > 50% as documented by catheter angiography and the anticipated rate of perioperative stroke or mortality is < 6%.

b. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure, with an understanding of patient preferences. It is reasonable to perform CEA in asymptomatic patients who have > 70% stenosis of the ICA if the risk of perioperative stroke, MI, and death is low.

c. Except in extraordinary circumstances, carotid revascularization is not recommended when atherosclerosis narrows the lumen by < 50%.

4. Combined CEA and coronary artery bypass grafting (CABG)

a. Patients with severe coronary disease may have severe carotid disease, and surgery in this population is a high-risk procedure. The optimal treatment strategy remains unclear.

b. Options include simultaneous CEA and CABG, staged CEA followed by CABG, or staged CABG followed by CEA. In staged procedures, CEA first increases risk of perioperative MI, and CABG first increases risk of perioperative stroke.

c. Some investigators have reported better results with simultaneous procedures, but patient selection is likely an important factor in achieving satisfactory outcomes. A meta-analysis of 16 studies with a total of 844 combined procedure and 920 staged procedure patients reported a higher risk of death, stroke, or MI among patients undergoing combined compared with staged procedures. Percutaneous intervention may be a better choice for this patient population, and this is an area that requires further investigation.

C. Percutaneous carotid intervention

1. Since the first description of carotid angioplasty in 1980, a number of registry studies and trials have been published reporting high rates of procedural success. However, percutaneous carotid angioplasty is rarely performed as a stand-alone procedure because of unacceptably high rates of recoil, restenosis, and adverse procedural outcomes due to distal embolization. Carotid stenting has become the standard of care for patients undergoing percutaneous carotid intervention.

2. Compared with angioplasty alone, carotid stenting improves procedural success rates, decreases periprocedural complications (including carotid artery dissection), and decreases restenosis. Several types of embolic protection devices are in use to prevent embolic complications of angioplasty and stenting. Results of observational studies have shown that embolic protection devices can reduce rates of adverse events during carotid artery stenting in experienced hands; however, inexperience can also worsen clinical outcomes when these devices are used. Benefit of these devices to prevent periprocedural events has not been established in randomized controlled trials.

3. Several manufacturers have stents approved for use in the carotid artery. Balloon-expandable stents are generally not used for carotid stenting because of the potential for structural deformation that can occur as a result of external forces such as those caused by neck movement. Self-expanding stents, such as the Wallstent (Boston Scientific Corp, Quincy, MA), Acculink carotid stent (Abbott Vascular Devices, Redwood City, CA, formerly Guidant Corp), Xact carotid stent (Abbott Vascular Devices, Redwood City, CA), and the carotid SMART stent (Cordis Endovascular, Warren, NJ), are commonly used, as they continue to exert outward radial force after deployment and resist crushing.

4. Trials

a. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) compared carotid angioplasty (without stenting) with CEA among patients with > 50% carotid stenosis and found similar rates of procedural bleeding, major stroke, or death between the two treatment strategies

at 30 days and 1 year. However, the CEA cohort did have a higher number of patients whose surgery was complicated by cranial nerve injury.

b. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first multicenter, randomized, controlled trial comparing carotid stenting with CEA in high-risk patients. Using the PRECISE nitinol stent (Cordis, Warren, NJ) and the AngioGuard (Cordis, Warren, NJ) distal protection device, 334 patients were randomized (167 to carotid stenting and 167 to CEA). An additional 409 patients were enrolled in a stent registry. The combined end point of death, stroke, and MI at 1 year was reached in 12.2% of patients in the stenting arm and 20.1% of patients in the CEA arm (p = 0.004 for noninferiority and p = 0.053 for superiority). This is the first randomized trial to show noninferiority of carotid stenting compared with CEA.

c. The Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS) trial was a phase I multicenter, prospective randomized trial comparing carotid stenting with CEA in a broad-risk group of symptomatic (with > 50% stenosis) and asymptomatic patients (with > 75% stenosis). The combined primary end point of stroke and death was 3.6% for CEA and 2.1% for carotid stenting at 30 days, and 13.6% for CEA and 10.0% for carotid stenting at 1 year. The authors concluded that carotid stenting was equivalent to CEA in both symptomatic and asymptomatic patients at 1 year.

d. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was a multinational, multicenter randomized trial evaluating carotid stenting with optional distal embolic protection versus CEA in 1,200 patients with symptomatic carotid artery stenosis. Unlike the SAPPHIRE trial, the SPACE trial was not limited to high-risk surgical patients. The SPACE trial was unable to demonstrate noninferiority of carotid stenting compared with CEA, as the rate of death or ipsilateral ischemic stroke at 30 days from procedure was 6.84% with carotid stenting versus 6.34% with CEA (p = 0.09). A criticism of the SPACE trial was that embolic protection devices were not required and were only utilized in 27% of the cases. However, no significant difference in the primary end point was observed with or without the use of embolic protection devices.

e. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a multicenter, randomized, noninferiority trial comparing carotid stenting with CEA in symptomatic patients with 60% to 99% carotid stenosis. The EVA-3S trial enrolled moderate-risk surgical patients. EVA-3S was stopped prematurely after enrollment of 527 patients, due to higher rates of stroke and death at 1 month (9.6% vs. 3.9%, p = 0.01) and 6 months (11.7% vs. 6.1%, p = 0.02) with carotid stenting versus CEA. A criticism of the EVA-3S trial was the lack of experience of the operators taking part in the study, as the interventionalists were required to have completed only two procedures with any device prior to its use in the trial. Furthermore, the use of embolic protection devices was optional at the onset of the trial, and a significant difference in the 30-day outcome of stroke and death was present between patients treated with and without embolic protection devices (7.9% vs. 25%, respectively). The use of embolic protection devices during carotid artery stenting did not significantly improve rates of stroke or death versus CEA.

f. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) randomly assigned 2,502 patients with carotid atherosclerotic disease (47% asymptomatic, 53% symptomatic) to CEA or stenting. The primary end point of the trial, a composite of any stroke, MI, or death within

30 days following treatment plus any ipsilateral stroke during long-term follow-up (median 2.5 years), was similar for stenting and CEA (7.2% vs. 6.8%, respectively; $p = 0.51$). For patients aged 70 years or older, the rates of the primary end point and adverse events increasingly favored surgery over stenting. A secondary analysis showed that for the subgroup of patients with symptomatic carotid disease, the periprocedural rate of stroke and death was significantly higher for those assigned to stenting compared with CEA (6% vs. 3.2%, respectively; $p = 0.02$). However, for both stenting and CEA, the rates of stroke and death were at or below those of previous randomized controlled trials and were within the complication thresholds suggested in current guidelines for symptomatic and asymptomatic patients.

g. In the International Carotid Stenting Study (ICSS, also known as CAVATAS 2), 1,713 patients with recently symptomatic carotid stenosis, suitable for either surgery or percutaneous intervention, were randomly assigned to treatment with either CEA or stenting. All patients had carotid artery stenosis of > 50% by NASCET criteria on noninvasive imaging. At 120 days, the proportion of patients who reached the combined end point of stroke, death, and MI was significantly higher for the stenting group than for the CEA group (8.5% vs. 5.2%, respectively; $p = 0.006$). Longer term follow-up of this patient group is currently pending.

5. Complications and management

a. The major periprocedural complications during carotid stenting are stroke, MI, and death. Other complications include TIAs, access site bleeding, bradycardia, hypotension, seizures, and intracranial hemorrhage. **Advanced age and long or multiple stenoses have been found to be independent predictors of periprocedural stroke**. In one study, stenting in the presence of a contralateral occlusion, stenting after a previous CEA, or combined carotid and coronary interventions **did not** increase the risk of adverse outcomes.

b. Periprocedural cerebrovascular events occur largely because of embolization of plaque debris and thrombus into the cerebral circulation during manipulation of the carotid plaque. Such emboli have been documented by the use of transcranial Doppler, and the amount of embolization has been correlated with the size of infarct during CEA. Emboli protection devices decrease the volume of distal embolization.

c. Embolic protection devices fall into three general categories (Figs. 28.5 and 28.6): distal occlusion balloon protection, distal filter, and proximal occlusion balloon. The PercuSurge GuardWire (Medtronic, Minneapolis, MN) system provides occlusion of distal flow during carotid stenting, enabling the removal of embolized debris (Fig. 28.5). The AngioGuard (Cordis, Warren, NJ) is one example of a filtration umbrella mounted on a 0.014″ guidewire, which is positioned distal to the plaque during stenting (Fig. 28.6). At the end of the procedure, the filter is removed using a retrieval catheter. Proximal occlusion balloon systems create reversal of flow in the ICA, preventing embolization of debris into the cerebral vasculature.

d. **Bradycardia and hypotension** occur often during carotid stenting because of instrumentation and stretching of the carotid sinus baroreceptors. These hemodynamic effects are usually transient but can persist for up to 24 hours after intervention. **Symptomatic patients** should be managed with **intravenous crystalloid infusion and potentially a low-dose infusion of an inotropic agent (e.g., dopamine) or temporary pacing as required**. Unless the patient is hypertensive, antihypertensive and negative inotropic medications are usually withheld immediately preprocedure and postprocedure. Telemetry monitoring should be continued for 24 hours, and the nursing staff should perform frequent neurologic checks postprocedure. All patients

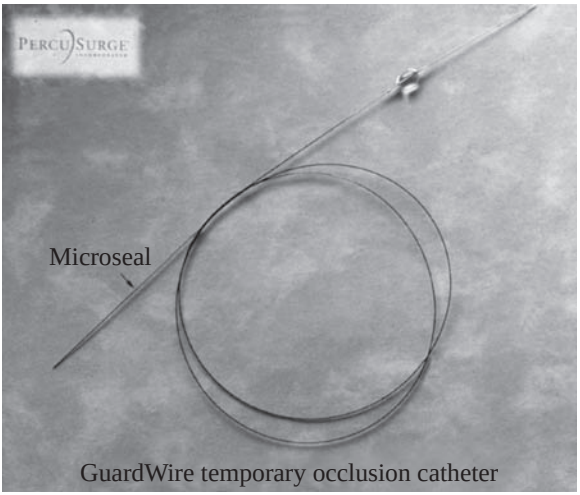

FIGURE 28.5 The PercuSurge GuardWire (Medtronic, Minneapolis, MN) system.

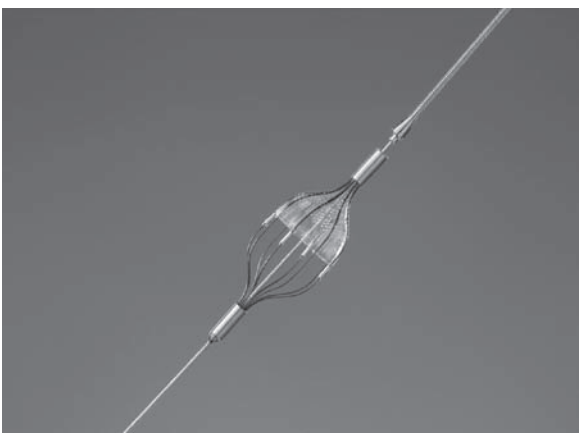

FIGURE 28.6 The AngioGuard (Cordis, Warren, NJ) emboli protection device.

should undergo a thorough and well-documented neurologic examination before and after the procedure. Standardized stroke scales are often utilized (e.g., NIHSS, Barthel, and modified Rankin).

e. **Hyperperfusion syndrome**, manifested by strokelike symptoms and signs, can occur because of the rapid return of flow to a chronically underperfused cerebral vascular bed, with resultant disordered autoregulation. Risk factors include **severe hypertension, critical carotid stenosis, and contralateral carotid occlusion**. Cerebral hemorrhage is a dreaded complication of the hyperperfusion syndrome.

f. Patients undergoing carotid stenting should be pretreated with aspirin (325 mg daily) and clopidogrel (75 mg twice daily) for 2 days before the procedure if possible. After the procedure, **lifelong aspirin therapy should be instituted**, and **clopidogrel (75 mg daily) should be continued for at least 6 weeks**. For patients with recurrent symptoms or a history of neck irradiation, clopidogrel should be continued indefinitely. The incidence of restenosis after carotid stenting is lower than after coronary stenting and ranges between 1% and 6% per year.

g. The routine use of adjunctive glycoprotein (GP) IIb/IIIa inhibitors has not been well studied in the setting of carotid stenting. Initial observational data suggest that their use may be safe. However, because of the potential for intracranial hemorrhage, especially among patients with hypertension or hyperperfusion syndrome after carotid stenting, and without clear evidence of benefit, GP IIb/IIIa inhibitors are not routinely used. Further studies are needed to better define the use of these agents in this arena; however, incremental benefit above and beyond the use of mechanical embolic protection devices may be difficult to demonstrate.

h. Patients with carotid stenosis frequently have concomitant CAD. Successful combined carotid stenting and percutaneous coronary intervention has been reported as a simultaneous procedure, and the two are frequently performed as staged procedures with satisfactory outcomes.

6. The ASA/ACCF/AHA recommendations for carotid stenting

a. Carotid stenting is an indicated alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by > 70% by noninvasive imaging or > 50% by catheter angiography and the anticipated rate of periprocedural stroke or mortality is < 6%.

b. It is reasonable to choose carotid artery stenting over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.

c. Prophylactic carotid artery stenting might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography and 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.

ACKNOWLEDGMENTS: *The author thanks Dr. Adnan Chhatriwalla and Dr. Christopher Bajzer for their contributions to earlier editions of this chapter.*

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SECTION VI

Adult Congenital Heart Disease

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CHAPTER 29

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Atrial Septal Defect and Patent Foramen Ovale

I. INTRODUCTION

A. Atrial septal defects (ASDs) constitute approximately 5% to 10% of congenital heart disease. Excluding bicuspid aortic valve and mitral valve prolapse, ASD is the most common form of congenital heart defect found among adults and is the most common acyanotic shunt lesion in adults as well.

B. Often, an atrial communication may go unrecognized into adulthood because the clinical symptoms and physical manifestations can be subtle.

C. Although survival into adulthood is the rule, the overall life expectancy is decreased in patients with an unrepaired ASD. Long-term exposure to chronic right heart volume overload can have deleterious effects, such as atrial arrhythmias, pulmonary vascular disease, and right heart failure. These clinical findings are directly related to patient age, with almost all patients becoming symptomatic by the fifth or sixth decade. The presence of an atrial communication is also a potential source of paradoxical embolus.

D. A patent foramen ovale (PFO) is a specific form of interatrial communication caused by incomplete closure of the foramen ovale after birth. PFOs are present in 25% to 30% of the general population. The prevalence of PFO in patients with cryptogenic stroke is approximately 40% to 50%.

E. Atrial septal aneurysms are congenital outpouchings of the atrial septum, near the fossa ovalis. These can perforate, resulting in an ASD with left-to-right shunting of blood. Atrial septal aneurysms can be detected in up to 10% of patients undergoing echocardiography and in up to 30% of patients with cryptogenic stroke, generally with a concomitant PFO.

II. ANATOMY AND EMBRYOLOGY.

The primitive atrium is first partitioned into right and left atria by growth of the septum primum—a thin, crescent-shaped membrane that grows from the roof of the primitive atrium toward the endocardial cushions located between the atria and ventricles. An atrial communication initially persists as the foramen primum, composed of the free edge of the septum primum and the endocardial cushions. Before closure of the foramen primum, fenestrations develop in the septum primum that coalesce to form the ostium secundum. As the septum primum then fuses with the endocardial cushions, the ostium secundum maintains a right-to-left atrial flow that is important in the fetal circulation. **Failure of this fusion results in the development of a primum ASD**. A second septum, the septum secundum, then forms to the right of the septum primum, growing toward the endocardial cushions and usually closing the ostium secundum. **Failure to close the ostium secundum results in the formation of a secundum ASD**.

The septum secundum forms an incomplete partition of the atria, leaving a foramen ovale (i.e., fossa ovalis). The remaining septum primum tissue on the left atrial (LA) side

becomes a flap valve, or valve of the foramen ovale, and allows for the continued right-to-left shunting in the fetal circulation. At birth, when LA pressure increases, the septum primum flap closes and eventually fuses to anatomically seal the atrial septum. A "true ASD" results from a deficiency in septal development or from resorption of atrial tissue, whereas a **PFO results from failure of this septum primum flap to adequately seal the fossa ovalis**. At autopsy, a "probe-patent" PFO remains in 25% to 30% of patients.

During development, if there is overabundant or weakened septal tissue, the septum becomes very mobile. This can be visualized during echocardiography, and the degree of excursion can be measured. If the maximal excursion of the interatrial septum is **15 mm or more**, this abnormality is called an **atrial septal aneurysm**. If the amount of septal excursion is < 15 mm, it is referred to as a redundant atrial septum.

ATRIAL SEPTAL DEFECTS

I. ASD TYPES (Fig. 29.1)

A. Ostium secundum defects or **secundum ASDs** constitute the most common type, accounting for 70% to 75% of ASDs. This defect, a true defect of the atrial septum, is located in the midportion of the atrial septum, within or including the fossa ovalis. Defects result from a deficient septum primum or an abnormally large foramen secundum. This type of ASD is two times more common in female patients. Isolated secundum ASD has been associated with mitral valve prolapse and other forms of congenital heart disease. It may also be associated with rheumatic mitral stenosis (i.e., Lutembacher syndrome).

B. Ostium primum defects or **primum ASDs** account for 15% to 20% of ASDs and are part of the spectrum of atrioventricular (AV) septal defects (also known as AV canal defects or endocardial cushion defects). These defects occur in the inferior–anterior portion of the atrial septum and are frequently associated with a cleft in the anterior leaflet of the mitral valve, leading to varying degrees of mitral regurgitation. In their complete form, they include a large ventricular septal defect and a common

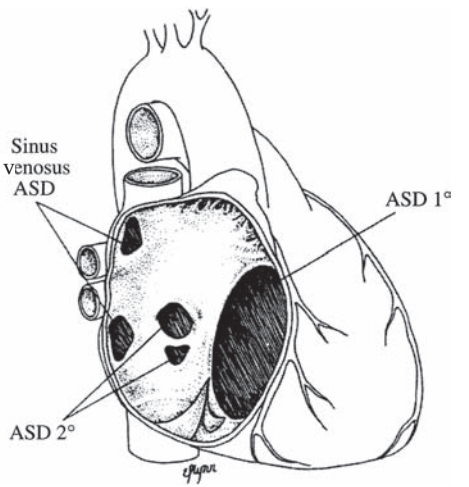

FIGURE 29.1 Diagrammatic representation of common atrial septal defects. ASD, atrial septal defect; 1°, primum; 2°, secundum. Reproduced from Fyler DC, ed. *Nadas Pediatric Cardiology.* Philadelphia, PA: Hanley & Belfus; 1992, with permission.

AV valve. Depending on the severity of dysfunction of the mitral valve, these patients may become symptomatic at a young age. This defect in the inlet septum is the most common ASD associated with Down's syndrome.

C. **Sinoseptal** defects constitute the remaining 5% to 10% of septal defects. Distinct from the true ASDs described previously, these lesions involve the portion of the atrial wall derived from the sinus venosus (i.e., there is no direct communication between the right and left atria). **Sinus venosus defects** are typically at the orifice of the superior vena cava (SVC) at the junction of the right atrium or, less frequently, in the region of the inferior vena cava (IVC). These sinus venosus defects are frequently associated with partial anomalous pulmonary venous drainage of the right pulmonary veins and require a high index of suspicion for diagnosis because they are generally not visualized by standard transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) is generally required for visualization in adults. Magnetic resonance imaging (MRI) or computed tomography may also be used for diagnosis. These defects should be considered in any patient with unexplained right atrial (RA) or right ventricular (RV) dilation. An uncommon sinoseptal defect is the partially or completely **unroofed coronary sinus**, which is located inferior and slightly anterior to the fossa ovalis. These defects are commonly associated with other forms of congenital heart disease, such as complete AV septal defect, or can be associated with an absence of coronary sinus and a left SVC that drains into the left atrium.

II. PATHOPHYSIOLOGY. The magnitude and direction of the shunt through the ASD depend on the size of the defect as well as the diastolic filling properties of the ventricles. Any condition that causes reduced left ventricular (LV) compliance, such as LV hypertrophy or LV scar, or increased LA pressure, such as mitral stenosis, will increase the degree of left-to-right shunting. Conversely, conditions that cause reduced RV compliance, such as pulmonary hypertension or pulmonary stenosis, or increased RA pressure, such as tricuspid stenosis, will reduce the degree of left-to-right shunting and, in some instances, even lead to shunt reversal. In general, the ASD must be at least 10 mm in its greatest dimension to cause a significant shunt, although this can be hard to measure, as most ASDs are not circular. A left-to-right shunt is considered significant when the ratio of pulmonary-to-systemic blood flow, or shunt fraction (Q_p/Q_s), is > 1.5:1.0 or when right heart chamber dilation is present.

III. CLINICAL MANIFESTATIONS. The clinical presentation of a patient with an ASD results from the effects of long-term left-to-right shunting and subsequent volume loading of the right heart. The age at which the symptoms occur is variable and does not necessarily depend on the size of the defect.

A. **Exercise intolerance** with **fatigue** and **dyspnea** may occur, but it is frequently not appreciated by the patient until after the defect has been closed. Late findings include **supraventricular arrhythmias**, such as atrial fibrillation or flutter, severe irreversible **pulmonary vascular disease**, and, eventually, **right heart failure**. Occasionally, a **paradoxical embolus** causing a stroke or transient ischemic attack (TIA) is the first clue to an ASD.

B. The physical findings may include a hyperdynamic cardiac impulse, the characteristic **widely or fixed split second heart sound**, and a **soft systolic murmur at the second left intercostal space** due to increased flow across the pulmonary valve. If the shunt is more than a shunt fraction (Q_p/Q_s) of 2.5:1, there may be a diastolic murmur secondary to increased flow across the tricuspid valve. A loud P_2 component of the second heart sound indicates the presence of pulmonary hypertension, which can affect up to 20% of patients; if cyanosis is present, this generally suggests advanced pulmonary hypertension with reversal of shunt flow (**Eisenmenger syndrome**). An important clue to the presence of Eisenmenger syndrome is an oxygen saturation that does not significantly improve with supplemental oxygen.

Another physical examination finding that may be encountered is a holosystolic murmur characteristic of mitral regurgitation, which is often heard in a patient with a primum ASD.

IV. LABORATORY EXAMINATION

A. Electrocardiogram (ECG). The ECG can provide clues to the possibility of an ASD. The rhythm may be sinus, but may also be atrial fibrillation or atrial flutter. Inverted P waves in the inferior leads suggest an absent or nonfunctional sinus node, as may be seen with a sinus venosus defect.

1. **Secundum ASD**
   - **(a)** RSR' pattern in lead V_1
   - **(b)** QRS duration < 0.11 seconds (incomplete right bundle branch block)
   - **(c)** Right-axis deviation
   - **(d)** RV hypertrophy
   - **(e)** First-degree AV block (20%)
   - **(f)** RA enlargement (about 50%) with a prominent P wave in lead II
2. **Primum ASD**
   - **(a)** RSR' pattern in lead V_1
   - **(b)** Left-axis deviation
   - **(c)** First-degree AV block, classically seen with right bundle branch block and left anterior fascicular block

B. Chest radiography may reveal cardiomegaly due to right heart enlargement. With large left-to-right shunts, the central pulmonary arteries and vascular markings may appear prominent. In the setting of advanced pulmonary vascular disease, however, the pulmonary arteries may appear large but have oligemic peripheral lung fields, so-called vascular pruning.

V. DIAGNOSTIC STUDIES

A. Echocardiography is the primary means by which an ASD is diagnosed. TTE can document the size of the defect as well as the direction of the shunt flow and occasionally the location of the pulmonary veins in the younger patient. In the adult, transesophageal studies are generally required for a full anatomic assessment. An ASD should be suspected when right-sided chamber enlargement is noted on echocardiography and no other cause is identified.

1. Typical transthoracic views for imaging an ASD include the parasternal short-axis view, the apical four-chamber view, and the subcostal coronal and sagittal views. Findings include RA and RV enlargement, which indicate a functionally important defect. An estimate of RV pressure should be made via the jet of tricuspid insufficiency, and evidence for RV pressure and volume overload should be noted via observation of septal motion in systole and diastole, respectively. Evidence of left-to-right (or right-to-left) shunting across the defect should be demonstrated using color Doppler techniques. Evidence of RA and RV enlargement in the absence of an obvious cause on echocardiography, such as tricuspid regurgitation or an ASD, should prompt a search for a sinus venosus defect and/or partial anomalous pulmonary venous drainage. Intravenous contrast (i.e., agitated saline) and TTE can identify a shunt, but TEE is usually required to demonstrate a sinus venosus defect. Of note, in isolated partial anomalous pulmonary venous return, the intravenous contrast study will be negative.
2. TEE is usually required in the adult patient for further anatomic definition and to determine whether the defect is amenable to percutaneous closure. Contrast studies with agitated saline are helpful in confirming the presence and location of atrial shunting. The midesophageal four-chamber and bicaval views are preferred, with injection of agitated saline through an upper extremity vein. Injection into the left arm may be particularly helpful to establish the presence of a

persistent left SVC that drains into the coronary sinus or directly into the left atrium. In the diagnosis of a sinus venosus defect, care must be taken to evaluate the location of the pulmonary veins for evidence of anomalous drainage.

B. Cardiac catheterization is typically not required for diagnostic purposes except to assess pulmonary pressures and resistance, to assess for coronary artery disease before planned surgical closure in the adult patient, or as part of a planned transcatheter device closure. Right heart catheterization can be performed in most cases using a standard end-hole catheter. The lateral camera is helpful in directing the catheter posterior before advancing across the ASD. Our standard is to perform a complete right heart catheterization, including oximetry measurements and hemodynamic assessment.

1. Oximetry samples obtained during catheterization demonstrate a step-up within the right atrium due to shunting across the defect. Careful interrogation of innominate vein saturation and SVC saturation is important to exclude a step-up at the SVC level that would support the existence of associated partial anomalous pulmonary venous drainage. Desaturation in the left atrium systemically confirms right-to-left shunting and should prompt further investigation of RV and pulmonary artery pressures. Other diagnoses producing a similar picture include large ventricular septal defects with tricuspid regurgitation, partial or complete AV canal defects, or systemic arteriovenous fistulas.

   The significance of the defect can be assessed by calculating the **shunt fraction (Q_p/Q_s)**, which is the ratio of pulmonary blood flow (Q_p) to systemic blood flow (Q_s). Oximetry values, obtained during right heart catheterization and used previously to determine if a step-up is present, can be helpful for shunt calculation as follows:

$$Q_p/Q_s = \frac{\text{aortic saturation} - \text{mixed venous saturation}}{\text{pulmonary vein saturation} - \text{pulmonary artery saturation}}$$

   The mixed venous saturation is obtained in the setting of an ASD by multiplying the SVC saturation by 3, adding the IVC saturation, and then dividing the sum by 4. If the pulmonary vein saturation is not directly measured, it can be assumed in the absence of considerable lung disease to be 95%.

2. Hemodynamic assessment may reveal modest elevations in RV and pulmonary artery pressures. An important assessment is comparison of pulmonary artery pressure with systemic pressure and measurement of pulmonary vascular resistance. If pulmonary pressures are elevated, the response to oxygen or other vasodilators should be assessed. Alternatively, the ASD can be balloon occluded with assessment of hemodynamics to ensure that closure is safe. Examples of the usual catheterization findings with and without pulmonary vascular disease are illustrated in Figure 29.2.

   Using a derivative of Ohm's law, $P = Q \times R$, an ASD will increase the flow (Q) to the lungs, and, therefore, increase the pulmonary pressure (P) without a significant change in resistance (R). Findings that may preclude eventual ASD closure include one or more of the following: pulmonary vascular resistance more than one-half of the systemic vascular resistance or an indexed pulmonary vascular resistance > 7 Wood units/m^2.

3. Angiography is typically not necessary for diagnostic purposes. Some transcatheter closure device protocols include angiography, typically performed in the right pulmonary vein or levophase from a main pulmonary artery injection in the left anterior oblique and cranial projections. This may be an important way to confirm the absence of additional defects, such as partial anomalous pulmonary venous drainage, before proceeding with transcatheter device closure.

C. Cardiac MRI can be helpful, as it can provide additional information beyond echocardiography. MRI provides an excellent assessment of RV size and function,

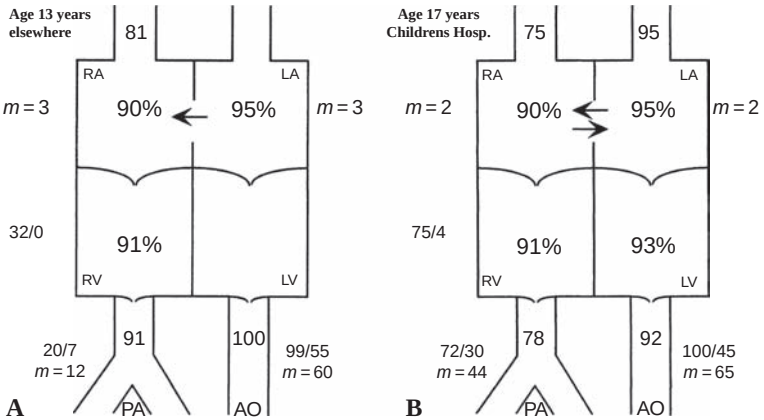

FIGURE 29.2 Catheterization data derived from two studies of the same female patient. The data obtained at age 13 (A) were interpreted as compatible with a small atrial septal defect of insufficient size to require closure. Some years later, she had developed pulmonary vascular obstructive disease (B) and was no longer shunting enough to recommend surgery. Death occurred 5 years later. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; numeric values within the schematic, oxygen saturation (%); numeric values outside the schematic, pressure (mm Hg). Adapted from Fyler DC, ed. *Nadas Pediatric Cardiology*. Philadelphia, PA: Hanley & Belfus; 1992.

especially if views obtained with echocardiography are not diagnostic. MRI is also excellent at determining the location of the pulmonary veins as well as calculating ventricular volumes and shunt fraction.

VI. TREATMENT. Medical intervention is typically not required preoperatively, because many patients are asymptomatic. Congestive symptoms may be improved with standard diuretic therapy. Rhythm disturbances such as atrial fibrillation require attention with respect to rate control and anticoagulation. Endocarditis antibiotic prophylaxis during dental procedures is not required in the setting of an isolated ASD before surgery, but it is warranted for 6 months after surgical or device closure (AHA/ACC class IIa).

A. Surgical or transcatheter therapy. The mainstay of therapy is closure of the defect by surgical or transcatheter techniques. Because of the reduced life expectancy associated with an unrepaired ASD, closure is recommended at diagnosis if there is evidence of a hemodynamically significant shunt ($Q_p/Q_s \geq 1.5{:}1$), evidence of right heart dilation, and evidence of probable paradoxical embolism or associated symptoms. In the setting of pulmonary hypertension, pulmonary reactivity to vasodilators should be documented and a net left-to-right shunt demonstrated during catheterization before consideration for closure. Alternatively, the defect can be temporarily balloon occluded at the time of catheterization, and the hemodynamic effects are directly measured. Situations in which ASD closure should not be pursued are listed in Table 29.1 and include advanced pulmonary hypertension (Eisenmenger syndrome) and severe LV dysfunction with elevated LA pressure.

B. Primary surgical closure has been the standard approach for many years. Generally, surgical closure is the treatment of choice for ostium primum and sinus venosus defects. Patients with secundum ASDs and anatomy that is not amenable to percutaneous closure (ASD diameter > 35 mm; inadequate septal rims to permit device deployment; or close proximity to AV valves, coronary sinus, or venae cavae) are

TABLE 29.1 Conditions Where Atrial Septal Defect Closure Is Not Favored

Defect is too small to be hemodynamically significant
Pulmonary hypertension is too advanced
Severe LV dysfunction, where ASD is acting as a "pop-off" valve for the left ventricle
In most cases where ASD is diagnosed in pregnancy, closure can be postponed until 6 months after delivery

ASD, atrial septal defect; LV, left ventricular.

also candidates for open surgical closure. Depending on the defect size and location, the secundum ASD can be closed by primary suture or, if needed, by the use of an autologous pericardial or synthetic patch. Ostium primum defects require patch closure as well as repair of the likely cleft mitral valve. Repair of sinus venosus defects is technically more challenging, as the pulmonary veins often have anomalous drainage and require rerouting.

1. Important preoperative risk factors include older age at operation, presence of atrial fibrillation, and elevated pulmonary pressure and resistance.
2. Postoperatively, patients are at risk for heart block, which is a significant complication in these cases. They are also at risk for postpericardiotomy syndrome, more so than after other surgery for congenital defects. Atrial arrhythmias may persist in short-term and long-term follow-ups because the RA and RV sizes may take time to return to normal, so anticoagulation is often recommended for several months after surgery. In some centers, prophylactic β-adrenergic blockade is advocated empirically for 3 to 6 months after surgery.

C. Transcatheter closure of a secundum ASD has become an attractive alternative to surgical closure and is now considered the treatment of choice. Any patient with an isolated secundum ASD may be suitable for transcatheter closure, which is generally assisted with TEE or intracardiac echocardiography in addition to fluoroscopy. Catheter closure decreases hospital length of stay, avoids surgical wounds and their possible complications, and significantly speeds up postprocedure recovery. With the devices available today, defects with a resting diameter of < 35 mm may be considered. In general, the gently stretched diameter of the defect is approximately 6 to 8 mm greater than the resting diameter. The defect must be located centrally with adequate room for the device to be positioned, without interference of other intracardiac structures such as the AV valves, coronary sinus, or pulmonary veins. The US Food and Drug Administration (FDA) has approved two devices for the closure of secundum ASDs: the Amplatzer Septal Occluder (AGA Medical Corporation, Golden Valley, MN) approved in December 2001 and the Helex Septal Occluder (WL Gore & Associates, Flagstaff, AZ) approved in August 2006. Studies have proved the safety and efficacy of catheter-based closure of a secundum ASD compared with surgical closure. The Amplatzer device consists of two disks made of Nitinol wire mesh filled with polyester fabric and separated by a narrower waist, which is appropriately fitted by balloon sizing. It is inserted percutaneously through a 6F to 12F sheath, depending on the device size required. The Helex device is also disklike and consists of expanded polytetrafluoroethylene (ePTFE) patch material supported by a single Nitinol wire frame. Major complications, such as cardiac perforation or device embolization, occur very rarely (generally fewer than 1% of cases), and successful closure of the defect is achieved in up to 95% of all patients. After closure, antiplatelet therapy, frequently aspirin and clopidogrel, is prescribed for a minimum of 6 months, after which time the device is generally believed to have endothelialized.

VII. PROGNOSIS. Hemodynamically significant ASDs are associated with increased morbidity and mortality. Long-term outcomes can be improved by closing these defects, especially if performed early in life. Atrial arrhythmias are common, especially in older patients, and are the result of long-standing atrial stretch. Arrhythmias, particularly atrial flutter and fibrillation, contribute to a significant portion of the morbidity and mortality of older patients, particularly the risk of systemic embolization and the resultant stroke. It has been demonstrated that age at the time of surgical repair is inversely related to the risk of subsequent atrial fibrillation or flutter after repair and argues for earlier closure. Some have advocated for consideration of a concomitant ablation procedure in high-risk patients, but the available data do not generally support this.

The functional capacity of patients frequently improves after closure of the ASD, and often they do not realize how severely their functional capacity had been affected until after the defect is closed. In addition, improvements in LV filling and systemic cardiac output are seen rapidly after defect closure. Reduced RA and RV volumes can be seen within 24 hours and continue to improve over the course of the first year following closure.

PFO AND ATRIAL SEPTAL ANEURYSM

I. PATHOPHYSIOLOGY. PFO can result in transient right-to-left shunting of blood flow, usually when RA pressure exceeds LA pressure such as during coughing or straining. These defects generally do not cause significant hemodynamic derangements. The clinical importance of an atrial septal aneurysm or a PFO is its impact on the risk of stroke. PFO features that increase the risk of a paradoxical embolus include large tunnel lengths (≥ 4 mm), high mobility of the valve of the foramen ovale, a well-formed eustachian valve, and a resting right-to-left shunt.

II. CLINICAL MANIFESTATIONS. Generally these defects are asymptomatic, most often coming to attention in patients with cryptogenic (unexplained) stroke. PFO is more common in patients with cryptogenic stroke than in the general population, but PFO alone has not been shown to be an independent risk factor for cryptogenic stroke. There are now accumulating data to suggest that an isolated PFO is not associated with an increased risk of recurrent ischemic stroke. The data in patients with both a PFO and an ASD are conflicting but suggest increased risk of recurrent stroke when both lesions are present. PFO should be suspected in young patients who sustain a stroke, as more than one-half of stroke patients younger than 45 years have a PFO. Other less common clinical associations with PFO include migraine headaches, platypnea–orthodeoxia syndrome, and decompression illness in divers and those who work in high altitudes.

III. DIAGNOSTIC STUDIES. **Echocardiography** can easily differentiate between an ASD and a PFO if the interatrial septum is well visualized. If this is not possible via a transthoracic approach, a TEE may be necessary. A simple way to determine if a shunt is present is the "**bubble study**," which is the injection of agitated saline via an upper extremity vein. If shunting is not present at rest, the patient can perform a Valsalva maneuver, which augments right-to-left shunt. If bubbles can be seen in the left atrium or the left ventricle within three cardiac cycles on TTE, the diagnosis of an interatrial right-to-left shunt is established. Generally, administration of agitated saline in patients with suspected right-to-left shunts is considered safe, but there have been rare case reports of cerebral ischemic events from passage of bubbles into the systemic circulation.

TEE will likely be required in most adults for better visualization of the interatrial septum. TEE helps to differentiate between a PFO and a secundum ASD, both of which can have positive bubble studies. TEE also allows assessment of other potential sources of emboli, such as atheroma in the aortic arch, thrombus in the LA appendage, or cardiac tumors.

TABLE 29.2 Contraindications to Percutaneous Patent Foramen Ovale Closure

Presence of an alternative source of emboli
Severe pulmonary hypertension
Recent gastrointestinal bleeding
Presence of congenital heart defect that needs surgical repair
Documented hypercoaguable state
Hypersensitivity or contraindication to antiplatelet or anticoagulant therapy
Unexplained fever or infection

IV. TREATMENT. Unfortunately, there is no clear consensus on primary or secondary prevention measures for patients found to have a PFO or atrial septal aneurysm. In general, atrial septal abnormalities are not treated for primary prevention of stroke. Regarding secondary prevention, most patients with neurologic events are treated with antiplatelet agents (either aspirin or a thienopyridine, or both), anticoagulants (warfarin), and percutaneous or surgical closure, although no clear consensus exists and the only randomized controlled study reporting results to date failed to demonstrate a benefit of closure over medical therapy. The CLOSURE I trial (reported at AHA 2010) examined the role of PFO closure for first time stroke/TIA and found no difference in the composite primary end point of stroke or TIA at 2 years, all-cause 30-day mortality, and neurologic mortality between 31 days and 2 years, with closure compared with aspirin, warfarin, or both. There are several other ongoing trials that are comparing percutaneous PFO closure with medical therapy. These include the CLOSE trial, the PC-Trial, the RESPECT trial, and the REDUCE trial. In general, device closure should be mainly performed in patients with recurrent cryptogenic stroke despite aggressive medical therapy. The same devices utilized for ASD closure are generally used to percutaneously close PFO. Contraindications to percutaneous closure are noted in Table 29.2.

Primary surgical closure of PFO is generally not pursued, unless the patient needs concomitant surgery for other conditions. Indiscriminant repair of PFO incidentally found at surgery may actually increase short-term stroke risk and should therefore be avoided.

There is a dearth of data to support PFO closure in patients with migraine headaches. The MIST (Migraine Intervention with STARFlex Technology) trial randomized 147 participants with severe migraine headaches and right-to-left shunt consistent with PFO to either percutaneous closure or sham procedure. After 6 months, there was no statistically significant difference in the primary end point of complete cessation of migraine headache or in a host of secondary end points including change in severity, quality, and frequency of headache as well as quality of life. As such, device closure should only be performed in migraine patients who are part of a randomized clinical study.

Patients with platypnea–orthodeoxia syndrome (acute arterial desaturation with change in position from supine to upright) should be considered for closure, as oxygen saturation generally improves with successful elimination of the right-to-left shunt.

ACKNOWLEDGMENTS: *The authors would like to gratefully acknowledge the contributions of Kellan Ashley, Niranjan Seshadri, and J. Donald Moore to previous editions of this manuscript.*

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CHAPTER 30

Christopher H. May

Ventricular Septal Defect

I. Introduction

A. Ventricular septal defect (VSD) is one of the most common congenital heart defects in both children and adults. The prevalence in neonates has been reported to be as high as 5% when screened with color Doppler echocardiography, although most of these are miniscule defects that close spontaneously within the first year. Thus the true prevalence is difficult to ascertain, given that many defects close spontaneously

and patients are frequently asymptomatic with smaller lesions. VSDs are frequently associated with other congenital defects, particularly infundibular stenosis or valvar pulmonary stenosis. Isolated VSDs account for about 20% to 25% of all congenital heart defects in childhood. Unlike many other congenital abnormalities, males and females appear to be affected equally.

B. Isolated VSDs are found in approximately 10% of adult patients with congenital heart disease. This reflects the natural tendency for spontaneous closure during infancy and an improved ability to confirm the diagnosis in childhood, which leads to surgical closure.

C. Natural history

1. **Spontaneous closure** occurs most commonly with smaller, restrictive VSDs, usually before the age of 2 years. In general, nearly 35% of perimembranous defects close spontaneously and 75% to 80% of all small VSDs close spontaneously by 10 years of age. These higher rates of spontaneous closure in more recent series are a reflection of the ability to diagnose much smaller defects with more contemporary echocardiographic modalities. Large and nonrestrictive defects have significantly lower spontaneous closure rates (approximately 10% to 15%); malalignment defects rarely close spontaneously. Defects close by two mechanisms: (1) by muscular septum growth and (2) by "aneurysmal tissue" from a septal leaflet of the tricuspid valve as in the case of perimembranous defects. For VSDs that persist, a restrictive nature can protect the patient from pulmonary vascular injury given the flow-limiting nature of these defects.
2. **Endocarditis** is a risk because of the presence of a high-velocity, turbulent jet into the right ventricle. Endocarditis most frequently involves the septal leaflet of the tricuspid valve apparatus at the point of jet impact. The risk of endocarditis is roughly 4% to 10% for the first 30 years of life. Muscular VSDs have a lower incidence of endocarditis, as the jet is attenuated prior to reaching the tricuspid valve.
3. A large VSD during childhood is typically associated with significant **left-to-right shunt** and eventual development of congestive heart failure. Children with very large defects usually present during infancy or early childhood with signs and symptoms of heart failure and pulmonary hypertension. Patients with moderate-sized VSDs can survive to adulthood before detection. Given the gradual development of symptoms in these patients, they may not present until late in the disease course. In these patients, the excess right-sided flow may lead to pulmonary vascular disease and Eisenmenger physiology if left untreated. As pulmonary vascular resistance increases, the left-to-right shunt changes to a right-to-left flow. The VSD murmur disappears during this transition and is often replaced by the murmur of tricuspid regurgitation. After Eisenmenger physiology has developed, patients rarely survive beyond the fourth decade. Complications in patients with Eisenmenger syndrome include pulmonary hemorrhage, endocarditis, cerebral abscess (from hypoxemia), ventricular arrhythmias, and the complications associated with erythrocytosis. Poor prognostic factors in this population include syncope, congestive failure, and hemoptysis.
4. Risk factors for decreased survival include cardiomegaly seen on the chest radiograph; elevated pulmonary artery systolic pressure (> 60 mm Hg and/or more than one-half of the systemic pressure); cardiovascular symptoms such as shortness of breath, fatigue, or dyspnea on exertion; and progressive aortic insufficiency. Good prognostic factors include normal left ventricular (LV) size and function, small left-to-right shunt, normal pulmonary pressures or resistance, an intact vasodilator response in the pulmonary vasculature, and a lack of symptoms.
5. Genetic factors play a significant role in this disease, as in other forms of congenital heart disease. Having an affected father increases the risk of VSD in

the offspring to 2%; moreover, an affected mother appears to confer an even higher risk of recurrence in offspring—as high as 6% to 10%. In general, VSDs arise due to a combination of polygenic, multifactorial abnormalities. However, several monogenetic abnormalities leading to VSDs such as mutations in the transcription factors TBX5 and GATA4 have recently been described.

II. ANATOMY

A. Embryology. Partitioning of the ventricular mass begins as a muscular ridge in the floor of the ventricle near the apex. This ridge later undergoes active growth, which forms the muscular ventricular septum. Concomitantly, the endocardial cushions fuse and the two regions meet, completing closure of the interventricular foramen. Figure 30.1 shows anatomic localization of VSDs.

B. Defect size. The consequences of a VSD depend on the size of the defect and the pulmonary and systemic vascular resistances. Smaller defects provide higher resistance to flow and will have little impact on right-sided flow. **The VSD is** described as **small** when the defect size is **less than one-third of the size of the aortic root, moderate** when the defect size is **less than one-half of the size of the aortic root,** and **large** when the defect size is equal to or **larger than the size of the aortic root.** However, other indirect measures, including clinical signs and symptoms and echocardiographic features, must be taken into consideration when determining the size and clinical significance of a VSD. VSD size is often classified on the basis of its hemodynamic consequences:

1. **Restrictive** VSDs result in a significant pressure gradient between the left and right ventricles (e.g., pulmonary/aortic systolic pressure ratio < 0.3) and are associated with a small shunt ($Q_p/Q_s \leq 1.4{:}1$).
2. **Moderately restrictive** VSDs produce an intermediate interventricular gradient and result in a moderate shunt ($Q_p/Q_s = 1.4$ to $2.2{:}1$).
3. **Nonrestrictive** VSDs are usually larger than 1 cm^2 and are associated with a large shunt ($Q_p/Q_s > 2.2{:}1$). The pressures in the left ventricle and right ventricle will eventually approach equalization, and the amount of flow across the defect will be determined by the ratio of pulmonary-to-systemic vascular resistance.

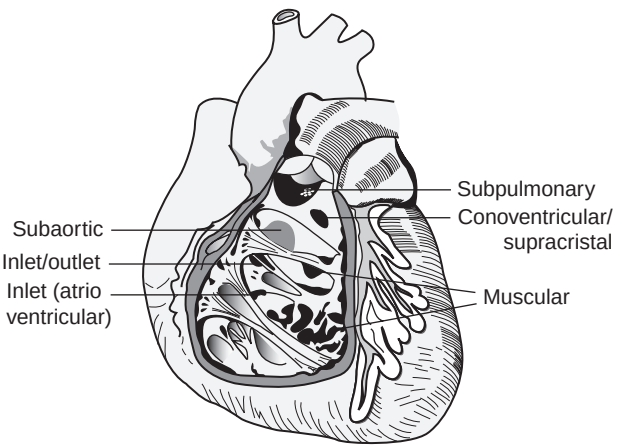

FIGURE 30.1 Anatomic localization of ventricular septal defects.

C. VSD types

1. **Membranous** defects are the most common type, accounting for approximately **70% to 80% of VSDs**. The membranous septum is the area under the aortic valve on the left side and next to the septal leaflet of the tricuspid valve on the right side. Most of these defects extend into the infundibular region and are then referred to as perimembranous. **Membranous defects** are less likely to be associated with additional intracardiac defects and **have a high rate of spontaneous closure**. However, when there is malalignment of the defect, spontaneous closure is unlikely.
2. **Muscular** defects account for approximately 5% to 20% of VSDs and can be single or multiple (i.e., Swiss cheese septum). These defects, when single, also have a high spontaneous closure rate.
3. **Inlet or atrioventricular (AV) canal–type** defects account for approximately 5% to 8% of cases. These defects rarely close spontaneously, are usually large, and are associated with abnormalities of the AV valves. These abnormalities range from cleft mitral and tricuspid valves to the common AV valve, as seen in complete AV canal defect. This type of defect in the inlet ventricular septum is commonly seen in patients with Down syndrome (Trisomy 21).
4. **Supracristal or subaortic** defects account for approximately 5% to 7% of cases and are located immediately beneath the pulmonary and aortic valves. These defects vary in size but are often small. Because of their **proximity to the aortic valve, aortic leaflet tissue can invaginate and result in their closure, with the unfortunate result of significant aortic regurgitation**.

D. Associated lesions. Approximately 20% of VSDs are associated with many other forms of congenital heart disease, including aortic coarctation, bicuspid aortic valve, and patent ductus arteriosus. Of patients who present with a VSD, 5% to 10% will develop aortic regurgitation because of poor support of the right coronary cusp and the Venturi effect caused by the VSD jet, resulting in prolapse of one of the aortic valve leaflets. Discrete, fibrous subaortic stenosis and right ventricular (RV) outflow tract obstruction are less common associations. Less than 10% develop subvalvular pulmonary stenosis or an obstructive muscle bundle referred to as a double-chamber right ventricle. VSD is also associated with transposition of the great arteries, tetralogy of Fallot, and Trisomies 13, 18, and 21.

III. CLINICAL PRESENTATION.

Adult presentation occurs most frequently in small, restrictive VSDs and occasionally occurs in patients with moderate lesions and associated pulmonary hypertension or with Eisenmenger syndrome in large, unoperated lesions.

A. Symptoms. The most common symptoms in adult patients with hemodynamically significant VSD are dyspnea on exertion and exercise intolerance. The symptoms are related to the degree and chronicity of left-to-right shunt and the resultant increase in pulmonary pressure and resistance.

B. Physical findings. The auscultatory findings classically include a holosystolic murmur of varying intensity. Smaller muscular defects may produce a high-frequency early systolic murmur that ends before the second heart sound (S_2) because of closure from muscular contraction of the septum. The pitch of the murmur can be a clue to the size and nature of the defect. Smaller and more restrictive defects produce higher pitched and louder murmurs that may be associated with a palpable thrill. Another important feature is the intensity of the pulmonary component of S_2, which if increased suggests increased pulmonary pressure. An RV heave may be appreciated in patients with RV volume overload. A diastolic flow rumble at the apex may be heard in large left-to-right shunts due to increased flow across an otherwise normal mitral valve. Depending on associated lesions, other findings may be present such as a diastolic murmur of aortic insufficiency that may occur with

subaortic defects. A prominent systolic ejection murmur at the left upper sternal border suggests subvalvular pulmonic stenosis or double-chamber right ventricle. As pulmonary hypertension and right-to-left shunting develop, other signs including cyanosis, elevated jugular venous pressure, enlarged and pulsatile liver, clubbing, and a decrease in murmur intensity may occur. A systolic murmur in this setting often reflects concomitant tricuspid insufficiency. Notably, the murmur of a large VSD is often less harsh and more blowing in nature than that of a small VSD because of the absence of a significant pressure gradient across the larger defect which results in less turbulent flow.

C. The **differential diagnosis** on examination includes tricuspid regurgitation, acyanotic tetralogy of Fallot with a pulmonary outflow murmur, isolated subvalvular pulmonic stenosis, and hypertrophic cardiomyopathy.

IV. LABORATORY TESTS

A. The **electrocardiogram (ECG)** may be unremarkable with small defects or reveal left atrial and LV enlargement in patients with larger defects. An inlet or AV canal defect can be diagnosed from the ECG based on the presence of marked left-axis deviation. Right-axis deviation suggests elevated RV and pulmonary artery pressure. After surgical repair, right bundle branch block may occur.

B. A **chest radiograph** is often helpful in determining the degree of left-to-right shunt. A small-sized or normal-sized heart with normal pulmonary vascular markings on the chest radiograph suggests a hemodynamically insignificant lesion, whereas cardiomegaly and left atrial and LV enlargement are seen with large left-to-right shunts. A large defect associated with a small heart and oligemic lung fields should raise the suspicion of pulmonary vascular disease.

V. DIAGNOSTIC TESTING

A. **Echocardiography** is the diagnostic modality of choice for VSDs and associated lesions. Transthoracic echocardiographic imaging is almost always sufficient in the child and young adult, but transesophageal echocardiographic imaging may be required in some older adult patients. Defect size and location should be defined using two-dimensional and color Doppler techniques. Complete scans of the ventricular septum should be made to rule out additional defects. Optimal images are usually obtained from the parasternal long-axis and short-axis views and the apical four-chamber view; other views may fail to visualize the VSD jet, owing to perpendicular alignment of the echocardiographic probe and the jet. In the younger patient, subcostal coronal and sagittal views may also be helpful. Measurements of left atrial and LV size are key to determining the amount of volume load and magnitude of the left-to-right shunt. Echocardiographic features of pulmonary hypertension are helpful in confirming the impending reversal of shunt. Quantification of shunt velocity provides an estimate of the restrictive nature of the defect. Higher velocities indicate a more restrictive defect, reducing the likelihood that the patient has experienced pulmonary vascular insult. Systemic blood pressure should be noted when the velocity across the VSD is measured. Assuming no LV outflow obstruction, RV pressure can then be estimated based on the gradient across the VSD. This pressure can also be estimated if tricuspid insufficiency exists. A **perimembranous VSD** can be associated with a **ventricular septal aneurysm formed by the septal leaflet of the tricuspid valve bowing into the defect**. Similarly, supracristal VSDs are associated with aortic insufficiency caused by prolapse of the right or left coronary cusps into the VSD. A complete evaluation is always indicated to exclude other associated findings such as aortic coarctation, atrial septal defect, patent ductus arteriosus, and RV or LV outflow tract obstruction.

B. Catheterization is seldom needed in the management of isolated VSD in the infant or child. Surgical correction, when indicated, proceeds in most cases based on echocardiographic evaluation. In the adult, catheterization should be considered if anatomic questions remain despite transthoracic and transesophageal echocardiography or if pulmonary hypertension is suspected based on these studies. Hemodynamic assessment should include quantification of cardiac index and careful oximetric definition of the shunt level and quantity. A step-up in saturation measured at the pulmonary artery level confirms persistent left-to-right shunt across the defect and should correlate with acceptable pulmonary artery pressures and resistance. Evidence of low pulmonary artery saturations is expected with elevations of pulmonary resistance. Simultaneous comparison of RV pressure with systemic pressure is mandatory in these cases, along with the documentation of changes in response to oxygen or nitric oxide administration. Left ventriculography performed with **left anterior–oblique and cranial angulation** demonstrates the defect in most cases. If an inlet-type defect is present, the hepatoclavicular view (about 40° left anterior–oblique and 40° cranial) is usually adequate. Right ventriculography does not adequately opacify the left ventricle unless there is suprasystemic RV pressure. Coronary angiography should be performed when patients are felt to be at risk for coronary artery disease and likely to require operative intervention. Aortography can be helpful in eliminating the possibility of an associated ductus arteriosus or coarctation of the aorta.

C. Cardiac **computed tomography** (CT) can be used to assess VSD anatomy in patients with suboptimal echocardiographic images, but unlike magnetic resonance imaging (MRI), CT does not provide added information about shunt fraction (see Chapter 52) and carries additional risk associated with radiation and intravenous contrast administration.

D. MRI, using spin–echo and velocity-encoded cine sequences, can also be used to delineate VSD location and shunt fraction. MRI is particularly helpful in patients with associated complex lesions and those with inadequate echocardiographic images (see Chapter 51).

VI. THERAPY. Factors supporting intervention include cardiomegaly on the chest radiograph, significant left-to-right shunt (pulmonary-to-systemic flow ratios > 1.5:1), elevated but responsive pulmonary vascular resistance, symptoms of congestive failure or associated lesions such as aortic insufficiency, RV or LV outflow tract obstruction, and recurrent endocarditis. Management of VSD after myocardial infarction is discussed separately in Chapter 3.

A. Medical management in symptomatic cases without Eisenmenger physiology involves anticongestive measures such as the use of diuretics and digoxin. Efforts should then be focused on addressing suitability for surgical closure. Endocarditis is a recognized complication of VSD. In the patient with culture-proven endocarditis, 4 to 6 weeks of antibiotics should be administered parenterally before consideration of intervention. This must be tailored to the individual patient's clinical status and the infective organism's identification and sensitivity as well as the presence of concomitant valvular lesions and prosthetic material. For patients who have developed elevated pulmonary vascular resistance, selective pulmonary vasodilators, including phosphodiesterase-5 inhibitors, prostacyclin analogs, and endothelin receptor antagonists, may improve hemodynamics and exercise tolerance (see Chapter 32).

B. Transcatheter device closure of VSDs is being performed on an investigational or compassionate-use basis in selected medical centers. The Amplatzer Muscular VSD Occluder is FDA approved and can technically close many muscular defects. Perimembranous defects, however, pose particular problems for transcatheter closure given their close proximity to the conduction system and the AV and semilunar valves, although recent data from the investigational Amplatzer Membraneous

VSD Occluder are promising. Although long-term data from these devices are lacking, recent studies show that the rate of complete closure for the Amplatzer membranous device at 6 months is 96% and is 100% for the muscular occluder at 3 to 96 months follow-up. Complications with these devices include early or late-onset complete heart block, arrhythmia, tricuspid valve damage resulting in stenosis or regurgitation, and mechanical device failure during deployment. Transcatheter closure of VSDs after ventricular septal rupture in the setting of myocardial infarction has also been performed in selected individuals who are considered high-risk surgical candidates. Surgery, however, is still the preferred treatment modality in this setting.

C. **Surgical closure** continues to be the primary means of defect repair. Outcomes after VSD closure are good in children, with low mortality rates of 2% to 3%. Repair of VSDs in patients with evidence of increased pulmonary artery pressure is generally performed before the age of 2 years and, in many centers, in the first year of life. Surgical closure in the symptomatic adult appears to be well tolerated, with acceptable mortality and improved functional status. Irreversible pulmonary vascular disease with Eisenmenger physiology, however, is a general contraindication for surgical closure because right heart failure will often develop thereafter. Pulmonary artery banding (performed to limit pulmonary blood flow) was more frequently done in the past and is now reserved for the few patients who are very small, have lung disease, or who have complex, multiple VSDs. Postoperative sequelae include residual patch leaks, as well as supraventricular and ventricular arrhythmias. More recent studies have shown the presence of a residual shunt following surgical closure in 5% to 31% of patients depending on the type of VSD that was repaired. Recent data suggest that postsurgical residual VSDs < 2 mm close spontaneously within 1 year in the majority (83%) of patients.

D. In children for whom transcatheter and surgical approaches are technically difficult or particularly high risk, a **hybrid approach** has been explored. In these patients, a sternotomy is performed, and the device is placed through the anterior wall of the right ventricle under fluoroscopic and echocardiographic guidance.

E. According to the American Heart Association (AHA) guidelines, **antibiotic prophylaxis** is recommended in three situations in relation to congenital heart disease: (1) unrepaired cyanotic defect (i.e., VSD with right-to-left shunt), (2) repaired defect (i.e., VSD) with prosthetic material/device for the first 6 months, and (3) repaired defect (i.e., VSD) with residual defect at the site of a prosthetic patch/device. In addition, excellent oral hygiene and regular dental examinations are an important component in reducing the risk of developing infective endocarditis.

F. **Eisenmenger syndrome** is usually referred to in the context of ***irreversible pulmonary hypertension from long-standing exposure of the pulmonary vasculature to left-to-right shunting*** across a VSD. However, this physiology can occur as a result of any left-to-right shunt, including patent ductus arteriosus and, less commonly, isolated atrial septal defect. As a result of the elevated pulmonary pressures, the direction of shunting is reversed across the defect, producing systemic cyanosis and its associated complications. As described above, newer agents aimed at decreasing resistance in the pulmonary vasculature may be beneficial in these patients. **Pregnancy is poorly tolerated and is contraindicated in the presence of Eisenmenger syndrome** (see Chapter 38).

G. Long-term follow-up is required in patients whose VSDs were repaired later in life, since the majority of patients already have some degree of pulmonary hypertension, LV dysfunction, or both. Patients with residual shunt after repair, arrhythmias, or conduction blocks also require continued follow-up.

ACKNOWLEDGMENTS: *The author thanks Drs. J. Donald Moore, Matthew Hook, and Samuel Unzek for their contributions to earlier editions of this chapter.*

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CHAPTER 31

Adam S. Goldberg
Richard A. Krasuski

Patent Ductus Arteriosus and Coarctation of the Aorta

I. PATENT DUCTUS ARTERIOSUS—INTRODUCTION

A. The ductus arteriosus is a fetal communication between the descending aorta just distal to the left subclavian artery and the main pulmonary artery near its bifurcation. A patent ductus arteriosus (PDA) occurs when the ductus arteriosus fails to close and regress after birth to form the ligamentum arteriosum. PDA occurs in approximately 1 of 2,000 live births, but it is relatively uncommon among the adult population. In infants, it accounts for 10% to 12% of all congenital heart disease.

B. Natural history. The natural history depends on the size of the PDA, the direction of the shunt, and the development of any associated complications. At birth, 95% of patients with isolated PDA have left-to-right shunts and normal, or near-normal, pulmonary pressures. Patients with normal pulmonary artery pressures and no evidence of chronic left ventricular volume overload have a better prognosis. If untreated, life expectancy of patients with PDA is shortened; one-third of patients with PDA die by the age of 40 and almost two-thirds die by the age of 60. With a PDA, **congestive heart failure (CHF) can occur** because of chronic left heart volume overload. In patients with death related to PDA, CHF is the most common cause. Development of right-to-left shunting is also an ominous sign because it reflects the development of advanced pulmonary vascular disease and associated elevation in right-sided cardiac pressures (see Chapter 32 for discussion on Eisenmenger's syndrome).

C. Risk factors. Factors that increase risk for PDA include maternal rubella infection, birth at high altitude, premature birth, female sex, and genetic factors. In infants born at < 28 weeks of gestation, there is a 60% incidence of PDA. PDAs are twice as common in female infants as in male infants and in some instances have a genetic component. In a family in which one child has a PDA, there is approximately a 3% risk of having a PDA in subsequent offspring.

II. ANATOMY AND PATHOPHYSIOLOGY

A. Embryology. The ductus arteriosus is a **normal and essential component** of cardiovascular development that originates from the distal sixth left aortic arch. A PDA is most commonly funnel shaped with the larger aortic end (ampulla) distal to the left subclavian artery, then narrowing toward the pulmonary end, with insertion at the junction of the main and left pulmonary arteries. The Krichenko classification system describes the angiographic appearance of PDA (Table 31.1). In right-sided aortic arch, the anatomy of PDA can vary significantly: the PDA can arise from the left innominate artery and insert into the proximal left pulmonary artery or arise distal to the right subclavian artery with insertion into the proximal right pulmonary artery. Bilateral PDAs can also occur.

B. Fetal circulation. The presence of the ductus arteriosus in the fetal circulation is essential to allow **right-to-left shunting of nutrient-rich, oxygenated blood**

TABLE 31.1 Krichenko Classification of Patent Ductus Arteriosus Appearance on Angiography

Type A	Conical	Well-defined aortic ampulla and constriction near pulmonary insertion
Type B	Window	Short, with narrowing near aortic insertion
Type C	Tubular	Tubular duct without constrictions
Type D	Complex	Multiple constrictions
Type E	Elongated	Long PDA with conical appearance and multiple constrictions

PDA, patent ductus arteriosus.

from the placenta to the fetal systemic circulation, thereby bypassing the fetal pulmonary circuit. In the normal fetal circulation, oxygenated blood travels from the mother through the placenta to the fetus. The oxygen-rich blood traverses the fetal inferior vena cava, right atrium, right ventricle, and main pulmonary artery. The fetal pulmonary arteries are constricted and have high pulmonary vascular resistance. Oxygenated blood bypasses the fetal pulmonary circulation and enters through the ductus arteriosus to the lower resistance systemic circulation. Oxygenated blood then enters the fetal aorta distal to the left subclavian artery, perfuses the fetal systemic circulation, becomes deoxygenated, and returns to the maternal circulation. **In the fetus, the ductus arteriosus is kept open by low arterial oxygen content and placental prostaglandin E2 (PGE2).**

C. Birth. Several **changes occur at birth** to initiate normal functional **closure of the ductus arteriosus within the first 15 to 18 hours of life.** Spontaneous respirations result in increased blood oxygen content. Prostaglandin levels decrease because of placental ligation and increased metabolism of prostaglandins within the pulmonary circulation by prostaglandin dehydrogenase. The combination of increased oxygen content and lowered circulating prostaglandin levels usually results in closure of the ductus arteriosus. Generally, the ductus arteriosus is hemodynamically insignificant within 15 hours and completely closed by 2 to 3 weeks. The **fibrotic remnant** of this structure persists in the adult as the **ligamentum arteriosum. Spontaneous closure of a PDA is unlikely in term infants after 3 months and in preterm infants after 12 months.**

III. CLINICAL PRESENTATION

A. Symptoms. Severity of symptoms depends on the degree of left-to-right shunting; and it is determined by the size of the PDA, ductal resistance, cardiac output, as well as the systemic and pulmonary vascular resistances. PDA size is categorized by the degree of left-to-right shunting determined by the pulmonary-to-systemic flow ratio: Q_p:Q_s (Table 31.2). Between 25% and 40% of patients with PDA are asymptomatic, especially those with a small PDA. They are often diagnosed by auscultation

TABLE 31.2 Patent Ductus Arteriosus Size by Q_p:Q_s

Q_p:Q_s	Size
< 1.5	Small
1.5–2.2	Moderate
> 2.2	Large

of a continuous murmur on examination or incidentally during diagnostic testing. With larger PDAs, symptoms may develop. The most common symptom is exercise intolerance followed by dyspnea, peripheral edema, and palpitations. As is often the case in adult congenital heart disease, a previously well-tolerated PDA may become manifest in the setting of acquired heart disease such as ischemia, essential hypertension, and valvular disease.

B. Physical examination. Patients with PDAs may present with a wide range of physical findings. Pulse pressure may be wide because of diastolic runoff into the PDA, and peripheral pulses may be bounding. The jugular venous pressure is often normal with a small PDA, whereas with a large PDA, prominent *a* and *v* waves may be present. Precordial palpation often reveals a normal precordial impulse with a small PDA and a prominent left ventricular impulse with a large PDA. A **harsh, continuous murmur may be heard at the left first or second intercostal space**. The murmur envelops the second heart sound (S_2) and decreases in intensity during diastole. A small PDA has a soft, high-frequency, continuous murmur, whereas a large PDA classically has a machinerylike, loud murmur. With a large PDA, a middiastolic apical murmur may occur because of increased diastolic flow across the mitral valve. If **pulmonary hypertension** is present, a right ventricular lift may be present and the pulmonic component of S_2 will have increased intensity. The duration of the diastolic murmur reflects pulmonary artery pressures; elevated pulmonary artery pressures lead to a decreased gradient for left-to-right flow through the PDA during diastole, which results in a shorter diastolic murmur. As pulmonary pressure increases, the systolic component of the murmur shortens. Right-to-left flow may not generate a systolic murmur. For patients with a right-to-left shunt, a pathognomonic physical finding is **differential cyanosis of the lower extremities and left hand**.

C. Complications. The most common complications of PDA include **CHF, infective endocarditis**, and **pulmonary hypertension**. CHF occurs through volume overload of the left side of the heart and may be accompanied by **atrial fibrillation**. Vegetations generally develop on the pulmonary side of the PDA, and septic lung emboli may occur. Untreated PDAs with audible murmurs have a risk of infective endocarditis of 0.45%/y after the second decade. Spontaneously occurring **aneurysms of the ductus arteriosus** have been reported, although they are typically seen in association with endarteritis or among very young or very old patients. Pulmonary hypertension develops as a result of increased pulmonary vascular flow from a large PDA with significant left-to-right flow. Elevation in right-sided pressures may eventually result in Eisenmenger's physiology, right-to-left flow, and isolated cyanosis and clubbing of lower extremities (occurring in 5% of unrepaired PDA patients) with signs of pulmonary hypertension.

D. Differential diagnosis. The differential diagnosis of PDA includes ventricular septal defect associated with aortic insufficiency, aortopulmonary window, pulmonary atresia with systemic collateral vessels, innocent venous hum, and arteriovenous communications such as pulmonary arteriovenous fistula, coronary artery fistula, systemic arteriovenous fistula, and ruptured sinus of Valsalva aneurysm.

IV. LABORATORY TESTING

A. Hematology. Blood laboratory results are generally unremarkable, although compensatory erythrocytosis may be present in the setting of long-standing cyanosis resulting from a right-to-left shunt.

B. Electrocardiogram (ECG). ECG is neither sensitive nor specific for PDA. The ECG for a patient with a small PDA is often normal. Depending on the duration and hemodynamic significance of the PDA, electrocardiographic criteria for left atrial enlargement or left ventricular hypertrophy may be present. If pulmonary hypertension exists, the ECG may demonstrate right ventricular hypertrophy or right atrial enlargement.

C. Chest radiography (CXR). CXR is neither sensitive nor specific for PDA. A normal chest radiograph implies a small, hemodynamically insignificant PDA. With a large PDA, left atrial and left ventricular enlargement may be present, as well as increased pulmonary vascularity. With right-to-left shunting from pulmonary hypertension, the main pulmonary artery is frequently enlarged. The PDA occasionally appears as a separate convexity between the aortic knob and the pulmonary trunk. Calcification of the PDA may be visualized in older individuals.

V. DIAGNOSTIC TESTING. Standard transthoracic echocardiography (TTE) is the preferred initial diagnostic modality because of its low cost and noninvasive nature. Transesophageal echocardiography (TEE) may be required in subjects with suboptimal echocardiographic windows. Cardiac catheterization is typically reserved for therapeutic intervention.

A. TTE has a 42% sensitivity and 100% specificity for the diagnosis of PDA. The suprasternal notch view is usually best for demonstrating the PDA, particularly its aortic origin. The complete course of a PDA may be difficult to follow in some patients because of its tortuosity. Color Doppler imaging can often reveal flow between the descending aorta distal to the left subclavian artery and the pulmonary trunk. It is imperative to demonstrate color Doppler flow within the pulmonary artery, typically on a high parasternal short-axis view. Color Doppler and continuous wave Doppler help determine the direction of flow in the PDA. The timing of flow (systolic or diastolic) depends on pressure gradients between the systemic and pulmonary circulation. Quantitative assessment of shunt velocity is valuable to estimate the degree of restriction across the PDA. This measurement becomes important when planning transcatheter intervention. Diastolic aortic flow reversal is seen in the descending aorta if the shunt is significant. Associated left atrial and left ventricular enlargement also suggest a hemodynamically significant lesion.

B. TEE may be required if TTE windows are suboptimal or nondiagnostic. TTE and TEE have nearly 100% specificity for the diagnosis of PDA, but TEE has a much higher sensitivity (97%) than TTE (42%).

C. Cardiac catheterization is rarely needed for diagnostic purposes. Rarely, PDAs undiagnosed by physical examination or noninvasive testing may be diagnosed during left heart or right heart cardiac catheterization by recognizing the unexpected course of the catheter as it crosses the PDA by measuring a step-up in the oxygen saturation at the level of the left pulmonary artery or by documenting pulmonary opacification by descending aortography.

1. A PDA is best demonstrated by a **descending aortogram** performed in the **lateral projection** with a standard angiographic catheter positioned just below the ductal ampulla. If biplanar imaging is used, the right anterior–oblique cranial projection is sometimes helpful.
2. A PDA can be crossed from the main pulmonary artery or from the descending aorta, with the latter being easier and best guided by the lateral projection. Oximetric sampling typically demonstrates an increase in saturation in the main pulmonary artery compared with the right ventricle. Pulmonary artery and right ventricular pressures may be slightly elevated but typically remain below systemic levels. The etiology is usually pulmonary arterial vascular disease, but it can also be due to pulmonary venous stenosis, mitral stenosis, or left ventricular failure. The presence of systemic pulmonary pressures generally indicates severe and advanced pulmonary vascular disease.

D. Magnetic resonance imaging (MRI) and computed tomography may be useful in defining the anatomy in patients with unusual PDA geometry and in patients with associated abnormalities of the aortic arch.

VI. THERAPY. ACC/AHA 2008 guidelines for adults with congenital heart disease recommend closure of PDA (catheter or surgical) if there is **left atrial or left ventricular**

enlargement or if pulmonary arterial hypertension (PAH) is present with net left-to-right shunt (class I); or of an **asymptomatic small PDA by catheter device** (class IIa). PDA closure is **contraindicated** in patients with **PAH and right-to-left shunt**. Successful closure of PDA generally results in a good prognosis and may prevent adverse left ventricular remodeling resulting from volume overload.

The shape and size of a PDA determine the mode of therapy. Small- or moderate-caliber PDAs are generally closed percutaneously with coils. Large PDAs may require the Amplatzer Duct Occluder (ADO) or surgery. Heavily calcified PDAs represent a relative contraindication to surgical closure because of an increased risk of bleeding and incomplete closure with surgery. Cardiopulmonary bypass may be required for heavily calcified PDAs. PDAs with significant right-to-left shunts and Eisenmenger's physiology should generally not be closed. In patients with pulmonary vascular resistance > 8 U/m^2, lung biopsy has been recommended to determine candidacy for closure. However, even histologically severe pulmonary vascular disease may resolve after closure of the PDA. Reactivity of the pulmonary vascular bed to pulmonary vasodilating agents or significant reduction in pulmonary artery pressure during test occlusion may signal reversibility of pulmonary hypertension, but the absence of these findings does not rule out the possibility of reversibility in the long-term and natural history may be significantly altered by treating with pulmonary vasoactive medications.

A. Since the early 1990s, **transcatheter techniques** have become the **first-line therapy for most PDAs**. Many centers use single or multiple stainless steel coils to achieve complete closure. Numerous devices have been adapted or are under clinical investigation to allow transcatheter closure of larger defects. These procedures can often be performed on an outpatient basis, and complete closure rates at follow-up generally exceed 90% to 95% in most studies. The mortality rate is typically < 1% at experienced centers. Success has been reported even when ductal calcification has been apparent, but large clinical series are lacking.

1. **Percutaneous coil occlusion.** Percutaneous coils were developed in 1992 and are the **preferred treatment for older children and adults with PDAs < 3.5 mm in diameter**. Embolization coils have thrombogenic strands spanning the coils and are placed across the PDA to occlude flow. Advantages include low cost, small-caliber venous access, and easy implantation. Advances include detachable coils and development of a snare-assisted technique, both of which allow assessment and fine-tuning to ensure correct coil position before actual release of the coil. The coils are loaded at the tip of a catheter, the catheter is placed in the PDA under fluoroscopic guidance, and the coils are then deployed. Selected coil sizes are 2 to 2.5 times the narrowest diameter of the PDA. With moderate-sized or large-sized PDAs, multiple coils may be used. However, as PDA size becomes larger (> 3.5 to 4.0 mm), percutaneous, 0.038" coils become a less desired closure option, and alternative therapies become preferred. Although complete closure is usually accomplished with a single coil in children, multiple coils are frequently needed for complete closure in the adult. Although coil embolization may occur, the snare-assisted technique is almost always successful at percutaneous removal of the coil.
2. The **ADO**, a cone-shaped plug occluder made of thrombogenic wire mesh delivered with a 5F to 7F venous system, is the **preferred device for percutaneous closure of moderate to large PDAs**. The ADO stents the PDA, and blood is forced to flow through the center of the device, which is lined with thrombogenic wire mesh. The PDA then essentially clots off. Advantages include simple implantation, ability to retract the ADO into the sheath and redeploy if needed, and high success rates. There is an 89% occlusion rate on postprocedure day 1 and 97% to 100% complete occlusion after 1 month.
3. **Complications** of transcatheter closure are rare. The most common complication is embolization of the coil or device. Embolized coils can usually be retrieved; but even when this is impossible, adverse consequences are rare. Other

potential complications include flow disturbance in the pulmonary artery or aorta from device protrusion, hemolysis from high-velocity residual shunting, vascular access complications, and infection.

B. Surgical closure. In 1938, the first successful closure of a PDA was performed, which, coincidentally, was the first repair of a congenital heart defect. Surgical closure is the most effective method for complete closure and is usually performed without cardiopulmonary bypass by double ligation and division of the PDA. Ligation may be performed without division, but there is a risk of recanalization of the PDA in up to 20% of cases. In neonates and premature infants, ligation without division is performed because of the small size of the structures. With continued advances in percutaneous closure devices, **surgery has become second-line therapy for most adults with PDAs**. If surgery is necessary, the procedure is > 95% successful and has a low complication rate. The operative mortality rate is < 1%. However, the thoracotomy approach can be painful for adults and necessitates inpatient recovery. Newer surgical techniques such as transaxillary thoracotomy and video-assisted thorascopic ligation have improved surgical morbidity.

C. Medical therapy. In adults, medical therapy is ineffective to close a PDA. Medical therapy is indicated to prevent and treat complications of PDA, including heart failure, atrial arrhythmias, and pulmonary hypertension. **The most recent guidelines from the American Heart Association (AHA)** recommend antibiotic prophylaxis for endarteritis only in the setting of transcutaneous closure of the PDA for 6 months after the procedure; and prophylaxis is not recommended for those with repaired PDA without residual shunt.

D. Follow-up. If immediate duct closure is demonstrated after the procedure, a 6-month follow-up with TTE should suffice to assess for residual flow through the PDA. If residual shunt exists after the procedure, TTE should be performed every 2 to 3 months and early repeat attempt of complete closure considered, depending on the size of the residual shunt or the presence of hemolysis. For long-term follow-up, annual transthoracic echocardiograms are adequate.

VII. COARCTATION OF THE AORTA.

Coarctation of the aorta (CoA) has been found at autopsy in approximately 1 in every 1,550 individuals. It accounts for 5% to 10% of congenital heart disease and occurs more frequently in whites (7:1) and males (2:1). The disorder is typically diagnosed in childhood but may go undetected well into adulthood. Most patients develop persistent systemic hypertension, often as children, and are at risk for premature coronary artery disease. Cases usually occur sporadically, but an autosomal-dominant inheritance pattern has been observed. It is frequently associated with bicuspid aortic valve, and coarctation should be excluded in patients with bicuspid aortic valve and hypertension. Coarctation also occurs in 15% to 35% of patients with Turner's syndrome. Potential catastrophic complications include aortic rupture or dissection and cerebral berry aneurysm rupture. The mean survival for unrepaired patients is 35 years, with a 25% survival rate beyond 50 years.

VIII. ANATOMY.

CoA usually consists of a **narrowing in the region of the ligamentum arteriosum**, the remnant of the ductus arteriosus, just distal to the origin of the left subclavian artery. Most coarctations, therefore, are juxtaductal. The exact anatomy, however, varies, and the coarctation may include a long segment, the transverse arch, or the abdominal aorta. Rarely, tortuosity of the arch is identified. The main anatomic substrate is a prominent posterior shelf of the aorta, composed predominantly of thickened media.

A. Embryology. The exact embryonic origin remains uncertain, but two main theories exist. The first suggests that the narrowing is caused by aberrant ductal tissue

that constricts the aorta at time of ductal closure. The second proposes that aortic hypoplasia develops as a consequence of reduced blood flow in utero.

B. Associated cardiac defects include **bicuspid aortic valve** in 50% to 85% of cases, valvular and subvalvular aortic stenoses, ventricular septal defects, PDA, and congenital malformations of the mitral valve (i.e., smaller orifice, supravalvular ring, and parachute mitral valve resulting from a single papillary muscle). Multiple left-sided heart lesions may be associated with CoA and are often referred to as the Shone complex.

C. Associated extracardiac defects include intracranial aneurysms, especially within the circle of Willis (3% to 5% of cases), hemangiomas, hypospadias, and ocular defects.

IX. CLINICAL PRESENTATION

A. Symptoms. For patients with CoA who survive to adulthood, symptoms are usually negligible and nonspecific. Patients may complain of headaches, nosebleeds, cool extremities, leg weakness, or claudication with exertion. More serious manifestations include angina and heart failure.

B. Physical examination

1. A thorough cardiovascular examination may identify a systolic ejection murmur at the left upper sternal border that radiates to the intrascapular area located immediately anterior or posterior to the CoA. The murmur may be longer in systole and even continue into diastole, depending on the degree of obstruction. Increased flow through the collateral intercostal arteries can produce a continuous murmur appreciated diffusely over the precordium.
2. Upper extremity hypertension is often present, usually in conjunction with **diminished and delayed femoral pulsations**. CoA should always be considered in the differential diagnosis of refractory hypertension, especially in younger patients.
3. Funduscopic examination may demonstrate a "corkscrew" tortuosity of the retinal arterioles.

X. DIAGNOSTIC TESTING

A. The **ECG** is frequently normal but may demonstrate manifestations of long-standing hypertension, such as left ventricular hypertrophy and left atrial enlargement.

B. Chest radiography. Cardiomegaly, dilated ascending aorta, and prominent pulmonary vasculature are common. **Rib notching** usually develops by 4 to 12 years of age and is caused by enlarged intercostal collaterals. The **classic "3" or inverted-E sign is pathognomonic** for CoA and is created by a dilated left subclavian artery above the CoA and poststenotic dilation of the aorta below the CoA.

C. Echocardiography is most useful in infants and children. In adults, the suprasternal notch view is most helpful; color Doppler can be used to localize the site of turbulence. Continuous wave Doppler can assess the pressure gradient. If severe narrowing is present, persistence of flow in diastole (widening of the flow profile from systole into diastole) is seen by continuous wave Doppler in the aorta below the coarctation, such as in the abdominal aorta. This is a useful method to ascertain the presence of significant coarctation, even if imaging the direct site of the obstruction is impossible. A complete study should measure left ventricular size and ascending aortic size, determine aortic valve anatomy and function, and identify any potential associated congenital anomalies. TEE can also better define the anatomy if TTE proves inadequate.

D. MRI provides excellent anatomic and hemodynamic information. MRI is increasingly utilized as a first-line investigation before catheterization, particularly in adults. This enables the precise anatomy to be delineated and helps in the decision making regarding surgery or catheterization as treatment options. Serial MRI scans may be

used to follow results of therapeutic procedures. It is also useful in evaluating the intracranial vessels for associated berry aneurysms.

E. Cardiac catheterization provides excellent image data and pressure information and is often more reliable than echocardiography in adults. An **aortic angiogram** in left anterior–oblique or caudal and direct lateral projections usually best defines the lesion. Pressures should be obtained in the left ventricle and the ascending aorta, and the gradient across the lesion should be measured. A **pullback pressure of > 20 mm Hg** signifies hemodynamic significance and usually warrants intervention if concomitant clinical factors allow. A **gradient of > 50 mm Hg** generally mandates intervention. The presence of collateral vessels may falsely diminish the gradient.

XI. THERAPY. Several factors need to be taken into account when deciding on optimal therapy for CoA, including the age of the patient, the anatomy of the coarctation, any prior CoA operations, and the local surgical expertise. Whatever mode of treatment is chosen, the presence of postprocedural upper extremity hypertension influences survival.

A. In general, **medical therapy** for CoA has very limited utility, but it may be useful in a supportive role along with mechanical treatment. Hypertension should be medically treated, with the goal of controlling blood pressure and preventing end-organ damage.

B. Percutaneous management

1. **Percutaneous balloon angioplasty** is generally less effective than surgery for treatment of primary coarctation. Neonates and infants treated with angioplasty experience high rates of recurrent CoA (about 50% to 60%) and aneurysm formations (5% to 20%); therefore, surgical repair is preferred in this patient population. Likewise, balloon angioplasty of the unoperated coarctation in adults is controversial, with data suggesting higher rates of restenosis and aneurysm formation compared with surgical repair. Procedural complications can include acute aortic rupture (rare), aortic dissection, femoral artery trauma, recurrent coarctation (8%), and aneurysm formation (8% to 35%). The suspected mechanism for late aneurysm formation is intimal tear at the site of cystic medial necrosis within the coarctation site. It should be noted that the clinical impact of aneurysm formation is unclear, as most defects are small and have a low risk of rupture. Percutaneous angioplasty, however, is the preferred therapy for recurrent postsurgical coarctation. The procedure is successful in reducing the gradient to < 20 mm Hg in approximately 80% of interventions, with only a 1.5% incidence of late aneurysm formation.
2. **Stent implantation.** Theoretically, stent implantation may mitigate the development of aneurysm or dissection for a few reasons. By apposing the torn intima to the media and through dispersion of force, stenting may limit vascular trauma. It can also oppose the vascular recoil of the coarcted segment and avoid overdilation. By allowing the use of smaller balloons and graded inflations in staged procedures, stents may also reduce rates of aneurysm formation. Early and intermediate outcomes are promising, with a good safety and efficacy profile as well as lower rates of restenosis and aneurysm formation compared with balloon angioplasty. Despite the lack of long-term outcome data, stenting has become the preferred treatment modality in adults and adult-sized adolescents with native CoA. For recoarctation, balloon angioplasty with or without stenting is preferred in adults as well, as long as the anatomy is suitable.

C. Surgery remains the therapy of choice in neonates and infants. Three types of surgical repair have been used for correction of CoA: resection of the stenosed segment with end-to-end anastomosis, use of a subclavian flap, and patch aortoplasty. The approach with the best long-term outcome and sustained resolution of obstruction has been resection of the stenosed segment with end-to-end anastomosis. This approach carries with it the lowest risk of recurrent CoA (3%) and late aneurysm

formation (rare). Paradoxical hypertension and bowel ischemia may occur in the postoperative period. Major surgical complications include paraplegia caused by perioperative spinal cord ischemia (0.4% to 1%), residual coarctation, aneurysm formation at the site of repair, and, rarely, death. Survival rates of > 90% at 10 years and 84% at 20 years have been reported. Late deaths after surgical repair are related primarily to coronary artery disease, CHF, and aneurysm rupture. Young age favorably influences outcomes after surgery.

XII. FOLLOW-UP. Lifelong follow-up is indicated after the diagnosis of CoA is established, especially after any type of mechanical repair. Key issues to be cognizant of include the progression of hypertension either at rest or with exercise, development of CoA recurrence, aneurysm formation, left ventricular dysfunction, and associated aortic valve dysfunction when bicuspid valve is present. In patients repaired at older ages, hypertension commonly persists despite treatment by percutaneous intervention or surgery. Serial echocardiography is an important component of follow-up. Advanced imaging modalities such as computed tomography or MRI are used increasingly post repair to screen for aortic wall complications, with a preference for MRI given the radiation and contrast issues. Therefore, these patients should be considered "treated" and not "cured" despite repair.

ACKNOWLEDGMENTS: *The authors thank Drs. Michael S. Chen, J. Donald Moore, Adrian W. Messerli, Matthew A. Kaminski, and Arman Askari for their contributions to earlier editions of this chapter.*

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CHAPTER 32

Matthew A. Cavender
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Complex Congenital Heart Disease

I. TETRALOGY OF FALLOT (TOF). TOF is the most common form of cyanotic heart disease. It occurs in approximately 1 in 3,000 live births and accounts for 10% of congenital heart disease in infants. It is also the most common congenital heart disease requiring surgical correction in the first year of life. The earliest description of TOF dates back to the 17th century; however, Fallot is credited with describing the classic features of the disease in 1888. Surgical treatment for TOF did not become available until well into the 20th century, and it dramatically improved life expectancy. The **current reparative approach has shifted from palliative shunt procedures to primary surgical repair**, most recently with valve-sparing techniques and usually performed in infancy. Without surgical intervention, only about 10% of patients survive beyond the age of 20 years. Adults with TOF usually have undergone surgical repair or palliation. A wide and complex spectrum of TOF exists including association with pulmonary atresia, absent pulmonary valve, and atrioventricular (AV) canal defects. Classic "simple" TOF is discussed here.

A. Anatomy

1. **Anterocephalad deviation of the outlet septum** results in four defining features:
   - **(a)** Right ventricular (RV) outflow tract obstruction
   - **(b)** Nonrestrictive ventricular septal defect (VSD)
   - **(c)** Aortic override of the ventricular septum (> 50% over the right ventricle)
   - **(d)** Right ventricular hypertrophy (RVH)
2. **Associated defects.** Anomalous origin of the left anterior descending coronary artery from the right coronary artery (5%) or a prominent conal branch from the right coronary artery can occur. These vessels cross the RV outflow tract. This anatomic feature is important to surgeons because infundibular resection or future conduit placement may be needed in this location and can lead to inadvertent arterial damage. Right aortic arch occurs in 25% of cases. A secundum atrial septal defect (ASD) occurs in 15% of cases, completing the pentalogy of Fallot. Persistent left superior vena cava is found in 5% of patients. Among adult patients, aortic insufficiency can occur naturally from long-term dilation of the aortic root, after endocarditis or as a postoperative sequela. Rare complications include pulmonary hypertension, supravalvular mitral stenosis, and subaortic stenosis. There is an association with deletion in the chromosome 22q11 region, which is also present in DiGeorge syndrome and/or velocardiofacial syndrome.

B. Clinical presentation

1. **Patients who have not undergone surgical repair** have variable clinical features depending on the amount of RV outflow tract obstruction, degree of aortic override, and, to a lesser extent, systemic vascular resistance, all of which dictate the amount and direction of shunting across the VSD.
   - **a.** With severe RV outflow tract obstruction, patients have central cyanosis and clubbing by 6 months of age. Hypoxic "spells" may be seen and are characterized by tachypnea, dyspnea, cyanosis, or even loss of consciousness or

death. If the obstruction is mild, however, the shunt through the VSD may be left-to-right, resulting in "pink tet" with minimal symptoms.

b. On physical examination, the patient is usually cyanotic and clubbed. A prominent RV impulse may be appreciated because of equalization of right and left ventricular pressures. A lift may be palpated under the right sternoclavicular junction in patients with a right-sided arch. The first heart sound (S_1) is usually normal, but the second heart sound (S_2) is often single because of an inaudible P_2. Auscultation is notable for a prominent systolic ejection murmur at the left upper sternal border, possibly with an associated thrill. The shorter the murmur, the more severe the infundibular pulmonary stenosis. The murmur of aortic insufficiency may be audible along with an aortic click resulting from a dilated overriding aorta. Continuous murmurs may be heard due to aortopulmonary collateral vessels. The presence of these vessels is more likely in the setting of pulmonary atresia, but they can also be acquired if RV outflow tract stenosis develops gradually.

2. Most adult congenital patients will have undergone surgical repair with or without a prior palliative procedure. The term "**palliation**" (as opposed to "repair") in these patients refers to a surgical procedure that consists of a **systemic-to-pulmonary artery shunt** (modified Blalock-Taussig shunt, classic Blalock-Taussig shunt, Potts shunt, or Waterston shunt; Table 32.1). These procedures are initially performed to supplement the deficiency of antegrade pulmonary

TABLE 32.1 Index of Postoperative Anatomy among Adult Patients with Congenital Heart Disease

Underlying pathology	Procedure	Notes
Single ventricle Hypoplastic left heart Tricuspid atresia	**1. Norwood**	Incorporation of native aorta and pulmonary artery (one of which may be hypoplastic or atretic) to produce a "**neo-aorta**" for the single ventricle
Pulmonary atresia with intact ventricular septum Unbalanced complete AV canal defect		Main pulmonary artery is transected from the heart Pulmonary flow is maintained with placement of a **Blalock-Taussig shunt** **Atrial septectomy** is often performed to allow complete mixing at the atrial level
	2. Bidirectional Glenn	Usually performed at 4–6 mo if pulmonary arterial anatomy, pressures, and resistances are adequate Anastomosis of the **superior vena cava to the pulmonary artery**, usually with takedown of a previously placed systemic-to-pulmonary artery shunt and repair of pulmonary arterial branch stenosis if necessary Term *bidirectional* is used in descriptions of this procedure because both right and left pulmonary arteries usually remain in continuity

TABLE 32.1 Index of Postoperative Anatomy among Adult Patients with Congenital Heart Disease (*Continued*)

Underlying pathology	Procedure	Notes
	3. Fontan	Usually performed at 1–5 y depending on growth of vasculature and cyanosis Anastomosis of **inferior vena cava to the pulmonary artery** by intra-atrial lateral tunnel or extracardiac conduit Pulmonary blood flow is achieved passively, without the assistance of a ventricular pumping chamber
dTGA (ventriculoarterial discordance)	**Rashkind**	**Atrial balloon septostomy** to create mixing of systemic and pulmonary circulation
	Blalock-Hanlon	Surgical atrial septectomy
	Mustard or Senning (atrial switch)	Baffle material (Mustard) or native atrial tissue (Senning) used to direct pulmonary venous blood → right ventricle → aorta; systemic venous blood → left ventricle → pulmonary artery
	Jatene (arterial switch)	Great arteries are transected and reanastomosed to the appropriate ventricle
		Coronary arteries are removed with a button of surrounding tissue and reimplanted to the appropriate sinuses
	Rastelli	For dTGA with VSD and pulmonary outflow tract obstruction
		VSD patch closure that directs left ventricular blood across the VSD to the aorta
		Pulmonary valve is oversewn
		Valved conduit from the right ventricle to the pulmonary artery to create RV outflow
Deficient pulmonary artery or RV outflow tract Pulmonary atresia Tetralogy of Fallot with hypoplastic pulmonary arteries	**Classic Blalock-Taussig** **Modified Blalock-Taussig** **Waterston shunt** **Potts shunt**	Native subclavian artery anastomosed to the right or left pulmonary artery Expanded polytetrafluoroethylene (Gore-Tex) material connecting the subclavian or innominate artery to the pulmonary artery Anastomosis between the ascending aorta and right pulmonary artery Anastomosis between the descending aorta and left pulmonary artery

AV, atrioventricular; RV, right ventricular; TGA, transposition of the great arteries; VSD, ventricular septal defect.

blood flow and are taken down at the time of complete repair. The latter two procedures have been abandoned owing to associated uncontrolled pulmonary blood flow and the subsequent development of pulmonary hypertension.

a. Patients who have undergone palliative repair alone have variable clinical findings depending on the type of palliation performed. In those who have undergone a classic Blalock-Taussig shunt, the brachial pulse on that side may be diminished or absent. If patent, shunts can produce a continuous murmur. Continuous murmurs can also result from aortopulmonary collaterals. Branch pulmonary artery stenosis at prior shunt insertion sites can produce unilateral systolic or continuous murmurs. Systolic ejection murmurs may be audible depending on the degree of antegrade flow across the outflow tract.

3. Complete (or total) repair consists of patch closure of the VSD and variable degrees of RV outflow tract resection and reconstruction. It may involve pulmonary valvotomy, RV outflow tract patch augmentation, transannular patch enlargement, or placement of a right ventricle–to–pulmonary artery conduit (i.e., bioprosthetic or homograft). Distal branch pulmonary artery stenosis may have been repaired, or residual lesions may be present. These patients typically have first undergone a palliative shunt procedure, but the current surgical approach has shifted to primary complete repair in infancy.

a. Patients are often asymptomatic. They may present with late symptoms such as dyspnea, exercise intolerance, palpitations, signs of right heart failure, or syncope.

b. The jugular venous pressure is usually normal unless there is RV dysfunction, in which case elevated jugular venous pressure with a prominent *a* wave is seen. The brisk pulse of aortic insufficiency may also be appreciated. On palpation, there may be an RV lift or a lift under the right sternoclavicular junction when the arch is right-sided. Some degree of turbulence almost always remains across the RV outflow tract and produces a variable systolic ejection murmur at the left upper sternal border, with radiation to the back and peripheral lung fields. Of importance is the presence of associated pulmonary insufficiency. This, even if severe, may occasionally be inaudible due to low-pressure hemodynamics. It is generally appreciated at the left upper sternal border, sometimes producing a to-and-fro murmur together with the outflow tract murmur. A high-frequency systolic murmur at the left lower sternal border suggests the presence of a residual VSD (often due to a small leak in the VSD patch). Continuous murmurs from collateral formation or prior shunts may be appreciated. The diastolic murmur of aortic insufficiency may also be heard.

C. Laboratory examination

1. Chest radiographic findings depend on the surgical history. The presence of a right aortic arch may be confirmed. A concave deficiency of the left heart border reflects various degrees of pulmonary arterial hypoplasia. Upturning of the apex from RVH causes the classic finding of a "boot-shaped" heart. Pulmonary vascular markings may vary throughout the lung fields, depending on associated branch pulmonary artery stenosis and relative blood flow. Calcification or aneurysmal dilation of surgical conduits or RV outflow tract repair may be visible on plain radiographs.

2. An **electrocardiogram** usually demonstrates sinus rhythm with RVH. Both atrial and ventricular rhythm disturbances can be present. The QRS axis is usually normal or rightward. If left axis deviation is present, an associated AV canal defect should be suspected. A patient who has undergone surgical repair typically has right bundle branch block. **A QRS duration of > 180 milliseconds is a predictor of sustained ventricular tachycardia and sudden cardiac death**.

D. Diagnostic testing

1. Echocardiography

a. For a child or young adult, transthoracic echocardiography may be the only modality necessary for diagnosis. For adults or patients who have undergone surgical intervention, catheterization or magnetic resonance imaging (MRI) may be necessary in order to identify the presence and location of residual lesions.

(1) Adequate views are obtained of the right heart, RV outflow tract, and proximal pulmonary arteries. Helpful views to identify a residual VSD or the presence of aortic insufficiency include the parasternal long-axis, parasternal short-axis, and apical four-chamber views. Further definition of residual lesions in the branch pulmonary arteries may be possible with a high parasternal short-axis view.

(2) Palliative shunts are often best visualized in the suprasternal notch view where the subclavian arteries course distally.

(3) Continuous flow is typically demonstrated with color Doppler techniques. Less common shunts may be difficult to image in adult patients. Aortopulmonary collateral vessels are extremely difficult to visualize, but may be seen in suprasternal notch views of the descending aorta.

b. Transesophageal echocardiography may allow improved imaging of the intracardiac anatomic structures in adults, but limitations often remain with regard to the distal pulmonary arteries, and additional testing is frequently necessary.

2. Cardiac magnetic resonance (CMR) imaging is considered the gold standard for evaluating the right ventricle and quantitating pulmonary insufficiency in these patients. It can demonstrate the presence of scar, distal pulmonary arterial anatomy, and RV aneurysms, as well as other associated defects. It can also provide hemodynamic information about residual lesions. Previously placed shunts and possibly aortopulmonary collateral vessels can be identified as well. The anatomic information may be sufficient to proceed with surgical treatment or to guide the interventional cardiologist in planning a transcatheter procedure.

3. Cardiopulmonary testing should be performed as a baseline study and with progression of symptoms. It is useful in determining the timing for reintervention in the setting of RV volume overload secondary to free pulmonary insufficiency.

4. Quantitative pulmonary flow scans are useful to determine discrepancies in pulmonary flow that may be caused by branch pulmonary artery stenosis. These scans also provide objective baseline clinical information when obtained after surgical or transcatheter intervention.

5. The role of **cardiac catheterization** is decreasing with the advent of other imaging modalities, but can be helpful in assessing residual shunts and pulmonary hypertension.

a. Right heart catheterization. Residual shunts are actively sought at the atrial and ventricular levels. The pulmonary arteries and branches are evaluated extensively in search of peripheral pulmonary stenosis. Findings at right heart catheterization and their clinical significance are as follows:

(1) RV pressure is generally systemic in a patient who has not undergone surgical repair.

(2) After surgical repair, elevated RV pressure suggests the presence of residual obstructive lesions, the levels of which are to be documented.

(3) Careful pullback recordings are performed from the branch pulmonary arteries to the right ventricle because stenosis at each level is possible.

(4) The presence of stenosis at a prior shunt site is expected.

(5) RV end-diastolic pressures may be elevated in the setting of pulmonary insufficiency.

b. Left heart catheterization is performed if noninvasive studies suggest residual VSD.

(1) Angiography includes a cranialized right ventriculography and possibly selective pulmonary arterial injections if hemodynamic findings suggest stenosis.

(2) Left ventriculography better demonstrates residual VSD in the presence of subsystemic RV pressures.

(3) Aortic root injection demonstrates the presence of aortic insufficiency, confirms the presence of grossly abnormal coronary artery origins or branching patterns, and reveals prior surgical shunts or aortopulmonary collateral vessels. If present, shunts and collateral vessels are best visualized in the posteroanterior and lateral projections after selective injection by hand.

(4) Selective coronary angiography is recommended in the care of adult patients to exclude acquired coronary artery disease and to identify the path of any anomalous coronaries before surgical intervention. **The anomaly that is not to be missed is the left anterior descending artery originating from the right coronary artery**—it crosses the RV outflow tract anteriorly and can be damaged during surgery.

E. Therapy and follow-up care

1. Medical treatment

a. If an adult has **not been surgically treated or has undergone palliative treatment**, a relatively well-balanced situation must exist. However, the following problems are to be expected.

(1) Long-term effects of RV outflow obstruction
(2) Progressive infundibular pulmonary stenosis
(3) Exposure of the pulmonary circulation to systemic shunt flow
(4) Development of distal pulmonary arterial stenosis, typically at shunt sites
(5) Erythrocytosis
(6) Chronic hypoxemia
(7) Pulmonary hypertension
(8) Paradoxical emboli
(9) Atrial and ventricular arrhythmias
(10) Increased risk of aortic insufficiency over time
(11) Endocarditis

b. Follow-up care increasingly involves **patients who have undergone surgical repair** and management of residual postoperative lesions.

(1) These patients are at increased risk for **sudden cardiac death**. Atrial and ventricular rhythm disturbances are common in the postoperative patient. Frequent Holter monitoring is warranted for this reason. Atrial tachyarrhythmias are found in up to one-third of patients and are predictive of morbidity and mortality. If patients are found to have nonsustained ventricular tachycardia, an electrophysiologic study and possibly an implantable cardioverter–defibrillator implantation can be considered. Atrial and ventricular arrhythmias may be the presenting problem for post-repair patients when a component of the repair is failing. There are no data to support prophylactic antiarrhythmic therapy to lower risk of sudden death in this patient population. An increased incidence of ventricular rhythm abnormalities has been associated with RV volume overload from pulmonary insufficiency and with QRS prolongation > 180 milliseconds (QRS duration correlates with degree of RV dilation).

(2) Pulmonary insufficiency can be tolerated for years, even decades, but chronic volume loading of the right ventricle can lead to diminished exercise tolerance, dysrhythmias, and **right heart failure**. Pulmonary

insufficiency is the most common indication for redo surgery after an initial repair.
(3) Residual VSD
(4) Progressive dilation of the ascending aorta
(5) Residual RV outflow tract gradient
(6) RV outflow tract aneurysm at previous patch site

c. Recent **infective endocarditis guidelines** have departed considerably from prior iterations such that antibiotic prophylaxis is recommended only for those who are at highest risk for adverse outcomes from endocarditis. Specifically, prophylaxis is still appropriate for patients with TOF who are unrepaired, including those who have undergone a palliative procedure. For patients with TOF who have undergone total repair, antibiotic prophylaxis is now recommended only for 6 months following the placement of prosthetic material or device or if there is a residual defect at, or adjacent to, the site of prosthetic material (VSD patch leak, for example). If the pulmonary valve has been replaced or repaired with prosthetic material, antibiotic prophylaxis is appropriate as well.

2. The primary therapeutic consideration for patients with TOF is **surgical intervention**—either repair or reintervention.
   a. The goal of **total repair** is to relieve the outflow tract obstruction while maintaining competency of a preferably native pulmonary valve with closure of the VSD. Some younger patients need extensive reconstruction of the RV outflow tract with early placement of a bioprosthetic valved conduit or homograft. In time, these usually become restrictive to flow and/or are insufficient. The result is progressive right heart hypertrophy, fibrosis, and failure if revision is not performed.
   b. A common indication for **reintervention** is pulmonary valve replacement (PVR) for severe pulmonary valve insufficiency. The ideal timing for PVR, however, remains controversial. Cardiac MRI may be helpful in determining optimal timing, and there is evidence to support pursuing pulmonic valve replacement before the RV end-diastolic volume index reaches 160 mL/m^2.
   c. Other indications for **reintervention** include the replacement or revision of conduits/homografts in the presence of symptoms, residual VSD with reasonable shunt (approximately 1.5:1), RV pressures greater than two-thirds of systemic pressures because of residual obstructive lesions, progressive aneurysmal dilation of RV outflow tract patch, residual systemic–pulmonary shunts with left ventricular volume overload, clinically significant arrhythmias, symptomatic or progressive aortic insufficiency, and dilated aortic root > 5.0 cm.
3. Although the mainstay of therapy has been surgical, **transcatheter techniques** are increasingly used to treat patients in certain situations. For the most part, transcatheter therapies for adults with TOF are limited to patients who have undergone prior surgical treatment, with attention to residual obstructive lesions in the main pulmonary artery, right ventricle–to–pulmonary artery conduit, or distal pulmonary arteries. Prior shunt sites may become stenotic with time and necessitate balloon angioplasty and possibly stent placement. Residual VSD and ASD may be closed percutaneously in select situations. Percutaneous pulmonic valve replacement has been approved for use both in Europe and the United States. The Melody valve (Medtronic; Minneapolis, MN) is a therapeutic option available for selected patients with stenotic or regurgitant conduits 23 mm or less in size.

II. COMPLETE TRANSPOSITION OF THE GREAT ARTERIES (D-TGA).

This is a relatively common congenital anomaly that occurs with a prevalence of 20 to 30 in 100,000 live births and is found more often in males (2:1). It is not associated with other syndromes and does not tend to cluster in families. Although it represents **5% to 8% of**

all congenital heart disease, it accounts for **25% of deaths in the first year of life**. Adult patients almost invariably have undergone prior surgery and carry with them important morbidities that require ongoing surveillance and care.

A. Anatomy

1. The defining feature of this anomaly is **ventriculoarterial discordance**, in which there is an abnormal alignment between the ventricles and great arteries. Hence the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle, creating two parallel circuits instead of one in series. Deoxygenated blood flows from the right atrium across a tricuspid valve → right ventricle → aorta, whereas oxygenated blood flows from the left atrium across the mitral valve → left ventricle → pulmonary artery. Unless there is bidirectional shunting at the atrial (ASD), ventricular (VSD), or great artery level (patent ductus arteriosus) to allow mixing of blood, this anatomy is incompatible with life (Fig. 32.1).
2. There is an abnormal spatial relationship between the great arteries such that instead of the normal spiral configuration, they run parallel to one another. The **aorta is rightward and anteriorly displaced**, whereas **the pulmonary artery occupies a position more leftward and posterior**. This is the most common pattern, but other configurations can also be seen such as side-by-side great arteries with the aorta to the right or an aorta directly anterior to the pulmonary artery.
3. Associated cardiac anomalies include **VSD in 40%** to 45% of cases (usually perimembranous but can involve any portion of the interventricular septum), **left ventricular (or subpulmonary) outflow tract obstruction in 25%**, aortic coarctation in 5%, patent foramen ovale (PFO), and patent ductus arteriosus. Patients with these associated cardiac anomalies are considered to have **complex** transposition, whereas patients without these associated anomalies are considered to have simple transposition.
4. This lesion is also referred to as "dTGA," in which the "d" refers to the dextroposition of the bulboventricular loop, which is characterized by a right-sided right ventricle.
5. The coronary anatomy in dTGA is variable. The aortic sinuses are described according to their relationship to the pulmonary artery, such that the "facing

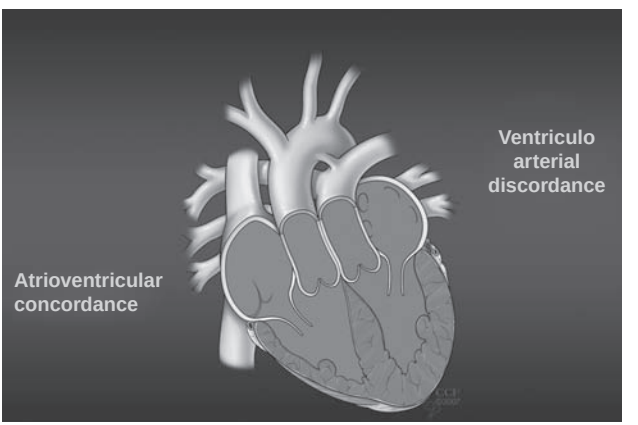

FIGURE 32.1 Complete (d) transposition of the great arteries.

sinuses" are closest to the pulmonary artery. The most frequent coronary arrangement is when the "left-facing" sinus gives rise to the left main coronary artery, whereas the "right-facing" sinus gives rise to the right coronary artery.

B. Natural history and surgical repair

1. Without surgical intervention, survival beyond infancy is dismal, with 89% mortality by the first year of life and worse outcomes for those without an associated lesion to allow for adequate mixing of blood. At birth, infants are treated with intravenous prostaglandin E to keep the ductus arteriosus open and some may undergo a **Rashkind procedure** (refer Table 32.1) to improve oxygenation until definitive surgery can be performed.
2. Adults invariably have undergone some type of cardiac surgery, although in rare cases they may present with Eisenmenger physiology (see subsequent text) if a "balanced" situation exists with a concomitant large VSD and pulmonary vascular disease. Surgical repairs include the atrial switch procedure **(Senning or Mustard operation)**, the **arterial switch** procedure (Fig. 32.2), or the **Rastelli operation** (Table 32.1).

C. Clinical presentation

1. The clinical presentation of the surgically repaired patient with dTGA depends on the type of previous surgery. Although no longer cyanotic, these patients have a host of mid- to late-term morbidities that require lifelong surveillance. Patients who have undergone an arterial switch procedure are approaching adulthood only now and presenting in adult congenital cardiology clinics.
2. **Atrial switch**
   a. Patients who have undergone an atrial switch operation often report New York Heart Association (NYHA) functional class I–II symptoms, but on exercise testing may have significant exercise intolerance. They have a systemic right ventricle, which, over time, can develop systolic dysfunction and progressive tricuspid regurgitation. These patients may present with signs and symptoms of congestive heart failure—the most common cause of death. Arrhythmias are common and patients may present with palpitations,

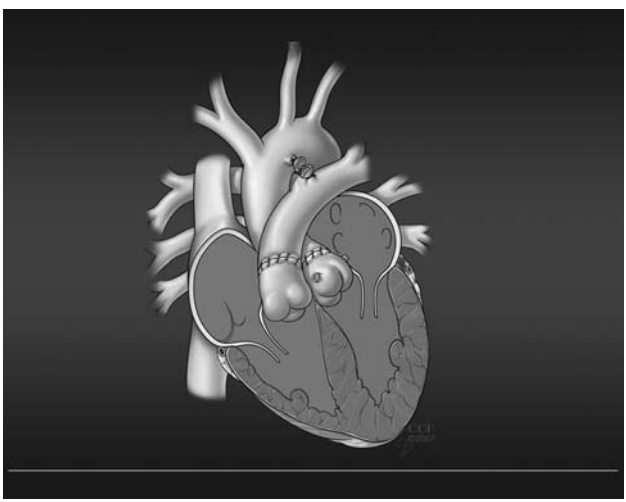

FIGURE 32.2 Arterial switch operation.

presyncope, or syncope. Venous baffle obstruction can lead to peripheral edema, hepatomegaly, ascites, and fatigue due to low cardiac output. The obstruction of the superior limb can produce a superior vena cava syndrome. Pulmonary venous baffle obstruction can lead to fatigue, exertional dyspnea, and chronic cough. Baffle leaks are often asymptomatic, but large leaks can lead to intracardiac shunting and cyanosis.

b. On physical examination, focus should be on signs of AV regurgitation and heart failure. There may be an RV heave at the left sternal border on palpation. S_2 is loud at the second left intercostal space from an anterior aorta. Audible splitting of the S_2 may indicate the development of pulmonary hypertension.

3. Arterial switch

a. The majority of these patients are asymptomatic with NYHA functional class I symptoms. Arrhythmias are not a significant problem with this subset. Few will present with chest pain, and in these patients ischemia must be ruled out.

b. The physical examination is sometimes notable for turbulence across the RV outflow tract, which may be palpated as a thrill. The diastolic murmur of aortic insufficiency should also be sought.

4. Rastelli operation

a. Both atrial and ventricular arrhythmias are mid- to late-term complications, and these patients may present with palpitations or syncope. Conduit obstruction may manifest as insidious exercise intolerance, dyspnea, or new-onset arrhythmias. On physical examination, the character of the pulmonic ejection murmur should be carefully noted to evaluate for conduit obstruction.

D. Laboratory examination

1. The **chest radiograph** of patients with dTGA displays a narrow mediastinum due to the parallel orientation of the great arteries. The cardiothoracic silhouette is normal. The pulmonary vasculature is normal in patients without pulmonary hypertension. The right ventricle–to–pulmonary artery conduit in patients who have undergone a Rastelli procedure may be visualized on plain radiograph due to calcification.

2. In patients who have undergone an atrial switch operation, the **electrocardiogram** may display an ectopic atrial or junctional rhythm due to loss of sinus node function. There is usually right-axis deviation and RVH as a result of the systemic position of the right ventricle. In patients who have undergone arterial switch, RVH is distinctly abnormal and suggests pulmonary outflow tract obstruction. After a Rastelli operation, the electrocardiogram is notable for a right bundle branch block and patients may develop complete heart block.

E. Diagnostic testing

1. Transthoracic echocardiography in atrial switch patients can assess the degree of tricuspid regurgitation and estimate RV function. Color Doppler is helpful in detecting baffle leaks or obstruction, although more detailed analysis may require transesophageal echocardiography. For those who have undergone arterial switch, transthoracic echocardiography can assess left ventricular function and help exclude supravalvular and pulmonary artery stenosis. Two-dimensional Doppler can be used to look for conduit stenosis after the Rastelli operation and estimate RV systolic pressures. It can also exclude any residual VSDs in these patients.

2. As in the TOF population, **CMR** imaging has emerged as an invaluable imaging modality for patients with repaired dTGA. For postatrial switch patients, CMR imaging is used to quantify the size and function of the right ventricle, assess tricuspid regurgitation, and evaluate the systemic and pulmonary venous limbs of the atrial baffle for potential obstruction or leaks. In patients who have undergone

arterial repair, right and left ventricular function can be quantitated and both the right and left outflow tracts examined. Focus is placed on the great arteries to look for the presence of supravalvular and branch pulmonary artery stenosis as well as dilation of the neo-aorta. Conduit stenosis and gradients as well as RV size and function can be determined in those who have had a Rastelli operation.

3. **Cardiopulmonary testing** is very useful in detecting subtle clinical changes and decrease in functional capacity. As mentioned previously, there is often a discrepancy between self-reported symptoms and performance on metabolic exercise testing. Patients who have undergone atrial switch often have chronotropic incompetence and may benefit from pacemaker implantation. Stress testing may be useful in patients after arterial switch to detect coronary artery stenosis and resultant ischemia.
4. **Quantitative pulmonary flow scans** are an important part of the diagnostic work-up for suspected pulmonary artery or branch pulmonary artery stenosis in those who have undergone arterial switch repair. It is useful to obtain these scans before and after potential intervention to assess for functional improvement.
5. **Cardiac catheterization** does not have a role in the routine management of these adult patients. It does have a role, however, in the diagnosis and treatment of baffle obstruction and leaks, pulmonary hypertension, pulmonary artery stenosis, coronary artery stenosis, conduit obstruction, and residual VSD.

F. Therapy and follow-up

1. Follow-up should focus on potential late complications after repair and depends on the type of surgery the patient has undergone.
   - **a.** Atrial switch
     - **(1)** Arrhythmias including sinus node dysfunction and intra-atrial reentry tachycardia (frequent Holter monitoring is recommended)
     - **(2)** RV dysfunction
     - **(3)** Tricuspid regurgitation
     - **(4)** Sudden cardiac death
     - **(5)** Baffle obstruction or leak
     - **(6)** Pulmonary hypertension
     - **(7)** Endocarditis
   - **b.** Arterial switch
     - **(1)** Supravalvular or peripheral pulmonary artery stenosis
     - **(2)** Pulmonary outflow tract obstruction
     - **(3)** Neo-aortic regurgitation and aortic root dilation
     - **(4)** Coronary artery stenosis leading to ischemia and sudden death
     - **(5)** Left ventricular dysfunction
     - **(6)** Endocarditis
   - **c. Rastelli operation**
     - **(1)** Atrial and ventricular arrhythmias
     - **(2)** Complete heart block
     - **(3)** Sudden cardiac death
     - **(4)** Left ventricular dysfunction
     - **(5)** Conduit stenosis
     - **(6)** Endocarditis
2. **Medical management**
   - **a.** In the treatment of systemic RV dysfunction, there are limited data to suggest any long-term benefits from applying the evidence-based drugs utilized for left ventricular dysfunction. Despite this, angiotensin-converting enzyme (ACE) inhibitors are often utilized for afterload reduction. β-Blockers should be used with caution in patients after atrial switch repairs, as this could precipitate heart block (due to sinus node and AV conduction abnormalities).
   - **b.** As mentioned previously, the latest **infective endocarditis** guidelines have changed such that in the absence of valve replacement or prosthetic material

used to repair a valve, implantation of prosthetic material within the last 6 months, or prosthetic material accompanied by residual leaks, it is no longer officially recommended that dTGA patients post-repair receive antibiotic prophylaxis.

3. Late intervention options include both surgical and transcatheter procedures and, again, depend on the type of repair. Systemic ventricular failure may ultimately require work-up for orthotopic heart transplantation.
   a. **Atrial switch**
      (1) The procedure of choice in patients with baffle obstruction is transcatheter stent implantation, with best results in the systemic venous baffle. Although technically more challenging, transcatheter dilation of the pulmonary venous baffle can be performed but may require surgical revision. Clinically significant baffle leaks can be treated with catheter-based techniques as well as with septal occluder devices.
      (2) Due to the high prevalence of atrial arrhythmias and sinus node dysfunction, these patients are referred for radiofrequency ablation procedures and pacemaker implantation.
      (3) Conversion to an arterial switch for systemic RV dysfunction or left ventricular "training" by pulmonary artery banding has not been reliably successful in the adult population and has been largely supplanted by cardiac transplantation in many centers.
   b. **Arterial switch**
      (1) Percutaneous balloon angioplasty with or without stent placement is an excellent option for those with pulmonary artery and supravalvular or branch pulmonary artery stenosis with suitable anatomy. Balloon angioplasty being a safe procedure, there is an approximately 15% restenosis rate, with lower risk after stent implantation. The greatest success lies with branch pulmonary artery stenosis.
      (2) Coronary artery stenosis can be treated with both stenting and coronary bypass surgery.
      (3) Severe neo-aortic regurgitation is treated surgically with either valve repair or replacement.
   c. **Rastelli operation**
      (1) All right ventricle to pulmonary artery conduits inevitably fail and require replacement. There is a role for percutaneous stenting of conduit obstruction in some patients, as this can delay the need for surgery. These transcatheter procedures have a risk of stent fracture as well as potential for coronary artery compression, which can lead to catastrophic outcomes in the catheterization laboratory.
      (2) Residual VSD leaks may be amenable to closure by percutaneous means, but often require surgical revision. Clinically significant residual left ventricular outflow tract obstruction is also managed surgically.

III. CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES (ccTGA).

Ventricular inversion or ccTGA is a rare congenital anomaly that occurs in < 1% of children with congenital cardiovascular defects. Among these patients, it is equally rare to have no other associated structural abnormalities. The natural history of ccTGA is gradual congestive failure caused by systemic AV valve insufficiency and systemic ventricular dysfunction, even in the absence of other associated malformations. The presence of associated defects and conduction abnormalities contributes to a further decrease in life expectancy without intervention. Life expectancy is generally good but does not reach normal.

A. Anatomy

1. The defining feature of this congenital abnormality of cardiac looping is **AV and ventriculoarterial discordance**. Blood flows from the right atrium across

a mitral valve → right-sided, morphologic left ventricle → pulmonary artery → lungs → left atrium across a tricuspid valve → left-sided, morphologic right ventricle → aorta (Fig. 32.3).

2. The great arteries are not in their normal configuration and often run parallel to one another instead of crossing. The pulmonary artery is more posterior and rightward than usual and the aorta is more anterior and leftward.
3. The anatomic coronary arteries, like the AV valves, follow their respective ventricles. The left-sided coronary artery resembles the anatomic right coronary artery as it courses in the AV groove and gives rise to infundibular and marginal branches. The right-sided coronary artery resembles the morphologic left coronary artery, which branches into the anterior descending and circumflex arteries (Fig. 32.4).
4. The conduction system likewise follows the respective ventricle, as the right-sided, morphologic left ventricle depolarizes first. Accessory AV nodal tissue is located anteriorly with respect to normal, and the His bundle must traverse

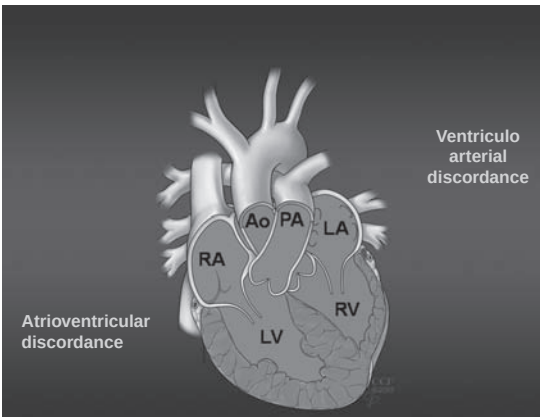

FIGURE 32.3 Congenitally corrected (l) transposition of the great arteries. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

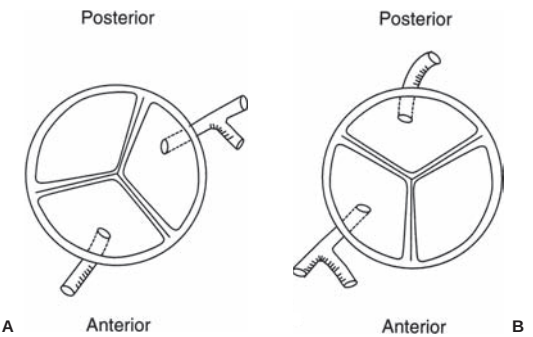

FIGURE 32.4 Schematic representation of coronary artery origins and branching in the normal heart (**A**) and in a congenitally corrected transposition (**B**).

anterior to the pulmonary artery and along the superior margin of a VSD if present. There is increased risk of acquired **complete heart block** in this lesion because of the abnormally placed AV node and its extended course. Approximately 30% of adolescents and adults develop complete heart block, the incidence of which is 2% per year without surgical intervention, with the site of block being within or above the His bundle. Accessory pathways have been described and are typically left-sided in the presence of an Ebstein anomaly–like malformation of the left-sided (tricuspid) AV valve.

5. Isolated ccTGA is the exception. **Associated lesions** are common and are considered in the diagnostic evaluation. They include VSD (70%), pulmonary outflow obstruction (~40% and usually subvalvular), or abnormalities of the left-sided, systemic tricuspid valve. Up to 90% of patients have an abnormality of the tricuspid valve in some form (i.e., dysplastic or Ebstein-like tricuspid valves).

B. Clinical presentation

1. Because physiologic blood flow is preserved, patients may have no symptoms through adulthood in the absence of other structural lesions or associated complications. This scenario is rare, however, because associated lesions commonly dictate the clinical features.
2. Without associated structural abnormalities, **failure of the systemic morphologic right ventricle** with various degrees of systemic AV valve (tricuspid) insufficiency is the norm. In this setting, the patient has nonspecific descriptions of fatigue, shortness of breath, and exercise intolerance or congestive failure. Patients may have **syncope or presyncope** caused by conduction abnormalities or complete heart block.
3. On physical examination, there is a loud A_2 due to an anterior and leftward aorta. The murmurs of a VSD or pulmonary stenosis may also be appreciated. Tricuspid insufficiency can be heard with systemic ventricular failure.

C. Laboratory examination

1. In the usual anatomic configuration of ccTGA, the aorta is anterior and to the left, which produces a **chest radiograph** with a straight left heart border. The left pulmonary artery is not well defined and the ascending aorta is not visible on the right. The chest radiograph may appear normal or reflect the presence of associated lesions, such as increased pulmonary flow from a VSD or decreased pulmonary flow in the setting of pulmonary stenosis. Dextrocardia occurs in approximately 20% of these patients and the diagnosis should be suspected if seen with abdominal situs solitus.
2. The typical **electrocardiogram** shows a left axis deviation. Among pediatric patients, there is loss of the usual Q waves in the precordial leads, with deep Q waves in leads II and aVF reflecting reverse septal activation. A variety of AV node conduction abnormalities may manifest with time and progress to complete heart block.

D. Diagnostic evaluation

1. In most instances, the diagnosis can be made with **echocardiography**. The essential findings of AV and ventriculoarterial discordance must be demonstrated. Imaging may be difficult in the presence of dextrocardia or mesocardia. Close attention must be paid to the morphologic details of each chamber.
   a. The morphologic **right ventricle** is identified on the basis of its **triangular** shape, the presence of **trabeculations and moderator band**, an inferiorly positioned AV valve, and the absence of AV valve attachments to the interventricular septum.
   b. The morphologic **left ventricle** is identified on the basis of its bullet shape, smooth wall, and more superiorly positioned AV valve and presence of AV valve attachments to the interventricular septum. In the case of ccTGA, these relationships are preserved but reversed.

c. There is lack of anatomic continuity between the **left-sided (tricuspid) AV valve and aorta**, but continuity is present between the **right-sided (anatomic mitral) valve and pulmonary artery**. The left-sided AV valve is displaced inferiorly relative to the right-sided (mitral) valve and may appear malformed or have the characteristics of Ebstein anomaly.

d. Apical four-chamber and subcostal images are particularly helpful. The suprasternal notch view is essential in evaluating the great vessels that lie parallel to each other.

e. The **aortic arch** typically lies to the left of midline in the sagittal plane and can often be visualized from the high left parasternal position. Because variations in great vessel position occur, the spatial orientation must be clarified.

f. **Associated defects** (e.g., systemic AV valve insufficiency, VSD, and outflow tract obstruction) with ccTGA must be excluded or defined.

2. **Catheterization is unnecessary** for the diagnosis of ccTGA, but may be helpful in preoperative planning with regard to the hemodynamic significance of associated lesions. In rare instances, ccTGA is diagnosed by catheterization and was not recognized during routine echocardiography. An unusual arterial catheter course is caused by the anterior and leftward position of the aorta in most instances. The left-sided coronary artery typically arises from the posterior sinus and assumes a right coronary branching distribution, whereas the right-sided coronary artery arises from the anterior and rightward sinus and assumes a typical left coronary branching distribution (Fig. 32.4). Because the ventricular septum often lies in the sagittal plane, ventriculography is usually best performed in the straight posteroanterior and lateral projections.

E. Therapy

1. **Medical management** is dictated primarily by the associated malformations.

a. In the rare case of isolated ccTGA, the risk of development of conduction abnormalities is cumulative over time; therefore, periodic Holter monitoring is warranted. Permanent pacemaker placement is often needed.

b. The systemic AV valve and ventricle may show signs of failure that necessitate initiation of heart failure measures in the form of diuretics and afterload reduction, although data are lacking for the use of agents such as ACE inhibitors or β-blockers in systemic right ventricles.

c. Associated lesions such as pulmonary stenosis or atresia, severe systemic AV valve regurgitation, or VSD may likewise contribute to the medical treatment of these patients, but often also necessitate surgical intervention.

d. The recent American Heart Association (AHA) guidelines do not recommend routine antibiotic prophylaxis for these patients unless they have had recent placement of prosthetic material within the preceding 6 months or have a leak at, or adjacent to, the site of a previous prosthesis.

2. **Surgery**

a. Infants and children who are brought to medical attention early often need surgical intervention in the form of relief of pulmonary outflow tract obstruction or placement of palliative shunts, depending on the associated lesions.

b. For selected children, a **double switch** procedure may be performed. An **atrial switch** corrects the AV discordance by baffling atrial blood to the appropriate ventricle (i.e., oxygenated blood diverted from the left atrium rightward to the right-sided left ventricle and vice versa by the Mustard or Senning procedure). **Arterial switch** is performed in the same operation to restore anatomic ventriculoarterial concordance. The double switch operation may necessitate a period of "training" of the left ventricle by means of pulmonary artery banding. The results of this operation are generally less favorable in older patients in whom the right ventricle has been the systemic ventricle for a more prolonged period. The intermediate-term results of this procedure are encouraging, but data for long-term results are limited. Those

with a large VSD may undergo atrial baffling with a **Rastelli operation** (see Table 32.1).

c. Adult patients with symptoms of progressive systemic AV valvular insufficiency may need valve repair or replacement. Most centers that have reported results with this procedure have found improved functional status after surgical treatment and acceptable risks. The timing of surgical intervention among patients with less severe symptoms is a topic of debate, but it is agreed that referral should be considered early before irreversible changes in ventricular function occur.

IV. EBSTEIN ANOMALY. This anomaly of the tricuspid valve represents 0.5% of congenital heart defects. The natural history of this lesion varies from early death to nearly normal expected survival, depending on the degree of tricuspid valve involvement and the presence and type of arrhythmias. An increased risk of **sudden death** irrespective of functional class, presumably caused by arrhythmia, has been observed. **Predictors of poor outcome** include earlier **age** at presentation, **cardiomegaly**, severe **RV outflow abnormalities**, and **disproportionate dilation of the right atrium** relative to the other chambers. There is an association with maternal lithium administration, but most cases are sporadic.

A. Anatomy

1. The **tricuspid valve** is morphologically and functionally abnormal. The basic features include adherence of the septal and posterior leaflet to the myocardium, which lowers the functional annulus toward the RV apex. This results in the classic **atrialization** of the right ventricle (Fig. 32.5) and dilation of the true tricuspid annulus. The anterior leaflet usually is not displaced, but is redundant and may be fenestrated and tethered.

2. **Associated structural anomalies** include **a PFO or ASD** (found in ≥ 80%), **VSD, mitral valve prolapse, and pulmonary stenosis**. ccTGA is associated with Ebstein-like anomaly of the tricuspid (systemic) valve.

B. Clinical presentation

1. **Signs and symptoms** are variable.

a. The presence of a severely insufficient valve can be apparent at birth because of right-to-left shunting across a stretched PFO or ASD, resulting in cyanosis. Pulmonary vascular resistance is high in the neonate and worsens cyanosis,

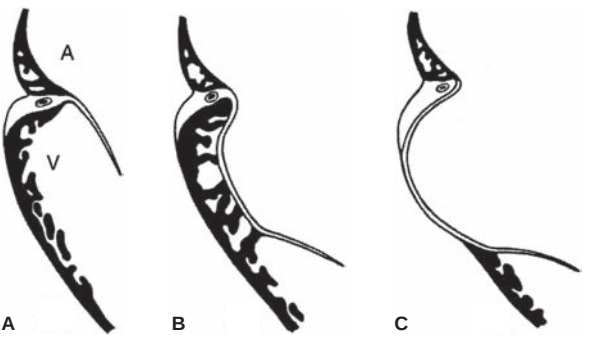

FIGURE 32.5 Section through the right atrioventricular junction. **A:** Normal heart, showing the right atrium (A) and right ventricle (V). **B:** Mild degree of Ebstein anomaly. **C:** Severe Ebstein anomaly. In (**B**) and (**C**), there is apparent displacement of the tricuspid valve. (From Adams FH, Emmanouilides GC, Riemenschneider TA, eds. *Moss' Heart Disease in Infants, Children, and Adolescents.* 4th ed. Baltimore, MD: Williams & Wilkins, 1989, with permission.)

but as pulmonary vascular resistance falls, cyanosis may resolve. In adulthood, as tricuspid regurgitation becomes longstanding with associated decreased RV compliance, cyanosis can reappear. In subtle cases, the anomaly may not be evident until adulthood and then results in nonspecific fatigue, shortness of breath, palpitations, near-syncope, or syncope. In the presence of an interatrial communication, patients may present with paradoxical embolization or brain abscess. Because the spectrum of involvement varies greatly, a high index of suspicion must be maintained.

b. The downward displaced septal leaflet creates a substrate for **accessory pathways**, and clinical Wolff-Parkinson-White syndrome is found in 10% to 25% of patients. Arrhythmias include supraventricular tachycardia mediated by an accessory pathway or caused by atrial arrhythmias from progressive atrial dilation. The combination of atrial fibrillation or flutter conducted rapidly across an accessory pathway is often poorly tolerated.

2. Physical examination

a. General inspection usually reveals normal jugular venous pulsations despite severe tricuspid regurgitation, which is masked by a large compliant atrium. Cyanosis may be present as a result of right-to-left shunting at the atrial level. Digital clubbing will vary depending on the amount of cyanosis.

b. The most common auscultatory findings are the regurgitant murmur of tricuspid insufficiency, gallop rhythms, multiple systolic ejection sounds, and a widely split S_2.

C. Laboratory examination

1. Chest radiography may reveal cardiomegaly, caused by right atrial enlargement from tricuspid insufficiency. Typically, it is described as a globe-shaped heart with a narrow waist.

2. The **electrocardiogram** can demonstrate PR prolongation, right atrial enlargement ("Himalayan" P waves), and superior axis with or without right bundle branch block (Fig. 32.6). The QRS amplitude is characteristically low over the right precordial leads due to a diminutive right ventricle. The preexcitation pattern, if present, is almost always type B (i.e., left bundle branch pattern). Deep Q waves may be seen in leads II, III, and aVF from fibrotic thinning of the RV free wall and/or septal fibrosis.

D. Diagnostic evaluation

1. The diagnosis can be confirmed with transthoracic or transesophageal **echocardiography**, with the tricuspid valve readily visualized in the parasternal short-axis, apical four-chamber, and subcostal views.

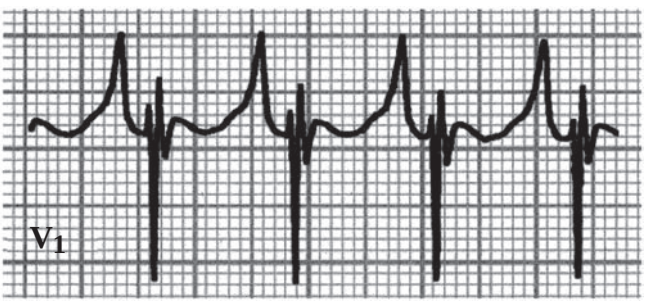

FIGURE 32.6 Lead V_1 of an electrocardiogram from a newborn infant with Ebstein anomaly demonstrates marked right atrial enlargement and an rSR′ pattern.

a. **Apical displacement of the septal leaflet** from the insertion of the anterior mitral valve leaflet by at least 8 mm/m^2 body surface area is considered diagnostic. In less obvious cases, only tethering of the septal leaflet may be found, defined as at least three accessory attachments of the leaflet to the ventricular wall causing restricted motion. An imperforate valve may rarely occur.
b. The **anterior leaflet** may produce functional obstruction of the pulmonary outflow tract. The leaflet in this circumstance is often called "sail-like." The pulmonary outflow is carefully studied to discern functional obstruction from such a leaflet rather than true anatomic atresia of pulmonary outflow.
c. Views of the **atrial septum** are included in all studies to assess the size of the ASD and degree of shunting, if present.
d. The size of the **right ventricle** and true tricuspid annulus is assessed because size guides the feasibility of surgical intervention.
e. The size and function of the **left ventricle** are assessed. The shape of the left ventricle may be unusual because of extreme leftward bowing of the ventricular septum. Left ventricular function can be affected, and abnormalities may affect long-term outcome.
f. **Associated lesions** must be excluded, such as ASD, RV outflow tract obstruction, patent ductus arteriosus, and, in rare instances, mitral valve abnormalities with associated insufficiency.

2. **Cardiac catheterization is unnecessary** for the diagnostic evaluation of Ebstein anomaly, except to exclude coronary artery disease in adult patients with risk factors for whom surgical intervention is planned. Increased risk of cardiac arrest during catheterization has been reported. A diagnostic right heart study may be indicated in the presence of associated hemodynamic abnormalities as part of preoperative planning.
3. Formal **electrophysiologic study** may be considered for patients with arrhythmias or for those being considered for surgical treatment. Radiofrequency ablation of accessory pathways is performed.

E. Therapy

1. A large number of adult patients may undergo **medical treatment**, which includes standard heart failure medications such as diuretics and digoxin. There are no good data to support ACE inhibitors in right heart failure due to Ebstein anomaly. Particular attention must be focused on the management of atrial dysrhythmias, which become more common with age. Permanent pacemaker therapy is required in 3.7% of patients, mostly for AV block and rarely for sinus node dysfunction. Endocarditis prophylaxis is no longer recommended for these patients unless they are cyanotic and unrepaired, have undergone placement of prosthetic material within the preceding 6 months (i.e., ASD occluder device), have a leak adjacent to or at the site of prosthetic material, or have had tricuspid valve replacement.
2. **Surgical correction** usually is recommended for patients with NYHA functional class III–IV symptoms despite medical therapy. The tricuspid valve may be repaired primarily or complete replacement may be necessary, and an interatrial communication, if present, is closed. Patients with symptomatic cardiomegaly, cyanosis, or arrhythmias are considered for surgical intervention. Favorable results have been achieved at centers experienced in the care of adult patients, and functional class has improved after therapy.
3. **Transcatheter closure** of an interatrial shunt can be considered in select patients with cyanosis at rest (oxygen saturation < 90%). Patient selection must be carefully evaluated, as closure of an ASD or PFO may lead to worsening RV dysfunction due to increased right-sided heart pressures. In the case of paradoxical embolic events (i.e., stroke), ASD/PFO closure is considered.

V. EISENMENGER SYNDROME. Eisenmenger syndrome is the clinical phenotype of an **extreme form of pulmonary arterial hypertension associated with congenital heart disease**. Over the last few decades, rapid advances in the modalities of diagnosis and treatment of congenital heart disease have resulted in the ability to repair defects at a much younger age. Pulmonary vascular injury is prevented in many of these children. However, Eisenmenger syndrome is still seen in older patients and occasionally in younger patients, particularly in those from developing countries where access to care may be limited. The natural history of Eisenmenger syndrome is variable; and although a cause of significant morbidity, many Eisenmenger patients survive 30 years or more after the onset of the syndrome.

A. Physiology. Patients with a systemic-to-pulmonary circulation connection will initially have left-to-right shunting of blood due to the lower pulmonary vascular resistance compared with systemic vascular resistance. Over time, because of excessive flow to the pulmonary vasculature resulting in increased shear and circumferential stress, pulmonary vascular resistance increases. Eventually, the shunt reverses, creating right-to-left flow. Although the classic form of the disease was initially used to describe the long-term consequences of a VSD, it can occur with any congenital defect with an initial left-to-right shunt including ASD, AV canal defect, patent ductus arteriosus, aortopulmonary window, and surgically created systemic-to-pulmonary artery shunts. It is important to note, however, that the **physiology and clinical presentation differ depending on the *level* of shunt**. In contrast to patients with nonrestrictive shunts at the ventricular or arterial level, most patients with ASDs do not develop Eisenmenger syndrome, and if they do, they present much later in life. In this case, atrial-level shunting is determined by the compliance of the ventricles and not due to systemic or supra-systemic pulmonary artery pressures.

B. Clinical presentation of Eisenmenger syndrome has multi-organ involvement

1. **Symptoms.** Pulmonary congestion (from the left-to-right shunt) in early childhood may be evident from the history, but improves as the shunt reverses with ensuing cyanosis. Exercise intolerance is very common. Hypoxemia can lead to erythrocytosis and symptoms of hyperviscosity (e.g., headache, dizziness, fatigue, and cerebrovascular accidents). These patients can have a bleeding diathesis due to thrombocytopenia and inadequate clotting factors. This can complicate the management of intrapulmonary thrombosis, which occurs in up to one-third of patients. Hemoptysis is a common symptom—alone or due to pulmonary infarction. Infectious complications include bacterial endocarditis and septic cerebral emboli. Atrial arrhythmias and symptoms of congestive heart failure are usually a late sign and are associated with an increased risk of sudden cardiac death.
2. **Physical examination.** The initial murmur of the associated lesion goes away with reversal of the shunt. Cyanosis and digital clubbing are present, and arterial pulses may be diminished. The cardiac examination reveals signs of elevated right heart pressure, such as jugular venous distention with a prominent *v* wave, a right parasternal heave, a loud pulmonary component of S_2 (sometimes palpable), a right-sided S_4, a holosystolic murmur of tricuspid regurgitation, and a diastolic decrescendo murmur of pulmonary regurgitation. Signs of congestive heart failure such as peripheral edema, ascites, and hepatosplenomegaly are seen later in the disease course.

C. Laboratory examination

1. **Chest radiography** is variable. It may show dilated, even calcified, central pulmonary arteries. Reduced peripheral lung markings are not commonly seen. Patients with ASDs tend to have cardiomegaly due to RV enlargement.
2. The **electrocardiogram** shows evidence of right atrial enlargement and RV hypertrophy. The presence of atrial arrhythmias should be investigated, particularly in the presence of palpitations.

D. Diagnostic evaluation

1. **Echocardiography.** Two-dimensional echocardiography helps in the detailed assessment of the level of the defect, associated lesions, and ventricular function. Doppler measurements can demonstrate and assess the size of the shunt as well as RV pressure and volume overload.
2. **Cardiac catheterization.** Cardiac catheterization is often necessary in these patients to assess the pulmonary vascular resistance. Demonstration of pulmonary vasoreactivity to oxygen, nitric oxide, or other pulmonary vasodilators is prognostic for these patients and can help identify which patients will most benefit from advanced therapies for pulmonary arterial hypertension.

E. Therapy

1. **Medical management**
   a. Chronic nocturnal oxygen therapy has not been shown to be beneficial, although it may improve symptoms in some patients. Anticoagulation is controversial because it can also predispose to hemorrhage or hemoptysis, but it is helpful in preventing thromboembolic events. Hyperviscosity can be managed in ***symptomatic*** patients by performing phlebotomy with isovolumic replenishment, but **routine phlebotomy is contraindicated** due to its effect on iron stores, oxygen-carrying capacity, and increased risk of stroke. Monitoring of iron levels and iron replacement, therefore, is paramount. The management of right-sided heart failure is problematic and the use of digoxin in these patients is controversial. Diuretics should be used cautiously because aggressive diuresis predisposes to hyperviscosity and decreases preload. Endocarditis prophylaxis is warranted.
   b. Over the last few years, there has been a paradigm shift regarding the treatment of pulmonary hypertension in Eisenmenger syndrome. While traditional therapy focused on preventive and palliative measures, there is accruing evidence to suggest that the **disease is in fact modifiable and that selective pulmonary vasodilators are not only safe but likely beneficial** in this population. These agents include endothelin antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors. The only randomized, placebo-controlled trial performed to date in Eisenmenger patients, BREATHE-5, showed reduction in pulmonary vascular resistance and improvement in exercise capacity (with no detriment to oxygen saturation) using bosentan (an endothelin antagonist). In general, intravenous treatments are avoided in this population due to the risk of paradoxical embolism and increased infectious risk with indwelling lines.
2. **Surgical management.** Selected patients may be candidates for combined heart–lung transplantation or lung transplantation with concomitant repair of the intracardiac defect, if feasible. Timing of these interventions may be difficult because of the relatively long-term survival of these patients after the onset of the disease process and the recent availability of selective pulmonary vasoactive therapy.

F. Eisenmenger syndrome in special situations

1. **Travel** to areas of high altitude should be avoided because it may result in acute right heart failure. Air travel, however, is not contraindicated, as cabin pressures during commercial flights are generally well-tolerated.
2. **Pregnancy** in these patients is high risk to the fetus and the mother (> 50% maternal mortality) and is generally contraindicated. Given the high risk of maternal and fetal mortality, contraceptive methods (preferably without the use of estrogen) are critical. Elective termination should be discussed with pregnant Eisenmenger patients.
3. **Noncardiac surgery** is also associated with high risk and should be performed under the supervision of anesthesiologists familiar with Eisenmenger syndrome.

ACKNOWLEDGMENTS: *The authors thank Drs. Yuli Kim, Athar Qureshi, Keith Ellis, J. Donald Moore, and Douglas S. Moodie for their contributions to earlier editions of this chapter.*

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SECTION VII

Clinical Cardiology

EDITOR

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CHAPTER 33

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Syncope

I. INTRODUCTION

A. Syncope is a common medical problem that accounts for approximately 6% of medical admissions and 3% of emergency room visits. Syncope is defined as a **sudden transient loss of consciousness with associated loss of postural tone. Recovery is spontaneous, without neurologic deficit and without requiring electrical or chemical cardioversion.** Generally, a fall in systolic blood pressure below 70 mm Hg or a mean arterial pressure of 40 mm Hg results in loss of consciousness. Cerebral blood flow usually decreases with aging, making the elderly at higher risk for syncope.

B. Syncope as a symptom can be caused by a **variety of medical diseases that produce a transient interruption of cerebral blood flow**.

1. A genuine effort should be made to **determine a specific cause of syncope**. Identifying a specific cause can help in the selection of therapy, prevent recurrences, minimize expensive evaluations, and decrease morbidity.
2. **Patients with cardiac syncope have higher rates of mortality and sudden death** at follow-up. Identifying and treating cardiac syncope can improve outcome.

II. CLINICAL PRESENTATION.

Although a variety of diagnostic tests are available for evaluation of syncope, a thorough history and physical examination are crucial to determine the cause and the best diagnostic approach. A good history and physical examination can provide a clue to the diagnosis in up to 50% of cases.

A. Signs and symptoms. Accurately described symptoms can lead to specific diagnostic considerations, as illustrated in Tables 33.1 and 33.2. Table 33.3 lists the prevalence of various causes of syncope as seen in the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) trial, a prospective systemic evaluation of consecutive patients referred to various emergency rooms for syncope.

1. **The most** important aspect of history taking is to **determine the circumstances before syncope (i.e., the prodrome)**; whether there is association with any particular activity, exertion, or change in position; and the frequency of occurrence.
2. The initial approach to any patient with syncope should include a **search for the presence of structural heart disease such as valvular stenosis, cardiomyopathy, or myocardial infarction**. The presence of any of these may suggest more malignant causes such as ventricular tachycardia.
3. **Symptoms of vasovagal syncope.** Calkins et al. (1) reported that a careful history could diagnose vasovagal syncope. They reported that **women (< 55 years) with a postsyncopal recovery period that included fatigue** and patients with **clear precipitating factors, diaphoresis, palpitations preceding syncope, and severe fatigue after syncope** were more likely to have vasovagal syncope than ventricular tachycardia or complete heart block.
4. **Convulsive syncope.** Occasionally, a syncopal episode is accompanied by **mild muscular jerking** as a result of cerebral anoxia. This phenomenon is not true epilepsy, and the physician must make every effort to distinguish between

TABLE 33.1 Cardiovascular Causes of Syncope

Neurally mediated (vasovagal)
Situational
Micturition
Defecation
Postprandial
Swallowing
Coughing
Sneezing
Glossopharyngeal neuralgia
Orthostatic syncope
Carotid sinus syncope
Cardioinhibitory
Vasodepressor
Mixed
Mechanical
Aortic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Mitral stenosis
Pulmonic stenosis
Pulmonary hypertension or embolism
Myocardial infarction
Cardiac tamponade
Electrical
Second- and third-degree atrioventricular block
Sick sinus syndrome
Supraventricular tachycardia
Ventricular tachycardia
Torsade de pointes
Pacemaker malfunction

syncope and a seizure. Syncope typically occurs without an aura and has a more deliberate onset. Seizures are characterized by severe jerking motions, longer periods of unconsciousness, and severe fatigue after the event (i.e., postictal state). Seizures may occur without regard to patient positioning. In contrast, syncope rarely happens when a person is recumbent.

5. Other entities that make diagnosis difficult are **vertigo, transient ischemic events, somatization disorders (e.g., conversion and hysteria), cataplexy, epilepsy, and drop attacks**.

TABLE 33.2 Clinical Features Suggesting Specific Causes

Symptoms or finding	Diagnostic consideration
After sudden unexpected pain, unpleasant sight, sound, or smell	Vasovagal syncope
During or immediately after micturition, cough, swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Bradycardia or vasodepressor
Upon standing	Orthostatic hypotension
Taking hypotensive medication	Drug-induced syncope
Symptoms within 1 h after meals	Postprandial hypertension
Prolonged standing at attention	Vasovagal
Well-trained athlete after exertion	Vasovagal
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Aortic stenosis, pulmonary hypertension, mitral stenosis, HOCM, coronary artery disease
With head rotation, pressure on carotid sinus	Carotid sinus syncope
Associated with vertigo, dysarthria, diplopia	TIA, stroke
With arm exercise	Subclavian steal syndrome

HOCM, hypertrophic obstructive cardiomyopathy; TIA, transient ischemic attack.

Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78–88.

TABLE 33.3 Causes of Syncope in the Evaluation of Guidelines in Syncope Study 2 Trial

Neurally mediated	Orthostatic hypotension	Cardiac arrhythmia	Structural cardiopulmonary	Nonsyncopal

• Vasovagal
• Carotid sinus
• Situational
  • Cough
  • Micturition
  • Defecation
  • Swallow
  • Others
	• Drug induced
	• ANS failure
	  • Primary
	  • Secondary
	• Volume depletion
		• Brady
		  • Sick sinus
		  • AV block
		• Tachy
		  • VT
		  • SVT
		• Inherited
			• AMI
			• Aortic stenosis
			• HOCM
			• Pulmonary HTN
			• Others
				• Metabolic
				• Epilepsy
				• Intoxications
				• Drop attacks
				• Psychogenic
				• TIA
				• Falls

66%	10%	11%	5%	6%

Unknown cause: 2%.

AMI, acute myocardial infarction; ANS, autonomic nervous system; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; VT, ventricular tachycardia.

Adapted from Brignole M. Diagnosis and treatment of syncope. *Heart.* 2007;93:130–136.

6. The examiner should always **carefully review the medications of a patient with syncope** for their potential role, directly or by interaction with other medications.

B. Physical findings

1. The **physical examination is especially important when the patient is unable to describe the event** and no witnesses are available, as certain findings on examination can direct the physician in the diagnostic evaluation.
2. The **comprehensive evaluation** should include a funduscopic examination of the eye for evidence of embolism. The evaluation should also search for the presence of carotid bruit and assessment of the carotid upstroke; subtle neurologic deficits that may result from a stroke or neuropathy; cardiac murmurs with attention given to valvular findings and extra heart sounds (such as tumor plop); peripheral pulses for evidence of peripheral vascular disease and entities such as subclavian steal; and dermatologic clues that may suggest collagen vascular disease or vasculitis.
3. In examining a patient with syncope, it is important to check **blood pressure in both arms as well as orthostatic blood pressure**. Repeated orthostatic blood pressure measurements may be needed when there is a high level of clinical suspicion for orthostatic syncope (see Section **II.C.1.c**).
4. Syncope in the absence of underlying heart disease is not associated with increased mortality. The morbidity of such episodes is related to harm that may occur in association with a syncopal event.

C. Etiology and pathophysiology

1. **Neurally mediated syncope.** Vasovagal or neurally mediated syncope is the **most common cause of syncope**. Many situations can lead to vasovagal "fainting." Examples include unpleasant smell, sudden pain, acute blood loss, and sustained upright posture. Vasovagal reactions are often preceded by an increase in heart rate and blood pressure.
   a. **Neurocardiogenic syncope** is thought to be the result of **autonomic overactivity followed by a fall in peripheral vascular resistance, without a significant rise in cardiac output**. In susceptible individuals, the stimulation of mechanoreceptors located in the inferior and posterior wall of the left ventricle by stretch, cardiac distention, or rapid systolic contraction leads to increased neural discharges through unmyelinated C fibers to the vasomotor center in the medulla, resulting in enhanced parasympathetic and decreased sympathetic activities. The withdrawal of the sympathetic nervous system results in sudden bradycardia or hypotension. Animal studies suggest that cardiac afferents may not be required to initiate a vasodepressor response and that other potential mechanisms, such as release of endogenous opioids or nitric oxide inhibition of sympathetic nerve firing and primary central nervous system activation, may play a role in vasodepressor syncope.
   b. **Situational syncope.** Patients often recall situational syncopal episodes. **Micturition, defecation, cough, and trumpet playing** are examples. The action causes a reflex vasodilation (vagally mediated) that is exacerbated if the patient performs a Valsalva maneuver, which decreases the blood return to the right heart.
   c. **Orthostatic syncope. Postural hypotension** is reported in up to 24% of elderly people. Normally when a person stands, the systolic blood pressure drops only 5 to 15 mm Hg, and the diastolic pressure rises slightly. In orthostasis, the decrease in systolic blood pressure exceeds 20 mm Hg; frequently, the diastolic pressure drops by > 10 mm Hg. This finding demands a search for a potential cause.
      (1) Common causes include **volume depletion, medications, diabetes, alcohol, infection, and varicose veins**.

(2) **Dysautonomic syndromes** causing orthostatic hypotension are divided into two categories: primary and secondary. Primary autonomic failure is idiopathic and includes pure autonomic failure (i.e., Bradbury-Eggleston syndrome) and multisystem atrophy (i.e., Shy-Drager syndrome). Secondary causes include amyloidosis, tabes dorsalis, multiple sclerosis, spinal tumors, and familial dysautonomia.

a. **Carotid sinus syncope.** Less than 1% of patients presenting with syncope have been given a diagnosis of carotid sinus syncope. This entity should be considered in patients with spontaneous symptoms while shaving, swimming, turning the head, or wearing a tight collar, as well as in older patients with recurrent syncope. A cardioinhibitory response (i.e., bradycardia) occurs in about 70%, and a vasodepressor response (i.e., hypotension) occurs in 10%. The remaining patients have a mixed response (i.e., bradycardia with hypotension). Carotid sinus syncope is elicited by manual pressure on the carotid sinus and can be blocked by atropine. Clinical presentation along with findings of carotid sinus hypersensitivity in the absence of other potential causes is enough to make the diagnosis. Symptom reproduction during carotid massage is not necessary for a diagnosis. A positive carotid test result is defined by cardiac asystole of 3 seconds or longer, a drop in systolic blood pressure of > 50 mm Hg, or a drop of > 30 mm Hg in blood pressure and symptoms. Carotid massage should be avoided in patients with a history of stroke or transient ischemic attack (TIA) within 3 months (unless they have had normal carotid Doppler results) or those patients in whom carotid bruits are heard on clinical examination.

2. **Cardiac syncope**

a. **Mechanical causes**

(1) Syncope or related symptoms frequently occur with exertion and arise from left ventricular outflow obstruction, as seen in aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM). With exertion, peripheral vascular resistance falls, but the cardiac output is fixed, leading to hypotension. Arrhythmias and altered baroreceptor response also play a role in syncope in patients with an obvious mechanical cause, such as aortic stenosis.

(2) **Right ventricular outflow obstruction** can also result in syncope. This condition can also trigger a vasodepressor component by mechanisms similar to neurocardiogenic syncope.

(3) **Myocardial ischemia and infarction, pulmonary embolus, and cardiac tamponade** should be kept in mind. **Syncope may be the initial complaint in 7% of patients older than 65 years presenting with myocardial infarction**.

(4) **Patients with hypertrophic obstructive cardiomyopathy** have an annual risk of sudden death in nonselective populations of approximately 1% per year. Syncope increases the relative risk of sudden cardiac death by approximately fivefold. The presence or absence of other sudden death risk factors (family history of sudden cardiac death, nonsustained ventricular tachycardia, marked left ventricular hypertrophy, and significant left ventricular outflow tract gradient) influences the risk of sudden cardiac death. Electrophysiologic (EP) testing plays a minimal role in risk stratification, as does genotyping for specific mutations currently. Treatment in high-risk patients usually includes the use of β-blockers, calcium channel blockers, disopyramide and other antiarrhythmics, and frequently implantable cardioverter–defibrillator (ICD) placement.

(5) **Arrhythmogenic right ventricular dysplasia** is a disorder in which syncope is caused by ventricular tachycardia originating in the right ventricle secondary to replacement of myocardium by adipose tissue

and/or fibrosis. The imaging modality of choice is cardiac magnetic resonance imaging (usually with fat suppression), which usually shows thinning, aneurysms, and replacement of right ventricular myocardium with adipose and fibrotic tissues. It is thought to be a common cause of sudden cardiac death in patients younger than 35 years and may be familial in 30% to 50% of patients. It is usually diagnosed based upon the presenting electrocardiogram (ECG), suggested by the presence of premature ventricular contractions or sustained ventricular tachycardia with a left bundle branch morphology. Treatment of syncope in this setting usually includes ICD implantation, and yearly ICD appropriate therapy rates are usually 15% to 20%.

(6) Ion Channel disorders

(i) Long QT syndrome. This is characterized by prolongation of the QT interval, with a measured QTc > 450 milliseconds. The long QT syndromes are actually a heterogeneous group of disorders and have been mapped to genetic defects in either cardiac potassium channels (LQT1 and LQT2) or sodium channels (LQT3). It is worthwhile mentioning that the potassium channel mutations involve a loss of function of the potassium channels, whereas sodium channel mutations involve a partial gain of function. The lifetime risk of syncope or sudden cardiac death increases with increasing QTc, reaching 50% for QTc > 500 milliseconds. Syncope is usually the result of an episode of torsade de pointes or self–terminating polymorphic ventricular tachycardia and is an ominous finding. Treatment options include β-blockers and ICD implantation, as well as lifestyle modifications, including the restriction of strenuous or competitive exercise and avoidance of QT-prolonging drugs.

(ii) Brugada syndrome is a disorder of cardiac sodium channels that results in transient downsloping ST elevations in the anterior precordial leads and leads to a susceptibility to polymorphic ventricular tachycardia. Patients with Brugada syndrome with syncope have a 2-year risk of sudden cardiac death of approximately 30%; therefore, treatment with an implantable defibrillator is recommended.

b. Electrical causes. Ventricular tachycardia, sick sinus syndrome, and atrioventricular block are the most common causes of syncope related to arrhythmias. One must also consider supraventricular tachycardia, Wolff-Parkinson-White syndrome, and torsade de pointes. Arrhythmic syncope carries the worst prognosis and must be thoroughly evaluated.

(1) Primary cardiac arrhythmias are the most common cause of syncope in patients with known cardiac disease, such as previous myocardial infarction, left ventricular dysfunction, or cardiomyopathy.

(2) Medications that prolong the QT interval and electrolyte abnormalities should also be considered as causes of arrhythmic syncope.

(3) Patients with pacemakers should have their pacemaker interrogated for possible malfunction. The possible causes include battery depletion, lead malfunction, or lead dislodgment. Individuals with pacemaker or implantable defibrillators should be educated about the devices and examined regularly. An observed phenomenon in patients with atrial fibrillation who undergo atrioventricular nodal ablation (and are subsequently pacemaker dependent) is the development of syncope secondary to ventricular tachycardia, presumably because of an R on T phenomenon. Because of this, such patients are usually programmed with a higher backup rate (at least 90 beats per minute) for the 4 to 6 weeks following atrioventricular nodal ablation.

3. **Noncardiovascular syncope**
   a. **Neurologic causes** include stroke, TIAs, normal pressure hydrocephalus, and seizures. Other causes include orthostatic hypotension from dysautonomia, and this diagnosis should be suggested based on history, screening neurologic examination, and orthostatic vital signs.
   b. **Metabolic causes** include arrhythmias induced by hypoglycemia, hypoxia, and hypokalemia.
   c. **Psychogenic causes** include anxiety disorder, panic disorder, hyperventilation, somatization, depression, hysterical syncope (i.e., no change in blood pressure or pulse), and conversion disorder.
   d. Drugs that can cause syncope include **nitrates, angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, quinidine, procainamide, disopyramide, flecainide, amiodarone, diuretics, vincristine, insulin, cocaine, and digoxin. The α-blockers** (e.g., prazosin) are potent agents and commonly cause orthostatic hypotension, especially in the elderly. These agents should be initiated with careful instructions to the patient regarding orthostasis and should be prescribed to be taken in the evening. Orthostatic hypotension can be induced by tricyclic antidepressants or antiparkinsonian agents as well.
4. **Unknown or unexplained causes.** Past studies indicated that 33% to 50% of patients with syncope had no identifiable cause. One study showed that these patients are still at a higher risk for subsequent death from any cause, with a multivariable-adjusted hazard ratio of death of 1.32 (95% confidence interval: 1.09 to 1.60). Other diagnostic tools such as tilt table testing, loop recorders, signal-averaged electrocardiography (SAECG), and EP studies may assist physicians in identifying a previously unknown cause of syncope.

   Stress testing, electroencephalography, computed tomography of the head, and cerebral angiography have a very low yield unless there is a history of trauma, stroke, or seizures.

III. DIAGNOSTIC TESTING. A single ECG offers the possible diagnosis in approximately 5% of cases. It can demonstrate sinus pause, high-degree atrioventricular block, prolonged QT interval, or Wolff-Parkinson-White syndrome. Echocardiography, Holter monitoring, loop recorders, SAECG, EP testing, and tilt table testing are major diagnostic tools. Their yield depends on the presence or absence of underlying structural heart disease.

A. In evaluating a patient with syncope, **it is important to differentiate patients with and without structural heart disease**. The goal of evaluation should be to obtain a correlation between symptoms and an abnormal finding during diagnostic testing. There are several key points:
1. Cardiac syncope carries a high mortality rate, and physicians should **admit any individual suspected of having cardiac syncope** for evaluation.
2. **Syncope in the elderly** is frequently multifactorial (e.g., drugs, structural heart disease, anemia, volume depletion, and decreased baroreceptor sensitivity).
3. The **workup should be individualized** to be cost-effective and accurate, as shown in Figure 33.1.

B. **Echocardiography** is routinely used for diagnosing patients with syncope who are suspected of having cardiac disease. The echocardiogram is useful in diagnosing valve pathology and myocardial processes that may contribute to syncope, such as aortic stenosis and cardiac tumors (i.e., myxomas). Some small studies and case reports suggest that echocardiographic data frequently aid in diagnosing a cardiac origin for syncope. However, larger studies have shown that the diagnostic yield of echocardiography is quite low in the absence of clinical, physical, or electrocardiographic findings, suggesting a cardiac abnormality. In patients with syncope or presyncope and a normal physical examination, mitral valve prolapse is the most common finding.

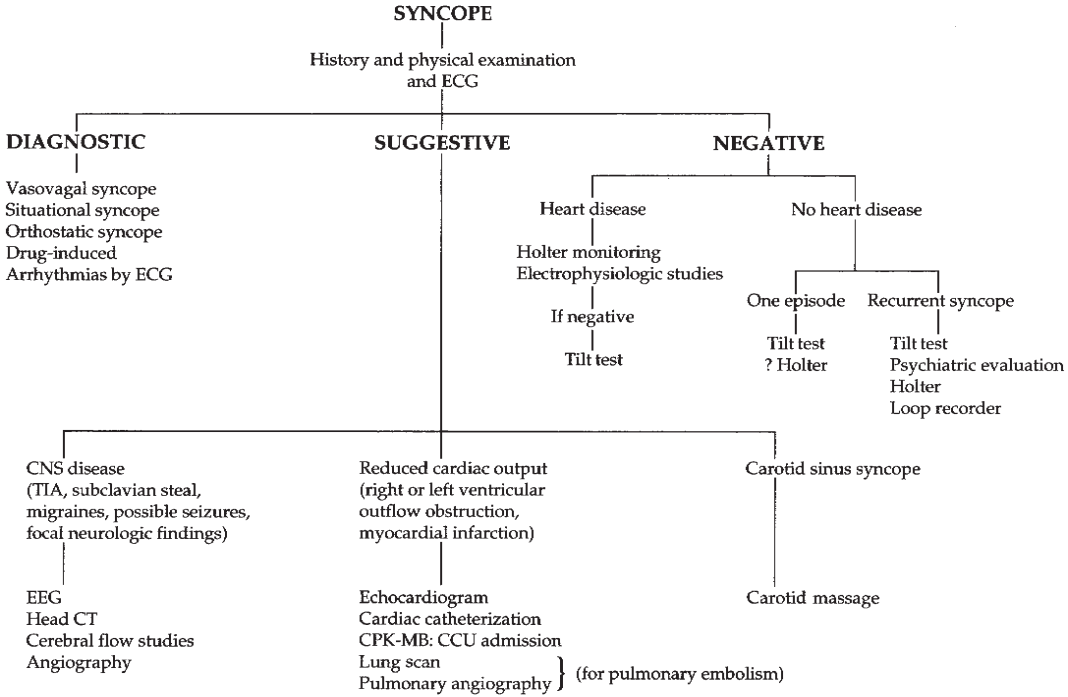

FIGURE 33.1 Schematic algorithm for the evaluation of patients presenting with syncope. ECG, electrocardiogram; CNS, central nervous system; TIA, transient ischemic attack; EEG, electroencephalogram; CT, computed tomography; CPK-MB, creatine phosphokinase-myocardial band; CCU, coronary care unit. (From Kapoor WN. Diagnostic evaluation of syncope. *Am J Med.* 1991;90:91–106, with permission.)

C. Holter monitoring. Holter or prolonged electrocardiographic monitoring is one of the most commonly used tests for the evaluation of syncope. However, symptomatic correlation of a cardiac arrhythmia with a syncopal spell occurs in only about 4% of cases. **A completely normal or negative Holter result may be just as helpful as a captured arrhythmia**. The sensitivity and specificity of electrocardiographic monitoring for arrhythmic syncope are not known because of the lack of criteria for abnormal results or a gold standard that is independent of arrhythmias diagnosed by monitoring. The difficulty is to establish a correlation between arrhythmia and asyncopal spell.

1. Gibson et al. reviewed 1,512 Holter recordings of patients referred for evaluation of syncope; a total of 255 (17%) patients reported syncope or related symptoms, of which only 30 (2%) were correlated with arrhythmias. Ventricular tachycardia was predominant in the syncope group, whereas supraventricular and sinus tachycardia were common in the presyncope group. There was an increasing incidence of supraventricular and ventricular tachycardia with age, but the correlation with syncope remained obscure.
2. Pratt et al. studied 80 patients with structural heart disease were investigated by Holter monitors and follow-up EP study. The authors concluded that the combination of a clinical presentation of syncope, presence of coronary artery disease, and left ventricular ejection fraction < 30% had a better positive predictive value in terms of inducibility of sustained ventricular tachycardia than any ambulatory electrocardiographic monitoring criteria.
3. Studies have shown that **sinus pauses longer than 2 seconds, second-degree atrioventricular block (type II) or complete atrioventricular block, and runs of nonsustained ventricular tachycardia on Holter monitoring should be taken seriously**.
4. The duration of electrocardiographic monitoring is an important issue. It appears that **48 hours is optimal**.

D. Loop recorder. When used correctly, **loop recorders effectively couple arrhythmias and syncope**. Loop recorders are **useful in patients with recurrent frequent syncope**, who benefit from prolonged monitoring for weeks to months. When activated by the patient, loop recorders permanently record the previous 4 to 5 minutes of rhythm data. The recorder can capture arrhythmias during a syncopal episode if the patient activates it after regaining consciousness. The next-generation loop recorders (e.g., Medtronic-Reveal) are implantable devices similar to a pacemaker. They continuously record a single-lead ECG. These devices have the capability to store a 15-minute segment of cardiac rhythm when activated during or after a syncopal episode by the patient and can also be programmed to automatically begin recording when triggered by a high or low heart rate.

Two randomized clinical trials have shown that implantable loop recorders (ILRs) are more likely to lead to a diagnosis of syncope than conventional management. In the Randomized Assessment of Syncope Trial (RAST), 60 patients were randomized to receive either an ILR or conventional testing. A diagnosis was made in 52% of the patients with an ILR and in only 20% of the patients receiving conventional testing ($p = 0.012$). In the Eastbourne Syncope Assessment Study (EaSyAS), 201 patients were randomized to receive an ILR or conventional diagnostic testing. An ECG diagnosis of syncope was established in 33% of the patients with ILR but in only 4% of the conventional strategy patients ($p < 0.0001$).

E. SAECG is useful in predicting inducibility of ventricular arrhythmias by EP testing, especially in patients with ischemic heart disease. However, it is not helpful in diagnosing sinus pauses or atrioventricular block. Most patients with syncope in the setting of structural heart disease are likely to require an EP study or implantation of a defibrillator if left ventricular dysfunction or coronary artery disease is present. SAECG may, therefore, be more appropriately employed in patients with

structurally normal hearts to predict whether an EP study is indicated. SAECG may also be helpful in identifying patients with arrhythmogenic right ventricular dysplasia or infiltrative cardiomyopathies.

1. **SAECG** is a collection of 100 to 300 single QRS complexes, which are amplified, filtered for noise, and averaged to determine the presence of late potentials. Late potential refers to the presence of low-amplitude, high-frequency signals in the terminal segment of the amplified QRS. **The late potentials seem to identify the presence of a reentrant substrate and may indicate an independent risk for the development of future life-threatening ventricular arrhythmias**.
2. **When combined with an ejection fraction of < 40%, the presence of late potentials can be used to identify patients with an even higher risk of ventricular tachycardia**. Studies evaluating this profile of patients have demonstrated sensitivity of 90% and specificity of 95% to 100% in predicting inducible, sustained ventricular tachycardia.
3. Various commercially available devices use different filters, lead configurations, and processing algorithms; therefore, the **criteria for abnormal SAECG may vary among manufacturers**. Abnormal SAECG findings include total QRS duration > 114 milliseconds, root mean square voltage of the terminal 40 milliseconds of the complex (RMS40) < 20 μV, or duration of low-amplitude signals (LASs) in terminal QRS (LAS) > 38 milliseconds. The total duration of the QRS complex, including the late potential, is independent of other measures of cardiac risk. RMS40 is probably the most sensitive and specific of all three variables.
4. **A positive SAECG finding suggests the need for further EP testing**, especially in individuals with known heart disease.
5. The **absence of late potentials has a high negative predictive value (94%)**. In patients with syncope and a negative SAECG result, EP study is not absolutely indicated. A normal SAECG result is associated with a < 5% risk of inducible ventricular tachycardia on EP testing.
6. **No satisfactory method of analysis is available for patients with bundle branch block**, because it is virtually impossible to distinguish between late activation due to the conduction defect and that due to the reentrant substrate.

F. EP study. EP study should be considered in **patients with underlying structural heart disease or in elderly patients with recurrent syncope**. Similar to Holter monitoring, induced arrhythmias during EP study do not usually produce syncope in the laboratory; therefore, a cause-and-effect relationship often has to be assumed. Regardless, EP testing is useful in better delineating a cardiac cause of syncope, especially in people with baseline bundle branch or bifascicular block.

1. **Indications** for EP study generally include the following:
   - **(a)** Known or suspected ventricular tachyarrhythmias, especially to guide therapy
   - **(b)** Uncertainty about the origin of wide QRS tachycardia
   - **(c)** Patients with unexplained syncope and history of heart disease
   - **(d)** Patients with nonsustained ventricular tachycardia, impaired left ventricular function, and late potentials on SAECG, used to stratify prognosis and guide therapy
   - **(e)** Patients with drug-refractory malignant ventricular arrhythmias who are candidates for ablative therapy
2. Some **EP findings** are considered important in the cause of syncope:
   - **(a)** Sustained monomorphic ventricular tachycardia
   - **(b)** Sinus node recovery time longer than 3 seconds
   - **(c)** Spontaneous or pacing-induced infranodal block or infrahisian block
   - **(d)** Baseline His-ventricle (HV) interval > 100 milliseconds or significant prolongation after procainamide challenge
   - **(e)** Paroxysmal supraventricular tachycardia with symptomatic hypotension

3. The sensitivity and specificity of induced, sustained monomorphic ventricular tachycardia are > 90%. However, the sensitivity of prolonged sinus node recovery time is low (69%), although the specificity is reported to be as high as 100% when EP studies are compared with results of Holter monitoring.
4. Patients with no known heart disease, ejection fraction > 40%, normal electrocardiographic and Holter results, and multiple syncopal episodes (more than five per year) often have **negative EP study results**. A 3-year follow-up of patients with negative EP test results revealed a 24% recurrence rate of syncope and a mortality rate of 15%; however, **a 3-year follow-up after positive EP study results and treatment revealed a 32% recurrence rate and higher mortality (61%)**.
5. For patients with coronary artery disease and syncope who have mild to moderate left ventricular dysfunction (left ventricular ejection fraction, 35% to 50%), inducible ventricular tachycardia during an EP study is unlikely, but the study is often appropriate, given the significant implications of a positive test.
6. Patients with stable coronary artery disease and severe left ventricular dysfunction (< 35%) have substantial benefits once treated with an ICD. Hence, an EP study is often not required.
7. Patients with severe nonischemic dilated cardiomyopathy (EF < 40%) and New York Heart Association (NYHA) class II–III symptoms do not benefit from an EP study, and there is no evidence to support the use of antiarrhythmic medications in these patients. Evidence from the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) supports the mortality benefit from ICD implantation in these patients with heart failure symptoms. Moreover, patients with wide QRS (> 120 milliseconds) and severe cardiomyopathy with NYHA class II–III symptoms benefit symptomatically from cardiac resynchronization therapy (CRT) and have an improvement in mortality compared with antiarrhythmic medications by receiving a CRT-defibrillator device.
8. **The limitations and disadvantages of EP testing** are high cost, invasive nature, lower specificity if a more aggressive electrical stimulation protocol is used, and poor prediction of bradyarrhythmias and several other arrhythmias of unknown clinical significance without symptoms. A detailed discussion of EP studies is provided in Chapter 63.

G. Upright tilt table testing

1. **Mechanism.** It is believed that a surge in catecholamines may paradoxically enhance the susceptibility to bradycardia and hypotension, resulting in syncope by the activation of cardiac mechanoreceptors. Vasovagal syncope can be induced by keeping susceptible individuals upright on a tilt table with or without chemical stimulation. The mechanism is not completely understood, but it is believed to be similar to the activation of the Bezold-Jarisch reflex.
2. The best candidate for a tilt table study is a **person with unexplained recurrent syncope, with underlying heart disease and a negative EP study or with no known structural heart disease**. In reviewing various tilt table studies, Kapoor et al. (2) found that 49% of patients had a positive response during tilt table testing, 66% had a positive response using isoproterenol with tilt table testing, 65% had a cardioinhibitory response, and 30% had a vasodepressor response. The **number of positive responses increased with an increasing angle of tilt and longer duration**; however, there was no correlation between positive responses and maximum dose of isoproterenol. Although limited information is available on the sensitivity of upright tilt table testing, it is reported to be about 70%. The specificity has ranged from 35% to 92% with isoproterenol. Kapoor et al. (2) reported higher false-positive rates with isoproterenol, especially at higher angle of tilt, indicating lower specificity.

3. It appears that **tilt table testing, when used in the appropriate setting, is beneficial in diagnosing previously unexplained syncope**, preventing recurrences, and reducing morbidity.

H. Adenosine triphosphate (ATP) test. The intravenous injection of ATP has been suggested to aid in the diagnosis of unexplained syncope. Patients are injected with a 20-mg bolus of ATP and are kept in a supine position with continuous electrocardiographic monitoring. Asystole lasting more than 6 seconds or atrioventricular block lasting longer than 10 seconds is considered abnormal. In patients with unexplained syncope, the ATP test may be able to diagnose syncope caused by transient atrioventricular block. However, it has not been able to reproduce sinus arrest. This test remains in the investigational phase, and outcome data are not yet available.

IV. TREATMENT.

Treatment of syncope is individualized and depends on the underlying cause.

A. Nonpharmacologic therapy. The treatment of syncope hinges on preventing recurrent episodes and lowering mortality. The neurally mediated reflex syncopal syndromes can be treated in part by behavior modification. Initial measures aimed at reducing these syncopal events include advising patients to avoid precipitating triggers. Patients should also be counseled on the avoidance of volume depletion. Medication regimens such as chronic vasodilator therapy may predispose to syncope and should also be avoided. Moderate exercise training, tilt training, and increased intake of salt and electrolytes are some initial measures that help in reducing vasovagal syncope.

Small trials have shown a benefit from tilt training and counterpressure maneuvers to prevent neurally mediated syncope. In tilt training, patients are subjected to progressively longer periods of upright posture in order to condition the neural and vascular systems to counter gravitational stress. In one small study of 42 patients with neurally mediated syncope, tilt training resolved symptoms in 36 patients during the period of training. Counterpressure maneuvers are isometric arm and leg exercises that patients perform at the first sign of a syncopal episode. These maneuvers raise peripheral vascular resistance and blood pressure and can prevent the syncopal spell. In one trial of 21 patients, patients were trained to perform isometric leg exercises during a tilt table test. The maneuver successfully raised blood pressure and prevented syncope during the tilt table test, and at follow-up in 10 months, 13 of 20 patients continued to use the maneuver in daily life. These treatments are often used as first-line therapy for neurally mediated syncope.

B. Medical therapy. Most long-term, randomized studies testing the utility of using medications to prevent syncope, including those of β-blockers, have failed to show any benefit over placebo, and these treatments are generally considered second line. Table 33.4 lists the various causes of syncope and potential medical treatment.

1. **Electrolyte abnormalities must be corrected** if they are suspected as the cause of arrhythmias (e.g., prolonged QT from hypomagnesemia or hypocalcemia).
2. **Particular attention should be given to the patient's medications**, since they may have drug–drug interactions or proarrhythmic potential that may cause orthostatic hypotension. Unnecessary medications should be discontinued.

C. Device therapy

1. **Symptomatic bradyarrhythmias and atrioventricular blocks require pacemaker implantation**
   a. Patients with an HV interval (i.e., impulse time from atrioventricular node to the ventricle) of > 100 milliseconds are at a high risk for **progression to heart block** and may benefit from a pacemaker.
   b. Although the mode of pacing is debated, in **patients with carotid sinus syncope**, a dual-chamber pacer with rate responsiveness is most desirable.

TABLE 33.4 Medical Therapy in Syncope

Cause	Treatment
Vasodepressor syncope	β-Blockers, disopyramide CR 200 mg bid, fluoxetine 20–80 mg daily, sertraline 50–200 mg daily, dual-chamber pacing, theophylline ER 300–600 mg daily, and scopolamine hydrobromide 0.4–0.8 mg bid–tid
Dysautonomic syncope	Elastic support hose, water exercise, increased sodium intake, fludrocortisones 0.05–0.2 mg daily, ephedrine sulfate 25–50 mg tid, midodrine 5–10 mg tid, erythropoietin, and methylphenidate 5–20 bid–tid
Situational syncope	Stool softeners, urinating while sitting down
Carotid sinus syncope	Avoidance of tight collars, surgical removal of carotid sinus tumor, pacemaker in patients with predominantly cardioinhibitory syncope
Tachyarrhythmias	Implantable defibrillators or trial of antiarrhythmic agents

CR, controlled release; ER, extended release.

Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78–88.

c. Dual-chamber pacing has reduced the short- and long-term likelihood of syncope in highly selected patients with recurrent vasovagal syncope. In patients with recurrent vasovagal syncope, dual pacing with hysteresis should be considered an option if other treatment modalities have been ineffective.

2. **Antiarrhythmic therapy** appears to decrease the frequency of syncope; however, it has not been shown to improve survival. In patients with malignant or life-threatening ventricular arrhythmias or inducible, sustained monomorphic ventricular tachycardia, **implantable defibrillators** are the best option based on study findings, especially in patients with unexplained syncope who have a history of coronary artery disease and severe left ventricular dysfunction.

D. Surgical therapy

1. **Patients who have exertional cardiac syncope** due to left or right heart outflow obstruction, such as HOCM, should be instructed to **avoid exertional activities** that precipitate syncope and **should be considered for surgical repair**.
2. Surgical septal myectomy is the procedure of choice in **patients with HOCM**; however, percutaneous septal ablation with alcohol is an alternative in patients who are considered at high surgical risk.
3. Coronary artery bypass grafting or percutaneous coronary intervention is strongly indicated in **patients with life-threatening arrhythmias (usually polymorphic ventricular tachycardias) due to myocardial ischemia**.

V. FOLLOW-UP. The follow-up of patients with syncope often depends on the cause and the therapy being instituted.

A. Patients with frequent spells of syncope without an identifiable cause should be considered for more extensive monitoring such as ILRs, because they may have an undiagnosed cardiac cause.

B. Patients with cardiac syncope require very close follow-up because their mortality rates are significantly higher than those of patients with other causes of syncope.

C. **Elderly patients** may require closer monitoring about their home situation, their need for assistance with activities of daily living, and changes in medications.

D. A consultant who diagnoses syncope should **communicate with the patient's primary physician about cause, therapy, and important warning signs** if devices such as pacemakers or defibrillators are implanted.

E. **Hospitalization.** The decision about which patients to hospitalize can be complex. The underlying heart disease has been found to be the most important factor in determining prognosis and risk stratification, and it mandates hospitalization for the evaluation of syncope. Patients without evidence of structural heart disease who have a normal ECG and a high probability of having neurally mediated syncope are at low risk and generally have good long-term outcomes. Outpatient evaluation of syncope may be appropriate for these patients in many instances. Physicians should also consider hospitalization for patients with exertional syncope, syncope causing severe injury, and those with a strong family history of sudden death.

Risk scores have been developed to help predict which syncope patients are at risk for a serious outcome and should be considered for hospitalization. One of these, the San Francisco Syncope Rule, can be remembered by the mnemonic CHESS (history of *c*hronic heart failure, *h*ematocrit < 30%, abnormal *E*CG, *s*hortness of breath, *s*ystolic blood pressure < 90 mm Hg). This risk score was derived from a group of 684 syncope patients who presented to the emergency department of a university hospital. Use of this score identified patients at risk of a serious outcome with 96% sensitivity and 62% specificity.

VI. POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS).

POTS is an emerging and still poorly understood syndrome in which patients feel an exaggerated increase in heart rate with tilt and exercise. They may also feel fatigue, dyspnea, and light-headedness on standing, but do not typically experience orthostatic hypotension or syncope. The disorder is the most common syndrome seen in young people referred to autonomic dysfunction clinics and is thought to affect 500,000 Americans. Patients typically present at age 14 to 45 years and are usually female (female to male ratio of 4 to 5:1). Patients often have multisystem complaints such as fibromyalgia, chronic fatigue syndrome, sleep disorders, and gastrointestinal symptoms, suggesting a diffuse autonomic dysfunction.

A. **Etiology.** POTS is thought to be a syndrome with multiple overlapping etiologies, with each etiology having varying importance in individual patients.

1. **Partial dysautonomia** refers to autonomic impairment in some parts of the nervous system, with efforts by the still-functioning nervous system to compensate. A number of studies have shown findings of distal denervation in POTS patients, including the following:
   (a) Lower extremity anhidrosis.
   (b) Impaired norepinephrine spillover in the legs. The rate of entry of norepinephrine into the femoral vein is reduced in response to hypotensive stimuli.
   (c) A decrease in muscle sympathetic nerve activity recruitment in the legs in response to nitroprusside-induced hypotension.
2. **Increased sympathetic activity.** Studies have shown that patients with POTS have elevated arterial norepinephrine levels and decreased norepinephrine clearance. Some patients also have increased resting heart rates and an exaggerated response to isoproterenol, suggesting adrenoreceptor hypersensitivity.
3. **Hypovolemia.** Studies have shown reduced blood volume and reduced erythrocyte volume. The cause of these findings is not clear, but some have postulated problems with the rennin–angiotensin–aldosterone axis, possibly due to renal denervation.
4. **Changes in venous function.** Patients with POTS have been shown to have increased venous pooling and a decrease in stroke volume on standing.
5. **Primary baroreflex abnormalities** may also cause the increase in heart rate without change in blood pressure that is seen on standing.

B. Diagnosis. There are no established criteria for the diagnosis of POTS. The characteristic finding is an increase in heart rate on tilt table testing or standing. Many centers use an increase in heart rate of > 30 beats per minute or a rise in heart rate to > 120 beats per minute in the first 10 minutes of tilt as their diagnostic criteria. Orthostatic hypotension does not typically occur. There may be an increase in plasma norepinephrine levels (> 600 ng/mL), both with rest and on standing. It is important to rule out other conditions, such as autonomic neuropathy, central dysautonomia, bedrest deconditioning, dehydration, and medication effects that may also cause these findings.

C. Treatment. Because of the heterogeneous etiologies of POTS, which contribute differently to each patient's symptoms, treatment can be very challenging and often requires multiple attempts with different regimens. There are no large controlled studies of therapy.

1. Volume expansion using oral fluid intake, a high salt diet, and the mineralocorticoid fludrocortisone can improve symptoms. This treatment can cause hypertension, fluid retention, and hypokalemia, and patients should be monitored closely.
2. Adrenoreceptor agonists such as midodrine may improve symptoms in patients with mainly peripheral autonomic denervation. Studies have shown improvement in heart rate response and symptoms during tilt testing with these treatments.
3. Patients with mainly hyperadrenergic symptoms may see improvement with β-blockers. In one placebo-controlled, randomized crossover study, low-dose propranolol (20 mg) improved tachycardia and reduced symptoms, but high-dose propranolol (80 mg) did not change or worsened symptoms.
4. Pyridostigmine, an acetylcholinesterase inhibitor, has been used to attenuate tachycardia.
5. Other centrally acting drugs, such as selective serotonin reuptake inhibitors, clonidine, methyldopa, and phenobarbital, have been used with some success, but experience with their use is very limited.

ACKNOWLEDGMENTS: *The author thanks Drs. Carlos Alves, Keith Ellis, and Vasant B. Patel for their contributions to earlier editions of this chapter.*

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CHAPTER 34

Chetan Vagesh Hampole

Assessing and Managing Cardiac Risk in Noncardiac Surgical Procedures

I. INTRODUCTION

A. Background. Patients undergoing noncardiac surgeries can be at risk for major perioperative cardiac complications, particularly if they are elderly. Worldwide, it is estimated that approximately 500,000 to 900,000 patients per year undergoing noncardiac surgery suffer a perioperative cardiac death, nonfatal myocardial infarction (MI), or nonfatal cardiac arrest. Given the increasingly advanced age of patients undergoing surgeries, this risk is expected to remain substantial. The risk of death from a perioperative MI may be as high as 50%. The elevated risk of perioperative MI is multifactorial and may be primarily due to increased sympathetic tone, a proinflammatory state,

hypercoagulability, and occasional hypoxia during the first few days after surgery. In 1977, Goldman et al. (1) developed a multifactorial index of risk for cardiac morbidity and mortality. Extensive work has subsequently been done on various aspects of perioperative cardiac evaluation, including clinical factors and noninvasive testing. The variety of strategies and practices used has led to high costs associated with preoperative risk assessment. Many studies have recently challenged common practices in the area of perioperative care that were found to have no clear benefit. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force Committee developed practice guidelines aimed at providing a more efficient approach to preoperative evaluation. These guidelines were most recently updated in 2007.

B. Objective. The purpose of preoperative evaluation is not to "clear" patients for an operation. The purpose is to **assess current medical status and cardiac risks posed by the planned operation** and **recommend strategies that may influence short- and long-term outcomes**.

1. Although the preoperative assessment is a complex process, a few **basic questions and observations** by a physician with regard to the patient's general health, functional capacity, cardiac risk factors, comorbid medical illnesses, and type of anticipated operation can assist in evaluating cardiac risk.
2. It is not prudent to order noninvasive tests for every patient. The physician tries to obtain as much information as possible by means of **history and physical examination**. Noninvasive tests are requested only if the results are likely to influence treatment and outcome.
3. **As a general rule, preoperative intervention is rarely needed unless it is indicated irrespective of the preoperative context**. Patients with clinically stable heart disease may not need extensive preoperative testing.
4. Communication is vital among primary physicians, consulting physicians, anesthesiologists, and surgeons for short- and long-term care of patients.

II. CLINICAL PRESENTATION

A. History

1. The clinician needs to identify cardiac conditions that place a patient at increased risk, such as recent MI, decompensated congestive heart failure (CHF), unstable angina, significant arrhythmias, and valvular heart disease.
2. Attention is directed at serious **comorbid conditions** such as diabetes mellitus, peripheral vascular disease, history of stroke, renal disease, and pulmonary disease.
3. **Functional capacity** is determined on the basis of the patient's ability to perform certain daily tasks (Table 34.1).

B. Physical findings. A thorough examination is crucial, and specific findings are addressed.

1. The physical examination includes checking blood pressure in both arms (supine and standing) and evaluation of carotid arterial pulse (character, volume, and upstroke), jugular venous pulsation, cardiac rhythm, heart sounds (murmurs, gallops, or rubs), and extremity pulses.
2. Lung fields are auscultated, and the abdomen is palpated for a possible aneurysm.
3. **High-risk findings** include severe aortic stenosis murmur, elevated jugular venous pressure, pulmonary edema, or S_3 gallop.

C. Indices to predict cardiac risk. Cardiac risk is a function of patient characteristics and the proposed operation.

1. **The Goldman index** was developed in 1977. The index is a score derived from nine independent variables that predict perioperative cardiac events, and each is assigned a point value (Table 34.2).
2. **Detsky et al.** (2) developed a modified multifactorial index to address the severity of coronary artery disease (CAD) and heart failure (Table 34.3).

TABLE 34.1 Estimated Energy Requirements for Various Activities

1 to 4 METs
Eat, dress, or use the toilet
Walk indoors around the house
Walk on level ground at 2 mph (3.2 km/h)
Do light housework such as washing dishes
4 to 10 METs
Climb a flight of stairs
Walk on level ground at 4 mph (6.4 km/h)
Run a short distance
Heavy work such as vacuuming or lifting heavy furniture
Play games such as golf or doubles tennis
More than 10 METs
Participate in strenuous activities such as swimming, singles tennis, basketball, or skiing

MET, metabolic equivalent.

TABLE 34.2 Original Goldman Multifactorial Cardiac Risk Index

Criteria	Points
History	
Age older than 70 y	5
MI in previous 6 mo	10
Physical examination	
S_3 gallop or JVD	11
Significant AS	3
Electrocardiogram	
Rhythm other than sinus or PACs on last preoperative ECG	7
Greater than 5 PVCs/min documented at any time preoperatively	7
General status (one or more of the following)	
$P_{O_2} < 60$ or $P_{CO_2} > 50$ mm Hg, $K < 3.0$ or $HCO_3 < 20$ mEq/L, BUN > 50 or Cr > 3.0 mg/dL; abnormal AST, signs of chronic liver disease, or patient bedridden from noncardiac causes	3
Operation	
Intraperitoneal, intrathoracic, or aortic operation	3
Emergency operation	4
Total	53

(continued)

TABLE 34.2 Original Goldman Multifactorial Cardiac Risk Index (*continued*)

Class	Points	Cardiac deaths (%)
I	0–5	0.2
II	6–12	2.0
III	13–25	2.0
IV	≥ 26	56.0

AS, aortic stenosis; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; ECG, electrocardiogram; JVD, jugular venous distention; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Adapted from Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297:845–850.

TABLE 34.3 Detsky's Modified Cardiac Risk Index

Variable	Points
Coronary artery disease	
MI within 6 mo earlier	10
MI more than 6 mo earlier	5
Canadian class of angina	
Class III	10
Class IV	20
Unstable angina within 3 mo	10
Alveolar pulmonary edema	
Within 1 wk	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Arrhythmias	
Sinus plus atrial premature beats or rhythm other than sinus on last preoperative electrocardiogram	5
Greater than five ventricular premature beats at any time before operation	5
Poor general medical status[a]	5
Age older than 70 y	5
Emergency operation	10
Total	120

[a]Defined as any of the following: $P_{O_2} < 60$ mm Hg, $P_{CO_2} > 50$ mm Hg, $K^+ < 3.0$, $HCO_3 < 20$ mEq/L, BUN = 18 mmol/L (> 50 mg/dL), serum Cr > 260 mmol/L (> 2.9 mg/dL), abnormal AST, signs of chronic liver disease, or patient bedridden because of noncardiac causes. AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; MI, myocardial infarction.

Adapted from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med.* 1986;1:211–219.

TABLE 34.4 Revised Cardiac Risk Index

Six independent predictors of major cardiac complications
High-risk surgery (intrathoracic, intraperitoneal, or suprainguinal vascular procedures)
History of ischemic heart disease (history of MI or a positive exercise stress test, current complaint of chest pain thought to be due to MI, use of nitrate therapy, or ECG with pathological Q waves; do not count prior coronary revascularization procedure unless one of the other criteria for ischemic heart disease is present)
History of heart failure
History of cerebrovascular disease
Diabetes mellitus requiring insulin therapy
Serum creatinine > 2.0 mg/dL (177 μmol/L)
Rate of cardiac death, nonfatal MI, and nonfatal cardiac arrest according to the number of predictors
No risk factors: 0.4% (95% CI, 0.1–0.8%)
One risk factor: 1.0% (95% CI, 0.5–1.4%)
Two risk factors: 2.4% (95% CI, 1.3–3.5%)
Three or more risk factors: 5.4% (95% CI, 2.8–7.9%)
Rate of cardiac death and nonfatal MI, cardiac arrest or ventricular fibrillation, pulmonary edema, and complete heart block according to the number of predictors and the nonuse or use of β-blockers
No risk factors: 0.4–1.0% versus < 1% with β-blockers
One to two risk factors: 2.2–6.6% versus 0.8–1.6% with β-blockers
Three or more risk factors: > 9% versus > 3% with β-blockers

Adapted from Lee TH, Marcantonio ER, Mangione CM et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation.* 1999;100:1043–1049.

3. In 1999, **Lee et al. (3) developed the Revised Cardiac Risk Index** to simplify the process using only six risk factors (Table 34.4). This is now the most widely used risk index and is the one incorporated in the ACC/AHA guidelines.

D. Clinical assessment of risk factors. Instead of dividing risk factors into major, intermediate, and minor groups, the new 2007 ACC/AHA guidelines adopted a more practical approach by recognizing the following conditions:

1. **Active cardiac conditions.** The presence of one or more of these conditions warrants intensive evaluation and management before proceeding with noncardiac surgery and may result in delay or cancellation of the scheduled surgery (Table 34.5).
2. **Clinical risk factors.** With the exception of the type of surgery, these factors are the same risk factors identified by the Revised Cardiac Risk Index (Table 34.4), and they include the following:
   - **(a)** History of ischemic heart disease
   - **(b)** History of compensated or prior heart failure
   - **(c)** History of cerebrovascular disease
   - **(d)** Diabetes mellitus
   - **(e)** Renal insufficiency
3. The original guidelines recognized a group of **minor** predictors that included advanced age, abnormal electrocardiogram (ECG), rhythm other than sinus, and

TABLE 34.5 Active Cardiac Conditions That Warrant Evaluation and Treatment before Noncardiac Surgery

Unstable coronary syndromes
Acute or recent myocardial infarction[a]
Unstable or severe[b] angina (Canadian class III or IV)[c]
Decompensated heart failure
Significant arrhythmias
High-grade atrioventricular block
Mobitz type II atrioventricular block
Third-degree atrioventricular block
Symptomatic ventricular arrhythmias
Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate
Symptomatic bradycardia
Newly recognized ventricular tachycardia
Severe valvular disease
Severe aortic stenosis (mean pressure gradient ≥ 40 mm Hg, aortic valve area ≤ 1.0 cm^2, or symptomatic)
Symptomatic mitral stenosis

[a]The American College of Cardiology National Database Library defines acute MI as within 7 d and recent MI as > 7 d and ≤ 1 mo.

[b]May include stable angina among patients who are unusually sedentary.

[c]Data from Campeau L. Grading of angina pectoris. *Circulation.* 1976;54:522–523.

Adapted from Fleisher LA, Beckman JA, Brown KA et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50:1707–1732.

uncontrolled hypertension. **Although the presence of many of these factors might lead to a *higher suspicion of CAD,* they have *not* been shown to increase perioperative risk independently, and therefore, they are no longer incorporated into the recommendations for treatment.**

III. TYPE OF OPERATION. In addition to clinical markers and functional capacity, **the proposed operation is an important factor, especially among patients with multiple clinical risk factors** (Table 34.6). The consultant uses all the information available to estimate cardiac risk and provides recommendations to minimize perioperative risk. For **surgical emergencies**, the patient should **proceed directly to the operating room**; emphasis in these circumstances is on postoperative evaluation and management. For **urgent surgical procedures**, evaluation must be **tailored to the underlying disease process**. Elective procedures allow for more thorough evaluation, and all care should be taken to minimize risk. **Testing is limited exclusively to those studies whose results might change management.**

TABLE 34.6 Cardiac Risk Stratification by the Type of Surgical Procedure

High-risk procedure (cardiac risk > 5%)
Aortic and other major vascular surgery (endovascular abdominal aortic aneurysm repair is considered intermediate risk) and peripheral vascular surgery (carotid endarterectomy is considered intermediate risk)
Intermediate-risk procedure (cardiac risk 1–5%)
Carotid endarterectomy and endovascular abdominal aortic aneurysm repair
Head and neck surgery
Intraperitoneal surgery
Intrathoracic surgery
Orthopedic surgery
Prostate surgery
Low-risk procedure (cardiac risk < 1%)
Breast surgery
Cataract surgery
Endoscopic procedures
Superficial procedures
Ambulatory surgery

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50:1707–1732.

IV. SUPPLEMENTAL PREOPERATIVE EVALUATION

A. Routine laboratory tests such as serum creatinine, hemoglobin, platelets, potassium, liver profile, and oxygen saturation are important in determining whether a patient needs special attention. Such patients include those with bleeding risk, renal failure, or liver disease.

B. Patients with **pulmonary disease** (i.e., chronic obstructive pulmonary disease or pulmonary fibrosis) undergo a preoperative **arterial blood gas evaluation**.

C. A 12-lead **ECG** is recommended for patients with at least one clinical risk factor who are undergoing vascular surgery and for patients with known history of CAD, peripheral vascular disease, or cerebrovascular disease who are undergoing an intermediate-risk surgical procedure. A 12-lead ECG is also reasonable in patients with no clinical risk factors who are undergoing vascular surgery and, possibly, in patients with at least one clinical risk factor who are undergoing intermediate-risk surgery.

D. Echocardiography. Echocardiograms can provide information about certain pathologic conditions (left ventricular dysfunction and aortic stenosis) that predispose to increased perioperative cardiac risk. However, the routine use of echocardiography is not helpful and should be reserved for patients who meet ACC/AHA clinical guidelines or for patients in whom the physical examination is suggestive of aortic stenosis, regardless of the planned surgery.

V. STEPWISE APPROACH TO PREOPERATIVE CARDIAC ASSESSMENT. The ACC/AHA Task Force developed an **algorithm for preoperative cardiac evaluation** to help physicians systematically identify clinical predictors and determine if noninvasive testing is indicated prior to the noncardiac surgery (Fig. 34.1).

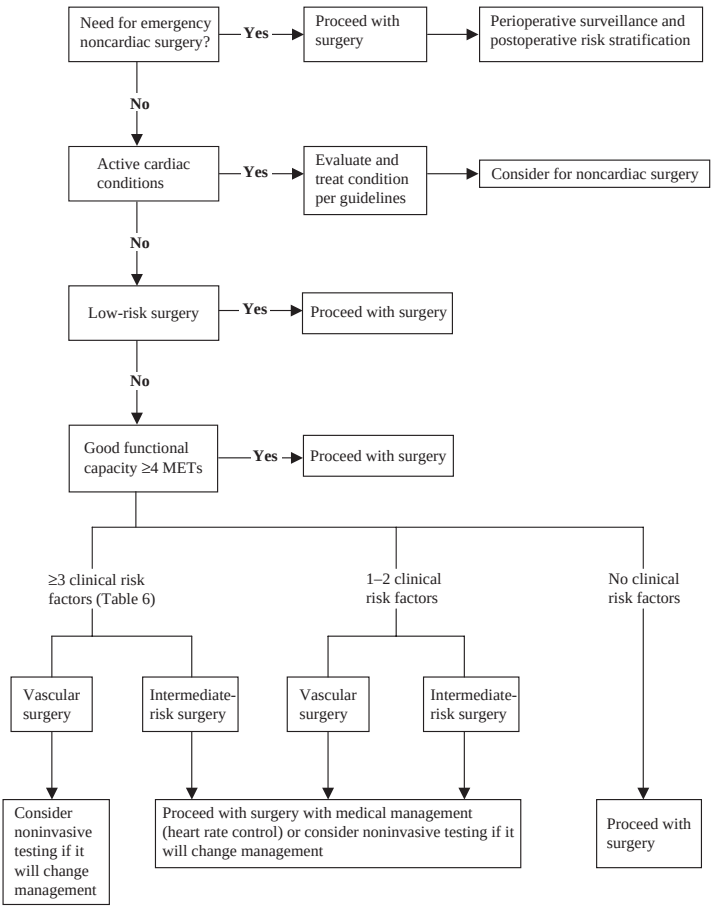

FIGURE 34.1 A stepwise approach to preoperative cardiac evaluation of a patient undergoing a noncardiac surgery. (Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50:1707–1732.)

VI. NONINVASIVE CARDIAC STRESS TESTING. The ability of noninvasive cardiac tests to predict perioperative risk is uncertain. Recently, there has been increasing evidence discouraging the need for their routine use in patients undergoing preoperative evaluation. This shift away from noninvasive testing was supported by the results of a randomized controlled trial of preoperative myocardial revascularization in vascular surgery patients that showed no improvement in perioperative or long-term outcomes associated with prophylactic revascularization. Another study challenged the old ACC/AHA guidelines by randomizing stable intermediate-risk patients undergoing major vascular surgery between cardiac stress testing strategy and no testing. By using excellent β-blocker therapy with tight heart rate control of 60 to 65 beats/min, there was no significant difference in the primary end point (composite postoperative cardiac death and/or nonfatal MI) between preoperative cardiac testing and no testing strategies. Therefore, **preoperative noninvasive cardiac testing should be reserved for patients who are candidates for these tests according to guidelines and who based on the results of these tests could potentially be considered for angiography and revascularization regardless of the planned surgery**.

These findings were reflected in the new ACC/AHA 2007 guidelines:

(A) Patients with **active** cardiac conditions (Table 34.5) should be **evaluated and treated before noncardiac surgery** (class I).

(B) In patients with **poor (< 4 metabolic equivalents of the task) or unknown functional capacity**, who have **three or more clinical risk factors** and are undergoing **vascular surgery**, noninvasive **testing is reasonable if it will change management** (class IIa).

(C) In patients with poor or unknown functional capacity who have one to two clinical risk factors and who are undergoing intermediate-risk surgery, noninvasive testing may be considered (class IIb).

(D) In patients with good functional capacity who have one to two clinical risk factors and who are undergoing vascular surgeries, noninvasive testing may be considered (class IIb).

(E) Noninvasive testing is **not** useful in patients ***without*** clinical risk factors who are undergoing **intermediate-risk surgery**.

(F) Noninvasive testing is not useful in patients who are undergoing low-risk surgery.

There are **different modalities for stress testing,** including exercise ECG, exercise or pharmacologic nuclear stress testing, and exercise or pharmacologic stress echocardiography. When ordering these tests, **it is important to remember the following**:

(A) When feasible, **exercise is the modality of choice** for stress testing because it provides an objective assessment of functional capacity. Pharmacologic stress testing (adenosine, dipyridamole, and dobutamine) should be reserved for patients who cannot exercise.

(B) Exercise and pharmacologic stress testing have **excellent negative predictive values** (90% to 100%) **but poor positive predictive values** (6% to 67%), meaning that although a negative study is reassuring, a positive one is still a relatively weak predictor of a perioperative cardiac event.

(C) Intravenous dipyridamole and adenosine should be avoided in patients with significant bronchospasm or critical carotid artery stenosis.

(D) Dobutamine should be avoided in patients with significant arrhythmias, severe hypertension, or hypotension.

(E) Stress echocardiography (exercise or dobutamine) offers the advantage of providing additional information about ventricular and valvular function.

VII. PREOPERATIVE CORONARY REVASCULARIZATION. The original ACC/AHA guidelines state that the indications for revascularization before noncardiac surgery should be similar to those in the general population. In other words, there is **no evidence to**

support the role of "prophylactic" preoperative revascularization, and the decision to pursue revascularization should be the same regardless of the planned surgery. However, these statements have been based on expert opinion, and there has been substantial variability among clinicians concerning general practice with cardiac revascularization preoperatively. **The Coronary Artery Revascularization Prophylaxis (CARP) trial** was the first large randomized trial that addressed this issue. It randomized 510 patients with established CAD, who were deemed to be at high risk for perioperative cardiac complications, to undergo either revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or no revascularization before elective major vascular surgery. After a median follow-up of 2.7 years, the death rates were the same in both groups. Even among the subsets of patients who were considered to be at especially high risk according to imaging results or by the Revised Cardiac Risk Index, there were no differences in outcomes between the two groups. Although the study was not designed to test short-term benefit of prophylactic revascularization, there was also no reduction in early postoperative cardiac complications.

Patients who undergo **PCI** represent a clinical challenge in terms of managing their antiplatelet therapy at the time of noncardiac surgery. Premature discontinuation of antiplatelet therapy (aspirin and clopidogrel) carries the risk of in-stent thrombosis. **Bare metal stent (BMS)** thrombosis is most common in the first 2 weeks after stent placement and is very rare after 4 weeks due to rapid endothelialization. On the other hand, there has been growing concern that drug-eluting stent **(DES)** carries greater risk for in-stent thrombosis compared with BMS. The optimal period to delay noncardiac surgery after the use of DES remains unclear.

A. The **indications for revascularization (CABG or PCI) before noncardiac surgery should be similar to those in the general patient population irrespective of the planned surgery:**
   (1) Stable angina with known left main disease
   (2) Stable angina with three-vessel disease (especially with ejection fraction [EF] < 50%)
   (3) Stable angina with two-vessel disease with significant proximal left anterior descending artery stenosis and either EF < 50% or ischemia on noninvasive testing
   (4) High-risk unstable angina or non–ST-segment elevation MI
   (5) Acute ST-elevation MI

B. Patients with **asymptomatic ischemia** (based on functional study) do not appear to benefit from preoperative revascularization prior to noncardiac surgeries.

C. Routine prophylactic revascularization should not be performed in patients with stable CAD before noncardiac surgery.

D. Small observational studies suggest that patients who undergo **CABG** should wait for at least 4 weeks before proceeding with noncardiac surgery.

E. Patients who undergo **balloon angioplasty without stenting** should wait for **at least 2 to 4 weeks** before proceeding with elective noncardiac surgery to allow adequate time for healing of the injured vessel. Daily aspirin should be continued whenever possible. The risk of stopping aspirin should be weighed against the benefit of reducing bleeding risk from surgery. Balloon angioplasty without the use of stent might provide a temporary bridge to go through noncardiac surgery with the intention of implanting stents after the surgery.

F. Among patients who undergo stenting with **BMSs**, it is safer to **wait for 6 to 8 weeks** on dual antiplatelet therapy (aspirin and clopidogrel) before proceeding with surgery to avoid the risk of in-stent thrombosis with premature discontinuation of antiplatelet therapy. After 4 to 6 weeks, clopidogrel could be stopped preoperatively, ideally 5 to 7 days before the noncardiac surgery. Daily aspirin use should be continued unless the risk of bleeding outweighs the benefit of continuing aspirin therapy.

G. Among patients who undergo stenting with the **DES**, the optimal duration for dual antiplatelet therapy is not well defined, but should be **at least 12 months**. Elective

noncardiac surgery that requires discontinuation of clopidogrel, or both clopidogrel and aspirin, should be delayed. In general, if noncardiac surgery is expected within the next 12 months, the physician should strongly consider avoiding the use of DES. BMS or balloon angioplasty might provide an alternative approach.

H. Perioperative management of patients with prior PCI undergoing unplanned surgery

1. The ideal waiting time before proceeding with noncardiac surgery should be at least
   (a) 2 to 4 weeks for balloon angioplasty,
   (b) 4 to 6 weeks for BMS, and
   (c) 12 months for DES.
2. For patients who need noncardiac surgery that falls within the time frame that requires dual antiplatelet therapy and cannot be delayed, strong consideration should be given to continuation of dual antiplatelet therapy whenever possible.
3. If the risk of bleeding with dual antiplatelet therapy outweighs the benefit, serious consideration should be given to continuation of at least aspirin whenever possible. Clopidogrel should be resumed as soon as possible after surgery.

I. It is important to recognize that **the recommended time frames for dual antiplatelet therapy are arbitrary and based on expert opinion**. These cases should be addressed individually with good communication between the cardiologist, anesthesiologist, and the surgeon. **Certain conditions might require longer dual antiplatelet therapy** (e.g., left main stenting, history of stent thrombosis, multivessel stenting, and stenting of the only remaining coronary artery or bypass graft).

Because of the lack of prospective studies as well as guidelines, there are a wide variety of potential approaches to the perioperative management of patients with stents taking dual antiplatelet therapy. The ACC/AHA/SCAI/ACS/ADA Science Advisory Panel notes the importance of 12 months of dual antiplatelet therapy after placement of a DES and educating the patient about the hazards of premature discontinuation. Therefore, management should be carried out on a case-by-case basis. Major factors that should be considered are surgical hemorrhagic risk and the thrombotic risk of the stent.

VIII. MANAGEMENT OF SPECIFIC PREOPERATIVE CONDITIONS

A. Valvular heart disease. In general, the indications for evaluation and treatment of valvular heart disease are similar to those in the nonpreoperative setting. Symptomatic stenotic lesions are associated with increased perioperative morbidity, whereas symptomatic regurgitant valve diseases can usually be managed medically and with close monitoring perioperatively.

1. Critical **aortic stenosis** must be recognized promptly and, if symptomatic, should be managed with valve replacement or, for selected patients, valvuloplasty as a short-term bridge through noncardiac surgery.
2. **Mitral stenosis** when mild and asymptomatic is managed medically with heart rate control. When mitral stenosis is severe and symptomatic, mitral valvuloplasty or valve replacement is considered before a high-risk operation is performed.
3. For patients with **aortic or mitral regurgitation,** the medical regimen is optimized with diuretics and afterload reduction.
4. Appropriate **prophylaxis for bacterial endocarditis** is administered for patients with valvular disorders according to the guidelines.
5. Patients with **prosthetic valves who need oral anticoagulation** can usually safely undergo minimally invasive procedures such as dental work or skin biopsy if the international normalized ratio is briefly reduced to a low or

subtherapeutic range. Full anticoagulation is resumed after the procedure. For patients undergoing extensive surgical procedures with prosthetic valves, intravenous unfractionated heparin therapy is initiated. Heparin can be reserved for the following patients:

(a) those with recent thromboembolic events (< 1 year);
(b) those with mechanical valve in the mitral position;
(c) those with a history of thromboembolism while not on anticoagulation
(d) those with Bjork-Shiley or Starr-Edwards valve; and
(e) those with three or more of the following risk factors (atrial fibrillation [AF], previous thromboembolism, hypercoagulable condition, mechanical prosthesis, and left ventricular EF < 30%).

Mechanical valves in the mitral position are usually more thrombogenic and, therefore, require a lower threshold for heparin conversion. The use of low-molecular-weight heparin may provide an alternative approach for anticoagulation, but is still controversial as valve thrombosis has been reported with its use. Oral anticoagulants are resumed as soon as possible after the procedure.

B. Arrhythmias. The ACC/AHA 2007 guidelines recognize **high-grade atrioventricular block, symptomatic bradycardia, symptomatic or newly recognized ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, and symptomatic bradycardia as active cardiac conditions that require further evaluation before proceeding with noncardiac surgery**. The following points are important to remember while evaluating arrhythmias in the preoperative setting:

1. Identification of any **underlying cardiac disease, drug toxicity, or metabolic disturbances** that could be the cause of the arrhythmia is very important.
2. For symptomatic and hemodynamically significant arrhythmias, therapy should target the underlying cause and then the arrhythmia itself.
3. The indications for antiarrhythmic therapy and cardiac pacing are similar to those in nonoperative setting.
4. Frequent premature ventricular beats and asymptomatic nonsustained ventricular tachycardias are not associated with increased perioperative cardiac risk.

C. Permanent pacemakers and implantable cardioverter–defibrillators (ICDs). It is important to identify patients who have pacemakers or ICDs. Patients who are completely pacemaker-dependent should have their device checked within 3 to 6 months before surgery, and their device should be reprogrammed to an asynchronous mode during surgery (VOO or DOO); in certain models, a magnet can be placed over the device during surgery. Electrocautery should be used only briefly and with caution. Bipolar pacing minimizes the risk of electrocautery. After the operation, all pacemakers are interrogated to ensure that the settings are optimal and that no changes occurred during the operation or electrocautery. ICDs are programmed to off preoperatively and then reprogrammed to on after the procedure.

D. Hypertension. In general, patients with hypertension may be indirectly predisposed to perioperative myocardial ischemia, since CAD is more prevalent among these patients. In addition, because of the stiffness of the vascular system, they are predisposed to intraoperative hypotension; therefore, they should be **monitored closely during an operation**.

1. Patients with **mild or moderate** hypertension may undergo elective operations with continued medical therapy.
2. **Severe** hypertension (systolic blood pressure ≥ 180 mm Hg and diastolic pressure ≥ 110 mm Hg) should be controlled before the surgery. If possible, the operation is delayed until the pressure is consistently controlled. If urgent surgical intervention is needed, rapid-acting agents are used. β-Blockers are preferred, especially because they act as anti-ischemic agents as well.

3. Withdrawal of β-blockers and clonidine from patients undergoing long-term therapy with these agents **must be avoided** to prevent a rebound phenomenon.

E. Heart failure is associated with increased risk of perioperative morbidity. Identification of the etiology of heart failure is very important, since the treatment **depends on the cause** and overall clinical status.

1. Heart failure should be optimally controlled preoperatively with special attention to avoid over-diuresis, which can exacerbate postoperative hypotension.
2. Patients **with hypertrophic cardiomyopathy** need close monitoring of volume status, heart rate, and systemic vascular resistance to avoid intraoperative hypotension and hypovolemia that can lead to exacerbation of dynamic outflow obstruction.

IX. PERIOPERATIVE MEDICAL THERAPY

A. β-Blockers: Several trials and meta-analyses have examined the role of β-blockers in preventing perioperative cardiac complications. However, there remain multiple limitations in interpreting the data due to the paucity of randomized clinical trials, the lack of clear protocol for initiation and titration of β-blockers, and the lack of comparison between different agents. These limitations regarding the use of β-blockers perioperatively were acknowledged by the ACC/AHA in the latest ACC/AHA 2007 guidelines. Since the publication of these guidelines, POISE (PeriOperative ISchemic Evaluation) trial, a randomized, controlled trial of fixed higher dose, extended-release metoprolol started the day of surgery in more than 8,000 patients undergoing noncardiac surgery, prompted a 2009 ACCF/AHA focused update on the subject of perioperative β-blocker therapy. It demonstrated a reduction in primary cardiac events including cardiovascular death, MI, and cardiac arrest in those receiving perioperative β-blocker therapy. However, there was also an increased risk of stroke and total mortality in the β-blocker group suggesting that routine administration of high-dose β-blockers without dose titration may be harmful to β-blocker–naïve patients undergoing surgery. Specifically, β-blockade should continue during the intraoperative period and postoperative period to maintain a heart rate of 60 to 80 beats/min to avoid the pitfalls of this class of drug. In patients with indications for β-blockers, these agents can be continued indefinitely, and if there is no indication they should be continued for at least 7 days, and preferably 30 days after the noncardiac surgery.

1. β-Blockers should be continued in all patients undergoing surgery who are already receiving β-blockers for any class I guideline indication (to treat angina, arrhythmias, hypertension, etc.).
2. β-Blockers titrated to heart rate and blood pressure should be administered to all high-risk patients identified by myocardial ischemia on preoperative assessment undergoing vascular surgery.
3. β-Blockers titrated to heart rate and blood pressure are reasonable for patients undergoing vascular or intermediate-risk surgery in whom preoperative evaluation reveals CAD.
4. β-Blockers titrated to heart rate and blood pressure are reasonable for patients undergoing vascular or intermediate-risk surgery who have more than one clinical risk factor.
5. The usefulness of β-blockers is uncertain for patients undergoing vascular or intermediate-risk surgery who have only one or no clinical risk factor.
6. β-Blockers should not be administered in preoperative patients with absolute contraindications to the agents.

B. α_2-Agonists suppress the release of catecholamines and may decrease the incidence of cardiac events in patients with known CAD and at least one clinical risk factor who are undergoing noncardiac surgery.

C. The role of **calcium antagonists** is not well defined and requires further research.

D. **Statins.** There has been growing evidence suggesting an association between perioperative statin therapy and decreased perioperative cardiac complications. Definite indications for perioperative statin use await the results of ongoing and future clinical trials. However, it is important to note that perioperative evaluation represents an opportunity to identify patients who meet National Cholesterol Education Program criteria and impact their long-term outcome.

1. Statins should be continued in patients who are already on statin therapy and undergoing noncardiac surgery.
2. For patients undergoing vascular surgery, it is reasonable to be on statin therapy.
3. Statins may be considered for patients with at least one clinical risk factor who are undergoing intermediate-risk surgery.

X. ANESTHETIC AGENTS AND PERIOPERATIVE HEMODYNAMIC MONITORING

A. Several studies have evaluated the effect of **anesthetic agents and techniques** on cardiac morbidity. It appears that there is **no one best myocardial protective agent.** All inhalational agents cause depression of myocardial contractility and afterload reduction, which can lead to hypotension. Several studies have suggested that **neuroaxial anesthesia (epidural and spinal)** may reduce pulmonary and thrombotic complications compared with general anesthesia. However, its role in lowering cardiac complications remains controversial. Decisions regarding anesthetic techniques are best left to the anesthesiologist. Perioperative pain management is important because it reduces postoperative catecholamine response and cardiac stress.

B. **Pulmonary artery catheters** are occasionally used in high-risk patients (advanced heart failure and severe CAD) who are undergoing procedures associated with significant hemodynamic stress. The ACC/AHA guidelines advise to assess the benefit versus risk when considering the use of pulmonary artery catheters. Catheter-guided volume optimization has no clear benefit perioperatively, and multicenter randomized trials have shown that pulmonary artery catheter use provides no benefit after noncardiac surgery or in the intensive care unit.

XI. POSTOPERATIVE MONITORING AND MANAGEMENT OF EVENTS

A. **Postoperative MI.** The pathophysiology of perioperative MI is not well defined and may be different from that of nonoperative MIs. Stress, inflammation, hypercoagulability, and hypoxia may all be contributing factors. The incidence of perioperative MI ranges from 2% to 6% in general. However, up to 50% of perioperative MIs may go unrecognized. The majority of perioperative MIs occur within the first 3 days after surgery, a period when the patients are receiving narcotics that could mask the pain, some patients are still intubated and sedated, and many of the clinical signs that patients normally manifest are attributable to other causes (e.g., hypovolemia, bleeding, and pain). Nonspecific findings, such as CHF, hypotension, nausea, or ST-segment depression, may be the only clues to postoperative ischemia. The prognosis of these unrecognized MIs is nevertheless similar to that of patients experiencing a recognized MI.

1. There are **no standard criteria for the diagnosis of perioperative MI in patients undergoing noncardiac surgery**.
2. **Troponin** is a more specific marker for perioperative MI than creatine kinase-myocardial band, which could be falsely positive after surgery.
3. **ECG and troponin** should be checked postoperatively in **patients with signs and symptoms suggestive of ischemia, but based on the current literature, routine measurement of troponin is not recommended after noncardiac surgery**.
4. It is also important to rule out **other causes for positive troponin, such as pulmonary embolism**.

5. Although there is an increase in use of intraoperative **transesophageal echocardiography** to monitor myocardial ischemia through wall motion abnormalities, there is insufficient information to make firm recommendations.
6. There are **no clear guidelines for the management of perioperative MIs. Identifying and treating correctible causes** is important (e.g., anemia and hypoxia). In general, primary PCI is preferred for **perioperative ST-elevation MI**. Although thrombolytic, antiplatelet, and anticoagulant therapies are beneficial in the treatment of non–ST-elevation MI or unstable angina in nonoperative setting, these therapies could potentially cause more harm than benefit in perioperative settings. Many drugs that are important in the long-term management of nonoperative MIs (e.g., aspirin, angiotensin-converting enzyme inhibitors, β-blockers, and statins) may not carry the same positive effect in perioperative MI patients. Large randomized clinical trials are needed to answer these questions.
7. Nonfatal perioperative MI is an independent risk factor for cardiovascular death and nonfatal MI during the 6 months following the surgery. Therefore, close follow-up with aggressive risk-factor modification is important for these patients.

B. The management of **postoperative heart failure and pulmonary edema** is not much different than in nonoperative settings. ECG and troponin should be checked to rule out MI.

C. Arrhythmias. Perioperative arrhythmias are common, especially among elderly patients and after thoracic surgeries. For patients with arrhythmias, the metabolic profile and medications should be reviewed, and any underlying reversible conditions should be corrected, including hypoxia, fever, bleeding, pain, and infection. β-Blockers and calcium channel blockers can reduce postoperative tachyarrhythmias.

1. Most **supraventricular tachycardias (SVTs)** necessitate rate control until the underlying cause is addressed. This can be achieved using β-blockers, calcium channel blockers, or digoxin. Adenosine can be effective in terminating certain reentrant tachycardias. New-onset **AF** raises embolic risk. To avoid the increased bleeding risk with anticoagulation after surgery, restoring sinus rhythm is often a preferred strategy. Rate control is advised and if the AF persists more than 24 hours, antiarrhythmic drugs could be used. Most AF will resolve within 36 to 48 hours, but if it persists, then anticoagulation is warranted. At any time if the SVT causes hemodynamic compromise or ongoing myocardial ischemia, electrical cardioversion is the therapy of choice.
2. Symptomatic **bradyarrhythmias** are managed with temporary pacing, and a permanent pacemaker can be implanted if and when indicated.

XII. POSTOPERATIVE MANAGEMENT. In most cases, the results of the preoperative evaluation determine whether a patient is at substantial cardiac risk. For these patients, postoperative care is dictated by the findings before the operation. In a few urgent cases, or for patients who did not undergo preoperative evaluation, postoperative evaluation and care are individualized.

A. After a patient has successfully undergone a procedure, the physician **assesses and manages risk factors** for coronary and peripheral atherosclerosis.

B. Management of risk factors, including smoking cessation, control of labile hypertension, aggressive management of hyperlipidemia, and glycemic control for patients with diabetes, is of paramount importance.

C. Particular attention is given to **patients who sustain perioperative MI or demonstrate perioperative ischemia** because these patients are at risk for recurrent MI or cardiac death in subsequent years. These patients should be followed closely and treated aggressively.

ACKNOWLEDGMENTS: *The author thanks Drs. Khaldoun G. Tarakji, John H. Chiu, and Vasant B. Patel for their contributions to earlier editions of this chapter.*

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KEY REVIEWS

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Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. American College of Cardiology Foundation, American Heart Association Task Force on practice guidelines, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Surgery. *J Am Coll Cardiol.* 2009;54:e13–e118.

RELEVANT BOOK CHAPTER

Roizen MF, Ellis J, Mantha S, et al. Perioperative anesthetic considerations in noncardiac surgery for those at high risk of cardiovascular disease. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:721–735.

CHAPTER 35

Kia Afshar

Hypertensive Crisis

I. INTRODUCTION

A. Epidemiology. More than 50 million people in the United States are diagnosed with systemic hypertension, many of whom are inadequately treated. Approximately 1% of those poorly treated progress to a crisis phase, accounting for more than 50% of all cases of hypertensive crisis. Although the incidence is decreasing due to improved awareness, treatments, and public health measures, patients with untreated hypertension or suboptimal blood pressure control remain more susceptible to acute rises in blood pressure. Patients with secondary causes of hypertension are also at higher risk for hypertensive crisis. Unless promptly recognized and treated, hypertensive crisis can lead to acute central nervous system, renal and cardiovascular dysfunction, and, possibly, death. Effective and prompt antihypertensive treatment improves prognosis.

B. Definitions. Hypertensive crisis is defined as having either a **hypertensive emergency or hypertensive urgency**. According to the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, normal blood pressure is defined as a systolic blood pressure < 120 mm Hg and a diastolic blood pressure < 80 mm Hg. Severe hypertension is defined as a systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 120 mm Hg.

1. **Hypertensive emergency.** Hypertensive emergency is defined as **severe hypertension with evidence of acute end-organ damage,** which can be manifested by a variety of syndromes (Table 35.1). Severe hypertension in the presence of chronic organ damage without associated acute manifestations does not constitute an emergency. Delineating hypertensive emergency from urgency is important because it implicates the need for immediate parenteral blood pressure lowering therapy in a monitored setting (typically intensive care unit [ICU]) to minimize tissue damage and long-term complications. Delay may cause irreversible organ dysfunction and death.
2. **Hypertensive urgency.** Hypertensive urgency, on the other hand, is generally defined as **severe hypertension without acute end-organ damage**. In the absence of symptoms or acute organ dysfunction, severe hypertension can be lowered over a period of days to weeks. Patients can be treated with oral medications and usually managed as outpatients.
3. **Pseudoemergencies.** Pseudoemergencies are acute rises in blood pressure attributed to **a physiologic trigger, causing a massive sympathetic or catecholamine surge**. These are typically seen as the result of pain, hypoxia, hypercarbia, hypoglycemia, anxiety, or a postictal state. These scenarios must be differentiated from true hypertensive crises because the management differs significantly. Treatment is directed at the underlying trigger and does not necessarily include antihypertensive medications.

TABLE 35.1 Hypertensive Emergencies

Severe hypertension (> 180/120 mm Hg) with any of the following:
Encephalopathy
Acute stroke, intracranial hemorrhage, head trauma
Acute aortic dissection
Pulmonary edema
Myocardial ischemia and/or infarction
After coronary artery bypass surgery
Postoperative bleeding at vascular suture lines
Acute renal failure and/or hematuria and proteinuria
Retinal hemorrhages, exudates, papilledema
Eclampsia

II. PATHOPHYSIOLOGY

A. Autoregulation. Understanding autoregulation is the cornerstone of managing hypertensive crises safely while minimizing the risk of iatrogenic complications. The kidney, brain, fundi, and heart all possess **autoregulatory mechanisms that maintain blood flow at near-constant levels despite fluctuations in blood pressure**. This protects these vital organs from the consequences of hypoperfusion with decrease in blood pressure and hyperperfusion with increase in blood pressure. The cardiovascular equivalent to Ohm's law in physics ($I = V/R$) is that blood flow is equal to pressure divided by resistance. Constant blood flow is maintained by parallel changes in these two parameters: pressure and resistance. The endothelial layer in these vessels controls local autoregulatory vasoconstriction when the perfusion pressure increases and vasodilation when perfusion pressure decreases. There is a range of pressures for which the autoregulatory mechanism functions normally. In **normotensive patients** or in those with adequate hypertension management, this range of mean arterial pressures (MAPs) is approximately between 60 and 120 mm Hg. Loss of autoregulatory control at an MAP of 120 mm Hg in patients without preexisting chronic hypertension explains why a seemingly trivial elevation in blood pressure (160/100 mm Hg) can have severe end-organ damage. Classic examples of this phenomenon occur with acute illnesses such as acute glomerulonephritis, preeclampsia, and cocaine abuse. However, in **chronically hypertensive patients**, either undiagnosed or inadequately controlled, the autoregulatory range is shifted to the right from arteriolar smooth muscle hypertrophy. This hypertrophy minimizes the transmission of pressure to the capillary bed, allowing tissue tolerance of higher blood pressures, but at the same time places the patient at risk for hypoperfusion if treated to normotensive pressures (Fig. 35.1). **This is the reason that blood pressure should not be reduced too quickly in chronically hypertensive patients since this will result in relative hypotension causing tissue hypoperfusion**. Gradual reduction in blood pressure allows the rightward-shifted autoregulatory curve to normalize as the arteriolar hypertrophy slowly regresses. Treatment must be tempered by the fact that **abrupt overzealous blood pressure reduction may lead to hypoperfusion and ischemia, with potential for irreversible neurologic damage**. Cerebrovascular accidents, blindness, paralysis, coma, myocardial

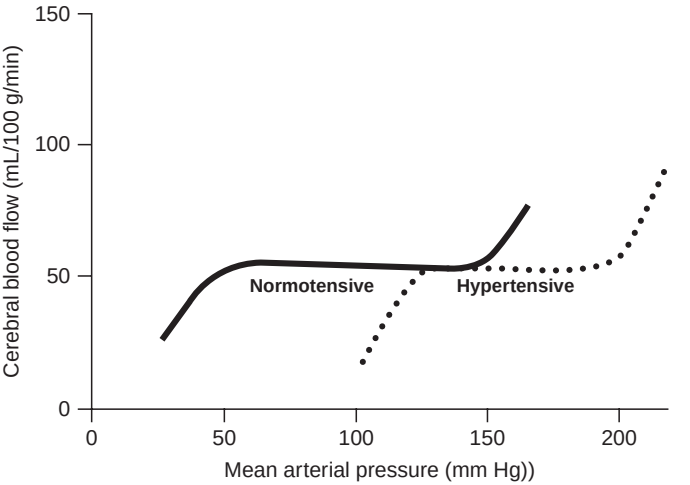

FIGURE 35.1 Autoregulatory cerebral blood flow response to changes in mean arterial pressure. Rightward shift of the autoregulation curve in chronically hypertensive patients. Adapted from Strandgaard S, Olesen J, Skinhoj, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *BMJ.* 1973;1:507–510.

infarction (MI), and death have been reported as consequences of overaggressive blood pressure reduction.

B. Endothelial damage. Hypertensive emergencies are triggered by an abrupt increase in systemic vascular resistance (SVR) caused by elevated levels of circulating vasoconstrictors (e.g., norepinephrine and angiotensin II). The resultant increase in blood pressure leads to **arteriolar fibrinoid necrosis and endothelial damage**. This endothelial damage is the etiology of the loss of autoregulatory function. In addition, the necrotic fibrinoid debris causes narrowing and obliteration of the vascular lumen. Target organ dysfunction ensuing from these two processes causes further release of vasoactive substances, producing a cycle of increasing SVR, elevated systemic blood pressure, vascular injury, and tissue damage. This is the vicious cycle that propagates the hypertensive emergency.

C. Manifestations. The endothelial damage and escape from autoregulatory control during a hypertensive crisis leads to the classic acute end-organ complications. Because the brain is encased in a finite space in the skull, the excess blood flow results in cerebral edema and elevated intracranial pressure (ICP), leading to encephalopathy and seizures. In the kidney, the fibrinoid necrosis as well as the excess blood flow destroy glomeruli, resulting in proteinuria, hematuria, and acute renal failure. The acute injury to the fundi is manifested by exudates, hemorrhage, papilledema, and potentially blindness. The cardiovascular system can suffer from myocardial ischemia and pulmonary edema from the increased afterload state as well as aortic dissection and hemolysis from the shear stress.

III. ETIOLOGY. It is estimated that 30% to 40% of patients with a hypertensive crisis have an identifiable underlying cause compared with < 5% of those with hypertension who have not had a crisis. Evaluation for such secondary causes and precipitants is indicated in all patients with a hypertensive crisis.

TABLE 35.2 Conditions That May Precipitate a Hypertensive Crisis

Essential hypertension from undiagnosed or poorly controlled hypertension (most common)
Nonadherence to antihypertensive medication regimen
Renovascular disease
Acute, as well as chronic, renal parenchymal diseases
Acute central nervous system insults (e.g., ischemic stroke and intracranial hemorrhage)
Drug-induced (e.g., interactions, idiosyncratic reactions, exaggerated effects, and abrupt withdrawal)
Collagen vascular disease and vasculitis (classically scleroderma)
Preeclampsia
Pheochromocytoma
Obstructive sleep apnea

A. A common scenario is that of a patient inadequately treated for chronic hypertension or one that is medically nonadherent.

B. Risk factors for progression to hypertensive crisis include male gender, black race, low socioeconomic status, cigarette smoking or other tobacco abuse, and oral contraceptive use. Unlike primary hypertension, the incidence of which increases with age, the peak incidence of hypertensive crisis occurs among people aged 40 to 50 years.

C. Underlying pathologic states that can precipitate hypertensive crises include renal parenchymal disease, renovascular hypertension, collagen vascular disease and scleroderma, pheochromocytoma, vasculitis, preeclampsia, and neurologic disorders (Table 35.2).

D. A number of **medications and illicit drugs** can cause marked elevations in systemic blood pressure. The most common offenders are **cocaine**, oral contraceptives, sympathomimetic agents (e.g., diet pills and amphetamines), cold remedies (especially pseudoephedrine), nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and monoamine oxidase inhibitors. Withdrawal from medications and illicit drugs can also precipitate severe hypertension. Examples include alcohol, benzodiazepine, and clonidine withdrawal.

IV. CLINICAL PRESENTATION

A. History

1. **Symptoms.** The history should focus on the organs that are known to suffer from end-organ damage: cardiovascular, neurologic, renal, and ocular. Cardiopulmonary symptoms include shortness of breath and chest pain. Neurologic symptoms include headache, confusion, lethargy, altered mental status, nausea, and vomiting. Oliguria and change in urine color to suggest hematuria may be the symptoms volunteered by the patient if there is renal damage. Blurred vision or change in vision suggests ocular involvement.
2. **Symptom chronology.** Among patients with severe hypertension, symptom chronology and the duration of uncontrolled blood pressure should be elicited, as this will guide the aggressiveness of blood pressure control.
3. **History of hypertension.** Most patients with hypertensive crises have an underlying history of chronic primary hypertension; however, a significant proportion have secondary forms of hypertension. Age of onset of hypertension as well as other potential clues to a secondary form of hypertension should be assessed.

4. **Contributory medication history** may include NSAIDs, oral contraceptives, erythropoietin, psychotropic agents, monoamine oxidase inhibitors, ephedrine, cyclosporine, tacrolimus, over-the-counter cold remedies, and many other medications. Withdrawal from clonidine is always a risk factor for a crisis in hypertensive patients to whom this medication has been previously prescribed. For those on antihypertensive medications it is crucial to elicit administration history, as a frequent, and potentially catastrophic, complication occurs when severe hypotension is induced by initiation of all outpatient medications in a patient with nonadherence.
5. **History of use of recreational drugs** such as **cocaine** and amphetamines, nonprescription stimulants including sympathomimetic weight loss pills, and performance-enhancing substances for athletes is important to elicit.
6. **Smoking history.** Smokers are at increased risk for progression to severe hypertension, perhaps due to endothelial dysfunction and dysfunctional autoregulation.

B. Physical findings

1. **Vital signs.** Blood pressure is measured in both upper and lower extremities to evaluate for stenosis or dissection of the aorta or great vessels. Severe hypertension is confirmed by taking two blood pressure measurements separated by 15 to 30 minutes. **No absolute level of blood pressure differentiates an emergency from an urgency.** ***The distinction is based upon the assessment of acute end-organ damage.***
2. **Optic fundi** are examined for signs of retinopathy, including exudates, hemorrhages, or papilledema.
3. **Neurologic assessment** is performed to assess mental status and neurologic motor deficits. Patients with hypertensive encephalopathy may manifest neurologic signs of confusion or seizure activity.
4. **Cardiovascular and pulmonary systems** are examined for the presence of an S_3, S_4, new murmur, and/or pulmonary edema. Total volume status should be assessed, as certain treatments can cause severe hypotension in the setting of volume depletion and other medications are less effective in the setting of fluid overload.
5. **Vascular system** is examined by palpation of pulses and auscultation for bruits, especially renal bruits.

V. DIAGNOSTIC EVALUATION. If a hypertensive emergency is suspected, appropriate arrangements for ICU admission and parenteral treatment should not be delayed while waiting for the results of further tests. Chest pain, shortness of breath, headache, blurred vision, signs of altered mental status, focal neurologic deficits, retinal exudates and hemorrhages, crackles, an S_3 gallop, and pulse deficits all point toward an emergency. Diagnostic testing can be performed after treatment has been instituted.

A. Complete blood count and blood smear. The presence of anemia with schistocytes should raise concerns for hemolysis and microangiopathic hemolytic anemia.

B. Blood chemistries to evaluate for renal function and electrolyte levels. Hypokalemia and other electrolyte disturbances may give a clue to a secondary cause of hypertension (e.g., primary hyperaldosteronism and Cushing's syndrome).

C. Urinalysis to look for proteinuria, hematuria, and casts. **Hematuria** and moderate to severe **proteinuria** are surrogate markers for glomerular damage.

D. Finger-stick glucose test should be performed to exclude hypoglycemia as the cause of altered mental status in the setting of suspected hypertensive encephalopathy as well as a cause of a pseudoemergency.

E. Electrocardiogram to evaluate for myocardial ischemia and chronicity of hypertension with evidence of left ventricular hypertrophy. **Cardiac markers** of ischemia (creatine kinase and troponin) should be checked but troponin is a very sensitive

marker and will commonly be slightly above the upper limit of normal in severely hypertensive patients. This, in isolation, should not be considered acute end-organ damage.

F. **Chest radiograph** assesses heart size, can confirm auscultatory findings of pulmonary edema, and may show a widened mediastinum to suggest an aortic dissection.

G. **Computed tomography and/or magnetic resonance imaging (MRI) of the brain** may be indicated to evaluate neurologic deficits and altered mental status, especially in the setting of suspected primary stroke, hemorrhage, or trauma.

H. A urinary **toxicology screen** should be collected, as cocaine and other illicit drugs frequently cause severe hypertension.

I. Prior to initiating treatment, especially in hypertensive urgencies, obtaining **renin and aldosterone** level measurements as well as serum and urine **metanephrine** samples assists with retrospective analysis for a secondary cause of hypertension. Many of the medications used to treat hypertension (β-blockers, diuretics, and angiotensin-converting enzyme [ACE] inhibitors) confound the interpretation of these tests. This diagnostic evaluation should never delay treatment of a patient presenting with hypertensive emergency.

J. After appropriate management and resolution of the crisis, work-up for common **secondary causes of hypertension should be performed**. Renovascular hypertension is very commonly seen in these patients. In addition, primary hyperaldosteronism, coarctation of the aorta, obstructive sleep apnea, and Cushing's syndrome are frequently undiagnosed and should be investigated if the particular patient has suggestive features.

VI. THERAPY. The presence of **acute or rapidly progressive end-organ damage, and not the absolute blood pressure reading, determines whether the situation is an emergency or an urgency**. This determination dictates the type of treatment (i.e., parenteral or oral) and the setting (i.e., ICU, hospital ward, or outpatient) in which it is implemented. Management of acute hypertensive syndromes should be tailored to each patient and based on the presence, absence, and type of end-organ damage. For example, a blood pressure of 130/90 mm Hg may represent a hypertensive emergency for a patient with an aortic dissection, whereas a blood pressure of 200/120 mm Hg for a patient with asymptomatic chronic hypertension without acute end-organ dysfunction does not necessitate emergent parenteral therapy. The appropriate diagnostic evaluation and therapeutic plan are also dictated by the different variations of hypertensive crisis. For example, a pregnant woman with preeclampsia, a man with acute pulmonary edema, and an elderly patient with hypertensive encephalopathy require different diagnostic and pharmacologic strategies.

A. **Hypertensive emergencies**

1. **Goals of therapy** include immediate but controlled reduction of the MAP. The pharmacologic characteristics and potential toxic side effects of antihypertensive agents must be understood and anticipated.
   a. Patients are **treated in an ICU**, where clinical status and vital signs can be constantly monitored with the aid of an intra-arterial line.
   b. **Blood pressure is reduced in a controlled and predictable manner**. It is recommended that **blood pressure be reduced initially by no more than 25% of MAP over minutes to hours**. After the first 24 hours, further reductions should occur over days to weeks in order to allow the autoregulatory mechanisms to reset. **Exceptions include aortic dissection, postoperative bleeding, and pulmonary edema, all of which demand more aggressive blood pressure reduction to prevent catastrophic complications**.
2. **Medical therapy.** A number of parenteral antihypertensive medications are available to manage hypertensive emergencies. Characteristics of an ideal agent include rapid onset and cessation of action, a predictable dose–response curve,

TABLE 35.3 Parenteral Medications Used to Manage Hypertensive Emergencies

Drug	Dosage	Onset/duration	Indications	Side effects
Nitroprusside sodium (Nipride, Nitropress)	Infusion: 0.25–10 µg/kg/min	Immediate/3–5 min	Most emergencies	Nausea, vomiting, sweating, thiocyanate, and cyanide poisoning
Nitroglycerin (a.k.a. glyceryl trinitrate) (Nitro-Bid)	Infusion: 5–200 µg/min	Immediate/3–5 min	Myocardial ischemia, myocardial infarction, left ventricular failure	Headache, methemoglobinemia, tolerance with prolonged infusion
Labetalol (Normodyne, Trandate)	Bolus: 20 mg/5 min until desired effect (max 80 mg) Infusion: 1–2 mg/min	5–10 min/1–8 h	Most emergencies except those complicated by left ventricular failure	Heart block, orthostatic hypotension
Nicardipine (Cardene)	Infusion: 5–15 mg/h	5–10 min/1–4 h	Most emergencies except those complicated by left ventricular failure	Reflex tachycardia, headache, nausea, flushing Avoid in heart failure
Clevidipine (Cleviprex)	Bolus: 1–2 mg/h with potential doubling every 90 s for desired effect	2–4 min/5–15 min	Most emergencies except those complicated by left ventricular failure	Avoid in heart failure
Phentolamine (Regitine)	Bolus: 5–15 mg IV Infusion: 0.2–5.0 mg/min	1–2 min/3–10 min	Pheochromocytoma crisis Crisis due to catecholamine excess	Tachycardia, headache, flushing
Hydralazine (Apresoline)	Bolus: 10–20 mg IV every 30 min until desired effect achieved or side effects occur	10–20 min/3–8 h	Eclampsia	Marked hypotension, tachycardia, flushing. Contraindicated in myocardial ischemia, aortic dissection, and elevated ICP
Enalaprilat (Vasotec IV)	1.25–5 mg every 6 h	15 min/6 h	Scleroderma crisis, left ventricular failure	Marked decreases in blood pressure in high-renin states, renal failure, hyperkalemia
Fenoldopam (Corlopam)	Infusion: 0.1–0.3 µg/kg/min	< 5 min/30 min	Most emergencies, renal insufficiency	Tachycardia, headache, nausea, flushing Caution with glaucoma

ICP, intracranial pressure.

and minimal side effects. Table 35.3 lists parenteral antihypertensive agents, dosages, side-effect profiles, and specific indications.

a. Sodium nitroprusside is the drug of choice for most hypertensive emergencies. This is due to its favorable hemodynamic profile, rapid onset, and rapid cessation of action. A potent, direct vascular smooth muscle relaxant, nitroprusside, decreases afterload and preload by means of dilating arterioles and increasing venous capacitance. Hemodynamic effects include a decrease in MAP, afterload, and preload; renal blood flow and renal function may improve if cardiac output improves. Although the direct cerebral vasodilation by nitroprusside may cause an adverse increase in cerebral perfusion, this is counteracted by a potent effect on MAP. Most patients with a neurologic crisis who need blood pressure control tolerate nitroprusside without a worsening of neurologic status. Unlike intravenous nitroglycerin, nitroprusside does not raise ICP or cause headaches. However, the theoretical possibility of an increase in cerebral blood flow as well as increased ICP must be kept in mind if there is further clinical deterioration despite a decrease in the MAP when using this agent.

(1) Administration. Sodium nitroprusside must be administered by constant intravenous infusion in an intensive care setting with invasive arterial blood pressure monitoring. It has a very rapid onset of action, and its effect ceases within 1 to 5 minutes of stopping the infusion.

(2) Side effects. Red blood cells and muscle cells metabolize nitroprusside to cyanide, which is converted to thiocyanate in the liver and excreted in the urine. **Thiocyanate levels rise in patients with renal insufficiency, and cyanide accumulates in patients with hepatic disease**. Signs of thiocyanate toxicity include nausea, vomiting, headache, fatigue, delirium, muscle spasms, tinnitus, and seizures. Monitoring for signs and symptoms of toxicity and maintaining thiocyanate levels at < 12 mg/dL allow safe use of nitroprusside. Thiocyanate toxicity is extremely rare in the extensive experience with nitroprusside at our institution.

b. Labetalol is useful in most hypertensive crises. The main disadvantage is its relatively long duration of action. Labetalol is an α-blocker and nonselective β-blocker. When given through continuous intravenous infusion, the relative β- to α-blocking effect of labetalol is 7:1.

(1) The **hemodynamic effects** of labetalol include a decrease in SVR, MAP, and heart rate and a decrease or no change in cardiac output. Cardiac output is often spared because the decrease in stroke volume from the β-blockade is offset by the decrease in afterload from the α-blockade. Labetalol has little direct effect on cerebral vasculature, does not increase ICP, and is **considered by some to be the drug of choice in situations characterized by markedly elevated ICP**. Labetalol begins to lower blood pressure within 5 minutes, and its effects can last 1 to 3 hours after cessation of the infusion.

(2) Contraindications. Labetalol is contraindicated for patients with acutely decompensated heart failure, cardiogenic shock, bradycardia, second- or third-degree heart block, and severe reactive airway disease known to be exacerbated by β-blockers.

c. Nitroglycerin is an important drug for managing hypertension in the setting of myocardial ischemia, acute MI, and acute cardiogenic pulmonary edema (ACPE). It is primarily a venodilator and has modest effects on afterload at high doses. The decrease in preload and afterload decreases myocardial oxygen demand. Nitroglycerin also dilates the epicardial coronary arteries, inhibits vasospasm, and favorably redistributes blood flow to the endocardium. **Nitroglycerin directly increases cerebral blood flow, raises ICP, and is not used in situations initially characterized by high ICP**.

Tachyphylaxis to nitroglycerin is well known and it is not uncommon for the blood pressure to rebound after prolonged administration. Headache is the most frequent side effect.

d. **Fenoldopam** is a selective peripheral dopamine-1-receptor agonist approved for the management of severe hypertension. Fenoldopam is an arterial vasodilator with a rapid onset of action and a relatively short half-life when administered intravenously. It may be of particular benefit in patients with renal insufficiency, as it has been shown to improve renal perfusion. Fenoldopam may cause reflex tachycardia, which can be blunted by the concomitant use of a β-blocker. Fenoldopam is contraindicated in patients with glaucoma, because it can increase intraocular pressure. It is a potent systemic vasodilator and is used primarily by anesthesiologists to control blood pressure intraoperatively.

e. **Nicardipine.** As a dihydropyridine calcium channel blocker, nicardipine inhibits vascular smooth muscle contraction but has little to no activity on the heart's atrioventricular or sinus nodes. It is particularly useful in the setting of postoperative hypertensive crises and neurological scenarios, as it does not raise ICP and directly reduces cerebral ischemia. It is contraindicated in advanced heart block, acute MI, and renal failure. It is administered via a continuous intravenous infusion. **Clevidipine** is a short-acting dihydropyridine calcium channel blocker administered as a continuous infusion that does not cause reflex tachycardia. Its benefit over nicardipine is that the half-life is shorter and thus relative hypotension can be reversed quickly with cessation of the infusion.

f. **Enalaprilat.** This is a short-acting intravenous ACE inhibitor that lowers blood pressure abruptly. It is not widely used in hypertensive emergencies, as it can precipitate hypotension, particularly in volume-depleted patients or those with renal artery stenosis. ACE inhibitors are first-line therapy for the management of scleroderma renal crisis.

g. **Hydralazine.** Although very commonly administered, the role of intravenous hydralazine in hypertensive emergency should be limited to the treatment of pregnant women with preeclampsia and eclampsia. Hydralazine is a direct arterial vasodilator with no effect on venous capacitance. It crosses the uteroplacental barrier but has minimal effects on the fetus. It is usually administered in intravenous boluses of 10 to 20 mg and has a long duration of action. Hydralazine decreases SVR, induces compensatory tachycardia, and increases ICP. It can exacerbate angina and is **contraindicated in the care of patients with ongoing coronary ischemia, aortic dissection, or increased ICP**.

h. **Clonidine.** Clonidine should be used primarily in cases where the cause of hypertensive emergency is clonidine withdrawal.

i. **Oral agents.** Once the blood pressure is controlled parenterally, switching to an oral regimen that benefits the patient in the long term, based on their particular comorbidities, is recommended. In chronically hypertensive patients, this usually requires at least two antihypertensive medications. Increasing the dose of existing medications or reinitiating therapy in nonadherent patients is appropriate.

3. **Management of specific emergencies**

a. **Neurologic emergencies.** Patients with neurologic findings and severe hypertension present a particular challenge. Neurologic emergencies can be the result of a hypertensive emergency that will then be exacerbated by the elevated blood pressure or the result of a primary neurologic insult that causes markedly elevated blood pressures to maintain necessary perfusion. One key differentiating point is that **neurologic alterations caused by severe hypertension are reversed when blood pressure is controlled**

appropriately, whereas primary neurologic disorders typically do not improve with blood pressure control.

(1) **Hypertensive encephalopathy.** This condition occurs when cerebral edema is induced by markedly elevated blood pressures that overwhelm the autoregulatory capabilities of the brain and is characterized by headache, irritability, and an altered state of consciousness. The treatment of choice is **sodium nitroprusside or labetalol**. Agents that depress the sensorium or increase ICP (i.e., intravenous nitroglycerin) should be avoided. Mental status will classically revert to normal within hours of blood pressure reduction. **If there is no improvement despite an appropriate decrease in blood pressure, the diagnosis must be reconsidered and concern should be for a primary neurologic insult causing secondary hypertension**. During the neurologic work-up, an MRI of the brain may reveal white matter edema in the parieto-occipital regions, termed reversible posterior leukoencephalopathy syndrome. Occasionally, hypertensive encephalopathy will manifest as seizures. Along with appropriate blood pressure control, concurrent anticonvulsive therapy to terminate active seizures is appropriate; however, chronic antiepileptic therapy is not necessarily indicated since treatment of the hypertension prevents further events.

(2) **Ischemic stroke.** Although hypertension is a risk factor for ischemic strokes, the management of hypertension in the setting of an acute stroke is controversial. The elevated blood pressure is thought to be protection from hypoperfusion due to vasodilation in the peri-ischemic regions. In general, patients should not be treated unless their blood pressure > 220/120 mm Hg or they have evidence of acute end-organ damage elsewhere (e.g., aortic dissection and myocardial ischemia). In addition, in those that are eligible for thrombolytic therapy, a blood pressure < 185/110 mm Hg is required. The goal reduction is 15% in the first 24 hours. Labetalol is the preferred agent, with calcium channel blockers being acceptable alternatives.

(3) **Intracranial hemorrhage.** Intracerebral hemorrhage and subarachnoid hemorrhage (SAH) are often associated with severe hypertension. Similar to an ischemic stroke, the increased blood pressure is thought to be protective. Due to the blood within the skull, ICP increases. In order to maintain the necessary cerebral perfusion pressure (CPP) of 60 to 80 mm Hg in the setting of elevated ICP, an increase in MAP is necessary (CPP = MAP – ICP). Neurology consultation along with neuroimaging and intracerebral pressure monitoring is frequently used to guide blood pressure management. Nimodipine is considered the standard of care for SAH, as it prevents vasospasm commonly seen in this condition.

b. **Cardiovascular emergencies.**

(1) **Aortic dissection.** As opposed to most other presentations of hypertensive emergency when appropriate care requires that blood pressure be normalized slowly, in the setting of an acute aortic dissection **blood pressure must be corrected immediately**. Patients with a **type A dissection** have a mortality rate of 1% per hour in the first 48 hours unless medical therapy is instituted rapidly and the patient is referred for **emergency surgical intervention**. In the setting of an uncomplicated **type B dissection, antihypertensive therapy** aimed at reducing vascular resistance and shear force on the vessel wall is the treatment of choice. Aortic dissections require decreased vascular shear force by means of reducing the inotropic state of the heart and the ratio of change in ventricular pressure to the change in time (dP/dt). **This should be accomplished via**

β-blockade prior to vasodilation in order to prevent reflex tachycardia and increases in d*P*/d*t*. **Aggressive blood pressure reduction** is indicated, even for patients with normal blood pressure, because shear force and afterload must be maximally reduced to prevent extension of the dissection and/or aortic rupture. A systolic blood pressure between 100 and 110 mm Hg (or lower if tolerated) with a heart rate between 50 and 60 beats per minute is the goal. Suspect hemopericardium with tamponade or aortic rupture if hypotension is present prior to initiating therapy. **Sodium nitroprusside with an intravenous β-blocker** (metoprolol) is the treatment of choice at our institution. Continuous infusion with labetalol is sometimes used due to its combined effects on myocardial contractility as well as SVR but the fixed β-blockade to α-blockade ratio makes independent titration of blood pressure and heart rate challenging. Fenoldopam, esmolol, and diltiazem infusions are options as well.

(2) **Acute cardiogenic pulmonary edema.** Often termed flash pulmonary edema, **ACPE due to severe hypertension** is best treated with **sodium nitroprusside or nitroglycerin**. Because of the pulmonary edema, a common reflexive action is to administer intravenous loop diuretics; however, this may have deleterious effects downstream. Accepting this seemingly paradoxical statement requires insight into the pathophysiology of pulmonary edema in this particular setting. The patients at risk for ACPE tend to be older in age with long-standing hypertension or diabetes, all of which impair diastolic function. The **acutely** elevated blood pressure results in left ventricular afterload mismatch; left ventricular end-diastolic pressure suddenly rises with concomitant elevation of the pulmonary venous pressure. On the pulmonary capillary level, increased Starling forces cause transcapillary leak and, ultimately, pulmonary edema. If the patient is euvolemic prior to the acute pressure change, then the pulmonary edema is due to maldistribution of the intravascular volume and not due to total body volume overload. Intravenous loop diuretics may have an initial beneficial venodilatory effect, but the subsequent volume depletion can cause future hemodynamic side effects. Thus, **treatment should be aimed at decreasing the acute pressure overload and afterload mismatch**, which will reverse the fluid shift in a time frame similar to the rate of decompensation. If nitroprusside or nitroglycerin infusions are not immediately available in this setting, **nitroglycerin tablets can be given sublingually** with repeated administration until goal blood pressure is achieved. Because the ACPE is often due to rapid onset of pressure overload and not due to chronically elevated blood pressure, normalization of the blood pressure in this hypertensive emergency is well tolerated without ischemic risks. It is not uncommon to see immediate relief of dyspnea and hypoxia in a patient with florid pulmonary edema once the blood pressure is lowered. β-Blockers and calcium channel blockers must be avoided in the decompensated state since the impaired inotropy and chronotropy will exacerbate the already afterload burdened ventricle.

(3) **Myocardial ischemia.** Preload, afterload, contractility, and heart rate determine myocardial oxygen consumption. Elevated blood pressure, and thus afterload, can induce ischemia from the increased oxygen demand. In addition, the significantly elevated blood pressure can rupture stable coronary plaques, resulting in an MI. Blood pressure reduction with nitroglycerin is the treatment of choice. Nitroprusside is added if further blood pressure reduction is required. Although the optimization of cardiac parameters is likely beneficial, it must not be forgotten

that **antiplatelet and antithrombotic therapies** are the mainstays of medical management of acute coronary syndromes. **Emergent reperfusion** is indicated in ST-elevation MIs. Heparin infusion should not be started with uncontrolled systolic blood pressures (190 mm Hg or greater), as the risk of intracerebral bleeding is significant.

(4) **Postoperative bleeding. Postoperative bleeding from vascular suture lines should be treated with immediate normalization of blood pressure, similar to an aortic dissection.** Parenteral treatment with sodium nitroprusside, nicardipine, or labetalol is preferred. **After coronary bypass grafting, nitroglycerin** is considered the initial drug of choice to maximize cardiac perfusion.

c. Pregnancy. In addition to delivery of the fetus and placenta in preeclampsia, **intravenous magnesium** therapy is the treatment of choice to prevent progression to eclampsia. Labetalol or hydralazine, combined with a β-blocker to prevent reflex tachycardia, can be used safely in pregnancy. ACE inhibitors and angiotensin receptor antagonists are contraindicated.

d. Pheochromocytoma. Phentolamine is an intravenous α-adrenergic blocker useful in cases of pheochromocytoma as it is effective in cases of catecholamine excess. β-Blockers should never be used in isolation because they can cause a paradoxical increase in blood pressure due to the effects of unopposed α-receptor stimulation from circulating catecholamines.

B. Hypertensive urgencies. Most patients diagnosed with hypertensive urgency actually have chronically severe hypertension and **are not in any immediate danger of progressing to hypertensive emergency**. They are often people with chronic hypertension who are suboptimally treated or nonadherent. As previously mentioned, the key to distinguishing hypertensive emergency from urgency is to assess whether there is evidence of acute end-organ damage.

1. Goal of therapy

a. Hypertensive urgencies can often be managed with **oral medication without admission to the hospital**. End-organ damage is not imminent, and blood pressure can be lowered modestly over a period of hours as long as adequate follow-up care is ensured. **The greatest danger lies in overtreating these patients and inciting hypotensive complications**. However, even in the absence of acute end-organ dysfunction, hospital admission should be considered for patients with a diastolic blood pressure > 140 mm Hg, those with a high risk of cardiovascular complications (known coronary disease or previous stroke), or those with uncertain outpatient follow-up.

b. Since hypertensive urgencies can have significant morbidity if treated aggressively, lower initial doses of antihypertensive medications are used to treat patients with known cerebrovascular disease or coronary artery disease or who are volume depleted. These patients tend to have exaggerated responses to drug therapy. In addition, they are also especially vulnerable to the effects of hypotension. Monitoring for 4 to 6 hours is necessary to judge treatment effect and to look for complications. Urgent follow-up care is mandatory within 24 to 48 hours. The outpatient goal is to normalize the blood pressure over the next 2 or 3 months.

2. Drug therapy. In adherent patients already prescribed with antihypertensive medications, increasing the dose of a current medication is usually sufficient. If initiation of a new agent is required, the choice should be a medication that benefits the patient in the long-term; therefore, underlying comorbidities should be taken into account. For example, ACE inhibitors would be best for those with diabetes, chronic kidney disease, or systolic dysfunction, and β-blockers for those known to have coronary artery disease or atrial fibrillation. Although considered a first-line agent for chronic hypertension, diuretics tend to have a

poor response in severe hypertension when given as a monotherapy. However, a long-acting dihydropyridine calcium channel blocker, β-blocker, or ACE inhibitor can be started in isolation. The medications commonly used for hypertensive urgencies include captopril, long-acting nifedipine, and oral labetalol, although many other adequate choices exist.

a. **Captopril.** Considered by some to be the drug of choice, captopril is a **fastest-acting oral ACE inhibitor**. At small doses, it rarely causes marked hypotension, although this potential exists in patients who are markedly volume depleted or who have renal artery stenosis. Captopril begins to work within 15 to 30 minutes of ingestion and the duration of activity is 4 to 6 hours. An initial dose of 6.25 mg should be given and if hypotension does not occur within 1 to 2 hours, the patient will tolerate doses of 12.5 to 25 mg three times daily.
b. **Nifedipine.** ***The short-acting and sublingual forms of nifedipine should not be used, as profound hypotension is easily precipitated.*** The long-acting form is a potent antihypertensive medication and should be initiated at 30 mg daily with uptitration as an outpatient. The onset of action is not as quick as labetalol or captopril but the daily dosing is favorable for adherence.
c. **Labetalol.** A combined α-blocker and β-blocker, labetalol, taken orally has a relative β-blocking to α-blocking effect of approximately 3:1. Dosage begins at 100 mg (taken orally twice daily) and is titrated to the desired response. The onset of action is 30 minutes to 2 hours after administration; the duration of action is 8 to 12 hours.

VII. PROGNOSIS. The prognosis of a patient with an untreated hypertensive crisis is poor. Before the introduction of effective antihypertensive agents, 1-year mortality exceeded 80% and 5-year mortality was approximately 99%. In the modern era of effective antihypertensive medications, 10-year survival has improved to 70%. Therefore, appropriate recognition of these clinical syndromes coupled with the treatment of blood pressure in a safe and controlled manner is paramount to significantly improving outcomes for these once mortal conditions.

ACKNOWLEDGMENTS: *The author thanks Drs. John H. Chiu, Harpreet Bhalla, and Daniel Cantillon for their contributions to earlier editions of this chapter.*

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CHAPTER 36

Sachin S. Goel
Samir R. Kapadia

Evaluation of Chest Pain in the Emergency Department

I. INTRODUCTION. Chest pain is one of the most common problems evaluated in the emergency department (ED).

A. Each year, approximately 5 million persons who arrive at an ED with chest pain are admitted to the hospital, mainly to an intensive care unit; 1.2 million of these patients are ultimately diagnosed with acute myocardial infarction (AMI). However, **2% to 4% of persons who arrive with chest discomfort and AMI are inappropriately discharged** to home. This error in diagnosing myocardial infarction (MI) is dangerous and costly. **Early recognition and treatment** are also important because time to treatment is the single most important factor in the management of ST-elevation MI.

B. **Rapid evaluation and risk stratification** of patients with chest pain are essential to identify life-threatening conditions and improve outcomes. Emergency treatment is initiated in the ED to minimize permanent myocardial damage and improve survival, especially in patients with MI. **The goal of treatment in ST-elevation MI** is to achieve reperfusion as soon as possible, either by primary percutaneous coronary intervention or by thrombolytic therapy. **Conversely, in patients with non–ST-elevation acute coronary syndrome (ACS), maintaining antegrade flow in the coronaries with prevention of distal embolization is important**. The Thrombolysis in Myocardial Infarction (TIMI) risk model is a validated mechanism to determine prognosis and guide therapy in patients with ACS. The model consists of seven variables, with one point for each variable: age > 65 years, three or more risk factors for heart disease, known coronary stenosis, multiple anginal episodes in the last 24 hours, use of aspirin in the last week, electrocardiographic changes, and elevated cardiac biomarkers (Table 36.1). **High-risk patients** are typically admitted to a coronary care unit for management with antiplatelet and antithrombotic therapies. Urgent (within hours) cardiac catheterization and appropriate revascularization are recommended in these patients. **Intermediate-risk angina patients** are directed to a monitored telemetry unit and undergo further risk stratification such as stress testing and assessment of left ventricular function with possible cardiac catheterization. **The lowest risk patients** can be observed in a chest pain unit or discharged directly to home, depending on the clinical situation.

C. **Assessment** of chest pain in ED involves careful patient **history, physical examination, and 12-lead electrocardiogram (ECG)**. Functional stress tests can supply additional data, but the data are not immediately available, and triage decisions are often made without them. With clinical history, physical examination, and initial ECG, 92% to 98% of cases of AMI and approximately 90% of cases of unstable angina can be identified.

TABLE 36.1 Rate of Complications in Non–ST-Segment ACS Based on TIMI Risk Score

# risk factors	0–1	1	3	4	6	6–7
N patients	85	339	627	573	267	66
% total patients	4.3	17.3	32	29.3	13.6	3.4
Rate of composite endpoint	4.7%	8.3%	13.2%	19.9%	26.2%	40.9%

TIMI, Thrombolysis in Myocardial Infarction; ACS, acute coronary syndrome; N, number.

Composite endpoint: Incidence of all-cause mortality; MI, repeat revascularization at 14 d.

Based on data from Antman EM, Cohen M, Bernink PJ, et al. TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835-842.

II. CLINICAL PRESENTATION

A. History

1. **Chest pain.** The initial history should accurately characterize the location and duration of the patient's discomfort, associated symptoms, and aggravating and alleviating factors (Table 36.2). Most patients with ischemic chest pain describe it as substernal pressure, squeezing feeling, or a sensation of suffocation. Some patients describe it as aching, burning, or tightness. The pain may radiate to the shoulder, neck, jaw, left or right arm, and the fingertips. Occasionally, the pain may be predominantly epigastric or interscapular.
2. **Atypical presentations.** Dyspnea is often associated with chest pain during an MI. **Dyspnea** may also be the only major presenting symptom in about 10% of patients with MI. Other atypical presentations include fatigue, syncope, altered sensorium, stroke, nausea or vomiting, and lethargy. **Atypical presentations of AMI are more common in the elderly, in patients with diabetes, and in women**.
3. **Risk factors.** Although several clinical factors have been associated with an increased risk of cardiovascular disease, only the **age** of patient, **history of coronary artery disease,** and **male** sex are predictive of ACS among patients with chest pain. In some studies, diabetes and family history have been associated with ACS, but the overall power of these risk factors in predicting an ischemic event is low. The **absence of risk factors cannot be used to exclude cardiac ischemia**.

B. Physical examination

1. The physical examination helps to identify **signs of left ventricular dysfunction and occult valvular heart disease**. The presence of a third heart sound (S_3 gallop), rales, sinus tachycardia, hypotension, and increased jugular venous distention is associated with adverse outcome. The presence of these signs and symptoms indicates cardiac origin of the chest pain. A thorough physical examination also helps identify the cause of nonischemic chest pain. Chest wall tenderness, skin lesions, and pleural or pericardial rub can be useful in this regard.

TABLE 36.2 Differentiating Cardiac from Noncardiac Chest Pain

Favoring ischemic origin	Favoring nonischemic origin
Character of pain	
Squeezing	Sharp, knifelike
Burning	Stabbing
Heaviness	Aggravated by respiration
Location of pain	
Substernal	Left submammary area
Across mid-thorax	Left hemithorax
Radiation to the arms, shoulders, neck, head, forearms, interscapular region	Discomfort localized with one finger
Associated with nausea, vomiting, diaphoresis	Back pain that suggests aortic dissection
Factors provoking pain	
Exercise	Pain after completion of exercise
Excitement	Pain relieved by exercise
Stress	Provoked by a specific body motion
Cold weather	
Duration of chest pain	
Minutes	Seconds
	Hours without evidence of myocardial damage

From Selzer A. *Principles and Practice of Clinical Cardiology.* 2nd ed. Philadelphia, PA: WB Saunders; 1983:17, with permission.

2. **Response to treatment is not reliable** in unraveling the cause of chest pain. **Pain relief after administration of nitroglycerin does not necessarily point to MI or unstable angina, as other etiologies for chest pain are relieved with nitroglycerin**.

III. DIAGNOSTIC TESTING

A. The **ECG** is integral to the evaluation of chest pain and has important diagnostic and prognostic value. It is even more important in the evaluation of persons with diabetes and elderly persons who tend to have atypical symptoms.

1. Almost 50% of patients with MI have a normal or nondiagnostic ECG on presentation to the ED. **Sensitivity** depends on a number of factors, including the time from symptom onset, coronary distribution of ischemia, baseline ECG abnormalities, and patient characteristics. Electrocardiographic findings should normalize rapidly after resolution of chest pain. The electrocardiographic findings of a patient who does not have active chest pain are difficult to interpret.

Circumflex distribution ischemia is notoriously silent on an ECG, as the posterolateral wall is underrepresented on a conventional 12-lead ECG.

2. Among patients with the ischemic type of chest discomfort, ST-segment elevation on an ECG has a specificity of approximately 90% and a sensitivity of approximately 50% for the diagnosis of AMI. Specificity decreases to 82% and sensitivity increases to 69% when ST-segment elevation or depression, Q waves, or left bundle branch block (LBBB) is used to define abnormal electrocardiographic findings.
3. The ECG can be used to identify a population of patients at low risk for MI. A normal ECG indicates < 3% risk for MI and < 6% risk for death in the following year. However, approximately one-third of patients with unstable angina may have a normal or equivocal ECG. The **ECG cannot be used alone to exclude ACS**.
4. Preexisting abnormalities, including left ventricular hypertrophy, LBBB, Q waves, preexcitation, and paced rhythms, make interpretation of the ECG difficult. Comparison of the initial ECG with a prior tracing is often helpful in this setting. Whether new or old, the presence of **LBBB is an adverse prognostic finding**. New LBBB suggests left anterior descending coronary artery ischemia or infarct. Preexisting LBBB alone defines a group of patients at high risk for cardiac morbidity and mortality. Although LBBB complicates the electrocardiographic diagnosis of AMI, criteria have been proposed for ascertaining whether a patient has AMI and LBBB from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) database.

B. **Biochemical markers** of myocardial necrosis are used in conjunction with the clinical history and ECG to confirm the diagnosis of MI. Biochemical markers include cardiac **troponins, creatine kinase–myocardial band (CK-MB) isoenzyme, and myoglobin**. These markers, especially troponins, are sensitive and specific for myocardial injury and can provide important prognostic information.

1. **Serial blood samples** are collected over a 24-hour period to measure a temporal rise and fall for the diagnosis of MI. All biochemical markers follow a predictable pattern of release after the onset of myocardial injury.
2. An **ideal serum marker** is specific to myocardium, highly sensitive, and quantitative; the serum concentration is proportional to the amount of myocardial tissue injured. Furthermore, the levels have to increase rapidly to allow early diagnosis. None of the available markers are optimal for the diagnosis of ACS. In most cases, the combination of serial measurement of markers and interpretation of clinical data such as ischemic symptoms and ECG changes leads to the accurate diagnosis of ACS.
3. Enzymes such as aspartate aminotransferase, lactate dehydrogenase, and total CK are released from dying myocytes but are relatively nonspecific for cardiac tissue.
   a. **CK-MB is released into the circulation after myocardial cell death.** There is some evidence in animal models that CK-MB can be released with reversible myocardial injury. However, this has not been shown in humans.
      - Most studies have confirmed that serial measurement of CK-MB for the diagnosis of AMI has a sensitivity of approximately 92% with a specificity of 98%. The initial level of CK-MB, however, does not carry equal statistical weight and does not have sufficient negative predictive value to exclude MI when used in isolation. The CK-MB level can be increased with normal or minimally elevated total CK levels; however, the significance of this finding is debatable.

   b. **Myoglobin** is a small heme protein that is not specific to cardiac tissue. The use of myoglobin as a marker of myocardial necrosis does not carry the

specificity of CK-MB measurement. **The advantage of myoglobin as a marker lies in its release kinetics**. Myoglobin is released rapidly after myocardial injury, and serum levels are detectable within 1 to 2 hours of the onset of symptoms. Peak serum levels are reached within 4 to 5 hours after MI. Within 1 to 3 hours of MI, serum myoglobin determination has a sensitivity of 62% to 100% in the detection of myocardial damage. Because of its short half-life, measurement of myoglobin may not help confirm the diagnosis for patients who seek treatment late after symptom onset. The specificity is low when there is a substantial release of skeletal muscle myoglobin and in the setting of renal failure.

c. Troponins

- Cardiac troponins are **proteins that regulate the calcium-dependent interactions between actin and myosin**. This interaction results in myocyte contraction and relaxation. **Troponin T** is a myofibrillary protein and is a constituent of the contractile apparatus of cardiac muscle. Cardiac troponins, like CK-MB, can be found in the serum soon after injury, but concentrations remain elevated for as long as 2 weeks. Cardiac troponin T and troponin I are useful in the diagnosis of ACS and have been shown to be very sensitive and specific markers of myocardial cell injury.
- A large, prospective analysis from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO IIa) trial has provided important data on the **value of cardiac troponins for diagnosis and risk assessment**.
  - **(i)** Among patients who present within 12 hours of the onset of myocardial ischemia, elevated levels of **troponin T** (> 0.1 mg/mL) are associated with significantly higher mortality within 30 days. This is true for all ECG subgroups examined, including those with ST depression, ST elevation, T-wave inversion, LBBB, and paced rhythms. A quantitative relation has also been demonstrated between levels of cardiac troponin T and long-term clinical outcome.
  - **(ii)** **Troponin I** also has similar prognostic value. Among patients with unstable angina and non–Q-wave MI, elevated cardiac troponin I levels (> 0.4 ng/mL) are associated with significantly higher mortality.
  - **(iii)** **Bedside tests** for cardiac-specific troponins are **highly sensitive** for the early detection of myocardial cell injury in ACS. Qualitative and quantitative point-of-care tests for troponin T and troponin I are fast, yielding results that are reliable and accurate within a few minutes. **Negative test results have been associated with low risk** and allow rapid and safe discharge from the ED of patients with an episode of acute chest pain, as long as these tests are done at least 8 hours after the onset of chest pain.

d. Novel biomarkers. B-type natriuretic peptide and C-reactive protein (CRP) are predictive of risk in patients with ACS. Measuring these markers in combination with troponin or CK-MB may improve the short- and long-term risk stratification of ACS patients. **Plasma myeloperoxidase** levels are elevated in persons with angiographically documented coronary disease and within culprit lesions prone to plaque rupture. Recent studies have shown that elevated myeloperoxidase levels predict cardiac risk in patients presenting to the ED with chest pain, independently of the level of CRP, troponin T, and other markers of inflammation. However, these novel biomarkers have yet to become incorporated into clinical practice guidelines for chest pain or ACS management.

C. Imaging studies. Although clinical history, initial electrocardiographic findings, and biochemical markers have been combined to diagnose ACS with high sensitivity

and specificity, atypical presentations and equivocal electrocardiographic findings can make diagnosis challenging. Investigations aimed at overcoming these problems have focused on myocardial perfusion and functional imaging.

1. **Echocardiography.** Two-dimensional echocardiography provides valuable diagnostic data on ventricular function and regional wall motion abnormalities.
   a. Myocardial ischemia can cause abnormal segmental function of the myocardium manifested as impaired relaxation, hypokinesis, akinesis, or dyskinesia.
   b. Although echocardiography alone has moderate sensitivity in the diagnosis of MI, it may be a useful adjunctive test, especially after reperfusion therapy. Echocardiography serves an important role in risk stratification after MI through assessment of left ventricular function.
   c. Normal findings at echocardiography cannot be used reliably to rule out myocardial ischemia.
   d. Echocardiography can be crucial in the evaluation of complications of MI, such as ruptured papillary muscle, free wall rupture, or ventricular septal defect.
2. **Radionuclide perfusion imaging** is useful to quantify myocardium at risk. It is rarely used for the diagnosis of ACS because of poor accessibility and cost.
   a. **Thallium 201 scintigraphy** has been used to detect the areas of reduced or absent perfusion in AMI. Areas of myocardium with a negative scintigraphic image, indicating decreased myocardial uptake, can be demonstrated in ischemic or infarcted myocardium within 6 hours of symptom onset. The diagnostic utility of such imaging is limited by the so-called moment-in-time problem; perfusion defects may represent acutely ischemic myocardium or preexisting areas of scar tissue. Thallium 201 imaging has relatively poor specificity in women because of difficulties in distinguishing between breast attenuation and perfusion defects caused by coronary artery disease.
   b. **Technetium 99m sestamibi tomographic imaging** has the advantage that it does not redistribute after initial injection. This type of imaging allows definition of an initial ischemic zone that can be studied even after reperfusion. Technetium-derived image quality is also superior to that of thallium and allows quantification of regional and global ventricular function by gated image acquisition. Perfusion imaging with technetium 99m appears to have a sensitivity equivalent to that of thallium 201 imaging in defining myocardium at risk.
3. **Computed tomography (CT)**. Recently, several studies have evaluated the role of multislice detector coronary CT angiogram in patients presenting to the ED with chest pain. The greatest promise of coronary CT angiogram appears to be in low-risk patients with chest pain, in whom absence of coronary artery disease has been shown to have a very high negative predictive value for subsequent diagnosis of ACS and very low rate of major adverse cardiovascular events during follow-up. The main limitation of this technology lies in the inability to determine the physiologic significance of coronary lesions of intermediate severity. Multislice detector CT has also been studied as a tool that can simultaneously assess for ACS, aortic dissection, and pulmonary embolism (PE). This approach appears promising; however, its use in the ED cannot be advocated until its clinical utility has been validated.

D. Early exercise stress testing. In general, exercise stress testing can be safely performed to further risk-stratify patients who are considered to be at a low clinical risk for MI. Studies have shown that this approach is safe in patients who have a normal or nondiagnostic ECG and negative biochemical markers for myocardial necrosis assessed within 6 to 12 hours of presentation to the ED.

IV. DIFFERENTIAL DIAGNOSIS. Differentiating ischemic from nonischemic causes of chest pain can be difficult (Table 36.3). It has been estimated that more than 50% of patients

TABLE 36.3 Differential Diagnosis of the Causes of Acute Chest Pain

Cardiac	Aortic	Pulmonary	Gastrointestinal	Miscellaneous
Acute coronary syndrome	Aortic dissection	Pulmonary embolus	Esophageal spasm/reflux	Costochondritis
Coronary spasm	Penetrating aortic ulcer	Pneumothorax	Esophagitis	Cervical spondylosis and other compression neuropathies
Syndrome X, microvascular disease	Aortic aneurysm	Pneumonia/ pleuritis	Esophageal rupture	Herpes zoster
Myopericarditis				Panic disorder
Aortic stenosis Hypertrophic cardiomyopathy				Anxiety

initially admitted to the hospital with a diagnosis of unstable angina are later discharged with a noncardiac diagnosis. Given that there is symptom overlap among a number of clinical entities, in most diagnostic strategies, it is assumed that **chest pain is cardiac in origin until proven otherwise**. It is important to understand the clinical characteristics that represent the leading noncardiac causes of chest pain. Life-threatening causes of chest pain that can be confused with ACS include aortic dissection, pericarditis with cardiac tamponade, and pulmonary embolus.

A. Pericarditis (see Chapter 40) is often accompanied by substernal chest pain, but the **pain** is more likely to be pleuritic in character and aggravated by recumbency, deep inspiration, and swallowing. **Physical examination** may reveal a three-component pericardial friction rub. The **ECG** often reveals ST elevation in multiple leads without reciprocal changes, whereas PR-segment depression in leads other than aVR and V_1 is a more specific sign of pericarditis. It is important to recognize that **pericarditis may be a late presentation of MI**. Cardiac tamponade is characterized by hypotension, elevated jugular venous pressure, and muffled heart sounds (Beck's triad). In addition, the presence of pulsus paradoxus, defined as an abnormally large (> 10 mm Hg) decline in systolic blood pressure during inhalation, is a very helpful sign in cardiac tamponade and reflects exaggerated ventricular interdependence, the key pathophysiologic mechanism in this life-threatening condition. Prompt bedside echocardiography wherever possible is very useful in confirmation of the diagnosis as well as guidance for percutaneous pericardiocentesis.

B. Aortic dissection (see Chapter 26) requires **urgent** diagnosis because early surgical intervention reduces the high short-term mortality rate. The **chest pain** of aortic dissection is typically described as sudden, severe, and tearing pain that radiates to the back and interscapular areas, which is most intense at onset. **Examination** may reveal a difference in right and left arm blood pressures, pulse deficits, and focal neurologic deficits. Aortic dissection may also involve the aortic valve or coronary ostia. The latter may be associated with the diastolic murmur of aortic insufficiency, myocardial ischemia, and ST-segment elevation on **ECG**. Diagnosis is primarily made by transesophageal echocardiography, multislice contrast-enhanced CT, or magnetic resonance imaging. All these imaging modalities have high sensitivity and specificity in the diagnosis of acute aortic dissection. The preferred initial diagnostic imaging

modality should be based on availability, local expertise, clinical stability, and renal function. At our institution, CT is the initial test of choice in most cases of suspected acute aortic dissection.

C. Pulmonary embolism is potentially life threatening and can be associated with chest pain. The **chest pain** of PE is typically pleuritic in character and is associated with dyspnea and tachypnea. There is often a **history** of recent surgical intervention, malignant disease, or immobility. The cardinal **clinical findings** include hypoxia and tachycardia. An **ECG** may demonstrate right-axis deviation, right bundle branch block, or occasionally the classic $S_1Q_3T_3$ pattern. In patients with low or moderate pretest probability of PE, a D-dimer level < 500 ng/mL by qualitative enzyme-linked immunosorbent assay or semiquantitative latex agglutination excludes PE with a very high negative predictive value. Spiral CT with contrast (CT pulmonary angiography) is the main imaging modality for diagnosing acute PE with very high specificity. However, when imaging results are inconsistent with clinical suspicion, additional testing in the form of V/Q scan or lower extremity ultrasonography may be necessary.

V. CONCLUSIONS. The ED is where life-saving therapy is initiated in patients with ACSs. It is important to rapidly and accurately risk-stratify patients with suspected ACS. Many patients will present with noncardiac conditions for chest pain, some of which are life threatening. It is important for the ED practitioner to have a working diagnosis of the varied causes of chest pain. There is a spectrum of ACSs, which ranges from high risk to low risk. The highest risk patients require emergent reperfusion therapy, whereas lower risk patients can undergo urgent invasive therapy or further risk stratification. Such an understanding can help direct patient care most appropriately and improve important outcomes, including survival.

ACKNOWLEDGMENTS: *The authors thank Drs. Jason B. Wischmeyer, Anthony Bavry, and Michael Yen for contributions to this chapter.*

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CHAPTER 37

Imran N. Ahmad

Cardiac Trauma

I. INTRODUCTION. Trauma represents the leading cause of death in males younger than 40 years in the United States. Cardiothoracic injuries are a primary or contributing factor in up to 75% of all traumatic deaths. Cardiac trauma occurs most commonly in the setting of motor vehicle accidents, interpersonal violence, cardiopulmonary resuscitation (CPR), falls from great heights, as well as sporting and industrial accidents. **Cardiac trauma can be easily overlooked in the presence of distracting injuries, as it can occur in the absence of chest pain or visible wounds.** Emergency department physicians lead the initial management, while contemporary trauma teams are typically led by surgical subspecialists. However, cardiologists play an important consultative role in the diagnosis and management of cardiac trauma.

- **A.** Cardiac trauma is divided into **blunt trauma** (i.e., motor vehicle accidents and falls) and **penetrating trauma** (i.e., primarily, knife and gunshot wounds).
- **B.** As many as 50% of people with cardiac injuries die in the field, but advances in diagnostic testing and surgical techniques have improved the prognosis of patients who reach emergency centers alive. Definitive management requires rapid mobilization of the surgical team and transport to the operating room.
- **C.** Initial attention is focused on the airway, breathing, and circulation, and the primary survey is performed according to the published Advanced Trauma Life Support (ATLS) guidelines. The cardiac physical examination should assess vital signs, peripheral pulses, murmurs, signs of heart failure, distended neck veins, and the presence of pulsus paradoxus. Routine laboratory evaluation should include cardiac

biomarkers, and a portable chest radiograph should be performed rapidly. **Transthoracic echocardiography (TTE) at the bedside is the preferred modality for the initial assessment of cardiac trauma**. Focused Assessment with Sonography for Trauma is a widely applied technique using bedside ultrasound to rapidly assess blunt trauma at multiple body sites, including the heart. An electrocardiogram (ECG) is indicated to evaluate for suspected coronary dissection or traumatic coronary thrombosis. The role for cardiac computerized tomography (CT) using intravenous contrast is expanding, and it remains the diagnostic study of choice to evaluate suspected trauma and/or dissection of the aorta and great vessels, along with transesophageal echocardiography (TEE).

II. BLUNT TRAUMA

A. Blunt cardiac trauma generally occurs in the setting of motor vehicle accidents, but it may also be related to falls, blows from blunt objects, or CPR.

B. Blunt trauma may injure the **pericardium**, **myocardium, valves or subvalvular apparatus**, **coronary arteries**, or the **great vessels.** The clinical presentation is generally one of **tamponade** or **hemorrhage**, depending on whether the pericardium is intact. Although hypotension and tachycardia are seen in both scenarios, tamponade is suggested by elevated neck veins, muffled heart sounds, and pulsus paradoxus and is easily confirmed by a bedside echocardiogram. A new murmur coupled with signs of heart failure should raise clinical suspicion for injury to the valves or subvalvular apparatus.

1. **Pericardium.** Increased shear forces during blunt trauma may lead to lacerations or tears in the pericardium. Clinically, the patient may experience pleuritic chest pain, and an ECG may reveal the typical findings of pericarditis. Management is with analgesics, although late cases of constriction occasionally develop after traumatic injury to the pericardium.
2. **Myocardium**
   a. **Myocardial rupture.** The myocardium can be injured by several mechanisms in sudden deceleration injuries. Compression between the sternum and the spinal column, as well as sudden overdistention with blood after abdominal injuries, may lead to myocardial rupture. The thin walls and large diameter of the right atrium predispose it to rupture, and **more than 50% of cases of cardiac rupture involve the right atrium**. The left atrium may be involved in as many as 25% of cases, with the remainder involving the thicker walled right and left ventricles. Most victims die immediately, but some series suggest that survival may approach 50% if patients arrive with intact vital signs. Management requires prompt thoracotomy and definitive surgical repair. Emergency pericardiocentesis is relatively contraindicated, as it can lead to reaccumulation and arrest, and is generally only considered as a desperate measure in an arresting patient when trained personnel are unavailable to perform a thoracotomy.
   b. **Myocardial contusion.** Blunt chest wall trauma may lead to focal injury and necrosis of cardiac myocytes, known as myocardial contusion. Definitive diagnosis is based on histology, and, therefore, the true incidence and clinical significance of myocardial contusion remain controversial. Patients may complain of precordial pain, but symptoms are usually difficult to interpret in the setting of chest wall trauma and associated injuries. A number of studies have investigated the use of ECG, cardiac enzymes, and TTE in diagnosing myocardial contusion, but none of these tests has been found to be sensitive or specific for the diagnosis. The ECG may be normal or may show nonspecific ST-T wave changes or findings consistent with pericarditis. Elevations in serum troponin levels and creatine kinase–myocardial band (CK-MB) isoenzymes are observed in some patients, but CK-MB may be masked by skeletal muscle CK-MM release, especially when total CK > 20,000 U/L.

TTE may reveal a small effusion or focal wall motion abnormalities. Patients with contusion are thought to be at increased risk for arrhythmic death during the recovery period, as the injured, inflamed myocardium behaves much like scar tissue as a substrate for slowed conduction and unidirectional block in the development of reentry cycles. However, findings on ECG, TTE, or laboratory tests are insensitive in predicting outcomes. From a practical standpoint, the diagnosis of cardiac contusion does not generally alter management, as treatment is mostly supportive care, observation, and analgesia. However, making the diagnosis should alert physicians to the potential for arrhythmias. Most centers perform a baseline ECG and monitor patients with blunt chest wall trauma for at least 12 hours before discharge.

3. **Valvular insufficiency.** Injury to cardiac valves, papillary muscles, or chordae tendineae during blunt cardiac trauma may lead to acute valvular regurgitation. A review of 546 autopsies after blunt trauma suggested that valvular injury may occur in as many as 9% of cases, with a slight increase in frequency in patients with preexisting valvular heart disease. The **aortic valve is most commonly involved**, followed in decreasing frequency by the mitral and tricuspid valves. A new murmur, hypotension, and fulminant pulmonary edema should suggest the diagnosis. The differential diagnosis of a new holosystolic murmur (occasionally with a new right bundle branch block or right-axis deviation on the ECG) should also include a traumatic ventricular septal defect. An emergency transthoracic echocardiogram and rapid transport to the operating room are generally required. Acute tricuspid regurgitation is generally well tolerated with lower extremity edema and fatigue as the presenting symptoms, although it occurs relatively rarely.
4. **Coronary arteries.** Blunt trauma occasionally leads to **thrombosis** or **dissection** of a coronary artery and subsequent myocardial infarction. In general, the prognosis after a traumatic myocardial infarction is better than that of the usual acute coronary syndrome because patients tend to be younger and have less atherosclerotic burden and less comorbidity. Nevertheless, patients with infarctions related to trauma are at risk for all the mechanical complications associated with atherosclerotic disease, such as left ventricular aneurysm or pseudoaneurysm formation, ischemic mitral regurgitation, and ventricular septal defect. In rare cases, blunt trauma contributes to the formation of an arteriovenous fistula between the coronary artery and another structure, such as the coronary sinus, great cardiac vein, right atrium, or right ventricle. Clinically, the patient may have a loud, widely radiating murmur, and ligation of the coronary artery or bypass surgery may be necessary.
5. **Commotio cordis.** Case reports of sudden cardiac death in children and adolescents after relatively low-impact chest wall trauma (most commonly, a baseball or hockey puck striking the chest) have received significant media attention in the past. The mechanism is unclear, but it appears that a blow to the chest during an electrically vulnerable period of cardiac repolarization may induce ventricular tachycardia or ventricular fibrillation. Victims have been surprisingly refractory to cardiac defibrillation, and few of them survive. Autopsy reports consistently show no evidence of underlying structural heart disease.
6. **Great vessels.** The aorta may also be injured in motor vehicle accidents and falls when sudden deceleration leads to tears or disruption of the vessel. Not surprisingly, most patients with aortic rupture die immediately, but 10% to 20% may reach emergency centers alive if the bleeding is limited by clot or by the pleura. Aortic rupture typically occurs at the proximal portion of the descending aorta, where the aorta is tethered against the spine by intercostal arteries and the ligamentum arteriosum. Patients frequently present with chest or back pain and hypotension, but a high index of suspicion is often needed to make the diagnosis. Increased pulse pressure in the upper extremities and diminished pulse pressure in the lower

extremities may be found on examination. The chest radiograph may reveal a widened mediastinum, large left pleural effusion, loss of the aortic knob contour, or deviation of the esophagus to the right. A normal chest radiograph, seen in as many as 25% of patients, does not rule out acute aortic pathology.

CT scan with intravenous contrast is generally the first-line imaging modality for the diagnosis of ascending aortic dissection and other suspected traumatic injury to the aorta. TEE is also useful and has the advantage that it can be performed rapidly at the bedside in a critically ill patient who is not suitable for transport. TEE requires sedation and may not be feasible in patients with maxillofacial or cervical spine injures. Although TTE cannot be used to exclude the diagnosis of aortic dissection, a limited and focused study can be performed more rapidly at the bedside than any other test, and visualization of a flap in the aortic root or ascending aorta can clinch the diagnosis. Magnetic resonance angiography is an alternative modality, but is not well suited for unstable patients due to the time required to perform the study. Aortography, once the gold standard, is now rarely performed out of concern for procedural complications in the setting of acute aortic injury. Definitive surgical repair is indicated for ascending aortic dissection or traumatic aortic rupture.

III. PENETRATING TRAUMA

A. Gunshot wounds and stabbings are the most common types of penetrating trauma. The prognosis depends entirely on the extent of injury and the number of chambers involved. Overall mortality is estimated at 60% to 93% for gunshot wounds, 22% to 62% for knife injuries, and 25% for bolting instruments (i.e., nail guns). Less frequently, iatrogenic catheter-induced injury can occur in the setting of temporary or permanent pacemaker placement.

B. As with blunt cardiac trauma, the clinical presentation tends to be one of **tamponade** or exsanguinating **hemorrhage**, depending on the integrity of the pericardium. **However, unlike in the case of blunt trauma, tamponade carries a favorable prognosis in penetrating trauma**. One series described a survival rate of 73% among patients with penetrating trauma with tamponade versus 11% among those without. Thrombus within the pericardium is thought to stabilize the rapid hemorrhagic shock associated with penetrating injuries. Pericardial lacerations may also seal spontaneously. Bleeding from the muscular, thicker walled left ventricle is also more likely to be self-limited, whereas injury to the relatively thin right ventricle or right atrium is more likely to be catastrophic and fatal. Knife wounds tend to be smaller and focal, whereas gunshot wounds tend to be larger, extensive, and more likely to present with frank hemorrhage.

C. **The right ventricle is the chamber most often involved in penetrating trauma** because of its anterior location in the chest. As described for blunt trauma, penetrating trauma may result in laceration of the pericardium or myocardium, valves, coronary arteries, or the aorta.

D. **Diagnosis.** In an unstable patient, a TTE should be obtained rapidly at the bedside. Although images may be suboptimal, both the sensitivity and the specificity of TTE for identifying cardiac abnormalities in this setting are 85% to 90%. A portable chest radiograph may reveal the presence of a pneumothorax or hemothorax.

E. **Management.** After the diagnosis of penetrating cardiac trauma has been made, the patient should be transported as rapidly as possible to the operating room for definitive surgical repair. The infusion of saline and blood products should be continued as needed. Warming of fluids is often needed to prevent hypotherma associated with massive volume resuscitation. There is no role for serial pericardiocentesis in patients with trauma and pericardial effusion, but emergency pericardiocentesis is occasionally necessary if there are delays in reaching the operating room.

IV. SPECIAL CONSIDERATIONS

A. Indwelling foreign bodies and missile embolization. Missile embolization from bullet fragments, air gun pellets, or shrapnel is an extremely rare complication from gunshot wounds or battlefield injuries. Data from the Vietnam conflict suggest that this phenomenon complicates 0.3% to 0.4% of all vascular missile injuries. Clinical suspicion for embolization should be raised in a scenario of multiple penetrating entrance wounds or a single penetrating entrance wound without a corresponding exit wound. The majority of patients with right heart or pulmonary embolization are asymptomatic, but up to 17.4% of patients develop chest pain, dyspnea, or hemoptysis. Up to 4% of patients may exhibit cardiac arrhythmias. Patients with undiagnosed indwelling foreign bodies may also develop subacute bacterial endocarditis as a latent presentation. Metallic missile fragments are usually radiopaque and detected on plain x-rays or a noncontrast CT scan. Intracardiac indwelling foreign bodies should be evaluated by TEE, especially when endocarditis is suspected. Ultimately, the decision to remove asymptomatic indwelling foreign bodies is made on a case-by-case clinical basis considering operative logistics and weighing risk against the potential benefit.

B. Device implants. An awareness of device-related complications in the setting of cardiac trauma is important, given the expanding patient population with pacemakers and/or implantable defibrillators. Common complications in the setting of blunt trauma would include pocket hematoma, lead dislodgement, or fracture. Penetrating trauma could expose the generator and/or tunneled leads and lead to bleeding or secondary infection. Lead perforation is an uncommon but life-threatening complication manifested as tamponade. Hypotension and bradycardia should prompt concern for lead fracture or dislodgement, especially if the patient is known to be pacemaker dependent. Emergent transcutaneous or transvenous pacing is indicated if the underlying bradyarrhythmia is not hemodynamically tolerated. Device interrogation can also be performed at the bedside to assess pacer dependence and the functional status of all leads using computer equipment provided by the major manufacturers.

ACKNOWLEDGMENTS: *The author acknowledges Drs. Daniel Cantillon and John Hostetter for their contributions to earlier editions of this chapter.*

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CHAPTER 38

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Brian P. Griffin
Russell E. Raymond

Pregnancy and Cardiovascular Disease

I. INTRODUCTION. Maternal cardiac disease is a major risk factor for nonobstetric mortality and morbidity in pregnant women. Substantial progress in the management of congenital heart disease has occurred over recent decades, so the majority of females born with heart defects now survive into their reproductive years. Advances in obstetrics have also enabled pregnancy in older mothers in whom hypertension and acquired heart disease are more prevalent and can pose challenges for the pregnancy. Rheumatic heart disease is less common than in the past, but is still encountered, especially in immigrant populations in the United States, and may manifest clinically for the first time in pregnancy. Cardiac disease has significant bearing on both maternal and fetal outcomes, and it is therefore essential that cardiologists and internists have a working knowledge of the impact of pregnancy on various cardiac diseases on pregnancy and can tailor management appropriately. In most cases, the presence of maternal heart disease does not preclude successful pregnancy, although thorough discussion and planning regarding risks and management strategies should begin prior to conception wherever possible.

II. NORMAL PHYSIOLOGIC CHANGES DURING PREGNANCY. A series of cardiocirculatory changes occur in pregnancy and peripartum. These changes **usually begin during the early first trimester** (5 to 8 weeks), peak in the late second trimester, and tend to plateau thereafter until the postpartum period. This second trimester peak in hemodynamic adaptations tends to correlate with the onset of clinical manifestations of cardiac complications during pregnancy.

A. The ***increase*** **in blood volume** during pregnancy is attributed to estrogen-mediated stimulation of the renin–aldosterone system, leading to salt and water retention along with various other maternal and placental hormones. **The plasma volume expansion varies from 20% to 100% and averages around 50%.** The relatively greater increase in plasma volume as compared with red blood cell mass leads to the physiologic anemia of pregnancy, which usually manifests around 30 weeks.

B. Cardiac output, stroke volume, and heart rate. Table 38.1 summarizes the changes in heart rate, stroke volume, and cardiac output. **The cardiac output is estimated to increase by approximately 30% to 50% above baseline.** The increase is attributed to higher preload as a result of increased blood volume, decreased systemic vascular resistance, and an increase in maternal heart rate by 10 to 15 beats/min. During the third trimester, stroke volume and cardiac output are dependent on body position and increase in the lateral position (particularly left lateral) and decline in the supine position due to compression of the inferior vena cava by the gravid uterus.

C. Blood pressure and systemic vascular resistance. The decline in systemic vascular resistance causes blood pressure to begin to fall in the first trimester and reach a nadir of about 10 mm Hg below baseline by the end of the second trimester. The pulse pressure widens due to the greater fall in diastolic blood pressure than in systolic pressure. As many as 11% of women develop the **uterocaval syndrome** of pregnancy, with a significant and symptomatic drop in blood pressure when lying supine

TABLE 38.1 Normal Hemodynamic Changes during Pregnancy and Postpartum Period

	Changes during different phases of pregnancy				
Hemodynamic parameter	**First trimester**	**Second trimester**	**Third trimester**	**Labor and delivery**	**Postpartum**
Heart rate	↑5–10%	↑10–15%	↑15–20%	↑20–30%	↓
Stroke volume	↑5–30%	↑30–40%	↓20–30%	↑300–500 mL with each contraction	↓
Cardiac output	↑5–30%	↑30–40%	↑> 40%	↑50%	Initial ↑ then ↓
Systolic BP	↔to ↓	↓	↔to ↑	↑	Baseline
Diastolic BP	↔to ↓	↓	↓to ↔	↑	Baseline
Systemic vascular resistance	↓10–30%	↓ 30–40%	↓ 30–40%	↑	Baseline

BP, blood pressure.

due to vena caval compression. **Weakening of the vascular walls** of the medium and large muscular arteries occurs because of decreased collagen deposition due to estrogen release and the effects of circulating elastase and relaxin. This makes pregnant women more susceptible to aortic dissection, especially in individuals with abnormally weak aortic tissue such as in Marfan syndrome. The addition of low-resistance vessels in the uteroplacental bed also contributes to the decrease in afterload.

D. A hypercoagulable state with decreased protein S, increased stasis, and venous hypertension is also observed.

E. Hemodynamic changes during labor and delivery. Each uterine contraction displaces about 300 to 500 mL of blood into the maternal general circulation (autotransfusion). There is an increase in stroke volume and heart rate, with cardiac output increasing by approximately 75% above baseline during contractions. Blood pressure and oxygen consumption also rise. The magnitude of these changes will be influenced by the mode of delivery—vaginal versus cesarean section—and also by the method of anesthesia and analgesia.

F. Hemodynamic changes postpartum. Despite the blood loss during delivery (averaging 300 to 400 mL for vaginal delivery and 500 to 800 mL for cesarean section), there is a **temporary increase in effective venous return due to the relief of caval compression and autotransfusion**. This may lead to an increase in stroke volume and cardiac output, resulting in augmentation in renal blood flow and a brisk diuresis. In women with preexisting cardiac disease, these rapid hemodynamic shifts may cause profound clinical deterioration. The hemodynamic changes associated with pregnancy usually persist for a few weeks postpartum and it may take up to 12 to 24 weeks for the parameters to return to their prepregnancy baseline.

III. CARDIOVASCULAR EVALUATION IN PREGNANCY

A. History. Fatigue, dyspnea, ankle swelling, and reduced exertional capacity are common in normal pregnancy and can mimic cardiac disease. Chest pain, orthopnea, or paroxysmal nocturnal dyspnea may represent cardiac pathology.

B. Physical examination. Table 38.2 highlights the important cardiac findings in normal pregnancy. Signs of jugular venous distention, displaced point of maximal

impulse, and peripheral edema are common in normal pregnancy. Normal auscultatory findings in pregnancy include exaggerated physiologic splitting of S_2, a physiologic S_3, a physiologic systolic murmur in the pulmonic area, and the continuous murmurs of "mammary soufflé" or a cervical venous hum. Examination findings that are not physiologic include an S_4, a loud systolic murmur, a purely diastolic murmur, and fixed splitting of S_2 or pulmonary crackles.

C. Noninvasive testing with echocardiography is considered safe in pregnancy and findings are as given in Table 38.2. Chest radiography should be performed only when absolutely necessary and with shielding of the pelvic area with protective lead. Magnetic resonance imaging is sometimes used for the diagnosis of cardiac disorders; its safety profile in pregnancy is unknown, and it should be avoided if possible.

TABLE 38.2 Findings in Normal Pregnancy

Symptoms
Fatigue
Dyspnea
Palpitations
Reduced exercise tolerance
Orthopnea
Lower extremity edema
Physical examination
Hyperventilation
Lower extremity edema
Distended neck veins with prominent *a* and *v* waves and brisk *x* and *y* descents
Increased heart rate and wide pulse pressure
Upward and leftward deviation of point of maximal impulse
"Flow" murmurs (pulmonic and aortic)
Mammary soufflé (left sternal border, continuous murmur)
Increased first heart sound and exaggerated splitting of second heart sound
Third heart sound
Electrocardiographic findings
Sinus tachycardia
Leftward axis deviation
Increased R/S ratio in leads V_1 and V_2
Repolarization changes
Echocardiographic findings
Increased left ventricular diastolic dimension
Increased left ventricular wall thickness
Mild increase in contractility
Moderate increase in size of right atrium, right ventricle, and left atrium
Functional pulmonary, tricuspid, and mitral regurgitation
Small pericardial effusion

D. Invasive testing with pulmonary artery catheterization (without fluoroscopy) can be utilized during pregnancy, labor, delivery, and the postpartum period for invasive monitoring and can be very useful for patients who suffer hemodynamic deterioration. Cardiac catheterization during pregnancy is rarely needed, except in the setting of acute myocardial infarction (MI) or to permit balloon valvuloplasty. Fluoroscopy and cine time should be minimized and direct irradiation to the fetus avoided. Vascular access from the arm rather than the leg is preferred whenever feasible.

IV. RISK ASSESSMENT AND GENERAL PRINCIPLES OF MANAGEMENT. One of the most important steps in managing a patient with heart disease who is considering pregnancy is to establish the level of maternal and fetal risk. This involves a multidisciplinary approach, with preconception counseling, contraception advice, and discussion of potential maternal and fetal acute and long-term morbidity and mortality. Baseline functional class, severity of cardiac disease, left ventricular function, and pulmonary pressures should guide the risk assessment. Table 38.3 delineates a stepwise approach for management of women with preexisting cardiac disease, and Table 38.4 lists high-risk predictors. **Maternal New York Heart Association (NYHA) class II symptoms or higher, left ventricular ejection fraction < 40% or left-sided obstruction** are factors known to be predictive of neonatal complications, including premature birth,

TABLE 38.3 Basic Management Principles for Pregnant Women with Valvular Heart Disease

Risk assessment

Preconception

- Thorough history of cardiac symptoms and arrhythmias
- Baseline exercise tolerance and functional class
- Baseline electrocardiogram and echocardiography with ventricular function and pulmonary pressures
- Detailed discussion with the patient about the potential risks to self and fetus

During pregnancy

- Follow-up evaluation at least once per trimester
- Close monitoring of new symptoms or change in functional class
- Serial echocardiography for development of any new symptoms or signs

Treatment

Preconception

- Effective and safe contraception until pregnancy is desired
- Consider valve repair or replacement, correction of anomaly prior to conception if pregnancy poses significant risk of worsening clinical status
- Adjust medications to prevent adverse fetal side effects

During pregnancy

- Minimize medication use to only those absolutely required and discontinue or replace medications contraindicated in pregnancy
- If symptoms worsen and if indicated, consider correction of anomaly or valve repair or replacement

(Continued)

TABLE 38.3 Basic Management Principles for Pregnant Women with Valvular Heart Disease (*Continued*)

Labor and delivery
Invasive monitoring as needed
Cesarean section for obstetric indication
Monitor for decompensated heart failure and pulmonary edema and treat accordingly
Postpartum
Adjust and optimize medications
Consider correction of anomaly or valve repair or replacement if indicated
Treat postpartum anemia
Counseling and contraception for future pregnancies

Adapted from Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart.* 2007;93:552–558.

TABLE 38.4 Risk Predictors of Adverse Maternal and Fetal Outcomes

Prior cardiac events or medication
Prior arrhythmia
NYHA class II or higher, or cyanosis
Ejection fraction < 40%
Pulmonary hypertension (pulmonary artery systolic pressure > 50% systemic pressure)
Severe aortic stenosis (valve area < 1.5 cm^2, Doppler jet velocity > 4 m/s
Symptomatic or severe mitral stenosis
Severe aortic or mitral regurgitation with NYHA class III or IV symptoms
Hypertrophic obstructive cardiomyopathy
Maternal anticoagulation

intrauterine growth restriction, respiratory distress syndrome, and death. Formal risk prediction scores include Cardiac Disease in Pregnancy (CARPREG), which is composed of four clinical features (prior arrhythmia or cardiac event, NYHA functional class > II or cyanosis, left heart obstruction, systemic left ventricular dysfunction with LVEF < 40%) with maternal cardiac event rates of 5%, 27%, and 75% for 0, 1, and > 1 of the features, respectively, and the more recent ZAHARA predictors derived from a large population of congenital heart disease patients.

Management of the pregnant patient with heart disease is a team effort involving the patient's primary care physician, high-risk obstetric team, and cardiologist, with active participation of the patients. **Prophylactic intervention for cardiac lesions that significantly increase the risk of pregnancy should be performed where appropriate and feasible *before* pregnancy is contemplated**. Most patients with relatively low-risk cardiac conditions are successfully managed throughout pregnancy, labor, and delivery with conservative medical measures designed to optimize intravascular volume and systemic

loading conditions. Simple measures help, such as bed rest and avoidance of the supine position. Medications should be used judiciously and only when absolutely required during pregnancy. Drugs that are contraindicated in pregnancy should be discontinued before conception if pregnancy is contemplated. **In certain conditions such as cyanotic congenital heart disease, Eisenmenger syndrome, or severe pulmonary hypertension, pregnancy should be strongly discouraged, as patients with these conditions do not tolerate the hemodynamic changes of pregnancy**.

Specific lesions and their management in pregnancy are described later. The list, although extensive, is not complete, as a detailed description of every lesion is beyond the scope of this chapter.

V. PREGNANCY IN WOMEN WITH CONGENITAL HEART DISEASE. In general, patients with noncyanotic congenital heart disease have a better outcome with pregnancy compared with patients with cyanotic disease. Where applicable, patients should be made aware of the potential inheritability of the congenital disease. The 2007 American Heart Association (AHA) endocarditis guidelines do not recommend the use of prophylactic antibiotics for vaginal delivery, even in high-risk patients, such as those with complex congenital heart disease or surgically constructed systemic–pulmonary shunts. However, owing to the difficulty in predicting complicated deliveries and the potential complications of endocarditis, some authors still suggest antibiotic prophylaxis as reasonable for all patients with congenital heart disease, except in isolated secundum atrial septal defects (ASDs) and corrected patent ductus arteriosus (PDA). The 2008 American College of Cardiology/AHA (ACC/AHA) guidelines on the management of adults with congenital heart disease do suggest antibiotics at the time of membrane rupture prior to vaginal delivery for patients with prosthetic cardiac material or unrepaired/palliated cyanotic defects.

A. ASD and patent foramen ovale (PFO). Isolated ASD or PFO is usually well tolerated in pregnancy and considered low risk in general. Paradoxical pulmonary embolism during pregnancy has been reported. Ideally, an ASD with a significant shunt (> 1.5:1) should be corrected prior to pregnancy. Secundum ASD that is repaired prior to pregnancy is not associated with an increased risk of complications.

B. Ventricular septal defect (VSD). Isolated VSD without pulmonary hypertension is usually well tolerated during pregnancy, and correction of VSD prior to pregnancy and before development of pulmonary hypertension eliminates the risk. In pregnant patients with VSD and pulmonary hypertension, a drop in blood pressure during or after delivery can result in transient shunt reversal. This may be prevented by close monitoring of blood pressure, volume replacement, and the use of vasopressors, if necessary. VSD is commonly inheritable.

C. Patent ductus arteriosus. PDA without pulmonary hypertension usually has a favorable outcome. In patients with pulmonary hypertension, the management principles are similar to those with VSD.

D. Coarctation of aorta (COA). Coarctation, although usually associated with favorable outcomes, has been associated with severe hypertension, congestive heart failure, or aortic dissection during pregnancy. There is an association with congenitally bicuspid aortic valves (AVs). It is also associated with circle of Willis aneurysms, and cerebral hemorrhage from rupture of an aneurysm during pregnancy is possible. Limiting physical activity and controlling blood pressure may prevent complications such as cerebral hemorrhage and dissection. β-Blockers are usually the antihypertensive drugs of choice, although care should be taken not to lower the blood pressure excessively as this may compromise uteroplacental circulation. Significant COA with evidence of systemic hypertension, heart failure, or a peak gradient > 20 mm Hg should be corrected prior to pregnancy. Women who underwent prior surgical repair of a coarctation remain at risk for dissection, as the aortic wall is still abnormally weak. Correction of COA during pregnancy is indicated in patients with severe uncontrollable hypertension or heart failure and may be performed percutaneously.

E. Congenital aortic stenosis (AS). A congenitally bicuspid AV is one of the most common causes of AS. These patients should be screened for other cardiac malformations including COA. The details of management are described later in Section **VI**.

F. Pulmonic stenosis. Isolated pulmonic stenosis is usually well tolerated in pregnancy. It should be corrected prior to pregnancy if severe (peak gradient > 60 mm Hg). Percutaneous balloon valvotomy during pregnancy may be required in patients with severe right ventricular failure.

G. Ebstein anomaly. Noncyanotic Ebstein anomaly is usually well tolerated. Cyanotic patients are at very high risk for maternal heart failure and fetal prematurity or death. During labor and delivery, care should be taken to prevent a drop in blood pressure, and close hemodynamic monitoring is required along with rest, oxygen, and blood gas monitoring. It is sometimes associated with Wolff-Parkinson-White syndrome and pregnancy may precipitate supraventricular arrhythmias.

H. Tetralogy of Fallot (TOF). Women with TOF who have undergone successful repair during childhood with little or no residual outflow tract gradient, no pulmonary hypertension, and preserved ventricular function usually tolerate pregnancy well. In women with uncorrected or only partially corrected TOF, increased blood volume during pregnancy with increased venous return and decreased systemic vascular resistance may result in right to left shunt and cyanosis. A similar process may also occur with a fall in blood pressure during labor and delivery. **The outcome of pregnancy is very poor for both mother and fetus once cyanosis occurs**. It is also associated with high rates of premature labor, spontaneous abortion, and fetal growth restriction. The risk of a cardiac defect in the neonate ranges from 3% to 17%; genetic counseling and screening for the 22q11 deletion should be offered to women with TOF. Patients with residual lesions after partial correction such as pulmonic regurgitation, right ventricular outflow obstruction, and right ventricular dysfunction are at risk for heart failure and arrhythmia during pregnancy. Poor prognostic signs include maternal hematocrit above 60%, arterial oxygen saturation below 80%, right ventricular hypertension, and syncopal episodes. Patients with cyanotic disease should be strongly encouraged against pregnancy.

I. Eisenmenger syndrome. Pregnancy in women with Eisenmenger syndrome is associated with a very high maternal mortality in the range of 30% to 50%, with a 50% risk of fetal loss if the mother survives. Maternal death occurs mostly between the first few days to first few weeks following delivery due to rapid hemodynamic deterioration. Therefore, patients with Eisenmenger syndrome should be strongly discouraged against pregnancy. Early therapeutic abortion may be considered given the danger to the mother. If pregnancy is continued, close monitoring is necessary. Restricted physical activity, continuous oxygen use for at least the third trimester, and consideration of pulmonary vasodilating drugs are recommended. Due to increased incidence of thromboembolism, anticoagulant therapy is recommended, starting from the third trimester until 4 weeks postpartum. An attempt to shorten the second stage of labor by the use of forceps or vacuum should be made; cesarean delivery is associated with significantly higher mortality.

VI. VALVULAR HEART DISEASE AND PREGNANCY. Lesions generally associated with high maternal and/or fetal risks include symptomatic mitral stenosis (MS), severe AS (with or without symptoms), NYHA class III and IV symptoms with mitral or aortic regurgitation, valvular disease with severe pulmonary hypertension or left ventricular dysfunction, mechanical prosthetic valve requiring anticoagulation, Marfan syndrome, and hypertrophic cardiomyopathy (HCM). Lesions generally associated with low maternal or fetal risk include asymptomatic AS with normal ventricular function, mitral valve prolapse, mild MS, and NYHA functional class I or II mitral or aortic regurgitation.

A. Mitral stenosis. MS is one of the most common rheumatic valvular lesions seen in pregnancy and is poorly tolerated. The physiologic changes in pregnancy with increased blood volume and heart rate can lead to an increased pressure gradient across the valve and decreased filling time, respectively. This leads to increases in left atrial pressure and ensuing symptoms of pulmonary edema with dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Occurrence of atrial fibrillation with a rapid ventricular rate often causes further clinical deterioration. Patients with moderate to severe MS are more susceptible to these hemodynamic disturbances. The rapid increase in venous return during labor and delivery may cause significant decompensation and requires very close monitoring.

Management depends upon the severity of stenosis, symptoms, and time of diagnosis. **If MS is diagnosed prior to pregnancy, patients with severe MS (valve area < 1 cm^2) or moderate symptomatic stenosis should be offered percutaneous mitral balloon valvuloplasty (PMBV) or valve repair if PMBV is not feasible, before pregnancy**. In patients with moderate asymptomatic stenosis, careful assessment of symptoms and exercise tolerance testing can help guide the decision for prepregnancy intervention. In patients with mild MS (valve area > 1.5 cm^2), pregnancy is usually tolerated with a favorable outcome. **Optimal management of an already pregnant patient with MS is aimed at reducing heart rate and left atrial pressure**. β-Blockers are the drug of choice, and selective β1-adrenergic drugs are preferred over nonselective β-blockers to avoid β2-adrenergic–mediated uterine relaxation. In patients with atrial fibrillation (Table 38.5), digoxin may also be used for ventricular rate control. Electrical cardioversion can be performed safely during pregnancy if the hemodynamic status warrants restoration of sinus rhythm. Left atrial pressure may be controlled by salt restriction and very judicious use of diuretics (excessive use can lead to reduced uteroplacental perfusion). In patients with symptoms and signs of clinical deterioration despite optimal medical therapy, PMBV may be necessary during pregnancy. This should be avoided in the first trimester if possible and proper abdominal and pelvic shielding must be used. Echocardiographic guidance by an experienced operator can limit radiation exposure. In cases with severe MS refractory to medical therapy and not amenable to PMBV, mitral valve repair or replacement may be considered. Cardiopulmonary bypass during pregnancy carries a risk of fetal demise and should be performed with normothermic perfusion and high flow volumes with the mother in the lateral decubitus position to maximize placental perfusion.

Most patients with MS can safely undergo vaginal delivery. Patients with symptomatic moderate and severe MS should have hemodynamic monitoring and optimization guided by pulmonary artery catheterization during labor and delivery

TABLE 38.5 ACC/AHA Guidelines for Management of Atrial Fibrillation in Pregnancy

Class I (benefits >>> risk) procedure/treatment should be performed/administered
Digoxin, a β-blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF
Direct current cardioversion is recommended in pregnant patients who become hemodynamically unstable due to AF
Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except for those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy

AF, atrial fibrillation.

and in the immediate postpartum period (12 to 24 hours) when relief of uterocaval obstruction can cause increased venous return and pulmonary edema. Epidural anesthesia is usually better tolerated than general anesthesia, and cesarean section is generally performed for obstetric indications only. Young pregnant women with a previous history of rheumatic carditis should continue to undergo penicillin prophylaxis postpartum as they did in the nonpregnant state.

B. Mitral regurgitation (MR). The most common cause of MR during pregnancy is either rheumatic heart disease or mitral valve prolapse. MR is usually well tolerated in pregnancy because the fall in systemic vascular resistance leads to a decreased left ventricular afterload. Atrial fibrillation and hypertension may sometimes cause acute symptomatic decompensation.

Asymptomatic patients are managed conservatively without any therapy, and patients with left ventricular dysfunction and decompensated heart failure are managed with diuretics and digoxin. In the peripartum period, increased venous return and systemic vascular resistance sometimes lead to decompensation requiring diuretics and afterload reduction. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are contraindicated during pregnancy because of their teratogenic effect. Hydralazine may be used in patients with MR and hypertension for afterload reduction. Acute MR due to ruptured chordae is rare in pregnancy and is usually not well tolerated. It may require intraaortic balloon pump placement and emergent surgery.

C. Aortic stenosis. The most common etiology for AS in childbearing age is a congenitally bicuspid valve. Rheumatic AS is less common, but may occur in conjunction with MS. Mild-to-moderate AS with preserved left ventricular function is usually well tolerated during pregnancy. **Severe AS (i.e., AV area < 1.0 cm^2 and mean gradient > 50 mm Hg) significantly increases the risk during pregnancy and may lead to significant hemodynamic deterioration, heart failure, and premature delivery**. Patients with severe AS should therefore be counseled against pregnancy or undergo surgery prior to conception. Symptoms such as chest pain, syncope, or dyspnea usually present late in the second trimester or early in the third trimester. Patients with bicuspid AV and aortic root dilation, especially those with coarctation of the aorta, are at increased risk for spontaneous aortic dissection.

When severe symptomatic AS is diagnosed during pregnancy, PABV should be performed before labor and delivery. Although PABV may reduce the risk of decompensation in patients with severe AS, it has limited durability and only suffices as a temporizing measure until the patient can safely undergo AV replacement. Aortic insufficiency that occurs as a postprocedural complication of PABV is usually well tolerated during labor and delivery.

Close invasive hemodynamic monitoring, as in patients with MS, may be required. Spinal anesthesia and epidural anesthesia are discouraged during labor and delivery because of their vasodilatory effects.

D. Aortic regurgitation/aortic insufficiency (AI). AI is generally well tolerated in pregnancy due to the combination of reduced systemic vascular resistance and shortened diastole with the rise in heart rate. In a young woman, AI may be due to a congenitally bicuspid valve, an infective endocarditis, an autoimmune disorder (e.g., rheumatoid arthritis), or a dilated aortic annulus. Marfan syndrome should always be excluded due to its implications regarding aortic root stability. AI without left ventricular dysfunction is usually well tolerated in pregnancy owing to decreased systemic vascular resistance and increased heart rate causing a shorter diastole and therefore reducing regurgitation. In symptomatic patients with decompensated heart failure, diuretics, digoxin, and hydralazine may be used for afterload reduction.

E. Hypertrophic cardiomyopathy. Most asymptomatic patients with HCM have a favorable outcome during pregnancy. The overall morbidity and mortality with HCM and pregnancy is, however, still higher than that in the general population. Symptoms such as chest pain, palpitations, worsening dyspnea, and syncope may

occur and are more common in women who were symptomatic prior to pregnancy. Various arrhythmias, including supraventricular tachycardias, atrial fibrillation with hemodynamic deterioration and fetal distress, and ventricular fibrillation, have also been reported. There is an increased risk of fetal prematurity. Women should receive genetic counseling before conception whenever possible; the risk of inheriting the disease may approach 50% in certain familial forms of HCM.

Management depends on the presence of symptoms and the severity of left ventricular outflow obstruction. Blood loss, volume depletion, and vasodilators should be avoided, and medications should be reserved for symptoms of heart failure and arrhythmias. β-Blockers are usually the drug of choice for symptomatic patients. Patients with a history of syncope, life-threatening arrhythmias, or a family history of sudden cardiac death should be considered for prophylactic implantable defibrillators prior to pregnancy due to the potential arrhythmogenic effect of pregnancy.

Vaginal delivery is considered safe, but tocolytics with β-adrenergic properties and prostaglandins should be avoided. Epidural anesthesia is used with caution because of the peripheral vasodilatory effect, and excessive blood loss should be promptly repleted with fluids or blood transfusion. The brisk diuresis immediately postpartum may lead to a rapid decrease in intravascular volume and, therefore, a symptomatic increase in outflow tract gradient. This can be avoided by gentle intravenous (IV) hydration decreasing over 24 to 48 hours postpartum to achieve a euvolemic state.

F. Prosthetic heart valves. The selection of an appropriate prosthetic valve in a woman of childbearing age is controversial. **Where possible, the patient's own valve should be conserved or repaired. When valve replacement is necessary, bioprosthetic and homograft valves are safer for mother and child, although their use is associated with an increased risk of degeneration in younger people, which may also be accelerated by pregnancy**. Mechanical valves, and their anticoagulation requirement, confer increased maternal mortality, morbidity, and fetal loss. A detailed preconception discussion with the patient should include potential complications during pregnancy, the potential for harm to the fetus and/or mother with various anticoagulation strategies, and recognition of the signs and symptoms of valve dysfunction or heart failure. The risk of complication during pregnancy depends on the type of valve, position of the valve, and prepregnancy cardiac function and functional capacity. Patients with NYHA class III or IV symptoms should be strongly advised against pregnancy. In pregnant patients with well-functioning bioprosthetic valves, the management is similar to that in patients with native valves. Patients should be made aware of the possibility of valve degeneration and should be monitored for signs and symptoms of this.

Pregnancy should be discouraged in patients with mechanical heart valves. In pregnant patients with mechanical heart valves, management of anticoagulation is challenging. Pregnancy is a thrombogenic state, and thrombosis has been reported in up to 10% to 15% of patients with mechanical prosthetic valves during pregnancy. The incidence is particularly high in patients with older generation valves (Björk-Shirley and Starr-Edwards) in the mitral position, but complications and deaths have also been reported in newer generation valves in the aortic position. Patients with prosthetic valves and poor left ventricular function are also at risk for heart failure from volume overload during pregnancy and arrhythmias.

The management of anticoagulation during pregnancy is discussed in detail in a separate section of this chapter.

VII. OTHER CARDIOVASCULAR DISEASES AND PREGNANCY

A. Hypertensive disorders in pregnancy. Hypertensive disorders complicate 8% to 10% of pregnancies and are a major cause of maternal and perinatal morbidity and mortality. Hypertensive disorders can be broadly classified into chronic hypertension, gestational hypertension, and the preeclampsia–eclampsia spectrum.

Chronic hypertension is defined as blood pressure of 140/90 mm Hg or greater before pregnancy, before 20 weeks of gestation, or persisting beyond postpartum day 42. It is associated with increased maternal and fetal morbidity and elevates the risk of preeclampsia development. Blood pressure treatment is aimed at minimizing maternal end-organ damage (such as left ventricular hypertrophy, renal failure, or intracerebral hemorrhage), balanced against concerns that excessive pressure lowering may negatively impact fetal growth. The threshold for initiating drug therapy is controversial and differing recommendations are offered by the various international society guidelines.

Gestational hypertension is defined as hypertension induced by pregnancy and diagnosed after 20 weeks of gestation and usually resolving within 42 days postpartum. The major clinical task is vigilance in the detection of any features of preeclampsia, including development of significant new-onset proteinuria, an increase in preexisting proteinuria, or any suggestive symptoms. Gestational hypertension may portend the development of future primary hypertension and cardiovascular disease, but is otherwise usually associated with good maternal and fetal outcomes.

Preeclampsia occurs in 2% to 5% of all pregnancies, 10% of first pregnancies, and 20% to 25% of women with chronic hypertension. It can be diagnosed with a blood pressure above 140/90 mm Hg, proteinuria exceeding 300 mg per 24 hour urine collection (or > 30 mg/mmol in a spot urine sample), an increase in proteinuria or loss of blood pressure control in a woman with chronic hypertension, or the onset of headache, blurred vision, abdominal pain, transaminitis, or hypertension. However, rare cases occur without significant proteinuria or an elevated blood pressure. Onset is usually in the third trimester with resolution after delivery, although postpartum cases are reported. Risk factors include maternal age over 40 years, Black ethnicity, nulliparity, multiparity, first pregnancy with the male partner, prior hypertension or preeclampsia, obesity, diabetes, chronic kidney disease, thrombophilia, systemic lupus erythematosus, or a history of migraines. Patients with preeclampsia usually require hospitalization for IV magnesium sulfate to prevent seizures, bed rest, close fetal monitoring, and sometimes corticosteroids for acceleration of fetal lung maturity. The pathology involves aberrant invasion of myometrial arteries, resulting in unusually resistive spiral arteries and placental hypoperfusion. Although the etiology remains incompletely understood, angiogenic and antiangiogenic placental peptides (including PAPP-A, PlGF, sFlt-1, sEng, and PP-13) are providing insights into the pathophysiology of preeclampsia and may establish a diagnostic role as biomarkers.

Eclampsia is the development of grand mal seizures in a woman with preeclampsia. When preeclampsia is accompanied by poor prognostic features such as severe hypertension, **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets), placental abruption, cerebral hemorrhage, pulmonary edema, or renal failure, the fetus must be delivered immediately. Expert opinion supports delivery within 24 hours for women with treatment-resistant hypertension or maternal or fetal compromise, regardless of gestational age or fetal lung maturity. Beyond 34 weeks of gestation or in cases where fetal lung maturity has been achieved, delivery should occur without delay. Because of the high risk of maternal and fetal mortality and morbidity, these patients should be managed at a tertiary care center with high-risk obstetrics and neonatology.

Table 38.6 lists different drug therapies used to treat hypertension in pregnancy. IV labetalol is the drug of choice for acute hypertensive urgency or emergency in pregnancy. Hydralazine may also be used as a vasodilator. Sodium nitroprusside is usually avoided, especially in later stages of pregnancy, due to concern for fetal cyanide toxicity if used for more than 4 hours and should be used only as a last resort in cases where emergent control of blood pressure is required. **Methyldopa, labetalol, and nifedipine are the most commonly used oral antihypertensive agents during pregnancy, although there is a paucity of evidence for optimal blood pressure targets or drug choices**. It is generally agreed that **systolic blood pressures of 150 to 160 mm Hg and/or diastolic blood pressures of 100 to 100 mm Hg and above should be treated**.

TABLE 38.6 Drug Therapy for Hypertension in Pregnancy

Drugs for hypertensive urgency and emergencies			
Drug	**Mechanism of action**	**Dosing**	**Comments**
Labetalol	α–β-Adrenergic blocker	20–80 mg IV q10-20min (up to 300 mg)	Appears efficacious; widely used; scant safety data
Hydralazine	Vasodilator	5–10 mg IV q15-30min	Efficacious and safe during pregnancy and lactation
Sodium nitroprusside	Arterial-veno dilator	0.5–5.0 μg/kg/min	Concern for fetal thiocyanate toxicity
Drugs for long-term treatment of hypertension			
Drug	**Mechanism of action**	**Dosing**	**Comments**
Methyldopa	Central α_2-agonists	250 mg tid up to 4 g/d	Most commonly used; safety well established; drug of choice
Labetalol	α–β-Adrenergic blocker	100 mg tid up to 2,400 mg/d	Appears efficacious; widely used; scant safety data
Nifedipine	Calcium channel blocker	once daily sustained release dosing up to 120mg/d	Short-acting nifedipine may precipitate severe hypotension and should be avoided; hypotension also possible with sustained release

Adapted from Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 7th ed. Philadelphia, PA: Elsevier Saunders; 2005:1965–1982.

B. Marfan syndrome. Marfan syndrome is a connective tissue disorder resulting from mutations in the fibrillin gene. It is inherited in an autosomal-dominant fashion. The clinical manifestations include skeletal abnormalities, ectopia lentis, and cardiovascular abnormalities, such as aortic root dilation with or without aortic regurgitation, aortic dissection, and mitral valve prolapse. **Aortic dissection** and rupture are the most feared complications of pregnancy in patients with Marfan syndrome due to hormonal influence on aortic wall integrity. Dissection is more likely to occur during the **third trimester and during labor and delivery and peaks at 3 to 20 days postpartum**.

Screening echocardiography should be performed before pregnancy. **Enlargement of the aortic root to more than 4.0 to 4.5 cm elevates the risk of aortic dissection and rupture from moderate risk to high risk**. Elective repair of the aortic root before conception is strongly advised with a root dimension above 4.5 cm; management should be individualized in the range 4.0 to 4.5 cm. The aortic root should be monitored by serial echocardiography during pregnancy.

Medical management during pregnancy involves the use of **β-blockers** throughout pregnancy to reduce the risk of aortic rupture, careful control of blood pressure, adequate analgesia during labor and delivery, and consideration of general anesthesia and cesarean section at the time of delivery to maximize hemodynamic control. Women with Marfan syndrome without cardiac abnormalities have a low complication rate and can usually tolerate normal vaginal delivery with spinal or epidural anesthesia to minimize pain and hypertension.

C. Aortic dissection. Aortic dissection during pregnancy has been reported in women with Marfan syndrome, systemic hypertension, coarctation of the aorta,

Turner syndrome, and cocaine use. It occurs most commonly in the third trimester and the peripartum period. Transesophageal echocardiography is the key diagnostic tool, and a β-blocker is the preferred medication for management during pregnancy.

D. Coronary artery disease. **MI during pregnancy is rare**, occurring in 6.2 per 100,000 deliveries in the United States in 2000 to 2002. The possibility of MI should always be entertained in a pregnant or immediately postpartum woman, especially if her symptoms and electrocardiogram are suspicious for coronary ischemia. **Most MIs occur during the third trimester in older women who have had multiple prior pregnancies.** ***Coronary spasm, in situ coronary thrombosis, and coronary dissection are more frequently the underlying precipitants of MI*** than classic obstructive atherosclerosis. Acute MI may be the initial clinical manifestation of an underlying hypercoagulable state, such as the antiphospholipid antibody syndrome. The diagnosis and management of acute MI in the pregnant patient should follow the guidelines established for the general population.

Medical therapy for acute MI must be modified in the pregnant patient. Thrombolytic agents increase the risk of maternal hemorrhage substantially (8%). Low-dose aspirin, β-blockers, and nitrates are considered relatively safe. Short-term heparin administration has not been associated with increased maternal or fetal adverse effects. ACE-Is, ARBs, and statins are contraindicated during pregnancy; there is no established safety data for clopidogrel or glycoprotein IIb/IIIa inhibitors. Coronary angiography should be performed only when emergent angioplasty or coronary artery bypass grafting is anticipated during pregnancy and, if possible, avoided in the first trimester. In general, bare metal (rather than drug-eluting) stents should be used if percutaneous intervention is necessary during pregnancy, as clopidogrel will need to be discontinued peripartum.

E. Arrhythmias. The most frequent rhythm disturbances, premature atrial complexes and premature ventricular complexes, are not associated with adverse maternal or fetal outcomes and do not require antiarrhythmic drug therapy. Atrial fibrillation and atrial flutter are rare during pregnancy. Rate control may be achieved with digoxin and β-blockers. Direct current cardioversion may be performed safely during any stage of pregnancy. Anticoagulation is recommended for chronic atrial fibrillation in the setting of underlying structural heart disease. **Atrioventricular nodal reentrant tachycardia** is the most common supraventricular arrhythmia in pregnant and nonpregnant women. It can lead to hemodynamic deterioration in women with underlying heart disease owing to rapid rates. Adenosine may be administered safely to the pregnant patient for both diagnostic and therapeutic purposes.

Ventricular tachycardia (VT) is rare during pregnancy. It may, however, be the presenting manifestation of peripartum cardiomyopathy (PPCM). VT has also been associated with thyrotoxicosis and hyperemesis gravidarum. Most antiarrhythmic medications used to treat VT are safe during pregnancy, **except for amiodarone**, which should be used with extreme caution and only for arrhythmias not responding to other medications, as it may lead to **neonatal hypothyroidism**. Bradyarrhythmias are uncommon during pregnancy. Complete heart block may be acquired or congenital. Pacemaker support is not usually required, unless the bradyarrhythmia is symptomatic or causes hemodynamic deterioration.

F. Peripartum cardiomyopathy. This is defined as the development of idiopathic left ventricular systolic dysfunction in the last month of pregnancy or within 5 months of delivery, in the absence of any identifiable or preexisting cause of heart failure. The incidence of PPCM in the United States is estimated to be 1 in 3,000 to 4,000 live births and is **more common in women older than 30 years**. The following risk factors for PPCM have been proposed: **multiparity, history of preeclampsia, eclampsia, or postpartum hypertension, African descent, low socioeconomic status, or tocolytic therapy with β-agonists**. Symptoms include fatigue, dyspnea on exertion, orthopnea, nonspecific chest pain, peripheral edema, and abdominal discomfort

and distention. PPCM has long been regarded as an idiopathic disease, but recent research has implicated a 16 kDa protein produced from cleavage of prolactin under oxidative stress, which is observed in higher levels in patients with PPCM. Bromocriptine, which inhibits prolactin secretion, has been administered with favorable outcomes in a small series of patients with PPCM. Standard management of pregnant patients presenting with decompensated heart failure includes oxygen, diuretics, digoxin, and vasodilators. ACE-Is and ARBs are absolutely contraindicated in pregnancy but should be commenced postpartum.

The prognosis after development of PPCM is variable. **Approximately 50% of women completely recover normal heart size and function, usually within 6 months of delivery**. The remainder either experience stable left ventricular dysfunction or continue to experience clinical deterioration. Estimated maternal mortality ranges from 10% to 50%. Women with PPCM and **persistent left ventricular dysfunction**, **or whose left ventricular ejection fraction was below 25% at initial presentation**, are at **very high risk for complications in a subsequent gestation** and should be counseled to avoid further pregnancies. Patients with severe cardiac dysfunction and decompensation should be evaluated for cardiac transplantation or mechanical support after pregnancy.

G. Primary pulmonary hypertension. This is associated with **very high maternal mortality (30% to 40%) and poor fetal outcomes**. Worsening of symptoms occurs in the second and third trimesters, and death is usually from right ventricular failure or arrhythmias. Pregnancy should be strongly discouraged in patients with this diagnosis, and early therapeutic abortion should be considered for those who become pregnant. Anticoagulation throughout gestation, or at least during the third trimester, is recommended. Close hemodynamic monitoring during labor, delivery, and the early postpartum period is advised, and oxygen plus pulmonary vasodilators may be used.

H. Pregnancy after cardiac transplantation. Pregnancy after cardiac transplantation is considered high risk for the mother and fetus. Maternal morbidity is increased from hypertension, preeclampsia, renal failure, premature rupture of membranes, and infection. Fetal growth restriction and preterm labor are also a concern, along with potential adverse fetal effects of immunosuppressive medications. One study examined the outcomes of 47 pregnancies in 35 transplant recipients. There was no increase in maternal mortality in this study, but increased maternal morbidity, premature deliveries, and fetal growth restriction were observed.

VIII. MEDICATION CONSIDERATIONS IN PREGNANCY

A. Cardiovascular drugs. The most commonly used cardiovascular drug classes and their potential adverse effects during pregnancy are shown in Table 38.7.

B. Anticoagulation during pregnancy. Conditions requiring anticoagulation during pregnancy include mechanical prosthetic heart valves, chronic atrial fibrillation, acute venous thromboembolism, Eisenmenger syndrome, antiphospholipid antibody syndrome, and inherited deficiencies predisposing to thromboembolism (e.g., prothrombin gene mutation and factor V Leiden deficiency).

The three most common agents considered for use during pregnancy are **unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin**. The Eighth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy has recommended three potential strategies for anticoagulation during pregnancy (Fig. 38.1) and the 2008 ACC/AHA guidelines for the management of patients with valvular heart disease are summarized in Table 38.8.

The choice of anticoagulation regimens depends on the preferences of the patient and physician after consideration of the **maternal and fetal risks associated with the use of each drug**.

1. Warfarin. Warfarin freely crosses the placental barrier and can adversely affect fetal development. It has been associated with a high incidence of spontaneous

TABLE 38.7 Cardiovascular Drugs and Pregnancy

Drug	Indication	FDA category	Potential maternal or fetal side effects
Adenosine	Arrhythmia	C	Limited data on use
Amiodarone	Arrhythmia	D	Hyper/hypothyroidism, IUGR, congenital goiter
ACE-I/ARB	Hypertension	D	Contraindicated, IUGR, oligohydramnios, renal failure, fetal death
Aspirin	Coronary artery disease	D in third trimester	IUGR and bleeding in mother and neonate
β-Blockers	Arrhythmia, hypertension, MI, HOCM, hyperthyroidism, Marfan syndrome, mitral stenosis	C/D	Fetal bradycardia, hypoglycemia, IUGR (atenolol is category D and should be avoided due to greatest IUGR concerns)
Calcium channel blockers	Hypertension	C	Maternal hypotension causing fetal distress reported, potential tocolytic effects
Digoxin	Arrhythmia, heart failure	C	Possible low birth weight, prematurity, but generally considered safe
Dofetilide	Atrial fibrillation	C	Possibly teratogenic in animal studies
Diuretics (thiazides)	Hypertension	B	Hypovolemia and reduced uteroplacental blood flow
Flecainide	Arrhythmia	C	Fetal death; limited data
Hydralazine	Hypertension, heart failure	C	Possible hypospadias, neonatal thrombo-cytopenia, neonatal lupus like syndrome
Lidocaine	Arrhythmia	B	Neonatal CNS depression
Methyldopa	Hypertension	B	Longest safety record, avoid in women with potential for depression
Nitrates	Hypertension	C	Maternal hypotension causing fetal distress reported
Procainamide	Arrhythmia	C	No adverse effects reported in third trimester
Propafenone	Arrhythmia	C	Limited data
Quinidine	Arrhythmia	C	Neonatal thrombocytopenia, mild oxytocic effect
Sodium nitroprusside	Hypertension, aortic dissection	C	Fetal thiocyanate toxicity
Sotalol	Arrhythmia	B/D	Fetal bradycardia, IUGR; category D in second and third trimesters

FDA category: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk. IUGR, intrauterine growth restriction; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; MI, myocardial infarction; HOCM, hypertrophic obstructive cardiomyopathy; CNS, central nervous system.

Data retrieved from Micromedex 2.0 correct as of October 1, 2011.

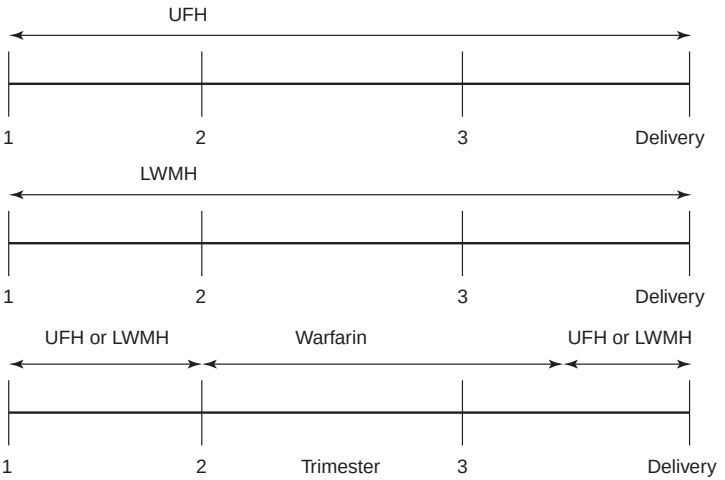

FIGURE 38.1 Anticoagulation options during pregnancy. UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

TABLE 38.8 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves

Class I (benefits >>> risk): procedure/treatment should be performed/administered	Level of evidence
All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring	B
For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored with discussions about subsequent anticoagulation therapy so that anticoagulation can be continued uninterrupted when pregnancy is achieved	C
Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH	C
For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis, and heparin-induced thrombocytopenia are relatively higher	C
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice-daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U/mL 4 h after administration	C

(Continued)

TABLE 38.8 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves (*Continued*)

Class I (benefits >>> risk): procedure/treatment should be performed/administered	Level of evidence
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should be at least twice the control	C
In pregnant patients with mechanical prosthetic valves who receive warfarin, the INR goal should be 3.0 (range 2.5–3.5)	C
In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2–3 weeks before planned delivery	C
Class IIa (benefits >> risk): it is reasonable to perform procedure/administer treatment	
In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation owing to the high risk of fetal defects	C
In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4–6 h after delivery and begin oral warfarin in the absence of significant bleeding	C
In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75–100 mg/d) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin	C
Class III (risk ≥ benefits): procedure/treatment should not be performed/administered	
LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4–6 h after administration	C
Dipyridamole should not be used instead of aspirin as an alternative antiplatelet agent in pregnant patients with mechanical prosthetic valves because of its harmful effects on the fetus	B

UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; aPTT, activated partial thromboplastin time; INR, international normalized ratio.
Level of evidence: A, multiple population risk strata evaluated; B, limited population risk strata evaluated; C, very limited population risk strata evaluated.

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol.* 2008;52:e1–e142.

abortion, prematurity, still birth, and fetal bleeding. **The incidence of warfarin embryopathy (fetal bone and cartilage formation abnormalities) has been estimated at 4% to 10%; the risk is highest when warfarin is administered during the 6th through the 12th week of gestation.** The risks are dose-dependent, and women maintained on a daily dose of < 5 mg daily have the lowest risks. When administered during the second and third trimesters, warfarin has been associated with fetal central nervous system abnormalities, such as optic

atrophy, microencephaly, intellectual disability, spasticity, and hypotonia. Warfarin's anticoagulant effects are more potent in the fetus than in the mother due to lower fetal levels of the vitamin K–dependent clotting factors and can cause neonatal intracranial hemorrhage or a retroplacental hematoma. Warfarin is considered safe during breast-feeding. Women taking warfarin prior to pregnancy should be counseled regarding the harmful effects, and if pregnancy is contemplated then frequent pregnancy tests or switching to UFH or LMWH should be considered.

2. **Unfractionated heparin.** UFH does not cross the placenta, and unlike warfarin does not have the teratogenic effects, and is, therefore, considered safer. **It is, however, associated with maternal osteoporosis, hemorrhage, thrombocytopenia, or thrombosis (heparin-induced thrombocytopenia with thrombosis [HITT] syndrome), and a high incidence of thromboembolic events with older generation mechanical valves**. UFH may be administered parenterally or subcutaneously throughout pregnancy. Subcutaneous (SC) heparin use in patients with mechanical valve carries an increased risk of valve thrombosis. The appropriate dose of UFH is based on an activated partial thromboplastin time (aPTT) of 2 to 3 times the control level. High doses of UFH are often required to achieve the goal aPTT because of the hypercoagulable state associated with pregnancy. Parenteral infusions should be stopped 4 hours before a cesarean section. In the event of preterm labor, spontaneous hemorrhage, or significant bleeding during delivery, UFH may be reversed with protamine sulfate.
3. **Low-molecular-weight heparin. The use of LMWH during pregnancy remains controversial, as it has not been adequately studied**. Its advantages over UFH include a more predictable anticoagulant response and lower incidences of HITT and osteoporosis. It does not cross the placenta, and it may be safer to the fetus even though data in this regard are limited. A twice-daily dosing schedule should be used. During pregnancy the volume of distribution for LMWH changes, and it is essential to monitor anti-Xa levels. The 4-hour-post dose target anti-Xa level varies between 0.7 to 1.2 and 1.0 to 1.2 U/mL depending on the guidelines followed; the manufacturer's specific target range should also be consulted. Although existing data support the use of LMWH with deep venous thrombosis in pregnancy, the safety and efficacy of LMWH in pregnant patients with mechanical valves remain controversial. One LMWH carries a manufacturer's warning regarding the safety of LMWH in patients with mechanical heart valves, but the true incidence of valve thrombosis in pregnant patients receiving LMWH is unclear. Small studies continue to demonstrate individuals with catastrophic valve thrombosis despite therapeutic anti-Xa levels, further underlining the limitations of the LMWH strategy. However, retrospective auditing of pregnancies managed with LMWH versus warfarin strategies has shown better neonatal outcomes with the LMWH option.
   (1) Therefore, anticoagulation for mechanical valves during pregnancy is challenging. The choice of anticoagulant should be made after detailed discussion with the patient. Overall, warfarin is probably the safer option for the mother, whereas heparin is less likely to result in fetal harm. In the event of unplanned pregnancy in a patient on warfarin, it is advisable to change from warfarin to UFH or LMWH until 12 weeks and then resume warfarin until the 35th week if the patient is willing to take it, with careful monitoring of the international normalized ratio (INR). The 2011 European Society of Cardiology guidelines on the management of cardiovascular disease during pregnancy offer a class IIaC recommendation for considering continuation of warfarin during the first trimester if the warfarin dose required for therapeutic anticoagulation is < 5 mg/d, after patient information and consent. The ACC/AHA guidelines for selection of anticoagulation regimen in pregnant patients with mechanical prosthetic valves, updated in 2008, are presented in Table 38.8.

(2) In patients with a **mechanical heart valve with high risk of thrombosis** (first-generation prosthesis; e.g., Starr-Edwards, Björk-Shiley in mitral position, atrial fibrillation, and history of thromboembolism) one of the following algorithms may be used: Continuous IV UFH (aPTT 2.5 to 3.5 times) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.5 times) for up to 35 weeks followed by IV UFH (aPTT 2.5 to 3.5 times) until delivery **or** SC twice-daily LMWH (anti-Xa level 0.7 to 1.2 U/mL) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.5 times) for up to 35 weeks followed by IV UFH (aPTT of 2.5 to 3.5 times) or SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL).

(3) In patients with a **mechanical heart valve with relatively lower risk of thrombosis** (second-generation prosthesis; e.g., St. Jude Medical, Medtronic-Hall, and any mechanical prosthesis in aortic position) options include the following: SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL) or SC twice-daily UFH (aPTT 2.0 to 3.0 times) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.0 times) for up to 35 weeks followed by IV UFH (aPTT 2.0 to 3.0 times) or SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL) **or** SC twice-daily UFH or SC twice-daily LMWH throughout pregnancy (data supporting this algorithm are limited).

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Arti Choure, MD, to a previous edition of this chapter.*

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CHAPTER 39

Sachin S. Goel

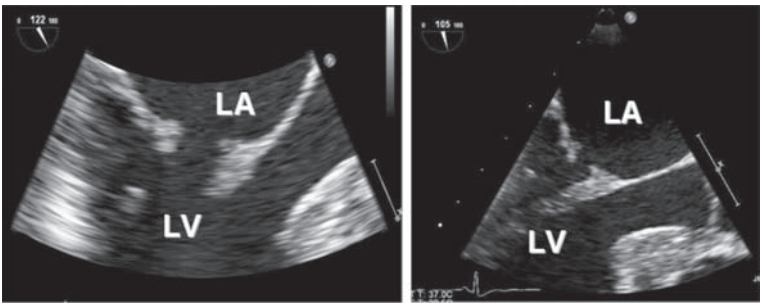
Cardiovascular Manifestations of Systemic Disease

Several systemic diseases involve the cardiovascular system, with important therapeutic and prognostic implications. It is vital for cardiologists to recognize, manage, and prevent cardiovascular involvement in various systemic diseases. This chapter reviews the cardiovascular manifestations of various systemic disorders.

I. RHEUMATOLOGIC DISORDERS

A. Rheumatoid arthritis (RA) is one of the commonest forms of chronic inflammatory polyarthritis resulting in joint destruction and deformation. It affects 1% to 3% of the population and is more common in women. It is characterized by chronic symmetrical polyarthritis that typically affects small joints of the hand, such as metacarpophalangeal and proximal interphalangeal joints, in addition to wrists and knees, and spares the thoracolumbar spine and distal interphalangeal joints. The most common cardiovascular manifestations of RA are as follows:

1. **Pericarditis** is very common and can be present in nearly 50% of patients with RA. It can vary from acute pericarditis and chronic asymptomatic effusive pericarditis to cardiac tamponade or chronic constrictive pericarditis, with significant hemodynamic consequences. Most cases with uncomplicated acute pericarditis will respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroid therapy may be needed for patients with severe pericarditis. Pericardiocentesis or surgical drainage may be required in cases of tamponade.
2. **Coronary artery disease (CAD)**. Patients with RA have increased mortality compared with the general population and the leading cause of death is cardiovascular disease. Patients with RA have accelerated atherosclerosis, likely a result of chronic systemic inflammation and use of corticosteroids. **After controlling for traditional risk factors of atherosclerosis, patients with RA have been shown to have two to three times greater risk of CAD compared with controls**. In the large prospective Nurses' Health Study, women with RA were found to have a twofold higher risk of myocardial infarction compared with controls. In addition to disease-modifying drugs to reduce systemic inflammation, aggressive lifestyle modification, including tight control of blood pressure and low-density lipoprotein cholesterol, seems warranted.
3. **Cardiomyopathy.** RA can cause granulomatous inflammation of the myocardium leading to cardiomyopathy or involve the conduction system resulting in varying degrees of heart block. Rarely, secondary amyloidosis can occur in RA, leading to an infiltrating cardiomyopathy.
4. **Valvular disease.** A small proportion of patients with RA can have valvular involvement in the form of rheumatoid nodules; however, clinically significant valve disease is very rare.



(A) (B)

FIGURE 39.1 Transesophageal echocardiogram demonstrating vegetations (Libman-Sacks endocarditis) on the atrial aspect of anterior and posterior mitral valve leaflets in a patient with systemic lupus erythematosus. Panel A is a zoom view of the valve leaflets whereas Panel B shows a less detailed image of the leaflets. LA, left atrium; LV, left ventricle.

B. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that occurs more commonly in women and is characterized by a wide range of organ involvement, including arthritis, dermatitis, glomerulonephritis, serositis, and hematologic abnormalities. Drug-induced lupus can occur with various cardiac medications, including procainamide, quinidine, and hydralazine, and this is associated with the development of anti-histone antibodies. SLE can affect the cardiovascular system in various ways:

1. **Valvular disease** is the most common type of cardiac involvement in SLE. The characteristic valvular lesions in SLE are nonmobile, noninfectious vegetations on the atrial aspect of the mitral valve or the arterial aspect of the aortic valve, referred to as Libman-Sacks endocarditis (Fig. 39.1). Studies have shown that valvular involvement is very common in SLE and occurs in > 50% of patients. The most common valvular abnormality is valvular thickening, followed by vegetations and valvular regurgitation or stenosis. Serial echocardiography should be performed to monitor for progression of valve disease. The vegetations can embolize and cause stroke or myocardial infarction in rare cases.
2. **Pericarditis** is very common in SLE and has been shown to occur in > 50% to 60% of patients. Associated pericardial effusion is usually exudative, with elevated protein and low glucose concentration, and infection must be ruled out in the setting of concomitant immunosuppressive therapy. Cardiac tamponade and chronic constrictive pericarditis can also occur.
3. **Coronary artery disease.** Premature coronary atherosclerosis has been shown to occur commonly in patients with SLE compared with age-matched controls. CAD can also manifest as coronary arteritis, thrombosis in the presence of antiphospholipid antibody syndrome (APLA—see Section **I.C**) or, rarely, embolism from Libman-Sacks endocarditis.
4. **Myocardial dysfunction** in patients with SLE can result from ischemia, valve disease, or long-standing hypertension. Patients with peripheral skeletal myositis have an increased risk of lupus myocarditis.
5. **Conduction system disease** with complete heart block can occur in infants born to mothers with SLE, particularly those with anti-Ro and anti-La antibodies. Women with SLE contemplating pregnancy should undergo screening for these antibodies prior to pregnancy and, if present, should undergo fetal echocardiography to screen for conduction abnormalities and myocardial dysfunction. There is some evidence suggesting a role for intrauterine dexamethasone in reversing fetal myocarditis and slowing conduction disease.

C. **Antiphospholipid antibody syndrome** is characterized by the presence of antiphospholipid antibodies or lupus anticoagulant, recurrent venous or arterial thrombosis, and miscarriages. APLAs can occur independently, referred to as primary APLAs, or can be associated with other autoimmune diseases such as SLE (10% to 30%) and are then referred to as secondary APLAs. Valvular disease is common in APLAs and is characterized by noninfectious vegetations similar to those seen in SLE (Libman-Sacks endocarditis). Management of arterial or venous thrombosis or significant valvular vegetations includes anticoagulation therapy with warfarin. Monitoring anticoagulant effect while on heparin or warfarin may be difficult, as these patients can have prolonged partial thromboplastin time or international normalized ratio at baseline, in which case monitoring of anticoagulant effect can be done using activity levels of factors II and X.

D. **Scleroderma** or systemic sclerosis is a rare autoimmune disorder, characterized by vasospasm, microvascular occlusion, and fibrosis of skin and multiple organs. Diffuse or progressive systemic sclerosis (PSS) results in widespread cutaneous and visceral involvement. Limited scleroderma, also known as CREST syndrome, is characterized by calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Cardiovascular involvement can occur in progressive as well as limited scleroderma.

1. **Pericardial disease** in the form of fibrinous pericarditis is present in over 70% of patients on autopsy studies, though it is clinically manifest as symptomatic pericarditis in only about 15% to 30% of patients. Small pericardial effusions can be detected in about 40% of patients by echocardiography, but are rarely significant. Acute pericarditis may be treated with NSAIDs, with close monitoring of renal function. Corticosteroids carry the risk of inducing scleroderma renal crisis.
2. **Pulmonary hypertension (PH)** is responsible for significant morbidity and mortality in patients with scleroderma and is more common in the limited type. Autopsy studies have shown histopathological changes consistent with PH in 65% to 80% of patients with scleroderma; however, < 10% of patients manifest PH clinically. Patients with scleroderma and PH appear to have a worse prognosis compared with those with primary PH, with a 2-year survival of < 50%. Drugs for PH, such as prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan), and phosphodiesterase inhibitors (sildenafil and tadalafil), have been studied in patients with scleroderma and PH. Some of these studies have demonstrated improvement in the 6-minute walk test, exercise capacity, and cardiopulmonary hemodynamics; however, no improvement in mortality has been demonstrated. Echocardiography should be used to screen for asymptomatic PH.
3. **Scleroderma renal crisis** is defined as the new onset of accelerated hypertension or rapidly progressive oliguric renal failure during the course of systemic sclerosis. It is usually associated with rising creatinine, thrombocytopenia, microangiopathy, and signs and symptoms of congestive heart failure. Scleroderma renal crisis occurs in about 10% of patients with scleroderma and is more common in the diffuse form of the disease. Angiotensin-converting enzyme inhibitors are the mainstay of therapy.
4. **Myocardial involvement** with patchy fibrosis can occur in patients with scleroderma. Epicardial coronary arteries are usually normal on angiography; however, ischemia can occur secondary to microvascular vasospasm. Diastolic dysfunction has been commonly found in these patients. Electrical abnormalities such as frequent ectopy, supraventricular arrhythmias, and nonsustained ventricular tachycardia (VT) can occur in patients with PSS. The risk of sudden cardiac death is higher in those with a history of syncope.

E. **Seronegative spondyloarthropathies** include HLA-B27 antigen–associated arthropathies such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease–associated arthritis. These disorders are characterized by

involvement of the spine and sacroiliac joints and inflammation of tendons, ligaments, and their insertion points into bones (enthesitis). In contrast to RA and SLE, these disorders occur more commonly in males. Ankylosing spondylitis results in ankylosis, sacroiliitis, and asymmetric peripheral arthritis. Reactive arthritis is characterized by conjunctivitis, genital ulcers, and asymmetric peripheral arthritis. Proximal aortitis with or without aortic regurgitation and conduction disturbances are most commonly associated with ankylosing spondylitis and reactive arthritis. **Proximal aortitis can lead to thickening, stiffness, and dilatation of the aortic root with aortic regurgitation**. Aortic or mitral valve thickening with nodularities of the aortic cusps and thickening of the anterior mitral valve leaflet resulting in a characteristic subaortic bump are commonly observed valvular abnormalities in patients with ankylosing spondylitis. Extension of the subaortic inflammation and fibrotic process into the basal septum can result in conduction abnormalities such as heart block, which is usually at the level of the atrioventricular (AV) node. Other less common cardiac abnormalities include pericarditis, diastolic dysfunction, and supraventricular arrhythmias.

F. Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory myopathies characterized by proximal skeletal muscle weakness and elevated levels of muscle enzymes, such as creatine kinase and aldolase. DM is characterized, in addition, by skin involvement such as erythematous scales on the knuckles (Gottron's papules), knees, and elbows, and periorbital swelling and violaceous rash around the eyelids (heliotrope rash). DM can be part of a paraneoplastic syndrome, particularly in the elderly. Cardiovascular manifestations of DM and PM include pericarditis, conduction abnormalities, and congestive heart failure secondary to myocarditis that can be focal or generalized and may be steroid responsive. Cardiac magnetic resonance imaging (MRI) with delayed gadolinium enhancement may be useful in monitoring response to therapy. Coronary vasculitis is a rare manifestation. The differentials for muscle weakness include the following: corticosteroid myopathy, which generally affects skeletal muscle but not cardiac or respiratory muscle and is associated with a normal creatine kinase, and statin myopathy, which can be differentiated based on history of statin use and myalgias or with electromyography and biopsy if needed. Management of DM and PM includes corticosteroids, and adjunctive therapies include methotrexate, azathioprine, and intravenous immunoglobulin (IVIg).

II. SYSTEMIC VASCULITIDES

A. Giant cell arteritis (GCA), also referred to as temporal arteritis, is the most common vasculitis in patients older than 50 years. It is more prevalent in women compared with men and in those of Northern European descent. GCA usually affects the extracranial branches of the aorta, sparing the intracranial vessels. Transmural inflammation of the vessels is followed by intimal hyperplasia, luminal occlusion, and end-organ ischemia. Branches of the external and internal carotid arteries are particularly susceptible, and the typical clinical presentation of GCA includes new-onset headache, scalp and temporal artery tenderness, jaw pain, acute visual loss, and polymyalgia rheumatica. Concomitant elevation in erythrocyte sedimentation rate (ESR) is almost always present. **Temporal artery biopsy is the gold standard for diagnosis and shows transmural chronic granulomatous inflammation with destruction of elastic laminae**. Treatment with corticosteroids should be initiated as soon as possible, without waiting for temporal artery biopsy. GCA is associated with thoracic and abdominal aortic aneurysms. According to one study, patients with GCA are 17 times more likely to develop thoracic aortic aneurysm and 2.4 times more likely to develop abdominal aortic aneurysm compared with age-matched controls. Rare cardiovascular manifestations include pericarditis, myocarditis, and coronary vasculitis. Studies have shown that MRI or fluorine-18-deoxyglucose positron emission tomography (FDG PET) can be useful for the detection of large vessel vasculitis. Transthoracic echocardiography and abdominal ultrasonography are useful in screening for thoracic and

FIGURE 39.2 Magnetic resonance angiogram in a patient with Takayasu arteritis demonstrating severe diffuse narrowing of both common carotid arteries and severe disease in the left subclavian artery (arrows).

abdominal aortic aneurysms. As mentioned, corticosteroids are the agents of choice in patients with GCA. Low-dose aspirin should be added, since it has been shown to reduce the rate of blindness and stroke in patients with GCA.

B. Takayasu arteritis (TA) is also a large vessel vasculitis like GCA, but it occurs in young women, particularly of Indian, Japanese, and African-American descent. It typically affects the aorta and its major branches (Fig. 39.2). In TA, arterial stenoses are more common than aneurysms. Clinically, TA is characterized by claudication (upper extremities more common compared with lower extremities), "pulselessness" or asymmetric pulses, and blood pressures. Systemic symptoms such as fever, malaise, arthralgias, myalgias, night sweats, and elevated ESR may indicate active disease. Renal artery stenosis can be associated with hypertension. Cardiac manifestations include aortic regurgitation secondary to aortic root dilatation and rarely coronary arteritis. Diagnosis is based on imaging studies that show vascular involvement typical of TA. Imaging modalities such as MRI and PET enable visualization of inflammation in the vessel wall. Therapeutic strategies include corticosteroids, immunosuppressants such as cyclophosphamide or methotrexate in steroid-resistant cases, and anatomic correction using an endovascular or surgical approach when feasible.

C. Kawasaki disease is an acute febrile illness that affects children, usually below the age of 5 years, with the highest incidence in those of Asian descent. Diagnosis is made largely on clinical grounds based on the following criteria: (1) fever ≥5 days; (2) conjunctival injection; (3) oropharyngeal changes including erythema, swelling and fissuring of the lips, diffuse erythema of the oropharynx or strawberry tongue; (4) extremity changes such as erythema of palms and soles, induration of hands and feet, desquamation of the skin of hands and feet; (5) polymorphous rash; and (6) cervical lymphadenopathy, usually a single node > 1.5 cm. Fever and four out of five remaining criteria must be present for a definitive diagnosis. Cardiovascular manifestations include pericarditis, myocarditis, aortitis, aortic regurgitation, and arrhythmias. Coronary vasculitis can occur, which if left untreated can lead to

coronary aneurysm formation in about 4 weeks. Aneurysms larger than 8 mm are referred to as giant aneurysms, and these can thrombose acutely, leading to myocardial infarction as well as sudden death. Treatment with aspirin and single-dose IVIg (dose 2 g/kg) reduces the formation and progression of coronary aneurysms. Recommendations by the American Heart Association include long-term follow-up and consideration of anticoagulation for children with multiple giant coronary aneurysms or known obstructive lesions, chronic low-dose aspirin therapy, and coronary artery bypass or percutaneous intervention if lesions are severe and symptomatic.

D. Idiopathic aortitis is commonly associated with disorders such as TA and GCA in addition to rheumatologic diseases such as SLE, Behçet's disease, seronegative spondyloarthropathies, antineutrophil cytoplasmic antibody–associated vasculitides, Cogan syndrome, and sarcoidosis. Although most cases of aortitis are noninfectious in etiology, infectious causative agents such as staphylococcus, streptococcus, salmonella, and syphilis must be considered. Aortitis can be diagnosed for the first time in surgically excised specimens after aortic surgery. In a 20-year review of over 1,200 aortic surgical specimens at Cleveland Clinic, 52 (4.3%) were clinically and pathologically classified as idiopathic aortitis. Of these, 67% were women. In 96% of cases with idiopathic aortitis and aneurysm formation, aortitis was limited to the thoracic aorta. In 96% of cases, signs of systemic illness were not present at the time of aortic surgery. In 31% (16 of 52), aortitis was associated with a remote history of vasculitis and a variety of other systemic disorders such as GCA, TA, SLE, and Wegener's. Over a mean follow-up of 41 months, new aneurysms were found in 6 out of 25 patients not treated with corticosteroids. It is prudent to follow these patients with serial imaging to identify new aneurysms. Treatment with corticosteroids requires evidence of an ongoing systemic inflammatory disease.

E. Churg-Strauss syndrome (CSS) is a rare small vessel vasculitis characterized by asthma, peripheral eosinophilia, pulmonary infiltrates, and varying degrees of cutaneous, renal, neurologic, and cardiac involvement. Histopathologically, it is characterized by eosinophilic granulomatous inflammation of small vessels of the involved organ. Cardiovascular manifestations are common in CSS and are responsible for significant morbidity and mortality in these patients. The most common cause of death is congestive heart failure secondary to cardiomyopathy, the cause of which may be small vessel vasculitis or eosinophilic infiltration of the myocardium followed by fibrosis or a combination of both pathologic processes. Other cardiac manifestations include myocarditis and pericarditis with or without pericardial effusion. Therapy mainly includes corticosteroids but other immunosuppressants may be needed.

F. Polyarteritis nodosa (PAN) is a rare nongranulomatous disease affecting medium-sized arteries that leads to weakening of the vessel wall secondary to necrotizing changes with aneurysm formation or intimal proliferation and stenosis. It is a systemic disease characterized by painful subcutaneous nodules, digital infarcts, mononeuritis multiplex, renal infarction and renal failure, hypertension, and pulmonary infarction. Cardiac manifestations include angina, myocardial infarction, congestive heart failure, and arrhythmias such as supraventricular tachycardia. Treatment is similar to CSS and primarily includes corticosteroids.

III. CONNECTIVE TISSUE DISEASES

A. Marfan syndrome was first described over 100 years ago by Antoine-Bernard Marfan, a French pediatrician. It is an autosomal dominant connective tissue disease secondary to mutations in the fibrillin-1 gene (*FBN1*) that encodes major constituent proteins of microfibrils, which form a significant component of the extracellular matrix. It is a common heritable condition with an estimated prevalence of 1 per 3,000 to 5,000 individuals. About 25% cases have no family history and are a result of de novo mutations. Marfan syndrome is characterized by disproportionate long bone overgrowth with long extremities and tall stature, joint hypermobility,

high-arched palate, and ectopia lentis. In addition, patients with Marfan syndrome can have pectus excavatum or carinatum, scoliosis, arachnodactyly, erosion of lumbar vertebrae from dural ectasia, apical pulmonary blebs with spontaneous pneumothorax, myopia, retinal degeneration, and cataracts. The diagnosis of Marfan syndrome is based on the Ghent criteria, based on consensus by an international expert panel, which have been revised recently with more weight on cardiovascular manifestations. In the absence of family history, the presence of aortic root aneurysm or aortic dissection and ectopia lentis establishes the diagnosis of Marfan syndrome. In the absence of either of these two, the presence of *FBN1* gene mutation or a combination of systemic manifestations listed above is required. Cardiovascular manifestations of the Marfan syndrome are as follows:

1. **Aortic aneurysm and dissection.** Defect in microfibrils results in degeneration of elastic fibers in the aortic media (sometimes inappropriately referred as "cystic medial necrosis"), with resultant aortic aneurysm formation. This typically occurs at the level of the aortic root and involves the sinuses of Valsalva. The aortic root diameter should be serially monitored with echocardiography or computed tomography/MRI. According to the current guidelines, annual imaging is recommended if stability in aortic root size is documented. If the baseline aortic diameter is > 4.5 cm or if there is significant growth from baseline, more frequent imaging should be considered. Elective surgical repair for aortic root aneurysm is usually performed at a threshold of 5 cm or greater in patients with Marfan syndrome. This threshold is smaller than for other disorders with aortic aneurysm, given the greater tendency for aortic dissection at smaller diameters in patients with Marfan syndrome. Indications for earlier repair at sizes < 5.0 cm include: rapid growth defined as > 0.5 cm/year, family history of aortic dissection at a diameter < 5.0 cm or the presence of significant aortic regurgitation. Aortic regurgitation usually occurs secondary to aortic root dilatation. Aortic dissection in Marfan syndrome is usually type A, i.e., starts in the ascending aorta and can extend to a variable degree distally. About 10% of dissections in Marfan syndrome begin distal to the origin of the left subclavian artery (type B). Type A dissection necessitates immediate repair, given the high risk of life-threatening complications if not treated promptly. Medical management in patients with Marfan syndrome includes β-blockers, which have been shown to reduce the risk of aortic dilatation and aortic dissection. The beneficial effect of β-blockers is largely due to the reduction in heart rate and the rate of pressure increase in the aorta, which leads to less stress on the aortic wall. Recently, angiotensin receptor blockade with Losartan was shown to slow the rate of aortic root dilatation in patients with Marfan syndrome, secondary to mitigation of excessive transforming growth factor beta signaling. Due to the risk of acute aortic dissection, patients with Marfan syndrome should be counseled to avoid isometric exercise, including heavy weight lifting, contact sports, and competitive athletics. Females of childbearing age with Marfan syndrome should be counseled regarding the high risk of transmission of their disease to the child. Enlargement of the aortic root to > 4.0 cm increases the risk of aortic dissection, particularly during the third trimester, parturition, and first few months postpartum. If the aortic root is < 4 cm, then the risk of dissection is considered low, and pregnancy can be allowed with β-blocker therapy and careful monitoring with serial echocardiography throughout pregnancy.
2. **Mitral valve prolapse** commonly occurs in patients with Marfan syndrome and is more common in women. The incidence is as high as 60% to 80%, and progressive mitral regurgitation occurs in about 25% of patients. The valve leaflets are usually thickened and redundant and occasionally ruptured chordae or prolapse may be present. Progressive untreated mitral regurgitation can lead to left ventricular dilatation, congestive heart failure, and PH. Tricuspid valve

prolapse can occur concomitantly. Standard management for chronic severe mitral regurgitation is indicated in symptomatic patients, with repair of the mitral apparatus if possible, but replacement may be necessary when the leaflets are very redundant or there is severe annular calcification or chordal damage.

3. **Dilated cardiomyopathy** independent of, or out of proportion to, valvular abnormalities can occur in patients with Marfan syndrome. This has been hypothesized to be secondary to a potential role of fibrillin mutations in the reduction of myocardial function.
4. **Arrhythmias**, both supraventricular and ventricular, can occur in patients with Marfan syndrome.

B. Loeys-Dietz syndrome (LDS) is a recently recognized autosomal dominant connective tissue disease with similarities to the Marfan syndrome but with important genotypic and phenotypic differences. It is caused by mutations in the genes encoding transforming growth factor beta receptors 1 and 2 (*TGFBR1* and *TGFB2*). Type I LDS is characterized by arterial tortuosity and aneurysms, most often in the aortic root but can involve other arteries, hypertelorism (widely spaced eyes), and bifid uvula or cleft palate or both. Patients with type II LDS are characterized by cutaneous manifestations such as velvety translucent skin, easy bruising, atrophic scars, and joint laxity, similar to vascular Ehlers-Danlos syndrome. Patients with LDS do not have ectopia lentis. They are, however, predisposed to more aggressive and widespread vascular disease, including aneurysm formation and dissection, compared with Marfan syndrome, with a mean age of death of 26 years. Patients with LDS can develop aortic dissection at aortic diameters < 5 cm; hence, elective repair is recommended at much smaller aortic root dimensions (4.0 cm) compared with Marfan syndrome. Surgical repair has not been associated with tissue fragility in patients with LDS. More than 50% of patients with LDS can develop aneurysms of other vessels; hence, yearly surveillance imaging of the entire vascular tree has been recommended.

C. Ehlers-Danlos syndrome, type IV or vascular form, is a rare autosomal dominant disorder associated with mutations in the gene for type III procollagen (*COL3A1*). It is characterized by easy bruising, thin skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines. Arterial rupture or dissections are the major causes of mortality in these patients and can occur in the thoracic or abdominal vessels, including aortic rupture or dissection. The median age of survival was about 48 years in a study of 220 patients with this disorder. In the same study, 25% of patients had a medical or surgical complication by the age of 25 years and > 80% had such complications by the age of 40 years. In contrast to LDS, tissues are friable in Ehlers-Danlos syndrome, and surgical repair after ruptured aneurysm or dissection can be complicated by hemorrhage or poor wound healing. The role of prophylactic surgical repair for unruptured aneurysms is unclear. Pregnant women have a 50% chance of transmitting the disorder to the child, and about 11.5% risk of mortality. Pregnancy should be considered high risk and women should be counseled against it.

IV. OTHER SYSTEMIC DISEASES

A. Sarcoidosis is an idiopathic systemic granulomatous inflammatory disease affecting mainly the lungs, but can involve the lymph nodes, skin, eyes, heart, kidneys, musculoskeletal system, nervous system, and endocrine system. Histopathologically, it is characterized by the presence of noncaseating granulomas. It is more common in young and middle-aged adults (peak incidence second to fourth decades) and in African-Americans. Cardiac involvement is found in 25% of patients with sarcoidosis on autopsy, but only 5% of patients have clinically apparent cardiac involvement. The most common sites of cardiac involvement are the basal interventricular septum, AV node and the His bundle, focal regions in the ventricular free walls, and the papillary muscles. Cardiovascular manifestations of sarcoidosis are as follows:

1. **Arrhythmias** can vary from conduction disturbances, including heart block to fatal ventricular arrhythmias. Complete heart block is the most common abnormality in

patients with clinically evident sarcoidosis and is found in 20% to 30% of patients. First-degree heart block and bundle branch blocks are also seen. Granulomatous infiltration of the ventricular myocardium can set up foci of automaticity, leading to ventricular arrhythmias. VT is the most common arrhythmia and is reported in about 20% of patients with sarcoidosis. Sudden cardiac death caused by an arrhythmia is one of the leading causes of death (> 60%) in patients with sarcoidosis.

2. **Congestive heart failure** may occur, secondary to widespread infiltration of the myocardium. It may also occur due to arrhythmias, cor pulmonale from long-standing PH, valvular abnormalities, or a combination of these abnormalities. Progressive congestive heart failure is the second most common cause of death in patients with sarcoidosis.
3. **Pericardial** involvement can manifest as pericarditis, pericardial effusion, and constrictive pericarditis.

Diagnosis of cardiac sarcoidosis may be difficult. Endomyocardial biopsy with noncaseating granulomas has high specificity, but poor sensitivity owing to the patchy nature of myocardial involvement particularly in the basal septum, whereas the location of biopsy is often the apical septum. Electrocardiogram often reveals conduction abnormalities but has poor sensitivity. Echocardiographic findings include increased ventricular septal thickness (secondary to granulomatous expansion) or wall thinning (due to fibrosis), aneurysms, regional wall motion abnormalities, and eventually ventricular dilatation. Contrast-enhanced MRI and 18-FDG PET are more sensitive modalities for detecting early cardiac involvement and findings correlate with disease severity. These imaging modalities can be used in evaluating response to therapy. Corticosteroid therapy can halt cardiac disease progression and improve survival; however, it does not prevent sudden cardiac death. Pacemaker implantation is often necessary in cases of symptomatic heart block or asymptomatic high-grade conduction disease. Implantable cardioverter defibrillator implantation is recommended for primary prevention in patients with cardiac sarcoidosis at risk for sudden cardiac death, such as those with a history of nonsustained VT or low ejection fraction. Cardiac transplantation for cardiac sarcoidosis is rarely used, as the disease can recur in the transplanted heart. However, it may be considered in young patients with severe end-stage heart failure or resistant VT.

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CHAPTER 40

Arun Dahiya

Pericardial Disease

I. INTRODUCTION. The pericardium is a fibrous sac composed of two layers. The inner monocellular visceral layer is composed of mesothelial cells and is adherent to the myocardium. The outer parietal layer is a fibrous layer < 2 mm thick that consists mostly of collagen and elastin. It is joined to adjacent intrathoracic structures by means of ligaments. Interspersed between the two layers is a small amount of serous pericardial fluid, generally about 15 to 35 mL. **The normal pericardium is distensible and permits unimpeded expansion of the ventricles during diastole. Normally, changes in intrathoracic pressure are easily transmitted to the heart**, resulting in increased venous return to the right side of the heart with inspiration and increased pulmonary venous return to the left side of the heart with expiration.

The pericardium helps to maintain the position of the heart within the chest cavity, acts to reduce friction during the cardiac cycle, and also acts as a barrier to infection and inflammation. The pericardium secretes prostaglandins that can modulate cardiac reflexes and coronary tone.

A. Acute pericarditis is a clinical syndrome caused by **inflammation of the pericardium,** and it is associated with **chest pain, a friction rub, and characteristic electrocardiographic changes**. The incidence of acute pericarditis is 2% to 6% in autopsy series, although it is diagnosed clinically in only 1 in 1,000 admissions. It is more **common in adults (20 to 50 years of age) and in men**.

B. Constrictive pericarditis is caused by **fibrous thickening of the pericardium** secondary to **chronic inflammation** from a variety of causes.

C. Pericardial effusion is a **fluid collection in the pericardial space**. The clinical presentation may range from being **asymptomatic to life-threatening** hemodynamic compromise, depending on the **underlying cause of the effusion** and the **rate of accumulation**, as discussed later in detail.

D. Cardiac tamponade is a clinical emergency that arises when a pericardial fluid collection impairs diastolic filling sufficiently to produce a low cardiac output state.

II. ACUTE PERICARDITIS.

There are a large number of potential etiologies of acute pericarditis. In practice, these are classified into the following groups: idiopathic, infectious, inflammatory, uremic, post-myocardial infarction (post-MI), neoplastic, and traumatic (Table 40.1).

A. Etiology

1. Idiopathic. Most cases of acute pericarditis are **idiopathic**, although many of these may be **viral in origin**.

TABLE 40.1 Causes of Pericarditis

Idiopathic (nonspecific)

Viral infections: coxsackievirus A, coxsackievirus B, echovirus, adenovirus, mumps virus, infectious mononucleosis, varicella, hepatitis B virus, and acquired immunodeficiency syndrome

Bacterial infections: *Pneumococcus, Staphylococcus, Streptococcus,* gram-negative septicemia, *Neisseria meningitidis, Neisseria gonorrhoeae,* tularemia, *Legionella pneumophila, and Mycobacterium tuberculosis*

Fungal infections: histoplasmosis, coccidioidomycosis, *Candida,* and blastomycosis

Uremia

Neoplasm: lung cancer, breast cancer, leukemia, Hodgkin's disease, and lymphoma

Radiation

Autoimmune diseases: acute rheumatic fever, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, Wegener's granulomatosis, and polyarteritis nodosa

Inflammatory disease: sarcoidosis, amyloidosis, inflammatory bowel disease, Whipple's disease, and temporal arteritis

Drugs

Hydralazine, procainamide, phenytoin, isoniazid, phenylbutazone, doxorubicin, and penicillin

Trauma

Postmyocardial–pericardial injury syndromes: postmyocardial infarction syndrome (Dressler's syndrome) and postpericardiotomy syndrome

Dissecting aortic aneurysm

Adapted from Lorell BH. Pericardial disease. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine.* 5th ed. Philadelphia, PA: WB Saunders; 1997:1482.

2. **Viral pericarditis.** The most commonly involved viruses are coxsackievirus B and echovirus. A **prodrome of upper respiratory tract symptoms** preceding the onset of chest pain, along **with a fourfold or higher rise in viral convalescent antibody titers**, supports the diagnosis. Most cases are self-limited; infrequent complications include myocarditis (i.e., myopericarditis), recurrent pericarditis, pericardial effusion, tamponade, and constrictive pericarditis.
3. **Purulent pericarditis.** Purulent pericarditis usually occurs as a **complication of pneumonia or empyema** caused by staphylococci, pneumococci, or other streptococci. Early diagnosis of purulent pericarditis is paramount, as **cardiac tamponade often develops and is associated with high mortality. Purulent pericarditis** is characterized by **acute onset of fever, shaking chills, night sweats, and dyspnea** of a few days duration. **Chest pain or pericardial friction rub is not necessarily present**.
4. **Tuberculous pericarditis.** Although uncommon in the United States, this entity should be considered in patients with fever and pericardial effusion, particularly if there is an underlying immunocompromised state. Pericardial involvement occurs in 1% to 2% of cases of pulmonary tuberculosis. **If the clinical suspicion is high, the patient should be hospitalized and started on triple drug therapy**, while definitive diagnostic testing is undertaken (acid-fast bacilli [AFB] testing and pericardial/pleural biopsy).
5. Post-MI pericarditis occurs most often after a large anterior wall MI. Because post-MI pericarditis is a marker for extensive myocardial necrosis, these **patients are at an increased risk for congestive heart failure and mortality at 1 year after MI**. It is notable that the rate of post-MI pericarditis has declined since the introduction of successful reperfusion therapies.
6. **Dressler's syndrome** usually **occurs weeks to several months after MI,** with an incidence of about 1%. It presents as **malaise, fatigue, and chest pain** that can be of concern for recurrent MI. The cause of Dressler's syndrome is unclear, although it has been proposed to be autoimmune in nature.
7. **Postpericardiotomy syndrome.** Although similar to Dressler's syndrome in presentation, it **usually occurs within the first 6 to 8 weeks following cardiac surgery**. The incidence varies from 10% to 40%, and the syndrome is believed to be caused by an autoimmune reaction.
8. Uremic pericarditis typically develops in patients who are just beginning renal replacement therapy with hemodialysis. The majority present with a **rub**, and the associated **pericardial effusions tend to be large**. The cause is unknown but does not seem to be related to the level of circulating uremic catabolites or toxins.
9. **Neoplastic pericarditis.** Tumors involving the pericardium are typically metastatic in nature (lung, breast, Hodgkin's and non-Hodgkin's lymphoma, and leukemia). It is important to **suspect cardiac tamponade in patients with a known malignancy who present with symptoms of relatively acute onset fatigue, dyspnea, or edema**.
10. **Autoimmune and inflammatory.** Lupus, rheumatoid arthritis, vasculitis, and other rheumatologic disorders are also associated with pericarditis.

B. Clinical presentation

1. **Signs and symptoms**
   - **a.** Chest pain from pericarditis is described as a severe, sharp retrosternal pain that may radiate to the neck, shoulders, and back, worsening when lying supine, coughing, or during inspiration. The pain may be alleviated when the patient leans forward.
   - **b.** There may be a **prodrome of fever and myalgias**.
   - **c.** Dyspnea may result from shallow breathing due to inspiratory chest pain.
   - **d.** Patients with **purulent pericarditis** may appear toxic with **high fevers, shaking chills, and night sweats**.

e. Tuberculous pericarditis is characterized by gradual onset of symptoms with chronic, nonspecific, constitutional symptoms such as **fever, chills, and night sweats**.

2. **Physical findings**
   a. The **pericardial friction rub is the major clinical finding in pericarditis,** but it is not present in all cases. It is described as a **scratchy, grating, and high-pitched sound**. The rub is often evanescent, changes in quality and intensity on serial examinations, and may be accentuated with deep respiration. Classically, it has **three components**, corresponding to atrial systole, ventricular systole, and early ventricular diastole. Most often, however, it is a **biphasic** rub consisting of the atrial and ventricular systolic components.
   b. **Auscultation of the rub is ideally performed** using the diaphragm of the stethoscope **at the left lower sternal border** during inspiration, with the patient leaning forward.

C. **Laboratory examination and diagnostic testing.** Pericarditis is a **clinical diagnosis based on history, physical examination, chest radiograph, and serial electrocardiographic changes**. Based on the clinical scenario, some patients may require further testing, such as tuberculin skin testing, fungal tests, viral serologies, cold agglutinins, thyroid function tests, heterophile antibodies, antinuclear antibodies, rheumatoid factor, bacterial culture, and cytology.

1. **Electrocardiography.** The associated electrocardiographic changes evolve through **four stages** (Table 40.2). Although these changes occur in most patients, their **absence does not exclude acute pericarditis**, particularly in patients with neoplastic or tuberculous pericarditis.
   a. The first stage usually occurs within hours of the onset of chest pain and is diagnostic of acute pericarditis (Fig. 40.1). The presence of **stage 1 electrocardiographic changes is most useful in confirming the diagnosis of acute pericarditis,** yet such changes are often **difficult to distinguish from changes associated with early repolarization and acute infarction**. There is **diffuse ST-segment elevation with upright T waves** in all leads

TABLE 40.2 Typical Electrocardiographic Evolution of Acute Pericarditis

Stage	J-ST	T waves	PR segment
"Epicardial" leads (I, II, aVL, aVF, and V_3–V_6)			
I	Elevated	Upright	Depressed or isoelectric
II (early)	Isoelectric	Upright	Isoelectric or depressed
II (late)	Isoelectric	Low to flat to inverted	Isoelectric or depressed
III	Isoelectric	Inverted	Isoelectric
IV	Isoelectric	Upright	Isoelectric
"Endocardial" leads (aVR, often V1, and sometimes V2)			
I	Depressed	Inverted	Elevated or isoelectric
II (early)	Isoelectric	Inverted	Isoelectric or elevated
II (late)	Isoelectric	Shallow to flat to upright	Isoelectric to elevated
III	Isoelectric	Upright	Isoelectric
IV	Isoelectric	Inverted	Isoelectric

Modified from Spodick DH. Electrocardiographic changes in acute pericarditis. *Am J Cardiol*. 1974;33:470.

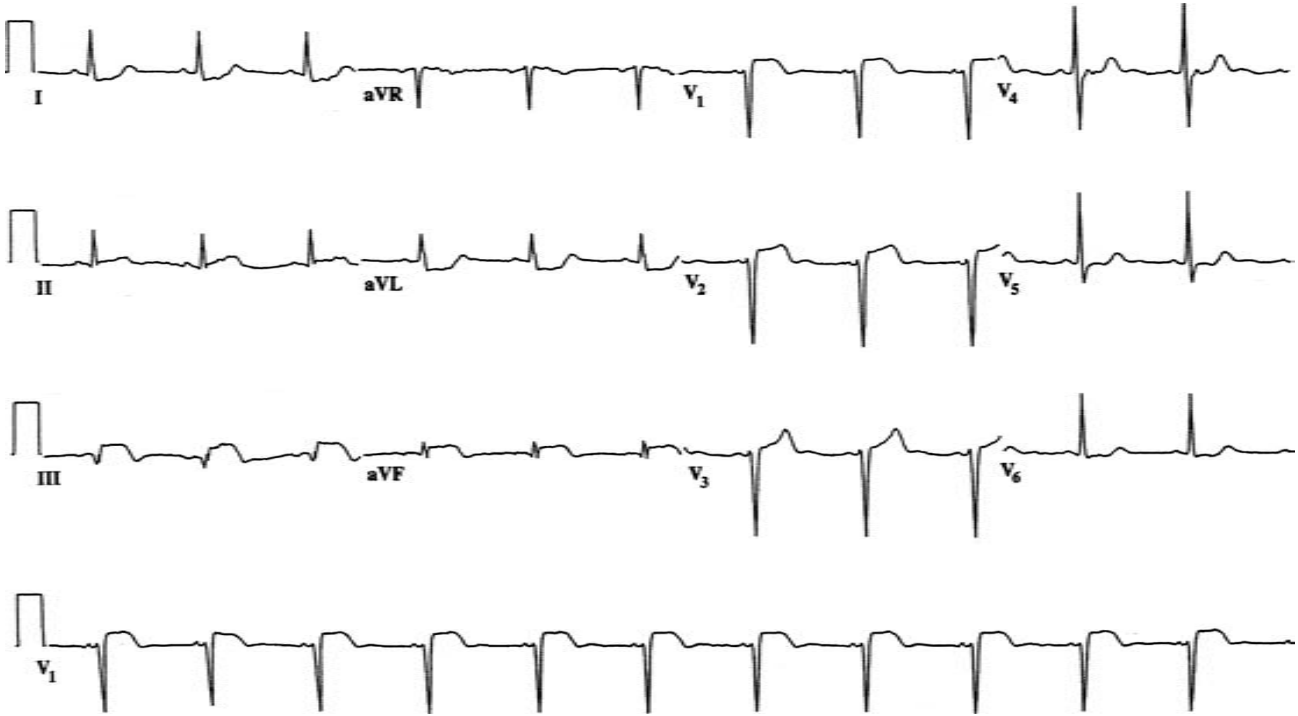

FIGURE 40.1 Stage 1 electrocardiographic changes in acute pericarditis. Note PR segment elevation in lead aVR, and diffuse ST elevation and the upsloping nature of ST segments as compared with acute myocardial infarction.

except aVR and V_1. **PR-segment depression** is seen in all leads except aVR and V_1. There is often PR-segment elevation in lead aVR (the "knuckle" sign).

b. Stage 2, which occurs several days later, is characterized by resolution of PR/ST segments to baseline and T-wave flattening.

c. The T-wave inversions mark **stage 3**.

d. Stage 4 occurs when T waves become upright again, which may take days to weeks.

e. With a large **effusion,** the electrocardiogram (ECG) may show **electrical alternans or low voltage**.

2. A chest radiograph may reveal **cardiomegaly** and may yield important information in support of tuberculous or neoplastic processes.

3. Blood cultures along with sputum and gastric aspirate for tuberculosis should be done where such a diagnosis of purulent or tuberculous pericarditis is suspected (including in immunosuppressed immigrants). Pericardial or pleural biopsy may be necessary to diagnose tuberculosis.

4. Blood tests may reveal leukocytosis or an elevated erythrocyte sedimentation rate, which are nonspecific markers of inflammation. Mild **elevations in the** creatine kinase myocardial band **(CK-MB) fraction or cardiac troponin levels can be seen** and suggest a more extensive acute inflammatory process involving the epicardium; significant elevations in these markers should raise suspicion for more extensive myocardial involvement, referred to as **myopericarditis**.

5. Echocardiography

a. Pericarditis is not an echocardiographic diagnosis and a normal echocardiogram does not preclude pericarditis. Echocardiography should be performed when **symptoms last longer than a week, to evaluate for hemodynamic abnormalities**.

b. If the patient has had **recent cardiac surgery,** is **elderly,** or if there is a **suspicion for pericardial effusion, echocardiography** should be done as **part of the initial workup**.

6. Computed tomography (CT), magnetic resonance imaging (MRI), or transesophageal echocardiography (TEE) can be done in select cases for further investigation of the pericardium (refer to Chapters 52, 51, and 68, respectively, for detailed discussions on these modalities).

D. Differential diagnosis

1. Chest pain from acute pericarditis can mimic **aortic dissection, pulmonary embolism, pneumothorax, or acute coronary syndrome**.

2. Electrocardiographic changes can also mimic **myocardial ischemia**; however, the ST segments of pericarditis are usually concave upward with upright T waves. Echocardiography may assist in distinguishing between pericarditis and ischemia by assessing for segmental wall motion abnormalities, which are usually absent in pericarditis.

E. Therapy. Most cases of acute pericarditis are **uncomplicated and self-limited and such patients can be managed in the outpatient setting. However, inpatient management should be considered in patients with large pericardial effusion or coexisting myocarditis**. These typically respond to conservative medical therapy. First-line therapy usually consists of **nonsteroidal anti-inflammatory drugs** (NSAIDs) **with the addition of colchicine in some cases**.

1. Medical therapy

a. Ibuprofen has a good safety profile and is a reasonable first-line therapy at doses of 600 to 800 mg orally three times a day for at least 2 weeks. A**spirin** 650 mg orally every 6 to 8 hours for 2 to 4 weeks is an alternative therapy. Other NSAID agents, including naproxen, seem to be similarly efficacious.

b. If the **patient does not respond to NSAIDs**, or in cases of recurrent pericarditis, **colchicine** should be considered in addition to NSAIDs. A randomized controlled trial, colchicine for acute pericarditis (COPE), of 120 patients

with a first episode of acute pericarditis demonstrated superior efficacy of a combined regimen of aspirin with colchicine. The usual dosing of colchicine is 1 to 2 mg for the first day and then 0.5 to 1 mg daily for 3 months.

c. **Prednisone** should be used only in patients with recurrent pericarditis with persistent symptoms despite NSAIDs and colchicine therapy or in cases where there is an underlying inflammatory disease that is responsive to corticosteroid therapy. Prednisone should be dosed at 1 to 1.5 mg/kg for at least 1 month and should be tapered slowly. In the COPE trial, **corticosteroid therapy was an independent risk factor for recurrence**.

d. **Post-MI pericarditis patients should *not* be treated with prednisone**, given the risk of myocardial rupture. Treatment with aspirin is recommended (650 mg every 6 hours).

e. In cases of suspected **purulent pericarditis, empiric antibiotic therapy directed against staphylococci and streptococci** should be instituted while cultures are pending.

f. For **tuberculous pericarditis**, standard triple drug therapy is recommended for at least 9 months, with 6 months of treatment following culture conversion.

g. Pericarditis due to Dressler's syndrome should be managed with NSAIDs or aspirin. If the condition is recurrent, a trial of prednisone may be warranted.

h. Intensive dialysis is the treatment of choice for symptomatic uremic pericarditis. **Dialysis is not necessary for patients who are asymptomatic** with relatively small pericardial effusions.

2. **Percutaneous therapy**

a. Because most cases of pericarditis are self-limited, there is no role for routine pericardiocentesis, intrapericardial administration of steroids, or pericardial biopsy.

b. In cases complicated by tamponade or suspected purulent effusion or neoplasm, pericardiocentesis should be performed. Pericardiocentesis should be reserved for large, hemodynamically compromising pericardial effusions or when fluid is needed for diagnostic purposes.

c. If the etiology is uncertain, **pericardial fluid should be sent for a hematocrit and a white blood cell count with differential, glucose, protein, cytologic, and microbiologic analyses (e.g., culture for various organisms and AFB staining)**. If there is a clinical suspicion of purulent pericarditis, pericardiocentesis should be performed promptly and the fluid sent for culture. If the pericardial fluid is **serosanguineous or grossly bloody**, the clinician should send it for cytologic examination, culture, and AFB staining.

3. **Surgical therapy**

a. Subxiphoid pericardiostomy is usually performed for neoplastic pericarditis with rapidly recurrent pericardial effusions. Sclerotherapy with tetracycline has been performed in severe cases of neoplastic pericarditis; however, the procedure is painful and is associated with arrhythmias and risk for constrictive pericarditis.

b. Pericardiectomy is reserved for severe recurrent pericarditis. More commonly it is employed in the management of constrictive pericarditis, as discussed later in this chapter.

F. Follow-up

1. Most patients with idiopathic or viral pericarditis **should receive 1-month follow-up** to ensure that their symptoms have resolved and that no evidence of constrictive pericarditis exists.

2. Patients with pericardial effusions should have serial echocardiograms to assess for recurrence or an increase in the size of the effusion.

G. Prevention of postpericardiotomy syndrome (PPS). In a recent multicenter, double-blind, randomized trial, colchicine was found to be useful in preventing PPS and its related complication; however, this approach has not been widely used because of the relatively low incidence of clinically significant PPS.

H. Complications

1. **Recurrent pericarditis** can occur after an episode of acute idiopathic pericarditis, open heart surgery, cardiac trauma, or Dressler's syndrome. Natural history studies suggest that **recurrent pericarditis occurs in 20% to 30% of patients**. Recurrent pericarditis may be very bothersome. However, with appropriate management of exacerbations and prophylaxis, it frequently responds favorably and eventually peters out.
   a. Clinical presentation is similar to that of acute pericarditis, with **variable onset** from months to years after the initial episode.
   b. **Therapy.** NSAIDs and colchicine should be administered. **Only if patients fail to respond should prednisone be administered** (1 to 1.5 mg/kg) for at least 1 month and tapered slowly. Intravenous methylprednisolone can be given depending on the severity of symptoms. Most patients respond within a few days but may have recurrence with cessation of steroids. **Surgical pericardiectomy is reserved for patients with persistent recurrent pericarditis accompanied by severe chest pain despite aggressive medical therapy. It too may fail, as it is difficult to remove all of the pericardium surgically**.
   c. **Prevention.** The COPE trial has shown that **colchicine is safe and effective in the prevention of recurrent pericarditis**.
2. Cardiac tamponade will occur in about 15% of patients, most commonly after a cardiac surgical intervention or with neoplasm.
3. **Constrictive pericarditis.** Approximately 9% of patients develop mild constrictive physiology. However, this usually resolves after 3 months. Some patients develop a subacute picture of **effusive–constrictive disease**, with both effusion and pericardial thickening. This may progress to symptomatic pericardial constriction. When it does so, the interval of onset of severe constrictive findings is much more rapid than in constriction without effusive changes.

III. CONSTRICTIVE PERICARDITIS results from **a fibrous thickening of the pericardium** secondary to chronic inflammation from a variety of injuries. Essentially, the **heart is encased by the rigid pericardium**, leading to a decrease in diastolic filling, an increase in intracardiac pressures, and a **dissociation of intracardiac pressure from intrathoracic pressure. The hallmark of pericardial constriction is the equalization of end-diastolic pressures in all four cardiac chambers**. The elevated cardiac pressures and diminished diastolic filling lead to increased venous pressure, both pulmonary and systemic, and thus to progressive **signs and symptoms of right and left heart failure**. Although constrictive pericarditis is a relatively uncommon cause of heart failure, recognition of this entity is important, as its **prevalence appears to be increasing and the diagnosis is often missed.**

A. Causes of constrictive pericarditis. The **factors involved in the development of constrictive pericarditis are varied** and are similar to those of acute pericarditis (Table 40.3). However, there is **a common pathophysiologic pathway** leading to **chronic inflammation and pericardial fibrosis**. Neoplastic disease is an exception because tumor infiltration of the pericardium is often responsible for constriction. The causes of constrictive pericarditis in the decreasing order of frequency are idiopathic factors, radiation therapy, postsurgical therapy, and infectious disease. This represents a significant change from a century ago when infectious disease, specifically tuberculosis, predominated.

1. Since the advent of effective antitubercular medications, the **number of cases attributable to tuberculosis has dropped precipitously in the United States**. However, tuberculosis remains the primary cause of constrictive pericarditis in most developing regions of the world.
2. Similarly, **bacterial infections of the chest** continue to represent a large number of cases on a global scale, but these **have largely disappeared in the United States** following the introduction of antibiotics and improved drainage procedures.
3. Most **"idiopathic"** cases are **likely infectious in nature**, due to viral infections caused by viruses such as **coxsackievirus and echovirus**; however, a clear etiologic

TABLE 40.3 Common Causes of Constrictive Pericarditis

Idiopathic
Infectious diseases
Tuberculosis
Bacterial
Viral (e.g., coxsackievirus B and echovirus)
Fungal
Parasitic
Trauma (including cardiac surgery)
Radiation
Inflammatory/immunologic disorder
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Sarcoidosis
Neoplastic disease
Breast cancer
Lung cancer
Lymphoma
Mesothelioma
Melanoma
End-stage renal disease

link is rarely established. Less common infectious agents include fungal and parasitic organisms.

4. Constrictive pericarditis is a **late complication of radiation therapy,** generally occurring **many years after the administration of radiation**. Risk factors for development of constrictive pericarditis include duration of therapy, total amount of radiation administered, and volume of the heart in the radiation field. In contrast to other causes of constrictive pericarditis, where the myocardium is typically normal in structure and function, there may be **associated radiation damage to the myocardium**.
5. Constrictive pericarditis is a well-documented **late complication of cardiac surgery, including** coronary artery bypass grafting and valvular surgery. **Risk factors** for development of postoperative constrictive pericarditis include **intraoperative hemorrhage into the pericardium, postoperative pericarditis,** and the occurrence of **postpericardiotomy syndrome**.
6. End-stage renal disease, neoplastic disease (primarily breast, lung, and lymphoma), and connective tissue disease are less common causes that must be considered in the initial differential.

B. Pathophysiology. In constrictive pericarditis, there is **thickening and fibrosis of the pericardium with associated perimyocardial tethering,** often with superimposed calcification, resulting in **decreased ventricular compliance** (ventricular compliance = end-diastolic volume/end-diastolic pressure). However, in a small percentage of patients with constrictive pericarditis, the pericardium may not appear thickened on noninvasive imaging.

As the pericardium thickens and limits ventricular compliance, there is an **increased end-diastolic pressure for any given end-diastolic volume**. This increase in pressure **affects both ventricles equally** and effectively decreases diastolic filling and thus end-diastolic volume of both ventricles. The increased pressure is transmitted backward and results in elevated pulmonary venous and systemic venous pressures. **Equalization of end-diastolic pressures in all four cardiac chambers then ensues and is an important characteristic of constrictive pericarditis**.

1. The myocardium is generally normal in structure and function; therefore, **systole is unimpaired**.
2. Diastolic function, on the other hand, **is markedly altered** by the constrictive process. In early diastole, the ventricles expand normally, and there is rapid filling secondary to the elevated pulmonary and systemic pressures. Once the **ventricles reach the confines of the rigid pericardium,** there is an **immediate increase in ventricular pressure** and **diastolic filling comes to an abrupt halt**.
3. The result is that **nearly all ventricular filling occurs in the second phase of diastole (early filling)** with little contribution from the third phase (diastasis) and the fourth phase (atrial systole).

C. Physical signs and symptoms

1. The **early symptoms** of constrictive pericarditis are often insidious, and the patient may have nonspecific complaints such as **malaise, fatigue, and decreased exercise tolerance**.
2. As the disease progresses, **symptoms consistent with systemic congestion and low cardiac output**, such as **marked jugular venous distention, ascites, peripheral edema, and worsening exercise tolerance**, may predominate. Symptoms due to right-sided failure usually predominate over left-sided failure due to equalization of pressures.
3. **Examination of jugular veins.** Nearly all patients have **jugular venous distention**, which simply reflects the elevated right-sided pressures. Many patients demonstrate a lack of inspiratory fall in venous distention, known as **Kussmaul's sign**. This finding is sensitive but lacks specificity, as other conditions such as right ventricular (RV) hypertrophy and RV infarction also produce this sign. Observation of the jugular venous pulsations reveals a **prominent *y* descent that is produced by the rapid ventricular filling in early diastole**. The jugular venous pressure is sometimes so high in constrictive physiology that the level is not evident in the neck on examination with the patient at a 45° angle, and the diagnosis is, therefore, missed. **Appreciation of the height of the pressure may only be evident on examining the patient upright**.
4. **Cardiac examination.** Cardiac auscultation may reveal **muffled heart sounds** due to decreased transmission through the thickened pericardium. Because the mitral and tricuspid valves are nearly closed by the end of diastole, there may be a **soft first heart sound (S_1). Occasionally, one may hear a pericardial knock** in early diastole (60 to 120 milliseconds after the second heart sound [S_2]). This represents the abrupt cessation of diastolic filling that occurs when further ventricular relaxation is impeded by the rigid pericardium. The pericardial knock **must be differentiated from other early diastolic sounds** such as an opening snap, third heart sound (S_3), and tumor plop. In general, the **pericardial knock is of a higher frequency, is heard best with the stethoscope diaphragm, and occurs slightly earlier than an S_3**. An opening snap may be similar in frequency and timing but is nearly always followed by a diastolic rumble.
5. **Pulmonary examination.** Auscultation of the lung fields may reveal **decreased breath sounds at the bases**, attributed to pleural effusions.
6. **Abdominal examination.** The abdominal examination may reveal evidence of right-sided heart failure, with **hepatomegaly and splenomegaly** being frequently noted. In **severe cases, there may be** liver dysfunction and **ascites**.

7. **Examination of the extremities.** Elevated central venous pressures due to RV impairment and sodium retention due to left ventricular (LV) impairment contribute to the development of **peripheral edema**.

D. Diagnostic testing. Confirming the diagnosis of constrictive pericarditis often presents a challenge, since no gold standard test exists. **The clinician must rely on a collection of findings from multiple diagnostic modalities to detect both anatomic and pathophysiologic abnormalities**. Perhaps, the greatest challenge lies in differentiating constrictive pericarditis from restrictive cardiomyopathy.

1. **Electrocardiography.** Low voltage is frequently seen with **generalized flattening of the T waves**. There may be **left atrial enlargement. Atrial fibrillation** is a common finding.
2. **Chest radiograph.** Pericardial calcification is relatively common in advanced disease. The calcification is usually best appreciated with a lateral film and frequently involves the right ventricle and atrioventricular groove. **Pleural effusions** occur frequently, and there may be evidence of both **left and right atrial enlargement**.
3. **Two-dimensional echocardiography**
   a. **Septal bounce.** This is the **sudden cessation of septal motion**, as the heart abruptly stops filling upon meeting the rigid pericardium.
   b. **Ventricular interdependence.** This is due to the fixed space in which cardiac filling occurs. Preferential filling of the right ventricle on inspiration causes the septum to move to the left, whereas on expiration the augmentation of LV filling causes the septum to move to the right.
   c. **Inferior vena cava (IVC) plethora.** IVC is typically dilated and does not collapse, due to elevated right-sided pressures.
4. **Doppler echocardiography.** Although imaging findings may suggest pericardial constriction, most of the findings described previously are relatively low in sensitivity and specificity. Doppler assessment of diastolic flow patterns and the respiratory changes in these patterns may provide **significant evidence for the presence of constrictive physiology** and assist in helping **exclude competing diagnoses**, such as restrictive cardiomyopathy.
   a. **Respiratory variation in mitral and tricuspid flows.** In constrictive pericarditis, the thickened pericardium isolates the cardiac chambers from respiratory changes in intrathoracic pressures.
      (1) During **inspiration**, the drop in intrathoracic pressure is transmitted to the pulmonary veins, but not to the left ventricle. This reduces the pressure gradient required for diastolic filling of the left ventricle; therefore, a **decrease in mitral flow is observed during inspiration**. Conversely, there is an **increased tricuspid flow during inspiration. Findings suggestive of constrictive physiology include the following**:
         (a) **Mitral valve inflow.** Peak E velocity decreases by 33% or greater (Fig. 40.2).
         (b) **Tricuspid valve inflow.** Peak E velocity increases by 44% or greater and peak A velocity increases by 38% or greater (Fig. 40.3).
      (2) **Opposite changes are seen with expiration.** Increased intrathoracic pressure is transmitted to the pulmonary veins and this increases the driving pressure for LV filling. There is a **decreased tricuspid flow. The wide respiratory variation in peak E velocities helps to differentiate constrictive pericarditis from restrictive cardiomyopathy, in which *minimal* respiratory variation occurs** (Figs. 40.2 and 40.3).
   b. **Pulmonary venous flow.** In a healthy individual, pulmonary venous flow consists of a peak velocity during ventricular systole (S wave) and a smaller peak velocity during ventricular diastole (D wave). There is normally little respiratory variation in these velocities. In constrictive pericarditis, there is an increase in early diastolic flow manifested as a larger D wave; therefore, the **pulmonary systolic/diastolic (S/D) flow ratio is decreased**. In addition, **both systolic**

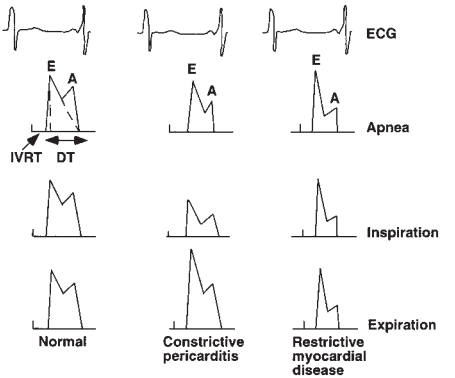

FIGURE 40.2 Respiratory variation in flow across the mitral valve in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. The peak early diastolic filling velocity is denoted as E and the peak late diastolic filling velocity (from atrial contraction) is denoted as A. The isovolumic relaxation time (IVRT) is the period between aortic valve closure and mitral valve opening. The deceleration time (DT) is the time it takes to go from peak E velocity to cessation of flow. In constrictive pericarditis, expiration results in a decreased IVRT and a marked increase in peak E and peak A velocities across the mitral valve. Similar changes are not observed in normals and those with restrictive disease. Patients with restriction have an increased E/A and shortened DT; however, there is no significant respiratory variation. ECG, electrocardiogram. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

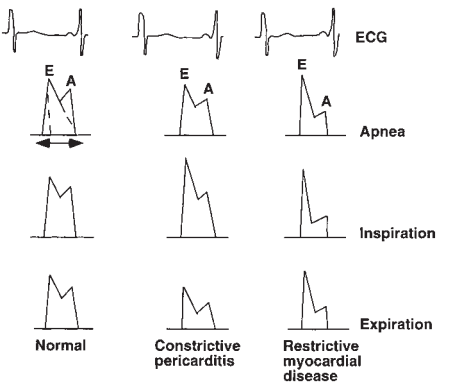

FIGURE 40.3 Respiratory variation in flow across the tricuspid valve in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. Constrictive pericarditis results in changes in flow across the tricuspid valve that are opposite to those described for the mitral valve in Figure 40.2. In constrictive pericarditis, inspiration results in increased peak E and peak A velocities across the tricuspid valve. Similar changes are not observed in normals and those with restrictive cardiomyopathy. Patients with restriction have an increased E/A and shortened DT; however, there is no significant respiratory variation. ECG, electrocardiogram. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

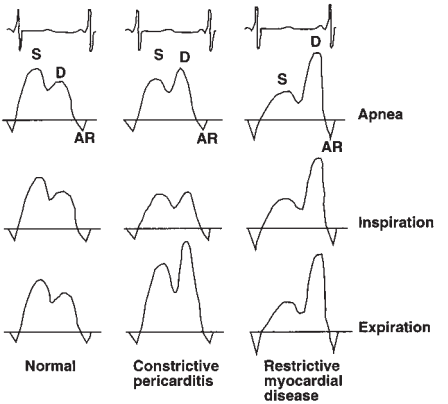

FIGURE 40.4 Respiratory variation in pulmonary venous flow in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. The peak pulmonary venous velocities during systole are denoted as the S wave and peak diastolic velocities are denoted as the D wave. The AR wave represents the small reversal in flow that is noted with atrial contraction. In constrictive pericarditis, there is a slight decrease in the S/D ratio and a marked increase in both velocities during expiration as compared with inspiration. This respiratory variation in pulmonary venous flows is not observed in normal individuals or those with restrictive disease. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

and diastolic pulmonary venous flows are markedly increased during *expiration*. This increase in expiratory pulmonary venous flow assists in distinguishing constrictive pericarditis from restrictive cardiomyopathy (Fig. 40.4).

c. Respiratory variation in hepatic vein flow. Hepatic venous flow reflects right-sided filling in much the same manner that pulmonary venous flow reflects left-sided filling. It is represented similarly by an S wave and a D wave, as well as a reversal in flow in atrial systole (AR wave) and a reversal in flow due to late ventricular systole (VR wave). Individuals with constrictive pericarditis and those without have a more prominent systolic flow than a diastolic flow; however, individuals without constrictive pericarditis have little respiratory variation in these flow velocities. **In constrictive pericarditis, there is a marked increase in the D wave during inspiration and a significant blunting during expiration. Expiration also results in prominent diastolic flow reversal demonstrated by increase in AR and VR.** In restrictive disease there is a reversal in systolic-to-diastolic flow ratios, but no respiratory variation exists in these flow velocities (Fig. 40.5).

d. Doppler tissue imaging

(a) Myocardial relaxation, and thus annular velocity, is typically **reduced in restrictive cardiomyopathies**, but the Doppler velocities of the medial mitral valve annulus in early diastole are **normal or slightly increased** in constrictive pericarditis. The pattern of these velocities is altered in constrictive pericarditis (Fig. 40.6). In normal individuals, peak early diastolic annular tissue velocity (E′) at the lateral mitral annulus is higher than that at the medial mitral annulus. **This relationship between the lateral and medial mitral annuli is reversed ("annulus reversus") in constriction, where E′ at the lateral mitral annulus is typically lower than E′ at the medial mitral annulus.** This is attributed to tethering of the LV lateral free wall to the pericardium in constriction. Similar effects of perimyocardial tethering on the RV free wall have been reported. These patterns

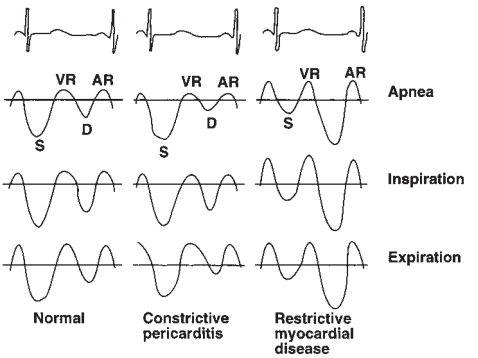

FIGURE 40.5 Respiratory variation in hepatic vein flow in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. Similar to pulmonary vein flow, the S wave represents peak systolic flow velocity and the D wave represents peak diastolic flow velocity. VR denotes the reversal in flow noted in late systole, and AR is the reversal in flow due to atrial contraction. In both normal subjects and those with constrictive pericarditis, there is an increase in both S and D waves with inspiration. During expiration, there is little change in normal subjects; however, those with constrictive pericarditis will have a marked drop in both S and D waves and an increase in both VR and AR. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol*. 1993;22:1935–1943.

may not occur in all cases of constrictive pericarditis because of the heterogeneity of tethering (annular sparing constriction) and coexisting myocardial disease.

(b) In restrictive cardiomyopathies, the early diastolic annular velocity is characteristically **low at both medial and lateral mitral annuli** (< 8 cm/s).

5. **Cardiac catheterization.** The hemodynamics obtained in the catheterization laboratory assists in both diagnosing constrictive pericarditis and differentiating it from restrictive cardiomyopathy. In general, both right and left heart catheterization are performed to obtain simultaneous ventricular pressure readings.

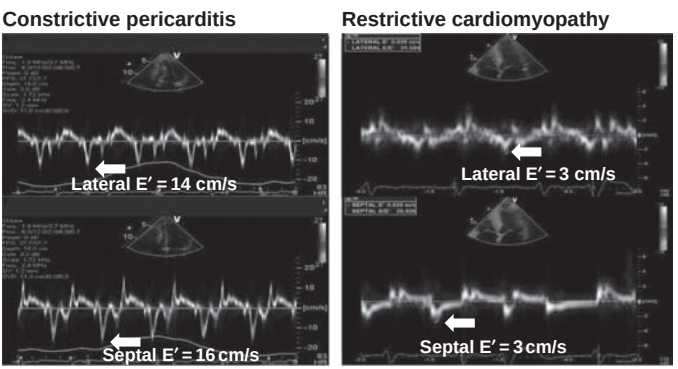

FIGURE 40.6 Annular tissue velocities from two patients. Note that tissue velocities are lower in restrictive cardiomyopathy compared with constrictive pericarditis. In addition, lateral E′ is lower than septal E′ in constrictive pericarditis, which is attributable to perimyocardial tethering of the lateral left ventricular free wall.

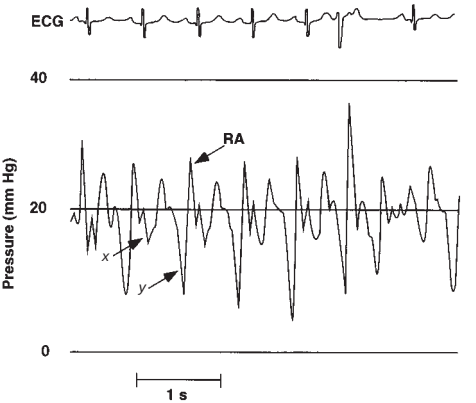

FIGURE 40.7 Right atrial (RA) pressure waveform in constrictive pericarditis. The preserved *x* descent and the prominent *y* descent contribute to the classic W-shaped atrial waveform. Adapted from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Baltimore, MD: Williams & Wilkins; 1996:801–822. ECG, electrocardiogram.

a. Atrial pressures. The right atrial pressure waveform has been described as having a **W-shaped configuration**. This morphology is produced by a prominent *a* wave as the atria contract against an elevated ventricular pressure, an exaggerated *x* descent, and a steep *y* descent, due to rapid ventricular filling in early diastole (Fig. 40.7).

b. Ventricular pressures

(1) Ventricular pressure waveforms demonstrate the classic **dip-and-plateau** physiology, commonly referred to as the **square root sign** (Fig. 40.8).

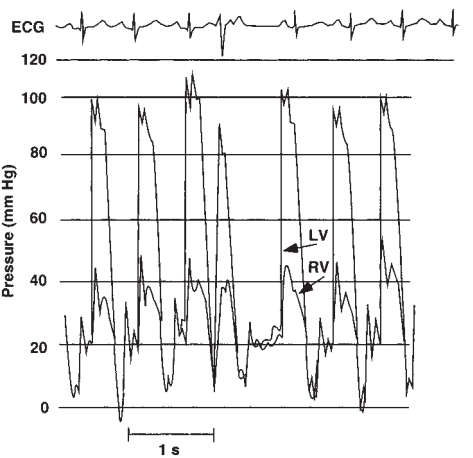

FIGURE 40.8 Right and left ventricular waveforms in constrictive pericarditis. Note the equalization of left ventricular and right ventricular end-diastolic pressures, generally within 5 mm Hg of one another. The rapid early diastolic filling and subsequent abrupt cessation of flow due to the rigid pericardium produces a dip-and-plateau waveform (square root sign), appreciated best in this waveform following the premature ventricular contraction. LV, left ventricular; RV, right ventricular; ECG, electrocardiogram. Adapted from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Baltimore, MD: Williams & Wilkins; 1996:801–822.

(2) The initial downward deflection reflects the drop in pressure during the isovolumetric relaxation period. The subsequent upward deflection reflects early diastolic filling. The terminal plateau represents the cessation of flow that occurs once the limit of the rigid pericardium has been reached.

(3) The end-diastolic pressures of both ventricles are not only elevated but also equal, with a < 5 mm Hg difference between the two. The RV systolic pressure is generally < 55 mm Hg, with an RV end-diastolic pressure that is one-third greater than the RV systolic pressure. **These findings assist in differentiating constrictive pericarditis from restrictive cardiomyopathy, where RV systolic pressure is often elevated to > 55 mm Hg.**

(4) **Meticulously performed cardiac catheterization can demonstrate ventricular interdependence, which is a hallmark of constrictive pericarditis and is most useful in differentiating constrictive pericarditis from restrictive cardiomyopathy**. The ratio of the RV to LV systolic pressure–time area during inspiration versus expiration (systolic area index) has been shown to be a useful measure of enhanced interventricular interaction (Fig. 40.9).

(5) **Hypovolemia can mask characteristic features of constrictive pericarditis, and fluid challenge in the cardiac catheterization laboratory may be required to unmask ventricular interdependence in patients who are volume depleted**.

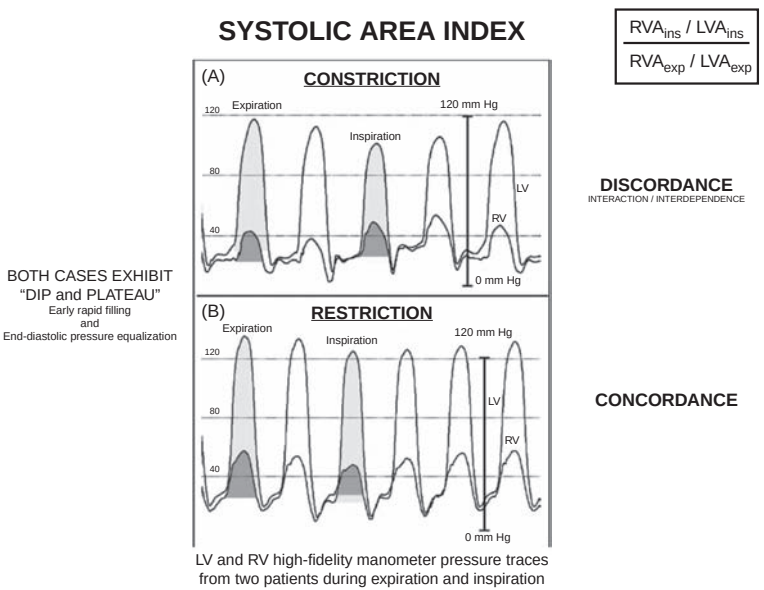

FIGURE 40.9 Respiratory ventricular interaction between RV and LV systolic area indexes in patients with constriction (A) and restriction (B). Note that in constrictive pericarditis patients (A), there is a rise in the area of RV pressure curve (darker-shaded area) and reduction in the area of LV pressure curve (lighter-shaded area), whereas in restrictive cardiomyopathy patients, there is a drop in the area of RV pressure curve during inspiration, with no change in the area of LV systolic pressure curve. LV, left ventricular; RV, right ventricular. RVA_{ins}, RV systolic area in inspirations; RVA_{exp}, RV systolic area in expirations; LVA_{ins}, LV systolic area in inspirations; LVA_{exp}, RV systolic area in expirations; Adapted from *J Am Coll Cardiol.* 2008;51:315-319.

(6) Role of cardiac CT and MRI in constrictive pericarditis

(a) Cardiac CT in constrictive pericarditis provides a superior three-dimensional delineation of the pericardium in comparison with echocardiography. A thickened pericardium > 4 mm is supportive of the diagnosis, although normal pericardial thickness does not exclude constrictive pericarditis. In a series reported by Talreja et al., (1) 18% of constrictive pericarditis patients had normal pericardial thickness. Cardiac CT is the best modality for assessing pericardial calcification, which may assist in surgical planning.

(b) Cardiac magnetic resonance imaging (CMR) provides both anatomical and hemodynamic information in constrictive pericarditis, without the radiation exposure that is associated with cardiac CT. Like echocardiography, MRI may demonstrate features of ventricular interdependence such as septal bounce and respirophasic variation in septal excursion. In addition, MRI is the best modality to assess pericardial inflammation, where an initial trial of medical therapy may be considered. Furthermore, MRI is excellent at tissue characterization, quantifying LV and RV systolic function, which is of value in patients where there is diagnostic uncertainty and restrictive myocardial disease is a consideration. CMR should be the non-invasive imaging modality of choice in a patient who is suspected to have constrictive pericarditis but has a nondiagnostic echo. The main limitation of MRI is that it cannot be performed in patients with MRI-incompatible implants or devices. MRI is also inferior to cardiac CT in assessing pericardial calcification.

(7) Differentiating constriction from restriction

In clinical practice, it is often challenging to differentiate constrictive pericarditis from restrictive cardiomyopathy, as both present as heart failure with preserved ejection fraction. Poor LV filling in constrictive pericarditis results from external constraints of a rigid pericardium, whereas a small LV cavity with impaired LV relaxation is usually the cause of diastolic dysfunction in restrictive cardiomyopathy. It is critical to differentiate between the two because of the different treatment strategies. Constrictive pericarditis is a potentially curable disease, whereas treatment options in restrictive cardiomyopathy are often limited to medical therapy. Despite the hemodynamic similarities, there are several key findings by echocardiography, cardiac catheterization, and CMR that can be used to differentiate these two clinical entities and are described in Table 40.4.

(8) Practical approach to diagnosing constrictive pericarditis

Basic workup of a patient with clinical features of constrictive pericarditis includes ECG and chest x-ray, which may reveal calcification. This should be followed by comprehensive echocardiography with a respirometer. If there is evidence of calcification on x-ray and echocardiography and there are convincing features of calcific constrictive pericarditis, then the patient may be directly referred to a cardiac surgeon. Some surgeons desire a preoperative right heart catheterization not only to confirm the diagnosis but also to get an accurate assessment of the cardiac index, which may assist in surgical planning. CMR should be strongly considered in cases where the echocardiogram is nondiagnostic and in patients where transient constriction is suspected. CMR will not only confirm the diagnoses of constrictive pericarditis but also assess pericardial inflammation. There is emerging evidence supporting medical therapy with anti-inflammatory medication as an initial strategy in a patient with inflamed constrictive pericarditis or effusive–constrictive disease. Cardiac CT should be limited to patients who

TABLE 40.4 Key Findings Used to Differentiate Constriction from Restriction

Investigation	Constrictive pericarditis	Restrictive cardiomyopathy
Echocardiography		
Annular tissue velocity (E′)	Preserved except at lateral mitral annulus and right lateral tricuspid annulus	Reduced
Diastolic dysfunction	Present	Present
Respirophasic interventricular septal shift	Present	Absent
Respirophasic variation in transvalvular/hepatic vein flow	Present	Absent
LV wall thickness	Normal	Normal or increased
Perimyocardial slippage (motion of LV, RV, and atrial free wall)	Reduced	Normal or reduced
Cardiac catheterization		
Elevated LVEDP	Present (equalization of diastolic pressures in all four chambers that are more suggestive of constriction)	Present
LV/RV discordance	Present	Absent
Cardiac MRI		
Respirophasic shift of interventricular septum	Present	Absent
Pericardial thickening or enhancement	Normal or increased	Normal
Myocardial scarring detected by post-gadolinium enhancement	Absent unless coexisting cardiomyopathy	Present

LV, left ventricular; RV, right ventricular; LVEDP, left ventricular end-diastolic pressure; MRI, magnetic resonance imaging.

are unable to undergo CMR or cases where three-dimensional assessments of pericardial calcification are warranted for surgical planning.

E. Therapy. Pericardiectomy is preferred in most cases, although there are certain patient populations in which medical therapy is appropriate.

1. Medical therapy

a. Patients who have NYHA class I symptoms may initially be treated with diuretics and a low sodium diet. One case series of 36 patients demonstrated resolution of pericardial constriction with the use of NSAIDs, colchicine, and/or steroids. However, most of these patients ultimately require pericardiectomy.

b. Medical therapy is also appropriate in **patients with severe comorbid illnesses** that limit life expectancy and/or place them at an unacceptably high risk for operative mortality. In addition trial of medical therapy maybe appropriate in inflammatory constrictive pericarditis.

2. **Surgical therapy**
   a. The treatment of choice is pericardiectomy. More than 90% of patients will report symptomatic improvement following the procedure.
   b. However, pericardiectomy carries an **operative mortality** that is reported to range from **5% to 20%**. The etiology of constrictive pericarditis can predict perioperative mortality. Patients who have constriction due to viral or idiopathic pericarditis have better outcomes than those who have radiation-induced constriction. Those patients with a poor preoperative functional class are at highest risk for perioperative death; therefore, most physicians advocate **early surgical intervention**.

IV. PERICARDIAL EFFUSION is a common clinical entity that is routinely diagnosed using echocardiography. It may be asymptomatic or present as life-threatening tamponade. **The presenting syndrome depends on the volume, the rate of accumulation, and the characteristics of the fluid**. Large effusions may be found unexpectedly and be asymptomatic, whereas rapidly accumulating small effusions may result in tamponade. An unstretched pericardium accommodates only 80 to 200 mL of rapidly accumulating fluid, without a significant change in hemodynamics. In contrast, the pericardial space may accumulate up to 2 L of fluid without any hemodynamic or clinical sequelae if this occurs slowly. **Compressive physiology** may occur with rapid accumulation of smaller amounts of fluid if the pericardium is stiff from fibrosis or infiltration by a tumor.

A. Clinical presentation

1. Slowly developing pericardial effusions, with no elevation of intrapericardial pressures, are **usually asymptomatic**.
2. Patients may complain of a **constant dull ache or pressure in the chest**.
3. There may also be a variety of symptoms from the space-occupying effects of the pericardial fluid on other organs in the chest. These include **dysphagia** from esophageal compression, **dyspnea** from lung compression and atelectasis, **hiccups** from compression of the phrenic nerve, and **nausea and abdominal fullness** from pressure on adjacent abdominal organs.
4. Large volume effusions may be associated with muffled heart sounds, Ewart's sign (dullness to percussion, bronchial breath sounds, and egophony below the angle of the left scapula), and rales in the lung field secondary to compression.
5. **Sinus tachycardia and hypotension are signs of hemodynamic compromise.**
6. **Patients with tamponade will have a pulsus paradoxus > 10 mm Hg**. The total intrapericardial volume is fixed; therefore, during inspiration, filling of the right ventricle pushes the septum into the left ventricle. This impairs left-sided filling, and there is a drop in systolic pressure during inspiration. Pulsus paradoxus is **not specific to cardiac tamponade** but may be seen in severe obstructive pulmonary disease, RV infarction, pulmonary embolism, or asthma.
7. Patients with tamponade will have jugular venous distention, and the *x* descent is typically the predominant waveform. **Beck's triad** includes jugular venous distention, distant heart sounds, and hypotension.

B. Etiology. Any cause of acute or chronic pericarditis (Table 40.5) may lead to the development of a pericardial effusion. Common causes of large chronic effusions include idiopathic pericarditis, uremia, pericarditis from malignancy or myxedema, congestive heart failure, nephrotic syndrome, cirrhosis, hypothyroidism, postcardiac surgery, and certain medications.

C. Laboratory examination and diagnostic testing

1. **Electrocardiogram.** The classic electrocardiographic finding consists of a **low-voltage tracing. Electrical alternans** is a marker of a massive pericardial effusion.
2. Chest radiography. **Increase in cardiothoracic ratio may occur if > 250 mL of fluid has accumulated. Increase in cardiothoracic ratio** with a large prominent superior vena cava, azygous vein, and decreased pulmonary vascularity should suggest the diagnosis of pericardial effusion.

TABLE 40.5 Causes of Pericardial Effusion

- Idiopathic
- Acute myocardial infarction
- Delayed postmyocardial–pericardial injury syndromes
  - Postmyocardial infarction syndrome (Dressler's syndrome)
  - Postpericardiotomy syndrome
- Metabolic
  - Uremia
  - Myxedema
  - Hypoalbuminemia
- Radiation
- Dissecting thoracic aneurysm
- Trauma
  - Pericardiotomy
  - Indirect trauma to the chest
  - Percutaneous cardiac interventions
  - Perforation of the heart by indwelling catheters
- Viral infections
  - Coxsackieviruses A, B5, and B6
  - Echovirus
  - Adenovirus
  - Mumps virus
  - Hepatitis B virus
  - Infectious mononucleosis
  - Influenza
  - *Lymphogranuloma venereum*
  - Varicella
  - Human immunodeficiency virus
- Bacterial infections
  - *Staphylococcus*
  - *Streptococcus*
  - *Pneumococcus*
  - *Haemophilus influenzae*
  - *Neisseria gonorrhoeae*
  - *Neisseria meningitidis*
  - *Legionella pneumophila*
  - Tuberculosis
  - *Salmonella*
  - Psittacosis
  - Tularemia
  - Bacterial endocarditis
- Fungal infections
  - Histoplasmosis
  - Aspergillosis
  - Blastomycosis
  - Coccidioidomycosis
  - Fungal endocarditis
- Other *infections*
  - Amebiasis
  - *Echinococcus*
  - Lyme disease
  - Mycoplasma pneumonia
  - Rickettsia
- Tumors
  - Primary
    - Mesothelioma
    - Teratoma
    - Fibroma
    - Leiomyofibroma and sarcoma
    - Lipoma and angioma
  - Metastatic
    - Breast carcinoma
    - Bronchogenic carcinoma
    - Lymphoma
    - Leukemia melanoma
    - Others
- Immunologic/inflammatory disorders
  - Rheumatic fever
  - Systemic lupus erythematosus
  - Ankylosing spondylitis
  - Rheumatoid arthritis
  - Vasculitis
  - Wegener's granulomatosis

(*Continued*)

TABLE 40.5 Causes of Pericardial Effusion (*Continued*)

Polyarteritis nodosa	Hydralazine
Scleroderma	Heparin
Dermatomyositis	Warfarin
Sarcoidosis	Phenytoin
Inflammatory bowel disease	Phenylbutazone
Whipple's disease	Cromolyn sodium
Behçet's syndrome	Dantrolene
Reiter's syndrome	Methysergide
Temporal arteritis	Doxorubicin
Amyloidosis	Penicillin
Familial Mediterranean fever	Minoxidil
Drugs	Colony-stimulating factor
Procainamide	Interleukin-2

3. Transthoracic echocardiogram (TTE) is the **modality of choice** for diagnosing and following pericardial effusions. It allows for accurate diagnosis, ensures the adequacy of drainage procedures, and enables a qualitative assessment in following pericardial effusions. Echocardiography is **not** useful in differentiating among the different etiologic factors.

a. Two-dimensional echocardiographic findings are as follows:

(1) An **echo-free space** is found between the visceral and parietal pericardium in both systole and diastole.

(2) The **motion of the parietal pericardium is decreased**.

(3) When the effusion is large, the **entire heart swings in the pericardium**. This swinging or rocking may occur along both the anteroposterior and the mediolateral axes of the heart, and it is thought to be the mechanism for electrical alternans seen on the ECG.

b. The Doppler echo findings in cardiac tamponade are described subsequently.

(1) Small effusions (< 100 mL) tend to localize at the posterior wall distal to the atrioventricular ring. These tend to be < 1 cm in width.

(2) Moderate effusions (100 to 500 mL). A moderate effusion could also be classified as one that surrounds the heart **but is 1 cm or less at its greatest width**.

(3) Large effusions (> 500 mL). Here, although the posterior accumulation continues, the heart seems to settle posteriorly with a greater expansion of the pericardial space laterally, apically, and anteriorly. The **effusion is > 1 cm at its widest point**.

c. The following may mimic a pericardial effusion on two-dimensional echocardiography.

(1) Pericardial fat tends to be **localized anteriorly**. Unless loculated, a pericardial effusion localized to the anterior wall is very rare.

(2) Seventy percent of **pericardial cysts** are found adjacent to the right cardiophrenic junction and adjacent to but separate from the right atrium in the apical four-chamber view.

(3) A pleural effusion can be differentiated from a pericardial effusion by virtue of the **position of the descending thoracic aorta in the parasternal long-axis view**. If the fluid is based in the pericardium, the aorta is displaced posteriorly to the effusion, away from the posterior wall of the left atrium. If the fluid is pleural based, the aorta retains its position immediately below the left atrium. Lung parenchyma may be seen in the pleural fluid.

(4) Other mimics of pericardial effusions are pericardial fibrous bands and pericardial calcification, anterior mediastinal tumors, peritoneal fluid, and a giant left atrium.

4. **Magnetic resonance imaging.** Although not usually required, MRI offers high sensitivity in the detection of pericardial effusions. It outlines the distribution and provides an estimate of the pericardial fluid volume that correlates well with echocardiography. It is very effective in facilitating detection of loculated pericardial effusions and pericardial thickening. Because of its high tissue contrast, MRI allows the visualization of the pericardium in multiple planes. It can also differentiate simple from complex effusions and pericardial fat from pathologic thickening.
5. **Computed tomography.** Using high-resolution axial images, CT provides excellent visualization of the pericardium. The size and distribution of the pericardial effusion are easily obtained using this technique. Moreover, differentiation among blood, exudate, chyle, and serous fluid may be achieved owing to the different attenuation coefficients for these substances.
6. Diagnostic pericardiocentesis and pericardial fluid examination should be considered in patients with large effusions without clear etiology. Aspirated pericardial fluid should be carefully inspected and immediately placed in sterile tubes for biochemical, microbiologic, and cytologic examination.

D. Therapy. The management of pericardial effusions depends on the underlying etiologic factor, volume, and hemodynamic significance.

1. **Pericardiocentesis** (see Chapter 69). Although the cause of the effusion is important, it can often be determined without pericardiocentesis by virtue of the clinical, systemic, and laboratory features of the presenting condition.
   a. Pericardiocentesis is **indicated if malignant, bacterial, mycobacterial, or fungal pericardial effusion is suspected**.
   b. **Pericardiocentesis is an indication in the setting of large pericardial effusion with associated pericardial tamponade (see subsequent text)**.
   c. With large effusions of recent onset, close clinical and echocardiographic follow-up is warranted. Pericardiocentesis **may be warranted in large asymptomatic pericardial effusions** when there are echocardiographic features of early tamponade.
2. Anticoagulation is best avoided until the effusion has resolved.

V. Cardiac tamponade occurs when an increase in pericardial fluid raises intrapericardial pressure and impairs diastolic filling. Cardiac tamponade is characterized by **elevated intracardiac pressures, a progressive limitation of ventricular diastolic filling, and a reduction in cardiac output**.

A. Pathophysiology

1. There appears to be an **inverse relationship between the volume of the pericardial effusion and the cardiac output once a critical volume is reached**. Beyond this, small increments in pericardial volume result in large increases in intrapericardial pressure. This critical volume depends on the compliance of the pericardium, the rate of fluid accumulation, and the status of the pericardial lining (infiltrations, calcification, or fibrosis).
2. The raised intrapericardial pressure results in a **decreased transmural distending pressure that results in decreased diastolic filling**.

3. The **cardiac output is initially maintained** by a heightened adrenergic tone, resulting in a resting tachycardia and peripheral vasoconstriction.
4. In severe tamponade, the compensatory mechanisms fail, resulting in a decreased cardiac output. Reduced coronary perfusion may cause subendocardial hypoperfusion, further compromising the stroke volume and the cardiac output. The finite space around the heart chambers also results in the equalization of filling pressures with that in the pericardium.
5. Following cardiac surgery, localized **pericardial hematoma** rather than fluid may impair filling of the heart. This most commonly occurs around the right atrium, is easily overlooked, and is difficult to diagnose using TTE. TEE should be considered in cases where **pericardial hematoma** is suspected but TTE images are nondiagnostic.

B. Clinical presentation. The signs and symptoms of cardiac tamponade all reflect a low cardiac output: **restlessness, agitation, drowsiness, or stupor; decreased urine output; dyspnea; chest discomfort and syncope or near syncope;** and **weakness, anorexia, and weight loss with a chronic effusion**.

1. **Physical findings**
   - **(a)** Raised central venous pressure. Characterized by a prominent *x* descent and an attenuated or absent *y* descent.
   - **(b)** Tachypnea. Reflects elevated pulmonary venous pressure.
   - **(c)** Tachycardia. Compensatory due to the low output state.
   - **(d)** Diminished heart sounds. Decreased transmission through the fluid-filled pericardium. A pericardial friction rub may be present in some cases.
   - **(e)** Pulsus paradoxus as described previously.
   - **(f) Hypotension (in severe cases)**.

C. Laboratory examination and diagnostic testing

1. TTE should always be performed when the diagnosis of cardiac tamponade is suspected. An echocardiogram may suggest findings consistent with cardiac tamponade, but the clinical diagnosis requires **synthesis of both bedside and echocardiographic findings**.
   - **a.** Echocardiographic signs of cardiac tamponade include the following:
     - **(1) Pericardial effusion**.
     - **(2)** Right atrial diastolic collapse typically begins in late diastole and continues into ventricular systole. It is best seen in the parasternal short-axis view, the subcostal view, and the apical four-chamber view. It is a **very sensitive sign, but its specificity is 82%,** with a positive predictive value of 50%. **The longer the duration of diastolic collapse, the more specific it is for tamponade**.
     - **(3)** RV early diastolic collapse (or RV diastolic inversion). **Although very sensitive in medical patients, it is less so in surgical patients due to the loculated nature of these effusions and the presence of adhesions**. When present, the collapse is described as a persistent posterior or inward movement of the RV free wall in diastole. It is seen most commonly in the anterior RV free wall and infundibulum with patients in the supine position. The parasternal long-axis and short-axis views of the heart are the best for evaluating this sign; M-mode recording through the right ventricle helps to outline the timing and duration of the event. **Isolated RV diastolic collapse appears to occur before the onset of clinical tamponade**. Conditions that raise RV intracavity volume and RV pressure (pulmonary hypertension, RV hypertrophy, and RV infarction) delay the occurrence of RV diastolic collapse until higher intrapericardial pressures are reached.
     - **(4)** Left atrial diastolic collapse—a rare but specific sign of tamponade.
     - **(5)** Abnormal inspiratory increase of **RV dimensions** with abnormal inspiratory decrease of LV dimensions.
     - **(6)** Respiratory variation in atrioventricular valve flow pattern, with an abnormal inspiratory increase in tricuspid valve flow and abnormal

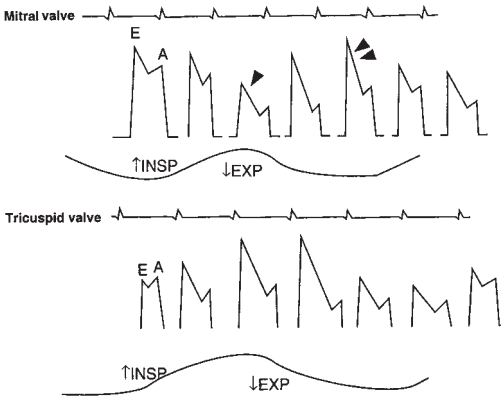

FIGURE 40.10 Pulsed wave Doppler for the mitral and tricuspid valves in a patient with cardiac tamponade. Note the marked respiratory variation of the inflow pattern, which in tamponade is a typical physiologic finding. INSP, inspiration; EXP, expiration.

inspiratory decrease in mitral valve flow (Fig. 40.10). Normally inspiration causes a decrease in mitral valve flow of up to 10% and an increase in tricuspid valve flow of up to 7%. **A decrease of the transmitral E wave of > 25% on inspiration is highly suggestive of significant tamponade**. A reduction of the tricuspid E wave of > 40%, together with prominent hepatic venous flow reversal during expiration, also suggests tamponade.

(7) IVC plethora. Failure to decrease the proximal diameter by at least 50% on sniff or deep inspiration has 97% sensitivity but only 40% specificity for tamponade physiology.

2. TEE is indicated in the postoperative patient with clinical signs of tamponade and inadequate surface images or in whom fluid is not present in the pericardium. TEE is highly sensitive for detecting hematoma in this setting.
3. Right heart catheterization is not necessary in patients for whom clinical and echocardiographic findings are consistent with tamponade and, in fact, may produce a delay in definitive treatment. However, right heart catheterization may be helpful in certain "borderline" cases for confirmation of the diagnosis of tamponade, quantitation of the hemodynamic compromise, and continuous assessment following pericardiocentesis. This is especially the case if pericardiocentesis is technically challenging.
   a. The **hemodynamic findings** include **equalization (within 4 mm Hg) of the right arterial pressure, pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure, and RV middiastolic pressure**, which are raised usually between 10 and 30 mm Hg; the right arterial pressure reveals a **preserved *x* descent with an absent or attenuated *y* descent**; during expiration, the PCWP is slightly greater than the intrapericardial pressure that promotes filling of the left heart. With inspiration, the PCWP decreases (transiently), rendering a low or negative pressure gradient between the pulmonary venous circulation and the left heart.
   b. Following pericardiocentesis, there is an initial decrease in all pressures (right atrial, RV diastolic, intrapericardial, PCWP, and LV end-diastolic). As the intrapericardial pressures continue to fall below the right atrial pressure, the *y* descent recovers to baseline. This may take as little as 50 mL of fluid

aspiration, due to the steep nature of the pressure–volume curve of the pericardium. These changes are accompanied by an increase in blood pressure and abolition of the pulsus paradoxus. Only with adequate hemodynamic monitoring, including arterial line and right heart catheterization, can these changes be followed. Lack of fall in atrial pressures post pericardiocentesis may indicate an effusive–constrictive process.

c. **Effusive–constrictive pericarditis** (constrictive epicarditis). Effusive–constrictive pericarditis has been described in patients with pericardial tamponade in whom intracardiac pressures remain elevated despite the relief of intrapericardial pressure post pericardiocentesis. Effusive–constrictive pericarditis is unique, as there is predominant involvement of visceral pericardium (epicardium), called constrictive epicarditis by some authors. Some patients may have resolution with a conservative approach but others require extensive epicardiectomy, which should be performed at experienced centers as it is technically challenging.

D. Therapy

1. **Priority of therapy.** Once the diagnosis of tamponade is made, one needs to consider immediate **drainage**. The timing and method of drainage ultimately depend on the etiology of the effusion, the patient's level of acuity, and the availability of trained physicians. The options include needle pericardiocentesis and surgical drainage (subxiphoid pericardiectomy, pericardial window, and subtotal pericardiectomy).
2. **Medical therapy.** Optimal medical management is important and includes volume expansion, inotropic support if the patient is hypotensive, and avoidance of diuretics or vasodilators.
3. **Percutaneous therapy**
   a. Pericardiocentesis allows the rapid drainage of pericardial fluid. Advantages are that it **can be performed quickly, is less invasive than other drainage methods, and requires minimal preparation**. Complications include laceration of the heart, coronary arteries, or lung. There is also the possibility of recurrent effusions or incomplete drainage. Pericardiocentesis is not recommended for small (< 1 cm) effusions or for those characterized by loculation, adhesions, or fibrinous stranding (see Chapter 69).
   b. Percutaneous balloon pericardiotomy is a technique involving balloon dilation of the pericardium after securing access to the pericardial space with a transcutaneous approach. It has been used for large pericardial effusions, particularly when caused by malignancy.
4. **Surgical therapy.** Surgical drainage allows for a more complete drainage and is preferred if there is a high likelihood of recurrence. In addition, a surgical approach permits direct examination of the pericardium and access to the pericardial tissue for histopathologic and microbiologic diagnoses and has the capability to drain loculated effusions. Surgical drainage is associated with more pain, a longer recovery time, and more periprocedural morbidity.

ACKNOWLEDGMENTS: *The author thanks Drs. Debra Kwon, Jenny Wu, Stanley Chetcutti, and Joel Reginelli for their contributions to earlier editions of this chapter.*

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CHAPTER 41

Parag R. Patel

Cardiac Tumors

I. INTRODUCTION. Cardiac neoplasms are **rare** in comparison with other forms of heart disease. Although secondary tumors of the heart are by definition malignant, primary tumors may be either benign or malignant. **Primary cardiac tumors occur approximately 30 times less frequently than cardiac metastases**. In most autopsy studies, the reported prevalence of primary tumors of the heart ranges from 0.001% to 0.03%, and about 75% are benign. Despite the relatively low prevalence, advances in curative operative therapy have made antemortem diagnosis of these tumors more clinically relevant.

II. CLINICAL PRESENTATION. Cardiac tumors often present with very nonspecific signs and symptoms. Patient complaints may be attributable to constitutional manifestations, embolic phenomena, or direct cardiac invasion/mass effect.

A. Constitutional symptoms. Many tumors, especially myxomas, are associated with a wide variety of systemic manifestations. Fever, chills, malaise, cachexia, and weight loss are not uncommon. Corresponding laboratory abnormalities, including leukocytosis, thrombocytosis or thrombocytopenia, hypergammaglobulinemia, as well as elevated erythrocyte sedimentation rate and C-reactive protein levels are frequently present as well. These findings are likely attributable to the constitutive production of **inflammatory cytokines** by the tumor or due to release from tumor necrosis. Myxoma cell production of **interleukin-6** and elevation of **antimyocardial antibodies** have been documented, with levels of these serum markers normalizing after tumor resection. Not surprisingly, patients with cardiac tumors often carry an incorrect antecedent diagnosis of collagen vascular disease, chronic infection, or noncardiac malignancy.

B. Embolic phenomena. Tumor embolization may account for the initial presenting symptoms, via either direct embolization of tumor fragments or thromboemboli released from the tumor surface. The type of emboli is dependent on tumor **location** as well as the presence of intracardiac shunts. **Right-sided** tumors, and left-sided tumors with left-to-right shunts, result in pulmonary emboli and if untreated may result in cor pulmonale. It may be difficult to clinically differentiate pulmonary tumor emboli from those due to venous thromboembolic disease. Chest radiography is usually not helpful. However, noninvasive imaging often has two unique characteristics that help differentiate tumor emboli from venous thromboemboli. First, tumor emboli may result in completely unilateral defects. Second, defects caused by tumor emboli generally do not resolve with time. **Left-sided** tumor emboli may result in visceral infarction, limb ischemia, myocardial infarction, or transient ischemic attack/stroke. In addition, multiple vascular aneurysms may develop. Of the benign primary cardiac tumors, embolization is most frequently noted with cardiac myxomas and even more so if the tumor has a villous surface. The brain is the most common site for systemic embolization in primary cardiac neoplasms, involving both hemispheres in approximately 40% of cases. Embolic findings in a young

person, in sinus rhythm and without valvular disease or endocarditis, should raise suspicion for the presence of an embolic source related to an intracardiac tumor.

C. Direct cardiac invasion/mass effect. Signs and symptoms are governed by tumor location and size. Intramyocardial tumors, which are most often found in the left ventricular free wall and intraventricular septum, generally remain asymptomatic when the tumor size is small but can result in arrhythmias, conduction abnormalities, and sudden cardiac death if they become larger. Impaired ventricular performance may mimic restrictive or hypertrophic cardiomyopathy. Rarely, ventricular rupture has been the initial presentation. Tumors of the left atrium, especially if mobile, may prolapse into the mitral valve, resulting in obstruction of atrioventricular (AV) blood flow. This results in signs and symptoms similar to mitral stenosis, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, and fatigue. Importantly, **syncope and sudden death** may also occur.

III. PHYSICAL EXAMINATION. Physical examination may show signs of pulmonary venous congestion. A fourth heart sound (S_4) may be present, as may a widely split, **loud first heart sound** (S_1). The loud S_1 is caused by late closure of the mitral valve, when the left ventricular–left atrial pressure crossover occurs at a higher pressure. Although this finding is also seen with mitral stenosis and preexcitation, the absence of a diastolic rumble or a short PR on an electrocardiogram should raise the possibility of left atrial tumor. Left atrial tumor may cause a holosystolic murmur at the apex radiating to the axilla (if tumor causes mitral incompetence) as well as diastolic murmur if the tumor obstructs mitral outflow. If the tumor obstructs the AV valve, a **presystolic crescendo murmur** may be present, which typically begins during ventricular systole as the tumor moves through the mitral orifice. This finding is present in approximately one-half of all patients with myxoma. The pathognomonic **tumor plop** manifests as an early diastolic sound, after an opening snap but before a third heart sound (S_3). Tumors of the **right atrium** often result in systemic venous congestion. Once significant pulmonary hypertension occurs, **systemic hypoxia, clubbing, and polycythemia** may develop as a result of right-to-left shunting. Right atrial tumors and intracavitary **right ventricular** tumors may present as right heart failure. A diastolic rumble that varies with inspiration may be noted and is due to tricuspid valve obstruction. The **P_2** is delayed and may have varying intensities. Jugular venous pressure waveform examination may demonstrate **prominent** a **waves and Kussmaul's sign**. Recurrent pulmonary emboli can potentiate pulmonary hypertension. **Left ventricular** tumors, when not intramural, typically result in signs and symptoms of pulmonary venous congestion or low-output states. Upon examination, findings may mimic aortic stenosis, subvalvular stenosis, or hypertrophic cardiomyopathy.

IV. DIAGNOSIS. Because no clinical sign or symptom is specific, more advanced diagnostic methodology is universally required.

A. Electrocardiography (ECG). In isolation, ECG provides little added clue to the diagnosis. However, changes in rhythm or voltage or development of new AV block on serial tracings may be the first sign of either extension of a primary cardiac tumor or development of secondary cardiac involvement.

B. Radiography. Chest radiography may be helpful in identifying epicardial tumors. Cardiomegaly, mediastinal widening, or cardiac silhouette irregularities may suggest the diagnosis. Calcifications are seen occasionally. Pulmonary congestion or oligemia may be noted in patients with large left or right intracavitary tumors, respectively.

C. Echocardiography. M-mode and two-dimensional echocardiography help establish the diagnosis in most patients. If a tumor is strongly suspected or a mass is noted by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) should be performed. TEE provides improved sensitivity (97% vs. 93% for TTE) and specificity, particularly with atrial masses, and allows for superior visualization of

anatomic details, such as contour, cysts, calcification, and presence of a stalk. Three-dimensional echocardiography is also increasingly helpful in evaluation due to its ability to visualize complex cardiac masses.

D. **Radionuclide imaging.** Although gated blood pool scanning has been used to identify cardiac tumors in the past, the inferior resolution and sensitivity have made this form of imaging uncommon in the workup. Positron emission tomography scanning is useful in identifying cardiac involvement in metastatic tumors and atrial myxomas.

E. **Computerized tomography (CT).** CT, especially multislice CT with contrast, is often used in the diagnosis and evaluation of cardiac masses. It can define tumor extension, although not as effectively as cardiac magnetic resonance (CMR), assess tumor calcification, and evaluate the adjacent extracardiac structures (pericardium and great vessels).

F. **Cardiac magnetic resonance.** Like CT, CMR has an important role in the evaluation of cardiac tumors. Specifically, it characterizes size, shape, and surface features, as well as evaluating tissue composition—giving information regarding the type of tumor that is present. Magnetic resonance imaging (MRI) has the highest soft tissue contrast of the imaging modalities, and it is particularly helpful in distinguishing thrombus from tumor. It is also the most sensitive imaging modality for detecting the extent of tumor infiltration.

G. **Angiography.** Cardiac catheterization is **not necessary in most cases**. However, in the following scenarios, the risk and cost of angiography may be worthwhile: clarifying inadequate noninvasive imaging, defining blood supply for suspected malignant tumors, and evaluating coexistent valvular or coronary artery disease that could alter surgical approach. The major additional risk of angiography is embolization of tumor or thrombus. A transseptal approach is relatively contraindicated in cases of suspected left atrial myxoma, given the high frequency of involvement of the fossa ovalis and the accompanying risk of embolization.

H. **Endomyocardial biopsy (EMB).** Limited data exist on the utility of EMB in the management of cardiac tumors. Generally, diagnosis is made from noninvasive imaging; however, EMB can be considered if imaging is equivocal or if a tissue sample is required prior to treatment decisions (i.e., chemotherapy).

V. PRIMARY CARDIAC MALIGNANCIES

A. **Benign neoplasms.** A description of specific benign cardiac tumors is given in subsequent text. Relative proportions are given in Table 41.1.

1. **Myxomas.** Most benign cardiac tumors are myxomas, accounting for approximately 30% to 50% in most series. For **sporadic myxomas**, which account for nearly 90% of all myxomas, about 65% of patients are female, with a mean age of 56 years. Eighty-six percent of sporadic myxomas are found in the left atrium and 90% are solitary masses. When multiple tumors are present, they are not necessarily limited to one chamber. The typical site of attachment within the left atrium is on or near the **fossa ovalis**. It is important to note that **tumors located on the posterior wall of the left atrium are usually not benign**. Less frequently, myxomas may be found in the right atrium, either ventricle, or arising from the AV valves. **Familial myxomas** comprise 4.5% to 10% of all cardiac myxomas. Although pathologically identical to sporadic myxomas, they have a number of unique clinical features. They have a well-characterized **autosomal dominant** transmission. They are often present within the construct of a larger syndrome. The **Carney complex**, or "syndrome myxoma," consists of both cardiac and noncardiac myxomas, spotty pigmentation (i.e., pigmented nevi), and endocrine overactivity (pituitary, adrenocortical, and endocrine testicular tumors). This may account for up to 7% of all cardiac myxomas. Patients with the Carney complex typically present in the third decade, often have bilateral tumors, and have high recurrence rates following resection. If a myxoma

TABLE 41.1 Relative Proportion of Benign and Malignant Tumors in Adults by Tumor Type

Benign tumor	% of group	Malignant tumor	% of group
Myxoma	46	Angiosarcoma	33
Lipoma	21	Rhabdomyosarcoma	21
Papillary fibroelastoma	16	Mesothelioma	16
Rhabdomyoma	2	Fibrosarcoma	11
Fibroma	3	Lymphosarcoma	6
Hemangioma	5	Osteosarcoma	4
Teratoma	1	Thymoma	3
AVN mesothelioma	3	Neurogenic sarcoma	3
Granular cell tumor	1	Leiomyosarcoma	1
Neurofibroma	1	Liposarcoma	1
Lymphangioma	1	Synovial sarcoma	1

AVN, atrioventricular nodal.

syndrome is suspected, **screening echocardiography is recommended** for all first-degree relatives, particularly if the index patient is young, has multiple tumors, or has typical noncardiac features of the genetic syndrome.

Pathologically, cardiac myxomas may be either smooth, round or gelatinous, or friable and irregular in appearance. They sometimes contain a hemorrhagic core and may attach via a sessile or pedunculated base. The typical diameter at presentation is 4 to 8 cm and the typical mass is 15 to 180 g. **Histologically**, myxomas have characteristic patterns of "lipidic" cells within glycosaminoglycan-rich myxoid stroma. **Ultrastructurally**, myxoma cells resemble embryonic mesenchymal cells. **Immunohistochemically**, they demonstrate variable activity for endothelial cell markers, with reliable positivity to vimentin, indicating a mesenchymal derivation. Myxomas also produce vascular endothelial growth factor, likely contributing to angiogenesis and tumor growth.

2. **Lipomas.** These benign tumors occur at **all ages,** with men and women affected equally. Tumors range in size depending on their location. Seventy-five percent of tumors are found in the subendocardium, whereas the remainder are subepicardial, intramuscular, or valvular. Many tumors are **clinically silent** and identified only at autopsy. Subendocardial tumors may result in symptoms related to cavity obstruction, whereas subpericardial tumors can lead to compression of the heart and/or development of pericardial effusion. Intramyocardial tumors may result in arrhythmias or conduction disturbances and possibly sudden death. Valvular lipomas can lead to valvular insufficiency and heart failure. Lesions are generally **well encapsulated** with a center of predominantly benign fatty cells. Without pathologic confirmation, lipomas can be confused with lipomatous hypertrophy of the interatrial septum. Both MRI and CT are useful in diagnosing cardiac lipomas based on the characteristic features of fatty tissue with these techniques.
3. **Papillary fibroelastomas.** The diagnosis of papillary fibroelastoma has increased with the more frequent use of TEE. They are the second most common primary cardiac tumors in adults and, grossly, these benign tumors resemble sea

anemones, with frondlike arms protruding off a central stalk. They are usually about 1 cm in length, single, and mobile in 40% of cases. The majority are located on the **ventricular surface of the aortic valve**, whereas the atrial side of the mitral valve is the second most common location. Rarely, they may present on the endocardial surfaces. Although these tumors are not associated with valvular dysfunction, in approximately 30% of cases, thrombus, with subsequent emboli, develops. Surgical resection is generally recommended for patients with a symptomatic presentation with embolization or in an asymptomatic patient with large, mobile tumors (1 cm or greater in diameter). Anticoagulation may be considered if recurrent embolization occurs in a nonsurgical candidate. Fibroelastoma may be differentiated from Lambl's excrescences by their location on noncontact areas of the valve.

4. **Rhabdomyomas.** Rhabdomyomas, the most common benign tumor in **children** and **infants**, are frequently located within one of the ventricles. These tumors are nearly always **multiple**, and the majority of patients have at least one intracavitary, obstructing lesion. The most common presentation for this type of cardiac tumor in adults is arrhythmia; however, it may be clinically silent if the tumors are small. There is a clear association with **tuberous sclerosis**: 80% of rhabdomyoma patients have the disease and 60% of tuberous sclerosis patients have rhabdomyomas. In some cases, rhabdomyomas may regress spontaneously during childhood.
5. **Fibromas.** Generally, fibromas are found in **pediatric** populations as well; these benign connective tissue tumors are almost universally **intramural**. They are usually firm, circumscribed but unencapsulated, and may grow to **several centimeters**. They have preponderance for the left ventricle and unlike rhabdomyomas do not spontaneously regress. The **Gorlin's syndrome** includes cardiac fibromas, multiple basal cell carcinomas, jaw cysts, and skeletal abnormalities.
6. **Hemangiomas/lymphangiomas.** These tumors are **very rare** and consist of benign collections of endothelial cells. Usually they are located within the intraventricular septum or AV node and as such may present as heart block, sudden cardiac death, or hemopericardium.

B. **Malignant neoplasms.** Histologically, **primary malignant tumors are virtually always sarcomas**. Suggestive **characteristics** include rapid growth, mediastinal invasion, hemorrhagic pericardial effusion, precordial pain, and pulmonary vein extension. Primary malignant neoplasms make up approximately 15% of all primary cardiac tumors.

1. **Angiosarcomas.** Almost always found within the right atrium, angiosarcomas, which include Kaposi's sarcoma, have a **2:1 male-to-female predilection** and are almost exclusively seen in adults. Hemorrhagic pericardial effusions are not uncommon. These tumors have ill-defined vascular channels lined with atypical endothelial cells. The blood flow through the tumor may produce a continuous precordial murmur. Despite resection and/or adjuvant therapy, clinical deterioration is rapid.
2. **Rhabdomyosarcoma.** Like angiosarcomas, these tumors of striated muscle are **more common in men**. However, there is no specific chamber that is preferentially affected. Tumors are generally infiltrative, but on occasion they may develop polypoid extensions, which can cause them to be mistaken for myxomas. Prognosis is poor.
3. **Mesothelioma.** The typical location of primary cardiac mesothelioma is the **pericardium**. Generally very diffuse, these tumors lead to symptoms consistent with pericarditis or hemorrhagic effusion. They may occasionally infiltrate the **AV node**, leading to conduction disturbances, sudden cardiac death, or tamponade. Much like cardiac sarcomas, these tumors carry a very poor prognosis.

4. **Other.** Fibrosarcomas, lymphosarcomas, liposarcomas, and other undifferentiated sarcomas represent the remainder of primary cardiac malignancies. These tumors are very rare and are generally infiltrative, involving multiple cardiac chambers. A clinical syndrome mimicking hypertrophic cardiomyopathy has been observed.

VI. SECONDARY CARDIAC MALIGNANCIES. As mentioned previously, most malignancies of the heart are secondary and, by definition, **metastatic**. The overwhelming majority of metastatic cardiac tumors occur in the **pericardium** and are usually **carcinomas**, as opposed to sarcomas. Due to increased prevalence, **the most commonly found metastatic tumor to the heart is lung cancer**. The typical presentation is of pericardial effusion or tamponade or pulmonary vein obstruction from direct extension. After metastatic lung cancer, breast cancer, lymphoma, leukemia, and renal cell carcinoma are the most common offenders. The tumor with **the greatest propensity to metastasize to the heart is melanoma**, followed by germ cell tumors and leukemia (Table 41.2). A new complaint referable to the heart in a patient with known extracardiac malignancy should prompt a thorough investigation to rule out cardiac malignancy. Unfortunately, prompt diagnosis usually does not favorably alter the prognosis.

VII. DIFFERENTIAL DIAGNOSIS. Establishing the correct diagnosis is imperative. A thorough differential diagnosis of **nonmalignant conditions** must be considered and ruled out. Possibilities include pericardial cysts, teratomas, lipomatous hypertrophy of the interatrial septum, thrombus, and sarcoid. Unfortunately, the final diagnosis in many cases must still be made pathologically.

VIII. THERAPY AND PROGNOSIS. The primary therapy for benign tumors remains **operative resection**, given the associated risk of lethal obstruction, arrhythmia, or embolization. Most surgeons perform excision with extracorporeal circulatory support in order to directly visualize the tumor, as well as a careful search for metasynchronous tumors. In higher risk patients, more extensive resection is recommended. The femoral or azygous vein is usually cannulated, as opposed to the right atrium, to avoid potential

TABLE 41.2 Metastatic Tumors to the Heart by Absolute Number and Greatest Propensity

Primary tumor	Absolute no.	Primary tumor	No. per 100 tumors
Lung	180	Melanoma	46
Breast	70	Germ cell	38
Lymphoma	67	Leukemia	33
Leukemia	66	Lymphoma	17
Esophagus	37	Lung	17
Uterus	36	Sarcoma	15
Melanoma	32	Esophagus	13
Gastric	28	Kidney	11
Sarcoma	24	Breast	10
Oral	22	Oral	9
Colon	22	Thyroid	9

tumor fragment embolization. Mitral valve repair or replacement is usually unnecessary in the absence of associated bacterial endocarditis. An analysis reviewing 106 operations for sporadic atrial myxomas noted only one perioperative death. Survival at 25 years is no different when compared with age- and sex-matched controls. There are limited data regarding the use of a minimally invasive or robotic approach to cardiac tumor resection. Small series suggest that parasternal or partial sternotomy access does not compromise the safety or efficacy while allowing for shortened hospitalization and better cosmetic results. Long-term follow-up is not yet available for this approach.

Regardless of the type of surgical resection or whether the tumor is sporadic, annual **follow-up noninvasive imaging is recommended** in all patients after resection. Recurrence rates of 12% to 22% have been quoted in patients with family histories, syndromes, and multiple tumors at original presentation versus 1% for patients with sporadic, isolated myxomas. Primary malignant tumors generally portend dismal prognoses. They are rarely cured by surgery because of the large amount of cardiac tissue involved. Adjuvant therapy (i.e., chemotherapy and radiation) after resection does not affect the prognosis, although it may slow progression in individual cases. **Palliative resection** is advocated for obstructive symptoms. **Cardiac transplantation** has been performed for patients with both benign and malignant tumors, but thus far, series have been too small to reliably predict outcomes.

ACKNOWLEDGMENTS: *The author would like to thank Drs. Adam W. Grasso and Nitin Barman for their contributions to earlier editions of this chapter.*

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CHAPTER 42

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Common Genetic Issues in Cardiovascular Disease

Genetic abnormalities have been associated with all types of cardiovascular disease, including coronary atherosclerosis, rhythm disorders, aortic disease, and structural heart disease. Since the initial descriptions of familial hyperlipidemia (FH) and the mutations in the low-density-lipoprotein (LDL) receptor (LDL-R), genetic studies have fostered an improved understanding of the underlying pathophysiology of various cardiovascular disease states. Furthermore, the sequencing of the human genome has ushered in the era of cardiovascular genomics. The ability to efficiently scour through the massive amount of genomic information will ultimately result in an improved understanding of the contributions of genetics to cardiovascular disease.

This understanding would potentially lead to an improved ability to accurately diagnose disease, prevent progression, and risk stratify at the individual level. Furthermore, this information will add to our understanding of the relationship between DNA variants and the response to drugs or other treatment modalities. The pharmacogenomic profiles developed may provide a refined approach to treatment with less toxicity. A more comprehensive assessment of future risk for both patient and potentially affected family members would also be feasible.

Although there are some examples within cardiovascular disease of simple monogenic disorders explained by principles of Mendelian inheritance, many of the entities, such as coronary atherosclerosis, acute myocardial infarction (MI), and atrial fibrillation (AF), are complex traits with multiple genes contributing to the phenotype. As opposed to Mendelian disorders, which are deterministic, complex traits are probabilistic.

It will require extensive time and effort to be able to define all the variations in all the genes that contribute to the susceptibility to or protection from a complex trait. Furthermore, the simple identification of genes involved does not address the issue of gene–gene and gene–environment interactions influencing complex traits. There have been extensive recent reports of genomic variants associated with risk of diseases. These variants are common, often accounting for 20% to 30% of the population attributable risk, but with an odds ratio of 1.2 or 1.3, for example, only 20% to 30% excess risk. These are common variants for common diseases. The hunt to find rare variants that induce susceptibility to common diseases with high risk (or protection) will be more challenging, but eminently feasible with sequencing technology and ultra high-throughput genotyping. At some point in the future, the major genomic underpinnings for most cardiovascular diseases will be known. Furthermore, the integration of all of the genomic variants for any cardiovascular disease has not been undertaken. What follows is a brief overview of what is known today about the genetic basis for a sampling of disease entities within cardiovascular medicine.

METHODOLOGY. The process of discovering relevant genetic underpinnings of generally complex traits requires an extensive analysis of genetic information in large populations. Complex traits without simple Mendelian patterns of inheritance are difficult to analyze, given that there are often multiple genes involved, with many gene interactions being important. However, even before attempting this task, perhaps the single most significant goal is to accurately and concisely define the phenotype in question. In addition, many variations

often exist within a single category of cardiovascular diseases such as hypertrophic cardiomyopathy (HCM) and acute MI. The ability to clearly define cases and controls is paramount to obtaining accurate and reproducible information.

There are three major methods of identifying DNA variants associated with cardiovascular disease. Of note, some of the single nucleotide polymorphism (SNP) variants that have been found are not in a gene, but actually in areas of the genome not associated with gene expression. It is not yet known how these variants exert their effect. Of note, the major variants for MI (at 9p21) and AF (at 4q25) fall into this category of intergene (i.e., not in a gene).

I. GENOME-WIDE ASSOCIATION STUDIES. Gene association studies utilize the concept that multiple SNPs, where a single nucleic acid substitution results in a different allele, can affect the risk of developing a disease in question. This is especially true in diseases of complex traits such as coronary artery disease (CAD) and MI. Using genes of interest in a particular disease phenotype, scans are conducted in areas of interest in both cases and controls to compare haplotype frequency to determine if a statistically significant difference between the two groups in the region of interest exists. One of the limitations of this technique is the inability to know whether the SNP of interest is involved in the pathogenesis or simply associated (in linkage disequilibrium) with another SNP that may actually be involved in the process. Utilizing this process of gene association across the entire genome is now possible with high-throughput sequencing technology of up to 1 million SNPs assessed per individual and the term "genome-wide" association has been coined. The SNPs assessed are tagging tiny bins of the genome, such that in a genome of an individual of European ancestry, there are only about 250,000 bins, most of which are sampled by current high-throughput genotyping. Each bin is typically inherited as a block (haplotype). The breakdown of the genome into bins via the International Haplotype map was critical in making current genome-wide association studies possible.

II. LINKAGE ANALYSIS. Linkage analysis is another tool used to identify genes that are possibly involved in the pathogenesis of complex traits. The use of linkage analysis begins without any assumptions as to the potential involvement of various genes. It is based on the idea that during the process of meiosis when recombination events occur, they tend to involve loci on a particular chromosome that are closer together than farther apart. By following the inheritance of certain known loci, assumptions can be made about the presence of alleles that cosegregate with them. Using linkage analysis, the potential exists to identify these known loci as markers and determine the transmission through a pedigree and its relationship to the phenotype in question. In doing so, it may be possible to suggest that an allele in proximity to known loci may be associated with a particular phenotype. The logarithm of odds ratio (LOD score) is used to estimate the (distance) relationship between the known locus of interest and an unknown locus thought to be associated with the disease phenotype. A LOD score of 3 is used to classify such a statistically meaningful linkage.

III. GENE EXPRESSION PROFILING. The identification of certain disease alleles or loci associated with disease-causing genes provides valuable information but remains limited in its scope. The statistical association of genes and disease **does not prove causation or even involvement** in disease. Gene expression profiling takes this concept one step forward in trying to delineate gene expression. The presence of transcription profiles may provide more useful information in terms of relevance of findings made in gene association studies or linkage analysis. Technology now permits the evaluation of large genomes in a rapid fashion to derive expression profiles, which can then be compared between diseased and healthy individuals to draw conclusions about which genes are transcriptionally active in certain phenotypes.

A. Coronary atherosclerosis and atherothrombosis. Coronary atherothrombosis and atherosclerosis remain significant causes of morbidity and mortality in the population as a whole. There is a great deal of variation in presentation in atherosclerosis and in acute MI. The presence of atherosclerosis is necessary but not sufficient

for atherothrombosis. There are separate factors involved that predispose to plaque rupture and thrombosis. Even within the category of plaque rupture, the clinical phenotypes vary significantly, as reflected by the spectrum of diseases that constitute the acute coronary syndromes. These entities are complex traits and are influenced by multiple pathways. Inflammation, endothelial dysfunction, and dyslipidemias are only a few of the pathways influencing the development of atherothrombosis and atherosclerosis. Delineating the genetic basis, in most cases, is a work in progress, but it may help to broaden our understanding of the disease.

1. **Dyslipidemia: familial hyperlipidemia and other genetic variants.** Dyslipidemia is a known risk factor for the development of atherosclerosis. Familial hyperlipidemia (FH) is a well-characterized, albeit relatively uncommon, entity defined by elevated levels of serum LDL levels, which predispose to coronary atherosclerosis. Often, these patients can develop atherosclerotic disease between 20 and 30 years of age. In FH, the dyslipidemia is often severe and not responsive to standard lifestyle and pharmacologic interventions.
   a. **Autosomal dominant.** The underlying problem in this form of FH has to do with an abnormality in the clearance of the *LDLR* gene, and, as a consequence, elevated levels of LDL persist. The *LDLR* gene located at 19p13.2 has approximately 1,600 known mutations, and these appear to affect many aspects of LDLR function. Alterations in the gene range from point mutations to gene rearrangements. homozygotes and heterozygotes for FH vary in terms of the severity of lipid levels. The majority of individuals are heterozygous, and those with homozygous patterns of inheritance are more severely affected. Typically, these patients and affected family members develop premature coronary atherosclerosis and MI.
   b. **Autosomal recessive.** This occurs as a result of a mutation in the low-density-lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene at 1p36-p35. The phenotype of this form of FH is milder than the autosomal dominant form of the disease and more amenable to treatment with lipid-lowering agents.
   c. **Familial defective apolipoprotein B.** The cellular mechanisms involved in cholesterol metabolism are complex, and there are many potential targets where mutations can significantly affect phenotype. One such example is a point mutation in the apolipoprotein B (apo B) component of the LDL molecule. The Arg3500Gln is the most common substitution in the apo B (*APOB*) gene and results in the inability of LDL to bind to its LDLR. This mutant allele is more common in Northern European populations as a cause of hyperlipidemia, but the phenotype appears to be less severe than in the familial hyperlipidemia caused by *LDLR* mutations.
   d. **Proprotein convertase subtilisin/kexin type 9 *(PCSK9)*.** Less than 5% of FH involves *PCSK9* gene, located at 1p32.3, responsible for increasing degradation of the LDL receptor. Mutations in *PCSK9*, such as D374Y, F216L, S127R, D129N, D374H, N425S, and R496W, confer gain in function and cause FH. Much rarer *PCSK9* mutations are those that result in loss of function and act to reduce serum cholesterol levels, thereby conferring a protection against coronary atherosclerosis. Many new *PCSK9* mutations have been identified, but their effect on *PCSK9* functions requires further investigation.

   In addition to the FH syndromes, there is a multitude of genes involved in more frequently occurring types of dyslipidemia. Phenotypically, these forms of dyslipidemia are less severe and more amenable to treatment than those observed in the FH population.
2. **Endothelial function.** *MEF2a* is a transcription factor that localizes to the endothelial cell of coronary arteries and is believed to be important in the function of endothelial cells. In 2003, a mutation in the *MEF2a* gene was described in a large family with autosomal dominant transmission of coronary atherothrombosis.

A 21-bp deletion in exon 11 was thought to result in loss of function. Three additional variants in the *MEF2A* thought to be associated with MI and CAD have also been reported. The findings from a large Spanish case-controlled study provided supporting evidence for only one of these variants, P279L. Further studies have failed to replicate these mutations in association with MI. The 21-bp deletion has not been found in any family apart from that in the original study. This particular mutation may be a "private mutation" for the family in the original study and therefore extremely difficult to replicate. In 2008, Lieb et al. (1) conducted a large German study, with 23 MI families, > 1,700 MI patients, and 2 large control populations, and did not find any evidence that the *MEF2A* gene had any linkage or association with MI/CAD.

3. **Inflammation.** The genes *ALOX5AP* (arachidonate 5-lipoxygenase–activating protein) and *LTA4H* (leukotriene A4 hydrolase) encode proteins involved in the leukotriene pathway, particularly in the synthesis of the proinflammatory leukotriene B mediators. The case for inflammation as a significant participant in acute MI has been made stronger by the discovery, through linkage analysis to a locus at 13q12-13, of a four SNP haplotype (Hap A) in the gene *ALOX5AP*. Carriers of the variant had higher levels of leukotriene B4. This variant was found to double the risk of MI and to almost double the risk of stroke. Another haplotype variant (Hap B) of the *ALOX5AP* gene was found to confer a doubling of the risk of MI in a British cohort. In Italy, researchers identified an increased risk for CAD with Hap B only. In a large German study, presence of the haplotype B indicated an association with an increased risk of MI. These studies provide strong evidence of the role of *ALOX5AP* gene for increased CAD risk in Europeans. In a case–control study of a US Midwestern population with European American ancestry, seven SNPs in the *ALOX5AP* gene along with two haplotypes (Hap A and Hap B) were genotyped. The results indicated that Hap B and one of the SNPs (SG13S377) were significantly associated with increased risk of premature CAD. In a meta-analysis conducted in 2010, the Hap B and SNP (rs1722842) variants in the *ALOX5AP* gene were associated with coronary heart disease, while Hap A was associated with the risk of MI.

   The *LTA4H* gene encodes leukotriene A4 hydrolase and is also involved in the inflammation pathway. A haplotype (HapK) in the *LTA4H* gene moderately increased the risk of MI in a cohort from Iceland. A moderate risk was also found in studies of three US cohorts with European Americans, but HapK, although rarer in African Americans, tripled their risk of MI. The results of these studies with the ALOX5AP and the LTA4H variants provide the basis for further research to develop new drugs targeting the leukotriene pathway, thereby preventing or reducing the risk of MI and CAD in the future.

B. Connective tissue abnormalities and disease of the aorta. Genetic mutations affecting the connective tissue and extracellular matrix typically affect multiple organ systems, but often the most devastating and lethal effects arise from those upon the cardiovascular system. Aortic dissection and rupture are often the consequences of such abnormalities, and what follows is a brief description of three such disorders.

1. **Marfan syndrome.** This disorder is inherited in an autosomal dominant fashion with variable penetrance, and it affects the connective tissue, leading to abnormalities of organs of the cardiovascular, skeletal, and ocular systems. The genetic defect is in the **fibrillin-1 (*FBN1*) gene on chromosome 15q21**. Often, the diagnosis is made on clinical grounds alone. The classic features of tall stature, arachnodactyly, dolichostenomelia, pectus excavatum, ectopia lentis, and a positive family history all support a diagnosis of Marfan syndrome. The cardiovascular system is affected, and the most common cause of death in these patients is from aortic dissection and aortic rupture. Other common related problems include aortic dilation, aortic valve regurgitation, mitral valve prolapse (MVP), tricuspid valve prolapse, and arrhythmias. When patients with Marfan syndrome present with dissection, they are typically younger and do not have hypertension.

The *FBN1* gene is responsible for producing a key constituent of microfibrils, which are important in the extracellular matrix. Microfibrils add to the elastic properties of extracellular tissue. Over 1,000 mutations in the *FBN1* gene have been recognized and appear to affect different aspects of cellular processing of fibrillin-1. These mutations can vary from a SNP to a premature stop codon. There are no specific relationships between mutations and phenotypes as of yet. Family members with Marfan syndrome and **the same *FBNI* gene mutation may show wide variation in onset and severity of cardiac symptoms**. The diagnosis of Marfan syndrome is generally made on a clinical basis. However, genetic testing for Marfan syndrome is available.

2. **Ehlers-Danlos syndrome.** Ehlers-Danlos syndrome is a group of connective tissue disorders caused by defects in proteins that are involved in the formation of collagen. It is uncommon and has an autosomal dominant pattern of inheritance. There are multiple types of Ehlers-Danlos syndrome based on the collagen type affected; however, the cardiovascular system is involved prominently in type IV, the vascular type of Ehlers-Danlos syndrome. The gene, ***COL3A1*, involved in this subtype is localized to chromosome 2q24.3-q31 and encodes for type III procollagen**. Vascular complications include dissections of the carotids and the vertebral arteries. Aortic dissections are the primary cause of death and often involve both the thoracic and the abdominal aortas. Diagnosis is usually ascertained clinically along with genetic testing for evidence of the mutation in the *COL3A1* gene.
3. **Loeys-Dietz syndrome.** Loeys-Dietz syndrome is a connective tissue disorder characterized by hypertelorism, cleft palate, and vascular disease in the form of arterial aneurysms and dissection. It is inherited in an autosomal dominant pattern. Clinically, these patients are at high risk for aortic dissection. Loeys-Dietz syndrome is caused by **mutations in the transforming growth factor beta (TGF-β) receptors I and II genes (*TGFBR1* and *TGFBR2*) on chromosome 3**. Phenotypically, the characteristics are like those in Marfan syndrome, and also these patients appear similar (with the exception of the craniofacial abnormalities) to Ehlers-Danlos patients with vascular involvement (type IV). The relevance of this distinction is that those with Loeys-Dietz appear to have much lower intraoperative mortality during corrective vascular surgery. Genetic testing to identify the mutation is needed for definitive diagnosis, but it is not available in all laboratories.

C. Cardiomyopathies. Primary disease of the myocardium affects both systolic and diastolic function and often results in heart failure or other adverse events over time. Many of the nonischemic cardiomyopathies have a strong genetic component to explain their phenotype. Perhaps, the most clinically relevant entities include dilated cardiomyopathy (DCM) and HCM. Cardiomyopathies can also occur as a secondary process in response to a separate unrelated factor (i.e., hypertension), and it is unknown to what degree genetic susceptibility determines the myocardial response/remodeling over time. Until recently, the classification of cardiomyopathies has been based on the phenotype and morphologic characteristics. However, with an improved knowledge of the genetics of these disorders, a new understanding and appreciation for the underlying mechanisms of disease in these disorders will undoubtedly influence how these entities are treated in the future.

1. **Dilated cardiomyopathy.** DCM is characterized by dilation of one or both of the ventricular chambers resulting in severe systolic dysfunction and characterized by congestive heart failure. A genetic cause is thought to account for 20% to 50% of DCM cases, and in many cases, the pattern of inheritance is autosomal dominant. However, recessive, X-linked, and mitochondrial patterns of inheritance are also seen. Many cases of DCM are secondary to other etiologies. Mutations in more than 30 genes have been associated with this phenotype, and although the products of most of these genes are important structural proteins, there are others involved in the handling of calcium and regulation of energy within the myocytes. Again, however, there are often subtle differences in the

various types of DCM, such as age of onset and degree of clinical symptoms, all of which may suggest separate genetic abnormalities are at play. Mutations in the sarcomere protein genes account for approximately 10% of DCM. Mutations in *LMNA* gene, which encodes lamin A and lamin C, are seen in DCM with prominent conduction system disease. Although mutations in *SCN5A* are also associated with this type of DCM, the clinical picture differs as ventricular dysfunction is usually present. Dystrophin gene mutations are seen in X-linked DCM. Mutations in the *ALMS1* gene are transmitted in a recessive pattern, resulting in DCM with hearing loss. Genetic testing is available for many of the gene mutations that have been identified. Table 42.1 lists some of the genetic variants that are believed to be associated with various DCM phenotypes.

2. **Hypertrophic cardiomyopathy.** HCM (see Chapter 10) is a highly variable and heterogeneous disease process that affects the myocardium, with clinical manifestations varying from completely asymptomatic to severe (sudden cardiac death). The

TABLE 42.1 Genetic Variants Associated with Dilated Cardiomyopathy

Gene	Location	Mode of inheritance	Gene product and function
MYH7	14q11	Autosomal dominant	Sarcomere gene—encodes β-myosin heavy chain Mutations may affect contractile mechanism
MYH6	14q12	Autosomal dominant	Sarcomere gene—encodes α-myosin heavy chain Mutations may affect contractile mechanism
TNNT2	1q32	Autosomal dominant	Sarcomere gene—encodes troponin T type Mutations may affect contractile mechanism
ACTC1	15q11-q14	Autosomal dominant	Sarcomeric gene—encodes cardiac actin Vital part of contractile apparatus of myocyte
TMPO	12q22	Autosomal dominant	Encodes thymopoietin—maintains functional integrity of nucleus
CSRP3	11p15	Autosomal dominant	Encodes cardiac muscle LIM protein Functions as a stretch sensor in myocyte
Phospholamban (*PLN*)	6q22	Autosomal dominant	Controls muscle relaxation through calcium regulation via calcium ATPase
DES	2q35	Autosomal dominant	Encodes desmin—cytoskeletal protein involved in stabilization of sarcomere and mutation may affect contractile force
Presenilin (*PSEN1/2*)	14q24.3 (*PSEN1*) 1q31-q42 (*PSEN2*)	Autosomal dominant	*PSEN1* encodes presenilin 1 *PSEN2* encodes presenilin 2 Transmembrane proteins
Lamin A/C (*LMNA*)	1q22	Autosomal dominant	Encodes lamin A and lamin C Structural proteins—affect structure of nucleus in myocytes **DCM with prominent conduction system disease**
SCN5A	3p21	Autosomal dominant	Cardiac sodium channel gene **DCM with prominent conduction system disease**

TABLE 42.1 Genetic Variants Associated with Dilated Cardiomyopathy (*Continued*)

Gene	Location	Mode of inheritance	Gene product and function
Dystrophin (*DMD*)	Xp21.2	X-linked	Encodes dystrophin More commonly involved in Duchenne's and Becker's muscular dystrophy Mutations can affect transduction of contractile force **X-linked DCM**
ALMS1	2p13	Autosomal recessive	Alstrom syndrome 1 Causes with DCM and hearing impairment Encodes for protein associated with obesity and diabetes **Autosomal recessive DCM**

DCM, dilated cardiomyopathy.

broad range of phenotypes and significant selection bias resulted in an overestimation of the mortality rate associated with this disease. The clinical spectrum of the disease is wide, and the ability to accurately predict outcomes remains challenging. The clinical variability of HCM is not only limited to the presenting phenotype but also related to age of presentation, clinical course, and eventual outcomes, making it very challenging to properly identify a phenotype of interest. The characteristic phenotype is an asymmetrically hypertrophied myocardium with a small ventricular chamber and occasionally a left ventricular (LV) outflow tract (with systolic anterior motion of the mitral valve) and/or an intracavitary gradient.

More than 700 mutations in 13 separate genes have been identified, with the majority of mutations in 3 of the genes: *MYH7* on chromosome 14, *MYBPC3* on chromosome 11, and *TNNT2* on chromosome 1. The genes involved encode proteins of the cardiac sarcomere unit. The products of these genes involved include troponin T, troponin I, β-myosin heavy chain, myosin light chains, myosin-binding protein C, α-myosin light chain, α-tropomyosin, and actin.

The importance of properly characterizing a phenotype as heterogeneous as HCM has been illustrated by the example of glycogen storage diseases mimicking the appearance of HCM. Mutations in the genes for AMP-activated protein kinase gamma2 (PRKAG2) and lysosome-associated membrane protein 2 (LAMP2) were found in phenotypes that closely resembled HCM but were differentiated based on serum protein levels and ventricular preexcitation.

3. **Arrhythmogenic right ventricular cardiomyopathy/dysplasia.** Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary abnormality resulting in fibrofatty infiltration of the myocardium, primarily the right ventricle. Clinical manifestations include right ventricular dysfunction and lethal ventricular arrhythmias. Diagnosis often includes a battery of tests, including an electrocardiogram demonstrating repolarization abnormalities and an epsilon wave, magnetic resonance imaging or computed tomography demonstrating fibrofatty infiltration of the right ventricle, and endomyocardial biopsy. Often a positive family history of the disorder is present. ARVC/D can be inherited in either an autosomal dominant (in most cases) or autosomal recessive pattern. Mutations in 12 genes associated with ARVC/D have been identified. Mutations in genes encoding desmoplakin, desmoglein-2, cardiac ryanodine receptor, and plakophilin-2 have all been associated with the autosomal dominant form of the

disease. In ARVC12, mutations in the *JUP* gene, encoding junction plakoglobin, have an autosomal dominant pattern of inheritance, whereas mutations in the same *JUP* gene with an autosomal recessive inheritance result in Naxos disease, a variant associated with the triad of ARVC/D along with dermatological manifestations such as wooly hair and palmoplantar keratoderma. Twelve subtypes of ARVC/D are distinguished on the basis of the gene involved and are described further in Table 42.2.

4. **Left ventricular noncompaction.** Left ventricular noncompaction (LVNC) is a relatively rare congenital abnormality of the myocardium resulting in a trabeculated appearance of the LV cavity. It is characterized by spongy myocardium that results from arrest in endomyocardial morphogenesis. It is seen in < 1% of adults. This disorder can occur in isolation or in association with other congenital anomalies. Over time, it is thought that noncompaction can proceed to DCM with severe systolic dysfunction. Different genes are thought to be involved in the pathogenesis for each of the LVNC variants. A mutation in the α-dystrobrevin gene (*DTNA*) on chromosome 18 has been linked to left ventricular noncompaction-1 (LVNC1). A mutation for LVNC2 has been identified on chromosome 11p15 (LVNC2). LVNC3 is caused by mutation in the *ZASP* gene on chromosome 10q22.2-q23.3. LVNC variants have been mapped specifically to mutations of the sarcomere genes: LVNC4 is caused by mutation in the *ACTC1* gene (chromosome 15q14), LVNC5 is caused by mutation in the *MYH7* gene (chromosome 14q12), and LVNC6 is caused by mutation in the *TNNT2* gene

TABLE 42.2 Genetic Variants of ARVC/D

ARVC/D variant	Chromosome/ gene	Comments
ARVC/D1	14q23-24/*TGFβ-3*	TGFβ-3 involved in embryogenesis and cell differentiation
ARVC/D2	1q41.1-q43/*RYR2*	Ryanodine receptor involved in Ca^{2+} release into cytosol
ARVC/D3	14q12-q22	In 1996, discovered in a study of three small families
ARVC/D4	2q32.1-q32.3	Some family members from affected cohort had involvement of the left ventricle
ARVC/D5	3p25.1/*TMEM43*	TMEM43 is a transmembrane protein expressed in blood and cardiac tissue
ARVC/D6	10p14-p12/*PTPLA*	Protein tyrosine *phosphatases* involved in cell growth and *PTPLA* is primarily found in cardiac tissue
ARVC/D7	10q.22.3 2q35/*DES*	
ARVC/D8	6p24/*DSP*	Desmoplakin (DSP) is a constituent protein of desmosomes
ARVC/D9	12p11/*PKP2*	Plakophilins are part of desmosomes and are also found in the nucleus regulating transcription PKP2 encodes plakophilin-2, an essential armadillo repeat protein of the cardiac desmosome
ARVC/D10	18q12.1-q12/*DSG2*	Encodes for desmogleins involved in desmosome cell adhesion
ARVC/D11	18q12.1/*DSC2*	Encodes for desmocollin, a desmosomal cadherin protein
ARVC/D12	17q21/*JUP*	Encodes junctional plakoglobin/JUP

From OMIM Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim/).

(chromosome 1q32). There is also an X-linked form of LVNC (LVNCX) caused by mutation in the gene encoding tafazzin (TAZ) and allelic to Barth syndrome.

D. Arrhythmogenic disorders

1. **Brugada syndrome.** Disorders of the conduction system of the heart lead to significant clinical manifestations, most notably ventricular arrhythmias and sudden cardiac death. Two entities, long QT syndrome (LQTS) and Brugada syndrome, have been well described, and their respective genetic abnormalities have been characterized. Brugada syndrome was initially described by Josep and Pedro Brugada in 1992. Clinically, ventricular arrhythmias and sudden cardiac death occur, particularly in middle-aged men. Characteristic electrocardiographic features can help make the diagnosis, and, in some cases, certain drugs, including sodium channel blockers and tricyclic antidepressants, can unmask the abnormality on a surface electrocardiogram. **Brugada syndrome is typically inherited in an autosomal dominant pattern**. However, a de novo mutation can occur in approximately 1% of cases. Mutations in eight genes have been identified as causing Brugada syndrome: *CACNA1C*, *CACNB2, GPD1L, HCN4, KCNE3, SCN1B*, *SCN3B,* and *SCN5A.* The *SCN5A* gene has been mapped to chromosome 3p22.2 and is a voltage-gated sodium channel gene. *SCN1B* (chromosome 19q13.12) and *SCN3B* (chromosome 11q24.1) are also voltage-gated sodium channel genes. *GPD1L,* an NAD-dependent glycerol-3-phosphate dehydrogenase gene, is associated with chromosome 3p22.3. *HCN4*, on chromosome 15q24, is a hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 gene. *KCNE3* (chromosome 11q13.4) is a voltage-gated potassium channel gene. *CACNA1C* (chromosome 12p13.33) and *CACNB2* (chromosome 10p12.33-10p12.31) are two subunits of the L-type voltage-dependent calcium channels. Genetic testing in Brugada syndrome is used to confirm a clinical diagnosis. A negative result does not necessarily exclude the diagnosis. It may reflect that the individual does not have the condition, but it may also mean that the individual either has a mutation in a gene not part of the testing panel or has a mutation in a Brugada-associated gene not included in the panel.
2. **Long QT syndrome.** LQTS encompasses a range of disorders characterized clinically by syncope and sudden cardiac death, with electrocardiographic abnormalities in the QT interval and in the T-wave morphology. LQTS is usually inherited in an autosomal dominant pattern. Recessive inheritance, seen in Jervell and Lange-Nielsen types 1 and 2, is rare. There are 12 different types of LQTS based on the type of gene involved. The various forms of LQTS are often distinguishable by clinical features and genetic abnormalities. One such distinguishing feature is that those with long QT syndrome 1 (LQT1) are typically at higher risk during periods of exercise, whereas those with the long QT syndrome 3 variant (LQT3) are at higher risk during sleep. The *KCNQ1* gene encodes the catecholamine-sensitive portion of the potassium channel responsible for conducting the delayed rectifier current (I_{Ks}) in the LQT1 variant, whereas the *SCN5A* gene is affected in the LQT3 variant. The underlying defect involving the sodium channel results in a prolonged depolarization current, whereas defects involving the potassium channel result in a longer QT duration secondary to inability to reestablish repolarization within the myocyte. The autosomal recessive phenotypes (Jervell and Lange-Nielsen types 1 and 2) are associated with bilateral sensorineural hearing loss.

   Hundreds of mutations are believed to be involved in LQTS. However, most of the prognostic information available is based on the gene involved and not the specific mutation. Having the genotypic information can help in prognosis and in determining response to therapy. The rates of ventricular arrhythmias and sudden cardiac death vary based on the gene involved, as does the response to therapy. This information may be particularly helpful in trying to decide between medical therapy, implantable cardioverter–defibrillator implantation, or both. Table 42.3 lists the 12 variants of LQTS and the genes involved.

TABLE 42.3 Genetic Variants Associated with Long QT Syndrome

LQT variant	Gene	Mode of inheritance	Function of gene product
LQT1	*KCNQ1*	Autosomal dominant	Catecholamine-sensitive portion of I_K potassium channel
LQT2	*KCNH2*	Autosomal dominant	α-Subunit of I_{Kr} potassium channel
LQT3	*SCN5A*	Autosomal dominant	Cardiac sodium channel
LQT4	*ANK2*	Autosomal dominant	Ankyrin protein
LQT5	*KCNE1*	Autosomal dominant	β-Subunit of I_{Ks} potassium channel
LQT6	*KCNE2*	Autosomal dominant	β-Subunit of I_{Ks} potassium channel
LQT7	*KCNJ2*	Autosomal dominant	Subunit of I_{Kr} potassium channel
LQT8	*CACNA1C*	Autosomal dominant	Subunit of the L-type voltage-dependent calcium channel
LQT9	*CAV3*	Autosomal dominant	Encodes caveolin-3, which is found in the membrane surrounding muscle cells *CAV3* gene mutations may affect the function of sodium channels
LQT10	*SCN4B*	Autosomal dominant	β-voltage–gated sodium channel subunit
LQT11	*AKAP9*	Autosomal dominant	Encodes the A-kinase anchor protein-9
LQT12	*SNTA1*	Autosomal dominant	Syntrophin, alpha 1 peripheral membrane protein associated with dystrophin, and dystrophin-related proteins
Jervell and Lange-Nielsen type 1	*KCNQ1*	Autosomal recessive	Subunit I_K channel
Jervell and Lange-Nielsen type 2	*KCNE1*	Autosomal recessive	β-Subunit of I_{Ks} potassium channel

3. **Atrial fibrillation.** AF is the most common of the arrhythmic disorders. The majority of adult-onset familial AF is inherited in an autosomal dominant pattern. A major breakthrough has occurred in the genomics of AF, with the finding that variants at **4q25 carry a risk of 1.6 and a population attributable risk of > 30%** in individuals of both European and Asian ancestries. The 4q25 variants are near a gene—*PITX2*—which is involved in left–right symmetry of the heart in development. It has not yet been proven how the variants at 4q25 exert their effect. Other genes contribute to a much smaller degree to the risk of AF. The majority of the mutations linked to AF have been found in the potassium ion channel genes (*KCNQ1*, *KCNJ2*, *KCNE2*, and *KCNH2*). The connexin 40 gene (*GJA5*) has also been implicated as a possible candidate. Due to the small number of mutations identified for familial AF, it is quite possible that there are many more mutations for familial AF that are still unknown. Genotype–phenotype correlations for familial types of AF have yet to be determined.

E. Valvular heart disease

1. **Mitral valve prolapse.** MVP (see Chapter 16) is a common disorder that appears to have a strong genetic component, and the familial form is likely inherited in an autosomal dominant pattern with variable penetrance. Although, in addition, it occurs in an idiopathic form, it is also associated with other valvular syndromes such as bicuspid aortic valve (BAV) and connective tissue diseases, which typically affect cardiovascular function such as Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome. Prolapse of the mitral valve occurs primarily in the connective tissue matrix of the valve itself. Myxomatous degeneration of the valve tissue leads to redundant tissue and weakening of both the valve and the subvalvular apparatus. Clinically, this manifests as displacement of the mitral valve leaflets into the left atrium during systole and may progress to mitral regurgitation and eventual congestive heart failure with occasional rupture of the chordae. Although surgical repair and replacement have improved the long-term prognosis of this disorder, understanding the genetic basis of this disease may allow the earlier diagnosis and development of therapies to prevent progression.

   Three genes have been identified with MVP inherited in an autosomal dominant manner. These are *MMVP1* (chromosome 16p12.1-11.2), *MMVP2* (chromosome 11p15.4), and *MMVP3* (chromosome 13q31.1-32.1). X-linked myxomatous valvular dystrophy (XMVD) has been mapped to chromosome Xq28, and the filamin A gene (*FLNA*) has been identified as a cause of XMVD. Filamin A may also have a role in MVP.

2. **BAV and aortic valve calcification.** Aortic valve disease (see Chapter 15) can be divided into two different types based on clinical characteristics: BAV and calcific aortic valvular disease. Calcific aortic valvular disease is typically a disease of the elderly and appears to be affected by those risk factors predisposing toward CAD. Vitamin D receptor polymorphisms have been implicated in the genesis of degenerative aortic valve disease, as has the apo E4 allele of the apolipoprotein E allele. BAV disease is believed to be a congenital abnormality that is typically discovered earlier on in life and is associated with disease of the aorta. What these two disorders have in common is the eventual progression to calcification of the aortic valve itself. Mutations in the *NOTCH1* gene on chromosome 9 have been implicated in BAV development. NOTCH1 is a transmembrane protein with transcriptional regulatory activity that is vital not only for aortic valve development but also for calcification. It is thought that mutations in this gene may allow the normally repressed transcription factor Runx2 to facilitate the development of valvular endothelial cells into osteoblastlike cells and promote valvular calcification. Mutations in the *ACTA2* gene on chromosome 10q23.3, which codes for actin, have also been linked to BAV. Mutations in ubiquitin fusion degradation 1-like gene (chromosome 22) have also been implicated in BAV. This gene codes for a signaling protein that is prevalent during embryonic formation of cardiac outflow tracts. Three additional loci associated with BAV have been identified on chromosomes 5, 13, and 18, but no specific genes have been discovered.

F. Inborn errors of metabolism. Cardiovascular disease is often a manifestation of genetic abnormalities in separate pathways, which produce secondary effects upon the cardiovascular system. Many of these genetic mishaps occur in multiple pathways essential to metabolism, and their resultant phenotypes often impose upon the cardiovascular system. Table 42.4 lists some examples of metabolic abnormalities and the associated cardiac manifestations.

G. Chromosomal abnormalities and cardiovascular disease. Chromosomal abnormalities that occur at the time of development can have serious implications with regard to the proper growth and development of a child. Although neuropsychiatric development is often delayed, the cardiovascular system is also affected in many of

TABLE 42.4 Cardiovascular Manifestations of Systemic Metabolic Disease

Metabolic disorder	Gene/protein defect	Effect upon cardiovascular system	Comments
Anderson-Fabry disease	α-Galactosidase deficiency	Accumulation of globotriaosylceramide Cardiomyopathy in the form of LVH, lethal arrhythmias, and coronary ischemia	X-linked
Hereditary hemochromatosis	*HFE*, an MHC class I-like protein, ferroportin, hepcidin, hemojuvelin, and transferrin receptor-2	Iron deposition involves the heart and results in cardiomyopathy	Can be acquired via transfusion-associated hemochromatosis
Niemann-Pick disease	Defect in sphingomyelinase	Accumulation of sphingomyelin in cardiac tissue leading to cardiomegaly	Affected children do not survive past first few years of life
Hurler's syndrome (type 1 mucopolysaccharidosis)	Deficiency in α-L-iduronidase	Biventricular enlargement, endocardial fibrosis, and valvular disease	Autosomal recessive
Hunter's syndrome (type 2 mucopolysaccharidosis)	Deficiency in iduronate sulfatase	Cardiac involvement includes valvular disease	X-linked
Danon disease	Deficiency in lysosome-associated protein type 2	Cardiac involvement includes LVH, CHF, and preexcitation	X-linked
Gaucher's disease	Deficiency of glucocerebrosides	Accumulation of glucocerebroside leading to cardiomyopathy, also calcification of aorta and aortic and mitral valves	
Pompe disease	Defect in glycogen storage	Biventricular concentric hypertrophy	Autosomal recessive transmission
L-Carnitine deficiency	*OCTN2* gene mutations affecting transport of carnitine	Cardiomegaly and dilated cardiomyopathy	Carnitine transport is vital for mitochondrial function. Cardioprotective benefits may be derived from protection from free radical damage

LVH, left ventricular hypertrophy. MHC, major histocompatibility complex; CHF, congestive heart failure.

TABLE 42.5 Common Chromosomal Abnormalities and Associated Cardiovascular Disease

Syndrome	Chromosomal abnormality	Associated CV abnormality
Down syndrome	Trisomy 21	Endocardial cushion defect, mitral valve prolapse, and tetralogy of Fallot
Turner syndrome	45X	Coarctation of the aorta, bicuspid AV, and anomalous PV return
Patau syndrome	Trisomy 13	Dextrocardia, ASD/VSD, and bicuspid AV
Edwards syndrome	Trisomy 18	PDA and left SVC
Fragile X syndrome	*FMR1* gene (X chromosome) with trinucleotide repeats	Mitral valve disease

CV, cardiovascular; ASD, atrial septal defect; AV, aortic valve; PV, pulmonary vein; PDA, patent ductus arteriosus; SVC, superior vena cava; VSD, ventricular septal defect.

these disorders and often survival may be limited due to the severity of congenital defects. Table 42.5 lists common syndromes associated with chromosomal structural abnormalities and the associated cardiovascular findings.

ACKNOWLEDGMENTS: *The authors acknowledge Dr. Eric Topol's contribution to an earlier version of this chapter.*

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SECTION VIII

Preventive Cardiology

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CHAPTER 43

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Dyslipidemia

I. INTRODUCTION. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world. It is estimated that 30% of all deaths worldwide can be ascribed to cardiovascular causes, and this number is expected to rise further as the incidence of CVD in the developing world increases as a result of lifestyle changes.

A. Morbidity and mortality. CVD is the number one killer in the United States, accounting for 36% of all deaths. CVD is responsible for one death every 36 seconds and claims more lives each year than cancer, accidents, chronic obstructive pulmonary disease, and diabetes mellitus combined. One of every five deaths in the United States is caused by coronary heart disease (CHD). There are 15.8 million Americans with a history of myocardial infarction (MI) or angina pectoris. As many as 865,000 Americans have a new MI each year, and 164,000 are victims of sudden cardiac death. The average age at first MI is 65.8 years for men and 70.4 years for women. According to the Centers for Disease Control and Prevention, elimination of all forms of CVD would raise the overall life expectancy by 7 years.

B. Economic consequences of CVD. The economic burden of CVD and stroke in the United States was estimated to be $431.8 billion in 2007. In 2004, CVD was the leading cause of hospitalization, contributing to > 6.4 million patient discharges and 4.2 million emergency department visits.

C. Prevention of coronary artery disease (CAD). Table 43.1 shows important targets for secondary prevention among patients with known coronary or noncoronary vascular disease. The goals for primary prevention are similar, but the cost-effectiveness of medical intervention is not so favorable in all populations. The consequences of modest population-wide risk reduction (e.g., reduction in fat intake [currently 33% of total calories] and cholesterol levels) and lifesaving technologies (e.g., surgery, angioplasty, and coronary care units) have reduced the death rate and possibly contributed to reduced morbidity, but the burden of CVD remains a major challenge.

II. HYPERLIPIDEMIA. Dyslipidemia is an important **correctable predictive factor for CAD**. There is a strong, independent, continuous, and graded relation between total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) level and risk of CAD events. This relation has been clearly demonstrated in men and women in all age groups. More than one-half of US adults (105 million) have TC levels > 200 mg/dL, and of these, 37 million have values > 240 mg/dL. In general, a 1% increase in LDL-C level leads to a 2% to 3% increase in risk of CAD.

A. Physiology

1. **Lipoproteins** are large molecular compounds that are essential to the transport of cholesterol and triglycerides within the blood. They contain a lipid core composed of triglycerides and cholesterol esters surrounded by phospholipids and specialized proteins known as **apolipoproteins**. The **five major families of lipoproteins** are **chylomicrons, very low density lipoproteins (VLDLs),**

TABLE 43.1 Goals for Secondary Prevention among Patients with Known Vascular Disease

Risk factor	Goal
Hypertension (mm Hg)	140/90 (130/80 if CKD or diabetes)
Dyslipidemia (mg/dL)	LDL < 100 (< 70 in high-risk patients)
	HDL ≥ 60
	Triglycerides < 100
Physical activity	30 min, three or four times per week
Body mass index	≤ 24.9 kg/m^2
Diabetes mellitus	Near-normal blood sugar (HbA1c < 6.5%)
Smoking	Complete cessation

CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDLs).

2. **Apolipoproteins** are necessary for the structure and enzymatic processes of lipids. Apolipoprotein A1 (**apo A1**) is a major component of **HDL**, and apolipoprotein B (**apo B**) is the main apolipoprotein for the remaining **non-HDL** lipoproteins.

B. Lipid-lowering trials. Aggressive lipid-lowering drug treatment of persons at various risk levels reduces CAD morbidity and mortality rates and increases overall survival. Although the association between hyperlipidemia and CAD was established much earlier, the demonstration of a relationship between reduction in serum lipid levels and a reduction in all-cause mortality had to await the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins." Multiple randomized trials have provided overwhelming evidence of the benefit of statins in both primary and secondary prevention of cardiovascular events.

1. **Primary prevention trials**
   a. The **West of Scotland Coronary Prevention Study (WOSCOPS) (1995)** demonstrated that treatment of men at relatively high risk with profoundly elevated cholesterol levels significantly reduced the risk of heart attack and death from heart disease. The double-blind study randomized 6,600 healthy men with a baseline mean LDL-C level of 193 mg/dL to pravastatin (40 mg/d) or to placebo, for an average of 5 years, and demonstrated a 31% relative reduction in the incidence of nonfatal MI or CAD death. Follow-up of this population published in 2007 showed that the statin group continued to experience lower rates of cardiovascular death after a further 10 years, even though only one-third continued to take statins during the additional follow-up period.
   b. The **Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (1998)** demonstrated benefit among patients with more typical risk profiles, including lower cholesterol values, than among those in the WOSCOPS. AFCAPS/TexCAPS patients had a baseline mean TC level of 220 mg/dL. The study randomized 6,600 patients to lovastatin 20 to 40 mg daily or placebo and demonstrated a 36% relative risk reduction (RRR) for first acute major coronary events in the lovastatin group.
   c. The **Heart Protection Study (HPS) (2002)** randomized 20,536 subjects in a 2 × 2 factorial design to daily simvastatin (40 mg) or placebo and to antioxidants or placebo (the antioxidant arm did not show any benefit or harm).

The study focused on patients who were deemed high risk for CVD but not thought to merit treatment with statins based on the prevalent clinical practice at that time. Increased risk was defined as presence of or history of CAD, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, or treated hypertension. Simvastatin therapy was associated with a 13% reduction in all-cause mortality, including an 18% reduction in coronary death rate. The beneficial impact of statin therapy was seen with respect to all cardiovascular end points, with significant reductions in risk of nonfatal MI, incidence of first stroke, and coronary and noncoronary revascularization. **Treating patients with LDL levels < 100 mg/dL was also associated with a beneficial reduction in vascular events**. The benefit was maintained in patients receiving other cardioprotective medications, such as angiotensin-converting enzyme inhibitors, β-blockers, and aspirin. Although not strictly a primary prevention trial, the HPS provided evidence to support treatment of risk as endorsed by the National Cholesterol Education Program (NCEP) guidelines. However, the HPS results refuted the threshold LDL level (as proposed by NCEP III at that time) below which statins were not previously indicated.

d. **Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) (2002)** randomized 5,804 patients between the ages of 70 and 82 years to placebo or pravastatin. These patients had preexisting coronary, cerebral, or peripheral vascular disease or had a history of smoking, hypertension, or diabetes. The study demonstrated a 15% reduction in the composite of coronary death, nonfatal MI, and stroke over a period of 3 years. The study demonstrated efficacy of primary and secondary prevention in the elderly.

e. The **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (2002)** randomized 10,355 hypertensive patients with one other coronary risk factor and a baseline mean LDL-C level of 148 mg/dL to pravastatin 20 to 40 mg/d or usual care. The study did not demonstrate a mortality difference in the two arms after a follow-up period of 4.8 years. This lack of observable difference in outcome might have resulted from the relatively modest LDL reduction (17% with pravastatin vs. 8% in usual care) or the fact that 26% of the patients in the "usual care" group were taking a statin at the end of the trial.

f. The **Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) (2003)** randomized 10,305 patients with hypertension and at least three other cardiovascular risk factors and a baseline mean LDL-C level of 133 mg/dL to atorvastatin 10 mg/d or placebo. The study was stopped prematurely after a median follow-up of 3.3 years by the safety monitoring committee because of a significantly higher incidence of the primary end point (nonfatal MI or fatal CHD) in the placebo group. The study demonstrated a 36% RRR for the primary end point in the atorvastatin group compared with the placebo group. Further analysis demonstrated that the benefit of statin therapy started after only 1 year of treatment. There was also a significant reduction (RRR of 27%) in the incidence of fatal and nonfatal stroke in the atorvastatin group. This study, like the HPS, provided further evidence of the benefit of statins in patients at high risk for CVD without regard for baseline TC or LDL levels.

g. The **Collaborative Atorvastatin Diabetes Study (CARDS) (2004)** randomized 2,838 diabetic patients with one additional cardiovascular risk factor, no history of CVD, and an average baseline LDL-C of only 117 mg/dL to atorvastatin 10 mg/d or placebo. This study was also terminated prematurely owing to an excess incidence of the primary end point (a composite of acute coronary events, coronary revascularization, or stroke) in the placebo group after a median follow-up of 3.9 years. Overall, the atorvastatin group

had an RRR of 37% for the primary end point and 27% for all-cause mortality. The importance of this trial was its demonstration of the clinical benefit of statin use in diabetic patients regardless of baseline LDL-C level, making a compelling case for statin use in all diabetic patients with at least one additional cardiovascular risk factor. According to the NHANES III data, 82% of diabetic patients in the United States would meet the entry criteria for the CARDS trial.

h. The **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (2005)** trial focused on the prevention of CHD in patients with type 2 diabetes using fenofibrates. The study randomized patients with type 2 diabetes diagnosed after 35 years of age with no clear indication for cholesterol-lowering therapy at baseline to fenofibrate (200 mg/d) or placebo. The study failed to show a difference in the primary composite end point of CHD or nonfatal MI between the two groups at 5-year follow-up. However, several secondary end points were lower in the fenofibrate group including nonfatal MI and coronary revascularization.

i. **Japan EPA Lipid Intervention Study (JELIS) (2007).** The goal of this trial was to evaluate treatment with the fish oil supplement eicosapentaenoic acid (EPA) in addition to statin therapy compared with statin therapy alone among patients with hypercholesterolemia. The study randomized patients in an open-label manner to treatment with EPA (1,800 mg/d) in addition to statin therapy (pravastatin 10 mg/d) or simvastatin (5 mg/d) or to statin therapy alone. At a mean follow-up of 4.6 years, there was a significant reduction in the primary end point of major adverse cardiovascular events in the EPA plus statin group (2.8% vs. 3.5%). This was driven primarily by a significant reduction in rates of unstable angina and a trend toward lower rates of nonfatal MI and revascularization. No difference was seen in sudden cardiac death or fatal MI.

j. The **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (2008)** trial focused on patients with normal LDL-C levels but increased levels of high-sensitivity C-reactive protein (CRP). This was the first clinical trial to demonstrate that statin therapy may benefit patients with low-to-normal LDL levels and no known CVD. The study randomized 17,802 healthy subjects with an LDL-C < 130 mg/dL and a CRP ≥ 2.0 mg/L to daily rosuvastatin of 20 mg or placebo. The trial was stopped early for a mortality benefit after a median follow-up of 1.9 years. The study demonstrated that after 1 year of therapy, there were lower levels of LDL-C (55 vs. 110 mg/dL) and lower levels of CRP (2.2 vs. 3.5 mg/L) in the rosuvastatin-treated group. There was also a lower incidence of the primary end point of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed death from cardiovascular cause (0.77 vs. 1.36 events per 100 person-life years) as well as the risk of all-cause mortality (1.00 vs. 1.25 deaths per 100 person-life years) in the rosuvastatin-treated group.

k. The **Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD Lipid) (2010)** was designed to evaluate whether the addition of fenofibrate to statin therapy among patients with type 2 diabetes would be effective in preventing cardiovascular events. The study randomized half of the patients within the initial ACCORD trial with type 2 diabetes and treated with a statin medication to fenofibrate (160 mg daily) or placebo. Although a significant reduction in triglyceride level (186 to 170 mg/dL) was seen with the addition of fenofibrate to statin therapy, there was no reduction in the primary end point (first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) when compared with statin therapy alone.

In a subgroup analysis, a trend toward benefit of fenofibrate was shown in the group of patients with diabetes that had a significant dyslipidemia (low HDL and high triglycerides). Additional subgroup analysis showed a trend toward harm in women (but not men) in the fenofibrate group that warrants further investigation in future studies.

2. **Secondary prevention trials**
   a. The **Scandinavian Simvastatin Survival Study (4S) (1994)** was the first secondary prevention trial to demonstrate a clear reduction in total mortality. Simvastatin reduced total mortality among patients with CAD by 30%, largely because of a 42% reduction in deaths from CAD. The 4S treated 4,444 men and women with CAD and mean baseline LDL of 188 mg/dL, with a range of 130 to 266 mg/dL.
   b. The randomized, controlled **Cholesterol and Recurrent Events Trial (CARE) (1996)** was designed to evaluate the effects of treatment with pravastatin on 4,159 persons who had experienced acute MI 3 to 20 months before randomization and had moderately elevated TC levels (mean 209 mg/dL). The benefits of pravastatin therapy in preventing recurrent coronary events were similar in the subset analysis of age, sex, ejection fraction, hypertension, diabetes mellitus, and smoking.
   c. The **Long-Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) (1998)** was the first to examine the use of a statin for patients with a history of unstable angina. The LIPID study provided new data on noncoronary mortality (i.e., stroke) and on other groups, such as women and patients with diabetes, who previously had been underrepresented in clinical trials. LIPID demonstrated improved CAD outcomes among all patients, including those with unstable angina.
   d. **The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (1999)** was a multicenter study that randomized patients with known CHD and low high-density lipoprotein cholesterol (HDL-C) (≤ 40 mg/dL) and LDL-C (≤140 mg/dL) levels to gemfibrozil (1,200 mg/d) or placebo with a mean follow-up of 5.1 years. The study showed that gemfibrozil therapy was associated with a significant 22% reduction in the combined incidence of nonfatal MI and CHD death. This was the first lipid intervention trial to show that raising HDL-C concentrations in patients with CHD and low HDL-C and LDL-C levels will reduce the incidence of major coronary events.
   e. **Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial (MIRACL) (2001).** This trial demonstrated cardiovascular benefits with initiation of early statin therapy following acute coronary syndrome (ACS). The trial randomized 3,086 adults with unstable angina or non–Q-wave MI to high-dose atorvastatin (80 mg/d) or placebo between 24 and 96 hours after hospital admission. There was a reduction in the primary end point of nonfatal infarction, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring hospitalization in the atorvastatin group (14.8% vs. 17.4%, RRR of 16%). The benefit was driven primarily by a 26% reduction in recurrent symptomatic ischemia. The trial did not show a mortality benefit (death, MI, or need for revascularization).
   f. **Pravastatin or Atorvastatin Evaluation and Infection Therapy–TIMI 22 (PROVE-IT–TIMI-22) (2004).** This trial was designed to determine whether intensive lipid-lowering therapy in patients with ACS reduced major coronary events and mortality more than "standard" lipid lowering. A total of 4,162 patients who had been hospitalized for ACS within the preceding 10 days were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d. After 2 years of follow-up, the composite end point (all-cause mortality, MI,

unstable angina, coronary revascularization, and stroke) was significantly reduced by 16% with atorvastatin compared with pravastatin. High-dose atorvastatin was well tolerated, with no cases of rhabdomyolysis. Of note, the LDL-C level attained on atorvastatin 80 mg/d was 33 mg/dL lower than on pravastatin with a mean of 62 mg/dL. These results suggested that the use of intensive lipid-lowering therapy to achieve very low LDL-C levels was of benefit in a group of patients at high risk for recurrent coronary events.

g. **A to Z Trial: Phase Z (2004)—Early Intensive vs. a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes (2004).** This trial studied whether early initiation of high-dose statin therapy would lead to a reduction in long-term cardiac events compared with a more conservative, delayed low-dose statin strategy in high-risk patients with ACS. The trial enrolled a total of 4,497 patients with a recent ACS, TC level ≤250 mg/dL, and at least one additional risk factor who were randomized to either intensive statin therapy strategy (simvastatin 40 mg for 1 month, followed by 80 mg through 2 years) or a conservative strategy (placebo for 4 months followed by simvastatin 20 mg through 2 years). Although the study showed an early and sustained reduction in LDL in the aggressive strategy arm, it did not show a significant reduction in the primary composite end point of cardiovascular events (cardiovascular death, MI, readmission for ACS, and CVA) or death from any cause compared with a more conservative strategy. There were also more patients who developed creatine kinase (CK) concentrations more than 10 times the upper limit of normal in the aggressive strategy arm (9 vs. 1) and 3 patients who developed rhabdomyolysis while on simvastatin 80 mg.

h. The **Treating to New Targets (TNT) (2005)** trial sought to demonstrate the benefit of intensive lipid-lowering therapy in patients with stable coronary disease. The trial randomized 10,001 patients with clinically evident CHD and baseline LDL-C levels < 130 mg/dL to atorvastatin 80 mg/d or atorvastatin 10 mg/d. After 4.9 years of follow-up, the group receiving atorvastatin 80 mg/d had a 22% RRR in the primary composite end point of death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke compared with the group receiving atorvastatin 10 mg/d. High-dose atorvastatin was remarkably safe, with a 1.2% incidence in elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than three times the upper limit of normal, compared with a 0.2% incidence in the atorvastatin 10 mg group. Rates of myalgias and rhabdomyolysis were similar between the two groups. This study provided compelling evidence that the use of intensive statin therapy to reduce LDL-C to levels below 100 mg/dL had marked clinical benefit in patients with stable CHD.

i. The **Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) (2005)** trial randomized 8,888 patients with a prior history of acute MI to atorvastatin 80 mg/d or simvastatin 20 mg/d. After 4.8 years of follow-up, there was a nonsignificant difference in the risk of the composite end point of coronary death, acute MI, or cardiac arrest. However, if either stroke or revascularization was added to the primary end point, the results favored the atorvastatin group, and the associated hazard ratios were similar to the results of PROVE-IT and TNT. Despite the published negative result of this trial, it provided complementary evidence for the benefit of intensive LDL lowering in patients at high risk for coronary events.

j. The **Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) (2011)** was a study that compared treatment of extended-release niacin versus placebo among statin-treated patients with established heart and vascular disease. The study randomized 3,414 patients with

optimally treated LDL-C and low HDL-C with established vascular disease (documented by coronary angiography or by prior MI, or carotid angiography or prior ischemic stroke, or peripheral arterial disease) to extended-release niacin (1,500 to 2,000 mg/d) or placebo. There was no significant difference in the primary composite outcome of CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization (16.4% in the extended-release niacin group vs. 16.2% in the placebo group). The study was terminated 18 months early after it was evident that the addition of extended-release niacin would not be beneficial. Furthermore, there was a small (numerical) excess in ischemic strokes and hospitalizations for ACS.

3. **Meta-analyses**
   a. **CTT Collaborators (*Lancet*, 2005).** A large meta-analysis of 90,056 individuals from 14 randomized trials of statin drugs, this analysis demonstrated an impressive 12% reduction in all-cause mortality for each 1 mmol/L (39 mg/dL) reduction in LDL. There was a 19% reduction in coronary mortality and 21% reduction in MI, coronary revascularization, and stroke. Statin use showed benefit within the first year of use, but was greater in subsequent years. Statins were also remarkably safe, with no increase in cancer seen and a 5-year excess risk of rhabdomyolysis of 0.1%.
   b. **Cannon—Intensive Statin Therapy (*J Am Coll Cardiol*, 2006).** A meta-analysis of 27,548 patients from four trials that investigated intensive versus standard lipid-lowering therapy found a significant 16% odds ratio reduction in coronary death or MI in the group that received intensive therapy. There was a nonsignificant trend toward decreased cardiovascular mortality.

C. Management of lipids. Despite overwhelming evidence supporting the treatment of dyslipidemia, a large number of patients remain untreated. The NCEP Adult Treatment Panel III (ATP III) has released guidelines for the treatment of hyperlipidemia in adults. These guidelines focus on identification of the risk of cardiovascular morbidity and appropriate targeting of therapy. The guidelines were last updated in 2004, with the next update planned for 2012.

1. **Guidelines for primary prevention of CAD events** based on the NCEP ATP III
   a. **TC, LDL-C, and HDL-C levels.** All adults 20 years or older and **without a history of CAD or other atherosclerotic disease** should have a fasting lipid panel (i.e., TC, LDL-C, HDL-C, and triglyceride levels) every 5 years. If a nonfasting lipid panel is obtained and the TC level is 200 mg/dL or the HDL-C is < 40 mg/dL, a follow-up fasting lipid panel is recommended (Table 43.2).
   b. **Determination of risk.** The patient's risk of future events is based on the presence of known CAD or clinical atherosclerosis in a noncoronary bed, diabetes mellitus (i.e., CAD equivalent), and other risk factors. These include age (men 45 years or older and women 55 years or older), smoking, hypertension (> 140/90 mm Hg or use of antihypertensive medication), family history of premature CAD (defined as CAD in first-degree male relatives before the age of 55 years and in a first-degree female relative before the age of 65 years), and low HDL-C (< 40 mg/dL). An **HDL-C level 60 mg/dL or greater is considered a negative risk factor**. Patients are classified into three categories of risk based on these factors.
      (1) **CHD risk.** Patients with highest risk of cardiovascular events are those with established CAD or evidence of atherosclerosis in noncoronary beds (i.e., abdominal aortic aneurysms, peripheral arterial disease, or symptomatic carotid disease), **diabetes mellitus**, or presence of multiple risk factors conferring a calculated 10-year risk of > 20%. The risk is calculated according to the Framingham risk score. The target LDL-C level for this group is < 100 mg/dL.

TABLE 43.2 Lipid Classification According to the National Cholesterol Education Program III

Risk factor	Goal
LDL-C	
< 100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high
Total cholesterol	
< 200	Desirable
200–239	Borderline high
≥ 240	High
HDL-C	
< 40	Low
≥ 60	High

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

(2) The second category includes patients with multiple risk factors and an estimated 10-year risk of adverse events between 10% and 20%. The target LDL-C level for this group is < 130 mg/dL.

(3) The third category includes those with no or one risk factor and an estimated 10-year risk of < 10%. The target LDL-C level in this group is < 160 mg/dL.

c. Treatment of dyslipidemia. The treatment of hyperlipidemia requires two approaches: therapeutic lifestyle changes (TLCs) and medications (Table 43.3). To achieve target LDL levels, most patients need both approaches simultaneously.

(1) CHD risk equivalent. These patients are at the highest risk of adverse events and, therefore, benefit the most from aggressive treatment. NCEP III, whose recommendations were published in 2001, had recommended therapy with a statin and TLCs if the LDL-C level was 130 mg/dL or greater. In patients with LDL-C levels between 100 and 130 mg/dL, it is suggested that the clinician use judgment as to whether to begin treatment with a statin, TLCs, or another agent such as niacin or a fibrate. **The 2004 update, however, was more definitive and recommended starting a statin and TLCs for all patients with a CHD risk equivalent with LDL-C levels 100 to 130 mg/dL.** This was based on cited evidence from the HPS and was further supported by the CARDS and ASCOT-LLA trials. In patients who have a baseline LDL-C concentration of < 100 mg/dL, the 2004 update stopped short of recommending initial use of a statin, but acknowledged that there was evidence for statin use in this group regardless of the LDL-C level. It did, however, state that initiation of a statin drug in patients with an initial LDL-C < 100 mg/dL who are

TABLE 43.3 Low-Density Lipoprotein Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk category	LDL goal (mg/dL)	LDL level at which to initiate TLC (mg/dL)	LDL level at which to consider drug therapy
CHD or CHD risk equivalent (10-y risk > 20%)	< 100	≥ 100	≥ 130 mg/dL (100–129 mg/dL: drug optional)
2+ risk factors (10-y risk ≤ 20%)	< 130	≥ 130	10-y risk 10–20%: ≥ 130 mg/dL 10-y risk < 10%: ≥ 160 mg/dL
0–1 risk factor	< 160	≥ 160	≥ 190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

CHD, coronary heart disease; LDL, low-density lipoprotein; TLC, therapeutic lifestyle changes.

at "very high risk" for future CVD events, with the goal of lowering the LDL-C to < 70 mg/dL, was a "reasonable therapeutic option." The cited evidence included the HPS and PROVE-IT–TIMI-22 trials. The publication of the TNT trial provided even more evidence for intensive lipid lowering in all patients with clinically evident CHD. **Given the balance of evidence in the most recently published trials and meta-analyses, a reasonable current approach for most clinicians would be to initiate statin therapy in all patients with CHD or a CHD risk equivalent, regardless of baseline LDL-C level, with a goal LDL-C of ≤ 70 mg/dL for patients with CHD or at high risk for future CVD events.**

(2) **Ten-year risk of 10% to 20%.** These are generally patients with two or more risk factors for CVD events. The target LDL-C level for this group is < 130 mg/dL. The 2004 ATP III update stated that an LDL-C goal < 100 mg/dL is a therapeutic option, and initiation of statin therapy along with TLCs for patients with baseline LDL-C level 100 to 130 mg/dL was reasonable. This recommendation was based on evidence from the HPS and ASCOT-LLA trials.

(3) **Ten-year risk < 10% and zero or one risk factor.** These patients should be treated with TLC to achieve a target LDL-C level < 160 mg/dL. If the LDL-C concentration remains above 160 mg/dL after 3 months of TLCs, drug therapy may be considered. Pharmacotherapy is recommended in those with LDL-C levels > 190 mg/dL. Factors favoring the use of drugs include a 10-year risk close to 10% or the presence of a severe risk factor such as a strong family history of premature CAD, a very low HDL level, poorly controlled hypertension, or heavy smoking.

2. **Types of therapy**

a. **TLCs** encompass **increased physical activity, ideal weight maintenance, and a diet** that includes a reduced intake of saturated fat (< 7% of total calories) and cholesterol (< 200 mg/d). Other TLCs are listed in Table 43.4. Intake of *trans*-fatty acids should be kept to a minimum. For most patients, it is essential to reduce saturated fat intake over total fat intake; for patients with metabolic syndrome, a fat intake of 30% to 35% may be optimal for reducing lipid and nonlipid risk factors. High-carbohydrate diets may worsen the lipid abnormalities in these patients. Dietary carbohydrates should be

TABLE 43.4 Components of Therapeutic Lifestyle

Component	Recommendation	Approximate LDL reduction
Diet		
Saturated fat	< 7% of total calories	8–10%
Dietary cholesterol	< 200 mg/d	3–5%
Polyunsaturated fat	Up to 10% of total calories	
Monounsaturated fat	Up to 20% of total calories	
Total fat	25–35% of total calories	
Carbohydrate	50–60% of total calories	
Dietary fiber	20–30 g/d	
Total protein	15% of total calories	
Therapeutic options for LDL lowering		
Plant stanols/sterols	2 g/d	6–15%
Increased viscous soluble fiber	5–10 g/d (consumption of 10–25 g/d may have added benefit)	3–5%
Physical activity	Enough moderate activity to expend at least 200 kcal/d	

LDL, low-density lipoprotein.

derived predominantly from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables. Daily intake of 5 to 10 g of viscous fiber reduces LDL levels by approximately 5% and the use of plant stanols and sterols (2 to 3 g/d) by another 6% to 15%. **TLCs can achieve an almost 30% reduction in LDL-C level in highly motivated individuals and should form the cornerstone of all preventive activity**. Benefits of LDL-C lowering may be evident within 6 to 12 months, although the individual response to a cholesterol-lowering diet depends on many factors. Some of the response is genetically determined, and increased body mass index is associated with less response to dietary change. LDL-C should be measured 6 weeks after initiating TLC diet, and if the goals are not met, intensification of TLCs and use of plant sterols or stanols should be considered. Referral to a dietitian for education and dietary counseling is often invaluable at this stage. If, after 3 months of TLCs, adequate control is not achieved, drug therapy should be considered.

b. Pharmacotherapy. The high efficacy of statins in lowering LDL-C level and their demonstrated mortality benefits make them the agents of first choice for treatment of most forms of hyperlipidemia. Table 43.5 summarizes the most commonly used agents affecting lipoprotein metabolism.

(1) HMG-CoA reductase inhibitors. The third report of the NCEP ATP included **HMG-CoA reductase inhibitors** among the first-line alternatives in the management of hypercholesterolemia. The category includes six drugs: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin.

TABLE 43.5 Drugs Affecting Lipoprotein Metabolism

Drug class	Agents and daily doses	Lipid/lipoprotein effects	Side effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–80 mg) Fluvastatin (20–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (10–40 mg)	LDL-C ↓ 18–55% HDL-C ↑ 5–15% TG ↓ 7–30%	Gastrointestinal distress Myopathy Increased liver enzymes	Absolute: – Active or chronic liver disease Relative: – Concomitant use of certain drugs[a]
Bile acid sequestrants	Cholestyramine (4–16 g) Colestipol (5–20 g) Colesevelam (2.6–3.8 g)	LDL-C ↓ 15–30% HDL-C ↑ 3–5% TG—no change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: – Dysbeta-lipoproteinemia – TG > 400 mg/dL Relative: – TG > 200 mg/dL
Nicotinic acid	Immediate release (crystalline nicotinic acid [1.5–3 g]) Extended release (Niaspan; 1–2 g) Sustained release (1–2 g)	LDL-C ↓ 5–25% HDL-C ↑ 15–35% TG ↓ 20–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: – Chronic liver disease – Severe gout Relative: – Diabetes – Hyperuricemia – Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg bid) Fenofibrate (200 mg) Clofibrate (1,000 mg bid)	LDL-C ↓ 5–20% (may be increased in patients with high TG) HDL-C ↑ 10–20% TG ↓ 20–50%	Dyspepsia Gallstones Myopathy	Absolute: – Severe renal disease – Severe hepatic disease

[a]Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P450 inhibitors (fibrates and niacin should be used with appropriate caution).

GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

(a) Effectiveness. When dietary measures are inadequate, HMG-CoA reductase inhibitors effectively **lower TC and LDL-C levels in patients with mixed hyperlipidemias** (i.e., elevated cholesterol and triglyceride levels). HMG-CoA reductase inhibitors are **extremely effective in reducing LDL-C levels in most patients with primary hypercholesterolemia.** HMG-CoA reductase inhibitors decrease TC by 15% to 60% and LDL-C by 18% to 55% and increase HDL-C levels by 5% to 15%. Declines in apo B levels commensurate with reductions in LDL have been demonstrated. Statins also reduce triglyceride levels by 7% to 30% but have minimal effects on apo A1, apo A2, and lipoprotein (a) [Lp(a)]. **All statin drugs at the starting dose and within one to two dose titrations are well tolerated, efficacious**, and reasonably equivalent with respect to safety profiles.

(b) Adverse effects. Statins are remarkably safe drugs, with a low incidence of side effects. However, they are contraindicated in pregnancy.

(i) Minor side effects. The most common side effects are **mild gastrointestinal disturbances** (e.g., nausea, abdominal pain, diarrhea, constipation, and flatulence). Headache, fatigue, pruritus, and myalgias are other minor side effects, but none of these complaints usually warrant discontinuation of therapy.

(ii) Liver function test abnormalities. Mild, transient elevations in liver enzymes have been reported with all HMG-CoA reductase inhibitors. Marked elevation of transaminases is rare, but clinicians should avoid or use caution before starting statins in patients with acute or chronic liver disease. In the HPS, only 0.5% of patients had to stop treatment because of elevated ALT levels. Even when taking the highest dose of atorvastatin (80 mg), patients in PROVE-IT and TNT had only a 3.3% and 1.1% incidence, respectively, of transaminase elevation more than three times the upper limit of normal. In general, for each doubling of a statin dose, there is a 0.6% increase in risk of elevation of transaminase levels. **Current recommendations state that therapy should be discontinued when greater than threefold elevation occurs**. Enzyme levels typically return to normal within 2 weeks. Lower doses of the same medication can be reinstituted or a different statin can be tried. **Monitoring of hepatic aminotransferase levels is recommended for those taking HMG-CoA reductase inhibitors, but the frequency of monitoring has been debated**. Current package inserts for most statins recommend obtaining a liver panel prior to initiation of statin therapy, prior to dose titration, and when "clinically indicated." More frequent monitoring is recommended for patients taking the highest dose of a statin. In recent clinical trials, the high-dose statin that appears to have the highest incidence of transaminase elevation is atorvastatin. A panel of hepatologists who examined the potential hepatotoxicity of statins made a recommendation to obtain a liver panel prior to initiating statins as a baseline measurement of hepatic transaminases and bilirubin. If the baseline measurements were within normal limits, the panel recommended follow-up measurement of transaminases only if there was symptomatic or physical evidence of liver disease. An ACC/AHA/NHLBI clinical advisory panel on the safety and use of statins recommends measurement of transaminases at baseline, 12 weeks after starting therapy, and then annually or more frequently if indicated.

(iii) **Myopathy**, a rare but potentially serious side effect of HMG-CoA reductase inhibitors, presents with muscle pain, stiffness, or aching and elevations in serum CK level to more than 10 times the upper limit of normal. **CK measurements are not needed unless symptoms occur**. Statin-naïve patients should be warned to report symptoms of muscle pain or stiffness immediately if they occur after starting the drug. The risk of myopathy may be increased in the elderly, those with a low body mass index, those with multisystem disease such as chronic renal failure, those in the perioperative period, and those on multiple medications. Simvastatin 80 mg has been associated with a slightly higher incidence of myopathy and rhabdomyolysis compared with other statins, especially when combined with gemfibrozil. This could be due to the decreased rate of plasma clearance of simvastatin in older versus younger patients. Death from statin-induced rhabdomyolysis is exceedingly rare, with an incidence of 1.5 deaths per 10 million prescriptions. Statin-associated myalgias (muscle symptoms without elevations in serum CK) occur with somewhat higher frequency, about 1.4% to 1.5% in published clinical trials, and can appear at any time during statin therapy, even years after initiation of treatment. Muscle symptoms usually resolve with discontinuation of the statin. There is recent evidence that statin inhibition of mitochondrial coenzyme Q10 may be responsible for statin-induced myalgias, and there is evidence from small clinical trials that oral coenzyme Q10 supplementation may decrease symptoms of statin-associated myalgias.

(iv) **Drug interactions.** When statins are used in combination with certain pharmaceutical agents, such as erythromycin, gemfibrozil, azole antifungals, cimetidine, methotrexate, or cyclosporine, the risks of CK elevation and myositis increase. These drug combinations should be avoided or used judiciously with interval measurements of CK levels and liver function. Pravastatin and fluvastatin are safer in combination with other drugs because these two drugs do not use the cytochrome P450 3A4 microsomal pathways for metabolism. Verapamil and amiodarone are two commonly used cardiovascular agents that inhibit this pathway, and the concurrent use of simvastatin, atorvastatin, or lovastatin may, therefore, predispose to an increased risk of myositis. Recently, the US Food and Drug Administration (FDA) has recommended that simvastatin should not be prescribed at a dose of 80 mg, given the higher rate of myopathy at this dose unless patients have already safely taken this dose for > 12 months. Patients requiring this dose to maintain lipid goals should be transferred to another statin drug capable of achieving that goal. Simvastatin dosage in combination with amiodarone, diltiazem, or verapamil should not exceed 10 mg daily and should not exceed 20 mg daily in combination with amlodipine or ranolazine.

(2) **Bile acid sequestrants** lower LDL-C level by interfering with reabsorption of bile acids in the distal ileum, reducing the amount returned to the liver. They are safe and free of systemic side effects because they are not systemically absorbed; however, gastrointestinal side effects such as constipation are common, and compliance is poor as a result. The average LDL level decrease is approximately 15% to 30%, with a small rise seen in HDL level (3% to 5%). Triglycerides show no change or may

rise; therefore, these agents should be avoided in patients with elevated triglycerides. Two small angiographic trials, the NHLBI Type II Coronary Interventional Study and the St. Thomas Atherosclerosis Regression Study (STARS), have demonstrated reduced progression of CAD on serial angiograms in men with hypercholesterolemia who were taking cholestyramine. These agents may be of particular benefit in patients with minor elevation in LDL-C, for young patients, for women considering pregnancy, and in combination with a statin in those with very high LDL-C levels. In a pregnant patient, additional supplementation of iron and folate may be necessary because resins used over the long term can interfere with their absorption.

(3) **Nicotinic acid or niacin.** Niacin affects all lipid parameters favorably (i.e., LDL reduction of 5% to 25%, triglyceride reduction of 20% to 50%, and HDL elevation of 15% to 35%). It is one of the only agents that reduces Lp(a) significantly (up to 30%). Unfortunately, compliance is poor because of frequent side effects. Flushing and pruritus, gastrointestinal discomfort, glucose intolerance, and hyperuricemia often accompany the use of niacin. Hepatotoxicity is rare but is more commonly seen with the sustained-release preparation. It is often heralded by a dramatic reduction in lipid levels. There are limited data on long-term therapy with this agent. Niacin may be particularly useful for patients who do not have substantial elevations in their LDL-C levels, and low doses may be used to treat diabetic dyslipidemia. High doses should be avoided in patients with diabetes, and the drug should be avoided in those with a history of gout, peptic ulcer disease, or active hepatic disease.

(4) **Fibrates are effective at lowering triglyceride levels** by 20% to 50% and raising HDL levels by 10% to 20%. The mechanism of action involves activation of the nuclear transcription factor peroxisome proliferator–activated receptor alpha, with resultant increases in hepatic synthesis of apo A1 and A2 (raising HDL) and increase in lipoprotein lipase–mediated lipolysis, thus lowering triglyceride levels. LDL level reduction varies with the agent used and may range from 5% to 20% in patients who are not hypertriglyceridemic. Fenofibrate appears to lower LDL more effectively than gemfibrozil. Although a higher mortality rate was seen in the clofibrate arm of the World Health Organization (WHO) clofibrate study, such a finding was not seen in subsequent studies of gemfibrozil or fenofibrate. These agents have been demonstrated to impart a reduction in risk of CAD events and are of use in patients with elevated triglycerides. The VA-HIT (1999) found a reduction in fatal and nonfatal MI with gemfibrozil use in men with CAD who had low HDL levels (mean of 32 mg/dL), but the FIELD trial (2005) did not find a significant reduction in the primary end point of CAD death or MI in diabetic patients. Although fibrates are often used in combination with statin therapy to treat mixed dyslipidemia, there are no studies demonstrating reduction in clinical events with this approach. This combination increases the risk of myopathy. For patients with very high triglyceride levels (> 1000 mg/dL), fibrate therapy reduces the risk of pancreatitis.

(5) **Cholesterol absorption inhibitors** such as ezetimibe inhibit cholesterol absorption by the enterocyte. Ezetimibe reduces cholesterol absorption from the small bowel by 23% to 50% and reduces serum LDL level by 14% to 20% when used in combination with a statin. Reduction in clinical end points or surrogate end points has not been demonstrated for this group of drugs in all people. The SHARP trial (Study of Heart and Renal Protection) reported that cholesterol lowering with a combination

of simvastatin and ezetimibe in patients with chronic kidney disease significantly reduced the risk of major atherosclerotic events by 17%, including significant reductions in the risk of nonhemorrhagic stroke and revascularizations, when compared with placebo. However, the ENHANCE study failed to demonstrate any additional benefit of the use of ezetimibe added to statin over statin alone in slowing progression of carotid intimal thickness in a cohort of patients with familial hyperlipidemia. A number of large-scale studies are currently in progress seeking to determine the utility of a statin ezetimibe combination on hard cardiovascular end points. IMPROVE-IT, a phase III trial comparing ezetimibe/simvastatin versus simvastatin in subjects with stabilized high-risk ACS, is currently underway.

(6) **Cholesteryl ester transfer protein (CETP) inhibitors** such as torcetrapib, dalcetrapib, anacetrapib, and evacetrapib inhibit the process in which triglycerides from VLDL or LDL are exchanged for cholesteryl esters from HDL, resulting in higher HDL levels and reduction of LDL levels. Results from a torcetrapib study in 2004 demonstrated a significant increase in HDL (61%) and a decrease in LDL (17%) when receiving the drug in addition to atorvastatin and a 46% increase in HDL when receiving the drug alone. However, the phase 3 ILLUMINATE trial was terminated in 2006 after an increase of cardiovascular events and mortality was shown to be associated with the drug. Early results from the DEFINE trial (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) have reported a decrease of LDL by 36% and increase of HDL by 138% without associated increased CVD death or events. This is a medium-sized safety trial with 2-year follow-up due to complete in December of 2012.

(a) **Choice of an agent and combination therapy.** The use of statin therapy for treatment of hyperlipidemia should be guided by the expected change in LDL-C levels (Table 43.6). Most statins have a log-linear dose–response pattern, with each doubling of dose associated with a further 7% reduction in LDL-C levels. Adverse effects of statins are also dose dependent and rise with the use of higher doses.

(i) **HMG-CoA reductase inhibitors and bile acid resins.** In isolated forms of LDL elevation, this combination exhibits highly complementary mechanisms of action. The combination of a statin with a bile acid sequestrant is ideal, owing to the lack of

TABLE 43.6 Average Reduction in Low-Density Lipoprotein Cholesterol Associated with the Starting Dose of Statin Agents

Agent	Average LDL-C reduction (%)
Lovastatin (20 mg)	24
Pravastatin (20 mg)	24
Simvastatin (20 mg)	35
Fluvastatin (20 mg)	18
Atorvastatin (10 mg)	37
Rosuvastatin (10 mg)	47

LDL-C, low-density lipoprotein cholesterol.

potentiation of side effects. The sequestrant provides little added toxicity, and the LDL-C lowering needed may not necessitate a full sequestrant dosage. Unfortunately, patient compliance with the combination is poor because of the common side effects of resins. Although the combination may reduce **LDL level by as much as 70% in some patients**, there appears to be a ceiling effect, with no LDL lowering occurring beyond the original level with an increase in dose of either agent.

(ii) **Combining a statin with niacin** is attractive because it can favorably influence all lipid subfractions. The side effects of the combination are increased but not synergistic, and the risk of myopathy may be lower than previously believed. The main serious side effect of the combination is hepatotoxicity, which may be reduced by using extended-release niacin. In small studies using this combination, the risk of hepatotoxicity (i.e., persistent elevation of AST or ALT of more than three times the upper limit of normal) at niacin doses of 2 g/d was about 1%.

(iii) The combination of a statin plus fibrate is highly effective for treating mixed hyperlipidemias. Although theoretically appealing, no reduction in clinical events has been demonstrated with this approach. The combination is associated with an increased risk of myopathy. Although earlier work suggested a higher incidence, later studies suggest this complication may be seen in approximately 1% of patients with the currently used agents.

(iv) The combination of a statin plus ezetimibe has been studied in small trials and has proved to be highly safe and effective at lowering LDL-C levels. Given the small number of patients treated and short follow-up periods, it is suggested that this combination should be reserved for the patients who fail maximal statin doses or are intolerant of statins.

3. Therapy of specific lipid disorders

a. Very high LDL levels usually result from inherited disorders of lipoprotein metabolism and carry a high risk of premature atherosclerosis with its attendant morbidity and mortality. **Hypothyroidism** may be associated with markedly elevated LDL levels and should be ruled out in any patient presenting with elevated LDL level. Most of these patients respond to high-dose statin therapy in addition to dietary restrictions. The addition of a bile acid sequestrant with an additional third agent (i.e., niacin) is often warranted to achieve target levels. Ezetimibe is another agent that may prove useful in this group. Therapy should be initiated early, and family members should be screened for hyperlipidemia. Patients with homozygous familial hyperlipidemia are deficient in LDL receptors, and measures that reduce cholesterol absorption (e.g., diet, ileal exclusion, bile acid sequestrants, and ezetimibe) or act by LDL receptor upregulation (e.g., statins) are largely ineffective. These patients are treated with LDL apheresis and should be managed in tertiary care centers only.

b. **Elevated triglyceride levels** may be caused by many factors, and more than one cause may be active in a given patient. **Minor elevations in triglyceride levels (150 to 299 mg/dL)** are usually caused by obesity, sedentary lifestyle, smoking, excess alcohol intake, and high-carbohydrate diets. In other patients, secondary causes such as diabetes, renal failure, Cushing's disease, nephrotic syndrome, or medications (e.g., protease inhibitors, corticosteroids, retinoids, and oral estrogens) may be responsible. Genetic causes may be pertinent to others. The therapy for this group of patients involves

identification and treatment of secondary causes (if present), change in medications, and lifestyle changes. These patients benefit from total caloric restriction and switching from a very high carbohydrate diet to a more balanced diet. Very high **triglyceride levels (≥500 mg/dL)** usually result from genetic defects of lipoprotein metabolism; in some patients, there is a combination of factors at play. These patients are at risk for acute pancreatitis (especially with triglyceride levels > 1,000 mg/dL), and treatment is directed at prevention of this condition. This is achieved with a combination of dietary measures (using very low fat diets [< 15% calories from fat] and substituting medium-chain fatty acids in patients with triglyceride levels > 1,000 mg/dL), increasing physical activity, maintaining optimal weight, and initiating fibrates or niacin therapy. Fibrates are especially efficacious in this group. Statins are not especially effective agents for triglyceride reduction and should be considered only after the other two agents. Patients with an **intermediate rise in triglyceride levels (200 to 499 mg/dL)** are a more heterogeneous group, with a wide array of underlying pathogenetic mechanisms at play. This pattern is often a result of an intersection of poor lifestyle, secondary causes, and genetic factors. These patients often have other markers of increased atherogenic risk, such as increased small LDL, low HDL, or elevated VLDL remnants. They need to be treated aggressively to bring the LDL level to the target; statins, with their ability to lower non-HDL-C, are the preferred agents. **After the LDL target has been achieved, the secondary goal is non–HDL-C (goal of 30 mg/dL higher than target LDL-C)**. These patients also need aggressive TLCs. High-dose statins often suffice to achieve the LDL-C and non–HDL-C goals, but for most patients, a second agent becomes necessary. The choices are niacin or fibrates in addition to a statin; these combinations carry an increased risk of hepatotoxicity or myopathy, and careful monitoring for these is essential. Refractory cases may benefit from fish oil supplements (> 3 g/d), which, by reducing VLDL production, can lower the serum triglyceride concentration by as much as 50% or more; however, many currently available over-the-counter fish oil supplements contain < 50% active omega-3 fatty acids. The commercial preparation Omacor, which has been available for many years in Europe and is now also available in the United States, contains 90% omega-3 fatty acids. The US FDA limited approval for Omacor to the treatment of severe hypertriglyceridemia (≥500 mg/dL) because of concerns that it appears to increase LDL-C levels. Weight loss by obese patients should be encouraged; it is associated with an improvement in the lipid profile and facilitates pharmacologic therapy if still necessary.

c. **Low HDL-C** levels often accompany minor or modest elevations in triglyceride levels. Low HDL level has been shown in epidemiologic studies to be an independent risk factor of CVD. However, despite a multitude of research on currently available therapies to raise HDL and recent investigation of several newer agents that raise HDL, there has been no conclusive evidence that raising serum HDL-C levels contributes to lower rates of CVD. Current guidelines specify that raising HDL should be a tertiary goal, after LDL and non–HDL-C goals have been reached. In patients who have isolated low HDL levels without any elevation in triglyceride levels, the first goal is to identify and modify lifestyle factors (e.g., high-carbohydrate diet, sedentary lifestyle, obesity, and smoking) and medications (e.g., progestational agents and anabolic steroids). The next step encompasses calculation of 10-year risk and treating LDL-C with a statin when appropriate. The AFCAPS/TexCAPS study found a clear benefit for statin therapy in patients with low HDL-C levels. In patients who continue to have low HDL-C levels despite

lifestyle modifications and who are at goal for LDL and triglycerides, either niacin or fibrate therapy is a reasonable choice to raise HDL-C.

d. Diabetic dyslipidemia. Patients with diabetes are at an increased risk for cardiovascular events and fare poorly after CAD manifests. Diabetes is associated with an increase in small LDL particles and is often associated with high triglyceride and low HDL levels. Hyperglycemia is an independent risk factor for CAD. Primary prevention is important in this group and was demonstrated to be efficacious in the HPS trial. **All diabetic patients (irrespective of LDL-C level) should be considered for statin therapy and TLCs**. Secondary goals include improved non–HDL-C levels and treatment for elevated triglyceride levels. Blood sugar control and insulin therapy often facilitate the former, but fibrates or low-dose niacin may be necessary in some patients. Patients with diabetes also often have coexisting hypertension. Blood pressure control and smoking cessation are essential because both interventions are highly effective at reducing cardiovascular events in this population.

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Drs. Hintinder S. Gurm, JoAnne Micale Foody, and Matthew Kaminski to previous editions of this chapter.*

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USEFUL INTERNET RESOURCES

Comprehensive Lipid News, Education, and Discussion from Baylor: http://www.lipidsonline.org/
Framingham 10-year risk calculator: http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=pub
NHLBI Guidelines based on NCEP/ATPIII: http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm
NHLBI National Cholesterol Education Program: http://www.nhlbi.nih.gov/about/ncep/

CHAPTER 44

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Nonlipid Cardiovascular Risk Factors

I. INTRODUCTION. Dyslipidemia constitutes a strong and well-described risk factor for the development of coronary artery disease (CAD). Almost one-half of myocardial infarctions (MIs) in the United States occur in individuals without overt lipid abnormalities. Additional risk factors, including hypertension (HTN), diabetes, obesity, and lifestyle, must be addressed to reduce the incidence of cardiovascular events. This chapter describes these cardiovascular risk factors (except diabetes, which is discussed in Chapter 45). Novel biomarkers and risk factors are also discussed.

II. HYPERTENSION. HTN contributes to all cardiovascular comorbidities: CAD, MIs, cerebrovascular accident (CVA), systolic heart failure, diastolic heart failure, and peripheral vascular disease (PVD). It is associated with increased total mortality among men and women of all ages and ethnic groups, regardless of CAD. It is defined as a blood pressure of ≥ 140/90 mm Hg **or** the need for antihypertensive medication. It is thought to be present in at least 30% of the US adult population. Evidence from the Framingham Heart Study suggests that this is underestimated, as normotensive 55-year-old persons have a 90% residual lifetime risk of developing HTN.

A. Etiology. HTN is a complex disease modified by environmental and genetic determinants.

1. **Genetics. HTN does not follow the classic Mendelian rules of inheritance** attributable to a single gene locus.
   a. However, Liddle syndrome (mutation of **chimeric 11-β-hydroxylase–aldosterone synthase gene**) and variants in the angiotensinogen locus are documented exceptions that cause primary HTN among whites.
   b. Other potential candidate genes include various components of the **renin–angiotensin–aldosterone system, the kallikrein–kinin system, and the sympathetic nervous system**.
2. Increased left ventricular (LV) mass and LV wall thickness and altered peripheral vascular capacity and responsiveness occur more frequently among patients with a family history of HTN.
3. Contributors to HTN include variations in sodium intake, alcohol intake, renal function, vascular function, the sympathetic nervous system, the renin–angiotensin system, hyperinsulinemia/insulin resistance, and prostaglandins.

B. HTN impact on cardiovascular risk and mortality

1. **Positive relationship between systolic and diastolic blood pressures and cardiovascular risk** has long been recognized.
   a. The **Multiple Risk Factor Intervention Trial (MRFIT)**. Prospective study (11.6 years of average follow-up period) with more than 361,000 subjects demonstrated the relationship between blood pressure and CAD. Baseline blood pressure elevations increased risk for CAD. The relationship was

stronger for systolic blood pressure than for diastolic blood pressure. Death rate for men with systolic blood pressures of 140 to 149 (2.4/1,000) and 150 to 159 mm Hg (3.1/1,000) was 40% higher compared with men with a baseline systolic blood pressure < 120 mm Hg.

b. Death rate at follow-up can be lowered by 36% with primary prevention of HTN in the general population. In addition, rates of stroke and CAD fall with antihypertensive therapy.

c. Subjects with blood pressure < 120/< 80 mm Hg have the fewest cardiovascular events. The recommended treatment cutpoint is 140/90 mm Hg.

d. Prehypertension. This is defined as blood pressure within the high-normal range (120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic) and which may confer some increased risk for cardiovascular disease. Risk ratios of 2.5 for women and 1.6 for men have been reported in patients in the prehypertensive range. These patients should undertake lifestyle modifications (e.g., diet, exercise, and weight loss) to help prevent or delay the development of frank HTN in the future.

e. The gradual rise in blood pressure over a person's lifetime and the increased prevalence of **HTN among the elderly** are **not benign**. Epidemiologic studies of the elderly demonstrate a U-shaped relationship between blood pressure and mortality. After adjustment for deaths within the first 3 years of the follow-up period, there is a positive linear relationship between blood pressure, cardiovascular disease mortality, and all-cause mortality. Isolated systolic HTN increases as the population ages, which confers increased risk for morbidity and mortality.

(1) Systolic Hypertension in the Elderly Program (SHEP) showed that 8% of persons aged 60 to 69 years have isolated systolic HTN, defined as systolic blood pressure > 160 mm Hg and diastolic blood pressure < 90 mm Hg, as do 11% of those aged 70 to 79 years and 22% of those aged 80 years or older.

(2) The relationship between systolic and diastolic blood pressures and cardiovascular events is more pronounced among persons aged 65 years and older. The association is stronger and more consistent for systolic blood pressure than for diastolic blood pressure and is evident at levels considerably < 140 mm Hg.

2. Rate of cardiovascular events. Elevations in diastolic or systolic blood pressure values translate into significant increases in cardiovascular events. Generally, the yearly percent risk of cardiovascular events (i.e., risk of event by end of study, divided by duration of study) is between 0.5% and 2.5% for hypertensive subjects aged 40 years or older. Beginning at 115/75 mm Hg, each increase in blood pressure of 20/10 mm Hg doubles the risk of cardiovascular disease.

3. Systolic blood pressure is a greater predictor of risk. Over the last few years, **greater emphasis has been placed on systolic blood pressure in characterizing cardiovascular risk**. Age-adjusted 10-year mortality in the MRFIT revealed systolic blood pressure to be a stronger predictor of events from CAD than diastolic blood pressure. High systolic blood pressure conferred a CAD risk regardless of diastolic blood pressure. A systolic blood pressure of 140 to 149 mm Hg confers greater CAD mortality risk than a diastolic blood pressure of 90 to 94 mm Hg. A systolic blood pressure of 150 to 159 mm Hg carries greater risk than a diastolic blood pressure of 95 to 100 mm Hg. According to the SHEP study, isolated systolic HTN, which accounts for 60% of cases of HTN among the elderly, is highly correlated with cardiovascular disease and it is important that it is controlled.

C. Clinical presentation. Detection of HTN begins with proper **blood pressure measurements**, which should be obtained at each health-care encounter.

1. Data for evaluation are acquired through the medical history, physical examination, laboratory tests, and other diagnostic procedures. Evaluation of patients with documented HTN has the following three objectives:
   a. To identify known causes of high blood pressure
   b. To assess the presence or absence of end-organ damage and cardiovascular disease, the extent of the disease, and response to therapy
   c. To identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment
2. A **medical history** should focus on identifying important risk factors or symptoms of HTN.
3. Repeated **blood pressure measurements** determine whether initial elevations persist and necessitate prompt attention, or the blood pressure has returned to normal and the patient needs only periodic surveillance. Ambulatory blood pressure monitoring is clinically helpful and is most commonly used to evaluate patients with suspected "office" or "white-coat HTN." It is also helpful in the care of patients with apparent drug resistance, hypotensive symptoms with antihypertensive medications, episodic HTN, and autonomic dysfunction.
   a. **Office visits.** Clinicians should explain to patients the meaning of their blood pressure readings and advise them of the **need for periodic remeasurement**. Blood pressure is measured in a standardized manner with equipment that meets certification criteria.
      (1) The patient sits in a chair with her or his back supported and the arms bared and supported at heart level.
      (2) Patients should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.
      (3) Measurement should begin after at least 5 minutes of rest.
      (4) The appropriate cuff size must be used to ensure accurate measurement. The bladder within the cuff should encircle at least 80% of the arm. Many adults need a large adult cuff.
      (5) Measurements are taken preferably with a mercury sphygmomanometer. Otherwise, a recently calibrated aneroid manometer or a validated electronic device can be used.
      (6) The systolic blood pressure and diastolic blood pressure are recorded. The first appearance of sound is used to define systolic blood pressure. The disappearance of sound is used to define diastolic blood pressure.
      (7) Two or more readings separated by 2 minutes should be averaged. If the first two readings differ by > 5 mm Hg, additional readings should be obtained and averaged.
   b. **Ambulatory blood pressure monitoring.** A variety of commercially available monitors that are reliable, convenient, easy to use, and accurate are available. These monitors are typically programmed to take readings every 15 to 30 minutes throughout the day and night while patients go about their normal daily activities. The readings can be downloaded for computer analysis.
      (1) **Normal** ambulatory blood pressure values are **lower than clinical readings while patients are awake** (< 135/< 85 mm Hg) and are **even lower while patients are asleep** (< 120/< 75 mm Hg). The blood pressure often falls by 10% to 20% during the night. This change is more closely related to patterns of sleep and wakefulness than to the time of day.
      (2) **Patients with HTN.** Ambulatory blood pressure correlates more closely than clinical blood pressure with a variety of measures of end-organ damage or left ventricular hypertrophy (LVH). Prospective evidence suggests that among patients for whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may help identify a group at relatively low risk for morbidity.

4. **Physical examination** should include the following components:
   a. **Funduscopic examination** for hypertensive retinopathy (e.g., arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes, hemorrhages and exudates, and disk edema).
   b. Examination of the **neck** for carotid bruits, distended veins, or an enlarged thyroid gland.
   c. Examination of the **heart** for abnormalities in rate and rhythm, increased size, precordial heave, clicks, murmurs, and S_3 and S_4.
   d. Examination of the **lungs** for rales and bronchospasm.
   e. Examination of the **abdomen** for bruits, enlarged kidneys, masses, and abnormal aortic pulsation. Abdominal bruits, particularly those that lateralize to the renal area and/or have a diastolic component, suggest renovascular disease. Abdominal or flank masses may indicate polycystic kidneys.
   f. Examination of the **extremities** for diminished or absent peripheral arterial pulsations, bruits, hair loss, and edema. Delayed or absent femoral arterial pulses and decreased blood pressure in the lower extremities may indicate aortic coarctation.
   g. **Neurologic assessment.**
   h. **Other assessments.** Labile HTN or paroxysms of HTN accompanied by any or all of the following symptoms and signs—chest discomfort ("pressure"), headache ("pain"), palpitations, pallor, and diaphoresis ("perspiration")—may indicate the presence of a pheochromocytoma. Truncal obesity with purple striae suggests Cushing's syndrome.

D. Laboratory evaluation

1. It is recommended that the clinician request routine laboratory tests before initiating therapy to determine the presence of end-organ damage and other risk factors. These include **urinalysis, complete blood cell count, blood chemistry, and 12-lead electrocardiogram (ECG)**.
2. Additional diagnostic procedures may be indicated to seek causes of HTN: poor response to drug therapy, well-controlled patients whose blood pressures begin to increase, and those with sudden onset of HTN. **Optional tests** include creatinine clearance; microalbuminuria, 24-hour urinary protein, blood calcium, uric acid, fasting triglyceride, low-density-lipoprotein cholesterol (LDL-C), glycosylated hemoglobin, and thyroid-stimulating hormone levels; and limited echocardiography to determine the presence of LVH.
   a. **Clues from laboratory tests** include unprovoked hypokalemia (i.e., primary aldosteronism), hypercalcemia (i.e., hyperparathyroidism), and elevated creatinine or abnormal urinalysis (i.e., renal parenchymal disease).
   b. The **presence of LVH** as determined by ECG or echocardiography is an important risk factor for adverse cardiovascular events and an independent predictor of high risk for CAD, cardiovascular disease, and all-cause mortality. LVH, the consequence of chronic pressure or volume overload and obesity, seems to be a stronger predictor of MI and CAD death than the degree of HTN. LV mass, as assessed with echocardiography, is a powerful predictor of cardiovascular events, cardiovascular mortality, and all-cause mortality.
3. **More complete assessment** of cardiac anatomy and function by means of conventional echocardiography, examination of structural alterations in arteries by means of ultrasonography, measurement of ankle–arm index, and plasma renin activity and urinary sodium determinations may be useful in assessing **cardiovascular status** in select patients.

E. Risk stratification

1. **Classification of blood pressure** is given in Table 44.1. The criteria are limited to patients not taking antihypertensive medication and without acute illness. Classification is based on the average of two or more blood pressure readings. When systolic blood pressure and diastolic blood pressure fall into different categories, **the higher pressure should be selected** to classify the patient's blood pressure.

TABLE 44.1. Classification of Blood Pressure for Adults Aged 18 Years and Older

Category	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)
Normal	< 120	and	< 80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥ 160	or	≥ 100

2. Risk for cardiovascular disease among patients with HTN is determined by the **blood pressure level** and by the **presence or absence of end-organ damage or other disease-modifying risk factors** (smoking, dyslipidemia, and diabetes). The presence or absence of these factors is determined during the routine evaluation of patients with HTN (e.g., history, physical examination, and laboratory tests). This classification stratifies patients with HTN into risk groups for therapeutic decisions. The World Health Organization Expert Committee on Hypertension Control recommends a similar approach. Obesity and physical inactivity are also predictors of cardiovascular risk and interact with other risk factors, but they are of less importance in the selection of antihypertensive drugs.
   a. **Risk group A** includes patients with prehypertension or HTN at stage 1 or 2 who do not have clinical cardiovascular disease, end-organ damage, or other risk factors. Persons with stage 1 HTN in risk group A are candidates for a longer trial (up to 1 year) of vigorous lifestyle modification with vigilant blood pressure monitoring. If the desired blood pressure is not achieved, pharmacologic therapy is added. For those with stage 2 HTN, drug therapy is warranted.
   b. **Risk group B** includes patients with HTN who do not have clinical cardiovascular disease or end-organ damage but have one or more of the risk factors except for diabetes mellitus. This group includes most patients with high blood pressure. If multiple risk factors are present, clinicians consider antihypertensive drugs as initial therapy. Lifestyle modification and management of reversible risk factors are strongly recommended.
   c. **Risk group C** includes patients with HTN and clinically manifested cardiovascular disease or end-organ damage. According to Joint National Committee 7 (JNC 7) criteria, some patients who fall into the prehypertensive category and have renal insufficiency or diabetes mellitus should be considered for prompt pharmacologic therapy. Appropriate lifestyle modifications are always recommended as adjunct treatment.
   d. **Therapy.** Antihypertensive treatment has proved **beneficial in the prevention and reduction of the progression of HTN, CVAs, congestive heart failure (CHF), renal insufficiency, and renal failure**. Among patients with mild to moderate HTN, antihypertensive therapy has not favorably influenced angina, MI, and other atherosclerotic diseases (e.g., PVD and aortic atherosclerosis). The lower-than-expected reduction in CAD risk in most trials of antihypertensive agents has been attributed to the choice of agents, such as thiazide diuretics and β-blockers, that might negatively influence risk for CAD and to the short duration of the trials. Overall, antihypertensive treatment markedly reduces the prevalence of CAD events: CAD mortality (by 16%), the rate of fatal stroke (by 40%), and the incidence of heart failure (by 50%), with similar numbers of deaths prevented.

1. **Nonpharmacologic therapy**
   a. **Weight reduction** reduces systolic and diastolic blood pressures. Most clinical trials have demonstrated that weight reduction is directly related to blood pressure reduction. A weight loss of approximately 10 lb (4.5 kg) may reduce both systolic and diastolic blood pressures by 2 to 3 mm Hg. Among patients with high-normal blood pressure, the need for medical therapy may be averted for one-half through weight reduction by means of physical activity and calorie restriction.
   b. **Exercise** reduces blood pressure by means of decreasing resting heart rate and peripheral vascular resistance and by modifying serum norepinephrine and insulin levels. After an increase in physical activity, both systolic and diastolic blood pressures have been demonstrated to fall by 7 mm Hg with or without weight reduction. Moderate-intensity exercise is as effective as high-intensity exercise for reducing blood pressure.
   c. **Diet.** A modest, independent benefit of **salt reduction** has been demonstrated. HTN is less common in societies that consume low-salt, high-potassium diets. Although the theory that excessive salt intake produces HTN has been difficult to prove in large clinical trials, most data support the role of dietary salt excess for some persons. In general, low-salt diets, such as the Dietary Approaches to Stop Hypertension (DASH; 2,300- and 1,500-mg sodium diets), are recommended to most patients with HTN. Pooled estimates have suggested that **salt restriction is most important for older persons, those with higher baseline levels of blood pressure, and particularly those who are salt sensitive**. Salt restriction reduces the need for combination antihypertensive medications.
   d. Tobacco and immoderate alcohol use (more than two daily drinks for men and more than one daily drink for women) increase blood pressure. **Cessation of smoking and excessive alcohol use** markedly reduces blood pressure and further reduces cardiovascular risk.
2. **Medical therapy**
   a. **Priority of therapy**
      (1) Therapy for most patients with **uncomplicated HTN** at stage 1 should **begin with the lowest dose** to prevent adverse effects. If blood pressure remains uncontrolled after 1 to 2 months, the next dose level may be prescribed. It may take months to adequately control HTN. Most antihypertensive agents may be taken once each day. To improve patient compliance, this regimen is used whenever possible.
      (2) For patients at **higher risk**, those in risk group 2, or those at particularly high risk for CAD or CVA event, drug therapy to **achieve maximum beneficial reductions** in blood pressure should **proceed without delay.** If blood pressure is elevated by 20/10 mm Hg above the goal, guidelines recommend starting two agents simultaneously.
      (3) There is **no debate regarding the need for aggressive blood pressure reduction** in patients with **diastolic blood pressures > 115 mm Hg and systolic blood pressures > 160 mm Hg**. JNC 7 aggressively targets the 140/90 mm Hg cut-point and incorporates hypertensive therapy into an algorithm of overall risk.
      (4) In the setting of hypertensive emergency **(HTN with end-organ damage, often with neurologic symptoms)**, patients with a systolic blood pressure > 200 mm Hg or a diastolic blood pressure > 120 mm Hg may need **hospitalization** for therapy.
      (5) Although some patients may respond to single therapy, **two or more drugs are often required**. The intervals between changes in regimen should not be prolonged, and the maximum dose of some drugs may be increased.

b. Medication selection. Special considerations include concomitant disease, demographic characteristics, quality of life, cost, and use of other drugs that may cause drug interactions.

(1) Concomitant diseases (see Table 44.2). Antihypertensive medications may worsen some diseases and improve others. Agent selection involves consideration of coexisting disease, simplification of regimens, and reduction of cost. Special emphasis should be given to diabetes and chronic renal disease. Such patients should be aggressively treated to maintain a goal blood pressure of < 130/80 mm Hg.

(a) Reduction of long-term cardiovascular morbidity and mortality. Diuretics and β-blockers were drug classes originally shown in randomized trials to reduce morbidity and mortality. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that angiotensin-converting

TABLE 44.2. Management of Hypertension in Specific Clinical Syndromes

Condition	Treatment
Acute coronary syndrome	β-Blockers or nitrates; CCB
Hypertension among African Americans	Diuretic or CCB
Arrhythmia	
Sinus bradycardia, SSS, or AV block	Diuretic, ACE inhibitor, or α-blocker
Atrial fibrillation or flutter and SVT	β-Blocker, diltiazem, verapamil, or clonidine
Benign prostatic hypertrophy	α-Blocker
COPD with bronchospasm or asthma	CCB or ACE inhibitor
Diabetes	ACE inhibitor
Advanced age (> 65 y)	Diuretic, CCB, or ACE inhibitor at lower doses to avoid postural hypotension
Gout	Any *except* diuretics
Congestive heart failure	
Systolic	ACE inhibitor, diuretic, β-blockers
Diastolic	CCB or β-blockers
HOCM	β-Blockers or verapamil
Liver dysfunction	Any *except* methyldopa and labetalol
Post–myocardial infarction	ACE inhibitor, β-blocker, or both
Osteoporosis	Thiazide diuretics
PVD	Vasodilator, ACE inhibitor, CCB, or α-blocker
Renal insufficiency (creatinine > 2 mg/dL)	Loop diuretics, ACE inhibitor, CCB, α-blocker, labetalol, or a combination of these
Diabetic nephropathy	ACE inhibitor
Smokers	α-Blockers, ACE inhibitors, or CCB
Isolated systolic hypertension	Diuretics, CCB, and ACE inhibitors

ACE, angiotensin-converting enzyme; AV, atrioventricular; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HOCM, hypertrophic obstructive cardiomyopathy; PVD, peripheral vascular disease; SSS, sick sinus syndrome; SVT, supraventricular tachycardia.

enzyme (ACE) inhibitors reduced the risk of cardiovascular events in patients with vascular disease or diabetes plus one other cardiovascular risk factor. However, the fact that HOPE was a trial with placebo control rather than active control suggests that blood pressure lowering, and not drug class effect, may have been responsible for the improved outcomes. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed a preferential reduction in cardiovascular events with the angiotensin receptor blocker losartan compared with atenolol in hypertensive patients. This improvement was primarily driven by a reduction in the number of strokes in the losartan group.

(b) Regression of LVH has been associated with a reduction in risk for cardiovascular events. All commonly used antihypertensive strategies, with the exceptions of direct vasodilators and weight loss, induce regression of LVH. Specifically, the ACE inhibitor ramipril has been shown to cause regression of electrocardiographic markers of LVH, with an associated reduction in death, MI, stroke, and CHF. The LIFE trial demonstrated a superiority of the angiotensin II receptor blocker losartan over the β-blocker atenolol in the absence of LVH regression, suggesting that LVH might not be as powerful a surrogate of risk as initially thought. Further study of this issue is needed.

(2) Dosage. For most patients, a **low dose of the initial drug** choice is initiated and then titrated to the desired effect. The optimal formulation provides 24-hour efficacy with a once-daily dose, with at least a 50% of the peak effect remaining at the end of 24 hours. Long-acting formulations increase adherence, reduce cost, provide consistent blood pressure control, and protect against early-morning sudden death. Diurnal blood pressure control is reported to improve when long-acting medication is taken at night rather than in the morning.

(3) Special populations. Neither sex nor age usually affects responsiveness to various agents. In general, HTN among **African Americans** is more responsive to monotherapy with diuretics and calcium channel blockers than with β-blockers or ACE inhibitors. However, if a β-blocker is needed for other therapeutic benefits, then differences in efficacy can usually be overcome with reduction of salt intake, higher doses of the drug, or addition of a diuretic.

(4) Drug interactions. Some drug interactions may be beneficial. For example, diuretics acting on different sites in the nephron may increase natriuresis and diuresis. Diltiazem may reduce the amount of cyclosporine needed in transplant recipients. Other interactions may be harmful. Nonsteroidal anti-inflammatory drugs may blunt the action of diuretics, β-blockers, and ACE inhibitors.

c. Treatment of the elderly. The benefit of blood pressure lowering is evident in the elderly, with a marked **reduction in all-cause mortality and CAD mortality**, as shown in multiple trials and studies. SHEP was the first study to show that antihypertensive treatment of the elderly can reduce these events. It is not clear, however, that all agents are equally effective in reducing the rate of cardiovascular events in the elderly.

d. Emerging evidence. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the incidence of cardiovascular events in hypertensive patients treated with a thiazide-type diuretic (chlorthalidone), calcium channel blocker (amlodipine), or ACE inhibitor (lisinopril) who were followed over 5 years. A fourth arm of the trial consisting of treatment with the α-blocker doxazosin had been stopped prematurely because of increased cardiovascular events, specifically a doubling in the risk

of CHF in the doxazosin arm compared with the chlorthalidone arm. The results indicated no difference in the three remaining groups regarding the primary outcome of combined fatal coronary heart disease or nonfatal MI. Chlorthalidone was superior to amlodipine in preventing heart failure and superior to lisinopril in preventing stroke and combined cardiovascular disease. Given their clear efficacy, relatively low cost, and high tolerability, thiazide diuretics are therefore considered initial agents of choice for most patients with HTN and core components of multidrug regimens.

III. OBESITY. Rates of obesity are rising at an alarming rate both in the severe obesity cases (body mass index [BMI] > 40 kg/m^2) and in adolescents. Currently, 66% of US adults are overweight, defined as having a BMI of > 25 kg/m^2. Moreover, 32% of Americans are classified as obese, with a BMI of 30 kg/m^2 or more. This has come to be a critical problem for African American women, among whom the prevalence of obesity is > 50%. The percentage of children and adolescents with obesity has doubled over the last 20 years. There are clear links between obesity and the development of cardiac risk factors: HTN, hyperlipidemia, and diabetes.

A. Link between obesity and cardiovascular disease

1. A positive association among BMI, increased total cholesterol and triglyceride levels, and a decreased high-density-lipoprotein cholesterol (HDL-C) levels has been documented in various age groups.
2. Distribution of fat appears to be a more important predictor of CAD than the total amount of fat because android fat patterns are more metabolically active and highly associated with dyslipidemia. Although BMI and waist-to-hip ratios have indicated a linear association between obesity and CAD, the **waist-to-hip ratio**, which accounts for abdominal adiposity, is viewed as a more **accurate predictor of CAD**. Among obese persons, those with central adiposity are at particularly high risk. In a cohort of 1,500 women observed for 20 years, the waist-to-hip ratio, but not BMI, was highly predictive of the occurrence of fatal MI.
3. The **National Center for Health Statistics still uses BMI**, defined as **weight (kg)/height (m^2), as the recognized measurement of obesity**. Their guidelines define obesity as a BMI of 27.8 kg/m^2 or more for men and 27.3 kg/m^2 or more for women. Morbid obesity has been defined as a BMI of 31.1 kg/m^2 for men and 32.3 kg/m^2 for women. The Nurses' Health Study showed that women with a BMI of 25 to 29 kg/m^2 had an age-adjusted relative risk for CAD of 1.8 compared with the leanest women. Women with a BMI > 29 kg/m^2 had a relative risk for CAD of 3.3.
4. Obesity among adults is associated with **increased LV mass,** a powerful independent predictor of mortality and morbidity from cardiovascular disease. LV mass in persons with obesity but without diabetes probably depends, at least in part, on the degree of insulin resistance and hyperinsulinemia and not on BMI and blood pressure.
5. Central obesity is part of the **metabolic syndrome**, which appears to be associated with increased risk for CAD in both sexes. This condition is characterized by elevated plasma triglyceride and low plasma HDL-C levels.
   a. An essential feature is the presence of **dense, atherogenic LDL**.
   b. Other features are HTN, impaired glucose intolerance with hyperinsulinemia, and decreased sensitivity to the action of insulin on peripheral tissues.
   c. Hyperinsulinemia is associated with **lipid derangements, increased production of plasminogen activator inhibitor, and enhanced proliferation of cells in atherosclerotic plaque**. Among patients with hyperinsulinemia, an increased prevalence of CAD and a relationship among abnormal insulin levels, glucose metabolism, and severity of CAD have been reported. The physiologic response to insulin resistance is increased secretion of insulin, which may lead to glucose intolerance or frank diabetes mellitus.

B. Therapy

1. **Calorie restriction, behavior modification, and exercise** are the main treatment modalities for weight loss. The greatest weight losses have occurred with a combined regimen of diet and exercise rather than diet or exercise alone.
2. Several **medications** can be used for the temporary management of obesity. Although pharmacologic agents temporarily aid in the struggle against obesity, the National Task Force on Obesity **cautions against the use of these agents for long-term maintenance because of the potential for unknown side effects**.
   a. **Noradrenergic drugs** influence weight loss through stimulation of the hypothalamus.
   b. **Orlistat,** a pancreatic lipase inhibitor, reduces weight through inhibition of fat absorption.
   c. **Serotonin reuptake inhibitors**, including sibutramine, fluoxetine, and sertraline, promote weight loss with various degrees of side effects.
   d. Use of dexfenfluramine and fenfluramine, already of concern because of rare instances of pulmonary HTN, has been discontinued because of associated acquired valvular heart disease.
3. In the most extreme cases, **surgical therapy** can be provided. Among morbidly obese patients (BMI > 40 kg/m^2) and obese patients (BMI between 35 and 40 kg/m^2) with coexisting conditions, jejunoileal shunts and gastroplasty often aid in the maintenance of weight loss. About 10 years after surgical intervention, 80% of patients maintain a weight 10% less than preoperative weight.
4. **Risk of weight loss.** Even if weight is lost, weight loss maintenance fails in most instances. Health risks that accompany weight cycling are increases in cardiovascular morbidity and mortality, abdominal fat, blood pressure, and insulin resistance.

IV. TOBACCO. Smoking, the single most preventable cause of death in the United States, is a leading risk factor for CAD, CVA, and PVD. Second-hand smoke has been shown to increase the risk for CAD. The causal role of smoking in cardiovascular disease has been derived from > 20 million person-years of follow-up study (NHLBI, 1996). Twenty-eight percent of white men and 25% of white women smoke, as do 34% of African American men, 22% of African American women, 24% of Hispanic men, and 15% of Hispanic women. It is estimated that 37% of the population is exposed to second-hand smoke. Exposure to second-hand smoke increases the risk of death from CAD by 30%. More than 90% of current smokers began their habit before they were 21 years of age.

A. Pathophysiology. Cigarette use activates platelets, increases circulating fibrinogen, increases heart rate, and elevates blood pressure. It appears to promote plaque disruption. A strong dose–response relationship exists between smoking and CAD. Duration of smoking and the daily amount markedly influence the risk of CAD. The number of cigarettes smoked per day is directly proportional to the risk of MI. The adverse effect of smoking is present among men and women (but may be stronger among women) of all ages and ethnic groups with or without prior CAD. Data suggest that risk for cardiac death is two to four times greater among current smokers than nonsmokers.

B. Risk reduction and therapy. Risk for cardiovascular disease begins to decline soon after smoking cessation, irrespective of age and sex. There is a 50% reduction in cardiovascular events within the first 2 to 4 years of cigarette cessation; however, increased cardiovascular risk still exists 10 years after cessation. It is thought to take as long as 20 years to regain baseline risk.

1. **Behavioral and psychosocial treatment.** Several techniques have been developed to help patients stop smoking and maintain cessation. These have variable effect.
2. **Pharmacotherapy**
   a. **Nicotine replacement therapy (NRT).** Approximately 50% to 70% of patients discontinue cigarette use after a major cardiac event, such as MI or coronary artery bypass grafting. Cessation for another 10% to 20% can be accomplished with cigarette cessation programs, which often incorporate

nicotine patches or the somewhat less efficacious nicotine gum. Programs that incorporate a nurse clinician increase cessation rate beyond 30%. An 8-week treatment appears to be as effective as longer periods of use.

(1) **The patch.** Clinical practice guidelines support the use of transdermal nicotine patch as the **primary pharmacologic agent for all patients who smoke**. The risk of use of the patch among patients with CAD is now considered to have been overstated. Use of the patch is contraindicated in persons who continue to smoke because it leads to nausea. **Side effects** of NRT include itching and skin rash among as many as 50% of patients. NRT approximately doubles cessation rate. One-year follow-up evaluations of patch-cessation therapy indicated cessation rates of 20% to 25% compared with 5% to 10% for a placebo.

(a) Standard dosages (Nicoderm, Prostep, and Nicotrol) include the maximum doses for 4 weeks and lesser doses for another 4 weeks.

(b) Because baseline nicotine levels (i.e., the number of cigarettes smoked per day) are inversely associated with cessation rates, **patients who smoke < 1 pack per day** may be adequately treated with **submaximal nicotine doses**.

(2) **Nicotine gum.** Use of gum for NRT appears to delay post-cessation weight gain, a typical deterrent to cigarette cessation. Multipack users should use 4 mg gum, whereas patients who smoke < 1 pack per day may need only 2 mg.

(3) **Nicotine nasal spray** has been approved as a smoking cessation treatment. Nasal spray provides a more rapid rise in nicotine level than that with gum or patch, with peak levels occurring in < 10 minutes. Nicotine nasal spray has markedly more severe **side effects** and appears to be best suited for patients who have not had success with other forms of NRT.

b. **Other pharmacologic agents.** For select patients, supplementation with agents other than NRT may be useful, even though NRT is the only strategy recommended in standard smoking cessation guidelines.

(1) **Bupropion,** which is approved for smoking cessation, has dopaminergic and noradrenergic properties. Clinical trials have demonstrated the efficacy of bupropion sustained release (SR) with or without transdermal nicotine for smoking cessation. The recommended dosage of bupropion is 150 mg two times per day. In clinical trials, the medication was typically started 1 to 2 weeks before cessation and was continued for 7 to 12 weeks after cessation. Abstinence rates at 12 months were 30% for patients treated with bupropion for 9 weeks in one study, and combination therapy with bupropion and a nicotine patch resulted in a 35.5% abstinence rate.

(2) Bupropion must be **avoided by patients with a seizure disorder or who are at risk for seizures** (i.e., patients with head injury, those who abuse alcohol, or those who have alcohol dependence) because the medication lowers seizure threshold. Common **side effects** of bupropion include headache, nausea, and restlessness. Bupropion has no serious adverse effects on the cardiovascular system.

(3) **Clonidine**, an α_2-agonist, **dampens the sympathetic activity associated with withdrawal**. Dosages used for smoking cessation typically range from 0.1 to 0.4 mg/d for 2 to 6 weeks in the oral or the transdermal preparation. The most common **side effects** are dry mouth, constipation, postural hypotension, and sedation. Clonidine is **recommended for patients who prefer not to take or who have not had success with NRT**. Nasal spray clonidine has been effective among nicotine-dependent women who are intolerant of the patch.

(4) **Varenicline** is a partial agonist of the nicotinic acetylcholine receptor, in particular, the $\alpha_{4\beta2}$ subtype. Several trials have demonstrated improved

efficacy in achieving smoking cessation when compared with NRT and bupropion SR. However, because of case reports of adverse psychiatric behavior occurring during varenicline administration, including suicidal ideation, suicidal behavior, and erratic behavior, practitioners are encouraged to monitor their patients closely for signs of psychiatric changes.

V. SEDENTARY LIFESTYLE

A. Pathophysiology. A sedentary lifestyle is associated with increased risk for CAD. Sedentary persons have almost double the risk for CAD death as that of active persons. In five prospective exercise studies, persons at the lowest levels of exercise conditioning had an age-adjusted CAD mortality risk 2 to 10 times that of the best-conditioned participants. Meta-analyses of epidemiologic studies suggest a nearly twofold increase in risk among sedentary persons for development of CAD and for CAD death. A sedentary lifestyle is also associated with obesity, HTN, diabetes mellitus type 2, and hypercholesterolemia, which point to the need for changes in exercise patterns. More than 50% of the US population do not exercise at least 20 minutes three times a week and 40% of adults are classified as sedentary. Only 22% of US adults partake in 30 or more minutes of exercise five times a week and 25% report no leisure-time physical activity.

B. Risk reduction. Even moderate physical activity provides a reduction in risk. Regular physical activity prevents obesity, may reduce weight, and promotes positive effects on blood pressure, LDL-C, HDL-C, and triglyceride levels. Independent of other risk factors, physical fitness has a direct protective effect against CAD events. Among patients who have had MI, controlled cardiac rehabilitation programs significantly reduce cardiovascular mortality by 20% to 25%. The American Heart Association (AHA) currently recommends that adults accumulate 30 minutes or more of moderate-intensity physical activity on most (preferably all) days of the week.

1. **Mechanism**
   - **a.** Exercise **improves glucose tolerance and insulin sensitivity, increases fibrinolysis, increases HDL-C levels, improves oxygen uptake** in the heart, and **increases coronary artery diameter**. Exercise reduces the sensitivity of the myocardium to catecholamines and the risk of ventricular arrhythmias. Exercise increases HDL-C and lowers LDL-C levels and, as such, reduces cardiac events. Exercise can alter the progression of coronary atherosclerosis. Among patients with angiographically documented CAD, exercise training may increase regression and reduce the progression of coronary lesions.
   - **b.** Studies on the effect of exercise have been difficult to conduct and are known to have difficulties in quantification of exercise. Reviews on the effects of cardiac rehabilitation on morbidity and mortality demonstrated reductions in all-cause mortality of 20% to 24% and in CAD mortality of 23% to 25%. The data support a reduction in anginal episodes and mortality, although the reduction in mortality is no better than 15%. A direct relationship has been shown between exercise intensity and angiographic modifications: 1,533 kcal/wk is necessary to stabilize coronary lesions and 2,200 kcal/wk is needed to induce coronary regression.
2. **Fitness** (measured in metabolic equivalents or METs achieved) and **physical activity** (measured in caloric expenditure per time period) appear to be closely linked, although it remains unclear which of the two is the better predictor of cardiovascular morbidity and mortality.
   - **a.** Several studies have shown that **higher degrees of physical activity** are associated with decreased risk for death from CAD. There is an inverse association between the increasing physical activity (measured in MET-hours/week) and the risk of cardiovascular events. These studies suggest that **changes in fitness from low to high levels and level of current activity are the best predictors of reduction in risk for CAD**.

b. **The death rate decreased by 50% among men** 60 years or older who changed from unfit to fit status over an 18-year follow-up period. The age-adjusted cardiovascular disease mortality rate decreased by 52%.

c. An important measurement of fitness among **older postmenopausal women** is leisure-time physical activity; it can substantially reduce the risk of MI. Even moderate-intensity exercise has been shown to confer substantial benefits for postmenopausal women. Such women who walk or exercise vigorously at least 2.5 hours each week have been shown to have a cardiovascular risk reduction of approximately 30%.

3. **Problems with compliance.** Only 50% of persons who begin an exercise program adhere to it for more than 6 months.

a. Physicians may need to help **tailor exercise programs for individual patients** to participate in activity that is sustained in the long-term.

b. As for healthy persons, **precautions** must be taken to **prevent injury**. The current guidelines may be **slightly modified for elderly exercisers** to emphasize a longer warm-up period to enable musculoskeletal and cardiorespiratory readiness for exercise and an adequate cool-down period to help dissipate heat.

VI. NOVEL RISK FACTORS. Screening studies have shown that HTN, hyperlipidemia, tobacco use, family history, and diabetes are predictive of less than half of all future cardiovascular events. Among patients with premature atherosclerosis, the predictive value of these traditional cardiovascular risk factors is limited. Many patients with few traditional risk factors experience life-threatening acute coronary syndromes without prior symptoms of disease. Several potential risk factors have been identified that may enhance risk for CAD. These are levels of C-reactive protein (CRP), lipoprotein(a) or Lp(a), homocysteine, fibrinogen, and myeloperoxidase (MPO), as well as genetic mutations and single-nucleotide polymorphisms (SNPs) in a number of candidate genes.

A. **CRP** is a marker of systemic inflammation. As the role of **inflammation** in the initiation and progression of atherosclerosis becomes better understood, CRP is gaining prominence as an important player in the assessment of cardiovascular risk.

1. **Pathophysiology**

a. CRP has been shown to be an independent risk factor for the development of cardiovascular events in both apparently healthy individuals and in patients with established coronary heart disease. The exact role that CRP plays in this association has not yet been well characterized. Initially, it was believed that CRP provided an indirect measurement of the inflammatory milieu in at-risk individuals. Emerging evidence, however, indicates that CRP itself may have a direct causal influence on the development of atherosclerosis. CRP binds to oxidized LDL, promoting the uptake of LDL by macrophage scavenger cells in the arterial wall and possibly enhancing the atherosclerotic process.

b. The degree of associated risk throughout various levels of CRP, often measured as high-sensitivity C-reactive protein (hsCRP), has been evaluated in several studies.

(1) Men in the Physicians' Health Study with the highest quartile CRP had **three times the risk of MI** and **twice the risk of ischemic stroke** compared with men in the lowest quartile.

(2) In women, the difference is even more pronounced. The relative risk of cardiovascular events in the highest quartile of CRP compared with the lowest quartile of CRP in women is **4.4**.

(3) An increased risk of sudden cardiac death has also been seen in patients with elevated CRP levels.

2. **Clinical use**

a. Standard CRP assays are not sufficiently sensitive to discriminate within the narrow range of CRP values associated with an increase in cardiovascular events. The development of hsCRP assays, however, has made this possible.

AHA/Centers for Disease Control and Prevention (CDC) guidelines have established cut-points of risk for hsCRP: a level of < 1 mg/L is considered low, 1.0 to 3.0 mg/L is average, and > 3.0 mg/L is high and is associated with increased cardiovascular risk. Higher levels (> 10 mg/L) suggest an alternative cause for inflammation, such as infection or underlying rheumatologic illness.

b. When deciding on whether to initiate statin therapy for the primary prevention of coronary events, hsCRP measurement may prove helpful in patients with a moderate level of cardiovascular risk (calculated 10-year major cardiac event risk of 10% to 20%). If found to have an elevated hsCRP level, these patients may benefit from a more intensified therapy, including dietary modifications and, perhaps, statin therapy. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), lovastatin reduced the incidence of cardiovascular events in patients with low lipid levels if CRP levels were elevated. No improvement was seen in the cohort of patients with low lipid levels and normal CRP values. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) study targeted individuals with elevated hsCRP levels without hyperlipidemia and showed that statin therapy substantially lowered cardiovascular events in this population.

c. The AHA/CDC panel recommends against widespread screening of the general population. In secondary prevention, hsCRP assessment can be performed, but proven intensified therapy (including statins) should not be withheld based on the level of hsCRP attained. Serial hsCRP measurements should not be used to monitor the effects of lipid treatment.

3. Risk reduction and therapy. Weight loss with caloric-restriction diets has been shown to decrease plasma CRP levels. Additional data indicate that women who exercise regularly have lower CRP levels compared with sedentary women. In primary prevention trials, pravastatin has been shown to reduce CRP levels by about 17%, in a manner independent of LDL lowering. Evidence suggests that simvastatin lowers CRP within the first 2 weeks of therapy, before any LDL-lowering effect is seen. What is not known, however, is whether reducing CRP by any such means confers an independent benefit in regard to lowering cardiovascular morbidity and mortality.

B. Lipoprotein (a) or Lp(a) is identical to LDL, except for the addition of apolipoprotein A (apoA), a highly glycosylated protein. Although it is a lipoprotein, Lp(a) is often considered a **marker of thrombosis**.

1. Pathophysiology

a. There is a striking amino acid sequence homology between apoA and plasminogen, suggesting that Lp(a) may play an important role in the connection between atherosclerosis and thrombosis. **Lp(a) may be atherogenic**; it accumulates in atherosclerotic lesions, binds to apoB-containing lipoproteins and proteoglycans, and can be taken up by foam cell precursors. It may also promote thrombosis when it binds to fibrin and blocks the fibrinolytic action of plasmin.

b. Lp(a) may be more predictive of CAD among younger men, women, and persons with hyperlipidemia.

c. Studies have had mixed results

(1) Cross-sectional and retrospective case–control studies have usually supported the role of Lp(a) in CAD. Lp(a) is a marker among patients at particular risk for poor outcomes, in terms of severity and progression of cardiovascular disease.

(2) Several prospective studies have correlated baseline Lp(a) levels with vascular disease in general.

(3) Other prospective studies have found little or no association between Lp(a) and CAD risk.

d. Few studies have been conducted on the role of Lp(a) in **women**. Cardiovascular risk tends to increase with an Lp(a) value > 30 mg/dL.

2. **Therapy.** Niacin is the only agent currently available that reduces Lp(a). However, due to the multiplicity of lipid effects exerted by niacin therapy, it is unknown if reduction in Lp(a) levels is beneficial. In addition, the atherogenicity of Lp(a) may be modified through **substantial reductions in LDL-C levels**.

C. Homocysteine is a product of folate metabolism. It is derived from the sulfur-containing amino acid methionine and is metabolized through pathways associated with folic acid, vitamin B_6, and vitamin B_{12} as cofactors.

1. **Etiology and pathophysiology**
   - **a.** Elevated plasma homocysteine levels (> 15 μ/L) confer an **independent risk for vascular disease**, according to the cross-sectional and prospective case–control studies. The risk was first identified because of increased thromboembolic events, including MI and stroke, in patients with **homocystinuria**, a rare inherited deficiency of cystathionine β-synthase characterized by very high serum homocysteine levels (> 100 μmol/L).
   - **b.** Elevated homocysteine levels are found among > 20% of patients with atherosclerotic disease, including PVD. In PVD, there may be direct endothelial toxicity, smooth muscle cell proliferation, enhanced LDL oxidation, abnormalities in platelet function, or increased thrombotic risk because of abnormal clotting factors (e.g., factor V and factor VII) or altered secretion of von Willebrand's factor.
   - **c.** The **relative risk of stroke and MI is approximately 2 for homocysteine levels > 15 μmol/L** compared with those < 10 μmol/L. The relative risk of PVD is much greater than 3. Risk enhancement is continuous over the spectrum of homocysteine values.
   - **d.** A meta-analysis of case–control observational studies is less compelling. This study examined patients with a genetic polymorphism of an enzyme involved in folate metabolism; this alteration resulted in elevated homocysteine levels. Individuals with this mutation had only a 16% higher risk of developing CHD compared with normal controls.
   - **e.** **Secondary causes** of increased homocysteine levels include age, male sex, menopause, renal function, and some medications (e.g., niacin, oral contraceptives with estrogen, phenytoin, methotrexate, and theophylline). Thyroid function is also relevant.
   - **f.** The mechanism by which homocysteine appears to promote vascular disease is **unclear**. Elevated homocysteine levels seem to play a role in the production of arterial lesions, but deficiencies of other factors, such as vitamin B_{12} and folic acid, may also be involved, especially in the elderly.
   - **g.** **Possible mechanisms** of increased risk are that hyperhomocysteinemia may impair release of nitric oxide from endothelial cells, stimulate proliferation of atherogenic smooth muscle cells, and contribute to thrombogenesis through activation of protein C.
     - **(1)** Deficiencies in the cofactors lead to elevated serum concentrations of homocysteine, although profound deficiencies are rare among persons with high homocysteine CAD.
     - **(2)** Rare defects in the genes for 5,10-methylene tetrahydrofolate reductase, cystathionine β-synthase (0.5% prevalence), methylene tetrahydrofolate homocysteine methyltransferase (rare), and methionine synthases (rare) can lead to increases in homocysteine.
2. **Laboratory examination.** For patients with abnormal homocysteine values, further evaluation includes thyroid-stimulating hormone, vitamin B_{12}, vitamin B_6, folate, and creatinine.
3. **Trials of homocysteine lowering.** The results of three such large, prospective, randomized trials have been reported in recent years. In the Vitamin Intervention for Stroke Prevention (VISP) trial, patients with a history of stroke were treated with two different doses of folic acid, vitamin B_6, and vitamin B_{12}.

Although a dose-dependent reduction in homocysteine levels was observed, no difference in vascular events was observed between the two groups. The Norwegian Vitamin Trial (NORVIT) randomized patients with history of MI to four different treatment groups: folic acid, vitamin B_6, and vitamin B_{12}; folic acid and vitamin B_{12}; vitamin B_6 alone; or placebo. After a mean 40 months of therapy, homocysteine levels were decreased by 27% in the group treated with folic acid and vitamin B_{12}. However, these subjects had no difference in the development of the primary end point (recurrent MI, stroke, or sudden death from CAD) compared with the placebo group. In the group treated with all three supplements, there was not only a marginally significant trend toward fewer strokes but also a near-significant trend toward more MIs. Finally, the Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial was a mixed primary and secondary prevention trial, treating vascular disease or diabetic patients with either a combination of folic acid, vitamin B_6, and vitamin B_{12} or placebo. Despite a significant decrease in homocysteine levels with active treatment, there was no significant difference in the primary outcome (MI, stroke, or death from cardiovascular causes) when compared with placebo treatment. There was a marginally significant decrease in stroke with vitamin administration. It is unknown whether the negative results of these studies result from incorrectness of the homocysteine atherosclerotic hypothesis or from pathologic effects of vitamin therapy offsetting possible benefit of homocysteine reduction. Regardless, given the lack of benefit (and in some cases, suggestion of harm) provided by folic acid with or without B vitamins, such therapy cannot be recommended for the prevention of cardiovascular disease.

D. Fibrinogen, a large hepatically synthesized glycoprotein, is a clotting factor that activates thrombin, induces platelet aggregation through the glycoprotein IIb/IIIa receptor, and stimulates smooth muscle proliferation.

1. **Etiology and pathophysiology.** There is increasing evidence that **fibrinogen is important in the development of premature atherosclerosis**. The link is likely and plausible.
   a. Several prospective studies, including the Framingham Heart Study, have shown an **impressive relationship between the plasma fibrinogen level and the occurrence of CAD and stroke**. Plasma fibrinogen levels > 350 mg/ dL are powerful independent risk factors for stroke and MI. A high fibrinogen level is an independent risk factor for CAD with a twofold to threefold increase in risk and markedly enhances risk for hypercholesterolemia.
   b. Clinical findings suggest that a **high fibrinogen level may also be a risk factor for the sequelae of CAD**. In the Northwick Park Heart Study, a fibrinogen level in the upper third was associated with a three times higher risk for cardiovascular disease than a plasma level in the lower third. In the Göteburg study, baseline fibrinogen level was significantly related to the incidence of MI and ischemic stroke.
2. **Cofactors.** Determinants of high fibrinogen levels include age, female sex, menopause, African American race, smoking, obesity, stress, use of oral contraceptives, pregnancy, and a consumption of large amounts of dietary fat.
3. **Risk reduction and therapy**
   a. Factors associated with a decrease in fibrinogen level include smoking cessation, physical activity, moderate alcohol intake, normalization of body weight, and postmenopausal hormone replacement.
   b. Although no clinical trial has identified a drug that reduces fibrinogen level safely and selectively, the following medications have been shown to decrease fibrinogen level in various clinical settings: fibrates, pentoxifylline, ticlopidine, *n*-3 polyunsaturated fatty acids, and anabolic steroids.

E. Myeloperoxidase. As discussed previously, inflammation plays a major role in the pathogenesis of CAD and the development of MI. MPO is a protein with enzymatic activity that is released during activation and degranulation of neutrophils and monocytes. For patients in the emergency department with chest pain, serum levels of MPO have been shown to predict risk for MI at 30 days and 6 months, even in the absence of myocardial necrosis. In patients with non–ST-elevation MI, MPO levels have recently been shown to predict 30-day risk of recurrent nonfatal MI or hospitalization for acute coronary syndrome.

F. Nonlipid genetic factors. Although a familial predisposition for CAD has been well documented, little is known about the causative factors leading to premature events in such kindreds. In one family, a seven–amino acid deletion in the gene encoding the MEF2A transcription factor was found to confer autosomal dominant susceptibility to CAD and MI. The thrombospondins are a family of glycoproteins that play a pivotal role in cell adhesion, vascular integrity, and thrombosis. SNPs in thrombospondin genes have been linked to premature atherosclerosis and MI, providing another example of how genetic variations may contribute to the development of coronary disease. Recently, the general excitement regarding genetics of CAD has been somewhat tempered by publications of negative findings. Nevertheless, the identification of genetic risk factors for cardiovascular disease and the elucidation of their mechanism of risk elevation are still among the newest and most promising areas of translational cardiology research.

ACKNOWLEDGMENTS: *The authors thank Drs. J. Christopher Merritt and JoAnne Micale Foody for their contributions to earlier editions of this chapter.*

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CHAPTER 45

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Diabetes and the Heart

I. INTRODUCTION. The presence of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) confers a marked increase of risk of coronary artery disease (CAD) development. **CAD accounts for as many as 80% of deaths among individuals with diabetes, compared with 30% in those without diabetes**. The prevalence of T2DM, which correlates closely with overweight and obesity, has shown a sharp rise over recent decades. Consequently, the management of diabetes, in parallel with the management of nonglycemic CAD risk factors including hypertension, dyslipidemia, and obesity, has become a prime focus in both the primary and secondary prevention of cardiovascular events. Significant uncertainty remains regarding the impact of tight glucose control on future cardiovascular events and the optimal glucose-lowering drug regimen. The revascularization strategies best suited to individuals with diabetes are also an area of ongoing research.

II. EPIDEMIOLOGY

A. Epidemiology of diabetes

1. Diabetes has been described as a worldwide epidemic and is now one of the most common chronic diseases in both developed and developing nations. This rise in prevalence is driven partly by rising levels of obesity, physical inactivity, and

TABLE 45.1 List of Countries with the Highest Numbers of Estimated Cases of Diabetes for 2000 and 2030

	2000		2030	
	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1	India	31.7	India	79.4
2	China	20.8	China	42.3
3	United States	17.7	Unites States	30.3
4	Indonesia	8.4	Indonesia	21.3
5	Japan	6.8	Pakistan	13.9

From Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. *Diabetes Care.* 2004;27(5):1047–1053.

urbanization, coupled with the aging population and greater longevity for patients with diabetes due to advances in diabetes management. The International Diabetes Federation reported that there were 30 million individuals with diabetes worldwide in 1985. The most recent analysis of data suggests this had grown to 171 million adults over 20 years in 2000 (1). If the age-specific prevalence remains constant, there will be a projected doubling in global diabetes cases between 2000 and 2030, bringing the expected total to a staggering 366 million.

2. The greatest burden of diabetes lies in developing countries, as illustrated in Table 45.1. India and China are notable for the exceptionally high prevalence in 2000 (31.7 and 20.8 million, respectively, compared with 17.7 million in the United States). The projected 2030 figures for individuals with diabetes are 79.4 million in India, 42.3 million in China, and 30.3 million in the United States (1). In developing countries, the majority of people with diabetes are in the 45- to 64-year age range. In contrast, the majority in developed countries are over 64 years of age.
3. **T2DM was once considered to be a disease of adulthood, but it has recently been recognized with increased frequency in children and adolescents**, particularly within some ethnic groups such as Native Americans (2). Ten years ago, 3% of new-onset diabetes in adolescents was type 2; currently, 45% of cases are designated T2DM (3). The onset of diabetes in the second decade of life coincides with the physiological occurrence of pubertal insulin resistance. Up to 75% of young people diagnosed with T2DM have a first- or second-degree relative with the condition.
4. **Diabetes prevalence is higher in men than in women, but there are more women in total with diabetes.** T2DM, in contrast to T1DM, is notable for its close association with conditions such as hypertension, dyslipidemia, and obesity, which further raises the impact of T2DM on the health outcomes of affected individuals.
5. In the United States, 95% of diabetes cases are T2DM, but T1DM has also shown increased incidence over recent years. The increase occurs largely in the youngest individuals (< 5 years) and those with moderate genetic susceptibility (4). A variety of environmental factors and the increasing incidence of childhood obesity are currently being studied as potential causes.

B. Spectrum of insulin resistance to T2DM

1. There is a continuum between the early pathological features of disordered glucose metabolism and T2DM.

TABLE 45.2 Criteria for the Diagnosis of Diabetes and Prediabetes

Diabetes:

- **HbA1c** ≥ 6.5%

or

- **Fasting plasma glucose** ≥ 126 mg/dL (7.0 mmol/L)

or

- **2-H plasma glucose** ≥ 200 mg/dL (11.1 mmol/L) in 75-g oral glucose tolerance test

or

- **Random plasma glucose** ≥ 200 mg/dL (11.1 mmol/L) with classic hyperglycemia signs/symptoms

In the absence of unequivocal hyperglycemia, results should be confirmed by a repeat test.

Prediabetes:

- **HbA1c** 5.7–6.4%

or

- **Fasting plasma glucose** 100–125 mg/dL (5.6–6.9 mmol/L) = impaired fasting glucose

or

- **2-H plasma glucose** 140–199 mg/dL (7.8–11.0 mmol/L) in 75-g oral glucose tolerance test = impaired glucose tolerance

From American Diabetes Association. Standards of Medical Care in Diabetes 2011. *Diabetes Care.* 2011;34(suppl 1):S11–S61.

a. A diagnosis of diabetes can be made on the basis of a fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) or a 2-hour plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test. A HbA1c ≥ 6.5% has now been added to the ADA criteria for the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, a positive result for any of these criteria should be confirmed on repeat testing. In the setting of classic hyperglycemic symptoms, a single random glucose ≥ 200 mg/dL is considered diagnostic (5). These diagnostic criteria are summarized in Table 45.2.

b. It is now recognized that the microvascular and macrovascular complications of diabetes are not limited only to individuals meeting the diagnostic criteria for established diabetes. The progression from normal glucose tolerance to T2DM involves intermediate stages of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), also collectively termed "prediabetes." This pathological continuum arises from dysregulation of the balance between insulin sensitivity and insulin secretion.

c. There is usually a long phase of asymptomatic pathology prior to the development of overt T2DM. Longitudinal studies suggest that insulin resistance onset occurs 10 to 20 years prior to the diagnosis of diabetes and is the best predictor of whether an individual will develop T2DM later. Insulin resistance places pressure on the pancreatic β-cells to augment secretion of insulin and, therefore, promotes β-cell dysfunction. Once the β-cell is unable to compensate sufficiently for the peripheral insulin resistance state, progression to T2DM will ensue. The underlying etiology of T2DM is complex, with both environmental and genetic predisposing factors promoting insulin resistance and β-cell dysfunction.

d. The most notable epidemiological evidence regarding the impact of prediabetes states comes from the DECODE group. They have demonstrated that subjects without a diagnosis of diabetes have no threshold level of fasting or 2-hour postload glucose concentration above which the risk of all-cause or cardiovascular mortality death increased sharply. The relationship between 2-hour postload glucose and cardiovascular mortality was linear, with a continuum of risk extending into and below the prediabetes glucose range (6).

e. Current interpretations of data sets suggest that the cardiovascular effects of postprandial or postglucose challenge hyperglycemia are greater than those of IFG (7). During the prediabetes phase, the cardiovascular event rate is modestly increased. There is evidence for a higher mortality in individuals with IGT compared with those with IFG, which is independent of HbA1c or fasting blood glucose (8). The Emerging Risk Factors Collaboration found that individuals without a diagnosis of diabetes showed only a modest nonlinear correlation between fasting blood glucose and cardiovascular end points; postprandial glucose was not investigated.

f. There is evidence that the pathogenic effect of hyperglycemia on the endothelial cells already exists in the prediabetes stage.

2. The full transition from the early metabolic abnormalities of prediabetes to established diabetes probably occurs in about two-thirds of individuals.

a. There is interest in determining **interventions that may decrease the likelihood of progression to diabetes** or reduce the future cardiovascular event rate once diabetes occurs. The Diabetes Prevention Program Research Group randomly assigned 3,234 participants without diabetes, but with elevated fasting and postload glucose concentrations, to placebo versus metformin (850 mg twice daily) versus a lifestyle modification program promoting exercise and weight loss (9). The incidence of diabetes over an average follow-up of 2.8 years was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. **The lifestyle intervention was significantly more successful in preventing diabetes than the metformin strategy**. Also of note is the STOP-NIDDM trial, which randomized individuals with IGT to acarbose (which primarily affects postprandial glycemia) or placebo (10). Patients in the acarbose group were observed to have a lower rate of diabetes diagnosis than those receiving placebo. Furthermore, a lower rate of cardiovascular disease and hypertension over a 3.3-year mean follow-up period was reported in the acarbose group (11).

C. Impact of diabetes on heart disease

1. Both T1DM and T2DM confer significantly elevated risks of CAD, acute coronary syndromes, post–myocardial infarction (MI) complications, heart failure, and probably also sudden cardiac death. In addition, the incidences of peripheral arterial disease, stroke, and end-stage renal failure are elevated in individuals with diabetes. The cardiovascular complications of T2DM account for the majority of the socioeconomic burden of this chronic disease on both individuals and society.

a. **As many as 80% of individuals with diabetes will die from cardiovascular causes**. Per the Framingham Heart Study, the risk of CAD is doubled in men and tripled in women with diabetes, compared with age-matched subjects without diabetes.

b. In the modern era of drug-eluting stents and dual antiplatelet therapy, the mortality associated with CAD is falling overall. However, women with diabetes were observed to have a rise in CAD mortality in the period 1995 to 2003 (12).

c. More recently, the Emerging Risk Factors Collaboration undertook a large meta-analysis that demonstrated a twofold excess risk of outcomes such as coronary heart disease, coronary death, and nonfatal MI among individuals with established diabetes (13). They also found diabetes to be a third more strongly related to fatal than to nonfatal MI, possibly suggesting more severe manifestations of

coronary disease in those with diabetes. Hazard ratios (HRs) were particularly elevated for cardiovascular disease among individuals with diabetes who were female, younger, and non-smokers or had lower-than-average blood pressure.

d. Patients with diabetes present differently from those without diabetes and are much more likely to experience an acute coronary syndrome without chest pain, known as "silent ischemia."

e. Various angiographic trials have demonstrated that patients with **diabetes undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) tend to have significantly more severe CAD**, with a preponderance of multivessel disease and greater severity of lesions than those without diabetes. Despite the more severe plaque burden, diabetes correlates with lesser collateral vessel formation.

f. A particularly high risk is observed among individuals with T2DM following their first cardiovascular event. Indeed, there are multiple studies suggesting poorer outcomes following cardiovascular events, even with revascularization, for individuals with diabetes compared with those without. Cubbon et al. (14) reported that diabetes conferred a higher 30-day mortality after urgent PCI (9.4% patients with diabetes vs. 5.9% without diabetes, $p < 0.001$).

g. Post-MI complications and mortality in patients with diabetes correlate with post-MI ejection fraction and the presence of multivessel coronary disease. **Cardiogenic shock is more common and more severe in post-MI patients with diabetes**. The higher in-hospital mortality among the post–acute coronary syndrome (ACS) population with diabetes is largely related to the greater incidence of acute decompensated heart failure and to a lesser extent the increased risk of reinfarction and infarct extension.

h. The CAD mortality arising from T1DM has also been studied. Laing et al. reported a prospective study of 23,751 individuals with T1DM where subjects were followed for up to 29 years (15). As is typical of a T1DM cohort, the relatively young age correlated with a low event rate. However, their CAD risk was several times higher than that of a matched population without diabetes.

i. There is now sufficient literature to conclude that **chronic hyperglycemia per se, rather than the associated cardiovascular risk factors, has a pathogenic role in the development of vascular disease in diabetes**.

D. Risk factors for CAD in patients with diabetes

1. The risk factors that predispose individuals with diabetes to develop cardiovascular disease are the same as those that raise cardiovascular risks in those without diabetes. However, the prevalence of known major risk factors for CAD is generally amplified among persons with diabetes. Given the overall higher cardiovascular risk conferred, the benefits of tighter risk factor control may be greater in those with diabetes than those without. The potential gains of aspirin, attaining a normal body weight and nonsmoking status, tight blood pressure control, and aggressive lipid management in diabetes have been the subject of several recent trials.

2. a. Dyslipidemia

(1) This is one of the most profound risk factors among individuals with diabetes. Diabetes is associated with small, dense low-density lipoprotein (LDL) particle composition, increased levels of apolipoprotein B and E, low levels of high-density lipoprotein (HDL) cholesterol, and high triglyceride (TG) levels. These lipid composition abnormalities cluster with insulin resistance and abdominal adiposity and appear to induce endothelial dysfunction and an increased susceptibility to thrombosis.

(2) Lipid-lowering therapy is now a cornerstone of T2DM management. In the Scandinavian Simvastatin Survival Study (4S), there was a 55% reduction in cardiovascular events among subjects with diabetes and a 25% reduction in the CARE trial. The National Cholesterol Education Program

(NCEP) considers diabetes a CAD equivalent in its Adult Treatment Panel III guidelines. Hence, a target of < 100 mg/dL—with an optional goal of < 70 mg/dL—is recommended (16). Statins are considered first-line agents to achieve these targets. Niacin may be of use in elevating HDL levels. Bile acid binding resins (along with thiazides, estrogens, and glucocorticoids) may increase TG levels and therefore should be avoided where possible.

b. Hypertriglyceridemia

(1) Elevated fasting TG levels are characteristic of the lipid panel in diabetes and **constitute an independent cardiovascular risk factor**. Hypertriglyceridemia correlates with abdominal adiposity.

(2) Fibrates have traditionally been considered an appropriate therapy to target hypertriglyceridemia and have often been added to statin therapy for this indication. The Helsinki Heart Study demonstrated the benefit of fibrates in a primary prevention trial to reduce cardiovascular end points (but not mortality), and the **VA HDL Intervention Trial (VA-HIT)** showed outcomes benefit in a secondary prevention setting. However, the lipid arm of the **ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial** did not demonstrate any benefit for subjects with T2DM in the addition of fenofibrate to simvastatin. The significant rhabdomyolysis risk with a fibrate and statin combination should also be considered.

c. Hypertension

(1) The prevalence of hypertension is increased in individuals with diabetes compared with those without. The presence of an elevated blood pressure serves as at least as strong a risk factor for CAD as it does for individuals without diabetes.

(2) There are multiple large trials supporting the benefit of blood pressure lowering in subjects with diabetes. In the UKPDS, lowering the blood pressure to a mean of 144/82 mm Hg (compared with 154/87 mm Hg) significantly reduced strokes, diabetes-related deaths, and heart failure, as well as microvascular complications. In that trial, there did not appear to be an outcome benefit between captopril and atenolol (17). However, several trials since have demonstrated the renal protective effects of angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor antagonists) over alternate agents, which has firmly established them as the first-line antihypertensives in diabetes.

The **Hypertension Optimal Treatment (HOT) trial** demonstrated the benefit of a lower diastolic target. Among the 3,000 subjects with diabetes, but not in those without diabetes, the relative cardiovascular risk was significantly reduced in the ≤ 80 mm Hg group, compared with the ≤ 90 mm Hg group (18). Major guidelines suggest a target blood pressure in patients with diabetes of < 130/80 mm Hg. The ACCORD trial randomized subjects with diabetes to a target systolic blood pressure of < 120 mm Hg or < 140 mm Hg. The lower target group showed no difference in the primary cardiovascular outcomes end point but did have a significantly lower stroke rate; however, this was at the expense of significantly more adverse drug events and an increased risk of a creatinine rise of > 1.5 mg/dL (19). There is currently insufficient evidence to recommend ACE inhibitors in normotensive patients with diabetes without microalbuminuria.

d. Tobacco. There is evidence that smokers with diabetes have a markedly increased risk of MI and peripheral arterial disease. Lipid abnormalities and the development of atherosclerotic plaques appear to be promoted by smoking in the setting of diabetes.

e. Obesity

(1) The prevalence of obesity has more than doubled in the United States since 1980. Obesity and overweight are typically defined in terms of

body mass index (BMI), with overweight being 25 to 30 kg/m^2, class I obesity 30 to 35 kg/m^2, class II obesity 35 to 40 kg/m^2, and class III obesity > 40 kg/m^2. Waist circumference and waist-to-hip ratio better reflect abdominal adiposity and are more reliable predictors of CAD outcomes than BMI (20). Obesity is an important determinant of cardiovascular health and is associated with widespread alterations in cardiac and vascular structure and function. It has been shown to be an independent risk factor for the development of cardiovascular disease. **T2DM correlates closely with obesity, especially central obesity**.

(2) Caloric restriction, behavior modification, and increased physical activity form the basis of weight management programs. Unfortunately, sustained weight loss is difficult to achieve with these conservative measures. Several medications have been marketed for temporary assistance with weight loss.

(a) Sibutramine is a combined inhibitor of neuronal norepinephrine, serotonin, and, to a lesser degree, dopamine reuptake. It is a sympathomimetic and therefore increases heart rate and blood pressure, leading to concerns reading its cardiovascular safety profile. It has recently been withdrawn from the market in multiple countries including the United States.

(b) Ephedrine and ephedra alkaloids ("ma huang") are sympathomimetic amines with a prolonged duration of action and increased peripheral effects. Due to safety concerns, ephedrine with or without caffeine and the ephedra alkaloids are not approved for treatment of obesity.

(c) Phentermine and diethylpropion are the only sympathomimetic drugs currently approved for the short-term treatment of obesity. Their use is not widespread.

(d) Orlistat is currently the only drug that is available for modulation of fat digestion. It inhibits pancreatic lipases, thus increasing the proportion of fat that is not completely hydrolyzed and is fecally excreted. The recommended prescription dose is 120 mg three times daily. A 60 mg over-the-counter version is available in some countries, including the United States. Major side effects include abdominal cramps, flatus, fecal incontinence, diarrhea, and oily stools; there is a rare association with severe liver injury.

Multiple trials have demonstrated a greater initial weight loss with orlistat, compared with placebo, and also slower weight regain in the longer term. In obese individuals with diabetes, orlistat not only promotes weight loss but also decreases A1c at 1 year in comparison with placebo (21).

(e) Other drugs that may have effects in supporting weight loss include antidepressants such as fluoxetine, sertraline, bupropion; anti-epileptics such as topiramate and zonisamide; and diabetes medications including metformin and the glucagonlike peptide (GLP) analogs.

(3) There is growing evidence regarding the beneficial effects of significant weight loss achieved by bariatric surgery on glucose metabolism. Bariatric surgery is generally restricted to individuals with BMI > 40 kg/m^2 or BMI 35 to 40 kg/m^2 with co-existing medical conditions such as diabetes, although the 2005 revision of the NIH consensus statement by the American Society for Bariatric Surgery expanded the indications to BMI 30 to 35 kg/m^2 with comorbidities.

(a) Bariatric surgery options include malabsorptive procedures such as the Roux-en-Y gastric bypass (currently accounting for the majority of bariatric operations in the United States) and restrictive procedures such as laparoscopic adjustable gastric bands and sleeve gastrectomy. The most recent data from the Longitudinal Assessment of Bariatric Surgery Consortium show a 30-day mortality rate of < 1% (22).

(b) Weight loss post bariatric surgery is typically expressed in terms of "excess weight," which refers to the difference between the actual and the ideal weights for an individual. Weight loss after malabsorptive bariatric surgery tends to reach a nadir at 12 to 18 months with an average of 70% excess body weight loss and a 35% decrease in BMI, with an approximate 10% weight regain in the following 10 years (23).

(c) A meta-analysis of 22,000 patients demonstrated that an average excess body weight loss of 61% was accompanied by significant improvements in T2DM, hypertension, dyslipidemia, and obstructive sleep apnea. Indeed, bariatric surgery has demonstrated an ability to completely reverse established diabetes in a large number of subjects. In the Swedish Obese Subjects Study (23), a prospective, nonrandomized, intervention trial of 4,047 obese subjects, 72% of individuals with diabetes who chose the bariatric surgery option showed reversal of their diabetes at 2 years, compared with 21% of those who followed a conservative weight loss regimen of diet and exercise. At 10 years follow-up, diabetes was reversed in 36% of the bariatric surgery group and 13% of the control group. In a smaller study of 165 obese patients with diabetes by Pories, 83% showed diabetes remission at a mean of 9.4 years (24). In the recent STAMPEDE trial, 150 patients with uncontrolled T2DM and a BMI between 27 and 43 kg/m^2 were randomized to intensive medical therapy alone, versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The proportion of patients with HbA1c ≤ 6.0% at 12 months was 12% in the medical therapy group, versus 42% in the gastric-bypass group ($p = 0.002$) and 37% in the sleeve-gastrectomy group ($p = 0.008$).

(d) There is growing evidence that there are both substantial modifications in the traditional CAD risk factors post bariatric surgery and that these risk modifications translate to a cardiovascular outcome benefit. The largest study of Framingham risk scores and actual cardiovascular events after gastric bypass involved 500 patients (without a control group) (25). At 1 year, the mean excess body weight loss was 68.7% ± 22%. The diabetes prevalence fell from 28% to 6% ($p = 0.001$). The average 10-year absolute cardiovascular event risk, as estimated from the Framingham data, was 5.4% at baseline. This reduced to 2.7% at 1 year postsurgery ($p = 0.001$). The actual rate of cardiovascular events observed in this cohort postoperatively was only 1%.

3. Multifactorial risk factor interventions should be targeted in all patients with diabetes, regardless of whether this is a primary or a secondary prevention strategy.

a. The Steno-2 trial randomized 160 patients with T2DM and microalbuminuria to intensive versus conventional therapy for a mean period of 7.8 years (26). The trial was designed to evaluate the effect on cardiovascular events of an intensified, targeted, multifactorial intervention comprising behavior modification and polypharmacologic therapy aimed at several modifiable risk factors in patients with T2DM.

b. The intensive management regimen included dietary fat restriction, 30 minutes of exercise three to five times per week, smoking cessation, ACE inhibitors or angiotensin receptor blocker administration irrespective of blood pressure, additional agents to target blood pressure < 130/80 mm Hg, 150 mg aspirin, stepwise glycemia management to target A1c < 6.5%, statins for hyperlipidemia, and fibrates for isolated hypertriglyceridemia. The intensive group achieved significantly lower blood pressure, HbA1c, LDL, and TGs. There was an absolute risk reduction of 20% in cardiovascular events.

c. The subjects were then followed up for a further mean of 5.5 years, at which point the primary end point of all-cause mortality was assessed (27).

Significant differences in blood pressure, A1c, LDL, and TGs were absent by this later follow-up point. The primary end point at 13.3 years was time to all-cause death, and an absolute risk reduction of 20% was found. Even beyond the period of tight risk factor control, the Kaplan-Meier curves for the first cardiovascular event continued to diverge. During the mean 13.3-year follow-up period, the mortality rate among the conventional therapy subjects was 50%, a finding that highlights the poor overall outcomes in patients with diabetes who are not intensively managed.

d. This study established that there were long-term benefits to aggressive multifaceted risk factor management, and that tight glycemic control and treatment with aspirin, antihypertensives, and lipid-lowering drugs appeared to be additive. Therefore, current society and national guidelines stress the importance of a broad approach to targeting multiple cardiovascular risk parameters. This body of evidence is much more firmly established than that regarding any benefit from tight glycemic control as a single approach to reducing cardiovascular risk.

E. Metabolic syndrome

The term "metabolic syndrome" describes the clustering of several of these cardiovascular risk factors in association with impaired glucose metabolism. There are slightly differing diagnostic criteria established by the WHO (28), the AHA and IDF (29), and the NCEP (30). The 2009 joint AHA/IDF criteria are summarized in Table 45.3. The value of the concept of the metabolic syndrome may lie in the emphasis it has placed on considering the patient as a whole and also the concept of abdominal adiposity being the more relevant predictor of CAD than BMI. However, several commentators have recently challenged the relevance of the metabolic syndrome, as it appears that accounting for the presence of the metabolic syndrome does not serve as a stronger predictor of cardiovascular risk than the individual component parameters (31).

F. Role in pathology of atherosclerosis

1. Diabetes accelerates the atherosclerosis process. Autopsy series have revealed more diffuse coronary involvement, greater severity of vessel stenosis, and more severe left main disease in persons with diabetes, compared with those without. Similarly, adverse coronary anatomy findings have been observed in autopsy studies of patients with a history of childhood onset of T1DM who died before the age of 40 years. The pathophysiology of atherosclerosis in diabetes remains incompletely understood but is thought to involve the hyperglycemia, lipid abnormalities, and

TABLE 45.3 Joint AHA and IDF Criteria for the Diagnosis of the Metabolic Syndrome

Metabolic syndrome

- **Waist circumference** in excess of population- and country-specific dimensions
- **Elevated triglycerides** ≥ 150 mg/dL (1.7 mmol/L), *or drug treatment for hypertriglyceridemia*
- **Low HDL** < 40 mg/dL (1.0 mmol/L) in males or < 50 mg/dL (1.3 mmol/L) in females, *or drug treatment for low HDL*
- **Elevated blood pressure** systolic ≥ 130 mm Hg and/or diastolic ≥ 85 mm Hg, *or antihypertensive drug treatment in a patient with diagnosis of hypertension*
- **Elevated fasting glucose** ≥ 100 mg/dL (5.6 mmol/L), *or drug treatment for hyperglycemia*

AHA, American Heart Association; HDL, high-density lipoprotein; IDF, International Diabetes Federation.

From Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation.* 2009;120:1640–1645.

dysfunctional endothelial and vascular smooth muscle function, coupled with a propensity for inflammation, thrombosis, and platelet activation.

2. It is recognized that the synthesis of nitric oxide (NO) by the vascular endothelium is reduced in subjects with diabetes. NO is among several key substances that maintain healthy endothelial function, which includes freedom from adhesion molecule activation, leukocyte diapedesis, platelet aggregation, and activation of thrombosis. However, the bioavailability of NO is adversely affected by hyperglycemia, high levels of free fatty acids, and insulin resistance. Current research reveals the impact of excessive oxidative stress (which can be induced by hyperglycemia, fatty acids, or insulin resistance) on NO production and also on the generation of advanced glycation end products, which are suspected to mediate various negative cellular effects in diabetes. Reactive oxygen species also activate protein kinase C with wide-ranging effects on cellular metabolism, including activation of the PI3K pathway, which has a role in mediating cell adhesion and migration. The ability of NO to act on vascular smooth muscle and cause vasodilation is reduced; endothelial cell dysfunction in diabetes is coupled with increased production of vasoconstrictors such as prostanoids and endothelin.

   Another key pathogenic feature of atherosclerosis in diabetes is the PI3K- and nuclear factor κB–stimulated alterations in adhesion molecule expression on the endothelial surface. This causes the endothelium to become more adherent to passing cells, and selectins on the surface of leukocytes attach to receptors such as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) and migrate into the intima. Here monocytes take on oxidized LDL and become macrophage foam cells, which are instrumental in the development of an atherosclerotic plaque. The tendency toward small, dense LDL particles in diabetes is another factor contributing toward atherosclerosis. Smooth muscle cell proliferation ensues, leading to deposition of collagen and other extracellular matrix proteins into the plaque.

   Platelet function is also abnormal in diabetes, with overexpression of the glycoprotein IIb/IIIa receptor promoting inappropriate platelet adhesion and activation. Upregulation of multiple coagulation factors such as factor VII, thrombin, tissue factor, and plasminogen activator inhibitor-1 increases the tendency toward clotting, therefore contributing to the risk of thrombosis at the site of a plaque rupture or stent placement.

III. MICROVASCULAR TRIALS (as summarized in Table 45.4)

A. The role of tight control of glycemia was firmly established in the 1990s with the publication of **two large trials demonstrating decreases in microvascular complications—primarily nephropathy and retinopathy—with lower glucose goals**.

1. The Diabetes Control and Complications Trial (DCCT) recruited 1,441 patients with T1DM, of whom 726 had no retinopathy at baseline and 715 had mild retinopathy (32). Subjects were randomly assigned to an external insulin pump or three or more daily insulin injections to target a fasting glucose < 6 mmol/L. Conventional therapy had no glucose goals beyond those needed to prevent symptoms and comprised one or two daily injections of insulin. The two treatment groups were followed for a mean of 6.5 years between 1983 and 1993, with the mean HbA1c attained being 7.4% and 9.1%, respectively. In the primary prevention cohort (those without baseline retinopathy), intensive therapy reduced the adjusted mean risk of retinopathy development by 76%. With the two cohorts combined, intensive glucose control reduced the occurrence of microalbuminuria by 39%.
2. The UK Prospective Diabetes Study (UKPDS) recruited 5,102 newly diagnosed T2DM patients from 1977 to 1991 with a median baseline HbA1c of 9.1% (33). The 4,209 patients who could not be controlled on diet alone were managed with differing therapies to determine if there were any specific advantages

TABLE 45.4 Characteristics of the Major Randomized Controlled Trials of Intensive Glucose Control in Type 2 Diabetes

	UKPDS 33	ACCORD	ADVANCE	VADT
Participants (*n*)	3,867	10,251	11,140	1,791
Diabetes duration (y)	0	10	7.9	11.5
Mean age (y)	53	62	66	60
History of CV disease (%)	Not reported	35	32	40
Duration of intervention (y)	10.0	3.5	5.0	5.6
Intensive group treatment	Sulfonylurea or insulin	Any oral drugs, insulin (91% rosiglitazone)	Gliclazide, other drugs including insulin	Glimepiride or metformin, plus rosiglitazone, or insulin
Standard group treatment	Diet	Any oral drugs, insulin (57% rosiglitazone)	Any oral drugs, insulin	Glimepiride or metformin, plus rosiglitazone, or insulin
Intensive group goal	FPG < 6.0 mmol/L	A1c < 6.0%	A1c ≤ 6.5%	1.5% absolute A1c reduction, cf. standard group
Standard group goal	FPG 6.1–15.0 mmol/L	A1c 7.0–7.9%	Local standards	Local standards
Baseline median A1c (%)	7.1	8.1	7.5	9.4
Achieved median A1c (%)	7.0 vs. 7.9	6.4 vs. 7.5	6.5 vs. 7.3 (mean)	6.9 vs. 8.4
Primary CV outcome	MI and sudden cardiac death	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, CV mortality, heart failure, vascular surgery, inoperable CAD, amputation
Hazard ratio for primary outcome	16% risk reduction ($p = 0.052$)	0.90 (95% CI 0.78–1.04)	Macrovascular 0.94 (95% CI 0.84–1.06)	0.88 (95% CI 0.74–1.05)
Hazard ratio for death	0.87 ($p = 0.006$)	1.22 (95% CI 1.01–1.46)	0.93 (95% CI 0.83–1.06)	1.07 (95% CI 0.80–1.42)

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

From Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med.* 2009;151:394–403.

or disadvantages between glucose-lowering agents. A total of 342 obese subjects were allocated to the metformin group; of the remaining patients, 30% were randomized to conventional therapy and 70% to insulin or a sulfonylurea. The intensive group aimed for a fasting plasma glucose < 6 mmol/L. The median HbA1c achieved was 7.0% in the tight control group versus 7.9% in the conventional group. There was a significant 25% risk reduction (95% confidence interval [CI] 7% to 40%) in the end point of renal failure or death from renal failure, vitreous hemorrhage, or photocoagulation in the intensive control group.

In summary, the two large trials published in the 1990s, DCCT and UKPDS, showed significant improvements in microvascular outcomes with tighter glycemic control in T1DM or T2DM.

IV. MACROVASCULAR TRIALS

A. Despite the convincing evidence for a reduction in microvascular complications, the relationship between glycemia and cardiovascular events remained unclear, with neither DCCT nor UKPDS showing a definitive advantage in terms of cardiovascular outcomes or mortality.

B. The DCCT did not reveal a significant difference in macrovascular outcomes between the two treatment groups, but this relatively young cohort of T1DM patients would have been expected to have a low event rate. However, intensive glycemic control did reduce hyperlipidemia development.

C. The UKPDS revealed a nonsignificant 16% risk reduction (95% CI 0% to 29%, $p = 0.052$) for fatal or nonfatal MI, or sudden death, with intensive management. In those subjects with > 120% ideal body weight who were allocated to the metformin strategy, there were significant benefits in terms of diabetes-related end points and all-cause mortality and a 39% risk reduction in MI. However, these results should be interpreted with caution due to the small numbers in the metformin subgroup.

D. Two follow-up studies, and three new trials of intensive glucose control, sought to clarify the relationship between glucose control and cardiovascular events. Both the DCCT and the UKPDS cohorts were followed up for more than a decade from recruitment and their macrovascular outcomes assessed.

1. The DCCT follow-up, known as EDIC (Epidemiology of Diabetes Interventions and Complications), monitored 93% of the original cohort until 2005, for a mean of 17 years of follow-up (34). Beyond 1993, DCCT subjects were placed onto whatever diabetes regimen their physician deemed appropriate, and so the distinction between standard and intensive management strategies was lost and the mean HbA1c's were the same. However, there was emergence of a macrovascular risk reduction in the group that had received the period of tight control earlier in the course of their T1DM; a 42% risk reduction for all cardiovascular events (95% CI 9 to 63, $p = 0.02$) was observed in this group.

2. Similarly, the UKPDS subjects were invited for posttrial monitoring, with 3,277 patients attending annual clinics for a further 5 years (35). No attempts were made to maintain their previously assigned therapies, and indeed there was no persisting difference in A1c between groups at 1 year after initial trial conclusion. Data were then analyzed by original trial groupings. The sulfonylurea/insulin group showed a sustained decrease at 10 years for MI (15%, $p = 0.01$) and death from any cause (13%, $p = 0.007$). The metformin group showed a significant risk reduction in MI (33%, $p = 0.005$) and all-cause mortality (27%, $p = 0.002$).

3. The DCCT/EDIC and UKPDS follow-up findings can be interpreted as showing "legacy" effects, whereby tighter management of glycemia early in the disease course confers cardiovascular and survival benefits more than a decade later. However, these potential delayed macrovascular benefits appear to be modest in comparison with long-term aggressive management of blood pressure and LDL.

E. Three further large trials added additional information regarding the potential relationship between glycemic control and cardiovascular outcomes.

1. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial randomized 11,140 patients with T2DM to standard versus intensive glucose control (36). Intensive control was achieved with the use of gliclazide (a sulfonylurea) plus other agents as necessary to achieve a HbA1c ≤ 6.5%. After 5 years' median follow-up, the mean A1c was 7.3% in the standard group and 6.5% in the intensive group. Insulin was prescribed for 40.5% and 24.1% of patients in the intensive group and the standard control group, respectively. There was a decrease in the incidence of microvascular events (primarily macroalbuminuria) but no significant effect of the type of glucose control on major macrovascular events (HR with intensive control 0.94), death from cardiovascular causes (HR 0.88), or death from any cause (HR 0.93). Of relevance, the nonglycemic risk factors were not fully optimized in many participants, with a mean systolic blood pressure of 135.5 ± 17.6 in the intensive glucose group and 137.9 ± 18.4 in the standard group and an LDL mean of around 120 mg/dL ± 20 in both groups.
2. The ACCORD trial also tested the effects of tight glucose control, recruiting a total of 10,251 T2DM patients who were randomized to a target A1c of < 6% versus 7.0% to 7.9% (37). These participants were slightly younger than those studied in ADVANCE; they also tended to be heavier, had a higher median baseline A1c, and were much more likely to be using insulin prior to entry. ACCORD was discontinued at a mean follow-up of 3.5 years due to an increased risk of death in the intensive treatment arm. The primary outcome of nonfatal MI, nonfatal stroke, and cardiovascular mortality occurred in 352 patients in the intensive group versus 371 in the standard group (HR 0.90, 95% CI 0.78 to 1.04, p = 0.16). Hypoglycemia requiring medical attention and weight gain > 10 kg were both more common in the intensive therapy group. The finding of harm with a very aggressive A1c target was surprising and could be related to adverse effects of hypoglycemia, especially in long-standing diabetes—19 of the 41 cardiovascular deaths were attributed to "unexpected or presumed cardiovascular disease," and so could have been hypoglycemia-related. In addition, the average weight gain of 3.5 kg in the intensive control group (presumably drug-mediated) may have impacted on outcomes. It has also been noted that 91.2% of intensive therapy patients were receiving rosiglitazone, which was subsequently associated in other literature with an excess cardiovascular mortality, versus 57.2% of the standard therapy group.
3. The VADT randomly assigned 1,791 predominantly male military veterans who had a suboptimal response to therapy for T2DM to receive either intensive or standard glucose control (38). The mean age was 60 years, 40% had already experienced a cardiovascular event, 52% were receiving insulin, and the mean baseline HbA1c was 9.4%. This high-risk cohort was followed for a mean of 5.6 years, during which time the mean A1c was 6.9% in the intensive group and 8.4% with standard care. However, there was no significant difference observed between the two groups in any component of the primary outcome or in all-cause mortality (HR 1.07, 95% CI 0.81 to 1.42; p = 0.62).

F. The conclusion currently drawn from these studies is that there may be an early window in which tight glycemic control has the potential to achieve cardiovascular outcome benefits more than a decade later. However, ADVANCE, ACCORD, and VADT trials did not demonstrate any gains from a lower HbA1c target over a follow-up period of 3.5 to 5.6 years. Additionally, there is a possibility that **very aggressive glucose lowering in patients with established diabetes may confer a survival disadvantage**.

G. Recent meta-analyses incorporating the above trials have added additional information to this topic. The analyses by Turnbull et al. (39) and Kelly et al. (40) reached

similar conclusions, with pooled data showing a reduced risk of major cardiovascular events in the group with intensive glucose control compared with less aggressive control. However, in both cases, the risk reduction was small: a 9% risk reduction (HR 0.91, 95% CI 0.84 to 0.99) in the study of Turnbull and a relative risk of cardiovascular disease of 0.9 (95% CI 0.83 to 0.98) in the study of Kelly. Both concluded that cardiovascular mortality was unchanged between the two management strategies. Intensive glucose control was also highlighted as conferring at least a twofold risk for severe hypoglycemia in both papers. Both groups also found a small risk reduction regarding MI—a 15% reduction in fatal and nonfatal MI in the study of Turnbull and a 16% reduction of nonfatal MI risk in the study of Kelly. Turnbull et al. described a subgroup of patients who did not appear to benefit from more intensive control: individuals with a history of macrovascular disease existing prior to randomization.

Another meta-analysis, incorporating similar trials as the Turnbull and Kelly analyses, reached a slightly different conclusion. Ray et al. determined that intensive glucose lowering resulted in a significant reduction in nonfatal MI and in all coronary heart disease events. Cardiovascular mortality was not reported; all-cause mortality was equivalent in the pooled standard and intensive treatment groups (41).

H. The 2009 ACC/AHA Scientific Statement supports a goal HbA1c of ≤ 7%, with acknowledgment of the benefits of tight control in terms of microvascular disease, but recognizes the paucity of evidence for a cardiovascular benefit (42). Based on the currently available literature, individuals with diabetes cannot be confidently advised that stricter glucose control will reduce their likelihood of future cardiovascular events or mortality.

V. DIABETES PHARMACOTHERAPY

A. The spectrum of medications available to manage diabetes has expanded greatly over recent years. There has been increasing recognition that there may be significant differences between the cardiovascular impact of the various medications, even if the glycemic effects are equivalent.

1. Insulin is available in short-, medium-, and long-acting preparations, with synthetic human insulin and analogs of human insulin differing in their rates of absorption and durations of action. Mixtures of rapid short-acting and intermediate-acting insulin are also commonly used. Recombinant human insulin is synthesized using *Escherichia coli* bacteria, and subtle variations in the amino acid chain deter the insulin molecules from forming aggregates, thus creating a faster-onset, shorter-acting drug than regular insulin.

a. The different recombinant rapid-acting insulins—lispro, aspart, and glulisine—each have differing amino acid substitutions. All three can be injected subcutaneously to prevent postprandial glucose elevations, for rapid correction of elevated glucoses, and in insulin pumps. The onset of action is 15 minutes, with peak effect around 1 hour and a duration of action around 3 to 4 hours. An inhaled short-acting insulin was marketed briefly, but has now been withdrawn due to limited patient uptake.

b. Regular insulin is designated as a short-acting preparation. It has onset of action within 30 to 60 minutes, a peak time of 2 to 4 hours, and a duration of action around 6 to 8 hours. It can be used in intravenous infusions, as well as subcutaneously.

c. Neutral protamine Hagedorn (NPH) is an intermediate-acting insulin. Its time to onset is 1 to 3 hours, and the total duration of action is 12 to 16 hours. It can be injected either once daily at bedtime to lower fasting glucose levels (typically in individuals on oral hypoglycemics who are above A1c target) or as a twice-daily basal medication in combination with a shorter-acting prandial insulin. This latter approach is known as a basal-bolus regimen

and is widely used to achieve tight glucose control. In the basal-bolus regimen, a twice-daily intermediate-acting insulin, or a once-daily long-acting insulin, provides basal coverage and controls the fasting glucose levels. The three prandial insulin doses, administered just before mealtimes, cover the ingested carbohydrates and so limit postprandial glucose elevation. This is considered to be the most "physiologic" method of insulin administration, as it simulates the insulin-release patterns of the β-cells.

d. Glargine and detemir are the available long-acting agents, usually injected at night, and show minimal peaking. Glargine has a 24-hour profile of action, whereas detemir is more variable at 6 to 24 hours.

2. Insulin pumps are devices that can be programmed to release a continuous infusion of insulin into the subcutaneous tissue. An abdominal infusion site is the usual location, and the catheter should be changed every 2 to 3 days. These pumps are generally used in patients with T1DM and are most suited to knowledgeable and motivated individuals. They have been demonstrated to achieve greater success with target A1c levels and reduce the number of severe hypoglycemic episodes, compared with traditional subcutaneous insulin injections. **A newer innovation is the subcutaneous continuous glucose-monitoring system that detects glucose levels in the interstitium of subcutaneous tissue**. The real-time display of glucose levels can assist patients in anticipating insulin requirements and avoiding severe hypoglycemia. The currently marketed devices are each limited to a few days of continuous wear. Closed-loop systems that consist of both a subcutaneous continuous glucose sensor and an insulin pump are in development.

Insulin can cause weight gain and carries a risk of severe hypoglycemia. The hypoglycemic risk is increased in patients with renal and/or hepatic dysfunction, as the liver and kidneys are responsible for the majority of gluconeogenesis and glycogenolysis; in addition, insulin is renal excreted. The associated weight gain and hypoglycemia raised questions when the ACCORD trial revealed higher mortality in the intense therapy arm, where 77% of subjects were using insulin (vs. 55% in the standard care arm). The recent Euro Heart study also suggested harm related to insulin use. Insulin-treated patients with diabetes had an adjusted 1-year HR for mortality of 2.23 (95% CI 1.24 to 4.03, $p = 0.006$) and for cardiovascular events of 1.27 (95% CI 0.85 to 1.87, $p = 0.230$) compared with those taking oral hypoglycemic agents (predominantly sulfonylurea, metformin, or a combination of the two) (43). However, this study was nonrandomized and the choice to prescribe insulin was made by the treating physicians.

a. Metformin addresses glycemia by several mechanisms: it reduces hepatic gluconeogenesis by inhibiting glucose-6-phosphate dehydrogenase and works as a peripheral insulin sensitizer, with promotion of insulin-induced glucose movement into skeletal myocytes and adipocytes. As it does not stimulate insulin release, there is minimal hypoglycemic risk. This drug is considered first line in overweight patients with T2DM and is not associated with the weight gain that is encountered with insulin and the sulfonylureas. Metformin's insulin-sensitizing mechanisms have also found a role in the treatment of metabolic syndrome, polycystic ovarian syndrome, and nonalcoholic fatty liver disease, each of which is associated with insulin resistance. There is evidence for improvements in lipid profiles with metformin use. Metformin is contraindicated with impaired renal function (creatinine > 1.5 mg/dL in males and > 1.3 mg/dL in females is often quoted as the threshold) and also decompensated heart failure, where the risk of lactic acidosis may be elevated. Lactic acidosis, which can arise in the setting of reduced renal lactate clearance coupled with insufficient uptake of lactate into the liver because of gluconeogenesis inhibition, is considered to be rare. However, **it is standard of care to discontinue metformin**

during periods of renal impairment or inpatient heart failure treatment and for 24 hours before and 48 hours after injection of iodinated contrast agents. The majority of the reported side effects are gastrointestinal and can include diarrhea, nausea, early satiety, and abdominal pain.

b. **Sulfonylureas** are **insulin-stimulating oral agents**, with action on the adenosine triphosphate (ATP)-sensitive potassium channel found on the pancreatic β-cell. Binding of a sulfonylurea causes a decrease in potassium efflux through the K^+_{ATP} channel, inducing membrane depolarization that leads to calcium influx into the β-cell. Insulin release from secretory granules results. The main side effect is hypoglycemia; weight gain can also be a complication. Questions have also been raised regarding their potential to inhibit ischemic preconditioning via blockade of myocardial K^+_{ATP} channels. The commonly used second-generation sulfonylureas, such as glipizide, glimepiride, and glyburide (also known as glibenclamide outside the United States), are largely metabolized by the liver and excreted renally.

c. **Thiazolidinediones** are a newer class of drugs that have attracted much controversy with regard to their effects on the heart. The two agents developed in this class, **rosiglitazone and pioglitazone, act by increasing insulin sensitivity in target peripheral tissues**. This is achieved via activation of the peroxisome proliferator–activated receptor (PPAR)-γ nuclear receptor in myocytes and adipocytes, encouraging insulin-stimulated glucose transport into the cell. Pioglitazone also acts as a partial agonist of the PPAR-α receptor, which is believed to be the reason for increased HDL and decreased LDL and TGs observed with this drug.

Peripheral edema is a noted side effect; hence, this class of drugs should ***not*** be used in patients with NYHA class III–IV heart failure due to concerns for sodium and water retention and possible precipitation of heart failure decompensation. Weight gain, by expansion of subcutaneous adipose tissues, is also an associated complication.

There is some evidence, mostly using surrogate outcomes such as carotid intimal thickness and progression of coronary atherosclerosis by intravascular ultrasound, for a deterrent effect on atherosclerosis by pioglitazone in comparison with a sulfonylurea (44, 45). Analysis of a database including 16,390 clinical trial participants demonstrated that pioglitazone is associated with a significantly lower risk of death, MI, or stroke among a diverse population of patients with diabetes (46). However, the risk of heart failure was increased with pioglitazone, although without an associated increase in mortality. Conversely, rosiglitazone has been associated with an excess risk of MI and cardiovascular mortality in a meta-analysis (47). This led to the subsequent publication of the RECORD trial, which demonstrated overall noninferiority for a combination of metformin and sulfonylurea, but an increased risk of heart failure hospital admission or death with rosiglitazone (48).

(a) **Meglitinides**, such as repaglinide and nateglinide, are relatively short-acting oral insulin secretagogues. They are taken just prior to a meal and help to lower postprandial glucose levels. Due to their short duration of action, meglitinides are useful in the elderly and individuals with erratic eating habits.

(b) **Alpha-glucosidase inhibitors** such as acarbose and miglitol delay the absorption of complex carbohydrates via their action on the glycosidase enzymes in the brush border of the small intestine. They are generally used as an adjunctive therapy and can be useful in controlling postprandial glycemia. As described above, the STOP-NIDDM trial suggested a role for acarbose in reducing the progression of IGT to diabetes (11). The major side effects are flatulence and abdominal pain.

(c) **Amylin** is also an adjunctive agent and can be combined with prandial insulin therapy in T1DM or T2DM patients not meeting glucose targets. Pramlintide is a synthetic version of endogenous amylin, which is synthesized by β-cells and secreted with insulin in response to a carbohydrate load. The major effects appear to be inhibition of gastric emptying and suppression of glucagon release. Insulin doses should be reduced on initiation of pramlintide injections to avoid potential hypoglycemia. This agent may assist in reducing body weight.

(d) **Incretins** are a new class of agents for T2DM and include the GLP-1 and glucose-dependent insulinotropic peptide (GIP). The incretin hormones stimulate β-cell proliferation in animal models and are found at lower-than-normal levels in patients with T2DM. The active form of GLP-1 is the amide GLP-1(7-36), which is secreted by entero-endocrine L cells of the ileum and colon in response to a carbohydrate load. Exenatide is a synthetic GLP-1 analog that is subcutaneously injected twice daily. It works by potentiating insulin secretion, decreasing postprandial glucagon, delaying gastric emptying, and promoting weight loss. Liraglutide works in a manner similar to exenatide but has a longer half-life and is dosed once daily. Side effects include diarrhea and vomiting, and hypoglycemia is also a concern.

(e) **Dipeptidyl peptidase-4 (DPP-4) inhibitors** work by deterring the DPP-4-mediated degradation of GLP-1 and GIP into inactive metabolites. The first DPP-4 inhibitor to be marketed was the once-daily oral agent sitagliptin, with saxagliptin and vildagliptin (not approved in the United States) following since. There have been postmarketing concerns regarding pancreatitis and suggestions that inhibition of DPP-4 could promote carcinogenesis. DPP-4 inhibitors are weight neutral and carry a low risk of hypoglycemia; both liraglutide and exenatide have demonstrated the ability to reduce systolic blood pressure. Liraglutide also has a positive effect on the lipid profile and cardiovascular risk biomarkers.

Hence, the GLP-1 analogs and DPP-4 inhibitors have attracted significant recent attention regarding the possibility of favorable cardiovascular effects. GLP-1 receptors are known to exist on cardiomyocytes, and animal models of heart failure have shown positive responses to GLP-1. Improvements in left ventricular ejection fraction were reported in 10 patients who received a 72-hour GLP-1 infusion post-MI with successful primary angioplasty, when compared with 11 controls (49). Sokos et al. also reported significant improvements associated with a GLP-1 infusion in advanced heart failure patients (50). Of the 18 participants in NYHA class III–IV failure, 11 received a 10-week subcutaneous infusion with an escalating dose of GLP-1 and 7 received a placebo infusion. Significant improvements in the GLP-1 group were reported for several end points including left ventricular ejection fraction, oxygen consumption, the 6-minute walk test, quality of life, NYHA class, and B-type natriuretic peptide levels. However, neither of these pilot studies was randomized.

B. With the host of contrasting mechanisms described, it is clear that the various medications for diabetes cannot be expected to have equivalent effects on the cardiovascular system and future cardiovascular events, irrespective of any similarities in the degree of glucose lowering. The potentially negative cardiovascular effects of insulin and the sulfonylureas are of particular interest for further investigation. BARI-2D aimed to shed light on this uncertainty, but did not reveal a cardiovascular outcome difference between individuals randomized to a insulin provision therapy (insulin or sulfonylurea) versus insulin sensitization (metformin or thiazolidinedione) over a mean of

5.3 years (51). However, the extensive use of rosiglitazone and a relatively high crossover rate between the randomized groups confounded the interpretation of this trial.

C. It is hoped that the next generation of large clinical trials addressing the relationship between glycemic control and cardiovascular outcomes will be able to tease apart the relative effects of the major drug classes on the heart. This may require a shift in focus away from HbA1c. As described above, postprandial glucose may be a useful parameter to follow in future cohorts.

D. A related area of investigation has been the implementation of intensive glucose control regimens in the period immediately after an acute coronary syndrome.

1. The use of insulin in the setting of an acute MI was first described in the 1960s, with the goal of facilitating potassium flux in the ischemic myocardium. After decades of investigation, the combination of intravenous glucose, high-dose insulin, and potassium ("GIK" therapy) was concluded to offer no benefit in the setting of ST-segment elevation myocardial infarction (STEMI) and may have caused harm in some studies (52). Hence, this practice has been abandoned and should be distinguished from trials of intensive intravenous insulin therapy for tight glucose control post-MI.
2. The first DIGAMI study actually used a GIK protocol and infused insulin at 5 units/h with intravenous glucose to achieve glucose in the 126 to 198 mmol/dL range. Therefore, it was not a study of tight glucose control, although it has often been misinterpreted as such. The DIGAMI study did, however, raise interest in post-MI glucose control by suggesting that a 24-hour insulin-glucose infusion followed by intensive subcutaneous insulin in patients with diabetes could improve long-term survival post-MI (53). The mortality benefit seen at 1 year continued out to 3.5 years, with an absolute mortality reduction of 11%. The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk.
3. The subsequent DIGAMI-2 trial employed three acute MI glucose management strategies: acute insulin-glucose infusion followed by insulin-based long-term glucose control versus insulin-glucose infusion followed by standard glucose control versus routine metabolic management according to local practice (54). In the first two groups, the objective was to decrease the plasma glucose as rapidly as possible and maintain a level between 126 and 180 mg/dL. This trial did not reproduce the benefits seen in DIGAMI-1, with no differences seen in mortality or nonfatal re-infarctions between the three groups. As a result, guidelines currently recommend a more conservative target of < 180 mg/dL in the post-ACS phase.
4. This more lenient approach was supported by the NICE-SUGAR trial, which randomized 6,104 patients to intensive glucose control (target blood glucose range of 81 to 108 mg/dL) or conventional glucose control (target < 180 mg/dL) (55). The intensive group showed a higher odds ratio (OR) for death of 1.14 (95% CI 1.02 to 1.28; $p = 0.02$). This was despite the incidence of hypoglycemia in the intensive control group (6.8%) being the lowest of all the post-MI trials published.
5. HEART2D sought to test the approach of tight postprandial hyperglycemia control in patients enrolled within 21 days of a hospital admission for acute MI (56). It showed no difference between a prandial insulin therapy arm and a basal insulin arm over a mean follow-up of 963 days, but the study was hampered by a low event rate, short follow-up period, and only minimal differences in glycemia achieved between the two groups.

E. **Novel and future diabetes therapies** offer new potential strategies to pursue normalization of glycemia. Islet cell transplantation, delivered via a catheter into the portal vein, is currently under investigation. Whole pancreas transplantation is occasionally performed, usually in the setting of a patient requiring renal transplant who is already receiving immunosuppressive medications. T1DM is caused by T-cell–mediated β-cell destruction. There are preliminary animal data that autoreactive T cells may be removed from the circulation using stem cells transduced

to express major histocompatibility complex class II β chains. Stem cells are also a potential source for regeneration of pancreatic β-cells. However, significant challenges include preventing autoimmune destruction of regenerated β-cells and inducing physiologic insulin release in these cells.

VI. REVASCULARIZATION IN PATIENTS WITH DIABETES

A. The cardiovascular management of patients with diabetes incorporates not only careful consideration of medical regimens but also review of the available literature with regard to revascularization strategies. There have been many advances in evidence-based management of obstructive coronary lesions over recent decades, and many of the trials have identified strategies that confer particular benefit in individuals with diabetes.

1. **CABG versus PCI.** A series of landmark trials in patients with obstructive CAD have defined current practice with regard to the decision between CABG and PCI. The finding in 1997 that **the BARI subgroup with diabetes had a significant survival benefit in favor of CABG heralded the onset of specific coronary strategies for patients with diabetes**. The subgroup was not prespecified, but the survival benefit was considerable: in subjects receiving insulin or oral agents for diabetes (347 of the total cohort of 1,829), those randomized to CABG had a 80.6% 5-year survival, whereas balloon angioplasty was associated with 65.5% survival (57). This was in the interventional era prior to coronary stenting, and the explanation for the poor PCI outcomes in BARI subjects with diabetes is a presumed high rate of vessel restenosis. In addition, patients with diabetes tend to have more diffuse CAD, and lesions distant from the angioplasty site are left unprotected by a PCI strategy.
2. **CABG versus PCI with bare metal stents (BMSs) and glycoprotein IIb/IIIa inhibitors.** The widespread adoption of coronary stenting—at this stage with BMS—was successful in reducing restenosis rates. Sustained angiographic coronary patency also correlated with superior survival outcomes, symptom scores, and improved regional left ventricular systolic function. The randomized Arterial Revascularization Therapy Study (ARTS) of CABG versus PCI in multivessel disease showed equivalence of major outcomes for CABG and PCI strategies, with the caveat that the incidence of repeat revascularization was higher in the PCI group (58).

   This trial was also notable for its diabetes subgroup results; **there was a benefit in terms of 1-year repeat revascularization and major cardiovascular events in patients with diabetes who underwent CABG, as compared with stenting**. Other studies of this era, including the Stent or Surgery (SOS) trial published in 2002 (59), demonstrated superiority of CABG over PCI in patients with multivessel disease in general, but these were performed prior to routine use of thienopyridines and glycoprotein IIb/IIIa inhibitors. The addition of a platelet glycoprotein IIb/IIIa inhibitor appears to be particularly beneficial for patients with diabetes presenting with an ACS. A meta-analysis by Roffi et al. involving 6,458 patients with diabetes and non–ST-segment elevation ACS showed a significant reduction in the aggregate 30-day mortality (OR 0.74, 95% CI 0.59 to 0.92) with use of a glycoprotein IIb/IIIa inhibitor (60). Although not based on a randomized assessment, this survival advantage appeared to be particularly marked in patients who underwent PCI during the hospitalization.
3. **CABG versus drug-eluting stents (DESs).** DESs offer a further deterrent to vessel restenosis, although at the expense of an early in-stent thrombosis risk, particularly if antiplatelet medications are insufficient or ineffective. These stents deliver an antiproliferative drug locally to inhibit neointimal hyperplasia and improve target lesion patency. They have been clearly demonstrated to reduce angiographic restenosis rates, although there has been less of an impact on cardiovascular outcomes and mortality.

A 2006 meta-analysis of 12 studies by Kumbhani et al., including 1,902 patients with diabetes treated with either a DES ($n = 1,089$) or a BMS ($n = 813$), demonstrated an association between DESs and significant risk reductions in major adverse cardiac events (MACE), target lesion revascularization, and in-stent restenosis (with the reductions in MACE being primarily driven by the significant reductions in revascularization) (61). Also of note was an analysis comparing the relative risk of in-segment restenosis between the two types of DESs, which found a nonsignificant benefit favoring sirolimus-eluting stents versus paclitaxel-eluting stents (PESs).

Although there appears to be a dramatic restenosis reduction with the use of DESs compared with BMSs, patients with diabetes still encounter a higher rate of cardiovascular events post-PCI than those without diabetes. The comparative effectiveness of PESs or sirolimus-eluting stents in diabetes remains controversial. Increases in late stent thrombosis or restenosis, which are particularly likely in patients with diabetes and renal failure or complex lesions, need to be considered.

The SYNTAX trial investigated the strategies of PCI with PES versus CABG in patients with triple-vessel or left main disease; approximately 26% of SYNTAX participants had diabetes (62). An evaluation of the 452 SYNTAX subjects with diabetes, 40% of whom received insulin, showed that mortality was significantly higher among subjects with diabetes compared with those without, regardless of the revascularization strategy (63). At 1 year, the only outcome difference between PCI and CABG in patients with diabetes was the excess of repeat revascularization in the PCI arm. **Patients with diabetes had significantly increased repeat revascularization rates compared with those without diabetes when treated with PES, but not after CABG**. The CARDia trial was underpowered, but reached a similar conclusion. Stroke was nonsignificantly higher in the SYNTAX CABG arm. Further information on the relative merits of CABG and PCI in patients with diabetes and multivessel coronary disease is expected from the ongoing FREEDOM trial.

4. **Current antiplatelet strategies.** Antiplatelet requirements post-PCI do not differ between patients with or without diabetes. However, given the higher risks of target lesion revascularization and in-stent restenosis in those with diabetes, it can be expected that patients with diabetes have the most to lose from insufficient or ineffective antiplatelet therapy. Current recommendations are that all patients with coronary stents remain on daily aspirin lifelong. A thienopyridine should be taken for a very minimum of a month post-BMS placement; patients who receive a DES should take a thienopyridine uninterrupted for at least 12 months. The recent introduction of prasugrel has relevance to individuals with diabetes. TRITON–TIMI 38 enrolled intermediate-risk/high-risk ACS patients and STEMI patients who underwent PCI (64). Participants were randomized to prasugrel 60 mg load and 10 mg daily maintenance versus 300 mg load and 75 mg daily clopidogrel. The primary composite end point was significantly reduced with prasugrel in patients without diabetes (HR 0.86) and even more significantly reduced in those with diabetes (HR 0.70).
5. **CABG outcomes. Bypass conduit attrition rates are known to be higher in patients with diabetes**. As in patients without diabetes, the use of the internal mammary arteries (IMAs) offers higher long-term patency (in the region of 90% at 10 years) compared with reversed saphenous veins (long-term patency varying between 40% and 75%). Therefore, IMAs are particularly attractive in patients with diabetes, although the practice of using bilateral IMA grafts is controversial due to the potential for sternal wound infections. In addition to wound infections, patients with diabetes have an elevated risk of perioperative stroke with CABG surgery, with an OR of 1.4 (95% CI 1.2 to 1.8) for stroke (65). PCI does not carry an additional stroke risk for patients with diabetes and, therefore, may be the preferable option in patients with diabetes who have multivessel disease

and a preserved left ventricular ejection fraction and coronary lesions amenable to stenting. There are various measures such as preoperative noninvasive carotid artery assessment and modifications of the cross-clamp technique that can help to minimize peri-CABG stroke rates in high-risk patients.

6. **Revascularization versus optimal medical therapy.** The COURAGE trial raised questions regarding the relative merits of a purely medical versus medical and PCI strategy in patients with obstructive CAD and stable symptoms (66). This somewhat controversial study concluded that PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal MI or reduce major cardiovascular events over a 2.5- to 7.0-year period. A third of the participants had diabetes. The 1,605 patients with diabetes enrolled in the PCI versus optimal medical therapy stratum of BARI-2D did not show any difference in cardiovascular outcomes (51). However, both of these trials randomized patients after an initial angiogram that defined anatomy, and the decision to enroll in the PCI arm of BARI-2D (as opposed to the CABG arm) was made once anatomy was known and at the discretion of the investigators.
7. **Screening asymptomatic patients with diabetes for CAD.** Given the elevated risk of CAD in patients with diabetes, investigators have attempted to determine whether identification of asymptomatic CAD can improve future outcomes for patients with diabetes. The Detection of Ischemia in Asymptomatic Diabetes (DIAD) study used a nuclear cardiac stress imaging protocol to identify patients likely to have CAD (67). At 5 years, there was no difference in nonfatal MI or mortality between the nuclear screening and standard care groups. However, the screening arm was notable for a very low rate of significant ischemia detection, and there was a very successful protocol of optimal medication therapy among trial participants.
8. **Screening for diabetes in patients with cardiovascular disease or risk factors.** Given the degree of excess cardiac morbidity and mortality attributable to diabetes, and the proposed early window for tight glucose control with potential to impact on later cardiovascular risk, there is an argument for asymptomatic screening of high-risk patients for diabetes. **With the ease of diagnosis by HbA1c criteria and long asymptomatic prediabetes phase, T2DM meets WHO thresholds for a condition where screening may be appropriate**. However, it remains unproven as to whether early identification and aggressive management of diabetes has the ability to attenuate future cardiovascular risk. ADDITION-Europe sought to clarify this question with a cluster-randomized trial that assigned subjects to standard care versus an intense multifactorial management protocol (68). This study was not able to demonstrate a significant cardiovascular outcome benefit for early detection and management of diabetes at 5.3 years and was hampered by a low event rate and a smaller-than-expected difference in risk factor management between the two groups.

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CHAPTER 46

Jun-Yang Lou

Heart Disease in Women

I. INTRODUCTION. Cardiovascular disease (CVD) is by far the leading cause of death of women in the United States and most developed countries, accounting for almost 39% of all female deaths in the United States. In 2007, CVD caused 421,918 deaths in women in the United States, approximately 1 per minute, **more than those claimed by cancer, chronic lower respiratory disease, Alzheimer disease, and accidents combined**. Despite aggressive campaigns by the American Heart Association (AHA) and other organizations, only 54% of the women surveyed in 2009 spontaneously listed coronary heart disease (CHD) as a woman's leading cause of death, and only 13% of the women surveyed identified CHD as a risk for them personally. Minority women are even less aware of their cardiovascular (CV) risk, which is higher than for age-matched white women.

Some important gender-related differences exist in the presentation and outcome of CVD. In a national registry of over 300,000 patients (40% women) admitted with acute myocardial infarction (MI) between 1994 and 1998, female patients were found to be older compared with males (approximately 72 years vs. 66 years, respectively). Women also had higher in-hospital mortality compared with men (17% vs. 12%). Risk of death is particularly high in younger women, more than twice that of men in the under-50 age group, and also in women who presented with ST-elevation myocardial infarction (STEMI). These differences highlight an urgent need to better understand and treat heart diseases in women. This chapter summarizes current understanding of the gender-specific features of CVD based on large-scale clinical trials and existing and emerging molecular science.

II. GENDER DIFFERENCES IN PATHOPHYSIOLOGY. Briefly, coronary artery disease (CAD) begins with **nascent atheroma**, the coalescence of small lipoprotein particles within the arterial intima. Over time, these lipoprotein particles become oxidized, inducing local cytokine elaboration. These inflammatory cytokines cause the increased expression of adhesion molecules for leukocytes, leading to leukocyte attraction and migration into the intimal layer. Blood monocytes become macrophages upon entering the intima and express scavenger receptors on their surface, owing to their interaction with certain cytokines present locally. These scavenger receptors promote the uptake of modified lipoprotein particles, leading to the formation of **foam cells**. Foam cells further elaborate inflammatory and attractant cytokines and other effector molecules. In response, smooth muscle cells migrate into the intima from the media, where they proliferate and form fatty streaks. Smooth muscle cell proliferation and extracellular matrix accumulation lead to the progression from a **fatty streak** to a **fibrofatty plaque**. Later stages are characterized by calcification and fibrosis, occasionally with smooth muscle cell death. This creates an acellular fibrous cap surrounding a lipid-rich core.

The process of atherosclerosis progresses slowly, and patients often remain unaware and asymptomatic for many years. This is likely attributable to the capacity of the arteries to remodel—expanding outwardly as the intima expands, thereby preventing plaque encroachment on the lumen of the vessel. However, at some point the plaque

burden exceeds the ability of the vessel to remodel, and narrowing of the lumen begins. Eventually, if unimpeded, atherosclerosis will progress until the degree of luminal narrowing impedes blood flow. Initially, this luminal narrowing is apparent mostly under the conditions of stress, where arterial oxygen supply is unable to meet demand. Once this occurs, the patient begins to develop symptoms, typically stable angina.

In some cases, however, the first manifestation of the underlying CAD is MI, unstable angina, or sudden death. In these instances, the underlying stenosis is usually < 50% of the lumen diameter. The inciting event leading to symptoms in these cases is either physical disruption of the fibrous cap of the plaque or superficial erosion of the intima. Either setting exposes the underlying lipid-rich core to blood components and initiates thrombosis (see Chapters 1 and 2 for more detailed discussions). Women, **especially younger women, are twice as likely to have plaque erosion as the underlying cause of MI**, whereas men and older women more often have plaque rupture. Compared to men, whose plaques tend to be more dense fibrous, women also tend to have more cellular fibrous plaques.

There appears to be other gender-based differences in the atherosclerotic process. Hormones have also been proven to influence many of the underlying pathophysiologic processes, including vasoreactivity, thrombosis and inflammation. Women have smaller coronary arteries than men and, interestingly, women taking androgens have much larger coronary arteries than their age-matched controls. For years it was noted that premenopausal women appeared to be protected from CAD and estrogen emerged as the most likely reason. A recent animal study suggests that estrogen appears to decrease oxidative stress via upregulation of the production of prostacyclin PGI_2, a molecule known to retard the progression of atherosclerosis. The full spectrum of sex hormone effects on the heart and vascular system has yet to be fully determined. In addition, there have been genetic links to the development of CAD that are noted to vary according to gender, with different single-nucleotide polymorphisms noted in men and others in women. There are also differences in terms of endothelial function and hemostasis (women have higher levels of fibrinogen and factor VII). Some of these or other mechanisms may eventually be identified as the reason for gender differences in the development and progression of CAD.

In recent years, microvascular dysfunction has been postulated as the underlying process leading to symptoms of CHD in some women. It is postulated that estrogen withdrawal in perimenopausal and postmenopausal women leads to impaired vasodilatation and/or enhanced vasoconstriction. This hypothesis stems from the diagnosis of **cardiac syndrome X, in which patients, predominantly postmenopausal women, exhibit symptoms of typical angina pectoris with transient abnormal** electrocardiogram (**ECG**) **and/or stress perfusion studies**, yet most have minimal angiographic evidence of CAD when undergoing left heart catheterization (LHC). Further studies are needed to better define the populations at risk for microvascular dysfunction and determine potential therapeutic interventions.

Stress (Takotsubo) cardiomyopathy is another novel disease entity affecting predominantly postmenopausal women, accounting for over 80% of cases. Alternatively known as apical ballooning syndrome or broken heart syndrome, stress cardiomyopathy is diagnosed when patients, often in the setting of severe emotional distress or physical trauma, present with chest pain, anterior ST elevations, mildly abnormal cardiac biomarkers, and characteristic appearance of an akinetic, ballooning apex on echocardiography or left ventricular (LV) ventriculogram. Angiography often reveals normal-appearing coronary vessels. The etiology of stress cardiomyopathy and the reason behind such strong female predilection are unclear. Catecholamine surge with stress has been implicated in a number of patient cohorts with this cardiomyopathy. The prognosis of stress cardiomyopathy is quite good, as the majority of patients regain systolic function within 6 months.

III. GENDER DIFFERENCES IN RISK FACTORS

A. Diabetes mellitus. Diabetes affects more women than men after the age of 60. It is associated with a higher incremental risk for CAD (two to four times the risk of women

without diabetes) and drastically increases the mortality of MI in women, much more so than in men. Type 2 diabetes is associated with other components of the metabolic syndrome, all of which increase risk for CAD. Diabetes is also strongly associated with the development of heart failure, with or without preserved ejection fraction.

B. Hypertension (HTN). More than 73% of women aged 65 to 74 years have HTN. The risk of developing HTN increases for women if they are 20 pounds or more overweight, have a family history of HTN, or have reached menopause. Risk for CVD related to HTN rises steeply with age, although most studies show that treatment attenuates this risk.

C. Hyperlipidemia. Lipid fractions in women are affected by their menopausal status. Premenopausal women have lower low-density-lipoprotein cholesterol (LDL-C) levels and higher high-density-lipoprotein cholesterol (HDL-C) levels than age-matched men. With aging, LDL-C increases and HDL-C decreases, causing the risk of CAD to increase. Total cholesterol and LDL-C are less predictive in women, unlike HDL-C, which is inversely associated with the risk. Non–HDL-C and total cholesterol to HDL-C ratio are more predictive in women than in men. In addition, triglycerides are a more potent independent predictor of CAD, especially in older women.

D. Cigarette smoking. This is the single most preventable risk factor. Smoking leads to more CVD deaths than any other risk factor, likely owing to its effects of increasing inflammation, thrombosis, and oxidation of LDL-C. Smoking also has an antiestrogen effect, inducing unfavorable changes in lipid levels. There is a sixfold to ninefold increased risk of MI in female smokers compared with age-matched nonsmokers; in fact, the risk from smoking is equivalent to the risk of weighing about 42 kg more than a nonsmoking woman. However, with smoking cessation, risk is cut in half after 1 year without smoking and eventually declines back to baseline nonsmoker's risk.

E. Obesity and metabolic syndrome. More than 30% of American women are obese, and this number continues to climb. In women, obesity and body fat distribution (i.e., abdominal location) are independent risk factors for CAD. As shown by an examination of a cohort of 115,195 women from the Nurses' Health Study, risk of death from CVD increased with increasing body mass index (BMI). Abdominal fat accumulation leads to the development of other components of the metabolic syndrome, such as HTN, diabetes, and hypertriglyceridemia. Obesity is also associated with elevated levels of C-reactive protein (CRP), more so in women.

Women with the metabolic syndrome more often have subclinical CAD than men. A substudy from the National Heart, Lung, and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation) study revealed that women with the metabolic syndrome have twice the risk for CHD-related events compared with age-matched women without the metabolic syndrome. The metabolic syndrome is defined by the National Cholesterol Education Program Adult Treatment Panel-III in women as the presence of three or more of the following components:

(1) Waist circumference > 35"
(2) Fasting triglycerides > 150 mg/dL
(3) HDL-C < 50 mg/dL
(4) HTN (systolic blood pressure ≥ 130 mm Hg, diastolic blood pressure ≥ 85 mm Hg, or use of antihypertensive drug therapy)
(5) Fasting glucose ≥ 110 mg/dL

F. Estrogen/menopause. Postmenopausal women have more CVD risk factors, such as obesity, HTN, and hyperlipidemia, likely owing to the changing hormonal environment (estrogen levels are one-tenth the premenopausal level). The predominant source of estrogen changes from estradiol in the premenopausal state to the much weaker hormone estrone (produced by the conversion of androgens in peripheral adipose tissue) during menopause. Animal studies have shown that estrogen can have favorable CV effects, reducing cellular hypertrophy, enhancing vessel wall elasticity, and providing antioxidative and anti-inflammatory actions.

As part of the WISE study results, endogenous estrogen deficiency in young women was shown to be a strong risk factor for CHD, with a 7.4-fold increased risk. Because of the protection from CAD afforded for premenopausal women, there was early enthusiasm for the use of hormone replacement therapy (HRT) to prevent CVD in postmenopausal women, sparked by data from observational studies. However, multiple randomized, placebo-controlled trials over recent years have shown evidence of increased risk for CVD with HRT, such that it is no longer recommended for primary or secondary prevention of CVD (see Section **VI.F**).

G. Physical inactivity. As women age, they become less physically active than their male counterparts. This contributes to weight gain and predisposes to the development of diabetes and HTN. In addition, with the cessation of estrogen production with menopause, there is increased abdominal fat deposition, further predisposing to CAD. There is a strong inverse association between the activity level and incidence of CV events (see Table 46.2).

H. Novel risk factors. It has been increasingly realized that the traditional risk factors underestimate CHD risk in women. For this and other reasons, research has been focused on identifying other novel biomarkers that can better define a person's risk. Multiple biomarkers have been investigated to various degrees (e.g., high-sensitivity C-reactive protein [hsCRP], brain natriuretic peptide, and fibrinogen), but the greatest promise appears to be with hsCRP. As part of the Women's Health Study, over 27,000 healthy American women had their CRP and LDL-C levels measured. The women were then followed for a mean of 8 years for the occurrence of the primary end point (MI, ischemic stroke, coronary revascularization, or death from CVD). Although minimally correlated with each other, both CRP and LDL-C levels had strong linear relationships with CVD events, with CRP being the stronger predictor. Each biomarker tended to identify different high-risk groups, but better prognostic values were obtained when both were used together. These data suggest that CRP shows promise when added to traditional risk factors for prediction of long-term risk.

IV. GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS.

Women often present differently than men, potentially because of differences in underlying pathophysiology. This is particularly true for diabetic women. Women usually present at an older age, usually 5 to 10 years later than men, and have more comorbidities on presentation than men do. As such, once the diagnosis of CAD is made, women are at higher risk for adverse outcomes.

A. Like men, women can present with typical symptoms of angina, such as substernal **chest pain** and **dyspnea on exertion** that is relieved by rest. These symptoms more often occur in older women, who present more similarly to men.

B. Women can also present with **atypical chest pain**; **shortness of breath**; **neck, shoulder, or arm pain**; **diaphoresis**; and **nausea/vomiting**.

C. Women are more likely to have subtle symptoms that require detailed history-taking to elicit, such as **chest "pressure or tightness," lightheadedness, palpitations, or fatigue**. Women most often have symptoms that occur at rest, wake them from sleep, or occur in times of psychological stress.

D. Women more often present acutely without preexisting prodromes of symptoms or with **sudden cardiac death**.

V. GENDER DIFFERENCES IN ASSESSMENT

A. Exercise electrocardiography. Exercise electrocardiography, the most frequently employed diagnostic modality, is useful only in women with normal baseline ECGs and with the ability to undergo moderate or high levels of exercise (generally on the treadmill). An abnormality is identified if there is ≥1 mm of ST-segment depression or elevation. Generally, exercise ECG has lower sensitivity and specificity than other modalities, and this is even more prominent in women (sensitivity and specificity

60% to 70% in women vs. 80% in men). This difference is not well understood, but it has been attributed to several factors, such as lower overall prevalence of CAD in women or more submaximal stress tests, owing to the inability of women to exercise to sufficient levels to produce a diagnostic test. If women are unable to achieve at least five metabolic equivalents (METS), studies have shown that they are at increased risk for future CV events.

B. Stress echocardiography (transthoracic echocardiography [TTE]). Stress TTE tends to have higher specificity and lower sensitivity than stress perfusion imaging, as wall motion abnormalities occur later than perfusion abnormalities. However, stress TTE has the advantages of eliminating radiation exposure, decreasing cost, and providing the ability to assess LV function and cardiac structures. It has been shown to be a cost-effective initial strategy for determining CV risk in patients at intermediate risk as compared with stress electrocardiography, and we now use it as a first-line diagnostic test for CAD in women.

C. Stress myocardial perfusion scan. Because of the limited sensitivity and specificity of exercise ECG in women, other modalities are frequently employed to assess the risk of CAD. The most frequently used test is the single-photon emission computed tomography (SPECT) scan, a radionuclide-based technique. Because alterations in myocardial perfusion generally occur earlier than electrocardiographic changes or wall motion abnormalities, this test is more sensitive than exercise ECG or echocardiography for estimating risk in either gender. For those individuals unable to exercise or attain target heart rates, adenosine or dipyridamole can be used as a pharmacologic stress agent. To increase specificity, the higher energy isotopes (technetium 99m) are recommended in women to reduce the soft tissue attenuation artifacts (influenced by both breast tissue and obesity) that tend to occur anteriorly and laterally. Other limitations of SPECT can be critical in women. Because women have smaller hearts, the limitations in spatial resolution of SPECT can lead to small areas of hypoperfusion being missed.

D. Magnetic resonance imaging (MRI). Although not as commonly used, this is an emerging modality owing to its ability to evaluate for subendocardial ischemia, precisely assess LV function and mass, and evaluate the anatomy of the myocardium and vasculature. MRI provides the best spatial and temporal resolution, which is thought to be especially helpful when imaging women. Other benefits include the ability to detect ischemia by identifying altered metabolism. This is achieved by magnetic resonance spectroscopy, which can detect alterations in high-energy phosphates and identify these areas of altered metabolism. Areas of altered metabolism have been shown in reports from the WISE study to be indicative of microvascular dysfunction, as women with nonobstructive CAD assessed by LHC have altered high-energy phosphate ratios indicative of ischemia identified by spectroscopy.

E. Coronary angiography. Diagnostic coronary angiography is the gold standard for diagnosing CAD in both men and women. When evaluated by LHC, however, women more often have minimal to no obstructive CAD. For reasons not fully elucidated, women tend to experience vascular complications such as bleeding and renal failure related to diagnostic LHC more frequently than men do. The occurrence of a complication is thought to be related to older age at the time of presentation, smaller body size, smaller vessel size, and higher prevalence of diabetes. A transradial approach to diagnostic and interventional coronary procedures has been shown to be safe and lead to less bleeding complications than transfemoral catheterizations in both men and women and thus might be considered the primary catheterization approach in women.

VI. GENDER DIFFERENCES IN THERAPIES. Most CVD in women, as in men, can be prevented if risk factor modification occurs early and aggressively. Until recently, most of the clinical trial data, on which the guidelines for prevention and treatment of both genders are based, were derived from trials conducted largely in men. This information

had been extrapolated to women because gender-specific trial data were lacking. Because of this uncertainty, more recent clinical trials have offered insights into gender-specific results, allowing for evidence-based guidelines for disease prevention and treatment in women. However, with only a few exceptions, the guidelines are the same for both men and women. The gender-specific results are highlighted here; for a full discussion, please see appropriate sections of previous chapters.

A. Aspirin. Aspirin (ASA) is the principal antiplatelet agent in patients with CAD. Its benefit in secondary prevention, as well as in acute coronary syndrome (ACS), STEMI, and after revascularization (coronary artery bypass grafting or percutaneous coronary intervention [PCI]), is well known and discussed elsewhere. However, there are very few gender-specific data in these instances, so most recommendations are extrapolated from trials conducted largely in men.

The role of ASA in primary prevention of CAD in women is better defined. Early data suggested that ASA may be protective as primary prevention for future CVD events in women, as it is in men. However, as part of the Women's Health Study, 39,876 healthy women older than age 45 were randomized to either ASA 100 mg on alternate days or placebo, and they were followed for the incidence of CV events (nonfatal MI, nonfatal stroke, or CV death) over 10 years. **Despite a 24% reduction in ischemic stroke, ASA had no benefit over placebo in reducing MI or CV death.** However, ASA did appear protective as primary prevention in those women aged 65 years or older, as it significantly decreased the risk of both MI and stroke in this age group. There was also an increased risk of bleeding observed, which highlights the need for an individualized approach to the use of ASA as primary prevention in older women. **Using "low-dose aspirin", i.e., 81 or 75 mg daily rather than the "full dose" of 325 mg daily, in women might confer effective CV protection without excessive bleeding risk.**

B. Thienopyridines. For two decades, the most commonly used agents in this class are clopidogrel and ticlopidine. The use of ticlopidine has decreased significantly with evidence of adverse effects, including neutropenia and thrombotic thrombocytopenic purpura. These agents have proven beneficial, when given with ASA, to reduce the rate of stent thrombosis after PCI. Clopidogrel has also shown benefit in secondary prevention of CAD, ACS, and STEMI (discussed in detail elsewhere). Few of the clinical trials using clopidogrel have given gender-specific data, but there are some data available for specific settings.

In the substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, in which the patients received PCI (PCI-CURE), 2,658 patients with non–ST-segment elevation ACS undergoing PCI were randomly assigned to aspirin plus clopidogrel or placebo for 9 months. Of the study population, 30.2% were women. Clopidogrel plus aspirin long-term therapy improved outcomes in those patients who received PCI. This was more significant in men, but a definite trend toward benefit in women was evident as well. Similar results were seen for women in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, where 29% of the 2,116 patients were women. The CREDO trial showed benefit of post-PCI therapy with ASA and clopidogrel out to 1 year of therapy, again with a trend toward benefit in women. CREDO trial also revealed, by subgroup analysis, equally beneficial effects of a loading dose of clopidogrel in men and women.

Prasugrel is the most recent addition to the class of oral antiplatelet agents. Pharmacokinetic studies have shown that prasugrel achieves faster onset and greater extent of platelet inhibition compared with clopidogrel. It was FDA approved for patients with ACS undergoing PCI in 2009. In the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), prasugrel had lower primary end points (CV death, nonfatal MI, or nonfatal stroke) than clopidogrel in 13,608 patients (one-fourth of whom were women) with moderate- to high-risk ACS with

scheduled PCI (9.9% vs. 12.1%). However, the prasugrel group did have higher rates of bleeding particularly in patients with history of stroke or transient ischemic attack, patients aged 75 years or older, or patients weighing less than 60 kg. These data are especially important for women, as there was slightly less observed benefit with prasugrel therapy in women—this difference is likely related to increased risk of bleeding of antiplatelet use of any kind in woman, as shown by a recent post hoc analysis of the TRITON-TIMI 38 data.

C. Statins. Prior to the last several years, almost 20,000 women participated in clinical trials of statin use, only about one-fourth of overall participants. Two exceptions to this were the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial (50% women) and the lipid-lowering therapy arm of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT), which had 49% female participation. ALLHAT-LLT, a primary prevention trial, did not release gender-specific results; PROSPER, having patients with history of or at risk for CVD, did not show a statistically significant benefit in women.

Otherwise, the other major primary and secondary prevention trials of statin therapy have shown similar benefit with statin therapy on reduction of CV events in men and women. The largest number of women enrolled to date in a statin trial was the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. With over 17,000 patients enrolled (38% of them women), this trial demonstrated encouraging evidence for the benefit of statin therapy in decreasing vascular events in both women and men with "normal" serum LDL-C and elevated serum CRP levels, with a ~45% reduction in combined end point of MI, stroke, or death from CV causes. In the Treating to New Targets (TNT) trial, patients who were given intensive lipid control treatment with higher dose of atorvastatin (80 mg) were shown to have a significantly reduced primary end point of a first major CV event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) over those on lower dose therapy (atorvastatin 10 mg). Even more encouraging was that this benefit also extended to women. In women (19% of total population) from the TNT trial, the relative and absolute reductions in the primary end point were 27% and 2.7%, respectively; this was actually better than those observed in men, who had 21% and 2.2% reduction, respectively.

D. β-Blockers. There are no gender-specific data for the use of β-blockers in women for primary and secondary prevention, as previous studies have included insignificant numbers of women. However, a meta-analysis of 5,474 patients (1,121 women) enrolled in five randomized trials revealed similar reductions in CV death in men and women with metoprolol.

E. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). With respect to the use of ACE inhibitors in women with LV dysfunction, the data are lacking, because trials have included very few women. Several trials have examined ACE inhibitors in primary and secondary prevention of CV events in patients without LV dysfunction, with conflicting results irrespective of gender. The Heart Outcomes Prevention Evaluation (HOPE) study showed that ACE inhibitors were associated with a mortality reduction in high-risk women that was similar to that in men. The EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) could not confirm these beneficial findings in women, as the trial included only 14.5% women, but it did show benefit in men. To date, it appears that data for ACE inhibitors in women are not as favorable as for men; however, this needs to be further delineated.

In terms of ARBs for therapy after MI, only two trials have been reported—VALsartan in Acute myocardial iNfarcTion (VALIANT) and OPtimal Trial In Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL). Neither of these reported gender-specific data.

F. Hormone replacement therapy. Despite beneficial evidence from previous observational studies, recent data from randomized controlled trials have shown no benefit of HRT in postmenopausal women for preventing CV events. The first of these randomized trials was the Heart and Estrogen/progestin Replacement Study (HERS). In this study of secondary prevention, 2,763 postmenopausal women with CAD were randomized to either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or placebo daily. After an average 4-year follow-up, there was no significant difference in the primary outcome of nonfatal MI or CHD death between the groups. Of interest, however, was the fact that the greatest numbers of CV events were noted within the first year in the HRT group. Not surprisingly, the HRT group had a greater incidence of venous thromboembolism and gallbladder disease.

Because of the high number of CV events in the first year, the investigators thought that beneficial effects of HRT might be observed after time, as it appeared that HRT became more protective by 4 to 5 years of follow-up in the HERS population. With this in mind, the HERS II study followed 2,321 of the original HERS patients, the majority of whom stayed on their original treatment in an open-label format, for an average of 6.8 years. After the longer follow-up, there was still no difference in nonfatal MI or CHD death between the groups.

To delineate the role of HRT in primary prevention of CV events, the Women's Health Initiative randomized 16,608 healthy, postmenopausal women to the same estrogen–progestin combination used in HERS or placebo. The primary end points were the same, nonfatal MI or death due to CHD. After a mean 5.2-year follow-up, the trial was stopped by the data and safety monitoring board due to untoward risks in the treatment arm. Estrogen and progestin therapy was associated with an increased risk for CV events, most impressively at 1 year. Despite some favorable effects on lipids, **HRT should not be recommended for either the primary or the secondary prevention of CVD in postmenopausal women**.

G. Lifestyle modification. The good news for women is that initiating lifestyle modifications can reduce CV risk by reducing the risk of developing diabetes. As part of the Diabetes Prevention Program Research Group, 3,234 patients (68% women) with impaired glucose tolerance were randomized to placebo, metformin (850 mg twice daily), or lifestyle modification (goal 7% weight loss and at least 150 minutes of physical activity per week). After almost 3 years of follow-up, the lifestyle modification group had a 58% reduction in the incidence of diabetes compared with 31% in the group with metformin. This translates to a decreased risk of CVD.

H. Folic acid and antioxidants. Despite previous recommendations to lower homocysteine levels with folic acid and vitamin B supplementation, there is now evidence to discourage this practice. Three randomized trials—the Norwegian Vitamin (NORVIT) study, the HOPE-2 trial, and Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)—showed no benefit in reducing CV events. The NORVIT study included both men and women post-MI and randomized the groups to one of four treatments: folic acid, vitamin B_{12}, and vitamin B_6; folic acid and vitamin B_{12}; vitamin B_6 alone; or placebo. Despite lowering of homocysteine levels, the treatment groups had no advantage in terms of reductions in the primary end point of recurrent MI, stroke, or sudden death attributed to CAD. In fact, the group that received all three therapies had a trend toward increased risk. Similar results were seen in the HOPE-2 trial. Therefore, these therapies should not be recommended. In addition, data from the Women's Health Study do not support the use of vitamin E in the primary prevention of CV events.

VII. EVIDENCE-BASED GUIDELINES FOR HEART DISEASE PREVENTION IN WOMEN.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines emphasize the importance of recognizing the wide-ranging spectrum of CV disease in women. In general, a woman aged 20 years or older is first classified as at high risk, at

risk, or at optimal risk based on the criteria in Table 46.1. Several factors should be evaluated, such as medical history, lifestyle, family history of premature CAD, Framingham risk score, and other genetic conditions, before decision regarding the aggressiveness of preventive therapy is finalized.

TABLE 46.1 Risk Classification of Cardiovascular Disease in Women

High risk	At risk	Optimal risk
• Known CAD	• **Subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened intima-media)**	• Fasting blood glucose < 100 mg/dL (untreated)
• Cerebrovascular disease	• Cigarette smoking	• Nonsmoker
• Peripheral arterial disease	• Poor diet	• Healthy (Dietary Approaches to Stop Hypertension (DASH)-like) diet
• End-stage renal or chronic kidney disease	• Physical inactivity	• Physical activity goal for adults < 20 y of age: > 150 min/wk moderate intensity, > 75 min/wk vigorous intensity, or combination
• Diabetes	• Obesity (especially abdominal location)	• BMI < 25 kg/m^2
• 10-y Framingham global risk > 10%	• Dyslipidemia (total cholesterol > 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia)	• Total cholesterol < 200 mg/dL (untreated)
	• HTN (SBP > 120 mm Hg, DBP > 80 mm Hg, treated HTN, or history of pregnancy-induced HTN)	• BP < 120/< 80 mm Hg (untreated)
	• Family history of premature CAD (< 55 y in men, < 65 y in women)	
	• Metabolic syndrome or history of preeclampsia or gestational diabetes	
	• Poor exercise capacity on exercise treadmill test and/or abnormal heart rate recovery after stopping exercise	
	• **Family history of premature CVD occurring in first-degree relatives in men < 55 y of age or in women < 65 y of age**	
	• **Autoimmune diseases (e.g., SLE or RA)**	

CAD, coronary artery disease; BMI, body mass index; HDL-C, high-density-lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CVD, cardiovascular disease; HTN, hypertension. SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Adapted from ACC/AHA guidelines 2011 update. *JACC*. 2011;57:1404–1423.

The guidelines are grouped into three main areas: lifestyle interventions, major risk factor interventions, and preventive drug interventions. Table 46.2 lists the class I and class IIa recommendations for primary or secondary prevention of CVD in women. These guidelines are suggested as a starting point, with therapy tailored to the needs of each individual patient.

TABLE 46.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women

Lifestyle interventions	Major risk factor interventions	Preventive drug interventions
• **Class I recommendations**		
Smoking cessation	Maintain optimal BP (< 120/80 mm Hg) with lifestyle modification	ASA in high-risk women (known CAD, cerebrovascular disease, PAD, AAA, ESRD, CKD, diabetes, and 10-y Framingham risk > 20%)
Exercise: 150 min/wk of moderate intensity exercise (e.g., brisk walking), 75 min/wk of vigorous intensity exercise (e.g., running), or combination	Pharmacotherapy for BP ≥ 140/90 mm Hg (≥130/80 mm Hg in CKD or diabetes). Thiazide should be initial agent unless compelling indications for β-blockers and/or ACE inhibitor/ARB exist (e.g., ACS/MI)	Clopidogrel therapy for high-risk women intolerant of ASA
Weight loss to BMI < 25 kg/m^2 and waist circumference ≤ 35"	Control of lipids through lifestyle modification (LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL, and non–HDL-C [total cholesterol–HDL-C] < 130 mg/dL)	β-Blockers for at least 1 y and up to 3 y in women after MI and ACS, with normal LV function. Use indefinitely if LV dysfunction present
Cardiovascular rehabilitation in those with recent ACS or PCI, angina, and recent CVA, PAD, or CHF	Pharmacotherapy of lipids in those with CAD or diabetes to goal LDL-C < 100 mg/dL	ACE inhibitors in those after MI or with clinical CHF, LV dysfunction (LVEF ≤ 40%), or diabetes. If intolerant of ACE inhibitor, ARB can be substituted
Diet counseling to promote intake of fruits and vegetables, whole grain and high-fiber foods, and fish at least two times per week. Limit consumption of saturated fat, cholesterol, alcohol, sodium, and *trans*-fatty acids	Pharmacotherapy of lipids in those with LDL-C ≥ 130 mg/dL after lifestyle modification and presence of multiple risk factors (or if LDL-C ≥ 160 mg/dL in those with multiple risk factors, even if Framingham risk < 10%)	Aldosterone blockade after MI in symptomatic women with LVEF ≤ 40% who are without renal dysfunction or hyperkalemia and who are already on an ACE inhibitor and β-blocker
	Pharmacotherapy of lipids in those with LDL-C ≥ 190 mg/dL regardless of other risk factors	

TABLE 46.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women (Continued)

Lifestyle interventions	Major risk factor interventions	Preventive drug interventions
	Maintain HbA_{1C} < 7% in diabetics	
• **Class IIA recommendations**		
	Goal LDL-C < 70 mg/dL is reasonable in the very high risk (known CAD + multiple major risk factors, severe and poorly controlled risk factors, or diabetes)	Low-dose ASA therapy (81 mg daily or 100 mg on alternate days) in women ≥65 y if benefits outweigh risk of bleeding
• **Class IIB recommendations**		
ω-3 Fatty acid in the form of fish or capsule (e.g., EPA 1,800 mg/d) may be considered in women with hypercholesterolemia or hypertriglyceridemia for primary or secondary prevention	Pharmacotherapy with niacin or fibrates when HDL-C is low or non–HDL-C is elevated in high-risk women (after LDL-C goal reached)	

AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASA, aspirin; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; HbA_{1C}, glycosylated hemoglobin; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mm Hg, millimeters of mercury; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Adapted from ACC/AHA guidelines 2011 update. *JACC.* 2011;57:1404–1423.

In general, it is suggested that the initial evaluation begin with a complete history, specifically eliciting symptoms of CVD, as well as a complete physical examination, with particular attention to blood pressure, BMI, and waist size. Laboratory evaluation should follow, including fasting lipids and glucose levels. During the evaluation, assessment of Framingham risk should be performed, as well as depression screening in those women with known CVD. **All class I lifestyle interventions** should be employed in **all women**, regardless of risk level.

If the woman is at **high risk** (established CAD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, chronic kidney disease, or Framingham risk > 20%), the **class I major risk factor and preventive drug interventions** should be initiated (see Table 46.2). Consideration should also be given to some of the class II recommendations, particularly the **LDL-C goal of < 70 mg/dL**.

There are some interventions that should not be considered under any circumstances. Table 46.3 lists those therapies that are **contraindicated** based on the results of recent clinical trials.

Novel risk factors, such as CRP (used as inclusion criteria in JUPITER), and newer screening modalities may have a role in the future, but this role is not yet defined. Further research is needed in these areas before they can be incorporated into the guidelines.

TABLE 46.3 Class III Interventions (Ineffective, Possibly Harmful in Cardiovascular Disease Prevention in Women)

Hormone replacement therapy or selective estrogen receptor modulators
Antioxidant vitamin supplementation (vitamin E, vitamin C, and β-carotene)
Folic acid with or without vitamin B_6 or B_{12} (Folic acid supplementation should be used in the childbearing years to prevent neural tube defects)
ASA in healthy women < 65 y

ASA, aspirin.

Adapted from ACC/AHA guidelines 2011 update. *JACC.* 2011;57:1404–1423.

VIII. CURRENT PROGRESS AND FUTURE INNOVATIONS. Despite clinical trial data that document the benefits of multiple therapeutic interventions, women are still inadequately treated. In fact, despite the vast amount of data on statins, the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) reported that only 10.2% of women with hyperlipidemia were receiving therapy compared with 14% of men. Men, when treated, were also much more likely to reach their goal LDL-C. Strikingly, in a study of patients receiving care in an academic medical practice, women with diabetes were the group most likely to be inadequately treated for their modifiable CVD risk factors. Furthermore, even higher risk patients (women with ACS) have been shown to be less aggressively treated than their male counterparts.

Despite the aggressive campaigns by the AHA and other organizations, women are still not well informed regarding their personal risk for heart disease. In the 2003 AHA-sponsored survey of women, only 40% considered themselves either "very well" or "well" informed about heart disease, even fewer in the most at-risk minorities. Although nearly all of the women were comfortable discussing their risk for CHD with their physician, only 38% reported that their physician had actually discussed this risk with them. This highlights the need for health-care providers to bridge this knowledge gap and seize the opportunities to discuss risks and risk factor modification with patients. Subsequently, health-care providers should aggressively treat the appropriate women based on guideline recommendations in order to improve long-term outcomes.

The population is aging, and the incidence of CVD is only likely to increase, unless we begin to institute preventive therapies earlier, and to aggressively continue them over a woman's lifespan. More attention should be paid by health-care providers to promote a woman's awareness of her risk for CVD as well as instituting therapies aggressively aimed at prevention that are tailored to a woman's specific needs.

Further research is needed in the area of gender-specific differences in CAD and all of its manifestations, as well as many of the pharmacologic and interventional therapies used in its treatment. Research that delves further into novel risk factors and the additional value that can be provided over traditional risk factors in terms of assessing risk for CVD, especially in women, is needed as well. Ongoing genetics research, as well as research related to sex hormones, could also provide useful information for tailoring gender-specific therapy. Novel imaging strategies such as cardiac Positron Emission Tomography (PET) with assessment of myocardial blood flow (MBF), are being studied and may provide important information. This may be especially important in women, given the difficulty with noninvasive diagnosis of obstructive CAD. Hopefully, once some of these diagnostic and therapeutic modalities become available, there will be appreciable changes in the occurrence and outcomes of CVD in women.

ACKNOWLEDGMENTS: *The author wishes to thank Dr. Kellan Ashley for contributions to this chapter in an earlier edition.*

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SECTION IX

Noninvasive Assessment

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CHAPTER 47

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Exercise Electrocardiographic Testing

I. INTRODUCTION

A. Exercise electrocardiographic testing is a field in flux. In the past decade, it has become clear that ST-segment changes during exercise have low sensitivity and specificity in the evaluation of coronary artery disease (CAD) and are poor predictors of risk. This may be partially due to the fact that stable obstructive plaques, which typically result in exercise-mediated ischemia, are less relevant to myocardial infarction (MI) and sudden cardiac death than unstable nonobstructive plaques. Although the bulk of obstructive CAD screening has now shifted towards various stress imaging modalities, many of the physiologic parameters measured during exercise have emerged as powerful prognostic indicators. As such, the main uses of exercise electrocardiographic testing should be *evaluation of prognosis* and as *a gateway to other imaging modalities.* Stand-alone testing for CAD diagnosis is reserved for patients with *intermediate risk for CAD* and should be ordered with a careful understanding of the limitations of the test for this purpose.

1. The **advantages** of exercise electrocardiographic testing are its ability to assess a variety of prognostic markers, most importantly **functional capacity**, which is a powerful predictor of mortality, widespread availability, safety, ease of administration, and relatively low cost. The assessment of functional capacity may be particularly advantageous in patients with valvular heart disease and congenital heart disease whereupon recognition of functional limitation is often difficult to ascertain by history alone.
2. **Disadvantages.** As a screening test for CAD in persons without symptoms, exercise electrocardiography is generally not helpful or indicated. It has a **low sensitivity and specificity,** which can be improved with careful selection of the patient population undergoing testing.

B. **Submaximal exercise electrocardiographic testing** (i.e., testing at submaximal heart rate, discussed later) is a useful assessment before hospital discharge for **patients who have had MI**. The advantages are as follows:

1. It assists in setting **safe levels** of exercise (exercise prescription) and reassuring patients and families.
2. It is beneficial in **optimization of medical therapy**, in triage for intensity of follow-up testing and care, and in recognition of exercise-induced ischemia and arrhythmias.
3. For patients with uncomplicated MI who have received reperfusion therapy, submaximal exercise testing may be safely **performed as early as 3 days after MI**, with maximal exercise testing 3 to 6 weeks later.

II. INDICATIONS.

The indications for exercise electrocardiographic testing are divided on the basis of the degree of likelihood of disease or severity of diagnosed disease, use in valvular heart disease, and use in congenital heart disease (Table 47.1).

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing

Exercise testing in the diagnosis of obstructive CAD

Class I[a]

- Adult patients (including those with complete right bundle branch block or < 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of sex, age, and symptoms

Class IIa

- Patients with vasospastic angina

Class IIb

- Patients with a high pretest probability of CAD on the basis of age, symptoms, and sex
- Patients with a low pretest probability of CAD on the basis of age, symptoms, and sex
- Patients with < 1 mm of baseline ST depression and taking digoxin
- Patients with electrocardiographic criteria of left ventricular hypertrophy and < 1 mm of baseline ST depression

Class III

- Patients with baseline electrocardiographic abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - > 1 mm of resting ST depression
  - Complete left bundle branch block
- Patients with a documented myocardial infarction or prior coronary angiographic findings of disease and an established diagnosis of CAD (ischemia and risk can be determined with testing)

Risk assessment and prognosis among patients with symptoms or a history of CAD

Class I

- Patients undergoing initial evaluation with suspected or known CAD (exceptions in class 2b), including those with complete right bundle branch block or < 1 mm of resting ST depression
- Patients with suspected or known CAD previously evaluated, now presenting with marked change in clinical status
- Low-risk unstable angina patients 8–12 h after presentation who have been free of active ischemic or heart failure symptoms
- Intermediate-risk unstable angina patients 2–3 d after presentation who have been free of active ischemic or heart failure symptoms

Class IIa

- Intermediate-risk unstable angina patients with initial cardiac markers that are normal, a repeat electrocardiographic study without significant change, cardiac markers 6–12 h after symptom onset that are normal, and no other evidence of ischemia during observation

Class IIb

- Patients with baseline electrocardiographic abnormalities
  - Preexcitation (Wolff-Parkinson-White) syndrome
  - Electronically paced ventricular rhythm
  - 1 mm or more of resting ST depression

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (*Continued*)

Complete left bundle branch block or any interventricular conduction defect with QRS duration > 120 milliseconds

Patients with a stable clinical course who undergo periodic monitoring to guide treatment

Class III

Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization

High-risk unstable angina patients

After acute myocardial infarction

Class I

Before discharge for prognostic assessment, activity prescription, or evaluation of medical therapy (submaximal at about 4–6 d)

Early after discharge for prognostic assessment and cardiac rehabilitation if the predischarge exercise test was not performed (symptom limited, about 14–21 d)

Late after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (symptom limited, about 3–6 wk)

Class IIa

After discharge for activity counseling or exercise training as part of cardiac rehabilitation of patients who have undergone coronary revascularization

Class IIb

Patients with electrocardiographic abnormalities

Complete left bundle branch block

Preexcitation (Wolff-Parkinson-White) syndrome

Left ventricular hypertrophy

Digoxin therapy

Electronically paced ventricular rhythm

> 1 mm of resting ST depression

Periodic monitoring for patients who continue to participate in exercise training or cardiac rehabilitation

Class III

Severe comorbidity likely to limit life expectancy or candidacy for revascularization

Patients with acute myocardial infarction and uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit exercise ability

Before discharge, patients who have been selected for or have undergone cardiac catheterization (stress imaging tests are recommended)

Exercise testing for persons without symptoms or known CAD

Class I

None

Class IIa

Asymptomatic persons with diabetes mellitus to start vigorous exercise

Class IIb

Persons with multiple risk factors

TABLE 47.1 ***Continued***

Men older than 45 y and women older than 55 y without symptoms
- Who plan to start vigorous exercise (especially if sedentary)
- Who are involved in occupations in which impairment might affect public safety
- Who are at high risk for CAD because of other diseases

Class III
- Routine screening of men or women without symptoms

Exercise testing for persons with valvular heart disease

Class I
- None

Class IIa
- Patients with chronic AR and equivocal symptoms to assess functional capacity and symptomatic response

Class IIb
- Asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses
- In asymptomatic or symptomatic patients with chronic AR (with radionuclide angiography) for assessment of left ventricular function

Class III
- Exercise testing should not be performed in symptomatic patients with AS

Exercise testing for persons with congenital heart disease

Class I
- None

Class IIa
- Asymptomatic young adults < 30 y of age to determine exercise capability, symptoms, and blood pressure response
- Adolescent or young adult patient with AS who has a Doppler mean gradient > 30 mm Hg or a peak velocity > 50 mm Hg if the patient is interested in athletic participation or if the clinical findings and Doppler findings are disparate
- Asymptomatic young adult with a mean Doppler gradient > 40 mm Hg or a peak Doppler gradient > 64 mm Hg or when the patient anticipates athletic participation or pregnancy
- As part of the initial evaluation of adolescent and young adult patients with TR and serially every 1–3 y
- In patients with atrial septal defect with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate PAH
- In patients with subvalvular AS testing to determine exercise capability, symptoms, ECG changes or arrhythmias, or increase in LVOT gradient is reasonable in the presence of otherwise equivocal indications for intervention
- In patients with supravalvular AS (along with other imaging modalities) testing can be useful to evaluate the adequacy of myocardial perfusion

Class IIb
- In patients with aortic coarctation, testing may be performed at intervals determined in consultation with the regional ACHD center

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (*Continued*)

Class III

Patients with atrial septal defect or patent ductus arteriosus with severe PAH

Symptomatic patients with AS or those with repolarization abnormality on ECG or systolic dysfunction on echocardiography

[a]*Class 1*, conditions for which there is evidence or agreement that a given procedure or treatment is useful and effective; *Class 2*, conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; *Class 2a*, weight of evidence or opinion is in favor of usefulness and efficacy; *Class 2b*, usefulness or efficacy is less well established on the basis of evidence and opinion; *Class 3*, conditions for which there is evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. CAD, coronary artery disease; AR, aortic regurgitation; AS, aortic stenosis; TR, tricuspid regurgitation; PAH, pulmonary arterial hypertension; ECG, electrocardiogram; LVOT, left ventricular outflow tract; ACHD, adult congenital heart disease.

From Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540, with permission. Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2008;52:e1–e142 and from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *J Am Coll Cardiol*. 2008;52:1890–1947.

III. CONTRAINDICATIONS. Contraindications to exercise testing are divided into absolute and relative categories (Table 47.2).

IV. LIMITATIONS OF EXERCISE ELECTROCARDIOGRAPHIC TESTING. Before ordering an exercise electrocardiography test, the physician should have an understanding of Bayes' theorem and the limitations of the test.

A. Bayes' theorem states that the probability of a positive test result is affected by the likelihood (i.e., conditional probability) of a positive test result among the population that has undergone the test (i.e., pretest probability). The higher the probability that a disease is present in a given individual before a test is ordered, the higher is the probability that a positive test result is a true-positive test result. Pretest probability is determined on the basis of symptoms, age, sex, and risk factors and can be divided into very low, low, intermediate, and high (Table 47.3).

B. Sensitivity and specificity. The likelihood that an abnormal electrocardiographic finding indicates CAD is much higher for an older person with multiple risk factors than for a young person with no risk factors. Sensitivity and specificity vary with the population being tested.

1. Exercise electrocardiographic testing is **best used** in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history.
2. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.
3. Exercise electrocardiographic testing has a higher sensitivity and specificity for **persons at high risk**. For most of these patients, however, invasive testing is preferred for a more definitive diagnosis and possible intervention. Excluding patients with left ventricular hypertrophy or resting ST depression and those taking digoxin also improves sensitivity and specificity.

TABLE 47.2 Contraindications to Exercise Testing

Absolute contraindications
Acute myocardial infarction (within 2 d)
High-risk unstable angina
Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
Symptomatic, severe aortic stenosis
Uncontrolled symptomatic heart failure
Acute pulmonary embolus or pulmonary infarction
Suspected or known dissecting aneurysm
Active or suspected myocarditis, pericarditis, or endocarditis
Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (e.g., infection, renal failure, or thyrotoxicosis)
Considerable emotional distress (psychosis)
Relative contraindications
Left main coronary stenosis or its equivalent
Moderate stenotic valvular heart disease
Resting diastolic blood pressure > 110 mm Hg or resting systolic blood pressure > 200 mm Hg
Electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia)
Fixed-rate pacemaker
High-degree atrioventricular block
Frequent or complex ventricular ectopy
Ventricular aneurysm
Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, and myxedema)
Chronic infectious disease (e.g., mononucleosis, hepatitis, and acquired immunodeficiency syndrome)
Neuromuscular, musculoskeletal, or rheumatoid disorders exacerbated by exercise
Advanced or complicated pregnancy
Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
Mental impairment leading to inability to cooperate

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription.* Baltimore, MD: Williams & Wilkins, 1995; from Fletcher GF, Fletcher GF, Blair SN, et al. Statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 1992;86:340–344; and from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol.* 2002;40:1531–1540.

C. Positive predictive value (PPV). After pretest probability and the sensitivity and specificity are known, PPV can be calculated. PPV is a measure of the likelihood that an abnormal test finding represents a true-positive result. It is highly dependent on pretest probability (i.e., prevalence of disease) in the population being tested. For example, in a population at low risk, the PPV of electrocardiographic exercise testing is only 21%, but in a population at high risk, PPV rises to 83%.

TABLE 47.3 Pretest Probability of Coronary Artery Disease according to Age, Sex, and Symptoms

Age (y)	Sex	Typical/ definite angina pectoris	Atypical/ probable angina pectoris	Nonanginal chest pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

Reproduced with permission from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540.

V. PATIENT PREPARATION

A. Instructions. Table 47.4 provides a typical list of instructions given to patients before testing.

B. Medications

1. Before diagnostic testing, **cardiovascular drugs are withheld** at the discretion of and under the guidance of the supervising physician. This greatly increases the sensitivity of the test.
   a. **β-Blockers** pose a special problem. Patients taking β-blockers often do not have an adequate increase in heart rate to achieve the level of stress needed for the test. Abrupt withdrawal of β-blockers is to be discouraged because of reflex tachycardia. The best possible solution is to withdraw the β-blocker over several days before an exercise test, if the test is for diagnostic purposes. This is not always possible, however, because of time constraints or the necessity of drug therapy. In these cases, the records should reflect β-blocker use at the time of testing.
   b. **Digoxin** may cause problems in test interpretation. To avoid a reading that cannot be used to confirm a diagnosis, digoxin should be withheld for 2 weeks before testing.
2. Patients undergoing diagnostic testing should take their **other usual medications** on the day of the test to reproduce more closely the conditions outside the exercise laboratory.

VI. EXERCISE PROTOCOLS.

There are advantages and disadvantages to each exercise protocol (Table 47.5). Selection depends on the patient characteristics, the equipment available, and the familiarity and comfort of the testing personnel with the protocol.

A. An **optimal protocol** achieves peak workload and maximizes the sensitivity and specificity of the test.

1. **Workload.** An optimal protocol incorporates a **gradual increase** in the level of work, so that the patient's true peak workload can be determined. If there are large increases in workload, maximum oxygen consumption ($M\dot{V}O_2$ max) may

TABLE 47.4 Patient Preparation

Patients should refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 h of testing.
Patients should be rested for the assessment, avoiding significant exertion or exercise on the day of the assessment.
Patients should wear clothing that allows freedom of movement, including walking or running shoes, and a loose-fitting shirt with short sleeves that buttons down the front. They should not wear restrictive undergarments during the test.
Outpatients should be warned that the evaluation may be fatiguing and that they may wish to have someone available to drive them home afterward.
If the test is for diagnostic purposes, it may be helpful for patients to discontinue prescribed cardiovascular medication after discussion with their physician. Antianginal agents alter the hemodynamic response to exercise and significantly reduce the sensitivity of electrocardiographic changes for ischemia. Patients taking intermediate- or high-dose β-blockers should taper their medication over a 2–4-d period to minimize hyperadrenergic withdrawal responses.
If the test is for functional purposes, patients should continue their medication regimen on their usual schedule so that the exercise responses will be consistent with responses expected during exercise training.
Patients should bring a list of their medications with them to the assessment.

Reproduced with permission from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's guidelines for Exercise Testing and Prescription*. Baltimore, MD: Williams & Wilkins; 1995.

fall between two levels. The test is also more comfortable for the patient if the increases in workload are not large.

2. **Duration.** The optimal duration for an exercise test is **8 to 12 minutes**. Periods longer than this measure muscular endurance rather than cardiovascular fitness. Periods shorter than this do not allow adequate time for the patient to warm up and achieve maximum workloads.
3. **Stage length.** Steady-state oxygen consumption is reached after about 2 minutes of exercise at a given workload. The optimal protocol would have stage lengths of **2 to 3 minutes**.
4. **Exercise method.** Although **bicycle riding** is a better method for testing, **treadmill testing** is more commonly used in the United States.
   a. The primary physiologic **advantage of bicycle riding** is the ability to take **direct measurements** of workload in watts, which has direct linear relation to $M\dot{V}O_2$. With a **treadmill**, the examiner can only **estimate workload** because workload depends on the efficiency of walking, the weight of the patient, and the change in energy expenditure between walking and running. Other advantages of a bicycle are the stable platform that it provides for electrocardiographic and blood pressure recordings, the smaller amount of space it occupies, quieter use, and a lower initial cost of equipment.

B. Protocol options

1. **Bruce protocol**
   a. **Advantages.** The Bruce protocol has been widely used in the past and is often the basis of older studies; therefore, **comparisons are easier**. Because the Bruce protocol has a final stage that cannot be completed, it is a good protocol for a highly fit person.
   b. **Disadvantages**
      (1) The main disadvantage of the Bruce protocol is the **large increments of change in workload between stages**. These large increases mean that

TABLE 47.5 Common Exercise Protocols

Functional class	O_2 cost mL/kg/min	MET	Treadmill protocol									
			Bruce (3-min stages mph/grade)		Cornell (2-min stages mph/grade)		Balke (2-min stages mph/grade)		Naughton (2-min stages mph/grade)		Jogger (2-min stages mph/grade)	
World-class athlete	70.0	20	—	—	—	—	—	—	—	—	—	—
	66.5	19	6.0	22	—	—	—	—	—	—	—	—
	63.0	18	—	—	—	—	—	—	—	—	6.0	20.0
	59.5	17	5.5	20	—	—	—	—	—	—	6.0	17.5
Athlete	56.0	16	5.0	18	5.0	18	—	—	—	—	6.0	15.0
	52.5	15	—	—	—	—	4.0	20	—	—	6.0	12.5
	49.0	14	—	—	4.6	17	—	—	—	—	6.0	10.0
Fit	45.5	13	4.2	16	4.2	16	3.5	20	—	—	6.0	7.5
	42.0	12	—	—	—	—	—	—	—	—	6.0	5.0
	38.5	11	—	—	3.8	15	3.0	20.0	—	—	5.5	2.5
Normal and 1	35.0	10	3.4	14	3.4	14	3.0	17.5	—	—	5.0	2.5
	31.5	9	—	—	—	—	3.0	15.0	—	—	—	—
	28.0	8	—	—	3.0	13	3.0	12.5	2.0	21.0	—	—
	24.5	7	2.5	12	2.5	12	3.0	10.0	—	7.5	—	—
2	21.0	6	—	—	2.1	11	3.0	7.5	2.0	14.0	—	—
	17.5	5	1.7	10	1.7	10	3.0	5.0	2.0	10.5	—	—
	14.0	4	—	—	—	—	3.0	2.5	2.0	7.0	—	—
3	10.5	3	1.7	5	1.7	5	3.0	0	2.0	3.5	—	—
	7.0	2	1.7	0	1.7	0	—	—	2.0	0	—	—
4	3.5	1	—	—	—	—	—	—	1.0	0	—	—

MET, metabolic equivalent; mph, miles per hour.

peak workload falls somewhere between stages for many people. This is a problem in evaluating functional capacity and may result in a lower sensitivity for the test.

(2) The fourth stage of the Bruce protocol is an awkward stage that can be run or walked, resulting in divergent oxygen costs and workloads.

2. **Modified Bruce protocol.** Developed for less-fit persons, the modified Bruce protocol adds additional stages 0 and 1/2. These stages, at 1.7 mph (2.7 km/h) with 0% and 5% grades, respectively, provide a **lower workload for persons with poor cardiovascular fitness**. However, even these workloads may be too heavy for some debilitated patients and may result in premature fatigue.
3. **Other protocols.** Protocols superior to the Bruce protocol have been developed. These protocols have more gradual increases in workload and can be modified to suit the individual.
   a. The **Naughton protocol** is good for older or debilitated persons and allows a gradual increase in workload.
   b. The **Balke protocol** is good for younger, fit persons. It maintains a speed of 3, 3.5, or 4 mph (4.8, 5.6, or 6.4 km/h) and increases the grade every 2 minutes.
   c. The **Cornell protocol** is good for a wider range of fitness levels depending on starting grade. It allows for a gradual increase in grade and speed and may be started at 0%, 5%, or 10% grade, depending on fitness level.
   d. **Ramp protocols** are computer-driven protocols that continuously increase workload until maximum exertion is reached. This is the ultimate in continuous advancement, but steady state may not be reached at any given workload.

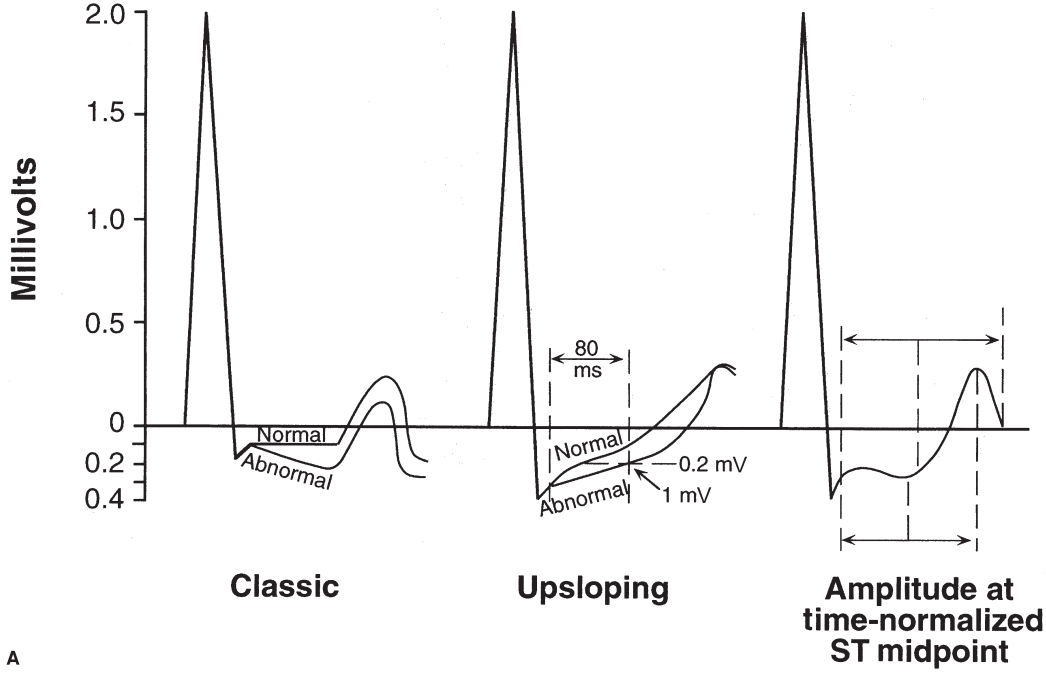
VII. DATA

A. Electrocardiographic data. Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The **portion of the electrocardiogram (ECG) most sensitive to ischemia** is the ST segment. The pathophysiologic mechanism of the ST change is net depression caused by a current of ischemia from the affected myocardial cells. The TP segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST changes are listed in Table 47.6.

1. **ST-segment changes**
   a. **Measurement of the ST segment.** There is no clear consensus as to where to measure the ST segment. Traditionally, it is measured 80 milliseconds past the J point, but some investigators suggest measuring at the J point or at the midpoint of the ST segment (using the end of the T wave or the peak of the T wave to determine the end of the segment) (Fig. 47.1A).

TABLE 47.6 Baseline Abnormalities That May Obscure Electrocardiographic Changes during Exercise

Left bundle branch block
Left ventricular hypertrophy with repolarization abnormality
Digitalis therapy
Ventricular paced rhythm
Wolff-Parkinson-White syndrome
ST abnormality associated with supraventricular tachycardia or atrial fibrillation
ST abnormalities with mitral valve prolapse and severe anemia


Millivolts
2.0
1.5
1.0
0.5
0
0.2
0.4
Normal
Abnormal
80
ms
Normal
Abnormal
0.2 mV
1 mV
Classic
Upsloping
Amplitude at
time-normalized
ST midpoint

A

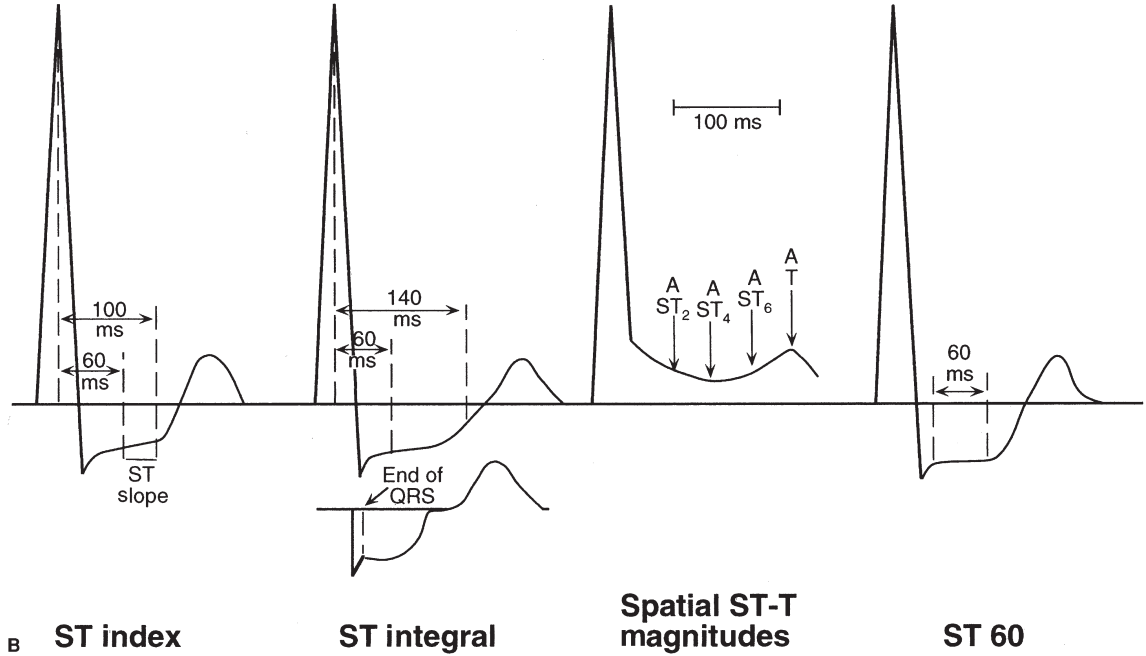


FIGURE 47.1 **(A)** Blomqvist recommended using the end of the T wave for measuring the midpoint of the ST segment, but Simons used the peak of the T wave. This change was made to have a more stable end point, because the end of the T wave is much more difficult to find than the peak of the T wave. **(B)** The ST integral, as defined by Sheffield, required that the end of the QRS complex, or J junction, be found and that the area measurement stop as soon as the ST segment crossed the isoelectric line or as the T wave began. The ST integral used by most commercial systems initiates the area at a fixed period after the R wave and then ends 80 milliseconds thereafter.

b. **ST-segment changes** are measured from the isoelectric baseline, which can be determined from the PR interval. If the ST segment is elevated at rest, any depression that occurs with exercise is still measured from the isoelectric line; early repolarization of the ST segment at rest is normal. If, however, the ST segment is depressed at rest, any further depression should be measured from the baseline ST segment (Fig. 47.1B).

c. **Normal response.** During exercise, there is depression of the J junction that is maximal at peak exercise and returns to baseline during recovery. This normal depression is upsloping and typically < 1 mm below the isoelectric line 80 milliseconds after the J point.

d. **ST depression** does not localize the area of ischemia.

(1) ST depression of at least 1 mm that is horizontal or downsloping is abnormal, as is upsloping ST depression of at least 2.0 mm.

(2) Baseline ST abnormalities are less likely to represent exercise-induced myocardial ischemia, and the baseline ST depression should be subtracted from the peak ST depression.

(3) **Criteria that increase the probability of ischemia** are the **number of leads** involved (i.e., more leads increase the probability of ischemia), the **workload** at which the ST depression occurs (i.e., lower workload increases probability), the **angle of the slope** (i.e., a downsloping angle has a higher probability than a horizontal one), **ST-segment adjustment relative to heart rate (ST/HR index)**, the **amount of time in recovery** before normalization of the ST segment (i.e., longer recovery increases the probability), and possibly the **magnitude of the depression**. Changes in the lateral leads, particularly V_5, are more specific than in any of the other leads. Changes in the inferior leads alone are likely to be a false-positive result.

e. The **meaning of ST elevation** depends on the presence or absence of Q waves of prior MI.

(1) ST-segment elevation **with Q waves of prior MI** is a common finding among patients who have had MI. It occurs among up to 50% of patients with anterior MI and 15% of patients with previous inferior MI, and it is not caused by ischemia. The mechanism is thought to be dyskinetic myocardium or ventricular aneurysms. There may even be reciprocal ST-segment depression. Patients with more extensive Q waves have more pronounced ST elevation. These patients typically have a lower ejection fraction than those without elevated ST segment with a Q wave. These changes do not imply ischemia (although they may imply viability) and should be interpreted as normal.

(2) ST-segment elevation **without Q waves of prior MI** represents marked transmural myocardial ischemia. ST elevation may also indicate the location of the ischemia. This finding should be interpreted as abnormal.

f. **ST normalization,** or the lack of ST changes during exercise, **may be a sign of ischemia.** This phenomenon occurs when ischemic ST depression and ST elevation cancel one another. This effect is rare, but it should be considered in tests of patients with no electrocardiographic changes but with a high likelihood of CAD.

2. **R waves may change in amplitude** during exercise. There is no diagnostic value in these changes.

3. **T-wave and U-wave changes**

a. The **T wave** normally decreases gradually in early exercise and begins to increase in amplitude at maximal exercise. One minute into recovery, the T wave should be back to baseline. T-wave **inversion is not a specific marker of ischemia** and may occur normally.

TABLE 47.7 Absolute and Relative Indications for Termination of an Exercise Test

Absolute indications
Acute myocardial infarction or suspicion of myocardial infarction
Onset of moderate to severe angina or increasing anginal pain
Drop in systolic blood pressure with increasing workload accompanied by signs or symptoms or drop below resting pressure
Serious arrhythmias (e.g., second- or third-degree atrioventricular block, sustained ventricular tachycardia or increasing premature ventricular contractions, and atrial fibrillation with fast ventricular response)
Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
Unusual or severe shortness of breath
Central nervous system symptoms, including ataxia, vertigo, visual or gait problems, or confusion
Technical inability to monitor the electrocardiogram
Patient's request
Relative indications
Pronounced electrocardiographic changes from baseline > 2 mm of horizontal or downsloping ST-segment depression or > 2 mm of ST-segment elevation except in aVR
Any chest pain that is increasing
Physical or oral manifestations of severe fatigue or shortness of breath
Wheezing
Leg cramps or intermittent claudication (grade 3 on 4-point scale)
Hypertensive response (systolic blood pressure > 260 mm Hg and diastolic blood pressure > 115 mm Hg)
Less serious arrhythmias such as supraventricular tachycardia
Exercise-induced bundle branch block that cannot be differentiated from ventricular tachycardia
General appearance

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription. 5th ed.* Baltimore, Md: Williams & Wilkins; 1995 and from Fletcher GF, Blair SN, et al. statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. Circulation. 1992;86:340–344

   b. If the U wave is upright at baseline, **U-wave inversion** may be associated with ischemia, left ventricular hypertrophy, and valvular disease.

4. **Arrhythmias.** Table 47.7 lists abnormal arrhythmias that may occur during exercise. Ectopic atrial and ventricular beats during exercise are not predictive of outcome, but ventricular ectopy during recovery may be associated with worse outcome. Sustained ventricular tachycardia and ventricular fibrillation are abnormal but occur rarely.
5. **Time to resolution of changes.** The longer into recovery that it takes for electrocardiographic changes to resolve, the higher is the probability that they are important. Rapid recovery (< 1 min) indicates less likelihood of disease and that disease if present is less severe.

6. Bundle branch block or conduction delay. Exercise-induced left bundle branch block is predictive of a worse outcome.

B. Age-predicted maximum heart rate (APMHR). Many formulas have been developed to predict maximum heart rate (MHR). These formulas are generated by measuring the MHR in a sample population and plotting a regression line against various factors that may affect heart rate. There is a great deal of scatter on either side of the regression line, and the fit of the line seldom reaches an r value > 0.9. Because MHR decreases with age, most equations incorporate age into the estimation. The two most common formulas are as follows:

$$\text{APMHR} = 220 - \text{age}$$

$$\text{APMHR} = 200 - \tfrac{1}{2}\,\text{age}$$

The APMHR may be much lower or much higher than a person's actual measured MHR. **Heart rate should not be used as an indicator of maximal exertion or in the decision to terminate testing, except in a submaximal test**. If MHR does not exceed 85% of APMHR during testing and there are no substantial electrocardiographic changes, the test is usually read as nondiagnostic. If there are substantial electrocardiographic changes, the test is read as abnormal, regardless of the heart rate achieved.

C. Rating of perceived exertion (RPE) is a better marker of maximal level of exertion.

1. A useful indicator of percentage of maximum workload achieved is the **RPE scale**. This is a subjective scale used to rate how much effort the subject feels he or she is expending during an exercise test. The subject should be advised to rate how he or she feels overall and not according to an individual element such as leg fatigue. Although subjective, the scale has been shown to be reproducible, and maximum ratings correspond well with maximum exertion.
   a. The **Borg scale** is used most often. The original scale ranges from 6 to 20, which is meant to correspond to a heart rate increase from 60 to 200 beats/min during exercise.
   b. The **modified Borg scale** ranges from 0 to 10. The scale includes word anchors, which are important for an accurate assessment of work level. The scales are not linear, and at higher workloads, the changes in RPE are closer together.
2. A maximal level of exertion is marked by a score > 18 (Borg scale) or 9 (modified Borg scale), respiratory quotient > 1.1 (if carbon dioxide exchange is monitored), and overall patient appearance.

D. In addition to electrocardiographic monitoring, **blood pressure monitoring** is an important aspect of the exercise test for safety and for the diagnosis of CAD. It should be checked in each walking stage. It may not be practical to check blood pressure while the subject is running.

1. **Systolic blood pressure** (SBP) normally rises during exercise. A **failure of SBP to rise** with increasing workload or a drop in SBP usually indicates the presence of CAD and is an indication to **terminate testing**.
2. **Diastolic blood pressure** decreases with exercise and may be audible down to 0 during vigorous activity. Unlike SBP, diastolic blood pressure is not useful in diagnosis or safety monitoring.

E. Symptoms. The presence or absence of symptoms and their change over time are included in the final report.

F. Functional capacity. Functional testing is a powerful marker for prognosis. Persons who achieve > 6 metabolic equivalents (METs) of workload have a significantly lower mortality rate than those who do not achieve this workload, regardless of electrocardiographic changes. On the basis of age and workload achieved, functional capacity can be divided into five classifications (Table 47.8). Among 3,400 patients with no history of diagnosed CAD undergoing exercise testing at the Cleveland Clinic, those with average or better classifications had a 2.5-year mortality of < 2% compared with 6%

TABLE 47.8 Functional Capacity Classifications by Age and Sex

Age (y)	Low[a]	Fair	Average	Good	High
Women					
20–29	< 7.5	8–10.3	10.3–12.5	12.5–16	> 16
30–39	< 7	7–9	9–11	11–15	> 15
40–49	< 6	6–8	8–10	10–14	> 14
50–59	< 5	5–7	7–9	9–13	> 13
60–69	< 4.5	4.5–6	6–8	8–11.5	> 11.5
Men					
20–29	< 8	8–11	11–14	14–17	> 17
30–39	< 7.5	7.5–10	10–12.5	12.5–16	> 16
40–49	< 7	7–8.5	8.5–11.5	11.5–15	> 15
50–59	< 6	6–8	8–11	11–14	> 14
60–69	< 5.5	5.5–7	7–9.5	9.5–13	> 13

[a]Functional capacities are given in metabolic equivalents.

and 14% for those who were in the fair and poor groups, respectively. The adjusted relative risk for fair or poor functional capacity in this population was almost 4.

VIII. TERMINATION OF EXERCISE TESTING. The American Heart Association (AHA) and American College of Sports Medicine (ACSM) have developed very similar indications for exercise termination (Table 47.7). The decision when to terminate a test ultimately relies on the expertise and judgment of those performing the test.

A. Absolute indications are all serious findings. A drop in SBP with increasing workload is a particularly ominous sign and usually, but not always, indicates the presence of severe CAD.

B. Relative indications for termination of testing are findings that should increase the level of concern and vigilance among those administering the test and possibly cause cessation of testing. Relative indications for termination rely heavily on the judgment of the personnel performing the test, and the decision to continue the test should not be made lightly (Table 47.7).

C. Indications for termination of submaximal exercise testing include any one of the following end points:

(1) Signs or symptoms of ischemia
(2) Achievement of a workload of 6 METs
(3) Eighty-five percent of the APMHR
(4) Heart rate of 110 beats/min for a patient taking β-blockers
(5) A score on the Borg RPE of 17 or modified Borg RPE of 7

D. Postexercise recovery

1. In **all routine exercise tests, a cool-down period** adds safety to the test. The length of the cool-down period may vary from 30 seconds to several minutes, depending on the person. A general rule is to allow enough time for the heart rate to drop to < 110 beats/min. A shorter cool-down period increases the sensitivity of exercise ECG because of increased venous return; resuming the supine position leads to increased wall stress. This same mechanism also increases the risk of testing.

2. The exception to observing a cool-down period may be made for exercise echocardiography, in which it is important to image the subject when he or she is as close as possible to MHR.

IX. INTERPRETATION OF DATA. An experienced clinician must interpret an exercise electrocardiographic test. Although the terms *positive* and *negative* are often used, these terms do not accurately describe the results of an exercise electrocardiographic test and should be avoided. The information to include in an exercise electrocardiographic report is listed in Table 47.9.

A. Exercise electrocardiographic test results can be normal, abnormal, normal except for, or nondiagnostic (Table 47.10). Nondiagnostic tests are those in which the subject does not achieve 85% of APMHR and has no abnormal electrocardiographic changes or in which baseline electrocardiographic changes are present that obscure ST changes (Table 47.6).

B. Prognosis

1. The **Duke nomogram** (Fig. 47.2) is a simple chart that factors in ST-segment deviation, amount of angina during exercise, and exercise capacity to give an estimate of a 5-year survival and average annual mortality. This nomogram was derived by means of regression analysis and can be a useful tool in determining prognosis and the degree of aggressiveness needed in treating a patient. The **Duke treadmill score (DTS)** is a numeric form of the nomogram and has been validated in several studies as an important predictor of mortality:

$$\text{DTS} = \text{duration of exercise (in minutes)} - (5 \times \text{maximal ST-segment deviation}) - (4 \times \text{angina score})$$

TABLE 47.9 Elements of Conclusion Section of a Modern Exercise Test Report

Exercise protocol used, duration of exercise, peak treadmill speed and grade, maximum heart rate and percentage of age-predicted maximum heart rate achieved, resting and peak blood pressure, and symptoms
Negative/positive/equivocal standard ST-segment response to exercise
"The ST/HR index of ≤ 1.6 μV/beats/min is consistent with the absence of obstructive coronary disease and makes anatomically, functionally, and prognostically important coronary disease unlikely"; "The ST/HR index > 1.6 μV/beats/min is consistent with the presence of obstructive coronary disease and predicts increased cardiovascular risk
The estimated functional capacity of (*x* METs) predicts (high/low) risk of all-cause mortality
The Duke treadmill score of (*x*) predicts a cardiac mortality of (*x*%) per year over the next 5 y. This implies a (low/intermediate/high) risk
The chronotropic response index of (0.*xx*) predicts an (increased/decreased) risk of death compared with the Duke treadmill score. For patients not on β-blockers, a value ≤ 0.80 raises concerns; for patients on β-blockers, a value ≤ 0.62 is abnormal
The heart rate recovery of (*x* beats/min) further predicts an (increased/decreased) risk of death
The presence/absence of frequent ventricular ectopy during recovery further increases/decreases predicted risk of death

Adapted from Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation.* 2006;114:2070–2082.

TABLE 47.10 Guidelines for Interpretation of Results of Exercise Electrocardiography

Variable	Normal	Normal except for	Abnormal
Symptoms	Neuromuscular chest pain	Angina as an isolated finding	Syncope
	Fatigue, shortness of breath, and leg or joint pain	Atypical angina	Angina when associated with ST- or T-wave changes, including borderline
		Chest discomfort of questionable causation	Angina when associated with exercise hypotension
		Claudication	
		Dizziness and lightheadedness	
		Other noteworthy symptoms	
Blood pressure response (mm Hg)	SBP increases > 10 but is < 230 at peak	SBP ≥ 230 at peak exercise	Any drop in SBP as exercise intensity increases
	DBP increases ≤ 10 but is < 120 at peak	DBP ≥ 120 at peak exercise	
	DBP stays the same or decreases	DBP increases ≥ 12 from rest if peak is ≥ 100	
	DBP increases ≥ 12 from rest but peak is < 100		
Arrhythmias	Occasional PVCs	Paroxysmal SVT	Sustained SVTs, AF, atrial flutter, or junctional rhythm
	PACs	Increased frequency of PVCs or couplets during exercise	Nonsustained VT
	Frequent PACs or PVCs at rest that abate during exercise	Isolated run of nonsustained VT	Second- or third-degree AV block

(Continued)

TABLE 47.10 Guidelines for Interpretation of Results of Exercise Electrocardiography (*Continued*)

Variable	Normal	Normal except for	Abnormal
	Chronic AF, atrial flutter	Ventricular couplets	AV dissociation
		Paroxysmal escape rhythms	Exercise induced before excitation
			Idioventricular rhythm
			Very abnormal
			Sustained VT (≥30 s)
			VF/cardiac arrest
			Asystole
ST segments	< 1.0 mm ST depression or elevation	Borderline ST changes (0.5–0.9 mm ST depression)	≥1.0 mm H or D ST depression
		ST elevation in leads in area of prior MI	≥1.5 mm U ST depression
		T-wave inversion	≥1.0 mm U ST depression if associated with anginal symptoms
		Pseudonormalization of resting T-wave abnormalities	≥1.0 mm ST elevation in leads without Q waves or not over a prior MI
			Very abnormal
			≥2.0 mm H or D ST depression
			≥2.5 mm U ST depression
			≥2.0 mm ST elevation in leads without Q waves or not over a prior MI
Functional capacity	Normal or mildly impaired exercise tolerance	Low exercise tolerance	Inability to achieve 3 MET workload

AF, atrial fibrillation; AV, atrioventricular; D, downsloping; DBP, diastolic blood pressure; H, horizontal; MET, metabolic equivalent; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction; SBP, systolic blood pressure; SVT, supraventricular tachycardia; U, upsloping; VF, ventricular fibrillation; VT, ventricular tachycardia.

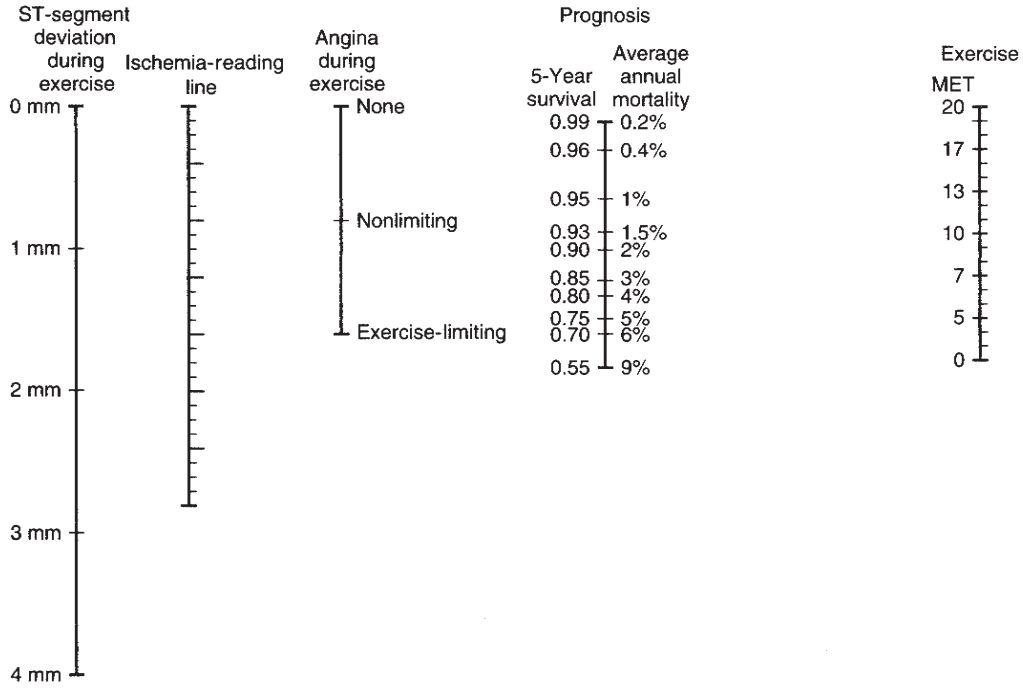


FIGURE 47.2 Duke nomogram for estimation of the prognosis. MET, metabolic equivalent.

In the previous equation, 0 = no angina, 1 = non–test-limiting angina, and 2 = exercise-limiting angina.

Low risk: DTS ≥ +5
Intermediate risk: DTS −10 to < +5
High risk: DTS < −10

2. The **heart rate recovery**, defined as the difference in heart rate at peak exercise and at 1 minute after cessation of exercise, has important prognostic significance. A heart rate recovery of 12 beats/min or less is considered abnormal during an upright cool-down period. For patients assuming an immediate supine position, such as during exercise echocardiography, a value of < 18 beats/min is considered abnormal.
3. The **chronotropic response index (CRI)** is a measure of MHR in relation to chronotropic reserve. A normal response is defined as a CRI of > 0.8 (0.62 for patients on β-blockers):

$$\text{CRI} = \frac{\text{peak HR} - \text{resting HR}}{\text{APMHR} - \text{resting HR}}$$

4. **Ventricular ectopy in recovery** from exercise, including frequent ventricular ectopics (> 7/min), couplets, bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation, has been shown to be predictive of all-cause mortality. These findings in recovery are a better predictor of death than ventricular ectopy during exercise.
5. A published nomogram (1) for patients with suspected CAD and a normal ECG undergoing exercise treadmill testing demonstrates how a simple combination of clinical and stress-testing variables can be used to predict mortality.

X. POTENTIAL COMPLICATIONS. Complications of exercise electrocardiographic testing are rare, but they do occur (Table 47.11). Exercise testing of healthy persons without CAD rarely results in cardiac complications, which are most likely to occur among persons with underlying CAD. Several researchers have looked at large numbers of unselected persons involved in various activities to determine risk.

A. Cardiac arrest

1. For the **general population**, there is approximately 1 cardiac arrest per 565,000 person-hours of exercise.
2. Among **persons with known CAD**, there is an estimated 1 arrest per 59,000 person-hours of vigorous activity. Exercise testing may precipitate acute coronary symptoms. Acute MI has been reported in approximately 1.4 per 10,000 exercise tests.
3. Among **persons at low risk** for CAD, however, the risk for cardiac arrest during exercise testing is much lower. In one study, no complications occurred in 380,000 exercise tests of young persons with presumably no heart disease.

B. Arrhythmic complications are a potential hazard of exercise testing (Table 47.10). Arrhythmias are more likely among persons with a history of arrhythmia. In this population, they occur in 9% of tests compared with an overall incidence of 0.1%.

1. **Atrial fibrillation** is the most common arrhythmia that occurs during testing, occurring in 9.5 per 10,000 tests.
2. **Ventricular tachycardia** is less common, occurring in 5.8 per 10,000 tests.
3. **Ventricular fibrillation** is even less common, occurring 0.67 times per 10,000 tests.

C. Deaths during exercise testing are exceedingly rare among well-monitored patients, but may occur in 1 of 25,000 tests. If death occurs, it is usually caused by sudden cardiac death or MI.

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testings

Cardiovascular complications

Cardiac arrest
Ischemia
- Angina
- Myocardial infarction

Arrhythmias
- Supraventricular tachycardia
- Atrial fibrillation
- Ventricular tachycardia
- Ventricular fibrillation

Bradyarrhythmias
- Bundle branch blocks
- Atrioventricular nodal blocks

Congestive heart failure
Hypertension
Hypotension
Aneurysm rupture

Underlying medical conditions predisposing to increased complications

Hypertrophic cardiomyopathy
Coronary artery anomalies
Idiopathic left ventricular hypertrophy
Marfan's syndrome
Aortic stenosis
Right ventricular dysplasia
Congenital heart defects
Myocarditis
Pericarditis
Amyloidosis
Sarcoidosis
Long QT syndrome
Sickle cell trait
Sudden death

Pulmonary complications

Exercise-induced asthma
Bronchospasm
Pneumothorax

(Continued)

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testing (*Continued*)

Exercise-induced anaphylaxis
Exacerbation of underlying pulmonary disease
Gastrointestinal complications
Vomiting
Cramps
Diarrhea
Neurologic complications
Dizziness
Syncope (fainting)
Cerebrovascular accident (stroke)
Musculoskeletal complications
Mechanical injuries
Back injuries
Joint pain or injury
Muscle cramps or spasms
Exacerbation of musculoskeletal disease

ACKNOWLEDGMENTS: *The author thanks Drs. Christopher Cole, Julie Huang, and Eiran Gorodeski for their contributions to earlier editions of this chapter.*

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CHAPTER 48

Santosh S. Oommen

Nuclear Cardiac Imaging

I. INTRODUCTION. Nuclear cardiology has an integral role in the noninvasive detection of coronary artery disease (CAD), assessment of myocardial viability, and stratification of risk. It imparts improved sensitivity and specificity over standard exercise stress testing. For example, the average sensitivity and specificity of single-photon emission computed tomography (SPECT) with technetium 99m have been reported to be 90% and 74%, respectively—though the exact performance characteristics depend on the prevalence of the disease in the population being studied. Nuclear imaging can provide functional and prognostic information that is quantifiable, reproducible, and readily obtainable in diverse patient populations.

II. INDICATIONS (Table 48.1)

A. Diagnosis of CAD. Nuclear perfusion studies are performed to establish noninvasively the diagnosis of CAD in the following situations: history of **stable angina; chest pain of unclear causation; unstable angina** after stabilization; **abnormal exercise test result** without symptoms; **risk stratification** in the setting of multiple factors thought to confer a high likelihood of subclinical CAD; scheduled standard exercise testing in the setting of an **abnormal electrocardiogram** (ECG; due to left ventricular hypertrophy with associated repolarization changes, ST depression >1 mm, manifest pre-excitation pattern on ECG, digoxin use, left bundle branch block, or ventricular-paced rhythm); and previously **nondiagnostic graded exercise test**.

B. Assessment of the physiologic importance of known CAD. Perfusion imaging can assist in the determination of the functional significance of a coronary stenosis that is in the "moderate-to-severe" (50% to 70%) range on angiographic evaluation. It can therefore be useful to evaluate a specific coronary lesion before proceeding to percutaneous intervention. This remains an accepted indication for nuclear perfusion imaging, although its use for this purpose is being supplanted by other modalities that can assess the functional significance of coronary lesions at the time of angiography (e.g., fractional flow reserve).

C. Assessment after therapeutic intervention. In the past, perfusion imaging was often performed as a routine follow-up procedure after percutaneous intervention and coronary artery bypass grafting (CABG). More recent recommendations on appropriate use of this modality suggest that routine screening in *asymptomatic* patients who have been successfully revascularized by either method is not necessarily warranted, except in the evaluation of patients more than 5 years after CABG. On the other hand, radionuclide perfusion imaging is certainly appropriate in patients who have undergone prior revascularization and are presenting with recurrent symptoms consistent with coronary ischemia.

D. Risk stratification. With nuclear imaging, it is possible to stratify risk among patients with stable angina or unstable angina, those who have had myocardial infarction (MI), and those about to undergo noncardiac operations.

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

Patient group	Condition	Imaging technique
ER patient with chest pain	For risk stratification in pt with *possible* ACS. Initial serum markers and enzymes. ECG is nondiagnostic.	Rest perfusion imaging (with ECG gating, if possible).
	For CAD diagnosis in pt with *possible* ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan.	Same-day rest/stress (ECG-gated) myocardial perfusion imaging.
Acute MI/unstable angina	Assessment of LV function.	Rest myocardial perfusion imaging with ECG gating (rest gated radionuclide angiography is alternative option).
ST-elevation MI	Measurement of infarct size and residual viable myocardium, in an unrevascularized asymptomatic stable patient after completion of the infarct.	Rest myocardial perfusion imaging with ECG gating or with stress perfusion imaging with ECG gating.
	Thrombolysis without coronary angiogram, to identify inducible ischemia and myocardium at risk.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
Non–ST-elevation MI/unstable angina	In an unrevascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the "culprit" vessel or in remote myocardium.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
	In individuals whose angina is stabilized on medical therapy or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.
	To assess the functional significance of a coronary stenosis on angiography.	Rest and stress myocardial perfusion imaging.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* able to exercise to 85% MPHR or more	Those with pre-excitation, LVH, on digoxin, or >1 mm ST-segment depression on resting ECG.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	Individuals with left bundle branch block or ventricular-paced rhythm.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	Patients with an intermediate- or high-risk Duke treadmill score.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	In an individual with prior abnormal myocardial perfusion scan and new or worsening symptoms.	Repeat rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* not able to exercise	To identify the extent, severity, and location of inducible ischemia.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.
Detection of CAD in patients with syncope.	Patients with intermediate and high risk for CHD and no ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative CV events, and poor (<4 METSs) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible *or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	In individuals with established or suspected CAD and poor (<4 METS) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible *or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	Diagnosis of CAD in patients with left bundle branch block or ventricular-paced rhythm and at least one risk factor for adverse perioperative CV events.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	In suspected or established CAD, prognostic assessment of those with left bundle branch block or ventricular-paced rhythm on rest ECG.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes.	Rest and adenosine or dipyridamole stress PET myocardial perfusion study.

(*Continued*)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (*Continued*)

Patient group	Condition	Imaging technique
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization.	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging *or* Rest/redistribution SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging *or* Resting sestamibi SPECT perfusion imaging.
	Prediction of improvement in natural history following revascularization.	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging *or* Rest/redistribution thallium 201 SPECT perfusion imaging *or* Myocardial perfusion plus FDG PET metabolic imaging.

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ER, emergency room; FDG, [18F]fluoro-2-deoxyglucose; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; MPHR, maximal age-predicted heart rate; PET, positron emission tomography; pt, patient; SPECT, single-photon emission computed tomography.

E. Identification of prior MI among patients with angiographically normal coronary arteries is afforded by nuclear imaging.

F. Assessment of left ventricular (LV) function. Although nuclear imaging is used less often for this purpose than in the past—due to the desire to reduce patients' radiation exposure when possible—gated blood pool imaging remains an accurate method of determining the ejection fraction.

III. CONTRAINDICATIONS.

In addition to standard contraindications to exercise stress testing, specific considerations apply uniquely to nuclear imaging in general and the subgroup of dipyridamole stress perfusion studies.

A. General contraindications to nuclear studies. Nuclear imaging is contraindicated for patients who have had **iodine 131 therapy** within 12 weeks; **technetium 99m studies** within 48 hours, including bone, lung, multigated acquisition (MUGA), liver, tagged red blood cell (to evaluate gastrointestinal bleeding), and renal scans; **indium 111 scans** within 30 days; **gallium 67 scans** within 30 days; and **oral intake** within 4 hours (except for water).

B. Contraindications to dipyridamole, adenosine, or regadenoson administration include allergy to any of these agents, allergy to aminophylline, ongoing theophylline therapy (must be discontinued for 36 hours), history of uncontrolled asthma or reactive airway disease, significant atrioventricular nodal block, and caffeine consumption within 12 to 24 hours.

IV. EQUIPMENT.

The most basic tool in nuclear imaging is the **gamma or scintillation camera**, which is used to detect gamma rays (i.e., x-ray photons) produced by the chosen radionuclide. Three types of gamma camera exist.

A. A single-crystal camera consists of one large sodium iodide crystal. Other essential elements of this camera include the **collimator**, a lead device that screens out background or scattered photons, and the **photomultiplier**, an electronic processor that translates photon interactions with the crystal into electric energy.

1. Electric signals from the photomultiplier are processed by the **pulse height analyzer** before reaching a final form. Only signals in a specified energy range are incorporated into the interpreted images. The range recognized by the pulse height analyzer is adjustable and is established on the basis of the radiopharmaceutical used.
2. **Digitalization** of the single-crystal camera has greatly enhanced its performance.

B. A **multicrystal camera** works with an array of crystals with increased count detection capability. Because of the availability of an individual crystal to detect scintillation at any given time, this type of camera can be used to detect many more counts than can a single-crystal camera.

C. In the case of positron emission tomography (PET) scanning, a **positron camera** is a gamma camera used to detect the photon products of positron annihilation. Interaction between a positron and an electron causes annihilation, with the generation of two high-energy photons (511 keV) that travel in opposite directions.

1. An array of multiple concentric rings of crystals constitute a positron camera. Each crystal is linked optically to multiple photomultipliers. The crystals are oriented in diametric pairs in such a way that each pair of crystals must be struck simultaneously by annihilation photons to record activity. Background interference and stray photon energy are automatically accounted for, and artifact is limited.
2. Most positron cameras contain **bismuth germanate** for annihilation photon detection. The clinical utility and radiopharmaceuticals for PET are discussed in Section **X**.

V. MECHANICS AND TECHNIQUES

A. Image acquisition. Basic perfusion imaging can be performed by means of **planar** and **tomographic** techniques. The tomographic, or SPECT, method is the most commonly used today.

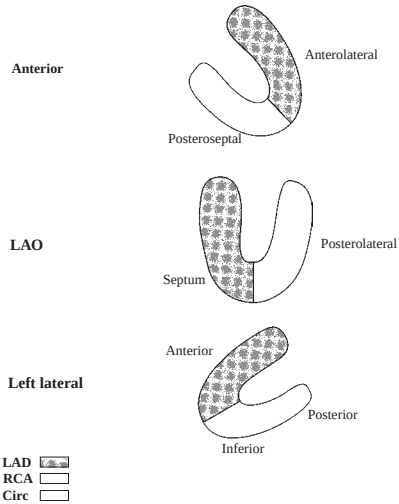

FIGURE 48.1 Standard planar views and vascular territories. Circ: circumflex artery; LAO, left anterior oblique; LAD: left anterior descending artery; RCA: right coronary artery.

1. **Planar images** are acquired in three views: **anterior, left anterior oblique (LAO)**, and **steep LAO** or **left lateral (LLAT) orientation** (Fig. 48.1). The patient is supine for anterior and LAO views but is placed in the lateral decubitus position for LLAT image acquisition. Although it allows examination of specific myocardial segments, planar imaging superimposes vascular distributions and therefore can compromise the ability to implicate a specific vascular supply when a defect is present. For example, normally perfused myocardial segments may overlap perfusion defects in a separate distribution.
2. Using **SPECT**, a series of planar images are usually obtained over a 180° arc to reconstruct a three-dimensional representation of the heart. The arc typically extends from the 45° right anterior oblique plane to the 45° left posterior oblique plane, with the patient in the supine position.
   a. Three orientations are analyzed in the final representation: **short axis, vertical long axis**, and **horizontal long axis**. A computer-generated display, the **polar map**, is also analyzed as a quantifiable representation of count density.
   b. Unlike planar imaging, **SPECT** can be used to **separate vascular territories** and improve image interpretation. SPECT, however, also **increases the time needed** for image acquisition and requires close attention to quality control issues.

B. Radiopharmaceuticals available for nuclear imaging include thallium 201, technetium 99m, and several positron imaging agents. Each possesses specific energy characteristics, kinetic profiles, and biodistribution (see below as well as Table 48.2 and Section **X** for further details).

1. **Thallium 201**
   a. **General characteristics.** Thallium 201 (i.e., thallous chloride) is a metallic element in group IIIA of the periodic table; it is produced in a cyclotron. Thallium emits gamma rays at an energy range of 69 to 83 keV and has a **half-life of 73 hours**. The biologic activity of this element is very similar to that of potassium; the ionic radii of the two elements are virtually identical. Thallium is actively transported into cells by the sodium–potassium adenosine triphosphatase (Na-K ATPase) pump.

TABLE 48.2 Characteristics of Common Perfusion Agents

Attribute	Thallium 201	Technetium 99m sestamibi	Technetium 99m tetrofosmin	Technetium 99m teboroxime
Energy (keV)	69–83	140	140	140
Dose (mCi)	2.5–3.5	20–30	20–30	20–30
Half-life (h)	74	6	6	6
Cyclotron required	Yes	No	No	No
Perfusion imaging	Yes	Yes	Yes	Yes
Viability evaluation	Yes	Yes	Yes?	No
Redistribution	Yes	Yes (minimal)	Yes (minimal)	Yes
Gating (electrocardiogram)	No	Yes	Yes	No

b. Kinetics. Approximately 5% of the administered dose of thallium 201 is distributed to the myocardium, proportionate to the blood flow delivered to the coronary circulation. Almost 85% of the thallium 201 is extracted by myocytes in the first pass.

(1) The **initial uptake** of thallium 201 by myocardium is directly related to regional blood flow. The myocardial extraction of thallium 201, however, increases at low flow rates (<10% of basal) and decreases at high flow rates (more than twice the basal rate).

(2) Washout. After initial uptake into myocytes, a state of continuous exchange across the cell membrane occurs. The distribution of this radiotracer changes after administration, and thallium 201 washes out from the myocytes, a process called **redistribution**. Thallium 201 washout generally approaches 30% at 2 to 2.5 hours after injection.

(3) Ischemic myocardium. Uptake of thallium 201 in ischemic myocardium is lower than uptake in nonischemic segments. Washout time from ischemic zones is slower than that from nonischemic zones.

(4) Over time, counts become equal in the ischemic and nonischemic regions (or thallium 201 concentration may increase in ischemic regions) so that thallium 201 concentrations in these disparate areas approach one another. This disparity is taken advantage of during thallium 201 viability imaging (described below).

2. Technetium 99m–labeled agents

a. General characteristics. Technetium 99m is a radiopharmaceutical that can be produced on-site in molybdenum 99–technetium 99m generators. It possesses several ideal imaging characteristics.

(1) Technetium 99m has a **half-life of 6 hours** and emits gamma rays with a single photopeak of 140 keV.

(2) Technetium 99m–labeled **perfusion agents** include ^{99m}**Tc-sestamibi**, ^{99m}**Tc-tetrofosmin**, and ^{99m}**Tc-teboroxime**. Although ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have similar properties, ^{99m}Tc-tetrofosmin may be less sensitive at detecting ischemic changes and its use for viability detection is less well validated.

b. Kinetics. After administration of ^{99m}Tc-sestamibi, approximately 40% to 60% of the agent is extracted by the myocardium. Initial uptake of the agent

is proportional to regional myocardial blood flow, and it is bound to the inner mitochondrial membrane. ^{99m}Tc-tetrofosmin has similar pharmacokinetics to ^{99m}Tc-sestamibi.

Myocardial washout of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin is very slow, and little redistribution occurs. The absence of redistribution requires two separate injections of the agent, at **rest** and at **peak exercise** (or with pharmacologic stress). This can be performed with a same-day or 2-day protocol.

VI. IMAGING PROTOCOLS

A. Thallium 201

1. **General features.** Stress imaging with thallium 201 involves **injection at peak exercise** (or with pharmacologic stress) and **immediate imaging**, followed by **redistribution images** 3 to 4 hours after injection.
   - **a.** Because of the long half-life of thallium 201 (i.e., 73 hours), to reduce the total radiation exposure to the patient, limited amounts are administered. Although a single injection is typically used because of the redistribution phenomenon, a second injection may be given to enhance the filling of reversible defects.
   - **b.** The low energy range of thallium 201 is marginal for imaging with the gamma camera because of scatter and diminished spatial resolution.
2. **Variations from standard protocol.** Exact imaging techniques vary among institutions. Initial thallium 201 doses range from 2 to 3.5 mCi, acquisition times vary from 20 to 40 seconds per image, and the number of images varies from 32 to 64 depending on whether 180° or 360° image acquisition is used.
   - **a.** The use of **360° versus 180° imaging** has been the subject of debate. With 180° tomography, contrast is better, there is less artifact, and imaging times are shorter. Slight variations also exist depending on the use of exercise stress testing or pharmacologic stress protocols.
   - **b.** When **exercise thallium 201 scintigraphy** is performed, the radionuclide (2 to 3.5 mCi) is usually injected approximately 1 minute before peak exercise to allow time for distribution. Initial images are obtained within 5 to 10 minutes of injection. Redistribution images are obtained 2.5 to 4 hours after the initial images.
   - **c.** In some cases, persistent defects that would ordinarily be interpreted as myocardial scar represent viable myocardium.
     - **(1)** For this reason, some advocate **delayed (late redistribution) imaging** 18 to 24 hours after injection. Some studies indicate that up to 40% of persistent defects exhibit radiotracer uptake after revascularization. Delayed imaging has resulted in further redistribution in as many as 45% of patients.
     - **(2)** Alternative approaches in **differentiating viable tissue from scar** include **rest reinjection** of thallium 201, in effect to boost fill-in of perfusion defects. As many as 50% of persistent defects have been shown to exhibit improved thallium 201 uptake after rest injection of 1 mCi of thallium 201, suggesting viability.
   - **d.** Minor changes in imaging protocol may be observed with **pharmacologic stress testing** with adenosine, regadenoson, dipyridamole, or dobutamine.

B. Technetium 99m.

The relative lack of redistribution requires **two injections** of technetium 99m to obtain rest and stress images.

1. **Basic protocols**
   - **a. Same-day protocol.** At peak exercise, 25 to 30 mCi of technetium 99m is injected. Rest images are obtained first, and stress imaging follows to minimize residual scintigraphic activity caused by the higher dose stress injection.

(1) **Rest images** are obtained with injection of 7 to 10 mCi of technetium 99m and image acquisition up to 1 to 1.5 hours later. Imaging is delayed because of slower liver clearance with rest injection.

(2) **Stress images** are obtained approximately 45 to 60 minutes after injection. Hepatic uptake of technetium 99m occurs within 15 to 30 minutes of injection, and the tracer is excreted into the gastrointestinal tract through the biliary system. Appearance of the tracer in the gastrointestinal tract can interfere with imaging of the inferior wall of the left ventricle.

b. The **separate-day protocol** allows time for decay of activity. Larger doses of technetium 99m can be administered for rest and stress images, and there is minimal interference between the images.

(1) Between 22 and 30 mCi of technetium 99m is injected for stress and rest imaging, separated by 1 to 2 days.

(2) The higher doses possible with the 2-day protocol produce increased count density and better image quality at the cost of inconvenience.

2. Factors that affect image quality. Consumption of a **fatty meal** can enhance biliary excretion of technetium 99m and improve image quality. Because of possible interference from noncardiac uptake, image processing with technetium 99m relies on normalization to the brightest cardiac pixel.

C. Dual isotope imaging. Use of both thallium 201 and technetium 99m substantially reduces the time required to obtain stress and rest images.

1. The patient receives thallium 201 at rest (3.5 mCi) and, immediately after rest imaging, undergoes stress. At peak stress, the patient is given an injection of 25 mCi of technetium 99m. Stress images are obtained 15 minutes later.

2. This technique makes use of the dissimilar energy levels of the two radionuclides to shorten the protocol while still allowing acquisition of ECG-gated images (because of the use of technetium 99m).

3. The sensitivity (91%) and specificity (75%) of this combination protocol are comparable to the values for conventional technetium 99m SPECT.

VII. STRESS PROTOCOLS

A. Exercise stress testing. Standard exercise testing (see Chapter 49) is frequently complemented with nuclear imaging. The radioisotope is injected at peak exercise, and time is allowed for circulation of the agents (usually at least 1 minute before termination of exercise).

B. For patients who are unable to exercise, **pharmacologic testing** is used in concert with nuclear imaging. Adenosine, regadenoson, and dipyridamole are vasodilators that are useful in noninvasive testing because of differences in coronary flow reserve. In the presence of marked coronary stenosis, the distal vessel is maximally dilated and therefore possesses little flow reserve.

1. Adenosine acts at several different receptors (A_1, A_{2A}, A_{2B}, and A_3) and thus has several physiologic effects. Its desired effect for the purpose of pharmacologic stress is to substantially enhance coronary flow in normal beds (i.e., normal flow reserve), although much less so in distributions supplied by a stenotic artery. The resultant disproportionate flow is the basis for heterogeneous radiotracer uptake.

a. Administration. Adenosine is infused at 140 μg/kg/min for 6 minutes. The radiotracer is injected after 3 minutes of infusion.

b. Side effects commonly experienced include chest pain, headache, nausea, and flushing. Atrioventricular block and bronchoconstriction are the result of effects on the A_1 and A_3 receptors, respectively.

2. Dipyridamole is an adenosine reuptake inhibitor, leading to increased extracellular concentrations of adenosine, and thus has very similar effects. It has a longer distribution half-life than adenosine, however, of approximately 25 minutes.

a. **Administration.** Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min). The maximum vasodilatory effect is achieved 4 minutes after completion of the infusion, and the radiotracer is injected at this point. A slight increase in heart rate (10 beats/min) and decrease in blood pressure (10 mm Hg) are frequently observed.

b. **Side effects.** Headache, nausea, chest pain, hypotension, dizziness, and flushing have been reported. Severe side effects may necessitate reversal of the dipyridamole effect with aminophylline, given as a 50- to 100-mg intravenous bolus.

3. **Regadenoson** is a selective A_{2A} receptor agonist that has been FDA approved for clinical use in myocardial perfusion imaging since 2008. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and 2—have demonstrated the safety of this agent in a total of 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.
   a. **Administration.** Regadenoson is given as a single 0.4 mg (in 5 mL) intravenous bolus and does not require adjustment for body mass index or renal or hepatic function. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes.
   b. **Side effects** of chest pain, headache, nausea, and flushing do occur with regadenoson. However, atrioventricular block and bronchoconstriction are far less common than with adenosine or dipyridamole, due to the lack of agonism of the A_1 and A_3 receptors with this A_{2A}-selective agent. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.
4. **Dobutamine** is an agonist of the β_1 and β_2 receptors and thus increases both heart rate and contractility (with a mild reduction in systemic vascular resistance).
   a. **Administration.** Infusion is begun at 5 μg/kg/min and increased every 3 minutes to a maximum dose of 40 μg/kg/min. The radiotracer is injected at maximum dose (or at 85% of age-predicted maximum heart rate), and the infusion is continued for 2 to 3 minutes.
   b. **Side effects** associated with dobutamine include ectopy, headache, flushing, dyspnea, paresthesias, and hypotension.

VIII. IMAGE INTERPRETATION

A. Standard view of normal anatomy. The uptake of radiotracer is homogeneous in persons with normal myocardial perfusion. The tracer is predominantly distributed to the left ventricle; the right ventricle usually appears as a faint, thin structure. Understanding and interpreting these images, however, requires an understanding of standard planar and SPECT views of LV anatomic features.

1. **Planar images** are represented as LAO, anterior–posterior (AP), and LLAT views.
2. Standard **SPECT views** include the short axis, vertical long axis, and horizontal long axis. The short-axis view is further divided into apical, midventricular, and basal views.
   a. As with planar views, SPECT images in various projections **correspond with specific myocardial segments** (Fig. 48.2).
   b. In addition to the standard SPECT sections, short-axis sections can be compiled into a so-called **bull's eye display** (i.e., **polar map**). This computer-generated polar map (i.e., "bull's eye" image) arranges short-axis tomographic images such that the central portion represents apical slices and the periphery consists of the basal segments.

B. Reviewing sequence. Review of nuclear images follows an organized sequence.

1. **Examine unprocessed images** for artifact, extracardiac uptake, and evidence of increased lung uptake.
2. **Compare rest and stress images** for enlargement of the LV cavity.

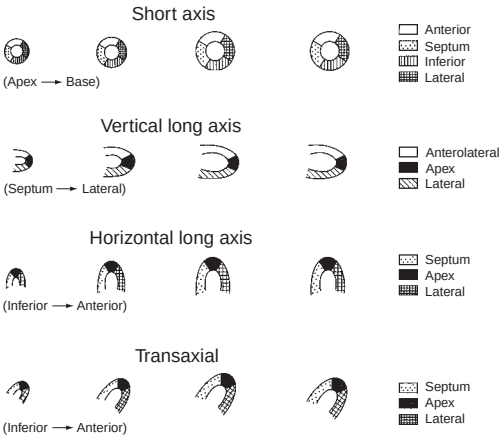

FIGURE 48.2 Standard tomographic projections and myocardial segments.

3. **Examine rest images.** Document fixed defects and the number of segments involved.
4. **Examine stress images.** Document defects and segments.
5. **Evaluate the polar map** in comparison with pooled normal images (derived from a database of patients with low probability of having CAD).
6. **Incorporate the gated SPECT images** to establish overall ventricular function and evaluate wall function in areas of questionable artifact. Segmental defects that demonstrate normal motion on gated SPECT images likely represent artifact.

C. **Characterization of defects.** Given that initial perfusion images represent regional myocardial blood flow, defects in these images represent an area of myocardium with relatively less uptake and diminished regional blood flow. Defects can be characterized as **fixed, reversible, or partially reversible** or as displaying **reverse redistribution**. (The term *redistribution* is not appropriately used in context with technetium 99m imaging.)

1. **Fixed defects.** Nonreversible or fixed defects are areas of absent tracer uptake that appear unchanged on both rest and stress images. Fixed defects can **represent scar or viable myocardium**. With thallium 201 imaging, nonreversibility suggests similar rates of clearance from the two regions.
   a. **Differentiating scar from viable myocardium** in the setting of a nonreversible defect can be accomplished through the use of **metabolic radiopharmaceuticals and PET, delayed imaging, or rest reinjection** with thallium 201. The level of tracer activity reflects viability. Severe deficits (<50% of normal counts) are less predictive of viability than are milder count deficits.
   b. Differentiating viable myocardium from scar is paramount because there is clinical and experimental evidence of improved LV function after revascularization of such hibernating regions (See Chapter 50). As methods of revascularization become increasingly applicable in an arena of increasingly complex patient problems, fully defining the so-called fixed defect through metabolic imaging assumes greater importance (see Sections **VIII.D.2** and **X.D**).
2. **Reversible defects** are present on initial stress images but resolve on rest or delayed images. This pattern is consistent with the presence of **ischemic myocardium** in the region of reversibility.

   a. In the setting of **thallium 201 imaging**, resolution of the defect is a function of variable tracer concentrations in ischemic and nonischemic segments, which approach one another as redistribution occurs, along with continuous exchange of myocyte and blood pool thallium 201. **Fill-in** of reversible defects on thallium 201 images can be enhanced by means of delayed imaging or rest reinjection.
   b. **Technetium 99m imaging**, which lacks redistribution, demonstrates reversibility on the basis of differential uptake during stress compared with rest.
3. **Partially reversible defects** are present on stress images and partially resolve on rest images but do not fill in completely. This type of defect is thought to reflect a **mixture of scar and ischemic myocardium**. Nonetheless, reversibility may be incomplete even in the absence of nonviable tissue and represent purely ischemic myocardium.
4. A pattern of **reverse redistribution** occurs when a defect appears larger on rest images or is absent on stress images but is present on rest images.
   a. Such a pattern is seen in the presence of **acute MI** when the infarct artery has been rendered patent through thrombolysis, percutaneous coronary intervention, autolysis, or another form of revascularization.
   b. The pattern is thought to reflect post-MI hyperemia with excess radiotracer uptake in a region of reperfused myocardium followed by accelerated myocardial washout of radiotracer in the defect region.
   c. The regions in question may demonstrate viability on PET imaging and do not indicate ischemia.
5. **Artifacts.** Apparent perfusion defects can be attributed to soft tissue attenuation, a problem that occurs more often with thallium 201 imaging than when a higher-energy agent (technetium 99m) is used.
   a. Common causes of the presence of artifacts include **breast attenuation** (affecting the anterolateral, septal, anteroseptal, and posterolateral walls of the ventricle) and **diaphragmatic attenuation** (predominantly altering the inferior and posterior walls).
   b. Planar images with perfusion defects seen in only a single view are suspect, and the presence of artifact must be considered.
   c. SPECT artifacts may be more elusive because of processing and reconstruction of tomographic images. However, with good technique, most are avoidable. When there is a suspicion for attenuation artifacts as above, **attenuation correction** processing techniques can be employed to account for these variables.
6. **High-risk perfusion scan.** Specific patterns of perfusion imaging that suggest high-risk coronary anatomic features include perfusion **defects in more than one vascular distribution, increased lung thallium uptake, and transient LV dilatation**.

D. Quantitative analysis. The principles of image analysis rely on visual inspection, which is fraught with observer variability.

1. **Computer-aided analysis** of planar data involves comparison of regional radionuclide activity on stress and rest images; count discordance coincides with reversibility. **SPECT** data are quantitatively analyzed by means of comparing count densities on short-axis images (displayed as a polar map) with normal count profiles. Although they improve sensitivity, these methods are **used in concert with visual analysis**.
2. **PET imaging**, although evaluated in large part in a visual manner, also possesses great clinical utility with the application of **quantitative analysis of myocardial perfusion and coronary flow reserve**. Moreover, significant advances have been made in the ability to quantify *absolute*—and not just relative—blood flow in different coronary vascular territories using PET imaging. On the basis of analysis of baseline blood flow and flow during vasodilator stress, this technique is

useful in revealing functionally important coronary lesions even in the presence of multivessel coronary disease.

The administration of adenosine, dipyridamole, or regadenoson should induce at least a twofold to threefold increase in coronary blood flow over baseline in a normal coronary vascular bed—but this "flow reserve" is not present in the setting of functionally significant epicardial coronary artery stenosis existing proximally to this bed (as discussed earlier in the chapter). Thus, relative differences in myocardial perfusion during hyperemia—which may not be appreciated on visual inspection—may be more precisely demonstrated with quantitative analysis of flow reserve. Furthermore, the ability to quantitate absolute myocardial blood flow regionally and globally may help surmount the difficulty in noninvasively diagnosing CAD in the setting of "balanced ischemia" from severe left-main or triple-vessel CAD.

IX. CLINICAL APPLICATIONS

A. Perfusion analysis

1. Detection of CAD

a. Sensitivity and specificity. Since the introduction of thallium 201 imaging in 1975, the utility of perfusion agents in the diagnosis of CAD has been well established. Quantitative planar imaging and SPECT demonstrate 90% or greater sensitivity.

(1) **Sensitivity** is affected by the number of vessels involved. Single-vessel disease is most likely to produce a false-negative finding. Multivessel CAD rarely produces a normal perfusion scan result. The **specificity** of planar imaging is 83% and that of SPECT is ~70%.

(2) In general, radionuclide imaging is best used to evaluate a population at intermediate risk for CAD. The choice of radionuclide agent seemingly has little effect on the accuracy of these techniques.

(3) The introduction of **PET**, however, has brought with it **advanced diagnostic accuracy**, with approximately 10% to 15% improvement over SPECT. The ability to detect CAD in a noninvasive manner offers numerous additional applications in risk stratification, prognosis, and imaging of acute infarction.

b. Causes of **false-positive** perfusion study results include attenuation defect, technical inadequacies, coronary vasospasm, anomalous coronary circulation, cardiomyopathy, conduction defects such as left bundle branch block, and recanalization of a thrombosed coronary artery.

c. Causes of **false-negative** perfusion study results include a submaximal exercise stress test, anti-ischemic medical therapy, collateral or overlap circulation, inaccurate interpretation of perfusion images or angiograms, acquisition of suboptimal images, presence of balanced coronary stenoses, and delay in stress imaging.

2. Risk stratification. In addition to indicators of higher risk taken from perfusion images, such as increased lung uptake, determinants in the assessment of risk are as follows.

a. Presence of reversible as opposed to fixed defects is associated with greater likelihood of cardiac events related to acute coronary syndrome at follow-up evaluation. This relation has clinical utility in a number of settings, including risk stratification after MI or in the preoperative setting. In one study involving patients who had had MI without complications, patients with single, fixed defects on thallium 201 images had a 6% cardiac event rate, compared with a rate of 51% for those with thallium 201 scans that indicated high risk of such an event.

b. Radionuclide **imaging abnormalities** have been identified as **independent predictors of subsequent infarction or death**. In general, the number of

abnormal segments identified on nuclear images can be seen as inversely proportional to survival rate. Normal findings on a nuclear perfusion study, however, suggest an excellent prognosis, with a yearly mortality rate <1% (in patients with a normal ejection fraction). The application of such prognostic information to the care of patients preparing for noncardiac operations reflects significantly on the patient's surgical risk and has an established role in preoperative evaluation and clearance. For this population, evidence of ischemia on perfusion images portends a higher risk of a perioperative cardiac event.

3. Myocardial perfusion imaging may aid in the diagnosis and risk stratification of patients with **acute coronary syndromes**.
   a. Patients with **chest pain of ill-defined origin** can be given an injection at rest of thallium 201 or technetium 99m. In the presence of true ischemia (i.e., without infarction), **reversible defects** are documented, and insight into **regional distribution of ischemia** and extent of myocardium involved is gained. The **absence of any perfusion defect with ongoing chest pain makes a diagnosis of angina less likely**.
   b. In the setting of **thrombolysis**, imaging with technetium 99m can provide important information about reperfusion or lack thereof. Injection of technetium 99m before initiation of thrombolysis captures a picture of hypoperfusion, which can, because of the extensive half-life, be imaged at a later time. Subsequent injections reveal the status of perfusion as the period after thrombolysis proceeds (i.e., persistent, large defect that represents failed reperfusion). Such applications in the setting of thrombolysis and in acute coronary syndromes have limited clinical utility because of the logistics of staffing and availability of radiopharmaceuticals.
   c. A further application that affects the arena of revascularization and management of ischemic syndromes involves **assessment of myocardial viability**.

B. Assessment of ventricular function. In addition to its use in perfusion analysis, radionuclide imaging can establish cardiac performance. Radionuclide-based assessment of ventricular function includes first-pass radionuclide angiocardiography and gated blood pool imaging.

1. **First-pass radionuclide angiocardiography** involves injection of a radionuclide and analysis as the agent passes through the central circulation.
   a. Technetium 99m–labeled agents are typically administered in bolus form, and scintigraphic data are recorded for 15 to 30 seconds after injection. Multicrystal cameras oriented in a straight anterior projection are used for detection of high count rates.
   b. This method of ventricular function analysis is more useful in evaluating **right ventricular function** than is gated blood imaging. In patients with **severe LV dysfunction**, the radiotracer may be dispersed, and proximal venous access and rapid administration may be necessary.
2. **Gated blood pool imaging**, also known as radionuclide angiography or MUGA, relies on ECG gating to correlate multiple individual images of the cardiac blood pool to specific phases of the cardiac cycle.
   a. The blood pool is labeled by means of removing a 2- to 3-mL sample of the patient's blood after the intravenous administration of stannous chloride. The sample is labeled with technetium 99m and reinjected into the patient intravenously. The stannous ions reduce the technetium, so they will not leak out of the tagged cells.
   b. A single-crystal gamma camera is used in the LAO, AP, LLAT, and sometimes left posterior oblique projections to obtain serial static images of the cardiac blood pool gated to the R-R interval.
   c. Because multiple cardiac cycles are averaged to obtain the final images, this technique is not optimal for evaluating regional wall motion. For many years, though, MUGA was considered a "gold standard" technique

for assessment of overall LV ejection fraction. Radionuclide angiography remains a well-validated and highly reproducible method of assessment of overall LV ejection fraction (and, importantly, retains this quality especially well at low ejection fractions). The use of this technique is diminishing in the current era of echocardiography and cardiac MRI.

3. **ECG-gated perfusion imaging.** Perfusion imaging with technetium 99m–labeled tracers produces sufficient count densities on individual images to allow ECG gating. The standard injection of 20 to 30 mCi of technetium 99m allows evaluation of **perfusion and function in a single study**. The *greatest* utility of ECG-gated perfusion imaging may be in elucidating perceived artifacts on perfusion images. For example, if a region has a perceived fixed perfusion defect, yet wall motion is normal in the same region, artifact becomes a more likely consideration as the cause of the filling defect.

   Comparison of this method with two-dimensional echocardiography in the evaluation of regional wall motion has shown good correlation between the two. This correlation is not applicable to stress echocardiography, however, because of the time lag from the period of stress to the acquisition of nuclear images.

X. POSITRON EMISSION TOMOGRAPHY.

PET has bolstered the evaluation of CAD by nuclear imaging techniques, both by improving blood flow imaging and by allowing evaluation of metabolic activity. Positron imaging agents can be divided into blood flow tracers and metabolic radiopharmaceuticals.

A. Blood flow tracers. A number of radiopharmaceuticals exist for the assessment of myocardial blood flow. They can be produced by a cyclotron or generator.

1. **Rubidium 82**, the most readily used blood flow tracer, can be generated on-site without the use of a cyclotron. Much like thallium 201, rubidium 82 is a potassium analogue that is actively transported into myocytes through the Na-K pump. **Uptake into myocardium** is proportionate to regional blood flow. Approximately 65% of the radiotracer is extracted at first pass. Because of a short half-life (76 seconds), rubidium 82–based imaging protocols can be used to assess myocardial blood flow rapidly (within 1 hour). However, the short half-life also precludes exercise stress PET imaging with this tracer.
2. Other perfusion agents include the cyclotron-produced **nitrogen 13 ammonia** (half-life 10 minutes) and **oxygen 15 water** (half-life 123 seconds). Image quality with **oxygen 15 water** is poor and requires extensive processing to subtract the blood pool. Rb 82 and ^{13}N-ammonia are the perfusion tracers that are used in clinical practice, with Rb 82 carrying the distinct advantage of requiring only a generator instead of a cyclotron. The image quality of ^{13}N-ammonia is excellent, although the impracticality of cyclotron production in most facilities is a limiting factor for this agent. For those facilities capable of ^{13}N-ammonia generation, however, it has the "upside" of a longer half-life than rubidium 82; thus, exercise stress cardiac PET imaging could be performed if desired.

B. Metabolic radiopharmaceuticals. Metabolic imaging with PET depends on the use of radiolabeled substrates of cardiac metabolism, largely in the form of [^{18}F] fluoro-2-deoxyglucose (FDG), carbon 11 palmitate, and carbon 11 acetate.

1. **FDG** is a glucose analogue used by ischemic myocardium because of a transition to alternative fuel sources in the hypoxic state. Ischemic myocardium diminishes the oxidation of long-chain fatty acids and increases the use of glucose as a secondary fuel source. FDG is phosphorylated to FDG-6-phosphate after transport across the cell membrane. FDG imaging therefore reflects myocardial use of exogenous glucose, and FDG is a widely used metabolic radiopharmaceutical. It has a half-life of 1.83 hours, which means it can be ordered on a daily basis by institutions that do not have an on-site cyclotron—making it the most commonly used metabolic PET imaging agent.

2. [^{11}C]Palmitate is taken up by myocytes, converted to acyl CoA, and relegated to triglyceride stores or β-oxidized to produce [^{11}C]carbon dioxide. The release of this product of β-oxidation is reflective of long-chain fatty acid oxidation in myocardium.
3. [^{11}C]Acetate is metabolized to [^{11}C]carbon dioxide after entering the tricarboxylic acid cycle. Measuring the production of [^{11}C]carbon dioxide in this setting correlates with myocardial oxygen consumption.

C. Protocols. Image acquisition with PET is similar to that with SPECT in that tomographic images are obtained in short-axis, horizontal long-axis (sagittal), and vertical long-axis (coronal) views. A positron camera consists of an array of crystals arranged in a circle. Unlike in SPECT, the camera remains stationary in PET.

1. The heart is localized with the patient's arms extended above the head. An **attenuation scan** is performed that allows the density of the surrounding thorax to be subtracted to leave only cardiac count activity. This performance of attenuation correction which makes **allowance for noncardiac interference** adds a great deal to the accuracy of PET.
2. After the attenuation scan, the **positron-emitting radiopharmaceutical is injected**, and **images are obtained** 2 to 5 minutes later. As mentioned earlier in the chapter, two photons are created by the annihilation of the emitted positron colliding with the nearest electron it meets in the tissue surrounding it. These two photons travel *exactly 180° apart* while the patient is lying in the circular scanner. This is an important concept because it means there is **no need for collimation**. The detector/analyzer merely has to "accept" the signal it receives only if a simultaneous signal strikes the detector directly across from it in the scanner. This *dramatically* improves the signal-to-noise ratio that can be achieved during imaging.
3. Metabolic imaging can be undertaken after flow imaging with the administration of 5 to 10 mCi of FDG. Tomographic images are typically obtained 30 to 50 minutes after FDG injection.

D. Patterns of perfusion and metabolic imaging. Specific patterns of perfusion and metabolic imaging are identifiable. For example, **normal flow–normal FDG (match)** indicates normal perfusion and normal metabolic activity. **Reduced flow with normal or increased FDG ("flow-metabolism mismatch")** demonstrates viability (i.e., hibernating myocardium). **Reduced flow–reduced FDG** identifies scar tissue.

E. Clinical applications

1. **Diagnosis of CAD.** Flow imaging with PET is highly sensitive and highly specific for the detection of coronary stenosis, approaching 93% for both.
   a. Higher-energy photons (511 keV), higher count densities, shorter half-life, and "built-in" attenuation correction place PET substantially ahead of SPECT in the accurate detection of CAD.
   b. As mentioned before, the ability to quantitate absolute blood flow regionally and globally may help improve the diagnosis of coronary ischemia in the setting of severe multivessel disease and balanced ischemia.
2. **Assessment of myocardial viability.** (see Chapter 50). The use of **PET with metabolic radiotracers is the standard for identifying viable myocardium**. The presence of a flow-metabolism mismatch, which indicates underperfusion in the presence of metabolically active myocytes, indicates hibernating myocardium. Revascularization of these zones as identified with PET has been shown to result in improvement in wall motion. This utility of nuclear imaging has found increasing application in the selection of patients for revascularization who have ischemic cardiomyopathy and heart failure with low ejection fraction.

ACKNOWLEDGMENTS: *The author would like to thank Drs. Jeffrey A. Skiles and Gregory Bashian for their contributions to earlier editions of this chapter.*

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CHAPTER 49

Michael P. Brunner

Stress Echocardiography

I. INTRODUCTION. Stress echocardiography (SE) is an **effective method of evaluating for myocardial ischemia**, based on the detection of **stress-induced regional wall motion abnormalities** (WMAs). Stressors include exercise, pharmacologic agents, and pacing. SE is used to **screen for coronary artery disease** (CAD), and it can help **identify the coronary vessels involved**. The accuracy of SE in the detection of significant coronary artery stenosis is 80% to 90%, which is superior to that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging. In patients with left ventricular (LV) dysfunction and documented CAD, SE can **differentiate viable myocardium from scarred myocardium**, which may help predict whether LV function will improve after revascularization. As a diagnostic test for CAD, **SE is safe and relatively inexpensive** and **can be rapidly performed by experienced hands**. However, interpretation of SE images remains primarily subjective and requires a considerable learning curve. SE can also be used to assess the severity of valvular disease, hypertrophic cardiomyopathy, and exercise-induced pulmonary hypertension. In addition, it provides important prognostic information after myocardial infarction (MI) and prior to noncardiac surgery.

II. PATHOPHYSIOLOGY

A. Exercise stress testing. Myocardial ischemia results from a mismatch between oxygen supply and demand. The ischemic cascade is illustrated in Figure 49.1. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than detected by the electrocardiogram (ECG) or the onset of symptoms, but usually after the onset of worsening diastolic function. Exercise can be performed with a treadmill or an upright or supine bicycle.

B. Pharmacologic stress testing. In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.

1. **Sympathomimetic agents.** Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an **increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload)**. Although a number of agents have been evaluated in combination with echocardiography, **dobutamine** is most widely used. Low-dose dobutamine has positive inotropic effects mediated through cardiac α_1 and β_1 receptors. At higher doses, it has positive chronotropic effects mediated through β_2 receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic wall motion, with only minimal effect on end-diastolic LV volume. It can be **combined with atropine** to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR).
2. A **vasodilator stress test** is performed with **dipyridamole** or **adenosine** infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (i.e., coronary steal) and into more normal coronary vessels. This may lead to wall motion abnormality in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE. Adenosine has fewer side effects than dipyridamole, owing to the former's shorter half-life. However, because of the shorter duration of action of adenosine, the echocardiographic findings tend to be less pronounced and of shorter duration, resulting in a lower sensitivity.

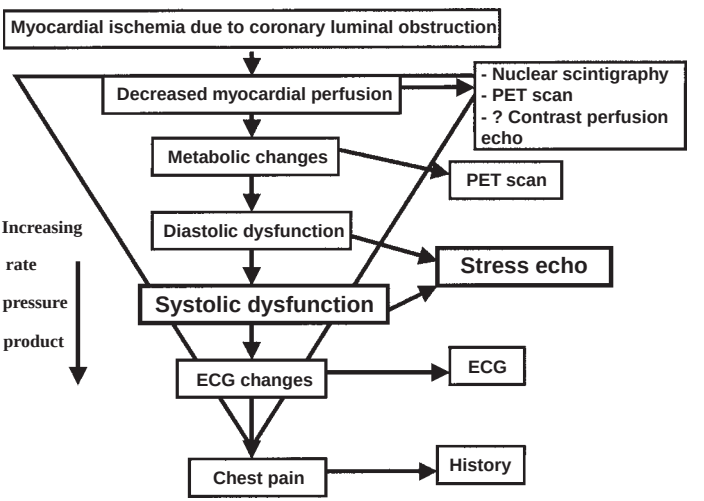

FIGURE 49.1 Ischemic cascade. PET, positron emission tomography; ECG, electrocardiogram.

3. **The 2007 American Society of Echocardiography (ASE) guidelines recommend dobutamine as the first-line agent for pharmacologic SE.** In addition, much of data for preoperative risk stratification and viability assessment using SE were derived from pharmacologic studies using dobutamine.

C. Atrial pacing. Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients that cannot exercise. In patients with a permanent pacemaker, stress is achieved by increasing the pacing rate until the target heart rate is reached. Transvenous and transesophageal pacing are considerations in patients without a permanent pacemaker.

III. INDICATIONS AND CHOICE OF STRESSOR

A. The **indications and contraindications** for SE testing are similar to those used for exercise electrocardiographic stress testing (see Chapter 47). The addition of an imaging modality improves the sensitivity and specificity of exercise electrocardiographic stress testing. Table 49.1 lists factors that may limit the sensitivity of electrocardiographic stress testing to detect CAD; patients with these factors benefit from a stress test utilizing an imaging modality (i.e., echocardiography, nuclear scintigraphy, or positron emission tomography [PET]).

B. **Additional contraindications** to SE occur **with pharmacologic stress** and depend on the underlying pharmacologic stressor. Patients with severe bronchospastic obstructive lung disease or high-grade atrioventricular (AV) block should avoid dipyridamole and adenosine. Patients with unstable ventricular arrhythmias should avoid dobutamine infusion. **Relative contraindications to SE** include unstable angina, severe baseline hypertension, uncontrolled arrhythmias, mobile LV thrombus, critical aortic stenosis (AS), hypertrophic obstructive cardiomyopathy, and decompensated heart failure.

C. Exercise stress is preferred over nonexercise stress because it more closely reproduces daily activity and is more sensitive in the detection of ischemia, provided the patient is able to achieve an adequate level of stress. No single **exercise modality** has been shown to have superior sensitivity, although the **treadmill** is more widely accepted among patients and physicians. **Bicycle ergometry** can be performed in the upright and supine positions. Images with treadmill stress testing must be obtained after exercise, whereas images may be obtained at peak exercise with bicycle ergometry while the patient continues to exercise. The sensitivity of treadmill testing to detect ischemia is reduced if images are not rapidly obtained (< 90 seconds) after exercise. However, the treadmill usually results in a greater level of stress than is associated with bicycle ergometry, which is more dependent on patient effort.

TABLE 49.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary Artery Disease

Left bundle branch block or other intraventricular conduction delay abnormalities
Paced rhythms
Abnormal ST segments at baseline:
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

D. Up to **30% of patients referred for exercise echocardiography may not be able to achieve an adequate level of exercise stress** because of peripheral vascular disease, chronic obstructive pulmonary disease, or musculoskeletal problems. **Pharmacologic stress testing is usually indicated** in these patients.

IV. METHODOLOGY

A. Patient preparation

1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly β-blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of the test results. If possible, these agents should be withheld before the stress test, unless the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia.
3. The **standard connections for a 12-lead ECG** may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results.

B. Equipment. All SE studies are conducted with **exercise electrocardiographic testing and standard hemodynamic monitoring equipment**. A SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of pre-stress images with peak stress or post–peak stress images. Resuscitation equipment and a defibrillator should be readily available.

C. Performing the test

1. **Exercise SE.** Regardless of the exercise modality, a quick, complete **baseline** echocardiographic scan is obtained for all patients. Resting images are obtained in the parasternal long- and short-axis and apical two- and four-chamber views and stored digitally. An apical long-axis view may be substituted for a parasternal long-axis view if the parasternal images are suboptimal. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.
   a. **Treadmill exercise** is performed with standard protocols according to the functional status of the patient. Exercise is continued until at least 85% of the APMHR is reached, but it is preferably continued to the level of maximum exertion to maximize test sensitivity. APMHR equals 220 – age. **Post–peak stress images** are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images in the same views as the baseline study are stored digitally and recorded on videotape. All post–peak stress images should be **obtained within 90 seconds of completing exercise** to maximize test sensitivity.
   b. During **upright bicycle echocardiography**, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. These images are recorded and digitized to allow comparable windows for the rest and peak stress images. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches his or her level of perceived maximal effort. During upright bicycle echocardiography, **images are obtained and digitized at rest, before peak, at peak, and after peak exercise**.
   c. With **supine bicycle exercise**, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are obtained and digitized **at rest, before peak, at peak, and after exercise**. This exercise modality is not widely used.
   d. **Study end points** for exercise SE include **target heart rate** (85% APMHR), **severe electrocardiographic ischemia** (ST-segment depression > 5 mm), **intolerable symptoms** (chest pain and dyspnea), **severe hypertension**

(systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg), **hypotension** (systolic BP < 90 mm Hg or a fall in systolic BP > 20 mm Hg from baseline), **ventricular tachycardia** or **sustained supraventricular tachycardia,** and the **development of new WMAs in at least two contiguous segments**.

2. **Pharmacologic SE**
   a. **Dobutamine SE**
      (1) **Dobutamine infusion** is started at 10 μg/kg/min and increased every 3 minutes to 20, 30, and 40 μg/kg/min. If the patient has not reached 85% of APMHR by the end of the 40 μg/kg/min dose, a 3-minute dosage of 50 μg/kg/min may be used. Infusion is begun at lower doses (5 μg/kg/min) if baseline LV function is abnormal and myocardial viability is being sought. Images are digitized at rest and at low dosage (5 to 10 μg/kg/min), pre–peak dosage (30 μg/kg/min), and peak dosage.
      (2) **Atropine** is used as needed to reach target heart rate > 85% of APMHR if dobutamine alone is not effective. Atropine (0.25 to 0.5 mg) is given intravenously every minute, starting at the 40 μg/kg/min dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients that have glaucoma or benign prostatic hypertrophy. Isometric handgrip may be performed at the peak infusion rate to help achieve target heart rate.
      (3) **Study end points** for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved without any other end points, it is preferable to complete the protocol to the end of the 40 μg/kg/min infusion to increase the sensitivity of the test.
      (4) **Side effects.** The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (e.g., arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of > 5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.
      (5) **If angina or severe side effects develop**, the effects of dobutamine may be **reversed with intravenous β-blockade** (0.5 to 1 mg/kg esmolol given over 1 minute or 2 to 5 mg/kg metoprolol given every 2 to 5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be preferable.
   b. **Dipyridamole or adenosine SE**
      (1) Patients with hypotension, AV block, or a history of severe bronchospasm **should not undergo** testing with these agents.
      (2) Different protocols of **dipyridamole infusion** have been studied. The protocol recommended by the ASE is a low-dose two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. **A high-dose** regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.
      (3) **Adenosine** is given as a continuous infusion because of its very short half-life. A typical protocol starts at a low dose of 80 μg/kg/min and is increased every 3 minutes by 30 μg/kg/min to a peak dose of 170 to 200 μg/kg/min.
      (4) **Regadenoson** is an adenosine receptor agonist with a 2 to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.

(5) **Study end points** for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (e.g., bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.

(6) **If hypotension, bradycardia, or bronchospasm occurs**, the effects of dipyridamole, adenosine, and regadenoson can be **reversed with intravenous aminophylline** 25 to 50 mg over 30 to 60 seconds.

D. Imaging techniques. Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame-by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor quality images. **Harmonic imaging** has improved endocardial definition, which can be further optimized with **microbubble contrast agents**.

1. **Contrast echocardiography.** Microbubble contrast agents provide **improved echocardiographic resolution** and allow **real-time assessment of intracardiac blood flow**. These agents are helpful when baseline SE images are suboptimal.
   a. **Intravenous agitated saline** improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. However, intravenous agitated saline is not able to cross the pulmonary circulation and opacify the left ventricle.
   b. **Second-generation microbubble contrast agents** such as **Optison** and **Definity** incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable, and are able to cross the pulmonary circulation and opacify the left ventricle.
   c. **These agents are well tolerated and have a low complication rate**. After initial concerns about safety, the FDA revised labeling requirements for second-generation contrast agents in 2008 and again in 2011. Patients with pulmonary hypertension or unstable cardiopulmonary conditions including acute coronary syndrome, worsening or unstable heart failure, serious ventricular arrhythmias, or respiratory failure no longer need to have their vital signs and oxygen saturation monitored for 30 minutes after injection. **Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts.** Intra-arterial injection is contraindicated.
2. **Real-time three-dimensional (3D) echocardiography.** Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. Three-dimensional imaging may shorten the acquisition period of post-exercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. However, 3D SE is not routine in clinical use and remains under investigation.

V. IMAGE INTERPRETATION

A. Qualitative versus quantitative approach

1. **Interpretation of SE findings is predominantly qualitative.** Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is **subject to interobserver and interinstitutional variability**. Suggestions to optimize interpretation of SE images are outlined in Table 49.2. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress-induced myocardial ischemia. SE responses and interpretation are summarized in Table 49.3.

TABLE 49.2 Suggestions to Optimize Interpretation of Stress Echocardiographic Images

1. Ensure that pre-stress and post-stress images are comparable views
2. Ensure that the apex is not foreshortened, especially in two-chamber views
3. True two-chamber views should not show any of the right ventricle
4. Use ultrasound microbubble contrast agents when resting images are suboptimal
5. Check that digital images are timed to begin at systole. If digital clips include diastole, there is an increased likelihood of calling a false-positive wall motion abnormality
6. Check the heart rate for each post-stress image. If images are obtained after the heart rate has returned toward normal, the sensitivity of the test will be reduced
7. Compare the wall motion of individual segments from rest to stress in the four-screen display to define ischemia and infarction. Then compare segments in the post-stress images to identify differences in contraction and in the development of "hinge points"
8. Confirm any wall motion abnormality in a second view if possible
9. Avoid overcalling ischemia in the basal inferior or basal septal segments
10. Avoid calling a new wall motion abnormality if it is limited to only one myocardial segment; the abnormality should involve at least two contiguous segments

TABLE 49.3 Stress Echocardiographic Responses and Interpretation

Resting or baseline function	Response to low-dose pharmacologic stress	Peak and post-stress function	Interpretation
Normal	Normal	Hyperdynamic	Normal myocardium
Normal	Normal or new WMA	New WMA or lack of hyperdynamic response; LV dilation or decreased EF (with exercise only)	Ischemic myocardium
WMA	No change	No change	Infarcted myocardium
WMA	Improved	Decreased (biphasic response)	Viable (hibernating) myocardium
WMA	No change	Improved	Nonspecific

WMA, wall motion abnormality; LV, left ventricular; EF, ejection fraction.

2. **Quantitative methods** of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, **the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use**. Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.
   a. **Tissue Doppler assessment** along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler

is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments.

b. **Strain rate** is a measure of the speed or velocity of regional myocardial contraction (time from QRS to the onset of regional myocardial relaxation). During dobutamine SE, strain rate increases (interval of time from QRS to myocardial relaxation decreases) in normal hearts and is reduced in areas of myocardial ischemia. The optimal cutoff for strain rate that gives the best sensitivity and specificity has been reported to be an increment of < 0.6 per second. Strain rate imaging is a reliable predictor of coronary stenosis, is **more specific** than visually assessed wall motion scoring, and may allow readers to detect intermediate severity coronary stenosis that produces only subtle WMAs.

B. 17-Segment model. Regional wall motion is assessed using a 17-segment model (Fig. 49.2), with results geographically represented on a circumferential polar plot (Fig. 49.3). A **16-segment model** had previously been utilized for SE, whereas a 17-segment model was utilized for other cardiovascular imaging modalities including magnetic resonance imaging, nuclear scintigraphy, and PET. In 2002, the American Heart Association (AHA) proposed that all tomographic cardiovascular studies utilize the 17-segment model to allow for standardized segmentation and nomenclature. The ASE recommended the 17-segment model in their 2007 SE guidelines.

1. The individual **myocardial segments can be assigned to coronary artery territories**, as illustrated in Figure 49.4. Of note, this approach makes assumptions that are not always correct due to anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent.
2. Wall motion is **subjectively graded** as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

C. Exercise SE

1. A **normal response** to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. **Resting WMAs** usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction, whereas hypokinetic segments may be partially infarcted or viable.
3. An **abnormal response to exercise is defined by the development or worsening of regional myocardial function**. Regional myocardial dysfunction, as **manifested by decreased endocardial excursion and wall thickening**, is **specific for myocardial ischemia**. Decreased excursion alone is less specific and can occur with conduction abnormalities and paced rhythms and in the normal basal inferior myocardial segments.
4. **Adjunctive diagnostic criteria** for a positive SE examination include **LV cavity dilation, a decrease in global systolic function diastolic dysfunction, and new or worsening MR**. However, these adjunctive diagnostic criteria are **more specific for detecting severe CAD and may not be sensitive** for detecting the presence of CAD.
5. **False-positive findings** may occur with left bundle branch block (septal WMA) and right ventricular pacing (apical WMA). A hypertensive response to exercise can cause LV dilation and systolic dysfunction.

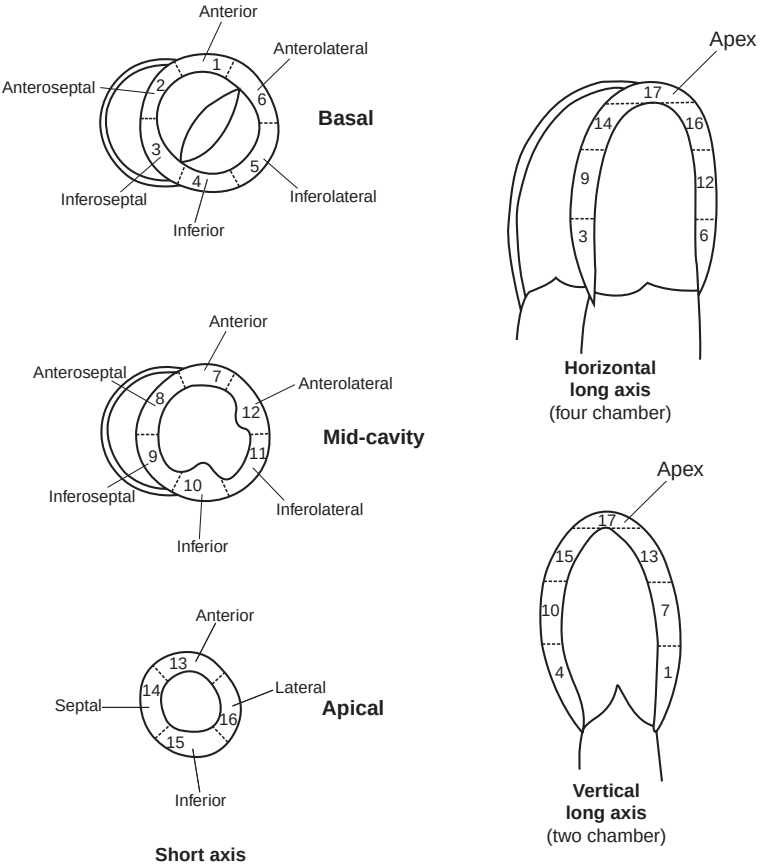

FIGURE 49.2 Diagram of vertical long-axis, horizontal long-axis, and short-axis planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the 17-segment system. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation.* 2002;105:539–542.

6. **False-negative findings** may occur with delay in capturing post-exercise images or low workload or heart rate response (i.e., inadequate stress). Additional causes of false-positive and false-negative findings are outlined in Table 49.4.

D. Pharmacologic SE. With only a few exceptions, the principles of interpretation of pharmacologic SE findings are similar to those used for exercise echocardiography.

1. The **typical ischemic response to dobutamine** is characterized by normal resting wall motion and an initial **hyperdynamic response at low doses followed by a decline in function at higher doses**. Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.

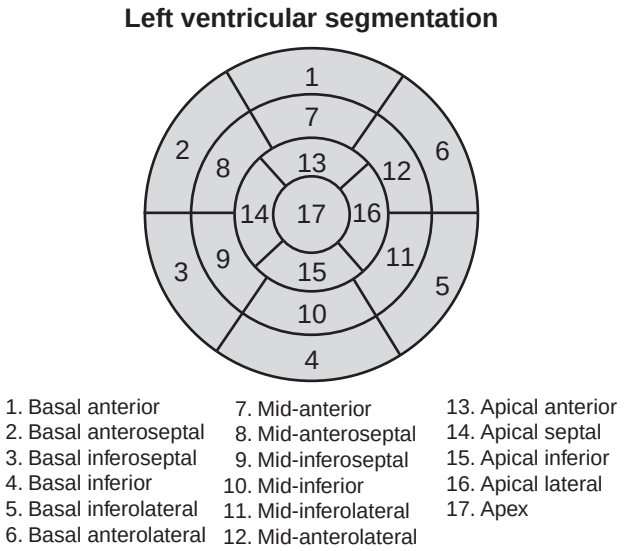

FIGURE 49.3 Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

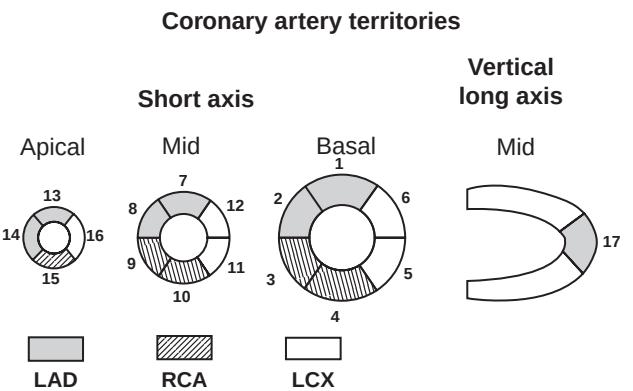

FIGURE 49.4 Assignment of the 17 myocardial segments to coronary artery territories. LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex coronary artery. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

TABLE 49.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of incorrect stress echocardiographic interpretation	Factors reducing specificity or sensitivity
False-positive results	
LBBB, prior cardiac surgery (e.g., myectomy)	Reduced or abnormal septal excursion with normal septal thickness
Right ventricular pacing	Apical WMA
Nonischemic cardiomyopathy	Regional WMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 220 mm Hg, DBP > 110 mm Hg)	Nonischemic WMAs and/or LV dilation
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; it is important to be blinded
Basal inferior or septal WMA	Areas most likely to be overcalled because of reduced excursion due to annular tethering effects
Poor image quality	
False-negative results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with β-blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Left circumflex disease	Lateral wall dropout; more likely to miss ischemia
Delay in capturing images after maximal stress	
Poor image quality	

DBP, diastolic blood pressure; LBBB, left bundle branch block; LV, left ventricular; SBP, systolic blood pressure; WMA, wall motion abnormality.

2. **LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE.** The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs due to severe CAD.
3. Interpretation of results obtained from **dipyridamole or adenosine SE** requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress.

E. Reproducibility. The person who interprets the images must be well trained to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be < 80%, particularly with technically difficult studies and studies of patients with mild CAD.

F. Limitations. The ability to interpret stress echocardiograms is mitigated by the image quality, the presence of arrhythmias, conduction abnormalities, respiratory

interference from hyperventilation, and difficulty in allowing for translational and rotational motion of the heart.

VI. DIAGNOSTIC ACCURACY. The **diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques**. Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, **sensitivity ranges from 75% to 92%, depending on lesion severity**, and **specificity ranges from 64% to 100%**. As with other imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease.

A. Exercise SE

1. **Comparison with exercise electrocardiographic testing.** Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, **SE has greater diagnostic sensitivity and specificity**, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade (Fig. 49.1). Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD (Table 49.1), and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.
2. **Comparison with myocardial perfusion scintigraphy**
   - **a.** Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (> 50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should theoretically have a higher sensitivity than SE for CAD.
   - **b.** Studies using **single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of > 90%, slightly higher than that for SE.** However, the **specificity of SE is superior to that of SPECT**, especially in cases with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses; the superior sensitivity of SPECT is balanced by the superior specificity of SE. The exception may be in women, where SE may be more accurate than SPECT, owing to less artifact from breast attenuation.
   - **c.** SE is **convenient** and **provides information on cardiac structure and function,** and **the results can be interpreted immediately**, with rapid feedback to the patient and referring physician. SE also **avoids exposure to radioactive tracers** and is substantially **less expensive than SPECT**.
   - **d.** SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients that have poor acoustic windows, for example, chronic obstructive pulmonary disease. **Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use**.

B. Pharmacologic SE

1. **Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%**, similar to the values for exercise SE. **Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%**. In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.

2. **Myocardial perfusion scintigraphy.** Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT.

VII. ASSESSMENT OF VIABILITY

A. Myocardial contractility ceases when 20% or more of the transmural thickness is ischemic or infarcted. Dobutamine SE can be used to detect **viable myocardium**, whether stunned or hibernating. **Myocardial stunning** after MI is common, and it is characterized by viable nonischemic noncontracting myocardium. Patients with **chronic ischemia** may experience **myocardial hibernation**. Hibernating myocardium is characterized by viable chronically ischemic noncontracting myocardium.

B. Dobutamine infusion may result in augmentation of regional myocardial function predictive of recovery of function after revascularization. This is important prognostically, as revascularization of hypoperfused but viable myocardium improves survival. A contractile response to dobutamine requires that at least 50% of the myocytes in a given segment are viable.

C. Demonstration of a **biphasic response** to low-dose (5 to 10 μg/kg/min) dobutamine strongly suggests viable myocardium. A biphasic response is present when a **resting WMA improves in response to low-dose dobutamine and decreases in function at peak stress or post-stress**. The initial improvement reflects recruitment of contractile reserve and hence viability. Higher doses lead to subendocardial ischemia and worsened WMA. A biphasic response predicts eventual functional recovery of the myocardium after revascularization. A uniphasic response is less predictive of recovery, and a classic ischemic response is not predictive of the recovery of resting function. Because the biphasic response is the most reliable finding, the preference is to induce ischemia whenever possible by proceeding to maximal stress (40 μg/kg/min).

D. **Myocardial wall thickness** is also an important marker of myocardial viability. When the wall thickness is **< 6 mm**, there is **a low likelihood of recovery of function**.

E. **The negative predictive value of dobutamine SE for determining viability is lower than that of thallium stress-redistribution-reinjection SPECT and Flourodeoxyglucose (FDG)-PET scanning**. However, **the positive predictive value is greater**. Concurrent use of β-blockers can reduce the number of viable segments detected and the sensitivity of testing.

F. **Assessment of myocardial perfusion with echocardiography.** Second-generation microbubble contrast agents are small in diameter and reliably traverse the myocardial microvasculature. The microbubbles are destroyed with ultrasound energy, and the rate of microbubble replenishment represents mean red blood cell velocity and myocardial perfusion. As contrast agents and detection algorithms improve, it is hoped that these techniques will allow real-time, noninvasive assessment of myocardial viability.

VIII. PROGNOSTIC ROLE OF STRESS ECHOCARDIOGRAPHY

A. **Suspected or known chronic CAD.** The **major determinants of prognosis** in patients with chronic CAD are **LV function and the anatomic extent and severity of myocardial ischemia**. SE is an excellent modality for the evaluation of both.

1. **Negative test result.** Perhaps the most important aspect of the prognostic literature is that **a negative test result portends an extremely low risk of subsequent cardiovascular events, as evidenced by an event rate of < 1%/y for the subsequent 4 to 5 years**. However, the risk is slightly higher in patients with diabetes or chronic kidney disease.
2. **Presence of ischemia.** Abnormal findings during SE indicate elevated risk for future cardiac events. Patients at intermediate risk for CAD who have abnormal SE findings have a 1-year cardiac event (i.e., MI, percutaneous coronary intervention, coronary

artery bypass grafting, or death) rate of 10% to 30%. However, this information needs to be integrated with other stress data (i.e., exercise capacity, hemodynamic responses to exercise, heart rate recovery, chronotropic index, Duke treadmill score, and the type and extent of WMA). Electrocardiographic changes and hypotension are relatively insensitive measures of ischemia during dobutamine SE. However, from the prognostic standpoint, the development of echocardiographic evidence of ischemia with dobutamine is analogous to its development during exercise.

3. **Presence of nonviable myocardium.** In patients with the same pretest probability of disease, those with evidence of nonviable myocardium during SE have higher rates of cardiac events than those with normal SE findings, but they have fewer events than those with evidence of ischemia during SE. Heart failure is a more common end point among the group of patients with nonviable myocardium.

B. Post–myocardial infarction. High-risk patients after acute MI are routinely identified by age, recurrent angina, LV failure, and shock. In addition, echocardiographic features predicting outcome after MI include LV ejection fraction, the extent of resting WMAs, inducible ischemia (detected as stress-induced WMA), and the amount of viable myocardium. All of these may be identified using SE, and several large studies (most with pharmacologic stressors) have gathered prognostic data using SE in patients post-MI.

C. Noncardiac surgery

1. Preoperative evaluation studies have been predominantly conducted with pharmacologic stress agents, primarily dobutamine. However, exercise SE should be considered if possible. A low ischemic threshold during stress (ischemia at heart rate < 70% APMHR) is the strongest predictor of perioperative cardiac events.
2. The predictive value of a positive test ranges from 7% to 25% for hard events (i.e., MI or death). The negative predictive value ranges from 93% to 100%. Only a few studies have compared SE and SPECT for the prediction of perioperative cardiac events. A meta-analysis concluded that the tests had comparable levels of accuracy, but the cost features weighted in favor of SE.

D. Cardiac transplantation. Transplant vasculopathy is a major cause of mortality after cardiac transplantation. Despite some promising data, SE appears to lack both sufficient sensitivity and specificity to be a viable alternative to routine angiography as a screening method.

E. Reading beyond wall motion. Important prognostic information can be obtained beyond traditional wall motion analysis. Ischemic heart disease may cause subclinical **diastolic dysfunction**. **Left atrial enlargement** correlates with the chronicity and severity of diastolic dysfunction. A normal resting left atrial volume index (< 28 mL/m^2) is strongly predictive of a normal stress echocardiogram. **Right ventricular dysfunction** is a significant predictor of events, independent of LV ischemia or ejection fraction.

IX. DIASTOLIC STRESS ECHOCARDIOGRAPHY

A. In many patients, "diastolic" heart failure is the dominant form of dysfunction, without any detectable systolic dysfunction at rest or during stress. The **transmitral peak early diastolic velocity (E)** and the **mitral annulus early diastolic velocity (e′)** are utilized to assess the diastolic dysfunction. In the presence of normal LV systolic function and volumes, an **E/e′ ratio > 15 suggests elevated LV filling pressure and diastolic dysfunction**, whereas a ratio < 8 excludes diastolic dysfunction. The primary utility of diastolic SE is to evaluate patients in whom diastolic dysfunction is suspected but the resting echocardiogram is indeterminate (i.e., E/e′ 8 to 15). Assessment for diastolic dysfunction should be completed during routine SE, as its presence and severity add to the negative prognostic value of resting or stress-induced systolic dysfunction.

B. Exercise or adrenergic stress normally results in improved myocardial lusitropy (relaxation) to allow for better filling in a shorter amount of time. The tachycardia associated with exercise results in an abbreviated diastolic filling period and an increase in the transmitral peak E velocity. In healthy patients, both the transmitral

peak E velocity and the mitral annulus early diastolic velocity increase with exercise, and the E/é ratio is not changed. However, **in patients with diastolic dysfunction, the mitral annulus early diastolic velocity is minimally affected by the change in preload caused by exercise and the E/é ratio increases**.

C. Assessment of diastolic dysfunction can be difficult at rest and is even more so with stress. Exercise SE is optimally performed using **supine bicycle ergometry**, as it allows for the acquisition of Doppler recordings during exercise. However, evaluation is routinely performed using treadmill exercise or dobutamine. Tachycardia may result in fusion of the transmitral E and A velocities at peak stress, making the tracings impossible to interpret. Therefore, Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery if possible.

X. STRESS ECHOCARDIOGRAPHY IN NONISCHEMIC CARDIAC DISEASE.

SE can be used to evaluate the functional significance of a variety of valvular lesions as well as hypertrophic cardiomyopathy. SE is especially helpful when there is a discrepancy between clinical symptoms and the assessment of valve severity at rest.

A. Aortic stenosis

1. Exercise testing is contraindicated (ACC/AHA class III recommendation) in patients with symptomatic AS. In asymptomatic patients, exercise testing may be considered (ACC/AHA class IIb recommendation) to elicit exercise-induced symptoms and abnormal BP responses.
2. Dobutamine SE is reasonable (ACC/AHA class IIa recommendation) in the diagnostic evaluation of patients with **low-flow/low-gradient AS**, defined as Doppler-derived aortic valve area < 1 cm^2 and mean gradients < 30 mm Hg. In these patients, **dobutamine is used to assess both the severity of AS and the presence of contractile reserve**.
3. In severe AS, low-dose (20 μg/kg/min) dobutamine infusion results in increased cardiac output with a parallel rise in the mean transvalvular gradient. Provided the calculated aortic valve area remains < 1 cm^2, **an increase in the mean transvalvular gradient to a value > 30 mm Hg or velocity > 3.5 m/s is consistent with severe AS**. If dobutamine infusion results in an increase in the valve area (typically to > 1 cm^2) with little change in the gradient, it is likely that LV dysfunction rather than AS is the critical problem, and aortic valve replacement is unlikely to be beneficial.
4. Dobutamine SE is also used to identify **contractile reserve** in patients with low-flow/low-gradient AS. Contractile reserve is defined as > 20% increase in stroke volume with dobutamine infusion. Lack of contractile reserve is associated with poorer prognosis with either medical or surgical therapy.

B. Mitral regurgitation. In asymptomatic patients with severe MR, exercise SE is reasonable (AHA/ACC class IIa recommendation) to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and severity of MR. SE can help predict latent LV dysfunction in patients with normal baseline LV systolic function, severe MR, and minimal or no symptoms. An increase in the LV cavity size or decrease in LV ejection fraction at peak stress suggests latent LV dysfunction and an increased risk of LV dysfunction after valve repair.

C. Mitral stenosis. Exercise SE should be performed (ACC/AHA class I recommendation) to assess the hemodynamic response of the mean gradient and pulmonary artery pressure in patients with mitral stenosis when there is a discrepancy among resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. An increase in the mean transmitral pressure gradient > 15 mm Hg and pulmonary artery systolic pressure > 60 mm Hg are indications to consider percutaneous valvotomy.

D. Hypertrophic cardiomyopathy. In patients with hypertrophic cardiomyopathy and high resting left ventricular outflow tract (LVOT) gradients, routine exercise testing is not performed owing to increased risks of arrhythmias and hypotension. Exercise SE provides valuable information, including exercise hemodynamics and the inducibility of LVOT, worsening of mitral regurgitation, and provocable

gradients in patients that are asymptomatic at rest. Although these patients may have only mild to moderately elevated resting LVOT gradients, using SE to identify elevated provocable gradients may help explain their exertional symptoms and quantify their exercise tolerance.

ACKNOWLEDGMENTS: *The author thanks Drs. Matthew Deedy, Patrick Nash, and Ryan Daly for their contributions to prior editions of this chapter.*

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CHAPTER 50

Arun Dahiya

Testing for Viable Myocardium

I. INTRODUCTION. Patients with left ventricular (LV) dysfunction secondary to coronary artery disease (CAD) have significant morbidity and mortality. Given the prognostic implications of poor ventricular function, it is imperative to identify any reversible myocardial dysfunction that may improve with revascularization.

II. DEFINITIONS

A. Viable myocardium is defined as myocardium that demonstrates abnormal function at rest and improves with revascularization.

1. From a pathophysiologic standpoint, chronically reduced perfusion leads to cellular changes that ultimately cause irreversible myocyte dysfunction.
2. Biopsies of myocardium reveal a spectrum of fibrosis and sarcomere loss that correlates with the likelihood of recovery of function. Several studies have found that once fibrosis is found in more than 35% of the myocardium, the likelihood of recovery of function is low.
3. **Stunning** refers to transient myocardial dysfunction, which is often caused by abrupt cessation of flow typical of an acute coronary occlusion.
4. Myocardial **scar** from cellular necrosis is irreversible and does not improve with revascularization.

B. Hibernation occurs when viable myocardium has altered its metabolism and thus reduced its contractile function as a mechanism to cope with chronically inadequate blood supply (chronic stable angina) or repetitive ischemic injury.

III. CLINICAL PRESENTATION. Ischemia, stunning, hibernation, scarring, and normal myocardium may coexist in the same patient. Unfortunately, clinical symptoms are unreliable in determining if a patient has viable myocardium, as often patients experience no symptoms in the face of considerable LV dysfunction and ischemia.

IV. TREATMENT OPTIONS. It has been demonstrated that revascularization of viable myocardium improves quality of life and survival. As medical and surgical technology improves in the field of cardiovascular medicine, it is important to accurately identify patients who will benefit from revascularization.

A. Thrombolytic therapy or emergency percutaneous revascularization is used in the setting of an acute thrombotic occlusion to restore normal blood flow and hopefully to minimize cellular damage.

B. Revascularization procedures, such as coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, may improve regional and global LV systolic function caused by significant CAD. The presence and extent of viable myocardium have been demonstrated as a marker for patients who will do significantly better with revascularization than with conventional medical care.

C. It is notable that patients with nonviable myocardium have similar outcomes with medical therapy as with revascularization.

D. Because not all patients benefit from revascularization procedures, the identification and referral of patients who will derive benefit are important to reduce costs and morbidity with the associated procedures. The goal, therefore, is to reliably identify patients who will benefit from revascularization and subsequently refer these patients for appropriate intervention.

V. TECHNIQUES TO ASSESS VIABILITY

(Fig. 50.1). Assessment of myocardial viability is indicated in patients with CAD and resting LV dysfunction who are eligible for revascularization. Coronary angiograms provide information about anatomy and feasibility of revascularization but do not predict recovery of function. Resting echocardiography provides information regarding overall LV function and segmental wall motion abnormalities but does not address recovery of function with revascularization techniques. Single photon nuclear imaging techniques (single photon emission computed tomography, SPECT), positron emission tomography (PET) with a metabolic agent, dobutamine echocardiography, contrast echocardiography, and, more recently, delayed-enhancement magnetic resonance imaging (MRI) have been identified as techniques that can distinguish viable myocardium from nonviable myocardium. Each technique exploits a separate property of dysfunctional myocardium to determine the potential for recovery of function after revascularization. The test that is used often depends on the strengths and preference of each medical center, although an approach based on the individual patient would be preferable.

A. Single photon emission computed tomography. SPECT is the most common technique used in the United States to identify viable myocardium. This technique has been successful because thallium 201 and technetium 99m radiopharmaceuticals act as perfusion agents that are only taken up by viable tissue. The long half-lives of these agents allow for regional distribution, which makes them feasible to use in medical centers without a generator or cyclotron. In addition, stress SPECT protocols (exercise or pharmacologic) are frequently used to assess for ischemia, which makes this technique cost-effective in a busy clinical center. Routine studies also include gated imaging analyses that provide further information regarding LV function and wall motion assessment, which are important in the evaluation of viability.

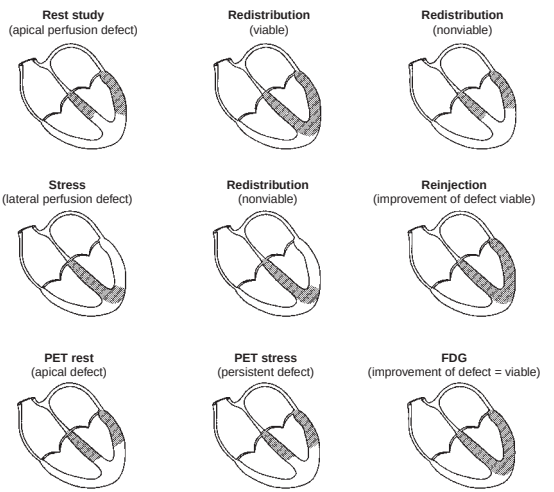

FIGURE 50.1 Viability testing.

FDG, 18F-fluorodeoxyglucose scanning

1. **Thallium 201** is a potassium analogue that utilizes the Na^+/K^+-ATPase active cellular transport system for concentration in cells and relies on intact cells. This characteristic of thallium makes it useful for the identification of viable cells as opposed to necrotic cells. Uptake of thallium is also dependent on regional myocardial perfusion.
   a. Thallium 201 has a relatively long half-life (73 hours), which means that a small dose (2 to 4 mCi) must be used. It emits x-rays from 68 to 80 keV (94% abundant) and γ-rays at 135 and 167 keV (10% abundant). There is a linear relationship between blood flow and uptake of thallium at rest, which is maintained with exercise making it as a reliable indicator of perfusion.
   b. **Redistribution** of thallium between the intracellular and intravascular spaces begins to occur after the first pass of thallium. It is recognized that with time, initial defects on thallium imaging improve. This is thought to be related to the accumulation of tracer in hypoperfused areas over time as well as rapid washout in normally perfused areas. On the basis of these principles, several protocols have been used to identify viable myocardium.
      (1) **Rest/redistribution thallium** imaging involves imaging 30 to 60 minutes after an initial injection followed by reimaging 4 hours later. Defects on the initial images that improve in 4 hours are considered to represent areas of viable myocardium. This protocol does not address ischemia and has been proven to be less sensitive for detecting viable myocardium than other protocols using thallium or PET with 18F-fluorodeoxyglucose (FDG).
      (2) **Stress/redistribution** imaging uses pharmacologic or exercise-induced stress with subsequent thallium injection and imaging, immediately followed by reimaging 4 hours later. Myocardium that is not perfused with stress or rest is considered to be scar. Myocardium that has a defect with stress but that improves on rest images is considered to be ischemic and viable. This protocol can identify ischemic viable myocardium, but it also shows lower sensitivity than other protocols, as many of the defects that do not improve at 4 hours may contain viable tissue. Imaging 24 hours after stress in a search for "late redistribution" improves sensitivity in the detection of viability but has low specificity and may be inconvenient. However, blood levels of thallium 201 may still be too low to be redistributed and picked up by viable myocardium. This led to the development of reinjection protocols mentioned later in this chapter.
      (3) **Stress/redistribution/reinjection** protocols involve the reinjection of 1 mCi of thallium with subsequent reimaging of the patient. This protocol is designed to increase the sensitivity by increasing the blood levels of thallium. It was shown that 50% to 70% of "scarred myocardium" after 4-hour redistribution imaging was actually viable, as demonstrated by this technique. Typically, reinjection of thallium and repeated imaging is performed immediately after the redistribution images or several hours after the initial stress images, followed by redistribution imaging 18 to 24 hours later. Sensitivity does not differ significantly between these two techniques. Scar is considered to be myocardium that has a defect on the stress images and does not improve upon reinjection and reimaging. Viable myocardium is indicated by uptake of tracer on reinjection in segments where no uptake occurred with stress.
2. **Technetium 99m–labeled radiopharmaceuticals** rely on mitochondrial function, sarcolemmal integrity, and intact energy production pathways for cellular accumulation.
   a. **Technetium characteristics.** Technetium 99m compounds have a shorter half-life (6 hours) than thallium, which allows for the administration of

larger doses (10 to 30 mCi), depending on the compound. Technetium 99m emits γ-rays at 140 keV. The commonly used agents include Tc 99m sestamibi, Tc 99m tetrofosmin, Tc 99m teboroxime, Tc 99m furifosmin, and Tc 99m NOET (bis(*N*-ethoxy, *N*-ethyl dithiocarbamato)nitrido).

b. Redistribution of technetium compounds is significantly less than that for thallium, making it relatively unhelpful as an aid in detecting viability.

3. Quantitation of SPECT imaging has been found to be a more accurate method to identify high- and low-risk populations than qualitative analysis. Quantification of perfusion has been proven to be an accurate predictor of recovery of function and superior to qualitative measurements at providing clinically useful information about future risk.

4. Diagnostic accuracy

a. Multiple studies have been performed comparing the various thallium protocols versus PET with FDG as the gold standard. Typically, sensitivity improves as one goes from redistribution to reinjection/redistribution and finally quantitative analysis of reinjection/redistribution. Semiquantitative analysis of stress/redistribution/reinjection has good concordance with PET.

b. In the prediction of functional improvement after revascularization, rest/redistribution thallium scans (sensitivity 90% and specificity 54%) and stress/redistribution/reinjection thallium scans (sensitivity 86% and specificity 47%) have been found to be less reliable. Regions that demonstrate < 60% regional thallium uptake on redistribution have a very low chance of recovery.

c. Unfortunately, attenuation and patient artifact frequently make SPECT thallium images difficult to interpret. In addition, methods for quantification have not been standardized across medical centers.

d. Quantification of sestamibi has compared favorably with that of thallium, with redistribution in the prediction of recovery of function after revascularization. Several other technetium compounds used for the assessment of viability have been tested (Tc 99m tetrofosmin, Tc 99m teboroxime, Tc 99m furifosmin, and Tc 99m NOET). None of these other agents has had significant use except for ^{99m}Tc-NOET, which has similar redistribution kinetics to that of thallium and may be a useful agent in the future. Sestamibi has a limited role in viability assessment owing to its cost.

B. PET in conjunction with a metabolic agent, usually FDG, has been considered the gold standard for assessment of myocardial viability. PET uses positron-emitting isotopes capable of releasing two high-energy (511 keV) photons at an angle of 180° from each other. The PET camera can detect these higher energy rays through coincidence counting. As a result, PET provides higher temporal and spatial resolution than SPECT, which translates into a higher quality image. Additional features of PET include quantification of the following:

1. Practical issues, including the cost of a PET camera and the short half-life of the several of the cyclotron-produced radiotracers, limit the use of PET to specialized medical centers.

2. Unlike SPECT, PET uses separate agents to measure perfusion and viability.

3. Perfusion agents commonly used in PET imaging include rubidium 82, nitrogen 13 ammonia, and oxygen 15 water.

a. Rubidium 82 is a generator-produced potassium analogue that relies on intact cellular functioning for its uptake and distribution. Hence, rubidium 82 is washed out of necrotic cells and trapped in viable cells.

b. Nitrogen 13 ammonia is cyclotron-produced radiotracer and also relies on intact cellular functioning for its uptake and distribution. This is the most commonly used perfusion agent in PET, and it can be used to quantify blood flow and assess for myocardial viability.

c. **Oxygen 15 water** is a freely diffusible agent that has been used to quantify blood flow. Blood flow < 0.25 mL/g/min within a region of myocardium is correlated with regions of scar. Unfortunately, intermediate blood flow ranges have not been reliable in predicting recovery of function, which makes this technology less useful for quantifying viability. Oxygen 15 water has also been used to create a perfusable tissue index that has been shown to improve the accuracy in the assessment of viable myocardium but has not been utilized by many centers.

4. **Metabolic agents** used in PET include FDG, carbon 11 acetate, and carbon 11 palmitate. **FDG** (cyclotron-produced) has the most clinical data to support its use. It has a long half-life, which makes its transportation to regional medical centers more practical. FDG is taken up by viable cells and then phosphorylated so that it cannot be metabolized further. This effectively traps FDG in the myocardium. In normal myocardium, free fatty acids are preferentially used. During periods of ischemia, metabolism is altered so that primarily glucose is utilized. The limitation of FDG has been in diabetics with impaired cellular uptake of glucose, where approximately 10% of studies are difficult to interpret owing to poor tracer uptake.
5. The combination of perfusion and metabolic tracers gives three possible interpretations:
   a. Normal perfusion is indicative of viability on its own and does not require specific assessment of metabolism.
   b. Reduced perfusion in myocardial segments with intact metabolic function as evidenced by the uptake of FDG is termed flow–metabolism mismatch and is indicative of hibernating, viable myocardium (Fig. 50.2).
   c. Impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar (Fig. 50.2).
6. **Diagnostic accuracy.** PET-FDG and cardiac MRI are considered the most reliable tests of myocardial viability. Image quality with PET is better than that with SPECT, and myocardial metabolism may be assessed directly with FDG. The sensitivity and specificity of PET in predicting functional improvement in myocardial segments after revascularization are 71% to 100% and 38% to 91%,

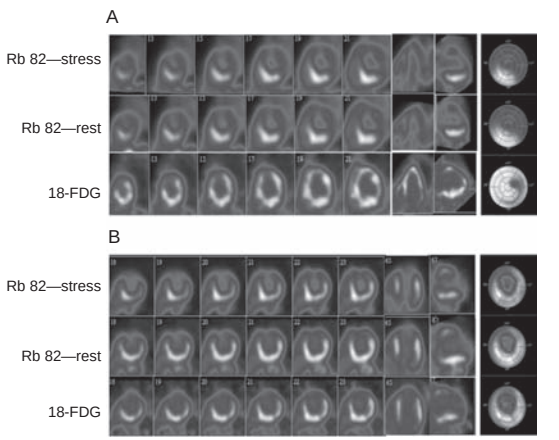

FIGURE 50.2 Rubidium PET followed by FDG PET: Patient **A** showing metabolism mismatch and is indicative of hibernating, viable myocardium. Patient **B** showing impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar.

respectively. PET has been shown to predict low surgical risk in patients with LV dysfunction and viability, improvement in exercise capacity with revascularization, and benefit from revascularization over medical therapy.

C. Dobutamine echocardiography has proven to be a reliable predictor of recovery of function after myocardial revascularization.

1. **Protocol.** Viability studies with dobutamine echocardiography use low doses of dobutamine starting as low as 5 μg/kg/min and slowly increasing the dose at 3-minute intervals up to 40 μg/kg/min for the development of other end points, such as target heart rate and symptoms. Imaging is performed throughout the study at each level of dobutamine infusion. Accurate, consistent results are contingent on the acquisition of excellent images for interpretation and on an experienced reader to interpret the study.
2. **Pathophysiology.** Dobutamine echocardiography exploits the inotropic effect of dobutamine at low doses on viable myocardium. This improvement in function and wall thickening is referred to as contractile reserve. In viable myocardium, with increasing doses of dobutamine, myocardial oxygen consumption increases, and ischemia develops with worsening of wall motion abnormalities. Therefore, in viable myocardium a segment with reduction in wall thickening at rest demonstrates an improvement or even normalization of wall thickening upon infusion of low-dose dobutamine. At higher doses of dobutamine, wall thickening deteriorates and may revert to the baseline level or may be even more severely reduced than at baseline. This **biphasic response** during dobutamine echocardiography is thought to be the most specific sign of dobutamine echocardiography for predicting improvement in function in myocardial segments with revascularization and indicates segments with underperfused but viable tissue. Myocardial segments with impaired contraction at rest that do not improve upon infusion of dobutamine are considered to be scarred (nonviable). Those segments with impaired thickening at rest that show improvement in thickening upon dobutamine infusion but that do not show deterioration in thickening at higher doses of dobutamine infusion are considered to have a **uniphasic** response. A uniphasic response is seen in the setting of myocardial damage with subsequent reperfusion (i.e., an open artery without a flow-limiting stenosis) and is much less predictive of improvement after revascularization.
3. **Diagnostic accuracy.** Dobutamine echocardiography has good specificity for the detection of viability. Part of the high specificity is derived from the fact that echocardiography is the most common method of assessing postoperative improvement. In addition, improvement of hypocontractile myocardium in response to low-dose dobutamine is the defined end point that revascularization is trying to achieve, although it is less sensitive than cellular metabolic function as a marker of viability. Sensitivity and specificity for recovery of function are 84% and 81%, respectively.
4. **Limitations** of dobutamine echocardiography include difficulty in obtaining images in patients with poor ultrasound windows, interobserver variability, even among expert readers, provocation of ventricular arrhythmias with testing, and reduced sensitivity in comparison with nuclear imaging.

D. Cardiac MRI. Delayed-enhancement MRI using gadolinium-based agents given intravenously (0.2 mmol/kg) has been shown to reliably distinguish infarcted from viable myocardium. Unlike SPECT-based techniques, MRI poses no risk of ionizing radiation exposure.

1. **Pathophysiology.** Gadolinium-based contrast agents are extracellular compounds that, when injected intravenously, pass quickly through normal areas of myocardium. In scarred tissue, the interstitial space between collagen fibers is larger than in normal myocardium, causing a delayed "wash-in" of gadolinium contrast. The gadolinium then remains trapped in the scarred tissue, causing

a longer "washout" of gadolinium from the infarcted or fibrotic myocardium. Delayed-enhancement MRI takes advantage of this delayed wash-in and washout of gadolinium to detect fibrotic or scarred myocardium, which appear as hyperenhanced (bright) areas of myocardium on images taken 10 to 20 minutes after contrast injection.

2. In patients with ischemic heart disease, scarred or nonviable myocardium occurs in a coronary artery distribution. Scarring typically begins at the subendocardial surface and extends outward at a variable distance toward the epicardium. The **transmural extent of hyperenhancement** on delayed-enhancement images is then used to determine the viability of each myocardial segment. Segments with **0% to 25% transmural extent of hyperenhancement represent viable tissue** with mostly normal myocardium and minimal fibrosis. **Segments with 75% to 100% transmural extent of hyperenhancement represent scarred, nonviable myocardium**. Segments with 25% to 75% transmural extent are said to have intermediate viability, although in clinical practice the amount of viable tissue in adjacent myocardium is often taken into account when classifying these intermediate segments. Finally, the amount of hyperenhancement within a region can be correlated with segmental wall function and rest/stress perfusion to determine ischemia and viability.
3. The absence of significant hyperenhancement has been shown to correlate well with improvement in function, whereas hyperenhancement of more than 75% has been correlated with irreversible injury. Of interest to note, the mean transmural extent of hyperenhancement that predicted irreversibility was 41 ± 14% by MRI, which correlates with a biopsy series wherein 35% fibrosis predicted similar lack of improvement after revascularization (Fig. 50.3).
4. **Diagnostic accuracy.** Studies comparing different imaging modalities for viability have shown superior sensitivity and specificity for MRI compared with SPECT and similar sensitivity with slightly improved specificity compared with PET. The main advantage of MRI is its ability to delineate the transmural extent of infarction, owing to its better spatial and contrast resolution. The pattern of hyperenhancement on MRI can also be used to identify nonischemic causes of cardiomyopathy.
5. **Limitations.** MRI is generally contraindicated in patients with implanted ferromagnetic objects (e.g., pacemakers, implantable cardioverter–defibrillators [ICDs], and ferromagnetic cerebral aneurysm clips), although some centers will image selected patients with permanent pacemakers/ICDs under careful electrophysiologic evaluation. Gadolinium is contraindicated in patients with chronic kidney disease (glomerular filtration rate < 30 mL/min), particularly in those

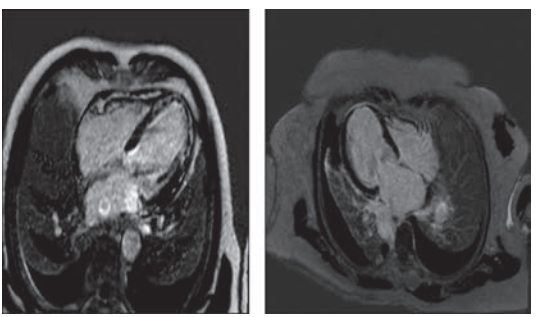

FIGURE 50.3 Late gadolinium-enhanced MRI: Both patients **A** and **B** have extensive akinesia in LAD territory; however, patient **A** has more extensive scar (> 50% in multiple segments) than patient **B** and is less likely to have LV function recovery post revascularization.

undergoing dialysis, owing to a small but important risk of nephrogenic systemic fibrosis (see Chapter 51). Finally, image quality may be compromised in patients unable to comply with breath-holding for the study (10 to 12 seconds each) and severe claustrophobia, as well as in patients with arrhythmias or frequent ectopy.

VI. CHOICE OF TECHNIQUE. Cost, clinical expertise, and access to radioisotopes are all issues that affect the appropriateness of each imaging technique. SPECT thallium and dobutamine echocardiography are significantly less expensive than PET and MRI, but they require significant clinical experience for appropriate data collection and interpretation. Both PET and cardiac MRI are robust techniques for the assessment of viability, but their use may be limited due to cost and availability, and, for MRI, the presence of patient's contraindications to MRI. The choice of technique is ultimately determined by local expertise and access to the appropriate technology. The recently published STICH (Surgical Treatment for Ischemic Heart Failure) viability trial failed to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to mortality. These findings are most likely explained by improved modern-day medical therapy; however, there were several limitations of this trial which should be noted. Although the main STICH trial was a randomized controlled trial, the STICH viability substudy was not randomized. It was an observational study on almost half of all the main STICH trial patients who managed to get a viability study. Furthermore, viability testing in the trial was performed by using SPECT, thallium, and dobutamine only, and more robust techniques of cardiac MRI and FDG PET were not used.

VII. WHO SHOULD GET A VIABILITY TEST? Patients who are most likely to benefit from viability testing (preferably by cardiac MRI or FDG PET) are those with high operative risk, where presence or absence of viability may influence the management strategy. Viability can also be useful in choosing the optimal revascularization strategy (PCI vs. CABG) in patients with multivessel disease. Viability testing should not be performed in patients where it is unlikely to change management, such as in a young patient with angina, good distal target vessels, and minimal comorbidities.

ACKNOWLEDGMENTS: *The author thanks Drs. Anne Kanderian, Benjamin Atkeson, and C. Patrick Green for their contributions to earlier editions of this chapter.*

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CHAPTER 51

João L. Cavalcante

Cardiovascular Magnetic Resonance Imaging

I. INTRODUCTION. Cardiovascular magnetic resonance imaging (CMRI) has undergone rapid developments over the last two decades and is now an important imaging technique of the heart and great vessels. Advantages of CMRI include its large field of view, high spatial and temporal resolution, and ability to do tissue characterization. In contrast to nuclear imaging and cardiac computed tomography (CT), magnetic resonance imaging (MRI) does not involve exposure to ionizing radiation. Applications of CMRI include acquisition of anatomic-quality still and cine images of the heart and great vessels in multiple planes, precise measurement of cardiac chamber volume and function, assessment of myocardial perfusion and fibrosis, quantification of blood velocity and flow, and noninvasive magnetic resonance angiography (MRA). As CMRI is not a "push-button" technique, clear communication between the ordering physician and the imaging staff is important, indicating the reason for the CMRI examination so that adequate pulse sequences and imaging planes are obtained aiming to answer the desired clinical question.

II. INDICATIONS. Common indications and components of the CMRI evaluation are listed in Table 51.1.

III. CONTRAINDICATIONS. Contraindications to CMRI are listed in Table 51.2.

IV. BASICS OF CARDIAC MRI

A. MRI Physics. Hydrogen is the most abundant atom in the body, and it is the excitation of hydrogen nuclei, often referred to as protons, that forms the basis for clinical MRI. Atoms behave like tiny bar magnets, aligning parallel to an external magnetic field while wobbling about the magnetic field at a certain frequency (precessional frequency) that creates the longitudinal magnetization. Application of a short radiofrequency (RF) pulse with the same precessional frequency as that of the atomic nucleus will cause excitation or resonance of the nucleus, temporarily changing its alignment within the magnetic field (transverse magnetization). However, this is an unstable state of higher energy. As the RF pulse is switched off, the spins quickly return to their resting state, i.e., aligned with the field, as this is energetically

TABLE 51.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications

Indication(s)	Applications
Aortic disease	Aortic aneurysm morphology and size; acute aortic pathology (dissection, intramural hematoma, penetrating ulcer); coarctation of the aorta; branch vessel disease; evidence of vasculitis; postoperative graft stenosis, infection, or leak; assessment for aortic regurgitation or other associated pathologies
Ischemic heart disease	Ventricular volumes and function; myocardial scar and viability; quantification of mitral regurgitation; assessment for LV aneurysm, thrombus, VSD, and other complications
Nonischemic cardiomyopathies	Ventricular volumes and function; myocardial wall thickness; LV outflow tract obstruction in hypertrophic cardiomyopathy; presence and patterns of myocardial scar/fibrosis; assessment for myocardial iron deposition in suspected hemochromatosis; quantification of mitral regurgitation; evaluation for ARVD in patients with ventricular arrhythmias or syncope
Pericardial disease	Pericardial effusion; pericardial thickening with or without calcification; pericardial tethering; signs of constrictive physiology including conical/tubular deformity of the ventricles, diastolic septal bounce, early cessation of diastolic filling, and dilated IVC
Congenital heart disease	Anatomic definition; ventricular volume and function; valve morphology and function; shunt calculation; assessment for anomalous origin of the coronary arteries; anomalies of the aorta, pulmonary arteries, and systemic and pulmonary veins
Valvular heart disease	Valve morphology; regurgitation and/or stenosis etiology and severity; ventricular size and function
Cardiac masses	Size and extent of mass; tissue characterization
Pulmonary veins	Pulmonary vein anatomy and stenosis; cardiac anatomy and function

ARVD, arrhythmogenic right ventricular dysplasia; IVC, inferior vena cava; LV, left ventricular; VSD, ventricular septal defect.

TABLE 51.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

Specific devices	Special issues
Cerebral aneurysm clips	Certain cerebral aneurysm clips pose a danger due to potential for displacement when exposed to a magnetic field. Aneurysm clips classified as "nonferromagnetic" or "weakly ferromagnetic" are safe.
Cardiac pacemakers and ICDs	The presence of a pacemaker/defibrillator is a strong relative contraindication to MRI owing to several potential problems, including (1) movement, (2) malfunction, (3) heating induced in the leads, and (4) current induced in the leads. In addition, artifact from the leads will often cause significant image degradation.
	FDA has recently approved the first MRI-safe pacing system (Revo MRI by Medtronic, Inc.) that allows patients to undergo, for example, brain and knee MRI scans. Currently it is not safe for the area of coverage to include the chest, although ongoing work is being done toward that goal.
Cardiovascular catheters	Catheters with conductive metallic components (e.g., pulmonary artery catheters) have the potential for excessive heating. Hence patients with such devices should not undergo MRI.
Cochlear implants and hearing aids	Most types of implants employ a strong magnet or are electronically activated. Consequently, MRI is contraindicated because of potential injury or damage to the function of these implants. External hearing aids can and should be removed before the MRI procedure.
Intravascular coils, stents, and filters	These devices typically become incorporated securely into the vessel wall within 6–8 wk after implantation; hence, most are considered MRI safe. However, specific information on the type of device should be obtained before MRI is planned (www.mrisafety.com). Intracoronary stents have been shown to be safe during MRI, even when performed on the day of implantation, although many stent manufacturers recommend waiting 6–8 wk.
ECG electrodes	MR-safe ECG electrodes are strongly recommended to ensure patient safety and proper ECG recording.
Foley catheters	Certain Foley catheters with temperature sensors have the potential for excessive heating. They are generally safe if positioned properly and disconnected from the temperature monitor during MRI.
Heart valve prostheses	All types of heart valve prostheses have been shown to be safe during MRI. However, prosthetic material may lead to image artifacts.
Metallic foreign bodies	All patients with a history of injury with metallic foreign bodies such as a bullet or shrapnel should be thoroughly evaluated, as serious injury may result from movement or dislodgement of the foreign body.
Metallic cardiac occluders (e.g., management of PDA, ASD, or VSD)	MRI is safe for nonferromagnetic devices immediately after implant. Weakly ferromagnetic devices are safe from approximately 6–8 wk after placement, unless there is concern about retention of the device.
Retained epicardial pacing wires	MRI in patients with retained epicardial pacing wires after cardiac surgery appears safe. Retained transvenous pacing wires are a contraindication to MRI.

ASD, atrial septal defect; ECG, electrocardiogram; ICD, implantable cardioverter–defibrillator; MR, magnetic resonance; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

the most favorable situation. The newly established transverse magnetization starts to disappear (a process called transversal relaxation), and the longitudinal magnetization grows back to its original size (a process called longitudinal relaxation). During this process, an RF signal is generated, which can be captured by the receiving coil and readily measured. This process constitutes the underlying principle of MRI.

The signal generated by an excited proton is dependent on its molecular environment, such that the magnetic resonance (MR) signal from a hydrogen atom in blood can be discriminated from the MR signal from a hydrogen atom in fat or other tissue types. An MRI machine, therefore, includes a strong magnet that creates a continuous magnetic field and RF coils for transmitting the excitation pulses and receiving the radio signals generated by the excited protons. Application of predictable variations or "gradients" in the magnetic field, using gradient coils within the magnetic bore, allows three-dimensional (3D) spatial localization of each signal. The raw data are initially mapped in "k-space" before a Fourier transformation to generate the final MRI image.

B. T1, T2, and image contrast. The rate of relaxation of an excited proton along the longitudinal axis (i.e., the direction of the external magnetic field) is described by its T1 time, whereas the transverse axis is described by its T2 time. T1 and T2 times depend on the molecular environment of the protons (intrinsic to the tissue characteristics) and the magnetic field strength. T1 and T2 relaxation times of different tissues are important determinants of image contrast and, although not measured directly, images can be either T1 or T2 "weighted" to facilitate tissue characterization.

C. Issues specific to CMRI. Cardiac and respiratory motion poses significant challenges to CMRI. In contrast to echocardiography, which is based on real-time imaging, CMRI sequences usually acquire a single image over several heart beats to optimize the spatial and temporal resolution. It is, therefore, necessary to gate images to the cardiac cycle with either an electrocardiographic or pulse signal. Electrocardiographic gating is usually retrospective, although prospective gating is sometimes useful, particularly in patients with arrhythmias. Respiratory motion is typically negated by performing breath-holds during the examination. In patients who are unable to maintain a breath-hold, averaging multiple MR signals may help to decrease the noise created by respiratory motion, at the expense of increasing the examination time by a factor of the *number of signals averaged*. Respiratory navigator sequences that coordinate imaging with a particular phase of diaphragmatic and hence respiratory motion are also effective, and they are typically used for pulse sequences that are too long for a single breath-hold, such as free-breathing whole-heart 3D coronary MRA sequences. Finally, real-time imaging using newer ultra-fast pulse sequences can be used in the absence of electrocardiographic or respiratory gating, at the expense of a significant decrease in temporal and spatial resolution.

D. CMRI pulse sequences and applications

1. **Spin echo.** Spin-echo sequences are characterized by a refocusing RF pulse after delivery of the initial excitation pulse. Rapidly flowing blood appears dark, hence they are also known as "black-blood" sequences. Spin-echo sequences provide still images, which are typically used for anatomic delineation of the heart and great vessels owing to their excellent tissue contrast and high signal-to-noise ratio (SNR). They are relatively insensitive to magnetic field inhomogeneities and artifacts related to ferromagnetic objects such as sternal wires and prosthetic heart valves. Turbo spin echo is a newer technique that provides faster acquisition times than standard spin echo does. The main disadvantage of spin-echo sequences is the relatively long time it takes to acquire an image, making them more susceptible to motion artifacts and unsuitable for cine imaging.
2. **Gradient echo.** Gradient echo sequences are characterized by the use of refocusing gradients after the delivery of the initial excitation pulse. Rapidly flowing blood appears bright, hence they are also known as "bright blood" sequences. Gradient echo is a fast imaging technique that is relatively insensitive to motion artifacts,

making it ideal for cine imaging. However, it has less tissue contrast and increased susceptibility to magnetic field inhomogeneities and ferromagnetic-related artifacts than spin-echo imaging but less than balanced steady-state free precession (B-SSFP). A variety of gradient echo sequences are widely used in CMRI for cine imaging, myocardial perfusion and scar assessment, coronary imaging, and MRA.

3. **Cine imaging.** The most widely used pulse sequence for cine imaging is a gradient echo sequence called balanced steady-state free precession (B-SSFP), which is characterized by high SNR, high image contrast between blood and myocardium, and low sensitivity to motion artifact. However, B-SSFP is relatively insensitive to blood flow and, therefore, can be suboptimal for imaging of valve dysfunction or intracardiac shunts, which can usually be better illustrated using other gradient echo pulse sequences, such as echo planar imaging or phase velocity mapping. In addition B-SSFP is also more susceptible to magnetic field inhomogeneities which can be problematic in patients with mechanical valves or other cardiac implants.
4. **Myocardial tagging.** RF pulses can be applied before the excitation pulse to generate dark saturation lines or grids on cine images, which are then tagged to the myocardium and further used to assess myocardial deformation. The tags can be used to help qualitatively assess myocardial motion and pericardial tethering or to quantitatively measure myocardial strain.
5. **Perfusion imaging.** Very fast gradient echo sequences are used for dynamic imaging of left ventricular (LV) myocardial perfusion during the first pass of a gadolinium contrast agent during rest and stress states. Fast gradient echo techniques are commonly used, such as fast low-angle shot or B-SSFP with a prepulse to null or darken the myocardium. Normally perfused myocardium shows an increase in signal intensity due to gadolinium contrast, whereas abnormally perfused areas remain dark or hypoperfused.
6. **Delayed imaging.** Delayed hyperenhancement imaging for myocardial scar or fibrosis is performed 10 to 30 minutes after injection of gadolinium contrast using gradient echo sequences with an inversion recovery prepulse to null signal from the myocardium. **Areas of myocardial scar or fibrosis have a larger extracellular space with a greater accumulation and slower washout of gadolinium and, therefore, appear bright compared with dark, normal myocardium on delayed imaging**.
7. **Phase-contrast velocity mapping.** The phase difference in the spin of protons in moving blood compared with nonmoving protons within a magnetic gradient is called the "spin phase shift" and is proportional to the velocity of the moving protons. A phase-encoded image is constructed, with the gray level of each pixel coded for velocity. Phase-contrast velocity mapping could be considered analogous to pulse wave Doppler echocardiography. It can be used to measure blood velocity and hence quantify cardiac output, shunts, and valve dysfunction. There are, however, limitations, given that the accuracy of this method is highly dependent on factors such as flow pattern, flow velocity, size, and tortuosity of the vessel. Flow-related signal loss can be a result of loss of phase coherence that can occur in cases of significant flow acceleration and even in higher orders of motion present in complex flow patterns.
8. **Magnetic resonance angiography.** MRA of the great vessels typically involves a 3D fast gradient–echo acquisition after injection of gadolinium contrast. The image resolution is typically $2 \times 2 \times 3$ mm, making MRA an excellent option for imaging of large to intermediate size arteries, but less optimal for imaging of smaller vessels.
9. **Parallel imaging.** A number of parallel imaging techniques make use of multiple receiving body coils to acquire extra data after each excitation pulse. This helps to decrease the imaging time and improve temporal resolution, but at the small relative cost of decrease in the SNR.

E. **Contrast agents.** A number of gadolinium chelates are used as contrast agents in clinical MRI. **Gadolinium significantly shortens the relaxation time of nearby**

protons, thereby increasing their signal intensity. These contrast agents are safe, with a low side-effect profile. Prevalence of adverse reactions is approximately 2% and includes transient headache, nausea, vomiting, local burning or cool sensation, and hives. Anaphylactoid reactions are extremely rare. Recently, gadolinium has been linked to a severe and rapidly progressive form of systemic sclerosis called **nephrogenic systemic fibrosis (NSF)**, which appears to be related to extracellular accumulation of gadolinium after its administration in patients with end-stage renal disease. The US Food and Drug Administration (FDA) has advised that **gadolinium contrast agents should not be administered to patients with a glomerular filtration rate of <15 mL/min. Caution should be exercised in patients with moderate or severe renal impairment**. Dialysis is only partly effective at filtering gadolinium and may not prevent development of NSF.

V. PRACTICAL CONSIDERATIONS

A. Safety

1. **Magnetic force.** Cardiac MRI scanners typically utilize powerful magnets of 1.5 to 3.0 T, several tens of thousands of times stronger than the earth's magnetic field (0.00005 T). Large or small ferromagnetic objects in the vicinity of the MRI magnet bore can become fast moving projectiles, which may cause severe injury to patients and/or damage the MRI scanner. A number of fatalities related to such events have been reported. Health-care professionals working in the vicinity of an MRI scanner require MRI safety training and should be vigilant to risk posed by patients and health-care professionals not familiar with the danger.
2. **Magnetic field gradients.** Switching of magnetic field gradients during a CMRI study produces high acoustic noise levels (up to 115 dB) and can also lead to peripheral nerve stimulation. The FDA has determined limits to the power of magnetic field gradients and noise exposure. Headphones and earplugs are recommended to prevent discomfort and hearing loss to patients and MRI staff in the vicinity of the scanner.
3. **Bioeffects of RF energy.** The majority of RF energy to the patient is dissipated as heat and is recorded as the specific absorption rate (SAR). One SAR equals 1 joule of RF energy per second per kilogram of body weight (i.e., watts per kilogram). The recommended SAR limit for the whole body is 4 W/kg.

B. Patient preparation

1. **Screening.** All patients should be screened for contraindications to MRI before the procedure (Table 51.2). Proper screening technique involves the use of a printed sheet and review of the completed form with the patient by an MR safety–trained health-care worker to verify the information.
2. **Patient size.** Although the maximum table load weight limit is fairly generous (~250 kg or 550 lbs), because of the fixed internal diameter of the magnet bore, very large patients may not fit within the MRI magnet. Typically, patients with a torso circumference of > 60 cm cannot be imaged. Discussion with the MRI technologist before scanning is recommended for specific recommendations related to your unit.
3. **Claustrophobia.** The enclosed space of the magnet poses problems for many patients, even those who do not have a history of claustrophobia. The study can usually be successfully completed with the help of clear communication with the patient before and during the procedure, presence of a friend or relative at the head of the MRI scanner, or light oral sedation (e.g., lorazepam 0.25 to 0.5 mg) 30 to 60 minutes before the procedure.

   Early versions of open MRI scanners had low magnetic field strength, gave poorer image quality than most closed systems, and required longer examination times. Newer open scanners include machines with higher magnetic field strengths and improved image quality and could become important alternatives in patients with claustrophobia.

4. **Attire.** Patients should wear a cotton hospital gown with no metal snaps. All metal items, jewelry, and nylon undergarments should be removed for reasons of safety and possible image degradation.
5. **Body coil.** Phased array body coils are placed on the patient's torso over the imaging area of interest. These use several smaller coils to acquire RF signals simultaneously and to facilitate parallel imaging. Some of these coils, for example, enable performance of 3D cardiac cine exams with full-ventricle coverage in a single breath-hold. The net result is not only better image quality but also reduced exam time for the patient.
6. **Electrocardiogram (ECG) monitoring.** A good electrocardiographic tracing is essential for CMRI. Although three or four MRI-safe, nonmetallic electrodes are placed on the patient's chest, and a single lead signal is used to trigger or gate the MRI images, the magnetic field affects the electrocardiographic tracing by inducing a voltage created by ions flowing within blood vessels (magnetohydrodynamic effect). This voltage artifact is commonly superimposed in the ST segment (during the ejection of blood in systole), which increases its amplitude causing false QRS detection in certain algorithms. Use of vector cardiogram allows the R-R interval to be registered as a 3D spatial vector that varies in magnitude and direction throughout the cardiac cycle. Furthermore, the use of fiber optic cables (instead of carbon leads) has also decreased the potential ECG interference of RF pulses and/or gradient field switches.
7. **Emergencies.** MRI is not appropriate in patients who are clinically unstable because of difficulties monitoring and treating patients within the magnet bore. Although MRI-safe equipment is available, it is safer to prescreen the patient's clinical status and determine the need of the MRI study before initiating the scanning.
8. **Pregnancy.** There is insufficient evidence regarding the safety of MRI in pregnant patients. Current guidelines state that MRI may be used in pregnant patients where other forms of nonionizing imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.
9. **Children.** CMRI may be necessary in pediatric patients with congenital and acquired cardiovascular disease. Typically, children younger than 8 years will require general anesthesia.

VI. CLINICAL APPLICATIONS

A. Diseases of the aorta

1. **Aortic aneurysm.** MRI can clearly visualize both the aortic vessel wall and lumen. It is a reliable method for the identification, characterization, and follow-up of thoracic and abdominal aortic aneurysms, with accuracy comparable to that of CT. A combination of spin-echo sequences for characterization of the vessel wall, gradient echo cine sequences for dynamic imaging of the aorta and aortic valve, and contrast-enhanced magnetic resonance angiography (CE-MRA) for aortic and branch vessel luminography is characteristically used. The aorta may be highly tortuous and should be imaged in multiple planes, with double-oblique measurements performed from true short-axis cuts using reconstructed images.
2. **Aortic dissection.** MRI is a highly sensitive and specific technique for the detection of aortic dissection (sensitivity 98% to 100%, specificity 98% to 100%). Spin echo, B-SSFP, and CE-MRA are used to identify the intimal flap, true and false lumens, and involvement of aortic branch vessels, including the coronary arteries. Administration of contrast is not critical to the examination, so that MRI may be particularly helpful in patients in whom there is concern for significant renal impairment. In addition, potential complications of aortic dissection (e.g., pleural effusion, pericardial tamponade, and aortic regurgitation) are easily evaluated. However, the longer study acquisition time with MRI compared with CT and its unsuitability for imaging of unstable patients limit its application in

the acute setting. However, as a safe, noninvasive, relatively fast technique and without use of ionizing radiation, MRI is well suited for follow-up of both surgically and medically treated aortic dissections, in particular for young patients.

3. **Intramural hematoma and penetrating aortic ulcer.** Intramural hematoma can be considered as the *forme fruste* of aortic dissection with the spontaneous rupture of one of the vasa vasorum within the media of the aortic wall. It occurs in up to 30% of all acute aortic syndromes and appears as a smooth crescentic to circumferential area of thickened aortic wall without evidence of blood flow in the false channel on either B-SSFP or spin-echo sequences. Because of the short T1-relaxation time of fresh blood, differentiation from the adjacent mediastinal fat may be difficult. Intramural blood can be best detected on fat-saturated T1-weighted gradient echo or black-blood techniques. Furthermore, on spin-echo ("black-blood") imaging, the intramural hematoma may be isointense (acute) or hyperintense (subacute) relative to skeletal muscle. Penetrating aortic ulcers appear as deep ulcerations of an aortic atheroma that extend through the intima to disrupt the underlying media and cause bulging of the outer aortic contour. They commonly appear at the isthmus beyond the left subclavian artery and in the distal descending thoracic aorta near the diaphragm. If acute, there may be evidence of intramural bleeding in the rim adjacent to the ulcer.
4. **Atherosclerotic disease.** MRI can clearly show irregular thickening of the aorta in atherosclerotic disease. CE-MRA has good accuracy for detecting significant peripheral stenoses and occlusions. Recent research has focused on the ability of MRI to accurately identify and characterize atherosclerotic plaques in the aorta and carotid arteries, as well as the development of novel contrast agents that target atherosclerotic plaques.
5. **Trauma to the aorta.** MRI may detect chronic or missed aortic tears, usually related to a previous motor vehicle accident. Tears are usually found in the area of the ligamentum arteriosum and are characterized by a localized saccular aneurysm, with or without an associated periaortic hematoma.
6. **Aortitis.** In patients with inflammatory disorders affecting the aorta such as Takayasu's disease (which tends to also involve the arch branch vessels) or giant cell arteritis, MRI can accurately detect diffuse wall thickening of the thoracic and abdominal aorta (specially after gadolinium administration in T1-weighted images) as well as stenosis and occlusion of the aortic branch vessels (CE-MRA sequences). Special imaging sequences using T2-weighting and short-tau inversion recovery for fat suppression, one can also assess for (peri)vessel edema and wall thickening/inflammation, respectively.
7. **Aortic stents and stent grafts.** Aortic stents and stent grafts can be safely imaged using MRI; however, both cine sequences (gradient echo and B-SSFP) are prone to ferromagnetic artifacts. Spin-echo imaging can be used successfully to evaluate stent graft morphology. Artifacts may limit assessment for graft leaks using CE-MRA.

B. Assessment of ventricular function and coronary artery disease (CAD)

1. **Assessment of global ventricular function.** CMRI is now the gold standard for the assessment of ventricular mass, volumes, and systolic function. A significant advantage of CMR is its reproducibility and accuracy compared with 2D planar or projection techniques that depend on geometric assumptions in order to define mass and volume determinations. As a result, small changes in myocardial mass and/or volume can be detected over time or as a result of therapy. A typical approach is to perform a short-axis stack of B-SSFP cine sequences through the left and right ventricles. Manual or semi-automated tracing of the endocardial borders at end-diastole and end-systole is later performed off-line, and ventricular volumes and ejection fraction are calculated using Simpson's method of discs.
2. **Assessment of regional ventricular function.** As mentioned before, development of multichannel phase-array coils has enabled parallel imaging and significant

improvements in spatial and temporal resolution and scan times. This has led CMRI to become superior to echocardiography for precise assessment of regional wall motion. B-SSFP cine sequences provide excellent blood-myocardial contrast that permits clear definition of the endocardial border. Furthermore, myocardial tagging methods have also improved the assessment of regional myocardial function.

3. **Myocardial ischemia.** CMRI stress testing can detect myocardial ischemia with either wall motion or perfusion analysis. The use of dobutamine stress CMRI for wall motion analysis is more established than stress perfusion imaging with adenosine or dipyridamole. Studies of stress CMRI with dobutamine have revealed good sensitivity (83% to 92%) and specificity (86%) for the detection of significant CAD on a per-patient level. Furthermore, CMR tagging may further improve the accuracy of dobutamine CMR for ischemia detection. Stress perfusion imaging by CMRI appears to have slightly higher accuracy to that of thallium single-photon emission computed tomography (SPECT), with a sensitivity of 91% and specificity of 81% for the detection of significant CAD reported in a recent meta-analysis. The absence of ionizing radiation with MRI is an important consideration, particularly in younger patients. However, it is important to note that to accomplish these multicenter results, a facility capable of performing the stress testing with appropriate physician and staff training is required.
4. **Myocardial infarction (MI) and viability.** T2-weighted spin-echo sequences with fat suppression may show areas of increased signal intensity consistent with tissue edema in the acute or subacute phase of a MI. This field of myocardial edema has been gaining interest as a target for clinical trials in acute coronary syndrome. The concept is that the myocardium at risk would correspond to the edematous minus the scarred area (seen on delayed enhancement). However, this technique has potential imaging artifacts (cardiac/respiratory motion, low signal-to-noise ratio, slow flow, coil intensity profile, etc) which could hinder the reproducibility of results seen in single-center studies. The current state-of-the-art technique for myocardial scar detection remains delayed enhancement imaging with an inversion recovery gradient echo sequence 10 to 30 minutes after injection of a gadolinium contrast agent. This method shows areas of myocardial scarring as bright and normal myocardium as dark and has shown excellent correlation with the location and extent of scar on histopathologic analysis. The superior spatial resolution of CMRI makes it more sensitive for the detection of myocardial scar, and in particular subendocardial scar, than SPECT or positron emission tomography. In addition, detection of areas of microvascular obstruction, despite adequate epicardial vessel reperfusion, can also be identified with CMRI and appear to be associated with worsened outcomes. The transmural extent of scar is associated with myocardial viability. Transmural or near-transmural scar (> 50%) suggests nonviable myocardium, whereas the absence of myocardial scar suggests that functional recovery is very likely post revascularization.
5. **LV thrombus.** CMR is more sensitive than echocardiography for the detection of LV thrombus which is associated with a greater morbidity. Due to its high spatial resolution and tissue characterization capabilities, CMR can be quite advantageous in establishing or ruling out the diagnosis of intracardiac thrombus. The typical signal characteristics would include lack of contrast perfusion on 1st pass of Gadolinium and low-signal intensity on post-contrast delayed imaging with long inversion time (dark filling defect on the endocardial surface of the left ventricle).

C. **Nonischemic cardiomyopathies** There is increasing recognition of diffuse myocardial fibrosis occurring as a separate entity in a variety of conditions in the absence of ischemia, including hypertensive and diabetic heart disease, hypertrophic cardiomyopathy (HCM), and idiopathic dilated cardiomyopathy (DCM). In these situations, use of standard delayed enhancement CMR may become a problem: due to the often diffuse nature of the fibrotic process, no true normal, nonfibrotic myocardium can be used as a frame of reference.

To overcome this limitation, several new CMR techniques have been developed in trials for the detection of nonischemic myocardial fibrosis. Contrast-enhanced T_1 mapping using a modified Look-Locker inversion recovery sequence is the most promising technique that allows quantification of diffuse, nonischemic myocardial fibrosis with high temporal resolution within a single breath-hold. However, before it can be used for clinical applications, a more standardized histologically validated technique needs to be identified and assessed in clinical studies on various and larger groups of patients and in multicenter settings.

1. **Dilated cardiomyopathy.** CMRI is useful for precise assessment of cardiac morphology and function in patients with DCM. Delayed enhancement imaging typically shows focal or diffuse enhancement in a mid-myocardial distribution, with a predilection for involvement of the lateral LV wall. Delayed enhancement during the acute presentation of DCM has been shown to correlate with areas of active myocarditis. Thus, CMRI may help guide myocardial biopsy and improve its sensitivity. The extent of delayed enhancement tends to improve over time, but patchy areas often remain and may represent areas of ongoing inflammation or fibrosis.
2. **Hypertrophic cardiomyopathy.** MRI is accurate for the evaluation of the pattern and extent of hypertrophy, systolic anterior motion of the mitral valve, resting left ventricular outflow tract (LVOT) obstruction, and secondary mitral valve pathology and regurgitation. Because of the precise anatomic definition provided by CMRI, it is particularly helpful in planning for surgical myectomy or alcohol septal ablation. CMRI can also help identify abnormal chordal or papillary muscle attachments, which may contribute to LVOT obstruction and have been reported in up to 20% of patients with HCM. Delayed enhancement is frequently seen in patients with HCM and corresponds to areas of interstitial fibrosis. It is typically seen in areas of increased wall thickness as well as the right ventricular (RV) insertion points in the interventricular septum. The extent of delayed enhancement in patients with HCM is associated with the presence of risk factors for sudden cardiac death and associated with worse outcomes. However, further research is needed to prospectively validate and establish a role for myocardial fibrosis detection in risk prediction in patients with HCM.
3. **Restrictive cardiomyopathy (RCM).** Infiltration of the myocardium may lead to RCM, which is characterized by normal ventricular size and systolic function, severe diastolic dysfunction, and biatrial enlargement. LV and RV wall thickness may or may not be increased. CMRI can clearly visualize the typical findings of RCM and simultaneously distinguish it from constrictive pericarditis, the main differential diagnosis. In addition, specific causes of RCM may be diagnosed by CMRI. Amyloidosis is associated with thickening of the interatrial septum and atrial free walls, as well as increased LV and RV wall thickness. Furthermore, **delayed enhancement imaging can show a typical pattern of diffuse subendocardial enhancement in patients with cardiac amyloidosis**, albeit a particular characteristic, best seen in the contrast-enhanced T1-weighted scout (Look-Locker) sequence, is the "early" nulling of the infiltrated myocardium—almost concomitant with the blood pool. Several findings have been noted in patients with cardiac sarcoidosis, including areas of increased or decreased signal intensity on T2-weighted images and patchy areas of delayed hyperenhancement. **Hemochromatosis is characterized by extensive signal loss on T2-weighted images, resulting from iron deposition in the myocardium**. Measurement of the T2 relaxation time of the myocardium (T2* technique) allows more precise detection of iron overload. Furthermore, T2* technique is also prognostically important in patients with thalassemia major, identifying patients at high risk for heart failure and arrhythmia more so than serum ferritin and liver iron.
4. **Arrhythmogenic right ventricular dysplasia (ARVD). CMRI is the primary imaging test for patients with suspected ARVD**, although nonimaging criteria are also required to confirm the diagnosis. Although CMRI can identify typical features

of ARVD including RV wall thinning, fibrofatty replacement, and focal RV wall aneurysms, according to the recent revised Task Force criteria (Marcus et al, Circulation 2010) presence of RV dilation, global RV dysfunction, and/or regional hypokinesia are more important findings. Fibrofatty replacement of the RV myocardium on CMRI is no longer a diagnostic criterion requiring histopathology confirmation.

The CMRI examination for ARVD is different than that for other cardiomyopathies. Axial and short-axis stacks of high-resolution T1-weighted spin-echo images are acquired through the right ventricle for anatomic definition of the RV and LV myocardium. The spin-echo pulse sequences may be repeated with fat saturation prepulses to facilitate detection of fatty infiltration of the RV free wall. B-SSFP cines are performed in the same axial and short-axis imaging planes for identification of RV wall motion abnormalities. Finally, delayed enhancement imaging is performed for identification of myocardial fibrosis. ARVD must be differentiated from right ventricular outflow tract (RVOT) tachycardia, which is associated with less dramatic findings on CMRI, including focal wall thinning and regional hypokinesis above the level of the crista terminalis in the right ventricle and in the RVOT.

D. Diseases of the pericardium. Normal pericardium appears on MRI as a thin (≤2 mm) curvilinear line situated between the epicardial and pericardial fat. The normal pericardium is of low intensity on both T1- and T2-weighted imaging sequences.

1. **Pericardial effusions** are typically of low intensity on T1-weighted spin-echo images and of high intensity on gradient echo images. The exception is hemorrhagic effusion, which is of high intensity on T1-weighted spin-echo images and of low intensity on gradient echo images.
2. **Pericarditis and constriction.** MRI can readily define the presence and extent of pericardial thickening (≥ 4 mm), which may be present in acute pericarditis as well as constrictive pericarditis. In **inflammatory pericarditis**, the pericardium may have increased signal intensity on delayed enhancement imaging. CMRI is now the imaging technique of choice in the diagnosis and management of **constrictive pericarditis**. Typical features include **pericardial thickening and tethering associated with conical or tubular deformity of the ventricles**. Secondary changes include atrial enlargement, systemic and pulmonary vein dilation, hepatomegaly, ascites, and pleural effusions. Cine sequences can demonstrate features of constrictive physiology, including diastolic septal bounce and abrupt limitation of late diastolic filling of the ventricles, which is distinguishable from the more generally delayed diastolic filling patterns seen with restrictive cardiomyopathies. Furthermore, real-time cine sequences with free breathing are also important to demonstrate the interventricular dependence with exaggerated septal shift toward the left ventricle during inspiration. MRI is of limited value compared with CT in the evaluation of calcification of the pericardium because of its inability to reliably distinguish between fibrous tissue and calcification.
3. **Congenital absence of the pericardium**, which may be complete or partial and often left sided, can be demonstrated on CMRI and is typically associated with a leftward orientation and "teardrop" appearance of the heart. Insinuation of lung tissue between the aorta and pulmonary artery and between the inferior surface of the heart and left hemidiaphragm is also characteristically seen.
4. **Pericardial cysts.** These are benign developmental lesions formed when a portion of the pericardium is pinched off during embryogenesis. Pericardial cysts are classically seen at the right cardiophrenic angle. They typically contain fluid and are well marginated. Spin-echo images demonstrate round or ovoid lesions that are often contiguous with the normal pericardium. Simple cysts demonstrate low signal intensity on T1-weighted and high signal intensity on T2-weighted images. Hemorrhagic or proteinaceous filled cysts show high signal intensity on T1-weighted images.

E. Congenital heart disease. CMRI is now an essential tool in the management and follow-up of patients with congenital heart disease. Scans can be performed safely and

reliably from infancy through adulthood. CMRI provides excellent anatomic definition of simple and complex heart defects and precise, noninvasive quantification of cardiac function and shunts. Because of the complex morphology and physiology in a given patient, MRI examinations are tailored to the individual, with frequent adjustments made during the examination. Consequently, the supervising radiologist or cardiologist should have a thorough understanding of congenital heart disease and be ready to assist at the scanner during the test. Common applications of CMRI in adult congenital heart disease include noninvasive quantification of intracardiac shunts; evaluation of pulmonary regurgitation severity, ventricular volumes and function, and pulmonary artery branch vessel stenosis in patients post tetralogy of Fallot repair; identification of RVOT or branch pulmonary artery obstruction in patients who are post arterial switch for dextro transposition of the great arteries (D-TGA); evaluation of baffle stenosis or leak and RV dysfunction in patients post Mustard or Senning procedure for D-TGA; and assessment for dysfunction of the systemic ventricle in patients with congenitally corrected or levo transposition of the great arteries (L-TGA).

F. Valvular heart disease. Although echocardiography remains the primary imaging modality for the diagnosis and management of valvular heart disease, CMRI may provide additional important information in select cases. Particular strengths of CMRI in the evaluation of valve dysfunction include an often clearer visualization of valve morphology, valve planimetry, precise quantification of regurgitant volumes, accurate and reproducible measurement of ventricular volumes and function, and assessment of associated abnormalities (e.g., bicuspid aortic valve and ascending aortic dilation).

G. Cardiac masses. CMRI plays a major role in the evaluation of cardiac and paracardiac masses, because in addition to providing excellent anatomic detail, it also has the ability to perform tissue characterization. Thrombus is the most common intracardiac mass. Fresh thrombus has higher signal intensity than myocardium on T1-weighted images. Older thrombi may have increased signal intensity on T1-weighted and decreased signal intensity on T2-weighted images. Thrombi usually have low signal intensity on delayed enhancement imaging and do not demonstrate delayed enhancement even with long inversion time. Myxomas are the most common intracardiac tumor and in addition to a variegated and irregular appearance typically have higher signal intensity than myocardium on T2-weighted spin-echo imaging. Lipomas have a distinctive short T1 and, therefore, high signal intensity on T1-weighted images. Fat saturation sequences that null lipomatous tissue confirm the diagnosis. Fibromas are an uncommon cardiac tumor and are typically seen within the ventricular myocardium in pediatric or young adult patients. They have decreased signal intensity relative to myocardium on T2-weighted images and show rim enhancement on delayed hyperenhancement imaging.

Primary malignant tumors of the heart are rare. Imaging findings suggestive of a malignant cardiac tumor include a right atrial location, invasiveness without respect to the anatomical borders (ie: involvement of > 1 cardiac chamber, extension into the mediastinum or great vessels), associated hemorrhagic pericardial effusion and moderate or greater contrast perfusion/uptake and subsequent heterogenous delayed-enhancement of the cardiac mass. The most common is angiosarcoma followed by rhabdomyosarcoma. Angiosarcomas are most commonly seen in the right side of the heart and have a heterogenous appearance with hyperintense areas on T1-weighted images. Delayed hyperenhancement shows heterogenous enhancement, most marked in the periphery of the tumor. Metastatic disease of the heart is more common and typically involves the myocardium or pericardium. It is not always possible to differentiate benign from malignant cardiac tumors. Features of malignant tumors are local invasion, pericardial involvement, and increased signal intensity relative to myocardium after injection of gadolinium suggestive of increased vascularity. One limitation of CMRI is its reduced sensitivity for the detection of calcification in cardiac masses.

H. Pulmonary veins. With the growth of percutaneous RF ablation procedures for atrial fibrillation, imaging of the pulmonary veins is being increasingly performed.

CMRI with spin and gradient echo sequences complemented by CE-MRA is effective in assessing pulmonary vein anatomy and stenoses before and after the procedure.

VII. FUTURE APPLICATIONS

A. Coronary artery assessment. Coronary imaging with CMRI is usually performed with two-dimensional (2D) or 3D gradient echo sequences, with either fat saturation or T2 prepulses to enhance the signal difference between the coronary lumen and the surrounding myocardium, as well as decrease the venous signal. Three-dimensional acquisition with navigator-corrected (free-breathing) data set has higher signal-to-noise ratio when compared with 2D sequences and has now become the established approach to contrast-enhanced MR coronary angiography.

Although CMRI can be used reliably for the detection of coronary artery anomalies, it has not yet fulfilled its early promise for noninvasive imaging of coronary atherosclerotic disease, especially when applied to the broader patient population. The coronary arteries provide significant challenges to imaging by MRI because of cardiac and respiratory motion, their small size and tortuosity, normal cyclic variations in coronary flow, and competing signal from neighboring blood pools. Nevertheless, it can be valuable in patients with a low to intermediate pretest likelihood of CAD (< 20%) where the negative predictive value is similar to CT (> 95%), reliably ruling out CAD. These patients, who are often younger, predominantly female, and require more than one scan over their lifetime, would highly benefit from a radiation-free imaging study.

B. Molecular imaging. MRI shows significant promise for the selective imaging of target tissue or cells using novel molecular contrast agents. Magnetically labeled mesenchymal stem cells have been successfully tracked by MRI in a pig model of stem cell therapy for myocardial injury. Supermagnetic nanoparticles have also been used to detect atherosclerotic plaque in both animal and human studies. Similar to what has been seen in nuclear cardiology, this is a fast growing field with several lines of research.

C. Interventional CMRI. The use of MRI in interventional procedures is appealing because it does not entail exposure to ionizing radiation. MRI has been used successfully to guide a variety of interventional procedures including balloon angioplasty and interatrial septal puncture in animals. In addition, the first human MRI-guided stenting of the iliac arteries has been reported in a study of 13 patients.

ACKNOWLEDGMENTS: *The author thanks Dr. Ronan Curtin for his contributions to earlier edition of this chapter.*

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RECOMMENDED WEB SITES

http://www.mrisafety.com
http://www.scmr.org

CHAPTER 52

Parag R. Patel
Milind Desai

Cardiovascular Computed Tomography

I. INTRODUCTION. Cardiovascular computed tomography (CT) has continued to rapidly evolve over the past decade, gaining new and expanded indications for noninvasive assessment of the heart, great vessels, and peripheral vasculature. Technological improvements, including increasing numbers of detectors, improved temporal and spatial resolution, and advanced postprocessing, have broadened the clinical utility of this imaging modality. Advanced multidetector computed tomography (MDCT) scanners and new scanning protocols have significantly reduced radiation and contrast dosages. Numerous considerations are involved in the proper selection of cardiovascular CT protocols, and skilled operators are required to plan and interpret these examinations.

II. BASICS OF CARDIAC CT

A. CT physics. In CT, images are created by rotating an x-ray source emitting a fan-shaped beam of x-rays, which then pass through the body. Some x-rays are absorbed or scattered, but others are transmitted and subsequently sensed by detectors located directly across the x-ray source. In MDCT, the x-ray tube and detectors are mounted on a gantry that rotates rapidly around the patient as he or she passes through the scanner. As in traditional x-ray radiography, different structures **attenuate** the x-ray beam to differing extents depending on their atomic composition and density, as well as the energy of the incident photons. The data collected by the detectors then go through a complex set of mathematical reconstruction algorithms that create a set of axial images through the technique of **backprojection**. Each voxel in the resulting axial image is ascribed a specific attenuation value, which is expressed in **Hounsfield units (H.U.)**. Using a reference of 0 H.U. for water, –1000 H.U. for air, and +1000 H.U. for bony cortex, different points are assigned their respective attenuation values. This information is then converted into a grayscale image that can be manipulated by the interpreting physician.

B. Technical challenges for cardiac imaging

1. The fast cyclical motion of the heart requires high **temporal resolution** to avoid blurring or degradation of images due to cardiac motion artifact. In cardiac CT, image acquisition is referenced, or **gated**, to the cardiac cycle. Although data can be acquired throughout the cardiac cycle, most image data sets are reconstructed during periods of minimal cardiac motion, typically a brief 100- to 300-millisecond interval in late diastole (60% to 75% of the R-R interval).
2. High **spatial resolution** is required to image relatively small vessels such as the coronary arteries. Current MDCT scanners (64-slice) provide a spatial resolution of 0.4 mm compared with approximately 0.2 mm for invasive angiography, the gold standard.
3. Respiratory motion artifact can be minimized by having the patient hold his/her breath during image acquisition. Most clinically available scanners can cover the entire heart in 10 to 12 seconds, whereas the newest 256-slice MDCT scanners can cover this area in just one or two heartbeats.
4. Rapid improvements in CT technology and protocoling have outpaced research in the field. Many studies investigating the diagnostic and prognostic yield of information gained from cardiac CT are not based on the newest MDCT scanners—but rather on single-beam/detector systems. Further investigation involving randomized controlled studies has been limited by the ethical issue raised by radiation exposure, although this has also been significantly reduced by innovative scanning approaches.

C. Current CT hardware

1. **MDCT** involves using an x-ray tube mounted opposite multiple detector rows on a gantry, which is then rotated around the patient at a rapid rate (220 to 400 ms/rotation). The patient is moved at either a fixed or variable speed, or **pitch**, through the scanner. An increasing number of detectors allows for an increased *z*-axis (cranial–caudal) coverage, permitting faster scans with improved image quality due to less cardiac and respiratory motion artifact. Temporal resolution is improved by faster gantry rotation, the use of **two x-ray tubes** and detector arrays mounted at 90° angles to each other (dual-source MDCT), and special reconstruction techniques. Dual-source/dual-energy scanners provide substantial improvements by utilizing dual-source MDCT technology as well as dual-energy sources to improve temporal resolution and decrease scatter. The fastest scanners provide a temporal resolution of 83 to 105 milliseconds. Spatial resolution is largely determined by detector architecture (typically 0.4 mm isotropic resolution), although thicker slices (1 to 5 mm) can be acquired to reduce radiation dose according to the study indication. MDCT can be used for both

cardiac and noncardiac studies, and it is now the most widely used type of CT hardware for cardiac imaging.

2. **Electron beam computed tomography (EBCT)**, although rarely used today, was specifically developed for cardiac imaging. It involves the use of a rapidly oscillating electron beam reflected onto a stationary tungsten target. Because there is no mechanical motion within the gantry, EBCT is capable of very high temporal resolution (50 to 100 milliseconds). EBCT was used primarily for the quantitative detection of coronary artery calcification (CAC).

D. Image acquisition techniques

1. **Acquisition modes.** Most current MDCT scanners use spiral retrospectively gated acquisition techniques for cardiac imaging, as this mode provides the greatest flexibility in image selection during different phases of the cardiac cycle and the ability to edit the image data set for artifacts due to ectopic beats. Recently introduced software has made the older prospectively gated axial acquisition mode possible for cardiac imaging in selected patients, and this has resulted in a 60% to 70% reduction in radiation dose.
   a. **Sequential (axial, "step-and-shoot") mode.** Single transaxial slices are sequentially acquired while the patient table is incrementally advanced between successive rotations of the gantry.
   b. **Spiral (helical) mode.** Data are continuously acquired during constant rotation of the gantry with simultaneous, constant (*z*-axis) movement of the patient through the scanner. As the tube does not perform a complete rotation in any plane, x-ray data are interpolated from a series of sequential frames to create a single tomographic image.
2. **Electrocardiogram (ECG) gating**
   a. **Prospective triggering.** The trigger signal is derived from the patient's ECG based on a prospective estimation of the R-R interval. The scan is usually triggered to begin at a defined point after the R wave, usually allowing image acquisition to occur during diastole. Prospective ECG triggering is one of the most dose-efficient ways of cardiac scanning, as only the very minimum scan data needed for image reconstruction are acquired. Limitations of prospective triggering (or "**gating**") include the fact that the acquired data set will be of a limited portion (or phase) of the cardiac cycle only, limiting the opportunity for evaluating image data sets from other cardiac phases. In addition, prospective triggering depends greatly on the regularity of the patient's heart rate and can result in serious misregistration artifact in the setting of arrhythmia.
   b. **Retrospective gating.** Unlike prospective triggering, retrospective ECG gating collects data during the entire cardiac cycle. Once the scan is complete, data from specific periods of the cardiac cycle are used for image reconstruction by retrospective referencing to the ECG signal. This approach allows reconstructions to be made from multiple segments of the cardiac cycle and allows some assessment of cardiac function via four-dimensional reconstruction. However, retrospective gating requires higher radiation dose exposure, although this can be somewhat mitigated by **dose modulation** (see subsequent text).
3. **Other imaging considerations**
   a. **Segmented reconstruction** refers to image acquisition algorithms that use scan data from more than one cardiac cycle for image reconstruction. This can reduce the effective temporal resolution of the scan at the cost of a slight increase in radiation dose.
   b. **Dose (or tube current) modulation.** MDCT scanners may operate with fluctuating tube currents that increase radiation dose during portions of diastole (when diagnostic images are most likely to be obtained) and reduce it

during systole. Dose modulation typically reduces effective radiation dose by approximately 33%, and it is most effective at lower heart rates.

4. **Image reconstruction and interpretation.** Images are most frequently viewed from axial and double oblique planes, in which the three-dimensional data set is manipulated by the interpreting physician so that multiple planes can be viewed to assess cardiac morphology and coronary anatomy. Additional postprocessing techniques can be performed to provide further diagnostic information or, more frequently, to present to the referring physician.
   a. **Multiplanar reformation** involves creating straight or curved image planes by cutting orthogonally or obliquely through the three-dimensional acquisition. This aids in evaluating complex three-dimensional structures, such as the coronary arteries.
   b. **Maximal-intensity projections** are created by compressing a predetermined volume of image data into a two-dimensional projection of the brightest voxels. This is similar in principle to the two-dimensional images created by typical invasive angiography.
   c. **Three-dimensional or volume rendering** is an advanced image processing approach that uses semitransparent visualization of the outer contours of volumetric data, giving the appearance of a three-dimensional structure. Although often not as useful for assessing smaller structures, these reconstructions can be very helpful for understanding complex spatial relationships between major intrathoracic structures.
   d. **Four-dimensional or cine imaging** from spiral retrospectively gated images generates cine images of the CT data for evaluating cardiac and valvular function.

E. Contrast-enhanced imaging. Administration of iodinated contrast media increases the attenuation of the blood pool, improving vessel delineation and tissue characterization. When using contrast, image acquisition must be timed such that images are acquired when the blood pool saturation in the target structure is maximal. Various techniques exist to time the arrival of the contrast bolus in the arterial tree and initiate imaging. The specific risks of contrast media are discussed in Section **IV**.

III. INDICATIONS. The role of cardiac CT in evaluating patients with cardiovascular disease continues to evolve. Generally accepted indications for cardiac CT are listed in Table 52.1 and are discussed in the context of specific clinical situations in Section **VI**. The following is a brief listing of the more common indications for MDCT.

A. Evaluation of chest pain is performed in patients with low to intermediate pretest probability of disease and persistent chest pain after an equivocal stress test.

B. Suspicion of coronary artery anomalies. Due to high spatial resolution and the ability to create three-dimensional reconstructions of the vasculature, MDCT has very high sensitivity and specificity for coronary anomalies.

C. Pulmonary vein evaluation can be performed often before or after pulmonary vein isolation (PVI) for atrial fibrillation.

D. Evaluation of cardiac masses in conjunction with or when other modalities such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI) are unrevealing.

E. Evaluation of pericardial disease in conjunction with or when other modalities such as TTE, TEE, or MRI are unrevealing.

F. Assessment of anatomy in complex congenital heart disease.

G. Presurgical evaluation, particularly before redo open heart surgery. MDCT can aid in describing prior bypass graft location, identifying safe sites for surgical approach.

H. Assessing graft patency after prior bypass surgery is feasible in many cases, although it is sometimes limited by artifacts related to calcium and surgical clips.

TABLE 52.1 Appropriate Indications for Cardiac Computed Tomography

Category	Specific appropriate indications
Suspected CAD with symptoms	Intermediate pretest probability of CAD with uninterpretable ECG or unable to exercise
	Acute chest pain with intermediate pretest probability of CAD and no ECG changes and negative serial enzymes
	Evaluation of anomalous coronary artery anatomy
	Chest pain syndrome with uninterpretable or equivocal stress test (exercise, perfusion, or stress echo)
Evaluation of intra- and extra-cardiac structures	Evaluation of cardiac mass in patients with limited images from TTE, MRI, or TEE
Pericardial disease	Evaluation of pericardial conditions (pericardial mass, constrictive pericarditis, or complications of cardiac surgery) in patients with limited images from TTE, MRI, or TEE
Congenital heart disease	Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels, and cardiac chambers and valves
Pulmonary vein anatomy	Evaluation of pulmonary vein anatomy prior to invasive radiofrequency ablation for atrial fibrillation
Biventricular pacing	Noninvasive coronary vein mapping prior to placement of biventricular pacemaker
Aortic disease	Evaluation of suspected aortic dissection or thoracic aortic aneurysm
Pulmonary disease	Evaluation of suspected pulmonary embolism
Surgical planning	Noninvasive coronary arterial mapping, including internal mammary artery, prior to repeat cardiac surgical revascularization

CAD, coronary artery disease; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Adapted from the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging. *J Am Coll Cardiol.* 2006;48:1475–1497.

I. **Evaluation of aortic disease.** MDCT is the test of choice for evaluating aortic aneurysm and suspected aortic dissection. It can be useful in the long-term follow-up of patients who have undergone prior aortic surgery or endovascular stenting.

J. **Evaluation of suspected pulmonary embolism (PE).**

IV. CONTRAINDICATIONS. Unlike with cardiac MRI, few absolute contraindications exist for cardiac CT. However, there are important risks associated with radiation and/or contrast exposure that must be weighed against the benefits of the scan. **Relative contraindications** to CT scanning are listed below.

A. **Renal insufficiency.** Given the potential for contrast-induced nephropathy, patients with significant renal insufficiency (i.e., Cr > 1.6 mg/dL) should not undergo contrast-enhanced CT unless the information from the scan is critical and the risks/benefits are thoroughly discussed with the patient.

B. Contrast (iodine) allergy. Patients with allergic reactions to contrast should be pretreated with diphenhydramine and steroids before contrast administration. A prior anaphylactic response to contrast is generally felt to be an absolute contraindication to intravenous iodinated contrast administration in many institutions.

C. Recent intravenous iodinated contrast administration. Patients who have received an intravenous dose of iodinated contrast should avoid contrast-enhanced CT scanning for 24 hours to reduce the risk of contrast-induced nephropathy. For younger patients with normal renal function without risk factors for contrast-induced nephropathy, contrast doses of up to 150 to 200 mL per 24 hours are generally well tolerated.

D. Hyperthyroidism. Iodinated contrast is contraindicated in the setting of uncontrolled hyperthyroidism due to possible precipitation of thyrotoxicosis.

E. Atrial fibrillation, or any irregular heart rhythm, is a contraindication to coronary CT angiography due to image degradation from suboptimal ECG gating.

F. Inability to breath-hold for at least 10 seconds. Image quality will be significantly reduced due to respiratory motion artifact, if the patient cannot comply with breath-hold instructions.

V. SAFETY

A. Radiation exposure is recognized as an important risk of various cardiac imaging modalities, including CT. Radiation doses of cardiac CT scans vary greatly depending on the scan parameter settings, scan range (cranial–caudal length of the scan), gender (women receive more radiation due to breast tissue), and patient's body habitus (obesity increases exposure).

1. **Estimates of radiation dose from MDCT** have varied widely in the literature. **Effective dose** is an estimate of the dose to patients during an ionizing radiation procedure and is expressed in **millisieverts (mSv)**. For reference, the estimated dose from a chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv. Invasive diagnostic coronary angiography provides effective doses of 2.1 to 4 mSv. In comparison, coronary CT angiography studies have reported doses ranging from 3.6 mSv to as high as 18 mSv, depending on the scan parameters, with most estimates ranging from roughly 4 to 11 mSv. Table 52.2 lists radiation dose ranges for the most commonly used cardiac imaging modalities.
2. **Feasibility of low-dose coronary CT angiography.** With the use of prospective ECG triggering, axial imaging modes, dose reduction, and software adaptations, recent studies have reported the feasibility of coronary CT angiography with comparable image quality and substantially reduced radiation doses (i.e., 1.1 to 3.0 mSv). This remains an area of active investigation.

B. Contrast-Induced Nephropathy. Iodinated contrast media can cause renal ischemia by reducing renal blood flow or increasing oxygen demand and may also have a direct toxic effect on tubular epithelial cells. If a contrast-enhanced CT study is necessary in patients with significant renal insufficiency, prophylactic measures should be taken to reduce the risk of renal damage. Most cardiac CT studies require between 80 and 100 cc of contrast dye.

1. **Risk factors**
   - **(a)** Preexisting renal insufficiency
   - **(b)** Diabetes mellitus
   - **(c)** Volume of contrast media
2. **Prophylactic measures** include saline hydration, use of low-osmolar agents, and sodium bicarbonate infusion, although the data for each of these measures remain somewhat controversial. The use of *N*-acetylcysteine has been shown to have no effect in slowing the progression of contrast-induced nephropathy.

TABLE 52.2 Estimated Radiation Exposure from Cardiac Imaging Procedures

Diagnostic procedure	Typical effective dose (mSv)	Equivalent period of natural background radiation
Natural background radiation	3–4 (range 1.5–7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (Kr 81m)	0.1	2–4 wk
Lung perfusion study (Tc 99m)	1	4–6 mo
Calcium scoring	0.8–2	3–6 mo
CT head	2	8 mo
Cardiac catheterization (diagnostic)	3–4	1 y
64-Slice MDCT (with dose modulation)	8–12	2–3 y
Myocardial perfusion (Tl 201)	15–18	4–5 y
CT abdomen/pelvis	10–20	3–6 y
Cardiac PET	14–20	4–6 y

PA, posterolateral; MDCT, multi-detector computed tomography; mSv, millisievert; CT, computed tomography; PET, positron emission tomography; R, Roentgen units.

VI. CLINICAL APPLICATIONS

A. Coronary calcium scoring uses the observation that coronary calcium is a surrogate marker for coronary atherosclerotic plaque. Studies have shown that the complete absence of coronary artery calcium makes the presence of significant coronary luminal obstruction highly unlikely and indicates a very low risk of future coronary events. Men tend to have higher calcium scores, and individuals of either gender with renal insufficiency or diabetes tend to have higher coronary calcium scores.

1. Either noncontrast EBCT or MDCT can be used (typically with 3.0 mm slice thickness). Contrast is not necessary because calcium is readily identified secondary to its very high x-ray attenuation coefficient (high H.U. score).
2. The **Agatston CAC volume score** is the most frequently used scoring system. It is derived by measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4, depending on the maximum CT attenuation within that lesion. It is important to realize the reproducibility of the Agatston score before applying the recommended guidelines for cut-off points. Importantly, the variability in the score has very little meaning at the very high and very low scores. Inter-reader variability can be as high as 3%.
   a. The **CAC score** can be classified into five groups: (1) zero, no coronary calcification; (2) 100, mild coronary calcification; (3) > 100 to 399, moderate calcification; (4) > 400 to 999, severe calcification; and (5) > 1000, extensive calcification.
   b. The CAC score is age specific and gender specific. Therefore, there has to be a comparison of the individual data with a "normal" cohort in order to produce meaningful data, usually presented as the percentile distribution. In

general, CAC develops 10 to 15 years later in life in women than in men. Similarly, CAC is generally five to seven times lower at any given age in women than in men.

c. In a typical cohort of coronary artery disease (CAD) patients, the median CAC score is 975 for men and 370 for women. In comparison with a CAC score of 0, the presence of any CAC is associated with a fourfold risk of coronary events over 3 to 5 years.

d. In patients at intermediate clinical risk for coronary events (e.g., by Framingham score), the CAC score can help reclassify patients to a higher or lower risk group. For instance, a CAC score of 0 confirms low risk of events. Conversely, a CAC score of > 400 is observed with a significant cardiac event rate (> 2% per year) in patients who appear to be of intermediate risk per Framingham score.

e. Because statins have no documented effect on CAC progression, there is no value in repeating CAC in persons with a score of > 100 or the 75th percentile.

3. However, not every atherosclerotic plaque is calcified, and even the detection of a large amount of calcium does not imply the presence of significant stenoses. Therefore, it adds only incrementally to traditional risk assessment and should not be used in isolation. The test is most useful in intermediate-risk populations, in which a high or low score may reclassify individuals to a higher or lower risk group, respectively. Unselected screening is not recommended.

B. Coronary CT angiography has been shown to be an accurate noninvasive modality for visualizing the coronary arteries, with high sensitivity (85% to 95%) and specificity (95% to 98%) compared with invasive angiography as the gold standard.

1. Coronary CT angiography for evaluating CAD is most useful in low- to intermediate-risk patients with angina or anginal equivalent. The **negative predictive value** of coronary CT angiography is uniformly high in studies, approaching 95% to 100%; in other words, coronary CT angiography is an excellent modality for ruling out coronary disease.
2. Patients who are generally poor candidates for coronary CT angiography include those who are likely to have heavily calcified coronary arteries (older than 75 years, end-stage renal disease, and Paget's disease), atrial fibrillation/flutter, frequent ventricular ectopic beats, or uncontrolled tachycardia. Quantification of stenosis severity is often impossible in densely calcified arteries, whereas image quality is significantly degraded in patients with arrhythmias or tachycardia. The negative predictive value dropped to 83% in one study, where patients with Agatston's CAC score of < 600 were included.
3. Known severe CAD is generally a contraindication to coronary CT angiography. However, cardiac CT has been shown to have high sensitivity and specificity for the assessment of bypass graft patency in patients with previous coronary artery bypass grafting (see subsequent text).
4. **Stent patency**. Patients with prior coronary artery stents are generally poor candidates for CAC and CT angiography, although selected patients with proximal left anterior descending or left main stents may be successfully imaged. Current CT technology does not allow for the accurate quantification of in-stent stenosis severity, due to blooming artifact from the metallic body of the stent.
5. When assessing the coronaries, **noncalcified plaque** appears as a low to intermediate attenuation irregularity in the vessel wall. **Calcified plaques** are bright, high-attenuation lesions in the vessel wall and may be associated with positive remodeling of the vessel. Densely calcified plaques are often associated with **calcium blooming artifact**, which can lead to overestimation of luminal stenosis severity.

6. The accuracy of coronary CT angiography is highest in the larger proximal to medium vessels, which are more likely to benefit from an invasive management strategy. Coronary stenoses are generally categorized as mild (< 50% diameter stenosis), moderate (50% to 70% diameter stenosis), or severe (> 70% diameter stenosis).

C. Bypass graft imaging

1. **Graft location.** MDCT can accurately characterize the origin, course, and touchdown of prior bypass grafts using intermediate slice thickness (e.g., 1.5 mm). This can be important for surgical planning (see details in subsequent text of this chapter).
2. **Graft patency.** Using a protocol similar to that used for coronary artery assessment (> 1 mm slice thickness), patency of both arterial and venous bypass grafts can be assessed. Studies have suggested that the sensitivity and specificity of MDCT for detecting stenosis or occlusion of bypass grafts, when compared with invasive angiography, are 97% and 97%, respectively. Occasionally, artifacts related to metallic clips can interfere with assessment of the distal anastomosis of an arterial graft (internal mammary or radial artery graft).

D. Coronary artery anomalies. Due to the three-dimensional data acquisition, MDCT is an excellent modality for assessing patients with known or suspected coronary artery anomalies. MDCT can accurately assess the origin and course of anomalous coronaries and can describe the relationship of the coronary artery to neighboring structures. Although MRI can also be used to assess anomalous coronaries without the need for radiation exposure, the spatial resolution, ease of data acquisition, and reliable image quality of MDCT make it a reasonable first choice. Intramyocardial **bridging** can also be detected with high sensitivity, although the clinical significance of this relatively common finding is uncertain.

E. Cardiac morphology/function. Contrast-enhanced MDCT can provide high-resolution morphologic images of the cardiac chambers as well as accurate assessment of right and left ventricular systolic function. However, other imaging modalities such as echocardiography or MRI, which do not require radiation exposure, are generally preferred initially for assessing cardiac morphology.

1. Patients with prior **myocardial infarction** can have fibrous replacement of myocardium with or without calcification, ventricular wall thinning, aneurysm formation, and cavitary thrombus. This is a rare indication for cardiac CT; rather, it is studied with delayed enhancement MRI.
2. **Ventricular dysplasia** is characterized by fibrous and/or fatty replacement of myocardium, ventricular wall thinning and/or focal aneurysm formation, and ventricular cavity dilation with regional or global wall motion abnormalities.
3. **Mass.** CT provides somewhat less information about tissue type than cardiac MRI, although the attenuation of a mass (in H.U.) can be helpful. For instance, lipomas have low CT numbers, cysts have water density (i.e., 0 to 10 H.U.), and thrombi have low to intermediate CT numbers. Atrial myxoma can be visualized easily in the left atrium, although right atrial masses may be difficult to visualize due to contrast mixing at the junction of the right atrium and inferior vena cava (IVC).

F. Pericardial diseases. The pericardium appears as a thin line (1 to 2 mm) surrounding the heart, usually visible with a small amount of adjacent pericardial fat. The pericardium normally enhances with contrast administration; hyperenhancement of the pericardium in the appropriate clinical setting is characteristic of pericarditis.

1. By CT, **congenital absence of the pericardium** is easily diagnosed.
2. Findings of pericardial **constriction** on CT include irregular pericardial thickening and calcification, conical or tubular compression of one or both ventricles,

enlargement of one or both atria, dilation of the IVC, and a characteristic diastolic bounce of the interventricular septum.

3. Pericardial effusions can be reliably detected by CT, and a small amount of fluid is normal even in healthy subjects. Pericardial tamponade is better evaluated by echocardiography, however, due to its ability to provide hemodynamic information.
4. A pericardial **cyst** will appear as a well-circumscribed paracardiac mass with characteristic water attenuation (H.U. = 0), usually in the right costophrenic angle.
5. Both primary **neoplasms** and, more commonly, metastatic neoplasms can be visualized in the pericardium.

G. Congenital heart disease. MDCT may be used in selected patients in whom echocardiography is nondiagnostic or inadequate and MRI is not available. The ability to evaluate cardiovascular anatomy in multiple planes is often helpful for delineating cardiac morphology in congenital heart disease, particularly with regard to the relationship of the great vessels, pulmonary veins, and coronary arteries. Specific situations in which MDCT is helpful include "hard-to-find" adult shunt detection (sinus venosus atrial septal defect and patent ductus arteriosus); visualization of pulmonary arteries in cyanotic congenital heart disease; precise definition of aortic anatomy in Marfan's syndrome or coarctation; and definition of partial or total anomalous pulmonary venous drainage. Additionally, CT can be useful for follow-up imaging in patients with congenital heart disease who have had prior pacemaker or ICD implantation, such as L-transposition of the great arteries.

H. Diseases of the aorta constitute a common and important indication for CT examinations. Contrast-enhanced MDCT is nearly 100% sensitive and specific for evaluating acute aortic syndromes. ECG gating is critically important for studies of the aortic root and ascending aorta, given the propensity for motion artifacts to appear similar to dissection flaps on nongated studies.

1. **Acute aortic dissection** (see Chapter 26) is characterized on CT by visualization of a dissection flap (i.e., separation of the intima from the media) that forms true and false lumens. The CT study can characterize the origin and extent of the dissection, classify it as type A or B, assess for concomitant aneurysmal aortic dilation, and identify branch vessel involvement.
2. **Aortic intramural hematomas** are believed to be caused by spontaneous hemorrhage of the vaso vasorum of the medial layer. They appear as crescent-shaped areas of increased attenuation with eccentric aortic wall thickening. Unlike dissections, hematomas do not spiral around the aorta.
3. **Aortic aneurysm** is a permanent dilation of 150% of the normal aortic caliber (usually > 5 cm in the thoracic aorta and > 3 cm in the abdominal aorta). Given the often tortuous course of a dilated aorta, it is important that these measurements be made in the true short axis of the aorta, as oblique cuts can result in erroneous overestimation of the aortic diameter. Quantitative measurements of an aortic aneurysm can be made for planning endovascular repair with a **stent graft**.
4. **Penetrating atherosclerotic ulcer.** These tend to be focal lesions of the descending thoracic aorta that appear as contrast-filled irregular outpouchings of the aortic wall.

I. Evaluation of pulmonary veins. In the context of electrophysiology interventions such as PVI, preprocedural MDCT can be used to define pulmonary venous anatomy and identify supernumerary veins, and postprocedural MDCT can be used to evaluate for pulmonary vein stenosis. Additionally, in the setting of congenital heart disease, CT can be used to identify anomalous pulmonary venous return.

J. Evaluation of PE. MDCT is highly accurate in detecting PE, which appears as a filling defect in the pulmonary arteries. This modality is most sensitive for proximal (main through segmental branches) thrombi, and small, distal emboli may be missed.

K. Valvular heart disease. Visualization of the valve leaflets, particularly the aortic valve, is feasible with newer generation scanners due to their improved temporal resolution. Nonenhanced MDCT is also useful for assessing mechanical valve leaflet motion in cases of suspected thrombosis or infection.

L. Surgical planning. The utility of MDCT in surgical planning before cardiothoracic surgery, particularly for reoperations, is increasingly recognized. Preoperative scans can evaluate the proximity of mediastinal structures to the sternum (i.e., aorta, right ventricle, and bypass grafts) and the degree of aortic calcification (i.e., to guide cannulation sites) and concomitantly provide information about cardiac morphology (e.g., presence of a ventricular aneurysm).

M. Peripheral arteries. MDCT can also be used to evaluate peripheral arteries, including the carotid, renal, visceral, and lower extremity vessels. Indeed, imaging these vessels is generally more straightforward than coronary imaging, due to their large caliber and minimal motion. CT can be used for planning and follow-up of vascular disease in these peripheral vascular beds. Given the larger caliber of these vessels, assessment of stent patency is often quite feasible.

ACKNOWLEDGMENTS: *The author thanks Drs. Deepu Nair, Paul Schoenhagen, Richard D. White, Sandra S. Halliburton, and Stacie A. Kuzmiak for their contributions to earlier editions of this chapter.*

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SECTION X

Electrophysiologic Procedures

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CHAPTER 53

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Electrophysiologic Studies

I. INTRODUCTION. Electrophysiologic studies (EPSs) are a specialized form of cardiac catheterization that help identify, characterize, and manage cardiac arrhythmias. Over the past 25 to 30 years, EPSs have advanced our knowledge of mechanisms of cardiac arrhythmias and revolutionized the way these arrhythmias are managed. The studies should be performed by trained clinicians with the help of skilled laboratory personnel in appropriately equipped laboratories. A joint task force of the American College of Cardiology and the American Heart Association in collaboration with Heart Rhythm Society has published guidelines outlining the accepted indications and the training required for personnel performing EPSs.

II. INDICATIONS. The indications for EPSs can be divided into three broad categories: bradyarrhythmias, tachyarrhythmias, and syncope.

A. Bradyarrhythmias can be caused by sinus node dysfunction, atrioventricular (AV) nodal disease, or infranodal conduction system disease. EPSs for bradyarrhythmias are rarely necessary because the decision to implant a pacemaker depends primarily on correlation between symptoms and documented bradycardia or demonstration of severe bradycardia or prolonged pauses. EPSs should complement the clinical evaluation, conventional 12-lead electrocardiogram (ECG), and Holter or event monitor. EPSs can be of value in identifying disorders associated with adverse outcome, such as severe infranodal conduction system disease.

B. More often, EPSs may suggest bradycardia as the underlying disorder among patients with **syncope** of unknown cause. Thus, patients with syncope of uncertain cause may benefit from EPSs.

C. EPSs are of tremendous value in evaluating **tachyarrhythmias**. They are generally more successful in reproducing re-entrant cardiac rhythms than those caused by triggered activity or enhanced automaticity. Among patients with re-entrant tachyarrhythmias, EPSs are useful in documenting the presence of the anatomic or physiologic substrate responsible for the arrhythmia, defining electrical mechanism of the arrhythmia and its associated hemodynamic response, as well as guiding therapy. The response of the tachyarrhythmia during an EPS to various drugs or pacing maneuvers may also be helpful in further defining the underlying substrate and prognosis.

III. EQUIPMENT AND SETTING

A. The most important element in the performance of a safe and useful EPS is the presence of **well-trained personnel**. The presence of at least one trained physician and well-trained laboratory support personnel, including a nurse, as well as engineering assistance to maintain and repair the laboratory equipment is necessary. Personnel involved should be familiar with basic electrophysiologic and electropharmacologic principles, the indications for EPSs, and the various diagnostic and therapeutic modalities that can be used in the laboratory.

B. It is important that the laboratory be equipped with appropriate high-quality **radiographic equipment**.

C. Appropriate selection of **tools** is a very important aspect of the performance of a safe and cost-effective EPS. The minimum instrumentation required for a complete study is a stimulator, an amplifier, display monitors, reliable recording devices, and an external defibrillator.

1. The **stimulator** must be capable of burst pacing, delivery of at least three or four extra stimuli, synchronization to appropriate electric events during intrinsic or paced rhythms, and an adjustable current output. An appropriate unit should have a constant current source and minimal current leakage. It should also be relatively easy to manipulate.
2. The **junction box** connects the electrode catheters to the recording apparatus and the stimulator.
3. **Recording** is best achieved on solid media (e.g., CD or other optical media).
4. The presence of at least two functioning **external defibrillators** is extremely important, particularly during studies in which ventricular arrhythmias may be induced.
5. The presence of a cardiac surgical team in the same institution is not mandatory for routine EPS or simple radiofrequency (RF) ablation procedures. However, for more complex RF ablation procedures where full heparinization is used and where cardiac perforation is a potential complication, the presence of a cardiac surgical team allows for prompt, definitive therapy when surgical intervention is required.

D. **Intracardiac signals** are recorded using various **electrode catheters**.

1. The most common catheters used are **quadripolar woven Dacron polyester** or **polyurethane**. The distal poles of these catheters can be used for pacing.
2. For general purpose sensing and pacing in the atrium or ventricle, a **nondeflectable catheter** is usually sufficient. Deflectable catheters facilitate mapping and ablation by allowing more precise movement.
3. Interelectrode distance varies from 2 to 10 mm. Smaller interelectrode distance is useful for precise mapping and timing.
4. For most EPSs, **bipolar recording** is used. However, in some situations, especially during mapping of tachyarrhythmias, unipolar recording can be of value in localizing the earliest sites of activity.

IV. TECHNIQUES AND PROCEDURES

A. Preprocedure preparation

1. Before the patient is taken to the EPS laboratory, a **discussion** of the indications and proposed procedure is conducted with the patient, and informed consent is obtained.
2. For most indications, EPS is an **elective** procedure. The patient's condition should be clinically **stable** at the time of the study. EPSs on patients who are unstable, including those with active, recent, or untreated coronary disease or those with clinical heart failure, carry much higher risk for complications.
3. **Electrolytes, serum digoxin level, and bleeding measurements** are checked and verified as being within the acceptable range.
4. Conscious sedation using a mild **sedative** (e.g., a benzodiazepine) and analgesic is administered.
5. The patient is attached to continuous ECG and blood pressure **monitoring** devices.

B. Access and catheter placement

1. The usual approach to inserting electrode catheters is through the **femoral veins under local anesthesia**, unless there is a clear contraindication to this approach, such as the presence of deep venous thrombosis or an inferior vena cava filter. In

the latter situations or when a coronary sinus (CS) catheter is difficult to insert, a superior vein approach may be used. We routinely utilize vascular ultrasound to directly visualize the femoral venipuncture, particularly when patients are on anticoagulation. This real-time visualization clarifies anatomic variants and enables us to avoid inadvertent arterial needlesticks and multiple passes that can lead to bleeding complications. Sheaths are then introduced into the vein over guidewires via the modified Seldinger technique.

2. Up to three **introducers** are placed in each femoral vein depending on the planned procedure. For patients with **left-sided bypass tracks or left ventricular (LV) tachycardia**, access to the left side of the heart is necessary. This can be achieved through the retrograde transaortic approach via an arterial access or by transseptal puncture via a femoral vein access. Systemic heparin is used for all left-sided procedures, and activated clotting time is monitored during the procedure to achieve adequate levels of anticoagulation.
3. **For a complete EPS, three catheters are needed.**
   a. One catheter is placed in the **high right atrium,** preferably in the appendage or against the high lateral wall. Another is placed in the **right ventricular (RV) apex**, and the third is placed across the **tricuspid valve** to obtain a His electrogram.
   b. To obtain a **His electrogram**, the electrode catheter is advanced into the right ventricle across the anterior septal portion of the tricuspid valve. Under gentle clockwise torque, the catheter is then slowly withdrawn to straddle the tricuspid valve. A high-frequency sharp deflection that precedes ventricular activation and follows septal atrial activation represents a **His** or **proximal right bundle potential**. If the catheter is drawn further, this sharp signal occurs slightly earlier. A satisfactory position of the His catheter is achieved when an atrial signal is recorded followed by the His potential and, finally, the ventricular potential is recorded via the same pair of electrodes.
4. In **supraventricular tachycardia (SVT)** studies, when a left-sided accessory pathway or left atrial origin is suspected, an octapolar or decapolar catheter may be placed in the CS rather than in the high right atrium. This more stable catheter position allows mapping of the left AV groove along the mitral annulus. Although the CS is easily entered from the superior venous approach, successful catheterization is expected in most attempts through the femoral approach as well. The catheter is placed in the CS with the proximal electrodes just inside the CS ostium.

C. Baseline assessment

1. When all the catheters are in place, a baseline ECG (generally leads I, aVF, V_1, and V_6) and intracardiac electrograms are obtained (Fig. 53.1).
2. In general, **cycle lengths** rather than beats per minute are measured. The following measurements are made at baseline: sinus cycle length and PR, QRS, QT, AH, and HV intervals. To convert an arrhythmia's rate from cycle length to beats per minute, divide 60,000 by the cycle length to obtain the arrhythmia rate in beats per minute.
   a. The **AH interval** is measured from the onset of the local A deflection to the H deflection on the His electrogram.
   b. The **HV interval** is measured from the H deflection on the His electrogram to the earliest ventricular activity in any lead (surface or intracardiac).
3. When measurements are made during pacing, it is important to **measure from the resulting deflection** rather than from the pacing artifact to avoid errors caused by latency (delay between the pacing artifact and activation at the recording site).
4. All measurements are recorded in **milliseconds**. Interpretation of baseline intervals is shown in Figure 53.2.

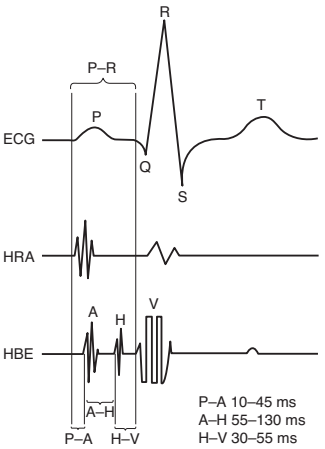

FIGURE 53.1 Normal baseline intervals. Typically, up to four surface ECGs (I, aVF, V_1, and V_6) are displayed along with atrial (CS), His (HBE), and ventricular (RVA) electrograms. CS7–8 refers to the proximal bipolar CS electrogram. Fast sweep speeds are used, ranging from 100 to 400 mm/s. On the time scale, each large division is 100 milliseconds, and each minor division is 10 milliseconds. In addition to intervals, pattern of atrial and ventricular activation should be evaluated. If the CS catheter is placed correctly (see text), the earliest A in sinus rhythm is seen on the HRA electrogram (not shown), then on the His electrogram, and progressively later along the CS electrograms. In the absence of bundle branch block or left-sided accessory pathway, the earliest ventricular activity is seen on right-sided electrograms (His and RV electrograms). (Adapted from *Dorland's Illustrated Medical Dictionary.*) CS, coronary sinus; ECG, electrocardiogram; HBE, His bundle electrogram; HRA, high right atrium; RVA, right ventricular apex.

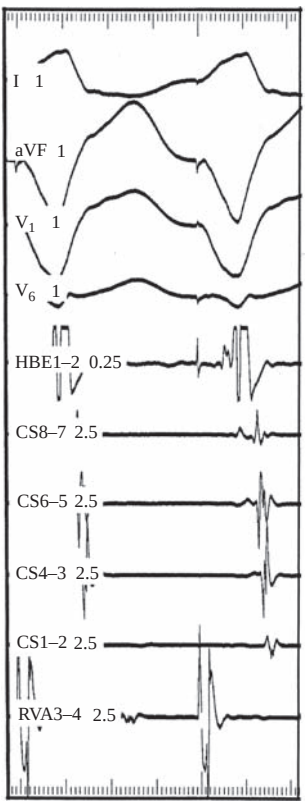

FIGURE 53.2 Programmed ventricular stimulation using double extra stimuli in a patient with AV node re-entry tachycardia. Note that the earliest retrograde atrial activity is seen on the His electrogram. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

D. Programmed stimulation

1. After baseline measurements are made, programmed stimulation is performed. The protocol used depends on the indication for the study and varies among institutions. During programmed stimulation, the **hemodynamic response** of the patient to pacing and induced tachycardia is closely monitored. For example, rapid ventricular pacing in patients with structural heart disease may result in transient hypotension. If this occurs, pacing should be limited in duration and adequate time between pacing drive trains should be allowed for hemodynamic recovery.
2. **Pacing stimuli** are usually delivered at 1 or 2 millisecond pulse width and at twice diastolic pacing thresholds. This is important during ventricular stimulation because pacing at higher outputs increases the risk of inducing nonclinical rhythms. There are two main types of programmed stimulation: burst pacing and the extra stimulus technique.
   a. **Burst pacing** involves continuous pacing at rates faster than the patient's intrinsic rate.
   b. In the **extra stimulus technique**, premature beats are introduced either during intrinsic rhythm (sensed extra stimuli) or after a paced drive train (paced extra stimuli). Extra stimulus techniques are useful in evaluating refractory periods of the AV node, atrial tissue, ventricular tissue, and accessory pathways. It is possible to evaluate infranodal conduction system refractory periods with atrial or ventricular stimulation. Extra stimulus techniques are also useful in inducing, terminating, and identifying re-entrant arrhythmias.
      (1) In the **sensed extra stimulus** technique, a single extra stimulus (S_2) is introduced initially with a coupling just below the intrinsic rate. The coupling interval is reduced progressively by 10 to 20 milliseconds until the premature stimulus no longer captures. A pause of 2 to 5 seconds is allowed between stimulation sequences. Multiple extra stimuli (S_3, S_4) can be added if necessary and the sequence repeated.
      (2) In the **paced extra stimulus** technique, a drive train of 6 to 10 beats at a fixed cycle length is followed by the premature beat. The drive train cycle length (S_1S_1) usually ranges from 350 to 800 milliseconds (most frequently 400 to 600 milliseconds) but depends on the resting heart rate. When this technique is used, testing at two drive train cycle lengths is recommended. The premature stimulus (S_2) is introduced with a coupling interval just below the S_1S_1. The coupling interval of the premature stimulus is decreased progressively by 10 to 20 milliseconds until it no longer captures. The longest coupling interval (S_1S_2) that does not capture the myocardium is the absolute refractory period. S_3 and S_4 are added if necessary. This protocol can be varied depending on the indication and operator preference.
3. **Continuous monitoring** and recording of external and intracardiac electrograms is maintained throughout programmed stimulation. When a particular event such as a tachycardia occurs, stimulation is stopped and the event evaluated. The operator should be ready to respond to the event appropriately, depending on the effect that the event has on the patient. For example, induction of a sustained tachycardia may result in severe hypotension, angina, or loss of consciousness. In such circumstances, expeditious termination of the tachycardia is indicated through overdrive pacing or cardioversion. The operator should also be ready to perform pacing or other maneuvers to further assess the mechanisms and re-entrant circuit of the induced tachycardia.

V. ATRIAL STIMULATION

A. An atrial study is an integral part of EPSs. The only time an atrial study is not performed is in the presence of persistent atrial fibrillation.

1. **Burst atrial pacing** at incremental rates causes slowing of AV nodal conduction (a process known as decremental conduction) and can induce tachycardia, including AV node re-entry tachycardia and AV re-entrant tachycardia. Other forms of tachycardia unrelated to AV nodal conduction can also be induced, such as atrial flutter, atrial fibrillation, atrial tachycardia, and certain forms of idiopathic ventricular tachycardia.
2. Burst pacing is performed by means of **continuous pacing** (e.g., 10 to 20 stimuli) at a fixed cycle length starting at 100 milliseconds below the baseline cycle length. Repeat burst pacing is performed at progressively shorter cycle lengths until 1:1 conduction through the AV node is no longer maintained. The shortest cycle length showing consistent 1:1 conduction through the AV node is recorded. This is related to the **effective refractory period** of the AV node, which is the longest A_1–A_2 interval that fails to be conducted to the His bundle. Another interval that can be measured is the **functional refractory period** of the AV node: it is defined as the shortest output interval from the AV node to the His bundle, given any input signal.
3. If a patient is believed to have **atrial flutter** or **atrial tachycardia**, repeat burst pacing at even shorter cycle lengths is performed until 1:1 atrial capture is no longer maintained.

B. Another form of atrial stimulation that is performed is paced extra stimulus.

1. The **effect of atrial premature beats** on the AH interval is assessed. The normal response of the AH interval is to progressively prolong with shorter A_1A_2 coupling. This is a direct demonstration of the normal decremental conduction properties of the AV node.
2. At a critical A_1A_2, the AV node fails to conduct, and on the His electrogram an atrial signal is seen without a His or ventricular deflection. This indicates that a **block has occurred in the AV node**. It is important to continue stimulation until the atrial refractory period is reached because a gap phenomenon may occasionally exist as a result of dual AV nodal pathways.
3. The **gap phenomenon** is demonstrated by apparent achievement of the AV nodal refractory period followed by resumption of conduction at shorter A_1A_2 coupling intervals. It reflects functional differences in conduction velocity or refractoriness in several regions of the AV junction.
4. If **narrow complex tachycardia** is induced, it is evaluated with regard to type, mechanism, response to maneuvers, and method of termination (see Section **IX.B.3**).

C. Sinus node evaluation. For patients who may have underlying sinus node dysfunction, sinus node tests are sometimes performed.

1. **Sinus node recovery time (SNRT)** is evaluated through burst pacing at various cycle lengths in the atrium for 30 to 60 seconds, followed by abrupt termination of pacing. SNRT is the escape interval between the last paced atrial beat and the first atrial recovery beat. A **corrected sinus node recovery time (CSNRT)** is calculated by means of subtracting the baseline sinus cycle length from SNRT. A normal value for CSNRT is < 550 milliseconds. SNRT is used to evaluate the automaticity mechanism of the sinus node.
2. **Sinoatrial conduction time (SACT)** is a combined measure of conduction in the atrial tissue that includes the area of the sinus node and sinus node automaticity. The assumptions are first that the conduction times into and out of the sinus node are equal, second that the pacing train does not alter the automaticity of the sinus node, and third that the pacemaking site does not change after premature stimulation. The SACT is measured with one of two methods.
   a. In the **Strauss method**, a sensed premature atrial beat is used to reset the sinus node, and the return cycle length after the premature beat is measured. The basic cycle length is subtracted from the return cycle length, leaving out

the time necessary to penetrate and leave the sinus nodal tissue. SACT is one-half this interval.

b. In the **method proposed by Narula**, the same measurements are obtained after pacing for eight beats at a rate slightly faster than the sinus rate. The upper range of SACT is 100 to 120 milliseconds.

The sensitivity of each individual (SACT and SNRT) test in diagnosing sinus node dysfunction is approximately 50% when used alone and 65% when combined. The specificity of the two combined tests is 88%, which gives the test a high positive predictive value. However, because of its low sensitivity, a normal test does not exclude sinus node disease.

VI. VENTRICULAR STIMULATION

A. Ventricular stimulation is performed in evaluations of suspected SVTs or ventricular tachyarrhythmias. Some SVTs, such as unusual forms of AV nodal re-entry, may be more easily induced with ventricular stimulation. To further characterize the tachycardia, the response of the tachycardia to premature ventricular beats can be assessed.

1. When ventricular stimulation is performed for the evaluation of ventricular or wide complex tachyarrhythmias, **pacing at two or more sites** maybe necessary. These sites are typically the RV apex and the RV outflow tract.

2. Before programmed stimulation is begun, pacing thresholds are determined, and the output of the pacing stimulus is set to twice the diastolic capture threshold. Higher outputs or coupling intervals shorter than 200 milliseconds may cause induction of nonclinical arrhythmias.

B. **Burst pacing in the right ventricle** is one of two techniques used when assessing retrograde ventriculoatrial (VA) conduction in the evaluation of SVT.

1. The presence of **retrograde atrial activation** is documented, and a sequence or pattern of atrial activation is evaluated.

2. The **earliest atrial activity** during retrograde conduction via the AV node is typically recorded on the His electrogram (see Fig. 53.2). This indicates that retrograde conduction has proceeded through the AV node fast pathway. **Absence of VA conduction**, with rare exceptions (e.g., the Mahaim type of accessory pathway which only conducts in the antegrade direction), excludes the presence of a bypass track. The **presence of eccentric atrial activation** (late atrial activation on the His electrogram; see Fig. 53.3) suggests the presence of a retrogradely conducting bypass track.

3. For some patients with no evidence of retrograde VA conduction, infusion of low doses of **isoproterenol** or a small dose of atropine (0.5 mg) restores this property to the AV node.

4. The **shortest paced cycle length** capable of 1:1 conduction to the atrium is documented.

C. Premature ventricular stimulation is another technique used to evaluate retrograde conduction properties of the heart.

1. If **retrograde conduction** is present, the refractory periods of the conducting pathways are determined with the extra stimulus technique.

2. In patients with **retrograde VA conduction through the AV node**, conduction block of a ventricular premature beat frequently occurs in the His-Purkinje system rather than in the AV node. His-Purkinje conduction block is more likely to occur at long drive trains. Such drive trains therefore are more likely to induce AV re-entry tachycardia (using a bypass track) by facilitating retrograde His-Purkinje block and allowing a retrograde conducted beat through the pathway to propagate antegrade through the AV node.

D. In patients being evaluated for **ventricular arrhythmias**, programmed stimulation with extra stimuli is the initial technique used. Pacing at two drive train cycle lengths (e.g., 600 and 400 milliseconds) is performed with single, double, and triple extra stimuli. Simultaneous atrial pacing at the same drive train cycle length is sometimes necessary to avoid competition from the intrinsic atrial pacemaker.

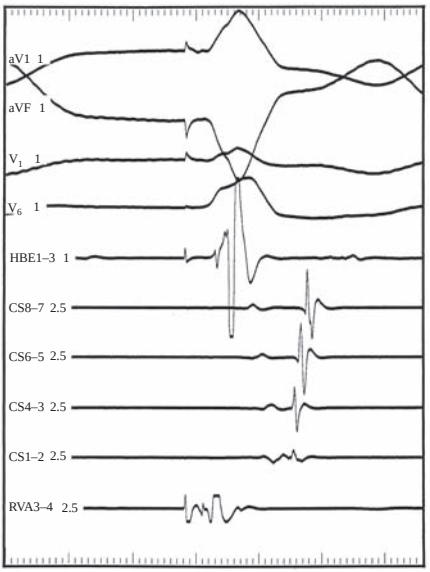

FIGURE 53.3 This is an example of a 17-year-old patient with left lateral manifest pathway. Ventricular stimulation results in retrograde atrial activation, with the earliest A seen in CS1–2 (eccentric atrial activation). CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

E. Like the A_1A_2 technique described earlier, **V_2 is introduced at progressively shorter coupling intervals** (V_1V_2) until V_2 no longer captures (ventricular refractory period). Then V_2 is set at a coupling interval longer than the refractory period and **V_3 is introduced** at progressively shorter coupling intervals until it no longer captures. The use of **triple extra stimuli** (V_3V_4) is usually reserved for patients being evaluated for ventricular arrhythmias.

A pause of 4 to 5 seconds is allowed after each cycle to assess response and for the patient to recover after ventricular pacing. An increase in the number of extra stimuli increases the sensitivity of the study in reproducing clinical arrhythmias, but at the cost of a lower specificity due to initiation of polymorphic ventricular tachycardia or ventricular fibrillation.

If programmed stimulation with ventricular extra stimuli does not induce ventricular tachycardia in a patient at very high risk, other techniques may be used. One is **burst pacing in the ventricle**. A series of 10 paced ventricular beats are introduced at a constant cycle length. The paced cycle length is then decreased by 50 to 100 milliseconds in successive bursts until reaching within 50 milliseconds of the predicted refractory period of the right ventricle, when the decrements proceed at 10-millisecond intervals until 1:1 capture is no longer maintained. Burst pacing in the atrium can at times induce idiopathic LV tachycardia in susceptible persons.

F. In some patients, particularly those with underlying dilated cardiomyopathy, **bundle branch re-entry (BBR) tachycardia** (see Fig. 53.4) may be induced.

1. This type of tachycardia usually involves the right bundle branch as the antegrade limb and the left bundle branch as the retrograde limb of the re-entrant circuit. It is usually a rapid and hemodynamically unstable tachycardia.
2. Because His bundle refractoriness increases after a pause, a short–long–short stimulation sequence can be used to cause retrograde block in the right bundle so that the paced stimulus can conduct retrograde up the left bundle branch and possibly initiate tachycardia if the right bundle branch is no longer refractory for antegrade conduction.

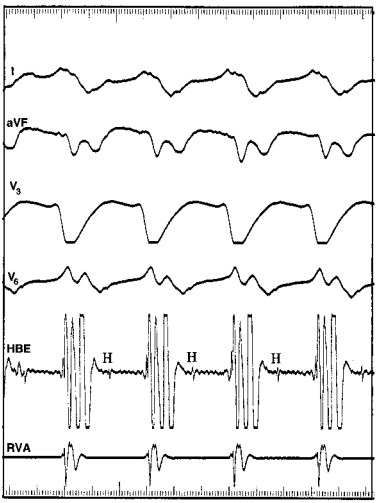

FIGURE 53.4 Bundle branch re-entry tachycardia. This example is from a 52-year-old man with dilated cardiomyopathy who presented with syncope. This ventricular tachycardia exhibits left bundle branch block morphology, and there is an H deflection preceding every V on the His electrogram. To be absolutely certain of this diagnosis (as opposed to myocardial ventricular tachycardia with retrograde His), one has to look for cycle length variation and document that changes in the H–H interval precede changes in the V–V interval. HBE, His bundle electrogram; RVA, right ventricular apex.

3. The sequence most commonly used consists of a 6-beat drive train at 400 milliseconds followed by V_2 coupled at 600 to 700 milliseconds. V_3 is then introduced at a coupling interval 100 milliseconds longer than the refractory period of the ventricle. V_2V_3 is progressively decreased until V_3 no longer captures. V_4 can be introduced if necessary.

VII. INDUCTION OF VENTRICULAR FIBRILLATION. Under certain circumstances, the operator may decide that induction of ventricular fibrillation is necessary. This is of value when testing implantable defibrillators for detection of arrhythmias and during assessment of defibrillation thresholds. Ventricular fibrillation can be induced by means of direct application of alternating current or rapid ventricular pacing at high output. The current can be delivered through a catheter electrode or through the **implantable cardioverter–defibrillator (ICD)** lead. Another means of inducing ventricular fibrillation is to deliver a low-energy shock (around 1 J) via the intracardiac leads at the peak of the T wave.

VIII. USE OF CARDIOACTIVE DRUGS DURING EPSs. Cardioactive drugs can be used during EPSs as diagnostic or therapeutic agents. The drugs most commonly used are isoproterenol, procainamide, atropine, and adenosine.

A. Isoproterenol in doses ranging from 0.5 to 5 μg/kg/min is used during EPSs to facilitate induction of SVTs and ventricular tachyarrhythmias.

1. For patients with SVTs that are AV node dependent, isoproterenol facilitates conduction through the AV node by means of shortening its refractoriness.
2. It is not absolutely certain how isoproterenol facilitates induction of ventricular tachycardia, but possible mechanisms include enhanced conduction, altered refractoriness, and enhanced automaticity related to delayed afterdepolarization.
3. Isoproterenol is particularly useful in evaluating patients with exercise-induced ventricular tachycardia and patients with the special type of RV outflow tract tachycardia. Isoproterenol is contraindicated in the presence of critical coronary artery disease.
4. Adrenergic stimulation with high doses of isoproterenol (up to 20 μg/min) also effectively induces repetitive rapid discharges from the pulmonary veins that frequently trigger initiation of atrial fibrillation (see Section **IX.B.3**).

B. Procainamide is used less frequently during EPSs. Among patients believed to have advanced underlying conduction disease, the response of the infranodal conduction system to procainamide infusion (10 to 15 mg/kg) is assessed during sinus rhythm and with atrial pacing.

1. Considerable prolongation of the HV interval or induction of infranodal block with atrial pacing at cycle lengths longer than 400 milliseconds is considered by many experts to be evidence of His-Purkinje disease. Procainamide can facilitate the induction of atrial and ventricular arrhythmias by means of slowing conduction.
2. Procainamide is often used to prevent recurrent atrial fibrillation when programmed atrial stimulation is necessary. An example would be a patient with atrial flutter who is being evaluated for ablation and is easily induced into atrial fibrillation during programmed stimulation.
3. Procainamide was widely used in the past for risk assessment among patients with inducible ventricular tachycardia. Studies have shown that patients with suppressible ventricular tachycardia have better long-term prognosis (lower rate of clinical recurrence and lower mortality) than those with non-suppressible ventricular tachycardia. However, with wider use of ICDs and evidence of their superiority even among persons with suppressible ventricular tachycardia, this application of procainamide may be of historical interest only.

C. Adenosine, in doses that produce transient AV block (6 to 18 mg), is used frequently in EPSs of patients with SVTs to define the mechanism of the tachycardia, establish AV node dependence, or document the presence or absence of accessory pathway conduction before and after RF ablation. It may also be used after atrial fibrillation ablation to assess inducibility of atrial fibrillation.

IX. INTERPRETATION OF FINDINGS IN EPSs

A. Bradyarrhythmia evaluation. EPSs are *not* indicated when symptomatic bradycardia is documented. Among patients who have a clear indication for implantation of a permanent pacemaker, findings of EPSs are unlikely to alter that decision. However, EPSs are more helpful to patients believed to have underlying **sinus node or conduction system disease and symptoms** but for whom noninvasive monitoring has failed to document a correlation between bradycardia and symptoms. EPSs are also helpful in assessing patients who continue to have symptoms after permanent pacemaker implantation.

1. **Baseline evaluation.** Sinus bradycardia, sinus arrest with junctional or ventricular escape, various degrees of heart block, and intraventricular conduction delay, isolated or in various combinations, may occur among patients with bradycardia and can be further evaluated by examining the intracardiac recordings.
   a. **Conduction intervals** are measured and evaluated. Disease in the AV node often produces prolongation in the AH interval, whereas disease in the infranodal conduction system produces prolongation in the HV interval.
   b. A long HV interval is suggestive but not diagnostic of an underlying bradyarrhythmia. It is commonly associated with wide QRS on surface ECG. A long HV interval at rest can be considered an indication for prophylactic pacemaker implantation (class IIa) if it exceeds 100 milliseconds.
   c. Documentation of intermittent spontaneous infranodal block or infranodal block in response to atrial pacing (see Fig. 53.5) or upon administration of procainamide is an indication for implanting a permanent pacemaker.
2. **Programmed stimulation**
   a. After baseline intervals are measured, **SNRT and SACT** are determined. SNRT is used to evaluate automaticity of the sinoatrial node.
   b. Rapid pacing causes overdrive suppression of the sinus node. Among patients with sinus node dysfunction, recovery time after cessation of pacing is

FIGURE 53.5 Infrahisian block in response to slow atrial pacing. This tracing is from a 70-year-old man who presented with syncope. Baseline H–V was 110 milliseconds. As shown in this tracing, burst pacing in the right atrium at cycle length of 700 milliseconds resulted in intermittent infrahisian block (H deflections not followed by V). This patient had a dual-chamber pacemaker implanted. HBE, His bundle electrogram; RVA, right ventricular apex.

prolonged. The situation is similar to sudden termination of atrial fibrillation, which can be followed by a prolonged post-conversion pause.

c. After cessation of pacing, the **longest SNRT following pacing at varying cycle lengths and secondary pauses** is documented. Secondary pauses are those intervals related to the sinus beats that occur after the first escape beat. CSNRT, which is calculated by means of subtracting baseline cycle length from SNRT, is considered abnormal if it exceeds 550 milliseconds.

d. **SACT** is used to evaluate conduction velocities in the atrium and in tissues surrounding the sinoatrial node. SACT is performed with the methods described earlier. A normal SACT is between 50 and 125 milliseconds. When both CSNRT and SACT are normal, symptoms are uncommon. The sensitivities of CSNRT (54%) and SACT (51%) combined are higher (64%), and the specificity is approximately 88%. The low sensitivity of these tests limits their value in predicting development of symptoms in asymptomatic patients.

e. **AV node and infranodal conduction system integrity** is tested with atrial stimulation techniques. Attention is paid to the AH and HV intervals during atrial pacing.

(1) The refractory period of the AV node is determined at two cycle lengths. The shortest cycle length with 1:1 AV conduction is also determined.

(2) The normal AV nodal response to burst pacing at short cycle lengths is second-degree Mobitz I AV block. HV interval prolongation or infrahisian block is not typically observed. If it occurs at cycle lengths longer than 400 milliseconds, HV interval prolongation suggests significant underlying His-Purkinje disease.

(3) Prolongation of the AV nodal refractory period is most frequently caused by high vagal tone or concomitant use of medications. It has no predictive or diagnostic value in evaluating patients believed to have bradycardia. However, a long AV nodal refractory period may mask underlying abnormal His-Purkinje refractoriness, and enhancement of AV nodal conduction with atropine or isoproterenol may be necessary during EPSs.

3. **Carotid sinus massage** is performed in all patients undergoing evaluation of bradycardia or syncope.

a. Firm pressure is applied over the carotid artery pulsation, behind the angle of the mandible.

b. A **positive cardioinhibitory response** is present if pauses of 3 seconds or more occur. A **vasodepressor response** is present if blood pressure decreases by > 50 mm Hg in the absence of marked bradycardia. Mixed responses are common.

B. SVT evaluation. One of the most important elements in the evaluation of tachyarrhythmias is careful analysis of the surface ECG during clinical tachycardia. This can give several clues to the underlying diagnosis and make the EPS more focused. Most SVTs that are induced in the EPS laboratory are re-entrant. They include AV nodal re-entry tachycardia, orthodromic AV re-entry tachycardia, atrial flutter, and re-entrant atrial tachycardia. Automatic tachyarrhythmias are relatively uncommon except in acutely ill patients. They characteristically exhibit a warm-up phenomenon and are difficult to induce with extra stimulus techniques, but may be induced with drugs such as isoproterenol.

1. **Baseline evaluation**
   a. Resting ECG and intracardiac recordings can provide important information about a possible cause even before any tachycardia is induced. The presence of a short PR interval on the ECG and wide QRS complex with a slurred initial deflection suggests preexcitation.
   b. Absence of preexcitation at rest does not rule out the presence of an accessory pathway. For the diagnosis of SVT, an atrial and a ventricular study have to be performed.
   c. If tachycardia is not induced at the baseline study, programmed stimulation in the atrium and ventricle is repeated with isoproterenol.
   d. Some SVTs, particularly those involving AV re-entry using a bypass tract, can be induced with ventricular stimulation, whereas atrial flutter and, to a lesser extent, atrial tachycardia are rarely induced by means of ventricular stimulation.
2. **Programmed stimulation** begins with burst pacing in the ventricle to document and characterize VA conduction. Absence of VA conduction practically excludes a concealed bypass tract, and ventricular extra stimulus technique may not need to be performed unless ventricular tachycardia is suspected.
   a. **Earliest retrograde atrial activity** is usually seen on the His electrogram during normal retrograde atrial activation through the AV node. Early retrograde atrial activity on the distal CS electrogram, if the position of the CS catheter is correct, suggests the presence of a left-sided accessory pathway (see Fig. 53.4). Early atrial activity in the proximal CS electrodes suggests a posteroseptal pathway or AV node slow pathway conduction.
      (1) Eccentric atrial activation is any atrial activation that does not activate the AV node and the area around the AV node first. This is frequently seen with retrograde ventricular stimulation, when the retrograde impulse finds the AV node refractory. The site of earliest atrial activation is then in the distal CS catheter and not in the proximal area closest to the AV node/His bundle. Evidence of eccentric atrial activation may not be clear during burst pacing when there is fusion of retrograde impulses, arriving through both the AV node and the accessory pathway.
      (2) The retrograde 1:1 cycle length should be documented.
      (3) Programmed ventricular stimulation is performed with single premature beats at two drive train cycle lengths (e.g., 600 and 400 milliseconds). During programmed stimulation, the following are recorded:
         (a) Retrograde refractory periods
         (b) The pattern and any changes in retrograde atrial activation
         (c) The site of retrograde VA block
         (d) The presence of dual retrograde AV node function
      (4) If an accessory pathway is found, its retrograde 1:1 conduction cycle length and refractory period are documented.

b. During atrial stimulation, particular attention is paid to the **AH and HV intervals.**

(1) Sudden prolongation of A_2H_2 of > 50 milliseconds in response to a decrement of 10 milliseconds in A_1A_2 is called a **jump** (see Fig. 53.6) and has been classically described as a sign of dual AV nodal physiology. **However, more recent reports have demonstrated that the normal AV node has dual pathways even if this "jump" is not demonstrated.** Furthermore, initiation of AV nodal re-entrant tachycardia does not require the presence of such a jump in the AV nodal conduction curve.

(2) Induction of re-entrant tachycardias generally depends on the occurrence of **unidirectional block and conduction delay**. In the case of AV nodal re-entry, antegrade block in the fast pathway combined with critical delay in the slow pathway allows the impulse to conduct retrograde on the fast pathway and excite the atrium. This first retrograde-conducted atrial depolarization is called an **echo beat** (see Fig. 53.6). If this echo beat succeeds in conducting antegrade down the slow pathway again and retrograde up the fast pathway, sustained AV nodal re-entry occurs.

(3) **Induction of AV node re-entry** is facilitated by use of shorter drive train cycle lengths and, if necessary, use of more than one extra stimulus or rapid burst atrial pacing. Occasionally, initiation of AV nodal re-entry requires ventricular pacing or premature beats.

(4) In the presence of an accessory pathway, the site of critical delay is also in the AV node. However, to induce orthodromic AV re-entry tachycardia, antegrade block of an atrial impulse has to occur in the accessory pathway so that it is excitable by the time the same impulse propagates

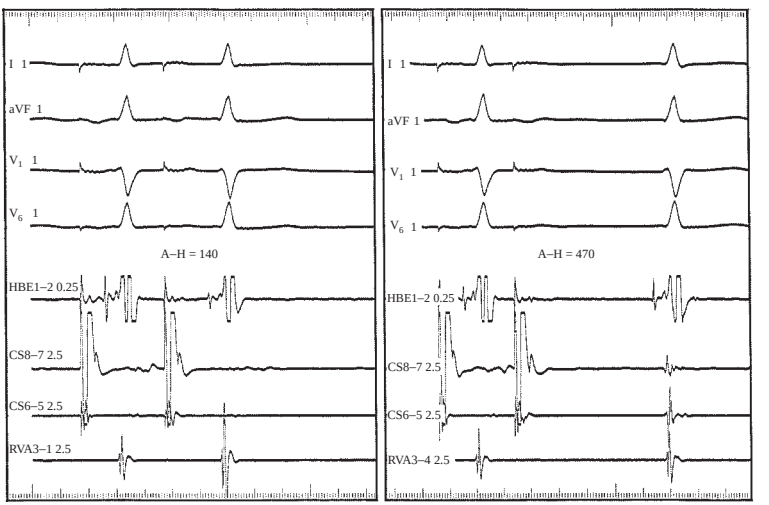

FIGURE 53.6 AV nodal jump and echo. A 10-millisecond decrement in S_1S_2 resulted in marked prolongation of A_2H_2 by > 300 milliseconds. In addition, an echo beat with a short H–A is seen on the CS electrogram, a definite evidence of dual AV node physiology. The atrial premature beat, blocked antegrade in the fast pathway, was conducted with sufficient delay in the slow pathway to encounter a nonrefractory retrograde fast pathway. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

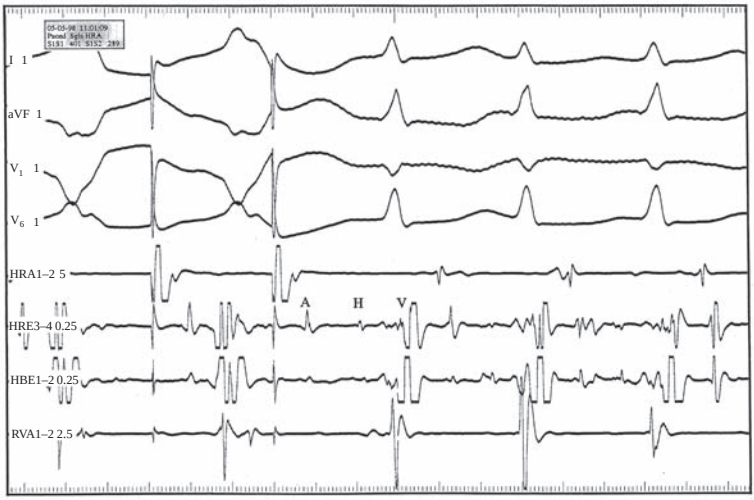

FIGURE 53.7 Orthodromic AV re-entry tachycardia. In this example from a patient with a manifest right-sided accessory pathway, premature atrial stimulation (S) blocks in the accessory pathway (resulting in a narrow QRS complex), conducts with a longer A–V, and re-excites the atrium. The tachycardia is narrow complex, with an H–A interval of 180 milliseconds. The earliest A is seen on the high right atrial catheter. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

through the AV node and ventricle and arrives to conduct retrogradely through the accessory pathway to the atrium (see Fig. 53.7).

3. **Evaluation of induced tachycardia**
   - **a.** If a tachycardia is induced, the first assessment is its **hemodynamic consequences**. Hemodynamically unstable tachycardia should be immediately terminated. Only if the tachycardia is hemodynamically stable can further evaluations during tachycardia be conducted.
     - **(1)** Whether the QRS is narrow or wide, the relation between atrial rate and ventricular rate is noted (AV association or dissociation).
     - **(2)** Lack of a 1:1 AV relation excludes AV re-entry tachycardia and, for practical purposes, AV nodal re-entry. In rare instances, AV node re-entry tachycardia can exhibit 2:1 AV block.
     - **(3)** If the atrial rate is faster than the ventricular rate, the diagnosis is **atrial tachycardia or atrial flutter**, depending on the rate and pattern of atrial activation.
     - **(4)** If the ventricular rate is faster than the atrial rate, the diagnosis is ventricular tachycardia. Alternative causes for AV dissociation include AV nodal re-entry tachycardia with block in the upper common pathway, re-entry tachycardia with a nodofascicular pathway, or a junctional tachycardia with retrograde block.
   - **b.** When a **1:1 AV relation** exists, **further evaluation** is needed. The following observations and techniques are helpful in arriving at the most likely mechanism:
     - **(1) Atrial activation.** The sequence of atrial activation during tachycardia is important in the differential diagnosis of SVT. Accurate placement of catheters is extremely important; catheter misplacement can lead to

inappropriate conclusions or interventions. The **earliest site of atrial activation** is noted. As mentioned above, if earliest atrial activation is in the distal CS, a left atrial tachycardia or AV re-entry using a left-sided accessory pathway is most likely. If an accessory pathway is located in the posterior septum, the earliest A is seen in the proximal CS electrogram. This is also true if the atria are being activated through the slow pathway of the AV node, as in atypical AV nodal re-entry tachycardia.

(2) The presence of **cycle length variation** during tachycardia helps predict the activation sequence. For example, a change in AA coupling interval before an equal change in HH or VV interval (with changing VA) suggests a diagnosis of atrial tachycardia.

(a) In cases of wide complex tachycardia in which there appears to be a 1:1 relation between H and V, HH interval change preceding VV interval change suggests supraventricular or BBR tachycardia.

(b) Cycle length variation may also be helpful when there is **slowing of tachycardia with the development of bundle branch block and acceleration with resolution of the block**. This finding is suggestive of AV re-entry using an accessory pathway ipsilateral to the bundle branch block as the retrograde limb. This can be appreciated on the surface ECG. In fact, prolongation in tachycardia cycle length in association with a bundle branch block is caused by prolongation of the VA interval. The activation wavefront must travel down the contralateral bundle and across the intraventricular septum before it reaches the pathway. The change in cycle length is more pronounced with lateral than with septal pathways.

(3) HA and VA intervals. A constant HA or VA relation despite cycle length variation (even in the absence of bundle branch block) is highly suggestive of **AV node re-entry or accessory pathway–mediated tachycardia.** The change in tachycardia cycle length is caused by varying antegrade conduction time through the AV node. The VA time can also be used to differentiate AV nodal re-entry from AV re-entry. A VA interval < 70 milliseconds is rarely seen with AV re-entry and strongly suggests the diagnosis of AV nodal re-entry (see Fig. 53.8). VA times in excess of 70 milliseconds are seen with AV re-entry and atypical AV nodal re-entry (so-called fast–slow AV nodal re-entry).

(4) Introduction of premature beats during tachycardia. Premature ventricular beats are typically introduced during tachycardia at intervals when the His bundle is refractory. Because the normal retrograde path (His-AV node) is refractory, preexciting the atrium with a premature ventricular beat at those intervals is diagnostic of the presence of an accessory pathway capable of retrograde conduction. Consistent termination of tachycardia with such premature beats without retrograde conduction to the atrium is also diagnostic of AV re-entry and excludes atrial tachycardia.

(5) Pacing maneuvers during SVT. During SVT, ventricular pacing maneuvers can be a useful first step in diagnosing the mechanism of tachycardia. Ventricular pacing at a cycle length slightly faster than the tachycardia cycle length is referred to as ventricular overdrive (VOD) pacing. Successful entrainment occurs when VOD resets the tachycardia such that the atrial rate is accelerated to the paced ventricular cycle length and returns to the tachycardia cycle length when ventricular pacing stops and the tachycardia continues. An atrial–atrial–ventricular response upon cessation of VOD, or V–A–A–V response, is diagnostic of atrial tachycardia. A V–A–V response is most consistent with a re-entry tachycardia. The relationship of the post-pacing interval to the tachycardia

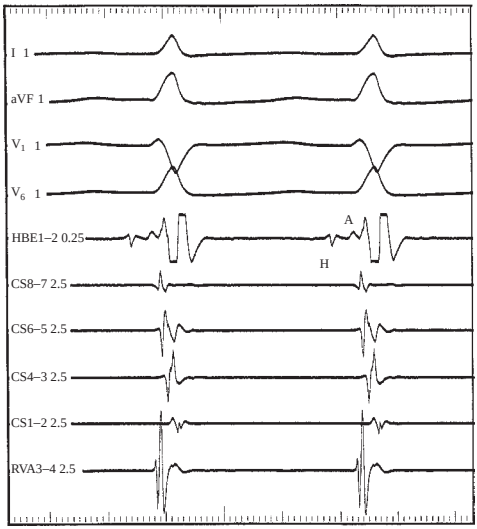

FIGURE 53.8 AV node re-entry tachycardia. Tachycardia is narrow complex and characterized by very short V–A interval and an H–A interval of < 70 milliseconds. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

cycle length can then be helpful in differentiating the type of re-entry tachycardia.

(6) Initiation and termination of tachycardia. To understand the mechanism of tachycardia, it is important to know the mechanism of initiation. For re-entry to occur, block in one limb of the re-entrant circuit and slow conduction in the other limb must take place. It is important to review the stimulation sequences that did not induce tachycardia and compare them with those that did. A sudden jump in the AH interval suggests, but is not diagnostic of, AV nodal re-entry. Orthodromic AV re-entry tachycardia develops during atrial stimulation after antegrade block in the accessory pathway takes place in combination with a critical delay in the AV node. With ventricular stimulation, AV re-entry tachycardia develops after block in the AV node or His-Purkinje system occurs. Termination of the tachycardia simultaneous with AV node block (A with no H) suggests AV node dependence and is helpful in excluding AV node–independent tachycardias (atrial tachycardia and flutter).

4. **Significance of induced tachycardia.** With the exception of atrial fibrillation, induced re-entrant SVTs signify the presence of an established anatomic circuit. Comparison with the clinical arrhythmia is important and, unless significant differences exist, it can safely be assumed that the induced tachycardia is clinically significant. If a wide complex tachycardia with a supraventricular mechanism is induced, the recording is compared with a clinical recording. If the QRS morphology is different from that of the clinical arrhythmia, a search for ventricular arrhythmia may be warranted.
5. **Atrial flutter**, a special type of atrial tachycardia that involves a well-defined anatomic circuit, is amenable to curative catheter ablation techniques.
   a. In the typical variety of atrial flutter, the waveform travels counterclockwise around the tricuspid annulus. The circuit is bounded anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and its inferior medial continuation as the eustachian ridge. The site of functional block appears to be in the isthmus region, which is the narrow corridor between

the inferior tricuspid annulus and the inferior vena cava. The site of conduction delay or slowing appears to be due to transverse conduction block into the crista, forcing the wavefront to enter the crista at its superior end before propagating down the crista into the isthmus region.

b. To induce counterclockwise atrial flutter, progressively more rapid (approximately 250 to 200 milliseconds) burst pacing appears to be most successful and is performed anywhere medial to the isthmus. The impulses block in the isthmus and conduct counterclockwise around the tricuspid ring with sufficient delay to sustain atrial flutter. If burst pacing is used lateral to the isthmus, clockwise atrial flutter may be induced. Successful ablation of typical atrial flutter necessitates generation of bidirectional isthmus block by applying a line of RF lesions that spans the posterior isthmus from the tricuspid valve to the inferior vena cava (the cavotricuspid isthmus).

c. Less commonly, different types of atrial flutter in which the subeustachian isthmus is not part of the circuit are induced. These atypical flutters have many varieties and locations but share a common re-entrant circuit that revolves around an area of conduction block or delay, usually scar tissue. Treatment involves creating an ablation line from the area of scar to an anatomic barrier or ablating critically narrowed re-entrant paths within a scarred region. The success rates in ablating these atypical forms of atrial flutter are not as high as for isthmus-dependent flutters.

6. Atrial fibrillation. Previous evidence favored multiple re-entrant wavelets as the predominant mechanism responsible for atrial fibrillation. However, it has been recently demonstrated that atrial fibrillation is frequently initiated by rapidly firing foci located predominantly in the pulmonary veins, where sleeves of atrial muscle with abnormal automaticity or perhaps re-entry are present. Our current concept of atrial fibrillation revolves around two factors: a triggering mechanism and a substrate that can maintain atrial fibrillation. Most atria, especially in relatively normal hearts, are quite resistant to initiation of atrial fibrillation. Thus, the concept of focal initiation of atrial fibrillation by rapid bursts of focal atrial tachycardia emerged as a triggering mechanism, making it possible to map and target these sites for catheter ablation. The current understanding is that a vast majority of these triggering sites are near the os of the pulmonary veins in the left atrium.

a. Ablation of these triggering foci requires left atrial access by transseptal puncture. Following transseptal puncture, a decapolar mapping catheter with a ring configuration called a lasso is used to record electrical activity around the circumference of each pulmonary vein ostium. It displays a far-field atrial signal and a near-field pulmonary vein potential. This is characterized as a very sharp spike following the atrial deflection during sinus rhythm. However, discharges from the vein will invert this activation sequence; the pulmonary vein potential will precede the atrial activation.

b. RF ablation is delivered around the roving circular lasso catheter along the antrum of the pulmonary veins to abolish the pulmonary vein potentials. Alternatively, a wide antral circumferential ablation around the pulmonary veins on each side is used to electrically isolate the pulmonary veins from the left atrium. In that manner, abnormal firing would be confined to the veins and no atrial fibrillation would be induced.

c. In a minority of cases, atrial fibrillation may be induced by rapid discharges originating from nonpulmonary vein foci, most commonly from the superior vena cava. Circumferential catheter ablation can be performed in the same fashion, aiming at abolition of all venous potentials (electrical isolation).

C. Evaluation of accessory pathways

1. The **most common locations** for accessory pathways in decreasing order of frequency are left free wall, posterior region, posteroseptal region, right free wall,

and anteroseptal region. Concealed accessory pathways (no evidence of antegrade conduction) with only retrograde conduction are more common than manifest pathways, which have antegrade conduction manifested by delta waves on the surface ECG, the slurred initial deflection of the QRS that implies preexcitation as described earlier.

   a. **Right-sided accessory pathways** are more likely than left-sided accessory pathways to be associated with **congenital heart disease**. An unusual type of right-sided accessory pathway is the atriofascicular accessory pathways, which originate in the right atrium, traverse the right anterior region of the tricuspid valve annulus, and insert in the region of the right bundle or the right-sided Purkinje network. These accessory pathways have unidirectional antegrade conduction with decremental conduction properties similar to an AV node. These pathways are frequently referred to as Mahaim pathways and typically do not conduct retrogradely.
   b. **Multiple accessory pathways** are more frequently encountered on the right side and in survivors of sudden death. In these patients, the most common combination is posteroseptal and right free wall pathways.
   c. Both antidromic and orthodromic AV re-entrant tachycardias require participation of the accessory pathway. In rare instances, antidromic tachycardia can involve one accessory pathway in the antegrade direction and a second pathway in the retrograde direction.

2. Evidence of preexcitation is supported by the presence of **short HV interval** (< 35 milliseconds) **at rest** or with atrial pacing and the appearance of increasing preexcitation either with atrial pacing or with administration of drugs that cause AV nodal conduction slowing, or with autonomic maneuvers. The electrophysiologic properties of the accessory pathway are examined, including its antegrade and retrograde conduction and refractory periods. If tachycardia is induced during atrial or ventricular stimulation, its mechanism is defined according to the techniques discussed earlier. This depends on whether the tachycardia is narrow or wide complex.
3. **Orthodromic AV re-entry tachycardia** is commonly initiated by a ventricular premature stimulus that blocks in the His-Purkinje system or, rarely, in the AV node, but conducts in a retrograde direction over the accessory pathway. It can also be induced by an atrial premature stimulus (echo beat) that blocks the accessory pathway and conducts slowly over the AV conducting system. Induction is facilitated by the presence of a relatively **long antegrade refractory period of the accessory pathway** or a **long retrograde refractory period of the His-Purkinje system**.
4. **Antidromic AV re-entry tachycardia** (see Fig. 53.9) can be initiated with burst pacing in the atrium or with a premature atrial stimulus that **blocks in the AV node** and **conducts over the accessory pathway**. Less often, it can be induced with a premature ventricular stimulus that blocks the accessory pathway in a retrograde manner and conducts over the AV node. Induction of antidromic tachycardia necessitates excellent retrograde conduction over the His-Purkinje system–AV node; it almost always involves a free wall accessory pathway as the antegrade limb and is frequently associated with the presence of multiple accessory pathways.
5. **Localizing accessory pathways**
   a. **Surface electrocardiographic localization**
   (1) **Delta wave vectors**
      (a) Left lateral: negative I, aVL; positive II, III, aVF, V_1–V_6
      (b) Left posterior wall: positive I, aVL; negative II, III, aVF; positive V_1–V_3/V_4
      (c) Posteroseptal: positive I, aVL; negative II, III, aVF; R/S < 1 in V_1
      (d) Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2
      (e) Anteroseptal: positive I, aVL; positive II > III; negative V_1–V_6

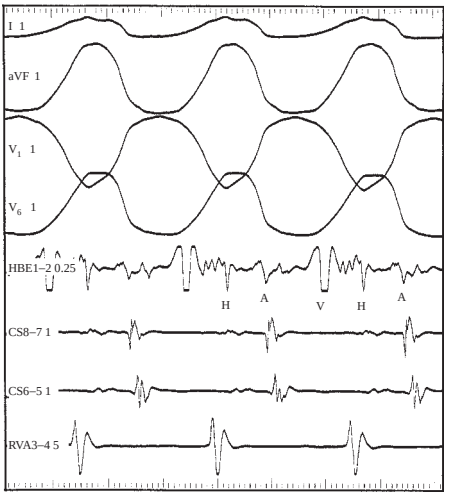

FIGURE 53.9 Antidromic AV re-entry tachycardia. This tachycardia was induced with atrial burst pacing in a young patient with two right-sided manifest accessory pathways. The tachycardia is rapid and wide complex, with the earliest retrograde A seen in HBE1–2, consistent with retrograde activation through the AV node. AV node re-entry with antegrade activation using the accessory pathway (bystander accessory pathway) was excluded by lack of evidence of dual AV node physiology. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

(2) P-wave morphology during orthodromic tachycardia
- **(a)** Left lateral: negative I, aVL; positive III > aVF > II; negative V_5 and V_6
- **(b)** Posteroseptal: positive aVR, > aVL; negative II, III, aVF
- **(c)** Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2

b. Localization during EPSs

(1) Pacing from multiple atrial sites: shortest A-delta occurs with pacing close to the atrial insertion site of AP and results in maximal preexcitation.

(2) Retrograde atrial activation during orthodromic tachycardia and V pacing
- **(a)** Atrial activation sequence
  - **(i)** Left and right free wall: eccentric
  - **(ii)** Posteroseptal: A_{CSos} earlier than A_{His}
  - **(iii)** Anteroseptal: A_{CSos} later than A_{His}
- **(b)** Atrial activation sequence when a ventricular premature stimulus is delivered during tachycardia at the time when His is refractory
- **(c)** The earliest site of atrial activation identifies the site of atrial insertion of an accessory pathway

(3) Relation of local ventricular electrogram to delta: earliest V correlates with ventricular insertion site. This may be slightly offset or oblique compared with the atrial insertion site.

(4) Effects of bundle branch block
- **(a)** Bundle branch block increasing the VA interval by > 35 milliseconds; ipsilateral free wall accessory pathway
- **(b)** With bundle branch block ipsilateral to septal accessory pathways, the increase in VA times is < 25 milliseconds
- **(c)** Left anterior fascicular block can increase VA times 15 to 35 milliseconds with left free wall accessory pathway, particularly with an anterolateral left-sided accessory pathway

(5) Recording of accessory pathway potential: sharp spike 10 to 30 milliseconds before the onset of the delta wave

6. Identifying the presence of multiple accessory pathways

a. Changing antegrade delta waves during sinus rhythm, atrial pacing, atrial fibrillation, and with antiarrhythmic drugs

- **b.** Evidence of multiple routes of retrograde atrial activation
  - **(1)** Changing VA time or activation sequence
  - **(2)** Failure to prolong VA time with ipsilateral bundle branch block
- **c.** Orthodromic tachycardia with antegrade fusion
- **d.** Preexcited tachycardia
  - **(1)** Antegrade conduction over septal accessory pathway
  - **(2)** Antidromic tachycardia faster than orthodromic tachycardia
- **e.** Atypical patterns of preexcitation
- **f.** Mismatch of site of antegrade preexcitation and retrograde atrial activation during AV re-entry tachycardia

D. Ventricular tachycardia evaluation

1. The most common reason for performing EPS on patients with suspected ventricular arrhythmias is documentation of inducible tachycardia, testing the effect and response to anti-tachycardia pacing and defibrillation, and endocardial mapping to direct attempts at ablation. Recent trials have stratified patients with ischemic or nonischemic cardiomyopathy, congestive heart failure, and reduced LV ejection fraction at higher risk for sudden cardiac death and thus reduced the usefulness of EPS in determining the need for ICD implantation.
2. An **atrial study** is considered for all patients undergoing evaluation of ventricular tachycardia. This serves three main purposes: diagnosis of the underlying advanced conduction system disease, documentation of coexisting SVT, and induction of rare forms of ventricular tachycardia that may be inducible only with atrial pacing.
3. **Programmed ventricular stimulation** is performed as described earlier. If ventricular tachycardia is not induced despite program stimulation from two RV sites (RV apex and outflow tract), repeat stimulation can be performed after isoproterenol infusion. However, isoproterenol should not be given to patients with active ischemic heart disease. It is primarily of value to those with exercise- or catecholamine-dependent ventricular tachycardia. LV stimulation is not necessary because RV stimulation techniques have adequate sensitivity and specificity, and the risk of left heart catheterization is avoided. If no ventricular tachycardia is induced with any of these techniques, the arrhythmia is deemed noninducible.
4. **Techniques for terminating induced ventricular tachycardia.** Pacing terminates as many as 85% of induced ventricular tachycardias in the laboratory. Success is more likely to be achieved with slower tachycardia rates (< 200 beats/min) and in hemodynamically tolerated tachycardias. Other factors predictive of success of pacing include the site of stimulation in relation to the tachycardia zone, ventricular conduction properties, and refractoriness. Pacing can also accelerate tachycardia, an important consideration when anti-tachycardia pacing is being considered.
5. **Techniques for terminating tachycardia with pacing.** One technique entails use of one or more **progressively earlier premature ventricular stimuli**. The other technique uses **burst pacing** to overdrive the tachycardia, but there is a greater risk of accelerating the tachycardia into a hemodynamically unstable arrhythmia. Techniques that can be used if pacing fails include delivery of ultrarapid train stimulation and synchronized direct current cardioversion.
6. There are a variety of **responses to programmed stimulation**. What is important is the correlation between these responses in different populations of patients and future risk of adverse outcome. For example, induction of single or double BBR beats has no bearing on long-term outcome among persons with normal LV function and is not considered an abnormal finding. Induction of sustained monomorphic ventricular tachycardia, particularly among persons with reduced LV ejection fraction, identifies a subset of patients at high risk for sudden death.

a. Sustained monomorphic ventricular tachycardia

(1) Induction of sustained monomorphic ventricular tachycardia is the **most important response** and has the highest predictive value. This is particularly true if the induced tachycardia is similar to the clinical arrhythmia in both rate and structure. Patients with easily induced ventricular tachycardia (e.g., with single premature beats) have worse outcome than those in whom tachycardia is more difficult to induce. It is important to document reproducibility of ventricular tachycardia during programmed stimulation. Slow, sustained tachycardia, particularly in patients with ischemic substrate, is typically more reproducible than more rapid tachycardias and tachycardias in those with nonischemic cardiomyopathies. Sustained tachycardia has clearly worse prognostic implications than nonsustained tachycardia. There is no agreement on what constitutes an abnormal response among patients with nonsustained tachycardia or whether any therapeutic intervention should be pursued for these patients.

(2) Among patients with ischemic substrate, programmed stimulation induces sustained monomorphic ventricular tachycardia in as many as 95% of patients with a history of clinical sustained ventricular tachycardia, approximately 60% of those with nonsustained ventricular tachycardia, and approximately 50% of patients experiencing sudden cardiac death. Induction of sustained monomorphic ventricular tachycardia in any of the above subsets has very high specificity (> 90%) for spontaneous clinical ventricular tachycardia and sudden death. Testing at two RV sites increases sensitivity without sacrificing specificity.

(3) Patients with **nonischemic substrate** are more challenging to evaluate because EPSs are less sensitive and specific. Although inducible sustained monomorphic ventricular tachycardia has a worse prognosis than the noninducible type, the positive predictive value of abnormal results of EPS is at best 70%. Patients with negative results of EPS are still at high risk for sudden death, even if they have no prior clinical events. The prognosis may be more favorable if inducible tachycardia is suppressed by drugs, but the risk of future events continues to be high. One can never be reassured about the outcome among patients with nonischemic cardiomyopathy using results of EPS.

(4) **BBR tachycardia** is a type of ventricular tachycardia with a well-defined macro re-entrant circuit. It occurs most often among patients with dilated cardiomyopathy and is frequently symptomatic.

(a) In the **typical pattern**, the impulse travels antegrade down the right bundle branch, across the interventricular septum, and retrograde up the left bundle branch. The tachycardia exhibits a left bundle branch block pattern, with a **His deflection preceding every QRS complex**. In sinus rhythm, the **HV interval is abnormally long**, and during tachycardia it is at least equal and frequently longer than the baseline HV.

(b) In rare instances, it is difficult to differentiate BBR tachycardia from an SVT with aberration or from a myocardial ventricular tachycardia with retrograde His deflections.

(c) BBR tachycardia is frequently rapid and exhibits AV dissociation. If cycle length variation takes place, it is important to assess the order of changes in the HH and VV intervals. If HH changes take place before VV changes, BBR is likely. A VV change that occurs before HH change and is also associated with a variation in the HV interval suggests myocardial ventricular tachycardia.

(d) Treatment with **antiarrhythmic agents**, including amiodarone, is not helpful and may lead to stabilization of the re-entrant circuit. BBR tachycardia is curable with RF ablation of the right bundle.

b. **Polymorphic ventricular tachycardia** frequently occurs with high-output stimulation. It is also more likely to occur with increasing numbers of extra stimuli.

(1) **Interpretation** of the induction of polymorphic ventricular tachycardia depends on the clinical situation. For example, inducible polymorphic ventricular tachycardia in a survivor of sudden cardiac death is considered significant. In a patient with ventricular ectopy and normal ventricular function, inducible polymorphic ventricular tachycardia is a nonspecific response.

(2) Similar interpretation applies to **induced ventricular fibrillation**. If the patient has never had clinical ventricular tachycardia or ventricular fibrillation and has no underlying heart disease, the induced ventricular fibrillation is considered a nonspecific finding that does not warrant therapy.

c. Patients with **hypertrophic cardiomyopathy** represent another subset for whom the predictive value of EPS is problematic. Induction of sustained monomorphic ventricular tachycardia, induction of ventricular fibrillation without aggressive stimulation protocols, and induction of ventricular arrhythmias with atrial pacing or as a result of atrial fibrillation are generally considered to be **poor prognostic signs**.

d. **Summary**. It is important to have a thorough understanding of the underlying clinical problem and anatomic substrate to assess the appropriateness of any EPS finding for an individual patient.

(1) Repetitive responses caused by BBR are usually physiologic, whereas intramyocardial repetitive ventricular responses are abnormal. However, neither of these responses should be used to guide therapy.

(2) Induced polymorphic ventricular tachycardia and ventricular fibrillation can be considered nonspecific findings or clinically significant depending on the clinical circumstances. However, they should not be used to guide drug therapy in any situation.

(3) Induced sustained monomorphic ventricular tachycardia identical to the clinical arrhythmia has the highest sensitivity and specificity and has greater importance in predicting outcome.

(4) The importance of nonsustained ventricular tachycardia remains controversial. Noninducibility in patients with nonischemic cardiomyopathy or survivors of sudden cardiac death may not provide prediction as accurate as that for patients with underlying ischemic substrate and documented nonsustained ventricular tachycardia. Therapeutic decisions therefore have been individualized.

(5) Guidelines derived from studies including the MADIT trials and the SCD-HeFT have obviated the need for performing EPS before deciding to implant ICDs in particular patient populations.

7. **Mapping of ventricular tachycardia.** Mapping of ventricular tachycardia involves identification of the **earliest sites of activation** during tachycardia and detailed outlining of the **tachycardia circuit**. Endocardial mapping has aided in the evaluation of mechanisms of tachycardia. More recently, mapping has been coupled with RF ablation with high rates of success.

a. Mapping can be performed with steerable electrode catheters during EPS or can involve introduction of specialized catheters with various configurations designed to compare several simultaneously acquired endocardial electrograms.

b. For the most part, mapping of ventricular arrhythmias takes place in the left ventricle. However, several types of ventricular tachycardia that originate from the right ventricle, including those from the outflow tract, have been successfully mapped and ablated.

c. Activation mapping takes place during the tachycardia. The objective is to identify the site of earliest activation. Because this lengthy process has to take place during tachycardia, it must be hemodynamically tolerable. The earliest activation site corresponds to the exit site of the circuit.

d. Sites of origin of tachycardia in patients with ischemic heart disease are usually found in the periinfarction zone or in the border of an LV aneurysm. To confirm the site, entrainment from that site is performed. Entrainment involves transient overdrive pacing and resetting of the tachycardia without terminating the tachycardia. When entrainment is achieved within the re-entrant circuit inside the slowly conducting scarred regions of the heart, or isthmus, pacing produces QRS morphologic match on all 12 surface ECG leads. The return cycle length of activation at the site of pacing after cessation of pacing equals the tachycardia cycle length (see Fig. 53.10). These two observations imply that depolarization caused by pacing has the same exit from the scar as the tachycardia and that the pacing site is within the circuit.

e. Pace mapping can be used in evaluations of patients with hemodynamically intolerable tachycardia. Ventricular pacing is performed at various sites at rates that do not cause hemodynamic instability. The site where pacing results in QRS match with clinical tachycardia corresponds to the exit sites of the tachycardia circuit.

f. **Electroanatomic mapping systems allow the** measurement of tissue voltage, providing accurate delineation of scar tissue and its boundaries. Thus, mapping in sinus rhythm allows for delimitation of the scar and areas of the scar border that are likely sites of tachycardia exit. Pace mapping can be used to identify those sites around the scar that correspond to tachycardia exits. Linear lesions, performed to interrupt these exit sites responsible for re-entrant circuits, can be undertaken, allowing successful ablation of tachycardias that would not be otherwise mapped due to patient intolerance of any sustained tachycardia. Another method of mapping a hemodynamically unstable ventricular tachycardia is to use a mapping system that can acquire the map of the entire endocardium in a single beat. This requires insertion of an "array" catheter into the left ventricle that acquires the electrograms from 64 points on the balloon and calculates the virtual activation on the endocardial surface. Alternatively, an intra-aortic balloon pump or percutaneous LV assist device may be considered to assist with mapping and ablation during prolonged or hemodynamically unstable VT.

g. Mapping can also be performed intraoperatively when endocardial resection is considered. Although this approach can still be used, it is infrequently recommended, as other approaches described above in combination with implantable defibrillators have yielded good patient survival and excellent success in eliminating problematic ventricular tachycardias.

h. Some patients including many with nonischemic cardiomyopathy or certain variants such as Chagas disease and hypertrophic cardiomyopathy may require both endocardial and epicardial approaches to VT mapping and ablation. Percutaneous access into the epicardial space is obtained with a subxiphoid approach under fluoroscopic guidance and small injections of contrast until the parietal pericardium is penetrated. In patients with dense pericardial adhesions that may limit catheter movement, an intraoperative subxiphoid incision or open sternotomy may be considered to allow for greater exposure and access.

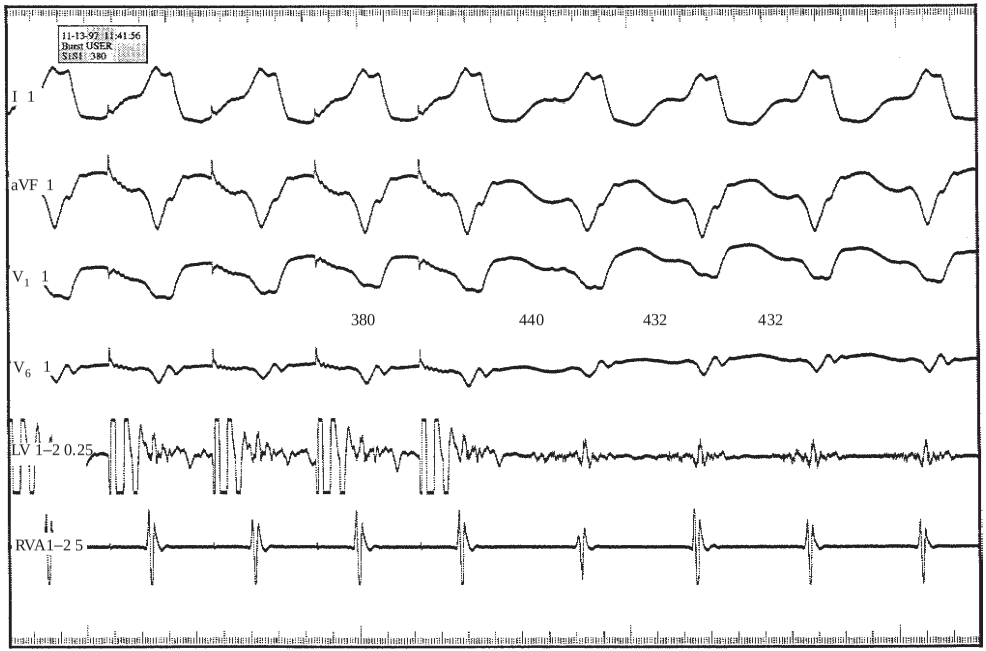

FIGURE 53.10 Entrainment of ventricular tachycardia. Pacing at a rate slightly faster (380 milliseconds) than tachycardia cycle length at a site believed to be the isthmus of the tachycardia resulted in QRS morphology very similar to the native ventricular tachycardia (concealed entrainment) in all 12 leads (only 4 leads shown). In addition, the post-pacing interval is very close to the tachycardia cycle length, suggesting that the pacing site is within the tachycardia circuit. Application of radiofrequency energy at this site resulted in successful ablation of this tachycardia. LV, left ventricular; RVA, right ventricular apex.

ACKNOWLEDGMENTS: *The author thanks Dr. Carlos Alves and Dr. Eduardo B. Saad for their contributions to prior editions of this chapter.*

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CHAPTER 54

Tyler L. Taigen

Cardiac Pacing

I. INTRODUCTION. The indications and technology of cardiac pacing continue to evolve, leading to a rapid increase in the number of pacemakers implanted. Pacemaker implantation rates increased from 329 implants per million population in 1990 to 612 per million population in 2002. In 2011, 400,000 cardiac devices were implanted and over 3 million people in the United States had implantable cardiac rhythm management devices. It is imperative that the physician caring for the pacemaker patient understand the basic physiology and technology of cardiac pacing and be able to apply these principles to effectively manage the unique problems with which these patients may present.

II. BASIC COMPONENTS OF CARDIAC PACEMAKERS

A. Pulse generator

1. **Power source (battery).** Lithium iodide is the most common chemical compound used. Lithium batteries deplete over a more predictable time course than other types of compounds, such as zinc mercuric oxide, that were used in prior generations of devices.
2. **Circuitry**
   a. **Output circuits.** These circuits control programmable features of the output pulse, including amplitude and pulse width.
   b. **Sensing circuits.** These circuits process the intracardiac electrogram, including amplification and filtering of the signal, and also provide other functions such as management of external electromagnetic interference (EMI). A bandpass filter allows signals of a certain frequency range to be passed while signals of other frequency ranges are blocked or attenuated. Pacemakers use a bandpass filter to distinguish between cardiac depolarization and repolarization signals from extracardiac signals, such as myopotentials from the chest wall musculature. Some appropriate signals that pass through the filter are small in amplitude, and a sense amplifier increases the appropriate signal for the device to process.
   c. **Timing circuits.** These circuits control the pacing intervals and sensing/refractory periods. They may be altered by input from the sensing circuits.
   d. **Telemetry circuit.** These circuits allow communication between an external programmer and the pulse generator for pacemaker programming or retrieval of information.
   e. **Microprocessor.** Most modern pacemakers have computer chips with memory (read only memory [ROM] and random access memory [RAM]) and therefore have enhanced capabilities, such as downloading of new features via telemetry and increased storage of diagnostic data.
   f. **Sensor circuit for rate-adaptive pacing.** See below.

B. Lead system

1. **Terminal pin.** The male portion of the proximal lead that connects to the pulse generator.

2. **Lead body.** Consists of conductor(s) and insulation. The conducting wire connects the stimulating and sensing electrodes to the terminal pin. The lead insulation is most commonly silicone rubber or a polyurethane material.
3. **Stimulating/sensing electrode(s).** The distal end of the lead that connects via a fixation mechanism to atrial or ventricular myocardium.
4. **Fixation device.** Passive fixation represents an attachment mechanism (e.g., "fins" or "tines") that anchors electrodes to the endocardial trabeculae. Active fixation leads are secured to the endocardium using a "screw-in" mechanism. Over the past decade, active fixation leads have been implanted much more commonly. These types of leads have a lower rate of early dislodgement and yet higher chronic capture thresholds than passive fixation leads.

C. Polarity. This refers to the electrode configuration of the pacing lead or the configuration of the pulse generator. Polarity may be unipolar or bipolar; however, some pacemakers can be programmed to pace in one polarity and sense in another (only if a bipolar lead is present).

1. **Unipolar.** Configuration in which the cathode (negative) is on the lead, usually the lead tip, and the anode (positive) is the pacemaker can. This results in a large sensing "antenna" and produces large pacemaker artifact (spikes) on the electrocardiogram (ECG) due to proximity of the circuit to ECG electrodes.
   a. **Advantages.** Better sensing of premature ventricular contractions (PVCs), low-amplitude signals, and shifted axis.
   b. **Disadvantages.** Oversensing of extraneous signals, especially pectoralis muscle activity (myopotentials), and inadvertent skeletal muscle stimulation may occur. Moreover, large pacemaker artifacts on the ECG may obscure native electrical activity.
2. **Bipolar.** Both electrodes are at the end of the lead—the cathode (negative) at the distal tip and the anode (positive) at the proximal ring. This results in a smaller sensing "antenna" with smaller pacemaker artifact (spikes) on the ECG. Myocardial stimulation occurs as electrons from the cathode travel through the myocardium and back to the anode.
   a. **Advantages.** Less myopotential oversensing and skeletal muscle stimulation, and the smaller pacemaker artifact on the ECG, do not obscure native wave morphology.
   b. **Disadvantages.** More complex lead design is more susceptible to malfunction/failure. Small pacemaker artifact on the ECG may be difficult to see.

D. Lead–heart interface. This is equivalent to the site of energy transfer (pacing) and sensing functions.

III. PACEMAKER CLASSIFICATION. The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group initially published a "pacemaker code" in 1983. Guidelines were later revised in 2002 and the five-position code remains the accepted nomenclature for pacemaker therapy (see Table 54.1). The first two positions (chamber paced and chamber sensed) are straightforward. The third position, however, is often misunderstood. As outlined in Table 54.1, the third position reflects the device response to a sensed event (labeled "I," "T," or "D"). 'I" (Inhibited)—the device will pulse the given chamber unless it senses an intrinsic event. Thus when programmed DDI, atrioventricular (AV) synchrony will only exist if the atrial chamber is paced. If the atrial activity is intrinsic and the ventricular response depends only on the sensed activity in that chamber, then AV synchrony will not be provided. "T" (Triggered)—this mode is used during device testing where a sensed event results in the device producing a pulse. "D" (Dual)—atrial and ventricular sensing and pacing with dual-chamber devices. When programmed DDD, a sensed atrial beat inhibits atrial pacing and, after a programmed time interval, triggers ventricular pacing. This mode enables tracking of intrinsic atrial activity and corresponding ventricular pacing to allow AV synchrony.

TABLE 54.1 Revised NASPE/BPEG Generic (NBG) Code for Antibradycardia, Adaptive Rate, and Multisite Pacing

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programmability, rate modulation	Multisite pacing
Letters	O = none	O = none	O = none	O = none	O = none
	A = atrium	A = atrium	T = triggered	R = rate modulation	A= atrium
	V = ventricle	V = ventricle	I = inhibited		V = ventricle
	D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)
Manufacturers' designation only	> S = single (A or V)	S = single (A or V)			

BPEG, British Pacing and Electrophysiology Group; NASPE, North American Society of Pacing and Electrophysiology. *Pacing Clin Electrophysiol*. 2002;25:260–264.

IV. INDICATIONS FOR PACEMAKER IMPLANTATION. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) published updated guidelines for indications for pacemaker implantation in device-based therapy of cardiac rhythm abnormalities in 2008 (see Table 54.2).

V. PHYSIOLOGY OF CARDIAC PACING

A. Pulse generator output. This is determined by the output voltage and duration of the stimulating pulse (pulse width). Most implanted cardiac pacemakers use constant-voltage output (as opposed to most temporary cardiac pacemakers, which use constant-current output).

B. Strength–duration relation. There is an exponential relationship between the stimulus amplitude for myocardial stimulation and the pulse width, such that there is a rapidly rising strength–duration curve at pulse widths < 0.25 millisecond and a flatter curve at pulse widths > 1.0 millisecond (see Fig. 54.1).

1. **Rheobase.** The flattened portion of the strength–duration curve indicating the point at which increasing pulse width is no longer associated with a progressive decrease in stimulus amplitude (voltage) required for myocardial stimulation. In general, the rheobase voltage is determined by assessing the threshold stimulus voltage at a pulse width of 2.0 milliseconds.
2. **Chronaxie.** This corresponds to the threshold pulse width at twice the rheobase voltage. The chronaxie pulse duration approximates the point of minimal threshold energy on the strength–duration curve.

C. Safety margins

1. **Voltage.** The voltage output should be programmed to a level that is approximately twice the capture (stimulation) threshold for a 2:1 output safety margin.
2. **Pulse width.** The pulse duration should be programmed to a level approximately three times the pulse width capture threshold for a 3:1 output safety margin. The typical range for pulse width is 0.2 to 1.0 millisecond.

D. Temporal changes in stimulation threshold. Typically, the stimulation threshold rises within 24 hours following implantation of a permanent pacemaker lead. The

TABLE 54.2 Indications for Cardiac Pacing

	Class I	Class II	Class III
SND	1. SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. 2. Symptomatic chronotropic incompetence. 3. Symptomatic sinus bradycardia that results from required drug therapy for medical conditions.	IIa: 1. SND with heart rate < 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. 2. Syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. IIb: In minimally symptomatic patients with chronic heart rate < 40 bpm while awake.	1.Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. 2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. 3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy.
Acquired AV block	1. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with the following conditions: – bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block. – arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia. – awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥3.0 s or any escape rate < 40 bpm, or with an escape rhythm that is below the AV node.	IIa 1. Permanent pacemaker implantation is reasonable for persistent third-degree AV block with an escape rate > 40 bpm in asymptomatic adult patients without cardiomegaly. 2. Permanent pacemaker implantation is reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study.	1. First-degree AV block. 2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian. 3. AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms).

TABLE 54.2 Indications for Cardiac Pacing

	Class I	Class II	Class III
	– awake, symptom-free patients with AF and bradycardia with one or more pauses of at least 5 s or longer – after catheter ablation of the AV junction – postoperative AV block that is not expected to resolve after cardiac surgery. – neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms. Permanent pacemaker implantation is indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block. Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node. Permanent pacemaker implantation is indicated for second- or third-degree AV block during exercise in the absence of myocardial ischemia.	IIb 1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease. 2. AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn.	
Hypertrophic CM	Permanent pacing is indicated for SND or AV block in patients with HCM	IIa: None	1. Permanent pacemaker implantation is not indicated for patients who are asymptomatic or whose symptoms are medically controlled.

(*Continued*)

TABLE 54.2 Indications for Cardiac Pacing (*Continued*)

	Class I	Class II	Class III
		IIb: Permanent pacing may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow tract obstruction. *(Level of Evidence: A.)* As for class I indications, when risk factors for SCD are present, consider a DDD ICD	2. Permanent pacemaker implantation is not indicated for symptomatic patients without evidence of LV outflow tract obstruction.
Post MI	1. Permanent ventricular pacing is indicated for persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment MI. 2. Transient advanced second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary. 3. Persistent and symptomatic second- or third-degree AV block.	IIa: None IIb: Persistent second- or third-degree AV block at the AV node level, even in the absence of symptoms	1. Transient AV block in the absence of intraventricular conduction defects. 2. Transient AV block in the presence of isolated left anterior fascicular block. 3. New bundle branch block or fascicular block in the absence of AV block. 4. Persistent asymptomatic first-degree AV block in the presence of bundle branch or fascicular block.
Chronic bifascicular and trifascicular block	1. Advanced second-degree AV block or intermittent third-degree AV block. 2. Type II second-degree AV block. 3. Alternating bundle branch block.	IIa: 1. Syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically VT. 2. Incidental finding at electrophysiological study of a markedly prolonged HV interval (≥100 ms) in asymptomatic patients.	1. Fascicular block without AV block or symptoms. 2. Fascicular block with first-degree AV block without symptoms.

TABLE 54.2 Indications for Cardiac Pacing (*Continued*)

	Class I	Class II	Class III
		3. Incidental finding at electrophysiological study of pacing-induced infra-His block that is not physiological. IIb. 1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms.	
Carotid sinus hypersensitivity (carotid sinus irritability) and neurally mediated syncope	Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 s.	IIa: Syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of 3 s or longer IIb: Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing.	1. Hypersensitive cardioinhibitory response to carotid sinus stimulation without symptoms or with vague symptoms. 2. Situational vasovagal syncope in which avoidance behavior is effective and preferred.
Termination of tachyarrhythmias		Symptomatic recurrent SVT that is reproducibly terminated by pacing when catheter ablation and/or drugs fail to control the arrhythmia or produce intolerable side effects.	Permanent pacing is not indicated in the presence of an accessory pathway that has the capacity for rapid anterograde conduction.

(*Continued*)

TABLE 54.2 Indications for Cardiac Pacing (*Continued*)

	Class I	Class II	Class III
Prevention of tachycardia	Sustained pause-dependent VT, with or without QT prolongation.	IIa: High-risk patients with congenital long QT syndrome IIb: Prevention of symptomatic, drug-refractory, recurrent AF in patients with coexisting SND.	1. Permanent pacing is not indicated for frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome. 2. Permanent pacing is not indicated for torsade de pointes VT due to reversible causes. 3. Permanent pacing is not indicated for the prevention of AF in patients without any other indication for pacemaker implantation.
Pacing after cardiac transplantation	Persistent inappropriate or symptomatic bradycardia not expected to resolve and for other class I indications for permanent pacing.	IIa: None IIb: 1. Relative bradycardia is prolonged or recurrent, which limits rehabilitation or discharge after postoperative recovery from cardiac transplantation. 2. Syncope after cardiac transplantation even when bradyarrhythmia has not been documented.	

AF, atrial fibrillation; AV, atrioventricular; CM, cardiomyopathy, ; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter–defibrillator; LV, left ventricular; MI, myocardial infarction; SCD, sudden cardiac death; SND, sinus node dysfunction; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia; .
Class I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of pacing.
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb: Usefulness/efficacy is less well established by evidence/opinion.
Class III: Conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.
From Epstein AE, DiMarco JP, Ellenbogen, KA, et al. 2008 ACC/AHA/HRS guidelines for device-based therapy. *J Am Coll Cardiol.* 2008;51;e1–e62.

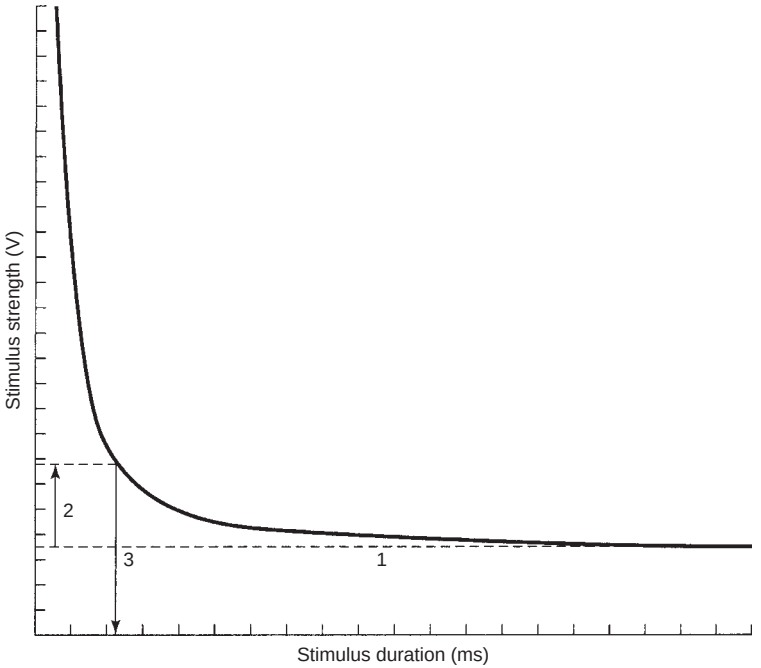

FIGURE 54.1 Strength–duration curve.

threshold peaks at 1 to 2 weeks, then gradually declines and plateaus at approximately 6 weeks at a level less than the acute peak, but greater than that measured at implantation. The absolute value of the temporal changes in stimulation thresholds varies between individuals and also between various types of electrodes.

VI. PACEMAKER TIMING CYCLES AND INTERVALS

A. Timing circuits. A pacemaker can be thought of as a series of timing circuits. An understanding of how these timing circuits interact can facilitate the analysis of pacemaker rhythms. The timing circuit runs until the cycle is completed or until it is reset. Completion of a timing cycle results in the release of a pacing output or the initiation of another timing cycle. Figure 54.2 illustrates the basic timing cycles and intervals for a dual-chamber pacemaker. The basic terms and abbreviations used for the pacemaker timing cycles and refractory periods are defined in the glossary.

B. Base rate behavior

1. Single-chamber pacemakers have a timing circuit that either is inhibited (reset) by a sensed native heartbeat or completes its cycle with a stimulus output. Dual-chamber pacemakers are more complex and incorporate more timing circuits. Figure 54.2 illustrates the timing cycles of a dual-chamber pacemaker in DDD mode. In general, base rate (lower rate) pacing for dual-chamber pacemakers involves two timing circuits.

a. The first timing circuit is the interval from a ventricular sensed or paced event to an atrial-paced event (atrial escape interval or AEI).

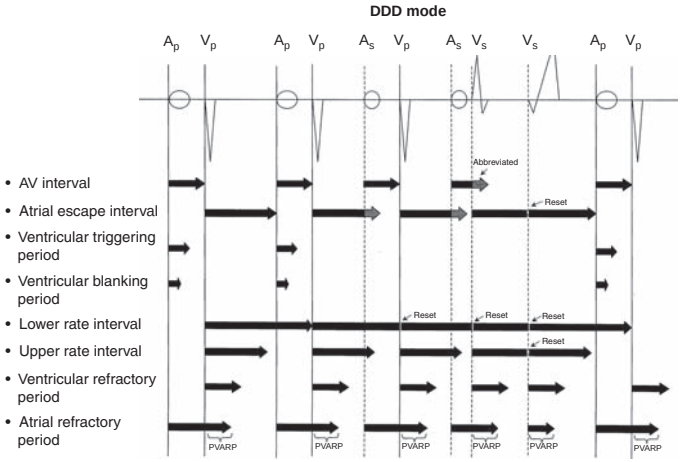

FIGURE 54.2 Timing cycles and intervals for a dual-chamber pacemaker. PVARP, postventricular atrial refractory period.

b. The second timing circuit is the interval from an atrial sensed or paced event to a ventricular paced event (atrioventricular interval, or AVI). An atrial sensed event that occurs before the completion of the AEI results in termination of that interval and initiation of the AVI.

2. The response of a dual-chamber pacemaker to a sensed ventricular signal varies among manufacturers. Some pacemakers use a ventricular-based timing system and others use an atrial-based timing system.
   a. Ventricular-based timing. In this type of pacemaker timing system, the AEI is fixed. A ventricular sensed event during the AEI will reset the timing circuit. A ventricular sensed event during the AVI terminates that interval and initiates the AEI.
   b. Atrial-based timing. In this type of pacemaker timing system, the AA interval is fixed. A ventricular sensed event during the AEI will reset the AA timing circuit and add the programmed AVI. A ventricular sensed event during the AVI will inhibit a ventricular output, but will not alter the AA interval.
3. Interpretation of pacemaker rhythm that has ventricular sensed beats requires knowledge of the type of timing system the pacemaker uses. Both the ventricular-based and atrial-based timing systems should be analyzed by measuring backward from an atrial-paced event. The point of ventricular sensing for a ventricular-based timing system will be found at the point before the atrial-paced event that is equal to the AEI. For an atrial-based timing system, the measurement before the atrial-paced event should be to the point that is equal to the AA interval. Knowledge of these principles allows one to evaluate the ventricular sensing for a given pacemaker. Be aware that some pacemakers have incorporated modifications of these systems that take advantage of features from both timing systems. For example, a pacemaker with an atrial-based timing system may behave as a ventricular-based timing system.
4. **Hysteresis** is a pacing feature that attempts to allow the heart's native conduction system to predominate and therefore modifies base rate behavior. This feature works by using a longer escape interval after a sensed beat than after

a paced beat. For example, the device sets the hysteresis rate at 50 bpm while the basal rate is 60 bpm. Therefore, if the patient's intrinsic rate is > 50 bpm, the device will not pace. However, if the patient's rate falls below 50 bpm, the pacer will pace at 60 bpm. As hysteresis can appear as an unusually long delay on the ECG strip, it can be misinterpreted as failure to pace or as inappropriate sensing.

C. Upper rate behavior

1. As the sinus rate accelerates, the sensed atrial events terminate the AEI and initiate the AVI. The result is P-wave synchronous ventricular pacing (unless the PR interval is shorter than the PV interval, in which case pacing will be fully inhibited).
2. The maximal atrial rate that a dual-chamber pacemaker can sense is determined by the total atrial refractory period (TARP). As defined earlier in this chapter, the TARP is composed of the AVI and the postventricular atrial refractory period (PVARP). The PVARP is an interval during which the atrial channel can see incoming signals, but will not respond to them. However, because signals are seen in PVARP, the pacer can use advanced features to assess whether high atrial rates are occurring. As the sinus rate accelerates, the native atrial intervals become shorter than the TARP, and some atrial events will not be sensed. An abrupt, fixed block occurs as the pacemaker only intermittently senses the P-waves, which may result in symptoms as the rate drops precipitously.
3. Maximal tracking rate interval (MTRI) or upper rate limit is an additional timing circuit designed to avoid abrupt blocks at upper pacing rates. It works in conjunction with the AVI to determine the highest ventricular pacing rate that can be achieved in response to atrial sensed events. A sensed atrial event initiates the AVI and the MTRI.
   a. If the AVI completes its cycle and the MTRI has also completed its cycle, then a ventricular output occurs at the programmed AV interval.
   b. If the AVI completes its cycle and the MTRI has not completed its cycle, then the ventricular output is delayed until the MTRI has timed out. This prolongs the PV interval and allows continued tracking of the atrial rate. However, the longer PV interval also places the ventricular output closer to the following P-wave.
   c. If the sinus rate accelerates to a sufficient rate, the delayed ventricular output may cause the following P-wave to fall within the PVARP and not be sensed. The result is an intermittent "dropped" beat and a pause similar to Wenckebach behavior. However, abrupt block is less likely. More modern pacemakers may incorporate features designed to limit the degree of fixed block at the upper rate limit, such as rate smoothing (adjustment of the AEI as the PV interval changes) and rate-responsive AV delay. However, fixed block at the upper rate limit may still occur, particularly if the device is suboptimally programmed.

VII. RATE-ADAPTIVE PACING.

The primary purpose of rate-adaptive pacing is to emulate the function of the sinus node for patients with chronotropic incompetence or atrial arrhythmias that preclude reliable sensing of native sinoatrial rhythm. This function is expressed with the letter "R" in the fourth position (AAIR, VVIR, DDDR, and so on).

A. Primary components of a rate-adaptive pacemaker system

1. A sensor located in the pacing lead or pacemaker itself detects a physical or physiologic parameter that is directly or indirectly related to metabolic demand.
2. Rate-modulating circuitry within the pacemaker contains an algorithm that translates a change in the sensed parameter to a change in the pacing rate.
3. Algorithm programmability such that a physician can make adjustments to accommodate the heart rate requirements of the individual patient.

TABLE 54.3 Sensors in Rate-Responsive Pacing

Methods	Physiologic parameters	Mechanism	Advantages	Disadvantages
Impedance sensing	Respiratory rate Minute ventilation Stroke volume	Impedance plethysmography	Highly physiologic Highly proportional to metabolic demand	Delayed response Susceptible to electrode motion artifact
Ventricular evoked response	Evoked QT interval (stim-T interval)	Reflects catecholamines	More physiologic	Requires ventricular pacing
Vibration, acceleration, gravitation, motion sensing	Body movement	Piezoelectric element	Rapid response No special lead needed	Nonphysiologic and nonspecific Late plateau response
Special sensors on pacing electrode	Central venous temperature[a] d*P*/d*t*[b] Mixed venous oxygen saturation[b]	Thermistor Piezoelectric element Optical sensor	More physiologic	Complex lead

[a]No longer produced, although still in use in Japan.
[b]Presently available only in clinical trials.

Adapted from Lau, Chu-Pak. The Range of Sensors and Algorithms Used in Rate Adaptive Cardiac Pacing. *PACE*, 1992: 1177–1190.

4. Pacemakers can set the sensor to on or off. Some pacemakers can be put in a passive mode in which they store information in order to predict how the pacer would act if set to rate-responsive behavior.

B. Basic technical categories of pacemaker sensors (see Table 54.3). Motion sensors are the most commonly used due to their simplicity, speed of response, and compatibility with standard unipolar and bipolar pacing leads. Other sensors are more physiologic but may require technically complex pacing leads. Of the physiologic sensors, only the minute ventilation type is widely available. Minute ventilation sensors are prone to interference from electromagnetic sources, coughing, hyperventilation, and arm swinging.

VIII. AUTOMATIC MODE SWITCHING. Automatic mode switching is a programmable response of a dual-chamber pacemaker during an atrial tachyarrhythmia (atrial tachycardia, atrial fibrillation, or atrial flutter) designed to avoid nonphysiologic ventricular pacing due to atrial tracking. Generally, the device switches from a DDD mode to a VVI mode, usually with a gradual reduction of the pacing rate. The device switches back to the DDD mode after the atrial tachyarrhythmia resolves. Mode switch information can also be helpful in documenting atrial arrhythmia burden in order to help dictate medical therapy for arrhythmias.

IX. BASIC PACING MODES. The choice of pacemaker generator and the mode of pacing depend mainly on the underlying rhythm disturbance and whether AV synchrony and rate response are desired (see Table 54.4).

TABLE 54.4 Guidelines for Choice of Pacemaker Generator in Selected Indications for Pacing

	Sinus node dysfunction	AV block	Neurally mediated syncope or carotid sinus hyperreactivity
Single-chamber atrial pacemaker	No suspected abnormality of AV conduction and not at increased risk for future AV block Maintenance of AV synchrony during pacing if desired RR if desired	Not appropriate	Not appropriate (unless AV block systematically excluded)
Single-chamber ventricular pacemaker	Maintenance of AVS during pacing not necessary RR available if desired	Chronic AF or other atrial tachyarrhythmia or maintenance of AVS not necessary RR available if desired	Chronic AF or other atrial tachyarrhythmia RR available if desired
Dual-chamber pacemaker	AVS during pacing desired Suspected abnormality of AV conduction or increased risk of AV block	AVS during pacing desired Atrial pacing desired RR available if desired	Sinus mechanism present RR available if desired
Single-lead, atrial-sensing ventricular pacemaker	Not appropriate	Normal sinus function and no need for atrial pacing Desire to limit the number of pacemaker leads	Not appropriate

AF, atrial fibrillation; AV, atrioventricular; AVS, atrioventricular synchrony; RR, rate response.

A. Ventricular demand pacing (VVI). This remains the most commonly used pacing mode worldwide. Although VVI pacing protects the patient from lethal bradycardias, AV synchrony is not restored or maintained nor does it provide rate responsiveness in the patient with chronotropic incompetence. Because AV synchrony is absent, the rate of pacemaker syndrome is high (up to 83% in randomized trials).

B. AAI (atrial demand pacing). This mode is appropriate for patients with sinus node dysfunction who have intact AV conduction. A sensed atrial event will inhibit atrial pacing, and expiration of a preset AA interval will pace the atrium at a preset rate. Because there will be no ventricular support if AV block should occur, careful testing of AV conduction is necessary at the time of pacemaker implantation (incremental atrial pacing). This mode is infrequently used in the United States.

C. AV sequential pacing

1. **DDI.** There are both atrial and ventricular sensing and pacing, but no atrial tracking can occur. The pacemaker rate is therefore fixed, and this mode is rarely used.

2. **VDD.** In this mode, ventricular stimulation can either be inhibited by a spontaneous ventricular beat or be initiated by an atrially tracked beat, and it can therefore be used in patients with normal sinus function but impaired AV conduction. This modality uses a "floating" sensing electrode on the atrial portion of the ventricular lead, but it is altogether rarely used.
3. **DDD.** This system provides the most physiologic pacing mode. The pacer can be totally inhibited with normal sinus rhythm, can pace the atrium with spontaneous ventricular depolarization, can pace the ventricle in response to a spontaneous P-wave, and can sequentially pace both the atrium and ventricle. This system is most appropriate in patients who have impaired AV conduction with either an intact or dysfunctional sinus node.

X. BIVENTRICULAR PACING.

Because patients with systolic left ventricular (LV) dysfunction and wide QRS complexes have dyssynergic contractility, the use of multisite atrial, right ventricular (RV), and LV pacing strategies has been proposed. For this purpose, an additional pacemaker lead is placed transvenously into the coronary sinus or epicardially during open chest surgery for simultaneous stimulation of the left and right ventricles.

A. Biventricular cardiac resynchronization pacing for heart failure has been accepted as standard therapy for patients with a depressed ejection fraction (EF < 35%), QRS duration > 120 milliseconds, and NYHA class III or IV symptoms despite appropriate medical therapy. Several randomized studies, including MUSTIC, MIRACLE, MIRACLE-ICD, PATH-CHF, and VENTAK-CHF/CONTAK-CD, have demonstrated improved functional status, exercise capacity, and quality of life with biventricular pacing. CARE-HF demonstrated a decrease in the primary end point of death and hospitalization with biventricular pacing (see Chapter 56) in heart failure patients with depressed systolic function, class III/IV symptoms, and wide QRS.

B. Consideration for implantation of a biventricular pacemaker should be given for patients with LV dysfunction who will require a high percentage of ventricular pacing. This recommendation is based on the findings from the DAVID trial where high rates of RV pacing caused ventricular dyssynchrony and more hospitalization for congestive heart failure (CHF) or death.

C. Although the overall rate of clinical improvement with biventricular pacing is high in these trials (about 70% of patients), it is not entirely clear how to identify patients who will respond ahead of time. Multiple echocardiographic and electrocardiographic measures have been investigated to help predict an individual patient's likelihood of clinical response, but so far no single modality has proven entirely reliable.

XI. PACEMAKER IMPLANTATION: PERTINENT ISSUES FOR THE PHYSICIAN

A. Preoperative issues. Several issues must be addressed for the patient scheduled for routine pacemaker implantation.

1. **History and physical examination.** Attention should be given to any findings that may affect the site and approach for pacemaker implantation, such as patient handedness (pacemakers are generally implanted on the contralateral side), history of mastectomy, presence of congenital abnormalities (e.g., anomalous venous drainage), current central venous lines, or tricuspid valve disease or surgery.
2. **Informed consent** (risks, benefits, and alternatives)
3. **Tests**
   - **a.** Posteroanterior and lateral chest radiograph.
   - **b.** Twelve-lead ECG should be obtained.
   - **c.** Blood tests may include serum electrolytes, complete blood count, creatinine, prothrombin/international normalized ratio (INR), and partial thromboplastin times.

4. **Medications**
   a. Most physicians prefer warfarin to be discontinued at least 3 days before the procedure. In some cases, such as primary implants or generator changes, coumadin can be kept close to therapeutic, with INR at approximately 2.0. Consider admission to hospital for intravenous heparin if the risk of discontinuation of anticoagulation is high. Heparin may be discontinued 4 to 6 hours before the procedure.
   b. The dosage of oral hypoglycemics or insulin may have to be adjusted.
5. **Patient preparation**
   a. The patient should have nothing by mouth for at least 6 to 8 hours before the procedure. Intravenous hydration should be initiated upon arrival to the laboratory to prevent hypovolemia, which may make venous cannulation more difficult.
   b. An intravenous catheter is particularly helpful if placed in the arm ipsilateral to the proposed pacemaker site. This allows the ability to perform a venogram if there is difficulty in obtaining venous access during pacemaker implantation.
   c. The patient should be shaved and cleansed (e.g., with povidone iodine) in the area from above the nipple line to the angle of the jaw and from the sternum to the axillary line on the side of the implantation site.
   d. Antibiotic prophylaxis before pacemaker implantation is a controversial issue, and various prospective studies have provided conflicting information. Some centers have advocated antibiotic prophylaxis with an agent active against staphylococci for patients at high risk for endocarditis, such as those with prosthetic valves or complex congenital heart disease, or for redo procedures or for prolonged or potentially contaminating procedures. Other centers use antibiotic prophylaxis routinely (systemically and/or locally).

B. **Postoperative issues**
1. **General recommendations.** Patients are usually admitted for overnight observation on telemetry after pacemaker implantation.
2. **Postoperative testing.** Posteroanterior and lateral chest radiograph should be obtained to document proper position of the pacemaker leads and connection of the terminal pins to the pulse generator. The radiograph should also be examined for evidence of pneumothorax, pericardial effusion, or pleural effusion.
3. **Resuming anticoagulation.** Anticoagulation should not be aggressive in the early post-implantation period due to the risk of pacemaker pocket hematoma, which has been associated with increased risk of complications such as reoperation and infection. Administration of therapeutic doses of unfractionated or low-molecular-weight heparin in the 48 hours following device implantation will increase the risk of hematoma and should generally be avoided. If warfarin was held prior to device implantation, it may be restarted the day prior to device implantation based on the INR.
4. **Pacemaker evaluation**
   a. Evaluation in the pacemaker clinic before discharge includes assessment of pacing and sensing thresholds and lead impedance. The pacemaker is programmed to optimize patient hemodynamics and minimize battery expenditure.
   b. Capture thresholds are expected to rise over the first 2 to 6 weeks after implantation. Therefore, the pacemaker should be programmed with an adequate safety margin to account for these changes.
   c. Rate adaptation for activity-sensing pacemakers may be programmed according to informal (e.g., hallway walking) or formal (e.g., treadmill) exercise testing.
5. **Discharge planning**
   a. **Discharge instruction.** Usually includes patient education regarding the recognition of pacemaker pocket complications, such as signs of infections,

bleeding, or hematoma. The patient is generally advised to avoid heavy lifting or vigorous activity (especially forceful abduction) with the arm ipsilateral to the implant site.

b. The patient should be provided with information regarding his or her pacemaker, including a wallet card identifying the pacemaker and lead(s) manufacturer, model numbers, and serial numbers.

c. The patient may be provided with and instructed in the use of a transtelephonic monitoring system for remote evaluation of the pacemaker.

d. Endocarditis prophylaxis is generally *not* recommended routinely for patients with pacemakers, according to the updated AHA guidelines.

XII. COMMON PACEMAKER PROBLEMS

A. Acute complications of pacemaker implantation

1. Pneumothorax/Hemothorax

a. This complication may be asymptomatic and detected only by chest radiograph. The diagnosis should be considered in a patient with dyspnea and/or pleuritic chest pain after implantation.

b. A small pneumothorax may resolve without intervention. However, the presence of severe symptoms, a pneumothorax > 10%, or an expanding or persistent pneumothorax often necessitates placement of a chest tube.

2. Pacemaker pocket hematoma

a. This is one of the most common complications of pacemaker implantation and is often due to small vessel venous bleeding inside the pacemaker pocket. Bleeding may also arise from arterial vessels or retrograde flow of venous blood along the pacemaker leads into the pocket.

b. Signs and symptoms may include pain, swelling, and sometimes bleeding at the pocket site.

c. Small hematomas may be managed conservatively with pressure dressings, elevation (head of bed at least 45°), and analgesics. The patient should be positioned on his or her side contralateral to the pacemaker site. Large hematomas may compromise the integrity of the incision site and result in dehiscence. The patient may require urgent surgical exploration and hematoma evacuation in the electrophysiology laboratory or operating room.

d. Percutaneous insertion of a needle to drain a hematoma increases the risk of infection and should be avoided.

3. Cardiac or central venous perforation. Perforation may lead to pericardial effusion and cardiac tamponade and should be suspected in the patient with chest pain, pericardial friction rub, or hypotension after pacemaker implantation. A chest radiograph may reveal an enlarged cardiac silhouette or an extracardiac lead tip. A change in the paced ventricular morphology, particularly a right bundle branch pattern, may indicate ventricular lead migration. The hemodynamically unstable patient with tamponade will require urgent pericardiocentesis and drainage of the effusion.

4. Diaphragmatic stimulation. Stimulation of the left diaphragm may occur with a pacing lead at the RV apex, particularly at high pacing outputs. The possibility of cardiac perforation should be considered. Stimulation of the right diaphragm may occur due to stimulation of the right phrenic nerve by a displaced atrial lead. Reduction in the pacemaker output voltage or lead repositioning may be necessary.

5. Local muscular stimulation

a. This may occur with a unipolar pacemaker configuration, particularly if the pulse generator is positioned upside down within the pocket (whereby a node is directly in contact with the pectoralis muscle).

b. A pacing lead fracture may result in leakage of current into the surrounding tissue, resulting in local muscle stimulation.

6. Pacemaker malfunction

a. The pulse generator may be defective or may have been damaged at the time of implantation (e.g., by electrocautery or direct current [DC] defibrillation).

b. Improper fixation of the terminal pins of the pacing leads into the pulse generator (e.g., loose-set screws) may result in complete or intermittent pacemaker malfunction with high impedance measurements.

7. Lead dislodgement or damage

a. Pacing leads may become dislodged soon after implantation before the lead has a chance to become more fixed in place through clotting and fibrosis. Lead dislodgement may be suspected by noncapture, high lead impedance, undersensing, or oversensing on telemetry or ECG and may be confirmed by chest radiography or formal pacemaker testing.

b. The lead may be damaged at the time of implantation by forceful handling or excessively tight retention sutures.

c. Interrogation of a device with a damaged lead may reveal changes in impedance. A break in the insulation of the lead results in low impedance. A contained fracture of the lead conductor, poor terminal pin to device connection, or lead dislodgement all result in high impedance.

B. Chronic complications of pacemaker implantation

1. Pacemaker system infection

a. The reported incidence of pacemaker infection is 1.9 per 1,000 device-years based on a large cohort study spanning 30 years (1). As noted earlier, the number of pacemakers implanted annually continues to increase, and yet the rate of device-related infections is increasing at a disproportionately higher rate. Recognition of these infections and appropriate treatment is critical for health-care providers managing patients with cardiac implantable devices. The infection may involve only the pacemaker pocket or the entire system, with subsequent life-threatening sepsis. There is a higher incidence with repeat operations (e.g., pulse generator replacement). Causative organisms tend to be skin flora such as *Staphylococcus* species.

b. Treatment should include intravenous antibiotics; however, antibiotic therapy rarely eradicates the infection unless the pacemaker system is removed. In the largest study to date (1), mortality rates for device-related endocarditis range from 31% to 66% without device removal. Mortality improves to 18% or less with a combined approach of medical therapy and complete device removal.

c. The timing of system removal depends on the clinical status of the patient; however, prolonged delays should be avoided.

2. Intravascular thrombosis or obstruction

a. Vascular complications are common with device therapy. They range from asymptomatic venous occlusion to extremity edema. Mortality from vascular complications is rare. Initial treatments may include heat and upper-extremity elevation. Symptomatic thrombosis of the subclavian or axillary veins may require anticoagulation or systemic thrombolytic therapy. It is recommended that documented deep venous thrombosis be treated with anticoagulation with warfarin for at least 6 months, unless contraindicated.

b. Superior vena cava stenosis or occlusion may require percutaneous balloon dilatation or surgical consultation for consideration of repair.

3. Twiddler's syndrome. A condition in which the pacemaker is turned, usually unintentionally, upside down within the pacemaker pocket. The leads may become twisted, resulting in excessive traction on the leads and dislodgement.

XIII. PACEMAKER SYSTEM MALFUNCTION

A. In assessing the patient with suspected pacemaker malfunction, it is important to interpret the ECG carefully. Ideally, intracardiac tracings obtained by pacemaker interrogation should be interpreted. Pacing artifacts or spikes are high-frequency signals and are often filtered out by newer digital surface ECG machines. Furthermore, pacing artifacts from bipolar leads are smaller and more difficult to see than artifacts from unipolar leads. It may be necessary to record multiple leads or use an older analogue recorder to clearly visualize the pacing artifact. Pseudomalfunction occurs when recording and digital artifacts are misinterpreted. Approaching the paced patient's ECG systematically will help to determine the appropriateness of pacing.

B. General evaluation for possible pacemaker malfunction

1. If a recent pacemaker interrogation is available, review the programmed parameters for the pacemaker, particularly the mode, base rate, upper rate limit, intervals, and the presence of other features such as automatic mode switching, hysteresis, rate-adaptive features, or managed ventricular pacing.
2. Obtain a 12-lead ECG and evaluate the following:
   - **(a)** Determine whether pacing stimulus artifacts are present and whether the appropriate chamber is captured.
   - **(b)** If no pacing stimulus artifact can be seen, native depolarization should be adequate.
   - **(c)** Evaluate whether native beats are appropriately sensed in relation to paced complexes.
   - **(d)** Evaluate the timing cycles of a dual-chamber pacemaker by measuring backward from an atrially paced event, as described in Section **VI.B.2**.

C. Patients with pacemaker system malfunction generally demonstrate absence of a pacing stimulus artifact, failure to capture, or failure to sense.

1. **Failure of pacemaker stimulus output.** A differential diagnosis of the more common causes of pauses during a paced rhythm is listed later in this chapter. Application of a magnet over the pacemaker should result in asynchronous pacing. If the pauses resolve when the magnet is applied, then the diagnosis of oversensing is most likely. If the pauses do not resolve, then one of the other causes should be considered.
   - **a. Pulse generator failure.** The pulse generator may be at the end of life (EOL), which may easily be detected with a pacemaker check.
   - **b. Lead failure.** This can be due to loose-set screw or terminal pin disconnection, lead conductor failure, or lead insulation failure. Suspicion of lead malfunction should prompt the clinician to obtain a chest radiograph. This may reveal the terminal pin not situated properly within the header of the pulse generator or it may demonstrate a defect in the lead insulation or conductor coil. A significant increase in the lead impedance suggests lead conductor failure, and a significant decrease in the lead impedance suggests lead insulation failure.
   - **c. Oversensing.** EMI, myopotentials, cross talk, or T-wave oversensing can lead to falsely interpreted signals.
   - **d. Pseudomalfunction.** Pacemaker malfunction can be mistakenly diagnosed if the small spikes from a bipolar system are not appreciated on the surface ECG. Malfunction can also be diagnosed mistakenly if attention is not paid to additional features that allow the heart rate to fall below or above the set base rate. It is important to remember additional features such as hysteresis, sleep settings, rate-adaptive behaviors, or automatic mode switch, each of which can be mistaken for pacemaker malfunction.
2. **Failure to capture**
   - **a. Elevated capture threshold.** Electrolyte disturbance (e.g., hyperkalemia and acidemia), antiarrhythmic drugs (particularly class Ic agents such as

flecainide), and myocardial fibrosis (e.g., cardiomyopathy and myocardial infarction [MI]) can increase the capture threshold.

b. Lead malfunction

(1) Lead fracture.

(2) Lead dislodgement or perforation may result in a change in the paced morphology, especially a change from left to right bundle branch morphology.

c. Exit block. Exit block is defined as failure of the pacing output at the distal electrode to stimulate adjacent myocardium. This is often caused by the inflammatory reaction that occurs at the pacemaker lead tip at the time of implantation. It occurs in approximately 5% of cases and may be managed with systemic steroids. Most pacing leads have steroid-eluting electrodes designed to minimize the degree of inflammation at the electrode tip and decrease the incidence of exit block.

d. Latency. Defined as the delay between the delivery of an output pulse and the onset of electrical systole, such as occurs with severe electrolyte disturbances.

e. Pseudomalfunction. Artifact with small spikes on the surface ECG, such as occurs when the patient's refractory periods interfere with pacer function.

3. Failure to sense

a. Lead dislodgement is usually accompanied by failure to capture (see discussion in Section **XIII.C.2**)

b. Lead insulation failure (see discussion in Section **XIII.C.1**)

c. Inadequate endocardial signal

d. Change in electrogram. Transient changes may occur due to electrolyte or acid–base disturbance, and permanent changes may occur due to MI or cardiomyopathy

e. Ectopic beats

f. Pulse generator failure (sensing circuits)

g. Functional undersensing. Defined as undersensing that occurs due to normal pacemaker function, such as refractory periods, blanking periods, or safety pacing.

D. Other pacemaker malfunctions

1. Pacemaker syndrome. Pacemaker syndrome is defined as the signs and symptoms that occur in the pacemaker patient because of inadequate timing of atrial and ventricular contractions. Pacemaker syndrome is commonly caused by retrograde ventriculoatrial (VA) conduction, which causes atrial contraction against closed mitral and tricuspid valves. Pacemaker syndrome may also occur during an exercise-induced atrial arrhythmia due to loss of AV synchrony when a device with an automatic mode-switching feature converts to VVI pacing.

2. Pacemaker-mediated tachycardia (PMT). This is defined as a paced tachycardia that is sustained by the continued active participation of the pacemaker in the rhythm. At first glance, the resultant wide-complex (paced) tachycardia may appear to be ventricular tachycardia, especially for pacemakers with bipolar leads where the pacing artifact may be difficult to discern on ECG.

a. One form of PMT is the rapid ventricular pacing that occurs as a dual-chamber pacemaker attempts to track the rapid atrial rate during an atrial tachyarrhythmic episode.

b. Another form of PMT occurs when there is oversensing in the atrial channel, such as myopotentials.

c. Endless-loop tachycardia (ELT). PMT in which a repetitive sequence of sensing of retrograde atrial activity results in triggering of a ventricular paced beat at the end of the MTRI. ELT requires a trigger for initiation, which may be any event that results in AV dissociation and allows retrograde VA

conduction to occur after a native or paced ventricular beat. The trigger may be a PVC, atrial undersensing, atrial oversensing, or atrial noncapture. ELT is sustained until there is VA block. Application of a magnet over the pacemaker will terminate ELT. The most reliable way to prevent ELT is to program the PVARP to a value that exceeds the VA conduction interval. Some of the more modern pacemakers have PMT or ELT recognition and termination algorithms designed to prevent and/or terminate PMT and ELT.

XIV. COMMON ISSUES FOR THE PATIENT WITH A PACEMAKER

A. Perioperative patient

1. **Preoperative assessment.** Review of pertinent history and a physical examination should be performed. The patient should undergo a pacemaker evaluation to assess the programmed parameters, pacing and sensing thresholds, and lead impedance.
2. The degree of pacemaker dependence should be determined. A patient who is pacemaker-dependent should have temporary pacing equipment readily available.
3. If the operative field is in the area near the pacemaker, the rate response feature of the pacemaker should be deactivated to avoid inappropriate rapid pacing due to vibrations or pressure transmitted to the pulse generator.
4. Electrocautery may result in temporary inhibition of pacemaker output due to oversensing of the EMI. Electrocautery should be used sparingly and in short bursts, and the cautery electrode should be placed at a distance from the pacemaker site.
5. Postoperatively, the pacemaker should be reevaluated for any sign of malfunction, the presence of a reset mode, and any change in lead threshold or impedance values. A chest radiograph should be obtained after cardiac surgery to evaluate for lead damage or dislodgement.

B. EMI in the hospital environment

1. **Magnetic resonance imaging (MRI).** The magnetic field generated by the electromagnet and the radiofrequency signal produced to modulate the magnetic field for MRI may cause torque forces or malfunction of cardiac pacemakers. More modern pacemakers contain fewer ferromagnetic components than previous pacemakers, so that torque forces are less common. The magnetic forces may close the pacemaker reed switch and result in asynchronous pacing. The radiofrequency signal may result in inhibition of pacing, rapid pacing, or reversion to reset mode. Unipolar pacemakers are more susceptible to interference from MRI. While a small number of centers have developed specific scanning protocols for patients with cardiac implantable electronic devices (CIEDs), in general, MRI should be avoided in most pacemaker patients unless absolutely necessary.

   Recently, MRI conditional pacemaker systems have emerged. Specifically, the RevoMRI SureScan System has been evaluated in a clinical trial (EnRhythm MRI SureScan Pacing System Study) and is now widely available for use in clinical practice. Of the 211 enrolled patients who underwent an MRI 9 to 12 weeks after receiving the device, no MRI-related complications were reported. As new applications for MRI continue to emerge in clinical practice, recent estimates suggest that as many as 50% to 75% of patients with CIED will have an indication for MRI during their lifetime. MRI conditional technology will undoubtedly continue to evolve and is likely to become standard in new pacemaker systems from all major manufacturers.
2. **Extracorporeal shock-wave lithotripsy (ESWL)**
   a. ESWL is a treatment for renal calculi that involves the production of focused hydraulic shock waves from an underwater spark gap. Interference or damage to a pacemaker may occur due to the spark gap or the shock

waves. Activity-based rate adaptation pacemakers with piezoelectric crystals may be damaged by the shock waves, and the shock waves may cause oversensing and subsequent nonphysiologic rapid pacing rates. Such pacemakers should be reprogrammed with the rate-adaptive feature deactivated before the procedure. If the pacemaker with a piezoelectric crystal is located in the abdomen, then ESWL should not be performed.

b. The shock waves may be misinterpreted as atrial activity; therefore, dual-chamber pacemakers should be programmed to VVI mode to avoid rapid ventricular pacing.

c. A patient with a pacemaker may undergo ESWL; however, the pulse generator should be as far as possible from the focal point of the lithotripsy shock waves, and a cardiologist who is experienced in pacemaker management should be available nearby during the procedure.

3. Radiation therapy

a. Diagnostic radiation does not interfere with cardiac pacemakers. Therapeutic radiation therapy to the thorax such as that used for breast or lung malignancies may result in interference and/or cumulative damage. The damage to the integrated circuitry of the pacemaker results from leakage currents between the insulated parts. This damage is directly related to the cumulative radiation dose.

b. The pacemaker should be assessed before and after a treatment session. ECG monitoring is recommended for patients who are pacemaker-dependent. The pulse generator should be shielded from the ionizing radiation or moved to another site if necessary.

4. Cardiac monitors. Cardiac monitors that inject current into the patient's body in order to measure minute ventilation may interfere with pacemakers that use minute ventilation for rate adaptation.

5. Transcutaneous electric nerve stimulation is considered safe for patients with bipolar pacemakers. Patients with unipolar pacemakers may require a reduction in sensitivity.

6. Dental equipment. Some types of dental equipment may cause pacemaker inhibition, particularly for unipolar pacemakers. Vibrations may increase the pacing rate of activity-sensing rate-adaptive pacemakers.

7. Cardioversion/defibrillation. The shock from a DC cardioversion or defibrillation may cause damage to the pulse generator or result in the device being reset. If DC cardioversion or defibrillation is necessary, the patch electrodes should be positioned as far as possible from the pulse generator. A pacemaker evaluation should be performed after the procedure.

8. Electroconvulsive therapy generally does not interfere with pacemaker function. The patient should have a pacemaker evaluation before and after each session. ECG monitoring during the session is prudent. Seizure activity during the procedure may produce myopotential inhibition of unipolar pacemakers.

9. Diathermy may result in pacemaker interference or damage if applied to the region near the pulse generator.

10. Electrocautery (discussed in Section **XIV.A.4**)

C. Environmental EMI

1. Cellular telephones. These devices are generally safe. Older models were reported to interfere with cardiac pacemakers while transmitting or receiving calls. A pacemaker patient should not carry a cellular telephone near the pacemaker site (i.e., shirt pocket) and should avoid holding the telephone to the ipsilateral ear during use.

2. Electronic article surveillance (EAS) is a type of antitheft system consisting of a gate that produces an electromagnetic field through which individuals must walk. The field may result in pacemaker interference, primarily inhibition of

pacemaker output. Patients with unipolar dual-chamber pacemakers are particularly susceptible to interference from EAS systems.

3. **Industrial electrical equipment.** This includes devices, such as arc welders, that may generate strong electrical fields. The strength of the electrical field varies among various types of equipment and if sufficiently strong may interfere with unipolar pacemakers. Patients may require individual environmental testing to ensure safety.
4. **Microwave ovens.** Due to better sealing of microwave ovens and improved shielding of pulse generators, interference with pacemakers by microwave ovens is no longer considered a significant problem.
5. **Metal detectors.** Although the metal detectors in public places such as airports may raise an alarm due to detection of a pacemaker, there is generally no significant interference with pacemaker function. Patients should avoid lingering around these devices and pass through them at a normal speed.
6. **High-voltage power lines and electrical substations.** These areas may cause inhibition or asynchronous pacing in unipolar pacemakers if the patient is quite close to the electrical field. At usual public distances from such areas, there should be no pacemaker interference.

D. Pacemaker response to EMI

1. **Pacing inhibition.** For obvious reasons, this may be catastrophic. The majority of pacemakers used today contain protective algorithms that make prolonged inhibition uncommon.
2. **Rapid pacing.** Oversensing of EMI by the atrial channel in a device set to DDD can cause the pacer to trigger ventricular pacing at or near the upper tracking limit. This response is usually well tolerated, but in certain individuals when sustained it may cause palpitations, hypotension, or angina. Rapid pacing may also occur via activation of minute ventilation sensors.
3. **Reversion to asynchronous pacing.** Most pacers have algorithms that protect against prolonged inhibition from noise. Algorithms are based upon the principle that detected rapid frequency signals are unlikely to represent myocardial activation. The pacemaker is programmed to have a noise sampling window during the ventricular refractory period. In most devices, repetitive signaling detected in the noise sampling window reverts the device to asynchronous pacing. Asynchronous pacing is generally safe, but it is not without the risks of losing AV synchrony. Also, pacing may rarely occur during the ventricular vulnerable period and may initiate ventricular arrhythmias.

XV. CARDIAC PACING: CLINICAL TRIALS

A. Conventional pacing trials

1. Numerous clinical trials, mostly small and nonrandomized, have been performed with regard to exercise capacity and quality of life for various pacemaker modes, chamber(s) paced, rate-adaptive pacing, and types of sensors.
2. Clinical trials have firmly established the superiority of rate-adaptive (VVIR) over fixed-rate ventricular pacing (VVI) with regard to quality of life and exercise performance.
3. Numerous clinical trials have been undertaken to prove the benefit of dual-chamber/atrial-based pacing in patients undergoing postoperative permanent pacemaker implantation for sinus node dysfunction or high-degree AV block.
4. There are conflicting data regarding the benefit of dual-chamber pacing over rate-adaptive ventricular pacing. Early nonrandomized trials demonstrated mortality benefit with DDD pacing over VVI in patients with complete heart block. However, in randomized prospective trials, atrial pacing has not been shown to decrease rates of death or heart failure in patients treated for sinus node

dysfunction and high-degree AV block. However, there are several randomized trials demonstrating that atrial-based pacing does, in fact, lead to a reduction in both atrial fibrillation and stroke. However, this benefit may be limited to patients with sinus node dysfunction. The one clear benefit that dual-chamber/atrial-based pacing provides is the avoidance of pacemaker syndrome, which can be seen in up to 10% of patients with VVI pacing.

5. The following paragraphs summarize some of the larger-scale, randomized studies of ventricular- versus atrial-based cardiac pacing modes.
   a. **Pacemaker Selection in the Elderly (PASE) trial.** A single-blind, randomized, controlled trial of ventricular pacing versus dual-chamber pacing in 407 patients older than 65 years. The primary end point was quality of life with up to 30 months follow-up. Quality of life improved with pacemaker implantation. Patients with sinus node dysfunction, but not AV block, had significantly better quality of life with dual-chamber pacing than with ventricular pacing (2).
   b. **Canadian Trial of Physiologic Pacing (CTOPP).** In this trial, 1,474 patients were assigned to ventricular pacing and 1,094 patients to physiologic pacing. During a mean follow-up period of 3 years, there was no significant effect on the risk of death, stroke, or hospitalization for CHF according to the type of pacemaker used. However, the annual rate of atrial fibrillation was significantly lower in the atrial pacing group, although there was a 2-year delay before this beneficial effect emerged. There was a 50% reduction in perioperative complications with the implant of ventricular pacing systems, but in the ventricular pacing group there was a 5% incidence of pacemaker syndrome that required upgrade to a dual-chamber device (3).
   c. **Mode Selection Trial in Sinus Node Dysfunction (MOST).** A randomized trial that attempted to compare dual-chamber with single-chamber ventricular pacing in 2,010 patients with sinus node dysfunction. There was no advantage for dual-chamber pacing over single-chamber ventricular pacing in terms of the trial's primary end point: death from any cause or nonfatal stroke over 33.1 months of follow-up. However, some advantages were seen with the dual-chamber modality in secondary end points, including reductions in atrial fibrillation and symptoms of heart failure and improvement in quality of life (4). There was no difference in heart failure admission rates between the two groups.
   d. **Pacemaker Atrial Tachycardia (Pac-A-Tach) trial.** This was a mode randomization study in 198 patients (median age 72 years), all of whom received dual-chamber rate-adaptive pacemakers programmed to either VVIR or DDDR pacing. Intention-to-treat analysis showed no significant difference in atrial tachyarrhythmia recurrence rates at 1 year (VVIR 43%; DDDR 48%; $p = 0.09$) (5).
   e. **UK Pacing and Cardiovascular Events (UK PACE) trial.** This was a trial comparing VVI(R) and DDD pacing in 2,021 elderly patients (mean age 80 years) with high-grade AV block. Patients were randomized to DDD (50%), VVI (25%), and VVIR (25%). No difference was detected in rates of stroke, atrial fibrillation, or heart failure hospitalizations (6).
   f. **Meta-analysis of trials comparing atrial- and ventricular-based pacing.** Healey et al. (5) in 2006 completed a large meta-analysis of all randomized controlled trials comparing ventricular- and atrial-based pacing modes. A total of 35,000 patient-years of follow-up were reviewed (7). There was no significant reduction in mortality or heart failure with atrial-based pacing. However, there was a significant reduction in atrial fibrillation (hazard ratio 0.80, 95% confidence interval [CI] 0.77 to 0.89) and a borderline reduction in stroke (hazard ratio 0.81, 95% CI 0.67 to 0.99).

6. The practice of RV apical pacing as the preferred method remains controversial. It provides a reliable and stable position for long-term ventricular pacing. However, RV pacing creates ventricular desynchronization and leads to several adverse effects, including LV systolic and diastolic dysfunction. Retrospective and prospective analysis has linked increased numbers of RV paced beats with increased incidence of atrial fibrillation and heart failure. Current forms of pacemaker technology that minimize RV pacing are preferred to older pacemaker technologies. The following are landmark trials that have associated RV pacing with deleterious outcomes.
   a. **DAVID.** The DAVID trial was the first study of ventricular pacing strategies in implantable cardioverter–defibrillator patients. The trial hypothesized that dual-chamber pacing would result in a lower rate of heart failure in these patients with EF < 40% (8). At 1 year, rates of death and first hospitalization for heart failure were significantly increased in the dual-chamber group. The authors noted an increased rate of RV apex pacing in the DDD-70 group (60%) versus the VVI-40 group (3%). The authors concluded that the greater exposure to the deleterious effects of RV pacing in the DDD group led to worse outcomes.
   b. **SAVE PACe.** This trial examined whether the application of newer technologies to limit frequency of ventricular pacing could lead to a decrease in atrial fibrillation in patients with dual-chamber pacemakers. Patients with sinus node disease, intact AV conduction, and a normal QRS interval were randomly assigned to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing with the use of features to promote AV conduction and reduce ventricular dyssynchrony (9). Persistent atrial fibrillation was found to occur less frequently in the dual-chamber minimal ventricular pacing group (hazard ratio 0.60, 95% CI 0.41 to 0.88) than in the conventional dual-chamber group
   c. **Recommendations.** The most recent recommendations for cardiac pacing and resynchronization released by the AHA/ACC/HRS in 2008 specifically address the implications of apical versus RV outflow tract/septal pacing. The recommendations mention that small trials have demonstrated septal pacing preserved LV function over the mid- to long term and that His bundle pacing also appears to be beneficial. However, the guidelines note that it is too early to propose a recommendation concerning the optimal location of the RV pacing lead.

XVI. EVOLVING INDICATIONS FOR PACEMAKER THERAPY

A. Hypertrophic cardiomyopathy

1. **Presumed mechanism of benefit.** The idea of RV pacing to treat hypertrophic cardiomyopathy is based on the effective increase in left ventricular outflow tract (LVOT) diameter caused by altered septal activation.
2. **Recommendations.** Pacing is a class IIb recommendation in the 2008 ACC/AHA/HRS guidelines and is reserved for symptomatic drug-refractory patients with significant LVOT gradients who have contraindications for septal ablation or myectomy (see Table 54.2).

B. Long QT syndrome

1. **Presumed mechanism of benefit.** In patients with long QT syndrome, life-threatening episodes of polymorphic ventricular tachycardia and Torsades are typically preceded by pauses or severe bradycardia. By preventing these episodes, pacing may decrease the likelihood of events.
2. **Recommendations.** The 2008 ACC/AHA/HRS guidelines state that permanent pacing is reasonable for high-risk patients with congenital long QT syndrome.

XVII. FUTURE DIRECTIONS

A. Sensor technology. Advances in physiologic sensors and rate adaptation algorithms include the following.

1. **Multiple sensors for more physiologic pacing.** For example, a desirable sensor combination is an activity sensor, which typically has a more rapid response, and another sensor such as minute ventilation, which typically has a more delayed but workload-proportional response.
2. **Sensor blending** refers to the relative contribution of each sensor during each phase of activity and may be programmable.
3. **Sensor "cross-checking"** is done to determine if an increase in the intrinsic atrial rate is appropriate. If the sensor does not confirm activity while the pacemaker senses an increased atrial rate, the pacemaker will use the sensor to dictate the appropriate heart rate. Also, pacemakers with multiple sensors are able to detect intersensor disagreement and thereby avoid inappropriately rapid pacing due to a false-positive response of one sensor.

XVIII. GLOSSARY

A. Cardiac pacing: basic terminology

1. **"60,000 rule".** Converts rate (bpm) to interval (milliseconds) and vice versa, as there are 60,000 milliseconds in 1 minute. Note the formula: 60,000/interval (milliseconds) = rate (bpm).
2. **Anode.** Refers to the positive pole. The anode of a unipolar pacing system is the pulse generator case. The anode of a bipolar pacing system is the proximal ring electrode of the pacing lead.
3. **Capture.** The effective cardiac depolarization resulting from a pacing stimulus.
4. **Cardiac stimulation threshold (mA).** The minimal electrical energy required to consistently depolarize cardiac tissue through a given electrode. This threshold changes with time after implantation (acute, subacute, and chronic).
5. **Cathode.** Refers to the negative pole. The cathode of a unipolar pacing system is the electrode at the distal portion of the pacing lead. The cathode of a bipolar pacing system is the distal tip electrode of the pacing lead.
6. **Cross talk.** In dual-chamber pacing systems, the inappropriate detection (sensing) of an event or signal in one chamber by the sense amplifier of the other chamber (usually inhibition of a ventricular output pulse due to ventricular channel detection of an atrial output pulse).
7. **Current** (***I***). The rate of transfer or the flow of electricity, measured in milliamperes (mA).
8. **Elective replacement interval (ERI), also known as elective replacement time (ERT) or recommended replacement time.** Terms indicating the pulse generator has reached a point in its service life where system failure will likely occur within 3 to 6 months. The ERI indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a change in pacing rate, mode, or function. Pacemaker manufacturers generally recommend pulse generator replacement when the ERI is identified. ERI/ERT indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.
9. **External EMI.** Electrical signals from noncardiac or nonphysiologic sources that may affect pacemaker function. Sources of EMI are discussed below.
10. **End of life.** Term indicating the depletion of battery power for the pulse generator. The EOL indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a decrease in the magnet-related pacing rate to a certain percentage of the beginning-of-life rate. There may also be a change in pacemaker mode (e.g., from DDD to VVI). Telemetry of the

cell impedance of the pulse generator also provides information regarding the status of battery power for those pacemakers with such a feature. Pacemaker manufacturers generally recommend urgent pulse generator replacement if EOL of a device is identified. EOL indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.

11. **Fusion.** Results when the pacemaker output occurs at the same time as an intrinsic event, and both contribute to cardiac depolarization. The morphology of the fused beat has characteristics of both the paced and intrinsic events.
12. **Impedance** (***Z***). Total resistance to the flow of current through a conductor. For pacemaker systems, this includes resistance produced by electronic components and body tissues. Temporal changes in pacing impedance usually include a decreasing impedance over the first 1 to 2 weeks following implantation, then increasing impedance to a level that is somewhat higher than the impedance at the time of implantation. Serial measurements of pacing impedance may be useful for assessing lead integrity, as discussed later in this chapter.
13. **Magnet mode.** The response of a pacemaker when a magnetic field of sufficient strength is applied and closes the pulse generator's reed switch. The pulse generator paces at a predetermined rate and mode, which vary among pacemaker models and manufacturers. Generally, the mode is asynchronous pacing. Magnet mode can be used to assess pacemaker function and battery status (see discussion on ERI in Section **XVIII.A.8** and on EOL in Section **XVIII.A.10**).
14. **Noncapture.** The absence of cardiac depolarization following a pacing stimulus.
15. **Ohm's law.** $V = I \times R$ (*voltage* = *current* × *resistance*).
16. **Output.** The output of a pacemaker is determined by the voltage and pulse width.
17. **Oversensing.** The sensing of inappropriate cardiac or extracardiac signals and responding to them as if they were appropriate native sensed events. "Oversensing results in underpacing."
18. **Pacemaker-mediated tachycardia.** Sudden onset of a sustained ventricular paced rhythm at the maximum tracking rate of the pacemaker. PMT is sustained by continued active participation of the pacemaker in the tachycardia circuit. PMT is discussed in more detail in Section **XIII.D.2**.
19. **Pacing interval (milliseconds).** The interval between two consecutive paced events.
20. **Pseudofusion.** Results when an intrinsic event occurs before the pacemaker output is delivered. When this happens, the pacemaker output does not contribute to cardiac depolarization. The morphology of the pseudofusion beat resembles the intrinsic event.
21. **Pseudo-pseudofusion.** Results when a PVC that resembles the ventricular paced complex follows an atrial output spike.
22. **Pulse width.** The measurement in milliseconds of the pacemaker output spike (also known as pulse duration).
23. **Reed switch.** A switch within the pulse generator that closes when a magnetic field of sufficient strength is applied to it (such as a ring or donut magnet, or a programming head). The pacemaker will convert to magnet mode.
24. **Resistance** (***R***). The opposition to the flow of electrical current through a material, measured in ohms.
25. **Sensing.** The ability of a pacemaker to recognize native cardiac signals. Refers to the amplitude of the signal (mV) required for the pacemaker to detect the signal. Higher numbers reflect less sensitivity; lower numbers reflect more sensitivity.
26. **Undersensing.** The failure to recognize and respond appropriately to cardiac signals. "Undersensing results in overpacing."
27. **Voltage** (***V***). The difference in potential energy between two points, measured in mV.

B. Cardiac pacing: timing cycles and refractory periods

1. A = atrial-paced event.
2. Absolute refractory period: The period following a sensed or paced event during which the sense amplifier is unresponsive to incoming signals.
3. AEI = atrial escape interval: For atrial single-chamber pacing systems, the period from a sensed atrial event to the next atrial-paced event. For dual-chamber pacing systems, the period initiated by a ventricular sensed or paced event and ending with the next atrial-paced event.
4. ARP = atrial refractory period, which is the atrial timing cycle during which the atrial sense amplifier is unresponsive to incoming signals. For single-chamber atrial pacing modes, the atrial refractory period is initiated by an atrial sensed or paced event. For dual-chamber pacing modes, the AV interval and the PVARP determine the TARP. TARP = AVI + PVARP.
5. AV = atrioventricular sequential pacing.
6. AVI = atrioventricular pacing interval (also known as AV delay): In dual-chamber pacing, the period between an atrial sensed or paced event and a ventricular paced event (usually programmable).
7. Blanking period: An interval (usually 12 to 125 milliseconds) initiated by an output pulse during which the sense amplifier is temporarily disabled. In dual-chamber pacing, the blanking period is designed to prevent the inappropriate detection of signals from the other chamber (cross talk). For example, an atrial sensed or paced event initiates a ventricular blanking period during which the ventricular sense amplifier is temporarily disabled.
8. CDW = cross talk detection window: In dual-chamber pacing, a timing cycle (usually 51 to 150 milliseconds) immediately following the ventricular blanking period during which a ventricular sensed event is considered to be cross talk but results in a triggered ventricular output at the end of an abbreviated AV interval (safety pacing).
9. LRL = lower rate limit (also known as base rate or minimum rate): The rate at which the pacemaker paces in the absence of sensed intrinsic events (generally programmable in most pacemakers).
10. MSR = maximal sensor rate: A programmable value in rate-adaptive pacemaker systems that designates the highest pacing rate that can be achieved in response to a sensor input. The MSR may be programmed independently of the MTR.
11. MTR = maximal tracking rate (also known as upper rate limit, URL): A programmable value for dual-chamber pacemaker sensing and tracking modes that designates the highest ventricular pacing rate that can be achieved in response to atrial sensed events with 1:1 AV synchrony at the programmed AV delay.
12. P = native atrial depolarization.
13. R = native ventricular depolarization.
14. Relative refractory period: A "noise sampling" period following the absolute refractory period during which some incoming signals (generally those signals in the frequency range of interference) are monitored by the sense amplifier. Sensed signals during this period may result in the initiation of a new refractory period but do not reset the timing circuit.
15. RRAVD = rate-responsive atrioventricular delay. A programmable feature of some dual-chamber pacing systems that progressively shortens the PV or AV interval as the sinus or sensor-driven atrial rate increases. This is designed to provide a more physiologic AVI at higher heart rates and to allow tracking of higher atrial rates (a shorter AVI decreases the TARP), thereby lessening the chance of a fixed-block upper rate response.
16. V = ventricular paced event.

17. VRP = ventricular refractory period. The timing cycle initiated by a ventricular sensed or paced event during which the ventricular sense amplifier is unresponsive to incoming signals. This is not the same as the ventricular blanking period (see information regarding this in Section **XVIII.B.7**).

ACKNOWLEDGMENTS: *The author thanks Drs. Barbara Hesse, Matthew Hook, and Timothy Mahoney for their contributions to earlier editions of this chapter.*

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CHAPTER 55

Christopher Ingelmo

Antitachycardia Devices

I. INTRODUCTION

A. The modern implantable cardioverter–defibrillator (ICD) is a multifunctional, multiprogrammable electronic device designed to abort life-threatening arrhythmias. It is programmed to automatically detect and manage episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), or bradycardia. Current ICDs are able to deliver multitiered therapies, which may include a combination of antitachycardia pacing (ATP), cardioversion, and defibrillation. The devices also offer bradycardic support, which may include rate-responsive single- or dual-chamber pacing and automatic mode switch function. Modern ICDs are able to deliver resynchronization therapy, a significant advancement in the management of heart failure. The devices are also able to store electrograms (EGMs), which can be easily retrieved. This function can be of immense use for follow-up management of the patient and programming of the device.

Multiple clinical trials have demonstrated the efficacy of ICDs to accurately detect and manage sudden cardiac death (SCD). The ICDs are superior to conventional therapy, with medications in both primary and secondary prophylaxis of SCD. The majority of patients who have indications for an ICD implant are those with left ventricular (LV) dysfunction, both ischemic and nonischemic.

B. Mirowski first introduced the concept of an ICD in the 1960s, with the first human implant reported in 1980. The early ICD implantations required a thoracotomy approach for placement of an epicardial lead system. Subsequent advancements in device and lead technology over the last 30 years have significantly reduced the size of the pulse generator, yet improved the programmability and diagnostic data stored within the device. An improved understanding of VF, defibrillation, and cardiac pacing has resulted in the development of biphasic shock waveforms and transvenous pace/defibrillation lead systems that preclude the need for epicardial patches. As a result, modern ICDs are more compact devices, with expansive programming capability placed by a transvenous approach. The newest generation of devices has the added capability of trans-telephonic interrogation.

II. ICD COMPONENTS

A. The current-day ICD is a sophisticated and intelligent computer. It consists of a generator and leads. The ICD generator consists of a battery, capacitors, DC–DC converter using an oscillator rectifier mechanism, a microprocessor, and telemetry communication coils and their connections. The generator serves as an active electrode within the shocking configuration in most of the modern ICDs and is thus called the "hot can." The battery used in most of the ICDs is a lithium–silver vanadium oxide cell. This can generate approximately 3.2 V at full charge. Because most ICDs use two batteries connected in series, the full initial voltage is approximately 6.4 V. The generator has capacitors that can charge within 7 to 30 seconds to store up to 30 to 40 J of energy. This can be delivered to the heart within a 10- to 20-millisecond interval when therapy is required.

B. The three essential functions of the ICD—**tachycardia detection, tachycardia therapy, and bradycardia pacing**—are delivered through the active electrodes, which are the noninsulated segments of the leads. Most of the current-day leads have sensing and pacing electrodes at the tip and a distal (right ventricle) and proximal (superior vena cava) shocking coil. The function of ventricular sensing and pacing is achieved by a technology similar to that in pacemakers. This is done through two "dedicated bipolar" electrodes at the distal end of the right ventricular (RV) lead (tip/ring). Sometimes, it may be achieved by "integrated bipolar" electrodes, wherein the bipole is formed by the tip of the ventricular lead and the distal shocking coil (tip/coil). Ventricular pacing in biventricular ICDs is from the tip of the RV and LV leads, respectively, to either the ring (true bipolar) or the distal shocking coil (integrated bipolar). The sensing could be from both RV and LV leads but could give rise to false tachycardia detection due to the problem of "double counting." It is for this reason that the newer devices restrict the sensing function to the RV lead alone.

C. For the delivery of shock therapy, most systems now incorporate a combined RV coil, superior vena cava coil, and active pulse generator can or sometimes a single RV coil with a hot can active pulse generator. Modern technology makes it feasible to incorporate all these electrodes and coils in a single lead implantable in a manner similar to a pacemaker.

III. INDICATIONS AND CONTRAINDICATIONS

A. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. These are the most current guidelines for the implantation of ICDs. The guidelines stratify the various indications as class I, class II (a and b), and class III on the basis of the data from clinical trials and opinion of a panel of experts.

B. Class I indications. These are clinical situations or conditions for which there is evidence and/or general agreement that ICDs are useful and effective.

(1) Survivors of SCD secondary to VF or hemodynamically unstable VT

(2) Syncope of unknown etiology with inducible VF or hemodynamically significant VT during electrophysiology study

(3) Structural heart disease and spontaneous hemodynamically unstable or stable VT

(4) Ischemic cardiomyopathy, New York Heart Association (NYHA) class I, and a left ventricular ejection fraction (LVEF) ≤ 30% who are at least 40 days post myocardial infarction (MI)

(5) Ischemic cardiomyopathy, NYHA class II or III with an LVEF ≤ 35% who are at least 40 days post-MI

(6) Ischemic cardiomyopathy, ejection fraction (EF) ≤ 40%, nonsustained ventricular tachycardia , and inducible VF or sustained VT at electrophysiology study

Nonischemic cardiomyopathy, NYHA class II or III, and LVEF ≤ 35%.

C. Class IIa indications. These are conditions for which there is conflicting evidence about the usefulness of ICD therapy, with the weight of evidence/opinion in favor of usefulness/efficacy.

1. Unexplained syncope with significant LV dysfunction and nonischemic cardiomyopathy

2. Normal or nearly normal LVEF with sustained VT

3. Patients with hypertrophic cardiomyopathy and at least one risk factor for SCD

4. Patients with arrhythmogenic RV dysplasia with at least one risk factor for SCD

5. Patients with long QT with syncope or VT while taking β-blockers

6. Patients waiting heart transplantation (nonhospitalized)

7. Patients with Brugada with a history of syncope or VT but no episodes of cardiac arrest

8. Patients with catecholaminergic polymorphic VT with syncope or sustained VT while taking β-blockers

9. Patients with cardiac sarcoid, giant cell myocarditis, or Chagas disease.

D. **Class IIb** (usefulness/efficacy is less well established by evidence/opinion)
   1. Nonischemic cardiomyopathy with an EF ≤ 35% and NYHA class I
   2. Long QT and risk factors for SCD
   3. LV noncompaction patients
   4. Patients with familial cardiomyopathy and a predisposition to SCD
   5. Patients with structural heart disease and syncope but with no identifiable etiology

E. **Class III indications/contraindications.** These are conditions for which there is a general agreement that ICDs are not useful and possibly harmful. These include patients with a structurally normal heart and syncope without any inducible ventricular arrhythmias. ICDs should also be avoided in patients with VT and a treatable/ablatable cause (Wolff-Parkinson-White syndrome, outflow tract VTs, fascicular VTs, etc.) or a reversible cause (acute MI, myocardial ischemia, electrolyte imbalance, drug toxicity, or trauma). It is also important to avoid using ICDs in patients with severe psychiatric illnesses or in patients with terminal illnesses, where the expected life span is less than 12 months. ICDs could do more harm than good in patients with incessant ventricular arrhythmias, where it is important to control the arrhythmia before ICD implantation to avoid recurrent painful shocks. ICDs are also contraindicated in patients with NYHA class IV heart failure that are drug refractory and are not candidates for heart transplantation or cardiac resynchronization therapy (CRT).

IV. IMPLANTATION

A. **Device implantation.** Currently, available devices are small enough to allow implantation in the left pectoral region. Animal studies have shown that the defibrillation efficacy of the hot-can ICDs is superior in the left pectoral or axillary regions followed by the right pectoral and then the abdominal sites. A right pectoral system may be necessary in patients who have vascular access problems on the left side or who have undergone pectoral surgery (e.g., mastectomy). For patients with high defibrillation thresholds (DFTs), additional lead placement, such as a subcutaneous array/coil, an azygous coil, a coronary sinus coil, or an epicardial patch, may be necessary. Epicardial patch placement is usually reserved for patients who have failed to meet implantation criteria with a transvenous lead system or if there has been previous bilateral pectoral or tricuspid valve replacement surgery.

   For pectoral implants, a single 2″ to 3″ incision is made transversely below the clavicle, about 1 cm below and parallel to the deltopectoral groove. Transvenous lead placement is achieved through a subclavian vein puncture or by cephalic vein cutdown. An "extrathoracic" subclavian vein puncture or cephalic vein cutdown for access minimizes the risk of pneumothorax and also the risk of lead failure due to subclavian crush injury.

B. **Lead placement.** The lead is advanced to the RV apex under fluoroscopic guidance, where the tip is secured via an active fixation screw or embedded in the trabeculae with passive fixation tines. It is important to assess the quality of signals at the time of implant, as it is the best guide to the adequacy of long-term sensing of the lead. The DFT is optimized with the lead placed at the RV apex; therefore, this position is often preferred even if there is compromise of the sensing thresholds. If there is already a pacemaker lead in the RV apex, then septal placement of the lead tip is chosen so that the lead tips are at maximal distance from each other to avoid device–device interactions. On occasion, placing an additional pacing-sensing lead in the right ventricle may be necessary when the defibrillation efficacy and pace-sense function of the leads are optimized at different locations.

C. **Threshold studies.** The lead is tested for pace-sense thresholds using an external high-voltage system analyzer or pacing system analyzer. In general, an acute pacing threshold of 2 V or less, R-wave amplitude of 5 mV or more, and lead impedance within the accepted range of the manufacturer (typically 300 to 1,200 Ω) are

necessary to meet the implant criteria. The lead is secured within the pocket with a suture sleeve tie-down. If the device uses an atrial and/or an LV lead, then these are implanted at this time. The leads are attached to the pulse generator and the system is placed in either a submuscular or a subcutaneous pocket. The pulse generator should be placed with excess lead coiled posteriorly to reduce the risk of damaging the leads at the time of generator change and to maximize the ability to communicate with an external programming wand. The device is then interrogated to assure appropriate communication. Pace-sense thresholds are again tested by telemetry to demonstrate consistency.

D. Defibrillation testing is best assessed by evaluating the DFT, which is defined as the lowest delivered shock strength required for successful defibrillation. A synchronized sinus test shock may be performed by delivery of a low-energy (<2 J) synchronized shock delivered on the QRS complex. This low-energy test allows the assessment of sensing as well as shock impedance (typically 35 to 90 Ω). For the purpose of defibrillation testing, VF is typically induced with a shock on T wave. Alternatively, or if shock on the T wave is unsuccessful, ultrafast burst pacing (30-millisecond intervals) or application of an alternating current may be used. Appropriate ICD detection and effective therapy are verified. In our lab, we typically start with a 10 to 15 J therapy, with subsequent therapies escalating in steps of 5 to 15 J. Usually a maximum of three device-based therapies are attempted before rescue with external defibrillation at maximum energy. Two successful therapies that are at least 10 J less than the maximal output of the device are generally required. In general, this approach identifies the level of energy required to achieve a 50% to 75% success rate of defibrillation. Defibrillation therapy is then programmed at a level at least 10 J over the DFT. Rarely, a patient may require the addition of a shocking coil in the superior vena cava, subcutaneous patch, or subcutaneous array to achieve an adequate safety margin.

E. Risks and complications. The risks involved with implantation are similar to those of pacemaker insertion. Operative risks include bleeding, pneumothorax, hemothorax, infection, myocardial damage, vascular/cardiac perforation, tamponade, thromboemboli, deep venous thrombosis, acceleration of arrhythmias, air embolism, and death. A rare but dangerous complication is the occurrence of electromechanical dissociation or refractory VF during DFT testing. Due to the nature of the procedure, a separate standby external pacemaker-defibrillator should be immediately available for rescue therapy should the implanted device fail to appropriately treat an arrhythmia. The overall mortality rate is much less than 1%. Late complications include chronic nerve damage, erosion, extrusion, fluid accumulation, infection, formation of hematomas/cysts, keloids, lead migration, lead dislodgment, and venous occlusion.

V. DEVICE REPLACEMENT

A. Battery status is determined by the measured voltage and this is retrieved with device interrogation. Generator replacement is generally recommended when the device reaches a battery voltage of around 2.6 V, termed elective replacement indicator. In such situations, the generator should be replaced within a few months. With continued depletion of the battery voltage, the generator reaches end of life, a situation that indicates a more urgent need for generator replacement as the battery voltage drops below 2.2 V. This may lead to longer charge times and incomplete or inappropriate function of the device.

B. Pulse generator replacement represents a vulnerable period for the ICD/lead system. A fourfold increased risk of infection has been reported with ICD pulse generator replacement. In the past, manufacturers have had multiple-lead models of variable pin lengths and diameters. Beginning in 1991, they adopted the 3.2-mm international pace-sense standard (IS-1) and the 3.2-mm defibrillation standard (DF-1). Prior to an attempted device replacement, assessment of the lead model should be done to verify that the appropriate replacement header or adapters are available at the time of surgery.

C. Leads may be inadvertently damaged during exploration of the pocket or during the exchange of pulse generators. Intraoperative assessment of lead function is imperative prior to introducing the replacement generator to the operative field. Replacement of a pace-sense or defibrillation lead may be necessary and requires the use of a different device header.

VI. TACHYCARDIA DETECTION AND THERAPY

A. EGM and tachycardia sensing. The ICD senses the intracardiac EGM signal via the implanted ventricular sensing electrodes. Recognition of a ventricular arrhythmia mainly depends on the analysis of the R-R intervals (heart rate is determined similarly). Accuracy of the EGMs depends on the health of the adjacent myocardium and appropriate contact. Accuracy also depends on far-field signals from the muscles, atrium, or other sources of electromagnetic interference. The sensed signals are passed through a band-pass filter that consists of high- and low-frequency cutoffs to represent true signal events. The accuracy of the signals in the newer devices has been further improved by analysis of the signal frequency, slew rate, amplitude, EGM width, autogain, and autothreshold. These variables are important in helping the device to differentiate VT and VF from other events like atrial fibrillation, sinus tachycardia, and other supraventricular tachycardias, thus reducing the incidence of spurious shocks.

Each EGM event and R-R interval is marked and detected, and there are various algorithms that attempt to identify the events as either normal or abnormal. The "abnormal" includes bradycardia that requires pacing, VT requiring ATP or low-energy synchronized shocks, or VF requiring defibrillation. Most of the algorithms depend on the ventricular rate criterion. Other variables, such as the suddenness of onset, variation in cycle length, and change in EGM morphology, help to increase the specificity for diagnosis but at some cost of reduced sensitivity. These should be adjusted and programmed based on the individual requirement and clinical scenario for every patient.

B. Event detection occurs if the device reaches a specified number of intervals programmed by the physician to detect VT or VF, at which point the ICD delivers the prescribed therapy. Most of the devices reconfirm the ongoing episode to avoid therapy for nonsustained events. After delivery of therapy, the device either confirms termination of the episode or meets criteria for redetection, and the next programmed therapy is delivered. The ICD automatically adjusts its sensitivity thresholds following sensed and paced events through an autogain mechanism. This allows the device to automatically adjust its sensitivity during a tachycardia episode in response to the changing amplitude of the ventricular signal.

C. Atrioventricular (AV) sequential devices incorporate programmable dual-chamber supraventricular criteria to exclude management of supraventricular tachyarrhythmias from inappropriate detection of VT or to identify concurrent VT and supraventricular tachycardia. Biventricular devices could pose problems of double counting and unnecessary therapies in patients with the older biventricular devices, where the sensed input is from both the RV and LV leads. The use of newer devices that have sensing inputs from only the RV leads should limit this problem. An additional feature of these devices is the capability to individually program the pacing output and timing of the RV and LV leads through separate ports.

D. Tachycardia therapy. Most devices allow for programming of several tachycardia zones. The VT zone is programmed with a lower detection cutoff that would include any clinical VT events. Ideally, the cutoff rate for the detection of tachycardia should be above the patient's maximal heart rate to avoid therapy for sinus tachycardia. ATP schemes include burst pacing and ramp pacing. Burst pacing sequences deliver a set of ventricular pulses at a fixed rate faster than that of the VT in an attempt to terminate the reentry VT by overdriving the circuit. Ramp pacing consists of a set of ventricular pulses in which each subsequent paced interval is incrementally shorter

than the preceding one. Although this is a more aggressive protocol, there is also a higher chance for the VT degenerating into VF with this therapy. Overall, some studies have shown about 90% success in termination of VT with ATP.

Following a failed ATP attempt, interburst decrement allows a more aggressive shortening of the intervals during either a burst or a ramp attempt. The first pulse of a burst or ramp sequence (S_1) is delivered at a calculated percentage of the tachycardia cycle length. The S_1 percentage cycle lengths, number of pulses, interburst decrement, and number of ATP attempts are all programmable features. In addition, cardioversion therapy (1 to 36 J) can be programmed in a VT zone. All VT zones have a programmable time limit on episode duration at which point the device defaults to the next zone. Also, if a tachycardia is accelerated to a faster arrhythmia, then the ICD will deliver the therapy appropriate for the rate of the accelerated tachycardia.

E. Defibrillation therapy. Successful ICD management of VF can only occur with defibrillation therapy. All devices are programmed with a VF zone due to the risk of acceleration with ATP or cardioversion. Because of the hemodynamic instability seen with fast VT or VF, most devices are typically programmed to manage any sustained episode with rates higher than 180 to 200 beats/min with defibrillation therapy. The device should be programmed with at least a 10-J safety margin over the DFT observed either at implant or during follow-up testing. Up to six additional shocks may be programmed, with maximal outputs programmed at the second or third shock and onward.

VII. BRADYCARDIA DETECTION AND THERAPY

A. All currently available ICDs provide basic VVI pacing with separate programmable post-shock lower rate limit and output. Some dual-chamber devices have been introduced with an atrial lead for diagnostic use only or for AV-synchronized pacing. These devices allow multiple programmable pacing modes, including single- and dual-chamber, fixed-rate, or rate-responsive pacing with automatic mode switch. These expanded pacing modes have obviated the need for a separate dual-chamber pacemaker. In addition, they may reduce the inappropriate shocks attributed to supraventricular tachycardia. Such devices may also have capabilities to detect and treat atrial arrhythmias in a manner similar to that for the ventricular arrhythmias. However, in patients without any pacing indications, it may actually be detrimental to pace the right ventricle, especially in patients with preexisting LV dysfunction. This has been well demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. Such patients should either be given a single-chamber ICD or, if there are indications for a dual-chamber ICD for tachycardia discrimination or atrial arrhythmias, be programmed for backup pacing in the VVI mode.

B. In AV-synchronized devices, the ICD can continue to sense tachyarrhythmias in both chambers regardless of the programmed bradycardic pacing mode. To maintain proper sensing, both atrial and ventricular sensing thresholds are adjusted with autogain. The ICD has multiple blanking periods to avoid post-pacing polarization, T-wave oversensing, and cross talk between chambers. To avoid undersensing of tachyarrhythmias, short cross-chamber blanking periods after paced events and no cross-chamber blanking after sensed events are necessary. The AV synchronous devices have programmable refractory periods available for bradycardia functions, but these refractory periods do not affect tachyarrhythmia detection.

VIII. MAGNET FUNCTION

A. Confusion abounds concerning the function of a magnet with ICDs. The pulse generator contains a reed switch that is closed when a magnet is placed over the device. Closure of the reed switch prevents delivery of tachyarrhythmia therapy. Unlike pacemakers, bradycardia pacing is not affected by the use of a magnet in ICDs. Normal device therapy resumes when the magnet is removed and the reed switch opens.

IX. DEVICE–DEVICE INTERACTION

A. Device–device interaction remains a significant issue when multiple-lead systems or devices are used. When a new lead is placed, the lead should be positioned as far from the other leads as possible (at least 2 cm). A dedicated bipolar sensing lead is preferred to minimize the potential of far-field oversensing of the alternate pacing lead.

B. During the implantation procedure, the devices should be tested for device–device interaction. To simulate a worst-case scenario, the pacemaker is programmed in a unipolar configuration at high output. The real-time ICD EGM and marker channels are observed for oversensing of the pacemaker output, resulting in double counting of the paced QRS complex. This may lead to an inappropriate ICD discharge. Defibrillation testing is performed with the pacemaker programmed to DOO/VOO at high output to verify appropriate VF detection and therapy. Pacing stimuli may lead to ICD undersensing of VT/VF, with interpretation of the pacing artifact as "sinus rhythm" and failure to recognize the underlying arrhythmia. In addition, the ICD may affect the pacemaker by resetting the pacemaker pulse generator with a high-voltage shock. The pacemaker is programmed with the sensor "on" during an ICD high-output defibrillation test. The pacemaker is subsequently interrogated to verify appropriate communication and programmed mode. Whenever multiple devices are present and inappropriate ICD discharges are suspected, electrophysiology lab testing for device–device interaction is warranted. Device–device interaction should also be considered when a patient presents with resetting of the programmed mode, output configuration, or failure of communication with the device.

X. MANAGING AND FOLLOWING PATIENTS

A. In the United States, the government mandates patient registration and tracking. Once registered, a patient receives a permanent identification card to carry at all times. A MedicAlert is strongly encouraged. Manufacturer guidelines suggest that patients should follow up every 1 to 4 months depending on clinical status. Even if trans-telephonic follow-up is available, it should be supplemented by clinic visits. Patients should be informed that they are likely to receive therapies. At the follow-up visit, a history of symptoms that might suggest tachyarrhythmias should be obtained. The diagnostic and episode data should be reviewed. Current devices also include stored-episode EGMs to allow review of aborted shocks as well as delivered therapies. Device pacing and sensing thresholds should be obtained. There are no specific guidelines for follow-up testing of ICD defibrillation function. In general, patients experiencing device activation should be evaluated shortly after the event to assess for safe and appropriate device function. When device function or concomitant antiarrhythmic therapy is modified, an evaluation of the sensing, pacing, and defibrillation thresholds is often necessary. Practice patterns vary widely regarding empirical device programming and electrophysiologic testing of modified ICD programming. Some sources recommend that operating a motor vehicle should be avoided for 6 months following a symptomatic arrhythmic event.

B. In general, ICD pulse generators have a 4 to 6 year longevity depending on usage. The programmer allows evaluation of battery status. As the device approaches the elective replacement interval, follow-up visits should be intensified. In general, once the device reaches the elective replacement interval, it operates normally for at least 3 months depending on the frequency of therapy. Capacitor deformation occurs during periods when no shocks are delivered and results in longer charge times as well as decreased battery longevity. Current ICDs perform an automatic capacitor reformation that charges the capacitors and delivers the energy to an internal test load. This function improves subsequent charge times and battery longevity. Capacitor reformations should be conducted manually every 3 to 6 months if not conducted automatically.

C. Typically, 40% of patients receive a therapy within the first year after implantation and 10% per year thereafter. If multiple ICD discharges are experienced, medical attention should be sought emergently. **Failure to discriminate between ventricular and supraventricular rhythms is the most common reason for inappropriate shocks**. It is important to evaluate the patients for appropriateness of therapy. The most common cause of inappropriate shocks is atrial fibrillation with a fast ventricular rate. Shocks delivered during physical exertion noted to have gradually increasing heart rates and gradually decreasing V-V intervals suggest sinus tachycardia. Therapy is likely to be inappropriate in this setting also. Ideally, the cutoff rate for the detection of tachyarrhythmias should be greater than the patient's maximal heart rate. In many cases, the VT rate falls within the patient's achievable sinus rate. Programmable enhancements, such as sudden onset and sustained high rate, can allow sinus tachycardia overlap into the VT zone without delivery of an inappropriate shock. Additional enhancements such as morphology discrimination of the ventricular EGM as well as the introduction of dual-chamber devices with timing intervals, marker channels, and mode-switching capabilities are likely to improve the specificity of device therapy.

D. In the event of multiple ICD discharges, a magnet can be used to inhibit ICD therapy so that the underlying rhythm can be appropriately assessed and managed. The device should be interrogated as soon as possible to assess ICD function and facilitate diagnosis. If a supraventricular tachycardia is present, then it should be managed as medically appropriate. For patient comfort, the magnet should be left in place to inhibit ICD therapy until the device can be reprogrammed or the supraventricular tachycardia is terminated. If VF is present, the device is assumed inoperable and cardiopulmonary resuscitation with external defibrillation should be applied.

E. Patients receiving ICDs may suffer from significant psychological and emotional disturbances. Education and psychological support are beneficial in improving these patients' quality of life.

XI. ELECTROMAGNETIC INTERFERENCE. Patients should be counseled to avoid sources of electromagnetic interference because such interference may cause the pulse generator to become inhibited and either fail to deliver appropriate therapy or deliver inappropriate therapy. Potential sources of electromagnetic interference include industrial transformers, radiofrequency transmitters such as radar, therapeutic diathermy equipment, arc welding equipment, toy radio transmitters, antitheft devices, and magnetic security wands. The safe use of medical technologies such as electrosurgery, lithotripsy, external defibrillation, and ionizing irradiation can be accomplished by deactivating the device before the event. Shielding of the device is also appropriate when possible. The device should be evaluated for appropriate operation following exposure. Magnetic resonance imaging is contraindicated. Reports of interference created by cellular phones may be related to either a magnetic field from within the phone or the radiofrequency signal generated by the phone. It is suggested that if a patient with ICD wishes to use a cellular phone, it should be held to the ear opposite the device and carried at least 6″ to 12″ from the pulse generator; in addition, the phone should not be carried in a pocket close to the device.

XII. FUTURE. ICD implantation rates have risen tremendously over the last two decades and are expected to rise further with evolving therapies and indications. Multiple clinical studies have demonstrated the role of ICDs in the primary and secondary prevention of SCD. Multiple trials have also demonstrated the role of an ICD in combination with CRT in reducing mortality and hospital admissions in patients with heart failure. Improvements in electronic technology will continue to expand programming capabilities of these devices while reducing their size. ICD lead technology is also expected to improve, thereby decreasing the number of lead-related complications. Leadless systems are in clinical trials and may be an option for select patients in the future.

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CHAPTER 56

John Rickard

Cardiac Resynchronization Therapy

I. INTRODUCTION. The prevalence of heart failure (HF) in the United States has increased considerably in the past two decades as a result of the aging population and better medical management of left ventricular dysfunction (LVD). Unfortunately, medical therapy is not completely effective in preventing or reversing the progression of HF, and as a result, patients with advanced HF have limited options. A subset of patients with systolic LVD who have associated ventricular conduction delay are at highest risk for HF progression and a poor overall outcome. Since the late 1970s, various investigators have shown that left bundle branch block (LBBB), right ventricular (RV) pacing, or intraventricular conduction delay (IVCD) is associated with a less favorable hemodynamic profile in those with LVD and even in normal subjects. **The mechanism for this phenomenon is thought to be due to asynchronous and inefficient contraction of opposing areas of the ventricular myocardium. More importantly, restoring synchronization, either via simultaneous pacing of the RV apex and the left ventricular (LV) free wall or with timed LV free wall activation, can lead to a significant hemodynamic improvement.** In 1994, two investigators in Europe applied cardiac resynchronization therapy (CRT) in the clinical setting for the first time. Subsequent small observational studies suggested benefit from synchronous pacing. Larger randomized clinical trials confirmed these findings. CRT was first approved for maximally medically managed patients with persistent New York Heart Association (NYHA) class III or IV HF symptoms due to severe LVD associated with prolonged QRS duration. Further randomized studies, powered for mortality, showed a significant survival benefit with CRT or the combination of CRT with a defibrillator (CRT-D). More recently, CRT has been shown to be beneficial in less symptomatic patients. Unfortunately, not all patients who are selected for CRT based on current guidelines respond. Furthermore, some patients who would not be selected for CRT based on the current guidelines may actually benefit from this therapy. One of the major current challenges in this field is the optimal definition of the appropriate and cost-effective use of this expensive technology.

II. MECHANISM OF LV DYSSYNCHRONY. The normal pattern of electrical activation of the ventricular myocardium, once the impulse passes through the atrioventricular (AV) node, starts in the His bundle, followed by simultaneous activation of the right and left bundles of the Purkinje system and then by myocardial depolarization. The Purkinje system is electrically isolated from the rest of the myocardium until it reaches its exit points at the Purkinje–myocardial junctions. As a result, typical LV myocardial activation occurs from the apex to base, simultaneously in the septum and in the LV free wall, and is described as synchronous. Due to tight electromechanical coupling of the myocardium, synchronous ventricular activation is followed by synchronous ventricular contraction.

In the setting of conduction delay, the electromechanical coupling of the heart is disrupted, leading to dyssynchrony. Over time, electromechanical uncoupling leads to impaired stroke volume, worsened mitral insufficiency, prolonged LV isovolumetric

events, and impaired diastolic filling. These effects contribute to adverse remodeling in the already impaired heart, creating a vicious cycle that perpetuates this process into more advanced HF. As a result, when comparing patients with similar degrees of LVD, **those with conduction delay have a worse overall prognosis**. CRT has been shown to reverse this deleterious process. Synchronized pacing has been shown to improve LV function without increasing oxygen demand, suggesting that the improvement is related to better efficiency of the LV chamber.

Interestingly, dyssynchronous activation and contraction have an undesirable effect in patients ***without*** LV systolic dysfunction also. When compared with normal controls, patients with LBBB have a lower ejection fraction (EF), are more likely to develop HF, and have a tenfold greater cardiovascular morbidity and mortality risk. In some patients (patients with chronic LBBB, frequent premature ventricular contractions, or chronic RV pacing), the conduction delay in and of itself may cause deterioration in the EF. In this population, treatment with CRT can have profound effects potentially normalizing the LV function.

III. TYPES OF DYSSYNCHRONY

A. AV dyssynchrony. In the setting of PR or QRS prolongation, the atrial contribution to LV filling is abnormal. Atrial systole occurs too early with respect to ventricular diastole, leading to early truncation of passive LV filling. Early atrial systole also causes an early rise in diastolic ventricular pressure, leading to diastolic mitral regurgitation (MR). Compromised LV filling and MR cause lower cardiac output. AV synchronization can improve cardiac output in HF by as much as 20%.

B. Interventricular dyssynchrony. Early RV activation present during LBBB, IVCD, or RV pacing leads to early RV contraction, creating a pressure gradient between the RV and LV that negatively affects LV filling, which translates to a decrease in LV preload and a subsequent decrease in cardiac output. In the early development of CRT, interventricular dyssynchrony was thought to be a major contributor to adverse events in patients with HF and conduction disease. More recently, however, interventricular resynchronization has not been shown to be of significant benefit, clinically calling the role of interventricular dyssynchrony in the failing heart into question.

C. Intraventricular dyssynchrony. In the presence of conduction delay, there is a substantial delay in the activation of certain LV segments compared with others, leading to an inefficient back-and-forth mechanical interaction that results in inefficient myocardial contraction. In the case of a native LBBB for example, there is a significant delay in activation between the early activated septum and the late activated posterolateral wall, often resulting in profound delays between segments. **Mitigation of intraventricular dyssynchrony** is currently thought to be the primary mechanism of improved myocardial performance with CRT.

IV. ASSESSMENT OF DYSSYNCHRONY (see Table 56.1).

While CRT has been established as an effective therapy for patients with conduction delay and LVD, approximately 30% of patients meeting current implantation criteria fail to respond (depending on one's definition of response). This has spawned a major research effort to identify dyssynchronous contraction preimplantation to refine appropriate patient selection for this procedure. In addition to the three varieties of dyssynchrony already discussed, dyssynchrony can also be broken into "mechanical" and "electrical." Electrical dyssynchrony refers to delays in depolarization from one segment to another, whereas mechanical dyssynchrony refers to contraction delays from one segment to another. While the two are presumed to be closely linked, **current measures of electrical and mechanical dyssynchrony have often shown poor agreement**. For example, almost all clinical trials have used prolonged QRS duration, a crude marker of electrical dyssynchrony, as a requisite for inclusion. The relationship, however, between QRS duration and various

TABLE 56.1 Commonly Used Echocardiographic Measurements of Dyssynchrony

Method	Measurement	Value (milliseconds)
M-mode	Septal to posterior wall delay	> 130
Pulsed tissue Doppler	Opposing wall delay onset velocity	> 60
Color tissue Doppler	Opposing wall delay peak velocity	> 65
Color tissue Doppler	12-Segment standard deviation	> 34
Tissue Doppler radial strain	Septal to posterior wall delay	> 130
Tissue speckle tracking radial strain	Septal to posterior wall delay	> 130
Three-dimensional echocardiography	12-Segment standard deviation	> 36

measures of mechanical dyssynchrony has been poor. Studies have revealed that up to 30% of patients with a prolonged QRS duration do not have mechanical dyssynchrony as assessed by magnetic resonance imaging (MRI) or echocardiography, whereas up to 30% of patients with a normal QRS duration and symptomatic HF have evidence of mechanical dyssynchrony on echo or MRI and could potentially benefit from resynchronization therapy. Currently, the development of new measures of both electrical and mechanical dyssynchrony is an area of intense research. While newer, noninvasive measures of electrical dyssynchrony other than the QRS duration are on the horizon, currently, the bulk of research on dyssynchrony has been dominated by the various metrics of mechanical dyssynchrony, mostly using various echocardiographic techniques.

A. Echocardiographic assessment of dyssynchrony. The assessment of cardiac mechanical dyssynchrony was initially made with M-mode and pulsed-wave Doppler. Subsequently, tissue Doppler imaging (TDI) and tissue synchronization imaging have been used. More recently, three-dimensional echocardiography and speckle tracking technology have shown considerable promise. The main difficulty with all measures of mechanical dyssynchrony has been reproducibility across centers. In the large, multicenter PROSPECT trial, multiple echocardiographic measures of mechanical dyssynchrony were tested. **None, however, were found to be both a sensitive and a specific predictor of subsequent response to CRT**. Technical and interpretative variability across centers was thought to be a major reason behind the only modest predictive ability.

1. **Pulsed-wave Doppler** has been used to assess interventricular dyssynchrony by measuring the time delay between initiation of RV and LV ejection, known as the presystolic ejection period. One advantage of this technique is good feasibility and reproducibility. While values > 40 milliseconds are considered to be abnormal, the clinical utility of this measure remains to be proven.
2. **Septal to posterior wall motion delay** as assessed by **M-mode** in the parasternal long or short axis view has been used to detect intraventricular dyssynchrony. A value > 130 milliseconds has been associated with a greater response to CRT in terms of symptomatic improvement, LV remodeling, and EF increase. Advantages include the ability to perform this measure on all echocardiographic systems without the requirement of specialized software. Unfortunately, this parameter has significant limitations. It evaluates dyssynchrony in only two segments of the myocardium: the septum and the posterior wall. Additionally, it may be difficult to obtain in up to 40% of patients due to poor acoustic windows

as one must be perpendicular to the myocardial walls, which is often difficult in patients with low parasternal windows.

3. **Tissue Doppler imaging.** This technique uses pulsed-wave Doppler to record myocardial velocities at the basal septum and the basal lateral wall as close as possible to the mitral valve annulus in the four-chamber view. Time from the onset of the QRS to the onset of systolic velocity or to the peak of systolic velocity is measured. So too is the difference in these measurements between the septum and the lateral wall. Values > 62 milliseconds for time to systolic velocity initiation and 65 milliseconds for time to peak systolic velocity are abnormal and have predicted a favorable clinical and echocardiographic response to CRT. TDI has excellent temporal resolution and does not require endocardial border identification for determining the degree of delay. The limitations of TDI are as follows: (1) occasional difficulty in identifying the true peak of systolic velocity and (2) because segments are not assessed simultaneously, heart rate variability and respiration can lead to false comparisons. To better deal with these limitations, computer software has been developed that allows postprocessing of Doppler data so that all of these measurements are determined from one image. Additional views (apical three-chamber and apical two-chamber) may be used to increase the number of myocardial segments assessed. This technique improves both specificity and sensitivity in the identification of mechanical dyssynchrony, as compared with older, less sophisticated methods.

   Another major problem with current methods of TDI is that they assess systolic motion only in the longitudinal plane of the heart and, therefore, may be prone to artifact from tethering and pulling. The heart contracts in three different planes: longitudinal, radial, and rotational. The latter two are not assessed by conventional TDI but have a greater contribution to ventricular contraction than the longitudinal plane.

4. **Three-dimensional imaging.** The development of three-dimensional echocardiographic technology now allows the measurement of endocardial wall motion in reference to a center point. Using computer assistance, the endocardial border is tracked. Only the end-systolic and end-diastolic positions of the ventricular apex and mitral annulus must be determined by the operator. This technique permits the calculation of the three-dimensional dyssynchrony index, which quantifies mechanical dyssynchrony as the standard deviation of the time to minimum systolic volume as a percentage of the cardiac cycle length. While three-dimensional motion delay imaging has shown promise as predictive of subsequent reverse remodeling following CRT, it remains limited by the need for good image quality and a stable heart rhythm.

B. New echocardiographic indices of mechanical dyssynchrony. Newer echocardiographic techniques focus on eliminating the shortcomings of longitudinal TDI, namely, the tethering and pulling artifact, and lack of radial and rotational strain assessment.

1. **Strain imaging** performed in the four-chamber and parasternal short axis views incorporates velocity sampling in two nearby points. The sampled velocity difference divided by the separation distance is proportional to strain rate, which when integrated over time can provide the strain value. Strain, unlike velocity, does not depend on tethering or pulling of the myocardium. The major limitation of this technique is that it is time consuming and requires extensive off-line postprocessing.
2. **Speckle tracking.** Speckle tracking relies on the automated tracking of unique acoustic backscatter during standard grayscale imaging. Both strain and its planar dimensions may be assessed using semiautomated off-line analysis, which improves reproducibility and feasibility. This technique is promising and is currently being used as a measure of mechanical dyssynchrony in ongoing clinical trials.

C. Alternative modalities for dyssynchrony assessment. Tagged MRI is ideal for measuring strain; however, due to its high cost, high level of complexity, and contraindications in patients with pacemakers or implantable cardioverter–defibrillators (ICDs), it is of limited use with respect to dyssynchrony assessment.

V. ROLE OF CRT. The primary role of CRT is **to improve systolic and diastolic LV performance via an improvement in chamber efficiency**, thereby leading to symptomatic improvements in patients with medication refractory HF. The **systolic improvement** is usually noticed **within a week** of device implantation. In clinical trials, the **EF improved by an average of about 5%** with a significant improvement in MR and was accompanied by symptomatic improvement, as evidenced by increased 6-minute walk time and quality of life index score (QOLS). **The remodeling of the LV takes at least 3 or more months**. On average, the LV systolic and diastolic dimensions decrease significantly following prolonged CRT. In studies in which biventricular (Bi-V) pacing was switched off after prolonged synchronized pacing, the systolic benefits disappeared rapidly; however, the LV dimensions were maintained for a longer period of time, suggesting that actual LV remodeling took place during CRT. There is also evidence that CRT may lead to electrical remodeling of the heart. In patients with LBBB or IVCD, CRT led to shortening of the duration of the native QRS complex. More recently, evidence from randomized clinical trials powered for mortality, in addition to symptomatic improvement, supports the use of CRT alone or in combination with an ICD in patients with ischemic and nonischemic etiologies of severe LVD.

VI. SUMMARY OF MAJOR CLINICAL TRIALS OF CRT. Most clinical trials evaluating CRT have addressed its role in patients in normal sinus rhythm (NSR) with severe LVD, class III to IV HF symptoms refractory to medical therapy, and indirect evidence of mechanical dyssynchrony represented by prolonged QRS duration (on average, > 120 milliseconds). More recently, large trials have focused on the benefits of CRT in patients with less symptomatic HF (NYHA classes I and II).

A. PATH-CHF. A longitudinal crossover study of 41 patients evaluating CRT (Bi-V or LV pacing) versus no therapy. Primary end points of peak Vo_2, 6-minute walk, NYHA class, and QOLS significantly improved during CRT.

B. MUSTIC. A small prospective randomized trial powered for symptomatic improvement as measured by hospitalization, 6-minute walk, and QOLS in patients in NSR or with atrial fibrillation at the time of enrollment. The trial showed significant improvements with CRT, and the benefit was similar in NSR and atrial fibrillation.

C. MIRACLE. The MIRACLE trial, completed in late 2000, randomized 453 patients with advanced HF and a QRS duration ≥ 130 milliseconds to CRT versus conventional therapy for HF. The trial revealed significant improvements in peak Vo_2 consumption, 6-minute hall walk, QOLSs, EF, NYHA class, and treadmill exercise times with CRT compared with controls. This trial led to the approval of CRT devices by the Food and Drug Administration.

D. MIRACLE-ICD. Very similar to MIRACLE, the MIRACLE-ICD trial was a moderate-sized prospective randomized trial evaluating the safety and efficacy of combining CRT with ICD therapy for a composite end point of mortality, hospitalization, and symptomatic improvement. At 6 months follow-up, the CRT-ICD arm had a significant improvement in the composite end point. Combining CRT with ICD was deemed safe.

E. CARE-HF. The CARE-HF was a large, open-label randomized controlled trial powered to assess mortality benefit with best medical therapy plus CRT versus medical therapy alone in patients with ischemic and nonischemic etiology of LVD. In addition to the conventional dyssynchrony criteria of QRS duration > 150 milliseconds, the trial was the first to implement echocardiographic markers of mechanical dyssynchrony in those patients with QRS duration between 120 and 150 milliseconds. At 3 years of

follow-up, the primary end point of all-cause mortality and hospitalization was significantly different in favor of the CRT group. Furthermore, the secondary end point of all-cause mortality reached statistical significance after 3 years of follow-up, and the survival curves continued to separate. The number needed to treat with CRT to save one life was estimated at nine patients.

F. COMPANION. A large, open-label randomized (1:2:2) prospective trial powered for mortality and hospitalization benefit in patients with ischemic and nonischemic etiologies of LVD comparing medical therapy versus CRT versus CRT-D. In addition to conventional QRS criteria for CRT, patients also had to have had one episode of hospitalization for HF in the year prior to randomization. The primary end point of all-cause mortality and hospitalization was significantly different in the device groups as compared with the medically treated group. The secondary end point of all-cause mortality was significantly different in the CRT-D group as compared with the medical controls. The CRT group showed a strong trend toward mortality benefit that did not reach statistical significance. The trial was not powered to compare mortality benefits between the two device groups. In the CRT-D group, the mortality benefit was noticed shortly after the beginning of the trial, as compared with 6 to 12 months after study initiation in CARE-HF. The early mortality benefit in this trial was thought to be ICD related. The later benefits were attributed to both ICD and CRT therapies. The results of this trial led to approval of combined CRT-D therapy in the above population of patients.

VII. MAJOR TRIALS OF CRT IN MINIMALLY SYMPTOMATIC HF

A. REVERSE. The REVERSE study, published in 2008, was a large randomized, double-blind trial designed to assess whether CRT in addition to medical therapy could delay progressive myocardial remodeling and/or prevent HF progression. The study enrolled 610 patients with a 2:1 enrollment design such that 419 patients received a CRT-D device and 191 patients received an ICD alone. Inclusion criteria for the study were NYHA class I or II symptoms, a left ventricular ejection fraction (LVEF) ≤ 40%, a left ventricular end-diastolic dimension ≥ 55 mm, NSR, and a QRS duration ≥ 120 milliseconds. The primary end point of REVERSE was a novel clinical composite end point developed by Packer and colleagues, which rates patients as "improved," "unchanged," or "worsened" based on the combination of mortality status, hospitalizations due to HF, withdrawal of consent, and worsening NYHA class. The American arm of the study concluded at 12 months, with the European arm proceeding to 24 months. While there was no difference in the primary end point at 12 months, patients in the CRT arm derived significantly greater reductions in the left-ventricular end-systolic volume index and the left-ventricular end-diastolic volume index, respectively, and improvement in LVEF compared with those without CRT. During the 12-month follow-up period, there was no difference in mortality between the two groups; however, CRT significantly lowered HF hospitalizations. In the European arm of the trial in which follow-up was continued for an additional year, the benefit of CRT in inducing reductions in LV volumes and improvement in LVEF persisted at 24 months.

B. MADIT-CRT. MADIT-CRT, published in 2009, sought to determine the impact of CRT on HF hospitalizations and all-cause mortality in patients with NYHA class I or II HF symptoms. This multicenter, unblinded study randomized 1,820 patients in North America and Europe with an LVEF ≤ 30%, NYHA class I or II symptoms (patients with nonischemic cardiomyopathy and NYHA class I symptoms were excluded), NSR, and a QRS duration ≥ 130 milliseconds to a CRT-D device or an ICD alone. The primary end point for the study was death from any cause or a nonfatal HF event. At a mean follow-up of 2.4 years, patients in the CRT arm had a significantly lower incidence of the primary end point compared with the ICD alone arm. Similar to what was shown in REVERSE, patients in the CRT arm of

MADIT-CRT realized significantly greater improvements in myocardial structure and function compared with those without CRT.

C. RAFT. The RAFT trial which began enrollment in 2003 was a large, double-blinded, randomized controlled trial of 1,798 patients with NYHA class II or III symptoms, an LVEF ≤ 30%, and a QRS duration ≥ 120 milliseconds (or a paced QRS > 200 milliseconds), which compared therapy with CRT-D versus that with an ICD alone. Originally, the trial sought to determine whether CRT in addition to an ICD would improve survival in patients with class II and III symptoms. After publication of the CARE-HF trial and subsequent guideline changes, however, the protocol was altered in early 2006 to include only patients with NYHA class II symptoms. Of 894 patients receiving a CRT-D device in the RAFT trial, 79.2% had NYHA class II symptoms. For inclusion, patients had to either be in NSR or have rate-controlled permanent atrial fibrillation or flutter. The primary end point of all-cause death or HF hospitalization occurred in 33.2% of the CRT-D group and in 40.3% of the ICD only group over a follow-up of 40 ± 20 months. In looking at only patients with NYHA class II symptoms, patients in the CRT arm had reductions in the primary end point as well as in both cardiovascular and all-cause mortality and hospitalizations due to HF.

VIII. NONRESPONDERS.

Up to **30% of patients who receive CRT based on current QRS criteria fail to benefit from the therapy depending on one's definition of response**. Their symptoms do not improve or worsen, and there is no echocardiographic evidence of reverse ventricular remodeling. A clear etiology of the lack of improvement from CRT in those patients has not yet been elucidated. One of the possibilities is that QRS duration alone is not a good indicator of mechanical dyssynchrony, and some patients, despite prolonged QRS duration, do not have mechanical dyssynchrony and worsen when Bi-V pacing is commenced. In subjects with normal baseline LV contraction, Bi-V or LV free wall pacing has an inferior hemodynamic profile when compared with native conduction. Therefore, it becomes important that CRT be only offered to those that truly have asynchronous contraction.

Another potential explanation for the lack of CRT benefit in certain patients is the presence of myocardial scar in the LV free wall territory. Areas of fibrous myocardium are electrically and mechanically nonviable; therefore, pacing at those sites may be of little value.

Lead position may play an important role in nonresponse. Typically, in nonischemic dilated cardiomyopathy with LBBB, the posterobasal segment has the most delayed activation and contraction. This is not always the case in patients with ischemic etiology of LVD, where occasionally the inferior wall becomes activated the latest. It is conceivable that, due to limitations in the myocardial venous system, inadvertent placement of the LV lead in an area that is not significantly delayed may lead to adverse hemodynamic effects. Trials are underway using echocardiographic techniques to determine the latest activated segment with implanters targeting placement of the LV lead in or near this segment.

IX. CURRENT GUIDELINES AND RECOMMENDATIONS.

Based on the inclusion criteria from the available large randomized trials at that time (see Table 56.2), the AHA/ACC 2008 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult gives CRT a class I indication (level of evidence A) in patients with ischemic or nonischemic etiology of depressed LV function, EF ≤ 35%, severe HF symptoms, and NYHA class III or IV, on optimal medical therapy, in sinus rhythm with wide QRS complex ≥120 milliseconds, and with LV end-diastolic diameter ≥ 55 to 60 mm. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology, in collaboration with the European Heart Rhythm Association, provides the following recommendations for CRT.

TABLE 56.2 Current Recommendations for the Use of Cardiac Resynchronization Therapy in Patients with Heart Failure

Recommendation	Class	Level of evidence
Symptomatic HF (NYHA class III or ambulatory class IV) despite optimal medical therapy, with an LVEF ≤ 35%, normal sinus rhythm, and a wide QRS complex (≥ 120 milliseconds), should be treated with CRT/D	I	B
Symptomatic HF (NYHA class III or ambulatory class IV) despite optimal medical therapy, with an LVEF ≤ 35%, and a frequent dependence on ventricular pacing should be treated with CRT/D	IIa	C
Symptomatic HF (NYHA classes III or ambulatory class IV) despite optimal medical therapy, with an LVEF ≤ 35% and atrial fibrillation, should be treated with CRT/D	IIa	B
Symptomatic HF (NYHA class I or II) despite optimal medical therapy, with an LVEF ≤ 35%, who are undergoing implantation of a permanent pacemaker or ICD with anticipated ventricular pacing should be treated with CRT	IIb	C
Asymptomatic patients with reduced EF in the absence of other indications for pacing should not be treated with CRT/D	III	B
CRT is not indicated in patients whose functional status and life expectancy are limited by predominantly noncardiac conditions	III	C

CRT, cardiac resynchronization therapy; CRT/D, CRT with a defibrillator; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Adapted from the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm.

A. The use of CRT or CRT-D is recommended in patients with HF who remain symptomatic in NYHA classes III–IV despite optimal medical therapy and with an LVEF ≤ 35%, LV dilation with LV end-diastolic diameter > 55 mm, NSR, and wide QRS complex (≥120 milliseconds) (class I, level of evidence A for CRT; class I, level of evidence B for CRT-D).

B. The use of CRT is also recommended in patients with HF with NYHA classes III–IV despite optimal medical therapy and with an LVEF ≤ 35%, LV dilation, and a concomitant indication for permanent pacing (first implant or upgrade of conventional pacemaker) (class IIa, level of evidence C).

C. The use of CRT is also recommended in patients with HF who remain symptomatic in classes III–IV despite optimal medical therapy and with an LVEF ≤ 35%, LV dilation, permanent atrial fibrillation, and indication for AV junction ablation (class IIa, level of evidence C).

D. The use of CRT is also recommended in patients with HF who remain symptomatic in classes III–IV despite optimal medical therapy and with an LVEF ≤ 35%, QRS ≥ 130 milliseconds, permanent atrial fibrillation, and indication for AV junction ablation (class IIa, level of evidence C).

X. IMPLANTATION PROCEDURE. Unlike conventional transvenous pacemaker or ICD implantation that requires lead placement in the right atrium and/or the right ventricle only, Bi-V pacing requires LV lead implantation. Initially, this was achieved via a

thoracotomy; however, currently up to 98% of Bi-V devices are placed via a transvenous approach. Although now used infrequently, some patients are still referred for a thoracotomy after a failed transvenous approach. Because most patients who qualify for CRT are also candidates for an ICD, current CRT devices have a combined pacemaker/ICD capability. The hybridization of CRT and ICD therapy increases the complexity of programming, follow-up, and troubleshooting of such devices.

The procedure is performed in an electrophysiology laboratory under sterile conditions. All patients receive preprocedural antibiotics at least 30 minutes before the procedure. A subcutaneous pocket is first prepared, making sure that appropriate hemostasis is achieved. Bi-V device implantation, due to the increased risk imposed by possible coronary sinus (CS) perforation, requires complete reversal of anticoagulation. Typically, a cephalic or axillary vein approach to venous access is used. The right atrial and RV leads are implanted in a fashion similar to a pacemaker or ICD implantation. The LV lead is placed through the CS into a CS branch on the lateral free wall of the left ventricle. Performing an occlusive CS venogram may help identify the appropriate vein. Various sheaths, catheters, and guidewires are available to cannulate the CS and advance the pacing lead into the appropriate vein. While the optimal site for LV lead placement is controversial, many experts agree that anterior and apical positions are suboptimal. Once the lead is advanced, its location should be confirmed by fluoroscopy, typically in the left anterior oblique (LAO) view. The goal is to document base to mid-posterolateral LV lead placement and maximal LV–RV lead separation in the LAO view. A steep angulation in the LAO view tends to be most accurate. It has been shown that LV–RV interlead distance on the **lateral chest radiograph** is predictive of CRT response. Pacing thresholds are acceptable if < 3 V at 0.5 milliseconds. Diaphragmatic capture is excluded by high-voltage pacing. If high pacing threshold or diaphragm capture occurs, the lead should be repositioned. CS trauma is frequent during lead placement, and it may range from dissection to frank perforation. Because the pressure in the venous system is low, serious sequelae are unusual and cardiac tamponade rarely results. After adequate LV lead placement and confirmed appropriate LV lead function, care must be taken during guidewire, CS platform, and stylet removal, so as not to disrupt lead position. Lead dislodgement occurs in as many as 5% to 10% of implantations. The time frame for the majority of dislodgements is the first 24 to 48 hours postimplantation, when patients resume activity. For that same reason, patients are encouraged to ambulate while still in-house to prevent any out-of-hospital dislodgement, which may have more serious consequences.

XI. PROGRAMMING AND FOLLOW-UP. Currently, multiple configurations for Bi-V pacing exist. The available pacing configurations vary by device manufacturer. Changing configurations for pacing can be very useful in cases of poor thresholds or diaphragmatic stimulation.

Ventricular pacing must be **continuous** during CRT in order to obtain maximal benefit. Typically, DDD mode with a short AV delay (80 to 110 milliseconds) to prevent native conduction is employed. If atrial pacing is undesirable due to increased incidence of atrial fibrillation or altered left-sided AV timing, VDD mode may be used. Ventricular pacing is usually simultaneous or with a slight V-V delay. Given the two ventricular inputs (right ventricle and left ventricle), one could foresee that ventricular timing cycles could be quite complex during Bi-V pacing. Therefore, in most devices, the right ventricle is the only sensing chamber.

Follow-up of CRT devices includes a 12-lead ECG to assess for Bi-V capture and device interrogation to assess pacing thresholds. In those patients who are deemed nonresponders, echocardiography may be used to optimally time the AV delay based on Doppler mitral valve inflow patterns or Doppler aortic velocity time integral. Generally speaking, interventricular timing (V-V interval), although programmable, is not taken into consideration during CRT programming. Limited studies suggest that AV

programming may lead to a better acute hemodynamic response to CRT in certain patients. The value of VV optimization is of considerable debate. In addition, specialized nonresponder clinics may help troubleshoot device issues, treat arrhythmias, maximize CHF medications, and optimize the AV interval. While such clinics are limited mostly to specialized centers, such clinics have been shown to convert some nonresponders to responders.

XII. LOSS OF CRT. CRT is transiently interrupted in up to 35% of patients and permanently interrupted in 5% at 2 years of follow-up. Fortunately, restoration of CRT can be accomplished via nonsurgical means in the majority of the cases. Pacing parameters, occurrence of atrial arrhythmias, and lead malfunction or dislodgement are common causes of CRT interruption. The goal of continuous pacing during CRT should be reflected in appropriate programming algorithms. Typically, the AV conduction status is what influences continuous delivery of Bi-V pacing. Because the majority of patients who require CRT have an intact AV node, any parameters that allow for preferential native conduction will reduce CRT delivery. Keeping the AV interval as short as possible while maintaining proper ventricular loading is therefore optimal. Atrial arrhythmias are common in advanced HF. Rapid ventricular rate during atrial arrhythmias with rapid AV conduction inactivates Bi-V pacing due to the upper tracking rate limit. Keeping patients in NSR is therefore desirable. Any evidence of lead malfunction or displacement should be dealt with promptly by reintervention. The loss of CRT results in symptomatic deterioration in HF and hospital admission in many instances.

XIII. FUTURE DIRECTIONS. While CRT has emerged as one of the most important advances in the treatment of LVD over the last 15 years, several important questions remain. Despite the myriad of parameters of mechanical dyssynchrony that are available, none has been shown to be a practical and reliable predictor of response. Developing a measure of dyssynchrony that predicts response accurately and can be used across multiple care settings remains a challenge. Whether CRT has a role in patients with a narrow QRS duration remains in question. While the ReTHINQ trial failed to show benefit in this population, a two-dimensional measure of dyssynchrony was used. In the ongoing ECHO-CRT trial, a three-dimensional dyssynchrony measure will be employed, which should shed considerable light on the applicability of CRT in this population. Lastly, the role of CRT in patients without a native or RV-paced LBBB morphology is an area of considerable controversy. Patients with right bundle branch block (RBBB) have early activation of the left ventricle and late activation of the right ventricle, calling into question the role of LV pacing for these patients. Still, most patients with RBBB have a wider QRS duration than would be expected from having a "pure" RBBB alone. This implies additional left-sided delay that may be mitigated by CRT. While retrospective studies have certainly called into question the benefits of CRT in this population, currently, there is no prospective randomized trial to provide a more definitive answer. Patients with nonspecific IVCD are a heterogeneous population, likely with both right- and left-sided delay. In retrospective studies, the response rate of this population is more akin to those with RBBB than LBBB; however, the studies have been small.

XIV. SUMMARY. CRT has emerged as an effective therapy in patients with LVD refractory to CHF medications and a wide QRS duration. Major clinical trials have proven significant morbidity and mortality benefits from CRT first in patients with advanced heart and more recently in those with minimal symptoms. The issue of nonresponse to CRT continues to be a major problem and much ongoing research continues to be dedicated to predicting which patients will respond to this therapy. While many studies have shown some predictive ability of various imaging modalities, none to date has been shown to be a reliable predictor of response that could be utilized across multiple

centers. While the response to CRT in patients with a native LBBB or RV-paced rhythm is well documented, the response in patients with RBBB or a nonspecific IVCD continues to be debated.

ACKNOWLEDGMENTS: *The author wishes to acknowledge the contribution of Dr. Peter Borek to the previous edition of this chapter.*

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SECTION XI

Common Cardiology Procedures

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CHAPTER 57

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Common ECG Patterns

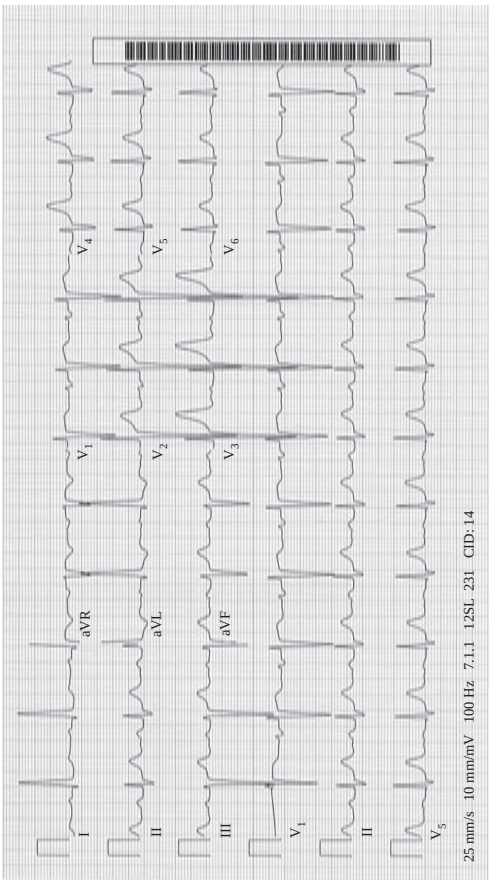

FIGURE 57.1 Left ventricular hypertrophy (LVH).

- Note that the R wave in lead aVL is > 11 mm, and the R wave in lead V_5 or V_6 + S wave in lead V_1 is > 35 mm.
- Left axis deviation is present.
- Left atrial enlargement, which often occurs with LVH, is also present (the terminal negative portion of the P wave in lead V_1 is ≥ 1 mm in depth and ≥ 40 ms in duration, and the P wave is broad in inferior leads).

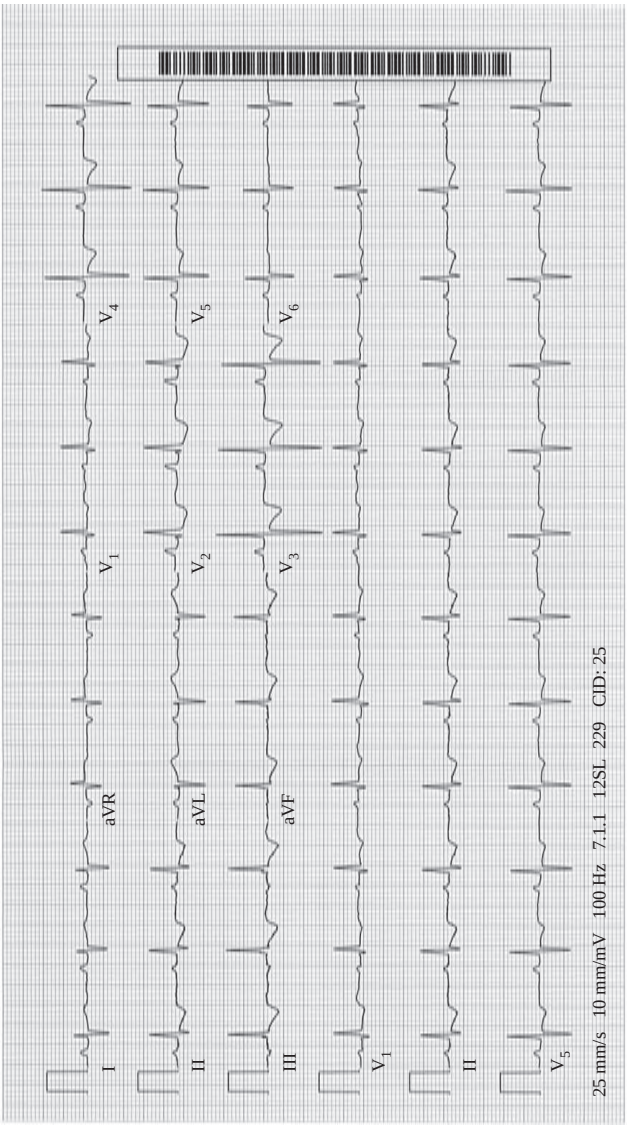

FIGURE 57.2 Right ventricular hypertrophy.

- The R wave in lead V_1 is > 6 mm, and there is right axis deviation (QRS axis > 100°).
- Other criteria include an R/S ratio in lead V_1 > 1 and an R/S ratio in lead V_5 or $V_6 \leq 1$.

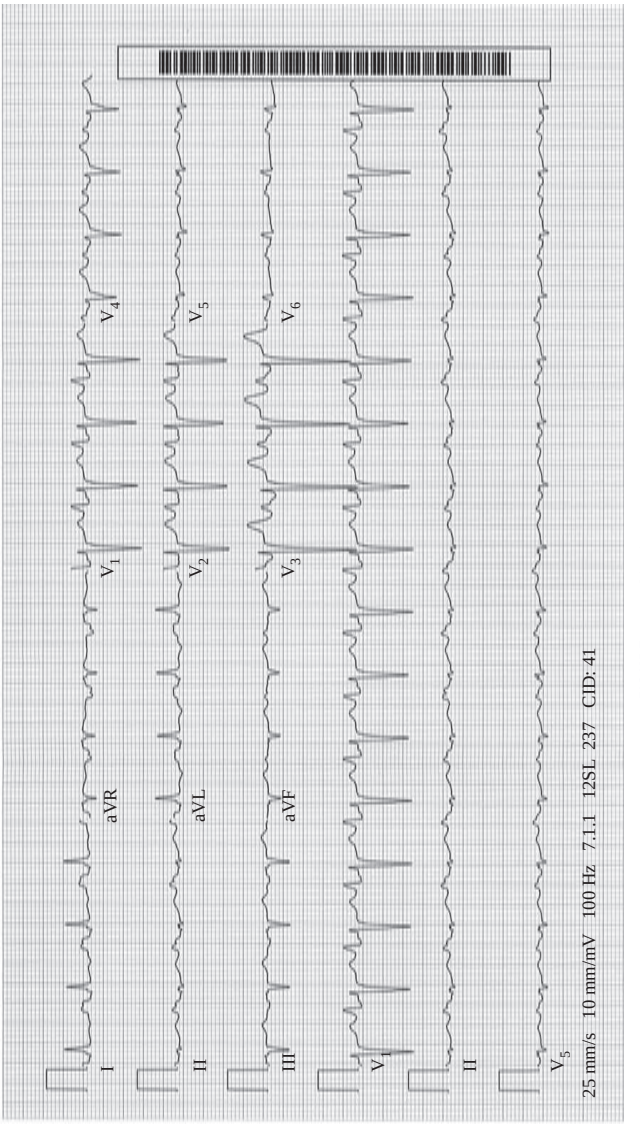

FIGURE 57.3 Biatrial enlargement.

- Left atrial enlargement is indicated by the negative terminal portion of the P wave in lead V_1 and the broad P wave in inferior leads.
- Right atrial enlargement is indicated by the height of the P wave in inferior leads and lead V_1.

Common arrhythmias

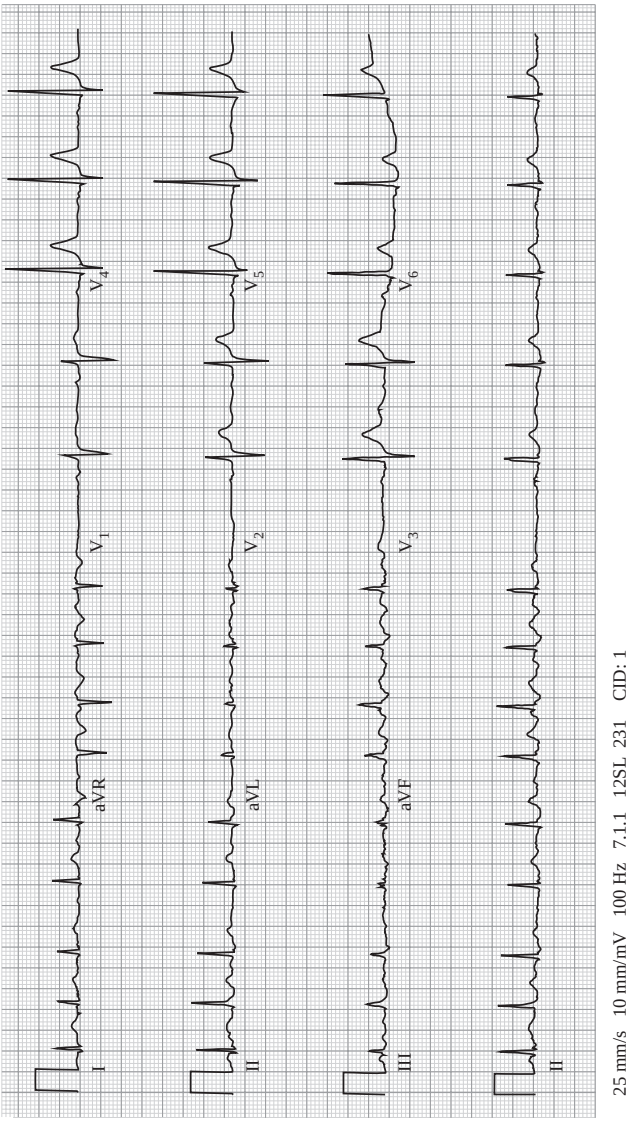

FIGURE 57.4 Atrial fibrillation.

- Irregular activity of the atria causes random oscillation of the baseline, and P waves are absent. The ventricular rate is irregularly irregular.
- The patient spontaneously converted to sinus rhythm midway through the rhythm strip.

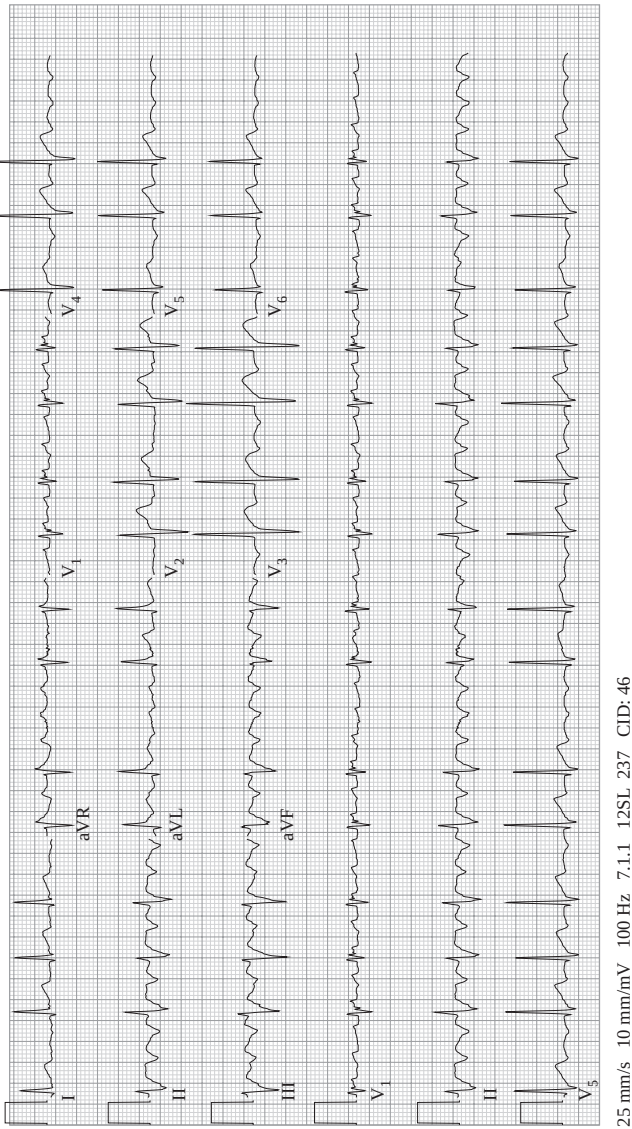

FIGURE 57.5 Typical atrial flutter.

- Flutter waves with a "sawtooth" appearance are present at around 300 beats/min. The waves are negative in inferior leads and positive in lead V_1.

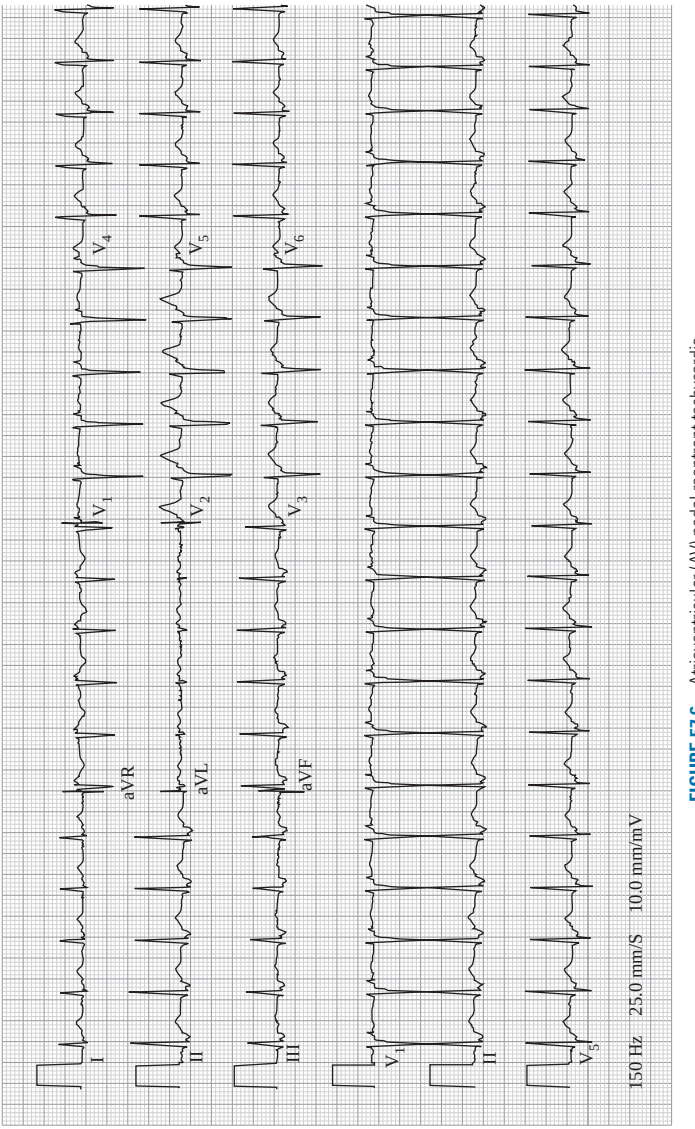

FIGURE 57.6 Atrioventricular (AV) nodal reentrant tachycardia.

- A regular, narrow QRS complex is present.
- A retrograde P wave is seen following the QRS complex in lead V_1 ("pseudo-R′").

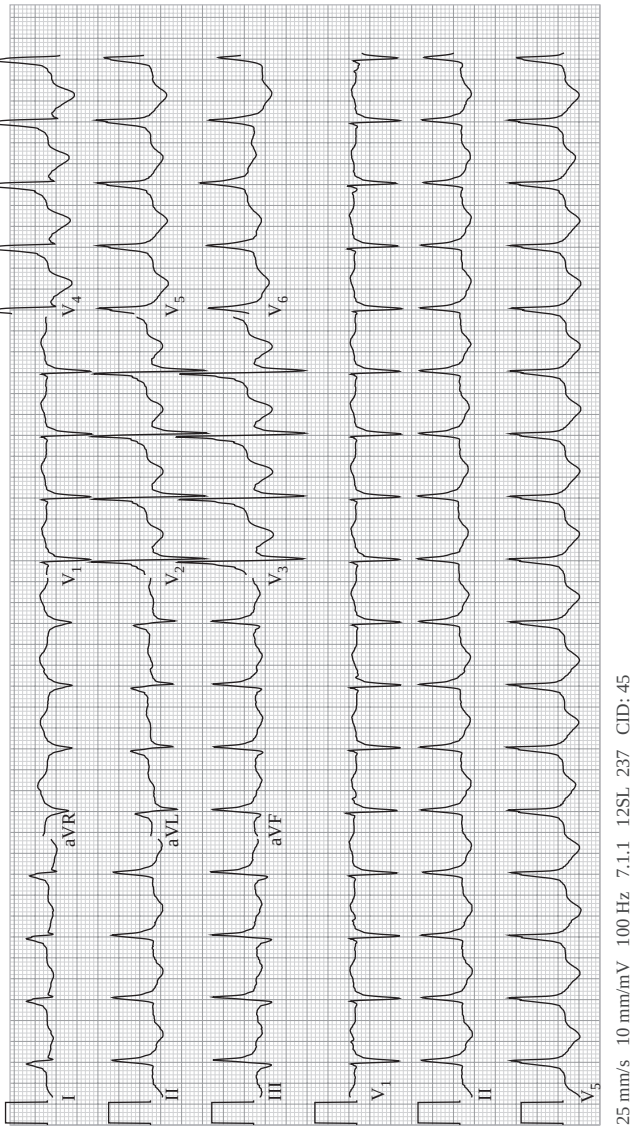

FIGURE 57.7 Ventricular tachycardia.

- A rapid, wide QRS complex is present. P waves are best seen in leads V_1 and II and are clearly dissociated from ventricular activity.

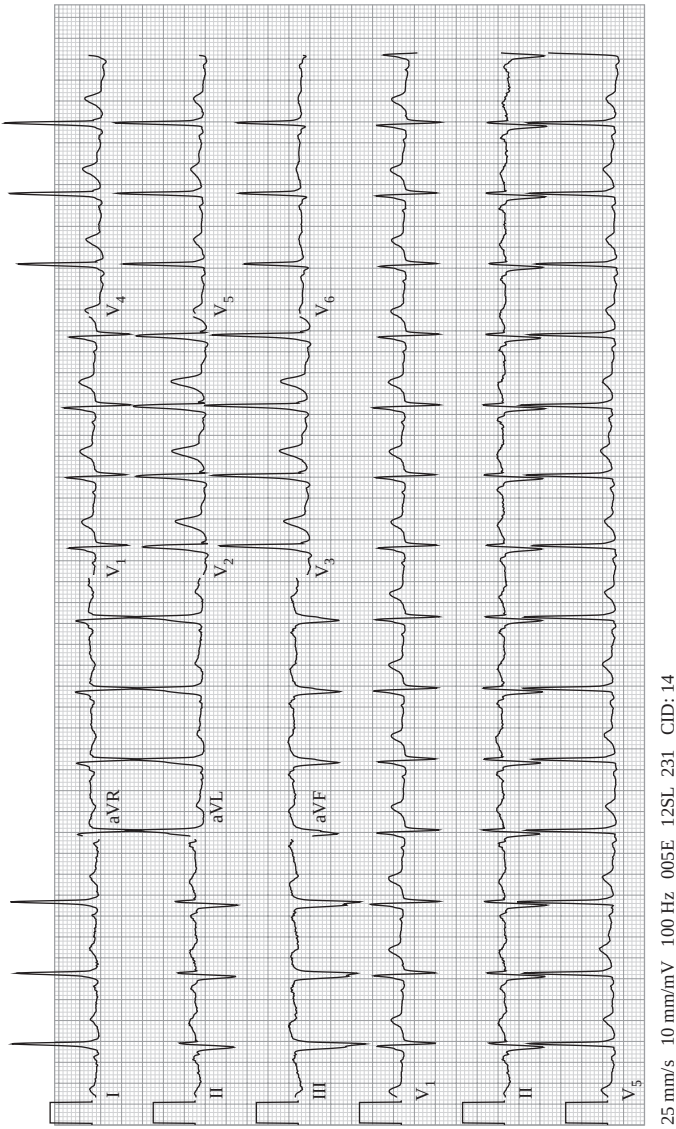

FIGURE 57.8 Wolff-Parkinson-White (WPW) pattern.

- Preexcitation of the ventricle causes a short PR interval and slurring of the initial portion of the QRS complex (delta wave).

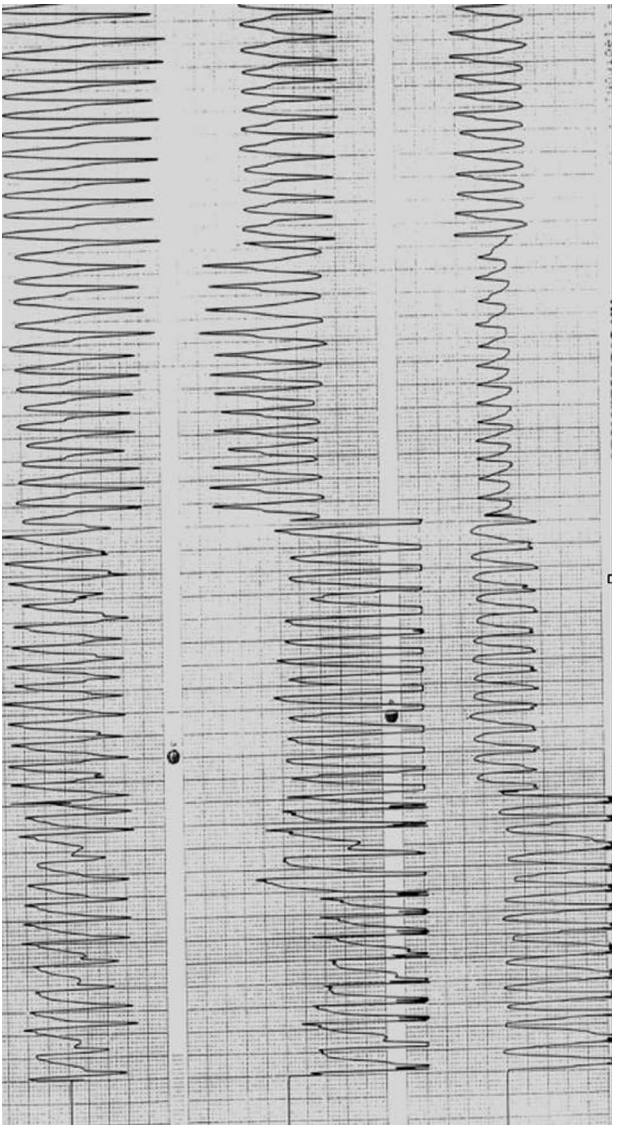

FIGURE 57.9 Atrial fibrillation with WPW.

- If atrial fibrillation develops, conduction to the ventricles can be very rapid. There is a varying degree of fusion between conduction through the AV node and conduction through the bypass tract, causing each beat to have a different morphology.

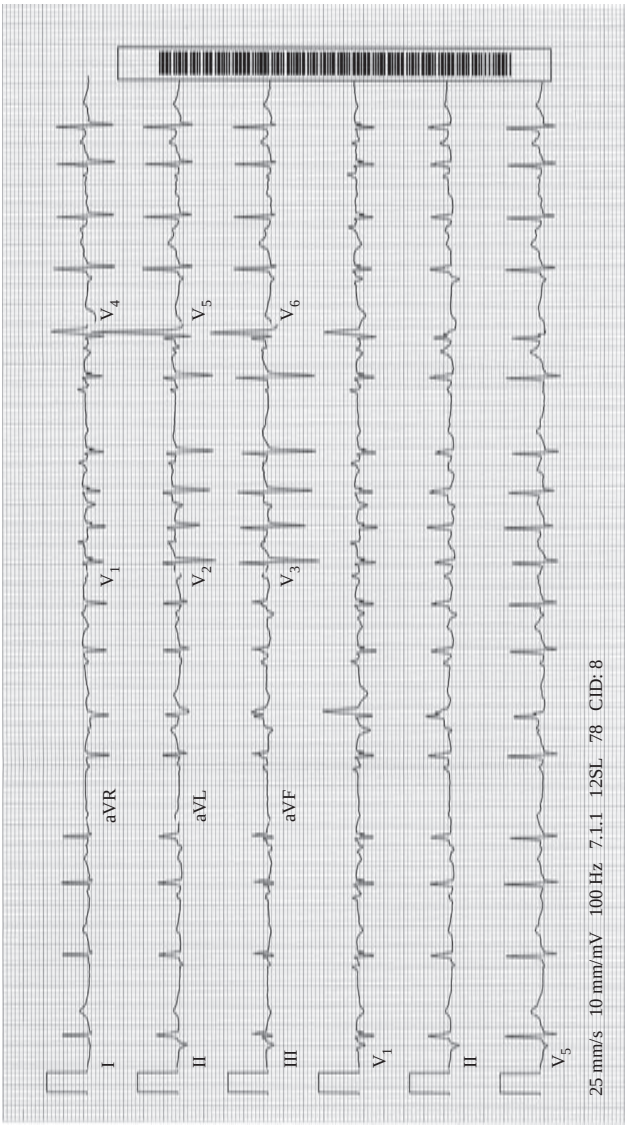

FIGURE 57.10 Multifocal atrial tachycardia.

- The atrial rate is rapid, and multiple P-wave morphologies are present.

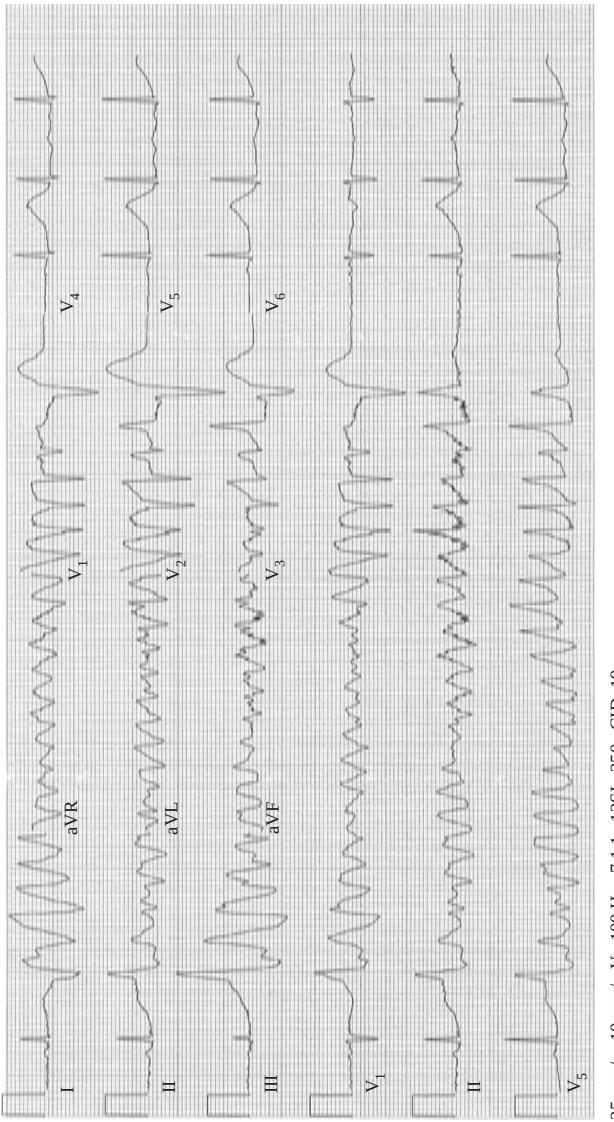

FIGURE 57.11 Torsades.

- A rapid ventricular rhythm with QRS complexes of varying axis ("twisting of the points") is present.

Conduction disease

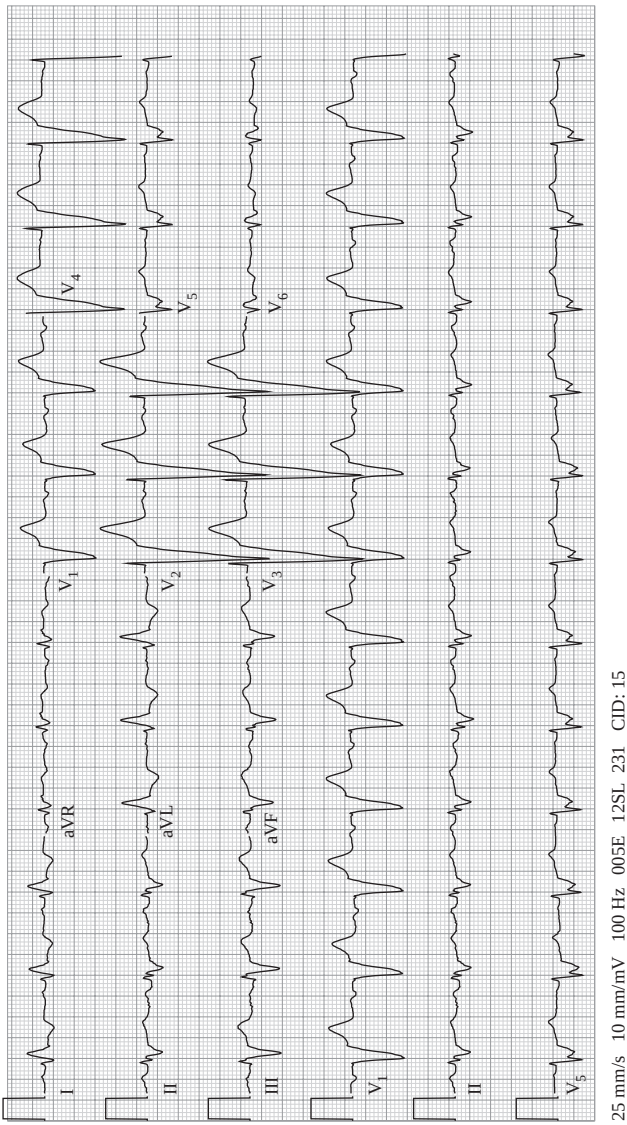

FIGURE 57.12 Left bundle branch block.

- The QRS duration is prolonged (> 120 ms).
- There is a broad R wave in leads I and V_6, representing delayed activation of the left ventricle.
- The right precordial leads have an rS complex.
- There are ST-segment changes in the direction opposite to the major QRS deflection.

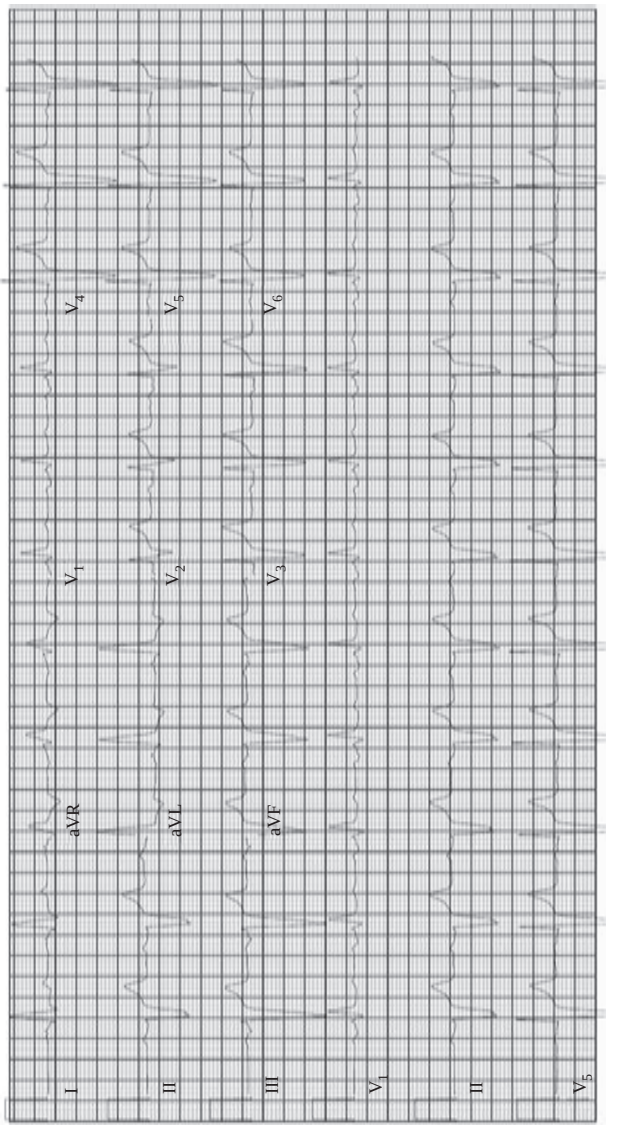

FIGURE 57.13 Right bundle branch block (RBBB) and left anterior fascicular block (LAFB).

- The QRS duration is prolonged beyond 120 ms.
- There is an rsR′ pattern in leads V_1 and V_2, representing delayed activation of the right ventricle.
- Leads I, V_5, and V_6 have a wide, slurred S wave.
- LAFB is indicated by the presence of left axis deviation without another cause (inferior infarction, LVH, chronic obstructive pulmonary disease, and ostium primum atrial septal defect) and the rS complex in inferior leads.

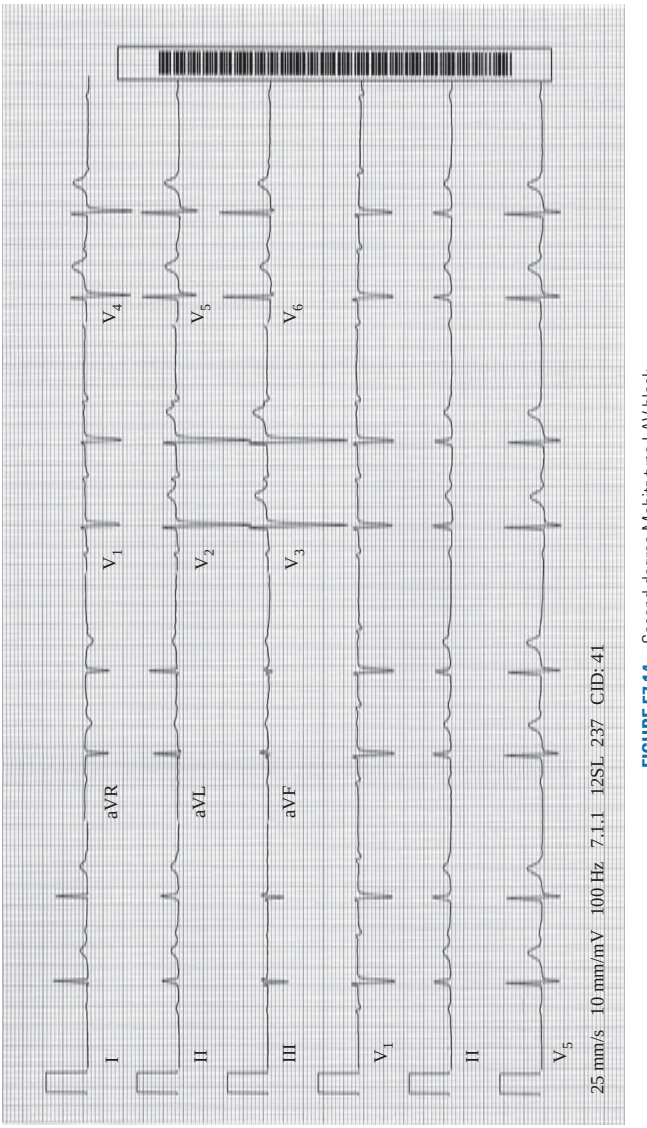

FIGURE 57.14 Second-degree Mobitz type I AV block.

- There is progressive prolongation of the PR interval until a P wave blocks.

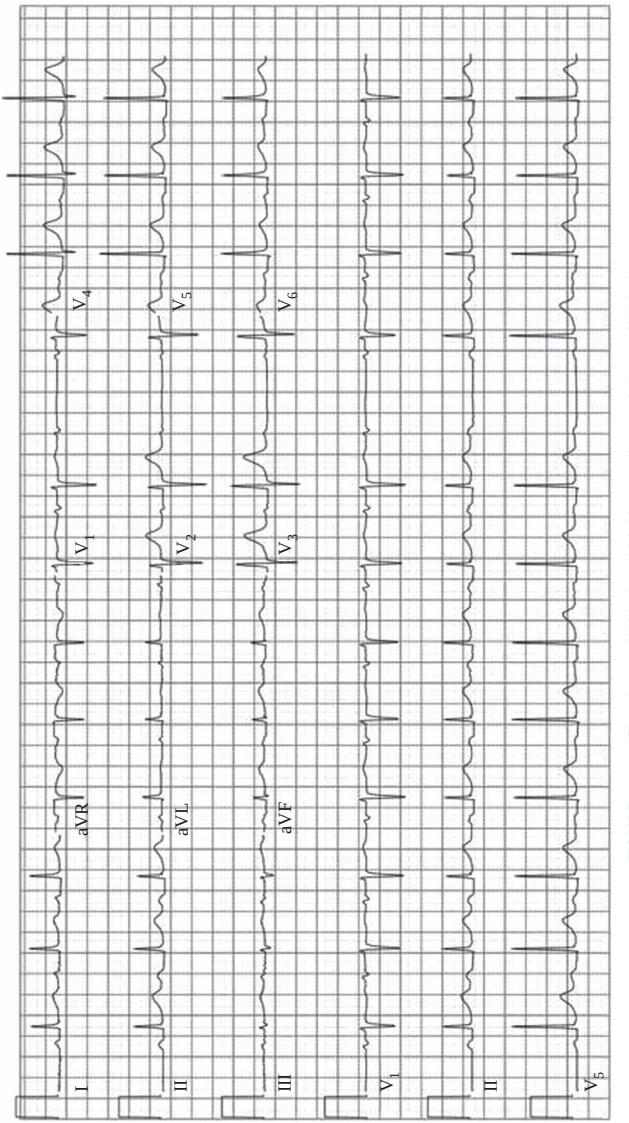

FIGURE 57.15 First-degree AV block and Mobitz type II second-degree AV block.

- The PR interval is more than 200 ms, indicating first-degree AV block.
- A P wave intermittently blocks. There is no lengthening of the PR interval prior to the dropped beat.

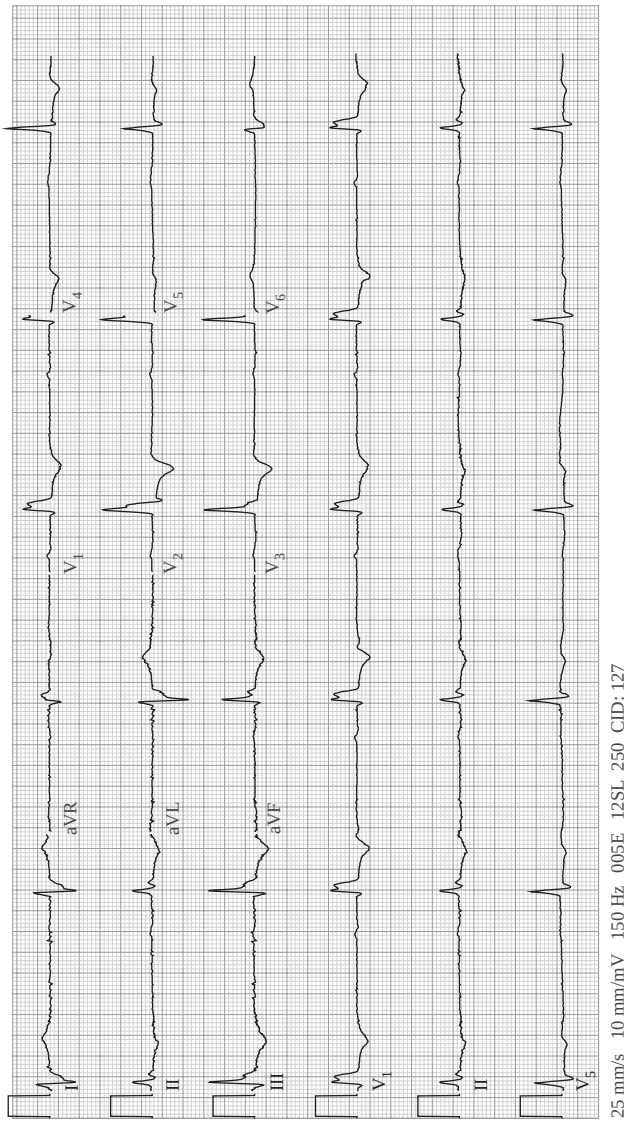

FIGURE 57.16 Complete heart block.

- P waves are not conducted to the ventricles, leading to atrial and ventricular rhythms that are independent of each other.
- The P-P and R-R intervals are constant, but the PR interval varies.

Metabolic disturbances

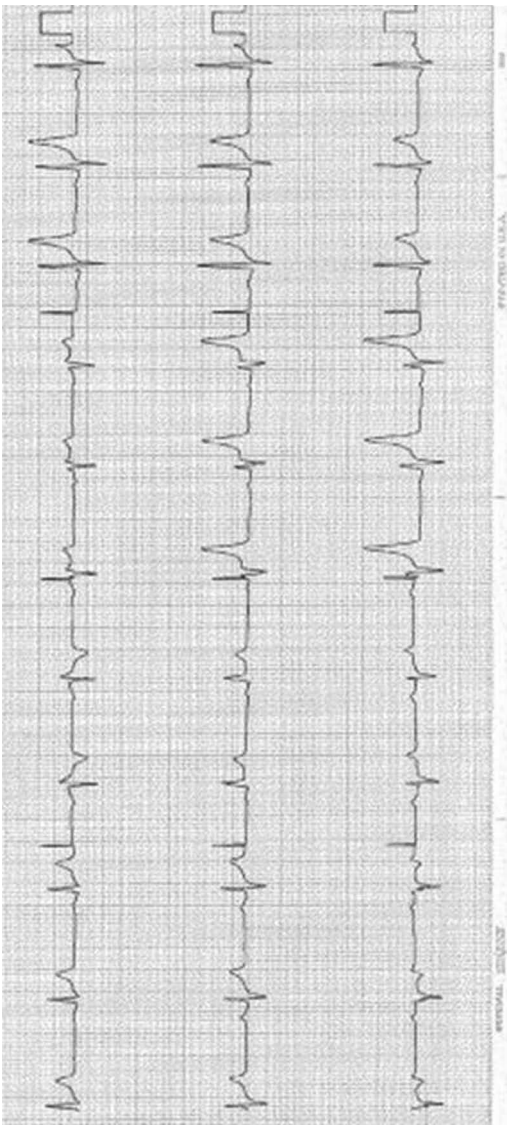

FIGURE 57.17 Hyperkalemia.

- Tall, peaked T waves are present.
- The QT interval is short.

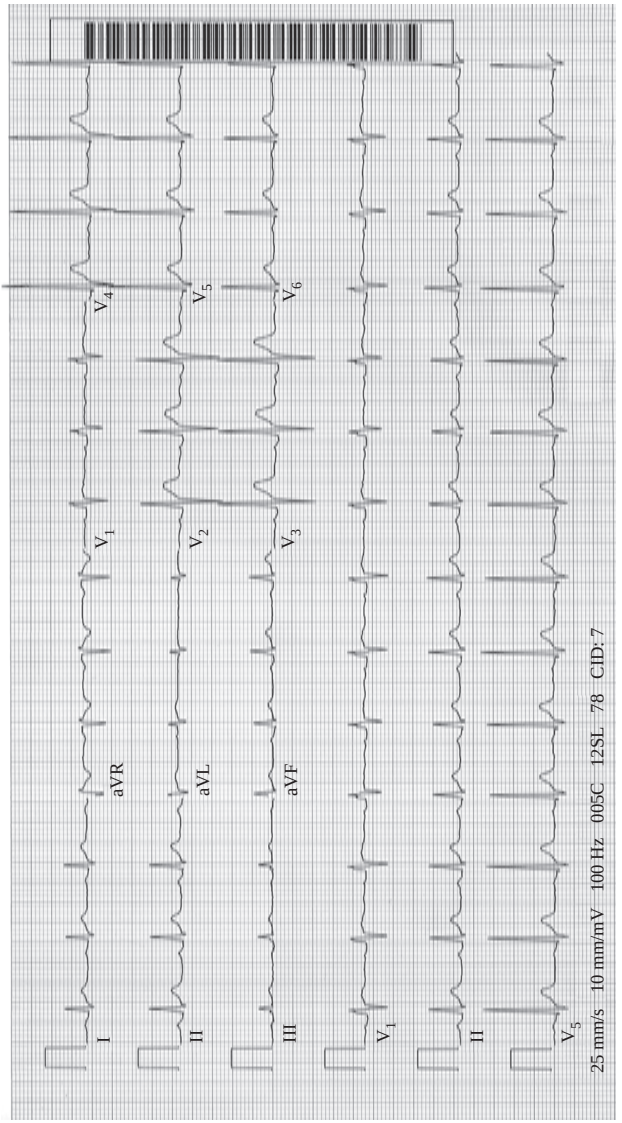

FIGURE 57.18 Hypercalcemia. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:552.

- The QT interval is short.

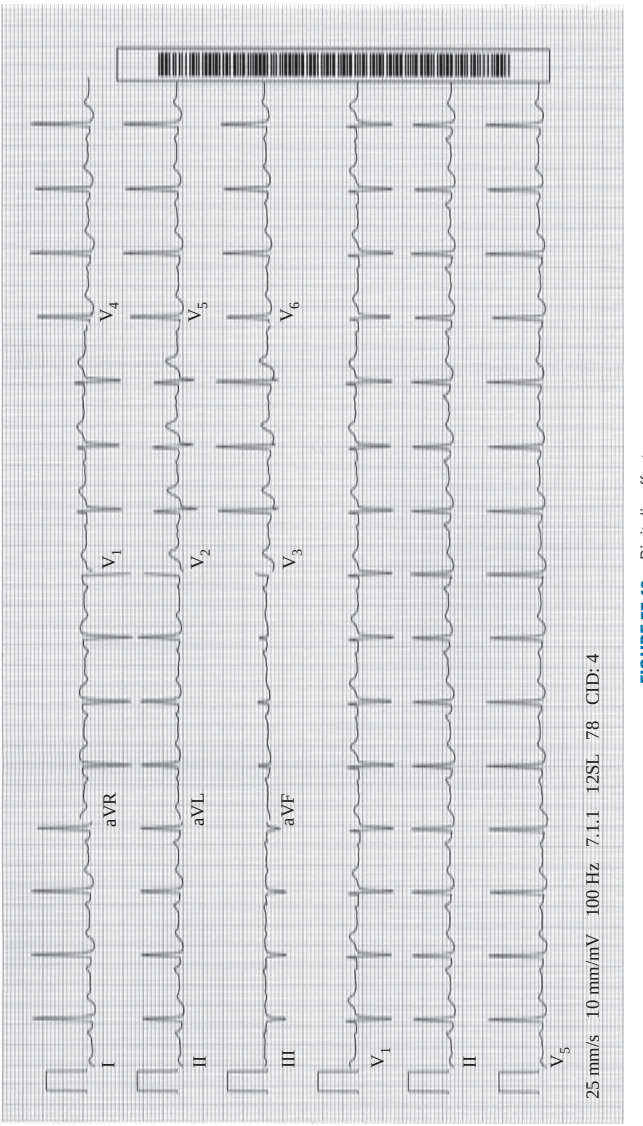

FIGURE 57.19 Digitalis effect.

- The ST segments sag downward and have upward concavity.
- The PR lengthens and the QT is short.

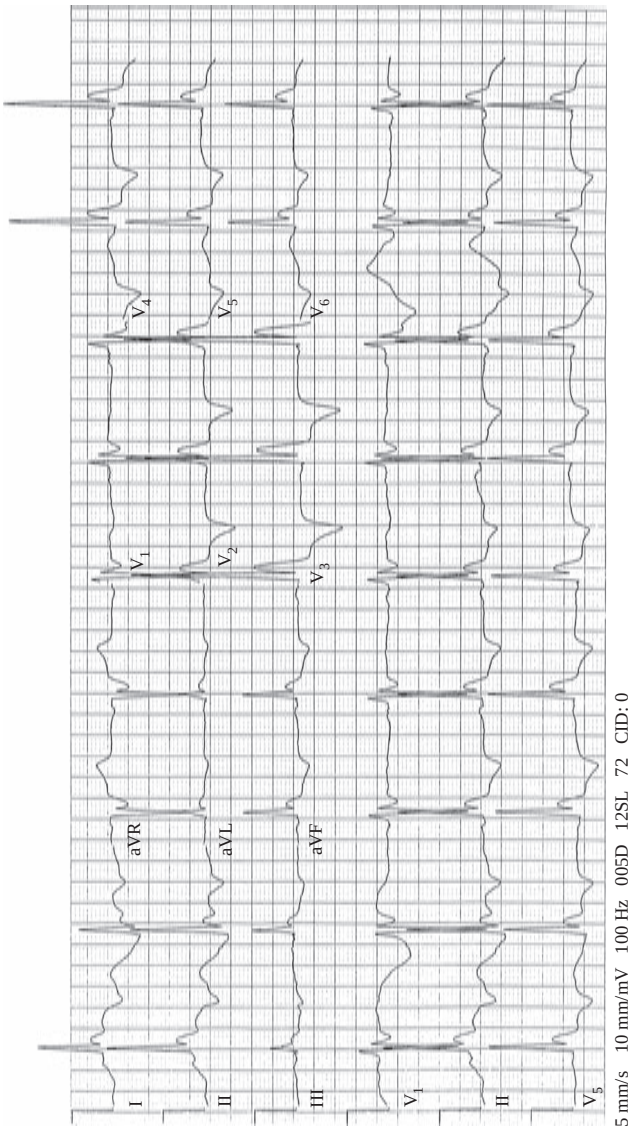

FIGURE 57.20 Hypothermia. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:588.

- An Osborn or J wave is present at the terminal portion of the QRS complex.
- The QRS interval is prolonged, and there is sinus bradycardia in this example. The PR and QT intervals may also be prolonged.

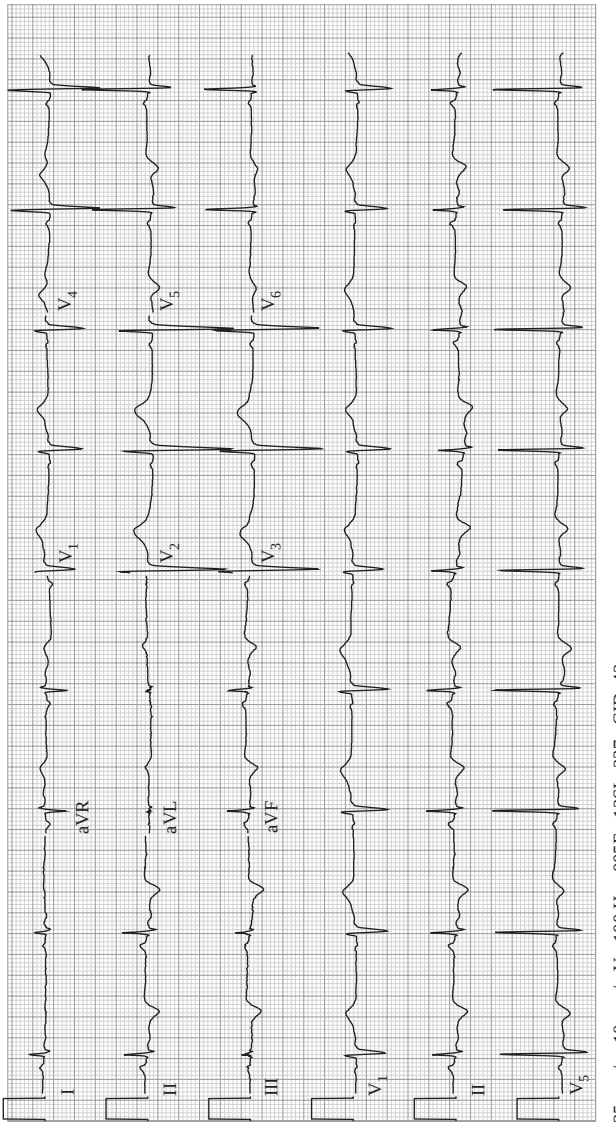

FIGURE 57.21 Long QT syndrome.

- The QTc interval is ≥ 440 ms.
- Congenital long QT type I was genetically confirmed in this patient.

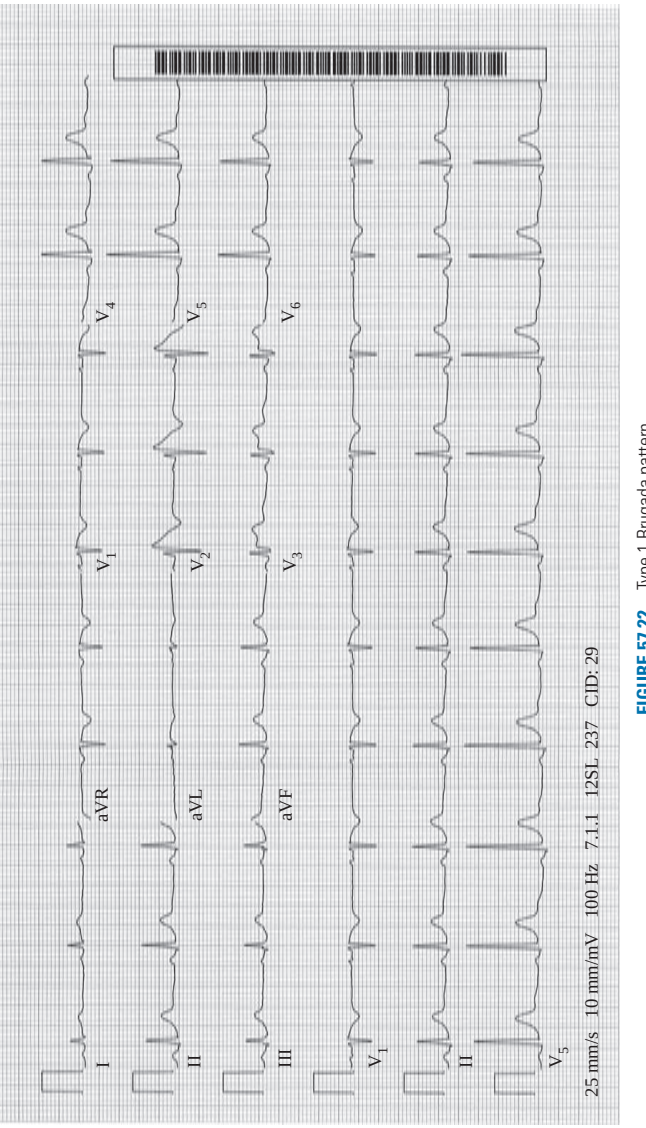

FIGURE 57.22 Type 1 Brugada pattern.

- There is an incomplete RBBB pattern with ST elevation in leads V_1 and V_2.

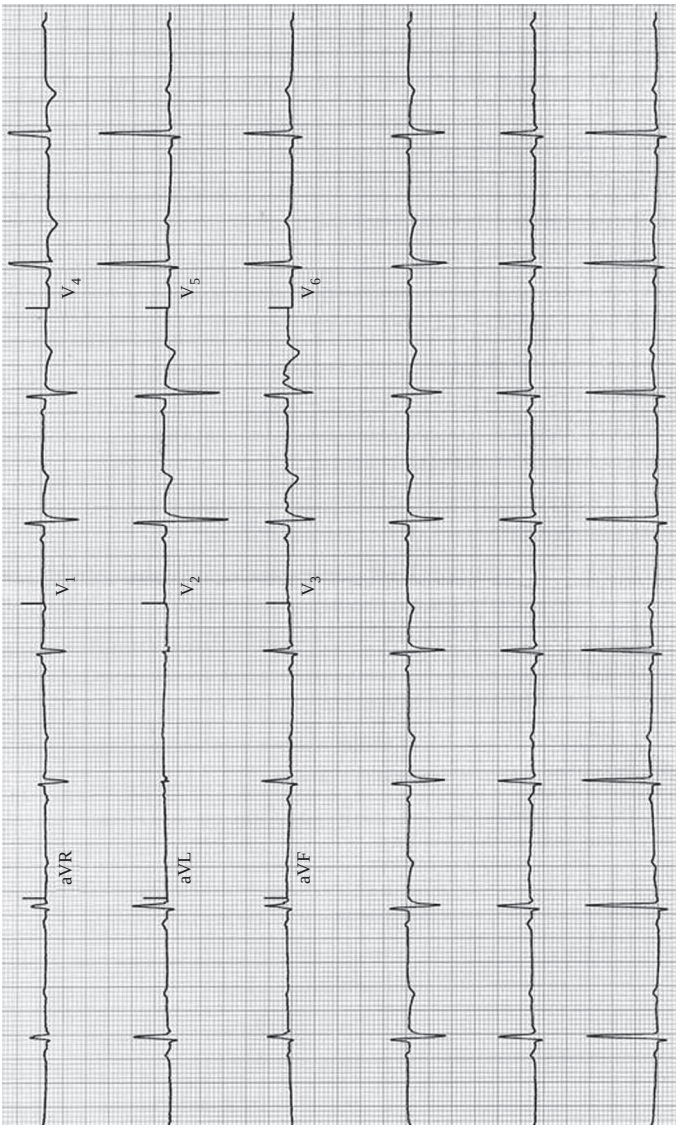

FIGURE 57.23 Arrhythmogenic right ventricular cardiomyopathy.

- An epsilon wave is present after the QRS complex in lead V_3. The epsilon wave may also be seen in leads V_2 and V_3.
- T-wave inversion in the anteroseptal leads is present.

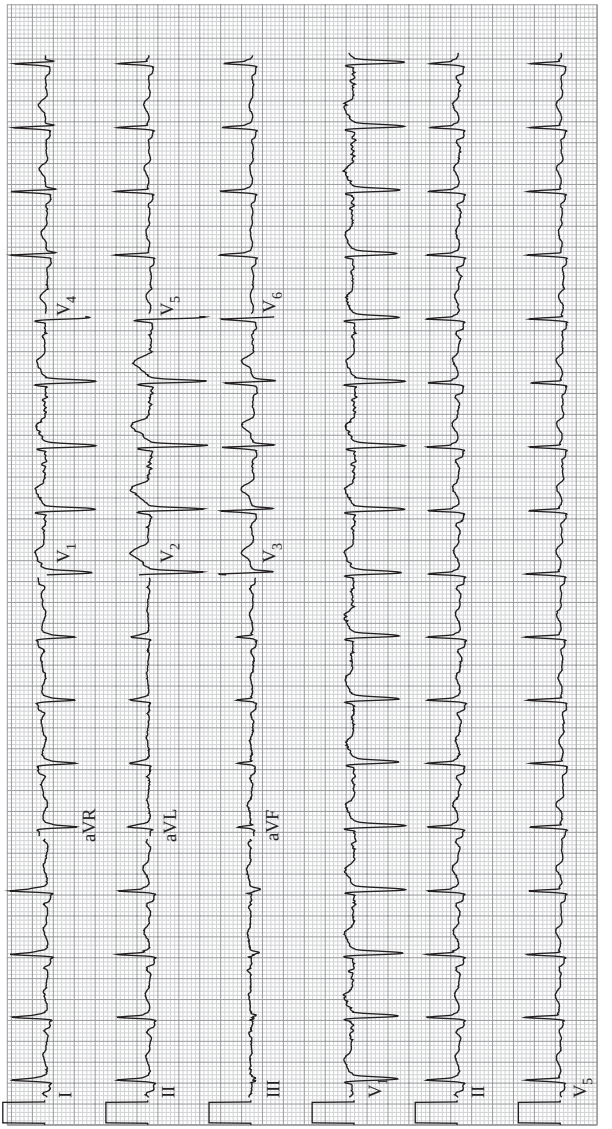

FIGURE 57.24 Pericarditis.

- There is diffuse, upwardly concave ST-segment elevation.
- The PR segment is depressed.

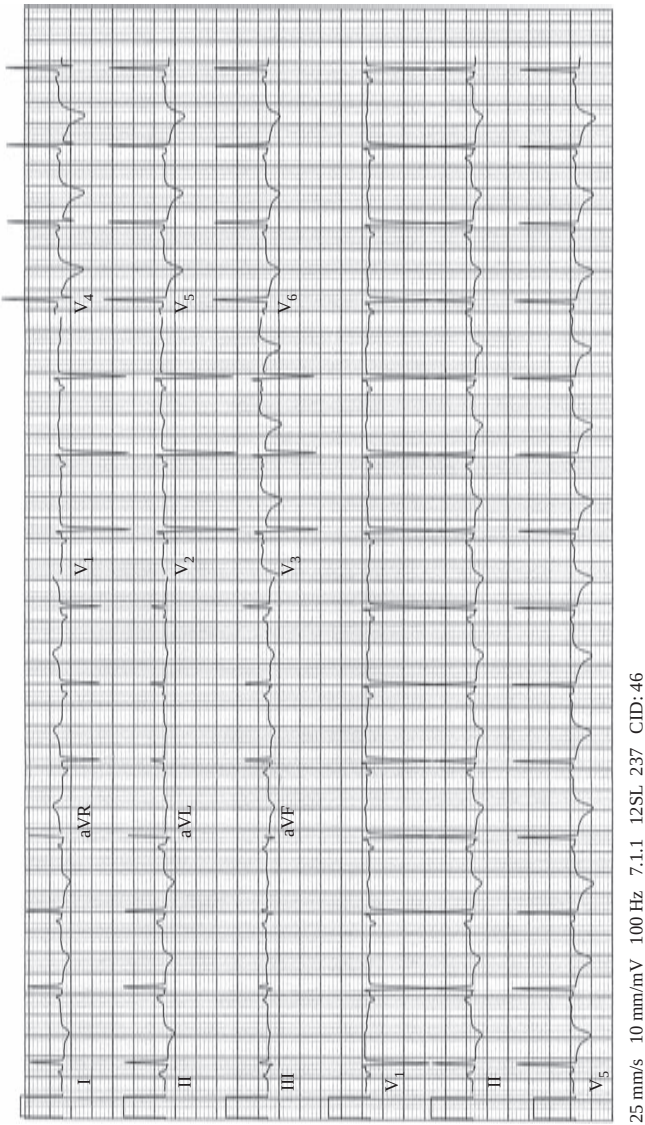

FIGURE 57.25 Takotsubo cardiomyopathy.

- Diffuse ST depression and T-wave inversion are present in this example. ST elevation may also be present.

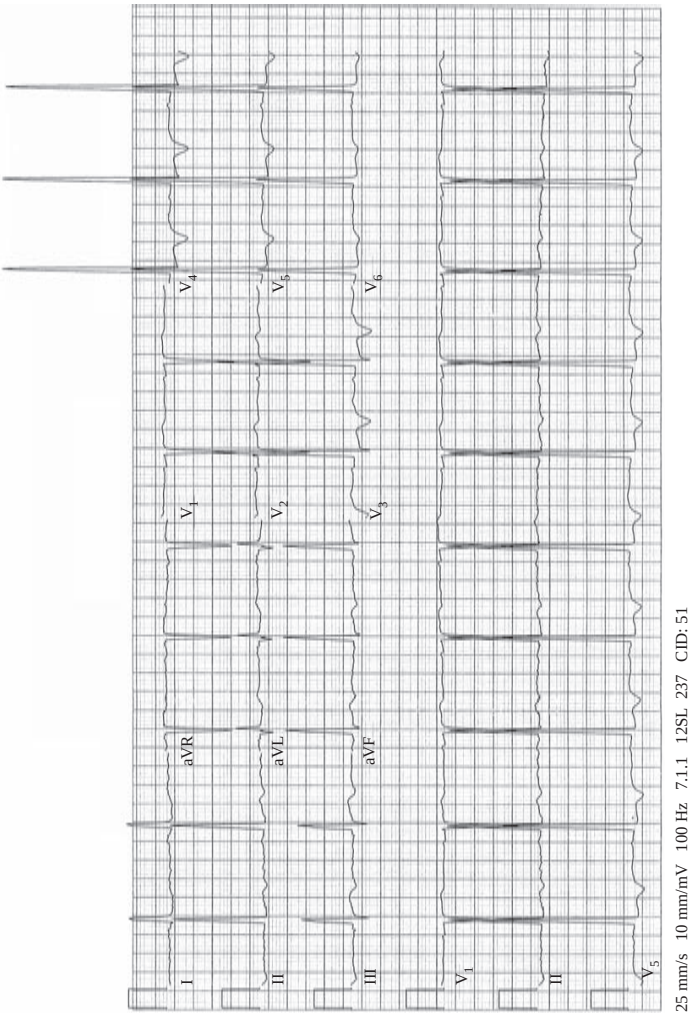

FIGURE 57.26 Apical variant of hypertrophic cardiomyopathy.

- Voltage in the precordial leads is increased and there is anterolateral T-wave inversion.

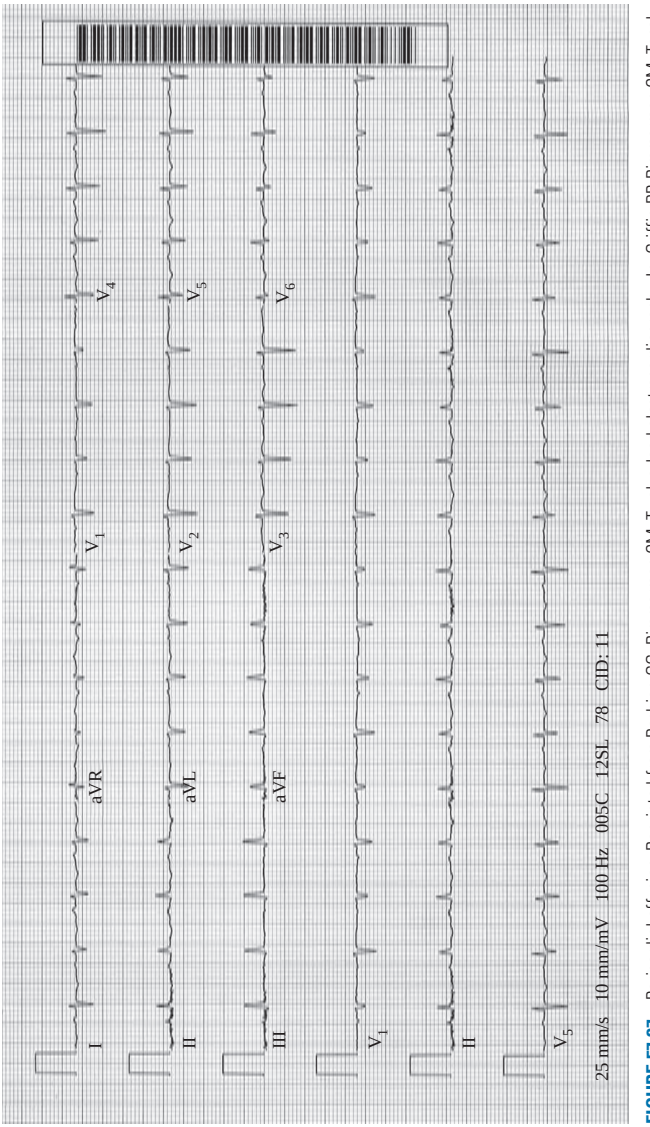

FIGURE 57.27 Pericardial effusion. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:573.

- Low voltage and electrical alternans are present. This is most apparent in lead V_1.

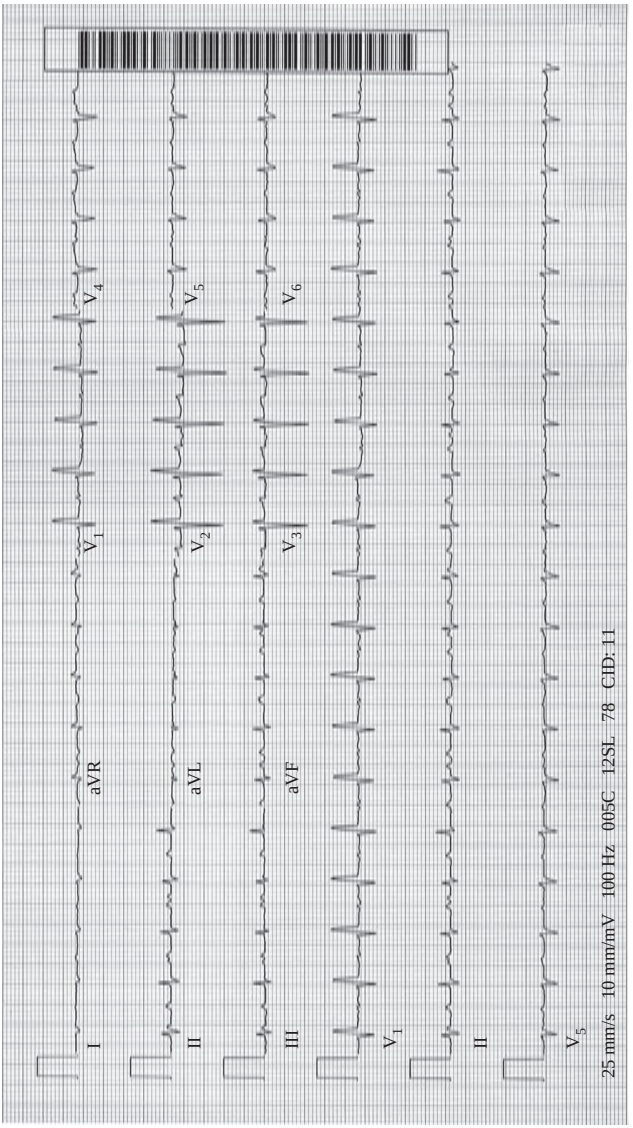

FIGURE 57.28 Cardiac transplant. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:541.

- Two sets of P waves, one from the native right atrium and one from the donor heart, are visible.
- Incomplete RBBB and first-degree AV block are also present.

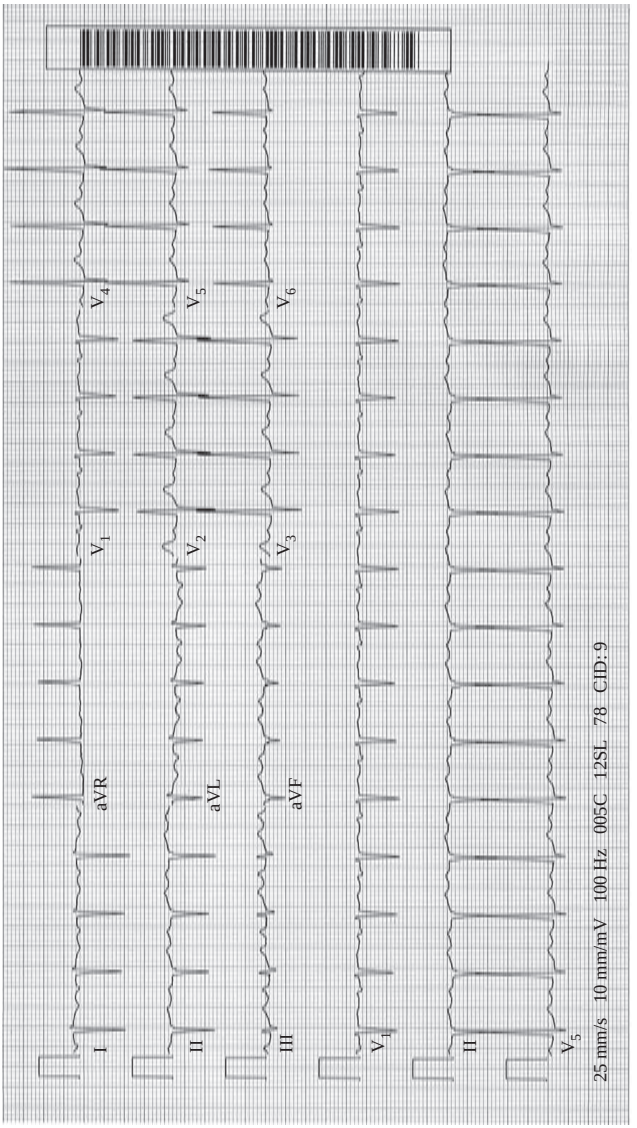

FIGURE 57.29 Limb lead reversal. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:555.

- The QRS complex is negative in lead I, with normal R-wave progression.
- The P wave is negative in leads I and aVL.

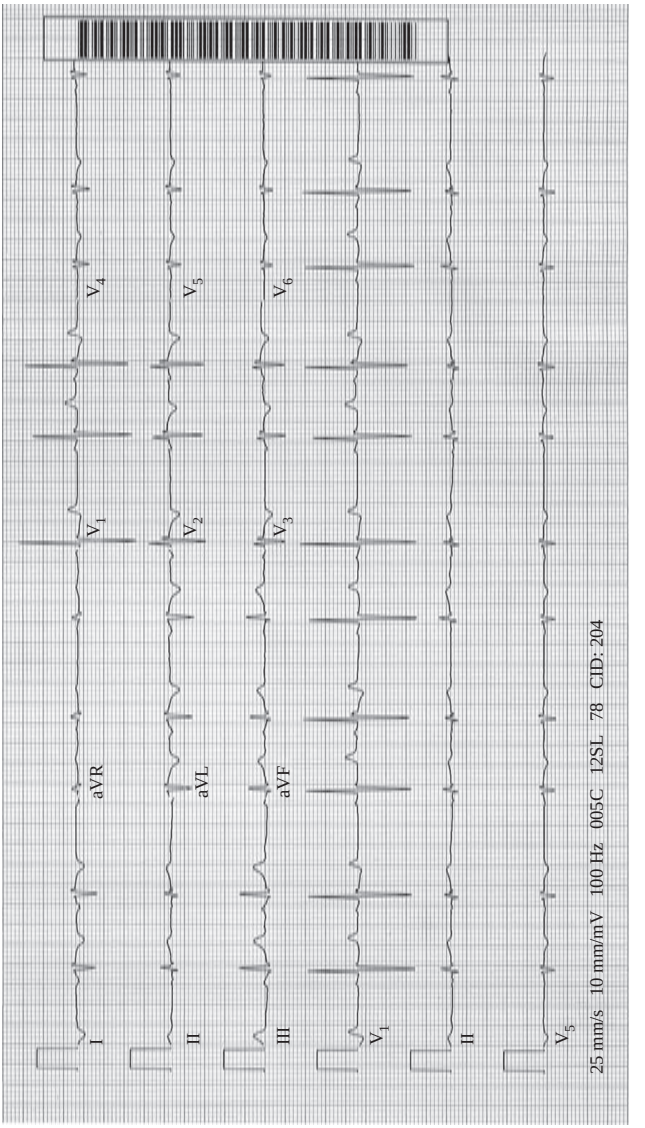

FIGURE 57.30 Dextrocardia. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:556.

- The QRS complex is negative in lead I, with R-wave regression across the precordium.
- The P wave is negative in leads I and aVL.
- A premature atrial complex is also present.

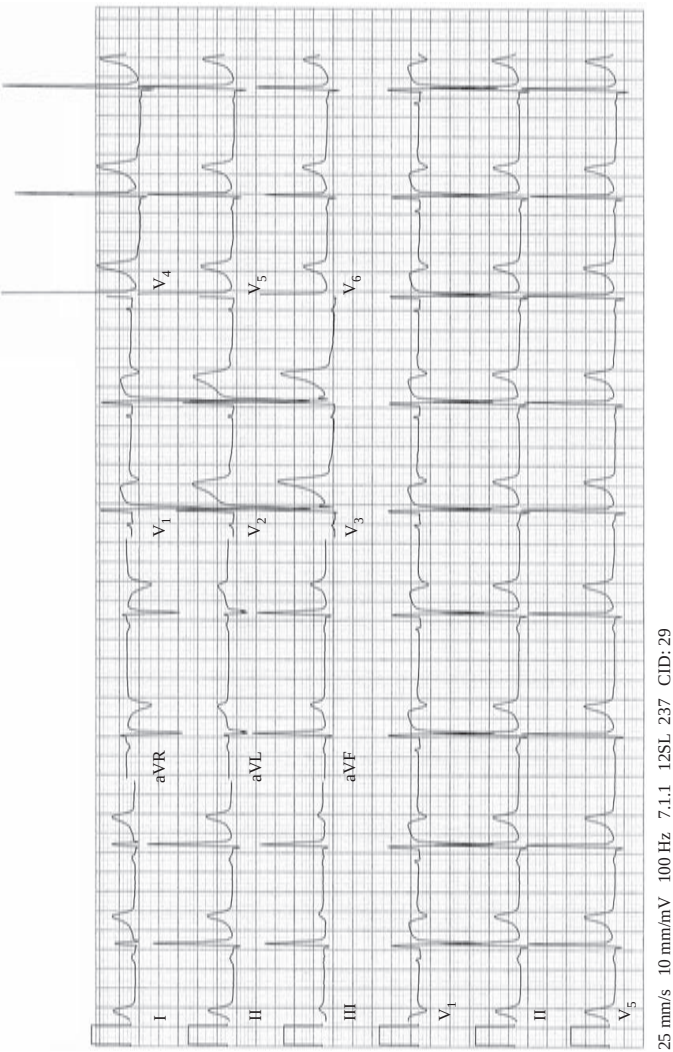

FIGURE 57.31 Early repolarization.

- This electrocardiogram from a young, well-trained athlete shows J-point elevation, concave ST-segment elevation, and large symmetrical upright T waves.
- There is a notch in the downstroke of the R wave.

CHAPTER 58

JoEllyn M. Abraham
Bryan J. Baranowski

Temporary Cardiac Pacing

I. INDICATIONS

A. Acute hemodynamically significant bradycardia or asystole. Temporary pacing is indicated in patients with acute hemodynamically significant bradycardia or asystole. Reversible causes such as digitalis toxicity, antiarrhythmic agents, and electrolyte disturbances such as hyperkalemia should be determined and reversed.

B. Termination of tachycardias (overdrive pacing). Temporary pacing is indicated for overdrive pacing and termination of atrial flutter (type I with long excitable gap) or supraventricular tachycardia due to a reentrant mechanism.

C. Bridge to permanent pacing. Temporary pacing may be used as a bridge to permanent pacing in patients with complete heart block, high-grade second-degree block, severe sinus node dysfunction, and asystole. Generally, temporary pacing in this setting is for patients with an acute illness (endocarditis and systemic infection elsewhere) that delays permanent pacemaker placement.

D. Ventricular tachycardia. Temporary pacing is indicated in patients with bradycardia-dependent ventricular tachycardia and recurrent tachyarrhythmias secondary to long QT syndrome or pause-dependent ventricular tachycardia. Monomorphic ventricular tachycardia can be terminated with antitachycardia pacing through a ventricular temporary wire by pacing at a rate faster than the tachycardia. This involves pacing the chamber in which the reentrant circuit exists. Overdrive pacing is initiated at 10 to 15 beats per minute (bpm) faster than the tachycardia. Pacing is done for several captured beats (up to 10 to 15 seconds) and then abruptly stopped. If tachycardia persists, the pacing rate is sequentially increased by 10 bpm and pacing repeated. The major potential complication of this technique is conversion to a faster or unstable rhythm. The advantage is that post-tachycardia pauses can be managed with pacing if necessary, and direct current cardioversion may be avoided.

E. Acute myocardial infarction. Indications for temporary pacing in this setting include development of a new bifascicular block (right bundle branch block [RBBB] with either left-axis [left anterior hemiblock] or right-axis deviation [left posterior hemiblock]), new left bundle branch block (LBBB) with first-degree atrioventricular (AV) block, alternating LBBB and RBBB, Mobitz type II block, and complete heart block. Patients with right ventricular infarction and loss of AV synchrony may benefit from AV sequential pacing.

F. Condition where there is a chance of recovery. In certain forms of myocarditis with heart block, such as Lyme disease, or post cardiac surgery, temporary pacing can be used because there is a significant chance of recovery of conduction.

G. Acute aortic regurgitation. Pacing to increase heart rate in patients with acute aortic regurgitation who have bradycardia and elevated left ventricular end-diastolic pressure can reduce diastolic filling time and improve hemodynamics.

H. Prophylactic. Prophylactic temporary pacing is considered in the following settings: (a) in patients undergoing right heart catheterization and/or myocardial biopsy in the

setting of an LBBB, (b) with complex intervention to the right coronary artery as this supplies the AV node in 90% of individuals, (c) cardioversion in patients with the sick sinus syndrome, although generally the use of transcutaneous pacing back up is used instead, (d) or new 1st degree AV block with acute endocarditis (especially of the aortic valve). Patients who are undergoing alcohol septal ablation for hypertrophic cardiomyopathy receive prophylactic transvenous pacers, given the significant risk of complete heart block during the procedure. Patients who are undergoing balloon aortic valvuloplasty and percutaneous aortic valve replacement have a temporary pacemaker placed for overdrive pacing during balloon inflation and valve implantation.

I. Electrophysiologic studies. Temporary atrial, coronary sinus, and ventricular pacemakers are frequently used for electrophysiologic studies.

J. Ischemic evaluation. Ischemic evaluation is occasionally performed via rapid atrial pacing.

II. PACING MODES

A. Transcutaneous pacing. Transcutaneous ventricular pacing involves placement of large-surface-area, high-impedance electrodes (Zoll pads) on the anterior (over lead V_3 or the palpable cardiac apex) and posterior chest walls (inferior aspect of the scapula, to the left or right of the spine). It usually requires long pulse widths (20 to 40 milliseconds) and high outputs of up to 100 to 200 mA. Transcutaneous pacing may be useful when transvenous pacing is contraindicated and in code situations. It avoids the complications associated with transvenous pacers such as pneumothorax, right ventricular perforation, infection, bleeding, and venous thrombosis. Failure to capture and severe patient discomfort are common.

B. Transesophageal or transgastric pacing. This technique uses a flexible electrode on the tip of a catheter that is advanced down the esophagus to a position just behind the left atrium and is usually successful in achieving atrial pacing. The electrode can also be advanced to the fundus of the stomach to pace the ventricle through the diaphragm. However, ventricular pacing is difficult to achieve consistently and without intolerable pain to the patient.

C. Epicardial pacing. Temporary epicardial pacing wires are typically placed at the time of valve surgery, given that there is a 6% rate of need for pacemaker prior to discharge in this population, as compared to 0.8% in the setting of coronary artery bypass grafting. Longer cross-clamp time, multiple valve surgical procedure, absence of preoperative sinus rhythm, and reoperation are all predictors of the need for pacemaker implantation in the valvular surgery population. The electrodes are typically removed with gentle traction when they are no longer needed or no longer functional.

D. Transvenous pacing

1. Relative contraindications
   - **a.** Poor vascular access
   - **b.** Bleeding disorders or anticoagulant therapy. If the international normalized ratio is >1.8 and platelets are < 50,000, then these conditions should be corrected prior to placement of a transvenous pacer if possible.
2. Patient preparation
   - **a.** Informed consent should be obtained for the procedure. However, if the patient is hemodynamically unstable because of a cardiac arrhythmia that could be improved with a pacemaker, this procedure is indicated emergently.
   - **b.** If the procedure is elective, peripheral intravenous access should be obtained before the start of the procedure.
   - **c.** The procedure should be performed in a monitored setting that is equipped for cardiopulmonary resuscitation and with fluoroscopy being available.
3. **Technique**
   - **a. Lead choice.** There is some evidence that active fixation leads allow for greater pacemaker stability and fewer complications than passive fixation

leads. However, active fixation leads can be technically more challenging to place.

b. Sites. The preferred site for pacemaker insertion is the right internal jugular vein. The subclavian vein, femoral vein, and external jugular vein can also be used. However, if a permanent pacemaker will eventually be inserted, the subclavian vein site ipsilateral to the planned permanent pacemaker site should be avoided, if possible. The easiest access in the catheterization laboratory is usually the femoral vein.

c. Position. The patient should be placed supine in bed. The patient may be placed in the Trendelenburg position for internal jugular and subclavian vein cannulation.

d. Placement

(1) Ventricular pacing. A venous sheath is inserted into one of the central veins, and pacing catheters are used. When using passive fixation leads, the pacing catheter is advanced through the venous sheath under fluoroscopic guidance (usually 20° to 30° left anterior oblique projection). The catheter is advanced to the tricuspid valve and turned either clockwise or counterclockwise to direct the tip anteriorly. An attempt is made to cross the valve directly. If unsuccessful, gentle pressure is applied and the catheter is torqued, allowing the middle portion to prolapse across the valve into the right ventricle. If the tricuspid valve is difficult to traverse, it may be possible to enter the right ventricle by looping the tip of the catheter against the lateral atrial wall and then rotating the loop medially (counterclockwise) toward the septum. Another option is to reshape the catheter manually, increasing the tip bend before attempting to traverse the tricuspid valve. Once the catheter has entered the right ventricle, it is rotated so that the tip points inferiorly to the apex with minimal movement in systole. The lead can also be advanced into the right ventricular outflow tract, then slowly pulled back until it drops, and then advanced into the apex as it drops. Some degree of buckling is acceptable; however, excessive buckling increases the risk of perforation. Ideally, the pacemaker tip should be near the apex of the right ventricle. The ideal catheter placement site is on the diaphragmatic surface or "floor" of the right ventricle anywhere between its midpoint and its apex. The floor of the more proximal ventricle is a second choice; the true apex is not a good choice for placement of the catheter tip. The paced electrocardiogram from this location usually shows an LBBB pattern with left-axis deviation. Ventricular pacing can also be done with the tip in the right ventricular outflow tract if the catheter cannot be placed on the floor of the right ventricle in a stable position. The pacer tip is considerably less stable at this site compared with the right ventricle floor and is more likely to be displaced; however, this is a very good position for a screw-in temporary pacing wire. Pacing from this location will show an LBBB pattern with an inferior axis. Use of a balloon-tipped temporary pacing electrode can aid in the advancement of the electrode into the proper position. In addition, echocardiographic guidance can be used to help guide lead placement in situations where fluoroscopy is not available or advisable (e.g., pregnant women).

(2) Atrial pacing. The right atrium is the easiest chamber to reach and pace, but the most stable position is usually found in the right atrial appendage. For atrial pacing, a J-tipped atrial pacing catheter is used. Alternatively, a temporary screw-in lead can be placed in a stable position with good pacing and sensing thresholds. The atrial appendage is directed anteriorly above the tricuspid annulus, and multiple planes are

frequently helpful in verifying the location. (The catheter appears as a "J" in the left anterior oblique projection or as an "L" in the right anterior oblique projection.)

(3) Both atrial and ventricular pacing may be performed by placing the catheter in the coronary sinus. The coronary sinus in its proximal portion courses along the left atrium. Ventricular pacing may be achieved by positioning the catheter in a cardiac vein off the coronary sinus. The threshold in the coronary sinus is frequently high, but sometimes it may be a more stable location for atrial pacing than the atrial appendage. Steerable electrophysiologic pacing catheters may be useful in such patients.

(4) For patients who need extended temporary pacing (those with pacemaker infections or Lyme disease), a permanent pacing wire can be placed in the appropriate chamber percutaneously and sutured to the skin. This can be connected to a temporary pulse generator. In addition, it can be attached to a resterilized permanent device that can be secured to the skin as well. This leads to a very stable intermediate-term pacing system.

4. **Testing.** Once a catheter is in a stable position, threshold testing should be performed. The distal electrode on the pacing catheter is used as the cathode and connects with the negative terminal, and the ring is used as the anode and connects with the positive terminal of the generator. The pacing catheter is attached via a cable to the pacemaker generator.
   a. **Pacing capture threshold.** Pacing is started at a rate 10 to 20 beats faster than the intrinsic rate with 5 mA output. If capture is not seen at this point, the catheter needs to be repositioned. Once capture is seen, the output is slowly decreased until loss of capture is seen. The lowest capturing current is the pacing *stimulation threshold*. If the catheter is in good position, the threshold should be < 1 mA. Pacing output should be three times the threshold, but pacing is usually performed at a minimum of 5 mA (even if three times the threshold is < 5 mA). This is because minor dislodgment can cause major changes in threshold and adds a safety margin.
   b. **Sensing threshold.** This is the degree to which the pacemaker sees native cardiac signals (in millivolts). Set the pacing rate to at least 10 bpm below the patient's intrinsic rate. The sensing setting is then gradually decreased until asynchronous pacing is seen. The pacer is set at one-half the sensing threshold.
   c. **AV interval.** For dual-chamber pacing, the AV interval will need to be programmed. A default of 150 milliseconds is frequently used, but the optimal AV delay may be different in individual patients. Patients with diastolic ventricular dysfunction may need longer AV delay for ventricular filling. In patients with marginal cardiac reserve, obtaining cardiac output measurements at various AV intervals and heart rates may help determine the optimal AV interval and heart rate.
5. **Post-placement chest radiography.** A postprocedure chest radiograph must be evaluated for pneumothorax. For right ventricular apex pacing, in the posteroanterior view, the electrode tip should be located to the left of the spine. In the lateral view, the electrode tip should be directed inferiorly and anteriorly. For pacing through the coronary sinus, the tip is to the left of the spine, directed posteriorly and superiorly.
6. **Pacer care**
   a. Check the catheter insertion site daily for signs of infection and apply a new sterile dressing at regular intervals.
   b. Obtain a daily 12-lead surface electrocardiogram, ideally with and without pacing, to assess changes in native conduction and appropriate pacemaker sensing and capture.

c. Check pacemaker function daily by determining the sensing and pacing threshold, and check the underlying rhythm daily by decreasing the pacing rate gradually to "off." Abrupt termination in pacing may increase the risk of long pauses.

7. Complications

a. Related to central venous access such as hematoma at the puncture site, pneumothorax, hemothorax, air embolism, thrombosis, inadvertent arterial puncture, arteriovenous fistula, thoracic duct injury, subcutaneous emphysema, brachial plexus injury, venous thrombosis, and infection.

b. Lead dislodgment, particularly with passive fixation leads.

c. Cardiac arrhythmias such as premature ventricular contractions, premature atrial contractions, ventricular tachycardia, and RBBB. These are usually of no consequence (although the latter can result in complete heart block in the setting of a preexisting LBBB).

d. Myocardial perforation with cardiac tamponade. The unipolar recording from the tip normally shows pronounced ST elevation in comparison with the proximal electrode. ST depression from the tip is associated with perforation. If perforation is suspected, an echocardiogram should be obtained immediately to assess for pericardial effusion. Even a very small pericardial effusion can cause hemodynamic collapse. If pre/tamponade is suspected, emergency pericardiocentesis should be performed. If perforation is suspected and the patient is hemodynamically stable, the temporary pacemaker should be withdrawn only when the physician has all equipment available and is prepared to perform an emergency pericardiocentesis.

e. Pacemaker dysfunction with generator failure, oversensing or undersensing, and electrode displacement with failure to capture.

f. Complete heart block in patients with preexisting LBBB caused by catheter irritation of the right bundle.

SUGGESTED READING

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CHAPTER 59

Sandeep Duggal

Electrical Cardioversion

I. INTRODUCTION. Delivery of electrical countershock to terminate cardiac arrhythmias is a safe and effective technique that is routinely performed in most hospitals. *Cardioversion* is defined by delivery of energy synchronized to the QRS complex, whereas random delivery of shock during the cardiac cycle (usually done for terminating ventricular fibrillation) is termed *defibrillation*.

II. MECHANISM. Although it has long been recognized that application of an electrical shock to the myocardium can restore a normal rhythm, knowledge of the fundamental mechanism underlying defibrillation remains incomplete. A rapidly delivered electric shock depolarizes the myocardial cells and creates a zone of myocardium with an extended refractory period. Activation fronts encountering tissue with a prolonged refractory period will not be able to propagate, thus terminating both macro- and micro-reentrant circuits. Atrial fibrillation and ventricular fibrillation are generally agreed to be more electrically stable rhythms and thus require higher current delivery for termination. This is likely because only regional depolarization in the path of an advancing wave front is required. The most common waveform shapes used in external defibrillation are the monophasic and biphasic waveforms. In biphasic waveforms, the polarity at each electrode reverses partway through the defibrillation waveform. The use of a biphasic waveform in cardioversion and defibrillation has been shown to be associated with an increased efficacy and may reduce the development of postshock arrhythmias.

III. INDICATIONS AND CONTRAINDICATIONS. The indications and contraindications of cardioversion are listed in Tables 59.1 and 59.2. **Cardioversion should not be performed in patients in whom the rhythm is sinus or the abnormal rhythm is secondary to increased automaticity (e.g., multifocal atrial tachycardia and junctional tachycardia). If the presenting rhythm is ventricular fibrillation or ventricular tachycardia with hemodynamic compromise, the only clear contraindication to defibrillation is clear expression of the patient's (or patient's surrogate's) informed wish not to be resuscitated.**

IV. PROCEDURE

A. Patient preparation

1. **Informed consent** should be obtained from the patient or surrogate (if the patient is unable to comprehend and give meaningful informed consent).
2. In elective cases, patient should **fast for a minimum of 6 to 8 hours**.
3. A review of the patient's medical **history and a focused physical examination** should be performed. **Special attention should be paid to the airway**. Inability to visualize the uvula, inability to open the mouth with at least 2 cm between the teeth, or difficulty in extending the neck are factors that may make potential

TABLE 59.1 Indications and Contraindications of Cardioversion

INDICATIONS

Cardioversion

1. Atrial fibrillation/atrial flutter
   - **a.** Patient with atrial fibrillation/atrial flutter > 48 h (or unknown) duration and anticoagulation for > 3–4 wk (INR 2–3)
   - **b.** Acute-onset atrial fibrillation/flutter with associated hemodynamic compromise
     1. Angina pectoris
     2. Myocardial infarction
     3. Pulmonary edema
     4. Hypotension
     5. Heart failure
   - **c.** Atrial fibrillation/flutter of unknown duration and absence of thrombus in left atrium or left atrial appendage on biplane transesophageal echocardiogram
   - **d.** Atrial fibrillation/flutter < 48 h duration → anticoagulation optional—depending on risk
2. Atrial tachycardia
3. Atrioventricular nodal reentrant tachycardia
4. Reentry tachycardias associated with Wolf-Parkinson-White syndrome
5. Ventricular tachycardia

Defibrillation

1. Ventricular fibrillation
2. Ventricular tachycardia with hemodynamic instability

CONTRAINDICATIONS

Cardioversion

1. Known atrial thrombus and no emergent indication
2. Sinus rhythm/tachycardia
3. Tachycardias associated with increased automaticity
   - **a.** Multifocal atrial tachycardia
   - **b.** Junctional tachycardia
4. Digitalis toxicity
5. Severe electrolyte imbalance and nonemergent indication
6. Unknown duration of atrial fibrillation or atrial flutter in a nonanticoagulated patient in the absence of transesophageal echocardiogram
7. Patient who cannot be safely sedated

Defibrillation

1. Prior expression of patients who wish not to be resuscitated

INR, international normalized ratio.

intubation difficult and may suggest the need for the presence of an anesthesiologist during the procedure.

4. The patient's **medication and anticoagulation status** (for patients in atrial fibrillation or flutter) should be confirmed. Because patients may not always have symptoms with arrhythmias such as atrial fibrillation and atrial flutter, convincing historical or electrocardiographic evidence of the tachycardia initiating within 48 hours of cardioversion should be documented before cardioverting a patient with atrial fibrillation or atrial flutter without adequate anticoagulation due to the risk of thromboembolism.

TABLE 59.2 Indications for Cardioversion in Patients with Atrial Fibrillation

Class I

1. Immediate electrical cardioversion in patients with paroxysmal AF and a rapid ventricular response who have electrocardiographic evidence of acute MI or symptomatic hypotension, angina, or HF that does not respond promptly to pharmacologic measures.
2. Cardioversion in patients without hemodynamic instability when symptoms of AF are unacceptable.

Class IIa

1. Electrical cardioversion to accelerate restoration of sinus rhythm in patients with a first-detected episode of AF.
2. Electrical cardioversion in patients with persistent AF when early recurrence is unlikely.
3. Repeated cardioversion followed by prophylactic drug therapy in patients who relapse to AF without antiarrhythmic medication after successful cardioversion.

Class III

1. Electrical cardioversion in patients who display spontaneous alteration between AF and sinus rhythm over short periods of time.
2. Additional cardioversion in patients with short periods of sinus rhythm who relapse to AF despite multiple cardioversion procedures and prophylactic antiarrhythmic drug treatment.

AF, atrial fibrillation; HF, heart failure; MI, myocardial infarction.

Adapted from ACC/AHA/ESC 2001 guidelines.

5. **Anticoagulation** is a key factor for patients in atrial fibrillation or flutter (Table 59.3) to prevent thromboembolism. The two key oral anticoagulants that may be used for anticoagulation are Coumadin and the newly approved dabigatran, which is used for nonvalvular atrial fibrillation or flutter. Therapeutic levels of anticoagulation for Coumadin and dabigatran differ in timing. For Coumadin, there is frequent laboratory monitoring that needs to be done with adjustment of dosing to reach a target international normalized ratio of 2 to 3, which on average takes 3 to 5 days. However, in regard to dabigatran, there is no laboratory monitoring needed, with therapeutic levels being achieved in about 12 hours. The dosing is fixed at 150 mg bid for patients with creatinine clearance (CrCl) > 30 mL/min and 75 mg bid with CrCl of 15 to 30 mL/min.
6. A 12-lead electrocardiogram (ECG) should be obtained to **confirm the presenting rhythm**, as well as to discern any suggestion of electrolyte abnormality (hypo- or hyperkalemia) or drug toxicity (digitalis). If any of these is suspected, appropriate blood levels should be checked. Routine measurement of digoxin levels is not recommended.
7. **Peripheral venous access** should be obtained for elective cases.
8. A good-quality **continuous ECG** should be obtained. Good contact of the skin and electrodes is essential, and proper skin preparation, including shaving of the chest hair (if present), is recommended.
9. **Oxygen and airway management** equipment (including suction with suction catheters, bag valve mask, laryngoscope, endotracheal tubes, and pulse oximeter) is required and should be checked prior to the procedure.

B. Technique

1. Once the patient is adequately prepared and an appropriately trained physician is present, **cardioversion patches are placed and the patient is sedated**.

TABLE 59.3 Anticoagulation Status and Cardioversion for Atrial Fibrillation/Flutter

Anticoagulation before cardioversion

1. Administer oral anticoagulation with Coumadin and ensure therapeutic INR (> 2) or dabigatran (no need for laboratory monitoring) for nonvalvular atrial fibrillation/flutter for a minimum of 3–4 wk prior to cardioversion (target INR 2–3)

or

2. Anticoagulate with heparin[a] to achieve a PTT 1.5–2 times control and screen for thrombus in left atrium or left atrial appendage by transesophageal echocardiography
   a. If no thrombus, cardiovert and continue heparin while loading Coumadin or dabigatran. In regard to Coumadin, continue the heparin until INR is therapeutic (≥ 2). If dabigatran is used, it would be reasonable to continue heparin until anticoagulation status is therapeutic, which is about 12 h

or

   b. If thrombus is visualized, anticoagulate for 3–4 wk with either Coumadin (target INR 2–3) or dabigatran and recheck transesophageal echocardiogram to confirm thrombus is resolved prior to cardioversion

3. If emergent indication

Administer heparin (unless contraindicated) to achieve PTT 1.5–2 times control prior to or immediately after cardioversion

Anticoagulation after cardioversion

Oral anticoagulation for at least 4 wk with Coumadin for a target INR 2–3 or dabigatran if no contraindications

[a]Limited data support the use of low-molecular-weight heparin (LMWH) before or after cardioversion (level of evidence: C). Use of LMWH in such clinical situations must be individualized after careful determination of the risks and benefits involved.

INR, international normalized ratio; PTT, partial thromboplastin time.

2. Electrode placement. Electrode placement on the chest is important to maximize current flow through the heart, which is what actually terminates the arrhythmia. Patches or paddles may be placed in the anteroapical or the anteroposterior position.

   a. Although the anteroapical position is easy to use in an emergency, it is associated with a lower delivery of current to the myocardium.

   b. The left anteroposterior position is commonly used for cardioversion of atrial arrhythmias because it is associated with a smaller interelectrode distance and a lesser interposition of lung parenchyma. This enhances delivery of current to the atria and improves the success of cardioversion.

   c. The right parasternal–left paravertebral electrode patch position is associated with better current delivery to both atria and is particularly useful in patients with atrial abnormalities (e.g., atrial septal defect and rheumatic valve disease). This electrode position is favored in our laboratory for cardioversion of atrial fibrillation (Fig. 59.1).

   d. Although internal cardioversion (using a right atrial catheter and a coronary sinus catheter as electrodes or using a right atrial and a posteriorly placed external electrode) has been used in the past for cardioverting morbidly obese patients or patients who are resistant to external cardioversion,

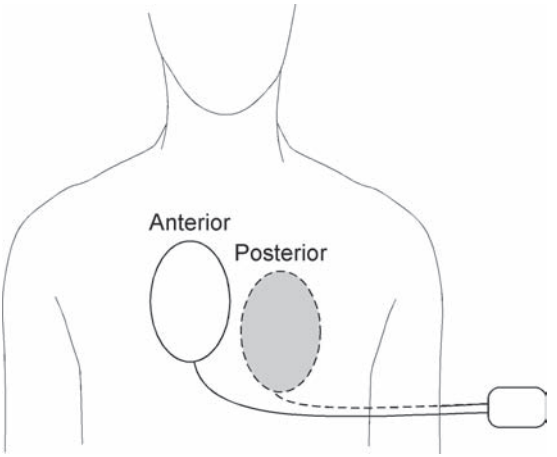

FIGURE 59.1 Right parasternal–left paravertebral electrode patch position.

it is now rarely necessary, given the widespread availability of biphasic cardioversion.

3. **Sedation.** Short-acting sedatives should be administered before all elective cardioversions, since the procedure is uncomfortable. Commonly used agents include methohexital (0.5 to 0.6 mg/kg body weight), etomidate (0.2 to 0.6 mg/kg body weight over 30 to 60 seconds), propofol (0.7 to 1.2 mg/kg, followed by 0.5 mg/kg every 3 to 5 minutes as needed), and midazolam (0.5 to 2 mg over 2 minutes, repeated every 2 to 3 minutes if necessary). Adequate sedation is confirmed by lack of response to verbal and pressure stimuli and loss of eyelash reflex. Airway, breathing, and oxygenation should be monitored until the patient makes a complete recovery, and appropriate support is provided as needed.
4. **Energy selection.** Success of cardioversion is dependent on adequate energy delivery to the heart. This in turn is dependent on the energy output, current vector, and the transthoracic impedance.
   a. The commonly used energy selection for various arrhythmias is outlined in Table 59.4. The energy selected differs between monophasic and biphasic devices.
   b. Impedance is defined as opposition to electrical flow or current. Higher impedance results in a reduction in current delivery to the myocardium. Therefore, initial energy selection should be individually tailored after consideration of important patient factors such as body habitus and the presence of lung disease, which may affect impedance. In addition, all efforts must be made to reduce impedance. A key factor that modulates impedance is electrode size, with optimal size approximating the size of the heart. Although smaller electrodes increase impedance, larger ones are associated with current wastage. The optimal diameter of an electrode for an adult patient is approximately 12 cm. Other measures to reduce impedance include application of pressure on the electrodes (approximately 12 kg) during shock delivery, shock during end-expiration, better skin–electrode interface and use of conducting gels, and repeat administration of shocks.

TABLE 59.4 Initial Energy Selection for Commonly Encountered Arrhythmias

Arrhythmia	Energy output (J)	
	Monophasic	Biphasic
Ventricular fibrillation (or unstable ventricular tachycardia)	200	120
Atrial fibrillation	200	100
Atrial flutter	50	50
Supraventricular tachycardia	150	100
Ventricular tachycardia (stable)	100	50–100

Conversely, increasing interelectrode distance and interposition of soft tissue or pulmonary parenchyma increases impedance.

5. **Synchronization.** Once the underlying rhythm is confirmed and a good-quality ECG is obtained, the synchronize mode is switched on (except for defibrillation where mode must be asynchronous). Synchronization is essential to prevent delivery of shock during the vulnerable period (from 80 milliseconds before to 30 milliseconds after the apex of T wave), with resultant ventricular fibrillation. Defibrillators are designed to time the shock to the R wave during synchronization mode. The position of the timing artifact on the R wave is confirmed on the monitor and on a printout, because the defibrillator may rarely synchronize to the T wave. Conversely, when defibrillating, the mode must be asynchronous because lack of identifiable QRS complex prevents a defibrillator in the synchronous mode from discharging.
6. **Delivery of shock.** Once the patient is adequately prepared, the electrodes are adequately positioned, and the appropriate output and mode are selected, the adequacy of sedation should be reconfirmed. The defibrillator capacitors are charged, the ancillary staff are warned to stay clear of the patient, proper synchronization is reconfirmed, and the appropriate shock is delivered. The patient is immediately assessed for adequacy of airway, breathing, and circulation. The ECG is inspected to confirm rhythm, and if sedation is still adequate, the procedure is repeated if necessary. The patient is monitored until complete recovery (generally 1 hour). Anticoagulation and antiarrhythmic medications (if any) must be addressed before discharge.

V. COMPLICATIONS OF CARDIOVERSION.

Complications after cardioversion are uncommon but include the following.

A. Thromboembolism. About 1% to 7% of patients in atrial fibrillation not anticoagulated before cardioversion develop arterial embolization after the procedure. In appropriately anticoagulated patients, the incidence of embolism is extremely low. In the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial, comparing anticoagulation for 3 weeks before cardioversion to transesophageal echocardiography (TEE)-guided therapy, the incidence of embolism was 0.5% in the conventional arm and 0.8% in the TEE-guided arm. TEE-guided cardioversion is now widely used in patients who require cardioversion urgently but who have not been adequately anticoagulated for 3 weeks.

B. Arrhythmias. It is not uncommon for patients to have premature atrial contractions or premature ventricular contractions after cardioversion. Although

some patients exhibit transient sinus arrest or atrioventricular block, this is usually self-limited. However, the ability to provide emergent temporary transthoracic pacing should be available for the rare patient who needs it. Malignant ventricular tachyarrhythmias are rare but may occur if the shock is delivered during the vulnerable period. The risk of malignant tachyarrhythmias is increased in the setting of hypokalemia or digoxin toxicity.

C. **Injuries.** The incidence and severity of chest wall burns can be reduced by the use of conductive gel, good skin and electrode contact, and use of lowest effective energy output.

D. **Airway compromise.** Excessive sedation may be associated with respiratory depression. This is more likely in the elderly or in those with hepatic or renal dysfunction. Appropriate adjustment of dose and monitoring of airway and oxygenation until complete recovery will minimize any undue effects of excessive sedation.

E. **Myocardial depression.** Cardioversion is a safe procedure with a wide margin of safety. Transient ST-segment elevation without apparent myocardial damage and minor elevations in creatine kinase myocardial band isoenzyme or in troponin I have been reported in rare instances. Rarely, patients have developed pulmonary edema after direct current cardioversion.

F. **Injuries to the operator.** Injuries to the operator are rare, with an incidence <1 in 1,700 in one series. Most are minor electrical injuries and manifest as extremity paresthesias. Major electrocution is extremely rare, and the reported cases have all been associated with equipment malfunction. Cardioversion in the presence of wet skin or nitroglycerin ointment can lead to arcing and may present a fire hazard.

VI. TROUBLESHOOTING

A. **Monitor does not work.** This is usually related to a mechanical problem. The power source, lead connections, and monitor lead electrode patches should be checked.

B. **Timing artifact falls on T wave.** Monitoring lead should be changed and the correct position of the timing artifact confirmed prior to cardioversion.

C. **Capacitor does not discharge.** When operating in the synchronized mode, the capacitor will not discharge until it recognizes a synchronized QRS. The switch should be pressed until the capacitor discharges. If this method fails, the monitoring lead should be changed and cardioversion attempted again.

D. **Cardioversion unsuccessful**

1. The first step should be to repeat the ECG to check the underlying rhythm to confirm diagnosis and to differentiate between failure to cardiovert and successful cardioversion that is followed by recurrence of the presenting arrhythmia.
2. For patients who truly fail to cardiovert, a higher energy level may be considered for a repeat attempt. A biphasic device should be used if available and all possible measures to reduce impedance applied (Section **IV.B.4.b**).
3. Another option for patients who truly fail to cardiovert is to reposition the patches to better capture the myocardium between the patches and, if not done initially, application of pressure on the electrodes (approximately 12 kg) during shock delivery to improve contact and decrease impedance.
4. Unsuccessful cardioversion may be secondary to a deranged metabolic milieu, and reversible causes (such as electrolyte imbalance or thyrotoxicosis) should be corrected.
5. Patients who are on long-term amiodarone therapy may present with atrial fibrillation as the first manifestation of amiodarone-induced hyperthyroidism, which may in turn make cardioversion more difficult.
6. In resistant cases where a biphasic device is unavailable, reversing the polarity of the electrodes with cardioversion at maximal energy, using two defibrillators to increase current, or internal cardioversion may be an option.

7. Use of appropriate antiarrhythmic drugs may facilitate cardioversion and maintenance of sinus rhythm, and the procedure may be repeated after loading with appropriate drugs. Pretreatment with 1 mg ibutilide has been shown to increase the likelihood of successful cardioversion. Ibutilide administration has been associated with the development of torsade de pointes. At our institution, patients pretreated with ibutilide are also given 1 g of IV magnesium sulfate in order to minimize this risk.
8. Predictors of unsuccessful cardioversion in chronic atrial fibrillation include long duration of atrial fibrillation, underlying structural heart disease, left atrial enlargement, and cardiomegaly.

VII. SPECIAL SITUATIONS

A. Preexisting permanent pacemaker or implantable cardioverter–defibrillator. Electric current can conduct along the implanted electrode lead and cause myocardial injury. This may manifest as a temporary or permanent increase in stimulation threshold, and, when pronounced, this may manifest as failure of capture-exit block. This can be avoided by **positioning electrodes away from the device**; therefore, the anteroposterior position is preferred. The device should be interrogated before and after cardioversion.

B. Pregnancy. Successful cardioversion has been carried out in all trimesters of pregnancy without ill effects to the mother or the fetus.

VIII. FUTURE DIRECTIONS.

A very important area for future improvement in a technique that has changed so little over the last several decades is to reduce the defibrillation thresholds. This could possibly serve to eventually eliminate pain, anesthesia, and sedation during shocks. Current research points to more effective cardioversion/defibrillation waveforms; shocks from ≥ 2 sites simultaneously and combination of shocks with cardiac pacing may prove particularly useful. In regard to the combination of shocks and cardiac pacing, we already know that pacing can influence and terminate reentrant or triggered arrhythmias. As noted in previous work with animal models and humans on the mechanisms of ventricular fibrillation and atrial fibrillation suggesting the presence of one or more drivers that may make this strategy plausible, the goal of this combination would be for less energy to be used to restore normal sinus rhythm.

IX. AUTOMATIC EXTERNAL DEFIBRILLATORS.

The automatic external defibrillator is a battery-operated microprocessor-based defibrillator that identifies tachyarrhythmias and, upon activation, delivers a shock to terminate them. This device is designed for use on an unresponsive patient with cardiac arrest. The system includes external self-adhesive pads that are applied on the victim, after which the device is switched on and cardiopulmonary resuscitation temporarily discontinued. The device analyzes the rhythm and advises the operator to press a switch to deliver a nonsynchronized shock, reanalyzes the resulting rhythm, and advises further delivery of shock if indicated. These devices are easy to use and designed to be used in the field by lay people. In various studies, the sensitivity and specificity of detection and success of termination of ventricular fibrillation and ventricular tachycardia have been > 90%, with a significant reduction in the response time for the first shock.

ACKNOWLEDGMENTS: *The author thanks Drs. Hitinder S. Gurm, Robert A. Schweikert, and Thomas Callahan for their contributions to earlier editions of this chapter.*

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CHAPTER 60

Jun-Yang Lou
Venu Menon

Right Heart Catheterization

I. INTRODUCTION. In 1947, Dexter et al. (1) observed that the pressure recorded by a catheter wedged in the pulmonary artery (PA) was similar to the filling pressure in the left ventricle. In 1970, Swan and colleagues (2) reported that PA catheterization could be performed at the bedside by using a specially designed balloon-tipped catheter. This landmark observation brought right heart catheterization (RHC) to the bedside and it remains an integral part of the diagnostic armamentarium of the cardiologist. Although the routine use of RHC data to guide treatment in critically ill patients in the intensive care unit has been associated with harm, it remains the gold standard in hemodynamic monitoring, and its use can be crucial in diagnosing and treating critically ill patients with cardiovascular disease.

The utility of hemodynamic variables obtained from RHC as a diagnostic and prognostic marker in patients with acute myocardial infarction (MI), cardiogenic shock, and heart failure (HF) is well established. Proving that a clinical benefit exists for continuous RHC hemodynamic monitoring has, however, been challenging. Retrospective observational analyses on the utility have been limited by patient selection as well as survival biases. In the National Heart Lung Blood Institute–supported ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, the utilization of PA catheters was not associated with worse outcomes. In this trial of 433 patients randomized to therapy for class IV HF guided by either clinical assessment or clinical assessment plus PA catheterization, there was no difference in the primary end point of days alive out of the hospital during the first 6 months after hospitalization. There was an increase in in-hospital adverse events in the PA catheter group; however, there were no deaths related to PA catheter use and no difference in in-hospital or 30-day mortality between the two groups.

II. INDICATIONS AND COMMON USES. See Table 60.1 for ACC recommendations for using PA catheterization.

(A) Acute MI complicated by hypotension, congestive heart failure, sinus tachycardia, right ventricular (RV) infarction, or mechanical complications (such as ventricular septal defect [VSD], pericardial tamponade, or acute mitral regurgitation [MR]).

(B) Assessment of volume status in patients in whom physical signs may be unreliable (e.g., morbidly obese or ventilated patients).

(C) Severe left ventricular (LV) failure to guide inotropic, diuretic, and afterload reduction management.

(D) Differentiation between various shock states (e.g., cardiogenic, distributive, or hypovolemic) and guidance of therapies.

(E) Risk stratification for patients during heart transplant evaluation.

(F) Cardiac tamponade. Although echocardiography is the diagnostic test of choice, PA catheterization may be used when echocardiography is not readily available or nondiagnostic and the risk or difficulty of pericardiocentesis is high.

(G) Assessment of the level and magnitude of an intracardiac shunt, especially if transthoracic echocardiography is nondiagnostic.

TABLE 60.1 Common Indications for the Use of Right Heart Catheterization

HF

1. To differentiate between cardiogenic and noncardiogenic pulmonary edema.
2. To differentiate between cardiogenic and noncardiogenic shock and to guide its pharmacologic or mechanical support.
3. To guide therapy in patients with biventricular HF.
4. To diagnose pericardial tamponade when echocardiography is unavailable or nondiagnostic.
5. Perioperative management of patients with decompensated HF undergoing high-risk surgery.
6. To identify reversible pulmonary hypertension in patients undergoing heart transplant evaluation.

Acute MI

1. To differentiate between cardiogenic and hypovolemic shock.
2. To guide pharmacologic and/or mechanical support of cardiogenic shock in patients with or without coronary reperfusion therapy.
3. Short-term guidance of pharmacologic and/or mechanical support in acute MR before surgery.
4. To establish severity and for short-term guidance of pharmacologic and/or mechanical support of ventricular septal rupture before surgery.
5. To guide management of right ventricular infarction that does not respond to intravascular volume expansion, low doses of inotropic drugs, and/or restoration of heart rate and atrioventricular synchrony.
6. To manage acute pulmonary edema that does not respond to treatment with diuretics, nitroglycerin, other vasodilators, and/or low doses of inotropic drugs.

Perioperative use in cardiac surgery

1. To determine the etiology of low cardiac output (hypovolemia vs. ventricular dysfunction) when exam and echocardiography are inconclusive.
2. To differentiate between right and left ventricular dysfunction and pericardial tamponade when exam and echocardiography are inconclusive.
3. To guide management of severe low cardiac output syndrome.
4. To diagnose and guide management of pulmonary hypertension in patients with systemic hypotension and evidence of inadequate organ perfusion.

PAH

1. To exclude postcapillary (elevated pulmonary capillary wedge pressure) causes of pulmonary hypertension.
2. To diagnose and establish the severity of precapillary (normal pulmonary capillary wedge pressure) pulmonary hypertension.
3. To select and establish the safety and efficacy of long-term vasodilator therapy based on acute hemodynamic response.
4. For hemodynamic assessment before lung transplantation.

HF, heart failure; MI, myocardial infarction; MR, mitral regurgitation; PAH, pulmonary arterial hypertension.

Adapted from Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document: present use of bedside right heart catheterization in patients with cardiac disease. *JACC*. 1998;32:840–864.

(H) **Differentiation between constrictive and restrictive cardiac physiology**.
(I) **Severe pulmonary hypertension (PH)**.
(J) **High-risk cardiac patients during preoperative, intraoperative, and postoperative periods** to monitor volume status and cardiac output (CO).
(K) **Severe adult respiratory distress syndrome (Noncardiogenic Pulmonary Edema)** during positive end-expiratory pressure trials to assess CO.

III. CONTRAINDICATIONS.

The absolute contraindications to PA catheter placement are right-sided endocarditis, a mechanical tricuspid or pulmonic valve prosthesis, thrombus or tumor in a right heart chamber, uncooperative patient, and terminal illness for which aggressive management is considered futile. Relative contraindications are profound coagulopathy (international normalized ratio > 2 or platelet count < 20,000 to 50,000), bioprosthetic tricuspid or pulmonic valve prosthesis, newly implanted pacemaker or defibrillator (unless fluoroscopic guidance is used), and left bundle branch block (LBBB). The latter is a relative contraindication because local trauma to the functioning right bundle while introducing the PA catheter may result in complete heart block and hemodynamic instability. **Consequently, temporary pacing should be immediately available when inserting a PA catheter in patients with preexisting LBBB**. Finally, it would be advisable to treat any pneumothorax/hemothorax on the contralateral lung before proceeding, in the event of an ipsilateral pulmonary injury caused by the procedure.

IV. TECHNIQUE

A. Venous introducer/sheath insertion. It is important to obtain informed consent in plain language from the patient before the procedure, addressing the utility and major complications of PA catheterization (Table 60.2). Once the procedure is ready to commence, a checklist system should be utilized to ensure safety and success, including a time-out process that confirms "right patient, right procedure, and right site of access." Using a central line kit is a convenient way to streamline the procedure. The patient should be prepped and draped in a sterile fashion from head to toe during the catheter insertion, regardless of the insertion site chosen. Multiple sites can be used for introducer placement; however, **a site that can be readily compressed, such as the internal jugular (IJ) vein, is preferred. Localization and entry into the vein is best performed under ultrasound guidance as an imaging-guided approach decreases procedural complications. Cannulation of the vein utilizing anatomical landmarks should only be used when ultrasound guidance is unavailable**.

TABLE 60.2 Complications of Right Heart Catheterization

Related to the introducer	Related to the catheter passage	Related to the catheter
Arterial puncture	Arrhythmia (PVC, NSVT, VF)	Thrombosis
Bleeding from insertion site	Complete heart block or RBBB	Thrombophlebitis
Pneumothorax	Coiling	
Nerve injury/Horner's syndrome	Valve trauma PA/RV perforation	PA infection Bacteremia ± endocarditis
Air embolism		Balloon rupture ± embolization

NSVT, nonsustained ventricular tachycardia; PA, pulmonary artery; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricular; VF, ventricular fibrillation.

1. The **IJ vein** (see Fig. 60.1) has multiple advantages, such as compressibility and minimal risk of pneumothorax. The disadvantages are the potential for accidental carotid artery puncture and limited neck mobility for patients. The IJ vein can be entered via an anterior or posterior approach. The right side is generally preferred because the vein runs a direct path to the right atrium. Often, it is easier to access the IJ vein if the patient is in the Trendelenberg position. The anterior approach uses the triangle created by the two heads of the sternocleidomastoid muscle and the clavicle. A finger should always be placed on the carotid artery to identify its position and to retract it medially. The needle should be inserted at the apex of this triangle and advanced in the direction of the ipsilateral nipple at a 45° angle. The vein can usually be entered 3 to 5 cm from the skin surface. In order to minimize complications, the vein should be found with a finder needle (20G) before using the large-bore catheter (16G) needle. Once the IJ vein is cannulated, the catheter-over-guidewire approach should be used to place the introducer. The guidewire minimizes damage to the vessel and should pass smoothly. Never force the guidewire. If difficulty in threading the wire is encountered, reattach the syringe and attempt to aspirate venous blood to ensure that the needle tip is still located in the vessel. An instructional video available from the *New England Journal of Medicine* web site (see reference) is a helpful tool for clinicians and students alike.

   An alternative IJ vein access is the posterior approach. The advantage of this approach is that it minimizes the risk of carotid artery puncture. First, the external jugular vein is located, and the IJ vein is cannulated 1 cm superior to the point where the external jugular vein crosses the lateral edge of the sternocleidomastoid muscle. Another posterior approach is to puncture along the posterior edge of the sternocleidomastoid muscle, two fingerwidths above the clavicle. The needle should be pointing toward the posterior aspect of the upper portion of the manubrium sterni.
2. **Cannulation of the subclavian vein** (see Fig. 60.1) is associated with greater patient comfort. However, there is an increased risk of pneumothorax and inadvertent subclavian artery cannulation, especially in patients on mechanical ventilation or with chronic obstructive pulmonary disease. The vein lies just under the clavicle at the insertion site for the clavicular head of the sternocleidomastoid muscle. This is where the vein should be cannulated. The subclavian artery lies just beneath the anterior scalene muscle, which is just below the subclavian vein, with the lung just underneath the artery. For better landmark definition and separation of the vein from the pleura, a rolled-up towel can be placed between the scapulae. There are two approaches to cannulating the subclavian vein: infraclavicular and supraclavicular. The infraclavicular approach is used more frequently.

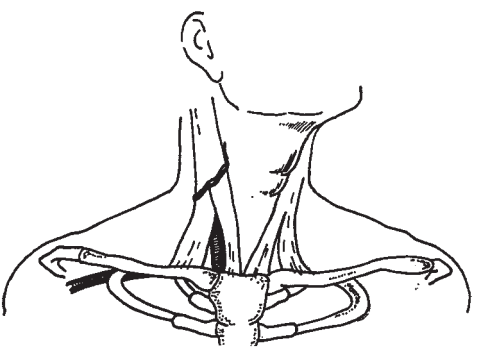

FIGURE 60.1 Neck anatomy.

The needle is inserted under the clavicle at about 1 cm lateral to the sternocleidomastoid muscle insertion point. The needle is then advanced horizontally, nearly parallel to the clavicle, toward the suprasternal notch.

With the supraclavicular approach, the vein is entered from above. The sternocleidomastoid muscle and the clavicle form an angle, and the needle is inserted at this point at a 45° angle. The vein should be cannulated no deeper than 2 cm below the skin surface. If there is uncertainty whether artery or vein has been cannulated, transduce pressure through the needle or obtain a blood gas sample to differentiate vein from artery before dilatation. An instructional video is available from the *New England Journal of Medicine* web site (see reference).

3. The **femoral vein** may also be used for PA catheterization, with the advantages being ease of cannulation, easy compressibility, and absence of pneumothorax risk. Palpate the femoral artery pulse at the level of the inguinal ligament. The femoral vein is usually located 2 cm medial to and 2 cm below the femoral artery. In some patients, the vein may lie closer to the artery. Sometimes, the Valsalva maneuver may make it easier to access the vein.

   Unfortunately, there is a high risk of bloodstream infection, associated with central venous access from femoral veins. It is recommended in the Center for Disease Control guidelines for the prevention of intravascular catheter-related infection that it not be used routinely for central venous access.
4. Venous cutdown is rarely necessary, in which case **right basilic and right median cubital veins are used**. However, due to venospasm and difficulty with catheter insertion and advancement, the antecubital route is reserved for those who have failed other routes.

B. PA catheter insertion

1. After the introducer/sheath is placed and secured, the PA catheter can be inserted. Always test balloon inflation, flush the ports, and make sure the catheter is properly calibrated before beginning the procedure. After the PA catheter is tested, insert it through the protective sterile covering and then through the introducer. Keep the balloon deflated at this stage. Ideally, **fluoroscopy and pressure waveforms should be used during PA catheter insertion for guidance**. The catheter should advance easily; if not, do not force the catheter, but make sure the introducer is properly positioned and flushed. Once the catheter has been inserted 15 to 20 cm or after the right atrial (RA) tracing is seen, **inflate the balloon** and advance across the tricuspid valve. The RV tracing should be visualized next, followed by the PA tracing, and finally the pulmonary capillary wedge pressure (PCWP) tracing (see Fig. 60.2). Not infrequently, the RV tracing is accompanied by a few premature ventricular ectopic beats. In general, the PA tracing should be reached within 50 to 55 cm if the catheter is inserted from the IJ vein or subclavian vein or 65 to 70 cm if via a femoral or an arm approach. If the PA tracing has not been visualized by this point, the catheter is likely coiled in the right ventricle. The balloon should be deflated and the catheter withdrawn. The process is repeated until proper placement is achieved.

   Once the PCWP tracing is obtained, deflate the balloon and reobtain the wedge pressure by inflating the balloon with 1.5 cm^3 of air. If the PCWP tracing is obtained even when the balloon is deflated or with < 1.5 cm^3 of air, the catheter has been advanced too far and needs to be pulled back. The pressure waveform should always be closely monitored when inflating balloon-tipped catheters to immediately identify this "overwedging." The likelihood of PA rupture and infarction increases when catheters are overwedged. In the nonventilated patient, the PCWP should be obtained at end-expiration. In general, wedging the catheter should be avoided in patients with severe PH.
2. It is much easier to float the catheter from the right IJ vein or either subclavian vein. From the femoral veins, it is slightly more difficult, **especially in patients with significant tricuspid regurgitation**. Often, the femoral PA catheter needs

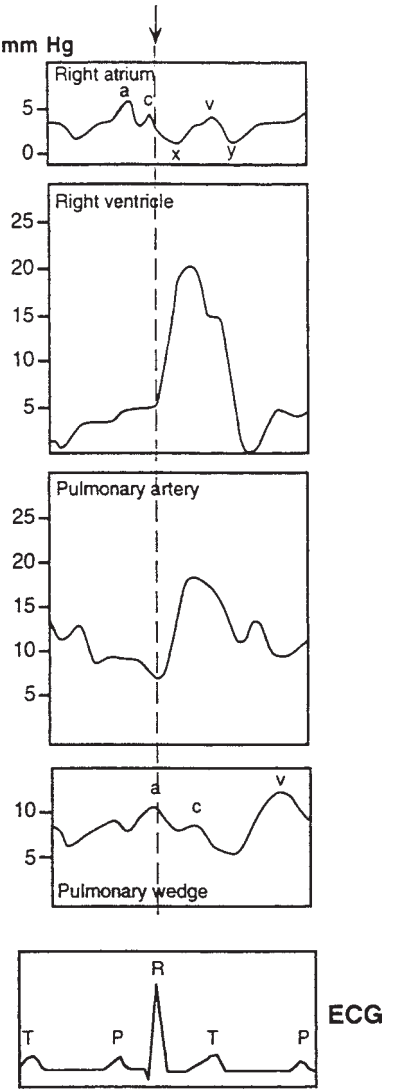

FIGURE 60.2 Waveforms.

to be inserted under fluoroscopic guidance and rotated in a continuous and clockwise motion, with the catheter tip resting just distal to the tricuspid valve until it begins to point upward. Forward motion is then applied to move the catheter into the PA. Alternatively, an S-shaped femoral Swan can be used. When using fluoroscopy, the camera should be in the anteroposterior position, and the balloon should be inflated under fluoroscopy.

3. Finally, check the catheter placement and check for pneumothorax after the procedure by obtaining a chest x-ray film. Catheter placement may be difficult in patients with low CO, severe tricuspid regurgitation, PH, or a dilated right atrium or right ventricle.
4. Catheter advancement may be facilitated by a deep inspiration or, in more difficult cases, by a guidewire with a 0.021" diameter. The wire can be placed inside the distal lumen of the catheter, improving the stiffness and making the catheter easier to manipulate. The distal end of the guidewire should always be under manual control and a hemostat can be placed on the end of the guidewire to ensure this.

V. COMPLICATIONS.

See Table 60.2.

VI. TROUBLESHOOTING.

See Table 60.3.

VII. WAVEFORMS.

See Figure 60.2.

A. Right atrium. When interpreting hemodynamic data, it is helpful to align pressure tracings with simultaneous electrocardiography (ECG). RA systole occurs after the *p* wave on the ECG and produces the *a* wave on the right atrial pressure (RAP) tracing. Atrial relaxation, the *x* descent, occurs with a decline in pressure. Tricuspid valve closure produces a slight upward deflection during the *x* descent, which is known as the *c* wave. The *c* wave follows the *a* wave by the PR interval and correlates with RV systole. The *v* wave occurs near the end of the *t* wave on ECG and marks atrial filling during early diastole. Finally, the *y* descent marks the opening of the tricuspid valve during RV diastole and emptying of the atrium. In the normal right atrium, the peak *a* wave is greater than the peak *v* wave.

B. Right ventricle. RV systole follows the QRS complex of the ECG. With ventricular relaxation, the pressure declines and the tricuspid valve opens. During the continuous filling from the right atrium, a small *a* wave is produced that marks atrial contraction and occurs after the *p* wave and just before the QRS on the ECG. End-diastole is the point just after the *a* wave and just before ventricular contraction. The peak systolic and end-diastolic measurements are used for right ventricular pressures (RVPs).

TABLE 60.3 Troubleshooting in Right Heart Catheterization

Problems	Solutions
Arrhythmia	Catheter may be in the RVOT. Pull the catheter back or advance forward
No PCWP tracing	Catheter tip is usually not advanced far enough, balloon has ruptured, or the catheter is coiled in the right ventricle. Use fluoroscopy for guidance
Continuous PCWP tracing	Balloon is inflated or the catheter is too far advanced ("overwedged")
Abnormal tracing	Catheter tip is up against a vessel wall or is too far advanced
Damped tracing	Tubing is kinked, air or thrombus is in the catheter, or catheter tip is up against the vessel wall. Flush and/or withdraw the catheter
Change in pressure tracing	Improper calibration, change in patient position or catheter location

PCWP, pulmonary capillary wedge pressure; RVOT, right ventricular outflow tract.

C. Pulmonary artery. The normal pulmonary arterial pressure (PAP) tracing contains a *v* wave, which corresponds to RV systole and follows the QRS complex. During the relaxation period, pulmonic valve closure produces the incisura, a notch during pressure decline on the *v* wave. The trough of the pressure decline marks end-diastole. Pulmonic arterial systolic pressure, end-diastolic pressure, and mean pressure are recorded.

D. The **PCWP tracing** is a transmitted left atrial pressure (LAP) and is considered an approximation for left ventricular end-diastolic pressure (LVEDP), i.e., LV preload. The waveforms are similar to an RAP tracing, with the *a* wave corresponding to left atrial systole, the *x* descent to relaxation, the *v* wave to filling, and the *y* descent to emptying. However, in contrast to the right atrium, the *v* wave is greater than the *a* wave in the left atrium and the *c* wave is not seen due to transmission through the pulmonary vasculature. Mean PCWP, *a* wave pressure, and *v* wave pressure are generally measured during end-expiration when intrathoracic pressures are equal to the atmospheric pressure.

VIII. PITFALLS OF THE PA CATHETER.

While the PA catheter remains the gold standard in monitoring hemodynamics, care should be taken to avoid errors in measurement and interpretation. Clinical decisions based on misleading PA catheter data may adversely impact on patient outcome.

Calibration and referencing. Before the PA catheter enters the body, it should be flushed to eliminate bubbles and calibrated/zeroed at the level of the patient's mid-thorax level, i.e., phlebostatic level. Serial hemodynamic measurements should be performed with the reference point moved to match the phlebostatic level, which changes with patient position.

Proper interpretation of PA catheter data is essential and must be carried out with an understanding of the clinical context. For example, the PCWP is an accurate measurement of LV filling pressure, except in pulmonary veno-occlusive disease (PCWP > LAP) or in mitral stenosis and obstructive left atrial myxoma (PCWP = LAP > LVEDP). In MR, LAP is greater than LVEDP; in acute aortic insufficiency or a noncompliant ventricle, LVEDP is greater than LAP. Furthermore, alterations in pulmonary alveolar and intrathoracic pressures (e.g., in respiratory failure with high positive end-expiratory pressure) can also significantly alter the PAWP waveform.

IX. CARDIAC OUTPUT

A. Measurement via **thermodilution** technique may be performed at the bedside but should be avoided in the setting of severe tricuspid regurgitation, intracardiac shunts, existing catheter thrombosis, and low CO.

(1) Prefill syringes with 10 mL of room temperature indicator (usually normal saline), then connect the syringe to the distal port of the PAC, which should rest in the right atrium.

(2) Check the position of the catheter. Make sure you can obtain the PCWP tracing with 1.5 cm^3 of air and no less. Then deflate the balloon and ensure the catheter tip rests in the proximal PA.

(3) After properly attaching the tubing to the thermistor, inject the contents of the syringe five separate times. Discard the highest and lowest values, taking the mean measurement of the remaining three values.

B. Calculation of CO using the **Fick equation**:

(1) Obtain patient's weight in kilograms.

(2) Draw peripheral arterial blood gas to obtain systemic oxygen saturation (Ao_2%).

(3) Draw blood gas from the distal lumen of the PA catheter (Vo_2%).

(4) Draw hemoglobin.

(5) $CO = [Wt \times 3\ mL\ O_2/kg]/[(Ao_2\% - Vo_2\%) \times 1.36 \times Hgb \times 10]$.

(6) Oxygen consumption can be measured from a metabolic hood or a Douglas bag. It can also be estimated as 3 mL O_2/kg.

TABLE 60.4 Clinical Scenarios in Right Heart Catheterization

Clinical scenarios	Data	Tracing
RV infarct	↑ RAP, ↓ CO, ↓ BP RAP > PCWP, steep *y* descent, square root sign (morphology in RV tracing diastolic "dip and plateau")	Figure 60.3
Acute mitral regurgitation	↑ PCWP, prominent *v* wave	Figure 60.4
Acute VSD	Oxygen saturation step up from the right atrium to PA	
Noncardiac pulmonary edema	Normal to low PCWP, with abnormal chest X-Ray	
Massive pulmonary embolism	↓ BP, ↓ CO, ↑ PAP, normal PCWP	
Pulmonary arterial hypertension (cor pulmonale)	↑ RAP, ↑ RVP, ↑ PAP, prominent *a* and *v* waves and normal PCWP. PAP and RV systolic pressure may reach systemic levels	
Tamponade	Diastolic equalization of pressures (RAP = RV diastolic pressure = PCWP) ↑ RAP, ↑ RVP, ↑ PCWP Paradoxical pulse, blunted *y* descent, prominent *x* descent on RA tracing	Figure 60.5
Constrictive pericarditis	↑ RAP, ↑ PCWP Dip and plateau in RVP tracing, M- or W-shaped jugular venous pressure tracing	Figure 60.6
Tricuspid regurgitation	↑ RAP, ↑ RV EDP Blunted *x* descent, prominent *v* wave, steep *y* descent, and ventricularization of RAP	

BP, blood pressure; CO, cardiac output; EDP, end-diastolic pressure; PA, pulmonary artery; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVP, right ventricular pressure; VSD, ventricular septal defect.

X. CLINICAL SCENARIOS. See Table 60.4.

A. Shock (see Table 60.5). Four classes of shock are characterized: hypovolemic, cardiogenic, distributive, and anaphylactic. Hypovolemic shock is due to a profound decrease in venous return and ventricular preload and can be caused by hemorrhage, dehydration, increased positive intrathoracic pressure, and depressed vasomotor tone. Hemodynamic data consist of decreased blood pressure (BP), CO, and PCWP with increased systemic vascular resistance (SVR). Cardiogenic shock results from failure of the cardiac pump to maintain adequate output and can be caused by a change in loading conditions (decrease in preload due to tamponade or increase in preload due to VSD), contractility (acute ischemia or infarction), or an abrupt increase in afterload. Low BP and CO but high PCWP and SVR characterize cardiogenic shock due to LV dysfunction. Contrary to classic teaching, patients in cardiogenic shock from predominant LV failure can have normal to reduced SVR. This drop in SVR in the setting of an MI is most commonly seen after a large anterior wall MI and among the elderly and is likely mediated by profound nitric oxide release in the setting of acute myocardial injury. In general, predominant elevation of RAP is indicative of RV failure, and isolated elevation of the PCWP is indicative of LV failure. The

TABLE 60.5 Interpreting Right Heart Catheterization Data in Shock

	Blood pressure	PCWP	CO	SVR
Distributive	Low	Low	High	Low
Cardiogenic	Low	High	Low	High/normal/low
Hypovolemic	Low	Low	Low	High

CO, cardiac output; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

hemodynamic indices characteristic of distributive shock are low BP, PCWP and SVR but high CO. A depressed CO as well as low BP, PCWP, and SVR can characterize the late phase of distributive shock. Finally, in terms of hemodynamics, not much is known about anaphylactic shock. However, there is a hyperkinetic phase, characterized by low SVR and high CO, as well as a later hypokinetic phase, dominated by profound hypovolemia with decreased CO.

B. RV failure (see Fig. 60.3 and Table 60.4) may be due to RV infarction, severe PH, pulmonary embolism, or increased preload due to left-to-right intracardiac shunt. An RV infarct (see Fig. 60.3) produces increased RAP and RV end-diastolic pressure, with low CO and BP. Because the right ventricle dilates and becomes less distensible, a dip-and-plateau pattern on the RVP tracing is seen. On the RAP tracing, there is a steep *y* descent. In the setting of severe tricuspid regurgitation and RV infarction, the dip-and-plateau pattern is lost. A blunted *x* descent, prominent *v* wave, and steep *y* descent are then seen on RAP tracing.

C. Acute MR (see Fig. 60.4 and Table 60.4) may be due to papillary muscle dysfunction or rupture. In this setting, the left atrium is subjected to a sudden increase in pressure. Regurgitation produces a large *v* wave in the PCWP tracing that occurs after the *T* wave on ECG. A *v*-wave pressure that is twice the value of PCWP is considered to be abnormal. In chronic MR, the *v* wave may be modest in amplitude due to chronic atrial dilatation. Other causes for prominent *v* waves are severe tricuspid regurgitation and VSD.

D. Tricuspid regurgitation (see Table 60.4). The RA systolic wave may resemble the RV tracing. There is increased RAP and RV end-diastolic pressure, a blunted *x* descent, a prominent "*c*-*v*" wave, and a steep *y* descent on RAP tracing.

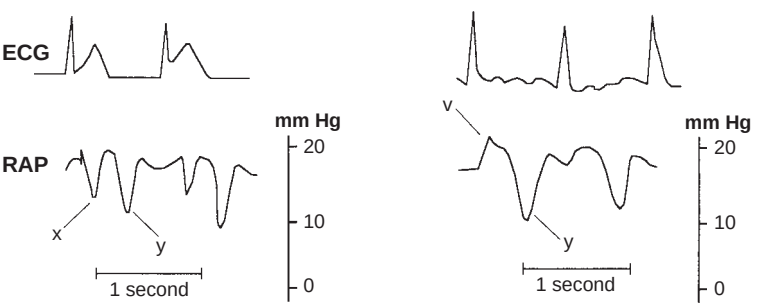

FIGURE 60.3 Right ventricular infarction without tricuspid regurgitation (*left*); right ventricular infarction with tricuspid regurgitation (*right*).

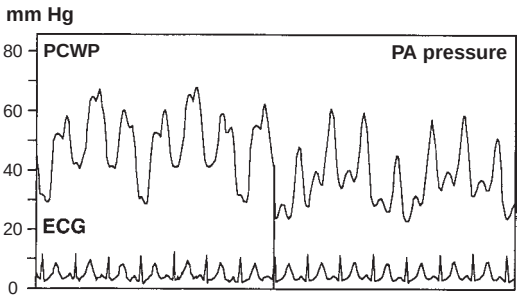

FIGURE 60.4 Acute mitral regurgitation.

E. Cardiac tamponade (see Fig. 60.5 and Table 60.4). The hallmark of tamponade is diastolic equalization of pressures, where RAP = RVP = PCWP. The RA waveform is characterized by a deep *x* descent and absent *y* descent (due to lack of RV filling at the beginning of diastole). In addition, RAP, RVP, and PCWP are increased.

F. Constrictive pericarditis (see Fig. 60.6 and Table 60.4) is characterized by brisk ventricular filling during early diastole and limited ventricular filling during late diastole. The constriction results in the elevation and equalization of RV end-diastolic pressure and LVEDP. The dip-and-plateau waveform is seen in constrictive pericarditis as well as restrictive cardiomyopathy, RV infarct, and massive pulmonary embolism.

G. Massive pulmonary embolism (see Table 60.4). There is ventricularization of the PA waveform with rapid end-systolic descent and a hardly visible, or absent, dicrotic notch due to obstruction in the PA.

H. Restrictive cardiomyopathy (see Table 60.6) includes a heterogeneous group of illnesses, such as hemochromatosis, amyloidosis, and endomyocardial fibrosis. This leads to impaired diastolic filling of the ventricles. There is a prominent *y* descent, but the dip-and-plateau waveform is less pronounced due to a pandiastolic hindrance to ventricular filling.

I. Pulmonary hypertension (see Table 60.4). PH is defined as a mean PAP > 25 mm Hg at rest. It can be caused by elevated pulmonary venous pressures due to LV dysfunction, left-sided valvular disease, and/or volume overload (i.e., elevated PCWP). It may also be caused by intrinsic pathology within the pulmonary arterial bed, i.e., pulmonary arterial hypertension (PAH). PAH is defined as mean PAP > 25 mm Hg at rest with PCWP < 15 mm Hg. Compensatory changes in the right heart to chronic PH or PAH result in elevations in RV and PA pressures with prominent *a* and *v* waves.

XI. FORMULAS (see Table 60.7)

(1) CO by Fick equation in L/min:

$$CO = [Wt \times 3\ mL\ O_2/kg]/[(Ao_2\% - Vo_2\%) \times 1.36 \times Hgb \times 10]$$

where Wt is weight in kilograms, Ao_2% is systemic arterial oxygen saturation, Vo_2% is mixed venous oxygen saturation, and Hgb is hemoglobin concentration.

(2) Cardiac index (CI) in L/min/m^2:

$$CI = CO/BSA$$

where BSA is body surface area in m^2.

(3) Stroke volume (SV) in mL/beat:

$$SV = CO/\text{heart rate}$$

(4) Pulmonary vascular resistance (PVR) in dynes × s/cm^5:

$$PVR = [(\text{mean PAP} - PCWP) \times 80]/[CO]$$

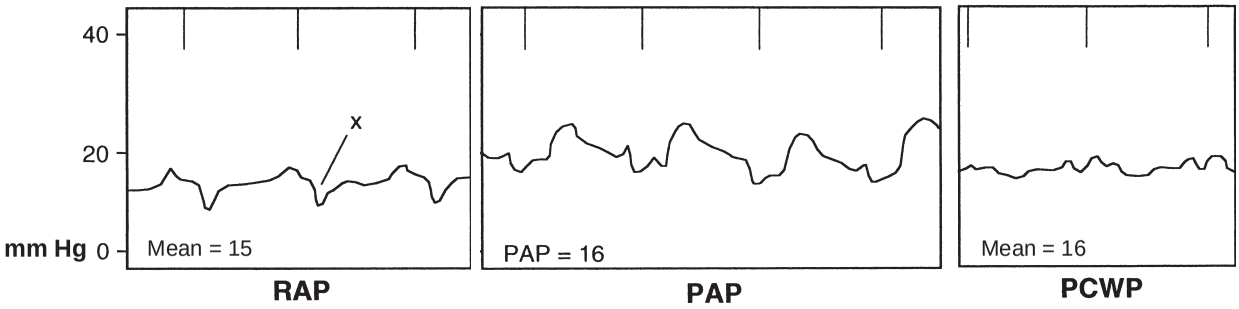

FIGURE 60.5 Cardiac tamponade.

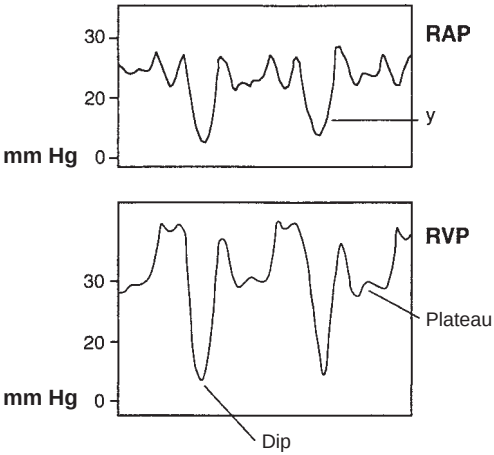

FIGURE 60.6 Constrictive pericarditis.

TABLE 60.6 Differentiating Diastolic Dysfunction

	Constrictive pericarditis	RV infarct	Tamponade	Restrictive cardiomyopathy
Pulsus paradoxus	Rare	Occasional	Frequent	Rare
RA waveforms	Prominent *y* descent	Prominent *y* descent	Prominent *x* descent	Prominent *y* descent
Equalization of diastolic pressures	Frequent	Frequent	Frequent	Rare
Dip and plateau (RV)	Frequent	Frequent	Absent	Frequent

RA, right atrial; RV, right ventricular.

where PAP is pulmonary arterial pressure and PCWP is pulmonary capillary wedge pressure.

(5) **Systemic vascular resistance** in dynes × s/cm^5:

$$SVR = [(MAP - CVP) \times 80]/[CO]$$

where MAP is mean arterial pressure and CVP is central venous pressure (can also substitute RAP for CVP).

(6) **Estimate of O_2 consumption** = 125 mL/min/m^2 = 3 mL O_2/kg.

(7) **O_2 content** = (Ao_2% – Vo_2%) × 1.36 × Hgb × 10.

(8) **CO = O_2 consumption/O_2 content**.

XII. INTRACARDIAC SHUNT. The existence of an intracardiac shunt can be evaluated by using a PA catheter and performing a saturation "run." Blood samples for oximetry are obtained from the PA as well as regions of the right ventricle, right atrium, superior vena cava, and inferior vena cava. With the catheter positioned in the PA, CO by the Fick equation can be obtained. As the operator manipulates and pulls the catheter back under fluoroscopic and pressure guidance, a blood sample from each location is

TABLE 60.7 Normal Values and Formulas

	Formula	Normal values
RA		0–8 mm Hg
RV		Systolic 15–30 mm Hg Diastolic 0–8 mm Hg
PA		Systolic 15–30 mm Hg Diastolic 3–12 mm Hg Mean 8–20 mm Hg
PCWP		6–12 mm Hg
CO	Fick equation: $[Wt \times 3\ mL/kg]/[(Ao_2\% - Vo_2\% \times 1.36 \times Hgb \times 10]$	4–8 L/min
CI	CO/BSA	2.8–4.2 L/min/m^2
SV	CO/HR	40–120 cm^3/beat
SVR	[(MAP – CVP) × 80]/CO	770–1,500 dynes s/cm^2
PVR	[(PAP – PCWP) × 80]/CO	20–120 dynes s/cm^2
Shunt fraction (Q_p/Q_s)	$[Ao_2\% - Vo_2\%]/[PVo_2\% - PAo_2\%]$	> 2.0 large defect 1.5–2.0 moderate defect

Ao_2%, peripheral arterial oxygen saturation; BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; Hgb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; PA, pulmonary artery; PAo_2%, pulmonary artery oxygen saturation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVo_2%, pulmonary vein oxygen saturation often assumed to equal Ao_2 in left-to-right shunt; PVR, pulmonary vascular resistance; Q_p, pulmonary flow; Q_s, systemic flow; RA, right atrium; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; Vo_2%, mixed venous oxygen saturation, Wt, weight in kilograms.

aspirated. A left-to-right shunt is suggested when a "step up," or increase, in the oxygen saturation in one chamber exceeds the oxygen saturation of a proximal compartment by more than 7% in the case of an atrial shunt or more than 5% in ventricular or great vessel shunts.

In a normal setting, the effective pulmonary blood flow should equal the systemic blood flow ie. $Q_p/Q_s = 1$. However, with a left-to-right shunt, pulmonary blood flow is equal to systemic blood flow plus the amount of shunt flow. Conversely, in a right-to-left shunt, the effective pulmonary blood flow is decreased by the amount of shunt flow. The shunt fraction is the ratio of pulmonary to systemic flow, denoted Q_p/Q_s (where Q_p is pulmonary flow and Q_s is systemic flow). For an atrial septal defect, the mixed venous oxygen saturation is computed as the sum of three times the superior vena cava saturation plus the inferior vena cava oxygen saturation, and the total is divided by 4.

A. Calculation of left-to-right shunt

(1) Shunt fraction = pulmonary flow in L/min (Q_p)/systemic flow in L/min (Q_s)

(2) $Q_p = O_2$ consumption/$[10 \times (PVo_2\% - PAo_2\%)]$

where PVo_2% is pulmonary vein oxygen saturation and PAo_2% is pulmonary artery oxygen saturation.

(3) $Q_s = O_2$ consumption/$[10 \times (Ao_2\% - MVo_2\%)]$

where Ao_2% is peripheral arterial oxygen saturation and MVo_2% is mixed venous oxygen saturation.

(4) Simplified calculation using saturation only:

$$Q_p/Q_s = (Ao_2\% - MVo_2\%)/(PVo_2\% - PAo_2\%)$$

Important note: A shunt fraction of > 1.5 often necessitates shunt closure.

ACKNOWLEDGMENTS: *The authors wish to acknowledge the contributions of Dr. Kellan E. Ashley and Dr. Leslie Cho to previous editions of this chapter.*

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CHAPTER 61

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W.H. Wilson Tang

Endomyocardial Biopsy

I. INDICATIONS AND CONTRAINDICATIONS. Endomyocardial biopsy (EMB) is less used now as a diagnostic tool for patients with systolic or diastolic dysfunction with the availability of more accurate noninvasive imaging techniques such as magnetic resonance imaging. Currently, the major indications for EMB are monitoring for allograft rejection after cardiac transplantation, as well as ruling out some potentially treatable forms of myocarditis. The role for this procedure in other disorders, such as arrhythmogenic right ventricular dysplasia, remains controversial because the diagnostic accuracy must be considered in relation to the lack of proven effective therapy. Potential indications and contraindications for EMB are listed in Tables 61.1, 61.2, and 61.3.

II. PATIENT PREPARATION. As with any other procedure, extensive patient education and informed consent are necessary before starting the procedure. Patients undergoing EMB should be informed that there is a very small chance (<1% in experienced hands) of cardiac perforation, with potential urgent cardiovascular surgery and even death as a consequence.

Sedation is seldom needed but may help anxious patients better tolerate the procedure. Monitoring of heart rate by continuous electrocardiographic telemetry, blood pressure (noninvasively), and pulse oximetry is essential throughout the procedure. The patient should be monitored for a couple of hours after the procedure, as myocardial perforation with subsequent pericardial effusion may only become apparent some time after EMB. The patient is always positioned flat regardless of the venous approach. Venous access may be obtained through the internal jugular (most common), subclavian, or femoral veins. Ultrasound guidance or maneuvers to increase central venous pressure such as Valsalva, leg elevation with a wedge, and Trendelenburg position are helpful in obtaining venous access. Most centers use fluoroscopy as the imaging method of choice to guide EMB. However, echocardiography can also be used, particularly when radiation exposure needs to be minimized, such as in pregnant women.

III. DEVICES

A. Sheath. Venous access is obtained using the Seldinger technique, and the sheath is always placed over a guidewire so as not to damage any vascular structures. A standard short sheath (11 cm, 7F or 8F) is generally sufficient for the right internal jugular or any subclavian approach. The intermediate-length sheath (24 or 35 cm) may be helpful to reduce venous angulation or to avoid damaging the vessel wall or a suture line when inserting the bioptome in patients with prior heart transplantation. For the left internal jugular approach, a longer sheath (40 cm, 7F) is used with a single- or double-curved tip based on operator preference and venous and cardiac anatomy. For a femoral approach, a curved 7F, 85-cm-long transseptal sheath is used, as it can be easily positioned into the right ventricle.

TABLE 61.1 Common Indications for Endomyocardial Biopsy

Clinical scenarios	Class of recommendation
New-onset heart failure of <2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	I
Heart failure of >3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	IIa
Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa
Heart failure associated with suspected anthracycline cardiomyopathy	IIa
Heart failure associated with unexplained restrictive cardiomyopathy	IIa
Suspected cardiac tumors	IIa
Unexplained cardiomyopathy in children	IIa

DCM, dilated cardiomyopathy.

Adapted from AHA/ACC/ESC 2007 Consensus Statement.

TABLE 61.2 Conditions Involving the Heart in Which Endomyocardial Biopsy Can Establish the Diagnosis, Listed According to the Presence or Absence of Proven Effective Therapy

Treatable conditions	Less treatable conditions
Cardiac allograft rejection	Myocarditis (non–giant cell)
Cardiac amyloidosis	Arrhythmogenic right ventricular dysplasia
Giant cell myocarditis	Glycogen storage disease
Hypereosinophilic syndrome	Rheumatic carditis
Staging of anthracycline toxicity	Chagas disease
Cardiac sarcoidosis	
Cardiac hemochromatosis	
Lyme carditis	
Fabry's disease	

B. Bioptome. There are two basic types of bioptomes: (1) independent and stiff, which does not require a long sheath but does rely on the operator skill to be maneuvered safely into the right ventricle, and (2) flexible, which requires a longer sheath advanced into the right ventricle for positioning. Resterilizable and reusable bioptomes are widely used, but disposable bioptomes are also available. For internal jugular and subclavian approaches, 50-cm-long bioptomes are used, whereas for femoral access, the bioptomes used are longer (up to 105 cm).

TABLE 61.3 Relative Contraindications for Endomyocardial Biopsy

Informed consent not obtained
Patient not cooperative (confused, agitated, etc.)
Profound hemodynamic compromise
No cardiac surgery backup available
Coagulopathy (INR > 1.5)
Mechanical tricuspid prosthesis
Significant right-to-left shunt (risk of air embolus)
Thinning of myocardium after MI or in case of ARVD
RA or RV thrombus

ARVD, arrhythmogenic right ventricular dysplasia; INR, international normalized ratio; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

IV. TECHNIQUE. Right ventricular endomyocardial biopsies can be performed from either the right or left internal jugular, subclavian, or femoral veins. If necessary, a left ventricular EMB can be obtained via the femoral artery approach, although this is rarely necessary.

A. Right ventricular biopsy

1. **Internal jugular vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 58) are identified. A pilot puncture with a 22G needle can be made to localize the vein. The internal jugular vein is punctured with an 18G (Cook) needle, and the sheath is introduced using standard technique. The bioptome, with jaws closed and tip straightened, is advanced under fluoroscopic or echocardiographic guidance across the atrial suture line (in allografts) until its tip lies against the lower third of the lateral right atrial wall. It is then rotated gently counterclockwise and simultaneously advanced into the right ventricular cavity. During this procedure, the tip is gently unstraightened. Rotation is continued until the catheter reaches the apical half of the right ventricle and the handle clamp points in the posterior direction. At this point, the tip of the bioptome rests on the interventricular septum. The position is confirmed by inability to further advance the bioptome, the generation of premature ventricular contractions, and fluoroscopic appearance. Generation of premature atrial contractions or absence of ventricular ectopy may indicate that the bioptome was advanced in the right atrium or in the coronary sinus. If there is any doubt about the position, the bioptome is withdrawn and the process repeated. Once in the desired position, the bioptome is withdrawn about 0.5 to 1 cm and advanced again after the jaws have been opened. When it touches the endocardium, the jaws are closed and the bioptome is gently withdrawn with its jaws closed under continuous fluoroscopic guidance. A small tug is often felt while withdrawing, but excessive tugging and multiple premature ventricular contractions should prompt consideration of repositioning. Usually four to six biopsy specimens are obtained in different areas of the septum to reduce sampling error. Once the procedure is completed, the venous sheath is removed and hemostasis achieved. Patients are monitored for about 2 to 4 hours after EMB.
2. **Femoral vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 60) are identified. The right (more common) or the left femoral vein is punctured with an 18G (Cook) needle, and a 0.038" guidewire is advanced up to the right atrium. A long (85-cm) 7F sheath

with dilator is advanced over the wire, and on entering the right atrium the dilator is withdrawn. The tricuspid valve is crossed with the help of the guidewire (a balloon-tipped catheter can also be used), and the sheath is advanced into the right ventricle toward the intraventricular septum. The pressure tracing, occurrence of ventricular ectopy, and fluoroscopy are used to confirm position. The side port of the sheath may be connected to a slow continuous intravenous infusion to prevent clot formation inside the sheath, especially if a long procedure is anticipated. A long nonsteerable bioptome is advanced through the sheath and is used to acquire samples. Biopsies are taken in a manner similar to that of the internal jugular vein approach.

3. **Subclavian vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 60) are identified. The subclavian vein is punctured using an 18G (Cook) needle followed by insertion of the sheath. The occurrence of ventricular ectopy and fluoroscopic images are used to confirm a position pointing toward the interventricular septum. Biopsies are taken as with the internal jugular vein approach.

B. Left ventricular biopsy

1. **Femoral arterial approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. The right (more common) or left femoral artery is punctured with an 18G (Cook) needle, and a short 8F sheath is inserted while a 0.035" long exchange guidewire is advanced up to the ascending aorta. A regular-length 7F pigtail catheter is advanced over the wire, and the aortic valve is crossed in the conventional manner. Afterward, the pigtail catheter is removed, while leaving the guidewire in the left ventricle, and exchanged with an 8F long, curved guiding sheath. The tip of this sheath is directed toward the interventricular septum, distal to the mitral apparatus, away from the thinner posterobasal wall. The position of the sheath is carefully reconfirmed (fluoroscopic images in two angulations and pressure tracings), and 5,000 U heparin is given intravenously before insertion of the bioptome. A long, nonsteerable bioptome is then advanced through the guiding sheath, and biopsy samples are collected as with right ventricular biopsy. It is important to note that catheters must be aspirated and flushed after each biopsy, since air can enter the sheath and clots can form in the sheath after removing the bioptome. Heparin is not reversed with protamine at the end of the procedure as it is thought to minimize thrombus formation at the biopsy sites.

V. COMPLICATIONS. In general, EMB can be performed more safely in heart transplant recipients than in patients with native hearts, because of the scarred and thickened pericardium in transplanted patients.

A. Mortality. Procedure-related deaths have been reported to be <0.05% in contemporary series.

B. Cardiac perforation and tamponade. The reported incidence of cardiac perforation is 0.3% to 0.5%, which can rapidly result in tamponade. The risk can be minimized by careful monitoring of catheter position to ensure that biopsies are obtained from the thicker interventricular septum and by gentle catheter advancement and EMB procurement. Symptoms of chest pain during or after the procedure, shortness of breath, a pericardial rub, or altered hemodynamics should suggest potential perforation and should prompt urgent echocardiography to rule out a new pericardial effusion or tamponade. Patients in whom a new pericardial effusion is suspected or detected should be monitored in the hospital for evidence of increasing pericardial effusion or tamponade, and an echocardiogram should be repeated at intervals as necessary and before discharge.

In patients early after heart transplantation, the atrial suture line also poses a higher risk of perforation. Very gentle advancement of the bioptome (and pulling back if any resistance is felt) and use of a longer sheath to pass the suture line if

needed will reduce this risk. Patients with suspected perforation should be closely monitored, and echocardiography, fluoroscopy, and cardiac tomography scanning can be used to confirm the diagnosis.

For both cardiac perforation and tamponade, careful monitoring is usually sufficient, although pericardiocentesis or even urgent cardiac surgery may be necessary if hemodynamic compromise develops.

C. Thromboembolism. Right-sided thromboembolism during EMB is possible in theory, but does not cause any clinically significant sequelae if it occurs. The risk of arterial embolization during left ventricular EMB is higher, owing to the longer sheath, and may have catastrophic consequences. Using heparin during a left-sided approach and aspirating air and flushing the sheath before inserting the bioptome minimize the risk of embolism.

D. Arrhythmia. Occasionally, a sustained atrial or, less commonly, a ventricular tachycardia is induced by EMB. These arrhythmias are almost always stopped by touching the wall of the right atrium or ventricle with the bioptome. Bradyarrhythmic episodes or bundle branch block induced by EMB is very rare and responds only to β_1-stimulants and not to atropine in heart transplant patients.

E. Tricuspid valve (or mitral valve for left ventricular biopsy) dysfunction. The bioptome can damage the chordae or papillary muscle and produce significant valvular regurgitation. The risk of this complication is minimized by careful confirmation of bioptome position before sampling. The cumulative risk of this complication is greater in heart transplant patients because they undergo many EMB procedures.

F. Damage to vena cava, coronary sinus, hepatic vein, and coronary arteries. Gentle advancement of the bioptome, use of a longer sheath, retraction of bioptome whenever resistance is felt, and position confirmation with multiple fluoroscopic views may minimize these complications. Fistula formation from a coronary artery branch to the right ventricle has occurred following EMB but is of no clinical significance.

G. Local complications. Hematoma, local infection, and injury to the lung (pneumothorax, incidence 0.9%) and nerve (recurrent laryngeal palsy and Horner's syndrome) are possible but rare while achieving vascular access. Careful identification of anatomic landmarks reduces the risk of these complications.

H. Pain. The EMB itself is usually painless, but some patients experience some mild degree of pain when the bioptome touches the heart or when a biopsy is taken.

ACKNOWLEDGMENTS: *The authors would like to thank Drs. Milind Shah, Wilfried Mullens, and Zuheir Adams for their contributions to earlier editions of this chapter.*

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CHAPTER 62

Clay A. Cauthen
Maria M. Mountis

Management of Continuous-Flow Ventricular Assist Systems: Troubleshooting and Complications

I. INTRODUCTION. This chapter is designed to briefly overview the mechanics of continuous-flow left ventricular assist systems (LVASs) and highlight the diagnosis and management of immediate and long-term complications of LVASs. LVAS support has emerged as the standard of care in patients with refractory stage D heart failure (HF) as both bridge to transplant and destination therapy.

(A) Continuous-flow LVASs are the most recent advances in permanent mechanical support systems.

(B) Continuous-flow LVAS can use either centrifugal-flow or axial-flow blood pumps. Both are designed similarly with a single rotating impeller that is designed to increase pressure and flow within the system.

(C) Bearings constrain the impeller within the device, allowing rotational movement. The bearings may be of three types: magnetic levitation, hydrodynamic, and blood immersed.

(D) Continuous-flow LVASs are smaller than pulsatile ventricular assist devices (VADs) that can accommodate most patients, including small women and children.

(E) Blood flow capacity is up to 10 L/min, which can provide constant unloading of the left ventricle. Unlike pulsatile-flow pumps that are primarily preload dependent, continuous-flow VADs are both afterload and preload dependent.

(F) As pulsatile VADs had either an automatic or fixed rate and stroke volume, continuous-flow VADs can be modulated by changes in the rotational velocity of the impeller.

(G) Axial-flow pumps include Thoratec Heartmate II, Jarvik 2000, HeartAssist 5, Incor, and Synergy.

(H) Centrifugal pumps include HeartWare HVAD, DuraHeart, Levacor VAD, and EVAHEART LVAS.

(I) HeartMate II is the most studied LVAS and has recently gained FDA approval for bridge to transplant and destination therapy. Jarvik 2000, HeartAssist 5, HeartWare HVAD, DuraHeart, Levacor VAD, and EVAHEART LVAS currently have investigational trial exemption for bridge to transplant in the United States.

(J) The use of implantable devices for lifetime support (destination therapy) has increased significantly since approval of the HeartMate II in 2010. As the technology improves, complications decrease, and more candidates for permanent mechanical support are identified, we will see more patients with permanent VADs in almost all cardiology clinical settings.

II. PREOPERATIVE CONSIDERATIONS. Patient selection, preimplant considerations, and implant timing are critical in optimizing outcomes in patients receiving LVAS support.

A. Patient selection involves determining the appropriateness for mechanical circulatory support, operative mortality, and family/social support at discharge.
(1) Highest risk of mortality is prior to discharge from hospital.
(2) Trend at many large centers is to implant early to minimize or avoid progressive end-organ damage.
(3) Important preimplant medical factors include nutritional status, pulmonary vascular resistance, improve congestive hepatopathy and nephropathy, and optimize right heart function, candidacy for coagulation, underlying infections, and other end-organ dysfunction (renal, hepatic, and pulmonary).
(4) Other important preimplant factors include patient's social support system, psychosocial status, and the ability to care for the device itself.

B. Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) patient profiles. INTERMACS is a registry designed to track patient selection, outcomes, and adverse events. Since inception, it has enrolled close to 6,000 patients and has provided key observations to improve patient selection and outcomes.
(1) INTERMACS (see Table 62.1) has defined patient profiles that highlight risk and timing of implantation.

TABLE 62.1 Interagency Registry of Mechanically Assisted Circulatory Support Patient Profile

Profile	Description	Comment
1	Critical cardiogenic shock	"Crash and burn profile." Definitive therapy is needed within hours. Has the lowest survival
2	Progressive decline on inotropic support	Inotropic-dependent patients. Progressive decline such as worsening renal function, nutritional status, or volume status despite increased inotropic support. Definitive therapy is needed within days
3	Stable but not inotrope dependent	Stable on lower doses of inotropes, but unable to wean. Stable volume status, organ function, and nutrition, but inotropic dependent. Elective therapy may be needed within weeks to a few months. Profile 3 has the best outcomes
4	Resting symptoms home on oral therapy	Patients have daily symptoms requiring fluctuating high-level doses of diuretics. Elective therapy may be needed within weeks to a few months. Outcomes for this level are under investigation for appropriateness
5	Exertion intolerant	Evidence of refractory volume-overloaded state. Able to perform ADLs and comfortable at rest, but have refractory symptoms with exertion or in a persistently volume-overloaded state. Patients in INTERMACS level 4 may overlap with this profile. Outcomes for this level are under investigation for appropriateness
6	Exertion limited	No evidence of refractory volume-overloaded state. Able to perform ADLs and comfortable at rest. Limited by symptoms within minutes of meaningful activity. Outcomes for this level are under investigation for appropriateness
7	Advanced NYHA class III symptoms	Transplantation or mechanical circulatory support is not currently indicated in this profile

ADLs, activities of daily living; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

III. TERMS AND BASIC MECHANICS OF LVASs. Basic terms, mechanics, and physiology are outlined in this section. When evaluating a patient with LVAS, no single parameter should be used for diagnosis.

- **A. Basic mechanism.** Volume of flow is determined by the speed of the rotary impeller and the change of pressure across the pump. At a fixed speed, flow is inversely related to pressure. Thus, when the pump pressure increases, the flow will decrease at a fixed speed.
- **B. Pump differential pressure** is equal to the aortic pressure minus the left ventricular (LV) pressure. Since the aortic pressure typically remains unchanged within a normal range, the change in pump differential pressure is primarily dependent on the LV pressure.
- **C. Pump speed** is a direct measurement of the rotational velocity. Continuous-flow ventricular assist system operates at a fixed pump speed. The optimal pump speed is typically determined by a ramp study (see Section **IV**). Substantial changes in pump speed are usually associated with abnormal conditions. Abrupt drops in pump speed followed by normalization may indicate suction events (see below).
- **D. Pump power** is a direct measure of motor voltage and current (power = current voltage difference). Pump speed, flow, and demand directly affect power. Gradual or sudden sustained increases in power may signify thrombus or debris accumulation in the motor.
- **E. Pump flow** is a calculated measurement that essentially maintains a linear relationship with power at a given speed. Within normal ranges, increased power results in increased flow. However, inherent to being a calculated value, pump flows may become unreliable at the low and high extremes of the flow–power relationship. For example, a thrombus may cause an abrupt increase in power and an incorrect calculation of increased flow. Suction events may also lead to incorrect flow values. Thus, in a given clinical situation, further assessment of pump function is required.
- **F. Pulsatility index (PI)** is the averaged measure of the magnitude of flow pulses over a 15-second interval. Flow pulses are determined by the contractile function of the left ventricle that produces changes in ventricular pressure. Higher PI values (range 1 to 10+) indicate greater LV contribution (filling and contractility), whereas lower PI values represent greater mechanical pump contribution. While the patient is at rest, there should be little change in the PI. Decreased PI may represent underfilling due to a change in contractile function or hypovolemia.
- **G. Suction event** occurs when the LV pressure becomes so negative that the left ventricle collapses.

IV. RAMPED SPEED STUDY. This is a method used to determine the speed that is the safest for the patient and provides the optimal LVAS support. Optimal speed is achieved when cardiac index, septum position, and LV dimensions are within normal ranges.

- **A. Initial optimum speed** is determined ideally while still in the operating room with transesophageal echocardiography.
- **B.** Ramped speed studies are best performed on hemodynamically stable, euvolemic patients and may use transthoracic echocardiography.
- **C.** Evaluation can be performed with echocardiography or invasive hemodynamics.
- **D.** Determination of **low fixed speed** is achieved by gradually decreasing the pump speed until the patient becomes symptomatic and the aortic valve opens with every beat when cardiac index falls below 2.5 L/min/m^2 or pulmonary vascular resistance begins to increase. For the HeartMate II, speed should never go below 8,000 rpm. At the low fixed speed, record the LV diameter, septal position, patient vitals, and, if available, hemodynamics.
- **E.** Determination of **high fixed speed** is achieved by increasing the rotational velocity of the pump until there is intraventricular flattening by echocardiography

(parasternal long or four-chamber view). At the high fixed speed, record the LV diameter, frequency of the aortic valve opening, patient vitals, and, if available, hemodynamics.

F. Determination of the **optimum fixed speed** is typically the median of the low fixed speed and high fixed speed. However, this speed should be adjusted based on clinical judgment as well as the desired frequency of aortic valve openings. It is also recommended that the pump speed is at least 400 rpm below the high fixed speed.

V. PUMP PARAMETER ABNORMALITIES

A. Pump speed

(1) Large speed changes in fixed speed mode are abnormal.

(2) A suction event has two phases of pump speed change: initial decrease to lower limit at the beginning of the suction event followed by a gradual increase to fixed speed at the end of the suction event.

(3) In the absence of suction events, consider primary pump or control issues.

B. Pump power

(1) Normal changes in power may be due to increased flow and demand or change in speed.

(2) Abrupt increases in power may be associated with pump thrombus.

(3) Gradual increases in power may be associated with in situ formation of bearing thrombus or bearing deposition.

C. Pump flow

(1) Flow is the calculated value based on pump speed and power. It becomes an imprecise estimation at extremely high and low values.

(2) Changes in flows should be used in parallel with other device and clinical parameters.

(3) During pump or bearing thrombus events, pump flow will be abnormally elevated.

D. Pulsatility index

(1) Under normal conditions, PI can increase with increased preload and LV contractility.

(2) Decreases in PI typically warrant further investigation as this may represent hypovolemia, obstruction of the inflow or outflow tract, or thrombus.

VI. DEVICE COMPLICATIONS

A. Suction event

1. Signs: Arrhythmias (ventricular tachycardia) and hypotension.

2. Parameter changes: In the HeartMate II, speed automatically decreases to low fixed speed followed by slow increase to set speed. Pump flow decreases.

3. Management: Chest radiograph to assess inflow cannula position. Assess volume status to rule out hypovolemia and assess right ventricular (RV) function. Consider decreasing pump speed with ramped speed study.

B. Inflow tract obstruction

1. Signs: New-onset HF symptoms, arrhythmias, and hemolysis.

2. Parameter changes: Increased pump power, decreased pump flow, and PI. High velocities across inflow by Doppler echocardiography.

3. Management: Consider reducing speed if septal obstruction is noted on ramped speed study. Chest radiography to assess inlet position (supine and upright). Echocardiography for tamponade and right heart function. Computed tomography scan to assess inflow cannula position.

C. Outflow tract obstruction

1. Signs: New-onset HF symptoms and hemolysis.

2. Parameter changes: Increased pump power, decreased pump flow, and PI.

3. Management: Ramped speed study looking for changes in LV dimension and in diastolic arterial pressures with speed changes. Echocardiography and angiography for outlet position and the presence of graft kink.

D. Deposition of thrombus

1. Signs: New-onset HF symptoms, hemolysis, change in pump sound with auscultation, and hypotension with increased pulse pressure.
2. Parameter changes: Increased pump power, pump flow, and decreased PI.
3. Management: Angiography and echocardiography to assess pump flow. Heparin may slow progression of thrombus formation. Consider thrombolytics (rarely). Consider pump replacement.

E. Mechanical pump failure

1. Signs: New-onset HF symptoms, vibration of pump, and hypotension with increased pulse pressure.
2. Parameter changes: Cannot maintain pump speed, PI > 10, and multiple red heart alarms.
3. Management: Contact surgeon. Consider replacement of pump.

VII. SPECIFIC CLINICAL SCENARIOS FOR PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICE (LVAD)

Diagnosis and management of clinical changes in patients with LVAD should include, when appropriate, physical examination and multimodality imaging: echocardiography, computed tomography, radiography, and invasive hemodynamics.

A. Hypovolemia

1. Signs: Hypotension and possible suction events causing syncope or arrhythmias.
2. Echocardiography may demonstrate decreased RV and LV dimensions.
3. Parameter changes encountered: Decreased PI.
4. Suggested management: Consider adjustment of diuretics, decreasing pump speed, and volume expansion.

B. RV failure

1. Signs: Hypotension, possible suction events causing syncope or arrhythmias, and return of HF symptoms.
2. Echocardiography may demonstrate decreased RV function and enlarged RV dimensions.
3. Parameter changes encountered: Decreased pump flow and pump speed below fixed speed.
4. Suggested management: Consider inotropes, pulmonary vasodilators, volume expansion, ramped speed study, and mechanical right ventricular assist device.

C. Tamponade

1. Signs: Hypotension and decreased postoperative chest tube drainage.
2. Echocardiography may demonstrate focal or circumferential effusion causing tamponade physiology.
3. Parameter changes encountered: Decreased pump flow.
4. Suggested management: Pericardiocentesis or exploratory thoracotomy.

D. Hypertension

1. Signs: Typically asymptomatic.
2. Parameter changes encountered: Decreased pump flow and pump power and increased PI.
3. Suggested management: Increased afterload reduction and diuretics.

E. Volume overload

1. Signs: Edema.
2. Echocardiography to assess ventricular and valvular function.
3. Parameter changes encountered: Increased pump flow, pump power, and PI.
4. Suggested management: Consider adjustment of diuretics, fluid restriction, and ramped speed study.

F. Recurrent HF

1. Signs: Hypotension, pulmonary edema, and low cardiac index.
2. Echocardiography may demonstrate decreased RV and/or LV function. Valvular function should be assessed.
3. Parameter changes encountered: Decreased pump flow and PI.
4. Suggested management: Ramped speed study, adjustment of diuretics, RV function assessment, invasive hemodynamics, and treatment of HF symptoms.

G. Aortic insufficiency

1. Signs: Hypotension and return of HF symptoms.
2. Echocardiography shows dilated LV with severe aortic insufficiency.
3. Parameter changes: Increased pump flow with dilated LV.
4. Suggested management: Decrease pump speed to decrease the amount of aortic insufficiency. May eventually need aortic valve surgery.

H. Arrhythmia

1. Signs: Ventricular tachycardia on electrocardiogram, Holter, or telemetry. Syncope or presyncope.
2. Echocardiography may demonstrate intermittent suction events, worsened LV or RV function, and new valvulopathy.
3. Parameter changes: Decreased pump flow, pump power, and PI.
4. Suggested management: Ramped speed study and assess inflow cannula to ensure proper placement.

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CHAPTER 63

Olcay Aksoy

Intraaortic Balloon Counterpulsation

I. INTRODUCTION. Intraaortic balloon counterpulsation (IABC) is usually used to **support hemodynamics** in cardiogenic shock and to **relieve medically refractory ischemia** in patients with severe coronary disease. The duration of support with an intraaortic balloon pump (IABP) is typically short, because multiple complications can develop in patients treated with IABC. Patients should be carefully selected for receiving IABC therapy and should be closely monitored in a critical care setting while the IABP is in place.

II. INDICATIONS

A. Cardiogenic shock

1. **Bridge to revascularization.** IABC provides temporary hemodynamic stabilization in patients with cardiogenic shock caused by acute myocardial infarction (MI). Hospital survival rates for cardiogenic shock with balloon pump support alone without revascularization are poor (5% to 20%). Early revascularization with percutaneous transluminal coronary angioplasty (PTCA) improves survival rates in cardiogenic shock caused by acute MI.
   a. In the **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I (GUSTO I)** trial comparing fibrinolytic regimens for acute ST-segment elevation myocardial infarction (STEMI), PTCA was the only factor associated with a lower 30-day mortality rate in 2,972 patients with cardiogenic shock.
   b. In addition, early placement of an IABP in this cohort of patients was associated with lower 30-day and 1-year mortality rates.
   c. Cardiogenic shock and hemodynamic support during or after percutaneous coronary intervention are the primary reasons for IABP placement in more than half of all patients treated with IABC. IABP placement is an **ACC/AHA class I** recommendation in patients with STEMI presenting with cardiogenic shock when shock is not quickly reversed with pharmacologic therapy. The IABP in this setting is a stabilizing measure for angiography and prompt revascularization.
2. **Bridge to a tertiary center.** Thrombolytic therapy alone in patients with cardiogenic shock is less successful than mechanical reperfusion. However, the addition of IABC to thrombolysis can improve outcomes in patients with cardiogenic shock. In 46 patients with acute MI and cardiogenic shock treated at community hospitals without angioplasty capabilities, simultaneous treatment with thrombolysis and IABC was associated with an improved 1-year survival rate (67% vs. 32%) and successful transfer to a tertiary facility for revascularization when thrombolysis failed.

B. Acute MI treated with catheter-based reperfusion.

The **benefits** of IABC in patients with acute MI without cardiogenic shock treated with catheter-based reperfusion are **uncertain.**

1. In a randomized trial of 182 hemodynamically stable patients who underwent direct PTCA for acute MI, prophylactic IABC for 2 days after the procedure

reduced recurrent ischemia and reocclusion of the infarct-related artery but had no effect on survival or reinfarction.

2. In the **Primary Angioplasty in Myocardial Infarction II (PAMI II)** trial, 437 high-risk patients (age > 70 years, multivessel coronary disease, reduced ejection fraction, vein graft disease, or persistent ventricular arrhythmias) treated with direct PTCA for acute MI were randomized to ±1 to 2 days of IABC after PTCA. Patients treated with IABC had a slight reduction in recurrent ischemia but had no reduction in mortality, reinfarction, or infarct-related artery reocclusion. Thus, hemodynamically stable patients with acute MI treated with catheter-based reperfusion are not likely to benefit from IABP support after the intervention.

C. High-risk percutaneous revascularization. Patients at high risk for complications during percutaneous revascularization include those with unprotected left main coronary disease, left ventricular dysfunction (ejection fraction < 40%), the target vessel supplying > 40% of the myocardial territory, or severe congestive heart failure (CHF). Placement of an IABP in these high-risk patients affords the operator a longer duration of ischemia during balloon inflation and wire manipulation.

1. In a study of 219 patients undergoing unprotected left main trunk stenting, elective IABP placement was associated with fewer intraprocedural major adverse cardiac events, including combined end points of severe hypotension, MI, need for urgent bypass surgery, and death.
2. Although there are no specific recommendations for when to use IABC during high-risk coronary interventions, improved percutaneous revascularization techniques with coronary stents and adjunctive glycoprotein IIb/IIIa receptor antagonists have reduced the need for prophylactic IABP placement in high-risk patients.

D. Mechanical complications of acute MI. **Acute mitral regurgitation (MR)** and **ventricular septal defect** are devastating complications of acute MI and frequently cause rapid deterioration progressing to cardiogenic shock. An IABP should be placed before surgical repair in patients with hemodynamically significant MR or ventricular septal defect after an MI. Placement of an IABP in the setting of STEMI and secondary acute mitral valve regurgitation is an **ACC/AHA class I** indication. Similarly, insertion of an IABP and prompt surgical referral are **class I** recommendations.

E. Refractory unstable angina. Patients with severe coronary disease who have refractory ischemia or hemodynamic instability show **dramatic improvement** when IABC is used before revascularization. The ACC/AHA clinical guidelines assign a **class I** recommendation in STEMI patients and a **class IIa** recommendation in Unstable angina/Non ST segment elevation myocardial infarct (UA/NSTEMI) patients for IABP placement in the setting of severe ischemia that is continuing or recurs frequently despite intensive medical therapy. In the setting of STEMI, refractory pulmonary congestion carries a **class IIb** recommendation for IABP placement.

F. Weaning from cardiopulmonary bypass/postoperative pump failure. Patients with severe left ventricular dysfunction or those with prolonged runs on cardiopulmonary bypass can be difficult to wean from bypass after open heart surgery because of stunned myocardium from prolonged cardioplegic arrest. For these patients, IABP support improves hemodynamics and facilitates weaning from cardiopulmonary bypass.

G. End-stage cardiomyopathy/bridge to cardiac transplantation. An IABP improves cardiac output and lowers filling pressures in patients with dilated and ischemic cardiomyopathy. It can be used for hemodynamic support before cardiac transplantation.

1. **Disadvantages** of prolonged IABP support in patients awaiting cardiac transplantation include a high risk of infection and the need for continuous bed rest.
2. However, with improved inotropic therapy and implantable left ventricular assist devices for patients awaiting cardiac transplantation, IABC is now used infrequently for prolonged mechanical support in patients with end-stage cardiomyopathy.

H. **Refractory ventricular arrhythmias.** Incessant ventricular tachycardia compromises left ventricular filling, reduces stroke volume, and causes or exacerbates ischemia. IABC improved hemodynamics, lessened ischemia, and controlled refractory ventricular arrhythmias in 86% of patients in a large case series. Placement of an IABP support in patients with STEMI and refractory polymorphic ventricular tachycardia carries an **ACC/AHA class IIa** recommendation.

I. **Support during noncardiac surgery.** Patients with severe coronary disease, recent MI, and severe left ventricular dysfunction are at high risk for cardiac complications when they undergo noncardiac surgery. Case reports have demonstrated that high-risk patients are stabilized hemodynamically and have acceptable postoperative outcomes when prophylactic IABP support is used during and after noncardiac surgical procedures.

J. **Decompensated aortic stenosis** can be managed with temporary IABP support to improve the stroke volume and reduce the transvalvular gradient before aortic valve replacement. In a study of 25 patients with severe aortic stenosis and cardiogenic shock, IABP support was associated with prompt improvement in cardiac output and filling pressures, allowing stabilization of patients before surgery. However, because aortic insufficiency often accompanies severe aortic stenosis, careful monitoring early after initiation of IABC is recommended to ensure that aortic insufficiency is not worsened by the balloon pump.

III. CONTRAINDICATIONS

A. **Aortic dissection.** Any type of aortic dissection precludes IABP use because of the potential of the balloon catheter to extend the dissection and to worsen ischemia of a peripheral vascular bed that may be involved by the dissection.

B. **Abdominal or thoracic aneurysm.** Using IABP with an abdominal or thoracic aneurysm can precipitate an acute aortic dissection, dislodgement of atheroemboli, or aortic rupture, so the presence of an aneurysm is a contraindication to IABP use.

C. **Severe peripheral vascular disease**

1. The majority of the complications of IABC are caused by vascular insufficiency in the accessed leg because of the **large size of the balloon sheath and catheter and the concomitant presence of peripheral vascular disease** in patients who typically need IABC. In the past, the IABP catheters had been available only in 8F and 9.5F sizes; however, with improving equipment, 7F catheters have been introduced, and these have diminished the rate of complications due to obstruction of arterial flow.
2. **Limb ischemia and threatened limb viability** can occur when peripheral perfusion is compromised by the balloon catheter and sheath. The IABP catheter can be inserted without a sheath to reduce the diameter of obstruction in the iliac vessels, but in patients with tortuous aortoiliac vessels, sheathless IABP insertion can be difficult.
3. Thus, severe peripheral vascular disease is a contraindication to IABP insertion, depending on the necessity of IABP support and the degree of vascular compromise.

D. **Descending aortic and peripheral vascular grafts**

1. **Prosthetic descending aortic grafts and iliofemoral vascular grafts** are relative contraindications to IABC. Consultation with a vascular surgeon is recommended before attempting balloon pump insertion in these patients.
2. **Iliac artery stents** are not an absolute contraindication to IABP placement. However, passage of the guidewire and balloon catheter through the stent must be performed under direct fluoroscopic guidance.

E. **Coagulopathy or contraindication to heparin**

1. The balloon catheter is thrombogenic, and intravenous heparin is commonly given while the IABP is in place to prevent the development of thrombi on the balloon surface. Patients with a contraindication to heparin, such as those with prior heparin-induced thrombocytopenia, can be **anticoagulated with alternative agents** such as direct thrombin inhibitors like bivalirudin.

2. After cardiac surgery, heparin can be avoided because of the increased risk of intrathoracic bleeding, but IABP support in such patients is usually of short duration. In nonsurgical patients, if an anticoagulant cannot be given or if a severe coagulopathy exists that could precipitate bleeding at the access site, IABC is discouraged, but it could safely be undertaken for a short period.

F. Moderate to severe aortic insufficiency. By inflating during diastole, the IABP can worsen aortic insufficiency when blood is displaced to the proximal aorta. No consensus exists as to what degree of aortic insufficiency absolutely contraindicates IABP use. Therefore, **careful monitoring** of patients with aortic insufficiency who absolutely need IABP support is recommended.

IV. HEMODYNAMICS OF BALLOON PUMP FUNCTION

A. Decreased afterload

1. As systole begins, the intraaortic balloon rapidly deflates and creates a negative pressure in the aorta, which reduces afterload and improves forward flow from the left ventricle. Afterload reduction occurs because the aortic end-diastolic pressure is reduced, resulting in an increase in cardiac output of approximately 20% and a decrease in the mean pulmonary capillary wedge pressure of approximately 20%.
2. The **overall hemodynamic benefit** of IABP appears to be a reduction in left ventricular wall stress from decreased filling pressures and decreased afterload, which in turn improves stroke volume and cardiac output (see Figs. 63.1 and 63.2).

B. Augmented coronary perfusion

1. When the balloon inflates during diastole, it displaces blood to the proximal aorta and augments aortic diastolic pressure and, thus, coronary perfusion pressure. The augmentation of coronary perfusion pressure is more dramatic when systemic hypotension is present (see Figs. 63.1 and 63.2).

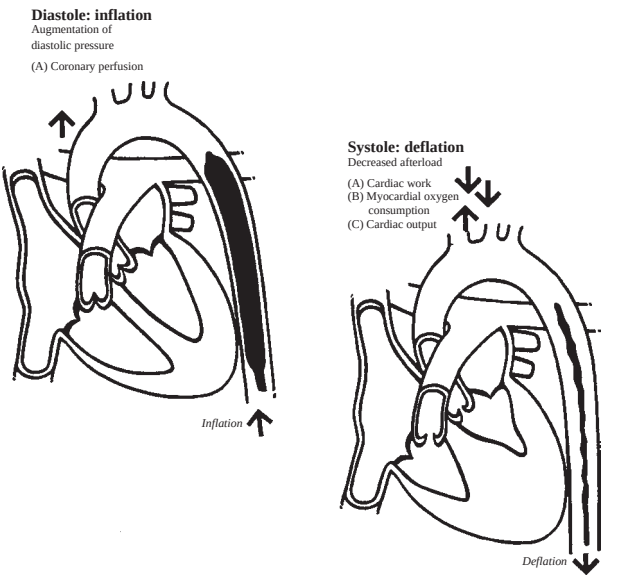
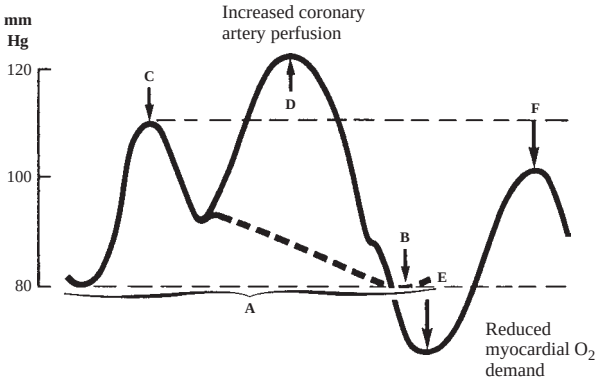


FIGURE 63.1 By inflating during diastole, the intraaortic balloon pump increases coronary perfusion. Deflation of the balloon at the onset of systole decreases myocardial wall stress and oxygen demand and increases cardiac output. Courtesy of Datascope Corp.



(A) One completed cardiac cycle
(B) Unassisted aortic end-diastolic pressure
(C) Unassisted systolic pressure
(D) Diastolic augmentation
(E) Assisted aortic end-diastolic pressure
(F) Reduced systolic pressure

FIGURE 63.2 Proper timing of balloon function occurs when the balloon inflates on the downslope of the systolic pressure waveform and deflates before the onset of the next systolic waveform. The intraaortic balloon pump inflation in diastole increases diastolic pressure to improve coronary artery perfusion and to increase mean arterial pressure. In addition, aortic end-diastolic pressure is reduced when the balloon deflates in end-diastole to lower afterload and myocardial oxygen demand than through increased coronary perfusion. Courtesy of Datascope Corp.

2. Doppler flow studies have demonstrated that peak coronary flow velocity is increased with IABP support, but there is no improvement in coronary flow past critical coronary stenoses (unless the obstructions are first relieved with percutaneous revascularization). Also, collateral coronary flow does not increase with IABP support. Thus, with severe, nonrevascularized coronary disease, IABP relieves ischemia more through decreased left ventricular wall stress and decreased myocardial oxygen demand than through increased coronary perfusion.

V. INSERTION TECHNIQUE/PATIENT EVALUATION AND MONITORING

A. Balloon sizing is based on the patient's height. Four common balloon sizes are available: 50 cm^3 for patients taller than 6′, 40 cm^3 for patients between 5′ 4″ and 6′, 34 cm^3 for patients between 5′ and 5′ 4″, and 25 cm^3 for patients shorter than 5′. Balloon length and diameter increase with each larger size. The 40-cm^3 balloon is most commonly used, whereas the 50-cm^3 balloon is rarely used because the balloon is too long for most patients.

B. Evaluating peripheral vasculature. Proximal and distal pulses are assessed in both legs, and ankle/brachial indices can also be determined. The leg with the strongest pulses and/or the best ankle/brachial index score should be chosen for access.

C. Insertion technique

1. **Gaining access/sheath insertion.** After careful evaluation of clotting parameters and peripheral vasculature, the leg chosen for access should be shaved and prepped with antiseptic solution from the umbilicus to the knee. After infiltration with a local anesthetic, the femoral artery is accessed with an 18G introducer needle, and a 0.030″ × 145 cm J-tipped guidewire is advanced through the needle to the aortic arch under **fluoroscopic guidance**. A smaller 5F dilator

is first inserted over the wire to dilate the subcutaneous tissues. Then the sheath, loaded with a larger dilator that is 1F smaller than the sheath, is inserted over the guidewire. The guidewire should be left in place in the aortic arch.

2. **Balloon insertion.** The two commonly available balloon catheter sizes are 8F and 9.5F. A 7F- and 7.5F-sized catheter and sheath have become available but pertinent data regarding their use are still limited. The prewrapped balloon is inserted over the guidewire and is advanced until the proximal tip is positioned 1 cm below the left subclavian artery and 2 cm above the carina. The guidewire is then removed, and the distal tip of the balloon is visualized under fluoroscopic guidance to ensure that it is out of the sheath.
3. **Insertion without fluoroscopy guidance.** Fluoroscopic guidance is recommended for placement of the IABP. However, if fluoroscopy is unavailable, the distance from the angle of Louis to the umbilicus and then to the common femoral artery insertion site is measured to determine the approximate distance the balloon must be advanced.
4. **Surgical insertion**
   a. Occasionally, balloon pumps can be inserted surgically **by directly exposing the common femoral artery** or by suturing a 6- to 12-mm prosthetic graft end-to-side to the femoral artery to provide a conduit for the catheter. Distal limb ischemia is reduced with these methods, but grafts must be removed surgically, and the femoral artery has to be directly repaired after IABP removal when surgical access is used.
   b. Balloon pumps can also be directly inserted into the ascending or thoracic aorta **during open heart surgery**.
5. **Difficulties with access.** If passage of the guidewire is difficult, a 5F sheath can be placed in the common femoral artery. Then the contrast medium can be injected through the sheath or through a pigtail catheter to define the iliofemoral anatomy.
   a. If severe iliac or femoral artery obstruction is demonstrated, the balloon can be inserted on the contralateral side, the obstructions can be treated with peripheral angioplasty and stenting before balloon insertion, or the procedure can be aborted.
   b. If severe obstruction or aneurysmal dilatation of the distal abdominal aorta is demonstrated, the balloon catheter should not be inserted.
6. **Sheathless insertion.** In patients with peripheral vascular disease, the balloon catheter can be inserted without a sheath, directly over the guidewire, after appropriate dilatation of the subcutaneous tissue. Retrospective reviews have shown that lower limb ischemia is reduced with this technique. However, a sheathless balloon catheter cannot be repositioned once placed and has a greater potential to become infected from skin flora than a sheathed balloon catheter. Smaller balloon catheters and stiffer guidewires are being developed to aid in sheathless insertion.
7. **Tortuous iliofemoral vessels**
   a. When the tortuosity of the iliofemoral vessels prevents passage of the 0.030" guidewire supplied in the IABP kit, a 0.035" Wholey wire can be used to traverse the tortuous vessels. A long (45 or 60 cm) flexible sheath is then placed in the descending aorta past the tortuous iliac vessels.
   b. A superstiff 0.038" wire is then exchanged through the sheath. The 11" IABP sheath is inserted over the superstiff wire, which provides more support for placement of the less flexible IABP sheath. The superstiff wire is then exchanged for the 0.030" standard IABP wire through the sheath, and the balloon catheter is inserted over this wire into the proper position.

D. Initial setup

1. After insertion, the helium gas line of the balloon catheter is connected to the IABP console, and the central lumen of the catheter is attached to an arterial pressure monitor device on the console with pressure tubing, after allowing the line to backbleed.
2. Balloon autoinflation is initiated from the console, the arterial line attached to the central lumen of the catheter is flushed, and the initial IABP inflation is at 1:2 (per cardiac cycle) while the timing is adjusted (Section **VI**).

3. Balloon inflation is then observed under fluoroscopic guidance to ensure that the balloon is completely out of the sheath. If the balloon is kinked or is not inflating fully, it should be repositioned by pulling the sheath back a few inches or it should be manually inflated.
4. Finally, the sheath and balloon catheter are sutured in place, dressed using sterile technique, and the inflation is changed to 1:1.

E. Monitoring

1. **A chest x-ray film is immediately obtained** after IABP placement to verify the catheter position, even if fluoroscopic guidance has been used.
2. **Intravenous heparin** is started once the balloon and sheath are secure to maintain the activated partial thromboplastin time at 50 to 70 seconds.
3. **Daily chest x-ray films** are recommended while the IABP is in place so that the physician can check the position of the catheter. If the catheter needs to be repositioned, it can be manipulated through a sterile plastic sleeve placed over the part of the catheter that extrudes from the sheath while the balloon is placed on standby mode.
4. Daily hemoglobin and platelet counts are followed to monitor for hemolysis and thrombocytopenia.

F. Care of the patient with an IABP

1. All patients with an IABP in place should be closely observed in a **critical care setting. The patient should be kept supine in bed,** and peripheral pulses should be regularly evaluated for **possible limb ischemia** (dorsalis pedis/posterior tibial pulses should be checked every 6 to 8 hours with use of Doppler if necessary).
2. **The accessed leg should be secured** to prevent inadvertent or involuntary movement by the patient.
3. **Use of prophylactic antibiotics is not recommended** while the IABP is in place.
4. **Blood samples generally should not be obtained from the central lumen of the IABP** because the risk of clotting the lumen is increased, and air or small thrombi can be injected through the central lumen during flushing of the tubing after blood withdrawal.

VI. BALLOON PUMP TRIGGERING AND TIMING

A. Triggering. Balloon pump inflation can be triggered by the surface electrocardiogram (ECG), the arterial pressure waveform, a paced rhythm, or an internal asynchronous mode.

1. Preferably, the surface ECG is used to trigger IABP inflation, which is appropriately delayed after the R wave to begin at the time in the cardiac cycle when the aortic valve closes (dicrotic notch).
2. If the IABP fails to trigger properly from the surface ECG, change the lead being evaluated, check surface electrode placement, or increase the QRS gain on the console monitor.
3. For patients with poor surface electrocardiographic tracings, the balloon can be triggered from the central arterial pressure waveform. Pacing spikes should be used to trigger the balloon in patients who are 100% paced.
4. When the patient is arresting or when the other triggering mechanisms are not working correctly, an internal asynchronous mode can be used to trigger the balloon to inflate at a regular interval.

B. Timing. Ideal balloon pump timing occurs when the balloon inflates on the downslope of the systolic pressure waveform before the dicrotic notch and deflates before the onset of the next systolic pressure waveform (see Fig. 63.2). Timing is usually adjusted manually, but it can be automatically adjusted by internal algorithms programmed in the console.

1. **Early inflation** (see Fig. 63.3) is defined as inflation of the IABP before aortic valve closure (dicrotic notch).

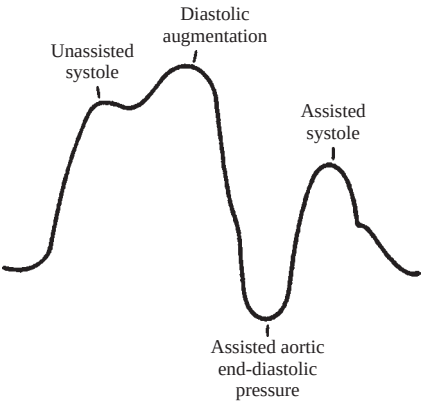


FIGURE 63.3 With early balloon inflation, the aortic valve closes prematurely, and left ventricular wall stress and myocardial oxygen demand are increased. Courtesy of Datascope Corp.

   a. There is premature closure of the aortic valve with increased afterload, left ventricular wall stress, and myocardial oxygen demand. Stroke volume is decreased.
   b. It is corrected by delaying inflation until after aortic valve closure.
2. **Late inflation** (see Fig. 63.4) is defined as inflation of the IABP well after closure of the aortic valve.
   a. There is diminished diastolic pressure augmentation and suboptimal coronary perfusion.
   b. It is corrected by adjusting inflation to occur just before the dicrotic notch.
3. **Early deflation** (see Fig. 63.5) is defined as deflation of the IABP before isovolumic left ventricular contraction.
   a. There is suboptimal diastolic augmentation, coronary perfusion, and afterload reduction, which then lead to increased myocardial oxygen demand.
   b. It is corrected by delaying deflation until just before the onset of systole.
4. **Late deflation** (see Fig. 63.6) is defined as deflation of the IABP after the onset of systole.
   a. There is impaired left ventricular emptying, increased afterload and preload, increased myocardial oxygen consumption, and reduced stroke volume.
   b. It is corrected by adjusting deflation to occur just before the onset of systole.

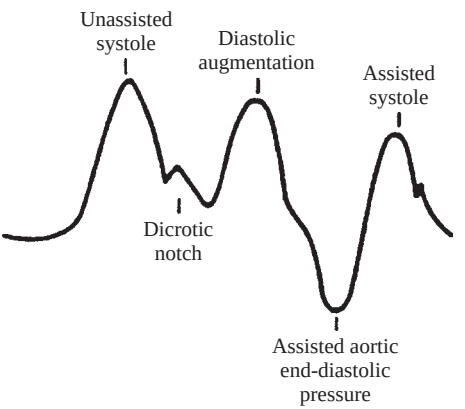


FIGURE 63.4 With late balloon inflation, there is suboptimal augmentation of diastolic aortic pressure and coronary perfusion. Courtesy of Datascope Corp.

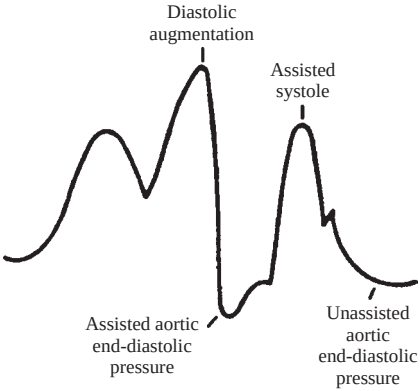


FIGURE 63.5 With early balloon deflation, there is suboptimal augmentation of coronary perfusion and afterload reduction. Courtesy of Datascope Corp.

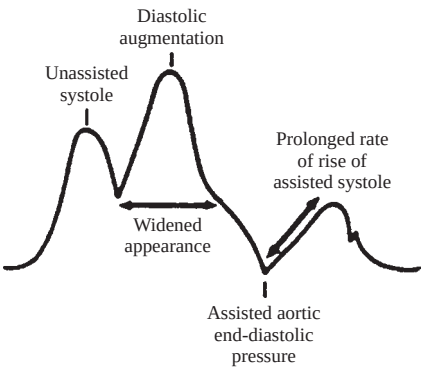


FIGURE 63.6 With late balloon deflation, there is no afterload reduction, and myocardial oxygen consumption is increased. Courtesy of Datascope Corp.

5. **During arrhythmias.** Adequate augmentation with the balloon pump is difficult to achieve with tachyarrhythmias. When heart rate approaches 150 beats/min, there is insufficient time for the helium gas to shuttle in and out of the balloon with each inflation. With rapid atrial fibrillation, variable systolic pressure waveforms caused by inadequate left ventricular filling and rapid pulse rates make augmentation especially difficult. Adjusting balloon inflation to 1:2 can sometimes improve augmentation with tachyarrhythmias.

C. Troubleshooting. In the situation of **console alarms**, there may be the following problems:

1. **Loose connections** in the gas drive line or arterial pressure tubing.
2. **Blood in the tubing.** If blood is detected in the gas drive lumen, put the balloon catheter on standby and evaluate for balloon rupture or entrapment (Section **VII**).
3. **Poor augmentation**
   - **a.** Adjust the timing.
   - **b.** Change the triggering mechanism (Section **VI.A**).
   - **c.** Evaluate inflation/deflation of the balloon and the catheter position under fluoroscopic guidance to detect balloon kinking.
   - **d.** If the IABP is thought to be positioned in a false lumen of the aorta because of poor augmentation, 10 to 20 mL of contrast media can be injected through the central lumen of the catheter to evaluate the position under fluoroscopy.

VII. COMPLICATIONS

A. Vascular. Common vascular complications of IABP include limb ischemia, hematoma around the access site, and bleeding from the access site. Rates of vascular complications have varied in the literature from 5% to 20%, depending on the patient populations studied. However, a contemporary series showed the incidence of limb ischemia to be 2.3% and incidence of major limb ischemia to be 0.5% in 5,495 consecutive patients with IABP. Diabetes, female sex, preexisting peripheral vascular disease, history of smoking, and catheter size are all independent risk factors that are strongly associated with the development of ischemic vascular complications from IABP use.

1. **Ischemia**
   - **a.** If ischemia develops in the accessed leg, the balloon catheter and sheath should be removed and hemostasis obtained at the access site.
   - **b.** If ischemia is still present, consultation with a vascular surgeon is indicated. Surgical intervention for ischemic limbs caused by IABP catheters includes thrombectomy, surgical bypass grafting, and, rarely, amputation.
2. **Bleeding**
   - **a.** Bleeding around the access site develops in 1% to 5% of patients treated with IABP. It is usually controlled with prolonged manual pressure at the access site.
   - **b.** Hematomas that develop at the access site may require transfusion of blood products and, occasionally, direct arterial repair.
   - **c.** Pseudoaneurysms after IABP removal are rare but often require surgical correction.

B. Infection. Infectious complications are rare and include access site infections, catheter infections, and bacteremia. No studies have addressed how frequently balloon catheters become infected and how frequently they need to be changed to limit infectious complications.

C. Balloon rupture should be considered if blood is detected in the gas drive line lumen or if balloon augmentation ceases.

1. Small leaks in the balloon can develop from damage to the balloon surface caused by inflation against calcified aortic plaques. Rates of balloon leak can be as high as 4.2%.
2. *Potential complications for the patient include helium gas embolism and balloon entrapment when blood leaks into the balloon, clots, and prevents adequate deflation of the balloon for removal.*
3. Use of standard-sized balloons (40 cm^3) in patients shorter than 170 cm (5'6") is associated with balloon rupture. This is thought to be caused by damage to the balloon when inflation occurs in the smaller and more plaque-laden distal abdominal aorta. Thus, a 34-cm^3 balloon should be used in patients shorter than 170 cm.

D. Balloon entrapment occurs when balloon rupture causes a clot to form within the balloon, preventing deflation during removal. When resistance is encountered during balloon catheter removal, balloon entrapment should be considered and fluoroscopy immediately carried out to assess the position of the retained catheter.

1. Management of balloon entrapment usually involves surgical extraction because forceful removal of a partially deflated balloon catheter could cause serious vascular injury.
2. Case reports have documented successful lysis of clots within the balloon by instilling thrombolytic agents through the gas drive lumen of the IABP catheter. The balloons were deflated after clot lysis and the catheters successfully removed.

E. Red blood cell and platelet destruction. Due to the shear forces of the balloon catheter, hemolytic anemia and mild thrombocytopenia can occur during IABP support. Daily hemoglobin and platelet values should be checked. Platelet counts < 50,000 are unlikely to be caused by the IABP and alternative causes should be sought.

F. Other complications. Rare complications of IABP use include acute renal failure, mesenteric ischemia, and paraplegia from plaque embolization leading to

thrombosis of the renal, mesenteric, or spinal arteries, respectively. Aortic dissections and aortic perforations, though rare, usually occur during insertion.

VIII. REMOVING THE IABP CATHETER

A. Weaning. Whether IABC needs to be weaned before the balloon catheter is removed depends on multiple factors, including the duration of the support, the hemodynamic status of the patient, and left ventricular function.

1. The usual practice is to change IABP inflation to 1:2 for a few hours and then to 1:3 with close hemodynamic monitoring.
2. At the same time, intravenous inotropic drugs are used to simulate the IABP's hemodynamic effects. Dobutamine or milrinone is used to maintain an adequate cardiac output, and nitroprusside is used to replace the afterload reduction provided by the IABP.
3. If weaning is tolerated hemodynamically, the balloon can then be removed.

B. Withdrawal of the balloon catheter and sheath

1. Intravenous heparin should be discontinued for at least 4 hours before removal of the catheter. The activated coagulation time is checked until it falls below 150 seconds or partial thromboplastin time normalized.
2. Percutaneously placed catheters can then be removed manually, but surgically placed catheters must be removed with direct arterial repair.
3. To begin removal of the balloon catheter, the balloon is changed to standby and the gas drive line is disconnected. Then, the balloon catheter is pulled back until resistance is met, indicating that the catheter is in the sheath. The sheath and the balloon catheter are then withdrawn together as a unit, but excessive force should never be applied.

C. Hemostasis

1. After the balloon is withdrawn, the puncture site is allowed to backbleed for 1 to 2 seconds while pressure is held distal to the puncture site to evacuate proximal thrombi.
2. Then manual pressure is applied proximal to the puncture site, and backbleeding is repeated to evacuate distal thrombi.
3. Manual pressure is then applied for 30 to 45 minutes over the puncture site until adequate hemostasis is achieved.
4. A compressive dressing is applied thereafter.

D. Monitoring during IABP removal

1. During the application of manual pressure to the puncture site, the distal pulses in the leg should be continually assessed, and pressure should be adjusted to maintain adequate distal perfusion.
2. The patient should be confined to strict bed rest for 6 to 12 hours after the catheter and sheath have been removed, and the leg should be periodically assessed for signs of ischemia.

IX. CHANGING THE IABP CATHETER

A. Reasons for changing the IABP

1. When patients require prolonged IABP support, some clinicians change the catheter and sheath every 4 to 5 days to prevent infectious complications. However, there is no consensus on using this approach.
2. Other reasons for changing the IABP include balloon entrapment and rupture, kinking of the catheter or sheath (which prevents adequate balloon inflation), or fever (which may indicate bacteremia from a line infection).

B. Simultaneous change. In patients who are critically dependent on IABP support and who need the IABP changed for one of the above reasons, the catheter and sheath must be changed simultaneously with placement of a new IABP.

1. **Contralateral femoral artery**
   a. When the contralateral femoral artery can be used, it is accessed and the sheath is placed. A guidewire is then positioned in the aortic arch while the old balloon is on standby.
   b. Counterpulsation is reinitiated, and the new balloon catheter is prepared and readied for use.
   c. The old balloon is then deflated and quickly withdrawn, while the new balloon catheter is placed over the guidewire from the contralateral femoral artery. This technique limits the period without IABP support during the change to < 30 seconds.
   d. Anticoagulation can safely be discontinued before and after a simultaneous change to aid in achieving hemostasis at the old access site.
2. **Same femoral artery**
   a. When the contralateral femoral artery cannot be used, the old catheter and sheath must be removed and changed under direct vision.
   b. The accessed femoral artery is exposed surgically, and a purse-string suture is placed around the preexisting sheath.
   c. The old sheath is then removed, and tension is applied to the suture for hemostasis.
      (1) The small dilator in the catheter package is directly inserted into the previous puncture site, and the guidewire is advanced to the aortic arch through it.
      (2) The sheath is advanced over the guidewire into the proper position, and the purse-string suture is tied down.
      (3) The balloon catheter is then inserted via the sheath, and the soft tissue and skin incision are closed with sutures.
   d. In emergency situations, the preexisting sheath can be rewired and a new balloon catheter inserted through the old sheath. However, infectious complications are high with this approach.

ACKNOWLEDGMENTS: *The author thanks Dr. Apur R. Kamdar and Dr. Matthew T. Roe for their contributions to earlier editions of this chapter.*

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CHAPTER 64

Andrew N. Rassi

Left Heart Catheterization

I. INTRODUCTION. In 1958, Dr. Mason Sones and colleagues at the Cleveland Clinic performed the first selective coronary arteriographic procedure. Since then, left heart catheterization (LHC) has become an important tool in diagnostic cardiology. More than 1.5 million cardiac catheterizations are performed yearly in the United States. Despite the advent of other imaging modalities, coronary arteriography remains the clinical gold standard for determining the presence of significant coronary artery disease (CAD).

LHC is an invasive procedure with serious potential risks. To be competent in LHC, a cardiologist-in-training must perform at least 300 catheterizations, serving as primary operator on 200. During training, the operator must be supervised by a cardiologist who is already competent in the procedure. Because there is the ability to treat a lesion with percutaneous intervention at the same time as the diagnostic angiogram, it is important to have a plan regarding how to use the information obtained.

II. INDICATIONS. The American College of Cardiology and the American Heart Association (ACC/AHA) have categorized reasonable indications for LHC as class I, when there is consensus that LHC is indicated, or class II, when there is no consensus that LHC is indicated, but nonetheless the procedure is frequently performed (see Table 64.1).

A. Acute myocardial infarction (MI). LHC is given a class I indication for routine use in acute MI, particularly in those who will likely undergo primary percutaneous cardiac intervention, those in cardiogenic shock or with other evidence of hemodynamic instability, or those with mechanical complications who are likely to undergo surgical repair. It can be used with the goal of performing primary angioplasty in patients with acute ST-segment elevation MI. There is evidence of the benefit of an early invasive strategy in stable patients with non–ST-segment elevation MI. In patients with non–ST-segment elevation MI, an early invasive strategy has received a class I indication in the presence of the following risk features: elevated cardiac troponins, new or presumed new ST-segment depression, heart failure (HF), depressed ventricular function, hemodynamic instability, sustained ventricular tachycardia, previous bypass surgery, and previous coronary intervention in the last 6 months. Patients with persistent pain or unresolved electrocardiographic changes after thrombolytic therapy are also class I candidates for LHC. Routine LHC soon after thrombolytic therapy in a patient who appears to have clinically reperfused is a class IIb indication.

B. Unstable angina. LHC is given a class I indication in the patient with refractory unstable angina that cannot be controlled by medical therapy. Its role in unstable angina that can be medically controlled is controversial.

C. Chronic stable angina. LHC is given a class I indication for purposes of revascularization in chronic stable angina for patients whose angina is poorly controlled by medicines or who are intolerant of antianginal medications.

D. Abnormal stress test. A stress test that is positive at a low work load (6.5 metabolic equivalents of oxygen consumption) or that is classified as high risk is a class I indication for LHC. An ST depression of 2 mm, especially in multiple leads or persisting into recovery 6 minutes, an ST elevation of 2 mm in leads without Q waves, a drop in blood pressure of > 10 mm Hg with exercise, or development of ventricular tachycardia with exercise constitutes a high-risk stress test. A high-risk stress test on a concomitant imaging modality showing left ventricle dilatation, a drop in ejection

TABLE 64.1 Indications and Contraindications to Left Heart Catheterization

Indications[a]	Contraindications[a]
- Acute myocardial infarction	- Active bleeding
- Unstable angina	- Coagulopathy
- Chronic stable angina, uncontrolled by medications	- Acute or chronic renal failure
- Abnormal stress test	- Active infection
- Ventricular arrhythmias	- Severe anemia
- Left ventricular dysfunction	- Electrolyte abnormalities
- Valvular heart disease	- Inability to lie supine (i.e., decompensated heart failure)
- Preoperative coronary assessment for cardiovascular surgery	- Malignant hypertension
- Preoperative risk assessment for noncardiovascular surgery	- Extensive comorbidities—risk of revascularization likely outweighs the benefit
- Periodic follow-up after cardiac transplantation	- Patient unable to cooperate or does not desire procedure

[a]See text for full details.

fraction of 10%, or multiple areas of ischemia is a class I indication for catheterization. These indications hold true even if the patient is asymptomatic. Positive stress tests without high-risk criteria are class II indications for LHC.

E. Ventricular arrhythmia. A history of sustained polymorphic ventricular tachycardia, without obvious metabolic cause, is considered a class I indication for LHC.

F. Left ventricular dysfunction. LHC can provide an estimate of left ventricular function and regional wall motion. Left ventricular dysfunction of unknown cause, with an ejection fraction of < 40%, is a class I indication for LHC to rule out CAD.

G. Valvular heart disease. LHC can be performed to assess the severity of outflow tract obstruction (aortic stenosis and hypertrophic obstructive cardiomyopathy). It can also help quantify aortic and mitral regurgitation (MR). With the advancements in Doppler and color echocardiography, the major role of cardiac catheterization is to provide confirmatory data and to rule out CAD as part of the operative workup. LHC has a class I indication in patients requiring valve surgery who are at risk for CAD. Most centers perform LHC before valve surgery in those older than 50 years to rule out clinically silent CAD. Younger patients may require LHC if cardiac risk factors are present or if coronary reimplantation may be needed as part of the surgery (homograft implantation, ascending aorta replacement, or Ross procedure).

H. Preoperative. LHC is performed before ascending aortic aneurysm surgery or some cases of ascending aortic dissection surgery. It is also performed on patients with congenital heart disease to evaluate lesions such as ventricular septal defects and to rule out concomitant coronary anomalies or atherosclerotic disease, if symptomatic. In patients with angina or a positive stress test who are to undergo high-risk surgery, LHC is given a class I indication.

III. CONTRAINDICATIONS.

The following are relative contraindications to LHC (see Table 64.1).

A. Coagulopathy. Coagulopathy must be corrected before elective catheterization. The usual recommendation for patients on warfarin (Coumadin) is to discontinue it 72 hours before the procedure. In elective cases, an international normalized ratio of < 1.8 is a cutoff that is often used. If the patient is heparinized, this is usually stopped 2 hours before the procedure. A platelet count of < 50,000 substantially increases the risk of bleeding. After thrombolytic therapy, bleeding is more likely and elective catheterization is best deferred. However, if the indication for the procedure is urgent, it is possible to proceed with caution, with blood products kept ready for support as needed. Antecedent glycoprotein IIb/IIIa inhibitor therapy poses much less of a risk. Body habitus is also a factor in deciding what level of anticoagulation is acceptable before a catheterization. Obesity increases the chances of bleeding (if multiple attempts at access are needed) and makes bleeding more difficult to detect. Finally, the availability of closure devices makes it possible to seal the artery after the procedure.

B. Renal failure. A rising creatinine is generally a reason to defer elective cardiac catheterization. In a patient on dialysis, catheterization is generally timed immediately after the dialysis. In a patient with stable but moderately severe renal failure, catheterization may be performed with an awareness of the increased risk of needing dialysis.

C. Dye allergy. A history of allergy to previous contrast administration should be sought. Although an allergy to shellfish and seafood has been linked to contrast reactions in some studies, other studies dispute such a relationship. Individuals with a history of asthma or atopy are at increased risk of developing contrast allergies. Treatment of patients with a history of dye allergy is described in Section **IV.F.2**.

D. Infection. Active infection is a reason to defer elective cardiac catheterization. Local skin infection at the site of the potential puncture is also undesirable. Fungal infection in groin creases should be controlled before elective cardiac catheterization by the femoral approach; this is a particular concern in obese patients. Alternatively, LHC may be performed through a brachial or radial approach in patients with fungal infection in groin creases.

E. **Laboratory abnormalities.** Severe anemia, hypokalemia, or hyperkalemia should be corrected before the elective procedure. In the presence of digitalis toxicity, elective catheterization is best deferred.

F. **Decompensated HF.** Severe HF raises the risks of cardiac catheterization. It is best to optimize medical therapy before elective catheterization. At a minimum, the patient should be able to lie supine without respiratory insufficiency.

G. **Severe peripheral vascular disease.** Symptoms of claudication warrant careful assessment of pulses. An inadequate lower extremity pulse favors an upper extremity approach. A synthetic vascular graft that is older than 6 months is not a strict contraindication to catheterization, but special care should be taken in gaining access as well as in obtaining hemostasis. However, the risk of embolization of friable atheroma or thrombus is heightened, and this risk increases with the age of the graft.

H. **Abdominal aortic aneurysm (AAA).** Presence of an AAA requires special care during a cardiac catheterization (see subsequent text). An arm approach obviates the need to cross the AAA altogether.

I. **Uncontrolled severe hypertension.** Blood pressure should be controlled before elective cardiac catheterization to maximize the safety of the procedure. In particular, severe bleeding can occur at the access site after sheath removal if the patient is very hypertensive, especially if above 180/100 mm Hg.

IV. PATIENT PREPARATION

A. **Informed consent.** A detailed discussion with the patient (and family) should outline the indication for the procedure, as well as the alternative treatment and diagnostic options. Specific mention of the serious risks of complications, such as death, MI, stroke, arrhythmia, bleeding, radiation exposure, and kidney failure, must be made (see complications in subsequent text). The possible need for emergency coronary artery bypass grafting (CABG) should be noted. The risk of serious complications should be individualized. Informed consent should be documented in the medical record.

B. **Precatheterization assessment.** Before proceeding with an LHC, a detailed clinical assessment is necessary, including a comprehensive history and physical examination. All peripheral pulses should be palpated, and arterial bruits, if any, should be documented before the catheterization as a baseline for future reference. In addition, laboratory data, including a comprehensive metabolic panel, complete blood count, and coagulation studies, should be obtained for all patients. Abnormalities in the laboratory parameters, if any, should be addressed before proceeding with LHC.

C. **Medications.** If percutaneous coronary intervention is likely, pretreatment with aspirin 325 mg by mouth (PO) should be given before the catheterization, as it has been shown to improve outcomes with angioplasty. If stenting is a strong possibility, clopidogrel 300 mg PO should be given as a loading dose before the procedure. Metformin should be stopped at the time of the procedure, although the risk of lactic acidosis is extremely low in a patient with normal creatinine.

D. **Education.** Patients should be warned that they might feel a hot sensation lasting about 30 seconds due to the injection of ionic contrast dye. Some patients may also feel nauseated. Patients should be specifically instructed to cough when they hear anyone in the room say "cough." This maneuver accelerates resolution of dye-induced bradycardia.

E. **Equipment.** Before performing a cardiac catheterization, it is essential to ensure that the monitoring equipment is fully functional. Continuous electrocardiographic monitoring of heart rate (HR), rhythm, and ST segments, an automated blood pressure cuff, and continuous pulse oximetry are mandatory. Resuscitation equipment should be tested and ready. In particular, defibrillators and intubation trays must be available next to the patient. If a long procedure is anticipated, many operators prefer placement of a Foley or Texas urinary catheter. Before actually beginning the procedure, the fluoroscopy and cine equipment should be tested by taking a picture

of the patient's nameplate. The usual frame rate of cine film is set at 30 frames/s; 60 frames/s can be useful for patients with tachycardia. In thin individuals who are bradycardic (< 60 beats/min), the frame rate can be lowered to 15 frames/s. In addition, the table should move freely to the level of the patient's groin.

F. Contrast dye

1. **Choice of contrast.** Ionic contrast dye was historically used during most cardiac catheterizations. In most circumstances, low-osmolar nonionic dye, which is now only slightly more expensive, can be used. The literature supports that nonionic dye produces less left ventricular dysfunction, bradycardia, and hypotension, as well as less nausea and emesis. Thus, it is useful in cases of suspected left main stenosis, severe left ventricular dysfunction, and severe aortic stenosis. Other indications for nonionic dye are severe renal dysfunction and a reported allergy to contrast dye. However, no reduction in acute renal failure or anaphylactoid reaction has been conclusively demonstrated with the use of nonionic dye. There is evidence that nonionic contrast is more thrombogenic than ionic contrast. Therefore, it should be used carefully in patients with acute coronary syndromes. Whenever nonionic contrast is used, 5 IU of heparin per cubic centimeter of contrast should be added.
2. **Dye allergy**
   a. **Premedication.** If a patient reports an allergy to contrast dye or a history of prior anaphylactoid reaction, it is customary to premedicate with steroids and antihistamines. Protocols vary widely. Common regimens include 50 mg of oral prednisone administered 13, 7, and 1 hour (q6h) prior to the procedure along with diphenhydramine 50 mg IV or orally 1 hour prior to the procedure. Intravenous steroids can be substituted in place of oral steroids 1 hour prior to the procedure (hydrocortisone 100 mg IV once). With a history of possible life-threatening dye allergies, it is also prudent to administer small quantities of dye (1 mL) and observe the patient for a few minutes before proceeding.
   b. **Treatment.** If a patient develops any sign of an allergic reaction, treatment should be prompt. If signs such as hives or rashes develop, treatment with diphenhydramine is usually sufficient. Hydrocortisone is also often given, though its effects may not manifest for several hours. In cases of oropharyngeal edema, bronchospasm, or hypotension, 0.3 mL of 1:1,000 epinephrine should be administered subcutaneously. With refractory symptoms, 10 μg/min of intravenous epinephrine can be administered until symptoms abate.
   c. **Latex allergy** has become increasingly recognized as a clinical entity, especially in patients who are health-care workers. True latex allergy can include urticaria, angioedema, laryngospasm, bronchospasm, and anaphylaxis. If a patient describes a possible latex allergy, allergy testing, including skin testing and rapid antigen serum testing, should be considered. Patients with latex allergy should be scheduled as the first case of the day to avoid latex dust from previous procedures. Written protocols outlining materials to be avoided should be strictly followed. A cart with latex-free items should be made available. The sheath is a source of latex exposure. Therefore, a sheathless approach involving catheter exchanges over a wire is preferred.
   d. **Sedation.** Commonly used sedatives include the benzodiazepines midazolam 1 to 2 mg IV or lorazepam 1 to 2 mg IV. Some operators use fentanyl 25 mg IV or morphine 1 to 2 mg IV for pain relief. Diphenhydramine 25 or 50 mg IV can also be used for sedation. Continuous pulse oximetry should be followed to ensure that sedation has not been excessive.
   e. **Radiation safety.** Radiation poses a threat to laboratory personnel; therefore, every effort should be made to reduce exposure. The source is scatter from the x-ray beam originating under the table. Lead aprons (with at least 0.5-mm thick lead lining) and thyroid collars are mandatory to minimize

radiation exposure. Leaded eyeglasses should also be considered. In addition, radiation badges are worn inside the lead apron and outside the thyroid collar to monitor cumulative radiation exposure. A leaded acrylic shield should be used between the patient and the operator closest to the patient. Standing further from the table also reduces radiation exposure by the inverse square of the distance. A number of additional steps can be taken to minimize radiation to both the operator and the patient. Fluoroscopy and, in particular, cine time should be minimized. The image intensifier should be positioned as close as possible to the patient to reduce radiation scatter. To decrease radiation, higher magnification should be used judiciously. "Coning down" on a region of interest with the use of collimators can also reduce the amount of radiation, as can the use of lung field collimators. Right anterior oblique (RAO) views produce less radiation scatter for the operator than left anterior oblique (LAO) views. Higher cine frame rates increase radiation exposure; use of 15 or 30 frames/s produces less radiation exposure than use of 60 frames/s. In the rare situation that a pregnant patient needs catheterization, a lead apron should be used. This precaution should also be taken for premenopausal women.

V. ACCESS SITE

A. Femoral artery. Femoral artery cannulation is the most common form of arterial access for cardiac catheterization (see Fig. 64.1). The patient is first positioned appropriately, with the knees about 12" apart. The table should allow enough movement to perform fluoroscopy of the groin. Anatomic landmarks are then identified. The inguinal ligament is located. Then the femoral pulse is palpated approximately 2 cm (finger breadths) below the inguinal ligament; this marks the site of arterial access.

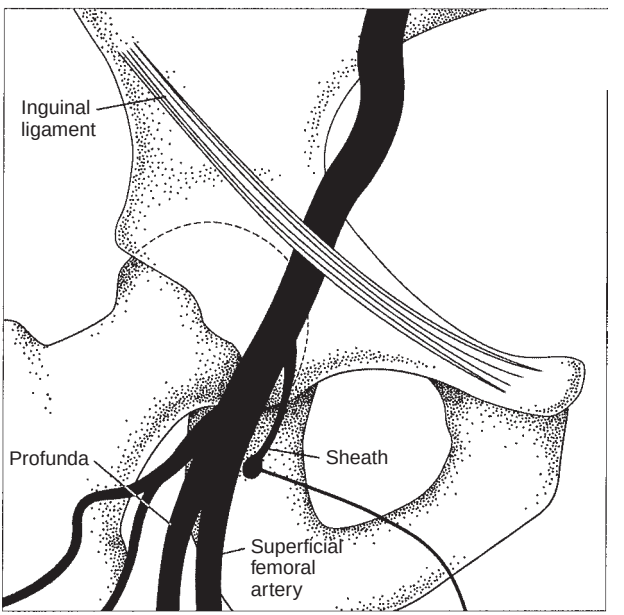

FIGURE 64.1 Landmarks for right femoral artery puncture.

Alternatively, fluoroscopy can be used to locate the femoral head. The entry point on the skin is located over the inferior border of the femoral head. Care must be taken not to enter the artery above the inguinal ligament, as this increases the chance of retroperitoneal bleeding. Arterial entry that is too low must also be avoided, as this can lead to pseudoaneurysm or arteriovenous fistula formation. Once the site of entry has been identified (and marked, if so desired), the area is cleaned with povidone iodine (Betadine) and surgically draped. Local anesthesia is given slowly (it hurts less when delivered slowly) while the clinician monitors the HR and watches for signs of a vagal reaction (nausea, lightheadedness, and yawning). The usual choice is procaine 1%. A subcutaneous wheal is raised with about 3 mL using a 25G needle. Next, an additional 6 to 10 mL is delivered to the deeper tissues with a 22G needle. In patients who are allergic to ester-type anesthetics, lidocaine 2% can be used. Once the site is anesthetized, an 18G Cook needle is inserted into the artery. Upon nearing the artery, a side-to-side motion of the needle indicates a position either medial or lateral to the artery. Up-and-down motion indicates correct positioning. In addition, when the needle is above the artery, it transmits the arterial pulsation to the fingertips. Once brisk arterial blood return is established, a 0.035″ J-tipped 45-cm guidewire is inserted, the needle is withdrawn, and an arterial sheath with a dilator is placed over the wire. Then the wire and dilator are removed. The sheath is then flushed with saline. A 5F or 6F sheath is generally used for diagnostic catheterizations in the United States, though 4F sheaths are often used in Europe. An 8F sheath is used for acute cases or planned interventions. A 5F sheath is preferred over larger sheaths for patients with peripheral vascular disease.

B. Brachial and radial approach. In certain patients, it may be desirable to perform the catheterization by a brachial or radial route, for which specialized equipment is available. Percutaneous brachial or radial access is similar to the femoral approach described above. In addition, a surgical cut-down was historically performed to enter the brachial arteries under direct visualization, though surgical cut-downs are rarely performed in the modern era. For a left brachial approach, Judkins catheters are adequate. For a right brachial approach, Amplatz or multipurpose catheters are used, although it may be difficult to engage a left internal mammary artery (LIMA) graft from the right arm; a specially designed brachial internal mammary artery catheter is available for the latter purpose. In rare circumstances, an axillary approach can be used, though the rate of neurovascular complications is higher.

Increasingly, operators now use the **radial approach** as the default approach. The radial approach has been associated with fewer bleeding complications when compared with the femoral approach and does not require a long period of immobilization of the patient afterward. It is thus preferred by patients. Radiation exposure data have been conflicting and can be influenced by multiple factors including the familiarity of the operator with the radial approach. To obtain vascular access from the radial site, the Allen test should be performed prior to radial artery catheterization. The patient's arm is abducted at a 70° angle and the wrist is hyperextended. The site is prepped and draped in a manner similar to the femoral and brachial access sites. Local anesthetic is injected. The radial site should be roughly 1 cm above the styloid process. Either an 18G needle or a micropuncture needle (22G) is inserted at 30° to 45° into the radial artery. A sheath is advanced in the same manner as described above using the Seldinger technique. Local infusions of nitroglycerin and/or verapamil can be injected to decrease radial artery spasm. Heparin 3,000 to 5,000 IU should be considered to avoid sheath thrombosis. Once access is obtained, a similar process of advancing a catheter over a guidewire is performed as in other access sites. Diagnostic and interventional procedures can be performed via the radial artery using traditional catheters as well as a number of newer catheters designed specifically for radial access such as the Jacky catheter or the Tiger catheter.

C. Special situations. In patients with prosthetic femoral grafts, it is preferable to use a dilator first before placing the sheath to prevent the sheath from kinking as it passes through the graft. This technique is also useful in obese patients. If a synthetic graft is old, fluoroscopy can be performed to determine if the graft is heavily calcified—a sign that it may not seal well after sheath removal. In patients with tortuous or diseased vessels, a Wholey wire or Terumo glidewire can be used to get catheters up the aorta. If marked iliac tortuosity is present and causes inability to torque catheters, a long sheath can be used to straighten out the iliac vessel. At times, a stiffer wire (such as an Amplatz wire) can provide better support to advance catheters. In patients with an AAA for whom a femoral approach is chosen, exchange wires should be used for every change of catheter. Use of a softer wire (such as a Wholey wire) can prove less traumatic to the vessel, as can use of a JR 4 to direct the guidewire.

D. Catheters. The catheters commonly used for coronary angiography include the Judkins and the Amplatz systems. For the left coronary artery (LCA), the size of the Judkins left (JL) catheters ranges from JL 3.5 to JL 6. The Amplatz left (AL) catheters used commonly range in size from AL I to AL III (Fig. 64.2 shows the shapes of the JL and AL catheters). Similarly for the right coronary artery (RCA), the Judkins right (JR) catheters range in size from JR 3.5 to JR 6. The Amplatz right (AR) catheters commonly used range from AR I to AR III. In addition, there is also an AR-modified catheter (Fig. 64.3 shows the shapes of the JR and AR coronary catheters commonly used). Other catheters used include the multipurpose catheters (multipurpose A1, A2, B1, and B2 catheters), which can be used for cannulating the left and right coronary arteries and bypass grafts. For coronary bypass grafts, the right or the left coronary bypass catheters may be used. The internal mammary artery may be cannulated using either the internal mammary or the internal mammary special catheters (see Fig. 64.4).

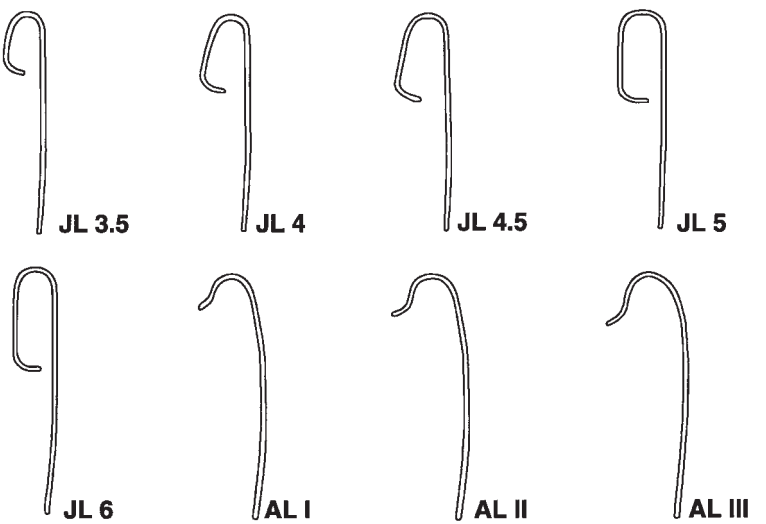

FIGURE 64.2 Catheters used for cannulating the left coronary artery. JL, Judkins left; AL, Amplatz left.

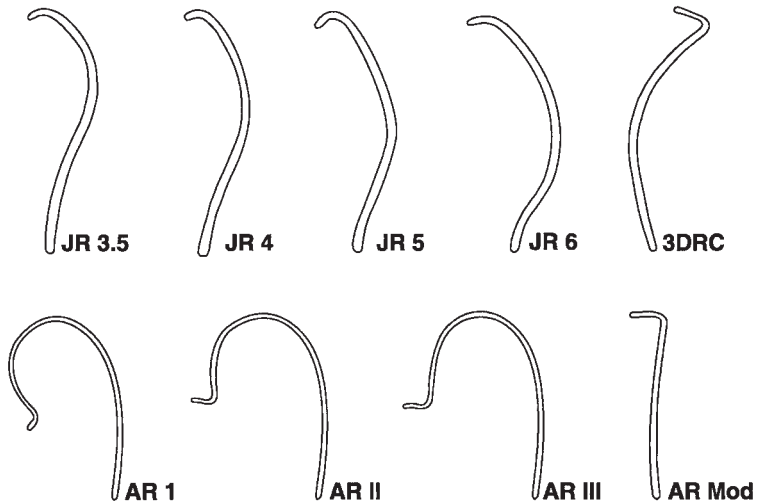

FIGURE 64.3 Catheters used for cannulating the right coronary artery. JR, Judkins right; AR, Amplatz right; 3DRC, no torque right coronary catheter; Mod, modified.

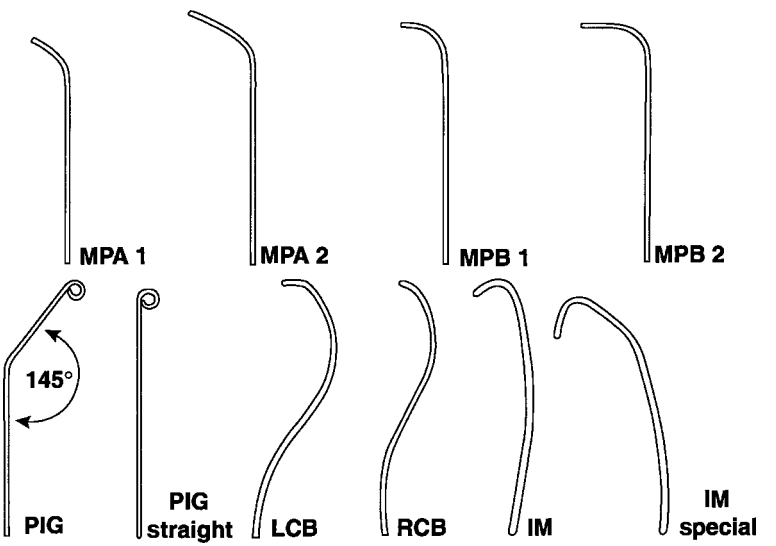

FIGURE 64.4 Other catheters used for cardiac catheterization. MP, multipurpose; PIG, pigtail; LCB, left coronary bypass catheter; RCB, right coronary bypass catheter; IM, internal mammary.

VI. TECHNIQUE

A. Engaging the vessel

1. **Left coronary artery.** Catheters are flushed with heparinized saline and passed through the sheath over a J-tipped guidewire. Using fluoroscopic guidance in the LAO projection, the left main coronary artery is cannulated, typically with a JL 4 (see Fig. 64.2). The catheter tip should be coaxial to the left main coronary artery, meaning that its tip should not be touching the upper wall of the left main coronary artery. In a small person, a JL 3.5 (see Fig. 64.2) catheter can be used. In a larger person or a person with a dilated aorta, a JL 5 or even a JL 6 (see Fig. 64.2) can be used. If the catheter does not engage the left main ostium easily, a slight clockwise or, more often, a counterclockwise rotation of the catheter hub may help. With the JL catheters, unless the aorta is dilated and provides no hinge point for the JL catheter, counterclockwise rotation moves the catheter tip anteriorly and clockwise rotation moves it posteriorly.

   Care should be taken to prevent the catheter from too deeply engaging ("deep-seating") the left main coronary artery. The pressure waveform must be observed for **damping** (a decrease in the systolic pressure) or **ventricularization** (when the waveform looks like a ventricular pressure tracing), both of which indicate a need to pull the catheter back and also raise the possibility of significant left main CAD. An adequate amount of dye reflux should be seen, unless ostial disease is present. If significant left main CAD is suspected, a cusp view (with the catheter placed in the left sinus of Valsalva) can be taken. Injection of contrast should be gentle and pressure gradually increased ("ramping"). Enough contrast should be injected to opacify the entire coronary artery and ensure reflux into the aorta (usually about 8 mL for the LCA). Injection force should be forceful enough to prevent "streaming," the inadequate opacification of coronary arteries that can create the illusion of stenoses. Care should be taken to inspect the injection syringe for air bubbles before each injection and to hold the syringe upright while injecting.
2. **Right coronary artery.** Catheterization of the RCA is similar to that of the LCA, except that a JR 4 (see Fig. 64.3) is advanced into the right coronary cusp, again in the LAO projection. The RCA is usually located anteriorly in the right sinus, in a position that is lower than the LCA ostium. As the catheter is slowly pulled back 2 cm above the aortic valve, it is rotated clockwise, causing it to engage. With the JR catheter, clockwise rotation moves the catheter tip anteriorly. In addition, clockwise rotation can cause the catheter tip to dip downward. Thus, it may be necessary to apply backward traction on the catheter as it is being rotated clockwise. Sometimes, it is necessary to repeat the clockwise rotation at different levels in order to engage the right coronary ostium. If the JR 4 does not easily engage the RCA or if the pressure dampens, ostial disease, spasm, selective intubation of the conus (which arises separately 50% of the time), or anatomic variation in the direction of the proximal RCA should be suspected. A cusp view can be taken to clarify these situations. Care should be taken to avoid subselectively intubating the conus branch.

   If difficulty is encountered in engaging the RCA because of the orientation of the ostium, a 3DR or a no-torque right catheter can be useful (see Fig. 64.3). Both catheters are designed to be placed above the aortic valve and pulled back without torquing maneuvers. An Amplatz or multipurpose catheter (see Figs. 64.3 and 64.4) can be useful for an upwardly angled ostium. An anterior or posterior origin can often be engaged with an Amplatz catheter. The most common cause of an incomplete LHC is a high and anterior RCA. To locate its ostium, less clockwise torque should be applied to the catheter so that it faces more anteriorly. Then the catheter can search for the ostium superior to the usual location. Less dye is needed to opacify the RCA than the LCA; overinjection can cause ventricular fibrillation. Sometimes, if a catheter is tenuously engaged, particularly in the right coronary ostium, a deep breath can dislodge it and should be avoided.

3. **Left internal mammary artery.** Catheterization of the LIMA is done either in the posteroanterior or shallow LAO projection. First, the catheter (usually a JR 4 catheter or a LIMA catheter; see Figs. 64.3 and 64.4) is positioned by pulling it back in the aorta while applying counterclockwise torque until it enters the left subclavian artery. At this point many operators will obtain an angiogram of the left subclavian artery to rule out a stenosis proximal to the LIMA and to give a hint of the angle of takeoff of the LIMA. The wire (J-tipped guidewire or Wholey wire) is then advanced into the subclavian artery. Next, the catheter is advanced over the wire into the subclavian artery, the wire is removed, and the catheter is slowly pulled back with a slight counterclockwise rotation until it engages the ostium of the LIMA. Movements around the ostium must be gentle to reduce the risk of dissection of the vessel; frequent test injections are helpful. In addition, if a 6F sheath is in place, switching to a 5F catheter will likely result in less trauma to the ostium of the LIMA. Turning the head to the left or right and pulling the arm caudally are maneuvers that can help engage the LIMA. If the ostium points downward at a sharp angle, the LIMA catheter is more likely to engage it selectively. The special LIMA catheter provides a slightly different angulation. It is best to use nonionic contrast to minimize the pain caused by ionic dye running through the arteries of the chest wall. If the ostium cannot be engaged successfully, a nonselective angiogram can be taken with the tip of the catheter as close to the ostium as possible. A blood pressure cuff should be inflated above systolic pressure in the left arm to facilitate dye movement down the LIMA.
4. **Right internal mammary artery (RIMA).** Catheterization of the RIMA is similar to that of the LIMA. The catheter (either JR 4 or LIMA; see Figs. 64.3 and 64.4) is placed in the brachiocephalic trunk by pulling it back in the aorta while applying counterclockwise rotation. The wire is advanced into the right subclavian artery. Care must be taken to avoid the right carotid artery. The wire is removed and the catheter is pulled back until it engages the ostium of the RIMA.
5. **Saphenous vein grafts (SVGs).** Catheterization of SVGs depends on the specific type of graft. The grafts are by necessity anastomosed to the anterior surface of the aorta. The orientation of SVGs from caudal to cranial is usually as follows: RCA, left anterior descending artery (LAD), diagonal branches of LAD, and marginal branches of left circumflex coronary artery (LCX). In the LAO view, grafts to the RCA usually point to the patient's right, whereas grafts to the left system are usually oriented more to the patient's left. It is the practice of some surgeons to place circular graft markers around the ostia of the vein grafts on the outer surface of the aorta. In the steep LAO projection, the catheter tip should extend beyond the plane of these markers, if the catheter is truly engaged in a vein graft. Injections into presumed vein graft stumps should be forceful to ensure that the graft is truly occluded, as opposed to poor opacification from a tenuously engaged catheter. Review of the operative note is mandatory before catheterization to know where grafts were placed. In particular, it should be noted whether any LIMA or RIMA grafts are in situ or free (attached to the aorta). A previous catheterization, if done, should be reviewed. Particular attention should be paid to the location of the grafts. The relative relationship with surgical clips should be noted, as this will save time and effort in finding grafts during the catheterization. If a graft cannot be found or a stump identified during a catheterization, an aortogram should be performed (Section **VI.E**).
   a. **SVG to RCA.** Engaging this graft can be as simple as pulling back on the JR 4 as it sits in the ostium of the RCA while in the LAO projection. Often, this graft has a steep downward orientation from the aorta. In this situation, a multipurpose catheter can be useful in engaging the graft. The multipurpose catheter can enter deeply into the graft if not handled carefully. Alternatively, a right bypass catheter or a right-modified Amplatz catheter can be useful in engaging the RCA graft.

b. **SVG to LAD.** The graft to the LAD is most easily engaged in the RAO view. To engage this graft, it is necessary to withdraw the catheter from the SVG to the RCA by pulling back. If the catheter does not fall into place, clockwise rotation of the JR 4 at an area cranial to the SVG to RCA graft ostium will locate the LAD graft. It may be necessary to move the catheter up and down along the anterior surface of the aorta several times. Left bypass, left Amplatz, and multipurpose catheters are all alternative catheters that can be used. A similar clockwise rotation to move the catheter tip along the anterior aortic surface is necessary.

c. **SVG to LCX.** To engage this graft, it is necessary to withdraw the catheter from the SVG to the LAD by pulling back, while remaining in the RAO projection. If the catheter does not fall into place, clockwise rotation of the JR 4 at an area cranial to the SVG to LAD graft ostium will locate the LCX graft. The technique is otherwise similar to that for engaging the graft to the LAD.

B. Imaging the vessels

1. **Normal coronary anatomy.** The left main coronary artery originates from the left coronary cusp. It usually bifurcates into an LAD and an LCX, although it sometimes trifurcates to include a ramus intermedius. The LAD courses along the anterior interventricular groove, supplying numerous septal perforators to the septum and a variable number of diagonal branches to the anterolateral wall of the left ventricle, and usually continues to the apex. The LCX courses along the left atrioventricular (AV) groove, providing a variable number of marginal branches to supply the lateral wall. In some institutions, the first marginal branch is called the high lateral branch of the circumflex, with subsequent branches called lateral or posterolateral branches depending on their destination. The LCX continues in the AV groove for a variable distance. In patients in whom the LCX is dominant (see subsequent text), the LCX reaches the posterior interventricular groove and gives rise to a posterior descending artery (PDA) branch.

   The RCA originates from the right coronary cusp and courses along the right AV groove, providing atrial branches (to the right atrium) and marginal branches (to the right ventricle). A conus branch originates as the first branch from the proximal RCA to supply the right ventricular outflow tract; about half of the time, this branch has an ostium that is separate from the RCA ostium. It is usually unnecessary to visualize a separate conus branch, unless collaterals to the LAD are suspected. The RCA gives off a branch to the sinus node about 60% of the time (otherwise a left atrial branch of the LCX serves this function). The first major branch the distal RCA gives off is the PDA, in a right dominant system. **Dominance** refers to which artery gives off a PDA and supplies the posterior part of the heart. In about 85% of patients, this will be the RCA; in 7% the RCA and LCX will be codominant; and in another 8% the LCX will be dominant. The PDA courses along the inferior interventricular groove, providing septal perforators to supply the inferior septum. After giving off a PDA, the RCA continues as a posterolateral segment supplying a variable number of posterior ventricular branches. From this posterolateral segment, the RCA usually (90% of the time) provides a branch to supply the AV node.

2. **Basic principles.** Several views of the coronary arteries are required to prevent excessive overlap of vessel segments and to delineate the severity of stenoses. A general principle that is useful is that in an RAO view the spine is on the left of the screen, conversely, in an LAO view the spine is on the right of the screen. Cranial views bring the silhouette of the diaphragm into the field of view. The diagonal and obtuse marginal branches tend to move in synchrony, because they supply the lateral aspect of the heart, whereas the LAD is located on the anterior portion of the heart. The AV continuation of the LCX lies in the AV groove, and (in patients with sinus rhythm) it has an "atrial kick" to it. This type of atrial kick can also be seen in atrial branches from either the LCX or the RCA. In the RAO view, a diagonal branch, and not the LAD itself, usually lies on the heart border. In the LAO view, the LAD runs along the border of the heart silhouette, not the

diagonal branches. Caudal angulation tends to move posterior vessels (such as the posterolateral branches of the RCA or the obtuse marginal branches of the LCX) inferiorly. Cranial angulation tends to move posterior vessels superiorly.

Patients should be instructed to take in a deep breath and hold it before most views for the purpose of moving the diaphragm out of the way. The RAO cranial view can be done at end of expiration to facilitate the splaying out of the diagonals from the LAD or at end of inspiration to view the proximal LCX. The LAO caudal can be done at end of expiration to visualize the left main and ostial LAD or at end of inspiration to view the LCX. Panning motion should be smooth and slow. It is best to wait for two to three systolic cycles and focus on proximal vessels before panning down the length of the artery of interest. It is important to pan to look for collaterals.

3. **Different views** (see Figs. 64.5 to 64.11)
   a. **Left coronary artery.** There is wide variation in the sequence of views obtained. Many operators start with a posteroanterior view and focus on the left main coronary artery, sometimes with a coned-down view to improve resolution. The problem with a pure posteroanterior view is that there is significant overlap with the spine. Therefore, a little bit of RAO angulation ("shallow RAO") can be used to get the coronaries off the spine. A steeper amount of RAO provides greater separation of the LAD from the LCX. A slight amount of caudal angulation can be used to decrease the foreshortening of the proximal circumflex in the straight RAO view and to place the diagonals below the LAD. Therefore, a **20° RAO, 20° caudal** is often the first view, displaying the entire left coronary system. This view also provides

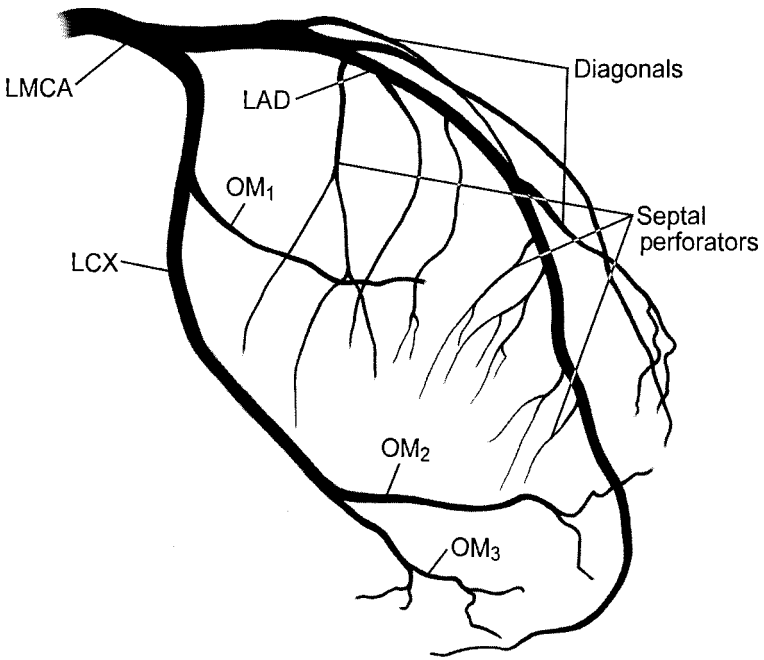

FIGURE 64.5 Posteroanterior view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery; OM_1, obtuse marginal branch 1; OM_2, obtuse marginal branch 2; OM_3, obtuse marginal branch 3.

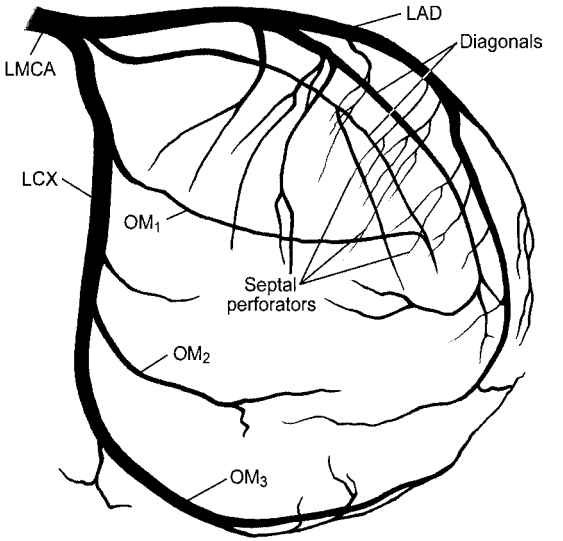

FIGURE 64.6 Right anterior oblique caudal view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery; OM_1, obtuse marginal branch 1; OM_2, obtuse marginal branch 2; OM_3, obtuse marginal branch 3.

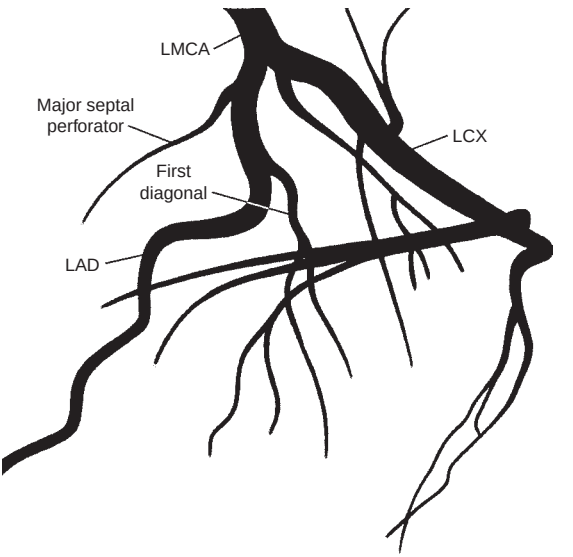

FIGURE 64.7 Left anterior oblique cranial view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

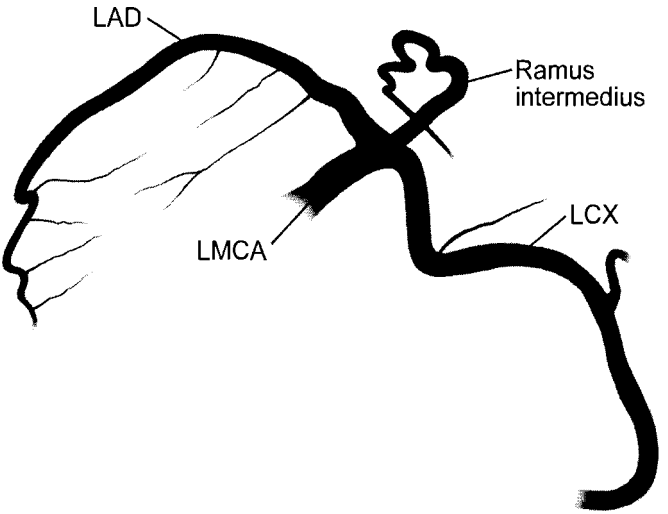

FIGURE 64.8 Left anterior oblique caudal view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

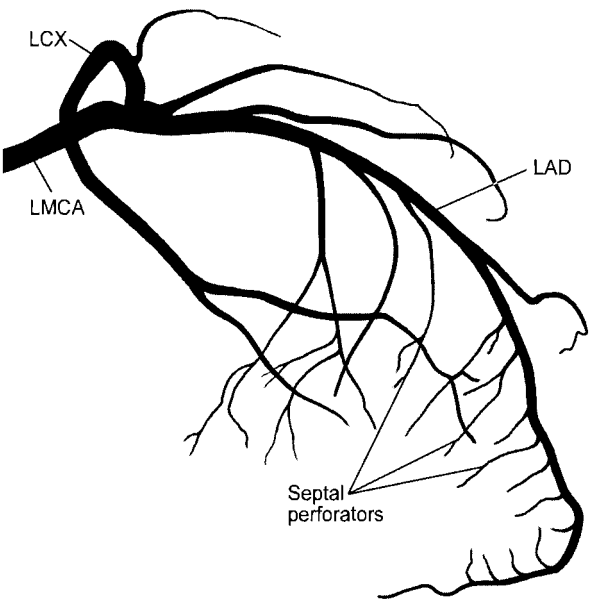

FIGURE 64.9 Right anterior oblique cranial view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

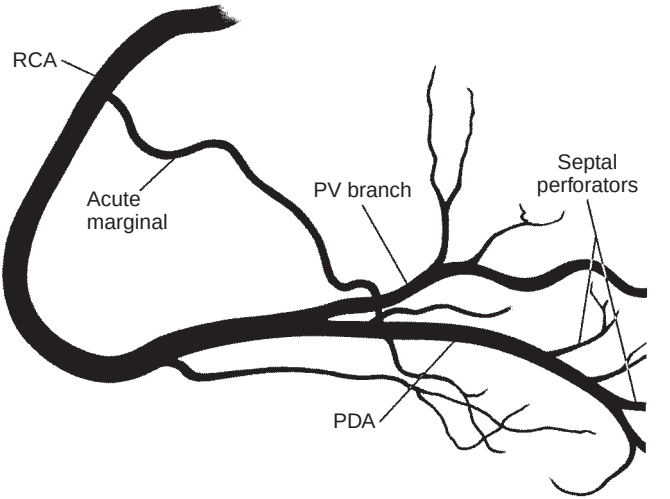

FIGURE 64.10 Left anterior oblique view of right coronary artery. RCA, right coronary artery; PV branch, posteroventricular branch; PDA, posterior descending artery.

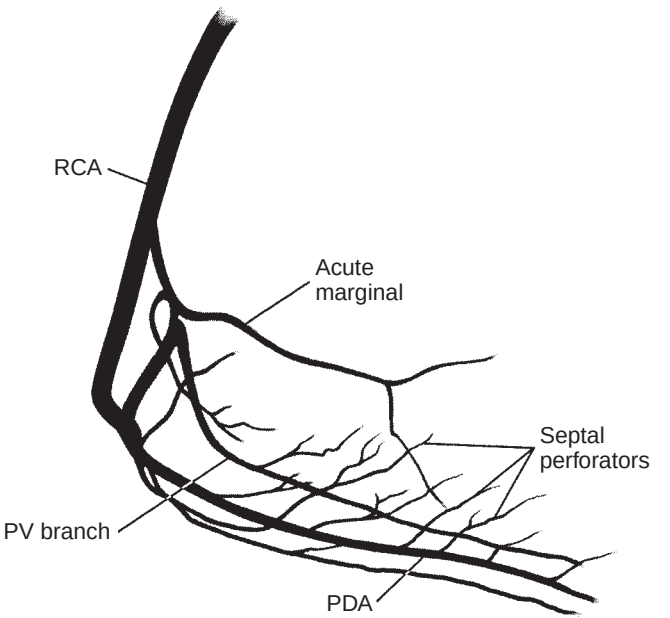

FIGURE 64.11 Right anterior oblique view of right coronary artery. RCA, right coronary artery; PV branch, posteroventricular branch; PDA, posterior descending artery.

a good view of the proximal LCX and of the origin of a ramus intermedius branch, if present. The contour collimator (called the wedge or the shield) should be moved to the upper right of the screen. A **30° RAO, 25° cranial** view can be used to separate the diagonals from the LAD, placing them above the LAD. The wedge should be placed in the upper right of the screen. A posterior–anterior view (PA) with **40° cranial** angulation can be useful in viewing the mid and distal portions of the LAD. The **45° LAO, 30° cranial** view is good for separating the LAD from its diagonal branches, especially for vertically oriented hearts. There should be enough LAO angulation to get the LAD off the spine. This view can also be good for a left-sided PDA branch. Steeper degrees of LAO further separate the LAD from the LCX and can get the LCX off the spine, but they can also cause the origins of the diagonals to overlap the LAD and cause the distal LAD to overlap the diaphragm. The **45° LAO, 30° caudal** ("spider" view) is useful for looking at the left main coronary artery and the proximal origin of the LCX. The proximal LAD is also seen but is foreshortened, unless the heart is horizontal in orientation. There must be enough LAO to get the cardiac silhouette off the spine. There is usually no need for a wedge, as it further increases the haziness of this view. Minimal to no panning is required. The **lateral** view provides delineation of the mid-LAD. In addition, the distal LAD does not overlap the diaphragm and the LCX is off the spine. The patient's hands should be placed behind the head for the lateral view. The shield should be placed above the course of the LAD. Panning involves dropping the table height and moving the table cranially. The **PA with 30° caudal** angulation provides a good view of the LCX.

b. **Right coronary artery.** The RCA is usually viewed in LAO and RAO views. The **30° RAO** view provides a good view of the proximal and mid-RCA and also of the PDA, which is laid out lengthwise. Cranial angulation can help separate the PDA from the distal vessel. The **40° LAO** view provides a good view of the proximal and mid-RCA, and if cranial angulation is added, a good view of the posterolateral arteries. The **PA with 30° cranial** can provide a useful view of the origins of the PDA and posterolateral branches. The lateral view of the RCA can provide a good view of the mid-RCA. In the RAO view, the right atrium and ventricle are separated by the RCA in the AV groove. Thus, atrial branches will be directed toward the atrium and marginal branches will be directed toward the ventricle.

c. **Bypass grafts.** An LAO view and an RAO view are required to visualize the body of the graft. Additional views are dictated by the grafted vessel. A particularly useful view for the LIMA–LAD anastomosis is the lateral view; cranial LAO and cranial RAO views can also be useful. The graft to the diagonal can be visualized in the cranial LAO and cranial RAO views. The graft to the marginal branch can be seen in the RAO and lateral views. The graft to the distal RCA can be visualized in the cranial LAO and lateral views.

4. **Congenital coronary artery anomalies.** Coronary artery anomalies should be suspected if there is an absent coronary artery and a large area of myocardium that appears nonperfused. The most common anomaly is an absent left main coronary artery trunk, in which the LAD and LCX have separate ostia (incidence 0.47%). If the LAD is first cannulated, the LCX can be engaged with a clockwise rotation; sometimes one size larger catheter (JL 5) is needed. Likewise, if the LCX is first cannulated, counterclockwise rotation, perhaps with a smaller-sized catheter (JL 3.5), is needed to engage the LAD. Other common anomalies in order of importance are the LCX originating from the right sinus of Valsalva (0.45%) and the RCA originating from the ascending aorta above the sinus of Valsalva (0.18%). The RCA originating from the left sinus of Valsalva is the next most common anomaly, originating superior and anterior to the left main (0.13%).

The origin of the left main artery from the right sinus is even less common (0.02%), but it can result in sudden death if the left main artery passes between the aorta and the pulmonary artery (extremely rare). The left main artery can also pass into the ventricular septum (most common), anterior to the pulmonary artery or posterior to the aorta. The 30° RAO view can help define the relationship between the coronary artery and the great vessels. If the course is septal, septal perforators can be seen originating from the left main.

The other coronary anomalies occur much less frequently. The Amplatz (left or right, depending on the cusp of origin) and multipurpose catheters are especially useful in cannulating anomalous coronary arteries.

Although not truly a congenital anomaly, every angiographer should be aware of **myocardial bridging**. This is an apparent narrowing of a coronary artery (usually the mid-LAD) that is present only during systole. There have been reports of bridging involving the diagonal branches of the LAD, the marginal branches of the LCX, and the distal RCA. Because the majority of coronary blood flow occurs during diastole, myocardial bridges are rarely pathologic, but there have been patients treated with CABG and, more recently, stenting. Nitroglycerin, by dilating epicardial vessels, can make bridging seem even more pronounced. A phenomenon similar to bridging can occur in hypertrophic obstructive cardiomyopathy, in which septal perforators from the LAD can become obliterated during systole.

5. **Quantification of coronary stenosis.** It is important to always obtain at least two perpendicular views of each coronary artery lesion. A single view, or even multiple views, can miss an eccentric lesion. Severity of a lesion is based on percent diameter stenosis compared with a "normal" reference segment. Lesions are generally classified as severe if 70% or more are in the LAD, LCX, and RCA or 50% are in the left main artery. When measuring the size of vessels and stenoses, it is useful to note that a 6F catheter has an external diameter of 2 mm. Formal quantitative coronary angiography or use of calipers can improve the measurement of coronary artery stenoses. Quantitative coronary angiography decreases the interobserver and intraobserver variabilities of grading stenosis severity. The minimal luminal diameter in the most severe view correlates best with perfusion imaging; minimal luminal diameters < 1.2 to 1.5 mm in proximal vessels typically reduce hyperemic flow.
6. **Limitations of coronary angiography.** Sometimes the severity of a lesion is difficult to gauge based on visual angiographic estimates alone, particularly in the presence of diffuse disease. Angiography only provides an outline of the lumen, the so-called luminogram. In addition, the angiogram can underestimate the presence of atheroma because of outward remodeling of the arterial wall (the Glagov phenomenon). Furthermore, angiography can only visualize arteries > 200 μm in diameter. The physiologic importance of 40% to 70% stenoses cannot be determined by angiography alone, and flow limitation should be demonstrated before percutaneous intervention. Techniques such as intravascular ultrasound and determining the fractional flow reserve can aid in determining whether ambiguous lesions on angiography are significant. Intravascular ultrasound provides a 360° tomographic view of the vessel lumen rather than a two-dimensional luminogram. Diagnostic applications of **intravascular ultrasound** include **imaging of angiographically indeterminate lesions, assessment of left main CAD, detection of transplant coronary vasculopathy, and identification of vulnerable plaques**. Intravascular ultrasound and optical coherence tomography can also be used during coronary interventions to help guide angioplasty, atherectomy, and stent placement (see Chapter 65, Percutaneous Coronary Intervention, for more details on these adjunct techniques of imaging).

C. Crossing the aortic valve

1. **Normal aortic valve.** The pigtail catheter is most commonly used to cross native aortic valves. Tissue valves can also be crossed, but crossing mechanical valves (e.g., St. Jude, Björk-Shiley, and Medtronic-Hall) risks catheter entrapment and is best

avoided. The catheter should be made to loop above the aortic valve. When pulled back very slowly, the catheter should give in, and it can then be rapidly advanced into the left ventricle during systole. Having the patient take a deep breath and hold it while the pigtail catheter is being unlooped can facilitate the passage of the catheter into the left ventricle. Sometimes the guidewire itself may be useful in crossing the valve, in which case the catheter is simply advanced over the guidewire into the left ventricle. A single operator can cross the aortic valve without assistance, but if two operators are present, one can move the catheter and change its orientation while the other moves the wire back and forth. The pressure in the left ventricle is recorded continuously; the catheter is pulled back into the aorta in a single motion to determine the aortic pressure, and the pullback pressure gradient can be calculated.

2. **Aortic stenosis.** In more severe cases of aortic stenosis, difficulty may be encountered in passing any catheter across the aortic valve. In this circumstance, a 0.038″ straight-tipped wire can be used to cross the valve. If this method is elected, some operators recommend a 5,000 IU bolus of heparin. The timer should be started, and not more than 3 to 4 minutes should be allowed per attempt at crossing. Between each attempt the wire should be withdrawn and wiped, blood aspirated and discarded, and the catheter flushed. Special care must be taken during this maneuver to avoid perforating the aortic cusps or potentially dissecting the coronary ostia. If a 6F sheath is used, a 5F pigtail catheter often provides the correct angle for wire passage; in addition, aortic and femoral pressures can be recorded concurrently and compared with the left ventricular pressure simultaneously using two transducers. A JR 4 or AL I catheter can also provide the correct orientation for wire passage across the aortic valve. The combination of a Feldman catheter and a Rosen wire is an alternative approach to cross stenotic aortic valves. Another way to determine the pressure gradient is to use a double-lumen pigtail catheter and measure the left ventricular and aortic pressures simultaneously.

D. Left ventriculography

1. **Setting up the view.** The pigtail catheter (commonly the angled version) is positioned in the midcavity of the left ventricle. The pigtail catheter should look like a "6" in the RAO projection. If the pigtail catheter twists with each beat, this indicates that it is caught in the mitral valve apparatus and needs to be repositioned. The monitor should be observed for ectopy. Once a stable rhythm is present, ventriculography can proceed. First, the left ventricular end-diastolic pressure (LVEDP) should be measured on a 40 scale. In patients with an elevated LVEDP (> 25 mm Hg), a left ventriculogram is generally contraindicated. If the decision to proceed with the left ventriculogram is made, sublingual nitroglycerin should first be given to lower the LVEDP. With more moderate degrees of left ventricular dysfunction, nonionic dye, which is less of a myocardial depressant, can be used. Digital subtraction can be used instead of cinefluoroscopy to obtain the left ventriculogram. This allows a smaller amount of contrast to be used. With digital subtraction, the view must be carefully centered because panning is not possible. **The left ventriculogram is best avoided in patients with critical aortic stenosis, significant left main artery disease, or severe left ventricular dysfunction**.
2. **Views.** The **30° RAO** view is used to look at the overall left ventricular function. In particular, the anterior, apical, and inferior walls can be assessed (see Fig. 64.12). Some operators routinely pan to the LIMA to assess its patency in a patient who might require CABG. The RAO view is also useful to assess mitral leaflet prolapse and MR. The LAO cranial view can also be used to assess MR, and it avoids the overlap of the aorta with the left atrium that occurs in the RAO view. **MR** can be graded on a scale of 1 to 4; 1 represents trace MR, with mild left atrial opacification that clears with one beat; 2 represents a mild to moderate degree of opacification, though less than that of the left ventricle; 3 represents moderate to severe opacification of the left atrium equal to that of the left

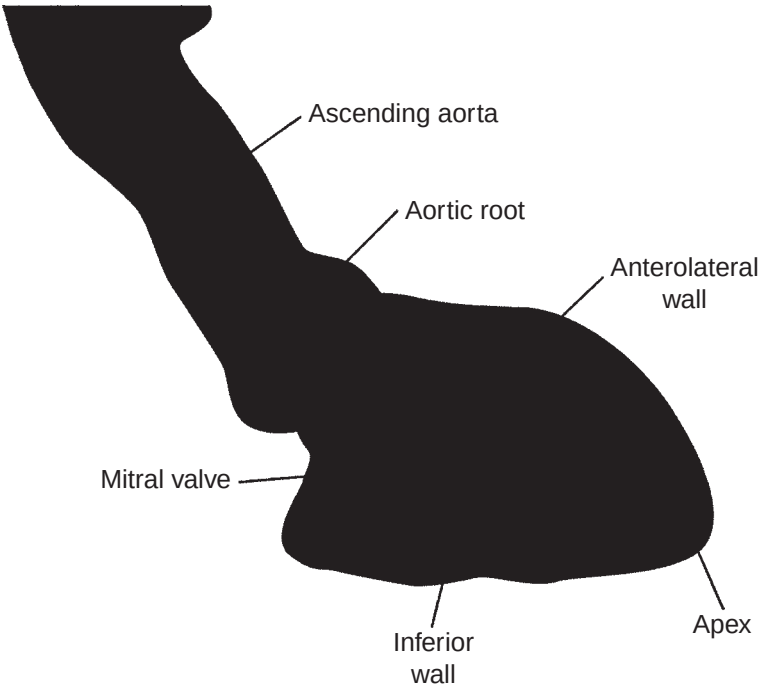

FIGURE 64.12 Thirty-degree right anterior oblique view of the left ventricle.

ventricle; and 4 represents complete opacification of the left atrium greater than that of the left ventricle. Panning toward the left atrium may be needed if MR is present. The catheter itself can cause MR if it is caught in the mitral valve apparatus or if it induces premature ventricular contractions. The correlation between angiographic and echocardiographic MR is excellent. The **60° LAO** projection allows evaluation of the septum and the posterior and lateral walls (see Fig. 64.13). Ventricular septal defects are best identified in the LAO projection with slight cranial angulation. If biplane imaging capability exists, RAO and LAO views of the left ventricle can be obtained simultaneously.

3. **Settings.** For a ventriculogram, the flow injector can be set at a rate of 10 to 15 mL/s for a total volume of about 35 to 50 mL, with a rate rise of 0.4 second (to minimize ectopy and to keep the catheter from moving abruptly) and a pressure of 600 PSI. The exact settings will vary depending on the size of the heart and the need to limit contrast.

E. Aortography. Aortography is usually performed in the LAO position, with the catheter about 2 cm above the aortic leaflets. Compared with a ventriculogram, a larger volume of contrast is needed to opacify the aorta. The flow injector is set to a higher total volume than for the left ventriculogram, usually about 60 mL at a rate of 20 to 25 mL/s. No rate rise is necessary (other than to keep smaller catheters from moving), and a pressure limit of 600 PSI is used. **Aortic insufficiency** can be identified with a grading system similar to that of MR; 1 represents trace aortic insufficiency that clears from the left ventricle with each beat; 2 represents mild left ventricular opacification that takes more than one beat to clear; 3 represents moderate left ventricular opacification

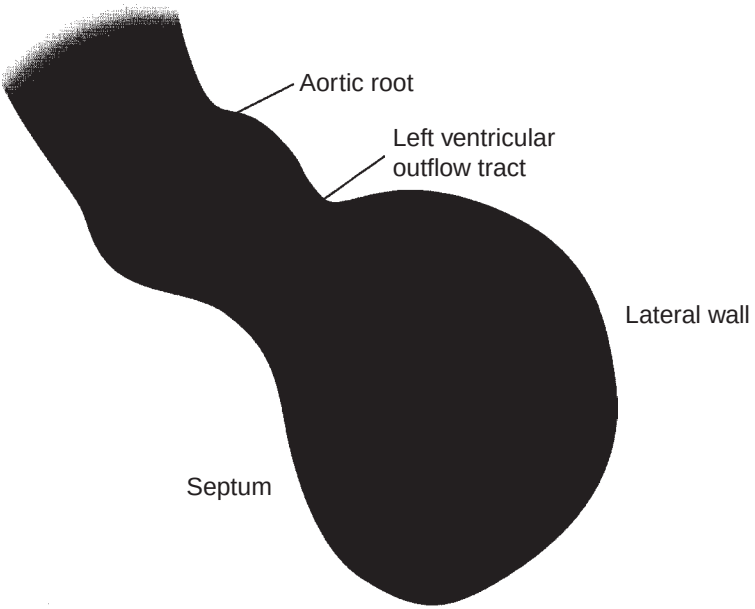

FIGURE 64.13 Sixty-degree left anterior oblique view of the left ventricle.

equal to that of the aortic root; and 4 represents complete opacification of the left ventricle greater than that of the aortic root. Diseases of the aorta such as aneurysms or dissection can also be identified. An aortogram can also aid in nonselective visualization of anomalous coronary arteries or grafts that are difficult to engage. However, the absence of filling of a bypass graft on an aortogram does not exclude its presence. The aorta must be completely opacified to ensure that grafts are seen.

An aortogram can be performed with the pigtail catheter placed in the descending aorta slightly above the level of the origins of the renal arteries (the L1 vertebral body) to rule out **renal artery stenosis**. A JR 4 can be used to obtain selective renal arteriograms by turning the tip of the catheter so that it points to either the left or the right in the posteroanterior view. The catheter is then gradually pulled back when it is in the vicinity of the renal artery ostia until it engages. Digital acquisition should be used.

Carotid angiography is sometimes necessary to confirm the degree of carotid artery stenosis seen on a noninvasive study. A variety of catheters (the Headhunter and Newton series) can be used to selectively cannulate the common carotid artery. These catheters are advanced to the aortic arch over a guidewire and pulled back to engage the artery of interest. A Newton 5 can be used to engage the right common carotid artery and a Newton 2, with its smaller curve, can be used to engage the left common carotid artery. There is a 0.5% to 1% risk of stroke with this procedure. Digital acquisition and use of nonionic contrast are mandatory.

F. **Pharmacologic testing.** In patients in whom coronary artery spasm is suspected, intravenous methylergonovine can be given to provoke spasm. Once significant angiographic stenosis has been ruled out, 0.05 mg of intravenous methylergonovine is administered. If the patient develops his or her typical chest pain or ST elevation on electrocardiographic monitoring, the coronary arteries are catheterized immediately. The electrocardiographic changes can help determine which coronary artery to cannulate

first. If there are no electrocardiographic changes or chest pain, the right coronary artery (which is statistically more likely to have spasm) and then the left coronary artery should be recatheterized 5 minutes after the methylergonovine has been administered. A positive response consists of a focal area of spasm that is relieved by intracoronary nitroglycerin (a usual dose of 100 to 200 μg). Diffuse spasm can be physiologic, and it is also managed with nitroglycerin and verapamil (also 100 to 200 μg). Because the half-life of methylergonovine is longer than that of sublingual nitroglycerin, it is important to realize that spasm can recur after a dose of nitroglycerin. If the initial dose of methylergonovine does not provoke a response, an additional dose of 0.2 mg can be given a few minutes after the first. Alternatively, some operators prefer giving a single dose of 0.2 mg.

Intracoronary vasodilators such as nitroglycerin are often used in the assessment of coronary anatomy. For example, if the operator is unsure if what appears to be ostial disease of a coronary artery may in fact be catheter-induced ostial spasm, an intracoronary injection of nitroglycerin and repeat angiography can help clarify. For more on the use of intracoronary vasodilator therapy (including nitroglycerin, nitroprusside, and adenosine) in the assessment and treatment of CAD, please see Chapter 65, Percutaneous Coronary Intervention.

Intravenous infusion of dobutamine can be useful in the evaluation of patients with low-flow/low-gradient aortic stenosis and left ventricular dysfunction. These patients can be a challenging population to evaluate, as it is unclear if the valve stenosis is in fact severe or moderate. The measurement of peak valve gradients and valve area at baseline and during administration of a dobutamine infusion can help clarify this question. Patients who do not have true anatomically severe aortic stenosis will exhibit an increase in valve area, with little change in the peak gradient during an increase in stroke volume caused by dobutamine infusion.

VII. POST-CATHETERIZATION CARE

A. Sheath removal. The sheath is removed once the procedure is complete. Adequate local anesthesia should be reinjected if the previously given dose has lost its efficacy. After the sheath is removed, hemostasis is generally obtained with direct manual pressure of the fingertips over the pulse, without sterile gauze to obscure the view. Pressure is held for approximately 20 minutes (about 3 minutes for each French size) until there is no bleeding. Manual pressure remains an important technique due to low cost, good safety profile (complication rate < 0.23%), short learning curve, and ability to be employed despite femoral artery dissection, significant peripheral vascular disease, or a low stick. To shorten the time of manual pressure, hemostatic pads can be used. These products are impregnated with a procoagulant mixture that causes local vasoconstriction and potentiates clot formation. Care must be taken to intermittently allow adequate blood flow to the distal extremity. It is, therefore, best if one can directly visualize the extremity to assess its color. If both arterial and venous sheaths are present, it is best to remove the venous sheath first and then obtain hemostasis before removing the arterial sheath. In patients with severe aortic stenosis or significant left main CAD, laboratory personnel should be prepared to rapidly manage a vagal episode, which can be life threatening in these situations. Adequate administration of anesthesia before removal of the sheath decreases the chance of a vagal reaction.

Bed rest is generally required for 6 hours after a femoral sheath is removed, although some operators require 1 hour for each French size. In fact, 2 hours is a sufficient period of bed rest for 5F sheaths. Two hours of keeping the arm straight is necessary after a brachial or radial procedure. During the postprocedure observation period, it is necessary to monitor the HR, temperature, blood pressure, urine output, distal pulses, and the access site (for pain, bleeding, or hematoma). Using sandbags over the groin site is discouraged. Before discharge, it is best to have the patient ambulate under observation. Specific discharge instructions should include the possibility of late access site bleeding and the need to hold pressure and call for emergency help.

Intravenous fluids are often given after a cardiac catheterization. The osmotic load of the contrast dye can cause a large diuresis. Intravenous fluids (e.g., normal saline at 100 mL/h for several hours) can prevent volume depletion. Care should be taken in patients with a history of congestive HF, in whom liberal intravenous fluids could contribute to pulmonary edema.

B. Compression/closure devices. The use of femoral artery closure devices offers the advantages of improved patient comfort, potentially lower complication rates, early sheath removal, and early hospital discharge, and anticoagulation may be continued without interruption in some patients. The currently available products include compression devices such as the FemoStop (RADI Medical Systems) and the C clamp, biosealants (Duett, vascular solutions), collagen plugs (Vasoseal; Datascope), vascular sandwiches (Angioseal; Daig), and percutaneous sutures (Perclose, Prostar, and Techstar; Abbott).

1. The **FemoStop** is a pneumatic compression device that can be used for holding pressure in cases of prolonged bleeding. The **C clamp** is a mechanical clamp that can also be used for holding prolonged pressure. If either of these devices is employed, direct supervision of the patient is required.
2. **Biosealant** (Duett) devices consist of a procoagulant mixture of collagen and thrombin that is deployed in the tissues surrounding the arterial puncture site through a balloon catheter. This device allows early ambulation. The disadvantages of this device include delayed reuse of the arteriotomy site (repeat arterial puncture cannot be performed for about 3 months) and possibility of infection due to the foreign material introduced; it can also be cumbersome to deploy, and in rare cases, inadvertent deployment of the procoagulant mixture into the femoral artery may result in arterial occlusion requiring surgical intervention.
3. The **Angioseal** (St. Jude/Kensey Nash) hemostatic puncture closure device can be used to obtain hemostasis in an uncomplicated femoral procedure if an 8F or a smaller sheath was used. Before deploying the Angioseal, it is advisable to obtain an angiogram of the femoral artery to ensure that the entry site of sheath is above the bifurcation of the common femoral artery. It is available in 6F and 8F sizes. A biodegradable collagen plug is deployed at the femoral artery puncture site using a guidewire and special sheath. No manual pressure is required, and ambulation can begin after 1 hour. The Angioseal device is user friendly due to its ease of deployment and general reliability. The disadvantage of this device is the introduction of foreign material that could be a potential source of infection, and repeat arterial puncture cannot be performed at the same site for about 45 to 60 days.
4. The **Vasoseal** (Datascope) is a collagen plug that is placed over the femoral artery puncture site. It comes in several sizes; to determine the appropriate size, it is necessary to place a depth marker on the needle during the initial arterial puncture. Ambulation can begin 1 hour after the placement.
5. The **Perclose** (Abbott) is a percutaneous vascular suture device that allows immediate ambulation (of course, after the effects of any sedation given during the procedure have worn off). Before its use, a 35°-RAO view of the right femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is currently available in 6F, 8F, and 10F sizes. Other improved devices are likely to be available in the near future.
6. The **StarClose Vascular Closure System** (Abbott) is a percutaneous vascular closure device that employs a nitinol clip. Before its use, a view of the right femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is delivered through a sheath onto the arteriotomy site, and the clip takes hold of the tissue in a circular manner and closes off the arteriotomy site.

VIII. COMPLICATIONS

A. Death. There is a 0.1% risk of death from LHC. This risk is substantially higher in patients undergoing urgent catheterization for acute coronary syndromes. In addition,

patients with left main CAD, severe aortic stenosis, or severe left ventricular dysfunction are known to be patient subgroups with a particularly increased risk. Advanced age increases the risk of death.

B. Myocardial infarction. There is a 0.05% risk of MI from LHC. MI can result from coronary dissection, disruption of a preexisting atheromatous plaque, and a large air embolus or a thrombus. Patients with acute coronary syndromes have a higher risk of MI.

C. Stroke. Stroke occurs in 0.05% of catheterizations. There is a risk of stroke from an inadvertent air embolus or thrombus. The presence of aortic atheroma is a risk factor for embolic complications. Dislodgement of atheromatous debris in the aorta can lead to a stroke. This risk can be minimized by the use of 260-cm exchange wires for catheter changes in patients with known severe aortic disease.

D. Coronary artery dissection. Engagement of the coronary arteries can rarely cause dissection. It is most often due to the injection of contrast through a catheter that is not coaxial to the coronary artery, causing rupture of a preexisting plaque, or placement of the catheter too deeply into the coronary artery (so-called deep throating). Particular caution should be used with Amplatz catheters. In cases of left main coronary artery dissection, a stent can be placed emergently and the patient can be placed on peripheral cardiopulmonary support until the surgical team can be mobilized.

E. Coronary artery spasm. Engagement of the coronary arteries, in particular the RCA, can cause spasm. This is best treated with withdrawal of the catheter. Subsequent reengagement and administration of intracoronary nitroglycerin (100 to 200 μg) may also be necessary for more rapid resolution of spasm.

F. Renal failure. Contrast dye can precipitate renal failure in any patient, although certain patients (those with elevated creatinine, diabetes, proteinuria, or dehydration) are at higher risk. Adequate prehydration with normal saline can reduce this risk. In some cases (especially in diabetics with renal insufficiency and those with renal artery stenoses), patients may need to be admitted to the hospital for hydration with 0.45% saline for several hours before the LHC to minimize risk of contrast-induced nephrotoxicity. The use of the antioxidant *N*-acetylcysteine (600 mg orally twice daily) before and after exposure to radiocontrast along with 0.45% saline prevented the decrease in renal function in patients with chronic renal insufficiency exposed to nonionic low-osmolality contrast agent. This study, however, enrolled only 83 patients. Other studies have examined the role of sodium bicarbonate infusions in preventing contrast-induced nephropathy. Several small studies have shown benefit with the use of sodium bicarbonate infusions (3 ampules of sodium bicarbonate in 1 L normal saline, infused at 3 mL/kg/h for 1 hour before procedure and 1 mL/kg/h during the procedure and for 6 hours following) or sodium bicarbonate plus *N*-acetylcysteine in preventing contrast-induced renal function. In a study of 129 patients with serum creatinine concentrations of 1.5 to 3.5 mg/dL who underwent coronary or aortofemoral angiography, use of the iso-osmolar, dimeric, nonionic contrast medium iodixanol was associated with decreased risk of nephropathy compared with the low-osmolar, nonionic, monomeric contrast medium iohexol. **The best way to minimize contrast-induced renal failure is to limit the amount of dye used**. Using < 30 mL of contrast dye dramatically reduces the incidence of renal failure in even the highest risk patients. Biplane cineangiography can maximize the amount of information obtained with each view.

G. Emergency CABG. There is a risk of needing emergency CABG as a complication of the catheterization (e.g., dissection of the left main coronary artery). There is also the possibility of identification of critical disease, such as severe left main CAD, that may prompt emergency CABG as the most expedient treatment.

H. Arrhythmias. A risk of ventricular fibrillation (0.5%) exists with catheterization. This rhythm is treated with electrical defibrillation. In particular, overinjection of contrast into the RCA can cause ventricular fibrillation. Contrast dye (less so nonionic dye) can cause transient bradycardia, best dealt with by having the patient cough and by minimizing the amount of dye injected with each angiographic procedure.

I. **Heart failure.** The osmotic load of contrast dye can put a patient with diminished cardiac or renal function into overt pulmonary edema. In patients with severe cardiac or renal disease, injection of contrast should be limited, and the use of nonionic, low-osmolar dye should be considered.

J. **Vagal reaction.** If a patient develops hypotension and/or bradycardia, a vagal reaction should be considered. It is a common occurrence when local anesthetic is being administered or when the sheath is being removed. Atropine 1 mg IV should be available and given in these situations. Adequate anesthesia can help prevent such reactions. In a patient with severe aortic stenosis or left main CAD, a vagal reaction can start a downward spiral that leads to death. Levophed (about 10 μg) should always be available and used immediately in such cases of hypotension.

K. **Vascular**

1. **Femoral.** Pseudoaneurysms, arteriovenous fistulas, arterial thrombosis, and peripheral emboli are possible vascular complications. Careful technique can minimize these events. In particular, paying attention to puncture location and obtaining adequate hemostasis after sheath removal are the best ways to decrease vascular complications. For example, smaller sheaths (5F) are preferred in patients with significant peripheral vascular disease. Frequent aspiration and discarding of blood from the arterial sheath, followed by gentle flushing, is useful. If an attempted cannulation is unsuccessful but an arterial puncture has been made, the needle should be withdrawn and adequate manual pressure held (about 5 minutes). If a venous puncture has been made inadvertently, the needle should be removed and pressure held (for about 3 minutes). Proceeding directly to arterial puncture without removing the needle and holding pressure increases the chance of arteriovenous fistula formation. If a venous puncture is planned, it should be made at a site lower than the arterial puncture site. Bruits should be auscultated both before and after the procedure. A new bruit may indicate a vascular complication. **Ultrasound** is an essential part of managing groin complications. If there is a large pseudoaneurysm present, surgery may be required after a trial of ultrasound-guided compression. Percutaneous injection of thrombin into the pseudoaneurysm has proven to be a more effective alternative to compression. Small pseudoaneurysms (< 2 cm) tend to close spontaneously but should be followed by serial ultrasound examinations. An arteriovenous fistula that does not close spontaneously in 2 to 4 weeks may require surgical repair.
2. **Brachial/radial.** When using an upper extremity approach, blood pressure should first be checked in both arms. If there is a difference in blood pressure between the arms, peripheral vascular disease should be suspected and the side with the higher blood pressure should be used. For a radial approach, an Allen test must be performed to assess the patency of collateral ulnar circulation. The rate of vascular complications such as thrombosis is higher with the upper extremity approach than with the femoral approach.

L. **Bleeding.** Access site bleeding can be significant. If there is a great deal of oozing around the sheath, it can be exchanged for a sheath 1F size larger. Adequate manual pressure is usually sufficient to stop bleeding after sheath removal. It is a typical practice to check the activated clotting time in patients who had been on heparin before the procedure and only proceed with sheath removal if the clotting time is below 160 seconds. Some institutions use protamine (1 mg/100 IU heparin) to reverse heparinization, but this exposes the patient to the potential for allergic reactions to protamine (namely, hypotension). Even more concerning is **retroperitoneal bleeding**. If a patient complains of severe back pain after a catheterization, this should be considered. An unexpected drop in hemoglobin after a catheterization should also raise this possibility. Obese patients, in particular, can have a major bleed without obvious external signs. Noncontrast computed tomography scan of the abdomen and pelvis can diagnose a retroperitoneal bleed, but it is important to assess the patient's clinical stability before sending them to such a study. Patients who have developed a documented retroperitoneal hematoma or are suspected of having this complication are monitored

closely in an intensive care unit, often with continuous blood pressure assessment using an arterial line and receive aggressive volume resuscitation with fluids and blood products until self-resolution with reversal of anticoagulation or definite treatment.

M. Infection. There is a risk of infection, as with any invasive procedure. This risk can be minimized with proper attention to sterile technique. There is usually no need for prophylactic antibiotics. However, some operators do give antibiotics after use of a percutaneous vascular suture device in patients who are at elevated risk for infection, such as obese or diabetic patients. Endocarditis prophylaxis for patients with valvular heart disease or prosthetic valves is unnecessary.

N. Neuropathy. There is a slight risk of damage to the femoral nerve from inadvertent puncture. Femoral hematoma (or retroperitoneal bleeding) can also cause compromise of the femoral nerve. Function usually improves with time, but complete recovery can take several months.

O. Allergy. As discussed above, contrast dye can cause adverse reactions, ranging from hives to anaphylaxis. Severe anaphylactoid reactions to contrast dye occur in about 0.1% of cases. Local anesthetics can also cause problems due to specific allergies to the amide or ester component or to the preservative. A variety of agents are available. Procaine (an ester agent), lidocaine (an amide agent), and bupivacaine (a preservative-free amide agent) are alternative agents.

ACKNOWLEDGMENTS: *The author thanks Drs. Saif Anwaruddin, Niranjan Seshadri, and Deepak L. Bhatt for their contributions to previous editions of this chapter.*

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CHAPTER 65

Amar Krishnaswamy
Samir R. Kapadia

Percutaneous Coronary Intervention

I. INTRODUCTION

A. Coronary atherosclerosis may result in a flow-limiting stenosis that leads to myocardial ischemia and/or myocardial infarction (MI). Andreas Gruentzig first managed these lesions percutaneously on September 16, 1977, when he advanced a fixed-wire, distensible balloon across a stenosis in the mid–left anterior descending (LAD) artery and briefly inflated it to 6 atm (90 psi). This procedure was termed percutaneous transluminal coronary angioplasty (PTCA). With the advent of stents and other therapeutic coronary devices, these procedures are now more broadly termed percutaneous coronary intervention (PCI). It is estimated that more than 1 million PCI procedures are completed in the United States and approximately 2 million worldwide annually.

B. The field of interventional cardiology continues to rapidly evolve, as a result of many important advances in equipment, strategies, and adjunctive medication. These advances have been paralleled by a concomitant improvement in the safety and efficacy profile of PCI. The assimilation of a large body of basic and clinical research encompassing all areas of interventional cardiology continues to redefine the standard of care paradigm.

II. PCI INDICATIONS

A. Central tenet. Although there is no substitute for sound clinical judgment, PCI is generally reserved for patients in whom there is an objective demonstration of myocardial ischemia or symptoms as well as angiographic demonstration of obstructive coronary disease. PCI may not be indicated for asymptomatic or mildly symptomatic patients who have only a small area of viable or jeopardized myocardium, have no objective evidence of myocardial ischemia, have other life-limiting disease processes, or have lesions that have a low likelihood of success (Tables 65.1 and 65.2).

B. ST-segment elevation myocardial infarction (STEMI). Primary PCI should be the preferred treatment strategy for patients presenting with STEMI to a facility experienced with and capable of performing PCI. Randomized trials have demonstrated that clinical outcomes are improved when such patients are emergently transferred to centers able to perform primary PCI as opposed to therapy with thrombolytics—despite a significant delay (mean time of 44 minutes) in time to therapy due to transport. This seems especially true of patients presenting 3 to 12 hours after symptom onset, where the superiority of primary PCI becomes clearly evident. In those presenting within 3 hours of symptom onset, mortality data would suggest that either therapy is equally efficacious in appropriate candidates. **For a more thorough discussion of the management of STEMI, please refer to Chapter 1**.

C. Non–ST-segment elevation acute coronary syndrome (NSTEACS). Unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI) are considered part of the spectrum of NSTEACS. Given that individual patients presenting

TABLE 65.1 Standard Prepercutaneous Coronary Intervention Evaluation

History

- Symptoms (angina, dyspnea, paroxysmal nocturnal dyspnea, syncope)
- Previous MI
- Previous cardiac interventions (PCI, CABG)
- Comorbidities (diabetes mellitus, hyperlipidemia, hypertension, etc.)

Medications (glucophage, statins, aspirin, thienopyridines, etc.)

Allergies (contrast dye, latex, etc.)

Physical exam (murmurs, jugular venous pressure, pulses, bruits, edema)

Laboratory data (creatinine, potassium, hemoglobin, platelets, INR)

Other tests (ECG, echocardiogram, stress tests)

Informed consent including risks, benefits, alternatives

CABG, coronary artery bypass grafting; ECG, electrocardiogram; INR, international normalized ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 65.2 Considerations for Every Percutaneous Coronary Intervention

Review clinical and angiographic risk factors

Develop strategy and anticipate problems

- Surgical backup
- Access
- Anticoagulation and antiplatelet therapy
- Consider diagnostic adjuncts (e.g., PA line)
- Consider therapeutic mechanical adjuncts (e.g., IABP)
- Guidewire
- Device (e.g., angioplasty, stent)
- Closure of vascular access site
- Post-PCI destination (telemetry ward, CICU)

CICU, cardiac intensive care unit; IABP, intraaortic balloon pump; PA, pulmonary artery; PCI, percutaneous coronary intervention.

with unstable angina/NSTEMI are at widely varying risk for subsequent morbidity and mortality, early and aggressive risk stratification including cardiac catheterization with subsequent percutaneous or surgical revascularization (rather than noninvasive stress testing) is recommended. This recommendation is supported by a number of clinical trials comparing an early invasive to delayed conservative strategy. **For a more thorough discussion of the management of NSTEACS, please refer to Chapter 2.**

D. Chronic stable angina. It is estimated that > 85% of all PCI procedures are performed in the elective setting for chronic stable angina. While recent trials have

questioned the mortality benefit of PCI or coronary artery bypass grafting (CABG) over optimal medical therapy in stable coronary artery disease (CAD), revascularization still remains the most rapidly effective treatment strategy for patients with angina. **For a more thorough discussion of the management of stable CAD, please refer to Chapter 6.**

III. CONTRAINDICATIONS. The only absolute contraindication to PCI is significant active bleeding, given the absolute need for procedural anticoagulation and continued dual antiplatelet therapy (DAT). Relative contraindications include a bleeding diathesis, unsuitable or high-risk coronary anatomy (e.g., chronic total occlusion in the absence of ischemia or diffuse distal disease), recurrent in-stent restenosis (ISR), and a short life expectancy because of a comorbid condition.

IV. PROGNOSIS. A patient's clinical status and coronary angiogram are powerful predictors of outcome. Certain clinical and angiographic variables have repeatedly been associated with adverse events (Table 65.3).

V. ANGIOGRAPHIC/PROCEDURAL/CLINICAL SUCCESS. Angiographic success is defined as a residual stenosis < 50% with PTCA or < 20% with stenting and is achieved in 96% to 99% of patients. The definition of procedural success is angiographic success without major in-hospital complications (i.e., death, CABG, or MI). Clinical success is defined as procedural success with relief of the symptoms and signs of myocardial ischemia.

VI. COMPLICATIONS

A. The incidence of complications (death 0.5% to 1.4%, periprocedural MI [defined by creatine kinase-myocardial band, CK-MB, elevation more than three times the upper limit of normal] up to 8%, and emergency CABG surgery 0.2% to 0.3%) has consistently decreased over the past 20 years with the advent of stents, new and more effective antiplatelet therapies, improved equipment, and increasing reliance upon evidence-based strategies.

B. **Abrupt closure** is the most common cause of a major adverse cardiac event (MACE) and typically occurs within 6 hours of intervention. The most common cause of abrupt

TABLE 65.3 Clinical and Angiographic Predictors of Adverse Outcomes

Clinical predictors	Angiographic predictors
• Older age	• Thrombus
• Unstable angina	• Bypass graft
• Acute MI	• Left main trunk
• Cardiogenic shock	• Lesion > 20 mm in length
• CHF	• Excessive tortuosity of proximal segment
• Left ventricular function	• Extremely angulated lesions > 90°
• Multivessel coronary disease	• Total occlusion > 3 months old and/or bridging collaterals
• Diabetes mellitus	• Inability to protect major side branches
• Renal impairment	• Degenerated vein grafts with friable lesions
• Peripheral vascular disease	• Unprotected left main trunk
• Small body size	

CHF, congestive heart failure; MI, myocardial infarction.

closure is suboptimal stent expansion or dissection followed by thrombus, spasm, and side branch occlusion. In the mid-1980s, the risk of abrupt closure approached 5%. The common use of periprocedural glycoprotein (GP) IIb/IIIa and/or direct thrombin-inhibiting anticoagulants and stent deployment has reduced this risk to < 1% in modern practice. Risk factors for abrupt closure include presentation with acute MI, poor coronary flow postintervention (i.e., less than Thrombolysis in Myocardial Ischemia [TIMI] II), complex lesion morphology (i.e., class C lesions), and suboptimal result as judged by angiography or intravascular ultrasound (IVUS) imaging.

C. **Atheroembolism and thromboembolism** probably occur to varying degrees in all interventions, but are most frequently encountered in cases involving degenerated vein grafts, in patients presenting with acute coronary syndromes (ACSs), and in cases using directional/rotational atherectomy. Distal embolization can result in "no-reflow" (decreased coronary flow), abrupt closure, and periprocedural MI. Thromboembolism can be minimized by using aspiration catheters (e.g., Pronto, Export, Extract) or rheolytic thrombectomy (Possis AngioJet) to remove thrombus as well as routine anticoagulant and antiplatelet therapy. The prevention of atheroembolus, most often encountered during vein graft intervention, is frequently addressed with the use of a filter device (e.g., FilterWire EZ or PercuSurge GuardWire) or proximal flow occlusion device (e.g., Proxis) to trap and remove the debris before it reaches the distal vascular bed. Intracoronary administration of vasodilators such as adenosine (36 to 72 μg repeatedly), nitroprusside (50 to 200 μg), and verapamil (200 μg) has been shown to prevent and manage no-reflow, but have no effect in preventing CK-MB elevation.

D. **Coronary perforation** is typically identified using the Ellis classification: Type I: extraluminal crater without extravasation; Type II: pericardial or myocardial blush without contrast jet extravasation; Type III: extravasation through frank (> 1 mm) perforation; Type III cavity spilling: perforation into an anatomic chamber, coronary sinus, etc. Coronary perforation is estimated to occur in 0.1% to 1.14% of routine PCI cases, 0.25% to 0.70% of cases using directional atherectomy, up to 1.3% of cases using rotational atherectomy, 1.3% to 2.1% of cases using extractional atherectomy, and 1.9% to 2.0% following excimer laser angioplasty. Contrast extravasation is typically evident in the majority of cases at the time of PCI; however, up to 20% of cases can present several hours after the procedure and are frequently due to hydrophilic wire perforation of a small vessel. Treatment usually requires prolonged balloon inflation (consider a perfusion balloon) and reversal of anticoagulation. Transthoracic echocardiography should be immediately performed in the setting of clinical instability in order to evaluate for the presence of a pericardial effusion and/or tamponade, in which case urgent pericardiocentesis is required. Covered stents, coils, or surgical repair may be required for definitive management.

E. **Vascular access site complications** remain the most common complication of PCI and occur in up to 5% of patients. The most common are blood transfusion (3%), arteriovenous fistula (< 2%), pseudoaneurysm (up to 5%), acute arterial occlusion (< 1%), and infections (< 0.1%). Shorter anticoagulation regimens, weight-adjusted heparin, use of bivalirudin, early sheath removal, vigilant monitoring of activated clotting times (ACTs), smaller sheaths, and avoidance of routine venous sheath insertion have all contributed to a reduction in complications. Stopping heparin after PCI and substituting clopidogrel for warfarin has also resulted in a reduction of bleeding and coronary complications.

F. **Contrast-induced nephropathy** occurs in 3% to 7% of patients, and the risk increases tenfold for patients with serum creatinine > 2.0 mg/dL, especially in the presence of diabetes mellitus. Data regarding methods to prevent renal failure are not definitive, but the most proven benefit is seen with conservative contrast utilization. In addition, use of biplane imaging can significantly reduce the amount of contrast required. Numerous studies have provided mixed results on the benefits of saline infusion before catheterization, administration of *N*-acetylcysteine (NAC) 600 mg po or IV bid for 1 day before and after the day of catheterization, single bolus dose

NAC prior to contrast load, using nonionic contrast dye, and infusion of a sodium bicarbonate solution.

G. Contrast-mediated reactions can be serious. Anaphylactoid reactions occur in 1% to 2% of patients receiving iodinated contrast. These reactions can be severe in 0.10% to 0.23% of patients. The risk of a severe reaction can be effectively decreased by using nonionic contrast, preprocedural corticosteroids (i.e., prednisone 40 to 60 mg) given the evening before and the morning of the procedure, and the use of H_1 and H_2 blockers. If a patients presents for emergent PCI (i.e., STEMI) without having undergone preprocedural steroid preparation, the emergent administration of hydrocortisone 100 mg IV and diphenhydramine 25 to 50 mg IV is reasonable and is shown to be safe in small series. In patients undergoing an elective procedure, caution is prudent and a full premedication regimen is recommended.

H. Stent thrombosis (ST) is discussed later in Section **XI.D**.

VII. EXPERIENCED OPERATORS/CENTERS

A. Procedural volume is an important predictor of PCI complications. **Elective PCI** should be performed in high-volume centers (> 200 interventions per year, with an ideal minimum of > 400 cases per year) by operators with an acceptable annual volume (> 75 cases per year) at institutions with fully equipped interventional laboratories, experienced support staff, and an on-site cardiovascular surgical program. **Primary PCI for STEMI** should be performed in similarly experienced/skilled centers by operators who perform > 75 elective cases per year and intervene on at least 11 cases of STEMI per year. **Elective PCI should not be** performed by low-volume operators (< 75 cases per year) in low-volume centers (< 200 cases per year), regardless of the availability of on-site cardiothoracic surgery, because of the increased risk of suboptimal outcomes. Referral to a larger regional center is recommended in this situation.

B. In cases of STEMI, there is an inverse relationship between the number of primary angioplasty procedures performed by an operator and in-hospital mortality. The data suggest that both door-to-balloon time and in-hospital mortality are significantly lower in institutions that perform a minimum of 36 primary angioplasty procedures per year.

VIII. SURGICAL BACKUP.

Emergency surgical intervention is a rare event and is required in 0.3% to 1.0% of cases of PCI, usually because of complications that cannot be addressed percutaneously or to provide urgent hemodynamic support. The most common reasons for emergency CABG surgery are dissection resulting in acute vessel closure, perforation, inability to retrieve a stent or other device, or aortic dissection. Emergency CABG after PCI has a mortality rate of 15% and periprocedural MI rate of 12%. The internal mammary artery may not be harvested, and surgery should not be delayed due to abciximab. Perfusion balloons may temporize a life-threatening perforation or dissection, and an intraaortic balloon pump (IABP) can minimize ischemic injury and stabilize hemodynamics. Data from the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) and Primary Angioplasty in Acute Myocardial Infarction with No Surgery On-Site (PAMI-No SOS) trials suggest that **primary PCI for STEMI** can be safely and effectively performed in centers that **do not** perform elective PCI and do not have on-site cardiac surgery capabilities if they implement a carefully developed and proven strategy capable of rapid and effective PCI (including an experienced operator with > 75 total PCIs and at least 11 primary PCIs for STEMI per year) with a predetermined transfer plan to a nearby center with on-site surgical backup.

IX. SHEATHS, GUIDES, AND WIRES

A. Typical arterial access involves placing a 6F to 8F short sheath in the common femoral artery using the modified Seldinger technique. Using fluoroscopic guidance when entering the femoral artery above the inferior margin of the femoral head but below the pelvic rim increases the likelihood of entering the common femoral artery

at a compressible site above the common femoral artery bifurcation and below the inferior epigastric artery. The superficial/profunda femoral artery bifurcation is best seen in the ipsilateral 30° to 40° projection. The brachial and radial arteries can accommodate up to 7F and 6F sheaths, respectively. Ulnar artery and digital arch patency should be confirmed via the Allen test in case the radial artery becomes occluded (approximately 5%). Radial access improves hemostasis and earlier ambulation but increases radiation exposure, lengthens the procedure, and limits the choice of coronary equipment (6F compatible).

B. Larger guide size (7F or 8F) provides extra support and permits the use of larger rotational atherectomy burrs and use of kissing balloons. For straightforward lesions, a 6F system is typically adequate. The XB (extra backup) and Amplatz guiding catheters provide good support; the Amplatz guide is especially effective in cases of an acutely angled left circumflex artery, anomalous left circumflex artery originating from the right sinus, very anteriorly originating right coronary artery, or a tortuous/calcified right coronary artery. The Amplatz guide catheter is also the most likely catheter to traumatize the ostial/proximal coronary artery in inexperienced hands due to its tendency to deeply engage the vessel.

C. The coronary lesion is initially crossed with a 0.014" diameter coronary wire, which serves as a "rail" for devices such as balloons and stents. The choice of a wire depends on the wire tip's stiffness, lubriciousness, and support characteristics. Stiff tips are helpful to penetrate chronic total occlusions but increase the risk of vessel dissection or perforation. Hydrophilic wires are quite slippery and may be used to cross tortuous high-grade lesions, but can easily cause dissection or end-vessel perforation. Support wires also typically have stiffer tips and are primarily used as a supportive rail to deliver coronary equipment through tortuous vessels. Generally, most operators routinely use a "workhorse" wire (i.e., Prowater or Balance MiddleWeight) and have "favorite" stiff (e.g., Miracle Bros series), hydrophilic (e.g., Whisper and Pilot series), and support (e.g., GrandSlam and Balance HeavyWeight) wires for use in appropriate situations. Both short (approximately 180 cm) and long (approximately 300 cm) wires are available. Most operators prefer the routine use of a rapid exchange (Rx) system, which uses a monorail that permits easy exchange over a short wire, although situations that require an over-the-wire system may be better served with the use of a longer wire to avoid dislodging the wire during equipment exchanges.

X. DIAGNOSTIC ADJUNCTS

A. IVUS (anatomic)

1. An IVUS catheter generates a cross-sectional tomographic image of both the lumen and the vessel wall. This complementary imaging modality can be invaluable when repeated angiographic views fail to determine the mechanism and/or significance of a coronary lesion. IVUS has proven helpful in assessing adequacy of coronary stent deployment, mechanism of ISR (neointimal hyperplasia versus inadequate stent expansion), a coronary lesion at a location difficult to image by angiography, a suboptimal angiographic result after PCI, coronary allograft vasculopathy after cardiac transplantation, coronary calcium when considering rotational atherectomy, and plaque location/circumferential distribution to guide directional coronary atherectomy (DCA). Further, IVUS can be indispensible in assessing the appropriate vessel size, especially during ACS when factors such as thrombus and vasoconstrictive substances can lead to significant stent undersizing.
2. IVUS provides anatomic, not physiologic, information. However, a lumen area < 4.0 mm^2 in the proximal LAD, left circumflex, or right coronary artery or < 6.0 to 7.0 mm^2 in the left main trunk suggests the presence of a hemodynamically significant lesion.

B. Optical coherence tomography (OCT). Similar to IVUS, OCT images are obtained by passing the catheter over a guidewire in the coronary artery. The catheter

acquires images during an automated pullback over 5.6 cm and requires the clearance of blood in the vessel, thereby necessitating a 15 to 18 cc contrast injection with each acquisition. In comparison with IVUS, it provides much greater image resolution but a more shallow penetration. Outside of research use, OCT is finding a place in the clinical armamentarium. The superior image quality allows an evaluation of stent apposition, poststent dissection, and analysis of plaque characteristics and plaque rupture. Recently, investigators have used OCT to evaluate endothelial stent coverage, which in the future may allow a further tailoring of antiplatelet therapy at the patient-specific level. Currently, there is a paucity of clinical outcomes data using OCT, but interest in this imaging modality is gaining momentum, with supportive data likely to follow.

C. Angioscopy (anatomic). Angioscopy uses a balloon-tipped catheter with a fiber optic viewport at the distal tip that allows direct visualization of the lumen. Angioscopically evident thrombus has been shown to be angiographically silent in up to 50% of patients. This imaging modality is only used for research purposes.

D. Coronary flow reserve (CFR) (physiologic)

1. A 0.014" wire capable of measuring coronary flow velocity permits assessment of epicardial and microvascular resistance. This information is helpful in determining whether a moderate-grade coronary stenosis (i.e., 30% to 70% stenosis) is hemodynamically significant. The ratio of hyperemic to basal flow is known as the CFR and is determined by giving an intracoronary vasodilator such as adenosine (36 to 64 μg). A normal CFR is 3 to 5. A CFR < 2.0 is abnormal and is consistent with a flow-limiting epicardial stenosis or increased microvascular tone.
2. The effect of the microvasculature can be eliminated by measuring the CFR in two vessels: the lesion-containing vessel and a normal-appearing vessel. This allows calculation of the relative coronary flow reserve velocity ($rCFR = CFR_{target}/CFR_{reference}$). A nonhemodynamically significant stenosis has an rCFR value of < 0.8 and is similar in prognostic value to negative stress testing. Unlike fractional flow reserve (FFR), CFR depends on hemodynamic and microcirculatory changes. In general, FFR is the preferred diagnostic modality for assessing the hemodynamic significance of a coronary lesion.

E. FFR (physiologic). A 0.014" wire with a pressure transducer is placed distal to a coronary stenosis and the translesional gradient measured. This allows calculation of the FFR, which is the ratio of this distal coronary pressure to aortic pressure during maximal hyperemia. A vasodilator such as adenosine (IV infusion 140 μg/kg/min or intracoronary 36 to 64 μg) is used. A coronary artery without flow-limiting coronary obstruction would have an FFR of 1.0. An FFR value of < 0.75 to 0.80 is consistent with a hemodynamically significant obstruction and positively correlates with myocardial ischemia on stress testing. Unlike CFR, the FFR reflects only the epicardial artery lesion. Prospective studies have demonstrated that an FFR-guided strategy to direct PCI of intermediate lesions results in less stents deployed, with a significant decrease in morbidity and mortality compared with an angiography-only strategy (8.4% vs. 23.9%, $p = 0.02$).

F. Pulmonary artery catheter (physiologic). A balloon-tipped Swan-Ganz catheter advanced to the pulmonary arteries allows measurement of right and left heart filling pressures as well as the cardiac output. This information can be helpful in patients presenting with cardiogenic shock, during high-risk PCI in the setting of severe left ventricular (LV) dysfunction, when there is a question of pericardial tamponade, or when the cause of hemodynamic deterioration is unclear.

XI. THERAPEUTIC DEVICES

A. Percutaneous transluminal coronary angioplasty. The coronary balloon remains the backbone of endovascular intervention, although its sole use is in decline. The initial gain in the coronary lumen achieved by balloon inflation results in localized dissection of the intima (and often the media) plus distension of the adventitia. The

dissection is covered by platelet-rich thrombus and later by new intimal layers. As a result of these inevitable dissections, the abrupt closure rate is 4% to 7%, although the use of GP IIb/IIIa inhibitors has reduced this rate. The 6-month angiographic restenosis rate of 30% to 40% is another downside to PTCA. Furthermore, the risk of cardiac morbidity, including anginal symptoms, progressively increases with subsequent episodes of ISR following balloon angioplasty. It is recommended that patients determined to have significant ISR following PTCA should be strongly considered for coronary stent implantation.

PTCA alone may still have utility in patients presenting with ACS found to have multivessel disease suitable for urgent/emergent CABG (e.g., PTCA alone rapidly restores patency to the infarct-related artery but may allow a break in the need for antiplatelet therapy, thereby allowing the patient to proceed to surgery without delay). Even in these situations, however, aspiration thrombectomy alone may be preferred if it provides reasonable flow to the infarct artery in order to avoid the risk of mechanical complications with PTCA, such as dissection or perforation, that would require stent deployment.

B. Bare-metal stents (BMSs)

1. Present-day coronary stents are flexible, laser-cut and polished, balloon-mounted, and expandable, slotted tubes composed of either stainless steel or metal composites such as cobalt–chromium. They have proven effective in treating dissections and reducing the incidence of abrupt closure, emergency CABG (< 1%), and restenosis. First implanted in 1986 and used for emergency treatment of coronary dissection after angioplasty, the early era of the intracoronary stent placement was plagued by high rates of subacute closure despite intensive anticoagulation regimens that often led to bleeding complications and prolonged hospitalization. Evolution of stent design and interventional technique led to a rapid reduction in procedural complication rates and marked improvement in the ease of stent delivery and deployment.
2. Although subacute vessel closure may still occur in up to 3% of cases following stent implantation, by providing a scaffold and reducing elastic recoil, BMSs have reduced the published rates of restenosis from > 50% following PTCA alone to 20% to 30%. **Restenosis risk is increased in patients with small reference vessel size, smaller postprocedural luminal diameter, or high degree of residual stenosis, long lesion length, diabetes, lesion location in the LAD artery, and presence of untreated edge dissection during the procedure**. Furthermore, while stents reduce the rate of restenosis and repeat revascularization as compared with PTCA alone, they have not been shown to reduce the incidence of death or MI.

C. Drug-eluting stents (DESs). The Achilles heel of BMS has been ISR. Antiproliferative agents such as sirolimus, paclitaxel, zotarolimus, and everolimus arrest cell division during the mitotic growth phase. The use of polymers to coat these agents onto a stent's surface and provide controlled, local drug delivery has dramatically reduced neointimal hyperplasia and thereby ISR. These DESs, introduced generally in 2003, were rapidly embraced and occupied almost 90% of the stent market by 2005. Concerns about ST and the need for prolonged DAT (discussed below) have since tempered their use, and DESs now account for approximately two-thirds of stents that are deployed. There are a number of DESs available, with various studies supporting their clinical use. While a thorough discussion of trial data is outside the scope of this chapter, a brief overview is summarized below.

1. **Cypher (Cordis, NJ) sirolimus-eluting stent (SES).** The Cypher DES makes use of the BxVelocity stainless steel platform. The pivotal Randomized Study with the Sirolimus-Coated Bx Velocity (RAVEL) trial randomized 238 patients with simple lesions to SES versus a standard BMS. At 1 year, the angiographic restenosis rate (> 50%) was 0% in the SES group and 26.6% in the BMS group. Five-year follow-up of the US-approved SIRIUS trial of patients with complex coronary disease revealed durable reductions in target lesion revascularization

(TLR) compared with BMS (9.6% vs. 24.7%), with negligible differences in death and MI. A number of trials and meta-analyses have highlighted the benefits of SES, and it remains in use today. Given its stainless steel platform, this stent is often used in heavily calcified lesions or those that require high radial strength. Unfortunately, Johnson & Johnson has announced plans to discontinue production.

2. **Taxus (Boston Scientific, MA) paclitaxel-eluting stent (PES).** The Taxus DES was initially supported by the Express platform and more recently by the thinner Liberte stainless steel BMS platform. The PES was developed almost simultaneous to the SES and first studied in the TAXUS I trial in a group of patients with simple lesions; at 6 months, the PES group displayed no significant angiographic restenosis. The TAXUS IV trial compared 1,314 patients with complex native vessel coronary disease randomized to either PES or BMS and demonstrated significant reduction in TLR (9.1% vs. 20.5%) with PES at 5-year follow-up, with negligible differences in death and MI.
3. **SES versus PES.** A number of studies, some of which have been randomized, have compared SES and PES in various patient groups. Most of these trials have found that SES is superior to PES. The SIRTAX trial randomly assigned 1,012 patients presenting to the catheterization laboratory to either SES or PES and demonstrated a significant reduction (10.8% vs. 6.2%) in the rate of MACE, primarily due to reduction in the rate of TLR observed in the SES group. Similarly, in a meta-analysis of almost 9,000 patients, SES was associated with less TLR (hazard ratio [HR] 0.74) and ST (HR 0.66) than PES, with no significant difference in death or MI, at 2 years of follow-up. There is a suggestion that PES performs better in patients with diabetes, although comparisons of SES and PES even in this subgroup yield lower rates of TLR with SES use.
4. **Endeavor, Resolute, and Resolute Integrity (Medtronic) zotarolimus-eluting stents (ZES).** The Endeavor DES elutes zotarolimus from a cobalt–chromium Driver stent platform. The ENDEAVOR series of trials (I to IV) have demonstrated the effectiveness of ZES in comparison with BMS, SES, and PES. Five-year follow-up of the patients randomized in ENDEAVOR II showed a significantly lower rate of TLR for ZES versus BMS (7.5% vs. 16.3%) and equivalent rates of very late ST (0.2% vs. 0.3%). The ENDEAVOR III trial was a small study of patients randomized to ZES ($n = 323$) or SES ($n = 113$) and showed significantly higher rates of total TLR (clinically and nonclinically driven, 9.8% vs. 3.5%) but nonsignificant differences in clinically driven TLR (6.3% vs. 3.5%, $p = 0.34$) for the ZES at 8 months. The ENDEAVOR IV investigators randomized 1,548 patients to ZES or PES and found a nonsignificant trend toward higher rates of angiographic late loss at 9 months (15.3% vs. 10.4%, $p = 0.284$) and TLR at 12 months (4.5% vs. 3.2%, $p = 0.228$) in the ZES group. The large-scale Patient Related Outcomes with Endeavor versus Cypher Stenting Trial (PROTECT) is currently underway. The Resolute stent makes use of the Driver platform with a newly designed polymer that allows a delayed release of the drug for out to 3 months. The RESOLUTE US trial revealed noninferiority of the Resolute in comparison with historical Endeavor controls at 1 year. The RESOLUTE AC trial revealed no significant differences in patient- or stent-related outcomes in comparison with the Xience V at 2 years, although one cause for concern is the trend toward greater ST with the Resolute (1.9% vs. 1.0%, $p = 0.077$). The Resolute Integrity stent, available only in Europe at this time, elutes zotarolimus from Medtronic's Integrity stent platform and prides itself on improved deliverability; studies are currently underway.
5. **Xience V (Abbott Vascular, CA) and Promus (Boston Scientific, MA) everolimus-eluting stent (EES).** Sold as Xience V and Promus, the EES is based on the cobalt–chromium MultiLink Vision stent platform. The SPIRIT series of trials (I to V) have demonstrated the efficacy of the Xience V EES in comparison with

the Taxus PES. The large-scale SPIRIT IV trial was powered to assess superiority of EES over PES. Recently reported 2-year follow-up revealed significantly reduced rates of target lesion failure (TLF; cardiac death, target vessel MI, ischemia-driven TLR) (6.9% vs. 9.9%), ischemia-driven TLR (4.5% vs. 6.9%), MI (2.5% vs. 3.9%), and ST (0.4% vs. 1.2%) for EES. Notably, in the diabetic subgroup at 1 year, there was no appreciable difference in TLF (6.4% vs. 6.9%). The SPIRIT V trial of EES versus PES in diabetic patients, however, suggests a benefit of EES in this group of patients (in-stent late loss at 9 months 0.19 vs. 0.39 mm, $p < 0.01$; TLF at 12 months 11.2% vs. 12.5%, $p = 0.71$; and ST 0% vs. 1.9%). Notably, though, this was a small trial (EES $n = 218$, PES $n = 106$).

6. **Large vessels.** Retrospective subgroup analysis had suggested that large vessel DES (SES and PES) provided no significant reduction in TLR compared with BMS but did result in increased rates of ST. To address this question prospectively, the BASKET-PROVE investigators randomized patients to the use of BMS, SES, or EES in lesions requiring stents 3.0 to 4.0 mm in diameter. They found statistically similar rates of death/MI with both DES and BMS, but a decrease in target vessel revascularization (TVR) with either type of DES compared with BMS at 2 years (~3.5% vs. ~9.0%). Furthermore, definite or probable ST was not significantly different between the SES, EES, and BMS groups. These data suggest that while the rate of BMS ISR in large vessels is lower than that in smaller vessels, the benefit of DES persists to further lower the rate of restenosis without a concomitant increase in the risk of ST (as long as DAT can be continued).

D. Stent thrombosis is defined as early (< 30 days), late (30 days to 1 year), and very late (> 1 year). It may be the result of stent-, procedure-, patient-, and antiplatelet therapy–related factors, and minimizing the risk of ST requires a conscious consideration of each of these issues. Compared with thrombosis of native coronary arteries, ST is associated with a higher thrombus burden and less frequent procedural success, all of which results in a much higher rate of death, recurrent MI, and recurrent ST.

1. **Stent-related factors.** Following BMS implantation, the vascular endothelium typically grows over the stent struts in 2 to 4 weeks, thereby eliminating contact between the stent and circulating platelets with a concomitant reduction in thrombotic risk. In contrast, **reendothelialization following DES implantation is significantly retarded** because of the antiproliferative effect of the coating polymer, thereby allowing for strut/platelet contact up to several years post-PCI (similar to the historical use of brachytherapy). In meta-analyses of large trials, the **overall incidence of ST is similar in both BMSs and DESs (0.5% to 1.0% per year). However, prolonged DAT is necessary in patients with DES** due to delayed endothelialization and is therefore associated with a higher risk of very late ST (approximately 0.5% per year) in patients who discontinue DAT than in patients with BMS. It is for this reason that BMS is a favored option in patients requiring PCI before major surgery or those that possess a significant contraindication to long-term antiplatelet therapy. In appropriately selected patients, however, DES is favored for its established benefits with respect to ISR and reduced need for repeat intervention.
2. **Procedure-related factors. Incomplete stent apposition to plaque/vessel wall, inadequate stent expansion (i.e., stent undersizing to the vessel), and stent-edge dissection** all increase the risk of ST. While angiography may indicate all of the above problems, stent sizing is routinely underestimated by the angiogram alone. Further interrogation of the vessel using IVUS or OCT (discussed in Sections **X.A** and **X.B**, respectively) may be necessary to optimize the chances of success and minimize the risk of ST. It is **recommended that stents be expanded to 80% of the minimal reference vessel area**. Additional risk factors for ST include long lesion length, small artery diameter, and complex lesion morphology (i.e., bifurcation stenting and chronic total occlusion).

3. **Patient-related factors.** Comorbid risk factors not only are important in assessing the relative benefit of DES but also increase the risk of ST. For instance, patients with **diabetes, impaired LV function, and renal disease** not only derive greater benefit from the antirestenotic properties of DES but also present a greater risk of ST. **Premature cessation of DAT** (due to nonadherence, need for surgery, bleeding complications, or financial considerations) as well as poor clopidogrel response (seen in up to 15% of patients) also increase the risk of ST, especially in patients treated with DES.
4. **Duration of antiplatelet therapy.** In patients with ACS, the use of 12 months of DAT is recommended for its established benefit in reducing MACE over aspirin alone. With respect to stent safety alone, however, use of 4 to 6 weeks of clopidogrel is sufficient to allow endothelialization of the BMS. For DES, numerous authors have demonstrated that cessation of DAT is a significant predictor of ST, and moreover that DES is associated with a greater risk of very late ST compared with BMS after cessation of DAT. Unfortunately, registry and small randomized trial have not proven an overall clinical benefit to prolonged DAT, although some studies have demonstrated a reduction in very late ST. Large randomized trials are currently underway to investigate the clinical conundrum of DAT duration after DES implantation. The ACC/AHA guidelines therefore recommend a minimum duration of DAT of 12 months (class I), with a consideration of DAT for > 15 months in patients with DES (class IIb).
5. Although DESs have dramatically reduced the incidence of ISR and MACE, especially in patients with diabetes and complex coronary lesions, a mounting body of evidence suggests an increased risk of late and very late thrombosis following the discontinuation of antiplatelet therapies. Therefore, **the decision to use BMS or DES in any given patient requires a thorough evaluation** of factors that may predispose the patient to premature discontinuation of DAT (which would favor BMS). In our laboratory, the use of BMS and DES is roughly equivalent.

E. Covered stents. Covered stents use a material such as polytetrafluoroethylene (PTFE), which covers the stent struts and seals off the vessel wall from the stent lumen. The Jomed covered stent has PTFE sandwiched between two Jostents. This covered stent is approved for use after coronary perforation by the Food and Drug Administration (FDA), but requires reporting of their use in this situation as a sentinel event. FDA approval can also be obtained on a case-by-case basis in patients with coronary aneurysm.

F. Cutting balloon atherectomy

1. These balloons were initially developed to create a "controlled dissection." A cutting balloon has three to four longitudinally mounted, razor-sharp atherotomes. These atherotomes cut into both plaque and vessel wall and allow vessel dilatation at a lower balloon pressure. Success in the treatment of balloon-resistant lesions led to FDA approval in 1995. Although randomized data have shown no difference between cutting balloon angioplasty and PTCA, many operators will use this device in lesions with high elastic recoil (i.e., ostial or bifurcation lesions) before DES. The AngioSculpt device consists of a balloon surrounded by a nitinol cage that prevents balloon slippage and scores the plaque. An alternative to these specialized balloons is to place a second guidewire as a "buddy" in the coronary artery, which serves as a makeshift cutting device at the lesion during balloon inflation over the first wire.
2. Cutting balloons have also found a niche in the treatment of ISR. Regular balloons often slip when inflated across these rubbery lesions. The Restenosis Reduction by Cutting Balloon angioplasty Evaluation III (REDUCE III) trial randomized 521 patients to cutting balloon or PTCA before stenting (with angiographic or IVUS guidance) and demonstrated a significantly lower rate of angiographic

restenosis in the cutting balloon before stenting group, primarily with IVUS guidance. The "buddy wire" technique may also be useful to increase friction and minimize balloon slippage in the treatment of ISR. It is important to use a second wire that does not have a hydrophilic coating in order to maximize effectiveness.

3. Care must be taken not to oversize cutting balloons, because perforation can occur. Placing these balloons through stent struts or down tortuous vessels can result in atherotome entrapment, as can a perforated balloon. These balloons should only be inflated to 6 to 10 atm in order to decrease the likelihood of balloon rupture.

G. Rotational atherectomy

1. Rotational atherectomy uses a 160,000 rpm, diamond-coated burr (i.e., drill bit) that is advanced over a 0.009" wire to the coronary lesion. The process generates microparticulate debris that embolize and may attenuate the coronary microcirculation, inducing transient myocardial stunning, periprocedural MI, and LV dysfunction in the region of the target vessel. Therefore, although limited clinical data suggest that rotational atherectomy can be safely performed in patients with depressed LV function in the hands of an experienced operator, it is not recommended.
2. Compared with plain balloon angioplasty, rotational atherectomy increases the chance of procedural success but has not been shown to reduce the risk of restenosis or MACEs in de novo or restenotic lesions. Although the use of rotational atherectomy has declined, it is recommended before stenting in patients with severely calcified lesions, undilatable lesions, chronic total occlusions, and bifurcation lesions to help ensure proper stent expansion and apposition in balloon-resistant lesions.
3. Familiarity with the device is essential. Sluggish coronary flow can occur, requiring a vasodilator such as verapamil, nitroprusside, or adenosine. Perforation occurs in approximately 1% of patients, typically when significant tortuosity forces the burr to the outside edge of a curve. Prophylactic pacing or aminophylline is frequently required if rotational atherectomy is performed in the vessel supplying the atrioventricular (AV) node. Rotational atherectomy is typically contraindicated in patients with thrombus, dissection, or severely reduced LV systolic dysfunction. GP IIb/IIIa inhibitors decrease the risk of CK-MB elevation.

H. Directional coronary atherectomy

1. John Simpson developed DCA in the 1980s in response to the high rate of balloon angioplasty complications. DCA uses a sharp blade that repeatedly shaves off eccentric plaque and requires an IVUS to ensure adequate debulking. This revascularization technique is effective in treating fibrotic, noncalcified, ostial, bifurcation, branch ostial, or bulky eccentric lesions in large proximal vessels (> 3 mm) and requires an experienced operator for safe and effective use.

   Despite multiple randomized prospective trials, optimal DCA has never been shown to have lower rates of TVR when compared with plain balloon angioplasty or stenting. As a result, DCA has little role in present-day interventional cardiology, although some cardiologists continue to use it for debulking bifurcation lesions and other eccentric, noncalcified, nonthrombotic lesions.

I. Excimer laser

1. The excimer (*excit*ed and di*mer*) laser catheter (excimer laser coronary atherectomy, ELCA) tip is brought into contact with the target lesion. It creates ultraviolet light (308 nm) at a rate of 25 to 40 pulses/s from a high-energy, metastable, dimeric molecule of xenon and chloride. This provides 45 mJ/mm^2, which can ablate 0.5 mm of tissue per second, and reduces the target tissue to gas and subcellular debris. The size of the lumen created is equivalent to that of the catheter (0.9 mm diameter).
2. The ELCA was approved by the FDA in 1992 for total occlusions, moderately calcified stenoses, balloon crossing/dilatation failures, ostial lesions, bypass grafts, and long diffuse disease. It is contraindicated in angulated lesions, coronary dissection, thrombotic lesions, and severely calcified lesions. However, long-term clinical data

have failed to demonstrate a significant restenosis benefit, and routine use increases the complication rate in comparison with plain balloon angioplasty. Therefore, the ACC/AHA PCI guidelines do not suggest use of ELCA as a primary strategy for revascularization and is used quite infrequently in the present day.

J. Thrombectomy

1. **Aspiration thrombectomy.** The use of a catheter to aspirate thrombus from the infarct artery is intuitively attractive and carries a class IIa indication in the ACC/AHA guideline management of STEMI. The Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) randomized 1,071 patients with STEMI to PCI with or without preparatory thrombus aspiration (TA) using the Export catheter. The primary end point of myocardial blush grade after intervention was higher with TA, along with less persistent ST-segment elevation, more ST-segment elevation resolution, and fewer pathological Q waves, along with a trend toward less death at 30 days ($p = 0.07$). Although clinical end points were not statistically different at 30 days, 1-year follow-up revealed significant reductions in all-cause mortality (4.7% vs. 7.6%, $p = 0.04$), cardiac death (3.6% vs. 6.7%, $p = 0.02$), and reinfarction (2.2% vs. 4.3%, $p = 0.05$) favoring TA. Similarly, a recent meta-analysis by Bavry and colleagues revealed a substantially lower mortality in patients assigned to receive aspiration thrombectomy (2.7% vs. 4.4%, $p = 0.018$) prior to PCI in STEMI. Currently, the most widely used aspiration catheters include the Pronto LP, Pronto V4, Export, and Extract (from smallest to largest lumen size; all these are compatible with a 6F system except the Extract which requires 7F).
2. **Rheolytic thrombectomy.** The Possis AngioJet is the dominant rheolytic thrombectomy device. The device is a 5F double-lumen, flexible catheter that contains a hypotube through which six high-speed saline jets create a low-pressure area at the tip (approximately –760 mm Hg), which serve to macerate and aspirate the thrombus back into the catheter lumen in accordance with the Venturi-Bernoulli principle. This catheter has proven to be successful in thrombotic vein grafts, for which it received FDA approval in 1998. Temporary prophylactic pacing is recommended when treating vessels supplying the inferior wall, because of temporary AV block. Temporary ST-segment elevation is frequent. Perforation can occur in vessels < 2.0 mm in diameter due to the high-pressure saline injection. Although small studies using the AngioJet in the setting of ACS have been encouraging, prospective randomized data demonstrating a clinical benefit have been lacking. The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AiMI) trial randomized patients with acute MI to AngioJet thrombectomy followed by PCI or PCI alone and concluded that mortality rates (4.6% vs. 0.8%, $p < 0.02$), infarct size (12.5 ± 12.1% vs. 9.8 ± 10.9%, $p = 0.02$), and MACE rates (6.7% vs. 1.7%, $p < 0.01$) were considerably **higher** in those undergoing thrombectomy. While not used in the routine care of patients, the AngioJet still holds a place in the interventional armamentarium for patients with overwhelming clot burden that is not adequately addressed by aggressive aspiration thrombectomy alone.

K. PercuSurge GuardWire

1. Atheromatous embolization is a frequent and dreaded complication of degenerated saphenous vein graft (SVG) intervention. The first distal emboli protection device approved by the FDA was the PercuSurge GuardWire and Export catheter. The PercuSurge GuardWire is a 0.014" hypotube (i.e., hollow tube) with a balloon mounted on the distal end near the fixed floppy wire. The deflated balloon is steered across the SVG lesion and inflated in a distal portion of the graft. This results in cessation of blood flow in the SVG. Angioplasty and stenting are then performed, followed by removal of the column of blood with the Export catheter and then deflation of the occlusive balloon.

2. In the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial, the use of the PercuSurge GuardWire resulted in the recovery of atheromatous debris (83 to 204 μm) in 93% of cases and a 42% reduction in MACE (i.e., death or MI). There was also a lower incidence of periprocedural slow flow.
3. Randomized data have failed to demonstrate the benefit of using the PercuSurge GuardWire in the setting of STEMI. The Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial found no benefit to using the PercuSurge GuardWire in regard to angiographically assessed myocardial reperfusion, ST-segment elevation resolution, or infarct size at 30 days.

L. Filters. Collapsible microporous polyurethane net attached to a nitinol ring anchored distally to a 0.014″ guidewire that can be advanced across high-risk SVG or carotid stenoses and then deployed downstream of the lesion. When deployed, these porous devices appear as a windsock or umbrella and allow blood to flow through while filtering any debris larger than 80 to 100 μm. Advantages are ease of use and avoidance of prolonged ischemia. Potential disadvantages are incomplete sealing, passage of smaller particles through the filter pores, overloading of the device, and spillage during device retrieval. The FilterWire EX Randomized Evaluation (FIRE) trial prospectively randomized 650 patients undergoing PCI of diseased SVGs to either the EPI FilterWire EX or the PercuSurge GuardWire embolic protection device and revealed equal efficacy of both types of devices in regard to the primary end point of death, periprocedural MI, or TLR at 30 days. This trial led to FDA approval of the FilterWire EX for use in degenerated SVGs.

XII. SVG INTERVENTIONS

A. Saphenous vein bypass grafts are frequently used in CABG surgery. However, 7% occlude the first week, 15% to 20% occlude the first year, and by the tenth year 50% of SVGs are occluded and 25% are severely degenerated. Redo CABG is high-risk surgery with high rates of morbidity and mortality that approach 7% to 10% nationally. At the Cleveland Clinic, the rate is 1.8%. A patient with a patent internal mammary artery graft to the LAD artery makes redo surgery less appealing. Patients with no arterial conduit, multiple failed SVGs, multivessel disease, and depressed LV systolic function are ideal candidates for redo surgery.

B. Early postoperative ischemia within the first 30 days usually reflects graft failure (often secondary to thrombosis) or incomplete revascularization, and urgent coronary angiography is indicated. Emergency PCI of the graft, even across suture lines, has been safely performed within days of surgery. Intracoronary thrombolysis should be used with caution. Mechanical thrombectomy is a safer choice. Given that SVG flow is pressure dependent, IABP use should be strongly considered in patients that present with hypotension or depressed LV function.

C. Recurrent ischemia 1 to 12 months after CABG surgery usually reflects perianastomotic graft stenosis. Distal anastomotic stenoses respond well to balloon inflation only. Midshaft vein graft stenoses are usually due to intimal hyperplasia.

D. Recurrent ischemia > 1 year after CABG surgery usually reflects the development of atherosclerosis. SVGs have greater plaque burden than native coronary arteries, and aspirates are composed of atherosclerotic rather than thrombotic elements. This may explain the lack of benefit seen with GP IIb/IIIa inhibitors. Unprotected PCI (i.e., no PercuSurge GuardWire or filter device) results in varying degrees of atheroembolization, with 15% of patients having a CK-MB more than five times normal. Therefore, use of distal protection devices during SVG interventions is strongly encouraged when technically feasible. The use of these devices is discussed above in Section **XI**. In situations of poor reflow after SVG PCI, copious administration of intracoronary adenosine and/or nitroprusside is recommended, with the goal of improving microvascular flow. It should also be noted that poor reflow may be seen due to a plaque-burdened filter, which should resolve with filter retrieval.

XIII. RESTENOSIS

A. Restenosis is the most commonly occurring late PTCA complication and typically occurs within 6 months due primarily to vessel contracture, elastic recoil, negative vessel remodeling, and neointimal hyperplasia. **ISR is almost entirely due to neointimal hyperplasia**. Not surprisingly, focal restenosis has a better outcome and response to treatment than does diffuse restenosis. **The predictors of restenosis include diabetes, unstable angina, acute MI, prior restenosis, small vessel diameter, total occlusion, long lesion length, SVG, proximal LAD artery, higher percent stenosis after the procedure, and smaller minimal luminal diameter after the procedure**. Strategies to decrease restenosis include maximizing stent expansion (i.e., bigger is better) and minimizing the distance of arterial injury.

B. Post-PTCA. Balloon angioplasty alone has a 6-month restenosis rate of 32% to 40%. For restenotic lesions managed with PTCA, the restenosis rate is comparable to de novo lesions. For a third episode of restenosis, PTCA has a restenosis rate approaching 50% (not 100%). With PTCA alone, late patency is 93% after three procedures. Only 1.6% of lesions require four or more procedures. Atheroablative approaches, such as excimer laser and rotational atherectomy, have not proven superior for managing restenosis. However, stents are superior to PTCA, with a 6-month TVR rate of 10% versus 32%.

C. In-stent restenosis. The risk of recurrent ISR after balloon angioplasty is 10% for focal ISR, 50% for diffuse restenosis, and 80% for total stent occlusion. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.

1. ISR occurs in 17% to 32% of patients treated with BMS depending upon such variables as vessel size, lesion length, diabetes mellitus, smaller postprocedure minimal luminal diameter, higher residual percent stenosis, and vessel location. In patients who cannot receive DES but for whom ISR is an issue, consideration may be given to a short course of oral sirolimus therapy. The Oral Rapamycin in ARgentina (ORAR studies I to III) investigators have found substantial reduction in TLR for BMS plus sirolimus (10 mg pre-PCI followed by 3 mg daily for 13 days) in comparison with BMS alone (8.3% vs. 38% at 1-year, $p < 0.001$) and equivalence in TLR compared with DES (8.2% vs. 7.0% at 18 months, $p = 0.84$) (1).
2. The observed rate of ISR is significantly lower with DES. As discussed previously, 5-year follow-up from the SIRIUS trial of Cypher SES yielded a 9.1% rate of TLR, similar to the 9.6% TLR rate at 5 years in the TAXUS IV trial of PES. Follow-up data for the EES (Xience V or Promus) have been published up to 2 years in SPIRIT IV and show an ischemia-driven TLR rate of 4.5%. The Intracoronary Stenting or Angioplasty for Restenosis Reduction—Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial compared SES and PES with balloon angioplasty in 300 patients with ISR following BMS and demonstrated a significant reduction in restenosis at 6-month follow-up in the DES groups as compared with angioplasty alone (8% vs. 33%). A comparison of EES and PES revealed a significant improvement in recurrent TLR with EES (1% vs. 11.5%, $p = 0.0193$) at 1 year, but similar rates of MI, death, and ST. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.

D. Brachytherapy. Brachytherapy damages chromosomes and prevents cell division, thereby inhibiting neointimal hyperplasia. Both beta and gamma brachytherapy catheter-based systems use closed-end lumen catheters that deliver the source and keep it out of contact with the blood, allowing reuse. Both gamma (iridium 192) and beta (phosphorus 32 and strontium 90) brachytherapy result in approximately a 50% reduction in ISR compared with balloon angioplasty alone. It is important to ensure brachytherapy delivery to all balloon-injured segments in the target vessel, or else inadequate radiation to an injured segment can cause neointimal proliferation.

Brachytherapy can only be used once in each vessel, and long-term DAT with aspirin and clopidogrel is essential, given the risk of late in-stent thrombosis. Ultimately, long-term data are disappointing with a high failure rate; brachytherapy has therefore fallen largely out of favor.

XIV. PHARMACOLOGIC ADJUNCTIVE THERAPY

A. Antithrombins. Antithrombins prevent the generation of thrombin and/or inhibit the activity of thrombin. An antithrombin such as unfractionated heparin (UFH), bivalirudin (direct thrombin inhibitor, DTI), or enoxaparin (low-molecular-weight heparin, LMWH) should be used during all coronary interventions to prevent thrombus formation on the equipment. This principle applies even to patients with a high international normalized ratio (INR). The following provides a brief overview of the anticoagulant agents used during PCI. For specific data regarding their use during ACS, please refer to **Chapter 2**.

B. Unfractionated heparin

1. UFH binds and induces a conformational change in antithrombin, converting it to a more efficient inhibitor of circulating thrombin (factor IIa), factor Xa, factor IXa, factor XIIa, and kallikrein. The typical dose is 60 to 100 units/kg bolus if no GP IIb/IIIa inhibitor is given. If a GP IIb/IIIa inhibitor is given, then 50 to 70 units/kg of heparin is infused as a bolus. No maintenance infusion is given. UFH boluses are given to maintain an ACT of 250 to 300 seconds without concomitant GP IIb/IIIa inhibitor and closer to 200 seconds with GP IIb/IIIa inhibitors. Maintenance of appropriate levels of anticoagulation is imperative to safely navigate the path between thrombosis and bleeding complications.
2. In uncomplicated PCI cases, prolonged postprocedural heparin infusions increase bleeding complications and do not lower the likelihood of abrupt vessel closure or the rate of restenosis. The sheath should be removed when the ACT is < 180 seconds.

C. Low-molecular-weight heparin

1. LMWH results in more predictable factor Xa inhibition. LMWHs are increasingly being used in the setting of ACS, as a result of data suggesting a possible reduction in the combination of recurrent angina, MI, and death associated with the use of enoxaparin as compared with UFH (ESSENCE and TIMI IIb trials).
2. If a hospitalized patient has been given subcutaneous enoxaparin, a reasonable strategy is as follows. If PCI is performed within 8 hours of subcutaneous enoxaparin administration, then no additional heparin is required. If PCI is performed within 8 to 12 hours, an additional IV dose of 0.3 mg/kg of enoxaparin should be administered. If PCI is performed > 12 hours after enoxaparin injection, standard doses of UFH can be used.
3. When using LMWH, ACT measurement does not reflect the degree of anticoagulation and there is no rapid method for determining factor Xa activity. This inability to confirm adequate antithrombin activity and assess the level of anticoagulation with a bedside test makes some interventional cardiologists uncomfortable. Significant anti–factor Xa activity persists for about 12 hours. LMWH is only partially reversed with protamine.
4. Dosing LMWH in obese patients provides a much less reliable level of anticoagulation. Extreme caution should be exercised in patients with moderate-to-severe renal insufficiency (i.e., creatinine clearance < 30 mL/min), as the renal elimination of LMWH may result in unexpectedly high degrees of anticoagulation for a prolonged period. In these cases, most interventionalists will use an alternative antithrombotic agent.
5. Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and induces a conformational change that increases its affinity for factor Xa. Fondaparinux has compared favorably with LMWH in both the NSTEMI and

STEMI settings, in large part due to a significant decrease in bleeding complications. However, there is an increased risk of guide-catheter thrombosis, which requires concomitant administration of UFH (OASIS-8).

D. Direct thrombin inhibitors (bivalirudin)

1. The initial DTI was isolated from leech saliva, although now these materials are synthesized using recombinant technology. These agents directly inhibit clot-bound thrombin without requiring an antithrombin cofactor. DTIs are better able to block both fluid-phase and clot-bound thrombin, which may be particularly important in a thrombus' platelet-rich environment.
2. A hirudin analog, bivalirudin, is becoming increasingly more common in catheterization laboratories and is an important anticoagulant for patients undergoing PCI. The REPLACE-2 trial compared bivalirudin with the combination of abciximab/UFH in a prospective, randomized, double-blind fashion and found it to be associated with fewer bleeding-associated complications and a statistically noninferior rate of MACEs. Bivalirudin has also shown similar salutary effects in patients with STEMI (HORIZONS-AMI) and NSTEACS (ACUITY). Please refer to **Chapter 2** for details of bivalirudin use in ACS.
3. Bivalirudin is given as a 1 mg/kg bolus followed by a 4-hour maintenance infusion of 2.5 mg/kg/h and by 0.2 mg/kg/h. A given bivalirudin dose provides a more predictable ACT than does UFH. The half-life is 25 minutes in patients with normal renal function, although in dialysis-dependent patients, the half-life may be as long as 3.5 hours. The maintenance infusion can be discontinued after completion of the coronary intervention. If a vascular closure device is not used, the sheath can typically be removed in 1 to 2 hours, given the drug's short half-life. Unfortunately, the effects of bivalirudin cannot be reversed.

E. Warfarin. Routine warfarin is no longer recommended unless a patient has a mechanical prosthetic valve, atrial fibrillation, or intracardiac thrombus. DAT has proven superior. An INR > 1.6 is a strong relative contraindication to elective cardiac catheterization. If emergent cardiac catheterization is required due to ACS or MI, consider accessing the radial artery because hemostasis is rarely an issue with this approach.

F. Antiplatelet therapy

1. Platelets are essential in thrombus formation, and some form of antiplatelet therapy is typically given at the time of PCI.
2. **Thromboxane A_2 inhibitor (aspirin).** Aspirin impairs platelet aggregation by irreversibly inhibiting platelet cyclooxygenase, thereby limiting thromboxane A_2 production. A loading dose of 325 mg of aspirin should ideally be given at least 2 hours before PCI and be continued at 325 mg daily for at least 1 month following the procedure. In the case of DES, higher-dose aspirin may be continued for longer periods. Secondary prevention trials have shown aspirin to reduce death, MI, and stroke by 27%. In PCI patients, aspirin reduces abrupt vessel closure.
3. **Adenosine diphosphate receptor antagonists (clopidogrel, ticlopidine, and prasugrel)**
   a. Thienopyridines such as clopidogrel and ticlopidine inhibit adenosine diphosphate–induced platelet aggregation by the $P2Y_{12}$ receptor. Clopidogrel is preferred to ticlopidine because of its better safety profile, although both require hepatic metabolism for activation.
   b. Ticlopidine is poorly tolerated with prolonged use, resulting in 20% of patients discontinuing the drug due to nausea, diarrhea, and rash. Neutropenia and thrombotic thrombocytopenic purpura (TTP) occur in 1% to 3% and 0.03% of patients, respectively. The complete blood count should be serially examined in the first several months of use (q2wk × 3 months).
   c. Clopidogrel is better tolerated than ticlopidine and has largely replaced it in clinical practice in the United States. The risk of TTP with clopidogrel is the

same as in the general population (11 in 3 million), and neutropenia is not an issue, making blood count monitoring unnecessary.

d. The ACC/AHA guidelines recommend routine clopidogrel pretreatment with a dose of 600 mg, although this recommendation is made on the basis of studies that included patients with ACS. In patients undergoing elective PCI, a recent study revealed no difference in ischemic or bleeding complications between 300 and 600 mg loading doses. Similarly, in patients on chronic clopidogrel therapy undergoing elective PCI, the ARMYDA-4 RELOAD investigators found no benefit to an additional 600 mg "reloading" dose of clopidogrel; the group of patients with NSTEACS did have a reduction in MACE at 30 days, however.

e. For a discussion of clopidogrel duration after PCI, please refer to Section **XI.D**. For details of clopidogrel use after ACS, please refer to **Chapter 2**.

f. The issue of clopidogrel nonresponsiveness, defined as platelet inhibition < 20%, is reported to be as high as 40% and is associated with worse clinical outcomes including ST, MI, and death. Mechanisms include genetic predisposition (i.e., CYP2C19 polymorphism that affects clopidogrel metabolism and thus activation) and drug–drug interactions (i.e., concomitant proton pump inhibitor use). Unfortunately, recent studies (including OASIS-7 and GRAVITAS) have not shown a benefit to higher maintenance dose clopidogrel (150 vs. 75 mg daily), even in patients with established high platelet reactivity while on clopidogrel. Management of these patients is therefore difficult, but we currently either use double-dose clopidogrel or change to prasugrel in cases of clopidogrel nonresponse.

g. Prasugrel is a novel thienopyridine prodrug that requires conversion to an active metabolite with high affinity for the platelet $P2Y_{12}$ receptor site, resulting in a potent antiplatelet effect. The TRITON-TIMI 38 trial randomized 13,608 patients with moderate-to-high risk ACS with scheduled PCI to either prasugrel or clopidogrel therapy and found a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke associated with prasugrel therapy. Prasugrel was also associated with a reduction in rates of MI, TVR, and ST. However, of some concern was a significant increase in major (HR 1.32, 95% CI 1.03 to 1.68, $p = 0.03$) and life-threatening (1.4% vs. 0.9%, $p = 0.01$) bleeding observed in the prasugrel group.

G. GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban)

1. GP IIb/IIIa receptor inhibition prevents these receptors from binding to fibrin and forming the platelet–fibrin cross-linking that is required for thrombus formation. GP IIb/IIIa receptor occupancy > 80% prevents the development of thrombus.
2. **Abciximab** is a human–murine chimeric antibody fragment that binds the GP IIb/IIIa receptor with high affinity, resulting in a slow dissociation rate (i.e., noncompetitive inhibition). Although abciximab remains detectable on platelets for the lifetime of the platelet, it is rapidly cleared from plasma, allowing platelet aggregation to return to normal in 12 to 36 hours. Rapid reversal of platelet inhibition in the event of bleeding requires discontinuation of the abciximab infusion, waiting 30 minutes for plasma clearance, and platelet infusion (12 units) so as to provide functional platelets. Profound thrombocytopenia occurs in 0.4% to 1.1% of patients. Platelet counts should be measured within the first 2 to 4 hours and the following day. Abciximab readministration has not been associated with hypersensitivity or anaphylaxis, although the risk of profound thrombocytopenia is somewhat higher (2.2%).
3. **Eptifibatide** is a cyclic heptapeptide and **tirofiban** is a tyrosine derivative nonpeptide mimetic. Both act as competitive inhibitors requiring high levels for adequate inhibition. Both have a short plasma half-life (2.0 to 2.5 hours), with platelet aggregation normalizing in 30 minutes to 4 hours. In the event of bleeding, the infusion should be stopped. Unlike abciximab, the effect cannot

be reversed and platelets remain inhibited until plasma drug levels fall. Profound thrombocytopenia is rare (0.0% to 0.3%).

4. The use of GP IIb/IIIa inhibitors versus heparin alone during PCI prevents 65 adverse events per 1,000 treated patients and is arguably beneficial for all types of interventions. These benefits are particularly enhanced for unstable angina, diabetes mellitus, and bail-out stenting. Even in the contemporary era of stents and thienopyridines, a recent meta-analysis has demonstrated the reduction in nonfatal MI compared with heparin alone, although there was an increase in minor bleeding.
5. For specific recommendations regarding the use of GP IIb/IIIa inhibitors during ACS, please refer to **Chapter 2**.

H. Intracoronary vasodilators. PCI can result in no-reflow, which is defined as a reduction in coronary flow without an obstructive lesion. The most probable causes of no-reflow are microvascular spasm and distal embolization. Potent microvascular vasodilators, such as adenosine (36 to 72 μg), nicardipine (100 to 200 μg), nitroprusside (50 to 200 μg), or verapamil (200 μg), often restore normal flow. Nitroglycerin is a logical choice for relieving epicardial spasm but has no effect on the microvasculature. Immediately before SVG intervention, verapamil pretreatment has been shown to prevent no-reflow but has never been shown to reduce the risk of CK-MB elevation.

XV. SUPPORTIVE ADJUNCTIVE THERAPY

A. The use of percutaneous circulatory support during PCI may be necessary during high-risk intervention or in cases of acute MI presenting with cardiogenic shock. A number of devices exist for this application, although the data supporting their use are scant. Nevertheless, each of these may be appropriate on a case-by-case basis based on the physician judgment. This brief overview will address the use of percutaneous support for elective PCI.

B. Intraaortic balloon pump. There is usually a low threshold for prophylactic IABP insertion in high-risk PCI patients (e.g., poor ventricular function, large area of myocardial ischemia, critical left main trunk disease, and cardiogenic shock). While observational studies have suggested a benefit to this strategy, the only randomized trial comparing prophylactic IABP with bail-out IABP for high-risk PCI found no difference in MACE, MI, death, or hospital discharge. The bail-out group did have a higher rate of hypotension and 12% of patients required "rescue" IABP. Because of the inherent risk of complications, such as atheroembolism, distal limb ischemia, infection, and thrombocytopenia, IABP should be reserved for selected patients in whom there is an appropriate risk/benefit ratio.

C. TandemHeart (TH). The TH system is used for percutaneous LV support and consists of an inflow cannula placed from the femoral vein to the left atrium via transseptal puncture (21F) and an arterial outflow cannula placed in the femoral artery and parked in the descending aorta (15 to 17F). The device provides up to 5.0 L/min of cardiac output. Among 33 patients with cardiogenic shock, the majority of whom had undergone PCI for acute MI, randomized to IABP ($n = 14$) versus TH ($n = 19$), there was an improvement with TH with respect to cardiac output, pulmonary capillary wedge pressure, and mean arterial pressure. There was no difference in survival, but the number of patients was relatively small. These findings were subsequently corroborated by the ISAR SHOCK trial of TH versus IABP (increase in cardiac index 0.49 vs. 0.11 L/min/m^2 at 30 min, $p = 0.02$; 30-day mortality in both groups: 46%).

D. Impella 2.5 and 5.0. The Impella device is essentially a pigtail catheter that sits across the aortic valve and draws blood out of the left ventricle and ejects blood into the ascending aorta. The catheter comes in two forms: a 9F device (inserted via a 13F sheath) that supports an output of 2.5 L/min and a 9F system that supports an output of 5.0 L/min. The larger device requires a cut down at the femoral site for placement of the catheter because while the LV portion of the device has a 21F caliber, the shaft is only 9F (so the purse-string suture at the femoral site is cinched around the shaft once the device enters the artery). Registry studies have demonstrated the feasibility

of use of both devices. The PROTECT II randomized trial comparing high-risk PCI (defined as unprotected left main coronary or the last patent conduit and a left ventricular ejection fraction [LVEF] under 35% or three-vessel disease and an LVEF over 30%) supported by prophylactic placement of an Impella 2.5 versus IABP, however, was stopped early due to difficulty in enrolling patients. Of the patients enrolled, there were no significant differences in the two arms at 30 days. The investigators are quick to point out, however, that there were significant differences between the two groups of patients, as the Impella group more often underwent rotational atherectomy and were more likely to have a "complete revascularization" performed.

E. In contrast to the IABP, which requires at least modest LV function, the two percutaneous left ventricular assist devices (pLVAD; TandemHeart and Impella) can provide support to patients with minimal LV function. The pLVAD may thus be well suited to situations where an IABP has been ineffective, or in patients with hemodynamic catastrophe, as opposed to placement as a first-line means of support.

XVI. POST-PCI MANAGEMENT

A. Access site care

1. The groin or arm access site should be examined for hematoma, pseudoaneurysm (systolic bruit), and arteriovenous fistulas (continuous murmur). A pulsatile mass also suggests a pseudoaneurysm. Ultrasound studies can confirm the diagnosis of pseudoaneurysm or arteriovenous fistula. Suprainguinal tenderness, back pain, lower quadrant abdominal pain, or hypotension should make one suspicious for retroperitoneal hemorrhage, which can be confirmed by computed tomography (CT). A hemoglobin level 1 day after PCI should be routine, and a decrease > 2 g/dL is concerning. Distal pulses should be examined as well. Pulselessness, pain, pallor, paresthesias, and a cool extremity suggest an acute arterial occlusion.
2. **Pseudoaneurysms** < 2 cm often close spontaneously; those 2 to 3 cm can often be closed by external, ultrasound-guided compression (90% success rate); and those > 3 cm generally require surgical correction. Another frequently successful option is thrombin injection if the pseudoaneurysm has a thin neck.
3. **Arteriovenous fistulas** are typically small and inconsequential, rarely causing high-output failure. Indications for ultrasound-guided compression (success rate > 80%) or surgical closure include significant shunting, extremity swelling/tenderness, CHF, and deep venous thrombosis.
4. A **retroperitoneal hemorrhage** can be treated by supportive care (i.e., transfusions, close observation, and bed rest) in > 80% of cases. Anticoagulation must be reversed, and frequent hemodynamic monitoring in an experienced intensive care unit is required. If required, transportation to CT scan should be deferred until the patient is hemodynamically stable. If the bleeding does not spontaneously stop, the patient may require vascular surgery consultation. Other options include balloon tamponade or coil embolization if a small side branch is the culprit.
5. **Acute arterial occlusion** may be due to dissection or thromboembolism. Both typically require angiography of the affected extremity with access from another extremity (e.g., with a cold right leg after right femoral artery access, left femoral access should be obtained and an angiogram of the right lower extremity can be performed by crossing over to the right common iliac artery). Dissection typically requires prolonged balloon inflation and possible stenting or surgery. Stenting at the common femoral artery is discouraged, because it is a flexion point and a frequent site of attaching bypass grafts. Thromboembolism can be treated with surgical (Fogarty catheter) or percutaneous mechanical thrombectomy (Possis AngioJet).

B. Monitoring for myocardial ischemia. A 12-lead ECG should be obtained before and after PCI in order to have a baseline. The patient should be monitored on a cardiac ward that has continuous electrocardiographic monitoring and nurses familiar with routine post-PCI care. The creatine kinase (CK) and CK-MB levels should be measured 12 hours after the intervention. A procedural MI is presently

defined as a CK-MB more than three times the normal (assuming a normal baseline CK-MB). Elevated CK, CK-MB, or electrocardiographic abnormalities occur in 5% to 30% of patients. Mechanisms include distal embolization, side branch occlusion, dissection, and spasm. Troponin levels are not routinely measured after PCI.

C. Monitoring for contrast-induced nephropathy. Nonsteroidal anti-inflammatory drugs, cyclosporine, and metformin should be withheld for 24 to 48 hours beforehand and for 48 hours afterward. Postprocedure saline hydration is continued at 75 to 150 mL/h for a total infusion of 1 to 2 L. Renal function (serum creatinine) should be monitored in patients with diabetes and renal dysfunction.

ACKNOWLEDGMENTS: *The authors thank Dr. Matthew Casey Becker and Dr. Kent Dauterman for contributions to earlier editions of this chapter.*

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CHAPTER 66

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Percutaneous Structural Heart Disease Procedures

The last decade witnessed a remarkable rise in the number of novel percutaneous, catheter-based procedures using new concepts and technologies for the treatment of structural heart disease. Most percutaneous therapies have largely evolved from concepts developed by surgeons and often incorporate the lessons learned from established surgical procedures. Currently, percutaneous catheter-based therapy is available for a number of valvular disorders, including aortic stenosis (AS), mitral stenosis (MS), mitral regurgitation (MR), and prosthetic paravalvular leaks (PVLs), as well as other structural cardiac disorders such as hypertrophic obstructive cardiomyopathy (HOCM), patent foramen ovale (PFO), and atrial septal defects (ASDs). While a comprehensive review of structural cardiac interventions is beyond the scope of this chapter, we provide an overview of the major devices and clinical studies that have been performed.

I. PERCUTANEOUS TRANSCATHETER MITRAL VALVE REPAIR (MVRE)

A. Background. MR is one of the most common valvular disorders, encountered in about 7% of the population aged > 75 years. MVRe, when feasible, produces superior outcomes, including lower operative mortality, improved long-term survival, and reduced incidence of endocarditis and thromboembolic complications, compared with mitral valve replacement (MVR). A number of percutaneous MVRe techniques have been developed that are analogous to surgical procedures. Percutaneous mitral annuloplasty leverages the close relationship of the coronary sinus (CS) to the posterior mitral annulus. The **Carillon** (Cardiac Dimensions, Kirkland, WA) device, which has been granted Conformité Européenne (CE Mark) approval, is deployed in the CS and serves to "cinch" the annulus, resulting in improved mitral valve (MV) leaflet coaptation. There are also numerous other devices in various stages of preclinical and clinical development.

The **MitraClip** (Abbott Vascular, Santa Clara, CA) remains the most widely tested system in humans and is currently the only device available (under trial basis) in the United States. A total of more than 4,000 procedures have been performed in the United States (under trial) and Europe (where the device has CE Mark approval). The technique is based loosely on the surgical Alfieri stitch, which brings the anterior and posterior leaflets in close apposition using a suture and creates an anatomic "double-orifice" MV.

B. Procedure. The MitraClip system uses a steerable 22F guide catheter that is introduced through the femoral vein and subsequently advanced to the left atrium via transseptal puncture (Fig. 66.1). Through this guiding catheter, a delivery system containing the V-shaped clip is introduced in the left atrium and positioned with the arms of the clip perpendicular to the MV line of coaptation using transesophageal echocardiography (TEE) guidance. The clip is advanced to the left ventricle in an open position and retracted to grasp the anterior and posterior MV leaflets at the desired location. After confirmation by TEE of clip position, the clip can be locked.

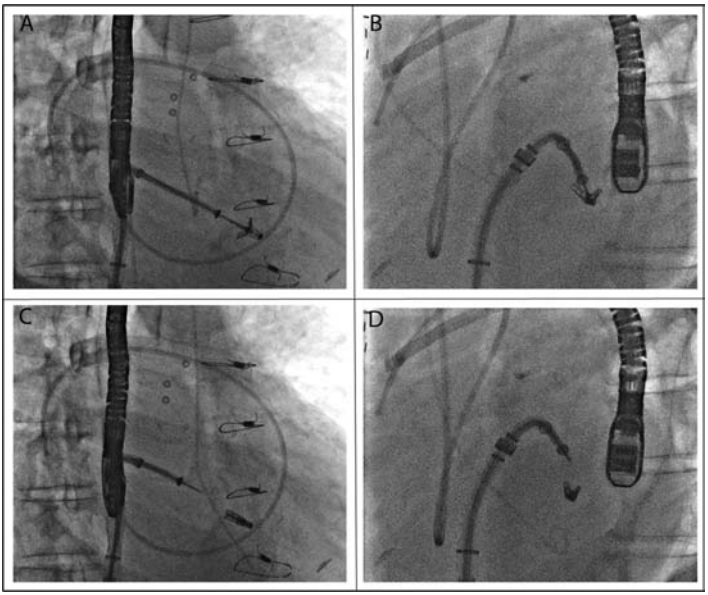

FIGURE 66.1 Percutaneous transcatheter mitral valve repair. Panel A demonstrates the right anterior oblique projection of the optimal positioning of the MitraClip device. Panel B demonstrates the left anterior oblique projection of the optimal positioning of the MitraClip device. Panel C demonstrates the right anterior oblique projection of MitraClip after its release from the delivery catheter. Panel D demonstrates the left anterior oblique projection of MitraClip after its release from the delivery catheter.

If satisfactory (by TEE), the clip can be released; otherwise, it can be reopened and the process repeated. If necessary, multiple clips can be deployed to achieve a satisfactory result. Care must be taken in this situation to not impede forward flow across the valve and trade MR for MS.

C. Complications. Routine complications associated with vascular access like major or minor bleeding are the most commonly encountered complications. Recurrent MR and the requirement for MV surgery are the prime limitations of the current technique, especially in ischemic MR or in the presence of a significant annular calcification. Partial clip detachment is the most important mechanical problem encountered with the procedure. These are generally not symptomatic and are treatable with MV surgery or placement of an additional clip. Iatrogenic MS is a significant complication that may arise as a result of this procedure. Careful echocardiographic evaluation of the MV apparatus is important prior to leaflet plication. A coaptation length of at least 2 mm, a baseline MV area of at least 4 cm^2, and central origin of the regurgitant jet should be ensured prior to the percutaneous repair, to maximize success and avoid complications.

D. Outcomes. The edge-to-edge repair technique was tested in the EVEREST I (Endovascular Valve Edge-to-Edge REpair Study) safety and feasibility trial, which demonstrated a 74% procedural success rate (reduction in MR to ≤ 2+) with a < 1% inpatient mortality rate. Freedom from death, MV surgery, or MR > 2+ was 66% at the end of 1 year. Data from the pivotal EVEREST II trial, which randomized 279 patients to MitraClip versus surgical repair in a 2:1 fashion, demonstrated freedom from the combined end point (death, MV surgery within 90 days, or MR > 2+ at

1 year) of 72.4% and 87.8% in the two groups, respectively, confirming noninferiority of the MitraClip to conventional surgical treatment.

The initial studies of the MitraClip concentrated on patients with degenerative disease. However, the EVEREST II trial and the clinical experience in Europe (where the device enjoys the CE Mark) have shown efficacy in a large number of patients with functional MR as well. Freedom from significant MR was enjoyed by more than 80% of high surgical risk patients, with resultant decreases in left ventricular (LV) volume, NYHA class, congestive heart failure (CHF) hospitalizations, and improved quality of life. Percutaneous MVRe procedures still remain investigational in the United States and in the current iterations available are applicable to patients in whom surgery is of relatively high risk, given the excellent outcomes with surgical MVRe in terms of both freedom from reoperation and significant MR and operative morbidity and mortality.

II. PERCUTANEOUS MITRAL BALLOON VALVULOPLASTY (PMBV)

A. Background. Although there has been a significant reduction in the prevalence of rheumatic heart disease in western countries, it still represents a major public health concern in the developing world. MS is one of the most common presentations of rheumatic heart disease. It continues to represent a major clinical problem in the United States primarily due to outmigration from developing countries or the occurrence of restenosis after previous surgical commissurotomy. Stenosis of the valve may occur due to commissural fusion, leaflet thickening, and/or chordal shortening and fusion.

Before the advent of PMBV, symptomatic MS was treated using surgical commissurotomy. Since the introduction of the percutaneous procedure in the early 1980s by Inoue and colleagues, PBMV has evolved to become the first line of therapy for appropriately selected patients with MS. The technique works similarly to commissurotomy, resulting in opening of the fused commissures.

B. Procedure. The Wilkins splitability score is the most widely used echocardiographic parameter to determine the safety and feasibility of PBMV, and this takes into consideration leaflet mobility, leaflet thickening, subvalvular thickening, and valve calcification (each scored 1 to 4 points). Multiple investigators have shown that patients with a score of 8 or less have the greatest freedom from death and valve surgery and the largest improvement in mitral valve area with PMBV.

Selection of the appropriate balloon size is one of the most important steps for accomplishment of a successful PBMV. A good rule of thumb is to use the following formula to determine the maximum balloon dilation size: Balloon size (mm) = patient height (cm)/10 + 10 mm. Sizing of the balloon with contrast inflation is confirmed ex vivo using a measurement device (provided). We routinely perform the procedure as follows: a 5F arterial access is obtained in order to obtain left ventriculography to understand the position of the MV and commissural anatomy in the fluoroscopic projection. Transseptal puncture is performed (most commonly with TEE guidance) using the standard Brockenbrough needle via a 9F Mullins sheath placed in the femoral vein. Once the sheath has entered the left atrium, it is exchanged for the Inoue balloon catheter.

The balloon catheter is slowly advanced into position in the left ventricle. The Inoue balloon consists of three portions with slightly different compliances. As pressure is added to the balloon, the distal portion inflates first followed by the proximal portion. As soon as the distal portion is inflated, the balloon is pulled until resistance is felt. On addition of more pressure, the proximal portion is inflated, which fixes the valve in the middle waist portion of the valve. The middle waist has the least compliance and dilates only when substantial pressure is added to the balloon, thereby securing the balloon across the valve prior to the dilation of the annulus.

In our institution, we routinely use TEE to guide the valvuloplasty in order to assess the result of balloon inflation (in addition to simultaneous left atrial [LA]–LV

gradient measurement) and, more importantly, to evaluate the degree of MR. Substantial increases in MR should preclude further inflation. In addition, the procedure should be aborted in the presence of left atrial appendage (LAA) clot. Some institutions have gained facility in using intracardiac echocardiography (ICE) in this application.

C. Complications. The most common serious complications include hemopericardium or severe MR. Perforation of cardiac chambers, which occurs with a rate of 0% to 2%, may happen while manipulating the catheters in the heart. While an increase in MR may routinely be noted after the PMBV, it rarely requires a surgical intervention.

D. Outcomes. Immediate postprocedural success with a final valve area > 1.5 cm^2 without moderate or severe MR is the best predictor of long-term outcome. The best results are obtained in young people with favorable anatomic characteristics. Randomized clinical trials have demonstrated that long-term results of PMBV in young patients are as good as open commissurotomy and are better than closed commissurotomy. In patients with optimal morphology, freedom from restenosis has been reported as 92% at 5 years, 85% at 10 years, and 65% at 15 years. Repeat PMBV has been recommended as first-line therapy in patients with symptomatic mitral restenosis after PMBV or commissurotomy in whom the mechanism of restenosis is commissural fusion.

III. BALLOON AORTIC VALVULOPLASTY (BAV)

A. Background. Degenerative or calcific AS is one of the most common valvular disorders encountered in western countries. Surgical aortic valve replacement (SAVR) is the treatment of choice for patients who are safely able to undergo cardiac surgery, and transcatheter aortic valve replacement (TAVR) is emerging as a favorable option in patients at high risk for surgical complications. Balloon dilation of the calcified aortic valve results in stretching of the fused commissures. Due to rapid reversibility of these effects, there is an early loss of effectiveness in severe degenerative AS, and the valve returns to pre-BAV size in 3 to 6 months.

In patients with severe AS who are hemodynamically unstable and for whom urgent aortic valve replacement (AVR) is not feasible, BAV may serve as a "bridge" to valve replacement. Similarly, we have also seen significant functional improvement in patients after BAV so that patients unable to undergo AVR initially have improved to a point that TAVR or SAVR could be performed safely. In patients who require urgent noncardiac surgery, BAV may be considered as a temporizing measure in the hope of reducing the risks of perioperative hemodynamic changes associated with anesthesia.

A number of patients with severe AS have other comorbidities, such as chronic obstructive pulmonary disease or liver or kidney disease, that make it difficult to discern the degree to which AS contributes to their symptoms. In such cases, BAV may provide a therapeutic answer; improvement of symptoms points to AS as the driver of symptoms and may push for a more definitive valve replacement option. Finally, in patients without any option for either TAVR or SAVR, BAV may be considered as a palliative measure.

B. Procedure. The femoral retrograde approach is the most commonly utilized method for BAV, although in patients with severe iliofemoral disease the procedure can be performed in an antegrade fashion via venous access and transseptal puncture. A Swan-Ganz catheter is placed in the pulmonary artery for continuous hemodynamic monitoring and assessment of cardiac output. A temporary pacemaker is placed in the right ventricle to perform rapid pacing (180 beats per minute) during balloon inflation to reduce cardiac output and minimize balloon movement in the annulus. After crossing the aortic valve using a 5F AL-1 diagnostic catheter and a straight wire, a stiffer wire is inserted and positioned in the left ventricle. BAV is typically performed using balloons ranging from 15 to 25 mm in diameter. The balloon is sized based on the annulus diameter on transthoracic echocardiography

(TTE); the maximum balloon size is 10% larger than the annulus, and we routinely begin dilation at smaller sizes and assess the hemodynamic result prior to increasing the balloon size. Procedural success with BAV is typically defined as a 50% reduction in mean aortic valve gradient and a 25% increase in aortic valve area (AVA); most patients usually experience almost a 50% increase in AVA.

C. Complications. It should be noted that BAV carries considerable risk. The 30-day mortality associated with the procedure may be up to 10%, usually due to either aortic regurgitation (as a complication of the balloon procedure) or persistent heart failure. Other complications (occurring in up to 15%) include stroke, peripheral vascular complications (due to the size of the devices used and concomitant incidence of peripheral arterial disease), coronary occlusion, need for permanent pacemaker implantation, cardiac tamponade, and cardiac arrest.

D. Outcomes. Despite a modest improvement in valve area, a significant improvement in the functional status is noted after BAV. However, the benefit of BAV gradually disappears over the course of the next few months. The poor functional status of the patients, as well as only moderate, transient effects of the technique, is primarily responsible for the overall grim long-term results of stand-alone BAV. Although there are no contemporary studies comparing SAVR with BAV, extensive data indicate that stand-alone BAV does not change the natural course of AS, even after repeated procedures. Despite this, BAV holds an important place in the treatment of patients with severe AS. In our current experience, BAV is most often performed to bridge severely symptomatic patients to TAVR or SAVR or to better understand the contribution of AS to functional limitation in patients with multiple comorbidities. BAV has tremendous potential to alleviate symptoms and provide an opportunity for functional improvement that allows definitive treatment with AVR and improved quality and quantity of life in patients with severe AS.

IV. TRANSCATHETER AORTIC VALVE REPLACEMENT

A. Background. Up to a third of patients with severe symptomatic AS do not undergo surgical AVR, as they are deemed to have a high surgical risk due to age or multiple comorbidities. The interest in percutaneous aortic valve implantation began in the early 1990s. The first human experience was reported by Cribier et al. in 2002. Since then, rapid advancements in the design of the stented valve and delivery catheters and improved facility in implantation techniques have led to a consistent improvement in the postprocedural outcomes and have heralded a new era in the treatment of valvular AS.

The procedure involves implantation of a tissue pericardial valve that is mounted within a stent. The key to TAVR success is a careful selection of patient population for the procedure and a judicious use of preprocedural and intraprocedural imaging modalities, including fluoroscopy and aortic angiography.

Currently, the indications for TAVR include severe symptomatic AS with a valve area of ≤ 0.8 cm^2, mean aortic valve gradient of ≥ 40 mm Hg, or a peak aortic jet velocity of ≥ 4.0 m/s with one or more of the following:

(1) High risk for conventional AVR (Society of Thoracic Surgeons score > 10 or logistic EuroSCORE > 20%) (web site 209.220.160.181/STSWebRiskCalc/).

(2) Contraindication to standard thoracotomy including prior multiple thoracotomies or radiation to the chest wall.

(3) Porcelain aorta.

B. Procedure. Two types of stented valves have been tested in humans: the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the self-expanding CoreValve ReValving system (Medtronic Inc., Minneapolis, MN) (Fig. 66.2).

1. Edwards SAPIEN. The largest human experience is with the Edwards Lifesciences series of balloon-expandable aortic valves. The valve consists of a tubular

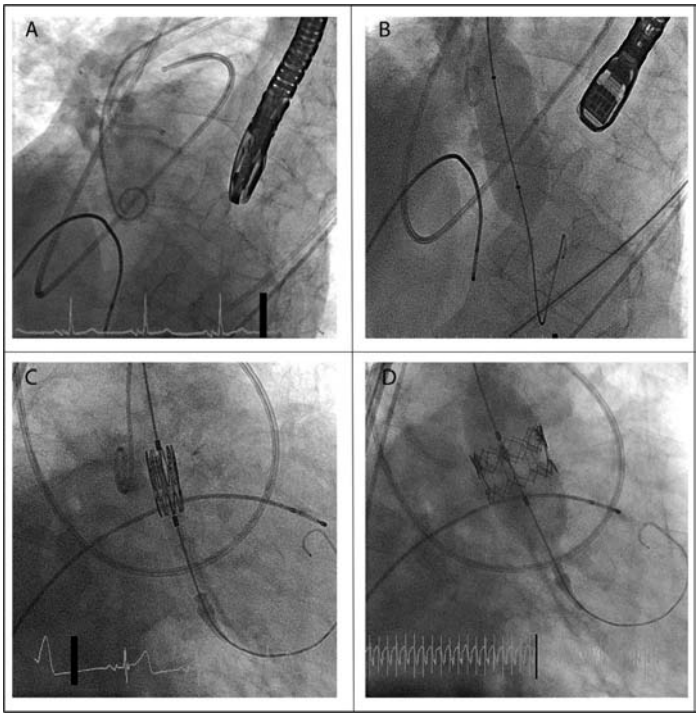

FIGURE 66.2 Transcatheter aortic valve replacement. Panel A demonstrates proper positioning of various catheters and devices for valve replacement: a transesophageal echocardiography probe in the esophagus, a Swan-Ganz catheter in the pulmonary artery, a pigtail catheter in the aortic root, AL-1 diagnostic catheter in the ascending aorta (prior to valve crossing), and a temporary pacemaker wire in the right ventricle. Panel B demonstrates aortic valvuloplasty being performed using a standard balloon. Panel C demonstrates proper positioning of the crimped Edwards SAPIEN prosthesis across the aortic valve. Panel D demonstrates the deployment of the valve using balloon inflation after initiation of rapid pacing.

stainless steel stent with a fabric valve cuff and contains valve leaflets derived from bovine pericardial tissue. This valve is available in two sizes, 23 mm (via 22F sheath access) and 26 mm (via 24F sheath access), and refers to the fully expanded internal stent diameter. Generally, a 23 mm valve is implanted in annuli that measure 18 to 22 mm, and a 26 mm valve is implanted in annuli that measure 23 to 26 mm. Although the valve was implanted initially using the transvenous access and subsequent transseptal puncture, it is now routinely implanted using either a retrograde transfemoral approach or an antegrade transapical approach. Furthermore, the newest iteration of the valve, the SAPIEN XT, which consists of a cobalt chromium stent and allows a smaller sheath size for insertion (18F for 23 mm valve and 19F for 26 mm valve), is currently in use in the Placement of Aortic Transcatheter Valves (PARTNER) II study.

The preprocedural assessment consists of TTE, iliofemoral contrast angiography or iliofemoral computed tomography, and coronary angiography. An iliofemoral diameter of at least 8 mm is required for implantation of the larger Sapien valve,

7 mm for the smaller Sapien valve, and 6 mm for the Sapien XT or CoreValve devices. Appropriate patient selection, which includes the anatomic characteristics of the aortic annulus and iliofemoral system, is imperative to procedural success.

a. **Transfemoral TAVR.** Transfemoral TAVR is usually performed under general anesthesia in a catheterization laboratory or hybrid operating room equipped with multimodality imaging equipment. Vascular sheaths are placed in a standard fashion in both femoral arteries and veins. Establishing early contralateral arterial and venous access is useful in case of ileofemoral trauma requiring emergency crossover endovascular repair or in case of the need to emergently establish a cardiopulmonary bypass circuit. A transvenous pacing wire is introduced into the right ventricle through the venous access port to enable rapid pacing (180 beats per minute) in order to minimize cardiac output and valve movement during valve deployment. An aortic angiogram is performed to delineate the aortic root anatomy and to facilitate optimal valve positioning. A BAV is then performed using standard technique, with a balloon that is slightly smaller than the size of the planned valve prosthesis.

   After routine sheath placement, the femoral access site is "preclosed" using either a Prostar device or two perpendicularly placed Perclose ProGlide devices (Abbott Vascular, Santa Clara, CA). The site is then sequentially dilated to allow placement of either a 22F (for 23 mm valve) or a 24F (for 26 mm valve) arterial sheath. The valve is crimped onto a balloon affixed to a steerable guiding catheter and advanced to the aortic root under fluoroscopic guidance. Once a suitable position is confirmed using fluoroscopy, aortic angiography, and TEE, rapid pacing is initiated and the valve is deployed by inflating the balloon. The final positions of deployment as well as degree of paravalvular aortic regurgitation are assessed using TEE.

   Inappropriate positioning may require a second valve deployment. Excessive paravalvular aortic regurgitation may be treated using further balloon dilation or deployment of a second valve. TEE and angiographic assessment for complications (including pericardial effusion, aortic root trauma, and coronary occlusion by the valve) are imperative prior to closure of the femoral access. Similarly, angiography of the iliofemoral system is necessary to evaluate for vascular trauma that might require endovascular or open surgical repair prior to completion of the procedure.

b. **Transapical TAVR.** Transapical TAVR is indicated in patients with significant narrowing of iliofemoral vessels and who otherwise meet criteria for TAVR. Preprocedural imaging as well as the valve sizing is similar to the transfemoral TAVR described above. After induction of general anesthesia, a 5 to 8 cm anterolateral thoracotomy incision is made to enter the pleural space, directly overlying the apex. The pericardium overlying the apex is opened and a thin portion of the ventricular apex is identified using palpation and TEE. Paired orthogonal U-shaped sutures are placed into the ventricular myocardium and subsequently passed through tensioning tourniquets. Taking due precaution to avoid entry of air into the left ventricle, a 7F sheath is placed into the LV cavity through the apex. A stiff wire is introduced into the sheath, passed across the aortic valve, and positioned into the descending aorta. Femoral access is utilized to place a pigtail catheter into the ascending aorta for aortic root angiography as required. The 7F sheath is upsized to a 14F sheath and aortic valvuloplasty is performed. Subsequently, the 14F sheath is exchanged for a 24F sheath. The mechanically crimped prosthesis is subsequently introduced using a balloon-tipped steerable catheter through this larger sheath and positioned across the aortic valve. After confirmation of optimal positioning using multimodality imaging, rapid pacing is initiated, and the valve is deployed by balloon inflation.

The sheath is then removed and hemostasis is secured with the previously placed sutures. Subsequently, the pericardium is approximated, drainage tubes are placed, and the chest incision is closed.

2. **CoreValve ReValving system.** The CoreValve system is a self-expanding porcine prosthesis mounted within a nitinol frame and is available in two sizes: 26 mm (intended for annuli 20 to 23 mm) and 29 mm (intended for aortic annuli 24 to 27 mm). The current third-generation device is delivered through an 18F system, commonly via transfemoral and rarely via trans-subclavian or transapical approaches. The general principles involved in the implantation of the valve are similar to balloon-expandable stent implantation. One specific difference in the two devices is that the CoreValve can be repositioned if initial placement is unsatisfactory.

C. Complications. Procedural success has ranged from 86% to 100% across the literature. After an initial learning curve, excellent procedural success rates with minimal intraprocedural mortality have been reported at major tertiary care centers performing TAVR. Vascular access complications are encountered more often (16% to 18% patients) than with other interventional procedures due to the large sheath sizes used for TAVR. Complications associated with limited thoracotomy are expected after transapical TAVR. Malposition of the aortic prosthesis may be encountered in about 1% to 3% of cases. Periprocedural strokes have been reported in 4% to 7% of patients undergoing TAVR with an Edwards SAPIEN valve and about 3% with the CoreValve prosthesis. Major complications following CoreValve implantation include the need for permanent pacemaker implantation in up to one-third of patients.

D. Outcomes. The PARTNER trial was the first multicenter randomized controlled trial of TAVR and provided two important randomized comparisons. Cohort B compared the outcomes in 358 patients with severe symptomatic AS who were unsuitable for surgery and were randomized to standard therapy including BAV versus TAVR with the Edwards SAPIEN valve. All-cause mortality at the end of 1 year was 30.7% in the TAVR group versus 50.7% with standard therapy ($p < 0.001$). Cohort A compared the outcomes in 699 high-risk AS patients randomized to TAVR versus surgical AVR. There were no significant differences in 30-day or 1-year mortality between the two groups; however, there were important differences in periprocedural complications. The TAVR group encountered a higher rate of stroke and vascular complications, and the surgical AVR group encountered a higher rate of atrial fibrillation (AF) and major bleeding.

Several prospective studies reported similar benefits using the CoreValve prosthesis. A large prospective registry of 663 patients undergoing TAVR with the third-generation CoreValve reported procedural success of 98%, with intraprocedural mortality of 0.9%. The cumulative incidence of mortality was 5.4% at 30 days and 15.0% at 1 year. Major complications after CoreValve implantation included postprocedural PVL (21%) and the need for a permanent pacemaker (10% to 33%).

Based on the encouraging results of PARTNER Cohort B, the Edwards SAPIEN valve was recently granted US FDA approval for use in inoperable patients. The CoreValve is still available for use in the United States only under the auspices of a clinical trial. Both valve systems have been granted CE Mark approval. A number of other valve systems are currently in various phases of preclinical and clinical development.

V. PFO CLOSURE

A. Background. PFO is a remnant of fetal cardiac circulation and is found in 27% to 33% of adults. Although generally believed to be an "innocent bystander," PFO has been associated with stroke, migraines, platypnea-orthodeoxia, and decompression sickness among divers. PFO arises when the septum primum and septum secundum fail to fuse despite some degree of overlap. Atrial septal aneurysms and prominent Chiari networks have been associated with PFO. Percutaneous PFO closure is currently recommended in patients with platypnea-orthodeoxia and in divers with decompression sickness. Although several observational studies have shown the

benefits of PFO closure in the prevention of migraine and cryptogenic strokes, these findings have not been confirmed in major randomized trials. Hence, controversy persists regarding definitive indications and settings for PFO closure for migraine and cryptogenic stroke prevention.

All PFO closure devices have a similar design, usually consisting of two atrial disks connected by a short neck. Under fluoroscopic and ICE guidance, the device is placed such that the two atrial disks lie on either side of the interatrial septum, with the neck positioned in the PFO tunnel. A large part of the atrial shunt is eliminated as a result of physical obstruction to flow. Most of the residual shunt is eliminated over the course of a few months after the procedure, as the device becomes endothelialized. Dual-antiplatelet therapy is generally recommended for the first 6 months after closure to minimize the risk of thromboembolism prior to device endothelialization.

B. Procedure. Several devices for transcatheter PFO closure have been tested in humans, including the Helex septal occluder device (WL Gore & Associates, Newark, DE) and the Amplatzer cribriform ASD occluder device (AGA Medical, Golden Valley, MN) (Fig. 66.3). As these devices are FDA approved only for ASD closure, use for PFO closure is "off-label." Sizing of the devices may vary based on the degree of associated atrial septal aneurysm; significant aneurysm generally requires a larger device.

Briefly, the procedure involves placement of an 8F to 12F vascular sheath (depending on device size) in one femoral vein and a 9F sheath in the contralateral femoral vein

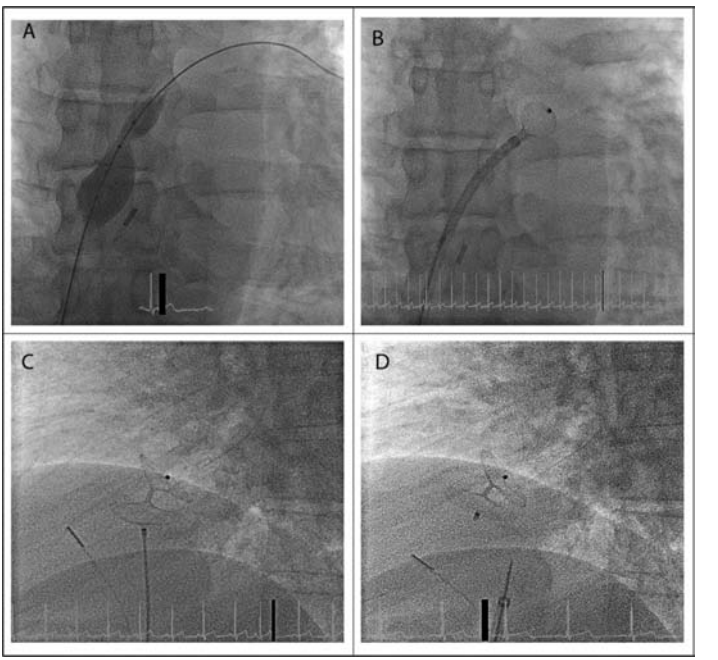

FIGURE 66.3 Patent foramen ovale closure using Amplatzer device. Panel A demonstrates balloon sizing of the PFO tunnel after crossing the PFO using a wire. The intracardiac echocardiography probe is visible next to the balloon. Panel B demonstrates deployment of the left atrial disk of the Amplatzer occluder device. Panel C demonstrates the deployment of the right atrial disk of the Amplatzer occluder device. Panel D demonstrates the device in place after its release from the delivery catheter.

for ICE. The ICE catheter is parked in the right atrium for procedural visualization. The PFO is usually crossed using a wire and a Goodale-Lubin (GL) catheter under ICE and fluoroscopic guidance. Through the GL catheter parked in the left superior pulmonary vein, the wire is exchanged for a stiffer wire over which the closure device delivery system is advanced. The LA disk of the device is deployed and the system slowly retracted. This action facilitates apposition of the septum primum to the septum secundum and effectively closes the PFO. The right atrial disk is then deployed. After confirmation of positioning and stability using ICE and fluoroscopy (and sometimes right atrial angiography), the device is released from the delivery catheter.

C. Complications. Transcatheter PFO closure is generally associated with a high procedural success rate and without significant risk of complication. Rare complications including device migration or embolization, symptomatic air embolism, and AF or chamber perforation with cardiac tamponade may occur intraprocedurally. Later complications associated with the procedure include thrombus formation (more common with CardioSEAL than Amplatzer), device erosion, or formation of a new ASD.

D. Outcomes. Several large observational studies have demonstrated benefit of PFO closure in secondary prevention of migraine and prevention of recurrent neurological thromboembolism in patients with cryptogenic stroke or transient ischemic attack (TIA). However, these findings have not been ratified in randomized clinical trials. The Migraine Intervention with StarFlex Technology (MIST) study failed to demonstrate any significant difference in migraine cessation between the closure and the "sham" arms. The preliminary results of the randomized controlled trial (CLOSURE I) comparing transcatheter PFO closure with the StarFlex device and optimal medical therapy in patients with cryptogenic thromboembolism failed to demonstrate any significant difference in the rate of recurrent stroke or TIA at the end of 2 years of follow-up in the transcatheter closure group (5.9%) and medical therapy (7.7%) ($p = 0.3$). It has been argued that the inclusion criteria may have been too liberal, however, and therefore could not show a significant difference between the two groups. Furthermore, the procedure was performed using the StarFlex device, which has since been taken off the market due to poor performance and increased risk of adverse events such as thrombus formation. Percutaneous closure of PFO is reasonable in certain clinical scenarios, and a thorough workup is necessary for appropriate patient selection.

VI. ASD CLOSURE

A. Background. ASD is one of the most common adult congenital heart diseases encountered in the US population. Although ASDs generally remain asymptomatic till early adulthood, they are associated with several clinical presentations, including right ventricular failure, atrial arrhythmias, pulmonary hypertension, and paradoxical embolism.

Patients with hemodynamically significant ASD should undergo elective closure either surgically or with the transcatheter technique. The hemodynamic significance of an ASD is determined by the presence of right ventricular enlargement in the presence of defect diameter > 1 cm or the presence of significant left-to-right shunting with an elevated shunt ratio (Q_p:Q_s > 1.5).

The principle of ASD closure is similar to that of PFO closure, entailing implantation of an occlusion device with atrial disks lying on either side of the interatrial septum and the central waist residing in the ASD. Due to significant variations in size and anatomy of ASD, transcatheter ASD closure is technically more challenging than PFO closure.

B. Procedure. Several devices have been used for percutaneous ASD closure. The Amplatzer atrial septal occluder (AGA Medical, Golden Valley, MN) has the largest reported human experience. The other major device available is the Helex (WL Gore & Associates, Newark, DE). The CardioSEAL and StarFlex occlusion devices (NMT Medical, Boston, MA) have been removed from the market due to adverse events.

The procedural approach to percutaneous ASD closure is similar to the percutaneous PFO closure approach as described above. A few important differences exist that are worth considering.

1. Due to a significant variation in the size of ASD and the shape of the defect, proper invasive balloon sizing (by ICE and fluoroscopy) is needed. Both oversizing and undersizing of the device may be hazardous and may lead to complications like device erosion or device embolization.
2. Device deployment and orientation during transcatheter ASD closure poses greater technical challenges than during PFO closure. The technical complexities are more frequent when ASDs are associated with other structural anomalies like atrial septal aneurysms or in cases of inadequate rim capture. It is imperative to demonstrate an adequate rim surrounding the defect for percutaneous closure.
3. Multiperforated septa demonstrate a particularly greater challenge to complete closure. In these cases, specific devices like the Amplatzer cribriform occluder or multiple devices may be needed to achieve a good clinical result.
4. The Amplatzer device is sized based on the defect size (i.e., 16 mm device for a 16 mm ASD) and can be used to close defects 2 to 38 mm in diameter. The Helex device is sized two times the size of the defect (i.e., 30 mm device for a 15 mm ASD) and can be used to close defects 2 to 17 mm in diameter.

C. Complications. As in transcatheter PFO closure, procedural success in experienced hands is high and complications are rare. Potential complications include device embolization, tamponade as a result of device erosion into the atrial or aortic wall, residual shunting, or atrial arrhythmias. ASD device mismatch is encountered in 2% to 5% of cases. Other rare complications include vascular access complications, sizing balloon rupture, and entrapment of right atrial structures. Chest discomfort or new onset of arrhythmia may be clues to device erosion or embolization and should prompt urgent echocardiographic evaluation.

D. Outcomes. Most patients demonstrate improved functional class and exercise capacity after a successful closure. Several observational studies have demonstrated an improvement in overall long-term survival. Timely ASD closure prevents the development of right heart failure and pulmonary hypertension. There has been evidence of reduction in the size of enlarged cardiac chambers with normalization of intracardiac pressures after successful ASD closure.

VII. VENTRICULAR SEPTAL DEFECT (VSD) CLOSURE

A. Background. Although isolated VSDs are a relatively common form of adult congenital heart disease, congenital VSDs of hemodynamic significance are rare, with a prevalence of 0.03% in the adult US population. More commonly, VSDs are acquired as a result of complication of MI, cardiovascular surgery, or chest trauma. Postinfarction ventricular septal rupture (VSR) is associated with > 90% mortality if left untreated. The postinfarction or traumatic VSRs may be located in the posterobasal (inferior infarct) or apical (anterior infarct) portions of the muscular ventricular septum and are typically irregular with multiple ruptures in necrotic myocardium that are prone to rupture or expansion. This presents significant challenges with respect to surgical as well as transcatheter repair.

Percutaneous VSD/VSR closure involves devices that are similar to those described for ASD closure. The device is positioned under fluoroscopy and echocardiographic guidance (TEE and/or ICE as needed) such that the two disks lie on either side of the ventricular septum and the waist lies in the septal defect. The width of the connecting waist determines device sizing.

B. Procedure. There are two devices that are approved for closure of congenital muscular VSDs: the CardioSEAL (NMT Medical, Boston, MA) and the Amplatzer muscular VSD occluder device (AGA Medical, Golden Valley, MN). There is a specially designed Amplatzer postinfarction muscular VSR occluder device, which is currently under investigation in the United States. It is similar to its congenital counterpart, except for a longer waist,

large disk diameter, and a larger waist diameter. In patients with postinfarct VSR, it may be necessary to use an atrial septal occluder, as the distance between the disks of the VSD occluder device may be too large. Again, this would be considered an "off-label" usage.

VSD closure can be achieved via the retrograde approach from the left ventricle or via the femoral or jugular vein. The VSD is crossed using a diagnostic catheter and wire, with the wire then externalized to the artery (if approached from the right ventricle) or vein (if approached from the left ventricle) to create a continuous arteriovenous (AV) loop. A delivery catheter containing the device is subsequently delivered over the loop. Under fluoroscopic and echocardiographic guidance, proper alignment and position are confirmed and the device is subsequently deployed.

C. Complications. The major complications of transcatheter VSD closure include device embolization, air embolism, residual shunting, defect enlargement, complete heart block requiring pacemaker implantation, arrhythmias, valvular regurgitation due to impingement, and intravascular hemolysis.

D. Outcomes. The results of transcatheter closure of congenital VSDs are encouraging; however, the closure of postinfarction VSR has yielded disappointing results in several studies. Although surgery has been recommended as the gold standard for the repair of postinfarction VSD, emergent surgical repair carries an operative mortality of about 50%. This often leads surgeons to recommend delaying the surgery for at least 2 weeks after the initial ischemic event, which may result in a lesser operative mortality and improve the chance of success. Due to this, several centers have attempted transcatheter VSR closure in patients who are either not surgical candidates or too unstable to survive the "waiting period." Data from observational studies have reported variable success, with mortality rates ranging from 20% to 100%.

VIII. LAA OCCLUSION

A. Background. AF is associated with 15% of all ischemic strokes. Autopsy studies have shown that up to 90% of the thrombi in nonvalvular originate in the LAA. Although warfarin has been demonstrated to reduce the rate of stroke in patients with AF, there are several limitations, including risk of bleeding, pharmacologic interactions, and need for prothrombin time (international normalized ratio [INR]) monitoring. In several patients, the use of warfarin may be contraindicated, necessitating another method of stroke prevention.

The LAA orifice is located between the left ventricle and the upper left pulmonary vein, extending over the atrioventricular groove toward the left circumflex coronary artery. Surgical amputation and exclusion of the LAA have been demonstrated to reduce the risk of stroke after MV surgery, without any significant impact on the rate of postoperative AF. In addition, LAA exclusion performed thoracoscopically by stapling the base of the LAA was found to be efficacious in small observational studies. Given the favorable location of the LAA for percutaneous closure, a number of methods have been developed.

B. Procedure. There are three devices with significant human experience available for LAA occlusion: the Percutaneous LAA Transcatheter Occlusion (PLAATO) device (ev3, Plymouth, MN), the Amplatzer Cardiac Plug (ACP) (AGA Medical, Golden Valley, MN), and the WATCHMAN device (Altritech Inc., Plymouth, MN). The WATCHMAN and ACP devices have CE Mark approval. The PLAATO device is available in several sizes ranging from 15 to 32 mm, the ACP device ranges from 16 to 20 mm, and the WATCHMAN device is available from 21 to 33 mm. The size and the shape of the LAA should be determined using TEE. Generally, the PLAATO device should be oversized by 20% to 40% and the WATCHMAN device by 10% to 20% for a good result.

The devices are generally implanted using 14F femoral venous access. A transseptal puncture is performed under fluoroscopic and TEE guidance. The device delivery system allows for collapse, repositioning, or removal of the device in case of unsatisfactory result. Adequacy of the LAA occlusion (defined as mild to absent leak) is confirmed using radiopaque contrast injection into the LA cavity.

C. Complications. The complications of the procedure include pericardial effusion, cardiac tamponade, residual leakage, or major vascular complications requiring transfusion.

D. Outcomes. In a large series of AF patients undergoing LAA occlusion with PLAATO, the observed annual stroke rate was 2.2%, which represented a 65% relative risk reduction with the PLAATO device. Similarly, the PROTECTion in patients with Atrial Fibrillation (PROTECT-AF) trial has demonstrated the non-inferiority of the WATCHMAN device compared with warfarin therapy for stroke prevention in patients with nonvalvular AF, despite a small increase in periprocedural complications in the device group. The WATCHMAN continued access registry demonstrated a substantial learning curve, with a reduction from 5.0% to 2.2% for pericardial effusion and 0.9% to 0.0% for stroke and increase from 89% to 95% for procedural success. By the same token, medical comparator groups are not ideal, with only half of patients in the PROTECT-AF trial demonstrating therapeutic INR. As with all other procedures, patient selection will be important to maximize benefits until we have a better sense of safety and outcomes.

IX. ALCOHOL SEPTAL ABLATION (ASA).

Septal myectomy is considered the gold standard for the treatment of HOCM. ASA has emerged as an attractive, less invasive alternative to myectomy for HOCM that is applicable to those patients who cannot or do not want surgery. Over the last 15 years, the number of ASA procedures done worldwide has surpassed the total number of myectomies performed in the last 50 years. ASA may be considered in patients who have clear evidence of septal hypertrophy (> 18 mm) projecting into the left ventricular outflow tract (LVOT), patients who have dynamic LVOT obstruction (gradient > 50 mm Hg at rest or upon provocation), and patients who have been refractory to medical therapy. Patients with coexistent abnormalities of mitral apparatus are best treated by surgery rather than ASA.

Selective coronary angiographic studies have demonstrated that the septum contributing to the LVOT obstruction is often supplied by the first septal perforator arising from the left anterior descending coronary artery. ASA entails creating a controlled myocardial necrosis by injecting alcohol into the first septal perforator. Postablation, the LVOT gradient demonstrates a triphasic response. There is an immediate reduction in the LVOT gradient after a successful procedure, attributable to the loss of septal contractility and myocardial stunning. Over the next few days, there is an increase in the LVOT gradient due to recovery of the stunned myocardium. The more permanent decrease in LVOT gradient happens over the course of the next few months secondary to myocardial thinning and septal remodeling.

A. Procedure. ASA is performed via femoral arterial access. A guiding catheter is introduced into the left main coronary artery and a guidewire advanced to the septal perforator of interest. Subsequently, a short "over the wire" (OTW) balloon is advanced to the septal perforator and inflated to obstruct backflow of alcohol from the septal to the left anterior descending artery. Angiographic contrast is injected through the balloon to ensure that there is absolutely no backflow into the LAD. Since transient heart block is common during the procedure, a temporary pacemaker is usually inserted.

Echocardiographic contrast is then injected through the OTW balloon in order to map the myocardium that would infarct as a result of ASA. This is an important step, as it helps determine the appropriateness of the procedure and helps in selecting the optimal branch for alcohol injection. Subsequently, 1 to 2 cc of alcohol is injected slowly through the balloon, with the balloon staying inflated for 5 minutes. Intravenous analgesia should be administered, as alcohol injection causes a short-lived but intense discomfort. The balloon is then deflated and removed. A final coronary angiogram is performed to verify lack of septal flow, and echocardiographic gradient is reassessed.

B. Complications. Besides the routine vascular complications that may arise in any interventional procedure, new-onset right bundle branch block is a significant complication of this procedure and is reported in up to 50% of patients in some

series. Complete heart block requiring a need for a permanent pacemaker may occur in about 10% of patients undergoing ASA. The other potential long-term complication includes ventricular arrhythmias, hypothesized to arise as a result of creation of arrhythmogenic myocardial scar. Recent meta-analyses have failed to demonstrate significant differences in ventricular arrhythmias between myectomy and ASA.

C. Outcome. Although there are no randomized comparisons between septal myectomy and ASA, large meta-analyses of observational data indicate no significant differences between the two modalities in terms of mortality and improvement in functional status postprocedure. The caveat of ASA is an increased incidence of conduction abnormalities and a small yet significantly higher LVOT gradient postprocedure.

X. PERCUTANEOUS PVL CLOSURE

A. Background. PVL is a rare but serious complication that may arise after surgical MVR or more rarely after SAVR. Although most PVLs are small and remain relatively asymptomatic, more than 10% of patients undergoing MVR or SAVR may develop large symptomatic PVLs with serious clinical consequences such as heart failure, endocarditis, or hemolytic anemia. Most PVLs become clinically apparent within 1 year after valve surgery, but a significant proportion may not require any definitive treatment till later. Several risk factors, including extensive annular calcification, evidence of endocarditis, large atria, renal failure, and older age, have been identified that may predispose a valve to develop PVL postsurgery.

Surgical intervention is typically the standard of care in management of patients with symptomatic PVL; however, reoperation is associated with a mortality rate of approximately 16%. Transcatheter closure of symptomatic PVL in a relatively small number of high-risk patients has been attempted in several centers over the last two decades. The devices approved for closure of other intracardiac defects like ASD, VSD, and PDA have been utilized in an off-label fashion for transcatheter PVL closure. We most commonly use an Amplatzer VSD occluder and/or Amplatzer vascular plug for these defects.

B. Procedure. In order to deploy an occlusion device across a PVL, it is first necessary to cross the defect with a delivery catheter. Aortic PVLs are generally crossed in a retrograde fashion from the femoral artery. The mitral PVL may be crossed in retrograde fashion from the femoral artery via the left ventricle, in the antegrade fashion by advancing a catheter from the right atrium into the left atrium via transseptal puncture, or via direct transapical access. Similar to percutaneous VSD/VSR closure, creation of an AV loop is usually mandatory to form a supportive rail for the passage of equipment. In addition to the use of fluoroscopy, TEE, and ICE during the procedure, three-dimensional echocardiography has recently gained popularity for optimal anatomical characterization and guiding device placement.

In the retrograde approach for mitral PVL closure, a diagnostic catheter (such as an internal mammary artery or JR4 catheter) is placed in the left ventricle. Subsequently, a 0.035" × 260 cm floppy glidewire is used to cross the defect, and the catheter is advanced over this wire into the left atrium. To provide adequate support for the device delivery catheter, an AV loop is typically established during this procedure; transseptal puncture and a GooseNeck snare are used to externalize the wire to form a continuous AV loop. Subsequently, the closure device is introduced through a delivery catheter from the venous side, while withdrawing the glidewire ("chasing the wire"). The device is subsequently deployed across the PVL in a standard fashion.

In the antegrade approach, transseptal puncture is carried out first. We typically use an Agilis steerable catheter (St. Jude Medical) to navigate the left atrium and direct the wire toward the defect. The location of the transseptal puncture is also highly variable and is directed by the location of the PVL. Through this catheter, a wire (preferably a 0.035″ glidewire) is advanced to cross the defect, and subsequently the catheter is advanced over this wire into the left ventricle. Subsequently, there is sequential delivery of increasingly supportive catheters (4F Bernstein, 6.5F JB1, Cook Medical) over more supportive wires (floppy glidewire, stiff glidewire, Amplatz

ES) to facilitate the placement of the device delivery sheath into the left ventricle via the PVL defect. Again, creation of an AV loop by externalizing the wire at the femoral artery or via the LV apex is usually necessary. The PVL occluder device is deployed in a standard fashion.

C. Complications. Transcatheter mitral PVL closure has had variable success. The initial technical success has ranged between 60% and 90%, with up to a 40% reintervention rate. Immediate and delayed device-related complications have been described as a result of technical failure. The early technical failure happens due to device impingement on nearby critical structures, and the delayed technical failure happens as a result of device embolization. Persistent PVL and/or its associated sequelae (i.e., CHF and hemolytic anemia) may be encountered after PVL closure. Although no procedure-related deaths have been described in any series, rare instances of strokes, dysrhythmias, and cardiac perforation have been described.

D. Outcomes. Transcatheter PVL closure is one of the most challenging structural heart disease interventions. The long-term outcomes after transcatheter PVL closure largely depend upon surmounting the limitations imposed by the current nonspecific devices for PVL closure, as well as challenges in imaging of the area of interest. Over the long-term follow-up described in a few relatively large case series, resolution of hemolysis was reported in 60% to 83% of patients, improvement in CHF symptoms was reported in 50% to 100% of the patients, and repeat surgery was required in only 4% to 18% of the individuals. The incidence of long-term mortality has ranged from 25% to 30% over 3 to 36 months of follow-up across various studies.

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CHAPTER 67

Kia Afshar

Transthoracic Echocardiography

I. INTRODUCTION. Transthoracic echocardiography is a reliable and versatile tool for the assessment of cardiac structure, function, and hemodynamics. It has advantages over other cardiovascular imaging modalities in that it is relatively inexpensive, does not incur radiation exposure to the patient, is noninvasive, displays live real-time images, and is widely available. Common indications and corresponding aims of the echocardiographic evaluation are listed in Table 67.1.

II. BASIC PRINCIPLES OF ECHOCARDIOGRAPHY. Sound waves consist of mechanical vibrations that produce alternating compressions and rarefactions of the medium through which they travel. **Ultrasound** consists of sound waves in the frequency range that is higher than what is audible by humans (> 20,000 Hz). All waves can be described by their frequency (f), wavelength (λ), velocity of propagation (v), and amplitude. The velocity of ultrasound in soft tissue (e.g., myocardium and blood) is 1,540 m/s. Frequency is defined by the number of cycles occurring per second (cycles/second or Hz) and wavelength is measured in meters (m). Velocity, frequency, and wavelength are described by the following relationship:

$$\textbf{Velocity} = \textbf{frequency} \times \textbf{wavelength} \quad \textbf{or} \quad v = f \times \lambda$$

The typical adult echocardiographic examination uses a transducer with ultrasound frequency between 2.5 and 3.5 million Hertz (MHz). Based on the equation above, a 3-MHz transducer results in an ultrasound wavelength of approximately 0.50 mm. This has important implications since image resolution cannot be > 1 to 2 wavelengths (e.g., 1 mm with a 3-MHz transducer). In addition, the depth of penetration of the ultrasound wave is directly related to the wavelength, with shorter wavelengths penetrating a shorter distance. Therefore, higher frequency transducers result in the use of shorter wavelengths that improve image resolution but at the cost of reduced depth penetration.

Transducers use a piezoelectric crystal to generate and receive ultrasound waves. A piezoelectric substance has the property of changing its size and shape when an electric current is applied to it. An alternating electrical current will result in rapid expansions and compressions of the material and thus produce an ultrasound wave. The piezoelectric crystal also deforms in shape when an ultrasound wave strikes the material, resulting in the production of an electric current. The transducer, and the piezoelectric crystal, thus oscillates between a short burst of transmitting ultrasound waves, with a brief period of no ultrasound transmission when it awaits reception of the reflected signals.

Tissue harmonic imaging has become the standard imaging technique in many laboratories. It utilizes the principle that as ultrasound waves propagate through tissue, the waveform becomes altered by the tissue, with the generation of new waveforms of higher frequency but which are **multiples of the baseline fundamental frequency**. Setting the transducer to receive only harmonic sound waves that are multiples of the fundamental frequency improves image quality significantly. This image quality improvement is based

TABLE 67.1 Common Indications and Corresponding Aims of Echocardiographic Evaluation

Indications	Echocardiographic evaluation
Valvular heart disease	Valve morphology, regurgitation and/or stenosis severity and etiology, and ventricular size and function
Infective endocarditis	Vegetation, abscess, fistula, valvular function, and ventricular size and function
Coronary artery disease	Wall motion abnormalities, ventricular function, and mitral regurgitation/ventricular septal defect and other ischemic complications
Congestive heart failure	Systolic function, wall motion abnormalities, chamber size, valvular pathology, and diastolic function
Pericardial disease	Pericardial effusion, pericardial thickening ± calcification, and RV size and function
Cardiac tamponade	Pericardial effusion; RA diastolic collapse; RV early diastolic collapse; respiratory variations in mitral, tricuspid pulmonary venous, and hepatic venous flow; and IVC size and respiratory variation
Ascending aortic pathology	Aneurysm, atheroma, dissection or intramural hematoma, and aortic valve pathology
Pulmonary hypertension	RV systolic pressure, RV and LV function, and tricuspid, pulmonary, and mitral valve pathology
	Interatrial shunt and respiratory effects on IVC diameter
Systemic hypertension	LV function, LV wall thickness, and evidence of aortic coarctation
Embolic disease	LA and LV thrombus, mitral valve pathology, aortic atheroma, LV function, and interatrial shunt
Arrhythmias	LA and LV thrombus, ventricular size and function, atrial dimensions, and mitral valve pathology
Syncope	LV outflow tract obstruction, aortic and mitral valve pathology, LV function, and congenital abnormalities
Cardiac trauma	Ascending aortic dissection, ascending aortic aneurysm, and cardiac tamponade
Congenital heart disease	Congenital anomaly and shunt calculation
Critical illness	LV function, valvular pathology, pericardial effusion/tamponade, right-to-left shunt, and volume status

IVC, inferior vena cava; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

on the fact that weak signals, which tend to be artifacts, create almost no harmonics. In addition, shallow structures, such as the chest wall, generate weak harmonic signals, whereas at depths of 4 to 8 cm, where the heart is located, maximal harmonic frequencies develop. These phenomena result in fewer near-field artifacts and better endocardial definition. One limitation of harmonic imaging is that valve leaflets appear thicker—an artifact generated during image processing that appears to be related to the rapid motion of the leaflets.

The steps involved in creating a final ultrasound image are transmission and reception of waves, conversion to electrical signals, filtering, and extensive computer processing. The details of image processing, formation of artifacts, advanced physics, and technical aspects of echocardiography are beyond the scope of this chapter, but these are briefly discussed in Section **VII**.

Patient and probe positioning, electrocardiographic lead placement, and transducer selection are the first steps to beginning the echocardiographic examination.

A. Patient and probe positioning. The probe can be held with the right or left hand depending on the patient side that one chooses to scan from. For the parasternal and apical positions, the patient should be in the left lateral decubitus position, with the left arm extended behind the head, as this brings the heart into contact with the chest wall. The subcostal and suprasternal views require the patient to be in the supine position.

B. Electrocardiographic lead placement. The ECG allows identification of arrhythmias and timing of cardiac events during the echocardiographic examination, and it is used as a timing marker for digital recording of images. Typically, digital "clips" are set to record a predefined number of cardiac cycles (usually one but sometimes two), with timing based on the ECG. It is important that irregular beats be identified and excluded from the analysis. For example, a postectopic beat will falsely increase the two-dimensional (2D) assessment of ejection fraction (EF) and the Doppler assessment of transaortic gradient. In general, any Doppler index requires the average of at least three measurements. For patients in atrial fibrillation, 7 to 10 beats should be averaged. For patients with very high heart rates, or with a noisy electrocardiographic signal, the digital clips can be set to record for a predefined period of time (usually 2 seconds).

C. Transducer selection. The adult echocardiographic examination typically begins with a 2.5- to 3.5-MHz phased array transducer. Transducer frequency is important, as at higher frequencies spatial resolution improves but at the expense of reduced depth penetration. Higher frequency (3.0 to 5.0 MHz) transducers may be used in thin or pediatric patients or intraoperatively for epiaortic scanning. Therefore, for optimal 2D resolution, select the highest frequency transducer that will provide adequate far-field penetration.

With regard to transducer frequency for the Doppler examination, lower frequency transducers can record higher velocities (see Doppler equation later in the chapter). The Pedoff probe is a continuous-wave (CW), nonimaging probe (typical frequency being 1.8 MHz) used mainly to detect higher velocity profiles and confirm velocities obtained by other imaging methods.

III. IMAGING MODALITES IN STANDARD ECHOCARDIOGRAMS

A. M-mode. Prior to 2D imaging, the echocardiogram was obtained when the transducer sent an ultrasound wave along a **single line** and then displayed the amplitude of reflected signal as well as the depth of that signal on an oscilloscope. This was called an A-mode echocardiography. When these line-of-sight ultrasound images were plotted with respect to time, "motion" mode, or M-mode, was produced. Despite the increasing emphasis on 2D imaging, the M-mode display remains a complementary element of the transthoracic examination. Its **high sampling rate** of approximately 1,800/s, compared with 30/s for 2D echocardiography, provides **excellent temporal resolution**, and thus it is very **useful in the timing of subtle cardiac events** that can be missed by the naked eye in 2D imaging. Rapidly moving structures such as the aortic valve, mitral valve, and endocardium have characteristic movements in M-mode. Deviations from these, such as diastolic fluttering of the mitral valve in aortic regurgitation (AR) and systolic aortic valve notching in dynamic left ventricular outflow tract (LVOT) obstruction, may be the only way to detect underlying dysfunction when they are not appreciated in other imaging modalities.

M-mode also has a great spatial resolution along the single line and can be used for precise size measurements such as ventricular dimensions in systole and diastole. The M-mode image is displayed like a graph, with **time on the *x*-axis and distance from the transducer on the *y*-axis**, with the structures closest to the transducer at the top of the image. In order to align the line of sight accurately, **2D imaging should be used to position the M-mode cursor** through the structures of interest.

B. Two-dimensional imaging. Two-dimensional imaging provides the **tomographic views** that are envisioned when one thinks of a transthoracic echocardiogram. It not only provides various 2D planes of cardiac structures but also acts as the platform that guides the M-mode and Doppler portions of the examination.

The 2D echocardiographic image is essentially the scan line from M-mode that, instead of having a fixed line of sight, is swept back and forth across an arc. After complex manipulation of the **data received by the transducer from the multiple scan lines**, a 2D tomographic image is generated for display.

Depending on the depth of the image, a finite amount of time is needed for each scan line to be sent and received by the transducer. As opposed to M-mode that has only one scan line and can provide over 2,000 frames/s, 2D echocardiographic imaging can utilize 128 scan lines but at the expense of a lower rate of 30 frames/s. Faster frame rates can be obtained by electronic manipulation using parallel processing on current ultrasound machines. Doppler overlay of the 2D image tends to slow down the frame rate. This **reduction in temporal resolution** reinforces the need for M-mode to complement 2D imaging in echocardiography, especially for rapidly moving structures and in precise timing of events.

C. Doppler echocardiography. The introduction of Doppler technique to echocardiography not only added new imaging capabilities but also transformed echocardiography into a modality that could provide **hemodynamic assessment** of the heart. Echocardiography has now become the preferred method, and in some cases the gold standard, over cardiac catheterization for certain hemodynamic assessments.

1. Doppler principles. The Doppler principle states that sound frequency increases as the sound source moves toward the observer and decreases as the source moves away. The change in frequency between the transmitted sound and the reflected sound is termed the **Doppler shift**. This phenomenon is appreciated daily when an ambulance's siren becomes higher pitched, due to the increase in wave frequency, as it approaches the observer and then lower pitched once it has passed. This Doppler frequency shift directly relates to the velocity of the red blood cell by the following **Doppler equation**:

$$v = \frac{c\,(f_R - f_T)}{2f_T\,(\cos\,\theta)}$$

where v = velocity, f_R = frequency received, f_T = frequency transmitted, c = speed of sound in blood (1,540 m/s), and θ = angle between moving object and ultrasound beam.

The cos θ in the Doppler equation makes the calculation of velocity depending on the angle between the beam and the moving structure (red blood cell). Echocardiography machines do not typically incorporate the angle for calculating the resultant velocity, and thus the goal is to have the angle between the ultrasound beam and the blood flow jet of interest to be as close to zero as possible (cos 0 = 1). When this is not possible, the angle should be < 20°, so that the true flow velocity is underestimated by < 6% (cos 20 = 0.94). Adhering to this requirement sometimes mandates off-axis or unusual 2D images to align the Doppler ultrasound signal with desired target. Reference Doppler velocities in the adult examination are given in Table 67.2.

TABLE 67.2 Normal Echo Dimensions in Adults

Factor	Ref. range (cm)	Factor	Ref. range (cm)
(i) Parasternal long axis (M-mode or 2D)			
LV end-diastolic diameter	3.5–5.7	LV end-systolic diameter	2.3–4.0
Septal thickness (ED)	0.6–1.1	Posterior wall thickness (ED)	0.6–1.1
Aortic root (ED—M-mode)	2.0–3.7	Left atrium (ES)	1.9–4.0
RV end-diastolic diameter	1.9–3.8		
Aortic annulus (systole—2D)	1.4–2.6	Midascending (2D)	2.1–3.4
(ii) Four-chamber view			
LV volume (ED) (cm^3)	96–157	LV volume (ES) (cm^3)	33–68
Ejection fraction (%)	59 ± 6		
Left atrial area (cm^2)	< 20		
(iii) Doppler velocities			
Mitral E wave (< 50 y) (cm/s)	72 ± 14	Mitral E wave (> 50 y) (cm/s)	62 ± 14
Mitral A wave (< 50 y) (cm/s)	40 ± 10	Mitral A wave (> 50 y) (cm/s)	59 ± 14
Deceleration time (ms)	140–210		
Ascending aorta (m/s)	1.0–1.7	LV outflow tract (m/s)	0.7–1.1
Pulmonary artery (m/s)	0.5–1.3		
Pulmonary vein S wave (cm/s)	56 ± 13	Pulmonary vein D wave (cm/s)	44 ± 16
Pulmonary vein A reversal (cm/s)	32 ± 7		

ED, end-diastole; ES, end-systole; LV, left ventricular; RV, right ventricular.

2. **Spectral analysis** is the term used to describe the way in which pulsed-wave (PW) Doppler and CW Doppler are displayed. By convention, the horizontal axis reflects time and is placed in the middle of the screen with upward deflections representing frequency shifts toward the transducer and downward deflections for frequency shifts away from the transducer. The vertical axis represents the blood flow velocity (or frequency shifts), with the density of pixels on a gray scale reflecting the amplitude of the signal. The final result is that at each time-point the spectral analysis shows blood flow direction, velocity/frequency shift, and signal amplitude.
   a. **PW Doppler.** The purpose of PW Doppler mode is to measure the Doppler shift, and thus velocity, at a **specific location of interest within a small sample volume** (e.g., mitral inflow velocity at the mitral valve leaflet tips, systolic velocity at the LVOT, and blood flow within the pulmonary veins). In this mode, a **single crystal** sends short bursts of ultrasound waves at a

specific pulse repetition frequency (PRF) to a specific location, which are reflected from moving blood cells at this location and received by the same crystal. The maximal velocity that can be measured is limited by the time required to transmit and receive the ultrasound wave. This is called the **Nyquist limit** (one-half of the PRF). If a velocity greater than the Nyquist limit is measured, the signal appears as a wrap around the baseline, known as **signal aliasing**. Hence, the peak velocity is limited by the depth of the area of interest and also by the transducer frequency (inverse relationship according to the Doppler equation; see previous text). **PW Doppler has excellent spatial/depth resolution, but it has limited capacity to measure high velocities due to the Nyquist limit**. It is, therefore, used primarily to measure low-velocity flow (< 2 m/s) at specific sites in the heart.

b. **CW Doppler.** CW Doppler employs **two crystals, one continuously sending ultrasound waves and the other continuously receiving the waves**. It measures Doppler shift **along the entire beam**, rather than at a specific location. Unlike PW Doppler, CW Doppler measures the **maximal velocity along the entire ultrasound beam** but it does not localize the precise position of that peak velocity. However, this is often apparent anatomically or can be deduced using PW Doppler or color flow Doppler. **In general, CW Doppler is used to assess high-velocity flow and PW Doppler is used to measure low-velocity flow in specific areas**. Clinical applications of PW versus CW Doppler are listed in Table 67.3.

c. **Color flow imaging.** Although spectral (pulsed-wave and continuous-wave) Doppler imaging is superior for accurate measurement of specific intracardiac blood flow velocities, the best way to visualize the overall pattern of intracardiac blood flow is with color flow imaging. Color flow Doppler is based on the principle of PW Doppler, with multiple sampling volumes at

TABLE 67.3 Differences and Uses of Pulsed-Wave Doppler and Continuous-Wave Doppler

Factor	Pulsed wave	Continuous wave
Transducer crystal	Same transmitting and receiving	Different transmitting and receiving
Spatial resolution	Excellent—localizes to precise point	Poor—may be anywhere along the entire beam
Ability to measure high velocity (> 2 m/s)	No (limited by Nyquist)	Excellent
Uses	Mitral inflow	Gradients in aortic stenosis
	Pulmonary venous flow and LVOT flow	Gradient and pressure halftime in mitral stenosis
	Hepatic vein flow	Peak velocity in mitral regurgitation and measurement of dp/dt
	Tricuspid inflow	
		TR velocity—estimate RV systolic pressure

LVOT, left ventricular outflow tract; RV, right ventricular; TR, tricuspid regurgitation.

varying depths along a single scan line. A full-color flow map is generated by combining multiple scan lines along the areas of interest. To accurately estimate the velocity along a given scan line, the instrument compares the Doppler shift changes from several successive pulses (typically eight), and this is known as the **burst length**. Where Doppler shifts are detected, color pixels are displayed at that location with the different colors representing the different degrees of Doppler shift based on a predetermined color spectrum. Tradition has set **blood velocity toward the transducer as shades of red and blood flow away as shades of blue (Blue Away)**.

Since this modality uses properties based on PW Doppler technology, color flow Doppler has limitations similar to those of PW Doppler for velocity determination. When the flow velocity is higher than the Nyquist limit (indicated on the color map), color aliasing occurs (depicted as color reversal, red to blue or blue to red transition). The fact that color aliasing occurs can actually provide important hemodynamic information, such as identification of flow acceleration or calculation of the proximal isovelocity surface area (PISA), which is discussed in Section **VI.C.6**.

d. Tissue Doppler imaging (TDI). TDI is based on adjusting standard Doppler to focus primarily on the low-velocity, high-amplitude **motion of the myocardium** (usually < 20 cm/s) instead of the high-velocity, low-amplitude motion of red blood cells. Decreasing the filters (which normally eliminates low-velocity signals) and the Doppler transmit gain (which excludes the low-amplitude blood signals) results in the Doppler focusing primarily on myocardial motion. TDI can be displayed as either PW Doppler, typically at one aspect of the mitral annulus (usually septal or lateral) or by color flow TDI mapping of the entire myocardial area of interest (Fig. 67.1). TDI has primarily been used as an adjunct for the evaluation of left ventricular (LV) diastolic function, where the mitral annular TDI pattern shows a systolic (S) wave toward the transducer and two diastolic waves away from the transducer (corresponding to early relaxation and late atrial diastolic myocardial motion, labeled as E′ and A′) (Fig. 67.2 and Table 67.4). With worsening diastolic function, E′ velocity decreases and is directly proportional to the rate of relaxation. TDI annular velocities decrease with age and may be affected by a myocardial infarction in the region adjacent to the annulus or surgery of the mitral valve. Therefore, TDI can be used to help differentiate

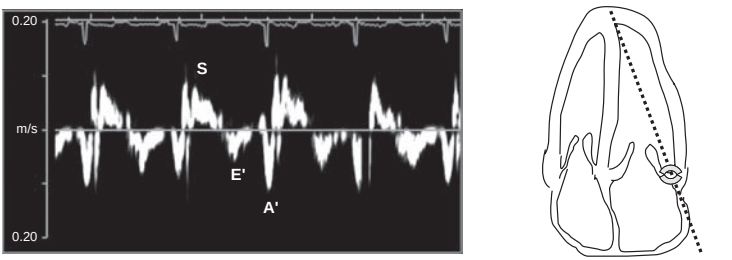

FIGURE 67.1 Tissue Doppler imaging (TDI) for diastolic function recorded from the apical four-chamber window using a 2-mm sample volume positioned in the lateral wall 1 cm from the mitral annulus. The TDI signal is toward the transducer in systole (S) as the myocardium moves toward the apex. In diastole, the myocardial velocity is directed away from the transducer first with early diastolic filling (E′) and then with atrial contraction (A′).

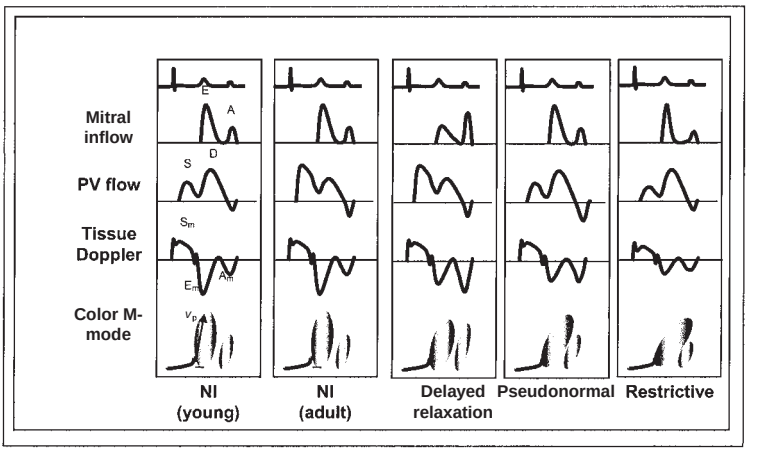

FIGURE 67.2 Diastolic function/dysfunction staging. PV, pulmonary vein; Tissue Doppler: mitral annular velocity by Tissue Doppler; NI, normal; S, systolic; D, diastolic; S_m, systolic annular velocity; E_m, early diastolic annular velocity (E′); A_m, atrial annular velocity (A′); V_p, velocity of propagation; E, early mitral inflow velocity; A, atrial kick mitral inflow velocity.

a normal mitral inflow pattern (normal E′) from a pseudonormal filling pattern (reduced E′) (Fig. 67.2 and Table 67.4). TDI can also be used to assess LV filling pressures, myocardial deformation, and ventricular dyssynchrony.

D. Color M-mode (CMM). This technique, whereby color flow Doppler is imposed on an M-mode image, permits excellent spatiotemporal distribution of velocity (color) data, although it is limited to the defined scan line. It is a valuable adjunct in the timing of cardiac events, which may not be readily appreciated by 2D and color flow imaging alone. Its primary use has been in evaluating diastolic filling pattern where the LV inflow CMM pattern typically has two appreciable waves, the first demonstrating the early passive filling wave and the second later wave resulting from atrial contraction (Fig. 67.2). The slope of the early filling wave (velocity of propagation, V_p) is primarily

TABLE 67.4 Diastolic Function/Dysfunction Staging

	Normal young	Normal adult	Normal elderly	Delayed relaxation	Pseudonormal filling	Restrictive filling
Stage	Normal	Normal	Normal	I	II	III
E/A ratio	> 1 (often > 2)	> 1	< 1	< 1	1–2	> 2
DT (ms)	< 220	< 220	> 220	> 220	150–200	< 150
S/D ratio	< 1	≥ 1	> 1	> 1	< 1	< 1
Ar (cm/s)	< 35	< 35	< 35	< 35	> 35	> 25
V_p (cm/s)	> 55	> 55	< 55	< 55	< 45	< 45
E′ (cm/s) (E annulus)	> 10	> 8	< 8	< 8	< 8	< 8

dependent on the rate of relaxation and is reduced with delayed relaxation. It is useful for differentiating a normal mitral inflow pattern (normal V_p) from a pseudonormal filling pattern (where impaired relaxation results in delayed flow propagation into the left ventricle, slower V_p) (Fig. 67.2 and Table 67.4).

Other uses of CMM are the accurate measurement of AR jet diameter in the LVOT in the parasternal views and, with its superior temporal resolution, detection of diastolic mitral regurgitation (MR), which may be seen in certain conditions (severe acute AR, advanced diastolic dysfunction, and complete heart block).

IV. TOMOGRAPHIC VIEWS AND CARDIAC ANATOMY. Most echocardiography laboratories have similar protocols for acquisition of a complete echocardiogram with only slight differences. Each echocardiographic view is labeled first by the transducer position (parasternal, apical, subcostal, and suprasternal) followed by the tomographic view of the heart (long axis, short axis, four chamber, and two chamber). To acquire these different views, the transducer is placed on different parts of the body and adjusted with rotation and angulation to optimize the final image. Standard imaging planes are illustrated in Figures 67.3 to 67.8; see Table 67.5 for standard examination protocol and Table 67.6 for useful examination tips.

A. Parasternal. The parasternal position is typically obtained by placing the transducer at the left of the sternal border in the third or fourth intercostal space. The optimal position for the patient is usually the left lateral decubitus position, but sometimes some hybrid between the steep left lateral and supine position is required to optimize the view. This position allows imaging of the long axis as well as the short axis of the heart.

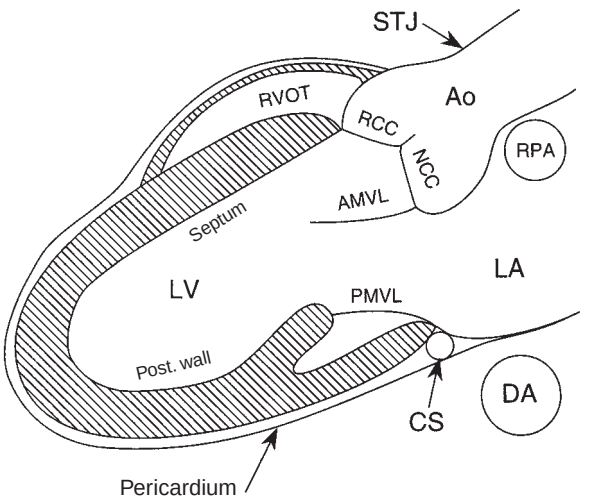

FIGURE 67.3 Schematic diagram of the parasternal long-axis view in diastole. AMVL, anterior mitral valve leaflet; Ao, aorta; CS, coronary sinus; DA, descending aorta; LA, left atrium; LV, left ventricle; NCC, noncoronary cusp; PMVL, posterior mitral valve leaflet; post. wall, posterior wall; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; STJ, sinotubular junction. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

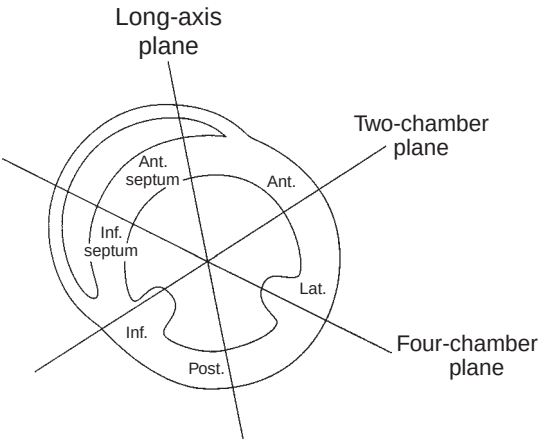

FIGURE 67.4 Schematic diagram of the parasternal short-axis view at the level of papillary muscles. Ant. septum, anterior septum; Ant., anterior wall; Inf. septum, inferior septum; Inf., inferior wall; Lat., lateral wall; Post., posterior wall. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

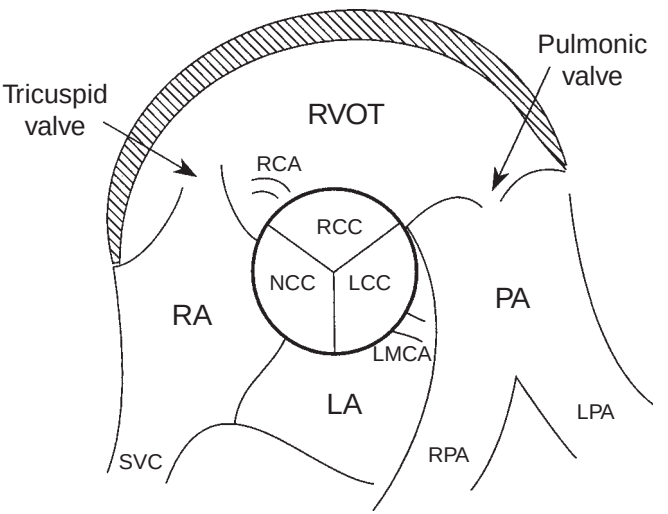

FIGURE 67.5 Schematic diagram of the parasternal short-axis view at the aortic valve level. LA, left atrium; LCC, left coronary cusp; LPA, left pulmonary artery; NCC, noncoronary cusp; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; SVC, superior vena cava; LMCA: left main coronary artery. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

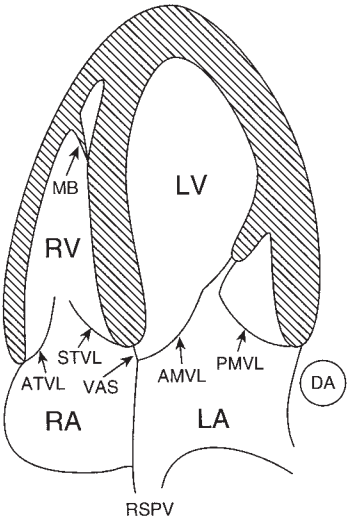

FIGURE 67.6 Schematic diagram of the apical four-chamber view. AMVL, anterior mitral valve leaflet; ATVL, anterior tricuspid valve leaflet; DA, descending aorta; PMVL, posterior mitral valve leaflet; LA, left atrium; LV, left ventricle; MB, moderator band; RA, right atrium; RV, right ventricle; STVL, septal tricuspid valve leaflet. VAS, ventriculoatrial septum (where communication from LV to RA may occur); RSPV, right superior pulmonary vein. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

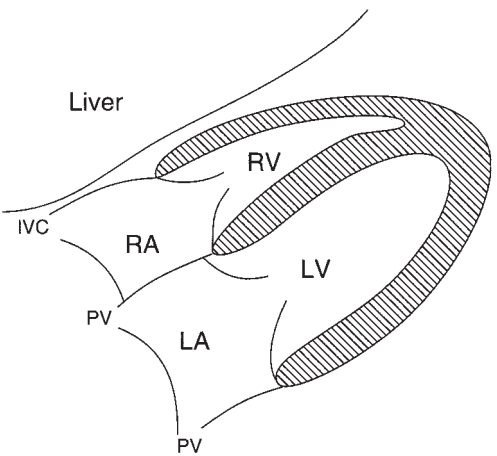

FIGURE 67.7 Schematic diagram of the four-chamber view from the subcostal approach. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PV, pulmonary vein. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995: 21–64, with permission.

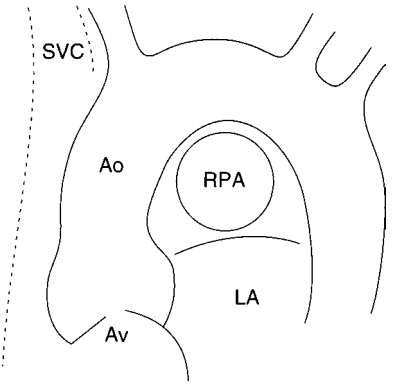

FIGURE 67.8 Schematic diagram of the aorta and right pulmonary artery from the suprasternal notch window. Ao, aorta; AV, aortic valve; LA, left atrium; RPA, right pulmonary artery; SVC, superior vena cava. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography.* Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

TABLE 67.5 Standard Transthoracic Examination

1. **PLAX**
   - Position transducer in third or fourth intercostal space parasternally (ridge toward right shoulder)
   - Color Doppler—mitral and aortic valve flow and interventricular septum (in cases of ventricular septal defect)
   - M-mode—three levels (below mitral leaflets, midmitral leaflets, and aortic valve)
   - Move up an intercostal space to get better view of ascending aorta
   - Tilt transducer inferomedially to assess RV inflow. Color Doppler to assess tricuspid regurgitation and CW Doppler to estimate RVSP
2. **PSAX**
   - Rotate transducer 90° clockwise from PLAX and tilt transducer from superior to inferior (LV apex view, mid-LV view, mitral valve view, and aortic valve level)
   - Color Doppler at mitral valve level (localize mitral regurgitation if present)
   - Color Doppler at aortic valve level (localize aortic regurgitation and assess flow in RVOT/pulmonic valve and tricuspid valve)
   - PW Doppler—RVOT (level of pulmonic valve annulus)
   - CW Doppler—RVOT/pulmonic valve and tricuspid valve (estimate RVSP)
3. **A4C**
   - Transducer at apex—ridge toward left (move laterally and inferiorly if necessary to get true apex)
   - Color Doppler—mitral flow and tricuspid flow
   - Measure PISA if mitral regurgitation (zoom, decrease Nyquist, and measure radius)
   - PW Doppler—mitral inflow—position at level of mitral leaflet tips (gate 1–2 mm)

TABLE 67.5 Standard Transthoracic Examination (*Continued*)

- PW Doppler—PV (usually right upper PV)—1–2 cm into vein (gate 3–4 mm)
- CW Doppler—across mitral valve (stenosis and/or regurgitation and to calculate PISA)
- CW Doppler—tricuspid flow (estimate RV systolic pressure)
- Tilt transducer anteriorly to obtain "five-chamber view," i.e., open up aortic valve/LVOT
- Color Doppler—LVOT/aortic valve
- PW Doppler—LVOT—at the level of the aortic annulus
- CW Doppler—LVOT/aortic valve
- Tilting transducer posteriorly will bring the coronary sinus in view (along AV junction, emptying into right atrium)

4. **A2C**
   - Rotate transducer ~60–90° anticlockwise
   - Tilt posteriorly and rotate clockwise to open out descending aorta
5. **Apical long axis (apical three chamber)**
   - Rotate transducer further 30–45° anticlockwise
   - Color Doppler—LVOT/aortic valve
   - Recheck CW Doppler across aortic valve if evaluating for aortic stenosis
6. **Subcostal view—patient supine and legs bent at knees**
   - Subxiphoid, midline, tilt anteriorly under sternum with groove toward patients left for four-chamber view
   - Color Doppler across interatrial septum to check for a PFO or ASD
   - Rotate transducer 90° from four-chamber view until groove is pointing anterosuperiorly
   - Same views as PSAX except rotated 90° clockwise
   - Sweep from left to right to get apical, midventricular, and aortic valve levels
   - IVC should be visualized when scan plane is directed toward the right midclavicular region with some counterclockwise rotation to open out long axis of IVC
   - Color Doppler—IVC flow
   - PW of hepatic veins (may need to angle posteriorly)
7. **Suprasternal view—patient supine and head tilted backward**
   - Transducer in suprasternal notch, with groove toward left (rotate to about 1 o'clock), parallel to trachea
   - Color Doppler in arch and upper descending aortas (especially if suspected coarctation)
   - PW Doppler in upper descending aorta (if assessing aortic regurgitation severity)
8. **Pedoff probe**
   - Especially for checking maximal aortic valve gradient in aortic stenosis
   - Apical position
   - Right upper sternal border (aortic stenosis)

A4C, apical four chamber; A2C, apical two chamber; AV, atrioventricular; ASD, atrial septal defect; CW, continuous wave; IVC, inferior vena cava; LV, left ventricular; LVOT, left ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; PFO, patent foramen ovale; PW, pulsed wave; PV, pulmonary vein; RV, right ventricular; RVOT, right ventricular outflow tract, RVSP, right ventricular systolic pressure.

TABLE 67.6 Tips for Transthoracic Two-Dimensional Examination

1. **Optimize patient position** (left lateral with left hand above head) and **environment** (darkened room).
2. Ensure imaging in **harmonics** mode.
3. Consider **contrast** to improve endocardial delineation for technically difficult studies.
4. When parasternal and apical images are limited (body habitus, surgical drains, dressings, etc.), the **subcostal window** may be the only accessible window.
5. Consider **off-axis views** to enhance visualization of specific structures.
6. Obtain images at **end of expiration,** as the heart is closer to the transducer.
7. **Avoid foreshortening LV apex** (especially in A2C)—true apex may be more inferior and lateral than expected.
8. If there is a **concern of LV thrombus,** zoom and check with low-velocity color Doppler to ensure flow throughout. Consider contrast if unclear.
9. If an object is suspicious for an artifact, reassess in other imaging planes.
10. **M-mode** can be useful especially for the accurate timing of cardiac events (especially RV or RA collapse in the setting of possible tamponade or assessment of possible systolic anterior motion of the mitral valve).
11. Adjust transducer **frequency** to maximum that permits adequate far-field penetration/depth.
12. Set **time gain compensation** in the midrange with lower gain in the near field and higher settings in the far field to compensate for attenuation of the beam with increasing distance from transducer.
13. Use the least amount of **depth** that adequately shows the entire area of interest.
14. Adjust the **transmit gain/output** to optimize image brightness/quality—too low, everything appears black, too high results in a "white-out." Initially set it to high and then adjust downward.
15. Adjust the **"compress"/dynamic range**. Decrease if image quality is poor to produce high-quality contrast images. Increasing it will "soften" images. Typically as compress is increased, the transmit gain should be decreased to maximize the spectrum of the gray scale.
16. Adjust the **focus** (focal zone) to include the area of interest, as the beam is narrowest (improves image resolution) within this area, especially when imaging near-field structures (e.g., looking for an apical LV thrombus from the apical windows).
17. Set the **persistence** to low.

LV, left ventricular; A2C, apical two chamber; RA, right atrial; RV, right ventricular.

1. **Parasternal long axis (PLAX).** The PLAX tomographic view is traditionally the first view of a standard transthoracic echocardiogram. The ultrasound beam is lined up between the patient's right shoulder and the left flank. The right ventricular outflow tract (RVOT) is located at the top of the image, the aorta to the right, the inferolateral (or posterior) wall on the bottom, and the cardiac apex on the left. The anteroseptum is visualized between the RVOT and the LV cavity. Therefore, the PLAX view of the heart is similar to the sagittal view of the left ventricle if viewed from the patient's left side in the supine position. Tilting

the transducer's tail toward the left shoulder with slight clockwise rotation aims the ultrasound beam inferomedially and brings the right ventricular inflow into view. This is good for obtaining the tricuspid regurgitation (TR) velocity as well as viewing the tricuspid valve, RV apex, and the right atrium.

2. **Parasternal short axis (PSAX).** While the transducer is still in the parasternal position, rotating the transducer clockwise to approximately 90° displays the heart in the short axis. The ultrasound beam in this case is roughly from the left shoulder to the right flank. Using different degrees of transducer tilting, and occasionally moving up or down an intercostal space, results in four traditional views of the heart. On tilting from superior to inferior, the views obtained are aortic valve–RV outflow, mitral valve level, midventricle at the papillary muscles, and the LV apex. The images appear as if viewing the heart from the apex and looking through to the base; therefore, the septum is on the left, lateral wall on the right, the anterior and anteroseptal walls at the top, and the posterior–inferior walls on the bottom of the screen.

B. Apical. The apical position is obtained with the patient still in the left lateral position and the probe placed at the apical impulse. This position obtains images in the long axis of the heart.

1. **Apical four chamber (A4C).** The A4C view is obtained with the ultrasound beam transecting the thorax in a superior–inferior fashion. Most institutions orient the transducer to place the left ventricle on the right side of the screen and the right ventricle on the left side. The apex is at the top of the image and the atria at the bottom regardless of the orientation. The inferoseptal and anterolateral walls as well as apex of the left ventricle can be assessed in this view.
2. **Apical five chamber (A5C).** A slight rotation of the transducer introduces a fifth "chamber" in view, the proximal aorta. The aortic valve and LVOT also appear. This view allows for hemodynamic assessment of the LVOT and aortic valve as well as an additional view for aortic valve pathology.
3. **Apical two chamber (A2C).** Further rotation, 90° counterclockwise from the A4C view, obtains the A2C view. In addition to the left atrium, the LV anterior wall, inferior wall, apex, and mitral valve are also well visualized.
4. **Apical three chamber (A3C).** A slightly more counterclockwise rotation (approximately 30°) brings the aorta back into view, resulting in the A3C, or apical long-axis, view. This essentially has the same anatomical structures as those in the PLAX view with a different orientation. The apex is better visualized and the RVOT usually drops out of the image. Additional information on mitral and aortic valve hemodynamics can be obtained in this view, which is not ideally obtained in the PLAX view.

C. Subcostal. In a standard transthoracic examination, the subcostal view provides additional views of the ventricles, atria, and atrial septum that had been acquired in earlier portions of the examination (but now with a different orientation). However, in some patients with poor parasternal and apical views (e.g., hyperinflated lungs), the subcostal view may be the only way to obtain images of the heart since the parasternal and apical locations may have poor windows.

The subcostal position is located caudal to the xiphoid process, with the patient in the supine position. The transducer is placed in the midline nearly parallel to the long axis of the patient's body so that the ultrasound beam slices toward the spine. This shows the right ventricle at the top right, the left ventricle at the bottom right, and their respective atria on the left. Clockwise rotation along with inferior tilting brings the inferior vena cava (IVC) and hepatic veins into view, which are used for right-sided hemodynamic assessments.

In patients with very poor parasternal and apical windows, modified views from the subcostal position can be incorporated in the examination to gather the images from a different perspective.

D. Suprasternal. Placing the transducer in the suprasternal notch and pointing inferiorly can assess the ascending aorta, aortic arch, and descending aorta. Hemodynamics from this position can better characterize AR as well as the presence of coarctation.

V. ADVANCED ECHOCARDIOGRAPHIC TECHNIQUES

A. Contrast echocardiography. Contrast echocardiography is performed by injecting either **agitated saline** or one of the **commercially available contrast agents** into an arm vein. The choice of agitated saline versus commercial contrast agents depends on whether the goal is to visualize the right atrium and ventricle versus the left ventricle and myocardium. Both are microbubbles that reflect ultrasound waves and opacify intracardiac chambers. The size of the microbubbles relative to the pulmonary capillary diameter determines whether they cross to the left side of the heart or get trapped in the pulmonary circulation.

Agitated saline is sterile saline (preferably mixed with some blood), combined with a small quantity of air, which has been exchanged rapidly using a three-way stopcock between two syringes to create small bubbles. These relatively large (and unstable) bubbles are caught in the lung and do not routinely appear in the left side of the heart. However, after the bubbles are seen within the right atrium, their appearance in the **left atrium within three beats** of the cardiac cycle suggests a right-to-left **intracardiac shunt**—typically from a small patent foramen ovale. Contrast may appear in the **left atrium more than four beats** after it is seen in the right atrium, and this more likely signifies an **intrapulmonary shunt** rather than an intracardiac shunt. There is a small risk of embolic complications in the use of agitated saline. Care should be taken to avoid injecting larger air bubbles by inspecting the syringe closely prior to injection and ensuring that the bubbles are very small. Additionally, injecting contrast in a known large shunt should be avoided.

Modern commercial contrast agents consist of either an albumin-based shell containing perfluorocarbon gas (Optison) or a synthetic phospholipid shell containing perfluoropropane gas (Definity). These **microbubbles are much smaller** (the size of a red blood cell) and more stable; therefore, they can **cross the pulmonary capillaries and appear on the left side of the heart, where they opacify the LV cavity. Their primary uses are to improve endocardial definition** and to clarify the presence/absence of a suspected LV thrombus/mass. Ultrasound waves, especially those of higher power, destroy microbubbles; therefore, for optimal contrast imaging, it is important to reduce the mechanical index (the output of the machine), typically to 0.4 to 0.6.

Contrast also enhances Doppler signals, and agitated saline can be useful to augment the signal from TR to better estimate peak right ventricular systolic function (RVSP), whereas commercial microbubble products (Optison and Definity) can be used to enhance the Doppler envelope in patients with aortic stenosis when the image quality is suboptimal.

Contrast echocardiography was the subject of a black box warning from the FDA because of concerns of significant adverse vents in patients who received it. More recent data suggest that adverse events following contrast injection are no more common than in those in whom it is not used when appropriate adjustment for severity of illness is made. Nevertheless, the FDA has recommended that patients with pulmonary hypertension or unstable cardiac conditions such as recent myocardial infarction, unstable angina, decompensated heart failure, ventricular arrhythmia, or respiratory failure should be monitored closely for at least 30 minutes after its use. It is contraindicated when a fixed or even transient right-to-left shunt is present or with documented allergy to its components such as blood products or albumin in the case of Optison.

B. Three-dimensional (3D) echocardiography is now emerging as a realistic imaging modality with improving image quality on newer generation 3D machines. Images are obtained using a transducer that transmits and receives data simultaneously in a 3D volume. Either real-time 3D images or biplane (orthogonal) simultaneous 2D images can be obtained. The 3D data set can then be manipulated using different software packages to assess function and anatomy. It is of particular benefit for the localization of valvular abnormalities (especially for the complex 3D mitral valve structure), accurate LV volume calculation, guiding surgical interventions (e.g., mitral valve repair), and complex congenital heart disease. Three-dimensional echocardiography allows for a better assessment of the right ventricle, which has a complicated geometry that is sometimes difficult to assess using 2D echocardiography. Three-dimensional color flow imaging allows for a comprehensive assessment of vena contracta and areas of flow convergence (PISA), which can improve the quantification of valvular regurgitation. It has been documented to allow for a more rapid evaluation of mitral valve area (MVA) in mitral stenosis as compared with conventional 2D planimetry. With the present technology, image resolution remains inferior to 2D imaging.

C. Myocardial mechanics—tissue strain, strain rate imaging, and speckle tracking. Strain rate imaging allows for the estimation of regional myocardial deformation and, therefore, function. **Tissue strain, a dimensionless entity, is a measure of the relative deformation of tissue**. Myocardial deformation in a segment of interest is assessed with reference to the adjacent segment, avoiding errors introduced by translational motion and tethering. **Strain rate is the rate of the deformation between two adjacent points of interest along a scan line and is expressed in seconds**. A strain rate curve can be derived by analyzing many adjacent segments along a scan line. Doppler techniques for assessing strain are not always ideal due to angle dependence, signal noise, and the need for a high frame rate. Doppler-independent techniques such as **speckle tracking** use ultrasonic reflectors (speckles) within tissues that can be followed from frame to frame through the cardiac cycle. This method can be used to assess the radial deformation and torsion of the ventricle. Strain rate is a relatively preload-independent measure of regional myocardial function. Clinical applications include assessment of myocardial ischemia, viability, diastolic function, subclinical LV dysfunction in valve disease, and cardiac involvement in systemic diseases such as diabetes or amyloidosis.

D. Dyssynchrony. Dyssynchrony occurs when different areas of the ventricles contract in an irregular pattern spatially and temporally. It is primarily seen in patients with impaired systolic function and electrophysiologic conduction delays. M-mode, 2D imaging, color Doppler, and tissue Doppler have all been employed to assess the amount of dyssynchrony but no consensus exists on the optimal approach to evaluate ventricular dyssynchrony (see Chapter 56). Some useful measures include the following:

1. A difference in the time to peak velocity of > 65 milliseconds between opposing walls (basal segments in four-chamber, two-chamber, and three-chamber views yielding a total of six segments) using pulsed tissue Doppler.
2. A difference of 40 milliseconds in the interval from the QRS complex to the onset of flow in the RVOT versus the LVOT using pulsed tissue Doppler.
3. Using M-mode or speckle tracking, a difference of 130 milliseconds in the septal to posterior wall delay.

After the implantation of a resynchronization device, Doppler echocardiography is used for the optimization of programmed timing.

VI. SPECIAL TOPICS

A. Systolic function. Two-dimensional imaging is currently the primary echocardiographic means of determining systolic function of the heart. The most utilized

measurement is the EF. In the past, a common way of determining the EF was based on estimation by visual inspection. Recently, echocardiographic societies have recommended using standardized objective methods to minimize interobserver differences. LV volume is best measured using the modified Simpson's method (disk summation method). This involves tracing the LV area from two orthogonal views (typically A4C and A2C) and dividing the left ventricle into a number of cylinders of equal height. Total ventricular volume is calculated by adding up all the volumetric cylinders. All modern machines and digital echo reading systems have integrated software to create and combine the volume data after simply tracing the LV areas in both apical views. Based on the volumes measured in diastole and systole using this method, stroke volume (SV) and EF can be estimated from volume data obtained by **Simpson's method:**

Stroke volume (SV) = end-diastolic volume (EDV) – end-systolic volume (ESV)

$$EF = SV/EDV \times 100\%$$

$$\mathbf{EF = EDV - ESV/EDV \times 100\%}$$

Newer semiautomated methods in 3D echocardiography using full matrix-array transducers give accurate, reproducible assessments of LV volume and EF that are superior to 2D methods when magnetic resonance imaging is used as the gold standard.

Finally, newer methods of assessing systolic function are becoming important. For example, LV torsion is a newer index for assessing LV systolic function that uses speckle tracking. The difference between the clockwise rotation of the base of the heart and the counterclockwise rotation of the apex of the heart (approximately 12°) can be evaluated using speckle tracking. Global strain also appears to be a robust parameter for assessment of LV function. Normally, LV peak systolic strain is negative and averages to $-18.6 \pm 0.1\%$.

In addition to the assessment of EF for the evaluation of systolic function, an assessment of regional wall motion and thickness is crucial in understanding the mechanism of disease. This is based on the fact that certain cardiac disease processes cause nonuniform abnormalities (coronary artery disease and sarcoidosis) and others cause global insults (hypertension and familial cardiomyopathy). For example, an EF of 35% that has a thin and akinetic anterior and anteroseptal wall would suggest an old transmural myocardial infarction due to occlusion of the left anterior descending artery. However, an EF of 35% with no regional wall abnormalities and thick myocardial walls could suggest amyloidosis or hypertension as the cause of the systolic dysfunction. Strain technology allows the display of regional variation in this modality that may be useful in understanding the regional manifestations of systolic dysfunction. For instance, in amyloidosis, strain is often preserved at the apex, but it is diminished in other areas of the heart.

B. Diastolic function. Doppler echocardiography remains the primary modality for assessing LV diastolic function, primarily by integrating information obtained from PW Doppler of mitral inflow and pulmonary venous flow combined with 2D assessment of left atrial size. Addition of CMM and TDI modalities can help optimize the assessment of degree of diastolic dysfunction, and combined mitral inflow/CMM (E/V_p) and mitral inflow/TDI (E/E′) indices can be used to estimate LV filling pressures.

Traditionally, diastolic function was determined solely based on the assessment of mitral inflow pattern; however, with worsening diastolic function, a "pseudonormal" pattern appears (due to the opposing effects of delayed LV relaxation and elevated LV filling pressures), and this is indistinguishable from a normal diastolic filling pattern. Pulmonary venous flow can help differentiate these. Conventionally, the normal anterograde S/D pattern (S > D) should be reversed (S < D) in patients with pseudonormal LV diastolic filling, with an

increased retrograde atrial reversal velocity. However, optimal pulmonary venous flow images can be difficult to obtain, and flow patterns can be affected by other factors, including rhythm (atrial fibrillation) and valvular dysfunction (MR). Both CMM (delayed V_p) and TDI (reduced E′) are useful to help confirm a pseudonormal filling pattern. An additional important key factor in assessing LV diastolic function is left atrial volume indexed to body surface area, which is invariably increased with worsening diastolic function. Significant diastolic dysfunction is unlikely to exist with a normal left atrial volume index. Accurate assessment of diastolic function not only is important for diagnosis of patients with primarily LV diastolic heart failure but is also of major prognostic importance for patients with systolic heart failure.

C. Hemodynamics

1. Transvalvular pressure gradient. The **Bernoulli equation** allows measurement of relative pressure differences across valves, shunts, or the LVOT. In its complete form, the Bernoulli equation is too complex for routine clinical use, as it incorporates three main components, namely, convective acceleration, inertial term (flow acceleration), and viscous friction. In many clinical situations, the latter two components can be ignored, leaving the flow gradient across an orifice to be derived from the convective acceleration term alone:

$$\Delta P = 4 \times (V_2^2 - V_1^2)$$

where V_2 is the velocity distal to an obstruction and V_1 is the velocity proximal to an obstruction.

The flow proximal to a narrowed orifice (V_1) is much lower than the peak flow velocity (V_2) and can be frequently ignored, leaving a **simplified Bernoulli equation**:

$$\Delta P = 4V^2$$

The simplified Bernoulli equation is unreliable

a. when V_1 is > 1 m/s, which occurs in serial lesions (subvalvular and valvular stenoses) and mixed stenosis with regurgitation.

b. when viscous resistance becomes significant in the evaluation of long stenoses (e.g., coarctation or a tunnel-like ventricular septal defect).

c. when the inertial term (flow acceleration) is not negligible (flow through normal valves).

It is important to realize that in aortic stenosis the Bernoulli equation represents the **maximal instantaneous gradient** across the valve, which is always higher than the customary peak-to-peak gradient measured in the catheterization laboratory since the LV systolic peak and aortic peak pressures do not occur at the same time and therefore are not instantaneous.

The flow within the heart is pulsatile; hence, mean gradients are an important measure and are obtained by integrating the velocity profile over the ejection time. This can be readily obtained with the software available on all modern echocardiography machines by simply tracing the area of the velocity profile. The mean pressure gradient is then derived from the mean velocity data using the Bernoulli equation.

2. Intracardiac pressure measurement

a. Estimated right atrial (RA) pressure can be derived from the size of the IVC and its response to changes in respiration or a sniff (Table 67.7). Using a dilated IVC to assess elevated RA pressures is not accurate in mechanically ventilated patients; however, a small IVC of size < 1.2 cm in a mechanically ventilated patient is 100% specific for an RA pressure < 10 mm Hg.

b. Pulmonary artery systolic pressure (PASP) is estimated from the TR peak velocity. Provided that there is no tricuspid valve obstruction, peak

TABLE 67.7 Estimation of Right Atrial Pressure

IVC	Change with respiration/sniff	Est. RA pressure (mm Hg)
Normal (< 1.7 cm)	Decrease > 50%	0–5
Dilated (> 1.7 cm)	Decrease > 50%	6–10
Dilated (> 1.7 cm)	Decrease < 50%	10–15
Dilated (> 1.7 cm)	No change	> 15

IVC, inferior vena cava; RA, right atrial.

TR velocity will depend on the pressure gradient between the right ventricle and the right atrium [difference between peak right ventricular systolic pressure (RVSP) and RA pressure]. Therefore, estimated RVSP is equal to this pressure difference, determined from the peak TR velocity, plus the estimated RA pressure (Table 60.7). If there is no obstruction across the pulmonic valve, the RVSP will be similar to the **PASP**:

$$\textbf{PASP} = 4 \times (\text{peak TR velocity})^2 + \text{estimated RA pressure}$$

c. Pulmonary artery diastolic pressure (PADP). Pulmonary regurgitation represents the pressure difference between the pulmonary artery (PA) and the right ventricle at end-systole. Hence, the end pulmonary regurgitation velocity can be utilized to measure the end-diastolic pressure difference between the PA and the right ventricle. The right ventricular end-diastolic pressure should be similar to the RA pressure; therefore, addition of estimated RA pressure to the end-diastolic pressure difference between the PA and the right ventricle will estimate the PADP:

$$\textbf{PADP} = 4 \times (\text{end pulmonary regurgitant velocity})^2 + \text{estimated RA pressure}$$

d. Estimated left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP). Provided that there is no mitral stenosis, LVEDP and LAP should be the same. This important measure of LV diastolic function can be estimated by several methods.

(1) Deceleration time (DT) of mitral inflow. A DT of < 150 milliseconds is strongly suggestive of an elevated LVEDP/LAP. In very young patients, a DT < 150 milliseconds may be normal. This results from a rapid equalization of pressures secondary to vigorous early diastolic relaxation and is not caused by an elevated LAP.

(2) Difference between pulmonary venous atrial duration and mitral atrial duration. Normally, mitral A wave duration is greater than pulmonary venous atrial reversal (Ar) duration. When LVEDP is increased, the velocity and duration of the mitral A wave decreased, whereas pulmonary vein Ar velocity and duration increased. The difference between the duration of the Ar wave and the mitral A wave correlates with LVEDP. An Ar-A duration of > 50 milliseconds is specific for an elevated LVEDP > 20 mm Hg. This is reliable in patients with reduced EF but not in patients with normal EF. The primary limitation with this method is the difficulty in accurately measuring the duration of Ar.

(3) Combined mitral inflow/CMM index (**E**/V_p ratio). This index has been demonstrated to correlate with LAP/LVEDP, especially when these filling pressures are elevated. A ratio of > 2 is suggestive of elevated filling

pressures. In patients with normal EFs, especially with small ventricles and hyperdynamic function, the flow propagation velocities are not accurate.

(4) **Combined mitral inflow/TDI index** (E/E′ ratio). This index has been shown to be a semiquantitative measure of LVEDP. A ratio of > 10 (using the lateral annulus) or > 15 (using the septal annulus) correlates with a wedge pressure of > 20 mm Hg. A ratio of < 8 (using the lateral annulus) correlates well with normal filling pressures. For values that fall in between these two limits, the clinician should look at all the other information provided by echocardiography such as left atrial size and pulmonary venous Doppler to assess whether filling pressures are elevated.

3. **d*P*/d*t*.** This index of LV contractility is the rate of pressure increase during isovolumic contraction and is traditionally obtained using invasive pressure transducers. It can be estimated from the CW Doppler of the MR jet. During isovolumic contraction, there is no change in LAP; therefore, MR velocity changes reflect d*P*/d*t*, with more rapid increases in MR velocity being associated with increased contractility. The pressure change between 1 m/s and 3 m/s = 4 ($V_2^2 - V_1^2$) = 32 mm Hg. The time it takes the ventricle to accelerate an MR jet velocity from 1 m/s to 3 m/s is measured and then the d*P*/d*t* is calculated as follows:

$$dP/dt = 32 \text{ mm Hg/time (in seconds)}$$

This has been demonstrated to correlate well with invasively measured d*P*/d*t*. It is considered normal when the calculated value is > 1,200 mm Hg/s.

4. **Continuity equation** is an application of the principle of conservation of mass, which states that flow across a conduit of varying diameter is equal at all points. This equation is especially useful in quantifying a stenotic aortic valve area (AVA) that cannot be accurately measured using planimetry from the transthoracic window. Flow at any point in the heart is the product of the cross-sectional area (CSA) and the flow velocity. As flow velocity varies during ejection in a pulsatile system, individual velocities must be integrated to measure total volume of flow (velocity time integral, VTI). This is determined by tracing the spectral Doppler profile, using standard measurement software built into all echocardiography machines.

$$\textbf{Flow at any point} = \textbf{CSA} \times \textbf{VTI}$$

Based on the continuity equation, flow through the LVOT must be equal to flow through the aortic valve; therefore, AVA can be calculated following these steps:

Flow across the LVOT = flow across the aortic valve

$$\text{Area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}} = \text{area}_{\text{aortic valve}} \times \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = \text{area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}}/\text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = (\text{diameter}_{\text{LVOT}}/2)^2 \times \pi \times \text{VTI}_{\text{LVOT}}/\text{VTI}_{\text{aortic valve}}$$

$$\textbf{Area}_{\textbf{aortic valve}} = (\textbf{diameter}_{\textbf{LVOT}})^2 \times \textbf{0.785} \times \textbf{VTI}_{\textbf{LVOT}}/\textbf{VTI}_{\textbf{aortic valve}}$$

The assumption is that the LVOT cross-section is a circle. The greatest source of error in this equation is in the measurement of the LVOT diameter because the value is squared, resulting in magnification of any initial measurement error. The appropriate place to measure the LVOT can be difficult to define accurately in some calcified valves. The **dimensionless index** (DI) is the ratio of the VTI of LVOT to the VTI of aortic valve, and it is preferable to use this to assess aortic

stenosis when accurate measurement of the LVOT diameter is not possible or in those patients with history of previous aortic valve replacement. A DI < 0.25 suggests severe aortic stenosis.

$$\mathbf{DI = VTI_{LVOT}/VTI_{aortic\ valve}}$$

Of note, the flow across the LVOT per beat is the SV, which can thus be calculated from the product of the LVOT diameter and flow velocity (VTI_{LVOT})

$$\mathbf{SV = (diameter_{LVOT})^2 \times 0.785 \times VTI_{LVOT}}$$

5. **Volumetric method to assess regurgitant volume/regurgitant fraction.** This is based on the conservation of flow, with total flow across a regurgitant valve being equal to the sum of the forward flow and the regurgitant flow. For example, for MR:

   Total transmitral flow volume = forward flow volume (LVOT flow) + regurgitant volume

   (LVOT flow can be assumed to be the same as the forward flow provided there is no AR.)

   Regurgitant volume = mitral forward flow – LVOT flow

$$\mathbf{Regurgitant\ volume = (diameter_{mitral}{}^2 \times 0.785\ VTI_{mitral}) - (diameter_{LVOT}{}^2 \times 0.785 \times VTI_{LVOT})}$$

$$\mathbf{Regurgitant\ fraction = regurgitant\ volume/total\ mitral\ flow}$$

   Because of the multiple assumptions and calculations performed, this method is prone to error and is rarely used clinically.

6. **The PISA** method is another application of the principle of conservation of mass. It is based on the phenomenon that flow accelerates proximal to a narrowed orifice. This is illustrated by the acceleration of water in a bathtub before it enters the drain pipe. Using color Doppler, as flow accelerates, its velocity may exceed the Nyquist limit which results in color reversal because of aliasing. This is seen as a series of colored ("isovelocity") hemispheres with color flow imaging, with the velocity of flow at the surface of this hemisphere being the aliasing velocity (Nyquist limit) of color flow in that direction. Decreasing the aliasing velocity will increase the size of the hemisphere, as the velocity at which color changes is reduced. In keeping with conservation of mass, blood flow at the surface of this hemisphere is the same as flow through the regurgitant orifice, and this is the basis of using the PISA method to estimate the regurgitant orifice area (ROA) of a valve. PISA has been most extensively used to estimate the mitral ROA to quantify MR.

   Flow at surface of hemisphere = flow through regurgitant orifice

   Surface area of hemisphere × velocity at hemisphere = ROA × peak velocity of regurgitation [using continuous wave Doppler (CW) through the mitral valve]

$$2 \times \pi\ (\text{radius})^2 \times \text{aliasing velocity} = \text{ROA} \times \text{peak MR velocity}$$

$$\mathbf{ROA = 2 \times \pi\ (radius)^2 \times aliasing\ velocity/MR_{CW}\ peak\ velocity}$$

   Therefore, the radius of the PISA hemisphere, the aliasing velocity, and the peak mitral regurgitation (MR) velocity are the measurements needed for calculating ROA. The greatest source of error is in defining the precise location of the ROA, so as to accurately calculate the radius.

This method can also be used to measure MVA in mitral stenosis (where forward flow convergence is seen and measured) and the aortic ROA in AR, although it may be difficult to obtain satisfactory visualization of the aortic PISA for quantification from the apical long-axis view (best view to appropriately line up AR jet with the Doppler). When the jet is eccentric, and a full hemisphere is not visible, an angle correction should be considered. The PISA equation for MR can be simplified if the aliasing velocity is set to 40 cm/s and it is assumed that peak MR velocity will be 5 m/s (equates to a normal LV-to-LA pressure gradient of 100 mm Hg). Using these two constants, the PISA equation is simplified to

$$\textbf{ROA} = (\textbf{radius})^2/2$$

Peak MR velocity will increase or decrease depending on the changes in LV systolic pressure and LAP, and it cannot always be assumed to be 5 m/s. However, this method is useful for semiquantification and rapid assessment. Regurgitant volume can be calculated as follows:

$$\textbf{Regurgitant volume} = \textbf{ROA} \times \textbf{VTI}_{\textbf{MRjet}}$$

7. Pressure half-time ($P\frac{1}{2}$) is used to estimate the MVA, as the time for the pressure to fall by half across a stenotic valve is proportional to the degree of stenosis. It is the time interval for the peak pressure gradient to fall by half. Using the Bernoulli equation to convert pressure to velocity, there is a constant relationship between peak velocity and the velocity at $P\frac{1}{2}$.

Pressure at half the peak pressure = 1/2 peak pressure

$$4 \times (V\tfrac{1}{2})^2 = \tfrac{1}{2}(4 \times V^2_{max}) \rightarrow V\tfrac{1}{2} = V_{max} \div \sqrt{2}$$

In addition, the $P\frac{1}{2}$ has a constant relationship with the deceleration time (DT) of the early mitral filling wave, and it is usually estimated from the following:

$$P\tfrac{1}{2} = 0.29 \times \text{DT}$$

Hence, $P\frac{1}{2}$ can be easily measured by using the DT or by simply measuring the time interval from peak to $\frac{1}{2}$ (which is determined from the V_{max}). Most echocardiographic measurement software packages automatically calculate $P\frac{1}{2}$ when the slope of the CW Doppler of the mitral inflow jet is measured. For mitral stenosis, an empirical constant has been validated to correlate $P\frac{1}{2}$ and MVA:

$$\textbf{MVA} = 220/P\tfrac{1}{2}$$

This has only been validated for native valves and will overestimate valve areas for prosthetic valves. The other primary use of $P\frac{1}{2}$ is to help quantify AR. The $P\frac{1}{2}$ of the AR Doppler velocity jet becomes shorter with worsening AR, as the more severe the AR, the more rapidly the pressures in the aorta and the left ventricle equilibrate. A $P\frac{1}{2} < 250$ milliseconds suggests a severe AR. There are many limitations with this, including the fact that $P\frac{1}{2}$ is affected by aortic and LV compliance and by a change in systemic vascular resistance.

VII. TECHNICAL ASPECTS AND ADVANCED IMAGE ACQUISITION

A. Machine settings. To obtain the best images and accurate Doppler information, it is important to optimize the machine settings during different parts of the examination (Tables 66.5 and 66.6).

1. **Time gain compensation.** These controls differentially amplify the echo signals returning from different depths to compensate for attenuation of the ultrasound beam with increasing distance from the transducer. This function is useful with

higher frequency transducers, as they are associated with more attenuation at greater depths.

2. **Depth.** Start with the greatest depth to get an overview and then decrease the depth to include all of the target structure. A depth of 16 cm is usually adequate for the apical window and 12 cm for parasternal imaging. Increasing the depth decreases the frame rate, reducing temporal resolution.
3. **Transmit gain.** This adjusts the displayed amplitude (power) of all received signals and, therefore, affects the brightness of echoes displayed. Setting the power too low results in inadequate returning signals and poor image quality, whereas setting it too high results in image whiteout.
4. **Compress.** The compress setting is also known as a **dynamic range**. It converts the range of returning echo intensities, which may vary a billion-fold in intensity, into 100 to 200 visual shades of brightness or the "gray scale." Increasing the compress will "soften" the image and allow identification of lower level signals. Decreasing the compress results in the production of high-quality contrast images such that weaker signals are eliminated, noise is reduced, and the strongest echo signals are enhanced. Therefore, the compress/dynamic range is decreased when image quality is poor.
5. **Focus (or position).** The focal zone of the transducer indicates the region of the image at which the ultrasound beam is narrowest, and hence where spatial resolution is maximal. Therefore, it is important to reposition the focus to the area of greatest attention/importance, especially those in the near field. When adjusted proximally, however, distal structures may appear blurred as the ultrasound beams scatter.
6. **Persistence.** Persistence is the temporal averaging of the latest frame with the previous frames to produce a smooth or less noisy display. Fast-moving cardiac structures (e.g., valve leaflets) may appear blurred if the persistence is set above low.

B. Imaging artifacts

1. **Acoustic shadowing.** Highly reflective structures block transmission of ultrasound to distal structures, causing poor imaging of these far-field structures. For instance, a mechanical mitral prosthesis prevents good visualization of the left atrium from the apical window.
2. **Reverberation.** This occurs when multiple linear echo signals are generated from a back and forth reflection between two strong reflectors of the ultrasound signal, before the signal returns to the transducer. These appear as multiple parallel irregular dense lines extending from the structure into the far field (e.g., linear echodensity in the ascending aorta in the PLAX view simulating a dissection flap, which is a reverberation from a more anteriorly lying structure, such as a rib). Reverberation artifacts will be present at a multiple of the distance between the two strong reflectors—usually at twice the distance between the strong reflectors. Careful analysis of the artifact in multiple views and with color Doppler should be performed. Color flow signals will be seen to pass through the artifact.
3. **Refraction.** Refraction of the ultrasound beam as it passes through a tissue layer can result in a side-by-side double image. This artifact is often seen in PSAX views of the aortic valve where the image appears to show two aortic valves overlapping.
4. **Beam width artifact.** Ultrasound beams are 3D and are reflected from 3D structures, but they are displayed in a 2D tomographic plane. Strong reflectors at the edge of a central beam, especially outside the narrow proximal focal zone, can be superimposed on a structure in the central zone with the resulting appearance of a structure within the image, that is, outside the 2D tomographic plane (e.g., an aortic valve in the left atrium in the A4C view).
5. **Range ambiguity.** Echo signals from earlier pulse cycles reach the transducer on the next receiving cycle because of re-reflection, resulting in deep structures that

appear closer to the transducer than their actual location, and are manifested as the appearance of an anatomically unexpected echo. This can be confirmed by the disappearance of the artifact when the depth setting is changed.

6. **Side lobe artifacts.** In addition to the central beam, transducers produce side lobes 10° to 30° off axis. All echoes returning from structures in these peripheral beams are displayed, as if they arose from targets within the main beam. Therefore, strong reflectors may be imaged by these low-intensity side lobes and displayed in an erroneous position on the screen. This is a major source of "clutter" in cardiac cavities. Harmonic echoes have much lower intensity side lobes, with a resulting reduction in side lobe artifacts in the image.

C. Factors affecting color Doppler image. Many factors affect spectral Doppler and color flow Doppler, and it is important to consider these. They can be broadly divided into three groups: machine settings, imaging factors, and hemodynamic factors (see Table 67.8 for tips to optimize Doppler settings).

TABLE 67.8 Tips for the Transthoracic Doppler Examination

1. Doppler (all modalities) is very **angle-dependent**—angle between the ultrasound beam and the blood flow jet of interest should be < 20°. In order to achieve this off-axis views are often required.

PW and CW Doppler

2. Shifting the **Doppler baseline** up or down can double the maximal velocity detected (still < 2 m/s) for PW.
3. Increasing the **depth** decreases the Nyquist limit and reduces the maximal velocity that can be measured with PW.
4. Recheck high-velocity jets with the **Pedoff (CW)** probe to confirm peak velocity (include right upper sternal border positions when trying to obtain peak aortic stenosis velocity).
5. Start with high-**gain setting** and reduce until noise and clutter are adequately suppressed.
6. Set **wall filter** to low to avoid overestimation of low velocities.
7. Decreasing the **compress** enhances the edges of the spectral envelope, increasing it enhances the various velocities displayed within the Doppler envelope.
8. Initially set **"reject"** at low (20–40%) to allow the display of a wide range of signals, then increase to remove signals that obscure the image (i.e., to reduce noise).
9. Adjust **gate width**—1–2 mm for mitral inflow and LVOT, 3–4 mm for pulmonary venous flow, and 5–10 for Doppler tissue imaging.

Color flow Doppler

10. **Narrow** the sector and minimize the **depth** to maximize color resolution (increase frame rate).
11. Spatial resolution is higher **axial** to the beam than lateral.
12. Higher **transducer frequencies** result in an increased area of flow disturbance (reduces the Nyquist and increases ability to visualize lower velocities)
13. Adjust **color gain** until just before noise appears in the color.
14. Minimize **wall filters** during analysis of PISA/flow convergence, to avoid overestimating low velocities.

(*Continued*)

TABLE 67.8 Tips for the Transthoracic Doppler Examination (*Continued*)

15. Decreasing the **Nyquist limit** increases the size of any regurgitant jet as lower velocities are detected (normally not color coded at higher Nyquist velocities); therefore, set at 50–60 cm/s initially.
16. Be careful not to miss or underestimate very **eccentric jets** of mitral regurgitation or aortic regurgitation.
17. Remember that **chamber constraint** reduces the size of a jet.

CW, continuous wave; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; PW, pulsed wave.

1. **Machine settings**
   a. **Nyquist limit.** At any given depth, in color Doppler imaging the Nyquist or aliasing velocity (which is related to the PRF) can be adjusted. Typically, it is set to 50 to 60 cm/s. The lowest velocity that is displayed on the color map is related to the Nyquist (minimal displayed velocity = Nyquist × 2/32). Therefore, decreasing the Nyquist increases the lowest velocity displayed, which has the effect of increasing the size of the jet area.
   b. **Transducer frequency.** In color flow imaging, higher transducer frequency reduces the peak velocity (Nyquist limit) that can be measured (see Doppler equation above). Lower Nyquist results in an increased color flow jet area. Therefore, higher frequency transesophageal echocardiography generally produces larger areas of flow disturbance than transthoracic echocardiography. In spectral Doppler imaging, lower frequency transducers can measure higher velocities.
   c. **Depth setting.** Minimizing the depth setting to encompass only the region of interest maximizes the PRF and frame rate.
   d. **Gain.** Adjust the color gain until just before random noise appears in the color. Increased color gain increases the size of color flow disturbance. Two-dimensional gain should be decreased during the color Doppler examination to maximize color flow disturbance because each pixel is assigned to either 2D or color. In PW and CW Doppler, start with a high-gain setting until the desired signal is appreciated. The gain is decreased until noise and clutter are adequately suppressed.
   e. **Baseline.** Used primarily for unwrapping aliased signals. Generally leave it in the middle of the color bar, but it can be adjusted to maximize the velocity that can be displayed with PW or color Doppler. This is also useful for highlighting a specific velocity as in proximal convergence analysis.
   f. **Wall filter.** Excludes low-velocity, high-amplitude signals from myocardial motion. If set too high, it tends to decrease the color flow disturbance. A typical initial setting is 400 Hz. The setting of the wall filter should be minimized during analysis of the proximal flow convergence region to avoid overestimation of low velocities (i.e., set low for PW Doppler and high for CW Doppler).
   g. **Beam width.** Beam width is especially important with PW and CW Doppler. As the ultrasound beam propagates, it spreads out. For example, when sampling pulmonary venous flow with pulse Doppler from the apical view, the sample volume may be at 16-cm depth and the ultrasound beam may be > 1 cm in width. This can lead to the detection of aortic flow, which is displayed as if it arose along the beam axis (from the pulmonary vein) leading to beam width artifact.

h. **Gate length or sample size.** This is the size of the PW Doppler sampling region. It is usually set at 3 to 5 mm. Narrowing the gate focuses the velocity data to a smaller spatial area and can help improve image quality, but it requires very accurate positioning to prevent missing of the appropriate sample area during cardiac motion.

i. **Scale.** Controls the range of Doppler velocities displayed. As the velocity scale increases, the velocity limits increase and the displayed waveform size decreases.

j. **Compress.** In spectral (PW and CW) Doppler, the compress setting adjusts the gray scale, which controls image softness. Decrease the compress to enhance the edges of the spectral envelope. Increase the compress to enhance the various velocities displayed within the Doppler spectrum. Set at 30 dB or higher initially.

k. **Reject.** In spectral Doppler, the reject control removes low-amplitude signals ("noise") from the spectral display. The reject control is initially set at a low level (20% to 40% maximum) to allow the display of a wide range of signals. The reject is then increased to remove signals that obscure the image.

2. **Imaging factors**

a. **Interrogation angle.** Color flow imaging measures only the component of flow that is parallel to the ultrasound beam. This is related to the true flow velocity by the cosine of the angle between the blood flow and the interrogating ultrasound beam. Satisfactory alignment (as parallel to the flow as possible) is vital to record the full and maximal velocity jet with spectral (both PW and CW) Doppler.

b. **Attenuation.** Loss of signal strength caused by too high a transducer frequency for the required depth results in a reduced area of color flow disturbance.

c. **Acoustic shadowing.** Loss of signal strength caused by a proximal reflector of ultrasound (e.g., a mechanical prosthetic valve preventing apical imaging of MR jet in the left atrium).

3. **Hemodynamic factors**

a. **Flow volume.** Increasing regurgitant volume results in an increased area of color flow disturbance, and this is the basis for the common practice of judging the severity of valvular regurgitation by the size of the color jet. However, as outlined in this chapter, many factors affect the size of the color flow jet area. Therefore, it is important to include other factors in the assessment of regurgitation, such as ventricular and atrial sizes, the morphologic appearance of the valve, the width of the color jet at its narrowest point (vena contracta), and, in particular, more quantitative analysis using the proximal flow convergence region (PISA). Several cardiac cycles should be inspected with minor adjustments in the angle of interrogation to ensure that the largest jet is visualized.

b. **Driving pressure.** Increased pressure gradient across a regurgitant orifice results in an increased color flow disturbance in the receiving chamber. Color jet size is closely related to jet momentum, given by flow rate multiplied by jet velocity.

c. **Chamber constraint in eccentric jets.** Impingement of a regurgitant jet against walls of the receiving chamber will decrease the size of the color disturbance. For example, severe but eccentric MR may have a very small area of color flow disturbance because the jet loses momentum to the constraining left atrial wall and appears narrower in a 2D view as it is splayed out over a larger surface area of the wall.

4. **Doppler artifact.** Mirror image artifact can be seen occasionally when the Doppler signal is duplicated on the other side of the baseline.

ACKNOWLEDGMENTS: *The author thanks Drs. Patrick J. Nash, Steven Lin, Guy Armstrong, and Ron Jacob for their contributions to earlier editions of this chapter.*

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CHAPTER 68

Lee Fong Ling
Maran Thamilarasan

Transesophageal Echocardiography

I. INDICATIONS. In general, transesophageal echocardiography (TEE) is performed when there is a clinical question for which the information obtained using transthoracic echocardiography (TTE) is insufficient. This may be to better define pathology that has been identified by TTE or to obtain better images when transthoracic images are inadequate. The close proximity of the esophagus to the heart allows for improved visualization of many cardiac structures, particularly those that are posteriorly located. In addition, higher frequency probes can be used, given the shorter distance between the probe and the heart, further enhancing the resolution. However, imaging planes are somewhat constrained by the relative position of the esophagus and heart, and some structures (e.g., prosthetic aortic valve) and certain Doppler measurements may be better assessed by TTE.

Indications for TEE in various conditions and clinical situations are listed in Table 68.1. Very common indications include examination to rule out a cardiac source of embolus, assessment of valves, prosthesis, and intracardiac device for endocarditis or its accompanying complications, such as abscess. The assessment of native and prosthetic valvular function, in terms of degree and mechanism of regurgitation or stenosis, is a frequent indication for TEE. Acoustic shadowing by prosthetic valves, particularly in the mitral position, poses less of a problem for TEE than it does for TTE. Given the increasing prevalence of atrial fibrillation, another frequent indication for TEE is to assess left atrial and left atrial appendage pathology and function, particularly prior to cardioversion. Congenital cardiovascular abnormalities, intracardiac shunts, as well as intracardiac tumors and masses can also be well delineated by TEE. Because of its ability to assess the ascending aorta, arch, and descending aorta, TEE also has an important role in the diagnosis of aortic dissection, aneurysms, and atheroma. In extremely technically difficult/limited transthoracic study such as in postoperative and mechanically ventilated patients, TEE may be used for usual TTE indications such as the assessment of left ventricular function.

TEE is a useful imaging modality in both the operating room and the cardiac catheterization laboratory. In cardiothoracic surgery, TEE is used to assess the mechanism of valvular abnormalities and subsequently evaluate the efficacy of valve repair or replacement. TEE can be used to guide the location of the aortic cross-clamp so that segments with severe atheromatous involvement can be avoided, thereby reducing the risk of embolization. In addition, TEE can provide an assessment of left ventricular function and regional wall motion. As newer transcatheter approaches have become common, including percutaneous valve procedures, closure of paraprosthetic leaks, atrial septal defects, ventricular septal defects, and patent foramen ovale as well as electrophysiological procedures, TEE has been increasingly utilized to help guide catheter position and placement of percutaneous valve or occluding device and evaluate the success and complications of the procedure.

II. CONTRAINDICATIONS

A. There are few **absolute** contraindications to the performance of TEE (Table 68.2). These include the **presence of pharyngeal or esophageal obstruction, active upper gastrointestinal bleeding, recent esophageal or gastric surgery, and suspected or**

TABLE 68.1 Indications for Transesophageal Echocardiography in Various Conditions and Clinical Situations

Condition	Indication
Infective endocarditis	Patients with at least moderate pretest probability such as *Staphylococcus* bacteremia, fungemia, prosthetic valves, or intracardiac device
	Detection of complications of endocarditis: abscesses and fistula
Cardioembolic source	Identification of left atrial and left atrial appendage thrombus or spontaneous echo contrast
	Identification of patent foramen ovale, atrial septal defect, or atrial septal aneurysm
	Identification of aortic atheroma
	Evaluation of mitral and aortic valve for vegetation, tumors, and valve strand
Valvular heart disease	Evaluation of mechanism and severity of mitral regurgitation
	Characterization of valvular pathology such as aortic morphology
Prosthetic valves	Evaluation of suspected prosthetic dysfunction (stenosis, thrombosis, or regurgitation)
Atrial fibrillation/flutter	Assessment of left atrial and left atrial appendage thrombus prior to cardioversion (e.g., if atrial fibrillation > 48 h) or ablation
	Follow-up for resolution of thrombus after anticoagulation prior to cardioversion or ablation
Aortic disease	Evaluation for suspected acute aortic pathology: dissection, aortic trauma, and intramural hematoma
	Characterization of aortic aneurysm and atheroma
Interventional procedures	Guiding performance of interventional cardiac procedures (e.g., percutaneous valve procedure, balloon valvuloplasty, closure of paraprosthetic leak, ASD, VSD, or PFO)
Intraoperative	Assessment of valve repair/replacement and evaluation of systolic function
Intracardiac masses	Detection of characterized masses such as tumors and thrombus
Critical care	Assessment of suspected papillary muscle rupture
	Assessment of mechanical complications of acute myocardial infarction or mural thrombus
	Evaluation of unexplained hypotension, especially in the ICU
	Assessment of early postoperative bleeding, which may result in localized accumulation of blood clots (especially posteriorly)
Congenital heart disease	Identification of site of origin and initial course of coronary arteries
	Detection of intracardiac shunts

ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; ICU, intensive care unit.

TABLE 68.2 Transesophageal Echocardiography Contraindications

Absolute
Esophageal or pharyngeal obstruction
Suspected or known perforated viscus
Gastrointestinal bleeding that has not been evaluated
Instability of cervical vertebrae
Relative
Esophageal varices or diverticula
Cervical arthritis
Oropharyngeal distortion
Bleeding diathesis or overanticoagulation
Uncooperative patient

known perforated viscus. If there is instability of the cervical vertebrae, then the examination cannot be performed.

B. **Relative** contraindications include the **presence of esophageal varices** and **suspected esophageal diverticulum**. In these cases, it is prudent to obtain gastrointestinal evaluation before proceeding, if the study must be performed. Severe cervical arthritis, in which patients may have difficulty with neck flexion, may make it difficult to pass the probe. Oropharyngeal pathology, anatomic distortion, or extreme muscle weakness can likewise make it difficult to proceed with the examination.

C. **Severe cardiopulmonary disease** is not a contraindication to evaluation by TEE (on the contrary, TEE can often provide critical information when used in these patients), but the operator must be particularly careful to minimize any stress on the patient. This is particularly true in **suspected aortic dissection**, where any sudden increase in blood pressure caused by patient discomfort could result in extension of the dissection. In cases where there is **respiratory instability**, endotracheal intubation with assisted ventilation should be considered prior to the procedure. Patients who are **hypotensive** may not be able to receive sedative agents, as these agents could lead to further hemodynamic compromise. In such patients, the examination may have to be performed with topical anesthesia alone. This is obviously much more difficult for the patient, and TEE should be done only if critical information is not obtainable by other methods.

D. Given the invasive nature of the procedure, prudence must be observed in patients who are prone to **bleeding**. The procedure is commonly performed on patients who are anticoagulated, such as in those with atrial arrhythmias prior to cardioversion. However, there is increased risk in those who are overanticoagulated. Although no set guidelines exist, it would seem advisable to **delay the examination if possible in patients with an international normalized ratio > 5 or a partial thromboplastin time > 100 seconds. Thrombocytopenia** may also increase the risk, particularly with platelet counts **< 50,000/mm^3**. TEE can still be performed if needed, as the absolute risk remains low, but meticulous attention must be given to nontraumatic esophageal intubation.

E. **Esophageal infections**, such as those that occur in the context of human immunodeficiency virus (HIV), do not necessarily represent contraindications to the procedure. **Patient discomfort** caused by the presence of the probe in the esophagus may preclude the examination. Universal precautions should be followed (as they should for any patient). The standard disinfectants used to clean the probe will inactivate HIV.

F. A patient who is very uncooperative is at significant risk for complications from the procedure. In such a case, consideration should be given to aborting the TEE or to increase the level of sedation and prophylactic endotracheal intubation if required.

III. PERSONNEL. The American Society of Echocardiography has proposed the following guidelines for operators who wish to perform TEE: as background, attainment of at least level 2 experience in transthoracic echocardiogram; a minimum of 25 esophageal intubations under guidance; and a minimum of 50 supervised TEE examinations during training. Furthermore, operators should perform a minimum of 25 to 50 TEE examinations yearly to maintain competency.

The presence of a skilled assistant is invaluable during the procedure. The assistant should be either a sonographer or a registered nurse. The role of the assistant is to monitor vital signs during the procedure, ensure proper suctioning of oropharyngeal secretions, and administer medications.

IV. EQUIPMENT. Necessary equipment is listed in Table 68.3.

V. THE TRANSESOPHAGEAL PROBE. The probe is a modification of the standard gastroscope, with transducers in place of fiber optics. The conventional rotary controls with inner and outer dials are present. The inner dial typically guides anteflexion and retroflexion, whereas the outer dial controls medial and lateral movement of the tip. A locking mechanism is present, which must not be in effect when the probe is advanced or withdrawn, as esophageal trauma may result. The multiplane probe also has a lever control to guide rotation. Biplane probes are no longer in common use, as they require switching between the transverse and longitudinal planes by a control switch on the echo machine. Advancement and withdrawal of the probe, rotation of the probe about its long axis, and the manipulations available using the above rotary controls constitute the means by which specific images can be obtained (Fig. 68.1).

TABLE 68.3 Equipment for Transesophageal Echocardiograph

1. Echo machine and probe (calibrate prior to intubation)
2. Sphygmomanometer
3. ECG rhythm monitor
4. Pulse oximeter
5. Supplemental oxygen
6. Wall suction with Yankauer
7. Intravenous lines and tubing
8. Topical anesthetic agents
9. Sedative medications
10. Bite block
11. Gloves and goggles
12. Emergency equipment
    - **a.** Drugs (e.g., atropine, epinephrine, naloxone, flumazenil, and lidocaine)
    - **b.** Defibrillator
    - **c.** Intubation supplies

ECG, electrocardiogram.

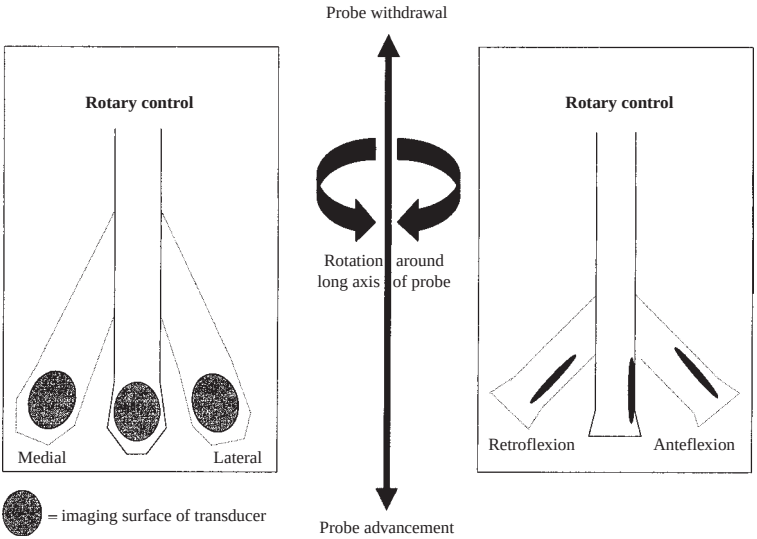

FIGURE 68.1 Specific images can be obtained by advancement and withdrawal of the probe, by rotation of the probe about its long axis, and by the manipulations that are possible using rotary controls.

VI. PATIENT PREPARATION (Table 68.4). The patient should have had nothing by mouth (NPO) for at least 4 to 6 hours before the procedure. Water is allowed up to 2 hours before the test. The clinician can rule out possible contraindications by asking for a history of odynophagia or dysphagia. It is important to be aware of any history of radiation therapy to the mediastinum or cervical region that may have resulted in stricture formation.

The extent of previous workup for any history of gastrointestinal bleeding must be reviewed. The clinician should review recent laboratory studies, paying particular attention to platelet count, hemoglobin level, and coagulation profile. Appropriate inquiries should be made with regard to allergies and former tolerance of sedative medications. The clinician should ensure that the patient understands the procedure, including risks and benefits, and that proper informed consent is obtained and documented before proceeding.

TABLE 68.4 Preparation for Transesophageal Echocardiography

Patient must have had nothing by mouth (NPO) for at least 4 h prior to the procedure
Assess for possible contraindications:
History of odynophagia or dysphagia
History of mediastinal or cervical radiation that might have resulted in stricture formation
History of and workup for gastrointestinal bleeding
Allergies to and previous tolerance of sedative medications
Patient understanding of procedure and indications
Informed consent of patient

VII. STEP-BY-STEP GUIDE TO THE EXAMINATION

A. The patient's **dentures** should be removed.

B. **An intravenous (IV) line** should be inserted to allow for administration of medications and saline contrast for study.

C. The American Heart Association does not recommend **antibiotic prophylaxis** for patients undergoing endoscopic procedures. The reported incidence of transient bacteremia with endoscopy is no higher than the contamination rates reported with blood cultures.

D. A **blood pressure cuff** should be placed on the patient's arm.

E. **Electrocardiographic leads** should be applied and connected to the telemetry monitor.

F. A **pulse oximeter** should be applied to the patient's finger or ear.

G. A **nasal cannula** should be used so that supplemental oxygen can be given as needed.

H. While sitting up, the patient should be asked to gargle **viscous 2% lidocaine** for 1 minute and then swallow it for topical anesthesia. **Lidocaine (xylocaine) spray (4%) or Cetacaine spray (10%)** is then sprayed on to the posterior tongue and upper pharynx. These procedures normally suppress the **gag reflex**, but if necessary, this can be verified using a tongue depressor or gloved finger; additional **topical anesthesia** is then applied until the reflex is dulled. By visualizing the area being sprayed, inadvertent spraying of the vocal cord and resultant laryngospasm can be avoided. Methemoglobinemia has been reported with the use of benzocaine-containing product (e.g., Cetacaine), which is usually manifested as central cyanosis and desaturation and can be treated with supplemental oxygen and methylene blue. Some operators advocate the use of drying agents to minimize oropharyngeal secretions (e.g., glycopyrrolate). We generally have not found a need for use of such agents, which can cause an increase in heart rate.

I. Have the patient lie down on the left side (left lateral decubitus position), facing the echo machine (alternatively, the patient can lie on the right side, with the machine on the right), with neck flexed. TEE can be performed with the patient sitting, but is easier in the lateral position.

J. **Midazolam**, a benzodiazepine, is the preferred agent for sedation, having the benefit of a short half-life. It also produces an antegrade amnesic effect and has anxiolytic properties. Typically, administer IV doses of 0.5 to 1 mg every 3 to 5 minutes until adequate sedation is achieved. The goal is to reduce anxiety without compromising respiratory drive and while maintaining the patient's ability to follow simple commands, such as swallowing when necessary. Check pulse oximetry and blood pressure before each dose. **Fentanyl**, a short-acting opioid analgesic, can be used for sedation (typically 25 μg IV per dose) in conjunction with midazolam and may be better tolerated in patients with poor left ventricular function or renal impairment. An alternative sedative is **meperidine**, which is typically given in 12.5 to 25 mg IV doses. Meperidine possesses an analgesic effect and helps to suppress the gag reflex as well. Again, **check vital signs before and after each dose**. Additional doses of these sedatives and anxiolytics may be administered during the procedure if necessary. Sedation can lead to potential respiratory suppression; therefore, a benzodiazepine antagonist (e.g., flumazenil 0.2 to 0.6 mg IV) and an opiate antagonist (e.g., naloxone, increments of 0.1 to 0.2 mg IV doses) should be available if required.

K. With adequate sedation and topical anesthesia (diminution of gag reflex), **begin probe insertion**. There are two approaches that are generally used.

1. The first is the **digital technique**, which is especially useful with the larger multiplane probe. With this method, the bite guard is inserted onto the shaft of the probe such that after esophageal intubation the bite guard can be moved into place. The distal end of the probe is lubricated. The imaging surface of the transducer is placed toward the tongue. The tip of the transducer is placed under the index finger, and it is slowly guided downward and posterior to the hypopharynx. At this point the patient is asked to swallow, and gentle pressure is applied with the other hand to guide the probe down. Swallowing results in relaxation of the upper

esophageal sphincter. If resistance is met, stop, let the patient relax, and reattempt or redirect as needed. Using the finger as a guide will help center the probe in the region of the hypopharynx over the esophagus and avoid the lateral recesses.

2. An **alternative method is to use the rotary controls on the TEE probe** to guide the intubation. The bite guard is inserted first. The probe is inserted through the bite guard, and gentle anteflexion is applied as the probe is passed over the back of the tongue. The probe is then returned to the neutral position, or with slight retroflexion, as it is passed down into the esophagus. The patient is asked to swallow as the probe is advanced past the upper esophageal sphincter. The operator is still able to guide the probe if needed by insertion of a finger around the side of the bite guard.

   Patients often gag as the probe enters the upper esophagus (even with adequate anesthesia); however, patients generally find it more comfortable once the probe has passed beyond this point (usually at 25 cm, past the level of the carina). The probe should be advanced to approximately 30 to 40 cm (midesophageal level).

   In intubated patients, it is important to **secure the endotracheal tube firmly to one side of the mouth** to prevent dislodgment and inadvertent extubation. Direct visualization with a laryngoscope may be needed. **Sedation** is equally important in these patients, and given the tendency for partially sedated patients to bite on their tubes, a **paralyzing agent** is often required. Intubation in the supine position is not a problem because the airway is protected. Other catheters in the esophagus, such as feeding tubes or nasogastric tubes, often have to be removed prior to the procedure; they may become interposed between the esophagus and the TEE probe, interfering with the images. If left in, these tubes may become dislodged by the TEE probe, and tube position should be reconfirmed after the echocardiographic examination.

   For patients with tracheostomies, some operators will carefully and gently deflate the cuff to facilitate probe insertion.

VIII. IMAGING. TEE technology has undergone much evolution, from the initial monoplane views to the current multiplane views. Monoplane TEE provides for images in the horizontal plane only, perpendicular to the shaft of the endoscope. Longitudinal relationships among cardiac structures are difficult to appreciate. With biplane TEE, the orthogonal longitudinal plane can also be obtained. Both monoplane and biplane systems required additional manipulation to obtain off-axis views, making the examination more difficult and more uncomfortable for the patient. With **multiplane TEE**, the transducer has a single array of crystals that can be rotated 180° around the long axis, producing a continuum of transverse and longitudinal images from a single probe position. This minimizes the probe manipulation necessary to obtain intermediate and off-axis images. Consequently, multiplane TEE has increased sensitivity for the detection of sometimes subtle abnormalities, including vegetations, periprosthetic leaks, left atrial appendage thrombi, and aortic dissection. The development of **real-time three-dimensional (3D) TEE** (see Section **VIII.C**) offers the possibility of assessing cardiac structures volumetrically. It has emerged as a clinically relevant modality by providing relatively high image quality, which may enhance clinical decision making especially in regard to structures with a complex anatomy such as the mitral valve. However, this technology is still evolving, particularly with regard to its value in routine clinical practice.

A. Basic views. The TEE examination tends to be more goal directed than the transthoracic examination, as there may be time constraints imposed by how long the patient can tolerate the esophageal probe. Initial views should focus on the question at hand, but it is still important to perform a comprehensive and thorough examination. Most operators prefer to begin with upper esophageal views before proceeding to transgastric views. The order of views obtained is not important, provided the operator develops a consistent and comprehensive approach.

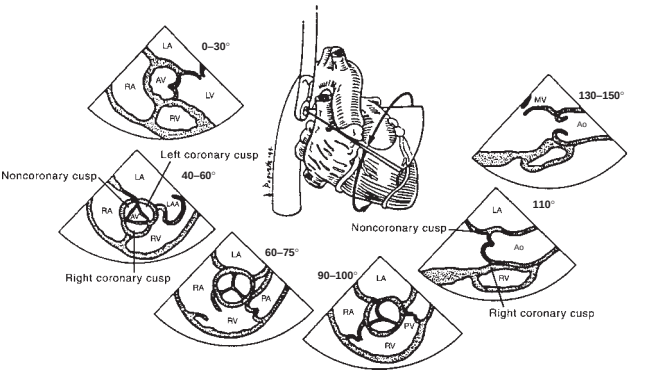

FIGURE 68.2 Schematic representation of selected multiplane transesophageal echocardiography views of the aorta and aortic valve from the upper esophagus. Ao, aorta; AV, atrioventricular; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PV, pulmonary valve; LAA, left atrial appendage; MV, mitral valve. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

The probe may inadvertently rotate during insertion and may require initial manipulation before starting the examination. The left atrium should be seen at the center of the screen. If the aorta is seen (which is posterior to the esophagus), then the probe must be rotated anteriorly. Slight retroflexion of the probe may be necessary to maintain adequate contact between the probe and the esophagus. Air in the esophagus, which is interposed between the probe and the heart, may affect image quality. This generally lessens as the examination progresses (from ongoing peristaltic activity in the esophagus). Similarly, the presence of a hiatal hernia may compromise image quality.

Views obtained from multiplane TEE are described first. These views are described in terms of degrees of rotation required to obtain particular images. At each transducer location, start array at 0° and rotate to 180° at 5° to 15° increments to obtain a complete sweep. The standard horizontal plane is designated as 0°. At approximately 45°, short-axis views are obtained. Ninety degrees is defined as the longitudinal plane, whereas at around 135°, the true long-axis cardiac views are obtained. At 180°, a mirror image view of the standard horizontal plane is obtained. Given the variable anatomic relationships between structures, the degree of probe manipulation required to obtain the standard views will vary from patient to patient.

1. **Upper esophagus (30 cm)—base of the heart** (Fig. 68.2). With the array at 0°, a five-chamber cross-sectional view of the left atrium, left ventricle, right atrium, right ventricle, and aortic valve is obtained. At 40° to 60°, the three leaflets of the aortic valve become visible (right coronary cusp at the bottom of the screen, noncoronary cusp on the top and to the left, and left coronary cusp on the right). Planimetry of the aortic valve orifice is often possible in this view. Subtle in-and-out movements allow for visualization of the proximal coronaries. The left atrial appendage is also seen in this view (zooming in on the atrial appendage, with subsequent rotation of the array, facilitates inspection for thrombus). At 60° to 100°, the tricuspid valve and right ventricular outflow tract/pulmonic valve become visible. At 120°, long-axis images of the left ventricular outflow tract, aortic valve (noncoronary and right coronary cusps), and proximal ascending aorta are seen. Slight withdrawal of the probe at 110° to 120° permits visualization of the ascending aorta. With the probe withdrawn further into the upper esophagus (Fig. 68.3), the pulmonary artery and its bifurcation can be visualized (from 0° to 45°).

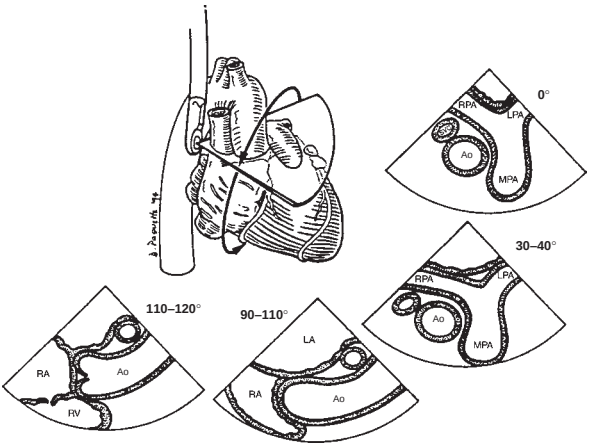

FIGURE 68.3 Schematic of some of the multiplane transesophageal echocardiography views of the aorta and pulmonary artery that can be obtained from the upper esophagus. Ao, aorta; LA, left atrium; LPA, left pulmonary artery; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

2. **Lower and middle esophagus** (Fig. 68.4A and B). With the array at 0°, a four-chamber view is obtained (some retroflexion of the probe is needed for a true four-chamber view, as with anteflexion one will see portions of the left ventricular outflow tract and aortic valve). This view is similar to an inverted transthoracic apical four-chamber view. With the left atrium and left ventricle kept in the center of the view field, rotation of the array allows for a thorough evaluation of the left-sided structures. Doppler interrogation of mitral inflow is generally performed with the array at 0° to 30°. Skillful maneuvers as the array is rotated to 90° allow for interrogation of both leaflets of the mitral valve, including the specific scallops of the leaflet. Rotation of the array to 90° to 110° reveals the two-chamber view (left atrium/left ventricle), with the anterior and inferior walls of the left ventricle visualized. The left atrial appendage and the left upper pulmonary vein are also seen. Long-axis views of the left ventricular outflow tract, aortic valve (right and noncoronary cusps), and proximal ascending aorta are obtained by rotation to 120° to 140°. The anterior mitral leaflet is particularly well visualized in these views. This complete sweep permits full delineation of the extent of mitral regurgitation.

   Similar views of right-sided structures and the interatrial septum can also be obtained from this position. At 0° (in the four-chamber view as described previously), the septal and anterior leaflets of the tricuspid valve can be seen. The endoscope is then rotated to bring the interatrial septum and the right atrium to the center of view (some withdrawal or advancement of the probe may be necessary to optimize visualization of the interatrial septum). By rotation of the multiplane array, the interatrial septum and fossa ovalis can be thoroughly examined for evidence of a patent foramen ovale or atrial septal defect. Agitated saline contrast can be given intravenously at this time to expose evidence of shunting; asking the patient to perform Valsalva maneuver or to cough can help identify right-to-left shunting. At approximately 100°, the superior vena cava and inferior vena cava can be seen entering the right atrium, and the right atrial appendage

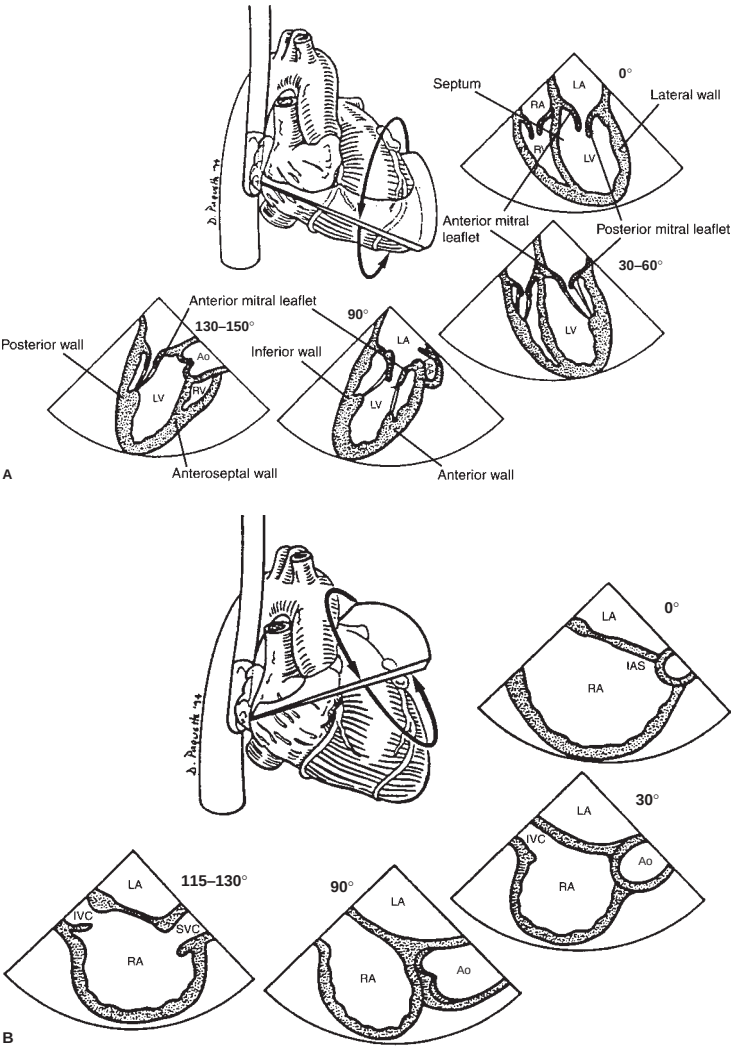

FIGURE 68.4 **A:** Schematic diagram showing some representative sections of the left heart that can be obtained with multiplane transesophageal echocardiography from the lower and middle esophagus. AA, left atrial appendage; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. **B:** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the atria and interatrial septum that can be obtained from the lower middle esophagus. Ao, aorta; IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava; IAS, interatrial septum. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

can also be seen. This is a good view to identify anomalous pulmonary venous drainage into the right atrium or superior vena cava or a sinus venosus atrial septal defect. Further rotation will allow for assessment of the right pulmonary veins.

3. **Transgastric views**
   a. **Proximal** (Fig. 68.5A). These are images obtained from the fundus of the stomach. A cross-sectional view of the left and right ventricles is obtained

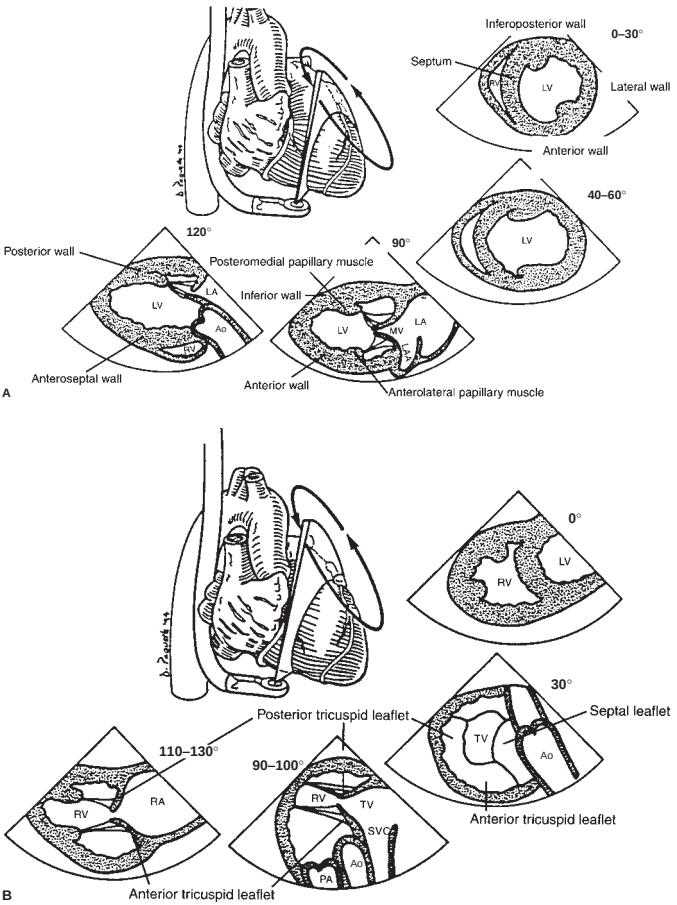

FIGURE 68.5 **A:** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the left heart from the proximal transgastric location. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; SVC, superior vena cava; LAA, left atrial appendage; MV, mitral valve. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. **B:** Schematic of images from a transgastric, multiplane sweep through the right ventricle. LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve; SVC, superior vena cava; PA, pulmonary artery; Ao, aorta. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

at 0°. By rotating the shaft of the endoscope to center with the left ventricle in the field of view, serial short-axis ("doughnut") views of the left ventricle can be obtained. Anteflexion of the probe will give rise to basal views, with the mitral and tricuspid valves seen in cross section. With the transducer in a more neutral position, middle and apical short-axis views will be obtained.

At 80° to 100°, a two-chamber view of the left atrium (with appendage) and left ventricle (anterior and inferior walls of the left ventricle, mitral leaflets, and papillary muscles) will be obtained. At ≥ 120°, a long-axis outflow tract view with aortic valve and ascending aorta will be visualized. The anteroseptal and posterior walls of the left ventricle are seen. Depending on the alignment with the transducer, this view may be useful in obtaining velocities across the aortic valve.

Bringing the array back to 0° and rotating the shaft of the endoscope to center the right ventricle in view will allow for interrogation of the right-sided structures (Fig. 68.5B). At 30° to 60°, the three leaflets of the tricuspid valve are visualized (anterior leaflet at the bottom, posterior leaflet on the top, and septal leaflet to the right). At around 70° to 80°, the right ventricular inflow tract view (superior vena cava and tricuspid valve with anterior and posterior leaflets) is obtained. At 90° to 100°, the right ventricular outflow tract and pulmonary valve become visible as well. At 110° to 130°, the two-chamber view of the right ventricle and right atrium can be seen. By rotating to 130° to 150°, the papillary muscles and chordae supporting the tricuspid valve are further delineated.

b. Deep transgastric. The probe is advanced further into the stomach with the tip anteflexed. At 0°, a foreshortened five-chamber view is obtained. This view allows for Doppler interrogation of the aortic valve and left ventricular outflow tract. By rotating the multiplane array, different segments of the left ventricle apex can be visualized in the search for thrombus or aneurysm.

4. Aorta. Counterclockwise rotation of the endoscope brings the aorta into view. Typically, the probe is advanced beyond the diaphragm and then slowly pulled back, following the aorta back to the arch. Rotation of the probe is required to keep the aorta in view in the center of the screen. At the level of the diaphragm, the aorta is posterior to the esophagus. In the midesophagus, the aorta is medial, whereas the ascending aorta and arch lie anterior to the esophagus. At 0°, the aorta is seen as a circular structure. Long-axis images (at 100° to 130°) provide additional information as needed at selected intervals. At the arch, the aorta is curved in front of the esophagus, presenting a sausage-shaped structure with the probe at 0°. Gentle clockwise rotation will follow the arch back to the ascending aorta. The ascending aorta is visualized in the longitudinal planes as discussed with the other views. Multiplane TEE has reduced the so-called blind spot of the ascending aorta (where the trachea is interposed between the esophagus and aorta, an area that poses a problem during horizontal plane imaging).

B. Biplane probe. There are times during which a biplane probe may be used. This is a smaller probe, so it may be beneficial to use in certain cases when there might be difficulty in esophageal intubation with the multiplane probe. By manipulating the probe via rotation about the long axis and using rotary controls, intermediate and off-axis images in addition to the standard transverse and longitudinal views described earlier can be obtained. Through hands-on experience, the operator will come to be familiar with these maneuvers.

C. Three-dimensional probe. The current 3D TEE probes use fully sampled matrix array transducers, allowing a pyramidal volume of data to be acquired. Besides standard two-dimensional imaging modalities, this transducer is able to perform

3D imaging in several modes: live X-plane imaging, live 3D echo, live 3D zoom, triggered full volume, and triggered 3D color. Real-time X-plane imaging allows simultaneous biplane imaging from the same heart beat. Live 3D mode displays real-time 3D images with a small pyramidal segment; 3D zoom mode displays the region of interest with a larger pyramidal segment in real time. Full volume mode acquires wider segment over several cardiac cycles, and color Doppler can also be added in this mode. Three-dimensional TEE is useful for the evaluation of native valves (in particular mitral valve and aortic valve), prosthetic valves, interatrial septum, and left atrial appendage and for the guidance of percutaneous interventional procedures (in particular mitral valve repair, aortic valve implantation, closure of atrial septal defect, and paraprosthetic leaks).

IX. PATIENT RECOVERY. The patient's NPO status should be maintained until the gag reflex has returned. The patient should be instructed to avoid oral intake for at least 1 to 2 hours after the test. When the patient commences oral intake, he or she should initially take a small sip of cold water. If the water does not feel cold in the back of the throat, then some topical anesthetic effect is still present. The patient should wait for another half hour and test the throat again. Until this has dissipated, the patient should avoid any hot drinks so as to avoid scalding. Appropriate precautions should be followed if sedatives were used, as the effects persist for several hours. Patients may have dizziness and orthostatic symptoms for up to several hours and should be instructed to sit or lie down if this occurs. Patients should not drive or operate heavy equipment until the next day.

X. PROBE CARE. Following use, the probe should be cleaned with soap, water, and an enzymatic solution to remove saliva. The nonimmersible parts of the probe, such as the handle and rotary controls, should be cleaned with alcohol. Afterward, the probe should be soaked in a glutaraldehyde solution for a minimum of 20 minutes and a maximum of several hours to eliminate bacteria. The probe should not be soaked in this solution overnight. It can then be rinsed with water and air-dried. The probe should be inspected closely for any tears or perforations.

XI. COMPLICATIONS. In reported series, the incidence of major and minor complications is 2% to 3%, with most being minor complications. Major complications (death, esophageal perforation, significant arrhythmias, congestive heart failure, and aspiration) occur with a frequency of 0.3%, with a reported mortality of < 0.01%. Reported minor complications include transient hypotension, hypertension (particularly with agitation), transient hypoxia, transient bronchospasm, and arrhythmias (such as supraventricular tachycardia, nonsustained ventricular tachycardia, and transient atrioventricular block). Methemoglobinemia has been rarely reported due to the anesthetic spray and should be considered if cyanosis occurs. Other complications of intubation include tracheal intubation, laryngospasm, and vocal cord paralysis. Sore throat is not uncommon after the procedure and may persist for a day. Anaphylaxis and other allergic reactions can occur due to the medications used.

XII. PITFALLS. The improved resolution and anatomic detail provided by TEE, as compared with TTE, is what makes it such a powerful diagnostic tool. However, this can also lead to misinterpretation of normal structures. Trabeculations in the atrial appendage can be mistaken for thrombi, and lipomatous hypertrophy of the interatrial septum can be incorrectly labeled as a mass, as can the eustachian valve. The transverse and oblique sinuses can be mistaken for abscess cavities. Off-axis images may create the appearance of a mass on the aortic valve when one of the cusps is cut obliquely. The lungs can give rise to reverberation artifacts, which can erroneously be diagnosed as dissection flaps (presence in nonanatomic planes, lack of disruption of color Doppler of blood flow, and crossing of

normal anatomy all favor diagnosis of artifact). Abnormal findings should be visualized and verified in several views to ensure that they do not represent imaging artifacts.

These pitfalls are best minimized by the experience of the operator, but variations in anatomy may provide diagnostic dilemmas for even the most skilled echocardiographer.

ACKNOWLDGMENTS: *The authors wish to thank Deepu Nair, MD, for his contributions to a previous edition of this chapter.*

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RELEVANT BOOK CHAPTERS

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CHAPTER 69

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Pericardiocentesis

I. INTRODUCTION. Pericardiocentesis is an important therapeutic and diagnostic procedure in cardiology. Most often, it is used to relieve tamponade and identify causes of pericardial effusions. When performed correctly by experienced operators, pericardiocentesis has proven to be both an effective and safe procedure.

II. INDICATIONS

A. Alleviation of cardiac tamponade. Cardiac tamponade is a clinical diagnosis classically characterized by hypotension, tachycardia, distended neck veins, pulsus paradoxus, and distant heart sounds. Echocardiographic data provide confirmatory evidence for this diagnosis and include effusion (regional or circumferential), inferior vena cava plethora, diastolic collapse of the right atrium and right ventricle, and increased respiratory variation of blood flow through the tricuspid and mitral valves. The normal pericardial cavity typically contains 15 to 50 mL of fluid. **The additional volume of fluid required to cause hemodynamic compromise is variable** and is dependent upon several factors, including the patient's volume status, the rapidity of fluid accumulation, and intrathoracic pressure (positive end-expiratory pressure increases intrathoracic pressure, impairing right heart filling and exacerbating tamponade physiology). Therefore, a relatively small but rapidly accumulating effusion can cause tamponade, particularly in the intravascularly depleted patient.

B. Evaluation of and therapy for pericardial effusion

1. **After open heart surgery.** Effusions after open heart surgery are common; rarely, they may be of hemodynamic significance. Data from the Mayo Clinic suggest that the incidence of significant effusion in patients 18 years of age or older up to 30 days after cardiac surgery with cardiopulmonary bypass is 1.5%. The risk of effusion is highest in patients undergoing heart transplant and lowest in patients undergoing coronary artery bypass grafting. Renal failure, immunosuppression, pulmonary thromboembolism, prolonged cardiopulmonary bypass, and high body surface area were all independent risk factors for significant effusion. The contribution of anticoagulation to effusion formation is less established, but it is likely a risk factor as well. It should be noted that approximately **50% of patients who were discharged with a small clinically insignificant pericardial effusion, especially those status post valve surgery, required readmission** approximately 2 weeks after surgery for treatment of tamponade.
2. **Idiopathic.** In patients presenting with large, idiopathic effusions, evaluation of pericardial fluid—including cytologic examination, culture, cell counts, and chemistries—frequently assists in diagnosis. In fact, data suggest that the causes of most effusions can be diagnosed with history, physical examination, laboratory evaluation, and pericardial fluid analysis. Fluid analysis has been shown to be more helpful than pericardial tissue biopsy for culture of viral and bacterial

pathogens, and cytology is positive in 65% to 85% of cases of malignant effusion. Some experts recommend that large pericardial effusions (> 20 mm) be drained if the effusion persists for more than 1 to 3 months. **Up to one-third of patients with large idiopathic pericardial effusions develop cardiac tamponade unexpectedly**.

3. **Malignant.** Malignant pericardial effusions are a rare manifestation of metastatic disease. Fluid cytology is usually positive and can be of value if the primary tumor is unknown. Lung, breast, and hematologic cancers are the most common etiologic factors. Controversy exists regarding the most appropriate management of malignant effusions. There are no prospective, definitive studies comparing surgical management and pericardiocentesis. Frequently, surgical approaches are used because of concerns about reaccumulation. Large malignant effusions treated with simple pericardiocentesis without prolonged catheter drainage reaccumulate in as many as 60% of cases. However, several studies have indicated that when a pericardial drain is left in place for several days until drainage is < 25 mL/d (average 4.8 days), the risk of reaccumulation is low—approximately 12%. Sclerotherapy has a similar failure rate, and the 30-day mortality risk of a pericardial window is approximately 8%. Therefore, pericardiocentesis with drain placement is a very reasonable initial procedure for the diagnosis and management of malignant effusions.

III. CONTRAINDICATIONS

A. Absolute. In emergent scenarios of cardiac tamponade, when circulatory collapse is imminent, there are no absolute contraindications. In these instances, pericardiocentesis is often a lifesaving intervention.

B. Relative

1. **Anticoagulation.** The risk of bleeding is low with pericardiocentesis; however, if time permits, prothrombin time and partial thromboplastin time (PTT) should be obtained in all patients undergoing pericardiocentesis. An international normalized ratio > 1.8 or PTT greater than twice the normal should be allowed to normalize or be managed with fresh frozen plasma before intervention. It should also be noted that **tamponade physiology, by leading to hepatic congestion, may produce or exacerbate coagulation abnormalities**.
2. **Thrombocytopenia.** Platelet counts should be > 50,000.
3. **Traumatic hemopericardium.** A patient with traumatic hemopericardium should be treated surgically.
4. **Type A aortic dissection.** Typically, hemorrhagic effusions secondary to type A dissections are treated emergently with surgery. However, in situations where tamponade and circulatory collapse are imminent, small volume (10 to 25 mL) pericardiocentesis is indicated to stabilize patients before surgery. Data suggest that larger volume taps may be detrimental. In general, however, effusions in the setting of a type A dissection should be treated with emergent surgery.
5. **Subacute free wall rupture.** As with dissections, free wall ruptures are best addressed surgically, but small volume taps may be necessary to stabilize patients in preparation for operative repair.
6. **Small, loculated, or posteriorly located effusions** are technically more difficult to tap and have increased risk of complication. Echocardiographic guidance is paramount if pericardiocentesis is attempted.
7. **Purulent effusions.** While suspected purulent or tuberculous effusions are considered an indication for pericardiocentesis, grossly infected pericardial fluid should be managed surgically.
8. **Malignant effusion.** As stated previously, management of malignant effusions is controversial. Although pericardiocentesis is an effective and proven first-line therapy, recurrent effusions should be considered for pericardial window.

IV. PERICARDIOCENTESIS VERSUS SURGICAL MANAGEMENT (Table 69.1). The choice of procedure for pericardial drainage varies depending on the underlying etiology of the effusion, chronicity, size, hemodynamic impact, and suspected recurrence rate. Surgical techniques include complete pericardiectomy, partial pericardiectomy, subxiphoid pericardiotomy, anterior transthoracic window, and pleuropericardial window—collectively carrying an 80% to 90% success rate depending on the patient and indication. When comparing with pericardiocentesis for drainage of effusions, however, the first surgical option is typically pericardial window. Pericardiectomy is typically limited to permanent constriction.

There is a dearth of prospective data regarding the best approach to managing pericardial effusions. Most of the data are empirical and management is often clinician-, institution-, and patient-dependent. General recommendations for percutaneous versus surgical management of effusions are listed in Table 69.1.

V. PATIENT PREPARATION. Ideally, pericardiocentesis is performed in a laboratory equipped for fluoroscopy and invasive hemodynamic monitoring.

A. Informed consent. Patients should receive a clear explanation of the risks and benefits of pericardiocentesis, including the rationale for performing the procedure.

B. Monitoring. Patients should have heart rate, blood pressure, and oxygen saturations measured throughout the procedure. In addition, electrocardiographic monitoring is necessary. Worsening hemodynamics or falling oxygenation should alert the operator to the possibility of a procedural complication. Frequent ectopy (premature ventricular contractions, premature atrial contractions, or nonsustained ventricular tachycardia) may indicate impending perforation of a cardiac chamber. Some authorities recommend pulmonary artery catheter placement prior to performing a tap; however, for routine cases, this is not necessary.

C. Sedation. Pericardiocentesis is an anxiety-producing procedure for the patient. Appropriate pain relief and sedation should be administered prophylactically when this is clinically indicated and where it will not interfere with an already tenuous hemodynamic or respiratory state.

VI. TECHNIQUES

A. Echo guided. Currently, ultrasound-guided pericardiocentesis is the standard approach at most institutions. Patients are placed supine or in a slightly left lateral decubitus position. The head is elevated approximately 30°, and a complete echocardiographic evaluation is performed with standard parasternal, apical, and subcostal

TABLE 69.1 Approach to Pericardial Drainage

Pericardiocentesis	Surgical management
Most cases of cardiac tamponade	Cardiac tamponade due to aortic dissection or cardiac trauma; recurrent tamponade
Large or symptomatic effusions refractory to medical treatment	Recurrence of large chronic effusions after failed pericardiocentesis
High suspicion of tuberculous, purulent, or neoplastic pericarditis	Purulent effusion
	Loculated effusion
	Need for pericardial biopsy
	Coagulopathy

views. Attention is focused on the site where the greatest amount of pericardial fluid is closest to the skin surface. In addition, the liver should be identified to avoid accidental laceration during the procedure. Because it is air filled, lung tissue will block ultrasound waves and preclude imaging of the heart; consequently, the risk of pneumothorax is low if a good echocardiographic window is selected for the tap. While imaging, it is imperative to take note of the distance to the fluid pocket as well as ***the probe trajectory***. Failure to maintain an appropriate trajectory is a common cause of failure in accessing a pericardial effusion percutaneously. Obviously, the trajectory of the needle during the pericardiocentesis should be identical to the trajectory of the echocardiographic probe when imaging. The echo may be used in real time to help monitor the needle tip during insertion, especially with the assistance of a second operator, although real time is not always necessary in the case of large effusions.

1. **Prepping the patient.** Once the best window is selected, the probe's location is marked with a permanent marker and scrubbed with sterile chlorhexidine-alcohol or povidone-iodine solution. The entire torso is draped with sterile towels. The patient should not move between the echocardiographic examination and the procedure.
2. **Marking the needle.** Using a sterile pen, a mark can be made on the pericardiocentesis needle at the approximate distance between the skin and effusion that was noted on the echocardiogram. The needle used should be 5 to 8 cm in length, with a short bevel to lessen the risk of lacerating structures at the needle's tip. In some instances, particularly in obese patients, longer needles will be needed. It is imperative to know in these situations how far the needle should be inserted before pericardial fluid is expected.
3. **Anesthetic.** Local anesthetic (e.g., 1% lidocaine) is applied to the skin over the mark. Then deeper anesthetic is given over the superior aspect of the rib (if a chest wall approach is used).
4. **Entering the pericardium.** Using a three-way stopcock, an 18G Cook needle is attached to a syringe that contains a few more milliliters of local anesthetic. The needle is advanced through the anesthetized tract, over the rib, along the same trajectory as the echocardiographic probe, until fluid is aspirated. Alternatively, a sheathed catheter may be used instead of the Cook needle. Upon aspiration of fluid, the catheter is advanced over the needle, and the needle is withdrawn.
5. **Confirming catheter/needle placement.** While imaging from a remote location, agitated saline may be injected through the stopcock. **The appearance of bubbles in the pericardial space confirms an appropriate location**. Bubbles appearing within a cardiac chamber suggest that the heart has been perforated and that the needle or catheter should be withdrawn. If agitated saline cannot be visualized, one should consider an intrathoracic needle position. If effusions are large, the agitated saline may not be visible from all echocardiographic windows; occasionally, it may be necessary to reinject saline and image from an alternative location.
6. **Placing the pericardial catheter.** Once the intrapericardial position is confirmed, a floppy-tipped, 0.035" guidewire is inserted through the needle into the pericardial space. A blade scalpel is then used to nick the skin over the needle, the needle is withdrawn, and a 6F dilator is used to broaden the tract into the pericardium. Finally, the dilator is removed and a 6F to 8F pigtail angiocatheter with side holes is threaded over the wire well into the pericardial space. The wire is removed, and catheter placement can again be confirmed with agitated saline injection. With a three-way stopcock, the catheter is then attached to a 30-cm length of plastic tubing, which in turn may be connected to a vacuum bottle or drainage bag. The catheter should be sutured in place.
7. **Bloody pericardial fluid or frank blood?** Occasionally, very bloody fluid may be aspirated during pericardiocentesis, and confirmation of the needle placement may be difficult. Therefore, differentiating between blood (chamber perforation)

and bloody effusion can be challenging. A few milliliters of the aspirate can be placed on a gauze pad; classical teaching suggests that if the fluid coagulates, it is blood from chamber perforation. Conversely, fluid that spreads out on the gauze forming a pinkish halo suggests an intrapericardial origin. In reality, effusions caused by cardiac rupture, dissection, or ongoing bleeding into the pericardial space may clot upon aspiration; this fluid should be sent for hematocrit (to confirm that it is blood), and cardiothoracic surgery consultation should take place emergently.

B. Electrocardiographic guidance. Electrocardiographically guided pericardiocentesis may be used if echocardiography is unavailable or it may be used in conjunction with echocardiography. However, most authorities agree that electrocardiographic guidance adds little to the safety of a carefully performed echocardiographically guided procedure. If used instead of echocardiography, a subxiphoid approach is typically preferred:

(1) The patient is positioned at a 45° incline.

(2) Electrocardiographic limb leads are attached to the patient in the usual fashion.

(3) The xiphoid process is identified, and a point just inferior and to one side of the process is marked.

(4) The region is prepared and draped sterilely, and local anesthetic is given around the mark with a 25G needle.

(5) A 21G steel spinal needle is attached to a syringe filled with local anesthetic. The needle should be approximately 10 cm long. With a sterile alligator clip, the V lead of the electrocardiography monitor is attached to the metal hub of the spinal needle.

(6) The needle should be directed posteriorly at approximately 90° to the patient until the tip is below the costal margin. Then the hub of the needle should be depressed toward the patient's skin and advanced toward the left shoulder at an angle of 15° to 30° to the patient. Local anesthetic is injected as needed, and gentle suction should be applied to the syringe when advancing.

(7) ST elevations or premature ventricular contractions on the electrocardiography monitor indicate that the needle is encountering the right ventricle. PR-segment elevation or frequent premature atrial contractions (PAC) indicate that the needle is penetrating the right atrium. In the average adult, the distance from skin to pericardium is approximately 6 to 8 cm (1).

(8) Once in the pericardial space, a catheter may be placed as described previously.

C. Fluoroscopic guidance. Fluoroscopy can be used as well to guide pericardiocentesis, although this approach has largely been supplanted by echocardiography. With fluoroscopy, a subxiphoid approach is again used. The needle is directed to the left shoulder and toward the anterior diaphragmatic border of the right ventricle. Upon penetration into the pericardial space, needle position may be confirmed with injection of radiopaque contrast media. A drainage catheter may then be placed as described earlier.

D. Blind approach. In emergent conditions, blind pericardiocentesis may be necessary. A subxiphoid approach is used as described above. However, because of the significantly higher rates of complications, blind taps should be avoided unless absolutely necessary.

VII. DIAGNOSTIC STUDIES. If the cause of the pericardial effusion is not clear, fluid should be sent for analysis. The primary causes of idiopathic effusions depend somewhat on the patient population but include tuberculosis (TB), viral infection, uremia, collagen vascular disease, neoplasia, surgery, and myocardial infarction. Therefore, all fluid from idiopathic effusions should be sent for bacterial, mycobacterial, and viral cultures; cytologic examination; acid-fast bacillus smear; cell count; protein; glucose; and lactate dehydrogenase. If TB is suspected, evaluate for adenosine deaminase, interferon gamma, pericardial lysozyme, and polymerase chain reaction. If malignancy is suspected, tumor

markers can be sent for evaluation. Blood samples should be sent for chemistry, complete blood count, blood cultures (if bacterial infection is likely), thyroid-stimulating hormone, erythrocyte sedimentation rate/C-reactive protein, antinuclear antibody, and rheumatoid factor (if connective tissue disease is suspected). Consideration should also be given to conducting a tuberculin purified protein derivative skin test.

VIII. COMPLICATIONS.

Using echocardiographic guidance, the rate of complications is low. The largest series of echo-guided pericardiocenteses comes from the Mayo Clinic. Among the 1,127 procedures studied, major complications occurred in 1.2% of cases, and these included one death from right ventricular perforation, five nonfatal perforations that required surgery, one intercostal artery laceration, five pneumothoraces, one episode of sustained ventricular tachycardia, and one episode of bacteremia. Minor complications occurred 3.5% of the time and included 11 chamber perforations that sealed spontaneously, 8 self-limited pneumothoraces, 9 pleuropericardial fistulas, and 2 episodes of nonsustained ventricular tachycardia.

Fluoroscopy appears to be associated with higher rates of complications. In one series of 352 procedures, complications included 2 (0.6%) deaths, 23 (5.6%) chamber perforations (3 requiring surgery), 5 (1.4%) arterial bleeds (3 diaphragmatic, 1 posterior descending artery, and 1 left internal mammary artery), and 2 pneumothoraces (2).

Blind pericardiocentesis has been associated with morbidity rates as high as 20% and mortality rates as high as 6%.

Therefore, complications are relatively rare in experienced centers, although one must be mindful of the following:

A. Pneumothorax. This is usually effectively avoided with echocardiographic imaging. If the parasternal approach is used, remaining close to the sternum decreases the risk of pneumothorax.

B. Chamber entry/cardiac laceration. This is usually asymptomatic and self-sealing, particularly if the left ventricle is entered. Right ventricular perforations have a somewhat higher likelihood of bleeding when perforated, but right atrial lacerations carry the highest risk. If laceration is suspected, the needle or catheter should be withdrawn and the patient should be observed overnight in an intensive care setting. Serial echocardiograms are indicated to assess for changes in effusion size.

C. Arterial laceration. The left internal thoracic/mammary artery runs down the chest wall about 1 to 2 cm lateral to the sternum, with the vein running slightly more medial (3). Left chest wall and subxiphoid approaches must take this anatomy into consideration. The posterior descending artery can be lacerated on subxiphoid approaches if the needle is aimed too medially. On a chest wall approach, the intercostal arteries are avoided by passing the catheter just superior to the rib.

D. Infection. Sterile technique during the procedure and meticulous catheter care afterward if a drain is left in place minimize this risk. As the Mayo series suggests, the risk of catheter-related infection is very low, even among cancer patients.

E. Death. This is exceptionally rare when procedures are performed by experienced operators with echocardiographic guidance.

IX. POSTPROCEDURE CARE

A. Chest radiography. A postprocedure chest film should be obtained in all patients to exclude pneumothorax.

B. Monitoring. Patients should be observed for 1 to 2 hours following the pericardiocentesis. Patients without significant comorbidities who have uncomplicated diagnostic taps do not require inpatient care following the procedure.

C. Drain care. Care of an indwelling pericardial catheter is similar to that for any central line. After the catheter is sutured in place, the site is treated with an antibacterial ointment and then dressed sterilely. The dressing should be changed every 2 or 3 days.

1. The drain should be aspirated every 6 hours. Continuous drainage can also be used, but the risk of catheter obstruction is higher. Following aspiration, the catheter is flushed with sterile or heparinized saline.
2. If the fluid becomes purulent or the patient becomes septic, the catheter must be removed.
3. Strict record of the volume of fluid draining from the catheter must be kept. The catheter is typically left in place for 1 to 2 days, but extended drainage has been associated with lower rates of effusion recurrence. When the drainage is < 25 to 50 mL/d, the catheter can be removed.

D. Follow-up echocardiography. Before pulling the drain, an echocardiogram should be obtained to ensure resolution of the effusion.

E. Patient care. Patients may be ambulatory with the drain securely in place. Pericardial pain is best managed with nonsteroidal anti-inflammatory medications.

ACKNOWLEDGMENTS: *The authors wish to thank Christian Gring MD for his contribution to an earlier edition of this chapter.*

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APPENDIX

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Commonly Used Cardiovascular Formulae

GENERAL HEMODYNAMICS

Mean arterial pressure (mm Hg) = Diastolic blood pressure (BP) + 1/3 (Systolic BP – Diastolic BP)

Stroke volume (mL) = End-diastolic volume – End-systolic volume

Cardiac output (L/min) = Heart rate × Stroke volume

Ohms law $V = IR$

V = Pressure difference across the system

I = Cardiac output or flow

R = Resistance across the system

$$\textbf{Systemic vascular resistance (Wood unit)} = \frac{\text{Mean arterial pressure} - \text{Central venous pressure}}{\text{Cardiac output}}$$

$$\textbf{Pulmonary vascular resistance (Wood unit)} = \frac{\text{Mean PA pressure} - \text{Mean PCWP}}{\text{Cardiac output}}$$

PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure

1 Wood unit = 80 dynes/s/cm^5

$$\textbf{Pulmonary vascular resistance (echo)} \text{ (Wood unit)} = \left(\frac{\text{Tricuspid regurgitation velocity}}{\text{RVOT VTI}}\right) \times 10 + 0.16$$

RVOT, right ventricular outflow tract; VTI, Velocity Time Integral

Transpulmonary gradient (mm Hg) = Mean PAP – PCWP

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure

Fick equation

$$\text{Cardiac output (L/min)} = \frac{\text{Vo}_2 \text{ (mL/min)}}{1.36 \text{ (mL O}_2\text{/g Hgb)} \times \text{Hgb (g/dL)} \times 10 \text{ (dL/L)} \left[\text{Sa}_{\text{O}_2} - \text{Sv}_{\text{O}_2}\right]}$$

Vo_2 (oxygen consumption)

$$\textbf{Cardiac index (L/min/m}^2\text{)} = \frac{\text{Cardiac output (L/min)}}{\text{Body surface area (m}^2\text{)}}$$

Body surface area (m^2) = [Height (cm) + Weight (kg) – 60]/100

$$\text{Dubois formula for body surface area (m}^2\text{)} = \sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3{,}600}}$$

Stroke work (g-m/beat) = Stroke volume × Mean arterial pressure × 0.0144

Stroke work index (g-m/m^2/beat) = $\frac{\text{Stroke work}}{\text{Body surface area}}$

Coronary flow reserve = $\frac{\text{Peak coronary velocity at maximal hyperemia}}{\text{Peak coronary velocity at baseline}}$

Fractional flow reserve = $\frac{\text{Mean distal coronary pressure beyond stenosis}}{\text{Mean aortic pressure}}$

VALVULAR DISEASE AND LEFT VENTRICULAR (LV) FUNCTION

Gorlin equation

Aortic valve area (cm^2) = $\frac{\text{Cardiac output (mL/min)}}{44.3 \times \text{Systolic ejection period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$

Mitral valve area (cm^2) = $\frac{\text{Cardiac output (mL/min)}}{38 \times \text{Diastolic filling period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$

Hakki equation

Aortic valve area (cm^2) = $\frac{\text{Cardiac output}}{\sqrt{\text{Peak to peak gradient}}}$ or $\frac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$

Mitral valve area (cm^2) = $\frac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$

Simplified Bernoulli equation

Pressure difference = 4 v^2

If proximal velocity > 1 m/s, then pressure difference = 4 [(distal jet velocity)^2 – (proximal velocity)^2]

Continuity aortic valve area (cm^2) = $\text{Diameter}_{\text{LVOT}}^2 \times 0.785 \times \frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{Aortic valve}}}$

LVOT, left ventricular outflow tract; VTI, velocity time integral

Dimensionless index = $\frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{Aortic valve}}}$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Stroke volume (mL) = $\text{Diameter}_{\text{LVOT}}^2 \times 0.785 \times \text{VTI}_{\text{LVOT}}$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Aortic regurgitant fraction (%) = $\frac{\text{Aortic regurgitant volume}}{\text{LVOT stroke volume}} \times 100$

LVOT, left ventricular outflow tract

Mitral valve area (mitral stenosis) (cm^2) = $\frac{220}{\text{Pressure half time}}$

Tricuspid valve area (tricuspid stenosis) (cm^2) = $\frac{190}{\text{Pressure half time}}$

Pressure half time (ms) = 0.29 × Deceleration time

Proximal isovelocity surface area (PISA) method in mitral regurgitation

$$\text{Regurgitant orifice area (cm}^2\text{)} = \frac{6.28\, r^2 \times \text{Aliasing velocity}}{\text{Mitral regurgitation velocity}}$$

r, radius of PISA

Simplified PISA when aliasing velocity ~40 cm/s and peak continuous wave mitral regurgitation velocity ~5 m/s

$$\text{Regurgitant orifice area (cm}^2\text{)} = \frac{r^2}{2}$$

r, radius of PISA

Mitral regurgitant volume (mL) = $1.9r^2 \times$ Aliasing velocity

r, radius of PISA

$$\textbf{Mitral regurgitant fraction } (\%) = \frac{\text{Mitral regurgitant volume}}{\text{Mitral valve flow}} \times 100$$

$$\textbf{Fractional shortening } (\%) = \frac{\text{LVED dimension} - \text{LVES dimension}}{\text{LVED dimension}} \times 100$$

LVED, left ventricular end diastole; LVES, left ventricular end systole

$$\textbf{Ejection fraction } (\%) = \frac{\text{End diastolic volume} - \text{End systolic volume}}{\text{End diastolic volume}} \times 100$$

Estimated pulmonary artery systolic pressure (mm Hg) =
RA pressure + 4 × (Peak tricuspid regurgitation velocity)^2

RA, right atrium

Estimated pulmonary artery end-diastolic pressure (mm Hg) =
RA pressure + 4 × (Pulmonary regurgitation end-diastolic velocity)^2

RA, right atrium

Assessment of right atrial (RA) pressure (by echo)

IVC diameter (cm)	IVC collapse	Estimated RA pressure (mm Hg)
≤ 2.1	> 50%	3 (range 0–5)
≤ 2.1	< 50%	8 (range 5–10)
> 2.1	> 50%	8 (range 5–10)
> 2.1	< 50%	15 (range 10–20)

IVC, inferior vena cava

Left atrial (LA) pressure (mm Hg) =
Systolic blood pressure − 4 × (Mitral regurgitation velocity)^2

LV mass (area length) = $1.05\{[5/6\ A1(a + d + t)] - [5/6\ A2\ (a + d)]\}$

A1 = area of LV short axis using epicardial perimeter

A2 = area of LV short axis using endocardial perimeter

t = myocardial thickness

a = long axis length from widest minor axis radius to apex

b = short axis radius

d = truncated long axis from widest short axis diameter to mitral annulus plane

Dp/dt $= \dfrac{32{,}000 \text{ mm Hg}}{dt \text{ (in seconds)}}$

Dt, time it takes velocity to go from 1 to 3 m/s

Tei index (myocardial performance index) =

$$\frac{\text{Isovolumic contraction time} + \text{Isovolumic relaxation time}}{\text{Ejection time}}$$

SHUNTS

Shunt fraction $(Q_p/Q_s) = \dfrac{(Sao_2 - Svo_2)}{(Pvo_2 - Pao_2)}$

Sao_2, systemic arterial oxygen saturation

Svo_2, systemic venous oxygen saturation

Pvo_2, pulmonary venous oxygen saturation

Pao_2, pulmonary arterial oxygen saturation

Mvo_2 (%) $= \dfrac{3 \times (\text{SVCsat}) + (\text{IVCsat})}{4}$

Mvo_2, mixed venous saturation

SVC, superior vena cava

IVC, inferior vena cava

Q_p/Q_s (echo) $= \dfrac{\text{RVOT Cross-sectional area} \times \text{RVOT TVI}}{\text{LVOT Cross-sectional area} \times \text{LVOT VTI}}$

RVOT, right ventricular outflow tract

VTI, velocity time integral

LVOT, left ventricular outflow tract

ELECTROPHYSIOLOGY/ECG

QT_c (ms) $= \dfrac{QT}{\sqrt{\text{RR interval (seconds)}}}$

Heart rate (beats/min) $= \dfrac{60{,}000}{\text{Cycle length (ms)}}$

Left ventricular hypertrophy

Limb lead criteria

(1) R wave in lead I + S wave in lead III > 2.5 mV
(2) R wave in aVL > 1.1 mV
(3) R wave in aVF > 2.0 mV
(4) S wave in aVR > 1.4 mV

Precordial lead criteria

(1) R wave in V_5 or V_6 > 2.6 mV

(2) R wave in V_6 + S wave in V_1 > 3.5 mV

(3) Largest R wave + largest S wave in precordial leads > 4.5 mV

Cornell criteria

R wave in aVL + S wave in V_3 > 2.0 mV for females and 2.8 mV for males

Duke treadmill score (DTS)

DTS = Exercise time (minutes) − (5 × Maximal ST deviation) − (4 × Angina score)

0 = no angina

1 = nonlimiting angina

2 = angina limiting further testing

DTS ≤ −11 = high risk

DTS − 10 to 4 = moderate risk

DTS ≥ 5 = low risk

Age-predicted maximal heart rate (beats/min) = 220 − Age

PHARMACODYNAMICS

Volume of distribution (L) $= \dfrac{\text{Amount of drug in body}}{\text{Plasma drug concentration}}$

Loading dose (mg) $= \dfrac{\text{(Volume of distribution)} \times \text{(Plasma drug concentration)}}{\text{(Fraction of dose that is active)} \times \text{(Bioavailability of drug)}}$

Clearance (L/h) $= \dfrac{\text{Rate of drug administration}}{\text{Steady-state plasma drug concentration}}$

Half-life (h) $= \dfrac{0.693 \times \text{Volume of distribution}}{\text{Clearance (L/h)}}$

MISCELLANEOUS

Cockcroft-Gault

Glomerular filtration rate (mL/min) $= \dfrac{[(140 - \text{Age}) \times \text{Weight (kg)}]}{72 \times \text{Creatinine}}$

If female, multiply by 0.85

Ankle-Brachial index $= \dfrac{\text{Pedal pressure}}{\text{Brachial pressure (higher of two sides)}}$

Law of Laplace

Wall tension $= \dfrac{\text{Pressure} \times \text{Radius}}{\text{Wall thickness}}$

Central perfusion pressure = Mean arterial pressure − Intracranial pressure

Assessment of appropriateness of ascending aorta size to height

Aortic index = $\frac{\text{Maximal cross-sectional area of ascending aorta (cm}^2\text{)}}{\text{Height (m)}}$

If ratio > 10, consider repair of aorta

Cholesterol mg/dL to mmol/L

1 mg/dL = 0.02586 mmol/L; 1 mmol/L = 38.7 mg/dL

Thus, 130 mg/dL = 3.45 mmol/L

Total cholesterol = LDL cholesterol + HDL cholesterol + 0.20 (Triglyceride level)

HDL, high-density lipoprotein; LDL, low-density lipoprotein

STATISTICS

	Disease present	Disease absent
Test result positive	a (True positive)	b (False positive)
Tests result negative	c (False negative)	d (True negative)

Sensitivity = $\frac{a}{a+c}$

Specificity = $\frac{d}{b+d}$

Positive predictive value = $\frac{a}{a+b}$

Negative predictive value = $\frac{d}{c+d}$

Likelihood ratio for a positive test = $\frac{\text{Sensitivity}}{1-\text{Specificity}} = \frac{a/a+c}{b/b+d}$

Likelihood ratio for a negative test = $\frac{1-\text{Sensitivity}}{\text{Specificity}} = \frac{c/a+c}{d/b+d}$

	Outcome positive	Outcome negative
Treated group	a	b
Control group	c	d

Relative risk = $\frac{\text{Risk of outcome in treated group}}{\text{Risk of outcome in control group}} = \frac{a/a+b}{c/c+d}$

Relative risk reduction = (1 − Relative risk) × 100%

Absolute risk reduction = Difference in risk of outcome between control group and treated group

Absolute risk reduction = c/c + d − a/a + b

Number needed to treat = $\frac{1}{\text{Absolute risk reduction}}$

Odds ratio = $\frac{\text{Number of outcome events/Number of subjects}}{1-(\text{Number of outcome events/Number of subjects})}$

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POCKET CARDIOLOGY

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Preface

With *Pocket Cardiology,* we now offer those taking care of patients with complex cardiovascular disease a focused and concise reference to aid them in their daily clinical care. *Pocket Cardiology* has been designed to either supplant the Cardiology section in *Pocket Medicine* or serve as a stand-alone handbook. *Pocket Cardiology* provides greatly expanded coverage of the latest treatment options for the major common cardiovascular diseases as well as new sections on advanced heart failure, vascular, and electrophysiology topics.

We have incorporated key references to the most recent high-tier reviews and important studies published right up to the time *Pocket Cardiology* went to press. We welcome any suggestions for further improvement. Although the recommendations herein are as evidence based as possible, sound clinical judgement must be applied to every scenario.

This book would not have been possible without the help of Melinda Cuerda, who shepherded the project from start to finish, with an incredible eye to detail to ensure that each page of this book was the very best it could be.

It is a privilege to take care of patients, especially when working with the house officers, fellows, and attendings at Brigham and Women's Hospital and the Massachusetts General Hospital. The rapid advances in cardiovascular medicine are truly amazing. We hope the information contained within *Pocket Cardiology* proves useful in your quest to deliver the best possible care to your patients.

Marc S. Sabatine, MD, MPH

Coronary Disease

ELECTROCARDIOGRAPHY

Approach *(a systematic approach is vital)*

- **Rate** (? tachy or brady)
- **Rhythm** (? P waves, ? relationship between P and QRS, ? regular)
- **Intervals** (PR, QRS, QT) and **axis** (? LAD or RAD)
- **Chamber abnormality** (? LAA and/or RAA, ? LVH and/or RVH)
- **QRST changes** (? Q waves, poor R-wave progression V_1-V_6, ST ↑/↓ or T-wave Δs)

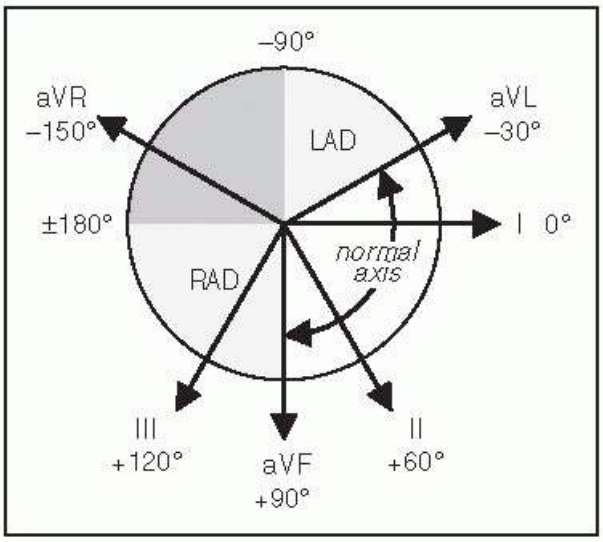


Figure 1-1 QRS axis

Left axis deviation (LAD)

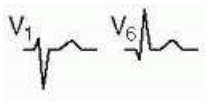
- **Definition:** axis beyond -30° (S > R in lead II)
- **Etiologies:** LVH, LBBB, inferior MI, WPW
- **Left anterior fascicular block (LAFB):** LAD (-45 to -90°) *and* qR in aVL *and* QRS <120 msec *and* no other cause of LAD (eg, IMI)

Right axis deviation (RAD)

- **Definition:** axis beyond +90° (S > R in lead I)
- **Etiologies:** RVH, PE, COPD (usually not > + 110°), septal defects, lateral MI, WPW
- **Left posterior fascicular block (LPFB):** RAD (90-180°) *and* rS in I & aVL *and* qR in III & aVF *and* QRS <120 msec *and* no other cause of RAD

Bundle Branch Blocks (*Circ* 2009;119:e235)

Initial depol. is left-to-right across septum (r in V_1 & q in V_6; nb, absent in

Normal		LBBB) followed by LV & RV free wall, with LV dominating (nb, RV depol. later and visible in RBBB).
RBBB		1. QRS ≥120 msec (110-119 = incomplete) 2. rSR' in R precordial leads (V_1, V_2) 3. Wide S wave in I and V_6 4. ± ST↓ or TWI in R precordial leads
LBBB		1. QRS ≥120 msec (110-119 = incomplete) 2. Broad, slurred, monophasic R in I, aVL, V_5-V_6 (± RS in V_5-V_6 if cardiomegaly) 3. Absence of Q in I, V_5 and V_6 (may have narrow q in aVL) 4. Displacement of ST & Tw opposite major QRS deflection 5. ± PRWP, LAD, Qw's in inferior leads

Bifascicular block: RBBB + LAFB/LPFB. Trifascicular block: bifascicular block + 1° AVB (nb, misnomer as 1° AVB involves AV node but no fascicle per se).

Prolonged QT interval (*NEJM* 2008;358:169; www.torsades.org)

- QT measured from beginning of QRS complex to end of T wave (measure longest QT)
- QT varies w/ HR → corrected w/ Bazett formula: QTc = QT/$\sqrt{RR}$ (RR in sec, can be estimated by 60/HR), overcorrects at high HR and undercorrects at low HR (nl QTc <440 msec ♂ and <460 msec ♀)
- Fridericia's formula preferred at very high or low HR: QTc = QT/ $\sqrt[3]{RR}$
- QT prolongation a/w ↑ risk TdP (espec >500 msec); perform baseline/serial ECGs if using QT prolonging meds, no estab guidelines for stopping Rx if QT prolongs
- Etiologies:

  Antiarrhythmics: class Ia (procainamide, disopyramide), class III (amio, sotalol, dofet)

  Psych drugs: antipsychotics (phenothiazines, haloperidol, atypicals), Li, ? SSRI, TCA

  Antimicrobials: macrolides, quinolones, azoles, pentamidine, atovaquone, atazanavir

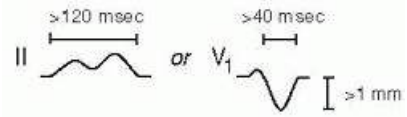
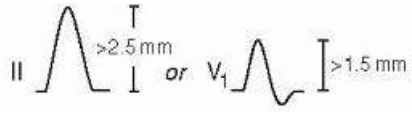
  Other: antiemetics (droperidol, 5-HT3 antagonists), alfuzosin, methadone, ranolazine

  Electrolyte disturbances: hypoCa (nb, hyperCa a/w ↑ QT), ± hypoK, ? hypoMg

  Autonomic dysfxn: ICH (deep TWI), stroke, carotid endarterectomy, neck dissection

  Congenital (long QT syndrome): K, Na, & Ca channelopathies (*Circ* 2013;127:126)

  Misc: CAD, CMP, bradycardia, high-grade AVB, hypothyroidism, hypothermia, BBB

ECG P-wave Criteria	**Left Atrial Abnormality (LAA)** 	**Right Atrial Abnormality (RAA)** 

Left ventricular hypertrophy (LVH) (*Circ* 2009;119:e251)

- Etiologies: HTN, AS/AI, HCMP, coarctation of aorta
- Criteria (all w/ Se <50%, Sp >85%; accuracy affected by age, sex, race, BMI)

  Romhilt-Estes point-score system (4 points = probable; 5 points = diagnostic):

Criteria	Points
Voltage (any of the following): R or S in limb leads ≥20 mm; S in V_1 or V_2 ≥30 mm; R in V_5 or V_6 ≥30 mm	3
ST-T displacement opposite to QRS deflection (either):	
◦ Pt not on digoxin	3
◦ Pt on digoxin	1
Left atrial enlargement	3
Left axis deviation	2
QRS duration ≥90 msec	1
Delayed intrinsicoid deflection (QRS onset to R peak) in V_5 or V_6 >50 msec	1

  Sokolow-Lyon: S in V_1 + R in V_5 or V_6 ≥35 mm or R in aVL ≥11 mm

  Cornell: R in aVL + S in V_3 >28 mm in men or >20 mm in women If LAD/LAFB, S in III + max (R+S) in precordium ≥30 mm

Right ventricular hypertrophy (RVH) (*Circ* 2009;119:e251)

- Etiologies: cor pulmonale, congenital (tetralogy, TGA, PS, ASD, VSD), MS, TR
- Criteria (all tend to be insensitive, but highly specific, except in COPD) R > S in V_1 or R in V_1 ≥7 mm, S in V_5 or V_6 ≥7 mm, drop in R/S ratio across precordium RAD ≥+110° (LVH + RAD *or* prominent S in V_5 or V_6 → *biventricular* hypertrophy)

Ddx of dominant R wave in V_1 or V_2

- Ventricular enlargement: RVH (RAD, RAA, deep S waves in I, V_5, V_6); HCMP
- Myocardial injury: posterior MI (anterior Rw = posterior Qw; often with IMI)
- Abnormal depolarization: RBBB (QRS > 120 msec, rSR'); WPW (↓ PR, δ wave, ↑ QRS)

- Other: dextroversion; Duchenne muscular dystrophy; lead misplacement; nl variant

Poor R wave progression (PRWP) (*Am Heart J* 2004;148:80)

- Definition: loss of anterior forces w/o frank Q waves (V_1-V_3); R wave in V_3 ≤3 mm
- Possible etiologies (nonspecific):

  old anteroseptal MI (usually w/ R wave V_3 ≤1.5 mm, ± persistent ST ↑ or TWI V_2 & V_3) cardiomyopathy

  LVH (delayed RWP with prominent left precordial voltage), RVH, COPD (which may also have RAA, RAD, limb lead QRS amplitude ≤5, $S_I S_{II} S_{III}$ w/ R/S ratio <1 in those leads)

  LBBB; WPW; clockwise rotation of the heart; lead misplacement; PTX

Pathologic Q waves

- Definition: ≥30 msec (≥20 msec V_2-V_3) or >25% height of R wave in that QRS complex
- Small (septal) q waves in I, aVL, V_5 & V_6 are nl, as can be isolated Qw in III, aVR, V_1
- "Pseudoinfarct" pattern may be seen in LBBB, infiltrative dis., HCM, COPD, PTX, WPW
- In WPW, Qw pattern may help localize site of accessory pathway (Bundle of Kent)

ST elevation (STE) (*NEJM* 2003;349:2128; *Circ* 2009;119:e241 & e262)

- **Acute MI** (upward convexity ± TWI) or prior MI with persistent STE
- **Coronary spasm** (Prinzmetal's angina; transient STE in a coronary distribution)
- **Pericarditis** (diffuse, upward concavity STE; a/w PR ↓ ; Tw usually upright)
- **HCM, Takotsubo CMP, ventricular aneurysm,** cardiac contusion
- **Pulmonary embolism** (occ. STE V_1-V_3; classically a/w TWI V_1-V_4, RAD, RBBB, $S_1Q_3T_3$)
- **Repolarization abnormalities**

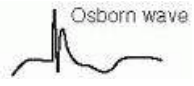
  LBBB (↑ QRS duration, STE discordant from QRS complex) dx *of* MI *in setting of* LBBB*:* Sgarbossa criteria (*NEJM* 1996;334:481) ≥1 mm STE concordant w/ QRS (Se 73%, Sp 92%) STD ≥1 mm V_1-V_3 (Se 25%, Sp 96%) STE ≥5 mm discordant w/ QRS (Se 31%, Sp 92%)

  LVH (↑ QRS amplitude)

  Brugada syndrome (rSR', downsloping STE V1-V2; Na channelopathy a/w SCD)

  Hyperkalemia (see below)

  Hypothermia: Osborn waves

  ⊕ deflection at J point, typically in R-precordial leads 

proportional to degree of hypothermia
- **aVR:** STE > 1 mm a/w ↑ mortality in STEMI; STE aVR > V_1 a/w left main disease
- **Early repolarization:** most often seen in V_2-V_5 in young adults (*JACC* 2015;66:470)

  1-4 mm elev of peak of notch or start of slurred downstroke of R wave (ie, J point); ± up concavity of ST & large Tw (∴ ratio of STE/T wave <25%; may disappear w/ exercise)

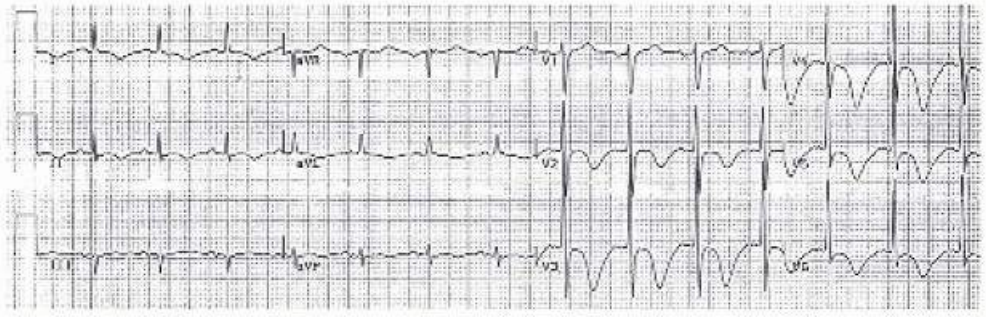
? early repol in inf leads may be a/w ↑ risk of VF (*NEJM* 2009;361:2529; *Circ* 2011;124:2208)

ST depression (STD)

- **Myocardial ischemia** (± Tw abnl) or acute true posterior MI (V_1-V_3)
- Digitalis effect (downsloping ST ± Tw abnl, does *not* correlate w/ dig levels)
- Hypokalemia (± U wave)
- Repolarization abnl in a/w LBBB or LVH (usually in leads V_5, V_6, I, aVL)

T wave inversion (TWI; generally ≥1 mm; deep if ≥5 mm) (*Circ* 2009;119:e241)

- Ischemia or infarct; *Wellens' sign* (deep, symmetric precordial TWI) → proximal LCA lesion

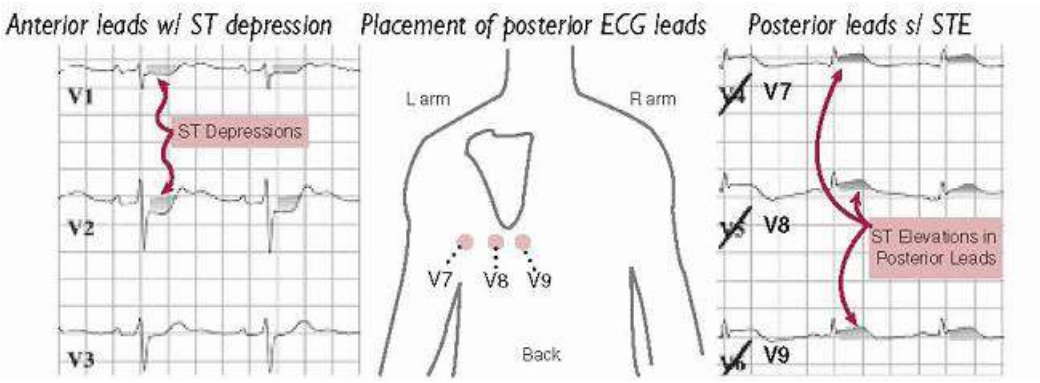


(Wellens' sign, from Cuculich PS and Kates AM. *The Washington Manual Cardiology Subspecialty Consult,* 3rd ed. Philadelphia: Wolters Kluwer Health, 2014:286.)

- Myopericarditis; CMP (Takotsubo, ARVC, apical HCM); MVP; PE (espec if TWI V_1-V_4)
- Repolarization abnl in a/w LVH/RVH ("strain pattern"), BBB
- Posttachycardia or postpacing
- Electrolyte, digoxin, PaO_2, $PaCO_2$, pH or core temperature disturbances
- Intracranial bleed ("cerebral T waves," usually w/ ↑ QT)
- Normal variant in children (V_1-V_4) and leads in which QRS complex predominantly ⊖

True posterior MI (posterior STE appearing as anterior STD)

- STD ± ↑ R wave in leads V1-V4 may correspond to acute posterior "ST-elevation" MI
- ✓ Posterior ECG leads; manage as a STEMI with rapid reperfusion



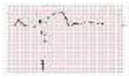
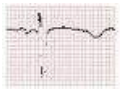
(Modified from Martindale JL, Brown DFM. *Rapid Interpretation of ECGs in Emergency Medicine*. Philadelphia:

Lippincott Williams & Wilkins, 2012:364,376)

Low voltage

- QRS amplitude (R + S) <5 mm in all limb leads & <10 mm in all precordial leads
- Etiologies: COPD (precordial leads only), pericardial effusion, myxedema, obesity, pleural effusion, restrictive or infiltrative CMP, diffuse CAD

Electrolyte Abnormalities

→ **K**	Tented Tw, ↓ QT Small Pw, ↑ PR, AVB Wide QRS → sinusoidal pattern STE (typically V_1-V_2)	
→ **K**	Flattened Tw U waves (⊕ deflection after T) ST depression Ectopy; ↑ QT & TdP	
↑ **Ca**	↓ QT, flattened Tw & Pw J point elevation	
↓ **Ca**	↑ QT; Tw Δs	

(ECGs modified from Wagner GS, Strauss DG. *Marriott's Practical Electrocardiography*, 12th ed. Philadelphia: Lippincott Williams & Wilkins, 2014)

CHEST PAIN

Disorder	Typical Characteristics & Diagnostic Studies
	Cardiac Causes
ACS (15-25% of chest pain in ED)	Substernal pressure radiating to neck, jaw, arm. ± Dyspnea, diaphoresis, N/V; a/w exertion; ↓ w/ NTG or rest; however, not reliable indicator (*Annals EM* 2005;45:581). ± ECG Δs: STE, STD, TWI, Qw. ± ↑ Troponin.
Pericarditis & myo-pericarditis	Sharp pain → trapezius, ↑ w/ respiration, ↓ w/ sitting forward. ± Pericardial friction rub. ECG Δs (diffuse STE & PR ↓, opposite in aVR) ± pericardial effusion. If myocarditis, same as above + ↑ Tn and ± s/s HF and ↓ EF.

Aortic dissection	Abrupt-onset severe tearing, knifelike pain (absence ⊖ LR 0.3), ant or post midscapular. HTN or HoTN. ± Asymmetric (> 20 mmHg) BP or pulse deficit (⊕ LR 5.7), focal neuro deficit (⊕ LR >6), AI, widened mediastinum on CXR (absence ⊖ LR 0.3); false lumen on imaging. (*JAMA* 2002;287:2262)
	Pulmonary Causes
Pneumonia	Pleuritic; dyspnea, fever, cough, sputum. ↑ RR, crackles. CXR infiltrate.
Pleuritis	Sharp, pleuritic pain. ± Pleuritic friction rub.
PTX	Sudden onset, sharp pleuritic pain. Hyperresonance, ↑ BS. PTX on CXR.
PE	Sudden onset pleuritic pain. ↑ RR & HR, ↓ S_aO_2, ECG Δs (sinus tach, RAD, RBBB, $S_IQ_{III}T_{III}$, TWI V_1-V_4, occ STE V_1-V_3). ⊕ CTA or V/Q.
Pulm HTN	Exertional pressure, DOE. ↓ S_aO_2, loud P_2, RV heave, right S_3 and/or S_4.
	GI Causes
Esophageal reflux	Substernal burning, acid taste in mouth, water brash. ↑ by meals, recum-bency; ↑ by antacids. EGD, manometry, pH monitoring.
Esoph spasm	Intense substernal pain. ↑ by swallowing, ↓ by NTG/CCB. Manometry.
Mallory-Weiss	Esophageal tear precipitated by vomiting. EGD.
Boerhaave syndrome	Esoph. rupture typically precipitated by vomiting. Severe pain, ↑ w/ swallowing. Palpable SC emphysema; mediastinal air on chest CT.
PUD	Epigastric pain, relieved by antacids. ± GIB. EGD, ± *H. pylori* test.
Biliary dis.	RUQ pain, N/V. ↑ by fatty foods. RUQ U/S; ↑ LFTs.
Pancreatitis	Epigastric/back discomfort. ↑ amylase & lipase; abd CT.
	Musculoskeletal and Miscellaneous Causes
Costochond	Localized sharp pain. ↑ w/ movement. Reproduced by palpation.
Zoster	Intense unilateral pain. Pain may precede dermatomal rash.
Anxiety	"Tightness," dyspnea, palpitations, other somatic symptoms

(*Braunwald's Heart Disease*, 10th ed, 2014)

Initial approach

- **Focused history:** quality & severity of pain; location & radiation; provoking & palliating factors; intensity at onset; duration, frequency & pattern; setting in which it occurred; associated sx; cardiac hx and risk factors

Pain Feature	Classic for ACS	Atypical for ACS
Quality	Pressure (⊕ LR 1.3), tightness, "Levine" sign (clenched fist over chest), squeezing, fullness, heavy weight, more than prior angina or ≈ prior MI (⊕ LR 1.8)	Sharp (⊕ LR 0.3)
Region/radiation	Substernal, radiating to L or R arm or shoulder (⊕ LR 2.3-4.7), jaw, teeth, neck	Small area, points w/ 1 finger, radiation to back
Provocation	Exertion (⊕ LR 2.4; but may be absent)	Pleuritic, positional or w/ palp (⊕ LR ≤0.3), eating
Associated sx	Diaphoresis (⊕ LR 2.0), N/V (⊕ LR 1.9), dyspnea	

(*JAMA* 2005;294:2623)

- **Targeted exam:** VS (including BP in both arms), cardiac gallops, murmurs or rubs; signs of vascular disease (carotid or femoral bruits, ↓ pulses), signs of heart failure; lung & abdominal exam; chest wall exam for reproducibility of pain
- **12-lead ECG:** obtain w/in 10 min; c/w priors & obtain serial ECGs. In addition, consider:

  posterior leads (V_7-V_9; remove V4-V6 and place in post axillary, mid-clavic & L paraspinal position) useful to ✓ for posterior STEMI if hx c/w ACS but stnd ECG unrevealing, espec if ST ↓ V_1-V_4 (ant ischemia vs post STEMI) or R/S V_1-V_2 > 1

  R-sided leads (place V_3-V_6 in mirror image position on R side of chest) in inferior STEMI to detect RV involvement

- **CXR;** other imaging (echo, PE CTA, etc.) as indicated based on H&P and initial testing
- **Biomarkers** (see below): Tn preferred biomarker, ✓ at baseline & 3-6 h after sx onset

Biomarkers

- **Troponin:** level >99th %ile w/ rise & fall in approp. setting is dx of MI; >95% Se, 90% Sp Detectable 1-6 h after injury, peaks 24 h, may remain elevated for 7-14 d in STEMI Tn may be ↑ in CKD in absence of ACS, ∴ add CK-MB/serial Tn for confirmation *Sensitive* Tn assays: 98% Se, 90% Sp, 75% PPV, 99% NPV w/in 3 h of admit to ED, 82% Se & 95% NPV at time of admission to ED (*JAMA* 2011;306:2684)

  High-sensitivity Tn assays quantify Tn in majority of healthy individ.; prog value in asx general pop., stable CAD & DM (*NEJM* 2009;361:2538 & 2015;373:610; *JAMA* 2010;304:2503)

- **CK-MB:** less Se & Sp than Tn for dx of MI

  Sources include skeletal muscle, tongue, diaphragm, intestine, uterus, prostate

  CK-MB relative index (ratio of CK-MB to CK) >2.5-3 suggests cardiac vs skel. muscle

  CK-MB begins to rise 4-6 h post MI (may take 12 h) and returns to baseline w/in 36-48 h

  May aid in gauging timing of MI (⊕ Tn & ⊖ CK-MB suggests MI several days ago)

  May help dx reinfarction if Tn already elevated; however, Tn should ↑ as well

- Myoglobin & heart-type fatty acid binding protein are smaller molecules that may appear in circulation as early as 30 min after MI, but lack of specificity limits utility

- **D-dimer:** low level useful to r/o PE (qv) and aortic dissection (qv)

- B-type natriuretic peptide (BNP): elevations not specific for ACS but suggest ↑ ventricular wall stress seen not only in decompensated HF, but also ACS & PE

Interpretation of elevated cardiac biomarkers (troponin or CK-MB)

- *Does it reflect true myocardial injury?* Almost always the case for Tn; CK-MB less specific.

- *If myocardial injury, what is the pathobiology?* Ddx includes:

  MI (injury due to ischemia): rise and/or fall in cardiac biomarker (preferably Tn)

  >99th %ile w/ ≥1 of the following:

  1) sx of ischemia

  2) new Qw

  3) new STΔ or LBBB

  4) intracoronary thrombus

  5) imaging evidence of new loss of myocardium or regional wall motion abnl non-ischemic injury (eg, myocarditis/toxic CMP, cardiac contusion) multifactorial (eg, PE, sepsis, severe HF, renal failure, Takotsubo, infiltrative disease)

- *If* MI*, what type?* (*Circ* 2012;126:2020)

Type	Descriptor	Features
1	Spontaneous	Pathologic process in wall of coronary artery (eg, plaque rupture) resulting in intraluminal thrombus
2	Supply-demand	Mismatch due to, eg, ↑ ↑ or ↓↓ HR or BP, profound anemia or

	mismatch not due to Δ in CAD	hypoxemia, coronary vasospasm, HCM, severe AS
3	Sudden cardiac death	
4a	Related to PCI	Tn >5x 99th %ile or >20% rise if already elevated +≥1 MI clinical/imaging criteria above
4b	Stent thrombosis	
5	Related to CABG	Tn > 10x 99th %ile + new Qw or LBBB, angio confirmation, or new wall motion abnl

- Classification important as antithrombotic Rx relevant for type 1 but not type 2 MI, whereas anti-ischemic Rx (↑ O_2 supply & ↓ demand) particularly important for type 2

Early noninvasive imaging (also see noninvasive evaluation of CAD)

- If low prob of ACS (eg, ⊖ ECG & Tn) & stable → noninvasive fxnal or imaging test
- Treadmill electrocardiography: can be performed after 6-8 h of evaluation
- Radionuclide imaging in Pts who cannot exercise or have uninterpretable ECG
- Can perform acute rest perfusion imaging if ongoing or recent (w/in 2 h) pain (⊖ scan r/o ischemia; ⊕ scan could represent ischemia or infarct, need pain-free rest images)
- Echo (w/ or w/o stress) to assess for regional wall motion abnl; interpretation difficult in those w/ h/o prior MI
- Coronary CT angio (CCTA): NPV 98% for signif CAD, but PPV 35% for ACS; helpful to r/o CAD if low-intermed prob of ACS. CCTA vs noninvasive fxnal test for ischemia → ↓ time to dx & LOS, but ↑ probability of cath/PCI, contrast exposure & ↑ radiation (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880)
- "Triple r/o" CT angiogram for CAD, PE, AoD

NONINVASIVE EVALUATION OF CAD

Stress testing (*Circ* 2007;115:1464; *JACC* 2012;60:1828)

- **Indications:** dx CAD, evaluate Δ in clinical status in Pt w/ known CAD, risk stratify s/p ACS, evaluate exercise tolerance, localize ischemia (imaging required)
- **Contraindications** (*Circ* 2002;106:1883; & 2012;126:2465)

  Absolute: AMI w/in 48 h, high-risk UA, acute PE, severe sx AS, uncontrolled HF, uncontrolled arrhythmias, myopericarditis, acute aortic dissection

  Relative: left main CAD, mod valvular stenosis, severe HTN, HCMP high-degree AVB, severe electrolyte abnl

Exercise tolerance test

- Generally preferred if patient can exercise to a meaningful level; Se ˜65%, Sp ˜80%
- Typically via treadmill

Protocol	Description
Standard Bruce	↑ speed & incline q3min until 85% max predicted HR or sxs
Modified Bruce	Adds two stages at start that require less work than standard Bruce stage 1; consider in sedentary/deconditioned Pt
Submaximal	Stop earlier (eg, 70% max predicted HR or 5 METs or any anginal sx); consider if recent MI

- Stationary cycle or arm ergometry (lower max workload) if Pt cannot walk
- Hold anti-ischemic meds (eg, nitrates, βB, CCB, ranolazine) if trying to dx obstructive CAD, but continue meds when assessing if Pt ischemic on current med regimen

Pharmacologic stress test (nb, requires imaging as ECG not interpretable)

- Use if unable to exercise, low exerercise tolerance, or recent MI. Se & Sp ≈ exercise.
- Preferred if LBBB or V-paced, as higher prob of false ⊕ exercise imaging (typically reversible or fixed anteroseptal defect).
- **Coronary vasodilator:** diffuse coronary arteriolar vasodilation → relative "coronary steal" from vessels w/ fixed epicardial disease. Reveals CAD, but *not* if Pt *ischemic* w/ *exercise.* Options include:

  Adenosine or dipyridamole (↑ adenosine reuptake). Side effects: flushing, bradycardia & AVB, dyspnea & bronchospasm.

  Selective A2A receptor agonist (eg, regadenoson): less flushing, dyspnea, bronchospasm

  Longer half-life of dipyridamole & regadenoson allow to be combined w/ exercise

  Avoid caffeine (adenosine receptor antagonist) w/in 12 h of test. Conversely, can use aminophylline to reverse effects of these agents.

  Contraindic: HoTN, sick sinus, high-degree AVB, bronchospasm (selective agents safer)
- **Chronotropes/inotropes** (more physiologic): dobutamine (may precip tachyarrhythmia)

Imaging for stress test (see Photo Inserts)

- Use if uninterpretable ECG (V-paced, LBBB, resting ST ↑ >1 mm, digoxin, LVH, WPW), after indeterminate ECG test, or if pharmacologic test
- Use when need to localize ischemia (often used if prior coronary revasc)
- Ideally use exercise as stress modality rather than pharmacologic
- **Radionuclide myocardial perfusion imaging** w/ images obtained at rest & w/ stress

  SPECT (eg, ^{99m}Tc-sestamibi): Se ~85%, Sp ~80%

  PET (rubidium-82): Se ~90%, Sp ~85%

ECG-gated imaging allows assessment of LV fxn (including regional systolic wall thickening or lack thereof as a sign of ischemia/infarction)

- **Echo** (exercise or dobuta): Se ~85%, Sp ~85%; no radiation; operator dependent
- Cardiac MRI (w/ pharmacologic stress) another option with excellent Se & Sp

Test results

- **HR** (must achieve ≥85% of max pred HR [220 - age] for *exer.* test to be dx), **BP** response, peak **double product** (HR × BP; nl >20k), HR recovery (HR_{peak} - $HR_{1\ min\ later}$; nl > 12)
- **Max exercise capacity** achieved (METS or min)
- Occurrence of **symptoms** (at what level of exertion and similarity to presenting sx)
- **ECG Δs:** *downsloping* or *horizontal* ST ↓ (≥1 mm) 80 ms after QRS predictive of CAD upsloping ST ↓ w/ rapid return to baseline usually due to ↑ HR & atrial repol artifact lead V_5 most sensitive; Δs isolated to inferior leads may be artifact location of ST ↓ does *not* localize ischemic territory

  STE: highly predictive of CAD & localizes; in aVR suggests LM CAD; nonspecific if in leads w/ prior Qw
- **Duke treadmill score** = exercise min - (5 × max ST dev) - (4 × angina index) [angina index = 0 none, 1 nonlimiting sxs, 2 limiting sxs]

Category	CAD	1-y mort	5-y survival
Low risk (≥5)	60% w/o signif stenosis	<1%	97%
Moderate risk (-10 to 4)	31% w/ 3VD or LM	2-3%	90%
High risk (≤-11)	74% w/ 3VD or LM	≥5%	65%

- **Imaging:** radionuclide defects or echocardiographic regional wall motion abnormalities reversible defect = ischemia; fixed defect = infarct; transient isch dilation = severe CAD false ⊕: breast → ant "defect" and diaphragm → inf "defect" false ⊖ may be seen if balanced (eg, 3VD) ischemia (global ↓ perfusion w/o regional Δs)

High-risk test results

- ECG: ST ↓ ≥2 mm *or* ≥1 mm in stage 1 *or* in ≥5 leads *or* ≥5 min in recovery; STE; VT
- Physiologic: ↓ or fail to ↑ BP, <4 METS, angina during exercise, Duke score ≤ -11; ↓ EF
- Radionuclide: ≥1 lg or ≥2 mod. reversible defects, transient LV cavity dilation, ↑ lung uptake
- High-risk test has PPV ~50% for LM or 3VD, ∴ consider coronary angio

Myocardial viability (*Circ* 2008;117:103; *Eur Heart J* 2011;31:2984 & 2011;32:810)

- Viable myocardium = dysfxn at rest, but not scarred and has potential for recovery
- Goal: identify hibernating or stunned myocardium that could regain fxn after revasc

Viability Test	Sens	Spec	Mechanism
MRI	~85%	~75%	Assesses cellular integrity
PET	~90%	~65%	Assesses cell metabolism
Dobut stress echo	~80%	~80%	Assesses contractile reserve
Myocard contrast echo	~85%	~50%	Assesses cellular integrity
Thallium: rest-redistrib or stress-reinjection	~85%	~55%	Assesses cellular integrity (K^+ analogue taken up by Na/K-ATPase)
Technetium-MIBI	~85%	~65%	Assesses cellular integrity (requires intact mitochondria)

- However, in Pts w/ ↓ EF, presence of viability did not identify differential clinical benefit from CABG vs med Rx (*NEJM* 2011;364:1617)

Coronary CT angio (CCTA; *NEJM* 2008;359:2324; *Circ* 2010;121:2509)

- High NPV to r/o CAD, but low PPV
- In Pts presenting with CP, presence of plaque sensitive (100%) but not specific (54%) for ACS, ∴ NPV 100%, PPV 17% (*JACC* 2009;53:1642). CCTA vs noninvasive fxnal test for ischemia → ↓ time to dx & LOS, but ↑ probability of cath/PCI, contrast exposure & ↑ radiation (*NEJM* 2012;366:1393 & 367:299; *JACC* 2013;61:880).
- In sx outPt, CCTA vs fxnal testing led to more radiation, coronary angiography & revascularization, but no difference in clinical outcomes (PROMISE *NEJM* 2015;372:1291)
- CCTA images may be limited if: HR >60-70 bpm, irregular rhythm, calcium deposition or stents (may create artifact), inability to breath hold 5 sec, vessel diameter < 1.5 mm. Image quality best at slower & regular HR (? give βB if possible, goal HR 55-60).
- Useful for assessing patency of bypass grafts

MRI angiography (*Lancet* 2012;379:453)

- Unlike CCTA, does not require iodinated contrast, HR control or radiation exposure. Can also assess LV fxn, enhancement (early = microvasc obstruction; late = MI). Limitations: cost, operator-dependent, long duration, ↓ spatial resolution.
- In head-to-head comparisons, CMRI and CCTA appear to have grossly comparable sensitivity and specificity (*JACC* 2005;46:92; *Annals* 2006;145:207)

Coronary artery calcium score (*NEJM* 2012;366:294; *JAMA* 2012;308:788)

- Quantifies extent of calcium; thus *estimates* plaque burden (but *not* % coronary stenosis)
- Compared w/ CCTA, CAC score assessment requires lower radiation exposure (1-2 mSv)
- CAC sensitive (91%) but not specific (49%) for presence of CAD; high NPV to r/o CAD

CAC Score	Suggested plaque burden
0	No disease
1-99	Mild disease
100-399	Moderate disease
>400	Severe disease

- ? value as screening test to r/o CAD in sx Pt (CACS <100 → 3% probability of signif CAD; but interpretation affected by age, gender)
- May provide incremental value to clinical scores for risk stratification (*JAMA* 2004;291:210). ACC/AHA guidelines note CAC assessment is reasonable in asx Pts w/ intermed risk (10-20% 10-y Framingham risk; ? value if 6-10% 10-y risk) (*Circ* 2010;122:e584).

STABLE ISCHEMIC HEART DISEASE

Epidemiology is U.S. (*Circ* 2015;131:e29)

- Prevalence: 20-39 y: <1%; 40-59 y: 5-6%; 60-79 y: 21% in ♂ & 11% in ♀; ≥80 y: 35% in ♂ & 19% in ♀; lifetime risk after age 40: 50% in men & 32% in women
- Ischemic heart disease (IHD) remains leading cause of death in both men & women

Workup (*Circ* 2012;126:e354)

- Initiate workup if suspected new dx of IHD or Δ in clinical status
- H&P, ECG (looking for ischemic or prior infarct Δs such as Qw, PRWP, ST or Tw abnl)

Pretest Likelihood of CAD (%) (*NEJM* 1979;300:1350; *Annals* 1993;118:81)

	Nonanginal (≤1 sx)		Atypical angina (2 sx)		Typical angina (all 3 sx)	
Age	Men	Women	Men	Women	Men	Women
35	3↔ 35	1 ↔ 19	8 ↔ 59	2 ↔ 39	30 ↔ 88	10 ↔ 78

45	9 ↔ 47	2 ↔ 22	21 ↔ 70	5 ↔ 43	51 ↔ 92	20 ↔ 79
55	23 ↔ 59	4 ↔ 21	45 ↔ 79	10 ↔ 47	80 ↔ 95	38 ↔ 82
65	49 ↔ 69	9 ↔ 29	71 ↔ 86	20 ↔ 51	93 ↔ 97	56 ↔ 84

Classic angina sx: substernal chest pain, provoked by exertion, relieved by rest or NTG. W/in each cell, 1st # is % for Pt w/o risk factors; 2nd is for Pt w/ DM, smoking, & hyperchol.

- **Noninvasive testing** (qv) if intermediate risk (ie, >10-20% & <80-90%). If Pt has low prob, then ↑ risk false ⊕; if very high prob, ⊖ test does not adeq r/o CAD, ∴ consider cor angio.
- **Coronary angio** if: high-risk noninv results (qv); very high pretest prob; refract angina; uncertain dx after noninvasive testing (& compelling need to determine dx), occupational need for definitive dx (eg, pilot) or inability to undergo noninvasive testing; survivor of SCD or life-threatening vent. arrhythmia; unexplained heart failure or ↓ EF; suspected spasm or nonatherosclerotic cause of ischemia (eg, anomalous coronary)

Optimal medical therapy (OMT) (*Circ* 2012;126:e354 & 2014;130:1749; HTN 2015;65:1372)

- **ASA** 75-162 βg/d; **βB** for 3 y post MI or if ↓ EF; **statin** (typically high intensity; see "Lipids")
- **ACEI** (or ARB) if HTN, DM, CKD or ↓ EF
- Risk factor targets: BP <140/90 (consider <130/80 if prior MI), Hb_{A1c} 7-9% (<7% if long life expect.), BMI 18.5-24.9 kg/m^2
- Smoking cessation; influenza vaccine
- Diet: ↑ veg, fruits, whole grains; ↓ sweets, sugar-sweetened bevs & red meat; sat fat 5-6% total cals, *trans* fat <1% total cals, chol <200 mg/d; Na ≤2400 mg/d (ideally ≤1500 mg/d)
- Exercise: ˜40 min moderate-to-vigorous physical activity 3-4x/wk

Medical therapies for symptomatic relief (*Circ* 2012;126:e354)

- **Beta blockers** 1st-line therapy
- **CCB** (verap/dilt or long-acting dihydro) or **long-acting nitrates:** add-on or if βB intolerant
- **Ranolazine** (↓ late inward Na+ current to ↓ myocardial demand): add-on or if βB intolerant

Coronary revascularization (*Circ* 2011;124:e574)

- If unacceptable angina despite max tolerated med Rx or if potential to improve survival
- OMT should be initial focus if stable & w/o critical anatomy & w/ normal EF
- Older studies showed survival benefit w/ revasc (CABG) vs med Rx (pre-statin era) if:

  LM (≥50% stenosis), 3VD (≥70% stenoses) espec if ↑ EF, 2VD w/ critical prox LAD, ? 1-2 VD w/ large area of viable, ischemic myocardium

Recent Studies of Revascularization in Modern Era of OMT

Compare	Trial	Pts	Result
PCI vs OMT	COURAGE[a]	1-3VD, EF >30%	PCI does *not* ↓ D/MI; faster sx resolution
	FAME-II[b]	≥1VD w/ FFR (qv) ≤0.8	PCI ↑ peri-PCI MI, but then 44% ↓ death/spont MI; ? greater benefit if FFR <0.65
CABG vs OMT	STITCH[c]	EF ≤35% (majority w/ 3VD)	CABG 20% ↓ CV death, no Δ in all-cause mortality
CABG vs PCI	SYNTAX[d]	3VD or LM	CABG ↓ D/MI & revasc but ± ↑ stroke High SYNTAX/SYNTAX II score[g] ID's those who benefit most from CABG
	PRECOMBAT[e]	LM	PCI ? noninferior but ↑ repeat revasc
	FREEDOM[f]	DM w/ ≥2VD	CABG ↓ D/MI, but ↑ stroke

[a] *NEJM* 2007;356:1503;

[b] *NEJM* 2014;371:1208;

[c] *NEJM* 2011;364:1607;

[d] *Lancet* 2013;381:629 & 639;

[e] *NEJM* 2011;364:1718;

[f] *NEJM* 2012;367:2375;

[g] www.syntaxscore.com

- LM or 3VD: CABG, espec if ↑ EF or DM; consider PCI if SYNTAX score ≤22 & high surg risk
- 2VD w/ prox LAD, ↓ EF, or extensive ischemia: CABG (espec if DM) or ? PCI
- ? 1VD (low FFR) w/ prox LAD + either ↓ EF or extensive ischemia: PCI or CABG (w/ LIMA)
- Exp't device to narrow coronary sinus ↓ angina (*NEJM* 2015;372:517)

LIPID DISORDERS

Measurements

- Lipoproteins = lipids (cholesteryl esters & triglycerides) + phospholipids + proteins include: chylomicrons, VLDL, IDL, LDL, HDL, Lp(a)
- Measure after 12-h fast; LDL is typically calculated w/ Friedewald equation:

  LDL-C = TC - HDL-C - (TG/5) [last term assumes TG:VLDL ratio = 5:1]; underestim. if TG >400 or LDL-C <70 mg/dL (*JAMA* 2013;310:2061); ∴ directly measure LDL-C

  Non-HDL-C (TC - HDL-C) and apoB are alternative nonfasting measures of risk

  Lipid levels stable up to 24 h after ACS and other acute illnesses, then ↓ and may take 6 wk to return to nl
- Metabolic syndrome (≥3 of following): waist ≥40" (♂) or ≥35" (♀); TG ≤150; HDL <40 mg/dL (♂) or <50 mg/dL (♀); BP ≤130/85 mmHg; fasting glc ≤100 mg/dL (*Circ* 2009;120:1640)
- Lp(a) = LDL particle bound to apo(a) via apoB; genetic variants a/w MI (*NEJM* 2009;361:2518)

Primary dyslipidemias

- Familial hypercholesterolemia (FH, 1:500): defective LDL receptor; ↑ ↑ chol, nl TG; ↑ CAD
- Familial defective apoB100 (1:1000): similar to FH
- Familial combined hyperlipidemia (1:200): polygenic; ↑ chol, ↑ TG, ↓ HDL; ↑ CAD
- Familial dysbetalipoproteinemia (1:10,000): ↑ chol & TG; xanthomas; ↑ CAD
- Familial hypertriglyceridemia (FHTG, 1:500): ↑ TG, ± ↑ chol, ↓ HDL, pancreatitis

Secondary Dyslipidemias

Category	Disorders
Endocrinopathies	Type 2 diabetes (↑ TG, ↓ HDL); lipodystrophy (↑ TG) Hypothyroidism (↑ LDL, ↑ TG); hyperthyroidism (↓ LDL) Cushing's syndrome & exogenous steroids (↑ LDL, ↑ TG)
Renal diseases	Renal failure (↑ LDL, ↑ TG); nephrotic syndrome (↑ LDL, ↑ TG)
Hepatic diseases	Cholestasis, PBC (↑ LDL); liver failure (↓ LDL); acute hepatitis (↑ TG)
Lifestyle	Obesity, sat & trans fat (↑ TG, ↓ HDL, ↑ LDL); sedentary lifestyle (↓ HDL); alcohol (↑ TG, ↑ HDL); tobacco (↓ HDL); anorexia (↑ LDL); very low-fat diet, high-refined-carb diet (↑ TG); preg (↑ LDL; ↑ TG)
Medications	Thiazides (↑ LDL, ↑ TG); βB (except carvedilol, ↑ TG, ↓ HDL); protease inhib (↑ TG); estrogens (↑ TG, ↑ HDL); androgens (↓ HDL); cyclosporine, amiodarone (↑ LDL); bile acid sequestrants, protease inhib, retin. acid, sirolimus, raloxifene, tamoxifen (↑ TG)

Physical exam findings

- Tendon xanthomas: seen on Achilles, elbows and hands; implies LDL >300 mg/dL
- Eruptive xanthomas: pimple-like lesions on extensor surfaces; implies TG >1000 mg/dL
- Xanthelasma: yellowish streaks on eyelids seen in various dyslipidemias
- Corneal arcus: common in older adults, imply hyperlipidemia in young Pts

Drug Treatment

Drug	↓ LDL	↑ HDL	↓ TG	Side effects/comments
Statins	20-60%	5-10%	10-25%	Doubling of dose → 6% further ↓ LDL. ↑ ALT in 0.5-3% (dose-dependent); ✓ before starting and then after as clinically indicated Myalgias <10% (not always ↑ CK), myositis 0.5%, rhabdo <0.1%, risk dose-dependent ↑ risk of DM (may be related to LDL-R; *JAMA* 2015;313:1029); screen if risk factors
Ezetimibe	15-20%	—	—	Well tolerated; typically w/ statin
Fibrates	5-15%	5-15%	35-50%	Myopathy risk ↑ w/ statin (gemfibrozil > fenofibrate). Dyspepsia, gallstones, ↑ Cr. ✓ renal fxn at baseline, 3 mo, q6mo.
Niacin	10-25%	~30%	40%	Flushing (less w/ sustained release; ASA preRx may ↓), hyperglycemia, ↑ UA. ✓ renal fxn, UA, glc ± HbA1c at baseline and q6mo or w/ uptitration.
Resins	20%	3-5%	↑	Bloating, binds other meds
Ω-3 FA	5% ↑	3%	25-50%	Dyspepsia, diarrhea, skin Δs, bleeding
PCSK9 inhibitors	40-65%	5-10%	15-25%	mAb inj SC q2w or q4w (*Lancet* 2012;380:2007 & *JACC* 2015;65:2638)
CETP inhibitors	~30%	140%	5-10%	*Investigational* (*NEJM* 2010;363:2406; *Lancet* 2015;386:452)

Treatment of LDL-C (*Lancet* 2014;384:607)

- **Statins:** every 1 mmol (39 mg/dL) ↓ LDL-C → 22% ↓ major vascular events (CV death, MI, stroke, revasc) in individuals w/ & w/o CAD (*Lancet* 2010;376:1670); ∴ *mainstay of therapy as potent, safe and well-tolerated*

- Consistent CV benefit even in individuals starting w/ LDL-C ≤60 mg/dL (*JACC* 2011;57:1666)
- No clear evidence to date to suggest any harm from achieving very low LDL-C levels
- Elevated hs-CRP *may* identify Pts who derive ↑ benefit (*NEJM* 2001;344:1959 & 2008;359:2195)
- Similar clinical benefit also seen w/ some older nonstatin Rxs (resins, fibrates, niacin) when sufficiently lowered LDL-C (*JACC* 2005;46:1855)
- **Ezetimibe:** ↓ major vascular events incl MI & stroke when added to statin post-ACS, w/ magnitude of benefit consistent w/ LDL-statin relationship (IMPROVE-IT, *NEJM* 2015;372:2387)
- **PCSK9 inhibitors:** ˜60% ↓ LDL on top of statin, as monoRx, and in FH (*EHJ* 2014;35:2249); prelim data w/ encouraging ↓ CV outcomes (*NEJM* 2015;372:1500), definitive trials ongoing

Treatment of HDL-C (*Lancet* 2014;384:618)

- Low levels of HDL-C associated with ↑ risk of MI
- However, Mendelian randomization studies do not support causal role (*Lancet* 2011;380:572)
- **Niacin:** in Pts w/ well-controlled LDL-C (<80 mg/dL) on a statin, minimally ↓ LDL, modestly ↑ HDL, and did not ↑ CV events (*NEJM* 2011;365:2255 & 2014;371:203)
- **CETP inhibitors:** one that ↑ HDL-C by 25% did not lead to clinical benefit in Pts w/ well-controlled LDL-C on a statin (*NEJM* 2012;367:2089); CV outcomes trials of inhibitors that ↑ HDL-C by 140% *and* ↑ LDL-C by ˜30% ongoing (*NEJM* 2010;363:2406; *JAMA* 2011;306:2099)

Treatment of hypertriglyceridemia (*Lancet* 2014;384:626)

- Reasonable to treat very high levels (>500- 1000 mg/dL) to ↓ risk of pancreatitis
- High levels of TG associated with ↑ risk of MI, but whether causal remains debated
- **Fibrates** (gemfibrozil & fenofibrate): mixed data in terms of ↑ vascular events, ? greater benefit if high TG (*Circ* 1992;85:37; *NEJM* 1999;341:410; *Lancet* 2005;366:1849; *NEJM* 2010;362:1563)
- **Fish oil** (containing Ω-3 fatty acids EPA & DHA): recent meta-analyses suggest supplementation w/o meaningful effect on CV events (*JAMA* 2012;308:1024)
- APOC3 inhibitors under study and ↑ TG by up to ˜70% (*NEJM* 2015;373:438)

Treatment of Lp(a)

- Consider ↓ to <50 mg/dL w/ niacin in intermed- to high-risk Pts (*EHJ* 2010;31:2844-53); however, benefit unclear espec if LDL-C well controlled (*JACC* 2014;63:520)

Guidelines (*Circ* 2014;129(Suppl 2):S1)

- Focus now on statin strategies, rather than achieving LDL-C goals
- Clinical atherosclerotic CV disease (ASCVD) includes h/o ACS, stable angina, arterial revasc, stroke, TIA, or PAD presumed to be of atherosclerotic origin
- 10-y CV Risk Score for CHD or stroke based on age, sex, race, SBP, TC, LDL, DM, tobacco, BP Rx; http://my.americanheart.org/cvriskcalculator
- Additional risk factors to consider include: LDL-C ≥160 mg/dL, genetic hyperlipid., FHx premature ASCVD, hsCRP >2 mg/L, CAC score ≥300 or ≥75th %ile, ABI <0.9.

2013 ACC/AHA Guideline of Treatment of Blood Cholesterol

Population	10-y CV risk	Statin Recommendation
Clinical ASCVD (ie, 2° prevention)	n/a	High intensity. If age >75 y, eval risk-benefit for high vs moderate intensity
LDL-C ≥190 mg/dL	n/a	High intensity
DM (type 1 or 2); age 40-75 y	≥7.5%	High intensity
	<7.5%	Moderate intensity
Age 40-75 y (and none of the above)	≥7.5%	High or moderate intensity
	5-<7.5%	Reasonable to offer moderate intensity
	<5%	Consider statin if additional risk factor

- If statin intolerant or LDL-C remains elevated despite high-intensity statin (as well as reinforcement of med adherence, lifestyle changes and exclusion of 2° causes of dyslipidemia) nonstatin LDL-lowering therapies remain reasonable
- If Pt does not tolerate high-intensity statin, consider dose reduction before d/c statin

Statin Doses & LDL-C Reduction

Intensity	↓ LDL-C	Rosuva	Atorva	Simva	Prava	Lova	Fluva	Pitava
High	≥50%	20-40	40-80	(80)				
Mod	30-50%	5-10	10-20	20-40	40-80	40	80	2-4
Low	<30%			10	10-20	20	20-40	1

Doses are in mg. Simva 80 mg has ↑ myopathy risk and should not be used unless dose already tolerated >12 mo.

ANGIOGRAPHY, PCI, & CABG

Precath checklist

- Document peripheral arterial exam (radial, femoral, DP, PT pulses; bruits); if plan for radial artery access, ✓ palmar arch intact (eg, w/ pulse oximetry & plethysmography), although value remains unproven (*JACC* 2014;63:1833)
- Ensure Pt can lie flat for several hours
- ✓ CBC, PT-INR (ideally ≤1.5), & Cr; blood bank sample
- NPO >6 h; IVF if appropriate (± bicarb; acetylcysteine no longer rec; see "CIAKI")

Vascular access

- Femoral artery commonly used; high puncture ↑ risk of retroperitoneal bleed; low puncture ↑ risk of peripheral arterial complic.; can access a synthetic graft if a few months old
- Radial artery: 33% ↓ major bleeding, trend to 15% ↓ in MACE & 28% ↓ mortality, espec if >80% of cases at center done radially (*Lancet* 2015;385:2465)

Periprocedural pharmacotherapy for PCI

- **Aspirin:** 325 mg × 1 (≥2 h prior to angio) → 81 mg qd
- **$P2Y_{12}$ inhibitor** *(choose one):*

  clopidogrel: 600 mg × 1 → 75 mg qd; preRx ↓ MACE (*JAMA* 2005;294:1224 & 2012;308:2507) prasugrel or ticagrelor (only in ACS, qv)

  cangrelor (IV, short-acting): ↓ early ischemic events vs clopi given w/o preload (*NEJM* 2013;368:1303)
- **GP IIb/IIIa inhibitor:** *consider adding* abciximab, eptifibatide, or tirofiban; data showing ↓ MACE largely before routine $P2Y_{12}$ inhibition and w/ UFH as anticoagulant. Remains reasonable espec if using clopidogrel and did not preRx.
- **Anticoagulant** *(choose one; typically* d/c'd *at end of* PCI*):*

  UFH: most common choice in U.S.

  bivalirudin: ↓ bleeding (espec vs UFH + GP IIb/IIIa inhib; *JAMA* 2015;313:1336), ± ↑ MI, ↑ stent thrombosis in STEMI (not mitigated by longer infusion), ↑ mortality in some but not all trials (*Lancet* 2014;384:599; MATRIX *NEJM* 2015); use if Pt has HIT enoxaparin (nb, cannot ✓ degree of anticoag)
- **Statin** (high-dose): PreRx ↓ peri-PCI myonecrosis (*Circ* 2011;123:1622) & ↓ risk of contrast-induced nephropathy (*JACC* 2014;63:71)

PCI options

- **Balloon angioplasty (POBA):** effective, but c/b dissection & elastic recoil & neointimal hyperplasia → restenosis; now reserved for small lesions & ? some SVG lesions
- **Bare metal stents (BMS):** ↓ elastic recoil → 33-50% ↓ restenosis & repeat revasc (to ˜10% by 1 y) c/w POBA; requires $P2Y_{12}$ inhibitor ≥4 weeks (ideally up to 6 mo)
- **Drug-eluting stents (DES)**

antiproliferative drug released over several weeks → ↓ neointimal hyperplasia ~75% ↓ restenosis, ~50% ↓ repeat revasc (to <5% by 1 y), no Δ D/MI (*NEJM* 2013;368:254)

delayed re-endothelialization & potentially proinflammatory polymers may cause ↑ in risk of late stent thrombosis; requires $P2Y_{12}$ inhibitor ≥6 mo

next generation DES (eg, w/ everolimus) w/ *lower* risk of stent thrombosis vs BMS (*Lancet* 2012;379:1393)

Other peri-PCI interventions

- **Fractional flow reserve (FFR):** ratio of max flow (induced by IV or IC adenosine) distal vs proximal to a stenosis; if used to guide PCI (ie, revasc only if FFR <0.8) → ↓ # stents & ↓ D/MI/revasc (*NEJM* 2009;360:213)
- Thrombus aspiration: small study showed manual aspiration of thrombus pre-PCI in STEMI ↓ mortality, but larger studies show no benefit and ↑ stroke (*Lancet* 2008;371:1915; *NEJM* 2013;369:1587 & 2015;372:1389)

Post-PCI complications

- Postprocedure ✓ vascular access site, distal pulses, ECG, CBC, Cr
- Vascular closure devices speed time to hemostasis and ↓ incidence of hematoma (*JAMA* 2014;312:1981)
- **Bleeding**

  hematoma/overt bleeding: **manual compression,** reverse/stop anticoag

  retroperitoneal bleed (if puncture above inguinal ligament)

  may p/w ↓ Hct ± flank or back pain; ↑ HR & ↓ BP late

  Dx w/ abd/pelvic CT (I^-)

  Rx: reverse/stop anticoag (d/w interventionalist), IV fluids/PRBC/plts as required; if bleeding uncontrolled, consult performing interventionalist or surgery

- **Vascular damage** (~1% of dx angio, ~5% of PCI; *Circ* 2007;115:2666)

  pseudoaneurysm: hematoma w/ continued communication to artery can present w/ triad of pain, expansile mass, systolic bruit; diagnose w/ U/S;

  Rx (if *pain* or >2 cm): U/S-directed thrombin injection (>95% success, depends on anatomy); surgical repair if very large or if minimally invasive Rx fails

  AV *fistula:* continuous bruit; Dx: U/S; Rx: surgical repair

  limb ischemia (emboli, dissection, clot): cool, mottled extremity, ↓ distal pulses; Dx: pulse volume recording (PVR), angio; Rx: percutaneous or surgical repair
- **Peri-PCI MI:** >5× ULN of Tn/CK-MB + either sx or ECG/angio/imaging Δs; Qw MI in <1%
- **Renal failure:** contrast-induced manifests w/in 24 h, peaks 3-5 d (see "CIAKI")
- **Cholesterol emboli syndrome**

  typically seen in middle-aged & elderly and w/ heavy burden of aortic atheroma multiple clinical manifestations (although may be delay between cath & s/s) including: intact distal pulses but livedo reticularis pattern and toe necrosis ("blue toe syndrome") renal failure: late and progressive (thus unlike CIAKI), ± eos in urine mesenteric ischemia: abd pain, GIB, pancreatitis

CNS: TIA, stroke, amaurosis fugax, Hollenhorst plaques (bright retinal lesion)

Dx: can only be confirmed by biopsy; may see ↑ circulating eos, ↓ complement, ↑ CRP, ↑ ESR, ↑ plts, ↑ fibrinogen

Rx: supportive; no clear benefit for anti-inflam or anticoagulant Rx

- **Stent thrombosis** (acute clot formation in stent): rare event, but high mortality can occur anytime between mins to yrs after PCI typically p/w ACS (often STEMI)

  typically due to either **mechanical problem** (stent underexpansion or unrecognized dissection, typically presents early) or **d/c of antiplt Rx** (espec if d/c both ASA & $P2Y_{12}$ inhib; *JAMA* 2005;293:2126)

- **In-stent restenosis** (neointimal hyperplasia): months after PCI, typically p/w gradual ↑ angina (10% p/w ACS). Due to combination of elastic recoil and neointimal hyperplasia; ↓ w/ DES vs BMS.

Duration of $P2Y_{12}$ inhibition

- In Pts w/ MI (qv), goal of antiplatelet therapy is ↑ CVD, MI, and stroke as well as rarer event of stent thrombosis. ∴ Long-term therapy *beyond* 12 mo is logical and has been shown to ↓ CV death, MI, and stroke (*NEJM* 2015;372:1791; *JACC* 2007;49:1982 & 2015;65:2211).
- In Pts w/ SIHD, concern for late (>30 d) stent thrombosis led to recs for 12-mo duration, but newer generation stents have lower risk of stent thrombosis
- Several small trials showed shorter duration of $P2Y_{12}$ inhibition (3-6 vs 12 mo) led to nonstatistically significant higher rates of MI and ST (but still infrequent) but less bleeding (*JACC* 2012;60:1340; *JAMA* 2013;310:2510; *EHJ* 2015;36:1252)
- Much larger DAPT trial showed that longer inhibition (30 vs 12 mo) led to 29% ↓ MACE and 71% ↓ ST (although rates and absolute risk reduction very low with newer generation stents), but ↑ bleeding and, in Pts w/ SIHD, marginally significant ↑ mortality (driven by non-CV mortality) (*NEJM* 2014;371:2155)

Need for premature discontinuation of antiplatelet therapy

- If possible, postpone major invasive procedures ≥1 mo after BMS or ≥3-6 mo after DES
- If not possible and high of risk bleeding during procedure, d/c prasugrel 7 d, clopidogrel 5 d, or ticagrelor 5 d (per prescribing information, but in major clinical trial, just ~3 d) prior to procedure. Continue ASA and resume $P2Y_{12}$ inhibitor w/ loading dose ASAP per surgery.
- If high-risk stent and bridging required, consider short-acting GP IIb/IIIa inhibitor (eptifi-batide or tirofiban) from 3 d until 4-6 h prior to surgery (*Circ* 2013;128:2785). Consider cangrelor (IV reversible $P2Y_{12}$ inhib) (*JAMA* 2012;307:265).

Advances in CABG technique

- **"Mini-CABG"** = minimally invasive. Thoracotomy or partial sternotomy rather than full sternotomy. Advantages include ↓ pain & ↓ LOS. May be on- or off-pump.
- **Off-pump** ("beating heart surgery"): avoids cardiopulmonary bypass but makes anastomotic suturing more challenging. In 1 study, ↑ CV death and ↓ graft patency at 12 mo c/w on-pump (*NEJM* 2009;361:1827); other studies w/ ≈ mortality w/ off- vs on-pump.
- **Robotic:** type of mini-CABG where endoscopic instruments inserted via small incisions to anastomose the

LIMA to the LAD on closed chest and beating heart

- **Hybrid procedures:** typically involves combo of LIMA-LAD mini-CABG with PCI of other vessels

ACUTE CORONARY SYNDROMES

Spectrum of Acute Coronary Syndromes

Dx	UA	NSTEMI	STEMI
Coronary thrombosis	Subtotal occlusion		Total occlusion
History	angina that is new-onset, crescendo or at rest; usually <30 min		angina at rest
ECG	± ST depression and/or TWI		ST elevations
Troponin/CK-MB	⊖	⊕	⊕⊕

Ddx (causes of myocardial ischemia/infarction other than atherosclerotic plaque rupture)

- **Nonatherosclerotic coronary artery disease**

  Spasm: Prinzmetal's variant, cocaine-induced (6% of CP + cocaine use r/i for MI)

  Dissection: spontaneous (vasculitis, CTD, pregnancy), aortic dissection with retrograde extension (usually involving RCA → IMI) or mechanical (catheter, surgery, trauma)

  Embolism (*Circ* 2015;132:241): AF, thrombus/myxoma, endocard., prosth valve; thrombosis

  Vasculitis: Kawasaki syndrome, Takayasu arteritis, PAN, Churg-Strauss, SLE, RA

  Congenital: anomalous origin from aorta or PA (coronary compressed), myocardial bridge (intramural segment)

- **Ischemic imbalance not due to plaque rupture** ("type 2" MI): ↑ myocardial O_2 demand (eg, ↑ HR, anemia, AS) or ↑ supply (hypotension, severe anemia)
- **Direct myocardial injury:** myocarditis; Takotsubo/stress CMP; toxic CMP; cardiac contusion

Clinical manifestations (*JAMA* 2005;294:2623)

- **Typical angina:** retrosternal pressure/pain/tightness ± radiation to neck, jaw or arms precip. by exertion, relieved by rest or NTG; in ACS, new-onset, crescendo or at rest; see "Chest Pain" for likelihood ratios for different sx
- **Associated symptoms:** dyspnea, diaphoresis, N/V, palpitations or lightheadedness
- Many MIs (˜20% in older series) are initially unrecognized b/c silent or atypical sx

- Atypical sxs (incl N/V & epig pain) may be more common with inferior ischemia
- Women may have ↑ freq of atypical sx vs men

Physical exam

- Signs of ischemia: S4, new MR murmur 2° pap. muscle dysfxn, paradoxical S_2, diaphoresis
- Signs of heart failure: ↑ JVP, crackles in lung fields, ⊕ S_3, HoTN, cool extremities
- Signs of other vascular disease: asymmetric BP (aortic dissection or subclavian disease), carotid or femoral bruits, ↓ distal pulses

ECG

- ✓ w/in 10 min of presentation, q15-30min × 1 h if initial ECG non-dx, w/ any Δ in sx, and routinely at 6-12 h; compare w/ baseline
- Signs of ischemia (*JAMA* 1998;280:1256)

  STE: generally ≥1 mm in ≥2 contiguous leads (see "STEMI" for details) new or presumed new (ie, not known to be old) LBBB w/ compelling H&P

  STD ≥0.5 mm (⊕ LR 3-5), TWI ≥2 mm (⊕ LR 2-3), hyperacute Tw
- Qw or PRWP may suggest prior MI, ∴ higher pretest probability of CAD
- Dx of STEMI if old LBBB (Sgarbossa's criteria): ≥1 mm STE *concordant* w/ direction of QRS (Se 73%, Sp 92%), STD ≥1 mm V_1-V_3 (Se 25%, Sp 96%) or STE ≥5 mm *discordant* w/ QRS (Se 31%, Sp 92%)

Localization of MI

Anatomic area	ECG leads w/ STE	Coronary artery
Septal	V_1-V_2	Proximal LAD
Anterior	V_3-V_4	LAD
Apical	V_5-V_6	Distal LAD, LCx or RCA
Lateral	I, aVL	LCx
Inferior	II, III, aVF	RCA (˜85%), LCx (˜15%)
RV	V_1-V_2 & V_4R (most Se)	Proximal RCA
Posterior	ST *depression* V_1-V_3 (= STE V_7-V_9 posterior leads)	RCA or LCx

If ECG non-dx and suspicion high, consider addt'l lateral (posterior) leads (V_7-V_9) to further assess distal LCx/RCA territory. Check right-sided precordial leads in patients with IMI to help detect RV involvement

(STE in V_4R most Se). STE in III > STE in II and lack of STE in I or aVL suggest RCA rather than LCx culprit in IMI.

Cardiac biomarkers

- Troponin (Tn) preferred over CK-MB
- ✓ Tn at baseline & 3-6 h after sx onset; may also ✓ beyond 6 h if high index of suspicion based on clinical presentation or ECGs or if sx Δ
- Rise to >99th %ile in approp. clinical setting dx of MI (see "Chest Pain")
- In Pts w/ ACS & ↓ CrCl, ↓ Tn still portends poor prognosis (*NEJM* 2002;346:2047)

Other potential dx tests

- If low prob, **stress test, CT angio** or rest perfusion imaging to r/o CAD (see "Chest Pain")
- TTE (new wall motion abnl) suggestive of ACS but not specific, as may be seen if old MI
- Coronary angio gold standard for evaluation of CAD

Prinzmetal's (variant) angina

- Coronary spasm → transient STE usually w/o MI (*but* MI, AVB, VT can occur)
- Pts usually young, smokers, ± other vasospastic disorders (eg, migraines, Raynaud's)
- Most frequent between midnight and early morning when vagal tone is highest
- Provocation testing: spasm can be precipitated at angio w/ IC ergonovine or acetylchol. positive test = severe narrowing w/ sx or ECG Δs; nonobstructive CAD typically seen; rarely done as risks include refractory/recurrent spasm or arrhythmia
- Noninvasive testing: hyperventilation, 12-lead Holter, exercise study
- Treatment: often initiated empirically without provocation testing: high-dose CCB (dilt, verap or nifed all roughly ≈) & standing nitrates (+SL prn) ? α-blockers/statins; d/c smoking

  avoid high-dose ASA (can inhibit prostacyclin & worsen spasm), nonselect βB, triptans
- Cocaine-induced vasospasm: use CCB, nitrates, ASA; ? avoid βB, but data weak and labetalol appears safe (*Archives* 2010;170:874; *Circ* 2011;123:2022)

Likelihood of ACS

Feature	High (any of below)	Intermediate (no high features, any of below)	Low (no high/inter. features, may have below)
History	Chest or L arm pain like prior angina, h/o CAD (incl MI)	Chest or arm pain age >70 y, male, diabetes	Atypical sx (eg, pleuritic, sharp or positional pain)
Exam	HoTN, diaphoresis, HF,	PAD or cerebrovas-	Pain reproduced on palp.

	transient MR	cular dis.	
ECG	New STD (≥1 mm) TWI in mult leads	Old Qw, STD (0.5-0.9 mm), TWI (>1 mm)	TWF/TWI (<1 mm) in leads w/ dominant R wave
Biomarkers	⊕ Tn or CK-MB	Normal	Normal

(Adapted from ACC/AHA 2007 Guideline Update for UA/NSTEMI, *Circ* 2007;116:e148)

Approach to triage

- If hx and initial ECG & Tn non-dx, repeat ECG q15-30min × 1 h & Tn 3-6 h after sx onset
- If remain nl and low likelihood of ACS, search for alternative causes of chest pain
- If remain nl, have ruled out MI, *but* if suspicion for ACS based on hx, then still need to r/o UA w/ stress test to assess for inducible ischemia (or CTA to r/o CAD);

  if low risk (eg, age ≤70; ø prior CAD, CVD, PAD; ø rest angina) can do before d/c from ED or as outPt w/in 72 h (0% mortality, <0.5% MI, *Ann Emerg Med* 2006;47:427)

  if not low risk, admit and initiate Rx for possible ACS and consider stress test or cath

Acute Anti-Ischemic and Analgesic Treatment

Nitrates (SL or IV) 0.3-0.4 mg SL q5min ×3, then consider IV if still sx	Use for relief of sx, control HTN or Rx of HF No clear ↓ in mortality *Caution* if preload-sensitive (eg, HoTN, AS, sx RV infarct); contraindic if recent PDE5 inhibit use
β-blockers eg, metop 25-50 mg PO q6h titrate slowly to HR 50-60 IV only if HTN and no HF	↓ ischemia & progression of UA to MI (*JAMA* 1988;260:2259) STEMI: ˜20% ↓ arrhythmic death or reMI, but 30% ↑ cardiogenic shock early (espec if signs of HF), & ∴ no Δ overall mortality (*Lancet* 2005;366:1622) In Pts w/o HF, IV βB prior to 1° PCI ↓ infarct size and ↑ EF (*Circ* 2013;128:1495) *Contraindic.* PR >0.24 sec, HR <60, 2°/3° AVB, severe bron-chospasm, s/s HF or low output, risk factors for shock (eg, >70 y, HR >110, SBP <120, late presentation STEMI)
CCB (nondihydropyridines)	If cannot tolerate βB b/c bronchospasm; otherwise has similar contraindications as βB Rx
Morphine	Relieves pain, ↓ anxiety, venodilation → ↓ preload ∴ use for persistent sx or CHF. Do not mask refractory sx. May delay onset of antiplatelet Rx (*JACC* 2014;63:630)
Oxygen	Use prn for resp distress or to keep S_aO_2 >90% ? ↑ infarct size in STEMI w/o hypoxia (*Circ* 2015;131:2143)

Other early adjunctive therapy

- **High-intensity statin therapy** (eg, atorvastatin 80 mg qd) ↓ ischemic events w/ benefit emerging w/in wks (*JAMA* 2001;285:1711 & *JACC* 2005;46:1405) ↓ peri-PCI MI (*JACC* 2010;56:1099); ↓ contrast-induced nephropathy (*JACC* 2014;63:71)
- **ACEI/ARB:** start once hemodynamics and renal function stable Strong indication for ACEI if heart failure, EF <40%, HTN, DM, CKD; ˜10% ↑ mortality, greatest benefit in ant. STEMI or prior MI (*Lancet* 1994;343:1115 & 1995;345:669)

  Start w/ low dose of short-acting (eg, captopril 6.25 mg tid), titrate up as tolerated ARB appear ≈ ACEI (*NEJM* 2003;349:20); give if contraindic to ACEI
- Ezetimibe, aldosterone blockade, and ranolazine discussed later (long-term Rx)
- IABP: can be used for refractory angina when PCI not available

NSTE-ACS (*Circ* 2014;130:e344)

Key issues are antithrombotic regimen and invasive vs conservative strategy

Antiplatelet Therapy

Aspirin 162-325 mg × 1, then 81 mg qd (non-enteric coated, chewable)	50-70% ↓ D/MI (*NEJM* 1988;319:1105) Low dose (˜81 mg) pref long term (*NEJM* 2010;363:930) If allergy, use clopi and/or desensitize to ASA

$P2Y_{12}$ (ADP receptor) inhibitor (choose one of the following in addition to ASA). Timing remains controversial. Some data support benefit of clopidogrel preRx prior to angiography (*JAMA* 2012;308:2507). Ticagrelor was given upstream in pivotal study. Prasugrel should be given once PCI planned (ie, anatomy defined). European guidelines recommend $P2Y_{12}$ inhibitor as soon as possible after presentation (*EHJ* 2011;32:2999).

• **Ticagrelor** 180 mg × 1 → 90 mg bid Reversible binding, but wait 3-5 d prior to surg Use only with ASA <100 mg qd	Preferred over clopidogrel More rapid and potent plt inhib c/w clopi 16% ↓ CVD/MI/stroke & 21% ↓ CV death c/w clopi; ↑ non-CABG bleeding (*NEJM* 2009;361;1045) Sensation of dyspnea (S_aO_2 & PFTs nl) and ventricular pauses; perhaps b/c blocks adenosine reuptake
• **Prasugrel** 60 mg × 1 at PCI → 10 mg qd (consider 5 mg/d if <60 kg) Wait 7 d prior to surgery	Use at time of PCI; preferred over clopidogrel More rapid and potent plt inhib c/w clopi 19% ↓ CVD/MI/stroke in ACS w/ planned PCI vs clopi, but ↑ bleeding (*NEJM* 2007;359:2001), incl fatal bleeds Not sup to clopi if med mgmt w/o PCI (*NEJM* 2012;367:1297) In NSTE-ACS, should be given at time of PCI and not upstream due to ↑ bleeding (*NEJM* 2013;369:999) Contraindic. if h/o TIA/CVA; ? avoid if >75 y

• **Clopidogrel**[*] 300-600 mg × 1 → 75 mg qd Requires ˜6 h to steady state	ASA+clopi → 20% ↓ CVD/MI/stroke vs ASA alone ↑ benefit if given hrs *prior* to PCI, but then if require CABG, need to wait >5 d after d/c clopi
• **Cangrelor** Only IV $P2Y_{12}$ inhibitor Rapid onset/offset; t½ 3-5 min	22% ↓ CV events (mostly peri-PCI MI and stent thrombosis) vs clopi 300 mg at time of PCI; no significant ↑ bleeding (*NEJM* 2013;368:1303) Unclear benefit if upstream clopi (*NEJM* 2009;361:2318) and no data vs prasugrel or ticagrelor
GP IIb/IIIa inhibitors (GPI) Abciximab: LD 0.25 mg/kg IV, then 0.125 mcg/kg/min Eptifibatide: LD 180 mcg/kg IV ×2, then 2 mcg/kg/min (½ dose if CrCl <50 mL/min) Tirofiban: LD 25 mcg/kg IV, then 0.15 mcg/kg/min (½ dose if CrCl <30 mL/min)	No clear benefit for routinely starting prior to PCI and ↑ bleeding (*NEJM* 2009;360:2176). Consider epti or tiro if refractory ischemia despite optimal Rx while awaiting angio. Consider in high-risk Pts (eg, large thrombus burden) at time of PCI, espec if using clopi and not preRx'd. Often administered 18-24 h post PCI, but shorter duration (˜2 h) may be as efficacious and with ↓ bleeding (*JACC* 2009;53:837); D/C eptifibatide/tirofiban ≥2-4 h and abciximab ≥12 h prior to urgent CABG.

[*]Utility of platelet function testing remains unproven (*JAMA* 2011;305:1097; *NEJM* 2012;367:2100), but studies underpowered. ˜30% pop has ↓ fxn *CYP2C*19 allele → ↑ CV events if PCI on clopi compared w/ wild type (*NEJM* 2009;360:354; *JAMA* 2010;304:1821).

Anticoagulant Therapy (choose one)

UFH: 60 U/kg IVB (max 4000 U) then 12 U/kg/h (max 1000 U/h initially) × 48 h or until end of PCI	24% ↓ D/MI (*JAMA* 1996;276:811) Titrate to aPTT 1.5-2× control (˜50-70 sec) Hold until INR <2 if already on warfarin
Enoxaparin (low-molec-wt heparin) 1 mg/kg SC bid (± 30 mg IVB) (qd if CrCl <30) × 2-8 d or until PCI	˜10% ↓ D/MI vs UFH (*JAMA* 2004;292:45,89). Can perform PCI on enox (*Circ* 2001;103:658), but ↑ bleeding if switch b/w enox and UFH.
Bivalirudin (direct thrombin inhibitor) 0.75 mg/kg IVB at PCI → 1.75 mg/kg/h	↓ bleeding (espec vs UFH + GPI), ± ↑ early MI (*Lancet* 2014;384:599). Use instead of UFH if HIT.
Fondaparinux (Xa inhibitor) 2.5 mg SC qd × 2-8 d	C/w enox, 17% ↓ death & 38% ↓ bleeding (*NEJM* 2006;354:1464). However, ↑ risk of catheter thrombosis; ∴ must supplement w/ UFH if PCI.

Coronary angiography (*Circ* 2014;130:e344)

- **Immediate/urgent coronary angiography** (w/in 2 h) if refractory/recurrent angina or hemodynamic or

electrical instability

- **Invasive (INV) strategy =** routine angiography w/in 72 h (*NEJM* 2009;360:2165)

  Early (w/in 24 h) if: ⊕ Tn, ST Δ, GRACE risk score (www.outcomes-umassmed.org/grace) >140

  Delayed (ie, acceptable anytime w/in 72 h) if no indication for early/immediate cath but has other high-risk predictors incl: diabetes, EF <40%, GFR <60, post-MI angina , TIMI Risk Score ≥3, GRACE score 109-140, PCI w/in 6 mo, prior CABG

  Invasive strategy leads to 32% ↓ rehosp for ACS, nonsignif 16% ↓ MI, no Δ in mortality c/w cons. (*JAMA* 2008;300:71); ↑ peri-PCI MI counterbalanced by ↓ ↓ in spont. MI; mortality benefit seen in some studies, likely only if cons. strategy w/ low rate of angio

  ↑ risk of death or MI if invasive strategy deferred beyond 72 h (*JAMA* 2003;290:1593)

- **Conservative (CONS) strategy =** selective angio. Medical Rx with pre-d/c stress test; angio only if recurrent ischemia or ⊕ ETT. *Indicated for:* low TIMI Risk Score, Pt or physician preference in absence of high-risk features, low-risk women (*JAMA* 2008;300:71).

TIMI Risk Score (TRS) for UA/NSTEMI (*JAMA* 2000;284:835)

Calculation of Risk Score		Application of Risk Score	
Characteristic	**Point**	**Score**	**D/MI/UR by 14 d**
Historical		0-1	5%
Age ≥65 y	1	2	8%
≥3 Risk factors for CAD	1	3	13%
Known CAD (stenosis ≥50%)	1	4	20%
ASA use in past 7 d	1	5	26%
Presentation		6-7	41%
Severe angina (≥2 episodes w/in 24 h)	1	Higher risk Pts (TRS ≥3) derive ↑ benefit from LMWH, GP IIb/IIIa inhibitors and early angiography (*JACC* 2003;41:89S)	
ST deviation ≥0.5 mm	1		
⊕ cardiac marker (troponin, CK-MB)	1		

RISK SCORE = Total points **(0-7)**

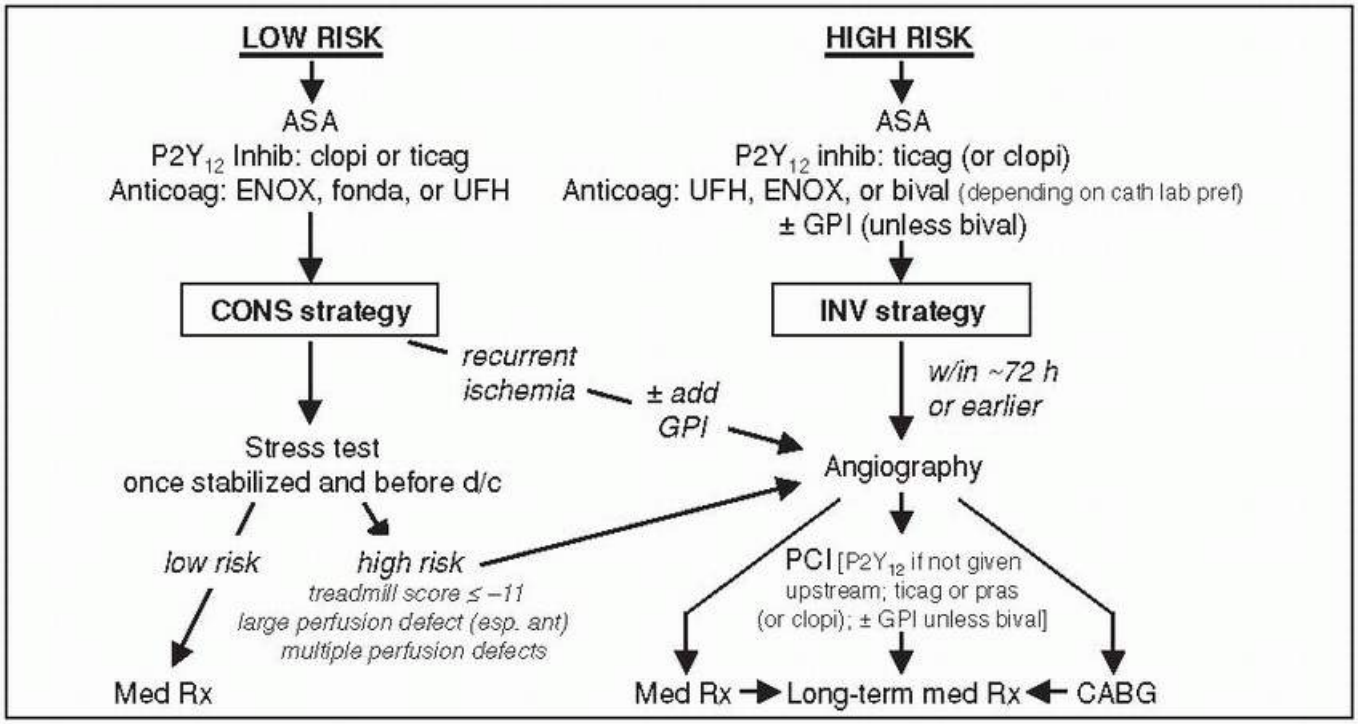


Figure 1-2 Approach to UA/NSTEMI

STEMI

Requisite STE (at J point)

- ≥2 contiguous leads w/ ≥1 mm (except for V_2-V_3: ≥2 mm in ♂ and ≥1.5 mm in ♀), or
- New or presumed new LBBB w/ compelling H&P, or
- True posterior MI: ST depression V_1-V_3 ± tall Rw w/ STE on posterior leads (V_7-V_9)

Reperfusion ("time is muscle")

- Immediate reperfusion (ie, opening occluded culprit coronary artery) is critical
- In PCI-capable hospital, goal should be **primary PCI w/in 90 min** of 1st medical contact
- In non-PCI-capable hospital, consider *transfer* to PCI-capable hospital (see below), o/w **fibrinolytic therapy** w/in 30 min of hospital presentation. If dx confirmed, administration of fibrinolytic in ambulance prior to arrival can be considered
- Do not let decision regarding *method* of reperfusion delay *time* to reperfusion

Primary PCI (*NEJM* 2007;356:47; *JACC* 2013;61:e78)

- Definition: immediate PCI upon arrival to hospital or transfer for immediate PCI
- Indications: STE + sx onset < 12 h; ongoing ischemia 12-24 h after sx onset; shock or severe HF regardless of time
- Superior to lysis: 27% ↓ death, 65% ↓ reMI, 54% ↓ stroke, 95% ↑ ICH (*Lancet* 2003;361:13)

- *Transfer* to center for 1° PCI superior to lysis (*NEJM* 2003;349:733). ∴ If initially seen at non-PCI capable hosp, transfer for PCI if door-in to door-out time can be ≤30 min and 1st medical contact to PCI time estimated to be ≤120 min.
- Thrombus aspiration: small study showed ↓ mortality, but larger studies show no benefit and ↑ stroke (*Lancet* 2008;371:1915; *NEJM* 2013;369:1587 & 2015;372:1389)
- Small studies have demonstrated ↓ MACE w/ complete revasc vs culprit artery alone (*NEJM* 2013; 369:1115; *JACC* 2015;65:963), large study ongoing; alternatively, could assess ischemia due to residual lesions w/ imaging stress (*Circ* 2011;124:e574)

Fibrinolysis vs Hospital Transfer for Primary PCI: Assess Time and Risk

1. **Time required for transport to skilled PCI lab:** door-to-balloon <120 min & [door-to-balloon]-[door-to-needle] <1 h favors transfer for PCI
2. **Risk from STEMI:** high-risk Pts (eg, shock) fare better with mechanical reperfusion
3. **Time to presentation:** efficacy of lytics ↓ w/ ↑ time from sx onset, espec >3 h
4. **Risk of fibrinolysis:** if high risk of ICH or bleeding, PCI safer option Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529)

Fibrinolysis

- Indic: STE/LBBB + sx <12 h + >120 min before PCI can be performed; benefit if sx >12 h less clear; reasonable if persist. sx & STE or hemodyn instability or large territory at risk
- Fibrin-spec lytics (TNK, TPA, RPA) ↑ artery patency vs streptokinase (*JACC* 2013;61:e78)
- Mortality ↓ ~20% in anterior MI or LBBB and ~10% in IMI c/w ø reperfusion Rx
- Prehospital lysis (ie, ambulance): further 17% ↓ in mortality (*JAMA* 2000;283:2686)
- ~1% risk of ICH; high-risk groups include elderly (~2% if >75 y), women, low wt
- Although age not contraindic., ↑ risk of ICH in elderly (>75 y) makes PCI more attractive
- Successful reperfusion gauged by sx & ECG: sudden CP resolution & ≥70% resolution of STE indicative of successful reperfusion; conversely, STE resolution <50% after 60-90 min should prompt consideration of rescue PCI (qv)

Contraindications to Fibrinolysis

Absolute contraindications	Relative contraindications
• Any prior ICH • Intracranial neoplasm, aneurysm, AVM	• Hx of severe HTN or SBP >180 or DBP >110 on presentation (? absolute contra. if low-risk MI)

- Ischemic stroke w/in 3 mo (unless acute w/in 4.5 h) or closed head trauma w/in 3 mo
- Active internal bleeding or known bleeding diathesis
- Head/facial trauma w/in 3 mo
- Head/spinal surgery w/in 2 mo
- Suspected aortic dissection
- Severe uncontrollable HTN
- For SK, SK Rx w/in 6 mo
- Ischemic stroke >3 mo prior
- Dementia
- Recent traumatic or prolonged CPR >10 min
- Trauma or major surgery w/in 3 wk
- Recent internal bleed (w/in 2-4 wk); active PUD
- Noncompressible vascular punctures
- Prior SK exposure (if considering SK)
- Pregnancy
- Current use of anticoagulants

Nonprimary PCI

- Facilitated or pharmacoinvasive PCI = upstream lytic, GPI or GPI + ½ dose lytic before PCI; in general no clear clinical benefit & ↑ bleeding (*Lancet* 2006;367:569; *NEJM* 2013;368:1379)
- Rescue PCI if shock, unstable, failed reperfusion or persistent sx (*NEJM* 2005;353:2758)
- Routine angio ± PCI w/in 24 h of successful lysis: ↓ D/MI/revasc (*Lancet* 2004;364:1045) and w/in 6 h ↓ reMI, recurrent ischemia, & HF compared to w/in 2 wk (*NEJM* 2009;360:2705);

  ∴ *if lysed at non-PCI capable hospital, consider transfer to PCI-capable hospital ASAP espec if high-risk presentation (eg, anterior MI, inferior MI w/ low EF or RV infarct, extensive STE or LBBB, HF, ↓ BP or ↑ HR)*
- *Late* PCI (median day 8) of occluded infarct-related artery: no benefit (*NEJM* 2006;355:2395)

Antiplatelet Therapy

Aspirin 162-325 mg × 1 (crushed/chewed) then 81 mg qd	23% ↓ in death (*Lancet* 1988;ii:349) Should not be stopped if CABG required
P2Y$_{12}$ inhibitor Give ASAP (do not wait for angio) Ticagrelor or prasugrel (if PCI) as detailed above Clopidogrel: 600 mg pre-PCI; 300 mg if lysis (no LD if >75 y) → 75 mg qd	*Lysis:* clopidogrel 41% ↑ in patency, 7% ↓ mort, no Δ major bleed or ICH (*NEJM* 2005;352:1179; *Lancet* 2005;366:1607); no data for pras or ticag w/ lytic *PCI:* prasugrel and ticagrelor ↓ CV events c/w clopi (*Lancet* 2009;373:723 & *Circ* 2010;122:2131) *Nb, antiplt effects delayed in STEMI Pts*
GP IIb/IIIa inhibitors abciximab, eptifibatide, tirofiban	*Lysis:* no indication (*Lancet* 2001;357:1905) *Peri-PCI:* 60% ↓ D/MI/UR (*NEJM* 2001;344:1895)

Adapted from ACC/AHA 2013 STEMI Guidelines Update (*Circ* 2013;127:529); *Lancet* 2013;382:633

Anticoagulant Therapy (choose one)

UFH 60 U/kg IVB (max 4000	No demonstrated mortality benefit ↑ patency with fibrin-specific lytics

U) 12 U/kg/h (max 1000 U/h initially)	Titrate to aPTT 1.5-2× control (˜50-70 sec)
Enoxaparin *Lysis:* 30 mg IVB → 1 mg/kg SC bid (adjust for age >75 & CrCl) *PCI:* 0.5 mg/kg IVB	*Lysis:* 17% ↓ D/MI w/ ENOX × 7 d vs UFH × 2 d (*NEJM* 2006;354;1477) *PCI:* ↓ D/MI/revasc and ≈ bleeding vs UFH (*Lancet* 2011;378:693)
Bivalirudin 0.75 mg/kg IVB → 1.75 mg/kg/hr IV (ongoing research on prolonged infusions)	*PCI:* ↓ bleeding (espec vs UFH + GP IIb/IIIa inhib), ± ↑ MI, ↑ stent thromb (not mitigated by longer infusion), ↓ mortality in some but not all trials (*Lancet* 2014;384:599; *JAMA* 2015;313:1336; MATRIX NEJM 2015)
Fondaparinux 2.5 mg IVB → 2.5 mg SC qd Contraindic if CrCl ≤30 mL/min	*Lysis:* superior to placebo & to UFH, with less bleeding (*JAMA* 2006;295;1519) *PCI:* risk of catheter thromb.; should not be used

Adapted from ACC/AHA 2013 STEMI Guidelines (*Circ* 2013;127:529); *Lancet* 2013;382:633

Intraaortic Balloon Pump (IABP) Counterpulsation

- Inflates during diastole and deflates during systole to ↑ coronary flow and ↑ afterload
- *Routine* use in high-risk STEMI → ↑ stroke/bleeds w/o Δ in survival, infarct size or EF (*EHJ* 2009;30:459; *JAMA* 2011;306:1329)
- In cardiogenic shock, no survival benefit w/ IABP if early revasc (*NEJM* 2012;367:1287); 18% ↓ death in Pts w/ cardiogenic shock treated with lytic (*EHJ* 2009;30:459)

LV failure (˜25%)

- Diurese to achieve PCWP 15-20 → ↑ pulmonary edema, ↓ myocardial O_2 demand
- ↓ Afterload → ↑ stroke volume & CO, ↓ myocardial O_2 demand can use IV NTG or nitroprusside (risk of coronary steal) → short-acting ACEI
- Inotropes if HF despite diuresis & ↓ afterload; use dopamine, dobutamine or milrinone
- **Cardiogenic shock** (˜7%) = MAP < 60 mmHg, CI <2 L/min/m^2, PCWP >18 mmHg; inotropes, mech support [eg, VAD, IABP (see above)] to keep CI >2; pressors to keep MAP >60; if not done already, coronary revasc (*NEJM* 1999;341:625)

IMI complications (*Circ* 1990;81:401; *NEJM* 1994;330:1211; *JACC* 2003;41:1273)

- **Heart block** (˜20%, occurs because RCA typically supplies AV node) 40% on present., 20% w/in 24 h, rest by 72 h; high-grade AVB can develop abruptly Rx: atropine, epi, aminophylline (100 mg/min × 2.5 min), temp pacing wire
- **RV infarct** (proximal RCA occlusion → compromised flow to RV marginal branch) Angiographically in 30-50%, but only ½ of those clinically signif. HoTN; ↑ JVP, ⊕ Kussmaul's; 1 mm STE in V_4R; RA/PCWP ≥0.8;

RV dysfxn on TTE

Rx: optimize preload (RA goal 10-14, *BHJ* 1990;63:98); ↑ contractility (dobutamine); maintain AV synchrony (pacing as necessary); reperfusion (*NEJM* 1998;338:933); mechanical support (IABP or RVAD); pulmonary vasodilators (eg, inhaled NO)

Mechanical complications (incid. <1% for each; typically occur a few days post-MI)

- **Free wall rupture:** ↑ risk w/ lysis, large MI, ↑ age, ♀, HTN; p/w PEA or hypoTN, pericardial sx, tamponade; Rx: volume resusc., ? pericardiocentesis, inotropes, **surgery**
- **VSD:** large MI in elderly; AMI → apical VSD, IMI → basal septum; 90% w/ harsh murmur ± thrill (*NEJM* 2002;347:1426); Rx: diuretics, vasodil., inotropes, IABP, **surgery,** perc. closure
- **Papillary muscle rupture:** more common after inf MI (PM pap. muscle supplied by PDA alone) than ant MI (AL pap. muscle supplied by diags & OMs); 50% w/ new murmur, rarely a thrill, → *v* wave in PCWP tracing; asymmetric pulmonary edema on CXR (often worse in RUL due to direction of jet). Rx: diuretics, vasodilators, IABP, **surgery.**

Arrhythmias post-MI

- Treat as per ACLS for unstable or symptomatic bradycardias & tachycardias
- **AF** (10-16% incidence): βB or amio, ± digoxin (particularly if HF), heparin
- **VT/VF:** lido or amio × 6-24 h, then reassess; ↑ βB as tol., replete K & Mg, r/o ischemia; early monomorphic (<48 h post-MI) does *not* carry bad prognosis. Beyond 48 h, VT/VF a/w worse prognosis → consider wearable defibrillator (qv).
- Accelerated idioventricular rhythm (AIVR): slow VT (<100 bpm), often seen after successful reperfusion; typically self-terminates and does not require treatment
- May consider ***backup* transcutaneous pacing** (TP) if: 2° AVB type I, BBB
- **Backup TP *or* initiate transvenous pacing** if: 2° AVB type II; BBB + AVB
- **Transvenous pacing** (TV) if: 3° AVB; new BBB + 2° AVB type II; alternating LBBB/RBBB (can bridge w/ TP until TV, which is best accomplished under fluoroscopic guidance)

Other Post-MI Complications

Complication	Clinical features	Treatment
LV thrombus	~30% incid. (espec lg antero-apical MI)	Anticoagulate × 3-6 mo
Ventricular aneurysm	Noncontractile outpouching of LV; 8-15% incid. (espec ant); persist STE	Surgery or perc repair if HF, thromboemboli, arrhythmia

Ventricular pseudoaneurysm	Rupture → sealed by thrombus and pericardium (espec in inf). Typically w/ narrow neck as c/w true aneurysm; Dx w/ cardiac MRI, CTA, or TEE.	Urgent surgery (or percutaneous repair)
Pericarditis	10-20% incid.; 1-4 d post-MI ⊕ pericardial rub; ECG Δs rare	High-dose ASA > aceta., colchicine, narcotics; minimize anticoag
Dressler's syndrome	<4% incid.; 2-10 wk post-MI fever, pericarditis, pleuritis	High-dose aspirin, NSAIDs

Prognosis

- In registries, in-hospital mortality is 6% w/ reperfusion Rx (lytic or PCI) and ~20% w/o
- Predictors of mortality: age, time to Rx, anterior MI or LBBB, heart failure (*Circ* 2000;102:2031)

Killip Class

Class	Definition	Mort.
I	no CHF	6%
II	⊕ S3 and/or basilar rales	17%
III	pulmonary edema	30-40%
IV	cardiogenic shock	60-80%

(*Am J Cardiol* 1967;20:457)

Forrester Class Mortality

		PCWP (mmHg)	
		<18	>18
CI	>2.2	3%	9%
	≤2.2	23%	51%

(*NEJM* 1976;295:1356)

TIMI Risk Score for STEMI

Characteristic	Points	Characteristic (cont)	Points	Score	30-d death
Age 65-74/≥75 y	2/3	Ant MI or new LBBB	1	0-2	˜1-2%
SBP <100 mmHg	3	h/o DM, HTN or angina	1	3-4	˜4-6%
HR >100 bpm	2	Wt <67 kg	1	5-6	˜10-15%
Killip class II-IV	2	Time to Rx >4 h	1	≥7	≥20%

(*JAMA* 2001;286:1356)

PREDISCHARGE CHECKLIST AND LONG-TERM POST-ACS MANAGEMENT

Risk stratification

- Stress test if anatomy undefined; consider stress if signif residual CAD post-PCI of culprit
- Assess LVEF prior to d/c; EF ↑ ˜6% in STEMI over 6 mo (*JACC* 2007;50:149)

Medications (barring contraindications)

- **Aspirin:** 81 mg daily
- **$P2Y_{12}$ inhib** (ticagrelor or prasugrel preferred over clopi): treat for *at least* 12 mo Prolonged Rx beyond 12 mo → ↓ CV death, MI, & stroke (& stent thrombosis) w/ ↑ in bleeding, but no ↑ fatal bleeding or ICH. For Rx beyond 1st 12 mo, comparable efficacy w/ ticagrelor 90 or 60 mg bid, better safety & tolerability with 60 bid (*NEJM* 2015;372:1791; *JACC* 2007;49:1982 & 2015;65:2211).

  Some PPIs interfere w/ biotransformation of clopi and ∴ plt inhibition, but no convincing impact on clinical outcomes (*Lancet* 2009;374:989; *NEJM* 2010;363:1909); use w/PPIs if h/o GIB or multiple GIB risk factors (*JACC* 2010;56:2051)
- **β-blocker:** 23% ↓ mortality after MI
- **Statin:** high-intensity lipid-lowering (eg, atorvastatin 80 mg, *NEJM* 2004;350:1495)
- **Ezetimibe:** ↓ CV events including MI and ischemic stroke when added to statin (IMPROVE-IT, *NEJM* 2015;372:1500)
- **ACEI:** lifelong if HF, ↓ EF, HTN, DM; 4-6 wk or at least until hosp. d/c in all STEMI ? long-term benefit in CAD w/o HF (*NEJM* 2000;342:145 & 2004;351:2058; *Lancet* 2003;362:782)
- **Aldosterone antag:** 15% ↓ mortality if EF <40% & either s/s of HF or DM; contraindic if renal dysfxn (Cr >2.5 in men, >2 in women) or K >5 (*NEJM* 2003;348:1309)

- Nitrates: standing if symptomatic; SL NTG prn for all
- Ranolazine: inhibits late inward Na current, prevents intracellular Ca overload; ↓ recurrent ischemia (*JAMA* 2007;297:1775)
- Oral anticoagulants: if warfarin needed in addition to ASA/clopi (eg, AF or LV throm-bus), target INR 2-2.5. ? stop ASA if at high bleeding risk on triple Rx (*Lancet* 2013;381:1107). Not FDA approved: low-dose rivaroxaban (2.5 mg bid) in addition to ASA & clopi → 16% ↓ D/MI/stroke and 32% ↓ all-cause death, but ↑ major bleeding and ICH (*NEJM* 2012;366:9).
- NSAIDs/COX2 inhib relatively contraindic b/c ? ↑ death, MI, HF, rupture (*Circ* 2006;113:2906)

ICD (*NEJM* 2008;359:2245)

- If sust. VT/VF >2 d post-MI not due to reversible ischemia; consider wearable defibril-lator or ICD (*JACC* 2014;130:94)
- Indicated in 1° prevention of SCD if post-MI w/ EF ≤30-40% (NYHA II-III) or ≤30-35% (NYHA I); need to wait ≥40 d after MI (*NEJM* 2004;351:2481 & 2009;361:1427)

Risk factors and lifestyle modifications (*Circ* 2014;129(Suppl 2):S1 & S76)

- Low chol. (<200 mg/d) & fat (<7% saturated) diet; ? Ω-3 FA
- Traditional LDL-C goal <70 mg/dL; new recs w/o LDL-C target, rather simply high-intensity statin; may change w/ IMPROVE-IT trial showing that lower is better (lower CV event rate in arm with achieved LDL-C of 54 vs 70 mg/dL)
- BP <140/90 and consider <130/80 mmHg (HTN 2015;65:1372); smoking cessation
- If diabetic, tailor HbA1c goal based on Pt (avoid TZDs if HF)
- Exercise (30-60 min 5-7×/wk); cardiac rehab; BMI goal 18.5-24.9 kg/m^2
- Influenza & pneumococcal vaccination (*Circ* 2006;114:1549; *JAMA* 2013;310:1711); screen for depression

CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Goal: characterize risk of Pt & procedure → appropriate testing (ie, results will Δ management) and interventions (ie, reasonable probability of → risk of MACE)

Preoperative assessment

- Clinical assessment: evidence of active cardiac disease and/or risk factors
- Functional capacity (METs)
- Surgery-specific risk

Clinical Assessment

Active cardiac conditions	Clinical risk factors
• MI w/in 30 d or current unstable or severe angina	• h/o ischemic heart

- Decompensated HF
- Significant arrhythmia (eg, Mobitz II, high-grade AVB, 3° AVB, new or sx VT, SVT w/ HR >100, sx brady)
- Severe AS or sx MS

disease
- h/o congestive HF
- h/o stroke or TIA
- Diabetes on insulin
- Renal insuffic. (Cr >2 mg/dL)

Functional Capacity

1-4 METs (poor)	4-10 METs (moderate-to-good)	>10 METs (excellent)
• ADLs • Walk indoors • Walk 1-2 level blocks	• Climb a flight of stairs/hill • Walk briskly; heavy housework • Golf, doubles tennis	• Strenuous sports

Surgery-Specific Risk

High (>5% risk)	Intermediate (1-5%)	Low (<1%)
• Aortic or other major vascular • Peripheral vasc.	• Intrathoracic; intraperitoneal; prostate & major urologic • CEA; head & neck • Orthopedic	• Endoscopic • Breast; superficial • Cataract; ambulatory • Dental

Noninvasive Testing Result

High risk	Intermediate risk	Low risk
Ischemia at <4 METs *manifested* by ≥1 of: • Horiz/down ST ↓ ≥*1* mm or STE • ≥5 abnl leads or ischemic ECG Δs lasting >3 min after exertion • SBP ↓ 10 mmHg or typical angina	***Ischemia at* 4-6 *METs*** *manifested by ≥ 1 of:* • Horiz/down ST ↓ ≥1 mm • 3-4 abnl leads • 1-3 min after exertion	***No ischemia or at* >7 METs w/** • ST ↑ ≥1 mm or • 1-2 abnl leads

Imaging with excellent NPV, poor PPV. Consider if high-risk patient.

- **Revised Cardiac Risk Index** (RCRI): 6 risk factors = 5 clinical risk factors above and type of surgery

(intrathoracic, intra-abd, or suprainguinal vascular) (*Circ* 1999;100:1043) # of risk factors predicts risk of MACE: ≤1 RF → <1%, 2 RFs → 6.6%, ≥3 RFs → 11%

- Comorbidity indices (eg, Charlson index) may predict mortality (*Am J Med Qual* 2011;26:461)

Preoperative testing (*Circ* 2014;130:e278)

- ECG if known cardiac disease and possibly reasonable in all, except if low-risk surgery
- TTE if any of the following and prior TTE > 12 mo ago or prior to Δ in sx:

  dyspnea of unknown origin

  hx of HF w/ ↑ dyspnea

  suspected valvular disease (eg, murmur on exam)

  ≥moderate stenosis/regurg
- Stress test (usually pharmacologic) if:

  active cardiac issues where stress testing is indicated (qv), or not low-risk surgery, RCRI ≥2, poor or unknown fxnal capacity, and results *will Δ mgmt* (ie, modify or delay surgery, undergo coronary revascularization, etc.) overall low PPV to predict periop CV events
- Angiography: based on noninvasive stress results for standard indications, although systematic angio ↓ 2-5 y mortality in Pts undergoing vascular surgery (*JACC* 2009;54:989)
- ? consider CXR & ECG in preop evaluation of severely obese Pts (*Circ* 2009;120:86)

Coronary artery disease

- If possible, wait ˜60 d after MI in the absence of revascularization before elective surgery
- After PCI: delay elective surgery 14 d after balloon angioplasty, 30 d after BMS implantation, and ideally 6 mo after DES implantation

- Coronary revascularization should be based on standard indications (eg, ACS, refractory sx, lg territory at risk). Has not been shown to Δ risk of death or postop MI when done prior to elective vasc. surgery based on perceived cardiac risk (*NEJM* 2004;351:2795) or documented extensive ischemia (*AJC* 2009;103:897).

Heart failure

- Decompensated HF should be optimally treated prior to elective surgery
- ↓ EF (<30%) associated with poor outcomes
- 30-d CV event rate: symptomatic HF > asx HFrEF > asx HFpEF > no HF

Valvular heart disease

- If meet criteria for valve intervention (qv), do so before elective surgery (postpone if necessary)
- If severe valve disease and surgery urgent, intra- & postoperative hemodynamic monitoring reasonable (espec for AS, since at ↑ risk even if sx not severe; be careful to maintain preload, avoid hypotension, and watch for atrial fibrillation)
- If severe AS and Pt not eligible for or impractical to do AVR prior to noncardiac surgery, balloon aortic valvuloplasty (BAV) and transcatheter aortic valve replacement (TAVR) can be considered but not routinely

recommended (*Circ* 2008;118:e523)

Cardiac implantable electronic devices (CIEDs)

- Includes PPM, CRT, ICD
- Should be discussion between surgical team & CIED team regarding: need for device (eg, complete heart block) & consequences if interference w/ fxn likelihood of electromagnetic interference consideration of reprogramming, magnet use, etc.

Pre- & perioperative pharmacologic management

- **ASA:** continue in Pts w/ existing indication. Initiation just prior to surgery does not ↓ 30-d ischemic events and ↑ bleeding (*NEJM* 2014;370:1494), but Pts w/ recent stents excluded.
- **Dual antiplatelet therapy** in Pts undergoing urgent surgery: continue 4-6 wk after PCI (BMS or DES) unless risk of bleeding > benefit of prevention of stent thrombosis. If must discontinue ADP receptor blocker, continue ASA and restart ADP receptor blocker ASAP.
- **β-blockers** (*Circ* 2009;120:2123; *JAMA* 2010;303:551; *Am J Med* 2012;125:953) Continue βB in Pts on them chronically. Do not discontinue βB abruptly postop, as may cause sympathetic activation from withdrawal. Use IV agents peri-operatively if Pt unable to take PO.

  In terms of initiating βB, conflicting evidence; may depend on how administered. Some studies show ↓ death & MI (*NEJM* 1996;335:1713 & 1999;341:1789), another showed ↓ MI, but ↑ death & stroke and ↑ bradycardia/HoTN (*Lancet* 2008;371;1839).

  ? consider initiating if intermed- or high-risk ⊕ stress test, or RCRI ≥3, espec if vasc surgery

  Ideally initiate at least 1 wk prior to surgery, use low-dose, short-acting βB, and titrate slowly and carefully to achieve desired individual HR and BP goal (? HR ~55-65). Avoid bradycardia and HoTN.
- **Statins:** ↓ ischemia & CV events in Pts undergoing vascular surg (*NEJM* 2009;361:980); may reduce AF, MI, LOS in statin-naïve Pts (*Arch Surg* 2012;147:181). Consider in Pts w/ a clinical risk factor undergoing non-low-risk surgery.
- ACEI/ARB: may cause HoTN perioperatively. If held before surgery, restart ASAP.
- Amiodarone: ↓ incidence of postop AF

  oral (eg, 600 mg qd × 7 d preop, then 200 mg qd until discharge) & IV regimens equivalent but effective only if initiated ≥1 d prior to surgery (*Pacing Clin Electrophysiol* 2013;36:1017)

  cardiac surgery: ↓ postop AF, length of stay & cost (*NEJM* 1997;337:1785) thoracic surgery: ↓ postop AF but *not* length of stay or cost (*J Thorac* CV *Surg* 2010;140:45; *Ann Thorac Surg* 2012;94:339; *Eur J Cardiothorac Surg* 2014;45:120). Not advised if severe lung disease or undergoing pneumonectomy (*Ann Thorac Surg* 2011;92:1144).

Postoperative monitoring

- ✓ Postop ECG if known CAD or high-risk surgery. Consider if >1 risk factor for CAD.
- ✓ Postop troponin only if new ECG Δs or chest pain suggestive of ACS. Elevated Tn postop predicts mortality, but may simply be a marker for underlying CAD (*Annals* 2011;154:523; *JAMA* 2012;307:2295). Routine ✓ postop in all Pts (even just high-risk Pts) has not been proven to modify outcomes and it is not routinely recommended.

Myocardial, Valvular, and Pericardial Disease

HEART FAILURE

Definitions (*Braunwald's Heart Disease*, 10th ed., 2014)

- Failure of heart to pump blood forward at sufficient rate to meet metabolic demands of peripheral tissues, or ability to do so only at abnormally high cardiac filling pressures
- Low output (↓ cardiac output) vs high output (↑ stroke volume ± ↑ cardiac output)
- Left-sided (pulmonary edema) vs right-sided (↑ JVP, hepatomegaly, peripheral edema)
- Backward (↑ filling pressures, congestion) vs forward (impaired systemic perfusion)
- Systolic (inability to expel sufficient blood) vs diastolic (failure to relax and fill normally)
- Reduced (HFrEF) vs preserved (HFpEF) left ventricular ejection fraction
- Some degree of systolic and diastolic dysfxn may occur regardless of ejection fraction

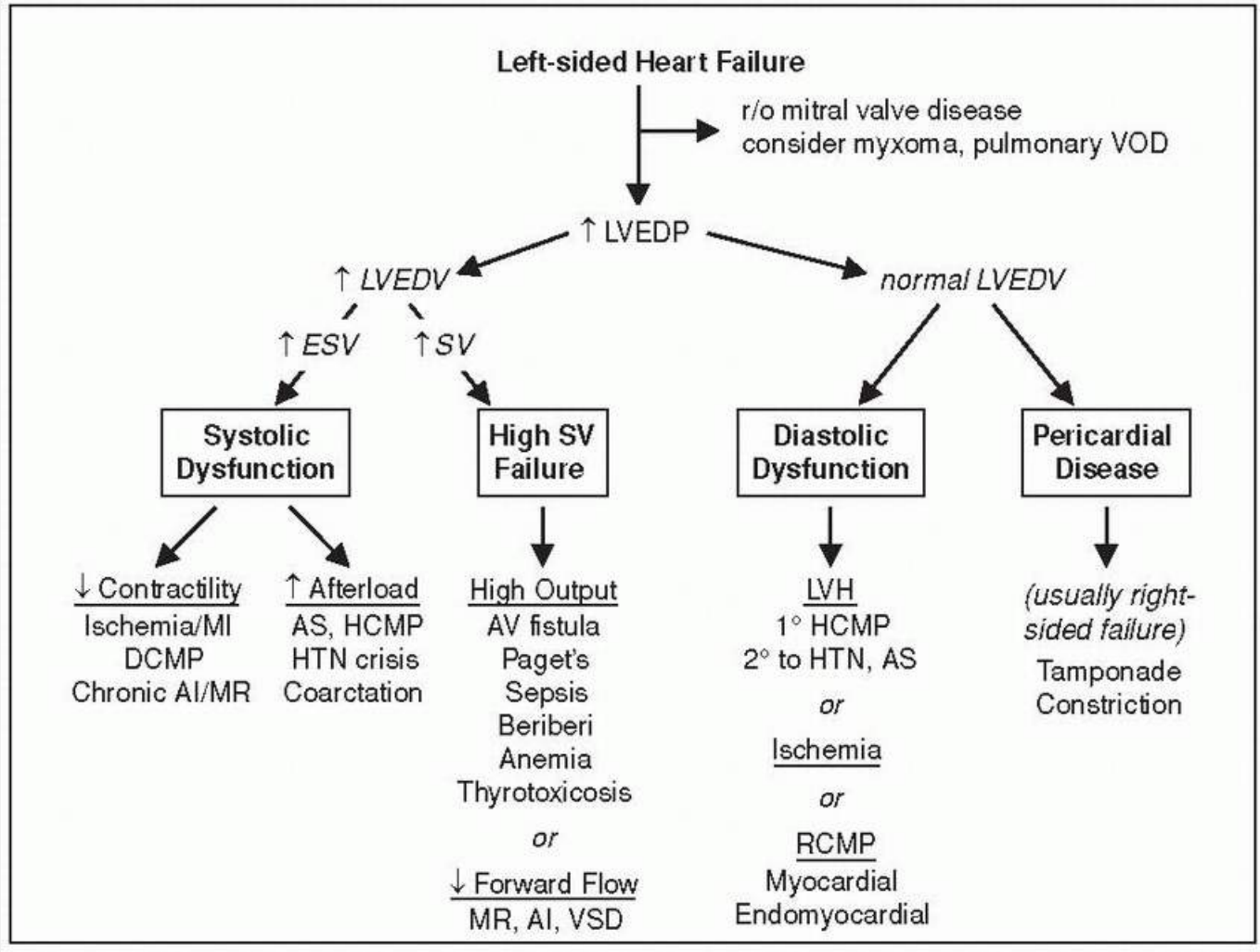


Figure 1-3 Approach to left-sided heart failure

History

- Low output: fatigue, weakness, exercise intolerance, Δ MS, anorexia
- Congestive: dyspnea, weight gain;

left-sided → orthopnea, paroxysmal nocturnal dyspnea

right-sided → peripheral edema, RUQ discomfort, bloating, early satiety

Stages in the Development of Heart Failure (*Circ* 2009;119:e391)

- A: At high **risk for HF**, but w/o structural heart disease or symptoms of HF
- B: **Structural heart disease**, but w/o signs or symptoms of HF
- C: Structural heart disease w/ prior or current **symptoms of HF**
- D: **Refractory heart failure** requiring specialized intervention

Functional classification (New York Heart Association class)

- Class I: no sx w/ ordinary activity; class II: sx w/ ordinary activity;

  class III: sx w/ minimal activity; class IV: sx at rest

Physical exam ("2-minute" hemodynamic profile; *JAMA* 1996;275:630 & 2002;287:628)

- **Congestion ("dry" vs "wet")**

  ↑ JVP (˜80% of the time RAP > 10 mmHg → PCWP >22 mmHg; *JHLT* 1999;18:1126)

  ⊕ hepatojugular reflux: ≥4 cm ↑ in JVP that persists for ≥15 sec w/ abdominal pressure Se/Sp 73/87% for RA >8 and Se/Sp 55/83% for PCWP >15 (*AJC* 1990;66:1002)

  Abnl Valsalva response: square wave (↑ SBP w/ strain), no overshoot (no ↑ BP after strain) S_3 (in Pts w/ HF → ˜40% ↑ risk of HF hosp. or pump failure death; *NEJM* 2001;345:574) rales, dullness at base 2° pleural effus. (*often absent* in chronic HF due to lymphatic compensation) ± hepatomegaly, ascites and jaundice, peripheral edema
- **Perfusion ("warm" *vs* "cold"): narrow pulse pressure (<25% of SBP) → CI <2.2 (91% Se, 83% Sp; *JAMA* 1989;261:884)**; other signs of low perfusion include soft S_1 (↑ dP/dt), pulsus alternans, cool & pale extremities, ↓ UOP, muscle atrophy
- Other signs to look for: periodic breathing/Cheyne-Stokes resp., abnl PMI (diffuse, sustained or lifting depending on cause of HF), S_4 (diast. dysfxn), murmur (valvular disease, ↑ MV or TV annulus, displaced papillary muscles), ↓ carotid upstroke

Evaluation for the presence of heart failure

- CXR (see Radiology insert): pulm edema, pleural effusions ± cardiomegaly, cephalization, Kerley B-lines
- BNP/NT-proBNP can help exclude HF; levels ↑ w/ age, renal dysfxn, AF, ↓ w/ obesity Se ≥95%, Sp ˜50%, PPV ˜65%, NPV ≥94% for HF in Pts p/w SOB (*BMJ* 2015;350:h910)
- Evidence of ↓ organ perfusion: ↑ Cr, ↓ Na, abnl LFTs
- Echo (see inserts): ↓ EF & ↑ chamber size ↑ systolic dysfxn; hypertrophy, abnl MV inflow, abnl tissue Doppler → ? diastolic dysfxn; abnl valves or pericardium; ↑ estimated RVSP
- PA catheterization: ↑ PCWP, ↓ CO and ↑ SVR (in low-output failure)

Evaluation of the potential causes of heart failure

- **ECG:** Q waves or PRWP (ischemic heart disease); LVH (hypertensive heart disease or HCM); low limb lead voltage (NICM or infiltrative); heart block (infiltrative)
- **TTE:** LV & RV size & function, valvular disease (and whether likely 1° or 2° to CMP), findings indicative of infiltrative or pericardial disease
- **Coronary angio** (or noninvasive imaging, eg, CT angio); if no CAD, w/u for NICM
- **Cardiac MRI:** multiparameter evaluation of cardiac structure & function including:

  LVEF, RVEF and volumes; regional wall motion abnormalities

  presence, pattern, & extent of myocardial scar (using late gadolinium enhancement, LGE) w/ Se/Sp of 100%/96% vs coronary angio for dx etiology of HF (*Circ* 2011;124:1351)

  myocardial inflammation or infiltration (eg, myocarditis, sarcoidosis, amyloidosis) restriction vs constrictive pericardial disease

Evaluation of Potential Causes of Heart Failure

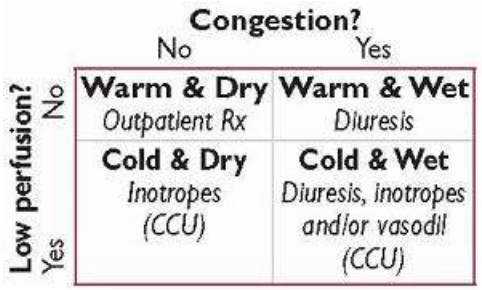
Etiology	ECG Pattern	Imaging Pattern
Ischemia, infarct	ST segment deviation, Qw	TTE: regional WMA, ± thinning/aneurysm Cor angio/CTA: obstructive CAD MRI: subendocardial or transmural LGE
Infiltrative	Low limb lead voltage, ± heart block, pseudoinfarct	TTE: LVH, "starry sky," ↑ biatrial size → amyloid MRI: inapprop nulling of myocardium + diffuse LGE → amyloid; patchy LV + RV LGE → sarcoidosis; ↓ T2 star → iron overload
Idiopathic DCM	Low limb lead volts, precordial LVH, BBB	TTE: 4 chamber dilation, diffuse hypokinesis MRI: mid-myocardial LGE
Tachy-myopathy	Persistent SVT	TTE: diffuse hypokinesis MRI: absent LGE in early stage
Myo(peri) -carditis	Pseudoischemia/-infarct. Pericard: diffuse concave STE w/ ST:T ratio >0.24 in V_6 and PR depression	TTE: typically global HK MRI: mid-myocardial + epicardial LGE, ↑ T2 and ↑ T1 ratios (edema)

Precipitants of acute heart failure

- **Dietary indiscretion or medical nonadherence** (˜40% of cases)
- **Myocardial ischemia or infarction** (˜10-15% of cases); myocarditis
- **Renal failure** (acute, progression of CKD, or insufficient dialysis) → ↑ preload

- **Hypertensive crisis (incl. from RAS), worsening AS** → ↑ left-sided afterload
- **Drugs** (βB, CCB, NSAIDs, TZDs), **chemo** (anthracyclines, trastuzumab), or **toxins** (EtOH)
- **Arrhythmias;** acute valv. dysfxn (eg, endocarditis), espec mitral or aortic regurgitation
- **COPD or PE** → ↑ right-sided afterload; **RV pacing**
- Other: **extreme emotional stress; anemia,** systemic **infection, thyroid** disease

Treatment of acute decompensated heart failure



- Assess degree of congestion & adequacy of perfusion
- For **congestion: "LMNOP"**

  Lasix IV w/ monitoring of UOP; total daily dose 2.5× usual daily PO dose → ↑ UOP, but transient ↑ in renal dysfxn vs 1× usual dose; Ø clear diff between cont gtt vs q12h dosing (*NEJM* 2011;364:797)

  Morphine (↓ sx, venodilator, ↓ afterload)

  Nitrates (venodilator)

  Oxygen ± noninvasive vent (↓ sx, ↑ P_aO_2; no Δ mortality; see "Mechanical Ventilation")

  Position (sitting up & legs dangling over side of bed → ↓ preload)

- For **low perfusion**, see below

- Adjustment of oral meds

  ACEI/ARB: hold if HoTN, consider Δ to hydralazine & nitrates if renal decompensation βB: reduce dose by at least ½ if mod HF, d/c if severe HF and/or need inotropes

Overview of Treatment of Heart Failure by Stage

Pt characteristics		Therapy
A	HTN, DM, CAD Cardiotoxin exposure FHx of CMP	Treat HTN, lipids, DM, SVT Stop smoking, EtOH; ↑ exercise ACEI/ARB if HTN/DM/CAD/PAD
B	Prior MI, ↓ EF, LVH or asx valvular dis.	All measures for stage A + ACEI/ARB & βB if MI/CAD or ↓ EF. ? ICD.
C	Overt HF	All measures for stage A, ACEI, βB, diuretics, Na restrict ↓ EF: aldo antag, ICD, consider CRT, nitrate/hydral, dig.

D	Sx despite max med Rx 4-y mortality >50%	All measures for stages A-C Consider IV inotropes, VAD, transplant, end-of-life care

- Utility of BNP-guided Rx remains debated (*Circ* 2013;301:500 & 509)
- Implantable PA pressure sensor in NYHA III → 37% ↓ risk of hosp (23% for HFrEF; 52% for HFpEF) (*Lancet* 2011;377:658)

Treatment of advanced heart failure (*Circ* 2009;119:e391)

- Consider PAC (qv) if not resp to Rx, unsure re: vol status, HoTN, ↑ Cr, need inotropes
- Tailored Rx w/ PAC; goals of MAP >60, CI >2.2 (MVO_2 >60%), SVR <800, PCWP <18
- **IV vasodilators:** NTG, nitroprusside (risk of coronary steal if CAD; prolonged use → cyanide/thiocyanate toxicity); nesiritide (rBNP) not rec for routine use (*NEJM* 2011;365:32)
- **Inotropes:** in addition to ↑ inotropy, consider additional properties:

  dobutamine: vasodilation at doses ≤5 mcg/kg/min; mild ↑ PVR; desensitization over time

  dopamine: splanchnic vasodil. → ↑ GFR & natriuresis; vasoconstrictor at ≥5 mcg/kg/min; does not enhance decongestion or preserve renal fxn in ADHF (*JAMA* 2013;310:2533)

  milrinone: prominent systemic & pulmonary vasodilation; ↑ dose by 50% in renal failure
- Ultrafiltration: similar wt loss to aggressive diuresis, but ↑ renal failure (*NEJM* 2012:367:2296)
- **Mechanical circulatory support (MCS)** (*JHLT* 2013;32:157; *JACC* 2015;65:e7 & 2542)

  Temporary MCS*:* depending on the device (Table), can be placed percutaneously or surgically to support LV or RV, as a bridge to recovery, for periprocedural support, or as a bridge to decision regarding transplant or durable long-term MCS

  Intra-aortic balloon pump (IABP): inflates in diastole & deflates in systole to ↓ impedance to LV ejection of blood, ↓ myocardial O_2 demand & ↑ coronary perfusion

  Axial flow pumps (eg, Impella): Archimedes screw principle in LV

  Extracorporeal magnetically levitated centrifugal pumps (eg, TandemHeart & CentraMag)

  Extracorporeal membrane oxygenation (ECMO, *Circ* 2015;131:676)

Short-Term Mechanical Circulatory Support in Cardiogenic Shock

Device	IABP	Impella 2.5 & CP	Impella 5.0	Tandem	CentriMag	ECMO
Max support (L/min)	0.5	2.5 & 3-4	5.0	5.0	10	6
RV support	N	Y (2^{nd} dev.)	N	Y (2^{nd} dev.)	Y (2^{nd} dev.)	Y

Support duration	wks	~4 wk	~4 wk	<4 wk	mos	wks
Percutan?	Y	Y	N	Y	N	Y
Contraindic.	≥ mod AI, severe PAD	LV thrombus, mech AV, severe AS		coagulop severe PAD	coagulop	coagulop

(*Circ* 2011;123:533 & 126:1717; *JACC* 2015;65:e7)

Durable Long-term MCS*:* surgically placed LVAD ± RVAD as bridge to recovery (*NEJM* 2006;355:1873) or transplant (HeartMate II or HeartWare LVAD or Total Artificial Heart if biventricular failure), or as destination Rx (HeartMate I: 52% ↓ 1-y mort. vs med Rx; *NEJM* 2001;345:1435, HeartMate II: 24% ↑ mort. vs HeartMate 1; *NEJM* 2009;361:2241)

- **Cardiac transplantation:** curative Rx but supply of organs limited (~2500/y in U.S.) 10% mortality in 1st year, median survival ~10 y

  Contraindications: active malignancy or infection, irreversible PHT (TPG>15, PVR>5WU despite pulmonary vasodilator Rx), active substance abuse or lack of social supports

  Relative contraindications: age (eg, >70 y), other end organ dysfunction (liver, kidney, lung, unless dual organ transplantation is performed)

Treatment of Chronic Heart Failure with Reduced Ejection Fraction

Diet, exercise	Na <2 g/d, fluid restriction, exercise training in ambulatory Pts
ACEI	↓ mortality: 40% in NYHA IV, 16% in NYHA II/III, 20-30% in asx but ↓ EF (*NEJM* 1992;327:685 & *Lancet* 2000;355:1575) High-dose more effic. than low. Watch for ↑ Cr, ↑ K (ameliorate by low-K diet, diuretics, Kayexalate; patiromer, another K binder, under review; *NEJM* 2015;372:211), cough, angioedema.
ATII receptor blockers (ARBs)	*Consider as alternative if cannot tolerate ACEI (eg, b/c cough)* Noninferior to ACEI (*Lancet* 2000;355:1582 & 2003;362:772) As with ACEI, higher doses more efficacious (*Lancet* 2009;374:1840) Adding to ACEI → ↑ risk of ↑ K and ↑ Cr (*BMJ* 2013;346:f360)
ARNi (ARB + neprilysin inhib)	Neutral endopeptidase (NEP, aka neprilysin) degrades natriuretic peptides as well as bradykinin & angiotensins. LCZ696 = valsartan + sacubitril (NEPi): ↓ CV mort & HF hosp c/w ACEi; more HoTN and trend to more angioedema (PARADIGM-HF, *NEJM* 2014;371:993).
Hydralazine + nitrates	*Consider if cannot tolerate ACEI/ARB or in blacks w/ NYHA III/IV* 25% ↓ mort. (*NEJM* 1986;314:1547); infer. to ACEI (*NEJM* 1991;325:303) 43% ↓ mort. in blacks on standard Rx (A-HEFT, *NEJM* 2004;351:2049)

β-blocker (data for carvedilol, metoprolol, bisoprolol)	*EF will transiently* ↓, *then* ↑. *Contraindic. in decompensated HF.* 35% ↓ mort. & 40% ↓ rehosp. in NYHA II-IV (*JAMA* 2002;287:883) Carvedilol superior to low-dose metop in 1 trial (*Lancet* 2003;362:7), but meta-analysis suggests no diff between βB (*BMJ* 2013;346:f55).
Aldosterone antagonists	*Consider if adeq. renal fxn and w/o hyperkalemia; watch for* → *K* 24-30% ↓ mort. in NYHA II-IV & EF ≤35% (*NEJM* 2011;364:11) 15% ↓ mort. in HF post-MI, EF ≤40% (EPHESUS, *NEJM* 2003;348:1309)
Cardiac resynch therapy (CRT, qv)	*Consider if EF* ≤35%, *LBBB and symptomatic HF* 36% ↓ mort. & ↑ EF in NYHA III-IV (CARE-HF, *NEJM* 2005;352:1539) 41% ↓ mort. if EF ≤30%, LBBB and NYHA I/II (*NEJM* 2014;370:1694)
ICD (see "Cardiac Rhythm Mgmt Devices")	*Use for* 1° *prevention if EF* ≤30-*35% or 2° prevention; not if NYHA IV* ↓ mort. in ischemic & non-isch CMP; no Δ mort. early post-MI (*NEJM* 2004;351:2481 & 2009;361:1427), ∴ wait ≥40 d
Diuretics	Loop ± thiazide diuretics (sx relief; no mortality benefit)
Digoxin	23% ↓ HF hosp., no Δ mort (*NEJM* 1997;336:525); ? ↑ mort w/ ↑ levels (*NEJM* 2002;347:1403); optimal 0.5-0.8 ng/mL (*JAMA* 2003;289:871)
Ivabradine (*If* blocker w/o ⊖ ino)	*Consider if HR* >70, *NSR on max βB.* 18% ↓ CV mort or HF hosp (*Lancet* 2010;376:875)
ω-3 fatty acids	9% ↓ mortality (included HF with normal LVEF) (*Lancet* 2008:372:1223)
IV iron supplementation	*? if NYHA II/III, EF* ≤40%, *Fe-defic* (ferritin <100 or ferritin 100-300 & TSAT <20%). ↓ Sx, ↑ 6MWD, independent of Hct (*NEJM* 2009;361:2436).
Anticoagulation	*If AF, VTE, LV thrombus,* ± *if large akinetic LV segments* In SR w/ EF <35%, ↓ isch stroke, but ↑ bleed (*NEJM* 2012;366:1859)
Heart rhythm	Catheter ablation of AF → ↑ in EF, ↓ sx (*NEJM* 2004;351:2373) No mortality benefit to AF rhythm vs rate cntl (*NEJM* 2008;358:2667) Pulm vein isolation ↓ sx c/w AVN ablation & CRT (*NEJM* 2008;359:1778)
Meds to avoid	NSAIDs, nondihydropyridine CCB, TZDs
Experimental	Serelaxin ± ↓ dyspnea & ? ↓ mortality (*Lancet* 2013;381:29)

(*Circ* 2009;119:e391; *NEJM* 2010;362:228; *Lancet* 2011;378:713 & 722)

Heart failure with preserved EF (HFpEF; "Diastolic HF") (*Circ* 2011;124:e540)

- Epidemiology: ~½ of Pts w/ HF have normal or only min. impaired systolic fxn (EF ≥40%); risk factors for HFpEF incl ↑ age, ♀, DM, AF. Mortality ≈ to those w/ systolic dysfxn.
- Etiologies (impaired relaxation and/or ↑ passive stiffness): ischemia, prior MI, LVH, HCMP infiltrative CMP, RCMP aging, hypothyroidism
- Precipitants of pulmonary edema: *volume overload* (poor compliance of LV → sensitive to even modest ↑ in volume); *ischemia* (↓ relaxation); *tachycardia* (↓ filling time in diastole), AF (loss of atrial boost to LV filling); HTN (↓ afterload → ↓ stroke volume)
- Dx w/ clinical s/s of HF w/ preserved systolic fxn. Dx supported by evidence of diast dysfxn:

  (1) echo: abnl MV inflow (E/A reversal and Δs in E wave deceleration time) & ↓ myocardial relax. (↑ isovol relax. time & ↓ early diastole tissue Doppler velocities)

  (2) exercise-induced ↑ PCWP (± ↓ response chronotropic & vasodilator reserve)
- Treatment: diuresis for vol overload, BP control, prevention of tachycardia and ischemia; no benefit to: ACEI/ARB (*NEJM* 2008;359:2456) or PDE5 inhib (*JAMA* 2013;309:1268) spironolactone ↓ CV death & HF hosp (at least in Americas) (*NEJM* 2014;370:1383);

  ARNi (*Lancet* 2012;380:1387) and serelaxin (*Lancet* 2013;381:29) under study

PA CATHETER AND TAILORED THERAPY

Rationale

- Cardiac output (CO) = SV × HR; LV SV depends on LV end-diastolic volume (LVEDV) ∴ manipulate LVEDV to optimize CO while minimizing pulmonary edema
- Balloon at tip of catheter inflated → floats into "wedge" position. Column of blood extends from tip of catheter, through pulmonary circulation, to a point just proximal to LA. Under conditions of no flow, PCWP ≈ LA pressure ≈ LVEDP, which is proportional to LVEDV.
- Situations in which these basic assumptions fail:

  (1) Catheter tip not in West lung zone 3 (and ∴ PCWP = alveolar pressure ≠ LA pressure); clues include lack of *a* & *v* waves and if PA diastolic pressure < PCWP

  (2) PCWP > LA pressure (eg, mediastinal fibrosis, pulmonary VOD, PV stenosis)

  (3) Mean LA pressure > LVEDP (eg, MR, MS)

  (4) Δ LVEDP-LVEDV relationship (ie, abnl compliance, ["nl" LVEDP may not be optimal)

Indications (*Circ* 2009;119:e391; *NEJM* 2013;369:e35)

- **Diagnosis and evaluation**

  Ddx of shock (cardiogenic vs distributive; espec if trial of IVF failed or is high risk) and of pulmonary edema (cardiogenic vs not; espec if trial of diuretic failed or is high risk)

  Evaluation of CO, intracardiac shunt, pulmonary HTN, MR, tamponade, cardiorenal syndrome

  Evaluation of unexplained dyspnea (PAC during provocation w/ exercise, vasodilator)
- **Therapeutics** (*Circ* 2006;113:1020)

Tailored therapy to optimize PCWP, SV, $S_{MV}O_2$, RAP, & PVR, in heart failure or shock

Guide to vasodilator therapy (eg, inhaled NO) in pulm HTN, RV infarction

Guide to perioperative management in some high-risk Pts, pretransplantation

Guide to candidacy for thoracic organ transplantation and mechanical circulatory support

- **Contraindications**

  Absolute: right-sided endocarditis, thrombus/mass or mechanical valve; PE

  Relative: coagulopathy (reverse), recent PPM or ICD (place under fluoroscopy), LBBB (˜5% risk of RBBB ↑ CHB, place under fluoro), bioprosthetic R-sided valve

Efficacy concerns (*NEJM* 2006;354:2213; *JAMA* 2005;294:1664)

- No benefit to routine PAC use in high-risk surgery, sepsis, ARDS
- No benefit in decompensated HF (*JAMA* 2005;294:1625); untested in cardiogenic shock
- But: ˜½ of CO & PCWP clinical estimates incorrect; CVP & PCWP not well correl.; ∴ use PAC to (a) answer hemodynamic ? and then remove, or (b) manage cardiogenic shock

Pulmonary Artery Catheter Features

Component	cm from distal tip	Function
Distal lumen	0	Sampling of blood for $S_{MV}O_2$
1.5-mL balloon	0.5	Inflation allows flow directed placement & determination of PCWP
Thermistor	4	Detection of temp Δ for CO calc
Proximal injectate port	26	Infusions & injection of saline for CO calc
Additional Optional Features		
Fiberoptic O_2 sat sensor	0	Allows continuous measurement of $S_{MV}O_2$
Thermal filament	˜10-25	Allows continuous CO calc by thermodilution
Pacing port	˜19	Allows placement of pacing wire in RV
Infusion port(s)	˜30	Additional infusion port(s)

Placement

- Insertion site: **R internal jugular** or **L subclavian veins** for "anatomic" flotation into PA
- **Inflate** balloon (max 1.5 mL) when **advancing** and to **measure PCWP**
- Use resistance to inflation and pressure tracing to avoid overinflation & risk of PA rupture
- Should require 1-1.5 mL air in balloon to float into wedge (<1 mL → pull PAC back; no PCWP at 1.5 mL → advance)
- **Deflate** balloon when **withdrawing** and at all other times
- CXR should be obtained after placement to assess for catheter position and PTX
- If catheter cannot be successfully floated (typically if severe TR or RV dilatation) or if another relative contraindication exists, use fluoroscopic guidance

Complications

- **Central venous access:** pneumo/hemothorax (~1%), arterial puncture (if inadvertent cannulation w/ dilation → surgical/endovasc eval), air embolism, thoracic duct injury
- **Arrhythmias:** ½ PVCs, 20% NSVT, 3% VT (minimize time PAC tip in RV); RBBB (5%)

- **Inability to advance:** difficulty RA → RV seen w/ lg RA and/or severe TR; difficulty RV → PA seen w/ lg RV; deflate balloon, withdraw 10 cm, inflate balloon & readvance. *If repeated attempts unsuccessful at bedside, then perform under fluoro* (to avoid PAC coiling & potentially knotting, which would require interventional cardiology to extract).
- **PA rupture:** risk factors include prolonged balloon inflation, PHT, anticoag. Presents w/ hemoptysis and, if severe, hypoxemia & hypovolemic shock. *Keep balloon inflated, intubate w/ dbl-lumen endotracheal tube, lateral decubitus position with affected side down, STAT interventional radiology and/or thoracic surgery consultation.*
- **Air embolism:** presents w/ dyspnea, chest pain, ↑ R-sided pressures, HoTN. *Place in Trendelenburg, high-flow* O_2.
- **Other:** infxn (espec if PAC >3 d old); thrombus; pulm infarction; valve/chordae damage

Intracardiac pressures

- Zero the transducer and level it with the right atrium (phlebostatic axis)
- Transmural pressure (≈ preload) = measured intracardiac pressure - intrathoracic pressure
- Intrathoracic pressure (usually slightly ⊖) is transmitted to vessels and heart
- **Always measure intracardiac pressure at end-expiration**, when intrathoracic pressure closest to 0 ("high point" in spont. breathing Pts; "low point" in Pts on ⊕ pressure vent.)
- If ↑ intrathoracic pressure (eg, PEEP), measured PCWP *overestimates* true transmural pressures. Can approx by subtracting ~½ PEEP (× ¾ to convert cm H2O to mmHg).
- PCWP: LV preload best estimated at *a* wave; risk of pulmonary edema from avg PCWP

Cardiac output

- **Thermodilution:** saline injected in RA. Δ in temp over time measured at thermistor (in PA) is integrated and is ≈ 1/CO. Inaccurate if ↓ CO, severe TR or shunt.
- **Fick method:** O_2 consumpt ([V with dot above]O_2) (L/min) = CO (L/min) × Δ arteriovenous O_2 content

  ∴ CO = [V with dot above]O_2 /C(a-v)O_2

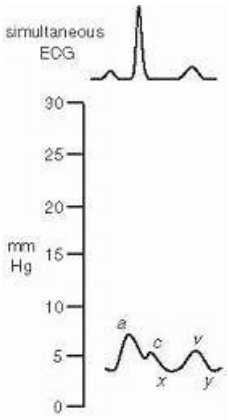
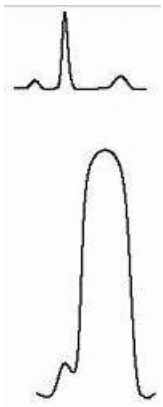
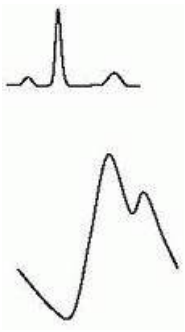
  [V with dot above]O_2 ideally measured (espec if ↑ metab demands), but freq estimated (125 mL/min/m^2)

  C(a-v)O_2 = [10 × 1.36 mL O_2/g of Hb × Hb g/dL × (S_aO_2-$S_{MV}O_2$)]

  $S_{MV}O_2$ is key variable that Δs *with acute interventions*

  If $S_{MV}O_2$ >80%, consider if the PAC is "wedged" (ie, pulm vein sat), L→ R shunt, impaired O_2 utilization (severe sepsis, cyanide, carbon monoxide), ↑ ↑ FiO_2

PA Catheter Waveforms

Location	RA	RV	PA	PCWP
Distance	~20 cm	~30 cm	~40 cm	~50 cm
Normal Pressure (mmHg)	mean ≤6	syst 15-30 diast 1-8	syst 15-30 mean 9-18 diast 6-12	mean ≤12
Waves				
Comment	*a* = atrial contraction, occurs in PR interval *c* = bulging of TV back into RA at start of systole *x* = atrial relaxation and descent of base of heart *v* = blood entering RA, occurs mid-T wave *y* = blood exiting RA after TV opens at start of diastole	RVEDP occurs right before upstroke and ≥ mean RA pressure unless there is TS or TR	Waveform should contain notch (closure of pulmonic valve). Peak *during* T wave PA systolic = RV systolic unless there is a gradient (eg, PS). PA diastolic ≈ PCWP unless ↑ trans-pulm gradient (eg, ↑ PVR).	Similar to RA except *dampened* and *delayed. a* wave *after* QRS, ± distinct *c* wave, *v* wave *after* T (helps distinguish PCWP w/ large *v* waves 2° MR from PA).

PCWP waveform abnormalities: large *a* wave → ? mitral stenosis; large *v* wave → ? mitral regurgitation; blunted *y* descent → ? tamponade; steep *x* & *y* descents → ? constriction.

Hemodynamic Profiles of Various Forms of Shock

Type of shock	RA	PCWP	CO	SVR
Hypovolemic	↓	↓	↓	↓
Distributive	variable	variable	usually ↑ (but can be ↓ in sepsis)	↓
Cardiogenic: 1° L-sided (eg, acute MI)	nl or ↑	↑	↓	↑
Cardiogenic: 1° R-sided (eg, RV infarct; PE)	↑	nl or ↓	↓	↑
Tamponade	↑	↑	↓	↑

Surrogates: JVP ≈ RA; pulmonary edema on CXR implies ↑ PCWP; UOP ∝ CO (barring AKI); delayed capillary refill (ie, >2-3 sec) implies ↑ SVR

Tailored therapy and management of shock (*Circ* 2009;119:e391)

- **Goals:** optimize both MAP and CO to promote end-organ perfusion, while ↓ risk of pulmonary edema & systemic venous congestion MAP = CO × SVR; CO = HR × SV (depends on preload, afterload and contractility) pulmonary edema when PCWP >20-25 (↑ levels may be tolerated in chronic HF) hepatic and renal congestion when CVP/RAP >15 mmHg
- **Optimize preload** = LVEDV ≈ LVEDP ≈ LAP ≈ PCWP (*NEJM* 1973;289:1263) goal **PCWP ˜14-18 in acute MI,** ≤1 **4 in acute decompensated HF** optimize in individual Pt by measuring SV w/ different PCWP to create Starling curve ↑ by giving NS (albumin w/o clinical benefit over NS; PRBC if significant anemia) ↓ by diuresis (qv), ultrafiltration or dialysis if refractory to diuretics
- **Optimize afterload** ≈ wall stress during LV ejection = [(˜SBP × radius) / (2 × wall thick.)] and ∴ ∝ MAP and ∝ SVR = (MAP - CVP / CO); goals: **MAP >60, SVR 800-1200** MAP >60 & SVR ↑ : vasodilators (eg, nitroprusside, NTG, ACEI, hydral.) or wean pressors MAP <60 & SVR ↑ (& ∴ CO ↓): temporize w/ pressors until can ↑ CO (see below) MAP <60 & SVR low/nl (& ∴ inappropriate vasoplegia): vasopressors (eg, norepinephrine [α, β], dopamine [D, α, β], phenylephrine [α] or vasopressin [V_1] if refractory)
- **Optimize contractility** ∝ CO for given preload & afterload; **goal CI = (CO / BSA) >2.2** if too low despite optimal preload & vasodilators (as MAP permits):

  ⊕ *inotropes:* eg, dobutamine (mod inotrope & mild vasodilator) or milrinone (strong inotrope & vasodilator, incl

pulm), both proarrhythmic, or epi (strong inotrope & pressor)

mechanical support devices: eg, IABP, percutaneous or surgical VAD (L-sided, R-sided, or both) or ECMO (*Circ* 2011;123:533)

Vasopressors and Inotropes Used in Shock

Drug	Receptors			Hemodynamics				Comment
	α_1	β_1	β_2	SVR	MAP	HR	CO	
Phenylephrine	+++	0	0	↑↑↑	↑↑	↓↓[a]	↓[a]	↑ PVR
Vasopressin[b]	0	0	0	↑↑↑	↑↑	↓↓[a]	↓[a]	↔PVR; ∴ attractive if RV dysfxn or PHT
Norepinephrine	+++	++	+	↑↑↑	↑↑	↔/↑	↔/↑	Better outcomes than w/ dopa
Epinephrine	+++	+++	+++	↓ / ↑[c]	↑	↑↑	↑	β predom at low doses
Isoproterenol	0	+++	+++	↓↓	↓	↑↑ ↑	↑↑	⊕ chronotrope
Dobutamine	+	+++	++	↓	↔/↓	↑↑	↑↑	↓ PCWP
Dopamine[d]	+	++	0	↔/↑[d]	↔/↑[d]	↑↑ ↑	↑	
Milrinone[e]	0	0	0	↓↓	↓	↔	↑↑ ↑	↓↓ PCWP; ↓ PVR; ∴ attractive if RV dysfxn or PHT

[a]Bradycardia seen due to vagal reflex if hypertension; ↓ CO due to ↑ afterload

[b]V_1 agonist

[c]Low doses ↓ SVR, high doses ↑ SVR

[d]Also a (D) dopa receptor agonist; 0.5-2 mcg/kg/min → D; 2-10 → D & β_1; > 10 → α_1, β_1, D

[e]PDE_3 inhibitor

CARDIOMYOPATHIES

Diseases with mechanical and/or electrical dysfunction of the myocardium

DILATED CARDIOMYOPATHY (DCM)

Definition and epidemiology (*Circ* 2013;128:e240; *JACC* 2013;62:2046)

- Ventricular dilatation and ↓ contractility ± ↓ wall thickness *in the absence of myocardial disease caused by ischemia/infarct, valvular disease or hypertension*
- Ventricular dysfunction usually global but can be regional variation
- May be accompanied by significant MR & TR due to impaired leaflet coaptation
- Incidence: 5-8/100,000/y; prevalence: 1/2500. Most common reason for heart transplant.

Etiologies (*JACC* 2011;57:1641; *Circ Res* 2012;111:131)

- **Familial** (>35%): defined as having DCM and at least 2 closely related family members with otherwise unexplained DCM; usually autosomal dominant pattern of inheritance; ~30 genes identified to date, encoding structural & nuclear proteins *sarcomere:* eg, titin (*TTN,* ~20%; *NEJM* 2012;366:619); β- & α-myosin heavy chain (*MYH7, MYH6,* ~5% each); troponin T (*TNNT2,* ~5%)

  nuclear envelope: eg, lamin A/C (*LMNA,* ~5%), often w/ conduction system disease (eg, sinus brady, AV block, atrial arrhythmias) (*NEJM* 2009;341:1715)

  ion channel: eg, Na channel (*SCN5A,* <5%), same gene as for LQTS & Brugada *Z-disc:* eg, myopalladin (*MYPN,* <5%), ankyrin (*ANKRD1,* <5%) *cytoskeletal:* eg, desmin (DES, <1%); dystrophin (*DMD,* <1%) *syndromic disorders:* eg, muscular dystrophies (Duchenne/Becker; limb-girdle)
- **Idiopathic** (<20%): ? undiagnosed infectious, alcoholic or genetic cause (in ~1/4 of Pts w/ "idiopathic" DCM, evidence of DCM found in 1° relative, suggesting undx genetic)
- **Infectious myocarditis** (10-15%, autoimmune response; *Lancet* 2012;379:738)

  Viruses (parvoB19 & HHV6 > coxsackie, adeno, echo, CMV, HCV): from subacute (dilated LV; mild-mod dysfxn) to fulminant (nondil., thick, edematous LV; sev dysfxn)

  Bacterial, fungal, rickettsial, TB, Lyme (mild myocarditis, often with AVB, qv)

  HIV: ~8% of asx HIV ⊕; due to HIV, 2° infxns, or antiretrovirals; HIV also associated w/ premature CAD (*JACC* 2012;59:779)

  Chagas: apical aneurysm ± thrombus, RBBB, megaesophagus/colon (*NEJM* 2015;373:456)
- **Toxic**

  alcohol (20-35%; *Prog* CV *Dis* 2010;52:289): typically 7-8 drinks/d × >5 y, but variable; male > female, typical age 30-55, may resolve w/ abstinence

  cocaine (primarily myocardial ischemia, but DCM is also seen); amphetamines & ephedra; anabolic steroids

  XRT (usually RCM); cobalt; chloroquine anthracyclines: risk ↑ >550 mg/m^2, may manifest late; usually irreversible cyclophosphamide, taxoids, mitomycin-C, 5-fluorouracil, and interferons trastuzumab: usually reversible
- **Infiltrative** (5%): often mix of DCM + RCM (qv) with thickened walls sarcoidosis, amyloidosis, hemochromatosis, tumor

- **Autoimmune**

  collagen vasc. dis./vasculitis (˜5%): PM, SLE, scleroderma, PAN, RA, Wegener's;

  peripartum (last month → 5 mo postpartum; *EHJ* 2015;36:1090): ˜1:3000 preg. ↑ risk w/ multiparity, ↑ age, Afr Am; stnd HF Rx except if preg then select drugs based on safety; ? bromocriptine to ↓ prolactin; 72% normalize EF; predictors of poor recovery include EF <30% & LVEDD ≥6 cm (*JACC* 2015;66:905); even if nl EF, ˜30% recur w/ next preg

  idiopathic giant cell myocarditis (GCM): avg age 42 y, may present as severe HF, high-grade AV block, or VT, historically poor prognosis (<6 mo median transplant-free survival; *NEJM* 1997;336:1860), but with modern immunosuppression 67% achieve HF remission with transplant-free survival of 77% at 1 y (*Circ* HF 2013;6:15)

  eosinophilic (variable peripheral eos): hypersensitivity (mild HF but at risk for SCD) or acute necrotizing eosinophilic myocarditis (ANEM; STE, effusion, severe HF)

- **Stress-induced** (Takotsubo = apical ballooning)

  typically seen in postmenopausal ♀ after psychological stressor

  ? due to catecholamine surge → microvasc dysfxn & Ca overload mimics MI (pain, ± STE & ↑ Tn; deep TWI & ↑ QT); mid/apex dyskinesis, sometimes w/ cardiogenic shock (caution w/ pressors as can induce LV outflow tract obstruction)

  ? Rx w/ βB, ACEI, anticoag if LV thrombus (but usually not just for dyskinesis given rapid resolution); usually improves over wks (*JAMA* 2011;306:277)

- **Tachycardia:** likelihood ∝ duration & rate (although avg HR ˜120); often resolves w/ rate control, which is only way to definitely make dx, over several mos (*Circ* 2005;112:1092)

- **Arrhythmogenic (right ventricular) cardiomyopathy** (ACM, formerly ARVC): see below

- **Metabolic/other**

  hypothyroidism, acromegaly, pheo; OSA; cirrhosis thiamine, selenium or carnitine deficiency

- **LV noncompaction:** see below

Clinical manifestations

- **Heart failure:** both congestive & poor forward flow sx; signs of L- & R-sided HF **diffuse**, **laterally displaced PMI**, **S3**, ± MR or TR (annular dilat., displaced pap. muscle)
- Embolic events (˜10%), supraventricular/ventricular arrhythmias, & palpitations
- Chest pain can be seen w/ some etiologies (eg, myocarditis)

Diagnostic studies and workup

- CXR: moderate to marked cardiomegaly, ± pulmonary edema & pleural effusions
- ECG: may see PRWP, Q waves or BBB; low-voltage; AF (20%); may be normal
- Echocardiogram: LV dilatation, ↓ EF, *regional or global* LV HK ± RV HK, ± mural thrombi
- Cardiac MRI: up to 76% Se, 96% Sp for myocarditis or infiltrative disease (*JACC Imaging* 2014;7:254); nontransmural delayed gadolinium enhancement in *noncoronary* distribution suggestive of DCM; extent of midwall fibrosis correlated w/ mortality in NICM (*JAMA* 2013;309:896)

- Laboratory evaluation: TFTs, iron studies, HIV, SPEP, ANA; others per clinical suspicion; viral serologies *not* recommended (*JACC* 2012;59:779)
- Stress test: useful to r/o ischemia (low false ⊖ rate), high false ⊕ rate, even w/ imaging
- Coronary angiography to r/o CAD if risk factors, h/o angina, Qw MI on ECG, equivocal ETT; consider CT angiography (*JACC* 2007;49:2044)
- ? Endomyocardial biopsy (*JACC* 2007;50:1914)

  yield 10%: of these, 75% myocarditis (for which no proven Rx) & 25% systemic disease

  40% false ⊖ rate (patchy dis.) & false ⊕ (necrosis → inflammation)

  ∴ biopsy if: acute & hemodynamic or electrical compromise (r/o GCM, ANEM); arrhythmia or RCMP features (r/o infiltrative); or suspect toxic, allergic, tumor
- Family hx & genetic testing (*JAMA* 2009;302:2471; *Circ* 2013;128:e240)

  family hx for ≥3 generations; incomplete penetrance and variable expression make dx of familial CMP challenging

  sequencing of DCM gene panels now available; typically test most clearly affected person

  if specific mutation identified, then can screen family using genetic testing

  if no mutation identified, consider cascade clinical screening (ECG, echo) of 1° relatives every ~3-5 years

Treatment (see "Heart Failure" for standard HF Rx)

- Implantation of devices may be tempered by possibility of reversibility of CMP
- Immunosuppression: for giant cell myocarditis (prednisone + AZA + cyclosporine), collagen vasc disease, peripartum (? IVIg), & eosinophilic; no proven benefit for viral myocarditis
- Prognosis differs by etiology (*NEJM* 2000;342:1077): postpartum (best), ischemic/GCM (worst)
- Abstain from EtOH (for alcoholic CMP and reasonable for others)
- Consider ACEI and/or βB if genotype ⊕ but currently phenotype ⊖

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Definition and epidemiology

- LV (usually ≥15 mm) and/or RV hypertrophy disproportionate to hemodynamic load
- Prevalence: 1/500; 50% sporadic, 50% familial, most asymptomatic
- Autosomal-dominant mutations (> 1500) in cardiac sarcomere genes most common genes involved: β-myosin heavy chain (*MYH7,* ~40%), myosin-binding protein C (*MYBPC3,* ~40%), cardiac troponin T (*TNNT2,* ~5%) and I (*TNNI3,* ~5%) no clear correlation between genotype and clinical course
- Noonan syndrome: HCM, pulmonic stenosis, ASD, short stature, pectus, webbed neck
- Ddx: LVH 2° to HTN, AS, elite athletes (wall usually <13 mm & symmetric and nl/↑ rates of tissue Doppler diastolic relaxation; LV cavity large; no late gadolinium enhancement on MRI; *Circ* 2011;123:2723), Fabry dis. (↑ Cr, skin findings)

Pathology

- Myocardial fiber disarray with hypertrophy, which creates arrhythmogenic substrate
- Morphologic hypertrophy variants: asymmetric septal; concentric; midcavity; apical
- LVH evolves over time, typically manifests in adolescence

Pathophysiology

- Subaortic outflow obstruction: narrowed tract 2° hypertrophied septum + systolic anterior motion (SAM) of ant. MV leaflet (may be fixed, variable or nonexistent) and papillary muscle displacement. Gradient (▽) worse w/ ↑ contractility (digoxin, β-agonists, exercise, PVCs), ↓ preload or ↓ afterload.

P.1-32

- Mitral regurgitation: due to SAM (mid-to-late, post.-directed regurg. jet) and/or abnl mitral leaflets and papillary muscles (pansystolic, ant.-directed regurg. jet)
- Diastolic dysfunction: ↑ chamber stiffness + impaired relaxation
- Ischemia: small vessel dis., perforating artery compression (bridging), ↓ coronary perfusion
- Syncope: Δs in load-dependent CO, arrhythmias

Clinical manifestations (70% asymptomatic at dx)

- **Dyspnea** (90%): due to ↑ LVEDP, MR, and diastolic dysfunction
- **Angina** (25%) even w/o epicardial CAD; microvasc. dysfxn (*NEJM* 2003;349:1027)
- **Arrhythmias** (AF in 20-25%; VT/VF) → palpitations, syncope, sudden cardiac death

Physical exam

- Sustained PMI, S_2 paradoxically split if severe outflow obstruction, ⊕ S_4 (occ. palpable)
- **Systolic murmur:** crescendo-decrescendo; LLSB; ↑ **w/ Valsalva** & standing (↓ preload)
- ± mid-to-late or holosystolic murmur of MR at apex
- Bifid carotid pulse (brisk rise, decline, then 2nd rise); JVP w/ prominent *a* wave
- Contrast to AS, which has murmur that ↓ w/ Valsalva and ↓ carotid pulses

Diagnostic studies

- CXR: cardiomegaly (LV and LA)
- ECG: LVH, anterolateral and inferior pseudo-Qw, ± apical giant TWI (apical variant)
- Echo: no absolute cutoffs for degree of LVH but septum/post. wall ≥1.3 suggestive, as is septum >15 mm; other findings include dynamic outflow obstruction, SAM, MR
- MRI: hypertrophy + patchy delayed enhancement (useful for dx & prog) (*Circ* 2015;132:292)
- Cardiac cath: subaortic pressure ▽ *Brockenbrough sign* = ↓ pulse pressure post-PVC (in contrast to AS, in which pulse pressure ↑ post-PVC)
- ? Genotyping for family screening, but pathogenic mutation ID'd in <½ (*Circ* 2011;124:2761)

Treatment (*Circ* 2011;124:e783 & 2012;125:1432; *Lancet* 2013;381:242; *EHJ* 2014;35:2733)

- Heart failure

  ⊖ **inotropes/chronotropes:** nonvasodilating βBs, CCB (verapamil), disopyramide

  Careful use of diuretics, as may further ↓ preload. Vasodilators only if systolic dysfxn. Avoid digoxin.

  If sx refractory to drug Rx + *obstructive* physiology (▽ >50 mmHg):

  (a) Surgical myectomy: long-term ↓ symptoms in 90% (*Circ* 2014;130:1617)

  (b) Alcohol septal ablation (*Circ* CV *Interv* 2011;4;256; *JACC* 2011;58:2322): gradient ↓ by ˜80%, only 5-20% remain w/ NYHA III-IV sx; 14% require repeat ablation or myectomy. Good alternative for older Pts, multiple comorbidities. Complic: transient (& occ. delayed) 3° AVB w/ 10-20% req. PPM; VT due to scar formation.

  No clear benefit of dual-chamber pacing (*JACC* 1997;29:435; *Circ* 1999;99:2927)

  If refractory to drug therapy and there is *nonobstructive* pathophysiology: transplant
- Acute HF: can be precip. by dehydration or tachycardia; Rx w/ fluids, βB, phenylephrine
- AF: rate control with βB, maintain SR with disopyramide, amiodarone; low threshold to anticoagulate
- SCD: ICD (*JACC* 2003;42:1687). Risk factors: h/o VT/VF, ⊕ FHx SCD, unexplained syncope, NSVT, ↓ SBP or rel HoTN (↑ SBP <20 mmHg) w/ exercise, LV wall ≥30 mm, extensive MRI delayed enhancement. EPS *not* useful. Risk 11%/y if h/o VT/VF, 4%/y if highrisk w/o h/o VT/VF (*JAMA* 2007;298:405).
- Counsel to avoid dehydration, competitive sports & extreme exertion
- Endocarditis prophylaxis not recommended (*Circ* 2007;16:1736)
- First-degree relatives: periodic screening w/ echo, ECG (as timing of HCM onset variable). Genetic testing if known mutation. ? CCB for preclinical HCM (*JACC* HF 2015;3:180).

RESTRICTIVE CARDIOMYOPATHIES (RCM)

Definition (*Circ* 2006;113:1807)

- Impaired ventricular filling with ↓ compliance in nonhypertrophied, nondilated ventricles; normal or ↓ diastolic volumes, normal or near-normal EF; must r/o pericardial disease

Amyloidosis (*Circ* 2011;124:1079 & 2012:126:1286)

- Extracellular deposition of misfolded proteins in a variety of organs (eg, heart, kidney, liver, autonomic nervous system; deposition leads to morbidity & mortality)
- Age at presentation ˜60 y; ♂: ♀ 3:2
- AL (primary; MM, light-chain, MGUS, WM): multiorgan disease (˜50% cardiac)
- ATTR (familial; mutation in transthyretin, TTR; *Circ* 2012;126:1286)

  V122I variant → 2.6× ↑ HF risk; 10% carriage in blacks >65 y w/ HF (*JACC* 2006:47:1724)

  V30M variant seen in European & Japanese

  T60R variant in Europeans, autonomic + peripheral neuropathy common

- SSA (senile; normal TTR): typically presents at age >70 y, prevalence >5% beyond age 80, ♂ >> ♀ (50:1), heart-only

- Workup

  ECG: ↓ QRS amplitude in AL (50%), pseudoinfarct pattern (Qw), AVB (10-20%), hemiblock (20%), BBB (5-20%)

  Echo: biventricular wall thickening (*yet* w/ *low voltage on* ECG), granular sparkling texture (30%), biatrial enlargement (40%), thickened atrial septum, valve thickening (65%), diastolic dysfxn, small effusions

  Normal voltage & septal thickness has NPV ˜*90%*

  Lab: SPEP, UPEP, serum free light chain ratio (<0.25 or >1.65 κ-to-λ ratio) 91% Se for AL amyloid (*Clin Chem* 2005;51:878)

  MRI: diffuse subendo late gado enhance, ˜90% Se/Sp vs bx (*JACC* 2008;51:1022)

  (99m)Tc-pyrophosphate PET: ↑ tracer retention in ATTR >> AL differentiates cardiac amyloid subtypes (*Circ Imaging* 2013;6:195)

  Cardiac bx: gold standard (˜100% Se due to widespread amyloid distrib) and permits subtyping of precursor protein. Abd fat pad bx 70% sensitivity for AL.

- Treatment: judicious loop diuretics often only tolerated Rx avoid digoxin (↑ toxicity w/ binding fibrils) and CCB (⊖ inotrope)

  βB or ACEI often poorly tolerated b/c of HoTN

  cardiac tx usually contraindic. b/c extracardiac involvement, but isolated cardiac AL amyloid combined heart/auto stem cell tx yields survival ≈ other RCM (*JHLT* 2014;33:149)

  LVADs not appropriate b/c small restricted LV and frequent RV dysfunction

- Prognosis (median survival after HF dx): AL <12 mo, ATTR ˜30 mo, SSA ˜60 mo

Sarcoidosis

- Noncaseating, granulomatous disorder that can involve any organ
- Recognized cardiac disease in ˜5% of those w/ systemic sarcoid, but imaging & autopsy data show myocardial involvement in >50%
- LV dysfxn (DCM ≥ RCM); MR can be due to involvement of papillary muscles
- ECG: AVB (75%), can be high grade; RBBB (20-60%); atrial & vent. arrhythmias
- Cardiac MRI: T2-imaging and early gadolinium detect acute inflammation (edema), nontransmural patchy delayed gado enhancement, particularly in basal and/or midventricular septum detects fibrosis/scar from chronic disease and predicts prognosis (⊕ LGE → 31× risk for adverse cardiac events; *JACC Imaging* 2013;6:501)
- Echo: regional WMA (particularly basal septum) with thinning or mild hypertrophy
- Nuclear imaging: thallium perfusion defects in a noncoronary distribution; gallium uptake in areas of active inflammation can guide steroid Rx; PET: ↑ FDG uptake in areas of active inflammation
- Cardiac bx w/ low yield as granulomas patchy
- Treatment: steroids are standard although have not been evaluated in RCTs; 47% of Pts w/ AV conduction disease improved w/ steroids (*Can J Cardiol* 2013;29:1034) and retrospective studies suggest ↓ mortality. For steroid-sparing or intolerance, consider MTX, AZA, chloroquine or anti-TNF drugs. Low threshold for PPM-ICD.

Hemochromatosis

- In middle-aged men (espec Northern European)
- 15% p/w cardiac sx, typically HF and conduction disturbances
- Cardiac MRI: myocardial T2* is reduced (<20 ms) in iron overload disorders and enables tracking of response to Rx
- Treatment w/ phlebotomy or, in one report, chelation has been associated with reversal of LV dysfunction (*JACC* 1986;8:436)

Other etiologies (*Circ* 2005;112:2047 & *JACC* 2010;55:1769)

- **Myocardial processes**

  Autoimmune (scleroderma, polymyositis-dermatomyositis)

  Infiltrative diseases (see primary entries for extracardiac manifestations, Dx, Rx)

  Storage diseases: Gaucher's, Fabry, Hurler's, glycogen storage diseases

  Diabetes mellitus

- **Endomyocardial processes**

  Chronic eosinophilic: Löffler's endocarditis (temperate climates; ↑ eos; mural thrombi that embolize); endomyocardial fibrosis (tropical climates; var. eos; mural thrombi; *NEJM* 2008;359:43); treat for heart failure, steroids early, anticoagulation for thrombus

  Toxins: radiation (also p/w constrictive pericarditis, valvular dis, ostial CAD), anthracyclines

  Serotonin: carcinoid, serotonin agonists, ergot alkaloids

  Metastatic cancer

Pathology & pathophysiology

- Path: normal or ↑ wall thickness ± infiltration or abnormal deposition
- ↓ myocardial compliance → nl EDV but ↑ EDP → ↑ systemic & pulm. venous pressures
- ↓ ventricular cavity size → ↓ SV and ↓ CO

Clinical manifestations (*Circ* 2000;101:2490)

- **Right-sided > left-sided heart failure** w/ peripheral edema ± ascites > pulmonary edema
- **Diuretic "refractoriness"**
- **Thromboembolic events**
- Poorly tolerated tachyarrhythmias; VT → syncope/sudden cardiac death

Physical exam

- ↑ JVP, ± Kussmaul's sign (JVP ↑ w/ inspiration, classically seen in *constrictive pericarditis*)
- Cardiac: ± S_3 and S_4 (usually absent in amyloid b/c atrial dysfxn), ± murmurs of MR and TR

- Congestive hepatomegaly, ± ascites and jaundice, peripheral edema

Diagnostic studies

- CXR: normal ventricular chamber size, enlarged atria, ± pulmonary congestion
- ECG: low voltage, pseudoinfarction pattern (Qw), ± arrhythmias
- Echo: ± symmetric wall thickening, biatrial enlarge., ± mural thrombi, ± cavity oblit. w/ diast dysfxn: ↑ early diast (E) and ↓ late atrial (A) filling, ↑ E/A ratio, ↓ decel. time
- Cardiac MRI/PET: may reveal inflammation or evidence of infiltration (but nonspecific)
- Initials labs: SPEP, UPEP & serum free light chains, Fe studies (transferrin sat, HFE mutation), BNP (typically higher in RCM than in constrictive pericarditis)
- Cardiac catheterization: atria: **M's** or **W's** (prominent *x* and y descents)

  Ventricles: **dip & plateau** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)

  Concordance of LV and RV pressure peaks during respiratory cycle (vs discordance in constrictive pericarditis; *Circ* 1996;93:2007)
- Endomyocardial biopsy if suspect infiltrative process; fat pad bx for amyloid
- Restrictive cardiomyopathy vs constrictive pericarditis: see "Pericardial Disease"

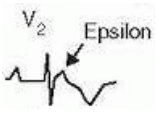
Treatment (in addition to Rx'ing underlying disease)

- Gentle diuresis. May not tolerate CCB or other vasodilators. Avoid digoxin in amyloid.
- Control HR (but can ↓ CO); maintain SR (helps filling). Digoxin ↑ arrhythmias in amyloid.
- Inotropes may have limited efficacy due to small ventricular cavity & preserved systolic fxn
- Anticoagulation (particularly with AF or low CO)
- Transplantation for refractory cases

OTHER CARDIOMYOPATHIES

Arrhythmogenic (right ventricular) cardiomyopathy (ACM, formerly ARVC)

- RV or biventricular (˜50%) or isolated LV (rare) dysfxn due to fatty infiltration and fibrous replacement (small amount of former normal variant) (*Lancet* 2009;373:1289)
- Due to mutations in desmosome (cell-cell coupling): eg, plakophilin 2, desmoglein, desmo-plakin; abnl Wnt signaling leads to myocytes → adipocytes
- Naxos syndrome (mutation in plakoglobin): wooly hair, palmar & plantar keratoses, ACM
- Clinical phases (*Circ* CV *Gen* 2015;8:437): (1) subclinical w/ nl imaging, but ↑ risk of SCD;

  (2) abnl ventricular fxn on imaging, sx ventricular arrhythmias (VT w/ LBBB morphology w/ superior axis), but no HF; (3) RV failure; (4) ? LV failure
- ECG: ± RBBB, TWI V_1-V_3, ε wave 

- Dx w/ MRI

- Avoid bx as septum usually *not* involved (∴ high false ⊖ rate) and risk of perforation w/ free wall bx
- Major dx criteria (*EHJ* 2010;31:806): (1) regional RV akinesia/dyskinesia and ↑ RVEDV;

  (2) fibrous replacement of RV free wall; (3) TWI V_1-V_3, (4) ε wave
- Treatment (*Circ* 2015;132:441): usual HF Rx; EP study & ICD; VT ablation as needed

Ion channelopathies (CMP despite lack of structural abnl; *Circ* 2006;113:1807)

- Defective ionic channel proteins lead to abnl cell membrane transit of Na and K ions
- Disorders include: LQTS, short-QT syndrome (SQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT)

LV noncompaction (LVNC; *JACC* 2015;66:578)

- Prominent trabeculae w/ deep intertrabecular recesses due to intrauterine arrest of compaction of loose interwoven myocardial meshwork
- Debated whether distinct genetic CMP vs morphological trait of other CMPs
- Clinical: HF, atrial and/or vent arrhythmias, cardioembolic events
- Dx w/ MRI > echo; >2:1 ratio of noncompacted to compacted myocardium at end-systole, thickened LV wall and prominent deep trabeculae
- Usual HF Rx; low threshold to anticoagulate

VALVULAR HEART DISEASE

AORTIC STENOSIS (AS)

Etiology

- **Calcific:** predominant cause in Pts >70 y; risk factors include HTN, ↑ chol., ESRD
- **Congenital** (ie, bicuspid AoV w/ premature calcification): cause in 50% of Pts <70 y
- **Rheumatic heart disease** (AS usually accompanied by AR and MV disease)
- AS mimickers: subvalvular (HCMP subAo membrane) or supravalvular stenosis

Clinical manifestations (usually indicates AVA <1 cm^2 or concomitant CAD)

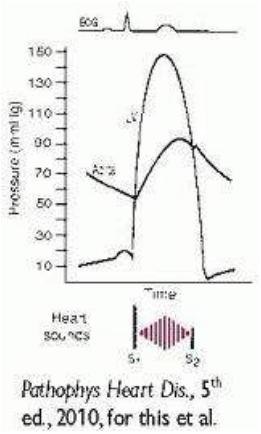
- **Angina:** ↑ O_2 demand (hypertrophy) + ↓ O_2 supply (↓ cor perfusion pressure) ± CAD
- **Syncope** (*exertional*): peripheral vasodil. w/ fixed CO → ↓ MAP → ↓ cerebral perfusion
- **Heart failure:** outflow obstruct + diastolic dysfxn → pulm. edema; espec If ↑ HR/AF (↓ LV fill.)
- Acquired vWF disease (~20% of sev. AS): destruction of vWF; GI angiodysplasia
- Natural hx: usually slowly progressive (AVA ↓ ~0.1 cm^2/y, but varies; *Circ* 1997;95:2262), until sx develop; mean survival based on sx: angina = 5 y; syncope = 3 y; CHF = 2 y

Physical exam

- **Midsystolic crescendo-decrescendo** murmur at **RUSB**, harsh, high-pitched, radiates to carotids, apex (holo-systolic = Gallavardin effect), ↑ w/ passive leg raise, ↓ w/ standing & Valsalva. In contrast, dynamic

outflow obstruction (HCM) ↓ w/ leg raise, ↑ w/ standing, Valsalva.

- Ejection click after S_1 sometimes heard with *bicuspid* AoV
- Signs of severity: *late-peaking* murmur, paradoxically split S_2 or inaudible A_2, small and delayed carotid pulse ("*pulsus parvus et tardus*"), LV heave, ⊕ S4 (occasionally palpable)



Pathophys Heart Dis., 5th ed., 2010, for this et al.

Diagnostic studies

- ECG: may see LVH, LAE, LBBB, AF (in late disease)
- CXR: cardiomegaly, AoV calcification, poststenotic dilation of ascending Ao, pulmonary congestion
- **Echo:** valve morphology, jet velocity, estim pressure gradient (∇) & calculate AVA, LVEF if concom severe AR: vel & ∇ may be ↑ than typical b/c of ↑ flow, but AVA calc valid if concom severe MR: vel & ∇ may be ↓ than typical b/c of ↓ flow, but AVA calc valid
- **Cardiac cath:** usually to r/o CAD (in ~½ of calcific AS); for hemodyn. if disparity between exam & echo: ✓ pressure gradient (∇) across AoV, calc AVA (underestim. if mod/sev AR)
- **Dobutamine challenge:** in cases with low flow, low ∇, and low LVEF, repeating echo (or cath) during low-dose dobutamine can differentiate:

Condition	Comment	SV	Jet Vel	∇	AVA
Afterload mismatch	Low EF 2° to severe AS; EF should ↑ post-AVR	≥20% ↑	↑	↑	no Δ
Pseudostenosis	Low AVA *artifact* of LV dysfxn	≥20% ↑	no Δ	no Δ	↑
Lack contractile reserve	EF prob. will *not* ↑ w/ AVR	no Δ	no Δ	no Δ	no Δ

Classification of Aortic Stenosis (*Circ* 2014;129:e521)

Stage	Sx	Severity	Max Jet Vel ($^m/_s$)	Mean Grad (mmHg)	AVA (cm^2)[a]	LVEF
n/a	N	Normal	1	0	3-4	nl
A	N	At risk	<2	<10	3-4	nl
B	N	Mild	2-2.9	<20	>1.5	nl
		Moderate	3-3.9	20-39	1-1.5	nl
C1		Severe	≥4	≥40	≤1.0	nl
	N	Very severe	≥5	≥60	≤0.8	nl
C2		Severe + ↓ EF	≥4	≥40	≤1.0	↓
D1		Severe	≥4	≥40	≤1.0	nl
D2	Y	Severe + low flow/∇ + ↓ EF[b]	<4	<40	≤1.0	↓
D3		Severe + low flow/∇ + nl EF[c]	<4	<40	≤1.0	nl

[a]AVA indexed to BSA <0.6 cm^2/m^2 also severe;

[b]DSE → max jet vel ≥4 & AVA ≤1.0;

[c]small LV w/ ↓ stroke vol.

Treatment (*Circ* 2014;129:e521 & *NEJM* 2014;371:744)

- Management decisions based on *symptoms*: once they develop AVR is needed. If asx, HTN can be cautiously Rx'd (probably best w/ ACEI/ARB rather than diuretics). Statins have not been proven to ↓ progression.
- **AVR**

  Indicated in: **sx severe AS** (ie, stage D1); **asx severe AS + EF <50%** (stage C2); or asx severe (stage C1) *and* undergoing other cardiac surgery.

  Reasonable if:

asx severe AS (stage C1) *but* either **sx or ↓ BP w/ exercise** (can *carefully* exercise asx AS to uncover sx, do *not* exercise sx AS) or **very severe**

sx severe w/ low flow/▽ w/ low EF & response to dobuta (stage D2) or normal EF but AS felt to be cause of sx (stage D3)

asx moderate AS (stage B) *and* undergoing cardiac surgery

- Transcatheter AoV replacement (TAVR, see below) indicated if surgical risk prohibitive or as reasonable alternative to surgery if high operative risk (STS predicted mortality 8-15%)
- Medical (if not AVR candidate or to temporize): careful diuresis prn, control HTN, maintain SR; digoxin if ↓ EF & HF or if AF; *avoid* venodilators (nitrates) & ⊖ inotropes (βB/CCB) if severe; avoid vigorous physical exertion once AS mod-severe; ? nitroprusside if p/w CHF w/ sev. AS, EF <35%, CI <2.2, & nl BP (*NEJM* 2003;348:1756)
- IABP: stabilization, bridge to surgery
- Balloon AoV valvotomy (BAV): 50% ↑ AVA & ↓ peak ▽, *but* 50% restenosis by 6-12 mo & ↑ risk of peri-PAV stroke/AR (*NEJM* 1988;319:125), ∴ bridge to AVR or palliation

TAVR (transcatheter AoV replacement)

- Catheter-based technique for replacing diseased AoV with bioprosthetic valve
- Valves: balloon-expandable (Edwards SAPIEN) or self-expanding (Medtronic CoreValve); balloon-expandable w/ less AR, less redo, less need for PPM (*JAMA* 2014;311:1503)
- Approaches: primarily retrograde via percutaneous transfemoral access; also retrograde via axillary artery or ascending aorta (via small sternotomy & aortotomy); alternatively transapical via direct LV apical puncture and antegrade implantation through small thoracotomy (if severe PAD or heavily calcified ascending Ao & arch)
- Periprocedural: local anesthesia w/ conscious sedation or general anesthesia; RV pacing (to decrease SV during deployment); TEE to guide placement
- Peri- & postprocedural complications: low CO, annular rupture or coronary occlusion (both rare), local vascular complications, paravalvular leaks & heart block (see below)
- ASA lifelong + clopidogrel × 6 mo
- Outcomes

  in nonoperative Pts vs med Rx: 44% ↓ mortality, but still ~20% annual mortality in TAVR group illustrating comorbidities in this population (*NEJM* 2012;366:1696; *JACC* 2014;63:1972)

  high-risk operative Pts vs surg AVR (*NEJM* 2012;366:1686 & 2014;370:1790) postop ≈ sx & hemodynamics mortality ≈ (balloon-expandable) or 26% ↓ (self-expanding) w/ TAVR vs surgery ↑ vasc complic; ↑ early risk of stroke/TIA w/ balloon-expandable heart block requiring PPM in ~20% w/ self-expanding; paravalvular leaks in ~7% prelim data in low-risk Pts shows lower mortality & stroke with TAVR (*JACC* 2015;65:2184)

AORTIC REGURGITATION (AR)

Etiology (*Circ* 2006;114:422)

- **Valve disease** (43%)

  rheumatic heart disease (usually mixed AS/AR and concomitant MV disease)

  bicuspid AoV: natural hx: ⅓→ normal, ⅓ → AS, 1/6 → AR, 1/6 → endocarditis → AR **infective endocarditis**

valvulitis: RA, SLE; anorectics (fen/phen) & other serotoninergics (*NEJM* 2007;356:29,39), XRT

- **Root disease** (57%)

  HTN

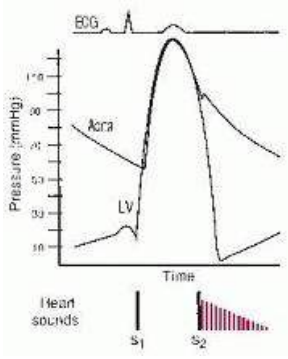
  aortic aneurysm or dissection, annuloaortic ectasia, Marfan syndrome

  aortic inflammation: giant cell, Takayasu's, ankylosing spond., reactive arthritis, syphilis

Clinical manifestations

- Acute: sudden ↓ forward SV and ↑ LVEDP (noncompliant ventricle) → pulmonary edema ± hypotension and cardiogenic shock
- Chronic: clinically silent while LV dilates (to ↑ compliance to keep LVEDP low) more than it hypertrophies → chronic volume overload → LV decompensation → CHF
- Natural hx: *variable* progression (unlike AS, can be fast or slow); once decompensation begins, prognosis poor w/o AVR (mortality ~10%/y)

Physical exam



- **Early diastolic decrescendo murmur at LUSB** (RUSB if dilated Ao root); ↑ w/ sitting forward, expir, handgrip; severity of AR ∝ duration of murmur (except in acute and severe late); *Austin Flint murmur:* mid-to-late diastolic rumble at apex (AR jet interfering w/ mitral inflow)
- **Wide pulse pressure** due to ↑ stroke volume, hyper-dynamic pulse → many of classic signs (see table); pulse pressure narrows in late AR with ↓ LV fxn; bisferiens (twice-beating) arterial pulse
- PMI diffuse and laterally displaced; soft S_1 (early closure of MV); ± S_3 (≠ ↓ EF but rather just volume overload in AR)

Classic Eponymous Signs in Chronic AR (*South Med J* 1981;74:459)

Sign	Description
Corrigan's pulse	“water hammer” pulse (ie, rapid rise/fall or distention/collapse)
Hill's sign	(popliteal SBP - brachial SBP) >60 mmHg
Duroziez's sign	to-and-fro murmur heard over femoral artery w/ light compression

Pistol shot sounds	pistol shot sound heard over femoral artery
Traube's sound	double sound heard over femoral artery when compressed distally
de Musset's sign	head-bobbing with each heartbeat (low Se)
Müller's sign	systolic pulsations of the uvula
Quincke's pulses	subungual capillary pulsations (low Sp)

Diagnostic studies

- ECG: can see LVH, LAD, abnl repol; CXR: cardiomegaly ± ascending Ao dilatation
- **Echo:** severity of AR (in addition to parameters below, severe AR requires holodia-stolic flow reversal in proximal abdominal Ao); LV size & fxn (chronic severe AR requires LV dilatation; LV dysfxn = EF <50% or LV end-syst. diam. [LVESD] >50 mm)
- Cardiac MR if TTE not sufficiently informative

Classification of Aortic Regurgitation

Severity	Regurg. fraction (%)	Jet width (% of LVOT)	ERO (cm^2)	Angio*
Mild	<30	<25	<0.1	1+
Moderate	30-49	25-64	0.1-0.29	2+
Severe	≥50	≥65	≥0.3	3/4+

*1+ = incomplete LV opac.; 2+ = opac. <Ao root & clears 1 beat; 3+ = LV = Ao root opac.; LV > Ao root opac.

Treatment (*Circ* 2014;129:e521)

- Acute decompensation (consider ischemia and endocarditis as possible precipitants):
  surgery usually urgently needed for acute severe AR, which is poorly tolerated by LV IV afterload reduction (nitroprusside) and inotropic support (dobutamine) ± chronotropic support (↑ HR → ↓ diastole → ↓ time for regurgitation) pure vasoconstrictors and IABP contraindicated
- In chronic AR, management decisions based on LV *size and fxn* (and before sx occur)
- **Surgery** (AVR, replacement or repair if possible):
  severe and **sx** (if equivocal, consider stress test)
  asx *and* either **EF ≤50%** or **LV dilation** (LVESD >50 mm) or undergoing cardiac surg
- Transcatheter AoV replacement (TAVR) being explored (*JACC* 2013;61:1577)

- Medical therapy: **vasodilators** (nifedipine, ACEI/ARB, hydralazine) if severe AR w/ sx or LV dysfxn & Pt not operative candidate or to improve hemodynamics before AVR; no clear benefit on clinical outcomes or LV fxn when used to try to prolong compensation in asx severe AR w/ mild LV dilation & nl LV fxn (*NEJM* 2005;353:1342)

MITRAL REGURGITATION (MR)

Etiology (*Lancet* 2009;373:1382; *NEJM* 2010;363:156)

- **Primary** (degeneration of valve apparatus)

  leaflet abnl*:* myxomatous (MVP), endocarditis, calcific RHD, valvulitis (collagen-vascular disease), congenital, anorectic drugs, XRT

  chordae tendineae rupture: myxomatous, endocarditis, spontaneous, trauma

  papillary muscle dysfxn b/c of ischemia or *rupture* during MI [usu. posteromedial papillary m. (supplied by PDA only) vs anterolateral (suppl. by diags & OMs)]

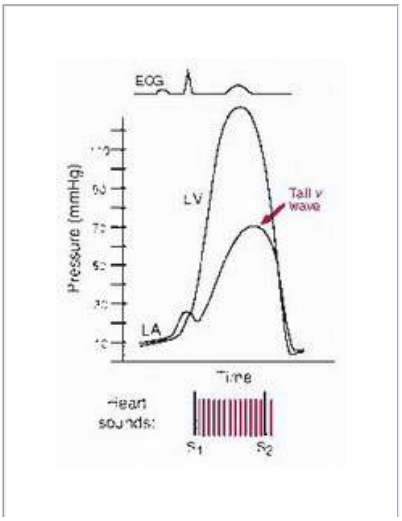
- **Secondary (functional):** inferoapical papillary muscle displacement due to ischemic LV remodeling or other causes of DCM (*JACC* 2015;65:1231)

Clinical manifestations

- Acute: **pulmonary edema**, hypotension, cardiogenic shock (*NEJM* 2004;351:1627)
- Chronic: typically asx for yrs, then as LV fails → progressive DOE, fatigue, AF, PHT
- Prognosis: 5-y survival w/ medical therapy is 80% if asx, but only 45% if sx

Physical exam

- **High-pitched, blowing, holosystolic murmur at apex;** radiates to axilla; ± thrill; ↑ w/ handgrip (Se 68%, Sp 92%), ↓ w/ Valsalva (Se 93%) (*NEJM* 1988;318:1572) ant. leaflet abnl → post. jet heard at spine post. leaflet abnl → ant. jet heard at sternum
- ± diastolic rumble b/c ↑ flow across valve
- Lat. displ. hyperdynamic PMI, obscured S_1, widely split S_2 (A_2 early b/c ↓ LV afterload, P_2 late if PHT); ± S_3
- Carotid upstroke brisk (vs diminished and delayed in AS)



Diagnostic studies (*NEJM* 2005;352:875)

- ECG: may see LAE, LVH, ± atrial fibrillation
- CXR: dilated LA, dilated LV, ± pulmonary congestion
- **Echo:** MV anatomy (ie, etiol); MR severity: jet area (can underestimate eccentric jets), jet width at origin (vena contracta) or effective regurgitant orifice (ERO; predicts survival); LV fxn (EF should be *supranormal* if compensated, [EF <60% w/ sev. MR = LV dysfxn); TEE if TTE inconclusive or pre/intraop to guide repair vs replace
- Cardiac MR if TTE not sufficiently informative
- **Cardiac cath:** prominent PCWP *c-v* waves (not spec. for MR), LVgram for MR severity & EF

Classification of Primary Mitral Regurgitation

Severity	**Regurg. fraction**	**Jet area** (% of LA)	**Jet width** (cm)	**ERO** (cm^2)	**Angio***
Mild	<30%	<20	<0.3	<0.2	1+
Moderate	30-49%	20-40	0.3-0.69	0.2-0.39	2+
Severe†	≥50%	>40	≥0.70	≥0.40	3/4+

*1+ = LA clears w/ each beat; 2+ = LA does not clear, faintly opac. after several beats; 3+ = LA & LV opac. equal.

†For secondary MR, because ERO underestimated & likely progressive LV dysfxn, ERO ≥0.20 is severe

Treatment (*Circ* 2014;129:e521)

- Acute decompensation (consider ischemia and endocarditis as precipitants) IV afterload reduction (nitroprusside), ± inotropes (dobuta), IABP, avoid vasoconstrictors *surgery* usually needed for acute severe MR as prognosis poor w/o (*JAMA* 2013;310:609)
- **Surgery** (repair [preferred if feasible] vs replacement w/ preservation of mitral apparatus)

  for **severe** *primary* MR indicated if **sx & EF >30%** or if **asx & either EF 30-60% or LV sys. diam. ≥40 mm** MV *repair* reasonable if asx & either EF >60% + LVESD <40 mm or new AF or PHT if AF, maze procedure or pulm vein isolation → ↓ AF recurrence, Ø Δ stroke; consider for sx cntl or if planning no anticoag (*NEJM* 2015;372:1399)

  for **severe** *secondary* MR*:* consider if NYHA III-IV; replacement results in more durable correction than repair but no difference in clinical outcomes (*NEJM* 2014;370:23)
- In Pts undergoing CABG w/ mod-sev fxnal MR, annuloplasty ↓ MR but longer surgery, ↑ neurologic events, & no impact on fxnal status or mortality (*NEJM* 2014;371:2178)
- Percut. MV repair (*Circ* 2014;130:1712): edge-to-edge clip less effective than surgery but consider for

sev. sx nonoperative Pt (*NEJM* 2011;364:1395); perc valve under study (*JACC* 2014;64:1814)

- Medical: Ø clinical benefit in asx Pts; βB preserve LV fxn (*JACC* 2012;60:833); if sx but not operative candidate ↓ preload (↓ HF and MR by ↓ MV orifice): diuretics, nitrates (espec if ischemic/fxnal MR); if LV dysfxn: ACEI, βB, ± BiV pacing; maintain SR

MITRAL STENOSIS (MS)

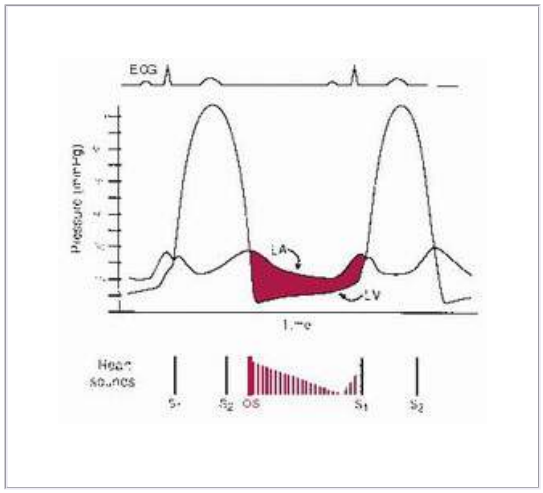
Etiology (*Lancet* 2012;379:953)

- **Rheumatic heart disease** (RHD): *fusion of commissures* → "fish-mouth" valve from autoimmune rxn to β strep infxn; seen largely in developing world today
- **Mitral annular calcification** (MAC): encroachment upon leaflets → functional MS
- Congenital, infectious endocarditis w/ large lesion, myxoma near MV, thrombus
- Valvulitis (eg, SLE, amyloid, carcinoid) or infiltration (eg, mucopolysaccharidoses)

Clinical manifestations (*Lancet* 2009;374:1271)

- **Dyspnea and pulmonary edema** (if due to RHD, sx usually begin in 30s) precipitants: exercise, fever, anemia, volume overload (incl. pregnancy), tachycardia, AF
- **Atrial fibrillation:** onset often precipitates heart failure in Pts w/ MS
- **Embolic events:** commonly cerebral, espec in AF or endocarditis

- Pulmonary: hemoptysis, frequent bronchitis (due to congestion), PHT, RV failure
- Ortner's syndrome: hoarseness from LA compression of recurrent laryngeal nerve



Physical exam

- **Low-pitched mid-diastolic rumble at apex** w/ presystolic accentuation (if not in AF); best heard in L lat decubitus position during expiration, ↑ w/ exercise; severity proportional to *duration* (not intensity) of murmur
- **Opening snap** (high-pitched early diastolic sound at apex) from fused leaflet tips; MVA proportional to S_2-OS interval (tighter valve → ↑ LA pressure → shorter interval)
- Loud S_1 (unless MV calcified)

Diagnostic studies

- ECG: **LAE** ("P mitrale"), ± AF, ± RVH
- CXR: **dilated LA** (straightening of left heart border, double density on right, left mainstem bronchus elevation)
- **Echo:** estimate pressure gradient (▽), RVSP, valve area, valve echo score (0-16, based on leaflet mobility & thick., subvalvular thick., Ca^{++}); exer. TTE (to assess Δ RVSP and ▽) if sx & severity of MS at rest discrepant; TEE to assess for LA thrombus before PMV
- **Cardiac cath:** ▽ from simultaneous PCWP & LV pressures, calculated MVA; LA pressure tall *a* wave and blunted y descent; ↑ PA pressures

Classification of Mitral Stenosis

Stage	Mean ▽ (mmHg)	Pressure ½ time	MV area (cm^2)	PA systolic (mmHg)
Normal	0		4-6	<25
Mild-Mod	<5	100-149	1.6-2	<30
Severe	5-9	150-219	1.1-1.5	30-50
Very severe	≥10	≥220	≤1	>50

Treatment (*Circ* 2014;129:e521)

- Medical: Na restriction, cautious diuresis, βB, sx-limited physical stress
- Antibiotic Ppx recommended if h/o RHD w/ valvular disease for 10 y or until age 40
- Anticoag if: AF; prior embolism; LA thrombus; ? LA >55 mm or lg LA w/ spont contrast
- Mechanical intervention indicated if **heart failure sx w/ MVA ≥1.5;**
  reasonable if asx but very severe (MVA ≤1) and morphology favorable for PMBC; may consider PMBC if MVA >1.5 but hemodyn signif w/ exercise, or if asx but MVA ≤1.5 and new-onset AF
- **Percutaneous mitral balloon commissurotomy** (PMBC): preferred Rx if RHD; MVA doubles, ▽ ↓ by 50%; ≈ MVR *if* valve score <8, ≤ mild MR, Ø AF or LA clot
- Surgical (MV repair if possible, o/w replacement): consider in sx Pts w/ MVA ≤1.5 if PMV unavailable/contraindicated (mod. MR, LA clot), or valve morphology unsuitable
- Pregnancy: if NYHA class III/IV → PMV, o/w medical Rx w/ low-dose diuretic & βB

MITRAL VALVE PROLAPSE (MVP)

Definition and Etiology

- Billowing of MV leaflet ≥2 mm above mitral annulus in parasternal long axis echo view
- Leaflet redundancy from myxomatous proliferation of spongiosa of MV apparatus

- Idiopathic, familial and a/w connective tissue diseases (eg, Marfan's, Ehlers-Danlos)
- Prevalence 1-2.5% of gen. population, ♀ > ♂ (*NEJM* 1999;341:1), most common cause of MR

Clinical manifestations (usually asymptomatic)

- MR (from leaflet prolapse or ruptured chordae); infective endocarditis; embolic events
- Arrhythmias, rarely sudden cardiac death

Physical exam

- High-pitched, midsystolic click ± mid-to-late systolic murmur
- ↓ LV volume (standing) → click earlier; ↑ LV volume or afterload → click later, softer

Treatment

- Endocarditis prophylaxis no longer recommended (*Circ* 2007:116:1736)
- Aspirin or anticoagulation if prior neurologic event or atrial fibrillation

TRICUSPID REGURGITATION

- Primary etiol: rheumatic, CTD, radiation, IE, Ebstein's anomaly, carcinoid, tumors
- Fxnal etiol: RV and/or pulm HTN (may be 2° to L-sided dis.), RV dilation and/or infarct

- Assess based on severity TR, annular dilation, leaflet coaptation (*JACC* 2015;65:2331)
- Consider repair, annuloplasty or replacement for sx and severe TR (eg, ERO ≥ 0.40 cm^2)

PROSTHETIC HEART VALVES

Mechanical (60%)

- Bileaflet (eg, St. Jude Medical); tilting disk; caged-ball
- Very durable (20-30 y), but thrombogenic and ∴ require anticoagulation consider if age <˜60 y or if anticoagulation already indicated (*JACC* 2010;55:2413)

Bioprosthetic (40%)

- Bovine pericardial or porcine heterograft (eg, Carpentier-Edwards), homograft
- Less durable, but min. thrombogenic; consider if >˜70 y, lifespan <20 y or Ø anticoag
- If 50-69 y, 2× reop but ½ bleeding or stroke vs mech (*JAMA* 2014;312:1323 & 2015;313:1435)

Physical exam

- Normal: **crisp sounds**, ± soft murmur during forward flow (normal to have small ▽)
- Abnormal: regurgitant murmurs, absent mechanical valve closure sounds

Anticoagulation & antiplatelet therapy (*Circ* 2014;129:e521)

- Assess for *high-risk features:* prior thromboembolism, AF, EF<30-35%, hypercoagulable

- **Warfarin:** low-risk mech AVR: INR 2-3

  mech MVR or high-risk mech AVR: INR 2.5-3.5

  high-risk bioprosthetic: INR 2-3; for 1st 3 mo, reasonable in low-risk MVR, consider in low-risk AVR
- **ASA** (75-100 mg) for all prosthetic valves; avoid adding to warfarin if h/o GIB, uncontrolled HTN, erratic INR or >80 y
- If thrombosis, ↑ intensity (eg, INR 2-3 → 2.5-3.5; 2.5-3.5 → 3.5-4.5; add ASA if not on)

Periprocedural "Bridging" of Anticoagulation in Pts with Mechanical Valve(s)

AVR w/o risk factors	d/c warfarin 2-4 before surg; restart 12-24 h after surg
MVR or AVR w/ risk factors	Preop: d/c warfarin, start UFH when INR <2 4-6 h preop: d/c UFH; postop: restart UFH & warfarin ASAP

Procedures include noncardiac surgery, invasive procedures, and major dental work

Correction of overanticoagulation (*Circ* 2014;129:e521)

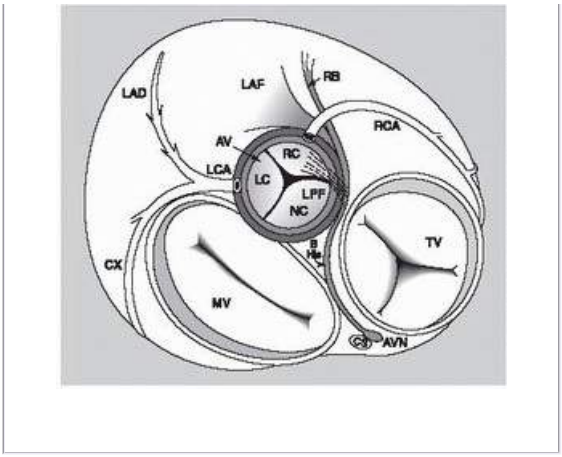
- Risk from major bleeding must be weighed against risk of valve thrombosis
- Not bleeding: if INR 5-10, withhold warfarin; if INR > 10 also give vit K 1-2.5 mg PO
- Bleeding: FFP or PCC ± low-dose (1 mg) vit K IV

Endocarditis prophylaxis: for all prosthetic valves (see "Endocarditis") Complications

- Structural failure (r/o endocarditis); mechanical valves: rare except for Bjork-Shiley; bioprosth: up to 30% rate w/in 10-15 y, mitral > aortic; consider TAVR (*JAMA* 2014;312:162)
- Paravalvular leak (r/o endocarditis); small *central* jet of regurg is normal in mech. valves
- Obstruction from thrombosis or pannus ingrowth: ✓ TTE, TEE, and/or fluoroscopy if ? clot significantly sx *pannus* ingrowth: remove w/ surgery

  thrombosis: surgery if L-sided valve & either severe sx or lg (? ≥0.8 cm) thrombus; lytic often *ineffective* for L-sided thrombosis & 12-15% risk of stroke; consider UFH ± lytic (? low-dose tPA via slow infusion, *JACC CV Imaging* 2013;6:206) if mild sx & small clot burden or poor surg candidate; lytic reasonable for R-sided
- Infective endocarditis ± valvular abscess and conduction system dis. (see "Endocarditis")
- Embolization (r/o endocarditis); risk ~ 1%/y w/ warfarin (vs 2% w/ ASA, or 4% w/o meds) mech MVR 2× risk of embolic events vs mech AVR (*Circ* 1994;89:635)
- Bleeding (from anticoag), hemolysis (espec w/ caged-ball valves or paravalvular leak)

HEART VALVES (superior view, *JAMA* 1976;235:1603)



AV = aortic valve

AVN = AV node

B His = bundle of His

CS = coronary sinus

Cx = circumflex artery

LAD = left anterior descending artery

LAF = left anterior fascicle

LCA = left coronary artery

LPF = left posterior fascicle

MV = mitral valve

RB = right bundle

RC/LC/NC = right/left/noncoronary cusp

RCA = right coronary artery

TV = tricuspid valve

CARDIOPULMONARY EXERCISE TESTING

Background, rationale, and measurements performed (*Circ* 2010;122:191)

- In exercise, to meet metabolic demands of active cells, need to ↑ effective ventilation, ↑ cardiac output, and ↓ pulmonary & systemic vascular resistance, ↑ O_2 extraction
- Dyspnea due to insufficient supply to or impaired uptake of O2 by skeletal muscle
- Ddx of dyspnea:

  impaired external respiration (ventilation & pulmonary gas exchange)

  impaired circulatory system (transport of O_2 and CO_2)

  impaired internal respiration (peripheral capillary gas exchange and O_2 utilization)
- Cardiorespiratory fitness predicts morbidity & mortality
- CPET is an individualized incremental exercise test that combines traditional cardiac stress test parameters: ECG, heart rate, BP quantification of O2 consumption ([V with dot above]O_2), CO_2 production ([V with dot

above]O_2), minute ventilation (V_E) if invasive (radial artery & PA cath): RAP, PAP, & PCWP; arterial & mixed venous sats can be coupled with cardiac imaging (eg, radionuclide ventriculography, TTE)

- Well tolerated even w/ advanced disease, 0.16% adverse event rate (*Circ* 2012:126:2465)

Indications for CPET

- Diagnose etiology of exercise intolerance or dyspnea by defining organ system limiting gas exchange (heart, pulm mechanical, pulm vasculature, muscles/mitochondria)
- Grade severity of advanced heart and lung diseases and predict prognosis

  Prioritize Pts for heart/lung transplantation, mechanical support:

  Heart transplant candidacy: peak [V with dot above]O_2 <14 ml/kg/min, <12 on βB, ± <50% predicted LVAD candidacy <12 ml/kg/min (*NEJM* 2001;345:1445)

  Determine whether to intervene on valvular disease, shunts/congenital heart disease
- To objectively measure responses to interventions (clinical trials, disability, rehabilitation)

Clinical relevance of measurement patterns

- RER (respiratory exchange ratio) = [V with dot above]CO_2/[V with dot above]O_2, indicator of volitional effort independent of chronotropic response (goal > 1.05)
- V_E/MVV (max voluntary vent): >70-80% indicates encroachment on pulm mechanical limit
- Peak [V with dot above]O_2: max aerobic capacity at peak exercise; indicator of cardiorespiratory fitness measured with metabolic cart but also represented by the Fick equation:

  [V with dot above]O_2 = (heart rate × stroke volume) × [(arterial - mixed venous) O_2 content]
- VAT (ventilatory anaerobic threshold): % of peak predicted [V with dot above]O_2 at which O_2 supply inadequate → anaerobic metabolism (normal value >40%); indep. of volitional effort, highly reproducible, and occurs at activity levels often assoc. w/ daily living. Low VAT reflects impaired O_2 delivery ± utilization but does not localize organ system responsible. In HFrEF, VAT<11 ml/kg/min assoc w/ 5× ↑ in 6-mo mortality (*Circ* 2002;106:3079).
- V_E/VCO_2 slope: ventilation required to exchange 1 L/min of CO_2 in addition, V_E/VCO_2 slope = constant / [P_aCO_2 × (1 - V_d/V_t)] high level (>36) especially seen in pulm vascular and/or RV dysfunction, where V/Q mismatch & ↓ pulm perfusion → ↑ V_d/V_t, and ↑ ventilatory drive → ↓ P_aCO_2

  high levels also indicate poor prognosis (*Circ* 2007;115:2410; *Circ* HF 2008;1:227)
- Exercise oscillatory vent: periodic breathing that reflects circul. delay (ie, low CO) relative to metab needs during exercise; assoc w/ 3× ↑ mort (*JACC* 2010;55:1814; *Circ* 2011;124:1442)
- mPAP/CO slope (serial measurements during exercise define the pulm artery pressure response to increased blood flow through the pulmonary circulation during exercise): mPAP = TPG + LAP mPAP/CO slope >3 indicates *either* abnl pulm vascular response to exercise *or* upstream transmission of high LAP (*Circ* 2013;128:1470), with TPG/CO (ie, PVR) that fails to fall and remains > 1.5 indicative of pulmonary vascular dysfunction and

  PCWP/CO slope >2 indicative of left-sided failure

- DPG (diastolic pulmonary gradient) = PAD - LAP; DPG >5-7 indicates pulm vasc disease and may be preferable to TPG (mPAP - LAP) for pulm vasc disease diagnosis b/c it is not significantly influenced by ΔLAP and CO (*Chest* 2013;143:758)

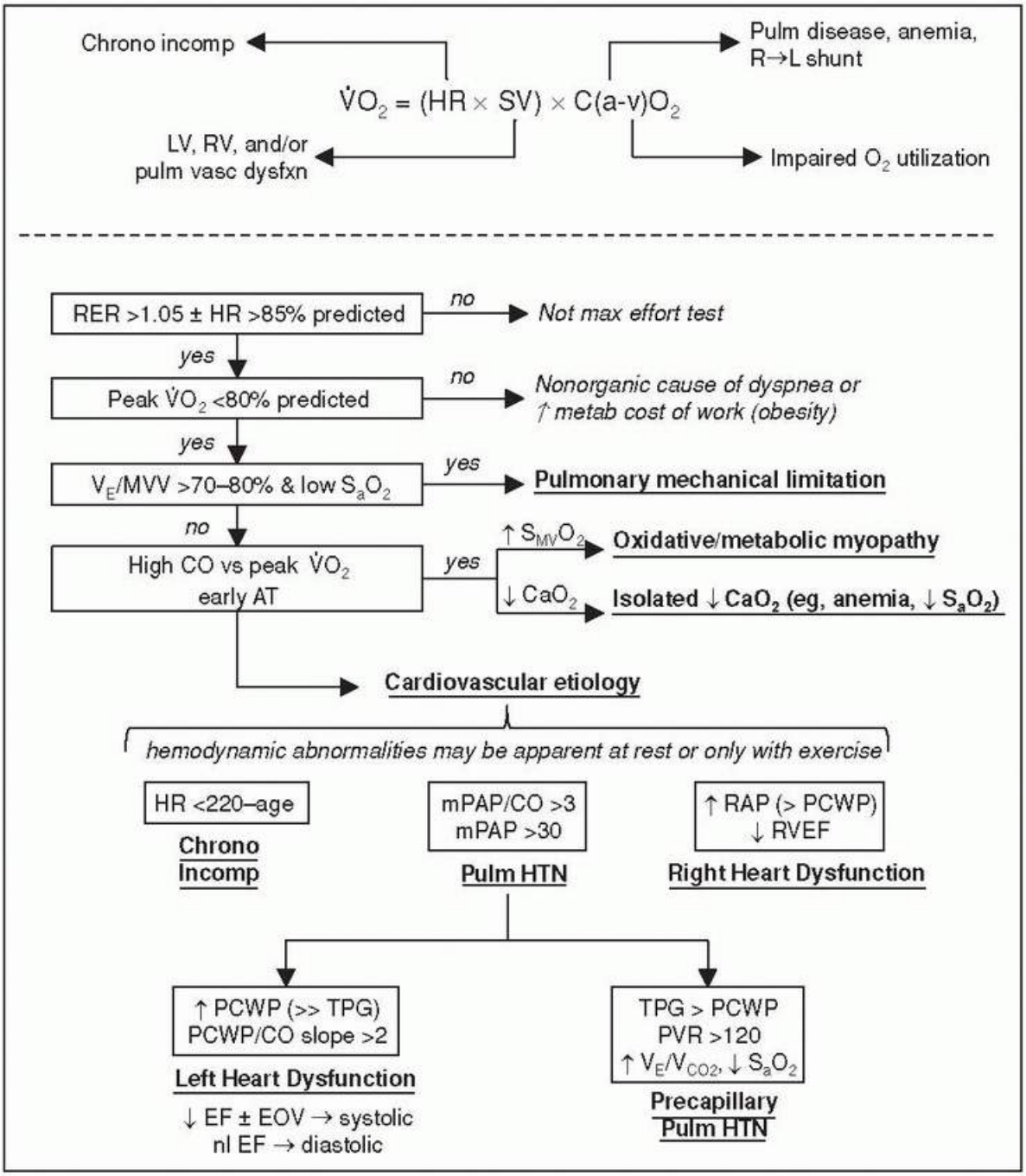


Figure 1-4 Approach to CPET

PERICARDIAL DISEASE

GENERAL PRINCIPLES

Anatomy

- 2-layered (parietal & visceral) tissue sac surrounding heart & proximal great vessels

Disease states

- Inflammation (w/ or w/o fluid accumulation) → pericarditis
- Fluid accumulation → effusion ± tamponade
- Decrease in compliance (sequela of inflammation) → constrictive pericarditis
- Tamponade and constriction characterized by increased ventricular interdependence

PERICARDITIS AND PERICARDIAL EFFUSION

Etiologies of Acute Pericarditis (*Lancet* 2004;363:717; *Curr Probl Cardiol* 2012;37:75)

Idiopathic (~90%)	Most presumed to be undiagnosed viral etiologies
Infectious (<5% can be confirmed infectious)	Viral: Coxsackie, echo, adeno, EBV, VZV, HIV, influenza Bacterial (from endocarditis, pneumonia or s/p cardiac surgery): *S. pneumococcus, N. meningitidis, S. aureus, Borrelia* (Lyme); TB Fungal: *Histo, Coccidio, Candida;* Parasitic: *Entamoeba, Echino*
Neoplastic (<10%)	*Common:* metastatic (lung, breast, lymphoma, leukemia, RCC) *Rare:* primary cardiac & serosal tumors (mesothelioma)
Autoimmune	Connective tissue diseases: SLE, RA, scleroderma, Sjögren's Vasculitides: PAN, Churg-Strauss, Wegener's Drug-induced: procainamide, hydralazine, INH, CsA
Uremia	~5-13% of Pts prior to HD; ~20% occurrence in chronic HD Pts
Cardiovascular	Acute STEMI, late post-MI (Dressler's syndrome), but both rare in modern era; proximal AoD; chest trauma/postpericardiotomy
Radiation	>40 Gy to mediastinum; acute or delayed; may be transudative
Effusions w/o pericarditis	HF, cirrhosis, nephrotic syndrome, hypothyroidism, amyloidosis Transudative

Clinical manifestations (*NEJM* 2014;371:2410)

- **Pericarditis:** retrosternal chest pain that is pleuritic, positional (↓ by sitting forward), radiates to trapezius; may be *absent* in TB, neoplastic, post-XRT and uremic pericarditis; ± fever; ± s/s of systemic etiologies
- **Effusion:** ranges from asx to tamponade (see below)

Physical exam

- **Pericarditis:** multiphasic **friction rub** best heard at LLSB w/ diaphragm of stethoscope. Notoriously variable and evanescent leathery sound w/ up to 3 components: atrial contraction, ventricular contraction, ventricular relaxation (*NEJM* 2012;367:e20).
- **Effusion:** distant heart sounds, dullness over left posterior lung field due to compressive atelectasis from

pericardial effusion (Ewart's sign)

Diagnostic studies (*EHJ* 2004;25:587; *Circ* 2006;113:1622 & 2010;121:916)

- ECG: may show diffuse STE (*concave up*) & PR depression (except in aVR: ST ↓ & PR ↑), TWI; classically and in contrast to STEMI, TWI do not occur until STs normalize Stages: (I) STE & PR ↓ ; (II) ST & PR normalize; (III) diffuse TWI; (IV) Tw normalize ECG may show evidence of large effusion w/ low voltage & electrical alternans (beat-to-beat Δ in QRS amplitude and/or axis due to swinging heart)
- CXR: if large effusion (>250 mL of fluid) → ↑ cardiac silhouette w/ "water-bottle" heart and epicardial halo
- **Echocardiogram:** presence, size, & location of *effusion;* presence of *tamponade physiology;* pericarditis itself w/o spec. abnl (∴ echo can be nl), although can see pericardial stranding (fibrin or tumor); can also detect LV/RV dysfxn (myocarditis ?)
- CT will reveal pericardial effusions, often appearing larger than on echocardiography
- CK-MB or troponin (⊕ in ~30%, *JACC* 2003;42:2144) if myopericarditis. Consider CRP/ESR.

Workup for effusion

- r/o infxn: usually apparent from Hx & CXR; ? value of ✓ acute and convalescent serologies
- r/o noninfectious etiologies: BUN, Cr, ANA, RF, HIV, screen for common malignancies
- Pericardiocentesis if suspect infxn or malignancy or large effusion (>2 cm) or recurrent ✓cell counts, TP, LDH, glc, Gram stain & Cx, AFB, cytology ADA, PCR for MTb, and specific tumor markers as indicated by clinical suspicion "exudate" criteria: TP >3 g/dL, TP_{eff}/TP_{serum} >0.5, LDH_{eff}/LDH_{serum} >0.6 or glc <60 mg/dL high Se (~90%) but *very low* Sp (~20%); overall low utility (*Chest* 1997;111:1213)
- Pericardial bx if suspicion remains for malignancy or TB

Treatment of pericarditis (*Circ* 2013;127:1723)

- High-dose **NSAID** (eg, ibuprofen 600-800 mg tid) or ASA (eg, 650-1000 mg tid) × 7-14 d then taper over wks; ASA preferred over NSAID in acute MI; consider PPI to ↓ risk of GIB
- Add **colchicine** 0.5 mg bid (qd if ≤70 kg) × 3 mo; ↓ risk of refractory or recurrent pericarditis by 50% (*NEJM* 2013;369:1522)
- Steroids (usually systemic; occ. intrapericardial) only for systemic rheum or autoimmune disorder, uremic, preg., contraindication to NSAID, or refractory idiopathic dis. Systemic steroids appear to ↑ rate of pericarditis recurrence (*Circ* 2008;118:667).
- Avoid anticoagulants (although no convincing data that ↑ risk of hemorrhage/tamponade)
- Infectious effusion → pericardial drainage (preferably surgically) + systemic antibiotics
- Acute idiopathic effusion self-limited in 70-90% of cases
- Recurrent pericarditis (*Circ* 2007;115:2739)

  risk factors: subacute, lg effusion/tamponade, T >38°C, lack of NSAID response after 7 d treatment: colchicine 0.5 mg bid × 6 mo (*Annals* 2011;155:409 & *Lancet* 2014;383:2232)
- Recurrent effusion: consider pericardial window (percutaneous vs surgical)

PERICARDIAL TAMPONADE

Etiology

- Any cause of pericarditis but espec **malignancy**, **uremia**, **idiopathic**, proximal aortic dissection with rupture, myocardial rupture
- Rapidly accumulating effusions most likely to cause tamponade as no time for pericardium to stretch (eg, to ↑ compliance) and accommodate ↑ intrapericardial fluid volume

Pathophysiology (*NEJM* 2003;349:684)

- ↑ intrapericardial pressure, compression of heart chambers, ↓ venous return → ↓ CO
- Diastolic pressures ↑ & equalize in all cardiac chambers → minimal flow of blood from RA to RV when TV opens → blunted y descent
- ↑ ventricular interdependence → pulsus paradoxus (pathologic exaggeration of nl physio) Inspiration → ↓ intrapericardial & RA pressures → ↑ venous return → ↑ RV size → septal shift to left. Also, ↑ pulmonary vascular compliance → ↓ pulm venous return. Result is ↓ LV filling → ↓ **LV stroke volume** & blood pressure.

Clinical manifestations

- **Cardiogenic shock** (hypotension, fatigue) **without pulmonary edema**
- Dyspnea (seen in ~85%) may be due to ↑ respiratory drive to augment venous return

Physical exam (*JAMA* 2007;297:1810)

- **Beck's triad** (present in minority of cases): **distant heart sounds**, ↑ **JVP**, **hypotension**
- ↑ JVP (76%) w/ blunted y descent
- Reflex tachycardia (77%), hypotension (26%; occasionally hypertensive), cool extremities
- **Pulsus paradoxus** (Se 82%, Sp 70%) = ↓ SBP ≥10 mmHg during inspiration

  ⊕ LR 3.3 (5.9 if pulsus >12), ⊖ LR 0.03

  Ddx = PE, hypovolemia, severe COPD, constriction (~⅓), RV infarct

  Can be absent if pre-existing ↑ LVEDP, arrhythmia, severe AI, ASD, regional tamponade
- Distant heart sounds (28%), ± pericardial friction rub (30%)
- Tachypnea but clear lungs

Diagnostic studies

- ECG: ↓ voltage (seen in 42%), electrical alternans (20%), ± signs of pericarditis
- CXR: ↑ cardiac silhouette (89%)
- **Echocardiogram:** ⊕ **effusion,** IVC plethora, **septal shift** with inspiration **diastolic collapse** of RA (Se 85%, Sp 80%) and/or RV (Se <80%, Sp 90%) **respirophasic** Δ's **in transvalvular velocities** (↑ across TV & ↓ across MV w/ inspir.) postsurgical tamponade may be localized and not easily visible
- Cardiac cath (right heart and pericardial): elevation (15-30 mmHg) and equalization of intrapericardial and

diastolic pressures (RA, RV, PCWP), blunted y descent in RA ↑ in stroke volume postpericardiocentesis = ultimate proof of tamponade if RA pressure remains elevated after drainage, may have effusive-constrictive disease (*NEJM* 2004;350:469) or myocardial dysfxn (eg, from concomitant myocarditis)

Treatment

- Volume (but be careful as overfilling can worsen tamponade) and ⊕ inotropes (avoid βB)
- Avoid vasoconstrictors as will ↓ stroke volume & potentially ↓ HR
- **Pericardiocentesis** (except if due to aortic or myocardial rupture, in which case consider removing just enough fluid to reverse PEA en route to emergent surgery)

CONSTRICTIVE PERICARDITIS

Etiology (*Circ* 2011;124:1270)

- Any cause of pericarditis (~1-2% incidence overall after acute pericarditis)
- Highest risk w/ **TB**, **bacterial**, **neoplastic**, connective tissue, postcardiac surgery
- **Viral/idiopathic**, as most common cause of pericarditis, also account for signif proportion

Pathophysiology

- Adhesion of visceral and parietal pericardial layers → rigid pericardium that limits diastolic filling of ventricles → ↑ systemic venous pressures
- Venous return is limited only after early rapid filling phase; ∴ rapid ↓ in RA pressure with atrial relaxation and opening of tricuspid valve and *prominent x and* y *descents*
- Kussmaul sign: JVP does not decrease with inspiration (↑ venous return with inspiration, but negative intrathoracic pressure not transmitted to heart because of rigid pericardium)

Clinical manifestations (*NEJM* 2011;364:1350)

- Right-sided > left-sided heart failure (systemic congestion > pulmonary congestion)

Physical exam

- ↑ **JVP** with **prominent y descent,** ⊕ **Kussmaul sign** (Ddx: tricuspid stenosis, acute cor pulmonale, RV failure and RV infarct, RCMP
- Hepatosplenomegaly, ascites, peripheral edema. Consider on Ddx of idiopathic cirrhosis.
- PMI usually not palpable, **pericardial knock**, usually no pulsus paradoxus

Diagnostic studies

- ECG: nonspecific, AF common (up to 33%) in advanced cases
- CXR: calcification (MTb most common), espec in lateral view (although not specific)
- Echocardiogram: ± thickened pericardium, "**septal bounce**" = abrupt displacement of septum during rapid filling in early diastole

- Cardiac catheterization: atria w/ **Ms** or **Ws** (prominent *x* and y descents) ventricles: **dip-and-plateau** or **square-root sign** (rapid ↓ pressure at onset of diastole, rapid ↑ to early plateau)

  discordance between LV & RV pressure peaks during respiratory cycle (*Circ* 1996;93:2007)

- CT or **MRI:** thickened pericardium (>4 mm; Se ~80%) w/ tethering (*Circ* 2011;123:e418)

Treatment

- Diuresis for intravascular volume overload; surgical pericardiectomy in advanced cases
- ? MRI able to predict reversibility with anti-inflammatory agents (*Circ* 2011;124:1830)

Constrictive Pericarditis vs Restrictive Cardiomyopathy

Evaluation	Constrictive pericarditis	Restrictive cardiomyopathy
Physical exam	⊕ Kussmaul sign Absent PMI ⊕ Pericardial knock	± Kussmaul sign Powerful PMI, ± S_3 and S_4 ± Murmurs of MR, TR
ECG	± Low voltage	Low voltage if infiltrative myopathy ± Conduction abnormalities
Echocardiogram	Respirophasic variation (25-40%): inspir. → ↑ flow across TV and ↓ flow across MV E′ (tissue velocity) nl/↑ (> 12) Expir. hepatic vein flow reversal Septal bounce during early diastole Normal wall thickness	<10% respirophasic variation Slower peak filling rate Longer time to peak filling rate E′ ↓ (<8 cm/sec) Inspir. hepatic vein flow reversal Biatrial enlargement ± ↑ wall thickness
CT/MRI	Thickened pericardium	Normal pericardium
NT-proBNP	Variable	Typically ↑ /↑ ↑ (*JACC* 2005;45:1900)
	Prominent *x* and *y* descents Dip-and-plateau sign	
Cardiac catheterization	LVEDP = RVEDP RVSP <55 mmHg (Se 90%, Sp 29%) RVEDP > ⅓ RVSP (Se 93%, Sp 46%) Discordance of LV & RV pressure peaks during respiratory cycle Systolic area index (ratio of RV to LV pressure-time area in inspir vs expir) >1.1 (Se 97%, Sp 100%)	LVEDP > RVEDP (esp. w/ vol.) RVSP >55 mmHg RVEDP <⅓ RVSP Concordance of LV & RV pressure peaks during respiratory cycle Systolic area index ≤1.1 (*JACC* 2008;51:315)

Endomyocardial biopsy	Usually normal	± Specific etiology of RCMP (fibrosis, infiltration, hypertrophy)

Vascular Disease

HYPERTENSION

Classification

Category	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Pre-HTN	120-139	80-89
Stage 1 HTN	140-159	90-99
Stage 2 HTN	≥160	≥100

Average ≥2 measurements >1-2 min apart. Confirm stage 1 w/in 1-4 wk; can Rx stage 2 immediately. ✓ q2y (if nl) or yearly (if pre-HTN). (*J Clin HTN* 2014;16:14)

Ambulatory Thresholds

Setting	Systolic (mmHg)	Diastolic (mmHg)
24-hr average	135	85
Day* (awake)	140	90
Night (asleep)	125	75

*Threshold of hypertension for home readings should be same as daytime ambulatory

Epidemiology (*Circulation* 2012;125:e2)

- Prevalence 33.5% in U.S. adults; >75 million affected (prevalence equal for men and women, highest in African American adults at 44%)
- ↑ Age → ↓ arterial compliance → systolic HTN
- Only 48% of patients with dx of HTN have adequate BP control

Etiologies

- **Essential** (95%): onset 25-55 y; ⊕ FHx. Unclear mechanism but ? additive microvasc renal injury over time w/

contribution of hyperactive sympathetics (*NEJM* 2002;346:913). Both genetic (*Nature* 2011;478:103) & environmental risk factors (Na, obesity, inactivity) Blacks more likely to be salt sensitive and have less activation of renin-angiotensin system, explaining preference for thiazides & CCB over ACEI or ARB

- **Secondary:** Consider if Pt <20 or >50 y or if sudden onset, severe, refractory HTN

Secondary Causes of Hypertension

Diseases		Suggestive findings	Initial workup
RENAL	**Renal parenchymal** (2-3%)	h/o DM, polycystic kidney disease, glomerulonephritis	CrCl, albuminuria See "Renal Failure"
	Renovascular (1-2%, qv) Athero (90%) FMD (10%, women) PAN, scleroderma	ARF induced by ACEI/ARB Recurrent flash pulm edema Renal bruit; hypokalemia (*NEJM* 2009;361:1972)	MRA (>90% Se & Sp, less for FMD), CTA, duplex U/S, angio, plasma renin (low Sp)
ENDO	**Hyperaldo or Cushing's** (1-5%)	Hypokalemia Metabolic alkalosis	See "Adrenal Disorders"
	Pheochromocytoma (<1%)	Paroxysmal HTN, H/A, palp.	
	Myxedema (<1%)	See "Thyroid Disorders"	TFTs
	Hypercalcemia (<1%)	Polyuria, dehydration, Δ MS	iCa
OTHER	**Obstructive sleep apnea** (qv)		
	Medications: OCP, steroids, licorice; NSAIDs (espec COX-2); Epo; cyclosporine		
	Aortic coarctation: ↓ LE pulses, systolic murmur, radial-femoral delay; abnl TTE, CXR		
	Polycythemia vera: ↑ Hct		

Standard workup (*J Clin HTN* 2014;16:14)

- Goals: (1) identify CV risk factors or other diseases that would modify prognosis or Rx;

  (2) reveal 2° causes of hypertension; (3) assess for target-organ damage
- History: CAD, HF, TIA/CVA, PAD, DM, renal insufficiency, sleep apnea, preeclampsia; ⊕ FHx for HTN; diet, Na intake, smoking, alcohol, prescription and OTC meds, OCP
- Physical exam: ✓ **BP in both arms**; funduscopic exam; BMI & waist circumference; cardiac (LVH, murmurs) including signs of HF, vascular (bruits, radial-femoral delay); abdominal (masses or bruits); neuro exam

- Testing: K, BUN, Cr, Ca, glc, Hct, U/A, lipids, TSH, urinary albumin:creatinine (if ↑ Cr, DM, or peripheral edema), ? renin, ECG (for LVH), CXR, TTE (eval for valve abnl, LVH)
- Ambulatory BP monitoring (ABPM): predictive of CV risk and ↑ Se & Sp for dx of HTN vs office BP (HTN 2005;46:156). Consider for suspected episodic or white coat HTN, resistant HTN, HoTN sx on meds, or suspected autonomic dysfxn. Rec by some guidelines to confirm HTN dx, so utilization may expand (*BMJ* 2011;342:d3621 & 343:d4891).

Complications of HTN

- *Each ↑ 20 mmHg* SBP *or 10 mmHg* DBP *→ 2× → CV complications* (*Lancet* 2002;360:1903)
- Neurologic: **TIA/CVA**, ruptured aneurysms, vascular dementia

- Retinopathy: stage I = arteriolar narrowing; II = copper wiring, AV nicking; III = hemorrhages and exudates; IV = papilledema
- Cardiac: **CAD**, **LVH**, **HF**, **AF**
- Vascular: aortic dissection, aortic aneurysm (HTN = key risk factor for aneurysms)
- Renal: proteinuria, **renal failure**

Treatment (*JAMA* 2014;311:507; *J Clin HTN* 2014;16:14; *JACC* 2015;65:1998)

- Goal: in general, <**140/90 mmHg**

  In elderly: data sparser, but benefit, albeit w/ less strict BP target (*NEJM* 2008;358:1887); thus, consider <150/90 mmHg if either (a) ≥80 y and w/o DM or CKD (ASH/ISH rec), or (b) ≥60 y (but no need to downtitrate if <140/90 & tolerating meds) (JNC 8 rec)

  In Pts w/ prior MI or stroke: reasonable to consider <130/80 (HTN 2015;65:1372)

  In Pts w/ DM and/or CKD: prior targets of <130/80 not supported by data (and harm if target <120; *NEJM* 2010;362:1575), but may consider if CKD & albuminuria for renal protection (ASH/ISH rec based on *NEJM* 1994;330:877)
- *Treatment results in 50% ↓ HF, 40% ↓ stroke, 20-25% ↓ MI* (*Lancet* 2014;384:591)
- **Lifestyle modifications** (each ↓ SBP ~5 mmHg) weight loss: goal BMI 18.5-24.9; aerobic exercise: ≥30 min exercise/d, ≥5 d/wk diet: rich in fruits & vegetables, low in saturated & total fat (DASH, *NEJM* 2001;344:3) sodium restriction: ≤2.4 g/d and ideally ≤1.5 g/d (*NEJM* 2010;362:2102) maintain adequate potassium intake through diet counseling (~120 mEq of dietary potassium) if no predisposition to hyperkalemia (*NEJM* 2007;356:1966)

  limit alcohol consumption: ≤2 drinks/d in ♂; ≤1 drink/d in ♀ & lighter-wt Pts avoid exacerbating exposures (eg, NSAID use)
- **Pharmacologic options** for HTN or pre-HTN w/ comorbidity (nb, pre-HTN w/o DM, CKD, CV disease, or other end organ dysfunction treated w/ lifestyle alone) **Pre-HTN:** ARB prevents onset of HTN, no ↑ in clinical events (*NEJM* 2006;354:1685) **HTN:** *choice of therapy controversial, concomitant disease and stage may help guide* Rx **uncomplicated:** CCB, ARB or ACEI, or thiazide (chlorthalidone preferred) are 1st line (*NEJM* 2009;361:2153); βB not 1st line (*Lancet* 2005;366:1545).

  For non-black Pts <60 y: reasonable to start w/ ARB or ACEI, then add CCB or thiazide if needed, and then add remaining class if still needed

  For black, elderly, and ? obese Pts (all of whom more likely to be salt sensitive): reasonable to start with

CCB or thiazide, then add either the other 1st choice class or ARB or ACEI if needed, and then all 3 classes if still needed

+CAD (*Circ* 2015;131:e435): ACEI or ARB (*NEJM* 2008;358:1547); ACEI+CCB superior to ACEI+thiazide (*NEJM* 2008;359:2417) or βB+diuretic (*Lancet* 2005;366:895); may require βB and/or nitrates for anginal relief; if h/o MI, βB ± ACEI/ARB ± aldo antag (see "ACS")

+HF: ACEI/ARB, βB, diuretics, aldosterone antagonist (see "Heart Failure")

+2° stroke prevention: ACEI (*Lancet* 2001;358:1033); ? ARB (*NEJM* 2008;359:1225)

+diabetes mellitus: ACEI or ARB; can also consider thiazide or CCB

+chronic kidney disease: ACEI or ARB (*NEJM* 1993;329:1456 & 2001;345:851 & 861)

- **Tailoring therapy**

  lifestyle Δs typically complementary rather than alternative to drug Rx [although if low risk (stage 1, no end-organ damage or risk factors), could start with lifestyle]

  if stage 1, start w/ monoRx; if stage 2, consider starting w/ combo (eg, ACEI + CCB; *NEJM* 2008;359:2417), as most will require ≥2 drugs

  typically start drug at ½ maximal dose; after 2-3 wk either titrate up or add new drug

Resistant hypertension (*JAMA* 2014;311:2216)

- BP > goal on ≥3 drugs incl diuretic, ~12-13% of hypertensive population (HTN 2011;57:1105)
- Differentiate between true & *pseudoresistance,* w/ latter due to: inaccurate measurement or use of wrong cuff size poor dietary compliance (Na/K intake, can assess w/ 24-hr urine for Na, K and Cr) suboptimal med dosing (eg, <50% of max dose) or poor med compliance volume expansion (inadequate diuretic dosing) white coat HTN (consider ABPM) 2° causes or external drivers (eg, OSA, steroids, NSAIDS, alcohol) (*Lancet* 2010;376:1903)
- True resistance = uncontrolled BP confirmed by ABPM despite compliance w/ optim. doses
- Treatment considerations:

  Persistent ↑ volume may contribute even if on standard HCTZ (*Archives* 2008;168:1159).

  Effective diuretic dosing required for most to achieve control (HTN 2002;39:982).

  Chlorthalidone over HCTZ (if renal function preserved). Loop diuretic favored over thiazide for initial Rx if eGFR <30; however, adding thiazide to loop can ↑ diuresis if insufficient response to loop alone.

  Adding aldosterone antagonist (if renal function preserved) (*PATHWAY-2, ESC* 2015)

  Adding β-blocker (particularly vasodilating ones such as labetalol, carvedilol, or nebivolol), centrally acting agent, α-blocker, or direct vasodilator

  Other Rx under investigation: renal denervation (see below); carotid baroreceptor stimulation; central AV anastomosis ↑ SBP by ~23 mmHg (*Lancet* 2015;385:1634)

- **Renal denervation:** catheter-based RF ablation of renal nerves modifying sympathetic outflow. Had appeared beneficial in unblinded and/or uncontrolled studies, but no effect on BP in controlled trial, so not currently an option in routine care (*NEJM* 2014;370:1393).

Special situations

- **Secondary causes**

  Renovascular (qv)

  Renal parenchymal disease: salt and fluid restriction, ± diuretics

  Endocrine etiologies: see "Adrenal Disorders"

- **Pregnancy:** methyldopa, labetalol, nifedipine, hydralazine; avoid diuretics; Ø ACEI/ARB

HYPERTENSIVE CRISES

- **Hypertensive emergency:** ↑ BP → acute target-organ ischemia and damage

  neurologic: encephalopathy (insidious onset of headache, nausea, vomiting, confusion), hemorrhagic or ischemic stroke, papilledema

  cardiac: ACS, HF/pulmonary edema, aortic dissection

  renal: proteinuria, hematuria, acute renal failure; scleroderma renal crisis

  microangiopathic hemolytic anemia; preeclampsia-eclampsia

- **Hypertensive urgency (severe asymptomatic HTN):** SBP >180 or DBP >120 (?110) w/ minimal or no target-organ damage

Precipitants

- Progression of essential HTN ± medical noncompliance (espec clonidine) or Δ in diet
- Progression of renovascular disease; acute glomerulonephritis; scleroderma; preeclampsia
- Endocrine: pheochromocytoma, Cushing's
- Sympathomimetics: cocaine, amphetamines, MAO inhibitors + foods rich in tyramine
- Cerebral injury: do *not* treat HTN in acute ischemic stroke unless Pt getting lysed, extreme BP (>220/120), Ao dissection, active ischemia or HF (*Stroke* 2003;34:1056)

Treatment (*Chest* 2007;131:1949)

- Tailor goals to clinical context (eg, more rapid lowering for Ao dissection)
- Emergency: ↓ MAP by ˜25% in mins *to 2* h w/ IV agents (may need arterial line for monitoring); goal DBP <110 w/in 2-6 h, as tolerated
- Urgency: ↓ BP to ≤160/100 in *hrs* using PO agents; goal normal BP in ˜1-2 d
- Watch UOP, Cr, mental status: may indicate a lower BP is not tolerated

Drugs for Hypertensive Crises

IV	Nitroprusside* 0.25-10 mcg/kg/min	Nitroglycerin 5-1000 mcg/min
	Labetalol 20-80 mg IVB q10min or 0.5-2 mg/min	Esmolol 0.5 mg/kg load → 0.05-0.2 mg/kg/min
	Fenoldopam 0.1-1.6 mcg/kg/min	Hydralazine 10-20 mg q20-30 min

	Nicardipine 5-15 mg/h	Clevidipine 1-16 mg/h
	Phentolamine 5-15 mg bolus q5-15min	Enalaprilat 1.25 mg
	Captopril 12.5-100 mg tid	Labetalol 200-800 mg tid
PO	Clonidine 0.2 mg load → 0.1 mg qh	Hydralazine 10-75 mg qid

*Metabolized to cyanide → Δ MS, lactic acidosis, death. Limit use of very high doses (8-10 mcg/kg/min) to <10 min. Monitor thiocyanate levels. Hydroxocobalamin or sodium thiosulfate infusion for treatment of cyanide toxicity.

Treatment Considerations for Specific Clinical Settings

Clinical	Setting Note	Treatment
Acute stroke	BP ↓ must be balanced w/ risk of worsening ischemia	Consult stroke team
Aortic dissection (qv)	✓ BP in both arms and treat higher value	βB first, then add vasodilator (eg, nitroprusside) if needed
Acute pulm edema	Avoid ⊖ inotropes (eg, βB) if LV dysfxn, unless ischemia	Vasodilator (eg, NTG) and loop diuretic
Antihypertensive withdrawal	Suspect if abrupt d/c of symp. blocker (eg, clonidine)	Restart d/c'd drug or consider labetalol or nitroprusside
Sympathetic activity (pheo, auton dysfxn, cocaine, MAO + tyramine-containing foods)	Avoid βB as could → unopposed α in vasculature → vasconstriction and further ↑ BP	Phentolamine (pheochromocytoma), nitroprusside

RENOVASCULAR DISEASE

Pathophysiology

- ↑ renal perfusion → activation of RAA system → vasoconstriction, ↑ aldo & vasopressin, ↑ sympathetic activity → volume retention & HTN → progressive renal dysfxn and CV risk

- Unilateral stenosis ↑ HTN
- Bilateral (or unilat involving solitary functioning kidney) → HTN & progressive renal insuffic

Etiologies

- **Atherosclerosis** (˜90%): usually involving ostial or prox segments. Often incidental finding as common in Pts w/ established athero (eg, CAD, PAD) but uncommon cause of HTN.
- **Fibromusclar dysplasia** (FMD, ˜10%): nonathero medial fibroplasia usually mid/distal female-predominant (85-90%); mean age 52 y (*Circ* 2012;125:3182) characteristic “string of beads” appearance (or concentric smooth stenosis) on angio usually > 1 territory involved (eg, carotid in ˜65%), explaining sx of HA, dizziness, tinnitus
- Other (uncommon): vasculitis (Takayasu's, GCA, PAN or eosinophilic granulomatosis w/ polyangiitis) often w/ ↑ inflammatory markers, systemic s/s; scleroderma; local aneurysm or dissection; embolism; retroperitoneal fibrosis

Diagnosis

- Consider testing if any of the following *and* if finding would modify treatment:

  Clinical picture consistent w/ secondary HTN w/ no other compelling etiology Severe HTN (SBP ≥180 and/or DBP ≥120 mmHg) and/or flash pulm edema/CHF Progressive renal insufficiency w/ bland sediment, unilateral small kidney (≤9 cm), renal asymmetry > 1.5 cm, or acute sustained Cr ↑ by ≥30% w/in 1 wk of starting ACEI/ARB

Testing for Renovascular Disease (*Am Fam Physician* 2009;80:273)

Modality	Se	Sp	Notes
Duplex Doppler US	85%	92%	Pt habitus & operator dependent. May be preferred if renal dysfxn. Allows quantification of resistive index.*
CTA	88-96%	97%	Less sensitive (˜30%) for distal disease such as FMD Contrast agent nephrotoxic
MRA	88-100%	>95%	Less sensitive (˜30%) for distal disease such as FMD Risk of nephrogenic systemic fibrosis if mod-sev CKD
Angiography (DSA)	gold standard		Allows measurement of gradients Invasive, contrast agent nephrotoxic
Plasma Renin Activity (PRA)	50-80%	low	Not 1st line. Can ↑ Se by measuring 1 hr after capto administration
Captopril Renal Scan	75-100%	n/a	Not 1st line, but can determine hemodynamic signif of stenosis. Not reliable in bilateral RAS or poor renal fxn.

*Resistive index = [(peak syst vel - end diast vel) / peak syst vel].

- Monitoring: for athero, repeat imaging only necessary if Δ in clinical status that would lead to intervention; for FMD image q6-12mo to assess for progression

Treatment

- If due to atherosclerosis, risk factor modification: quit smoking, ↓ chol
- Antihypertensive Rx effective for most Pts: diuretic + ACEI/ARB (watch for ↑ Cr) or CCB
- Revascularization (typically percutaneous w/ stenting):

  Had considered if refractory HTN, recurrent flash pulm edema, worsening CKD

  However, clinical trials enrolling stable Pts w/ mod stenosis (50-70%) and HTN on ≥2 agents showed no benefit on # of BP meds, renal fxn or CV outcomes (*NEJM* 2000;342:1007; 2009;361:1953; 2014;370:13). Unknown if beneficial in more severe stenoses or in higher-risk Pts (eg, recent CHF, >3 meds).

  Resistive index >80 on U/S implies intrinsic renal damage and thus less likely to benefit from revasc, so may predict outcome after intervention (*NEJM* 2001;344:410). Operator dependent and some studies have not replicated findings, so not utilized broadly.

  Renal vein renin measurements, PRA, captopril renogram may provide supportive evidence as to hemodynamic significance of RAS, but limited utility due to low Se

  For FMD (usually more distal lesions): PTA ± bailout stenting
- Surgery (very rare): resection of pressor kidney
- Bilateral RAS: 20-46% of Pts w/ RAS. Associated w/ higher creatinine and worse CV outcomes. In addition to anti-HTN Rx, consider revasc if likely to benefit (failure of meds, recurrent pulmonary edema, progressive renal failure). Trials including Pts w/ bilateral RAS did not show benefit but included moderate stenoses.

AORTIC ANEURYSMS

Definitions

- **True** aneurysm (≥50% dilation of all 3 layers of aorta; <50% called ectasia) vs **false or pseudoaneurysm** (rupture contained by adventitia)
- **Location:** root (annuloaortic ectasia), thoracic aortic aneurysm (TAA), thoracoabdominal aortic aneurysm (TAAA), abdominal aortic aneurysm (AAA)
- **Type:** fusiform (circumferential dilation) vs saccular (localized dilation of aortic wall)

Epidemiology (*Circ* 2010;121:e266, 2011;124:2020 & 2013;127:e6; *Nat Rev Cardiol* 2011;8:92)

- In U.S., ~15,000 deaths/y from aortic ruptures; overall ~50,000 deaths/y from Ao disease
- **TAA:** 10/100,000 Pt-yrs, ♂:♀ 2:1; ~60% root/ascending; 40% descending

- **AAA:** ~4-8% prev in those >60 y (although may be ↓ ; *Circ* 2011;124:1118); 4-6× more common in ♂ vs ♀; mostly infrarenal
- Arch & TAAA rarer

Pathophysiology (*NEJM* 2009;361:1114; *Nat Med* 2009;15:649)

- Medial degeneration and/or ↑ wall stress

  Medial degeneration = muscle apoptosis, elastin fiber weakening, mucoid infiltration

  Wall stress ∝ [(ΔP × r) / (wall thickness)], LaPlace's law
- **TAA:** most commonly medial degeneration; seen w/ connective tissue disorders & aortitis
- **AAA:** most commonly long-standing HTN + athero/inflammation → medial weakening

Risk factors

- Classic: **HTN**, **atherosclerosis**, **smoking**, **age**, **male sex**
- **Marfan syndrome** (mutations in fibrillin-1, *FBN*-1): cardinal features are Ao root aneurysm & ectopia lentis. Other suggestive signs include: tall stature; arachnodactyly w/ *thumb sign* (entire distal phalanx of adduct. thumb extends beyond ulnar border of palm) and/or *wrist sign* (tip of thumb covers 5th finger fingernail when wrapped around contralat wrist); pectus deformities; scoliosis; dural ectasia; spontaneous PTX; MVP.
- **Loeys-Dietz syndrome** (mutation in TGF-β receptors 1 or 2, *TGFBR1/2*): triad of arterial tortuosity & aneurysms, widely spaced eyes, bifid uvula or cleft palate. Also w/ velvety & hyperlucent skin and bluish sclera.
- Vascular **Ehlers-Danlos syndrome** (mutation in type III procollagen, *COL3A1*): easy bruising; thin, translucent skin w/ visible veins (but not excessively stretchable); acrogeria (aged appearance of hands & feet); flexible digits; uterine or intestinal rupture; distinctive facial features (protruding eyes, thin nose & lips, sunken cheeks, small chin)
- Other genetic disorders: **bicuspid AoV**; Turner syndrome (45X; short stature, ovarian failure, Ao coarctation); other familial aortopathies (mutations in smooth muscle myosin & actin genes including MYH11 and ACTA2)
- **Aortitis:** Takayasu's, GCA, spondyloarthritis, IgG4-related disease
- **Infection** (ie, mycotic aneurysm): salmonella, TB, syphilis

Screening (*Circ* 2010;121:e266 & 2011;124:2020; *Annals* 2014;161:281; *JAMA* 2015;313:1156)

- **TAA:** if bicuspid AoV or 1° relative w/: (a) TAA or bicuspid valve, (b) Marfan, Loeys-Dietz, Turner; known relevant genetic mutation (see above)
- **AAA:** ✓ for pulsatile abd mass; U/S ♂ >60 y w/ FHx of AAA & ♂ 65-75 y w/ prior tobacco

Diagnostic studies (*Circ* 2010;121:e266 & 2011;124:2020)

- **Contrast CT:** quick, noninvasive, high Se & Sp for all aortic aneurysms
- **TTE/TEE:** TTE most useful for root and proximal Ao; TEE can visualize other sites of TAA
- **MRI:** preferred over CT for aortic root imaging for TAA; also useful in AAA but time-consuming; noncontrast “black blood” MR to assess aortic wall

- **Abdominal U/S:** screening and surveillance test of choice for infrarenal AAA

Treatment principles (*Circ* 2006;113:e463; 2008;117:1883; 2010;121:1544 & e266)

- Goal is to prevent rupture (50% mortality prior to hospital) by modifying risk factors
- **Smoking cessation:** smoking associated w/ ↑ rate of expansion (*Circ* 2004;110:16)
- **Statin** (to achieve LDL-C <70 mg/dL): ↓ death and stroke & possibly ↓ rate of expansion (*Eur J Vasc Endovasc Surg* 2006;32:21)
- **BP control: βB** (↓ dP/dt) ↓ aneurysm growth (*NEJM* 1994;330:1335)

  ACEI a/w ↓ risk of rupture (*Lancet* 2006;368:659)

  ARB may ↓ rate of aortic root growth in Marfan (*NEJM* 2008;358:2787)

  βB and ARB similar ↓ rate of Ao root growth in children and young adults w/ Marfan (*NEJM* 2014;371:2061)

- Moderate cardiovascular exercise okay, but no burst activity/exercise requiring Valsalva maneuvers (eg, heavy lifting)
- **Indications for intervention** (surgery/endovascular repair)

  Individualize based on FHx, body size, gender, anatomy, surgical risk

  TAA (*Circ* 2010;121:1544 & e266) symptoms

  ascending Ao ≥5.5 cm (4-5 cm if Marfan, bicuspid AoV, Loeys-Dietz, vascular EDS, or other genetic/familial disorder)

  descending >6 cm ↑ >0.5 cm/y

  aneurysm >4.5 cm and planned AoV surgery

  AAA (*NEJM* 2002;346:1437 & 2014;371:2101) symptoms infrarenal ≥5.5 cm, but consider ≥5.0 cm in ♀ ↑ >0.5 cm/y; inflam/infxn

Surgery (*Circ* 2010;121:e266; *EHJ* 2014;25:2873)

- Ascending aorta

  No root involvement: resection & replacement w/ Dacron tube graft

  Root involvement: need to address AoV integrity; depending on AoV itself: modified Bentall: Dacron Ao root + prosthetic AoV, reattach coronaries valve-sparing: reimplant native AoV in Dacron Ao graft; reattach coronaries

- Arch: high-risk, complex surgery because of the arch branches; variety of combinations of partial/complete resection, stent graft & bypass of arch vessels
- Descending thoracic aorta: resection & grafting vs endovascular repair (qv)

Endovascular repair (EVAR) (*NEJM* 2008;358:494; *Circ* 2011;124:2020 & 2015;131:1291)

- Depends on favorable aortic anatomy
- TEVAR (thoracic EVAR) for descending TAA ≥5.5 cm may ↑ periop morbidity and possibly mortality (*Circ* 2010;121:2780; *JACC* 2010;55:986; *J Thorac CV Surg* 2010;140:1001 & 2012;144:604)
- AAA

Guidelines support open repair or EVAR for infrarenal AAA in good surg candidates ↓ short-term mort., bleeding, LOS; but long-term graft complic. (3-4%/y; endoleak, need for reintervention, rupture) necessitate periodic surveillance, with no proven Δ in overall mortality in trials, except ? in those <70 y (*NEJM* 2010;362:1863, 1881 & 2012;367:1988)

In observational data, EVAR assoc w/ ↑ survival over 1st 3 y, after which survival similar. Rates of rupture over 8 y 5.4% w/ EVAR vs 1.4% w/ surgery (*NEJM* 2015;373:328)

In Pts unfit for surgery or high periop risks: ↓ aneurysm-related mortality but no Δ in overall mortality over medical Rx (*NEJM* 2010;362:1872). EVAR noninferior (? superior) to open repair in ruptured AAA w/ favorable anatomy (*Ann Surg* 2009;250:818).

- Pt selection for endovascular includes requirement to comply with long-term surveillance

Complications (*Circ* 2010;121:e266; *Nat Rev Cardiol* 2011;8:92)

- **Pain:** gnawing chest, back or abdominal pain; new or worse pain may signal rupture
- **Rupture:** risk ↑ w/ diameter, ♀, current smoking, HTN

  TAA: ~2.5%/y if <6 cm vs 7%/y if >6 cm

  AAA: ~1%/y if <5 cm vs 6.5%/y if 5-5.9 cm rupture p/w severe constant pain and hemorrhagic shock; ~80% mortality at 24 h
- **Aortic insufficiency (TAA)** and **CHF**
- **Acute aortic syndromes** (qv)
- **Thromboembolic ischemic events** (eg, to CNS, viscera, extremities)
- **Compression of adjacent structures** (eg, SVC, trachea, esophagus, laryngeal nerve)

Follow-up (*Circ* 2010;121:1544 & e266; *Nat Rev Cardiol* 2011;8:92; *JAMA* 2013;309:806)

- Expansion rate ~0.1 cm/y for TAA, ~0.3-0.4 cm/y for AAA
- AAA: <4 cm q2-3 yrs; 4-5.4 cm q6-12 mos; more frequent if rate of expansion >0.5 cm in 6 mo
- TAA: 6 mo after dx to ensure stable, and if stable, then annually (*Circ* 2005;111:816)
- Screen for CAD, PAD and aneurysms elsewhere, espec popliteal. About 25% of Pts w/ TAA will also have AAA, and 25% of AAA Pts will have a TAA: consider pan-Ao imaging.
- Patients with endovascular repair require long-term surveillance for endoleak & to document stability of aneurysm

ACUTE AORTIC SYNDROMES

Definitions (*Circ* 2005,112:3802 & 2010;121:e266; *Eur Heart J* 2012;33:26)

- **Aortic dissection** (AoD): intimal tear → blood extravasates into Ao media (creates false lumen). Rate 3-16/100,000 Pt-yrs. False lumen acts as "wind sock," ↑ in size and compressing true lumen (patency of false lumen associated with outcome).
- **Intramural hematoma** (IMH): vasa vasorum rupture → medial hemorrhage that does not communicate with aortic lumen; 6% of aortic syndromes; clinically managed as AoD

- **Penetrating ulcer** (PAU): atherosclerotic plaque penetrates elastic lamina → medial hemorrhage. PAU in setting of IMH assoc. w/ similar outcomes as AoD. Outcomes for isolated PAU less well defined but considered AAS. Rx depends on clinical context.

Classification (proximal twice as common as distal)

- **Proximal:** involves ascending Ao, regardless of origin (= Stanford A, DeBakey I & II)
- **Distal:** involves descending Ao only, distal to L subclavian art. (= Stanford B, DeBakey III)
- **Other Considerations:** isolated to arch generally treated as proximal; distal with involvement of subclavian depends on overall clinical picture.

Risk factors

- **Classic** (in older Pts): **hypertension** (h/o HTN in >70% of dissections); **age** (60s-70s), **male sex** (~70% ♂); **smoking**
- **Genetic or acquired predisposition** (may present younger; see "Aortic Aneurysms"):

  Connective tissue disease/congenital anomaly: Marfan, Loeys-Dietz, vascular Ehlers-Danlos, bicuspid AoV, coarctation (eg, in Turner's), other familial aortopathies, PCKD

  Aortitis: Takayasu's, GCA, Behçet's, syphilis

  Pregnancy: typically 3rd trimester
- Other environmental factors:

  Trauma: blunt, deceleration injury

  Cardiovascular procedures: IABP, cardiac or aortic surgery, cardiac catheterization

  Acute ↑ BP: cocaine, Valsalva (eg, weightlifting)

Clinical Manifestations and Physical Exam* (*JAMA* 2000;283:897)

Feature	Proximal	Distal
"Aortic" pain (abrupt, severe, tearing or ripping quality, *maximal at onset* [vs crescendo for ACS])	**94%** (chest, back)	**98%** (back, chest, abd)
Syncope (often due to tamponade)	**13%**	4%
HF (usually due to acute AI)	**9%**	3%
CVA	**6%**	2%
HTN	36%	**70%**
HoTN or shock (tamponade, AI, MI, rupture)	**25%**	4%

Pulse deficit (if involves carotid, subclavian, fem)	**19%**	**9%**
AI murmur	**44%**	12%

*S/S correlate w/ affected branch vessels & distal organs; may Δ as dissection progresses.

Initial evaluation (*Circ* 2010;121:e266)

- H&P, including bilateral BP and radial pulses for symmetry

  High-risk conditions: Marfan, CTD, FHx AoD, recent Ao manip., AoV dis., Ao aneurysm

  High-risk pain features: chest, back or abd pain described as [both (abrupt onset or severe intensity) and (ripping, tearing, sharp or stabbing) (absence ⊖ LR 0.3)]

  High-risk exam features:

  perfusion deficit [pulse deficit (⊕ LR 5.7), systolic BP differential (>20 mmHg), or focal neuro deficit + pain (⊕ LR >6)], or

  murmur of AI (new or not known to be old and in conjunction w/ pain), or hypotension or shock
- 12-lead ECG: often abnl but non-dx; may show STE if prox AoD involving coronary
- CXR: abnl in 60-90% [↑ mediast. (absence ⊖ LR 0.3), L pl effusion] but *cannot* r/o AoD
- *Obtain expedited Ao imaging if:* ≥2 high-risk features, 1 high-risk feature w/o clear alternative dx, or 0 features but unexplained HoTN or widened mediastinum on CXR

Diagnostic studies (*Circ* 2010;121:e266; *JACC CV Img* 2014;7:406)

- **CT:** quick, noninvasive, readily available, Se ≥93% & Sp 98%; however, if ⊖ & high clin. suspicion → additional studies (⅔ w/ AoD have ≥2 studies; *AJC* 2002;89:1235)
- **MRI:** Se & Sp >98%, but time-consuming test & not readily available
- Axial studies (CT, MRI) should be gated to ECG to evaluate Ao root; if high index of suspicion, study should include entire aorta (chest, abd, & pelvis)

- Echo

  TTE: low Se (∴ not dx study) but can show effusion, AI, & dissection flap (if proximal)

  TEE: Se >95% prox, 80% for distal; can assess cors/peric/AI; "blind spot" behind trachea
- **Aortography:** Se ~90%, time-consuming, cannot detect IMH; can assess branch vessels
- **D-dimer:** Se/NPV ~97%; ? <500 ng/mL to r/o dissec (*Circ* 2009;119:2702) but not in Pts at high clinical risk (doi:10.1016/j.annemergmed.2015.02.013); does not r/o IMH

Initial medical treatment (*Lancet* 2008;372:55; *Circ* 2010;121:1544; *JACC* 2013;61:1661)

- ↓ **dP/dt** targeting HR <60 & central BP <120 (or lowest that preserves perfusion; r/o pseudohypotension, eg, arm BP ↑ due to subclavian dissection; use highest BP reading)

- ***First* with IV βB** (eg, esmolol, labetalol) to blunt reflex ↑ HR & inotropy that would occur in response to vasodilators; verap/dilt if βB contraindic.
- ***Then* ↓ SBP with IV vasodilators** (eg, nitroprusside)
- HTN control may require multiple agents (median of 4 in one study; *J Hum Hypertens* 2005;19:227). If unable to control readily: 1st evaluate for complication (eg, visceral ischemia); Rx pain w/ MSO_4; if no complication, then consider other drivers (eg, EtOH withdrawal).
- **If HoTN:** urgent surgical consultation, IVF to achieve euvolemia, pressors to keep MAP 70 mmHg; r/o complication (eg, tamponade, contained rupture, severe AI)

Treatment of proximal AoD (*Circ* 2010;121:1544; *Lancet* 2015;385:800)

- *Acute:* all cases should be considered for emergent surgery

  root replacement; valve sparing unless bicuspid or valve involvement

  acute stroke should not necessarily dissuade from surgery (mortality w/o surgery ~100%, *Circ* 2013;128:S175)

  prior AoV surgery postulated to be protective from complications, but most would operate

  need for preop coronary angio debatable as procedure nontrivial in setting of dissection and likelihood of performing concomitant CABG low
- *Chronic:* consider surgery if complicated by progression, AI or aneurysm

Treatment of distal AoD (*Circ* 2010;121:1544; *JACC* 2013;61:1661; *Lancet* 2015;385:800)

- Intervention warranted if complication (see below)
- Endovascular intervention (fenestrate flap to decompress false lumen, open occluded branch, stent entry tear) may be preferred over surgery due to possible ↑ mort. (*JACC* 2013;61:1661 & *Circ* 2015;131:1291)
- Stent graft for *uncomplicated* cases may ↓ risk of aorta-related complications and adverse remodeling (*Circ Cardiovasc Interven* 2013;6:407)

Complications (occur in ~20%; *Circ* 2003;108:II-312 & 2010;121:e266)

- *Monitor all Pts w/ frequent assessment (sx, BP, UOP), pulse exam, labs (Cr, Hb, lactic acid), imaging (~7 d or sooner if sx or significant lab Δ)*
- *Uncontrolled BP despite intensive IV Rx or continued or → pain may indicate complication*
- **Progression:** propagation of dissection, ↑ aneurysm size, ↑ false lumen size
- **Rupture:** pericardial sac → tamponade (avoid pericardiocentesis unless PEA); blood in pleural space, mediast., retroperitoneum; ↑ in hematoma on imaging portends rupture
- **Malperfusion** (partial or complete obstruction of branch artery) can be *static* (avulsed/thrombosed) or *dynamic* (Δs in pressure in true vs false lumen) coronary → MI (usually RCA → IMI, since dissection often along outer Ao curvature) innominate/carotid → CVA, Horner intercostal/lumbar → spinal cord ischemia/paraplegia innominate/subclavian → upper extremity ischemia; iliac → lower extremity ischemia celiac/mesenteric → bowel ischemia (can be subtle w/ nonspecific GI sx, anorexia, pain) renal → acute renal failure or gradually ↑ Cr, refractory HTN
- **AI:** due to annular dilatation or disruption or displacement of leaflet by false lumen
- Mortality (*Circ* 2013;127:2031; *JACC* 2015;66:350)

~50% prior to hospital

historically ~1%/h × 48 h for acute prox AoD who survive to hospital w/ 47% subseq mort at 30 d; more recent data w/ 22% in-hospital mortality

13% at 30 d for acute distal overall but 25% if complications mortality similar for proximal and distal that survive to discharge: ~85% at 5 y

Long-term monitoring

- Major concern is progression to aneurysm or recurrent dissection
- Treat BP, risk factors aggressively
- **Serial imaging for all** (CT or MRI, latter may be preferred to lower cumulative radiation exposure) at 1, 3, and 6 mo, and then annually (18 mo, 30 mo, etc.)
- Pts treated endovascularly need close follow-up to monitor for complication (eg, endoleak)
- Partial thrombosis of false lumen associated with worse outcomes/mortality (*NEJM* 2007;357:349)
- In patients who present at young age or other indications of predisposing factor, consider genetic evaluation and screening of family members

PERIPHERAL ARTERY DISEASE (PAD)

Epidemiology and risk Factors

- Prev. ↑ w/ age: <1% if <40 y, ~15% if ≥70 y; risk factors incl. **smoking**, **DM**, HTN, chol
- More frequent in Pts w/ other symptomatic atherosclerotic disease (eg, coronary, carotid)
- Associated w/ ↑ risk of CV events (*JAMA* 2007;297:1197)
- If sx, 3-y risk of stroke ~3%, acute limb ischemia ~4%, periph revasc ~22% (*Circ* 2013;112:679)

Clinical Features

- **Asymptomatic** (~35%) or **atypical** sx (~40%): often undertreated in terms of risk factor modifying therapy (*Circ* 2011;124;17)
- **Claudication** (~25%): dull ache, often in calves precip by walking & relieved by stopping (vs spinal stenosis, qv)

  Leriche syndrome (aortoiliac occlusive disease): buttock & thigh claudication, ↑ or ø femoral pulses, & erectile dysfxn
- **Critical limb ischemia** (CLI, 1-2%): 1 or more of the following 3 manifestations

  rest pain: ↑ w/ elevation b/c ↓ perfusion

  ulcer: typically at pressure foci, often dry (in contrast, venous ulcers are more often at medial malleolus, wet, and with hemosiderin deposition)

  gangrene: more typically “dry” (ie, distal limb, dry shrunken and dark red, lack of pus) as a manifestation of ischemia due to impaired blood flow rather than “wet” (ie, infected, pus present, fetid smell), which may occur in the setting of infection or injury may be chronic (ie, sx >2-wk duration) vs acute limb ischemia, which is a

vascular emergency (see below)

a/w poor outcome: 45% amputation & 20% mortality at 6 mo (*J Vasc Surg* 2000;31:S1)

- Blue toe syndrome: most likely atheroembolic disease with occlusion of digital arteries

PAD Clinical Symptom Classification

Rutherford		Fontaine		Typical ABI*
Stage	**Definition**	**Stage**	**Definition**	
0	Asx	1	Asx	0.9-1.0
1	Mild claudication	2a	Sx at distance >650 ft	0.4-0.9
2	Mod claudication			
3	Severe claudication	2b	Sx at distance <650 ft	
4	Rest pain	3	Nocturnal or rest pain	<0.4
5	Ischemic ulceration not exceeding ulcer on digits of foot	4	Necrosis (death of tissue) and/or gangrene of limb	
6	Severe ischemic ulcers or frank gangrene			

*ABI is generally, but not absolutely correlated w/ clinical measures of lower extremity fxn & sx

Diagnosis

- Ddx includes

  nonvascular:

  neurogenic claudication (spinal stenosis): pain w/ standing, relieved by sitting, lying, or forward flexion; a/w neurologic abnl (weakness, sensory Δs, h/o deg. disc disease)

  musculoskeletal/arthritis: joint pain, morning stiffness, associated joint pathology or instability, crepitus or effusion

  Baker's cyst: posterior knee pain, knee stiffness, mass behind knee, discomfort w/ prolonged standing, impairment of bending

  non-athero vascular:

  venous claudication (uncommon): pain w/ walking in setting of proximal venous obstruction & no arterial obstruction

  dissection, embolism, aneurysm, or vasculitis

popliteal artery entrapment (exercise-induced lower leg pain)

- Physical exam: ↓ peripheral pulses ± femoral bruits if severe: pallor of feet w/ elevation, dependent rubor, cyanosis other signs of chronic PAD: hair loss/shiny or cool skin, skin atrophy, nail hypertrophy

Testing

- **Ankle:brachial index (ABI):** nl 1-1.4; borderline 0.91-0.99; abnl ≤0.90; if > 1.4, non-dx, likely due to calcified/noncompressible vessel
- **Toe:brachial index (TBI)** helpful if noncompressible (toe artery less likely to calcify); but ranges different than ABI (>0.7 nml, 0.5-0.7 mild, 0.35-0.5 mod, <0.35 mod-severe, severe if toe pressure <30 mmHg)

- **Segmental pressures** to determine level of disease (20 mmHg gradient between segments indicates stenosis)
- **Pulse volume recording (PVR)** done w/ segmental pressures: determine site and severity of disease. Abnormal waveform can indicate disease in noncompressible vessel, but pressures used over waveform if vessels are compressible.
- If ⊕ sx but nl ABI: ✓ **exercise ABI** (some consider even in asx Pt w/ risk factors for PAD if will modify therapy)
- Treadmill study (or 6-min walk test) to quantify magnitude of functional limitation
- **Imaging** (Duplex arterial U/S; CTA w/ distal run-off; MRA or angio) if dx in question or considering intervention. Some do routine Duplex U/S to monitor graft/stent patency.

Medical treatment (*JACC* 2013;61:1555; *JAMA* 2013;309:453; *Circ Res* 2015;116:1579)

- **Treat risk factors:** smoking cessation, high-intensity statin, control HTN & DM, smoking cessation (*JACC* 2010;56:2105). βB OK if indicated for another reason (eg, CAD, AF).
- **Antiplatelet Rx:** benefit shown primarily for ↑ CV risk (*BMJ* 2002;324;71)

  If asx: benefit of antiplt Rx unclear espec if ABI only borderline (*JAMA* 2010;303;9)

  If sx: ASA or clopidogrel

  ASA: 23% ↓ risk of major CV events seen in meta-analysis of older studies (mostly ASA but also other antiplatelet Rx) (*BMJ* 2002;324:71)

  Clopidogrel: superior to ASA, but single, older study (*Lancet* 1996;348:1333)

  ASA+clopi may be better than ASA alone, but only posthoc data (*EHJ* 2009;30:1992)

  Vorapaxar (PAR-1 antag.) further ↓ risk on top of ASA or clopidogrel (*Circ* 2013;112:679)
- Anticoagulation w/ warfarin not beneficial (*NEJM* 2007;357:217)
- **ACEI/ARB** to ↓ CV risk (*NEJM* 2000;342:145)
- **Improve claudication**

  Supervised exercise: sx-limited, ≥3×/wk, ≥30-45 min/session, ↑ as tolerated; beneficial including ↑ walking time 50-200% (*Cochrane* 2014;7:CD990); structured exercise more effective than home-based, but home-based still effective (*JAMA* 2013;310:57)

  ACEI & statins may ↓ sx (*Circ* 2003;108:1481)

  Cilostazol (nb, interacts w/ diltiazem & omeprazole; may cause headache or diarrhea; do not use in Pts w/

CHF); pentoxifylline likely less effective

- **Limb preservation:** foot exams for ulcers/wounds, revasc (qv), vorapaxar (PAR-1 antag) ↓ acute limb ischemia (*Circ* 2013;112:679), statin use assoc. w/ ↓ amput (*EHJ* 2014;35:2864)

Revascularization

- Consider if limiting sx despite exercise/medical Rx or if CLI; also consider as 1st-line Rx for isolated aortoiliac disease given high rate of long-term patency (*Circ* 2013;128:2704)
- **Endovascular** (angioplasty or stenting) usually favored over **surgical** (bypass or endarterectomy), but depends on lesion complexity & location (aortoiliac or "inflow" vs infrainguinal or "outflow") and Pt comorbidities
- Decision for stent vs angioplasty alone depends on lesion length & complexity, location (eg, over joints) (*J Vasc Surg* 2007;33:S1)
- Angioplasty w/ paclitaxel-coated balloon associated with ↑ primary patency vs regular balloon for femoropopliteal disease (*NEJM* 2015;373:145)
- Durability of endovascular revascularization depends in part on location, with greater longterm patency for iliac vs femoral interventions (*JACC* 2006;47:e1)
- Dual antiplatelet (DAPT, ASA + clopidogrel) commonly prescribed after endovascular intervention for 1-3 mo, but no prospective data. DAPT after bypass surgery not beneficial overall but possibly in subgroup w/ prosthetic grafts (*J Vasc Surg* 2010;52:825).
- Anticoagulation with warfarin does not improve patency (*NEJM* 2007;357:217), but may be indicated in subgroups with high thrombotic risk
- Stents not ferromagnetic, so MRI safe, but both MRI & CT may have artifact. Duplex U/S useful to assess stent patency and is used by some for serial routine monitoring of stent or graft patency, even in asx Pts.
- If coronary angiography needed, avoid access through CFA stent or femoral bypass

Acute limb ischemia (ALI)

- Sudden decrement in limb perfusion that threatens viability; *viable* (no immed threat of tissue loss): audible art. Doppler signals, sensory & motor OK *threatened* (salvage requires prompt Rx): loss of arterial Doppler signal, sensory or motor
- Etiologies: embolism > acute thrombosis (eg, athero, APLA, HITT), trauma to artery
- Clinical manifestations (**6 Ps**): pain (distal to proximal, ↑ in severity), poikilothermia, pallor, pulselessness, paresthesias, paralysis
- Testing: thorough pulse & neuro exam; arterial Doppler; angiography, either CT w/ bilateral run-off through feet or arteriography
- Urgent consultation w/ vascular medicine and/or vascular surgery
- Treatment: immediate anticoagulation ± intra-arterial lytic; angioplasty or surgery

CEREBROVASCULAR DISEASE

EXTRACRANIAL DISEASE

Pathobiology

- Involving portions of carotid or vertebral arteries outside skull. Most commonly at carotid bifurcation but may involve common (CCA), internal (ICA), or external carotid (ECA).
- Most common etiology is athero; others include FMD, vasculitis, dissection, & radiation
- Associated w/ ↑ risk of systemic CV events including ipsilateral TIA/stroke
- Progressive narrowing, thrombosis or unstable plaque in CCA or ICA → embolization and/or ↑ distal perfusion → ischemia → TIA/stroke
- Asx *chronically occluded* vessel associated w/ low risk, as no embolization and Circle of Willis provides collateral flow

Diagnosis (*Circ* 2011;124:354)

- Stenosis defined as % lumen diameter at most severe stenosis relative to either ICA, probable lumen diameter at site of stenosis, or proximal common carotid (*J Neuroimaging* 1994;4:222). Significant stenosis is >50%.
- Carotid bruit suggestive but not sensitive
- **Duplex U/S:** Se >80%, Sp ~85%; 1st-line test

  Peak systolic velocity (PSV) for severity

  ↑ end diastolic velocity (EDV), spectral broadening, carotid index (ratio of PSV in ICA vs CCA) and echolucent plaque each associated w/ ↑ risk

  PSV >200 cm/s + EDV > 140 cm/s + carotid index > 4.5 has Se 96% for significant stenosis (*Stroke* 1996;27:1965; *Mayo Clin Proc* 2000;75:1133)
- Transcranial Doppler (TCD) as adjunct to U/S may show severe stenosis, evidence of occlusion (collateral flow), or microemboli by high-intensity signal transients (HITS)
- If significant but nonsevere stenosis, repeat study at 6 mo to determine if stable and then annually thereafter
- If stenosis appears severe (≥70%) or requires further characterization, then either CT angio (Se ~90%, Sp ≥95%) or MRA (Se ~95%, Sp ≥95%). Caution with contrast & risk of either renal dysfxn (CTA) or nephrogenic systemic fibrosis (MRA).
- Angiography gold standard but invasive and assoc w/ risk of stroke

Asx carotid stenosis (*Curr Treat Opt CV Med* 2013;252:63; *Expert Rev CV Ther* 2014;12:437)

- Cause of <15% of strokes and risk <1% annually in Pts on standard med Rx (see below)
- General management

  lifestyle intervention (smoking cessation, diet modification, exercise)

  antiplatelet therapy: ASA 75-325 mg/d or clopidogrel 75 mg/d if ASA allergic (*Circ* 2011;124:354)

  high-intensity statin (see "Lipids") and **BP control** (see "HTN")
- **Revascularization** (see options below) for selected Pts w/ ≥70% stenosis

  older trials have shown ↓ stroke risk vs med Rx alone, but not compared to modern med Rx (*NEJM*

1993;328:221; *JAMA* 1995;273:1421; *Lancet* 2004;363:1491)

due to low rate of associated stroke, absolute risk reduction likely small and benefit of intervention debated

consider Pt preference, risk of procedure, overall life expectancy (eg, ≥5 y), gender (benefit less certain in women), lesion characteristics of ↑ stroke risk (eg, echolucent plaque, TCD evidence of microemboli)

Symptomatic carotid stenosis (*NEJM* 2013;369:12)

- Symptomatic stenosis indicative of severe/unstable plaque and associated w/ ↑ risk of stroke. ∴ determination of sx important regarding treatment plan.
- Defined as recent (<6 mo) focal neurologic sx, sudden in onset, referable to carotid distribution. May include TIA or minor stroke [incl amaurosis fugax (transient monocular blindness)]. Vertigo & syncope unlikely related and generally not considered sx.
- For acute treatment for stroke, see “Stroke”
- All Pts w/ sx stenosis should receive med Rx as above
- Revascularization (*NEJM* 1991;325:445; *Lancet* 2004;363:915)

  recommended for 70-99% stenosis, generally w/in 2 wk unless severe comorbidity w/ limited lifespan, severe ipsilateral stroke w/ persistent deficit, occluded carotid, or high operative risk (≥6%)

  consider for 50-69% stenosis, depending on Pt-specific factors

  not indicated if <50% stenosis

Revascularization options

- **Carotid endarterectomy** (CEA): gold standard. Risk of procedural stroke or death <3% for asymptomatic disease and <6% for sx disease in experienced centers.
- Carotid artery stenting (CAS; *JACC* 2014;64:722): compared w/ CEA, periprocedural risk of stroke ↑ (espec in elderly) & MI ↑ (although many asx), subsequent rates of stroke similar (*NEJM* 2010;363:11; *Lancet* 2010;376:1062). Consider if not surgical candidate (anatomy or comorbidities). Generally requires DAPT (ASA + clopidogrel) for 30 d.

INTRACRANIAL DISEASE

- Cerebral and basilar arteries and distal branches thereof
- Most common etiology is athero & assoc w/ traditional athero risk factors (*Circ* 2014;1407:14); others include: dissection, FMD, vasoconstriction, vasculitis, moyamoya
- Estimated to cause 5-10% of ischemic strokes and more prevalent among blacks, Hispanics and Asians (*Stroke* 1995;26:14)
- Diagnosis: MRA, CTA, or TCD vs angio (see above); duplex U/S not useful
- Medical treatment similar as in extracranial; however, consider ASA+clopidogrel for sx disease for 90 d (*NEJM* 2011;365:993)
- Stenting and intracranial bypass not shown to be beneficial and not routinely recommended (*NEJM* 2011;365:993; *JAMA* 2015;313:1240)

PHARMACOLOGIC SECONDARY STROKE PREVENTION

Antiplatelet therapy (*NEJM* 2012;366:1914)

- In general monotherapy preferred to multiagent therapy for long-term prevention due to ↑ ICH risk w/ multiagent therapy
- **ASA:** ↓ death & repeat stroke; equal to warfarin in nonembolic stroke (*NEJM* 2001;345:1444)
- **Clopidogrel:** marginally superior to ASA, slightly ↑ ICH (*Lancet* 1996:348:1329)
- **Multiagent antiplatelet therapy:**

  ASA + clopi: not more effective than ASA alone and ↑ bleeding & ICH (*Lancet* 2004;364:331; *NEJM* 2012;367:817). In *minor stroke/*TIA, ASA + clopi × 21 d → clopi monoRx vs ASA monoRx resulted in ↓ stroke w/o ↑ ICH (*NEJM* 2013;369:11).

  ASA + dipyrimadole: superior to ASA (*Lancet* 2006;367:1665), but ↑ ICH and poor compliance

  Addition of vorapaxar to ASA or ASA+clopi ↑ first stroke in Pts w/ athero, but contra-indicated in patients w/ prior stroke due to ICH risk (*NEJM* 2012;366:1404; *Stroke* 2013;691:8)

Anticoagulation

- Not routinely indicated. Anticoag if cardiac/paradoxical emboli (except bacterial endocarditis) or hypercoag state. See "AF" and "VTE" for details.
- **Hold off on anticoag** in large strokes for ~2-4 wk given risk of hemorrhagic conversion.

Risk factor management

- BP (see "HTN"): long-term SBP target 120-139 mmHg (*JAMA* 2011;306:2137)
- LDL: high-intensity statin therapy (*Circ* 2014;129(*Suppl* 2):S1)

OTHER CEREBROVASCULAR DISEASES

Cervical artery dissection

- May involve intracranial or extracranial arteries. Manifests as luminal stenosis, thrombo-embolism or aneurysm. ~20% of ischemic strokes in young Pts (primarily embolic).
- Etiologies: trauma, physical activity, ? neck manip.; can be spontaneous (if assoc cond.)
- FMD most common assoc. condition (seen in 15-20%). Others infrequent: vascular EDS, Marfan, osteogenesis imperfect, homocystinuria, PKD, α_1-AT.
- Most (>60%) report HA or neck pain, Horner's in ~25%, tinnitus, rarely eye pain
- Imaging may show "crescent sign" of hematoma, string sign, tapering stenosis, flap or dissected aneurysm. Duplex U/S can be initial screen but lower Se (68-95%) and limited utility at skull base. CTA & MRA w/ similar Se & Sp; angio if inconclusive noninvasive imaging.
- Treatment: if stroke, see "Stroke." In general, thrombolysis should not be withheld if indicated. If SAH, manage accordingly.
- Antithrombotic therapy: either anticoagulation (AC) or antiplatelet Rx may be considered for extracranial dissection; however, large meta-analysis showed no benefit of AC over antiplatelet

  Rx (*Neurology* 2012;79:686). If AC chosen, typically for 3-6 mo, then Δ to antiplatelet. Intracranial dissection treated with antiplatelet monotherapy and not AC.

- Endovascular therapy or surgery considered for selected Pts, particularly if recurrent ischemia; however, no trials to demonstrate benefit.

Patent foramen ovale (PFO; in ˜27% of population) (*NEJM* 2005;353:2361)

- ↑ stroke risk: ≥4-mm separation, R → L shunting at rest, ↑ septal mobility, atrial septal aneurysm
- If PFO & stroke/TIA: no benefit of warfarin over ASA (*Circ* 2002;105:2625), but consider if at high risk for or has DVT/PE. No sig benefit shown for PFO closure so far, albeit studies small & w/ favorable trends (*NEJM* 2012;366:991; 2013:1083 & 1092).

Intracranial aneurysm (*Stroke* 2015;46:2368)

- Prevalence of saccular aneurysms 3.2%, w/ equal sex ratio (*Lancet Neurol* 2011;10:626); 20-30% having > 1 aneurysm
- Associated with family hx, hereditary syndromes (eg, EDS, polycystic kidney), smoking, HTN, aortic coarctation, ? estrogen deficiency (female preponderance after menopause) (*Stroke* 2001;32:606)
- Clinical presentations: most commonly incidental finding on brain imaging may be found in those presenting with SAH, which typically presents as “worst headache of my life,” ± syncope, nausea, vomiting, meningismus (*Neurology* 1986;36:1445) rarely unruptured aneurysms become symptomatic (eg, headache, visual change, cranial neuropathy, facial pain)
- Diagnosis: CTA or MRA
- Instruct Pt to avoid smoking, heavy EtOH use, illicit drugs, straining/Valsalva
- Treatment requires consideration of size, location, Pt age and comorbidities. In general: if sx or SAH → repair if no sx/SAH and ≥7-10 mm, consider repair if <7 mm observe (CTA or MRA q6mo and every 2-3 y once showing no Δ) endovascular coiling ↑ periprocedural morbidity & mortality vs surgical clipping, but ↑ risk of recurrence

Extracranial aneurysm

- Rare (<1% of arterial aneurysms) (*Surgery* 1983;93:319)
- True aneurysm may be associated with athero, trauma, dissection (qv), infection, vasculitis or radiation. Male:female predominance (2:1).
- Infected pseudoaneurysm may occur at site of prior carotid intervention.
- Clinical presentation: TIA/stroke; less likely mass effect or rupture
- Diagnosis: see approach for carotid disease above
- Instruct Pt to avoid smoking, heavy EtOH use, illicit drugs, straining/Valsalva
- Treatment: sx disease should be repaired; consider repair if asx and >2 cm, w/ thrombus, or ≤2 cm but ↑ 'ing. Surgical and endovascular options depending on anatomy & Pt risk.

Cerebral venous thrombosis (CVT) (*Circ* 2012;125:1709)

- Uncommon (<2/100,000/yr); female predominance (3× more common)
- >85% w/ risk factor including: hypercoagulable state, OCP, pregnancy, malignancy, infection, prior trauma, vasculitis, other inflammatory states (eg, IBD), hematologic disorders, nephrotic syndrome

- Clinical presentation variable and includes HA (˜90%), seizure, focal deficits, encephalopathy, sx of isolated intracranial hypertension (HA ± vomiting, papilledema, visual problems) may occur if hemorrhage or edema
- Diagnose w/ MR venography or CT venography (traditional head CT normal in ˜30% of CVT). D-dimer may be elevated but does not reliably exclude.
- Acute treatment

  treat elevated ICP

  consider antiseizure Rx if seizure on presentation or otherwise high risk

  anticoagulation (UFH or LMWH; see VTE for dosing) if no contraindication (nb, presence of ICH not absolute contraindication)

  consider endovascular venous recanalization with direct thrombolysis if progressive neurologic worsening despite anticoagulation
- Chronic treatment

  anticoagulation w/ VKA w/ INR 2-3 for 3-6 mo if provoked or 6-12 if unprovoked

  consider indefinite duration if recurrent, complicated by DVT or PE, or severe thrombophilia

  if occurred in setting of OCP, change to nonestrogen-based contraception
- Monitoring: imaging at 3-6 mo after dx to assess for recanalization

VENOUS THROMBOEMBOLISM (VTE)

Definitions

- Superficial thrombophlebitis: pain, tenderness, erythema along superficial vein
- Deep venous thrombosis (DVT)

  Proximal: thrombosis of iliac, femoral, or popliteal veins (nb, “superficial” femoral vein part of deep venous system)

  Distal: calf veins below knee; lower risk of PE/death than prox (*Thromb Haem* 2009;102:493)
- Pulmonary embolism (PE): thrombosis originating in venous system and embolizing to pulmonary arterial circulation; 1 case/1000 person y; 250,000/y (*Archives* 2003;163:1711)

Risk factors

- Virchow's triad for thrombogenesis

  stasis: bed rest, inactivity, CHF, CVA w/in 3 mo, air travel >6 h (*NEJM* 2001;345:779)

  injury to endothelium: trauma, surgery, prior DVT, inflammation, central catheter

  thrombophilia: APC resistance, protein C or S deficiency, APS, prothrombin gene mutation,↑ factor VIII, hyperhomocysteinemia, HIT, OCP, HRT, tamoxifen, raloxifene
- Malignancy (12% of “idiopathic” DVT/PE)
- History of thrombosis (greater risk of recurrent VTE than genetic thrombophilia)
- Obesity, smoking, acute infection, postpartum (*JAMA* 1997;277:642; *Circ* 2012;125:2092)

- Statin therapy ↑ risk (*NEJM* 2009;360:1851)

Thromboprophylaxis (*Chest* 2012;141:e195S, 227S, 278S)

Patient & situation	Prophylaxis
Low-risk med; same-day surg & <40 y	Early, aggressive ambulation
Minor surgery in mobile Pt	Mechanical Ppx
High-risk medical (eg, immobilized, h/o VTE, thrombophilia or cancer) Most surgery Pts	**UFH** 5000 U SC bid or tid, or **LMWH**, or fonda (if HIT ⊕), or mech Ppx (espec if high bleed risk)
High-risk surg (eg, trauma, recent stroke or spinal cord injury, h/o VTE or thrombophilia)	**[LMWH** or **UFH** SC**] + mech Ppx**
Orthopedic surgery	**LMWH** [or fonda, direct oral anticoag (qv) or warfarin (INR 2-3)] **+ mech Ppx** Start before or shortly after (<12 h) surgery & cont. up to **35 d** (hip) or 1**0-14 d** (knee). LMWH or fonda favored over UFH or VKA. Direct oral anticoagulants overall appear favorable vs LMWH.

For enoxaparin, 30 mg bid for highest risk or 40 mg qd for moderate risk or spinal/epidural anesth. Dose adjust: qd in CrCl <30 mL/min, ↑ 30% if BMI >40 (*Ann Pharmacother* 2009;43:1064).

- **Direct oral anticoagulants vs LMWH** (*Annals* 2012;156:710)

  Dabigatran (approved in Europe & Canada; 110 mg 1-4 h after surgery & hemostasis or 220 mg if not initiated on day of surgery; 220 mg qd maintenance) noninferior to LMWH after hip and knee surgery (*Lancet* 2007;370:949)

  Rivaroxaban (10 mg qd 6-10 h postop) ↓ VTE by ˜25-50% vs enox 40 mg qd, with ≈ bleeding after hip or knee replacement (*NEJM* 2008;358:2765 & 2776; *Lancet* 2009;373:1673)

  Apixaban (2.5 mg bid 12-24 h postop) ↓ VTE by ˜50% vs enox 40 mg qd, with ≈ bleeding after hip replacement (*NEJM* 2010;363:2487)

  Edoxaban (30 mg qd 6-24 h after surgery) ↓ VTE vs enox *20 mg qd,* but no comparison to standard dose enox (*Thromb Res* 2014;134:1198)

- Evolving role for Ppx in ambulatory cancer Pts w/ low bleeding risk and additional VTE risk factors (*NEJM* 2012;366:601). Khorana score (cancer site, plt & WBC counts, Hb, BMI) risk predictor (*Blood*

2008;111:4902). Semuloparin (ultra LMWH) ↓ VTE by ˜2/3 w/o ↑ major bleeding in Pts w/ met. or locally adv. cancer receiving chemo (*NEJM* 2012;366:601).

Clinical manifestations—DVT

- Calf pain, swelling (>3 cm c/w unaffected side), venous distention, erythema, warmth, tenderness, palpable cord, ⊕ Homan's sign (calf pain on dorsiflexion, seen in <5%)
- *Phlegmasia cerulea dolens:* massive proximal DVT → stagnant blood → edema, *cyanosis,* pain, compartment syndrome → can lead to limb loss or death
- 50% of Pts with sx DVT have asx PE
- Palpable tender superficial veins c/w superficial thrombophlebitis rather than DVT
- Popliteal (Baker's) cyst: related to knee pathology, may result in calf pain & may lead to DVT due to compression of popliteal vein

"Simplified Wells" Pretest Probability Scoring of DVT (*JAMA* 2006;295:199)

Clinical variable	Point score
◦ Active cancer (Rx ongoing or w/in 6 mo or palliative)	1
◦ Paralysis, paresis, or recent immobilization of lower extremities	1
◦ Recently bedridden for ≥3 d or major surgery w/in 12 wk	1
◦ Localized tenderness along distribution of deep venous system	1
◦ Entire leg swelling	1
◦ Calf ≥3 cm larger than asx calf (at 10 cm below tibial tuberosity)	1
◦ Pitting edema confined to sx leg	1
◦ Collateral superficial veins (nonvaricose)	1
◦ Previous DVT	1
◦ Alternative dx at least as likely as DVT	-2

Pretest Probability Assessment

Score ≤0	Score 1 or 2	Score ≥3
Low probability (5%)	Moderate probability (17%)	High probability (53%)

- For UE DVT, + 1 point each for venous cath, local pain, & unilateral edema, -1 if alternative dx. ≤1 = unlikely; ≥2 = likely. U/S if likely or if unlikely but abnl D-dimer (*Annals* 2014;160:451).

Diagnostic studies—DVT

- D-dimer: <500 helps r/o; ? use 1000 as threshold if low risk (*Annals* 2013;158:93)
- Compression U/S >95% Se & Sp for sx DVT (lower for asx DVT); survey whole leg rather than just proximal if ≥mod prob (*JAMA* 2010;303:438); venography rarely used

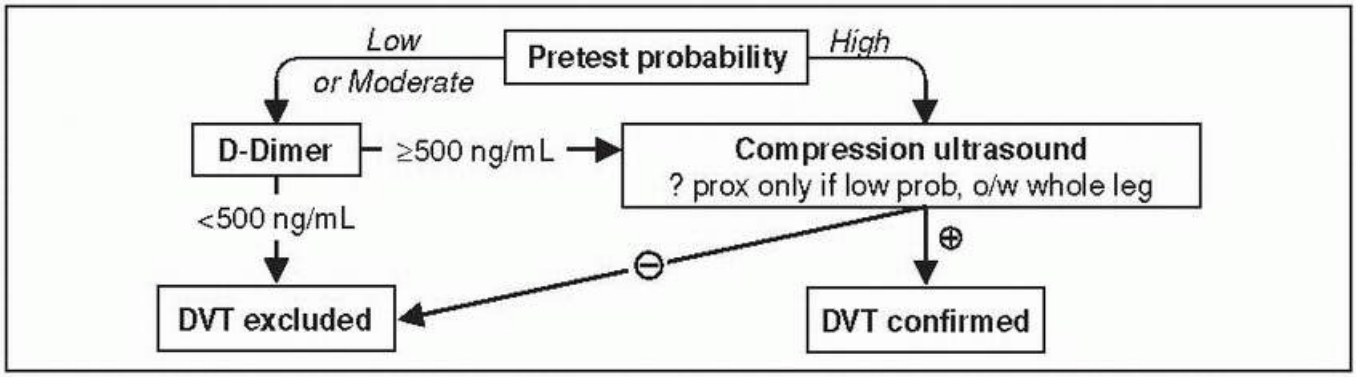


Figure 1-5 Approach to suspected DVT (*Chest* 2012;141:e351S)

Clinical manifestations—PE

- Dyspnea (73%), pleuritic chest pain (66%), cough (37%), hemoptysis (13%)
- ↑ RR (>70%), crackles (51%), ↑ HR (30%), fever, cyanosis, pleural friction rub, loud P_2
- *Massive:* syncope, HoTN, PEA; ↑ JVP, R-sided S3, Graham Steell (PR) murmur

Simplified Wells Pretest Probability Scoring for PE (*Annals* 2011;154:709)

- Prior PE or DVT
- Active cancer
- Immobilization (bed rest ≥3 d) or surgery w/in 4 wk
- Alternative dx less likely than PE
- Clinical signs of DVT
- HR >100 bpm
- Hemoptysis

Dichotomized Wells Probability Assessment

≤1 Variable = "Unlikely" (13% probability)

> 1 Variable = "Likely" (39% probability)

Diagnostic studies—PE (*NEJM* 2010;363:266)

- CXR (limited Se & Sp): 12% nl, atelectasis, effusion, ↑ hemidiaphragm, Hampton hump (wedge-shaped density abutting pleura); Westermark sign (avascularity distal to PE)
- ECG (limited Se & Sp): sinus tachycardia, AF; signs of RV strain → RAD, P pulmonale, RBBB, $S_IQ_{III}T_{III}$ & $TWIV_1$-V_4 (McGinn-White pattern; *Chest* 1997;111:537)
- ABG: hypoxemia, hypocapnia, respiratory alkalosis, ↑ A-a gradient (*Chest* 1996;109:78), 18% w/ room air P_aO_2 85-105 mmHg, 6% w/ nl A-a gradient (*Chest* 1991;100:598)
- D-dimer (*JAMA* 2015;313:1668): high Se, poor Sp (˜25%); ⊖ ELISA has >99% NPV ∴ use to r/o PE if "unlikely" pretest prob. (*JAMA* 2006;295:172) consider age-specific cutpoint: 500 if <50 y, 10× age if ≥50 y (*JAMA* 2014;311:1117)
- Echocardiography: useful for risk stratification (RV dysfxn), but not dx (Se <50%)
- V/Q scan: high Se (˜98%), low Sp (˜10%). Sp improves to 97% for high prob VQ. Use if pretest prob of PE high and CT not available or contraindicated. Can also exclude PE if low pretest prob, low prob VQ, but 4% false ⊖

(*JAMA* 1990;263:2753).

- **CT angiography** (CTA; see Radiology inserts; *JAMA* 2015;314:74): Se ~90% & Sp ~95% w/ MDCT (*NEJM* 2006;354:2317); PPV & NPV >95% if imaging concordant w/ clinical suspicion, ≤80% if discordant ([need to consider both); CT may also provide other dx
- Lower extremity compression U/S shows DVT in ~9%, sparing CTA, but when added to CTA, does not Δ outcomes (*Lancet* 2008;371:1343)

- Pulmonary angio: ? gold standard (morbidity 5%, mortality <0.5%), infrequently performed
- MR angiography: Se 84% (segmental) to 100% (lobar) (Lancet 2002;359:1643); if add MR venography, Se 92%, Sp 96% (Annals 2010;152:434)

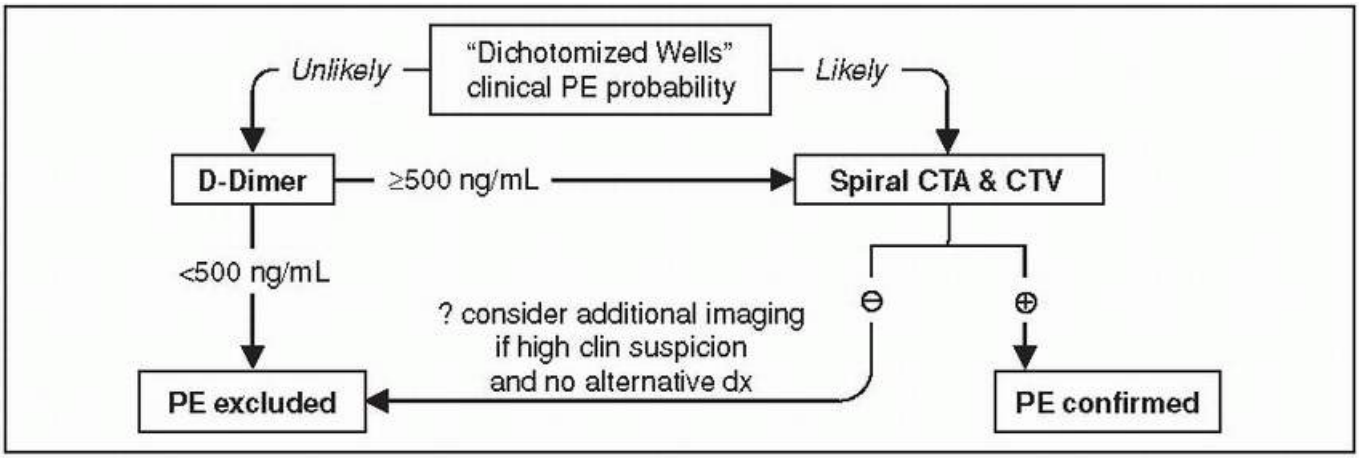


Figure 1-6 Approach to suspected PE using CTA

Workup for idiopathic VTE

- **Thrombophilia workup:** ✓ if ⊕ FH, may be helpful but consider timing as thrombus, heparin and warfarin Δ results. May not be helpful for Pt if will not change management (eg, plan for long-term anticoagulation regardless), although could be of use to relatives (*JAMA* 2005;293:2352; *Blood* 2008;112:4432; *Am J Med* 2008;121:458).
- **Malignancy workup:** 12% Pts w/ "idiopathic" DVT/PE will have malignancy; ageappropriate screening adequate; avoid extensive w/u (*NEJM* 1998;338:1169 & 2015;373:697)

Risk stratification for Pts with PE

- **Clinical:** hypotension and/or tachycardia (~30% mortality), hypoxemia
- **CTA:** RV / LV dimension ratio >0.9 (*Circ* 2004;110:3276)
- **Biomarkers:** ↑ troponin & ↑ BNP a/w ↑ mortality; w/ ⊖ Tn, decomp extremely unlikely (*Circ* 2002;106:1263 & 2003;107:1576; *Chest* 2015;147:685)
- **Echocardiogram:** RV dysfxn (even if normal troponin) (*Chest* 2013;144:1539)
- Simplified PE Severity Index: 0 RFs → 1.1% mort.; ≥1 → 8.9% mort (*Archives* 2010;170:1383) RFs: age >80 y; h/o cancer; h/o HF or lung disease; HR ≥110; SBP <100; S_aO_2 <90%

Whom to treat (*Lancet* 2012;379;1835; *Chest* 2012;141:e419S)

- **Superficial venous thrombosis:** elevate extremity, warm compresses, compression stockings, NSAIDs for sx. *Anticoag* if high risk for DVT (eg, ≥5 cm, proximity to deep vein ≤5 cm, other risk factors) for 4 wk as ~10% have VTE w/in 3 mo (*Annals* 2010;152:218).
- **LE DVT:** proximal → anticoag. If distal: anticoag if severe sx, o/w consider serial imaging over 2 wk and anticoag if extends (although if bleeding risk low, many would anticoag).
- **UE DVT:** anticoagulate (same guidelines as LE; *NEJM* 2011;364:861). If catheter-associated, need not remove if catheter functional and ongoing need for catheter.
- **PE:** anticoagulate

Anticoagulation options (*Chest* 2012;141:e419S; *JAMA* 2014;311:717)

- *Initiate immediately if high clinical suspicion or intermed but dx test results delayed for ≥4 h*
- Either (a) initial parenteral anticoag → long-term oral anticoagulant (eg, warfarin or Xa inhibitor) or (b) solely with an oral Xa inhibitor
- **LMWH** (eg, enoxaparin 1 mg/kg SC bid *or* dalteparin 200 IU/kg SC qd)

  Preferred over UFH (espec in *cancer*) except: renal failure (CrCl <25), ? extreme obesity, hemodynamic instability or bleed risk (*Cochrane* 2004;CD001100)

  No need to monitor anti-factor Xa unless concern re: dosing (eg, renal insuffic.)

  Attractive option as outPt bridge to long-term oral anticoagulation
- If cancer, LMWH ↓ recur. & mort. c/w UFH & warfarin (*NEJM* 2003;349:146; *Lancet Oncol* 2008;9:577; *JAMA* 2015;314:677); ✓ head CT for brain mets if melanoma, renal, thyroid, chorioCA
- **Fondaparinux:** 5-10 mg SC qd (*NEJM* 2003;349:1695); use if HIT ⊕; avoid if renal failure
- DVT & low-risk PE can be treated completely as outPt (*Lancet* 2011;378:41)
- **IV UFH:** 80 U/kg bolus → 18 U/kg/h → titrate to PTT 1.5-2.3 × cntl (eg, 60-85 sec); preferred option when contemplating thrombolysis or catheter-based Rx (qv)
- IV Direct thrombin inhibitors (eg, argatroban, lepirudin) used in HIT ⊕ Pts
- **Warfarin** (goal INR 2-3): start same day as parenteral anticoag unless instability and ? need for lytic, catheter-based Rx or surgery; overlap ≥5 d w/ parenteral anticoag & until INR ≥2 × ≥24 h
- **Oral Xa inhibitor:** effect wears off w/in 24 h, but not easily immediately reversed

  Can give as sole anticoag (nb, initial doses higher than for AF): **rivaroxaban** (15 mg bid for 1st 3 wk → 20 mg/d) as good/better than LMWH → warfarin in preventing recurrent VTE, ↓ bleeding (*NEJM* 2010;363:2499 & 2012;366:1287); **apixaban** (10 mg bid × 7 d → 5 bid) ≈ LMWH → warfarin in preventing recurrent VTE, ↓ bleeding (*NEJM* 2013;369:799)

  Can initiate after ≥5 d of parenteral anticoag (1st dose when d/c IV UFH or w/in 2 h before when next LMWH dose would have been due): both **dabigatran** (150 mg bid) & **edoxaban** (60 mg qd) ≈ warfarin but w/ ↓ bleeding (*NEJM* 2009;361:2342 & 2013;369:1406)

Systemic thrombolysis (*Chest* 2012;141:e419S)

- Typically TPA 100 mg over 2 h or wt-adjusted TNK bolus

- Indications & efficacy below; risk of ICH ~1.5%, ↑ w/ age; see contraindications in "ACS"
- **Massive PE** (hemodynamic compromise): ↓ death and recurrent PE each by ~50% (*Circ* 2004;110:744; *JAMA* 2014;311:2414; *EHJ* 2015;36:605) & lower PVR long term (*JACC* 1990;15:65)
- **Submassive PE** (hemodyn. stable but RV dysfxn on echo or enlargement on CTA, or ? marked dyspnea or severe hypoxemia): ↑ death & ↑ bleeding; may consider if low bleed risk (see lytic contra-indic.; *EHJ* 2015;36:605). Benefit/risk may be more favorable if <75 y (*NEJM* 2014;370:1402; *JAMA* 2014;311;2414). Some centers prefer catheter-directed Rx (qv).
- **Moderate PE w/ large clot burden** (≥2 lobar arteries or main artery on CT or high prob VQ w/ ≥2 lobes w/ mismatch): *low-dose lytic* (50 mg if ≥50 kg or 0.5 mg/kg if >50 kg; for both 10 mg bolus → remainder over 2 h) ↓ pulm HTN w/ ≈ bleeding vs heparin alone; await further validation (*Am J Cardiol* 2013;111:273)
- **DVT:** consider if all are present (a) acute (< 14 d) & extensive (eg, iliofemoral), (b) severe symptomatic swelling or ischemia (phlegmasia cerulea dolens), (c) catheter-directed Rx not available, and (d) low bleeding risk

Mechanical intervention

- **Catheter-directed therapy** (fibrinolytic & thrombus fragmentation/aspiration)

  Consider if extensive DVT (see above) and to ↓ post-thrombotic synd (*Lancet* 2012;379:31)

  Consider if PE w/ hemodyn. compromise or high risk & not candidate for systemic lysis or surgical thrombectomy (*Circ* 2011;124:2139). Preferred to systemic lytic by some centers.

  U/S-assisted → improves hemodynamics & RV fxn vs anticoag alone (*EHJ* 2015;36:597)
- **Thrombectomy:** if large, proximal PE + hemodynamic compromise + contra. to lysis; consider in experienced ctr if large prox. PE + RV dysfxn (*J Thorac CV Surg* 2005;129:1018)
- **IVC filter:** use instead of anticoagulation if latter contraindicated

  No benefit to adding to anticoag (including in submassive) (*JAMA* 2015;313:1627)

  Consider removable filter for temporary indications

  Complications: migration, acute DVT, ↑ risk of recurrent DVT & IVC obstruction (5-18%), which may lead to worsening LE sx (*Archives* 1992;152:1985)

Duration of full-intensity anticoagulation

- Superficial venous thrombosis: 4 wk
- 1st prox DVT *or* PE 2° reversible/time-limited risk factor *or* distal DVT: 3-6 mo
- 1st *unprovoked* prox DVT/ PE: ≥3 mo, then reassess; benefit to prolonged Rx (see below). Consider bleeding risk, Pt preference and intensity of extended Rx.
- 2nd VTE event or cancer: indefinite (or until cancer cured) (*NEJM* 1997;336:393 & 2003;348:1425)
- Does *not* appear that can rely on D-dimer testing to guide d/c (*Annals* 2015;162:27)

Extended antithrombotic strategies (*JAMA* 2015;314:72)

- After ≥6 mo of anticoag, following strategies have been compared w/ *no extended* Rx*:*
- Full-dose dabigatran, rivaroxaban, or apixaban: 80-90% ↓ recurrent VTE, 2-5× bleeding, but no signif excess

in major bleeding (*NEJM* 2010;363:2499; 2013;368:699 & 709)

- Full-dose warfarin: 85% ↓ reduction in recurrent VTE (*JAMA* 2015;314:31)
- Low-intensity warfarin (INR 1.5-2.0): 64% ↓ reduction in recurrent VTE (*NEJM* 2003;348:1425)
- Low-intensity apixa (2.5 mg bid): 80% ↓ recur. VTE, w/o signif ↑ bleeding (*NEJM* 2013;368:699)
- Aspirin: 32% ↓ recurrent VTE (*NEJM* 2012;366:1959 & 367:1979)

Other therapeutic interventions

- Early ambulation
- For DVT: fitted graduated compression stockings (min 20-30 mmHg → 30-40 mmHg) for sx & to ↓ risk of postthrombotic synd (occurs in 23-60%; *J Thromb Thrombolysis* 2009;28:465)
- Leg elevation and exercise (use of calf muscle pump) also may be helpful
- Anticoag teaching: avoidance of high-risk activities, med alert bracelet, dietary instructions

Complications & prognosis

- Post-thrombotic syndrome (23-60%): thrombosis → injury to vein/valves → pain, edema, venous ulcers (*J Thromb Thrombolysis* 2009;28:465)
- Recurrent VTE: 1%/y (after 1st VTE) to 5%/y (after recurrent VTE) after only 6 mo of Rx: 5%/y & > 10%/y, respectively

  predictors: abnl D-dimer 1 mo after d/c anticoag (*NEJM* 2006;355:1780); ⊕ U/S after 3 mo of anticoag (*Annals* 2002;137:955); thrombin generation >400 nM (*JAMA* 2006;296:397)
- Chronic thromboembolic PHT after acute PE ~3.8% (*NEJM* 2004;350:2257), consider thromboendarterectomy
- Mortality: ~10% for DVT and ~10-15% for PE at 3-6 mo (*Circ* 2008;117:1711)

PULMONARY HYPERTENSION (PHT)

PA *mean pressure ≥25 mmHg at rest*

Pathobiology (*NEJM* 2004;35:1655)

- Smooth muscle & endothelial cell proliferation; mutations in bone morphogenic protein receptor 2 (*BMPR2*) in ~50% familial & ~26% sporadic cases of IPAH (*NEJM* 2001;345:319)
- Imbalance between vasoconstrictors and vasodilators

  ↑ vasoconstrictors: thromboxane A_2 (TXA_2), serotonin (5-HT), endothelin-1 (ET-1)

  ↓ vasodilators: prostacyclin (PGI2), nitric oxide (NO), vasoactive peptide (VIP)
- *In situ* thrombosis: ↑ TXA_2, 5-HT, PAI-1; ↓ PGI_2, NO, VIP, tissue plasminogen activator

Etiologies of Pulmonary Hypertension (Revised WHO Classification)	
Pulmonary arterial HTN	• Idiopathic (IPAH): mean age of onset 36 y (♂ older than ♀); ♀:♂= ~2:1,

(PAH) (group 1)	usually mild ↑ in PAP • Familial (FPAH) • Associated conditions (APAH) Connective tissue disorders: CREST, SLE, MCTD, RA, PM, Sjögren Congenital: L→R shunts: ASD, VSD, PDA, 1° PHT of newborn Portopulmonary HTN (? 2° vasoactive substances not filtered in ESLD; ≠ hepatopulmonary syndrome) HIV; drugs & toxins: anorexic agents, rapeseed oil, L-tryptophan • Pulmonary veno-occlusive disease: ? 2° chemo, BMT; orthopnea, pl eff, nl PCWP; art vasodil. *worsen* pulm edema (*AJRCCM* 2000;162:1964) • Pulmonary capillary hemangiomatosis
Left heart disease (group 2)	• Left atrial or ventricular (diastolic or systolic) dysfunction • Left-sided valvular heart disease (eg, MS/MR > AS/AR) • Congenital: left-sided inflow/outflow obstruction, CMP
Lung diseases and/or chronic hypoxemia (group 3)	• COPD • ILD • Sleep apnea • Alveolar hypoventilation (eg, NM disease) • Chronic hypoxemia (eg, high altitude) • Developmental abnormalities
Chronic thrombo-embolic dis (group 4)	• Prox or distal PEs; ~½ w/o clinical h/o PE (*Circ* 2014;130:508) • Nonthrombotic emboli (tumor, foreign body, parasites)
Miscellaneous (group 5) (*Circ* 2013;62:25S)	• Sarcoidosis, histiocytosis X, LAM, schistosomiasis • Metab: thyroid, glycogen storage, Gaucher • Heme: chronic hemolytic anemia, myeloprolif d/o, splenectomy • Other: compression of pulm vessels (adenopathy, tumor, fibrosing mediastinitis, histoplasmosis, XRT); HHT (multifactorial)

Clinical manifestations

- Dyspnea, exertional syncope (hypoxia, ↓ CO), exertional chest pain (RV ischemia)
- Symptoms of R-sided CHF (eg, peripheral edema, RUQ fullness, abdominal distention)
- WHO class: I = asx w/ ordinary activity; II = sx w/ ord. activ.; III = sx w/ min activ.; IV = sx at rest

Physical exam

- PHT: prominent P_2, R-sided S4, RV heave, PA tap & flow murmur, PR (Graham Steell), TR
- ± RV failure: ↑ JVP, hepatomegaly, peripheral edema

Diagnostic studies & workup (*Circ* 2014;130:1820)

- *IPAH yearly incidence 1-2 per million, ∴ r/o 2° causes*

- High-res chest CT: dil. & pruning of pulm arteries, ↑ RA and RV; r/o parenchymal lung dis.
- ECG: RAD, RBBB, RAE ("P pulmonale"), RVH (Se 55%, Sp 70%)
- PFTs: disproportionate ↓ $D_L$co, mild restrictive pattern; r/o obstructive & restrict. lung dis.
- ABG & polysomnography: ↓ P_aO_2 and S_aO_2 (espec w/ exertion), ↓ P_aCO_2, ↑ A-a gradient; r/o hypoventilation and OSA
- TTE: ↑ RVSP (but estimate over/under by ≥10 mmHg in ½ of PHT Pts; *Chest* 2011;139:988)

  ↑ RA, RV (RV:LV area >1) and PA size; TR, PR

  ↑ RVSP → interventricular septum systolic flattening ("D" shape)

  ↑ RAP → interatrial septum bowing into LA

  ↓ RV systolic fxn: TAPSE (tricuspid annular plane systolic excursion) < 1.6 cm; lateral-septal tissue-Doppler imaging disparity (reflecting relatively more systolic dysfxn of RV lateral wall vs septum, which is shared with LV)

  ↑ PA impedance ↑ RVOT Doppler notching

  r/o LV dysfxn, MV or AoV disease, and congenital heart disease
- RHC: ↑ RA, RV, & PA pressures; ✓ L-sided pressures and for shunt if PAH: nl PCWP, ↑ transpulm gradient (mean PAP-PCWP > 12-15), ↑ PVR, ± ↓ CO if 2° to L-heart disease: PCWP (or LVEDP) > 15; if PVR nl → "passive PHT"; PVR >240 suggests mixed picture: if ↓ PCWP → ↓ PVR, then "reactive" PHT; if no Δ, then "fixed"

- CTA (large/med vessel), V/Q scan (small vessel to r/o CTEPH), ± pulmonary angiogram: r/o PE and chronic thromboembolic disease
- Vasculitis labs: ANA (˜40% ⊕ in PAH), RF, anti-Scl-70, anticentromere, ESR
- LFTs & HIV: r/o portopulmonary and HIV-associated PAH
- 6-min walk test (6MWT) or cardiopulmonary exercise testing to establish fxnl capacity

Differentiating Left Heart Disease from Alternative PHT Etiologies

Feature	Favors Left Heart Disease	Favors Alternative Etiology
History	Prior MI, CMP,AoV or MV disease, CV risk factors (HTN, diabetes), ↑ age	Family hx PHT, connective tissue disorder, pulm, liver or hematologic disease, HIV, h/o VTE
PEx	L-sided S3, S4 L-sided murmurs Displaced apical impulse Coarse rales	Cyanosis, clubbing Fine rales; signs of COPD Raynaud's, sclerodactyly, telangiectasia Splenomegaly, spider angiomata
ECG	Q waves, LVH, LBBB	Isolated RAE, RVH, $S_IQ_{III}T_{III}$ pattern

Echo	LV systolic or diastolic dysfxn LVH, ↑ LA size ≥Moderate MV or AoV disease	Isolated RV or RA enlargement Interventricular septum systolic flattening and/or interatrial septum bowing into LA ↓ RV systolic fxn
RHC	↑ L-sided filling pressures Abrupt ↑ PCWP (to > 20-25) w/ exercise or volume loading	PCWP <15 mmHg Exercise PCWP <20-25 mmHg

Treatment (*JACC* 2013;62:25S & 2015;65:1976)

- Principles

  1) prevent and reverse vasoactive substance imbalance and vascular remodeling

  2) prevent RV failure: ↓ wall stress (↓ PVR, PAP, RV diam); ensure adeq. systemic DBP

- **Supportive**

  Oxygen: maintain S_aO_2 >90-92% (reduces vasoconstriction)

  Diuretics: ↓ RV wall stress and relieve RHF sx; *gentle* b/c RV is preload dependent

  Digoxin: control AF, ? counteract neg. inotropic effects CCB

  Dobutamine and inhaled NO or prostacyclin for decompensated PHT

  Anticoagulation: ↓ VTE risk of RHF; ? prevention of *in situ* microthrombi; ? mortality benefit even if in NSR, no RCTs (*Circ* 1984;70:580; *Chest* 2006;130:545)

  Supervised exercise training (*Eur Respir J* 2012;40:84)

- **Vasodilators** (right heart catheterization prior to initiation) *acute vasoreactivity test:* use inhaled NO, adenosine or prostacyclin to identify Pts likely to have a long-term response to oral CCB (⊕ vasoreactive response defined as ↓ PAP ≥10 mmHg to a level <40 mmHg with ↑ or stable CO); ˜10% Pts are acute responders; no response → still candidates for other vasodilators (*NEJM* 2004;351:1425)

Vasoactive agents	Comments (data primarily in Group 1 PAH)
Oral CCB Nifedipine, diltiazem	If ⊕ acute vasoreactive response; <½ will be long-term responder (NYHA I/II & near-nl hemodynamics) & have ↓ mortality. Side effects: HoTN, lower limb edema (*NEJM* 1992;327:76; *Circ* 2005;111:3105).
IV Prostacyclin Epoprostenol (Flolan)	Vasodilation, ↓ plt agg, ↓ smooth muscle proliferation; benefits ↑ w/ time (? vascular remodeling). ↑ 6MWT, ↑ QoL, ↓ mortality. Side effects: HA, flushing, jaw/leg pain, abd cramps, nausea, diarrhea, catheter infxn (*NEJM* 1996;334:296 & 1998:338:273; *Annals* 2000;132:425).
Prostacyclin analogues Iloprost (inhaled) Treprostinil (IV, inh, SC) Beraprost (PO)	Same mechanism as prostacyclin IV, but easier to take, ↓ side effects, and w/o risk of catheter infxn, ↓ sx, ↑ 6MWT; trend to ↓ clinical events w/ iloprost but not treprostinil. Beraprost w/o sustained outcome improvement (n/a in U.S.) (*NEJM* 2002;347:322; *AJRCCM* 2002;165:800).

Endothelin receptor antagonists (ERAs) Bosentan, ambrisentan, macitentan	↓ Smooth muscle remodeling, vasodilation, ↓ fibrosis, ↓ sx, ↑ 6MWT, ↓ worsening PAH or need for prostanoids w/ trend for ↓ PAH mortality (w/ macitentan). Side effects: ↑ LFTs, headache, anemia, edema, teratogen (*NEJM* 2002;346:896; *JACC* 2005;46:529; *Circ* 2008;117:3010; *NEJM* 2013;369:809).
PDE-5 Inhibitor Sildenafil, tadalafil	↑ cGMP → vasodilation, ↑ smooth muscle proliferation, ↓ sx, ↑6MWT, no data on clinical outcomes. Low side-effect profile: HA, vision Δ's, sinus congestion (*NEJM* 2009;361:1864).
Soluble guanylate cyclase stimulator Riociguat	NO-independent ↑ cGMP → vasodilation, ↑ smooth muscle proliferation, ↓ sx, ↑ 6MWT in PAH; ↓ sx, ↓ PVR, ↑ 6MWT in CTEPH (*NEJM* 2013;369:319 & 330)

- Up front combination Rx (tadalafil + ambrisentan vs monotherapy): ↓ sx, ↓ NT-BNP, ↑ 6MWT, ↓ hospitalizations (*NEJM* 2015;373:834)
- Treat underlying causes of 2° PHT; can use vasodilators, although little evidence beyond riociguat use for CTEPH as described above
- Refractory PHT:

  balloon atrial septostomy: R→ L shunt causes ↑ CO, ↓ S_aO_2, net ↑ tissue O_2 delivery lung transplant (single or bilateral); heart-lung needed if Eisenmenger physiology

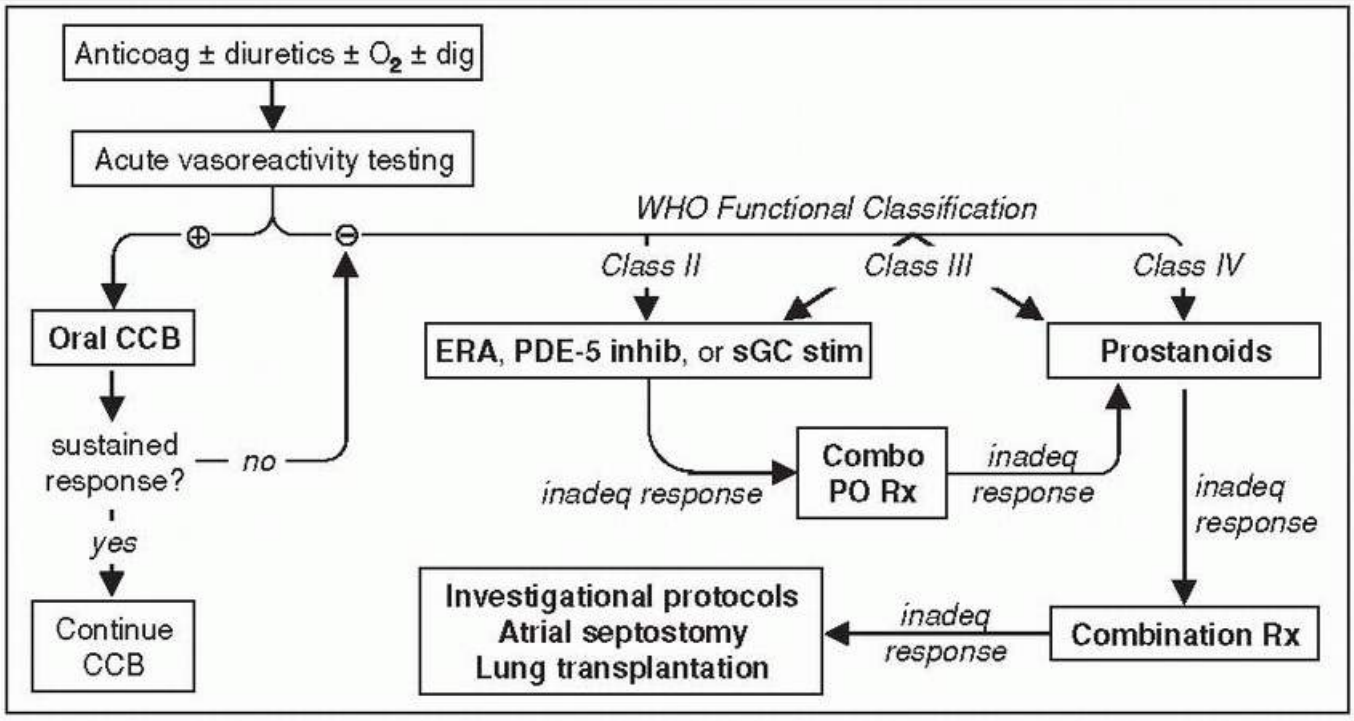


Figure 1-7 Treatment of PAH (modified from *JACC* 2009;54:S78)

Management of ICU patient

- Avoid overly aggressive volume resuscitation
- Caution with vasodilators if any L-sided dysfunction
- May benefit from inotropes/chronotropes
- Mechanical RV support (RVAD, ECMO) (*Circ* 2015;132:526)
- Consider fibrinolysis if acute, refractory decompensation (eg, TPA 100 mg over 2 h)

Prognosis

- Median survival after dx ~2.8 y; PAH (all etiologies): 2-y 66%, 5-y 48% (*Chest* 2004;126:78-S)
- Poor prognostic factors: clinical evidence of RV failure, rapidly progressive sx, WHO (modified NYHA) class IV, 6MWT <300 m, peak VO_2 <10.4 mL/kg/min, ↑ RA or RV or RV dysfxn, RA >20 or CI <2.0, ↑ BNP (*Chest* 2006;129:1313)
- Lung transplant: 1-y survival 66-75%; 5-y survival 45-55% (*Chest* 2004;126:63-S)

Arrhythmias

BRADYCARDIA AND AV BLOCK

BRADYCARDIAS

Sinus bradycardia (SB) (*NEJM* 2000;342:703)

- Etiologies: **meds** (incl βB, CCB, amio, Li, dig), → **vagal tone** (incl. in athletes, sleep, IMI), **metabolic** (hypoxia, sepsis, myxedema, hypothermia, ↓ glc), OSA, ↑ ICP
- Treatment: if no sx, none; atropine, β_1 agonists or long-term permanent pacing if sx
- Most common cause of sinus pause is *blocked premature atrial beat*

Sick sinus syndrome (SSS)

- Features may include: periods of unprovoked SB, SA arrest, paroxysms of SB and atrial tachyarrhythmias ("tachy-brady" syndrome), chronotropic incompetence w/ ETT
- Treatment: meds alone usually fail (adeq. control of tachy → unacceptable brady); usually need **combination of meds** (βB, CCB, dig) for tachy & **PPM** for brady

Pseudobradycardia

- Intermittent PVCs (with low stroke volume and hence low pulse wave) followed by compensatory pause can cause ascertainment of HR by palpation of radial pulse to be artifactually low

AV BLOCK AND AV DISSOCIATION

AV Block

Type	Features
1°	Prolonged PR (>200 ms), all atrial impulses conducted (1:1)
2° Mobitz I (Wenckebach)	Progressive ↑ PR until impulse not conducted (↑ "grouped beating") Due to **AV node** conduction delay: ischemia (IMI), inflammation (myocarditis, MV surgery), high vagal tone (athletes), drug-induced QRS duration most often normal AVB usually worsens w/ carotid sinus massage, improves w/ atropine & exercise Often paroxysmal/nocturnal/asymptomatic; no Rx required
2° Mobitz II	Occasional or repetitive blocked impulses w/ consistent PR interval. Nb, do not confuse with APBs in bigeminal pattern; to dx AVB, atrial rate should be *regular* and P waves should be the *same.* Due to **His-Purkinje** conduction delay: ischemia (AMI), degeneration of conduction system, infiltrative disease, inflammation/valve surgery QRS duration most often prolonged AVB usually improves w/ carotid sinus massage, worsens w/ atropine & exercise (both of which should be *avoided* if dx suspected) Risk of progression to 3° AVB. Zoll at bedside when recognized; temp pacing wire or PPM often required.

3° (complete)	No AV conduction, with ventricular rhythm slower than atrial rhythm Escape, if present is regular and can be narrow (jxnal) or wide (vent.) Urgent temporary pacing as bridge to permanent pacing is appropriate in most scenarios, especially when syncope present

Nb, if 2:1 block, cannot distinguish type I vs II 2° AVB (no chance to observe PR prolongation); usually categorize based on other ECG & clinical data. High-grade AVB usually refers to block of ≥2 successive impulses. All categories above assume SR in atrium, criteria do not apply during rapid atrial rates, such as in atrial flutter or tachycardia.

AV dissociation

- *Default:* slowing of SA node allows subsidiary pacemaker (eg, AV junction) to take over
- *Usurpation:* acceleration of subsidiary pacemaker (eg, AV junctional tach, VT)
- *3° AV block:* atrial pacemaker unable to capture ventricles, subsidiary pacemaker emerges; distinguish from *isorhythmic dissociation* (A ≈V rate, some P waves nonconducting)

Temporary pacing wires

- Consider w/ bradycardia with hemodyn instability or unstable escape rhythm when perm pacer not readily available. Risks: RV perf, VT, PTX, CHB if existing LBBB, etc.
- Consider instead of PPM for sx bradycardia due to reversible cause (βB/CCB O/D, Lyme, myocarditis, SBE, s/p cardiac surgery/trauma), TdP, acute MI (sx brady, high-grade AVB)

SUPRAVENTRICULAR TACHYCARDIAS

PALPITATIONS

Etiologies

- PACs, PVCs; SVT, AF, VT, respiratory sinus arrhythmia; pauses; noncardiac

Workup

- History: duration & frequency; initiating & aggravating factors: exercise, alcohol, stimulants (caffeine, pseudoephedrine, other prescription & recreational drugs); h/o presyncope or syncope; FHx of arrhythmia, CMP, SCD
- Structural evaluation w/ echo; consider ETT if exercise-induced or other RF; TFTs
- Ambulatory cardiac monitoring: *must monitor during symptoms to diagnose!* Holter (worn continuously): if sx typically occur within a 24-48-hr period Looping event monitor (worn continuously): if sx fleeting Nonlooping event monitor (put on during sx): if rarer episodes lasting minutes

Treatment (for SVT and VT, see respective sections)

- Simple ectopy in structurally normal heart: reassurance, βB, CCB. If refractory, frequent sx with poor QoL, antiarrhythmic drug, such as flecainide, can be tried in consultation w/ electrophysiologist. Rarely catheter ablation for frequent PVCs.

- If NICM and > 13% PVCs, elim of ectopy w/ catheter ablation can significantly ↑ EF (*JACC* 2013;62:1195). However, risk of *developing* CMP due to frequent PVCs not established.

SUPRAVENTRICULAR TACHYCARDIAS (SVTS)

Arise above the ventricles, ∴ ***narrow QRS*** *unless aberrant conduction or pre-excitation*

Common Etiologies of SVT (*NEJM* 2006;354:1039 & 2012;367:1438)

	Type	Features
Atrial	Sinus tachycardia (ST)	Caused by pain, fever, hypovolemia, hypoxia, anemia, anxiety, β-agonists, etc.
	Atrial tachycardia (AT)	Originate at site in atria other than SA node. Seen w/ CAD, COPD, ↑ catechols, EtOH, dig.
	Multifocal atrial tachycardia (MAT)	↑ automaticity at multiple sites in the atria. Seen with underlying pulmonary disease.
	Atrial flutter (AFL)	Macroreentry, usually w/in right atrium
	Atrial fibrillation (AF)	Chaotic atrial activation and rapid, irregular bombardment of AVN
	AV nodal reentrant tach (AVNRT)	Reentrant circuit using dual pathways w/in AVN
	AV reciprocating tachycardia (AVRT)	Reentrant circuit using AVN antegrade and accessory pathway retrograde. When in sinus rhythm may show pre-excitation (WPW) or not (concealed accessory pathway).
AV Jxn	Paroxysmal junctional reciprocating tachycardia (PJRT)	Reentry using AVN & slowly conducting concealed posterosept acc path. More common in peds, at times w/ tachy-induced CMP.
	Nonparoxysmal junctional tachycardia (NPJT)	↑ jxnal automaticity. May see retrograde P's & AV dissoc. A/w myo/endocarditis, cardiac surg, IMI, dig.

Diagnosis of SVT Type (*NEJM* 2006;354:1039 & 2012;367:1438)

Onset	Abrupt on/off argues against sinus tachycardia

Rate	Not dx as most can range from 140-250 bpm, *but:* ST usually <150; AFL often conducts 2:1 → vent. rate 150; AVNRT & AVRT usually >150
Rhythm	Irregular → AF, AFL w/ variable block, or MAT
P wave	Long RP: ST (P same as sinus), AT, MAT (≥3 morphologies), PJRT Short RP, P inverted in inf. leads → *retrograde* atrial activation via AVN AVNRT: buried in or distort terminal portion of QRS (pseudo-RSR' in V_1) AVRT: slightly after QRS (RP interval > 100 ms favors AVRT vs AVNRT) NPJT: either no P wave or retrograde P wave similar to AVNRT *Fibrillation or no P waves* → AF *Saw-toothed "F" waves* (best seen in inferior leads & V_1) → AFL
Response to vagal stim. or adenosine	Slowing of HR often seen with ST, AF, AFL, AT, whereas reentrant rhythms (AVNRT, AVRT) may abruptly terminate (classically w/ P wave after last QRS) or no response. Occ AT may terminate. AFL & AF → ↑ AV block → unmasking of "F" waves or fibrillation

Short RP: P wave closer to preceding than following QRS (ie, RP < PR). Long RP: P wave closer to following than preceding QRS (ie, PR < RP).

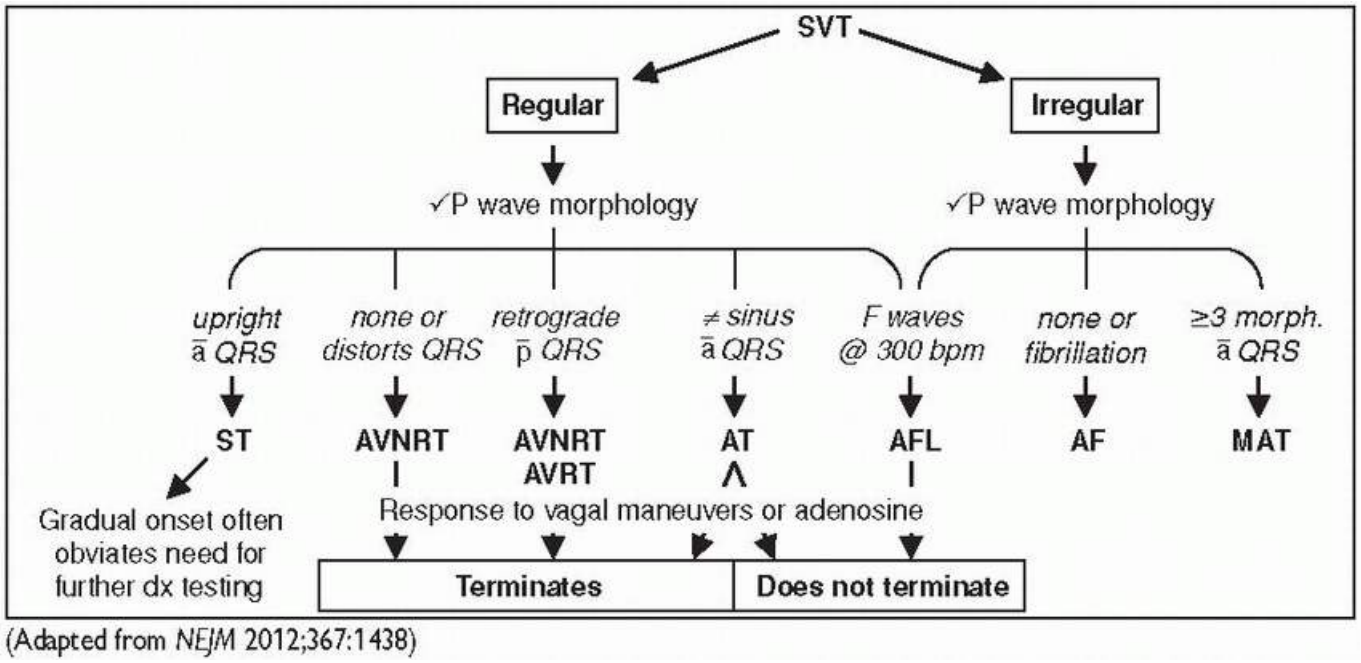


Figure 1-8 Approach to SVT

Treatment of SVT

Rhythm	Acute treatment	Long-term treatment
Unstable	**Cardioversion** per ACLS	n/a

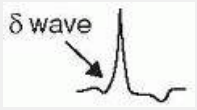
ST	Treat underlying stressor(s)	n/a
AT	βB, CCB or amiodarone; ? vagal maneuvers or adenosine	βB or CCB, ± antiarrhythmics, possibly radiofrequency ablation (RFA)
AVNRT or AVRT	**Vagal maneuvers** **Adenosine** (caution in AVRT*) **CCB** or βB	*For AVNRT* (*see next section for AVRT*): **RFA.** CCB or βB (chronic or prn) ± Class IC antiarrhythmics (if nl heart)
NPJT	**CCB, βB, amiodarone**	Rx underlying dis. (eg, dig tox, ischemia)
AF	**βB, CCB, digoxin, AAD**	See "Atrial Fibrillation"
AFL	**βB, CCB, digoxin, AAD**	RFA; βB or CCB ± antiarrhythmics
MAT	CCB or βB if tolerated	Treat underlying disease process AVN ablation + PPM if refractory to meds

*Avoid adenosine & nodal agents if accessory pathway + preexcited tachycardia, see below (*JACC* 2003;42:1493)

- *Catheter ablation:* high overall success rate (AFL/AVNRT ˜95%, AVRT ˜90%, AF ˜80%) Complications: stroke, MI, bleeding, perforation, conduction block (*JAMA* 2007;290:2768)

ACCESSORY PATHWAYS (WOLFF-PARKINSON-WHITE)

Definitions

- **Accessory pathway** (bypass tract) of conducting myocardium connecting 

atria & ventricles, allowing impulses to bypass normal AVN delay
- **Preexcitation (WPW) pattern:** ↓ PR interval, ↑ QRS width w/ δ wave (slurred onset, *can be subtle*), ST & Tw abnl (can mimic old IMI);

  only seen w/ pathways that conduct antegrade (if pathway only conducts retrograde then ECG will be normal during SR; "concealed" bypass tract)

  PAC can exaggerate preexcitation if AV node conduction slowed
- **WPW syndrome:** accessory pathway + paroxysmal tachycardia

Classic tachycardias of WPW

- **Orthodromic AVRT:** *narrow-complex* SVT (typically), conducting ↑ AVN & ↑ accessory pathway; requires retrograde conduction and ∴ can occur w/ concealed bypass tracts
- **Antidromic AVRT** (less common): *wide-complex* regular tachycardia, conducting ↓ accessory pathway & ↑

AVN. Can meet many ECG morphology criteria for VT. Requires antegrade conduction and ∴ should see WPW pattern during SR.

- **AF** w/ rapid conduction down accessory pathway; ∴ wide-complex irregular SVT; requires antegrade conduction; ∴ should see WPW pattern in SR. Rarely can degenerate into VF.

Treatment

- **AVRT:** vagal, βB; caution w/ adenosine (can precip. AF); *have defibrillator ready*
- **AF/AFL** w/ conduction down accessory pathway: need to Rx arrhythmia *and* ↑ pathway refractoriness; use **procainamide**, **ibutilide**, or DCCV; avoid CCB & βB, dig/adenosine (can ↓ refractoriness of pathway → ↑ vent. rate ↑ VF)
- **Long term:** Rx sx tachycardias w/ RFA, antiarrhythmics (IA, IC) if not candidate for RFA.

  Consider RFA if asx but AVRT or AF inducible on EPS (*NEJM* 2003;349:1803) or if rapid conduction possible (✓ w/ EPS if preexcitation persists despite exercise testing).

  Risk of SCD related to how short RR interval is in AF and # of accessory pathways present. Exercise testing to look for loss of pre-excitation can be used as a proxy for short RR interval in AF: if pathway still present at peak exercise, more concerning.

ATRIAL FIBRILLATION

Classification (*Circ* 2014;130:2071)

- **Paroxysmal** (terminates spontaneously or w/ Rx w/in 7 d) vs **persistent** (sustained >7 d) vs **long-standing persistent** (>1 y) vs **permanent** (no plan to restore or maintain SR)
- **Nonvalvular** (AF absent rheumatic MS, prosthetic valve or mitral valve repair) vs **valvular**
- **Lone AF** = age <60 y and w/o clinical or echo evidence of cardiac disease (including HTN)

Pathophysiology

- Disorganized atrial electrical activity → ineffective atrial mechanical contraction
- For paroxysmal AF, >90% triggered by rapid firing in pulmonary veins (*NEJM* 1998;339:659)

Epidemiology and etiologies (*Annals* 2008;149:ITC5-2)

- 1-2% of pop. has AF (8% of elderly); lifetime risk 25%; mean age at presentation ~75 y
- Acute (up to 50% w/o identifiable cause)

  Cardiac: HF, myo/pericarditis, ischemia/MI, hypertensive crisis, cardiac surgery

  Pulmonary: acute pulmonary disease or hypoxia (eg, COPD flare, PNA), PE, OSA

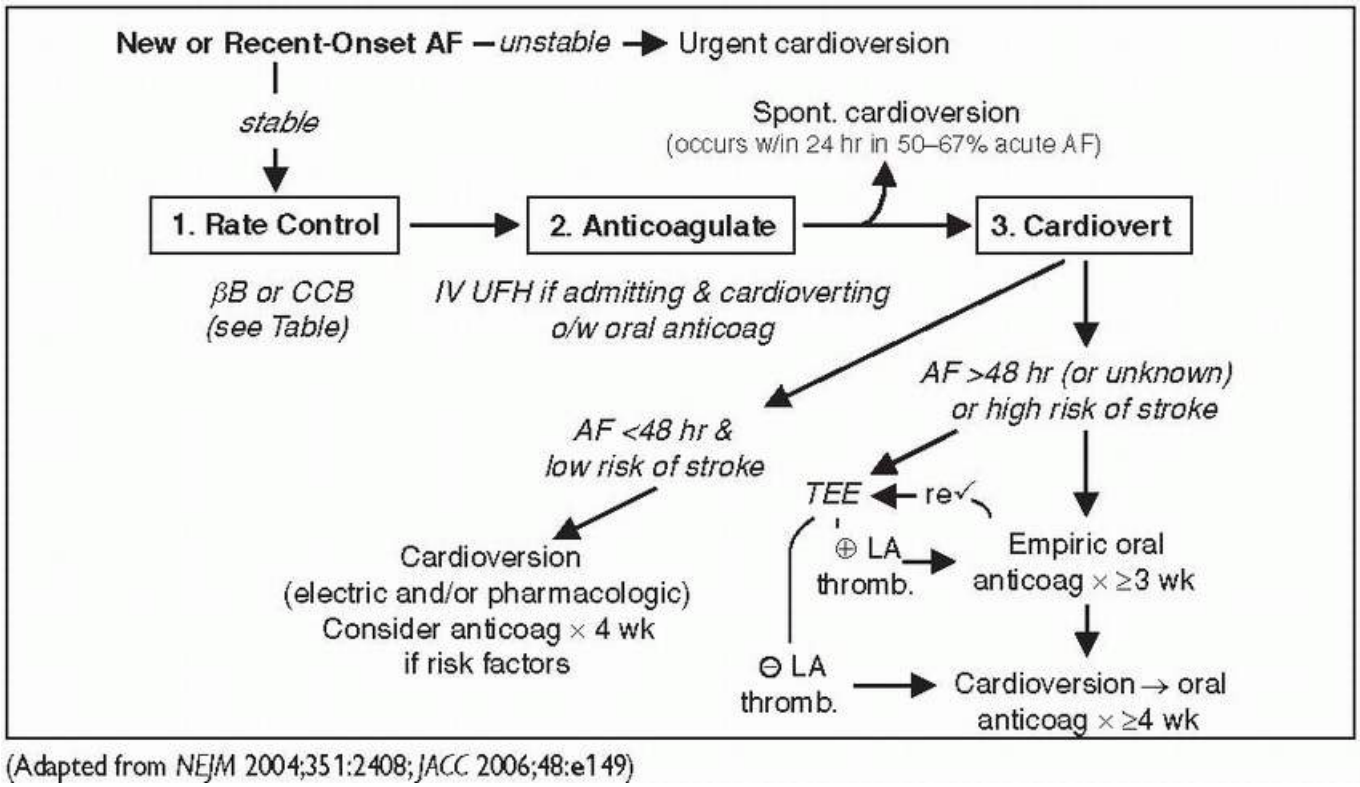
  Metabolic: high catecholamine states (stress, infection, postop, pheo), thyrotoxicosis

  Drugs: alcohol (“holiday heart”), cocaine, amphetamines, theophylline, caffeine

  Neurogenic: subarachnoid hemorrhage, ischemic stroke
- Chronic: ↑ age, HTN, ischemia, valve dis. (MV, TV, AoV), CMP, hyperthyroidism, obesity

Evaluation

- H&P, ECG, CXR, TTE (LA size, thrombus, valves, LV fxn, pericardium), K, Mg, FOBT before anticoag, TFTs; r/o MI not necessary unless other ischemic sx



(Adapted from *NEJM* 2004;351:2408; *JACC* 2006;48:e149)

Figure 1-9 Approach to acute AF

Rate control

- If sx, goal HR <80; if asx & EF >40%, goal HR <110 at rest (*NEJM* 2010;362:1363)
- AV node ablation + PPM if pharmacologic Rx inadequate (*NEJM* 2001;344:1043; 2002;346:2062)

Rate Control for AF

Agent		Acute (IV)	Maint. (PO)	Comments
CCB	**Verapamil**	5-10 mg over 2′ may repeat in 30′	120-360 mg/d in divided doses	↓ BP (Rx w/ Ca gluc) Can worsen HF Preferred if severe COPD Can ↑ dig levels
	Diltiazem	0.25 mg/kg over 2′ may repeat after 15′ 5-15 mg/h infusion	120-360 mg/d in divided doses	
βB	**Metoprolol**	2.5-5 mg over 2′ may repeat q5′ × 3	25-100 mg bid or tid	↓ BP (Rx w/ glucagon) Preferred if CAD Risks: HF & bronchospas.

Digoxin* (onset >30 min)	0.25 mg q2h up to 1.5 mg	0.125-0.375 mg qd (adj for CrCl)	Consider in HF or low BP Poor exertional HR ctrl
Amiodarone	300 mg over 1 h → 0.5-1 mg/min × 24 h	100-200 mg QD	Consider in HF or low BP Long-term potential tox

IV βB, CCB and digoxin ***contraindicated*** if evidence of WPW (ie, pre-excitation or WCT) since may facilitate conduction down accessory pathway leading to VF; ∴ use procainamide, ibutilide or amiodarone

*Many meds incl. amio, verapamil, quinidine, propafenone, macrolides & azole antifungals ↑ digoxin levels.

Cardioversion

- Consider pharm or electrical cardioversion w/ 1st AF episode or if sx; if AF >48 h, 2-5% risk stroke w/ cardioversion (*pharmacologic or electric*) ∴ either TEE to r/o thrombus or ensure therapeutic anticoagulation for ≥3 wk prior if need to cardiovert urgently, anticoagulate acutely (eg, IV UFH)
- Likelihood of success ∝ AF duration & atrial size; control precip. (eg, vol status, thyroid)
- Consider pre-Rx w/ antiarrhythmic drugs (eg, ibutilide), espec if 1st cardioversion fails
- For pharmacologic cardioversion, class III and IC drugs have best proven efficacy
- If SR returns (spont. or w/ Rx), atria may be *mech. stunned;* also, high risk of recurrent AF over next 3 mo. ∴ **Anticoag postcardioversion ≥ 4 wk** (? unless <48 h and low risk).

Rhythm control (*Lancet* 2012;379:648; *Circ* 2014;130:2071)

- No clear survival benefit or ↓ stroke risk vs rate control (*NEJM* 2002;347:1825 & 2008;358:2667)
- Consider if *symptomatic* w/ rate control (eg, heart failure), difficult to control rate, or tachycardia-mediated cardiomyopathy

Antiarrhythmic Drugs (AAD) for AF (*Circ* 2011;123:104 & 2012;125:381; *EHJ* 2012;33:2719)

Agent	Conversion	Maintenance	Comments
Amiodarone	5-7 mg/kg IV over 30-60′ → 1 mg/min, 10 g load	200-400 mg qd (most effective AAD for SR)	↑ QT, but TdP rare Low rate of acute conversion. May convert wks after load, ∴ attention to anticoag Pulm, liver, thyroid toxicity ✓ PFTs, LFTs, TFTs Potentiates warfarin, ∴ → warfarin by ˜50%
Dronedarone	n/a	400 mg bid	↓ side effects but also ↓ effic. c/w amio;

				contraindic. in perm AF or sx HF / ↓ EF; risk of liver toxicity
III				
	Ibutilide	1 mg IV over 10′ may repeat × 1	n/a	Contraindic. if ↓ K or ↑ QT ↑ QT, 3-8% risk of TdP Mg 1-2 g IV to ↓ risk TdP Lasts 4-6 h
	Dofetilide	500 mcg PO bid	500 mcg mg bid	↑ QT, ↑ risk of TdP; renal adj
	Sotalol	n/a	80-160 mg bid	✓ for ↓ HR, ↑ QT; renal adj
	Flecainide	300 mg PO × 1	100-150 mg bid	PreRx w/ AVN blocker *Contraindic. if structural or ischemic heart disease*
IC				
	Propafenone	600 mg PO × 1	150-300 mg tid	
IA	Procainamide	10-15 mg/kg IV over 1 h	n/a	↓ BP; ↑ QT ± PreRx w/ AVN blocker

Underlying disease	**Maintenance AAD of choice**
None or minimal (incl HTN w/o LVH)	class IC (“pill in pocket”), sotalol, dronedarone
HTN w/ LVH	amiodarone
CAD	sotalol, dofetilide, amiodarone, dronedarone
HF	amiodarone, dofetilide

Radiofrequency ablation (*JAMA* 2015;314:278)

- **Rationale:** Controlling triggers in pulmonary veins can control AF when little atrial scar present. As progress to persistent and permanent, LA substrate more complex due to scarring and is likely harder to ablate with pulmonary vein isolation alone.
- **Indication:** reasonable alternative to AAD in structurally normal heart
- **Approach:** for paroxysmal AF, circumferential pulm. vein isolation done via ablation in LA myocardium (ablation in PVs causes stenosis) w/ ~80% success (*Lancet* 2012;380:1509). In AF w/o ↑ ↑ LA or ↓ EF, RFA still superior to AAD, but lower success rate w/ AF recurring in ~1/2 over 2 y and 2nd RFA often required to prevent LA flutter (*NEJM* 2012;367:1587; *JAMA* 2014;311:692). Utility of upfront additional lines of block unclear (*NEJM* 2015;372:1812).
- Often performed on uninterrupted/minimally interrupt. warfarin or Xa inhib (*Circ* 2014;129:1688)

- **Risks and complications**

  → arrhythmia & pericarditis during healing post ablation

  left atrial flutters may persist and need additional "touch up" ablation

  rarer complications (1-2%): stroke, tamponade, phrenic nerve injury, PV stenosis, LA-esophageal/mediastinal communication (˜3 wk after procedure, severe dysphagia, fever, CNS signs of thromboembolism; dx w/ CT scan or barium study, *no* TEE*; emergent* thoracic surgery)

- Surgical "maze" procedure (70-95% success rate) option if undergoing cardiac surgery

Oral anticoagulation (*Circ* 2014;130:2071; *JAMA* 2015;313:1950)

- *All valvular* AF (ie, rheum MS, valve prosthesis or repair), as stroke risk very high
- Nonvalvular AF (NVAF): stroke risk ˜4.5%/y, but varies depending on patient; anticoagulation → 68% ↓ stroke but carries risk of bleeding; ∴ use a risk score to guide Rx
- **CHA_2DS_2-VASc: C**HF (1 point), **H**TN (1), **A**ge ≥75 y (2), **D**M (1), **S**troke/TIA (2), **V**ascular disease (MI, PAD, or aortic plaque) (1), **A**ge 65-74 y (1), ♀ **S**ex **c**ategory (1) annual risk of stroke (*Lancet* 2012;379:648): at low end, ˜1% per point: 0 → ˜0%, 1 → 1.3%, 2 → 2.2%, 3 → 3.2%, 4 → 4.0%; at higher scores, risk ↑ ↑ (5 → 6.7%, ≥6 → ≥10%)
- Anticoagulation recommendations: **score ≥2 → anticoagulate**

  score 1 → consider anticoagulation or antiplatelet Rx (? latter reasonable if risk factor 65-74 y, vasc disease or ♀) or no Rx

  score 0 → reasonable to not anticoagulate
- **HAS-BLED** (*Chest* 2010;138:1093)

  HTN (1 point if >160 mmHg), **A**bnl renal/liver fxn (1 for each), **S**troke (1), **B**leeding hx or predisposition (eg, anemia), **L**abile INR (time in therapeutic range <60%), **E**lderly (eg, age >65, frailty), **D**rugs/alcohol concom (1 point for antiplt or NSAID; 1 for alcohol)

  ≥3 → ↑ risk for bleeding, ∴ consider closer monitoring or different drug/dose selection
- Special situations in Pts w/ indication for anticoagulation:

  plan for rhythm control: continue anticoagulation

  Pt refuses anticoag: ASA + clopi or, even less effective, ASA alone (*NEJM* 2009;360:2066) underwent PCI: ? Rx w/ anticoagulant & clopidogrel, omit ASA (*Lancet* 2013;381:1107)
- **Anticoagulant options: factor Xa or direct thrombin inhib** (NVAF only) or **warfarin** (INR 2-3; w/ UFH bridge if high risk of stroke)
- Periop rate of arterial embolization in AF (w/o mech valve) <0.5%; Ø benefit to bridging anticoag w/ LMWH & ↑ bleeding c/w stopping warf 5 d before (*NEJM* 2015;373:823)

Novel Oral Anticoagulants for Nonvalvular AF

Anticoag	Dosing	Efficacy & safety vs warfarin

Dabigatran (Direct thromb inhib)	150 mg bid (110 not avail in U.S.) (75 mg bid if CrCl 15-30)	150 mg: ↓ ischemic stroke & ICH 110 mg: ≈ ischemic stroke & ↓ major bleed/ICH Risks: GI side effects, ↑ MI c/w warfarin
Rivaroxaban (FXa inhib)	20 mg qd (15 mg qd if CrCl 15-50) w/ pm meal	≈ ischemic stroke & ↓ major bleed incl ICH
Apixaban (FXa inhib)	5 mg bid (2.5 mg bid if ≥2 risks: ≥80 y, ≤60 kg, Cr ≥1.5 mg/dL)	≈ ischemic stroke & ↓ major bleed incl ICH, 11% ↓ death. In Pts felt not cand for warfarin, apixa 55% ↓ stroke w/o ↑ bleed vs ASA alone.
Edoxaban (Fxa inhib)	60 mg qd if CrCl 51-95 (30 mg if CrCl 15-50) (30/15 mg regimen not available in U.S.)	60/30 mg: ≈ ischemic stroke & ↓ major bleed incl ICH, 14% ↓ CV death 30/15 mg: ↑ ischemic stroke & ↓ ↓ major bleed incl ICH, 15% ↓ CV death

- Rapid onset (w/in several hrs) and offset. Consequently do not need to bridge when starting. However, missing 1 dose could lead to inadequate protection.
- No monitoring required
- Require dose adjustment based on renal fxn, which should be monitored while on drug
- Difficult to reverse if bleeding. Prothrombin complex concentrate or recombinant FVIIa needed. Dabi can be reversed w/ idarucizumab (Ab frag; *NEJM* 2015;373:511).

(*NEJM* 2009;361:1139; 2011;364:806; 365:883 & 981; 2013;369:2063; *Lancet* 2014;383:955)

Nonpharmacologic stroke prevent (ACC/HRS/SCAI 2015 Overview, *JACC* 2015)

- Percutaneous occlusion of left atrial appendage (LAA) w/ watchman device (nitinol cage w/ polyethylene membrane). Postprocedure: warfarin × ˜45 d followed by clopi × ˜4.5 mo and ASA lifelong. In NVAF w/ $CHADS_2$ ≥1-2, c/w warfarin, ≈ stroke (↓ hemorrhagic, ↑ ischemic), ≈ bleeding (↑ procedural, ↓ non-proc), ↓ CV death (*JACC* 2015;65:2614). Does not address issue of high-risk anticoag Pt w/ *existing* LAA thrombus.
- Epicardial snare to ligate LAA (lariat device). High rate of initial technical success (*JACC* 2013;62:108), but long-term clinical outcomes & safety to be defined.
- Surgical LAA resection reasonable if another indication for cardiac surgery. Resection superior to ligation, which can recanalize.

Atrial flutter

- Macroreentrant atrial loop typically involving cavotricuspid isthmus (usually counter-clockwise w/ flutter waves ⊖ in inf leads & ⊕ in V_1, but can be clockwise).
- Risk of stroke similar to that of AF; ∴ same mandate for stroke prevention.
- Ablation of cavotricuspid isthmus has 95% success rate w/ only 0.5% complication rate. Pts remain at risk for atrial fibrillation.

WIDE-COMPLEX TACHYCARDIA (WCT)

Etiologies (*Lancet* 2012;380:1520)

- **Ventricular tachycardia (VT):** accounts for 80% of WCT in unselected population
- **SVT conducted with aberrancy:** either fixed BBB, rate-dependent BBB (usually RBBB), conduction via an accessory pathway or atrially triggered ventricular pacing

Monomorphic ventricular tachycardia (MMVT)

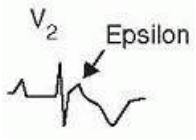
- All beats look similar; predominantly upward in V_1 = RBBB-type vs downward = LBBB-type
- Most commonly in obviously ***structurally abnormal heart*: prior MI** (scar); **CMP**

  mechanism is most commonly re-entry around areas of electrically silent scar tissue with slow myocardial conduction through adjacent areas of surviving myocytes

  focal arrhythmias also occur (RVOT, Ao root, fascicles, papillary muscles)

  re-entry utilizing the Purkinje system is also seen (Bundle Branch Reentry); "typical" form occurs in Pts w/ LBBB in sinus and VT w/ very similar morphology to sinus

- May occur in ***apparently* nl *heart that is actually diseased:***



  Arrhythmogenic (RV) CMP (ACM, qv): incomplete RBBB, ε wave (terminal notch in QRS) & TWI in V_1-V_3 on resting ECG, LBBB-type VT, dx w/ MRI (*Lancet* 2009;373:1289)

  subtle HCMP sarcoid; myocarditis (incl giant cell); anom coronary

- In structurally ***normal heart*** w/ nl resting ECG (prog generally good):

  RVOT VT: LBBB-type VT w/ inferior axis; often seen immediately after exercise; can suppress with CCB or βB or ablate

  idiopathic LV VT: RBBB-type VT w/ superior axis; responds to verapamil or can ablate

Polymorphic ventricular tachycardia (PMVT)

- QRS morphology and/or axis changes from beat to beat
- Etiologies: **ischemia; CMP**

  torsades de pointes (TdP = "twisting of the points," PMVT + ↑ QT): ↑ QT ***acquired*** (meds, lytes, stroke; see "ECG") w/ risk ↑ w/ ↑ HR, freq PVCs (pause dependent) *or* ***congenital*** (K/Na channelopathies) w/ resting Tw abnl & TdP triggered by sympa-thetic stimulation (eg, exercise, emotion, sudden loud noises) (*Lancet* 2008;372:750)

  Brugada syndrome (Na channelopathy): ♂ > ♀; pseudo-RBBB w/ STE in V_1-V_3 (provoked w/ class IA or IC) on resting ECG

  catecholaminergic (CPVT): familial; mutations in ryanodine receptor or calsequestrin 2; presents during emotional or physical stress

Diagnostic clues that favor VT (assume until proven otherwise)

- **Prior MI, CHF** or **LV dysfxn** *best predictors* (90%) that WCT is VT (*Am J Med* 1998;84:53)

- Hemodynamics and rate do *not* reliably distinguish VT from SVT
- MMVT is regular, but may have initial "warmup period" and may be slightly irregular (as compared w/ SVT, which is extremely regular); *grossly* irregularly irregular rhythm suggests PMVT or AF w/ aberrancy
- More the QRS morphology is like QRS morphology in SR, more likely SVT
- ECG features that favor VT (*Circ* 1991;83:1649; *EHJ* 2007;28:589)

  AV *dissociation* (independent P waves, capture or fusion beats) proves VT; physical exam correlates: variable S_1 and cannon *a* waves on JVP

  very wide QRS (> 140 ms in RBBB-type or > 160 in LBBB-type)

  extreme axis deviation; RBBB-type w/ LAD; LBBB-type w/ RAD; shift in axis >40°; initial R wave in aVR

  QRS morphology atypical for BBB

  RBBB-type: absence of tall R′ (or presence of monophasic R) in V_1, r/S ratio <1 in V_6

  LBBB-type: onset to nadir >60-100 ms in V_1, q wave in V_6 longest RS interval in any precordial lead > 100 ms and R wider than S ratio of voltage Δ in initial 40 msec to Δ in terminal 40 ms ≤1

  concordance (QRS in all precordial leads w/ same pattern/direction)

Acute management

- If stable: conscious sedation & sync cardioversion; if unstable (↓ BP, angina, ΔMS, HF): emergent cardioversion; if pulseless → ACLS w/ CPR & cardioversion
- Refractory: consider amiodarone, procainamide, and lidocaine (if suspect ischemia)
- If suspect PPM-mediated tachycardia → place magnet (switches device to VOO or DOO)
- If ICD: should deliver Rx, but do not rely on for VT resolution. If stable, can interrogate ICD. If repeated, appropriate & successful shocks → antiarrhythmics to suppress arrhythmia. If repeated shocks (approp or inapprop) w/o arrhythmia term → disable device (magnet).

Long-term management (*JACC* 2006;48:1064)

- Workup: **echo** to ✓ LV fxn, **cath** or **stress test** to r/o ischemia, ? MRI and/or RV bx to look for infiltrative CMP or ARVC, ? **EP study** to assess inducibility

- **ICD:** 2° prevention after documented VT/VF arrest (unless due to reversible cause) 1° prev. if high risk, eg, EF <30-35%, ACM, Brugada, certain LQTS, severe HCM. See "Cardiac Rhythm Management Devices." ? Wearable vest if reversible etiology while waiting for ICD (*Circ* 2013;127:854).

  Antitachycardia pacing (ATP = burst pacing faster than VT) can terminate VT w/o shock
- **Meds:** βB, antiarrhythmics (eg, amio, mexiletine) to suppress VT, which could trigger shock
- If med a/w TdP → QT >500 ± VPBs: d/c med, replete K, give Mg, ± pacing (*JACC* 2010;55:934)
- **Radiofrequency ablation** if isolated VT focus or if recurrent VT triggering ICD firing; ablation before ICD implantation ↓ discharge rate by 40% (*Lancet* 2010;375:31)

SUDDEN CARDIAC DEATH (SCD)

Definition

- Sudden cessation of cardiac activity with hemodynamic collapse
- Technically sudden cardiac arrest (SCA) or "aborted SCD" if resuscitated
- Frequently due to sustained VT/VF

Etiologies

- **Coronary artery disease** (~60-70%)

  acute ischemia: ACS; spasm; congenital coronary artery anomaly

  scar from prior MI
- **Structurally abnormal heart or vasculature** (~10-15%)

  cardiomyopathy: DCM, HCM, ACM; myocarditis

  valvular heart disease

  myocardial rupture, tamponade, Ao dissection

  PE
- **Apparently structurally normal heart** (~10-15%)

  LQTS (acquired or congenital); Brugada syndrome; catecholaminergic polymorphic VT

  ACM or infiltrative cardiomyopathy

  Wolff-Parkinson-White (typically w/ antegrade conduction of AF → VF)

  complete heart block

  commotio cordis (*NEJM* 1995;333:337)

Precipitants

- Ischemia
- Drugs: antiarrhythmics, QT-prolonging, diuretics
- Electrolytes (usually not sufficient to cause SCD; always search for underlying cause)

Workup (*JACC* 2006;48:1064)

- Hx (usually very limited): may have had prodrome c/w ACS or HF; PMH; meds; FHx
- Exam: signs of cardiovascular disease
- ECG: ischemia, infarction, conduction block, QT, pre-excitation, abnormal V_1-V_3 (eg, pseudo-RBBB + STE, ε wave + TWI), LVH
- Echocardiogram; MRI if echo unrevealing and no other obvious cause
- Coronary angiography (? or CT angio)

  if STE or ? chest pain prodrome, urgent angio (unless poor neurologic prognosis)

  even w/o STE, 33-40% will have evidence of acute occlusion (*NEJM* 1997;336:1629 & *JACC Intv* 2015;8:1031)

- EP study (qv) if above workup unrevealing, programmed stimulation to look for accessory pathway, drug infusions to provoke arrhythmia from CPVT, LQTS, Brugada
- Exercise testing to provoke CPVT or assess resolution of pre-excitation to risk stratify WPW
- If genetic or unexplained SCD, evaluation of family members

SYNCOPE

Definition

- Sudden transient loss of consciousness due to global cerebral hypoperfusion
- If CPR or cardioversion required, then SCD (qv) and not syncope (different prognosis)
- Presyncope = prodrome of light-headedness without LOC

Epidemiology

- Incidence ↑ w/ age, particularly above 70 y; similar in men & women
- Lifetime incidence ~1 in 3

Etiologies (*NEJM* 2002;347:878; *JACC* 2006;47:473; *EHJ* 2009;30:2631)

- **Neurocardiogenic** (a.k.a. vasovagal, ~25%; *NEJM* 2005;352:1004)

  ↑ sympathetic tone → vigorous contraction of LV → mechanoreceptors in LV trigger ↑ vagal tone (hyperactive Bezold-Jarisch reflex) → ↓ HR (cardioinhibitory) and/or ↓ BP (vasodepressor)

  cough, deglutition, defecation, & micturition → ↑ vagal tone and thus can be precipitants

  carotid sinus hypersensitivity is a related disorder w/ an exaggerated vagal resp to carotid massage

- **Cardiovascular** (~20%, more likely in men than women)

  Arrhythmia (15%): challenging to dx as often transient

  Bradyarrhythmias: SSS, high-grade AV block (Stokes-Adams attack), ⊖ chronotropes, PPM malfunction

  Tachyarrhythmias: VT, SVT (syncope rare unless structural heart disease or WPW)

  Mechanical (5%)

  Endocardial/Valvular: AS, MS, PS, prosthetic valve thrombosis, atrial myxoma

  Myocardial: outflow obstruction from HCMP (can also cause VT), MI (more likely VT)

  Pericardial: tamponade

  Vascular: PE, PHT, aortic dissection, ruptured AAA, subclavian steal

- **Orthostatic hypotension** (~10%) hypovolemia/diuretics, deconditioning; vasodilat. (espec if combined w/ ⊖ chronotropes) autonomic neuropathy

  1° = Parkinson's, Shy-Drager, Lewy body dementia, postural orthostatic tachycardia syndrome (POTS, dysautonomia in the young)

  2° = DM, EtOH, amyloidosis, CKD (*NEJM* 2008;358:615)

- **Neurologic** (~10%): vertebrobasilar insufficiency (occlusion, dissection or steal), impaired perfusion to all

cerebral vessels (very rare), SAH

- Remainder of cases with unknown etiology
- Misc. causes of LOC (but not syncope): seizure, TIA/stroke, migraine, hypoglycemia, hypoxia, anemia, anaphylaxis, narcolepsy, psychogenic

Workup (etiology cannot be determined in ˜40% of cases)

- *H&P incl. orthostatic* VS *have highest yield and most cost-effective* (*Archives* 2009;169:1299)
- **History** (from Pt and *witnesses* if available) activity and posture before the incident precipitating factors:

  exertion → AS, HCMP PHT

  positional Δ → orthostatic hypotension

  stressors such as sight of blood, pain, emotional distress, fatigue, prolonged standing, warm environment, N/V, cough/micturition/defecation/swallowing ↑ vasovagal

  head turning or shaving → carotid sinus hypersensitivity arm exercise → subclavian steal

  prodrome: sx such as diaphoresis, nausea, blurry vision for >˜5 sec suggests vasovagal; abrupt onset suggests cardiac or seizure

  associated sx: chest pain (MI), palpitations (tachycardia)

  neuro: aura prior to event, neuro sx, postictal state, bowel/bladder incontinence, & lateral tongue biting suggestive of seizure; brief convulsive activity for < 10 sec may occur w/ syncope & mimic seizure, but true tonic then clonic activity is indicative of seizure
- **PMH:** prior syncope, previous cardiac or neurologic dis.; no CV disease at baseline → 5% cardiac, 25% vasovagal; CV disease → 20% cardiac, 10% vasovagal (*NEJM* 2002;347:878)
- **Medications that may act as precipitants** vasodilators: α-blockers, nitrates, ACEI/ARB, CCB, hydralazine, phenothiazines, antidep. diuretics; ⊖ chronotropes (eg, βB and CCB)

  proarrhythmic or QT prolonging: class IA, IC or III antiarrhythmics (see "ECG") psychoactive drugs: antipsychotics, TCA, barbiturates, benzodiazepines, EtOH
- **Family history:** CMP, SCD, syncope (vasovagal may have genetic component)

- **Physical exam**

  VS including *orthostatics* (⊕ if supine → standing results in >20 mmHg ↓ SBP, >10 mmHg ↓ DBP, or > 10-20 bpm ↑ HR), BP in both arms

  persistently abnormal VS *concerning*

  cardiac: HF (↑ JVP, displ. PMI, S_3), murmurs, LVH (S_4, LV heave), PHT (RV heave, ↑ P_2)

  vascular: ✓ for asymmetric pulses, carotid/vertebral/subclavian bruits

  carotid sinus massage to assess for carotid hypersensitivity (if no bruits and no h/o TIA or stroke); ⊕ if asystole >3 sec or ↓ SBP >50 mmHg

  neurologic exam: focal findings, evidence of tongue biting; FOBT
- **ECG** (abnormal in ˜50%, but only definitively identifies cause of syncope in <10%)

  Conduction abnl: SB <40 bpm, repetitive sinus pauses >3 sec, AVB (partic. Mobitz II 2° or 3°), IVCD or BBB

(partic. bifascicular block or alternating BBB) (*EHJ* 2009;30:2631)

Arrhythmia: ectopy, ↑ (or ↓) QT, preexcitation (WPW), Brugada, ε wave (ACM), SVT/VT Ischemic changes (new or old): atrial or ventricular hypertrophy

- Place on telemetry while diagnostic workup ongoing
- Lab: glc, Hb, preg test (child-bearing age ♀), ? D-dimer, ? troponin (low yield w/o other s/s)

Life-threatening dx

- *Arrhythmia:* VT, high-grade AVB, long sinus pauses
- *Cardiovascular structural disease:* critical AS, HCMP tamponade, aortic dissection, PE
- *Massive hemorrhage* (eg, large GIB, Ao rupture, splenic rupture, ectopic preg, RP bleed)
- *Neurologic:* SAH (headache + syncope)

High-risk features (*J Emerg Med* 2012;42:345)

- Advanced age (? >60 y), h/o CAD, HF/CMP, valvular or congenital heart disease, arrhythmias, or FHx SCD
- Syncope c/w cardiac cause (lack of prodrome, exertional, supine, or resultant trauma) or recurrent syncope (risk of recurrence if ≥2 prior episodes >50%)
- Complaint of chest pain or dyspnea; abnl VS or cardiac, pulmonary or neuro exam
- Abnormal ECG suggesting arrhythmia, conduction abnormality, ischemia/infarction; Pt w/ PPM/ICD (unless interrogated and found to have no arrhythmia)

Disposition

- High-risk Pts should usually be admitted w/ telemetry and further testing (qv)
- Low-risk Pts may be discharged with follow-up testing
- Obvious vasovagal syncope can be discharged

Other diagnostic studies (consider based on results of H&P and ECG)

- Ambulatory ECG monitoring: if suspect arrhythmogenic syncope

  Holter monitoring (continuous ECG 24-48 h): useful if *frequent* events arrhythmia + sx (4%); asx but signif. arrhythmia (13%); sx but no arrhythmia (17%)

  Event recorder (activated by Pt to record rhythm strip): limited role, as only useful if established prodrome (because must be Pt activated)

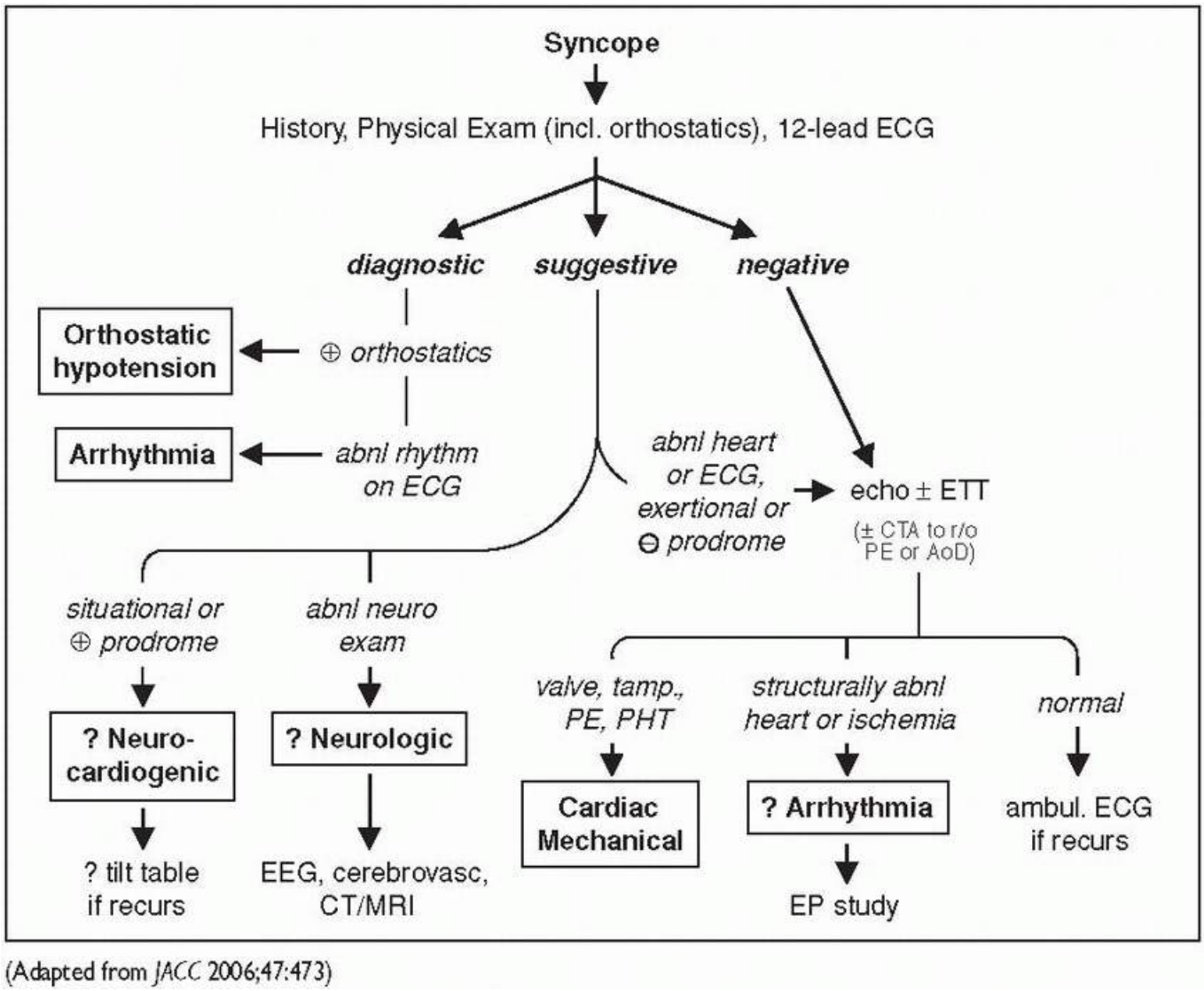
  External intermittent loop recorders (continuously saves rhythm, ∴ can be activated *after* an event): useful for episodes (including w/o prodrome) likely to occur w/in 1 mo

  Implantable loop recorders (inserted SC; can record up to 3 y): useful for infrequent episodes (< 1/mo); recommended for recurrent syncope w/o prodrome. Appears to establish a dx (often bradycardia) more frequently (55% vs 19%) than conventional testing (external loop recorder, tilt table, etc.; *Circ* 2001;104:46)
- Echo: consider to r/o structural heart disease (eg, CMP [incl HCMP & ACM], valvular disease [incl AS, MS, MVP], myxoma, amyloid, PHT, ± anomalous coronaries)
- ETT: espec w/ exertional syncope; r/o ischemia- or catecholamine-induced arrhythmias

- Cardiac catheterization: consider if noninvasive tests suggest ischemia
- Electrophysiologic studies (EPS, qv): consider in high-risk Pts in whom tachy or brady etiology is strongly suspected but cannot be confirmed;

  50% abnl (inducible VT, conduction abnormalities) if heart disease, but ? significance

  3-20% abnl if abnl ECG; <1% abnl if normal heart and normal ECG (*Annals* 1997;127:76)
- ? Tilt table testing: utility is debated due to poor Se/Sp/reproducibility; consider only if vasovagal dx suspected but cannot be confirmed by hx
- Cardiac MRI: helpful to dx ARVC if suggestive ECG, echo (RV dysfxn) or ⊕ FHx of SCD
- Neurologic studies (cerebrovascular studies, CT, MRI, EEG): if H&P suggestive; low yield



(Adapted from *JACC* 2006;47:473)

Figure 1-10 Approach to syncope

Treatment

- Arrhythmia, cardiac mechanical or neurologic syncope: treat underlying disorder
- Vasovagal syncope (*Int J Cardiol* 2013;167:1906): benefit for midodrine, SSRI

  ? 16 oz of H_2O before at-risk situations (*Circ* 2003;108:2660)

No proven benefit w/ βB (*Circ* 2006;113:1164) or tilt training

No benefit w/ PPM in RCT comparing active pacemaker vs pacemaker programmed in backup mode only. However, guidelines permit implant if ≥3 episodes/2y & loop recorder w/ asystole >3 sec (*Circ* 2012;125:2566).

No data for fludrocortisone, disopyramide

- Orthostatic syncope: volume replete (eg, 500 mL PO q a.m.); if chronic → rise from supine to standing *slowly,* compressive stockings, midodrine, atomoxetine (HTN 2014;64:1235), fludrocortisone, high Na diet

Prognosis (*Ann Emerg Med* 1997;29:459; *NEJM* 2002;347:878)

- 22% overall recurrence rate if idiopathic, else 3% recurrence
- Cardiac syncope: 2-fold ↑ in mort., 20-40% 1-y SCD rate, median survival ˜6 y
- Unexplained syncope w/ 1.3-fold ↑ in mort., but noncardiac or unexplained syncope w/ nl ECG, no h/o VT, no HF, age <45 → low recurrence rate and <5% 1-y SCD rate
- Vasovagal syncope: Pts not at increased risk for death, MI or stroke
- ✓ state driving laws and MD reporting requirements. Consider appropriateness of Pt involvement in exercise/sport, operating machinery, high-risk occupation (eg, pilot).

ANTIARRHYTHMIC DRUGS (AAD)

Procainamide (class IA = moderate Na channel blocker)

Dose	10-15 mg/kg IV over 1 h; 1-2 g bid (oral form not available in U.S.)
Uses	Converting AF & maint. SR; emergent Rx of VT or WCT of ? etiology
Side effects	→ QT, TdP. HoTN (w/ IV use); lupus-like synd. Metab by hepatic N-acetylation. NAPA K channel blocker and renally cleared; ✓ proc & NAPA levels.

Quinidine (class IA = moderate Na channel blocker)

Dose	200-648 mg tid (slowly uptitrate); can be given IV
Uses	Prevention of VT (used mainly in refractory cases). Blocks I_{TO} (Rx VF storms in Brugada syndrome).
Side effects	→ QT, TdP. Diarrhea often limiting. Moderate anticholinergic effects. α blockade → HoTN. Tinnitus, hemolytic anemia, thrombocytopenia.

Disopyramide (Norpace) (class IA = moderate Na channel blocker)

Dose	200-600 mg bid (slowly uptitrate)
Uses	Rx for AF in HCMPP Rx for HCMPP(b/c ⊖ inotrope)
Side effects	→ QT, TdP. Marked anticholinergic effects. ⊖ inotrope (∴ contraindic in Pts w/ ↓ EF).

Lidocaine (class IB = mild Na channel blocker)

Mech	Blocks activated & inactivated but not resting Na channels; ∴ selectively blocks ischemic arrhythmogenic tissue
Dose	100 mg IVB, subsequent 50 mg IVB prn × 2; infusion 1-4 mg/min
Uses	Emergent treatment of VT/VF
Side effects	Δ MS, slurred speech, twitching; ✓ lido levels, toxicity can manifest as seizure
Other	**Mexiletine:** IB that can be given PO (200-300 tid) to suppress VT/VF

Flecainide (Tambocor) (class IC = marked Na channel blocker)

Dose	50-150 mg bid (slowly uptitrate); 200-300 mg × 1 (pill-in-pocket)
Uses	Maintenance of SR (PAF, PSVT); acute cardioversion (test in-hosp first!) PreRx with AV nodal blocker to prevent rapid ventricular conduction.
Side effects	→ mortality if structural heart disease (∴ *contraindic if ischemic or structural heart disease*). Metallic taste, negative inotropy.
Other	**Propafenone** (Rhythmol): similar indications & contrindic. Also βB. 150-300 mg tid or 225-425 bid (slowly uptitrate); 450-600 mg × 1 (pill-in-pocket).

Amiodarone (Cordarone) (class III = K channel blocker)

Mech	Primarily K channel blocker, but also Na channel blocker, βB, & CCB
Dose	IV load: 150 mg over 10 min → 1 mg/min × 6 h → 0.5 mg/min × 18 h → cont IV drip or Δ PO load for total ~10 g. PO load: 400 mg tid → total ~10 g Maintenance: 200 (for AF) to 400 (for VT) qd Emergent Rx of VT/VF: 300 mg IVB ± another 150 mg IVB if persists/recurs
Uses	Cardioversion of AF & maintenance of SR; treatment & suppression of VT/VF
Side effects	HoTN when given IV; bradycardia. Hypo- (~10%) or hyper- (~3%, typically in iodine-defic Pts) thyroidism. ↑ LFTs; pneumonitis or pulmonary fibrosis.
Other	**Dronedarone:** noniodine-containing derivative of amio w/ ↓ efficacy but better tolerability. Used for paroxysmal AF (400 mg bid). Contraindic if HF or perm AF.

Sotalol (Betapace) (class III = K channel blocker)

Mech	K+ blocker, and nonselective βB *d* and *l* isomers, respectively
Dose	Start 80 mg bid, ↑ to 120 and then up to 160 mg bid as needed.
Uses	Maintenance of SR in Pts w/ AF, prevention of VT in pts with ICD
Side effects	→ QT (contraindic if QTc >450 msec, adjust dose to keep <500 ms), TdP. ∴ monitor in hospital for ≥3 days on maintenance dose. Renally cleared.

Ibutilide (Corvert) (class III = K channel blocker)

Dose	1 mg IV over 10 min, may repeat × 1. Mg 2 g IV routinely during infusion.
Uses	Conversion of AF
Side effects	→ QT, TdP (~5%). Replete K & Mg before Rx. Continuous ECG monitoring (including for several hrs after last dose) and be prepared to defibrillate.
Other	**Dofetilide** (Tikosyn): maintenance of SR in Pts w/ AF. 0.5 mg bid. ↑ QT, TdP.

ELECTROPHYSIOLOGY STUDY (EPS)

Indications

- Syncope (w/ high-risk features or abnl ECG); identification of unsuspected tachyarrhythmias; distal

conduction disease (not good for ruling out paroxysmal sinus node dysfunction)

- Determination of mechanism of narrow [eg, AVNRT (dual AV node physiology), AVRT (bypass tract), ectopic atrial tachycardia] and wide complex tachycardias
- Diagnosis in Pts post cardiac arrest
- Risk stratification for SCD (ie, inducibility of VT/VF) in structural heart disease

Preprocedural evaluation

- Coronary angiography to r/o signif CAD (either as cause of ischemia-induced arrhythmia and/or to fix before inducing VT)
- TEE to r/o LA clot before left atrial procedures

Commonly used catheters and measurements

- Most often electrode catheters placed via femoral vein and placed at high right atrium (HRA), His bundle (HBE) and right ventricular apex (RVA). For SVT, also have a catheter in coronary sinus (CS), coursing to left side of heart around mitral annulus.

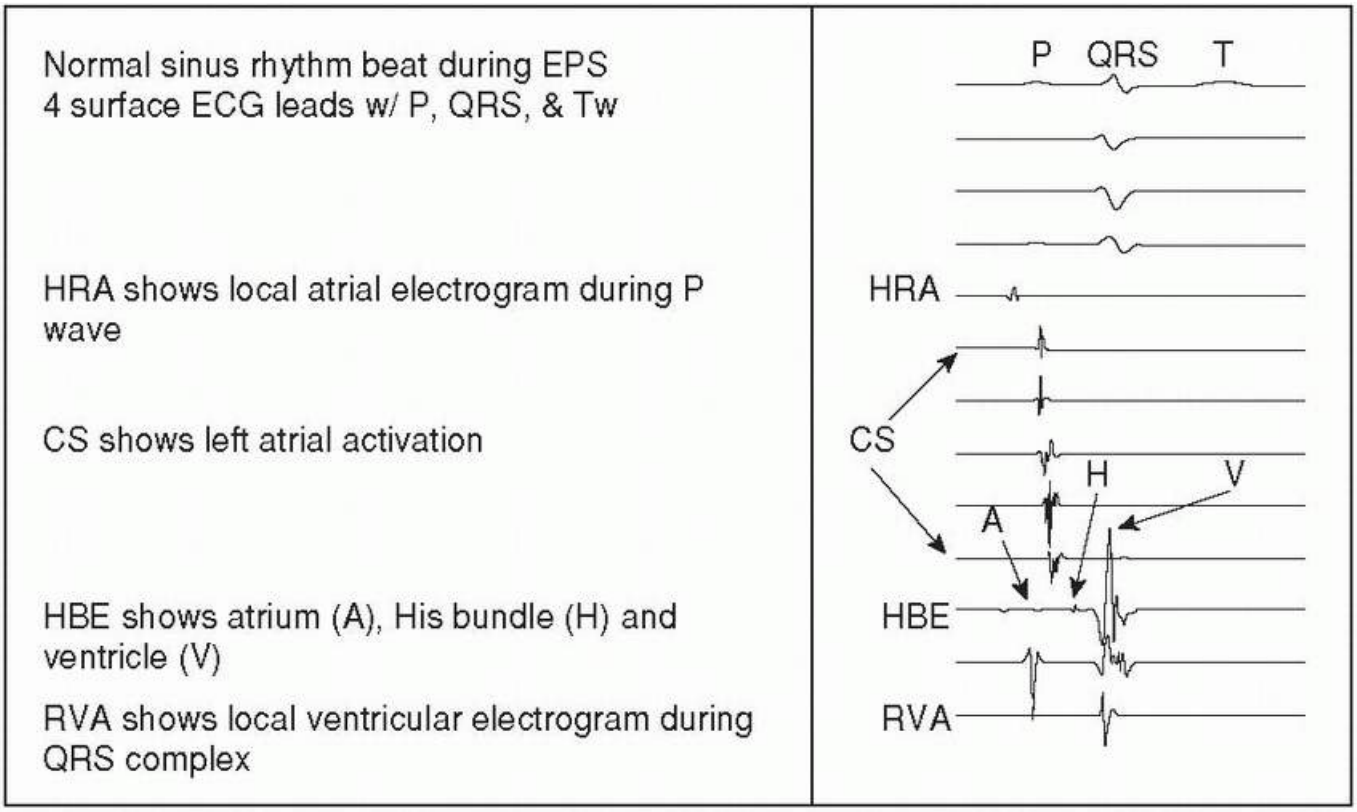


Figure 1-11 Tracing from EPS

- His bundle electrogram allows measurement of AVN conduction (AH interval) and distal conduction system (HV interval, nl 35-55 ms):

  HV interval <35 ms: pre-excitation (WPW)

  HV interval >35 ms: conduction system disease. LBBB typically 55-65 ms, > 70 ms w/ syncope needs PPM, > 100 ms needs PPM

- Current driven through electrodes used to pace heart and introduce extra beats following 8-beat drive train (programmed electrical stimulation, PES) usually done at HRA and RVA

- Atrial PES can be used to reveal evidence of dual AVN pathways or accessory pathways. Can also be used to induce SVT, AF, AFL.
- Ventricular PES can be used to reveal evidence of concealed accessory pathways, assess inducibility of VT/VF (and thereby risk of SCD), particularly in ischemic heart disease.
- Drug infusions (eg, epinephrine, procainamide) can help to dx LQTS, CPVT and Brugada

Complications

- Vascular injury at site of access
- Damage to tricuspid valve
- Arrhythmias
- Cardiac chamber perforation ± tamponade
- If ablation:

  heart block ± need for PPM

  chamber perforation ± tamponade for AF ablation: PV stenosis, phrenic nerve injury, atrio-esophageal fistula

CARDIAC RHYTHM MANAGEMENT DEVICES

Pacemaker Code

A, atrial; V, vent; O, none; I, inhibition; D, dual; R, rate-adaptive	1st letter	2nd letter	3rd letter	4th letter
	Chamber paced	Chamber sensed	Response to sensed beat	Program features

Common Pacing Modes

VVI	Ventricular pacing on demand w/ single lead in RV. Sensed ventricular beat inhibits V pacing. Used in chronic AF with symptomatic bradycardia.
DDD	A & V sensing/pacing (RA & RV leads). Native A beat inhib A pacing & *triggers V pacing* → tracking of intrinsic atrial activity. Maintains AV synchrony, ↓ AF.
Mode Switch	In atrial tachyarrhythmia (usually atrial flutter or fibrillation), pacemaker switches from DDD to nontracking mode (like VVI) in order to prevent pacing the ventricle at the upper rate limit (max rate at which PPM will pace ventricle) in an attempt to track the rapid atrial arrhythmia

Magnet (place over generator)	Pacemaker will pace at fixed rate regardless of intrinsic activity (= VOO/DOO). ICD: no detection/shock, but pacing programming preserved. Indications: ✓ ability to capture; ✓ battery life (to which rate will be proportional; uses less energy than programmer and does not require a programmer); during surgery w/ electrocautery; hemodynamic instability due to inappropriate PPM inhib, failure to mode switch or PM-mediated tachy; inapprop ICD shocks.

Indications for Permanent Pacing (*Circ* 2012;126:1784)

AV block	3° or type II 2° AVB a/w sx or w/ either HR <40 or asystole ≥3 sec (≥5 sec if in AF) while awake; ? asx 3° or type II 2° AVB; bifascicular or alternating left & right BBB
Sinus node	SB, pauses, chronotropic incompet a/w sx or ? if sx w/o clear assoc
Tachy-arrhythmia	Most common: AF w/ SSS, where pacing permits rate support of sinus rhythm in setting of rate controlling drugs for episodes of AF Pacing after AV junctional ablation for uncontrolled rates in AF Sustained pause-dependent VT Selected Pts w/ congenital long QT may benefit from pre-emptive pacing from their ICD
Syncope	Carotid sinus hypersensitivity with asystole >3 sec ? Neurocardiogenic syncope w/ prominent cardioinhib. response ? Syncope with bi/trifascicular block and not likely 2° to other causes

Pacing Complications (Pacemaker or ICD)

Issue	Manifestation	Description
Failure to pace	Bradycardia	Oversensing (ie, inappropriate inhibition) due to noise from lead fracture or set screw problem, myopotentials, EMI source outside body such as electrocautery or metal detector Sensitivity too low Battery depletion
Failure to capture	Pacing impulses delivered, but no P waves or QRS evoked	Elevated pacing threshold due to lead dislodgement, local tissue reaction or injury
Failure to sense	Inapprop. pacing	Lead dislodgment or disease of local myocardium (measured electrogram from leads too small to sense) or sensing threshold too high
PM-	WCT at device	Seen w/ DDD. VA retrograde conduction; sensed by A lead →

mediated tachycardia	upper rate	triggers V pacing → etc.
PM syndrome	Palpit, HF	Seen w/ VVI in Pts w/ intact AV conduction, due to loss of AV synchrony
SVC syndrome	Facial plethora	Thrombosis acutely or scarring a/w chronic intravascular lead(s)
Infection	Fever, ⊕ BCx	See below

Cardiac resynch therapy (CRT)/Biventricular (BiV) pacing (*Circ* 2012;126:1784)

- LBBB and standard RV apical pacing w/ resultant LBBB-like morphology causes dyssynchrony: LV septum activated before LV lateral wall. Wasted myocardial energy due to: prolonged time of contraction (sometimes continuing after AoV closure), sequential rather than simultaneous activation of papillary muscles → functional MR.
- 3-lead pacemaker (RA, RV, coronary sinus to LV lateral wall - LV lead can also be placed surgically by thoracotomy); pre-excites LV lateral wall in attempt to overcome dyssynchrony. R>S in V_1 & predominantly negative in I suggests approp LV capture. QRS width depends on degree of LV pre-excitation; can be narrower or wider than baseline.
- **Indications:** LVEF ≤35% + NYHA II-IV despite med Rx + SR + LBBB ≥150 (? ≥120) ms; mortality benefit only if LBBB (regardless of QRS width) (*NEJM* 2014;370:1694) can also consider in AF, but rate control or AVN ablation necessary to allow ventricular capture, as the greater proportion of time paced, the greater the CRT effect;

  ? NYHA I w/ LVEF ≤30% + LBBB ≥150 ms;

  ? EF ≤50% w/ AVB + indic for PPM (*NEJM* 2013;368:1585)
- **Benefits**

  acutely: simultaneous contraction of LV walls and reduction in MR

  after 3-6 mo: improvement in one NYHA class in 2/3 of Pts; some "super-responders" will normalize EF

  clinically: ↓ HF sx, ↓ HF hosp., ↑ survival (*NEJM* 2005;352:1539; 2010;363:2385)

  ineffective when LV lead location poor or LV scarring prevents pacing and/or improvements in wall motion

Implantable cardiac defibrillator (ICD) (*NEJM* 2003;349:1836; *JACC* 2009;54:747)

- RV lead: pacing and sensing like pacemaker lead, coils plus outside housing of ICD can participate in shocking circuit (± antitachycardia pacing [ATP] = burst pacing faster than VT rate to stop VT w/o painful shocks); ± RA lead for dual chamber pacing
- Uninterrupted warfarin at time of ICD (or PPM) placement ↑ risk of pocket hematoma vs bridging with UFH (*NEJM* 2013;368:2084)
- Subcutaneous ICD contains only shocking function (no ATP, no pacing) implanted in the left parasternal area with pulse generator in left lateral thoracic area. Reasonable for those with poor central access and those w/o

pacing requirement (*Circ* 2013;127:854).

- Wearable defibrillator vest can act as a “bridge” for Pts who cannot have an implanted defibrillator for weeks to a few months due to infection or other issue. Not yet demonstrated benefit as a bridge for those who do not yet meet guidelines for ICD (eg, early post MI or new NICMP (*JACC* 2013;62:2000). Data do not support home AED for these Pts either (*NEJM* 2008;358:1793).
- **Pt selection** (*NEJM* 2004;350:2151 & 351:2481; 2005;352:225; 2009;361:1427; *Circ* 2012;126:1784)

  2° prevention: survivors of VF arrest, unstable VT w/o reversible cause (*NEJM* 1997;337:1576); structural heart disease & spontaneous sustained VT (even if asx)

  1° prevention:

  LVEF ≤30% & post-MI *or* LVEF ≤35% & NYHA II-III *or* LVEF ≤40% & inducible VT/VF wait ≥40 d if post-MI, >9 mo after dx of NICM, or if presumed reversible; *however,* consider ICD if hemodyn signif VT/VF w/in window (& >48 h after AMI) (*Circ* 2014;130:94)

  consider for HCM, ARVC, Brugada, sarcoid, LQTS, Chagas or congenital heart disease if risk factors for SCD

  life expectancy must be > 1 y
- **Benefits:** ↓ mortality from SCD c/w antiarrhythmics or placebo
- **Risks:** inapprop shock in ~15-20% at 3 y (most commonly due to misclassified SVT); lead fracture
- ICD discharge: ✓ device to see if approp; r/o ischemia, other proximate cause; if recurrent VT, ? drug Rx (eg, amio + βB; *JAMA* 2006;295:165) or VT ablation (*NEJM* 2007;357:2657); ablation at time of ICD ↑ risk of VT by 40% (*Lancet* 2010;375:31)
- Telemonitoring may improve outcomes (*Lancet* 2014;384:583)

Device infection (*Circ* 2010;121:458; *JAMA* 2012;307:1727; *NEJM* 2012;367:842)

- Presents with one or more of the following: *pocket infection* (warmth, erythema, tenderness), *fever, bacteremia* and/or *sepsis*
- Incidence ~2% over 5 y; if *S. aureus* bacteremia, infxn in ≥35%
- More common a complication of generator change
- TTE/TEE used to help visualize complic. (eg, vegetation), but even ⊖ TEE does not r/o
- Treatment: abx and *removal of system* if evidence of pocket infection or GPC bacteremia (*Heart Rhythm* 2009;7:1085)
- Prophylaxis: no recommendation for routine abx prior to invasive procedure

Rapid Cardiac Care

Rapid Cardiac Care

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WILEY Blackwell

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John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial Office
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Library of Congress Cataloging-in-Publication Data

Names: Menzies-Gow, Emma, author. | Spiers, Christine, author.
Title: Rapid cardiac care / by Emma Menzies-Gow, Christine Spiers.
Description: Hoboken, NJ : Wiley, 2017. | Includes index. |
Identifiers: LCCN 2017030441 (print) | LCCN 2017030987 (ebook) | ISBN 9781119220282 (pdf) | ISBN 9781119220343 (epub) | ISBN 9781119220275 (paper)
Subjects: | MESH: Cardiovascular Diseases–therapy | Acute Disease–therapy | Cardiovascular Diseases–diagnosis | Diagnostic Techniques, Cardiovascular
Classification: LCC RC667 (ebook) | LCC RC667 (print) | NLM WG 166 | DDC 616.1–dc23
LC record available at https://lccn.loc.gov/2017030441

Cover Design: Wiley
Cover Image: © Caiaimage/Sam Edwards/Gettyimages

Set in 9.5/11.5pt Frutiger Light by SPi Global, Pondicherry, India

10 9 8 7 6 5 4 3 2 1

Dedication

Heidi Simpson (née Clinton)

This book is dedicated to our much loved friend Heidi, an outstanding nurse whose contribution to healthcare education has influenced the clinical practice of many nurses and practitioners working in acute and intensive care

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List of Abbreviations

ABGs Arterial blood gases
ACE-I Angiotensin-converting-enzyme inhibitors
ACLS Advanced Cardiac Life Support
ACS Acute coronary syndromes
AED Automated external defibrillator
AF Atrial fibrillation
ALP Alkaline phosphatase
ALT Alanine transaminase
APTT Activated partial thromboplastin time
ARB Angiotensin receptor blocker
ARVC Arrhythmogenic right ventricular cardiomyopathy
AS Aortic stenosis
AST Aspartate transaminase
AV Atrio-ventricular
AVNRT A-V nodal re-entry tachycardia
AVRT A-V re-entry tachycardia
BBB Bundle branch block
BNP B-type natriuretic peptides
BP Blood pressure
bpm beats per minute
CCBs Calcium channel blockers
CK-MB Creatinine kinase myocardial isoenzyme
CMR Cardiac magnetic resonance
COPD Chronic obstructive pulmonary disease
CPAP Continuous positive airway pressure
CPR Cardiopulmonary resuscitation
CRP C-reactive protein
CRT Cardiac resynchronisation therapy
CRT-D Cardiac resynchronisation therapy – defibrillator
CRT-P Cardiac resynchronisation therapy – pacemaker
CT Computed tomography
CXR Chest X-ray
DCCV Direct current cardioversion
DCM Dilated cardiomyopathy
ECG Electrocardiogram
EDV end diastolic volume
eGFR Estimated glomerular filtration rate
ESR Erythrocyte sedimentation rate
FBC Full blood count
GTN Glyceryl trinitrate
HbA1c Glycated haemoglobin
HCM Hypertrophic cardiomyopathy

HF	Heart failure
HF-PEF	Heart failure with Preserved Ejection Fraction
HF-REF	Heart failure with Reduced Ejection Fraction
ICD	Implantable cardioverter defibrillator
IE	Infective endocarditis
JVD	Jugular venous distension
LAD	Left anterior descending coronary artery
LAFB	Left anterior fascicular block
LBB	Left bundle branch
LBBB	Left bundle branch block
LCx	Left circumflex
LDL	Low-density lipoproteins
LMWH	Low molecular weight heparin
LPFB	Left posterior fascicular block
LQTS	Long QT syndrome
LV	Left ventricle
LVEDP	Left ventricular end diastolic pressure
LVEDV	Left ventricular end diastolic volume
LVF	Left ventricular failure
LVH	Left ventricular hypertrophy
LVOT	Left ventricular outflow tract
mV	millivolts
MR	Mitral regurgitation
NOAC	Non-vitamin K oral anti-coagulant
NSAIDs	Non-steroidal anti-inflammatory drugs
NSTEMI	Non ST-segment elevation myocardial infarction
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
PA	Posterior-anterior
P-PCI	Primary percutaneous coronary intervention
PCI	Percutaneous coronary intervention
PDA	Posterior descending artery
PEA	Pulseless electrical activity
PMH	Past medical history
PVCs	Premature ventricular contractions
QTc	Corrected QT
RAAS	Renin-angiotensin-aldosterone system
RBB	Right bundle branch
RBBB	Right bundle branch block
RCA	Right coronary artery
RV	Right ventricle
RVH	Right ventricular hypertrophy
RVOT	Right ventricular outflow tract
SA	Sino-atrial (node)
SCN5A	Sodium channel gene 5A

STEMI	ST-segment elevation myocardial infarction
SVT	Supraventricular tachycardia
TAVI	Transcutaneous aortic valve implantation
TEVAR	Thoracic endovascular aortic repair
TOE	Trans-oesophageal echocardiogram
TC	Takotsubo cardiomyopathy
TOE	Transoesophageal echocardiogram
TTE	Trans-thoracic echocardiogram
UA	Unstable angina
U&E	Urea and electrolytes
UFH	Unfractionated heparin
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White

Preface

Many cardiac conditions present suddenly, requiring a rapid response from healthcare practitioners. 'Rapid Cardiac Care' provides a concise text to guide the assessment and management of patients experiencing a variety of cardiac conditions. A systematic approach has been used to structure your assessment of the patient data and to prioritise management interventions. An overview of cardiac anatomy and physiology precedes sections on cardiac assessment, investigations, history taking, physical examination, symptom review and cardiac rhythm evaluation. The 12-lead ECG is a pivotal investigation in the evaluation of many cardiac conditions and therefore a tool to guide rapid interpretation is also provided. The care of patients with a range of cardiac conditions is presented in an A–Z format, which will direct the reader straight to the relevant sections.

Acknowledgements

We would like to thank the team at Wiley for their assistance throughout the production of this book.

Sincere thanks are extended to our families, for their constant support, patience and encouragement. We would especially like to acknowledge our fathers who influenced our lives immensely.

Part 1 Cardiac Anatomy and Physiology

Rapid Cardiac Care, First Edition. Emma Menzies-Gow and Christine Spiers.
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1

Anatomy

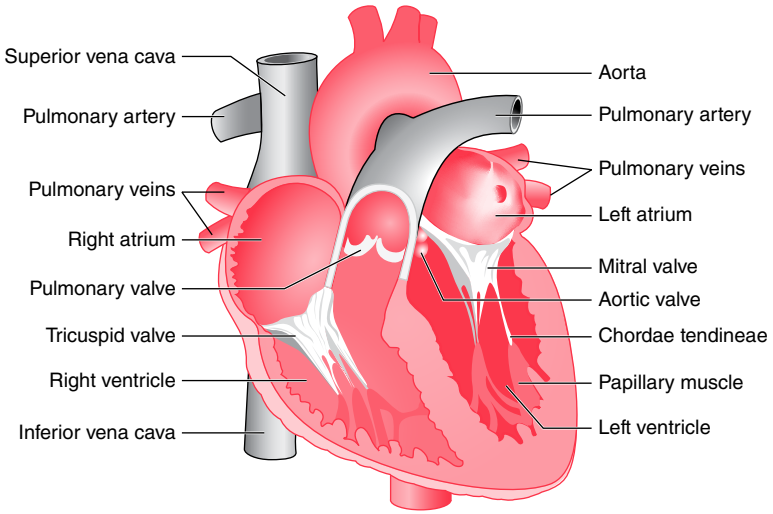

Figure 1.1 Cardiac anatomy.

The heart is a cone-shaped, muscular organ with four chambers that propel blood through the circulatory system (Figure 1.1). The two upper chambers, the atria, and the ventricles below are separated by the annulus fibrosus (AV ring), a layer of connective tissue that forms the cardiac skeleton, seen on the external surface of the heart as the atrio-ventricular (AV) groove. The mitral and tricuspid (AV) valves and aortic and pulmonary (semilunar) valves form part of the AV ring. Each valve consists of two or three cusps arising from an annulus. Healthy valves maintain forward blood flow through the heart, opening and closing in response to changes in pressure between the chambers. The interatrial septum separates the two atria; the ventricles are separated by the interventricular septum, which is visible on the outside of the heart as anterior-posterior interventricular groove.

The heart wall is formed from three layers of tissue that provide different functions. The external layer is the pericardium, which surrounds the heart and the roots of the aorta and pulmonary arterial trunk. It consists of two distinct layers: the outermost fibrous layer and serous layer beneath. The serous pericardium has a visceral layer, known as the epicardium, which surrounds the myocardium and doubles back on itself to form the parietal pericardium, which lines

the tough, outer fibrous layer. The space between the two layers contains a small volume of fluid to reduce friction during myocardial contraction. The central, thickest layer of the heart wall is the myocardium. It contains clusters of cardiac muscle cells known as myocytes, each surrounded by connective tissue and a network of capillaries. The internal surface of the heart is lined with a single, continuous layer of endothelial cells known as the endocardium. This facilitates smooth blood flow through the chambers and across the valves and provides some protection from the formation of thrombi.

Cardiac cycle

Cardiac output is the volume of blood ejected from the left ventricle (LV) in one minute, i.e. heart rate × stroke volume. It is approximately 4–7 L/min. The cardiac conduction system controls heart rate variability and co-ordinated systolic (contraction) and diastolic (relaxation and filling) activity of the cardiac chambers to maximise cardiac output.

The superior and inferior vena cava empty into the right atrium, enabling the return of deoxygenated blood to the heart. The coronary sinus, a large cardiac vein, also drains deoxygenated blood from the myocardium into the right atrium. The tricuspid valve opens to permit blood to enter the right ventricle (RV); atrial contraction provides extra force to expel blood from the chamber, known as the 'atrial kick', to optimise the end diastolic volume (EDV) of the ventricles.

During systole, the three papillary muscles in the RV contract, tightening the chordae tendineae, attached to the cusps of the tricuspid valve to ensure the valve leaflets remain closed, preventing regurgitation of blood into the right atrium. Pressure within the RV will rise until it exceeds the pressure within the pulmonary circulation beyond, forcing the pulmonary valve to open and blood to flow into the pulmonary arterial trunk. During ventricular diastole, the pulmonary arteries will rapidly recoil to enable blood to fall back towards the RV, closing the pulmonary valve.

Having completed gaseous exchange within the alveoli and pulmonary capillaries, oxygenated blood returns to the left atrium via four pulmonary veins. The increase in pressure within the atrial chamber forces the mitral valve to open and ventricular filling to begin. During diastole, the ventricular myocytes will stretch to accommodate the volume of blood, which directly correlates with the force of contraction that occurs during systolic contraction (Frank Starling's Law). The two papillary muscles contract first, once systole begins, tightening the chordae tendineae attached to the two cusps of the mitral valve to prevent regurgitation. The LV and septum then contract to increase the pressure (preload) within the LV. Once the preload pressure exceeds the pressure in the aorta beyond the aortic valve (afterload), blood will leave the LV, referred to as the stroke volume, crossing the aortic valve into the aorta to supply the arterial circulation. The term 'ejection fraction' refers to the stroke volume as a percentage of the left ventricular EDV (LVEDV), usually approximately 60–70% at rest. As systole ends, diastole begins again and a small volume of blood in the aorta will return towards the LV, closing the aortic valve cusps and simultaneously perfusing the coronary arteries originating at the aortic root.

Cardiac conduction system

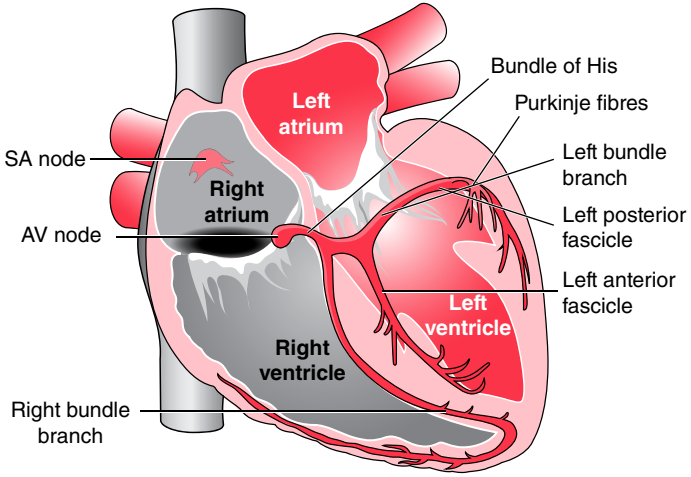

Figure 1.2 Cardiac conduction system.

The cardiac conduction system lies beneath the endocardium within the myocardium and consists of specialised myocytes responsible for generating and transmitting an impulse across the heart (Figure 1.2). The sino-atrial (SA) node, located on the posterior wall of the right atrium, is the primary pacemaker of the heart and therefore determines heart rate. It is capable of regular spontaneous depolarisation without external stimulus. However, the autonomic nervous system controls the SA nodal firing rate, permitting heart rate variability in response to fluctuating metabolic demand. Increased sympathetic activity will cause an increase in the SA nodal firing rate, for example during exercise. The heart rate is slowed via the vagus nerve, part of the parasympathetic nervous system.

Transition cells surrounding the SA node transfer the impulse across to the surrounding atrial myocytes, which in turn propagate the impulse to the remaining atrial cells, causing depolarisation and contraction. The annulus fibrosus, or AV ring, prevents direct transmission of the impulse to the ventricle. In response to atrial stimulation, the AV node transmits the impulse to the ventricular myocardium via the His-Purkinje system. After leaving the AV node, the impulse traverses the Bundle of His, which divides into two bundle branch systems. The right bundle branch is a thin, long strand, which runs down the right side of the interventricular septum and supplies conduction to the RV. The left bundle branch comprises shorter, thicker fibres, which divide into two branches called fascicles. The left anterior fascicle is the thinner of the two fascicles and supplies the septum,

anterior and lateral walls of the LV. The shorter, thicker left posterior fascicle supplies the electrical impulse to the posterior wall of the LV. A network of Purkinje fibres deliver the impulse first to the papillary muscles and then rapidly across the ventricles, resulting in simultaneous contraction. If the SA node fails to fire, the AV node, His-Purkinje system and ventricular myocardium are capable of generating an electrical impulse but at a slower rate than the SA node.

Movement of ions across the cell membrane, using diffusion and active transport mechanisms, is necessary to initiate myocardial depolarisation (systole) and repolarisation (diastolic relaxation).

The movement of ions across the cell membrane, known as the cardiac action potential, is responsible for initiating myocardial depolarisation (systole) and repolarisation (relaxation). A difference in electrical charge exists across the cell membrane, created by differences in the concentration of ions in the intracellular and extracellular fluid. This is known as the transmembrane potential. During the resting phase of the cardiac cycle, the transmembrane potential is approximately –90 mV (phase 4). At this stage, there is a higher concentration of intracellular potassium and lower concentration of intracellular sodium relative to their respective extracellular levels. This creates a concentration gradient, permitting the movement of ions across the cell membrane by diffusion and altering the transmembrane potential. Once this reaches –70 mV (threshold potential), early myocardial depolarisation will be triggered. Therefore, a sodium-potassium (Na^+/K^+) pump within the cell membrane uses active transport to move sodium out of the cell and potassium back into the cell to maintain the resting transmembrane potential of –90 mV during phase 4.

Myocardial depolarisation begins when sodium channels within the cell membrane open, permitting entry of sodium into the cell (phase 0). Once the transmembrane potential reaches the threshold potential of approximately –70 mV, fast sodium channels open, increasing the transmembrane potential to +30 mV. Repolarisation of the cell begins immediately afterwards, with a slight drop in transmembrane potential due to the closure of the sodium channels and an influx of chloride ions (phase 1). Myocardial contraction is maintained through the influx of calcium ions into the cell, causing the transmembrane potential to plateau at approximately 0 mV (phase 2). Repolarisation continues as the potassium channels open, allowing potassium to leave the cell, causing a dramatic fall in transmembrane potential (phase 3) until the resting membrane potential of –90 mV is reached and maintained using the Na^+/K^+ pump, rendering the cell inactive again (phase 4).

Coronary circulation

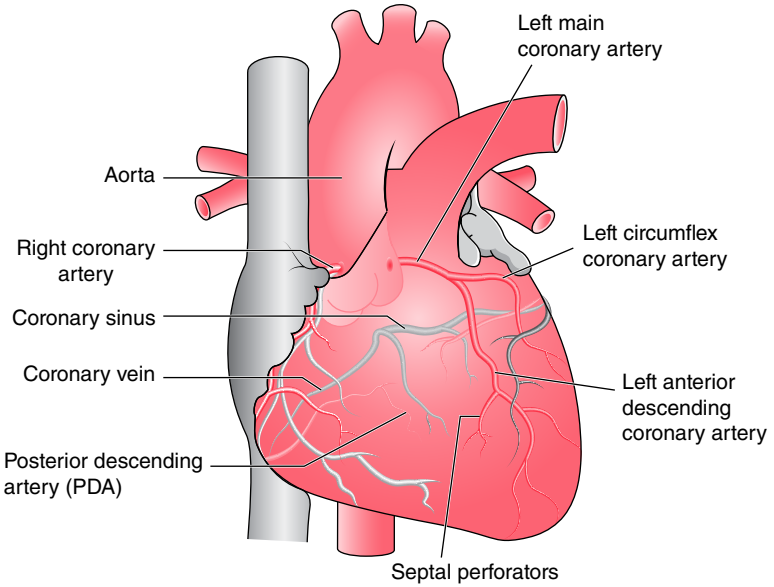

Figure 1.3 Coronary circulation.

Situated within the epicardium, the coronary arterial circulation is a network of arteries, arterioles and capillaries that penetrate the myocardium to provide the oxygen and nutrients necessary for aerobic metabolism (Figure 1.3). The right and left coronary arteries arise from two sinuses positioned at the root of the aorta behind two of the aortic valve cusps. Perfusion of the arteries occurs only during the diastolic phase of the cardiac cycle as the cusps of the aortic valve obstruct the sinuses during systole. The coronary arteries have four distinct layers of tissue: the endothelium, tunica intima, media and adventitia.

The right coronary artery (RCA) extends along the right side of the AV groove to the posterior wall of the heart, from where it proceeds inferiorly towards the apex and then terminates. The RCA provides perfusion for the right atrium, RV and the inferior surface of the LV, as well as the SA and AV node, in the majority of the population. The RCA also perfuses the posterior fascicle of the left bundle branch via the posterior descending artery (PDA).

The left coronary artery emerges from the aortic root, extending down the left atrium to the AV groove, where it bifurcates into the left anterior descending (LAD) and circumflex arteries. The LAD gives rise to diagonal branches and septal perforators, which perfuse the anterior surface of the LV, the anterior papillary muscle and the anterior aspect of the interventricular septum, including the right

bundle branch and the left anterior fascicle of the left bundle branch. The circumflex extends around the left AV groove to supply the lateral wall of the LV, via the obtuse marginal branches, as well as the left posterior fascicle, which is also supplied by the LAD.

The term dominance is used to describe the RCA when it perfuses the PDA, supplying the posterior wall of the LV and the AV nodal artery. Approximately 80–85% of the population have a dominant RCA. The circumflex is considered the dominant vessel in approximately 10–15% of the population, when the PDA emerges from the circumflex. A co-dominant circulation exists in approximately 5% of people in which both the RCA and circumflex extend to supply the posterior wall of the LV.

A collateral circulation exists between arterioles across the myocardium. In addition, portions of the subendocardial layer of myocardium may be perfused directly from the LV via the Thebesian veins.

Venous return from the myocardium occurs via the coronary veins, which follow the same route as the arterial circulation. The coronary veins drain into the coronary sinus, a large vessel situated along the posterior AV groove, which returns the deoxygenated blood into the right atrium. The myocardium also has a lymphatic circulation, which is also aligned with the arterial circulation.

Part 2 Rapid Cardiac Assessment

Rapid Cardiac Care, First Edition. Emma Menzies-Gow and Christine Spiers.
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2

Introduction

A systematic approach to patient assessment is fundamental to undertaking a comprehensive review of the acutely ill adult. The assessment should raise concerns about red flags, identify unsuspected problems and generate logical differential diagnosis to guide investigation and treatment. A set of vital signs: respiratory rate and character, oxygen saturations, heart rate and rhythm, bilateral blood pressure (BP), temperature and blood glucose will allow comparison of patient findings to those expected in a normal subject.

Cardiac history taking

The history-taking process is fundamental and should not be omitted unless the patient is in a critical state and requires an ABDCE assessment. Accurate history taking should take a systematic approach and be conducted in a logical manner.

Presenting complaint

A variety of cardiac and non-cardiac specific symptoms may be elicited; cardinal symptoms include:

- Chest/arm/back pain – tightness or discomfort.
- Breathlessness – on exertion, lying flat, at night.
- Palpitations – fast, slow, irregular.
- Syncope/fainting/dizziness – related to exercise, on standing, at rest.
- Pain in legs or calves – on walking, at rest.
- Ankle swelling.

Symptom assessment

Further elucidation of the symptom/complaint should establish the frequency, duration, exacerbation and severity of symptoms; assessment tools provide a framework for assessment and SOCRATES is a popular tool:

S – Site
O – Onset
C – Character
R – Radiation
A – Associated symptoms
T – Timing
E – Exacerbating factors
S – Severity.

Chest pain assessment

Chest pain is a commonly presenting symptom and the underlying diagnosis may range from trivial to potentially life threatening. Assessment can be augmented with the addition of other tests such as 12-lead ECG, blood tests for markers of cardiac injury (Troponin, CK-MB) or infection (CRP). Echocardiography, CXR and CT scans can provide further valid information. Cardiac causes of chest pain include acute coronary syndromes (ACS), pericarditis, myocarditis and aortic dissection. Respiratory conditions such as pneumonia, pneumothorax and pulmonary embolism can also present with chest pain. Musculoskeletal causes of chest pain include chest wall injuries, costochondritis and secondary tumours of the ribs.

S - Site – the pain of myocardial ischaemia may be located in the jaw, throat, both arms, retrosternally and in the back. The pain from

pericarditis may be in the central chest, back or in the shoulders. Aortic dissection pain is located retrosternally and radiates into the back and the abdomen.

O - Onset – angina may be precipitated by exercise, emotion or cold weather. Pain associated with ACS may present at rest, on exertion or in the early hours of the morning on wakening. Pericardial pain may follow a period of flu-like symptoms or occur 3-6 weeks after acute MI.

C - Character – myocardial ischaemia is described as tight and crushing, but may also be an ache or heaviness. Aortic dissection pain has a tearing quality and pericardial pain is severe and constant.

R - Radiation – cardiac pain tends to radiate; ischaemic pain may radiate from the chest to the arms, jaw or back. The pain of aortic dissection often radiates into the back and occasionally the abdomen. Pericardial pain is frequently referred to the trapezius ridge (shoulder).

A - Associated symptoms – patients with myocardial infarction may present with dyspnoea, diaphoresis, nausea, syncope and extreme anxiety. Patients with ACS may present with one or several symptoms. In pericarditis, the pain is worse on inspiration. Aortic dissection may be associated with collapse and neurological involvement if a major vessel to the head and neck is compromised by the dissection.

T - Timing – myocardial ischaemia may have a sudden onset and the pain may last for longer than 20 minutes without relief. Aortic dissection tends to be of sudden onset and remains constant. Pericarditis and myocarditis may be preceded by a history of viral or flu-like symptoms.

E - Exacerbating factors – angina may be exacerbated by exercise, emotion, following meals or extreme weather temperatures. Pericardial pain is relieved by leaning forwards and made worse by deep inspiration.

S - Severity – whilst many patients with cardiac pain will describe the pain on the high end of a scale of 0–10, some patients, notably older patients and those with diabetes may experience little or no pain.

Risk factors

An evaluation of lifestyle and risk factors pertinent to cardiac disease should be undertaken. It is important to be non-judgemental but to ask questions sensitively and objectively. Key lifestyle factors include: cigarette smoking, misuse of alcohol, recreational drug use, lack of exercise and/or obesity. Cigarette smoking is the strongest modifiable risk factor for heart disease. Seek to evaluate if the patient has ever

smoked and if so, how much and for how many years. Clarification of number of pack years is calculated by the following formula and is used to estimate the risk of smoking-related health problems:

$$\frac{\text{Number of cigarettes smoked per day} \times \text{Number of years smoked}}{\text{20 (number of cigarettes per pack)}}$$

Estimate the amount of alcohol consumed per week; hazardous drinking is more than 2 units of alcohol per day for women, 3 units for men. One unit of alcohol is equivalent to a small glass of wine or half a pint of beer. Excessive alcohol use is implicated in hypertension, atrial fibrillation and dilated cardiomyopathy.

The increasing use of recreational drugs, particularly amphetamines and 'legal highs', is implicated in tachyarrhythmias. Cocaine may cause coronary artery vasospasm leading to ACS. Intravenous drug injection may act as a source for bacterial endocarditis. Obesity increases the risk of heart disease by inducing hypertension, hyperlipidaemia and diabetes. Diabetes is a significant risk factor for vascular and heart disease. Diabetes also magnifies the effects of other risk factors for cardiovascular disease.

Medications and allergies

Establish whether any medications have been prescribed and question whether these are being taken. The patient's current medications may help to confirm a suspected diagnosis, whilst newly prescribed drugs may have caused or aggravated symptoms; bronchodilators may precipitate tachycardia, beta-blockers may exacerbate heart failure or peripheral vascular disease and calcium channel blockers can cause oedema. Specific questioning around alternative, supplementary or 'over-the-counter' medications may raise suspicion of a drug-induced event; 'recreational' drugs such as cocaine may induce coronary artery spasm and ACS. Take note of any known allergies to medications.

Family history

Any known inherited or familial problems should be documented. A positive family history is a specific risk factor in coronary heart disease, and premature death in first degree relatives (<55 in males, < 60 years in females) indicates a familial risk. Similarly, a sudden premature death in the family may indicate undiagnosed arrhythmic syndromes such as Brugada or Long QT syndrome or structural abnormalities such as Hypertrophic Cardiomyopathy. Familial hyperlipidaemia leads to premature coronary artery disease and familial clotting disorders may precipitate venous thromboembolism.

Past medical history (PMH)

PMH and cardiovascular risk factors should be considered in the context of the presenting complaint. Links between other diseases such as hypertension, diabetes mellitus, respiratory and renal disease should also be considered. Recent cytotoxic therapy may be the aetiology of acute heart failure, whereas obstructive pulmonary disease may lead to chronic right-sided heart failure. Hyperthyroidism may cause tachyarrhythmias such as atrial fibrillation and patients with Marfan's syndrome may present with acute aortic dissection. Immunisation and any recent foreign travel may also be relevant.

Physical examination

The aim of the physical examination is to gather objective data to confirm or refute any differential diagnoses identified from the focussed history. Initial assessment should clarify if the patient is in pain or anxious, and any evidence of dyspnoea, pallor, diaphoresis or cyanosis would require urgent investigation. Examination of the cardiovascular system should include the whole circulatory system, not just the heart and utilises the following approach: inspection, palpation and auscultation.

Inspection

Inspection of the face, eyes, neck, hands, feet and chest will often provide evidence of heart disease. Facial dysmorphic features raise the suspicion of Down's syndrome and William's syndrome, which may cause significant structural heart disease. Evidence of hyperlipidaemia may be evident in xanthelasma (yellowish deposits in the skin near the eyelids) or corneal arcus (a white ring around the iris). Malar flush may be associated with mitral stenosis or chronic low-output states. Pallor may indicate anaemia (a cause of chest pain), and cyanosis is seen in patients with cyanotic congenital heart disease. Pallor and cyanosis is best evaluated in the mucous membranes of the eyes or by inspection of the mouth and tongue. Gingivitis and poor dental hygiene is a common source of bacterial endocarditis. A high arched palate with crowded teeth is seen in patients with Marfan syndrome.

Evaluate the neck for evidence of jugular venous distension (JVD), which is seen in right-sided heart failure, pericardial constriction or superior vena cava obstruction. Raised JVD is identified if the jugular pulsation can be seen more than 3 cm above the clavicle with reference to the sternal notch when a patient is lying at an angle of 45°. The hands are a good source of cardiac signs – clubbing of the fingers is seen in cyanotic congenital heart disease, peripheral cyanosis may be evident at the fingertips and splinter haemorrhages may be evident in bacterial endocarditis. Chest wall or sternal abnormalities, such as pectus excavatum (funnel chest) or pectus carinatum (pigeon chest), may displace the heart and limit cardiac function. Any evidence of previous cardiac surgery (sternotomy or chest drain scars) and any infraclavicular scars from placement of cardiac devices (pacemakers and implantable cardioverter defibrillators) should be noted. Evaluation of the legs and feet for oedema, skin discolouration or loss of hair growth may indicate heart failure, peripheral vascular disease or venous insufficiency.

Palpation

Evaluate the rate, rhythm, character and volume of the peripheral pulses. Absence of a pulse is often indicative of ischaemia due to atherosclerosis or embolism. The radial pulse should be 60–100 beats

per minute (bpm) in an adult. Bradycardia (heart rate less than 60 bpm) may be normal in athletes and during sleep, but may also indicate hypothyroidism, heart block (AV block) or be drug induced – (Digoxin or beta-blockers). Tachycardia is normal during exercise or anxiety but may indicate sepsis, hyperthyroidism, shock due to blood or fluid loss, heart failure or drug overdose. Abnormalities of pulse volume or character are rare and generally seen when the underlying valvular disease such as aortic regurgitation and aortic stenosis is moderately severe. When a pulse is not palpable it may be audible by Doppler flow evaluation. Limb pulses should be equal and when deficits are identified this may be due to aortic dissection (radial to radial delay), aortic aneurysm (femoral to femoral delay), or atrial fibrillation (radial-apical deficit). The chest can be palpated for any evidence of palpable murmurs (thrills), heaves or thrusts in right ventricular or left ventricular enlargement. The apical impulse is identified in the fifth intercostal space in the mid-clavicular line and deviation from this site may indicate left ventricular enlargement. A 'tapping' quality to the apex beat may be due to mitral stenosis, and a diffuse apical impulse is commonly associated with mitral regurgitation.

Auscultation

The auscultation landmarks are identified in Figure 2.1. These landmarks correspond to the place where the sounds generated by each heart valve is heard best. The sounds, referred to as 'lub-dup', relate to the closure of first the atrioventricular (tricuspid and mitral) followed by closure of the outlet (pulmonary and aortic) valves. The diaphragm of the stethoscope identifies high-pitched sounds (normal

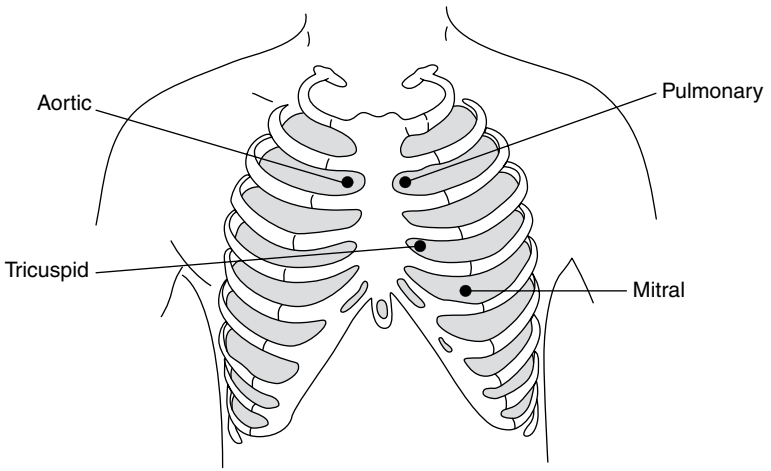

Figure 2.1 Cardiac auscultation landmarks.

heart sounds, systolic and diastolic murmurs), whereas the bell transmits the low-pitched sounds of mitral stenosis and the third and fourth heart sounds.

Auscultation of the lungs should include the anterior, posterior and lateral chest areas. Normal breath sounds are heard with the diaphragm of the stethoscope and include bronchial, broncho-vesicular and vesicular sounds.

Commonly identified murmurs in acute cardiac care include: third heart sound heard in heart failure, ejection systolic murmur in aortic stenosis and pan-systolic murmur in mitral regurgitation. Adventitious breath sounds in cardiac conditions include crackles associated with pulmonary oedema if bilateral and infection if unilateral.

Cardiac monitoring

Cardiac electrical activity can be recorded using a range of equipment that includes the 12-lead ECG and 3, 5 or 12-lead cardiac monitoring. Patients should be advised of the purpose of cardiac monitoring, their consent to proceed established and their dignity maintained throughout the procedure. The patient should be positioned comfortably and advised to remain resting while cardiac monitoring is being used, with a call bell available if help is needed. The electrodes must be placed directly onto clean, dry skin; hair may need to be removed to ensure good contact. If the patient's skin is clammy or has been recently moisturised, their skin should be cleaned with soap and water and thoroughly dried before applying electrodes.

In 3-lead monitoring, the limb lead electrodes should be positioned equidistant from the patient's heart around the upper chest and lower abdomen or on the upper and lower limbs, in the following sequence: Right Arm (red), Left Arm (yellow), Left Leg (green/black). If a fourth lead is available, this should be placed on the Right Leg (black). 5-lead monitoring involves an additional white lead, which should be connected to an electrode placed in the V_1 position (Figure 2.2). If 12-lead ECG monitoring is available, the electrodes should be positioned as for the 12-lead ECG.

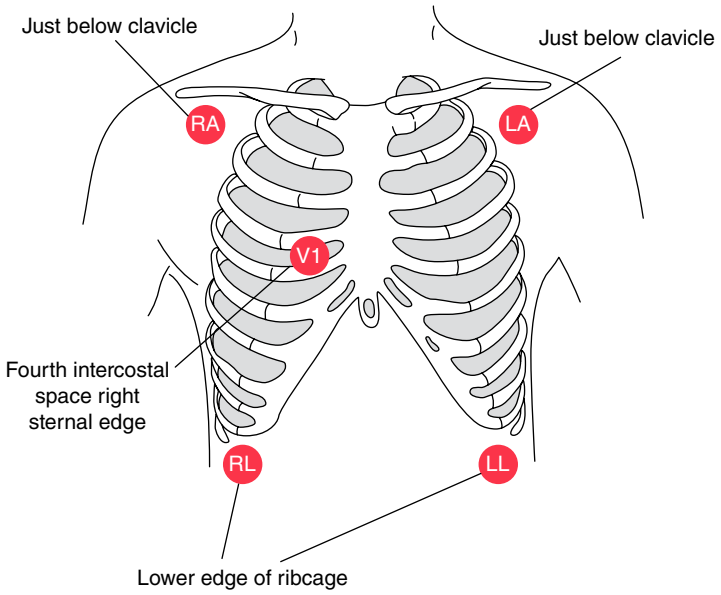

Figure 2.2 5-lead cardiac monitoring.

Lead II should be selected as it provides the clearest view of both atrial and ventricular activity. The size of the trace on the screen should be adjusted to ensure all waveforms are clearly visible. Artefact, or electrical interference, can severely affect the quality of the recording and impede rhythm recognition. It can be minimised by advising the patient to avoid excessive movement, ensuring the electrodes have good contact with skin and by limiting interference from nearby electrical equipment. The monitor alarm parameters should be adjusted for individual patients to alert the healthcare professional of a rise or fall in heart rate that may indicate the need for further assessment.

Rapid rhythm recognition

Once cardiac monitoring using lead II is established, systematic assessment can facilitate rapid rhythm recognition:

Assess ventricular rate and rhythm
Assess the QRS duration
Assess atrial activity, rate and rhythm
Assess relationship between atrial and ventricular activity
Assess PR and QT intervals
Identify the rhythm

The monitor records heart rate accurately but it can also be calculated from an ECG rhythm strip using the following formula:

$$\text{Heart rate} = \frac{1500}{\text{the number of small squares between two QRS complexes}}$$

Sinus rhythm: Normal waveforms and intervals

Sinus rhythm is the normal heart rhythm originating from the sino-atrial node. It is present when sequential conduction of the atria and ventricles, as described in Part 1, generates P, QRS and T waveforms that emerge from an isoelectric line. It is a regular rhythm, identified when the interval between consecutive QRS complexes, known as the R-R interval, is regular and constant, with a rate of between 60 and 100 bpm (Figure 2.3).

Normal atrial depolarisation, originating from the sinoatrial node, creates a small rounded P wave that emerges from the isoelectric line. In sinus rhythm, the P wave will be positive in lead II, appearing before the QRS complex. Each P wave should be followed by a QRS complex and T wave, representing ventricular depolarisation and repolarisation. The QRS duration will be less than 100 ms, indicating normal ventricular depolarisation using the His-Purkinje system. T waves should follow the direction of the QRS complex (concordant) in lead II, but can only be fully assessed using the 12-lead ECG.

The PR interval is a measurement taken to evaluate the delay in transmission though the AV node. Normally, the PR interval is 120–200 ms, measured from the beginning of the P wave to the beginning of the QRS complex. The QT interval is a measurement of the time taken for ventricular depolarisation and repolarisation to occur, measured from the beginning of the QRS complex to the end of the T wave. Rapid identification of a normal QT interval can be established if the QT interval is less than half the preceding R-R interval. However, as the QT interval is inversely proportional to rate, the corrected QT (QTc) interval should be calculated using Bazett's formula: $QT/\sqrt{RR}$ interval, as it adjusts the interval correctly for variation in heart rate.

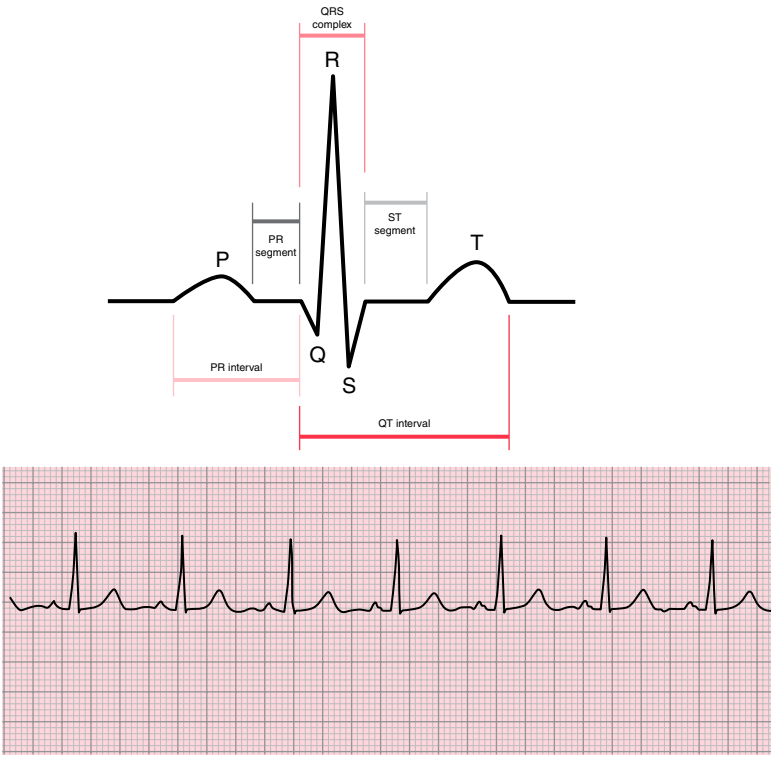

Figure 2.3 Normal ECG waveforms and sinus rhythm (lead II).

Sinus tachycardia

Sinus tachycardia is present when sinus rhythm has a QRS rate greater than 100 bpm. Stress and anxiety may cause an increase in sympathetic activity, increasing the sinoatrial node firing rate. However, sinus tachycardia may also occur in response to pain, ACS, sepsis, shock, heart failure or use of recreational drugs.

Sinus bradycardia

Sinus bradycardia is present when the sinus rhythm has a QRS rate of less than 60 bpm. This may be associated with high levels of fitness but may also be due to hypoxia, myocardial ischaemia, hypothermia or drugs that interfere with nodal conduction, such as beta-blockers.

Sinus arrhythmia

Sinus rhythm may appear to be irregular in some patients, particularly young people and the very elderly. This is known as sinus arrhythmia but is not considered an abnormal finding.

Cardiac investigations

Blood tests

A range of venous blood tests can provide data to aid the assessment, diagnosis and management of patients with suspected cardiac disease. Measurement of serum troponin I or T is useful in the diagnosis of patients presenting with chest pain or other symptoms associated with ACS. Troponin is a protein released as a result of myocardial damage. Most assays will begin to detect troponin around 4–6 hours after symptom onset. The sensitivity of available assays is improving with the emergence of high sensitivity troponins, able to detect troponin rise within 0–3 hours in patients with suspected ACS. However, other conditions may elevate troponin levels, such as arrhythmias, heart failure and chronic kidney disease. Creatine kinase (CK) and an isoenzyme of CK, CK-MB, are supplemental biochemical markers of current myocardial damage.

Elevated or low levels of potassium, magnesium, sodium, and calcium levels may cause atrial or ventricular ectopic beats and arrhythmias. Urea, creatinine levels and estimated glomerular filtration rate (eGFR) are used to assess renal function, which may be impaired in patients with cardiac conditions such as heart failure. Evaluation of renal function is particularly important for patients prior to coronary angiography or primary percutaneous coronary intervention (P-PCI), due to administration of radio-opaque contrast. The contrast is excreted by the kidneys and thus must be used with caution in patients with renal dysfunction.

The BNP and NT-pro-BNP will be elevated in patients with left ventricular dysfunction. Both assays correlate with the severity of heart failure and are predictive of cardiovascular events and mortality.

Liver function tests, including AST, ALT, LDH and ALP, may indicate hepatic dysfunction associated with heart failure or reveal a coagulopathy. Hyperthyroidism and hypothyroidism are both known risk factors for cardiovascular disease. Capillary blood glucose, fasting glucose and HbA1c assays are useful to diagnose diabetes, a known risk factor for cardiovascular disease and to ascertain the presence of hyperglycaemia during ACS. A fasting lipid profile can be used to guide lifestyle advice and medical therapy for patients with hyperlipidaemia. A full blood count will provide evidence of anaemia or infection.

Arterial and venous blood gases provide information on oxygen and carbon dioxide levels, acid-base balance and lactate levels, providing useful data in patients with, for example, dyspnoea and sepsis.

The 12-lead electrocardiograph (ECG)

A 12-lead ECG can be used to identify myocardial ischaemia and arrhythmia. Patients with symptoms of chest, neck, arm, jaw or

abdominal pain should have a 12-lead ECG as this may reveal ischaemia, as should patients presenting with palpitations, dyspnoea and syncopal symptoms. Ambulatory 24-hour ECG (Holter) monitoring and event recording can be used to identify paroxysmal arrhythmias, to record heart rate variability or a signal-averaged ECG, and to guide the use of implantable cardioverter defibrillator (ICDs). Tilt testing, during which BP and an ECG are continuously recorded, may be used to investigate patients with syncopal symptoms or vasovagal episodes. The ECG may used in exercise tolerance testing, in which the patient walks or runs on a treadmill to ascertain the presence of arrhythmia or ischaemia, although the use of this test is diminishing with the emergence of more sensitive imaging techniques such as stress echocardiography.

Cardiac imaging

The cardiac structures can be visualised using a chest X-ray taken in the posterior-anterior (PA) view and, if required, the lateral view when the patient has taken a deep breath. Chest X-ray (CXR) can facilitate assessment of heart size, dimensions of the thoracic aorta and pulmonary artery and signs of pericardial effusion, atrial and ventricular enlargement and ascending aortic dissection. A CXR may reveal signs of pulmonary oedema associated with heart failure.

Echocardiography uses ultrasound to assess cardiac function. A trans-thoracic echocardiogram (TTE) is recorded by placing a transducer on the patient's chest while they are lying on their left side, with their left arm out. A TTE can examine the movement of the chambers, septum and valves and approximate left ventricular ejection fraction, normally 50–65%. Doppler can be used to ascertain direction of blood flow, valuable in diagnosing valvular regurgitation. Three-dimensional echocardiography can be used to aid diagnosis of mitral and aortic disease and congenital heart disease. Stress echocardiography can establish the presence of hibernating or stunned myocardium. The 'stress' is produced through administration of dobutamine or by conducting the scan while the patient walks or runs on a treadmill, although there is an associated risk of inducing ventricular arrhythmias. Transoesophageal echocardiography (TOE), in which the transducer is advanced into the oesophagus, can provide high-quality images of valvular function and is used to visualise vegetation associated with endocarditis. This procedure requires local anaesthesia and sedation and is frequently used in the intensive care setting.

Cardiac magnetic resonance (CMR) imaging is an increasingly popular non-invasive technique used to investigate patients with cardiovascular disease. CMR can be used to provide diagnostic information for patients with a variety of cardiac conditions including

ischaemic, aortic, congenital and valvular heart disease. It is a non-invasive procedure that does not expose the patient to radiation nor require anaesthesia or sedation but may be unsuitable for patients with certain cardiac devices such as pacemakers.

A computed tomography (CT) coronary angiogram, using a peripheral infusion of contrast, is highly effective in the diagnosis of coronary artery disease. Other non-invasive cardiac investigations include the use of CT scans to assess the thoracic aorta if aneurysm or dissection is suspected and to undertake coronary artery calcium scoring in patients with ischaemic heart disease. A 'thallium' scan is a nuclear imaging test during which radioactive thallium is administered intravenously to identify areas of viable myocardium that may respond to reperfusion with coronary bypass graft surgery.

Invasive cardiac investigations

Cardiac catheterisation is an invasive procedure used to conduct coronary angiograms, aortography and investigate right heart function. During a coronary angiogram, X-rays are recorded of coronary blood flow while radio-opaque dye is injected into the right and left coronary arteries via a catheter inserted into the right femoral or radial artery. It can also be used to assess left ventricular ejection fraction. Angiography can be used to diagnose ischaemic heart disease and to determine if the patient would benefit from insertion of an intracoronary stent or from coronary artery bypass graft surgery.

Right heart function can be assessed using a venous catheter advanced into the right ventricle and pulmonary artery to directly measure pressure within each chamber. Pulmonary arterial 'wedge' pressure can be used as an indirect measure of left atrial pressure and left ventricular end-diastolic pressure. This test is conducted in patients prior to cardiac transplantation and in those with pulmonary hypertension.

In an electrophysiology study, electrodes are advanced via a venous catheter to locate abnormal electrical pathways, such as a re-entry circuit seen in supraventricular tachycardia (SVT). This information is used to establish the patient's suitability for interventions such as radiofrequency ablation, cryoablation or insertion of an ICD.

Part 3 Rapid 12-lead ECG Interpretation

Rapid Cardiac Care, First Edition. Emma Menzies-Gow and Christine Spiers.
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3

Introduction

The Electrocardiogram (ECG) is a graphic record of the electrical activity generated by the cells of the heart, recorded at the body surface by electrodes and displayed onto a cardiac monitor or ECG paper as a visual record. The electrodes detect the electrical current generated by depolarisation and repolarisation of the atria and ventricles during each cardiac cycle.

ECGs are recorded onto grid paper that records time in seconds along the horizontal axis, and voltage or amplitude in millivolts (mV) on the vertical axis. Each small square is equivalent to 1 mm or 40 ms in time and 5 small squares is separated by a dark vertical line representing 5 mm or 200 ms. The ECG should be calibrated and recorded at 25 mm/second and 1 mV should produce a 10 mm deflection on the ECG.

Whereas cardiac monitoring employs three or four leads monitoring in a single plane, a 12-lead ECG evaluates the heart in two planes utilising 12 leads or 'views' to evaluate the electrical activity. Four electrodes are applied to the limbs in the following sequence: Right Arm (red), Left Arm (yellow), Left Leg (green), Right Leg (black) and six electrodes are applied to the chest or precordium. These leads are referred to as the 'V' leads or 'chest' leads and are recorded by applying the electrodes to prescribed areas over the anterior chest wall (V_1–V_6).

Simply put, an ECG lead is a recording of the heart's electrical activity from one viewpoint, the 12-lead ECG views the heart from 12 perspectives and helps to build up a three-dimensional picture of the cardiac electrical activity. Six of the leads view the frontal plane of the body and these leads are derived from the four electrodes placed on the limbs (the 'limb leads'). Leads V_1–V_6 view the horizontal or transverse plane of the body and are referred to as the 'chest leads' (Figure 3.1).

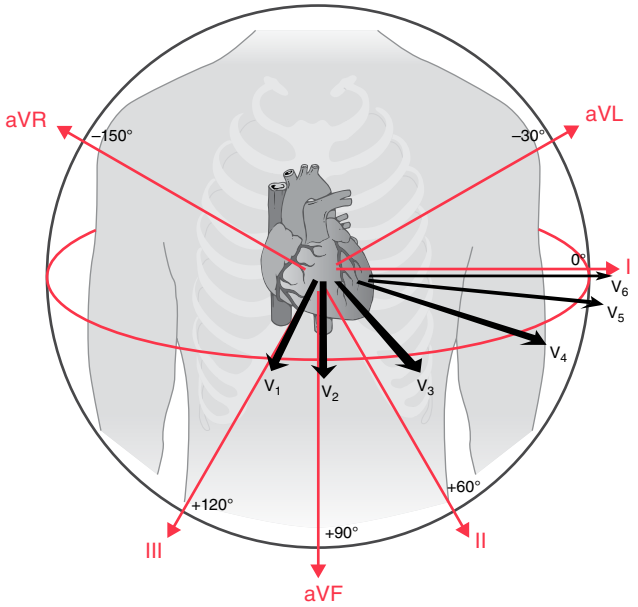

Figure 3.1 Orientation of the 12 ECG leads.

Cardiac vectors and axis

Atrial and ventricular depolarisation and repolarisation generates an electrical current that flows from the sino-atrial node, towards the atrio-ventricular node and downwards through the His-Purkinje system towards the left ventricular apex. The electrical current is described as the cardiac vector or the cardiac axis and this is a composite view of the general direction of the electrical current (Figure 3.2). The average direction of the vectors that result from ventricular depolarisation is called the mean QRS axis and this can be calculated using the 360° circle known as the hexaxial reference figure on which are inscribed the six limb leads. The figure is divided into quadrants by the bisection of lead axis I (at 0° on the circle) and aVF (at +90° on the circle). Axis deviation can result from many cardiac abnormalities and its calculation is an essential part of the initial interpretation of the 12-lead ECG.

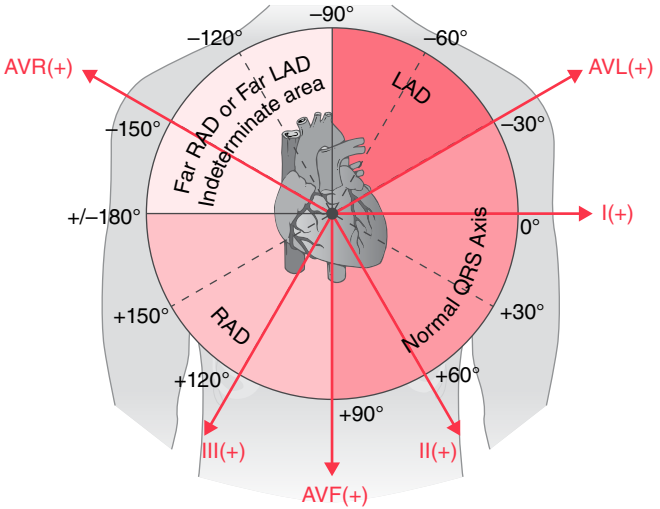

Figure 3.2 Hexaxial reference system showing four quadrants – normal, left, right and indeterminate axis.

Rapid ECG analysis tool

Rapid ECG assessment in the cardiac patient utilises a quick and systematic tool, which ensures that significant abnormalities are identified early and that important information is not missed.

Significant QRS abnormalities (QRS confounders) should be identified early: Wolff-Parkinson-White (WPW), bundle branch block (BBB) and fascicular block, all of which cause electrical impulses to be conducted abnormally throughout the ventricles and may mimic ischaemia and infarction to complicate the diagnosis. In this tool, significant QRS confounders are ruled out first before looking for evidence of myocardial ischaemia or infarction:

Rapid ECG Analysis Assessment:

Heart rate and rhythm using the rhythm analysis tool
QRS axis
Evidence of pre-excitation
Evidence of bundle branch and fascicular blocks
Evidence of myocardial ischaemia and infarction
Evidence of other conditions guided by the patient's clinical presentation

Rate and rhythm assessment

Heart rate and cardiac rhythm is an important aspect of patient assessment and this should be evaluated first by the analysis tool.

Assess ventricular rate and rhythm
Assess the QRS duration
Assess atrial activity, rate and rhythm
Assess relationship between atrial and ventricular activity
Assess PR and QT intervals
Identify the rhythm

QRS axis calculation

The QRS axis reflects the general direction of the electrical current as it flows across the heart. Normally the QRS axis is directed downwards and to the left due to the dominance of the left ventricle. The QRS axis is identified by using the hexaxial reference system and is measured using the frontal plane leads. A simple three-step method facilitates the measurement of the mean frontal plane QRS axis and is based on the understanding that the biphasic lead is 90° to the mean frontal plane axis. This method of axis determination is quick, simple and accurate:

1. Identify the biphasic lead – this is the lead which has the most equal positive and negative components and is often the smallest QRS complex.
2. Identify the lead that is oriented 90° or perpendicular to this lead using the hexaxial reference system.
3. Consider the direction of the QRS complex in the lead identified in step 2. If the QRS is predominantly positive, the axis is heading towards this lead on the hexaxial reference system. If the QRS is predominantly negative, the axis is heading away from this lead (identified as the negative pole on the hexaxial reference system). A list of possible causes of axis deviation is provided in Table 3.1.

Table 3.1 Causes of axis deviation

Right axis deviation +90° to +180°	Left axis deviation –30° to –90°
Can be normal in thin, tall, young individuals	Can be normal in elderly patients, obesity and third trimester of pregnancy
RBBB	LBBB
RVH	LVH
Left posterior fascicular block	Left anterior fascicular block
Pre-excitation syndrome left sided accessory pathway	Pre-excitation right-sided accessory pathway
Lateral wall myocardial infarction	Inferior wall myocardial infarction
COPD or acute pulmonary embolism	Hyperkalaemia
Dextracardia	Artificial cardiac pacing

Pre-excitation syndromes

The characteristic findings of shortened PR interval (<120 ms), a delta wave (a slurring of the proximal portion of the QRS) altering the normal shape, duration and voltage of the QRS complex and a subsequent discordant ST segment or T wave is the characteristic ECG pattern of ventricular pre-excitation known as Wolff-Parkinson-White (WPW) (Figure 3.3). Both WPW and a rarer form of ventricular pre-excitation, which results in a short PR interval but no other significant ECG abnormalities, put the patient at risk of supraventricular tachycardia.

The presence of accessory pathways, which conduct electrical impulses from the atria to the ventricles, bypassing the atrio-ventricular (AV) node, produces these characteristic ECG findings. This notching and widening of the QRS complex with discordant ST segments and T waves can mimic other pathological conditions including BBB, ventricular hypertrophy and myocardial infarction and therefore ventricular pre-excitation must be ruled out early in the ECG analysis. The accessory pathways may bypass the AV node with subsequent loss of the protective decremental properties of the AV node and allows a potentially fatal tachyarrhythmia to evolve.

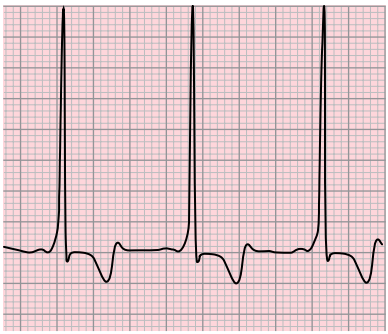

Figure 3.3 WPW pattern.

Bundle branch block and fascicular block

Bundle branch block and fascicular block typically cause axis deviation and abnormalities of the QRS complexes, ST-segments and T waves.

The intraventricular conduction system rapidly conducts electrical impulses to the ventricles. The right bundle branch (RBB) carries impulses to the right ventricle, and the left anterior fascicle and left posterior fascicle of the left bundle branch (LBB) depolarise the left ventricle. Normal conduction to the ventricles is fast and depolarisation of the ventricles occurs in a right to left sequence producing characteristic QRS complexes which are narrow (<100 ms). The initial depolarisation of the interventricular septum by the LBB is from left to right producing a small 'septal' r wave in V_1 lead. This is followed by simultaneous depolarisation of the right and left ventricles with the mean direction of current from right to left and thus the QRS complex primarily reflects depolarisation of the left ventricle.

When BBB occurs, the ventricle affected depolarises slower and aberrantly producing: QRS > 100 ms, abnormal QRS complexes with notching, ST segment and T wave abnormalities and axis deviation. The findings of BBB are best evaluated in the chest leads, primarily in V_1 and V_6.

Right Bundle Branch Block (RBBB)

A typical RBBB pattern produces a wide QRS complex (>100 ms) with an rSR′ wave in V_1 and V_2 (Figure 3.4) and a slurred S wave in V_6, with possible right axis deviation and ST and T wave abnormalities seen in V_1 and V_2.

In RBBB, septal activation occurs in the normal way from the LBB, and this wave of current is from left to right resulting in the normal small 'r' wave in V_1. The left ventricle is activated through the normally functioning LBB, causing an S wave in V_1 as the impulses travel away from the V_1 lead. The right ventricle depolarises late and abnormally via the myocardial cell structure, causing delayed RV activation and this results in a wide second R wave in V_1, V_2 (the characteristic rSR' pattern) and a slurred S wave in V_6. There may also be right axis deviation and ST and T wave abnormalities in the right-sided chest leads.

Left Bundle Branch Block (LBBB)

The left ventricle and the left bundle branch dominate the electrical forces on the ECG and thus LBBB produces changes, which are manifest in *most* or *all* leads on the 12-lead ECG. LBBB produces wide notched QRS complexes (>100 ms) in all ECG leads, QS (negative QRS) or rS in V_1 (Figure 3.5), a broad positive QRS in V_5,V_6, ST-segment deviation and T wave discordancy in *all* ECG leads. In particular, the

Figure 3.4 rSR' pattern associated with RBBB as seen in V_1.

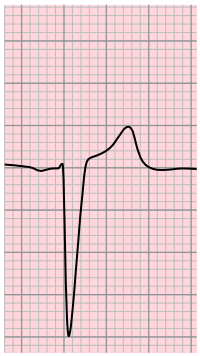

Figure 3.5 QS pattern associated with LBBB as seen in V_1.

patient may exhibit ST-segment elevation in V_1–V_3, which can mimic MI to the untrained eye.

In LBBB, the septum does not depolarise in the normal left to right direction and this causes the loss of the 'septal r wave' in V_1. The left ventricle depolarises late and abnormally via cell-to-cell conduction and this produces a wide (and sometimes notched) QRS complex in all leads. Additionally, there is abnormal repolarisation of the myocardial tissue and this results in ST segment and T wave discordance seen in all ECG leads.

Fascicular block

Fascicular block refers to abnormal, delayed or blocked conduction through the left anterior or left posterior fascicle of the LBB. Abnormal conduction through these fascicles disrupts normal ventricular depolarisation producing characteristic changes to QRS morphology and axis deviation.

Left anterior fascicular block (LAFB) causes left axis deviation of greater than –45° with an rS pattern in aVF and III, qR pattern in I and aVL.

Left posterior block causes right axis deviation of greater than 120° with a qR pattern in aVF and III and rS in I and aVL.

LAFB is more common than left posterior fascicular block, as the left anterior fascicle is more vulnerable to damage because of its anatomic position, single blood supply and close association with the aortic valve.

Bifascicular block

Fascicular blocks can occur alone or in conjunction with RBBB. LAFB and RBBB is the more usual presentation of bifascicular block (due to the shared LAD blood supply). Bifascicular block may deteriorate into complete heart block, particularly in the presence of acute MI. In the presence of first-degree AV block, trifascicular block is said to be present.

Myocardial ischaemia or infarction

Acute coronary syndromes (ACS) are sudden life-threatening events, which demonstrate classic ECG changes that are sequential and dynamic and create changes in T waves, ST segments and the Q wave:

- Myocardial ischaemia – T wave changes and ST-segment deviation.
- Myocardial infarction – ST-segment deviation and Q waves.

12-lead ECG changes indicative of ST-segment elevation myocardial infarction (STEMI) are:

- ST-segment elevation > 1 mm in any two contiguous leads except for V_2 and V_3 where the following rules apply:
  - Males under 40 years ST-segment elevation > 2.5 mm.
  - Males over 40 years ST-segment elevation > 2 mm.
  - Females any age ST-segment elevation > 1.5 mm.

12-lead ECG changes indicative of non-STEMI or unstable angina are:

- ST-segment depression 0.5 mm in two contiguous leads.
- T wave inversion in two contiguous leads.

Myocardial infarction and ischaemia manifest changes in the ST segments and T waves as indicated in Figures 3.6a–c.

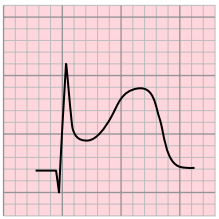

Figure 3.6a ST elevation.

Figure 3.6b ST depression.

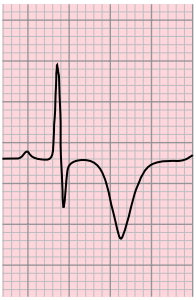

Figure 3.6c T wave inversion.

The leads in which these changes occur reflect the anatomical location of the damage, the likely culprit coronary artery and potential complications that can be identified in the Table 3.2 below:

Table 3.2 Possible complications due to 12-lead ECG changes

Culprit coronary artery	Anatomical territory/infarct area	ECG leads	Possible complications
LAD (septal branch)	Antero-septal LV	V_1–V_2	RBBB, Bifascicular block, LVF
LAD (diagonal branch)	Anterior LV	V_3–V_4	RBBB, Bifascicular block, LVF
LCx	Anterolateral LV	V_5–V_6, 1 and aVL	LVF, AV block
LCx or RCA	Posterior LV	Tall R waves V_1, V_2 or leads V_7–V_9	LVF, AV block
RCA	Inferior LV	II, III, aVF	Sinus node arrhythmias and AV block
Proximal RCA	Right ventricle	V_3R and V_4R	Hypotension, right heart failure

LAD Left anterior descending; LCx Left circumflex; RCA right coronary artery

Consider specific conditions based on the patient's history and presentation

Chamber enlargement such as atrial or ventricular hypertrophy can produce ECG waves of increased amplitude, duration and axis deviation. Left ventricular hypertrophy is characterised by:

- Tall R waves in leads facing the LV – V_5, V_6, I and aVL.
- QRS axis $\leq$ –30°.

- ST depression and/or T wave inversion in leads facing the LV – V_5, V_6, I and aVL.
- Wide notched P waves > 100 ms, demonstrating left atrial enlargement ('p mitrale').

Right ventricular hypertrophy is rare but is demonstrated by:

- Tall 'dominant' R waves in leads facing the RV – V_1 and V_2.
- QRS axis ≥ +90°.
- ST and/or T wave inversion in leads facing the RV – V_1 and V_2.
- Tall peaked P waves > 2.5 mm demonstrating right atrial enlargement ('p pulmonale').

Other clinical conditions may mimic the presence of infarction or make the ECG more difficult to analyse. Certain conditions such as Brugada syndrome, Takotsubo cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy (ARVC), pericarditis and myocarditis can all produce ST-segment elevation on the ECG and these conditions are known as infarct imposters. The reader is advised to read the relevant chapters elsewhere in this book.

Other abnormalities seen on the 12-lead ECG

To conclude the analysis, the ECG findings should be considered in the context of the patient's presenting signs, symptoms and other clinical criteria. If the patient has clinical symptoms but the ECG remains normal, serial ECG recordings should be undertaken alongside other clinical examinations and assessments. Additionally, supplemental leads and serial ECG recordings should be made in patients with clinical symptoms of ischaemia but non-diagnostic ECGs. In patients with inferior and suspected right ventricular involvement, V_3R and V_4R may demonstrate ST-segment elevation. Posterior wall (infero-basal) infarction should be suspected in patients with tall R waves in V_1, V_2 and ST-segment depression and the addition of leads V_7–V_9 is strongly recommended to evaluate the posterior myocardial wall.

Part 4 Cardiac Conditions A–Z

Rapid Cardiac Care, First Edition. Emma Menzies-Gow and Christine Spiers.
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A

Acute coronary syndromes

'Acute coronary syndromes' (ACS) is an umbrella term referring to conditions caused by an episode of myocardial ischaemia occurring at rest or on minimal exertion. Sudden onset of chest pain is the most common symptom associated with ACS. The electrocardiogram (ECG) and cardiac biomarkers are used to differentiate between a diagnosis of ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation MI (NSTEMI) and unstable angina (UA). All three diagnoses are medical emergencies requiring rapid treatment to restore coronary perfusion and reduce the significant risk to mortality and morbidity.

Pathophysiology

ACS usually occur when there is erosion or disruption of a coronary atheromatous plaque, triggering thrombus formation within a coronary artery that can result in myocardial ischaemia, injury and necrosis (infarction). Cardiac risk factors such as hypertension, smoking and diabetes can contribute to the breakdown of the coronary endothelium and the fibrous cap around the plaque, leading to exposure of the thrombogenic lipid core to blood. This initiates rapid accumulation and activation of platelets and thrombosis within the coronary lumen. Activated platelets induce localised vasoconstriction, leading to rapid partial (NSTEMI/UA) or total occlusion (STEMI) of the coronary artery. This obstruction of coronary perfusion inhibits oxygenation of the myocardium beyond, causing ischaemia. Systolic activity of the ischaemic myocardium will initially continue while the myocytes function anaerobically. However, in the absence of rapid reperfusion, the affected portion of myocardium will soon cease contraction (myocardial injury) and eventually die (infarction).

History

Many patients live with chronic health issues that will significantly increase their risk of experiencing an ACS, such as diabetes, hypertension and obesity. Some have made lifestyle choices that also increase cardiovascular risk, such as smoking, adopting a high cholesterol, salt or sugar diet or taking limited or no regular exercise. Risk of ACS is significantly increased in patients who have a family history of heart disease and who may exhibit modifiable or non-modifiable risk factors that would contribute to the development of atherosclerosis.

Signs and symptoms

Many patients typically experience a sudden onset of retrosternal chest pain that is commonly described as a sharp pain, a crushing heaviness or a dull ache that radiates down their left arm or into their neck or lower jaw. These classic symptoms of ACS are caused by myocardial ischaemia. Others, particularly women, the elderly and patients with renal disease or diabetes, experience more ambiguous symptoms such as arm or jaw ache or heaviness, or nausea, vomiting and fatigue. Some will not experience any symptoms at all. The symptoms frequently commence at rest, for example while asleep, or during minimal exertion, but do not dissipate with rest or change in position. This differs significantly from the presentation of stable angina, where chest pain will ease with rest. Patients presenting with ACS may have had recent episodes of similar symptoms that have previously resolved, either with rest or with anti-anginal treatment, although for others this will be the first occurrence.

ACS can be life threatening and are the most common cause of sudden cardiac death among adults in the UK. Acute reduction in oxygenation of the myocardium not only induces chest pain but also increases the propensity for potentially fatal ventricular arrhythmias and acute heart failure, which could manifest as the initial clinical presentation. Additional symptoms may also be evident such as tachypnoea, arrhythmias, cool, clammy skin and a pale, grey pallor associated with increased sympathetic neurohormonal activity. Acute anxiety and distress frequently accompany ACS, with many patients expressing an overwhelming fear of imminent death. Ventricular tachycardia/ventricular fibrillation (VT/VF) cardiac arrest may occur soon after the onset of symptoms for which early defibrillation is essential to ensure survival.

The symptoms associated with ACS are common to all three diagnoses and, therefore, cannot be used to differentiate between UA, NSTEMI and STEMI. Similarly, the severity of symptoms is not a diagnostic indicator of the underlying form of ACS. Rapidly establishing a diagnosis is paramount for patients presenting with suspected ACS, to ensure that treatment is expedited swiftly to reduce the risk to mortality and long-term morbidity.

Assessment and investigations

Assessment should be prioritised to optimise patient safety. Initial observations should include assessment of respiratory rate, oxygen saturation level, pulse and blood pressure, which should be repeated at frequent intervals. Cardiac monitoring should be commenced rapidly to observe for arrhythmias and a 12-lead ECG recorded to diagnose or rule out ACS. If inconclusive, posterior and right ventricular lead ECGs should be recorded and the patient should have an urgent echocardiogram.

A focussed medical history should be obtained to ascertain the nature, onset and duration of the patient's symptoms and to establish the likelihood of ACS due to the existence of cardiac risk factors and family history of cardiac disease. Evaluating the nature, quality, onset and radiation of chest pain and the patient's response to anti-anginal therapy can be useful tools in establishing the likelihood of ACS where the ECG is inconclusive.

ACS is diagnosed from the patient's clinical presentation, ST-T wave changes on the 12-lead ECG and serum cardiac troponin levels. STEMI is present when there is 1 mm of ST-segment elevation, measured at the J point in two or more contiguous leads, other than in leads V_2 and V_3, where ST-segment elevation is higher and is age and gender specific. New left bundle branch block (LBBB) may also develop in the context of STEMI. The ECG changes associated with UA/NSTEMI are T wave inversion, ST-segment depression or transient ST-segment elevation in two contiguous leads. If the standard ECG is inconclusive, posterior (V_7–V_9) and right ventricular leads (V_3R and V_4R) should be recorded and analysed for signs of ischaemia.

A range of serum blood tests should be conducted, including samples for urea and electrolytes, cardiac troponins, full blood count and a clotting screen. Cardiac troponin levels should be assessed on initial presentation and repeated 12 hours later (high sensitivity troponin can be measured within 0 to 3 hours). The troponin level will be raised in STEMI and NSTEMI but remain negative in UA. GRACE and CRUSADE scores should be calculated to estimate prognosis and quantify bleeding risk respectively.

Treatment

Treatment of ACS should be expedited to ensure haemodynamic stability, alleviate symptoms and anxiety, establish coronary reperfusion and minimise short- and long-term risk of morbidity and mortality. Administration of opiate analgesia with anti-emetic should be prioritised while ensuring the patient remains on bed rest. Reassurance should be given where possible to help address anxiety. Resuscitation equipment should be immediately available, as patients with ACS are at risk of life-threatening arrhythmias and sudden cardiac death.

Dual anti-platelet (aspirin and P2Y12 inhibitor) and anti-thrombin therapies should be commenced as soon as possible in the absence of contraindications. Rapid delivery of primary percutaneous coronary intervention (P-PCI) is the mainstay of treatment for STEMI. Patients with NSTEMI/UA should also have percutaneous coronary intervention (PCI) but with less immediacy. However, PCI should be expedited for patients identified as being at high ischaemic risk by using the GRACE score or if the patient develops haemodynamic instability, refractory angina or life-threatening complications such as arrhythmias or heart failure.

Secondary prevention should be commenced at the earliest opportunity to prevent recurrence of ACS and complications associated with myocardial damage. Dual anti-platelet therapy should be continued in conjunction with a beta-blocker, an ACE-inhibitor and an HMG CoA reductase inhibitor (statin) in the absence of contraindications. Rivaroxaban may be commenced once the anti-thrombin agent has been stopped during the in-patient stay. Cardiac rehabilitation should be offered to patients 3–4 weeks post-discharge.

Acute coronary syndromes: treatment and interventions

Pathophysiology

Acute coronary syndromes (ACS) encompasses a range of clinical conditions which cause myocardial ischaemia, discussed in the preceding chapter. Patients who have sustained an ST-segment elevation myocardial infarction (STEMI) will undergo Primary Percutaneous Coronary Intervention (P-PCI) (angioplasty and stent implantation) but where timely P-PCI is not available, thrombolytic (fibrinolytic) therapy may be offered. Patients who have non-STEMI (NSTEMI) or unstable angina (UA) are also likely to undergo coronary angiography and intervention (stent deployment) to achieve perfusion to the jeopardised myocardium by reopening the culprit coronary artery. The onset of ACS generally results from rupture of the atheromatous plaque and exposure of the lipid core. Platelet adhesion at the site and platelet activation and aggregation leads to stimulation of the clotting cascade and potential thrombus formation. Antiplatelet therapy aims to inhibit platelet activation and aggregation and longer term pharmacological therapy aims to enhance thrombus resolution and prevent recurrent thrombotic events. In addition, optimisation of secondary preventive strategies prevents left ventricular remodelling and reduces the risk of further coronary events.

Antiplatelet strategies

Reducing platelet activation is crucial and, unless absolutely contraindicated, all patients should be prescribed *Aspirin* which exerts its antiplatelet effect by irreversibly binding to the cyclooxygenase-1 (COX-1) enzyme, reducing production of thromboxane A_2, a powerful vasoconstrictor. The addition of a second antiplatelet drug is indicated when a patient has received an intracoronary stent. Thienopyridines block the adenosine diphosphate (ADP) P2Y12 receptor on platelets and include *Clopidogrel*, *Prasugrel* and *Ticagrelor*. Clopidogrel is a prodrug that requires two stage metabolism to achieve the active metabolite. This results in a slow onset of efficacy and the dual hepatic activation results in variable individual patient response to the drug. The use of Prasugrel overcomes some of the limitations of Clopidogrel. Prasugrel also exerts its antiplatelet effect by irreversibly binding to the ADP P2Y12 receptor, but it only requires one metabolic step to become active and hence it achieves its effect faster and with less inter-patient variability of response. It does however cause an increased risk of bleeding and it is not recommended for use in patients older than 75 years or under 60 kg and patients who have previously sustained Transient Ischaemic Attacks or stroke should not take this drug. Ticagrelor is a reversible, oral ADP P2Y12 receptor antagonist that does not need metabolising; it has a short half-life of 12 hours

and thus twice daily dosing is required. It is a potent drug but this benefit comes with an increased risk of bleeding and in a trial comparing Ticagrelor with Clopidogrel, higher rates of dyspnoea were observed in the ticagrelor group.

Abciximab, Eptifibatide and *Tirofiban* are potent antiplatelet agents, which bind to the GP IIb/IIIa receptor and are administered intravenously. Their use has been superseded by the thienopyrodines discussed above, but they remain useful in the acute stage for ACS patients who are clinically unstable or when there is slow flow or no reflow following PCI.

Anticoagulant drugs

Anticoagulation is used to prevent acute thrombus formation at the site of the plaque rupture or to prevent in-stent thrombosis after PCI. ACS patients should receive *Fondaparinux*, low molecular weight heparin (LMWH), *Bivalirudin* or unfractionated heparin (UFH). Newer indirect factor-Xa inhibitors (Fondaparinux) and direct thrombin inhibitors (Bivalirudin) inhibit thrombin mediated platelet activation and are now recommended in national guidance. *LMWH (Enoxaparin)* inhibits factor Xa and anti-thrombin and has a more sustained and predictable anticoagulant effect than UFH. It is administered subcutaneously twice daily and does not require aPTT monitoring. *UFH* exerts a number of effects; action on circulating antithrombin, which inactivates factor IIa, factor IXa and factor Xa. This leads to marked variation in patient response to therapy and monitoring is required with aPTT. High risk ACS patients may be commenced on a direct factor Xa inhibitor within 7 days of the acute event but Rivaroxaban is only currently licensed with Aspirin and Clopidogrel.

Reperfusion therapy

P-PCI provides a mechanical means of enlarging the lumen of the affected coronary artery by the insertion of a balloon-tipped catheter into the affected artery and inflation of the balloon to dilate the arterial lumen in a procedure known as balloon angioplasty. This is followed by deployment of a coronary artery stent and thrombectomy or atherectomy. The efficacy of P-PCI over fibrinolysis (thrombolysis) as the appropriate reperfusion treatment option in ACS is now indisputable. However, in rare circumstances when P-PCI is not immediately available (rural settings where transport times to PCI centres are prolonged), thrombolysis can be used if given within 30 minutes of acute presentation. Thrombolytics convert plasminogen to plasmin, which degrades fibrin and thrombus. Third-generation thrombolytics include *Reteplase* and *Tenecteplase*, both of which have enhanced fibrinolytic potency and can be given by bolus injection enhancing ease of administration. To prevent reocclusion of the infarct-related artery

ancillary anticoagulant therapy such as Fondaparinux, LMWH or UFH should be given. Absolute contraindications to thrombolytic therapy include intracranial haemorrhage, uncontrolled hypertension or recent closed head or facial trauma. Practitioners should check the list of contraindications issued by the drug manufacturers.

Secondary prevention Beta-Blockers, ACE-inhibitors and Statins

Reduction in post-ACS mortality is achieved with the use of beta-blockers, ACE-I and statins.

Beta-blockers should be commenced as soon as possible after the ACS event. Beta-blockers such as *Bisoprolol* block the effect of catecholamines on adrenergic receptors in the myocardium, reducing myocardial contractility and slowing the heart rate. The beneficial effects are to decrease cardiac output, reduce myocardial oxygen demand and increase diastolic filling time hence augmenting coronary blood flow.

Angiotensin-converting enzyme inhibitors (ACE-I) block the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. ACE-I such as *Ramipril* have been shown to reduce mortality and left ventricle (LV) remodelling post ACS. Patients who cannot tolerate ACE-I can be given angiotensin receptor blockers (ARBs).

Statins such as *Atorvastatin* inhibit HMG CoA reductase production in the liver and lower LDL cholesterol. Unless contraindicated, all patients with ACS should take a statin to lower and then maintain a normal LDL cholesterol level.

Administration of an insulin infusion for patients presenting with hyperglycaemia during or immediately following an episode of ACS has been shown to reduce the risk of further cardiac events or death, even in patients not known to have diabetes.

Adherence and side-effects

Most patients with ACS will be taking at least 5 drugs: aspirin, thienopyridine, ACE-I, beta-blocker and statin. The importance of optimal secondary prevention to ensure long-term survival is evident, but the use of 5 drugs poses a challenge for patient adherence. Patients should be encouraged to persevere with all drugs, but also advised of any risks. Patients taking dual-antiplatelet therapy are advised to be vigilant for evidence of bleeding which will not resolve. Patients taking ACE-I should have renal function monitored regularly and patients taking statins should be advised of the possibility of long-term muscle pain. All patients should be referred for cardiac rehabilitation to optimise lifestyle gains. They should be advised and supported with smoking cessation, weight loss and increase in exercise levels if appropriate.

Acute heart failure

Acute heart failure is a life-threatening condition in which the patient experiences rapid onset of the symptoms associated with heart failure. Rapid assessment and treatment is necessary to ensure the comfort and safety of the patient. Several factors are known to trigger acute heart failure, such as acute coronary syndrome and tachyarrhythmia, which usually require additional treatments.

History

Acute heart failure may occur in response to the sudden onset of an acute cardiovascular event, such as acute coronary syndrome, aortic dissection, tachyarrhythmia or pulmonary embolus. However, many patients with chronic heart failure may experience an episode of acute decompensation, precipitated by new onset of infection, arrhythmia or non-adherence to prescribed medications or fluid and dietary salt restrictions.

Signs and symptoms

Paroxysmal nocturnal dyspnoea, orthopnoea, cough, peripheral oedema and weight gain are common symptoms associated with pulmonary congestion, caused by fluid overload. Dizziness, fatigue and confusion are symptoms associated with low cardiac output. Patients with acute heart failure often feel anxious and distressed.

Clinical signs include tachypnoea, hypoxaemia, use of respiratory accessory muscles and bilateral pulmonary crackles on auscultation. Sputum may appear white or pink and frothy. Hypoperfusion may cause hypotension, diaphoresis, cool extremities and oliguria and if associated with a systolic BP < 90 mmHg, cardiogenic shock is diagnosed. Additional signs include narrow pulse pressure, jugular venous distension, congested hepatomegaly and ascites.

In addition, the patient may experience symptoms and signs associated with the precipitating event, such as sepsis, tachyarrhythmia or acute coronary syndrome.

Assessment and investigations

Rapid assessment and history taking is necessary to establish a diagnosis of acute heart failure and to ascertain the cause of the episode. Patients should be closely monitored during the first hour, with regular observations and continuous pulse oximetry, cardiac monitoring and non-invasive haemodynamic monitoring. A record of urine output and fluid balance should be kept. Investigations should include a 12-lead ECG, chest X-ray and echocardiogram to ascertain the extent of cardiac dysfunction and identify the cause. Blood tests should include natriuretic peptides, such as B-type natriuretic peptides (BNP) and NT pro-BNP, cardiac troponin, urea, creatinine and

electrolytes, as well as liver and thyroid function tests and arterial blood gas sampling. Once the patient is stable, their weight should be recorded.

Treatment

Patients with acute heart failure should be treated in a setting that provides close monitoring and rapid access to resuscitation equipment. The patient should be positioned upright in the high Fowler's position and high flow oxygen should be administered if the patient is hypoxaemic. Patients may be frightened and so reassurance is essential. Opiates may be required for patients in considerable distress but should be administered cautiously as bradycardia, hypotension or respiratory depression may result. Anxiolytics may be necessary to treat patients with delirium.

In patients diagnosed with acute heart failure with a systolic BP > 90 mmHg, intravenous diuretics, nitrates and continuous positive airway pressure (CPAP) can relieve pulmonary congestion and improve respiratory function. However, all three interventions should be administered with close monitoring as they could worsen hypotension and precipitate cardiogenic shock. Inotropic support is indicated in patients with severe hypoperfusion in the absence of hypovolaemia. Cautious administration is again necessary as inotropes can cause sinus tachycardia, myocardial ischaemia and arrhythmias. Ultrafiltration is an alternative intervention in patients with an acute exacerbation of chronic heart failure who no longer respond to diuretic therapy. Patients with acute heart failure may develop AF for which thromboembolic prophylaxis and digoxin are appropriate treatments.

Once haemodynamic stability is restored, patients diagnosed with chronic heart failure should be offered a range of treatments and lifestyle advice to minimise recurrence of symptoms, prevent acute exacerbations and optimise quality of life. ACE-Inhibitors (ACE-I) and beta-blockers have been demonstrated to reduce mortality and morbidity and the introduction of aldosterone inhibitors, such as Spironolactone or Eplerenone, also have proven benefits. Diuretics, such as Furosemide, Bumetanide or Metolazone, may be offered to control fluid retention. Recent data has revealed that a new drug, Sacubitril Valsartan, that combines a neprilysin inhibitor and angiotensin receptor blocker (ARB), may be a more effective alternative to an ACE-I in some patients with a reduced ejection fraction. Cardiac resynchronisation therapy, also known as bi-ventricular pacing, may additionally offer some improvement in symptoms for patients with a symptomatic heart failure.

Patients are encouraged to manage their condition themselves through careful monitoring and lifestyle adjustments. They should be advised to strictly limit salt and water intake to reduce weight and fluid

gains. A cardiac rehabilitation programme provides education and support, as well as a supervised exercise programme, which has been shown to improve patients' exercise capacity, reduce hospital admissions and improve quality of life. Many patients frequently experience anxiety and depression for which self-help groups provide support for patients and their carers in learning to live with this long-term condition.

Aortic aneurysm

An aortic aneurysm is a localised dilatation of the thoracic or abdominal aorta resulting from weakening of all three layers of the arterial wall. An aneurysm is diagnosed when the diameter of the aorta is found to have increased by at least 50%. The most significant complications associated with aortic aneurysm are rupture or dissection, resulting in blood loss, hypotension and cardiac arrest.

History

Aortic aneurysms develop when the elastin fibres within the aorta degenerate as a result of ageing, hypertension or specific connective tissue disorders such as Marfan syndrome. Aortic aneurysms affecting the descending thoracic and abdominal aorta are strongly associated with atherosclerosis and cardiovascular risk factors, such as hypertension, dyslipidaemia, smoking and advancing age, which contribute to weakening of the vessel wall. A pseudoaneurysm (false aneurysm) occurs when blood passes from the lumen through a channel within the intima and medial layers and collects within the adventitia.

Signs and symptoms

Patients with aortic aneurysm are frequently asymptomatic. However, symptoms may occur if the aneurysm is large enough to compress adjacent structures, such as the trachea, bronchus or oesophagus resulting in stridor, hoarseness, dyspnoea, cough or dysphagia. Ascending aortic aneurysms may dilate the aortic valve, resulting in the symptoms associated with aortic regurgitation and heart failure. Rupture of an aortic aneurysm may occur with a slow leak or sudden burst, causing hypotension and tachycardia associated with profound blood loss and may result in cardiac arrest.

Assessment and investigations

Patients presenting with a ruptured aortic aneurysm will require rapid assessment and close monitoring prior to transfer for emergency surgery. Thoracic aortic aneurysm is often an incidental finding from investigations such as chest X-ray, echocardiogram, CT scan or MRI. Once identified, a CT scan will enable identification of the exact location and dimensions of the aneurysm, which will be used to guide the management of the patient. An aortogram may also be used to identify which arterial branches of the aorta are affected.

Treatment

Rapid surgical intervention is the only curative option for patients with ruptured aortic aneurysm. In the absence of rupture or dissection, treatment for patients is guided by the diameter of the aorta. The risk

of rupture significantly increases as the aorta widens beyond 6 cm. Open surgical deployment with a prosthetic graft is recommended once the aortic diameter is more than 6 cm or if rupture has occurred. Thoracic Endovascular Aortic Repair (TEVAR) with a stent graft is an increasingly common alternative intervention. Close monitoring and conservative pharmacological blood pressure management to reduce the risk of rupture is recommended for patients with an aortic diameter of less than 6 cm and for those unsuitable for surgical intervention.

Aortic dissection

Aortic dissection occurs when a tear in the intimal layer of the aorta creates a false channel that permits blood flow into the tunica media. Aortic dissection is a life-threatening condition requiring emergency surgical intervention.

History

Thoracic aortic dissection occurs more frequently in men and is associated with advancing age, hypertension, Marfan syndrome and trauma. A classification system is used to specify the region of the aorta affected by the dissection. Stanford Type A dissection affects the ascending thoracic aorta, the most commonly affected region, which may extend to the aortic root, the aortic arch or the descending thoracic aorta. Stanford Type B dissections affect the descending thoracic aorta and may extend to the abdominal aorta.

Signs and symptoms

Aortic dissection is characterised by a 'tearing' or 'ripping' pain located either between the scapulae, associated with a type B dissection, or in the central chest region, suggesting type A dissection. The location of the pain may spread throughout the chest and back or to the abdomen if the dissection extends beyond the thoracic aorta. An array of additional symptoms, such as limb ischaemia and acute kidney injury, may emerge, dependent upon whether major arteries originating from the aorta are affected. For example, the patient may appear confused or with reduced level of consciousness if the left common carotid artery arising from the aortic arch is affected. Tachycardia and hypertension usually occur, initially due to the sympathetic response to pain or reduced renal perfusion, but will deteriorate if reduced myocardial perfusion or cardiac tamponade, associated with a type A dissection, occur.

Assessment and investigations

Rapid, systematic assessment of the patient with suspected aortic dissection is required to aid diagnosis and selection of an appropriate treatment strategy. Cardiovascular assessment should include cardiac monitoring, regular pulse assessment and blood pressure recordings from both arms, which may be different if the dissection originates in the aortic arch. Acute coronary syndrome should be rapidly ruled out using comprehensive chest pain assessment and serial 12-lead ECGs. It should be noted that ST-segment elevation, usually affecting the inferior leads, may be evident if right coronary arterial perfusion is affected in type A aortic dissection. A urinary catheter should be inserted to facilitate accurate fluid balance monitoring. Serum bloods should include full blood count, urea and electrolytes, troponin,

clotting screen and cross-match prior to surgery. A chest X-ray may reveal a widened mediastinum associated with type A dissection; CT, MRI or transoesophageal echocardiogram will confirm the presence of aortic dissection.

Treatment

Preventing progression of the dissection should be prioritised in the management of both type A and type B aortic dissection, by maintaining the patient's systolic blood pressure between 100–120 mmHg with beta-blockers and intravenous vasodilator infusions such as glyceryl trinitrate (GTN). Emergency cardiac surgery is usually necessary for patients with type A dissection to either repair or replace the damaged intimal layer with a prosthetic graft, although research is on-going into the role of Thoracic Endovascular Aortic Repair (TEVAR) to treat dissection. Conservative medical therapy alone may be recommended for patients with type B dissection, unless complications affecting major arterial branches necessitate urgent endovascular stenting or surgical repair.

Aortic regurgitation

Aortic regurgitation (AR) is reflux of blood from the aorta into the left ventricle (LV) across the leaking aortic valve during diastole. This results in pressure and volume overload in the LV, which hypertrophies to accommodate the regurgitation, the stroke volume increases and the major arteries become visibly pulsatile. As the disease progresses LV end diastolic pressure (LVEDP) rises and the increased LV mass becomes increasingly inefficient with reduced coronary perfusion. Increased LVEDP may also cause mitral regurgitation and subsequent left atrial dilatation, increased pulmonary pressure and symptoms of atrial arrhythmias and left ventricular failure (LVF).

History

AR may be caused by chronic untreated hypertension, abnormalities of the aortic valve cusps (bicuspid aortic valve, endocarditis or rheumatic heart disease) or diseases of the aortic root (Marfan syndrome, syphilis, aneurysm or dissection). Chronic AR may develop over many years and during this period the patient may be asymptomatic. It is only when the compensatory mechanisms fail that LV dysfunction leads to a reduction in left ventricular ejection fraction. In acute AR, due to aortic dissection or infective endocarditis, the LV is of normal size and cannot cope with the increased volume. LVF develops rapidly and raised left atrial and pulmonary capillary pressure leads to catastrophic pulmonary oedema.

Signs and symptoms

In chronic AR, the patient may have an awareness of the heart beat or palpitations on exertion, during stress or when lying on the left side. This may also be associated with a pounding sensation in the head. As the disease progresses and LVF ensues, symptoms of dyspnoea, paroxysmal nocturnal dyspnoea, fatigue and weakness will develop. Clinical signs in AR are due to the hyper-dynamic circulation; a large volume or 'collapsing pulse', bounding peripheral pulses, a widened pulse pressure and a displaced heaving apex beat. There may be an early diastolic murmur, a systolic murmur and bilateral inspiratory crackles with pulmonary oedema. Patients may develop angina due to increased LV mass and reduced coronary perfusion. The 12-lead ECG may show LV hypertrophy, left axis deviation and left ventricular strain pattern.

Acute AR presents with a sudden onset of heart failure and reduced cardiac output. Tachycardia, hypotension, cardiovascular collapse and cardiogenic shock all require urgent intervention.

Assessment and investigations

Acute AR requires urgent assessment and treatment of the patient. Airway and respiratory assessment including rate, depth, breathing pattern and peripheral oxygen monitoring should be undertaken.

Heart and breath sounds, pulse, blood pressure and cardiac rhythm should be monitored for cardiogenic shock, atrial and ventricular arrhythmias and evidence of heart failure. A 12-lead ECG may demonstrate LV hypertrophy and myocardial ischaemia; ACS should be excluded. An echocardiogram will confirm AR as the cause of the patient's symptoms and a chest X-ray will evaluate pulmonary oedema and cardiomegaly. Arterial blood gases will be required, venous samples will assess urea and electrolytes (U&Es), full blood count (FBC), troponin, B-type natriuretic peptides (BNP) and glucose levels. Fluid balance and weight should be monitored and fluid restrictions may be required.

Treatment

In the acute phase, patients may need oxygen therapy and treatment with vasodilators and inotropes. In chronic AR, systolic blood pressure is controlled with ACE inhibitors or calcium channel blockers. Timing of aortic valve/root replacement or repair is crucial and may be performed before the patient becomes symptomatic to avoid development of LV dysfunction.

Aortic stenosis

Aortic stenosis (AS) occurs when the leaflets (cusps) of the aortic valve become stiffened. During ventricular systole, the opening of the valve is significantly impeded, reducing stroke volume and eventually resulting in heart failure.

History

The most common cause of AS is age-related sclerosis, which causes the cusps to stiffen and fuse together, preventing the valve from opening fully during left ventricular systole. Early detection of AS is difficult as the patient will not usually experience symptoms until the disease is in the advanced stages, when the valve orifice has been reduced to approximately one-third of its normal size. Less commonly, AS can occur with a congenital bicuspid aortic valve or as a result of streptococcal infection in childhood (rheumatic fever). AS is also known to be a rare form of congenital heart disease.

Signs and symptoms

AS produces a triad of classic clinical symptoms, usually occurring on exertion: dyspnoea, chest pain, pre-syncope or syncope. The patient may experience fatigue as well as other symptoms caused by heart failure, such as ankle swelling and palpitations, which may be due to atrial or ventricular arrhythmias. AS can cause sudden cardiac death.

Clinical signs include a slow rising, low volume pulse and signs associated with heart failure, including jugular venous distension (JVD) and peripheral oedema. On auscultation, AS will produce an ejection systolic murmur and possibly an ejection systolic click; a soft 2nd heart sound, S3 and bilateral (inspiratory/expiratory) crackles associated with pulmonary oedema. The 12-lead ECG may show evidence of left ventricular hypertrophy, atrial enlargement, left anterior fascicular block or left bundle branch block.

Assessment and investigations

Initial assessment of the patient should prioritise baseline observations, continuous cardiac monitoring, chest pain assessment and 12-lead ECG to rapidly rule out acute coronary syndrome as the cause of the symptoms. The patient should be assessed for the signs of heart failure and a chest X-ray and blood samples taken to assess for renal dysfunction, including estimated glomerular filtration rate (eGFR), electrolyte imbalance, full blood count, troponin and B-type natriuretic peptides (BNP). A fluid balance chart should be commenced immediately and the patient may require a urinary catheter. Once stable, the patient should be weighed daily. An echocardiogram will establish the diagnosis of AS and measure the LV ejection fraction.

An angiogram will assess the severity of the AS by measuring the difference in systolic pressure between the left ventricle (LV) and aorta (gradient).

Treatment

The treatment for hypoxia, dyspnoea, chest pain or anxiety should be prioritised initially with bed rest, oxygen therapy, frusemide and morphine, with an anti-emetic if required. Nitrates should be avoided due to the vasodilator effect that can reduce ventricular preload, which would further decrease cardiac output. Electrolyte imbalance should be corrected to prevent possible arrhythmias. The patient should be encouraged to rest to minimise exertion and prevent symptoms. Most patients with symptomatic AS will require surgical intervention urgently. Aortic valve replacement surgery remains the mainstay of treatment but if the patient is unsuitable for surgery, transcutaneous aortic valve implantation (TAVI) is an effective alternative. Conservative management includes avoidance of strenuous exercise and pharmacological therapy including beta-blockers or calcium channel blockers to reduce myocardial work.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) or dysplasia (ARVD) is a rare, inherited form of cardiomyopathy in which heart failure is caused by fibro-fatty replacement of myocytes, predominantly within the right ventricle (RV). The risk of ventricular arrhythmias is increased, principally on exertion and therefore ARVC is a known cause of sudden cardiac death.

History

ARVC is an autosomal dominant inherited condition in which genetic mutation causes damage to the proteins within the desmosome, the bridge that joins myocytes together. As the desmosome weakens, the myocytes separate, allowing deposition of adipose and fibrous tissue, forming scar tissue. This process is thought to accelerate with strenuous exertion. Structural changes to the RV will initially be minimal, usually affecting the inflow, outflow and apical regions. Later, the fibro-fatty tissue may extend to all regions of the RV, causing dilatation and systolic dysfunction. Some patients may eventually develop left ventricular involvement.

Signs and symptoms

The clinical features of ARVC develop over time, although disease progression is variable among patients and some patients remain asymptomatic. Premature ventricular contractions (PVCs), and non-sustained and sustained VT may occur at any stage of the condition; the first presentation may be cardiac arrest, usually following strenuous activity. ARVC should be considered in patients presenting with right ventricular outflow tract (RVOT) tachycardia (left bundle branch block pattern with a rightward mean QRS axis). Patients may also describe symptoms associated with heart failure or syncope.

Assessments and investigations

Approximately 30–50% of patients with ARVC have a family history of the condition. Currently there is no single test to identify AVRC; genetic testing will only be helpful in some cases. International criteria are used to diagnose AVRC using familial, histological, electrocardiographical and structural data. The 12-lead ECG may reveal QRS prolongation or Epsilon waves. Late potentials may be evident on the signal-averaged ECG. 24-hour Holter monitoring and exercise testing should be used to identify the occurrence of ventricular arrhythmias. An echocardiogram may reveal RV dilatation and reduced RV ejection fraction with normal LV function. Invasive diagnostic tests include electrophysiology studies, right ventriculogram and endomyocardial biopsy.

Treatment

The treatment for ARVC aims to prevent the occurrence of life-threatening arrhythmias and to limit the extent of right ventricular systolic dysfunction. Pharmacological therapy includes anti-arrhythmic agents such as beta blockers or amiodarone to prevent arrhythmias. The patient may be offered radio-frequency ablation and an implantable cardioverter defibrillator (ICD) to prevent or treat ventricular arrhythmias. ACE-inhibitors may be prescribed to minimise systolic dysfunction. Close relatives of the patient should be offered genetic counselling prior to screening for ARVC.

Atrial fibrillation

Atrial fibrillation (AF) is a commonly occurring arrhythmia that may result in acute heart failure or stroke. AF occurs when multiple, rapid re-entry circuits cause the atria to fibrillate at a rate of 300–600 bpm. The AV node protects the ventricles by restricting the conduction of impulses through to the ventricles. This results in an irregular, narrow QRS complex arrhythmia with a ventricular rate between 30 and 180 bpm. AF may be paroxysmal or permanent.

History

AF is the most common sustained arrhythmia affecting individuals over 65 years of age and is frequently idiopathic in origin. Reversible causes of AF include hypoxia, chest infections, excess alcohol or caffeine consumption, electrolyte imbalance, emotional stress, fluid overload or drugs that can induce tachycardia, for example Salbutamol. AF can also be caused by acute exacerbation of heart failure and is strongly associated with conditions that dilate the atria, such as mitral valve regurgitation, dilated cardiomyopathy or hypertension. AF commonly occurs after cardiac surgery.

Signs and symptoms

The patient may present with sudden onset of palpitations, dyspnoea, chest pain, fatigue, pre-syncopal or syncopal symptoms, or other signs associated with heart failure. The patient's pulse will be irregular, weak and thready on palpation. The diagnosis will be made from the cardiac monitor, 12-lead ECG or 24-hour tape that will typically show an irregular rhythm at a rate of 30–180 bpm with a normal duration QRS complex (<100 ms) (unless bundle branch block is present). No discernible P waves will be evident, although fibrillatory waves may be visible (Figure 12.1).

AF is associated with a high risk of stroke due to stasis and coagulation of blood within the fibrillating atria. If sustained for more than 48 hours, thrombus formation will occur, particularly within the left atrial appendage from which emboli could be displaced into the systemic circulation. This risk is increased when sinus rhythm is restored.

Assessment and investigations

Initial systematic assessment of a patient with new onset AF should use the ABCDE approach and include a 12-lead ECG. Continuous

Figure 12.1 Atrial fibrillation (AF) as seen in lead II.

cardiac monitoring, regular observations and fluid balance measurements are necessary to monitor for acute deterioration. Establishing the cause of AF should be prioritised. Serum blood tests should be taken to identify electrolyte imbalance and renal dysfunction and record a clotting screen. Individual risk assessment should be conducted using the 'CHA_2DS_2-VASc' score to establish risk of thromboembolism, offset against the risk of bleeding associated with anti-coagulant therapy using the 'HAS-BLED' score.

Treatment

Emergency treatment will be required for the patient who becomes haemodynamically unstable with AF. This will usually be rapid direct current cardioversion (DCCV) unless the ventricular response is very slow, in which case the patient will require transcutaneous pacing. Beta-blockers or calcium channel blockers are suitable drug treatments to slow the ventricular response rate in fast AF; Digoxin is preferred in patients with heart failure. Amiodarone is recommended where cardioversion is sought, for example post-cardiac surgery. Elective DCCV, radio-frequency and cryoablation are therapeutic options if AF persists.

Anti-coagulation should be considered for all patients with paroxysmal or permanent AF, to reduce the risk of thromboembolic complications such as stroke. During the acute phase, anti-thrombin therapy, such as low molecular weight heparin, should be initiated and continued until therapeutic levels of anti-coagulation are established. Warfarin may be prescribed for this or, alternatively, a non-vitamin K oral anticoagulant (NOAC), such as Rivaroxaban, may be suitable, although not recommended for patients with AF caused by valve disease. Aspirin does not protect against the thromboembolic risk and is therefore not recommended.

Atrial flutter

Atrial flutter is a relatively uncommon arrhythmia that may result in acute heart failure or stroke. Atrial flutter occurs when an ectopic atrial site, usually close to the atrio-ventricular (AV) node, generates regular impulses at a rate of 300/min. The rhythm is the result of either increased automaticity or a rapid macro re-entry circuit in the atria. The atrial flutter completely suppresses the activity of the sino-atrial (SA) node. The ectopic atrial pacemaker fires rapidly and the series of atrial impulses create a waveform with a characteristic saw-tooth appearance called an F wave. The AV node will have a decremental effect on the rapid F wave rate, blocking conduction to the ventricles in a ratio of 2:1, 3:1 or 4:1. This results in a narrow, complex, regular rhythm of 150, 100 or 75 bpm respectively. There may also be variable conduction through the AV node, resulting in an irregular QRS rate. Atrial flutter may be paroxysmal or permanent.

History

Atrial flutter, whilst relatively rare, has many reversible causes including hypoxia, chest infections, excess alcohol or caffeine consumption, electrolyte imbalance, emotional stress, fluid overload or use of drugs that can induce tachycardia, for example Salbutamol. Atrial flutter can occur during acute heart failure and is strongly associated with conditions that dilate the atria, such as mitral valve regurgitation, dilated cardiomyopathy or hypertension. Atrial flutter commonly occurs after cardiac surgery.

Signs and symptoms

A patient with an acute onset of atrial flutter may present in a collapsed state with signs of shock, particularly if the conduction rate is 2:1 or if the patient has pre-existing ventricular dysfunction. A sudden onset of atrial flutter may cause palpitations, anxiety, dyspnoea, chest pain and syncope or signs of heart failure. Atrial dysfunction results in blood stasis and the potential for atrial thrombus, which may embolise resulting in pulmonary embolus or stroke. The diagnosis will be made from the ECG, which will typically show a regular, narrow complex QRS with the characteristic saw-tooth flutter waves known as F waves (Figure 13.1). In Lead II, a typical F wave has an inverted negative deflection reflecting abnormal atrial depolarisation followed by a positive F wave deflection reflecting atrial repolarisation.

Assessment and investigations

Initial systematic assessment of a patient with new onset atrial flutter should use the ABCDE approach and include a 12-lead ECG and SpO_2 monitoring. Continuous cardiac monitoring, regular vital signs and

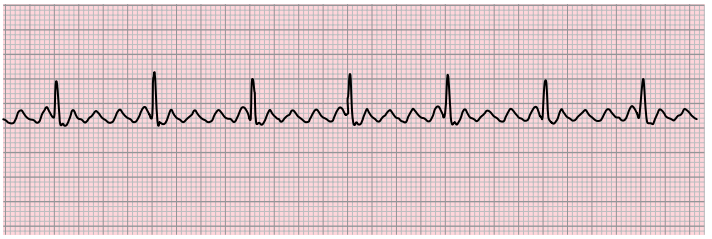

Figure 13.1 Atrial flutter.

fluid balance measurements are necessary to monitor for acute deterioration. Serum blood tests should be taken to identify electrolyte imbalance, renal dysfunction and to record a clotting screen. The risks of thromboembolism offset against the risk of bleeding associated with anti-coagulant therapy should be assessed using 'CHA_2DS_2-VASc' and 'HAS-BLED' risk scores. Sudden resumption of sinus rhythm increases the risk of stroke.

Treatment

The treatment depends on the haemodynamic consequences of the arrhythmia. A ventricular rate of 150 bpm will often cause rapid collapse and deterioration in most patients. Emergency treatment is directed to restoring sinus rhythm using direct current (DC) cardioversion. If the patient has a ventricular rate of less than 150 bpm and is not haemodynamically compromised, acute pharmacological cardioversion using class 1c (flecainide) or class III (Sotalol or Amiodarone) antiarrhythmic drugs can be used. Patients who have been in atrial flutter longer than 48 hours should be anticoagulated and cardioversion delayed until the thromboembolic risk has reduced. Recurrent atrial flutter can be prevented by Sotalol or Amiodarone to control the ventricular rate, although the treatment of choice for recurrence is catheter ablation to permanently interrupt the atrial re-entry circuit.

B

Brugada syndrome

Brugada syndrome is an autosomal dominant ion-channelopathy, which occurs in structurally normal hearts. The condition may only manifest when the patient presents with an aborted sudden cardiac death, but pre-morbid symptoms may include syncope, palpitations and seizures. The most common cardiac arrhythmia is polymorphic ventricular tachycardia (VT), which may deteriorate to ventricular fibrillation. It is a leading cause of sudden cardiac death in healthy individuals.

History

The syndrome was first described in 1992, by the Brugada brothers, as a distinct clinical and electrocardiographic syndrome following investigation of eight patients who had survived an out-of-hospital cardiac arrest and who were found to have characteristic ECG abnormalities. This was subsequently linked to a high incidence of sudden cardiac deaths in the Philippines and Thailand, where syndromes had been respectively described as 'bangungut' (to rise and scream in the night) and 'lai tai' (death during sleeping). In 1998, the mutation of the sodium channel gene 5A (SCN5A) was identified and the hereditary nature of the syndrome was confirmed.

Signs and symptoms

There is a wide phenotype variation and some patients may be asymptomatic and only diagnosed on routine 12-lead ECG examination. Some patients may suffer with palpitations and syncope; the underlying arrhythmia is polymorphic VT. Many patients die during sleep and death may be preceded by chest pain, seizures, loss of bladder control and laboured breathing. The first arrhythmic events tend to occur around 40 years of age, but may occur between 1 and 70 years.

Assessment and investigations

The diagnosis is aided by patient and family history, electrocardiogram and genetic testing. Patients are normally fit and healthy and hence physical examination will be normal. The 12-lead ECG presentation is characterised by down-sloping ST-segment elevation in V_1–V_3 with a right bundle branch block pattern (Figure 14.1). In patients with a 'concealed form' of Brugada Syndrome, the ECG pattern or arrhythmia may only be revealed after provocation during an electrophysiological study, a VT stimulation study or the administration of Ajmaline. Genetic testing may identify the SCN5A gene and help in predictive testing for other family members.

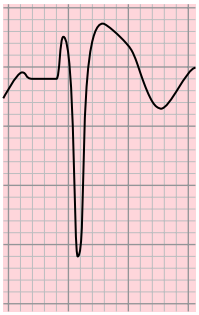

Figure 14.1 Brugada Sign: down-sloping ST elevation with right bundle branch block pattern (V_1).

Treatment

Anti-arrhythmic drug therapy is not useful in Brugada syndrome and the only effective treatment is implantation of an internal implantable cardioverter defibrillator (ICD). Genetic testing and counselling is essential for any family members affected.

C

Cardiac arrest

Cardiac arrest is defined as sudden cessation of effective systemic blood flow due to failure of cardiac contraction. It is rapidly accompanied by absent respiratory effort and loss of consciousness. If not treated, death will occur within minutes.

History

Most sudden unexpected deaths are due to cardiac arrest, which is preceded by cardiac symptom onset. The underlying arrhythmias are ventricular fibrillation or ventricular tachycardia; rarely the presentation may be extreme bradycardia or asystole. Cardiac arrest is usually caused by underlying cardiac conditions such as acute coronary syndrome, aneurysm, cardiomyopathy, electrophysiological abnormalities, infective heart disease or valvular heart disease. Other causes include pulmonary embolism, cerebral or subarachnoid haemorrhage, electrolyte or metabolic disturbances.

Assessment

Ensure it is safe to approach the patient and assess responsiveness by shaking him and shouting in his ear. Open the patient's airway by placing the patient on his back, flexing the neck and extending the head using the 'head tilt – chin lift' method. Rapidly check (no more than 10 seconds) if the patient is breathing by looking for chest movement, listening at the mouth for breath sounds and feeling for air on your cheek. At the same time, check for presence of the carotid pulse. If the patient is unresponsive and there are no other signs of life, help should be sought and basic life support commenced. Apply personal protective clothing as soon as possible and especially if the patient has a known infective condition.

Treatment

The Resuscitation Council (UK) guidance was issued in 2015 and is approved by the National Institute of Health and Care Excellence. The 'Chain of Survival' (Figure 15.1) includes early recognition of warning signs, early activation of emergency services, early basic life support including cardiopulmonary resuscitation (CPR), early defibrillation and early Advanced Cardiac Life Support (ACLS). When a patient is found to be in cardiac arrest, the in-hospital resuscitation team or emergency services should be summoned immediately.

CPR should be commenced, in cycles of 30 regular chest compressions, at a rate of 100–120/min, depressing the sternum by 5–6 cm, followed by 2 effective breaths. As soon as possible, the

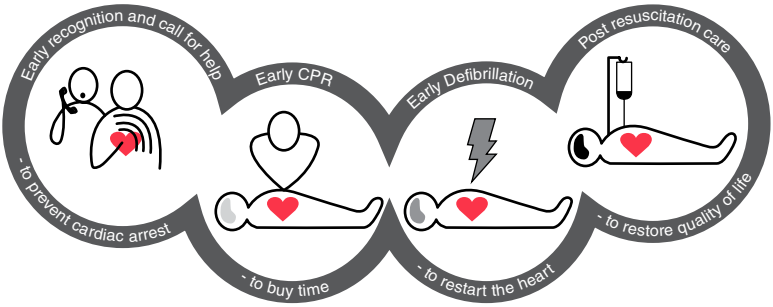

Figure 15.1 The Chain of Survival.

patient should be attached to a defibrillator/monitor to assess cardiac rhythm. If the patient has a 'shockable rhythm' (ventricular tachycardia or ventricular fibrillation) an unsynchronised shock of 150–200 J biphasic (360 J monophasic) should be delivered followed immediately by 2 minutes of CPR. If the patient remains in ventricular tachycardia/ventricular fibrillation (VT/VF), this cycle of CPR and shocks should be repeated. Amiodarone should be administered after the third shock. If the patient has a 'non-shockable rhythm', i.e. asystole or pulseless electrical activity (PEA), continuous CPR should be administered and the rhythm reassessed every 2 minutes.

Vascular access should be established promptly to facilitate administration of adrenaline every 3–5 minutes. Oxygen delivery should be maintained, although the patient's airway may need to be secured using endotracheal intubation or a supraglottic airway.

Treatable causes should be considered using the 4 'H's' (Hypoxia, Hypovolaemia, Hyper/Hypokalaemia and Hypothermia) and 4 'T's' (Thromboembolism, Tension Pneumothorax, Tamponade and Toxins). Percutaneous coronary intervention should be expedited for cardiac causes, even if the patient remains in cardiac arrest.

On return of spontaneous circulation, the patient should be systematically assessed and closely monitored using the ABCDE approach and a 12-lead ECG recorded. Patients may require ventilator support, necessitating transfer to an intensive care setting. Targeted temperature management may be implemented, although this remains disputable.

Cardiac arrhythmias: treatment and interventions

Cardiac arrhythmias can be treated using a variety of medications and devices that can control the rate of the rhythm, address the underlying cause of the arrhythmia or return the heart to a stable rhythm.

Mechanisms of arrhythmias

Anti-arrhythmic drugs are used to treat cardiac arrhythmias that are caused by three mechanisms affecting the action potential of cardiac myocytes: enhanced automaticity, triggered activity and re-entry.

Enhanced automaticity refers to the accelerated activation of depolarisation that can occur in both pacemaker cells and cardiac myocytes at the end of phase 4 of the action potential. Sinus tachycardia can occur when adrenaline enhances the normal automaticity of the sino-atrial (SA) node. Cardiac disease, drugs and low potassium levels may accelerate depolarisation of cardiac myocytes, referred to as enhanced abnormal automaticity.

Triggered activity can occur when the action potential of cardiac myocytes fails to return to the resting membrane potential of –90 mV during phase 3. Early or delayed after-depolarisations can occur when the transmembrane potential oscillates around the threshold potential of approximately –70 mV. Myocardial damage can cause early after-depolarisations that initiate ventricular arrhythmias, including Torsades de Pointes.

Re-entry mechanisms can cause tachyarrhythmias when an ectopic beat causes activation of two pathways within a ring of tissue: one that is refractory, as it has recently depolarised and is slow to repolarise (α), and another pathway that is slow to depolarise (β) but is ready to be activated due to fast repolarisation. If the ectopic beat is conducted slowly down the β pathway, the α pathway may be ready to be activated, conducting the impulse back up to the tissue above. This re-entry circuit results in a circus movement tachycardia, such as supraventricular tachycardia (SVT) or ventricular tachycardia (VT).

Anti-arrhythmic drugs

Anti-arrhythmic drugs modify cardiac conduction and are categorised within the Vaughan Williams classification based on their primary effect on the cardiac action potential. As well as treating arrhythmias, these drugs can be pro-arrhythmic and reduce ventricular contractility and therefore must be administered with caution.

Class I

Class I anti-arrhythmic drugs reduce the rate of sodium entry into the cell during depolarisation (phase 0) to prevent tachyarrhythmias. Drugs in this class should not be offered to patients with structural heart

disease, as they are associated with increased mortality. Administration of these drugs is usually initiated under close cardiac monitoring in a hospital setting:

Class I drugs are further stratified into 3 subtypes:

- Class Ia drugs, such as disopyramide, additionally prolong the refractory period of the action potential, increasing the QT interval.
- Class Ib drugs, such as Lidocaine, shorten the refractory period and have no effect on the QT interval.
- Class Ic agents, such as Flecainide, have minimal effect on the refractory period but severely depress sodium entry into the cell.

Class II

Beta-blockers, or β-adrenergic receptor antagonists, are categorised as Class II anti-arrhythmic drugs. Beta-blockers limit the effect of catecholamines in phase 4 of the cardiac action potential, particularly affecting nodal tissue. Cardioselective beta-blockers include Metoprolol and Bisoprolol. Beta-blockers are effective for ventricular rate control in patients with fast atrial fibrillation due to their depressant effect on atrio-ventricular (AV) nodal conduction. However, they may also cause hypotension, as well as numerous other side-effects such as fatigue, and are not recommended for use in patients with asthma or chronic obstructive pulmonary disease (COPD).

Class III

Class III anti-arrhythmic drugs slow the re-entry of potassium into the cell during phase 3 of the action potential, resulting in prolongation of the refractory period and hence the QT interval. Sotalol and Amiodarone are considered to be 'mixed class', as Sotalol is also a beta-blocker, and amiodarone additionally affects the sodium and calcium channels. Amiodarone is indicated for both atrial and ventricular arrhythmias, even in patients with structural heart disease. However, it is associated with numerous serious side-effects that include pulmonary fibrosis.

Class IV

Class IV anti-arrhythmic drugs are the non-dihydropyridine calcium channel blockers (CCBs), such as Verapamil. These drugs prolong the refractory period of the AV node and reduce myocardial contractility, by slowing the influx of calcium into the cell during phase 2 of the action potential. CCBs may be suitable for patients with atrial arrhythmias and SVTs, although due to their negative inotropic effect, they may cause hypotension and should consequently be administered with caution.

Other drug treatments for arrhythmias

Certain drugs used to treat arrhythmias, such as Digoxin, Adenosine and Isoprenaline are not included this classification, as they do not affect the cardiac action potential.

Digoxin will reduce the ventricular rate in atrial arrhythmias and is often indicated in patients with atrial fibrillation and heart failure. Adenosine causes rapid, transient blockade of the AV node that is useful for treating patients with SVTs caused by re-entry mechanisms. Isoprenaline is a beta-adrenergic receptor agonist administered to increase the rate of depolarisation of the SA node.

Anti-coagulation, using Warfarin or a non-vitamin K oral anti-coagulant (NOAC), such as Rivaroxaban, may be indicated for stroke prevention in patients with atrial arrhythmias.

Therapeutic procedures for cardiac arrhythmias

A range of therapeutic procedures is available to treat patients who experience symptoms associated with cardiac arrhythmias.

Pacing

Cardiac pacing is primarily used to augment cardiac output by increasing heart rate in patients experiencing symptomatic bradyarrhythmia. When the patient is haemodynamically compromised, emergency cardiac pacing can be delivered using transcutaneous pacing controlled by an Automated External Defibrillator (AED) or via a transvenous pacing wire advanced into the right ventricle and connected to an external pulse generator. Epicardial pacing may be suitable for patients immediately following cardiac surgery.

When a permanent pacemaker is required, a small device is inserted into a subpectoral pocket, with one or two electrodes advanced into the right atrium and/or right ventricle to deliver single or dual chamber pacing. The pacemaker is capable of sensing underlying cardiac activity and delivering a small electrical current to trigger depolarisation when required to maintain a safe heart rate. Many permanent pacemakers are rate-responsive to facilitate adjustment of the patient's heart rate based on their level of exertion. Recent advances in technology have led to the development of wireless pacemakers.

Synchronised direct current cardioversion

Patients who become severely haemodynamically unstable due to the sudden onset of tachyarrhythmias may require synchronised direct current cardioversion (DCCV) to restore sinus rhythm. This involves a transthoracic electric shock that is timed by the defibrillator to coincide with the QRS complex, to avoid delivering the shock during ventricular repolarisation (T wave), which can induce the 'R on T' phenomenon that can trigger Torsades de Pointes or ventricular fibrillation. Cardioversion should be conducted while the patient is under sedation with appropriate airway management.

Catheter ablation

Radio-frequency ablation and cryoablation are invasive percutaneous interventions used for symptomatic tachyarrhythmias. The origin of the

arrhythmia must first be established before a catheter is advanced via the femoral circulation to the site where radiofrequency waves or cryotherapy is delivered to destroy the tissue that triggers the arrhythmia. This treatment is particularly useful for arrhythmias caused by a re-entry mechanism such as A-V re-entry tachycardia (AVRT), A-V nodal re-entry tachycardia (AVNRT) and atrial flutter. Ablation may also be administered during cardiac surgery, particularly for atrial fibrillation.

Implantable Cardioverter Defibrillators (ICDs)

Implantable Cardioverter Defibrillators (ICDs) may be offered to patients who have life-threatening ventricular arrhythmias. A small device is implanted in a sub-pectoral pocket, from which electrodes are advanced into the right atrium and right ventricle. The ICD has the same capabilities as a permanent pacemaker, but in addition can detect and respond to tachyarrhythmias. The response is individually programmed within each ICD, usually involving initial anti-tachycardia pacing followed by a series of electrical shocks until sinus rhythm is restored. This may be extremely uncomfortable for the patient, who may lose consciousness during the event.

Cardiac resynchronisation therapy (CRT)

Cardiac resynchronisation therapy (CRT) may be offered to patients with advanced heart failure to optimise left ventricular function. CRT-P refers to the use of biventricular pacing that requires placement of three electrodes. The right atrial and ventricular electrodes facilitate dual chamber, rate-responsive pacing. An additional electrode activates the left ventricle from its position in the coronary sinus, accessed via the right atrium. Stimulation and depolarisation of the three chambers is individually timed to optimise ventricular diastolic and systolic function. A defibrillator function may be added to the device for patients at risk of VT associated with heart failure (CRT-D).

Cardiogenic shock

Cardiogenic shock is a severe form of acute heart failure, diagnosed when the patient shows signs of organ hypoperfusion, such as cyanosis, confusion and oliguria, in the absence of hypovolaemia, with a systolic blood pressure below 90 mmHg.

History

Cardiogenic shock usually occurs immediately following an acute cardiovascular event, such as acute coronary syndrome (ACS), tachyarrhythmia, myocarditis, thoracic aortic dissection or pulmonary embolus.

Signs and symptoms

Patients in cardiogenic shock present with symptoms associated with acute heart failure, including severe dyspnoea, ankle swelling and reduced level of consciousness. Peripheral and central pulse assessment will usually reveal tachycardia and jugular venous distension. Systolic blood pressure will be less than 90 mmHg; pulse pressure and mean arterial pressure are likely to be low, indicating reduced stroke volume and poor organ perfusion. Cardiorespiratory auscultation may reveal pulmonary crackles and third and fourth heart sounds. Signs of peripheral and central cyanosis may be present, such as cool, clammy skin that is mottled in appearance. Peripheral oedema is highly likely to be present.

Assessment and investigations

Patients with suspected cardiogenic shock should undergo rapid assessment and should be cared for in a high dependency environment. Observations should include assessment of airway, respiratory rate, depth and use of accessory muscles alongside continuous pulse oximetry. The patient should be commenced on continuous 3-, 5- or 12-lead cardiac monitoring. Insertion of an arterial line will provide continuous mean arterial pressure monitoring and permit regular arterial blood gas analysis. Central venous cannulation is useful for both invasive haemodynamic monitoring and inotropic drug administration. An echocardiogram should be conducted to establish the extent of ventricular dysfunction. A urinary catheter should be inserted and fluid balance closely monitored. A blood glucose level should be recorded and serum blood samples taken for natriuretic peptides, troponins, urea and electrolytes, lactate, C-reactive protein (CRP), D-dimer, liver function and thyroid function tests, full blood count and a clotting screen. A 12-lead ECG should be recorded promptly to rule out ACS as the cause of cardiogenic shock. If ACS is suspected, patients should have immediate coronary angiography, followed by primary percutaneous coronary intervention (PCI), if indicated.

Treatment

The aim of treatment for patients in cardiogenic shock is to improve organ perfusion by improving cardiac output and blood pressure. Administration of intravenous inotropes such as Dobutamine, and vasopressors such as Norepinephrine, may improve mean arterial pressure but will also induce tachycardia, which may prove detrimental. These drugs may be combined if there is insufficient response or insertion of an intra-aortic balloon pump may provide an alternative means of improving organ perfusion. Mechanical devices, such as the left ventricular assist device, can provide a bridge to cardiac transplantation or provide symptomatic relief for patients with end-stage heart failure.

D

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) refers to a spectrum of myocardial disorders resulting in ventricular dilatation and systolic impairment. DCM is the most common type of cardiomyopathy and causes significant morbidity and mortality; DCM is a major cause of sudden cardiac death and is also the most frequent cause of heart failure.

History

There are multiple aetiologies for DCM including idiopathic, familial (genetic), viral, toxic, alcoholic or ischaemic. Familial (genetic) DCM is caused by mutations in the structural proteins which comprise the cardiac myocytes. Ischaemic DCM is the result of the remodelling process of the left ventricle in response to injury, with a consequent reduction in ejection fraction. Toxins, such as anti-cancer therapies (anthracyclines), alcohol and infections (viral, bacterial, fungal or parasitic) are also implicated in damage to the contractile processes in the heart. Autoimmune and infiltrative causes, such as systemic lupus erythematosus or amyloidosis, are rare. Pathologically, there is an increase in myocardial mass and a reduction in ventricular wall thickness. The heart becomes globular in shape with diffuse ventricular dilatation, atrial enlargement, thrombus formation in the atrial appendages and development of an intraventricular conduction delay.

Signs and symptoms

Patients with DCM may present with symptoms of heart failure, arrhythmias, conduction defects (bundle branch blocks), thromboembolism or sudden death. Common features are fatigue, breathlessness, chest pain, palpitations and fluid overload. Syncope or palpitations at rest are worrying symptoms as they may predict sudden cardiac death. Onset of symptoms may be slow and insidious or sudden and acute, dependent on the aetiology. Mitral regurgitation is a common feature in DCM and patients may present with a left ventricular heave and a pan-systolic murmur on auscultation.

Assessment and investigations

Careful history taking is essential to establish the aetiology and to identify reversible and secondary causes. Risk factors, such as excessive use of alcohol, past medical history of cancer or recent febrile events, may point to the aetiology. Patients with high risk symptoms, such as syncope or palpitations on exertion, should be treated with a high index of suspicion.

Vital signs should be carried out to evaluate the temperature (infectious causes), heart rate and rhythm (atrial and ventricular arrhythmias), respiratory rate and oxygen saturation (heart failure). Physical examination will include palpation of the heart for apical thrill, left ventricular heave and auscultation of the heart for evidence of mitral regurgitation. A 12-lead ECG should be performed and may reveal widespread T wave and ST-segment changes, arrhythmias (ventricular arrhythmias are common), conduction defects, particularly right bundle branch block (RBBB) or left bundle branch block (LBBB). Continuous monitoring should be commenced to monitor for these abnormalities.

Echocardiography is the cornerstone of diagnosis and will assess ventricular size and function and valvular impairment. Regular echocardiography is utilised to guide and evaluate efficacy of management. Coronary angiography should be undertaken to exclude coronary artery disease. Chest X-ray will demonstrate global dilatation of the heart and may show pulmonary oedema in heart failure.

Treatment

Initial evaluations are tailored to finding the cause, thereafter treatment is aimed at optimising cardiac function. Patients in heart failure are treated with beta-blockers, ACE inhibitors and diuretics. In patients with New York Heart Association (NYHA) III/IV heart failure, cardiac resynchronisation therapy and implantable cardioverter defibrillator (ICDs) are appropriate. In some cases, cardiac transplantation may be a suitable treatment option.

H

Heart blocks

Atrio-ventricular (AV) blocks, commonly referred to as heart blocks, are bradyarrhythmias resulting from AV nodal dysfunction. Interference with AV nodal conduction results in several forms of block, which may cause haemodynamic instability.

History

Heart blocks may be transient or permanent. They can arise from degenerative disease affecting the AV node associated with advancing age or from administration of pharmaceutical agents such as beta-blockers, calcium channel blockers, Digoxin and Amiodarone. Vasovagal episodes, myocardial ischaemia, inflammation or trauma resulting from cardiac surgery, such as transcutaneous aortic valve implantation (TAVI) or valve replacement, may also induce heart block.

Signs and symptoms

Patients may be asymptomatic with heart block, although bradycardia may cause fatigue, dyspnoea, pre-syncope, syncopal symptoms on exertion and hypotension. Assessment of the patient's ECG is necessary to identify and differentiate heart block.

- **1st degree AV block** (Figure 19.1): characterised by PR interval prolongation (>200 ms). QRS duration will be normal. The patient's pulse will be regular, but the rate may be normal or < 60 bpm.
- **2nd degree AV block Mobitz Type I (Wenckebach)** (Figure 19.2): characterised by progressive prolongation of the PR interval and intermittent loss of QRS complex. Pulse and ventricular rate will be irregular and usually < 60 bpm.
- **2nd degree AV Block Mobitz Type II** (Figure 19.3): characterised by a PR interval that is fixed, and often normal, and sudden loss of QRS complex.
- 2:1 block is characterised by an alternating pattern of P, QRS and T followed by a P wave which is not conducted.
- **3rd degree (complete) AV Block** (Figure 19.4): characterised by dissociated atrial and ventricular rhythms. The SA node gives rise to the regular atrial rhythm, which bears no correlation to the ventricular rhythm, which will either be a regular, normal QRS (<100 ms) rhythm at a rate of 40–60 bpm (junctional escape rhythm); or a regular, wide QRS (>100 ms) rhythm at a rate of 20–40 bpm (ventricular escape rhythm).

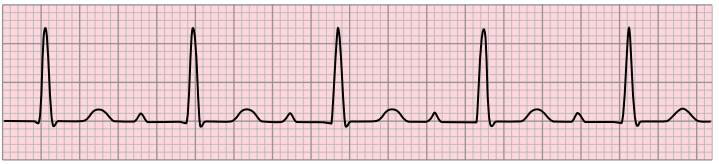

Figure 19.1 1st degree AV block.

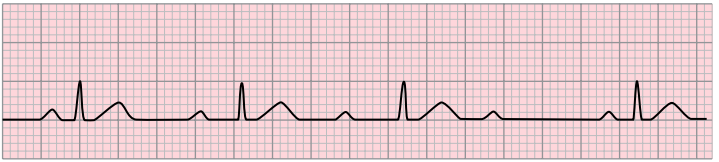

Figure 19.2 2nd degree AV block Mobitz Type I (Wenckebach).

Figure 19.3 2nd degree AV block Mobitz Type II.

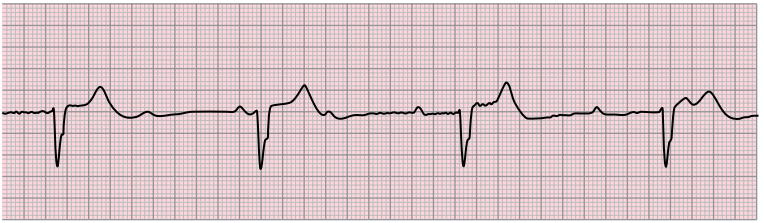

Figure 19.4 3rd degree (complete) AV block.

Assessment and investigations

Patients should be closely monitored for signs of haemodynamic compromise, including respiratory assessment, pulse, blood pressure and urine output. A 12-lead ECG should be recorded to rule out ischaemia as the cause and a history taken from the patient to establish any reversible cause of heart block.

Treatment

Patients who are tolerating heart block well should be closely monitored for signs of haemodynamic instability but may not require immediate intervention. Any reversible cause should be addressed immediately. Emergency treatment will be necessary if the patient shows signs of haemodynamic instability, usually associated with 3rd degree (complete) AV block. Atropine may be effective, particularly during vasovagal episodes, as it transiently inhibits the effect of the vagus nerve on the nodal tissue, but will be short-acting. Emergency transcutaneous pacing can rapidly augment cardiac output by increasing heart rate. However, it is likely to be very uncomfortable for the patient, hence opiate analgesia and/or sedation may be required. Insertion of a temporary transvenous pacing wire will be necessary if the bradyarrhythmia persists. Epicardial pacing may be a suitable alternative for the patient immediately following cardiac surgery. The patient may require a permanent pacemaker if the arrhythmia persists due to an irreversible cause.

Hypertension

Hypertension is known to cause coronary heart disease, stroke, heart failure, chronic kidney disease and peripheral vascular disease. It is defined as the level at which blood pressure (BP) could cause organ damage, currently established as 140/90 mmHg and 150/90 mmHg for patients over 80 years of age. Diagnosis should be made from a series of BP recordings and for treatment purposes is classified as stage 1 (>140/90 mmHg); stage 2 (>160/100 mmHg) and severe hypertension (systolic > 180 mmHg, diastolic > 110 mmHg).

History

The prevalence of hypertension is known to increase with age, although the exact cause cannot be identified in the majority of patients. Family history, insulin resistance, obesity and diabetes are strongly associated with elevated BP. Occasionally, a cause may be identified such as chronic kidney disease, thyroid or endocrine dysfunction.

Signs and symptoms

Patients with hypertension are often asymptomatic, although symptoms may manifest as a result of ensuing organ damage, such as coronary heart disease, stroke or kidney disease.

Assessment and investigations

BP should be recorded from the brachial artery when the patient is resting using either an automated device or, if the patient has an irregular rhythm, a manual sphygmomanometer and stethoscope. If the BP is found to exceed 140/90 mmHg, recordings should be taken on both arms and repeated during the consultation. The diagnosis should be made following ambulatory or home monitoring over the course of several days.

Patients diagnosed with hypertension should have their 10-year cardiovascular risk calculated as well as blood tests to establish creatinine, estimated glomerular filtration rate (eGFR), electrolytes, glucose, total cholesterol and HDL levels. A urine sample should be tested for protein, haematuria and albumin:creatinine ratio. A 12-lead ECG should be recorded and scrutinised for evidence of damage associated with chronic hypertension, such as left ventricular hypertrophy or left bundle branch block. An echocardiogram may be indicated for further investigation. Hypertension may cause retinopathy and hence the fundi should also be examined.

Treatment

Lifestyle modification is an essential element of treatment. Patients should be advised to take regular exercise and increase their dietary intake of fresh fruit and vegetables and reduce salt, saturated fat and

alcohol intake. Cardiovascular risk factors, such as hyperlipidaemia, diabetes, lack of physical exercise and smoking should also be addressed.

Pharmacological therapy is indicated for all patients with stage 2 hypertension or stage 1 hypertension associated with diabetes, renal or cardiovascular disease, evidence of organ damage or a 10-year cardiovascular risk of ≥20%. Patients under the age of 55 years should be offered a once daily ACE-Inhibitor or angiotensin receptor blocker. Older patients, and those of African or Caribbean descent, should be offered a calcium channel blocker. If the response is inadequate, these treatments may be combined or supplemented with a diuretic. Specialist review may be necessary, particularly if the patient is under 40 years of age or has resistant hypertension.

If severe hypertension is found, the patient should be referred to hospital for urgent specialist review. Gradual reduction of BP over 1–2 days using oral medications such as a calcium channel blocker is necessary to avoid the risk of cerebral, renal or cardiac ischaemia, unless a specific indication, such as aortic dissection, demands more rapid BP reduction with intravenous beta-blockers or glyceryl trinitrate (GTN).

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease and is the leading cause of sudden cardiac death in people under the age of 35 years in the UK. A genetic mutation results in thickened myocardium, which reduces the filling capacity of the left ventricle, inhibiting wall compliance and diastolic function, though the heart size remains normal. Syncope or pre-syncope, chest pain, heart failure and life-threatening arrhythmias may occur on exertion, although many patients remain asymptomatic and subsequently unaware of the condition.

History

HCM is caused by a genetic mutation responsible for the abnormal, chaotic arrangement of myofibrils in the ventricles that can cause arrhythmia. Significantly, this differs from the organised pattern of myofibrils seen in left ventricular hypertrophy (LVH). HCM may be identified through genetic screening of families of individuals who have the condition or who have died from sudden cardiac death. The inheritance is usually autosomal dominant.

Signs and symptoms

Patients are frequently asymptomatic with HCM although diastolic dysfunction may cause dyspnoea and other symptoms associated with heart failure. Patients may experience symptoms associated with myocardial ischaemia due to insufficient oxygenation of the enlarged ventricle, even with normal coronary arteries. Palpitations may occur due to atrial or ventricular arrhythmias. Some patients may have left ventricular outflow tract (LVOT) obstruction caused by the abnormal anterior motion of the mitral valve during systole, which may induce syncope or pre-syncopal symptoms on exertion. The first presentation may be cardiac arrest, caused by ventricular arrhythmias, most often occurring during exertion.

Assessments and investigations

Baseline observations may be normal. However, the 12-lead ECG may show increased QRS amplitude in the precordial leads, with non-specific ST-T abnormalities suggestive of LVH and ‘dagger-like’ Q waves in the inferior and lateral leads associated with septal hypertrophy. Cardiac auscultation may reveal a fourth heart sound or double apical pulsation caused by forceful atrial contraction into a stiffened left ventricle. Obstruction of the LVOT may be evidenced by an ejection systolic murmur heard at the left sternal border. A pansystolic murmur may be present reflecting mitral regurgitation. While the chest X-ray is usually normal in patients with HCM, the echocardiogram will provide diagnostic information. Symmetrical or

asymmetrical hypertrophy of the left ventricle will be seen, along with vigorous left ventricular contraction and the systolic anterior motion of the mitral valve and subsequent regurgitation. Analysis of the family pedigree is useful to establish genetic inheritance and should be used to identify family members who may also have the condition.

Treatment

Avoiding strenuous exercise and competitive sports is strongly advised, as the increased myocardial oxygen demand and subsequent ischaemia may induce life-threatening arrhythmias. Beta blockers are usually prescribed to reduce heart rate, which will enhance diastolic function and limit the occurrence of ventricular ectopic beats. Calcium channel blockers can improve ventricular compliance. Implantable cardioverter defibrillator (ICD) implantation is recommended for prevention of cardiac arrest and some patients with LVOT obstruction may benefit from permanent pacing. Patients experiencing recurrent symptoms may be offered myomectomy or percutaneous alcohol ablation to reduce the obstructive element of the septum. Genetic counselling should be offered to all patients and family members should be screened for the condition, regardless of the presence of symptoms.

I

Infective endocarditis

Infective endocarditis (IE) refers to an infection of the endocardium. The condition is relatively uncommon, but can be deadly with a high mortality and morbidity. The pathological process results from endocardial injury followed by transient or persistent bacteraemia allowing bacterial adherence to the damaged surface. Infected vegetations may develop on the heart valves, which may fragment and embolise. Additionally, the heart valve and its supportive structures may become damaged, necessitating surgical replacement.

History

IE usually occurs in the presence of existing structural heart disease (valvular abnormality, prosthetic valves or congenital heart disease) and is characteristically caused by *Staphylococcus* or *Streptococcus*. It may also be due to fungal infection or as a result of drug abuse, which may cause tricuspid valve endocarditis. IE may present insidiously with the patient giving a history of a 'flu-like' illness for several weeks. Alternatively, patients may present acutely as a result of embolic events, sepsis or heart failure.

Signs and symptoms

Symptoms of IE include night sweats, malaise, weight loss and fever. Some patients may present with acute heart failure, caused by valvular regurgitation. Petechial haemorrhages in the skin, Janeway's lesions on the palm of the hands or soles of the feet, splinter haemorrhages under the nail beds or Osler's nodes, which are painful nodules on fingers or toes, probably due to vasculitis, are all extremely rare and only seen in advanced untreated endocarditis. Many patients will have a murmur on acute presentation due to valvular regurgitation.

Assessment and investigations

Careful history taking is essential to establish the diagnosis as the non-specific symptoms may mislead or confuse. Patients in high risk groups (congenital heart disease, prosthetic heart valves) who present with a fever and new heart murmur should be treated with a high index of suspicion.

Vital signs should be carried out to evaluate the temperature, heart rate and rhythm, respiratory rate and oxygen saturation. Urinalysis may reveal proteinuria or microscopic haematuria. Physical examination will include auscultation of the heart for evidence of heart murmurs. A 12-lead Electrocardiogram (ECG) should be performed and may reveal

conduction defects, particularly AV-blocks or bundle branch block, suggesting development of myocardial abscess. Continuous cardiac monitoring should be commenced to observe for these conduction defects.

Physical examination may identify the features of splinter haemorrhages, Janeway's lesions or Osler's nodes. Blood cultures are a pivotal diagnostic tool and at least three blood samples should be taken at 30-minute intervals using meticulous aseptic techniques. The blood cultures will identify any causative micro-organisms although 30% of IE cases may be culture-negative. Serum blood tests will assess white blood cell count, C-reactive protein and ESR to assess for sepsis severity, urea, electrolytes, and creatinine will assess renal function as glomerulonephritis is common in acute IE.

An Echocardiogram will verify the presence of vegetations on heart valves, a Transoesophageal echocardiogram (TOE) provides better resolution and also enables assessment of structural dysfunction. Echocardiograms will evaluate the progress of the vegetations, assess for valve damage and detect abscess formation.

Treatment

In suspected IE, intravenous antibiotics should be commenced after the blood cultures have been retrieved. The majority of patients will require intravenous antibiotic therapy for 4–6 weeks and approximately 50% of patients require cardiac surgery to replace damaged valves. Patients are usually required to restrict physical activity whilst in hospital and consequently patients may become depressed because of the limitations to their lifestyle. IE is a serious condition with an in-hospital mortality rate of 20% and requires specialist cardiology care.

L

Long QT syndrome

Long QT syndrome (LQTS) is an inherited condition affecting the sodium and potassium ion channels of cardiac myocytes resulting in prolonged ventricular repolarisation. It can be identified on the 12-lead Electrocardiogram (ECG) as a prolonged QTc interval. Patients frequently have no symptoms but, in the event of a critically timed premature ventricular contraction (PVC), may experience the sudden onset of palpitations and syncope associated with torsades de pointes. This may deteriorate into ventricular fibrillation and therefore LQTS can potentially cause sudden death.

History

LQTS may be identified in patients with a history of cardiac events such as syncope. It can be an incidental finding on a 12-lead ECG recording or identified during a genetic screening programme. LQTS is classified by the genetic variations affecting the myocyte ion channels identified so far. The most common forms, LQT1, LQT2 and LQT3, are associated with different triggers for arrhythmia: exercise, emotion and acoustic stimuli, and rest or sleep, respectively.

Hypokalaemia, hypomagnesaemia or hypocalcaemia, bradycardia or acute myocardial infarction may cause QT prolongation, even in patients without LQTS. It can also be brought about by prolonged fasting, liquid protein diets and prescribed pharmacological treatments, such as Methadone, or specific drugs from the following groups: tricyclic anti-depressants, anti-psychotic drugs, anti-fungal agents, macrolide or quinolone antibiotics and anti-arrhythmic drugs.

Signs and symptoms

There are usually no physical signs associated with LQTS. Patients are frequently unaware of the condition until the sudden onset of palpitations and syncope, or possibly sudden death, caused by an episode of torsades de pointes. Torsades de pointes is characterised by an irregular, broad QRS tachyarrhythmia, originating in the ventricles (Figure 23.1) triggered by the occurrence of a PVC during the prolonged period of repolarisation, often referred to as the ‘R on T phenomenon’.

Assessments and investigations

In the absence of arrhythmia, the QT interval can be measured on the 12-lead ECG from the beginning of the QRS complex to the end of the T wave. Broadly speaking, the R-R interval should be less than half

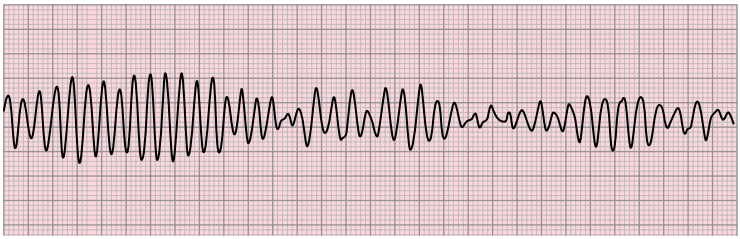

Figure 23.1 Torsades de Pointes.

the QT interval. As the QT interval is inversely proportional to heart rate, the corrected QT interval (QTc) is used for diagnostic purposes, calculated using the equation QT/√R-R interval. The QTc may be considered prolonged if greater than 440 ms in men or 460 ms in women, but often patients with LQTS have a QTc greater than 500 ms. It should be noted that short QT syndrome, another ion channelopathy similar to LQTS and Brugada, is also associated with arrhythmias.

Patients experiencing episodes of torsades de pointes will require close monitoring of respiratory function, pulse, blood pressure and continuous cardiac monitoring. 12-lead ECGs should be recorded in-between spells of the arrhythmia to establish the presence of QT interval prolongation. Previous medical history, including family and drug history, should be taken as well as blood tests, including serum potassium, calcium and magnesium.

Treatment

Torsades de pointes often self-terminates but may deteriorate into ventricular fibrillation, requiring advanced life support. Intravenous magnesium sulphate or isoprenaline may be effective, coupled with correction of electrolyte disturbance. Cardiac pacing may be beneficial to shorten the QT interval to prevent further episodes of torsades de pointes. Possible causative agents should be withheld immediately.

As there is no specific treatment for LQTS, patients are advised to avoid triggers for arrhythmia such as competitive sport, strenuous exercise, emotional distress and drugs that prolong the QT interval. Beta-blockers, cardiac pacing and implantable cardioverter defibrillator (ICD) therapy may be offered to reduce the risk of arrhythmia, although increasingly treatments vary based on the genetic type. Specialist counselling and genetic screening should be offered to the patient and their families.

M

Marfan syndrome

Marfan syndrome is an autosomal dominant genetic abnormality caused by mutation of the FBN-1 gene which encodes for the production of fibrillin, a protein essential for the formation of elastin fibre in connective tissue. Within the body, connective tissue provides scaffolding, anchorage and support for the skeletal, ophthalmic and cardiac systems. Abnormalities in fibrillin-1 cause the tissues to progressively stretch and weaken resulting in the potential for aortic root dissection, aortic regurgitation and mitral valve prolapse. Patients with Marfan syndrome may demonstrate a range of health problems throughout the body.

History

There may be a familial history, but 20–30% of patients present with a new mutation of the gene. Patients may be identified serendipitously when the ophthalmic (dislocation of the lens and myopia) or skeletal abnormalities (joint hypermobility, scoliosis, chest deformity or high arched palate) are identified. Marfan syndrome predominantly affects the mitral and aortic valve due to higher pressure in the left heart. Prolapse of both the mitral and aortic valves is common and may lead to mitral and aortic regurgitation. The aorta may also be affected; aortic root dilatation and dissecting aortic aneurysm are the consequence.

Signs and symptoms

There is a wide phenotype variation and those with milder forms of the disease may never be diagnosed. However, for patients with more severe forms of the condition, serious cardiac abnormality is evident. Sudden cardiac death can occur due to aortic dissection; left ventricular (LV) failure results from mitral regurgitation (MR) or aortic regurgitation. The regurgitant valves cause dilation of the LV and LA chambers predisposing the patient to arrhythmias, particularly atrial fibrillation (AF).

Assessment and investigations

Careful history taking, including familial history of sudden death, is helpful in establishing the diagnosis. Physical examination may uncover the physical features of Marfan syndrome. The Ghent criteria provide a nosology for diagnosis of the syndrome and genetic testing may identify the FBN-1 mutation. Investigations include echocardiogram and magnetic resonance imaging to assess the aortic valve size and

aortic root diameter. A 12-lead ECG may identify AF or LV hypertrophy and cardiac auscultation will reveal a pan-systolic murmur in MR or an early diastolic murmur associated with aortic regurgitation.

Treatment

If Marfan syndrome is diagnosed following genetic testing, yearly follow-up and family screening is recommended. Aortic root dilatation and LV function is measured regularly using echocardiography. Beta-blockers reduce the rate of aortic root dilatation and improve survival, and the angiotensin receptor blocker (ARB) Losartan has been demonstrated to be effective, too. Medical therapy aims for a systolic blood pressure of ≤ 120 mmHg. Prophylactic aortic root and/or ascending aorta graft surgery are undertaken once the aortic root dilates to greater than 5 cm in diameter. Elective repair of aortic dissection is also undertaken to prevent sudden cardiac death. Women with a diameter of ≥ 4.5 mm are advised to avoid pregnancy without prior repair and a Caesarean section delivery may be advised. All patients with Marfan syndrome are advised to avoid exertion at maximum capacity.

Mitral regurgitation

Mitral regurgitation (MR) occurs when the valve cusps fail to fully close during ventricular systole. Leakage of blood through the valve into the left atrium results in reduced stroke volume, atrial dilatation and increased pulmonary capillary pressure, causing symptoms associated with heart failure and, frequently, atrial arrhythmias.

History

Mitral valve prolapse, age related calcification, rheumatic fever, infective endocarditis, aortic stenosis and dilated cardiomyopathy can damage the valve cusps or dilatation of the annulus, causing MR and gradual development of heart failure. The left atrium will dilate to accommodate the additional volume, often causing atrial fibrillation (AF) or flutter. Haemodynamic compensation to maintain systolic function eventually results in left ventricular enlargement. Without intervention, right ventricular (RV) failure will ultimately result from raised pulmonary and RV pressure, RV dilatation and tricuspid valve regurgitation. Acute rupture of the chordae tendineae or papillary muscles will result in severe valvular dysfunction and acute heart failure.

Signs and symptoms

Symptoms of MR arise due to heart failure. Patients may describe weakness, fatigue, breathlessness on exertion, orthopnoea and paroxysmal nocturnal dyspnoea. AF or flutter can arise from left atrial dilatation, which may additionally cause palpitations. The Electrocardiogram (ECG) may show 'p mitrale', indicating left atrial dilatation, and ECG criteria associated with left ventricular chamber enlargement. A pansystolic murmur may be heard on auscultation at the apex, with S3 and gallop rhythm. Bilateral inspiratory/expiratory wheeze and crackles may also be heard, associated with pulmonary oedema. Late signs, such as peripheral oedema, jugular venous distension (JVD) and increased abdominal girth, are associated with RV failure.

Assessment and investigations

Patient assessment should include respiration rate, depth, symmetry, use of accessory muscles and peripheral oxygen saturation levels. Following pulse and blood pressure assessment, cardiac monitoring should be commenced to observe for atrial or ventricular arrhythmias. A 12-lead ECG should be recorded to exclude acute coronary syndrome (ACS) as the cause of heart failure, to identify signs of chamber enlargement and possible myocardial ischaemia. A chest X-ray will identify pulmonary oedema and cardiomegaly if present. An echocardiogram is necessary to confirm MR as the cause of heart

failure. The patient should be examined for signs of peripheral oedema, such as ankle swelling and JVD. Arterial blood gases should be taken as well as venous blood samples for urea and electrolytes (U&Es), full blood count (FBC), troponin, B-type natriuretic peptides (BNP) and glucose levels. A fluid chart should be maintained; a urinary catheter may be required to establish accurate output measurement and patient comfort.

Treatment

If the patient presents with heart failure associated with MR, oxygen therapy, diuretics and nitrates will be required. Morphine may be indicated if the patient is distressed. Supplemental treatment may be necessary for AF or flutter. Once stable, treatment should address the underlying cause where possible and aim to limit disease progression with diuretics and angiotensin-converting-enzyme inhibitors (ACE-I). Surgical repair of the mitral valve or mitral valve replacement will usually be necessary.

Mitral stenosis

Mitral stenosis occurs when calcification and fusion of the cusps reduces the diameter of the open valve. It can occur in patients with a history of rheumatic fever; most remain asymptomatic for several decades until symptoms of dyspnoea emerge. Treatment is dependent upon the severity of the condition, ranging from medical therapy to surgical replacement of the valve and annulus.

History

Mitral stenosis most frequently occurs in patients with a history of rheumatic fever in childhood, although there are other, much rarer causes. The group A β-haemolytic Streptococcus infection causes inflammation, thickening, fusion and calcification of the valvular cusps, which gradually reduces the diameter of the open valve. This limits ventricular diastole and causes a progressive rise in left atrial pressure, resulting in hypertrophy, dilatation and often atrial fibrillation (AF). Pulmonary capillary pressure subsequently increases, leading to pulmonary oedema and eventually pulmonary hypertension. Right ventricular hypertrophy and dilatation will ensue if mitral stenosis is left untreated, eventually causing tricuspid valve regurgitation.

Signs and symptoms

Patients typically experience symptoms once the valve opening has diminished from approximately 5 cm^2 to 2 cm^2, usually decades after the initial infection. The most common symptom is dyspnoea, often coupled with a cough and frothy, blood-tinged sputum associated with pulmonary oedema, caused by the raised left atrial pressure. The severity of these symptoms may worsen with episodes of AF. Eventually, elevated pulmonary pressure will cause peripheral oedema, weakness and fatigue.

The reduction in end diastolic volume causes patients to have a low volume pulse, which will be irregular if AF is present. Jugular venous distension (JVD) may occur with a prominent 'a' wave visible if the patient is in sinus rhythm. Murmurs will be evident on auscultation, usually a loud opening snap heard after the second heart sound followed by a low, rumbling mid-diastolic murmur heard best at the apex. Discolouration of both cheeks, known as malar flush, is associated with severe mitral stenosis.

Assessments and investigations

Baseline observations, cardiorespiratory assessment, chest X-ray, 12-lead Electrocardiogram (ECG) and echocardiogram are necessary to establish the diagnosis of mitral stenosis. Left atrial enlargement may be visible on the chest X-ray and seen on the ECG as a prolonged, notched P wave of > 120 ms duration (known as a bifid P wave or

'p mitrale'). The 12-lead ECG may also suggest right ventricular chamber enlargement in patients with severe mitral stenosis. These findings must be confirmed with an echocardiogram, which will establish the severity of valvular dysfunction and the extent of cardiac remodelling. Transoesophageal echocardiography (TOE) may also be used for more detailed assessment prior to percutaneous or surgical intervention.

Treatment

Symptoms associated with mild to moderate mitral stenosis may be treated with diuretics, alongside treatment for AF if required. Surgical intervention should be considered if pulmonary oedema continues, despite medical therapy or if pulmonary hypertension develops. Percutaneous trans-septal balloon valvotomy involves a balloon catheter, advanced from the femoral vein to the right atrium, where it then punctures the interatrial septum to access the left atrium and the mitral valve. The balloon is inflated to separate the cusps and then swiftly deflated and removed. Surgical valvotomy or mitral valve replacement are alternative therapeutic options that usually require cardiopulmonary bypass.

Myocarditis

Myocarditis is a life-threatening inflammatory disease affecting the myocardium. It can occur as a result of infection or from a non-infectious cause, such as sarcoidosis. The subsequent myocardial inflammation can lead to systolic dysfunction and eventually dilated cardiomyopathy, manifesting as acute heart failure, cardiogenic shock or life-threatening ventricular arrhythmias.

History

Myocarditis is most frequently caused by viral infection such as enteroviruses or Parvovirus, but can also be due to bacterial, fungal, parasitic or protozoal infection (Chagas disease). In addition to sarcoidosis, non-infectious causes include toxins, including cocaine, and autoimmune disease, such as inflammatory bowel disease.

Signs and symptoms

Diagnosis of myocarditis is notoriously difficult due to the array of clinical features associated with it, which may differ with the underlying cause. The patient may present with systemic symptoms associated with either a respiratory or gastrointestinal virus but, as the condition progresses and myocardial dysfunction ensues, chest pain, dyspnoea and other symptoms associated with heart failure may emerge.

Assessment and investigations

Patient assessment may reveal signs associated with infection and heart failure but also acute coronary syndromes (ACS), which must be rapidly ruled out. Taking a detailed history is essential as data derived from the investigations detailed below may imitate ACS. Cardiac monitoring should be commenced due to the high risk of ventricular arrhythmias and fluid balance should be closely observed.

The 12-lead Electrocardiogram (ECG) may reveal non-specific ST-T wave changes, left ventricular hypertrophy, atrial enlargement, left bundle branch block or atrial fibrillation. Cardiac troponin and B-type natriuretic peptides (BNP) are likely to be elevated along with other markers of inflammation. The echocardiogram may show wall-motion abnormalities suggestive of dilated cardiomyopathy. Cardiorespiratory auscultation may reveal signs associated with pulmonary oedema and a 3rd heart sound. Jugular venous distension may also be evident. Cardiac Magnetic Resonance imaging will enable visualisation of myocardial inflammation, oedema, necrosis and fibrosis. Endomyocardial biopsy is the gold standard diagnostic tool to enable identification of the cause of myocarditis.

Treatment

Close monitoring is essential due to the high risk of sudden death and bed rest advised to minimise myocardial exertion and to limit the extent of heart failure. Treatment for patients with myocarditis will focus on correcting arrhythmia and reducing the symptoms associated with heart failure. Drugs that might suppress ventricular contraction, such as calcium antagonists, should be avoided. Currently, no antiviral therapies for myocarditis are available. If active infection has been ruled out from the biopsy, immunosuppression therapy may be offered, particularly where non-cardiac autoimmune disease is the established cause of myocarditis. Patients may require a significant period of convalescence before returning to normal life after myocarditis, although some may not fully recover and may require cardiac transplantation.

P

Pericarditis

Pericarditis is an inflammatory disease of the pericardium. In one-third of cases it will also include inflammation of the myocardium, when it is labelled myopericarditis. Pericarditis generally presents acutely, although when associated with other pathology, the onset may be insidious. In most cases resolution is complete in 4–6 weeks, but in some cases recurrent or chronic pericarditis may develop. Pericarditis may occur following Acute Coronary Syndromes (ACS) and typically the patient may present 4–6 weeks after the acute coronary event.

History

The causes of pericarditis are varied and can be classified as infectious (viral, bacterial, fungal or parasitic) or non-infectious (neoplastic, metabolic, autoimmune or post-ACS). Infectious pericarditis will often present acutely with the patient giving a 2–3 week history of a 'flu-like' illness and the patient may have a fever. However, patients with a malignancy, an autoimmune or metabolic cause may present more insidiously and signs of the primary pathology may be the presenting feature.

Signs and symptoms

Classic presentation includes the following: chest pain, a fever, a pericardial friction rub, 12-lead ECG changes, evidence of a pericardial effusion and raised inflammatory markers. Chest pain is typically sharp, made worse by deep inspiration and improved by sitting up and leaning forwards. The pain is often very severe and incapacitating and the patient may be very anxious. A pericardial friction rub can be sporadic and heard over the left sternal edge with the diaphragm of the stethoscope.

Assessment and investigations

History taking is essential to establish the onset, duration and possible causes and to expedite early treatment. A detailed history of any recent infections, travel abroad or exposure to toxic substances should be carried out. Evaluation of the chest pain: onset, character, quality, duration and the factors which relieve and provoke the pain will inform the diagnosis. Typically the pain is described as continuous, sharp or pleuritic in character and widespread across the precordium. The patient may state that sitting up and leaning forward reduces the pain. A set of vital signs should be carried out to evaluate the temperature, heart rate and rhythm, respiratory rate and oxygen

saturation. Physical examination may include percussion and auscultation of the lungs and heart to rule out other causes of chest pain such as respiratory infections, TB or malignancies; it may also reveal the classical pericardial friction rub. A 12-lead ECG should be performed and may reveal widespread ST-segment elevation without reciprocal ST-segment changes hence differentiating it from ACS. In addition, P-R segment depression may be seen in the acute phase of presentation, and inverted T waves may develop during the resolution phase. An Echocardiogram may establish the presence of a pericardial effusion. Serum blood tests should include full blood count, urea, electrolytes, creatinine and inflammatory markers such as C-reactive protein (CRP).

Treatment

The aim of the treatment is to alleviate the patient's pain and concomitant anxiety as quickly as possible. Opiates will not be effective in pericarditis and the mainstay of medical treatment initially is to give doses of an anti-inflammatory drug either orally or rectally to relieve the acute pain. Continued use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDS) is advocated until the inflammation subsides and Colchicine may be beneficial in the long-term to prevent recurrences. The patient should be advised to rest until the symptoms resolve. Where the cause is due to systemic disease (autoimmune or renal disease, TB) or neoplasms (particularly lung and breast cancer) subsequent therapy is directed by the primary cause. Hospitalisation is only generally indicated for high risk patients or if invasive treatments are required for cardiac tamponade, large pericardial effusions, constrictive pericarditis or where cancer or metabolic disease is undiagnosed but suspected. Patients who are managed conservatively should be advised to restrict physical activity until symptom free.

S

Supraventricular tachycardia

Supraventricular tachycardia (SVT) is a term that describes a tachyarrhythmia arising above the ventricles at a rate greater than 150 bpm. This may include a number of tachyarrhythmias: atrial tachycardia, AV nodal re-entry tachycardia (AVNRT), AV re-entry tachycardia (AVRT), atrial flutter and junctional tachycardia. Atrial flutter and atrial fibrillation are considered separately in other chapters in this book.

History

Paroxysmal SVT is an umbrella term for any rhythm faster than 150 bpm, which originates above the ventricles. The term SVT is used when the exact mechanism cannot be identified from the surface ECG. Atrial tachycardia and A-V nodal re-entry tachycardia (AVNRT) may occur in healthy but susceptible individuals with no apparent underlying heart disease. A-V re-entry tachycardia (AVRT) is a re-entrant tachycardia associated with the Wolff-Parkinson-White (WPW) syndrome. SVTs may be precipitated by increased catecholamine or sympathetic tone, amphetamines and cocaine misuse, acid base or electrolyte imbalance, over exertion, or stimulants such as stress, alcohol or tobacco. SVTs may also be triggered by atrial and ventricular ectopics. The underlying arrhythmogenic mechanism in atrial tachycardia is enhanced automaticity; a re-entry mechanism for AVNRT and AVRT. The re-entry circuit may involve the AV node (AVNRT) or the AV node and an accessory pathway (AVRT) in WPW. The initiation of the tachycardia is generally sudden with the onset often precipitated by a premature atrial ectopic. There may be a brief period of asystole at the termination of the tachycardia. The tachycardia may last from a few seconds to several hours and may be paroxysmal, persistent or permanent.

Signs and symptoms

The tachycardia is accompanied by symptoms of palpitations, anxiety and evidence of reduced perfusion and cardiac output: dizziness, breathlessness and syncope or pre-syncope. The rapid heart rate increases the workload of the heart and also reduces diastolic filling time, hence reducing myocardial perfusion, causing chest pain and possibly precipitating heart failure and cardiogenic shock. Syncope may occur after termination of the arrhythmia due to the brief period of asystole experienced.

Assessment and investigations

Cardiac monitoring or 12-lead ECG recording will enable identification of a regular, narrow QRS complex tachycardia with a rate of between 150 and 250 bpm (Figure 29.1).

In atrial tachycardia, the rhythm arises from rapid firing of an atrial ectopic focus. P waves will be present but abnormal in morphology, R-R intervals are regular and the conduction ratio is 1:1, the ventricular rate is extremely fast, usually in the range of 140–180 bpm but can be as fast as 250 bpm, at which point AV block will develop to reduce the ventricular rate. Atrial tachycardia usually begins and ends suddenly and may occur in short bursts or be present for prolonged periods.

AVNRT is twice as common in women, may occur spontaneously or is triggered by noxious stimulants. It may also terminate suddenly or continue until medical intervention occurs. AVNRT arises due to the presence of a fast and slow conducting pathway within the AV node. In normal sinus rhythm, the impulse proceeds through the AV node, utilising the fast pathway. However, in AVNRT, if an atrial ectopic occurs early, the fast pathway is refractory and the slow pathway transmits the impulse to the ventricles. The impulse then travels backwards up the fast pathway which has recovered its excitability and this initiates a 're-entry tachycardia'. On the ECG, the ventricular rate is 140–250 bpm, and atrial impulses are either hidden within or occur after the QRS due to retrograde conduction. The QRS complex is usually narrow, unless a bundle branch block is present.

In AVRT there is a macro re-entry circuit created by the incomplete separation of the atria from the ventricles during foetal development of the heart. Abnormal collections of myocardial fibres (known as accessory pathways) are invested through the AV groove allowing a large circuit including the AV node, Bundle of His and the accessory pathway to conduct a fast reciprocating tachycardia. Patients with this anatomical abnormality, who also have symptomatic tachycardia, have a syndrome known as Wolff-Parkinson-White (WPW) syndrome. If the accessory pathway (known as the Bundle of Kent) excites the ventricles early during sinus rhythm, the excitation wave depolarises the ventricles abnormally (pre-excitation) and this manifests on the ECG

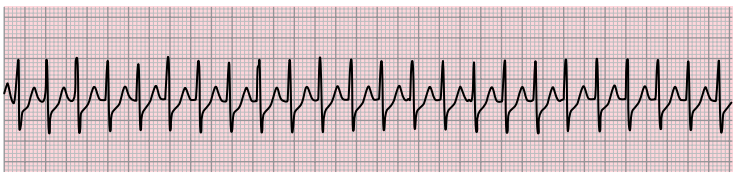

Figure 29.1 Supraventricular tachycardia (SVT).

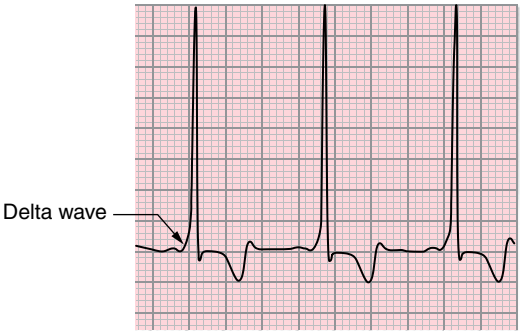

Figure 29.2 WPW pattern.

as a short P-R interval (due to bypass of the AV node) and a wide QRS with a slurred upstroke known as a delta wave (Figure 29.2). If a tachycardia develops, the circuit evolves from the atria to the ventricles via the AV node and enters retrogradely via the accessory pathway. This tachycardia is known as orthodromic AVRT. The tachycardia is fast, 140–180 bpm, with a narrow QRS complex (delta waves are absent), the P waves are seen after the QRS and before the T wave due to retrograde conduction.

Patients should be closely monitored for signs of haemodynamic compromise, including respiratory assessment, pulse, blood pressure and urine output. A lengthy period of tachycardia may cause cardiomyopathy and this may induce polyuria. A 12-lead ECG should be recorded and a history taken from the patient to establish any precipitant causes of the SVT and to enable differentiation of the possible type of SVT.

Treatment

In emergency situations, identification of the type of SVT may be difficult but the treatment is essentially the same. If the patient is haemodynamically stable, vagal procedures, such as the Valsalva manoeuvre may be effective. Examples include blowing into a syringe or facial immersion in cold water. Emergency treatment will be necessary if the patient shows signs of haemodynamic instability such as hypotension, pulmonary oedema or circulatory collapse. Bolus doses of intravenous adenosine will cause transitory AV block due to its short half-life, which generally terminates the SVT. Patients should be advised that the side-effects include flushing, chest pain and a sense of impending doom, but these symptoms are brief and will dispel quickly. An emergency electrical cardioversion under sedation with airway support may be necessary if the adenosine is not successful. Following resolution of the tachycardia, further investigation of causes should be undertaken and a cardiology referral made.

T

Takotsubo cardiomyopathy

Takotsubo cardiomyopathy (TC) is characterised by acute presentation of chest pain and/or dyspnoea due to sudden onset of left ventricular (LV) systolic dysfunction, classically triggered by an emotional or physical stressor such as anger, sadness or acute physical illness. The condition was first described in 1990 and initially it was thought that TC only affected patients of Asian origin. However, since 2003, when a Caucasian patient was noted with the syndrome, the condition is now known to be a worldwide phenomenon. In Japan, a 'tako-tsubo' is a round bottomed, narrow necked pot used to catch octopus and the shape of this pot directly mimics the LV apical ballooning seen at angiography in the presentation of this syndrome. The cause is unknown but it is thought to be due to abnormal responses to catecholamine release resulting in vasospasm and transient myocardial stunning. During coronary angiography, the patient is found to have no coronary artery occlusion, despite the presence of ST-segment elevation on the 12-lead ECG. The exact prevalence of TC is not known but there is a higher prevalence amongst post-menopausal women and hence it is suspected that oestrogens may play a role in the disease. However, TC has been observed in younger women and also in men.

History

The acute phase of TC can be life threatening and is generally triggered by an acute stressor. The onset is sudden and the patient may present in a collapsed state with chest pain and/or dyspnoea of sudden onset, which may be accompanied by arrhythmias, cardiac arrest and cardiogenic shock.

Signs and symptoms

Classically patients with TC present with symptoms similar to acute coronary syndromes (ACS) such as chest pain, dyspnoea, arrhythmias and syncope. Some patients present in cardiogenic shock or cardiac arrest. As the symptoms are identical to ACS, differentiation can only be made using angiography. The coronary arteries are found to be patent but an area of hypokinesia is present in the LV, giving rise to the characteristic 'octopus pot' shape to the LV and the potential for acute heart failure.

Assessment and investigations

The patient is likely to be very distressed on presentation and reassurance is vital. Initial assessment of vital signs should include respiratory rate, oxygen saturation and blood pressure undertaken

frequently in the initial stages. The patient should be attached to a cardiac monitor to assess heart rate and rhythm and a 12-lead ECG performed. The 12-lead ECG will be abnormal and is likely to show ST-segment elevation, particularly in the anterior leads. Importantly, there may no reciprocal ST-segment depression, which differentiates this syndrome from ACS. There may also be a prolonged QT interval, which makes patients vulnerable to ventricular arrhythmias in the recovery period.

Careful history taking is essential as a preceding emotional or physical trigger may be identified. Assessment of chest pain should elicit the duration of onset, precipitating factors, nature and radiation of pain and relieving factors. The patient may be poorly perfused with reduced capillary refill and may present in acute heart failure or cardiogenic shock.

Serum blood tests will be performed including urea and electrolytes, full blood count, clotting screen and serum markers of cardiac damage such as troponin and B-type natriuretic peptides (BNP). An urgent coronary and LV angiogram should be performed within 60 minutes of presentation, which will usually demonstrate patent coronary arteries with regional wall hypokinesia and apical LV ballooning.

Treatment

Acute management is directed towards relief of myocardial ischaemia. Opiates, such as intravenous morphine, will relieve the patient's pain and distress. Antiplatelet therapy is likely to be given in advance of the angiogram but can be discontinued when normal coronary arteries are visualised. However, anticoagulation is used to prevent stroke arising from thrombus associated with the apical dilatation. Intra-aortic balloon pump for LV support may be used if cardiogenic shock develops; diuretics are used for acute pulmonary oedema. ACE-inhibitors are used to support the LV dysfunction; most patients recover normal LV function within weeks. Beta-blockers, which inhibit the sympathetic-adrenal response to stress, may be used as prophylaxis against recurrence. Nearly all patients survive and the prognosis is good.

V

Ventricular tachycardia

Ventricular tachycardia (VT) is a life-threatening arrhythmia frequently associated with Acute Coronary Syndromes (ACS) that may present as cardiac arrest. On the ECG, VT appears as a series of 3 or more premature ventricular contractions (PVCs) that occur either in short salvos that terminate independently or as a sustained arrhythmia, lasting for more than 30 seconds. Monomorphic VT produces a regular tachyarrhythmia with uniform, abnormal QRS complexes that originate in the myocardium below the Bundle of His. VT can cause severe left ventricular dysfunction and may deteriorate into ventricular fibrillation (VF).

History

Patients may experience acute symptoms associated with ACS immediately prior to developing VT. Ventricular scar tissue caused by ischaemic heart disease, cardiomyopathy, myocarditis, congenital abnormalities and systemic disease, such as sarcoidosis, can permit the development of an electrical re-entry mechanism producing VT. VT may also occur in a structurally normal heart through the mechanisms of triggered activity or enhanced automaticity. VT may be due to electrolyte imbalance, particularly hypokalaemia and hypomagnesaemia, as well as the inherited ion channelopathies, such as Long QT or Brugada syndromes.

Signs and symptoms

VT is diagnosed from the ECG, which will reveal a fast, regular rhythm with abnormal but uniform QRS complexes (>100 ms) (Figure 31.1). If P waves are visible, they will not be associated with the QRS. Reduced cardiac output during an episode of sustained VT often results in hypotension, potentially causing symptoms of pre-syncope or syncope, dyspnoea, angina or reduced level of consciousness. Clinical signs include a rapid pulse (100–250 bpm) and cannon 'a' waves in the jugular vein due to atrio-ventricular (AV) dissociation. Signs associated

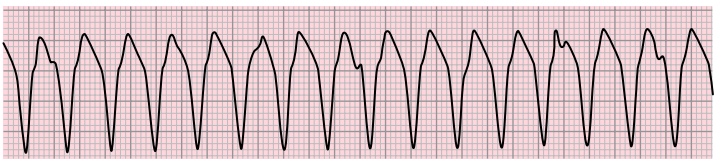

Figure 31.1 Ventricular tachycardia.

with pulmonary oedema may be evident. However, VT may be tolerated well in patients with normal left ventricular systolic function, with few signs of haemodynamic compromise.

Assessments and investigations

Patients should be rapidly and systematically assessed as VT may be life-threatening. If the patient has a pulse, continuous cardiac monitoring and regular respiratory and haemodynamic assessment, including urine output, should be conducted to closely observe for early signs of deterioration. A 12-lead ECG should be recorded and repeated once sinus rhythm has been restored to assess for myocardial ischaemia. Blood samples should include electrolytes and cardiac biomarkers to establish the cause of the arrhythmia. Regular AVPU and GCS scoring will be necessary to assess level of consciousness.

Treatment

Rapid treatment is necessary as the arrhythmia may deteriorate into VF. If the patient has already lost cardiac output (pulseless VT), advanced life support including defibrillation and airway support should be commenced. If the patient shows signs of haemodynamic compromise, such as hypotension or pulmonary oedema, synchronised electrical cardioversion may be indicated. Intravenous anti-arrhythmic drugs are suitable to restore sinus rhythm if the patient is haemodynamically stable. Identification of the cause, such as ischaemia or electrolyte imbalance, is necessary to guide the treatment to prevent recurrence. Primary percutaneous coronary intervention (P-PCI) may be indicated if ACS is suspected. Long term, an internal cardioverter defibrillator and anti-arrhythmic drug therapy should be considered as a means of reducing the risk of sudden cardiac death.

W

Wolff-Parkinson-White syndrome (Pre-excitation syndrome)

Wolff-Parkinson-White syndrome (WPW) is a congenital condition, which affects approximately 0.1–0.3% of the population. During foetal development of the heart, muscle strands or accessory pathways (APs) intersect the atrioventricular groove creating an extra electrical connection between the atria and the ventricles. This results in early excitation and depolarisation of the ventricular tissue. Most APs connect the atrial and ventricular myocardium at the mitral and tricuspid annuli and, as the APs may conduct either anterogradely or retrogradely, this creates a substrate for potential re-entry arrhythmias. In some patients there is a small risk of sudden cardiac death.

History

In WPW, the heart is usually structurally normal, although the APs also occur in association with serious congenital heart disease such as Ebstein's anomaly or transposition of the great vessels. The APs may conduct rapidly or slowly, bypassing the AV node, which has important decremental properties that protect the ventricles against fast atrial rates. If conduction across the AP is rapid, as in atrial fibrillation, a potential for life-threatening ventricular fibrillation (VF) may occur.

Signs and symptoms

The clinical features of WPW are variable, many patients remain asymptomatic, whilst others develop a variety of arrhythmias which may cause dizziness, syncope and palpitations causing them to seek medical assistance; in rare cases the first presentation may be due to cardiac arrest. In some patients, the ECG pattern of WPW is only discovered during routine ECG screening.

The arrhythmias associated with WPW include supraventricular tachycardia (SVT) and atrial fibrillation (AF). In the presence of AF, conduction to the ventricles via the AP causes a rapid, irregular rhythm with a widened QRS complex, which may deteriorate into VF.

Assessments and investigations

A focussed history and a 12-lead ECG form the basis of initial assessment. The 12-lead ECG will reveal a short P-R interval, less than 120 ms (reflecting the bypassing of the AV node) and a wide QRS (>100 ms) with a delta wave (Figure 32.1).

The delta wave is a slurring or widening of the proximal portion of the QRS complex, which reflects the early depolarisation of the

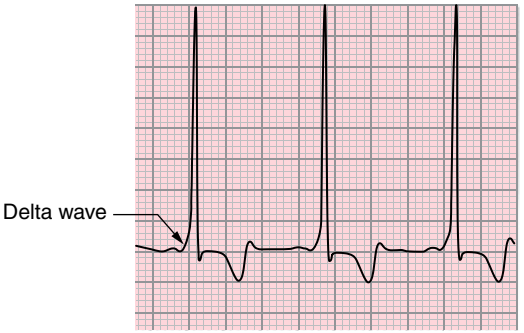

Figure 32.1 Characteristic ECG findings associated with WPW.

ventricular tissue. However, the remainder of the excitation to the ventricles is normal, thus the second portion of the QRS is normal. The QRS is therefore a fusion beat of early depolarisation via the AP and normal depolarisation via the His-Purkinje system. Abnormal ventricular depolarisation may produce QRS complexes of increased amplitude and there may also be ST-segment and T wave abnormalities, which may mimic conditions such as myocardial infarction, bundle branch block and chamber enlargement. Invasive diagnostic tests include electrophysiology studies to map the APs and to test the inducibility of arrhythmias.

Treatment

Emergency treatment for SVT or AF associated with WPW requires careful pharmacological management. Drugs which block AV nodal conduction such as Adenosine are not used, but Flecainide or Amiodarone may be suitable alternatives. Once back in sinus rhythm, the patient's ECG should be examined to rule out WPW as the cause. The long-term treatment for WPW depends on the degree of symptoms and the risk of sudden cardiac death. AP ablation is offered to patients considered at high risk of cardiac arrest.

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The Arrhythmic Patient in the Emergency Department

A Practical Guide for Cardiologists and Emergency Physicians

Massimo Zecchin
Gianfranco Sinagra
Editors

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ISBN 978-3-319-24326-9 ISBN 978-3-319-24328-3 (eBook)
DOI 10.1007/978-3-319-24328-3

Library of Congress Control Number: 2015958251

Springer Cham Heidelberg New York Dordrecht London
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Foreword

Treatment of patients with cardiovascular diseases has dramatically changed over the past 20 years. Accompanied by an incredible increase in pathophysiological understanding and availability of treatment options, specialized fields of expertise have rapidly evolved.

Electrophysiology is one of these newcomers. Based on the analysis of basic principles of electrical activation in the human heart, the field has developed into sophisticated treatment strategies of device therapy and catheter ablation. The majorities of today's EP patients originate from the mainstream of everyday clinical cardiology and present with endemic, bradycardic, and tachycardic arrhythmias.

With this background, electrophysiology has also arrived in the ER department.

Now it is our obligation to transport our knowledge and expertise for treatment of arrhythmia patients to our cardiology colleagues and specialized ER physicians who encounter emergency situations due to or accompanied by cardiac arrhythmias in a significant number of patients, next to a variety of other medical emergencies.

Dedicated literature on that topic is really scarce. I therefore want to thank the editors and authors of this book to take the challenge, efforts, and work and to bring together a vast amount of EP knowledge and to focus it to the special situation in the ER.

This book should become an integral part of training for young cardiology fellows, and it will be a practical guide and help for all medical staff involved into the management of ER patients.

Christopher Piorkowski
Head of EP Department – University of Dresden

Preface

The book is a practical guide designed for physicians (both emergency physicians and cardiologists) who first evaluate and treat patients with arrhythmias or potentially arrhythmic problems in the emergency setting. It can also be a useful learning tool for students and residents in Cardiology and Emergency Medicine.

In all chapters, every effort was made to provide a brief but comprehensive summary of the topic with both theoretical and practical suggestions, considering the different needs of the specialists involved in the primary care of arrhythmic patients.

The diagnostic pathways and treatment options of patients presenting in the Emergency Department with syncope or arrhythmias, including bradyarrhythmias, atrial fibrillation, and narrow and wide QRS tachycardias, are discussed. In addition, clear advice for the management of patients with cardiac devices and possible dysfunction, electrical storm, or a requirement for urgent surgery are provided.

Practical suggestions are offered for short-term management, e.g., regarding the decision on when to hospitalize the patient and some hints for long-term pharmacological and non-pharmacological treatment.

In the first chapter, an overview of the management of arrhythmic patients, from the emergency physician's point of view, is provided. In the second chapter, some considerations, beyond published guidelines, for the management of syncope are given by a leading expert. An extensive theoretical overview of brady- and tachyarrhythmias are then followed by practical flowcharts in Chaps. 3, 4 and 5, while in the following chapter the differential diagnosis of wide-QRS tachycardias with clear examples are discussed by one of the greatest experts in this field. Chapters 7 and 8 deal with quite rare cardiac conditions, sometimes not so known by emergency physicians and even by cardiologists, who nonetheless in such cases sometimes face difficult decisions. Differently, situations frequently observed in the Emergency Department, but with an arrhythmogenic potential which is not always well defined, are presented in Chaps. 9 and 10. Finally, in the last three chapters, some indications for the management of patients with implanted cardiac devices presenting in Emergency Department or who need urgent surgery are provided, again considering the different skills of the various medical figures involved in the primary care of such patients.

Considering the heterogeneity of the topics, some differences in the chapters' frameworks were necessary. However, the book was conceived to offer quick information and solutions to the single issues, as required in the emergency setting, rather than providing a systematic review.

Trieste, Italy Massimo Zecchin
Gianfranco Sinagra

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Management of Arrhythmic Patients in the Emergency Department: General Principles

1

Alessandro Surian and Luca Visintin

Arrhythmic patients are common in the duty of the emergency physician and the cardiology consultant. Both specialists, with their different approach and method, well know the clinical and statistical relevance of arrhythmias.

A wide range of symptoms leading the patient to the emergency department may be related to a cardiac rhythm disorder. They may vary from simple palpitations to a cardiac arrest. Otherwise, the diagnosis of arrhythmia can be made in patients who came to the ED for other diseases.

Emergency physician is the first doctor approaching the patient and must initially define the hemodynamic state induced by the arrhythmia. The need to assure hemodynamic stability must be assumed as the first important target and should not be delayed by any other consideration.

Once a stabilization is obtained, the consultant cardiologist can improve diagnostic and therapeutic definition. A tight cooperation between the two specialists warrants the best patient outcome.

1.1 Triage

Triage of arrhythmic patient must focus on hemodynamic state and time of onset of symptoms and signs. Unstable arrhythmias should be admitted as soon as possible to physician evaluation, while asymptomatic patients may wait longer.

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© Springer International Publishing Switzerland 2016

M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_1

Hemodynamic criteria for quick admission are:

- SBP (systolic blood pressure): <90 mmHg
- DBP (diastolic blood pressure): <60 mmHg
- Heart rate per minute: >120 and <50 bpm
- Respiratory rate per minute: >30 and <10
- Body temperature: >39.0 °C and <36.0 °C
- Sat O_2: <90 %

Moreover, chest pain, dyspnea, acute heart failure, acute altered mental status, and signs of shock are evaluated during triage.

Unstable patients should be addressed immediately to the shock room of the ED, while stable patient can wait or be addressed to an examination room provided with ECG for a first evaluation and subsequently be treated when the adequate setting is available [1, 2].

1.2 Emergency Department Physician Approach to the Arrhythmic Patient

Emergency physician's main task is to identify "*hemodynamically unstable*" patients, quickly evaluating parameters like level of consciousness, ventilation, oxygenation, heart rate, and blood pressure (Table 1.1). Clinical evaluation is focused on the investigation of signs of shock (altered mental status, cool and clammy skin, weak and rapid pulse, rapid and shallow breathing, anxiety, lightheadedness, chest pain, decrease of urine, thirst and dry mouth, hypoglycemia, confusion, nausea, lackluster eyes) dyspnea and tachypnea, or oxygen desaturation.

Patient's ECG, blood pressure, and O_2 saturation (sat O_2) should be immediately put under continuous monitoring and intravenous line with blood samples provided. Airways have to be kept patent, breathing assisted, and oxygen given if sat O_2 is below 94 %. A 12-lead ECG should be obtained as soon as possible for a correct diagnostic evaluation of the arrhythmia. Medical history must be gathered.

Table 1.1 First steps

Look for:
shock signs
Chest pain
Respiratory distress
Do:
Monitor the patient, IV line, blood samples
Ensure patent airway and ventilation and give oxygen (if needed)
Support perfusion pressure (use mean arterial pressure as a good index)
12-leads ECG; gather medical history
Treat reversible causes

Should a cardiac arrest occure, advanced life support protocols have to be applied.

Hemodynamic instability, defined as an acute organ failure or a near-cardiac arrest situation, may be due to tachy- or bradyarrhythmia.

In the event of a tachyarrhythmia, an immediate defibrillation or synchronized cardioversion should be done regardless of the arrhythmia mechanism.

In addition, bradyarrhythmias may lead to a severe decrease in cardiac output, causing hemodynamic instability with hypotension, mental dizziness, decreased consciousness level, cyanosis, dyspnea, etc.

A treatment based on atropine, catecholamine, or an electrical stimulation may be helpful or even lifesaver [1, 2].

1.2.1 Tachyarrhythmia

By definition, tachycardia is a heart rate exceeding 100 beats per minute.

By far the most common tachycardia diagnosed in the emergency department is sinus tachycardia.

In the healthy patient, it is a physiological response to physical stress or anxiety. Sinus tachycardia is also a normal condition during the pregnancy. In most other cases, it is due to an underlying pathological condition (e.g., fever, dehydration, anemia and hypoxia, ACS, P.E., hyperthyroidism, high blood pressure, smoking, alcohol, beverages containing caffeine, medication side effects, abuse of recreational drugs, such as cocaine, or imbalance of electrolytes) [3].

"Appropriate" sinus tachycardia offsets an underlying condition, while "inappropriate" sinus tachycardia can be a consequence of deficit of vagal tonus or a hyperactivity of/excessive sensibility to the sympathetic nervous system. During sinus tachycardia heart rate is usually lower than 140–150 bpm, even if, in young people under extreme stimulation, it can exceed 220 bpm. Typically, in sinus tachycardia, the P wave is positive in inferior and lateral leads (as in sinus rhythm). As sympathetic activation increases AV conduction, PR interval is shorter than in sinus rhythm; therefore, with few exceptions, the coexistence of long PR and sinus tachycardia is unlikely, even in patients with I degree AV block during normal sinus rhythm, and usually suggests other mechanisms of tachycardia, as atrial tachycardia or atrial flutter, possibly with 2:1 conduction and a P wave hidden within the QRS complex.

In order to identify if the tachycardia is the main cause of the patient's symptoms, a complete physical examination, blood draw to test metabolic and renal function, emogasanalysis (EGA), 12-lead ECG results and medical history should be performed and any potential reversible causes should be corrected.

Usually tachycardia may be considered as hemodynamically significant when they exceed 150 bpm.

However, it is important to remark that even frequencies lower than 150 bpm may cause hemodynamic compromise, mainly if it is sustained for a prolonged time and/or coexists with an underlying heart disease, leading to chest pain, altered mental status, pulmonary edema, or cardiogenic shock, requiring an emergency electrical cardioversion.

It is advised to perform an effective pre-procedural sedation if the patient is conscious, although hemodynamically unstable.

1.2.1.1 Procedural Sedation/Anesthesia During Cardioversion

Sedative or dissociative drugs, coupled with or analgesics, are used to relieve the patient from unpleasant procedures. Many of these drugs can lead to central nervous system and cardiac and/or respiratory depression. Given the potential risks, regulatory agencies are debating about the medical privileges needed to perform this procedure, particularly about the presence of an anesthesiologist during the procedure.

Recommendations for a safe employ consist of a proper setting (ECG, respiratory rate, sat O2, NIBP monitoring, advance life support trained personnel, devices for life support) and frequent reevaluations (prior to, during, and after procedure); trained staff should choose appropriate drugs and dosing depending on the distinctive features of each patient.

A growing literature highlights the safety of administration of ketamine, midazolam, fentanyl, propofol, and etomidate in the ED [4–6].

- *Equipment and supplies*: oxygen, suction, reversal agents, advanced life support medications and equipment, defibrillator, and CO_2 capnography. An IV line should be set; reversal agents should be available whenever opioids and benzodiazepines are administered.
- *Personnel*: during the procedure, personnel dedicated to patient monitoring should focus only to the sedation and not to other tasks.
- *Training*: the physician should know drug's pharmacology of the agents used and their antagonists. Personnel with experience in Advanced Cardiac Life Support should be present.
- *Drugs*. Electrical cardioversion is a brief but painful procedure. Light sedation is inadequate for a pain-free relaxed patient. Therefore, a moderate to deep sedation and analgesia or general anesthesia is required. In most US and Europe hospitals, emergency physicians are not allowed to provide general anesthesia, so sedation can be the only option if an anesthesiologist is not present. Drugs: midazolam and fentanyl are commonly used, but their long-lasting effects make them not handy or straight dangerous. Instead, for a brief and titratable deep sedation, it makes more sense to employ propofol, etomidate, or methohexital combined with fentanyl. There are contradictory statements from the American Society of Anesthesiologists (ASA) guidelines about authorization for propofol use by emergency physicians. Evidence is accumulating that non-anesthesiologist-administered propofol sedation has a safety and efficacy profile comparable or superior to that provided by benzodiazepines with or without opioids. Medications should be administered gradually, allowing sufficient time between dose and effect assessment. Concurrent administration of sedative and analgesic drugs requires evaluation on dose reduction.
- *Recovery*: observation should be prolonged until there are no more risks for cardiorespiratory depression. Medical institution should set up appropriate discharge criteria [4–6].

1.2.1.2 Cardioversion/Defibrillation

If cardioversion is chosen, set the defibrillator into the synchronized mode. This to avoid shock delivery during ventricular "electric vulnerability" period (apex and descending branch of T wave), a potential trigger of ventricular fibrillation. Defibrillation, used for interruption of pulseless VT, VF, and torsade de pointes synchronization, should be avoided, as QRS complexes may not be identified.

Emergency physician should be trained to recognize the presence of the P wave and distinguish between narrow-complex (supraventricular) tachycardia and wide complex tachycardia, which in condition of urgency should be considered and treated as ventricular tachycardia.

The different types of tachycardia can be treated with different energies:

- As recommended by international guidelines for regular narrow-complex tachycardia, the initial energy cardioversion should be 50–100 J with biphasic defibrillators and 200 J if monophasic (Class IIa, LOE B).
- For irregular narrow-complex tachycardia, the recommended initial biphasic energy is 120–200 J (Class IIa; LOE A).
- Regular wide complex tachycardia may resolve after discharge at 100 J by both biphasic and monophasic defibrillators (Class IIb, LOE C).

Anyway, if the first shock is inadequate to resolve the arrhythmia, increase energy "in a stepwise fashion."

When using monophasic defibrillators, initial energy should be set to 200 J, proceeding in a stepwise fashion in the event of failure.

The irregular wide complex tachycardia should be treated with high-energy unsynchronized shock (i.e., defibrillation), because of the difficulty of the machine to distinguish between the QRS complex and T wave.

Even if there were doubts whether the tachycardia is monomorphic or polymorphic, the shock should not be delayed and a high-energy unsynchronized shock must be delivered.

In the unstable patient (if not hypotensive) presenting with a regular narrow QRS complex tachycardia, *adenosine* is safe to be used while cardiac electrical cardioversion is being set up both for therapeutic (in case of tachycardia involving the AV node as a part of the reentry circuit) and diagnostic (in case of atrial arrhythmias, unmasking atrial activity slowing AV conduction (Class IIb (LOE C)).

If the patient with tachycardia is stable, the emergency physician will have more time for a correct diagnosis and to choose the most appropriate therapy, with the help of a cardiologist if necessary.

After obtaining a complete medical history and a careful physical examination, QRS complex evaluation is needed. QRS duration should be measured in at least two orthogonal derivations: narrow-complex tachycardia (QRS duration <120 ms) should be always considered, by definition, as supraventricular: examples are sinus tachycardia, atrial fibrillation (AF), atrial flutter, AV nodal reentrant tachyarrhythmia (AVNRT), tachyarrhythmia mediated by accessory pathways, atrial tachycardia, multifocal atrial tachycardia (MAT), and junctional tachycardia (rare in adults) .

Based on ECG findings, the regularity of RR intervals and the relationship between P waves and QRS complexes along with the timing of onset of tachycardia may help to differentiate among the various kinds of supraventricular tachyarrhythmia.

If the anamnesis highlights sudden onset of palpitations and its rapid resolution, it is likely to be atrial fibrillation, atrial flutter, AVNRT, atrioventricular reciprocating tachycardia, and atrial tachycardia. Instead, sinus tachycardia, permanent atrial fibrillation, and permanent flutter, together with MAT and premature atrial contractions, show symptoms that arise and resolved more gradually [7].

P waves immediately preceding the QRS complexes address the ED physician's diagnosis to sinus tachycardia, atrial tachycardia, multifocal atrial tachycardia or multiple atrial premature contractions.

P waves following QRS complexes suggest atrioventricular nodal reentrant tachycardia, atrioventricular reciprocating tachycardia, or atrial tachycardia. However, heart rate can be high enough to have T waves overlapping the P waves.

If tachycardia has a narrow QRS complex, vagal maneuvers and, if ineffective, the administration of adenosine at doses of 6–12 mg, (always under cardiac monitoring) may have a dual purpose:

- *Diagnostic*, since the increase of degree of AV block can unmask the nature of the underlying rhythm; a transient slowing of ventricular rate may highlight atrial fibrillation, atrial flutter, and sinus tachycardia, while there might not be any effect on multifocal atrial tachycardia or frequent atrial premature contractions.
- *Therapeutic*, because the increase in parasympathetic tone may slow electrical conduction through the AV node interrupting reentrant arrhythmias involving tissues sensitive to vagal stimulation (AV nodal reentrant tachycardia, AV reciprocating tachycardia, and sometimes atrial tachycardia).

If vagal maneuvers and adenosine are unsuccessful in converting to sinus rhythm or atrial fibrillation and atrial flutter are diagnosed, it is recommended to administer:

- *Diltiazem* (15–20 mg or 0.25 mg/kg IV over 2 min); if needed, after 15 min an additional IV dose of 20–25 mg (0.35 mg/kg) can be administered; the infusion dose is 5–15 mg/h, titrated according to heart rate.
- *Verapamil* (2.5–5 mg IV bolus over 2 min); if no response and non-drug-induced adverse events occur, it is possible to repeat doses of 5–10 mg every 15–30 min up to a total dose of 20 mg.
- *Beta-blockers* (metoprolol, atenolol, propranolol, esmolol, and labetalol).

These drugs are able to convert the reentrant tachycardia by acting on the nodal tissue or slowing the ventricular response in case of other supraventricular arrhythmias [1].

In patients with atrial fibrillation/flutter/tachycardia lasting more than 48 h (or if the onset of the arrhythmia is unknown), electrical or pharmacological cardioversion should not be attempted in absence of adequate anticoagulation in the

preceding 3 weeks. Otherwise, when prompt restoring of sinus rhythm is needed or preferred, cardioversion can be done after excluding the presence of thrombi in the left atrium by transesophageal echocardiography (Class IIa, LOE B) [8].

In most cases the patient with narrow QRS tachycardia is treated in ED, restoring the RS or starting a therapy aimed to control the heart rate, and resigned to be entrusted to the outpatient cardiologist, who will complete the diagnostic process and improve, if necessary, the treatment started in the emergency department.

Handling of wide-QRS complex tachycardia (>120 ms) is different. These tachycardias cannot be treated in PS only but require both an initial cardiac evaluation in the emergency department, including a careful analysis of the ECG and echocardiography, and hospitalization in the specialist department.

1.2.1.3 When should the Cardiology Consultant be called?

Cardiologist called in ED for a patient with a wide-QRS complex tachycardia has a daunting task. In fact, a mistaken diagnostic may lead to disastrous effects in terms of prognosis.

A wide-complex tachycardia can be:

- Ventricular tachycardia.
- Supraventricular tachycardia in a patient with preexisting bundle branch block.
- Tachycardia-dependent bundle branch block (aberrancy).
- Tachycardia caused by drug that have a widening effect on QRS.
- Atrial arrhythmias in the presence of ventricular pre-excitation.

In the diagnostic path of a wide-QRS complex tachycardia, attention must be paid to the clinical examination (variability of the first tone and amplitude variable radial pulse lay for the presence of AV dissociation) and the careful analysis of the ECG [9].

Here is a summary of some general criteria that can help the cardiologist identify the origin of tachycardia (for detailed discussion of the ECG, see Chap. 6):

A. Search if the electrical activity of the atria is present; P waves, independent of QRS, are separated by constant intervals, paying more attention in derivation II and V1, where these waves can be easier to find.

   If some ventricular impulses are not conducted to the atria and the QRS/P ratio is greater than 1, a diagnosis of ventricular tachycardia can be made.

   Small deflections, fitting in a rhythmic manner inside the QRS complexes, suggest the presence of underlying sinus P waves when their rate is lower than the ventricular rate. Hence, a diagnosis of ventriculoatrial dissociation and therefore of ventricular tachycardia can be made. If there is a mathematical relationship between ventricular and atrial electrical activity, a retrograde ventricular-atrial conduction is likely, as it can be found in about 50 % of cases..

   In presence of a clear QRS/P ratio = 1, the diagnosis may be more difficult; it may be expression of atrial tachycardia, sinus rhythm with aberrant conduction, nodal reentrant tachycardia, automatic junctional tachycardia, reciprocating orthodromic tachycardia with aberrant conduction, or ventricular tachycardia with 1:1 retrograde conduction.

B. Search for "concordance" aspect of QRS in the precordial leads. The presence of concordance suggests that the tachycardia has a ventricular origin. Common definitions are "*positive concordance*" if the QRS complex is "R wavelike" from V1 to V6 and "*negative concordance*" in the presence of a "QS-like" morphology from V1 to V6.

   Cardiologists must remember that although a negative concordance is absolutely specific for VT, the positive could, in rare cases, be expression of a pre-excited tachycardia due to a left posterior Kent bundle (pre-excited tachycardia with conduction through ancillary pathway).

C. As stated by Brugada et al., in the diagnostic algorithm of regular wide-QRS complex tachycardia, the presence of RS complexes (R waves followed by S wave) in precordial leads suggests a diagnosis of VT when the interval between the beginning of the R wave and nadir of the S wave is >100 ms [10].

D. The analysis of QRS complexes, in particular in leads V1 and V6, is certainly useful.

In a wide-QRS complex tachycardia with right bundle branch block (positive QRS in V1), morphologies R, Rs, RrĐ, qR in V1 and QS, qR, rS in V6 are suggestive of ventricular tachycardia.

A three-phasic morphology of V1 (rsR' and rSR'), biphasic morphology in V1 (rRĐ), or three-phasic morphologies in V6 (qRs) suggest a supraventricular genesis with aberrant conduction.

In wide-QRS complex tachycardia with left bundle branch block (negative QRS in V1), an initial R wave >30 ms in V1, an interval between the beginning of the QRs complex and nadir of the S wave >60 ms, the presence of a notch in the descending limb of the S wave, and Q wave in V6 (qR aspects, QRS or QS) suggest a ventricular origin of arrhythmia.

Initial R wave <30 ms and an interval between the QRS onset and the S wave nadir <60 ms are suggestive of supraventricular tachycardia with aberrant conduction.

The maneuvers of vagal stimulation can be useful in the diagnosis of wide complex tachycardia, and depending on the response, we can obtain important information:

- If the tachycardia ceases, a supraventricular reentrant tachycardia is likely (but in some cases even the idiopathic ventricular tachycardia is resolved with the vagal stimulation).
- Modifications of the atrioventricular conduction in atrial tachycardia and atrial flutter can be observed.
- In ventricular tachycardia with ventriculoatrial (VA) 1:1 conduction, a variation of VA interval or transient second-degree retrograde VA block may be recorded.

1.2.1.4 Treatment of a Wide-QRS Complex Tachycardia

As mentioned earlier, if the patient gets worse and becomes unstable, staff must be ready to perform an *immediate electrical cardioversion* or to deliver high-energy unsynchronized shock, if ventricular fibrillation emerges or instability is caused by a polymorphic VT.

When diagnostic doubts about the origin of tachycardia are present, it should be treated as if it were of ventricular origin.

In presence of regular and monomorphic complexes, it is reasonable to administer *adenosine*, considered safe, and useful for both diagnosis and treatment purposes (Class IIb, LOE B). Adenosine should not be administered if the patient is unstable or has irregular or polymorphic complexes: in this condition, it could lead to degeneration in VF (Class III, LOE C).

Once diagnosed a ventricular tachycardia, treatment consists of antiarrhythmic drugs such as *procainamide* (Class IIa, LOE B), *amiodarone* (Class IIb, LOE B), or *sotalol* (Class IIb, LOE B) or *electrical cardioversion*.

In patients with known long QT during sinus rhythm, procainamide and sotalol should be avoided.

Procainamide is administered in the initial dose of 10 mg/kg, at rate of 20–50 mg/min. Maximum dose is 17 mg/kg. Maintenance infusion is 1–4 mg/min.

Amiodarone is given 150 mg IV over 10 min; dosing should be repeated to a maximum dose of 2.2 g IV for 24 h.

If an antiarrhythmic drug was already administered without success, it is advisable not to use a second drug without a cardiologist consult (Class III, LOE B) or proceed with electrical cardioversion (Class IIa, LOE C).

Lidocaine is now considered a drug of second choice for the treatment of ventricular tachycardia (dose: 1–1.5 mg/kg IV bolus). Maintenance infusion is 1–4 mg/kg (30–50 mcg/kg per min).

If the wide-QRS complex tachycardia is irregular, the underlying rhythm is likely to be an atrial fibrillation with aberrant conduction. In this case some considerations about the best treatment (rate control or rhythm control) are necessary, in particular:

- Avoid cardioversion if the arrhythmia has been present for more than 48 h (and the patient is stable enough). Consider treatment options with the consultant cardiologist, in particular transesophageal echocardiography to exclude the presence of a thrombus in the left atrium.
- Administer IV *heparin* before cardioversion if not contraindicated.

Irregular polymorphic tachycardia needs an immediate defibrillation. Drugs that may prolong the QT interval should be withdrawn and serum electrolytes corrected.

Myocardial ischemia is the most common cause of polymorphic VT in absence of a prolonged QT interval. In this circumstance amiodarone and sotalol are able to reduce the recurrence of the arrhythmia (Class IIb, LOE C).

1.2.2 Bradycardia

A heart rate below 60 bpm is usually defined as bradycardia. While in young healthy subjects and particularly in athletes it can be a common and non-suspect remark, it can conceal various kinds of diseases.

Usual symptoms of bradycardia are asthenia, fatigue, dyspnea, chest discomfort or pain, pre- or complete loss of consciousness, light-headedness, and decreased level of

consciousness. Signs often noticeable are hypotension and/or orthostatic hypotension, diaphoresis, bradycardia-related (escape) frequent premature ventricular complexes, or other ventricular tachyarrhythmias. All the signs and symptoms are due to the discrepancy between the low heart rate and the metabolic requests of the organism.

Usually symptoms are relevant when lower than 40 bpm or higher in presence of a pre- or coexistent cardiac disease [1, 2, 11–13].

First approach: whatever is the underlying cause, ED physician must define the hemodynamic compensation. If low heart rate is the cause of the symptoms, the patient should be immediately treated with drugs and percutaneous or transvenous pacing. The consultant cardiologist should be called to provide support to the diagnosis and treatment.

If the bradycardia is asymptomatic or the hemodynamic condition is acceptable, the thorough diagnosis can be ruled out with more smoothness.

As soon as possible, a 12-lead ECG should be obtained, with a long stripe in II or V1, to unmask atrial activity, for example, the presence of not-detected 2:1 AV block. A complete physical examination and blood tests for troponin, drugs, electrolytes, and serum creatinine must be performed in the meanwhile. If available, an echocardiogram should be used. Chest X-rays or thoracic echography can help to clear up pulmonary edema or congestive heart failure [1, 2, 11, 12].

Based on the ECG findings, we can discern the following rhythms:

1.2.3 Sinus Bradycardia

It can be a sign of underlying pathologies (e.g., vagal hypertonia, drug effect, hypoxia, ischemia of sinoatrial node due to occlusion of right coronary arteria, etc.).

ECG shows a regular sinus rhythm with heart rate lower than 60 bpm and a constant 1:1 AV conduction with PR interval of 120–200 ms (in the absence of coexistent AV block); P waves are regular, with identical waveform, axis between 0 and 90°.

Symptoms can be absent at rest and may appear only during effort.

Common causes are listed in Table 1.2.

Table 1.2 Common causes of sinus bradycardia

Vagal stimulus	Vomit, abdominal pain (i.e., acute retention of urine, acute abdomen, aortic aneurysm), Valsalva maneuver, carotid sinus hypersensitivity
Drugs	β-blockers, Ca^{++} channel blockers, ivabradine, digoxin, amiodarone, quinidine, and virtually all the antiarrhythmic drugs
Hyperkalemia	Acute or chronic heart failure, ACE-I or K+ savers drugs
Hypothermia	
Hypothyroidism	Autoimmune diseases, inappropriate levothyroxine dosage in known hypothyroidism
Endocranial hypertension	Acute endocranial hemorrhage
Sinoatrial node hypoperfusion	Right coronary ischemia
Sinoatrial sick syndrome	

It is clear from the analysis of the abovementioned causes how crucial it is to find the underlying etiology of the sinus bradycardia [14].

1.2.4 Pitfalls

Not maintaining a high and broad index of suspicion for underlying causes

1.2.5 Low-Rate Atrial Fibrillation

It is characterized by the absence of recognizable P wave, irregular RR intervals, and narrow or wide QRS complexes depending on the previous history of the patient.

Most common causes are drugs (as most antiarrhythmic drugs, digoxin, β-blockers, Ca^{++} antagonists), especially in older patients with reduced renal and/or liver function, vagal hypertonia (mainly in young subjects), or atrioventricular (AV) block. The presence of complete AV block ventricular rate is regular, because of junctional (usually at about 35 bpm) or infrahisian ventricular escape (<30 bpm).

Treatment of symptomatic extreme bradycardia consists in drugs (amines) or transcutaneous or intracardiac transvenous pacing to reach hemodynamic stability.

In elderly patients the most bradyarrhythmias are drug related and will wear off as the involved drugs (e.g., digoxin, β -blocker) wash out; in some cases consider starting with atropine followed by amines [7].

1.2.6 Sinus Node Dysfunction: Sick Sinus Syndrome

Sick sinus syndrome is a condition characterized by a wide spectrum of rhythm disturbances: bradycardia, sinusal arrest, paroxysmal atrial tachycardia, and bradycardia/asystole.

Clinical appearance ranges from asthenia, mental dizziness to syncope, vertigo, and cardiac failure.

Common causes are idiopathic degeneration of sinoatrial node and/or the atrial conduction tissue, right coronary ischemia, and flogistic and infiltrative diseases. More often drugs can be blamed, as beta-blockers, digoxin, Class I and III antiarrhythmic agents, and Ca++ channel blockers.

Tricyclic antidepressant, 4-phosphodyesterase inhibitors and Beta stimulant may induce atrial tachyarrhythmia.

Diagnosis can be reached by anamnesis, ECG, dynamic ECG (Holter, loop recorder), and electrophysiological study (endocavitary or transesophageal).

Depending on the prevalence of tachy- or bradycardia and the underlying cardiac disease, the therapy can vary from drugs to definitive pacing.

Indications for pacemaker implant are symptoms related to bradycardia.

1.2.7 Atrioventricular (AV) Blocks

AV blocks are commonly caused by:

- Lesions of the electrical conduction system of the heart (necrosis, fibrosis, sclerosis)
- Vagal hypertonia (inferior acute myocardial infarction, hypersensitivity of carotidal sinus, vagal maneuvers, abdominal pain, etc.)
- Increase of the refractory period (drugs)

Based on clinical and ECG findings, AV blocks are divided into:

- First-degree AV block (*prolonged* AV conduction *without any AV interruption*)
- Second-degree AV block (*intermittent* AV conduction)
- Third-degree (or complete) AV block (*complete* interruption of AV conduction)

1.2.8 First-Degree AV Block

PR interval is >200 ms with all P waves conducted to the ventricle; it is most commonly iatrogenic in patients treated with β- and Ca + channel blockers and digoxin or can be secondary to vagal hypertonia; less often the cause is an acute coronary syndrome of the right coronary artery involving AV node [15].

1.2.9 Second-Degree AV Block Type I (Wenckebach: Mobitz I)

There is a progressive increase of the PR interval, until a P wave is not followed by a QRS complex. The block is usually located in the AV node ("suprahisian"). Most common causes are drugs (β- and Ca^{++} channel blockers, digoxin) and vagal hypertonia. It can also be secondary to ischemia of the AV branch of the right or the circumflex coronary artery. It can rarely evolve to a higher degree AV block. Therefore therapeutic options are based on the identification of the causes and usually require no more than observation. When symptomatic and if vagal tone is involved, atropine 0.5 mg IV bolus (up to 3 mg in total) can transiently improve clinical status.

1.2.10 Higher Degree AV Blocks (Second-Degree AV Block Type II and Third-Degree AV Block)

Advanced AV blocks are a severe condition, which can quickly evolve into hemodynamic instability and/or cardiac arrest.

1.2.11 Second-Degree AV Block Type II (Mobitz II)

One or more P waves are not followed by a QRS complex without a progressive increase of the PR interval. Causes can be drugs (β- and Ca^{++} channel blockers,

digoxin, and other drugs as lithium) or a damage of the conduction pathways. It can be related to an acute coronary syndrome sometimes involving the left anterior descending coronary or one of its septal branches. It may easily evolve to a third-degree block or asystole, so it should be closely monitored.

1.2.12 Third-Degree AV Block

The ECG in the complete AV block shows a complete dissociation between atrial and ventricular activity with the complete absence of any AV conduction. Depending on the level of the block (suprahisian or infrahisian), the QRS morphology and ventricular rate can be different: in suprahisian block, escape rhythm arises from the AV junction (usually at 35–40 bpm, with narrow QRS complex); in infrahisian block, the rhythm arises from the ventricle; rate is less than 30 bpm with wide QRS complex.

In the presence of acute coronary syndrome, suprahisian blocks are usually secondary to an ischemia of the right coronary artery, while infrahisian blocks are frequently due to a huge ischemia within the interventricular septum due to a stenosis/occlusion of the left anterior descending coronary. Suprahisian blocks, like second-degree AV block type I, can be secondary to ischemia of the AV branch of the right or circumflex coronary artery and are usually more benign and recover spontaneously.

Complete AV block may also be related to drugs reducing AV conduction (β- and Ca^{++} channel blockers or digoxin) or reducing intraventricular conduction (as most antiarrhythmic drugs, leading to infrahisian blocks).

1.2.13 Accelerated Idioventricular Rhythm

In the presence of increased automaticity, ventricular rate may be higher than sinus rate (especially in the presence of sinus bradycardia), despite not exceeding 100/min. It is usually benign and asymptomatic; it can be a sign of reperfusion during acute coronary syndromes and should be treated only in presence of significant symptoms or hemodynamic impairment with drugs increasing sinus rate amines and atrial or ventricular pacing.

1.2.14 Treatment:

Treating an advanced-degree AV block requires fast choices [11–13, 16, 17]:

If hemodynamically unstable (Table 1.3):

- Activate the cardiologist for an IV pacing; discuss with him about the value of a coronarography when acute coronary syndrome is likely.
- As soon as possible, start transcutaneous pacing (with sedation).
- If not available, start drugs: dopamine (2–10 mcg/kg/min) or adrenaline (2–10 mcg/min).

Table 1.3 Unstable bradyarrhythmias

Treatment basic points consist in:
ECG, blood pressure, heart rate, respiratory rate, sat O_2 monitoring, hemodynamic assessment
Drugs: atropine, adrenaline or dopamine, isoproterenol
Guarantee the normal hemodynamic state
Emergency pacing should be considered if the need to maintain hemodynamic stability is imminent. As obvious this can be used only as a temporary means to bring the patient to a more stable solution (e.g., IV pacemaker)

If stable:

Evaluate the patient, and collect medical and drugs history; discuss with the cardiologist the management.

1.2.15 Pitfalls

- Confounding third-degree AV block with other bradyarrhythmias, in particular when similar atrial and ventricular rate are present ("iso-rhythmic dissociation"). It is necessary to evaluate very carefully the presence of the P wave (especially in leads V1 and DII) and the correlation with ventricular activity.
- Know your drugs: Atropine is quite ineffective on infrahisian blocks; amines increase oxygen consumption; isoprenaline–isoproterenol may provoke ventricular tachyarrhythmias, so it should be avoided, if possible, in the presence of ischemia.
- Always check if the transcutaneous pacing is achieving consistent capture by checking the femoral pulse.
- A low heart rate may not always be the cause of symptoms; it can be just a sign of other diseases. For example, sinus bradycardia and hypotension may be due to the vagal response in the presence of aortic dissection or Cushing's reflex during intracranial hypertension; in acute renal failure, elevated serum potassium can lead to significant bradyarrhythmias, while dehydration in prerenal acute renal failure can be the cause of the hypotension.

1.2.16 When Should the Consultant Cardiologist Be Called?

Any hemodynamic instability requires immediate intervention and support by the cardiologist to define the underlying causes and to help in the treatment.

High-degree AV blocks should be admitted to a monitoring-capable structure. Drugs withdrawn and indication to permanent pacemaker implantation have to be defined with the cardiologist [13].

A drug-related bradyarrhythmia may resolve after withdrawing the proarrhythmic treatment and requires amines or only temporary pacing.

Not all bradyarrhythmias need to be admitted into a cardiology ward. In the absence of high-degree AV block, stable patients may be safely admitted into medicine ward or even considered for discharge with an outpatient clinic follow-up program [1, 13, 17].

1.2.17 Definitive Pacemaker Indications

Briefly, indications to permanent pacing, in absence of transient or correctable causes, can be summarized as follows [19]:

Alternating or progressive bundle block (right bundle alternating with left bundle, right bundle + left anterior alternating with left posterior fascicular hemiblock)

Second-degree type II AV block: requires pacing when hemodynamically unstable and when the block is located in His bundle or below, even in asymptomatic patients

Third-degree AV block: indicates pacing in all acquired types, associated with syncope, hemodynamic instability, HR <40 bpm, or RR >3000 ms pauses

In older patients it's often difficult to determine the real cost/benefit ratio of a permanent pacemaker, and the balance between conservative and aggressive therapy should be discussed.

Absence of symptoms, a basal heart rate greater than 40 bpm, and the capacity of substitutive rhythm to increase the rate during physical activity may allow an observational strategy instead of a pacing immediate intervention [17].

1.2.18 A Suggested Algorithm/Pathway for Diagnosis and Treatment

	What to do	**How to do**
All patients	Assess hemodynamic status	Clinical evaluation NIBP, HR, RR, sat O2, body temperature monitoring, IV access
	Identify arrhythmia	ECG
	Identify underlying causes	Medical history, clinical evaluation, ECG, labs, EGA, echocardiography, chest X-ray, expert consulting
	Treat hemodynamic instability	Treat reversible causes; administer appropriate drugs; consider cardioversion or pacing if indicated

Tachyarrhythmia		**What to do**	**How to do**
		Treat instability	Perform immediate cardioversion (with procedural sedation if possible)
		Identify arrhythmia	ECG
	If narrow QRS complex		Manual maneuvers, adenosine if regular, beta-blockers, or Ca++ channel blockers. Consider rhythm control (CVES or drugs) if onset <48 h or rate control ± anticoagulant therapy if >48 h. Consider cardiologist consultant. Admit to ward if poorly tolerated hemodynamic status, severe or evolving underlying pathology, and uncontrolled heart rate regardless initial therapy
	If wide QRS complex		Consider adenosine only if regular monomorphic QRS is present; antiarrhythmic infusion, cardiologist consulting. Admit to ward if evolutive organic cardiopathy, persistence of tachyarrhythmia regardless antiarrhythmic therapy, polymorphic tachycardia, poorly tolerated hemodynamic status

Bradyarrhythmia	**What to do**	**How to do**
	Treat instability	Use atropine, dopamine, adrenaline, or isoprenaline or isoproterenol or perform immediate transthoracic pacing (with procedural sedation if possible). Consult the cardiologist
	Sinus bradycardia	Hemodynamic support, atropine. Identify and treat the underlying causes
	Identify arrhythmia	ECG
	Sick sinus syndrome	Dynamic ECG loop recorder, cardiologist evaluation; consider pacemaker implant
	If First-degree A V block or Second-degree AV block type I	Identify and treat underlying causes. Admit to ward if poorly tolerated hemodynamic status, severe or evolving underlying pathology, uncontrolled heart rate regardless initial therapy
	If high-degree AV blocks (II type II or III)	Be prepared to pace; consult the cardiologist. Admit to a monitoring capable ward

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Syncope: First Evaluation and Management in the Emergency Department

2

Franco Giada and Andrea Nordio

2.1 Epidemiology of Syncope

Epidemiological studies conducted in the USA have estimated that 30 % of the general population experience at least one episode of syncope in their lifetime [1], which is responsible for about 1–3 % of admissions to the emergency department (ED) and 1–3 % of hospitalizations [2]. In Italy, syncope accounts for 1–2 % of both admissions to the ED and all hospitalizations [3–7]. About half of the patients attending emergency facilities for syncope are subsequently hospitalized; the mean duration of hospitalization is about 8 days [3–7]. Moreover, in industrialized countries the progressive aging of the population, together with the higher prevalence of syncope among elderly subjects, are likely to increase the impact of syncope on healthcare systems in the near future [6].

2.2 Costs of Syncope

The fact that syncope may be caused by pathological conditions that have a severe prognosis, together with the lack of a diagnostic gold standard, results in frequent hospitalization and the prescription of numerous costly instrumental investigations, which increase healthcare costs. One North American study [8] estimated in 1993 that the mean annual cost per patient hospitalized for syncope was US$4132. In the case of recurrent syncope, this figure rose to US$5281. In the USA the total annual

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_2

cost of syncope amounts to $2.4 billion, similar to that for chronic respiratory diseases and human immunodeficiency virus. In studies conducted in Italy, the mean cost per patient hospitalized for syncope is reported to vary from €1000 to €3000 [9]. These costs are chiefly conditioned by the duration of hospitalization and by the number and type of diagnostic investigations carried out.

Thus, syncope places a considerable burden on healthcare resources. The implementation of an appropriate diagnostic and therapeutic strategy for tackling the problem of syncope in the ED therefore constitutes a challenge from clinical, organizational, and economic standpoints.

2.2.1 Difficulties in the Management of Patients with Syncope in the ED

Syncope is defined as a self-limiting transient loss of consciousness (TLOC), which usually causes falls. The onset of syncope is relatively sudden and the recovery is spontaneous, complete, and rapid. The underlying pathophysiological mechanism is transitory global brain hypoperfusion [10].

The first difficulty encountered in ED in the management of patients who present with TLOC is to distinguish syncope from losses of consciousness (Fig. 2.1) not caused by cerebral hypoperfusion (e.g., epilepsy, metabolic disorders, vertebrobasilar transient ischemic attack, hypoxia), or from conditions with only apparent loss

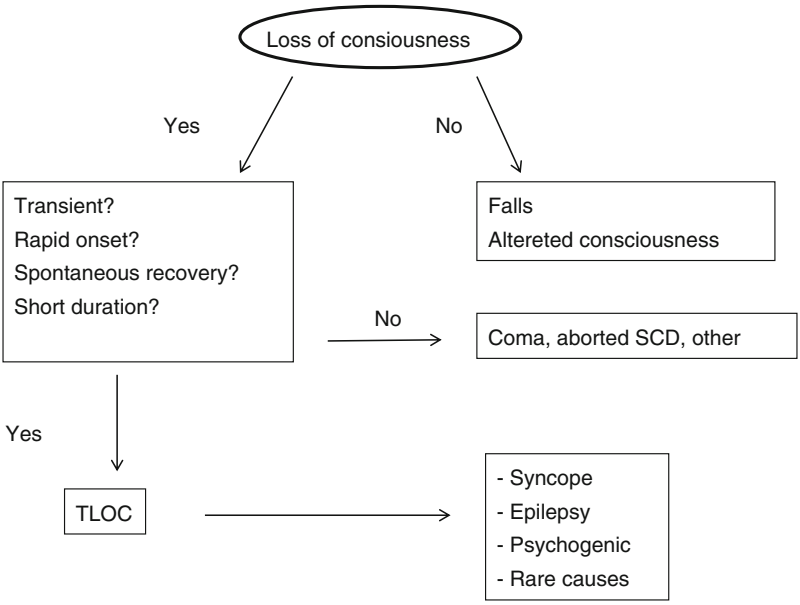

Fig. 2.1 Context of transient loss of consciousness. *SCD* sudden cardiac death, *TLOC* transient loss of consciousness

Table 2.1 Conditions incorrectly diagnosed as syncope

Disorders with partial or complete LOC (without global cerebral hypoperfusion)
Epilepsy
Metabolic disorders including hypoglycemia, hypoxia, hyperventilation with hypocapnia
Intoxication
Vertebrobasilar TIA
Disorders without impairment of consciousness
Cataplexy
Drop attacks
Falls
Functional (psychogenic pseudosyncope)
TIA of carotid origin

LOC loss of consciousness, *TIA* transient ischemic attack

of consciousness (drop attack, cataplexy, psychogenic pseudosyncope, accidental falls in the elderly) [10] (Table 2.1). Moreover from an etiological standpoint, syncope is classified within three main groups: neuromediated or reflex (representing the epidemiologically prevalent cause of syncope), orthostatic, and cardiac (arrhythmic or structural, the second most common cause of syncope). Each of these groups comprises numerous disorders that may manifest in the form of syncope and are not always easy to evaluate (Table 2.2). Finally, the prognostic significance of syncope depends on the underlying pathology, ranging from the generally benign prognosis seen in neuromediated syncope to the more severe prognosis associated with cardiac syncope.

This syncope often raises diagnostic and therapeutic problems which is proved by the diversity of the pathways followed by patients attending the ED. Indeed, data from the literature [4–7] reveal that these patients may be hospitalized in cardiology, neurology, pediatric, geriatric, internal medicine, and orthopedic wards. These patients then undergo, often inappropriately, several instrumental examinations that are costly and have a low diagnostic yield. The result is that hospitalization is prolonged and healthcare costs rise, while a correct diagnosis of the cause of syncope fails to be reached in a high percentage of cases. As the risk of malpractice suits is high in this field, ED physicians often adopt a strategy of "self-defense," which results in an increase of the number of hospitalizations and inappropriate instrumental investigations. Thus, the current management of syncope displays little diagnostic efficacy and considerable economic inefficiency.

The factors underlying these disappointing results can be summed up as follows: insufficient competence and attention on the part of physicians with regard to the differential diagnosis of TLOC, owing to the difficulty of tackling this problem in a multidisciplinary manner; a "defensive" stance prompted by the possible legal implications of a wrong diagnosis; and, in various healthcare institutions, the lack of diagnostic and therapeutic facilities specialized in the management of syncope patients [11, 12].

Table 2.2 Classification of syncope

Neurally mediated syncope
Vasovagal cause
Mediated by emotional distress (fear, pain, instrumentation blood phobia)
Orthostatic stress
Situational
Sneeze, cough
Gastrointestinal stimulation (defecation, abdominal pain, swallowing)
After micturition
After exercise
Postprandial
Others
Carotid sinus syncope
Forms without apparent triggers or atypical presentation
Orthostatic hypotension syncope
Primary autonomic failure
Pure autonomic failure, multiple atrophy, Parkinson disease with autonomic failure
Lewy body dementia
Secondary autonomic failure
Diabetes, amyloidosis, uremia, spinal injuries
Drug-induced orthostatic hypotension
Alcohol, vasodilators, diuretics, antidepressants
Volume depletion
Hemorrhage, diarrhea, vomiting, etc
Cardiovascular syncope
Arrhythmia as primary cause
Bradycardia: sinus node dysfunction, AV conduction system disease, implanted device dysfunction
Tachycardia: supraventricular, ventricular
Drug-induced bradycardia and arrhythmias
Structural disease
Cardiac: valvular diseases, AMI, hypertrophic cardiomyopathy, etc
Others: acute aortic dissection, pulmonary hypertension, pulmonary embolus

2.2.2 The Recommended Management of Syncope in the ED

Most of the direct cost of syncope is attributable to hospitalization. A proper diagnostic evaluation and prognostic stratification of syncope in the ED should limit hospitalization to patients suffering from heart disease, serious neurological diseases, or severe secondary traumas.

In 2009 the European Society of Cardiology developed guidelines on the management of syncope [10]. This document defined what has become the current standard for the management of patients with TLOC and the most valuable diagnostic pathway, and gave recommendations on indications and interpretation of diagnostic tests with indications for hospitalization and treatment.

According to the guidelines, the cornerstone in syncope management in the ED is the initial clinical evaluation, i.e., history, physical examination, recumbent and orthostatic blood pressure measurement, and electrocardiogram (ECG).

Patients should be interrogated about:

- The circumstances (position and activity of the patient, presence of predisposing factors) and symptoms (nausea, dizziness, palpitations) occurring just before the attack
- Manner of fall (slumping or kneeling over), duration, and whether movements were present during LOC (if witnessed)
- Number, frequency of spells, and age at first episode
- Family history of cardiac disease or sudden death, neurological history, metabolic disorders

Consultation by a cardiologist is indicated when a cardiac cause is suspected or ascertained, particularly in cases of:

- Presence of definite heart disease, family history of sudden death, or channelopathy
- Syncope during exertion or in supine position
- Sudden onset of palpitation prior to the syncope

ECG abnormalities such as intraventricular delay with QRS duration >120 ms, Mobitz II second-degree atrioventricular block, sinoatrial pauses >3 s, nonsustained ventricular tachycardia, preexcitation, long or short QT intervals, Brugada pattern, negative precordial T waves suggestive of right ventricular dysplasia, Q waves suggesting previous myocardial infarction, pacemaker/implantable cardioverter-defibrillator malfunction.

Neurological consultation (Fig. 2.2) is indicated for a nonsyncopal TLOC cause (epilepsy, transient ischemic attack, subclavian steal syndrome, psychogenic pseudosyncope), especially in cases of:

- Presence of aura before the event
- Tonic-clonic movements coinciding with the onset of LOC (and not some seconds later) or hemilateral
- Clear automatisms or tongue biting
- Prolonged confusion after the episode
- Family history of seizures, sleepiness or headache after the event

Specific tests such as neurological investigations or blood tests are only indicated for a suspicion of nonsyncopal TLOC.

This strategy requires adequate clinical competence on the part of all of the physicians involved in the management of these patients. Table 2.3 presents the diagnostic criteria that permit a diagnosis of the causes of syncope in the ED by means of initial evaluation, and Table 2.4 lists the clinical features that suggest a diagnosis.

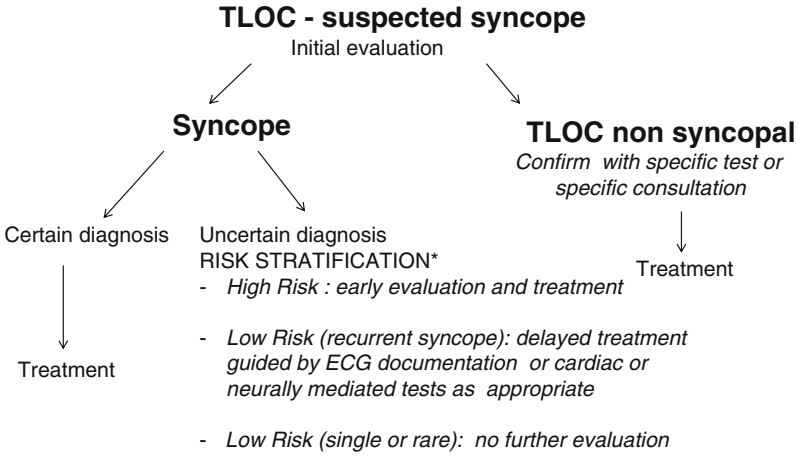

Fig. 2.2 Diagnostic flowchart of patients with suspected T-LOC.*May require laboratory investigations. *ECG* electrocardiographic, *TLOC* transient loss of consciousness

Table 2.3 Diagnostic criteria of causes of syncope with initial evaluation

Vasovagal syncope is diagnosed if syncope is precipitated by emotional distress or orthostatic stress, and is associated with typical prodrome
Situational syncope is diagnosed if syncope occurs during or immediately after specific triggers listed in Table 2.2
Orthostatic syncope is diagnosed when it occurs after standing up and there is documentation of OH
Arrhythmia-related syncope is diagnosed by ECG when there is:
Persistent bradycardia (<40 bpm in awake or repetitive sinoatrial block or sinus pauses >3 s)
Mobitz II or III degree AV block (second or third degree)
Alternating BBB (left and right)
VT or rapid paroxysmal SVT
Polymorphic VT nonsustained and long or short QT interval
PM or ICD malfunction with cardiac pauses
Cardiac ischemia related syncope is diagnosed when syncope presents with ECG evidence of acute ischemia with or without myocardial infarction
Cardiovascular syncope is diagnosed when syncope presents in patients with prolapsing atrial myxoma, severe aortic stenosis, pulmonary hypertension, pulmonary embolus, or acute aortic dissection

AV atrioventricular, *BBB* bundle-branch block, *ECG* electrocardiogram, *PM* pacemaker, *ICD* implantable cardioverter-defibrillator, *OH* orthostatic hypotension, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia, *VVS* vasovagal syncope

The ideal TLOC management should lead, through initial clinical evaluation, to an identification of the nature of the TLOC (syncope or syncope-like conditions) and, in the case of syncope, to an etiological diagnosis and a rapid stratification of patients into three categories (Fig. 2.3):

Table 2.4 Clinical features suggesting a diagnosis at initial evaluation

Neurally mediated syncope
Absence of heart disease
Recurrent syncope history
After sudden unexpected unpleasant sight, sound, smell, pain
Vomiting, nausea during syncope
Prandial or postprandial
After exertion
With head rotation or pressure on carotid sinus
Syncope due to orthostatic hypotension
After standing up
Start or changes of dosage of vasodepressive drugs
Prolonged standing (crowded hot places)
Autonomic neuropathy or Parkinsonism
Standing after exertion
Cardiovascular syncope
Structural heart disease
Family history of channelopathy or USD
Supine or during exertion
ECG findings suggesting arrhythmic syncope:
LBBB or RBBB combined with LA or LP fascicular block
Intraventricular conduction abnormalities (QRS >120 s)
Mobitz I second-degree AV block
Asymptomatic inappropriate sinus bradycardia (<50 bpm)
Nonsustained VT
Preexcited QRS complexes
Long or short QT intervals
Early repolarization
RBBB pattern with ST elevation in leads V1–V3
Q waves suggesting myocardial infarction

USD unexpected sudden death, *LBBB* left bundle-branch block, *RBBB* right bundle-branch block, *LA* left anterior, *LP* left posterior, *VT* ventricular tachycardia

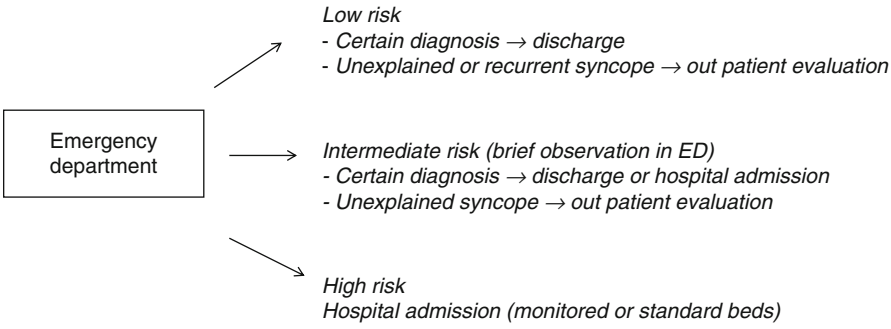

Fig. 2.3 Diagnostic pathway for the management of patients admitted to the ED for syncope

- *Low-risk patients*, who can be handled in the outpatient clinic by the general practitioner or specialist, on an ordinary time schedule, and requiring few, if any, selected examinations [15]; this group includes patients with very likely neurogenic syncope and without injuries
- *Intermediate-risk patients*, who need to be managed within a short time in a specialist outpatient clinic or by means of brief observation in the emergency department, when high risk is not evident but cannot be immediately excluded
- *High-risk patients*, who need to be hospitalized urgently and to immediately undergo appropriate diagnostic and therapeutic procedures. This group includes patients with severe structural or coronary heart disease (heart failure, severe left ventricular dysfunction, previous myocardial infarction), clinical or ECG features suggesting arrhythmic syncope (see above), or important comorbidities (Table 2.5)

Finally, the European guidelines recommend that rapid risk stratification in the ED can be achieved by using the following two scores:

- The OESIL Risk Score [12], which is easy to apply and it includes age >65 years, underlying disease, syncope without prodromes, and an abnormal ECG. A total score of 0 represents 0 % mortality and a score of 1 is associated with <1 % mortality at 1 year. Scores of 3 (mortality of 35 % derivation/29 % validation sets) and 4 (mortality of 57 % and 53 % derivation and validation sets, respectively) carry significantly greater risk.
- The EGSYS Risk Score [13], which shows that the presence of abnormal ECG and/or the presence of structural cardiac disease are the main factors predictive

Table 2.5 Clinical criteria to identify short-term high-risk patients

Severe structural CAD (HF, low LVEF, MI)
Clinical or ECG aspects suggesting arrhythmic syncope
During exertion or supine
Palpitations (during the syncope)
Bifascicular block
Intraventricular conduction abnormalities (QRS >120 ms)
Inadequate sinus bradycardia or SA block in absence of negative chronotropic medications or physical training
Preexcited QRS complex
Prolonged or short QT interval
RBBB pattern with ST elevation (V1–V3 leads)
Negative T waves in right precordial leads, epsilon waves, and ventricular late potentials (ARVC)
Important comorbidities
Anemia (severe)
Electrolyte disturbance

CAD coronary artery disease, *HF* heart failure, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *RBBB* right bundle-branch block, *ARVC* arrhythmogenic right ventricular cardiomyopathy

Table 2.6 Risk stratification at initial evaluation in OESIL and EGSYS studies

Study	Risk factors	Score	Endpoints	Results (validation cohort)
OESIL [12]	Abnormal ECG	0–4 (1 point each item)	1 year total mortality	0 % score 0
	Cardiovascular disease (history)			0.6 % score 1
	Lack of prodrome			14 % score 2
	Age >65 years			29 % score 3
EGSYS [13]	Palpitations before syncope (+4)	Sum of + and − points	2 year total mortality	2 % score < 3
	Abnormal ECG and or heart disease (+3)			21 % score ≥3
	Syncope during effort (+3)			
	Syncope while supine (+2)		Cardiac syncope	2 % score < 3
	Predisposing/precipitating factors (−1)			13 % score 3
	Autonomic prodrome (nausea, vomiting) (−1)			33 % score 4
				77 % score > 4

of mortality in 2 years; this score has a very good diagnostic yield in identifying syncope of cardiac origin (Table 2.6).

This strategic course underlines that prognostic stratification and the choice of instrumental investigations selected on the basis of the characteristics of each patient are crucial to the cost-effective management of patients with syncope in the ED [14–17].

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Management of Bradyarrhythmias in Emergency

3

Luca Salvatore, Silvia Magnani, Gerardina Lardieri, and Elena Zambon

The sudden appearance in patients of changes in heart rhythm is a situation that requires rapid diagnosis and treatment in emergency departments and intensive care units. The slowdown and block of cardiac impulse conduction form the basis of symptomatic bradycardia.

The prevalence of cardiac bradyarrhythmias and conduction disturbances in outpatients evaluated for the first time is 30–40 %, with an incidence of 3 % for atrioventricular (AV) block and sinus node dysfunction, and 8 % for disorders of intraventricular conduction [1].

Dysfunction of the sinus node has significant clinical implications. Development of concomitant AV block is not uncommon (incidence 8.4 %), as is the presence or appearance of atrial fibrillation (AF), especially in patients already treated with only ventricular pacing (incidence 22 %), with a consequent high risk of systemic thromboembolism [2, 3]. In elderly patients a low heart rate can promote the development or worsening of heart failure, even in the presence of preserved systolic function [4].

The onset of arrhythmias after cardiac and noncardiac surgery, a relatively common occurrence, is a major predictor of morbidity of surgical procedures and is associated with a prolonged hospital stay, although severe bradyarrhythmias requiring treatment occur in less than 1 % of cases. Triggers are generally transient events such as hypoxia, myocardial ischemia, excess catecholamine, or electrolyte disorders [5, 6].

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_3

3.1 Anatomy and Pathophysiology

The cardiac impulse begins in the *sinus atrial node*, located in the upper lateral wall of the right atrium near the superior vena cava, vascularized by the right coronary artery (60 %) and the circumflex artery (40 %). The impulse reaches the AV node, which, through the nodal-Hisian system, connects the atria with the ventricles. The nodal-Hisian system is formed by the *AV node* (located in the front part of the Koch triangle, vascularized by the right coronary artery) and the *bundle of His* (vascularized by both the left and right coronary artery). The bundle of His is divided into the *right branch* (vascularized by the anterior descending artery and right coronary artery) and the *left branch*, which in turn is divided into two bundles, the anterior (vascularized by the anterior descending artery) and the posterior (vascularized by the circumflex artery). From here the Purkinje fibers originate, guaranteeing simultaneous activation of the ventricles.

3.2 Bradycardia

A heart rate of less than 60 bpm is usually considered as bradycardia. The usual symptoms of bradycardia are asthenia, fatigue, dyspnea, chest discomfort or pain, prior or complete loss of consciousness, light-headedness, and decreased level of consciousness. Frequent noticeable signs include hypotension and/or orthostatic hypotension, diaphoresis, bradycardia-related (escape) frequent premature ventricular complexes, or other ventricular tachyarrhythmias. Usually the symptoms are relevant when the heart rate is lower than 40 bpm, or higher in the presence of a pre- or coexistent cardiac disease.

Hemodynamically unstable bradycardia may represent a serious life-threatening emergency, with 30-day mortality rates of up to 16 % being reported [7–9]. Bradycardia can be the expression of the dysfunction of *automaticity* or the *conduction* of the electrical impulse, and can be detected at all levels of the conduction system (sinoatrial node, AV node, intraventricular branches).

3.3 Sinus Node Dysfunction

The main manifestations of sinus node dysfunction are *sinus bradycardia* and *sinus arrest*.

Sinus node dysfunction recognizes *intrinsic* causes: degenerative disease, chronic or acute ischemia, infiltrative disease (amyloidosis, hemochromatosis, tumors), inflammatory causes (pericarditis, myocarditis), musculoskeletal disease (Duchenne dystrophy, Friedreich ataxia), vasculitis (systemic lupus erythematosus, scleroderma), and surgical (atrial septal defect correction); and *extrinsic* causes: drugs (amiodarone, flecainide, propafenone, sotalol, chinidina, disopyramide, procainamide), electrolyte disorders (hyperkalemia), endocrinopathies (hypothyroidism), vagal reflex during ischemia, neuromediated syndrome (vasovagal, cough, carotid sinus hypersensitivity), intracranial hypertension, and obstructive jaundice.

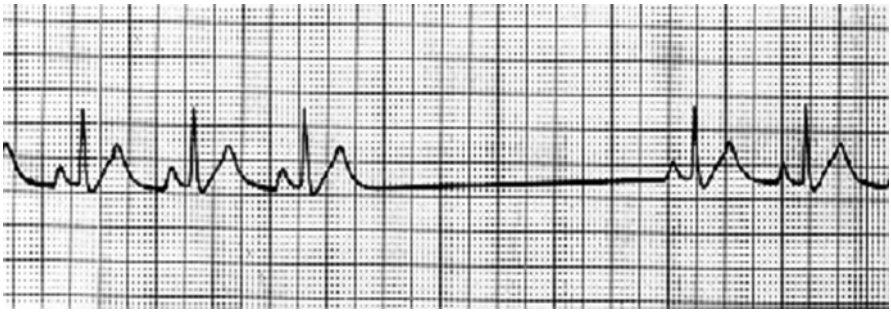

Fig. 3.1 Sinus arrest

3.3.1 Sinus Bradycardia

Sinus bradycardia can be secondary to intrinsic factors such as fibrosis (aging or loss of "pacing cells" [10, 11] resulting from inferior myocardial infarction, or to extrinsic factors such as an increased vagal tone, an abnormal neurocardiogenic reflex, drugs such as β-blockers or Ca^{2+} antagonists, or drugs reducing sympathetic tone such as sympatholytic antihypertensives [12].

The electrocardiogram (ECG) shows a regular sinus rhythm with heart rate lower than 60 bpm and a constant 1:1 AV conduction, with a normal PR interval (120–200 ms); P waves are regular, with the same shape and axis between 0° and 90°.

Symptoms can be absent at rest and may appear only during effort. In general, sinus bradycardia does not require treatment; intravenous atropine can be effective, but is useful only for short-term treatment because of its short half-life; sometimes temporary or permanent pacing may be necessary, favoring atrial over ventricular stimulation [13, 14].

3.3.2 Sinus Arrest

Sinus arrest is the absence of onset of spontaneous atrial impulse. It is generally considered significant when this pause lasts longer than 3 s. The most common causes are tissue fibrosis, ischemia, digoxin intoxication, cerebral ischemia, and excessive vagal tone (Fig. 3.1).

3.4 Atrioventricular Block

Atrioventricular block occurs when the conduction of the atrial impulse to the ventricles slows down or is blocked (paroxysmal or permanently), even though the AV junction is not physiologically refractory.

In the presence of a high atrial rate (e.g., atrial tachycardia or AF), the term AV block is correct only if the ventricular rate is lower than 60 bpm.

There are three anatomical sites of block: (1) above Hisian (inside the AV node), (2) intra-Hisian (inside the His bundle), and (3) infra-Hisian (distal His bundle or bundle branches).

The identification of anatomical site is relevant, as the distal blocks are those with the worst prognosis.

3.4.1 First-Degree AV Block

Every single atrial impulse is followed by a QRS complex, but the PR interval is greater than 200 ms. The block is usually above the AV node, even if there may be a wide QRS complex caused by a coexisting bundle-branch block. In general it is not associated with heart disease, and is usually secondary to increased vagal tone or is drug related (β-blocker or digoxin), although sometimes it can be associated with myocardial ischemia, infiltrative myocardiopathies, myocarditis, Addison disease, or congenital heart disease (septal defect, Ebstein). Prognosis, however, is benign, and no treatment is required. An exception can be the occurrence of a first-degree AV block in aortic valve endocarditis resulting from an abscess of the interventricular septum.

3.4.2 Second-Degree AV Block

Conduction from the atria to the ventricles is intermittent. There are two types of second-degree AV block.

Type I, also known as Mobitz I or Luciani-Wenckebach, involves progressive increase of the PR interval and consequent shortening of the RR interval until a nonconducted P wave develops. The morphology of the QRS complex is normal. The site of the block is usually at or above the AV node [15]. Etiology mainly includes digoxin intoxication, myocardial ischemia (inferior myocardial infarction), excess calcium deposits such as occur in aortic stenosis, or renal insufficiency. It can be also observed in both trained athletes and normal persons during sleep, attributable to increased vagal tone [16–18]. Prognosis is excellent if asymptomatic, while the onset of symptoms such as syncope or heart failure may require the placement of a definitive pacemaker.

Type II (Mobitz II) shows a sudden block of a P wave with a ratio of 3:2, 4:3, and so forth. PP and RR intervals are regular (Fig. 3.2). The block is intra- or infra-Hisian, and tends to progress toward complete AV block with prolonged ventricular pause and syncope [19]. Guidelines favor permanent pacing even in asymptomatic patients with type II block [20].

3.4.3 Atrioventricular Block with 2:1 Conduction

This condition is characterized by an intermittent block with a P/QRS ratio of 2:1, thus having features of both Mobitz I and II. Block can be at any nodal site and

Fig. 3.2 II degree–Mobitz 2 AV block (with intraventricular delay)

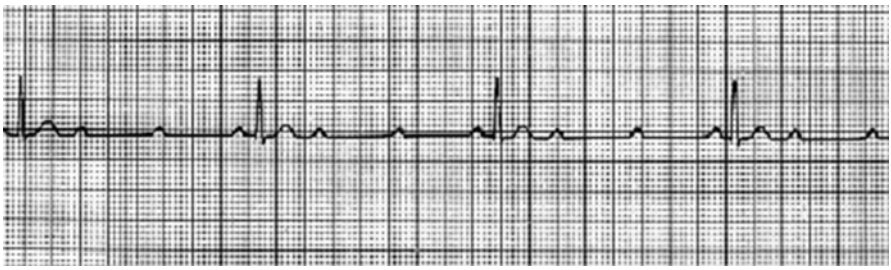

Fig. 3.3 Advanced (3:1) tipo II AV block

intra- or infra-Hisian, the severity depending on the resultant ventricular rate. In an asymptomatic patient a 2:1 block with a coexisting bundle-branch block is an indication for pacing, assuming that the block is infranodal [21].

3.4.4 Advanced AV Block

In advanced AV block, two or more consecutive P waves are blocked with a P/QRS ratio of 3:1, 4:1, and so forth (Fig. 3.3). In everyday practice this term is also used for low-rate permanent AF.

3.4.5 Low-Rate Atrial Fibrillation

The absence of recognizable P wave, irregular RR intervals, and narrow or wide QRS complexes characterizes low-rate AF. Causes are usually drugs (antiarrhythmic, digoxin, β-blockers, Ca^{2+} antagonists), especially in elderly patients with impaired renal and/or liver function, vagal hypertone (young subjects), or impaired AV conduction.

Treatment consists in ensuring hemodynamic normality using drugs (atropine followed by amines) or transcutaneous or transvenous pacing in symptomatic bradycardia.

3.4.6 Third-Degree AV Block

The inability of P waves to conduct to the ventricles (complete block of AV conduction) characterizes third-degree AV block. There is no relationship between P waves and QRS complexes, which are escape beats. Narrow QRS escape rhythms, with regular RR and a frequency between 40 and 60 bpm, are secondary to blocks within the AV node. Wide QRS escape rhythms with frequency between 40 and 20 bpm are secondary to infra-Hisian blocks.

In patients with AF and complete AV block a regular ventricular rate is observed, because of junctional (usually at about 35 bpm) or infra-Hisian escape rhythm.

Third-degree AV block can be secondary to pharmacologic treatments (digoxin, β-blockers, Ca^{2+} antagonists, quinidine, procainamide) or sclerodegenerative phenomena of conduction fibers, or may occur during the acute phase of myocardial infarction. Prognosis is more favorable if associated with inferior myocardial infarction (supra-Hisian block, narrow QRS escape rhythm, and generally spontaneous resolution), while the prognosis is worse in anterior myocardial infarction (infra-Hisian block and wide QRS escape rhythm, generally associated with a wider area and less reversibility of ischemic injury).

Less common causes include infectious diseases (myocarditis, Lyme disease, Chagas disease), rheumatic etiology (Reiter syndrome, scleroderma, rheumatoid arthritis), infiltrative disease (amyloidosis, sarcoidosis, multiple myeloma), electrolyte disorders, and iatrogenic factors (cardiac surgery, radiofrequency ablation) (Fig. 3.4).

3.4.7 Interventricular Block

Left bundle-branch block (LBBB) is a rare finding in the young population, and when present should raise the suspicion of an underlying heart disease. Incidence increases with age [22] and is associated with various causes of heart disease (hypertensive, ischemic, valvular, idiopathic dilated cardiomyopathy). Prognosis depends on the severity of the underlying disease.

Left anterior hemi-block (LAHB), more frequent in the adult male population, is associated with hypertension and ischemic heart disease. Progression to LBBB or complete AV block is uncommon [23].

Left posterior hemi-block (LPHB) is a rare isolated finding because of both the short course and double vascularization of the left posterior fascicle.

Right bundle-branch block (RBBB) as an incidental ECG finding is not often linked to heart disease, but may be associated with systemic hypertension, pulmonary heart disease, or ischemic heart disease.

Bifascicular block commonly indicates the association of an interruption or delay in impulse conduction along both sets of left bundle branch, or along the right branch and one of the two sets of left bundle branch.

RBBB + LAHB, a more common condition, shows a progression to complete AV block in less than 6 % of patients, while RBBB + LPHB, less frequent, has a greater progression toward complete AV block (close to 75 %).

Patients with bifascicular block associated with first-degree AV block (especially infranodal, when the HV interval, documented during invasive electrophysiological evaluation, is >100 ms) have a higher risk for developing complete AV block, and some authors recommend permanent cardiac stimulation [24]. The diagnosis of trifascicular block can be made on surface ECG only in the presence of alternating bundle-branch block (LBBB alternating with RBBB, or RBBB + LAHB alternating with RBBB + LPHB).

3.4.8 Atrioventricular Dissociation

AV dissociation is present when atrial activity is independent from ventricular activity, both occurring at regular rates. AV dissociation is not synonymous with AV block; in fact while patients with AV block also have an AV dissociation, patients with AV dissociation may not have an AV block, for example when an escape junctional (or ventricular) rate is higher than the sinus rate in the absence of retrograde ventricular-atrial conduction.

Elderly patients with degenerative cardiac disease are more likely to have AV dissociation [25].

Treatment depends on the causes, and ranges from antiarrhythmic drug treatment to permanent pacemaker placement.

3.4.9 Conduction Disturbances during Acute Myocardial Infarction

Sinus node dysfunction in the course of myocardial infarction may be secondary to the occlusion of the circumflex artery or the right coronary artery. The bradycardia that follows may favor escape rhythms with narrow QRS, which originate at the junction or in the His bundle and have a heart rate of about 50–60 bpm becoming stable over time, whereas escape rhythms with wide QRS originate from the Purkinje fibers with a heart rate below 40 bpm, are less stable, and may evolve to asystole. The AV block that occurs in the early stages of myocardial infarction is generally secondary to hypervagotonia and is reversible with atropine, while blocks occurring later are frequently related to ischemia of the AV node.

Second-degree type I AV block during inferior myocardial infarction tends to resolve spontaneously within 48 h and does not require invasive treatment unless there is hemodynamic compromise.

Second-degree type II AV block is more likely to progress to complete AV block, and occurs more frequently in anterior myocardial infarction, although it can also occur in inferior myocardial infarction because of occlusion of a large posterior descending artery.

Complete AV block, which is present in 8–13 % of patients with myocardial infarction, occurs in both inferior and anterior myocardial infarction, and can be preceded by fascicular blocks or bundle-branch block with second-degree AV block.

It is associated with a higher incidence of ventricular fibrillation/tachycardia, pulmonary edema, and in-hospital mortality [26].

3.4.10 Cardiac Arrest and Sudden Cardiac Death

The incidence of sudden cardiac death (occuring within 1 h from the onset of cardiac symptoms) is variable, depending on the varying prevalence of coronary disease in different countries [27]. In the USA there are 300,000 cardiac deaths annually, with a total annual incidence of 1 in 1,000 individuals [28].

Ventricular fibrillation is the first rhythm detected in 75–80 % of cases, while in the remaining 20–25 % extreme bradycardia or pulseless electrical activity are causes of cardiac arrest.

Bradyarrhythmic cardiac arrest is secondary to the inability of cardiac automatism to emerge and replace the sinus node or normal function of the AV junction.

Cardiac arrest is more common in advanced cardiac disease, generally as a consequence of extracellular potassium accumulation (secondary to hypoxemia, acidosis, shock, or renal insufficiency), which reduces myocellular automatism.

Pulseless electrical activity is an electrical stable cardiac rhythm in the absence of any effective myocardial contraction. The *primary form* is generally the terminal event of a severe cardiopathy or expression of acute myocardial ischemia, and the *secondary form* is a severe expression of a sudden failure in venous return, such as in pulmonary embolism, cardiac tamponade, or acute cardiac prosthetic valve dysfunction.

Reversible causes such as hypovolemia, hypoxia, cardiac tamponade, pneumothorax, acidosis, and hyperkalemia must be detected and corrected. Pharmacological support involves the use of intravenous epinephrine or atropine (the latter, however, is not effective in infra-Hisian AV block).

External cardiac pacing can be useful, although "asystolic" patients still have a poorer prognosis, regardless of the effectiveness of the stimulation [29].

3.5 Treatment

Sinus node dysfunction generally does not require treatment if asymptomatic. When needed, parasympatholytic drugs (atropine 0.5 mg intravenously, repeatable) can acutely increase the automaticity of the sinus node and improve sinus atrial conduction. Sympathomimetic drugs (theophylline per os) are less frequently used for long-term treatment because of their low efficacy and frequent side effects.

If there is any hemodynamic compromise, such as during an inferior myocardial infarction with right ventricle involvement, temporary endocardial pacing is preferred.

The presence of low cardiac output or heart failure, secondary to bradycardia, should be treated with permanent cardiac stimulation, preferably of the right atrium, to allow the spontaneous maintenance of AV conduction and avoid ventricular stimulation.

Supra-Hisian II AV block generally acutely responds to vagolytic drugs. As mentioned earlier, these drugs should be used with caution in suspected infra-Hisian blocks, which can be exacerbated by the increased cardiac rate and supra-Hisian conduction.

Sympathomimetic drugs such as isoproterenol, which are able to increase the automatism of ventricular "pacemaker subsidiary," can be used in the short term regardless of the level of AV block, in particular when it is likely that the block can be transient or if a temporary pacemaker cannot be immediately applied.

In third-degree AV block vagolytic drugs are not particularly effective, especially in the presence of infra-Hisian block, while sympathomimetic drugs provide valuable support in the acute phase while awaiting a permanent pacemaker.

3.5.1 Temporary Pacemaker

Temporary cardiac pacing is used acutely for critically ill patients who require immediate treatment, and sometimes in noncritical situations when patients are at high risk of developing advanced blocks or cardiac arrest.

An intracardiac approach is usually preferred, generally through the internal jugular vein, the subclavian vein, or the femoral vein.

Transcutaneous pacing, despite not having shown a significant benefit in patients with cardiac arrest [29], may be beneficial for the treatment of severe bradycardia as a "bridge" to a permanent pacemaker.

The main indication remains hemodynamically unstable acute myocardial infarction (Table 3.1). Drug treatment with digitalis, quinidine, class 1C antiarrhythmics, β-blockers, and some calcium antagonists can inhibit sinus node automatism up to the development of severe bradycardia, requiring, if associated with signs and symptoms of hemodynamic compromise, temporary pacing to allow pharmacological washout in safety [30].

Hypervagotonia can occur in carotid sinus hypersensitivity, in pharyngeal or gastroesophageal handling during intubation and/or endoscopy, and with parasympathomimetic or sympatholytic drugs. It is associated with three types of clinical response: the first, or cardioinhibitory, with hemodynamically significant bradyarrhythmia; the second, vasodepressor, with hypotension by peripheral vasodilation; and the third, which is a combination of the first two forms. Sometimes temporary pacing can be useful in intensive care, although these clinical situations are easily reversible with atropine [31].

Myocarditis can require temporary pacing because of transient involvement of the ventricular conduction system.

Complications of temporary pacing include capture failure caused by electrode dislocation (25 %), ventricular tachyarrhythmia related to local irritation of the electrode (10 %), pericarditis (5 %), and cardiac tamponade secondary to right atrium perforation (1 %).

Complications related to central venous access are air embolism (1 %), arterial trauma (1.2 %), pneumothorax (1 %), phlebitis (5.1 %), venous thrombosis (18-34 %), and bacteremia (50 %), although infection of the electrode is low [31].

Table 3.1 Therapeutic approach in conduction disturbances

Sinus atrial dysfunction	Asymptomatic patient: observation Symptomatic patient: atropine 0.5 mg iv repeatable up to 2 mg temporary/ permanent pacemaker
AV block	First-degree AV block: observation Second-degree AV block Type I asymptomatic: observation symptomatic – atropine 0.5 mg iv repeatable up to 2 mg Type II asymptomatic (advanced or Mobitz 2) or symptomatic → pacemaker implantation narrow QRS → atropine, if ineffective → pacemaker wide QRS → PM implantation Third-degree AV block a/symptomatic: narrow QRS → atropine, if ineffective → pacemaker wide QRS → PM implantation
AV block during myocardial infarction	Inferior myocardial infarction First-degree AV block → observation Second-degree AV block: Type I → atropine, if ineffective → temporary pacemaker Type II → temporary pacemaker Third-degree AV block → atropine, if ineffective → temporary pacemaker Anterior myocardial infarction: First-degree AV block → observation Second-degree AV block Type I atropine, if ineffective → temporary pacemaker Type II → temporary pacemaker Third-degree AV block → temporary pacemaker

3.5.2 Permanent Pacemaker

Sinus node dysfunction is a major reason for pacemaker implantation (about 46 % of implanted devices) [32] and has a long natural history with a good prognosis in the early stages, although with the progress of the disease and the appearance of symptoms the prognosis becomes less favorable [33].

Atrial pacing is preferable to ventricular pacing alone, although the advantage is reduced in the presence of thromboembolic events or the occurrence of AF [14, 34].

AV block is the second leading cause of pacemaker implantation. Permanent cardiac pacing has improved survival in patients with complete or advanced AV block, particularly if associated with symptoms (syncope or hemodynamic compromise) or in the presence of heart disease [35].

Asymptomatic first- and second-degree (type I) AV blocks do not require permanent cardiac pacing.

Symptomatic or second-degree AV block with slow escape rhythm (type I) and asymptomatic type II block are class II indications for permanent pacemaker implantation.

Complete or advanced AV block (both asymptomatic and symptomatic) and second-degree (type II) AV block, regardless of the level of block, are class I indications for a permanent pacemaker.

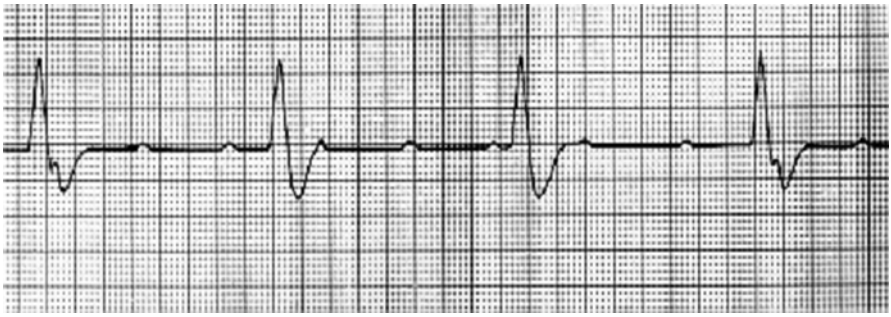

Fig. 3.4 III degree AV block with wide QRS (infra-hisian) escape

Care should be taken in cases of reversible AV block.

Survival in patients with complete AV block not treated with pacemaker implantation is 60 % at 1 year and 30 % at 5 years [35]. Patients treated with permanent pacemakers have been shown to have a 1-year survival comparable with that of the general population [36].

European and American guidelines for Pacemaker implantation [37, 38]
Class I indications
Sinus node dysfunction
Symptomatic sinus bradycardia or chronotropic incompetence
AV block
Second-degree AV block type II
Advanced AV block during sinus rhythm or AF
Complete AV block
Intraventricular block
Trifascicular block (RBBB alternating with LBBB, RBBB + LAHB alternating with RBBB + LPHB)
Bifascicular block (LBBB, RBBB + LAHB, RBBB + LPHB) and second-degree type II or third-degree AV block

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Supraventricular Arrhythmias in Emergency

4

Elisabetta Bianco, Marco Bobbo, and Davide Stolfo

The term "supraventricular tachycardia" refers to arrhythmias requiring atrial or atrioventricular nodal tissue, or both, for their initiation and maintenance. Supraventricular tachycardias are often recurrent, occasionally persistent, and a frequent cause of visits to emergency departments (ED) [1].

The following chapter is organized in two main sections dedicated to physician working in ER and cardiologist in order to discuss arguments related to each specific expertise so that patients can receive assessment and treatment personalized on global clinical condition, not only on arrhythmia, in the ED.

4.1 What Physicians Working in ED Should Know

- Timing and modality to treat arrhythmias depends on patient's hemodynamic condition.
- Hemodynamic instability imposes emergent treatment with electrical cardioversion before diagnosis.
- In case of hemodynamic stability it is possible to think about diagnosis and choose best treatment.
- Hemodynamic instability depends on heart rate and on patients' features as age, underlying cardiomyopathy or chronic therapies, electrolyte disturbance, hyperthyroidism, hyperthermia, and drugs intoxication rather than on the type of arrhythmia [2, 3].

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_4

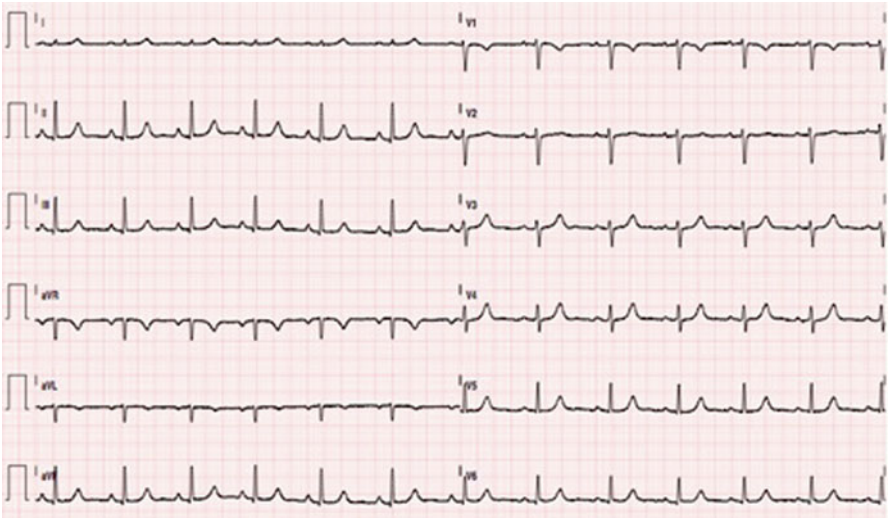

Fig. 4.1 ECG in normal sinus rhythm; with usual setting (paper speed 25 mm/s) 1 mm equals with 40 ms interval

Supraventricular arrhythmias are [4]:

1. Sinus tachycardia
2. Atrial flutter (typical or atypical)
3. Atrial fibrillation (AF)
4. Atrioventricular nodal reentrant tachycardia (AVNRT)
5. Atrioventricular reciprocating tachycardia (AVRT)
6. Atrial/junctional tachycardia (AT)

ECG during arrhythmias differs from normal ECG observed in sinus rhythm. So, first of all, normal ECG must be known [5, 6] (Fig. 4.1):

- Each QRS complex is preceded by a *P wave* with a rate between 60 and 100 bpm with the exception of newborns and infants in whom normal HR is higher (150–230 bpm in newborn) [7].
- P wave is positive in leads I–II and aVL–aVF and in precordial leads from V2–3 to V6, is negative in aVR and can be negative in III, and is biphasic in V1–V2; P wave lasts 120 ms (3 mm).
- Between P wave and QRS complex, there is an isoelectric region (flat line on ECG) which lasts 120–200 ms: the *PR interval.*
- *QRS is narrow* (<110 ms).

While approaching a patient with symptomatic supraventricular tachycardia, physicians must evaluate the patient's clinical status to identify potential reversible causes of tachycardia and to assess the degree of instability and understand if it is related to the tachycardia itself.

Arterial blood pressure, oxygen saturation, electrolyte, and hemoglobin must be evaluated; ECG monitoring and intravenous access must be established.

If possible a 12-lead ECG should be performed during the arrhythmia (and after its interruption) [2].

4.1.1 Patients in Unstable Condition

If the patient demonstrates rate-related cardiovascular compromise with signs and symptoms such as acute altered mental status, ischemic chest discomfort, acute heart failure, hypotension, or other signs of shock suspected to be due to a tachyarrhythmia, proceed to immediate synchronized electrical cardioversion (after sedation of the patient if conscious); provide oxygen if oxygen saturation is below 94 % [2]:

- Narrow regular tachycardia → biphasic synchronized direct current shock 50–100 J
- Narrow irregular tachycardia → biphasic synchronized direct current shock 120–200 J
- Wide regular tachycardia → biphasic synchronized direct current shock 100 J
- Wide irregular tachycardia → biphasic NOT synchronized direct current shock 200 J

If there's no response to the first shock, it may be reasonable to increase the dose in a stepwise fashion.

Cardioversion with monophasic waveforms should begin at 200 J and increase in stepwise fashion if not successful [2].

In newborn, use 0.5 → 2 J/kg [3].

Heparin (low molecular weight or unfractionated heparin) should be administered before cardioversion in case of atrial flutter or atrial tachycardia and after it, depending on patients' features (CHA_2DS_2VASc – HAS BLED) [8].

In patients with implanted pacemaker or defibrillator pads, it should be positioned 8 cm from the device battery; anteroposterior paddle positioning and biphasic energy are recommended [2, 4, 8].

4.1.2 Patients in Stable Condition

The initial assessment should:

1. Distinguish between narrow and wide complex tachycardia.
2. Determine whether the rhythm is irregular or regular (<10 % of variation in cycle length).
3. Consider the rapidity of onset.
4. Identify sinus tachycardia (the theoretical upper rate is 220bpm minus the patient's age in years).

Supraventricular tachycardias have narrow QRS in 90 % of cases. Wide QRS complex could be due to pre-excitation through an accessory pathway or to bundle-branch block or to pacemaker stimulation. Previous ECG and ECG after termination of tachycardia can help to make the diagnosis.

While considering the patient's history, the clinician should assess the duration and frequency of episodes, the mode of onset, and possible triggers (including the intake of alcohol, caffeine or other drugs) as well as previous cardiac or other diseases or previous ECGs.

Supraventricular tachycardias have a sudden onset and termination, in contrast to sinus tachycardias or atrial tachycardias, which accelerate and decelerate gradually; however, some patients do not perceive the sudden onset of supraventricular tachycardia; furthermore, sometimes, they describe sudden onset and gradual offset due to reactive sinus tachycardia after termination of paroxysmal SVT. It may be misdiagnosed as panic disorder [5, 9].

Physical examination during episodes may reveal the "frog sign" which is a prominent jugular venous A waves due to atrial contraction against the closed tricuspid valve. After sinus rhythm is restored, physical examination is usually normal, but a careful examination is warranted to rule out evidence of structural heart disease [11, 12].

4.1.3 Management

4.1.3.1 Narrow QRS

If narrow QRS is present, atrioventricular conduction is certainly entirely through atrioventricular node. That's why maneuvers that increase vagal tone and block atrioventricular conduction are safe: they can interrupt tachycardias depending on AV node conduction (TRNAV or orthodromic TRAV) and can slow down those which don't depend on AV node conduction (atrial flutter or atrial fibrillation). They also interrupt focal tachycardia due to enhanced automaticity.

Physicians have these possibilities:

- *Vagal maneuvers* (Valsalva, carotid sinus massage, facial immersion in cold water, and bearing down). The efficacy is about 25 % [13]. Remember that carotid sinus massage is contraindicated in case of carotid stenosis.
- *Adenosine:* very short-acting endogenous nucleotide (<10 s). It blocks atrioventricular nodal conduction and terminates most of atrioventricular nodal reentrant tachycardias and atrioventricular reciprocating tachycardias as well as up to 80 % of atrial tachycardias [14–16]. Since it may also have proarrhythmic effect (atrial fibrillation in 12 % of patients), it must be administered under ECG monitoring with an accessible defibrillator.

  Common side effects include chest tightness, flushing, and a sense of dread. Avoid in asthmatic patients since it can produce bronchospasm; patients with autonomic failure and with cardiac transplant or patient chronically treated with

antiarrhythmic drugs are more sensitive to adenosine [17]; that's why doses must be halved.

Way of administration and doses: 0.1–0.2 mg/kg (usually 6–12 mg) through peripheral vein; start with 6 mg in a rapid flush immediately followed by 20 ml of saline flush. If there is no effect, try again with 12 mg. Same dose for newborn.

- *Verapamil-diltiazem*: Intravenous verapamil and diltiazem are effective in interrupting tachycardias or can slow down AV conduction, but can cause hypotension thus are not recommended as first choice in the emergency setting [18]. They are contraindicated in heart failure and in newborn because of risk of cardiac arrest or atrioventricular dissociation [3, 19].
- *Electrical cardioversion*: best choice for atrial fibrillation and atrial flutter (typical o atypical) with onset within 48 h or in anticoagulated patients [8]. Biphasic synchronized shock (50 → 200 J; 0.5 → 2 J/kg in infants) is recommended in sedated patient. Before cardioversion, a heparin bolus is recommended in all patients not yet anticoagulated. If there is no efficacy or there is arrhythmia recurrence, pharmacological therapy can be added.

Remember that:

- Sinus tachycardia is usually reactive to other causes so identification and treatment of them are required. No specific drug treatment is usually necessary.
- Atrial fibrillation and atrial flutter can give rise to endocardial thrombus which can cause stroke or thromboembolism: the risk is higher after 48 h of persistent tachycardia and in patients with some specific features ($CHA_2DS_2VASc > 1$). For this reason, anticoagulation (for at leat 3 weeks) is mandatory before cardioversion (or, in alternative, perform trans-esophageous echo to rule out intracardiac thrombi); in case of arrhythmias lasting more than 48 h or non-datable; nevertheless, heparin administration before cardioversion is preferable in all patients. For more details, see specific guidelines [16, 19–21].
- Patients with uncomplicated tachycardias and without cardiomyopathy can be discharged after sinus rhythm restoration; cardiological evaluation can be postponed.
- Sodium channel blockers increase both pacing threshold and the energy required to defibrillation [22, 23].
- Being genetic setting unknown, the effect of an antiarrhythmic drug given for the first time is *never* predictable. That's why administration of antiarrhythmic medications for the first time must be done under ECG monitoring lasting for at least the drug's half-time; after discharge, if chronic therapy is set up, ECG must be checked at the steady state (five half-times) (Fig. 4.2).

4.1.3.2 Wide QRS

Wide QRS can be due to preexisting or frequency-dependent bundle-branch block or to conduction over an accessory pathway. Nevertheless, the majority of wide QRS complex tachycardia has ventricular origin. If the patient is in stable hemodynamic condition, it is better to refer him/her to a specialist for diagnosis and treatment.

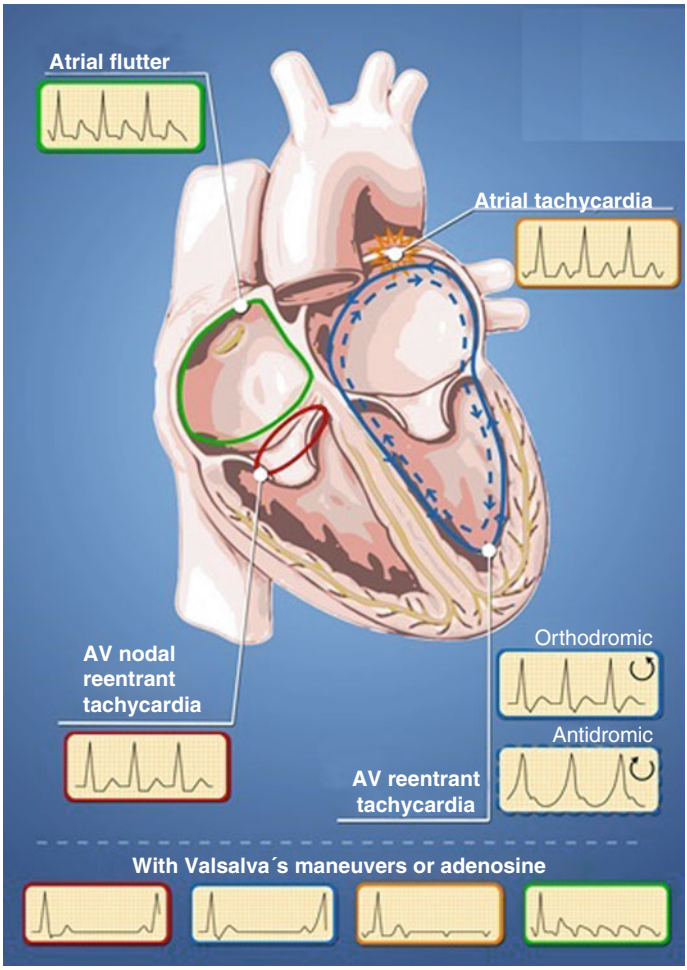

Fig. 4.2 Supraventricular tachycardias (Data from Delacrétaz [12])

4.2 What Cardiologists Should Know

Cardiologist should evaluate all patients with hemodynamic instability related to tachycardias after their stabilization with cardioversion in order to exclude or confirm the presence of cardiomyopathy, to decide the best medical treatment, and to decide for hospitalization or discharge and follow-up.

Non-urgent cardiological examination within few weeks can be reserved to uncomplicated tachycardias, in absence of cardiomyopathy, especially in case of preexisting diagnosis.

Cardiologist should know mechanisms underlying arrhythmias and modality of action of antiarrhythmic drugs in order to choose and combine them, to maximize

efficacy and minimize proarrhythmic and side effects [22, 23], and to remove precipitating features as ischemia and electrolyte imbalance.

For this reason, the next part of the chapter is dedicated to pharmacology of antiarrhythmic drugs and basic electrophysiology.

At the end of the chapter, a scheme of therapies for each arrhythmia is provided.

4.2.1 Basic Electrophysiologic Principles

Every heart contraction is driven by inversion of cell potential from negative to positive. At the cell membrane site, this potential variation from negative to positive (depolarization) and back to negative (repolarization) is called action potential (AP). This is possible thanks to the activation in sequence of different channels driving ion currents (I) inward and outward the cell; every channel is designed to allow passage of its own specific ion and to do it only during a specific phase of AP (some channels open only at negative potential, other at positive). Potassium (K^+) is mainly inside the cell, while sodium (Na^+) is outside and calcium (Ca^{++}) is both outside and stored inside the cell; sodium and calcium are linked to one another. To generate cell depolarization, a specific potential threshold must be reached.

Action potential has been divided in five phases:

- 0 → Depolarization
- 1 → Fast repolarization
- 2 → Plateau
- 3 → Terminal repolarization
- 4 → Resting

During the first phase of action potential, cell membrane is depolarized, and no external stimulus can modify it (absolute refractoriness); during repolarization, external factors can excite the cell with "extra-AP" (relative refractoriness).

Propagation of action potential from a cell to another is called conduction and is characterized by a speed and a safety factor.

Action potential has different morphologies in different tissues (sinus node, AV node, atrioventricular cells). This is due to different kinds of channels and explains the heterogeneous effects of antiarrhythmic drugs on each cardiac tissue.

For example, AV node cell depolarization is mainly calcium mediated, while atrial and ventricular depolarization is sodium mediated; automaticity of sinus node is due to specific channels (HCN) which are permeable to both sodium and potassium and open only at very negative potentials (hyperpolarization).

Function alteration of ion channels (pathological, heart rate or drug mediated) or modifications of ion concentrations modify action potential in terms of duration, velocity of depolarization, or repolarization and determine abnormal rhythm propagation [5, 21].

4.2.2 Mechanisms of Arrhythmias

Arrhythmias are divided into focal and reentrant.

4.2.2.1 Focal

Focal supraventricular tachycardias are defined as an activation starting rhythmically from a small area in atria or AV junction and spreading out centrifugally. Focus can be single or multiple. Mechanism underlying focal tachycardias is automaticity, triggered activity, and micro-reentrant.

- *Triggered activity*: abnormal fluctuations of action potential occurring after or during the repolarization (phase 2–3 or 4 of action potential), which are able to depolarize cell membrane to the depolarization threshold; differently from automatic foci, they are linked to the previous action potential. Three kinds of triggered activities are known (Fig. 4.3):

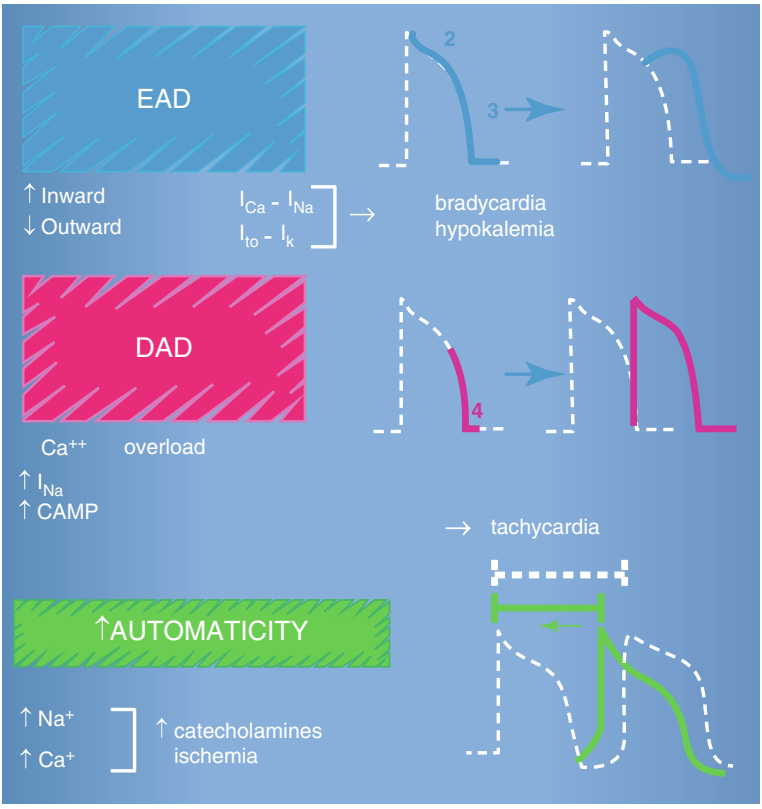

Fig. 4.3 Effects of early after depolarization (EAD), delayed after depolarization (DAD), and automaticity on action potential

(a) *Early after depolarization (EAD)* → occurring during repolarization (phases 2–3 of action potential), due to decreased potassium conductance (typically bradycardia, hypokalemia, or class III antiarrhythmic drugs). They are suppressed by factors that increase potassium outward current (*overdrive – tachycardias*, *K+ channels activators*) or suppress sodium/calcium inward currents (e.g., *magnesium*).
(b) *Delayed after depolarization (DAD)* → occurring during diastolic phase of action potential (phase 4) as consequence of Ca^{++} intracellular overload and Ca^{++} sparks due to increase of I_{Na} (ischemia or digoxin intoxication) or cAMP after beta-stimulation (tachycardia). They are suppressed by *beta-blockers*, *calcium channel blockers*, *vagal stimulation*, or *adenosine*.
(c) *Enhanced automaticity:* positive ionic influx (mostly inward calcium current) during phase 4 (diastolic) depolarization (normal automaticity is driven by sodium current while pathological by calcium). Beta-adrenergic stimulation enhances calcium current and facilitates these arrhythmias. Automatic tachycardias are the most common kind of focal arrhythmias and are characterized by sudden onset with a "warm-up" period. *Vagal stimulation*, *adenosine*, *beta-blockers*, or *calcium channel blockers* may suppress them.

Focal tachycardias are:

- *Atrial tachycardias* → P wave is generally visible with a morphology different from sinus one; 1:1 AV ratio is expected; heart rate can be very variable.
- *Inappropriate sinus tachycardia* → normal P wave morphology; 1:1 AV ratio; heart rate > 100 bpm not related to physiological needs.
- *Junctional tachycardia* → QRS not preceded by P; P wave can be visible after QRS, with morphology typical of AV junction origin (negative in DII–DIII and aVF, positive in V1 or not visible); similar to nodal or atrioventricular reentrant tachycardias; typical of infants.
- *Polymorphic atrial tachycardia/atrial fibrillation* → recurrent paroxysms of polymorphic premature beats starting with warm-up and degenerating in disorganized atrial activity; P wave is polymorphic and not always visible (during AF, sometime P is visible only in V1–V2 due to organization of atrial activity around tricuspid annulus).

4.2.2.2 Reentry

Reentry is a self-perpetuating circuit in which, during a single cardiac cycle, areas still depolarized and areas repolarized coexist. Reentry can be functional or anatomical. If the reentry circuit is >2–3 cm, it's classified as a macro-reentrant; if the reentry circuit is <2–3 cm, instead it's classified as micro (focal tachycardia) [25].

To have a reentry, the following features are required: unidirectional conduction (one way block usually due to extra beat), areas of different conduction rate (short and fast), and shortening of refractory period. Common triggers of reentry

are sympathetic or parasympathetic stimulation, premature beats, and myocardial ischemia.

Wave length (WL) is the product of conduction velocity (CV) and refractory period (RP); WL is theoretical and is always shorter than the real one, so there is an excitable gap (EG) inside the circuit. Reentry has a wave front, a tail, and an excitable gap between them. Excitable gap is necessary to perpetuate reentry.

Factors eliminating the excitable gap block the reentrant circuit making the wave front crash on the tail. There are two ways to obtain it: to *increase the refractory period* (with potassium current blockers or sodium current blockers with slow kinetics) or to *increase the conduction velocity*. In addiction to drugs, the excitable gap can be suppressed stimulating the circuit at a rate just faster than the arrhythmia (overdrive pacing), possible in patients with dual chamber (or atrial) pacemakers.

Ablation can eliminate reentrant circuits by targeting areas of slow conduction that sustain circuit (called isthmus of the tachycardia) and blocking them (creating a permanent lesion with bidirectional block). When ablation lesion is incomplete, it can create an area of slower conduction that is potentially proarrhythmic.

Sometimes, the degree of increase of refractory period brought by drugs is not enough to interrupt tachycardia even at therapeutic concentration: this is more frequent in large anatomic circuit and with drugs that slow down propagation velocity as INa^+ blockers. In this situation arrhythmia became more stable and resistant to therapies. Examples are AVNRT slow/slow or permanent junctional reciprocating tachycardia (PJRT) after calcium or beta-blockers or transformation of atrial fibrillation (small circuit) in atrial flutter (large circuit) after flecainide or propafenone administration.

Reentrant tachycardias are:

- *Atrial flutter (typical and atypical)* → organized atrial rhythm; typical flutter is characterized by negative/positive sawtooth waves (F wave) in leads II, III, and aVF and positive in V_1; in atypical flutter, F waves have different axis depending on circuit; atrial heart rate is between 250 and 350 bpm (but can vary in patient previously treated with ablation or in patients taking antiarrhythmic drugs). In typical atrial flutter, circuit is counterclockwise around tricuspid annulus; slow conduction is between tricuspid annulus and inferior vena cava and conduction block along the crista terminalis and Eustachian ridge.
- *Post-incisional atrial tachycardia* → organized atrial activity due to reentrant around a scar; typical of patients with a history of cardiac surgery or catheter ablation.
- *AVNRT* → P wave arising from junction (negative in DII–DIII and aVF, positive in V1) with RP <PR; two limbs are slow and fast nodal pathways. Reentrant circuit is most of the time down through slow pathway and back through fast pathway (slow/fast), and P wave is visible as a pseudo-r′ in V1 or a pseudo-s′ in inferior leads (P can be not visible); in atypical AVNRT, circuit is down through slow or fast pathway and back through slow (slow/slow, fast/slow), and P wave is separated from QRS; RP >PR). The circuit is inside the AV node so that the

onset of atrioventricular block during tachycardia doesn't interrupt it (AVNRT can have 2:1 AV ratio).

- *AVRT* → reentrant circuit across AV node and accessory truck. It's called orthodromic when it passes from the atrium to the ventricle through AV node and back from the ventricle to the atrium through accessory pathway (RP >PR); it's called antidromic when anterograde wave front is through accessory pathway. The atria and ventricles are part of the circuit, and AV dissociation is not possible without interrupting tachycardia. Presence of pre-excitation is not diagnostic of AVRT (accessory pathway can be a "bystander" during AVNRT or atrial tachycardia, meaning that ventricles are partially or totally activated through the accessory pathway, which nevertheless is not part of the reentry circuit causing the arrhythmia). Evidence of tachycardia cycle length (=RR) augmentation of more than 35 ms (more and less 1 mm with 25 mm/s paper speed) in case of ipsilateral bundle brunch block is diagnostic of AVRT [24], because the ipsilateral block causes a lengthening of the circuit.
- *Permanent junctional reciprocating tachycardia (PJRT) – Mahaim tachycardia* → are rare AVRT through accessory pathway with particular features. PJRT is due to a septal accessory path with only retrograde conduction and decremental properties; it determines incessant narrow QRS tachycardia. Mahaim pathway is an accessory path with decremental properties generally right sided (from anterolateral atrial portion of tricuspid annulus to right ventricle or right bundle); in sinus rhythm, there is typically little or no pre-excitation; during antidromic tachycardia, the QRS is wide (150 ms), with left bundle block morphology, transition after V4.

4.2.3 Antiarrhythmic Drugs

Antiarrhythmic drugs are channel or receptor blockers. They bind specific sites on protein and modify its function with an affinity that varies on the ion channel state (open-inactivated-resting). Furthermore each drug has a specific rate of recovering from block which is a constant time ($T_{recovery}$).

This is why antiarrhythmic drugs that bind open channel, untie during resting state, and have long $T_{recovery}$ (as flecainide – 11 s) reach the steady state earlier having greater effect when a higher percentage of cells are depolarized as during ischemia or high heart rates (direct use dependence). Those drugs that, instead, own affinity for inactivated/resting channels (amiodarone or lidocaine) and own a very short $T_{recovery}$ (lidocaine – 0.1 s) have a greater effect (anti- and proarrhythmic!) under the condition that prolong action potential duration (as bradycardia-hypokalemia) and on rapidly driven tissue (ventricular tachycardia).

Antiarrhythmic drugs have been divided in four classes according to their main effect on action potential (Vaughan Williams classification) [25, 26]. However mostly all of them share properties among multiple classes (quinidine below to I°

class but have also III° class properties). Moreover, ivabradine, digoxin, and adenosine don't belong to any of the four classes (Table 4.1) (Fig. 4.4):

- INa+blockers (I class): shorten action potential, reduce propagation velocity, and act on refractoriness depending on kinetics (flecainide increase relative refractory period; lidocaine no); suppress EAD; reduce inotropism.
- Ica++ blockers (class IV): reduce propagation velocity; suppress abnormal automaticity, EAD, and DAD; reduce inotropism. All have direct use dependence.
- IK+ (class III): lengthening of action potential and of absolute refractory period. Increase inotropism. Have inverse use dependence. Proarrhythmic trough induction of EAD (during hypokalemia/bradycardia)

Key Messages

Remember that:

- *Electrolytes MUST be known, and their alterations MUST be correct before administering any antiarrhythmic drug!*
- Effect of antiarrhythmic drugs can be very different (and very dangerous) among patients with altered function of ion channels (channelopathies, myocardial ischemia) or variants of metabolic capacity or concomitant therapies [27–29]. Therefore, in patients with supraventricular arrhythmias and altered basal ECG (conduction disturbance, repolarization abnormalities), it is important to exclude those abnormalities and choose the correct therapy. When a channelopathy is suspected, further evaluation must be organized [30]; the decision about hospitalization or delayed ambulatory evaluation depends on the risk of arrhythmic death (arrhythmic instabilities, predisposing factors).
- Being genetic setting usually unknown, the *effect of an antiarrhythmic drug given for the first time is never predictable* [31]. That's why the first administration of any antiarrhythmic medications should be done under ECG monitoring lasting for at least the drug's half-time; after discharge, if chronic therapy is set up, ECG must be checked at steady state (five half-times).
- Ic are *effective on accessory pathway*.
- Ic are *poorly effective on atrial macro-reentrant tachycardias (flutter o post-incisional)*; they slow atrial cycle length without interrupting tachycardia; if AV nodal conduction is enhanced (e.g., during exercise), they can promote 1:1 AV conduction. For this reason it's better to associate an AV blocker (Ca^{++} or Na^{+} blocker) to a Ic drug. Vernakalant is not effective on atrial flutter.
- Ic *have a marked negative inotropic effect*; if administered in rapid bolus, it causes broad hypotension even in people without cardiomyopathy so they must be administered under arterial pressure monitoring.
- *Calcium-blockers are dangerous in newborn* because of risk of cardiac arrest and are contraindicated in this setting [3, 19].
- *In newborn and children, beta-blockers are highly effective* especially if combined with amiodarone [32, 33]. Procainamide has also been demonstrated to be more effective than amiodarone in sinus rhythm conversion of pediatric SVT [34].

Table 4.1 The effects, doses, side effects, and contraindications of antiarrhythmic drugs

CLASS	DRUG		INTRAVENOUS	MAINTENANCE (day)	$T_{1/2}$	ELIMINATION	SIDE EFFECTS	CONTRAINDICATIONS
I_a ↓ phase 0 ↓ conduction ↑ repolarization	DISOPYRAMIDE	↓ Na^+,K^+ ↓ M_2	//	400-800 mg →300/400 mg	4-8h	renal/hepatic	↑QT, TdP,gastrointestinal ailment,vasculitis, glaucoma, hypoglycemia	SA dysfuncion, bifascicular BBB, BAV II-III, severe heart failure, hypokalemia, CrCl <20 ml/min
	PROCAINAMIDE	↓ Na^+,K^+	30 mg/min (max 1 g) + 1-4 mg/min	250-1000 mg	3-4h	hepatic, renal	Hypotension, QRS widening, TdP	Severe heart failure, QRS widening > 50% basal
	QUINIDINA	↓ Na^+,K^+ ↓ M_2 α,β	//	275mg(x3) 250-500mg (bid)		hepatic, renal	↑QT, diarrhea	
I_b ↓ Na^+ in phase 2 (effective on VT in abnormal tissue)	Lidocaine	↓ Na^+	//	//	//	//	//	//
	Mexiletin	↓ Na^+	//	//	//	//	//	//
	Tocainide	↓ Na^+	//	//	//	//	//	//
	Phenytoin	↓ Na^+	//	//	//	//	//	//
I_c ↓ phase 0 ↓ conduction	FLECAINIDE	↓ Na^+,K^+	2 mg/Kg in 10′	3-5 mg/Kg	12-20h	renal	Hypotension, negative inotropic effect, QRS widening, SA,AV block, dizziness, visual impairment, gastrointestinal ailment	Heart failure, Brugada Syndrome, LQT3, ischemic heart disease
	PRPPAFENONE	↓ Na^+, β	2 mg/Kg in 10′	10 mg/Kg	variable	hepatic		
	MORICIZINA	↓ Na^+						
II **β-blockers**	ESMOLOL	↓ β	500 γ/Kg 1′ →20-200 γ /Kg/min	//	8	esterases - renal	Bradicardia Heart block Hypotension, Negative inotropic effect Bronchospasm	Asthma II-III degree AV block Heart failure
	METOPROLOL	↓ $β_1$	5 mg in 2 ′→ max 15 mg in 15′	50-200 mg	variable	hepatic		
	PROPANOLOL	↓ $β_1$- $β_2$	0,15-0,2 mg/Kg in 2′	80-240 mg	4 h	hepatic		
	ATENOLOL	↓ $β_1$	2,5 mg in 1′ →every 5′, max 10 mg	25-100 mg	6 h	renal		
	NADOLOL	↓ $β_1$- $β_2$	//	20-80 mg	20 h	renal		
	BISOPROLOL	↓ $β_1$	//	2,5-10		hepatic/renal		
III ↑repolarization	AMIODARON	↓K^+↑Na^+, Ca^{++},β	5 mg/Kg in 20′-2h →15 mg/Kg/24h	20 mg/Kg/week	240h	hepatic/renal	Skin discoloration, dyshyroidism, gastrointestinal up- set, hepatotoxicity, corneal deposits, tremor, optic neuropathy, pulmonary toxicity	LQT,hypokalemia Severe heart failure
	SOTALOL	↓ K^+, β	//	3-5 mg/Kg (bid)	8 h	renal	↑QT, TdP, bradicardia, heart block, hypotension, negative inotropic effect, bronchospasm	LQT, hypokalemia, severe heart failure asthma, renal failure
	DOFETILIDE	↓ K^+	//	1 mg	10h	renal/hepatic	↑QT, TdP (start in hospital)	LQT, ↓ K^+, SA dysfuncion, AV II-III
	IBUTILIDE	↓K^+,↑Na	1 mg in 10′x2 (if <60Kg 0,01 mg/Kg)	//	2-12h	renal	↑QT, TdP,bradicardia	LQT, ↓ K^+,Mg^{++}, SA dysfuncion, BAV II-III, recent MI
	DRONEDARON		//	800 mg		renal		LQT, -SA dysfuncion, BAV II-III, heart failure
	VERNAKALANT	↓ K^+,Na^+	//	//	//	//	//	//
IV **Ca^{++}Antagonist**	VERAPAMIL	↓ Ca^{++}	5mg/KginS′→max10mg	120-480 mg	3-7 h	hepatic	Bradicardia, SA,AV block, hypotension, negative inotropic effect	II-III degree AV block, heart failure, newborn
	DILTIAZEM	↓ Ca^{++}	0,25-0,35 mg/Kg in 2′ → 5-15 mg/h	180-360 mg	4h	hepatic		
	ADENOOSINE	↓A_1	0,1-0,2 mg/Kg	//	<10″	esterases	bronchospasm, flushing	asthma
	DIGOXIN	↑M_2	1 mg/12-24 h	0,125-0,375 mg	36h	renal	tachyarrhythmias, SA,AV block	hypokalemia, severe renal disease
	IVABRADINE	↓	//	2,5-7,5 mg (bid)	12 h	renal	bradicardia, bradicardia-mediated VT and AF, phosphenes, headhache	bradyarrhythmias, LQT, severe heart failure

Different colors identify the four classes of Vaughan Williams classification; in *black* drugs not belonging to any class. Drugs without indications for supraventricular tachycardias are only mentioned

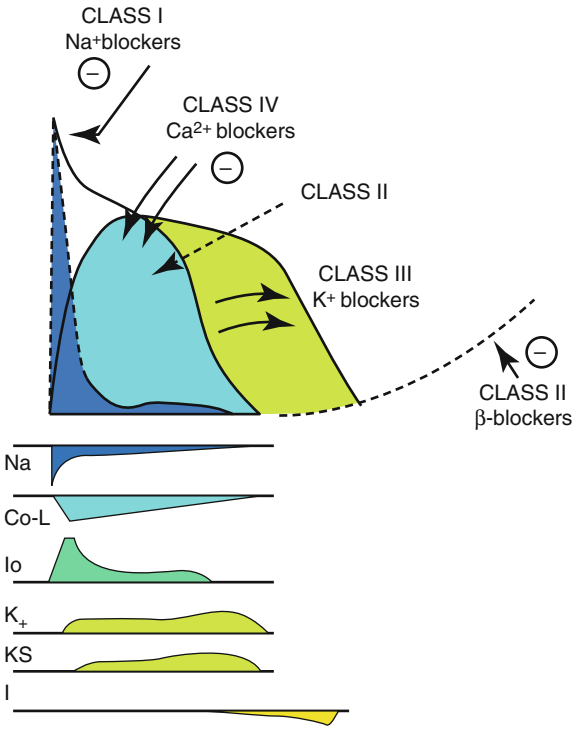

Fig. 4.4 Major effects of antiarrhythmic drugs on action potential

- *Newborn and children aren't* "small adults": they have different metabolism that MUST be known (usually they are better metabolizer than old people); drug's doses must be setup on body weight.
- Amiodarone is effective on different substrates due to its multiple antiarrhythmic affect (class from I to IV).
- *Risk of EAD due to a drug that blocks IK is reduced by addition of a INa/ICa blocker* (as quinidine + verapamil).
- *Supraventricular tachycardias can be associated with troponin level and/or ST abnormalities that rise in absence of coronary artery disease* [35, 36]. Suspicion of coronary syndrome must be based on risk factors, symptoms, ECG, or echocardiographic alteration.
- *Catheter ablation is safe and highly effective in curing supraventricular arrhythmias permanently*. It is a reasonable option of antiarrhythmic therapies in most of tachycardias and must be considered and proposed to patients [4, 37, 38] (Fig. 4.5).

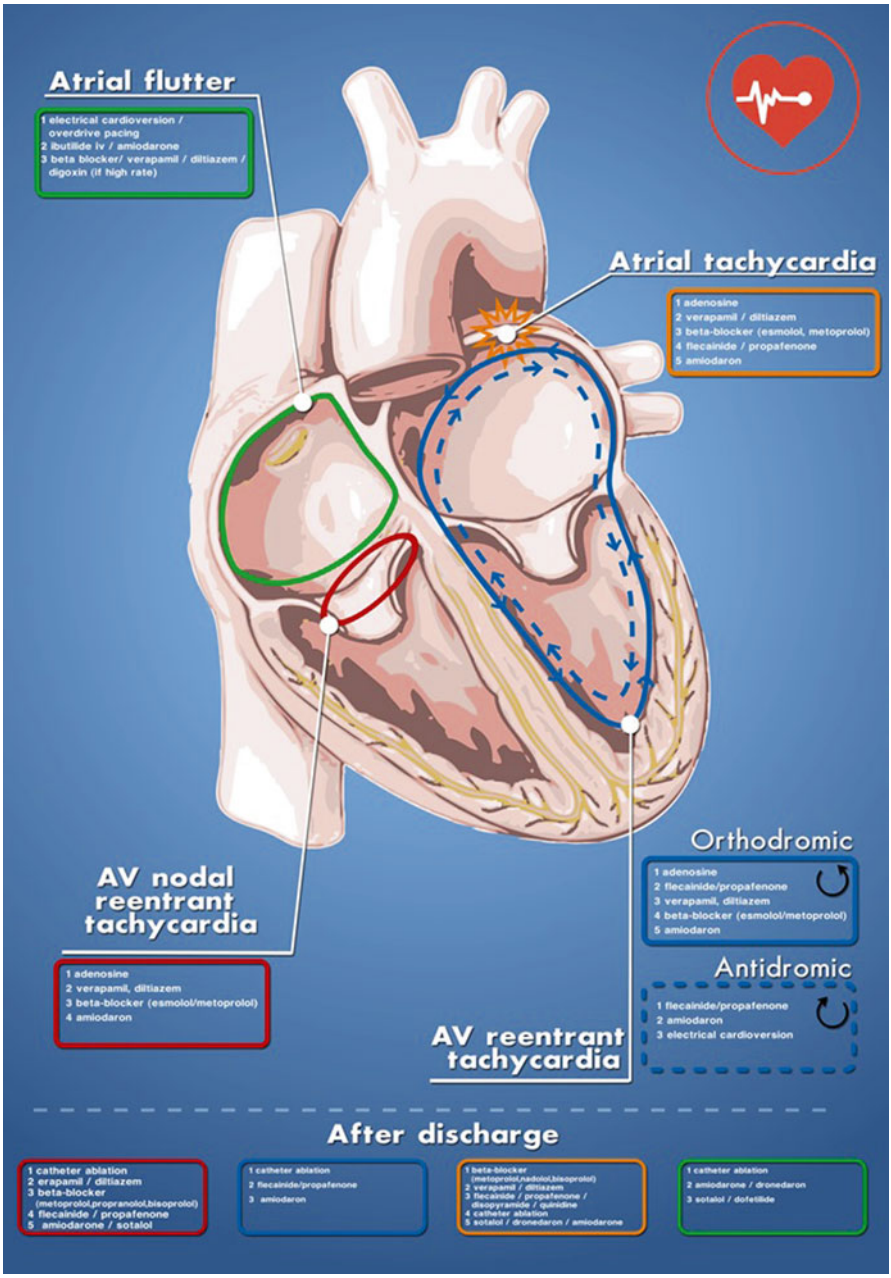

Fig. 4.5 Mechanisms, acute and long-term treatment of major supraventricular arrhythmias due to reentry circuits

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Atrial Flutter and Fibrillation in the Emergency Setting

5

Ermanno Dametto, Martino Cinquetti, Federica Del Bianco, and Matteo Cassin

5.1 Focus on the Topic

Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by uncoordinated atrial activation which determines on the electrocardiogram (ECG) the presence of fibrillatory waves of different timing, shape and amplitude, associated with an irregular and frequently rapid ventricular response (Fig. 5.1). It is the most frequent arrhythmia with a prevalence of 1.5–2 % in the general population [1], increasing with age and is the most frequent cause of arrhythmic access to the emergency department (ED), 1.5 % in "FIRE" and 3.1 % in "HERMES-AF" registries [2, 3] and hospitalisation (3.3 % in "FIRE" registry [2]).

European (ESC 2010) [4] and US (AHA/ACC/HRS 2014) [5] guidelines (GL) classify AF as *first diagnosed* or *recurrent*. Recurrent AF episodes are defined as *paroxysmal* if they terminate spontaneously (AHA/ACC/HRS 2014 GL [5] include also AF treated with cardioversion within 7 days), *persistent* (lasting longer than 7 days), *long-lasting persistent* (continuous for more than 12 months with intention of rhythm control strategy) or *permanent* (further attempts to restore and/or maintain sinus rhythm excluded).

AF may be asymptomatic, so the patient may be referred to the ED by a general physician for an occasional finding of irregular heart rhythm, or symptomatic. Symptoms described on arrival at the ED are most frequently palpitations (69.2 %), followed by dyspnoea (27.5 %), congestive heart failure (10.9 %), fatigue (105), angina (9 %), pulmonary oedema (4.5 %), syncope (3.3 %), transitory ischaemic attack (TIA) or stroke (2.2 %) [2]. Apart from acute symptoms, atrial fibrillation

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_5

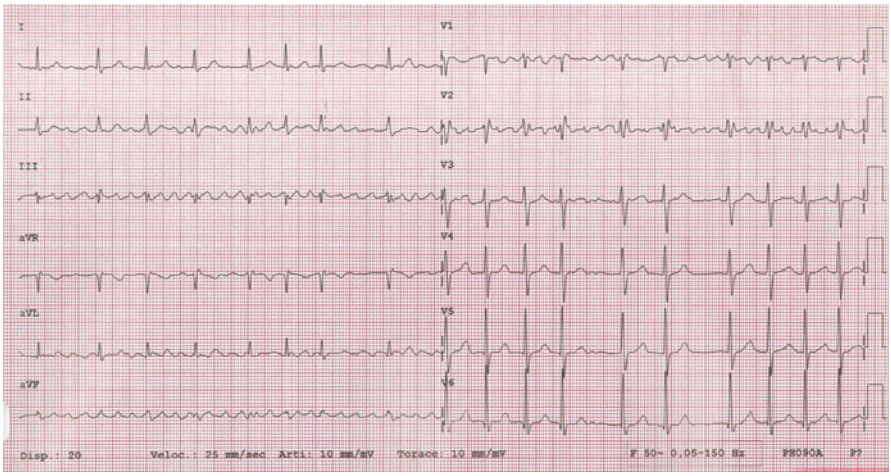

Fig. 5.1 *Atrial fibrillation* with moderately fast ventricular response (about 100 bpm). RR intervals are irregular and coarse F waves are visible

causes a fivefold risk of stroke, a threefold risk of heart failure and doubles dementia and mortality [5]. Furthermore, it reduces the quality of life [6]. For stroke, risk stratification and treatment of *nonvalvular* and *valvular AF* are distinguished. Valvular AF carries a very high thromboembolic risk if not anticoagulated: in patients with mitral stenosis and AF it is about 20 times over patients not affected by AF. Definition of valvular AF is not univocal; according to the AHA/ACC/HRS 2014 Guidelines, it is defined as AF associated with rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve or mitral valve repair [5].

Atrial flutter (*AFL*) is less common (about 10 % of ED admissions for AF or AFL were due to AFL in the "FIRE" registry [2]) but shares similar clinical features and treatment with AF. It is a macroreentrant atrial arrhythmia with regular atrial activation and shows electrocardiographically continuous atrial activity in at least one lead which may have various morphologies depending on the location of the circuit. The ventricular rate is usually regular due to a fixed atrioventricular (AV) conduction rate, mostly 2:1 with a frequency of 120–150 bpm (Fig. 5.2), but may be slower or irregular due to a variable AV conduction rate.

Both arrhythmias are usually associated with cardiovascular pathologies, mostly hypertension (64 %) but also coronary artery disease (32 %), heart failure (32 %), valvular hear disease (26 %) and cardiomyopathy (10 %). Chronic obstructive pulmonary disease (COPD) may be associated in 13 % of the patients and thyroid disease in 9 %. In about 10 %, none of these comorbidities are found, and the arrhythmia is called "lone atrial fibrillation" (or flutter), if the patient is younger than 65 years old [7].

Acute diseases may be associated with AF/AFL like myocardial infarction, pulmonary embolism, pneumonia, severe infections, alcohol abuse, drug toxicity, hypothermia and electrolyte abnormalities [8].

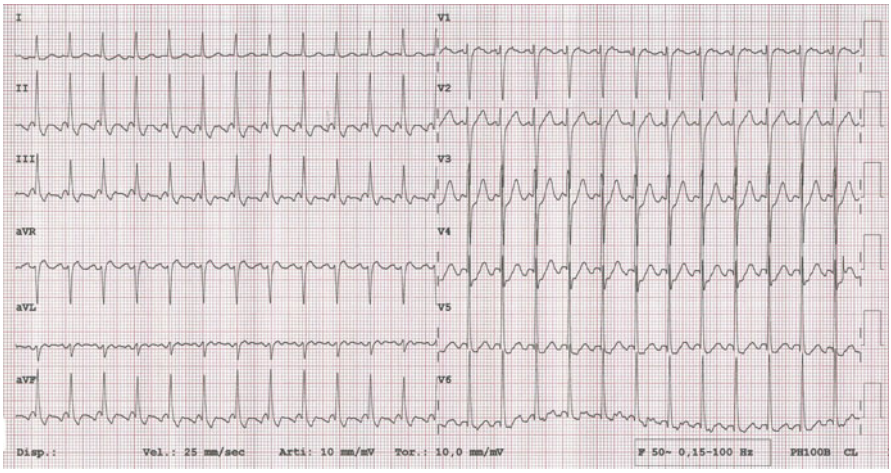

Fig. 5.2 *Atrial flutter with 2:1 AV conduction and quite rapid ventricular rate* of 150 bpm. Regular RR intervals

5.2 What Physicians Working in ED Should Know

The ED physician has several tasks:

1. *Rule out severe clinical instability*

Altered mental status, hypotension, pulmonary oedema and ongoing ischemia necessitate acute electrical cardioversion (ECV) once diagnosis of AF/AFL is confirmed and is thought to be the primary cause [9], at least if there is no prompt response to rate control therapy [4, 5, 10].

2. *Diagnosis of the arrhythmia*

The pulse presents irregular in case of AF but is usually regular in case of flutter. Electrocardiographic diagnosis of AF is usually easy for the irregular RR intervals and f waves. Atrial flutter appears usually as a regular arrhythmia due to fixed conduction rate, mostly 2:1 with ventricular rates around 120–150 bpm, but may be less or conduction may be variable. When rapid conduction is present, the flutter waves may not be so evident. In these cases and if the patient is stable, we recommend to perform a continuous 12-lead ECG registration during carotid sinus massage (after exclusion of any carotid bruit) or adenosine infusion (6, 12 or 18 mg bolus followed by 20 ml saline solution flush) to clear up differential diagnosis with other supraventricular arrhythmias and to record the flutter wave morphology, which helps the cardiologist to define the long-term therapeutic approach (e.g. radiofrequency ablation). *Typical atrial flutter* (also called *cavotricuspid isthmus-dependent atrial flutter*) is a macroreentrant circuit posterior to the tricuspid annulus, crossing the

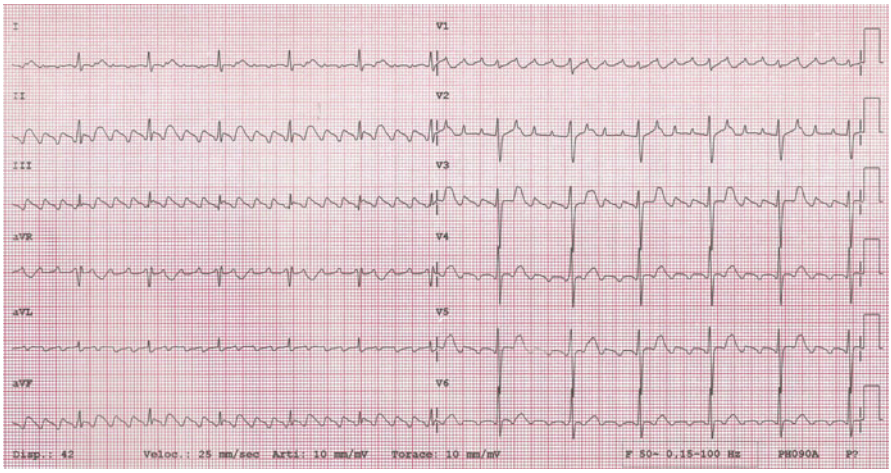

Fig. 5.3 *Typical atrial flutter with counterclockwise atrial activation (common atrial flutter)* with 4:1 AV conduction, 70 bpm. Atrial flutter waves are clearly seen: negative in inferior leads and positive in V1

isthmus between the inferior vena cava orifice and tricuspid annulus. Activation sequence is more frequently counterclockwise (downwards the right atrial free wall and upwards the interatrial septum), and in this case, the arrhythmia is called *common atrial flutter* or *counterclockwise AFL* (Fig. 5.3). Less common is *clockwise typical atrial flutter*, also called *reverse AFL* (Fig. 5.4). On ECG, the former shows classical "sawtooth" flutter waves with negative polarity in inferior leads and positive in V1, and the latter shows flutter waves with positive polarity in the inferior leads and negative in V1. Atypical flutters (noncavotricuspid isthmus dependent) show flutter waves with other morphologies (Fig. 5.5) [5].

In patients with AFL treated with flecainide or propafenone sometimes rapid 1:1 AV conduction is favoured due to flutter wave slowing. This phenomenon is frequently accompained by conduction aberrancy and QRS widening (Fig. 5.6).

In patients with Wolff–Parkinson–White Syndrome, a *pre-excited AF* (Fig. 5.7) is characterised by irregular RR intervals with various degrees of QRS widening (various degrees of fusion between accessory pathway and nodal conduction). In case of fast conduction properties of the accessory pathway, ventricular rate can be extremely high, possibly leading to severe haemodynamic consequences or even to ventricular fibrillation. *Pre-excited AFL* appears as a wide QRS tachycardia.

3. *Clinical history and physical examination for evaluation of concomitant heart disease and comorbidities*

A complete medical history including previous cardiac and noncardiac diseases, history of former AF, medication use and drug or alcohol abuse should be obtained. Onset of the current AF episode should be carefully defined as it is a crucial point for decision making, in particular, it has to be cleared if onset is within or more than

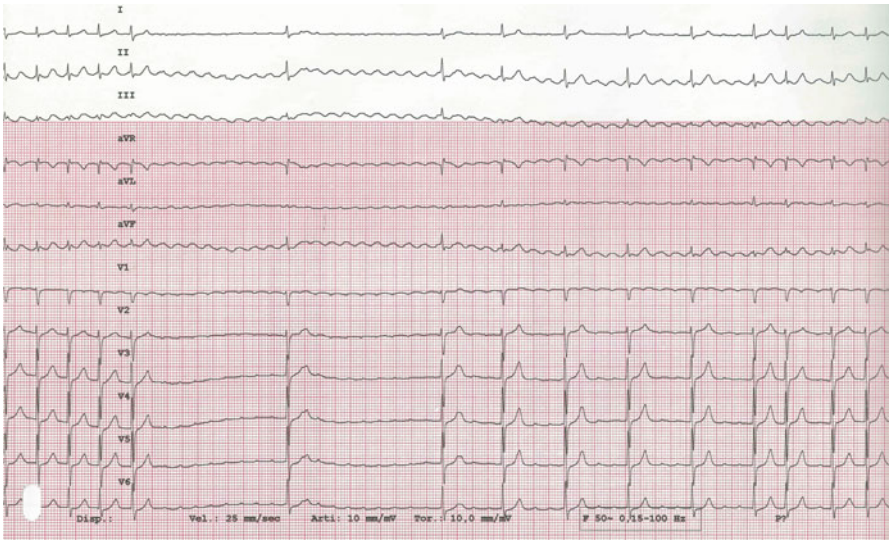

Fig. 5.4 *Typical atrial flutter with clockwise atrial activation (reverse atrial flutter) during adenosine injection*. Initially 2:1 AV conduction, 150 bpm and masked flutter waves. A marked conduction slowing follows, unmasking flutter waves: positive in inferior leads and negative in V1. Diagnosis was confirmed by electrophysiological study

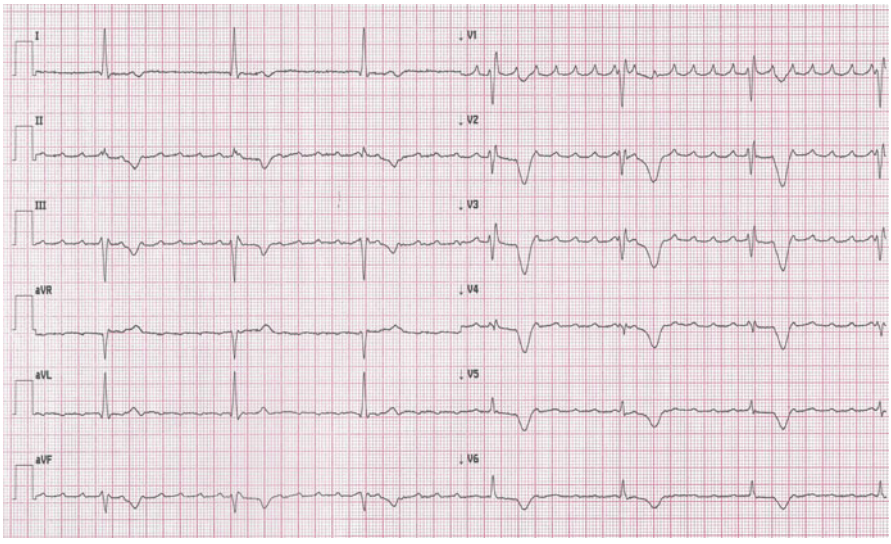

Fig. 5.5 *Atypical atrial flutter:* flutter waves are positive in inferior leads and in V1

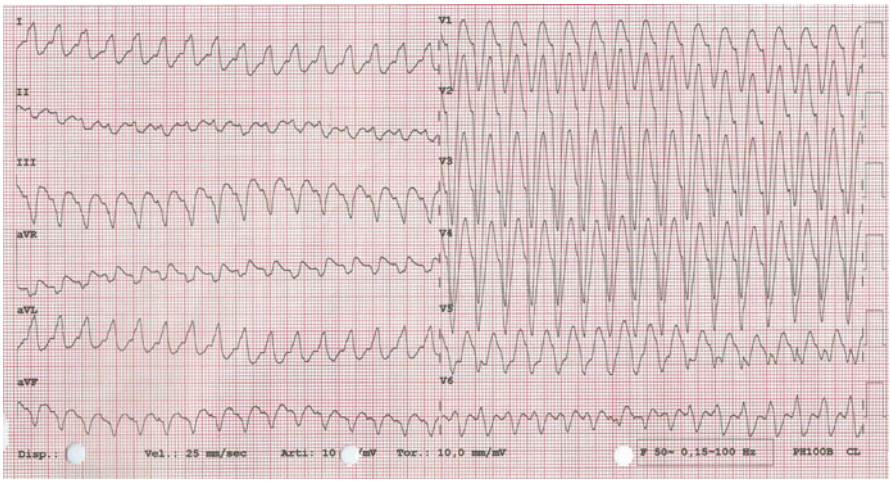

Fig. 5.6 *Atrial flutter with 1:1 AV conduction and aberrancy* 190 bpm (during i.v. flecainide infusion). Flutter waves are not visible. Resembles a wide QRS tachycardia

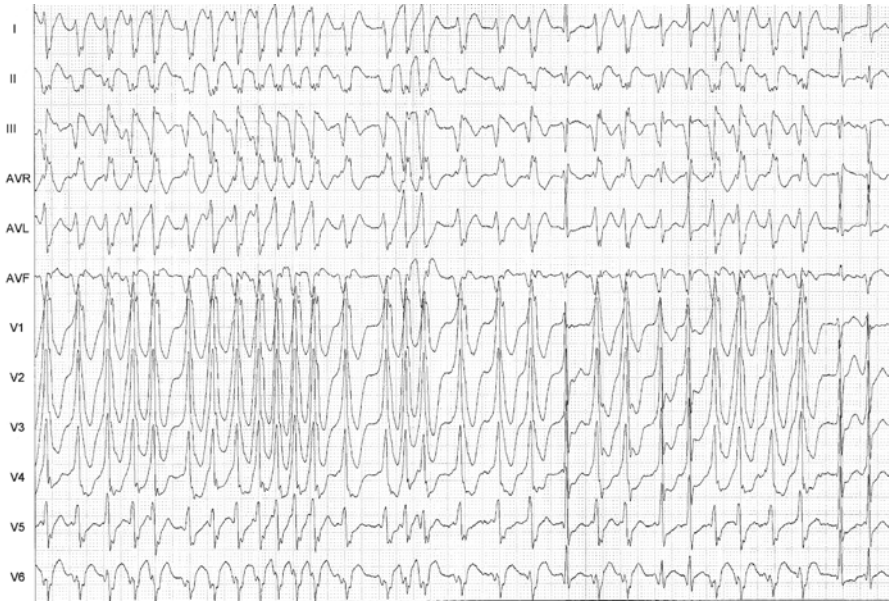

Fig. 5.7 *Pre-excited atrial fibrillation with fast AV conduction*, at times near 300 bpm. Bizarre wide QRS morphology with irregular RR intervals. In between, there are a few beats with normal QRS, conducted through the AV node

48 h (time within acute cardioversion without previous anticoagulation can be considered). Frequently, AF presents as continuous palpitations with acute onset. In this case, onset definition is easy. Other times, palpitations are perceived intermittently

or other symptoms dominate as dyspnoea or fatigue which can be vague. In these cases, it can be of help if patients are used to evaluate daily their pulse (often evaluated together with arterial pressure in the hypertensive). If onset of AF cannot be clearly dated, the arrhythmia should be regarded as *"AF of undefined onset"*.

Physical examination should initially be aimed to vital signs like blood pressure, pulse frequency, signs of pulmonary or peripheral congestion and oxygen saturation. Cardiac assessment should include evaluation of heart sounds and murmurs and a careful evaluation of both arterial and jugular pulse (to assess the rhythm and possible AV dissociation).

Laboratory tests should be tailored to patient's presentation. A complete blood count, serum electrolytes, renal and hepatic function tests, coagulation status and thyroid-stimulating hormone should be routinely obtained. Brain natriuretic peptide, troponin I or T, C-reactive protein and D-dimer test help ruling out heart failure, myocardial ischemia, concomitant inflammatory or infectious disease and pulmonary embolism if these conditions are suspected.

Thyroid disease is not uncommon in AF patients and overt hyperthyroidism is associated in about 4 % of AF patients [11]. Thyroid-stimulating hormone is a reliable screening tool which can be applied in some EDs and may help in decision making (choosing rate control strategy or defining contraindication for amiodarone use [12].

An urgent echocardiogram should be performed in haemodynamically compromised patients [4]. Alternatively, a focused ultrasonography performed by the ED physician can determine underlying cardiac condition like structural heart disease, pericardial effusion and pulmonary embolism, or clarify causes of shock or hypotension and guide resuscitation by volume repletion measuring the inferior vena cava diameter. Ultrasound competence is not uniformly available among ED physicians, but a focused examination of the heart may help guiding therapy in AF management [13]. However, a complete echocardiographic examination should be performed as part of initial evaluation [4, 5, 14] as soon as possible, even on outpatient basis in stable patients.

4. *Symptom relief by cardioversion (electrical or pharmacological) or rate control*

Unstable patients In patients with haemodynamic compromise like hypotension, pulmonary oedema or ongoing myocardial ischemia thought to result mainly from acute AF or AFL, electrical cardioversion is indicated [9], especially if it does not respond promptly to pharmacological rate control measures [4, 5, 10].

Anticoagulation with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) should be initiated as soon as possible. Do not delay ECV if the patient is extremely unstable [9]. In the author's opinion if the patient is hypotensive, ECV is preferable, whereas if pulmonary oedema or myocardial ischaemia is present, rate control should be tried first.

Atrial fibrillation can be an epiphenomenon of an "alternative" primary diagnosis, and in these cases, mortality rate is high (11 % in the study of Atzema et al. [15]). Patients may present with vague symptoms. Scheuermeyer et al. [16] reported

on a series of patients with underlying medical illness like sepsis, acute coronary syndrome (ACS), decompensated heart failure, pulmonary embolism, obstructive pulmonary disease exacerbation, acute renal failure and gastrointestinal bleedings. Those who underwent immediate rate or rhythm control attempts suffered a much higher complication rate (40.7 %) than those who did not (7.1 %) and were unlikely to achieve success. So it is more advisable to delay rhythm management strategies and manage these patients first correcting the primary acute disease, administrating intravenous fluids guided by bedside echocardiography (to assess volume status) and performing frequent reassessments while waiting for confirmatory diagnostic tests [16].

Stable patients with recent-onset AF (<48 h) There is still controversy on optimal management of these patients, being rate and rhythm control the two alternative strategies without clear-cut evidence favouring one or the other. *Rate control strategy* in the ED consists of pharmacological control of ventricular rate and anticoagulation treatment if indicated. With *rhythm control strategy*, the patient is cardioverted to sinus rhythm (SR) either pharmacologically or electrically, usually discharged from the ED and followed as outpatient afterwards. A delayed cardioversion (CV) after at least 3 weeks of adequate anticoagulation can be planned in some patients if the initial rate control strategy is not well tolerated.

Although several trials on AF patients like the AFFIRM [17] did not find significant differences on the main clinical outcomes between rate and rhythm control, the latter seems the preferred strategy worldwide in the long treatment of AF [18, 19]. General indications for preference of either strategy are listed in Italian guidelines on AF management [20]: rhythm control strategy should be the option for (1) patients with first AF episode (taking into account also age and comorbidities) and (2) for patients with recurrent AF with high probability of long-term sinus rhythm maintenance, or in whom rate control proved uneffective or if AF determines negative haemodynamic effects. Rate control strategy is preferred for (1) patients refractory to antiarrhythmic therapy, with frequent AF relapses non-candidable to AF ablation or not candidable to rhythm control strategy because of age or underlying heart disease and (2) for older asymptomatic patients with persistent AF or older patients with recurrent AF, heart failure and poor ventricular function.

As far as ED practice concerns, there is a considerable variability among different countries: rate control strategy is largely favoured in the USA (74 %), while in Canada, most patients undergo cardioversion (66 %). The UK and Australia adopt rate or rhythm control in equal proportions [21].

In our clinic, rhythm control is generally the preferred management strategy.

The theoretical advantages of an aggressive rhythm control approach are rapid discharge without hospital admission, immediate resumption of normal activities, potential avoidance of medications and minimization of healthcare resources and costs. In addition, with rate control strategy, many patients can derive physical and psychological inconvenience maintaining the arrhythmia and drugs after discharge [22].

A recent review of five studies involving 1593 cases undergoing ED cardioversion [23] demonstrated that success rate was high (around 90 %), with a discharge rate of about 90 % and a complication rate generally lower than 5 %, exceptionally leading

to hospital admission. Thromboembolic complication rate was very low (0.06 %). So in selected patients with recent-onset AF, ED physicians should feel comfortable with this approach which should ideally be standardised by a local ED protocol and include timely and appropriate follow-up. The first description of an ED protocol dealing with recent-onset AF or flutter was the "Ottawa Aggressive Protocol" [24]. Excluding patients presenting with AF onset >48 h or of unknown duration and those with other primary diagnosis necessitating admission, it involved sequential pharmacologic and, when indicated, electrical cardioversion by the emergency physician. It allowed discharge of 96.8 % of the 660 enrolled patients, 93.3 % of those in sinus rhythm, after a median length of stay of 4.9 h overall. Adverse outcomes, mainly transient hypotension, occurred in 7.6 % and only 3.2 % of patients required hospitalisation. No patient died or suffered a stroke. Despite these encouraging results, limited data help guide emergency physicians on which AF patients can be safely managed as outpatients (see below). An interesting implementation of an ED cardioversion protocol for acute AF patients after exclusion of high-risk features was described by Bellone et al. [13]; their workup included morphological echocardiographic investigation before treatment by certified emergency physicians, which has the potential of improving the risk stratification and the therapeutical choice.

Another management strategy consists in conservative "wait-and-watch approach" which relies on the known discrete likelihood of spontaneous cardioversion of recent-onset AF (from 20 % up to 68 % in the study of Danias et al. [25]); early (<24 h) presentation is the best predictor of spontaneous cardioversion. Patients may be discharged on rate control medication and anticoagulation if appropriate and scheduled for return visit to ED to permit CV within the 48 h period [26] from symptom onset if AF persists, or may be admitted to an ED observation unit, reassessed after some hours and eventually cardioverted if AF persists [27]. This strategy can be applied following the patient's preference but may be an option if ED is overcrowded.

Stable patients with AF onset >48 h or with AF of uncertain onset If the patient has properly been anticoagulated for at least the preceeding 3 weeks, acute cardioversion can be considered as an alternative to rate control. On the contrary, in non-anticoagulated patients, rate control is generally the most appropriate strategy. In the acute setting, the target ventricular rate should usually be 80–100 bpm [4]. Once rhythm control is achieved and anticoagulation started, the patient can be considered for discharge and referred to a cardiologist or a general practitioner. If adequate rate control is not achieved, the patient is still symptomatic or if new ventricular dysfunction is to be detected, cardioversion should be considered: the patient must be fully anticoagulated independently of the thromboembolic risk (start with UFH or LMWH for immediate action and bridge then with vitamin K antagonists; novel anticoagulants may be used as alternative), then undergo a transoesophageal echocardiogram (TEE) to exclude intracardiac thrombi and finally electrically cardioverted. Anticoagulation should be continued at least 4 weeks or indefinitely, according on the thromboembolic risk profile. If thrombosis is detected, the patient should undergo another TEE after at least 3 weeks of effective anticoagulation and if it has resolved undergo ECV thereafter [4, 5, 10].

According to the Canadian Guidelines 2014 [10], the TEE-based CV approach should also be applied for a AF patients presenting <48 h after AF onset if high-risk features like valvular AF or stroke/TIA in the last 6 months are present.

5. *Antithrombotic therapy*

It is generally believed that antithrombotic therapy is the mainstay of AF management in any care setting, as from this therapy, most of prognostic benefit in terms of morbidity (stroke prevention) and mortality has to be gained. Nevertheless, it is still much underprescribed, usually in less than 55 % of AF patients, as results from studies are conducted in different settings. EDs constitute excellent opportunities to start thromboprophylaxis in the absence of contraindications and help filling this gap [3]. Treatment options include LMWH or UFH, vitamin K antagonists (VKAs) and novel oral anticoagulants (NOACs).

Immediate anticoagulation can be obtained with unfractionated heparin (i.v. bolus of 80 UI/kg followed by continuous i.v. infusion adjusted to an activated partial thromboplastin time of twice the control value (initially 18 UI/kg/h)) [28] or LMWH (most popular being enoxaparin 100 UI/kg BID) based on ACUTE II [29] ad ACE trials [30]. Heparin therapy is generally used as bridging with VKAs which have a delayed onset of action which takes some days.

At present, three NOACs have been tested for AF cardioversion (prospectively or in post hoc analysis) [31–33]:

Dabigatran 150 mg twice daily (TD) if creatinine clearance > 50 ml/min, 110 mg TD if CrCl between 30 and 50. In the USA, the FDA approved 150 mg TD if CrCl >30 and 75 mg TD if ClCr 30–15. Do not use in association with dronedarone; reduce dose if concomitant verapamil is used.
Rivaroxaban 20 mg once daily or 15 mg if CrCl 49–30 ml/min.
Apixaban 5 mg TD or 2.5 mg TD if two or more risk factors for bleeding: age <80 years, weight <60 kg, creatinine >1.5 mg/dl.
Time to peak action is around 3 h for all three.

Valvular AF carries a very high risk per se and must always be treated with VKAs. NOACs were not tested or resulted inferior to VKAs in this setting [5, 34].

For patients with nonvalvular AF, a number of risk stratification schemes have been proposed, the mostly recommended [1, 5] being the CHA2DS2-VASc scoring system [35] (Table 5.1). As chronic therapy, anticoagulation is not indicated for score = 0, indicated for score ≥2, recommended for score = 1 by European guidelines [4], while US guidelines [5] indicate alternatively oral anticoagulants, aspirin or no antithrombotic treatment (Class IIb). We favour oral anticoagulation for patients with score = 1 unless at risk of bleeding.

Any type of AF (paroxysmal, persistent, permanent) carries a similar risk of stroke, so anticoagulation should be chosen regardless of AF type. Atrial flutter has shown to have similar thromboembolic risk as AF and should be managed the same way.

All patients with AF >48 h duration (including those with CHA2DS2-VASc score = 0) candidate to cardioversion must be adequately anticoagulated for at least

Table 5.1 CHA2DS2-VASc scoring system

Acronym	Risk parameter	CHA2DS2VASc score	Stroke rate (%/year)
C	Cardiac failure or dysfunction	0	0
H	Hypertension	1	1.3
A (2)	Age >75	2	2.2
D	Diabetes	3	3.2
S (2)	Stroke/TIA or thromboembolism	4	4
V	Vascular disease	5	6.7
A	Age 65–74	6	9.8
Sc	Sex category (female)	7	9.6
		8	6.7
		9	15.2

Based on Lip et al. [35]
One point is assigned to each parameter except for Age >75 and Stroke whom 2 points are assigned

the three preceding weeks before the procedure, unless intraatrial thrombus has been ruled out by TEE or in case of rare emergency situations and continued on anticoagulation for at least 4 weeks afterwards. Lifelong anticoagulation is indicated for patients at high risk of stroke or AF recurrence.

For patients with AF onset <48 h, current guidelines [4, 5, 10] indicate cardioversion without previous anticoagulation, as former studies demonstrated low embolic complications (0.8 % stroke at 30 days in the study of Weigner et al. [36]). Some concern has raised as it was demonstrated that 4–14 % of these patients had an intraatrial thrombus on transoesophageal echocardiography [37, 38], and ESC 2010 guidelines [4] recommend to start anticoagulation with UFH or LMWH before cardioversion even for AF lasting <48 h. In high-risk patients, heparin therapy has to be followed by long-term oral anticoagulation (class I recommendation), while in patients with no risk factors, heparin therapy may be considered only pericardioversion (IIb, level C recommendation), but this latter recommendation is not evidence based. The 2014 AHA/ACC/HRS guidelines [5] make similar recommendations on use of peri- and postcardioversion antithrombotic therapy, adding the option to use NOACs for the purpose (Class I recommendation). In this context, also a recent European Expert Consensus [28] agrees with the use of NOACs with a class IIa recommendation. A recent large cohort study [39] on 7660 cardioversions of AF lasting <48 h supports the recommendation of prolonged anticoagulation in high-risk patients after CV: without anticoagulation, thromboembolic risk resulted 0.7 % at 30 days. Risk factors were age, heart failure, diabetes, and female gender (elements of CHA2DS2-VASc score system). Patients without risk factors experienced a very low complication rate of 0.2 %, whereas those with multiple risk factors had a thromboembolic risk approaching 10 %.

For patients with AF lasting >48 h or of unknown origin with no risk factors (CHA2DS2-VASc = 0), anticoagulation is not advised unless a delayed cardioversion is planned.

6. *Decision for cardiologist consultation or hospitalisation*

Consultation with a cardiologist should be requested for:

- Unstable patients (hypotension, angina, heart failure)
- Patients with known significant cardiac disease
- If significant underlying heat disease is suggested by objective findings, laboratory data or diagnostic testing
- If rate or rhythm control has not been achieved
- If cardiovascular complications have occurred as consequence of antiarrhythmic or rate control therapy
- If cardioversion preceded by TEE is the choice
- If Brugada pattern emerges on ECG after pharmacological cardioversion

Most of these patients will also require hospitalisation, as well as patients with concomitant acute illness (sepsis, pneumonia, pulmonary embolism, etc.).

5.3 What Cardiologists Should Know

"Pill-in-the-pocket approach": useful treatment strategy for patients with no or minimal heart disease, no conduction disturbances and infrequent but prolonged and well tolerated AF recurrences. Patients have to take orally 200–300 mg flecainide or 450–600 mg propafenone (the higher dosage for weight >70 kg). This approach should be prescribed by a cardiologist after full diagnostic workup (and therefore in the author's opinion avoided in first diagnosed AF) and must first be tested in the ED for safety and efficacy before it can be used at home. If this strategy is the choice, the cardiologist should specify this indication on his written evaluation of the patient so that instructions can be promptly be followed in the ED for the first test treatment. In the original article by Alboni et al., [40] rapid 1:1 flutter complicated only 1 case (0.6 %), so ESC 2010 guidelines [4] recommend this strategy as it was described, but AHA/AC/HRS 2014 [5] and CCS 2010 [41] guidelines recommend addition of beta blocker or nondihydropyridine calcium channel blocker to avoid this side effect. This strategy should not be used for patients with AFL.

Patients already on chronic antiarrhythmic therapy may present to the ED with relapsing acute onset AF. If cardioversion is judged to be the choice, we suggest electrical CV as first choice. Alternatively, pharmacological cardioversion (PCV) with the same antiarrhythmic agent administered intravenously at reduced dose can be performed although there is little evidence in literature. In our centre, it has been common practice for more than a decade to use flecainide or propafenone half dose bolus (1 mg/kg in 10 min) on top of chronic therapy with the same agents or intravenous amiodarone with conventional dosages and infusion rates on top of chronic amiodarone therapy, after checking for contraindications. We have not yet experienced significant side effects. Patients are discharged on the same antiarrhythmic agent, even at higher dose, as single or few AF relapses should not be interpreted as treatment failures if the antiarrhythmic burden is lowered on medication. We advise

in general against the use of different antiarrhythmic drugs on top of chronic antiarrhythmic drug therapy although limited experience on intravenous ibutilide in patients taking amiodarone, propafenone or flecainide seems safe [42, 43].

Coronary artery disease and atrial fibrillation are often associated diseases [7] and share common risk factors. AF may complicate myocardial infarction in about 18 % [44] and is frequently associated with severe LV damage and heart failure. Fast ventricular rate contributes to increased myocardial damage and heart failure, requiring prompt treatment. Adequate rate control can be obtained preferably by administration of beta blockers (uniformly class I recommendation by ESC 2010, AHA/ACC/HRS 2014, ESC 2012 STEMI guidelines [4, 5, 45]) or in alternative nondihydropyridine calcium antagonists (class IIa in ESC 2010; class IIb in AHA/HRS/ACC 2014; class I in ESC STEMI 2012), in patients who do not display HF or haemodynamic instability. In patients with associated severe left ventricular dysfunction, or signs and symptoms of heart failure, rate control is more safely achieved with i.v. amiodarone or i.v. digoxin (class I in ESC STEMI 2012 [45]; Class IIb in AHA/ACC/HRS 2014 [5]), also in association [45]. Urgent electrical cardioversion should be considered in patients presenting with atrial fibrillation and intractable ischaemia or haemodynamic instability [45].

Pharmacologic cardioversion should be considered if ischemic trigger has resolved with amiodarone being the agent of choice [45].

A still yet unsolved issue is the significance of two common findings, *mildly elevated troponin I (TnI) levels or ST depression* on ECG in the absence of overt acute coronary syndromes (ACS). It is common practice in the EDs to check troponin levels in patients presenting with AF even after excluding primary diagnosis of acute coronary syndrome (76 % of 662 patients in the study of Gupta et al. [46]). The prevalence of mildly positive TnI tests in acute AF patients without evident ACS varies from 9 [47] to 44 % [46]. Troponin I elevation predicts increased the risk of death [48, 49] or MI [46, 48] in the long term. This seems true in the acute setting for minor TnI elevations (detectable but subthreshold) as well as for positive TnI tests (with the higher the value the higher the risk [48]), but also in more chronic AF settings [49]). Troponin elevation is associated with older age, CAD risk factors, known CAD disease, creatinine elevation and ventricular rate but not with angina or ischemic ST depression [46, 28].

It is known that TnI elevations can occur also in the absence of significant coronary stenoses probably because of supply–demand mismatch or atrial–ventricular stretch [46]. Moreover, it has to be taken into account that troponin levels may be elevated for other reasons in acute AF patients (79 % in the study of Meshkat et al. [50] including demand-related rise in 36 %, congestive heart failure in 29 %, renal failure in 17 %, sepsis in 14 % and pneumonia in 2 %).

TnI elevation leads to increased prescription of diagnostic tests for CAD which demonstrated mild diagnostic yield (absent in the study of Gupta et al. [46], useful leading to threefold coronary revascularisation rate and better outcome in the study of Conti et al. [47]). Although these studies confirm that biomarkers seem useful for improving risk prediction in AF, the link between AF and coronary artery disease needs additional investigation.

ECG changes suggesting ischemia (ST segment depression) even in the absence of angina or troponin elevations are also frequent. The positive predictive value for

significant CAD varies from 31 [51] to 50 % [52]. Pradhan et al. [51] observed a strong correlation between grade of ST depression and ventricular rate. In their series, the percentages of positive results for diagnostic tests for CAD did not differ significantly between patients with (31 %) or without (21 %) ST depression during AF, so in conclusion, they stated that ST depression during AF is a prevalently rate-related phenomenon.

Absence of ECG changes resulted highly reassuring in the study of Tsigkas et al. [52] (only 4 % prevalence of CAD). In the series of Androulakis et al. [53], the prevalence of ST depression during fast FA was 32.5 %, and non-invasive diagnostic tests performed quite well in identifying patients with CAD.

So what to do in the presence of TnI elevation or new "ischemic" ECG changes during rapid AF?

- *Negative TnI* and *no ECG changes* do not require further investigation.
- *Mildly positive TnI values or ECG changes* should be evaluated in a polyparametric context which accounts for risk factors and cardiac comorbidities.
  - *Lower-risk* patients may be discharged after 12-24 h in an observation unit if stable and troponin descending, possibly after an echocardiogram and non-invasive provocative test for CAD (otherwise these tests should be arranged shortly after as outpatients).
  - *Higher-risk* patients should be admitted.

Heart failure (HF) and AF are strongly associated diseases and can interact to promote their perpetuation as onset of AF can worsen symptoms in patients with HF. These patients should be managed according to clinical severity. If markedly compromised (pulmonary oedema), they should be cardioverted if there is no prompt response to rate control (amiodarone or digoxin are agents of choice) [4]. If clinical presentation is less severe and AF duration is less than 48 h, pharmacological cardioversion with amiodarone or ECV can be considered as alternative to rate control strategy. For rate control purposes, cautious use of beta blockers in patients with systolic heart failure (or diltiazem if HF with preserved EF) can be considered (AHA/ACC/HRS 2014 class I recommendation) [5].

Conversely, worsened HF can promote a rapid ventricular response in permanent AF. These patients usually do not respond to cardioversion and rate control is as well more difficult to achieve. The mainstay of therapy in this setting should be aimed to optimise HF treatment.

Patients may present with newly detected HF in the presence of AF with a rapid ventricular response. These should be presumed to have a rate-related cardiomyopathy, with the arrhythmia being a potentially reversible cause of HF [54]. In this situation, two options can be considered: (1) rate control and re-evaluation for EF improvement and (2) rhythm control, which common practice is to initiate amiodarone and cardiovert in the patient electrically at least 3 weeks later [54]. In our clinic, we try to pursue a more rapid rhythm control strategy for patients with suspected tachycardiomyopathy which consists in performing TEE after clinical stabilisation with HF medications, rate control and anticoagulation. If no thrombus is

detected, the patient receives a 24 h amiodarone infusion after which ECV is performed and followed by oral loading dose of amiodarone.

AF in Pre-excitation If very rapid and unstable, urgent ECV should be performed [4, 5, 9]. If heart rate is not too high and the arrhythmia is well tolerated, it can be cardioverted with intravenous flecainide, propafenone, ibutilide and procainamide. The same agents are effective of rate control [4, 5, 20]. Drugs acting on the AV node, like calcium channel blockers, digitalis and adenosine, are contraindicated, because conduction over the accessory pathway is favoured and the rate transmission to the ventricle may become very rapid potentially inducing ventricular fibrillation. Amiodarone has recently been defined as harmful in the AHA/ACC/HRS 2014 guidelines [5], whereas ESC guidelines 2010 [4] recommend it class I for rate control. Beta blockers are contraindicated according to ESC guidelines 2010 [4] but might be used with caution according to the AHA/ACC/HRS 2014 guidelines [5].

5.4 A Possible Algorithm/Pathway for Diagnosis and Treatment

The management of patients with AF depends on their clinical presentation which may be unstable (Fig 5.8), stable with AF onset < 48 hours (Fig. 5.9) or stable with AF onset > 48 hours/undefined onset (Fig 5.10).

If cardioversion is the choice, check potassium levels (unless emergent ECV is necessary) and correct it if necessary proceeding. If patient is on chronic digoxin therapy, plasma level should be checked (ECV is contraindicated in case of intoxication).

In general, ECV is more effective than pharmacological cardioversion (PCV) and requires less time, but greater organisational efforts.

SR is achieved in about 90 % with ECV and 70 % with PCV [55]. If PCV fails, ECV restores SR in the majority of cases. On the contrary, if AF relapses immediately (IRAF) after ECV, the use of an antiarrhythmic agent before repeat CVE enhances the probability of maintaining SR. If AF does not convert to sinus rhythm with ECV (no or a maximum single sinus beat achieved, as defined by ESC 2010 guidelines [4]), the patient can be pretreated with ibutilide (1 mg over 10 min) which lowers defibrillation threshold and facilitates greatly achievement of SR on repeat ECV [56].

Pharmacologic cardioversion is little effective after 7 days of AF onset; therefore, in this case, ECV is preferred.

Atrial flutter poorly responds to antiarrhythmic drugs except for ibutilide; therefore, ECV should be first choice. If propafenone or flecainide are used for AFL conversion, slowing of atrial rate occurs, which sometimes can conduct faster to the ventricles (from usual 2:1 to 1:1 conduction), often with conduction aberrancy (Fig. 5.6). The result is a very rapid, frequently untolerated arrhythmia which should be electrically cardioverted. So if these agents are used for treatment of AFL, co-administration of rate control drugs is advised. The same phenomenon may occur when flecainide or propafenone is used for conversion of AF, as in some cases AF

organizes into AFL ("IC flutter"). In rare cases of patients treated with these agents, an electrocardiographic "Brugada pattern" may become evident (coved-type ST elevation in at least one lead from V1 to V3). These patients should undergo cardiologic consultation before eventual discharge.

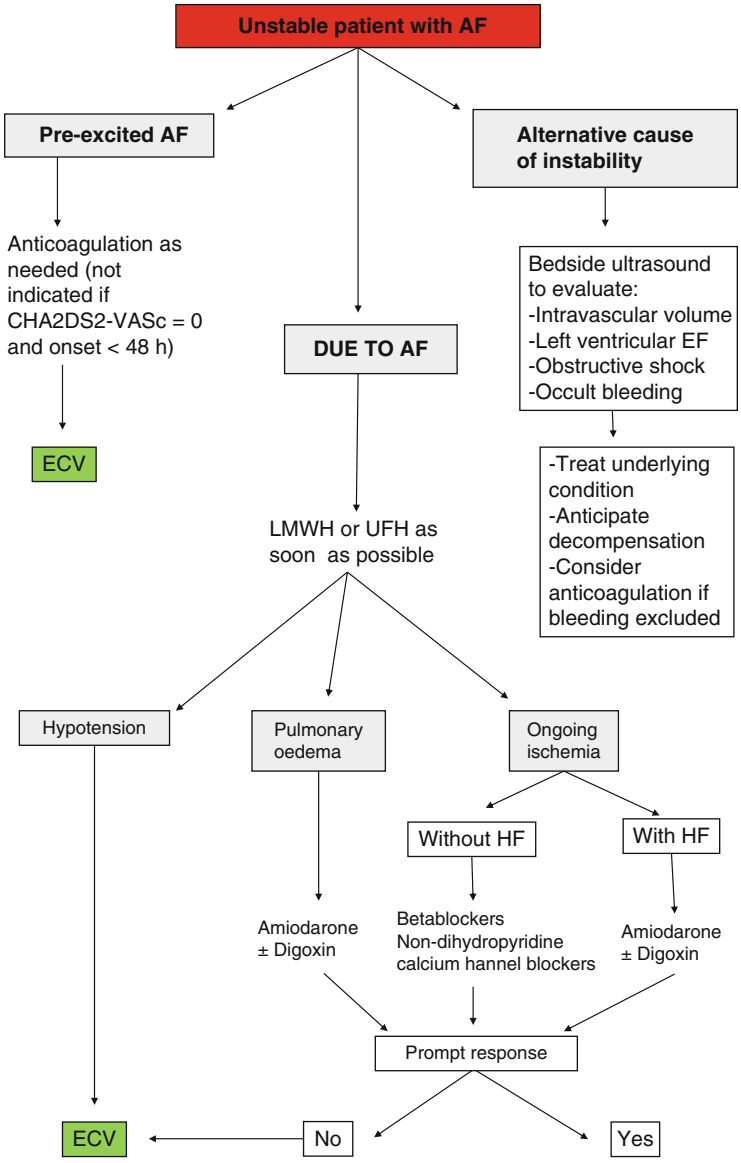

Fig. 5.8 Algorithm for management of patients with unstable AF

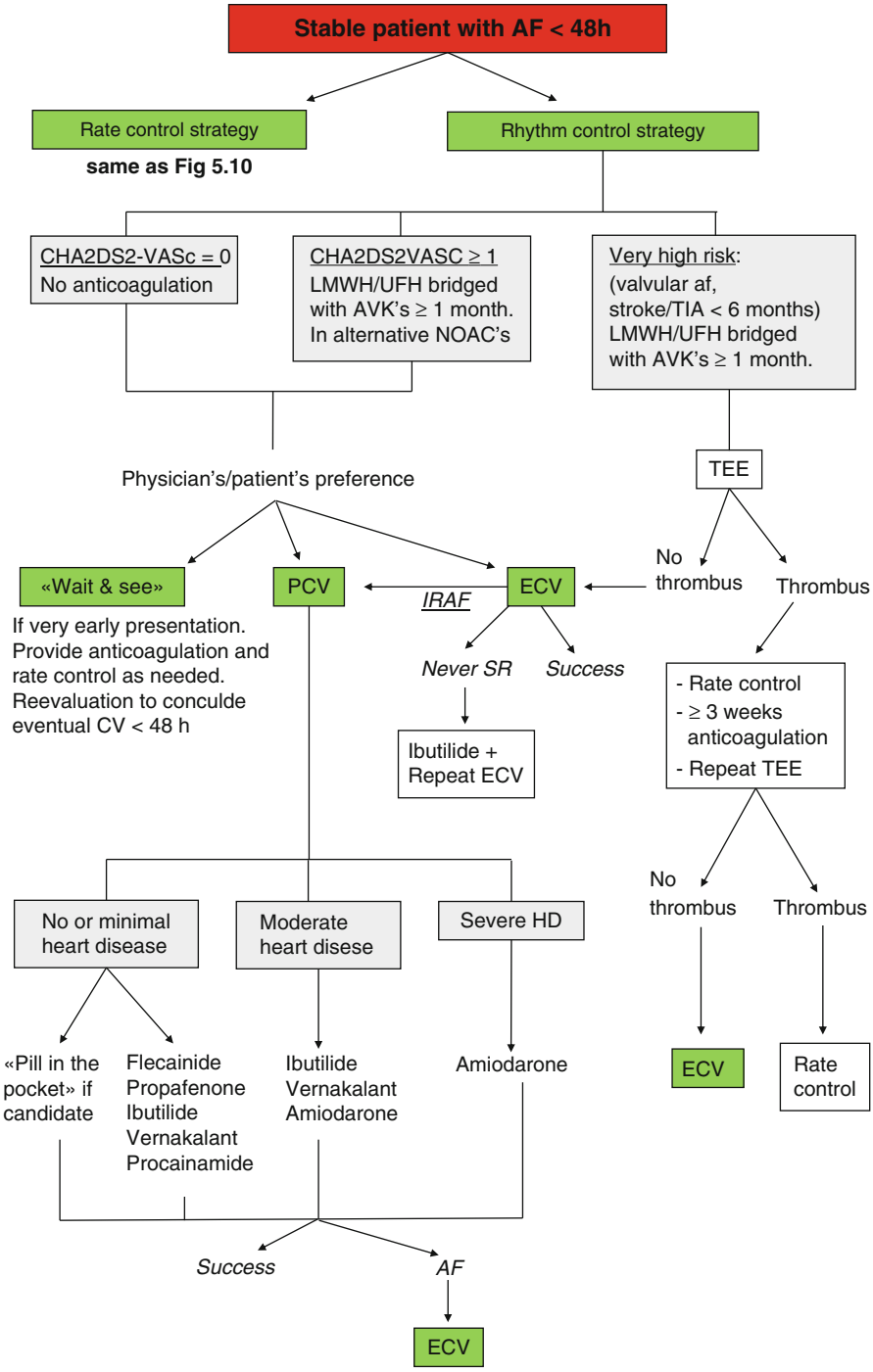

Fig. 5.9 Algorithm for management of patients with stable AF presenting <48 h from onset

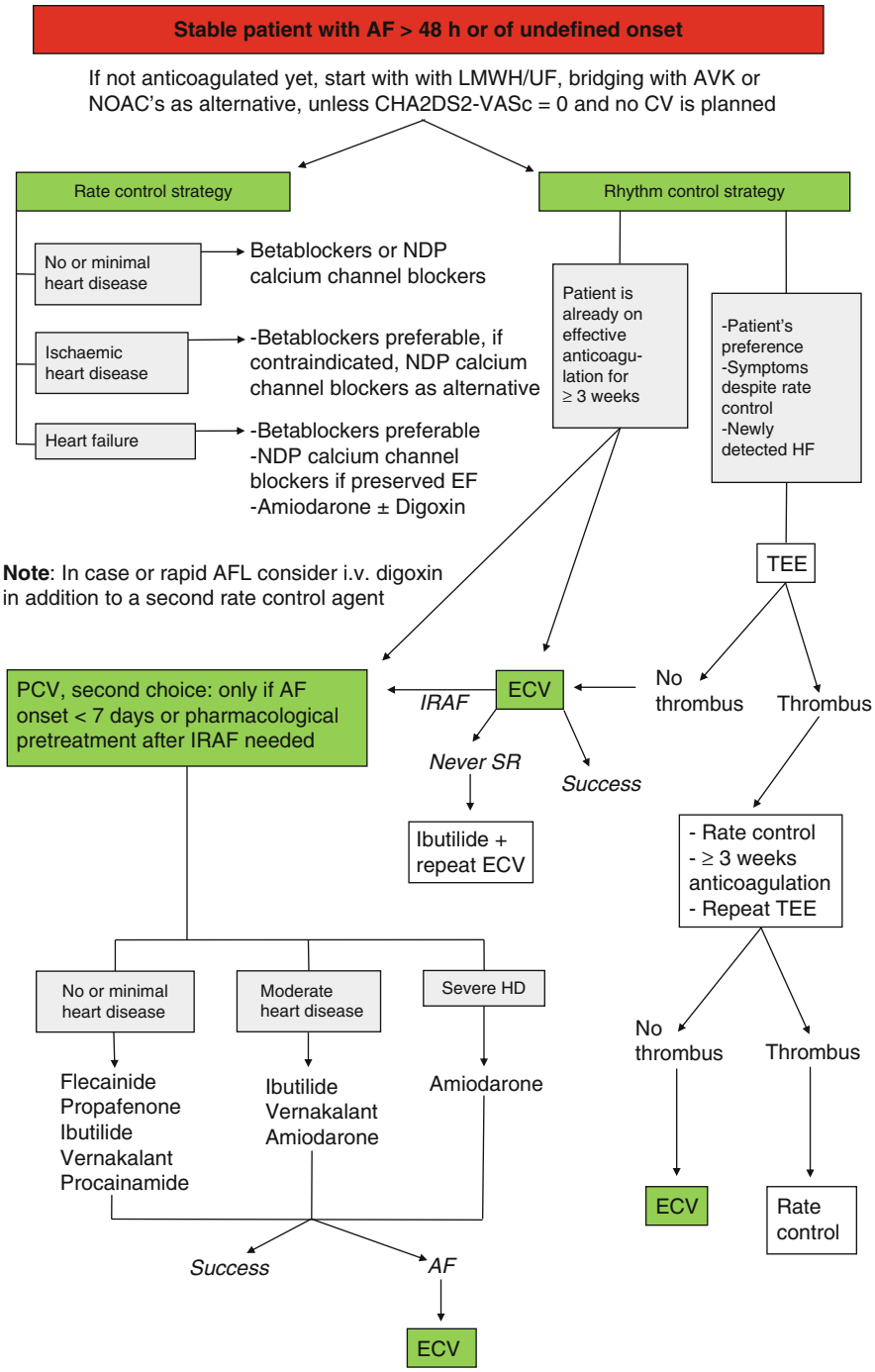

Fig. 5.10 Algorithm for management of patients with stable AF presenting >48 h from onset

A patient who has undergone pharmacological cardioversion should be monitored for a period afterwards (usually half of the drugs elimination's half life) to rule out bradycardia, AV block or ventricular proarrhythmia or hypotension, before discharge. If a patient has been electrically cardioverted, at least 3 h of monitoring is needed [4].

5.4.1 Electrical Cardioversion

Sedation can be provided by different professionals, based on competence, organisation and therapy used. Emergency physicians are involved in the great majority throughout the world for AF cardioversion in the ED. Less often, cardiologists or anaesthesiologists supervise the procedure [21].

A number of medications can be used, like benzodiazepines, narcotics and propofol, alone or in combination. *Midazolam*, a benzodiazepine with a short half-life is gaining increased diffusion because of its pharmacodynamics, wide therapeutic range and availability of a reversal agent (flumazenil). In the two major series [57, 58], adequate sedation was achieved in nearly all patients and no serious complications were observed. Usually, initial bolus doses of 0.01–01 mg/kg are used (the higher ones when the agent is used alone), which may be followed by repeated boli. Mean total dosage used throughout major studies on the use of midazolam as single agent was around 10 mg [59]. *Propofol* is another popular agent for sedation as it has an even more rapid onset of action and washout. On the other hand, it has a greater potential for hypotension and respiratory depression. It is used at dosages of 1–2.5 mg/kg [60].

The procedure can be performed with older monophasic or newer biphasic defibrillators. The latter are more effective with lower energy requirements [61]. The device is connected to the body by a couple of adhesive pads or a couple of handheld paddles.

Four pad positions are currently used: anterolateral, anteroposterior, anterior–left infrascapular and anterior–right infrascapular. They are equally effective to treat atrial or ventricular arrhythmias [62]. If paddles are used (anterolateral position), the operator should press firmly, the optimal force being 8 kg. If the patient has an implantable cardioverter defibrillator (or a pacemaker), anteroposterior or anterolateral locations are acceptable and the nearest pad or paddle should be positioned at least 8 cm away from the device [63]. After the procedure, the device should be interrogated and evaluated to ensure normal function [4]. The DC shock must be synchronised to the R wave to avoid the risk of inducing ventricular fibrillation.

The recommended initial biphasic energy dose for ECV of adult atrial fibrillation is 120–200 Joules (J), whereas for atrial flutter, 50–100 J is usually sufficient. If CV fails, energy should be stepwise increased or the position of the pads changed. For monophasic defibrillators, cardioversion should start at 200 J (100 J for AFL) [10, 62, 63].

Complications They are more often related to arrhythmias, usually transient asystole or bradycardia (0.9 % in the acute CV setting of the Fin CV study [39]).

Pre-cardioversion antiarrhythmic therapy, rate control therapy or slow ventricular rate did not predict bradyarrhythmias, whereas older age, female sex or unsuccessful CV did.

Thromboembolic complications are rare but not negligible if patients are adequately stratified and treated.

Ventricular arrhythmias are exceptional as are episodes of pulmonary oedema.

Complications can rarely be related to sedation like hypotension and prolonged respiratory arrest but are managed with conventional support (fluids and manual ventilation) in the great majority.

5.4.2 Drugs for Rhythm and Rate Control

- Note1: not all drugs or formulations for i.v. or oral use are available in all countries.
- Note 2: for rate and rhythm control drugs, dosages and infusion protocols usually vary between the different guidelines [1, 4, 5, 10, 20, 41]. If there is agreement between sources (or with little variations), one protocol is reported, which also corresponds to the author's practice. If there are marked differences, alternative protocols are mentioned.

5.4.2.1 Rhythm Control Drugs

Flecainide Sodium channel blocker with quite rapid action restores SR in 67–92 % in 6 h. Dosage: 2 mg/kg i.v. over 10 min. Ideal agent for patients with no or minimal heart disease. Avoid in patients with ischaemic heart disease, left ventricular dysfunction, intraventricular conduction delay or Brugada Syndrome. Risks are ventricular proarrhythmia, AV block and electromechanical dissociation. When used for conversion of AFL, 1:1 conduction may ensue with rapid ventricular rate if no rate control agent has been associated. In some countries (USA), approved only for oral use. In this case, 200–300 mg is administered orally (the same dose as the "pill-in-the-pocket" approach), AHA/ACC/HRS 2014 [5] and CCS 2010 [64] guidelines recommending administration of a beta blocker or calcium channel blocker before.

Propafenone Similar properties, indications and efficacy as for flecainide. Dosage: 2 mg/kg i.v. over 10 min. Avoid also in severe COPD because of its weak noncompetitive beta blocking property. In the USA available orally only: administrate 450–600 mg preceded by AV node-blocking agent as above.

Procainamide Sodium channel blocker. Dosage: 15–17 mg/kg i.v. over 1 h with conversion rate around 60 %. Very popular in Canada. Recommended for AF conversion in stable patients in CCS guidelines 2010 [64]. Causes transient hypotension in 5 %.

Amiodarone Multichannel blocker, also with beta- and calcium channel blocking activity if used intravenously. Prolongs prevalently refractoriness in chronic use. Dosage: 5 mg/kg in 1 h, then 50 mg/h for 24 h (ESC 2010 [4]) or 150 mg in 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h (AHA/ACC/HRS 2014 [5]).

Amiodarone should be diluted in 5 % glucose solution (otherwise there is a risk of crystallisation of the solution). It restores SR with delayed action but similar efficacy as flecainide and propafenone at 12–24 h. It has also significant rate-slowing properties. It is the agent of choice for patients with severe heart disease for both purposes of cardioversion and rate control. Contraindicated in hyperthyroidism, avoid if possible in patients with severe COPD and hypothyroidism. Most common acute side effects are hypotension (especially if infusion is too fast) and phlebitis (the longer the infusion lasts, the more probable).

Ibutilide Rapid-acting agent, prolongs repolarisation. Dosage: 1 mg i.v. over 10 min, if unsuccessful, repeat after 10 min same dose. AF conversion rate is around 50 % with time to conversion about 30 min. Best available conversion agent for AFL. It carries a considerable risk of QTc prolongation and torsades de pointes (4 %). Patients should be monitored for a minimum of 4 h after. Some authors suggest pretreatment with 1–2 g $MgSO_4$ to lower the proarrhythmic risk. Contraindicated if patients are hypotensive, have manifest congestive heart failure, have very low EF (<30 %) and hypokalemic or if QTc >440 ms. Pretreatment with 1 mg over 10 min facilitates great ECV in patients who failed it before.

Dofetilide Prolongs repolarization. Has been mostly studied in the setting of persistent AF. A response may take days or weeks, and therefore it is not an ideal agent in the ED setting. Mentioned and recommended class I only in 2014 AHA/ACC/HRS guidelines [5]. Dosages: 500 mcg BID if creatinine clearance (CrCl) >60, 250 mcg BID if 40–60, 125 mg BID if 20–40. Do not use if CrCl under 20 ml/min. Do not initiate treatment out of hospital (risk of torsades de pointes).

Vernakalant Fast-acting atrial selective multichannel blocker with conversion rate around 50 % and median time to conversion about 10 min. Dosage: 3 mg/kg i.v. over 10 min, followed, if unsuccessful, by second infusion of 2 mg/kg i.v. over 10 min after 15. Contraindicated in hypotensive patients (<100 mmHg), NYHA 3–4 heart failure, FE <35 %, ACS in the last 30 days, severe aortic stenosis and QTc >440 ms.

5.4.2.2 Rate Control Drugs

Beta blockers Very effective, first choice in acute coronary syndrome or heart failure patients (avoid or use with extreme caution in acute decompensation). Do not use in severe COPD and pre-excitation syndrome. Metoprolol, atenolol and propranolol can be used intravenously and orally and are therefore the most useful for acute and chronic treatment. Esmolol is available intravenously only and is frequently used in the intensive care setting. Other beta blockers like bisoprolol or carvedilol are available for oral administration only and can be used if rate control is not too urgent and for chronic therapy.

- Metoprolol: 2.5–5 mg i.v. in 2 min every 5 min up to three doses (max 15 mg), oral maintenance dose 50–200 mg/day
- Atenolol: 2.5 mg i.v. at a rate of 1 mg/min to be repeated at intervals of 5 min up to a maximum of 10 mg
- Propranolol 1 mg i.v. over 1 min up to three doses at 2 min intervals, oral maintenance dose 30–160 mg/day
- Esmolol 0.5 mg/kg i.v. bolus over 1 min, then 50–300 mcg/kg/min i.v.

Nondihydropyridine (NDP) and Calcium Channel Blockers (Diltiazem, Verapamil) Very effective, diltiazem is the less inotropic negative and hypotensive of the two. Avoid in heart failure patients (with the exception of HF with preserved systolic function if not acutelly decompensated) and pre-excitation syndrome.

- Verapamil: 0.075–0.15 mg/kg i.v. bolus over 2 min, may repeat 10 mg bolus after 30 min if uneffective, then 0.005 mg/kg/min infusion [5]. Oral maintenance dose 160–360 mg/day
- Diltiazem 0.25 mg/kg i.v. bolus over 2 min, may give a second dose of 0.35 mg/kg, then 5–15 mg/h infusion. Oral maintenance dose 180–360 mg/day

Amiodarone Usually second-line agent. It is well tolerated in critically ill patients where it can be the first choice.

Digoxin Usually a second-line agent with moderate and delayed efficacy on rate control. When used intravenously, onset of action takes 1 h and peak rate-slowing activity is reached at 6 h. It is first-line agent in patients with acute heart failure. Due to its vagomimetic activity, it tends to transform atrial flutter in fibrillation (about 25 %, personal observation) so it turns out very helpful in rate control for flutter, which is harder to achieve than for AF. In the author's practice, digoxin is used as first-line agent, associated with another rate control drug when fixed. 2:1 AV conduction with rapid ventricular rate is present. Avoid in moderate or severe renal failure due to risk of intoxication.

Dosage 0.25–0.5 mg i.v. with repeat dosing, maximum 1.5 mg/24 h. Oral maintenance dose 0.0625–0.25 mg/day

5.5 Indications for Hospitalisation, Follow-Up and Referral

Hospitalisation should be in general considered for patients with AF and severe symptoms (heart failure, severe angina, syncope), when a significant heart disease is suspected, important comorbidities are present, symptoms are not properly controlled (failed cardioversion or rate control) or if complications occur during first approach treatment.

Decision algorithms like RED-AF [65] and AFFORD [66] have recently developed for predicting 30 days adverse events in AF patients presenting to ED with AF. Nomograms contain many clinical predictors and points are assigned to each predictor. Adverse events vary from ED return visit for recurrent AF to death, through different grades of severity. The AFFORD [66] model fared well in risk prediction and in the identification of patients at very low risk which the authors stated could be safely discharged after cardioversion or adequate rate control, but these were only 17 % of the total. This still poses the problem of the acceptable risk threshold for indicating hospitalisation (e.g. is it worth to hospitalise a patient to avoid return visit for AF relapse? Is stroke preventable by hospitalisation if patient is properly anticoagulated also at home?). Furthermore, the same authors

admit that the effect of hospitalising ED patients with acute AF on short-term adverse events remains unanswered [65] (RED-AF). Uncertainties on hospitalisation criteria are still reflected by the wide discrepancy of the discharge rate after successful CV: 85 % in Canada, 76 % in Australasia, 48 % in the USA and 27 % in the UK [21].

In the absence of obvious severe presentation or comorbidities, careful individual judgement on high-risk features should be performed to guide this decision.

It should be stressed that new-onset AF carries a worse prognosis [7, 18]. In the study of Miyasaka et al. [67], hazard ratio for mortality risk was 9.6 within the first 4 months and 1.7 thereafter, compared with age- and gender-matched general population. The main reason is thought to be that AF complicates underlying conditions with poor prognosis like cardiovascular diseases or malignancies. As a consequence, patients with first episode should undergo a rapid medical workup which can be done of course during hospitalisation, but alternatively, if there is no clinical instability, on outpatient basis. In order to favour the latter strategy, diagnostic pathways which include evaluation by cardiologist and other professionals as well as diagnostic testings should be defined locally and be easily accessible, which is unfortunately not always the case and gives reason for the high percentage of hospitalisation of AF patients in some countries [23].

Follow-up of AF patients should be individualised and take into account symptomatic status, comorbidities (which should be followed up as specifically needed), antiarrhythmic treatment, thromboprophylaxis and complications. Visits should be usually performed by the primary care physician or a cardiologist.

Asymptomatic patients in sinus rhythm without medications and comorbidities do not need a structured follow-up, and a periodic self-check of pulse regularity should be recommended.

Patients on antiarrhythmic or on rate control medications should get an ECG 1 week after beginning or up-titration of therapy to check for efficacy and proarrhythmic complications and a visit every 6–12 months.

At every follow-up visit, the following issues should be reassessed:

- Effectiveness of symptom control either while pursuing rate or rhythm control strategy
- Need for antithrombotic therapy, re-evaluation of risks and benefits
- Optimization of therapy for comorbidities
- Lifestyle counselling and check for adequate compliance

Furthermore, in relation to individual therapy, there may be a need for periodical lab tests (e.g. thyroid function for patients on amiodarone, liver function for patients on dronedarone, blood count and renal function for patients using novel anticoagulants, etc.).

Echocardiography should be performed as recommended for underlying structural heart disease or in case of worsening symptoms despite apparent achievement of rate or rhythm control. Holter recording may be needed for assessment of

adequate rate control or if proarrhythmia is suspected. An exercise stress test can help to adjust rate control medications in active patients with permanent AF who complain uncontrolled palpitations during exercise.

Referral to a cardiologist *is generally indicated for patients with a first AF episode.* A possible exception is older patients with asymptomatic AF with adequate rate control. Basic screening examinations like laboratory tests, thyroid function and echocardiography should be arranged before referral. Other reasons for referral to a cardiologist are inadequate rhythm control strategy (ineffective or not tolerated antiarrhythmic medications), ineffective rate control strategy (inadequate rate control or poor quality of life despite adequate rate control) and evaluation for radiofrequency ablation.

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Wide QRS Complex Tachycardia in the Emergency Setting

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6.1 Wide QRS Complex Tachycardia

A wide QRS complex tachycardia can be (1) ventricular tachycardia (VT); (2) supraventricular tachycardia (SVT) with bundle branch block that may be either preexisting or due to aberrant conduction, namely, tachycardia-dependent abnormal intraventricular conduction; a further possibility is the effect of some antiarrhythmic drugs that slow down intraventricular conduction, resulting in marked QRS complex widening; and (3) supraventricular tachycardia with conduction of impulses to the ventricles over an accessory pathway (preexcited tachycardia).

In the presence of wide QRS tachycardia, the correct diagnosis is of paramount importance, since the treatment commonly used in SVT is different from that of VT, and some drugs useful in the former (e.g., verapamil) are harmful in the latter [1–3].

The origin of a wide QRS complex tachycardia can be reliably identified using a "holistic" approach, namely, taking into account all of the available items: no single criterion is able to provide a simple and quick solution of the problem in all cases. The available ECG signs are, without any exception, suggestive of ectopy, namely, ventricular origin of the impulses; SVT with aberrant conduction may only be diagnosed by excluding all of the items favoring VT. The recognition of ventricular or supraventricular origin of wide QRS complex tachycardias is not difficult if a

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_6

detailed analysis is used, taking into account several diagnostic signs: [4–12] the idea that a single quick item can offer an immediate and reliable solution is something of an illusion.

If, despite a complete diagnostic approach, the dilemma cannot be resolved, it is necessary to assume a ventricular origin of the arrhythmia since (1) a wide QRS tachycardia is more likely VT than SVT and (2) it is less dangerous to treat an SVT like it were ventricular in origin than applying to a patient with VT the treatment commonly used for SVTs. In particular, intravenous verapamil should be avoided whenever SVT diagnosis is not certain, since this drug is harmful in some VT patients [1–3].

6.2 General Criteria

6.2.1 Atrioventricular Dissociation

Whenever the electrical activity of the atria is recognizable, two different situations may occur:

1. Atrioventricular (A-V) dissociation
2. Relationship between P waves and QRS complexes.

A-V dissociation demonstrates the ventricular origin of the wide QRS complexes and occurs in a percentage variable from 19 to 70 % of VT cases [5, 6, 10, 11]. Dissociation, however, is often difficult to be diagnosed since in several cases, sinus P waves are not easily recognizable, being simultaneous to QRS complexes or T waves. Moreover, in the presence of atrial fibrillation, A-V dissociation cannot be appreciated. Before excluding, in a wide QRS complexes tachycardia, the presence of P waves independent of QRS complexes, however, one should observe with great attention the configuration of several consecutive complexes in all 12 leads, paying the greatest attention to leads II and V1 (the ones where sinus P waves are usually evident). Aim of this analysis is comparing consecutive complexes searching for slight differences in QRS or T morphology: with this approach it is not rare to discover, in the presence of VT, that in some leads, slight variations in QRS complex or T wave configuration occur. To be sure that such differences express the presence of P waves dissociated from QRS complexes, and superimposed on these, it is necessary to measure the intervals separating the "disturbing" events: in case of A-V dissociation, they are separated from relatively constant intervals, being "long" intervals in multiples of the "short" ones (Fig. 6.1a). When, in contrast, the intervals separating the changes in morphology of T waves and/or QRS complexes are irregular, it is more likely that artifacts, rather than dissociated sinus P waves, are involved (Fig. 6.1b).

The best ECG leads to be analyzed, searching for "dissociated" P waves, are leads II and V1, the ones where sinus P wave voltage is usually relatively high; it is also advisable to observe the leads where the QRS complex and/or the T wave is of

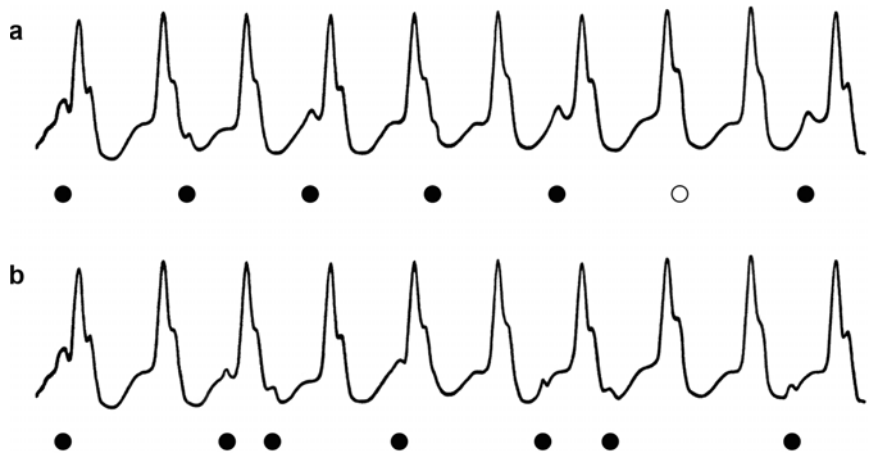

Fig. 6.1 Diagrams (**a**, **b**) show two wide QRS complex tachycardias. In both diagrams, small positive deflections, independent of QRS complexes, are present. In diagram (**a**) these deflections are rhythmic and separated by constant intervals; whenever a deflection is invisible, being coincident with a QRS complex (*circle*), the interval between two manifest waves is twice the basic interval. These small waves are, therefore, sinus P waves: accordingly, A-V dissociation can be diagnosed, revealing a ventricular origin of tachycardia. In diagram (**b**), in contrast, the small positive deflections are arrhythmic: they are not P waves but artifacts

low voltage, since it is relatively easy to detect the small atrial waves whenever these are not "buried" within large QRS or T deflections. This is expressed by the "haystack principle": if you are searching for a needle in a haystack, select a small haystack" (Fig. 6.2).

The bedside diagnosis of A-V dissociation can be improved by heart sound auscultation and arterial pulse palpation: whenever the atrial contraction is dissociated from ventricular activity, it is possible to appreciate a variable loudness of the 1st heart sound and variability in peripheral pulse amplitude. This is because (1) whenever atrial contraction occurs immediately before ventricular systole, the blood flow "opens" the atrioventricular valves, resulting in a relatively loud 1st heart sound, a phenomenon that does not occur if mitral and tricuspid valves are closed at the time of atrial systole, and (2) if atrial contraction occurs when the A-V valves are open, the diastolic ventricular filling is improved, resulting in a relatively increased stroke volume: accordingly, the pulse amplitude will be higher with respect to that of heart beats in which atrial systole occurs while the A-V valves are closed.

6.2.2 Second-Degree V-A Block

In ventricular tachycardia, atrial electrical activity may be not dissociated from ventricular one if retrograde ventricular-atrial (V-A) conduction occurs, as it happens in about one half of cases. The V-A ratio may be 1 (every QRS complex is followed by a

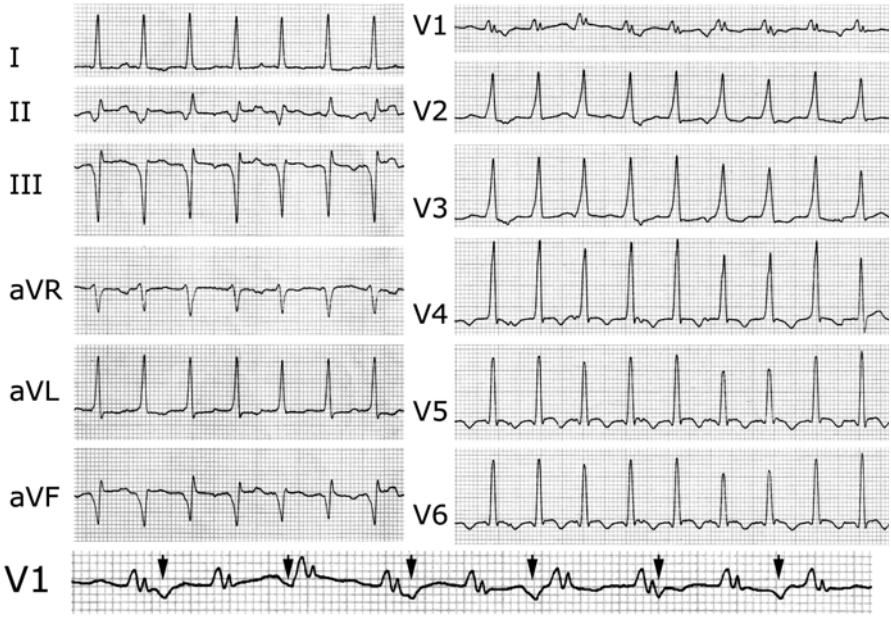

Fig. 6.2 Wide QRS complex tachycardia. QRS duration is 0.12 s, but since in some leads ventricular complexes are relatively narrow, a supraventricular tachycardia could be diagnosed at first glance. The ventricular origin of tachycardia is demonstrated by A-V dissociation; the P waves independent of ventricular complexes (*arrows*), and separated from constant intervals, are easily recognized in lead V1, since in this lead both QRS complexes ant T wave voltages are very low (the haystack principle)

retrograde P wave) or less than 1 when some ventricular impulses are not conducted to the atria. In a wide QRS complex tachycardia, a QRS/P ratio >1 (more QRS complexes than P waves) demonstrates the ventricular origin of the arrhythmia [6–8, 12], (Fig. 6.3), whereas a 1:1 ratio does not permit any definite conclusion since P waves may (a) express a supraventricular tachycardia with 1:1 A-V conduction or (b) represent the retrograde atrial activation during ventricular tachycardia. If analysis of P wave configuration is possible, a main P vector directed inferiorly demonstrates supraventricular origin of the arrhythmia, whereas a P vector directed superiorly (negative P waves in the inferior leads) does not permit any conclusion since not only VT but also several supraventricular tachycardias share a retrograde activation of the atria. In some cases of VT, however, retrograde P waves appear as positive in the inferior leads, a phenomenon that has been called "the illusion of retrograde positive P waves" (Fig. 6.4) [8, 13, 14].

6.2.3 Capture and Fusion Beats

The presence of narrow, or relatively narrow, beats during wide QRS tachycardia suggests a diagnosis of VT, *provided that narrow complexes are preceded by a P wave with an interval consistent with anterograde A-V conduction of the impulse*. The narrow, or less wide, complexes are *capture* or *fusion* beats that occur

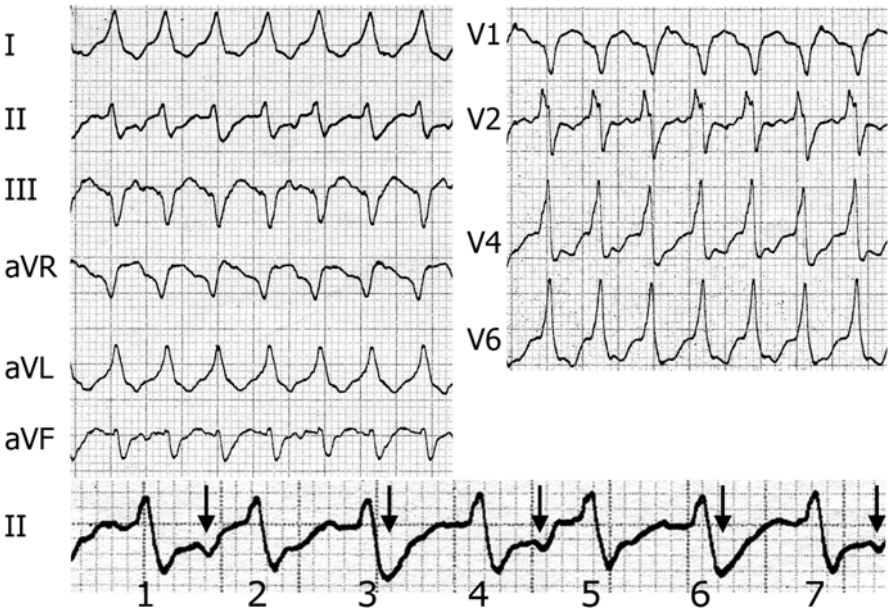

Fig. 6.3 Ventricular tachycardia with 3:2 retrograde block of the Wenckebach type. Lead II (enlarged in the *bottom row*) analysis reveals that ventricular complexes *1*, *4,* and *7* are followed by negative P waves occurring midway between two consecutive QRS complexes. Beats *3* and *6*, in turn, show very wide "S waves" that never occur in the other beats, whereas complexes *2* and *5* do not show any of the 2 above characteristics (negative P wave, wide "s wave"). It is, therefore, evident that in a group of 3 beats, the 1st one (complexes *3* and *6*) is followed by a retrograde P wave with a short R-P interval, whereas the P wave following the 2nd beat of the group (complexes *1*, *4*, *7*) occurs with a relatively long interval, and after the 3rd complex of the series (beats *2* and *5*), no P wave occurs. In other words, there is a retrograde 2nd-degree 3:2 Wenckebach type block, and this establishes the diagnosis of ventricular tachycardia. In this tracing, the r wave peak time in lead II is 30 ms

whenever, during VT, a sinus or supraventricular impulse succeeds in reaching the ventricles, whose depolarization is due totally (capture) or partially (fusion) to that impulse (Fig. 6.5). Capture and fusion beats are reliable signs of VT, but they are rare (4 % in a study based on 96 cases of proved VT [10]) and can be observed only in the presence of A-V dissociation. Since the latter phenomenon is, in itself, a clear sign of VT, the further help provided by capture and fusion beats is trivial, provided that these never occur whenever the heart rate is very high, being the A-V node made always refractory by ectopic ventricular impulses [6, 8].

6.2.4 Precordial QRS Concordance

A "concordant" QRS morphology in all the precordial leads, namely, ventricular complexes totally negative (QS pattern) or positive (R or qR pattern), demonstrates a ventricular origin of tachycardia, since no intraventricular conduction

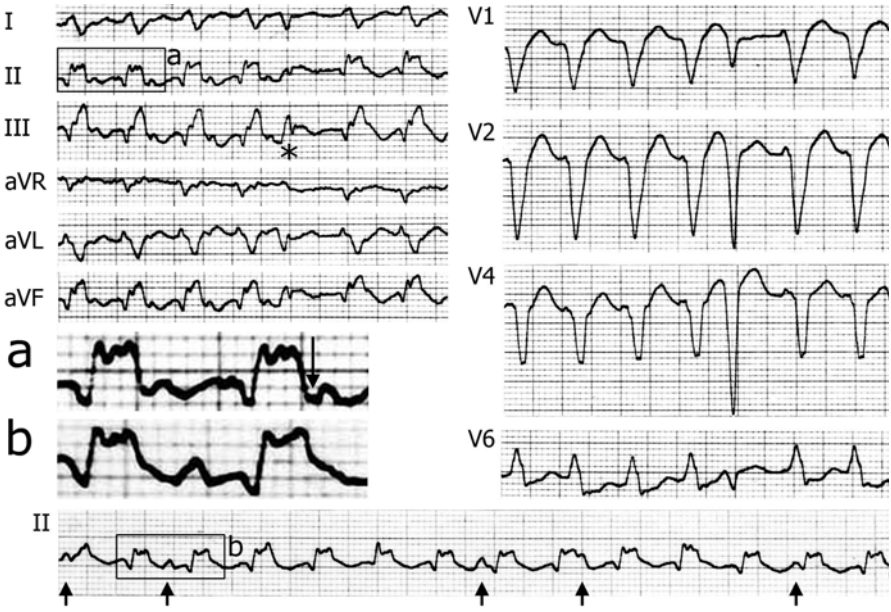

Fig. 6.4 Ventricular tachycardia with retrograde P waves apparently positive in the inferior leads. In all leads, that are simultaneous, apart from the tracing in the bottom strip, the 5th beat (*asterisk*) is a ventricular extrasystole. Beats 1–4 are followed by P waves that seem, at first glance, positive in the inferior leads and negative in aVR and aVL. The premature beat alters the relationship between QRS complexes and P waves, being the last two ventricular beats not followed by P waves. The bottom strip (lead II) has been recorded later with respect to the others and clearly shows A-V dissociation: P waves of sinus origin are positive (*arrows*) and independent of QRS complexes; some sinus P waves, occurring simultaneously with ventricular complexes, are invisible, being "buried" within the ventricular complexes. Panels (**a**, **b**) show enlarged beats: during retrograde V-A conduction, P waves are negative (*arrow* in section **a**), not positive as they seem at first glance. In section (**b**), a positive P wave is evident in between two QRS complexes, demonstrating A-V dissociation

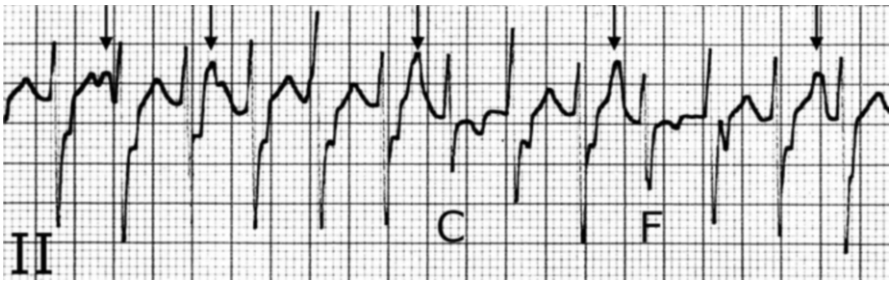

Fig. 6.5 Capture and fusion beats during ventricular tachycardia. In this ECG strip, A-V dissociation is evident (*arrows* point out sinus P waves that modify T wave morphology). In two occasions, the sinus impulse is conducted to the ventricles, giving rise to a narrow QRS complex (capture beat, labeled *C*) or to a fusion beat (labeled *F*). These are intermediate in configuration between ectopic wide complexes and capture beat

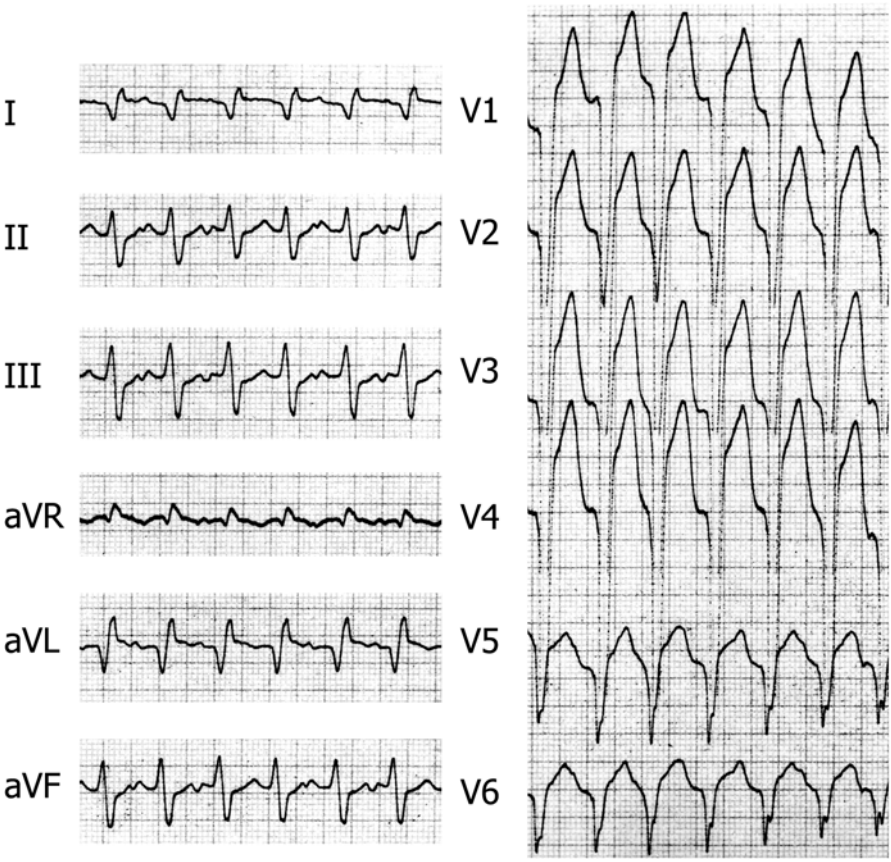

Fig. 6.6 Precordial concordance. In this tachycardia, wide QRS complexes with QS morphology are present in all precordial leads. This pattern demonstrates without any exception the ventricular origin of tachycardia. Analysis of the inferior leads also reveals a 2nd-degree V-A block with 3:2 ratio; the retrograde negative P waves modify the T wave configuration in two consecutive beats, whereas in the 3rd QRS complex, the T wave is not affected

disturbance can result in such a configuration [15]. Concordance, however, cannot be diagnosed if rS, Rs, or rs complexes occur even in one single precordial lead. In a study based on 232 electrocardiograms with bundle branch block analyzed during sinus rhythm, none showed precordial concordance, suggesting a 100 % specificity of this sign indicating the ventricular origin of the arrhythmia [16]. Negative concordance (QS morphology in all precordial leads, Fig. 6.6), however, is specific of VT, whereas positive concordance could be observed, although rarely, in a preexcited tachycardia due to a left-sided Kent bundle [7, 8]. Negative concordance in the bipolar limb leads (I, II, III) has also been proposed as a specific pattern suggesting VT; [17] such a configuration demonstrates an extreme right axis deviation, a phenomenon that never occurs in adults, apart from some cases of congenital heart disease or dextrocardia.

6.2.5 Absence of RS Complexes in the Precordial Leads

In several cases of VT, none of the precordial leads shows ventricular complexes with a configuration characterized by an R wave followed by an S wave (rs, RS, rS, or Rs). This sign, expressing in a slightly different manner the concept of "precordial concordance," suggests a ventricular origin of the arrhythmia. The sign specificity was 100 % both in the original study [5] and in another research based on 133 patients with wide QRS tachycardia; [10] in a different series, however, specificity was 81 and 98 % in the presence of positive and negative precordial QRS complexes, respectively [16].

6.2.6 Interval >100 ms from QRS Complex Beginning to S Wave Nadir in a Precordial Lead

It has been observed that whenever, in a wide QRS complex tachycardia, the interval from QRS complex beginning to S wave nadir exceeds 100 ms in a precordial lead, tachycardia is ventricular in origin [5]. The above criterion was fulfilled in 41 % of patients with previous myocardial infarction and VT [18]. In subjects with slowed down intraventricular conduction, however, leads V4–V6 show at times the above-mentioned sign even during sinus rhythm, particularly in the presence of left axis deviation. In a study based on electrocardiograms with left bundle branch block and sinus rhythm, 34 % of cases had an interval from QRS complex beginning to S wave nadir >100 ms [16], demonstrating a low specificity of this sign in revealing VT.

6.2.7 Vagal Stimulation Maneuvers

In the presence of QRS wide complex tachycardia, vagal stimulation can result in the following responses:

1. No change in tachycardia morphology or rate: the question remains open.
2. Sinus rhythm restoration: supraventricular reentrant tachycardia with a circuit incorporating the A-V node.
3. Variation in A-V conduction ratio, with appearance of P or F waves: atrial tachycardia or atrial flutter.
4. Variation in V-A conduction ratio, demonstrated by QRS complexes not followed by a retrograde P wave: ventricular origin of tachycardia.

6.3 The Electrocardiogram in the Absence of Tachycardia

An ECG recorded in the absence of tachycardia can be at times helpful, since a conduction disturbance or preexcitation observed during sinus rhythm can be the key to recognize the mechanism underlying the wide QRS complexes. In the great

majority of cases, however, no ECG recorded during sinus rhythm is available at the moment of the arrhythmic emergence. Whenever the ECG during tachycardia is identical to that obtained in sinus rhythm, the arrhythmia is supraventricular in origin, apart from a single exception: the bundle branch reentry tachycardia [19]. In the latter condition, a tracing in sinus rhythm can be misleading, since it suggests a supraventricular, rather than ventricular, origin of the arrhythmia [19].

6.4 QRS Complex Morphology in Leads V1 and V6

Analysis of QRS complex configuration represents an important tool in wide QRS complex tachycardia. Whenever other diagnostic signs (A-V dissociation, capture and fusion beats, precordial concordance, etc.) are either absent or controversial, the distinction between supraventricular and ventricular tachycardia lies on morphologic analysis of ventricular complexes, taking particularly into account leads V1 and V6. The 1st step is tachycardia classification based on QRS morphology in lead V1: whenever ventricular complex is mainly positive in this lead, tachycardia will be defined as "RBBB type," whereas if in that lead ventricular complexes are negative, tachycardia will be classified as "LBBB type." In any situation, the leads to be analyzed are V1 and V6.

6.4.1 Wide QRS Complex Tachycardia with Right Bundle Branch Block-Type Configuration (Positive QRS Complex in Lead V1)

V1. Ventricular complexes with morphology *R* or *Rr′* (the 1st R wave higher than the 2nd one), as well as *qR* or *RS* complexes, suggest VT, whereas both a triphasic (*rsR*Đ or *rSR*Đ) or biphasic configurations *rR*Đ with the 2nd R wave higher than the 1st one suggest SVT with aberrant conduction (Fig. 6.7).
V6. In this lead, *rS*, *QS,* or *qR* complexes are specific of VT (Fig. 6.8), whereas *qRs* complexes suggest aberrant conduction (specificity 95 %). Whenever the R/S ratio, however, is <1 (larger S wave than R wave voltage in lead V6), the ventricular, rather than supraventricular, origin of tachycardia is more likely [10, 16, 20].

6.4.2 Wide QRS Complex Tachycardia with Left Bundle Branch Block-Type Morphology (Negative QRS Complex in Lead V1)

V1. In the presence *of SVT with aberrant conduction and LBBB morphology, this lead shows either a QS configuration or a small and relatively narrow (≤30 ms) r wave* followed by a deep S wave with an early (<60 ms) nadir. R wave duration >30 ms or S wave nadir later than 60 ms from the QRS complex beginning suggest ventricular origin of the arrhythmia. Moreover, a notch in the proximal (descending) limb of S wave indicates VT (Fig. 6.8).

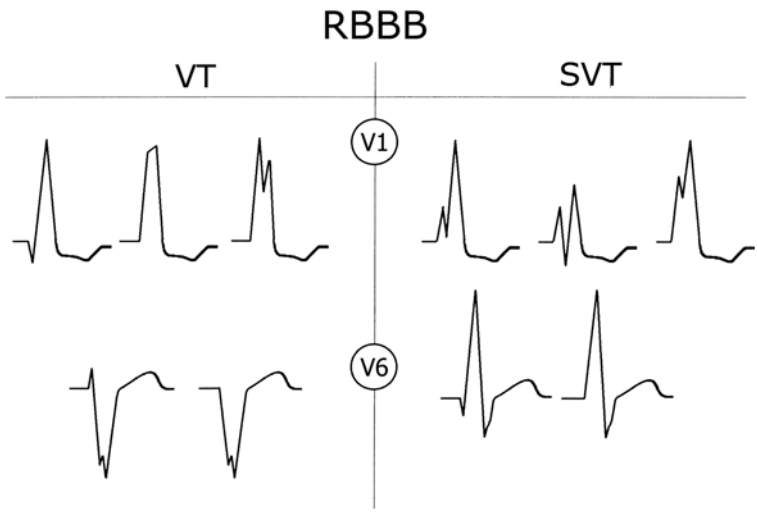

Fig. 6.7 Ventricular complex morphology suggesting either VT or SVT with aberrant conduction in wide QRS complex tachycardia with RBBB-like configuration (QRS complex mainly positive in lead V1)

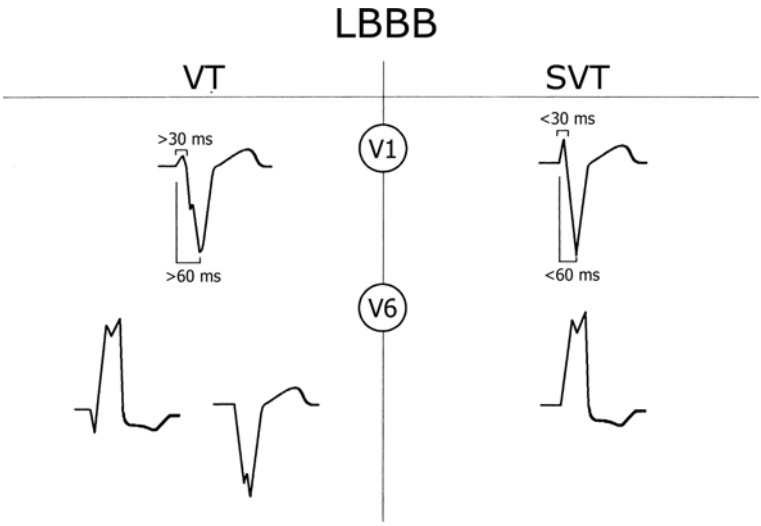

Fig. 6.8 Ventricular complex morphology suggesting either VT or SVT with aberrant conduction in wide QRS complex tachycardia with LBBB-like configuration (QRS complex mainly negative in lead V1)

V6. In a wide QRS complex tachycardia, negative or predominantly *negative QRS complexes in lead V6 suggest at first glance a ventricular origin* of the arrhythmia independent of the associated intraventricular disturbance pattern [20]. Impulses

of ventricular origin show often (69 % of cases) a negative net QRS amplitude (algebraic sum of positive and negative deflections) in V6, whereas this pattern is relatively rare (27 % of cases) in supraventricular tachycardia.

These signs based on QRS morphology in leads V1 and V6, introduced by Kindwall [21], express the slow initial progression of the ventricular wave front when the depolarization is not due to an impulse conducted over the His-Purkinje system. In true LBBB, thus, the 1st ventricular vector, expressing the right-to-left septal depolarization, is directed to the left and anteriorly: lead V1, thus, cannot show a *wide* r wave since the initial ventricular depolarization is fast, being the supraventricular impulse conducted over the Purkinje system. Accordingly, *in a broad QRS tachycardia with LBBB configuration, a relatively wide (≥30 ms) r wave in lead V1 strongly suggests a ventricular origin of the arrhythmia*. The same holds true for a relatively late (>60 ms) S wave nadir in lead V1 and for the presence of a notch in the descending S wave limb. The specificity of the above "ectopic" QRS morphologies in lead V1, however, is not 100 %: a study based on electrocardiograms with LBBB during sinus rhythm has reported a specificity of 78, 66 and 66 % for r wave duration in lead V1 >30 ms, S wave nadir >60 ms, and notch in the descending S wave limb, respectively [16].

6.4.3 Limitations of Criteria Based on QRS Morphology in Wide QRS Complex Tachycardia

Despite being useful, morphologic criteria are not absolute; the equations *typical bundle branch block = aberrant conduction, atypical bundle branch block = ventricular tachycardia* suffer some *limitations and may lead to wrong conclusions in patients treated with antiarrhythmic drugs, particularly those belonging to class 1C*. This is because these drugs slow down the intraventricular conduction, resulting in very abnormal ventricular complexes. Patients treated with 1C drugs may show extremely wide QRS complexes during SVT, to the extent that morphological analysis leads to a wrong diagnosis. This occurs not rarely in patients with atrial flutter treated with 1C antiarrhythmic drugs, that result in tachycardia rate reduction, favoring 1:1 A-V conduction of atrial impulses, and QRS complex widening.

6.5 Other Signs

6.5.1 QRS Duration >140 ms

It has been observed that a wide complex tachycardia with QRS duration >0.14 s is very likely ventricular in origin [11], but this criterion has a low specificity, ranging from 43 % [16] to 69 % [10]. Moreover, QRS complexes can be, although rarely, relatively narrow (<0.12 s) in ventricular tachycardia.

6.5.2 QRS Axis Deviation

In several cases of VT, left or right axis deviation occurs [9–11], and rarely the QRS axis is normal (between 0° and +90°) in VT. Superior QRS axis deviation, however, has been considered not suggestive of VT in the presence of ventricular complexes with LBBB configuration, whereas an RBBB morphology is often associated with VT (87 % specificity) [16].

6.5.3 Regularity

Apart from atrial fibrillation and atrial flutter or tachycardia with variable A-V conduction ratio, supraventricular tachycardias are usually regular. This is also true for sustained ventricular tachycardias, although irregularity in itself does not exclude VT, the variability of R-R intervals being not uncommon in focal tachycardias, particularly at the beginning or at the end of tachycardia. Sustained VT cycle variability has also been attributed to exit block [22] or longitudinal dissociation in the reentry pathway of tachycardia [23, 24].

6.6 Lead aVR Analysis

A new algorithm based on lead aVR analysis has recently been proposed to distinguish ectopy from aberrant conduction in wide QRS complex tachycardia [25, 26]. The procedure is based on four steps (Fig. 6.9): the first three ones are simple and quick, whereas the 4th step requires complicated voltage measurements. Whenever the sign looked for in steps 1, 2, or 3 is present, the diagnosis is VT, whereas only in step 4 becomes possible the recognition of SVT with aberrant conduction (Fig. 6.9).

6.6.1 Step 1: Dominant Initial R Wave

146 out of 482 cases of wide QRS tachycardia showed in lead aVR *a dominant initial R wave*, which was the largest ventricular complex deflection (Figs. 6.9 and 6.10). This pattern *demonstrated a ventricular origin* of the arrhythmia, confirmed by intracardiac recordings, in 144/146 cases (sensitivity 38.9 %, specificity 98.2 %).

6.6.2 Step 2: q or r initial Wave with Duration >40 ms in qR or rS complexes

A ventricular complex starting, in aVR, *not with a dominant R wave but with a low voltage q or r wave whose duration was ≥40 ms* was present in 74 out of 336 cases without a dominant initial R wave. In 65 of these, the diagnosis was VT (sensitivity 28.8 %, specificity 91.8 %).

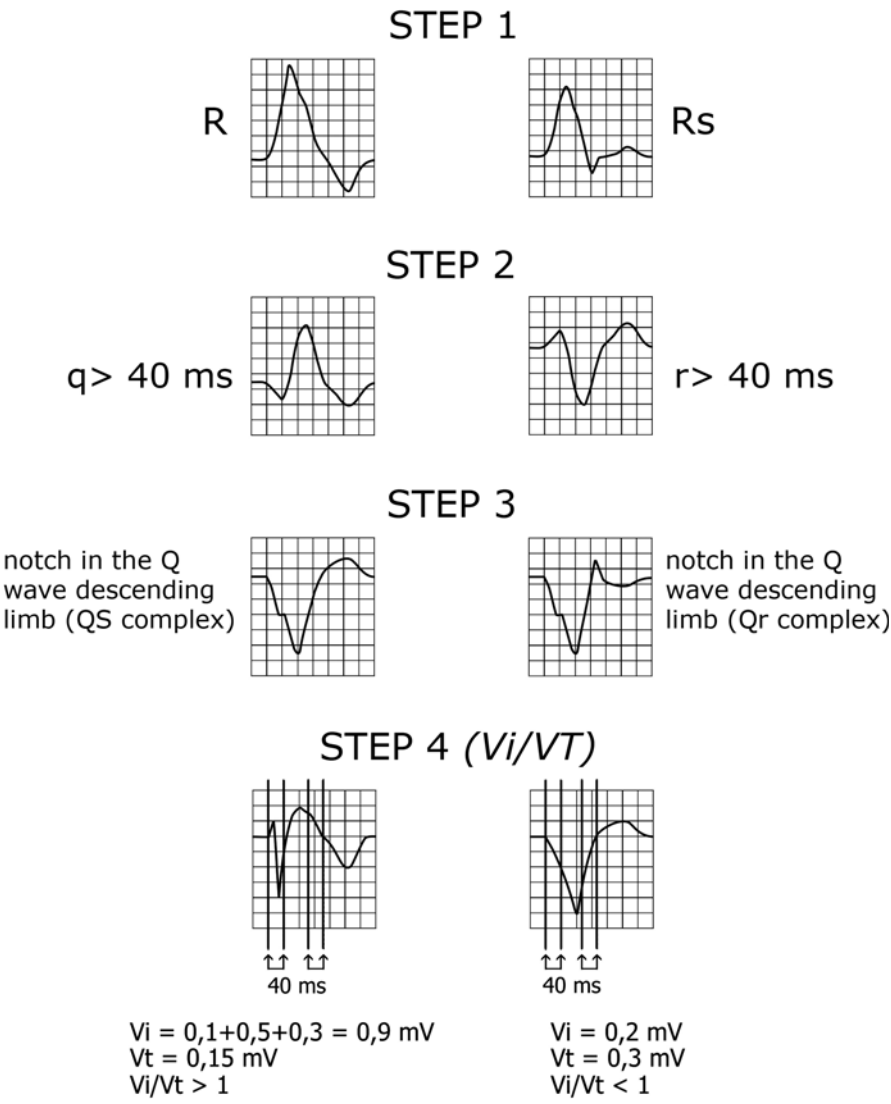

Fig. 6.9 Algorithm based on aVR analysis. *Vi* voltage of the first 40 ms, *Vt* voltage of the final 40 ms (see text)

6.6.3 Step 3: Notch in the Descending Q Wave Limb of a Negative (QS or Qr) Ventricular Complex

This pattern was present in 32 over 37 VT cases where the first 2 criteria were absent (sensitivity 19.9 %, specificity 95 %).

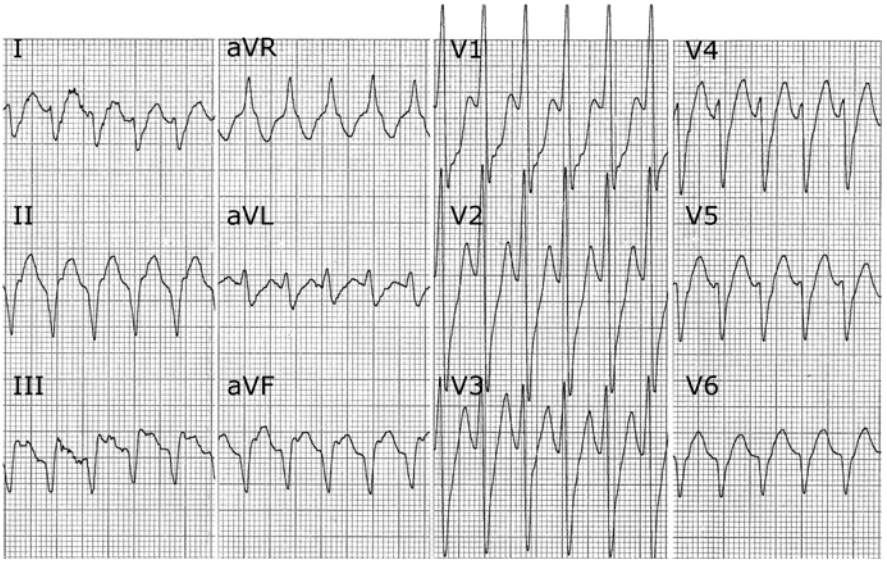

Fig. 6.10 Ventricular tachycardia. In this wide QRS complex tachycardia, negative P waves follow ventricular complexes in the inferior leads. The arrhythmia cannot be classified as "RBBB morphology" or "LBBB morphology" since lead V1 shows complexes with RS configuration. Both QS complexes in lead V6 and aVR analysis (entirely positive complexes) suggest VT

6.6.4 Step 4: *Vi*/*Vt* Ratio

The presence of any sign in steps 1–3 demonstrates the ventricular origin of the arrhythmia, but *the absence of these criteria does not permit to exclude VT and does not demonstrate SVT.* In this situation it is necessary to evaluate the *Vi/Vt ratio, namely, the ratio between the voltages recorded during the first 40 ms of the QRS complex (Vi) and those measured during the last 40 ms of the complex (Vt*). To calculate *Vi* (initial voltage) and *Vt* (terminal voltage), it is necessary to sum the amplitude of *all the deflections present in the first and the last 40 ms*, respectively (Fig. 6.10). This is not a very easy task, since the authors suggest to measure not the simple voltage of the deflection, but to take into account separately any limb of the waves. For example, if an R wave of 3 mm is present at the beginning of the ventricular complex, the corresponding calculated voltage is 6 mm (3 of the ascending limb + 3 of the descending limb). Unfortunately, it is not easy to distinguish exactly the moment of QRS complex beginning and/or termination, to the extent that the authors suggest to use a simultaneous recording of several leads (at least aVR, aVL, aVF) in order to make easier the identification of QRS complex beginning and/or termination.

A Vi/Vt ratio ≥1 suggests a diagnosis of SVT with aberrant conduction, while *a ratio ≤1 speaks in favor of VT.* This criterion has a logical basis: in VT, intraventricular conduction is totally independent of the conduction system, and the ectopic impulse is slowly conducted; accordingly, a small amount of ventricular muscle is

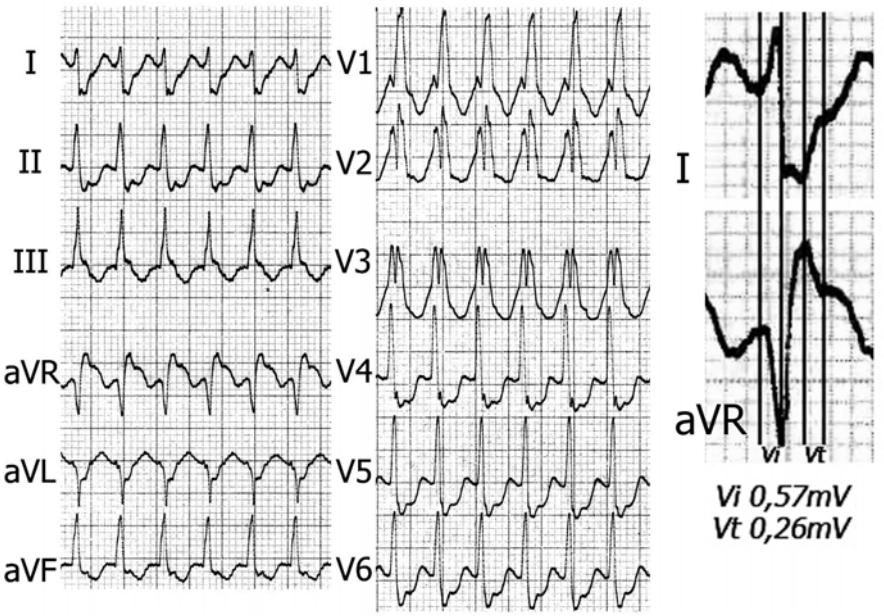

Fig. 6.11 Supraventricular tachycardia with aberrant conduction. Neither P waves nor signs of A-V dissociation are recognizable in this ECG. The morphology of ventricular complexes (rsR′ in V1, Rs with wide s wave in V6) suggests aberrant conduction. The same diagnosis results from lead aVR analysis, since neither dominant initial R wave nor wide q or r wave with duration >40 ms occurs, and is also absent a notch in the proximal q wave limb. Moreover, the ratio between the initial (first 40 ms, *Vi*) and the terminal (final 40 ms, *Vt*) voltage is >1, pinpointing the diagnosis of aberrant conduction

depolarized during the first 40 ms, resulting in a relatively low voltage of the corresponding ECG deflections. When, in contrast, the initial ventricular depolarization occurs using the Purkinje system, as it happens in bundle branch block, a relatively large myocardial mass is depolarized during the first 40 ms, resulting in relatively high voltage-related deflections. Examples of correct diagnosis arrived by means of aVR analysis are reported in Figs. 6.11, 6.12, and 6.13.

In conclusion, aVR analysis can be very helpful whenever one of the signs described in steps 1–3 is present, but becomes less useful in their absence.

6.7 R Wave Peak Time at Lead II

It has recently been reported that the *R wave peak time (RWPT) duration in lead II (the interval from the QRS complex beginning to the 1st change in polarity*) permits a quick and reliable distinction between VT and SVT [27]. The authors have observed that an *RWPT ≤50 ms demonstrates a supraventricular origin* of the arrhythmia, whereas an *RWPT ≥50 ms in lead II suggests VT*. The underlying reason why a long RWPT speaks in favor of ventricular origin of tachycardia is

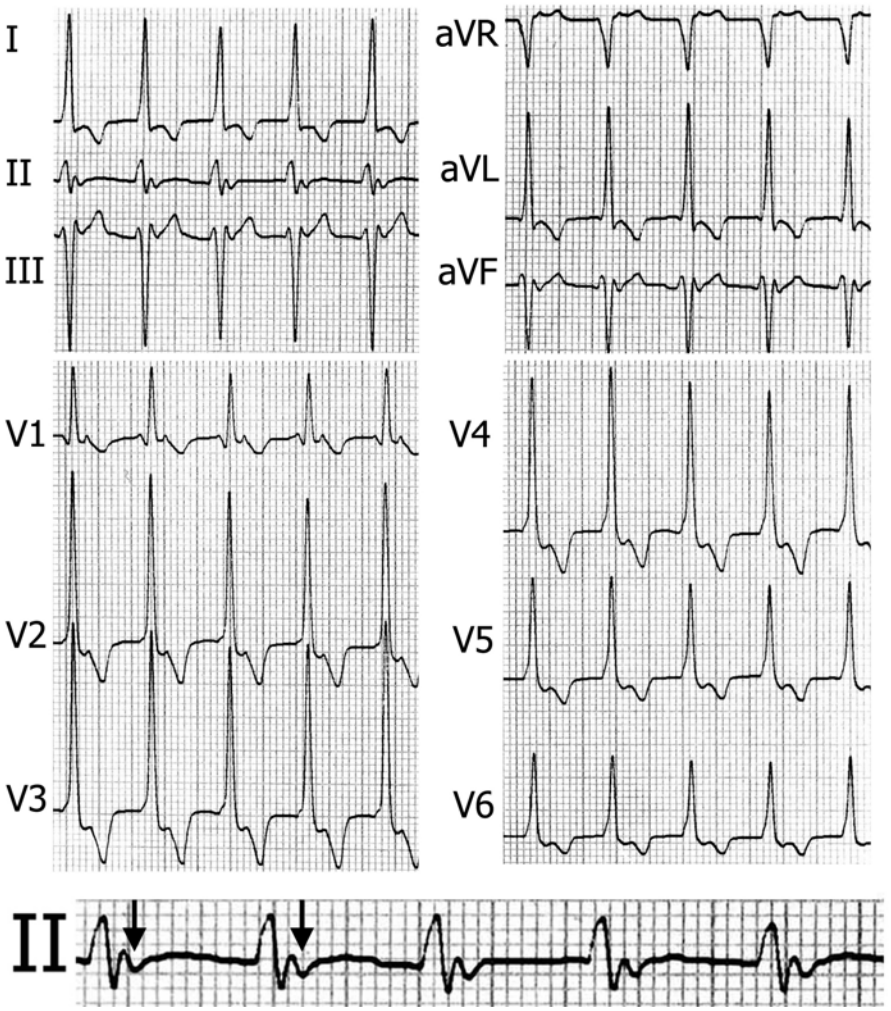

Fig. 6.12 Wide QRS tachycardia with 1:1 V-A conduction. Negative P waves follow ventricular complexes with constant R-P interval in the inferior leads (*arrows* in the *bottom strip*, representing lead II enlarged). This pattern suggests a diagnosis of ventricular (fascicular) tachycardia, despite the relatively narrow QRS complexes

likely the slow initial diffusion of the depolarization wave front in VT. In SVT, in contrast, at the beginning of ventricular depolarization, the supraventricular impulse is normally conducted over a bundle branch (or a fascicle) and the Purkinje system, in such a way that a relatively large myocardial mass is quickly depolarized, resulting in a short RWPT. In the case of VT, in contrast, the cardiac impulse slowly travels over the common myocardial tissue, resulting in a long RWPT. The efficacy of this sign in discriminating VT from SVT is very high in the study that has described such a criterion; the experience of our group,

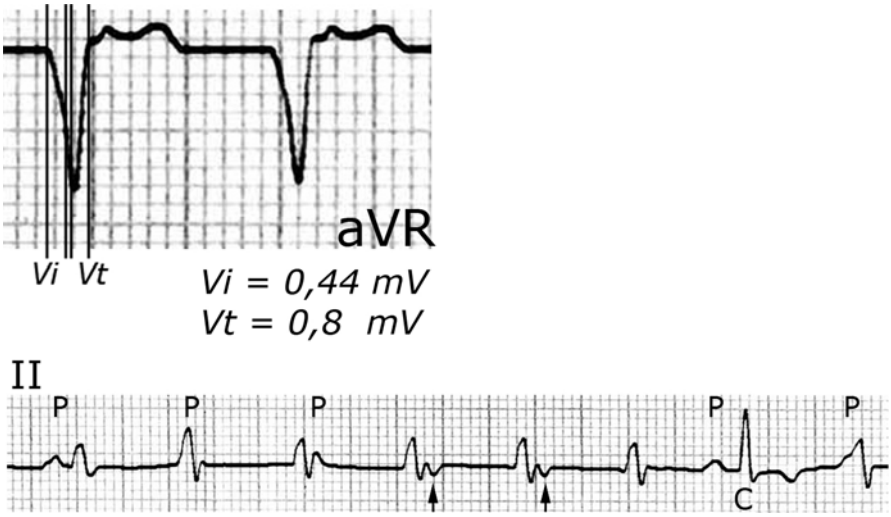

Fig. 6.13 Same case of the preceding figure. Analysis of lead aVR (*top*) and effect of verapamil administration (*bottom*). Despite the absence of (a) dominant initial R wave, (b) q wave with duration >40 ms, (c) notch in the q wave descending limb, the ratio between the voltages of the first and the final 40 ms (*Vi/Vt*) is less than 1, supporting the diagnosis of VT. The ECG recorded during intravenous verapamil administration (strip of lead II) shows A-V dissociation (the 1st three and the last QRS complex) and a capture beat (*C*); *arrows* indicate retrograde conduction restarting

however, is less satisfactory. Further research is necessary to evaluate the real efficacy of RWPT in lead II. Figure 6.3 shows a case of VT in which the RWPT does not exceed 30 ms.

In conclusion, the classic diagnostic criteria to distinguish VT from SVT with aberrant conduction include the following:

1. A-V dissociation, characterized by absence of any relationship between QRS complexes and P waves; this phenomenon is at times immediately recognizable but more often can be discovered only by means of a detailed analysis of the tracing.
2. Second-degree ventriculoatrial block, namely, a relationship between P waves and QRS complexes, but with more ventricular complexes than P waves.
3. Fusion and/or capture beats.
4. Concordant precordial pattern, a sign that can be also expressed as absence of RS (or even rs, Rs, rS) complexes in the precordial leads.
5. Analysis of QRS complexes aimed at discriminating a typical pattern of intraventricular conduction disturbance from a QRS configuration that is impossible or unlikely whenever the ventricular depolarization is dependent on a supraventricular impulse.

Several further criteria have been introduced to identify the origin of wide QRS complex tachycardia, but none of these is able to provide a simple and quick solution of the problem.

Vagal maneuvers and analysis of previous electrocardiograms recorded during sinus rhythm, if available, can provide further keys to the diagnosis. Some criteria proposed in the past, such as QRS axis or ventricular complex duration, are nowadays no longer considered; in addition, it has been demonstrated that items such as age, hemodynamic status, heart rate, and regularity of R-R intervals can be misleading and should not be taken into account.

Analysis of QRS configuration in leads V1 and V6 is a keystone in distinguishing the origin of wide QRS tachycardias: diagnostic criteria rely upon the assumption that aberration is due to a functional bundle branch block, whereas ectopy derives from a totally abnormal activation of the ventricles. Aberration, thus, results in a "typical" bundle branch block morphology, whereas ectopy is expressed by an "atypical" bundle branch block. Specific criteria, based on analysis of leads V1 and V6, have been developed to distinguish from each other the two conditions. Criteria based on QRS configuration, however, suffer from limitations since unexpected complicating factors, such as a previous myocardial infarction, can result in an "atypical" form of bundle branch block even in the presence of supraventricular tachycardia.

Recently proposed items (lead aVR analysis, peak R wave time in lead II) can be at times useful, but they need further investigation to confirm the results obtained by the authors that introduced such criteria.

6.8 Ventricular Versus Preexcited Tachycardia

In preexcited tachycardia, supraventricular impulses are conducted to the ventricles over an accessory pathway, resulting in wide QRS complexes; this is because ventricular depolarization is entirely (or, less commonly, partially) due to the impulse conducted over the abnormal conduction pathway. Such a situation may occur in the presence of (1) atrial tachycardia, (2) atrial flutter, (3) A-V nodal reentrant tachycardia, and (4) antidromic A-V reentrant tachycardia.

In all of these conditions, ventricular depolarization is due to the accessory pathway, and the QRS complexes are very wide ("pure" delta waves), mimicking a VT. It is, thus, necessary to distinguish VT from preexcited tachycardia, since at first glance QRS complex morphology suggests in the latter ventricular, rather than supraventricular, origin of the arrhythmia. In antidromic A-V reentrant tachycardia due to Mahaim fibers, however, the morphology of QRS complexes suggests supraventricular, rather than ventricular, origin of the arrhythmia, since the accessory pathway is usually connected with the right bundle branch, resulting in a typical left bundle branch block pattern [28].

Distinction between VT and preexcited tachycardia is based on the following concept: VT can originate from any part of the ventricular myocardium, whereas in preexcited tachycardia, ventricular depolarization starts (apart the rare exception represented by Mahaim fibers) from the atrioventricular rings, in correspondence of ventricular insertion of the Kent bundle. Accordingly, there is a relatively limited possible patterns, and each of them is characteristic of a defined Kent bundle

location. Since the ECG in sinus rhythm permits in most cases a reliable localization of the accessory pathways [29, 30], the question to be raised in the presence of a wide QRS complex tachycardia should be the following: "Is the morphology of this arrhythmia consistent with the typical pattern of ventricular depolarization due to an accessory pathway?" If the answer is "yes," a preexcited tachycardia is possible, whereas in the case of negative answer, such a diagnosis can be excluded.

It has been reported that in a wide QRS complex tachycardia, the following morphologies suggest VT rather than preexcitation: [4]

1. Negative QRS complexes in V4–V6
2. Negative precordial QRS concordance (negative QRS complexes in all precordial leads)
3. Deep Q waves or Qr complexes in a precordial lead except V1

Although Q waves in precordial leads other than V1 are virtually impossible in preexcitation, negative complexes in V4–V6 are not rarely observed in preexcitation due to a posteroseptal accessory pathway, since the superiorly directed vector can result in large S waves.

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Acute Management of Arrhythmias in Patients with Known Congenital Heart Disease

7

Francesca Bianchi and Stefano Grossi

7.1 Focusing on the Issue

Surgical advances for congenital heart disease (CHD) allow long-term survival for a unique group of patients who would otherwise have died during early childhood. Improved longevity had eventually exposed to late complications, atrial and ventricular arrhythmias contributing to sudden cardiac death (SCD) [1]. Arrhythmias are the consequences of both native abnormalities and surgical procedures. It seems that the arrhythmic burden is the price paid to survival and mostly occurs in adults with CHD. It is now estimated that there are over 1.8 million of adult patients with CHD in Europe [2] and one million in North America [1].

Some defects are best known since studies have focused on specific lesions with predilection for common malformations with effective surgical solution and large number of patients surviving into middle age: this is the case of tetralogy of Fallot that has been studied more extensively than other conditions and so arrhythmic mechanisms and risks are best known [1]; other conditions, less common or with a more recent improvement of survival, are less known.

The entire spectrum of arrhythmias may be encountered in adults with CHD, with several subtypes often coexisting. For some conditions, arrhythmias are intrinsic to the structural malformation itself, as is the case with Wolff-Parkinson-White syndrome in the setting of Ebstein's anomaly, twin atrioventricular (AV) node tachycardia in heterotaxy, or AV block in the setting of "congenitally corrected" transposition of the great arteries (L-TGA). For most other CHD patients, arrhythmias represent an acquired condition related to the unique myocardial substrate

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_7

created by surgical scars in conjunction with cyanosis and abnormal pressure/volume loads of long duration [3, 4].

Arrhythmia substrate and consequent management is peculiar for any CHD, but some general principles can be identified, and recently international scientific boards have provided evidence-based recommendations on best practice procedures for the evaluation, diagnosis, and management of arrhythmias [5, 6].

Arrhythmia management is strictly connected to anatomical native and surgical substrate and to hemodynamic status. Classification of CHD complexity (simple, moderate, and great/severe) proposed by the ACC/AHA task force [7] reported in Table 7.1 is used to orientate management.

7.2 What Physicians Working in ED Should Know

Facing acute arrhythmias in CHD patients needs an early interplay between emergency physician and cardiologists.

Hemodynamically poorly tolerated tachycardia or ventricular fibrillation resulting in pulseless arrest requires management according to AHA/ACC/ESC guidelines for Adult Cardiac Life Support (ACLS) [8]. When direct current cardioversion is required, paddles or patches have to be positioned taking into account cardiac location in the chest [6].

In tolerated arrhythmias, 12-lead electrocardiogram (ECG) of the event should be registered. Knowledge of anatomical defect and collection of surgical reports are also fundamental for best acute and long-term management and should be obtained as soon as possible.

Hemodynamically tolerated tachycardia should be managed according to well-established adult guidelines, while taking into consideration CHD-specific issues [6] on drug therapy: antiarrhythmic drugs (AAD) are frequently poorly tolerated due to negative inotropic and other side effects, and few data exist on their safety and efficacy [6].

For atrial arrhythmias the *thromboembolic risk* must be assessed before cardioversion, reminding that in moderate and severe complexity CHD, it is high even when onset is <48 h [6].

Unexplained syncope in adults with CHD is an alarming event that may have several potential etiologies, including conduction abnormalities and bradyarrhythmias, atrial and/or ventricular arrhythmias, and nonarrhythmic causes [6].

In patients with CHD, the majority of *sudden cardiac deaths* (SCD) have an arrhythmic etiology, but up to 20 % may be nonarrhythmic, as in cerebral or pulmonary embolism, myocardial infarction, heart failure, and aortic or aneurysmal rupture [5]. SCD is responsible for approximately one-fifth of the mortality in adult's CHD, with a greater risk observed in certain malformations (tetralogy of Fallot, Ebstein's disease, left-sided obstructive disease). However, the annual mortality rates are low compared with adult population (0.1–0.3 % per patient-year) [1].

Table 7.1 Complexity of diagnosis in adult patients with congenital heart disease

Simple	Moderate complexity	Great/severe complexity

Native disease:
Isolated congenital aortic valve disease
Isolated congenital mitral valve disease (except parachute valve, cleft leaflet)
Small atrial septal defect
Isolated small ventricular septal defect (no associated lesions)
Mild pulmonary stenosis
Small patent ductus arteriosus
Repaired conditions:
Previously ligated or occluded ductus arteriosus
Repaired secundum or sinus venosus atrial septal defect without residua
Repaired ventricular septal defect without residua
	Aorto-left ventricular fistulas
	Anomalous pulmonary venous drainage, partial or total
	Atrioventricular septal defects, partial or complete
	Coarctation of the aorta
	Ebstein's anomaly
	Infundibular right ventricular outflow obstruction of significance
	Ostium primum atrial septal defect
	Patent ductus arteriosus (not closed)
	Pulmonary valve regurgitation, moderate to severe
	Pulmonary valve stenosis, moderate to severe
	Sinus of Valsalva fistula/ aneurysm
	Sinus venosus atrial septal defect Subvalvular or supravalvular aortic stenosis
	Tetralogy of Fallot
	Ventricular septal defect with:
	  Absent valve or valves
	  Aortic regurgitation
	Coarctation of the aorta
	  Mitral disease
	  Right ventricular outflow tract obstruction
	  Straddling tricuspid or mitral valve
	  Subaortic stenosis
		Conduits, valved or nonvalved
		Cyanotic congenital heart disease (all forms)
		Double-outlet ventricle
		Eisenmenger syndrome
		Fontan procedure
		Mitral atresia
		Single ventricle (also called double inlet or outlet, common, or primitive)
		Pulmonary atresia (all forms)
		Pulmonary vascular obstructive disease
		Transposition of the great arteries
		Tricuspid atresia
		Truncus arteriosus/hemitruncus
		Other abnormalities of atrioventricular or ventriculoarterial connection not included above (e.g., crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)

Adapted from Warnes et al. [7]; with permission

7.3 What Cardiologist Should Know

Atrial tachyarrhythmias (ATs), the most frequent in CHD, have been identified as a risk factor for SCD. The mechanism has been attributed to rapid AV conduction, most notably at times of exertion, with hemodynamic instability caused by the atrial

tachyarrhythmia itself or by its degeneration into a secondary ventricular tachyarrhythmia [7].

Prevalence of ATs is 3 times higher than what is observed in general population, and it is reported that 20-year-old patients with CHD have an equivalent risk of a 55-year-old women without CHD: patients with CHD are young with aged hearts [9]; atrial fibrillation (AF) is less common than atrial flutter accounting for 20–30 % of all ATs [10, 11].

The most common mechanism of tachycardia seen in the adult CHD patient population is macro-reentry within the atrial muscle. It is defined as *intra-atrial reentrant tachycardia (IART*) [7].

This arrhythmia usually is a late postoperative disorder, and it may arise after nearly all procedures involving a right atriotomy (even simple closure of an atrial septal defect); the incidence is clearly highest after the Mustard–Senning and Fontan operations, in which 30–50 % can be expected to develop a symptomatic episode during follow-up. Generally, IART tends to be slower than typical flutter, with atrial rates in the range of 170–250 beats per minute. In the setting of a healthy AV node, these rates will frequently allow a pattern of 1:1 AV conduction that may result in hemodynamic instability, syncope, or possibly death [3, 7]. Rate control should be achieved as soon as possible. Beta-blocking drugs and nondihydropyridine calcium channel antagonists can be used to achieve ventricular rate control with insufficient evidence to recommend one agent over another; since beta-blockers are associated with a decreased incidence of ventricular tachyarrhythmias in many conditions, it may be reasonable to liberalize their use in this patient population if well tolerated [6].

Sustained IART or AF lasting ≥48 h is an established *risk for thromboembolism* [12, 13], but moderate and complex forms of CHD have a predisposition to thromboembolic complications estimated to be10- to100-fold higher than in age-matched controls: in these patients it may be prudent to rule out intracardiac thrombus prior to cardioversion regardless of the duration of IART or AF [6].

Once atrial arrhythmia is recognized and thromboembolic risk ruled out, acute interruption can be performed with electrical cardioversion, overdrive pacing (in patients with implanted atrial or dual chamber pacemaker/defibrillators), or antiarrhythmic drugs.

Reciprocating tachycardia and some non-automatic focal atrial tachycardias may be terminated by vagal maneuvers, intravenous adenosine, or non-dihydropyridine calcium channel antagonists, with the exception of patients with an anterograde conducting accessory pathway (WPW).

There is a paucity of literature regarding pharmacologic conversion of IART or AF in adults with CHD; ibutilide has been tested in a small pediatric series [14], but there are no efficacy and safety data regarding acute conversion of IART or atrial fibrillation with class IA and IC and other class III drugs in patients with CHD [6]: *electrical cardioversion should therefore be preferred*. Anterior–posterior pad positioning may be needed in the setting of marked atrial dilation [5].

Experience with chronic pharmacologic therapy for IART in adults with CHD has been discouraging [6, 10, 11, 15], resulting in a growing preference for nonpharmacologic options in most centers.

Nevertheless, in those with moderate or complex forms of CHD, a rhythm control treatment strategy (i.e., maintenance of sinus rhythm) is generally preferred to rate control as the initial management approach [6].

Ventricular arrhythmias. There are several scenarios in which high-grade ventricular arrhythmias may develop in CHD. The most familiar involves macroreentrant VT as a late complication in postoperative patients who have undergone ventriculotomy and/or patching such as tetralogy of Fallot repair which is the best studied. Reentry circuit is caused by conduction corridors around regions of scar in the RV outflow tract (RVOT). The incidence of late VT or SCD for repaired tetralogy has been estimated between 0.5 and 6.0 % in various series [3, 7]. Some patients with slow organized VT may be hemodynamically stable at presentation, but VT tends to be rapid for the majority, producing syncope or cardiac arrest as the presenting symptom. Serious ventricular arrhythmias may also develop in a number of other malformations, even in the absence of direct surgical scarring to ventricular muscle when the right ventricle supports the systemic circulation or in the presence of a failing systemic ventricle. The appearance of ventricular arrhythmias in these cases commonly coincides with deterioration in hemodynamic status [7].

Cardioversion should be expeditiously performed for any sustained ventricular arrhythmia; electrical cardioversion in tolerated arrhythmias has the disadvantage of requiring sedation, while drugs carry the disadvantage of delayed effect.

The most efficacious pharmacologic agent is intravenous amiodarone; this agent may be associated with hypotension if administered rapidly: patients should be continuously observed and intravenous sedation and cardioversion readily available. Beta-blockers can be combined to amiodarone to improve rhythm stability, while lidocaine is a third-choice drug for short-term treatment [8].

When triggered activity is the suspected underlying mechanism, intravenous beta-blockers or calcium channel antagonists may be used, but the latter can be more harmful in the presence of scar-related macroreentry or ischemic ventricular tachycardia [6, 8].

7.4 Indications for Hospitalization, Follow-Up, and Referral

Guidelines recommend that health care for adults with CHD and arrhythmias should be coordinated by regional adult CHD centers of excellence with multidisciplinary staff that serve the surrounding medical community for consultation and referral [5–7, 16].

Syncope, ventricular arrhythmias, and in general arrhythmias in the setting of moderate to severe complexity CHD should be hospitalized.

The onset of arrhythmias may be a signal of hemodynamic decompensation, and the risk associates may be amplified in the presence of the abnormal underlying circulation [16]; a new evaluation with echocardiography and eventually further imaging (transesophageal echocardiogram, MRI/CT scan) or catheterization should be planned after a new-onset arrhythmic event.

Unexplained syncope and "high-risk" CHD substrates should be evaluated with an *electrophysiologic study,* which is also useful in life-threatening arrhythmias or resuscitated sudden cardiac death when the proximate cause for the event is unknown or there is potential for ablation [5, 6].

Before planning any invasive procedure, patients should undergo an individualized and multidisciplinary evaluation and the best knowledge of cardiac and vascular anatomy achieved [5, 6].

Patients with *AF/flutter/IART* and simple forms of CHD could be reasonably managed according to AF guidelines for AF or flutter and no or minimally heart disease [6, 12, 13] for rate/rhythm control strategies as well for anticoagulation: in *nonvalvular simple CHD,* CHADSVASC and HASBLD score should be used and either vitamin K antagonists (VKA) or a novel anticoagulant (NOAC) can be used [5].

In all patients initial therapy for atrial arrhythmias should include adequate rate control, best performed with beta-blockers, if tolerated.

Late postoperative atrial tachyarrhythmias in adults with CHD are most often due to *cavotricuspid isthmus-dependent,* and catheter ablation has proven to be safe and considerably effective, generally preferred over long-term pharmacologic management [6].

In CHD of moderate to severe complexity, an initial strategy of rhythm control is reasonable [5], and patients should be treated with VKA; NOAC is not recommended in this context due to lack of safety data [5, 6]. Non-pharmacologic strategy for rhythm control should be preferred to long-term pharmacologic therapy even if acute success rates of catheter ablation (CA) in CHD seem to be lower compared with the general adult population [5, 11]. If catheter ablation is not feasible or unsuccessful, long-term pharmacologic therapy can be necessary [6, 7]. Class I drugs and dronedarone are not recommended in this setting. *Sotalol* can be considered in patients with preserved ventricular function and without renal insufficiency, hypokalemia, severe sinus node dysfunction, or QT prolongation; *amiodarone* can be considered as first-line antiarrhythmic agent for the long-term maintenance of sinus rhythm in the presence of pathologic hypertrophy of the systemic ventricle, systemic or subpulmonary ventricular dysfunction, or coronary artery disease; in all other conditions, it is a second-line therapy due to high time and dose-dependent side effects; induced thyrotoxicosis is especially common in women with CHD and cyanotic heart disease or univentricular hearts with Fontan palliation and in those with a body mass index $\leq$21 kg/m2 [5, 14]. *Dofetilide* appears to be a reasonable alternative to amiodarone in normal QT patients if available [5].

Rate control may be the definitive therapeutic strategy after failed attempts at rhythm control and in whom rate control is well tolerated [6].

Catheter ablation is also recommended in recurrent symptomatic and/or drug-refractory supraventricular tachycardia related to accessory AV connections or twin AV nodes and in high-risk or multiple accessory pathways and can be beneficial for recurrent symptomatic and/or drug-refractory AV nodal reentrant tachycardia [5, 6].

Ventricular arrhythmias: *ICD* is the first-line therapy for the secondary prevention of sudden death in adults with CHD [17] and should be considered in high-risk patients [5, 6, 8, 15, 19].

Abnormal systemic venous pathways, impaired or lack of venous access to the ventricle, or right-sided AV valve disease may need *epicardial and/or subcutaneous coils* [5].

The subcutaneous ICD may be a reasonable option in adults with CHD in whom transvenous access is not possible or desirable and in whom anti-bradycardia and ATP functions are not essential [5].

Beta-blockers are associated with a decreased incidence of ventricular tachyarrhythmias in patients with transposition of the great arteries and atrial switch surgery, and they should be used in long-term VA prevention if tolerated [5, 6].

Catheter ablation is indicated as adjunctive therapy to an ICD in adults with CHD and recurrent monomorphic ventricular tachycardia, a ventricular tachycardia storm, or multiple appropriate shocks that are not manageable by device reprogramming or drug therapy [6]. The most common CHD associated with sustained ventricular tachycardia is tetralogy of Fallot: a macroreentry mechanism is at the base of monomorphic ventricular tachycardias, which can be cured with catheter ablation as an alternative to drug therapy; in limited Fallot series after VT ablation, ICD was considered necessary only if CA was unsuccessful [16, 18].

Frequent ventricular ectopy associated with deteriorating ventricular function can reasonably be treated by catheter ablation.

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Acute Management of Arrhythmias in Patients with Channelopathies

8

Francesca Bianchi and Stefano Grossi

The term "channelopathies" defines a group of inherited arrhythmic syndromes caused by mutations of genes encoding for proteins that regulate ion currents [1] in patients without structural heart disease. Mutations disrupt the balance in the cardiac action potential favoring peculiar ECG abnormalities and the risk of life-threatening arrhythmias.

A gain or a loss of function of ionic channels or trafficking proteins underlies the development of arrhythmogenic triggers and substrate and the amplification of transmural heterogeneities [2]. It is estimated that inherited arrhythmia disorders (long and short QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, early repolarization syndrome, idiopathic ventricular fibrillation) cause 10 % of the1.1 million sudden deaths in Europe and the USA [3].

Due to the peculiarity of these rare disorders, some of the commonly used emergency protocols should be applied with caution, since some of antiarrhythmic and resuscitation drugs could be contraindicated and potentially worsen arrhythmias in this specific group of patients.

The congenital *long QT syndromes (LQTS)* are the most common channelopathies, with an estimated prevalence of 1:2000–2500 [4], and are characterized by prolonged repolarization, resulting in a prolonged QT interval on the ECG, and by a susceptibility to polymorphic ventricular arrhythmias known as torsades de pointes [2]. Causes for this primary electrical myocardial disease are mutations in genes coding for cardiac potassium and sodium channels and proteins associating with potassium channels, or mutations in the ankyrin-B gene, that reduce net repolarization currents in the ventricular myocardium prolonging repolarization phase and predispose to early afterdepolarization (EAD)-induced triggered activity. Once

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_8

triggered by EADs, torsades de pointes can be maintained by a reentrant mechanism [1, 4–6].

Short QT syndrome (SQTS), characterized by a short QT interval on ECG with a high sharp T wave and a reduced repolarization phase, has a high familial incidence of palpitations, atrial fibrillation, syncope, and SCD [7, 8], typically during childhood. It is considered the most lethal channelopathy; incidence and prevalence are difficult to determine due to limited data [4, 6–8].

The *Brugada syndrome (BrS)* is an autosomal dominant inherited arrhythmic disorder characterized by an ECG pattern consisting in coved-type ST segment elevation in atypical right bundle branch block in right precordial leads (V1–V3) and risk of SCD resulting from episodes or polymorphic ventricular arrhythmias [9–11]; men are affected with a ratio 8:1 in respect to women; reported prevalence in Europe is 1:2000, while in Asian population, it is 2,4:2000; life-threatening events typically involve young male adults (30–40 years old) during sleep [6, 11].

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare but highly malignant genetic disease leading to an increase in intracellular Ca^{++} concentration, resulting in polymorphic arrhythmias due to a cascade of delayed afterdepolarization and triggered activity occurring during emotional or physical stress that cause syncope and high mortality (30 % by the age of 30 years); the estimated prevalence is 1:10,000 [4, 12].

Recently, several studies have reported that J-point and ST segment elevation in the inferior or lateral leads, which is also called early repolarization (ER) pattern, can be associated with ventricular fibrillation (VF) and SCD in patients without apparent structural heart diseases. However, J-wave elevation is fairly commonly seen in young healthy individuals (estimated prevalence, 1–9 %) and frequently considered to be benign [6]: the vast majority of patients with the ECG pattern are asymptomatic and have a low arrhythmic risk, while strategies for risk stratification remain suboptimal. It is reported that unexplained syncope in patients with an ER pattern, particularly with a "malignant variant" of the pattern, may be an important predictor of future arrhythmic events [4, 13]; the presence of an ER pattern with otherwise unexplained ventricular arrhythmia is commonly referred to as *ER syndrome* [4, 6, 13, 14].

8.1 Focusing on the Issue

The ED physician could deal with a patient with an already established diagnosis of inherited arrhythmia, eventually already treated with drugs and or implanted cardiac defibrillator (ICD).

On the other hand, the referral event could be the first clinical manifestation of an unrecognized inherited arrhythmogenic disorder that, especially in young and otherwise healthy subject, must be suspected, investigated, and finally confirmed or ruled out.

All patients with a known or suspected channelopathy who refer for arrhythmic suggestive symptoms should be ECG monitored and a cardiologic evaluation sought.

Patients resuscitated from cardiac arrest must be rapidly evaluated for the presence of structural heart disease, an inherited arrhythmia syndrome, a triggering ventricular arrhythmia focus, or a noncardiac cause [15].

Most of inherited arrhythmic disorders could be diagnosed on the basis of a standard 12-lead ECG that should therefore be obtained as soon as possible as the chance to make a correct diagnosis is highest in proximity of the arrhythmic event [15]. This is a simple and useful instrument to confirm the presence or suspect a channelopathy, aside from excluding other acquired acute cardiac conditions (such as acute coronary syndrome); however, a single normal resting ECG may not exclude all forms of channelopathies. ECG recording of arrhythmic event, when possible, could be useful for the subsequent management [15].

In all cases it is indicated to avoid pro-arrhythmic triggering conditions and discontinue potentially harmful drugs that are specific for any different channelopathy: currently used antiarrhythmic and resuscitation drugs may hasten the electrical instability in these particular patients and should be therefore avoided when a specific channelopathy is known or suspected (see below).

8.2 Different Ways of Presentation

Cardiac arrest and hemodynamic nontolerated arrhythmias should be managed with early defibrillation [15] with special considerations required for drug administration.

Polymorphic ventricular tachycardia is defined as ventricular rhythm faster than 100 bpm with clearly defined QRS complexes that change continuously from beat to beat; it is the typical life-threatening arrhythmia observed in patients with channelopathies; its occurrence, in the absence of structural heart disease, suggests the presence of an inherited arrhythmia syndrome [15]; it could be self-terminating or degenerate into VF.

Bidirectional ventricular tachycardia, characterized by two alternating QRS complex morphologies with different polarity, is recognized as a hallmark of CPVT; it can degenerate into polymorphic ventricular tachycardia and VF. It may be encountered also in the rarest Andersen-Tawil syndrome and in several other conditions which predispose to delayed afterdepolarizations (DADs) and triggered activity (i.e., digitalis intoxication) [4, 16] See Fig. 8.2.

The term *torsades de pointes* (TdP) was coined by Dessertenne [17] in 1966 as a polymorphic ventricular tachycardia characterized by a pattern where the QRS complexes appear to be twisting around the isoelectric baseline [15]. The trigger for TdP is thought to be a PVC that results from an EAD generated during the abnormally prolonged repolarization phase; this arrhythmia has a typical long-short ventricular cycle length as initiating sequence and is typical for congenital or acquired long QT syndrome. TdP usually self-terminates and it is often responsible for syncopal episodes but when it deteriorates into VF may cause sudden death [4] see fig. 8.2. Since TdP is strongly associated with drugs or electrolyte imbalances that further delay repolarization, precipitating factors should promptly be searched and corrected [15, 18, 19].

Ventricular tachycardia/ventricular fibrillation storm represents a true medical emergency that requires a multidisciplinary approach to care [15] (see Chap. 11).

In patients with known diagnosis of channelopathy (including known gene carriers), the occurrence of *syncope* is an independent predictor of life-threatening arrhythmic events [4].

In most patients, syncope is the first clinical manifestation of inherited arrhythmic disorders that should therefore be evaluated.

Atrial fibrillation (AF) affects 1–2 % of the population and increases in prevalence with aging [20]. Ion channel disorders can predispose to atrial fibrillation, and prevalence in this population is increased, since the same imbalance of the action potential that causes ventricular arrhythmias could affect the atria. On the contrary, AF could be the first manifestation of an inherited cardiac arrhythmia (sometimes unmasked by drug administration [21]) which should be always considered in young otherwise healthy subjects.

Since commonly used drugs for rhythm or heart rate control may be contraindicated due to the potentially life-threatening pro-arrhythmic effect, a non-pharmacological strategy should be considered, with immediate electrical cardioversion always indicated in poorly tolerated AF, but also drugs for anesthesia/sedation should carefully be considered as potentially harmful: for example, propofol should be avoided in Brugada patients, who have a reported prevalence of atrial fibrillation between 9 to 25 and 39 % [21]. Short QT syndrome is characterized by atrial fibrillation [7, 8] with young age onset, being the first clinical manifestation in several reported SQTS cases, since a short repolarization time is a known mechanism in AF [22]: it was observed in 15 % of SQTS population, also younger than 35 years [23]. Adrenergically mediated atrial arrhythmias are also common manifestation of CPVT [4]. In LQTS frequent short-lasting atrial arrhythmias have been reported [23, 24].

Patients presenting with *ICD discharge* should be ECG monitored and device interrogation, even by remote monitoring when available, performed as soon as possible: appropriate shocks due to ventricular arrhythmia should be promptly managed, according to the peculiar diagnosis of the patient. Inappropriate shocks (which may have a high incidence in this population due to young age, high incidence of AF, and sometimes peculiar ECG [25] leading to incorrect recognition of the rhythm) and discharges on non-sustained VT should be avoided as part of the emergency treatment: painful shocks can increase the sympathetic tone and trigger further arrhythmias leading to a malignant cycle of ICD shocks and even death [15]; inhibition through magnet application could be the first intervention before device specialist intervention in case of incessant and clearly inappropriate shocks.

Therapy: The first step of management of acute events in these patients is to avoid and correct potentially triggering conditions:

Fever: In *Brugada* syndrome avoidance of fever is generally accepted to be an important part of prophylactic treatment since it is a well-known trigger of cardiac events [26, 45, 27]. Fever can also be a risk factor for the development of life-threatening ventricular arrhythmias in the *LQT2* form of congenital long QT syndrome [28, 29].

Autonomic influences play an important role in unmasking the electrocardiographic phenotype and precipitating lethal arrhythmias. Sympathetic stimulation precipitates tachyarrhythmias and sudden cardiac death in CPVT and LQTS, while in BrS and ER, it can prevent them [30]. Most episodes of VF in patients with Brugada syndrome and some in LQT3 are observed during periods of high vagal tone, such as at rest, during sleep, or after alcohol intake [30]. In LQTS 1 and 2 and CPVT patients, sympathetic stimulation and sympathomimetic drugs should be avoided, and the use of sedation to reduce emotional stress may be considered as a support to drug therapy.

Drugs to avoid: Several AAD as well as noncardiac drugs may have a pro-arrhythmic effect in this group of disease. Arrhythmias are due to the effects of drugs on ion channels (with worse harm for potassium channel blockers in LQTS and sodium channel blockers in Brugada), that is, a target effect in AAD and a collateral effect of several other compounds. These drugs should be avoided or discontinued as a principal part of acute arrhythmia management in channelopathies; two panels of experts have created a web-based platform reporting and periodically updating all drugs that should be avoided in LQTS and Brugada syndrome: www.crediblemeds.org and www.brugadadrugs.org, respectively [18, 19, 26, 45].

These websites should be promptly consulted while managing these patients, mostly in emergency setting. In SQTS, at present, only one drug is known to have pro-arrhythmic effect and should be avoided (rufinamide, an antiepileptic drug), but other molecules may shorten QT in experimental isolated hearts and the list could grow in the future. *Electrolyte* abnormalities should be corrected (see Chap. 8) and sometimes overcorrected: *Potassium* repletion to 4.5–5 mmol/L may be considered for patients who present with torsades de pointes [31]; in CPVT patients calcium should not be administered.

Management with intravenous *magnesium sulfate* is reasonable for patients who present with *LQTS* and episodes of *torsades de pointes. Beta-blockers* can be combined with pacing for patients who present with TdP and sinus bradycardia [31]. In LQT3 intravenous *lidocaine or oral mexiletine* may be considered.

Acute drug therapy of *polymorphic ventricular arrhythmia in Brugada* syndrome is based on isoproterenol infusion which increases the L-type calcium currents (1–2 μg bolus i.v. followed by continuous infusion of 0.15–2.0 μg/min) and/or quinidine (300–1500 mg/day) [18, 21, 26]; quinidine is also useful for atrial fibrillation in Brugada patients and should be considered in chronic prevention of recurrences of both atrial and ventricular arrhythmias [4, 18, 21, 45]. Electrical storm in patients with early repolarization syndrome has to be managed by *isoproterenol infusion* (initiated at 1 μg/min targeting a 20 % increase in heart rate or an absolute heart rate >90 bpm, titrated to hemodynamic response, and suppression of recurrent ventricular arrhythmia); *quinidine* can be helpful for acute and long-term treatment [4, 32].

In CPVT patients therapy of acute ventricular arrhythmias is mainly based in adrenergic suppression; *verapamil* i.v. could be of use for short-term therapy [4, 16, 33].

8.3 What Cardiologists Should Know

Cardiologist should be promptly involved in the management of "channelopathy patients" in the setting of acute arrhythmias in order to:

1. Rule out structural heart disease and secondary causes that mimic channelopathies.
2. Define diagnosis.
3. Provide risk stratification in order to plan long-term management.

Diagnosis in channelopathies is essentially 12-lead ECG based, and more than 1 recording is usually indicated; triggering conditions could give a clue. *LQTS* diagnosis is based on QT measurement [34] corrected with Bazett formula: a QTc value ≥480 ms in repeated 12-lead ECG is diagnostic [45]; LQTS is diagnosed also in the presence of a risk score ≥3 [4, 35, 36, 45] or in the presence of an unequivocally pathogenic mutation in one of the LQTS genes. LQTS can be diagnosed in patients with QTc > or = 460 ms and unexplained syncope in the absence of secondary causes [4, 45].

Most arrhythmic events occur during physical or emotional stress in LQT1, at rest or in association with sudden noise in LQT2, and at rest or during sleep in LQT3 [37].

The use of provocative tests have been proposed to unmask LQTS in patients with normal QTc at resting ECG, like measurement during change from supine to standing position, in the recovery phase of exercise testing; clinical use of epinephrine for unmasking LQTS, however, is not unequivocally accepted [4].

SQTS is diagnosed in the presence of QTc ≤340 ms and diagnosis should be considered if QTc ≤360 ms in the presence of a pathogenic mutation or family history of SQTS/SCD at age <40 years or a VT or VF episode in the absence of heart disease [4, 45]. In one of the largest published SQTS series, it is reported that more than 60 % of the subjects had symptoms at presentation: cardiac arrest, the first clinical manifestation in one third of the patients, can occur in children during first year of life and in males between the second and fourth decade; syncope is the second most frequent clinical manifestation (15 % of cases). Events may occur both at rest and during effort, so it is not possible to identify a uniform trigger.

Brugada syndrome is diagnosed when a type 1 ST segment elevation is observed in at least one right precordial lead placed in a standard or superior position (up to the 2nd intercostal space) spontaneously or after intravenous administration of a sodium channel-blocking agent, as aymaline or flecainide [4, 9–11, 45]. Arrhythmic events typically occur during sleep or vagal stimulation. Risk stratification is based on the presence of spontaneous type 1 pattern and symptoms; there is no consensus on the value of electrophysiologic study in predicting long-term arrhythmic events [4].

CPVT is diagnosed in the presence of unexplained exercise or catecholamine-induced bidirectional or polymorphic ventricular tachycardia in individual without structural heart disease and with normal resting ECG [45]. In individuals >40 years of age, it can be diagnosed, but in this population, coronary artery disease should be excluded. CPVT is also diagnosed in patients with a pathogenic mutation [4, 45]. Arrhythmic events are typically induced by exercise and emotional stress and since basal ECG is usually normal and exercise stress test and loop recorders are pivotal investigations for diagnosis [4].

8.4 A Possible Algorithm/Pathway for Diagnosis and Treatment (Fig. 8.1; Table 8.1)

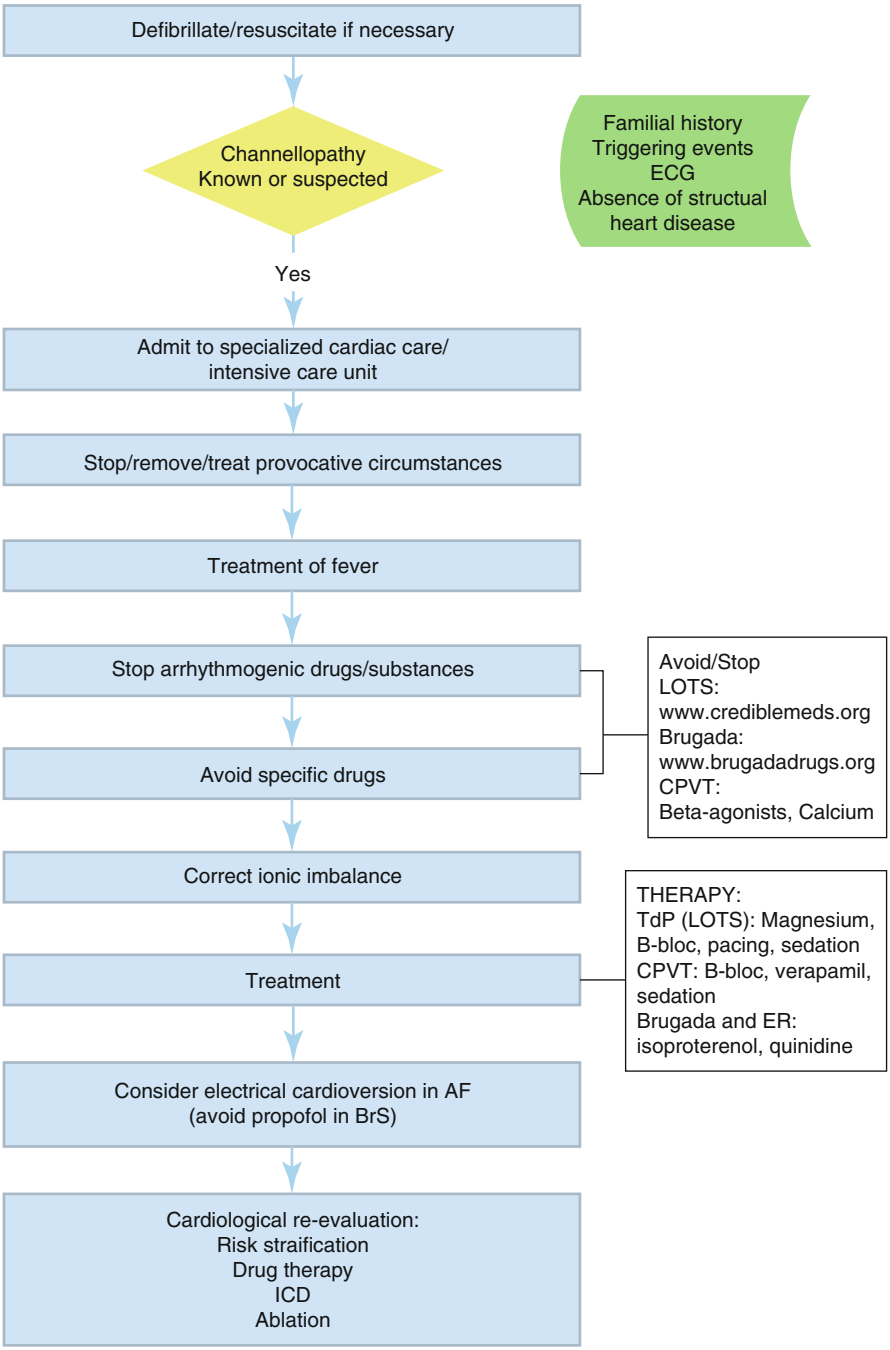

Fig. 8.1 A possible algorithm/pathway for diagnosis and treatment of arrhythmias in patients with channelopathies

Table 8.1 Conditions that can cause PVT/VF and potential therapies

Clues	Test to consider	Diagnoses	Therapies
Long QT/T wave alternans TdP History of seizures Specific triggers (loud noise)	ECG/monitor Epinephrine challenge Exercise stress test Genetic testing	Congenital LQTS	Beta-blockers Avoid QT-prolonging drugs In LQT3: mexiletine/flecainide PM/ICD Stellatectomy
Incomplete RBBB with STE in leads V1–V2 Fever	ECG Drug challenge Genetic testing	BrS	Isoproterenol/quinidine Antipyretic Ablation ICD
J-point elevation	ECG	Early repolarization	ICD
Short QT interval	ECG	SQTS	ICD Quinidine or sotalol
Bidirectional VT exercise induced	Exercise stress test Genetic testing	CPVT Andersen-Tawil syndrome	Beta-blockers/flecainide/verapamil ICD

Adapted from [15]: with permission

8.5 Indications for Hospitalization, Follow-Up, and Referral

Following the arrhythmic index event, channelopathy patient should be reevaluated for risk stratification and prevention of recurrences. Expert centers with a focus on inherited arrhythmias should be involved in complex cases [4].

Atrial arrhythmias in low-risk patients could be managed in out-of-hospital setting with referral to arrhythmia experts to set up indication for pharmacological or non-pharmacological strategy. Thromboembolism should be managed according to AF guidelines using CHA_2DS_2VASC score [20]. First line therapy consists in avoiding potentially pro-arrhythmic drugs and conditions: a complete list should be supplied to the patient and to the general practitioner.

CPVT and LQT patients should be advised to limit/avoid competitive sport, strenuous exercise, and exposure to stressful environments (which in LQT2 should include exposure to loud/abrupt noises, i.e., alarm bell); Brugada patients should avoid excessive alcohol intake and large meals and should be advised to a prompt treatment of fever [45].

Syncope and life-threatening arrhythmias require hospitalization.

Aborted sudden death and sustained ventricular arrhythmias require an ICD for secondary prevention [4, 15, 31, 45] with or without adjunctive therapy.

CPVT and LQTS patients should be treated with *beta-blockers: nadolol and propranolol* are the drugs of choice [1, 4, 33]; in patients with recurrent symptoms/arrhythmias already on beta-blockers, it should be considered *flecainide for CPVT*

Fig. 8.2 Panel (**a**):12-lead ECG from a 9-year-old boy with ryanodine-positive CPVT shows a transition from triggered bidirectional ventricular tachycardia followed by brief polymorphic ventricular tachycardia to reentrant ventricular fibrillation. With permission from Elsevier Roses-Noguer F. et al. [43]: Copyright © 2014 Heart Rhythm Society. Panel (**b**): torsades de point. With permission from Van der Heide et al. [44]

patients [33] and *flecainide or ranolazine or mexiletine in LQT3* patients [4]; ICD and left cardiac denervation should be considered in patients refractory to pharmacological therapy [4, 33]. Repeated exercise stress test is used in CPVT patients to evaluate drug efficacy.

Brugada and SQTS patients symptomatic for syncope should be treated with *ICD*; quinidine therapy could be used as adjunctive therapy or in cases in which ICD is refused or contraindicated or in recurrent appropriate ICD intervention [22, 26].

Hydroquinidine has proven to play a role in AF recurrence prevention in Brugada patients [4, 21].

Refractory electrical storm could be evaluated for catheter ablation of triggers [15, 39–41, 45].

All clinically diagnosed patients with LQTS and CPVT should undergo *genetic evaluation* if not previously performed, and it can be useful in Brugada (type1) patients and SQTS [42]. Routine genetic testing is not indicated for the survivor of an unexplained out-of-hospital cardiac arrest in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy [42] (Figs. 8.2 and 8.3)

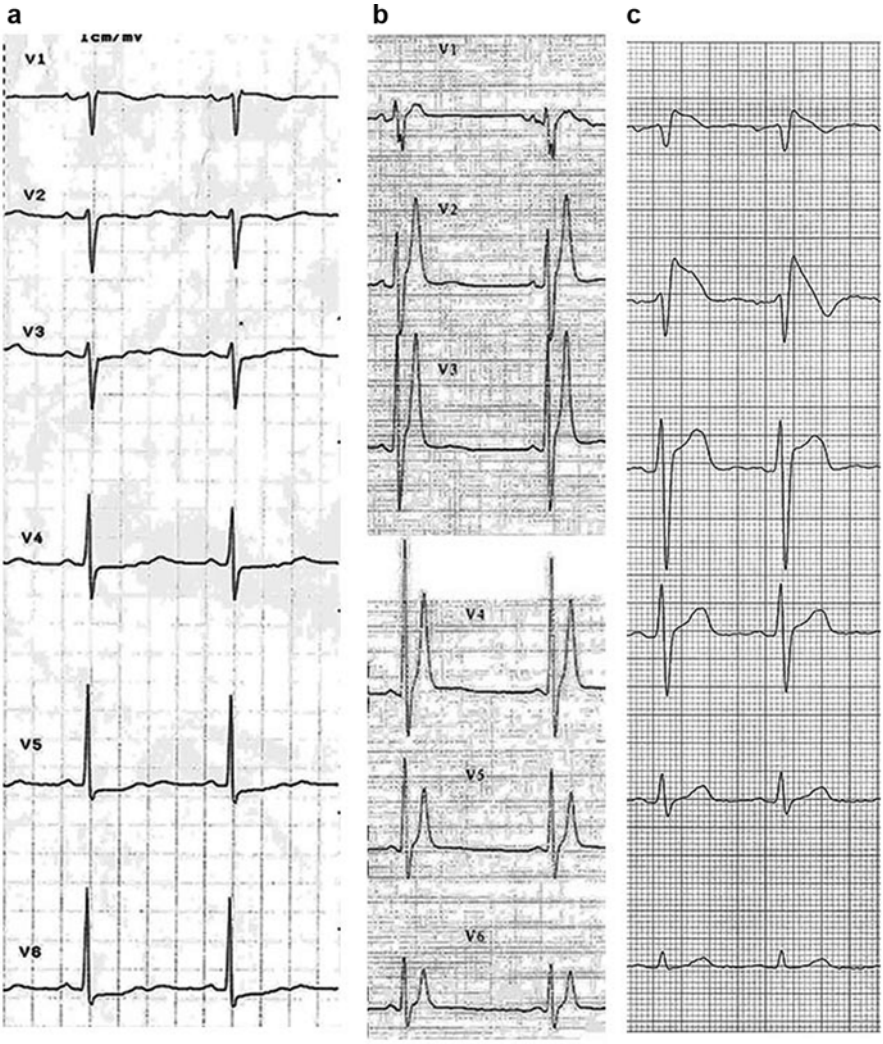

Fig. 8.3 Precordial leads ECG in patients with panel (**a**), long QT syndrome, heart rate 58 beats per minute, QTc 600 ms; panel (**b**), short QT syndrome, heart rate 52 beats per minute (bpm), QT 280 ms*; panel (**c**), Brugada syndrome, coved ST elevation in V1–V2. *With permission from Gaita F. et al. [7]

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9 Acute Management of Patients with Arrhythmias and Non-cardiac Diseases: Metabolite Disorders and Ion Disturbances

Stefano Bardari, Biancamaria D'Agata, and Gianfranco Sinagra

9.1 Focusing on the Issue

Acute metabolic disorders are relatively common amongst medical and surgical patients, especially if critically ill. Whilst increasing the complexity of management plans, these circumstances also increase the risk of cardiac complications, such as arrhythmias, and furthermore are associated with increased mortality. Arrhythmic risk is promoted by electrolyte, acid-base and fluid balance disturbance, increased sympathetic drive and cardiac ischaemia. Particularly, electrolyte abnormalities may generate or facilitate clinical arrhythmias, even in the setting of normal cardiac tissue, by modulating ion conduction across (specific) cardiac cell membrane channels [1], and management of the underlying pathology may be all that is required to allow rapid normalisation of the metabolic profile. Moreover, complex pharmacological regimes may exacerbate the situation [2].

9.1.1 Metabolite Disorders

Endocrine disorders can induce ventricular tachycardia (VT) and sudden cardiac death (SCD) by excess or insufficient hormonal activity on myocardial receptors (e.g. pheochromocytoma, hypothyroidism). The endocrinopathy can also cause myocardial changes (e.g. acromegaly) or electrolyte disturbances produced by

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_9

hormone excess (e.g. hyperkalaemia in Addison disease and hypokalaemia in Conn syndrome), and certain endocrine disorders can accelerate the progression of conditions such as underlying structural heart disease secondary to dyslipidaemia or hypertension, increasing the risk of serious arrhythmias [3].

In addition to electrolyte shifts and ischemia, other systemic influences found in the critically ill patient, such as acid-base abnormalities, hypoxia and enhanced catecholamine levels, can also predispose to ventricular arrhythmias [4]. The mechanism of these arrhythmias is due to automaticity or triggered activity through stimulation of the β-adrenergic receptor, sympathetic activation or exogenous catecholamines. Re-entry may also be facilitated, particularly in the presence of ischemia [5]. The management of ventricular arrhythmias secondary to endocrine disorders should address the electrolyte (potassium, magnesium and calcium) imbalance and the treatment of the underlying endocrinopathy.

9.1.1.1 Thyroid Disorders

Thyrotoxicosis commonly causes atrial arrhythmias; cases of VT/SCD are extremely uncommon but may occur with concomitant electrolyte disturbances. VT/SCD is more common in hypothyroidism, the basic underlying mechanism being possibly related to prolongation of the QT interval [6, 7]. Thyroxin replacement therapy usually corrects this abnormality and prevents any further arrhythmias, but antiarrhythmic drugs, such as procainamide, have been used successfully in an emergency.

9.1.1.2 Phaeochromocytoma

Phaeochromocytoma may present with VT/SCD, but there are no data to quantify its incidence, best mode of management or response to treatment. Conventional antagonism of catecholamine excess with α-receptor blockers followed by β-blockade helps control hypertension and reverses or prevents any further structural deterioration [8], but there is only anecdotal evidence that it prevents recurrence of ventricular arrhythmia [9]. Early definite surgical treatment of the phaeochromocytoma should be a priority, especially in cases with documented life-threatening arrhythmias. In some patients with VT associated with phaeochromocytoma, a long QT interval has been identified [10, 11].

9.1.1.3 Acromegaly

SCD is an established manifestation of acromegaly, and life-threatening arrhythmias are likely to be an important cause [12]. Up to one half of all acromegalic patients have complex ventricular arrhythmias on 24-h Holter recordings, and of these, approximately two thirds are repetitive [13]. Appropriate surgical management of the pituitary tumour is paramount for improved long-term outcome, as cardiac changes are reversible, especially in the young [14, 15]. Somatostatin analogues such as octreotide and lanreotide have both been shown to improve the ventricular arrhythmia profile [16–18].

9.1.1.4 Primary Aldosteronism, Addison Disease, Hyperparathyroidism and Hypoparathyroidism

Severe electrolyte disturbances form the basis of arrhythmogenesis and VT/SCD associated with the previously mentioned endocrinopathies. Electrocardiographic (ECG) changes including prolongation of QRS and QTc intervals can accompany

the electrolyte disturbance. Electrolyte imbalance requires immediate attention before definitive treatment of the underlying cause [19–21].

9.1.1.5 Diabetic Ketoacidosis (DKA)

As its name suggests, DKA is defined by the presence of metabolic acidosis, along with hyperglycaemia, as a result of insulin deficiency. These factors are generally accompanied by severe dehydration, catecholamine release and disordered potassium homeostasis; deviation of magnesium, sodium and other electrolytes can also occur. The syndrome is most often precipitated by sepsis or poor medication compliance with direct cardiac consequences, such as arrhythmias [22]. With appropriate insulin and fluid therapy, the acidosis is reversed and concomitantly potassium is forced into cells, often resulting in rebound hypokalaemia. Without frequent biochemical monitoring, such dynamic metabolic changes may deviate from normality without being acted upon, so increasing the likelihood of cardiac compromise.

During the acute phase of treatment, the rapid transition of potassium gradients changes the type of arrhythmia susceptibility. Initially, hyperkalaemia slows conduction and normal automaticity favouring bradycardias, re-entrant VT and ventricular fibrillation (VF). Later, hypokalaemia favours re-entrant arrhythmias, polymorphic VT and atrial fibrillation (AF) due to triggered activity. However, the broader spectrum of dynamic metabolic changes present in DKA will also impact upon the risk of arrhythmia, potentially through complex interactions between all of the mechanisms outlined earlier. This has led to recommendations of continuous electrocardiographic monitoring during the acute phase of treatment, although the evidence of benefit for this as a routine approach is lacking [23].

9.1.2 Ion Disturbances

Electrolyte abnormalities are commonly associated with cardiovascular emergencies. These abnormalities are amongst the most common causes of cardiac arrhythmias, and they can (cause or) complicate resuscitation attempts and post-resuscitation care. If extreme, even isolated electrolyte deficiency or excess can cause life-threatening cardiac involvement in patients with structurally normal hearts. Clinical syndromes that create hypo- and hyper-concentrations of potassium, calcium and magnesium are associated with the most common and clinically important disturbances of cardiac rhythm related to electrolyte abnormality. Despite the frequency of sodium abnormalities, particularly hyponatraemia, its electrophysiological effects are rarely clinically significant. It is important to identify clinical situations in which electrolyte problems may be expected. In some cases therapy for life-threatening electrolyte disorders should be initiated even before laboratory results become available. Of all the electrolyte abnormalities, hyperkalaemia is the most rapidly fatal. A high degree of clinical suspicion and aggressive treatment of underlying electrolyte abnormalities can prevent these abnormalities from progressing to cardiac arrest [24]. Electrocardiographic findings associated with these disturbances can provide clues to the diagnosis as well as guide therapeutic interventions. Although discussed individually, it is important to remember that there is a dynamic physiologic interrelationship to electrolyte homeostasis and that aberration in one ‘compartment’ may have impact on another [25].

9.1.2.1 Potassium

Potassium (K^+) is the most abundant intracellular cation with only 2 % of the total body potassium in the extracellular space, and hypokalaemia is the most common electrolyte abnormality in clinical practice. Potassium plays an important role in maintaining the electrical potential across the cellular membrane as well as in depolarisation and repolarisation of the myocytes. The electrophysiological effects of potassium depend not only on its extracellular concentration but also on the direction (hypokalaemia *vs* hyperkalaemia) and rate of change. Although the mechanism of potassium regulation between compartments is complex, there are two main transport processes. An active transport process involves the Na^+/K^+ ATPase pump, insulin, beta-adrenergic agents and mineral corticosteroids and a passive transport that results from alterations in the pH and extracellular cellular fluid osmolality. Homeostatic serum potassium concentration is maintained by terminal nephron segments of the kidney. Factors that lead to alterations in serum potassium regulation include renal failure and medications such as non-steroidal anti-inflammatory agents, angiotensin-converting enzyme inhibitors, diuretics and digitalis [26, 27]. Alterations in serum potassium levels can have dramatic effects on cardiac cell conduction and may lead to EKG changes, and the electrocardiogram is a useful screening tool for gauging the severity of the serum potassium abnormality and the urgency of therapeutic intervention [28, 29].

Hyperkalaemia

Hyperkalaemia is a common disorder, although less common than hypokalaemia, occurring both in the outpatient setting and in up to 8 % of patients who have been admitted to hospital, mainly in the setting of compromised renal function [30–33]. Hyperkalaemia is defined as an excess concentration of potassium ions in the extracellular fluid compartment above the normal range of 3.5–5.0 mEq/L. Moderate (6–7 mEq/L) and severe (>7 mEq/L) hyperkalaemia is life-threatening and requires immediate therapy. Although mild hyperkalaemia is often asymptomatic and easily treated, acute and severe hyperkalaemia, if left untreated, can result in fatal cardiac arrhythmias [34–36].

The most common clinical presentation of severe hyperkalaemia involves patients with end-stage renal failure. Identification of potential causes of hyperkalaemia will contribute to rapid identification and treatment of patients who may be experiencing hyperkalaemic cardiac arrhythmias [37–39]. Potassium-sparing diuretics such as spironolactone, triamterene and amiloride are well-recognised causes of hyperkalaemia. Use of angiotensin-converting enzyme (ACE) inhibitors can also lead to elevation of serum potassium, particularly when combined with oral potassium supplements. Moreover, non-steroidal anti-inflammatory medicines can cause hyperkalaemia through direct effects on the kidney.

Physical symptoms of hyperkalaemia include weakness, ascending paralysis and respiratory failure.

Electrocardiographic manifestations of hyperkalaemia. The EKG manifestation of hyperkalaemia depends on serum K^+ level. Studies validate a good correlation with hyperkalaemia and EKG changes, but 50 % of patients with potassium levels greater than 6.5 mEq/L will not manifest any ECG changes.

The increased extracellular concentration of K^+ causes an influx of K^+ into the cells. There is an alteration of the transmembrane potential gradient, a decrease in

magnitude of the resting potential and a decrease in velocity of phase 0 of the action potential. The K^+ influx causes a shortening of the action potential and results in delayed conduction between the myocytes and ECG change, such as the *T wave tenting*, classically described as symmetrically narrow or peaked, though the deflection is often wide and of large amplitude [40]. In addition, inverted T waves associated with left ventricular hypertrophy can *pseudonormalise* (i.e., flip upright) [41]. These T wave changes occur as a result of the acceleration of the terminal phase of repolarisation, are most prominently seen in the precordial leads and are often seen when potassium levels exceed *5.5 mEq/L*. With higher levels of serum potassium, cardiac conduction between myocytes is suppressed. Reduction in atrial and ventricular transmembrane potential causes an inactivation of the sodium channel, decreasing the cellular action potential. Atrial tissue is more sensitive to these changes earlier, and, as a result, P wave flattening and PR interval prolongation may be seen before QRS interval prolongation. These changes generally occur when potassium levels exceed *6.5 mEq/L* [42]. As the serum level continues to rise to levels above *twice the normal value*, there is suppression of sinoatrial and atrioventricular conduction, resulting in sinoatrial and atrioventricular blocks, often with escape beats. Other blocks including intraventricular conduction delay, bundle branch block and fascicular blocks have been reported. The bundle branch blocks associated with hyperkalaemia are atypical in the sense that they involve the initial and terminal forces of the QRS complex. Shifts in the QRS axis indicate disproportionate conduction delays in the left bundle fascicles [43]. As hyperkalaemia progresses, depolarisation merges with repolarisation, expressed in the ECG with *QT shortening* and *apparent ST segment elevation* simulating acute injury [44]. Atypical bundle branch blocks (LBBB and RBBB), intraventricular conduction delays, VT, ventricular fibrillation and idioventricular rhythm are more commonly seen in cases of severe hyperkalaemia.

Hypokalaemia

Hypokalaemia, defined as a serum potassium level *<3.5 mEq/L*, is the most common electrolyte abnormality encountered in clinical practice. It is observed in over 20 % of hospitalised patients [45], because of the high prevalence of patients on medications that can result in hypokalaemia, as 10–40 % of patients on thiazide diuretics have low potassium levels [46]; moreover, almost 50 % of patients resuscitated from out-of-hospital VF [47].

The most common causes of low serum potassium are gastrointestinal loss (diarrhoea, laxatives), renal loss (hyperaldosteronism), severe hyperglycaemia, potassium depleting, diuretics, carbenicillin, sodium penicillin, amphotericin B, intracellular shift (alkalosis or a rise in pH) and malnutrition.

The major consequences of severe hypokalaemia result from its effects on nerves and muscles (including the heart). The myocardium is extremely sensitive to the effects of hypokalaemia, particularly if the patient is taking a digitalis derivative. Symptoms of mild hypokalaemia are weakness, fatigue, paralysis, respiratory difficulty, constipation, paralytic ileus and leg cramps; more severe hypokalaemia will alter cardiac tissue excitability and conduction.

Electrocardiographic manifestations of hypokalaemia. In cases of severe hypokalaemia, EKG changes can be a very useful, quick, inexpensive and widely

available diagnostic tool. The ECG manifestations of hypokalaemia [48] are due to its effects on repolarisation and conduction. As serum potassium levels decline, transmembrane potassium gradient decreases. The effect on cell membrane is elevation in resting membrane potential and prolongation of the action potential, particularly phase 3 repolarisation and refractory periods.

The *earliest ECG change* associated with hypokalaemia is a *decrease in the T wave amplitude*.

As potassium *levels further decline*, *ST segment depression and T wave inversions* can be seen and the *U wave becomes more prominent*. The *PR interval can be prolonged,* and there can be an *increase in the amplitude of the P wave*.

With *even lower serum potassium levels*, the classic ECG change associated with hypokalaemia is the development of *U waves*. The U wave is described as a positive deflection after the T wave that is often best seen in the mid-precordial leads, such as V2 and V3. These changes have been reported in almost 80 % of patients with potassium levels <2.7 mEq/L [49].

With *extreme hypokalaemia*, *giant U waves* may often mask the smaller preceding T waves or following P waves [50]. The characteristic reversal in the relative amplitude of the T and U waves is the most distinctive change in waveform morphology in hypokalaemia. The U wave in hypokalaemia is caused by prolongation of the recovery phase of the cardiac potential, the relative refractory period predisposing to re-entrant tachyarrhythmias.

Magnesium

Although magnesium is the fourth most common mineral and the second most abundant intracellular cation (after potassium) in the human body, the significance of magnesium disorders is controversial partly because of the frequent association of other electrolyte abnormalities. Magnesium is an important cofactor in several enzymatic reactions contributing to normal cardiovascular physiology.

The average adult contains about 24 g of magnesium, with only 1 % found in the extracellular space [51]. One third of extracellular magnesium is bound to serum albumin. Therefore, serum magnesium levels are not reliable predictors of total body magnesium stores. It plays an important role in stabilising excitable membranes and may influence the incidence of cardiac arrhythmias through a direct effect, by modulating the effects of potassium, or through its action as a calcium channel blocker. Magnesium deficiency is thought to interfere with the normal functioning of membrane ATPase and thus the pumping of sodium out of the cell and potassium into the cell [52].

Hypermagnesaemia. Hypermagnesaemia is defined as a serum magnesium concentration *>2.2 mEq/L* (normal: 1.3–2.2 mEq/L). Magnesium balance is influenced by many of the same regulatory systems that control calcium balance and by diseases and factors that control serum potassium. As a result, magnesium balance is closely tied to both calcium and potassium balance. The most common cause of hypermagnesaemia is renal failure. Hypermagnesaemia may also be iatrogenic (caused by overuse of magnesium) or caused by continued use of laxatives or antacids containing magnesium (an important cause in the elderly). Severe symptoms include neurological symptoms, areflexia, muscular weakness, paralysis, ataxia,

drowsiness, confusion, respiratory failure and, rarely, cardiac arrest. Gastrointestinal symptoms include nausea and vomiting. Moderate hypermagnesaemia can produce vasodilation, and severe hypermagnesaemia can produce hypotension. Extremely high serum magnesium levels may produce a depressed level of consciousness, bradycardia, hypoventilation and cardiorespiratory arrest [53].

Electrocardiographic manifestations of hypermagnesaemia. ECG changes of hypermagnesaemia include the following:

- Increased QRS duration
- Increased PR and QT intervals
- Variable decrease in P wave voltage
- Variable degree of T wave peaking
- Complete AV block and asystole

Hypomagnesaemia. Hypomagnesaemia, defined as a serum magnesium concentration <1.3 mEq/L, is far more common than hypermagnesaemia. It is caused by decreased intake, increased losses or altered intracellular-extracellular distribution. Hypomagnesaemia usually results from decreased absorption or increased loss, either from the kidneys or intestines (diarrhoea). Alterations in parathyroid hormone and certain medications (e.g. pentamidine, diuretics, alcohol) can also induce hypomagnesaemia. Lactating women are at higher risk of developing hypomagnesaemia.

Measurement of serum levels do not correlate well with clinical manifestations. Hypomagnesaemia is associated with far-reaching adversity across the physiologic spectrum, including central nervous system effects (seizures, mental status changes), cardiovascular effects (dysrhythmias, vasospasm), endocrine effects (hypokalaemia, hypocalcaemia) and muscle effect (bronchospasm, muscle weakness) [54].

Electrocardiographic manifestations of hypomagnesaemia. A number of ECG abnormalities occur with low magnesium levels, including the following:

- ST segment depression
- Prolonged QT and PR intervals
- T wave inversion
- Flattening or inversion of precordial P waves
- Widening of QRS
- Torsades de pointes, treatment-resistant VF (and other arrhythmias) and worsening of digitalis toxicity [55]

Calcium

Calcium (Ca^{++}) is the most abundant mineral in the body. It is essential for bone strength and neuromuscular function and plays a major role in myocardial contraction. The human body has a nearly inexhaustible reservoir of Ca^{++} stored as hydroxyapatite in skeletal bone. Of the total 1–2 kg of adult total body Ca^{++}, only 1 g of calcium is present in plasma. Ca^{++} is important in a myriad of regulatory mechanisms, skeletal muscle contraction and control of enzymatic reactions and is a key ion in myocyte electrical activity and myocardial contraction [56]. Although total

serum calcium $Ca^{++,}$ is directly related to serum albumin, the ionised Ca^{++} is inversely related to serum albumin. The lower the serum albumin, the higher the ionised calcium. Isolated abnormalities of extracellular Ca^{++} produce clinically significant electrophysiological effects only when they are extreme in either direction.

Hypercalcaemia. Hypercalcaemia is defined as a serum Ca^{++} concentration above the normal range of 8.5–10.5 mEq/L (or an elevation in ionised calcium above 4.2–4.8 mg/dL).

Hypercalcaemia is the cardinal feature of *hyperparathyroidism*. Primary hyperparathyroidism and malignancy account for >90 % of reported cases [57]. It is typically chronic, mild and well tolerated. Severe hypercalcaemia with serum levels *above 14 mg/dL* can be precipitated in these patients by dehydration from gastrointestinal losses, diuretic therapy or ingestion of large amounts of calcium salts.

Symptoms of hypercalcaemia usually develop when the total serum Ca^{++} concentration reaches or exceeds 12–15 mg/dL and can be relatively vague, including fatigue, lethargy, motor weakness, anorexia, nausea, constipation and abdominal pain. Effects on the kidney include diminished ability to concentrate urine; diuresis, leading to loss of sodium, potassium, magnesium and phosphate; and a vicious circle of calcium reabsorption that further worsens hypercalcaemia. At higher levels patients may exhibit hallucinations, disorientation, hypotonicity and coma. Cardiovascular symptoms of elevated Ca^{++} levels are variable. Myocardial contractility may initially increase until the Ca^{++} level reaches *15–20 mg/dL. Above* this level myocardial depression occurs. Automaticity is decreased, but arrhythmias occur because the refractory period is shortened, many patients develop hypokalaemia and digitalis toxicity is worsened [58].

Electrocardiographic manifestations of hypercalcaemia. The effect of hypercalcaemia on the electrocardiogram is the opposite of hypocalcaemia with the hallmark of abnormal shortening of the QTc interval. Cardiac conduction abnormalities may occur, with bradydysrhythmias being the most common [59]. ECG changes of hypercalcaemia include the following:

- Prolonged PR and QRS intervals
- Shortened QT interval (usually when Ca^{++} is >13 mg/dL)
- Increased QRS voltage with notching of QRS complex
- T wave flattening and widening
- AV block, progressing to complete heart block and to cardiac arrest when serum calcium is >15–20 mg/dL

Hypocalcaemia. Hypocalcaemia is defined as a serum calcium concentration below the normal range of 8.5–10.5 mg/dL (or an ionised calcium below the range of 4.2–4.8 mg/dL). Hypocalcaemia is classically seen with *functional parathyroid hormone deficiency*, either as absolute hormone deficiency (primary hypoparathyroidism), post-parathyroidectomy or related to a pseudo-hypoparathyroid syndrome. Other causes of hypocalcaemia include *vitamin D deficiency, congenital disorders of calcium metabolism, chronic renal failure, acute pancreatitis, rhabdomyolysis and sepsis*. Hypocalcaemia is commonly seen in critically ill patients, with a reported incidence of as high as 50 % [60]. Furthermore, hypocalcaemia is often

associated with hypomagnesaemia. Symptoms usually occur when ionised levels fall *below 2.5 mg/dL.* Neuromuscular irritability is the cardinal feature, with carpal-pedal spasm being the classical physical sign that may progress to tetany, laryngospasm or hyperreflexia and positive Chvostek and Trousseau signs.

Hypocalcaemia prolongs phase 2 of the action potential. *Prolongation of the QTc interval* is associated with early after-repolarisations and triggered dysrhythmias. Torsades de pointes potentially can be triggered by hypocalcaemia but is much less common than with hypokalaemia or hypomagnesaemia.

Severe symptoms and life-threatening dysrhythmias mandate immediate treatment; in addition, associated electrolyte abnormalities, including hypomagnesaemia, phosphate abnormalities and acidemia, may need to be corrected.

Electrocardiographic manifestations of hypocalcaemia. Hypocalcaemia results in *prolonged ST segment and QT interval,* a potential cause of torsades de pointes, although much less commonly than with hypokalaemia or hypomagnesaemia [61]. Whereas electrocardiographic conduction abnormalities are common, serious hypocalcaemia-induced dysrhythmias such as heart block and ventricular dysrhythmias are infrequent.

9.1.2.2 Management of Arrhythmic Complications

Encountering a seriously ill patient with complex metabolic derangement and cardiac, or multi-organ, compromise can be daunting. Firstly, the basic principles of resuscitation provide a means of optimising basic cardiorespiratory physiology whilst giving time to consider the more complex metabolic needs of the patient. Depending on the underlying presentation or disorder, an appropriate initial assessment of electrolytes, acid-base and fluid balance status should be made. The results of this, in addition to the likelihood of rapid changes due to treatment or the natural history of the disorder, should be used to guide timing of repeat assessments. Furthermore, a strategy to normalise the patient's biochemical profile should be planned and regularly updated; addressing the underlying disorder may be all that is required in some cases. Where profound derangement is present, or when treatment of the underlying disease is failing to achieve the goal of physiological normalisation, it may be necessary to provide additional treatment targeted at specific metabolic parameters. This may involve electrolyte correction, rehydration and reduction of other factors, such as hypoxia, which worsens ischaemia. *Manipulation of acid-base status is generally not recommended* [62, 63]; in DKA, or other forms of acidosis, expert consensus suggests sodium bicarbonate therapy results in net harm, perhaps by worsening intracellular acidosis. Bicarbonate is still administered on occasions, but in the most profoundly acidotic patients and often as an act of desperation.

Unfortunately, the evidence base to guide such decisions is limited and so relies upon expert consensus. A 12-lead ECG with continuous recording of the rhythm strip provides invaluable information, but should not be allowed to interfere with emergent treatment where required. If the patient is 'compensating' haemodynamically for their rhythm disturbance, then time is available to classify the rhythm disturbance and manage according to accepted guidance [64]. It is crucial to remember that any 'antiarrhythmic' pharmacotherapy commenced may have unintended pro-arrhythmic consequences, particularly in the setting of metabolic abnormalities

[65]. The principle of never prescribing antiarrhythmic 'cocktails' is even more pertinent in this scenario.

Treatment of Hyperkalaemia

A variety of treatment options are considered for the acute management of hyperkalaemia, including insulin, β2-adrenergic agonists (inhaled, nebulised and intravenous), bicarbonate, resins, fludrocortisone, aminophylline and dialysis.

The treatment of hyperkalaemia is determined by its severity and the patient's clinical condition. First you need to stop the sources of exogenous potassium administration (e.g. consider supplements and maintenance IV fluids) and evaluate drugs that can increase serum potassium (e.g. potassium-sparing diuretics, ACE inhibitors, non-steroidal anti-inflammatory agents). The level of potassium at which treatment should be initiated has not been established by evidence. Several treatment options have been proposed, particularly for shifting potassium into the cells, with differing onset and duration of action [66].

For *mild* elevation *(5.5–6 mEq/L)*, remove potassium from the body with the following:

1. Diuretics—furosemide 1 mg/kg IV slowly
2. Resins—Kayexalate 15–30 g in 50–100 mL of 20 % sorbitol either orally or by retention enema (50 g of Kayexalate)

For *moderate* elevation (*6–7 mEq/L),* shift potassium intracellularly with the following:

1. Sodium bicarbonate—50 mEq IV over 5 min (sodium bicarbonate alone is less effective than glucose plus insulin or nebulised albuterol, particularly for the treatment of patients with renal failure; it is best used in conjunction with these medications) [67, 68]
2. Glucose plus insulin—mix 50 g glucose and 10 U regular insulin and give IV over 15–30 min
3. Nebulised albuterol 10–20 mg nebulised over 15 min

For *severe* elevation *(>7 mEq/L* with toxic ECG changes), you need to shift potassium into the cells and eliminate potassium from the body. Therapies that shift potassium will act rapidly, but they are temporary; if the serum potassium rebounds, you may need to repeat those therapies. In order of priority, treatment includes the following:

- *Shift potassium into cells:*
  1. Calcium chloride (10 %): 500–1000 mg (5–10 mL) IV over 2–5 min to reduce the effects of potassium at the myocardial cell membrane (lowers risk of VF)
  2. Sodium bicarbonate: 50 mEq IV over 5 min (may be less effective for patients with end-stage renal disease)
  3. Glucose plus insulin: mix 25 g (50 mL of D50) glucose and 10 U regular insulin and give IV over 15–30 min

4. Nebulised albuterol: 10–20 mg nebulised over 15 min

- *Promote potassium excretion:*
  5. Diuresis (furosemide 40–80 mg IV)
  6. Kayexalate enema: 15–50 g plus sorbitol PO or per rectum
  7. Dialysis

Treatment of Hypokalaemia

Treatment of hypokalaemia focuses on parenteral and oral potassium supplementation as well as identification and treatment of the source of the electrolyte abnormality. IV administration of potassium is indicated when arrhythmias are present or hypokalaemia is *severe* (*<2.5 mEq/L).* Gradual correction of hypokalaemia is preferable to rapid correction unless the patient is clinically unstable. Acute potassium administration may be empirical in emergent conditions. When indicated, maximum IV K^+ replacement should be 10–20 mEq/h with continuous ECG monitoring during infusion. Central or peripheral IV sites may be used. A more concentrated solution of potassium may be infused if a central line is used, but the catheter tip should not extend into the right atrium.

If cardiac arrest from hypokalaemia is imminent (i.e. malignant ventricular arrhythmias), rapid replacement of potassium is required. Give an initial infusion of 10 mEq IV over 5 min; repeat once if needed. In the patient's chart, document that rapid infusion is intentional in response to life-threatening hypokalaemia. Once the patient is stabilised, reduce the infusion to continue potassium replacement more gradually. Estimates of total body deficit of potassium range from 150 to 400 mEq for every 1 mEq decrease in serum potassium. The lower range of the estimate would be appropriate for an elderly woman with low muscle mass and the higher range for a young, muscular man.

Treatment of Hypermagnesaemia

Hypermagnesaemia is treated with administration of *calcium*, which removes magnesium from serum. Cardiorespiratory support may be needed until magnesium levels are reduced. It is important to eliminate sources of ongoing magnesium intake. Administration of 10 % solution of calcium chloride (5–10 mL [500–1000 mg] IV) will often correct lethal arrhythmias. This dose may be repeated if needed. Dialysis is the treatment of choice for hypermagnesaemia. Until that can be done, if renal function is normal and cardiovascular function adequate, IV saline dieresis (IV normal saline and furosemide) can be used to increase renal excretion of magnesium until dialysis can be performed. However, this diuresis can also increase calcium excretion; the development of hypocalcaemia will deteriorate signs and symptoms of hypermagnesaemia.

Treatment of Hypomagnesaemia

Treatment of hypomagnesaemia depends on its severity and the patient's clinical status. For severe or symptomatic hypomagnesaemia, administer 1–2 g IV MgSO4 over 5–60 min. For torsades de pointes with cardiac arrest, give 1–2 g of MgSO4 IV pushed over 5–20 min. If torsades de pointes is intermittent and not associated with

arrest, administer the magnesium over 5–60 min IV. If seizures are present, administer 2 g IV MgSO4 over 10 min. Calcium gluconate administration (1 g) is usually appropriate because most patients with hypomagnesaemia are also hypocalcaemic [69]. Replace magnesium cautiously in patients with renal insufficiency because there is a real danger of causing life-threatening hypermagnesaemia.

Treatment of Hypercalcaemia

If hypercalcaemia is due to malignancy, careful consideration of the patient's prognosis and wishes is needed. Therapy for hypercalcaemia is generally instituted based on clinical signs more than absolute serum levels, although empiric therapy is often started at levels of 12 mg/dL even in the asymptomatic patient. In patients with hypoalbuminaemia, measured serum calcium levels may mask significant elevations in free ionised extracellular calcium. Treatment is instituted at a level *>15 mg/dL* regardless of symptoms. Immediate therapy is directed at promoting calcium excretion in the urine. The mainstays of treatment are intravenous volume repletion and bisphosphonate agents that inhibit osteoclastic bone resorption. This is accomplished in patients with adequate cardiovascular and renal function with infusion of 0.9 % saline at 300–500 mL/h until any fluid deficit is replaced and diuresis occurs (urine output 200–300 mL/h). Once adequate rehydration has occurred, the saline infusion rate is reduced to 100–200 mL/h. This diuresis will further reduce serum potassium and magnesium concentrations, which may increase the arrhythmogenic potential of the hypercalcaemia. Thus, potassium and magnesium concentrations should be closely monitored and maintained. Hemodialysis is the treatment of choice to rapidly decrease serum calcium in patients with heart failure or renal insufficiency [70]. The use of loop diuretics (furosemide 1 mg/kg IV) to promote calciuresis is often recommended but is problematic in the hypovolemic patient.

Treatment of Hypocalcaemia

Calcium exchange is dependent on concentrations of potassium and magnesium, so treatment depends on replacing all 3 electrolytes.

Treatment of hypocalcaemia requires administration of calcium. Treat acute, symptomatic hypocalcaemia with 10 % calcium gluconate, 90–180 mg of elemental calcium IV over 10 min. Follow this with an IV drip of 540–720 mg of elemental calcium in 500–1000 mL D5W at 0.5–2.0 mg/kg per hour (10–15 mg/kg). Measure serum calcium every 4–6 h. Aim to maintain the total serum calcium concentration between 7 and 9 mg/dL.

Vitamin D and oral calcium supplementation can be administered for chronic hypocalcaemia.

9.1.2.3 When Should Electrolyte Level Be Rechecked?

The studies did not address the frequency and duration of monitoring of patients with ion disturbances; therefore, recommendations regarding ongoing assessment are based on opinion. In the acute management of electrolyte deficiency/excess, the frequency of monitoring depends on the electrolyte level as well as underlying comorbidities. After initial interventions, electrolyte level should be rechecked

within *1–2 h*, to ensure effectiveness of the intervention, following which the frequency of monitoring could be reduced. Subsequent monitoring depends on the electrolyte abnormalities and the potential reversibility of the underlying cause.

We believe the management and treatment of metabolic disorders and ion disturbances that can lead to severe complications, such as life-threatening arrhythmias, should be common knowledge for both the physician working in ED and for the cardiologist. Here, however, we emphasise some peculiarities related to the disorders described that can be particularly useful.

9.2 What Physicians Working in ED Should Know

Profound diarrhoea has the potential to 'waste' large quantities of essential electrolytes, in addition to water and bicarbonate. Without appropriate and timely management, it is possible to develop a highly proarrhythmic situation with metabolic acidosis, increased adrenergic activity, hypokalaemia, hypocalcaemia, hypomagnesaemia and so on. Vomiting can equally result in many of these abnormalities and so in combination with diarrhoea, or when added to other disease states such as DKA, can cause a significant combined cardiac insult. Appropriate identification of these metabolic and fluid balance abnormalities is imperative in order to prevent complications. Thus, regular assessment of hydration, acid-base and electrolyte status is crucial.

Potassium

- Evaluation of serum potassium must consider the effects of changes in serum pH. When serum pH falls, serum potassium rises because potassium shifts from the cellular to the vascular space. When serum pH rises, serum potassium falls because potassium shifts intracellularly. In general, serum K decreases by approximately 0.3 mEq/L for every 0.1 U increase in pH above normal. Effects of pH changes on serum potassium should be anticipated during therapy for hyperkalaemia or hypokalaemia and during any therapy that may cause changes in serum pH (e.g. treatment of diabetic ketoacidosis). Correction of an alkalotic pH will produce an increase in serum potassium even without administration of additional potassium. If serum potassium is 'normal' in the face of acidosis, a fall in serum potassium should be anticipated when the acidosis is corrected, and potassium administration should be planned.
- Hypokalaemia exacerbates digitalis toxicity. Thus, hypokalaemia should be avoided or treated promptly in patients receiving digitalis derivatives.
- The ECG correlates of hypokalaemia can be confused with myocardial ischemia. In addition, it can be difficult to differentiate a U wave from a peaked T wave that is present in hyperkalaemia.
- The use of a beta-agonist appeared to be effective in rapid reduction of hyperkalaemia: salbutamol is effective when given intravenously, in a nebulised form and

as a multi-dose inhaler. IV insulin and glucose is effective and has a rapid onset of action. The evidence for the use of bicarbonate in hyperkalaemia is equivocal, and it is not recommended as monotherapy. If used in conjunction with other treatments, the possible effects on pH and extracellular volume must be carefully considered in the assessment of the risk-benefit ratio for an individual patient.

Combining insulin-glucose with salbutamol (albuterol) probably leads to greater reductions in serum potassium than either alone. In animal and human studies, IV calcium stabilises membranes and reduces the arrhythmic threshold. Though no randomised evidence exists to support its use, it is recommended that calcium chloride be given in the presence of ECG changes or arrhythmia and repeated as needed.

Magnesium

- Abnormalities in magnesium, potassium and pH must be corrected simultaneously.
- Untreated hypomagnesaemia will make hypocalcaemia refractory to therapy.

Calcium

- The concentration of ionised calcium is pH dependent. Alkalosis increases the binding of calcium to albumin and thus reduces ionised calcium. Conversely, the development of acidosis will produce an increase in the ionised calcium level.
- In the presence of hypoalbuminaemia, although total calcium level may be low, the ionised calcium level may be normal.
- Calcium antagonises the effects of both potassium and magnesium at the cell membrane. Therefore, it is extremely useful for treating the effects of hyperkalaemia and hypermagnesaemia.
- Calcium may also be lowered by drugs that reduce bone resorption (e.g. calcitonin, glucocorticoids).

9.3 What Cardiologists Should Know

A diverse array of metabolic disorders is known to precipitate arrhythmia, though their individual proarrhythmic effects can be simplified by considering broad unifying pathophysiological mechanisms.

Metabolic disturbance mediates re-entry because regions of physiologically and pathological conduction (accelerated myocyte repolarisation or reduced myocardial conduction velocity) are both present, although anatomical substrates can interact and so produce complex disturbances of myocardial excitation and conduction.

Acidosis is proarrhythmic through promoting re-entry and triggered activity [71]. It is notable that re-entry on a much larger scale is the cause of certain supraventricular tachycardia, for example, atrioventricular re-entry tachycardia in the Wolff-Parkinson-White syndrome. Metabolic derangement can alter the conduction

properties of the abnormal anatomic pathways in these disorders, promoting re-entry and/or augmenting the maximum heart rate supported by the circuit. More complex re-entry is also a contributory factor to other arrhythmias witnessed in critically ill patients, such as atrial fibrillation and VT. After-depolarisation, or triggered activity, is the other major mechanism through which electrolyte disturbance encourages arrhythmias.

This process may be repeated resulting in tachycardia, and it is through this mechanism in which polymorphic VT, or torsades de pointes, develops. Delayed after-depolarisations are less relevant to proarrhythmia in the context of pure metabolic disarray, though in certain circumstances remain relevant. The classical example is arrhythmia due to digoxin toxicity which is aggravated by hypokalaemia and hypercalcaemia. Catecholamine excess and myocardial ischaemia are also important, and relatively common, precipitants in patients with metabolic disarray.

Potassium

- Interestingly, bypass tracts are more sensitive to delayed conduction from potassium elevation, which can result in the normalisation of the ECG and loss of the delta wave in patients with Wolff-Parkinson-White syndrome.
- With extremely high serum potassium levels, a markedly prolonged and wide QRS complex can fuse with the T wave, producing a slurred, 'sine-wave' appearance on the ECG. This finding is a pre-terminal event unless treatment is initiated immediately. The fatal event is either asystole, as there is complete block in ventricular conduction, or ventricular fibrillation.
- Hyperkalaemia can induce a Brugada-like pattern in the ECG [72]. This usually occurs in critically ill patient with significant hyperkalaemia (serum potassium >7.0 mmol/L) and is associated with pseudo-right bundle branch block and persistent coved ST segment elevation in at least two precordial leads. Prompt recognition of this ECG entity will enable clinicians to identify severe hyperkalaemia, which may result in high mortality.
- The effect of hyperkalaemia on QRS morphology of ventricular paced beats has also been studied [73]: hyperkalaemia is the most common electrolyte abnormality to cause loss of capture. In patients with pacemakers, hyperkalaemia causes two important clinical abnormalities: [1] widening of the paced QRS complex (and paced P wave) on the basis of delayed myocardial conduction; when the K level exceeds 7 mEq/L, the intraventricular conduction velocity is usually decreased and the paced QRS complex widens, [2] and increased atrial and ventricular pacing thresholds with or without increased latency.
- In patients with cardiac resynchronisation therapy, the hyperkalaemia can result in a loss of capture and/or sensing failure of even only one of the two ventricular electrodes, leading to a biventricular activation failure.
- Several cardiac and non-cardiac drugs are known to suppress the HERG K+ channel and hence the IK and, especially in the presence of hypokalaemia, can result in prolonged action potential duration and QT interval, early after-depolarisations and torsades de pointes.

- Hyperkalaemia is a common disorder that can be fatal if unrecognised or untreated. Insulin administered intravenously has the fastest onset of action and is very effective in reducing serum potassium. β2-Adrenergic agonists are as effective as insulin for lowering serum potassium and have a longer duration of action. The combination of β2-agonists and insulin is more effective than either treatment alone. The use of intravenously administered sodium bicarbonate for the management of acute hyperkalaemia is supported only by studies with weak and equivocal results [74] .
- Changes in pH inversely affect serum potassium. Acidosis (low pH) leads to an extracellular shift of potassium, thus raising serum potassium. Conversely, high pH (alkalosis) shifts potassium back into the cell, lowering serum potassium. Metabolic alterations such as alkalosis, hypernatraemia or hypercalcaemia can antagonise the transmembrane effects of hyperkalaemia and result in the blunting of the ECG changes associated with elevated potassium levels.
- Hyperkalaemia inhibits glycoside binding to (Na+, K+) ATPase, decreases the inotropic effect of digitalis and suppresses digitalis-induced ectopic rhythms. Alternatively, hypokalaemia increases glycoside binding to (Na+, K+) ATPase, decreases the rate of digoxin elimination and potentiates the toxic effects of digitalis.

Magnesium

- Low potassium in combination with low magnesium is a risk factor for severe arrhythmias.
- It is well known that both supraventricular and ventricular dysrhythmias can be potentiated if not directly caused by hypomagnesaemia.
- Magnesium has been shown to be efficacious in the management of atrial tachydysrhythmias although there is no correlation between rhythm conversion and plasma concentration.
- Magnesium sulphate is considered first-line therapy by the American Heart Association ACLS Guidelines for torsades de pointes.

Calcium

- The combination of hyperkalaemia and hypocalcaemia has a cumulative effect on the atrioventricular and intraventricular conduction delay and facilitates the development of VF. Hypercalcaemia, through its membrane-stabilising effect, counteracts the effects of hyperkalaemia on AV and intraventricular conduction and averts the development of VF.
- Half of all calcium in the extracellular fluid is bound to albumin; the other half is in the biologically active, ionised form. The ionised form is most active. The serum ionised calcium level must be evaluated in light of serum pH and serum albumin.
- Hypocalcaemia can exacerbate digitalis toxicity Table 9.1.

Table 9.1 Ion disturbances: etiology, diagnosis and treatment

Ione	Disorders	Aetiology	Signs	EKG changes	Treatment
K+	Hyperkalaemia mild (5–6 mEq/L)	Drugs End-stage renal disease Rhabdomyolysis Metabolic acidosis Pseudohyperkalaemia Hemolysis Tumour lysis syndrome Diet Hypoaldosteronism (Addison disease, hyporeninemia) Type 4 renal tubular acidosis Hyperkalaemic periodic paralysis	Weakness Ascending paralysis Respiratory failure	Flattened P waves Prolonged PR interval Widened QRS complex Deepened S waves Merging of S and T waves Sine-wave pattern Idioventricular rhythm Asystolic cardiac arrest	1. Furosemide 1 mg/kg IV slowly 2. Kayexalate 15–30 g in 50–100 mL of 20 % sorbitol
	Hyperkalaemia moderate (6–7 mEq/L)				1. Sodium bicarbonate—50 mEq IV over 5 min 2. Glucose plus insulin—mix 50 g glucose and 10 U regular insulin and give IV over 15–30 min 3. Nebulised albuterol 10–20 mg nebulised over 15 min
	Hyperkalaemia severe (>7 mEq/L)				1. Calcium chloride (10 %): 500–1000 mg (5–10 mL) IV over 2–5 min 2. Sodium bicarbonate: 50 mEq IV over 5 min 3. Glucose plus insulin: mix 25 g (50 mL of D50) glucose and 10 U regular insulin and give IV over 15–30 min 4. Nebulised albuterol: 10–20 mg nebulised over 15 min 5. Furosemide 40–80 mg IV) 6. Kayexalate enema: 15–50 g plus sorbitol PO or per rectum 7. Dialysis
	Hypokalaemia mild (3.5–2.5 mEq/L)	Diarrhoea, Laxatives Hyperaldosteronism Hyperglycaemia Potassium depleting Diuretics Carbenicillin, sodium penicillin, amphotericin B Intracellular shift (alkalosis or a rise in pH) Malnutrition	Weakness Fatigue Paralysis Respiratory difficulty Constipation Paralytic ileus Leg cramps	U waves T wave flattening Ventricular arrhythmias –Pulseless electrical activity (PEA) Asystole	Gradual correction of hypokalaemia is preferable to rapid correction
	Hypokalaemia severe (<2.5 mEq/L)				1. Maximum IV K replacement should be 10 to 20 mEq/h 2. Infusion of 10 mEq IV over 5 min (if cardiac arrest)

(continued)

Table 9.1 (continued)

Ione	Disorders	Aetiology	Signs	EKG changes	Treatment
Mg+	*Hypermagnesaemia* (>2.2 mEq/L)	Renal failure Overuse of mg+ Use of laxatives/antacids containing mg+	Areflexia Muscular weakness Paralysis Ataxia Drowsiness Confusion Respiratory failure Nausea Vomiting Hypotension Hypoventilation	Increased PR and QT Increased QRS Decrease P wave voltage Degree of T wave peaking Complete AV block Asystole	1. 10 % solution of calcium chloride (5–10 mL [500–1000 mg] IV) 2. Dialysis 3. Furosemide [1 mEq/kg]
	Hypomagnesaemia (<1.3 mEq/L)	Bowel resection Pancreatitis Diarrhoea Renal disease Diuretics Pentamidine Gentamicin Digoxin Alcohol Hypothermia Hypercalcaemia Diabetic ketoacidosis Hyperthyroidism Hypothyroidism Phosphate deficiency Burns Sepsis	Seizures Mental status changes Dysrhythmias Vasospasm Hypokalaemia Hypocalcaemia Bronchospasm Muscle weakness	Prolonged QT and PR intervals ST segment depression T wave inversion Flattening P waves Widening of QRS Torsades de pointes VF	1. 1–2 g IV MgSO4 over 5–60 min 2. For torsades de pointes 1 to 2 g of MgSO4 IV over 5–20 min

Ca++	*Hypercalcaemia* > 10.5 mEq/L (or > 4.8 mg/dL ionised calcium)	Hyperparathyroidism Malignancy	Fatigue Lethargy Motor weakness Anorexia Nausea Constipation Abdominal pain Diuresis Hallucinations Disorientation Hypotonicity	Shortened QT interval Prolonged PR and QRS intervals Increased QRS voltage T wave flattening and widening Notching of QRS AV block	1. 0.9 % saline at 300 to 500 mL/h 2. Hemodialysis 3. Chelating agents 4. Furosemide 5. Calcitonin, glucocorticoids
	Hypocalcaemia < 8.5 mg/dL (or < 4.2 mg/dL ionised calcium)	Toxic shock Abnormalities in serum magnesium Tumour lysis syndrome	Neuromuscular irritability Carpal-pedal spasm –Tetany Laryngospasm Paraesthesias of the extremities and face Muscle cramps Hyperreflexia Positive Chvostek and Trousseau signs	QT interval prolongation Terminal T wave inversion Heart blocks Ventricular fibrillation	1. 10 % calcium gluconate, 90–180 mg of calcium IV over 10 min 2. IV drip of 540–720 mg of elemental calcium in 500–1000 mL D_5W at 0.5–2.0 mg/kg per hour (10–15 mg/kg)

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Cardiac Arrhythmias in Drug Abuse and Intoxication

10

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10.1 Focusing on the Issue

Cardiac arrhythmias are common in acute intoxication, although epidemiological data are often restricted to specific substances. A 10 % incidence of cardiac arrhythmias during acute intoxication has been reported by a referral poison center in Germany that analyzed the data of 91,285 patients referred between 1995 and 2003 using the inquiries of physicians and paramedics [1].

A large amount of substances and their association can lead to worsening of preclinical or active cardiovascular diseases and, on occasion, to ex-novo cardiovascular diseases or arrhythmic manifestations. Negative cardiovascular effects are mainly caused by the pharmacokinetics of substances, in particular if drugs are administered or abused in combination, or in cases of concomitant metabolic, renal, or liver diseases; moreover, negative effects can be the result of pharmacodynamics, as in the presence of an interaction between a not otherwise toxic substance and an altered morphofunctional cardiac substrate (e.g., long QT or Brugada syndrome).

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_10

10.2 What Physicians Working in Emergency Departments Should Know

The management of patients with a certain diagnosis or at high risk for "poisoning" or "drug abuse" should be oriented toward the acute handling of symptoms of intoxication and support of hemodynamics (e.g., intubation and respiratory support, electrolyte substitution and hydration, and temporary pacing in the case of bradycardia).

Physicians working in the emergency department (ED) should be aware that people using or abusing illicit drugs are often prone to mix different substances, alcohol being the most abused and coabused substance. Cannabis is the most frequently used illicit drug, followed by cocaine, ecstasy, and amphetamines [2]. Physicians in the ED should be familiar with the telephone number of the local poison control center as well as internal protocols and resources.

When deciding the therapeutic strategy, the medical history of the patient plays a pivotal role, and it is important to follow a systematic approach, starting with the following:

- Habitual medications
- Coexisting diseases
- Which substance or mix was taken, and when
- If a mix of substances was taken, which was the sequela
- Way of substance abuse: pills, sublingual, intravenous, inhalation

It is then important to initiate a treatment as soon as possible in order to achieve a stabilization:

- Cardiopulmonary support including fluids, direct current shock if hemodynamically unstable arrhythmia, or temporary pacing if bradycardia
- Gastrointestinal decontamination of an ingested drug
- Administration of an antidote if available
- Correction of acid–base and electrolyte alterations

10.3 What Physicians Working in the ED and Cardiologists Should Know

In order to offer a pragmatic approach to the management of patients presenting with arrhythmias associated with drug abuse and intoxication, this section focuses firstly on recreational drugs and secondly on the most common prescription drugs.

10.3.1 Recreational Drugs

The use and abuse of recreational drugs is increasing, and every year new "designer drugs" appear on the recreational drug market, such as the novel class of cathinone

derivatives, often proposed as "legal highs" by categorizing them as odorizers, stain removers, potpourri, or most recently the notorious "bath salts" [3].

An updated list of many recreational drugs can be easily found by consulting the web site of the World Anti-Doping Agency [4] (WADA list 2015, updated yearly; www.wada-ama.org). This list comprises all those substances abused by the general population and in particular by athletes with ergogenic scope during their lifetime. Many of these drugs can induce cardiovascular effects, particularly arrhythmias, during short-, mid-, and long-term use [5–8].

10.3.1.1 Stimulants

The heterogeneous group of stimulants includes many classes of drugs, widely used to obtain a performance enhancement, a raise in aggressiveness and competitiveness levels, and a reduction of fatigue perception, or simply for "recreational" purposes.

Among stimulants, amphetamines also are widely used for weight-loss regimens [9–11]. Ephedrine and other similar alkaloids are also contained in the herbal product ephedra, marketed as dietary supplement [12, 13].

The amphetamines are the chemical basis of many designer drugs usually sold as "club drugs": methylenedioxymethamphetamine (MDA) is well known as the "love pill," and 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) is commonly available under confounding names such as "clarity" or "lover's speed," but many chemical variants are commonly abused. The tablets can contain between 50 and 200 mg, and the toxic effects can be manifest starting from a dose of 50 mg [14, 15].

This class of stimulants (amphetamine or ephedrine derivatives) acts through the release of noradrenaline, dopamine, and serotonin. The symptoms of patients presenting in the ED can include sympathomimetic effects such as arterial hypertension, hyperthermia, mydriasis, dry mouth, and tachycardia. Commonly the patients also present with hyperactivity reactions such as logorrhea, restless syndrome, anxiety, tremors, myoclonus and coma.

Regarding the arrhythmias, patients present commonly with sinus or atrial tachycardia, although atrial flutter, atrial fibrillation, supraventricular reentrant tachycardia, and ventricular tachycardia have also been reported. Re-entry arrhythmias may be due to adrenergic activity during myocardial refractory periods [16, 17]. These patients should be treated with intravenous saline volumes, electrolyte substitution, and a β-blocker can be used through a slow intravenous injection for the management of tachycardia and hypertension.

Several cases of cardiac arrest and sudden death in users were reported to be associated with coronary artery disease, cardiomyopathy and myocarditis, and others with direct myocyte toxicity [14, 16]. In patients with Wolff-Parkinson-White (WPW) syndrome, stimulants can induce rapid atrial fibrillation and ventricular fibrillation [18], increasing atrial and ventricular excitability and shortening accessory pathway refractoriness.

Particular attention should be paid to young patients intoxicated with Ecstasy after physically extreme activity (e.g., "rave parties" or athletes after competitions) presenting with a "serotonin syndrome": the combination of central effects (i.e., hyperthermia) and severe dehydration and electrolyte disorders can lead to

malignant arrhythmias whose management must combine arrhythmia therapy (cardioversion or β-blocker) with cooling, rehydration, and electrolyte replacement.

Physicians in the ED should also keep in mind that patients with amphetamine intoxication commonly present with associated rhabdomyolysis.

In recent years patients taking a new class of recreational designer drugs based on cathinones mixed with amphetamine, so-called bath salts, have been admitted to the ED. 3,4-Methylenedioxypyrovalerone (MDPV), 4-methylmethcathinone (4-MMC or mephedrone), and 4-methylephedrone are some examples. In the USA, MDPV seems to be the primary active ingredient in the majority of bath salts; on the other hand, in the European Union mephedrone is more common [19].

Cathinone is a β-ketone amphetamine analogue naturally present in the leaves of the plant *Catha edulis* (also known as *Khat*) [3]. Cathinone acts as a mild stimulant by inhibiting monoamine transporters for dopamine, serotonin, and norepinephrine within the central nervous system, and is internationally regulated.

Patients who have taken MDPV may present in the ED with sinus tachycardia and other arrhythmias including ventricular tachycardia [3]. Many different symptoms have been reported, particularly related to a dopaminergic mechanism that leads to serotonin syndrome. It is important to be aware of the prolonged psychogenic effects, which may last for up to 1 week [20]. Deaths after the use of bath salts have been reported [3].

Among cathinone derivatives, only bupropion is legally approved for medical purposes as an antidepressant medication.

10.3.1.2 Cocaine

Cocaine is an alkaloid derived from a plant, *Erythroxylum coca*. It can be inhaled or smoked, only rarely being injected [21, 22]. On the illicit drugs market it can be found as a salt (hydrochloride or sulfate) or a free Base ("crack"). Indeed, this alkaloid may cause different kinds of focal or re-entry supraventricular and ventricular arrhythmias, such as ectopic beats, atrial fibrillation, atrioventricular node re-entry tachycardia, WPW arrhythmias, and nonsustained and sustained ventricular tachycardia and ventricular fibrillation. Arrhythmias are frequently associated with physical effort, which can induce a sympathomimetic effect synergic with cocaine addiction [23].

Regarding electrocardiographic (ECG) alterations and arrhythmias, experimental animal studies on the effects of cocaine showed prolongation of PR, QT, and QTc intervals, a wider QRS, supraventricular and ventricular ectopic activity, ventricular tachycardia, and ventricular fibrillation [21, 24–26].

Cocaine can lead to cardiac side effects through multiple arrhythmogenic mechanisms:

- Local anesthetic effect with block of both sodium and potassium channels
- Sympathomimetic effect with α- and β-receptor stimulation, and consequent increase in heart rate and atrial and ventricular excitability
- Intracellular calcium overload (afterdepolarization arrhythmias)
- Arrhythmias due to ischemia/reperfusion mechanisms
- Increase in heart rate through vagolytic effect
- Inhibitor of generations and conduction of the action potential, with prolongation of QRS caused by sodium channel-blocking effects [27].

Arrhythmias may be also "secondary" to systemic effects of the drug such as hyperthermia, acidosis, stroke or subarachnoid haemorrhage or in Crack-smokers also to pneumotorax.The ability of cocaine to cause myocardial infarction, frequently with severe complications, is well known [22, 23, 28, 29], with the risk in the first hour after use increasing by up to 24-fold [30].

Myocardial infarction as well as various arrhythmias can occur even after the first administration of cocaine, regardless of dose.

In the ED the patients who have used/abused cocaine may present with many different types of arrhythmias whether in the setting of ischemic/reperfusion events or not. "Chaotic atrial arrhythmia," similar to that observed in severe respiratory insufficiency or acute myocarditis, is considered a typical toxic cocaine-related arrhythmia (Fig. 10.1). Moreover, supraventricular tachycardia, atrial fibrillation, ventricular tachycardia/fibrillation, torsade des pointes due to secondary long QT syndrome frequently related to hERG potassium channel blockade [25, 31], asystole (sporadic reports of asystole treated with emergent cardiac pacing), and cardiac arrest [18] have also been reported. Cocaine-induced wide complex ventricular tachycardia may be considered a typical toxic arrhythmia, frequently caused by high doses of the drug [22], and the treatment is based on administration of sodium bicarbonate [32].

Cocaine can also induce ECG modifications such as a V1–V3 ST elevation (coved type) typical for Brugada syndrome, due to a selective block of myocardial sodium channels in subjects with latent arrhythmic disease [33].

Moreover, patients abusing cocaine also commonly mix it with different substances such as hallucinogens, strychnine ("dead hit"), heroin ("speedball"), and alcohol ("liquid lady"): in case of associated intake of alcohol and cocaine the risk of sudden death has been found to be higher probably because of the additive effects of a metabolite, coca-ethylene, which can block the dopamine reuptake, enhancing the toxic effect of the cocaine used alone [34].

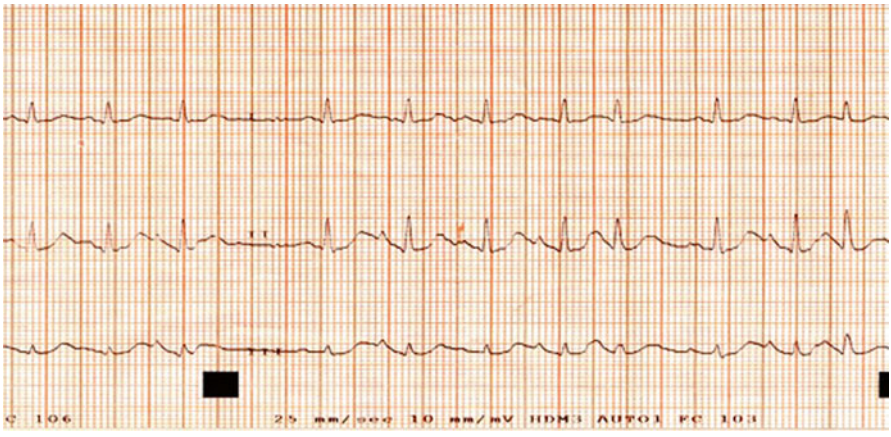

Fig. 10.1 Amateur football player, 17 years old, suspected cocaine intoxication and "chaotic atrial arrhythmia," i.e., sinus rhythm and polymorphic supraventricular ectopic beats

10.3.1.3 Cannabinoids

Many patients can present to the ED after consumption of cannabinoids, including marijuana and hashish, with different arrhythmic disorders: exercise-related sinus tachycardia, atrial fibrillation, paroxysmal supraventricular tachycardia, supraventricular and/or ventricular ectopic beats, and severe ventricular arrhythmias [35, 36], which can be mediated by catecholamines (Fig. 10.2).

The onset of arrhythmias is usually 30 or 60 min after smoking, and the arrhythmic disorders are related to the dose. At low and moderate doses there is an increase in sympathetic activity and a decrease in parasympathetic activity, and patients commonly present with sinus tachycardia, ectopic beats, or paroxysmal supraventricular tachycardia. At higher doses, there is a decrease in sympathetic activity and an increase in parasympathetic activity that can favour atrial fibrillation [37].

10.3.2 Prescription Drugs

Different common prescription drugs can induce arrhythmic complications in cases of involuntary abuse, suicidality, or in case of multiple interactions. Rather than providing an exhaustive list of all possible arrhythmias related to the use or abuse of prescription drugs, this section aims to help physicians working in the ED to get

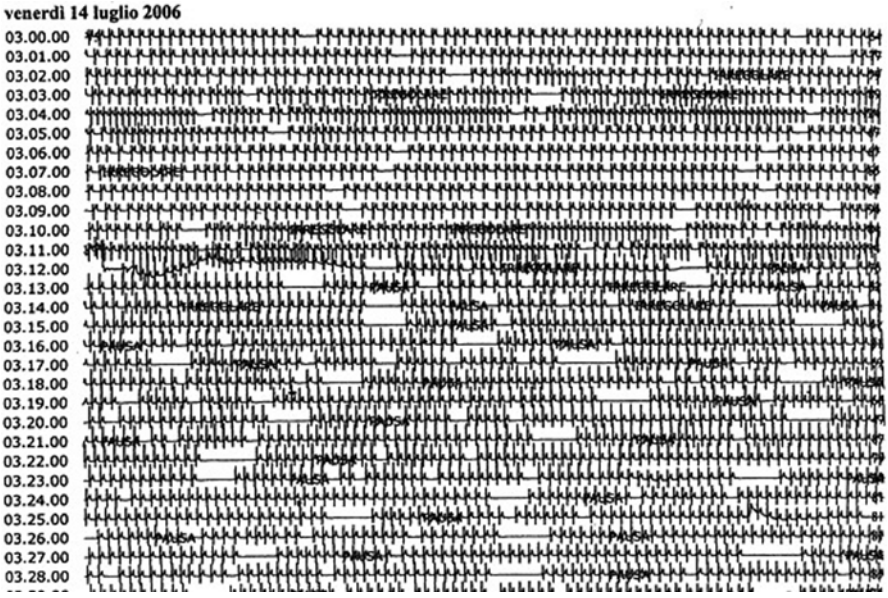

Fig. 10.2 ECG-Holter monitoring of a young male athlete (soccer player), 22 years old. Chronic use of cannabinoids and sporadic use of cocaine. This ECG-Holter tracing taken overnight shows a sick sinus syndrome with sinus arrest, sinus tachycardia, and nonsustained atrial tachycardia

used to a comprehensive attitude on managing not only the arrhythmias but also the whole pathologic affections.

Here, the most common prescription drugs whose abuse or misuse can present with arrhythmias are reviewed.

10.3.2.1 β-Blockers

Abuse of β-blockers can induce bradyarrhythmias with atrio-ventricular blocks of various degrees, sinus bradycardia, junctional and ventricular escape rhythms, bradycardia-dependent ventricular ectopic beats, and asystole, especially in patients with underlying structural and electrical disorders. Among the β-blockers, sotalol is associated with a high rate of cardiac dysrhythmias [1] and related QT prolongation. Other symptoms can be associated as hypotension, syncope, muscular contractions, mydriasis, bronchial obstruction and often hypoglycaemia especially in children.

The doctors in the ER should perform a gastrointestinal decontamination with activated charcoal and a correction of the hypoglicemia and other electrolyte disorders if present. Intravenous dopamine or adrenaline may be necessary, and the cardiologist should prepare a central venous access for a promt temporary pacing if required.

10.3.2.2 Digitalis

Patients presenting in the ED with symptoms of digitalis intoxication, mainly gastrointestinal in nature, such as anorexia, nausea, and vomiting, may suffer from many different dysrhythmias involving almost any rhythm or conduction disturbance [38–40]. The most common disorders are first-degree AV block or more advanced AV block degree and premature ventricular contractions.

Digoxin has two main actions in the cardiac myocyte: inhibition of the Na^+-K^+ Adenosinetryphosphate pump, interfering with AV conduction and increase in calcium concentrations, enhancing automaticity [41].

It is therefore important to recognize associated electrolyte disturbances, acid-base alterations, and renal or hepatic failure. In digoxin intoxication, hyperkalemia can be also sustained via a toxic mechanism of the Na^+-K^+ pump, which can be difficult to treat and can result after the treatment in hypokalemia.

In the presence of bradyarrhythmias, both atropine and cardiac pacing are usually effective. The most effective treatment for digitalis overdose is the administration of antidigitalis immunoglobulin IgG. The administration of magnesium and lidocaine often successfully treats premature ventricular contractions.

10.3.2.3 Antiarrhythmic Drugs

A patient with a history of atrial fibrillation treated with an antiarrhythmic drug such as flecainide or propafenone can present at the ED with an atrial flutter with a 2:1 or 1:1 atrioventricular conduction, or, in cases of drug abuse, also with a wide complex tachycardia related to class I effects on Na channels and QRS prolongation (Fig. 10.3).

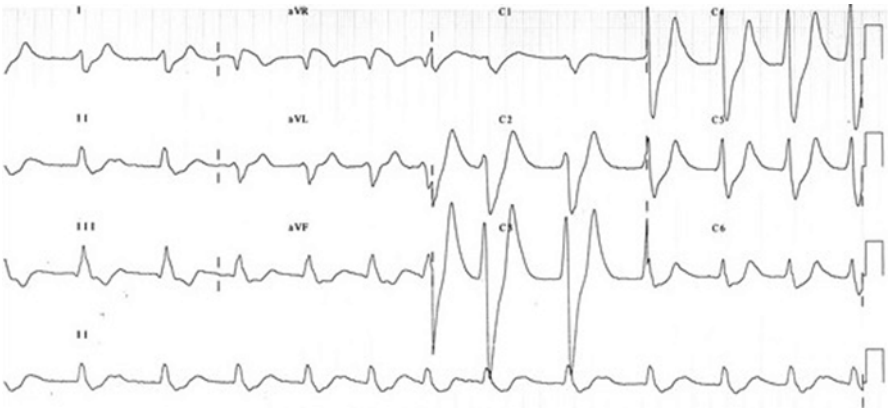

Fig. 10.3 A 60-year-old woman, 60 kg, with a history of paroxysmal atrial fibrillation; intake of 300 mg flecainide per os

10.3.2.4 Benzodiazepine

When a patient with a history of anxiety presents at the ED with palpitations, the medical history plays, as usual, an important role; in fact, discontinuation of benzodiazepine (BDZ) can cause a withdrawal syndrome with reactions that vary in severity and duration. Withdrawal syndrome is more common with triazolam and BDZs with a short to intermediate half-life, in particular if taken in repeated doses during the day, whereas the syndrome is rare with long-half-life BDZs and virtually absent with BDZ analogues such as zolpidem and zopiclone.

Arrhythmias during withdrawal syndrome are induced by autonomic arousal caused by sympathetic hyperactivity, and include mainly sinus tachycardia and ectopic beats, often associated with blood pressure imbalance (orthostatic hypotension and mild systolic hypertension). The administration of β-blockers or clonidine can help in managing reactions resulting from sympathetic hyperactivity [42].

10.3.2.5 Antidepressant Agents

Depressed patients seem to be predisposed to cardiac arrhythmias, one of the proposed mechanisms involves a reduced parasympathetic nervous system activity, that can be often present as a decreased heart rate variability [43].

In patients with depression presenting with dysrhythmias in the ED, it is important to recognize the different classes of drugs.

- *Tricyclic antidepressant agents* (TCA), such as imipramine, amitriptyline, and clomipramine, act as nonselective monoamine reuptake inhibitors. TCAs induce quinidine-like effects that are frequently encountered in older patients and children. On surface ECG it's often recognizable an intraventricular block and atrio-ventricular conduction block of different degrees with an increase in QRS width and PR interval; moreover, there are repolarization abnormalities with QT interval prolongation and negative T waves: therefore these patients present with

a higher risk of ventricular arrhythmias, in particular torsade de pointes. TCA can also induce sinus tachycardia (5–20 % of patients treated), with a mean increase of 15–20 bpm, probably caused by peripheral anticholinergic activity. Patients with cardiac diseases treated with class IC antiarrhythmic drugs (flecainide, propafenone) or quinidine should be closely monitored because the interaction between these drugs can lead to an increase in TCA blood concentration.

- *Selective serotonin reuptake inhibitors* (SSRI) include fluoxetine, sertraline, paroxetine, and citalopram, among others. A sinus tachycardia can be frequently recorded and, rarely, palpitations. In older patients SSRI can lead to sinus bradycardia and, rarely, syncope. In the case of drug overdose rhythm disorders, both bradyarrhythmia and tachyarrhythmia, as well as hypotension, are frequently present [44]. SSRI inhibits hepatic CYP3A4 and it is important to avoid or administer with reduced doses antiarrhythmic drugs as amiodarone, flecainide, propafenone, and lidocaine (i.v.) or sildenafil. [44, 45].
- *Monoamine oxidase inhibitors* (MAOI), such as phenelzine, tranylcypromine, and isocarboxazid, comprise the third main group of drugs used in clinical practice. A patient taking MAOI and presenting at the ED with palpitations and either tachycardia or bradycardia should be evaluated for a hypertensive surge, which has sometimes been reported as fatal. The anamnesis plays a pivotal role; in fact if the patient has ingested cheese or other foods with a high tyramine content, the arrhythmias could be due to norepinephrine release and an exaggerated adrenergic reaction induced by high tyramine blood levels [46–48].

10.3.2.6 Antibiotics

Patients treated with antibiotics can often present at the ED with sinus tachycardia or palpitations related to ectopic beats or to high rate atrial fibrillation; both dysrhythmias are probably related to the underlying condition (usually an infection) and subsequent fever and electrolyte disturbances.

In any event, a 12-lead ECG is mandatory to exclude a QTc prolongation and the risk of ventricular arrhythmias, in particular torsade de pointes.

These arrhythmias can be due to the following classes of antibiotics:

- *Macrolides* such as erythromycin, clarithromycin, and azithromycin. The risk of QT prolongation is higher if an H1 antagonist (e.g., terfenadine, astemizole) is administered at the same time. QT prolongation has been described with erythromycin, spiramycin and, less frequently, clarithromycin and azithromycin. Moreover, palpitations have been reported in patients taking azithromycin. An increase in digoxin levels has been reported in patients receiving erythromycin attributable to killing of digoxin-metabolizing bacteria [49].
- *Fluoroquinolones* such as levofloxacin and ciprofloxacin. Rarely, ventricular arrhythmias resulting from QT prolongation have been described during fluoroquinolone therapy.

10.4 A Suggested Algorithm/Pathway for Diagnosis and Treatment

All patients with bradyarrhythmia or tachyarrhythmia and suspected drug abuse or intoxication	What to do	How to do it
	Medical history and identification of suspected drug/s	Habitual medications Coexisting diseases Which substance or mix was taken (! alcohol) When the substance/mix was taken If a mix of substances was taken, which was the sequela Route of substance abuse: tablets, intravenous, inhalation, transdermal, sublingual
	Search for antidote	Contact local poison control center (the telephone number should be available in every ED)
	Medical management	Cardiopulmonary support including fluids DC shock if hemodynamically unstable arrhythmias or temporary pacing if bradycardia Gastrointestinal decontamination of an ingested drug Administration of an antidote if available Correction of acid–base and electrolyte alterations

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Pacemaker Malfunction: Myth or Reality?

11

Roberto Verlato, Maria Stella Baccillieri, and Pietro Turrini

11.1 Focusing on the Issue

Pacemaker (PM) and implantable cardiac defibrillator (ICD) malfunction is a serious and frequent finding in clinical setting. Depending on baseline rhythm and the type of malfunction, symptoms with different severity can occur, from no symptoms to syncope and sudden death due to asystole or ventricular fibrillation. Unfortunately, symptoms, such as asthenia, dizziness, dyspnea, and palpitations, are often vague, and this can lead to a dangerous delay in cardiac implantable electronic device (CIED) malfunction detection. An ECG recording and careful device and lead evaluation by means of telemetry are necessary for the diagnosis. A great help to early detection of CIED malfunctions is coming from remote control, allowing therapeutic interventions within 24 h since the malfunction occurs in most cases.

CIED malfunctions include two main categories: problems with sensing and problems with pacing. Problems with sensing are made of failure to sense, or *undersensing*, and excessive sensing of noncardiac or cardiac signals, called *oversensing*. Undersensing causes asynchronous inappropriate and not necessary pacing, which in turn can precipitate ventricular arrhythmias due to pacing during the ventricular refractory period (R-on-T phenomenon). Oversensing of spurious signals will lead to lack of stimulation and asystole in PM-dependent patients. In ICDs, inappropriate shocks are frequently caused by oversensing. Undersensing and oversensing are mostly due to lead-related problems, either insulation failure or conductor fractures. A connection defect must be considered as differential diagnosis. The problems with pacing have a common final result: PM spikes ineffective to capture the myocardium. If such malfunction is of minor importance in the atrium, it is a life-threatening emergency in PM-dependent patients, which can exit in sudden death.

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© Springer International Publishing Switzerland 2016

M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_11

In patients with an implanted biventricular PM or ICD for cardiac resynchronization therapy (CRT), the loss of left ventricular capture is associated with recurrence of heart failure symptoms.

Battery depletion can lead to asynchronous pacing and other functional abnormalities mimicking either under- and oversensing.

11.2 What Physicians Working in Emergency Department Should Know

11.2.1 About Basic Function of Pacemakers and ECG Interpretation

The basics of PM are illustrated in Fig. 11.1, showing the normal function of a dual chamber (DDD) PM. These systems are preferred by cardiologists as they reproduce the normal atrioventricular (AV) conduction and physiology. They can sense and pace both the atrium and the ventricle. When they sense an atrial signal, a ventricular impulse is delivered at the end of the programmed AV delay. If no atrial signal is detected at the end of the programmed escape interval, the atrium is paced. If a ventricular spontaneous signal is sensed within the AV delay, no ventricular impulse is delivered to the ventricle [1].

The basics of single chamber (SSI), more often ventricular (VVI) PM, are more simple: the ventricle is paced at the end of the programmed escape interval, or basic rate, when nonsensed signal occurs within this time. In rate-responsive PM, either VVI or DDD, the stimulation rate is increased during effort according with sensors [1].

11.2.2 Most Important, Basic Programmable Functions in a Pacemaker

(a) *Lower rate*: it is the rate below which the pacemaker will stimulate the heart. If spontaneous activity is higher than the programmed lower rate, pacemaker output is inhibited. If programmed rate is higher than spontaneous rate and PM spikes are not visible, a malfunction is present, usually oversensing. The only exception is the presence of a "hysteresis" algorithm programmed on.

(b) *Hysteresis*: if this function is activated, the lower heart rate below which the PM will start the stimulation is different from the programmed pacing lower rate. For example, if hysteresis is programmed at 40/min and lower rate at 70/min, the PM will start the stimulation only if spontaneous heart rate drops below 40/min, but stimulation rate will be 70/min. The PM will check periodically the presence of spontaneous rate between 40 and 70/min.

(c) *Rate-responsive pacing*: the stimulation rate is increased when activity sensors detect patient movements (accelerometers). Respiratory activity sensors or other algorithms are also able to increase the basic pacing rate.

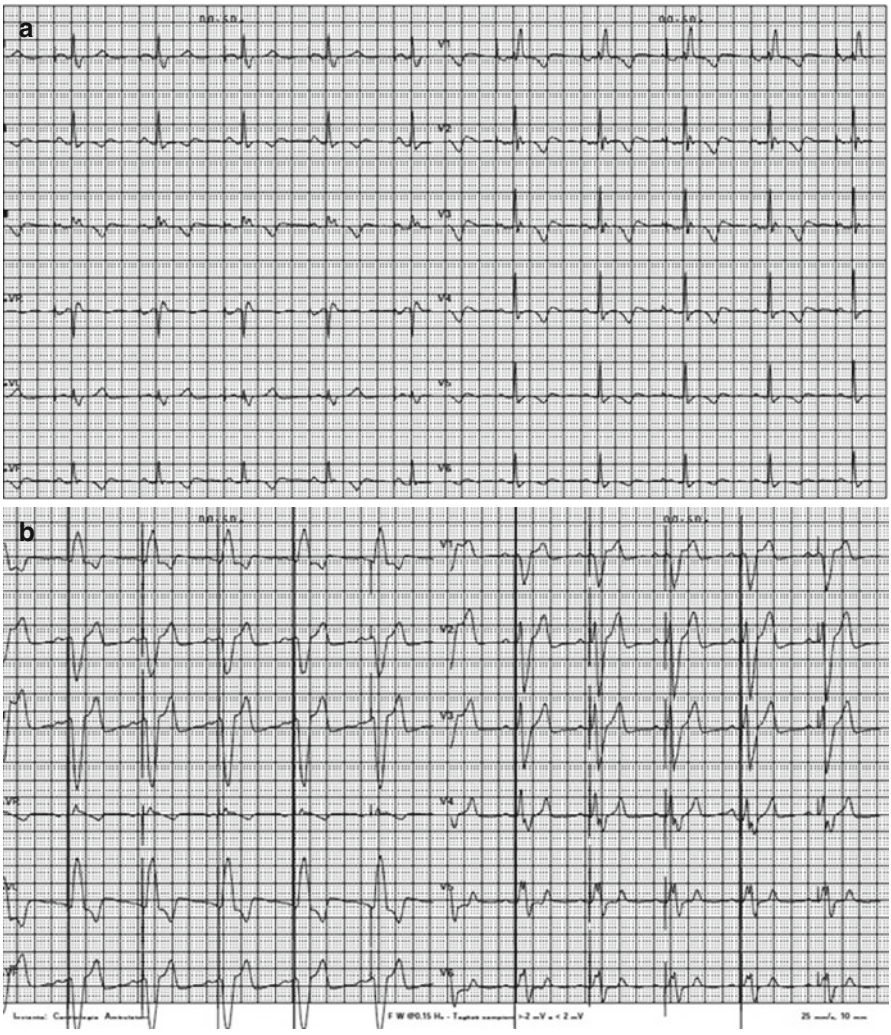

Fig. 11.1 *Top panel* (**a**). DDD pacemaker. Atrial rhythm is paced at 60 bpm. Spontaneous QRS with right bundle branch morphology occurs after 180 ms that inhibits ventricular pacing. This is called atrial-driven rhythm. *Bottom panel* (**b**): spontaneous sinus rhythm is present; each P wave is followed by a ventricular stimulus at the end of the programmed AV delay (120 ms) that captures the ventricular myocardium. The QRS morphology is left bundle branch block with superior axis, typical of right ventricular apical pacing

(d) *Upper rate*: it is the maximum stimulation rate either in case of atrial-driven or sensor-driven stimulation. If the PM stimulates at a rate higher than the programmed upper rate, a hardware/software malfunction is present. This can happen in case of unprotected exposition to strong electromagnetic fields, such as magnetic resonance imaging.

(e) *Algorithms to reduce ventricular pacing:* in order to reduce unnecessary ventricular pacing, several algorithms are present in modern dual chamber PM. Most commonly, only the atrium is stimulated (AAI mode) if atrioventricular conduction is preserved; when one or two (depending on the model and device programming) consecutive A-V blocks occur, the mode of stimulation automatically changes to atrioventricular pacing (DDD mode). Other algorithms prolong the programmed A-V interval up to 400 ms to detect if spontaneous A-V conduction is present. When these algorithms are activated, it is sometimes difficult to understand if the PM is working normally or not, for example, in case of single atrial beats without any ventricular activity; this can be a normal behavior of the device, when followed by DDD pacing, but can be expression of ventricular oversensing. Knowledge of the device programming, PM interrogation, or real-time telemetry can be necessary for the diagnosis.
(f) *Pacing voltage*: this is the voltage of PM stimulus. If it is programmed below the ventricular pacing threshold, spikes will be ineffective leading to an *exit block*.
(g) *Pulse duration*: this is the duration of PM stimulus. If it is programmed too short, spikes could be ineffective leading to an exit block.
(h) *Autocapture*: this algorithms automatically reduce PM output energy to values just above the ventricular pacing threshold. In case the delivered stimulus doesn't capture the ventricle, a second high-energy stimulus is provided: this is a normal behavior of modern PM and not a malfunction.
(i) *Mode switch*: when this algorithms are activated in dual chamber PM, the mode of stimulation automatically switches from DDD(R) to VDI(R) when an atrial tachycardia/fibrillation is detected. If atrial arrhythmia terminates, the mode of stimulation will return from VDI to DDD [1].

11.3 What Cardiologists Should Know

Cardiologists must be familiar with basic PM functions, mode of stimulation, PM algorithms, and interpretation of ECG recordings in PM patients. Modern PMs are very complex, fully programmable devices, with a lot of therapeutic and diagnostic capabilities. PM interrogation, evaluation of battery and lead data, analysis of real-time telemetry, and stored data are necessary for the final evaluation of PM functions. It would be desirable that cardiologists were trained and capable to use at least basic functions of PM programmers and the meaning and utilization of the following:

(a) *Magnet*: the application of a magnet above the PM pocket induces asynchronous pacing (VOO or DOO in single chamber or dual chamber PM, respectively). In case a PM is apparently not working (because spikes are not evident) but bradycardia (below lower rate, including hysteresis) is present, it is useful to apply a magnet on the PM. If PM spikes appear and capture the ventricle, oversensing inhibiting PM stimulation is likely. When necessary, in this cases magnet function is also useful for emergency treatment of the bradycardia.

(b) *ERI*: this is a message of "low battery charge" (Elective Replacement Indicator), meaning that the device will soon (usually after about 3 months) reaches the complete battery depletion, or EOL (End Of Life); ERT (Elective Replacement Time) and EOS (End Of Service) are synonymous of ERI and EOL, respectively, used by some manufacturers.
(c) *Pacing impedance*: this value is normally in the range between 350 and 900 Ω. Pacing impedance is influenced by the integrity of pacing circuit (conductors and insulation), by the lead model (i.e., active or passive fixation, steroid eluting or normal electrodes), and by electrode endocardial contact surface. When pacing impedance drops below 250 Ω, an insulation failure of the lead is likely. When pacing impedance is above 1500–2000 Ω (depending on the lead model), a conductor fracture or a connection defect is possibly present. In case of an abnormal pacing impedance in bipolar pacing and sensing configuration, PM reprogramming to unipolar pacing and sensing is recommended.

All cardiologists involved in emergency evaluation of PM patients should be trained to recognize the most commonly PM malfunctions, i.e., undersensing, oversensing, and exit block [1–3].

11.3.1 Undersensing in Cardiac Pacemakers

Undersensing occurs when the PM fails to sense the spontaneous atrial or ventricular activity. In this case the PM will ignore the spontaneous activity and pace the heart at the programmed rate as if the patient had no rhythm. This results in the so-called "asynchronous" pacing, that is, pacing competitive with spontaneous cardiac activity. Ventricular pacing during the vulnerable period of cardiac cycle (T wave) can occur, triggering ventricular arrhythmias including ventricular fibrillation [1–3].

An example of ventricular undersensing is illustrated in Fig. 11.2.

11.3.1.1 Causes of Undersensing

Causes of undersensing include lead failure, pacemaker failure, and environmental and physiologic changes. Lead failure is the most frequent cause of under- and oversensing in current CIEDs. Both insulation failure and lead fracture are able to induce undersensing, so it is pivotal to interrogate the pacemaker to evaluate pacing impedance. An increase of pacing impedance > 2000 Ω is diagnostic of conductor damage. A decrease of pacing impedance below 250 Ω is diagnostic of insulation failure. A connection defect is usually associated with a high pacing impedance, >3000 Ω, and this must be distinguished from conduction fracture in the presence of high pacing impedances. To identify a connection defect, chest X-ray is useful, as it can show the lead connector incompletely inserted into the PM head. An example of connection defect is illustrated in Fig. 11.3.

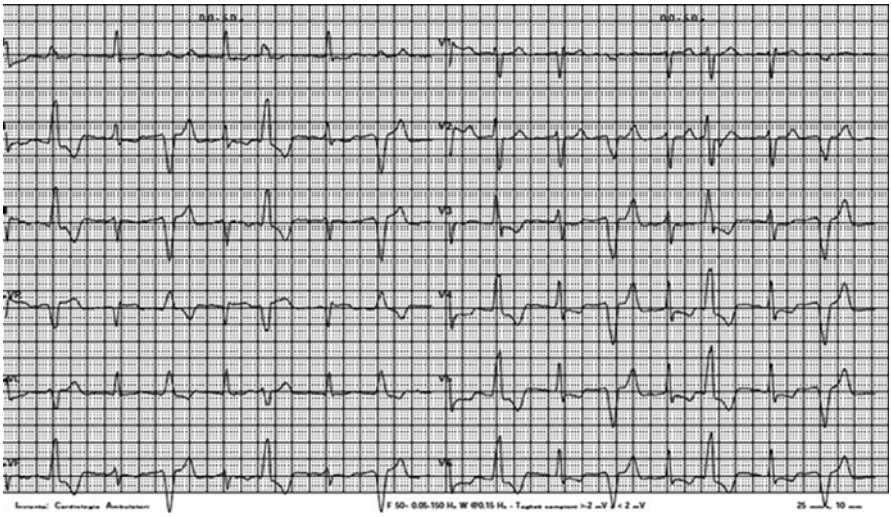

Fig. 11.2 VVI pacemaker. Spontaneous rhythm is present interrupted by premature beats of different morphology. At careful ECG inspection, small pacemaker spikes (bipolar) precede the QRS with left bundle branch morphology and left axis deviation. Other spikes follow spontaneous QRS in random sequence (asynchronous pacing). Undersensing of ventricular activity is present

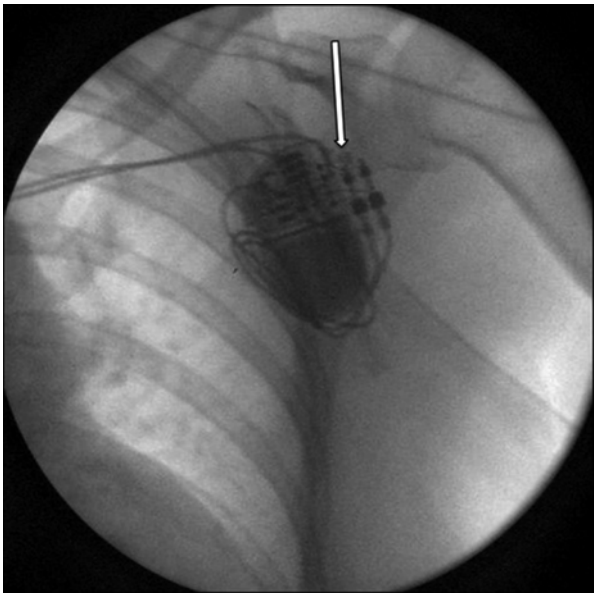

Fig. 11.3 Chest X-ray showing a close-up of pacemaker pocket. Patient had undergone to device replacement 1 week before and presented with high pacing impedance (>3000 Ω), under- and oversensing. The connector of the atrial lead, the lateral one, is completely inserted into the head of pacemaker, and its terminal pin is visible outside the electrode ring. The ventricular connector (*arrow*) is incompletely inserted and its terminal end is not visible

Chest X-ray is less useful to detect lead failure as leads seem apparently intact in most cases.

Pacemaker failure can cause undersensing. The most frequent situation is battery depletion (end of service, or EOL message at telemetry interrogation is displayed): this switches the mode of stimulation to asynchronous pacing.

Environmental causes of undersensing are strong magnetic fields, such as anti-theft devices, great motor engines, the application of a magnet on the pacemaker pocket, and magnetic resonance imaging. A frequent environment cause of undersensing is cardiac defibrillation. In this case undersensing but also an exit block with lack of ventricular capture can occur due to tissue damage at the myocardium-tip electrode interface.

Physiologic cardiac and noncardiac changes can facilitate undersensing, reducing the amplitude of cardiac sensed signals. New bundle branch block, myocardial infarction, hypokalemia and other ionic abnormalities, and old age of the implanted lead, associated with fibrous tissue growing around the electrode tip, are all situations associated with PM undersensing.

11.3.1.2 Treatment of PM Undersensing

In the case of reduced amplitude of sensed signals (measured by telemetry), it's possible to increase the PM sensing function by reprogramming, even if this in turn increases the risk of oversensing, in particular for unipolar leads. PM or lead replacement is the only way to correct the malfunction when battery depletion or lead failure is present [1–3].

11.3.2 Undersensing in ICDs

Undersensing in ICDs recognizes the same causes as in cardiac PM. Lead failure, either insulation or conductor defects, is the most dangerous situation in ICD patients, and it must be excluded in the presence of undersensing or oversensing. In ICDs either lead-related undersensing or oversensing may be intermittent, making diagnosis more difficult. A "physiologic" degree of undersensing is frequently observed in ICDs due to low voltages of cardiac signals during ventricular tachycardia and fibrillation, but this is rarely a clinical problem. Otherwise, prolonged ventricular undersensing during ventricular fibrillation (VF) could result in patient death, and the only possible treatment is an external rescue shock. However, in ICDs the most frequent cause of ventricular tachycardia (VT) undersensing is a programming "error," that is, the cutoff detection rate set at values above the rate of spontaneous VT. Reprogramming of VT detection rate will correct the problem [1].

11.3.3 Oversensing in Cardiac Pacemakers

Oversensing occurs when a PM senses noise, artifacts, or physiologic cardiac or noncardiac signals different from the atrial or ventricular depolarization and classifies such signals as atrial or ventricular depolarizations. The result will be inhibition of ventricular pacing when oversensing occurs at ventricular level or unnecessary ventricular pacing when oversensing occurs at atrial level. Pacing during oversensing is erratic, irregular, and completely unrelated with the programmed lower rate. In the case of prolonged pacing inhibition in PM-dependent patients, asystole will occur [1–3].

11.3.3.1 Causes of Oversensing

Lead failure is by far the most frequent cause of oversensing. Insulation failure, conductor fracture, and lead dislodgement are all able to induce oversensing of noise. Lead problems are identified by means of pacing impedance measurements, as described for undersensing. High pacing impedance is diagnostic of conductor problems, low impedance of insulation defect. Lead dislodgement and connection defect are often visible on X-ray imaging.

Environmental electromagnetic interferences (EMI) are the second more frequent cause of oversensing. They can reach the distal dipole of PM leads because electromagnetic currents flow through the patient's body, which acts as a volume conductor. Electrocautery, extracorporeal shock lithotripsy, and MRI (when CIED presence is ignored) are frequent causes of oversensing in the hospital setting. Noise signals can also originate from metal to metal friction in patients with multiple implanted pacemaker or defibrillation leads.

Myopotential oversensing can occur at pocket level (pectoral muscle oversensing), especially when programmed unipolar sensing, but more frequently the PM can sense the diaphragmatic respiratory activity.

T wave oversensing is the most common situation of oversensing of cardiac physiologic signals; it leads to a decrease of pacing rate as the escape interval is reset by the T wave sensing [1–3].

11.3.3.2 Treatment of Oversensing

The application of a magnet on the pocket will immediately induce (in PM, not in ICDs) atrial and ventricular asynchronous pacing. In the emergency setting this is the only maneuver that must be immediately applied to the patient, especially if symptomatic bradycardia is present.

If the PM programmer is available, sensing function must be reprogrammed to decrease PM sensitivity. In the case of unipolar sensing, the change of sensing configuration to bipolar, if a bipolar lead is implanted, will reduce or even could completely correct the oversensing of muscle potentials. In case T wave oversensing is present, longer ventricular refractory periods must be programmed.

The switch of pacing mode to VOO, or asynchronous, is the safest option in PM-dependent patients with oversensing due to lead problems to correct the bradycardia. In this case replacement of the failing lead is mandatory [1–3].

11.3.4 Oversensing in ICDs

Oversensing is the second leading cause of inappropriate detection and therapy of arrhythmias, including inappropriate shocks after atrial tachyarrhythmias. Lead failure must be suspected in any case of inappropriate shocks and noise stored in device memories. Several algorithms have been developed for early detection of lead failure based on the presence of very short intervals between sensed signals. The presence of a connection defect must always be considered as an alternative source of noise oversensing. Failing ICD leads must be replaced, with or without lead extraction based on careful evaluation of individual risk/benefit profile of lead extraction.

When noise oversensing is due to interference between implanted leads, lead extraction is mandatory [1–4].

11.3.5 Problems with Pacing

The most frequent situation is the presence of pacemaker spikes visible on monitor screens or ECG recordings, not followed by ventricular or atrial depolarizations (exit block). The failure to capture must be immediately recognized as it is a life-threatening malfunction.

In Fig. 11.4 an example of failure to capture is shown. PM spikes are delivered by pulse generator, not followed by ventricular depolarization [1–3].

Fig. 11.4 Patient with PM presenting to the emergency room after a syncope. 12-lead ECG shows several pacemaker spikes not followed by ventricular depolarization (exit block). A failure to capture is certainly present. Real-time telemetry showed high pacing impedance (2500 Ω). Combining the two findings of exit block plus high pacing impedance, the diagnosis of lead fracture was made. Lead replacement was necessary in this case

11.3.5.1 Causes of Failure to Capture

In the period just following pacemaker implantation, lead dislodgement and cardiac perforation are the most common causes of failure to capture. Chest X-ray is necessary for the diagnosis, and reintervention for lead repositioning must be performed as soon as possible. Sometimes perforation is subtle, and a CT scan can be helpful to identify the relationship and exact position of the electrocatheter tip and the pericardium.

If the exit block occurs several weeks after implantation (the most frequent situation), it is usually due to an increase in stimulation threshold because of fibrosis maturation close and around to the electrode tip. Steroid-eluting leads are less frequently involved, while the risk is higher for active fixation leads, where an increase of pacing threshold frequently occurs during the first weeks after implantation. Such increase is usually transient, although it can rarely persist or even worsen (especially in young people) during follow-up.

Failure to capture can be also caused by too low voltage and/or duration of the stimulus emitted by the pacemaker in proximity of battery end of life or in the case of battery failure, but usually it depends by an inappropriate PM programming. Autocapture algorithms in modern pacemaker ensure ventricular capture.

Cardiac defibrillation and strong electromagnetic fields emitted by MRI can cause exit block due to tissue damage by current flow through the lead up to the electrodes, a sort of inadvertent tissue ablation, in particular when insulation failure is present.

Lead failure, in PM and especially in ICDs, is very often associated with deterioration of pacing and sensing thresholds, in addition with under- and oversensing [1–3].

11.3.5.2 Treatment of Failure to Capture

Acute perforation usually presents as an emergency in operating room. It requires pericardiocentesis and immediate lead repositioning.

Subacute and chronic perforation may be difficult to recognize. Symptoms may be minor; pericarditis, chest pain, diaphragmatic stimulation, and sometimes pneumothorax may be present. Perforation may occur at both atrial and ventricular levels. Loss of capture is almost always present together with sensing problems. Device reprogramming can transiently be useful to correct sensing and pacing abnormalities, but again lead revision/repositioning is absolutely required to solve the problem once the diagnosis is made.

When failure to capture occurs due to increased pacing thresholds, device reprogramming and selection of higher energy output, in terms of pulse voltage and duration, are the solutions in the acute setting. However, in current pacemaker technologies, the programmation of high pacing energies, i.e., voltage amplitude of 5–6 V and pulse duration of 1–2 ms, is associated with a marked reduction of battery longevity, up to less than two years. Lead revision, reposition, or replacement must be considered in pacemaker-dependent and/or young people with high pacing threshold.

Failure to capture occurring after MRI or cardiac defibrillation requires lead revision.

11.4 False Malfunctions

In modern devices, the complexity of some algorithms can sometimes make the ECG interpretation and the distinction between normal behavior and malfunctions quite difficult.

For this reason, to reach a correct ECG interpretation, it is necessary to know the model and the programming of the device, because what can be considered a normal behavior in some models and with some programming can be a malfunction in other cases [5].

- For example, a spontaneous rate below the lower rate programmed can be normal when a hysteresis is programmed, but a marker of oversensing in the absence of this function.
- In order to prevent sudden changes of the heart rate, an algorithm called "rate smoothing", "flywheel" or "ventricular rate stabilization," according to the manufacturer, can be enabled. In this case, stimulation can transiently occur beyond the lower rate, even if a rate response function is not present, just after a spontaneous fast activity, allowing a "smooth" reduction of heart rate. This can frequently happen during atrial fibrillation with very irregular rate, after ectopic ventricular beats or at the end of a tachycardia.
- Convincing data have shown that stimulation of the right ventricle is hemodynamically unfavorable and can sometimes cause or worsen congestive heart failure. In some devices, algorithms for minimizing ventricular pacing are enabled. In this case it is possible to observe an extremely long PQ interval, or even two consecutive P waves (spontaneous or stimulated) not followed by any ventricular activity, before the automatic switch from AAI (or ADI) to DDD mode occurs (Fig. 11.5).

Finally, a very short paced AV interval (about 100 ms) can sometimes be observed.

This is due to a function called "ventricular safety pacing," which consists in the delivery of a ventricular stimulus when a signal is detected in the ventricular channel immediately after an atrial stimulation. As in practice, the device is not able to distinguish whether the signal is derived by the artifact of atrial pacing detected at ventricular level (crosstalk) or a real ventricular beat (as an ectopic ventricular beat), so it immediately delivers a ventricular stimulus ensuring stimulation (in the presence of crosstalk) but with an interval short enough to fall, in the presence of a beat of ventricular origin, in its refractory period, avoiding the risk of triggering dangerous arrhythmias. Ventricular safety pacing can be present even in case of a lack of atrial sensing, when the atrial stimulus coincides with the spontaneous QRS complex, as in the course of sinus rhythm and normal AV conduction.

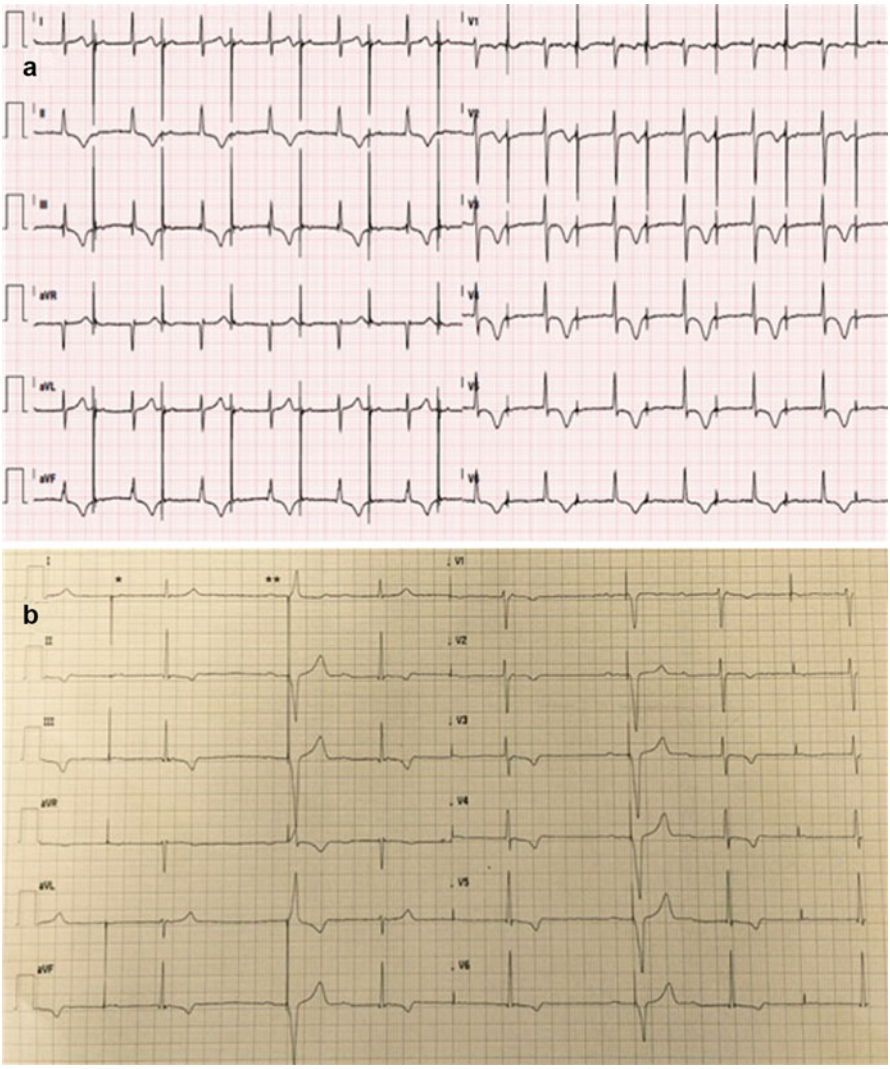

Fig. 11.5 Apparent malfunctions due to algorithm for reduction of ventricular pacing. (**a**) Atrial stimulation with spontaneous AV conduction with very long (440 ms) PQ interval. (**b**) Alternation of AAI (*) and DDD (**) mode, resulting in excessively low ventricular rate

11.5 What to Do in Case a Pacemaker Malfunction Is Suspected

If a PM malfunction is suspected, the patient must be immediately monitored and a complete standard 12-lead ECG obtained.

If artifacts of stimulation are not visible on ECG recording, a magnet must be applied on the device pocket. This will induce asynchronous pacing in both the

atrium and ventricle (VOO, DOO). If pacemaker stimuli become visible, it will be possible to evaluate if they capture the heart (paced P waves and QRS).

If the bradycardia is corrected by magnet application, oversensing is present and lead failure must be considered the most likely cause. The main differential diagnosis is with the presence of a connection defect, especially if the patient has recently undergone PM replacement.

If PM artifacts are visible but fail to capture, either constantly or intermittently even with magnet application, lead dislodgment, cardiac perforation, lead failure, high pacing thresholds, tissue ablation, and programmation errors are the possible causes of the exit block.

Device control by means of real-time telemetry is essential for the final diagnosis. Pacing impedance instant value and trends must be examined. High or low pacing impedances (>2000 or <250 Ω) are diagnostics of lead failure. As they can be intermittent, the temporal impedance trends must be obtained as well. The presence of even only one out-of-range value allows the diagnosis of lead failure. Pacing and sensing thresholds may be evaluated in real time and temporal trends examined.

Battery level is immediately displayed on programmer screen after interrogation, and a message of alert is displayed if battery level is low (ERI, EOS, EOL messages).

Chest X-ray must be obtained to check for connection defects or visible lead fracture, in particular in ICDs recipients. If cardiac perforation is suspected, an echocardiogram and CT scan are recommended.

If a malfunction of the generator is present, like battery exhaustion, PM replacement is necessary. Lead revision/replacement reposition is necessary in most of the other cases as discussed above.

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Management of the Electrical Storm in Patients with ICD

12

Daniele Muser, Domenico Facchin, Luca Rebellato, and Alessandro Proclemer

12.1 Focusing on the Issue

Current definition of electrical storm (ES) is the occurrence of three or more episodes of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) within 24 h requiring appropriate medical intervention. The same definition applies in implantable cardioverter-defibrillator (ICD) carriers in which ES is defined by three or more appropriate and separate (at least 5 min) device interventions in 24 h, either with antitachycardia pacing (ATP) or shock [1].

Current guidelines recommend ICD implantation for secondary prevention of sudden cardiac death (SCD) in survivors of cardiac arrest with no correctable causes and in patients with sustained symptomatic VT of different etiology. They also recommend ICD implantation for primary prevention in patients with ischemic or non-ischemic dilated cardiomyopathy and ejection fraction equal or lower than 35 % after at least 3 months of optimized medical therapy [2] and in other less frequent inherited arrhythmogenic syndromes.

Considering that approximately 1–2 % of the adult population in developed countries suffer from heart failure (HF) and that at least half of these patients have a low ejection fraction [3], the number of ICD carriers is wide spreading. Moreover, the improving therapies of HF ensure a long survival of patients making them older and affected by more comorbidities. For these reasons, ES is an increasingly

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© Springer International Publishing Switzerland 2016

M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_12

frequent cause of access to emergency department (ED). It is estimated that about 25 % of ICD carriers experience at least one ES episode per year follow-up [4]. ES is definitely a medical emergency requiring a multidisciplinary approach.

12.2 What Physicians Working in ED and Anesthesiologists Should Know

12.2.1 How Is an ICD Made and How Does It Work?

The ICD is a subcutaneous implantable device able to monitor cardiac rhythm and terminate potentially life-threatening arrhythmias. It consists of two main components:

- The *generator* that contains the battery, all the circuits that run the device, and the operator communicating system. It is implanted in a subcutaneous pocket, usually under the left clavicle.
- The *leads* that reach heart chambers through the venous system and allow the device to either monitor heart electrical activity and deliver therapies. The ICDs have a lead implanted in the right ventricle apex able both to record ventricular activity and release therapies like pacing and/or direct current shock. In adjunct some ICDs have another lead implanted in the right atrium to record atrial electrical activity, improving discrimination between supraventricular arrhythmias (SVA) and ventricular ones and to pace the atrium (ICD-DR). ICDs with cardiac resynchronization therapy (CRT-D) have a third lead that paces the left ventricle, through the coronary venous system, synchronously to the right ventricle improving contractility. Some recent devices are implanted entirely subcutaneously, leads included (subcutaneous ICD), and can deliver high-energy shocks only (without long-term pacing capabilities) without a direct contact with the heart chambers and no leads inserted in the venous system.

ICDs use mathematical algorithms defined by the manufacturer to discriminate life-threatening ventricular arrhythmias from SVA and deliver appropriate therapy. Sometimes correct recognition fails, and in this case the therapy delivered is defined *inappropriate*. In other cases the delivered therapy may not be able to terminate the ventricular arrhythmia, and in this case it is called *ineffective*:

- The operator interfaces with the ICD through a programmer able to communicate with the device. Each manufacturer uses a different programmer, so it is imperative *to know the manufacturer and use the right equipment*. The programmer establishes an initial connection with the device through a head which must be positioned on the skin above the ICD. Usually green lights turn on to indicate the head is in the right place. At this point, depending on the features of the device, it may be necessary to maintain the head above the ICD throughout the query to allow communication, or, in some devices, the head can be removed since the communication continues via Wi-Fi.

The programmer allows the operator to visualize all the data stored in the device such as:

- *Arrhythmic events*: the device registers all arrhythmic events recognized as such on the basis of user-defined criteria. Each event provides endocavitary (or external for subcutaneous ICDs) electrocardiogram lead recording and therapies delivered.
- *Battery status*.
- Information about *lead integrity*.

On the basis of stored data, the operator may decide to change some settings such as:

- Arrhythmia recognition criteria (heart rate, time before treatment, algorithms for SVT recognition, etc.) and intervention criteria
- Type and characteristics of therapies delivered

12.2.2 How Does the ICD Recognize and Treat Arrhythmias (Appropriate Therapies)?

VT recognition is primarily based upon tachycardia cycle length (to distinguish from normal sinus rhythm) and duration (to detect non-sustained episodes). Both of these parameters are tailored on the patient's characteristics. Thus, ICD uses ventricular rate zones for rhythm classification. The boundaries between zones are defined by two main principles:

- The recognition of unstable fast VT/VF must be highly sensitive even at the cost of inappropriate rapid SVA treatment.
- The recognition of slower VT (generally better tolerated) has to be more specific to avoid inappropriate therapies even at the cost of some delay in detection.

The ICDs treat ventricular tachyarrhythmias by:

- *Antitachycardia pacing* (*ATP*): it is a brief ventricular pacing (6–8 beats) with a cycle length slightly lower (thus at a faster rate) of the arrhythmia (usually 81–88 %), in the attempt of resetting the reentrant circuit and interrupting the arrhythmia. Sometimes the paced cycle shortens from beat to beat, and in this case it is referred as ATP ramp.
- *Direct current shock* (*DC shock*): it is a biphasic electrical shock provided between the generator case and the coil localized on the right ventricular lead. The energy released may vary, reaching up to 40 J with the latest generation high-energy devices.

Basing on several studies [5–7], ICD programming should empirically involve the use of three rate zones:

- A slow VT zone up to 320 ms cycle length (<188 bpm)
- A fast VT zone from 320 to 240 ms (188–250 bpm)
- A VF zone from 240 ms (>250 bpm)

In both VT zones, a variable number of ATP attempts precede shocks delivery. In the slow VT zone, a greater number than in fast VT zone are usually programmed (e.g., 3 ATPs followed by 3 ATP ramps), as fast arrhythmias are usually less tolerated.

In the VF zone, the hemodynamic instability of the arrhythmia and its high life-threatening potential require an immediate shock delivery (usually at the maximum energy from the beginning). In modern devices an ATP during capacitor charging (usually requiring less than 10 s) is delivered, avoiding the shock in the case of arrhythmic interruption.

VT/VF detection not only is based upon ventricular rate but also requires a programmable duration of the arrhythmia to avoid detection of non-sustained episodes. Usually a VT/VF is detected when a certain percentage of ventricular sensed beats meets cycle length criteria. The type of counting used varies between detection zones and among manufacturers. In order to improve sensibility, according to some manufacturers, the arrhythmia is detected when a certain percentage of beats (not necessarily consecutive) falls in VF zone, while consecutive interval counting is required in the VT zone, increasing specificity. The time to detection in the VT zone should be longer enough to allow spontaneous termination of non-sustained episodes [6, 8].

12.2.3 Inappropriate Therapies

Inappropriate therapies (especially shocks) are one of the main issues to be avoided as they cause patient discomfort, are potentially proarrhythmic, and reduce battery life.

The two main causes of inappropriate shock are failure in discriminating SVA and signal misinterpretation.

Frequently SVA is associated with a fast ventricular response leading ventricular rate to fall into VT/VF detection zone causing inappropriate therapy release. This problem occurs more frequently with single-chamber ICDs that do not have atrial sensing capabilities. Dual-chamber devices can compare atrial and ventricular rates to set the origin of the. ICDs use a variety of algorithms to discriminate SVA from VT; major ones are listed below:

- *Atrioventricular rate comparison*: applies only in dual-chamber ICDs; when the ventricular rate is faster, the diagnosis is VT. When atrial and ventricular rates are equal, additional criteria are required for discrimination.
- *Onset*: useful for discrimination of gradually accelerating sinus tachycardia from sudden-onset VT. It applies when the RR interval shortens by a programmed percentage if compared with the average number of preceding beats. May fail in case of VT occurring during sinus tachycardia.
- *Stability*: useful for discrimination of fast response AF. It evaluates RR variability; when greater than a programmed percentage (e.g., 20 %), AF is supposed. It may fail in the case of very fast AF in which there is a pseudo-regularization of ventricular rate, in atrial flutter or in irregular VT.

- *Morphology*: it compares endocavitary electrocardiograms recorded during sinus rhythm and during VT. It is useful in single-chamber ICDs lacking of atrial information but may fail in intraventricular conduction delays and in rate-dependent conduction delays.
- *Rate duration*: it is an extreme lifesaving measure. It results in shock delivery after a programmable time interval even if the episode is classified as SVA; this algorithm is usually activated when there is a high risk of undertreatment of VT erroneously recognized as SVA, but it increases the risk of overtreatment.

Signal misinterpretation is the other big deal leading to inappropriate shocks. It may depend on some programmed variables; easily editable, external, and far-field interferences; or device/lead failure that usually requires an interventional approach. Main causes of signal misinterpretation are listed below:

- *T wave oversensing*: it happens when a high amplitude T wave is erroneously recognized as an R wave. It may happen because of the low ventricular sensing threshold necessary to recognize even low-amplitude VF. This problem can be solved by increasing sensing threshold, lengthening refractory period, or changing sensing decay parameters to suppress T wave detection.
- *Electromagnetic external interference*: external electromagnetic fields can be mistaken for intracardiac signals resulting in inappropriate arrhythmic detection and therapy. Common household appliances are not generally a problem, but some high-intensity fields such as high-voltage power lines, electric motors, magnetic resonance imaging, TENS units, electrocautery during surgery, neurostimulators, and radiotherapy should be avoided.
- *Myopotentials*: far-field myopotential recording may lead to inappropriate arrhythmic detection. This problem occurred in the past with unipolar leads using large sensing fields (from the lead tip to the generator case) and is now largely avoided with the modern bipolar leads, recording more localized signals only.
- *Lead failure*: lead fracture or insulation loss of continuity may cause external noise recording and inappropriate detection. In these cases lead extraction and/or new lead insertion is the only choice. Modern devices usually provide alerts for lead integrity.

12.2.4 Electrical Storm

12.2.4.1 Incidence and Clinical Predictors

Several studies examined the incidence of ES in ICD recipients, although ES definition was not standardized and the inclusion criteria and follow-up period were not homogeneous. Considering current definition, the incidence varies from 4 to 28 % in a follow-up period between 1 and 3 years [9]. In the sub-analysis of the AVID trial [10], including 499 patients treated for secondary prevention, the rate

of ES was 20 % at 3-year follow-up. Of note, the incidence of ES in primary prevention trials appears lower (4 % in MADIT II), and in our experience [11], after a mean 2-year follow-up, only 13 patients (2 %) experienced an ICD treatment configuring an ES.

A recent meta-analysis [9] evaluated the real weight of ES as a risk factor and its clinical predictors. On the basis of 13 studies, a trend toward an increased prevalence of ES was associated with advanced age and male gender. Other factors related to ES in ICD carriers were heart failure-related clinical variables (as lower ejection fraction), an ICD implant for secondary prevention, the presence of monomorphic VT as triggering arrhythmias instead of polymorphic VTs and VF, and the treatment with class I antiarrhythmic drugs but not with amiodarone and beta-blockers. On the contrary, no significant differences between patients with ischemic or nonischemic dilated cardiomyopathy were reported. After meta-regression analysis, no significant interaction between any of the examined clinical variables and the increased risk of ES was confirmed.

The main clinical characteristics and clinical predictors of ES in the group of patients treated with a CRT-D have been considered in a multicenter experience including 631 patients, with a mean follow-up of 19 ± 11 months. In this study VT or VF episodes were detected and treated in 141 patients (22 %), and ES occurred in 45 (7 %). At univariate analysis, the only predictors of ES were the nonischemic etiology of cardiomyopathy and secondary prevention indication, while other common variables such as age, male gender, ejection fraction lower than 25 %, and advanced NYHA class did not correlate.

Our experience included 62 patients (mean age 66 years, 90 % male) admitted for ES during the period 2006–2012. The mean interval from implant to ES was 47 months. Ischemic heart disease was present in 30, nonischemic cardiomyopathy in 11, and other etiologies in 14, and 60 % of patients had been treated with ICD for secondary prevention. Mean ejection fraction was 35 %. In 23 patients the arrhythmia at admittance was incessant VT, while the remaining 39 experienced several VT/VF episodes, with a mean number of 6 shocks per patient. In more than half of patients (31), there wasn't a clear trigger and the ES rises from a primitive electrical instability. In the remaining the most frequent triggers were worsening heart failure, electrolyte imbalances, myocardial ischemia, and proarrhythmic drug side effects.

12.2.4.2 Prognosis

The majority of papers evaluating the role of ES as a mortality risk factor showed that it was associated with a threefold risk of death. ES maintained a significant value as risk factor even when compared with unclustered sustained VT/VF [9]. For the composite end point of all cause mortality, heart transplantation and hospitalization for heart failure ES was associated with a 3.39-fold increased risk.

The reported mortality among large series [12] of patients with ES treated by catheter ablation appeared extremely variable between 15 and 29 % during a follow-up ranging from 1 to 2.5 years. In our series, including patients treated not exclusively by catheter ablation, the overall survival of patients experiencing their first ES episode was 60 %, 50 %, and 44 % after 1, 2, and 3 years, respectively.

Considering that ES is associated with increased SCD and non-sudden cardiac mortality, Guerra et al. evaluated the association between ES and heart failure in patients with chronic heart failure and ICD. They reported that during 5-year follow-up, the survival estimates were not significantly different between patients with ES and HF worsening (36.4 vs. 38.5 months), while it was significantly lower in comparison to survival of patients with unclustered VT/VF episodes (49.2 months). The primary mortality cause in ES group was refractory heart failure (59 %), followed by noncardiac conditions and by SCD in only two patients. Even hospitalization-free rate was lower in both ES and HF worsening groups in comparison to patients with unclustered VT/VF episodes (15.4 vs. 20.1 vs. 36.1 months), while the hospitalization rates were not significantly different between ES and HF worsening groups. The conclusions of the authors were that heart failure patients admitted for ES show important outcome analogies with patients admitted for acute heart failure and that ES should be identified as an important clinical consequence of heart failure decompensation.

12.3 What the Cardiologist Should Know

ES is a medical emergency potentially leading to acute cardiac failure and cardiogenic shock and requiring a multidisciplinary approach.

Initial diagnostic workup includes physical examination, electrocardiogram (ECG), chest X-ray, echocardiogram, blood gas analysis, electrolytes, serum creatinine evaluation, and ICD interrogation.

The first issue to assess in a patient with multiple ICD shocks is to seek ICD intervention causes.

In case of appropriate therapies due to VT/VF, it is necessary first of all to rule out reversible causes of ES including electrolyte imbalances, acute ischemia, worsening heart failure, infective state, hyperthyroidism, and proarrhythmic drugs. In a large series reversible causes of ES account for no more than 10 % of cases referred to EP labs [4].

Following initial evaluation, an accurate patient's risk stratification should be made according to hemodynamic tolerance of the clinical VT and comorbidities [13]. Hemodynamic decompensation defined as sustained hypotension (i.e., systolic blood pressure <80–90 mmHg) despite increasing doses of vasopressors and requiring mechanical hemodynamic support (i.e., intra-aortic balloon pump, left ventricular assist devices, or extracorporeal membrane oxygenation) [14] makes the patient at high risk by itself and in some cases even at the temporary restoration of sinus rhythm. In case of hemodynamically tolerated VT, the presence of at least one comorbidity such as left ventricular ejection fraction less than 30 %, serum creatinine level >1.5 mg/dl, chronic occlusion of left anterior descending coronary artery, and severe chronic lung disease makes the patient particularly high risk [13]. All high-risk patients should be admitted to intensive care unit (ICU) and, if necessary, undergo circulatory and/or ventilatory support and/or hemodialysis.

All the efforts should be made to reduce VT/VF episodes to avoid further shocks considering even in combination of a complex strategic approach including antiarrhythmic drug therapy, device reprogramming, deep sedation/mechanical assistance, and catheter ablation.

12.3.1 Antiarrhythmic Drugs

Initial treatment of ES usually involves the use of antiarrhythmic drugs, weighing their proarrhythmic risk and negative inotropic effect, to prevent arrhythmic recurrences.

The cornerstone of antiarrhythmic therapy still remains sympathetic blockade with *beta-blockers* to suppress the adrenergic drive to VT recurrence [15]. Although all beta-blockers are able to reduce susceptibility to VT/VF as class action, most of the studies analyzed *propranolol*. In patients with HF, propranolol resulted to be more effective than *metoprolol* in reducing sympathetic tone due to its capability of blocking both β1 and β2 receptors and to its lipophilic nature that enables penetration within the central nervous system blocking also presynaptic adrenergic receptors [16, 17]. Sympathetic blockade is able not only to suppress ES [18] but also to improve short-term survival more than the combined antiarrhythmic therapy with lidocaine, procainamide, and bretylium [15]. In severely compromised patients, intravenous short-acting drugs like *esmolol* should be preferred [19]. The first-choice antiarrhythmic drug should be *amiodarone*, even in combination with propranolol that effectively controlled ES and improved survival [15, 18]. When amiodarone is administered intravenously, it reduces adrenergic tone, blocks sodium and L-calcium channels without prolonging ventricular refractoriness, and, when administered, orally prolongs ventricular refractory period [20, 21]. When ineffective alone or in combination with beta-blockers, amiodarone may be helpful even in adjunct to other agents [22]. Even patients who previously keep amiodarone may beneficiate from a reloading dose/therapy adjustment if serum levels of amiodarone/desethil-amiodarone are under therapeutic levels. The acute administration is relatively safe even in patients with depressed ejection fraction due to its low inotropic negative effect. It can increase the defibrillation threshold, making potentially ineffective ICD therapy; consequently ICD defibrillation energy should be re-tested or re-evaluated. Long-term amiodarone assumption is burdened by several side effects like thyroid, liver, and lung toxicity, sometimes forcing to therapy discontinuation. In case of amiodarone failure, other additionally drugs may be considered such as procainamide both orally or intravenously. The use of multiple antiarrhythmic drugs makes the drug-to-drug interaction unpredictable, potentially increasing the side effect occurrence. The use of *lidocaine* is limited by its relatively incapacity to terminate scar-related VT [23]. Lidocaine is a sodium rapid channel blocker that binds to channels in a use-dependent way. During ischemic VT, the altered membrane potential as the pH reduction [24] increases the rate of drug binding, making lidocaine effective in terminating arrhythmias. The pharmacodynamic proprieties

make lidocaine not so effective in settings different from ischemic arrhythmias, maintaining a role only for the treatment of polymorphic VT associated with ischemia (IIb recommendation according to the American College of Cardiology/American Heart Association guidelines [25]).

Procainamide (not available in all countries) is another IC class antiarrhythmic drug commonly used as second- or third- line therapy in refractory VTs. Procainamide acts as fast sodium channel blocker, while its active metabolite N-acetylprocainamide blocks potassium channels and accounts for much of the antiarrhythmic effect in vivo as well as side effects like QT interval prolongation. Care must be taken in administering the drug in patients with low ejection fraction due to the high risk of hypotension.

12.3.2 Device Reprogramming

Several studies demonstrated that repeated ICD shocks are associated with increased mortality as well as with a reduction of quality of life [10]. For these reasons optimization of ICD programming in order to avoid unnecessary shock is mandatory in patients experiencing ES. As stated above, arrhythmic detection and treatment by ICD is a step process including several variables such as heart rate threshold, number of intervals to detect, discrimination of SVA, and type and number of therapies released. Each of these steps can be tailored upon patient characteristics to avoid unnecessary treatment.

12.3.2.1 Higher Heart Rate Threshold

Usually patients treated with ICD for primary prevention tend to develop fast VT, while patients treated for secondary prevention usually have slower VT with a wider overlap with SVA [26]. On this basis, the first may benefit from higher rate detection zones, while the latter needs slower rate detection zones and improved SVA discriminating algorithms. Even better, rate detection zones can be tailored upon patient's clinical history when previous arrhythmia episodes occurred. In three trials (PREPARE, MADIT-RIT, and PROVIDE), higher rate detection zones demonstrated reduce ICD shocks without increasing both syncope and death risk.

12.3.2.2 Longer Detection Period

The effect of prolonging arrhythmic detection time is well studied especially in the primary prevention setting with lower data available in the setting of secondary prevention.

The REVELANT study showed that a higher number of intervals for arrhythmic detection (30/40 vs. 12/16) significantly reduced the incidence of ICD intervention without increasing syncope or death in patients with ICD for primary prevention and nonischemic cardiomyopathy. MADIT-RIT trial showed a reduction of both inappropriate therapy and all-cause mortality with a 60-s delay at 170–199 bpm, a

12-s delay at 200–249 bpm, and a 2.5-s delay at ≥250 bpm vs. conventional programming. These results were recently confirmed by ADVANCE III trial [27] in which the combination of a higher number of intervals to detection (30/40 vs. 18/24) with ATP therapy during charge significantly reduced either appropriate or inappropriate therapies regardless of ICD type and indication. Even in the PROVIDE trial, multi-parametric programming including higher detection rate, longer detection intervals, and optimized SVA discriminating algorithms was associated with better overall survival and reduction of ICD shocks without increasing arrhythmic syncope risk, and the PainFree SST trial confirmed that longer detection intervals are safe in terms of risk of syncope. Of all these studies, only ADVANCE III and the PainFree SST included patients with both primary and secondary preventions for ICD, while the remaining trials focused only on patients treated for primary prevention.

12.3.2.3 Improving ATP Programming

ATP therapy demonstrated to be highly effective in terminating VTs, reducing unnecessary shocks and consequently improving survival, quality of life, and generator life. In several studies 85–90 % of "slow" VTs (<188–200 bpm) [28] and 54–72 % of "fast" VTs (188–250 bpm) [29, 27] were terminated by ATP. As stated before, ATP therapy can be administered as *bursts or ramps* on the basis of the pacing cycle length variations. Bursts and ramps proved similar efficacy in treating slower VTs [28], while fast VTs (>200 bpm) were best treated by bursts that also showed a lower risk of arrhythmic acceleration than ramps. Due to less efficacy of ATP in terminating fast VTs (>200 bpm) and the negative hemodynamic consequences of such arrhythmias, usually in the fast VT and VF zone, *ATP is delivered during capacitor charge* to avoid any delay in shock therapy. The majority of VTs were effectively interrupted by one or two ATP attempts with only a minority of patients responsive to more than three attempts [30, 31], and for this reason programming more than three ATP attempts should be discouraged. In CRT-D recipients, biventricular ATP should be preferred to right ventricular ATP due to its higher efficacy and safety [32, 33]. The last key point in ATP programming is burst cycle length that can be empirically programmed at 85–90 % of the arrhythmic cycle length for fast VTs and at 70–80 % for slower ones. When ATP appears ineffective in VT termination, the analysis of the post pacing interval can allow tailoring ATP programming upon patient characteristics, for example, by shortening drive cycle length or by increasing the number of paced beats [34].

Accordingly to all these data, the increase of detection time and threshold rate in patients experiencing ES helps to prevent both inappropriate and unnecessary shocks, making ICD reprogramming a mandatory step in the clinical workup of ES.

In case of inappropriate therapies, specific measures must be taken: e.g., change ICD detection parameters, enhance drug therapy, or consider catheter ablation in case of SVA; temporarily turn off the device before lead replacement in case of lead fracture/failure.

12.3.3 Sedation, General Anesthesia/Mechanical Ventilation, and Mechanical Hemodynamic Support

The sympathetic adrenergic activation in patients experiencing multiple shocks due to ES may perpetuate VT/VF [35] and render the arrhythmias life threatening and refractory to several maneuvers. Therefore, some patients with ES should be sedated or even undergo general anesthesia to reduce sympathetic tone and suppress ventricular electrical instability. *Propofol* has been reported to suppress ES [36, 37], but this beneficial effect may be offset by the inotropic negative effect. In this regard, only few data are available in literature about the effect of deep sedation/general anesthesia on the prognosis of ES patients, and most of them are extrapolated from patients undergoing catheter ablation to treat ES. Drugs inducing general anesthesia should be considered with attention because they can exacerbate hypotension and depress cardiac function [14]. Deep sedation with *remifentanil* even in association with a *benzodiazepine* like midazolam should be preferred as it is able to reduce sympathetic hypertone and provide analgesia avoiding dangerous negative inotropic effects [38–40]. A valuable alternative may be *dexmedetomidine* [41], an α2 presynaptic adrenergic receptor agonist able to markedly reduce sympathetic tone by both enhancing central vagal tone [42] and inhibiting presynaptical adrenaline release [43]. However, it has important side effects like hypotension and bradycardia [44] that should be rigorously monitored during its usage.

General anesthesia and mechanical ventilation should be reserved only to patients with hemodynamically non-tolerated arrhythmias refractory to all therapies. Such patients may benefit from hemodynamic mechanical support like *intra-aortic-balloon pump* (IABP), *left ventricular assistance devices* such as the Impella (Abiomed Inc., Danvers, MA) [45–47], and even *extracorporeal membrane oxygenation* (ECMO) [48, 49]. These devices can not only suppress ischemic VTs by increasing coronary perfusion but can be effective in suppressing ES reducing LV afterload and wall tension [50] as well as prevent multiple organ failure sustaining organ perfusion. Last but not least, they have a key role in mapping and ablating unstable VTs. Some patients experiencing refractory unstable arrhythmias should also be carefully evaluated for urgent check for cardiac transplantation.

12.3.4 Neuraxial Modulation (Thoracic Epidural Anesthesia, Cardiac Sympathetic Denervation)

Given the importance of the autonomic nervous system in triggering and maintaining ventricular arrhythmias, sympathetic neuromodulation through thoracic epidural anesthesia [51], cardiac sympathetic denervation (CSD), and spinal cord stimulation may help in reducing arrhythmic burden in selected patient with ES refractory to multiple antiarrhythmic drugs and catheter ablation. CSD is usually performed via video-assisted thoracic surgery and consists of removal

the lower third of the stellate ganglia (to avoid Claude-Bernard-Horner syndrome) as well as T2–T4 thoracic ganglia. The resection is usually performed on the left side, reserving bilateral CSD for selected cases. The procedure should be performed in referral centers only, due to special anesthesiology skills required such as selective bronchus intubation management. Most of what we know about the results of the procedure results from case reports [52, 51, 53], but in a prospective study of 41 patients with ES refractory to medical therapy and catheter ablation, CDS demonstrated to be effective in prolonging ICD shock-free survival at 1-year follow-up with greater effect of bilateral CDS compared to left CDS only [54].

12.3.5 Catheter Ablation

Currently, radiofrequency catheter (RF) ablation represents the mainstay treatment of recurrent VTs and even of ES. Several studies demonstrated how catheter ablation may prevent VT recurrence as well as improve survival of ES patients with a growing effectiveness due to technological improvement and deeper knowledge of arrhythmogenic substrate [14]. In the past, RF ablation was considered as the last chance treatment in patients refractory to multiple antiarrhythmic drugs, but in the last decade there has been a growing evidence for early referral to RF ablation in case of recurrent ICD therapies or even prophylactically [55–57]. RF ablation showed to be highly effective in suppressing refractory VTs in the acute management of ES, reaching an acute success rate of 80 % in the largest series [40, 12, 58, 59], especially when the end point of non-inducibility of all clinical VTs was reached [12]. As stated before, patients with unstable hemodynamic VTs should be referred for mechanical assistance in order to allow mapping and ablation but also those with apparently stable arrhythmia may develop acute hemodynamic decompensation during RF ablation procedure. In a preliminary study, a simple score named PAINESD taking in account patient's baseline comorbidities (Pulmonary chronic obstructive disease, Age older than 60, Ischemic cardiomyopathy, NYHA class III or IV, Ejection fraction lower than 25 %, Storm at presentation, and Diabetes mellitus) was tested to predict acute decompensation during VT catheter ablation in order to select patients who may benefit prophylactic mechanical support [14] (Fig. 12.1).

12.4 Indication for Follow-Up and Referral

All patients who experienced an ES episode remain at high risk of recurrences even if effectively treated with catheter ablation and multiple antiarrhythmic drug prophylaxis. Often ES is the expression of worsening of the underling heart disease. For these reasons all patients who developed at least one episode of ES

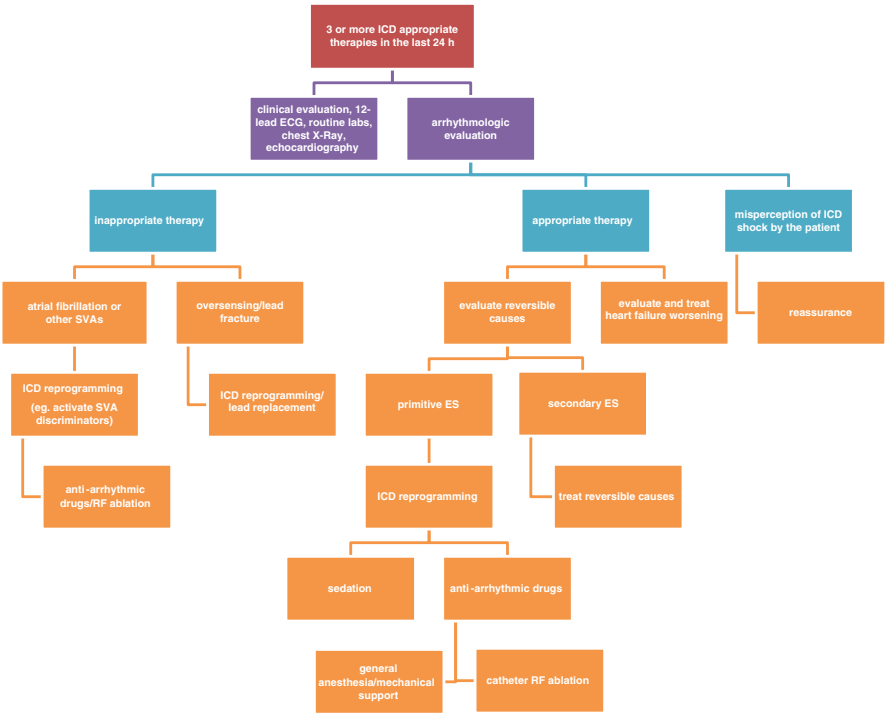

Fig. 12.1 A suggested algorithm/pathway for diagnosis and treatment of ES

should be referred both to a heart failure specialist and proper electrophysiological management in order to optimize the heart failure therapy and evaluate indication to heart transplantation or left ventricular assistance devices both as a bridge to transplant and as destination therapy. Arrhythmic follow-up may be best done with home monitoring of the ICD that allows a prompt evaluation of arrhythmic events.

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Emergency Surgery and Cardiac Devices

13

Massimo Zecchin, Luigi Rivetti, Gianfranco Sinagra, Marco Merlo, and Aneta Aleksova

13.1 Focusing on the Issue

The number of patients with CIED (Cardiac Implantable Electric Devices) who need emergency surgery has been increasing in the last decades, considering the spread of ICD (Implantable Cardiovetrer-Defibrillator) and CRT (Cardiac Resynchronization Therapy) implantations for sudden death prevention and heart failure treatment.

It is estimated that about three million patients worldwide have a pacemaker (PM) and about 500,000 patients have an ICD [1]. According to EUCOMED data, in Europe nearly 1000 PM and 170 ICD new implantations were performed every million inhabitants in 2012. Although the implant rate of PMs has not significantly changed, there has been an increase of ICD and CRT implantations in the last decade, after the publication of several trials proving their efficacy. Despite some regional differences, this trend can be observed in most western countries.

In case of urgent surgical intervention, patients with CIED (especially ICD) can be considered at high risk for many reasons, mostly due to the underlying cardiac disease, hemodynamic impairment/left ventricular dysfunction (in particular those with ICDs), and the advanced age (in particular those with PMs) [2].

In addition, during surgical interventions, transient or even permanent malfunctions of the device, because of electromagnetic interferences or mechanical damages, are possible [3].

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M. Zecchin, G. Sinagra (eds.), *The Arrhythmic Patient in the Emergency Department: A Practical Guide for Cardiologists and Emergency Physicians*,
DOI 10.1007/978-3-319-24328-3_13

Electromagnetic fields can potentially cause several malfunctions: damage to the CIED circuitry, pacemaker inhibition, noise tracking, asynchronous pacing, communication failure, etc. [4].

An electromagnetic field is characterized by a wavelength, a frequency, and a field strength. The range of frequency emitted by sources such as magnetic resonance imaging (MRI) and electrosurgery is between 0 Hz and 450 MHz. The electric field strength is measured in volts per meter, while the magnetic field intensity components of electromagnetic fields are measured in amperes per meter. Electromagnetic field energy decreases as an inverse squared function of distance from the source, so the risk of exposure is fourfold lower just doubling the distance from the source.

Even static magnetic fields can be a possible cause of CIED malfunction; sterile magnetic drapes, frequently used during surgery to hold metal instruments, can potentially interfere with the function of PM and ICDs if positioned at a distance less than 15 cm [5].

Electrocautery is associated with tissue heating. However, conductive devices and leads, particularly when placed in a loop configuration, can increase the risk of burns due to the inductive heating of the lead conductor from radiofrequency fields.

In recent years, a great effort to minimize CIED has been performed. Generators are shielded by hermetically sealed titanium or stainless steel cases. The extent of shielding varies depending on the manufacturer, weight of the device, and dimensions and usually rejects electric fields >2 MHz.

EMI are also reduced by the use of bipolar sensing and low-pass filters. However, frequencies between 0 and 60 Hz overlaps the cardiac signal range so a "noise reversion feature" is activated when signals are detected in the noise-sampling period of the atrial and ventricular refractory periods, programming the device in asynchronous pacing.

Additionally, lead design was modified to improve shielding from radiofrequency and time-varying gradient magnetic fields.

13.2 What Physicians Working in ED, Anesthesiologists, and Surgeons Should Know

The PM is a pulse generator, generally placed in the left (less frequently right) subclavian region, usually subcutaneously or under the pectoral muscle. It is connected with the heart across the cephalic, axillary, or subclavian vein by one or two leads reaching the right ventricle, the right atrium, or both; in patients with cardiac resynchronization therapy (CRT), another lead is positioned in a branch of the coronary sinus for left ventricular pacing. Depending on the needs of an individual patient and model of the PM, programming and pacing function will differ from one device to another.

The ICDs differ from PMs for their antitachycardia properties, as they can recognize and automatically interrupt (by overdrive pacing or high-voltage DC shock) potentially fatal arrhythmias, as sustained ventricular tachycardias or ventricular fibrillation, the leading causes of sudden death. In patients with left ventricular dysfunction of any origin, as well as in those with other cardiac conditions at high risk of sudden death, treatment with ICD is associated with an improved survival even in

Table 13.1 NASPE code for pacing modalities

I	II	III	IV	V
Chamber (s) paced	Chamber (s) sensed	Response to sensing	Rate modulation	Multisite pacing
O → none A → atrium V → ventricle D → dual (A + V)	O → none A → atrium V → ventricle D → dual (A + V)	O → none T → triggered I → inhibited D → dual (A + V)	O → none R → rate modulation	O → none A → atrium V → ventricle D → dual (A + V)
S → single (A or V)	S → single (A or V)			

the absence of previous history of ventricular arrhythmias. With the exception of some newly released entirely subcutaneous ICD, without intravascular leads (s-ICD), all ICDs have PM properties. In addition, it is possible to program the minimum rate and duration of arrhythmias required to be recognized and treated, to avoid unnecessary therapies in the case of slow and/or brief self-terminating tachycardias.

13.2.1 PM Programming Modes

Pacing modalities are expressed according to the North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group (NASPE/BPEG) revised code (see Table 13.1) [6]. The first letter indicates the chamber in which pacing occurs, while the second indicates the chamber with sensing capabilities. The third letter indicates the effect of sensing on the triggering or inhibition of subsequent pacing stimuli. The fourth and the fifth letter, not always used in clinical practice, respectively indicate the presence (R) or absence (O) of an adaptive-rate mechanism and whether multisite pacing (as in CRT) is present.

13.2.2 Unipolar Versus Bipolar Leads

Artifacts during electrocauterization can be erroneously considered by the CIED as spontaneous fast electrical activity of the heart (oversensing) [7]. Nearly all leads implanted in the last decade are bipolar, meaning that both the cathode and the anode are on the tip of the catheter, reducing the inter-electrode distance and the likelihood of external interferences. However, in some patients, especially with less recent implantations, unipolar leads can still be present. In these patients, the risk of oversensing is particularly high, as the sensed field is included between the tip of the lead (functioning as a cathode) and the generator (anode).

13.2.3 Unipolar Versus Bipolar Electrocautery

Electrosurgery current usually occurs in the frequency range between 100 and 5000 kHz and is typically delivered in a unipolar configuration between the

cauterizing instrument and ground electrode. Bipolar electrosurgery involves the use of an electrical forceps where each limb is an electrode; it is used far less commonly because it is useful only for coagulation and not dissection. Bipolar systems deliver the current between two electrodes at the tip of the instrument, reducing the likelihood for EMI with CIEDs. Therefore, malfunctions are associated with unipolar electrocautery only, while bipolar electrosurgery does not cause EMI when not directly applied to CIED.

EMI usually occur when electrosurgery is performed within 8–15 cm from the device. Electrosurgery below the umbilicus with the grounding pad placed on the thigh is therefore unlikely to result in EMI with thoracic CIEDs.

EMI are more likely with the cutting mode rather than with the coagulation mode of surgical electrocautery, probably because of the higher power and the longer period of time applied for tissue cutting than coagulating a bleeding vessel.

The use of a harmonic scalpel, an ultrasonic cutting and coagulating instrument, can avoid surgical diathermy, according to some data [8].

13.2.4 Effects of EMI on CIED: General Considerations

Depending on the type of devices and lead, the programming of the devices and the type of surgery, different malfunctions can be found.

The possible effects of EMI can be transient (due to oversensing) or permanent (initiation of noise reversion, electrical reset mode, or increase of pacing thresholds).

Permanent damages are extremely rare, unless the energy is applied directly to the pulse generator or system electrode. There are some old reports of various serious effects, such as failure to pace, system malfunction, and even inappropriate life-threatening uncontrolled pacing activity [3]. However, because of the advances in lead and generator technology, most recent reports suggest that nowadays these effects infrequently occur.

13.2.4.1 Reset

Resetting of PMs has been reported in presence of energy coursing through the pulse generator (i.e., when the electrocautery touches, or is very close to, the generator) and simulates the initial connection of the power source at the time of manufacture. During reset, pacing parameters are automatically programmed in VVI mode with a lower rate from 60 to 70/min (depending on the manufacturer) and high output energy. For ICD, beside a VVI 60–70/min pacing mode, a fixed antitachycardia therapy (with lower rate cutoff ranging from 146 to 190/min according to the manufacturer) is programmed.

13.2.4.2 Generator Damages

The application of electrosurgery either in immediate close proximity or directly to the pulse generator can cause failure or permanent damage to a CIED, especially to older pacemakers (with voltage-controlled oscillators, no longer manufactured).

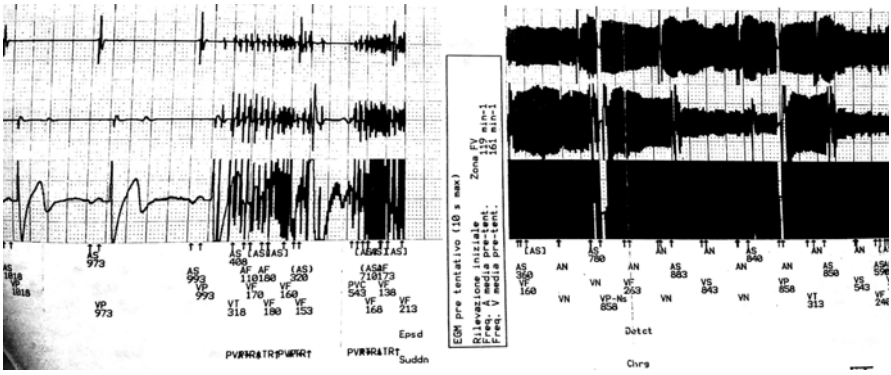

Fig. 13.1 Ventricular oversensing during thoracic surgery leading to ICD charge

ICDs may be more resistant, but energy can still enter the pulse generator in presence of breaches of lead insulation.

13.2.4.3 Lead-Tissue Interface Damage

Damage to the lead-myocardial interface is unlikely to occur with modern devices, but monopolar electrosurgery pathways crossing a pulse generator can produce enough voltage to create a unipolar current from the pulse generator case to a pacing electrode in contact with myocardium. This can result in a localized tissue damage with an increase in pacing threshold and possible loss of capture [9].

13.2.4.4 Oversensing

The most frequent CIED interaction with EMI is oversensing, leading inappropriate inhibition of pacing output and false detection of a tachyarrhythmia, with possible inappropriate CIED therapy (Fig. 13.1).

Electrosurgery applied below the umbilicus is much less likely to cause PM or ICD interference than when applied above the umbilicus. However, endoscopic gastrointestinal procedures that use electrosurgery may result in interference (Fig. 13.2). In a recent analysis on 71 subjects with ICD, EMI were recorded in 50 % of thoracic and head or neck procedures, 22 % of upper extremity procedures, 7 % of abdominal/pelvic procedures (laparoscopic cholecystectomies only), and 0 % of lower extremity procedures. No EMI in any lower abdominal procedures were recorded [10].

13.2.4.5 Pacemaker Response to EMI

When programmed in inhibited pacing modes (AAI, VVI, or DDI), pacing inhibition can occur in presence of EMI, with consequent bradycardia or asystole in PM-dependent patients. When programmed in tracking mode (DDD), sensing of EMI in the atrial channel (more likely to occur, because of the higher sensitivity necessary to detect atrial signals) could result in increased rate of ventricular pacing or false atrial arrhythmia detection and consequent "mode-switch" to inhibited pacing modes (VDI, VVI, or DDI).

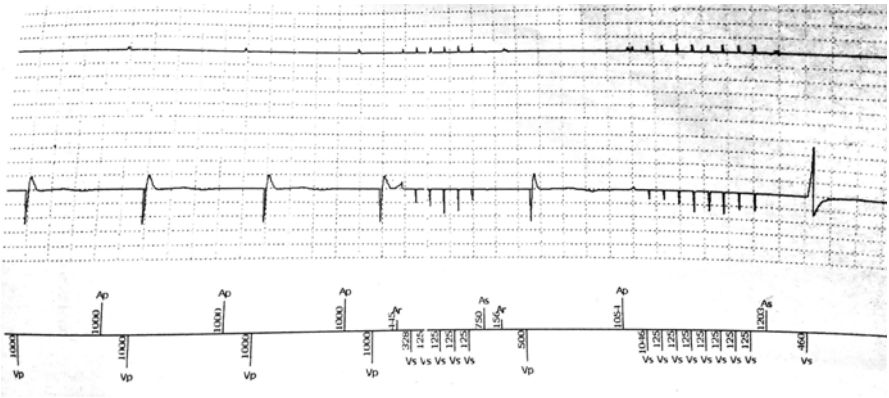

Fig. 13.2 EMI during polypectomy

For a patient with spontaneous underlying rhythm, pacing inhibition does not have any consequences, while in PM-dependent patients, a prolonged (>4–5 s) pacing inhibition can result in significant hemodynamic compromise. Therefore, *limiting electrosurgery usage to shorter bursts* is desirable and may be a safer approach than either reprogramming the CIED or placement of a magnet over the pulse generator [3].

In patients with cardiac resynchronization therapy (CRT), ventricular stimulation is, or should be, always present at surface ECG; however, these patients are not usually pacemaker dependent, so will not experience hemodynamic difficulties if biventricular pacing is transiently interrupted, with the exception of patients with advanced spontaneous AV block and those treated with AV node ablation ("ablate and pace").

13.2.4.6 ICD Response to EMI

The ICDs require a certain duration (several seconds) of continuous high-rate sensing to satisfy arrhythmia detection criteria and consequently start the treatment (antitachycardia pacing or DC shock). Therefore, short bursts (<5 s) of electrosurgery alternating with pauses lasting some seconds are unlikely to result in false tachyarrhythmia detection and inappropriate antitachycardia therapies.

Inappropriate ICD shocks, although painful in nonsedated patients, should not be necessarily considered a serious danger for both the patient (apart from skeletal muscle contraction even if the patient is paralyzed by curare) and the people surrounding, who will not experience any shock. There is, however, a rare but possible proarrhythmic effect of DC shocks, which can initiate ventricular fibrillation.

13.2.5 Effects of the Magnet

A simple magnet (typically 90 G) should always be present in the operating room when a patient with a CIED undergoes a procedure potentially causing EMI. However, the effect of the magnet positioned on the skin just above the device (Fig. 13.3) differs between pacemakers and ICDs.

Fig. 13.3 A magnet placed on the CIED pocket

13.2.5.1 Pacemakers

When a magnet is applied on a pacemaker, it usually causes "asynchronous pacing" (generally VOO or DOO), meaning that pacing at a fixed rate is provided, independently from any sensed activity, ensuring cardiac stimulation (or avoiding inappropriate triggered activity) even in the presence of persistent artifacts. The pacing rate in the presence of a magnet is CIED characteristic and varies according to the battery charge.

If spontaneous ventricular activity is adequate, asynchronous pacing (provided by the magnet or by CIED reprogramming) can be unnecessary or even inappropriate and potentially dangerous, as the magnet rate may compete with the patient's rate; however, the risk that asynchronous pacing in patients with intrinsic rhythm can potentially induce atrial or ventricular arrhythmias, although widely feared, is very low [11].

13.2.5.2 Implantable Defibrillators

In ICDs, arrhythmias detection or tachycardia therapy can be disabled by magnet application and is automatically re-enabled when the magnetic field is removed. In some elderly Boston Scientific (former Guidant) ICDs, antitachycardia therapy may be permanently, and not transiently, deactivated by magnet application, necessitating reprogramming of the device or magnet repositioning to restore prior function. For this reason, and because it is possible to turn off magnet response in some devices, careful monitoring is required during the procedure to determine the effects of cauterization.

If inappropriate antitachycardia therapies (shock or antitachycardia pacing) should be delivered despite the magnet, shorter bursts (<5 s) with pauses between bursts, or bipolar cautery, are mandatory. On the other side, when true sustained

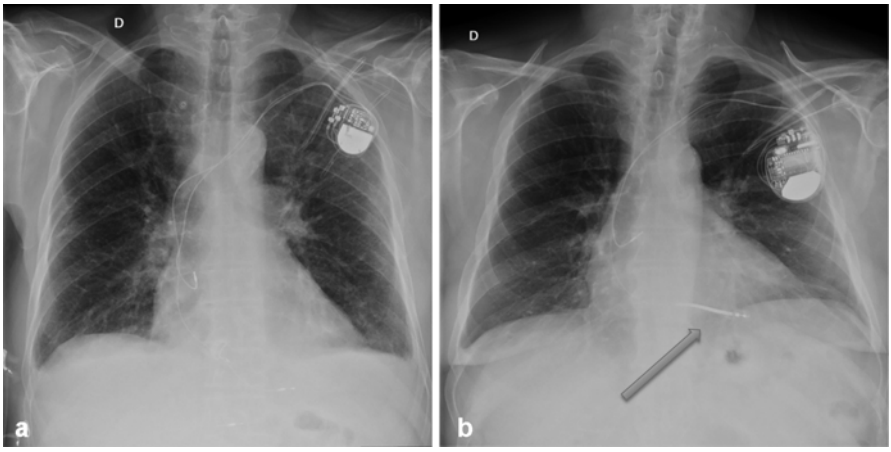

Fig. 13.4 Posterior anterior thoracic X-ray in a patient with a pacemaker (**a**) and an ICD (**b**). The shocking coil along the right ventricular lead in the ICD patient is indicated by the *arrow*

ventricular arrhythmias occur, appropriate antitachycardia therapies can be delivered by the device by just removing the magnet or by using an external defibrillator. In this case, external pads should be placed in the anteroposterior rather than anterolateral position, ensuring the anterior (apical) pad is at least 5 cm away from the device.

Differently from PM, the *magnet does not affect ICD antibradycardia pacing functions*. As a consequence, *in PM-dependent patients with ICD, reprogramming is more desirable* to avoid pacing inhibition when EMI are expected to be significant.

13.2.6 How to Recognize that a Patient Has a CIED and if Is PM Dependent

When data from medical history or files are not available, a CIED can be easily recognized by the presence of the wound in the infraclavicular region, more frequently on the left side. In less skinny patients, some devices, as some recent PMs, cannot be always detected because of the small dimensions and the position, sometimes several centimeters away from the original site under the wound.

All patients should always carry a device identification card, necessary to understand the type (PM, ICD, or CRT) and devices' manufacturer; these information are particularly important, as every device can be interrogated by the programmer from its manufacturer only. In emergency situations, chest radiograph is useful to distinguish a PM from an ICD, as the latter presents a shocking coil (section of the lead which are wider and more radiodense) along the right ventricular lead, close to the tip (Fig. 13.4). Sometimes another coil is present along the same lead, more proximally, in the superior vena cava. In addition, chest X-ray often allows the recognition of the model and even the device's serial number.

A patient with spontaneous activity is not, by definition, PM dependent. Even if the risk of bradyarrhythmias can be present, the occurrence of pauses contemporary to the inhibition of pacing during EMI is very unlikely. Therefore, PM reprogramming or magnet positioning is usually unnecessary in these patients, when the CIED is not an ICD.

When feasible, in paced patients, the PM dependence should be evaluated by the cardiologist during a preoperative PM evaluation, reprogramming the device at a low (usually 30 or 40/min) rate to detect spontaneous activity. This is particularly important in patients with CRT, where 100 % biventricular pacing is usually present, even in the absence of bradyarrhythmias. When interrogation cannot be performed before the operation, all patents with constant paced rhythm should be considered as PM dependent.

Routine PM check is usually performed every 6–12 months (3–6 for ICD). Therefore, most patients should have been evaluated in the past year; in addition, an increasing number of devices are regularly followed by "remote monitoring": using a base unit (similar to a modem), connected to the internet (via a standard phone line connection or a cell phone communication technology) and communicating wirelessly with the CIED, most information available during routing ambulatory evaluation are transmitted to designed servers and can be viewed by authorized personnel whenever desired. Data are automatically sent according to fixed intervals, in the presence of significant events (as arrhythmias or malfunctioning) or manually by the patient. Current systems, however, do not permit remote device reprogramming.

13.2.7 How to Minimize the Risk

The risk of EMI is greatest when the current field crosses the CIED or the leads or is closer than 15 cm from the CIED. During electrosurgical application, the return electrode should be placed on the ipsilateral heel or flank; however, for operations involving the ipsilateral arm of the CIED, the return electrode should be placed on the same arm to avoid the full exposure to the electrosurgical energy.

The umbilicus can be not a precise anatomical landmark especially in obese patients and many abdominal laparoscopic surgical procedures go through the umbilicus. Therefore, *iliac crest as the landmark below which no magnet or reprogramming need to be performed should be recommended. Utilization of the magnet, rather than turning off the ICDs, significantly reduces the time of exposure to the risk of untreated life-threatening arrhythmias* [10].

In addition, there is a potential risk of not re-enabling tachycardia therapies after the surgical intervention, leaving the patient unprotected in the case of ventricular arrhythmias, as demonstrated by a report on 67,410 remote follow-up patients in which the most common "red alert" was that detections and therapies for ventricular fibrillaton were "off".

Equipment for urgent cardioversion, defibrillation, and emergent pacing should be immediately available. It is important to remember, however, that artifacts can be also present at surface ECG, and arrhythmias can be difficult to detect by

electrocardiographic monitoring during electrosurgical application. Therefore, cardiac activity should be monitored with other modalities, like invasive or noninvasive continuous arterial pressure monitoring or pulse oxymeter.

Therefore, *application of short burst of electrocautery (<5 s), with some seconds of pause, is the best mode to minimize the risk* of both significant bradyarryhythmias in PM-dependent patients and inappropriate antitachycardia therapy in patients with an ICD.

13.3 What the Cardiologist Should Know

When an urgent or emergent surgical intervention is needed, a cardiologist may not be immediately available, and not all cardiologists are practical with CIED programming. However, whenever possible, the cardiologist or, better, an electrophysiologist should be involved in the management of the patient, especially in case of thorax, head, or upper limbs surgery.

Clearly, the cardiologist should be aware of the patient's cardiac problems, including the reason for CIED implantation, whether the patient is PM dependent, and the model, the manufacturer, and the programming of the CIED, as responses to EMI and to magnet application vary among different CIED and according to the programming. For example, in impedance-based rate responsive systems (as in minute-ventilate sensors), EMI may result in pacing at the sensor-triggered upper rate limit if rate response is activated.

In the presence of significant EMI, a "noise reversion" may occur, during which time the CIED paces asynchronously and tachyarrhythmia therapy is suspended. Noise reversion mode is an algorithm designed to minimize the effects of EMI, and, differently from reset, it is automatically disabled once the noise is no longer present. However, noise reversion algorithms are manufacturer specific and can be useful mainly in the presence of persistent EMI; they may not provide an adequate protection in presence of sporadic and/or transient EMI, as encountered in the operating room; therefore, transient inhibition of pacing or inappropriate pacing at the programmed upper rate is more likely in this context.

13.3.1 Magnet Responses

Magnet responses vary according to different manufacturers, and different models continuously change as manufacturers release new devices. In addition, pacing rate is different at beginning of life (BOL) and at elective replace indicator (ERI).

13.3.2 Pacemakers

In PM, the magnet generally causes asynchronous pacing by closing a magnetic switch.

At BOL, VOO or DOO pacing rate vary from 85/min (Medtronic) to 100/min (Boston Scientific and S. Jude. At ERI, it decreases to lower values (Medtronic 65/min, Sorin and Biotronik 80/min, S. Jude 85–86.3/min). Other different responses can be found when magnet response is programmable (Biotronik, Boston, S. Jude).

In some devices with atrial antitachycardia therapies (Medtronic AT500), antitachycardia pacing only is suspended, but there is no conversion to an asynchronous pacing mode.

Rate response is always suspended.

In some devices (Biotronik, Boston Scientific and Medtronic), pacing amplitude remains unchanged as programmed, while if autocapture algorithm is operating, the output is usually reset above the autocapture threshold value.

13.3.3 ICD

In all ICDs, antitachy-therapy is suspended while PM functions are usually unchanged; only in Sorin devices pacing rate changes (96/min at and 80/min at ERI), continuing in demand mode (therefore, not switching in asynchronous pacing).

In some models (Boston and S. Jude), it is possible to disable magnet response to ICD.

When placing the magnet on the device, tones can be audible in some models (R wave-synchronized beep in Boston devices, steady tone in Medronic devices). However, if the device continues to emit a tone after magnet removal, it should be interrogated because of a possible fault.

13.4 A Suggested Algorithm/Pathway for Diagnosis and Treatment

13.4.1 Preoperative/Preanesthesia Assessment

In urgent/emergent setting, a preoperative assessment, as required in elective procedures, may be difficult to achieve. However, information available in the patient's records should be sufficient to generate most perioperative prescriptions, as most patients are regularly followed by ambulatory or remote evaluations.

If such evaluation has not been performed in the appropriate time frame (12 months for PM, 6 months for ICD/CRT), a consultation with an available CIED team is desirable prior to the procedure, when feasible.

13.4.2 Before Surgery

See Table 13.2

13.4.3 During Surgery

See Table 13.3

Table 13.2 Before Surgery

	What to do	How to do
All patients	Identify CIED patient	Check medical records, physical examination
	Identify the device (PM, ICD, CRT), manufacturer, and model (always)	Check medical records, patient card, or chest X-ray
	Verify CIED indications (whenever possible)	Check medical records or patient card
	Verify PM dependency (whenever possible)	Preoperatory ECG; in absence of evident spontaneous activity at surface ECG, check medical records or assume PM dependency when preoperatory interrogation and programming is not feasible
Patients with pacemaker		
PM-dependent patients *and* procedures *above* the umbilicus or iliac crest, unipolar cautery necessary	Verify underlying rhythm and spontaneous heart rate (whenever possible)	Preoperatory interrogation and transient programming at the lower rate (if not recently performed during PM routine evaluation)
	Heart rate monitoring (always)	Monitor patient with plethysmography or arterial line rather than ECG only
	Verify response to magnet placement (always)	Verify heart rate during magnet placement
	Alternative stimulation mode available (whenever possible)	Transcutaneous pacing available
Patients with ICD		
All procedures	Heart rate monitoring (always)	Monitor patient with pulse oxymeter or arterial line rather than ECG only
Procedures *under* the umbilicus or iliac crest; bipolar cautery	No reprogramming required	
Procedures *above* the umbilicus or iliac crest, unipolar cautery necessary		
Magnet available and device accessible during the operation (non PM-dependent patients)	Disable antitachycardia therapies (always)	Position a magnet over the device
Magnet unavailable/device *not accessible* during the operation (but CIED personnel readily available)	Disable antitachycardia therapies (always)	Disable tachyarrhythmia therapies by programming and *ensure postoperative reprogramming*

(continued)

Table 13.2 (continued)

	What to do	How to do
PM-dependent patients (and CIED personnel readily available)	Ensure adequate heart rate	Preoperatory reprogramming in asynchronous mode (VOO or DOO) at appropriate rate and *ensure postoperative reprogramming*
PM-dependent patients; magnet unavailable/device *not accessible* during the operation; *no CIED personnel readily available*	Extreme attention to minimize EMI during electrocautery (always)	Electrosurgical return electrode placed on the ipsilateral heel or flank (or the same arm for operations involving the ipsilateral arm)

Table 13.3 During Surgery

	What to do	How to do
All procedures	Heart rate monitoring (always)	Monitor patient with pulse oxymeter or arterial line rather than ECG only
	Avoid magnetic fields (if possible)	Position sterile magnetic drapes >15 cm far from the CIED
Procedures *under* the umbilicus or iliac crest or bipolar cautery	No reprogramming required	
Procedures *above* the umbilicus or iliac crest, unipolar cautery necessary		
All patients, but particularly PM-dependent ICD patients (even with the magnet applied) ICD patients, no magnet applied PM-dependent PM patients, no magnet applied (*and* CIED personnel not readily available)	Minimize EMI during electrocautery (always)	Short electrosurgical bursts (<5 consecutive sec) with pauses >5 s
PM-dependent PM patients (magnet applied)	Verify response to magnet (always)	Verify heart rate during cauterization (with and without magnet placement)
ICD patients (therapies disabled by the magnet)	Ensure proper treatment in the case of intra-procedure ventricular arrhythmias (always)	Remove the magnet to enable tachycardia therapies
ICD patients (therapies disabled by reprogramming)		External DC shock

13.4.4 After Surgery

After surgery, CIED personnel should be contacted as soon as possible when:

- Reset of the CIED occurred during surgery.
- Reprogramming (asynchronous pacing in PM-dependent patients, disabling of antitachycardia therapy in ICD patients) before surgery was performed.
- Significant brady- or tachyarrhythmias occurred during the operation.

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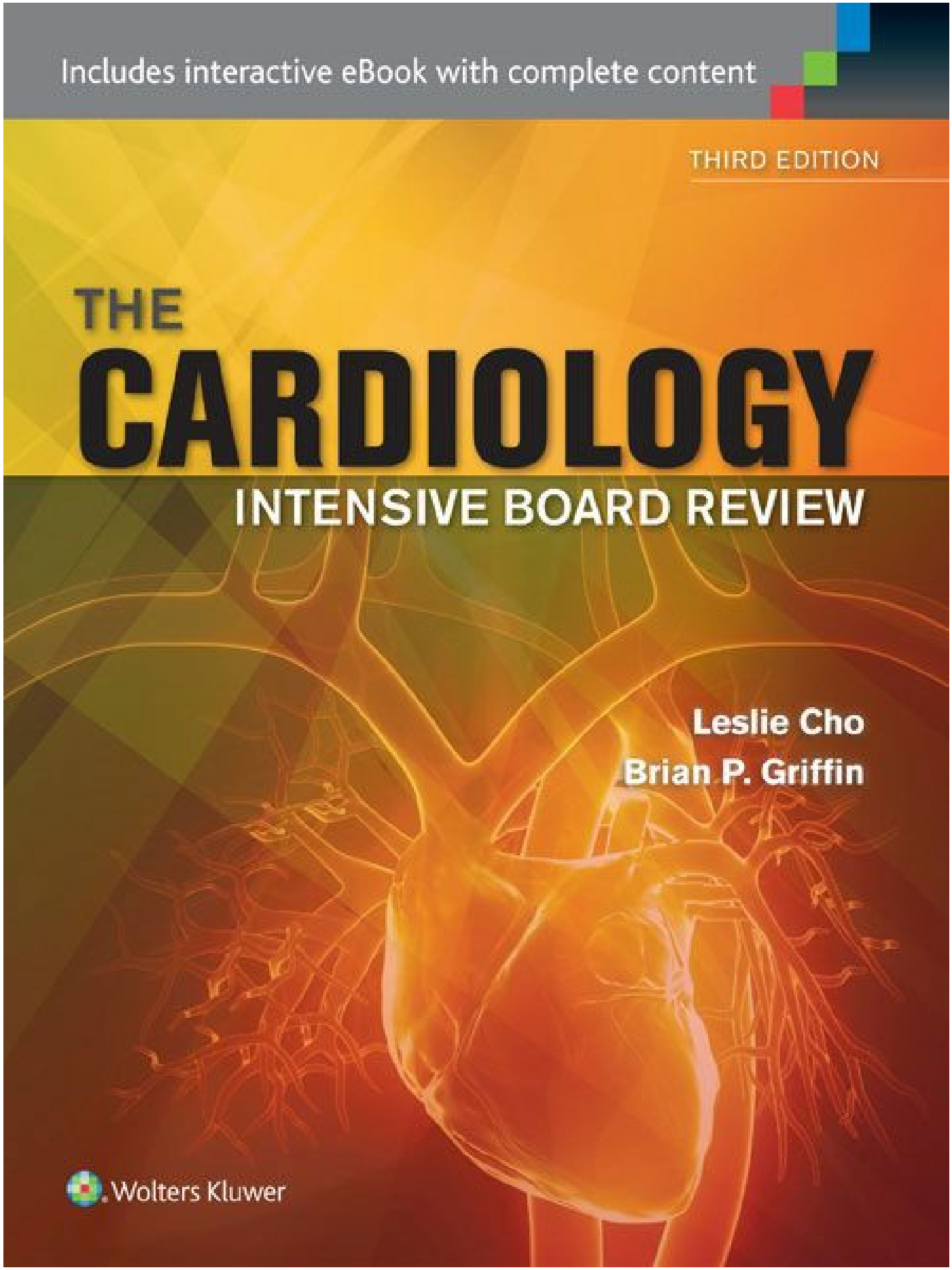
THIRD EDITION

THE CARDIOLOGY INTENSIVE BOARD REVIEW

Leslie Cho
Brian P. Griffin



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The Cardiology Intensive Board Review

Third Edition

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Third edition

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9 8 7 6 5 4 3 2 1

Printed in China

Library of Congress Cataloging-in-Publication Data

Cardiology intensive board review question book.
The cardiology intensive board review / editors, Leslie Cho, Brian P. Griffin.--3rd edition.
p. ; cm.
Preceded by: Cardiology intensive board review question book / edited by Leslie Cho, Brian P. Griffin, Eric J. Topol. 2nd ed. c2009.
Includes bibliographical references and index.
ISBN 978-1-4511-7671-1
I. Cho, Leslie, editor. II. Griffin, Brian P., 1956-, editor. III. Title.
[DNLM: 1. Cardiovascular Diseases--Examination Questions. 2. Cardiovascular Diseases--drug therapy--Examination Questions. 3. Heart--physiology--Examination Questions. WG 18.2]
RC669.2
616.1'20076--dc23
2014031891

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To our families and to the cardiovascular disease fellows past, present, and future

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Preface

The third edition of this book has been updated to reflect changes in guidelines and practice since the last edition. The aim of the book remains the same: to help those certifying or recertifying prepare for the cardiovascular board examination. As in prior editions, we have included subjects, images, and tracings that are important not only for examinations but also relevant to clinical practice. The questions are presented in formats that are commonly used on the boards.

We would like to thank all of the contributors to this and prior editions, our colleagues and fellows from whom we learn on a daily basis, and especially our families who support and encourage our academic activity in addition to our busy clinical practices. We hope you enjoy the book and find it helpful.

Leslie Cho, MD
Brian P. Griffin, MD

Abbreviations

AAA	abdominal aortic aneurysm
ABI	ankle brachial index
ACC	American College of Cardiology
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ACS	acute coronary syndrome
ACTH	adrenocorticotropic hormone
AED	automated external defibrillator
AFib	atrial fibrillation
AHA	American Heart Association
AI	aortic insufficiency
AMI	acute myocardial infarction
AP	action potential
aPTT	activated partial thromboplastin time
AR	aortic regurgitation
ARB	angiotensin receptor blocker
AS	aortic stenosis
ASA	atrial septal aneurysm
ASD	atrial septal defect
AV	atrioventricular
AVNRT	atrioventricular nodal reentrant tachycardia
AVR	aortic valve replacement
AVRT	orthodromic atrioventricular reentrant tachycardia
β-AR	beta-adrenoreceptor
bFGF	basic fibroblast growth factor
BMI	body mass index
BNP	brain natriuretic peptide
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CABG	coronary artery bypass grafting
CAD	coronary artery disease
cAMP	cyclic adenosine monophosphate
CBC	complete blood count
cDNA	complementary DNA
CHB	complete heart block

CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CK-MB	MB fraction of creatine kinase
CPK	creatine phosphokinase
CRP	C-reactive protein
CS	coronary stenting
CT	computed tomography
CTA	computed tomographic angiography
CTEPH	chronic thromboembolic pulmonary hypertension
CXR	chest X-ray
DC	direct current
DTI	direct thrombin inhibitor
DVT	deep venous thrombosis
ECG	electrocardiogram
EF	ejection fraction
EGD	esophagogastroduodenoscopy
EMD	electromechanical dissociation
EMS	emergency medical service
EP	electrophysiology
ESR	erythrocyte sedimentation rate
ET	exercise training
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in the first second of expiration
GI	gastrointestinal
GP	glycoprotein
GU	genitourinary
HBE	His bundle electrogram
HF	heart failure
HIT	heparin-induced thrombocytopenia
HR	heart rate
HRA	high right atrium
HRR	hazard rate ratio
HTN	hypertension
IABP	intraaortic balloon pump
ICD	implantable cardioverter–defibrillator
IgE	immunoglobulin E
IgG	immunoglobulin G
INR	international normalized ratio
IQR	interquartile range
IRBBB	incomplete right bundle branch block
ISA	intrinsic sympathomimetic activity

ISR	in-stent restenosis
IV	intravenous(-ly)
IVC	inferior vena cava
JNC	Joint National Committee
JVP	jugular venous pulse
LA	left atrium(-al)
LAD	left anterior descending artery
LBBB	left bundle branch block
LCC	left coronary cusp
LCx	left circumflex artery
LDL	low-density lipoprotein
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
LV	left ventricle(-ular)
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
LVOT	left ventricular outflow tract
MAT	multifocal atrial tachycardia
MET	metabolic equivalents
MI	myocardial infarction
MR	mitral regurgitation
MRA	magnetic resonance angiography
MRI	magnetic resonance image(-ing)
MS	mitral stenosis
MTHFR	methylenetetrahydrofolate reductase
MV	mitral valve
MVP	mitral valve prolapse
NCC	noncoronary cusp
NSAID	nonsteroidal anti-inflammatory drug
NSR	normal sinus rhythm
NTG	nitroglycerin
OR	odds ratio
P	pulse
PA	pulmonary artery
PAD	peripheral arterial disease
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PDA	patent ductus arteriosus
PE	pulmonary embolus
PEA	pulseless electrical activity
PET	positron emission tomography
PFO	patent foramen ovale

PJRT	permanent junctional reciprocating tachycardia
PMI	point of maximum impulse
PO	oral(-ly)
PT	prothrombin time
PTCA	percutaneous transluminal coronary angioplasty
PVARP	post-ventricular atrial refractory period
PVC	premature ventricular contraction
QOL	quality of life
RA	right atrium(-al)
RAO	right anterior oblique
RAS	renal artery stenosis
RBBB	right bundle branch block
RCA	right coronary artery
RCC	right coronary cusp
RR	risk ratio
RT-PCR	reverse transcriptase-polymerase chain reaction
RUSB	right upper sternal border
RV	right ventricle(-ular)
RVH	right ventricular hypertrophy
RVSP	right ventricular systolic pressure
SAM	systolic anterior motion
SBE	subacute bacterial endocarditis
SC	subcutaneous(-ly)
SERCA2	sarcoplasmic-endoplasmic reticulum calcium ATPase type 2
SL	sublingual(-ly)
SSS	sick sinus syndrome
STEMI	ST-segment elevation myocardial infarction
SVR	systemic vascular resistance
SVT	supraventricular tachycardia
TAO	thromboangiitis obliterans
TdP	torsades de pointes
TEE	transesophageal echocardiography
TIA	transient ischemic attack
TID	transient ischemic dilation
TIMI	thrombolysis in myocardial infarction
tPA	tissue plasminogen activator
TR	tricuspid regurgitation
TTE	transthoracic echocardiogram
TVR	target vessel revascularization
UA	unstable angina
UA/	unstable angina and non–ST-segment elevation NSTEMI myocardial infarction
UFH	unfractionated heparin

VF	ventricular fibrillation
VSD	ventricular septal defect
VT	ventricular tachycardia
VTE	venous thromboembolism
VTI	velocity time integral

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chapter 1

tahir99

Arrhythmia

Bryan J. Baranowski

QUESTIONS

1. Which of the following antiarrhythmic medications would be the best choice for treatment of a patient with atrial fibrillation (AFib) and significant renal insufficiency?

   a. Propafenone
   b. Sotalol
   c. Dofetilide
   d. Flecainide

2. Which of the following antiarrhythmic medications has active metabolites?

   a. Amiodarone
   b. Sotalol
   c. Dofetilide
   d. Flecainide

3. A patient arrives at the emergency department with symptomatic narrow complex tachycardia. The patient is hemodynamically stable. The decision is made to administer intravenous (IV) adenosine. Under which of the following circumstances should the dosage of adenosine be reduced?

   a. The patient is taking theophylline.
   b. The patient is taking dipyridamole.
   c. The patient has significant valvular regurgitation.
   d. The patient has a significant left-to-right shunt.

4. Which of the following medications is contraindicated for use with dofetilide?

a. Digoxin
b. Diltiazem
c. Verapamil
d. Propranolol

5. Which of the following antiarrhythmic drugs may be more likely to have proarrhythmia at increased heart rates?

a. Sotalol
b. Flecainide
c. Quinidine
d. Dofetilide

6. Which of the following statements i s true regarding antiarrhythmic drugs with reverse-use dependence?

a. Antiarrhythmic drugs with reverse-use dependence have greater efficacy for arrhythmia prevention than termination and have less risk for ventricular proarrhythmia at slower heart rates.
b. Antiarrhythmic drugs with reverse-use dependence have less efficacy for arrhythmia prevention than termination and have greater risk for ventricular proarrhythmia at slower heart rates.
c. Antiarrhythmic drugs with reverse-use dependence have greater efficacy for arrhythmia prevention than termination and have greater risk for ventricular proarrhythmia at slower heart rates.
d. Antiarrhythmic drugs with reverse-use dependence have less efficacy for arrhythmia prevention than termination and have less risk for ventricular proarrhythmia at slower heart rates.

7. Which of the following is true regarding the Cardiac Arrhythmia Suppression Trials (CAST I and II)?

a. The treatment drugs increased mortality for patients without heart disease.
b. All class IC antiarrhythmic drugs were found to decrease mortality.
c. The treatment drugs effectively suppressed premature ventricular complexes (PVCs).
d. The antiarrhythmic drugs studied were flecainide, propafenone, and moricizine.

8. Which of the following antiarrhythmic drugs is the most potent sodium channel blocker?

a. Flecainide
b. Lidocaine

c. Disopyramide
d. Procainamide

9. Which of the following effects is expected when administering adenosine to a patient with recent cardiac transplantation (denervated heart)?

a. No effect
b. Diminished effect
c. Enhanced effect
d. Delayed effect

10. A patient presents with regular narrow QRS tachycardia. A 12-lead electrocardiogram (ECG) demonstrates an r' in lead V_1 that was not seen on ECG when the patient was in sinus rhythm. An esophageal electrode shows a 1:1 atrial-to-ventricular relationship during tachycardia. The ventriculoatrial (VA) interval is measured as 55 milliseconds. Which of the following is the most likely diagnosis?

a. Orthodromic atrioventricular reentrant tachycardia (AVRT)
b. Atrial tachycardia
c. AV nodal reentrant tachycardia (AVNRT)
d. Permanent junctional reciprocating tachycardia (PJRT)

11. A 17-year-old patient who is known to have Wolff-Parkinson-White syndrome presents with a regular narrow complex tachycardia with a cycle length of 375 milliseconds (160 bpm) that occurred with a sudden onset. You note that there is a 1:1 atrial-to-ventricular relationship and that the RP interval is 100 milliseconds. The best initial treatment is

a. IV procainamide.
b. atropine.
c. vagal maneuvers.
d. catheter ablation.

12. A 25-year-old patient presents with the sudden onset of tachycardia and is found to have a regular narrow QRS tachycardia with a cycle length of 340 milliseconds (176 bpm). An ECG appears to show P waves visible just after each QRS complex. You place an esophageal electrode and confirm a 1:1 atrial-to-ventricular relationship with a VA interval of 110 milliseconds. During the tachycardia, there is spontaneous development of left bundle branch block (LBBB), and a slower tachycardia with a VA interval of 150 milliseconds is now seen. What is the most likely diagnosis for the second tachycardia?

a. AVNRT

b. Orthodromic AVRT using a right-sided accessory pathway
c. Orthodromic AVRT using a left-sided accessory pathway
d. Ventricular tachycardia (VT) with 1:1 VA conduction

13. A 65-year-old man presents after an arrest while eating at a local restaurant. On arrival, paramedics documented ventricular fibrillation (VF), and he was successfully resuscitated. He has a history of myocardial infarction (MI) and congestive heart failure (CHF). Serum electrolytes are remarkable only for mild hypokalemia. MI is ruled out by ECG and serial blood tests of myocardial enzymes. Subsequent evaluation includes cardiac catheterization, which shows severe three-vessel coronary artery disease (CAD) and severe left ventricular (LV) systolic dysfunction. A nuclear myocardial perfusion scan shows a large area of myocardial scar without significant viability in the territory of the left anterior descending coronary artery. The decision is made to treat the CAD medically. Which of the following is the best management strategy for his arrhythmia?

a. PO amiodarone
b. Implantable cardioverter defibrillator (ICD) implantation if an electrophysiologic (EP) study shows inducible VT or VF
c. ICD implantation
d. β-Blocker medication

14. A 55-year-old woman has CAD and moderately severe LV systolic dysfunction (LV ejection fraction, 34%). Routine ambulatory Holter monitoring shows asymptomatic frequent ventricular ectopy with PVCs and occasional runs of nonsustained VT. Which of the following statements about the management of this patient is true?

a. Implantation of an ICD is indicated.
b. Implantation of an ICD is indicated if an EP study shows inducible VT.
c. Treatment with amiodarone is indicated, and if the arrhythmia recurs, then an EP study is indicated.
d. No treatment is indicated unless the arrhythmia becomes symptomatic.

15. A patient arrives at the emergency department after experiencing multiple shocks from his ICD. The shocks were not preceded by any symptoms. He is noted to be in sinus rhythm on presentation, and, while on the monitor, he receives several more shocks from the ICD without any arrhythmias noted. Which of the following is the most appropriate initial step in the management of this patient?

a. Immediately arrange for a programmer for interrogation and reprogramming of the ICD.
b. Arrange for urgent surgery in the EP laboratory.

c. Initiate antiarrhythmic drug therapy.
d. Place a "donut" magnet over the ICD site.

16. Which of the following is most important for successful resuscitation of an adult patient with out-of-hospital cardiac arrest?

a. IV epinephrine
b. Early direct current (DC) shock defibrillation
c. IV antiarrhythmic drugs
d. Early intubation

17. Which of the following rhythms documented at the time of resuscitation from cardiac arrest carries the poorest prognosis for long-term survival?

a. Asystole
b. Electromechanical dissociation (EMD) or pulseless electrical activity (PEA)
c. VF
d. VT

18. Which of the following rhythm disturbances is most commonly documented for an adult with out-of-hospital sudden cardiac death resuscitated within the first 4 minutes after arrest?

a. Asystole
b. EMD or PEA
c. Monomorphic VT
d. VF

19. Which of the following treatment options has been most consistently shown to be effective for the primary prevention of sudden cardiac death in patients with CAD and recent MI?

a. D-Sotalol
b. β-Blocker medications
c. Amiodarone
d. Dofetilide

20. Which of the following is the most common condition associated with sudden cardiac death in the United States?

a. Hypertrophic cardiomyopathy
b. CAD
c. Valvular heart disease

d. Dilated cardiomyopathy

21. A 55-year-old man is referred for recurrent syncope. The episodes consist of a prodrome of weakness and nausea followed by loss of consciousness. Physical examination is unremarkable. ECG and exercise treadmill stress test were normal. Which of the following is the most appropriate next step?

a. EP study
b. Signal-averaged ECG
c. Head-upright tilt-table testing
d. Ambulatory Holter monitoring

22. A 40-year-old woman presents to the emergency department with tachycardia. An ECG shows regular narrow complex tachycardia at 160 bpm. Atrial activity is difficult to discern in the tracing, but during tachycardia, there appears to be an "r'" in lead V_1 that is not present on an ECG during sinus rhythm recorded a few months earlier. Which of the following is the most likely diagnosis?

a. AVNRT
b. AVRT
c. Atrial tachycardia
d. Atrial flutter

23. An 80-year-old man with chronic AFib of 15 years' duration is admitted with recurrent episodes of dizziness and a recent episode of syncope. He has normal LV function and no evidence of CAD. In-hospital telemetry confirms the presence of slow ventricular rate and frequent pauses (4 seconds) that correlate with his lightheadedness. His medications consist of warfarin sodium (Coumadin). The most appropriate course of action includes which of the following?

a. Reassuring the patient and instructing him to come back if he has recurrence of syncope
b. Prolonged monitoring with a loop recorder
c. EP testing to evaluate for ventricular arrhythmia
d. Permanent pacemaker implant
e. ICD implant

24. A decision was made in the previous case to proceed with a permanent pacemaker. Which would be the most suitable pacing modality?

a. Dual-chamber system programmed to DDDR
b. Dual-chamber system programmed to DDDR with mode switching
c. Dual-chamber system programmed to DDIR

d. Single-chamber system in the ventricle programmed to VVIR
e. Single-chamber system in the atrium programmed to AAIR

25. Which one of the following is true about "pacemaker syndrome"?

a. Symptoms usually include fatigue, dizziness, and hypotension.
b. It occurs equally in atrial-based and ventricular-based pacing systems.
c. It does not occur in patients who have 1:1 VA conduction.
d. It can be treated with fludrocortisone.
e. It is treated by increasing the VVI baseline pacing rate.

26. Of the following patients, who is the most likely to carry the diagnosis of sick sinus syndrome (SSS)?

a. A 65-year-old woman with a resting sinus arrhythmia varying from 70 to 85 bpm
b. A 30-year-old with sinus pauses 1.5 seconds in duration
c. A 20-year-old athletic man with sinus bradycardia at 25 bpm while sleeping
d. A 73-year-old man with persistent AFib and a ventricular rate of 40 bpm during peak treadmill test
e. A 70-year-old with sinus bradycardia and AV block secondary to a β-blocker overdose

27. A 76-year-old patient with dilated cardiomyopathy and LBBB on baseline ECG is undergoing evaluation for syncope. Placement of a catheter near his bundle during EP testing is most likely to

a. induce AFib.
b. induce VT.
c. perforate the atrium.
d. perforate the ventricle.
e. induce complete heart block (CHB).

28. A 25-year-old patient with a history of depression is brought to the emergency room after ingesting some of her mother's prescription medications, including diltiazem and metoprolol. Her pulse rate is 25 bpm, and her BP is 90/50 mmHg. Her ECG shows sinus bradycardia and high-grade AV block. In preparation for temporary pacemaker placement, which of the following is most likely to be effective?

a. IV calcium gluconate
b. Isoproterenol infusion
c. IV atropine
d. IV magnesium sulfate
e. IV glucagon

29. A young patient is admitted to the intensive care unit with amitriptyline overdose. Three hours after gastric lavage, he develops hypotension and wide complex tachycardia that is recurrent despite cardioversion. Appropriate management includes which of the following?

a. IV bretylium
b. Temporary pacemaker with overdrive pacing
c. IV calcium gluconate
d. IV hypertonic sodium bicarbonate
e. IV magnesium sulfate

30. An 80-year-old undergoes dual-chamber pacemaker placement for CHB. Excellent ventricular and atrial capture thresholds were obtained at the time of the implant. The pacemaker programmed parameters are as follows: mode, DDD; lower rate, 70 bpm; upper rate, 130 bpm; atrial sensitivity, 0.25 mV (most sensitive setting); ventricular sensitivity, 1.00 mV; AV delay, 175 milliseconds; pace/sense configuration, bipolar. The next day, the following rhythm strip was recorded (Fig. 1.1): This rhythm strip shows

a. normal pacemaker function for the programmed parameters.
b. atrial noncapture.
c. ventricular noncapture.
d. atrial undersensing.
e. ventricular undersensing.

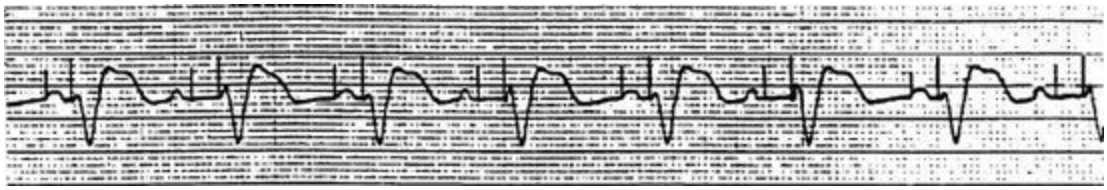

Figure 1.1

31. A 50-year-old man with chronic obstructive pulmonary disease related to chronic smoking presents to the emergency room with palpitations. ECG shows narrow QRS tachycardia at 165 bpm. His BP is 125/60 mmHg. Expiratory wheezes are heard on lung examination. His medications include albuterol inhaler and theophylline. The most appropriate initial treatment includes which of the following?

a. Adenosine IV bolus
b. Digoxin loading over 6 hours
c. Verapamil IV bolus

d. Propafenone IV bolus
e. Immediate cardioversion

32. A 55-year-old woman returns to the clinic after a recent dual-chamber pacemaker placement. She reports frequent palpitations and fatigue. These episodes last for several minutes before stopping. A Holter monitor recorded the following rhythm (Fig. 1.2): The pacemaker is programmed to mode DDD; lower rate, 80 bpm; upper rate, 150 bpm; AV delay, 200 milliseconds; postventricular atrial RP, 150 milliseconds. The latter part of this rhythm strip shows

a. VT induced by the pacemaker.
b. initiation of atrial tachycardia with atrial tracking.
c. pacemaker-mediated tachycardia.
d. pacemaker function failure with inappropriate rapid ventricular pacing.
e. artifact.

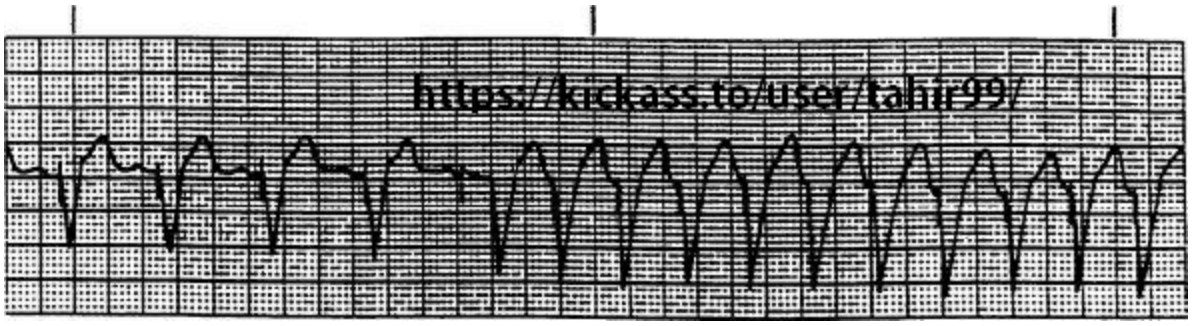
https://kickass.to/user/tahir99/

Figure 1.2

33. An 82-year-old man receives a dual-chamber pacemaker for SSS. Routine transtelephonic check (without and with magnet) shows the following strips (Fig. 1.3). Which of the following is true?

a. The pacing mode is VVI secondary to automatic mode switch.
b. There is consistent atrial capture on the magnet strip.
c. There is consistent ventricular capture.
d. Ventricular sensing cannot be determined by the available strips.
e. Atrial sensing cannot be determined by the available strips.

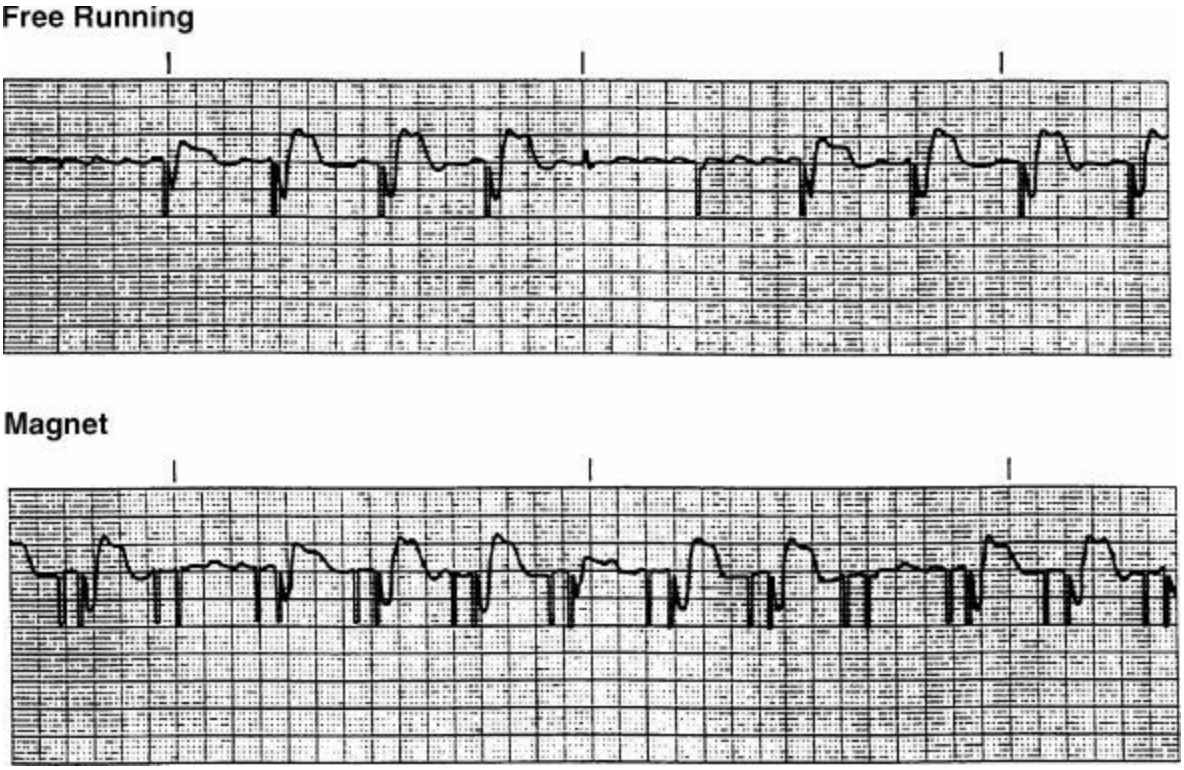

Figure 1.3

Questions 34–37

The following tracings (Figs. 1.4, 1.5, 1.6, and 1.7) are obtained during EP evaluation of AV conduction in different patients. HRA (high right atrium) and HBE (His bundle electrogram) are the intracardiac electrograms, recording from the high right atrium and the His bundle regions, respectively. Which of the following is true for these tracings?

Figure 1.4

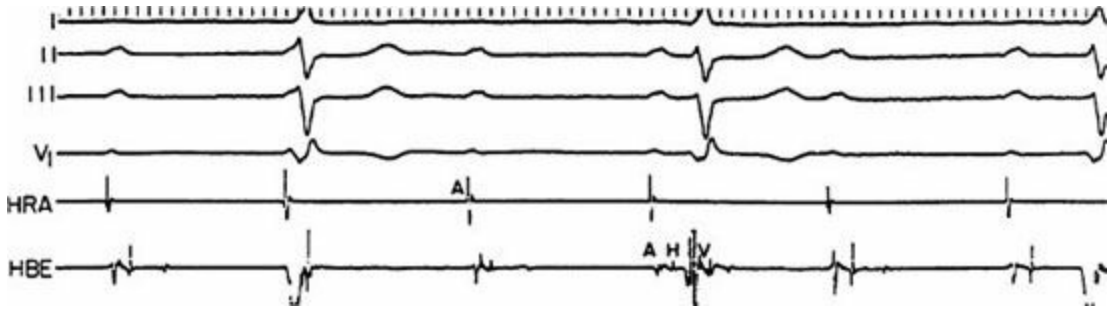

Figure 1.5

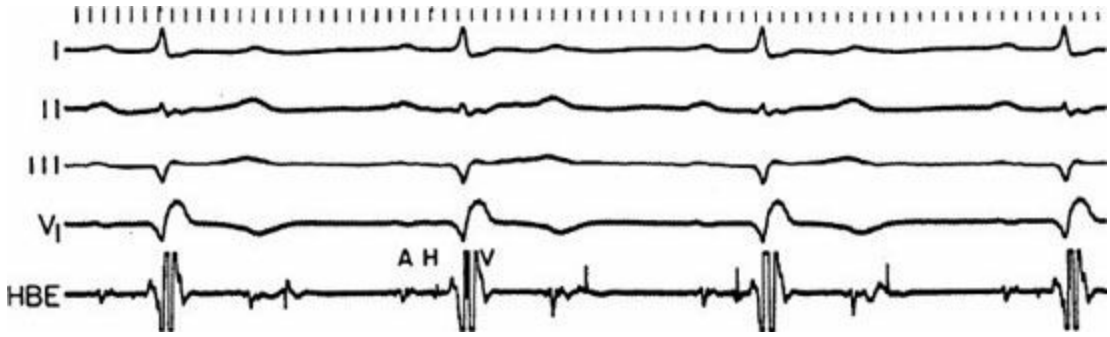

Figure 1.6

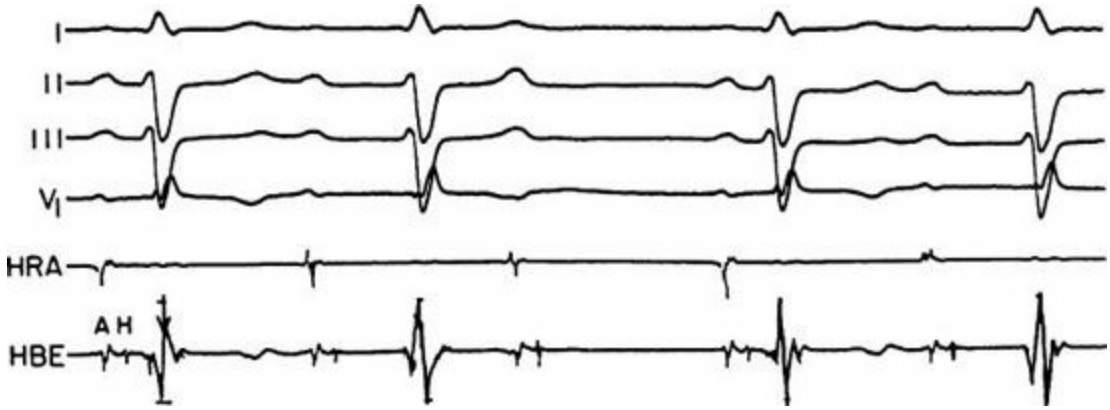

Figure 1.7

a. CHB at the level of the AV node
b. CHB at the infra-Hisian (below the His bundle) level
c. Second-degree AV block at the AV node level
d. Second-degree AV block at an infra-Hisian level
e. First-degree AV block

38. A 38-year-old woman with congenital CHB undergoes a dual-chamber permanent pacemaker. A 12-lead ECG obtained after the procedure shows normal sinus rhythm (NSR) with atrial tracking (a sense–V pace behavior). The ventricular-paced complex has a right bundle branch block (RBBB) morphology. Further

evaluation should include

a. obtaining a portable anteroposterior chest X-ray (CXR) to evaluate lead position.
b. obtaining a two-view (anteroposterior and lateral) CXR to evaluate lead position.
c. repeating the 12-lead ECG.
d. requesting a pacemaker interrogation.
e. reassuring the patient without ordering further tests.

39. Which of the following is true regarding EP testing of the conduction system?

a. It is indicated in patients with symptomatic third-degree heart block to identify the level of block.
b. An abnormal sinus node recovery time is an indication for pacemaker placement.
c. A normal sinus node recovery time rules out the diagnosis of SSS.
d. Patients with evidence of infra-Hisian block during EP testing should be considered for permanent pacing.
e. Ambulatory ECG is less reliable than EP testing in evaluating SSS.

40. Which of the following statements is true regarding Brugada syndrome?

a. It is characterized by ST elevation and a pseudo-RBBB pattern in the right precordial leads with persistent ST elevation.
b. The ECG manifestations can be exacerbated by sotalol.
c. It is the leading cause of death in young men in the Middle East.
d. AFib is the most frequently reported arrhythmia.
e. It is effectively treated with β-blockers.

41. In patients with long-QT syndrome

a. EP testing is indicated to evaluate for inducible ventricular arrhythmias.
b. the mechanism of torsades de pointes (TdP) is believed to be related to early afterdepolarization.
c. sotalol is effective for the treatment of the associated ventricular tachyarrhythmias.
d. hyperkalemia increases the risk of TdP.
e. cardiac arrest typically occurs at rest in LQT1 syndrome.

42. A 75-year-old man is admitted with upper gastrointestinal (GI) bleeding. His ECG shows sinus rhythm at 90 bpm, with a PR of 220 milliseconds, RBBB, and left anterior fascicular block. He had one episode of near syncope 2 days before this admission. His current hematocrit is 20. You are consulted regarding the need for a

pacemaker. Which of the following is true?

a. You should proceed with permanent pacemaker placement in the setting of bifascicular block.
b. You should proceed with ICD placement.
c. You should perform EP testing to evaluate the AV conduction system.
d. You should reassure the patient and suggest no further testing.
e. You should prescribe β-blockers to slow down the sinus rate.

43. Which of the following criteria is most helpful in differentiating supraventricular tachycardia (SVT) from VT in a patient presenting with wide complex tachycardia?

a. The patient is older than 65 years.
b. The tachycardia rate is >160 bpm.
c. The patient is awake with a BP of 110/65 mmHg.
d. There is an RS pattern in V_2.
e. There is AV dissociation.

44. A 76-year-old man walks into the emergency room reporting palpitations and dizziness. A 12-lead ECG shows wide complex tachycardia at a rate of 160 bpm. His BP is 110/50 mmHg. He reports that he recently sustained an MI. He has not had any similar symptoms before. Which of the following should be included in further evaluation and treatment of his arrhythmia?

a. Verapamil, 10-mg IV bolus, to treat SVT with aberrancy, as the patient is hemodynamically stable
b. Immediate DC cardioversion
c. Procainamide, 15 mg/kg IV over 30 to 60 minutes
d. Immediate cardiac catheterization and angioplasty, as needed
e. Digoxin, 1 mg IV over 6 hours in four divided doses

45. A 55-year-old man had a pacemaker initially implanted 8 years ago over the left prepectoral area. Two months earlier, his old pacemaker reached end-of-life, and he underwent replacement of the pacemaker using the existing leads. He is presenting now with dull pain, swelling, and mild erythema over the pacemaker pocket site that started 1 week earlier, together with low-grade fever. He reports some purulent drainage from the incision site. Blood cultures were drawn. The best course of action is

a. to prescribe PO antibiotics for 2 weeks.
b. to admit the patient for IV antibiotics and pacemaker-system extraction.
c. to prescribe long-term suppressive PO antibiotics, as the pacemaker and leads system are too old to be extracted.

d. to remove the recently implanted pulse generator on the left, leaving the old leads in place, and implant a new pacemaker system on the right prepectoral area.
e. to incise and drain the pacemaker pocket and allow it to heal with secondary intention with daily change of dressing.

46. Which of the following is a correct statement concerning external cardioversion of AFib?

a. Acute MI is a contraindication to cardioversion, as it results in further myocardial damage.
b. A nonsynchronized shock should be delivered because the rhythm is irregular.
c. Inadequate synchronization may occur with peaked T waves, low-amplitude signal, and malfunctioning pacemakers.
d. Digoxin therapy should be discontinued for 48 hours before elective cardioversion.
e. Patients with pacemakers should not undergo cardioversion because of the risk of pacemaker damage.

47. In patients with Wolff-Parkinson-White syndrome, with which of the following is acute pharmacologic treatment of AFib best achieved?

a. Diltiazem
b. Lidocaine
c. Verapamil
d. Procainamide
e. Adenosine

48. A 75-year-old patient with a history of ischemic cardiomyopathy develops worsening heart failure symptoms during episodes of AFib despite a controlled ventricular rate. Which of the following is included in a reasonable trial of pharmacologic therapy?

a. Flecainide
b. Sotalol
c. Verapamil
d. Disopyramide
e. Amiodarone

49. Which of the following is true regarding the use of digoxin in AFib?

a. It is superior to placebo for the acute conversion of AFib.
b. It controls ventricular rate during exercise in most patients.

c. It can control ventricular rate at rest in many patients.
d. It effectively maintains sinus rhythm after cardioversion.
e. Because of its hepatic clearance, it is safe to use in patients with renal insufficiency.

50. Which of the following statements regarding flecainide as a treatment of AFib is true?

a. It may contribute to an increase in the digoxin level.
b. It may be used without an AV nodal blocking agent because of its potent effect on the AV conduction system.
c. It has been shown to be effective and safe for use in patients with hypertrophic cardiomyopathy.
d. It has no effect on the acute conversion of AFib but only on maintenance of sinus rhythm postcardioversion.
e. It is used for the treatment of AFib but not atrial flutter.

51. Which of the following mechanisms is responsible for AFib occurring in the immediate postoperative period after a maze procedure?

a. Change in the atrial refractory period as a result of the surgical manipulation
b. Autonomic imbalance as a result of the surgical intervention
c. Misplacement of a suture line
d. An incomplete or omitted suture line
e. Inhibition of atrial natriuretic peptide secretion as a result of the surgical manipulation

52. The following tachycardia was induced during EP testing of a 36-year-old woman with recurrent palpitations (Fig. 1.8). Which of the following is the most likely diagnosis?

a. AVNRT
b. Orthodromic reentrant tachycardia
c. Antidromic reentrant tachycardia
d. VT
e. Idiopathic left VT

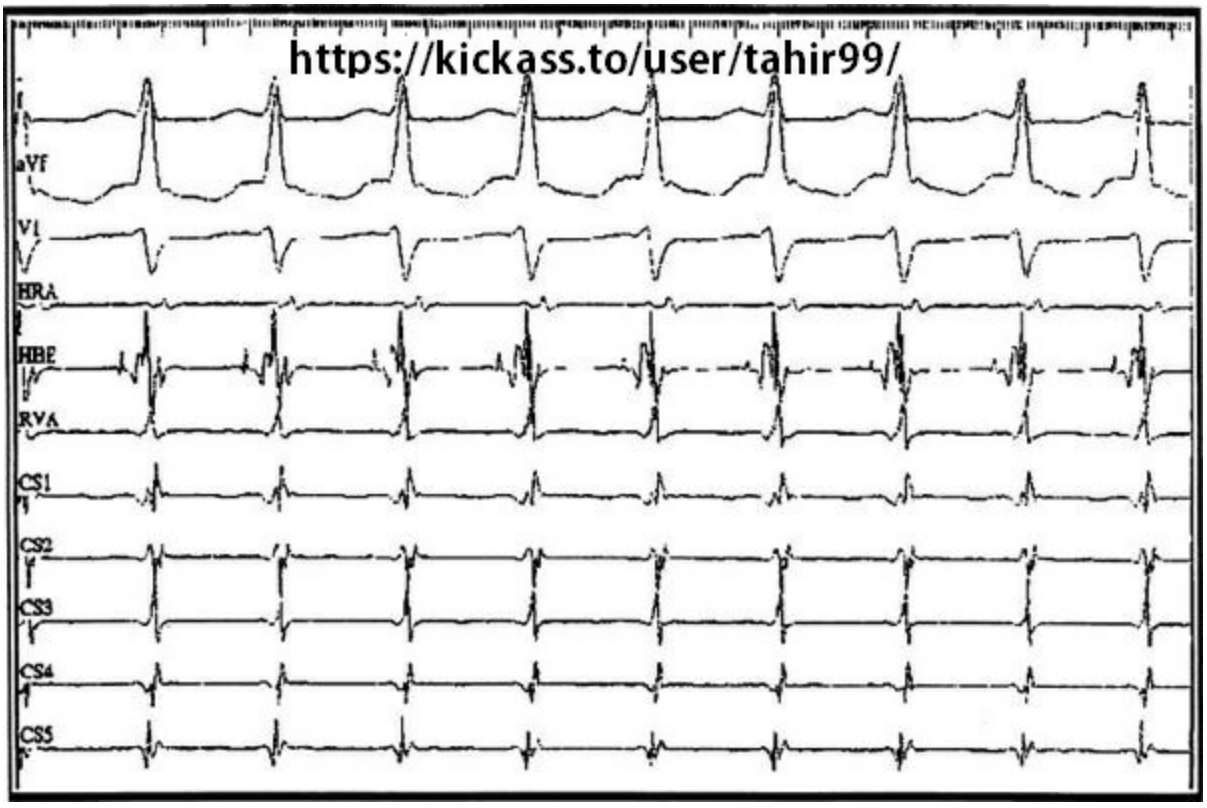

Figure 1.8

ANSWERS

1. **a.** Propafenone. Sotalol and dofetilide are primarily excreted by the renal route and should be used cautiously, if at all, in patients with significant renal insufficiency. Flecainide primarily undergoes hepatic elimination (approximately 70%) but has 25% renal elimination. The route of elimination for propafenone is 99% hepatic.

2. **a.** Amiodarone. Sotalol, dofetilide, and flecainide do not have significant active metabolites. Amiodarone is metabolized to the active metabolite desethylamiodarone.

3. **b.** The patient is taking dipyridamole. Dipyridamole potentiates the effect of adenosine by interfering with metabolism; therefore, a reduced dose of adenosine is recommended. Although not a part of this question, it is important to remember that adenosine also needs to be used with extreme caution in heart transplant patients as a markedly exaggerated response to adenosine can be seen in the denervated heart. An increased dose of adenosine is recommended in the presence of methylxanthines such as theophylline, which antagonizes the effect of adenosine (blocks receptors), and other factors such as slow circulation time, valvular regurgitation, and left-to-right shunts that reduce the effectiveness of adenosine.

4. **c.** Verapamil. Verapamil may increase serum levels of dofetilide because of interference with renal excretion and hepatic metabolism.

5. **b.** Flecainide. Flecainide is a class IC antiarrhythmic drug, and these agents exhibit "use dependence." This refers to the property of increased drug effect at increased heart rates. Sotalol and dofetilide are class III antiarrhythmic drugs that exhibit "reverse-use dependence"—that is, greater drug effect at slower heart rates. Quinidine has effects on both sodium and potassium channels. While the effects on the sodium channels are use dependent, it is far less pronounced compared with the Ic agents such as flecainide. The potassium-blocking properties and resulting QT prolongation are more pronounced at slower heart rates— reverse-use dependent.

6. **c.** Antiarrhythmic drugs with reverse-use dependence have greater efficacy for arrhythmia prevention than termination and have greater risk for ventricular proarrhythmia after AFib termination (at slower sinus rates) than during AFib. Antiarrhythmic drugs with use dependence, such as sotalol and dofetilide, have greater antiarrhythmic effect at slower heart rates. Consequently, drug efficacy is enhanced at the relatively slower rates in sinus rhythm, making these drugs more effective for prevention of AFib than those drugs with use dependence. Likewise, for proarrhythmia, the antiarrhythmic drugs with reverse-use dependence are more likely to produce ventricular proarrhythmia after conversion to sinus rhythm at the relatively slower sinus rate or with a postconversion pause.

7. **c.** The treatment drugs effectively suppressed premature ventricular complexes (PVCs). CAST studied the concept that PVC suppression in the postinfarction period would reduce the incidence of sudden cardiac death. Patients without heart disease were, therefore, excluded from these studies. CAST I studied flecainide, encainide, and moricizine versus placebo. Demonstration of effective suppression of PVCs by one of the drugs was necessary before a patient could be randomized to drug or placebo treatment. Propafenone, another class IC antiarrhythmic drug, was not studied. CAST I was prematurely terminated by the safety committee after only a 10-month average follow-up because of significantly increased incidence of arrhythmic death and nonfatal cardiac arrests in the flecainide and encainide treatment groups. CAST II was a continuation of the study with only moricizine versus placebo, but this study was also terminated early because of an increased incidence of cardiac arrest in the moricizine treatment group.

8. **a.** Flecainide. All of these drugs are class I antiarrhythmic medications and have sodium channel–blocking properties to various degrees. Class IC agents, such as flecainide, have the most potent sodium channel–blocking effects, and class IB

agents, such as lidocaine, have the least potent sodium channel–blocking effects.

9. **C.** Enhanced effect. Patients with denervated hearts are supersensitive to the effects of adenosine.

10. **C.** AV nodal reentrant tachycardia (AVNRT). Atrial tachycardia and PJRT are long RP tachycardias and, therefore, would not have such a short VA interval. PJRT is a special type of orthodromic AVRT that involves a posteroseptal accessory pathway with decremental (AV nodal-like) conduction properties and, hence, has a long RP (long VA) interval. Because of the time required to reach the accessory pathway for the retrograde portion of the arrhythmia circuit, orthodromic AVRT generally has a VA interval longer than 70 milliseconds. Therefore, a VA interval shorter than 70 milliseconds excludes orthodromic AVRT and makes AVNRT the most likely diagnosis. A small r' wave (pseudo r' wave) can sometimes be seen at the terminal portion of the QRS (usually best in lead V_1). This deflection represents retrograde activation of the atrial (a retrograde P wave) occurring shortly after the QRS complex.

11. **C.** Vagal maneuvers. A sudden onset of a regular narrow complex tachycardia with a cycle length of 375 milliseconds and an RP interval of 100 milliseconds is a short RP tachycardia (the PR interval would be 375 milliseconds – 100 milliseconds = 275 milliseconds, so the RP is shorter than the PR). This patient most likely presents with orthodromic AVRT, a reciprocating tachycardia circuit that involves antegrade conduction through the AV node and retrograde conduction through the accessory pathway (however, AVNRT is also possible). As the AV node is a necessary component of the arrhythmia circuit, AV nodal blockade effectively terminates this type of tachycardia. Vagal maneuvers, such as Valsalva, coughing, or carotid sinus massage, may be quite effective and avoid the potential risks associated with administration of medications. Verapamil and other drugs that block AV conduction, such as β-blockers and adenosine, may be quite useful for termination of AVRT. This should not be confused with the management of AFib in the setting of Wolff-Parkinson-White syndrome, in which administration of AV nodal blocking drugs, such as verapamil, is contraindicated due to a concern for uninhibited and thus rapid AV conduction of the AP, which if rapid enough can induce ventricular fibrillation. When AV conduction is occurring through both the AV node and AP, retrograde, concealed conduction into the AP can limit its antegrade conduction properties. If preexcited, AFib with IV procainamide or DC cardioversion is the correct management. A precautionary note regarding the use of adenosine for regular narrow QRS tachycardia in patients with Wolff-Parkinson-White syndrome: Adenosine may precipitate AFib and result in a very rapid

ventricular response (preexcited tachycardia). Atropine has no role in the treatment of these types of arrhythmia. Catheter ablation is not generally an acute treatment option for this arrhythmia, although this approach may be an excellent option for chronic treatment (cure).

12. **c.** Orthodromic AVRT using a left-sided accessory pathway. A regular narrow QRS tachycardia that has VA interval prolongation with the development of bundle branch block is most consistent with an orthodromic AVRT using an accessory pathway ipsilateral to the bundle branch. During AVRT, the antegrade limb of the circuit is the AV node and His-Purkinje/bundle branch system, and the retrograde limb is the accessory pathway. Block in a bundle branch ipsilateral to an accessory pathway creates a larger circuit, as the antegrade limb must now use the contralateral bundle branch, and therefore, the VA interval increases. This results in an increase in the tachycardia cycle length (a slower tachycardia). Of note, a slower tachycardia with bundle branch block itself does not necessarily have the same significance. Other types of tachycardia may slow because of a change in conduction of other components of the tachycardia circuit, such as the conduction through the AV node (A–H interval). Thus, it is important to demonstrate VA interval prolongation during bundle branch block to implicate an ipsilateral accessory pathway participating in AVRT.

13. **c.** ICD implantation. Cardiac arrest with VT or VF in the absence of reversible causes (e.g., MI, severe electrolyte or metabolic disorders) is a class I indication for ICD implantation. ICD implantation for such patients is superior to amiodarone drug therapy, as demonstrated in the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial. The Canadian Implantable Defibrillator Study examined a similar population of patients and, although not statistically significant, showed a strong trend for the superiority of ICDs. Demonstration of inducible VT or VF in these types of patients is not necessary.

14. **b.** Implantation of an ICD is indicated if an EP study shows inducible VT. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) evaluated patients with CAD, ischemic cardiomyopathy with an LV ejection fraction of <35%, and nonsustained VT. This study showed that for patients with inducible VT at baseline EP study and after administration of IV procainamide, treatment with an ICD was superior to treatment with antiarrhythmic drugs. A follow-up study, MADIT II, assessed the role of ICD implantation in patients with an ischemic cardiomyopathy and an ejection fraction ≤30%. Nonsustained VT was not required to undergo ICD implant, nor was an EP study. The study was terminated early after an average follow-up of 20 months because the ICD significantly reduced all-cause mortality

(14.2% versus 19.8% for conventional therapy). This study helped expand ICD implant indications. This is a class I indication for ICD implantation.

15. **d.** Place a "donut" magnet over the ICD site. The patient is having inappropriate or spurious shocks from the ICD, most likely caused by detection of electrical noise from a malfunction of the ICD lead. It is imperative that further shocks be prevented immediately, not only for patient comfort but also to prevent induction of life-threatening ventricular arrhythmias (including ventricular arrhythmia storm) caused by the ICD shocks. The most effective action at this point is placement of a magnet over the ICD site. This prevents the ICD from delivering any therapies. It would not be optimal to delay the prevention of further shocks while waiting for an ICD programmer. Of note, unlike pacemakers, ICDs do not have an asynchronous pacing response to application of a magnet.

16. **b.** Early direct current (DC) shock defibrillation. The two most crucial factors that determine the value of out-of-hospital resuscitation for patients who experience sudden cardiac death are citizen-bystander cardiopulmonary resuscitation and early DC shock defibrillation.

17. **a.** Asystole. EMD or PEA and, in particular, asystole tend to be found in increasing proportions as the time since arrest increases. This is likely caused by degeneration of prolonged VF. When VF is the documented rhythm at the time of resuscitation, the long-term survival is approximately 25%. When EMD or PEA is the documented rhythm, the long-term survival rate drops to approximately 6%, and it drops even further, to approximately 1%, when asystole is documented.

18. **d.** VF. The initial rhythm documented in a patient who undergoes sudden cardiac death is dependent on the time elapsed since the arrest. Most episodes of sudden cardiac death (approximately 65% to 85%) that are documented electrocardiographically are caused by malignant ventricular arrhythmias such as VF. Monomorphic VT is uncommonly documented as a cause of out-of-hospital sudden cardiac death, perhaps caused by degeneration of unstable VT to VF. Asystole and EMD or PEA are found in greater proportions as the time since arrest increases, as these rhythms are likely the result of prolonged VF.

19. **b.** β-Blocker medications. Several randomized trials of the use of β-blocker medications for patients after MI have shown efficacy for the prevention of sudden cardiac death (including propranolol, timolol, metoprolol, and acebutolol). Trials of amiodarone in this setting have provided mixed results. Two large randomized trials, the European Myocardial Infarct Amiodarone Trial (EMIAT) and the

Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), examined the use of amiodarone in patients after MI and did not show a reduction in overall mortality with the use of amiodarone. The Polish Amiodarone Trial showed that amiodarone improved survival only in patients with preserved LV function after MI. The Survival with Oral D-sotalol (SWORD) trial studied the use of the D-isomer of sotalol (D-sotalol) in patients with recent MI and LV dysfunction. This study found worse survival in the group treated with D-sotalol than in the group treated with placebo. The Danish Investigations of Arrhythmias and Mortality on Dofetilide (DIAMOND) studies showed that dofetilide had a neutral effect on total mortality compared with placebo in the treatment of post-MI patients with LV dysfunction.

20. **b.** CAD. CAD is the predominant disease process associated with sudden cardiac death in the United States, accounting for 64% to 90% of cases. The other cardiomyopathies, such as dilated and hypertrophic cardiomyopathies, together account for approximately 10% to 15% of cases of sudden cardiac death.

21. **c.** Head-upright tilt-table testing. Syncope in the absence of structural heart disease is most likely neurally mediated (vasovagal). The head-upright tilt-table test is the most appropriate test to evaluate for this condition. This test initiates the vasovagal episode by maximizing venous pooling, sympathetic activation, and circulating catecholamines. In general, the test involves at least 30 minutes of 70-degree head-up tilt angle without a saddle support. An addition of a catecholamine challenge with isoproterenol is sometimes used. Among symptomatic patients, the sensitivity of the head-upright tilt-table test is approximately 85%. The specificity of the head-upright tilt-table test is good, with the frequency of an abnormal tilt-table test in control subjects being 0% to 15%. In the absence of structural heart disease, EP study, ambulatory Holter monitoring, and the signal-averaged ECG are low yield.

22. **a.** AVNRT. An "r'" in lead V_1 during regular narrow complex tachycardia that is not present during sinus rhythm indicates the inscription of the P wave in the terminal QRS, is consistent with a very short VA interval, and is very specific for AVNRT.

23. **d.** Permanent pacemaker implant. This patient has evidence of symptomatic bradycardia on Holter monitoring, which constitutes a class I indication for permanent pacemaker placement. He has AV conduction system disease with no obvious reversible causes, which is most probably caused by idiopathic fibrosis (Lev disease). Prolonged monitoring will probably show more episodes of bradycardia, which was already seen during telemetry, and which places this elderly patient at risk for syncope and injury. EP testing for ventricular arrhythmia

is not indicated in view of the absence of structural heart disease. Likewise, ICD is not indicated.

24. **d.** Single-chamber system in the ventricle programmed to VVIR. This patient is in chronic AFib, and, therefore, physiologic pacing in the atrium cannot be achieved. Furthermore, conversion and long-term maintenance of sinus rhythm in this situation are very unlikely. Therefore, there is no indication for placement of an atrial lead. DDDR with mode switching and DDIR will behave like a VVIR system in this patient, at the expense, however, of an additional lead (atrial) and a more expensive dual-chamber pacemaker.

25. **a.** Symptoms usually include fatigue, dizziness, and hypotension. Pacemaker syndrome is caused by pacing the ventricle asynchronously, which results in AV dissociation or VA conduction. Symptoms consist of fatigue, dizziness, dyspnea, and weakness, with or without hypotension. The mechanism is believed to be related in part to atrial contraction against a closed AV valve and release of atrial natriuretic peptide. It occurs with ventricular pacing and therefore is worsened by increasing pacing rate and relieved by allowing intrinsic conduction (if present) by lowering the pacing rate, programming rate hysteresis, or upgrading to a dual-chamber system. Therapy with fludrocortisone and other volume-expansion modalities is not helpful.

26. **d.** A 73-year-old man with persistent AFib and a ventricular rate of 40 bpm during peak treadmill test. The 73-year-old man with AFib and slow ventricular rate during exercise is the classic example of SSS. This usually indicates degenerative disease of the cardiac conduction system involving the AV node as well as the sinus node. Function of the sinus node can only be assessed after AFib has been terminated, usually by DC cardioversion. In this patient's case, it would not be uncommon to manifest a long postconversion pause, followed by either marked sinus bradycardia or complete sinus node arrest with a resulting junctional or ventricular escape rhythm (hopefully) following cardioversion. The finding of sinus arrhythmia varying by 15 bpm in an older patient, the profound nocturnal bradycardia in young athletes, and the sinus pauses in young patients are related mostly to a high vagal tone and do not indicate sinus node disease.

27. **e.** Induce complete heart block (CHB). Patients with true complete LBBB are at risk for developing transient CHB during catheter manipulation in the septal region of the tricuspid valve. This is caused by transient traumatic block of the right bundle branch. A similar scenario can result when placing a Swan-Ganz catheter in patients with LBBB.

28. **e.** IV glucagon. This patient has an overdose of diltiazem and metoprolol. These drugs slow sinoatrial and AV conduction. Calcium and magnesium have no effect in reversing these bradycardic effects. Isuprel and atropine are not likely to overcome the β-blockade of metoprolol. IV glucagon acts on a specific receptor. This results in an increase in intracellular cyclic adenosine monophosphate, which enhances both sinoatrial and AV node conduction despite the presence of β-blockade.

29. **d.** IV hypertonic sodium bicarbonate. Amitriptyline has sodium channel–blocking properties and induced QRS widening and VT. Increasing the extracellular sodium concentration by the administration of sodium bicarbonate decreases the association of this drug with the sodium channel.

30. **d.** Atrial undersensing. This rhythm shows evidence of atrial undersensing. The pacemaker is programmed to DDD. In this mode, an appropriately sensed P wave should cause inhibition of the atrial spike; a ventricular spike is then delivered after the programmed AV interval or inhibited by an intrinsic R wave. In this strip, the P wave is present in each complex. However, in complexes 2, 4, 6, and 8, an atrial spike follows the intrinsic P wave because the intrinsic P wave was not appropriately sensed by the pacemaker. The noncapture of the atrium following the atrial spike on complexes 2, 4, 6, and 8 is anticipated as the atrium would still have been refractory from the preceding P wave. Capture of the atrium on complexes 1, 3, 5, and 7 is suggested by the P wave that is different in morphology (wider) than the intrinsic P wave. Atrial undersensing occurring early after implantation may be the result of lead dislodgment. A CXR should be obtained to assess lead position. Other possibilities include inappropriate programmed sensitivity, which can be assessed on a device check. Finally, inflammation at the lead tip–endocardium interface can result in a decrease in sensing amplitude. This may improve over several weeks as the lead matures and inflammation resolves.

31. **c.** Verapamil IV bolus. Adenosine is commonly used to terminate SVT. However, this patient is on theophylline, which is an effective blocker of the adenosine receptor. Propafenone might be poorly tolerated by this patient because of its associated β-blocking activity, which might increase airway resistance. Digoxin shortens the refractory period of the atrium and might potentially accelerate an atrial tachycardia. Immediate cardioversion is not needed, as the patient appears hemodynamically stable, and it would be reasonable to attempt pharmacologic therapy initially with verapamil.

32. **c.** Pacemaker-mediated tachycardia. In this strip, there is evidence of atrial undersensing (fifth complex). As a result, the fifth ventricular-paced beat comes

"late" relative to atrial activation. This allows enough time to go by for the AV node to recover its conduction properties. This allows retrograde P-wave conduction following ventricular pacing, which is sensed by the pacer (because of short programmed postventricular atrial refractory period [PVARP]), and results in ventricular triggered pacing, causing a pacemaker-mediated tachycardia or endless-loop tachycardia. Acute treatment of this condition includes the application of a magnet to inhibit atrial sensing, thereby breaking the tachycardia loop. The spontaneous termination of these episodes in this patient is most probably related to intermittent atrial undersensing, which interrupts the tachycardia loop. Further prevention of these episodes includes reprogramming the PVARP, AV delay, or atrial sensitivity. Pacemaker-mediated tachycardia is an abnormal consequence of normal pacemaker function.

33. **a.** The pacing mode is VVI secondary to automatic mode switch. The initial rhythm strip shows background AFib with VVI pacing, most probably related to automatic mode switch. The absence of atrial pacing suggests adequate atrial sensing (of the fibrillation), which resulted in the mode switch behavior. Atrial pacing cannot be determined in the presence of AFib. There is adequate ventricular sensing, as determined on the nonmagnet strip (fifth complex—the small intrinsic QRS is sensed by the pacemaker which results in inhibition of pacing); however, there is intermittent ventricular capture noted (ventricular pacing spike followed by a lack of ventricular depolarization).

34. **a.** CHB at the level of the AV node. In this tracing, there is NSR with CHB and a narrow escape rhythm that is junctional in origin. This is apparent in the HBE tracing, in which the atrial deflections are completely dissociated from the H–V deflections. Therefore, the atrial impulse entering the AV node is not conducting down to the His bundle (A is not followed by His potential), indicating that the level of block is at the level of the AV node.

35. **b.** CHB at the infra-Hisian (below the His bundle) level. In this tracing, there is NSR with CHB and a relatively wide escape rhythm. In the HBE tracing, each atrial deflection is followed by an initial His deflection and a third, smaller deflection, H', indicating that there is conduction delay within the His bundle itself. This is suggestive of significant His-Purkinje conduction disease. Therefore, the atrial impulse enters the AV node, conducts down to the His bundle (normal AH interval), where it encounters conduction delay (a "split" His made up of both an H and an H'), and then fails to propagate to the ventricle, indicating that the level of block is at or below the level of the bundle of His. There is obvious AV dissociation with a ventricular escape rhythm.

36. **d.** Second-degree AV block at an infra-Hisian level. In this tracing, the surface ECG shows NSR with 2:1 AV block. The HBE tracing shows constant AH with 2:1 block below the level of the His bundle.

37. **d.** Second-degree AV block at an infra-Hisian level. In this tracing, the surface ECG shows NSR with second-degree type I AV block (Wenckebach). This pattern of block is usually localized to the AV node. However, in rare circumstances the block can occur within or below the His bundle. The wide QRS seen on the surface leads are a clue in this case that the patient has conduction disease below the level of the AV node; however, the site of block can only be determined by reviewing the His bundle recordings. In this situation, the HBE tracing shows progressive prolongation in the HV interval before it blocks in a 3:2 conduction pattern. Therefore, the conduction delay is not at the level of the AV node but at or below the His bundle. As opposed to Wenckebach in the AV node, which is usually benign in nature, this type of infra-Hisian block indicates His-Purkinje conduction system disease and is an indication for pacemaker placement, as it may progress to CHB.

38. **b.** Obtaining a two-view (anteroposterior and lateral) CXR to evaluate lead position. The presence of an RBBB-paced QRS complex pattern suggests that the ventricular lead may be in the LV. The lead may enter the LV through an atrial septal defect or ventricular septal defect or via perforation of the interventricular septum. It may also be inadvertently introduced into an artery and passed retrogradely through the aortic valve. Another possibility is placement into one of the LV branches of the coronary sinus. Although sometimes an apical position in the RV in a rotated heart can potentially give an RBBB-paced pattern, a two-view CXR should be obtained to rule out LV positioning. A single-view portable AP will not distinguish an LV from an apical RV placement. If LV placement is confirmed on the lateral radiograph, repositioning of the lead is indicated.

39. **d.** Patients with evidence of infra-Hisian block during EP testing should be considered for permanent pacing. Patients with symptomatic CHB do not need EP testing because the decision for a permanent pacemaker is already made. The sensitivity and specificity of sinus node recovery time are approximately 70%, making this test less than ideal; in most cases, the decision as to whether to implant a pacemaker in cases of suspected sinus node dysfunction depends on symptoms and correlation with ambulatory monitoring rather than results of EP testing. Patients with infra-Hisian block tend to have an unpredictable course and should be considered for permanent pacing.

40. **a.** It is characterized by ST elevation and a pseudo-RBBB pattern in the right

precordial leads with persistent ST elevation. Brugada syndrome has been described worldwide but is most common in Asian countries and is the leading cause of death in young men in part of Thailand. It is characterized by ST-segment elevation and a pseudo-RBBB pattern in the right precordial leads with persistent ST elevation. These features can be induced with sodium channel blockers such as flecainide and ajmaline. (Sotalol is a potassium channel blocker.) It is related to a mutation in the sodium channel gene. Mutations in SCN5A, which encodes the α-subunit of the cardiac sodium channel gene, have been found in up to 30% of families with Brugada syndrome. It is associated with a high incidence of sudden cardiac death resulting from VF. Risk assessment and therapy remain poorly defined at this time, but the implantation of an ICD has been advocated in patient with a Brugada pattern on their ECG and additional risk factors including a history of syncope or sudden cardiac death.

41. **b.** The mechanism of torsades de pointes (TdP) is believed to be related to early afterdepolarization. The pathognomonic arrhythmia associated with long-QT syndrome is TdP. The mechanism is believed to be related to early afterdepolarization and triggered activity. Sotalol causes QT prolongation and is contraindicated in patients with long QT. Hypokalemia, not hyperkalemia, is associated with an increase of TdP in this situation. EP testing is of no value and is not indicated for the risk stratification of patients with long-QT syndrome. Cardiac arrest occurs typically with vigorous activity and infrequently during sleep in LQT1 syndrome. Acute arousal events (emotion or noise) are much more likely to trigger events in LQT1 and LQT2 than LQT3. Events in LQT3 syndrome are common during sleep.

42. **c.** You should perform EP testing to evaluate the AV conduction system. The patient had an episode of near-syncope, which could be related to his GI bleeding, but the possibility of intermittent heart block in the setting of bifascicular block cannot be ruled out. This is a class I indication for EP testing to evaluate AV conduction. If there is evidence of abnormally prolonged HV interval, then a permanent pacemaker should be considered. If the syncopal episode was remote from the GI bleeding and based on the clinical history of the events there was a concern for intermittent high-degree AV block causing symptoms, then empiric placement of a PPM without an EP study prior would carry a class IIa indication. There is no indication for ICD placement in this setting. β-Blockers would blunt a reactive tachycardia resulting from the patient's anemia.

43. **e.** There is AV dissociation. In patients presenting with wide complex tachycardia, the presence of AV dissociation is highly specific for VT. All the other listed

parameters suffer from significant overlap between SVT and VT.

44. **c.** Procainamide, 15 mg/kg IV over 30 to 60 minutes. Wide complex tachycardia occurring after MI is most likely to be VT. Verapamil is contraindicated in this setting, as it might lead to hypotension and VF. DC cardioversion can be used if the patient does not respond to antiarrhythmic therapy or if he becomes hemodynamically unstable. Procainamide is the drug of choice because it treats ventricular as well as supraventricular arrhythmia. There is no role for digoxin and no need for urgent cardiac catheterization in this situation.

45. **b.** To admit the patient for IV antibiotics and pacemaker-system extraction. This presentation is consistent with pacemaker-system infection, which occurred following the recent pulse generator replacement. Antibiotics PO or IV without extraction of the pacemaker system have limited efficacy in eradicating the infection. The patient should undergo pacemaker-system extraction, followed by IV antibiotics, until negative blood cultures are obtained. A new pacemaker system can then be implanted on the right side.

46. **c.** Inadequate synchronization may occur with peaked T waves, low-amplitude signal, and malfunctioning pacemakers. Cardioversion is the delivery of electric energy synchronized on the R wave. A synchronized shock should be used in AFib. A nonsynchronized shock may result in VF if they fall near the middle of the T wave when there is a marked dispersion of refractoriness within the ventricle. Improper synchronization may occur in a situation in which more than one peaked signal exists, such as with pacemakers and peaked T waves. On the other hand, a low QRS signal may not synchronize at all. In patients with pacemakers, the pads are positioned at least 3 inches away from the pulse generator to minimize damage. MI and digoxin intake are not contraindications for DC cardioversion as long as digoxin toxicity is not suspected.

47. **d.** Procainamide. Procainamide can slow down conduction across the accessory pathway and potentially converts AFib. Diltiazem (Cardizem) and verapamil cause hypotension and a reflex increase in sympathetic activation and may result in increased ventricular response and in rare circumstances can lead to VF. Adenosine is of no use in this setting. Lidocaine has little effect on the refractory period of the accessory pathway.

48. **e.** Amiodarone. Amiodarone may allow maintenance of sinus rhythm in patients with AFib and cardiomyopathy. In low doses, the side effects are minimized. Flecainide and disopyramide are not used in patients with cardiomyopathy because of their

potential for proarrhythmia and their negative inotropic effects. Verapamil is not effective for maintenance of sinus rhythm. Sotalol might not be tolerated in patients with heart failure and has the potential for proarrhythmia in patients on diuretics prone to hypokalemia.

49. c. Digoxin can control the ventricular rate at rest in patients with AFib, but not with exercise. It is as effective as placebo for the acute conversion of AFib and does not help in maintaining NSR.

50. a. It may contribute to an increase in the digoxin level. Flecainide (amiodarone, propafenone [Rythmol], and verapamil) can increase digoxin level. Flecainide can regularize and slow the atrial rhythm in patients with AFib and can, therefore, lead to increased ventricular response because of improved conduction of the atrial impulses through the AV node. It is, therefore, important to use an AV nodal blocking agent in patients with AFib treated with flecainide. It is used for AFib as well as flutter; however, it needs to be used with caution in atrial flutter patients, as it may slow the cycle length of the flutter circuit and result in more rapid conduction to the ventricle. There are no definite data on its safety in patients with hypertrophic cardiomyopathy. It is effective for acute conversion as well as maintenance of NSR postconversion.

51. a. Change in the atrial refractory period as a result of the surgical manipulation. The occurrence of AFib post-cardiac surgery is believed to be related to shortening of the refractory period of atrial tissue as it recovers from surgical manipulation, cardioplegia, and, potentially, ischemia. This nonuniformity of recovery results in reentry as the mechanism of AFib.

52. a. AVNRT. This tracing shows AVNRT. It is a narrow complex tachycardia using the slow pathway of the AV node in the antegrade direction (long AH) and the fast pathway of the AV node in the retrograde direction (short HA). It is unlikely to be orthodromic reentrant tachycardia in which the retrograde limb of the circuit is an accessory pathway, because the QRS-A time is very short (atrium and ventricle are activated almost spontaneously), not long enough to involve ventricular activation as part of the circuit. Because the QRS is narrow, VT is not a likely diagnosis. Idiopathic LV-VT can sometimes be narrow but has an RBBB morphology on the surface ECG.

SUGGESTED READINGS

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Valvular Heart Disease

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QUESTIONS

Case 1

A 60-year-old man presents to the emergency room with complaints of weakness, lethargy, and severe dyspnea. One week prior, his family notes that he complained of chest pressure that lasted for several hours. On physical examination, he appears to be in respiratory distress. Blood pressure (BP) is 80/50 mmHg. Heart rate is 130 bpm. His oxygen saturation is 87% on room air. Chest examination reveals diffuse crackles. Cardiac examination reveals a nondisplaced point of maximum impulse (PMI). Third and fourth heart sounds are heard, as is an apical systolic murmur. No thrill is present. Electrocardiogram reveals inferior Q waves without ST-segment elevation. He is urgently intubated and pressors are started. An intra-aortic balloon pump is placed. A surface echocardiogram reveals a normal-sized left atrium and a mild jet of mitral regurgitation (MR).

1. What test do you perform first?

   a. Cardiac catheterization
   b. Transesophageal echocardiography (TEE)
   c. Right heart catheterization with an oxygen saturation run
   d. Administration of thrombolytic therapy

2. A TEE is performed urgently (Fig. 2.1 shows a 3D view of the mitral valve from above). What is the most likely diagnosis?

   a. Endocarditis involving the mitral valve
   b. Posterior papillary muscle rupture as it has a single blood supply
   c. Anterior papillary muscle rupture as it has a single blood supply
   d. Severe mitral valve prolapse secondary to recent myocardial infarction

Case 2

A 65-year-old woman presents to your office for follow-up of a murmur she was told about several years prior. She denies any symptoms, but is not very active. Her past medical history is significant for hypertension and diabetes, both of which have been well controlled. On examination, she is in no acute distress. BP is 125/75 mmHg, with a resting heart rate of 70 bpm. Lungs are clear. Cardiac examination reveals a displaced PMI. S_1 is soft. S_2 reveals an increased P_2 component. There is a right ventricular (RV) lift. An S_3 is present. There is a grade III/VI holosystolic murmur heard at the apex radiating to the base. She has no peripheral edema. Chest X-ray demonstrated cardiomegaly with prominence of the central pulmonary vasculature.

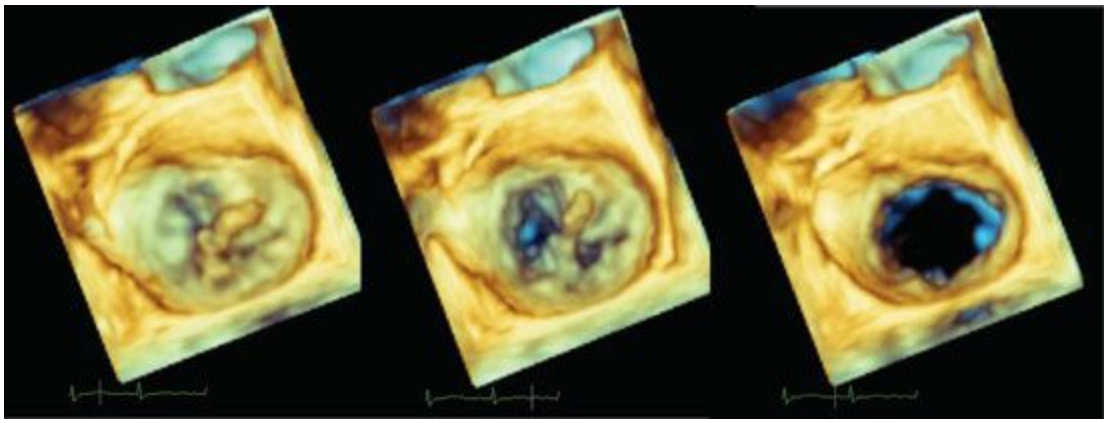

Figure 2.1

3. An echocardiogram is performed on this patient (Fig. 2.2). Left ventricular (LV) systolic dimension is 4.7 cm. Ejection fraction is 45%. There is posterior leaflet prolapse. There is a very eccentric jet of MR, which is read out as 2+. Which of the following is most likely?

    a. MR is unlikely to account for her presentation.
    b. She likely has more severe MR than is evident on the echocardiogram.
    c. Her LV function is better than it appears on the echocardiogram.
    d. TEE is unlikely to be helpful here.

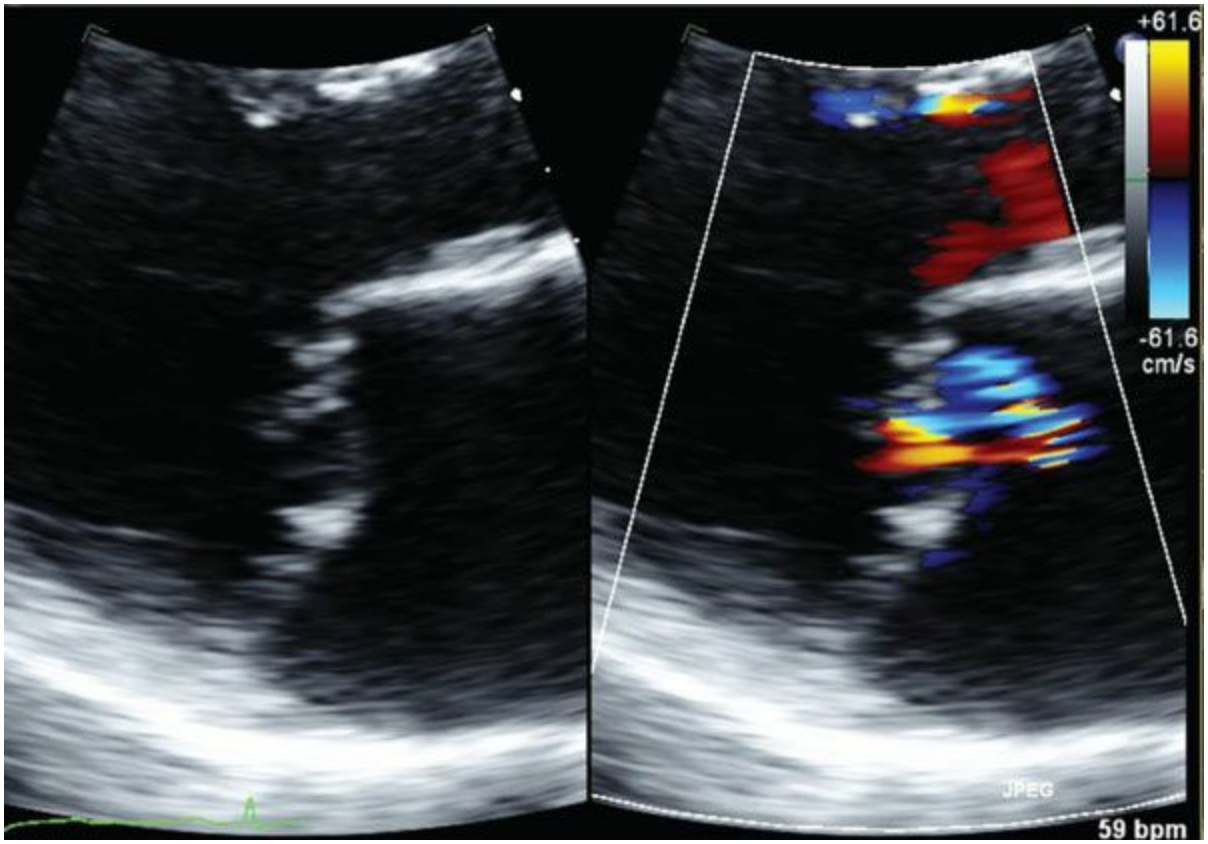

Figure 2.2

4. What do you recommend next?

   a. Stress echo, to assess LV and PA (pulmonary artery) pressures post stress
   b. Mitral valve surgery
   c. Start an angiotensin-converting enzyme inhibitor (ACEI) and reassess in 3 months
   d. Start a β-blocker

Case 3

A 40-year-old woman is referred to your office for evaluation of a murmur heard during a routine physical examination. She is asymptomatic. She used to jog 2 to 3 miles a day without problems but over the past few years has stopped exercising. She had frequent febrile illnesses as a child, but her past medical history is otherwise unremarkable.

Physical Examination

BP 120/70 mmHg, pulse 73 bpm.
She is in no acute distress.
Jugular venous pulse (JVP) is not elevated.
Chest is clear.
Cardiac—PMI not displaced. Regular rate and rhythm. S_1 is increased in intensity.

S_2 is normal. A high-pitched diastolic sound is heard at rest and is heard best between the apex and left sternal border, 0.10 seconds after S_2. This is followed by a low-pitch decrescendo murmur with pre-systolic accentuation.
Abdomen—No organomegaly.
Extremities—No edema. Normal distal pulses. Good capillary refill.

An echocardiogram is performed (Fig. 2.3); proximal flow convergence radius (PFCR) using color 3D across the mitral valve indicates an orifice area of 1.2 cm^2. Resting PA pressures are 35 mmHg. Splittability score is 5. LV size and function are normal.

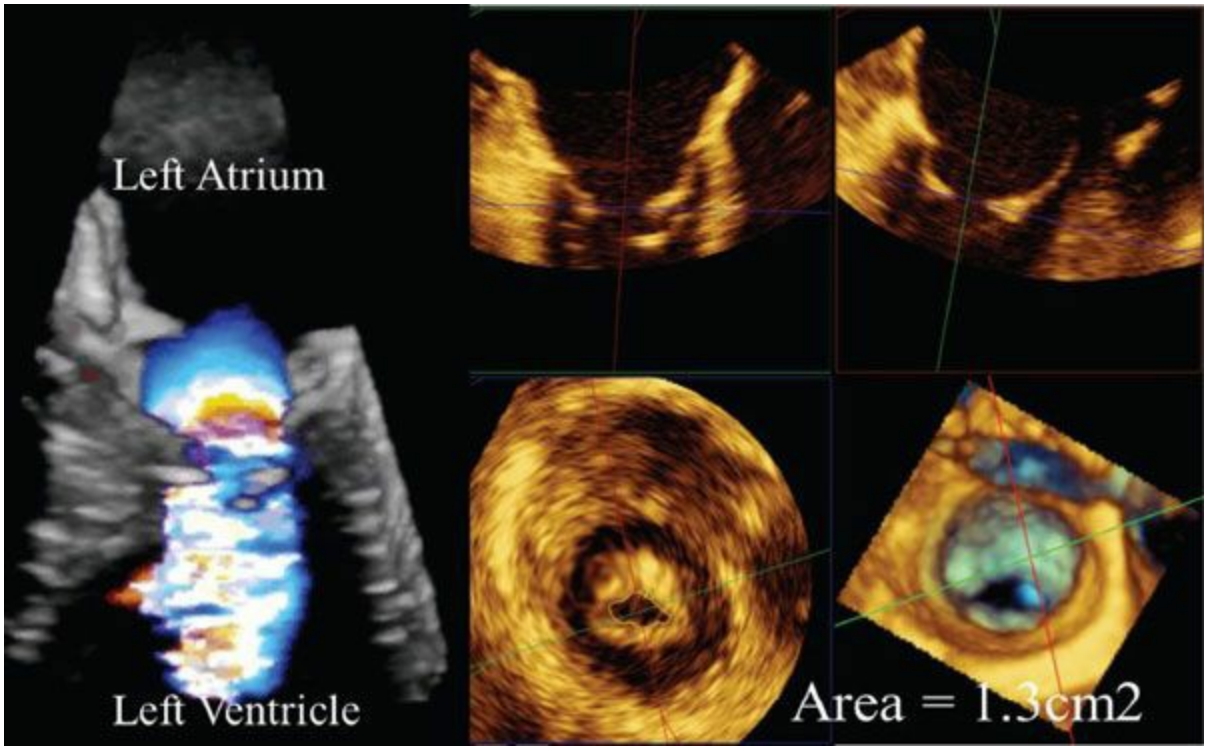

Figure 2.3

5. Which of the following would be the most reasonable next step in management?

   a. Immediate referral for surgery
   b. Immediate referral for percutaneous valvuloplasty
   c. Stress echocardiogram, to assess for mitral pressures post stress
   d. Follow-up in 2 years

6. A stress echocardiogram is performed. Patient exercises for 6 metabolic equivalents (METs). Right ventricular systolic pressure post stress is estimated at 70 mmHg. Which of the following would be an appropriate next step?

   a. Consideration for percutaneous valvuloplasty

b. Mitral valve replacement
c. Start β-blocker and return for follow-up in another 2 years
d. Start digoxin

Case 4

A 50-year-old woman presents to you for evaluation. She complains of easy fatigability, as well as abdominal fullness and right upper quadrant pain. She also notes marked swelling in her legs. She has recently been diagnosed with asthma and is also undergoing evaluation for recurrent diarrhea. On examination, she has a BP of 100/60 mmHg. Heart rate is 96 bpm. There is elevation in jugular venous pressure, with a large a wave and a prominent v wave. Lungs are clear. Cardiac examination reveals a nondisplaced PMI. Rhythm is regular. S_1 and S_2 (including P_2) are normal. A diastolic murmur is heard along the sternal border, which increases with inspiration. A pansystolic murmur is also heard in this area. Hepatomegaly is present, along with ascites and peripheral edema.

7. What is the most likely cause of this patient's signs and symptoms?

a. Rheumatic heart disease
b. Carcinoid
c. Primary pulmonary hypertension
d. Cirrhosis of the liver secondary to chronic hepatitis

Case 5

A 28-year-old man is referred to your office for a second opinion regarding his hypertension. On physical examination, he is in no acute distress. BP is 160/90 mmHg, symmetric in both arms. Pulse rate is 75 bpm. Cardiac examination reveals a nondisplaced PMI. S_1 is normal. It is followed by a high-pitched sound widely transmitted throughout the precordium. A short II/VI systolic ejection murmur is heard. S_2 is normal.

8. What is the most important diagnostic test to perform next?

a. Check plasma catecholamines.
b. Check serum potassium level.
c. Check lower extremity BP.
d. Check plasma cortisol levels.

Case 6

A 59-year-old man presents for further evaluation of recurrent congestive heart failure. He appears to be in no acute distress on your evaluation. BP is 100/60 mmHg. Carotid upstrokes are weak, but not delayed. Chest examination shows minimal bibasilar rales. PMI is displaced and sustained. A summation gallop is present. There is an increased

P_2. There is mild peripheral edema. An echocardiogram reveals a dilated LV with an ejection fraction of 25%. The aortic valve does have some calcification, with restricted leaflet excursion. Peak/mean gradients are 25/15 mmHg. By the continuity equation, the aortic valve area is calculated as 0.7 cm^2.

9. What is your next step?

- **a.** Immediate referral for aortic valve replacement (AVR)
- **b.** Referral for cardiac transplant
- **c.** Dobutamine echocardiogram
- **d.** Start an ACEI

10. With dobutamine echocardiography, the gradients across the valve increase to 60/40 mmHg, and the calculated valve area stays at 0.7 cm^2. What do you recommend?

- **a.** AVR
- **b.** Continued medical management
- **c.** Cardiac transplant evaluation
- **d.** Balloon aortic valvuloplasty

11. Alternatively, how would you interpret the following results: an increase in stroke volume by 5% and an increase in peak/mean gradients to 30/19 mmHg without a significant change in the aortic valve area?

- **a.** Patient has true severe aortic stenosis (AS) and should proceed to surgery.
- **b.** Patient has pseudo-AS and should be managed with medical therapy alone.
- **c.** Patient has a lack of contractile reserve and should be managed with medical therapy alone.
- **d.** Patient has a lack of contractile reserve but should still be considered for AVR.

Case 7

A 32-year-old man with known bicuspid aortic valve is referred to you for management of aortic insufficiency (AI). He is completely asymptomatic and jogs 3 miles a day as well as doing other aerobic exercise for 30 minutes daily. He has a grade III/VI systolic and diastolic murmur at his left sternal border, a collapsing pulse on examination, and his BP 170/70 mmHg. An echocardiogram reveals a mildly dilated LV (end-diastolic dimension of 6.0 cm) with an ejection fraction of 65%. There is prolapse of the conjoined aortic leaflet with 3 to 4+ insufficiency.

12. What is your recommendation?

- **a.** Referral for surgery

b. Addition of vasodilator therapy
c. Observation for now, return for follow-up in 3 years
d. Cardiac catheterization

13. What do you tell him is his yearly risk of sudden death?

a. <1%
b. 2%
c. 3% to 5%
d. >5%

14. The above patient undergoes a gated computed tomography angiography of the thorax (Fig. 2.4), what would you recommend?

a. Observation with echocardiography every 6 months
b. Start a β-blocker and reassess in 6 months
c. Refer to computed tomographic (CT) surgery for surgical replacement of his aortic valve
d. Referral for surgical intervention to repair or replace his aortic valve and to replace his ascending aorta

Case 8

A 76-year-old woman has been accepted for AVR for severe symptomatic AS. Your opinion is sought by the cardiothoracic surgeon regarding best management of reported concomitant valvular lesions. On review of the echocardiogram you confirm severe AS. In addition, you note a morphologically normal mitral valve, mild MR, and moderate tricuspid regurgitation (TR) associated with annular dilation (45 mm). There is also mild pulmonary hypertension.

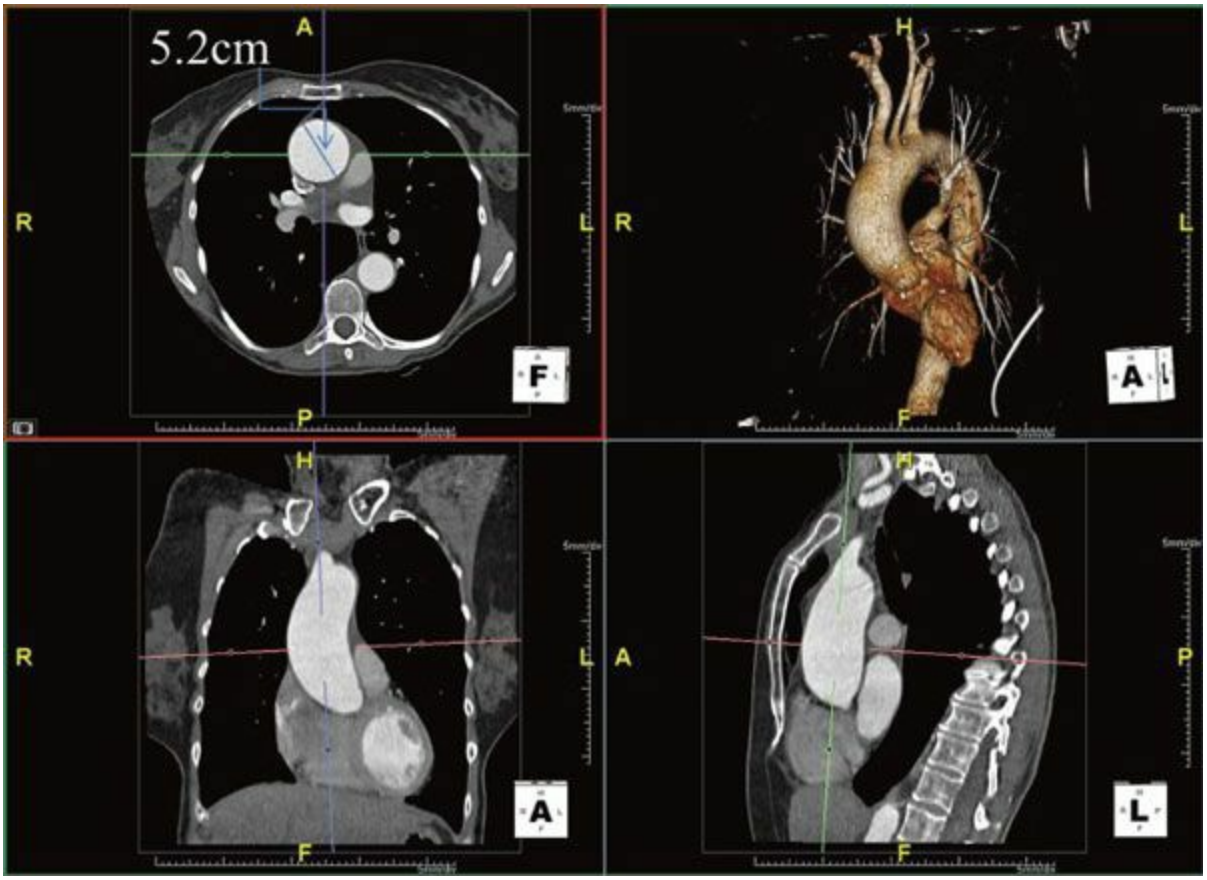

Figure 2.4

15. What do you recommend?

- **a.** AVR alone
- **b.** AVR with mitral and tricuspid valve repair
- **c.** AVR with tricuspid valve replacement
- **d.** AVR with tricuspid valve repair if feasible
- **e.** AVR and mitral valve repair alone

Case 9

A 46-year-old woman with chronic obstructive pulmonary disease is referred by her pulmonologist for evaluation of a murmur and concern that her symptoms of shortness of breath with moderate exertion may be related to severe MR diagnosed on an outside echocardiogram. On examination, her body mass index is 19 kg/m^2, BP is 130/75 mmHg, and her heart rate is 75 bpm and regular. Her apex beat is nondisplaced. On auscultation, S_1 and S_2 are normal; there is a mid-systolic click with a grade IV/VI late systolic murmur heard best at the apex. An echocardiogram is performed (Fig. 2.5A).

16. Assuming an aliasing velocity of 40 cm/s and an MR V_{max} of 5 m/s, based on the PFCR seen here, what is the estimated effective regurgitant orifice area (EROA)?

a. 0.4 cm^2
b. 0.45 cm^2
c. 0.18 cm^2
d. Not enough information to calculate an EROA

17. A continuous-wave signal is provided through the mitral valve (Fig. 2.5B); based on the data provided how would you classify this MR?

a. 1+, mild
b. 2+, moderate
c. 3+, moderately severe
d. 4+, severe

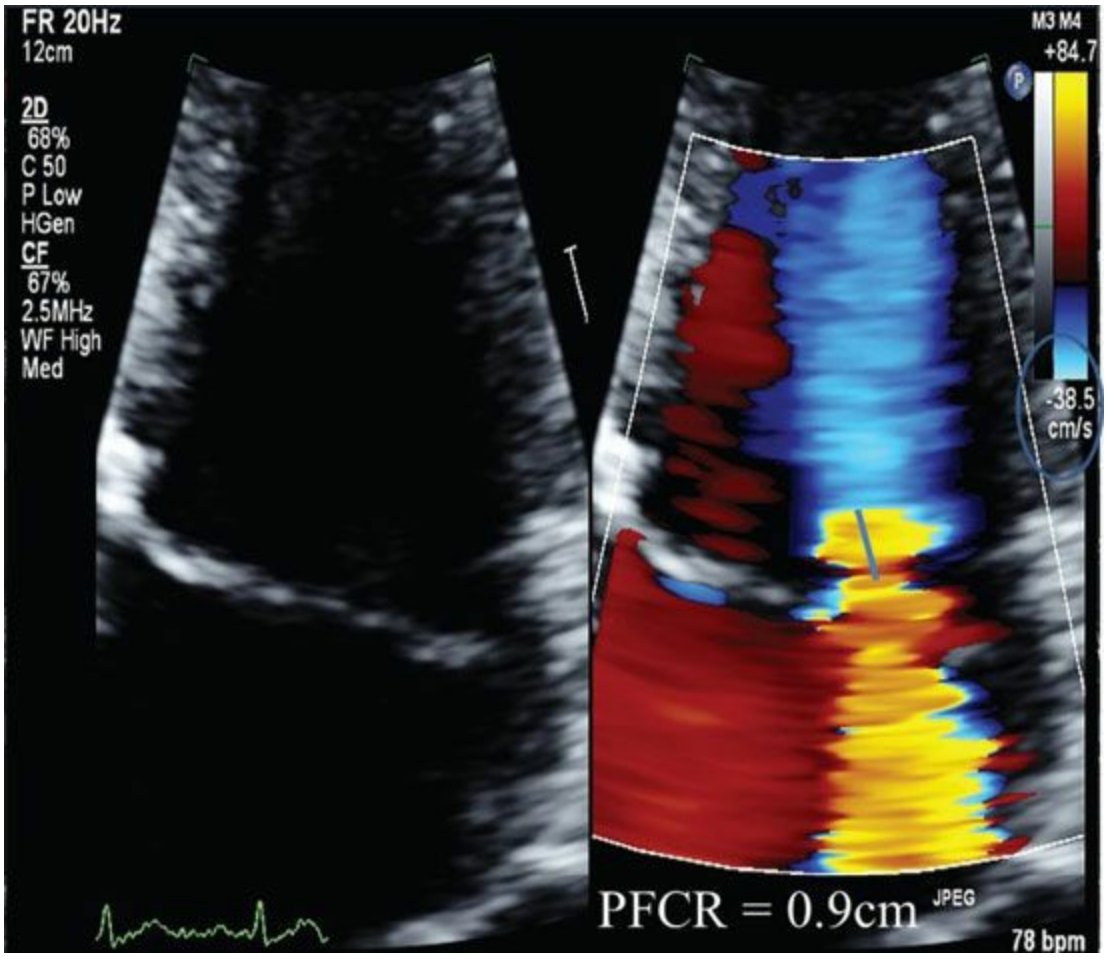

Figure 2.5A

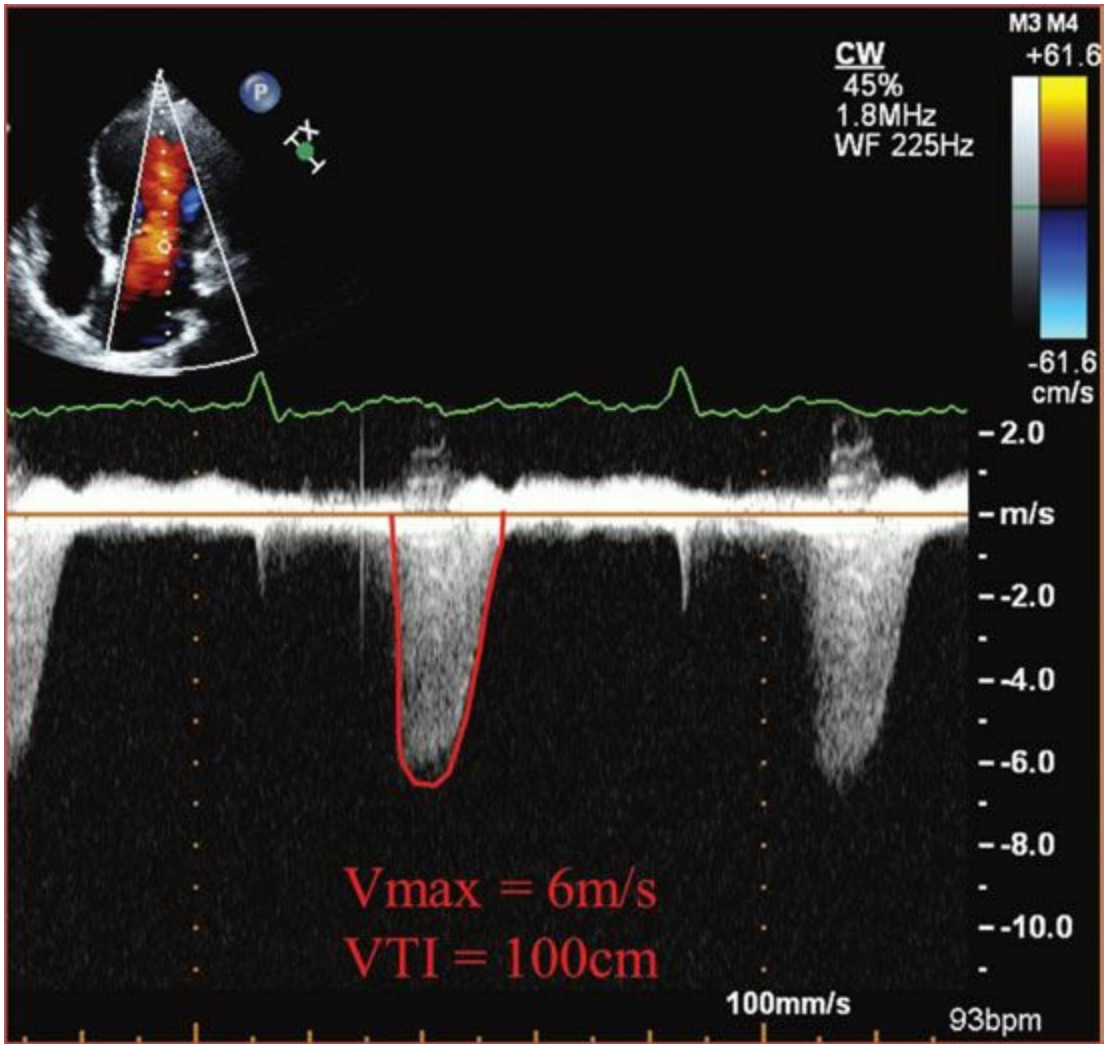

Figure 2.5B

Case 10

A 45-year-old man with rheumatic mitral stenosis presents for further evaluation. In the past 2 to 3 years, he has noted progressive dyspnea with less than moderate activity. He was started on a β-blocker 1 year ago, but remains symptomatic. Echocardiogram reveals a mean mitral gradient of 4 mmHg with a valve area of 1.6 cm^2. As there was a discrepancy between the degree of symptoms and resting hemodynamics you proceed to a stress echocardiogram that revealed a post stress PA pressure of 70 mmHg and a mean transmitral gradient of 17 mmHg. You decide to send this patient for percutaneous intervention.

18. What is the most appropriate test to order at the time of or prior to the valvuloplasty procedure?

a. Transesophageal echocardiogram
b. 24-Hour electrocardiographic monitoring to assess for paroxysmal atrial fibrillation

c. Cardiac CT to assess for aortic calcification
d. Stress nuclear perfusion study

Case 11

A 65-year-old man is referred to you for evaluation of a heart murmur. He denies any symptoms at this time. On physical examination, he is in no acute distress. BP is 135/75 mmHg; pulse is 82 bpm and regular. Carotid upstrokes are diminished. The PMI is sustained and displaced. A_2 is soft. A late-peaking systolic murmur is heard at the base. You order an echocardiogram. This reveals LV hypertrophy with moderate global impairment of LV function, calculated ejection fraction of 35%. There is severe calcific AS, with peak/mean gradients of 75/45 mmHg. Aortic valve area is 0.5 cm^2.

19. What is the role of AVR in this setting?

a. It is absolutely indicated.
b. It is absolutely not recommended.
c. There is some evidence/opinion that would favor valve replacement.
d. Dobutamine echocardiography is needed to determine whether this is truly severe AS.

Case 12

A 76-year-old woman is referred to your clinic with recent onset of exertional chest pain. She has a long-standing history of hypertension and atrial fibrillation. On examination, her body surface area is 2.0 m^2, BP is 150/100 mmHg, and heart rate is 80 to 90 bpm and irregular. The carotid upstroke is delayed and diminished. The apex beat is nondisplaced but sustained. S_1 is normal, and S_2 is soft and paradoxically split. There is a grade II/VI ejection systolic murmur heard best at the right upper sternal border that radiates to the carotids. An echocardiogram reports normal ejection fraction with a stroke volume of 55 mL. The peak and mean gradients across the aortic valve are 44/28 mmHg. The dimensionless index is 0.21 and the calculated aortic valve area is 0.83 cm^2. You review the echocardiogram (Fig. 2.6) and confirm the accuracy of the left ventricular outflow tract (LVOT) diameter and are satisfied that multiple windows were used to obtain the gradients.

20. Which of the following statements is true?

a. The patient has moderate AS confirmed by gradients across the valve and should be followed up in 6 months with a repeat echocardiogram.
b. The echocardiogram shows inconsistent data and should be repeated.
c. This is a definite contraindication to AVR.
d. The rate of mortality, for a patient with these findings, is higher compared with patients with severe AS and high gradients across the aortic valve, but aortic

valve surgery has resulted in better outcomes in these patients.

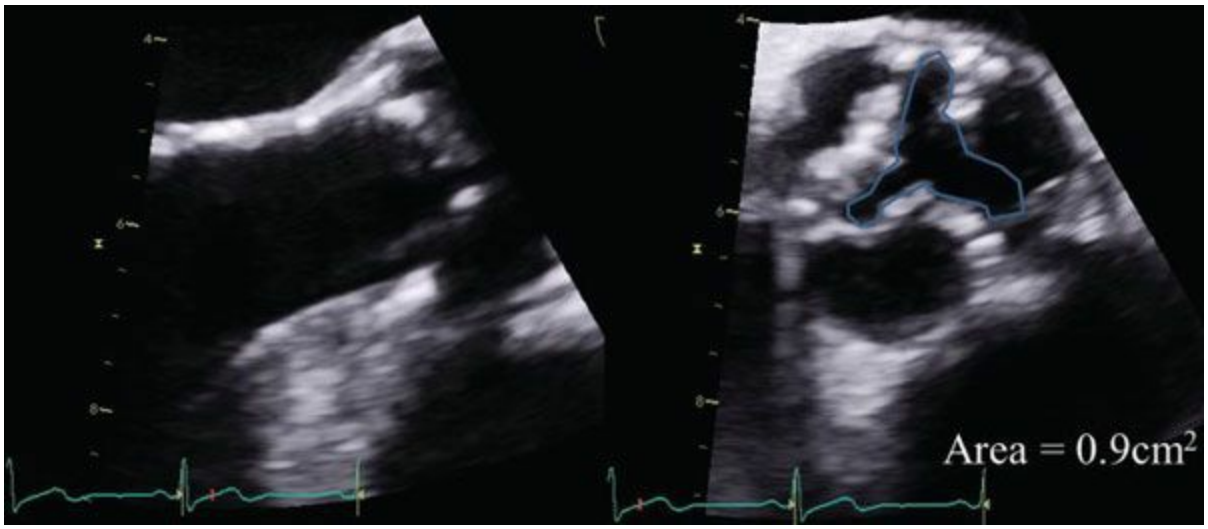

Figure 2.6

Case 13

A 75-year-old man is referred to you for evaluation of aortic regurgitation. He has no symptoms at this time. His past medical history is significant only for hypertension. On physical examination, he is in no acute distress. BP is 170/60 mmHg. Arterial pulses are brisk. A bisferiens pulse is noted in the brachial artery. The apical impulse is displaced and hyperdynamic. S_1 is not loud, and no opening snap is heard. A high-frequency holodiastolic murmur is heard, loudest along the right sternal border. A late diastolic apical rumble is heard as well.

21. You order an echocardiogram. Which of the following are you most concerned about?

- **a.** Aortic valve commissural anatomy
- **b.** Degree of AI
- **c.** Aortic root dimension
- **d.** Mitral valve

22. The above patient returns for follow-up 6 months later. He now reports symptoms of marked exertional dyspnea. An echocardiogram is read as 2+ central aortic regurgitation, with an LV end-diastolic dimension of 6.9 cm and an ejection fraction of 50%. What do you do next?

- **a.** Cardiac catheterization with aortography
- **b.** Start an ACEI, reassess in 6 months
- **c.** Continue observation
- **d.** Start a β-blocker, reassess in 6 months

Case 14

A 56-year-old man presents to the emergency room with the sudden onset of chest pain. He is tachypneic on presentation. O_2 saturation is 82% on room air. BP is 80/60 mmHg. Heart rate is 125 bpm. Lung examination reveals diffuse bilateral crackles. Cardiac examination reveals a nondisplaced PMI. S_1 is soft. P_2 is loud. An S_3 is present. A short decrescendo diastolic murmur is heard at the upper sternal border. Extremities are cool. Electrocardiogram reveals inferior ST-segment elevation. He is promptly intubated, and pressors are started. A brief echocardiogram is performed at the bedside. The study is difficult, but reveals premature closure of the mitral valve. There is hypokinesis of the inferoposterior walls.

23. Which of the following would be your next course of action?

- **a.** Transesophageal echocardiogram, emergent cardiac surgical consultation
- **b.** Intra-aortic balloon pump to stabilize hemodynamics, followed by emergent angiography
- **c.** Administer thrombolytics
- **d.** Send patient for magnetic resonance imaging (MRI)

Case 15

A 77-year-old patient is admitted to the hospital for urosepsis. His past medical history is significant only for having undergone AVR 5 years prior. On examination, he is febrile to 102°F. Heart rate is 106 bpm. Carotid upstrokes are full. Chest examination reveals clear lung fields. Cardiac examination reveals a hyperdynamic apical impulse, which is not displaced. S_1 and S_2 are normal. An early-peaking systolic murmur is heard at the sternal border. No diastolic murmur is heard. An echocardiogram is performed. Peak/mean gradients are 50/30 mmHg. LVOT VTI (velocity time integral) is 36 cm and aortic valve VTI is 78 cm. The aortic valve itself is not well seen. Flow in the descending thoracic aorta is normal. An echocardiogram 2 years prior had revealed peak/mean gradients of 24/12 mmHg. LVOT VTI was 19 cm and aortic valve VTI 41 cm.

24. What do you conclude about prosthetic aortic valve function?

- **a.** He has prosthetic valve stenosis
- **b.** No evidence for dysfunction
- **c.** He has severe prosthetic valve regurgitation
- **d.** He likely has endocarditis

25. The above patient remains febrile despite 1 week of antibiotic therapy. Electrocardiogram reveals a new long first-degree atrioventricular (AV) block. The patient becomes progressively dyspneic. A short, regurgitant murmur is heard.

What do you recommend?

a. TEE with surgical consultation
b. TEE
c. Change antibiotic regimen
d. Monitor closely with daily electrocardiogram

Case 16

A 56-year-old man with mitral stenosis presents for evaluation. He has NYHA class II-III shortness of breath.

Physical Examination

He is in no acute distress.
JVP is mildly elevated.
Pulse is regular at 80 bpm.
Chest is clear.
Cardiac: Nondisplaced PMI. Opening snap heard 0.09 milliseconds after S_2. Long diastolic rumble. No peripheral edema.
Echocardiogram reveals a planimetered mitral valve area of 1.2 cm^2. Mean gradient 10 mmHg. Pressure half-time of 185 milliseconds.
He undergoes percutaneous valvuloplasty. The following morning, on examination, you note that he is comfortable. His oxygen saturation is 100% on room air. Opening snap is 0.12 milliseconds after S_2. A shorter decrescendo diastolic rumble is heard. You obtain a predischarge echocardiogram. The report indicates a pressure half-time of 180 milliseconds.

26. What do you do next based on the echocardiogram?

a. There was a less-than-optimal result from the valvuloplasty. No significant change in mitral valve area was achieved. You plan to send him for another procedure or surgery.
b. There was an error in half-time measurement. You order a repeat assessment of pressure half-time later that day.
c. Repeat echocardiogram with planimetry of mitral valve area.
d. Consider TEE to see the valve opening better.

27. The echocardiogram reveals a small left-to-right shunt at the atrial level by color. What do you recommend?

a. Observation
b. Referral for percutaneous closure
c. Referral for surgical closure

d. Indefinite anticoagulation

Case 17

An 80-year-old man underwent successful AVR with a bioprosthetic valve 4 months ago. He presents to your office for a routine follow-up visit. He is asymptomatic. He is in sinus rhythm. Echocardiogram reveals a normally functioning prosthetic valve. Chamber dimensions are normal with normal biventricular function. He has no clinical history of embolic events.

28. Which of the following should you recommend?

a. Antibiotic prophylaxis, office visits if he feels unwell
b. Antibiotic prophylaxis, with yearly office visits
c. Warfarin therapy indefinitely
d. Clopidogrel therapy indefinitely

Case 18

A 28-year-old 20-week pregnant woman is referred to your clinic after being diagnosed with mitral valve prolapse and severe MR on an echocardiogram ordered by her obstetrician. She reports no symptoms prior to pregnancy but since being told her diagnosis is extremely worried and has noticed some shortness of breath on exertion (New York Heart Association [NYHA] class II). She is clinically euvolemic.

29. What do you recommend?

a. Antibiotics at the time of delivery
b. Commence afterload reduction with an ACEI given her new onset symptoms
c. Refer to an experienced surgeon for consideration for mitral valve repair as there is a high likelihood of successful durable repair
d. Commence afterload reduction with diuretics and hydralazine
e. No therapy at present but follow carefully with serial clinical and echo evaluation

Case 19

A 67-year-old woman is referred to your office for evaluation of a heart murmur. She describes symptoms of significant and limiting exertional dyspnea. On examination, she is normotensive. Pulse rate is 67 bpm and regular. Cardiac examination reveals a sustained but nondisplaced PMI. S_1 and S_2 are normal. An S_4 is present. A loud III/VI systolic ejection murmur is heard throughout the precordium. Carotid upstrokes are delayed and diminished. An echocardiogram is performed (Fig. 2.7); continuous-wave Doppler evaluation reveals a 4.5-m/s jet across the LVOT.

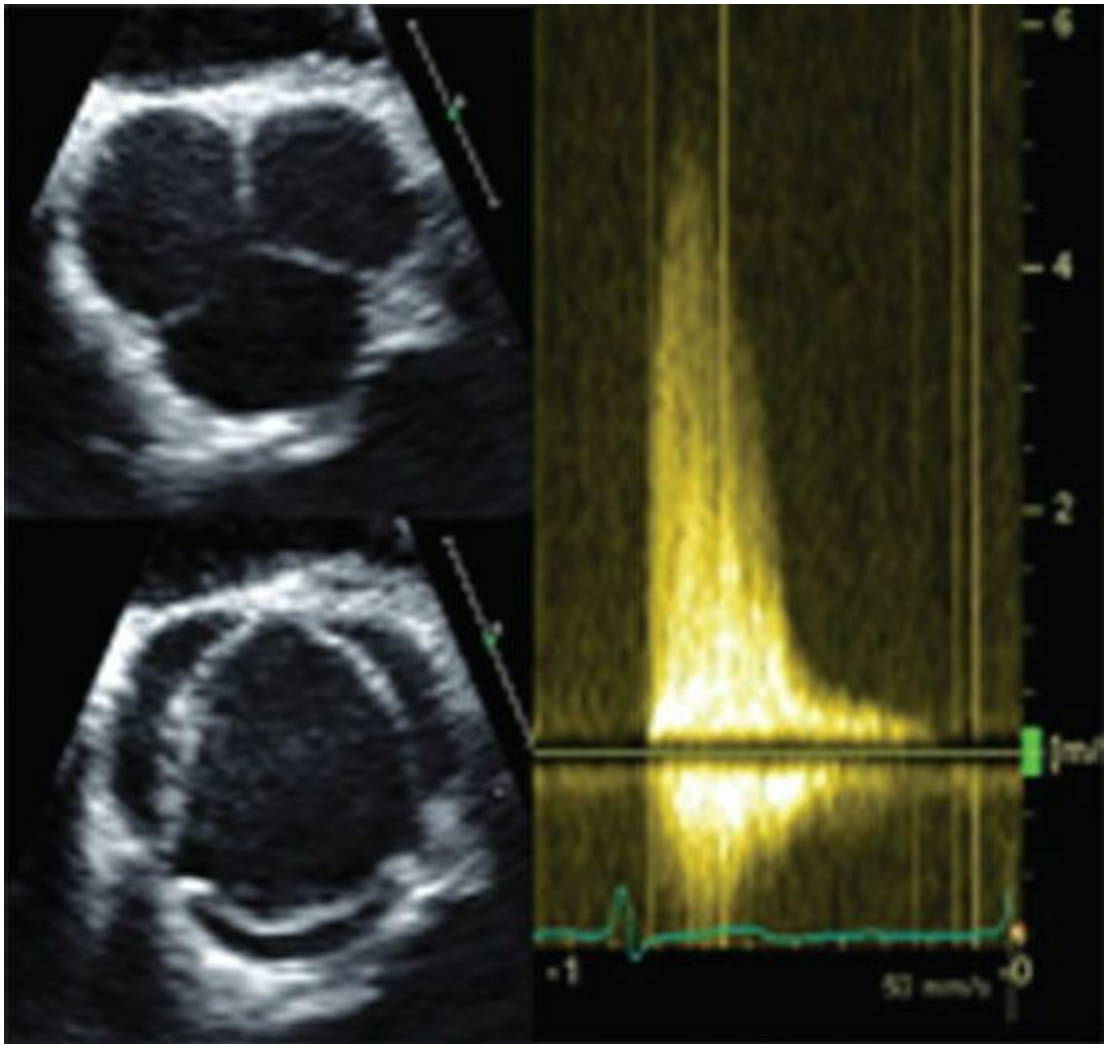

Figure 2.7

30. Which of the following would you do next to arrive at a diagnosis?

a. TEE
b. Repeat echocardiogram with amyl nitrate
c. Stress echocardiogram
d. Dobutamine echocardiogram
e. The Pedoff probe has picked up an MR signal, the MR appears mild on all other views, no need for further investigation

Case 20

A 30-year-old woman presents to your office for a routine physical examination. She is asymptomatic. BP is 95/65 mmHg, with a resting heart rate of 65 bpm. Physical examination is remarkable for a mild pectus deformity. On cardiac auscultation, a mid-systolic click is heard. The click is heard earlier in systole with standing, and later in systole with squatting. No murmur is heard at rest, but a soft systolic murmur becomes audible with dynamic maneuvers.

31. Echocardiography demonstrates no high-risk features. What is the role of aspirin therapy in such patients who have had no evidence of embolic events?

a. Should be prescribed to all patients
b. May play a role, if a murmur is heard
c. There is no clear role for aspirin therapy in such patients

Case 21

A 50-year-old man with severe AI is referred to you for a second opinion. He is asymptomatic. An echocardiogram reveals a mildly dilated LV (end-diastolic dimension of 6.2 cm and end-systolic dimension of 3.5 cm) with a normal ejection fraction. He has already undergone a stress echocardiogram. He exercised for 14 METs. No symptoms or electrocardiographic changes were noted. Resting ejection fraction was calculated at 65%. Post stress, the ejection fraction is 60%. No segmental wall motion abnormalities were seen.

32. What do you recommend?

a. Surgical intervention
b. Continue with vasodilator therapy and reassess in 6 months
c. Cardiac catheterization
d. Stress nuclear ventriculogram

Case 22

A 70-year-old man presents to your office with complaints of exertional dyspnea. He is mildly hypertensive on examination. Carotid upstrokes are brisk, with a secondary upstroke. A loud III/VI systolic murmur is heard along the sternal border radiating to the neck. S_1 and S_2 are normal. An S_4 is heard. The murmur increases in intensity with Valsalva and decreases with handgrip.

33. An echocardiogram reveals a <2-m/s jet across the LVOT. What is your next step?

a. Repeat the echocardiogram, but have Doppler interrogation performed in other views and with a nonimaging transducer. The degree of AS has been underestimated
b. Repeat the echocardiogram with amyl nitrate
c. Transesophageal echocardiogram to better assess the valves
d. Coronary angiography

Case 23

A 26-year-old woman with a history of hypertrophic obstructive cardiomyopathy is referred for consideration for septal myectomy. She has NYHA class III dyspnea on exertion despite maximal medical therapy. On echocardiography, there is severe asymmetric septal hypertrophy with severe systolic anterior motion of the mitral valve.

There is a late-peaking gradient across the LVOT of 60 mmHg, which increased to 105 mmHg with Valsalva. She has a structurally normal mitral valve on cardiac MRI with moderately severe posteriorly directed MR (Fig. 2.8).

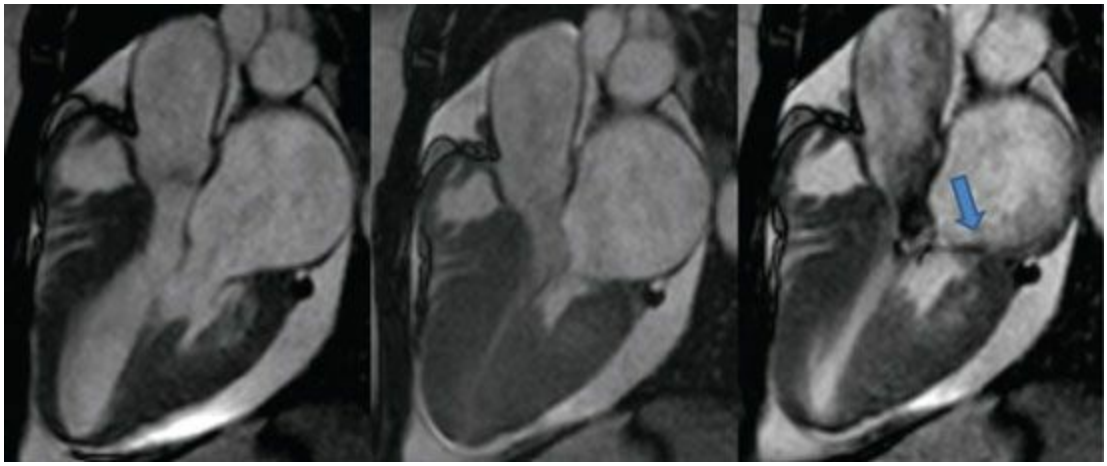

Figure 2.8

34. What would you advise her regarding surgery?

- **a.** She will probably require mitral valve replacement at the time of surgery.
- **b.** She will probably require mitral valve repair during surgery.
- **c.** She will probably not need surgery on her mitral valve.
- **d.** She may need plication of her papillary muscles.

Case 24

A 62-year-old man with a history of rheumatic heart disease presents to your office with complaints of exertional dyspnea. No constitutional complaints are present. He had undergone a mitral valve replacement with a bileaflet tilting disk mechanical valve 11 years prior. He is normotensive with a heart rate of 73 bpm. On examination, you note a grade II/VI holosystolic murmur at the apex. An echocardiogram is performed, which reveals normal LV and RV function. Peak mitral gradient is 30 mmHg. Mean transmitral gradient is 7 mmHg. Pressure half-time is 80 milliseconds.

35. What is your next diagnostic step?

- **a.** Fluoroscopy of the valve
- **b.** Transesophageal echocardiogram
- **c.** Invasive assessment of hemodynamics
- **d.** Draw blood cultures

36. Which of the following would be the expected physical findings in this patient if the valve were functioning normally?

a. Prominent closing click, soft and brief diastolic rumble
b. Prominent opening and closing clicks, soft and brief diastolic rumble
c. Prominent opening click, long diastolic rumble
d. Prominent closing click, systolic murmur

37. If the patient had a ball-and-cage valve instead, what would you expect to hear?

a. Prominent closing click, soft and brief diastolic rumble
b. Prominent opening and closing clicks, soft and brief diastolic rumble
c. Prominent opening click, long diastolic rumble
d. Prominent closing click, systolic murmur

38. Recommended antithrombotic therapy for a patient with a mechanical mitral valve replacement without a prior thromboembolic event or other high-risk features is

a. Warfarin therapy with a target international normalized ratio (INR) of 3.0 to 4.0
b. Warfarin therapy with a target INR of 2.5 to 3.5
c. Warfarin therapy with a target INR of 2.0 to 3.0 plus aspirin 75 to 100 mg
d. Warfarin therapy with a target INR of 2.5 to 3.5 plus aspirin 300 mg
e. Warfarin therapy with a target INR of 2.5 to 3.5 plus aspirin 75 to 100 mg

Case 25

A 65-year-old man presents to your office for evaluation of valvular heart disease. He is asymptomatic. He walks 5 miles a day without difficulty. An echocardiogram reveals severe AS, with a maximum aortic jet velocity of 4.7 m/s by Doppler echocardiography. LV systolic function is preserved. There is mild LV hypertrophy (wall thickness 1.4 cm). He walks on a treadmill for 9 minutes, with a normal hemodynamic response.

39. Continued observation is recommended. What do you tell him is his yearly risk of sudden death, provided he remains asymptomatic?

a. <2%
b. 5%
c. 5% to 10%
d. >10%

40. What is the likelihood that he will become symptomatic, or come to surgery, within the next 3 years?

a. 10%
b. 10% to 25%
c. 25% to 50%
d. >50%

Case 26

A 52-year-old man who previously underwent AVR with a tilting disk valve presents to you several months following a documented transient ischemic attack (TIA). He has no symptoms at present. Workup at the time of his TIA included carotid Dopplers, and transthoracic and transesophageal echocardiogram. These were unremarkable. The valve was well seated and was functioning normally. No thrombus was seen. Only minimal aortic atheroma was seen. No intracardiac shunt was identified. He has been on warfarin throughout and has maintained an INR between 2 and 3. INR was 2.2 at the time of his TIA. On examination, he is in no acute distress. BP is 120/80 mmHg; pulse is 68 and regular. Carotid upstrokes are full and not delayed. Crisp valve closure sound is heard along with a short, early-peaking systolic ejection murmur at the base. No S_3 is heard. P_2 is normal. No peripheral edema is noted.

41. Which of the following would you recommend?

- **a.** Start ASA (acetylsalicylic acid), 325 mg/day.
- **b.** Increase warfarin, to achieve an INR of 3.5 to 4.5.
- **c.** Increase warfarin, to achieve an INR of 4.0 to 5.0.
- **d.** Start ASA, 81 mg/day, and increase warfarin, to achieve an INR of 2.5 to 3.5.

42. If his transesophageal study had revealed a small (1 to 2 mm) echodensity on the valve strut—suggestive of thrombus—but no obstruction to valve function, what should have been done?

- **a.** Intravenous heparin
- **b.** Bolus thrombolytic therapy
- **c.** Reoperation
- **d.** Intravenous IIb/IIIa inhibitors

Case 27

You are following a 50-year-old man with moderate mitral stenosis, who had been asymptomatic. He presents to the emergency room with complaints of mild exertional dyspnea and palpitations, present for the past 3 to 4 days. On arrival, he appears comfortable, with an O_2 saturation of 99% on room air. His pulse rate is 140 bpm and irregular. BP is 130/75 mmHg. Electrocardiogram reveals atrial fibrillation.

43. The above patient spontaneously converts to sinus rhythm. Which of the following are you most likely to recommend?

- **a.** Therapy with warfarin
- **b.** Percutaneous valvuloplasty
- **c.** Mitral valve replacement

d. No change in therapy

Case 28

A 34-year-old woman presents to your office for evaluation because she had been on treatment with anorectic agents 5 years ago. She is asymptomatic at this time. She is now at her ideal body weight. On examination, she is in no acute distress. BP is 107/68 mmHg. Jugular venous pulsations appear normal. Chest is clear. Cardiac examination reveals a nondisplaced PMI. S_1 and S_2 are normal, with an appropriate physiologic split of S_2. P_2 is not loud. No S_3 or S_4 is heard. Auscultation is performed with the patient sitting, supine, and in the left lateral decubitus position. No murmur is heard.

44. What do you most likely recommend for this patient?

a. Reassurance, with a repeat physical examination in 6 months
b. Echocardiogram
c. Stress test
d. TEE

Case 29

A 50-year-old man presents for his first physical examination in several years. He notes that a murmur had been documented a number of years ago. He is entirely asymptomatic. On examination, he has a BP of 120/70 mmHg with a pulse rate of 58 bpm. Neck veins are not distended. Carotid upstrokes are brisk. Lungs are clear. Cardiac examination reveals a nondisplaced PMI. S_1 is soft; S_2 is normal (with a preserved A_2). An S_3 is heard. A III/VI holosystolic murmur is heard at the apex radiating to the base and carotids, which increases with handgrip.

Echocardiogram reveals myxomatous mitral valve disease with posterior leaflet prolapse and severe MR. The prolapse involves the P_2 (middle) segment and is severe. There is no calcification of the valve. End-systolic dimension is 3.0 cm; end-diastolic dimension is 5.6 cm. Ejection fraction is 65%. TR velocity is 2.9 m/s.

45. Which of the following would be most appropriate at this time?

a. Referral for mitral valve replacement
b. Consider elective mitral valve repair at a hospital where repair is performed with a high degree of success or if he wishes to defer surgery, follow up at 6 monthly intervals with echo
c. The addition of an ACEI and follow-up in 2 years
d. The addition of amiodarone to prevent atrial fibrillation
e. Follow-up in 2 years without an echocardiogram

46. The above patient agrees to close medical follow-up. However, he does not present back to your office until 2 years later, now with complaints of dyspnea. A repeat echocardiogram reveals an ejection fraction of 45% with an end-systolic dimension of 4.7 cm. What do you recommend?

a. Referral for mitral valve repair
b. Start an ACEI and reassess in 3 months
c. Mitral valve replacement
d. Start a β-blocker and reassess in 3 months

Case 30

An 80-year-old man with severe AS is turned down for surgical AVR due to significant comorbidities. He is referred to you for consideration for transcatheter AVR.

47. Which of the following findings is considered a contraindication for this procedure?

a. Calcified and tortuous femoral arteries
b. The apex is not accessible
c. Life expectancy <1 year
d. A history of treated endocarditis
e. Annulus size of 20 mm

Case 31

A 35-year-old man presents to your office for evaluation of valvular heart disease. He complains of shortness of breath with only modest amounts of exertion, as well as two-pillow orthopnea. He also complains of easy fatigability, as well as lower extremity edema and abdominal fullness. On examination, he is in no acute distress. He is normotensive. Jugular venous pressure is elevated, with a prominent a wave. The v wave is not easily discerned. S_1 is loud. S_2 is normal. A sound is heard in diastole, 0.07 milliseconds after S_2. A diastolic rumble is heard at the apex. A diastolic murmur is also heard along the left sternal border, which increases with inspiration. Mild hepatomegaly is present. There is 2+ peripheral edema.

48. What is your diagnosis?

a. Mitral stenosis
b. Mitral stenosis with tricuspid insufficiency
c. Mitral and tricuspid stenosis
d. Mitral stenosis and AS
e. Tricuspid stenosis

Case 32

An 80-year-old man presents to your office with complaints of chest tightness when

climbing up a flight of stairs. His past medical history is unremarkable. On physical examination, he is in no acute distress. BP is 140/80 mmHg; pulse is 78 bpm and regular. Chest is clear. Carotid upstrokes are diminished. The PMI is sustained, but not displaced. A fourth heart sound is present. The second heart sound is diminished and single. A loud late-peaking systolic murmur is heard, loudest at the second intercostal space, radiating to the neck.

49. Which of the following would be a reasonable next step in this patient's management?

- **a.** Stress sestamibi
- **b.** Stress electrocardiogram
- **c.** Cardiac catheterization
- **d.** Prescribe prn SL (sublingual) NTG (nitroglycerin) and review back in one week

50. The above patient is found to have an aortic valve area of 0.7 cm^2 with a mean gradient of 60 mmHg. Following catheterization, he develops massive upper gastrointestinal bleeding. Endoscopy reveals a gastric ulcer with a bleeding vessel at its base. Cauterization is performed, which temporarily stops the bleeding. However, the bleeding recurs and urgent partial gastrectomy is recommended. He complains of chest pain during these bleeding episodes. What is the best course of action?

- **a.** Proceed to AVR first.
- **b.** Refer for percutaneous balloon valvuloplasty, followed by gastrectomy.
- **c.** Start nitroprusside and proceed with gastric surgery.
- **d.** Proceed with gastric surgery directly.

51. What valve would you recommend to an 80-year-old patient with severe symptomatic AS?

- **a.** Bovine pericardial valve
- **b.** Ball-and-cage mechanical valve
- **c.** Bileaflet mechanical valve
- **d.** Aortic homograft

Case 33

A 28-year-old man presents for evaluation of difficult to control hypertension. He initially denies any symptoms but on further questioning admits to some leg fatigue and weakness and cold feet. On examination his BP is 180/90 mmHg, heart rate is 77 bpm and regular. His radial pulses are easily palpable but his femoral pulses are weak and there is radiofemoral delay. An ejection systolic murmur is heard at the left upper sternal border that radiates to the intrascapular region. In addition, there is a soft

continuous murmur heard throughout the precordium.

52. Based on your suspicion you order a CT aorta (Fig. 2.9). What is the most common associated lesion?

a. ~5% of cases have a bicuspid aortic valve.
b. ~50% of cases have mitral valve prolapse.
c. ~50% of cases have a bicuspid aortic valve.
d. ~5% of cases have an associated cleft mitral valve.
e. This lesion is rarely associated with concomitant cardiac abnormalities.

Figure 2.9

Case 34

A 65-year-old man with a history of rheumatoid arthritis (well controlled) presents for evaluation of a heart murmur. He notes some increase in fatigue and decrease in activity level over the past 2 years, but denies any specific complaints of dyspnea. He leads a

rather sedentary lifestyle. On examination, he is 6-ft, 1-in. tall. BP is 150/50 mmHg. Heart rate is 80 bpm and regular. Carotid upstrokes are brisk with a rapid upstroke and decline. Apical impulse is displaced and hyperdynamic. S_1 and S_2 are normal. A decrescendo, nearly holodiastolic murmur is heard along the left sternal border, loudest with the patient sitting up. An echocardiogram is performed, which reveals a dilated LV (end-diastolic dimension of 6.8 cm and end-systolic dimension of 3.5 cm). Ejection fraction is 55%. There is significant aortic regurgitation.

53. What do you most likely recommend?

- **a.** Stress test
- **b.** Reassess with repeat echocardiogram in 6 months
- **c.** Start vasodilator therapy and reassess in 2 years
- **d.** Refer to surgery

54. He is started on a vasodilator and is seen back in 6 months. He reports no change in symptoms. A repeat echocardiogram demonstrates an end-diastolic dimension of 7.6 cm. Ejection fraction remains normal. What do you recommend now?

- **a.** Stress test
- **b.** Surgical intervention
- **c.** Increase vasodilators and reassess in 6 months
- **d.** MRI to assess LV volumes

Case 35

A 42-year-old woman, who underwent mitral valve replacement with a bileaflet tilting disk valve for rheumatic disease, presents to the emergency room with complaints of severe dyspnea. On examination, she has a BP of 120/60 mmHg. Heart rate is 83 bpm. Chest reveals bilateral crackles, one-third up. Cardiac examination reveals a nondisplaced PMI. Prosthetic clicks are muffled. A long diastolic rumble is heard at the apex. Her past medical history is otherwise unremarkable.

55. An echocardiogram is ordered on the above patient. Which of the following would you expect to see?

- **a.** Severe MR
- **b.** Mean gradient across the mitral prosthesis of 17 mmHg
- **c.** Pressure half-time of 80 milliseconds
- **d.** Ejection fraction of 20%

Case 36

A 26-year-old woman presents to your office for evaluation. She was told she had a murmur many years ago. She has a history of palpitations, but is otherwise

asymptomatic. On examination, she is in no acute distress. Prominent v waves are noted in the JVP. Carotid upstrokes are normal. Chest is clear to auscultation. Cardiac examination reveals a nondisplaced PMI. Auscultation reveals a widely split first heart sound, with a loud second component that sounds like a click. A holosystolic murmur is heard at the right sternal border, which increases with inspiration. Hepatomegaly is present. An echocardiogram is performed (Fig. 2.10).

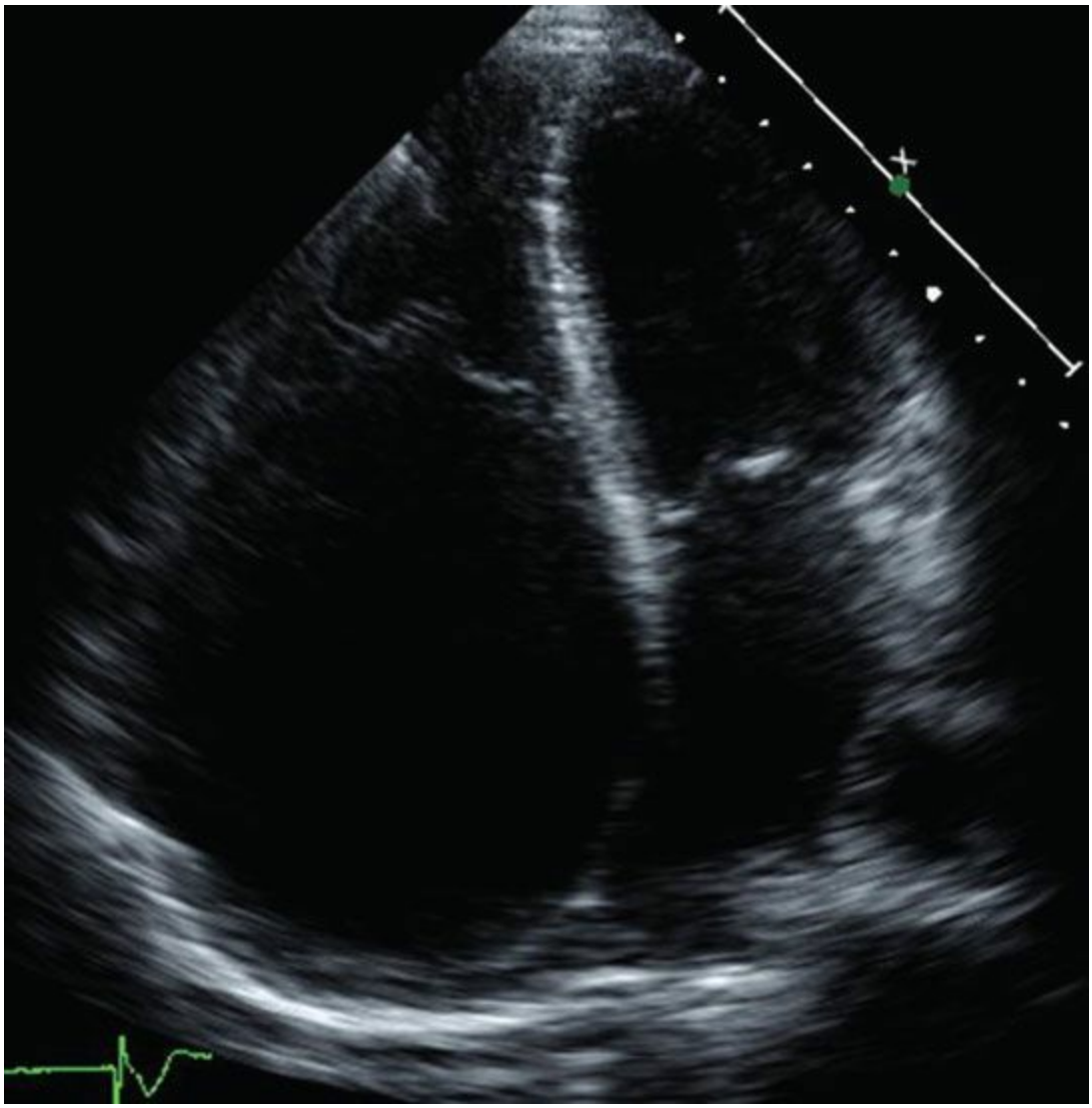

Figure 2.10

56. What is the most likely cause for her palpitations?

a. Arrhythmias secondary to an accessory pathway
b. AV nodal reentrant tachycardia
c. Ventricular tachycardia
d. Atrial fibrillation
e. Anxiety

57. No intervention is performed for the above patient. She returns to your clinic 3 months later. She describes an episode of transient word-finding difficulty, which lasted for a number of seconds. This occurred while she was recovering from a fractured tibia. A CT scan was performed, which was negative. She is concerned that she may have a recurrence. What is the most appropriate next test for her?

a. Echocardiography with saline contrast study
b. Carotid Dopplers
c. 24-hour ambulatory electrocardiographic monitoring
d. Right heart catheterization with oxygen saturation run

Case 37

A 21-year-old man presents to your office for evaluation. He tells you that a murmur was noted a few days after birth. He is presently asymptomatic. On examination, he is normotensive. Pulse is 65 bpm and regular. Carotid upstrokes are normal. Chest is clear. Cardiac examination reveals a nondisplaced PMI. An RV lift is present. A systolic thrill is present in the suprasternal notch. A high-pitched sound is heard after S_1. A crescendo–decrescendo systolic murmur is heard at the left second intercostal space. A_2 is normal.

58. Which of the following would you expect to find on echocardiography?

a. V_{max} across the aortic valve of 4 m/s
b. V_{max} across the pulmonic valve of 4 m/s
c. A wide jet of mitral insufficiency
d. Flow reversal in the hepatic veins

59. The above patient returns 1 year later for follow-up. Which of the following is a definite indication for intervention?

a. He tells you of an episode of syncope
b. No symptoms, but RV to PA peak gradient of 30 to 39 mmHg
c. No symptoms, but RV to PA peak gradient of 20 to 29 mmHg
d. He has occasional feelings that his heart has extra beats

60. If intervention is recommended, what is the preferred treatment approach?

a. Percutaneous valvuloplasty
b. Ross procedure
c. Mechanical valve
d. Bioprosthetic valve

61. In the setting of AS with moderate insufficiency, which of the following methods

would provide the most accurate estimate of aortic valve narrowing?

a. Invasive hemodynamics, using the Gorlin formula
b. Doppler echocardiography, using the continuity equation
c. Pressure half-time
d. Bernoulli equation

62. Which of the following valves has the lowest incidence of endocarditis?

a. Mechanical valve
b. Bioprosthetic valve
c. Aortic homograft
d. Stentless mitral valve

63. What is the most common cause of TR in an adult population?

a. Rheumatic tricuspid disease
b. Carcinoid
c. Congenital abnormalities
d. Pulmonary hypertension resulting from primary left-sided disease
e. Myxomatous disease of the tricuspid valve

64. The most common organism seen in native valve endocarditis is what?

a. Streptococcus viridans
b. Enterobacter faecalis
c. Staphylococcus aureus
d. Chlamydia pneumoniae
e. HACEK organisms

65. A patient presents with systemic embolic events 1 month after uncomplicated mitral valve replacement. He has been febrile for the past week. TEE demonstrates multiple echodensities on the valve ring. Blood cultures that are drawn are most likely to grow which of the following?

a. Streptococcus viridans
b. Staphylococcus aureus
c. Staphylococcus epidermidis
d. E. faecalis
e. Candida albicans

ANSWERS

1. **b.** Transesophageal echocardiography (TEE). The clinical history is of a patient who had an inferior wall myocardial infarction approximately 1 week ago. He now presents in shock with acute congestive heart failure. Mechanical complication of myocardial infarction is first on the differential. The presence of a ventricular gallop and an apical murmur without a thrill makes papillary muscle rupture the leading diagnosis (as opposed to ventricular septal defect). Transthoracic echocardiography may miss eccentric jets in this setting. TEE should be performed to make the diagnosis. He will certainly need a cardiac catheterization (at which time a saturation run may be performed), but a TEE should be done quickly at the bedside to confirm the diagnosis so that the surgical team can be mobilized.

2. **b.** Posterior papillary muscle rupture as it has a single blood supply. The 3D reconstruction of the mitral valve shown here is orientated in the "surgeons view," looking down on the mitral valve from the left atrium with the aortic valve situated on top, the anterior mitral valve leaflet adjacent to it, and the posterior mitral valve leaflet inferiorly. We see a bulky mass (the posterior papillary muscle) protruding into the left atrium in systole. The middle panel (early diastole) clearly shows that the mass is attached to the posterior leaflet. The posterior papillary muscle has a single blood supply (usually the right coronary artery), while the anterior papillary muscle often has dual blood supply. For this reason, post infarction rupture of the posterior papillary muscle is more common.

3. **b.** She likely has more severe MR than is evident on the echocardiogram. Her examination is suggestive of severe MR. The echo confirms LV dilation and mitral leaflet pathology, which could be consistent. The eccentric nature of the jet suggests that it may have been underestimated by transthoracic imaging. A more definitive imaging procedure such as TEE will be helpful here.

4. **b.** Mitral valve surgery. The presence of mild LV dysfunction with LV dilation is a class I indication for surgery. TEE would be the next test of choice prior to surgery to confirm the severity and mechanism of MR and assess suitability for surgical repair. While exercise echo is reasonable in asymptomatic patients with severe MR to assess functional capacity the patient already has indications for surgery.

5. **c.** Stress echocardiogram, to assess for mitral pressures post stress. She has moderate mitral stenosis. The fact that she has stopped exercising may be a clue to the onset of symptoms. An assessment of functional capacity and post-stress mitral pressures would be useful in management There are insufficient data for immediate referral for intervention. Follow-up in a short period of time may not be unreasonable; however, 2 years is too long a period.

6. **a.** Consideration for percutaneous valvuloplasty. Her functional capacity is below average for her age. Her valve is favorable for percutaneous valvuloplasty (splittability score of 6) and she had a significant rise in PA pressures post stress. Ideally, the splittability index should be 8 or less for optimal results post balloon valvuloplasty. A increase in mean valve gradient of 15 mmHg with exercise is a class I indication by the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines. A β-blocker would not be an unreasonable addition, but she should be followed more frequently than every 2 years. In addition, she does have class I indication for intervention. She has normal LV function and is in sinus rhythm—there is no role for digoxin in this setting. Valve replacement is considered only if the valve is deemed unsuitable for percutaneous valvuloplasty or surgical repair.

7. **b.** Carcinoid. The history and examination are consistent with tricuspid stenosis and regurgitation. (She has symptoms of fatigability from decreased cardiac output, signs, and symptoms of systemic venous congestion—hepatic distension and right upper quadrant pain, peripheral edema, and ascites. There is a diastolic murmur along the sternal border, which increases with inspiration, along with a prominent a wave in the JVP. In addition, she has a pansystolic murmur and a prominent v wave.) However, no evidence for mitral stenosis is noted on examination. Isolated rheumatic tricuspid stenosis is very rare. Thus, other causes for tricuspid stenosis should be considered. The second most common cause of tricuspid stenosis is the carcinoid syndrome. She also has bronchospasm and diarrhea, which go along with this diagnosis. She has a normal P_2, making primary pulmonary hypertension unlikely. Liver disease in and of itself would not produce elevation in the JVP.

8. **c.** Check lower extremity BP. He has a bicuspid aortic valve (an ejection sound is heard, along with a short systolic ejection murmur). There is an association between bicuspid aortic valves and coarctation of the aorta. Therefore, looking for discrepancy between the upper and lower extremity BP would be paramount.

9. **c.** Dobutamine echocardiogram. This is a patient presenting with low-gradient AS in the setting of LV dysfunction. It may be that the patient has severe AS, but the gradients are now low secondary to decreased stroke volume. However, the degree of AS may not be that significant, but because of decreased cardiac output, the continuity equation overestimates AS severity. In this setting, low-dose dobutamine echocardiography may be useful. With inotropic stimulation, an improvement in stroke volume and cardiac output may help to differentiate true severe AS from what has been labeled pseudo-AS. If true severe AS is not present, then valve area will increase. It would not be prudent to send such a patient to aortic valve surgery

without performing such an evaluation. It would be necessary to exclude severe stenosis before proceeding with transplant evaluation. ACEI may be beneficial, but it would be important to proceed with the workup as above first. Afterload reduction would need to be introduced with very careful hemodynamic monitoring if true severe AS were in fact present. The use of dobutamine echocardiographic testing to evaluate low-gradient AS in the setting of LV dysfunction is a class IIa indication by ACC/AHA guidelines.

10. **a.** AVR. The patient has true, severe AS and although may have a higher potential complication rate with surgery is likely to benefit prognostically and symptomatically from surgery. Balloon aortic valvuloplasty has not been shown to improve survival without the addition of a more definitive procedure such as aortic valve surgery. It is only indicated for palliation or as a bridge to a more definitive procedure such as transcatheter aortic valve replacement (TAVR) or surgery.

11. **d.** Patient has a lack of contractile reserve but should still be considered for AVR. There are three possible outcomes to a low-dose dobutamine test in this situation: true AS, pseudo-AS, and absence of contractile reserve. As was the case in Question 10, there may be an increase in stroke volume (defined as ≤20% increase from baseline) associated with an increase in transvalvular gradients (mean gradient >40 mmHg) without a significant increase in aortic valve area (AVA) (AVA increase <0.2 cm^2) indicative of true AS. Conversely, in pseudo-AS the increase in stroke volume is associated with an increase in AVA without a significant change in gradients. Finally, absence of contractile reserve is defined as failure to increase the stroke volume by ≤20% from baseline. In this case, dobutamine does not help to differentiate between the former two scenarios. While there is a significantly higher mortality during the perioperative period in those with the absence of contractile reserve compared with true AS, for those that survive surgery their 5-year survival is significantly better than those treated with medical therapy alone. Therefore, surgery should be considered on an individual basis.

12. **b.** Addition of vasodilator therapy. The patient is asymptomatic with good functional capacity. He has a normal ejection fraction with a mildly dilated LV. Surgery is a class III indication (harmful) in this setting. Vasodilator therapy may have some benefit in this asymptomatic population with preserved ejection fraction and LV dilation, although this is not definite. This is a class IIb indication. However, he has systolic hypertension which is likely at least in part related to his aortic regurgitation, and vasodilator therapy is an optimal therapy for this. Observation alone would be reasonable, but such a patient should be followed at 6-month

intervals initially and not every 3 years. There is no role for cardiac catheterization at this juncture.

13. **a.** <1%. From the available published literature, as summarized in the ACC/AHA consensus guidelines, the risk is about 0.2% per year in those asymptomatic patients with preserved LV function.

14. **d.** Referral for surgical intervention to repair or replace his aortic valve and to replace his ascending aorta. An aortic dimension >5.0 cm (or growth >0.5 cm per year) in a patient with a bicuspid aortic valve is a class I indication for surgery. The valve is often repairable in bicuspid valve associated with predominant aortic regurgitation assuming the mechanism is due to prolapse of the conjoint cusp, and there is no significant stenosis or calcification of the valve.

15. **d.** AVR with tricuspid valve repair if feasible. The mitral valve appears morphologically normal. After relief of the outflow tract obstruction, the MR will likely improve; therefore, mitral valve repair is not indicated. Tricuspid valve repair for moderate TR at the time of left-sided valve surgery is reasonable in the context of annular dilation and elevated PA pressures. This is a class IIb indication from the ACC/AHA guidelines but receives a class IIa recommendation from the European Society of Cardiology (2012). Tricuspid valve repair is favored over replacement.

16. **a.** 0.4 cm^2. The EROA based on the assumptions above is 0.4 cm^2 consistent with severe MR. The EROA is calculated using the abbreviated proximal isovelocity surface area (PISA) method as $r^2/2$ (r = radius of the PFCR). In this case, the radius is 0.9 cm; therefore, the EROA can be estimated as 0.4 cm^2.

17. **b.** 2+, moderate. Using the complete PISA method and calculating the regurgitant volume, the MR is determined to be only moderate in severity which is consistent with the brief duration of MR heard on physical examination. The complete method for calculating the EROA is $(2\pi r^2 \times AV)/ V_{max}$ (AV: aliasing velocity; V_{max}: maximum velocity across the mitral valve); therefore, in this case the EROA = $(2\pi(0.9)^2 \times 38.5)/600 = 0.33$ cm^2. However, as we see from the continuous-wave Doppler signal, the MR only occurs in late systole consistent with mitral valve prolapse. The regurgitant volume is equal to EROA × VTI_{MR} (VTI_{MR} = velocity time integral of the mitral regurgitation), which in this case is = 0.33 × 100 = 33 mL consistent with 2+ MR. If we used the EROA from the abbreviated PISA method (0.4 cm^2), the regurgitant volume is 40 mL, which is still consistent with moderate

MR.

18. **a.** Transesophageal echocardiogram. Left atrial and appendage thrombus should be excluded prior to proceeding with percutaneous valvuloplasty and is recommended by ACC/AHA guidelines to be performed prior to the procedure. Transthoracic echocardiography does not have sufficient sensitivity for this purpose. Documentation of atrial fibrillation by ambulatory monitoring may make the likelihood of finding a thrombus higher, but the transesophageal echocardiogram should be performed regardless. Routine surveillance for aortic calcification has no role in this setting. A nuclear perfusion study would not be necessary here (angiography can be performed if needed at the time of the procedure).

19. **a.** It is absolutely indicated. Given LV dysfunction (EF < 50%), this is a class I indication for surgery. There is no question as to the severity of the AS given the gradients and the aortic valve area; thus dobutamine echocardiography is not of value here.

20. **d.** The rate of mortality, for a patient with these findings, is higher compared with patients with severe AS and high gradients across the aortic valve but aortic valve surgery has resulted in better outcomes in these patients. This woman has paradoxical low-gradient, severe AS with preserved ejection fraction. Her clinical history, examination, and 2D imaging of the aortic valve are consistent with severe AS. She has a low indexed stroke volume (<35 mL/m^2), resulting in low gradients across the AV but the dimensionless index and AVA both are consistent with severe AS. When there is discordant echocardiographic data the accuracy of measurements should always be looked at again; however, in this case, the low gradients are consistent with low-stroke volume. There are currently no guidelines from the ACC or AHA on how to manage these patients; however, the recent 2012 European Society of Cardiology guidelines for valvular heart disease provide a class IIa recommendation for AVR in symptomatic patients with paradoxical low-gradient, severe AS with preserved ejection fraction. A number of studies have confirmed that the rate of mortality is higher in this cohort when compared with patients with severe AS and high gradients but surgery on the aortic valve is associated with significantly better outcomes.

21. **c.** Aortic root dimension. The patient clinically has severe AI. The murmur is loudest at the right sternal border, suggesting aortic root dilation as a potential cause of his AI. The presence of root dilation (≤5.5 cm) may lead to earlier surgery, hence is vital to know. The diastolic rumble is most likely an Austin Flint murmur and not concomitant mitral stenosis (no opening snap, S_1 not loud).

22. **a.** Cardiac catheterization with aortography. Clinically, the patient has severe aortic regurgitation. He is symptomatic. Consistent with this, the echocardiogram reveals a dilated LV with low normal systolic function. The degree of aortic regurgitation must be underestimated by this study. When there is such discrepancy, proceed with aortography to confirm aortic regurgitation severity and to assess coronaries prior to surgical referral. As he is symptomatic, continued observation and/or medical therapy is not the preferred treatment approach. β-Blockers, by prolonging the diastolic filling period, could actually increase regurgitant volume.

23. **a.** Transesophageal echocardiogram, emergent cardiac surgical consultation. The patient has a clinical presentation of severe acute AI (short diastolic murmur, soft S_1 from premature mitral valve closure, low output state, and pulmonary edema). In the context of chest pain, this scenario suggests aortic dissection until proven otherwise. The dissection flap likely involves the ostium of the right coronary artery, producing the inferior ST-segment elevation. Thrombolytics should not be used until dissection is ruled out. Even if there is no dissection, an intra-aortic balloon pump should not be used with severe AI. The augmented diastolic pressure worsens the severity of the insufficiency. MRI would also provide the diagnosis, but given the hemodynamic instability of the patient, a bedside TEE would be a safer and quicker option to arrive at the diagnosis.

24. **b.** No evidence for dysfunction. The physical examination does not suggest either stenosis or insufficiency. He appears to be in a high-output state, secondary to his febrile illness. As a result, the gradients are increased. The LVOT VTI is also increased, secondary to the increased cardiac output. The LVOT/aortic valve VTI ratio is the same in the two echocardiograms, which would speak against any significant obstruction.

25. **a.** TEE with surgical consultation. The clinical scenario, with a new first-degree AV block and acute aortic regurgitation, is highly suspicious for prosthetic valve abscess and possibly even partial dehiscence. A transesophageal echocardiogram should be performed, but prompt surgical consultation should also be requested given the high suspicion for aortic root abscess and the onset of heart failure symptoms.

26. **c.** Repeat echocardiogram with planimetry of mitral valve area. With acute changes in atrial and ventricular compliance (as with valvuloplasty), the half-time is unreliable. Usually 72 hours or more is required after the procedure before the half-time can be used with reasonable reliability. Planimetry, if performed correctly, would provide a more reliable estimate of stenosis severity. Clinically, the patient

seems to have had a good result (longer S_2–OS interval, shorter murmur). TEE rarely provides incremental data on mitral stenosis if the transthoracic images are reasonable.

27. **a.** Observation. The shunt is secondary to the valvuloplasty procedure where the interventionalist must perform an interatrial septal puncture in order to access the mitral valve. Most of these small shunts will close over the next 6 months without any intervention. The shunt is left to right by color. He has good O_2 saturation on room air, making any significant right-to-left shunting unlikely. Anticoagulation with an atrial septal defect/patent foramen ovale may be recommended in certain settings, however not indefinitely, given the good chance that the defect will close.

28. **b.** Antibiotic prophylaxis, with yearly office visits. He requires antibiotic prophylaxis with a prosthetic valve (by 2007 guidelines, prosthetic cardiac valves are an indication for subacute bacterial endocarditis prophylaxis prior to dental procedures). These patients still require close follow-up with complete evaluation on a yearly basis. Some advocate a 3-month period of warfarin therapy after bioprosthetic valve placement. He is now 4 months out, and has no other indications or a high-risk profile (LV dysfunction, prior embolic event, and atrial fibrillation); thus warfarin is no longer needed at this time. Similarly, there is no specific indication in this man for clopidogrel therapy.

29. **e.** No therapy at present but follow carefully with serial clinical and echo evaluation. Antibiotics are not recommended routinely for prophylaxis at the time of delivery for patients with valvular heart disease unless infection is suspected. If there is evidence of pulmonary congestion treatment with diuretics and afterload reduction with hydralazine is recommended but ACEIs are teratogenic and are absolutely contraindicated in pregnancy. Your patient is clinically euvolemic and therefore medical therapy need not be initiated. Surgery should only be performed if the mother's life is threatened due to the associated high fetal mortality rate (20% to 30%). Management will involve close follow-up and monitoring by her cardiologist and obstetrician and treatment only if her clinical situation deteriorates.

30. **a.** TEE. The echocardiogram reveals a normal-appearing aortic valve. Yet, the profile of the continuous-wave Doppler jet is more consistent with a fixed obstruction, as opposed to the dagger shape of dynamic obstruction. These findings are suggestive of the presence of a subvalvular membrane. TEE would be useful to better delineate this area and identify the membrane. The patient already has a 5-m jet in the absence of systolic anterior motion; therefore, it would not be prudent to

use provocation with amyl nitrate. A stress echocardiogram would have no diagnostic value and may have some risk in the setting of symptomatic LVOT obstruction. One should always consider contamination with an MR signal; however, the physical examination is consistent with outflow tract obstruction and the continuous-wave Doppler signal begins after the QRS (after isovolumetric relaxation) consistent with outflow tract obstruction. The MR signal will begin earlier relative to the QRS (through isovolumetric contraction).

31. **c.** There is no clear role for aspirin therapy in such patients. If there is echocardiographic evidence for high-risk mitral valve prolapse (leaflet thickening, elongated chordae, left atrial enlargement, and LV dilation), aspirin therapy is considered a class IIb indication. Therapy is clearly recommended if there have been documented stroke or transient ischemic events.

32. **b.** Continue with vasodilator therapy and reassess in 6 months. By ACC/AHA guidelines, decline in ejection fraction following stress echocardiography by itself is not an accepted indication for referral to surgical intervention. Owing to the high afterload and the increase in afterload on exercise, a small-to-modest decline in ejection fraction (<10%) may still be consistent with well-compensated AI. This patient has normal resting ejection fraction and mildly dilated LV with excellent functional capacity.

33. **b.** Repeat the echocardiogram with amyl nitrate (Fig. 2.11). The physical examination is highly suggestive of hypertrophic cardiomyopathy (brisk, bisferiens carotid pulse, normal S_2, and murmur increasing with Valsalva and decreasing with handgrip). The patient may not have a significant resting gradient, but may have a significant provocable gradient. Generally, a transesophageal echocardiogram is not needed to make the diagnosis. Invasive hemodynamics with provocation would be useful, but angiography alone would not be sufficient.

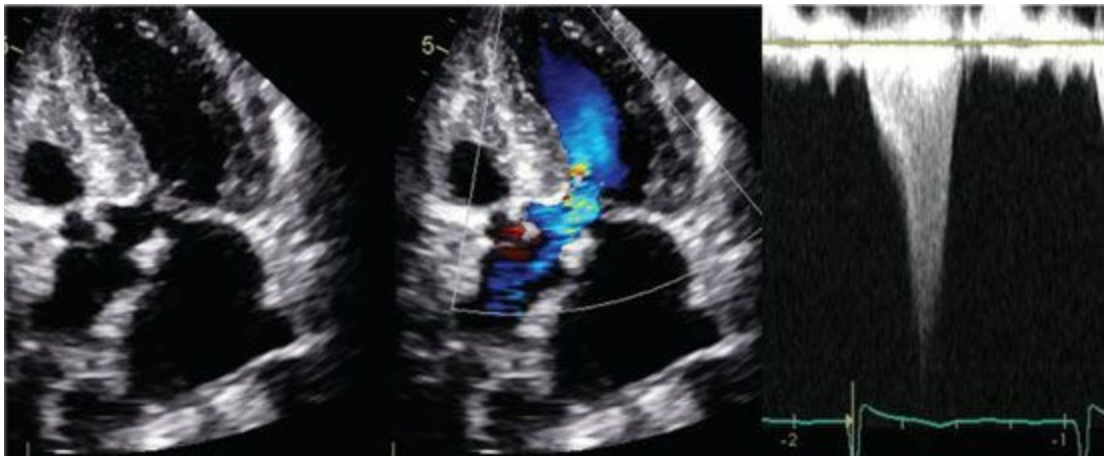

Figure 2.11

34. **c.** She will probably not need surgery on her mitral valve. MR secondary to systolic anterior motion of the mitral valve is related to hydrodynamic drag and Venturi effects on the anterior mitral valve. Often there are intrinsic mitral valve abnormalities that, in combination with septal hypertrophy, predispose to systolic anterior motion. Abnormal chordal attachments or hypermobile papillary muscles seen best on cardiac MRI may mandate chordae remodeling or papillary muscle reorientation; however, in this case the mitral valve apparatus is noted to be structurally normal. Relief of the hydrodynamic effects of a narrowed LVOT after myectomy will usually result in significant improvement in MR without further surgery. Before chest closure, careful assessment of MR should be done after the myectomy, usually with isoproterenol infusion, to ensure resolution.

35. **b.** Transesophageal echocardiogram. By examination, the patient has mitral insufficiency. The echocardiogram is consistent with this, with an elevated peak transmitral gradient. Pressure half-time is not prolonged; thus there does not appear to be any significant stenosis (gradients elevated owing to increased flow from regurgitant volume). A TEE would be the most useful to confirm the diagnosis. Fluoroscopy may identify partial dehiscence, but would not be helpful if there were a leak in the setting of a well-seated valve. There is no evidence for stenosis, where fluoroscopic evaluation of leaflet motion could be diagnostic. There is no clinical evidence for endocarditis.

36. **a.** Prominent closing click, soft and brief diastolic rumble. The bileaflet mechanical valves do not typically produce a loud opening sound, but do have prominent closing sounds. A brief diastolic rumble may be heard in a normally functioning prosthetic valve in the mitral position.

37. **b.** Prominent opening and closing clicks, soft and brief diastolic rumble. With the ball-and-cage valves, one would expect to hear the opening click as well.

38. **e.** Warfarin therapy with a target INR of 2.5 to 3.5 plus aspirin 75 to 100 mg. All patients with a mechanical valve require warfarin. The risk of thromboembolic events is higher for prosthetic valves in the mitral position; therefore, the recommended therapeutic range is higher than that for mechanical valves in the aortic position. The addition of low-dose aspirin (75 to 100 mg) further reduces the risk of thromboembolic event and reduces mortality from cardiovascular disease. Therefore, aspirin is recommended for all patients with valvular prostheses. Higher doses of aspirin have not been shown to be beneficial and increase the bleeding

risk.

39. **a.** <2%. In the absence of symptoms, natural history studies would suggest a relatively low risk of sudden death.

40. **d.** >50%. He has a velocity across the aortic valve of >4 m/s. Observational studies would suggest a high likelihood of symptom development in the next 3 years.

41. **d.** Start ASA, 81 mg/day, and increase warfarin to achieve an INR of 2.5 to 3.5. ACC/AHA guidelines recommended an INR of 2.5 to 3.5 for patients with bileaflet tilting disk mechanical valves in the aortic position who have had a thromboembolic event, and who have atrial fibrillation, LV dysfunction, or a hypercoagulable state. Addition of low-dose ASA (75 to 100 mg) is a class I indication for all patients with mechanical heart valves, and those with the above risk factors and bioprosthetic valves.

42. **a.** Intravenous heparin. Since a small clot was present (without any obstruction to valve function) the patient would benefit from increased anticoagulant therapy. If he were to fail this, then the other alternatives could be considered, such as continuous infusion thrombolytic therapy. Such continuous therapy (although not bolus) could also be used as primary treatment. No established indications exist at this time for glycoprotein IIb/IIIa inhibitors in this clinical setting. It would not be advisable to proceed to reoperation just yet, in the absence of a large clot burden or obstruction to inflow. If treatment with heparin leads to clot resolution, then subsequent warfarin dosing should be increased to maintain INR in the 3.0 to 4.0 range.

43. **a.** Therapy with warfarin. He should be on warfarin. Valvuloplasty in this setting (onset of atrial fibrillation, in an otherwise asymptomatic patient) is a class IIb indication by current guidelines.

44. **a.** Reassurance, with a repeat physical examination in 6 months. If a thorough physical examination reveals no signs of cardiopulmonary disease and the patient has no symptoms, then reassurance and follow-up are all that are required. Echocardiography should be performed if obesity limits the physical examination or if signs or symptoms are present.

45. **b.** Consider elective mitral valve repair at a hospital where repair is performed with a high degree of success or if he wishes to defer surgery, follow up at 6 monthly intervals with echo. Referral for surgery is reasonable (class IIa indication) if chance of repair is >95%. There are no data to suggest a beneficial

role for the addition of afterload-reducing agents in the absence of systemic hypertension (again by ACC/AHA guidelines). There is absolutely no role for the prophylactic use of amiodarone. Close clinical follow-up is reasonable, but repeat evaluation should not be deferred for 2 years. Guidelines use LV dimensions and ejection fraction to guide surgical intervention, even in the absence of symptoms. As such, these patients should have clinical reevaluation and echo every 6 months.

46. a. Referral for mitral valve repair. He is now symptomatic with depressed ejection fraction and a dilated LV. This is a class I indication for surgery. Valve repair as opposed to replacement is the preferred surgical treatment. Medical therapy may be needed as an adjunct, but is insufficient as the sole treatment.

47. c. Life expectancy <1 year. Life expectancy of <1 year, despite treatment of AS, is an absolute contraindication for TAVR. Severe peripheral artery disease precludes a transfemoral approach; however, the procedure may be done via a transapical approach, a transsubclavian approach, and even a transaortic approach. Severe pulmonary disease and an inaccessible apex preclude a transapical approach but the other approaches remain available. Active endocarditis is a contraindication to the procedure. The available valves are suitable for annular sizes between 19 and 29 mm.

48. c. Mitral and tricuspid stenoses. The loud S_1, opening snap, and apical diastolic rumble are features of mitral stenosis. The presence of the diastolic rumble along the sternal border, which increases with inspiration, along with the prominent a wave in the JVP and evidence of systemic venous congestion (hepatomegaly and peripheral edema) suggests that concomitant tricuspid stenosis is present as well.

49. c. Cardiac catheterization. By physical examination, the patient has severe AS (no A_2 of second heart sound, late-peaking murmur, and diminished carotid upstrokes). A stress test would not be appropriate in a patient with symptomatic AS. An echocardiogram would usually be the first step, but proceeding directly to catheterization to measure transvalvular gradients and assess coronary anatomy would be reasonable. SL NTG could have disastrous consequences in this setting. By reducing preload, it may precipitate syncope.

50. b. Refer for percutaneous balloon valvuloplasty, followed by gastrectomy. He has symptomatic critical AS. AVR, with concomitant need for anticoagulation while on cardiopulmonary bypass, is not an attractive first option. Proceeding directly to gastric surgery would carry high risk, given the ongoing symptoms. Valvuloplasty would be a reasonable bridge to lower risk from the noncardiac surgery.

51. **a.** Bovine pericardial valve. He is at an age where there is substantial durability of the bioprosthetic valve. He is at increased risk for anticoagulation; thus, mechanical valves would not be the valve of first choice. By history, he would not appear to need anticoagulation for any other indication. Homograft is not unreasonable, but there would not appear to be any hemodynamic or durability benefits for an 80-year-old patient, and its insertion requires a more difficult operation.

52. **c.** ~50% of cases have a bicuspid aortic valve. Coarctation of the aorta is suspected clinically and confirmed on a gated CT angiogram of the thoracic aorta. This lesion is frequently associated with concomitant congenital cardiac anomalies, the most frequent of which is a bicuspid aortic valve (occurs in ~50% to 85% of cases).

53. **a.** Stress test. The patient has significant aortic regurgitation with a dilated LV although not yet at the dimension that would be an indication for surgery in the absence of symptoms (his end-systolic dimension is <5.0 cm and end-diastolic dimension is <7.0 cm). He leads a sedentary lifestyle, and although he has no dyspnea, he does relate some equivocal symptom. A stress test would be useful to assess functional capacity and to objectively assess symptoms. If he were to develop symptoms at a low level of exercise, this may be an indication for surgical intervention. A vasodilator may be useful (class IIb indication with dilated LV), but he would need more frequent follow-up, given the LV dilation.

54. **b.** Surgical intervention. (Refer for surgery.) His ventricle has dilated even further. An end-diastolic dimension of >7.5 cm is a class IIa indication for surgery and is associated with an increased risk of sudden death, even in the absence of symptoms.

55. **b.** Mean gradient across the mitral prosthesis of 17 mmHg. The clinical presentation and examination are suggestive of prosthetic mitral stenosis (long diastolic rumble, muffled closing click, and clinical heart failure). The PMI is not displaced, so it is unlikely that she has significant LV dysfunction. There are no clinical signs of severe MR. Given the acute onset of symptoms, acute valvular thrombosis leading to valvular obstruction is high on the differential. If this were the case by ACC/AHA guidelines, reoperation would be the preferred treatment approach. If other comorbidities were prohibitive, thrombolytic therapy could be considered.

56. **a.** Arrhythmias secondary to an accessory pathway. The examination is highly suggestive of Ebstein anomaly (presence of TR, widely split first heart sound). The echocardiogram confirms this. Accessory pathways are frequently associated with this condition.

57. **a.** Echocardiography with saline contrast study. Ebstein anomaly is frequently associated with cardiac shunts (either patent foramen ovale, or atrial or ventricular septal defect). The setting of a TIA in someone who has been immobilized (such as with a fracture) raises the concern of paradoxical embolism of a venous thrombus to the systemic circulation.

58. **b.** V_{max} across the pulmonic valve of 4 m/s. The physical examination is consistent with pulmonic stenosis (presence of thrill, RV heave, ejection click, and crescendo-decrescendo murmur loudest over the pulmonic area). Normal carotid upstrokes and preserved A_2 make significant AS unlikely. The murmur is not consistent with a regurgitant murmur.

59. **a.** He tells you of an episode of syncope. The presence of exertional dyspnea, angina, syncope, or near-syncope are class I indications for intervention. For gradients between 30 and 39 mmHg, there is some divergence of opinion about the role of intervention (class IIb for gradients 30 to 39). There is no role for intervention in those with gradients <30 mmHg who have no symptoms. A peak-to-peak gradient >40 mmHg by catheterization is a class I indication for intervention, even in an asymptomatic patient.

60. **a.** Percutaneous valvuloplasty. This is the preferred treatment for young adults with pulmonic stenosis.

61. **b.** Doppler echocardiography, using the continuity equation. With significant insufficiency, the Gorlin formula becomes less reliable. Pressure half-time is not used to calculate aortic valve area, but does give a clue to the severity of the AI.

62. **c.** Aortic homograft. Mechanical and bioprosthetic valves have a similar incidence of endocarditis, which is higher than that seen for homografts. In the setting of acute bacterial endocarditis of a prosthetic aortic valve, homografts are the valve of first choice when surgery is indicated.

63. **d.** Pulmonary hypertension resulting from primary left-sided disease. The most common cause of tricuspid insufficiency is pulmonary hypertension that results from primary pathology on the left side of the heart. This includes aortic and mitral valvular diseases, as well as LV dysfunction from coronary artery disease or other cardiomyopathies.

64. **a.** Streptococcus viridans accounts for up to 50% of cases. Staphylococcus aureus is the next most common pathogen.

65. C. Staphylococcus epidermidis. This patient presents with early prosthetic valve endocarditis (within 2 months of surgery). This is usually acquired during the operation, and the skin species Staphylococcus epidermidis is the most frequent pathogen encountered. Late prosthetic valve endocarditis is similar to native valve endocarditis in terms of the spectrum of pathogens involved.

SUGGESTED READINGS

2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. Circulation. 2014 Jun 10;129(23):2440–92. doi: 10.1161/CIR.0000000000000029.

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Acute Myocardial Infarction

Venu Menon • Bhuvnesh Aggarwal

QUESTIONS

1. Which one of the following statements is true regarding trends in incidence of acute coronary syndrome (ACS) in the United States?

   a. Percentage of ACS with ST-segment elevation myocardial infarction (STEMI) is declining.
   b. Percentage of ACS with non–ST-segment elevation myocardial infarction (NSTEMI) is declining.
   c. Percentage of ACS with unstable angina (UA) is increasing.
   d. Overall incidence of ACS is decreasing.
   e. All of the above.

2. Which of the following processes represents the dominant initiating event in the pathogenesis of an ACS?

   a. Plaque rupture
   b. Plaque erosion
   c. Platelet activation
   d. Venous stasis
   e. None of the above

3. What is the most important clinical predictor of 30-day mortality in a patient presenting with acute STEMI?

   a. Age
   b. Systolic blood pressure (BP)
   c. Heart rate
   d. Killip classification stage

e. Location of myocardial infarction (MI)

4. Which of the following is a prodrug and requires bioactivation?

a. Aspirin
b. Clopidogrel
c. Prasugrel
d. Ticagrelor
e. Both b and c

5. Which of the following statements regarding prasugrel is true?

a. Prasugrel has faster onset of action when compared with clopidogrel.
b. Unlike clopidogrel, prasugrel is not influenced by polymorphisms in cytochrome P450 enzyme pathway.
c. Prasugrel provided no net mortality benefit when compared with clopidogrel in patients with ACS in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI)-38 trial.
d. Prasugrel is contraindicated in patients with a prior history of transient ischemic attack (TIA)/stroke.
e. All of the above.

6. A 72-year-old presents with sudden-onset chest pain at a local emergency department. He has a past medical history significant for hypertension, hyperlipidemia, and gastroesophageal reflux disease. On examination his BP is 95/60 mmHg and heart rate is 90 beats per minute and he is breathing at 90% on ambient air. He reports this is the first time he has had any episode of chest pain. His electrocardiogram (ECG) reveals ST elevation in V_1 to V_4. The nearest hospital with percutaneous coronary intervention (PCI) capability is 3 hours away. What is the next step in management?

a. Perform fibrinolysis; administer unfractionated heparin, aspirin, and clopidogrel; and admit to hospital.
b. Administer unfractionated heparin, aspirin, and clopidogrel and admit to hospital.
c. Administer unfractionated heparin, aspirin, and clopidogrel followed by transfer to PCI-capable hospital.
d. Computed tomography (CT) of the chest with intravenous contrast.
e. Perform fibrinolysis; low-molecular-weight heparin (LMWH), aspirin, and clopidogrel; and transfer to the hospital for possible PCI.

7. The above patient is given intravenous tenecteplase and started on aspirin, clopidogrel, and unfractionated heparin. Thirty minutes into treatment his chest pain has now completely resolved. A repeat ECG shows complete resolution of the earlier noted ST elevation. What is the next step in management?

   a. Continue unfractionated heparin, aspirin, and clopidogrel and transfer to the nearest hospital with PCI capabilities.
   b. Admit to local hospital for observation.
   c. Discharge home with outpatient follow-up following a submaximal stress test.
   d. Discharge home with plan for possible angiography after 4 to 6 weeks.
   e. None of the above.

8. Which of the following is true for management of acute STEMI?

   a. The administration of aspirin has a much larger treatment effect than streptokinase.
   b. The administration of streptokinase has a much larger effect than aspirin.
   c. Streptokinase and aspirin each have a similar effect on outcome.
   d. When streptokinase and aspirin are used together, their effects are blunted.
   e. None of the above.

9. Which of the following is the mechanism of action of ticagrelor?

   a. Thromboxane inhibition
   b. Glycoprotein (GP) IIb/IIIa receptor blockade
   c. Adenosine diphosphate blockade
   d. Increase in cyclic adenosine monophosphate production
   e. Free radical scavenger

10. Which of the following is true regarding use of GP IIb/IIIa inhibitors in STEMI?

   a. Routine upstream use of GP IIb/IIIa inhibitors has been shown to reduce target vessel revascularization (TVR).
   b. Routine GP IIb/IIIa inhibitor use is associated with reduced incidence of recurrent MI.
   c. Routine GP IIb/IIIa inhibitor use is associated with increased risk of bleeding.
   d. Small-molecule GP IIb/IIIa inhibitor use has been shown to reduce 30-day mortality.
   e. Upstream use of GP IIb/IIIa inhibitors is given a class I indication in current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.

11. In the setting of primary angioplasty for acute MI, which of the following have stents

been convincingly shown to do compared with balloon angioplasty alone?

a. Decrease subsequent repeat TVR.
b. Decrease long-term mortality.
c. Decrease long-term MI risk.
d. Decrease the incidence of heart failure.

12. Which of the following is true about reteplase in Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO-III)?

a. It had a significantly higher rate of stroke than alteplase.
b. It significantly reduced mortality compared with alteplase.
c. It significantly reduced mortality, but increased stroke compared with alteplase.
d. It had similar rates of mortality compared with alteplase.

13. Which of the following statements is true regarding non–ST-segment elevation (NSTE)-ACS?

a. NSTEMI has poorer prognosis than UA.
b. Elevated troponin is associated with worse prognosis in NSTE-ACS.
c. ST-segment deviation is associated with increased risk of long-term ischemic events.
d. One in five patients with NSTEMI has normal ECG.
e. All of the above.

14. A 46-year-old man presents to the emergency with complaints of sudden, severe chest pain radiating to his right arm. He admits to snorting crack cocaine 2 hours prior to the development of chest pain. His BP is 180/100 mmHg and heart rate is 96 per minute. An ECG done reveals downsloping ST depression and T-wave inversion in V_2 to V_4. What is the next best step in management?

a. Administer aspirin, sublingual nitroglycerin, and intravenous metoprolol.
b. Administer aspirin and sublingual nitroglycerin.
c. Administer aspirin, sublingual nitroglycerin, and heparin.
d. Administer activated charcoal.

15. The patient is started on aspirin, nitroglycerin, and intravenous heparin. He continues to have severe substernal chest pain. Repeat ECG is unchanged. Troponin T is borderline elevated to 0.04 ng/mL. What is the next best step in management?

a. Activate the catheterization laboratory for emergent left heart catheterization.
b. Administer diazepam and let the patient rest.
c. Administer tissue plasminogen activator.

d. Cycle cardiac biomarkers and monitor the patient.
e. None of the above.

16. A 64-year-old man is brought to the emergency room for complaints of chest pressure, difficulty breathing, and palpitations. He has a past medical history of hypertension and type 2 diabetes and ischemic stroke and his home medications include metformin, glyburide, lisinopril, and aspirin. ECG on arrival reveals ST-segment elevation in leads I, avL and V_5 to V_6. Catheterization laboratory is activated and the patient is given 325 mg of aspirin and started on nitroglycerin drip. Which of the following additional therapies is currently indicated?

a. Clopidogrel 300 mg, fondaparinux, and atorvastatin 80 mg
b. Prasugrel 60 mg, unfractionated heparin, and atorvastatin 80 mg
c. Ticagrelor 90 mg, unfractionated heparin, and atorvastatin 80 mg
d. Clopidogrel 600 mg, bivalirudin drip, and atorvastatin 80 mg
e. Both a and d are correct

17. Which of the following is true regarding adjunctive medical therapy in patients with acute MI receiving primary PCI?

a. Routine intravenous β-blocker within 24 hours improves mortality.
b. Intravenous angiotensin-converting enzyme inhibitor (ACEI) within 24 hours improves mortality.
c. Mortality benefit with routine intravenous nitroglycerin is not established.
d. Intravenous magnesium improves mortality when used as an adjunct to reperfusion.

18. Which of the following statements is incorrect with regard to acute MI?

a. Primary PCI is associated with reduced rate of intracerebral hemorrhage as compared with fibrinolysis.
b. If rapidly available, primary PCI provides a mortality benefit as compared with fibrinolysis.
c. Primary PCI may be considered 12 hours after symptom onset in patients with signs of ongoing ischemia.
d. Routine PCI of the totally occluded infarct-related artery should be avoided after 24 hours of presentation in hemodynamically stable patients without signs of ischemia.
e. Fibrinolysis should be considered 12 hours after symptom onset in hemodynamically stable patients with signs of ongoing ischemia.

19. Which of the following is an absolute contraindication for use of fibrinolytics for

acute MI?

a. History of ischemic stroke
b. Pregnancy
c. Concomitant use of warfarin for another indication
d. Suspected aortic dissection
e. History of seizure disorder
f. All of the above

20. Which of the statements is true regarding ventricular septal rupture (VSR) after acute MI?

a. VSR is more common in men when compared with women.
b. VSR is more likely after recurrent MI.
c. Presence of collateral circulation in the infarct zone reduces risk of VSR.
d. Fibrinolysis is associated with increased risk of VSR.
e. VSR is more likely after anterior wall MI as compared with nonanterior wall MI.

21. An 82-year-old woman calls 911 after developing sudden-onset chest pain, nausea, and lightheadedness. An ECG done by emergency medical service (EMS) reveals 3-mm ST elevation in leads II, III, and aVF. The nearest catheterization laboratory is activated and the patient undergoes PCI to the right coronary artery (RCA) with drug-eluting stent. She is transferred to the intensive care unit (ICU) in stable condition after the procedure. Two days later, the patient develops sudden-onset lightheadedness and left-sided chest pain. Her vitals reveal BP of 115/60 mmHg, heart rate of 90 per minute and SaO_2 of 92% on ambient air. Physical examination reveals new systolic murmur at the left sternal border that radiates to the apex. An ECG done immediately reveals Q waves in leads II, III, and aVF. No new ST-T changes are noted. A stat bedside echocardiogram reveals basal septal VSR with left-to-right shunt and moderate mitral regurgitation. A pulmonary artery (PA) catheter is placed and shunt fraction (Q_p/Q_s) is calculated at 1.3. What is the next best step in management?

a. Left heart catheterization with ventriculography for better assessment of septum
b. Cardiac magnetic resonance imaging (MRI) to better assess the size of septal rupture
c. Intravenous nitroprusside for afterload reduction
d. Intra-aortic balloon pulsation (IABP) placement
e. Urgent surgical repair

22. Which of the following statements is true regarding ventricular free wall rupture

complicating acute MI?

a. Incidence of ventricular free wall rupture is higher after fibrinolysis when compared with that after primary angioplasty.
b. Ventricular free wall rupture usually presents with acute-onset signs and symptoms of cardiac tamponade, or sudden death.
c. Type I rupture usually occurs within 24 hours of MI.
d. All of the above.

23. Which of the following is true?

a. Ventricular aneurysm is more common than ventricular pseudoaneurysm after MI.
b. Most ventricular pseudoaneurysms resolve over time and require no specific therapy.
c. Ventricular aneurysm is more common with inferior wall MI when compared with anterior MI.
d. Ventricular pseudoaneurysm is more common with anterior wall MI as compared with inferior wall MI.
e. All of the above.

24. A 63-year-old woman presents to the clinic after an episode of sudden transient left-sided vision loss. Symptoms lasted about 15 minutes with spontaneous resolution. Her past medical history is significant for an anterior MI 3 weeks ago treated with PCI with bare metal stent (BMS) to the left anterior descending artery (LAD). Other medical conditions include hypertension, type 2 diabetes mellitus, and hyperlipidemia. Current medications are aspirin, prasugrel, atorvastatin, metformin, and metoprolol. Physical examination is normal. There are no carotid bruits. Ophthalmologic examination is within normal limits. An ECG reveals sinus rhythm with persistent ST elevations in V_2 to V_4. What is the next step in management?

a. Exercise stress test with nuclear imaging
b. MRI of the brain with contrast
c. Carotid ultrasound
d. Left heart catheterization
e. Transthoracic echocardiogram

25. A previously healthy and independently functional 77-year-old man is brought to the catheterization laboratory after developing sudden-onset chest pain radiating to the jaw and shortness of breath. ECG by EMS during transfer revealed ST elevation in V_2 to V_4 and leads I and aVL. The patient was in respiratory distress during transfer requiring emergent endotracheal intubation. His BP is 70/30 mmHg and heart rate is 110 per minute. Angiogram reveals fresh mural thrombus in proximal LAD, which

is stented with BMS with resultant TIMI-2 flow. No significant disease is noted in the RCA and circumflex vessels. An echo reveals a left ventricular ejection fraction (LVEF) of 30% with no significant valvular pathology. He is subsequently transferred to the critical care unit (CCU) in critical condition. His current vital signs are as follows: BP 80/40 mmHg, HR 120 beats per minute, and SaO of 92% on 60% FiO_2. A PA catheter is placed. Which of the following readings is associated with worst prognosis in this patient?

a. Pulmonary capillary wedge pressure (PCWP) 30, Cardiac Index (CI) 1.6
b. PCWP 24, CI 3.2
c. PCWP 10, CI 1.8
d. PCWP 16, CI 2.4

26. What is the next step to be considered in the management of this patient?

a. Consideration for advanced mechanical support
b. IV nitroprusside
c. Refer for urgent coronary artery bypass grafting (CABG)
d. Repeat left heart catheterization

27. A 72-year-old woman is admitted to the hospital with acute STEMI. She has no other past medical history. She underwent BMS to the left circumflex artery with good subsequent flow. She is now free of chest pain and feels well. Echocardiogram revealed an estimated ejection fraction of 30%. In addition to aspirin and clopidogrel what other medications must be considered in the patient's discharge medication regimen?

a. Atorvastatin, lisinopril, and carvedilol
b. Atorvastatin, lisinopril, carvedilol, and warfarin
c. Atorvastatin, lisinopril, carvedilol, and eplerenone
d. Lisinopril, metoprolol, eplerenone, and niacin

28. The above patient had a brief (10 seconds) episode of nonsustained ventricular tachycardia (VT) at a rate of 180 beats per minute on the day of admission in the catheterization laboratory that spontaneously converted to sinus rhythm. What additional therapy is warranted for this patient?

a. Amiodarone at the time of discharge
b. Intravenous lidocaine in the hospital and amiodarone at discharge
c. Only intravenous lidocaine in the hospital
d. Implantable cardioverter–defibrillator (ICD) placement prior to discharge
e. Cardiac Resynchronization Therapy with Defibrillator (CRT-D) device placement prior to discharge

f. None of the above

29. A 45-year-old man presents to an emergency room with 30 minutes of crushing chest pain. The nearest catheterization laboratory is 45 minutes away and a decision to transfer for primary PCI is made. What is the optimal door in door out that has been associated with decreased mortality?

a. 60 minutes
b. 45 minutes
c. Within 120 minutes
d. Within 30 minutes
e. Within 24 hours

30. A 46-year-old man develops sudden chest pain and collapses to the ground. Bystander Cardio-Pulmonary Resuscitation (CPR) is immediately initiated. On EMS arrival 8 minutes later, he is noted to be in ventricular fibrillation and is promptly defibrillated. His ECG shows ST elevation in the inferior leads. The patient is comatose and is intubated for airway protection. Apart from performance of primary PCI which of the following actions is associated with mortality benefit?

a. Bolus of 2 L of normal saline
b. Intravenous lidocaine initiation to prevent recurrent arrest
c. Initiation of transvenous pacing to prevent polymorphic VT
d. Initiation of hypothermia protocol
e. Placement on Extracorporeal Membrane Oxygenation (ECMO)

31. An 85-year-old man presents with increasing intensity of his typical angina pain associated with shortness of breath. His ECG is unchanged from prior tracings. He has a history of established coronary artery disease and has previously refused revascularization. A decision is made to manage him conservatively. Which of the following interventions would be considered inappropriate?

a. Initiation of anticoagulation with fondaparinux
b. Treatment with clopidogrel 300 mg followed by 75 mg daily
c. Initiate treatment with prasugrel bolus 60 mg followed by 5 mg once daily
d. Increase the dosage of prior β-blocker therapy
e. Continue treatment with aspirin

32. Which of the following is not a direct thrombin inhibitor?

a. Bivalirudin
b. Argatroban
c. Hirudin

d. Dabigatran
e. Apixaban

33. Which of the following is true regarding pericarditis in acute MI?

a. Fibrinolysis has no effect on the incidence of pericarditis in MI.
b. Fibrinolysis reduces the incidence of pericarditis in MI.
c. Fibrinolysis increases the incidence of pericarditis in MI.
d. No data have examined this issue.

34. Which of the following are potential indications for IABP in the setting of acute MI?

a. Refractory ischemia despite intensive medical therapy
b. STEMI and secondary acute mitral regurgitation
c. STEMI and refractory polymorphic VT
d. STEMI and refractory cardiogenic shock
e. All of the above

35. A 66-year-old man presents to the emergency with complaints of on–off episodes of chest discomfort for the last 24 hours. Each episode lasts from 15 to 45 minutes and occurs at rest. He denies any history of similar pain in the past. He has a past medical history of hypertension, diabetes mellitus, and peripheral vascular disease. He is an active smoker with 40 pack-year history. An ECG done reveals nonspecific ST-T wave changes. Troponin T is elevated at 0.62. He is taken to the catheterization laboratory and a 90% lesion is noted in first diagonal via a transfemoral approach. He is treated with overlapping BMSs with subsequent TIMI-3 flow. He is transferred to CCU in stable condition. About 4 hours later, the patient develops hypotension with BP of 80/40 mmHg and heart rate of 110 per minute. There is no jugular venous distension. He is pale, diaphoretic, and dizzy. Cardiac auscultation is unchanged. A repeat ECG done is similar to admission ECG. No pericardial effusion is noted on a bedside echocardiogram. Which of the following is most likely to identify the cause of his current condition?

a. Repeat left heart catheterization
b. CT chest with contrast
c. CT abdomen without contrast
d. Chest X-ray
e. Bedside transesophageal echocardiography

36. A 48-year-old man presents to the emergency room agitated after abusing cocaine. His heart rate is 110 per minute, his BP is 200/120 mmHg, and an ECG shows ST elevation in the inferior leads. On examination he is diaphoretic with clear lung

sounds. Auscultation is pertinent for a diastolic murmur at the base of the heart that accentuates with expiration. What is the appropriate next step for definitive diagnostic evaluation?

a. Performance of a CT pulmonary embolus protocol
b. Performance of a gated CT of the aorta
c. Activation of the catheterization laboratory for primary PCI
d. Initiation of intravenous heparin and load with ticagrelor
e. Performance of a two-dimensional echocardiogram at the bedside

37. A 78-year-old man calls 911 because he has sudden-onset chest pain. On EMS arrival he has a BP of 120/80 mmHg and a heart rate of 80 beats per minute. His lungs are clear to auscultation and he has a left ventricular (LV) S_4 noted. ECG done on the field confirms an anterior MI with ST elevation from V_1 to V_4. He is given an aspirin and a sublingual nitroglycerin and transfer is initiated. Within 5 minutes while en route his BP is noted to be 60 mmHg and a saline bolus is initiated. Cardiovascular examination is unchanged and no murmurs are noted. Which of the following scenarios may likely explain his observed hemodynamic deterioration?

a. Hypotension resulting from bleeding due to administration of aspirin
b. Right ventricular (RV) infarction
c. Anaphylaxis reaction from aspirin
d. Recent exposure to a phosphodiesterase 5 inhibitor
e. Massive pulmonary embolism

38. A 42-year-old mother is visiting her child who is undergoing chemotherapy in the Children's Hospital. She suddenly develops chest pain and is noted to be nauseous and diaphoretic. An ECG is performed (Fig. 3-1). On angiography, the coronaries are free of significant epicardial stenosis. A ventriculogram shows apical ballooning with an LVEF of 25%. The patient is admitted to the CCU. Which of the following statements will most likely define her clinical course?

a. She will likely require an ICD as LV function is unlikely to recover.
b. Her prognosis will likely be excellent with full recovery of LV function.
c. She is at risk for recurrent atherosclerotic ischemic events.
d. Indefinite anticoagulation with warfarin will be indicated.
e. She is at higher risk for a malignancy in the ensuing year.

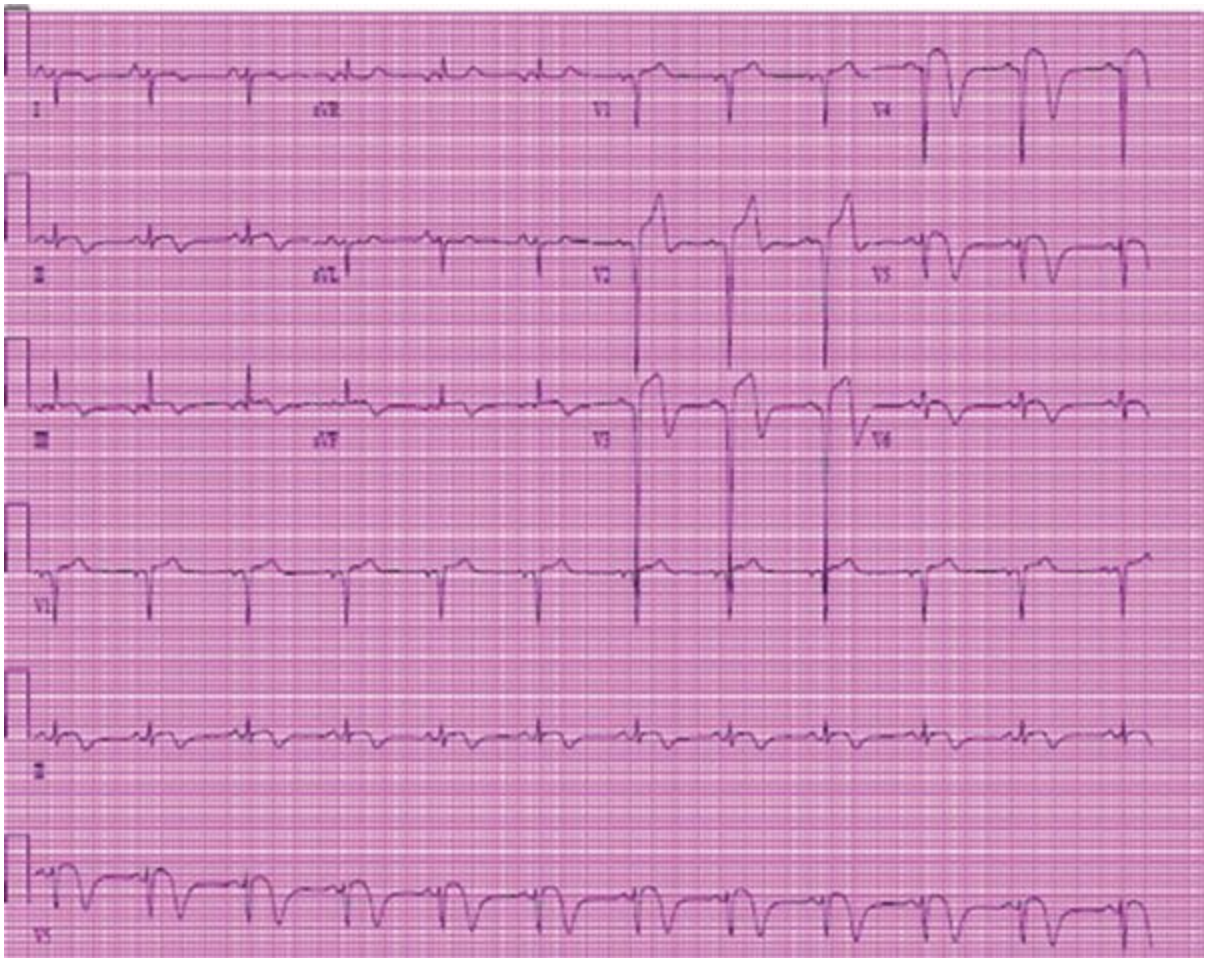

Figure 3.1

39. A 91-year-old man with a history of prior CABGx2 is brought from the nursing home with shortness of breath and hypotension. He is debilitated and has required 24/7 nursing care for activities of daily living. His ECG shows diffuse ST-segment depression, and he is noted to be in pulmonary edema. His heart rate is 110 per minute and his BP is 70/40 mmHg. He has a recent stroke 3 months prior and has stage 4 chronic kidney disease. History is also relevant for a diagnosis of prostate cancer with extensive metastasis to his spine. Which of the following is indicated?

a. Discussion with the family explaining his poor prognosis and the near futility of escalating care
b. Emergent catheterization and revascularization as indicated by anatomy
c. Placement of an IABP for medical stabilization
d. Plan for emergent dialysis
e. Urgent oncology consultation to estimate his prognosis from his prostate cancer

40. A 64-year-old man presents with ST elevation and is taken for primary angioplasty (see Fig. 3-2). Identify the infarct-related artery?

a. LAD
b. Diagonal
c. RCA
d. Left Circumflex
e. Obtuse marginal

41. A 45-year-old man is status post hip replacement. He develops sudden-onset shortness of breath. On examination, he is hypotensive with a BP of 80/40 mmHg. An ECG shows sinus tachycardia at 100 beats per minute with ST elevation in V_1 to V_2. A bedside echo is performed (Fig. 3-3). What is the most appropriate intervention?

a. Activate catheterization laboratory to perform a primary PCI.
b. Perform a CT angiogram to rule out a dissection.
c. Initiate intravenous heparin and assess risks and benefits of fibrinolysis.
d. Perform a saline contrast study to assess right-to-left shunt.
e. Initiate antibiotics and perform blood cultures.

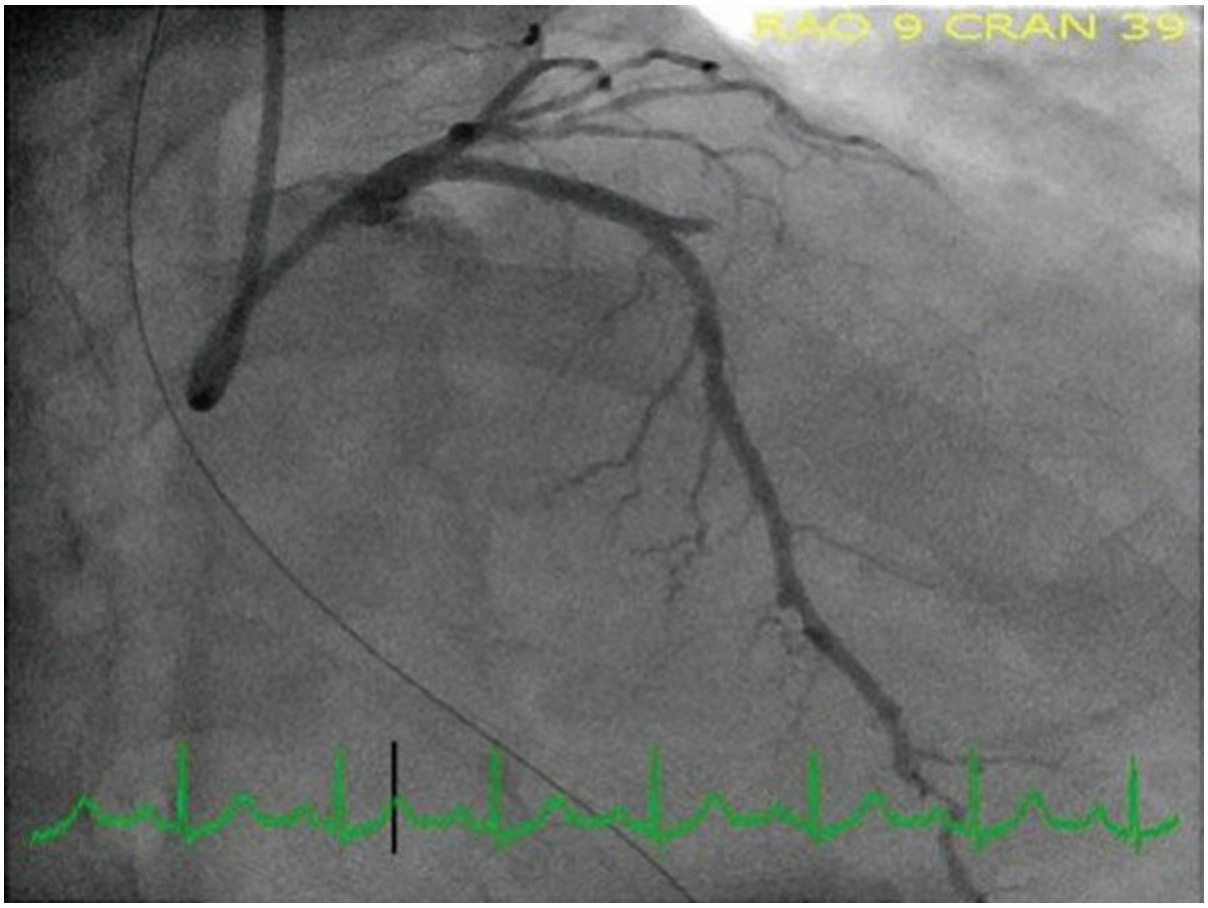

Figure 3.2

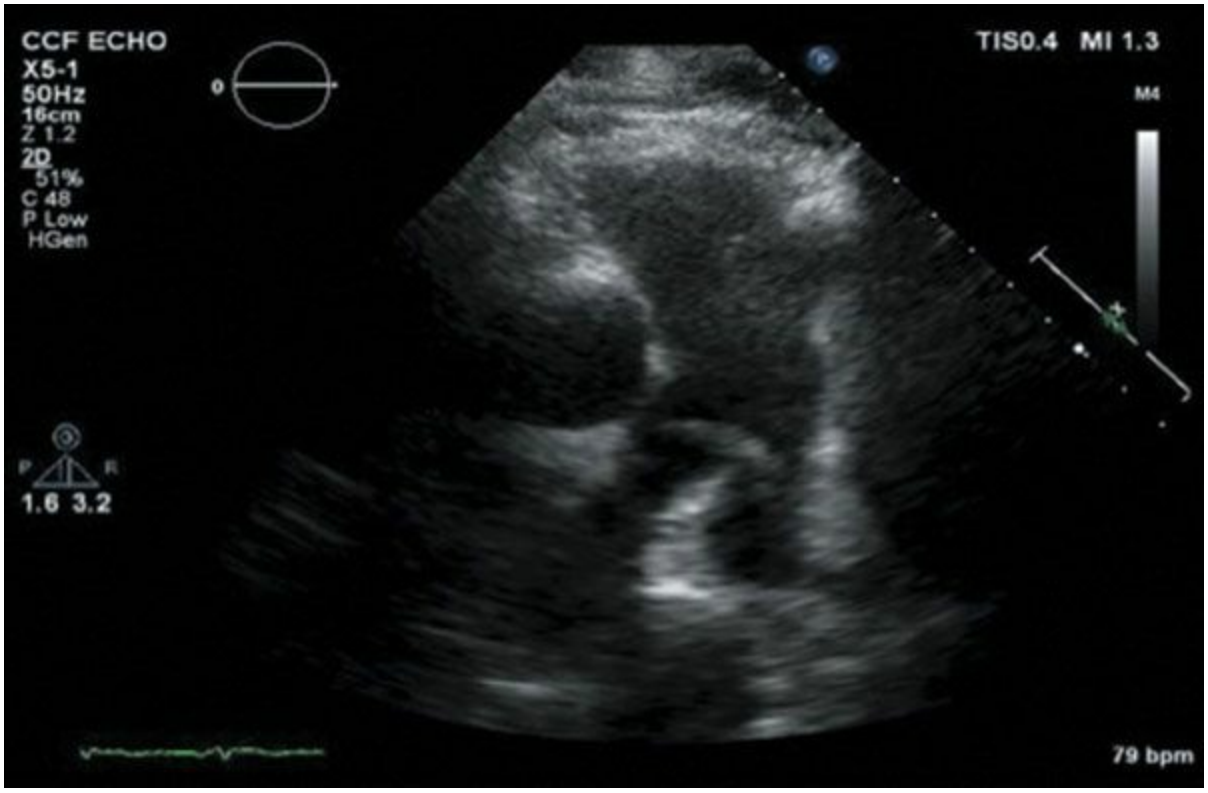

Figure 3.3

42. A 75-year-old woman presented with shortness of breath and generalized malaise of 1-week duration. Her heart rate was 90 per minute and BP was 90/50 mmHg. Examination revealed rales in bilateral lung bases, an elevated jugular venous pulse, and a loud systolic murmur in the left parasternal area. An echo (Fig. 3-4) was performed. What is the likely infarct-related artery?

a. Proximal LAD
b. Distal LAD
c. Obtuse marginal in a dominant circumflex
d. Mid-RCA in dominant RCA
e. Proximal nondominant RCA

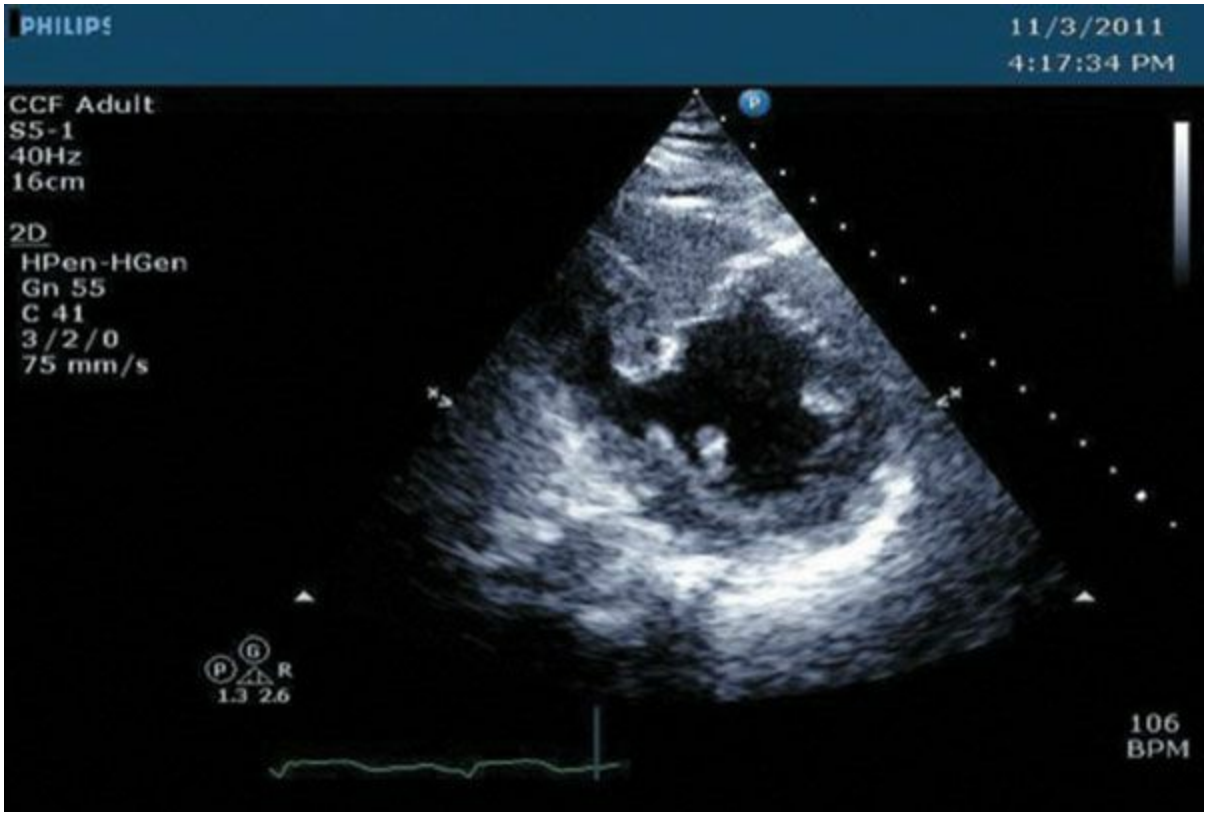

Figure 3.4

43. A 42-year-old male nurse in a rural emergency room develops crushing chest pain 30 minutes after he smoked a cigarette during a break in his shift. An ECG (Fig. 3-5) is performed. What is the most appropriate intervention?

a. Load with clopidogrel 600 mg and initiate heparin for a diagnosis of NSTEMI ACS.
b. Load with prasugrel 60 mg once daily and transfer for primary PCI to a laboratory 4 hours away.
c. Treat with intravenous verapamil for vasospasm.
d. Initiate fibrinolytic therapy with reteplase with adjunctive treatment with aspirin and intravenous heparin.
e. Treat with intravenous metoprolol 5 mg three times.

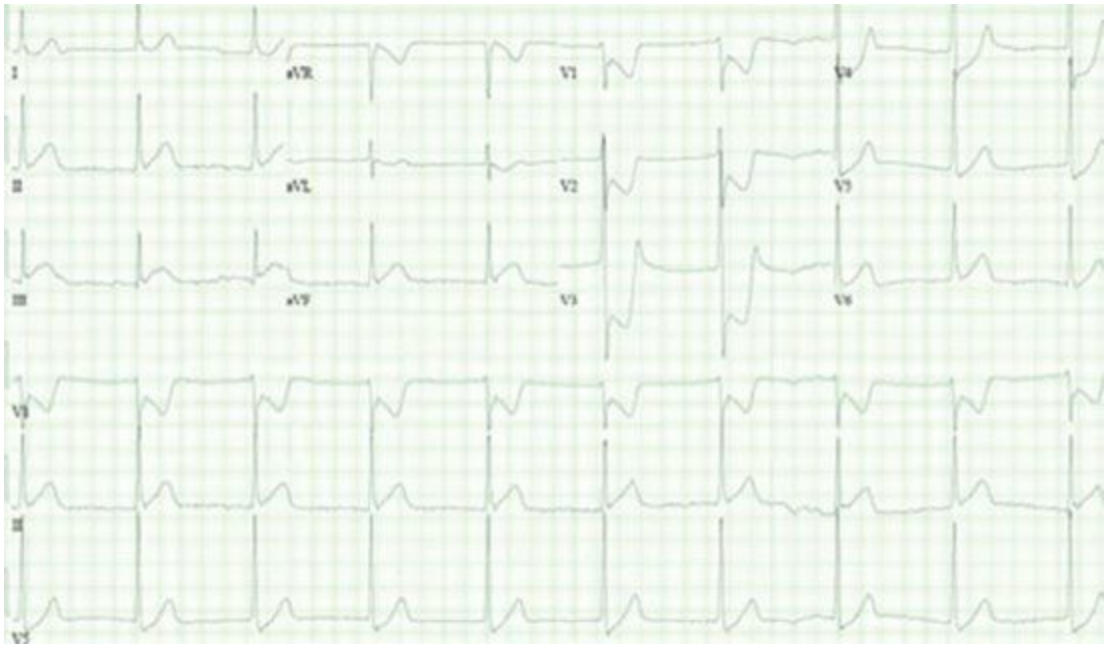

Figure 3.5

ANSWERS

1. **e.** All of the above. Based on data from national heart disease stroke statistics, while the incidence of overall ACS, STEMI, and NSTEMI has declined with time, the incidence of UA has been increasing in the last decade. The observed decline in the rate of UA is largely attributable to the availability of sensitive troponin assays that detect myocardial necrosis.

2. **a.** Plaque rupture. Plaque rupture is the dominating initiating event of acute MI. Rupture of the fibrous cap of the coronary atheroma exposes the underlying subendothelial matrix eventually leading to activation of platelets, thrombin generation, and final thrombus formation. While erosion of the plaque without rupture can lead to thrombus formation, it is not as frequent an event as plaque rupture and accounts for a third of MIs.

3. **a.** Age. Based on results of the large GUSTO-I trial the strongest predictor of mortality following STEMI is advanced age. In addition to age, other major predictors of poor prognosis on presentation include systolic BP <100 mmHg, heart rate >100 per minute, higher Killip classification stage, and anterior infarction.

4. **e.** Both b and c. Aspirin, clopidogrel, prasugrel, and ticagrelor are all antiplatelet agents. Aspirin irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. While clopidogrel and

prasugrel are prodrugs that require hepatic bioactivation to their pharmacologically active metabolite, ticagrelor is phenotypically active and is not affected by hepatic metabolism.

5. **e.** All of the above are correct. Prasugrel has faster onset of action and potency of platelet inhibition when compared with clopidogrel. Unlike clopidogrel, prasugrel is not influenced by P-450 genetic polymorphisms. In the large, randomized TRITON-TIMI-38 trial, investigators compared prasugrel with clopidogrel in patients with ACS initiated following coronary angiography. While there was no difference in mortality, there was a reduction in composite of major adverse cardiovascular events primarily driven by reduction in nonfatal MI. A higher incidence of bleeding with prasugrel when compared with clopidogrel was noted. Post hoc analysis showed net harm in patients with prior history of TIA/stroke and prasugrel should be avoided in these patients.

6. **e.** Fibrinolysis; low-molecular-weight heparin (LMWH), aspirin, and clopidogrel; and transfer to hospital for possible PCI. This patient has acute STEMI. Current ACC/AHA guidelines recommend (class I) administration of fibrinolytic therapy (within 30 minutes) when there is an anticipated delay to performing primary PCI within 120 minutes of first medical contact. In addition to fibrinolysis, adjunctive antiplatelet therapy (aspirin 162 to 325 mg loading dose and clopidogrel 300 mg loading dose in patients aged <75 years) and antithrombotic therapy (weight-adjusted unfractionated heparin or LMWH) should be promptly initiated. Adjunctive LMWH in the setting of fibrinolysis was compared with heparin in the randomized ENTIRE-TIMI-23 trial. The study showed reduced ischemic events (death/recurrent MI) with LMWH when compared with unfractionated heparin at 30 days (4.4% versus 15.9%). The benefit of early routine angiography regardless of symptom status and hemodynamic stability has been confirmed in a number of clinical trials. As a result, transfer to a PCI hospital following lytic administration is encouraged.

7. **a.** Continue unfractionated heparin, aspirin, and clopidogrel and transfer to the nearest hospital with PCI capabilities. Repeat ECG reveals resolution of ST-segment elevation that likely indicates reperfusion. As previously stated, a significant proportion of patients receiving fibrinolysis may undergo reocclusion of the infarct artery. Therefore, it is reasonable to transfer patients to the nearest PCI-capable hospital (ACC/AHA class IIa recommendation). Angiography 3 to 24 hours after fibrinolysis is now recommended in these subjects regardless of hemodynamic status. Discharge home after stress test and referral for delayed angiography are not preferred options for patients with acute STEMI treated with

fibrinolysis.

8. **c.** Streptokinase and aspirin each have a similar effect on outcome. Based on results of International Studies of Infarct Survival (ISIS-2) trial from the fibrinolytic era, aspirin provides as much mortality benefit as streptokinase and the combination provides additive benefit in acute MI.

9. **c.** Adenosine diphosphate blockade. Ticagrelor reversibly blocks adenosine diphosphate receptors of subtype $P2Y_{12}$ on platelet cell membranes eventually leading to inhibition of platelet activation. Aspirin acts by a thromboxane inhibition and abciximab is a chimeric human monoclonal antibody that works by blockade of the activated GP II/IIIa receptor on the platelet surface.

10. **c.** Routine GP IIb/IIIa inhibitor use is associated with increased risk of bleeding. While prior studies documented benefits of routine intravenous GP IIb/IIIa in STEMI, the emergence of potent platelet adenosine diphosphate $P2Y_{12}$ receptor inhibitors sparked controversy regarding their additive benefit. Most subsequent trials demonstrated no clinical benefit with possible increased risk of bleeding with routine use of these agents in addition to dual oral antiplatelet therapy. A benefit for upstream GP IIb/IIIa inhibition was also not evident in the Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome (EARLY ACS) and Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trials. Use of these agents is now reserved in the catheterization laboratory for patients undergoing high-risk PCI with high thrombus burden and for bailout.

11. **a.** Decrease subsequent repeat TVR. Stents decrease the rate of subsequent TVR compared with balloon angioplasty alone, but there is no favorable impact on TIMI-3 flow or mortality.

12. **d.** It had similar rates of mortality compared with alteplase. It had similar rates of mortality to alteplase. This noninferiority trial randomized over 15,000 patients with STEMI to intravenous alteplase or reteplase. The rates of mortality (11.20% and 11.06% at 1 year, respectively) and stroke were similar for reteplase and alteplase. The major advantage of reteplase was that it could be given as two boluses rather than as an infusion.

13. **e.** All of the above. Results from large TIMI registry indicate that biomarker elevation (NSTEMI) and ST-segment deviation on admission ECG carries poorer prognosis in patients with NSTE-ACS. In addition, one in five patients with NSTE-

ACS may have normal or nonspecific changes on ECG.

14. **c.** Administer aspirin, sublingual nitroglycerin, and heparin. The patient has signs and symptoms suggestive of cocaine-induced ACS. The dominant underlying pathophysiologic factor in cocaine-induced ACS can be coronary spasm or thrombus formation caused by α-adrenergic stimulation. Atherosclerosis is also accelerated by cocaine use. This patient should be started on aspirin, sublingual nitroglycerin, and intravenous heparin. β-Blockers are contraindicated as they may allow unopposed β-adrenergic stimulation and have been associated with increased mortality.

15. **a.** Activate the catheterization laboratory for emergent left heart catheterization. The patient has persistent ischemia after initiation of antianginal therapy. He needs to be sent for emergent left heart catheterization. Intravenous benzodiazepine can temporarily relieve cocaine-induced chest pain but this patient has ischemic symptoms with ECG changes suggestive of ACS. Fibrinolytics have not been shown to be useful in cocaine-induced chest pain without evident thrombosis.

16. **d.** Clopidogrel 600 mg, bivalirudin drip, and atorvastatin 80 mg. This patient has acute MI. Current ACC/AHA guidelines mandate adjunctive medical therapy in addition to aspirin, including loading dose of $P2Y_{12}$ receptor inhibitor (clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg) and anticoagulant therapy (unfractionated heparin or bivalirudin). Fondaparinux (a) should not be used as a sole anticoagulant to support primary PCI as it has been shown to increase catheter thrombosis. Prasugrel is contraindicated in patients with history of stroke.

17. **c.** Mortality benefit with routine intravenous nitroglycerin is not established. Although widely used, no randomized trial has established a mortality benefit with intravenous nitroglycerin. Intravenous ACE-I formulations have no proven benefit and were associated with increased mortality in Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS 2). Routine intravenous β-blocker use within 24 hours also did not have any impact on mortality and led to higher rates of cardiogenic shock in the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2) megatrial. No benefit with intravenous magnesium was noted in the National Heart, Lung and Blood Institute (NHLBI)-supported Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial.

18. **e.** Fibrinolysis should be considered 12 hours after symptom onset in hemodynamically stable patients with signs of ongoing ischemia. Fibrinolysis has

not been shown to be useful and may even lead to harm after 12 hours of symptom onset in patients with STEMI. Two large, randomized trials (Late Assessment of Thrombolytic Efficacy (LATE) and Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERAS)) investigated the utility of late fibrinolysis in patients with STEMI and found no mortality benefit beyond 12 hours of symptom onset. Primary PCI is associated with reduced rate of intracerebral hemorrhage when compared with fibrinolysis. If rapidly available, primary PCI has been convincingly shown to reduce mortality when compared with fibrinolysis. Primary PCI may be considered 12 hours after symptom onset in patients with signs of ongoing ischemia. While primary PCI should be considered in patients with signs of ongoing ischemia 12 to 24 hours after symptom onset, routine PCI of the totally occluded infarct-related artery >24 hours after presentation in hemodynamically stable patients without signs of ischemia provides no additional benefit and may even be harmful. Delayed PCI (3 to 28 days after MI) of the occluded asymptomatic Infarct Related Artery (IRA) was evaluated in the randomized Occluded Artery Trial (OAT). While PCI did not reduce the occurrence of death, reinfarction, or heart failure, there was a trend toward excess reinfarction during long-term follow-up in stable patients.

19. **d.** Suspected aortic dissection. Suspected aortic dissection is an absolute contraindication for use of fibrinolysis. History of stroke, pregnancy, use of warfarin, and history of seizure disorders are all relative contraindications for fibrinolysis.

20. **c.** Presence of collateral circulation in the infarct zone reduces risk of VSR. VSR is more likely in women and after first MI. Fibrinolytic therapy is not associated with increased risk of VSR but may accelerate rupture in vulnerable subjects. VSR is equally likely after anterior or nonanterior wall MI.

21. **e.** Urgent surgical repair. This patient has VSR after acute MI. Although the shunt fraction is small, the rupture may rapidly progress in an unpredictable manner and lead to hemodynamic collapse and death. Although controversial, urgent surgical closure remains the treatment of choice. Vasodilators (nitroprusside) and IABP placements can reduce shunt fraction and increase forward flow and can be utilized in hemodynamically unstable patients as bridge to surgery. This patient is hemodynamically stable with a small shunt fraction.

22. **d.** All of the above. Acute ventricular free wall rupture usually presents with acute onset cardiac tamponade, pulsus paradoxus, and sudden death. It accounts for approximately 10% of mortality after MI. Fibrinolysis may increase risk and this

potentially accounts for the "early hazard" with thrombolytic therapy as noted in the randomized clinical trials. Type I rupture is a slit-like full-thickness rupture that is usually seen within the first 24 hours. It usually occurs in the border zone between the akinetic infarct-related segment and the adjacent hyperkinetic noninfarct zone.

23. **a.** Ventricular aneurysm is more common than ventricular pseudoaneurysm after MI. True ventricular aneurysm is more likely than pseudoaneurysm (contained rupture of LV free wall). While ventricular aneurysm is more likely with anterior MI, pseudoaneurysms occur more often after inferior wall MI. In contrast to patients with true aneurysms that are initially managed with medical therapy, pseudoaneurysms have a high risk of rupture and surgical therapy is recommended irrespective of size or presence/absence of symptoms.

24. **e.** Transthoracic echocardiogram. This patient presents with symptoms suggestive of TIA. He had a recent anterior wall MI. Persistent ST elevation in V_2 to V_4 suggests apical aneurysm that increases the risk of mural thrombus formation. Current symptoms suggest an embolic event secondary to LV mural thrombus. Echocardiogram must be done to confirm the diagnosis. Although the patient has persistent ST elevation on ECG, there are no clinical signs of recurrent ischemia and repeat left heart catheterization is not indicated.

25. **a.** Pulmonary capillary wedge pressure (PCWP) 30, confidence interval (CI) 1.6. This patient has acute STEMI complicated by cardiogenic shock. Cardiogenic shock is defined as evidence of ineffective tissue perfusion arising from cardiac dysfunction supported by the presence of a systolic BP <90 mmHg, PCWP >15 mmHg, and cardiac index <2.2 L/min/kg/m^2. Classic study performed in the pre-reperfusion era by Forrester risk stratified patients with cardiogenic shock based on PCWP and CI. Patients with both elevated PCWP and low CI have worst prognosis. In the GUSTO-I trial low cardiac output (and cardiac index) remained the strongest hemodynamic predictors of death in patients with cardiogenic shock.

26. **a.** Consideration for advanced mechanical support. Advanced mechanical support with IABP, ECMO, or TANDEM heart is indicated at this time. IABP reduces afterload, increases cardiac output, and reduces myocardial oxygen requirement by means of reduction in wall stress. The recently conducted Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP SHOCK-II) trial failed to show a mortality benefit in this setting with IABP counterpulsation, as a result IABP support in the setting of shock is now downgraded to a IIa indication in the most recent ACC/AHA guidelines. Other supportive devices such as the TANDEM and Impella have been shown to provide

superior hemodynamic support to IABP alone, although no clear benefits with regard to mortality have been noted. The patient described achieved satisfactory mechanical reperfusion and urgent CABG or repeat angiography is not indicated and nitroprusside would not be considered in this setting.

27. **c.** Atorvastatin, lisinopril, carvedilol, and eplerenone. Current guidelines in post reperfusion care include medical management for optimal risk factor control and treatment of myocardial dysfunction. High-potency statins (atorvastatin or rosuvastatin) and β-blockers are indicated in the absence of contraindications in all patients with STEMI. ACEIs are indicated in all patients after MI with ejection fraction <40% or anterior wall MI and aldosterone antagonists are indicated in patients with MI and ejection fraction <40% with clinical signs of heart failure.

28. **f.** None of the above. This patient had a brief episode of nonsustained VT in the setting of MI. Routine antiarrhythmic therapy with amiodarone or lidocaine is not indicated in patients with MI and brief, self-limited, and hemodynamically insignificant arrhythmias within 48 hours of symptoms. This patient has low ejection fraction and warrants consideration for a primary prophylaxis ICD based largely on the Multicenter Automatic Defibrillator Implantation Trial (MADIT II) trial if ventricular function does not recover. Early use of ICD post MI was not associated with benefit in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) and Immediate Risk Stratification Improves Survival (IRIS) trials. Patients with MI and low ejection fraction need to be reevaluated after 40 days on optimal medical therapy to determine candidacy for device therapy.

29. **d.** Within 30 minutes. Door in door out time in the setting of STEMI is the time from patient presentation to discharge from a non-PCI hospital to a PCI-capable hospital. A door in door out time of less than 30 minutes is associated with decrease in mortality.

30. **d.** Initiation of hypothermia protocol. Initiation of therapeutic hypothermia in post cardiac arrest patient has been shown to be associated with a significant mortality benefit. The patient is not in shock and administration of normal saline may lead to pulmonary edema. Prophylactic intravenous lidocaine in this setting has not been shown to have any clinical benefit and may lead to harm. The patient does not have polymorphic VT and there is no role for transvenous pacing in ischemically triggered polymorphic VT. While ECMO has been shown to be useful in patients with refractory cardiogenic shock, it is not indicated in a hemodynamically stable patient post cardiac arrest.

31. **b.** Treatment with clopidogrel 300 mg followed by 75 mg daily. This patient has UA and will likely rule in for an NSTEMI. Initiation of antiplatelet therapy with a bolus dose of clopidogrel 300 mg followed by 75 mg once daily is indicated based on the results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. The use of prasugrel in the elderly is associated with increased risk of bleeding. In this patient who is not undergoing revascularization, the use of bolus dose prasugrel cannot be supported. In addition to antiplatelet therapy with aspirin, the patient also needs to be started on antithrombotic therapy (with unfractionated heparin, LMWH, or fondaparinux). Lastly, since he has refused revascularization, medical antianginal therapy should be maximized. Increasing β-blocker as tolerated is indicated.

32. **e.** Apixaban. Bivalirudin, argatroban, and hirudin are intravenous direct thrombin inhibitors and dabigatran is an oral direct thrombin inhibitor. Apixaban is an oral factor Xa inhibitor.

33. **b.** Fibrinolysis reduces the incidence of pericarditis in MI. Several studies, including Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (Italian) (GISSI 1), have examined this issue and found that fibrinolysis reduces the incidence of pericarditis in the setting of acute MI. Indeed, in the era of reperfusion therapy, the rate of both early and late pericarditis has decreased. Probably, by reducing infarct size, reperfusion decreases the incidence of pericarditis, which is more common with large MIs.

34. **e.** All of the above are acceptable indications for IABP use.

35. **c.** CT abdomen without contrast. The patient has signs and symptoms suggestive of massive retroperitoneal bleeding after left heart catheterization. Retroperitoneal bleeding is a common complication after left heart catheterization through femoral access. Patients present with anemia that may be hard to detect on clinical examination. CT abdomen without contrast is the test of choice to confirm bleeding. He has no signs of recurrent ischemia on ECG and as such repeat catheterization to look for stent thrombosis (a) is not indicated. Lack of elevated jugular venous pulse makes pulmonary embolism (b) or cardiac tamponade/acute mitral regurgitation (e) unlikely.

36. **b.** Performance of a gated CT of the aorta. This patient has acute aortic regurgitation and performance of gated CT aorta is urgently indicated. Development of a new diastolic murmur at the base of the heart that accentuates with expiration should raise suspicion of acute aortic regurgitation. Acute aortic regurgitation is usually

secondary to endocarditis or acute ascending aortic dissection. Ascending aortic dissection can involve the coronary cusps leading to acute coronary dissection that can present with chest pain and ST elevations on ECG. Cocaine use is a major risk factor for acute aortic dissection. While nongated CT with pulmonary embolus protocol can often detect acute aortic detection, it is often associated with motion artifacts in the aortic root and is not the ideal test. The patient has a suspected acute aortic dissection, and activation of catheterization laboratory for revascularization or antiplatelet therapy is not indicated. Confirmation by the performance of a CT aorta followed by immediate surgical consultation appears warranted. While two-dimensional echo can often detect an aortic dissection flap, absence of the same does not rule out aortic dissection.

37. **d.** Recent exposure to a phosphodiesterase 5 inhibitor. This patient developed immediate hypotension after administration of nitroglycerin. Administration of nitrates in patients who have recently taken phosphodiesterase 5 inhibitors such as sildenafil acetate can lead to severe hypotension, circulatory collapse, and death. The patient is unlikely to develop massive hemorrhage within 5 minutes of aspirin load, and anaphylaxis in this setting is extremely uncommon. Administration of nitrates can cause profound hypotension in RV infarction but this patient has ST elevations in V_1 to V_4, suggesting anterior-apical wall MI.

38. **b.** Her prognosis will likely be excellent with full recovery of LV function. This patient has Takotsubo cardiomyopathy, also known as transient apical ballooning syndrome. This transient weakening of LV apex is often triggered by emotional stress, such as the death of a loved one, a breakup, or constant anxiety, and is most often seen in middle-aged women. Most patients achieve complete recovery within few months. There is no indication for ICD and there is no increased risk of atherosclerosis or malignancy. Routine anticoagulation with warfarin is not indicated in the absence of apical thrombus.

39. **a.** Discussion with the family explaining his poor prognosis and the near futility of escalating care is the ideal next step in this scenario. The patient presents with acute STEMI complicated by cardiogenic shock. The large randomized SHOCK trial did not show any benefit for a revascularization strategy in patients >75 years with cardiogenic shock. Data from multiple registries suggest that aggressive measures (IABP, heart catheterization, and revascularization) should be considered in patients with good baseline functional status, and such efforts are likely to be futile in this patient with poor functional status, extensive history of coronary artery disease, and multiple medical comorbidities.

40. **b.** Diagonal. The culprit infarct-related artery is the diagonal branch of LAD.

41. **c.** Initiate intravenous heparin and assess the risks and benefits of fibrinolysis. The echo shows a linear density in the main PA extending into the left PA. Findings are most consistent with a hemodynamically significant pulmonary embolism. Starting intravenous heparin and assessment for fibrinolysis are urgently indicated.

42. **d.** Mid RCA in dominant RCA. The echo shows a VSR in the basal inferoseptum. This area is usually supplied by the PDA. As a result, a dominant RCA infarction likely accounts for these changes.

43. **d.** Initiate fibrinolytic therapy with reteplase with adjunctive treatment with aspirin and intravenous heparin. The ECG shows significant anterior ST depression with upright T waves consistent with a true posterior current of injury. Although no benefit is noted with fibrinolytic therapy over placebo in randomized clinical trial, a benefit was noted in patients with true posterior injury defined as ST depression >2 mm in the anterior precordial leads. This patient is in the golden hour. Transfer to a remote location for PCI 4 hours later would be inappropriate.

Coronary Artery Disease

Baris Gencer • Debabrata Mukherjee • Marco Roffi

QUESTIONS

1. A 67-year-old man presents to the emergency room with increasing frequency of chest pain on exertion and one episode of rest pain lasting 15 minutes the day of admission. Other than for hypertension and hyperlipidemia his medical history is unremarkable. He quit smoking (1 pack a year for 20 years) 11 years ago. On physical examination he is afebrile, his pulse is 78 bpm, and his blood pressure is 138/76 mmHg. Cardiac and pulmonary auscultations are unremarkable. His current medications include aspirin, metoprolol, ramipril, and atorvastatin. The electrocardiogram (ECG) at admission reveals deep T-wave inversion in the precordial leads and no pathologic Q waves. You admit the patient to the hospital and start intravenous (IV) unfractionated heparin (UFH) and nitroglycerine. The first available serum troponin I level is 1.4 μg/L (upper limit of normal, 0.09 μg/L). Cardiac echocardiography shows an anterior and apical hypokinesia with mildly depressed left ventricular function. The next step in his management would be

   a. low-level exercise stress ECG next morning.
   b. to continue IV heparin and nitroglycerin, increase β-blocker, and add a calcium antagonist until completely free of chest pain for 24 hours, then discharge home.
   c. coronary angiography within 48 hours followed by percutaneous intervention/surgical revascularization if indicated.
   d. dobutamine echocardiogram or myocardial perfusion scan within 48 hours.
   e. continue IV heparin and nitroglycerin, increase β-blocker, and add a calcium antagonist until completely free of chest pain for 24 hours, then transfer to a cardiac rehabilitation program.

2. A 57-year-old man presenting with unstable angina (UA) was successfully treated with percutaneous coronary intervention (PCI) of a significant lesion of the right

coronary artery (RCA) in the presence of a normal left ventricular ejection fraction (LVEF). He is referred for cardiac rehabilitation program. What is the expected benefit?

a. Reduced risk of stent restenosis
b. Lower rate of hospital readmission
c. Reduction in maximal $\dot{V}O_2$
d. Higher event rate related to exercise
e. Reduced risk of stent thrombosis

3. A 66-year-old man with stable angina at low exertion level was investigated with coronary angiography that showed an isolated significant lesion (70%) of the ostium and mid-portion of the left main coronary artery in the presence of a normal left ventricular function. What is the correct statement regarding the recommended approach?

a. Heart team discussion between the interventional cardiologist and the cardiac surgeon to select the best treatment option is the recommended approach.
b. Coronary artery bypass grafting (CABG) is the recommended approach for all patients with left main disease.
c. PCI is the recommended approach for all patients with left main disease.
d. A calculation of the Society of Thoracic Surgeons (STS) and SYNTAX (Synergy between PCI with TAXUS and Cardiac Surgery) scores is not recommended at this stage.
e. The choice of treatment is independent of the clinical presentations (stable angina or acute coronary syndromes [ACSs]).

4. A 58-year-old man with coronary artery disease (CAD) and severe chronic obstructive pulmonary disease (COPD) with forced expiratory volume in the first second of expiration (FEV_1)/forced vital capacity <0.74 with FEV_1 <40% predicted had stenting of the mid-left anterior descending artery (LAD) 10 months prior to admission with a 3.0 mm × 24 mm bare metal stent (BMS). He presents now with recurrent angina despite intensified medical treatment, and coronary angiography reveals a severe and diffuse in-stent restenosis (ISR). A reasonable next therapeutic option would be

a. plain balloon angioplasty.
b. coronary artery bypass surgery.
c. drug-eluting stent (DES) implantation (stent-in-stent).
d. medical therapy.
e. brachytherapy.

5. A 66-year-old man had in the last few months sporadic episodes of chest pain on exertion. His cardiovascular (CV) risk factors included diabetes, hypertension, and hypercholesterolemia. He had no other comorbidity. Coronary angiography revealed a lesion of 60% of the RCA in addition to multiple nonsignificant plaques affecting the three coronary arteries. The fractional flow reserve (FFR) of the RCA (0.0.85) and LVEF were normal. What is the recommended treatment for this patient?

   a. CABG is the first recommended approach as the risk of surgical procedure is low.
   b. PCI is the first recommended approach as the SYNTAX score is low.
   c. Perform an additional imaging (myocardial perfusion scan or magnetic resonance [MR] perfusion scan) in addition to optimal medical management.
   d. Guideline-directed medical therapy is the first recommended approach.
   e. Repeat coronary angiography after 6 months to exclude disease progression in addition to optimal medical management.

6. A 58-year-old male smoker treated for hypertension complained about chest pain on exertion in the preceding 4 weeks. To investigate the clinical symptoms, you performed a stress perfusion cardiac magnetic resonance showing hypoperfusion during IV administration of adenosine. Which area of the myocardium is more vulnerable to hypoperfusion?

   a. Subepicardium
   b. Mid-myocardium
   c. Subendocardium
   d. Pericardium
   e. All of the above

7. A 73-year-old man presents to the emergency room with severe mid-sternal chest discomfort. He appears anxious and in distress. His heart rate is 66 bpm, blood pressure is 92/68 mmHg, and respiratory rate is 14. There is marked jugular venous distention. Cardiac auscultation is unremarkable and the lungs are clear. ECG reveals 2-mm ST-segment elevation in leads II, III, and aVF. The most likely diagnosis is

   a. acute pericarditis.
   b. acute aortic dissection.
   c. pneumothorax.
   d. inferior wall myocardial infarction (MI) with right ventricular infarction.
   e. pneumonia.

8. A 65-year-old hypertensive man was hospitalized for non-ST-segment-elevation myocardial infarction (NSTEMI). The clinical examination shows a fourth heart sound (S_4). What is expected to be found at the echocardiography?

   a. Reduction in left ventricular compliance
   b. Rapid deceleration of transmitral flow during protodiastolic filling of the left ventricle
   c. Increased inflow into the left ventricle
   d. Reduced left ventricular systolic function
   e. Aortic sclerosis

9. A 66-year-old man known for diabetes mellitus treated with oral glucose lowering medications presents with UA. Coronary angiography reveals a three-vessel disease: 70% mid-LAD lesion, complex, long, and calcified; 70% focal proximal left circumflex artery (LCX) stenosis; and 70% focal mid-RCA lesion. A hybrid coronary revascularization was proposed. All the following statements are correct regarding hybrid coronary revascularization, with the exception of one.

   a. Hybrid revascularization is defined as the planned combination of surgical and percutaneous revascularization (typically left internal mammary artery [LIMA]-to-LAD and PCI of ≥1 additional vessel).
   b. Hybrid revascularization is reasonable in patients with limitations to traditional CABG, such as heavily calcified proximal aorta.
   c. Hybrid revascularization is reasonable in patients with lack of suitable graft conduit.
   d. Hybrid revascularization is reasonable in patients with unfavorable LAD artery for PCI.
   e. Hybrid revascularization mandates surgical and percutaneous revascularization during the same procedure.

10. A 57-year-old female smoker presents to the emergency department for an ongoing new typical chest pain lasting 30 minutes. The physical examination is unremarkable and she is hemodynamically stable. The ECG reveals T inversion in II, III, and aVF leads. Which of the following biomarker elevation has been associated with an improved benefit of ticagrelor therapy over clopidogrel in patients hospitalized with ACS?

    a. Ultrasensible C-reactive protein
    b. Interleukin-6
    c. High-sensitive troponin T (Hs-TnT)
    d. D-dimers
    e. Lactate dehydrogenase

11. A 58-year-old man known for a metabolic syndrome shows increasing frequency of chest pain on exertion in the preceding 2 weeks. Resting ECG did not show significant abnormalities. Which of the exercise parameters are associated with adverse prognosis?

a. Duration of symptom-limiting exercise <5 METs (metabolic equivalents)
b. Failure to increase systolic blood pressure ≥120 mmHg, or a sustained decrease ≥10 mmHg, or below rest levels, during progressive exercise
c. ST-segment depressions ≥2 mm
d. Angina pectoris at low exercise workloads
e. All of the above

12. A 58-year-old man presented stable chest pain on moderate effort exertion in the preceding 12 months. The medical history is relevant for hypertension and hyperlipidemia. His current treatment includes lisinopril, atorvastatin, metoprolol, and aspirin. He is addressed for coronary angiography that showed a 70% to 90% lesion of the LCX successfully treated with PCI with a placement of a DES. The LVEF was normal. What was the expected benefit of a PCI over a medical therapy?

a. Decrease of total mortality
b. Decrease of CV mortality
c. Decrease of MI
d. Decrease of heart failure events
e. No improvement of any of the mentioned endpoints

13. The same patient was investigated with stress imaging before and after PCI to assess the extension of myocardial ischemia. Which of the following statements is correct regarding the benefit of PCI over medical therapy in this setting?

a. A greater reduction in the extension of residual myocardial ischemia
b. A greater resolution of angina episodes
c. An increased benefit of ischemia reduction in patients with extensive ischemic areas at baseline
d. A greater improvement in symptoms
e. All of the above

14. A 63-year-old man has been successfully treated with percutaneous coronary revascularization for a stable angina pectoris. His low-density lipoprotein cholesterol (LDL-C) value was 143 mg/dL. Which of the following statement is incorrect regarding the impact of prescribing intensive lipid-lowering therapy (e.g., 80 mg atorvastatin daily) compared with less intensive therapy (e.g., 10 mg atorvastatin daily)?

a. Higher LDL-C level reduction
b. Significant absolute risk reduction of major adverse cardiovascular events (MACE) of ~2% over 5 years
c. Significant relative risk reduction of MACE of ~20% over 5 years
d. Increased incidence of persistent liver aminotransferase levels of 1%
e. Significant reduction of overall mortality

15. A 67-year-old man is treated with PCI. Which of the following statement is not correct regarding periprocedural anticoagulation?

a. An anticoagulant should be administered to all patients undergoing PCI.
b. Administration of IV UFH is useful in patients undergoing PCI.
c. An additional dosage of IV enoxaparin should be administered at the time of PCI to patients who received the last subcutaneous dose of enoxaparin 12 hours or more prior to PCI.
d. The appropriate diagnostic test to check for the level of anticoagulation with UFH during PCI is the activated clotting time.
e. Fondaparinux might be used as the sole anticoagulant to support PCI.

16. A 65-year-old male hypertensive smoker benefited from primary PCI of the RCA for inferior STEMI. Which of the following statements is not correct regarding secondary prevention in this patient?

a. Medically supervised cardiac rehabilitation programs are recommended.
b. Blood pressure should be controlled with a goal of <140/90 mmHg.
c. Statin therapy should be uptitrated to achieve an LDL-C <70 mg/dL
d. Smoking cessation program should be proposed.
e. Even in the absence of symptoms, routine periodic stress testing is indicated.

17. A 60-year-old male patient was treated 2 years earlier with PCI and the implantation of BMS in the LAD for NSTEMI. He complains about recurrent worsening exertional chest pain in the last week. Coronary angiography reveals ISR. What are the predisposing factors for BMS restenosis?

a. Diabetes
b. Increasing stent length
c. Increasing stent number
d. Decreasing stent diameter
e. All of the above

18. A 60-year-old healthy colleague on no medication with an LDL-C level of 123 mg/dL and High-sensitivity C-reactive protein (hs-CRP) level >2.0 mg/L asked to

you whether he should take rosuvastatin 20 mg a day. Which of the following statements is incorrect regarding JUPITER trial?

a. Rosuvastatin 20 mg/day reduced LDL-C levels by 50%.
b. Rosuvastatin 20 mg/day significantly decreased the incidence of MI.
c. Rosuvastatin 20 mg/day reduced hs-CRP by 37%.
d. Rosuvastatin 20 mg/day did not significantly decrease the incidence of stroke.
e. Rosuvastatin 20 mg/day significantly increased the incidence of physician-reported diabetes.

19. A 65-year-old man with diabetes presented typical chest pain on exertion in the previous 2 months. Coronary angiography revealed significant complex multivessel coronary disease (SYNTAX score, 34). What is the expected benefit of a revascularization with CABG versus PCI?

a. CABG is associated with a reduction of death only.
b. CABG is associated with a reduction of stroke only.
c. CABG is associated with a reduction of death and of MI, but not of stroke.
d. CABG is associated with a reduction of all following individual endpoints: stroke, myocardial infraction, and death.
e. CABG is associated with a reduction of MI only.

20. A 41-year-old male smoker was admitted for STEMI and quitted smoking after hospitalization. Which of the following statements is incorrect regarding smoking cessation?

a. Smoking cessation reduces the relative risk of total mortality by >30% over a mean follow-up of 5 years.
b. Smoking cessation reduces the relative risk of nonfatal MI by >30% over a mean follow-up of 5 years.
c. More than 70% of patients quit smoking after ACS.
d. Smoking cessation counseling program is effective to help smokers to quit smoking.
e. Smoking cessation counseling program should be proposed during hospital stay and continued after discharge.

21. Six hours after the start of chest pain, a 55-year-old diabetic man was admitted to the emergency department for anterior STEMI with hemodynamic instability (cold extremities, heart rate of 110 bpm and blood pressure of 85/50 mmHg) and severe reduced LVEF (25% to 30%) estimated by echocardiography. What is the correct statement regarding the decision to perform an emergent revascularization versus an initial medical stabilization according to the SHOCK trial?

a. Significant reduction of mortality with early revascularization compared with intensive medical therapy at 30 days
b. No significant difference of mortality with early revascularization compared with intensive medical therapy at 30 days
c. Significant reduction with intensive medical therapy compared with early revascularization at 30 days
d. Significant reduction of mortality with early revascularization compared with intensive medical therapy at 6 months
e. Answers b and d are correct

22. A 63-year-old man known for chronic kidney disease (CKD) due to long-term uncontrolled hypertension is hospitalized for elective coronary angiography. Which of the following statements is not correct?

a. Patients with CKD undergoing cardiac catheterization should receive adequate preparatory hydration.
b. In patients with CKD, the volume of contrast should be minimized.
c. Administration of N-acetyl-cysteine is useful for the prevention of contrast-induced acute kidney injury (AKI).
d. Contrast-induced AKI is one of the leading causes of hospital-acquired AKI.
e. In elective cases, patients should be assessed for risk of contrast-induced AKI before coronary angiography.

23. A 45-year-old man benefited from primary PCI for STEMI. The adjunctive antithrombotic therapy consisted of aspirin, heparin, and abciximab. The addition of abciximab is associated with

a. no significant difference in the risk of stroke.
b. a significant increase in the risk of stroke.
c. a significant decrease in the risk of stroke.
d. a significant decrease of nonhemorrhagic stroke only.
e. a significant increase of hemorrhagic stroke only.

24. A 65-year-old diabetic man known for a multivessel coronary disease underwent revascularization with CABG. What is the target LDL-C that should be aimed?

a. 160 mg/dL
b. 130 mg/dL
c. 100 mg/dL
d. 70 mg/dL
e. 50 mg/dL

25. A 62-year-old man was hospitalized for an NSTEMI and underwent invasive strategy with DES-based PCI. Which of the following statements about antiplatelet therapy is wrong?

a. Patients not on aspirin should be given nonenteric aspirin 325 mg before PCI.
b. After PCI, use of aspirin should be continued indefinitely.
c. Additional aspirin (81 to 325 mg) is recommended in all patients on chronic aspirin therapy before PCI.
d. A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI with stenting at the latest after completion of PCI (e.g., clopidogrel 600 mg, prasugrel 60 mg, and ticagrelor 180 mg).
e. In patients receiving a stent (BMS or DES) during PCI for ACS, $P2Y_{12}$ receptor inhibitor should be given for 12 months.

26. A 50-year-old white female nonsmoker without history of cardiovascular disease (CVD) and treated only with ramipril for hypertension was hospitalized for UA. The ECG revealed T inversion in the lateral leads. The medical student who admitted the patient asks you what is the proportion of patients that undergo coronary angiography for ACS who have nonsignificant CAD.

a. <5%
b. 10% to 15%
c. 20% to 30%
d. 25% to 35%
e. 30% to 40%

27. A 59-year-old man was successfully treated with PCI for NSTEMI. During the procedure, the patient received bivalirudin. Due to closure device failure, the patient suffered a major bleeding at the access site difficult to control with manual compression and you are in need of reversing the anticoagulation. Your treatment of choice is

a. fresh frozen plasma.
b. prothrombin complex.
c. epsilon aminocaproic acid.
d. protamine.
e. vitamin K.

28. A 63-year-old man presents typical chest pain at moderate exertion in the preceding month and he is admitted to the hospital for coronary angiography. While considering the best access for the procedure, which of the following statements is not correct regarding a radial vascular access?

a. The radial vascular access may be useful to decrease access site complications.
b. The radial vascular access is preferred in patients with coagulopathy.
c. The radial vascular access is preferred in patients with morbid obesity.
d. The radial vascular access is preferred in patients with an elevated INR.
e. The radial vascular access is more frequently performed in the United States than in Europe.

29. Which of the following conditions does not justify immediate coronary angiography and, if needed, revascularization?

a. A 57-year-old man presenting with typical chest pain lasting 60 minutes up to emergency department arrival. As cardiologist on call you are called in immediately and when you see the patient, his pain has virtually disappeared while ECG shows 2-mm ST-segment elevation in the inferior leads.
b. A 60-year-old diabetic man known for previous coronary disease presenting with not better defined chest discomfort lasting for 10 hours and currently decreasing in intensity, pulmonary edema, and 3-mm ST-segment elevation in the anterior leads on ECG in the absence of Q waves.
c. A 65-year-old man known for CAD complaining of progressive shortness of breath since 1 week. At admission, no ongoing chest pain with stable hemodynamic status but bibasilar rales at lung auscultation. The ECG revealed ST-segment elevation as well as Q waves in the anterior leads.
d. A 70-year-old man presenting to the emerging department with on–off chest pain in the preceding 20 hours. Upon your arrival he has mild chest pain and on ECG 2-mm ST elevation in the lateral leads in the absence of Q waves.
e. A 68-year-old diabetic man presenting to the emerging department with chest pain lasting 4 hours, hypotension, and tachycardia and on ECG 3-mm ST-segment elevation in the anterior and lateral leads.

30. A 76-year-old man with no prior cardiac history presents to the emergency department with acute retrosternal chest pain. He had a single episode of chest pain lasting 4 hours 5 days ago. At that time he did not seek medical attention. Physical examination reveals a slightly confused diaphoretic patient, with heart rate of 95 bpm, blood pressure of 76/42 mmHg, and cold extremities. He is able to lie flat, the lungs are clear, and the jugular veins are distended even if the upper part of the body is raised at 45°. On cardiac auscultation a loud systolic murmur is audible, while on ECG Q waves associated with ST-segment elevation are detected in the inferior leads. The most likely diagnosis is

a. severe left ventricular failure.
b. ventricular septal defect.

c. acute mitral regurgitation.
d. right ventricular infarction.
e. cardiac rupture.

31. Considering the suspected diagnosis for the patient described in the previous question, what is the next diagnostic step?

a. Cardiac enzymes
b. Chest X-ray
c. Transesophageal echocardiography
d. Immediate coronary angiography
e. Transthoracic echocardiography

32. While considering surgery for the patient described in the previous two questions, the most effective cardiac unloading treatment for him is

a. fluid resuscitation.
b. β-blockers.
c. mechanical ventilation with positive end-expiratory pressure.
d. vasopressors.
e. intra-aortic balloon pump.

33. A 66-year-old man with a history of diabetes was referred for coronary angiography. The procedure showed complex multivessel disease. Which of the following statements justify the use of DES over BMS?

a. Patient with diabetes mellitus
b. Long coronary lesions
c. Multifocal coronary lesions
d. Small vessel disease
e. All of the above

34. A 63-year-old male smoker with no history of CVD and a treatment for hypertension complains of typical chest pain on exertion the preceding 2 months without any aggravation. He is scheduled for coronary angiography in 7 days. In the meantime, you should start the following antiplatelet treatment(s):

a. Low-dose aspirin daily
b. Clopidogrel 75 mg daily without loading dose
c. A loading dose of clopidogrel 300 mg followed by 75 mg daily should be given
d. A loading dose of ticagrelor 180 mg followed by 2 × 90 mg/day should be given
e. No antiplatelet therapy needed prior to coronary angiography

35. A 66-year-old man with intermediate probability of ischemic heart disease is scheduled for stress testing. Which of the following strategies is not recommended?

a. Exercise ECG if able to exercise and ECG interpretable
b. Exercise echocardiography if able to exercise but uninterpretable ECG
c. Pharmacologic stress with nuclear myocardial perfusion imaging if able to exercise and ECG interpretable
d. Exercise stress with nuclear myocardial perfusion imaging if able to exercise but uninterpretable ECG
e. Pharmacologic stress with cardiac MR imaging if unable to exercise and interpretable ECG

36. A 65-year-old man with hypercholesterolemia, diabetes, and hypertension presents new, worsening, typical angina symptoms. The angiogram (Fig. 4.1) shows

a. occluded LAD.
b. occluded left circumflex coronary artery.
c. severe ostial and moderate distal left main trunk stenosis.
d. normal coronary arteries.
e. normal RCA.

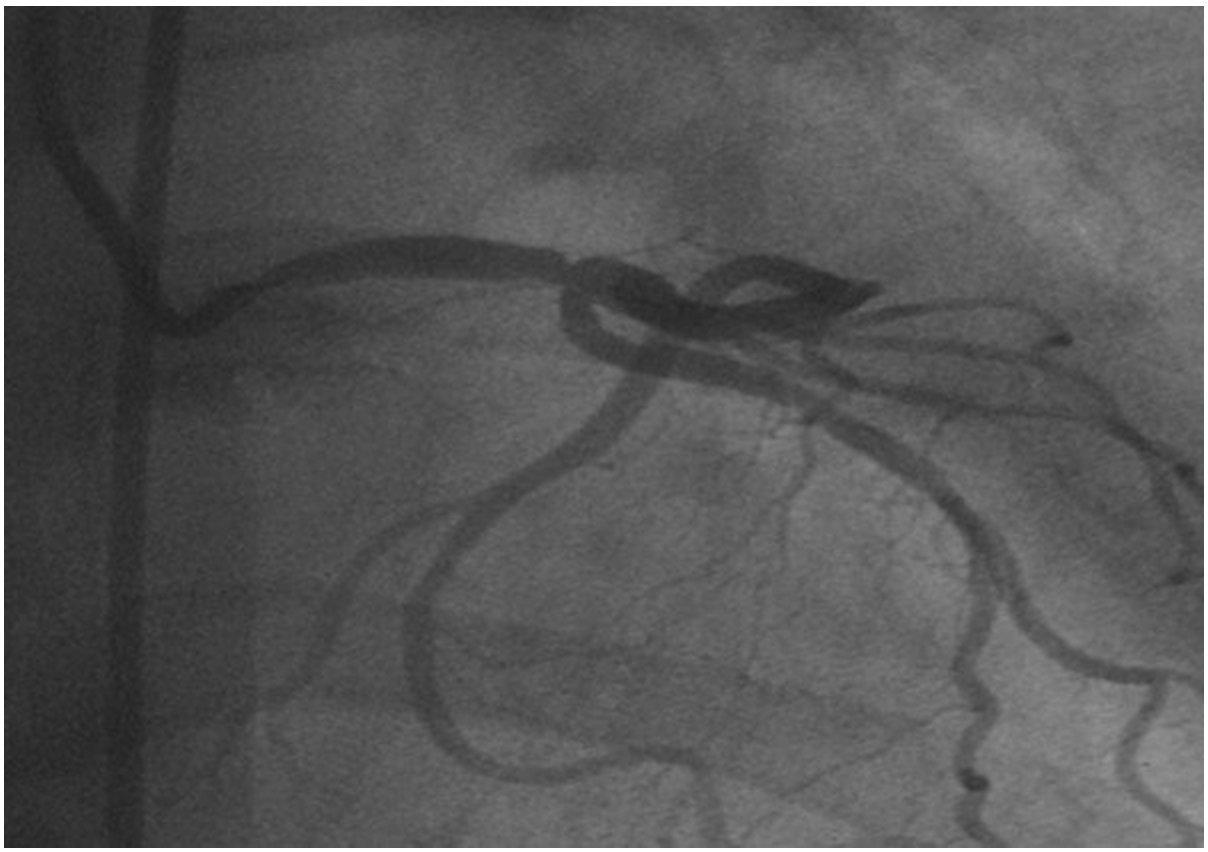

Figure 4.1

37. A 64-year-old man with stable ischemic heart disease (SIHD) wants to know whether he is at high risk for mortality. Which of the following clinical and exercise testing data are useful to predict the risk?

a. Typical angina symptoms
b. Diabetes
c. ST-segment depression during exercise
d. Proportion of predicted METs achieved
e. All of the above

38. A 48-year-old woman presents with congestive heart failure. The etiology of her heart failure based on the coronary angiogram (Fig. 4.2) is

a. severe CAD.
b. arteriovenous fistula.
c. aortic regurgitation.
d. absent RCA.
e. coronary perforation.

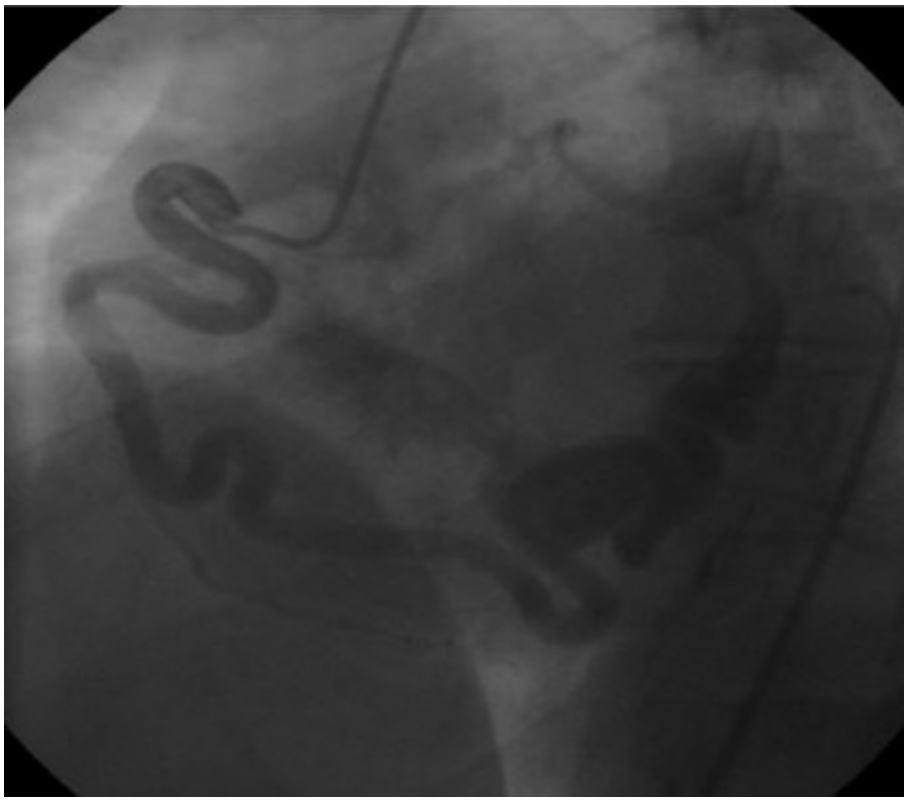

Figure 4.2

39. A 72-year-old man known with a history of coronary heart disease presents typical chest pain. During the transport to the PCI center, the patient had two episodes of ventricular fibrillation requiring electrical reanimation. ECG shows inferolateral

ST depression. What does the angiography show (Fig. 4.3)?

a. Lesions at bifurcation
b. Stenosis of the ostium of the LCX
c. Stenosis of the ostium of the LAD
d. Stenosis of the distal left main trunk
e. All of the above

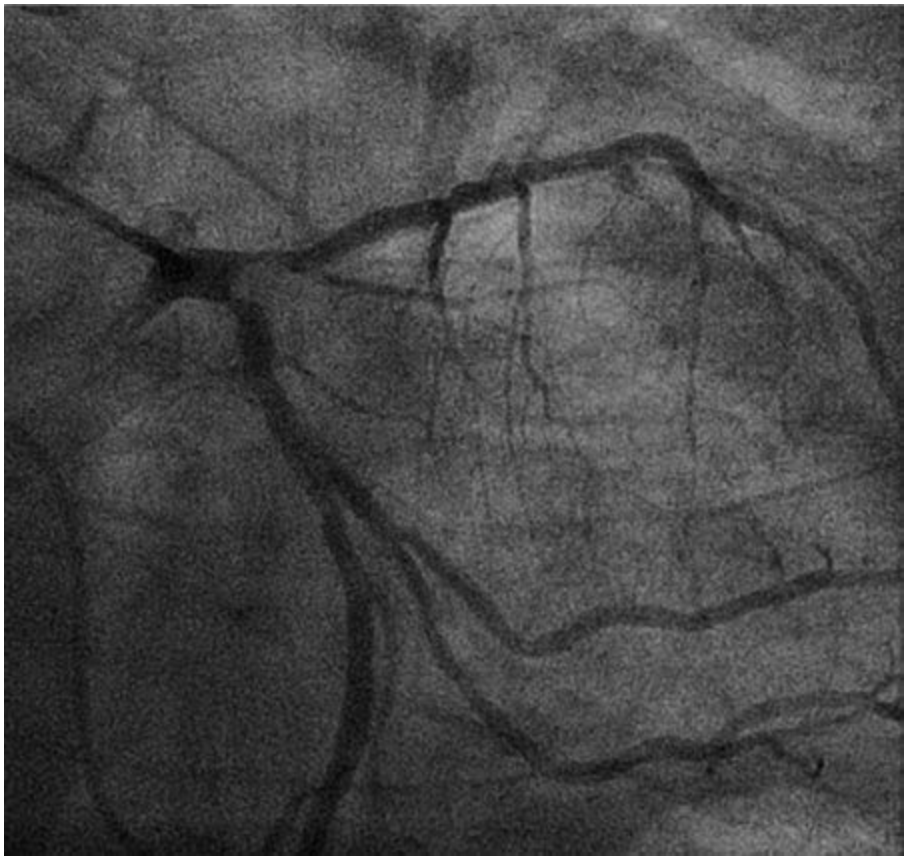

Figure 4.3

40. During coronary angioplasty of the RCA, this 72-year-old patient developed sharp chest pain with rapid development of hypotension and tachycardia. The etiology based on Figure 4.4 is

a. abrupt closure of the RCA.
b. dissection of the RCA.
c. perforation of the RCA.
d. allergic reaction.
e. distal embolization of an atherosclerotic plaque.

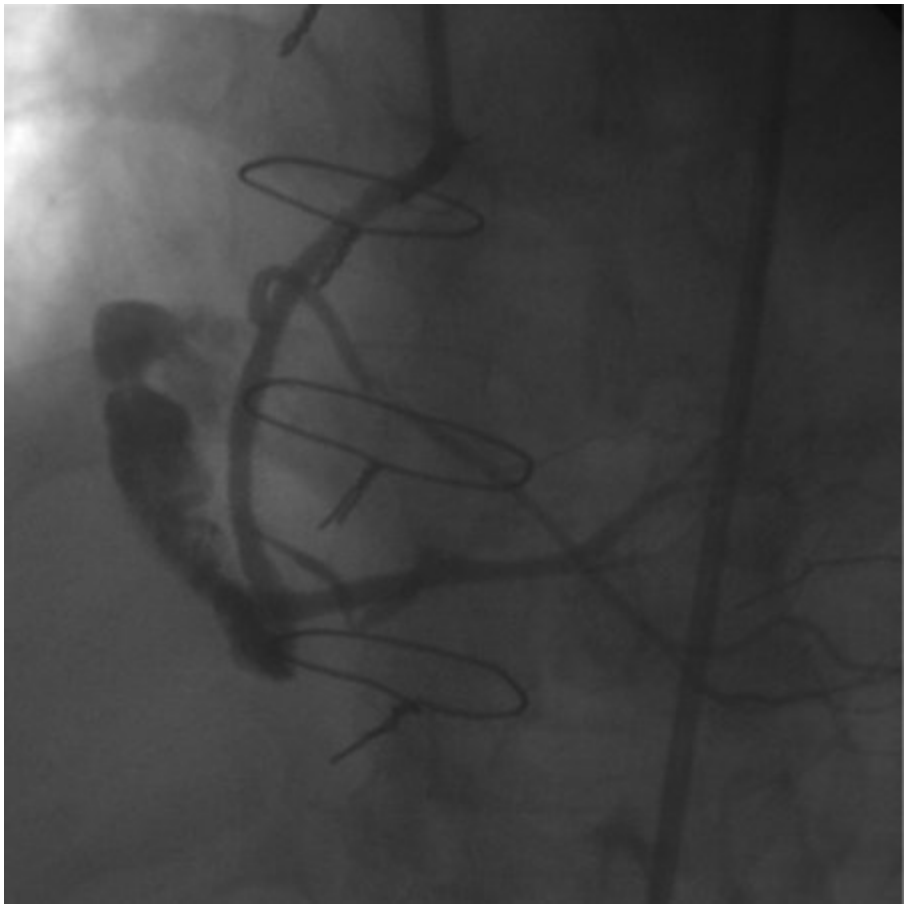

Figure 4.4

41. For which clinical situation is coronary angiography not recommended in patients with SIHD?

- **a.** Risk assessment in patients with SIHD not candidates for revascularization because of comorbidities
- **b.** Risk assessment in patients with SIHD who have preserved LV function and low-risk criteria on noninvasive testing
- **c.** Risk assessment in patients who are at low risk according to clinical criteria and have not undergone noninvasive risk testing
- **d.** Risk assessment in asymptomatic patients with no evidence of ischemia on noninvasive testing
- **e.** All the mentioned clinical situations do not justify coronary angiography in the initial phase of patient management

42. A 66-year-old man with diabetes with no hypertension but end-stage renal failure treated with hemodialysis in the last 15 years presents with worsening dyspnea and suspicion of ischemia at the stress imaging. What are the most characteristic findings relating to the coronary arteries to be found at angiography?

a. Tortuous coronary vessels
b. Calcified coronary arteries
c. Ectatic coronary arteries
d. Coronary arteries with anomalous origins
e. Normal coronary arteries (symptoms caused by small vessel disease)

43. A 65-year-old man with SIHD wants to optimize secondary prevention. Which of the following statements does not apply?

a. Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged.
b. Patients should be screened for depression and treated when indicated.
c. Treatment with clopidogrel is reasonable when aspirin is contraindicated.
d. Dipyridamole is not recommended as antiplatelet therapy for patients with SIHD.
e. Acupuncture might be used for the purpose of improving symptoms of patients with SIHD.

44. A 74-year-old man was hospitalized for a subacute MI. He presented 1 week prior to admission one episode of chest pain lasting 3 hours but he did not seek medical attention. The ECG at admission revealed deep Q waves and persisting ST-segment elevation in the anterior leads. The angiography showed a total occlusion of the proximal left anterior ascending coronary artery. Which statement about the benefit of revascularization in this particular patient does apply?

a. PCI reduces the occurrence of death.
b. PCI reduces the occurrence of reinfarction.
c. PCI reduces the occurrence of heart failure.
d. CABG should be preferred to PCI.
e. PCI does not reduce the occurrence of death, reinfarction, or heart failure.

45. A 60-year-old man with a history of PCI 3 years previously asks for your advice with respect to his pharmacologic treatment. He is asymptomatic and his CV risk factors include smoking, hypertension, hypercholesterolemia, and impaired glucose tolerance. His medications include aspirin, atorvastatin, metoprolol, metformin, and lisinopril. His friend told him that clopidogrel should be added to his regimen. What is the correct statement about that suggestion in this particular patient?

a. There is no significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from CV causes.
b. There is a significant benefit associated with clopidogrel plus aspirin as

compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from CV causes.

c. The rate of severe or moderate bleeding is not significantly greater with clopidogrel and aspirin compared with aspirin alone.

d. The rate of severe or moderate bleeding is significantly greater with clopidogrel and aspirin compared with aspirin alone.

e. Answers a and d are correct.

46. A 60-year-old woman was discharged after an MI. Pharmacologic secondary prevention with antiplatelet agents, statins, β-blockers, and angiotensin-converting enzyme inhibitors is associated with

a. significant reduction in recurrent angina but no mortality benefit.

b. significant survival advantage.

c. no significant clinical benefit.

d. significant reduction in recurrent hospitalization but no mortality benefit.

e. significant survival advantage only in patients treated with PCI.

47. A 55-year-old man presents since 3 months typical chest pain at moderate exertion. The angiography revealed single-vessel disease. An optimal therapy has been started; what is the benefit of a treatment with PCI of the culprit lesion?

a. PCI would reduce the risk of death, MI, or other major CV events when added to optimal medical therapy (OMT).

b. PCI may reduce the episodes of angina in the presence of moderate-to-severe ischemia at stress single-photon emission computed tomography (SPECT) but not the risk of death, MI, or other major CV events when added to OMT.

c. PCI would not reduce the risk of death, MI, angina episodes, or other CV events when added to OMT.

d. The benefit of revascularization in patients with stable angina and ischemia detected on SPECT is independent of the extent of ischemia.

e. Selective ischemia-driven PCI approach should be avoided, as thus not improved clinical outcomes.

48. A 67-year-old man known for hypertension and hypercholesterolemia presented significant ST elevation in inferoposterior leads during the treadmill test. The angiogram shows (Fig. 4.5)

a. severe LCX stenosis.

b. severe left main trunk stenosis.

c. severe LAD stenosis.

d. severe RCA stenosis.

e. no significant coronary artery stenosis.

Figure 4.5

49. A 66-year-old man hospitalized for an NSTEMI was successfully treated with DES for a subtotal lesion of the proximal LAD. What is the recommended minimal duration of dual antiplatelet therapy according to the 2011 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on PCI?

a. 1 month
b. 3 months
c. 6 months
d. 12 months
e. 24 months

50. A 54-year-old man known for smoking and hypertension is admitted to the emergency department with an NSTEMI. Echocardiography reveals abnormalities in the acute lateral wall motion. The angiogram (Fig. 4.6) shows

a. severe LCX stenosis.
b. severe left main trunk stenosis.
c. severe LAD stenosis.
d. severe RCA stenosis.

e. no significant coronary artery stenosis.

Figure 4.6

51. A 75-year-old man has been treated 1 month ago with a DES in the proximal LAD for ACS. At that time he did not mention that he was supposed to require surgery for debilitating knee arthritis. Which of the following statements is correct?

a. The recent implantation of a DES is not problematic as long as aspirin can be continued during surgery.
b. The recent implantation of DES is not problematic as long as clopidogrel can be continued during surgery.
c. The recent implantation of DES is not problematic as long as aspirin and clopidogrel can be continued during surgery.
d. Discontinuation of dual antiplatelet therapy followed by noncardiac surgery in the first few weeks following stent implantation is associated with increased ischemic cardiac events with both DES and BMS.
e. Discontinuation of dual antiplatelet therapy followed by surgery in the first few weeks following stent implantation is problematic with DES but not BMS.

52. A 66-year-old woman had a second-generation DES implantation after an acute MI.

What is the correct statement?

a. To prevent DES late thrombosis, dual antiplatelet therapy with aspirin and clopidogrel is recommended for 3 years.
b. Based on the results of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management, and Avoidance) trial, aspirin and clopidogrel should be administered for at least 2 years in patients with an acute coronary event, independently of the implantation of a DES.
c. At 1 year, clopidogrel may be discontinued but if the patient is on low-dose aspirin, the dose of aspirin has to be increased to 325 mg/day.
d. In patients who have already suffered a stent thrombosis dual antiplatelet therapy may be extended long term, although currently there are no data to support this strategy.
e. Following DES implantation, aspirin should be discontinued at 12 months and clopidogrel administered indefinitely.

53. A 60-year-old man known for current smoking is admitted to the emergency department for prolonged typical chest pain. The 12-lead ECG is shown in Figure 4.7. What is the most likely finding at the coronary angiography?

a. Occlusion of the first marginal branch of the left circumflex coronary artery
b. Occlusion of the proximal left anterior descending coronary artery
c. Occlusion of the dominant RCA
d. Occlusion of the left main trunk
e. Occlusion of the first diagonal branch

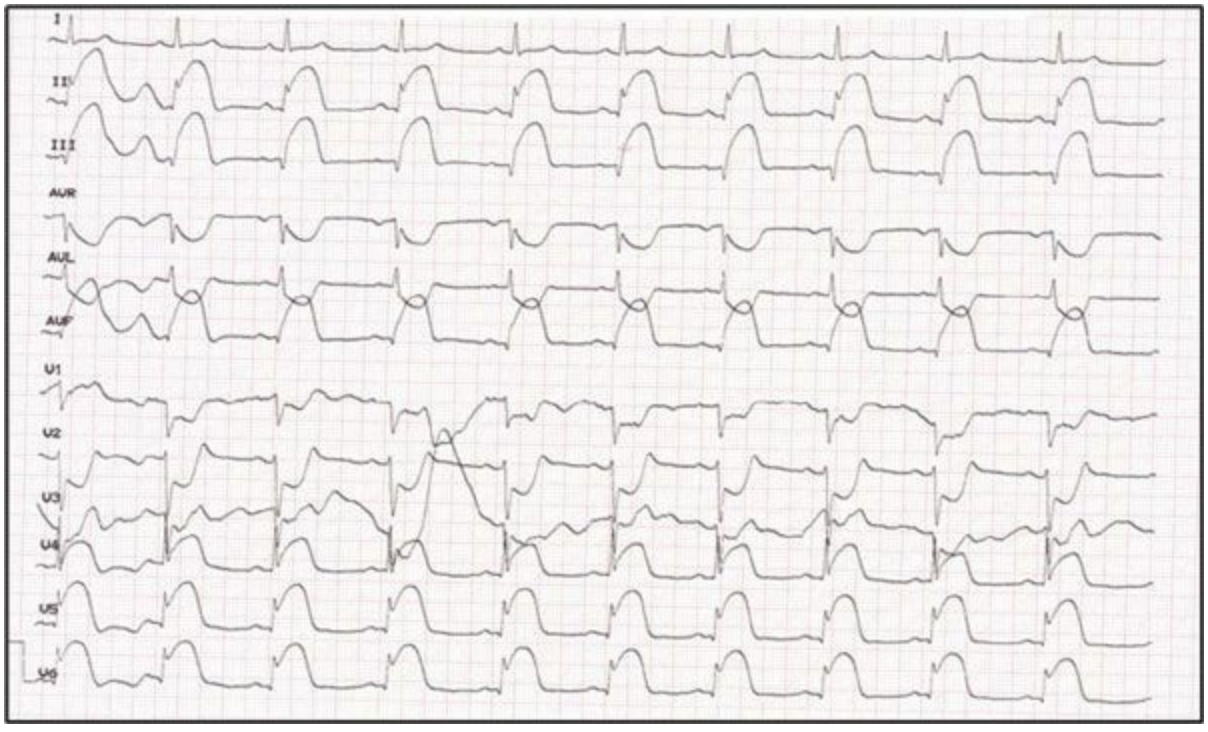

Figure 4.7

54. A 37-year-old man known for obesity felt typical chest pain while playing tennis accompanied by nausea, dyspnea, and sudations. The ECG shows ST-segment elevation. He is immediately admitted to the catheterization laboratory (Fig. 4.8). What is the underlying pathology?

a. Thrombotic occlusion of the left main trunk
b. Anomalous origin of the left main trunk
c. Dissection of the left main trunk
d. Vasospasm of the left main trunk
e. None of the above

55. A 58-year-old man known for hypertension and smoking suffered chest pain and dyspnea in the previous 48 hours. He consulted emergency department for persisting symptoms. The rest 12-lead ECG at admissions is shown in Figure 4.9. What is the diagnosis?

a. Takotsubo cardiomyopathy
b. Pericarditis
c. Anterior subacute MI
d. Cardiomyopathy hypertrophic obstructive
e. Hypertensive heart disease

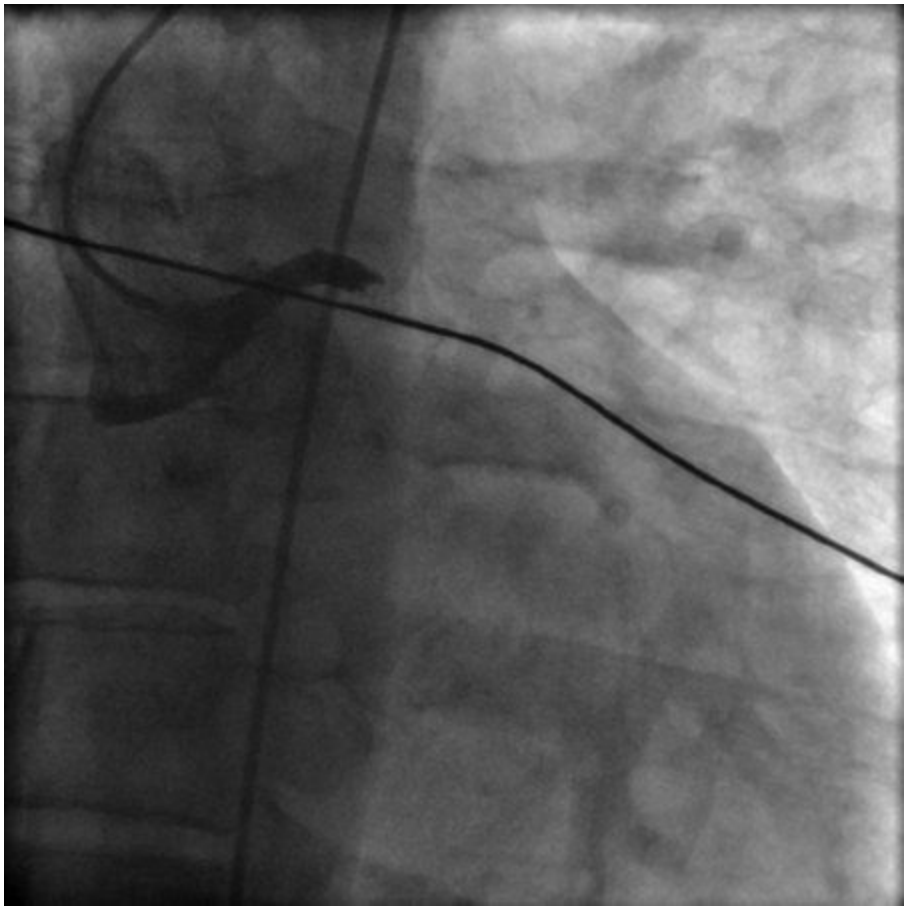

Figure 4.8

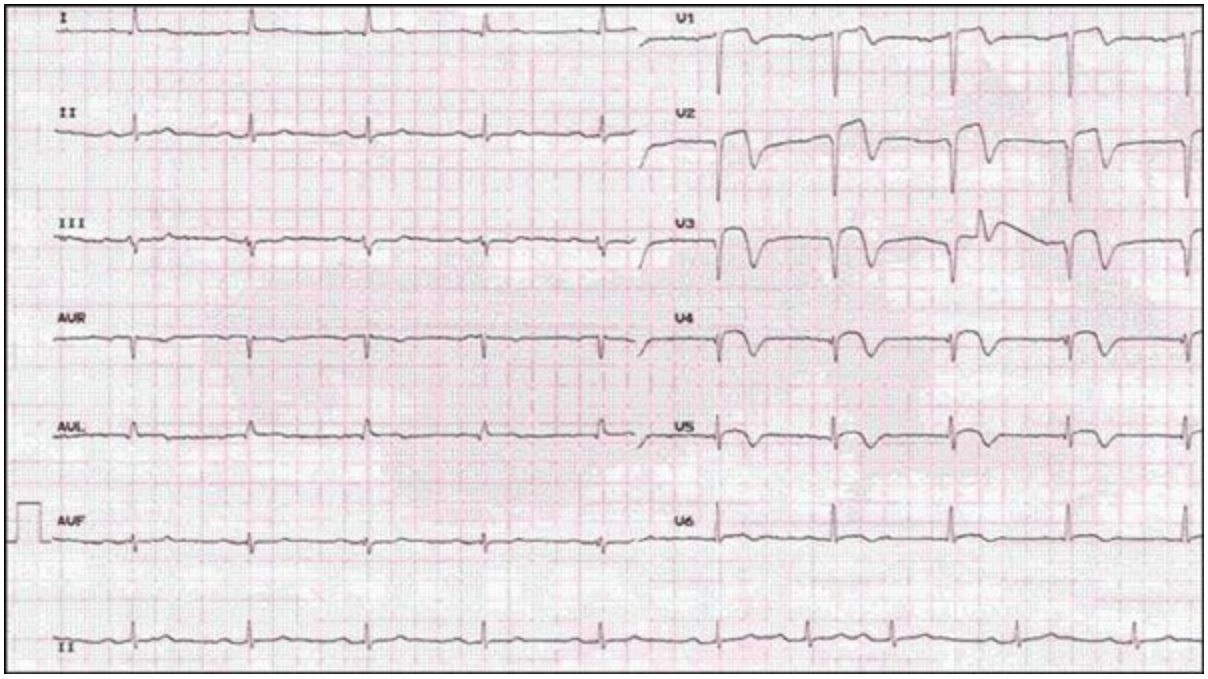

Figure 4.9

56. A 28-year-old male smoker presented after wakeup typical inaugural chest pain. The

12-rest ECG at admission is shown in Figure 4.10. He is transferred immediately to the catheterization laboratory. What is the most likely finding?

a. Occlusion of a large diagonal branch
b. Occlusion of the left anterior descending coronary artery
c. Occlusion of the left circumflex coronary artery
d. Occlusion of the RCA
e. Normal coronary angiogram

57. A 69-year-old man known for hypertension and diabetes consulted emergency department for typical chest pain. The ECG did not show significant changes. Troponins were elevated (1.4 µg/L). Coronary angiography (Fig. 4.11) shows

a. no significant lesion of the RCA.
b. perforation of the mid-portion of the RCA.
c. anomalous origin of the RCA.
d. visible thrombus in the mid-portion of the RCA.
e. dissection of the mid-portion of the RCA.

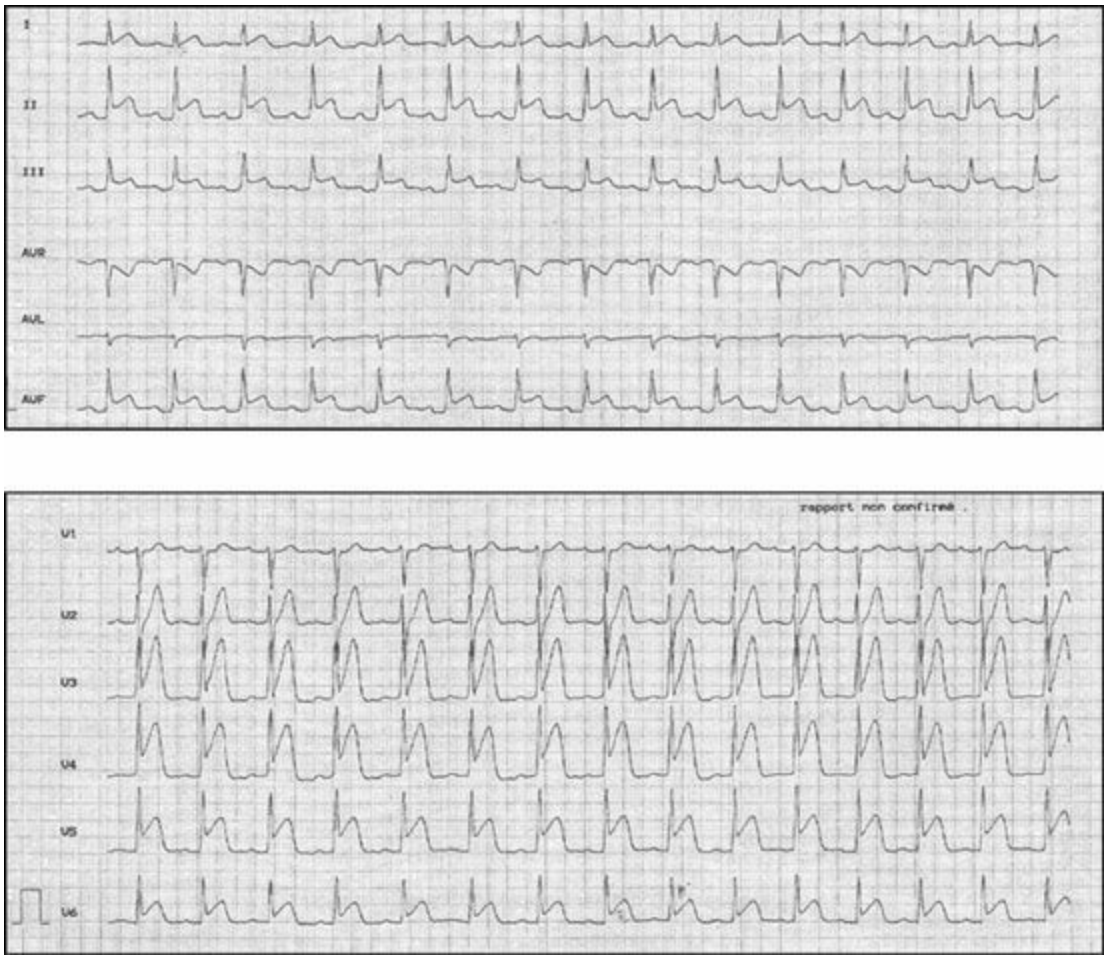

Figure 4.10

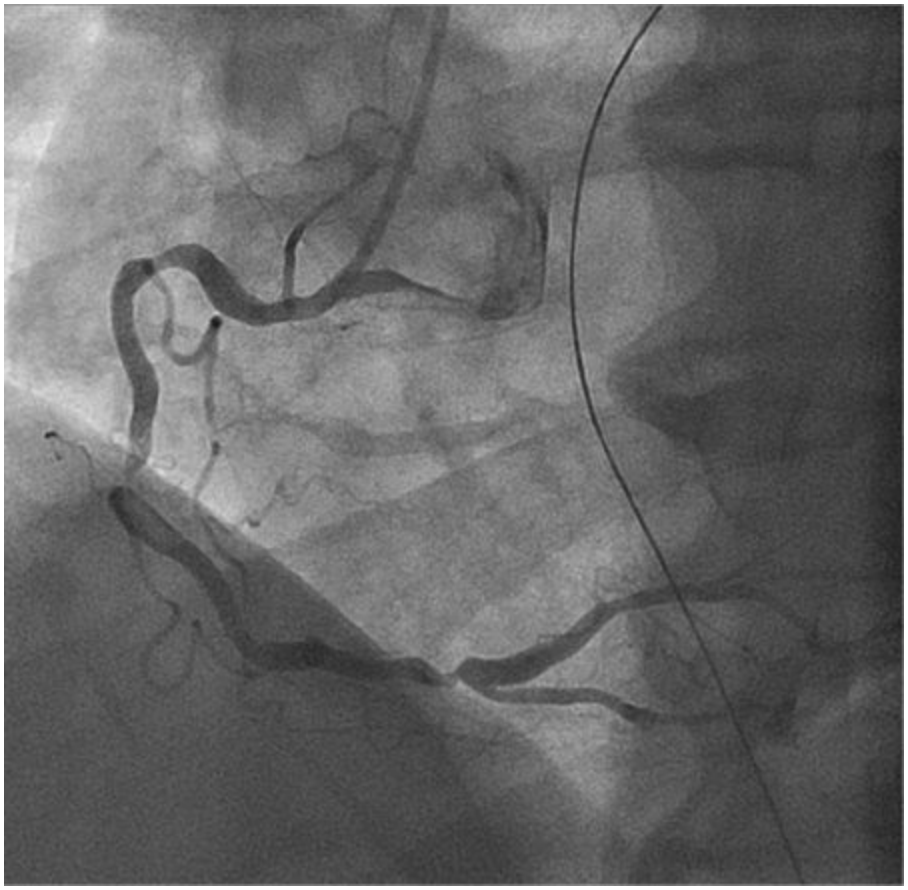

Figure 4.11

58. A 41-year-old overweight heavy-smoker construction worker presented with chest pain while on the job associated with diaphoresis and dyspnea. In the field, no ECG could be obtained due to the extreme diaphoresis. In the ambulance, the patient developed hypotension, bradycardia, and subsequently asystole. Under cardiopulmonary resuscitation he was transferred to the cardiac catheterization laboratory and circulation was reestablished using extracorporeal membrane oxygenation. Subsequently, coronary angiography (Fig. 4.12) shows

- **a.** subtotal occlusion of the left main trunk.
- **b.** aortic dissection.
- **c.** anomalous origin of the left main trunk.
- **d.** left main trunk stenosis equivalent (i.e., severe stenosis of the left anterior descending coronary artery and left circumflex).
- **e.** severe aortic stenosis.

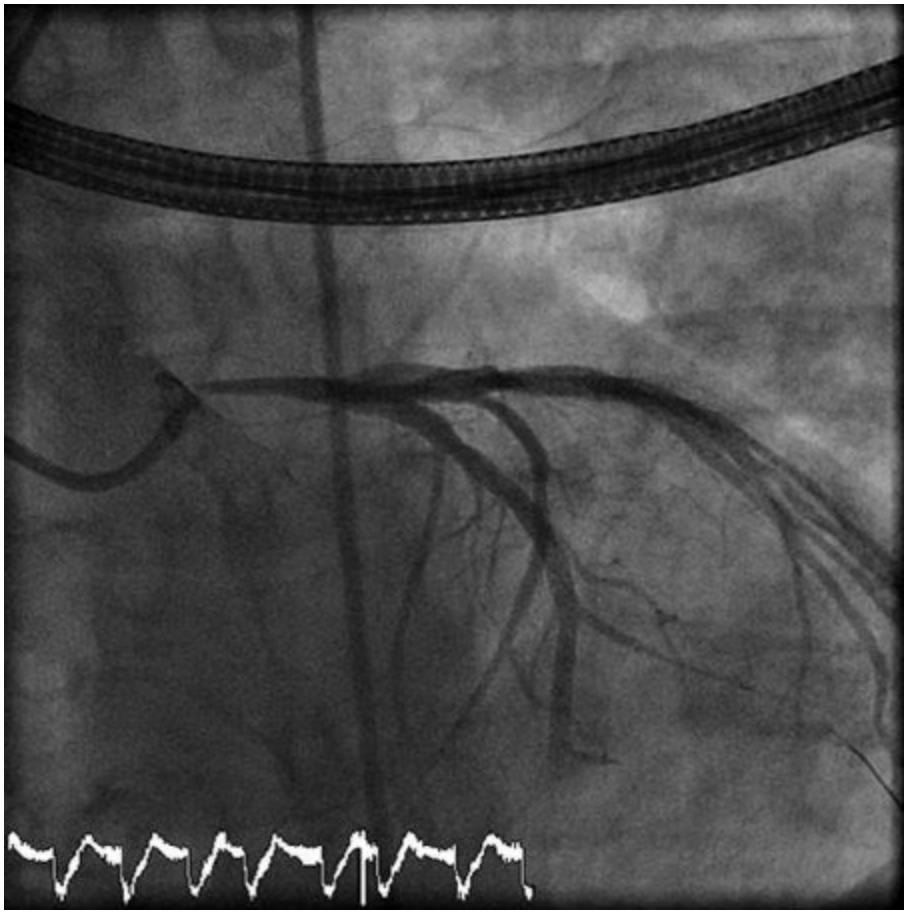

Figure 4.12

59. A 61-year-old man known for diabetes, hypercholesterolemia, hypertension, and a history of PCI with stenting of the mid-left anterior descending coronary artery 10 years earlier presents with worsening typical angina on exertion and a positive stress test. Coronary angiography (Fig. 4.13) shows

- **a.** ISR of the left descending coronary artery.
- **b.** significant stenosis of LCX.
- **c.** stenosis of the ostium of the left main trunk.
- **d.** normal coronary arteries.
- **e.** none of the above.

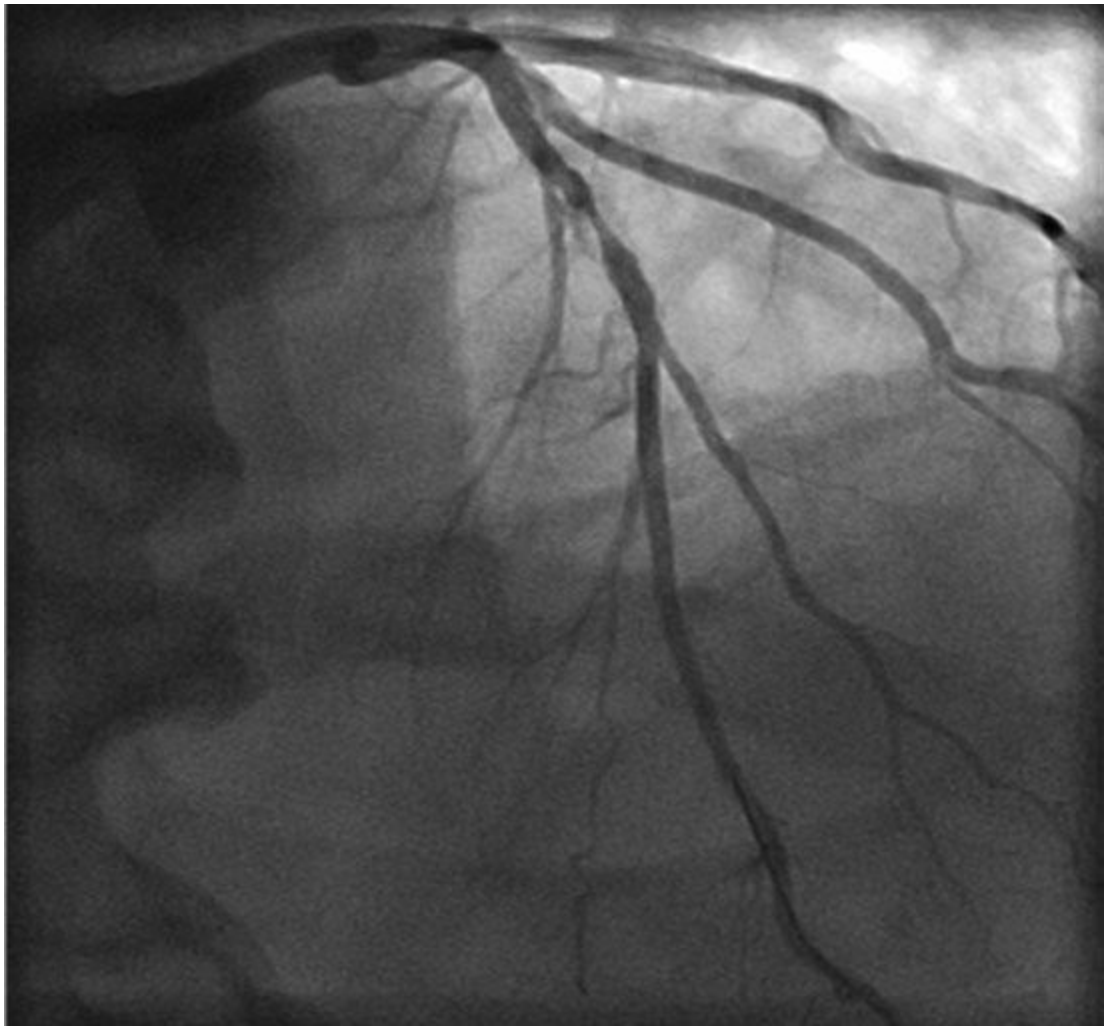

Figure 4.13

ANSWERS

1. **C.** Coronary angiography within 48 hours followed by percutaneous intervention/surgical revascularization if indicated. There is continued debate as to whether a routine, early invasive strategy is superior to a conservative strategy for the management of UA and NSTEMI. A pooled analysis of randomized controlled trials with 5,467 patients compared the impact of routine invasive (RI) strategy with selective invasive (SI) strategy: Over 5 years, 14.7% of patients randomized to an RI strategy experienced CV health or nonfatal MI versus 17.9% in the SI strategy (hazard ratio [HR]: 0.81; 95% confidence interval [CI]: 0.71 to 0.93; P = 0.002). However, the largest absolute effect was mainly observed in higher-risk patients (11.1%).[1] Another meta-analysis using data from eight trials (3,075 women and 7,075 men) compared early invasive versus conservative treatment strategies in women and men with UA and NSTEMI and reported comparable odds ratio (OR)

for reducing MACE (death, MI, and rehospitalization for ACS) of 0.81 (95% CI: 0.65 to 1.01) in women and 0.73 (95% CI: 0.55 to 0.98) in men. In contrast, an invasive strategy was not associated with a significant reduction in low-risk (biomarker-negative) women.[2] The 2012 ACC/AHA guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction recommend an early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) in patients who have refractory angina or hemodynamic or electrical instability, and in those initially stabilized who have an elevated risk of clinical events.[3] Table 4.1 lists patients at elevated risk and in whom invasive strategy is preferred based on the ACC/AHA 2011 guidelines. Our patient has several high-risk criteria (ongoing angina, elevated biomarkers, and echocardiographic abnormalities). TIMI (Thrombolysis in Myocardial Infarction) risk score revealed 5 points (26% risk at 14 days of MACE) and GRACE (Global Registry of Acute Cardiac Events) risk score showed a high risk of mortality.

2. **b.** Lower rate of hospital readmission. Belardinelli et al. addressed the effects of exercise training (ET) on functional capacity and quality of life (QOL) in patients who received percutaneous transluminal coronary angioplasty (PTCA) or coronary stenting (CS). The authors studied 118 consecutive patients with CAD (mean age 57 ± 10 years) who underwent PTCA or CS on one (69%) or two (31%) native epicardial coronary arteries. Patients were randomized into two matched groups. Group T (n = 59) was exercised three times a week for 6 months at 60% of peak VO_2. Group C (n = 59) was the control group. Only patients in the active group had significant improvements in peak VO_2 (26%, P <0.001) and QOL (26.8%, P = 0.001 versus C). The angiographic restenosis rate was unaffected by ET (T: 29%; C: 33%, P = not significant). However, residual diameter stenosis was lower in trained patients (–29.7%, P = 0.045). In patients with angiographic restenosis, thallium uptake improved only in group T (19%, P <0.001). During the follow-up (33 ± 7 months), trained patients had a significantly lower event rate than controls (11.9% versus 32.2%; risk ratio [RR]: 0.71; 95% CI: 0.60 to 0.91; P = 0.008) and a lower rate of hospital readmission (18.6% versus 46%; RR: 0.69; 95% CI: 0.55 to 0.93; P <0.001). Moderate ET improved functional capacity and QOL after PTCA or CS. During the follow-up, trained patients had fewer events and a lower hospital readmission rate than controls, despite an unchanged restenosis rate.[4] The 2011 ACC/AHA guidelines for PCI recommend (class I, evidence A) medically supervised exercise programs to patients after PCI, particularly for moderate- to high-risk patients for whom supervised ET is warranted.[5] Participation in cardiac rehabilitation is associated with significant reductions in all-cause mortality (OR 0.80; 95% CI: 0.68 to 0.93)[6] in several community-based surveys and meta-

analyses.[6-8]

3. **a.** Heart team discussion between the interventional cardiologist and the cardiac surgeon to select the best treatment option is the recommended approach. The 2011 AHA/ACC guidelines for PCI recommend the heart team approach (class I, evidence C) for the revascularization of patients with unprotected left main trunk disease.[5] Several trials used protocols that involve a multidisciplinary approach.[9,10] The heart team is composed of an interventional cardiologist and a cardiac surgeon and aims at (1) reviewing patients' medical history, (2) determining the approach of revascularization (PCI versus CABG), and (3) discussing with the patient the options of revascularization. The guidelines endorse a heart team approach in patients with unprotected left main CAD and/or complex CAD in whom the optional strategy is not straightforward. Because the STS score and the SYNTAX score predict clinical outcomes, their use is often useful in making revascularization decisions.[11,12]

TABLE 4-1 Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

Preferred Strategy	Patient Characteristics
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers (TnT or TnI)
	New or presumably new ST-segment depression
	Signs or symptoms of HF or new or worsening mitral regurgitation
	High-risk findings from noninvasive testing
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 mo
	Prior CABG
	High risk score (e.g., TIMI, GRACE)
	Reduced left ventricular function (LVEF 40%)
Conservative	Low risk score (e.g., TIMI, GRACE)
	Patient or physician preference in the absence of high-risk features

TnT, troponin T; TnI, troponin I; HF, heart failure; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Cardiac Events; TIMI, Thrombolysis in Myocardial Infarction; LVEF, left ventricular ejection fraction.

Adapted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 2002 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiol* 2007;50:e1–e157.

4. **C.** Drug-eluting stent (DES) implantation (stent-in-stent). In the randomized trial TAXUS V ISR (treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Stent trial), the slow-release, polymer-based, paclitaxel-eluting stent was found to be not only noninferior to β-source vascular brachytherapy but also superior in terms of reducing clinical and angiographic restenosis at 9 months after treatment of bare-metal ISR lesions. Because of both greater acute gain and less late loss, luminal dimensions were significantly larger with paclitaxel-eluting stents compared with brachytherapy in the injury zone, at the distal edge, and over the entire analysis segment. Proximal edge luminal dimensions were also numerically larger with the paclitaxel-eluting stent.[13] Similarly, the Sirolimus-Eluting Stent with Vascular Brachytherapy for the Treatment of In-Stent Restenosis (SISR) trial demonstrated a marked reduction in target vessel failure with the sirolimus-eluting stent, driven predominantly by a reduction in the rate of target vessel

revascularization.[14] Based on available data and the severity of the patient's COPD, DES implantation is the best option for this patient with BMS restenosis. Brachytherapy is no longer available except in a few research centers.[15]

5. **d.** Guideline-directed medical therapy is the first recommended approach. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, 2,287 patients with stable CAD were randomized to undergo PCI and medical therapy or to medical therapy alone. The primary outcome was death from any cause and nonfatal MI during a follow-up of 2.5 to 7.0 years. The cumulative event rates were 19.0% in the PCI group and 18.5% in the medical therapy group (P = 0.62). As an initial management strategy, PCI did not reduce the risk of death, MI, or other MACE in the COURAGE trial.[16] About 314 patients were enrolled in the nuclear substudy of the COURAGE study to perform serial stress imaging. The addition of PCI to medical therapy improved ischemia reduction in patients with significant ischemia at baseline.[17] A recent meta-analysis of 10 randomized controlled trials (6,752 patients) comparing PCI with medical therapy in stable CAD did not detect significant differences in PCI versus CABG; the relative risk (RR) for all-cause mortality was 0.97 (95% CI: 0.84 to 1.12), CV mortality RR 0.91 (95% CI: 0.70 to 1.12), MI RR 1.09 (95% CI: 0.92 to 1.29), or angina relief RR 1.10 (95% CI: 0.97 to 1.26).[18] According to the AHA/ACC guidelines CABG or PCI should not be performed to improve symptoms or survival in patients with CAD with one or more coronary stenoses who do not meet anatomic (≥70% non-left main stenosis diameter), physiologic (FFR >0.80, no or mild ischemia on noninvasive testing) criteria for revascularization and involve only LCX or RCA, or subtend only a small area of viable myocardium.[5] The multiple meta-analyses comparing PCI versus medical therapy in patients with SIHD showed that PCI reduced the incidence of angina, but has not been demonstrated to improve survival or lower the long-term risk of MI in stable patients.[17,19] Our patient does not have criteria for coronary revascularization, and the first-line therapy should be an aggressive medical therapy.

6. **c.** Subendocardium. The subendocardium is most susceptible to ischemic damage. Although the mechanisms of subendocardial ischemia remain to be fully defined, they are clearly associated with the transmural distribution of intramyocardial systolic pressures. Even though almost all the myocardium is perfused in diastole, a reduction of diastolic perfusion pressure or duration will result in subendocardial ischemia.[11] The abnormal subendocardial perfusion in patients with cardiac syndrome X (typical angina, abnormal exercise test results, and normal coronary arteries) has been described with CV MR imaging during the IV administration of

adenosine.[20]

7. **d.** Inferior wall myocardial infarction (MI) with right ventricular infarction. The association of inferior wall MI on ECG and elevated jugular venous pressure with clear lungs is suggestive of additional right ventricular infarction. Tall c–v waves of tricuspid regurgitation may be evident in patients with necrosis or ischemia of the right ventricular papillary muscles.

8. **a.** Reduction in left ventricular compliance. An S_4 is frequently present in patients with acute MI and is related to auricular contraction and ventricular compliance reduction during ventricular filling.[21] Rapid deceleration of transmitral flow during protodiastolic filling of the left ventricle and increased inflow into the left ventricle are responsible for the third heart sound (S_3). A systolic ejection murmur is suggesting for aortic sclerosis.

9. **e.** Hybrid revascularization mandates surgical and percutaneous revascularization during the same procedure. According to the ACC/AHA PCI guidelines, hybrid coronary revascularization is defined as the planned combination of LIMA-to-LAD artery grafting and PCI of ≥1 non-LAD coronary arteries and intended to combine the advantages of CABG (i.e., durability of the LIMA graft) and PCI. Hybrid revascularization is particularly suitable in patients with limitations to traditional CABG (e.g., heavily calcified proximal aorta, lack of graft conduits, or a non-LAD coronary artery unsuitable for bypass but amenable to PCI) and situations in which PCI of the LAD artery is not feasible (e.g., excessive tortuosity or calcification, complex bifurcation lesion, and very long lesion). The procedure may be performed in one operative setting or as a staged procedure. CABG before PCI is preferred.[5] Preliminary reports suggest that this approach is feasible and safe,[22] but randomized data are lacking.

10. **c.** High-sensitive troponin T (Hs-TnT). In the PLATO (Platelet Inhibition and Patient Outcomes) trial, 9,946 patients presented with non-ST-elevation ACS: 5,357 were revascularized and 4,589 managed conservatively. High-sensitive elevated Hs-TnT (>14.0 ng/L) have been described to predict substantial benefit (reduction rate of CV death, MI, and stroke) of ticagrelor over clopidogrel in patients who were revascularized or treated conservatively, while no apparent was observed in those who had normal Hs-TnT.[23]

11. **e.** All of the above. Patients with extensive and severe CAD are more likely to present abnormal exercise ECG results.[24] Early onset of angina, ischemic ST

depression ≥2 mm, downsloping ST segment starting at <5 METs, involving ≥5 leads and persisting ≥5 minutes into recovery, and fall in blood pressure at low exercise are all associated with adverse prognosis.

12. **e.** No improvement of any of the mentioned endpoints. The COURAGE trial enrolled 2,287 patients with significant CAD to an initial strategy: (1) PCI and OMT or (2) OMT only. There were no significant differences between the PCI group and the medical therapy group in the composite of death, MI, and stroke (HR: 1.05; 95% CI: 0.87 to 1.27), and hospitalization for ACS (HR: 1.07; 95% CI: 0.84 to 1.37) or MI (HR: 1.13; 95% CI: 0.89 to 1.43). The authors concluded that as initial management strategy in patients with stable CAD, PCI did not reduce the risk of death, MI, or other MACE when added to OMT.[16] According to the 2011 ACC/AHA PCI guidelines, revascularization should not be performed to improve survival in patients with SIHD with one or more coronary artery stenoses that are not anatomically significant, or involve only the LCX or RCA, or subtend only a small area of viable myocardium.[5]

13. **e.** All of the above. In the COURAGE patients, 314 were enrolled in the substudy of myocardial perfusion SPECT performed before treatment and 6 to 18 months after randomization. At follow-up, the reduction in ischemic myocardium was greater with PCI + OMT than with OMT (–2.7% versus –0.5%, P <0.0001). The patients with PCI + OMT exhibited significant ischemia reduction (33% versus 19%, P = 0.0004), especially those patients with moderate-to-severe myocardial ischemia at baseline (78% versus 52%, P = 0.007).[17] The 2012 AHA/ACC guidelines for PCI mentioned in patients with stable ischemic coronary heart disease a benefit of angina reduction and symptom improvement with PCI versus OMT; however, PCI has not been demonstrated to improve survival in stable patients.[5]

14. **b.** Significant absolute risk reduction of major adverse cardiovascular events (MACE) of ~2% over 5 years. The 2012 ACC/AHA guidelines for the management of SIHD recommend the prescription of moderate or high dose of a statin therapy in addition to lifestyle changes (class I, evidence A).[25] The Treating to New Targets (TNT) study randomized 10,001 patients with stable coronary heart disease and LDL >130 mg/dL to receive atorvastatin 10 or 80 mg daily. The mean LDL-C was 2.0 mmol/L during the treatment with 80 mg of atorvastatin, whereas it was 2.6 mmol/L during the treatment with 10 mg of atorvastatin. About 8.7% of patients in the group with intensive lipid-lowering therapy and 10.9% in the group with moderate lipid-lowering therapy presented MACE during a median follow-up of 4.9 years, representing a significant absolute reduction in the rate of MACE of

2.2% and a 22% relative reduction in risk. There was no difference between both treatment groups in the overall mortality.[26]

15. **e.** Fondaparinux might be used as the sole anticoagulant to support PCI. The 2011 ACCF/AHA PCI guidelines made the following recommendations regarding anticoagulant therapy during the procedure. Following recommendations are class I: (1) All patients undergoing PCI should receive an anticoagulant to prevent thrombus formation during the procedure; (2) the administration of IV UFH is a useful standard therapy in patients undergoing PCI; (3) an additional dose of 0.3 mg/kg IV enoxaparin should be administered at the time of PCI to patients who have received fewer than two therapeutic subcutaneous doses (e.g., 1 mg/kg) or received the last subcutaneous enoxaparin dose 8 to 12 hours before PCI; and (4) for patients undergoing PCI, bivaluridin is useful as an anticoagulant with or without prior treatment with UFH. In contrast, fondaparinux should not be used as the sole anticoagulant to support PCI.[5] An additional anticoagulant with anti-IIa activity should be administered because of the risk of catheter thrombosis. Fondaparinux is an indirect factor Xa inhibitor, but no effect on thrombin (IIa). The use of fondaparinux alone was associated with thrombus catheter formation and therefore the anticoagulant with anti-IIa should be used during PCI.[27]

16. **e.** Even in the absence of symptoms, routine periodic stress testing is indicated. According to the 2011 AHA/ACC PCI and 2011 AHA/ACC secondary prevention guidelines, the following interventions and targets are strongly recommended in patients with CHD to reduce morbidity and mortality: (1) to refer to a medically supervised cardiac rehabilitation program post discharge, (2) to manage lipid-lowering treatment for an LDL-C target <70 mg/dL, (3) to control blood pressure with the goal of <140/90 mmHg, and (4) to advise patients for complete smoking cessation. Conversely, there is no proven benefit or indication for routine periodic stress testing in patients after PCI, and thus, it is not indicated.[24]

17. **e.** All of the above. The clinical situations associated with higher risk of BMS restenosis have been defined by the 2011 AHA/ACC PCI guidelines as follows: (1) left main disease, (2) small vessels, (3) ISR, (4) bifurcations, (5) diabetes, (6) long lesions, (7) multiple lesions, and (8) saphenous vein grafts. The ISR of BMS presented by the patient should be treated with DES,[5] as sirolimus- or paclitaxel-eluting stents are superior to balloon angioplasty.[28] The use of DES over BMS had decreased the incidence of ISR by over 70%.[13,28]

18. **b.** Rosuvastatin 20 mg/day significantly decreased the incidence of MI. The

JUPITER trial randomized 17,802 men and women without CVD presenting an LDL-C lower than 130 mg/dL, but high levels of hs-CRP, to rosuvastatin, 20 mg daily, or to placebo. Rosuvastatin reduced LDL-C levels by 50% and hs-CRP levels by 37%. The primary endpoint outcome was a composite of MI, stroke, arterial revascularization, hospitalization for UA, or death from CVD. The study was interrupted after 1.9 years at interim analyses because of a significant decrease for primary outcome (HR: 0.56; 95% CI: 0.46 to 0.69). HR for MI was 0.46, 95% CI (0.30 to 0.70), and HR for stroke was 0.52, 95% CI (0.34 to 0.79). In the adverse events section, the physician-reported diabetes was more frequent in the rosuvastatin group (n = 270) than in the placebo group (n = 216, P = 0.01); the difference in the median glycated hemoglobin value was minimal (5.9% versus 5.8%, respectively, P = 0.001).[29]

19. **c.** CABG is associated with a reduction of death and of MI, but not of stroke. The future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized 1,900 patients with diabetes and multivessel CAD to a revascularization strategy with (1) CABG or (2) PCI. The primary outcome was defined as death from any cause, nonfatal MI, or nonfatal stroke. The primary outcome rate at 5 years was 26.6% in the PCI group and 18.7% in the CABG group. The benefit of CABG was observed in reduction of death (P = 0.049) and MI (P <0.001) rates, but stroke was more frequent in the CABG group than the PCI group (5.2% versus 2.4%, P = 0.03).[30]

20. **c.** More than 70% of patients quit smoking after ACS. About 50% to 70% of smokers continue to smoke after an ACS,[31] despite the fact that smokers who quit smoking have a 36% reduction in the risk of mortality and 32% in the risk of recurrent nonfatal MI in comparison with continuing smokers over a mean follow-up of 5 years.[32] Smoking cessation intervention is a major target of secondary prevention of CVD and should be one of the priorities of clinicians providing care to such patients. Given the large benefits of smoking cessation, promotion of smoking cessation is the most effective intervention to reduce morbidity and mortality in smokers with CHD.[32] Unfortunately smoking receives less attention from cardiologists than other CV risk factors,[33] and many smokers with CHD are unable to quit smoking without assistance. Based on a systemic review, several studies found a beneficial effect on smoking cessation rates through a smoking cessation intervention that started in hospital and continued in the ambulatory setting.[31]

21. **e.** Answers b and d are correct. The leading cause of death in patients hospitalized

for acute MI is cardiogenic shock. The SHOCK investigators conducted a randomized trial to evaluate early revascularization in patients with cardiogenic shock. Patients with shock caused by left ventricular failure complicating MI were randomly assigned to emergency revascularization (152 patients) or initial medical stabilization (150 patients). Revascularization was accomplished by either CABG or angioplasty. Intra-aortic balloon counterpulsation was performed in 86% of the patients in both groups. The primary endpoint was mortality from all causes at 30 days. Six-month survival was a secondary endpoint. The mean age of the patients was 66 ± 10 years; 32% were women and 55% were transferred from other hospitals. The median time to the onset of shock was 5.6 hours after infarction, and most infarcts were anterior in location. Ninety-seven percent of the patients assigned to revascularization underwent early coronary angiography, and 87% underwent revascularization; only 2.7% of the patients assigned to medical therapy crossed over to early revascularization without clinical indication. Overall mortality at 30 days (primary endpoint) did not differ significantly between the revascularization and medical therapy groups (46.7% and 56.0%, respectively; difference, –9.3%; 95% CI for the difference, –20.5% to 1.9%; P = 0.11). However, at 6 months mortality was lower in the revascularization group than in the medical therapy group (50.3% versus 63.1%, P = 0.027).[34]

22. **a.** Patients with CKD undergoing cardiac catheterization should receive adequate preparatory hydration. The 2011 ACC/AHA PCI guidelines made recommendations regarding contrast-induced AKI. Contrast-induced AKI is considered one of the most frequent causes of iatrogenic AKI. Risk factors for developing contrast-induced AKI are hypotension, intra-aortic balloon pump, congestive heart failure, CKD, diabetes, age >75 years, anemia, and volume of contrast.[35] The following recommendations are of class I for the prevention of AKI: (1) Patients should be assessed for risk of contrast-induced AKI before PCI; (2) patients undergoing catheterization with contrast media should receive adequate preparatory hydration; and (3) in patients with CKD (creatinine clearance <60 mL/min), the volume of contrast media should be minimized. However, the administration of N-acetyl-cysteine is not useful for the prevention of contrast-induced AKI and is not recommended based on the results of several randomized controlled trials.[36]

23. **a.** No significant difference in the risk of stroke. Abciximab, a potent inhibitor of the platelet glycoprotein IIb/IIIa receptor, reduces thrombotic complications in high-risk patients undergoing PCI in the setting of ACS compared with a regimen of aspirin and UFH. Akkerhuis et al. combined analysis of data from 8,555 patients undergoing PCI assigned to receive a bolus and infusion of abciximab (n = 5,476) or matching placebo (n = 3,079). No significant difference in stroke rate was

observed between patients assigned abciximab (n = 22 [0.40%]) and those assigned placebo (n = 9 [0.29%]; P = 0.46). The rate of nonhemorrhagic stroke was 0.17% in patients treated with abciximab and 0.20% in patients treated with placebo (difference: –0.03%; 95% CI: –0.23% to 0.17%), and the rates of hemorrhagic stroke were 0.15% and 0.10%, respectively (difference: 0.05%; 95% CI: –0.11% to 0.21%). Abciximab in addition to aspirin and heparin does not increase the risk of stroke in patients undergoing PCI.[39]

24. **d.** 70 mg/dL. For patients with established CAD, LDL-lowering therapies significantly reduce the risk of MACE and yield highly favorable cost-effectiveness ratios. In high-risk persons, the recommended LDL-C goal is <100 mg/dL. An LDL-C goal of <70 mg/dL is a therapeutic option on the basis of available clinical trial evidence, especially for patients at very high risk. Diabetic patients with established advanced CAD, like the mentioned patient, should be considered at very high risk for MACE and qualify for the ambitious target of LDL <70 mg/dL.[42]

25. **c.** Additional aspirin (81 to 325 mg) is recommended in all patients on chronic aspirin therapy before PCI. The 2011 AHA/ACC PCI guidelines recommend the use of antiplatelet therapy before PCI.[5] Aspirin reduced ischemic CV events after PCI[37,38] and should be given at least 2 hours before PCI after which aspirin has to be continued indefinitely.[39] In addition to aspirin, a loading dose of $P2Y_{12}$ receptor inhibitor might be given to patients undergoing PCI with stenting.[40-42] Options include clopidogrel 600 mg, prasugrel 60 mg, or ticagrelor 180 mg. The duration of $P2Y_{12}$ receptor inhibitor after stent implantation (BMS or DES) for ACS should be of at least 12 months.[43,44] Options include clopidogrel 75 mg daily, prasugrel 10 mg daily, and ticagrelor 90 mg twice daily. In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for 12 months if patients are not at high risk for bleeding.[45] In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months.[44] A benefit of additional aspirin in patients on chronic aspirin undergoing PCI has never been demonstrated.

26. **c.** 20% to 30%. A proportion of patients who present with suspected ACS are found to have insignificant CAD during coronary angiography. Of the 5,767 patients with non-ST-segment-elevation ACS who were enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (Eptifibatide) Therapy (PURSUIT) trial and who underwent inhospital angiography, 88% had significant CAD (any stenosis >50%), 6% had mild CAD (any stenosis >0% to ≤50%), and 6% had no CAD (no stenosis identified). Overall, 12% of the patients

had nonsignificant CAD.[44] Patients with nonsignificant CAD were more likely to be women, non-white, younger, nondiabetic, nonhypercholesterolemic, without history of CVD, without ST-segment changes, but with more T-wave inversion compared with patients with significant CAD. Based on the profile of the patient admitted, her probability of having nonsignificant CAD is >12%.

27. **b.** Prothrombin complex. Bivaluridin is a naturally occurring anticoagulant secreted by the salivary glands of the leech Hirudo medicinalis. It is a potent and specific anticoagulant and exerts its action by binding directly to the active catalytic site of thrombin. Unlike heparin, it does not require a cofactor (antithrombin) and does not appear to cause immune-mediated thrombocytopenia. It is also a more potent inhibitor of platelet function than heparin, probably because of a direct inhibitory effect on thrombin. Unlike heparin, which is readily neutralized by protamine or platelet factor 4, a specific agent useful in reversing the effects of bivalirudin is unavailable. Irani et al. demonstrated the first clinical experience, suggesting benefit from prothrombin complex concentrate in neutralizing the effect of r-hirudin. Although the specific mechanism of action remains unclear, the generation of additional thrombin probably plays a role. Also, epinephrine-induced platelet aggregation in hirudinized platelet-rich plasma is restored by addition of prothrombin complex concentrate, most probably by additional thrombin generation. Adverse effects of prothrombin complex concentrate include intravascular thrombosis, particularly in patients with liver disease and possible viral hepatitis. As the product contains some activated clotting factors (II, VII, IX, and X) and has thrombogenic potential, it should be used as a last resort, especially in patients with liver disease. Clinical experience suggests that prothrombin complex concentrate in a dose of 25 to 30 UI/kg can be considered for patients with life-threatening hemorrhage caused by bivalirudin.[45]

28. **e.** The radial vascular access is more frequently performed in the United States than in Europe. Radial site access is used more frequently in Europe and Canada than in the United States.[46] The 2011 AHA/ACC PCI guidelines recommend radial artery access to decrease access site complications.[5] In fact, it has been demonstrated that radial access, compared with femoral access, decreases the rate of access-related bleeding and complications.[47] Its utility is more pronounced in patients at higher risk for bleeding or vascular access complications such as in patients with coagulopathy, anticoagulated, or morbid obesity.

29. **c.** A 65-year-old man known for CAD complaining of progressive shortness of breath since 1 week. At admission, no ongoing chest pain with stable hemodynamic

status but bibasilar rales at lung auscultation. The ECG revealed ST-segment elevation as well as Q waves in the anterior leads. The 2011 AHA/ACC PCI guidelines elaborated indication of PCI in patients with STEMI.[5] Primary PCI should be performed in patients within 12 hours of onset of STEMI, within 90 minutes of the first medical contact in patients presenting to a hospital with PCI capabilities and within 120 minutes of the first medical contact in patients presenting to a hospital without PCI capabilities ("systems goal").[48–50] Primary PCI should be performed in patients with STEMI who are candidates for primary PCI, who develop severe heart failure or cardiogenic shock irrespective of time delay,[34,51] and who had clinical and/or ECG evidence for ongoing ischemia between 12 and 24 hours after symptom onset.[52] Delayed PCI in patients with STEMI is reasonable in patients with infarct artery reocclusion or demonstrating ischemia on invasive testing.[53] PCI of hemodynamically significant stenosis in patent infarct artery greater than 24 hours after STEMI might be considered as part of an invasive strategy (class of recommendations IIb).[54,55] PCI of a totally occluded infarct artery greater than 24 hours after STEMI should not be performed in asymptomatic patients with one- or two-vessel disease if patients are hemodynamically stable and do not present evidence of severe ischemia (class III).[56]

30. **d.** Right ventricular infarction. Rupture of the interventricular septum is one of the mechanical complications of MI, less frequent than left free wall rupture.[57] It occurs in general 3 to 5 days after acute MI. An increase in risk is observed in patients with occlusion of LAD wrapping the distal inferior wall and inferior septum (inferior MI with large anterior MI). The ECG findings of the interventricular septum rupture are typical for ST elevation and Q waves in the inferior leads II, III, and aVF.[58] Clinically, the patients present a rapid onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new harsh, loud, holosystolic murmur best heard at the lower left sternal border.[59]

31. **d.** Immediate coronary angiography. The septal defect and the associated turbulent transseptal flow can be visualized by a transthoracic echocardiography using color flow Doppler imaging.[60] The addition of Doppler to echocardiography improves significantly the sensitivity of the examination demonstrating the transseptal turbulent flow and diastolic–systolic turbulences in the right ventricle.

32. **c.** Mechanical ventilation with positive end-expiratory pressure. The timing of surgical repair with post-MI ventricular septal rupture is controversial. In patients with cardiogenic shock, a fatal prognosis is inevitable in the absence of urgent

surgical treatment. First, stabilization with an intra-aortic balloon pump counterpulsation, inotropic agents, diuretics, and, if tolerated, vasodilators is attempted.[61] This is followed by cardiac catheterization to define the coronary anatomy and then surgical repair.

33. **e.** All of the above. The 2011 ACC/AHA PCI guidelines assessed the risk–benefit profile for the use of BMS versus DES. DES is preferred to BMS when high risk of stent restenosis is present with BMS. The clinical situations associated with higher risk of restenosis are (1) left main disease, (2) small vessels, (3) ISR, (4) bifurcations, (5) diabetes, (6) long lesions, (7) multiple lesions, and (8) saphenous vein grafts. All the criteria mentioned above increased the risk of restenosis, suggesting the use of DES over BMS.[5]

34. **a.** Low-dose aspirin daily. The patient will have coronary angiography for a high suspicion of SIHD. Until the angiogram is performed, he should be treated with optimal medical treatment including aspirin, statins, control of blood pressure (β-blockers/angiotensin converting), and additional medical therapy for the relief of symptoms (β-blockers, calcium channel blockers, long-acting nitrates, or sublingual nitroglycerin).[25] The efficacy of clopidogrel pretreatment compared with the administration in the catheterization laboratory is controversial.[62] There is no evidence to give prasugrel or ticagrelor in patients with SIHD.

35. **c.** Pharmacologic stress with nuclear myocardial perfusion imaging if able to exercise and interpretable ECG. Patients with intermediate pretest probability of CAD are those who most benefit from stress testing to improved diagnostic accuracy. The choice of stress test depends on two questions: Is the patient able to exercise? Is the resting ECG interpretable?[25] The ACC/AHA SIHD guidelines recommend standard exercise ECG testing for interpretable ECG and at least moderate physical functioning or no disabling comorbidity (level of evidence A, class I).[63] Exercise with nuclear myocardial perfusion imaging or echocardiography is recommended for patients with an intermediate to high pretest probability of ischemic heart disease who have an uninterpretable ECG and at least moderate physical activity functioning or no disabling comorbidity.[64,65] Pharmacologic stress with cardiac MR can be useful for patients with an intermediate to high pretest probability who have an uninterpretable ECG and at least moderate physical functioning or no disabling comorbidity.[66] Pharmacologic stress with nuclear myocardial perfusion imaging, echocardiography, or cardiac MR is not recommended for patients who have an interpretable ECG and at least moderate physical functioning or no disabling comorbidities.[67]

36. **c.** Severe ostial and moderate distal left main trunk stenosis. The coronary angiography shows severe ostial and moderate distal left main trunk stenosis.

37. **e.** All of the above. The 2012 AHA/ACC guidelines on SIHD[25] recommend using a nomogram to predict the risk of death in patients with SIHD.[68] This score is based on following clinical and exercise testing variables: age, male gender, typical angina, diabetes, cigarette smoking, hypertension, proportion of predicted METs achieved, ST-segment depression, test-induced angina, abnormal heart rate recovery, and frequent ventricular ectopy during recovery.

38. **b.** Arteriovenous fistula. The coronary angiography reveals large coronary AV fistula involving the RCA. Patient underwent surgical ligation of the fistula with resolution of her symptoms.

39. **e.** All of the above. The coronary angiography shows a bifurcation lesion involving the distal left main trunk as well as the ostium of the left anterior descending and left circumflex coronary arteries.

40. **c.** Perforation of the RCA. The coronary angiography demonstrates extravasation of contrast caused by perforation of the RCA.

41. **e.** All the mentioned clinical situations do not justify coronary angiography in the initial phase of patient management. According to 2012 AHA/ACC SIHD guidelines,[25] coronary angiography is not recommended as an initial testing strategy to assess risk in the following clinical situations (class III, no benefit): (1) patients with SIHD who elect not to undergo revascularization or who are not candidates for revascularization because of comorbidities or individual preferences; (2) patients with SIHD who have preserved left ventricular function and low-risk criteria on noninvasive testing; (3) low risk according to clinical criteria and who have not undergone noninvasive risk testing; and (4) asymptomatic patients with no evidence of ischemia on noninvasive testing.

42. **b.** Calcified coronary arteries. Patients with long-standing terminal nephropathy have frequently severely calcified vessels including the coronary arteries.[69] Qualitative analysis of the coronary arteries showed significantly more calcified plaques of coronary arteries in patients with end-stage renal failure. Plaques of nonuremic patients were mostly fibroatheromatous, while coronary plaques in patients with end-stage renal failure were characterized by increased media thickness and marked calcification. Deposition of calcium within the plaques may contribute to the high event rate in uremic patients.

43. **e.** Acupuncture might be used for the purpose of improving symptoms of patients with SIHD. According to 2012 AHA/ACC SIHD guidelines,[25] acupuncture should not be used for the purpose of improving symptoms or reducing CV risk in patients with SIHD (class III, no benefit). Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home should be encouraged (class I), dipyridamole is not recommended as antiplatelet therapy for patients with SIHD (class III, no benefit), treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD (class I), and it is reasonable to consider screening SIHD patients for depression and to refer or treat when indicated (class IIa).

44. **e.** PCI does not reduce the occurrence of death, reinfarction, or heart failure. The Occluded Artery Trial (OAT) study showed high rates of procedural success with PCI and sustained patency but no clinical benefit during an average 3-year follow-up with respect to death, reinfarction, or heart failure.[56] There was, in fact, a trend toward excess nonfatal reinfarction when routine PCI was performed in stable patients who were found to have occlusion of the infarct-related artery 3 to 28 days after MI. A strategy of CABG was not tested in the OAT.

45. **e.** Answers a and d are correct. In the CHARISMA trial of 15,603 patients with established stable atherothrombotic disease or at high risk for such disease, there was no significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary endpoint of MI, stroke, or death from CV causes. Clopidogrel was associated with a significant increase in the rate of moderate bleeding.[70]

46. **b.** Significant survival advantage. A cohort study of approximately 1,400 patients demonstrated that the use of combination evidence-based medical therapies was independently and strongly associated with lower 6-month mortality in patients with ACSs.[71] Furthermore, there was a gradient of benefit across the different TIMI risk groups with higher-risk patients obtaining higher absolute benefit.[72] The 2013 AHA/ACCA STEMI guidelines[73] recommend (1) indefinitely aspirin 81 to 325 mg daily maintenance dose after PCI (class I), (2) β-blockers should be continued after hospitalization for all patients with STEMI and with no contraindications to their use (class I), (3) angiotensin-converting enzyme inhibitors are reasonable for all patients with STEMI and no contraindications to their use (class IIa and class I if presence of reduced LVEF), and (4) high-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.

47. **b.** PCI may reduce the episodes of angina in the presence of moderate-to-severe ischemia at stress single-photon emission computed tomography (SPECT) but not the risk of death, MI, or other major CV events when added to optimal medical therapy. The COURAGE trial compared OMT alone or in combination with PCI as an initial management strategy in patients with stable CAD. Although the addition of PCI to OMT reduced the prevalence of angina, especially in case of moderate-to-severe ischemia detected by SPECT, it did not reduce long-term rates of death, nonfatal MI, and hospitalization for ACSs.[16]

48. **d.** Severe RCA stenosis. Coronary angiography shows severe mid-RCA stenosis explaining the inferior ischemia.

49. **d.** 12 months. The 2011 AHA/ACC PCI guidelines recommend the continuation of aspirin indefinitely (class I) and the duration of $P2Y_{12}$ inhibitor after stent implantation as follows: (1) BMS or DES during PCI for ACS, at least 12 months; (2) DES for a non-ACS indication, at least 12 months if patients are not at high risk for bleeding; and (3) BMS for a non-ACS indication, a minimum of 1 month, and ideally up to 12 months (unless the patient is at increased risk for bleeding).[5]

50. **a.** Severe LCX stenosis. The coronary angiography of the left circulation shows severe mid-left circumflex coronary artery stenosis.

51. **e.** Discontinuation of dual antiplatelet therapy followed by surgery in the first few weeks following stent implantation is problematic with DES but not BMS. In patients scheduled for noncardiac surgery in the year following PCI, the implantation of DESs should be avoided. Accordingly, one of the most frequent predisposing conditions to DES thrombosis is the (partial or complete) discontinuation of dual antiplatelet therapy because of urgent or elective noncardiac surgery.[74] Although preliminary data suggest that continuation of dual antiplatelet therapy during surgery, if feasible, may be protective of DES thrombosis, no recommendation can be made at this time. Conceptually, the potential for stent thrombosis remains because of the intrinsic prothrombotic state related to surgery. Perioperative thrombosis of BMS implanted shortly prior to noncardiac surgery have been described and associated with prohibitive morbidity and mortality. Therefore, whenever possible, noncardiac surgery should be postponed for at least 6 weeks following implantation of a BMS and 6 to 12 months following DES implantation.

52. **d.** In patients who have already suffered a stent thrombosis dual antiplatelet therapy may be extended long term, although currently there are no data to support this

strategy. Currently, there are no data to support an extension of dual antiplatelet therapy beyond 12 months. Nevertheless, in selected patients at high risk for stent thrombosis, aspirin and clopidogrel may be administered for a longer period of time. The CHARISMA trial[70] did show a benefit of prolonged aspirin and clopidogrel therapy over aspirin only in the secondary prevention setting, but did not specifically address the PCI population. According to the 2011 AHA/ACC PCI, continuation of $P2Y_{12}$ inhibitor after stent implantation for ACS should be at least 12 months.[5]

53. **e.** Occlusion of the first diagonal branch. The ECG showed inferoposterolateral STEMI. Coronary angiography showed a thrombotic occlusion of mid-portion of the dominant RCA.

54. **a.** Thrombotic occlusion of the left main trunk. The coronary angiography shows thrombotic occlusion of the left main trunk artery. This lesion has been treated with thromboaspiration and implantation of a DES.

55. **c.** Anterior subacute MI. ECG reveals ST elevation of anterolateral fields. Due to persisting chest pain, the patient has been investigated with angiography. The ventriculography showed occlusion of the mid-portion of the left anterior descending coronary artery treated with thromboaspiration and implantation of a BMS. The image of the thrombus extracted is shown in Figure 4.14.

Figure 4.14

56. **b.** Occlusion of the left anterior descending coronary artery. The coronary angiography showed an occlusion of the proximal left anterior descending coronary artery. The fact that the vessel perfused the apex including the inferoapical portion of the left ventricles explains the ST elevations in the anterior and inferior leads.

57. **d.** Visible thrombus in the mid-portion of the RCA. The coronary angiography showed a subtotal stenosis of the mid-RCA followed by a filling defect compatible with a large thrombus. The thromboaspiration was successfully performed and the lesion was subsequently treated with stenting.

58. **a.** Subtotal occlusion of the left main trunk. Coronary angiography showed subtotal occlusion of the left main trunk and the lesion was treated with stenting. Ventriculography showed a severely reduced LVEF (15%) under a mechanical chest compression system. The patient did not recover and subsequently died.

59. **a.** ISR of the left descending coronary artery. Coronary angiography shows a ISR of

the mid-left anterior descending coronary artery.

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Pharmacology

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QUESTIONS

Pharmacokinetics and Pharmacodynamics

1. P. M. is admitted to the coronary intensive care unit (ICU) with atrial fibrillation (AFib) and rapid ventricular rate. After controlling the ventricular rate with metoprolol, it is decided to initiate procainamide by intravenous (IV) infusion. P. M. weighs 80 kg. How much of a loading dose would be required to target a level of 8 µg/L? The average steady-state volume of distribution (V_d) for procainamide is 2 L/kg. The bioavailability of the IV formulation is 100%, whereas the oral (PO) form is only 83%.

   a. 1,000 mg
   b. 1,300 mg
   c. 1,500 mg
   d. 1,700 mg

2. L. M. has been receiving digoxin 0.25 mg PO tablets daily. Her serum drug level is 1.8 ng/mL. She is no longer able to take PO medications and needs to receive digoxin IV. By what percentage do you need to decrease the dose to maintain the current digoxin level?

   a. 10%
   b. 25%
   c. 40%
   d. 50%

3. What two pharmacokinetic parameters alter the half-life of medications?

   a. Loading dose and clearance

b. Absorption and clearance
c. V_d and clearance
d. Absorption and V_d

4. What is the relationship between drug concentration and pharmacologic effect known as?

a. Pharmacokinetics
b. Pharmacogenetics
c. Pharmacology
d. Pharmacodynamics

5. Each line in Figure 5.1 represents a β-blocker in development. Which β-blocker is the most potent?

a. A
b. B
c. C
d. Potency cannot be determined from the above graph

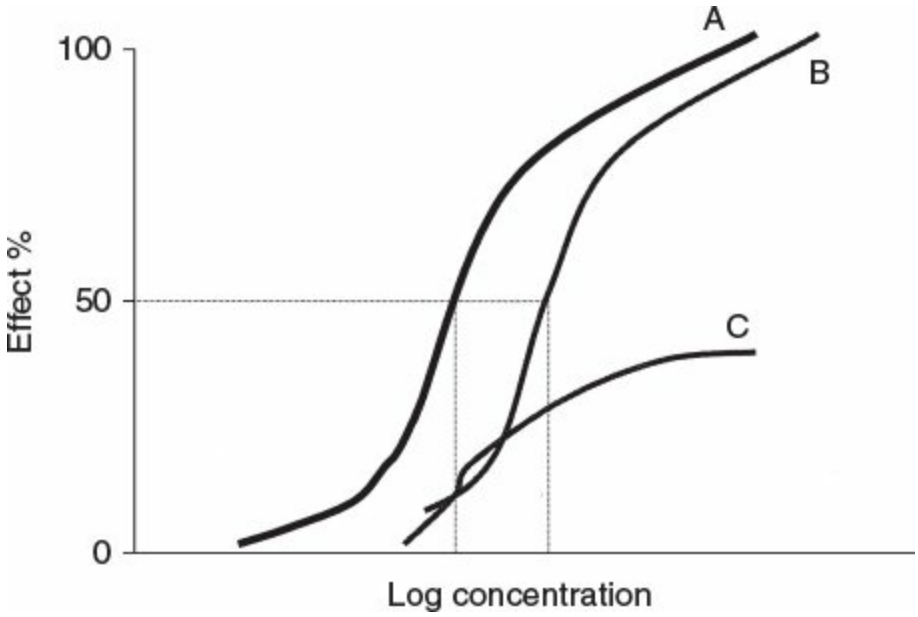

Figure 5.1 • Relationship between drug concentration and effect.

6. Ethanol alters the metabolism of warfarin. Two types of ethanol abuse are chronic ethanol abuse and binge ethanol drinking. How do these types of ethanol use alter warfarin metabolism? Chronic ethanol use _____ and binge ethanol drinking _____.

a. decreases warfarin metabolism, increases warfarin metabolism

b. decreases warfarin metabolism, decreases warfarin metabolism
c. increases warfarin metabolism, decreases warfarin metabolism
d. increases warfarin metabolism, increases warfarin metabolism

7. Which of the following drugs can significantly increase digoxin concentrations?

a. Amiodarone
b. Metoprolol
c. Simvastatin
d. Fenofibrate

Angiotensin-Converting Enzyme (ACE) Inhibitors

8. Which of the following statements is true with regard to ACE inhibitors?

a. Mortality benefit in heart failure (HF) patients is a class effect with ACE inhibitors, and all are Food and Drug Administration (FDA) approved for this indication.
b. ACE inhibitor dose is negligible in HF with regard to mortality benefit.
c. Sodium depletion is an important factor in the development of renal insufficiency associated with ACE inhibitors.
d. ACE inhibitor–associated potassium retention is related to the increase in feedback that leads to aldosterone release.

β-Blockers

9. Match the properties with the associated β-blocking agents.

1. Pindolol i. α-Blockade
2. Propranolol ii. Intrinsic sympathomimetic activity (ISA)
3. Labetalol iii. Membrane-stabilizing activity
4. Bisoprolol iv. β_1-Selectivity

a. (1) iv; (2) ii; (3) iii; (4) i
b. (1) iii; (2) i; (3) ii; (4) iv
c. (1) ii; (2) iii; (3) i; (4) iv
d. (1) ii; (2) iv; (3) iii; (4) i

Calcium Channel Blockers (CCBs)

10. By which of the following mechanisms do diltiazem and verapamil slow ventricular rate in patients with AFib?

a. They decrease the conduction velocity within the atrioventricular (AV) node.
b. They decrease the refractory period of nodal tissue.

c. They stimulate vagal tone.
d. They prolong the refractory period of atrial tissue.

11. Which of the following CCBs is indicated in patients presenting with a subarachnoid hemorrhage?

a. Verapamil
b. Diltiazem
c. Isradipine
d. Nimodipine

Diuretics

12. Which of the following loop diuretics is a not a sulfonamide and can, therefore, be given to a patient with a sulfonamide allergy?

a. Ethacrynic acid
b. Bumetanide
c. Torsemide
d. Furosemide

13. True or False: Conivaptan is indicated for the treatment of hyponatremia for patients with underlying HF.

a. True
b. False

Inotropic Agents

14. How does digoxin improve myocardial contractility?

a. Inhibition of the Na^+/K^+-adenosine triphosphatase
b. Inhibition of the breakdown of cyclic adenosine monophosphate (cAMP)
c. Increases intracellular K^+, leading to the opening of calcium channels
d. Directly stimulates calcium release from the sarcoplasmic reticulum

15. F. F. is a 75-year-old man with a history of HF and AFib and was initiated on amiodarone and warfarin. He has been treated for many years with captopril, furosemide, potassium, amlodipine, and digoxin. After 3 days in the hospital, the patient was sent home. One week after discharge, he developed nausea, vomiting, confusion, and symptomatic ventricular tachycardia (VT). His serum digoxin concentration was 3.9 ng/mL and serum potassium level was 5.8 mmol/L. The rhythm was treated with lidocaine, and the patient is now having episodes of nonsustained VT with a blood pressure (BP) of 80/40 mmHg during each episode.

What should be your next course of action?

a. Discontinue the amiodarone and digoxin and observe.
b. Discontinue the digoxin and administer digoxin-specific antibodies.
c. Decrease the dose of digoxin.
d. Discontinue digoxin and observe.

16. N. M. is a 75-year-old woman with a long-standing history of HF secondary to viral cardiomyopathy. She presents to the outpatient clinic for routine follow-up. On examination, she was short of breath and reported increasing orthopnea. She was admitted to the ICU for right heart catheterization. Initial readings show a cardiac index of 1.8 L/min/m^2, elevated pulmonary capillary wedge pressure (25 mmHg), and high pulmonary pressures (72/45 mmHg). Her initial BP was 105/55 mmHg, and she had a heart rate of 105 beats per minute (bpm). Home medications include captopril, spironolactone, metoprolol XL, and furosemide. Which of the following inotropic agents would be most appropriate?

a. Dopamine
b. Dobutamine
c. Milrinone
d. Isoproterenol

Anticoagulation

17. Which of the following statements is true regarding vitamin K administration?

a. Subcutaneously administered vitamin K exhibits the same bioavailability as oral or IV vitamin K
b. IV vitamin K is superior at lowering the INR than oral vitamin K at similar doses
c. IV vitamin K works faster to lower the INR than oral vitamin K at similar doses
d. Rates of anaphylaxis are similar between oral and IV administration of vitamin K

18. Which of the following agents bind only to factor Xa?

a. Enoxaparin
b. Fondaparinux
c. Bivalirudin
d. Unfractionated heparin (UFH)

19. A. F. is a 52-year-old man with a history of AFib, transient ischemic attacks, hypertension (HTN), and rheumatic heart disease. The recommendations from the

Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy suggest that this patient be initiated on _____ for antithrombotic therapy because of AFib.

a. aspirin, 81 mg daily
b. aspirin, 325 mg daily
c. warfarin, with a target goal international normalized ratio (INR) of 2.5
d. warfarin, with a target goal INR of 3.5

20. The patient above is going to be electively cardioverted. What is the timing of PO anticoagulant therapy?

a. Warfarin with a target INR of 3.5 for 4 weeks before cardioversion and continued for 6 weeks after cardioversion
b. Warfarin with a target INR of 3.5 for 3 weeks before cardioversion and continued for 6 weeks after cardioversion
c. Warfarin with a target INR of 2.5 for 3 weeks before cardioversion and continued for 4 weeks after cardioversion
d. Warfarin with a target INR of 2.5 for 6 weeks before cardioversion and continued for 6 weeks after cardioversion

21. Heparin must first bind to _____ to exert its anticoagulant activity.

a. antithrombin
b. thrombin
c. factor X
d. protein C

22. J. M. was initiated on heparin and was given a 5,000-unit bolus. Five minutes after the loading dose of heparin, she began to have bloody emesis, and her systolic pressure dropped to 80 mmHg. How much protamine will she require?

a. 25 mg
b. 50 mg
c. 75 mg
d. 100 mg

23. Patients who develop heparin-induced thrombocytopenia have an in vitro cross-reactivity with low-molecular-weight heparin (LMWH) by what percent?

a. 90% to 100%
b. 60% to 70%
c. 25% to 45%

d. 5% to 10%

24. A patient with a recent history of heparin-associated antibodies presents with new-onset symptomatic AFib and requires anticoagulation. Other significant past medical history includes severe renal failure secondary to long-standing HTN. The patient's baseline serum creatinine is 4 mg/dL, with an estimated creatinine clearance of 10 mL/min. Which of the following choices is the best initial therapy?

a. Lepirudin, 0.4 mg/kg bolus, then 0.15 mg/kg/h
b. Lepirudin, 0.2 mg/kg bolus, then 0.15 mg/kg/h
c. Argatroban, 2 μg/kg/min
d. Enoxaparin, 1 mg/kg SC daily

Antiplatelet Agents

25. What is the maximum dose of aspirin that can be concomitantly administered with ticagrelor?

a. 81 mg
b. 100 mg
c. 162 mg
d. 325 mg

26. All of the following are differences between clopidogrel and ticagrelor except?

a. Time to maximum platelet inhibition after bolus administration
b. Number of metabolic enzyme activations to active drug
c. Irreversible versus reversible effect at the $P2Y_{12}$ receptor
d. The number of days to discontinue therapy prior to CABG

27. Respiratory diseases should be closely monitored with the use of which of the following antiplatelet agents?

a. Clopidogrel
b. Prasugrel
c. Ticagrelor
d. Eptifibatide

28. Which of the following side effects differentiate ticlopidine from clopidogrel?

a. Diarrhea
b. Rash
c. Neutropenia
d. Thrombotic thrombocytopenic purpura

29. By which of the following mechanisms do clopidogrel and ticlopidine exert their antiplatelet effects?

a. Cyclo-oxygenase inhibitor
b. Glycoprotein IIb/IIIa inhibitor
c. Adenosine diphosphate (ADP) inhibitor
d. Direct thrombin inhibitor

30. Which of the following glycoprotein IIb/IIIa inhibitors has the highest incidence of severe thrombocytopenia?

a. Tirofiban
b. Abciximab
c. Eptifibatide
d. The incidence is not different between the different agents

31. Which of the following glycoprotein IIb/IIIa inhibitors has the shortest half-life but the longest duration of therapy?

a. Tirofiban
b. Eptifibatide
c. Abciximab
d. Lamifiban

Antiarrhythmic Agents

32. Dronedarone use is contraindicated in which patient population?

a. Post-acute myocardial infarction
b. Severe renal impairment
c. NYHA class IV heart failure
d. 1st degree AV block

33. Y.K is a 65-year-old male with symptomatic paroxysmal atrial fibrillation and heart failure recently admitted to the hospital for decompensation. The decision has been made to restore sinus rhythm and utilize antiarrhythmic therapy for rhythm control. Which of the following antiarrythmic agents is most appropraite to use in this patient for rhythm control?

a. Dofetalide
b. Dronedarone
c. Flecanide
d. Quinidine

34. Which of the following agents is effective for converting AFib to sinus rhythm and for maintaining sinus rhythm after it is restored?

a. Digoxin
b. Amiodarone
c. Diltiazem
d. Propranolol

35. M. G., a 50-year-old man, collapsed at home after shoveling his sidewalk. His son initiated cardiopulmonary resuscitation immediately, and an emergency medical service was called. When the squad arrived, it was determined that M. G. was in ventricular fibrillation (VF), and he was cardioverted with 200, 300, and 360 J. Epinephrine was given, and M. G. was shocked again. M. G. was still in VF. It was decided to initiate antiarrhythmic therapy. Choose the most appropriate agent from the list below.

a. Lidocaine
b. Amiodarone
c. Procainamide
d. Bretylium

Acute Coronary Syndromes

36. G. M. is a 45-year-old man presenting with a non-ST-segment-elevation myocardial infarction (MI). His creatinine clearance is estimated to be 30 mL/min. You would like to initiate eptifibatide. Which of the following doses would be the best choice?

a. Loading dose of 180 µg/kg and a maintenance of 2 µg/kg/min
b. Loading dose of 90 µg/kg/min and a maintenance dose of 2 µg/kg/min
c. Loading dose of 180 µg/kg and a maintenance dose of 1 µg/kg/min
d. Loading dose of 90 µg/kg/min and a maintenance dose of 1 µg/kg/min

37. M. M. is a 39-year-old man with an inferior wall non-ST-segment-elevation MI. He has a history of poorly controlled HTN and diabetes mellitus (DM). You initiate aspirin, clopidogrel, and atorvastatin. His baseline serum creatinine is 3.4 mg/dL and you estimate his creatinine clearance to be 25 mL/min. What dose of enoxaparin would you choose?

a. 1 mg/kg every 12 hours
b. 1 mg/kg daily
c. Enoxaparin is not indicated at this time
d. Fondaparinux is safer to use in M. M.

38. B. B. is a 77-year-old man who presents with typical chest pain and pressure. He has ST elevations in lead $V_{2–4}$. He is 80 kg with a serum creatinine of 0.7 mg/dL with an estimated creatinine clearance of 75 mL/min. You initiate aspirin, clopidogrel, metoprolol, and atorvastatin. You want to initiate enoxaparin and reteplase. What is the enoxaparin dose for this patient?

a. Loading dose of 30 mg IV once followed immediately by 1 mg/kg every 12 hours
b. Loading dose of 30 mg IV once followed by 0.75 mg/kg every 12 hours
c. 1 mg/kg daily
d. 0.75 mg/kg every 12 hours

39. Which of the following is not a risk factor for intracranial hemorrhage in patients receiving fibrinolytic therapy in the treatment of ST-segment-elevation MI?

a. HTN
b. Body weight
c. Age
d. Time to presentation

40. R. M. is a 65-year-old man presenting to the emergency department (ED) with an ST-segment-elevation MI. It is decided to initiate thrombolytic therapy to induce reperfusion. The patient weighs 72 kg. What is the most effective dose of alteplase for this patient?

a. 0.9 mg/kg, with a maximum of 90 mg
b. 15 mg bolus; then 54 mg over 30 minutes; then 36 mg over 60 minutes
c. 15 mg bolus; then 50 mg over 30 minutes; then 35 mg over 60 minutes
d. 60 mg over 1 hour; then 20 mg per hour for 2 hours

Hyperlipidemia

41. M. R. is a 74-year-old man with a history of hypercholesterolemia treated with simvastatin. Two months ago he had a permanent pacemaker placed for sick sinus syndrome. He now presents with a 1-month history of fever, chills, and unexplained weight loss. On physical examination he has a new tricuspid regurgitation murmur. A transesophageal echocardiogram confirms your suspicion of endocarditis. Which of the following antibiotics increases the risk of rhabdomyolysis when given with simvastatin?

a. Ceftriaxone
b. Vancomycin
c. Daptomycin
d. Linezolid

42. Put the following regimens in order according to their low-density lipoprotein (LDL)-lowering ability.

Atorvastatin, 10 mg daily (A)
Cholestyramine, 8 g daily (C)
Pravastatin, 20 mg daily (P)
Gemfibrozil, 600 mg twice daily (G)

a. A > P > C > G
b. P > A > G > C
c. A > P > G > C
d. A > C > P > G

43. D. L. is a 76-year-old white man with a past medical history significant for DM type 2 and HTN. Chronic AFib was recently diagnosed with coronary artery disease (CAD) and hypercholesterolemia and he was initiated on gemfibrozil 600 mg twice daily and atorvastatin 40 mg daily. His other medications include glyburide, metoprolol, furosemide, levothyroxine, insulin, and aspirin. Two weeks later, he began to experience pain in his right calf, with pain and stiffness throughout his back, buttocks, and thigh. After another week, he was admitted to the hospital with similar heightened symptoms. On admission, his blood urea nitrogen was elevated, and the urinalysis showed orange, cloudy urine; protein, greater than 300; glucose, greater than 1,000; ketones, 2+; hemoglobin, 3+; red blood cell count, 6 to 10; and myoglobin, 1,367. Which of the following statements is true?

a. The patient is experiencing rhabdomyolysis secondary to the drug interaction of atorvastatin and glyburide.
b. Forced diuresis with urine alkalinization and discontinuation of gemfibrozil and atorvastatin are indicated for this patient.
c. Atorvastatin is contraindicated in a patient with DM type 2 and HTN.
d. If nicotinic acid, rather than gemfibrozil, had been used for hypercholesterolemia, this reaction would have been prevented.

Hypertension

44. N. H. is a 57-year-old man status post MI with a BP of 150/88 mmHg and a heart rate of 87 bpm. He is currently on aspirin, clopidogrel, atorvastatin, and lisinopril. Which agent would be the most appropriate addition for treatment of his HTN?

a. Hydrochlorothiazide
b. Metoprolol
c. Clonidine
d. Losartan

45. B. T. is a 56-year-old woman with long-standing HTN that is difficult to control. She is currently being treated with amlodipine 10 mg daily, lisinopril 40 mg daily, hydrochlorothiazide 25 mg daily, and clonidine 0.4 mg three times daily. She presented to the emergency room, and her initial BP was 200/110 mmHg. She states she had run out of one of her medications. Which one of her medications would most likely be implicated in causing hypertensive urgency?

a. Amlodipine
b. Lisinopril
c. Hydrochlorothiazide
d. Clonidine

46. C. P. is a 46-year-old white man admitted with worsening headache, and nausea and vomiting over 48 hours. The patient is status post single-lung transplant secondary to α_1-antitrypsin deficiency. His immunosuppression regimen includes cyclosporine, prednisone, and azathioprine. As a result of the cyclosporine, he has HTN and renal dysfunction (baseline serum creatinine, 1.9 mg/dL). His BP is controlled with clonidine 0.2 mg twice daily and metoprolol tartrate 25 mg twice daily. Two months ago, he was changed to metoprolol from amlodipine because of peripheral edema. The patient was in his usual state of health until approximately 1 week ago, when he experienced diarrhea, which has since resolved. On admission, his BP was 208/110 mmHg and his serum creatinine was 3.8 mg/dL. What is the most appropriate regimen to control this patient's BP?

a. Change back to amlodipine 10 mg daily
b. Initiate nitroprusside drip and give IV fluids
c. Add captopril to the regimen and titrate to effect
d. Give sublingual nifedipine

Heart Failure

47. R. W. is a 60-year-old woman with HF (left ventricular ejection fraction <30%) who has HTN with a BP of 152/90 mmHg. Her potassium is 4.0 mg/dL and serum creatinine is stable at 1.5 mg/dL. She is currently on digoxin and furosemide. Which regimen is most appropriate to initiate in this patient?

a. Hydralazine 25 mg four times daily
b. Metoprolol tartrate 12.5 mg twice daily
c. Valsartan 20 mg twice daily
d. Lisinopril 5 mg daily

48. A. V. is a 49-year-old woman with a history of HF presenting to the ED for the

second time in a month with acutely decompensated HF. She has dyspnea at rest and 3+ edema in her lower extremities. Her serum creatinine is 1.8 mg/dL and BP is 90/60 mmHg. Her home regimen includes enalapril 20 mg twice daily, carvedilol 3.125 mg twice daily, and furosemide 40 mg PO daily. Which of the following is most appropriate for this patient?

a. Admit her to the hospital for IV furosemide therapy and hemodynamic monitoring.
b. Admit her to the hospital for diuresis with nesiritide.
c. Initiate an infusion of nesiritide in the ED and reassess in 4 hours.
d. Schedule intermittent outpatient infusions of nesiritide.

49. A patient with New York Heart Association class III HF was hospitalized 2 months ago for an exacerbation of his HF. The patient was discharged on lisinopril, furosemide, and digoxin. His lungs are clear and his vital signs are as follows: BP, 105/56 mmHg; heart rate, 84 bpm; and respiration rate, 18. Which regimen is most appropriate to initiate in this patient?

a. Atenolol 50 mg daily
b. Carvedilol 3.125 mg twice daily
c. Carvedilol 25 mg twice daily
d. Metoprolol tartrate 50 mg twice daily

50. Which β-blockers are recommended for use for patients with HF?

a. Metoprolol tartrate, pindolol, propranolol
b. Carvedilol, metoprolol succinate, bisoprolol
c. Metoprolol succinate, metoprolol tartrate, carvedilol
d. Metoprolol tartrate, carvedilol, bisoprolol

51. Y. J. is a 67-year-old African American man with HF who has been treated with lisinopril 20 mg daily, metoprolol succinate 25 mg daily, furosemide 40 mg twice daily, and spironolactone 12.5 mg daily. Despite his current therapy, he still complains of shortness of breath while conducting usual daily activities. What is the most appropriate change that should be made to his regimen?

a. Increase spironolactone
b. Start hydralazine
c. Initiate isosorbide dinitrate and hydralazine
d. Increase lisinopril

52. Which of the following statements is true?

a. Serum levels are used to guide the selection of the dose of digoxin.
b. Because spironolactone was found to have mortality benefit in the Randomized Aldactone Evaluation Study (RALES), the addition of spironolactone should be considered for all HF patients.
c. The benefit of long-term IV inotropic therapy may outweigh the increased mortality risk in refractory patients unable to be weaned from IV inotropic support.
d. Digoxin exhibits both symptomatic and mortality benefit in patients with HF.

Endocarditis

53. One month ago, a 37-year-old woman with sinus infection responded well to a 14-day course of amoxicillin/clavulanate 875/125 mg twice daily. She is scheduled for a root canal in 1 week. In the past, her dentist had prescribed one dose of clindamycin 600 mg, 1 hour prior to any dental work, for endocarditis prophylaxis because of her history of mitral valve prolapse. Realizing she has not received her prescription, the patient calls the dentist's office for an antibiotic. What prophylaxis is indicated for this patient?

a. Amoxicillin 2 g PO 1 hour before the procedure
b. Clindamycin 600 mg PO 1 hour before the procedure
c. Azithromycin 500 mg PO 1 hour before the procedure
d. No prophylaxis recommended in this patient

54. S. C. is a 59-year-old woman diagnosed with enterococcal endocarditis. She has no known drug allergies. Which of the following would exhibit standard therapy?

a. Penicillin G, 5 million units IV every 4 hours for 4 to 6 weeks, plus gentamicin, 2.5 mg/kg IV every 8 hours for 4 to 6 weeks
b. Ampicillin, 2 g IV every 4 hours for 4 to 6 weeks, plus gentamicin, 1 mg/kg IV every 8 hours for 4 to 6 weeks
c. Ampicillin, 2 g IV every 4 hours for 4 to 6 weeks, plus gentamicin, 1 mg/kg IV every 8 hours for 3 to 5 days
d. Vancomycin, 30 mg/kg per 24 hours in two equally divided doses for 4 to 6 weeks

ANSWERS

1. **b.** 1,300 mg. To determine the loading dose of a one-compartment drug, three items are needed: (a) the drug's V_d (L/kg), (b) the desired steady-state concentration (Cpss [mg/L]), and (c) the patient's weight. Loading dose = $V_d \times$ Cpss. Kilograms

and liters cancel, and you are left with the loading dose in milligrams.

2. **b.** 25%. The bioavailability of digoxin tablets is 75%. Therefore, when converting from PO to IV administration (bioavailability of 100%), there is a 25% increase in bioavailability. Without altering the dose of digoxin, this patient would most likely have an increase in digoxin level to approximately 2.4 ng/mL. This could lead to potential digoxin toxicity.

3. **c.** V_d and clearance. Half-life is a function of both clearance (Cl) and V_d. The elimination-rate constant (k_{el}) is determined by two independent factors: Cl and V_d. $k_{el} = Cl/V_d$. Half-life is determined by the equation $0.693/k_{el}$. Therefore, as the apparent V_d and Cl change, the half-life of a drug may change.

4. **d.** Pharmacodynamics. Pharmacodynamics has been defined as the study of the biologic effects resulting from the interaction between drugs and biologic systems. Pharmacokinetic principles consider drug distribution, metabolism, clearance, and bioavailability, whereas pharmacodynamic principles take this one step further and relate these factors to pharmacologic response. Pharmacogenetics is the study of heredity on variations in drug response among individuals and populations. Pharmacogenetic studies have established that genetics play an important role in the dose–concentration–response relationships of medications, whereas pharmacology is simply the study of drugs.

5. **a.** Drug A is the most potent agent. This is based on the fact that at any given concentration of this agent, the effect is greater than that of the other drugs at similar concentrations. Drug B has the same maximal effect; however, it occurs at a higher concentration. Drug C is similar to drug B; however, it is less efficacious, because its maximal effect occurs at a concentration that is 50% lower than that of drug B.

6. **c.** Increases warfarin metabolism, decreases warfarin metabolism. Chronic ethanol consumption can lead to increased hepatic metabolism of many medications that are cleared through the liver. Increased hepatic metabolism is related to enhanced enzyme function. Therefore, chronic ethanol users typically need higher-than-usual doses of warfarin to achieve therapeutic INRs. Acute ingestion of large amounts of ethanol at a time may inhibit warfarin metabolism. This may lead to elevated INRs and increase the risk of hemorrhagic complications. Moderate ingestion of ethanol does not seem to affect the metabolism of warfarin.

7. **a.** Amiodarone. Amiodarone significantly increases the levels of digoxin. Amiodarone decreases the clearance of digoxin and inhibits p-glycoprotein.

Amiodarone can increase digoxin levels by 50% to 70%. This interaction can occur in the first days of therapy and a 50% dosage reduction is required immediately. Metoprolol does not increase the levels of digoxin; however, it can have synergistic effects on lowering heart rate and should be monitored closely. Simvastatin and fenofibrate do not alter the levels of digoxin.

8. **c.** Sodium depletion is an important factor in the development of renal insufficiency associated with ACE inhibitors. Patients with hyponatremia, dehydration, and severe HF are most dependent on the maintenance of renal perfusion by angiotensin II–mediated vasoconstriction of the efferent arteriole. Prevention of hyponatremia by decreasing diuretics can reduce such risk. Numerous studies, including the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial, Veterans' Administration Heart Failure Trial (V-HeFT) II, and Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), have shown ACE inhibitors to reduce mortality in patients with ischemic and nonischemic cardiomyopathy and mild-to-moderate HF. ACE inhibitors are considered to be associated with a class benefit; however, not all ACE inhibitors carry the FDA indication for HF. The ACE inhibitors that are approved for the treatment of HF include captopril, enalapril, lisinopril, quinapril, fosinopril, and ramipril. In 1998, the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial showed that high doses of lisinopril were superior to low doses in decreasing risk of death or hospitalization. Therefore, an effort to use target doses used in clinical trials is important (e.g., captopril 50 mg thrice daily, enalapril 10 mg twice daily, and lisinopril 20 mg daily). Potassium retention of ACE inhibitors is caused by a reduction in the feedback of angiotensin II to stimulate aldosterone release. Caution is necessary when initiating a potassium supplement in a patient on ACE inhibitor therapy.

9. **c.** (1) ii; (2) iii; (3) i; (4) iv. Agents exhibiting α-blockade include labetalol and carvedilol. Agents with ISA are pindolol, penbutolol, carteolol, and acebutolol. Agents with membrane-stabilizing activity are propranolol, labetalol, and acebutolol. β_1-Selective agents include bisoprolol, betaxolol, atenolol, acebutolol, and metoprolol.

10. **a.** Diltiazem and verapamil decrease conduction velocity within the AV node and increase refractory period of nodal tissue. This then causes slowing of ventricular rate.

11. **d.** Nimodipine. Nimodipine is the only agent indicated for patients with subarachnoid hemorrhage. Nimodipine decreases the influx of extracellular

calcium, thus preventing vasospasm.

12. **a.** Ethacrynic acid. Ethacrynic acid is the only loop diuretic that is not a sulfonamide. It is used only in patients allergic to other either loop or thiazide diuretics. Disadvantages of ethacrynic acid include gastrointestinal intolerance and a narrower dose–response curve.

13. **b.** False. Conivaptan is a dual vasopressin antagonist indicated for the treatment of euvolemic and hypervolemic hyponatremia. Its predominant pharmacodynamic effect is through the V_2 antagonism of vasopressin in the renal collecting ducts that results in excretion of free water. Because of the limited number of HF patients with hypervolemic hyponatremia treated with conivaptan, safety in HF patients has not been established; therefore, its use in HF patients may be considered only when the clinical benefit outweighs the risk of adverse effects.

14. **a.** Inhibition of the Na^+/K^+-adenosine triphosphatase. Digoxin inhibits the Na^+/K^+-adenosine triphosphatase pump on the myocardial cell surface. This inhibits the ability of the cell to exchange potassium for sodium and thus leads to an increase in intracellular sodium. This increase in intracellular sodium leads to exchange of sodium for calcium, increasing intracellular calcium concentrations. Increased intracellular calcium enhances contraction coupling.

15. **b.** Discontinue the digoxin and administer digoxin-specific antibodies. Digoxin-immune Fab is indicated for patients with life-threatening ventricular arrhythmias relating to digoxin toxicity. It is also indicated in patients with progressive bradyarrhythmias, such as severe sinus bradycardia or second- or third-degree heart block not responsive to atropine. It should not be used for milder forms of digoxin toxicity. Also, in the setting of hyperkalemia and digitalis intoxication, digoxin-immune Fab fragment is indicated. Digoxin-immune Fab fragment is ovine derived; there is a potential for hypersensitivity reactions, and there are no data available in regard to readministration.

16. **c.** Milrinone. Milrinone is a phosphodiesterase inhibitor classified as inodilator. Thus, milrinone produces positive inotropic effects and vasodilation. Milrinone inhibits the phosphodiesterase III enzyme, leading to an increase in intracellular cAMP, thus causing increased intracellular levels of calcium. In addition, milrinone will decrease pulmonary pressures and left ventricular (LV) end-diastolic pressures more predictably than the other agents listed. These combined effects lead to minimal increases in myocardial O_2 consumption. Also, milrinone may be useful in this patient secondary to chronic metoprolol therapy.

17. **c.** IV vitamin K works faster to lower the INR than oral vitamin K at similar doses. The onset of action of IV vitamin K is 1–2 hours compared to 6–10 hours for oral vitamin K. As a result, INR values return to normal quicker with IV vitamin K. The overall reduction in INR is dose dependent and not route dependent when comparing IV and oral formulations. Subcutaneous vitamin K has variable absorption which can lead to variations in time to onset as well as INR lowering effect.

18. **b.** Fondaparinux. Fondaparinux, a pentasaccharide, selectively inhibits activated Xa through its binding to antithrombin. Enoxaparin and UFH bind to both thrombin (IIa) and activated Xa, whereas bivalirudin binds directly to thrombin. UFH binds to thrombin and activated factor Xa in a 1:1 ratio, whereas LMWHs vary in their binding ratios.

19. **c.** Warfarin, with a target goal international normalized ratio (INR) of 2.5. This patient is at high risk for a thromboembolic event. Recommendations for antithrombotic therapy include risk stratification. Risks are stratified into high, moderate, and low. High-risk patients include patients with prior stroke or transient ischemic attack or systemic embolus, history of HTN, poor LV systolic function, age older than 75 years, rheumatic mitral valve disease, and a prosthetic heart valve. Moderate risk factors include age between 65 and 75 years, DM, and CAD with preserved LV systolic function. Low-risk patients are those younger than 65 years old with no clinical or transthoracic echocardiogram evidence of cardiovascular disease.

20. **c.** Warfarin with a target INR of 2.5 for 3 weeks before cardioversion and continued for 4 weeks after cardioversion. Recommendations from the Sixth ACCP Consensus Conference on Antithrombotic Therapy state that patients undergoing elective cardioversion for AFib should be initiated on oral anticoagulant therapy for 3 weeks before and at least 4 weeks after elective direct current cardioversion. The grade of evidence is 1C+. Also, an alternative approach would be to initiate anticoagulation, have the patients undergo a transesophageal echocardiography, and have the cardioversion performed if no thrombi are seen. Warfarin should be continued for at least 4 weeks, as long as the patient maintains normal sinus rhythm. This is a grade 1C recommendation.

21. **a.** Antithrombin. Heparin must first bind to antithrombin to exert its anticoagulant effect. This complex accelerates antithrombin effect. Heparin potentiates antithrombin's effect by binding to a glucosamine unit within a pentasaccharide sequence.

22. **b.** 50 mg. Every 1 mg of protamine will antagonize approximately 100 units of heparin. Because this patient just received the bolus, she would require 50 mg of protamine. If she had received the dose 30 to 60 minutes ago, then a dose of 0.50 to 0.75 mg of protamine per 100 units of heparin would be required. If she had been on a continuous infusion of heparin, then the dosing would be dependent on the time and dose of the last bolus of heparin and the rate of infusion. In this scenario, most patients require approximately 25 to 50 mg of protamine.

23. **a.** 90% to 100%. There have been several reports of patients who have heparin-induced thrombocytopenia being treated with LMWH. However, the cross-reactivity in vitro approaches 100%. The use of LMWH should be considered a contraindication unless there is a documented negative test for antibodies against LMWH.

24. **c.** Argatroban, 2 µg/kg/min. Argatroban is hepatically cleared and, therefore, does not require dosing adjustment for patients with renal dysfunction and may be a safer alternative for anticoagulation. Lepirudin is reasonable as well; however, patients with significant renal dysfunction require appropriate dosing adjustments. Continuous infusion should not be used in patients with a creatinine clearance <15 mL/min because of accumulation of drug. LMWHs have a high likelihood for in vitro and in vivo cross-reactivity of 80% to 100%, and there is a potential for an increase in thrombotic complications.

25. **b.** 100 mg. The Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) trial evaluated antiplatelet strategies in addition to aspirin post-ACS. The trial did not mandate a specific aspirin maintenance dose which was left to the discretion of the provider. After trial completion, a subset analysis was performed which favored ticagrelor use with low maintenance dose aspirin (≤100 mg) as higher doses resulted in decreased ticagrelor effectiveness. The package insert for ticagrelor recommends the maintenance dose of aspirin to be 75–100 mg daily if being used concomitantly with ticagrelor. An initial 325 mg dose of aspirin should still be given with ticagrelor in the ACS setting.

26. **d.** The number of days to discontinue therapy prior to CABG. The recommended number of days prior to CABG surgery to stop clopidogrel or ticagrelor is 5. Patients in both the Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) trial and the Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation (CURE) trial had increased bleeding if the agents were not stopped at least 5 days prior to surgery. Although the competitive antagonist property of ticagrelor at the $P2Y_{12}$

receptor and its short half-life (~7 hours) would lead clinicians to believe that ticagrelor could be stopped earlier than 5 days prior to surgery, that has not proven to be true.

27. **c.** In the Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes (PLATO) trial, patients were more likely to experience dyspnea in the ticagrelor arm versus the clopidogrel arm (14% vs. 8 %). Also, more patients had to discontinue ticagrelor than clopidogrel because of dyspnea (0.9% vs. 0.1%). The mechanism for increased dyspnea is hypothesized to be triggered by adenosine. Ticagrelor inhibits the clearance of adenosine thereby increasing its concentration in the circulation. Although, more dyspnea results from ticagrelor use, there were no differences in forced expiratory volume in 1 second (FEV1) between ticagrelor and clopidogrel.

28. **c.** Neutropenia. Ticlopidine causes neutropenia in 2.4% of patients who are initiated on therapy. Nearly 1% of patients develop severe neutropenia. Therefore, a complete blood count is required every 2 weeks during initiation of therapy for the first 3 months of therapy. Both agents can cause diarrhea and rash. Structurally, these two drugs are so similar that allergic cross-reactivity is expected. Thrombotic thrombocytopenic purpura has been reported with both agents. There have been >100 cases of thrombotic thrombocytopenic purpura reported with the use of ticlopidine and clopidogrel.

29. **c.** Adenosine diphosphate (ADP) inhibitor. ADP is released from red blood cells, activated platelets, and damaged endothelial cells, leading to platelet adhesion and aggregation. However, the precise mechanism of its action has not been completely identified. ADP blockade decreases the expression of the glycoprotein IIb/IIIa receptor. Platelet inhibition occurs at maximal effect within 3 to 5 days and produces approximately 40% to 50% platelet inhibition. The onset and degree of platelet inhibition can be expedited with use of loading doses (300 to 600 mg).

30. **b.** Abciximab. All glycoprotein IIb/IIIa inhibitors may cause thrombocytopenia. However, abciximab has the highest rate of all, based on the clinical trials.

31. **c.** Abciximab. Abciximab has a serum half-life of 10 to 30 minutes; however, because of its high binding affinity to the glycoprotein IIb/IIIa receptor, it maintains its activity for many hours after discontinuation of therapy, and abciximab can be detected in the serum for longer than 2 weeks. The short-acting inhibitors have half-lives of approximately 2 hours, depending on renal function; however, because of their competitive inhibiting nature, once the infusion is discontinued, their effects

wane relatively quickly.

32. **c.** NYHA class IV heart failure. The Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) was a mortality trial comparing dronedarone to placebo in patients with moderate to severe heart failure for rhythm control. The trial was prematurely terminated as a significantly higher mortality rate was seen in the dronedarone arm versus placebo (8.1% vs. 3.8%). The risk of death was highest in patients with severely depressed left ventricular systolic function. The package insert for dronedarone states the drug is contraindicted in patients with NYHA Class IV heart failure or symptomatic heart failure with recent decompensation requiring hospitalization because it doubles the risk of death.

33. **a.** Dofetalide. Structural heart failure limits the use of antiarrythmic therapies for rhythm control in atrial fibrillation due to mortality concerns. Dofetalide has not shown to increase mortality in patients with atrial fibrillation who also have heart failure unlike dronedarone, flecanide, and quinidine. The agent of choice in this situation; however, would likely be amiodarone unless the patient has other contraindications for amiodarone therapy.

34. **b.** Amiodarone. Although amiodarone does not carry an FDA indication for the treatment of AFib, it can convert to and maintain normal sinus rhythm. The other agents listed are only used for rate control when used for AFib.

35. **b.** Amiodarone. The most recent advanced cardiac life support guidelines recommend that amiodarone be the first-line agent in patients with pulseless VT/VF. This recommendation is based on the Amiodarone for Resuscitation after Out-of-Hospital Cardiac Arrest due to Ventricular Fibrillation (ARREST) trial, which showed that amiodarone increased the likelihood of admission to the hospital after an out-of-hospital arrest. This is further supported by the recently presented Amiodarone versus Lidocaine in Pre-Hospital Refractory Ventricular Fibrillation Evaluation (ALIVE) trial. Lidocaine is now considered Class Indeterminate based on the lack of controlled trials supporting its use in pulseless VT/VF. Procainamide administration is prolonged and not suitable for rapid administration. Bretylium is no longer available secondary to lack of raw materials.

36. **c.** Loading dose of 180 µg/kg and a maintenance dose of 1 µg/kg/min. Based on product information, eptifibatide loading dose should not be changed and the maintenance infusion should be initiated at 1 µg/kg/min. Eptifibatide is contraindicated in patients on dialysis and there is limited experience using this

agent in this patient population. Tirofiban is not contraindicated in patients on dialysis; however, there are limited data to support its use in dialysis patients.

37. **b.** Enoxaparin 1 mg/kg daily. Enoxaparin is approved for both ST-segment-elevation and non-ST-segment-elevation MI. In patients with a creatinine clearance >30 mL/min then the standard dose of 1 mg/kg every 12 hours is appropriate. However, when the creatinine clearance is <30 mL/min then the dose should be reduced to 1 mg/kg once daily. Fondaparinux is contraindicated in patients with a creatinine clearance <30 mL/min.

38. **d.** Loading dose of 30 mg IV once followed by 0.75 mg/kg every 12 hours. Enoxaparin was recently approved for the treatment of ST-segment-elevation MI with fibrinolysis based on the ExTRACT-TIMI 25 trial. In the older patients, lower enoxaparin doses were used to minimize bleeding. There was a lower risk of the primary endpoint in those that received enoxaparin versus those receiving UFH. There was no difference in intracranial hemorrhage; however, there was a significantly higher rate of major bleeding with enoxaparin (2.1% versus 1.4%).

39. **d.** Time to presentation. Time to presentation is not a risk factor for intracranial hemorrhage in patients receiving thrombolytic therapy. In clinical trials, the risks for intracranial hemorrhage included age older than 65 years, low body weight (<70 kg), HTN on hospital admission, and the use of alteplase. Also, the levels of concomitant anticoagulation can also increase the risk of intracranial hemorrhage.

40. **c.** 15 mg bolus; then 50 mg over 30 minutes; then 35 mg over 60 minutes. Based on the first GUSTO trial, the most effective dosing for acute ST-segment-elevation MI is front-loaded tissue plasminogen activator. The maximum dose should be 100 mg and, therefore, Answer b may increase the risk of major bleeding, specifically intracranial hemorrhage. Answer d is standard dosing of recombinant tissue-type plasminogen activator and was found inferior to front loading. Finally, Answer a is the recommended dosing for acute ischemic stroke.

41. **c.** Daptomycin. Daptomycin may cause elevations in creatine phosphokinase (CPK) levels. The product literature for daptomycin recommends temporary discontinuation of medications that can raise CPK levels when a patient is receiving this antibiotic. Even though this adverse reaction is rare, CPK levels should be monitored weekly in patients receiving daptomycin alone and more frequently if statin therapy is continued.

42. **a.** A > P > C > G. HMG-CoA reductase inhibitors decrease LDL by 18% to 55%.

Atorvastatin is the most potent agent statin of the group. Bile-acid sequestrants decreased LDL by 15% to 30%. Fibrates decrease LDL by 5% to 20%.

43. **b.** Forced diuresis with urine alkalinization and discontinuation of gemfibrozil and atorvastatin are indicated for this patient. Rhabdomyolysis secondary to the interaction of atorvastatin and gemfibrozil is responsible for this clinical picture. Rhabdomyolysis is defined as the disintegration of muscle, associated with the excretion of myoglobin in the urine. Clinical signs and symptoms include myalgias, elevated creatine kinase, elevated urine and serum myoglobin, and dark urine. Complications of rhabdomyolysis are numerous and may include renal failure, disseminated intravascular coagulation, metabolic acidosis, and cardiomyopathy. HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins) can be considered direct myotoxins and may induce rhabdomyolysis when used alone. However, the risk of toxicity increases when statins are used in combination with fibric acid derivatives (gemfibrozil or fenofibrate), nicotinic acid, cyclosporine, itraconazole, or erythromycin, to name a few. Treatment of the underlying cause, in this case discontinuation of the offending agents, is necessary. In addition, renal failure caused by products of tissue degradation must be combated with urinary alkalinization and maintenance of a high urine volume.

44. **b.** Metoprolol. The American College of Cardiology (ACC) and American Heart Association (AHA) recommend the use of β-blockers in patients after surviving an MI to decrease mortality, sudden death, and reinfarction. Therefore, if this patient is not already on a β-blocker, one would be indicated, not only for HTN but also for secondary prevention.

45. **d.** Clonidine. Abrupt withdrawal of an α2-agonist is the most likely cause of severe rebound HTN. Typically, this is seen within 24 to 48 hours of discontinuation of clonidine and typically occurs in patients taking large doses for longer than 3 months. The best treatment for this is to restart clonidine. β-Blockers could make the situation worse by causing unopposed α1-stimulation.

46. **b.** Initiate nitroprusside drip and give IV fluids. Hypertensive emergencies are defined by the presence of end-organ damage in the face of high BP. This patient was dehydrated from diarrhea and had uncontrolled BP because of the medication change that occurred. Use of nitroprusside would be most appropriate in this patient because of the emergent situation of the renal insufficiency and possible cerebrovascular involvement exhibited by the headache. Typically, parenteral antihypertensive agents are initiated for hypertensive emergencies. In addition, it is necessary to correct the underlying cause of the hypertensive episode, if it can be

identified; therefore, rehydration in this patient is prudent. Nitroprusside is the drug of choice because it has a quick onset of action yet is easily titratable. Sublingual nifedipine is no longer advocated because of the precipitous drop in BP and the subsequent adverse effects.

47. **d.** Lisinopril 5 mg daily. Because the patient is not already receiving ACE inhibitor therapy, an ACE inhibitor is indicated in patients with HF and a reduced ejection fraction (less than 35% to 45%) to decrease morbidity and mortality, as shown in the SOLVD, V-HeFT, and CONSENSUS trials. The patient has no contraindications to such therapy. If the patient's renal function were changing, thereby making an ACE inhibitor inappropriate, then hydralazine plus a nitrate would be indicated, because V-HeFT I showed mortality benefit compared with placebo and an α-blocker. An angiotensin receptor blocker (ARB), like valsartan, would be indicated if the patient were intolerant to ACE inhibitors in the past. Both ACE inhibitors and ARB should be initiated at low doses, and titrated (as tolerated) to doses proven in clinical trials to reduce cardiovascular events.

48. **a.** Admit her to the hospital for IV furosemide therapy and hemodynamic monitoring. Nesiritide is contraindicated for use in patients with systolic BP <90 mmHg. However, based on meta-analyses that raised questions of increased renal dysfunction and mortality associated with nesiritide, the FDA convened a panel to assess available data and provide recommendations regarding appropriate use of nesiritide. These recommendations state that nesiritide should be limited to hospitalized patients with decompensated HF with dyspnea at rest and it should not be used to replace diuretics. Furthermore, because of insufficient evidence, nesiritide should not be used for intermittent outpatient infusions, for scheduled repetitive use, to improve renal function, or to enhance diuresis. A large-scale clinical trial to assess outcomes and further assess the risks of nesiritide versus standard therapy is currently being conducted.

49. **b.** Carvedilol 3.125 mg twice daily. All patients with stable, class II or III HF should be initiated on a β-blocker, unless a contraindication (bronchospastic disease, symptomatic bradycardia, or advanced heart block) or intolerance is exhibited. Initiation of β-blocker therapy is recommended in stable patients with mild-to-moderate HF and a low ejection fraction (less than 35% to 40%). The mortality benefit of β-blocker use was seen when added to a preexisting regimen of an ACE inhibitor and diuretic, with or without digoxin. It should be noted that β-blockers must be initiated at very low doses and only gradually increased if low doses have been well tolerated.

50. **b.** Carvedilol, metoprolol succinate, bisoprolol. Overwhelming mortality benefit in patients with chronic HF has been proven in clinical trials for carvedilol, metoprolol succinate, and bisoprolol when added to standard HF therapy. These agents are specifically recommended in the ACC/AHA guidelines for the management of chronic heart failure. Despite survival benefit with each of these β-blockers, a class effect with all β-blockers should not be assumed as demonstrated by the Carvedilol or Metoprolol European Trial (COMET). The COMET compared carvedilol with metoprolol tartrate in HF patients and concluded that carvedilol exhibited superior mortality benefit. β-Blockers with ISA should not be used on patients with HF. Pindolol and others with ISA (such as penbutolol, carteolol, and acebutolol) are partial β-agonists and can maintain normal sympathetic tone. This activity prevents the benefits seen with the reduced heart rate, cardiac output, and peripheral blood flow caused by other β-blockers.

51. **c.** Initiate isosorbide dinitrate and hydralazine. The ACC/AHA guidelines recommend the initiation of isosorbide dinitrate and hydralazine as a reasonable addition to standard therapy in blacks with New York Heart Association class III/IV HF. The A-HeFT trial evaluated a proprietary drug combination (hydralazine 37.5 mg and isosorbide dinitrate 20 mg per tablet) in African Americans with HF along with standard treatment; because of significant mortality benefit, the study was prematurely discontinued.

52. **c.** The benefit of long-term IV inotropic therapy may outweigh the increased mortality risk in refractory patients unable to be weaned from IV inotropic support. Because long-term IV positive inotropic therapy may cause an increased risk of death, such therapy is not regularly recommended. This risk, however, may be outweighed in patients who cannot be weaned from continuous support. Such patients with refractory HF may experience an improved quality of life because of the relative clinical stability afforded by the inotrope; therefore, IV positive inotropic therapy may be considered as a palliative measure in end-stage HF. The DIG (Digitalis Investigation Group) trial showed that digoxin's benefit in HF was the alleviation of symptoms and improvement in clinical status. These findings were associated with a decreased morbidity (fewer hospitalizations) but not mortality. Because digoxin has negligible effect on survival, it is recommended that digoxin be used in conjunction with diuretics, ACE inhibitors, and β-blockers to decrease the clinical symptoms of HF. Furthermore, little evidence supports the practice of dosing digoxin according to serum levels. This is because of the lack of data exhibiting a relationship between digoxin serum concentrations and therapeutic effect. In the RALES trial, spironolactone was shown to be associated with reduced mortality and morbidity. However, the patients who were included in this trial

were patients with class IV HF. Therefore, it would only be prudent to consider spironolactone in patients with recent or current severe HF symptoms. Efficacy and safety of spironolactone's use in patients with mild-to-moderate HF is yet to be determined.

53. d. No prophylaxis is recommended in this patient. The recommendations according to the 2007 Guidelines for Prevention of Infective Endocarditis no longer recommend prophylactic antibiotics prior to dental procedures for people with mitral valve prolapse, rheumatic heart disease, bicuspid valve disease, calcified aortic stenosis, or congenital heart conditions such as ventricular septal defect, atrial septal defect, and hypertrophic cardiomyopathy.

54. b. Ampicillin, 2 g IV every 4 hours for 4 to 6 weeks, plus gentamicin, 1 mg/kg IV every 8 hours for 4 to 6 weeks. Treatment of enterococcal endocarditis is complicated because of the high levels of resistance to penicillin, extended-spectrum penicillins, and vancomycin. However, penicillin, ampicillin, or vancomycin in combination with an aminoglycoside causes synergistic bactericidal effect on these organisms. Treatment with an aminoglycoside for the full 4 to 6 weeks at a synergistic dose (1 mg/kg IV every 8 hours) in addition to the penicillin agent or vancomycin is required.

SUGGESTED READINGS

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Aorta

Craig R. Asher • Gian M. Novaro

QUESTIONS

Case 1 (Questions 1 to 3)

A 78-year-old woman is referred to cardiology clinic for management of aortic regurgitation. The patient has no cardiac risk factors except mild hypertension (HTN) on monotherapy and has not previously undergone cardiac testing. A review of systems is notable for recent onset of headaches and myalgias.

Physical Examination

Blood pressure (BP)—138/78 mmHg in both arms; pulse—62 bpm.

Funduscopic examination reveals no changes consistent with hypertensive retinopathy. The heart examination is notable for a normal S_1 and increased intensity S_2 (A_2). An S_4 gallop, II/VI diastolic decrescendo murmur heard best at the right sternal border, and III/VI early-peaking systolic ejection murmur heard at the left sternal border are present. There is no systolic ejection click. The carotid pulse is of normal intensity and contour and the pulses in the upper and lower extremities are strong and equal.

Electrocardiogram (ECG) reveals sinus rhythm with nonspecific ST changes.

1. What is the most likely explanation for the patient's heart murmur?

   a. Bicuspid aortic valve with severe aortic regurgitation
   b. Bicuspid aortic valve with severe aortic stenosis and moderate aortic regurgitation
   c. Degenerative severe aortic valve stenosis and moderate aortic regurgitation
   d. Aortic dilatation with moderate aortic regurgitation and mild aortic stenosis

A transthoracic echocardiogram (TTE) is performed showing normal left ventricular

(LV) size and function with a trileaflet aortic valve. Aortic measurements are as follows: sinus of Valsalva—4.0 cm; sinotubular junction—4.4 cm; mid-ascending aorta —4.5 cm with moderate effacement of the sinotubular junction. Peak and mean aortic gradients are 22/13 mmHg with moderate (2+) aortic regurgitation. A small circumferential pericardial effusion is present. Laboratory tests reveal an erythrocyte sedimentation rate of 74.

2. What additional test would be most helpful in determining the etiology of the patient's aortic dilatation and aortic regurgitation?

   a. Coronary angiogram and aortography
   b. Magnetic resonance angiography (MRA) of the great vessels
   c. Computed tomographic angiography (CTA) of the ascending aorta
   d. Transesophageal echocardiography (TEE)

3. What is the most likely diagnosis to explain the patient's aortic dilatation and aortic regurgitation? See Figure 6.1.

   a. Takayasu arteritis
   b. Degenerative aortic disease
   c. Connective tissue disorder
   d. Giant cell arteritis

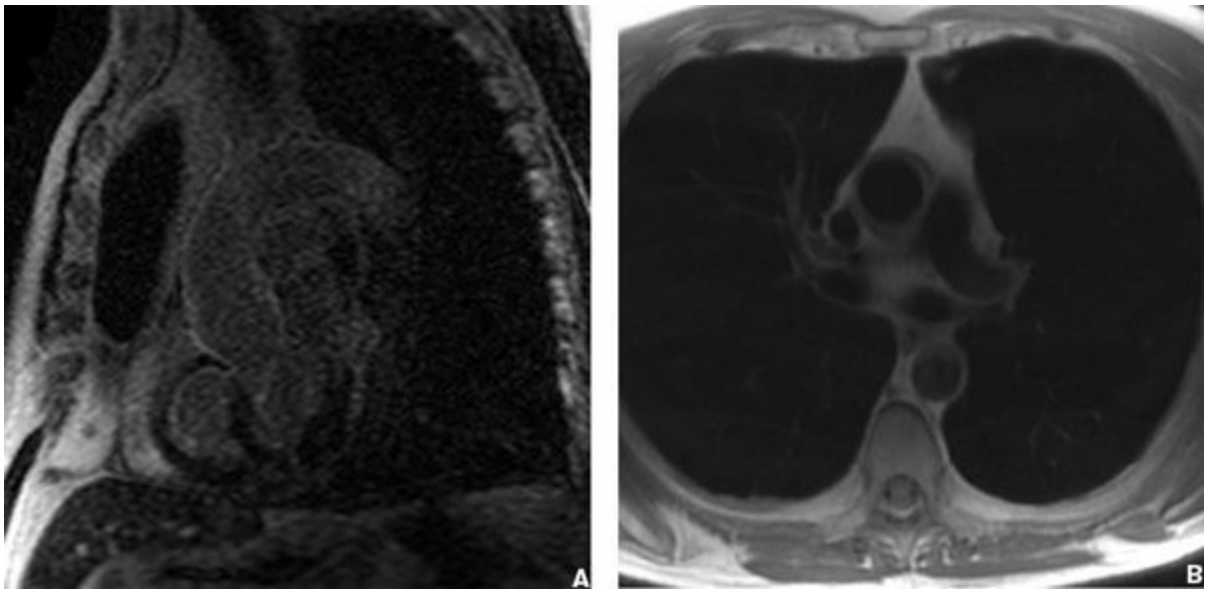

Figure 6.1

Case 2 (Questions 4 to 6)

An 18-year-old woman presents for her annual physical examination. She had a brother with Marfan syndrome who was 24 years old when he died suddenly. She is active and asymptomatic.

Physical Examination

5 feet 7 inches (170 cm) and 150 pounds (68 kg).
Arm span-to-height ratio = 1.07.
Head and neck examination is notable for a high-arched palate and a slit-lamp examination shows ectopia lentis. Musculoskeletal examination is notable for a pectus carinatum and positive wrist and thumb sign. Cardiac examination is notable for a mitral valve click and a soft murmur of mitral regurgitation.

4. What additional testing is needed to determine whether this young woman has Marfan syndrome?

   a. TTE
   b. Genetic testing
   c. CT angiogram of the aorta
   d. No additional testing

A TTE is performed that shows mitral valve prolapse with mild (1+) mitral regurgitation. The aortic root is dilated at 5.0 cm with effacement of the sinotubular junction and a mid-ascending aortic measurement of 3.6 cm. The aortic valve is trileaflet with no aortic regurgitation.

5. What is the most important recommendation to be made to this patient?

   a. Repeat the TTE in 6 months
   b. Initiate a β-blocker
   c. Avoid strenuous exertion, contact sports, and pregnancy
   d. Elective aortic replacement

The patient wishes to schedule surgery but prefers to wait 2 months until the end of the school year. Her father who is an internal medicine physician has read about the potential benefit of angiotensin receptor blockers (ARBs) for patients with aneurysms and asks your advice regarding treatment.

6. What is the postulated mechanism of action whereby ARBs reduce progression of aortic disease in Marfan syndrome?

   a. Reduction of BP through angiotensin II type 1 receptor blockade
   b. Complete blockade of the renin–angiotensin–aldosterone system
   c. Reduction in activity of transforming growth factor (TGF)-β
   d. Increase production of matrix metalloproteinases (MMPs)

Case 3 (Questions 7 and 8)

A 67-year-old man with long-standing HTN presents to the emergency room (ER) with sudden-onset chest pain described as ripping in quality, subsiding since its onset. He

underwent a cardiac catheterization 6 months previously that showed a 40% lesion in the mid-left anterior descending coronary artery. His medications include aspirin, gemfibrozil, and nifedipine.

Physical Examination

He appears diaphoretic. HR—110 bpm; BP—106/54 mmHg (right arm); 72/35 mmHg (left arm). Jugular venous pressure—12 cm H_2O. Heart sounds are soft and there is no audible systolic or diastolic murmur. Left radial and brachial pulses are weak.

ECG on presentation shows ST elevations in the inferior leads and low voltage.

Chest X-ray (CXR) shows cardiomegaly with a globular-shaped heart and interstitial edema.

7. Which of the following is the first diagnostic test that should be performed?

- **a.** Cardiac enzymes
- **b.** MRA of the aorta
- **c.** TTE
- **d.** Cardiac catheterization

A TTE was performed showing a pericardial effusion and signs of cardiac tamponade. A CT angiogram is also performed and shown in Figure 6.2.

8. What intervention should be performed next for the management of this patient?

- **a.** Cardiac catheterization
- **b.** Emergent aortic surgery
- **c.** Swan-Ganz catheterization
- **d.** Pericardiocentesis

Case 4 (Questions 9 and 10)

A 36-year-old man with a bicuspid aortic valve develops sudden onset of headache, mental status changes, and unequal pupils. He is rushed to an ER and a head CT scan is done that shows an intracranial bleed. BP on presentation is 158/78 mmHg.

Figure 6.2

Except for a history of HTN, he has no known medical problems and no history of drug abuse. A visit to his physician's office 1 week earlier revealed a BP of 120/75 mmHg on metoprolol and ramipril.

9. What is the most likely reason for the patient's intracranial bleed?

- **a.** Hypertensive crisis
- **b.** Aortic dissection
- **c.** Cerebral aneurysm rupture
- **d.** Mycotic aneurysm associated with endocarditis

10. What other structural abnormality is most commonly associated with coarctation of the aorta?

- **a.** Atrial septal defect
- **b.** Ventricular septal defect
- **c.** Pulmonary stenosis
- **d.** Mitral valve prolapse

Case 5 (Questions 11 and 12)

A 74-year-old man presents to the ER with upper back pain ongoing for 3 hours. The pain is described as sharp and severe occurring at rest. He has no associated symptoms of shortness of breath, chest pain, or presyncope. His past medical history is notable for

a coronary artery bypass graft (CABG) 2 years previously, HTN, and ongoing tobacco use. At the time of his CABG, he was noted to have a 4.4-cm ascending aortic aneurysm that was not repaired. His medications include aspirin, an angiotensin-converting enzyme inhibitor, and a β-blocker.

Physical Examination

BP—180/110 mmHg.
Pulse rate—90 bpm.
Lung and cardiac examinations are unremarkable and no cardiac murmur is heard. The abdomen is mildly tender with no bruit. Pulses are equal but diminished in the lower extremities.
ECG shows sinus rhythm with nonspecific ST changes and an old inferior myocardial infarction (MI).
Laboratory tests including cardiac enzymes, liver function tests, amylase, and lipase are normal.

11. What is the most appropriate diagnostic procedure to perform next?

a. TTE
b. TEE
c. CTA of the chest and abdomen
d. Aortography

A CT scan demonstrates an ascending aortic aneurysm of 4.8 cm and a descending thoracic aortic aneurysm of 6.0 cm but no evidence of dissection. There is no abdominal aortic aneurysm (AAA). The patient continues to have ongoing pain despite high doses of β-blockers, sodium nitroprusside, and opioid analgesics.
ECG and cardiac enzymes remain normal.
D-dimer level is >500 ng/mL.

12. What is the most appropriate next decision for management?

a. Cardiac catheterization
b. MRA of the chest/aorta
c. TEE
d. Intensify medical therapy

Case 6 (Question 13)

A 62-year-old man presents for a routine annual examination. He has a history of HTN that is managed with monotherapy. He is active and has no symptoms.

Physical Examination

BP—162/88 mmHg in both arms. Pulse rate—70 bpm. Heart and lung examination is

unremarkable. Abdominal examination reveals a pulsatile mass.
ECG shows sinus rhythm and a complete right bundle branch block.
Abdominal ultrasound shows an infrarenal AAA of 4.2 cm.

13. What is the most appropriate management step?

a. Initiate a β-blocker and repeat ultrasound in 6 months
b. Initiate a β-blocker and repeat ultrasound in 3 months
c. No medical therapy and repeat ultrasound in 1 year
d. No medical therapy and repeat ultrasound in 2 years

Case 7 (Questions 14 and 15)

A 76-year-old man presents to the ER with severe sharp chest pain that began 2 hours previously. He has a history of HTN and had CABG 3 years ago after an MI. He continues to smoke. The CABG was performed off-pump because of severe atheroma in the ascending aorta seen by intraoperative TEE. The patient's pain has not subsided with the initiation of IV heparin, nitroglycerin, and β-blockers. The pain is different in character from the pain before his MI.

Physical Examination

BP—160/94 mmHg.
Pulse—76 bpm.
Heart and lung sounds are normal. Pulses are diminished in the lower extremities.
ECG shows a left bundle branch block.
Cardiac enzymes are normal × 1.

Despite severe atheroma in the aorta, the physician taking care of the patient is not convinced that he does not have an acute coronary syndrome and performs a cardiac catheterization. It shows that the grafts are patent and there is no culprit lesion in the native vessels. He then decides to perform aortography and a focal outpouching is seen in the aortic wall in the distal ascending aorta (Fig. 6.3A). Contrast dye collects slowly in this region. The patient's chest pain is intensifying. A TEE is also performed (Fig. 6.3B).

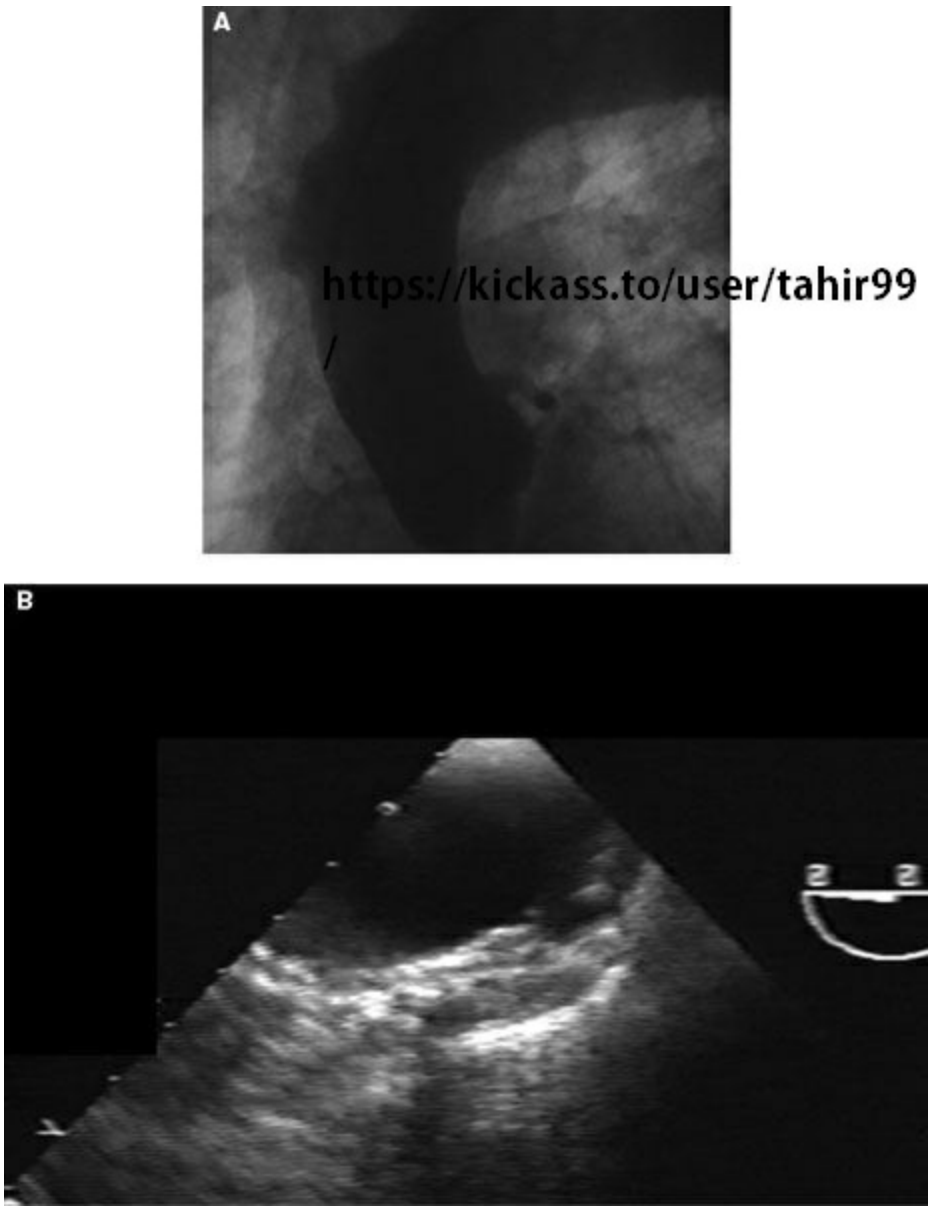

Figure 6.3

14. What is the correct diagnosis?

a. Aortic dissection
b. Aortic aneurysm
c. Intramural hematoma
d. Penetrating aortic ulcer

15. What is the most appropriate next management step to take?

a. Medical management with β-blockers and afterload reduction
b. Transfer to the operating room immediately for replacement of the ascending aorta
c. Medical management and obtain a CT chest/aorta

d. Medical management and obtain an MRA of the aorta

Case 8 (Questions 16 and 17)

A 45-year-old woman presents with discomfort in her left leg with walking, dizziness, headaches, and a cold right hand. She has no chest pain or shortness of breath. There is no significant past medical history and she does not smoke.

Physical Examination

BP—170/82 mmHg (left arm) and 140/68 mmHg (right arm). Lung sounds are clear. Cardiac examination is notable for a normal S_1 and S_2 and II/VI diastolic decrescendo murmur at the left sternal border. The right brachial pulse is diminished and lower extremity pulses are diminished. A bruit is heard over the left carotid artery and right subclavian artery.

16. What test would be most useful for diagnosing the patient's condition?

a. TEE
b. Carotid duplex ultrasound
c. Magnetic resonance imaging (MRI) of the head
d. Angiography

17. What is the most likely diagnosis?

a. Behçet disease
b. Relapsing polychondritis
c. Giant cell arteritis
d. Takayasu arteritis

Case 9 (Questions 18 to 21)

A 21-year-old woman with Turner syndrome has a history of surgical repair for periductal coarctation of the aorta at age 4 years. Her presentation was for HTN and heart failure, both of which resolved after the procedure. She was lost to follow-up after childhood and recently reestablished with a cardiologist. She has been experiencing dyspnea and claudication in the past year.

Physical Examination

BP—188/94 mmHg (left arm); 192/100 mmHg (right arm); 100/60 mmHg (right leg). Pulses are notable for normal upper extremity and reduced lower extremity pulses with a brachial–femoral delay. Cardiac examination is notable for normal S_1 and paradoxically split S_2 with an ejection click and S_4 gallop. A continuous murmur III/VI in intensity is heard under the left scapula.

18. Which of the following statements is correct regarding the echocardiographic image

from this patient obtained from the suprasternal notch (Fig. 6.4)?

a. Pressure gradients are usually underestimated using the simplified Bernoulli equation
b. Pressure gradients are usually accurate using the simplified Bernoulli equation
c. Pressure gradients shown are not consistent with severe coarctation
d. Presence of systolic and diastolic flow is consistent with severe coarctation

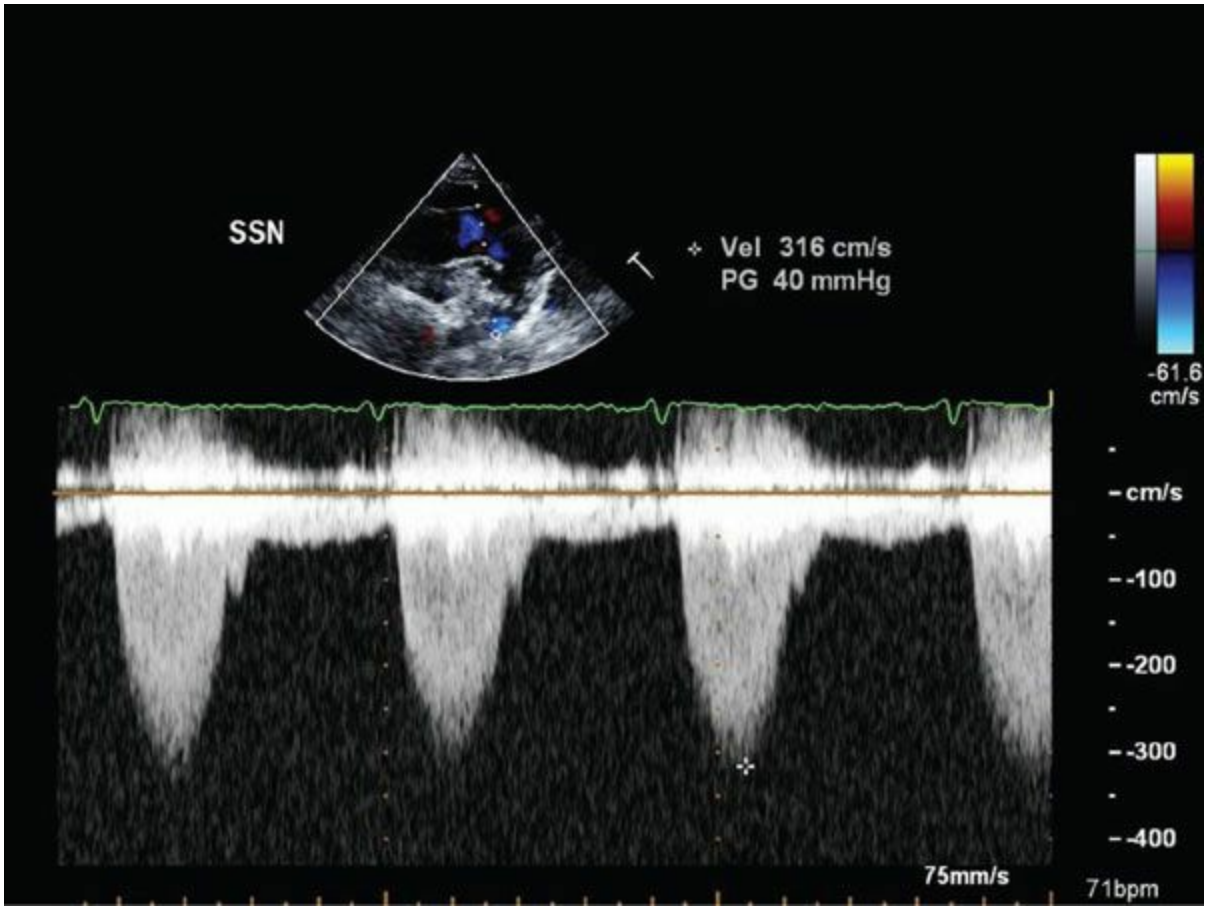

Figure 6.4

19. Which of the following statements is correct regarding the echocardiographic image from this patient obtained from the abdominal aorta (Fig. 6.5)?

a. The hallmark of coarctation is the presence of low systolic velocities
b. The presence of coarctation cannot be determined without knowing the timing of the pulse delay relative to aortic ejection
c. The hallmark of coarctation is the presence of persistent antegrade flow in diastole
d. The presence of coarctation cannot be determined without additional Doppler images proximal to the coarctation site

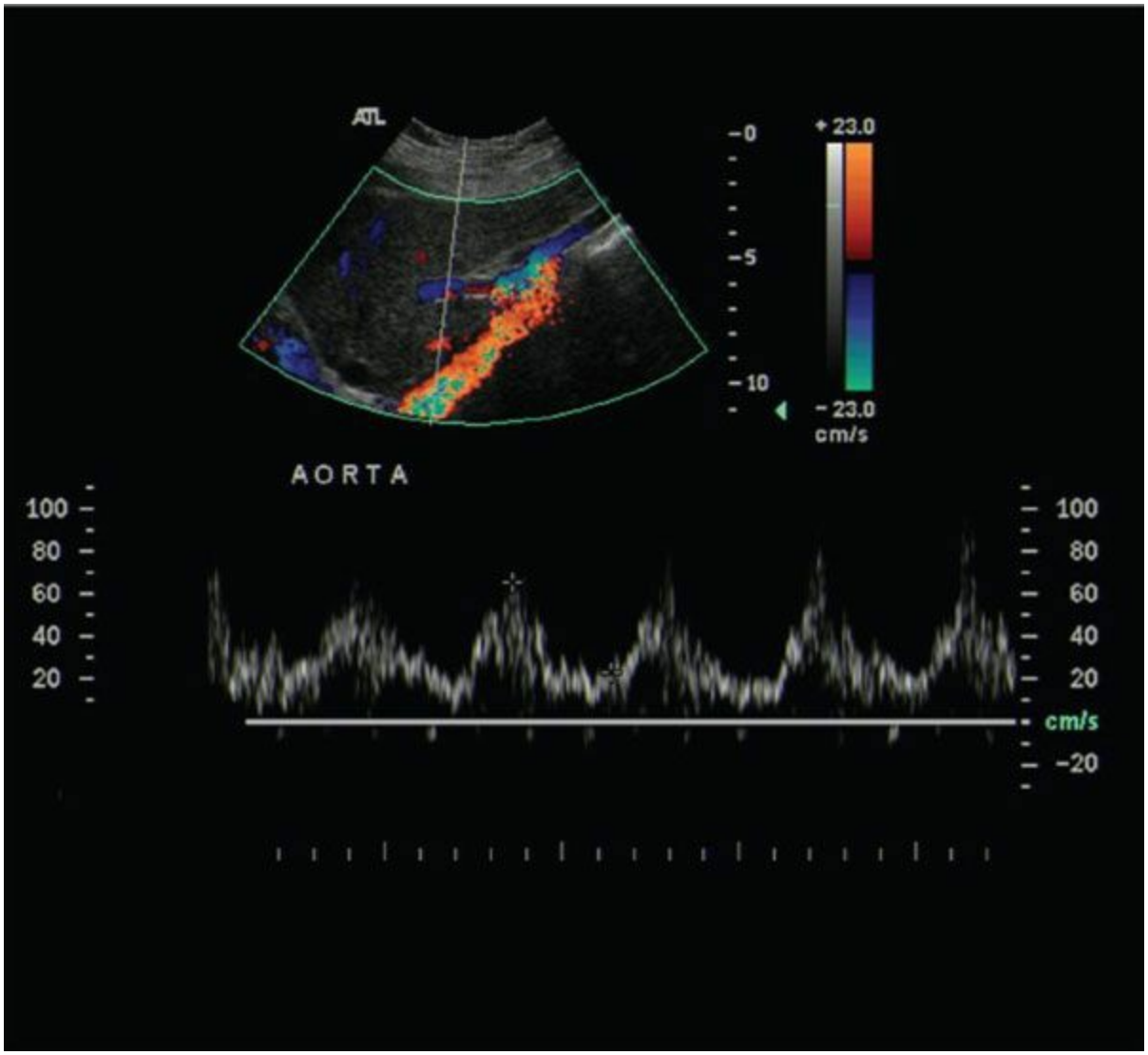

Figure 6.5

20. Which of the following recommendations is most appropriate regarding reintervention in this patient (Fig. 6.6)?

a. Surgery is generally recommended
b. No intervention should be performed until maximal medical therapy is attempted
c. Balloon angioplasty with or without stents is generally recommended
d. There is no consensus and either surgery or balloon aortoplasty (with or without stenting) are equal options

Figure 6.6

21. Which of the following is an indication for aortic coarctation intervention?

- **a.** Symptomatic patient with dyspnea at rest, regardless of the coarctation gradient
- **b.** Asymptomatic patient with normal BP at rest and with exercise and a peak-to-peak gradient across the coarctation site of 19 mmHg
- **c.** Asymptomatic patient with a peak-to-peak gradient across the coarctation site of 15 mmHg with extensive collaterals
- **d.** Symptomatic patient with a bicuspid aortic valve and severe aortic regurgitation undergoing aortic valve replacement and a peak-to-peak gradient across the coarctation of 15 mmHg

Case 10 (Question 22)

A 30-year-old man is referred to cardiology clinic for evaluation of a heart murmur. He had an uneventful childhood except that on four separate occasions he fractured his arms or legs requiring multiple surgical repairs. He has no family history of heart disease or congenital abnormalities.

Physical Examination

Normal stature. Vital signs are normal. Arm span-to-height ratio is normal.

No pectus deformity, scoliosis, wrist sign. Cardiac examination is notable for a decreased S_1 and normal S_2 intensity with a III/VI diastolic decrescendo murmur and no gallops. Pulses are normal and the extremities are hypermobile. No abnormality of the skin is present.

TTE shows a dilated sinus of Valsalva of 4.7 cm with severe aortic regurgitation. Left ventricular ejection fraction (LVEF) = 65% with LV dimensions of (diastole 6.4 cm; systole 5.1 cm).

22. What is the most likely diagnosis for this patient?

- **a.** Ehlers-Danlos syndrome
- **b.** Marfan syndrome
- **c.** Osteogenesis imperfecta
- **d.** Homocystinuria

Case 11 (Questions 23 and 24)

A 65-year-old man presents to the ER with severe, tearing lower back pain that started while he was shoveling snow. He has a history of poorly controlled HTN and coronary artery disease with a stent to the left anterior descending coronary artery 4 months previously. Other medical problems include severe O_2-dependent chronic obstructive pulmonary disease.

Physical Examination

BP—190/110 mmHg.

Pulse—90 bpm.

Cardiac examination is notable for a normal S_1 and S_2 with an S_4 gallop and II/VI early-peaking systolic ejection murmur at the left sternal border.

ECG shows sinus rhythm and no ST changes.

An initial set of cardiac enzymes is normal.

23. What is the most appropriate initial medical therapy?

- **a.** Intravenous metoprolol
- **b.** Intravenous diltiazem
- **c.** Intravenous enalapril
- **d.** Intravenous nitroprusside

A CT angiogram is performed (Fig. 6.7).

24. Which of the following statements regarding the appearance of this form of acute aortic syndrome is most accurate?

- **a.** There is low attenuation of the aortic wall

b. It is not continuous
c. Intimal calcium is nondisplaced
d. It is circumferential or crescentic

Case 12 (Questions 25 to 28)

A 44-year-old man is admitted to the hospital because of a left hemisphere stroke with right arm and leg weakness. He has no history of HTN or smoking, although his total cholesterol level is 334. ECG shows sinus rhythm. Carotid duplex ultrasound shows less than 20% obstruction bilaterally. Head CT demonstrates a recent stroke in the left cortex in the region of the middle cerebral artery. A TTE shows normal valves, chamber sizes, and LV function.

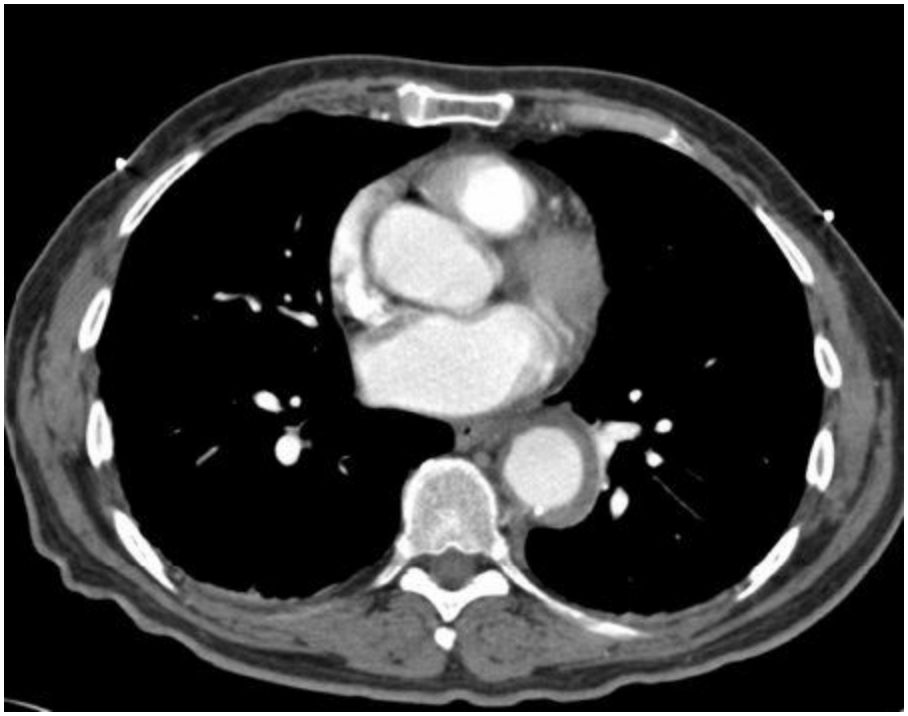

Figure 6.7

25. Which test is most likely to reveal the etiology of the patient's stroke?

a. TTE with bubble study
b. 30-Day event recorder
c. MRA of the head and neck
d. TEE

26. Which of the following medical regimens is most appropriate for a patient with a cardioembolic stroke and the following finding seen on TEE (Fig. 6.8)?

a. Statin and aspirin
b. Statin and warfarin

c. Aspirin and dipyridamole
d. Statin, antiplatelet agent, and warfarin

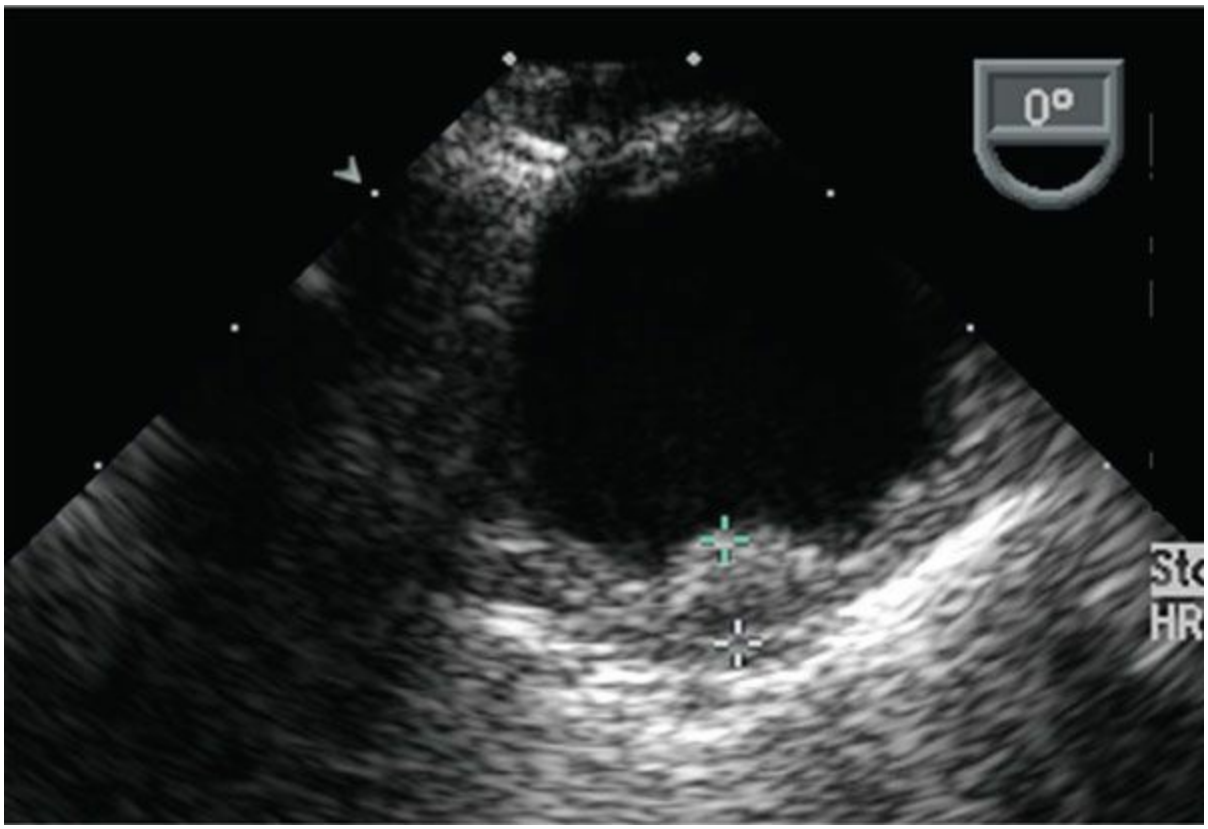

Figure 6.8

27. Which of the following atheromatous plaques is least likely to be associated with a cardioembolic event?

a. 3-mm plaque with severe calcification and no mobile components
b. 4-mm plaque with small mobile components and no calcification
c. 5-mm plaque with multiple mobile components, no calcification, and a small ulceration
d. 2-mm plaque with calcification, a small mobile component, and large ulceration

28. Which statement is correct regarding performing CABG in a similar patient with aortic arch atheroma and focal areas of atheroma in the ascending aorta?

a. Palpation of the aorta by the surgeon for calcified plaque correlates with findings of atheroma by TEE.
b. Alternative sites for cross-clamping or cannulation may reduce stroke risk.
c. Aortic arch endarterectomy is recommended.
d. Replacement of the ascending aorta is recommended because of increased likelihood of stroke.

Case 13 (Question 29)

A 21-year-old man is referred to a cardiology clinic for exertional dyspnea. As a child he was evaluated for a heart murmur by a pediatric cardiologist.

Physical Examination

BP—140/84 mmHg (left arm); 120/68 (right arm).

Cardiac examination is notable for a normal S_1 and increased intensity S_2/A_2, absence of an ejection click, and III/VI systolic ejection murmur heard best in the first right intercostal space radiating to the neck and increases with expiration. There is a thrill in the suprasternal notch. The left carotid and brachial pulses are diminished relative to the right carotid and brachial pulses.

29. What diagnosis best explains the patient's disorder?

a. Patent ductus arteriosus
b. Coarctation of the aorta
c. Supravalvular pulmonary stenosis
d. Williams syndrome

Case 14 (Questions 30 to 32)

A 30-year-old man with a history of congenital heart disease is referred to you because of symptoms of dysphagia and an abnormal CXR. As a child he was told that his CXR was abnormal because of an "aortic anomaly" and that it was benign.

Physical Examination

Vital signs are normal.

Cardiac examination is notable for normal intensity S_1 and S_2 heart sounds. An ejection click is heard in the right upper sternal border (RUSB) though no murmur is audible. Upper and lower extremity pulses are equal.

30. The CXR (Fig. 6.9) shows what abnormality?

a. Bovine aortic arch
b. Cervical aortic arch
c. Right-sided aortic arch
d. Aberrant right subclavian artery

Figure 6.9

31. What is the most common congenital defect associated with the aortic anomaly seen in Question 30?

- **a.** Tetralogy of Fallot
- **b.** Truncus arteriosus
- **c.** Atrial septal defect
- **d.** Transposition of the great vessels

32. The patient's dysphagia is likely caused by what abnormality associated with his aortic anomaly?

- **a.** Aberrant left subclavian artery and diverticulum of Kommerell
- **b.** Coarctation of the aorta
- **c.** Isolated aberrant right subclavian artery
- **d.** Interrupted aortic arch

Case 15 (Questions 33 and 34)

A 30-year-old man presents for follow-up after undergoing a surgical coarctation repair at age 9. He has no records and is uncertain of the type of repair. He has not had any testing done in the past 10 years. He has used antibiotic prophylaxis for dental

procedures. He takes no other medications. He feels well, is active, and has no complaints.

Physical Examination

BP—138/72 mmHg (right arm); 126/70 mmHg (left arm); pulse—80 bpm, regular.

Heart sounds are of normal intensity. An aortic ejection click is present in the RUSB. There is a brief, short duration systolic ejection murmur in the RUSB without a diastolic murmur. Upper and lower extremity pulses are equal and there is no radial or brachial to femoral delay.

33. Which test would be least appropriate for this patient?

a. TTE
b. CTA of the chest/aorta
c. Exercise treadmill stress test
d. 24-Hour Holter monitoring

34. How often should the coarctation repair site be evaluated by chest imaging in this patient (CTA or MRA)?

a. Generally every 5 years
b. Generally every 10 years
c. Generally every 2 years
d. Not recommended unless there is specific concern

Case 16 (Questions 35 and 36)

A 38-year-old man is referred for a cardiac surgical evaluation for bicuspid aortic regurgitation. He has a long-standing aortic valve disorder for 10 years. He is fully active with no limitations. He plays tennis on a regular basis.

Physical Examination

BP—120/40 mmHg; pulse—68 bpm. Cardiac examination is notable for a reduced intensity S_1 and increased intensity S_2/A_2. Three murmurs are present, a mid-peaking crescendo/decrescendo systolic ejection murmur beginning after an ejection click, a long-duration high-pitched diastolic decrescendo murmur along the left sternal border and a low-pitched mid-diastolic rumble heard at the apex.

Stress echocardiography is performed and shows a bicuspid aortic valve with right–left fusion. There is calcification of the raphe between the conjoined leaflets. Peak/mean gradients = 30/15 mmHg. Holodiastolic flow reversal is present in the descending aorta. The aortic root measures 4.0 cm and the mid-ascending aorta is 3.9 cm with no sinotubular junction effacement. LV cavity measurements are as follows: LVIDd—5.8 cm; LVIDs—3.9 cm; LVEF—58%. There is reduction in LV cavity size with 13

metabolic equivalents of exercise and no symptoms.

35. What is the most appropriate surgical recommendation?

- **a.** Elective aortic valve surgery and ascending aortic grafting
- **b.** Elective aortic valve surgery without ascending aortic grafting
- **c.** Medical therapy/observation and add a β-blocker
- **d.** Observation only

Six months later the patient has developed dyspnea with moderate exertion and a significant reduction in exercise tolerance. Repeat echocardiogram shows similar LV cavity dimensions and LVEF calculated at 57%. Aortic root dimension is 4.0 cm and the mid-ascending aorta is 4.6 cm.

36. What is the appropriate recommendation at this time?

- **a.** Aortic valve replacement
- **b.** Aortic valve repair
- **c.** Aortic valve replacement and aortic graft
- **d.** Stress echocardiogram to confirm change in exercise tolerance

Case 17 (Questions 37 to 40)

A 66-year-old man is seen by his internist for an annual evaluation. Past medical history is notable for HTN and tobacco use. His BP is 136/80 mmHg on monotherapy. Cardiac and abdominal examinations are unremarkable.

He has a friend who was detected to have an AAA on routine screening and asks his physician whether it is indicated for him to be screened.

37. Which of the following statements regarding AAA screening is correct?

- **a.** Consensus guidelines recommend routine screening of all women >60 years of age or older
- **b.** Screening men >65 years old is associated with a reduction in aneurysm-related deaths compared with unscreened males of similar ages
- **c.** Sensitivity and specificity of ultrasound screening in appropriate patients in accredited laboratories are >70%, respectively
- **d.** After a negative screening examination in a man aged 65 years or older, a repeat examination should be performed 5 years later

A screening abdominal ultrasound is performed in this patient and shows an infrarenal AAA of 5.5 cm. The patient is advised to undergo repair though wishes to consider the option of an endovascular stent graft (EVAR) rather than an open repair.

38. Which of the following statements is true regarding recommendations for AAA

repair?

a. Repair is indicated for any AAA > 5.0 cm
b. Size cutoffs for AAA repair should be based on age, weight, and height
c. Inflammatory or infectious aneurysms should be repaired at any size
d. Women should undergo repair only for AAA > 5.5 cm

39. Which statement regarding EVAR is correct?

a. Open repair and EVAR are associated with similar 30-day mortality
b. Open repair and EVAR are associated with similar long-term mortality
c. EVAR is associated with decreased late complications compared with open repair
d. EVAR is associated with less repeat interventions compared with open repair

40. Which of the following statements regarding endoleaks is correct?

a. They occur with a similar prevalence with EVAR and open procedures
b. Endoleaks may occur as a result of retrograde flow of small arterial branches back into the aneurysm sac
c. They are rare and generally do not lead to repeat procedures
d. Type IV endoleaks (leakage through graft material) are the most common

Case 18 (Questions 41 and 42)

A 38-year-old woman is admitted to the internal medicine service for chest pain. She is experiencing sharp chest pain unrelated to exertion and dyspnea for 2 days. Her family history is unknown since she was adopted. Past medical history is not well defined but notable for an uncharacterized connective tissue disorder. She was told at a younger age to avoid pregnancy.

Admission ECG and cardiac enzymes are negative. She is unable to exercise because of her symptoms and therefore is sent for an adenosine nuclear stress test. The test shows mild anteroseptal ischemia with no ECG changes.

The cardiology service is consulted for a cardiac catheterization.

Physical Examination

She is thin and in mild distress. Vital signs are normal. General examination and skin examination are notable for a translucent appearance to the skin, joint hypermobility, hyperextensible skin, and bruises. There are no findings suggestive of Marfan syndrome. Cardiac examination reveals a normal S_1 and S_2 and a soft diastolic decrescendo murmur at the right sternal border.

41. What do you recommend?

a. Coronary angiography
b. No further testing
c. Cardiac MRI to assess for coronary anomalies
d. CTA of the chest and aorta

42. What should be done to more definitively characterize the patient's condition?

a. Diagnosis based on clinical criteria
b. DNA sequencing
c. Blood analysis for chromosomal abnormalities
d. Clinical laboratory markers of inflammation

Case 19 (Questions 43 to 45)

A 24-year-old man is referred to cardiology clinic for consultation regarding an aortic aneurysm. He has a family history of ascending aortic aneurysms. Echocardiography showed a trileaflet aortic valve and mid-ascending aortic aneurysm of 4.4 cm that is confirmed by CTA.

Physical Examination

BP—120/64 mmHg; pulse—70 bpm. Head and neck examination is notable for widely set eyes. The oropharynx is shown (Fig. 6.10). Cardiac and skin examinations are normal.

Figure 6.10

43. What is the patient's diagnosis?

a. Cogan syndrome
b. Loeys-Dietz syndrome

c. Ormond disease
d. Behçet disease

44. What is the gene defect associated with this condition?

a. COL3A1
b. TGFBR1 or TGFBR2
c. ACTA2
d. FBN1

45. What further recommendation is correct regarding management of this patient?

a. Start a β-blocker
b. Start an ARB
c. Recommend aortic repair
d. Observation only

Case 20 (Question 46)

A 40-year-old man is transferred via air ambulance to a level 1 trauma center after a motor vehicle accident (MVA). He had a head-to-head collision with another car traveling at a high speed and was propelled forward but was partially restrained by his seat belt and deployed air bags.

Physical Examination

BP—162/62 mmHg (right arm); HR—110 bpm. General condition notable for intubated, sedated man with a cervical collar. Cardiac examination is notable for normal heart sounds and a soft systolic murmur. Lower extremities are mottled and pulseless.

ECG shows sinus tachycardia with no ST changes.

CXR shows no broken ribs bilaterally, a widened mediastinum, and left pleural effusion.

46. Which of the following diagnoses are most likely for this patient?

a. Complete aortic transection
b. Ascending aortic dissection and cardiac tamponade
c. Descending aortic partial transection with pseudoaneurysm
d. Descending aortic intramural hematoma/dissection

Case 20 (Questions 47 and 48)

A 79-year-old man with HTN underwent a routine CXR and is found to have a thoracic aneurysm. He is asymptomatic with well-controlled BP on a β-blocker. A CT angiogram of the chest is performed showing a descending thoracic aortic aneurysm of

5.4 cm distal to the left subclavian artery with a chronic dissection. The aneurysmal segment does not extend into the abdomen. The ascending aorta is 4.5 cm in the mid-portion and 4.0 cm in the mid-arch. The patient has no other comorbid conditions.

47. What recommendation is most appropriate for this patient based on current guidelines?

- **a.** Open repair is recommended
- **b.** TEVAR (thoracic endovascular aortic repair) is recommended
- **c.** Medical therapy is recommended
- **d.** An elephant trunk procedure is recommended

48. Which statement is correct comparing TEVAR with open repair for thoracic aortic aneurysms?

- **a.** TEVAR is associated with higher rates of hospital mortality
- **b.** TEVAR is associated with higher risks of paraplegia
- **c.** TEVAR is associated with a 30-day risk of endoleaks of 10%
- **d.** TEVAR is associated with lower long-term mortality in randomized trials

Case 21 (Questions 49 and 50)

A 45-year-old woman with a history of fibromuscular dysplasia presents to the ER with an acute ST-elevation inferior MI. She is taken immediately to the cardiac catheterization laboratory for primary percutaneous intervention of the right coronary artery (RCA). The first injection of the RCA shows a dissection extending from the ostium to the posterior descending artery. A subsequent aortogram after stenting of the RCA is performed (Fig. 6.11).

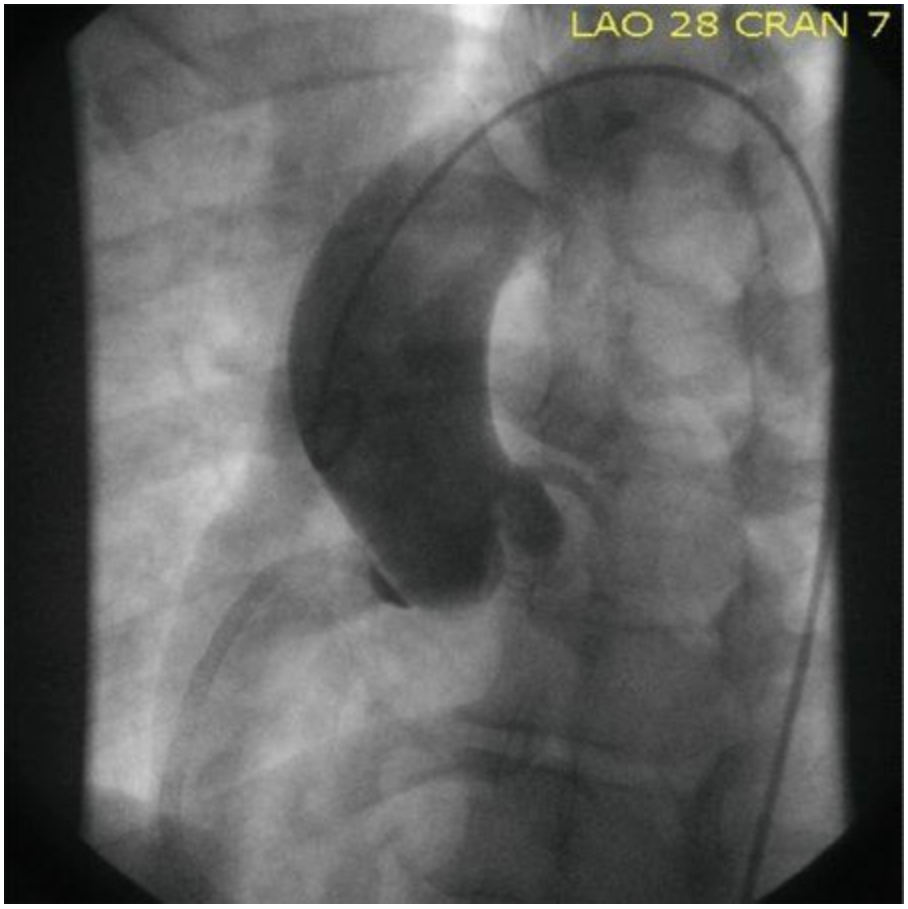

Figure 6.11

49. What does the aortogram show?

- **a.** Aortic root aneurysm
- **b.** Aortic root pseudoaneurysm
- **c.** Anomalous RCA from the left cusp
- **d.** Aortic root localized dissection

50. What further evaluation or management do you recommend for this patient?

- **a.** Observation and medical therapy
- **b.** Open heart surgery
- **c.** Intravascular ultrasound of the RCA
- **d.** TEE

ANSWERS

1. **d.** Aortic dilatation with moderate aortic regurgitation and mild aortic stenosis. A bicuspid aortic valve is not likely in a 78-year-old with an initial presentation of aortic valve disease. An aortic ejection click is often present in patients with

bicuspid aortic valve disease when the valve is still pliable and is not heard in this patient. Furthermore, the examination is not consistent with severe aortic regurgitation because the diastolic BP is normal (not reduced), the S_1 sound is normal in intensity (not reduced as a result of premature closure of the mitral valve), and the carotid pulsations are normal (not bisferiens). The examination is not consistent with severe aortic stenosis because the murmur is early peaking and S_2 (A_2) is audible and not reduced in intensity. The intensity of a systolic ejection murmur is related in part to the stroke volume and not a good single indicator of severity of stenosis. Therefore, the most likely explanation for the heart murmur is aortic dilatation with nonsevere aortic regurgitation and stenosis. Of note, aortic regurgitant murmurs originating from aortic abnormalities are generally heard best along the right sternal border and those originating from valvular disease heard best along the left sternal border.

2. **b.** Magnetic resonance angiography (MRA) of the great vessels. The presence of a pericardial effusion and an elevated erythrocyte sedimentation rate in a patient with aortic dilatation suggests an inflammatory etiology. Etiologies of aortic aneurysms are listed in Table 6.1. Inflammatory aortitis includes systemic diseases and primary large-vessel vasculitis. Numerous systemic diseases may involve the aorta, including systemic lupus erythematosus, rheumatoid and psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis, systemic sclerosis, relapsing polychondritis, Behçet syndrome, and Reiter syndrome. Primary vascular disorders include Takayasu and giant cell arteritis. MRA of the aorta may distinguish characteristic thickening and tissue edema that are diagnostic of aortitis.

3. **d.** Giant cell arteritis. The presence of systemic symptoms including headaches and myalgias with an elevated sedimentation rate in an elderly woman is suggestive of temporal arteritis. Temporal arteritis affects women twice as often as it does men and is most commonly seen after age 55 years. Temporal artery tenderness may be present with the potential for blindness to occur. Biopsy of the temporal arteries is diagnostic. Associated giant cell arteritis with involvement of the aorta and branch vessels with aneurysm formation may occur. Diagnostic criteria are sensitive and specific for giant cell arteritis if at least three of the following findings are present: (a) >50 years of age, (b) recent onset of localized headaches, (c) temporal artery tenderness or pulse attenuation, (d) erythrocyte sedimentation rate >50 mm/h, and (e) arterial biopsy showing necrotizing vasculitis.

   The MRA of this patient shows features of vessel thickening of the ascending aorta and arch with “edema”-weighted characteristics and mural enhancement suggestive of an inflammatory aortitis and consistent with giant cell aortitis. Corticosteroids therapy can be used to reduce inflammation seen with aortitis with

guidance from serial MRA imaging. Cardiac MRI. Sagittal delayed enhancement (phase-sensitive inversion recovery) image (**A**) and axial black-blood (double IR) (**B**) images demonstrating diffuse mural enhancement (**A**) and thickening of the ascending aorta and arch (**B**) consistent with an inflammatory arteritis. This patient has giant cell arteritis of the aorta (see Figure 6.1).

TABLE 6-1 Etiologies of Aortic Aneurysms

- Degenerative (HTN, arteriosclerosis, age related)
- Systemic connective tissue disorders
- Trauma (deceleration injury, dissection)
- Infectious diseases (syphilitic, mycotic)
- Primary vasculitis (Takayasu and giant cell aortitis, postoperative aortitis)
- Genetic (Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos type IV, familial thoracic aneurysm and dissection syndrome/FTAAD, Turner and Noonan syndrome)
- Congenital (unicuspid, bicuspid aortic valve, coarctation)
- Miscellaneous conditions (pregnancy, polycystic kidney disease, idiopathic, cocaine, steroids)

HTN, hypertension; FTAAD, familial thoracic aortic aneurysm disease.

4. **d.** No additional testing. The revised Ghent criteria are based primarily on clinical criteria although genetic testing for the FBN1 mutation can aid in diagnosis. There are criteria for individuals with and without a family history of Marfan syndrome (see Table 6.2). The patient presented has ectopia lentis and a family history of Marfan syndrome. Therefore, no additional information is required to make a diagnosis. She does additionally have systemic criteria that are consistent with the diagnosis, including pectus carinatum, wrist and thumb sign, high-arched palate, and mitral valve prolapse. An increased arm span-to-height ratio is no longer considered a diagnostic criterion for Marfan syndrome.

5. **d.** Elective aortic replacement. The timing of surgery for patients with ascending aortic aneurysms caused by Marfan syndrome is addressed in the 2010 guidelines for thoracic aortic diseases. Surgery is recommended for asymptomatic patients with Marfan syndrome or other genetic etiologies for thoracic ascending aortic aneurysms between 4.0 and 5.0 cm (class I) or when the ratio of the maximal ascending aortic or aortic root area ($\pi \times \text{radius}^2$) in cm^2 divided by the patient's

height in meters exceeds 10 (class IIa). In this patient, the calculation would be as follows: ($\pi \times 2.5^2 = 3.14 \times 6.25 = 19.6$ cm^2/1.70 m = 11.5), well above the 10:1 ratio. For women anticipating pregnancy, elective surgery should be performed when the ascending aortic dimension is >4.0 cm. Additional factors of importance include rate of change of aortic size >0.5 cm/year, presence and severity of aortic regurgitation, family history of dissection or sudden cardiac death, and the extent of aortic involvement. See Table 6.3 for timing of surgery in aortic diseases. An open-label study of adult patients with aortic dilatation and Marfan syndrome who were randomized to propranolol or no treatment showed less aortic dilatation and aortic complications among patients on propranolol. Therefore, β-blockers should be advised for this patient although this is not the most important recommendation.

TABLE 6-2 Revised 2010 Ghent Criteria for Marfan Syndrome

In the absence of family history or findings consistent with other syndromes—the following criteria are sufficient for the diagnosis of Marfan syndrome:

1. Aortic root dilatation or dissection and ectopia lentis
2. Aortic root dilatation or dissection and FBN1 mutation
3. Aortic root dilatation or dissection and systemic score ≥7 points
4. Ectopia lentis and FBN1 mutation

In the presence of family history—any of the following criteria are sufficient for the diagnosis of Marfan syndrome:

1. Ectopia lentis
2. Systemic score ≥7 points
3. Aortic root dilatation

Systemic score:

3 points = wrist and thumb sign

2 points = pectus carinatum deformity, hindfoot deformity, spontaneous pneumothorax, dural ectasia, protucio acetabulae

1 point = wrist or thumb sign, pectus excavatum or chest asymmetry, plain flat foot, scoliosis or thoracolumbar kyphosis, reduced elbow extension, three of five facial features, skin striae, severe myopia, mitral valve prolapse

TABLE 6-3 Timing of Surgery for Thoracic Aortic Aneurysms

Aortic Root or Ascending Aorta	Size
Degenerative etiology	≥5.5 cm or >0.5 cm growth/yr
Chronic aortic dissection	≥5.5 cm
Genetic etiology[a]	4.0–5.0 cm, >10:1 ratio[b] or >0.5 cm growth/yr
Bicuspid aortic valve	4.0–5.0 cm, >10:1 ratio[b] or >0.5 cm growth/yr
	>5.5 cm[c]
	>5.0 cm[c] (and ≥ 0.5 cm growth/yr or FH dissection
Loeys-Dietz syndrome	≥4.4 cm
Marfan syndrome (anticipating pregnancy)	>4.0 cm
Aortic valve repair or replacement (bicuspid valve or genetic etiology)	>4.5 cm
Aortic Arch	
Low risk	>5.5 cm
Descending Aorta	
Low risk	>5.5 cm
High risk (limited endovascular options)	>6.0 cm
Abdominal Aorta	
All patients	>5.5 cm
Women and smaller men	>5.0 cm

[a]See Table 6.1 for genetic etiologies.
[b]Ratio of maximal aortic root or ascending aortic area (πr^2) in cm^2 divided by the patient's height in meters.
[c]2014 American Heart Association/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease
FH = family history

6. **C.** Reduction in activity of transforming growth factor (TGF)-β. The ARB losartan has been associated with a reduction in the rate of aortic dilatation and aneurysm growth in both experimental mouse studies and recently an open-label randomized trial of Marfan syndrome patients (COMPARE trial). A larger prospective randomized trial comparing atenolol versus losartan sponsored by the NIH is in progress. The postulated mechanism of action is independent of BP lowering. Because of defective production in fibrillin due to the FBN1 mutation, there is overexpression of TGF-β activity. TGF-β activity leads to an increase in destructive MMPs, which cause aortic wall weakening. Losartan appears to block the overproduction of TGF-β and MMPs so that aortic wall integrity is maintained.

7. **C.** TTE. A TTE should be performed immediately in this patient since the clinical findings are highly suggestive of a proximal ascending aortic dissection (character

of chest pain, differential BPs, and weak pulses) and cardiac tamponade (tachycardia, elevated jugular venous pressure, soft heart sounds, and globular-shaped heart on CXR with interstitial edema). Cardiac enzymes may determine the presence of myocardial injury but not reveal the cause. An acute inferior MI is likely due to the aortic dissection involving the origin of the RCA and not due to occlusive coronary artery disease.

The advantages and disadvantages of CTA, MRA, and TEE for the diagnosis of aortic dissection have been reviewed in detail. Each of these tests has high diagnostic accuracy for diagnosing aortic dissection. The test of choice for a given patient should be determined based on the relative expertise of each institution, the rapid availability of the test and its interpretation, and the specific individual circumstances of a patient. Given the likelihood of an aortic dissection and the possibility of cardiac tamponade in this patient, a TTE or a TEE is best suited for this patient. A limited TTE could assess whether a pericardial effusion and cardiac tamponade are present followed by either a TEE or CTA of the aorta to confirm and determine the location and extent of dissection.

8. **b.** Emergent aortic surgery. A proximal aortic dissection with hypotension or cardiac tamponade should be treated by emergent aortic surgery. A rapid confirmatory test can be performed on the way to or in the operating room. Small retrospective reviews have raised concerns regarding pericardiocentesis in patients with cardiac tamponade and aortic dissection. Rapid decompensation and death can occur in some patients due to propagation of dissection and increased bleeding into the pericardium. Most importantly, the presence of cardiac tamponade with aortic dissection should mandate immediate surgery. Pericardiocentesis can be performed if the patient is deteriorating rapidly and surgical assistance is not readily available or if the patient is in pulseless electrical activity.

Controversy also exists regarding cardiac catheterization for patients with proximal aortic dissection. Proponents of cardiac catheterization argue that patients with severe obstructive coronary disease require grafting at the time of surgery and that failure to do so will increase the risk of perioperative and postoperative cardiac events. Those who favor not performing cardiac catheterization argue that any delay may increase the risk of death and that an invasive procedure will add further risk of dissection, tamponade, or rupture. One study comparing outcomes of patients undergoing surgery for aortic dissection found that those not undergoing cardiac catheterization had similar mortality than those undergoing the procedure. The 2010 guidelines for thoracic aortic diseases recommend that coronary angiography should be considered if the patient is over 40 years of age, stable, and has either known CAD, significant risk factors for CAD, or an ischemic presentation. Computed tomographic angiography of the chest. Sagittal oblique

reconstruction shows an ascending aortic and aortic arch aneurysm with a dual lumen consistent with a type A aortic dissection (see Figure 6.2).

9. **c.** Cerebral aneurysm rupture. The history of HTN requiring treatment in a young man with a bicuspid aortic valve suggests the likelihood of an aortic coarctation. Given his recent well-controlled BP, aortic dissection, hypertensive crisis, and endocarditis are unlikely. A known association between aortic coarctation and cerebral aneurysms involving the circle of Willis is well established. Testing for this abnormality with MRA or CTA of the brain should be performed for coarctation patients when any neurologic symptoms are present. However, at least a 1 time scan of the brain for intracranial aneurysms is recommended for all patients with coarctation accordingly to the 2008 guidelines for management of congenital heart disease.

10. **b.** Ventricular septal defect. Several cardiac structural lesions are associated with coarctation of the aorta. The most common is a bicuspid aortic valve occurring in up to 85% of patients. Valvular, subvalvular, or supravalvular stenosis may occur. Aortic ectasia or aneurysm involving the ascending thoracic aorta and arch is often present. Other associated structural abnormalities include patent ductus arteriosus, perimembranous ventricular septal defect, and mitral stenosis (parachute mitral valve) as part of the Shone complex of left heart obstructive lesions.

11. **c.** CTA of the chest and abdomen. The patient's history is most suggestive of a thoracic aortic aneurysm or AAA or dissection. He is known to have thoracic aortic dilatation and atherosclerosis, and presents hypertensive with back pain and diminished pulses. Although TEE may be accurate for diagnosis of aortic dissection above the diaphragm, a CT scan may extend imaging to the entire aorta including the abdominal aorta and provide information regarding the involvement of branch vessels. Therefore, CT imaging would be preferable. Aortography is invasive and could cause further injury to the aorta. However, it could provide useful information along with angiography regarding the patency of the patient's bypass grafts and native circulation.

12. **b.** MRA of the chest/aorta. The patient is experiencing ongoing pain refractory to medical therapy and the clinical history remains suggestive of an acute aortic syndrome. The types of acute aortic syndromes are listed in Table 6.4. Although CT imaging is highly accurate in diagnosing aortic dissection, there are false-negative readings. In the International Registry of Aortic Dissection (IRAD) registry, many patients with suspected aortic dissection required more than one imaging test. Therefore, additional imaging should be performed in this patient especially since

an alternative diagnosis for the patient's symptoms is not available. An acute coronary syndrome is not likely in view of recent CABG and unremarkable ECG and cardiac enzymes. Biomarkers are emerging as a diagnostic aide in diagnosing acute aortic syndromes. A D-dimer level <500 ng/mL and a low C-reactive protein make aortic dissection unlikely.

13. **a.** Initiate a β-blocker and repeat ultrasound in 6 months. To determine the stability of an AAA between 4.0 and 4.9 cm (4.2 cm in this patient), it is generally recommended to do an initial follow-up ultrasound in 6 months. However, most patients with AAA size = 4.5 cm should be referred to a vascular surgeon for subsequent follow-up and risk assessment for surgical consideration and have a baseline CT of the aorta to assess for anatomic feasibility for endovascular repair. β-Blockers have been shown to delay the rate of AAA enlargement and would be indicated for this patient with suboptimal control of BP.

TABLE 6-4 Types of Aortic Syndromes

- Classic dissection (intimal tear with double lumen)
- Intramural hematoma (no intimal tear)
- Limited dissection (rare without hematoma, most often in Marfan syndrome)
- Penetrating aortic ulcer (associated localized hematoma or saccular aneurysm)
- Iatrogenic (catheter or trauma related)
- Symptomatic aneurysm

14. **d.** Penetrating aortic ulcer. A penetrating aortic ulcer occurs when aortic atheroma ruptures into the aortic media through the internal elastic lamina. Subsequently, an aneurysm, pseudoaneurysm, localized dissection, hematoma, or aortic rupture may develop. Penetrating ulcers can be diagnosed by aortography, CTA, MRA, or TEE. They more typically occur in the descending aorta. Typical findings include a focal outpouching or ulcer crater in the region of severe, calcified atheroma. Localized flow may be seen by contrast opacification or color Doppler. The aortogram in this patient shows multiple penetrating aortic ulcers, seen as outpouching on the greater curvature of the ascending aortic wall. Contrast aortogram (**A**) shows several outpouchings on the greater curvature of the ascending aorta consistent with penetrating ulcers. Transesophageal echocardiogram (**B**) showing a break in the lesser curvature of the aorta in the same patient in the region of diffuse calcific atheroma also consistent with a penetrating aortic ulcer (see Figure 6.3).

15. **b.** Transfer to the operating room immediately for replacement of the ascending aorta. The patient has an acute aortic syndrome with a symptomatic penetrating ulcer in the ascending aorta. Immediate surgery is indicated to prevent the possibility of aortic rupture. Further confirmatory imaging is not required.

16. **d.** Angiography. The patient presents with pulse deficits, bruits, and symptoms consistent with arterial insufficiency in multiple distributions, including the upper and lower extremities. Angiography (either CTA/MRA or invasive) of the arterial system would define the site and extent of arterial disease. The appearance of the lesions may also help with determining the etiology of the vascular disease (i.e., atherosclerotic versus vasculitic).

17. **d.** Takayasu arteritis. Takayasu arteritis ("pulseless disease") is an inflammatory disease of large sized arteries. Both stenotic lesions and aneurysms may be present with involvement of proximal segments of the aortic arch vessels. Aortic regurgitation is not uncommon due to involvement of the aortic root and aortic valve with inflammatory disease. Although most commonly described in Japanese patients, it has been described throughout the world.

    A diagnostic classification proposed by the American College of Rheumatology requires three of six criteria: (a) age at onset younger than 40 years, (b) intermittent claudication, (c) diminished brachial artery pulse, (d) >10 mmHg difference in systolic BP between arms, (e) bruit of the subclavian arteries or the aorta, or (f) angiographic narrowing or occlusion of the aorta or branches.

18. **d.** Presence of systolic and diastolic flow is consistent with severe coarctation. The peak Doppler pressure gradient as obtained from the simplified Bernoulli often overestimates the gradient obtained across the coarctation as measured by invasive hemodynamics. Since the pre-coarctation velocity is often increased due to abnormality of aortic valve, it must be accounted for in the Bernoulli equation. This requires using the modified Bernoulli equation, where pressure = $4\ (V_2^2 - V_1^2)$, in which V_2 is the peak Doppler velocity across the coarctation and V_1 is the pre-coarctation velocity. The typical sawtooth pattern of aortic coarctation is shown in this example with an elevated systolic velocity and a lower velocity forward flow in diastole. The presence of a continuous flow across the coarctation is consistent with severe obstruction regardless of the peak pressure gradient. Transthoracic suprasternal notch (SSN) view with continuous Doppler in the upper descending aorta. The Doppler profile shows a high-velocity antegrade velocity of 316 cm/s consistent with a 40-mmHg systolic gradient. There is a lower velocity antegrade flow during diastole. These findings are consistent with coarctation of the aorta (see Figure 6.4).

19. **C.** The hallmark of coarctation is the presence of persistent antegrade flow in diastole. The image is a pulsed Doppler spectral recording from the abdominal aorta consistent with coarctation of the aorta. The findings consistent with coarctation are a blunted or low-velocity systolic flow and persistent antegrade flow in diastole (absent retrograde flow). The presence of early diastolic reversal excludes significant coarctation. Other findings consistent with coarctation include a low systolic-to-diastolic velocity ratio, decreased pulsatility, and a prolonged pulse delay. Transthoracic subcostal view with pulsed Doppler in the abdominal aorta. A blunted or low-velocity systolic flow and persistent antegrade flow in diastole (absent retrograde flow) are specific features consistent with coarctation of the aorta (see Figure 6.5).

20. **C.** Balloon angioplasty with or without stents is generally recommended. The patient has severe recoarctation of the aorta after surgical repair. The choice of intervention for coarctation remains controversial and should be made in a center experienced with congenital heart disease among a team of surgical and interventional specialists. However, for recurrent coarctation after surgical repair, catheter intervention with or without stents is generally preferred if the anatomy is suitable. Favorable anatomy is a discrete, nontortuous short segment of narrowing without aneurysms, pseudoaneurysm, or hypoplasia of the aorta. Additional consideration should be given to women considering pregnancy where there is concern regarding the tissue fragility and risk of aortic complications with residual coarctation tissue. In that setting, surgery may be considered. Cardiac MR angiography. Sagittal oblique maximum intensity projection showing a discrete, short region of coarctation in the upper descending aorta without associated dilatation of the adjacent segments (see Figure 6.6).

21. **C.** Asymptomatic patient with a peak-to-peak gradient across the coarctation site of 15 mmHg with extensive collaterals. According to the American College of Cardiology (ACC)/American Heart Association (AHA) 2008 guidelines for adults with congenital heart disease intervention for coarctation of the aorta is recommended if (a) peak-to-peak gradient across the coarctation is ≤20 mmHg or (b) peak-to-peak gradient across the coarctation is <20 mmHg but there is anatomic evidence of severe obstruction and radiologic evidence of collateral flow. For the patient undergoing aortic valve replacement for bicuspid severe aortic regurgitation, the coarctation of the aorta should be reassessed after surgery to determine whether it is clinically significant.

22. **C.** Osteogenesis imperfecta. The patient has osteogenesis imperfecta, a heritable disease of the connective tissue with mutations in procollagen that are associated

with bone fragility (with multiple fractures), ocular changes (most notably blue sclerae), abnormal dentition, and hearing loss. Cardiovascular manifestations may occur and are similar to Marfan syndrome with aortic root dilatation, aortic regurgitation, and mitral valve prolapse.

23. **b.** Intravenous diltiazem. The initial management of aortic dissection is aimed at reduction in heart rate, BP, LV wall stress, and the force of LV contraction (d_p/d_t). The goals are a heart rate less than 60 bpm and BP less than 120 mmHg systolic. β-Blockers are the drug of choice if contraindications are not present. The patient described has severe COPD and therefore if a β-blocker is used it should be short-acting esmolol and not metoprolol. Otherwise, nondihydropyridine calcium-channel blocking agents such as diltiazem and verapamil are alternative options. Vasodilator therapy such as intravenous nitroprusside is contraindicated when initiated prior to atrioventricular blockade because of associated increase in reflex tachycardia, aortic wall stress, and LV force of contraction.

24. **d.** It is circumferential or crescentic. The CT demonstrates an intramural hematoma involving the descending aorta. The mechanism for intramural hematomas is thought due to rupture of the vasa vasorum in the media or small intimal tears. Typical features as seen by CT include the following: (a) absence of an intimal flap; (b) circumferential, focal, or crescentic appearance; (c) displacement of intimal calcium; and (d) high-attenuation thickening consistent with hematoma. Additional features that are seen by TEE include echolucent regions with flow consistent with intramural blood vessels.

Of note, the 2010 guidelines for thoracic aortic diseases state that intramural hematoma should be treated similar to aortic dissection in the corresponding segment of the aorta. Computed tomographic angiography axial image showing a descending thoracic aortic intramural hematoma. The intramural hematoma is evident given the circumferential appearance of high attenuation density of the aortic wall (see Figure 6.7).

25. **d.** TEE. A cardioembolic source of stroke is most likely given the territory of a middle cerebral artery event. The patient has a cholesterol level >300 suggestive of a heritable dyslipidemia and premature atherosclerosis and therefore aortic atheroma would be the most likely finding. A patent foramen ovale may be an alternative source of emboli in this young patient and would be the most likely etiology if the patient did not have a lipid disorder. Intracranial small-vessel disease detected by MRA would be less likely despite a dyslipidemic disorder. There is no information to suggest atrial fibrillation and therefore an event recorder would not likely be revealing.

26. **a.** Statin and aspirin. The TEE shows a large protruding sessile atheroma in the distal descending aorta/distal aortic arch. Treatment for aortic atheroma remains controversial. Antiplatelet therapies such as aspirin and statins are the mainstay of treatment. Systemic anticoagulation with warfarin or warfarin alternatives is unproven due to limited data. However, several observational reports particularly for aortic arch atheroma demonstrate resolution or reduction of large mobile thrombus/atheroma and embolic events in patients on warfarin. Transesophageal echocardiogram with a short-axis view of the upper descending aorta. A large sessile protruding atheromatous plaque is seen (see Figure 6.8).

27. **a.** 3-mm plaque with severe calcification and no mobile components. Predictors of embolic events in patients with aortic atheroma include (a) plaque thickness >4 mm, (b) mobile components, (c) ulceration, and (d) lack of calcification. Therefore, a smaller atheroma without mobile debris and with calcification is the least likely to be associated with an embolic event.

28. **b.** Alternative sites for cross-clamping or cannulation may reduce stroke risk. Alternative sites for cross-clamping and cannulation such as femoral and axillary arteries may reduce the risk of stroke in a patient with significant ascending aortic atheroma. Aortic arch endarterectomy has been found to increase the risk of perioperative stroke and is seldom recommended. Replacement of the ascending aorta is not generally recommended as a prophylactic measure to reduce the risk of stroke in patients with severe atheroma of the ascending aorta because of the additive surgical morbidity and mortality. Palpation of the aorta by the surgeon is usually not accurate in finding noncalcified atheroma that may be detected by TEE.

29. **d.** Williams syndrome. The physical examination findings are classic for supravalvular aortic stenosis, with a left-sided systolic ejection murmur (increase with expiration) heard best in the first right intercostal space, an increased intensity S_2/A_2 heart sound, increase in right-sided BP and pulses relative to the left side, and thrill in the suprasternal notch. Differential BP and pulses in the upper extremities is due to the Coanda effect with preferential deflection of blood flow toward the right brachiocephalic artery. Patent ductus arteriosus and severe coarctation of the aorta typically have continuous murmurs and would not typically have arm pulse differences. Supravalvular pulmonary stenosis would also not have pulse differences and the ejection murmur would decrease with expiration. Supravalvular aortic stenosis typically occurs in association with the Williams syndrome and associated mental retardation, and hypercalcemia. Supravalvular aortic stenosis is a form of aortopathy where obstruction occurs above the aortic sinuses usually at the sinotubular junction and is due to mutation in the elastin gene.

The obstructive aortopathy is due either to a fibrous diaphragm, hour-glass deformity, or diffuse hypoplasia of the aorta.

30. **c.** Right-sided aortic arch. The CXR (Fig. 6.9) shows a right-sided aortic arch with the aortic knob on the right side and absence of a left-sided aortic knob. A bovine aortic arch is an anatomic variant where the origin of the innominate artery and the left carotid artery arises from a common origin or the left carotid artery arises from the innominate artery. This variant occurs in approximately 13% of individuals and has no clinical significance. A cervical arch refers to the takeoff of the aortic branch vessels above the sternum into the soft tissues of the neck before turning downward to the descending aorta. It may present as a pulsatile mass in the neck or supraclavicular region and be associated with compressive symptoms and other vascular anomalies.

31. **a.** Tetralogy of Fallot. A right-sided aortic arch is most commonly associated with tetralogy of Fallot, particularly for the mirror image form. There are several types of right-sided aortic arch, but the mirror image and the non-mirror image variety are the most common. With the non-mirror image type, the order of branches from left to right are as follows: left carotid, right carotid, right subclavian, and left subclavian artery. The left (aberrant) subclavian artery arises from the descending aorta. The mirror image type is much more frequently associated with congenital anomalies than the non-mirror image type. Chest X-ray PA projection shows tracheal deviation to the left and round opacity on the right with absence of a distinct aortic knob on the left. This is most consistent with a right-sided arch (see Figure 6.9).

32. **a.** Aberrant left subclavian artery and diverticulum of Kommerell. Aortic arch anomalies may result in dysphagia, stridor, or wheezing associated with vascular rings that compress the esophagus or trachea. With the non-mirror image right aortic arch, the left subclavian artery arises from the right side and crosses posterior to the esophagus and trachea. This causes a vascular ring that may cause compressive symptoms. Aberrant vessels such as the left subclavian artery may arise from an aneurysmal segment called a diverticulum of Kommerell. An aberrant right subclavian artery may be an isolated anomaly in a normal left-sided aortic arch and is the most common aortic arch abnormality. Although generally asymptomatic, it may also be associated with a vascular ring.

33. **d.** 24-Hour Holter monitoring. CTA or MRA of the aorta is required to assess postoperative complications of prior coarctation repair. Complications include recoarctation and aneurysms in the ascending aorta, aortic arch, or descending aorta

in the region of the repair. In adults, a TTE does not adequately visualize the descending thoracic aorta, although gradients can be obtained to assess hemodynamic significance. Exercise-induced HTN may occur late after coarctation repair even among patients who are normotensive at rest and should be assessed for by exercise stress testing. TTE is important to assess the aortic valve and the possibility of a bicuspid valve, as well as associated structural abnormalities. Arrhythmias are an infrequent consequence of a corrected coarctation in an asymptomatic patient and therefore Holter monitoring is not necessary.

34. a. Generally every 5 years. The ACC/AHA 2008 guidelines for adults with congenital heart disease recommend at least a one-time CT or MR angiogram for repaired or unrepaired coarctation for complete evaluation of the thoracic aorta. In addition, follow-up should be performed at intervals of 5 years or less depending on the prior findings.

35. d. Observation only. Based on examination and echocardiography, the patient has mixed but predominantly severe congenital bicuspid aortic regurgitation. Holodiastolic flow reversal in the descending aorta is the key confirmatory finding supporting severe aortic regurgitation. The three murmurs described include the systolic murmur of bicuspid aortic stenosis and the diastolic murmurs of aortic regurgitation with the associated Austin Flint murmur. There are no clinical or echocardiographic indications for surgery based on aortic valve or aortic disease. β-blockers for aortic root dimensions >4.0 cm should generally be used only if severe aortic regurgitation is not present because of concern of increasing regurgitant volume and fraction with slower heart rates.

36. c. Aortic valve replacement and aortic graft. Surgery is indicated in this patient both for symptomatic aortic regurgitation and because of significant progression in aortic size. ACC/AHA valvular heart disease guidelines for bicuspid aortic valves recommend replacement of the aortic root or ascending aorta if the diameter is greater than 4.5 cm at the time of aortic valve replacement. Aortic valve repair can be performed successfully in select patients with bicuspid aortic regurgitation but is usually not performed when stenosis is present or if there are unfavorable anatomic findings such as calcification. Therefore, aortic valve replacement with either a mechanical or bioprosthetic valve is indicated along with an aortic graft. The aortic graft may incorporate the aortic root or may be in the supracoronary position.

37. b. Screening men >65 years old is associated with a reduction in aneurysm-related deaths compared with unscreened men of similar ages. Guidelines to screen for AAA vary among different governing bodies. The United States Preventive

Services Task Force (USPSTF) recommends one-time screening for any male former or present smoker between ages 65 and 75 years. They do not recommend screening in women based on the lower expected prevalence of AAA. Other vascular societies have less restrictive screening recommendations for men and women. However, screening in patients with first-degree relatives with AAA is recommended. Randomized controlled trials of ultrasound screening for AAA in predominantly men aged 65 to 75 years show a reduction in aneurysm-related mortality compared with unscreened age-matched controls. Ultrasound screening of at-risk patients in accredited laboratories is associated with sensitivities and specificities of over 90%, respectively. Repeat screening after a negative study is not recommended.

38. **c.** Inflammatory or infectious aneurysms should be repaired at any size. Two large trials of predominantly males showed that early elective AAA repair for aneurysms (4.0 to 5.5 cm) resulted in a similar mortality compared with medical therapy. Therefore, repair is generally indicated for asymptomatic AAA if (a) >5.5 cm; (b) increase in size ≤0.5 cm in 1 year; (c) inflammatory, traumatic, or infectious etiology; or (d) there is a family history of rupture. However, since AAAs may rupture at smaller sizes in women and smaller men, repair should be considered at 5.0 cm or even smaller in low-risk candidates for repair.

39. **b.** Open repair and EVAR are associated with similar long-term mortality. Endovascular repair of AAA is an alternative to open repair. Comparative trials including EVAR and DREAM have demonstrated a lower short-term morbidity and mortality (at 30 days) for EVAR compared with open repair. However, in long-term follow-up mortality was similar for the two procedures. EVAR is associated with more complications including endoleaks and need for repeat interventions and may require conversion to an open procedure.

40. **b.** Endoleaks may occur as a result of retrograde flow of small arterial branches back into the aneurysm sac. Endoleaks refer to the occurrence of repressurization of the excluded aneurysmal sac after an EVAR procedure. There are four main types: I—proximal or distal stent attachment site bleeding around the graft; II—leaking back into the sac from branch arterial vessels; III—mechanical failure of stent graft components; IV—leakage of blood through the graft material. Type II leaks are most common. Types I and III may require immediate reintervention, whereas type II can be monitored by repeat surveillance but may require repeat intervention if the aneurysm sac continues to expand.

41. **d.** CTA of the chest and aorta. The patient's history and examination has several

features suggestive of Ehlers-Danlos syndrome. Since she has a low pre- and posttest probability of coronary ischemia, a cardiac catheterization is not advisable. The vascular type of Ehlers-Danlos syndrome (type IV) is associated with spontaneous or iatrogenic arterial or organ rupture (e.g., rupture of gravid uterus or intestines). Aortic complications including dissection and rupture can occur and therefore arterial puncture is generally contraindicated. A CTA of the chest and aorta would exclude pathologies found in Ehlers-Danlos syndrome, including aortic and pulmonary aneurysm and dissection.

42. **b.** DNA sequencing. Diagnosis of Ehlers-Danlos type IV is generally made based on clinical and family history and DNA sequencing for the COL3A1 gene mutations. However, a negative test does not definitively rule out disease since not all causative mutations are known. A punch biopsy of the skin to obtain fibroblasts for culture and detection of defective type III collagen can also be performed.

43. **b.** Loeys-Dietz syndrome. Loeys-Dietz is an autosomal dominant genetic aortic aneurysm syndrome. It predominantly involves children and young adults with risk of rapid progression to aneurysms, arterial tortuosity, and dissection. It is associated with a bifid uvula (shown in Fig. 6.10), cleft palate, and hypertelorism. Other clinical findings similar to Marfan syndrome may be present. Cogan syndrome is a rare large-vessel vasculitis that involves the aorta and is associated with vestibular and ocular abnormalities including uveitis and keratitis. Ormond disease is an inflammatory form of aortitis associated with retroperitoneal fibrosis. Behçet disease is an instead of a arteritis associated with oral and genital ulcers and skin lesions. Image of the oropharynx of a young boy with Loeys-Dietz syndrome showing a bifid uvula (see Figure 6.10).

44. **b.** TGFBR1 or TGFBR2. The genetic defect associated with Loeys-Dietz syndrome is a mutation in transforming growth factor β-receptor, TGFBR1 or TGFBR2. Table 6.5 shows the most common gene mutations associated with aortic diseases.

TABLE 6-5 Most Common Mutations Associated with Aortic Diseases

Condition	Mutation
Marfan syndrome	FBN1
Loeys-Dietz syndrome	TGFBR1/TGFBR2
Ehlers-Danlos syndrome	COL3A1
Familial aortic aneurysms/dissections	ACTA2

45. C. Recommend aortic repair. Because of high risk of aortic dissection in patients with Loeys-Dietz, surgery is recommended at smaller aortic sizes. The 2010 guidelines for thoracic aortic diseases recommend aortic repair based on CTA or MRA for a dimension ≤4.4 cm.

46. C. Descending aortic partial transection with pseudoaneurysm. The patient experienced blunt cardiac trauma with injury to the aorta. This type of deceleration MVA as occurs with a head-to-head car collision may result in catastrophic aortic transection, rupture, or pseudoaneurysm. The typical site of injury occurs at the aortic isthmus (level of the ligamentum arteriosum or junction of the aortic arch and descending thoracic aorta) as a result of fixation of the aorta to the spine by intercostal arteries. The favorable hemodynamics in this patient are not suggestive of either aortic transection or cardiac tamponade. The preserved upper extremity BP and reduced perfusion in the lower extremities are suggestive of partial transection of the descending aorta with a pseudoaneurysm. The pseudoaneurysm is suggested by the widening of the mediastinum on CXR.

47. C. Medical therapy is recommended. Medical therapy should be recommended for this patient. The timing of surgery for descending thoracic aneurysms is addressed by the 2010 guidelines for thoracic aortic diseases. Most descending thoracic aneurysms or chronic dissections (not including thoracoabdominal aneurysms) that are of degenerative, traumatic, or connective tissue etiologies should be repaired when the size is >5.5 cm if comorbidity-related risks are acceptable.

48. C. TEVAR is associated with a 30-day risk of endoleaks of 10%. There are no randomized trials comparing TEVAR with open aortic repair. However, nonrandomized comparisons show a lower rate of hospital complications including paraplegia and death relative to open repair. Despite TEVAR patients generally being older with more comorbid conditions, long-term mortality seems similar. The

estimated rate of type I endoleaks with TEVAR is approximately 10% due to difficulties achieving an adequate proximal anastomosis.

49. d. Aortic root localized dissection. Localized staining of contrast dye is seen in the region of the right sinus of Valsalva. This finding is consistent with an iatrogenic localized dissection. In this patient, it is likely due to either catheter trauma or retrograde propagation of the RCA dissection into the corresponding sinus of Valsalva. Coronary dissection is commonly associated with fibromuscular dysplasia. Contrast aortogram with staining of contrast seen in the right sinus of Valsalva that occurred post MI and following percutaneous coronary stenting in a young woman with fibromuscular dysplasia and RCA dissection. Contrast aortogram with staining of contrast seen in the right sinus of Valsalva that occurred post MI and following percutaneous coronary stenting in a young woman with fibromuscular dysplasia and RCA dissection (see Figure 6.11).

50. a. Observation and medical therapy. Most localized iatrogenic intramural hematomas or dissections occurring in the cardiac catheterization laboratory can be observed and managed medically even when involving the ascending aorta. In general, the site of tear seals and propagation or expansion does not occur. However, repeat aortic imaging should be performed to confirm stability.

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Peripheral Vascular Disease

Douglas E. Joseph • Hemantha K. Koduri

QUESTIONS

1. A 53-year-old man with a history of obesity, obstructive sleep apnea, hypertension, and hypercholesterolemia presents to the clinic complaining of a nonhealing ulcer on his left ankle present for the past month. His blood pressure is 160/78 mmHg. His physical examination is remarkable for mild bilateral lower leg edema as well as lipodermatosclerosis and hyperpigmentation around the ankles. A mildly tender, superficial ulceration is observed with an irregular pink base above his medial malleolus. His feet and toes are warm, pink, and have 2-second capillary refill and intact sensation. Laboratory tests on this patient include a random blood sugar of 160 mg/dL, creatinine of 1.1 mg/dL, calcium of 10.4 mg/dL, phosphorus of 4.4 mg/dL, and serum intact parathyroid hormone level of 50 pg/mL. What is the most likely etiology of the ulceration?

   a. Diabetes mellitus
   b. Chronic venous insufficiency
   c. Peripheral arterial disease (PAD)
   d. Calciphylaxis
   e. Brown recluse spider bite

2. A 49-year-old woman with a 60-pack per year history of smoking presents to the emergency department (ED) with complaints of constant, worsening right foot pain and tingling in the toes for several hours. She denies a history of trauma. On examination, she is in moderate distress from pain and has a regular cardiac rhythm at a rate of 104 bpm. Her right lower extremity has a palpable femoral pulse and cool, pale foot with nonpalpable pedal pulses. There is a faint dorsalis pedis arterial signal with continuous-wave handheld Doppler evaluation. Strength is intact in the foot and toes, but she reports pain during examination. What is the most

appropriate next step?

a. Admit to the hospital; begin a heparin infusion and antiplatelet therapy. Obtain an urgent echocardiogram to identify the source of embolism.
b. Obtain urgent ankle–brachial indices (ABIs) and pulse volume recordings to determine the severity of disease and begin aggressive risk-factor–modifying medical therapy.
c. Admit to the hospital for an urgent diagnostic abdominal aortogram with runoff and potential endovascular revascularization.
d. Admit to the hospital for pain control and obtain a lumbar magnetic resonance imaging to evaluate for lumbar canal stenosis and pseudoclaudication.
e. Obtain ABIs at rest and with exercise to assess for lower extremity PAD and a venous plethysmography of the lower extremities with exercise to evaluate for venous claudication.

3. A 65-year-old man presents with progressive, short-distance, intermittent claudication in his right leg and a declining ABI. He undergoes an abdominal aortic angiogram with runoff demonstrating a discrete 90% stenotic lesion of the superficial femoral artery. Percutaneous transluminal angioplasty followed by placement of a self-expanding nitinol mesh stent is performed with good post-procedural angiographic results. Which of the following is the most appropriate post-procedure surveillance program for this patient?

a. Regular visits with assessment for interval change in symptoms, vascular examination, and ABI measurement beginning in the immediate post-procedure period and at intervals for at least 2 years
b. Regular visits with assessment for interval change in symptoms, vascular examination, and arterial duplex at 1 month, 3 months, and at month 12
c. Regular visits with assessment for interval change in symptoms, vascular examination, and ABI measurement at 3 months, 6 months, 9 months, and at month 12
d. Regular visits with assessment for interval change in symptoms, vascular examination, and arterial duplex at 3 months, 6 months, 12 months, and 2 years
e. Annual visits with assessment for interval change in symptoms, vascular examination, ABI measurement, and arterial duplex

Case 1 (Questions 4 and 5)

A 59-year-old morbidly obese woman is admitted for cholecystectomy and postoperatively is placed on deep venous thrombosis (DVT) prophylaxis with mini-dose subcutaneous heparin. On hospital day 2, a peripherally inserted central venous catheter is placed in the right arm. The patient is discharged to a rehabilitation facility on hospital day 5 after removal of the venous catheter. Two days later she presents to

the emergency room with right upper extremity pain and swelling. She reports she has not felt well enough to participate with physical therapy since being discharged from the hospital. Venous duplex of the right arm demonstrates acute thrombosis of the right cephalic vein. Complete blood count (CBC) and chemistries are within normal range with a platelet count of 180 K/μL.

4. What is the most appropriate management of this patient?

   a. Admit to the hospital and start on intravenous (IV) anticoagulation with heparin or a direct thrombin inhibitor (DTI).
   b. Prescribe enoxaparin 1 mg/kg every 12 hours and coumadin. Admit for 4 to 5 days of overlap and discontinue enoxaparin once the international normalized ratio (INR) is within therapeutic range for 2 consecutive days. Continue anticoagulant therapy for 3 months.
   c. Prescribe enoxaparin 1 mg/kg every 12 hours and coumadin. Discharge with instructions for 4 to 5 days of overlap and discontinue enoxaparin once the INR is within therapeutic range for 2 consecutive days. Continue anticoagulant therapy for 6 months.
   d. Prescribe enoxaparin 1 mg/kg every 12 hours and coumadin. Discharge with instructions for 4 to 5 days of overlap and discontinue enoxaparin once the INR is within therapeutic range for 2 consecutive days. Continue anticoagulant therapy for 12 months.
   e. Warm compresses and nonsteroidal anti-inflammatory drugs for pain.

5. What should the target activated partial thromboplastin time (aPTT) be to achieve optimal efficacy and safety if anticoagulation with a DTI were to be initiated in this patient?

   a. An aPTT of 3.0 to 4.0 times the baseline value
   b. An aPTT of 2.5 to 3.0 times the baseline value
   d. An aPTT of 2.0 to 3.0 times the baseline value
   e. An aPTT of 1.5 to 2.0 times the baseline value

Case 2 (Questions 6 to 8)

A 15-year-old man presents to the clinic accompanied by his mother for evaluation of "red hands." He earned money last winter clearing sidewalks of snow and plans to do so again in the upcoming weeks. He reports developing red discoloration of his hands after returning home from the cold. The discoloration persisted for a few minutes until his hands were rewarmed. He denies weakness, paresthesia, pain, or skin lesions. He is otherwise healthy. At the time of consultation, inspection of his hands is unrevealing. Radial and ulnar pulses are 2+/2 bilaterally. The Allen test and reverse Allen test reveal return of color to the hands in 7 seconds bilaterally. His mother reports that she

and her mother both have Raynaud phenomenon. The patient's mother expresses concern that her son may have systemic lupus and she requests further testing.

6. What is the most likely diagnosis?

   a. Raynaud disease
   b. Raynaud phenomenon
   c. Normal physiologic cold response
   d. Acrocyanosis
   e. Thermal injury

7. Of the following, which is the most appropriate next step to objectively evaluate this patient?

   a. Obtain an upper extremity angiogram with selective imaging of the digital vessels and before and after administration of nitroglycerin.
   b. Obtain digital pulse volume recordings and transcutaneous partial pressure of oxygen measurements of the digits.
   c. Order a C-reactive protein level, erythrocyte sedimentation rate, and perform nailfold capillaroscopy.
   d. Order a C-reactive protein level, erythrocyte sedimentation rate, and plasma homocysteine level.
   e. Order antinuclear antibodies, erythrocyte sedimentation rate, and perform nailfold capillaroscopy.

8. When would be the most appropriate time to schedule a follow-up appointment?

   a. 5 years
   b. 3 years
   c. 2 years
   d. 1 year
   e. As needed

Case 3 (Questions 9 and 10)

A 49-year-old man presents to the clinic with complaints of progressive exertional dyspnea for several weeks. His speech is mildly breathless. Neck veins are distended bilaterally and there is moderate lower extremity edema. He denies chest pain. Electrocardiogram (ECG) shows sinus tachycardia without ST-segment abnormality. Physical examination reveals a parasternal heave and systolic ejection murmur. Past medical history is significant for splenectomy after a car accident several years ago.

9. Which of the following will most accurately confirm the underlying cause of this patient's symptoms?

a. Chest computed tomography (CT) with IV contrast
b. Transthoracic echocardiogram
c. Transesophageal echocardiogram
d. Pulmonary arteriogram
e. Ventilation–perfusion scan

10. Which of the following statements is most accurate concerning this patient's underlying diagnosis?

a. Inflammatory mechanisms have not been implicated in the pathogenesis.
b. Patients should be anticoagulated with a vitamin K antagonist and target INR of 2.5 to 3.5.
c. IV epoprostenol is an effective therapy in patients with advanced disease.
d. Inhaled iloprost has been demonstrated to improve exercise capacity.
e. Bosentan has been shown to improve exercise capacity in patients with mild-to-moderate liver disease.

11. You are consulted for recommendations regarding a deep vein thrombosis in a patient who is status post aortic valve replacement with a bioprosthetic valve 4 days prior. Earlier on the day of consult he complained of pain and was diagnosed with a partially occlusive left femoral vein thrombosis. His postoperative course has been otherwise uncomplicated. On examination, the patient is tender around the surgical site. There is moderate pitting edema in the legs bilaterally. He has palpable pulses in all extremities. What do you recommend?

a. Bolus subcutaneous low-molecular-weight heparin (LMWH) 80 mg/kg, then dose at 1 mg/kg subcutaneously every 12 hours
b. Placement of a retrievable inferior vena cava filter
c. Catheter-directed thrombolysis
d. Begin a DTI
e. Begin a weight-based unfractionated heparin infusion

12. A patient with a history of heparin-induced thrombocytopenia (HIT) 8 years ago presents to your office for preoperative evaluation for bioprosthetic aortic valve replacement and coronary artery bypass grafting. He requires anticoagulation while on cardiopulmonary bypass pump during surgery. A recent ELISA (enzyme-linked immunosorbent assay) antiplatelet factor-4 antibody test is negative (<0.400 optical density). He has had no subsequent heparin exposures over the last 8 years. What is the most appropriate anticoagulation regimen you should recommend for this patient?

a. Administration of IV fondaparinux intraoperatively with subsequent daily monitoring of platelet counts
b. Administration of IV LMWH intraoperatively with subsequent daily monitoring of platelet counts
c. Administration of IV argatroban intraoperatively with subsequent daily monitoring of platelet counts
d. Administration of IV hirudin intraoperatively with subsequent daily monitoring of platelet counts
e. Administration of IV unfractionated heparin intraoperatively with subsequent daily monitoring of platelet counts

13. A patient comes to your office 1 month after a hospital stay for gastric bypass surgery. She was diagnosed with a mesenteric vein thrombosis postoperatively. She denies a prior history of venous thromboembolism (VTE). She and her husband have questions about the duration of anticoagulant therapy. They bring copies of laboratory results showing she was checked for a hypercoagulable condition. One laboratory test indicates she is heterozygous for a mutation of the methylenetetrahydrofolate reductase (MTHFR) enzyme. All other laboratory tests are within normal range. She asks you how these results impact duration and intensity of anticoagulation. The most accurate reply is

a. all first-episode DVTs are treated similarly; thus, the discovery of this genetic mutation is of doubtful clinical significance.
b. given the clinical circumstances the laboratory finding is of doubtful clinical significance and you advise she should be anticoagulated with a vitamin K antagonist for 3 months with a target INR of 2.0 to 3.0.
c. she should be anticoagulated with a vitamin K antagonist for 3 months with an increased target INR of 2.5 to 3.5 because of increased thrombogenicity induced by the genetic mutation.
d. she should be anticoagulated with a vitamin K antagonist with a target INR of 2.0 to 3.0 for an extended duration of therapy to 6 months because of increased thrombogenicity induced by the genetic mutation.
e. she should be anticoagulated with a vitamin K antagonist with an INR target of 2.0 to 3.0 indefinitely because of the high rate of recurrent VTE associated with the heterozygous form of this genetic mutation.

14. A 34-year-old woman with a history of deep vein thrombosis who is chronically anticoagulated with warfarin discovers she is pregnant. Her due date is 34 weeks from now. Currently, she is on warfarin and has an INR of 2.2. She presents to the clinic for recommendations regarding her anticoagulation management. Which of the following is true regarding venous thromboembolic disease, anticoagulation

therapy, and pregnancy?

a. When deep vein thrombosis of the lower extremities complicates a pregnancy, the right leg is affected significantly more often than the left, presumably because of exaggeration of the compressive effects of the left iliac artery compressing on the right iliac vein during pregnancy.
b. The incidence of teratogenic complications of pregnancy caused by warfarin, including nasal hypoplasia and stippled epiphyses, is greatest if warfarin exposure occurs during weeks 14 through 24.
c. Warfarin is contraindicated in the nursing mother because of a high incidence of inducing an anticoagulant effect in the infant fed with breast milk from a mother on warfarin therapy.
d. Fatal pulmonary embolism is a leading cause of maternal mortality in the Western world.
e. LMWHs have been proven safe and efficacious in pregnant woman with prosthetic heart valves, and supplanted unfractionated heparin as the standard of care in this setting.

Case 4 (Questions 15 and 16)

A 65-year-old man presents to the clinic with complaints of episodic burning pain involving the soles of his feet and toes. He reports symptoms are most severe when the weather becomes hot and generally occurs when he is outside in the heat. His feet and toes turn red and feel hot to touch during episodes. When he returns to an air-conditioned area, symptoms begin to dissipate or some episodes may take hours for complete resolution. Elevating his legs relieves symptoms as does walking barefoot on cold tile floors. His past medical history includes hypertension, well controlled with atenolol, and he takes once daily low-dose aspirin for primary prevention.

Physical Examination

Blood pressure is 120/70 mmHg and pulse is 84 bpm.
The cardiac and lung examinations are normal.
The abdomen is soft and nontender with a normal-sized palpable aortic pulsation.
No bruit can be heard over the neck, abdomen, or either groin.
Radial, dorsalis pedis, and posterior tibial pulses are 2+/2 bilaterally.
A mild erythema and increased warmth are noted in toes and soles of the feet.

15. Which of the following is the most likely diagnosis?

a. Heat urticaria
b. Erythromelalgia
c. Chilblains (perniosis)
d. Raynaud phenomenon

16. What laboratory values should be followed serially in patients with this condition?

a. Electrolytes, blood urea nitrogen, and creatinine
b. Erythrocyte sedimentation rate
c. Ionic calcium
d. Complete blood count with differential (CBC with diff)

17. A 17-year-old boy was involved in a motor vehicle accident, which resulted in multiple fractures as well as internal injuries that necessitated multiple abdominal surgeries over a 2-week period. He is expected to recover fully. An intraluminal filling defect was incidentally identified consistent with DVT of the right external iliac vein on a contrast-enhanced abdominal CT scan. Anticoagulation was contraindicated because of a retroperitoneal hemorrhage. It was determined that placement of an inferior vena cava filter was necessary. Of the following types of filters, which filter is most appropriate in this case?

a. Bird's Nest vena cava filter
b. Gunther Tulip retrievable vena cava filter
c. TrapEase inferior vena cava filter
d. Greenfield vena cava filter
e. Simon Nitinol inferior vena cava filter

Case 5 (Question 18)

You are called to the bedside of a 68-year-old man in mild distress who underwent cardiac catheterization earlier in the day. He is complaining of increasing right groin pain. He complains of weakness and tingling in his foot and toes. He is presently on a heparin infusion because of atrial fibrillation. On inspection you note a large area of skin in his right groin and proximal thigh to be dark blue and there is a large, palpable, hard pulsatile mass. With ultrasound using color Doppler you note an irregular shaped area of flow measuring 4.0 cm × 3.3 cm near the common femoral artery, approximately 4.0-cm deep and connected to the artery by a 0.5-cm neck. There is surrounding hematoma observed. Spectral waveform analysis of the neck demonstrates a to-and-fro pattern.

18. What is the best treatment option for management of this patient's condition?

a. Placement of a femoral compression device overnight and analgesics for pain
b. Injection of thrombin by ultrasound guidance
c. Ultrasound-guided compression for 30 minutes
d. Surgical evacuation of the hematoma and suture repair of the artery
e. Placement of a compression dressing with snugly applied bandages around the leg and serial duplex scans to monitor for resolution

19. A 74-year-old man is in the ICU (intensive care unit) recovering from coronary artery bypass surgery and has developed a hemorrhagic pericardial effusion. He is currently stable, but has noted swelling and pain in his left leg. An ultrasound is ordered and reveals acute thrombus in the left peroneal vein. Which of the following is the best management option?

a. No action is required because calf vein thrombus is not clinically important
b. Pneumatic compression stockings and enoxaparin 40 mg every 24 hours
c. Follow up with serial duplex ultrasound scans
d. Initiate a continuous unfractionated heparin infusion
e. Proceed with placement of an inferior vena cava filter

Case 6 (Questions 20 and 21)

A 25-year-old man presents to the clinic with complaints of pain in his feet with walking. He reports this has been going on for several months and has progressively worsened in the past few weeks. He is beginning to develop symptoms in his right calf and earlier this week noticed a black area on his great toe. He has no medical problems, takes no medications, and is in good health overall. He is a smoker and works as a computer salesman. He reports a family history of VTE; his mother had a pulmonary embolism at the age of 50 and was diagnosed with the antiphospholipid antibody syndrome.

20. What is the most likely cause of his symptoms?

a. Elevated anticardiolipin antibodies
b. Thromboangiitis obliterans (TAO, Buerger disease)
c. Takayasu arteritis
d. Premature atherosclerosis
e. Livedoid vasculitis (atrophie blanche)

21. What is the most important aspect of therapy for this patient?

a. Anticoagulation with a vitamin K antagonist
b. Cessation of exposure to all forms of tobacco
c. Initiate immunosuppressive therapy with glucocorticoids
d. Antiplatelet therapy with aspirin
e. Admit to the hospital to begin tissue plasminogen activator therapy

Case 7 (Questions 22 and 23)

A 24-year-old woman presents with complaints of a swollen, painful left leg. She has a history of two episodes of deep vein thrombosis in the past. She recalls that they were both on the left side, but is unsure of which veins were involved. She was on warfarin in the past but discontinued it when she began attempting to conceive. Venous duplex

demonstrates an acute deep vein thrombosis of the left femoral vein. You initiate treatment with LMWH.

22. What is the most likely diagnosis?

a. Heterozygous prothrombin gene mutation
b. Heterozygous factor V Leiden mutation
c. May-Thurner syndrome
d. Klippel-Trenaunay syndrome
e. Klippel-Trenaunay-Weber syndrome

23. Which of the following is the best management option?

a. Indefinite anticoagulant therapy with warfarin
b. Indefinite monotherapy with enoxaparin
c. Venography for thrombus removal and stent placement
d. Placement of an inferior vena cava filter and discontinue anticoagulants
e. Anticoagulate with either warfarin or enoxaparin for 6 months

24. A 68-year-old gentleman underwent coronary artery bypass surgery using the saphenous vein harvested from his left leg. He has done well postoperatively except for failure of the left leg incision to heal completely. Four months after surgery, his leg is still not fully healed and a peri-incisional ulcer is now present. He has significant edema in his leg, which was present prior to surgery. There are no symptoms or physical findings suggestive of infection. His ABI is 0.94 on the right and 0.89 on the left. You order an ultrasound, which is negative for acute thrombus but does reveal significant venous valvular incompetence in the deep veins. Which of the following is most likely to improve this patient's wound healing?

a. Whirlpool therapy
b. Antibiotics and topical steroids
c. Compression stockings
d. Plastic surgery consult
e. Revascularization

25. You are providing postoperative care for a patient who is in the cardiovascular surgery postoperative ICU, status post coronary artery bypass surgery. A venous duplex ultrasound was performed to evaluate for new-onset bilateral leg swelling. Results are reported as negative for DVT, but with monophasic flow noted within the bilateral common femoral veins. Which of the following is the next best step?

a. CT venogram of the lower extremities

b. CT venogram of the abdomen and pelvis
c. Enoxaparin therapy 1 mg/kg subcutaneous injections every 12 hours
d. Enoxaparin therapy 40 mg subcutaneous injections every 24 hours

Case 8 (Questions 26 and 27)

A 39-year-old man presents to the ED with shortness of breath and tachycardia. He eventually develops hypotension with a systolic blood pressure of 80 mmHg. A stat CT scan of the chest reveals a saddle pulmonary embolism involving the main pulmonary artery trunk.

26. Which of the following is the next most appropriate step?

a. Begin an IV unfractionated heparin infusion at 18 U/kg/h
b. Begin alteplase 100 mg IV over 2 hours
c. Begin enoxaparin subcutaneous injections 1 mg/kg every 12 hours
d. Insert an inferior vena cava filter

27. Which of the following findings or laboratory values could be used to predict his prognosis?

a. C-reactive protein
b. Atrial arrhythmia
c. Left ventricular dysfunction
d. Prolonged QT interval
e. Elevated serum myoglobin

28. A 52-year-old man with metastatic prostate cancer has developed left lower extremity swelling. You order an ultrasound and a left acute external iliac deep vein thrombosis is visualized. You hospitalize the patient and his initial labs reveal hemoglobin 14.5 g/dL and creatinine 1.0 mg/dL. Which of the following treatment options is most appropriate?

a. Begin a weight-based unfractionated heparin infusion and bridge to warfarin.
b. Begin enoxaparin 1 mg/kg subcutaneous injections every 12 hours.
c. Place an inferior vena cava filter.
d. Begin unfractionated heparin 5,000 units subcutaneous injections every 8 hours.

29. A 55-year-old man is admitted to the hospital with upper gastrointestinal bleeding. He is transfused with 2 units of packed red blood cells and undergoes esophagogastroduodenoscopy. A bleeding gastric ulcer is discovered and treated with epinephrine injection. Several days into his admission he begins complaining of right calf discomfort. Venous duplex ultrasound is performed demonstrating acute deep vein thrombosis of the popliteal and posterior tibial veins. What is the

next appropriate step in the management of this patient?

a. No action is required because calf vein thrombus is not clinically important.
b. Pneumatic compression stockings and enoxaparin 40 mg every 24 hours.
c. Follow up with serial duplex ultrasound scans.
d. Initiate a continuous unfractionated heparin infusion.
e. Proceed with placement of an inferior vena cava filter.

30. A 58-year-old man presents to the clinic with a complaint of bilateral lower extremity cramping muscular pain with exertion relieved after a few minutes of rest. His medical history includes coronary artery disease status post left anterior descending artery stent 2 years ago, diabetes mellitus type 2, and essential hypertension. An ABI is performed in your office demonstrating a right ABI of 1.10 and left ABI of 1.04. What is the most appropriate next step in the evaluation of this patient?

a. Reassurance and suggest low-impact exercise, i.e., swimming
b. Referral to a peripheral vascular interventionalist for lower extremity angiogram
c. Order bilateral ABI measurements in the vascular laboratory at rest and following an exercise protocol
d. Order magnetic resonance imaging of the lumbosacral spine to confirm the likely diagnosis of pseudoclaudication
e. Have him return in 6 months and repeat the resting ABI measurements

31. A 68-year-old woman recently diagnosed with PAD presents to the clinic for follow-up. A fasting lipid profile obtained prior to the appointment demonstrates a low-density lipoprotein (LDL) level of 145 mg/dL. You decide to initiate therapy with a hydroxymethyl glutaryl coenzyme-A reductase inhibitor (statin). Which of the following LDL target levels is most appropriate?

a. Less than 150 mg/dL
b. Less than 130 mg/dL
c. Less than 100 mg/dL
d. Less than 50 mg/dL
e. There is no defined LDL target

32. A 52-year-old woman with a history of PAD, diabetes mellitus type 2, and active smoking presents to the clinic with a blood pressure of 150/95 mmHg. What blood pressure target should you recommend for this patient?

a. Less than 150/90 mmHg
b. Less than 140/90 mmHg
c. Less than 130/80 mmHg

d. Less than 120/75 mmHg
e. Less than 100/70 mmHg

33. For the above patient you decide to start her on a new antihypertensive medication. Which of the following class of medications are contraindicated?

a. β-Adrenergic blockers
b. Thiazide diuretics
c. Angiotensin-converting enzyme inhibitors
d. Angiotensin II receptor blockers
e. None of the above

Case 9 (Questions 34 and 35)

A 68-year-old man with a 30 pack-year history of smoking is seen in the clinic for follow-up after a non-ST-elevation myocardial infarction (NSTEMI). Because of his smoking history and age you order an ultrasound of his abdomen to rule out abdominal aortic aneurysm (AAA). He is discovered to have an infrarenal AAA measuring 5.0 cm × 4.9 cm.

34. After this initial baseline study, how often should you repeat the ultrasound of the abdomen?

a. Every 3 months
b. Every 3 to 6 months
c. Every 6 to 12 months
d. Every 12 months
e. Every 24 months

35. At what size measurement should you refer a patient for repair of an asymptomatic infrarenal AAA?

a. 4.0 to 5.0 cm
b. 4.5 to 5.0 cm
c. 5.0 to 5.4 cm
d. 5.5 cm or greater
e. 6 cm or greater

36. Which of the following population groups is it appropriate to do a screening ultrasound of the abdomen for an AAA?

a. Men >60 years of age with a first-degree relative with an AAA
b. Women >60 years of age with a first-degree relative with an AAA
c. Men 65 to 75 years of age with a smoking history

d. Women 65 to 75 years of age with a smoking history
e. All of the above groups are appropriate to screen for an AAA

Case 10 (Questions 37 and 38)

A 70-year-old man presents for follow-up in the clinic 1 month after undergoing right internal carotid artery stenting.

37. When should you get a post-procedure baseline carotid duplex ultrasound?

a. Four weeks after the intervention
b. Six weeks after the intervention
c. Two months after the intervention
d. Six months after the intervention
e. Twelve months after the intervention

38. A baseline carotid duplex ultrasound demonstrates patency of the stent and no evidence of residual stenosis or restenosis of the right internal carotid artery after the procedure. One year after the carotid intervention, how often is it recommended to perform repeat carotid ultrasound surveillance in an asymptomatic patient?

a. Every 6 months
b. Every 12 months
c. Every 18 months
d. Every 24 months
e. Every 36 months

Case 11 (Questions 39 to 42)

A 65-year-old man presents for a routine physical examination. During the interview he complains about swelling behind his right knee. You order an ultrasound of the area (findings illustrated in Fig. 7.1).

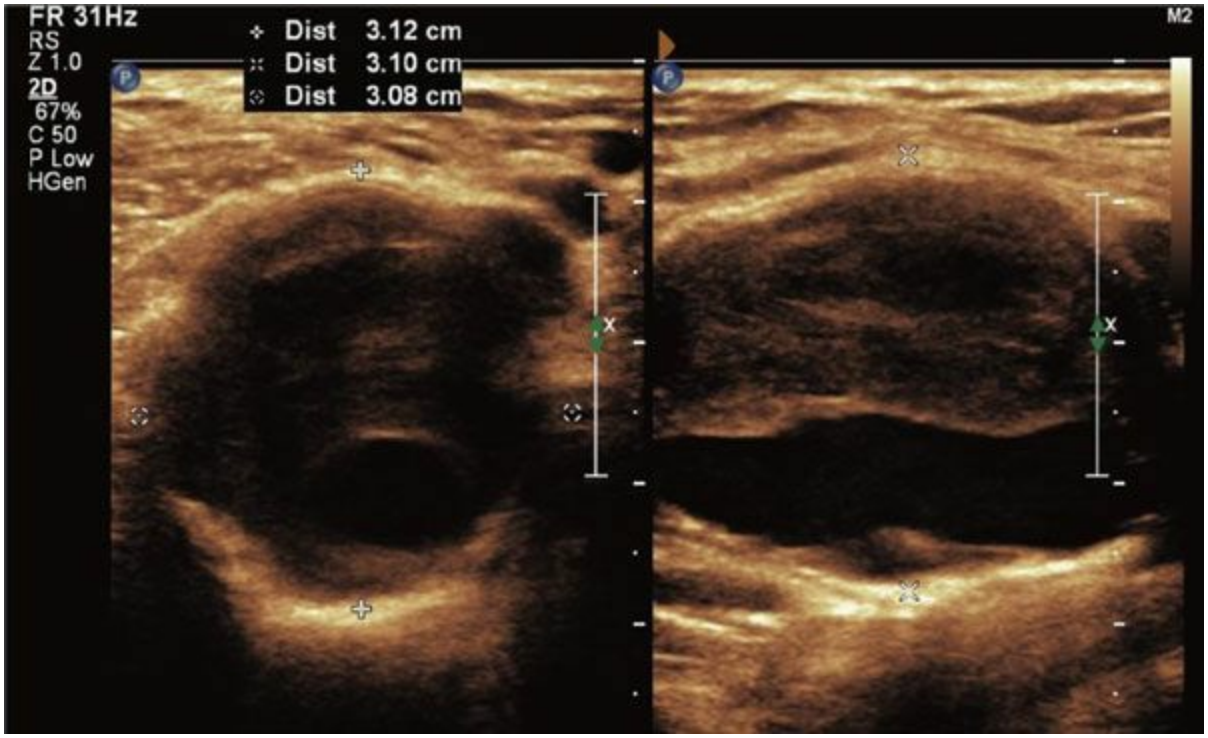

Figure 7.1

39. What is the most likely diagnosis?

- **a.** Abscess
- **b.** Baker cyst
- **c.** Popliteal artery aneurysm
- **d.** Enlarged lymph node
- **e.** Lipoma

40. What percentage of patients with a popliteal artery aneurysm have concomitant AAA?

- **a.** 10%
- **b.** 20%
- **c.** 40%
- **d.** 50%
- **e.** 60%

41. After finding the results illustrated in Figure 7.1 you refer the patient for ultrasound of the abdomen and contralateral popliteal artery. No additional abnormalities are discovered. What is the next appropriate step in his management?

- **a.** The finding is benign and no intervention is indicated.
- **b.** Repeat the ultrasound in 3 months.
- **c.** Repeat the ultrasound in 6 months.

d. Repeat the ultrasound in 1 year.
e. Refer for the repair of the aneurysm.

42. What is the most common complication of untreated, symptomatic popliteal artery aneurysms measuring more than 2.5 cm in greatest dimension?

a. Rupture
b. Thromboembolism
c. Infection
d. No complications
e. Popliteal vein thrombosis

43. During rounds in the telemetry unit you evaluate a 55-year-old woman 1 day after she underwent a left heart catheterization. She complains of right groin pain and swelling at the vascular access site. You order a duplex ultrasound of the right groin. Findings of the ultrasound are illustrated in Figure 7.2A and B. What is your diagnosis?

a. Hematoma
b. Arteriovenous fistula
c. Abscess
d. Pseudoaneurysm
e. Enlarged lymph node

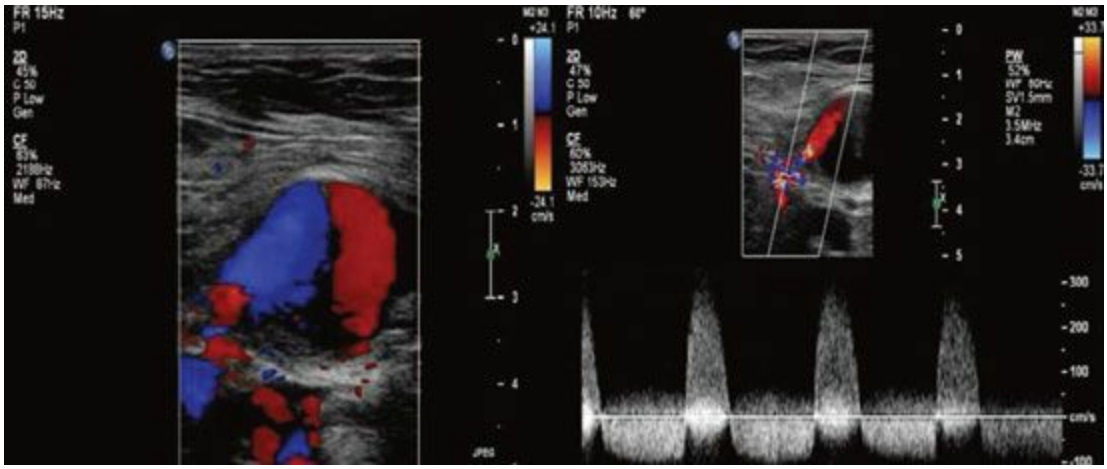

Figure 7.2

44. A 64-year-old woman presents to the clinic for evaluation prior to coronary artery bypass surgery. She underwent carotid duplex ultrasound demonstrating normal bilateral internal carotid arteries. Images from her scan are illustrated in Figure 7.3. What unexpected condition is demonstrated by her ultrasound images?

a. Subclavian artery aneurysm

b. Subclavian artery thrombosis
c. Subclavian artery stenosis
d. Subclavian vein thrombosis
e. Hematoma surrounding the subclavian artery

45. A 55-year-old woman with a history of deep vein thrombosis 2 months ago for which she was on warfarin was admitted to the hospital for chest pain. She underwent chest CT angiography which was negative for pulmonary embolism. She underwent a left heart catheterization after her INR normalized. During her procedure she received IV heparin. Her coronary arteries were free of disease. Following the procedure she was prescribed 10 mg of warfarin daily for 3 days. During this time her CBC was monitored and her hemoglobin and platelet counts showed minor fluctuations. A day later she developed a lesion on her abdomen illustrated in Figure 7.4. What is the likely cause of the skin lesion?

a. Heparin-induced skin necrosis
b. Vasculitis
c. Warfarin skin necrosis
d. Eczema
e. Allergic reaction

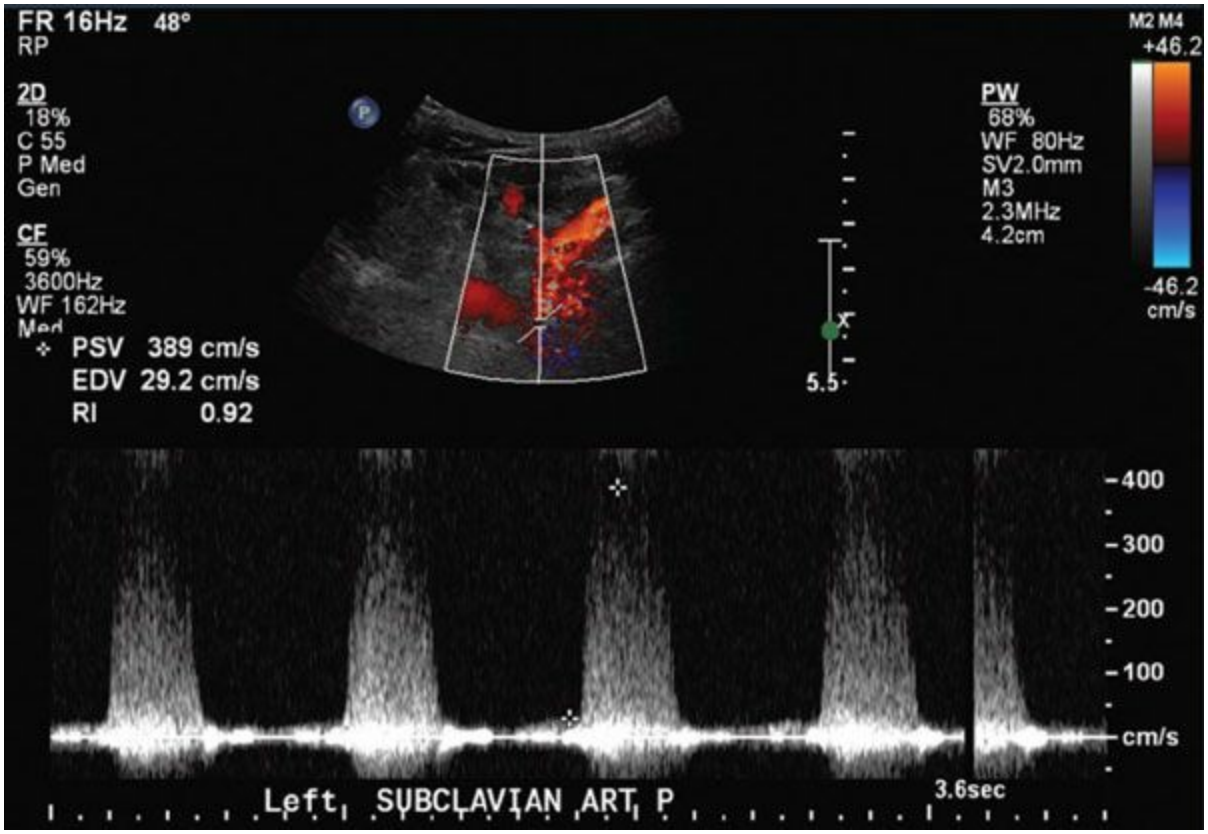

Figure 7.3

Figure 7.4

46. A 70-year-old man is admitted to the telemetry unit for workup of dizziness of 2 days' duration. He denies chest pain or shortness of breath. His heart rate is 60 bpm and blood pressure is 130/50 mmHg. On physical examination, a systolic murmur is heard over the left sternal border. Carotid duplex ultrasound is performed demonstrating the spectral waveforms of the bilateral internal carotid and vertebral arteries illustrated in Figure 7.5. Which of the following conditions is suggested by the carotid duplex waveforms?

a. Pulmonary valve stenosis
b. Systolic heart failure
c. Pericardial tamponade
d. Aortic valve stenosis
e. Mitral regurgitation

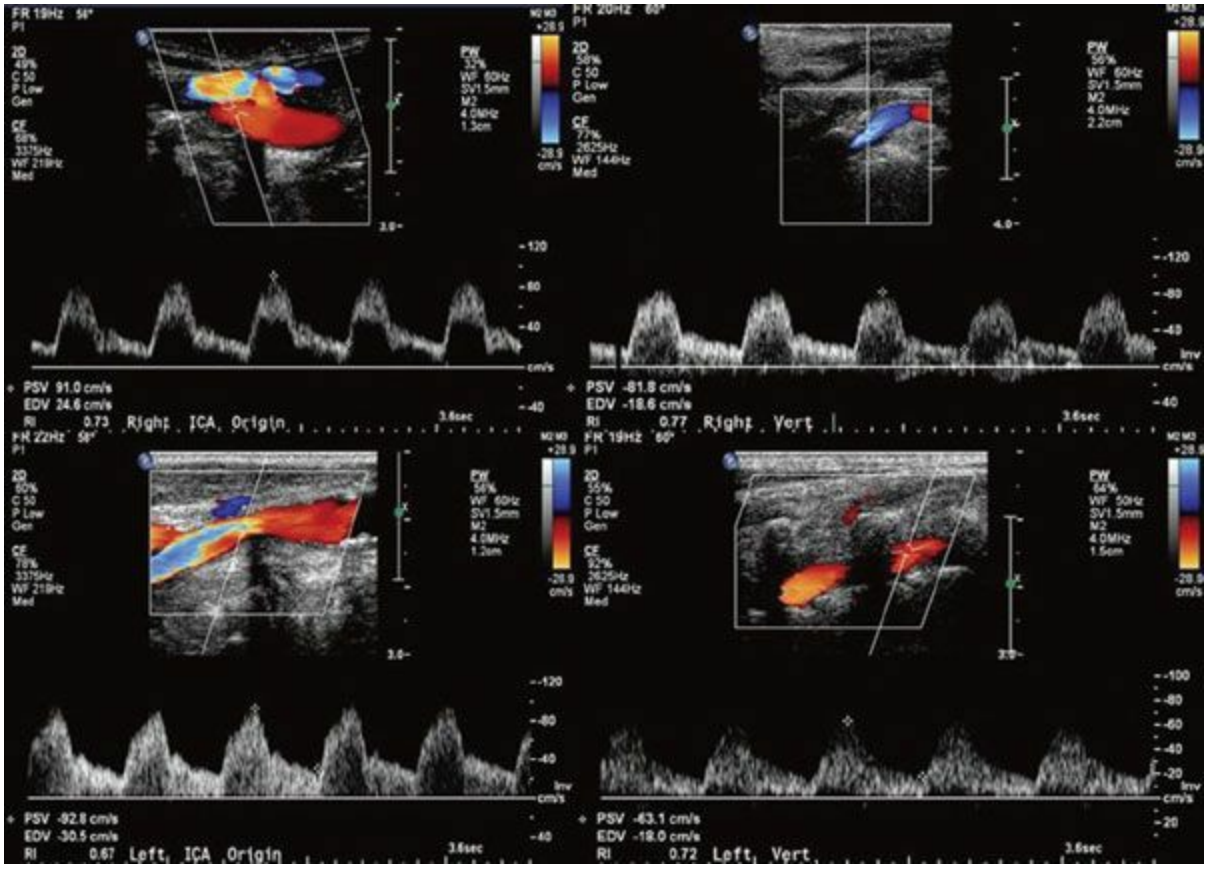

Figure 7.5

47. A 55-year-old woman presents to the ED with precordial chest discomfort and shortness of breath. Her body mass index is 34. Her medical history includes essential hypertension, diabetes mellitus type 2, and a 30 pack-year smoking history. Laboratory results include a troponin of 2.4 mg/mL and a B-type natriuretic peptide of 840 pg/mL. An ECG reveals no ST-segment elevation and nonspecific ST-T wave changes. The ED physician requests cardiology consultation for an NSTEMI. When you arrive to see the patient you order an IV contrast-enhanced chest CT scan of the lungs. Findings are demonstrated in Figure 7.6. What is the diagnosis?

a. Type A aortic dissection
b. Myocarditis
c. Pneumonia
d. Saddle pulmonary embolism
e. Interstitial lung fibrosis

48. Which of the following cardiovascular risk factor assessment tools has not been demonstrated to be useful in the risk assessment for a first atherosclerotic cardiovascular event?

a. High-sensitivity C-reactive protein
b. Coronary artery calcium score
c. Carotid intima-media thickness
d. ABI
e. Family history of premature coronary vascular disease

Figure 7.6

ANSWERS

1. **b.** Chronic venous insufficiency. This patient has no history of neuropathy and has intact sensation, making a neurotrophic ulcer often associated with diabetes unlikely. While his glucose is elevated, inadequate information is provided to make the diagnosis of diabetes mellitus. Bilateral leg edema, hyperpigmentation of the ankles, and the location of the ulcer over the medial malleolus ("gaiter distribution") are findings consistent with a venous stasis wound. Ulcers secondary to arterial disease are usually painful, involve the toes, and are well circumscribed. The information provided suggests adequate arterial supply. Wounds associated with calciphylaxis may be anywhere. They are usually very painful, involve large areas of skin, and are associated with black eschar formation. These wounds are most often seen in patients with renal impairment and hyperparathyroidism, neither of which is true in this case. Nothing in the clinical vignette is suggestive of a brown recluse spider bite.[11]

2. **c.** Admit to the hospital for an urgent diagnostic abdominal aortogram with runoff and potential endovascular revascularization. The patient described is suffering from acute critical limb ischemia. The hallmarks of acute limb ischemia are the five "P's", which are suggestive of impending tissue necrosis. They are pain, paralysis, paresthesia, pulseless, and pallor and some add poikilothermia (coldness) for a sixth "P." Our patient exhibits all but paralysis. Based on the Society for Vascular Surgery/International Society for Cardiovascular Surgery classification scheme for clinical categories of acute limb ischemia, her limb is marginally to intermediately threatened. Acute limb ischemia requires prompt diagnosis and intervention to avoid limb loss and life-threatening systemic illness resulting from tissue gangrene.[12]

3. **a.** Regular visits with assessment for interval change in symptoms, vascular examination, and ABI measurement beginning in the immediate post-procedure period and at intervals for at least 2 years. Unlike follow-up of autologous vein bypass grafts, well-established evidence-based guidelines for surveillance of post-endovascular revascularization patients do not exist. However, it is considered standard of care to evaluate these patients with interval history, examination, and measurement of the ABI regularly for at least 2 years after their percutaneous revascularization procedure.[13]

4. **e.** Warm compresses and nonsteroidal anti-inflammatory drugs for pain. Empiric anticoagulation, including outpatient anticoagulation, for superficial vein thrombosis is not routinely recommended. The clinical scenario may represent HIT and she should have a follow-up platelet count in 2 days. Her prior platelet counts from her recent hospitalization should be evaluated for a drop in platelets of ≥50% from baseline.[15]

5. **e.** An aPTT prolongation of 1.5 to 2.0 times the baseline value. Although the recommended range for therapeutic anticoagulation for VTE with a DTI is 1.5 to 2.5 times the baseline, which is not given as an option, published data indicate that anticoagulation with a DTI target aPTT of 1.5 to 2.0 times the baseline is just as efficacious and is associated with less bleeding risk.[16]

6. **c.** Normal physiologic cold response. This patient is exhibiting a normal response to prolonged exposure to cold. The diagnosis of Raynaud phenomenon is clinical and includes the presence of pallor or acrocyanosis and pain with cold exposure. Redness of the hands with warming after prolonged cold exposure, without concomitant pain, may be a normal response in a healthy young individual. He should be counseled to wear gloves and report any change in his symptoms, as his

family history does predispose him to development of Raynaud phenomenon.[17]

7. **e.** Order antinuclear antibodies, erythrocyte sedimentation rate, and perform nailfold capillaroscopy. If all these tests are normal, it is very unlikely that this patient has secondary Raynaud phenomenon and no further testing is necessary.[18]

8. **e.** As needed. Although the patient does not have Raynaud phenomenon, he should be encouraged to follow up as needed because of his family history. Patients who have primary Raynaud phenomenon should have clinical follow-up for a minimum of 2 years after diagnosis.[17]

9. **d.** Pulmonary arteriogram. An arteriogram is the test most likely to confirm pulmonary artery hypertension in this patient presenting with cor pulmonale, although a right heart catheterization is usually done first. This patient most likely has chronic thromboembolic pulmonary hypertension (CTEPH), a condition seen in otherwise healthy postsplenectomy patients. Other predisposing conditions include history of pulmonary embolism, myeloproliferative disorders, and chronic inflammatory conditions.[19]

10. **c.** IV epoprostenol is an effective therapy in patients with advanced disease. Patients with CTEPH may be bridged to pulmonary endarterectomy with IV epoprostenol. The other answers are incorrect. Anticoagulation with a vitamin K antagonist is indicated; however, the INR target of 2.0 to 3.0 is recommended. The Aerosolized Iloprost Randomization (AIR) study did not demonstrate improved exercise capacity with inhaled iloprost. Bosentan does improve exercise capacity and decreases pulmonary vascular resistance, but is not advocated for use in patients with moderate-to-severe hepatic dysfunction.[19]

11. **e.** Begin a weight-based unfractionated heparin infusion. Although LMWH may be appropriate as the initial anticoagulant of choice for the treatment of an acute DVT in the ambulatory as well as hospitalized patient, it does not require a bolus. In the setting of the postoperative state where rapid reversal of anticoagulation may be required, unfractionated heparin is favored. An inferior vena cava filter would be an appropriate recommendation if anticoagulation could not be administered at therapeutic levels. Thrombolytic therapy is contraindicated in the setting of recent open heart surgery. Use of a DTI is not indicated for routine anticoagulation.[22]

12. **e.** Administration of IV unfractionated heparin intraoperatively with subsequent daily monitoring of platelet counts. The nature of immune response to heparin is

anamnestic; this means a second exposure in the absence of positive antibodies is not associated with the development of a clinical hyperacute immune response. Perioperatively, heparin products should be avoided in patients with a history of HIT even with undetectable antiplatelet antibodies prior to cardiac surgery or vascular surgery. Nevertheless, heparin is favored over DTIs in cardiac and vascular surgery because of its reversibility and relative ease of use. Acute HIT is unlikely to occur even in patients who have a remote history of HIT as long as there has been no heparin exposure within the previous 100 days. This recommendation is based on expert opinion (level 1C) and not on randomized controlled trials.[15]

13. **b.** Given the clinical circumstances the laboratory finding is of doubtful clinical significance and you advise she should be anticoagulated with a vitamin K antagonist for 3 months with a target INR of 2.0 to 3.0. While the site of thrombosis is somewhat out of the ordinary, it was in the setting of abdominal surgery and was her first episode; therefore, a routine course of 3 months of anticoagulation with a vitamin K antagonist and an INR target of 2.0 to 3.0 is appropriate. All first-episode venous thrombotic events are not treated the same. Patients with malignancy-related thrombosis, idiopathic events, and those with certain thrombophilic conditions such as the antiphospholipid antibody syndrome require a longer duration of therapy relative to patients with transient risk factors for VTE. The MTHFR genetic mutation in the absence of hyperhomocysteinemia is not associated with increased risk of recurrence after discontinuation of anticoagulant therapy and has not been shown to increase thrombogenicity requiring a higher than usual INR target.[23]

14. **d.** Fatal pulmonary embolism is a leading cause of maternal mortality in the Western world. Thromboembolism is clearly the leading direct cause of maternal mortality according to the Seventh Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. The May-Thurner syndrome involves compression of the left iliac vein by the right iliac artery. The greatest teratogenicity of warfarin is seen during weeks 6 through 12. Use of LMWH in pregnant women who have prosthetic heart valves is highly controversial and certainly not the standard of care.[24]

15. **b.** Erythromelalgia. The name of this condition is based on three Greek words: erythro meaning red, melos meaning extremity, and algos meaning pain. It is uncommon, affecting about 1 in 40,000. It may be primary or secondary. Primary erythromelalgia is usually bilateral, not associated with gangrene, and patients have normal pulses. Secondary erythromelalgia is often unilateral, can be associated with gangrene, and patients have variable pulses. Secondary erythromelalgia can be

associated with medications including bromocriptine, nifedipine, nicardipine, and verapamil. It may also herald the onset of a myeloproliferative disease such as polycythemia vera or essential thrombocythemia.[24]

16. **d.** Complete blood count with differential (CBC with diff). Patients with this condition should have a CBC with diff checked periodically for at least 2 to 3 years. It is important for treating physicians to recognize that erythromelalgia can precede the laboratory manifestations of a myeloproliferative disorder by up to 2 to 3 years.[28]

17. **b.** Gunther Tulip retrievable vena cava filter. This patient is young and his deep vein thrombosis is situational. He is expected to recover fully with no sequelae; thus he does not require placement of a permanent inferior vena cava filter. Proximal iliac thrombus in the setting of a hospitalized trauma patient following multiple abdominal surgeries is a very high-risk scenario for development of serious, life-threatening VTE. Anticoagulation is the treatment of choice when it can be safely administered; however, when contraindicated an inferior vena cava filter should be placed without delay. Patients with a temporary contraindication for anticoagulants should be reassessed at short intervals and, if circumstances permit, anticoagulants should be instituted for treatment of their VTE and to prevent recurrence. Of the filter types listed, only the Gunther Tulip is approved in the United States for retrieval. The OptEase is also approved for retrieval. The Bird's Nest filter is the only filter available for use in patients with a so-called megacava (vena cava greater than 28 mm). The Bird's Nest filter can be placed into an inferior vena cava of up to 42 mm in diameter. The TrapEase, Greenfield, and Simon Nitinol filters were not designed to have the option of retrieval.[25]

18. **d.** Surgical evacuation of the hematoma and suture repair of the artery. The patient complains of developing numbness in the setting of developing a large hematoma and pseudoaneurysm. To relieve the compressive effect of the hematoma, prevent irreversible injury, and relieve pain, the most appropriate method of repair in this patient is to evacuate the hematoma. Most small to moderately sized pseudoaneurysms can be treated with either ultrasound-guided compression, thrombin injection, or when very small may be observed for spontaneous resolution. Placement of a femoral compression device (Fem-Stop) is not appropriate in this setting, and bandages should not be wrapped proximally around the thigh as this will cause worsening swelling and pain.[26]

19. **c.** Follow up with serial duplex ultrasound scans. The peroneal vein is a calf vein with less propensity for clinically significant sequelae. Anticoagulant therapy for

calf vein DVT is controversial. However, in this setting there is a clear contraindication to anticoagulate. Even prophylactic doses of anticoagulants are not advisable in patients with hemorrhagic pericardial effusions status post open heart surgery. Serial ultrasound scans have been studied as an alternative to anticoagulant therapy. If no propagation after several weeks, no anticoagulant therapy is necessary. If propagation occurs, then anticoagulation versus placement of an inferior vena cava should be considered.[27]

20. **b.** Thromboangiitis obliterans (TAO, Buerger disease). TAO classically manifests in young, male patients with a recent history of heavy tobacco use. The clinical presentation is consistent with ischemia, beginning distally and involving the small- and medium-sized arteries. Usually the lower extremities are involved, with ischemia or claudication of the feet or legs. Foot or arch claudication is typical. Occasionally, the hands are involved. If the disease progresses with continued exposure to tobacco, patients are at significant risk for progressive ischemia, ulceration, gangrene, and eventually amputation. Antiphospholipid antibody syndrome is certainly possible, but it is not a hereditary condition and most often manifests with venous thrombosis. Takayasu arteritis does not usually present in this way. Nothing is suggestive of atrophie blanche, and premature atherosclerosis presenting in a 25-year-old man with claudication and ischemia would be highly unusual.[28]

21. **b.** Cessation of exposure to all forms of tobacco. The strong link between tobacco abuse and TAO is well recognized. There have been suggestions that some patients may demonstrate an abnormal sensitivity to a component of tobacco, which leads to small vessel occlusive disease. It has been shown that patients with TAO have higher tobacco consumption as well as higher carboxyhemoglobin levels than do patients with atherosclerosis.[28]

22. **c.** May-Thurner syndrome. Also known as iliac vein compression syndrome, Cockett syndrome, or iliocaval compression syndrome, May-Thurner syndrome is caused by compression of the left common iliac vein by the right common iliac artery and the underlying vertebral body. A history of chronic left lower extremity edema with or without the presence of DVT is suggestive of May-Thurner syndrome, especially in a female population. This phenomenon causes a partial obstruction caused by physical entrapment of the vein under the artery as well as by repetitive pulsatile force resulting in intimal hyperplasia of the vein. It has been estimated that this condition occurs in 2% to 5% of patients who are evaluated for lower extremity venous problems.[29]

23. **c.** Venography for thrombus removal and stent placement. May-Thurner syndrome is an anatomical anomaly that results in repeated venous trauma and often subsequent thrombus formation. Removal of thrombus followed by angioplasty, if needed, and placement of a stent is a potentially definitive treatment that could avoid the need for indefinite anticoagulant therapy in the young woman presented in this case.[29]

24. **c.** Compression stockings. The importance of edema control is often underestimated for wound healing. This patient has deep system venous reflux. He has no signs of infection complicating the healing of his incision, so antibiotics are unlikely to be helpful. Topical steroids offer no benefit in this case. His ABIs suggest adequate arterial inflow for wound healing. Whirlpool therapy is helpful in select cases, most often when multiple small wounds are present, which need cleansing and gentle debridement. Although the size of the wound is not clearly stated, these wounds are most often small and referral for skin grafting is not indicated.[30]

25. **b.** CT venogram of the abdomen and pelvis. Monophasic (loss of respiratory phasicity) flow is suggestive of proximal venous obstruction, especially in a patient with swollen limbs and under high-risk circumstances for VTE. Monophasicity is not specific to thrombosis. Other potential causes include obesity, pregnancy, and a pelvic mass. Respiratory or cardiac dysfunction may also produce an abnormal venous flow pattern.[31]

26. **b.** Begin alteplase 100 mg IV over 2 hours. The patient presented has a clinically massive pulmonary embolism with hemodynamic compromise; thus thrombolytic therapy is indicated.[32]

27. **b.** Atrial arrhythmia. There have been many laboratory, ECG, and echocardiogram findings shown to be predictive of mortality and prognosis. Right ventricular dysfunction, particularly when accompanied by hypotension, is predictive of pulmonary embolism–related hospital mortality. Elevated serum troponin and elevated brain natriuretic peptide have also been shown to predict an increased risk of death. Additional findings associated with a poorer prognosis include atrial arrhythmia, right bundle branch block, inferior Q waves and precordial T-wave inversions, and ST-segment changes. The other distracters have not been shown to predict prognosis.

28. **b.** Begin enoxaparin 1 mg/kg subcutaneous injections every 12 hours. Cancer patients are at a sixfold increased risk of developing VTE. Patients with active cancer make up about 20% of all new VTE diagnosed in the community. The risk, however, varies somewhat with cancer type, and those that incur a higher risk

include malignant brain tumors and adenocarcinoma of the ovary, pancreas, colon, stomach, lung, prostate, and kidney. Several studies have demonstrated a benefit to treatment with LMWH when compared with coumadin in this patient population. One study, which compared dalteparin with coumadin, reported 27 of 336 patients in the LMWH group had recurrent VTE when compared with 53 of 336 in the coumadin group in a 6-month follow-up period. There was no increased risk of bleeding in the LMWH group.[33,34]

29. **e.** Proceed with placement of an inferior vena cava filter. The patient has a proximal DVT with a contraindication for anticoagulation. This scenario represents an absolute indication for the placement of an inferior vena cava filter. Pneumatic compression stockings are indicated for the prevention of VTE but not for treatment. Serial duplex ultrasound scans may be an acceptable strategy for management of isolated acute calf vein thrombosis but not for proximal DVT. IV unfractionated heparin or enoxaparin 1 mg/kg subcutaneous injections would be appropriate treatment options if the patient did not have a recent gastrointestinal bleed requiring transfusion.[35]

30. **c.** Order bilateral ABI measurements in the vascular laboratory at rest and following an exercise protocol. The patient in the clinical vignette presented with classic intermittent claudication symptoms suggestive of PAD. A normal resting ABI does not rule out PAD in a patient presenting with ambulatory symptoms.[36] Performing the test following exercise often unmasks significant disease revealing markedly lower ABI values. Exercise may be an appropriate suggestion but it will not help to establish the diagnosis of this patient's presenting problem. It would be premature to refer this patient for intervention. Pseudoclaudication may present similarly, but this patient has risk factors for PAD; therefore, a post exercise ABI would be the most appropriate next step in their workup. Repeating the resting ABI in 6 months is not likely to provide new information.

31. **c.** Less than 100 mg/dL. The most recent practice guidelines for the management of PAD, updated in March 2013, recommend a target LDL of less than 100 mg/dL for patients with an established diagnosis of PAD.[36]

32. **c.** Less than 130/80 mmHg. The most recent practice guidelines for the management of PAD, updated in March 2013, recommend a target blood pressure of less than 140/90 mmHg for patients with PAD. The guidelines recommend a lower target, less than 130/80 mmHg, for patients with PAD and concomitant diabetes mellitus or renal insufficiency.[36]

33. **e.** None of the above. Thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-adrenergic blockers are all acceptable medications to achieve blood pressure targets in patients with PAD.[36]

34. **c.** Every 6 to 12 months. According to the appropriate use criteria published by the intersocietal committee on peripheral vascular testing and the American College of Cardiology Foundation/American Heart Association practice guidelines for PAD, patients with an asymptomatic AAA measuring 4.0 to 5.4 cm should have surveillance imaging every 6 to 12 months in the first year.[36,37]

35. **d.** 5.5 cm or greater. The patient should be referred for repair once the infrarenal AAA reaches a diameter of 5.5 cm or greater due to an increased risk of spontaneous rupture.[36] Surveillance imaging is advised at regular intervals for aneurysms less than 5.5 cm.

36. **e.** All of the above groups are appropriate to screen for an AAA. According to the appropriate use criteria published by intersocietal committee on peripheral vascular testing all of the groups listed are appropriate for AAA screening.[37]

37. **a.** Four weeks after the intervention. All patients should get a baseline carotid duplex ultrasound within 4 weeks after a carotid artery stenting or endarterectomy procedure.[37]

38. **b.** Every 12 months. It is recommended to repeat carotid duplex ultrasound every 12 months after the first year following carotid artery stenting to assess for evidence of in-stent restenosis.[37]

39. **c.** Popliteal artery aneurysm. Shown is a transverse and longitudinal image of a large popliteal artery aneurysm containing mural thrombus. The appearance is not suggestive of an abscess, Baker cyst, lymph node, or lipoma.

40. **d.** 50%. A large number of patients with a popliteal artery aneurysm will also have an AAA. Furthermore, 50% of patients with a popliteal artery aneurysm will have an aneurysm of the contralateral popliteal artery.[38]

41. **e.** Refer for repair of the aneurysm. Popliteal artery aneurysms measuring greater than 2.5 cm are at risk for thrombosis, embolism, or rupture and therefore should be repaired.[36] Popliteal artery aneurysms measuring less than 2.5 cm are imaged at regular intervals.

42. **b.** Thromboembolism. Popliteal artery aneurysms most commonly cause thromboembolism that can lead to popliteal artery occlusion or painful distal embolic lesions. Rupture of popliteal artery aneurysms occurs infrequently.[38,39]

43. **d.** Pseudoaneurysm. The spectral Doppler waveform shown is a typical to-and-fro signal seen within the neck of the pseudoaneurysm. The incidence of pseudoaneurysm complicating percutaneous arterial procedures ranges between 0.2% and 0.5%. Patients typically present post catheter-based procedure with a painful pulsatile mass. When small these may resolve spontaneously, while others require intervention such as ultrasound-guided thrombin injection or surgical repair.[5]

44. **c.** Subclavian artery stenosis. Color Doppler imaging shows significant color aliasing, spectral broadening, and turbulent high-velocity flow within the subclavian artery. It is important to recognize severe subclavian artery stenosis prior to coronary artery bypass surgery in which the internal mammary artery may be utilized. Severe subclavian artery stenosis can lead to retrograde flow in the internal mammary artery predisposing to early graft failure. In an aneurysm usually the velocities are decreased.

45. **c.** Warfarin skin necrosis. Pictured is a large erythematous lesion with surrounding violaceous borders. Given the history of several days of high doses of warfarin without parental anticoagulation makes warfarin skin necrosis the most correct response. Heparin skin necrosis has been described but usually occurs at the site of subcutaneous injections.

    HIT can rarely be associated with necrotic skin lesions but in this case her platelets remained stable. A vasculitis can cause skin necrosis but is unlikely in the given scenario.

46. **d.** Aortic valve stenosis. The waveforms in the bilateral internal carotid and vertebral arteries have a Tardus-Parvus morphology. They have a blunted and slow upstroke, suggesting more proximal or central narrowing. In this patient, these findings along with a systolic murmur are suggestive of aortic valve stenosis.

47. **d.** Saddle pulmonary embolism. This patient has a pulmonary embolism involving both main pulmonary arteries. Massive and submassive pulmonary embolism can cause an increase in troponin and B-type natriuretic peptide as seen in acute myocardial infarction. The image shown illustrates a filling defect within the main pulmonary artery at the bifurcation. There are no findings suggestive of aortic

dissection, pneumonia, or interstitial fibrosis.

48. C. Carotid intima-media thickness. According to the latest American College of Cardiology/American Heart Association cardiovascular risk assessment guidelines, there is insufficient evidence available to recommend use of carotid intima-media thickness, ApoB, albuminuria, glomerular filtration rate, or cardiorespiratory fitness in cardiovascular risk assessment. There is adequate evidence to recommend use of high-sensitivity C-reactive protein, ABI, coronary artery calcium score, and a family history of premature cardiovascular disease for refinement of cardiovascular risk assessment.[40]

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Congestive Heart Failure

Miriam S. Jacob • Gary S. Francis • Leslie Cho

QUESTIONS

1. Your patient is a 50-year-old woman with nonischemic cardiomyopathy who just received an orthotopic heart transplant. Which of the following is NOT important to help prevent transplant vasculopathy?

   a. Empirically starting statin therapy
   b. Strict control of hypertension (HTN) and diabetes
   c. Use of rapamycin as part of the immunosuppressive regimen
   d. Abstinence from smoking

2. You are taking care of a 65-year-old man with history of coronary artery disease and prior bypass surgery. He is currently taking carvedilol and lisinopril at maximum doses. He was recently hospitalized for heart failure 3 months ago. Which of the following criteria would make it reasonable to add eplerenone to his regimen?

   a. Ejection fraction (EF) of 15% with creatinine clearance of 20 mL/min/1.73 m^2
   b. EF of 20% and dyspnea while doing chores at home (New York Heart Association [NYHA] class II symptoms)
   c. EF of 35% with QRS >130 milliseconds
   d. EF of 45% and dyspnea with walking less than a block

3. For a patient with heart failure, coronary artery bypass grafting (CABG) is not reasonable for a patient with severe three-vessel coronary artery disease and

   a. chest pain on exertion.
   b. no viability found on dobutamine echo with EF of 15%.
   c. recent ST-elevation myocardial infarction (MI).
   d. heart failure with preserved EF.
   e. systolic heart failure with EF of 30% and viable myocardium.

4. A 60-year-old African American man comes to your clinic with few months' history of fatigue, dyspnea on exertion, and lower extremity edema. He has no history of prior coronary artery disease or heart failure. What features on an echo would not be consistent with amyloid heart disease?

   a. Presence of a pericardial effusion
   b. Biatrial enlargement
   c. Normal tissue Doppler measurement of the left ventricular (LV) lateral and septal walls
   d. LV hypertrophy
   e. Grade 3 diastolic dysfunction

5. Which of the following characterizes heart failure?

   a. Downregulation of β_1- and β_2-receptors
   b. Downregulation primarily of β_1-receptors with little change in β_2-receptors
   c. Downregulation of G proteins and β_1- and β_2-receptors
   d. Increase in myocardial norepinephrine stores
   e. Intact baroreceptor function

6. In the Veterans Administration Heart Failure Trial II (V-HeFT II), which combination of medications improved LV function and exercise tolerance?

   a. Angiotensin-converting enzyme (ACE) inhibitors
   b. Hydralazine plus nitrates
   c. ACE inhibitor plus hydralazine plus nitrates
   d. ACE inhibitor plus nitrates

7. A 56-year-old man presents to your clinic for follow-up after being discharged from the hospital 6 weeks ago. He underwent a successful primary angioplasty for acute anterior MI; however, his EF is now 40%. He is currently taking simvastatin (Zocor), acetylsalicylic aspirin, clopidogrel bisulfate (Plavix), metoprolol tartrate (Lopressor), and losartan (Cozaar). He states that he cannot afford all of these medications. He would like to know which medications are essential for a longer life. Which medications should you tell him are essential?

   a. All of them
   b. All of them except clopidogrel bisulfate
   c. All of them except losartan
   d. All except clopidogrel bisulfate and losartan

8. A 78-year-old woman with congestive heart failure (CHF) (EF, 25%), chronic atrial

fibrillation (AFib), gastroesophageal reflux disease, HTN, hyperlipidemia, diabetes, and osteoporosis takes 12 different pills. At the recent senior citizen day at the local church, a nurse told her that she does not need to take digoxin because she is on amiodarone. She wants to eliminate digoxin from her medication regimen, and she wants to know why you put her on it in the first place. What is your answer?

a. Digoxin improves survival.
b. Digoxin reduces hospitalization.
c. Digoxin improves contractility.
d. Digoxin decreases the volume of distribution of amiodarone.
e. Digoxin reduces sympathetic nervous system activity.

9. Recently, a 43-year-old lawyer received heart transplantation. His hospital course was unremarkable, and he was discharged. He found out from the heart failure nurses that allograft vasculopathy is the leading cause of long-term morbidity and mortality in transplant patients. He wants to know what proven treatments prevent allograft vasculopathy. Which of the following treatments should you recommend?

a. Annual cardiac catheterization, intravascular ultrasound, and percutaneous coronary intervention (PCI), as needed
b. Annual stress test
c. Biannual stress test
d. Statins
e. No known treatment

10. A 72-year-old woman is transferred from another hospital. She was initially admitted with palpitation, diagnosed with AFib, and treated with amiodarone. A transthoracic echocardiogram (TTE) showed an EF of 10% with a regional wall motion abnormality. She underwent cardiac catheterization and was found to have a heavily calcified 80% lesion in the mid–left anterior descending artery (LAD), a 40% lesion in a nondominant circumflex, and an 80% lesion in the posterior descending artery. Her children want to know what you plan to do for her. What should you recommend?

a. She has terrible EF and should be on medication only because CABG would be of too high risk.
b. She should undergo PCI because she is too high risk for CABG.
c. She should undergo CABG because this is the definitive treatment.
d. She should have a positron emission tomography (PET) scan to assess the area of viability before proceeding with CABG or PCI.

11. A 53-year-old woman with a history of CHF presents to the emergency room (ER). She is cool and clammy. She reports being short of breath. Her blood pressure (BP) is 71/40 mmHg, her heart rate (HR) is 110 bpm, and her respiratory rate is 30. She has elevated neck veins and a prominent S_3. Her echocardiogram (ECG) shows sinus tachycardia. She is admitted to the CCU (coronary care unit) with heart failure. A pulmonary artery (PA) catheterization is performed, and her hemodynamics are as follows: right atrial (RA) pressure, 12 mmHg; PA pressure, 62/30 mmHg; cardiac output, 1.9 L/min/m^2; pulmonary capillary wedge pressure (PCWP), 36 mmHg; and systemic vascular resistance (SVR), 2,000 dyne/s/cm^5. Which of the following is your next step?

a. Start furosemide (Lasix).
b. Start dopamine.
c. Insert intra-aortic balloon pump (IABP).
d. Begin dobutamine.
e. Start nesiritide.

12. This patient continues to deteriorate after your initial treatment. Her BP is 64/32 mmHg, and her HR is 132 bpm. She is now intubated on maximal pressor support and has an IABP in place. Which of the following should be your next therapeutic option?

a. There is no option. She is on maximal therapy.
b. Consider emergent cardiac transplant.
c. Consider LV assist device.
d. Consider cardiopulmonary bypass.

13. A 35-year-old man with a history of HTN presents to the ER in respiratory distress. He is intubated in the ER for respiratory distress. His BP is 73/48 mmHg, his HR is 130 bpm, and his respiratory rate is 20. He is taken to the medical ICU (intensive care unit), and a PA catheterization is performed. His hemodynamics are as follows: RA pressure, 22 mmHg; PA pressure, 20/10 mmHg; cardiac output, 3.5 L/min/m^2; PCWP, 12 mmHg; and SVR, 1,690 dyne/s/cm^5. What is your diagnosis?

a. Pulmonary embolism
b. Cardiogenic shock
c. Acute right ventricular (RV) failure
d. Decompensated heart failure
e. Hypovolemic shock

14. You receive a call from a cardiologist in a small community hospital regarding a patient in heart failure. She states that the patient was admitted last night with heart

failure and was started on intravenous (IV) nitroglycerin; IV furosemide infusion; captopril, 12.5 mg t.i.d.; and digoxin. There has been no improvement; therefore, the cardiologist placed a Swan-Ganz catheter this morning. The patient's hemodynamics are as follows: BP, 120/89 mmHg; HR, 89 bpm; cardiac output, 2.0 L/min/m^2; PCWP, 29 mmHg; and SVR, 1,766 dyne/s/cm^5. The cardiologist also added dobutamine. Which of the following additional therapies should you recommend to the cardiologist for this patient?

a. Begin patient transfer arrangement.
b. Suggest nitroprusside.
c. Suggest nesiritide.
d. Suggest dopamine.
e. Suggest IABP.

15. A 57-year-old woman, who experienced inferior wall MI in 1992, has an EF of 30% and was diagnosed with nonsustained ventricular tachycardia (VT) (four beats of VT) at another hospital on a routine ECG that she needed before cataract surgery. She has been in excellent health and has never been hospitalized for CHF. She has never had palpitation or syncopal episodes. Her doctors advised her that she would need an implantable defibrillator. She does not agree and wants a second opinion. She wants to know whether there is any evidence to support the implantable defibrillators. What is your advice?

a. Place an implantable defibrillator.
b. Do not place an implantable defibrillator: A single episode is probably insignificant.
c. Perform an electrophysiologic (EP) study.
d. Begin β-blockers with amiodarone.

16. A 49-year-old man is admitted with new-onset heart failure. He is diagnosed with dilated cardiomyopathy with an EF of 20%. On hospital day 1, he is diuresed and started on a regimen of furosemide, digoxin, acetylsalicylic aspirin, captopril, and simvastatin. A medical student wants to know why you did not start him on a β-blocker. What is your explanation?

a. β-Blockers have not been shown to decrease mortality in dilated cardiomyopathy patients. Only ischemic cardiomyopathy patients have derived benefit.
b. There have been several conflicting results from randomized trials; therefore, β-blockers are not recommended as the first line of therapy.
c. β-Blockers have been shown to improve survival but should only be used in patients with an EF greater than 25%.
d. β-Blockers should be started in stable CHF patients.

17. The same medical student wants to know whether the patient should also be started on calcium channel blockers. What is your answer?

a. There has never been a study to demonstrate the benefit of calcium channel blockers.
b. Diltiazem has proved to be of small but significant benefit in nonischemic cardiomyopathy patients and should be started.
c. Calcium channel blockers should be started after discharge once the patient has been stabilized.
d. Felodipine has proved to be of small benefit only in ischemic cardiomyopathy patients. This patient does not fit this criterion.
e. Amlodipine proved to be of small benefit in a NYHA class III or IV patient with an EF <30%. This benefit was seen more in dilated cardiomyopathy patients.

18. A 24-year-old female medical student presents to urgent care with 5 days of fever and shortness of breath. She is diagnosed with a viral infection and sent home. Five months later during her physical examination class, she is found to have an S_3 by her fellow students. She presents to your office for a second opinion. On examination, she appears healthy and in no distress. Her BP is 96/50 mmHg, with an HR of 71 bpm and a respiratory rate of 12. Her neck veins are not distended, and her examination is unremarkable except for an enlarged heart. You do not appreciate an S_3. You order a TTE, which shows an EF of 20% with a dilated heart. There is no valvular abnormality. Which of the following is your recommendation?

a. Begin ACE inhibitor, β-blockers, and steroid.
b. Begin ACE inhibitor and β-blockers.
c. Begin ACE inhibitor, β-blockers, diuretics, and digoxin.
d. Begin ACE inhibitor, β-blockers, diuretics, and spironolactone.
e. She is well compensated; nothing needs to be done.

19. A 79-year-old man with diabetes, HTN, chronic renal insufficiency, and ischemic cardiomyopathy was recently admitted with CHF exacerbation. At home, he takes captopril, 75 mg t.i.d.; digoxin, 0.125 mg per day; furosemide, 60 mg b.i.d.; aspirin; and atorvastatin calcium (Lipitor). When admitted, he was in heart failure with elevated neck veins and S_3. During his admission, he was diuresed with IV furosemide and metolazone. His baseline creatinine was 1.7 and now is 2.5, with blood urea nitrogen of 100. What is your next step?

a. Stop captopril.
b. Stop diuretics.
c. Rule out renal artery stenosis.

d. Stop aspirin and ACE inhibitor.

20. The severity of symptomatic exercise limitation in heart failure

a. is caused by elevated PCWP.
b. is caused by reduced blood flow to skeletal muscles.
c. bears little relation to the severity of LV dysfunction.
d. can be reversed by inotropic therapy.
e. is related to markers of central hemodynamic disturbance.

21. A 59-year-old woman with CHF and an EF of 30% comes to your office for follow-up. She is on carvedilol (Coreg), enalapril, aspirin, atorvastatin calcium, digoxin, and furosemide. She has been doing well without any rehospitalization. However, she wants to improve her exercise tolerance. What should you recommend?

a. Cardiac transplantation
b. IV dobutamine
c. Higher doses of ACE inhibitor
d. Adding spironolactone
e. Enrolling her in an exercise training program

22. Prognosis in heart failure correlates best with which of the following?

a. Peak $\dot{V}O_2$ during exercise
b. $\dot{V}_E/\dot{V}O_2$ slope during exercise
c. EF at rest
d. Blood gases during exercise
e. Myocardial contractility measurements

23. An 86-year-old woman is transferred from a nursing home in respiratory distress. She was found to be short of breath. On examination, she has labored breathing, and her BP is 62/34 mmHg with an HR of 60 bpm. She is intubated in the ER and admitted to the CCU. She is started on norepinephrine and dopamine at high doses without significant effect. Her ECG shows sinus bradycardia but is otherwise unremarkable. Her chest X-ray (CXR) shows pulmonary edema. The nursing home calls and says that she has mistakenly received 100 mg IV metoprolol tartrate. Which of the following should be your next step?

a. Glucagon and milrinone
b. Glucagon and dobutamine
c. IABP
d. Fluid resuscitation
e. Transvenous pacemaker

24. A 62-year-old man with an EF of 20% and chronic renal insufficiency presents to your office for follow-up. He has non-insulin-dependent diabetes mellitus and has developed worsening renal failure caused by diabetes. His medication regimen includes a β-blocker that is significantly affected by reduced renal function. Which of the following β-blockers is he taking?

a. Propranolol
b. Atenolol
c. Carvedilol
d. Metoprolol
e. Sotalol

25. A 38-year-old patient with CHF is transferred from another hospital. You are doing rounds in the CCU while the clinicians are performing a TTE. They ask you to assess his LV function. You notice that the E:A wave ratio is greater than 1.5, with an E-wave deceleration time of 120 milliseconds. Which of the following do you guess is his PCWP?

a. PCWP is 12 mmHg.
b. PCWP is 18 mmHg.
c. PCWP is 26 mmHg.
d. You cannot tell from the E:A wave ratio and deceleration time.

26. For the patient in the previous question, the E:A wave ratio and the E-wave deceleration time indicate which of the following?

a. Low filling pressure and reduced LV compliance
b. High filling pressure and increased LV compliance
c. Low filling pressure and increased LV compliance
d. High filling pressure and reduced LV compliance

27. A 67-year-old patient with HTN, hyperlipidemia, and an EF of 45% comes to your office for a second opinion. He had an exercise test and was told that his HR recovery was abnormal. His physician told him not to worry unless his heart function deteriorates. He is not convinced and wants your opinion and treatment. What should you recommend?

a. Abnormal HR recovery does not predict mortality in patients with an EF greater than 35%; therefore, no treatment is needed.
b. Abnormal HR recovery predicts mortality only in patients after MI; therefore, no treatment is needed.
c. Abnormal HR recovery predicts mortality in all patients; however, there is no

treatment.

d. Abnormal HR recovery predicts mortality in all patients, and exercise training is the treatment of choice.

28. A 41-year-old man presents to the CCU with CHF symptoms. On examination, he has elevated neck veins, severe peripheral edema, and S_3 gallop. He is started on medication and has improvement in all of his symptoms. He has a PET scan, which shows a large area of hibernating myocardium. His cardiac catheterization reveals mild disease in the right coronary artery, a focal 80% lesion in the circumflex, and a focal 70% lesion in the LAD. All of his lesions are type A American College of Cardiologists/American Heart Association score. His EF is 15%. According to randomized clinical trials, which of the following is the best treatment for this patient?

a. Percutaneous transluminal coronary angioplasty (PTCA)/stent with abciximab and clopidogrel bisulfate
b. PTCA/stent with cardiothoracic surgery backup
c. CABG
d. PTCA/stent with abciximab and IABP

29. A 28-year-old woman comes to your office for a second opinion. She had peripartum cardiomyopathy and wants to get pregnant again. You obtain a TTE, which shows a normal LV. What should you recommend?

a. She should not have another pregnancy because she is likely to have recurrent cardiomyopathy.
b. She may conceive again because her LV is normal. Her chance of having recurrent cardiomyopathy is less than 5%.
c. She may conceive again because her LV is normal. However, her chance of having recurrent cardiomyopathy is 30% to 50%.
d. She should undergo exercise testing for better assessment.

30. A 78-year-old retired federal judge comes to your office for follow-up. He has long-standing HTN and has undergone PTCA/stent for a mid-LAD lesion. He has normal LV function and is active and healthy. Currently he is on ramipril (Altace), atorvastatin, and aspirin. He heard on television that the combination of aspirin and ramipril increases mortality. He wants your opinion. What is your answer?

a. These are only observational studies, and they have not been proven. Continue the current regimen.
b. There are randomized studies to support this; however, the sample size was too small to make any conclusive recommendations. Continue the current regimen.

c. This has been shown in large trials; we should change aspirin to clopidogrel bisulfate or ramipril to metoprolol tartrate.
d. Although this has been seen in retrospective trials, it has not been validated in a randomized trial; therefore, continue the current regimen.

31. A 56-year-old man with dilated cardiomyopathy with an EF of 15% comes to your office for an opinion regarding medication. He is in NYHA class II and wants to know about biventricular pacing. He heard on television news that this may save lives. His ECG shows a sinus rate of 71, a PR interval of 210 milliseconds, a QRS duration of 188 milliseconds, and a QT/QT_C of 364:427 milliseconds. What should you recommend?

a. Refer the patient for biventricular pacing based on PR interval.
b. Refer the patient for biventricular pacing based on QRS duration.
c. Refer the patient for biventricular pacing based on QT/QT_C interval.
d. Refer the patient for exercise test to further assess.

32. A 31-year-old woman with hypertrophic cardiomyopathy presents to your office for follow-up. She has been doing well. She denies any palpitation or syncope. She has researched her disease on the Web and found out that most people die of arrhythmia. She would like to have an EP study. Which of the following is the predictive value of the EP study for ventricular arrhythmia?

a. 20%
b. 40%
c. 50%
d. 80%
e. 100%

33. A 61-year-old woman with an EF of 50% is admitted with an AFib with rapid ventricular response. She is started on metoprolol tartrate with excellent rate control and heparin. Her daughter, who is a nurse, wants to know why you did not start her on dofetilide because this is the best new drug. What is your response?

a. Dofetilide showed increased mortality when compared with amiodarone and would be a bad choice for her mother.
b. Dofetilide had safety and efficacy comparable to those of β-blockers.
c. Dofetilide was used in patients with an EF less than 35%.
d. Dofetilide has safety and efficacy comparable to those of calcium channel blockers.
e. Dofetilide is reserved for patients with chronic renal insufficiency.

34. A 79-year-old woman with HTN and non-insulin-dependent diabetes mellitus comes to your office for a second opinion. She is doing well and is currently on enalapril, aspirin, simvastatin, glipizide, and metformin. She read in her monthly American Association of Retired Persons newsletter that losartan is better than enalapril. She wants you to change her prescription. Based on trial data, which of the following is your recommendation?

a. Losartan did not show mortality benefit but did show reduced hospitalization; because she has no history of CHF, there is no reason to change her medication.
b. Losartan showed neither mortality benefit nor reduced hospitalization.
c. Losartan did not show mortality benefit but decreased the risk of MI; therefore, she should have her prescription changed.
d. Losartan did show mortality benefit, but only in patients younger than 60 years.

35. A 61-year-old woman with CHF and an EF of 25% is admitted with CHF exacerbation to your partner's service. On the day of discharge, your partner is sick, and you must explain her discharge medications. You explain to her the benefits of lisinopril, simvastatin, aspirin, digoxin, and furosemide. Finally, you want to explain the benefit of spironolactone (Aldactone) to her. What is your explanation?

a. Spironolactone in addition to standard therapy (ACE inhibitor, diuretic) does not decrease mortality or morbidity.
b. Spironolactone in addition to standard therapy only decreases rehospitalization —it does not improve NYHA functional class.
c. Spironolactone in addition to standard therapy decreases mortality and rehospitalization.
d. Spironolactone only benefits those not on standard therapy.

36. A 63-year-old man with non-insulin-dependent diabetes mellitus, HTN, hyperlipidemia, and chronic renal insufficiency is admitted with acute anterior wall MI 10 hours after symptom onset. He is taken emergently to the cardiac catheterization laboratory. He is noted to have proximal LAD occlusion, and he undergoes a successful PTCA/stent to the LAD with abciximab and heparin. His EF is noted to be 30% on a TTE performed 3 days later. On hospital day 4, he reports chest pain and is found to be in AFib with an HR of 121. His BP is 90/44 mmHg, and he is short of breath and anxious. Which of the following should you administer next?

a. Procainamide
b. Lidocaine
c. Amiodarone

d. Metoprolol tartrate
e. Cardioversion

37. An LV pressure–volume loop is shown in Figure 8.1. Label 1, 2, 3, and 4.

a. Mitral valve opening
b. End diastole
c. Aortic valve opening
d. End systole

38. A 57-year-old man with a history of CHF presents with acute pulmonary edema. His BP is 110/60 mmHg with an HR of 92 bpm. His examination is consistent with heart failure. His hemodynamics are as follows: PA pressure, 62/27 mmHg; PCWP, 12 mmHg; cardiac output, 1.8 L/min/m^2; and SVR, 1,968 dyne/s/cm^5. Which way should the LV pressure–volume loop be shifted?

a. To the right
b. To the left
c. Up
d. Down

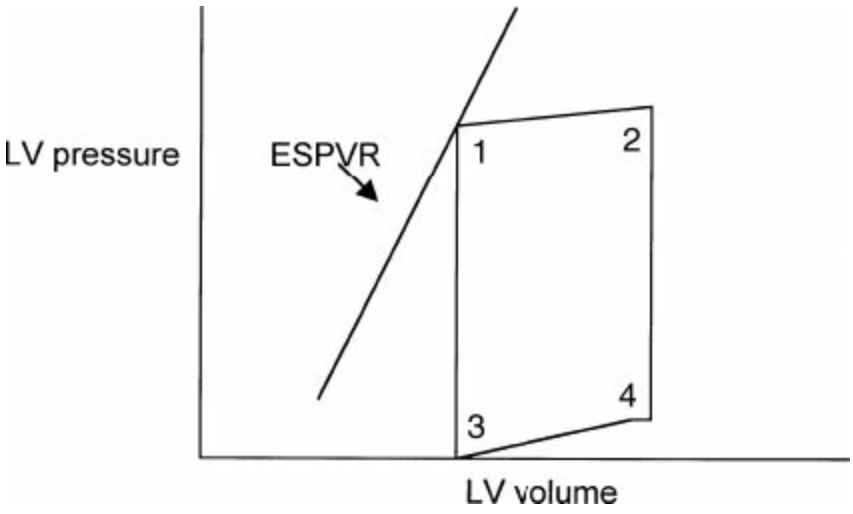

Figure 8.1 ESPVR, end-systolic pressure–volume relation (From Little WC, Braunwald E. Assessment of cardiac function. In: Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine, 5th ed. Philadelphia, PA: WB Saunders; 1997, with permission.)

Questions 39 to 43

Figures 8.2, 8.3, 8.4, 8.5, and 8.6 are schematic illustrations of the carotid pulse. Match the diagnosis with the pulse.

a. Normal
b. Aortic stenosis
c. Aortic regurgitation

d. Hypertrophic cardiomyopathy
e. Severe CHF decompensation

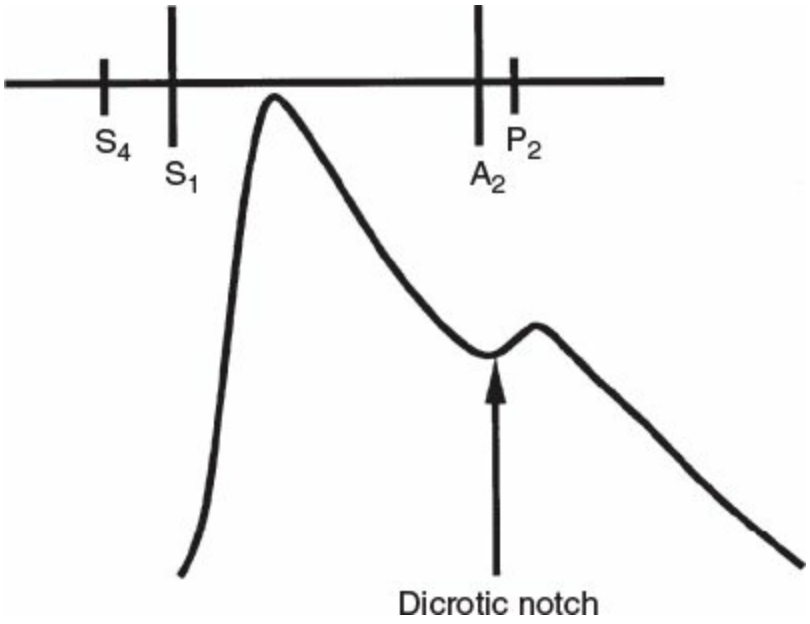

Figure 8.2 (From Chatterjee K. Physical examination. In: Topol EJ, ed. Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: Fig. 15.2, with permission.)

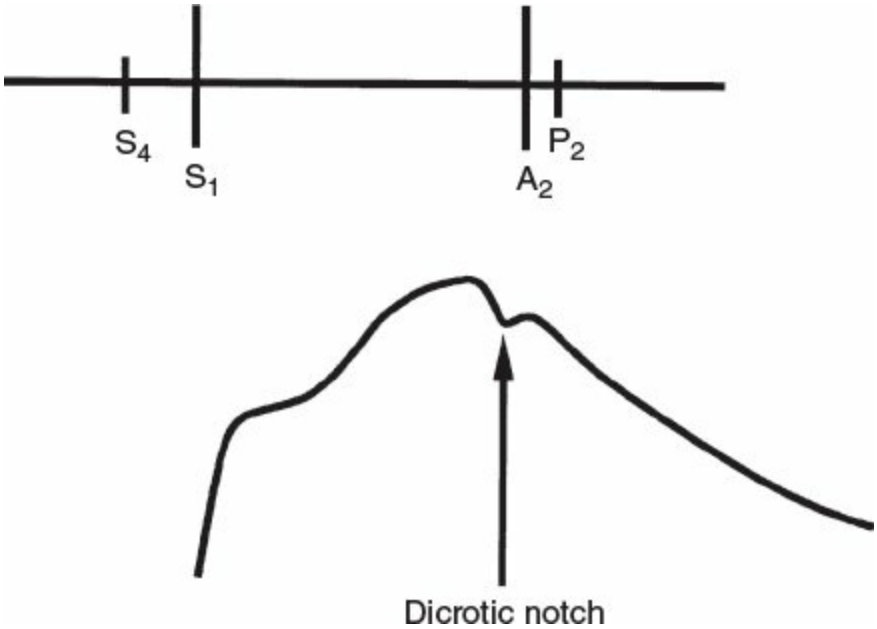

Figure 8.3 (From Chatterjee K. Physical examination. In: Topol EJ, ed. Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: Fig. 15.2, with permission.)

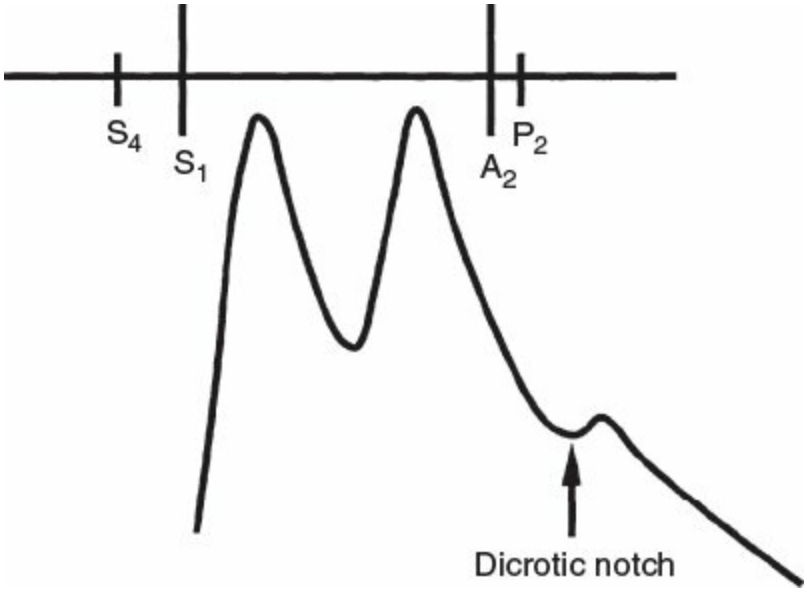

Figure 8.4 (From Chatterjee K. Physical examination. In: Topol EJ, ed. Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: Fig. 15.2, with permission.)

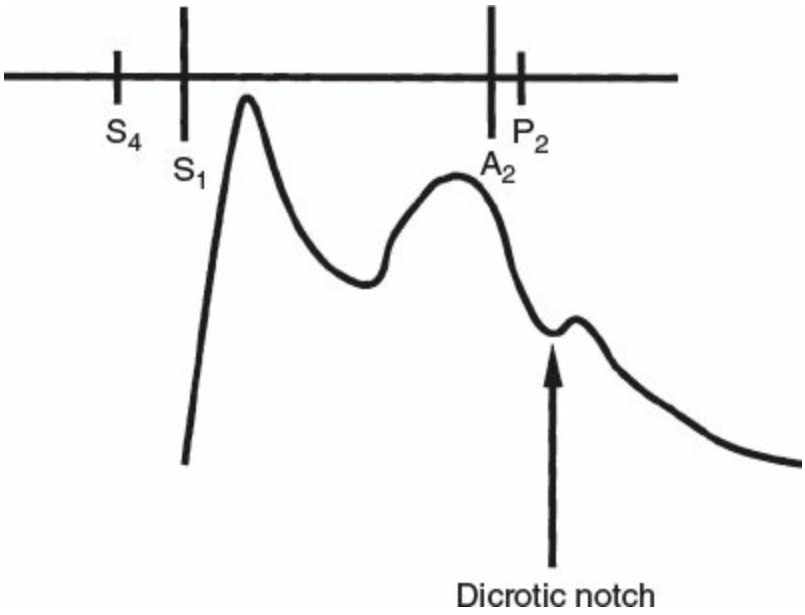

Figure 8.5 (From Chatterjee K. Physical examination. In: Topol EJ, ed. Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: Fig. 15.2, with permission.)

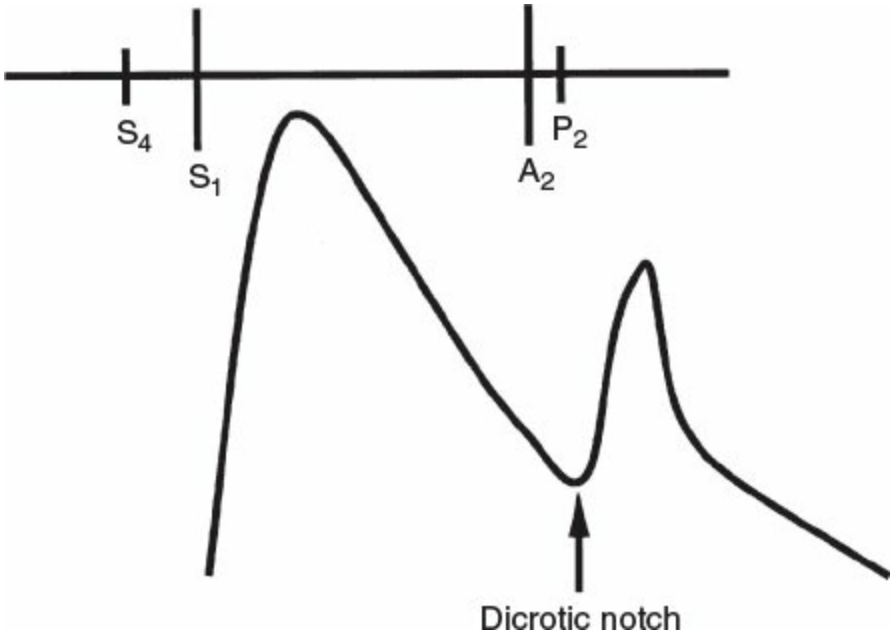

Figure 8.6 (From Chatterjee K. Physical examination. In: Topol EJ, ed. Textbook of Cardiovascular Medicine, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002: Fig. 15.2, with permission.)

44. During physical examination, you notice an elevated systemic venous pressure with sharp y-descent Kussmaul sign and quiet pericardium. What might the patient have?

a. Constrictive pericarditis
b. Restrictive myocardial disorder
c. Tricuspid regurgitation
d. Pulmonary HTN
e. Tamponade

45. During another physical examination, you notice a prominent v wave with a sharp y descent. What condition does the patient have?

a. Constrictive cardiomyopathy
b. Restrictive cardiomyopathy
c. Tricuspid regurgitation
d. Pulmonary HTN
e. Tamponade

46. Again you notice an elevated systemic venous pressure without obvious x or y descent and quiet precordium and pulsus paradoxus. What does the patient have?

a. Constrictive cardiomyopathy
b. Restrictive cardiomyopathy
c. Tricuspid regurgitation
d. Pulmonary HTN

e. Tamponade

ANSWERS

1. **c.** Use of rapamycin as part of the immunosuppressive regimen. Transplant vasculopathy is a possible complication after transplant that is best to be avoided. The recommended intervention is to control cardiovascular risk factors and start every patient on a statin. Once there is vasculopathy, proliferation signal inhibitors (PSIs) such as sirolimus and everolimus can be used (substituted for mycophenolate mofetil or azathioprine).

2. **b.** EF of 20% and dyspnea while doing chores at home (New York Heart Association [NYHA] class II symptoms). Based on the results of Emphasis-HF trial, patients with NYHA class II symptoms and EF <30% are eligible for adding eplerenone to their regimen if they were hospitalized in the last 6 months or had an elevated brain natriuretic peptide. This extended the patients who could be placed on an aldosterone blocker. Previous studies studied the benefit of spironolactone in patients with NYHA class IV symptoms in the last 6 months and EF ≤35% and eplerenone in patients 2 weeks post-MI with EF ≤40% and signs of heart failure. Aldosterone antagonists should not be used in patients with creatinine clearance <30 mL/min/1.73 m^2. EF or QRS alone are not enough to determine patients who would benefit. Functional class assessment is important.

3. **b.** No viability found on dobutamine echo with EF of 15%. The use of surgical revascularization of coronary disease and systolic heart failure is reasonable in patients with acute coronary syndrome and symptomatic angina. Although in the STITCH (Surgical Treatment for Ischemic Heart Failure) trial, a study of medical therapy versus CABG in patients with EF ≤35%, there was no difference in all-cause mortality, there was a suggestion of a trend toward patients with CABG having fewer hospitalizations for heart failure or death from cardiovascular causes. The choice of CABG in a patient with no viability and very low EF is unlikely to be successful in improving morbidity or mortality from heart failure.

4. **c.** Normal tissue Doppler measurement of the left ventricular (LV) lateral and septal walls. Patients with amyloid heart disease usually show restrictive pattern of diastology with low tissue Doppler of the LV myocardium.

5. **b.** Downregulation primarily of β_1-receptors with little change in β_2-receptors. In the cardiac myocyte, there are 3 adrenergic receptors (α_1, β_1, and β_2). In a normal heart

the predominant β receptor is β_1. In a failing heart there is selective down-regulation of β_1 receptors not β_2 receptors.

6. **b.** Hydralazine plus nitrates. In the V-HeFT II trial, although ACE inhibitors improved survival, it was hydralazine in combination with nitrates that had greater improvement in LV function and exercise tolerance.

7. **c.** All of them except losartan. There is no trial evidence that angiotensin II receptor blocker improved mortality in post-MI patients. The Studies of Left Ventricular Dysfunction (SOLVD) prevention used ACE inhibitors in patients with an EF less than 35%.

8. **b.** Digoxin reduces hospitalization. In the large Digitalis Investigation Group study, digitalis only improved hospitalization. It had no effect on survival.

9. **e.** No known treatment. Allograft vasculopathy is the leading cause of long-term morbidity and mortality for cardiac transplant patients. Routine cardiac catheterization has been advocated for these patients but has not shown survival benefit with revascularization. Statin therapy appears to improve long-term survival in these patients and should be used for all heart transplant patients. However, its effect on allograft vasculopathy is unknown.

10. **d.** She should have a positron emission tomography (PET) scan to assess the area of viability before proceeding with CABG or PCI. This patient is at high risk for any type of intervention because of her low EF. However, if there are areas of viability on the PET scan, her EF might improve with complete revascularization. Studies have consistently shown that patients with low EF do better with CABG than with PCI.

11. **b.** Start dopamine. This patient is in cardiogenic shock. She needs BP support before all else. In these patients, dopamine is the first line of choice, followed by norepinephrine. If there is no change with dopamine and norepinephrine, then dobutamine may be added while the patient is being prepared for IABP placement.

12. **c.** Consider LV assist device. This is a relatively young patient with no contraindication to cardiac transplant. However, in the current state, she is not eligible for transplantation. LV assist device as a bridge to transplant has been performed with success.

13. **c.** Acute right ventricular (RV) failure. His hemodynamic pressures are

characteristic of acute RV failure. He needs aggressive fluid resuscitation.

14. **b.** Suggest nitroprusside. This patient is in heart failure and needs to have her BP and SVR lowered. BP is adequate and does not need vasopressor or IABP support. Although nesiritide has been approved for use in acute heart failure, it only mildly lowers the BP.

15. **a.** Place an implantable defibrillator. She fits the criteria of the initial Multicenter Automatic Defibrillator Trial (MADIT). Therefore, based on randomized clinical trial data, she would benefit from an implantable defibrillator. Also, secondary prevention trials such as the Antiarrhythmics Versus Implantable Defibrillators Trial, the Canadian Implantable Defibrillator Study, and the Cardiac Arrest Study Hamburg trial also support an implantable defibrillator in this patient.

16. **d.** β-Blockers should be started in stable CHF patients. They should not be started when the patient is congested. Although nonselective agents with vasodilating effects may be preferred, this is not clear at this time.

17. **e.** Amlodipine proved to be of small benefit in a NYHA class III or IV patient with an EF <30%. This benefit was seen more in dilated cardiomyopathy patients. In the Prospective Randomized Amlodipine Survival Evaluation Trial, in which NYHA class III or IV patients with an EF less than 30% were enrolled, there was a statistically insignificant reduction in the combined mortality and morbidity in the amlodipine group. However, the benefit appeared to be greater in patients with nonischemic cardiomyopathy.

18. **b.** Begin ACE inhibitor and β-blockers. She has well-compensated cardiomyopathy. Only medication that prolongs her life needs to be started. She does not need medication for symptom relief; therefore, ACE inhibitor and β-blockers should be started.

19. **b.** Stop diuretics. This patient has prerenal azotemia caused by aggressive diuresis. His renal function should recover.

20. **c.** Bears little relation to the severity of LV dysfunction. Short-term administration of positive inotropic agents and vasodilators does not improve maximal exercise capacity in patients with CHF. Moreover, ACE inhibitors have failed to show consistent improvement in exercise tolerance. Numerous studies have not shown a correlation between LV function and exercise tolerance.

21. **e.** Enrolling her in an exercise training program. As stated, there is no medication that has consistently shown improvement in exercise tolerance; exercise training is the only method that has shown consistent improvement in these patients.

22. **b.** $\dot{V}_E/\dot{V}O_2$ slope during exercise. This is the best correlate of prognosis. There is a higher ventilation for any given CO_2 production ($\dot{V}_E/\dot{V}O_2$ slope), which reflects the severity of heart failure and prognosis.

23. **a.** Glucagon and milrinone. Milrinone is a second-generation phosphodiesterase inhibitor. It has no β-effect; therefore, it is an ideal vasopressor in the setting of β-blocker overdose. Although a pacer is a good idea and should be placed, giving medication is faster and should be instituted first.

24. **b.** Atenolol. Atenolol is most affected by reduced renal function. Depending on how severe his creatinine clearance is, he should have his medication dose or frequency adjusted.

25. **c.** PCWP is 26 mmHg. Restrictive mitral inflow pattern in the presence of a short E-wave deceleration time has been shown to correlate with high pulmonary capillary pressure, impaired functional class, and bad prognosis in postinfarction patients.

26. **d.** High filling pressure and reduced LV compliance. These conditions are indicated by a restrictive mitral inflow pattern with short E-wave deceleration time.

27. **c.** Abnormal HR recovery predicts mortality in all patients; however, there is no treatment. A delayed decrease in HR after exercise or an abnormal HR recovery predicts all-cause mortality in healthy adults and in patients referred for exercise testing—independent of ischemia. However, at this time, there is no treatment to improve abnormal HR recovery.

28. **c.** CABG. This patient has left main trunk equivalent with low EF. He is a candidate for CABG with left internal mammary artery to the LAD. CABG will prolong his long-term survival compared with PTCA/stent.

29. **d.** She should undergo exercise testing for better assessment. Recurrent peripartum cardiomyopathy occurs in 20% of patients with normal resting LV function but abnormal stress ventricular response. Recurrent peripartum cardiomyopathy with decompensation occurred in 41% of patients with abnormal resting LV function.

30. **d.** Although this has been seen in retrospective trials, it has not been validated in a

randomized trial; therefore, continue the current regimen. In a substudy done by the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, aspirin did not decrease the mortality benefit of lisinopril after MI or increase the risk of adverse clinical events. There have been some retrospective studies to assess this question that have had conflicting results; therefore, it is best to stay with the current regimen.

31. **b.** Refer the patient for biventricular pacing based on QRS duration. Patients with QRS duration greater than 150 to 160 milliseconds derived the greatest benefit from biventricular pacing.

32. **a.** 20%. There is no role for routine EP study in the asymptomatic hypertrophic cardiomyopathy patient.

33. **c.** Dofetilide was used in patients with an EF less than 35%. The study compared dofetilide with amiodarone. Dofetilide did not increase mortality. It has not been studied against β-blockers or calcium channel blockers in patients with normal EF.

34. **b.** Losartan showed neither mortality benefit nor reduced hospitalization. In the large Evaluation of Losartan in the Elderly II study, losartan did not show mortality benefit or reduced hospitalization. Losartan was better tolerated than captopril. Because the patient has no side effects with enalapril, her prescription should not be changed.

35. **c.** Spironolactone in addition to standard therapy decreases mortality and rehospitalization. In the Randomized Aldactone Evaluation Study, patients with NYHA class III or IV with an EF less than 35% had improvement in mortality, reduction in hospitalization, and improvement in functional class when spironolactone was taken in addition to standard therapy (ACE inhibitor and diuretic).

36. **e.** Cardioversion. This patient has post-MI AFib. He has LV dysfunction and renal insufficiency. Procainamide should be used in patients with normal LV and renal clearance. Amiodarone would take too long to work, and he is already in distress. Lidocaine is not used in AFib. Metoprolol tartrate would exacerbate his heart failure; therefore, cardioversion is the only choice.

37. An LV pressure–volume loop.

a.= 1. Mitral valve opening
b.= 2. End diastole

c.= 3. Aortic valve opening
d.= 4. End systole

38. **c.** Up. The response of the LV to increased afterload is to shift the loop up. Increased preload would shift the loop to the right.

39. **a.** Normal. The initial peak of the carotid puse waveform reflects the ejection of the blood from the LV into the aorta before it goes into the periphery. After the pressure peaks, it begins a decline as ejection slows and blood continues to flow to the periphery. There is a reversal of blood flow from the compliant central arteries back toward the ventricle. With this reversal of flow, the aortic valves close. A notch on the descending limb of the aortic pressure curve is associated with this transient reversal of blood flow. The smaller secondary positive wave is attributed to the elastic recoil of the aorta and aortic valve.

40. **b.** Aortic stenosis. Pulsus parvus et tardus which is characteristic of aortic stenosis. Small and delayed carotid pulse.

41. **c.** Aortic regurgitation. Pulsus bisferiens or bifid arterial pulse.

42. **d.** Hypertrophic cardiomyopathy. This can also be characterized by a bisferiens carotid pulse with rapid fall in first wave with rapid rise of the second.

43. **e.** Severe CHF decompensation. Demonstrates the dicrotic pulse which can occur in diastole in patients with low stroke volume being ejected. This can occur in severe heart failure, cardiac tamponade, and hypovolemic shock.

44. **a.** Constrictive pericarditis. The high initial venous wave (a wave) is characteristic of atrial contraction. The rapid y descent is suggestive of rapid ventricular filling.

45. **c.** Tricuspid regurgitation. The v wave is a reflection of ventricular contraction and the pressure that is transmitted back to the atrium from a tricuspid valve that pushes back into the atrium. In the tricuspid regurgitation, there is increased pressure during ventricular systole.

46. **e.** Tamponade. There is constant pressure from the pericardium that does not allow for atrial relaxation so the y descent is blunted.

SUGGESTED READINGS

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Adult Congenital Heart Disease

Luke J. Burchill

Adult Congenital Heart Disease Source Material

Published guidelines for the management of adult congenital heart disease (ACHD) patients provide an excellent overview of ACHD and are a rich source of questions for the cardiology boards.[1–5] The questions in this section relate directly to existing guidelines for the care of ACHD patients, with particular emphasis given to the American Heart Association (AHA) guidelines.

QUESTIONS

1. A 55-year-old woman with a history of unrepaired ventricular septal defect (VSD) and Eisenmenger physiology presents to your clinic. Her most recent hemoglobin measured 17.5 g/dL (11.5 to 15.0), hematocrit 55% (36 to 46), mean corpuscular volume (MCV) 76 (83 to 99), and platelet count 140 × 10^3 cells/μL (150 to 400). She reports New York Heart Association class III limitations with increasing fatigue and infrequent headaches over the last 6 months. Blood pressure (BP) 110/70 mmHg, heart rate (HR) 70 BPM, and regular, O_2 saturation 77% on room air. Cardiac examination reveals peripheral clubbing and cyanosis, a parasternal heave, loud P_2, and a murmur of tricuspid regurgitation (TR). Electrocardiogram (ECG) shows sinus rhythm. She has had repeat phlebotomy for treatment of presumed hyperviscosity syndrome but does not feel any better. What of the following options is the most appropriate next step in management?

   a. Phlebotomy should continue until symptoms improve.
   b. Refer for heart–lung transplantation.
   c. Measure serum erythropoietin.
   d. Commence a pulmonary vasodilator.
   e. Obtain iron studies.

2. A 25-year-old man presents to your clinic with 48-hour history of documented fever and chills. He has a history of a "hole in the heart" and examination reveals a 4/6 systolic murmur heard loudest at the lower left sternal edge. A restrictive muscular VSD is confirmed on echocardiogram. Which of the following is the most appropriate next step?

   a. Oral antibiotics
   b. Intravenous (IV) antibiotics
   c. Blood cultures
   d. Transesophageal echocardiogram
   e. Cardiac surgery consult

3. Blood cultures are positive for Streptococcus viridans and the patient is treated for infective endocarditis (IE). A small mobile echodensity is noted adjacent to the VSD. At clinic review 3 months later he is much improved, repeat blood cultures are negative, and transesophageal echocardiography (TEE) is negative for vegetations. The patient asks whether his VSD should now be closed. What is the best answer?

   a. Closure is indicated in those with a VSD complicated by IE.
   b. VSD closure is NOT indicated in those with a VSD complicated by IE.
   c. VSD closure is only indicated in the presence of a significant shunt (Q_p/Q_s, pulmonary to systemic blood flow ratio ≥ 2.0).
   d. VSD closure is only indicated in the presence of a significant shunt accompanied by symptoms.

4. For which of the following conditions is IE prophylaxis not required prior to extensive dental procedures (more than one option may be correct)?

   a. Ebstein anomaly without prior intervention
   b. 4 weeks following percutaneous closure of a secundum atrial septal defect (ASD)
   c. Mechanical aortic valve replacement (AVR) for bicuspid aortic valve disease
   d. Eisenmenger syndrome
   e. Tetralogy of Fallot (TOF) with residual VSD at the site of prior surgical repair

5. With which of the following adult congenital heart conditions can the following ECG tracing be seen (Fig. 9.1)?

   a. Primum ASD
   b. Congenitally corrected transposition
   c. Ebstein anomaly
   d. VSD

e. Coarctation of the aorta

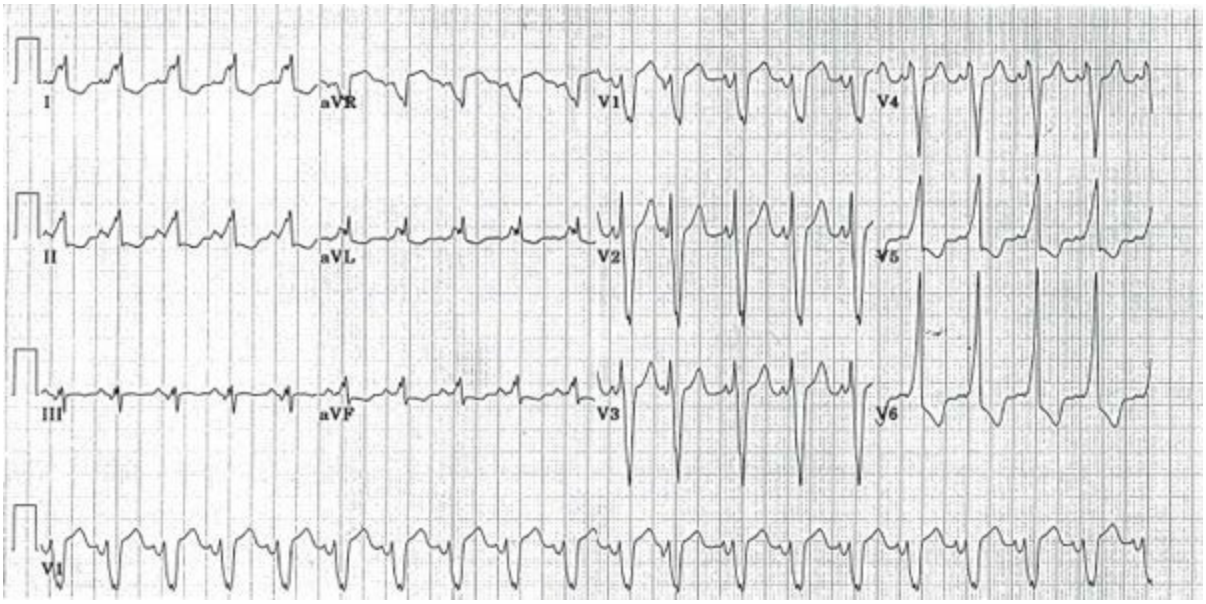

Figure 9.1

6. Which of the following is an absolute contraindication to pregnancy?

   a. Surgically corrected transposition of great arteries
   b. Congenitally corrected transposition of great arteries
   c. Ebstein anomaly
   d. Eisenmenger syndrome
   e. Status post Fontan operation

Questions 7 to 11

Match the following conditions with their corresponding surgical procedures. There may be more than one answer for each question.

7. Pulmonary atresia

8. D-transposition of great vessels

9. Tricuspid atresia

10. Congenitally corrected transposition of the great arteries

11. Aortic stenosis

   a. Ross
   b. Blalock-Taussig
   c. Senning or Mustard

d. Arterial switch
e. Fontan
f. Rashkind
g. None of the above

Questions 12 to 16

Match the following disease conditions with their gender preponderance.

12. VSD

13. ASD

14. Bicuspid aortic valve

15. Coarctation of the aorta

16. Pulmonary atresia with an intact ventricular septum

a. Predominantly male
b. Predominantly female
c. Equal preponderance

Questions 17 to 21

Match the following cardiac catheterization still-frame slides (Figs. 9.2, 9.3, 9.4, 9.5, and 9.6) to their respective diagnoses.

17. Figure 9.2

18. Figure 9.3

19. Figure 9.4

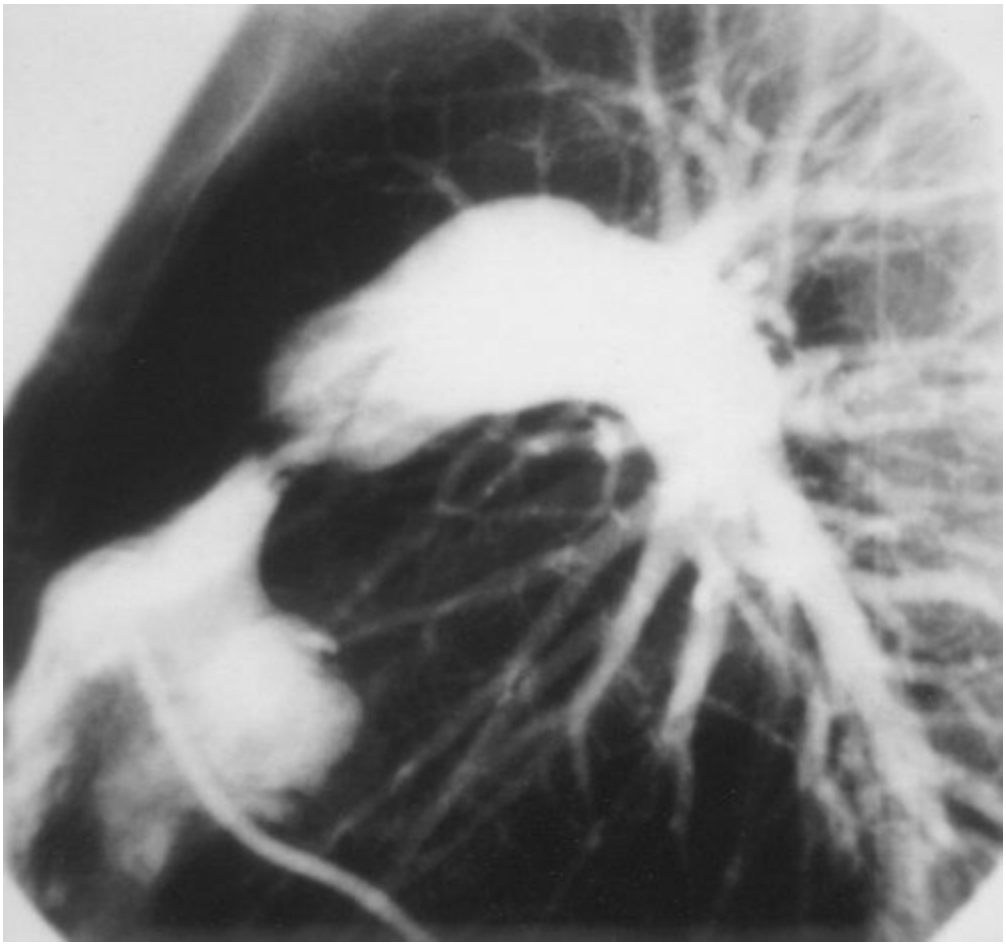

Figure 9.2

Figure 9.3

20. Figure 9.5

21. Figure 9.6

a. Coarctation of the aorta
b. Patent ductus arteriosus (PDA)
c. Hypertrophic cardiomyopathy
d. Pulmonic stenosis
e. VSD

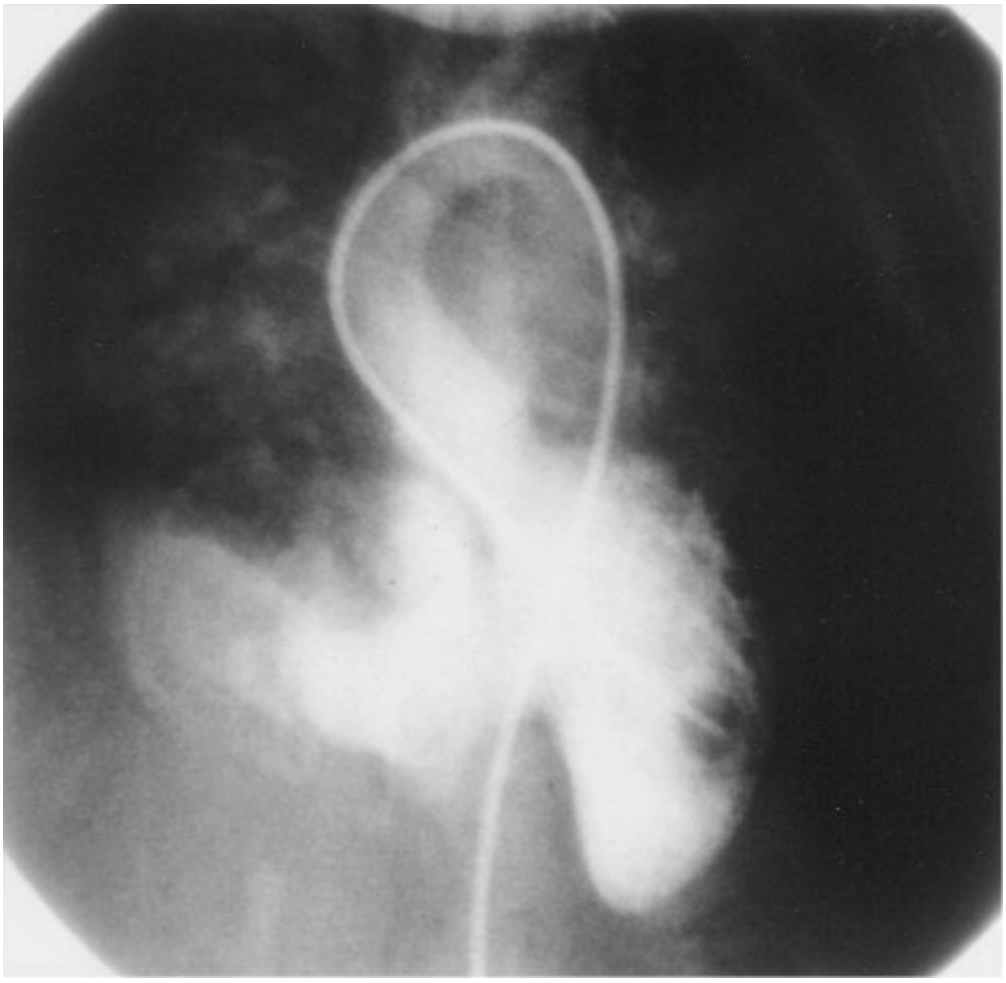

Figure 9.4

Figure 9.5

Questions 22 to 26

Match the physical examination findings with the corresponding adult congenital heart disorder.

22. Right ventricular (RV) lift with a loud systolic ejection murmur along the left sternal border, with a single S_2

23. Systolic ejection click, loud S1, holosystolic murmur, split S2 and hepatomegaly

24. Weak or delayed femoral arterial pulses, harsh systolic ejection murmur in the back, and a systolic ejection click in the aortic area

25. Cyanosis, digital clubbing, loud P_2, and a variable Graham Steell murmur

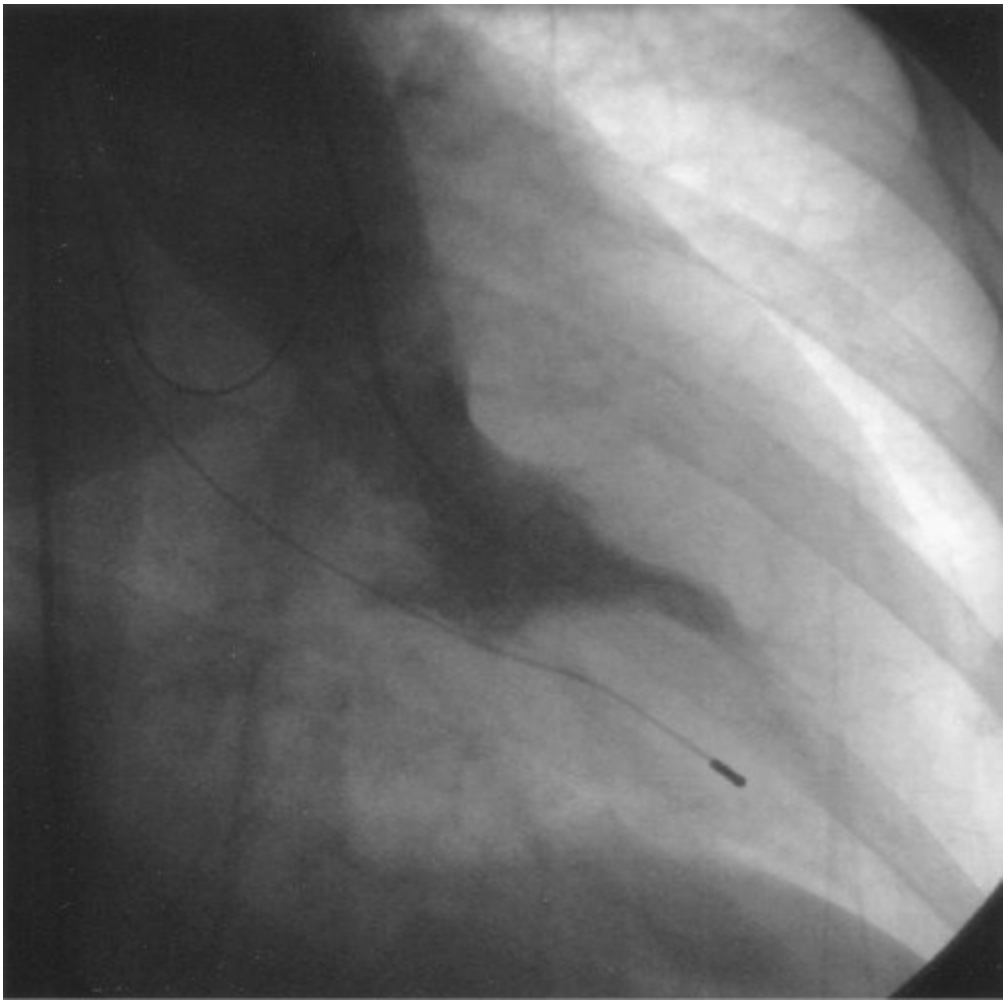

Figure 9.6

26. Wide pulse pressure, prominent left ventricular (LV) impulse, and a continuous machinery murmur enveloping S_2

- **a.** Eisenmenger syndrome
- **b.** Coarctation of the aorta
- **c.** PDA
- **d.** Ebstein anomaly
- **e.** TOF

Questions 27 to 31

Match the following congenital defects with their associated disease conditions. (more than one may apply)

27. Ostium primum ASD

28. Noonan syndrome

29. Coronary sinus ASD

30. Williams syndrome

31. Sinus venosus ASD

a. Supravalvular aortic stenosis
b. Supravalvular pulmonic stenosis
c. Cleft mitral valve
d. Anomalous pulmonary venous drainage
e. Persistent left superior vena cava (SVC)

Questions 32 to 36

Match the characteristic chest radiography findings with the corresponding congenital disorder.

32. Prominent central pulmonary arteries (PAs) (possible calcifications) and peripheral pruning

33. Right aortic arch, RV enlargement, and a "boot-shaped" heart

34. Marked cardiomegaly, severe right atrial (RA) enlargement, and normal lung fields

35. Posterior rib notching and a "reverse E" or "3" sign

36. Pulmonary plethora, prominent ascending aorta, proximal PA dilatation, and opacity at the confluence of the aortic knob and descending aorta

a. Eisenmenger syndrome
b. Coarctation of the aorta
c. PDA
d. Ebstein anomaly
e. TOF

Questions 37 to 41

Match the following congenital cardiac disorder with the characteristic transthoracic echocardiogram (TTE) finding (Figs. 9.7, 9.8, 9.9, 9.10, and 9.11).

37. Bicuspid aortic valve

38. Cor triatriatum

39. Ostium primum ASD

40. Quadricuspid aortic valve

41. Subaortic valve stenosis

    a. Figure 9.7
    b. Figure 9.8
    c. Figure 9.9
    d. Figure 9.10
    e. Figure 9.11

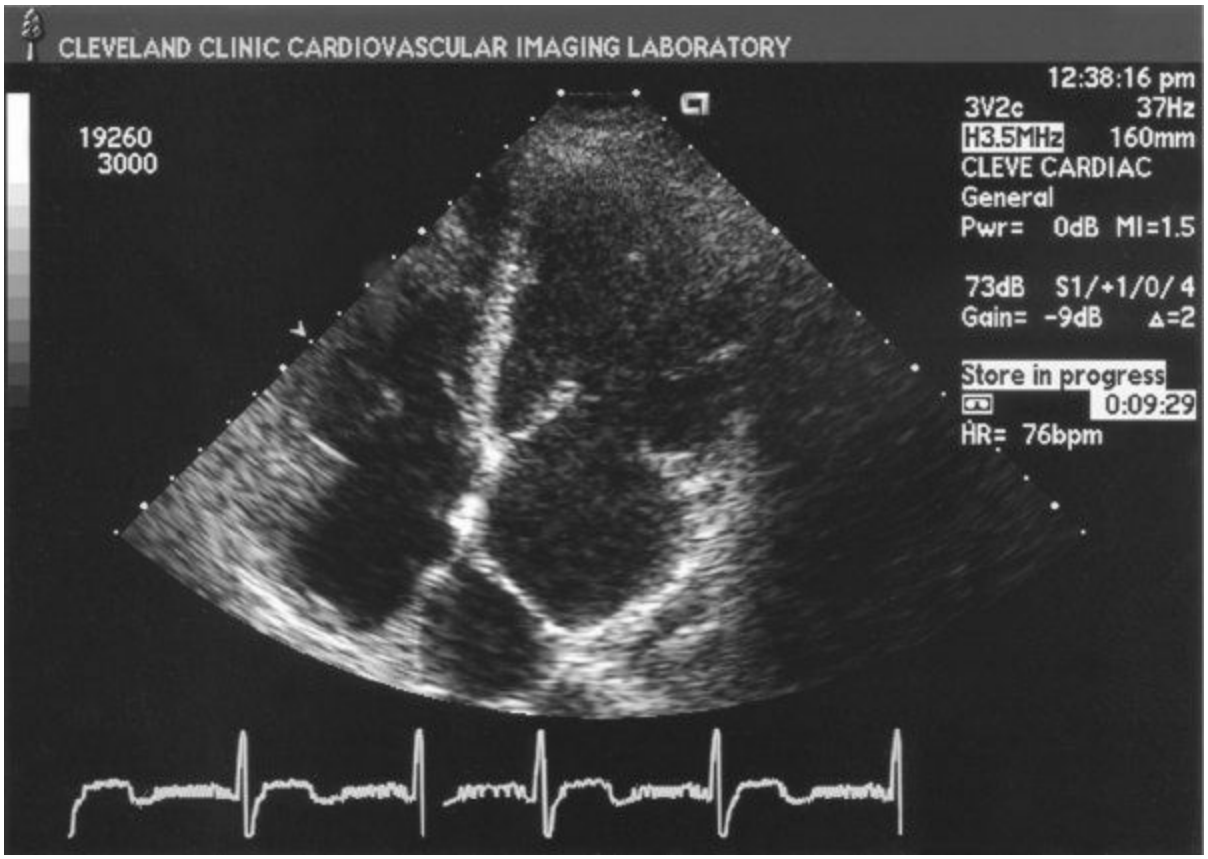

Figure 9.7

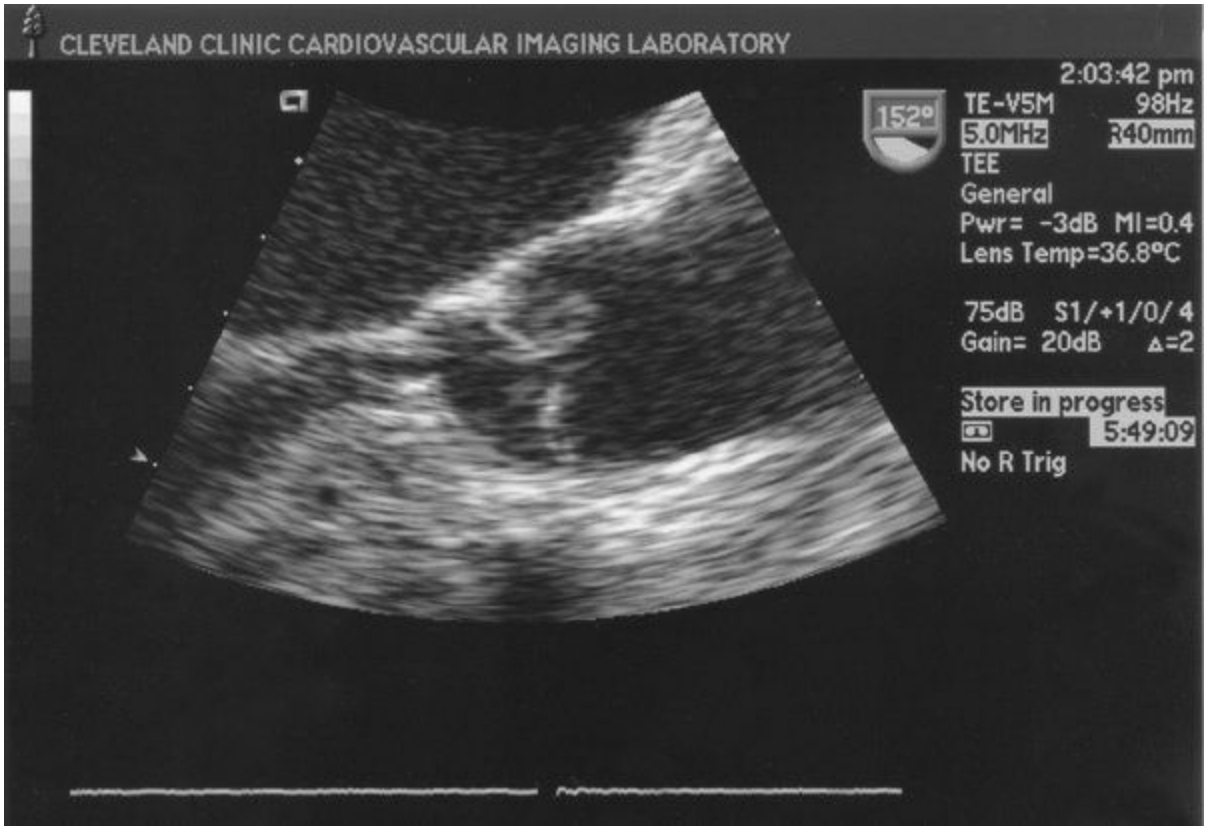

Figure 9.8

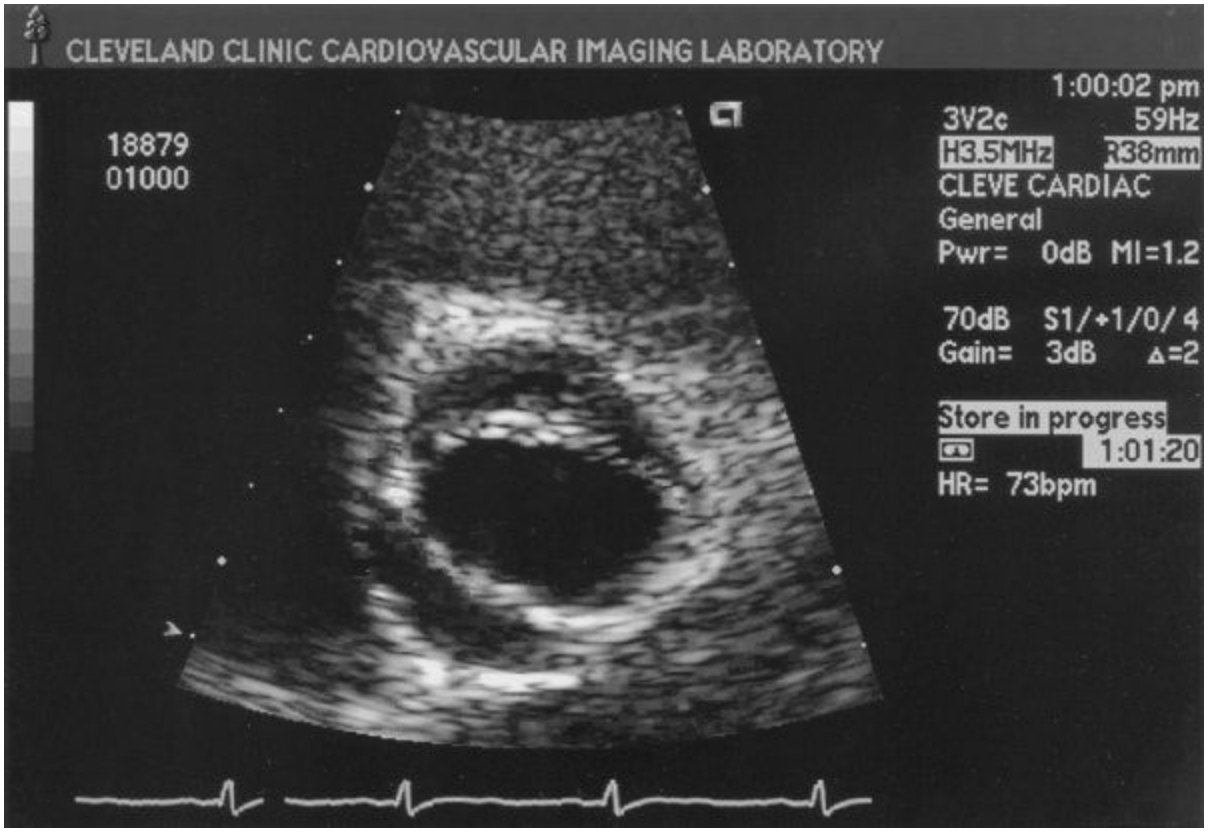

Figure 9.9

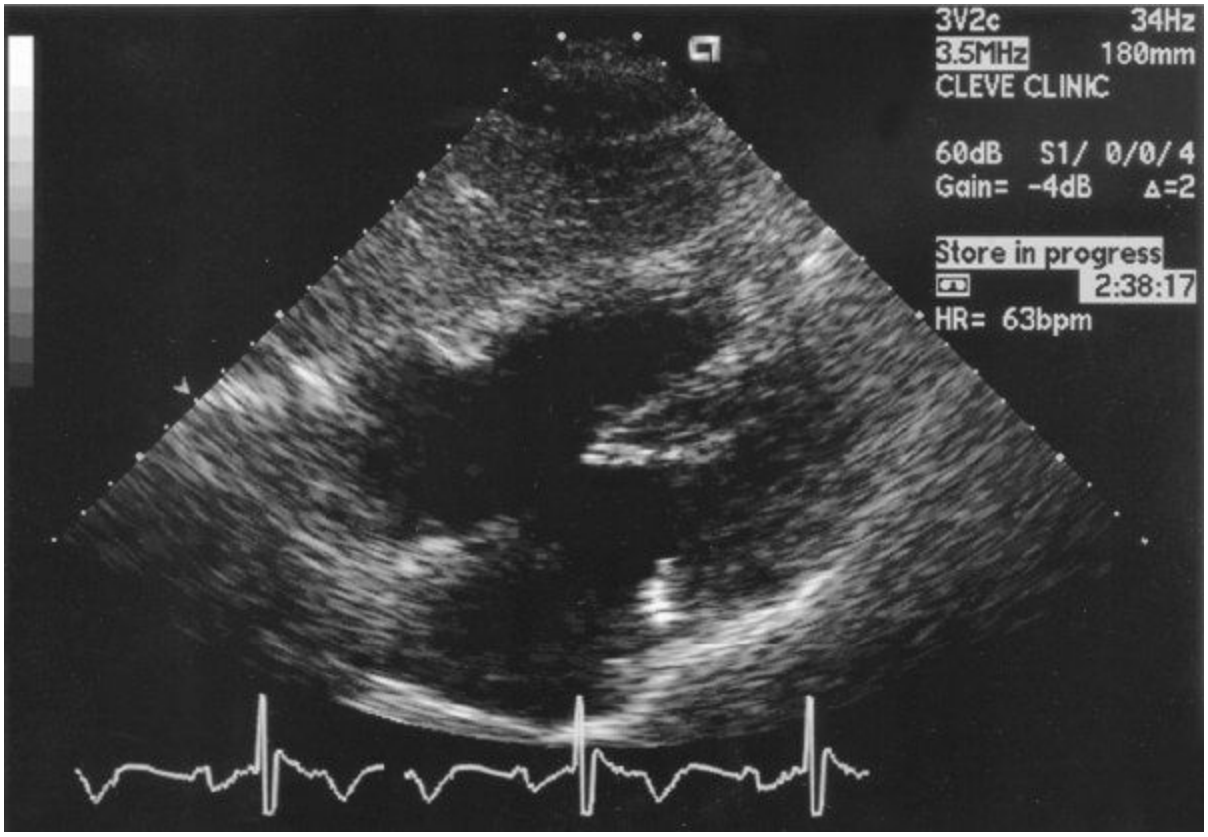

Figure 9.10

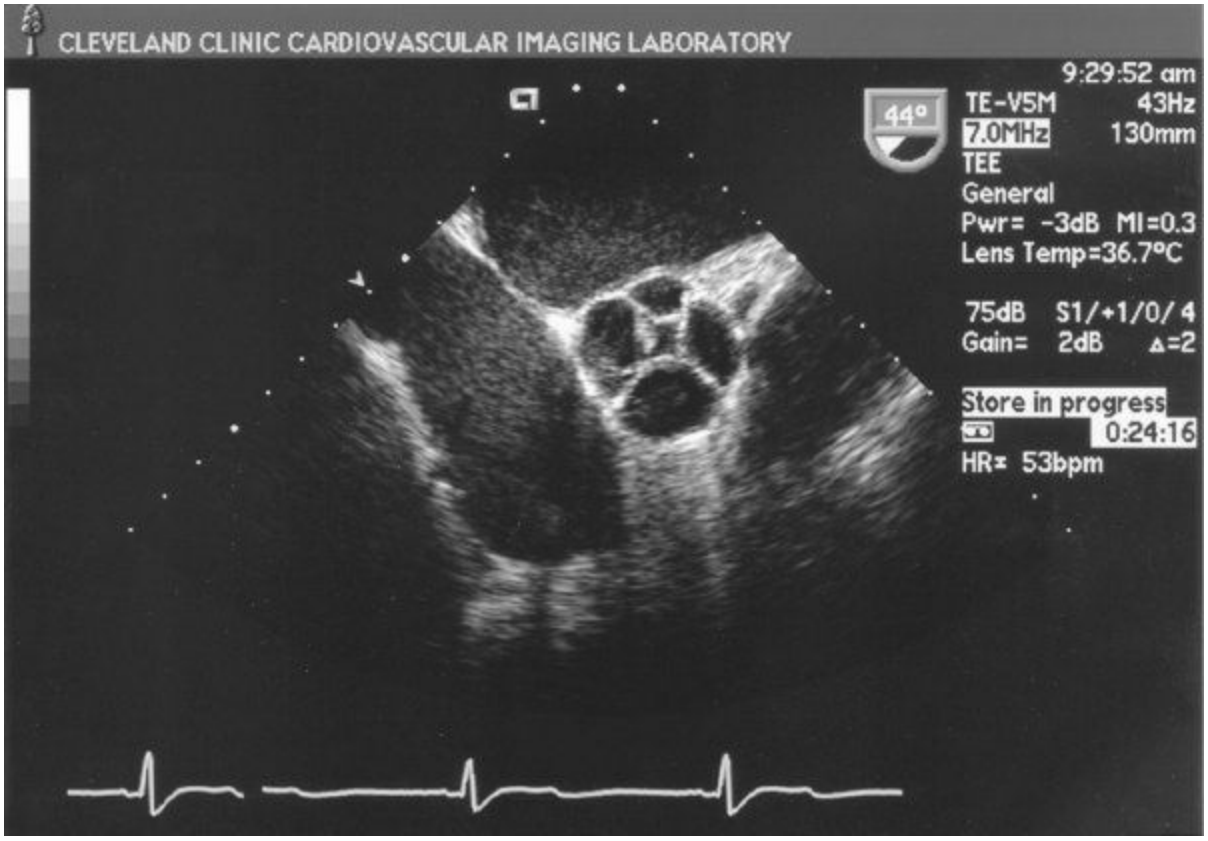

Figure 9.11

Intracardiac Shunts

42. Which of the following are associated with patent foramen ovale (PFO)?

a. Migraine
b. Platypnea-orthodeoxia
c. Decompression sickness
d. Paradoxical embolism & stroke
e. All of the above

43. A 25-year-old man is referred to you for an abnormal heart sound. The patient is asymptomatic and very active. BP is 130/50 mmHg. He has a continuous murmur at the left upper sternal border. A TTE reveals a small PDA with mildly dilated left atrium (LA) and mildly dilated LV but normal RV size and normal pulmonary pressures. How would the patient be best managed?

a. Ligation or percutaneous closure of the PDA
b. Repeat TTE in 1 year
c. Stress echocardiography to determine LV enlargement or dysfunction postexercise
d. Pulmonary vasodilator
e. TEE

44. Which of the following is **most** commonly associated with a sinus venosus ASD?

a. Coarctation of the aorta
b. Bicuspid aortic valve
c. Anomalous right pulmonary venous connection
d. Inlet VSD
e. Persistent left SVC

45. The best echocardiographic scan plane for demonstrating a secundum ASD is

a. apical four-chamber view.
b. parasternal long-axis view.
c. parasternal short-axis view.
d. subcostal four-chamber view.
e. suprasternal long-axis view.

46. Review the image taken at the time of percutaneous closure of an intracardiac shunt in a 25-year-old patient (Fig. 9.12). Which of the following defects was closed in this patient?

a. Primum ASD

b. Secundum ASD
c. Sinus venosus ASD
d. Unroofed coronary sinus
e. Atrioventricular septal defect (AVSD)

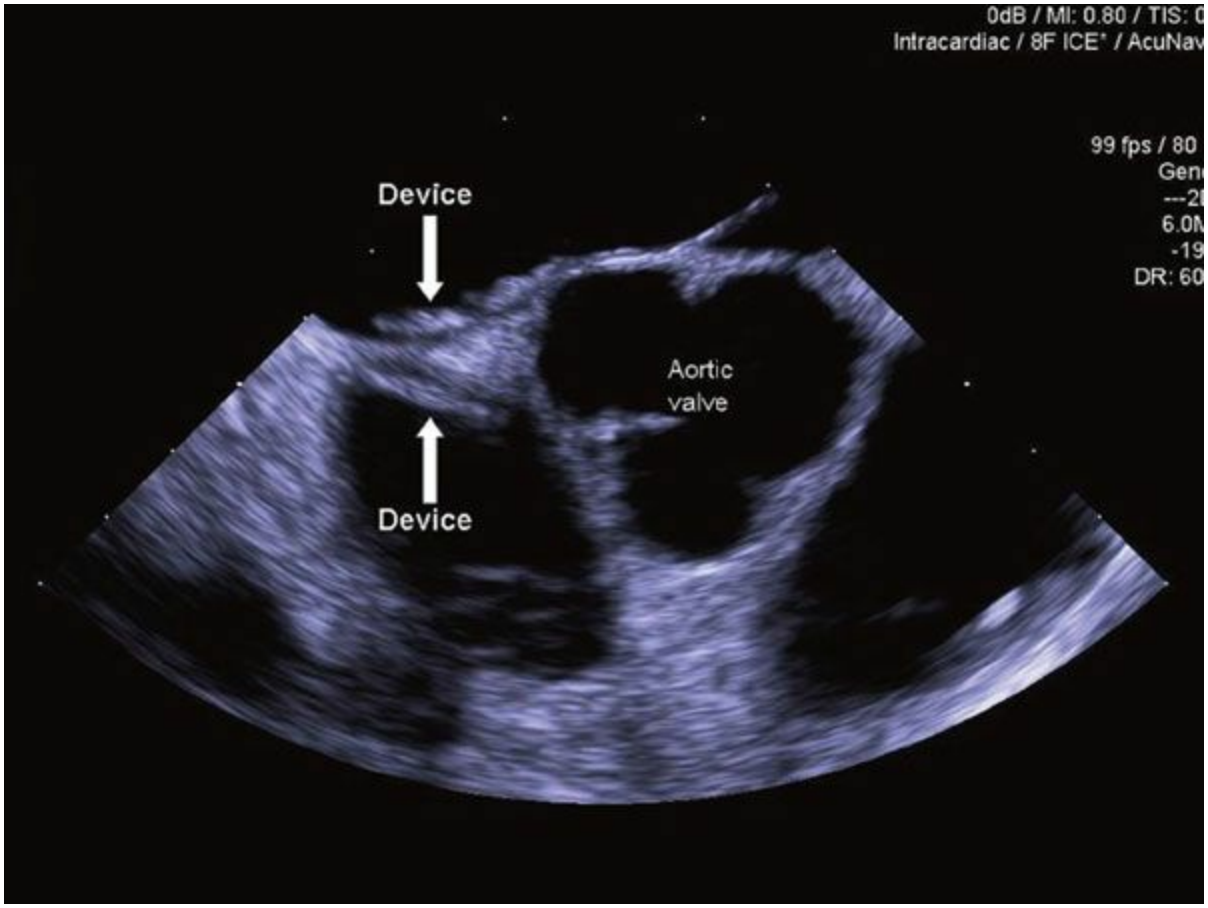

Figure 9.12

47. Secundum ASDs may be associated with

a. pulmonary hypertension.
b. mitral valve prolapse.
c. partial anomalous pulmonary venous connection.
d. pulmonic stenosis.
e. all of the above.

48. Which type of VSD is demonstrated in Figure 9.13?

a. Type 1/supracristal
b. Type 2/perimembranous
c. Type 3/inlet
d. Type 4/muscular

49. Percutaneous VSD closure is approved by the U.S. Food and Drug Administration for which type of VSD?

a. Type 1/supracristal
b. Type 2/perimembranous
c. Type 3/inlet
d. Type 4/muscular
e. None: Surgery is the only approved treatment for VSD closure

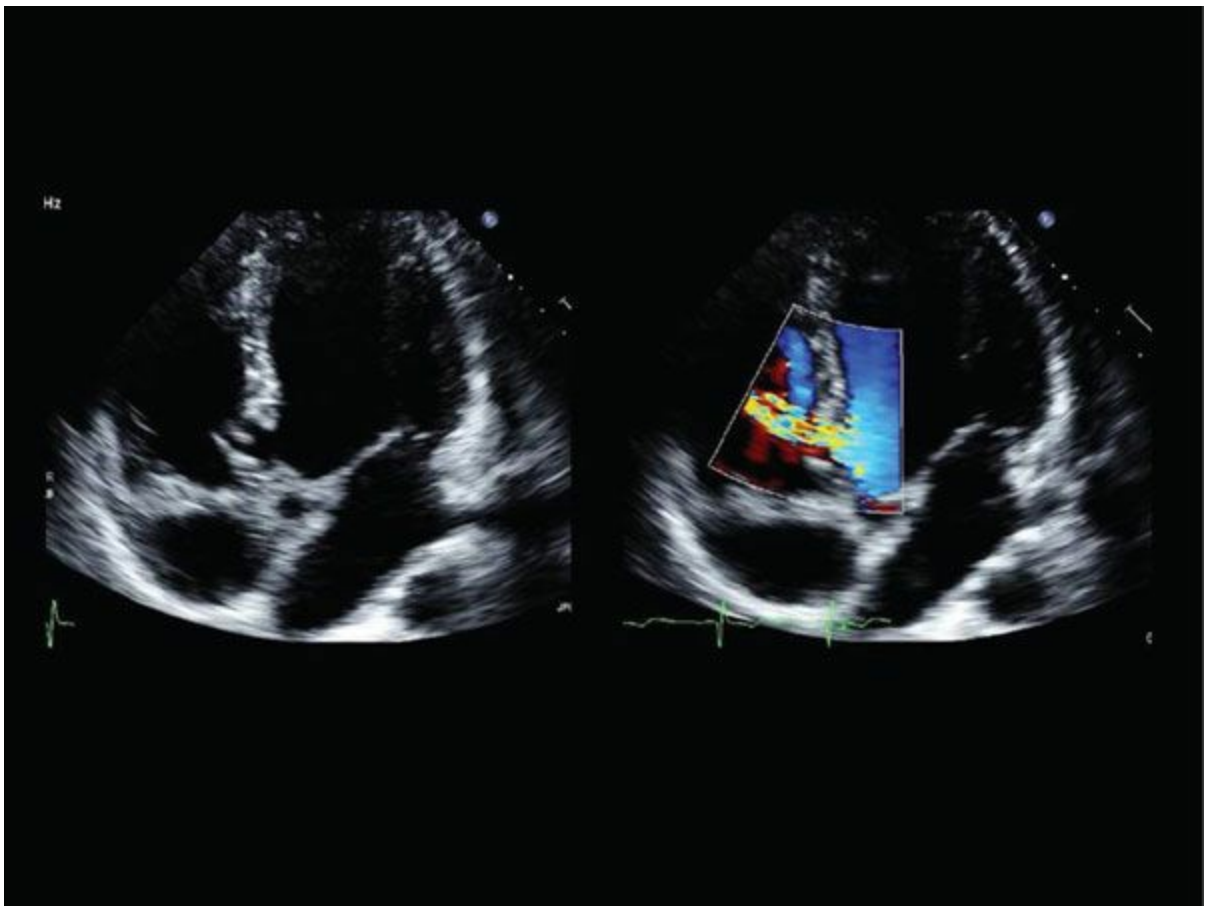

Figure 9.13

Left-Sided Lesions

50. What is the most common coexisting congenital anomaly in patients with coarctation of the aorta?

a. Cleft mitral valve
b. Bicuspid aortic valve
c. Ebstein anomaly
d. VSD
e. PDA

51. A 20-year-old man is referred for further evaluation of hypertension. He has remained hypertensive despite a 12-week trial of β-blocker treatment. Examination reveals a right upper extremity BP of 150/100 mmHg and a right lower extremity BP of 130/90 mmHg. HR is 88 bpm. There is brachial– femoral pulse delay. The rest of the physical and neurologic examinations are within normal limits. A TTE confirmed a diagnosis of coarctation of the aorta, with a maximum gradient of 30 mmHg. He is referred for cardiac catheterization. Intervention for coarctation is recommended when the coarctation gradient is greater than which of the following?

a. 10 mmHg
b. 20 mmHg
c. 40 mmHg
d. 60 mmHg
e. None of the above; indications for intervention in coarctation are determined by symptoms and not the coarctation gradient

52. Which of the following is the most common coronary artery anomaly?

a. Bland-Garland-White syndrome (left main coronary arising from the PA)
b. Coronary arteriovenous fistula
c. Left circumflex artery arising from the right coronary artery
d. Left coronary artery arising from the right sinus of Valsalva
e. Coronary cameral fistula

53. Which of the following statements about coronary arteriovenous fistula is true?

a. The left coronary artery is most commonly involved.
b. The fistula most commonly empties into the LV.
c. Despite the success of surgical closure, the prognosis is still poor.
d. Spontaneous closure rarely occurs.
e. A large right-to-left shunt may cause congestive heart failure (CHF).

54. Which of the following differentiates valvular aortic stenosis from subvalvular aortic stenosis?

a. Male preponderance
b. Surgical risk of repair
c. Dilatation of the ascending aorta
d. Aortic regurgitation
e. Valvular calcification

55. Echocardiography in a 20-year-old asymptomatic man reveals a subaortic membrane with a peak gradient of 20 mmHg. The aortic valve remains mobile, but there is

associated mild to moderate aortic valve insufficiency. LV size is normal ejection fraction is 60%. What should you advise this patient?

a. There is no indication for intervention at this time.
b. Surgical resection of the membrane and debridement of the aortic valve to reduce aortic regurgitation is indicated.
c. Transluminal balloon dilatation is the best treatment option in this case.
d. AVR and membrane resection is indicated.

56. The peak age range for surgical intervention for patients with a bicuspid aortic valve is

a. 10 to 20 years.
b. 20 to 40 years.
c. 40 to 60 years.
d. 60 to 80 years.

Right-Sided Lesions

57. A 45-year-old man with known Ebstein anomaly seeks your advice with regard to optimal management. He is asymptomatic and has an active lifestyle without any limitations. His physical examination is remarkable for the absence of cyanosis. He has a loud holosystolic murmur at the left lower sternal border that is accentuated with respiration. He has no organomegaly or peripheral edema. His TTE reveals moderately severe 3+ TR with an RV systolic pressure of 35 mmHg and normal LV and RV systolic function. There is no evidence of interatrial communication. Which of the following should you recommend?

a. Furosemide and digoxin
b. Tricuspid valve repair
c. Tricuspid valve replacement
d. Dual-chamber pacemaker
e. Regular follow-up with repeat TTE in 6 months

58. The most common problem in adults with surgically repaired TOF is

a. ventricular tachycardia.
b. pulmonary hypertension.
c. pulmonary regurgitation.
d. cyanosis.
e. residual VSD.

59. A 34-year-old gentleman reports a history of TOF, Blalock-Taussig shunt at

10 months, and complete repair at age 3. Although he has been reasonably active for several years, he has noted progressive exercise intolerance in recent months. Examination reveals a III/VI systolic ejection murmur loudest at the second left intercostal space and a II/IV diastolic murmur along the left sternal edge. Jugular venous pulse is not elevated. Lungs are clear and there is no hepatomegaly or peripheral edema. An echocardiogram demonstrates RV dilatation, moderate-to-severe pulmonic regurgitation but no significant TR. The ECG shows sinus rhythm and right bundle branch block with a QRS duration of 160 milliseconds. The most reasonable next step in the evaluation of this patient would be

a. repeat echocardiogram with a saline bubble study.
b. electrophysiologic study for ventricular arrhythmias.
c. cardiac catheterization.
d. cardiac magnetic resonance imaging study.
e. diuretics and digitalis.

60. A 35-year-old man is referred for evaluation of dyspnea and a loud cardiac murmur. Examination reveals an RV lift, a palpable systolic thrill at the second left intercostal space, and a widely split second heart sound. There is a loud and harsh ejection systolic murmur heard loudest at the second left intercostal space. BP is 130/80 mmHg, HR 90 bpm, and regular, oxygen saturation 98% on room air. What is the most likely diagnosis?

a. Unrepaired TOF
b. ASD
c. VSD
d. PDA
e. Pulmonary stenosis

61. Echocardiography confirms doming valvular pulmonary stenosis with a mean Doppler gradient of 40 mmHg. There is no significant pulmonary regurgitation or TR. ECG is normal. The patient undergoes cardiac catheterization (results below):

	Pressure	Saturation
SVC		82
IVC		78
RA	Mean 15	
RV	70/15	
PA	23/15 mean 19	82
PCWP	Mean 6	
Aorta	130/80 mean 90	98

What is the most appropriate management for this patient?

a. Referral to a pulmonary hypertension specialist
b. Repeat cardiac catheterization with vasodilator challenge
c. Balloon valvotomy
d. Surgical repair
e. Diuretics

62. Which complications are seen in adults late after the atriopulmonary Fontan procedure among those born with tricuspid atresia?

a. Protein-losing enteropathy
b. Thromboembolic events
c. Intra-atrial reentrant tachycardia (IART)
d. All of the above

Syndromes

63. Which of the following syndromes is associated with pulmonary arteriovenous fistula?

a. Williams syndrome
b. Weber-Osler-Rendu syndrome
c. Bland-Garland-White syndrome
d. Kartagener syndrome
e. Crouzon syndrome

64. What is the most common cardiac defect seen in patients with Noonan syndrome?

a. AVSD
b. Pulmonary stenosis
c. Coarctation of the aorta

d. Hypertrophic cardiomyopathy
e. Mitral valve prolapse

65. The most common chromosomal abnormality associated with TOF is

a. 22q11.2 microdeletion.
b. 7q11.23 microdeletion.
c. missense mutations in the PTPN11 gene on chromosome 12.
d. Trisomy 21.
e. Monosomy X (45, X).

66. Which of the following is true for Loeys-Dietz syndrome (LDS)?

a. Inheritance is autosomal recessive.
b. FBN1 mutations have been implicated.
c. The risk of aortic dissection is lower than for patients with Marfan syndrome.
d. Patients are characteristically tall with long extremities.
e. Hypertelorism, bifid uvula, and arterial tortuosity are common features.

67. Which of the following syndromes is/are NOT associated with pulmonary stenosis?

a. Noonan syndrome
b. Williams syndrome
c. Shone syndrome
d. Congenital rubella syndrome
e. LEOPARD syndrome

ANSWERS

1. e. Obtain iron studies. Eisenmenger syndrome is the most extreme manifestation of pulmonary arterial hypertension associated with any nonrestrictive congenital heart defect that exposes the pulmonary vascular bed to systemic pressures. The development of pulmonary obstructive arteriopathy and increased pulmonary vascular resistance leads to shunt reversal and cyanosis. Secondary erythrocytosis is a physiologic response to chronic hypoxemia. Eisenmenger syndrome is a multisystem disease that also results in abnormal clotting, impaired renal function, altered uric acid and bilirubin metabolism, and musculoskeletal disease including gout. A common misconception in the management of patients with cyanotic coronary heart disease (CHD) is that an increased hematocrit level alone is an indication for phlebotomy. In fact, therapeutic phlebotomy has a very limited role in patient management and should only be performed if the hemoglobin is more than 20 mg/dL and the hematocrit is greater than 65% with symptoms of hyperviscosity

and no evidence of dehydration. Symptoms of hyperviscosity include headache, fainting/dizziness, altered mentation, altered vision, tinnitus, myalgias, and restless legs. Hyperviscosity symptoms should disappear after adequate phlebotomy.

Eisenmenger patients with a history of repeat phlebotomies are at increased risk for iron deficiency anemia, which itself is associated with increased stroke risk.[6] The patient's history of phlebotomies, persistent fatigue, low MCV, and low hemoglobin (relative to oxygen saturation) are all suggestive of iron deficiency anemia. Iron studies are the most appropriate next investigation in this context. Pulmonary vasodilator therapy has been shown to improve 6-minute walk distance in patients with Eisenmenger physiology[7]; however, further investigations are generally indicated prior to commencement (e.g., pulmonary function tests with volumes and CO_2 diffusion, computed tomography for exclusion of pulmonary emboli, cardiac catheterization with vasodilator challenge). Heart–lung transplantation may be considered in Eisenmenger patients with severe limitations; however, long-term survival after heart–lung transplantation is often inferior to continuing conservative management in this population.

2. **c.** Blood cultures. The incidence of IE in young adults with CHD is almost 35-fold that of the general population.[8] Hence, a high index of suspicion for IE is required in these patients. ACHD patients who present with fever and potential IE should have blood cultures drawn before antibiotic therapy is initiated to avoid subsequent false-negative blood cultures and, in the instance of positive blood cultures, to guide antibiotic treatment. In this case, blood cultures should be taken as the first step in the patient's management and prior to commencement of antibiotic therapy. Since the sensitivity of TTE is too low to exclude IE, TEE should be performed after multiple sets of blood cultures are taken. Surgery for IE is indicated in patients with recurrent emboli, medically uncontrolled infection, prosthetic material infection, CHF, and development of heart block.

3. **a.** Closure is indicated in patients with a VSD complicated by IE (AHA guidelines, class I recommendation, level of evidence C[1]). VSD closure is also indicated in the following circumstances:

   - Patients with attributable symptoms; LV volume overload; deteriorating ventricular function due to volume (LV) or pressure (RV) overload; and/or a Q_p/Q_s (pulmonary-to-systemic blood flow ratio) $\geq$1.5:1 in the absence of advanced pulmonary vascular disease
   - Significant RV outflow tract (RVOT) obstruction (catheter gradient > 50 mmHg)
   - VSD closure may also be considered in patients with a perimembranous or

subarterial VSD and more than mild or progressive aortic regurgitation[3]

- In deciding whether to close a defect, TTE ± TEE is essential to define the size and location of the defect and to identify coexisting septal defects as more than one muscular defect is common.

4. **a.** Ebstein anomaly without prior intervention. Current AHA guidelines for ACHD patients recommend antibiotic prophylaxis before dental procedures in the following patient subgroups[1]:
   - Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
   - Prior IE
   - Unrepaired and palliated cyanotic congenital heart disease, including surgically palliated constructed palliative shunts and conduits
   - Completely repaired CHD with prosthetic materials, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
   - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that inhibits endothelialization

5. **c.** Ebstein anomaly. The ECG demonstrates a short PR interval, presence of delta waves, and wide QRS interval that are all consistent with preexcitation and Wolff-Parkinson-White syndrome. Wolff-Parkinson-White syndrome is commonly associated with Ebstein anomaly. Catheter ablation can be beneficial for treatment of recurrent supraventricular tachycardia in some patients, although recurrence is common due to the presence of multiple accessory pathways.[9] (see also question 57).

6. **d.** Eisenmenger syndrome. Eisenmenger syndrome is one of few conditions that pose an absolute contraindication to pregnancy[1–3] due to very high maternal mortality and fetal loss.

7. **b, e.** Blalock-Taussig and Fontan (see also Table 9.1).

8. **c, d, f.** Senning or Mustard, arterial switch, and Rashkind.

9. **e, f.** Fontan and Rashkind.

10. **g.** None of the above.

11. **a.** Ross. Please refer to Table 9.1, which provides a complete overview of common

surgical procedures for congenital heart disease.

12. **c.** Equal preponderance.

13. **b.** Predominantly female.

14. **a.** Predominantly male.

15. **a.** Predominantly male.

16. **c.** Equal preponderance.

17. **Figure 9.2, d.** Pulmonic stenosis. A left lateral right ventriculogram demonstrates pulmonic stenosis with dilatation of the proximal main PA.

18. **Figure 9.3, a.** Coarctation of the aorta. Left lateral view of the LV and aorta. The catheter was advanced from the femoral vein and crossed a large patent foramen ovale to reach the left side of the heart. A discrete area of narrowing (coarctation) is seen in the upper descending aorta.

19. **Figure 9.4, e.** VSD. A left ventriculogram obtained in the left anterior oblique view allows optimal visualization of the interventricular septum and demonstrates a large VSD with significant left-to-right shunt of contrast.

TABLE 9-1 Common Surgical Procedures for Congenital Heart Disease

Procedure	Description	Intent	Result
Blalock-Taussig	Subclavian artery to PA anastomosis	PAL	Increases PBF
Central shunt	Conduit or anastomosis between the aorta and PA	PAL	Increases PBF
Fontan	Anastomosis or conduit between the right atrium and PA	PAL	Increases PBF in cases of univentricular heart or tricuspid atresia
Hemi-Fontan	SVC to PA anastomosis with baffle placed in the right atrium so that inferior vena cava blood flow goes across ASD to left heart	PAL	Increases PBF and sets the stage for Fontan completion
Glenn (bidirectional Glenn)	SVC to PA anastomosis	PAL	Increases PBF
Jatene arterial switch	Transection of the aorta and PA with reimplantation onto the proper ventricles, coronary arteries reimplanted	COR	Creates normal relationship between the ventricles and great arteries in d-TGA
Konno	Replacement of aortic valve with aortic valve annular enlargement	COR	Alleviates subaortic obstruction and replaces abnormal aortic valve
Mustard/Senning	Atrial switch with intra-atrial baffle made of pericardium (Mustard) or atrial wall flaps (Senning)	COR	Reestablishes proper flow sequence to PA and aorta in d-TGA
Norwood (first stage)	PA anastomosis to aorta, conduit from the aorta to main PA	PAL	Increases flow to aorta for subaortic obstruction with single ventricle
PA band	Constrictive band around main PA	PAL	Decreases PBF
Potts	Descending aorta-to-PA shunt	PAL	Increases PBF (rarely done anymore)
Rashkind	Atrial septostomy with catheter balloon	PAL	Increases mixing of blood for d-TGA or tricuspid atresia
Rastelli	Closure of VSD + valved conduit from RV to PA	COR	Increases PBF, may reestablish proper sequence of flow to aorta and PA
Ross	Pulmonary autograft to aorta, pulmonary homograft	COR	Correction for aortic stenosis; avoids mechanical and bioprosthetic valves
Waterston	Ascending aorta to right pulmonary anastomosis	PAL	Increases PBF (rarely done anymore)

ASD, atrial septal defect; COR, total correction; d-TGA, D-transposition of the great arteries; PA, pulmonary artery; PAL, palliation; PBF, pulmonary blood flow; RV, right ventricle; SVC, superior vena cava.

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20. **Figure 9.5, b.** Patent ductus arteriosus (PDA). An aortogram in straight lateral view. There is a large abnormal communication between the upper descending aorta and the main PA, confirming the diagnosis of PDA.

21. **Figure 9.6, c.** Hypertrophic cardiomyopathy. A left ventriculogram in right anterior oblique projection demonstrates a small ventricle with marked ventricular hypertrophy and narrow left ventricular outfl ow tract (LVOT).

22. **e.** TOF. On cardiac palpation and auscultation, patients with TOF demonstrate RV lift (RV hypertrophy) and a systolic ejection murmur over the pulmonic region caused by RVOT obstruction. A soft, short systolic ejection murmur suggests severe obstruction. The intensity and severity of the ejection murmur are inversely related to the severity of RV obstruction. P_2 is absent, and only the aortic component of S_2

is audible.

23. **d.** Ebstein anomaly. Patients with Ebstein anomaly have a widely split S_1 (reflecting delayed closure of the anterior tricuspid leaflet) and split S_2 (delayed closure of the pulmonary valve due to associated right bundle branch block). The "sail sound" contributes to a loud S_1 and reflects increased tension in the large mobile anterior leaflet as it reaches the limits of its systolic excursion. The systolic murmur of TR is typically grade 2/6 to 3/6 and heard loudest overlying the tricuspid area. Ejection clicks, opening snaps, and diastolic murmurs may be heard. Hepatomegaly caused by passive congestion and elevated RA pressure may be present.

24. **b.** Coarctation of the aorta. Patients with coarctation of the aorta have systolic hypertension and higher BP in their arms than in their legs, resulting in delayed femoral arterial pulses. Because many patients also have bicuspid aortic valve, a systolic ejection click is frequently present, and the aortic component of S_2 is accentuated. A harsh systolic ejection murmur is audible along the left sternal border and radiates to the back, especially over the point of discrete coarctation.

25. **a.** Eisenmenger syndrome. Patients with Eisenmenger syndrome demonstrate cyanosis and digital clubbing, the severity of which depends on the magnitude of right-to-left shunting. An RV lift and loud P_2 caused by pulmonary hypertension are usually present. The murmur caused by ASD, VSD, or PDA is no longer present when Eisenmenger syndrome develops because left- and right-sided pressures have equalized. Many patients will have a tricuspid or pulmonary regurgitation murmur, or both.

26. **c.** PDA. Patients with PDA exhibit hyperdynamic LV impulse with wide pulse pressure. A continuous machinery murmur, heard best in the pulmonic region, is a characteristic finding.

27. **c.** Cleft mitral valve. (see also question 45).

28. **b.** Supravalvular pulmonic stenosis.

29. **e.** Persistent left SVC. (see also question 45).

30. **a.** Supravalvar aortic stenosis and b. Supravalvar pulmonary stenosis

31. **d.** Anomalous pulmonary venous drainage. (see also question 44).

32. **a.** Eisenmenger syndrome.

33. **e.** TOF.

34. **d.** Ebstein anomaly.

35. **b.** Coarctation of the aorta.

36. **c.** PDA.

37. **c.** Figure 9.9. This is a parasternal short-axis view at the aortic valve level using TTE. Two leaflets showing a "fish-mouth" opening during systole are seen instead of three leaflets.

38. **a.** Figure 9.7. This is an apical four-chamber view using TTE. There is a membrane separating the LA into a posterior chamber, usually where the pulmonary veins empty, and an anterior chamber that contains the mitral valve.

39. **d.** Figure 9.10. Subcostal TTE view showing the ASD in the lower atrial septum, with downward displacement of the atrioventricular (AV) valve. (see also question 45).

40. **e.** Figure 9.11. This is a parasternal short-axis view at the aortic valve level, using TTE. There are four visible leaflets.

41. **b.** Figure 9.8. A magnified TEE long-axis view of the LVOT, aortic valve, and ascending aorta. There is a membrane visible in the LVOT, consistent with a subaortic membrane.

42. **e.** All of the above. The foramen ovale is the interface between the septum primum and septum secundum and in utero provides an important route for blood as it bypasses the collapsed fetal lungs (oxygenation being achieved via the placenta). In about 25% of humans the flap of tissue making up the foramen ovale does not fuse after birth and results in a PFO. Stroke patients with PFO and atrial septal aneurysm (ASA) have an average annual risk of recurrent stroke of 4.4%.[10] PFO is also associated with decompression sickness, platypnea-orthodeoxia, and migraine. Factors associated with a greater risk of paradoxical embolism are large PFO size and the presence of an ASA. Though several management strategies exist for patients with cryptogenic stroke and PFO, including anticoagulation, antiplatelet therapy, and closure via percutaneous or surgical means, no clear consensus

regarding therapy exists.

43. **a.** Ligation or percutaneous closure of the PDA. PDA is the persistence after birth of an in utero communication between the aorta and the left PA, which, along with the foramen ovale, is designed to bypass blood away from the collapsed fetal lungs. It is the third most common congenital heart defect in adults and is generally found in isolation in the adult. Frequently, this lesion is discovered by the unusual quality of a continuous "machinery" murmur at the left upper sternal border. Because a patent ductus is an aortopulmonary communication, the pulse pressure frequently is widened and the pulses are brisk to bounding.

Closure of a PDA either percutaneously or surgically is indicated for LA and/or LV enlargement or in patients with prior endarteritis.[1] It is reasonable to close a small asymptomatic PDA by catheter device so as to decrease the future risk of endarteritis (0.45% per year after the second decade of life); however, this is somewhat controversial. Surgical repair is recommended in those who meet indications and with PDAs too large for device closure or distorted ductal anatomy. Pulmonary vasodilators are not indicated in this patient due to the absence of pulmonary hypertension. By lowering pulmonary vascular resistance, pulmonary vasodilators could conceivably increase left-to-right shunting in those with moderate-to-large PDAs. Endocarditis prophylaxis is recommended for ACHD patients with a residual shunt including PDA.

44. **c.** Anomalous right pulmonary venous connection. Sinus venosus ASDs constitute 2% to 3% of interatrial communications. Strictly speaking, this defect lies outside the true atrial septum and is an abnormality of the venous connections. These defects are located on the right side of the upper or posterior atrial septum, most commonly at the SVC/RA junction and less commonly at the level of the inferior vena cava (IVC). Because of their superior location, sinus venosus defects are easily missed on TTE. Partial anomalous venous return of the right upper pulmonary vein is a common association (seen in up to 85% of patients). A bicaval view on TEE or demonstration by CT/MRI is diagnostic.

45. **d.** Subcostal four-chamber view. ASDs and anomalous pulmonary venous return should be suspected in patients with unexplained RV dilatation and volume/pressure overload (Fig. 9.14).

A secundum ASD is the common type of ASD and is located centrally in the interatrial septum at the site of the fossa ovalis. The defect may be single, multiple, or fenestrated. This defect is best viewed by transthoracic echocardiography in the subcostal view (due to ultrasound waves being better reflected off the interatrial septum in this view). Coexisting partial anomalous pulmonary venous drainage is

seen in 5% of patients with a secundum ASD. The atrial septal defect occurs when the interatrial septum is deficient at the crux of the heart/level of the atrioventricular valves.

A primum ASD occurs as part of the spectrum of AVSD. Partial AVSD commonly describes a primum ASD in combination with a so-called cleft mitral valve, more correctly described as a trileaflet left-sided AV valve. Primum ASDs are often well demonstrated from the apical four-chamber view (± subcostal) in association with mitral regurgitation from a trileaflet left-sided AV valve (Fig. 9.15).

A coronary sinus defect is located in the wall that separates the coronary sinus from the LA. It may be fenestrated or completely absent. There is an associated left-sided SVC contributing to dilatation of the coronary sinus seen best on parasternal long-axis views. A coronary sinus defect should be suspected in a patient who has evidence of RV volume or pressure overload but no suggestion of a defect in the central portion of the atrial septum. Injection of agitated saline into the left arm leads to contrast in the coronary sinus, then the RA and finally the RV. An unroofed coronary sinus contains fenestrations such that bubbles travel from the left sided SVC and into the left atrium.

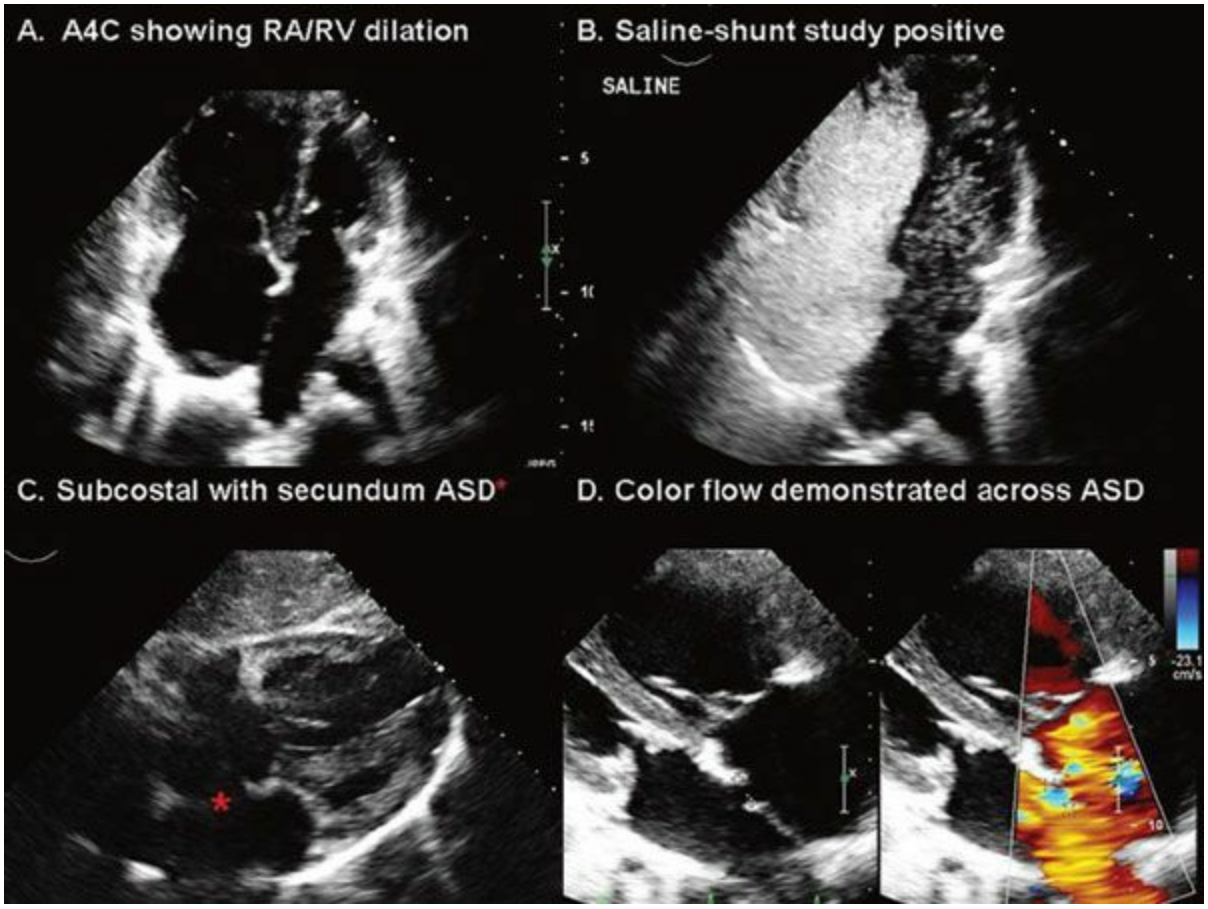

Figure 9.14 The findings of RA and RV dilatation in the apical four-chamber (A4C) view (**A**) and significant

right-to-left shunting of agitated saline (**B**) are highly suggestive of an ASD ± anomalous pulmonary venous return. A secundum ASD is confirmed as a defect in the mid-portion of the interatrial septum, best seen in subcostal scan plane (**C**) and with color flow Doppler (**D**). ASD, atrial septal defect; RA, right atrium; RV, right ventricle.

46. **b.** Secundum ASD. The majority of secundum ASDs can be closed with a percutaneous catheter technique. ASD closure is indicated for RA and RV enlargement with or without symptoms. Small ASDs (<5 mm) with no evidence of volume overload do not require closure unless associated with cryptogenic paradoxical embolism. Sinus venous, coronary sinus, and primum defects are not amenable to device closure (Fig. 9.16; see also Question 3).

47. **e.** All of the above. Large ASDs can lead to RV volume overload, excessive blood flow to the pulmonary circulation, and pulmonary hypertension. Associated lesions are listed in Table 9.2 for each ASD type.

48. **b.** Type 2/perimembranous. See Table 9.3.

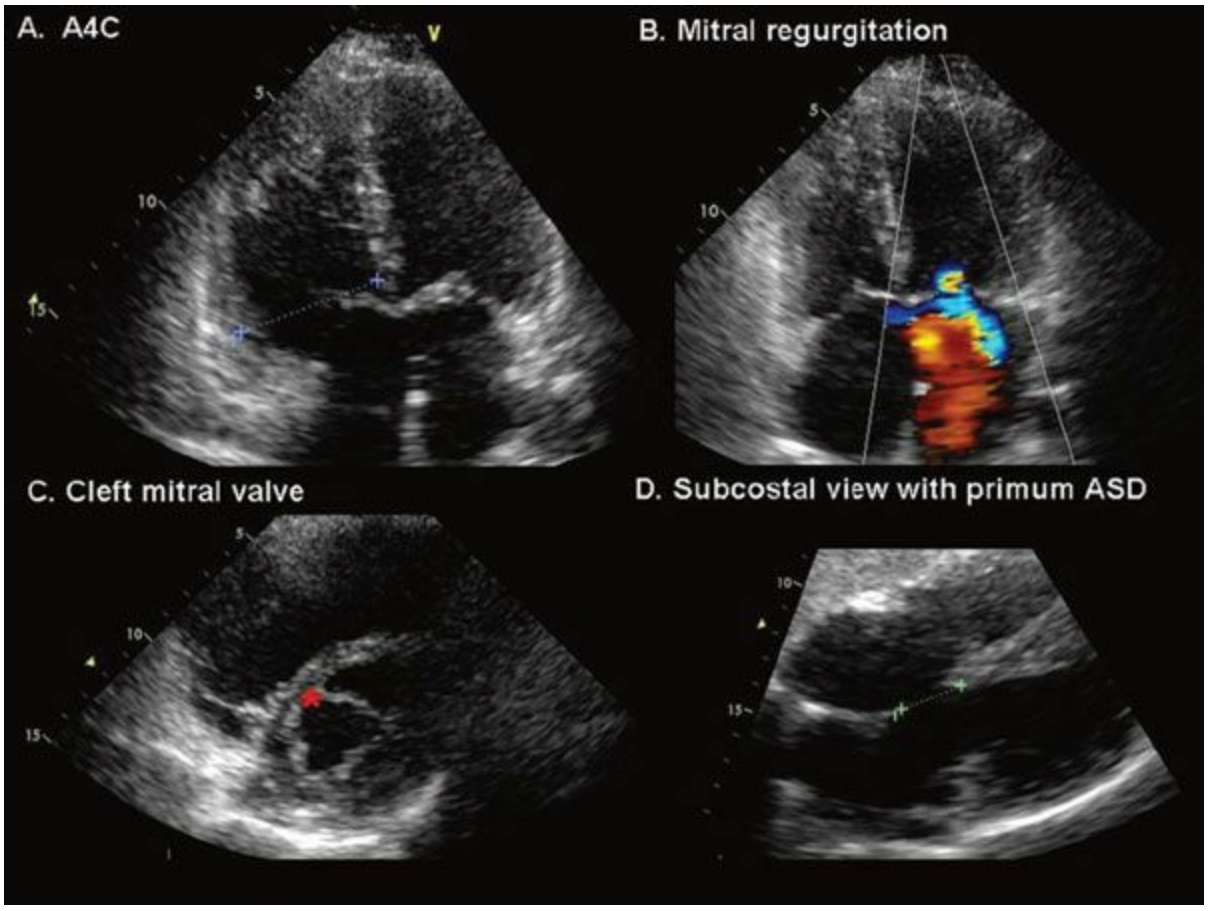

Figure 9.15 Primum ASD and its associated features. Note that the septal leaflet of the tricuspid valve is on the same plane as the mitral valve (**A**). Normally the septal leaflet of the tricuspid leaflet is apically displaced compared with the mitral valve. Mitral regurgitation frequently coexists with primum (**B**). (**C**) Short-axis views of the mitral valve show a “cleft” pointing toward the septum (*). (**D**) The cleft is more accurately

characterized as a commissure between the superior and inferior bridging leaflets of the common AV canal. Additional echocardiographic features of AVSD (not demonstrated here) include elongation of the LV outflow tract (gooseneck deformity) ± LVOT obstruction. A4C, apical 4 chamber; ASD, atrial septal defect.

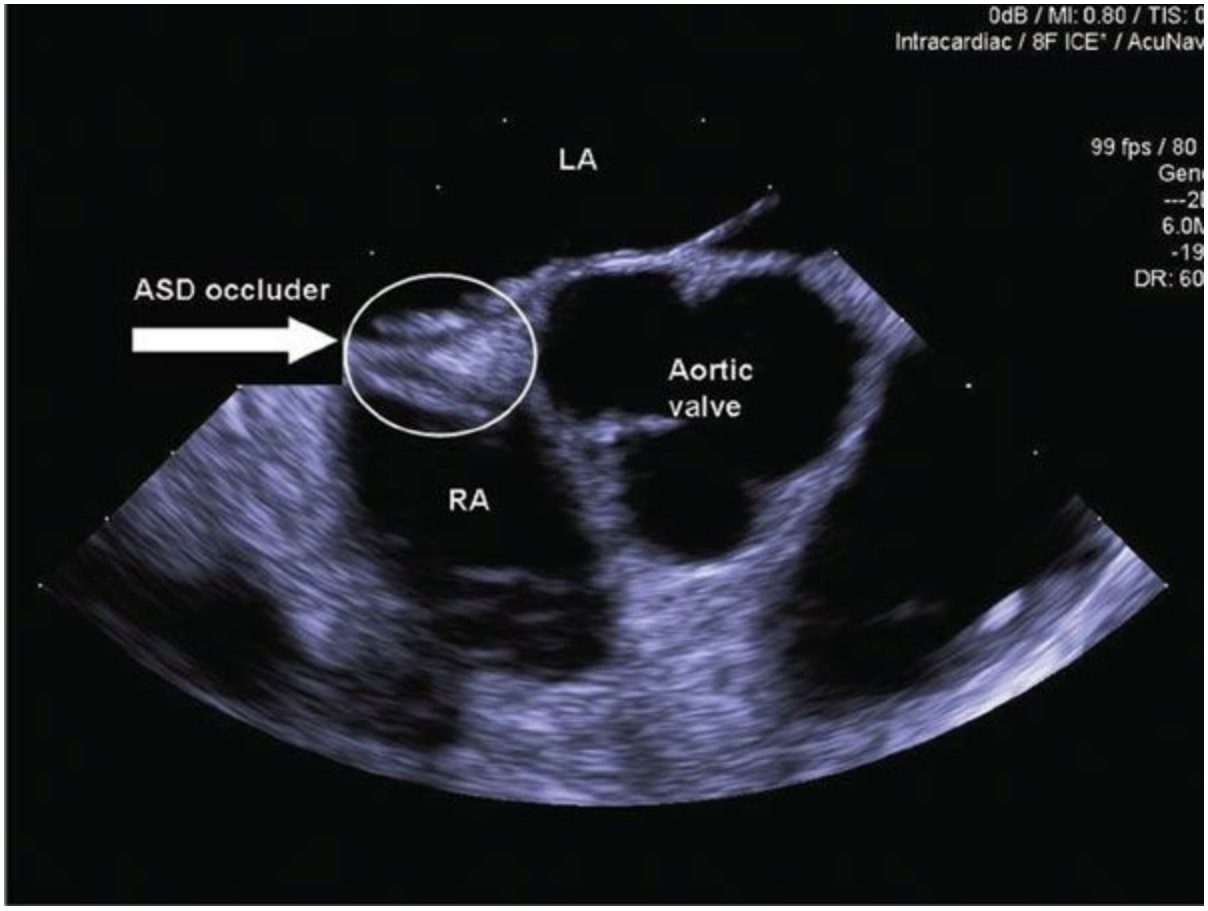

Figure 9.16 An atrial septal defect (ASD) occlusion device is seen positioned across a secundum ASD. The image was acquired using intracardiac echocardiography and consists of a short-axis view of the heart demonstrating the aortic valve and the interatrial septum dividing the left atrium (LA) and right atrium (RA).

TABLE 9-2 Atrial Septal Defects and Associated Lesions

Type of Atrial Septal Defect	Associated Lesions
Secundum	Pulmonic stenosis Mitral valve prolapse Partial anomalous pulmonary venous connection (5%)
Primum	Trileaflet left-sided AV valve aka "cleft" mitral valve LVOT obstruction / RVOT obstruction Pulmonary vascular disease risk highest in Trisomy 21[11]
Sinus venosus	Partial anomalous pulmonary venous connection (right upper pulmonary vein in 80%)
Coronary sinus	Persistent left-sided SVC Partial anomalous pulmonary venous connection

AV, atrioventricular; LVOT, left ventricular outflow tract; RVOT, right ventricular outflow tract; SVC, superior vena cava.

Modified from Warnes et al.[1]

TABLE 9-3 Classification of Ventricular Septal Defects

VSD Type	Synonyms	Location	Echocardiographic Views and Associated Features
Type 1	Conal Supracristal Subarterial Doubly committed juxta-arterial	Below the aortic and pulmonary valves in the conal/outlet septum	Short-axis view VSD flow in the RVOT and just below the aortic valve annulus Aortic valve prolapse is most common in this group due to progressive prolapse of the aortic valve
Type 2	Perimembranous Paramembranous Membranous	Involves the membranous septum and is bordered by an AV valve (commonly the aortic valve)	Parasternal long-axis Aortic valve prolapse may be present Aneurysm formation involving the septal leaflet of the tricuspid valve can accompany complete or partial closure of the VSD
Type 3	Inlet AV canal type	In the inlet portion of the RV septum inferior to the AV valve apparatus	Apical four-chamber/subcostal Left- and right-sided AV valves on the same level Primum ASD + "cleft" mitral valve with mitral regurgitation Gooseneck deformity (elongation) of the LVOT ± LVOT obstruction
Type 4	Muscular	A VSD completely surrounded by muscle Single or multiple Apical, posterior, or anterior	Apical four-chamber/subcostal/PLAX VSDs may occur in association with left-sided obstructive lesions such as bicuspid aortic valve, subaortic stenosis, aortic coarctation

Small VSDs ≤25% of the aortic annulus diameter/main PA <20 mmHg/Q_p:Q_s < 1.2:1. Usually restrictive and do not cause pulmonary arterial, left atrial, or LV dilatation.

Moderate VSDs 25–75% of the aortic annulus diameter/main PA = 35 mmHg/Q_p:Q_s > 1.2:1. Moderately restrictive but can lead to mild-to-moderate pulmonary/LA/LV dilatation.

Large VSDs ≥75% of the aortic diameter are usually nonrestrictive and the LV pressure is directly transmitted to the RV and pulmonary vascular bed. Significantly elevated pulmonary pressures. The majority of patients with large VSDs will develop irreversible pulmonary vascular disease in the first 1–2 y of life.

ASD, atrial septal defect; AV, atrioventricular; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; PA, pulmonary artery; RV, right ventricle; RVOT, right ventricular outflow tract; VSD, ventricular septal defect.

49. d. Type 4/muscular. When indicated (see also Question 9), percutaneous device closure of a muscular VSD may be performed in VSDs remote (>4 mm) from the tricuspid and aortic valves. Percutaneous VSD closure is NOT approved by the U.S. Food and Drug Administration in the presence of the following:

- High pulmonary vascular resistance and/or irreversible pulmonary vascular disease
- Perimembranous or post-infarction VSDs
- Sepsis or an active bacterial infection
- Contraindications to antiplatelet therapy
- Weight < 5.2 kg

50. b. Bicuspid aortic valve. Aortic coarctation is a common congenital defect that

usually occurs in the region of the ligamentum arteriosus. It is most often discrete but may be associated with diffuse hypoplasia of the aortic arch and isthmus. Bicuspid aortic valve is the most common coexisting anomaly. However, the presence of VSD, PDA, and malformations of the mitral valve apparatus is well documented. Intracranial aneurysms have been reported in 3% to 10% of patients with coarctation of the aorta.[12] There is no association between aortic coarctation and Ebstein anomaly (the latter being associated with right-sided lesions).

51. **b.** 20 mmHg. Intervention for coarctation is recommended in those with a peak-to-peak coarctation gradient greater than or equal to 20 mmHg.[1,4] In the presence of significant collateral vessel blood flow, catheter-based and Doppler systolic gradients may underestimate the degree of obstruction and intervention may be considered with gradients <20 mmHg in this setting.

    The most appropriate intervention for adults with native coarctation of the aorta remains controversial and either surgical or percutaneous intervention may be considered according to anatomy, comorbidities, center outcomes, and patient preference. In most ACHD centers, stenting has replaced balloon dilatation as the percutaneous intervention of choice, although this is not recommended in those with long segments of coarctation, vessel tortuosity, and transverse arch hypoplasia. Early mortality is usually less than 1% for primary operation in aortic coarctation.

52. **d.** Left coronary artery arising from the right sinus of Valsalva.

53. **d.** Spontaneous closure rarely occurs. Coronary fistulae rarely close spontaneously. The most common origin of coronary arteriovenous fistula is the right coronary artery, with a fistulous communication into the RV, RA, or coronary sinus (appearance on echocardiography demonstrated on the next page). Less commonly, it empties into the LV, LA, or PA. Complications may include CHF from left-to-right shunt, bacterial endocarditis, coronary ischemia, and rupture or thrombosis of the fistula. Surgical closure is associated with a good outcome (Fig. 9.17).

54. **e.** Valvular calcification. Both valvular and subvalvular aortic stenoses have male preponderance and may be associated with dilatation of the ascending aorta. The indications and risk of operation are similar. Although aortic regurgitation is more common in subvalvular aortic stenosis, it may also occur in valvular aortic stenosis. Valvular calcification is usually not observed in subvalvular aortic valve stenosis.

55. **c.** Transluminal balloon dilatation is the best treatment option in this case. Subaortic valve stenosis involves the presence of a membranous diaphragm in the LVOT that

creates a turbulent flow across the LVOT. This frequently causes damage to the aortic valve and may cause aortic valve insufficiency. Surgical intervention is recommended for patients with subaortic stenosis and a peak instantaneous gradient of 50 mmHg or mean gradient of 30 mmHg on echo Doppler.[1] Elective surgical resection is also indicated with lesser gradients <30 mmHg in the presence of progressive aortic regurgitation, LV systolic dysfunction (<55%), or dilatation (end-systolic diameter >50 mm). Although recurrences occur, surgical resection is frequently curative. Patients with aortic regurgitation may undergo valve repair at the time of subaortic stenosis resection. AVR would best be avoided unless the valve is severely damaged as it would involve the patient having to have further surgery if a biologic valve or be on long-term anticoagulation if a mechanical valve.

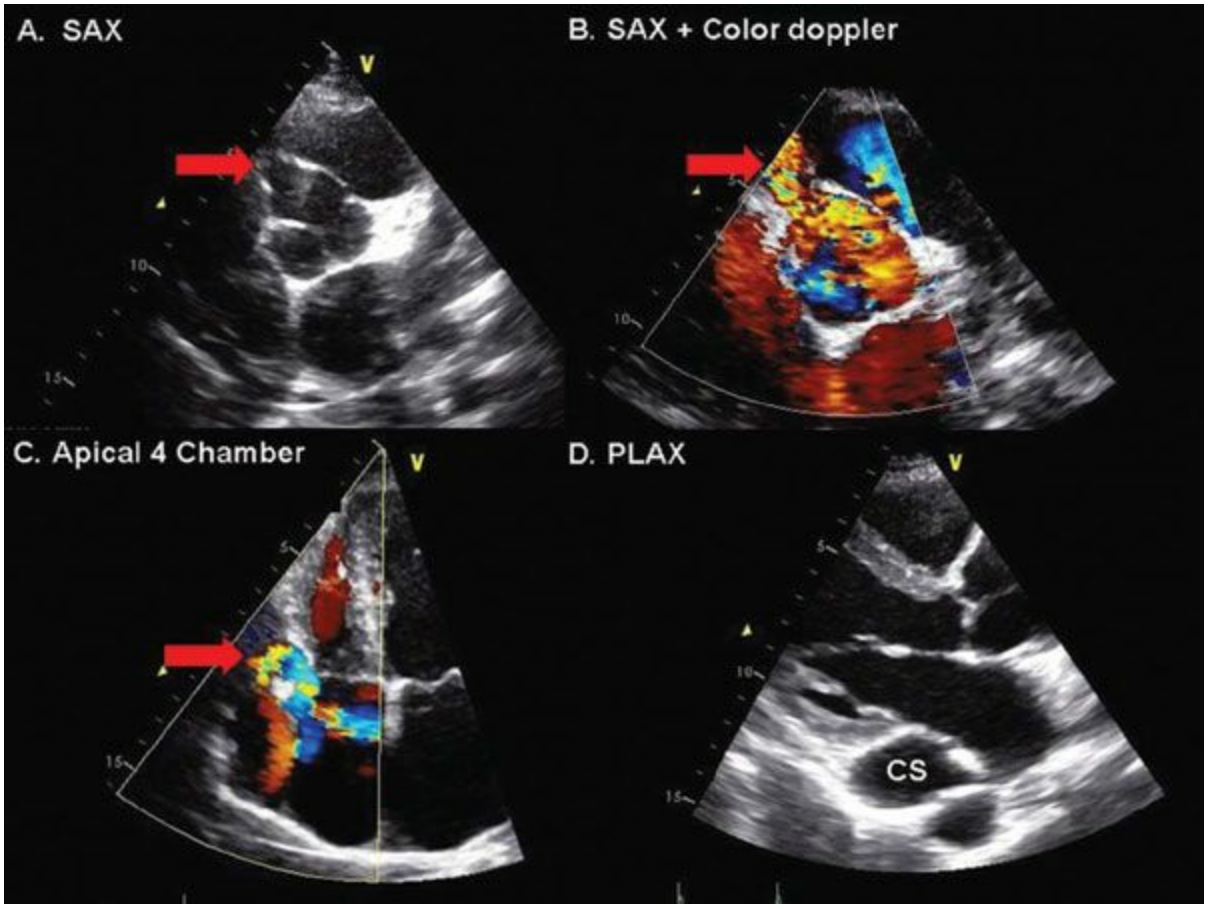

Figure 9.17 The right coronary artery fistula (red arrow) is seen in transthoracic short- axis (SAX) views arising from the right coronary cusp of the aortic valve (**A**) confirmed with color flow Doppler (**B**). In this case, the right coronary fistula drained into the right atrium (**C**) via a dilated coronary sinus (**D**). PLAX, parasternal long axis.

56. **d.** 60 to 80 years. Bicuspid aortic valve is the most common congenital cardiac anomaly with an incidence of 1% to 2% and a male predominance (4:1 sex ratio). Bicuspid aortic valve is sometimes inherited as an autosomal dominant trait with

variable penetrance. Three morphologic types are recognized on the basis of commissural fusion: fusion of the left and right coronary cusps (most common), fusion of the right and non-coronary cusps, and fusion of the left and non- coronary cusps (least common). Sclerosis of the bicuspid aortic valve begins in the second decade and calcification may appear as early as the fourth decade.[13] The peak age range for surgical intervention is between 60 and 80 years.[14] Bicuspid aortic valve disease is associated with intrinsic abnormalities of the aortic media that predisposes to aortic root dilatation/aneurysm/rupture, and/or dissection. Other left-sided lesions associated with bicuspid aortic valve include coarctation of the aorta, subaortic stenosis, parachute mitral valve, VSD, and PDA.

57. e. Regular follow-up with repeat TTE in 6 months. Ebstein anomaly is characterized by apical displacement of the septal tricuspid leaflet of >8 mm/m^2 and the presence of an elongated anterior tricuspid leaflet. The clinical presentation of Ebstein anomaly is influenced by numerous factors including the extent of tricuspid leaflet distortion and regurgitation, the degree of pulmonary stenosis, RA pressure, right heart size, and the presence of a right-to-left shunt. More than 50% of patients have a shunt at the atrial level with either a PFO or secundum ASD. Tricuspid valve repair or replacement is recommended by the AHA for the following indications[1]:

- Symptoms or deteriorating exercise capacity
- Cyanosis (saturations < 90%) due to right-to-left shunting
- Paradoxical embolism
- Progressive RV dilatation or reduction in RV systolic function
- The patient has moderately severe TR with preserved RV systolic function. He has no symptoms and no evidence of CHF. There is no indication for intervention at this time.

58. c. Pulmonary regurgitation. TOF comprises (1) RVOT obstruction, (2) a VSD, (3) an aorta that overrides the VSD, and (4) RV hypertrophy. Primary repair in the first year of life consists of VSD closure and relief of RVOT obstruction, the latter achieved by increasing the RVOT diameter through patch augmentation or placement of a transannular patch. The integrity of the pulmonary valve is frequently disrupted at the time of repair and predisposes patients to pulmonary regurgitation, the most common residual abnormality seen in adults with repaired TOF.

Although less common than pulmonary regurgitation, ventricular tachycardia is an important cause of late mortality in adults with repaired TOF. TOF patients at highest risk for ventricular tachycardia and sudden death include those with

significant residual pulmonary regurgitation/RVOT obstruction, reduced RV or LV function, QRS duration >180 milliseconds, high-grade ectopy on Holter monitoring, and inducible ventricular tachycardia.[15–17]

59. **d.** Cardiac magnetic resonance imaging study. Pulmonary valve replacement is recommended in adults with repaired TOF, severe pulmonary regurgitation, and any of the following[1]:

- Moderate-to-severe RV dysfunction
- Moderate-to-severe RV enlargement (generally defined as >160 to 170 mL/m^2)
- Development of symptomatic or sustained atrial and/or ventricular arrhythmias
- Moderate-to-severe TR

Surgery in adults with repaired TOF may also be considered for residual RVOT obstruction (peak gradient >50 mmHg), residual VSD with shunt greater than 1.5:1, and severe aortic regurgitation with associated symptoms or more than mild LV dysfunction.

Due to the complex geometry of the RV and limitations of echocardiography, cardiac magnetic resonance imaging is the gold standard investigation for assessment of RV dimensions and function in repaired TOF. Further evaluation of pulmonary regurgitation is also possible.

A positive bubble study would be helpful in confirming the presence of an ASD but would not help in deciding timing of pulmonary valve replacement. An ASD is unlikely to explain the degree of RV dilatation seen in this patient, particularly in the presence of a clear etiology (severe pulmonary regurgitation). Formal electrophysiologic testing is not indicated in TOF patients without a history of presyncope or palpitations. Invasive hemodynamics would not provide additional diagnostic or prognostic information. Since there is no evidence of volume overload, the initiation of diuretics and digoxin would not be recommended.

60. **e.** Pulmonary stenosis. The clinical findings (RV lift, a palpable systolic thrill at the second left intercostal space, a widely split second heart sound, and harsh ejection systolic murmur heard loudest at the second left intercostal space) are consistent with significant pulmonary stenosis. The RV lift is evidence of a pressure-loaded RV. The second heart sound is split due to delayed closure of the pulmonary valve. Pulmonary valve stenosis is heard loudest at the second left intercostal space and may be associated with a palpable thrill.

61. **c.** Balloon valvotomy. Echocardiography (TTE ± TEE) generally provides a definitive diagnosis in most patients with pulmonary stenosis. Doppler gradients

from echo are adequate for deciding on the timing of intervention. Cardiac catheterization may be used to confirm the diagnosis of pulmonary stenosis and to exclude pulmonary hypertension in cases where this is a concern.

The cardiac catheterization results confirm RV hypertension (RV systolic pressure 70 mmHg) with a slightly elevated end-diastolic RV pressure (15 mmHg). RV hypertension should be differentiated from pulmonary hypertension: The finding of normal main PA pressures distal to the site of valvar stenosis (+ normal transpulmonary gradient) excludes pulmonary hypertension in this patient. Hence, vasodilator challenge and referral to a pulmonary hypertension are not indicated.

For patients with domed valvular pulmonary stenosis, balloon valvotomy is the treatment of choice. Balloon valvotomy is recommended in patients with a peak instantaneous Doppler gradient greater than 60 mmHg or a mean gradient greater than 40 mmHg (assuming less than moderate pulmonary regurgitation).[1] There is no role for medical therapy in valvular pulmonary stenosis patients who meet criteria for intervention.

62. **d.** All of the above. Protein-losing enteropathy is a condition diagnosed in <5% of Fontan patients,[18] in which protein is lost via the gut resulting in ascites, peripheral edema, and pleural and pericardial effusions. The precise cause of protein-losing enteropathy is unknown, although elevated systemic venous pressures appear to play a role. The diagnosis is made by measuring increased a1-antitrypsin in the stool.

Thromboembolic complications occur in up to 20% of patients with the slow passive flow in the Fontan circuit and the coagulation abnormalities consequent on liver congestion both playing a role.

Atrial tachyarrhythmias are very common in adults after the Fontan operation,[19] the most common type being an atypical form of atrial flutter called "intra-atrial reentrant tachycardia" or IART. IART arises from macroreentrant circuits around surgical scars and patches and tends to be slower than typical flutter. Early recognition and treatment of IART is important for preventing complications such as thromboembolism, hemodynamic instability, syncope, and death. Unfortunately, recurrence of IART is common even in the setting of chronic antiarrhythmic medications and catheter-based ablation.

63. **b.** Weber-Osler-Rendu syndrome. Pulmonary arteriovenous fistula involves direct communication between pulmonary arteries and veins. Most patients have associated Weber-Osler-Rendu syndrome, a condition associated with the presence of multiple telangiectasias. Williams syndrome is associated with mental retardation, elfin facies, and supravalvular aortic and pulmonic stenosis. Bland-Garland-White syndrome involves the anomalous origin of the left coronary artery

from the PA. Kartagener syndrome is associated with situs inversus, sinusitis, and bronchiectasis. Crouzon syndrome is associated with PDA and aortic coarctation (see also Table 9.4).

64. **b.** Pulmonary stenosis. Pulmonary stenosis is the most common cardiac abnormality (40%) seen in patients with Noonan syndrome. Other associations include AVSDs (13.8%), coarctation of the aorta (12.5%), and hypertrophic cardiomyopathy (8.8%).[20] Although less common in Noonan syndrome patients, LVOT obstruction may be due to asymmetric hypertrophy and valvular or supravalvar aortic stenosis.[21]

65. **a.** 22q11.2 microdeletion. See Table 9.4.

TABLE 9-4 Common Chromosomal Abnormalities Seen in Adult Congenital Heart Disease

Chromosomal Abnormality	Syndrome	Cardiac Defects	Extracardiac Manifestations
22q11.2 microdeletion Autosomal dominant	22q11.2 microdeletion syndrome Previously called DiGeorge/CATCH-22	Conotruncal defects Tetralogy of Fallot Truncus arteriosus Interrupted aortic arch Double outlet right ventricle	C–Cardiac defects A–Abnormal facies* T–Thymic hypoplasia C–Cleft palate H–Hypocalcemia + Psychiatric conditions (schizophrenia)
7q11.23 microdeletion Autosomal dominant Defects involving the elastin gene	William syndrome	Pulmonary artery stenosis Supravalvar LVOTO	Elfin facies (small chin, patulous lips, upturned nose, broad forehead), infantile hypercalcemia Short stature "Cocktail" personality
Chromosome 12/PTPN11 gene Autosomal dominant	Noonan syndrome	Dysplastic pulmonary valve stenosis Pulmonary artery stenosis TOF ASD Hypertrophic cardiomyopathy	Short stature, ptosis, hypertelorism, webbed neck, flat chest, pectus deformity, lymphedema, inguinal hernia, undescended/cryptorchid testes Intellectual impairment in 1/3
Trisomy 21	Down syndrome	AVSD VSD Mitral valve prolapse Aortic regurgitation Pulmonary HT	Short stature, characteristic facial appearance Intellectual impairment Atlantoaxial instability Thyroid disorders White blood cell disorders
Monosomy X (45, X) 45 XO karyotype in 50% 45XO/XX mosaics and other X-chromosome abnormalities in the remainder	Turner syndrome	Coarctation of the aorta (postductal) Left-sided obstructive lesions PAPVR without ASD Aortic dissection/rupture Systemic HT	Short stature, webbing of the neck, wide set nipples, small chin, prominent ears, absent pubic hair Intellectual function is grossly intact

ASD, atrial septal defect; AVSD, atrioventricular septal defect; HT, hypertension; LVOTO, LV outflow tract obstruction; PAPVR, partial anomalous pulmonary venous return; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

*hypertelorism, low set ears, micrognathia, small mouth, malformed nose, and down-slanting palpebral fissures

66. **e.** Hypertelorism, bifid uvula, and arterial tortuosity are common features. LDS is an autosomal dominant syndrome caused by transforming growth factor-fl receptor gene mutations and characterized by the triad of (a) arterial tortuosity and aneurysms, (b) hypertelorism, and (c) bifid uvula or cleft palate.[22] Almost all patients with LDS will develop aortic root dilatation that requires early surgical intervention due to the increased risk of dissection and rupture in these patients. Surgical intervention is recommended once the aortic root (or other aortic segments) is >4.0 cm or rapidly expanding (>0.5 cm over 1 year).[23] Other aortic segments and branch vessels may also be involved. While there is overlap in the skeletal manifestations of Marfan syndrome and LDS (both demonstrate joint hyperlaxity, arachnodactyly, pectus deformity, and scoliosis), long limbs and tall stature are not characteristic of LDS.

67. **c.** Shone syndrome. The key learning point is that Shone syndrome/complex describes left-sided obstructive lesions and is therefore not implicated in pulmonary stenosis (Table 9.5).

TABLE 9-5 Adult Congenital Heart Disease Syndromes Associated with Pulmonary Stenosis

Syndrome	Cardiac Defects
Noonan syndrome	Dysplastic pulmonary valve stenosis, pulmonary artery stenosis
	Tetralogy of Fallot, atrial septal defect, hypertrophic cardiomyopathy[21]
Williams syndrome	Pulmonary artery stenosis
	Supravalvar aortic stenosis[24,25]
Shone syndrome	Multilevel obstruction of left ventricular inflow and outflow
	Mitral stenosis (parachute mitral valve, supramitral ring)
	Subvalvular left ventricular outflow tract obstruction
	Valvular outflow tract obstruction
	Coarctation of the aorta[26]
	May be familial
Congenital rubella syndrome	Pulmonary artery stenosis, peripheral pulmonary artery stenosis
	Patent ductus arteriosus
	Non-cardiac: Cataracts, retinopathy, deafness, intellectual impairment[27]
LEOPARD syndrome	Pulmonary stenosis
	Non-cardiac: Café-au-lait spots and multiple lentigines[28]

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Physiology/Biochemistry

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QUESTIONS

1. At the level of the endothelium, nitric oxide (NO) causes the following:
   a. Promotes smooth muscle relaxation
   b. Reduced leukocyte adhesion
   c. Increased smooth muscle proliferation
   d. Downregulation of oxidative enzymes

2. The following cells are considered most important to the process of atherosclerosis:
   a. Monocyte/macrophage lineage
   b. Platelets
   c. Red blood cells
   d. B cells

3. The following are characteristics of a vulnerable plaque except
   a. high concentration of macrophages.
   b. high concentration of collagen.
   c. neovascularization.
   d. large necrotic core.

4. Arterial thrombosis after plaque rupture is initiated by
   a. tissue plasminogen activator.
   b. factor XIII.
   c. protein C.
   d. activated protein C.
   e. tissue factor.

5. Low levels of gene expression can be detected by

   a. Northern blot.
   b. Western blot.
   c. reverse transcriptase-polymerase chain reaction (RT-PCR).
   d. Southern blot.
   e. gene transfer.

6. The final common pathway of platelet aggregation is mediated through

   a. adenosine diphosphate (ADP) binding.
   b. collagen.
   c. thrombin.
   d. $\alpha_v\beta_3$ receptor.
   e. glycoprotein (GP) IIb/IIIa receptor.

7. Inducers of smooth muscle cell proliferation include the following except

   a. platelet-derived growth factor-β.
   b. basic fibroblast growth factor (bFGF).
   c. transforming growth factor-β (TGF-β).
   d. thrombin.
   e. oxidized low-density lipoprotein (LDL).

8. Inhibitors of cardiac myocyte apoptosis include

   a. insulin-like growth factor-1β.
   b. dobutamine.
   c. ischemia.
   d. caspase 3.
   e. Bid cleavage.

9. The following are endothelium-independent vasodilators except

   a. nitroglycerin.
   b. papaverine.
   c. adenosine.
   d. acetylcholine (ACh).
   e. verapamil.

ANSWERS

1. **C.** Increased smooth muscle proliferation. NO has important effects on the

endothelium to produce vasodilation, reduced leukocyte adhesion and platelet reactivity, and downregulation of oxidative enzymes. Consistent with these beneficial effects, NO results in a reduction in smooth muscle proliferation, not an increase.

2. **b.** Monocyte/macrophage lineage. These cells bind oxidized LDL to form foam cells, which then release proinflammatory cytokines to perpetuate the atherosclerotic process.

3. **b.** High concentration of collagen. It is in fact the low concentration of collagen (due to low levels of smooth muscle cells) that results in the collagen-poor thin cap of vulnerable plaques. These plaques display high concentrations of macrophages (foam cells) and T-lymphocytes (producing interferon-γ), as well as significant neovascularization and a large necrotic core that is vulnerable to rupture and propagate thrombosis. In fact, saphenous vein graft (SVG) lesions tend to have a larger necrotic core than native coronary lesions, which is one factor that contributes to greater plaque friability and worse outcomes with SVG stenting.

4. **e.** Tissue factor. Tissue factor binding to factor VII is the initiating event for the extrinsic blood coagulation cascade. The complex can also cleave factor IX and contribute to activation of the intrinsic cascade as well. Tissue factor is normally not expressed in the vasculature, but, in atherosclerotic vessels, tissue factor is expressed by macrophages and smooth muscle cells. Tissue factor expression is increased in the lesions of patients who present with unstable angina. On plaque rupture, the exposure of tissue factor to blood-borne coagulation factors leads to thrombus formation.

5. **c.** Reverse transcriptase-polymerase chain reaction (RT-PCR). RT-PCR is capable of finding a single copy of RNA. Northern blot analysis requires at least 5 to 10 μg of total RNA. Western blot analysis is for determining protein levels. Southern blot analysis is for genotyping and requires multiple copies of DNA. Gene transfer is not a detection method.

6. **e.** Glycoprotein (GP) IIb/IIIa receptor. ADP, collagen, and thrombin bind independently, leading to platelet activation and, ultimately, to expression of the GP IIb/IIIa receptor. GP IIb/IIIa receptor expression leads to platelet clumping by binding to surrounding activated platelets. The $\alpha_v\beta_3$ receptor does not lead to platelet aggregation.

7. **c.** Transforming growth factor-β (TGF-β). Platelet-derived growth factor-β, bFGF,

and thrombin are all smooth muscle mitogens. Oxidized LDL causes smooth muscle cell proliferation through the autocrine release of bFGF. TGF-β alters the smooth muscle cell phenotype from a proliferative to a synthetic state and, thus, is antiproliferative.

8. **a.** Insulin-like growth factor-1β. Insulin-like growth factor-1β overexpression has been shown to be cardioprotective because of decreased apoptosis in the setting of myocardial ischemia. Dobutamine has been shown to induce cardiomyocyte apoptosis. Caspase 3 and Bid cleavage are cytoplasmic markers of apoptosis, but do not directly influence apoptosis itself.

9. **d.** Acetylcholine (ACh). ACh, acting through muscarinic receptors, exerts its effect on the endothelium by promoting the conversion of L-arginine to NO. This in turn produces smooth muscle cell relaxation and consequent vasodilation. ACh is therefore an endothelium-dependent vasodilator. In patients with endothelial dysfunction, this effect is lost, and the direct action of ACh on smooth muscle cells producing vasoconstriction is more pronounced. The other agents listed are all endothelium-independent vasodilators.

SUGGESTED READINGS

Annex BH. Differential expression of TF protein in directional atherectomy specimens from patients with stable and unstable coronary syndromes. Circulation. 1995;91:619–622.

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Hypertension

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QUESTIONS

1. A 35-year-old woman at 24 weeks of pregnancy is found to have several blood pressure readings in the range of 145 to 158 mmHg systolic, 80 to 92 mmHg diastolic. This is her first pregnancy and she has no prior history of hypertension. She reports bilateral mild ankle swelling and nausea, but no right upper quadrant pain, visual changes, headaches, or dyspnea. A 24-hour urine collection shows 360 g protein. The hemoglobin is 8.0 g/dL and the platelet count is 43,000 cells/mm^3. Which of the following is the correct diagnosis?

   a. Chronic hypertension
   b. Gestational hypertension
   c. Preeclampsia
   d. Eclampsia

2. A 42-year-old woman presents for post hospitalization follow-up. She was recently admitted to hospital for 3 days due to sudden-onset dyspnea. Her blood pressure on presentation was 164/98 mmHg. Her examination and chest radiograph were consistent with pulmonary edema. She responded well to intravenous diuretics and was discharged on lisinopril. She has no family history of hypertension. On examination during the clinic visit, her blood pressure is 158/90 mmHg. She is normal in weight and has a normal cardiovascular examination except for a right-sided carotid bruit. Her blood tests are notable for a rise in creatinine from 0.9 to 1.8 mg/dL since hospital discharge. What is the most appropriate follow-up investigation?

   a. Coronary angiogram
   b. Duplex ultrasonography of the renal arteries
   c. Urinary catecholamines

d. 24-Hour urinary-free cortisol

3. An 83-year-old woman presents to cardiology clinic for follow-up of her hypertension and coronary artery disease. Her only current symptom is dizziness on standing from a sitting position. The dizziness caused her to lose balance and fall on two occasions. Her current resting blood pressure is 144/90 mmHg with pulse 60 beats per minute (bpm). Her medications include hydrochlorothiazide 25 mg daily, doxazosin 2 mg daily, metoprolol XL 50 mg daily, simvastatin 40 mg daily, and aspirin 81 mg daily. What changes in medication therapy would you recommend?

   a. Discontinue hydrochlorothiazide and start lisinopril 20 mg daily.
   b. Discontinue atenolol and increase hydrochlorothiazide to 50 mg daily.
   c. Discontinue doxazosin and initiate clonidine 0.4 mg twice daily.
   d. Discontinue doxazosin and start lisinopril 5 mg daily.
   e. Discontinue doxazosin and increase metoprolol to 100 mg daily.

4. A 64-year-old woman with hypertension, stage III chronic kidney disease (CKD), and diabetes is not yet at blood pressure goal on the following antihypertensives: lisinopril 40 mg, hydrochlorothiazide 25 mg, and metoprolol XL150 mg. Which of the following additional agents is contraindicated?

   a. Aliskiren
   b. Hydrochlorothiazide
   c. Amlodipine
   d. Methyldopa

5. A 57-year-old woman with multidrug-resistant hypertension presents to her primary care doctor with multiple complaints. Her antihypertensive regimen consists of valsartan, hydralazine, amlodipine, captopril, and hydrochlorothiazide. Which of the following pairings of medication and side effect are most likely to be correct?

   a. Valsartan and cough
   b. Hydralazine and ankle edema
   c. Amlodipine and insomnia
   d. Captopril and constipation

6. A 19-year-old young man presents with an aortic root diameter of 4.4 cm and a strong family history of aortic dissection. His father died of a type A dissection at age 42, and his older brother recently underwent aortic root repair for an aneurysm measuring 5.6 cm in diameter. Both brothers have the fibrillin-1 gene mutation. The patient currently receives metoprolol 50 mg daily, with a pulse of 55 bpm and

blood pressure measurements in the range of 115 to 125/65 to 75 mmHg. Which additional medication should be added?

a. No additional medications
b. Amlodipine
c. Ramipril
d. Losartan

7. A 62-year-old man with type 1 diabetes mellitus receives intermittent hemodialysis for his end-stage renal disease. His blood pressure has become elevated over the past year and has not reached goal levels despite initiation of three antihypertensive medications. He takes several medications for comorbid conditions, several of which may be exacerbating his elevated blood pressure. Medications for which of the following conditions would not be expected to have a side effect of hypertension?

a. Diabetes
b. Anemia
c. Hyperparathyroidism
d. Glaucoma
e. Osteoarthritis

8. A 58-year-old man with resistant hypertension returns for outpatient follow-up. His blood pressure is 168/79 mmHg and pulse 70 bpm, despite 25 mg hydrochlorothiazide daily, 200 mg metoprolol XL daily, 320 mg valsartan daily, 10 mg amlodipine daily, and a 0.1 mg/24 hour clonidine patch. He is considering entering a sympathetic denervation trial and has some questions about the procedure. Which of the following is the most accurate brief description of the denervation procedure?

a. Access through a femoral vein, cryoablation of a unilateral renal artery
b. Access through a femoral artery, radiofrequency ablation of a unilateral renal artery
c. Access through a femoral vein, radiofrequency ablation of bilateral renal arteries
d. Access through a femoral artery, alcohol ablation of bilateral renal arteries
e. Access through a femoral artery, radiofrequency ablation of bilateral renal arteries
f. At this time renal denervation cannot be recommended for this patient population

9. Which of the following patient characteristics is a risk factor for development of angiotensin-converting enzyme inhibitor (ACEI)-induced angioedema?

a. Diabetes

b. Female gender
c. Age <45 years
d. Age >65 years

10. A 76-year-old man with hypertension has inadequate blood pressure control on chlorthalidone 25 mg daily. His primary care doctor is choosing a second antihypertensive agent. Which of the following comorbidities would be an evidence-based indication for choosing ramipril over amlodipine as the second agent?

a. Heart failure with preserved ejection fraction (HFPEF)
b. Peripheral arterial disease
c. Sleep apnea
d. Aortic aneurysm

11. A 30-year-old man with no past medical history presents to his primary care physician complaining of new-onset morning headaches that have been ongoing for the past few weeks. His blood pressure is noted to be 220/100 mmHg with a gradient between his brachial and popliteal arteries. On auscultation, there is a II/VI systolic crescendo–decrescendo murmur heard across the precordium. His electrocardiogram is significant for left ventricular hypertrophy. A chest X-ray shows cardiomegaly with evidence of rib notching. The patient most likely has what valvular abnormality?

a. Bicuspid aortic valve
b. Mitral regurgitation
c. Tricuspid regurgitation
d. Pulmonary stenosis

12. A 55-year-old man with diabetes mellitus presents to his cardiologist with a blood pressure of 165/95 mmHg. According to the JNC (Joint National Committee) 8 guidelines, what is his target blood pressure measurement?

a. Prehypertension, 140/90 mmHg
b. Stage 2, 130/80 mmHg
c. Stage 1, 140/90 mmHg
d. Stage 2, 110/70 mmHg

13. What is the mechanism of action of the antihypertensive medication aliskiren?

a. ACEI
b. Nonselective β-blockade
c. Angiotensin receptor blocker (ARB)

d. Direct renin inhibitor

14. A 35-year-old woman with no past medical history, not receiving oral contraceptives, and with a family history of hypertension presents with a gradual increase in blood pressure over the past few years. Today in clinic her blood pressure is 155/95 mmHg. What is the most appropriate next step?

a. Patient has essential hypertension; start thiazide diuretic
b. She is asymptomatic; therefore, observe patient and have her follow-up in 1 year
c. Have her follow-up in a few weeks for repeat blood pressure measurements
d. Renal magnetic resonance imaging (MRI)

15. A 68-year-old man with coronary artery disease, hypertension, diabetes mellitus, and stage II hypertension presents for routine follow-up in the cardiology clinic. His blood pressure is 180/100 mmHg. He is compliant with all his medications and is currently on hydrochlorothiazide, lisinopril, metoprolol, amlodipine, and isosorbide mononitrate. He recently has had two episodes of noncardiogenic pulmonary edema in the setting of an ejection fraction of 55% with no evidence of diastolic dysfunction. What is the most appropriate next step in the management of his hypertension?

a. Addition of minoxidil
b. Renal MRI
c. Discussion of medical adherence
d. Addition of hydralazine

16. A 44-year-old woman had a blood pressure of 115/75 mmHg a few years ago. She now has a blood pressure of 155/75 mmHg, which was confirmed on a repeat visit. How much has her risk for cardiovascular disease increased?

a. No change
b. Twofold
c. Fourfold
d. Tenfold

17. Which of the following antihypertensive agents is a known cause of autoimmune hemolytic anemia?

a. Metoprolol
b. Methyldopa
c. Captopril
d. Losartan

18. A patient is initiated on an ACEI. What is the recommended cutoff for rise in creatinine before stopping the medication?

a. 10% increase in creatinine
b. 20% increase in creatinine
c. 35% increase in creatinine
d. 50% increase in creatinine

19. A 68-year-old man with hypertension and history of a stroke presents for further management of his hypertension. He is currently prescribed a thiazide diuretic; however, his blood pressure remains elevated. From the standpoint of decreasing his future risk of stroke, which of the following drug classes would be most beneficial?

a. Calcium channel blocker
b. ACEI
c. ARB
d. β-Blocker

20. A 56-year-old woman presents to your clinic for physical examination. She has no significant past medical history and is asymptomatic. Her vital signs are significant for a blood pressure of 145/95 mmHg. What are the next steps in her evaluation for hypertension?

a. She should return in 1 year for her yearly physical examination.
b. She should have a repeat blood pressure measurement at a later time point during her visit and return in a few weeks to obtain repeat testing if that measurement is elevated.
c. Start patient on thiazide diuretic at the initial clinic visit.
d. Begin evaluation for secondary causes of hypertension.

21. A 45-year-old woman with no significant past medical history is noted to have a blood pressure of 145/90 mmHg in the outpatient clinic. This is confirmed on repeat visits. Which of the following tests would not be indicated at this time?

a. Electrocardiogram
b. Urinalysis
c. Creatinine
d. Urine metanephrines

22. A 26-year-old man with no significant history presents to his primary care physician with complaints of episodic palpitations, morning headaches, and diaphoresis. He denies any illicit drug use. His physical examination is notable for a blood pressure

of 230/120 mmHg. His ophthalmologic examination is significant for AV nicking. What is the most appropriate next step?

a. Toxicology screen
b. Urine metanephrines
c. MRI thorax
d. Start thiazide diuretic with follow-up in 1 month

23. A 65-year-old man with a history of hypertension and dyslipidemia is admitted to the coronary care unit with a diagnosis of a myocardial infarction. He undergoes an emergent cardiac catheterization with insertion of a drug-eluting stent to his left circumflex coronary artery. His vital signs show a blood pressure of 170/90 mmHg with a heart rate of 85 bpm and no evidence of heart failure on examination. Which of the following medications would be most appropriate to treat this patient's hypertension?

a. Amlodipine
b. Verapamil
c. Metoprolol
d. Nitroprusside

24. Which of the following antihypertensive drug classes is most effective at reducing carotid intimal thickness?

a. Calcium channel blocker
b. β-Blocker
c. ACEI
d. Thiazide diuretic

25. What is the long-term antihypertensive mechanism of action for thiazide diuretics?

a. Decreased plasma volume
b. Natriuresis
c. Decreased cardiac output
d. Decreased peripheral resistance

26. A 46-year-old woman, status post orthotopic heart transplantation, is currently taking mycophenolate, prednisone, and tacrolimus as an immunosuppressive regimen. On routine laboratory evaluation, she is found to have leukopenia. Mycophenolate levels have not been elevated in the past few months. Which of the following antihypertensive agents is the most likely culprit?

a. Hydrochlorothiazide

b. Metoprolol
c. Captopril
d. Clonidine

27. A 34-year-old man with isolated essential hypertension presents to clinic and is found to have a blood pressure of 180/100 mmHg after intensive lifestyle modifications. What is the most appropriate next step?

a. Start hydrochlorothiazide.
b. Start hydrochlorothiazide and lisinopril.
c. Repeat blood pressure in 4 weeks.
d. Start amlodipine.

28. A 62-year-old man with isolated essential hypertension, currently taking hydrochlorothiazide 25 mg PO daily, comes to you for his first clinic visit. He notes that his blood pressure at home is always less than 140/80 mmHg, but in clinic it is always at least 155/95 mmHg. What is the next step?

a. Increase dose of thiazide
b. Addition of second antihypertensive medication
c. Do nothing as he has white coat hypertension
d. Evaluate for secondary causes of hypertension

29. A 48-year-old man with diabetes mellitus, hypertension, and hyperlipidemia presents to the emergency room with hypertensive emergency. His mean arterial pressure is 150 mmHg, pulse 58 bpm. The electrocardiogram is notable for sinus bradycardia with PR prolongation (260 milliseconds) and no ST deviations or T-wave abnormalities. Which medications would be the most appropriate therapy for this patient?

a. Intravenous nitroprusside
b. Sublingual nifedipine
c. Intravenous labetalol
d. Intravenous nitroglycerin

30. A 48-year-old obese man with hypertension, dyslipidemia, and diabetes mellitus presents to the outpatient clinic for his yearly physical. He has refused medications in the past, but now is willing to consider treatment. His blood pressure is 145/95 mmHg with a heart rate of 80 bpm. His laboratory data are significant for a creatinine of 1.3 mg/dL with the presence of microalbuminuria. Which of the following mediations would be most appropriate?

a. Carvedilol

b. Lisinopril
c. Chlorthalidone
d. Terazosin

31. A 34-year-old woman with essential hypertension is considering becoming pregnant. Which of the following medications would be absolutely contraindicated to control her blood pressure during pregnancy?

a. Methyldopa
b. Labetolol
c. Captopril
d. Nifedipine

32. A 48-year-old Caucasian man with impaired fasting glucose presents to his physician for a follow-up visit after he was noted to have a blood pressure of 150/95 mmHg. On repeat evaluation his blood pressure is 155/95 mmHg. Which of the following medications would be the least favored?

a. Hydrochlorothiazide 25 mg PO daily
b. Lisinopril 10 mg PO daily
c. Atenolol 25 mg PO daily
d. Chlorthalidone 25 mg PO daily

33. A 65-year-old African American man with isolated hypertension presents to clinic for his yearly physical examination. He is noted to have a blood pressure of 170/95 mmHg. He is currently prescribed lisinopril and metoprolol. Which of the following medication changes would be most appropriate?

a. Continue current medications at increased doses
b. Conversion of patient to a calcium channel blocker and thiazide diuretic
c. Addition of clonidine
d. Stopping lisinopril because of concern for renal artery stenosis

34. A 42-year-old woman with a new diagnosis of diabetes mellitus presents for management of hypertension. She was previously an avid athlete, but over the past few years has noted increased weight gain, a radial fracture after a minor fall, and increasing hirsutism. She is currently on hydrochlorothiazide, amlodipine, and lisinopril. What is the most appropriate next step in the management of this patient's hypertension?

a. Referral to nutrition specialist to assist her with weight loss
b. Addition of clonidine
c. 24-Hour urine cortisol test

d. MRI of the brain

35. A 69-year-old woman with diabetes mellitus and hyperlipidemia and no history of hypertension is noted at her yearly clinic visit to have new-onset hypertension with a blood pressure of 180/110 mmHg. She undergoes screening for secondary causes of hypertension and is found to have a pheochromocytoma. What of the following medications is contraindicated as monotherapy?

a. Metoprolol
b. Lisinopril
c. Phentolamine
d. Hydrochlorothiazide

36. A 42-year-old man presents for a routine physical examination. He is noted to have a body mass index of 30 kg/m^2, impaired fasting glucose, and a blood pressure of 135/85 mmHg. What is the best treatment plan for this individual?

a. Aggressive lifestyle modification
b. Institute thiazide diuretic regimen
c. No treatment at this time
d. Initiate ACEI

37. A 50-year-old man with CKD and hypertension has a blood pressure of 165/110 mmHg. What is this patient's target blood pressure according to the JNC 8 guidelines?

a. 140/90 mmHg
b. 130/80 mmHg
c. 120/80 mmHg
d. 110/70 mmHg

38. A 36-year-old patient, status post heart transplantation, is found to have hypertension. He is currently taking prednisone, mycophenolate, and cyclosporine. Which of the following antihypertensive medications would increase cyclosporine levels?

a. Lisinopril
b. Hydrochlorothiazide
c. Diltiazem
d. Metoprolol

39. A 56-year-old man with resistant hypertension begins to take a new antihypertensive agent. Within the next few weeks he is diagnosed with pericarditis. Which of the

following agents is most likely responsible?

a. Carvedilol
b. Minoxidil
c. Amlodipine
d. Captopril

40. A 27-year-old woman presents to the cardiology clinic for evaluation of uncontrolled hypertension. She was diagnosed 2 years ago and is currently taking hydrochlorothiazide, lisinopril, and amlodipine. She denies nonadherence and has a blood pressure of 170/100 mmHg that is equal in both arms. On routine laboratory examination, she has a potassium level of 2.9 mEq/L with a sodium level of 148 mEq/L. What is the most appropriate diagnostic test?

a. Renal MRI/magnetic resonance angiography
b. Morning renin and aldosterone concentrations
c. Adrenal vein sampling
d. 24-Hour urine cortisol concentration

41. A 58-year-old obese man with hypertension, diabetes mellitus, hyperlipidemia, and recent myocardial infarction presents for his annual physical examination. He is currently prescribed atenolol, hydrochlorothiazide, amlodipine, and quinapril. His blood pressure is at target values. His HbA1c is at goal. However, he has noted increasing lower extremity edema over the past few months and had a near-fatal car accident after falling asleep while driving. His echocardiogram reveals an ejection fraction of 65% with no evidence of diastolic dysfunction. Which of the following management decisions would be most appropriate at this time?

a. Discontinue calcium channel blocker
b. Polysomnography
c. Addition of loop diuretic
d. Maintain current regimen with advisement that his symptoms are typical with aging

42. A 56-year-old man on hydralazine, hydrochlorothiazide, lisinopril, and metoprolol begins to develop a malar rash and arthralgias. Which of the above antihypertensive agents is known to cause drug-induced lupus?

a. Hydralazine
b. Hydrochlorothiazide
c. Lisinopril
d. Metoprolol

43. A 47-year-old man with coronary artery disease, diabetes mellitus, and hypertension is currently taking clonidine. He is found to have a blood pressure of 170/90 mmHg after forgetting to take his medication for 48 hours. What is the best strategy to control his blood pressure?

a. Restart clonidine.
b. Start nitroprusside.
c. Start esmolol.
d. Add thiazide diuretic.

ANSWERS

1. **c.** Preeclampsia. Chronic hypertension is characterized by blood pressure ≤140/90 mmHg present before pregnancy, before the 20th week of gestation, or persisting beyond the 42nd postpartum day. Conversely, gestational hypertension develops beyond 20 weeks of gestation and usually resolves within 42 days postpartum. Preeclampsia is characterized by hypertension presenting beyond 20 weeks of gestation with >300 mg protein in a 24-hour urine collection or >30 mg/mmol in a spot urine sample, although in rare cases hypertension or proteinuria can be absent. Thrombocytopenia in this patient is very concerning for HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), a life-threatening condition showing significant overlap with preeclampsia. Eclampsia is the occurrence of seizures in a pregnant woman with preeclampsia. Edema is no longer considered to be part of the diagnostic criteria for preeclampsia because it occurs in more than half of normal pregnancies.

2. **b.** Duplex ultrasonography of the renal arteries. This young woman likely has hypertension secondary to fibromuscular dysplasia (FMD). FMD is a noninflammatory, nonatherosclerotic vascular condition typically affecting young women. It most frequently presents with hypertension, transient ischemic attack, stroke, or an asymptomatic cervical bruit. Sudden onset of pulmonary edema and a significant rise in creatinine after ACEI/ARB initiation are also common manifestations and reflect the presence of renal artery stenosis. About 60% to 75% of cases of FMD involve the renal arteries. Duplex ultrasonography is a noninvasive investigation that is highly specific and sensitive for renal artery stenosis, whether the stenosis is caused by atherosclerosis or FMD, and therefore is often the first test for diagnosis of this condition. Duplex ultrasonography of the carotids would also have been a good choice in this patient given the presence of a carotid bruit. The classic "string-of-beads" appearance of the arteries may be seen on angiography. The clinical history is not suggestive of pheochromocytoma

(Answer c) or Cushing syndrome (Answer d).

3. **d.** Discontinue doxazosin and start lisinopril 5 mg daily. The likely culprit of this patient's postural dizziness and falls is doxazosin. Elderly patients are more susceptible to drug side effects and management of hypertension should take into account such symptoms. Doxazosin demonstrated less effective blood pressure lowering than a thiazide in the antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT) study and was associated with excess cardiovascular events and incident heart failure. It would therefore be appropriate to discontinue doxazosin. There is minimal additional efficacy increasing from 25 to 50 mg of hydrochlorothiazide. The β-blocker should be continued due to the coronary artery disease history, but increasing to 100 mg metoprolol risks bradycardia. Clonidine 0.4 mg twice daily would also lower the heart rate and would be an excessive dose for initiation in an elderly patient who is already near blood pressure goal. The JNC recommendation of a "start low, go slow" approach in the elderly is intended to limit drug side effects, including hypotension. The discontinuation of doxazosin and initiation of 5 mg lisinopril is therefore the most appropriate option.

4. **a.** Aliskiren. The U.S. Food and Drug Administration issued a black box warning in 2012 that aliskiren should not be used with ACEIs or ARBs in patients with diabetes, because of the risk of renal impairment. There is also a warning to avoid the use of aliskiren with ACEIs or ARBs in patients with a glomerular filtration rate <60 mL/min. Conversely, methyldopa usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction. Normal or elevated plasma renin activity may decrease during methyldopa therapy. Hydrochlorothiazide may be a useful addition in stage III CKD but is unlikely to be effective in patients with a glomerular filtration rate <30 mL/min. Amlodipine is also a reasonable add-on medication to consider in this scenario.

5. **b.** Hydralazine and ankle edema. Vasodilatory lower extremity edema is most commonly seen with direct arteriolar dilators such as hydralazine and minoxidil. Dihydropyridine calcium antagonists, such as amlodipine, and α-adrenergic antagonists, such as doxazosin, are also associated with extremity edema. ACEIs are associated with an approximate 20% incidence of cough, which is purported to be bradykinin mediated. Angiotensin receptor antagonists, such as valsartan, do not directly inhibit angiotensin-converting enzyme activity or inhibit the breakdown of bradykinin. However, there are reports of angiotensin receptor antagonist-associated cough, but the incidence, severity, and frequency of dry cough in patients receiving valsartan or losartan are equivalent to those receiving placebo. Sleep

disturbance is a side effect of β-blockers, especially those that cross the blood-brain barrier (e.g., propranolol and metoprolol). Constipation is a frequent side effect of verapamil.

6. **d.** Losartan. Both brothers carry the gene mutation for Marfan syndrome; presumably their father's fatal aortic dissection was also a result of this connective tissue disease. Recent data suggest that the ARB losartan may slow the progression of aortic root dilatation in Marfan syndrome. Initially promising animal model studies demonstrating the benefits of transforming growth factor-beta pathway blockade by losartan have now translated into human clinical trials demonstrating benefit for patients with Marfan syndrome. In a randomized controlled trial of 233 Marfan patients, aortic root dilatation rate per MRI was significantly lower in the losartan group, when compared with controls, at a mean of 3-year follow-up.

7. **a.** Diabetes. There are no established links between hypertension and oral or subcutaneous therapies for diabetes. However, all four other conditions can be treated with medications that may be iatrogenic causes or contributors to hypertension. Approximately 20% to 30% of patients who receive erythropoietin intravenously for anemia of CKD develop an elevation in diastolic pressure of 10 mmHg or more. Secondary hyperparathyroidism is common in CKD patients, and cinacalcet can lower parathyroid hormone levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium. However, hypertension is an adverse effect in approximately 7% of patients. Systemic absorption of ophthalmic drops is limited, but α-adrenergic agonists such as brimonidine may raise the pulse and blood pressure. Nonsteroidal anti-inflammatory medications such as ibuprofen are a common cause of fluid retention and hypertension exacerbation, especially for patients with renal dysfunction.

8. **e.** Access through a femoral artery, radiofrequency ablation of bilateral renal arteries. Current renal denervation catheters are introduced via standard femoral artery access. These catheters have a radiofrequency energy electrode tip that delivers a series of 2-minute ablations along the lumen of each renal artery to disrupt the sympathetic nerve fibers. Symplicity HTN-2 was a randomized, controlled trial comparing 54 patients receiving standard medical therapy for resistant hypertension with 52 patients who underwent percutaneous renal sympathetic denervation. The denervation group demonstrated a mean 32/12 mmHg blood pressure reduction at 6 months, compared with a 1/0 mmHg reduction in controls. However, the larger Symplicity 2 study did not show any difference. Thus, at this time, renal denervation cannot be recommended as therapy.

9. **b.** Female gender. ACEIs are the leading cause of drug-induced angioedema in the United States because they are so widely prescribed, accounting for 20% to 40% of all emergency room visits for angioedema. ACEIs induce angioedema in approximately 0.2% of recipients and the risk appears equivalent between the different ACEI medications. Severe reactions can be observed many months or even years after initiation of ACEI therapy. One large Veteran's Affairs study by Miller et al. documented an almost fourfold higher rate of ACEI angioedema in blacks compared with whites, a 50% higher rate in women and a 12% lower rate in patients with diabetes. Patient age quartiles were unassociated with angioedema risk.

10. **b.** Peripheral arterial disease. There is now evidence to support the specific use of ramipril in patients with peripheral arterial disease and intermittent claudication. Ramipril has been associated with a significant increase in pain-free and maximum treadmill walking times at 6 months, as compared with placebo. Relative to placebo, ramipril also significantly improved the physical functioning component of a quality of life score. Although blood pressure control is an important management component for hypertensive patients with HFPEF, there is no compelling evidence for superiority of one medication over another in this setting. There is also no strong evidence to guide a specific antihypertensive choice for a patient with sleep apnea, although the presence of increased sympathetic nerve activity and a nocturnal diuresis in sleep apnea patients may explain reports that β-blockers tend to lower blood pressure more than thiazide diuretics in this setting. β-Blockers and ACEIs or ARBs are commonly used for blood pressure control in patients with aortic aneurysms.

11. **a.** Bicuspid aortic valve. This young man has a classic presentation of coarctation of the aorta. This secondary cause of hypertension is the result of stenosis of the aorta, usually at the embryonic site of the ligamentum arteriosum and is typically distal to the origin of the left subclavian artery. The presentation in adulthood is varied and is twice as common in men. Symptoms of hypertension or congestive heart failure are common. The electrocardiogram is characterized by left ventricular hypertrophy. Right ventricular hypertrophy is common if a concomitant ventricular septal defect is present. The most common associated valvular abnormality is a bicuspid aortic valve seen in 22% to 42% of cases. Intracranial aneurysms are seen in up to 10% of cases. Patients will often have a characteristic systolic precordial murmur secondary to the development of collateral arteries. Long-term management involves surgical or transcatheter correction. Patients will often continue to have systemic hypertension after repair and should be treated accordingly.

12. **b.** Stage 2, 130/80 mmHg. The most recent JNC 8 guidelines recommend that patients with diabetes have blood pressure goal of less than 140/90 mmHg based on the large ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes — Blood–Pressure-lowering arm) study. The new guideline makes no distinction between patients with CKD or diabetes mellitus with no or with otherwise uncomplicated hypertension in patients less than 60 years of age. The most controversial aspect of the new guideline involves patients >60 years whose treatment goal is now <150/90 mmHg if they have no CKD or diabetes mellitus.

13. **d.** Direct renin inhibitor. Aliskiren is a direct renin inhibitor. The renin enzyme controls the rate-limiting step in the generation of angiotensin II. Aliskiren reaches peak concentration in 2 to 4 hours with a half-life of 24 to 36 hours. It is 50% protein bound. Diarrhea is the most common side effect occurring in up to 9.5% of patients. A dose of 150 mg daily will decrease systolic blood pressure on average 12.5 mmHg with a further 2.7 mmHg decrease when the dose is increased to 300 mg PO daily as compared with placebo. Aliskiren has been shown to have similar blood pressure-lowering effects when compared with thiazide diuretics as well as ACEIs. However, to date there are limited data on the effect of aliskiren on hypertension-induced end-organ damage and clinical outcomes.

14. **a.** Patient has essential hypertension; start thiazide diuretic. The patient likely has essential hypertension. The age of onset is typically between the early 20s to the late 50s. The presence of a family history of hypertension, the mild elevation in blood pressure, and the gradual onset make the diagnosis of essential hypertension more likely. First-line therapy in this individual, assuming she is not trying to become pregnant, is the use of a thiazide diuretic. Reevaluation in 1 year would not be appropriate, given the long-term complications associated with uncontrolled hypertension. A repeat evaluation in a few weeks is not necessary, given the documented hypertension over the past few years. The presence of unilateral renal artery stenosis from vascular hyperplasia is a possibility; however, the clinical history is most consistent with essential hypertension.

15. **b.** Renal MRI. The distinction between essential hypertension and secondary causes is critical in the management of a patient with long-standing hypertension that is difficult to control. In this scenario, the inability to control the patient's blood pressure with multiple medications increases the pretest probability of a secondary etiology. In this individual, the presence of multiple cardiac risk factors, along with repeat episodes of noncardiogenic pulmonary edema, suggests the diagnosis of bilateral renal artery stenosis. Addition of further antihypertensive medications would be indicated, but not prior to initiating a workup for renal artery stenosis. A

renal MRI would be the most appropriate of the mentioned answers.

16. **b.** Twofold. Increasing blood pressure beginning at 115/75 mmHg is noted to be a risk factor for stroke, heart failure, and myocardial infarction. For every 20 mmHg increase in systolic blood pressure and for every 10 mmHg in diastolic blood pressure, there is a twofold increase in the risk of cardiovascular disease. For the above patient, her risk of cardiovascular disease has increased by twofold.

17. **b.** Methyldopa. The central α-agonist methyldopa is known to cause an autoimmune hemolytic anemia in up to 20% of patients taking the medication. Other common side effects include sedation, insulin resistance, and galactorrhea. Methyldopa is not a first-line agent for treatment of hypertension and is usually reserved for pregnant patients and those with resistant hypertension.

18. **c.** 35% increase in creatinine. According to the JNC 7 guidelines, patients initiated on an ACEI should be continued on that medication unless the creatinine increases by more than 35% or another indication for discontinuation presents itself.

19. **a.** Calcium channel blocker. The Blood Pressure Lowering Treatment Trialist Collaboration Study found that calcium channel blockers provided a greater benefit in the reduction of stroke when compared with other antihypertensive agents. However, there was no difference in cardiovascular mortality or overall cardiovascular events.

20. **b.** She should have a repeat blood pressure measurement at a later time point during her visit and return in a few weeks to obtain repeat testing if that measurement is elevated. The JNC 7 guidelines suggest that the diagnosis of hypertension requires at least two separate blood pressure measurements during a clinic visit. The patient should be resting in a chair for at least 5 minutes and should have her arm supported at heart level when the blood pressure is measured. Blood pressure measurements should be evaluated in the contralateral arm and while standing as well. Elevations in blood pressure should be confirmed in a timely manner on a repeat visit, the timing of which is dependent on the level of hypertension and the presence of comorbid conditions. The patient in this vignette has mild isolated hypertension and should return in a few weeks (6 to 8 weeks). Those with more elevated blood pressure should return sooner. Antihypertensive medications should not be initiated on this initial visit as diurnal variations in blood pressure are common and she may not have hypertension. Ambulatory monitoring of blood pressure should be attempted. An evaluation for secondary cause is premature as the diagnosis of hypertension is not confirmed. Waiting to reevaluate the patient in

1-year time is unacceptable, as hypertension, if left untreated, increases the risk of stroke, myocardial infarction, heart failure, and renal insufficiency.

21. **d.** Urine metanephrines. The initial assessment of any patient with a new diagnosis of hypertension requires evaluation for evidence of hypertension-induced end-organ damage. All patients with a new diagnosis of hypertension should have the following testing: serum hematocrit, blood urea nitrogen, serum creatinine, serum potassium, serum calcium, blood glucose, an electrocardiogram, an ophthalmologic examination, a fasting lipid panel, and a urinalysis. Evaluation for secondary causes of hypertension should be limited to those with uncontrolled hypertension after treatment.

22. **b.** Urine metanephrines. This patient's medical history is consistent with a diagnosis of pheochromocytoma. Pheochromocytomas arise from chromaffin cells. These tumors are most commonly found in the adrenal glands, but may be present anywhere there are sympathetic nerves. Classic symptoms are episodic palpitations, headaches, and diaphoresis. Rarely, patients may present with orthostatic hypotension. Initial diagnostic testing would involve the evaluation of a urine specimen for urine metanephrines. A toxicology screen is not indicated given his clinical history. An MRI of the abdomen would be helpful to evaluate for intra-abdominal masses, but an MRI of the thorax would be of limited benefit. Starting a thiazide diuretic would be beneficial, but ultimately the patient requires surgical therapy for correction of his hypertension.

23. **c.** Metoprolol. The initial choice of antihypertensive medication in this patient should be a β-blocker. Multiple studies have shown the benefit of β-blockers in the post-myocardial infarction period. The morphine in acute myocardial infarction (MIAMI-1) and International Study of Infarct Survival (ISIS-1) trials in the fibrinolytic era both showed trends toward a decrease in mortality with the use of intravenous β-blockers. The clopidogrel and metoprolol in myocardial infarction (COMMIT) trial found decreases in the rate of reinfarction and ventricular fibrillation with intravenous metoprolol followed by oral metoprolol; however, there was a 30% increase in the risk of cardiogenic shock. A meta-analysis of the post-myocardial infarction use of β-blockers has shown up to a 40% decrease in cardiovascular mortality. The American Heart Association 2013 ST-segment elevation myocardial infarction (STEMI) guidelines recommend initiation of oral β-blockers in the first 24 hours, providing that heart failure signs, evidence of a low-output state, risk factors for cardiogenic shock, or other contraindications to β-blockers are absent. However, intravenous β-blockers carry a class IIa indication in STEMI, given the concern for possible complications.

24. **a.** Calcium channel blocker. Calcium channel blockers are the most effective of the antihypertensive regimens at reducing carotid atherosclerosis. Studies comparing various calcium channel blockers with thiazide diuretics, ACEIs, and β-blockers have shown that calcium channel blockers have greater ability to decrease carotid intimal thickness.

25. **d.** Decreased peripheral resistance. The initial mechanism of action for lowering blood pressure is a decrease in plasma volume secondary to natriuresis. This triggers an increase in the activity of the rennin-angiotensin system, resulting in a return of plasma volume to normal. However, there is a long-term decrease in peripheral resistance that produces the chronic antihypertensive effects of thiazide diuretics.

26. **c.** Captopril. Aside from mycophenolate, the ACEI captopril is the most likely cause of this patient's leukopenia. When immunosuppressive therapy is combined with ACEIs, there are reports of the development of anemia, neutropenia, leukopenia, and agranulocytosis. The best treatment strategy in this patient would be to use an alternative antihypertensive agent and monitor blood counts closely.

27. **b.** Start hydrochlorothiazide and lisinopril. The most appropriate initial step in the management of the patient in this clinical vignette is the initiation of two antihypertensive medications as recommended in the JNC 7 guidelines. In general, if patients have a blood pressure of greater than 20/10 mmHg above goal, they should be initiated on two antihypertensive agents because monotherapy will typically be ineffective in achieving target blood pressure. Most patients should be started on a thiazide diuretic when commencing treatment of hypertension, as confirmed by the results of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial. Care should be taken in patients at risk for hypotension, specifically elderly patients, those with diabetes, and those with autonomic dysfunction.

28. **c.** Do nothing as he has white coat hypertension. The patient in the above clinical vignette has a diagnosis of white coat hypertension. It is defined as a clinic blood pressure of >140/80 mmHg in at least three clinic settings, with blood pressure measurements of <140/80 mmHg in at least two nonclinic settings, and with absence of end-organ damage. Multiple studies have been undertaken to evaluate if isolated elevations in blood pressure in the medical setting are associated with increased cardiovascular events. A 10-year follow-up study comparing cardiovascular events between patients with white coat hypertension and those with sustained hypertension found worse outcomes in those with sustained hypertension.

The risk of myocardial infarction was two times greater and the risk of a cerebral vascular event was four times greater in the sustained hypertension group. Comparison of normotensive patients with those with white coat hypertension has noted a greater prevalence of left ventricular hypertrophy in the white coat hypertension group. However, there are no clear data that white coat hypertension increases long-term cardiovascular events. Treatment of white coat hypertension is associated with decreases in clinic blood pressure with no significant decrease in ambulatory blood pressure. Patients with white coat hypertension should be monitored closely for development of sustained hypertension, but do not need to be initiated on antihypertensive therapy.

29. **a.** Intravenous nitroprusside. Treatment of hypertensive emergency requires the use of intravenous medications to decrease the mean arterial blood pressure by 25% in the first few hours. Lower target blood pressure goals increase the risk of inducing a cerebral vascular event from decreased cerebral perfusion. Sublingual nifedipine is no longer used for hypertensive emergencies due to its dramatic and unpredictable blood pressure–lowering effects and the associated adverse clinical outcomes. Nitroprusside, labetalol, and nitroglycerin are all reasonable options. However, given the rapid onset and offset of nitroprusside, and the evidence of conduction delay that may limit labetalol use, nitroprusside would be the most appropriate medication for rapid and safe titration of blood pressure.

30. **b.** Lisinopril. The patient in the vignette has a target blood pressure of 130/80 mmHg according to the JNC 7 guidelines. The correct choice of initial blood pressure medication in this patient would be an ACEI. The ALLHAT study suggested that patients with diabetes mellitus have better long-term outcomes when using a thiazide diuretic compared with an ACEI. However, the patient in this vignette has evidence of protein in his urine. JNC 7 recommends that a thiazide diuretic should be first-line therapy, unless there is a specific indication. In this patient, the presence of proteinuria and diabetes mellitus makes the choice of an ACEI a better option than the thiazide. α-Blockers are not considered first-line therapy in hypertensive patients. In the ALLHAT study, there was an increased incidence of heart failure when comparing the α-blocker group (doxazosin) with the thiazide group.

31. **c.** Captopril. ACEIs and ARBs are contraindicated during pregnancy, because of the increased risk of congenital malformations. Methyldopa is the medication most commonly used to control blood pressure in pregnancy. There is significant evidence that it does not produce any harmful outcomes to the fetus. β-Blockers have been used in pregnancy with what appear to be safe results. However, the data

are contradictory. There is some evidence that β-blockers, especially when used early in pregnancy, may increase the risk of fetal bradycardia, hypoglycemia, small placental weight, and a small-for-gestational-age fetus. Calcium channel blockers have been used in pregnancy without deleterious results, but the number of published cases is small. In general, methyldopa is the safest antihypertensive during pregnancy. β-Blockers and calcium channel blockers may be used with caution. ACEIs and ARBs are absolutely contraindicated due to teratogenic effects including renal dysplasia and intrauterine growth restriction.

32. **c.** Atenolol 25 mg PO daily. The least effective option is atenolol. The ALLHAT study showed that the use of thiazide diuretics as first-line therapy for treatment of uncomplicated hypertension was as effective as, if not superior to, amlodipine and lisinopril in preventing fatal coronary artery disease and nonfatal myocardial infarction. The choice of an ACEI would be reasonable, given the presence of glucose intolerance. β-Blockers would not be indicated as first-line therapy in this patient. Multiple meta-analysis comparing β-blockers with placebo or other antihypertensive agents have shown no statistically significant decreases in mortality, myocardial infarction, and stroke. The Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) trial comparing atenolol with amlodipine found a 23% greater risk of stroke in the atenolol group versus the amlodipine-based regimen.

33. **b.** Conversion of patient to a calcium channel blocker and thiazide diuretic. Analysis of the clinical trials in hypertension has noted that there are differences in the effectiveness of antihypertensive medications between different ethnic groups. African Americans are more responsive to calcium channel blockers and thiazide diuretics than other antihypertensive agents. This patient is on an ACEI and a β-blocker. Altering his regimen to include more effective antihypertensive agents would be indicated rather than increasing his medications, adding additional medications, or evaluating him for secondary causes of hypertension. The new JNC 8 guidelines make recommendation of medication based on the race of the patient.

34. **c.** 24-Hour urine cortisol test. This patient's medical history is consistent with a secondary cause of hypertension, in particular, Cushing syndrome. This syndrome is characterized by an excess of cortisol. It may be secondary to a pituitary tumor/hyperplasia (Cushing disease), an adrenal tumor, or ectopic adrenocorticotropic production. Clinical manifestations include diabetes mellitus, hypertension, obesity, hypokalemia, osteoporosis, and fungal infections. The initial step in diagnosis is a 24-hour urine free cortisol test. Treatment is surgical.

35. **a.** Metoprolol. Pheochromocytoma is a rare cause of hypertension. Treatment

ultimately requires surgical removal. The use of β-blocker monotherapy is contraindicated as part of the medical management of pheochromocytomas. The catecholamines secreted by these tumors activate both peripheral α- and β-receptors. Blockage of these peripheral β-receptors results in unopposed α-activation. This can result in severe hypertension. Typical medical management of pheochromocytomas involves the use of antihypertensives with α-blocking capability. For example, prazosin or phenoxybenzamine may be used. Only once α-blockade is established should the use of a β-blocker be entertained.

36. **a.** Aggressive lifestyle modification. Patients with prehypertension are at increased risk for cardiovascular events compared with normotensive individuals; therefore, care of these patients should be focused on aggressive control of all cardiovascular risk factors. Analysis of the Women's Health Initiative compared cardiovascular outcomes in prehypertension patients with normotensive patients and found that the prehypertension patients had hazard ratios indicating a 1.58 (95% confidence interval [CI], 1.12 to 2.21) greater risk for cardiovascular death; 1.76 (95% CI, 1.40 to 2.22) greater risk for myocardial infarction; 1.93 (95% CI, 1.49 to 2.50) greater risk for stroke; 1.36 (95% CI, 1.05 to 1.77) greater risk for hospitalized heart failure; and a 1.66 (95% CI, 1.44 to 1.92) greater risk for any cardiovascular event. Not only are these patients at increased risk for cardiovascular events, but they also have a high incidence of hypertension development. In the Trial of Preventing Hypertension (TROPHY) trial, patients with prehypertension were randomized to candesartan or placebo. Over a period of 4 years, 67% of the untreated group developed hypertension as defined by the JNC 7 guidelines. These data suggest that patients with prehypertension are a high-risk population and should be treated aggressively. According to the JNC 7 guidelines, these individuals should increase their activity level, modify their diet, avoid excessive alcohol, and attempt weight loss. Initiation of antihypertensive medications should be reserved for those who progress to evident hypertension.

37. **a.** 140/90 mmHg. JNC 8 guidelines recommend that in patients with CKD or diabetes mellitus, the target blood pressure should be <140/90 mmHg.

38. **c.** Diltiazem. Patients who have undergone heart transplantation often have preexisting hypertension or develop hypertension subsequent to the heart transplant. This is a unique patient population as many of the immunosuppressive medications used after transplantation have multiple drug interactions. With respect to antihypertensive agents, most if not all calcium channel blockers have been shown to increase cyclosporine levels. Diltiazem and verapamil, in particular, are potent inhibitors of protein P-glycoprotein and CYP3A4. These enzymes are critical for

the metabolism of diltiazem, and their inhibition can increase cyclosporine levels up to sixfold. It is recommended that patients who require diltiazem and are on cyclosporine have their cyclosporine dose decreased by 25% to 50%. Diltiazem can also increase tacrolimus levels.

39. **b.** Minoxidil. Pericarditis is a known complication of the direct vasodilator minoxidil often accompanied by a pericardial effusion. Its other major side effect is hirsutism. Prompt withdrawal of the medication once the diagnosis of a pericardial effusion or pericarditis is made is recommended. Minoxidil is a potent peripheral vasodilator and is typically reserved for patients with severe or difficult-to-control hypertension.

40. **b.** Morning renin and aldosterone concentrations. The patient in this vignette has secondary hypertension from Conn syndrome. This is primary hyperaldosteronism from uncontrolled secretion of aldosterone. Classic laboratory findings include hypokalemia and mild hypernatremia. The initial diagnostic test of choice is an aldosterone-renin ratio. A ratio of >20 is considered diagnostic. In this patient, the presence of lisinopril complicates the testing. ACEIs are known to decrease renin levels, and ideally the test should be done in the early morning after withdrawal of ACEI therapy. Adrenal vein sampling would be helpful in the diagnosis of primary hyperaldosteronism; however, it is not the initial test of choice. A 24-hour urine test would be more appropriate if Cushing syndrome were suspected. The patient's clinical description is not consistent with this diagnosis. The presence of FMD should be suspected in any young woman with suspected secondary hypertension. However, the laboratory abnormalities are more suggestive of Conn syndrome than renal artery stenosis.

41. **b.** Polysomnography. The patient's clinical history is consistent with the presence of obstructive sleep apnea; therefore, polysomnography (an overnight sleep study) would be the best option. Multiple studies have found evidence for increased risk of hypertension in patients with obstructive sleep apnea. There is no definitive evidence that treating patients with sleep apnea can lower blood pressure; however, there is an increasing hypertension risk as the number of overnight apneic episodes increases. Patients with >30 apnea or hypopnea episodes per hour have an odds ratio of 1.37 of developing hypertension versus those patients with <1.5 apnea or hypopnea episodes per hour.

42. **a.** Hydralazine. Hydralazine is known to cause a lupus-like syndrome in 5% to 20% of patients taking the medication. This syndrome is characterized by arthralgias, myalgias, pericarditis, fever, and rash. Lisinopril, metoprolol, and

hydrochlorothiazide are not known to induce lupus. Other side effects of hydralazine include nausea, vomiting, tachycardia, anorexia, flushing, and diarrhea. Treatment of hydralazine-induced lupus involves withdrawal of the medication.

43. a. Restart clonidine. Rebound hypertension is a known complication of clonidine. Immediate treatment of clonidine withdrawal involves reinstitution of therapy with a slow taper. The mechanism of action is thought to be an increase in sympathetic nervous system activity.

SUGGESTED READINGS

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Hyperlipidemia

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QUESTIONS

1. Familial hypercholesterolemia (FH) is a common autosomal dominant disorder resulting from mutations leading to impaired hepatic clearance of low-density lipoprotein (LDL) from the circulation. All of the following statements are true regarding heterozygous FH except that

   a. it occurs in 1 in 5,000 persons.
   b. it is associated with serum low-density lipoprotein cholesterol (LDL-C) two to three times above the average.
   c. it is associated with four- to sixfold increased risk of premature coronary heart disease (CHD).
   d. without treatment, the average age for development of symptomatic CHD is 45 years in men and 55 years in women.
   e. ninety percent of FH heterozygotes exhibit detectable xanthomas on the extensor tendons of the hands or on the Achilles tendons by the age of 39.

2. Phenotypic presentation of FH has been demonstrated to be caused by various mutations associated with all but one of the following:

   a. Defects in the hepatic LDL receptor (LDL-R)
   b. Defects in apolipoprotein B (apoB)
   c. Loss-of-function mutation of PCSK9
   d. Loss-of-function mutation of LDLRAP1

3. A 31-year-old man is referred to you for hyperlipidemia assessment. He has no previous cardiovascular history himself and denies any first-degree relatives with a history of CHD although his father and paternal uncle are treated for elevated

cholesterol and triglycerides (TGs). He reports that two uncles and a cousin have had heart attacks at young ages. His physical examination reveals a body mass index (BMI) of 32, arcus cornea and xanthelasmas but no xanthomas, and a blood pressure (BP) of 150/80 mmHg. His fasting lipid profile is as follows: total cholesterol (TC) 300 mg/dL, TGs 430 mg/dL, high-density lipoprotein cholesterol (HDL-C) 50 mg/dL, direct LDL-C 202 mg/dL. Fasting blood glucose is 112 mg/dL. Which primary dyslipidemia is this patient most likely to have?

a. Polygenic hypercholesterolemia
b. Heterozygous FH
c. Familial combined hyperlipidemia
d. Hyperapobetalipoproteinemia
e. Familial endogenous hypertriglyceridemia

4. Which of the following statements regarding FH is NOT true?

a. The Food and Drug Administration (FDA) indications for LDL apheresis after maximal tolerated pharmacologic therapy include (a) homozygous FH patients and (b) heterozygous FH in the absence of CHD when LDL-C ≥300 mg/dL and in the presence of CHD when LDL-C ≥200 mg/dL.
b. Mipomersen (which inhibits the translation of apoB100 mRNA, thus blocking the production of apoB100 and formation of very low-density lipoprotein [VLDL] and LDL particles) lowers LDL-C by 28% to 36% in individuals with homozygous and heterozygous FH.
c. TC levels are generally >600 mg/dL with LDL-C levels 6- to eightfold higher than average in individuals with homozygous FH.
d. Lomitapide has been approved to treat homozygous and heterozygous FH.
e. Simon Broome Register Group criteria for definite FH requires (a) TC >290 mg/dL in adults or TC >260 mg/dL in children under 16 years OR LDL-C >190 mg/dL in adults or >155 mg/dL in children PLUS (b) tendon xanthomas in the patient, or first- or second-degree relative OR DNA-based evidence of mutations such as LDL-R mutation or familial defective apoB100.

5. Recent statistics from the American Heart Association (AHA) Statistical Update in 2014 report that all of the following regarding dyslipidemia in the United States are true EXCEPT that

a. 98,900,000 U.S. adults over 20 years of age have elevated TC >200 mg/dL (43.4%).
b. 35.8% of adults have LDL >130 mg/dL (71 million adults).
c. 48.7 million adults (21.8%) have HDL <40 mg/dL.
d. National Health and Nutrition Examination Survey (NHANES) data through

2006 reported that 10.3% of adolescents (12 to 19 years) have abnormal lipid levels.

e. inadequate control of dyslipidemia is responsible for 4 million yearly deaths worldwide and 350,000 in the United States.

f. 68.2% of adults and 31.8% of children/adolescents are overweight or obese.

6. Many randomized clinical trials (RCTs) and meta-analyses have contributed to the lipid management guidelines over the past two decades. Which of the following statements is NOT correct?

   a. PROVE-IT/TIMI-22 showed that individuals post myocardial infarction (MI) treated with the more potent statin atorvastatin versus pravastatin had a 16% relative risk reduction.

   b. The JUPITER trial demonstrated that in individuals without documented cardiovascular disease (CVD) and median LDL-C of 108 mg/dL, aggressive statin therapy with rosuvastatin offered greater benefit in individuals with ultrasensitive C-reactive protein (usCRP) >2 versus <2 mg/L.

   c. Primary prevention hypertensive patients in the ASCOT-LLA trial showed reductions in nonfatal MI, CHD death but not all-cause mortality when patients with average lipids and hypertension were treated with atorvastatin 10 mg daily for an average of 3.3 years.

   d. WOSCOPS and AFCAPS/TexCAPS were both primary CHD prevention studies, which showed significant clinical benefits for statin therapy, with similar percentage reductions in LDL-C. The main difference between these trials was that subjects in AFCAPS/TexCAPS had considerably lower baseline LDL-C levels than those in WOSCOPS.

   e. Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), and Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) all involved secondary prevention of CHD.

   f. Meta-analyses have demonstrated a >20% reduction in CHD events for every 1 mmol/L reduction in LDL-C with similar proportional reductions in diabetics versus nondiabetics. Similar percent reductions were seen even in lower-risk groups with <5% 5-year risk for CVD.

7. The Framingham Risk Score (FRS) was popularized in the National Cholesterol Education Project: Adult Treatment Panel (NCEP ATP) III guidelines. Potential limitations of the FRS include the following:

   1. Does not take family history into account

   2. May overestimate lifetime risk in individuals ≤50 years of age with ≥1 NCEP risk factor

3. May not accurately calculate risk in certain ethnic groups because original Framingham population was almost entirely of European origin
4. Incorporates risk due to insulin-resistant conditions such as metabolic syndrome
5. Does not include emerging risk factors such as CRP, lipoprotein(a), and apoB

a. All of the above
b. 1, 3, and 5
c. 1, 3, 4, and 5
d. None of the above

8. Based on the definition proposed by the NCEP ATP III guidelines, metabolic syndrome would be present if three or more of five criteria were present. Which of the following is NOT one of the criteria?

a. BP ≥130/≥85 or on treatment for hypertension
b. TGs ≥150 mg/dL
c. HDL-C of <40 mg/dL in men and women
d. Fasting glucose =100 mg/dL
e. Waist circumference of >40 inches in men and >35 inches in women

9. NCEP ATP III was published in 2001. Modifications to NCEP ATP III published in 2004 include all of the following except that

a. LDL-C goal <70 mg/dL is a therapeutic option for very high-risk patients.
b. LDL-C goal <70 mg/dL extends to patients at very high risk even with baseline LDL-C <100 mg/dL.
c. factors that favor the optional goal of <70 mg/dL include CVD plus multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (especially smoking), metabolic syndrome, and acute coronary syndromes.
d. for moderately high-risk patients, LDL-C <100 mg/dL is an option with consideration of initiation of therapy with statins for LDL-C between 100 and 130 mg/dL.
e. both higher-dose statins and addition of fibrates and niacin to achieve non–HDL-C goals should be considered to achieve secondary targets and to further reduce cardiovascular event rate.

10. A 53-year-old obese, sedentary woman undergoes lipid screening, revealing TC of 310, TG of 720, HDL-C of 41. LDL-C was not calculated due to elevated TG. HbA1c is 5.9 and thyroid-stimulating hormone (TSH) is normal. NCEP ATP III guideline recommendations for TGs and HDL-C management include all but which of the following:

a. If TGs are ≥500 mg/dL, then TG is the primary target with use of therapeutic options to prevent pancreatitis including fibrates or niacin before LDL-lowering therapy, than treat LDL-C to goal.
b. In patients attaining LDL-C goals, those with TG ≥200 mg/dL have an increased cholesterol content of TG-rich, atherogenic lipoprotein particles. Non–HDL-C takes into account cholesterol in these and LDL particles and is a secondary target for therapy.
c. Therapeutic goal for TG is <150 mg/dL and for HDL-C is >40 in men and >50 in women.
d. HDL-C <40 mg/dL is defined as low and is a risk factor for CVD.
e. Non–HDL-C goal equals the LDL-C goal +30 mg/dL.
f. Combining a fibrate or nicotinic acid with an LDL-C-lowering drug can be considered.

11. Guidelines for management of dyslipidemia emphasize the importance of weight management, dietary choices, and exercise. TLC or Therapeutic Life Style Therapies for primary prevention of CVD include all of the following except

a. diet to reduce intake of saturated fats and dietary cholesterol with total fat range of 25% to 30% of total calories, saturated fat <7% of calories, and low intake of transfatty acids and <200 mg/day of cholesterol.
b. increased intake of plant stanols/sterols up to 2 g/day as a therapeutic option to reduce LDL-C.
c. increased intake of viscous (soluble) fiber to at least 5 to 10 g/day.
d. omega-3 polyunsaturated fatty acid supplements of 800 to 1,000 mg a day.
e. regular physical activity: >30 minutes five to seven times per week or enough moderate activity to expend at least 200 kcal/day.
f. weight loss to maintain BMI <25 kg/m^2.

12. Secondary causes of dyslipidemia include all EXCEPT which of the following?

a. Hyperthyroidism
b. Obstructive liver disease/biliary cirrhosis
c. Renal disorders including nephrotic syndrome and chronic renal failure
d. Drugs including estrogen/progestins, protease inhibitors, anabolic steroids, corticosteroids, isotretinoin (Accutane®), and cyclosporine
e. Metabolic syndrome or diabetes mellitus (DM)
f. Pregnancy

13. According to NCEP ATP III, CHD risk equivalent defines high-risk individuals who would benefit from more intensive lipid-modifying therapies and include

individuals with all of the following except

a. diabetes and additional cardiovascular risk factors.
b. FRS indicating a 10-year risk of MI or coronary death of >10%.
c. claudication with an ankle brachial index of 0.78.
d. individual status post aortic aneurysm endograft.
e. history of transient ischemic attack (TIA) followed by carotid endarterectomy.

Questions 14 to 16

You see a 52-year-old man with a history of type 2 DM on metformin. He has a history of hypertension controlled on amlodipine and an angiotensin-converting enzyme inhibitor. His BMI is 31.7 and waste circumference is 41 inches. His father had a coronary stent at the age of 54. He has the following fasting laboratory values:

Total C: 212 mg/dL
LDL-C: 120 mg/dL
HDL-C: 36 mg/dL
TG: 278 mg/dL
Non–HDL-C: 176 mg/dL
Glucose: 156 mg/dL
HbA1c: 7.6%
TSH: 1.2 mU/L
LFTs (liver function tests): WNL (within normal limits)

14. Based on NCEP ATP III and American Diabetes Association (ADA) guidelines, the most appropriate lipid goals for therapy in this patient are

a. LDL <70 mg/dL and non-HDL <100.
b. LDL <100 mg/dL and non-HDL <130.
c. LDL <70 mg/dL and non-HDL <130.
d. LDL <130 mg/dL and non-HDL <160.

15. Additional secondary goals for therapy in this patient based on these guidelines include

a. apoB <80 mg/dL.
b. apoB <90 mg/dL.
c. LDL particle number (LDL-P) <1,200.
d. LDL-P <1,000.
e. usCRP <2.
f. Answers a and d.
g. Answers a and e.

16. The best initial treatment for this patient's dyslipidemia would be

a. atorvastatin 40 mg/day.
b. fenofibrate 148 mg/day.
c. extended release niacin 2,000 mg/day.
d. simvastatin 20 mg/day.
e. ezetimibe 10 mg/day.
f. omega-3 fish oil 4,000 mg/day.

17. The patient above was started on rosuvastatin 20 mg/day, metformin dose was increased, an aerobic exercise program was recommended, and he was referred for dietary advice. Repeat laboratory values in 4 months are as follows:

	Baseline	4 Months
Total C	212	150 mg/dL
LDL-C	120	66 mg/dL
HDL-C	36	38 mg/dL
TG	278	229 mg/dL
Non–HDL-C	176	126 mg/dL
Glucose	156	112 mg/dL
A1C	7.6	6.8%
LFT	WNL	WNL

The most appropriate additional therapies recommended by NCEP ATP II at this time would include all but

a. nicotinic acid.
b. fenofibrate.
c. ezetimibe.
d. intensification of diet, exercise, and weight loss program.
e. intensification of statin therapy, increase rosuvastatin to 40 mg/day.
f. all of the above.
g. none of the above.

18. Patients such as the one above with diabetes are considered at high risk for CVD events. Which of the following statements is not true in regard to patients with diabetes?

a. Atherosclerosis accounts for approximately 65% to 75% of all diabetic mortality with 75% of these deaths due to coronary atherosclerosis.

b. A diabetic patient without a clinical history of prior MI or coronary artery disease (CHD) has a mortality rate from CHD and MI rate equal to a nondiabetic who has had a previous MI.
c. NHANES data from 2010 indicate that although goals of HbA1c <7 mg/dL, systolic BP <130 mmHg, and LDL-C <100 mg/dL are recommended for diabetics, only 32% of diabetics in the survey currently achieve all three of these goals.
d. Risk for atherosclerotic events is two- to fourfold greater in diabetics than in nondiabetics.
e. Atherosclerosis begins years to decades prior to diagnosis of type DM2 and >50% already have clinical CHD at the time of the diagnosis of DM.

19. Additional markers beyond standard risk factors have been shown to help reclassify risk assessment particularly in individuals in an intermediate-risk category (e.g., FRS of 10% to 20% or American College of Cardiology [ACC]/AHA guideline risk score of 5% to 7.5%). All but one of the following may be useful in hyperlipidemia treatment decisions:

a. usCRP
b. LDL-P
c. Coronary artery calcification score (CACS)
d. HDL particle size and number
e. Lipoprotein(a)

20. Major differences in the ACC/AHA hyperlipidemia treatment guidelines of 2013 compared with NCEP ATP III recommendations include all of the following except

1. elimination of LDL-C and non–HDL-C targets for therapy.
2. a focus on risk reduction targeting therapy to four major groups demonstrated to benefit from statin therapy based on RCT data rather than targeted to risk category and LDL-C level.
3. replacing the FRS with a newly developed risk calculator that includes ethnicity and family history and broadens the outcome events to include stroke.
4. that since the absolute benefit in CVD risk reduction is proportional to the baseline risk of the individual and to the intensity of statin therapy, treatment is focused on intensity of statin treatment and does not recommend use of low-dose statin therapies.
5. that decreasing statin dose is reasonable if LDL-C on therapy is <40 mg/dL.

a. None, all are true
b. 1, 3, and 5

c. 3 and 5
d. All are not true
e. 3, 4, and 5

21. The ACC/AHA hyperlipidemia guidelines of 2013 identify four groups shown to benefit from high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention of CVD. High-risk individuals who would be a candidate for high-intensity statin therapy for LDL-C lowering would include all except

a. those with clinical atherosclerotic cardiovascular disease (ASCVD).
b. primary elevations of LDL-C ≥160 mg/dL.
c. individuals with diabetes aged 40 to 75 years with LDL-C 70 to 189 mg/dL without clinical ASCVD and with ASCVD risk ≥7.5%.
d. without clinical ASCVD or diabetes with LDL-C 70 to 189 mg/dL and estimated 10-year ASCVD risk ≥7.5%.

22. The American Academy of Pediatrics (AAP) 2008 lipid management recommendations for children and teenagers include all of the following except

a. screening as early as 2 years of age in setting of family history of CVD or hyperlipidemia.
b. lower LDL cut points for initiation of treatment dependent on risk level.
c. bile acid sequestrants as initial therapy in younger patients under 16 years of age.
d. considering initiation of therapy as early as 8 years of age in high-risk children.
e. emphasis on overweight, high TG, and low HDL managed with lifestyle interventions and weight management.
f. fiber up to 20 g/day and use of dietary plant stanols/sterols.

23. In decisions regarding screening for and treating hyperlipidemia in children and adolescents, it is important to remember that all of the following are true except that

1. cholesterol is lowest intrauterine and at birth.
2. concentrations are similar to young adult levels by 2 years of age with strongest relation to adult levels at 5 to 10 years and 17 to 19 years.
3. cholesterol levels decrease from 10% to 20% during pre-pubertal and pubertal development.
4. low-fat diets should not be implemented until after age 5 years.
5. statins have not been shown to have an adverse effect on sexual or physical maturation.
6. impact on the atherosclerotic process and clinical outcomes has been

demonstrated with statin treatment in children and adolescents.

a. None of the above
b. 2, 4, and 6
c. 4 and 6
d. 3, 5, and 6
e. All of the above

24. Although statin therapy and LDL-C reduction is the main thrust of pharmacologic therapies, there has been an interest in treating beyond LDL-C with other therapies directed toward HDL-C and TG to further reduce CVD events. This concept is supported by the following observations except that

a. cardiovascular events occur in individuals with treated LDL-C even after aggressive LDL lowering with statins.
b. patients with diabetes studied in clinical trials on statins have CVD event rates higher than the CVD event rates of those patients without diabetes on placebo.
c. intravascular ultrasound (IVUS) studies have shown LDL-C <70 to 80 mg/dL to be associated with plaque regression but the 20% of individuals that progress on therapy often have DM, less increase in HDL, and less decrease in apoB on treatment.
d. the action to control cardiovascular risk in diabetes clinical trial (ACCORD) trial demonstrated a benefit of fenofibrate when added to baseline simvastatin therapy in diabetic patients.
e. observational studies have noted an impact of low/abnormally functioning HDL, VLDL remnants, elevated TG small dense LDL, LDL-P, and apoB/apoA ratios on adverse outcomes.
f. epidemic of obesity, diabetes, and metabolic syndrome associated with dyslipidemia is marked by only modest elevations in LDL-C but increases in HDL-C and TG.

25. In the setting of strong observational and epidemiologic data supporting HDL-C's relationship to CVD risk, the limitations of current therapies, and the increase in incidence of diabetes/metabolic syndrome, there remains a strong interest in focusing on other therapeutic interventions in addition to LDL-C lowering, particularly HDL modulation. HDL is more than a simple carrier of cholesterol. Which of the following statements regarding HDL-C metabolism and function is not true?

a. In addition to reverse cholesterol transport, HDL may have beneficial effects due to antioxidant and anti-inflammatory effects.
b. ATP-binding cassette transporter 1 (ABCA1) and ABCG1 both facilitate free

cholesterol efflux to lipid-poor pre-β1-HDL.

c. Cholesteryl ester transfer protein (CETP) enables exchange of cholesterol esters for TGs between HDL and apoB-containing lipoproteins (LDL and VLDL).

d. HDL can deliver cholesterol to the liver via both direct and indirect reverse cholesterol transport.

26. Since most lipid-lowering guidelines emphasize the use of statin therapy and at potent doses in the highest-risk individuals, it is important to recognize side effects. Clinically significant adverse effects of statins include all of the following except

a. muscle-related adverse events.
b. liver-related adverse events.
c. renal insufficiency.
d. headaches.
e. dyspepsia.

27. You see a 68-year-old woman recently started on a statin for a calculated FRS of 18% 10-year risk and elevated usCRP. She returns in 6 weeks complaining of left lower extremity aching, which she had not experienced before. Regarding muscle-related side effects with statin drugs, all of the following statements are true except that

a. myopathy occurs in approximately 0.1% to 0.5% of patients on statin monotherapy and is dose dependent.
b. the incidence of statin-associated rhabdomyolysis across large, randomized, controlled statin trials is <0.1% and the reported incidence of fatal rhabdomyolysis with statins is extremely rare with 0.15 death per 1 million prescriptions.
c. a review of five large-scale controlled clinical trials of statin safety reported a rate of myopathy ranged from 0.1% to 0.6% and rate of rhabdomyolysis ranged from 0.03% to 0.05%.
d. myalgia symptoms reported in prescribing information range from 5% to 10%.
e. identifying factors that may contribute to myopathy should lead to statin dose reduction.

28. For the patient in Question 27, you obtain a creatine phosphokinase (CPK) which is 282 (upper normal in laboratory of 220 U/L). No baseline CPK is available for comparison. She has no reproducible pain or weakness on examination. She denies darkening of the urine. Should you stop the statin?

a. Yes
b. No

29. You see a 49-year-old obese, sedentary woman with type 2 DM, hypertension, and family history of coronary stent in her father at age 53. LDL-C was 173 mg/dL. Based on NCEP ATP III and 2013 ACC/AHA guidelines she is a candidate for intensive statin therapy. Laboratory values obtained 3 months after treatment with 40 mg of atorvastatin revealed alanine transaminase (ALT)/aspartate transaminase (AST) of 102/96 (upper normal in laboratory of 50/42 U/L). Which of the following regarding liver abnormalities with statin use is not true?

a. Reversal of transaminase elevation is frequently noted with continuation of statins or a reduction in statin dose.
b. Elevations do not often recur with either readministration or selection of another statin.
c. Statins have been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C.
d. In this patient review other drugs and supplements, continue the current dose, and repeat in 6 to 12 weeks.
e. Baseline measurement of ALT should be performed before starting therapy.

30. Later that afternoon you are referred a 58-year-old man with waist circumference of 42 inches, fasting glucose of 112 mg/dL, hypertension, current smoker with brother with MI at age 54. LDL-C is 163 mg/dL, TG 275 mg/dL, and HDL-C 47 mg/dL. When first seen prior to initiation of any therapy, he had LFTs similar to those reported for the patient in the previous question (approximately two times upper limit of normal [ULN]). The patient is very worried about taking statins due to concerns of liver failure. Which of the following can you tell him? 10 year risk by Framingham Risk Score is >30% and ACC/AHA calculator score is 21.2.

a. Statin use has not been investigated in patients with baseline LFT abnormalities but should be used due to his high risk.
b. Statins have been studied in patients with baseline elevations and have been shown to further increase the LFTs.
c. Elevations of LFTs greater than two times ULN is a contraindication to starting statins.
d. Statin therapy may lower the LFTs in patients with fatty liver infiltration.
e. Progression to liver failure has never been reported.

31. In 2012, the FDA issued an alert reporting a relationship between statin use and increase in blood glucose and new incidence of diabetes. Which of the following statements is TRUE?

1. A large meta-analysis has reported an approximate 18% increase in relative risk of developing diabetes on statin therapy.

2. This observation appears to be dose dependent with a meta-analysis of high- versus moderate-dose trials reporting an absolute increase in rate of 0.4%.
3. Increase in blood glucose with statins does not attenuate the CVD reduction benefit of statins.
4. Development of diabetes on statin therapy is independent of risk factors for diabetes.
5. Reducing the dose of statin should be utilized to avoid diabetes development in those at risk, for example, metabolic syndrome, obesity, and impaired fasting glucose.

a. All of the above
b. 1, 3, and 5
c. 2 and 3
d. 2, 3, and 5
e. None of the above

32. Your patient is a 51-year-old man with heterozygous FH with predrug therapy LDL-C of 202 mg/dL who had been tried on atorvastatin, simvastatin, and lovastatin in the past but stopped all three due to complaints of muscle aching, had gastrointestinal complaints with resins, and refused further treatment. He recently had an ST-segment elevation MI treated with direct stenting. He was given a prescription to start atorvastatin again but was hesitant to have it filled and comes to you for advice. He has increased his frequency of aerobic exercise and has been following a low-saturated fat diet. LDL-C measured 2 months after the MI was 188 mg/dL. Appropriate options to consider in managing this patient include

1. trial of rosuvastatin beginning at 5 mg two to three times a week followed by slow titration.
2. pretreatment with coenzyme Q10 followed by rechallenge with a different statin or lower dose of previously used statin.
3. niacin titrated to highest tolerated dose in combination with ezetimibe.
4. LDL-C apheresis.
5. emphasis on aggressive lifestyle intervention including very low saturated fat to vegetarian diet, plant sterols/stanols, and high dietary and supplementary fiber.
6. mipomersen.

a. All of the above
b. 1, 2, 3, and 5
c. 1, 2, 3, 4, and 5
d. 1, 3, and 5

e. None of the above

33. Statements regarding fibrates include all of the following except that

a. side effects include gastrointestinal complaints, gallstones, and increase in need for cholecystectomy and elevated hepatic transaminase levels.
b. monotherapy trials have not uniformly demonstrated reductions in CVD risk but subanalysis of groups with a metabolic pattern (elevated TG and low HDL) have been more strongly associated with CVD event reduction.
c. although difficult to demonstrate in individual studies, meta-analysis of fibrate trials has demonstrated reduction in cardiovascular mortality on therapy.
d. myopathy has been reported with both monotherapy and combination therapy with statin.
e. increase in creatinine is more common with gemfibrozil compared with fenofibrate.

34. The following statements regarding use of niacin are true except that

a. possible concerns with niacin use include risk of gout, worsening glucose control, and flushing.
b. combination therapy of statins with niacin has been shown to exert favorable effect on some surrogate markers for CVD outcomes.
c. the Coronary Drug Project in the pre-statin era demonstrated a beneficial effect on MI and mortality in secondary prevention patients with coronary disease treated with high-dose niacin.
d. niacin can raise HDL-C from 20% to 25% and lower TGs from 30% to 50% depending on dose and pretreatment TG levels but has little effect on LDL-C.
e. to reduce adverse event severity, start niacin at low dose and titrate over weeks, take with a light snack, and take aspirin 30 minutes prior.

ANSWERS

1. **a.** It occurs in 1 in 5,000 persons. Homozygous FH occurs in 1 in 1 million individuals while heterozygous FH in 1 in 500 individuals. The other statements are true.

2. **d.** LDLRAP1 mediates internalization of LDL-C via clathrin-coated pits, and loss-of-function mutations would decrease LDL-C clearance. Defects in apolipoprotein B (apoB). The LDL-R on the hepatocyte binds to apoB (acts as ligand, binding LDL particle to receptor) on the LDL particle inducing internalization via clathrin-coated pits (mediated by LDLRAP1) and endocytosis of the complex. Defects in the

receptor itself or the apoB molecule may reduce LDL-C clearance. The protein PCSK9 can bind to the LDL/LDL-R complex and when internalized prevents recycling of the LDL-R to the hepatocyte surface. A gain in function mutation of PCSK9 (by further reducing recycling of LDL-Rs) has been shown to be associated with increase in LDL-C and CVD.

3. **c.** Familial combined hyperlipidemia. Familial combined hyperlipidemia is a common dyslipidemia (1 in 33 to 1 in 100 individuals) characterized by complex inheritance. Xanthomas are rarely present (unlike in heterozygous FH), but xanthelasmas and arcus cornea can be seen. They are generally overweight, are hypertensive, and have insulin resistance or diabetes. Affected individuals generally exhibit a TC of 250 to 350 mg/dL, LDL-C of 200 to 300 mg/dL, and TG of >140 mg/dL (two-thirds of patients have TG of 200 to 500 mg/dL). Patients with polygenic hypercholesterolemia (1 in 20 to 1 in 100 individuals) have alterations in the function or expression of several key proteins involved in LDL metabolism including defective LDL-R and apoB100, and the presence of the apoE4 allele (which has a higher affinity for the LDL-R than the other apoE isoforms leading to downregulation of LDL-R). They have similar elevations in LDL-C as familial combined hyperlipidemia except they do not generally have elevated TG. Hyperapobetalipoproteinemia is associated with increased apoB synthesis. TG may be normal or elevated and arcus cornea and xanthelasmas may be present. However, LDL-C is typical below 160 mg/dL. Familial endogenous hypertriglyceridemia is associated with increased hepatic VLDL formation and TG of 200 to 500 mg/dL but without significant elevations in LDL-C and is not consistently linked with increased CVD risk.

4. **d.** Lomitapide has been approved to treat homozygous and heterozygous FH. Homozygous FH occurs in 1 in 1 million individuals. TC levels are generally >600 mg/dL, with LDL-C levels six- to eightfold higher than average. Without treatment, death from MI occurs in the first or second decades of life. In addition to the xanthomas observed in heterozygotes, FH homozygotes are commonly affected by interdigital xanthomas; tuberous xanthomas on the hands, elbows, buttocks, and feet; and planar xanthomas on the posterior thighs, buttocks, and knees. The mainstay of therapy for FH homozygotes is LDL apheresis and has been associated with stabilization or regression of atherosclerotic lesions and improvement in symptoms. Since immediate reductions in LDL-C of 50% to 80% rebound quickly, the process is performed every 2 to 4 weeks to keep intrapheresis LDL-C ≤120 mg/dL.

   Both mipomersen and lomitapide were FDA approved in 2013 as orphan drugs for management of patients with homozygous FH only. Mipomersen is a subcutaneously injectable RNA antisense oligonucleotide. Lomitapide blocks microsomal TG

transport protein (a key protein in assembly and secretion of apoB-containing lipoproteins in the liver and intestines) reducing hepatic secretion of VLDL. These therapies have a small target population, require risk evaluation and mitigation strategy limiting use to specialized centers, and have concerns with liver toxicity and hepatic steatosis due to accumulation of TGs not secreted into VLDL.

Several clinical diagnostic criteria for FH exist, with the 15-year Simon Broome Register Group being the most commonly used. Definite FH is as defined above. Possible FH by this criteria is defined as (a) above PLUS and (b) MI before age 50 in second-degree relative, or before 60 in first-degree relative or elevated cholesterol in first-degree relative, or >290 mg/dL in second-degree relative.

5. **d.** National Health and Nutrition Examination Survey (NHANES) data through 2006 reported that 10.3% of adolescents (12 to 19 years) have abnormal lipid levels. In adolescents between the ages of 12 and 19, the number of individuals with one or more abnormal lipid level is higher at 20.3% and increases further to 42.9% in association with obesity. All the other facts noted are true. The AHA has established TC <170 mg/dL in children and <200 mg/dL in adults as one of seven goals for ideal cardiovascular health. In one survey in 2010, 38.1% of children and 52.7% of adults did not meet these criteria. Although average adult TC levels have been dropping over the past two decades from 208 to 197 mg/dL, obesity and lack of physical activity (two factors associated with dyslipidemia and diabetes risk) have been on the rise. From 2011 to 2012 only 20.7% of adults and 49.5% of adolescents, respectively, achieved recommended activity levels. These facts and more can be found in the most recent Heart Disease and Stroke Statistics-2014 Update from the AHA published in Circulation.

6. **b.** The JUPITER trial demonstrated that in individuals without documented cardiovascular disease (CVD) and median LDL-C of 108 mg/dL, aggressive statin therapy with rosuvastatin offered greater benefit in individuals with ultrasensitive C-reactive protein (usCRP) >2 versus <2 mg/L. JUPITER demonstrated that primary prevention patients with only modest elevations in LDL-C but elevated usCRP above 2 mg/L benefited from treatment with statins. However, the trial only enrolled individuals with usCRP >2 mg/L. There was no comparison arm to individuals with low LDL-C and low usCRP. While ASCOT-LLA showed reductions in nonfatal MI and CHD death, coronary events or procedures, stroke, and chronic stable angina, but did not show a reduction in total mortality. However, this trial did demonstrate that initiation of moderate intensity statin therapy in higher-risk individuals without clinical CVD and without significant elevations in LDL-C significantly reduced CVD events. The study with average LDL-C at entry of 130 mg/dL was stopped early by the safety monitoring board. Primary prevention

trials WOSCOPS and AFCAPS/TexCAPS and secondary prevention trials including 4S, CARE, PIPID, and Heart Protection Study (HPS) across a wide range of pretreatment LDL-C and using various statins demonstrated approximately 1% reduction in CVD events for every 1% reduction in LDL-C.

7. **b.** 1, 3, and 5. In making treatment decisions regarding initiation and intensity of treatment for dyslipidemia in patients without documented CVD or diabetes, assessment of future risk of CVD development is important. In individuals with two or more standard cardiovascular risk factors (hypertension, family history, low HDL-C, and smoking), the FRS can be used to calculate 10-year risk of MI or coronary disease mortality. The calculator is based on assessment of TC (or LDL-C), HDL-C, hypertension history, age, and smoking stratified by gender. It does not incorporate family history, assessment of metabolic syndrome, or other nontraditional risk markers such as usCRP, lipoprotein(a), and CACS. Risk may be underestimated in younger individuals and data may not be transferable to ethnic groups not well represented in the cohort. Other risk assessment tools include some of these additional risk markers such as the Reynolds Risk Score (usCRP and family history), PROCAM (prospective cardiovascular Münster heart study) Score (TG and family history), and SHAPE (Screening for heart attack prevention and education) guidelines (carotid intimal medial thickness [CIMT] and CACS). The recent 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults has promoted a new Pooled Cohort Equations risk calculator that incorporates race into the calculation and stroke as an outcome event.

8. **c.** HDL-C of <40 mg/dL in men and women. Metabolic syndrome is characterized by abdominal obesity, an atherogenic dyslipidemia with elevated TG, increased number of small LDL particles, low HDL-C, elevated BP, insulin resistance (glucose intolerance), a prothrombotic state, and a proinflammatory state. There is an increased risk of CVD development of two- to fourfold in individuals with metabolic syndrome. Focus of treatment should be on intensive lifestyle intervention. In the NCEP ATP III recommendations for diagnosis of metabolic syndrome, cutoffs for HDL-C are <40 mg/dL in men but <50 mg/dL in women. The other criteria listed are correct. Modifications since initial publication include lowering the fasting glucose cutoff to 100 mg/dL and population-specific waist circumferences such as ≥90 cm in men and ≥80 cm in women of South Asian ancestry. Metabolic syndrome is present if three or more of these criteria are identified.

9. **e.** Both higher-dose statins and addition of fibrates and niacin to achieve non-HDL-

C goals should be considered to achieve secondary targets and to further reduce cardiovascular event rate. Between NCEP ATP III in 2001 and the update in 2004, multiple randomized controlled clinical trials offered new information supporting more aggressive treatment of hyperlipidemia and led to lowering the treatment goals and pretreatment LDL-C cutoffs for treatment in high- and intermediate-risk individuals (Table 12.1). The HPS demonstrated statin benefit in high-risk patients even with low pretreatment LDL-C. The ASCOTT LLA and Collaborative Atorvastatin Diabetes Study (CARDS) trials showed benefit when treating high-risk primary prevention patients with hypertension or DM even if LDL-C was not significantly elevated. Studies such as Treat to New Targets (TNT) and PROVE-IT TIMI-22 demonstrated that increasing the intensity of LDL-C lowering using higher doses or more potent statins in secondary prevention populations was associated with incremental cardiovascular risk reduction. The guidelines recommend that in treating individuals with hyperlipidemia the first priority of treatment is to lower LDL-C; the first line of drug therapy to manage LDL-C is statin therapy and intensity of therapy should be selected to achieve at least a 30% to 40% LDL reduction. Intensity of therapy and LDL-C goals should be based on level of CVD risk. Although NCEP ATP III recommended non-HDL-C (TC minus HDL-C) as a secondary therapeutic goal after achieving LDL-C goals and considering addition of niacin and fibrates to achieve this goal, this has not yet been definitively shown in clinical trials to reduce adverse cardiovascular events when added to adequate statin therapy.

TABLE 12-1 Treatment Goals and Low-Density Lipoprotein Cholesterol Levels for Initiation of Pharmacologic Therapies Based on Modifications of the National Cholesterol Education Project: Adult Treatment Panel III Guidelines in 2004

Risk Category	LDL-C (mg/dL)	Non–HDL-C (mg/dL)	Consider Drug Therapy for LDL-C
CHD/CHD risk equivalents (10-y risk >20%)	<100 Optional <70	<130 Optional <100	≥100 Optional <100
≥2 risk factors (10-y risk 10–20%)	<130 Optional <100	<160 Optional <130	>130 Optional 100–129
≥2 risk factors (10-y risk <10%)	<130	<160	>160
0–1 risk factor	<160	<190	>190 Optional 160–190

CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

10. **e.** Non–HDL-C goal equals the LDL-C goal +30 mg/dL. Although the ADA, the American Association of Clinical Endocrinologists (AACE), and the AHA/ACC women's preventive guidelines set specific goals for TG below 150 mg/dL and HDL-C >50/40 mg/dL in women/men, NCEP ATP III guidelines do not and instead focus on non–HDL-C targets. The primary target for therapy is LDL-C reduction and statins remain the primary therapy for reducing LDL-C. However, in individuals with TGs >500 mg/dL initial therapy with aggressive diet and lifestyle intervention and medications should be first addressed. Non–HDL-C is recommended as a secondary target after achieving LDL-C goals if TG are greater than 200 mg/dL with therapeutic options to lower non–HDL-C including more intense LDL-C lowering or addition of niacin, fibrates, or high-dose omega-3 fish oils. Bile acid sequestrants should be avoided in individuals with TG over 300 mg/dL. NCEP ATP III recognizes a role for HDL-C as an important determinant of risk and if low a reason to achieve LDL-C and non–HDL-C goals as well as cause

to emphasize diet and exercise. Although specific treatment to raise HDL-C may be considered in very high-risk individuals, the best therapies to accomplish this are not known and clinical trials documenting CVD risk reduction with HDL-C–directed therapies are lacking. An appropriate approach to HDL-C management is lifestyle. Dietary changes are associated with a 3% to 15% increase in HDL-C with an average 0.35 mg/dL increase in HDL for each 1 kg of weight loss. About 120 to 180 minutes of aerobic exercise a week and discontinuation of smoking can each raise HDL-C by 5% to 10%.

11. **d.** Omega-3 polyunsaturated fatty acid supplements of 800 to 1,000 mg a day. Diets high in omega-3 saturated fat are recommended but universal use of supplements is not. The AHA recommends 800 to 1,000 mg/day in dietary consumption and to consider supplements in secondary prevention patients without an adequate dietary source. Omega-3 fatty acids have a role in managing high TGs (>500 mg/day) by using high doses of prescription or supplement forms at 2,000 to 4,000 mg/day. Long-term outcome data supporting definitive reduction in CVD events with omega-3 supplementation in primary prevention populations are lacking. All of the other recommendations listed are supported by the guidelines.

12. **a.** Hyperthyroidism. Identifying and treatment of or modifying secondary causes of dyslipidemia is an important component in the management of dyslipidemia. Treating hypothyroidism and better control of diabetes may have significant impact on correcting lipid abnormalities. If possible, identification of medications associated with dyslipidemia and substitution of alternate medications when possible may help. Cholesterol and TGs rise progressively throughout pregnancy. Drugs such as statins, niacin, and ezetimibe are contraindicated during pregnancy and lactation.

13. **b.** FRS indicating a 10-year risk of MI or coronary death of >10%. Any clinically significant non-coronary vascular diseases such as peripheral artery disease, carotid artery disease, and aortic disease would qualify. Diabetics also fall into this category, particularly those >40 years of age and with at least one additional CVD risk factor. CHD risk equivalent status is present in individuals without clinically evident CHD, other CVD, or diabetes but with two or more CVD risk factors and FRS associated with a 10-year risk of a fatal or nonfatal MI of >20% not >10%. All of these individuals would be candidates for aggressive lipid management. The NCEP ATP III guidelines recommend LDL-C goals <100 mg/dL and optional LDL-C goals <70 mg/dL in this group. The ACC/AHA 2013 hyperlipidemia guidelines have eliminated LDL-C goals for therapy and recommend high-intensity statin therapy to achieve LDL-C lowering of >50% in

high-risk groups <75 years old. This includes individuals with coronary and non-coronary disease, diabetics with new Pooled Cohort Equation calculator risk of >7.5% 10-year risk.

14. **a.** LDL <70 mg/dL and non-HDL <100.

15. **f.** Answers a and d.

16. **a.** Atorvastatin 40 mg/day. Patients with diabetes are CHD risk equivalent patients and therefore at high cardiovascular risk and candidates for aggressive lipid-lowering therapy. The NCEP ATP III update in 2004, ACC/ADA consensus statement in 2008, and the ADA and AAACE (American Association of Clinical Endocrinologists) guidelines in 2013 all support a primary LDL-C goal of <70 mg/dL and secondary non–HDL-C goal of <100 mg/dL. In addition, the consensus statement and recent ADA/AACE guidelines recommend considering apoB of <80 mg/dL and LDL-P of <1,000 as secondary targets for therapy. usCRP is a marker for CVD risk and reduced by many therapies including statins and lifestyle interventions but is not a recognized specific target or therapeutic goal (Tables 12.2 and 12.3).

    The first-line therapy is statins, at a dose needed to achieve LDL-C reductions of at least 30% to 40%. Only atorvastatin 40 mg/day would achieve recommended treatment goals. Simvastatin at this dose is unlikely to result in sufficient LDL-C reduction to achieve goals and since the FDA alert in 2011, doses higher than 20 mg are not recommended in combination with amlodipine. Monotherapy with ezetimibe generally lowers LDL-C <20% and outcome benefit has not been demonstrated. Although LDL-C is not significantly elevated and the TG and HDL-C abnormalities may be improved by the other listed therapies, statins remain the primary treatment choice, supported by beneficial outcome data in trials such as CARDS and diabetic subsets in other large prospective trials and meta-analyses. Outcome data regarding cardiovascular risk reduction with these other listed therapies are lacking or less robust. New lipid treatment guidelines from the ACC/AHA published in November 2013 recommend a different approach to the management of lipids. These new guidelines support therapy initiation and intensity dependent on the level of risk and they recognize that most patients with diabetes are candidates for high-intensity statin therapy (defined as a statin able to achieve >50% reduction in LDL-C, e.g., 40 to 80 mg of atorvastatin or 20 to 40 mg of rosuvastatin).

TABLE 12-2 Treatment Goals: American Diabetes Association/ American College of Cardiology Consensus Statement 2008

	LDL-C (mg/dL)	Non–HDL-C (mg/dL)	apoB (mg/dL)
Highest-risk patients			
Known CVD or diabetes plus one or more additional CVD risk factors	<70	<100	<80
High-risk patients			
No diabetes or known CVD but two or more major CVD risk factors or diabetes but no other CVD risk factors	<100	<130	<90

CVD, cerebrovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

TABLE 12-3 American Association of Clinical Endocrinologists Lipid Targets for Patients with Type 2 Diabetes

	Moderate-Risk Patients	High-Risk Patients
LDL-C (mg/dL)	<100	<70
Non–HDL-C (mg/dL)	<130	<100
Triglycerides (mg/dL)	<150	<150
TC/HDL-C	<3.5	<3.0
ApoB (mg/dL)	<90	<80
LDL particle number (nmol/L)	<1,200	<100

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

17. **f.** All of the above. On statin therapy, the LDL-C goal of <70 mg/dL has been achieved but non–HDL-C remains above an ideal goal of <100 mg/dL. Any of these therapies would help to achieve the secondary non–HDL-C goals. NCEP ATP III recommends intensification of statins, further LDL-C lowering with non-statin therapies, niacin, or fibrates to achieve secondary non–HDL-C goal. There are

clinical trial data to support further risk reduction with intensification of statin therapy although outcome data are absent when niacin, fibrates, fish oil, or ezetimibe is added to adequate statin therapy. Intensification of lifestyle interventions should be a part of any pharmacologic intervention in this patient. The patient is on a high-intensity statin with <50% reduction in LDL-C. Based on new ACC/AHA 2013 guidelines for management of hyperlipidemia, there is insufficient RTC evidence that adding additional therapies will further reduce cardiovascular events. Intensification of statin therapy does appear to offer benefit. In individuals receiving maximum tolerated intensity of statin with less than anticipated therapeutic response and in high-risk groups, the addition of non-statin therapy may be considered if the CVD risk reduction benefits outweigh the adverse effects.

18. **c.** NHANES data from 2010 indicate that although goals of HbA1c <7 mg/dL, systolic BP <130 mmHg, and LDL-C <100 mg/dL are recommended for diabetics, only 32% of diabetics in the survey currently achieve all three of these goals. The NHANES survey in 2010 demonstrated that although greater than 50% of diabetic patients achieved LDL <100 mg/dL, systolic BP <130 mmHg, or HbA1c <7 mg/dL, only <20% achieved all three goals. Studies such as the East-West study in 1998 demonstrated that a diabetic without CHD history had a similar approximate 20% incidence of MI over 7 years compared with a nondiabetic with known previous MI. Diabetics have a two- to fourfold increased risk of CVD events and the majority of deaths in patients with diabetes are due to CVD, accounting for up to 75% of deaths. These observations emphasize the concept of diabetes as a CHD equivalent and a rationale for intensive therapy of hyperlipidemia.

19. **d.** HDL particle size and number. usCRP has been shown in studies such as the Women's Health Study (WHS) to reclassify risk when added to the FRS and in the JUPITER trial to be a factor in determining benefit of early statin therapy for primary prevention of CVD. Similar reclassification of risk has been demonstrated with anatomic measurements for preclinical atherosclerosis such as CACS and CIMT. Post hoc analyses of studies such as the WHS and MESA (multi-ethnic study of atherosclerosis) have demonstrated LDL-P to be a better predictor of future cardiovascular risk, and the National Lipid Association has recommended it as a tool for further risk assessment. However, data supporting the benefit and use of HDL particle size and number in assessing risk and guiding treatment are absent. NCEP ATP III recommends that intermediate-risk patients (FRS 10% to 20% estimated 10-year risk) with these additional risk markers should be considered for more intensive therapies. The ACC/AHA hyperlipidemia guidelines in 2013 suggest that in selected individuals, particularly those with a 10-year CVD risk of 5% to 7.5% not falling into defined treatment groups for high- or moderate-intensity

statin therapy, factors including LDL-C >160 mg/dL, family history of premature CVD, usCRP >2 mg/dL, CACS >300 Agatston units or >75th percentile for age/sex/ethnicity, and ankle brachial index <0.9 may be used to consider initiation or intensification of pharmacologic therapy.

20. **a.** None, all are true. The ACC/AHA 2013 guidelines have attempted to offer recommendations based on a balance of benefit and therapeutic risk of treatment strategies as supported whenever possible by RTCs. The guidelines are based on observations including the absolute benefit in CVD risk reduction is proportional to baseline risk; cholesterol-lowering medications used in clinical trials (particularly statins) reduce risk of cardiovascular events proportional to the intensity of stain therapy rather than LDL-C achieved and therefore more intensive statin therapy could reduce risk more than moderate- or lower-intensity statin therapy; and statins are associated with similar relative risk reductions for CVD events across the majority of patient groups studied, and little clinical trial evidence to support use of other non-statin therapies particularly when added to treatment with statins. Therefore, in these guidelines a greater degree of emphasis is placed on level of treatment with statins and less on other lipid-lowering therapies either alone or in combination with statins. Patients or groups at higher baseline absolute risk will derive greater absolute benefit from initiation of statin therapy over a period of 5 to 10 years as studied in clinical trials. Like the NCEP ATP III recommendations, intensity of therapy is based on a measure of level of CVD risk but defined as dose or potency of statin therapy to be used rather than titration to specific LDL-C and non–HDL-C goals. Both sets of guidelines recommend statin therapy as primary and most beneficial therapy for CVD risk reduction although the ACC/AHA recommendations deemphasize the use of add-on non-statin therapies in the absence of RCT data and balance the risk of pharmacologic therapies in lower-risk populations. The ACC/AHA guidelines position treatment of TGs and use of non–HDL-C in treatment decision making as future clinical questions to be addressed and updated after future clinical trials. It should be mentioned that since these guidelines have appeared many have offered criticism of the document, including the elimination of LDL-C targets and concern with use of a new risk assessment tool that has not been prospectively validated, may overexpand treatment of lower-risk populations, and delay treatment in other high-risk populations. It should be remembered that these are guidelines and not doctrine and individual treatment plans should be tailored to the individual patient's risk and needs after carefully assessing side effects and risk of treatment and discussion with the patient.

21. **b.** Primary elevations of LDL-C ≥160 mg/dL. In these recommendations, LDL-C would need to be above 190 mg/dL to be considered for high-intensity statin

therapy (Table 12.4). Clinical ASCVD is defined as acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease of atherosclerotic origin. It is recommended that the absolute 10-year ASCVD risk (defined as nonfatal MI, CHD death, and including nonfatal and fatal stroke) should be used to guide the initiation and intensity of statin therapy and should be estimated using the Pooled Cohort Equations for the primary prevention of ASCVD in individuals without clinical ASCVD and LDL-C 70 to 189 mg/dL and to determine intensity of therapy in diabetics (DM types 1 and 2). For those with clinical ASCVD or with LDL-C ≥190 mg/dL who are already in a statin benefit group, it is not appropriate to estimate 10-year ASCVD risk. In individuals over 75 years of age falling into these groups or diabetics with 10-year risk <7.5%, consider moderate-intensity therapy to reduce possible side effects.

22. **C.** Bile acid sequestrants as initial therapy in younger patients under 16 years of age. The AAP recommends screening beginning as early as 2 years of age and before age 10 in children with family history of hyperlipidemia or premature CVD in parents and grandparents or if family history is not known and other risk factors (overweight, obese, hypertension, smoking, and DM) are present. They now recommend considering pharmacologic treatment with statins as the first choice drug rather than resins and consider beginning pharmacologic therapy as early as 8 years of age if after lifestyle intervention LDL-C remains >190 mg/dL, >160 mg/dL with one or more other cardiovascular risk factors (including obesity), or >130 mg/dL if diabetes is present.

TABLE 12-4 American College of Cardiology/American Heart Association 2013 Guidelines: Four Treatment Groups and Intensity of Statin Therapy

High-Intensity Statin Therapy (average LDL-C lowering >50%)	Moderate-Intensity Statin Therapy (average LDL-C Lowering 30–50%)
Indicated for	**Indicated for**
1. Clinical ASCVD age <75	1. Clinical ASCVD age ≥75
2. LDL-C ≥190 mg/dL	2. LDL-C ≥190 mg/dL (unable to tolerate high-intensity statin)
3. Diabetics aged 40–75 with LDL-C 70–189 mg/dL with 10-y ASCVD risk ≥7.5%	3. Diabetics aged 40–75 with LDL-C 70–189 mg/dL with 10-y ASCVD risk <7.5%
4. Others aged 40–75, LDL-C 70–189 mg/dL and ASCVD risk ≥7.5%	4. Others aged 40–75 with LDL-C 70–189 mg/dL with 10-y ASCVD risk ≥7.5%
Considered high-intensity statins	**Considered moderate-intensity statins**
Atorvastatin (40)–80 mg	Atorvastatin 10 (20) mg
Rosuvastatin 20 (40) mg	Rosuvastatin (5) 10 mg
	Simvastatin 20–40 mg
	Pravastatin 40 (80) mg
	Lovastatin 40 mg
	Fluvastatin XL 80 mg
	Fluvastatin 40 mg bid
	Pitavastatin 2–4 mg

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

23. C. 4 and 6. Child and Adolescent Trial for CV Health reported that 13.3% of fourth graders had TC >200. NHANES 2010 notes that approximately 8% of adolescents have TC >200. A population approach including weight maintenance, healthy diet, and exercise is recommended for all children. An individual approach to therapy is reserved for those at higher risk for CVD and with elevated LDL-C levels as summarized in the previous question. Other high-risk children and adolescents for whom earlier pharmacologic therapy may be considered include post transplantation, human immunodeficiency virus (HIV), chronic inflammatory disease such as lupus and rheumatoid arthritis, renal disease (nephrotic syndrome), Kawasaki disease, overweight/obese with metabolic syndrome, and childhood cancer survivors. Statins have not been shown to delay or adversely affect physical and sexual development. Cholesterol levels may drop significantly during pubertal development. Therefore, screening before or after is most representative. Studies in

ages 7 months to adolescents have shown safety of low total fat, saturated fat, and cholesterol diets and initiation of low-fat diet is recommended after age 2 years. Benefits of statin treatment on the atherosclerotic process have been demonstrated in children using surrogate markers such as flow-mediated dilatation and CIMT. However, the impact on clinical outcomes has not been studied in large prospective trials. Since there are little outcome data to show that treatment in childhood decreases adult CVD, treatment recommendations are based on extrapolations from adult studies.

24. **d.** The ACCORD trial demonstrated a benefit of fenofibrate when added to baseline simvastatin therapy in diabetic patients. Observational studies support that for every 1 mg/dL increase in HDL-C, there is a 2% to 3% decrease in CVD risk. The Framingham Heart Study recognized that the lower the level of HDL-C, the greater the risk of a coronary event, regardless of LDL-C level. In fact, a person with a "desirable" LDL-C of 100 mg/dL but a low HDL-C of 25 mg/dL had the same risk of a cardiac event as a person with an LDL-C of 220 mg/dL and an HDL-C of 45 mg/dL. Further strengthening the link between HDL-C and TG and poor CVD outcomes is the observation that patients presenting with a new diagnosis of CHD have higher TGs and lower HDL-C than those without CHD. In the TNT trial, this relationship continued to exist even following aggressive statin therapy. When a subgroup of individuals all achieving LDL-C below 70 mg/dL was examined, CVD events increased significantly when HDL-C was below 42 mg/dL even in this group with very low LDL-C levels. A meta-analysis in 2010 of multiple statin trials reported that the inverse relationship of HDL-C to CVD events was not altered by statin therapy. Meta-analyses have shown a relationship between elevations of TG and CVD risk even when controlling for confounding factors and HDL-C. In the treatment arms of statin placebo-controlled studies and even when including those in which very low LDL-C levels are achieved, a significant residual CVD risk persists. NHANES reports that of the 48% of U.S. adults with dyslipidemia approximately a third have elevations in TGs and/or HDL-C. With the growing prevalence of obesity, diabetes, inactivity, and metabolic syndrome more individuals are presenting with a combined dyslipidemia characterized by only moderate elevation of LDL-C but increased numbers of small dense LDL and other atherogenic apoB particles, elevated TGs, and low high density HDL-C. Particularly in these groups it is reasonable to hypothesize that therapies beyond LDL-C lowering may be beneficial. Evidence supports titration of statin to higher doses or use of more potent statins to achieve greater risk reduction. However, data from long-term outcome studies demonstrating incremental benefit when therapy directed toward low HDL-C and TG is added to statins have been disappointing. The AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low

HDL/High Triglycerides: Impact on Global Health) trial and HPS-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) did not demonstrate improved outcomes when niacin preparations were added to individuals with well-controlled LDL-C on statin ± ezetimibe (LDL-C prerandomization of 74 and 63, respectively). The ACCORD trial did not demonstrate benefit when fenofibrate was added to baseline statin therapy in the total population of diabetics studied. A prospectively defined but subanalysis noted a borderline statistically significant 31% CVD event reduction in a subgroup with TG above 204 mg/dL and HDL-C below 34 mg/dL. However, until further studies are available there still may remain a role for niacin, fibrates, or ezetimibe in the management of elevated non-HDL after maximally tolerated statin therapy, those not at LDL-C goal after maximally tolerated statin therapy, or those intolerant to statins. The NCEP ATP III, ADA, and ACCE guidelines do recommend considering therapies including niacin and fibrates to achieve non–HDL-C goals after treating LDL-C. The AHA/ACC 2013 guidelines are less enthusiastic regarding the addition of non-statin therapies. Also note that other recommendations still recommend treatment targets and utilization of non-statin therapies in certain populations.

25. **b.** ATP-binding cassette transporter 1 (ABCA1) and ABCG1 both facilitate free cholesterol efflux to lipid-poor pre-β1-HDL. There are many proposed mechanisms offered to explain the beneficial anti-atherosclerotic activity of HDL-C including increase in nitric oxide production and enhanced endothelial function, inhibition of LDL-C oxidation, reduction of cytokine-induced endothelial vascular cell adhesion molecule induction and macrophage infiltration, as well as anti-inflammatory, antithrombotic (including reduction of platelet activation/ aggregation, activation of protein C–mediated anticoagulant effects, and stimulation of fibrinolysis), and antioxidant effects. However, reverse cholesterol transport, the transfer of cholesterol from the peripheral tissues to the liver for excretion in the feces or bile, appears to offer the greatest cardioprotective role. The mature α-HDL particles are generated from lipid-free apolipoprotein A1 (apoA1) or lipid-poor pre–β1-HDL as the precursors are produced by the liver or intestine, released from lipolyzed VLDL and chylomicrons or released by interconversion of mature HDL particles. ABCA1 facilitates efflux of cholesterol from cells and initial lipidation of these precursors. Lipid efflux to more mature HDL particles also occur via ABCG1-mediated transfer. Enzymatic modification with lecithin cholesterol acyltransferase (LCAT) enables esterification of cholesterol and generates spherical particles that continue to grow with ongoing cholesterol esterification. The larger mature HDL particles are converted into smaller HDL particles via CETP-enabled exchange of cholesterol esters for TGs between HDL and apoB-containing lipoproteins (LDL and VLDL) and scavenger receptor class-B type 1 (SR-B1) selective uptake of

cholesteryl esters into liver and steroidogenic organs. HDL can deliver cholesterol to the liver via the SR-B1 receptor or by holoparticle uptake (direct reverse cholesterol transport). It may also dispose of cholesterol via CETP-mediated transfer of cholesterol esters to LDL and VLDL and removal through normal clearance by hepatic LDL-Rs (indirect reverse cholesterol transport).

Studies in atherogenic animals show that raising HDL-C via genetic modification, infusion of HDL has favorable effects on experimental plague size and structure and reports of the ability of apoA1 Milano infusion therapy to reduce IVUS measured atherosclerotic plaque volume over a short period of 6 weeks in individuals following MI rekindled the interest in newer HDL-directed therapies. This raised hopes that synthetic forms of HDL, HDL mimetics, reconstituted HDL, reinfusion of delipidated HDL, and other therapies designed to increase HDL-C would be potential therapeutic approaches to reduce CVD. Upregulation of liver X receptor (LXR), the nuclear receptor that protects cells from cholesterol toxicity, may be of benefit by resulting in the cellular transduction of the ATP-binding cassette sterol transporters that efflux free cholesterol into either nascent HDL or mature HDL. Enhancing LCAT activity increases the esterification of cholesterol in HDL, resulting in HDL maturation. Modifying the holoparticle uptake of HDL (a possible mechanism of niacin) may delay catabolism by allowing the HDL particle to continue circulating and potentially increase reverse cholesterol transport. Genetic and pharmacologic studies in mice suggest that overexpression of apoA1 and SR-B1 or LXR agonists may be beneficial. Unfortunately methodology, delivery concerns, and off-target adverse effects have so far limited the use of these therapeutic approaches in humans. Despite many new possible therapeutic strategies only inhibiting CETP which increases HDL particle size and delays catabolism of HDL is currently under active clinical phase 3 trial investigations. Two previous studies with CETP inhibitors (which raise HDL-C anywhere from 30% to 140%) were stopped early for adverse events with torcetrapib or lack of benefit/futility with dalcetrapib, but ongoing outcome trials with the more potent anacetrapib and evacetrapib continue.

26. **C.** Renal insufficiency. Statins have not been shown to worsen renal function. There was concern raised when proteinuria was noted in clinical trials with rosuvastatin. However, in analyses of RCTs, creatinine has not been shown to worsen and may improve. The other adverse effects listed above have all been noted with statins. In a meta-analysis by Naci et al. in 2013 comparing statins to placebo, the odds ratio for elevation in LFTs was 1.51, diabetes development 1.09, myalgia 1.07, CPK abnormality 1.13, and cancer 0.96, statistically significant only for liver test abnormalities and diabetes. Concerns have been raised about memory loss but there is a lack of large prospective trials designed to address this question and limited. A

recent report in fact suggests a reduction in dementia with statin therapy.

27. **d.** Myalgia symptoms reported in prescribing information range from 5% to 10%. Definitions specified by the ACC/AHA NHLBI (National Heart, Lung, and Blood Institute) 2002 Clinical Advisory offer the following terminology to describe muscle injury: myalgias (muscle ache/weakness without CPK elevation), myopathy (muscle symptoms with CPK levels more than 10 times ULN), rhabdomyolysis (muscle symptoms with marked CPK elevation typically more than 10 times ULN with creatinine elevation and often with urinary myoglobin). Myalgia is reported in prescribing information at 1.2% to 3.2% but up to 11% in registries. Myopathy occurs in 0.1% to 0.5% of patients in a dose-dependent fashion. Fortunately, the risk of rhabdomyolysis is quite rare and reported <0.1%. Meta-analysis has reported rates of 0.03% to 0.05%. Muscle symptoms are more likely to occur at higher doses and doses should not exceed those recommended to achieve treatment goals. Attention should be paid to factors that may increase risk for myopathy. Concomitant medications such as fibrates, nicotinic acid (rarely), cyclosporine, azole antifungals, itraconazole, ketoconazole, macrolide antibiotics, erythromycin, clarithromycin, HIV protease inhibitors, nefazodone (antidepressant), verapamil, amiodarone, large quantities of grapefruit juice (>1 qt/day), and alcohol abuse may increase drug exposure and increase myopathy risk. This may be particularly true for simvastatin (metabolized via CYP3A) prompting an FDA advisory not to exceed 40 mg dose in general and reduce dose to 10 to 20 mg with concomitant use of drugs such as high-dose niacin, verapamil, ranolazine, and amiodarone. Other factors contributing to a higher likelihood of muscle symptoms include advanced age (especially >80 years; women more than men), small body frame, frailty, multisystem disease (e.g., chronic renal insufficiency, especially due to diabetes), and perioperative periods.

28. **b.** No. Routine measurement of CPK on statin therapy is not recommended but it is reasonable to obtain at baseline prior to therapy in individuals at higher risk for myopathy and if new symptoms develop on treatment. When a patient presents with complaints of pain, tenderness, stiffness, cramping, weakness, or fatigue the first approach should be to document the severity of the symptoms, obtain CPK, creatinine, and urinalysis to exclude rhabdomyolysis, and search for other causes (such as hypothyroidism, rheumatologic disorders, vitamin D deficiency, and steroid use). If there are clinical signs of severe pain, new muscle weakness, CPK greater than 10 times ULN, or myoglobinuria the statin should be stopped. If symptoms are mild to moderate and CPK is less than three times ULN it is reasonable to hold the statin until symptoms can be evaluated. If symptoms resolve rechallenge with the same or lower dose of the statin to establish whether a causal

relationship exists. If so starting a low dose of a different statin is reasonable followed by slow titration. If an asymptomatic individual on statin therapy has an elevated CPK, complete a thorough muscular examination and if unremarkable check for other causes. If greater than 10 times ULN, hold statin and evaluate for other primary or secondary myopathies. If a baseline CPK is known to be elevated prior to therapy, it is not an absolute contraindication to initiate statin therapy if less than three times ULN and asymptomatic. If higher, a search for other causes such as hypothyroidism, recent injury, and other myopathies would be prudent before initiating therapy with a statin and consideration of referral to a rheumatologist for further evaluation.

29. **c.** Statins have been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C. Dose-related elevation in AST or ALT has been reported between 0.1% and 2%. Statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C. A search for other causes of LFT elevations is essential including review of prescription and over-the-counter drugs and supplements, recent infections, and alcohol use. In this patient with LFT less than three times ULN, it is reasonable to repeat in 6 to 12 weeks on the same or a lower dose. If LFTs greater than three times ULN repeat in 2 weeks and if continued elevation stop statin, recheck in 2 to 4 weeks and if improving consider rechallenge with a lower-dose or different statin. Reversal of transaminase elevation is frequently noted with a reduction in statin dose, and elevations do not often recur with either readministration or selection of another statins.

30. **d.** Statin therapy may lower LFTs in patients with fatty liver infiltration. Prior to initiation of statin therapy it is reasonable to exclude other causes for LFT elevation. However, there are small studies supporting the safety of use in appropriate patients. Kiyici et al. examined 44 patients with biopsy-proven NASH (nonacoholic steatosis) and found that on atorvastatin 10 mg for 6 months there was a decrease in cholesterol, AST, ALT, AP (alkaline phosphatase), and GGT (gammaglutaryl transferase). Chalasani et al. examined the effect of statins over 6 months in patients with baseline moderate elevations in LFTs. In patients with normal LFTs placed on statin, the incidence of mild/moderate or severe elevation in LFTs was 1.9% and 0.2%, respectively, in those with baseline elevations placed on statin (4.7% and 0.6%) compared with those not placed on statin (6.4% and 0.4%). Progression to liver failure due to statins is not zero but exceedingly rare reported at 0.02 to 0.07 per million treated. In this patient, an ultrasound of the liver confirmed fatty infiltration. Manufacturer's prescribing information lists unexplained ALT greater than three times ULN as a contraindication to statin

therapy. The best approach is to counsel on a diet program low in sugar and carbohydrates, weight loss, and exercise, and start statin therapy following the LFTs more closely.

31. **c.** 2 and 3. Sattar in a meta-analysis of 13 statin trials in 91,140 patients noted that 4,278 developed DM (4.89% on statins versus 4.5% on placebo; 0.39% absolute increased difference and 9% relative risk of incident diabetes). This represented 1 additional case of DM per 1,000 patient-years. Preiss published a meta-analysis of 5 trials in 32,772 patients comparing high- versus moderate-dose statins and reported 2,749 developed DM (8.8% versus 8.4% or an absolute increase of 0.4%). There were two additional cases of DM (18.9 versus 16.9) per 1,000 patient-years of follow-up. The development of diabetes did not appear to reduce the benefits of treatment. Sattar found 5.4 less cardiac events for 255 patients treated over 4 years for each 1 mmol/L reduction in LDL-C compared with 1 extra case of diabetes for the same time period. Preiss noted 1 additional case of diabetes for every 498 patients over 1 year compared with 1 fewer CVD event for every 155 patients over 1 year. In a separate analysis of three high-dose atorvastatin trials, Waters et al. reported no difference in CVD events occurring in 11.3% with new DM and 10.8% without new DM. This compared with those with diabetes at baseline (10.1% versus 17.5%). The FDA reported this association in February 2012 but added that it does not appear to reduce the benefits of statin therapy in appropriately selected patients. Therefore, statin therapy should not be denied or appropriate doses reduced to avoid diabetes. However, since the individuals that developed diabetes are those at risk for diabetes it is prudent to measure for glycemic control more frequently and emphasize lifestyle interventions to reduce diabetes risk. This approach has been supported in the ACC/AHA 2013 guidelines.

32. **b.** 1, 2, 3, and 5. This patient is at very high risk for recurrent events. Since the greatest reduction in CVD events has been demonstrated with statins, further attempts to rechallenge with statins are appropriate. Small clinical trials and observational studies have shown that tolerance may be improved by trying multiple alternate statins, often using a potent statin beginning at low and intermittent rather than daily dosing with slow titration. Small investigations of coenzyme Q10 appear to lower the incidence of muscle complaints when added to statins. An analysis of patients referred to the Cleveland Clinic for intolerance to statins (the majority due to muscle complaints) revealed that over two-thirds of patients were able to tolerate some statin regimen with average LDL-C reduction of ~28% in those able to tolerate daily dosing. Niacin in high doses has been shown in the Coronary Drug Project to reduce recurrent MI and mortality after MI and is a

reasonable component of a combination therapy program in patients resistant to all statins. Both LDL-C apheresis and mipomersen can lower LDL-C but with LDL-C levels in this range he would not meet the FDA recommendation for apheresis and although trials with mipomersen have been shown to be effective in both homozygous and heterozygous FH patients it is only currently approved for homozygotes.

33. **c.** Although difficult to demonstrate in individual studies, meta-analysis of fibrate trials has demonstrated reduction in cardiovascular mortality on therapy. An increase in myopathy has been reported with both gemfibrozil and fenofibrate as monotherapy but to a greater extent when added to statins (5.5-fold increased risk of myopathy when combined with statins) and more so with gemfibrozil compared with fenofibrate. A meta-analysis of monotherapy fibrate trials published in 2007 in the American Heart Journal reported a reduction in nonfatal MI but no reduction in fatal MI or total/cardiovascular mortality. Subanalyses of individuals with a metabolic dyslipidemia in fibrate trials such as BIP (bezafibrate infarction prevention), FIELD (fenofibrate intervention and event lowering in diabetes), and ACCORD trials demonstrated significant reduction in the primary endpoint of combined cardiovascular events, although not in the overall populations studied. Renal status should be evaluated within 3 months of initiation of therapy and every 6 months thereafter. Plasma half-life of fenofibric acid is prolonged in renal insufficiency and requires lower dose with glomerular filtration rate (GFR) 30 to 59 and avoidance if GFR <30. An increase in creatinine of 12% was reported in the FIELD study using fenofibrate, usually reversible with discontinuation of therapy.

34. **d.** Niacin can raise HDL-C from 20% to 25% and lower TGs from 30% to 50% depending on the dose and pretreatment TG levels but has little effect on LDL-C. Flushing and skin reactions are the most common reasons limiting niacin use. Gout episodes are more common in individuals with a prior history of gout. A small increase in blood glucose levels and HbA1c has been reported but is generally not of clinical significance and manageable with adjustments in glucose-lowering therapies. Baseline LFTs, fasting glucose, or HBA1c and uric acid should be obtained prior to therapy. While studies have suggested a benefit on surrogate markers for CVD events such as CIMT in the Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trials, there are currently no large longitudinal controlled trials demonstrating incremental benefit on clinical events when niacin is added to adequate statin therapy. Results of the AIM-HIGH and HPS-THRIVE were reviewed in Question 25. Niacin has a beneficial effect on multiple components of the lipid panel including a 20% to 35%

increase in HDL-C, up to 20% lowering of LDL-C, and up to 30% to 50% reduction in TG. The Coronary Drug Project, initiated in the late 1960s, was a large secondary prevention study among men with several treatment arms, one of which utilized up to 3 g/day of niacin (Table 12.5). Compared with placebo, niacin lowered TC by 10% and TG by 26% (although HDL-C data not available) and after 6 years, significantly reduced nonfatal MI by 27%. A 15-year follow-up analysis (9 years after the interventions had ended) revealed a significant 11% decrease ($p < 0.004$) in total mortality. Further analysis has demonstrated equivalent reductions in CVD risk regardless of entry fasting glucose level, presence or absence of diabetes at entry, or change in fasting glucose while on therapy.

TABLE 12-5 Pharmacologic Therapies for Lipid Management

Drug	% Decrease LDL	% Increase HDL	% Decrease TG	Side Effects	Contraindications
Statins	18–55	5–15	7–30	Myopathy, increased LFTs, diabetes	Liver disease
Bile acid sequestrants	15–30	3–5	May increase	GI distress, constipation, decreased drug absorption	Very elevated TG
Cholesterol absorption inhibitor	15–25	1–3	5–14	GI distress, increased LFTs, myopathy	Liver disease
Nicotinic acid	5–25	15–35	20–50	Flushing, GI distress, increased LFTs, increased glucose and uric acid	Liver disease, severe gout, peptic ulcer disease
Fibric acids	5–20, may increase	10–20	20–50	GI distress, gallstones, myopathy	Severe renal disease or liver disease
Omega-3 fish oil	May increase	10–20	20–50	GI distress	Fish allergy

GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LFTs, liver function tests; TG, triglyceride.

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Pericardial Disease

Wael A. Jaber • Parag R. Patel

QUESTIONS

1. A 62-year-old man is admitted with chronic obstructive pulmonary disease (COPD) and mild left ventricular (LV) dysfunction (ejection fraction [EF] 45%) as well as symptomatic, recurrent atrial fibrillation (heart rate [HR] 120s to 150s) despite antiarrhythmic drug therapy and direct current cardioversion in the past. After rate control with intravenous (IV) β-blockers, the HR improves and the patient feels better. Given his recurrent atrial fibrillation despite optimal medical therapy, the patient is referred for radiofrequency ablation of atrial fibrillation (pulmonary vein isolation) procedure. The procedure is performed on anticoagulation (international normalized ratio >2.0) and is deemed a success, with no inducible atrial fibrillation at the end of the case. A small atrial septal defect (ASD) was noted with intracardiac echocardiography at the end of the case, with no other remarkable findings. That evening in the post-anesthesia care-unit (PACU), the patient is noted to be hypotensive and tachycardic with increasing dyspnea. There is a concern for cardiac tamponade; however, the arterial line does not show a significant respiratory variation of the blood pressure (BP) waveform (pulsus paradoxus). An echocardiogram is performed, demonstrating a large circumferential effusion and the patient is referred for urgent pericardiocentesis. Which of the following explains why the patient did not develop a pulsus on the arterial line, despite a large, hemodynamically significant pericardial effusion?

   a. Presence of an ASD
   b. Administration of excess IV fluid during the ablation
   c. LV dysfunction
   d. COPD

2. A 38-year-old patient with no prior medical history presents to the emergency room

with 4 days of chest discomfort. He denies any recent trauma, fever, or use of anticoagulants. The pain is positional and the patient reports mild upper respiratory infection (URI) symptoms in the preceding week. Laboratory work is notable for elevated white blood cell count (neutrophil predominance) as well as elevated erythrocyte sedimentation rate (ESR)/high-sensitivity C-reactive protein (hsCRP); his troponin and other laboratory work is otherwise negative/normal. Electrocardiogram (ECG) is consistent with pericarditis. There is a low suspicion for acute coronary syndrome, and acute pericarditis is diagnosed with small effusion on the echocardiogram; the pain improves with analgesics. Which of the following regimens is the most appropriate therapy for this patient to treat the acute episode and maintain remission?

a. Ibuprofen 600 TID for 2 weeks followed by taper and colchicine 0.5 mg BID for 3 months
b. Aspirin 325 daily and colchicine 0.5 mg BID for 2 weeks followed by taper
c. Ibuprofen 400 BID and colchicine 0.5 mg BID for 2 weeks followed by no taper
d. Prednisone 10 mg daily and ibuprofen 600 TID for 3 months followed by no taper

3. A 62-year-old man with cardiac risk factors of tobacco use, hypertension, and diabetes mellitus returns for follow-up after late-presenting mid-left anterior descending artery (LAD) ST-elevation myocardial infarction (MI). He had an occluded mid-LAD, which was successfully aspirated and stented with a single drug-eluting stent; no significant disease elsewhere is noted. The next day he reports progressive chest discomfort and mild fever and has developed a two-component pericardial friction rub on physical examination. His ECG is concerning for pericarditis (Dressler syndrome) and an echo is performed showing no interval change from discharge other than the presence of a small pericardial effusion. Which of the following regimens would be the most appropriate therapy in this patient?

a. Aspirin 650 TID for 2 weeks with taper to 81 mg daily + colchicine 0.5 mg BID for 3 months
b. Aspirin 325 daily for 2 weeks, then taper to 81 mg daily + ibuprofen 600 mg TID for 3 months
c. Ibuprofen 600 mg TID for 2 weeks with taper + colchicine 0.5 mg BID for 3 months
d. Indomethacin 50 mg TID for 3 months as well as aspirin 650 mg TID for 3 months with taper to 81 mg

4. A 45-year-old male patient with a history of acute pericarditis now returns for

outpatient follow-up with increasing dyspnea and lower extremity edema. The patient was seen and started on high-dose aspirin and colchicine (no nonsteroidal anti-inflammatory drugs [NSAIDs] due to allergy) and has not been able to taper for the past 6 months due to persistent low-level symptoms. He has an elevated jugular venous pulse without inspiratory decline, 2+ pedal edema, and congested liver without ascites, as well as a soft pericardial knock. Laboratory values are notable for mild transaminitis as well as elevated ESR/hsCRP. ECG is unremarkable and echo shows a small persistent pericardial effusion with tubular-shaped LV with normal function, along with diastolic bounce and conical-shaped right ventricle (RV) as well as plethoric inferior vena cava and respirophasic transmitral and trans-tricuspid variation all consistent with constrictive pericarditis. Which of the following would be the next most appropriate step in management?

a. Initiate steroid therapy (0.25 to 0.5 mg/kg/day) along with colchicine, and initiate PO diuretic
b. Admit for IV diuresis and transition to PO diuretic regimen after cardiac catheterization for constriction evaluation
c. Repeat echo in 2 to 3 months aspirin and colchicine at current doses
d. Surgical evaluation for pericardiectomy/stripping

5. A 39-year-old patient with no prior medical visits presents with cardiac tamponade and undergoes urgent pericardiocentesis. He is from sub-Saharan Africa and has never been seen by a physician before—reports feeling progressively ill for the past month and brought to the hospital after syncopal episode today. Fluid analysis is performed and listed below:

Gram stain: no gram-positive/gram-negative bacteria noted
Peripheral cell count: normal (peripheral cell count $<10 \times 10^9$ cells/L)
Pericardial fluid differential (lymphocyte/neutrophil): >1.0 (monocytes present as well)
Protein: elevated
hsCRP: markedly elevated
Lactate dehydrogenase (LDH): elevated (>2.0 times peripheral LDH level)
Adenosine deaminase (ADA): >40 U/L
Interferon gamma: >50 pg/mL
Glucose: low
Culture and cytology/acid fast staining: pending

The most likely etiology for the effusion would be

a. tuberculous pericarditis.
b. endemic malignancy (i.e., Epstein-Barr virus–associated Burkitt's) with

metastatic spread.

c. malarial (Plasmodium vivax).

d. unable to determine—require pericardial biopsy to confirm.

6. A 47-year-old man with constrictive pericarditis is undergoing an echocardiogram for follow-up. The sonographer asks you to explain the difference between the annulus reversus and annulus paradoxus phenomena. Which of the following statements is correct?

   a. Annulus reversus refers to reversal of septal and lateral mitral tissue Doppler velocities (E′ septal > E′ lateral) and annulus paradoxus refers to inverse correlation of E/E' and LV end-diastolic pressure.

   b. Annulus reversus refers to reversal of septal and lateral mitral tissue Doppler velocities (A′ septal > A′ lateral) and annulus paradoxus refers to inverse correlation of E/E′ and LV end-diastolic pressure.

   c. Annulus reversus refers to reversal of septal and lateral mitral tissue Doppler velocities (E′ septal < E′ lateral) and annulus paradoxus refers to positive correlation of E/E′ and LV end-diastolic pressure.

   d. Annulus reversus refers to reversal of septal and lateral mitral tissue Doppler velocities (A′ septal < A′ lateral) and annulus paradoxus refers to a positive correlation of E/E′ and LV end-diastolic pressure.

7. A 51-year-old male patient is admitted to the hospital with anasarca and progressive dyspnea and functional limitation. He has a prior history of coronary artery bypass grafting and post-pericardiotomy syndrome with relapsing pericarditis that has likely advanced to constrictive physiology (despite slow taper steroid therapy), given his presenting symptoms and physical examination findings. During the admission he is aggressively diuresed with IV diuretics with improvement in his renal and liver function, as well as symptom improvement (edema and dyspnea). He is unable to go for a magnetic resonance imaging (MRI) for further assessment (prior metallic implant in his spine for scoliosis) and his echocardiogram images are technically difficult due to his distorted spine and prior cardiac surgery.

   He is referred for dual transducer cardiac catheterization for hemodynamic evaluation of right- and left-sided pressures as part of his diagnostic workup. The catheterization laboratory team begins the procedure and calls you to discuss the case. They note a sinus rhythm at 90 bpm with occasional premature ventricular contraction and a central venous pressure of 4 mmHg and nonelevated end-diastolic pressures at the beginning of the study (due to recent diuresis); they are unable to elucidate diastolic equalization of pressures, significant “dip and plateau,” or respiratory discordance of the ventricular pressure waveforms.

   A potential mechanism for the discordant catheterization findings would be

a. lack of preload due to overdiuresis.
b. borderline tachycardia and ectopy preventing accurate analysis.
c. presence of only mild constrictive physiology.
d. presence of restrictive cardiomyopathy and physiology.

8. A 32-year-old white man presented initially with low-grade fever, cough, and pleuritic chest pain. He was found on ECG to have diffuse ST-segment elevation. A transthoracic echocardiogram (TTE) revealed a large pericardial effusion, and serologies were positive for coxsackievirus B infection. He was diagnosed with acute viral pericarditis and treated with indomethacin. He returns 4 weeks later for follow-up and states that he no longer has any pain, but he notes some mild ankle swelling. His ECG is normal. A repeat TTE shows resolution of the effusion but new findings consistent with mild constriction. What is the next step in managing this patient?

a. Obtain cardiac MRI to better assess the pericardium.
b. Have a cardiothoracic surgical consultation for pericardiectomy.
c. Reassure the patient and observe him over the next 3 months for worsening of symptoms.
d. Start a course of steroids.

9. A 45-year-old woman with a history of treated carcinoma of the breast presents to the local emergency department with a few days of severe chest pain. In the emergency department, she appears ill and pale and in moderate discomfort. Her BP is 135/60 mmHg; her respiratory rate is 24 breaths per minute; her HR is 82 bpm; and her temperature is 100.8°F. The resident on call reads her chest X-ray (CXR) as unremarkable. Her ECG is shown in Figure 13.1. What is the most reasonable next step?

a. Give aspirin and nitroglycerin and prepare to administer thrombolytics.
b. Call the cardiac intervention team and rush the patient to the catheterization laboratory for emergency coronary intervention.
c. Give a nonsteroidal anti-inflammatory medication.
d. Discharge the patient and refer her for a gastroenterology follow-up as an outpatient.

10. A 59-year-old man with a history of coronary artery disease (CAD) and remote coronary bypass surgery presents with progressive dyspnea and vague chest pain. He had a stress echocardiogram for these symptoms that demonstrated normal LV function with no stress-induced wall motion abnormalities. However, he returned to the emergency department a few days later with recurrent symptoms. This time the house officer examining the patient notes 3+ pedal edema. The patient is admitted

and started on diuretics. His blood tests are as follows:

White blood cell count = 11,000
Hemoglobin = 14.2
Platelets = 172,000
Albumin = 4.6
Urea = 11
Creatinine = 0.9

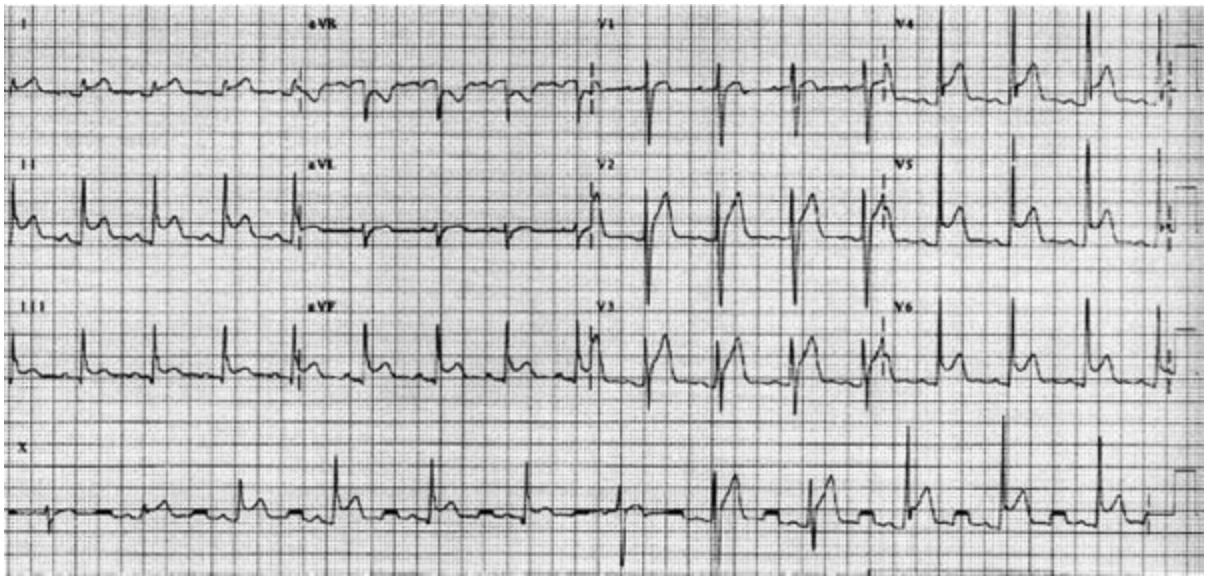

Figure 13.1 • (From Wagner GS, ed. Marriott's Practical Electrocardiography, 9th ed. Baltimore, MD: Williams & Wilkins; 1994, with permission.)

Owing to the recurrent symptoms, his cardiologist decides to refer him for a right and left heart catheterization. The coronary grafts are all patent. The tracings from the study are shown in Figure 13.2. What is the most logical explanation for this patient's symptoms?

a. Constrictive pericardial disease
b. Small-vessel CAD
c. Diastolic dysfunction related to his chronic CAD
d. Cardiac amyloid
e. Cardiac tamponade

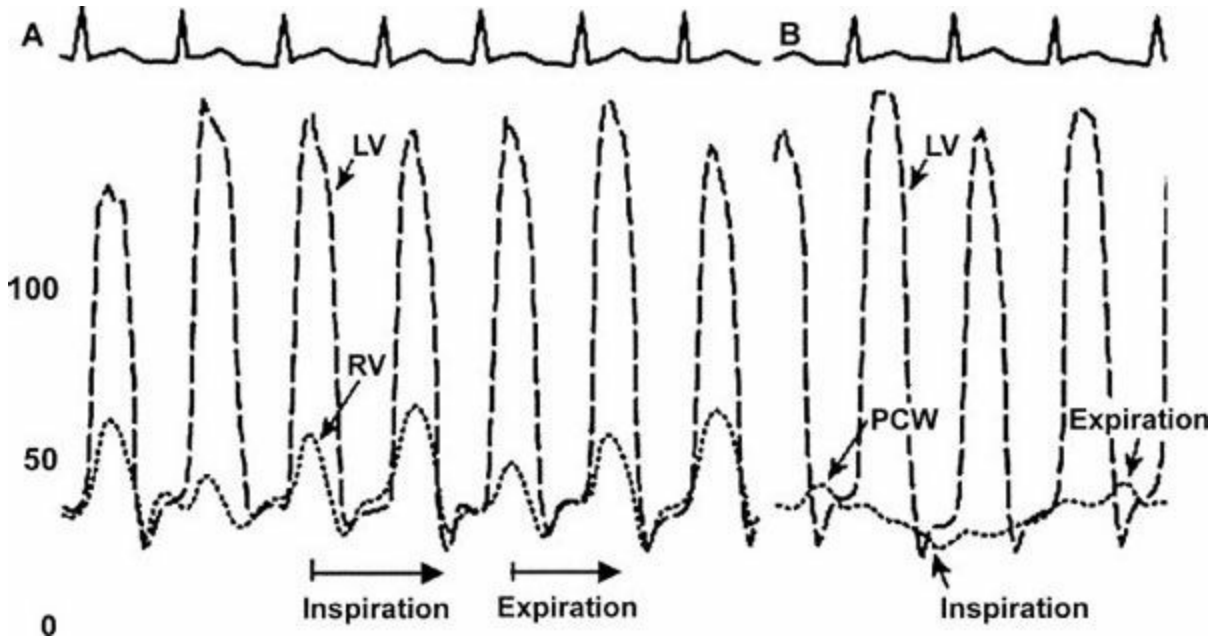

Figure 13.2 • PCW, pulmonary capillary wedge.

11. A 73-year-old man with no cardiac history presents with chronic lower extremities edema. His primary care physician attributed his symptoms to old age. He was treated with hydrochlorothiazide. Initially, he reported a good response to the therapy, but, over the past few months, his edema recurred, and doubling the diuretic dose did not alleviate his symptoms. On his initial examination, you notice distended neck veins and a quiet precordium. He has mild hepatomegaly and 4+ pedal edema. A TTE is suboptimal because of the patient's inability to lie flat and obstructive lung disease. His blood work is as follows:

White blood cell count = 6,000
Hemoglobin = 12.7
Platelets = 225,000
Urea = 43
Creatinine = 2.4
Albumin = 3.6

A cardiac catheterization is performed. He has normal coronary arteries with mild impairment in LV systolic function. The tracings from the study are shown in Figure 13.3. What is your explanation of his symptoms?

a. You agree with his primary care physician. You tell the patient that he probably has peripheral venous insufficiency.
b. This patient has significant diastolic dysfunction, and his prognosis is guarded.
c. This patient's symptoms are due to the LV systolic dysfunction and volume overload.

d. This patient should be referred for surgical evaluation for possible pericardial stripping.

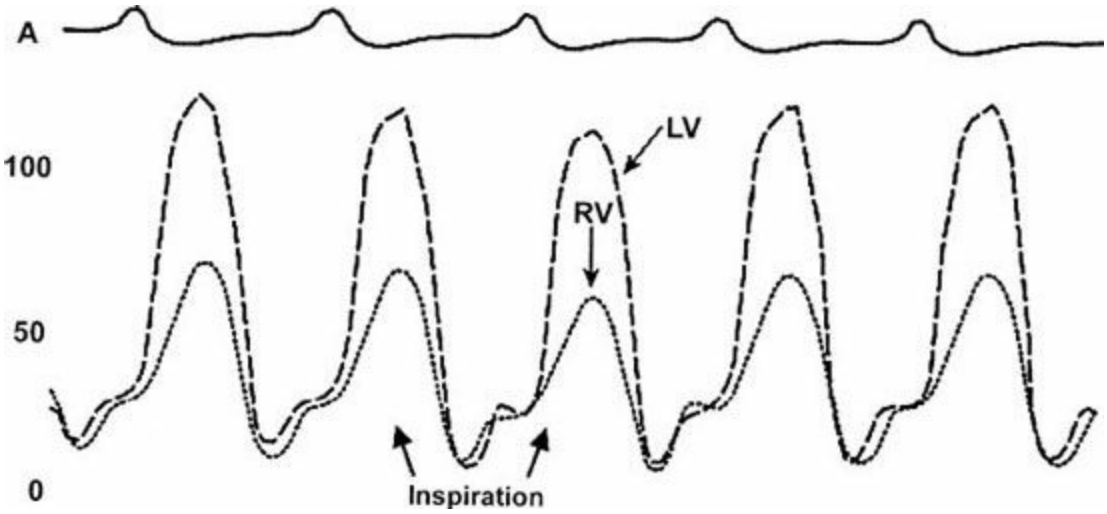

Figure 13.3 • Pressure tracings in the LV and RV.

12. A 56-year-old male smoker with a family history significant for CAD is presenting with dyspnea on exertion and nonexertional vague chest pain. His physical examination and his initial ECG are unremarkable. His CXR demonstrates an increased cardiac silhouette. There is also a small nodule seen in his right upper lobe. The radiologist is not certain about its significance. Given his risk factors and symptoms, he is referred for a perfusion stress test. The images from the stress test are shown in Figure 13.4. Which of the following does the patient clearly have?

a. He has coronary ischemia and should be referred for coronary angiography.
b. There is no evidence of pathology to justify his symptoms.
c. His symptoms are related to impairment of RV filling and pericardial disease.
d. He has mild ischemia and can be treated medically.

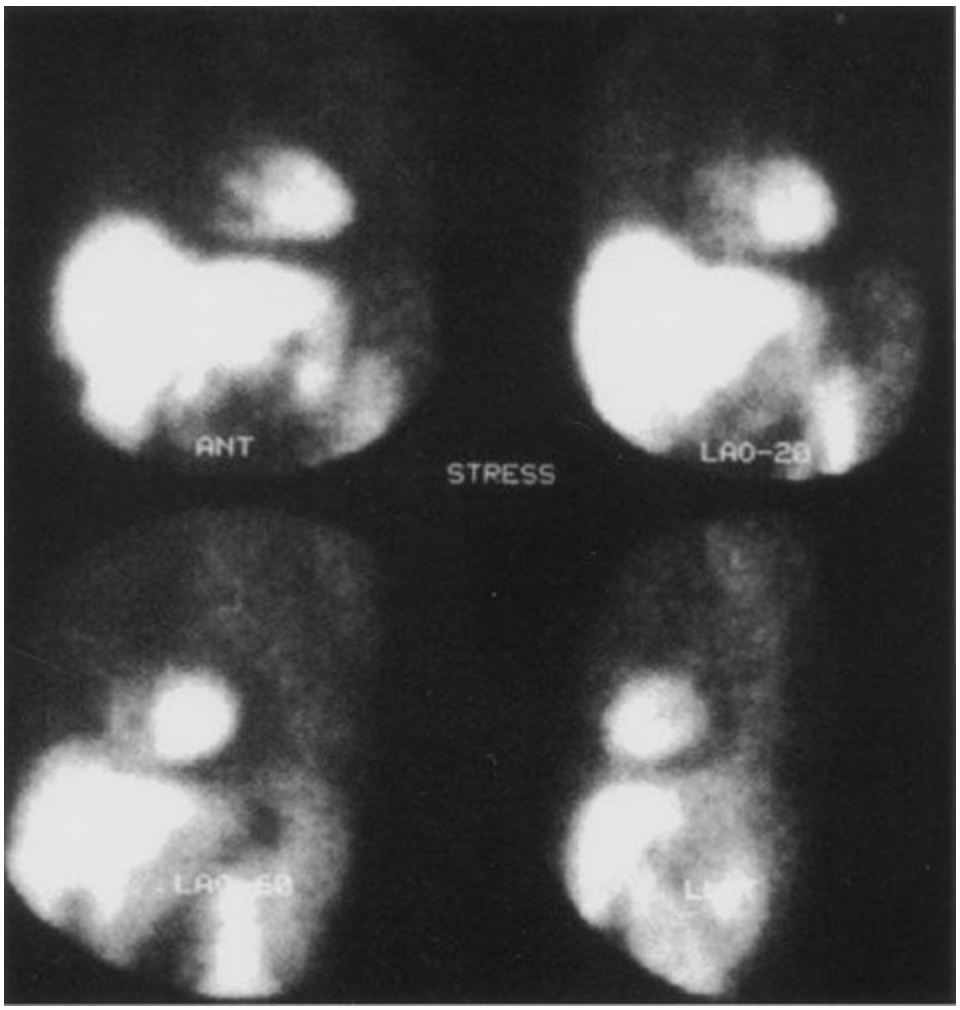

Figure 13.4 • (From Pohost GM, O'Rourke GA, Berman DS, et al., eds. Imaging in Cardiovascular Disease. Philadelphia, PA: Lippincott Williams & Wilkins; 2000, with permission.)

13. A 58-year-old man, with cardiac risk factors of tobacco use, hypertension, and hypercholesterolemia, presented to the emergency department a few days ago with an acute onset of left-sided chest pain. His evaluation revealed a diaphoretic man in moderate discomfort. An ECG was performed and showed a pattern consistent with an inferior wall acute MI. The patient was treated with thrombolytics. Forty-five minutes after the initial dose of the thrombolytics, he felt better and had complete resolution of his symptoms and normalization of the ECG. On the third day after the event, he reports midsternal chest pain, vague in nature, with mild diaphoresis and shortness of breath. An ECG is performed, as shown in Figure 13.5. Which of the following should you tell the patient is the next step in managing his condition?

a. There is evidence of reocclusion of the infarct-related artery, and a percutaneous intervention is needed.
b. There is evidence of reocclusion of the infarct-related artery, and rebolus with thrombolytics and heparin is indicated.
c. He is showing signs of early postinfarction pericarditis, and a nonsteroidal anti-

inflammatory medication should be started.

d. An LV aneurysm has developed, and a TTE is needed to evaluate the extent of the aneurysm.

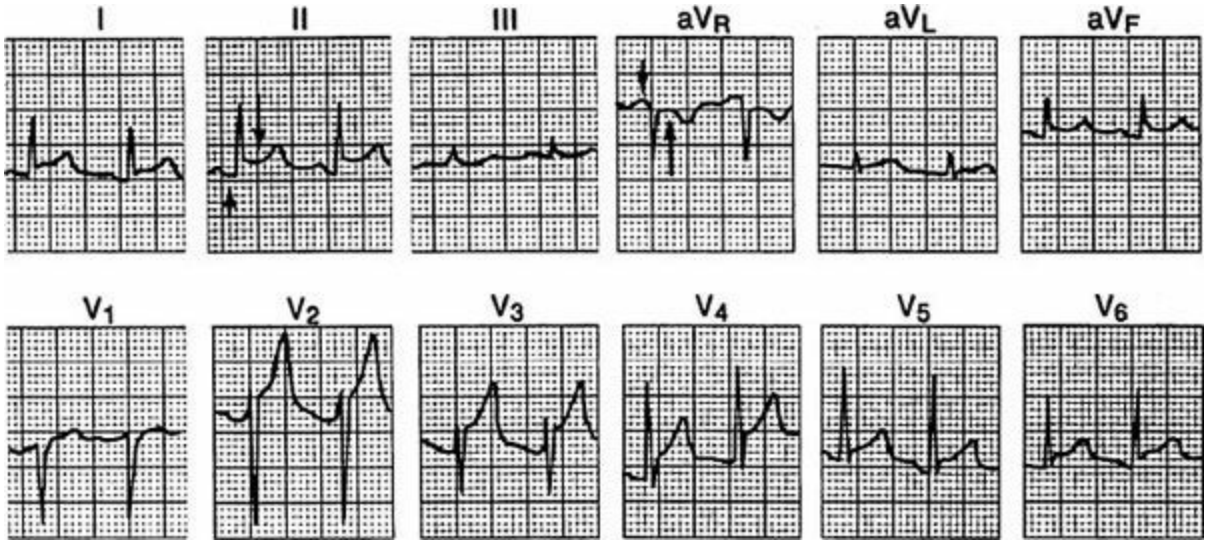

Figure 13.5 • (From Braunwald E, ed. Heart Disease: A Textbook of Cardiovascular Medicine, 5th ed. Philadelphia, PA: WB Saunders; 1997, with permission.)

14. A 19-year-old male college student presents to his local physician for evaluation of a dry cough. His symptoms started 3 days ago but now appear to be resolving. He had planned a trip overseas but was concerned and is now seeking advice. His physical examination is unremarkable. A CXR is performed and is read as showing an enlarged right cardiac silhouette. A TTE is ordered, which is shown in Figure 13.6. The patient most likely has which of the following conditions?

a. He has a pericardial cyst that is benign; no further treatment should be offered.
b. He has cardiac tamponade requiring a pericardial tap.
c. He has a pleural effusion.
d. There is no pathology. The CXR was misread.
e. He has mesothelioma.

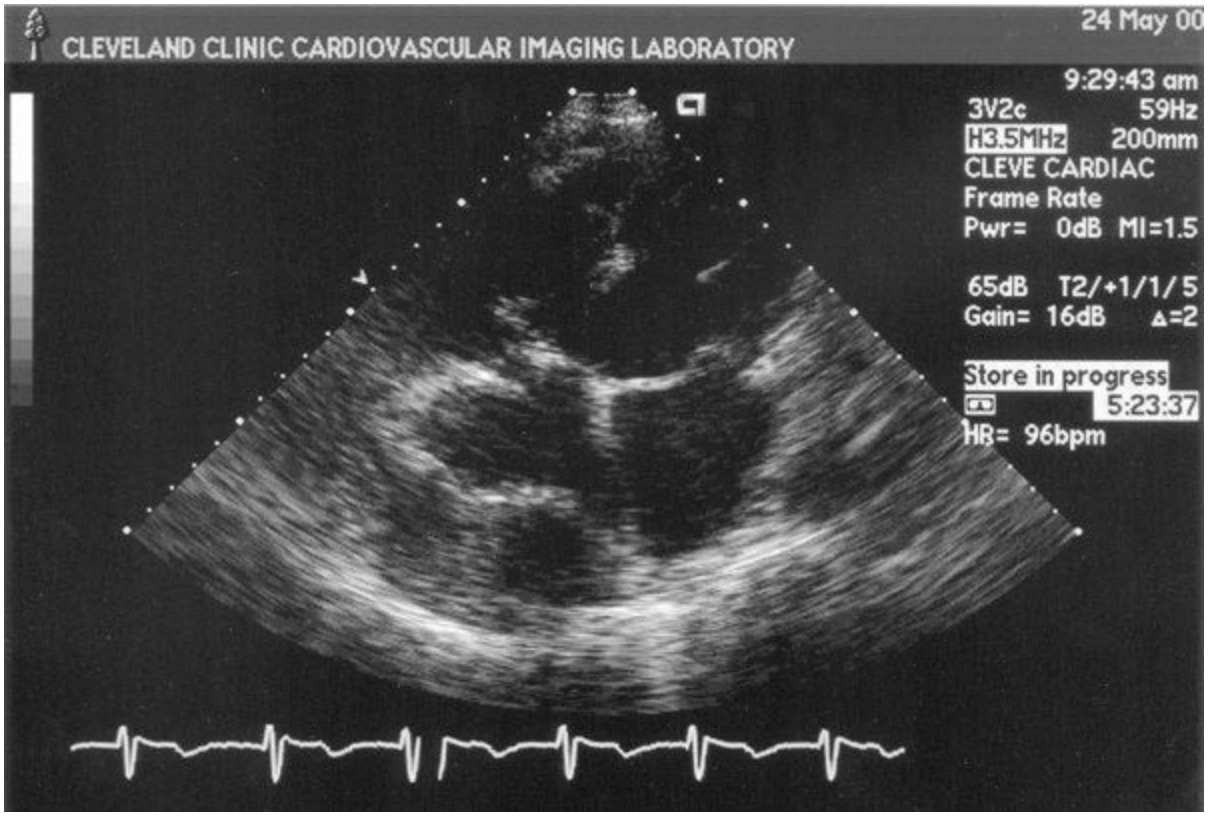

Figure 13.6

15. You are called to the emergency department to see a 74-year-old man. He has a history of heavy smoking and hypertension. The patient cannot remember his medications, but he reports not taking them on a routine basis. In the past few hours before presentation, he experienced a sudden onset of severe left-sided chest pain with radiation to the left scapula. Approximately half an hour later, he noted some difficulty breathing. In the emergency department, he is noted to be diaphoretic and in significant respiratory distress. His physical examination reveals a BP of 160/90 mmHg, elevated jugular venous pressures, and a quiet precordium. His ECG is reported as sinus tachycardia with no acute ST-T changes. After initial pain and BP management, a transesophageal echocardiography (TEE) is performed to rule out aortic dissection. The findings of the TTE are shown in Figure 13.7. What is your recommendation?

a. The patient should have immediate surgical intervention.
b. The patient needs BP control and surgical evaluation once he is medically stabilized.
c. The patient should have percutaneous pericardial drainage to manage the cardiac tamponade and then a surgical evaluation.
d. The diagnosis is unclear; a computed tomographic (CT) scan or an aortic angiogram is needed.

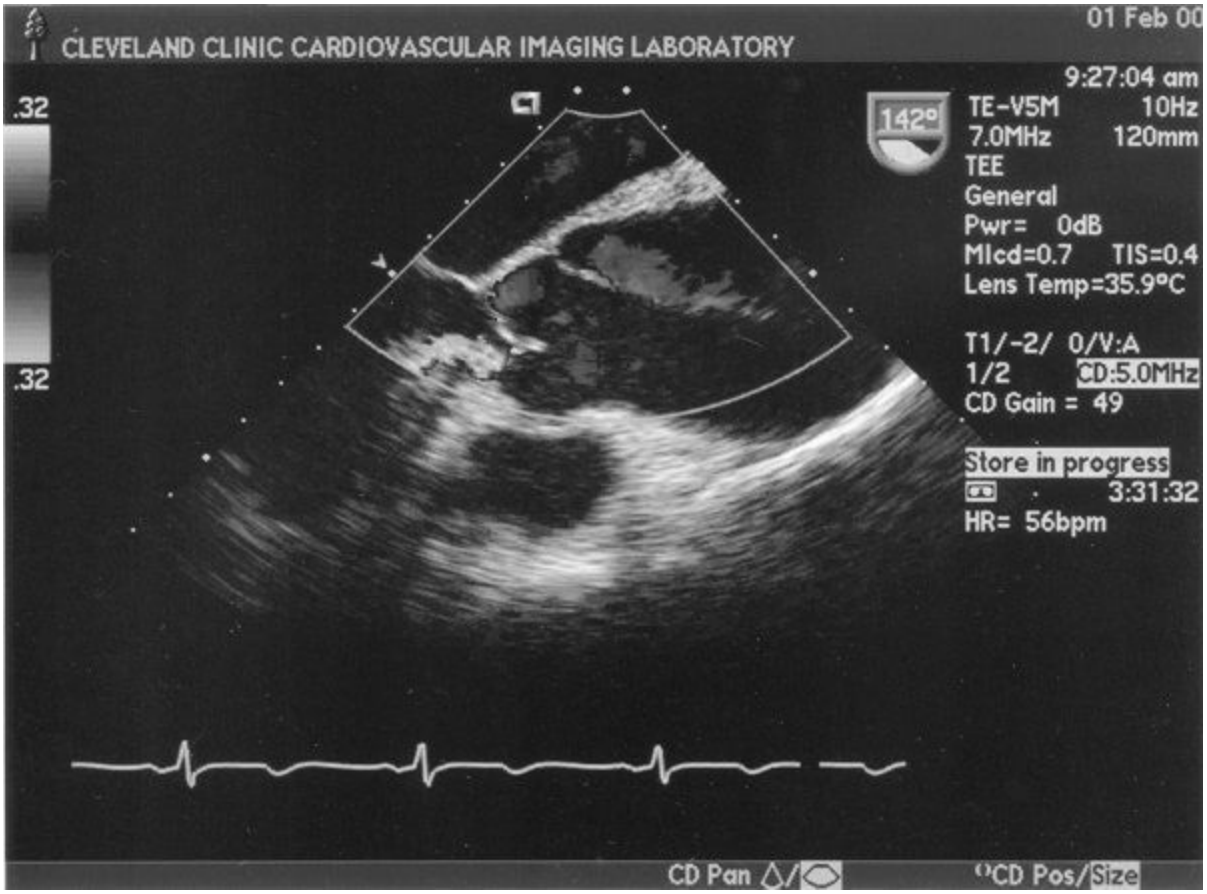

Figure 13.7

16. A 42-year-old man was referred for evaluation of symptomatic mitral regurgitation. He was diagnosed with mitral valve prolapse that was not suitable for repair. Given his family history of CAD and tobacco use, he underwent a coronary angiogram, which revealed no evidence of obstructive coronary disease. He underwent an uneventful mitral valve replacement. He was extubated and transferred from the intensive care unit 48 hours after the operation. On postoperation day 3, you note the patient to be pale and lethargic and in mild respiratory distress. His BP is 100/60 mmHg. His cardiac and lung examination is compromised by the presence of rapid breathing and chest tubes. His ECG reveals normal sinus rhythm (NSR) at 97 bpm with no acute ST-T changes. A TTE is performed. Selected views are shown in Figure 13.8A. As the patient continues to deteriorate and becomes hypotensive, a TEE is performed next, as shown in Figure 13.8B. What should you recommend?

a. Immediate surgical exploration of the pericardium
b. Percutaneous aspiration of the fluid present in the pericardium
c. Immediate surgical intervention for malfunction of the prosthetic mitral valve
d. A 500-cc bolus of IV normal saline solution should be started because the patient is dehydrated, and no further intervention is needed

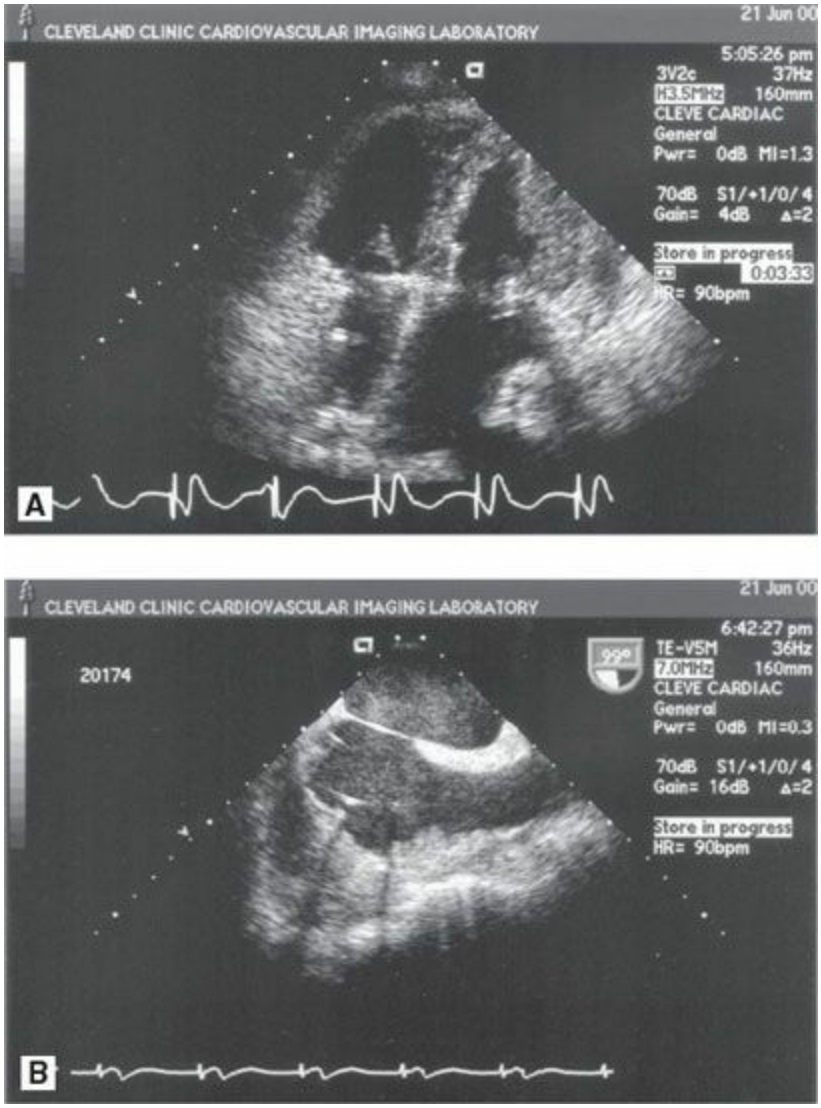

Figure 13.8

17. A 49-year-old black man with hypertension and chronic renal insufficiency presents with dyspnea and fluid overload with decreased urine output. He is treated in the hospital with diuretics, and his symptoms improve. However, his renal function continues to deteriorate with an increasing blood urea nitrogen of 90 and a creatinine of 5.4. In addition, the patient is noted to have several bruises on his arms from needlestick blood draws and IV lines. On hospital day 4, the patient is noted to be hypotensive and tachycardic: BP, 80/40 mm Hg; HR, 110 bpm. No jugular venous distention is noted, but heart sounds are diminished, and a loud pericardial rub is heard. His TTE is shown in Figure 13.9. What is the next step in management?

a. Urgent pericardiocentesis
b. IV hydration
c. Immediate dialysis

d. The continuation of diuretics with serial TTE

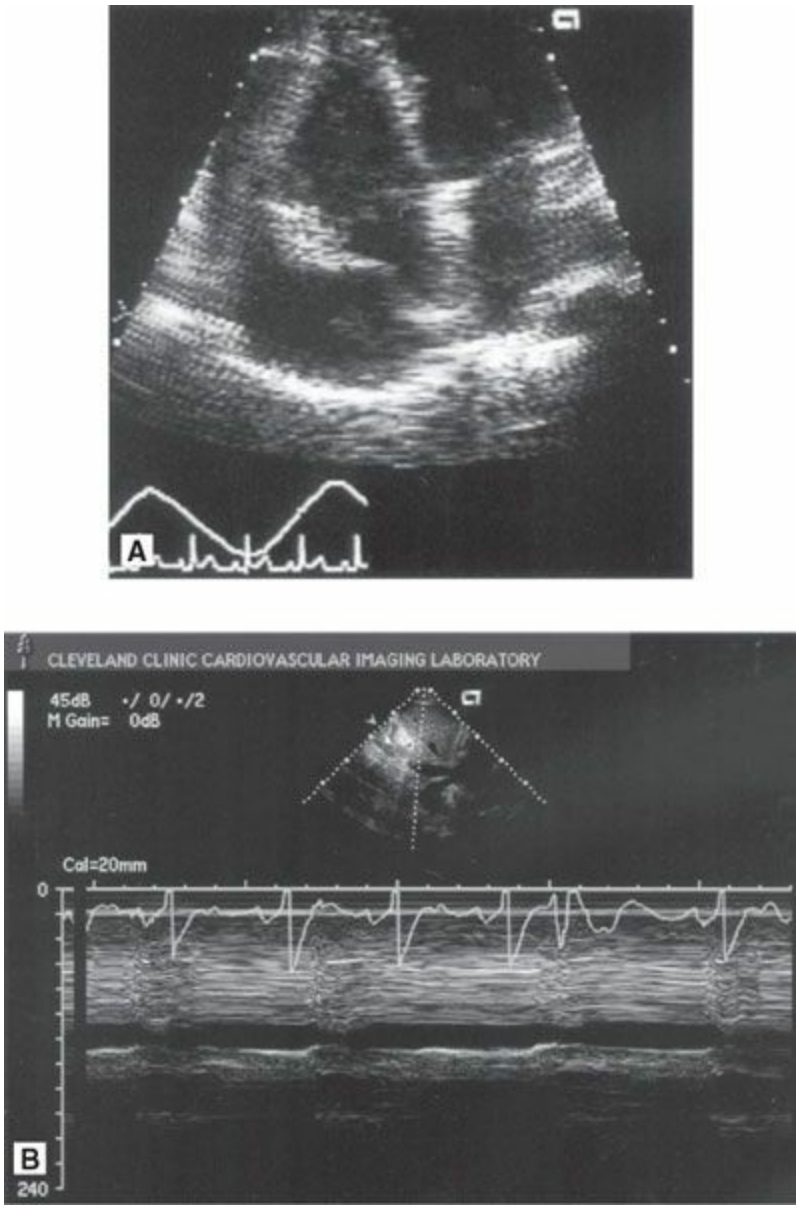

Figure 13.9 • (From Otto CM, Pearlman AS. Textbook of Clinical Echocardiography. Philadelphia, PA: WB Saunders; 1995, with permission.)

18. A 42-year-old white male chef is brought into the emergency department after a motor vehicle accident in which he fell asleep at the wheel and ran into a tree. He is reporting anterior chest discomfort and shortness of breath. He relates no prior medical conditions and takes no medications. Vitals are stable with a BP of 120/60 mmHg and an HR of 90 bpm. His ECG is shown in Figure 13.10A. A TTE is performed. Diastolic images are shown in Figure 13.10B. Laboratory tests show modest elevation of creatinine phosphokinase at 240. Which of the following is the most reasonable next step in managing this patient?

a. Start the patient on a nonsteroidal anti-inflammatory agent with follow-up as an outpatient in 1 week.
b. Admit the patient for observation on telemetry with a follow-up TTE.
c. The patient needs immediate percutaneous revascularization.
d. Send the patient for surgical treatment of pericardial rupture.

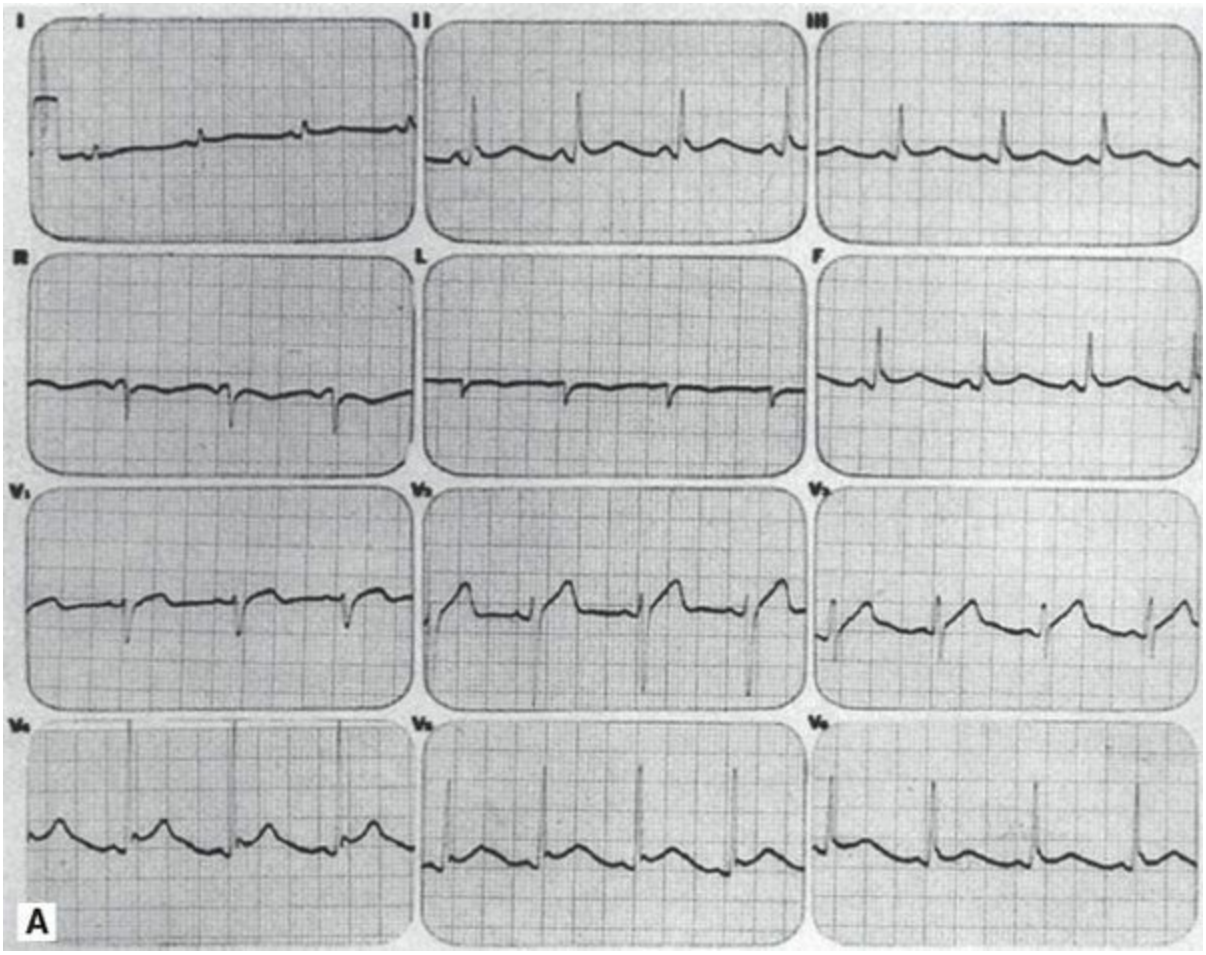

Figure 13.10A • (From Chou T-C. Electrocardiography in Clinical Practice, 4th ed. Philadelphia, PA: WB Saunders; 1996, with permission.)

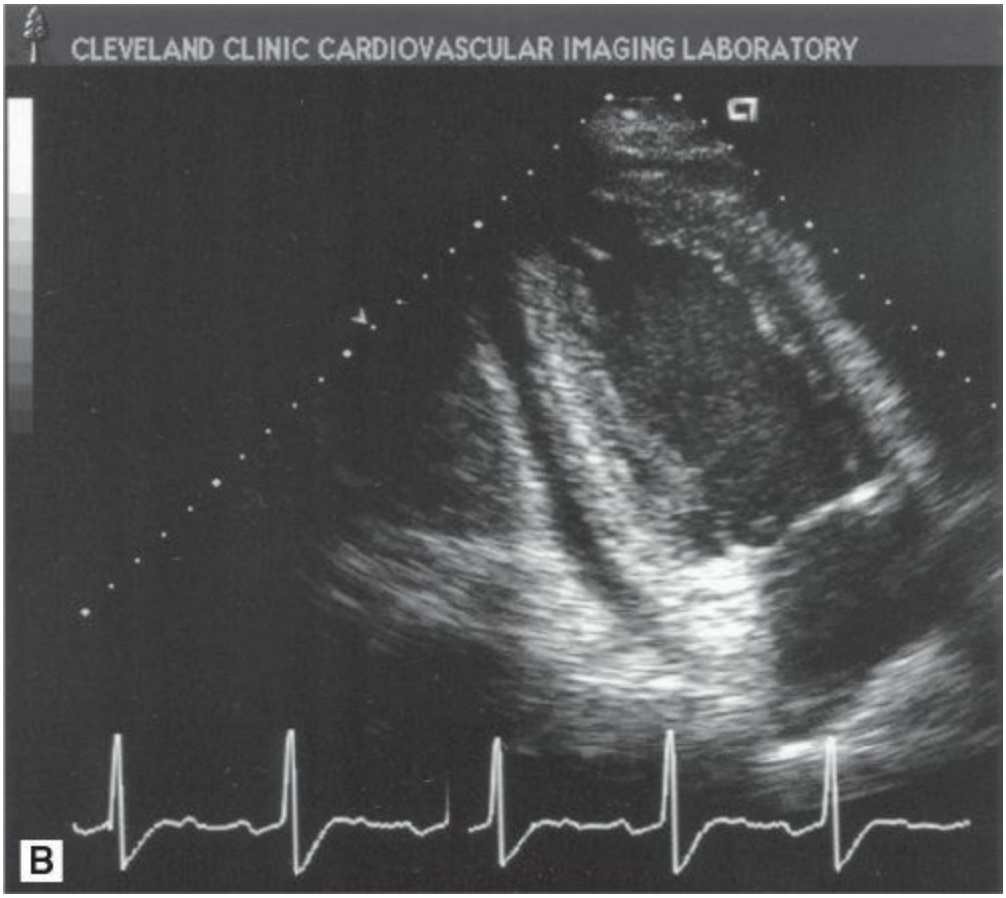

Figure 13.10B • (From Chou T-C. Electrocardiography in Clinical Practice, 4th ed. Philadelphia, PA: WB Saunders; 1996, with permission.)

19. A 22-year-old white man is newly diagnosed with non-Hodgkin lymphoma. He undergoes a metastatic workup that includes an MRI of the chest and abdomen, which is shown in Figure 13.11. The plan is for chemotherapy, but you are consulted for cardiac assessment before beginning chemotherapy. Radionuclide ventriculography shows a normal LV EF of 65%. What should you recommend?

a. Ordering a TTE to delineate the abnormality
b. Cardiothoracic surgical consultation before starting chemotherapy
c. Exercise stress testing
d. Proceeding with chemotherapy without further cardiac evaluation

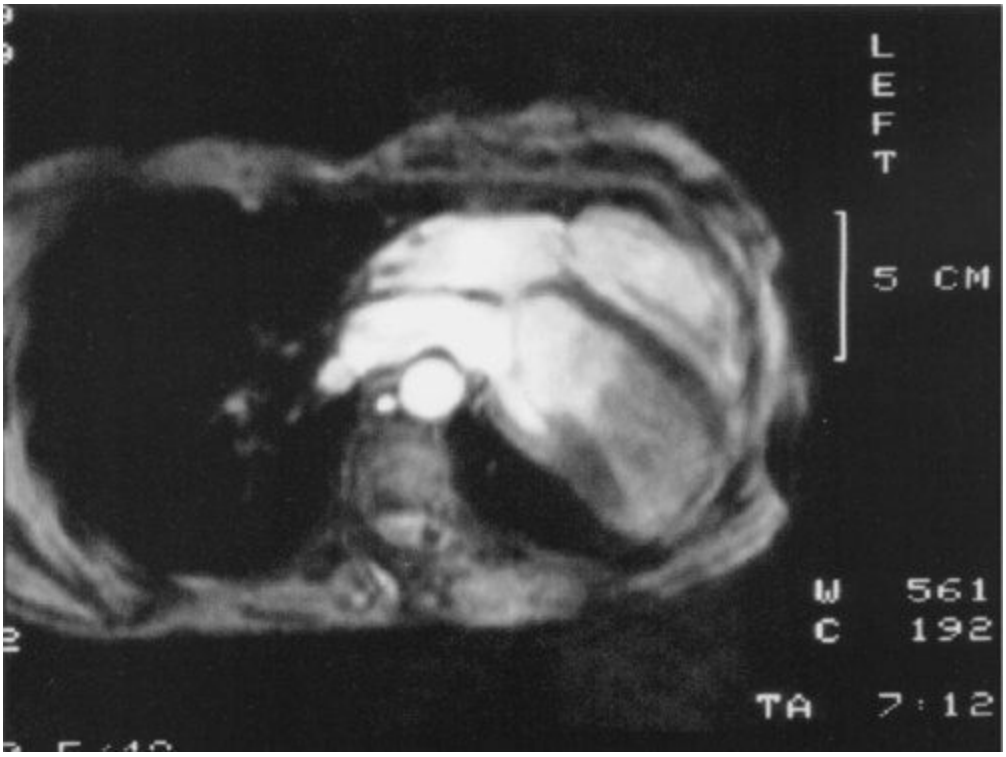

Figure 13.11 • (MRI image was provided by Dr. Richard White, Head, Section of Cardiovascular Imaging, Departments of Radiology and Cardiovascular Medicine, The Cleveland Clinic Foundation.)

20. A 44-year-old white man with rheumatoid arthritis is referred to your office for evaluation after his rheumatologist heard a loud heart sound. On questioning, the patient mainly reports joint pains in his fingers. He denies any chest discomfort or shortness of breath. He has been on methotrexate and prednisone for the past year. His examination is significant for mild erythema and swelling of his distal interphalangeal joints, rheumatoid nodules on his right forearm, clear lungs, distant heart sounds with a loud friction rub, and moderate peripheral edema. You order a TTE to further assess his heart. Selective images are shown in Figure 13.12. What is your recommendation?

a. Because he currently has no cardiac symptoms, no further treatment is needed except to continue methotrexate and prednisone.
b. You want the patient to start indomethacin, continue methotrexate and prednisone, and follow up in 4 weeks.
c. The best treatment at this time for his pericardial effusion is drainage with the instillation of steroids to prevent recurrence.
d. A surgical evaluation for pericardiectomy is necessary because the findings on his TTE indicate that he will develop problems in the future if this is not taken care of soon.

21. A 55-year-old white man presents for evaluation of chest pain. He has no prior

medical problems, but he has noted burning epigastric and chest discomfort for the past few months for which he was taking antacids with some relief of his symptoms. However, because the symptoms persisted, he sought medical attention and was referred for an esophagogastroduodenoscopy, which was performed earlier today. He was found to have a fundal hiatal hernia with a gastric ulcer that was cauterized, and he was started on omeprazole. On returning home, he noted a new sharp anterior chest pain, somewhat positional related, that was not relieved with antacids or omeprazole. This pain progressively worsened over the next few hours, and he came to the emergency department. Examination in the emergency department revealed a temperature of 38.1°C, an HR of 110 bpm, and a BP of 120/70 mmHg. Lung sounds were clear. Heart sounds appeared normal with the patient sitting upright, but they were diminished with the patient lying in the supine position. An ECG did not show any acute ST-T wave abnormalities to suggest infarction. A CXR was performed, as shown in Figure 13.13. You are called to further assess the patient. After reviewing the available data, which of the following is your next step?

a. Immediate surgical consultation
b. Immediate pericardiocentesis
c. Start a nonsteroidal anti-inflammatory medication and admit him for observation
d. No further treatment is needed because his symptoms are caused by the hiatal hernia

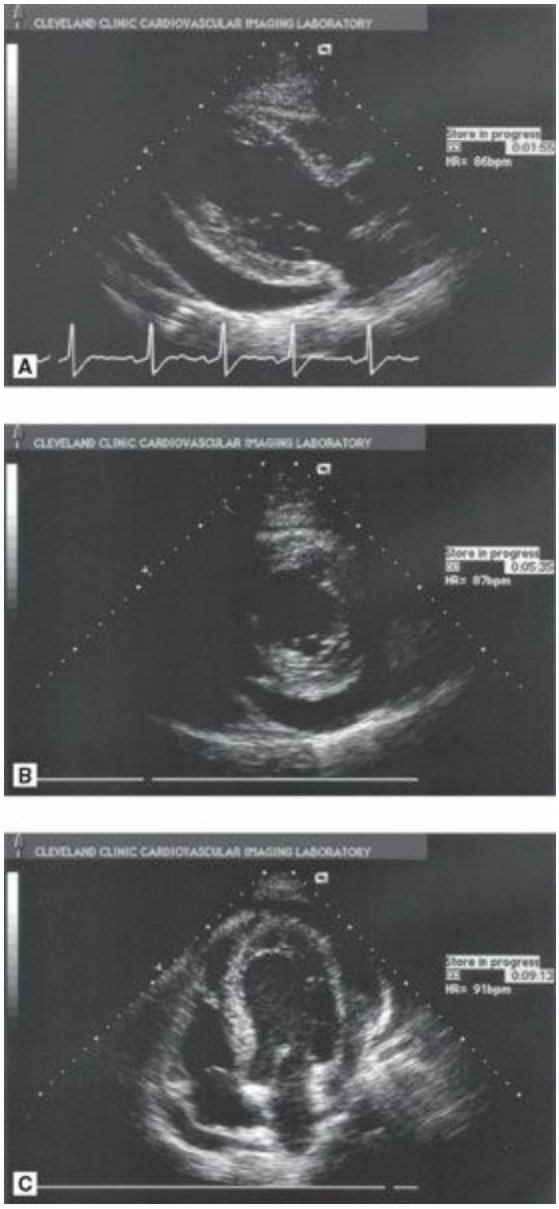
CLEVELAND CLINIC CARDIOVASCULAR IMAGING LABORATORY
Store in progress
HR= 86bpm
A
CLEVELAND CLINIC CARDIOVASCULAR IMAGING LABORATORY
Store in progress
HR= 87bpm
B
CLEVELAND CLINIC CARDIOVASCULAR IMAGING LABORATORY
Store in progress
HR= 91bpm
C

Figure 13.12

Figure 13.13 • (From Spodick DS. The Pericardium: A Comprehensive Textbook. New York: Marcel Dekker; 1997, with permission.)

22. A 71-year-old man presents to the hospital with palpitations of 2 to 3 days' duration. He has no known medical history, and he is not on any medications. Initial evaluation is unremarkable except for a BP of 160/90 mmHg and an ECG showing atrial fibrillation with a ventricular rate of 120 to 130 bpm. Given the duration of his symptoms, he is treated with β-blockers for rate control and heparin for anticoagulation. On hospital day 2, he is referred for early transesophageal-guided cardioversion. The TEE reveals normal LV and RV function. There are no echocardiographic contraindications for cardioversion. An uneventful cardioversion is performed, and the patient converts to NSR. On hospital day 3, the patient is found in marked respiratory distress. On physical examination, he has a regular HR with a loud audible click over the precordium. A CXR is performed, as shown in Figure 13.14. What does this patient have?

a. He has a pulmonary embolism and should be treated with thrombolytics.
b. He has a hiatal/diaphragmatic hernia with compression of the heart by the fundus of stomach.
c. He has an iatrogenic pneumohydropericardium; immediate drainage and surgical attention are needed.
d. He has a recurrence of atrial fibrillation.

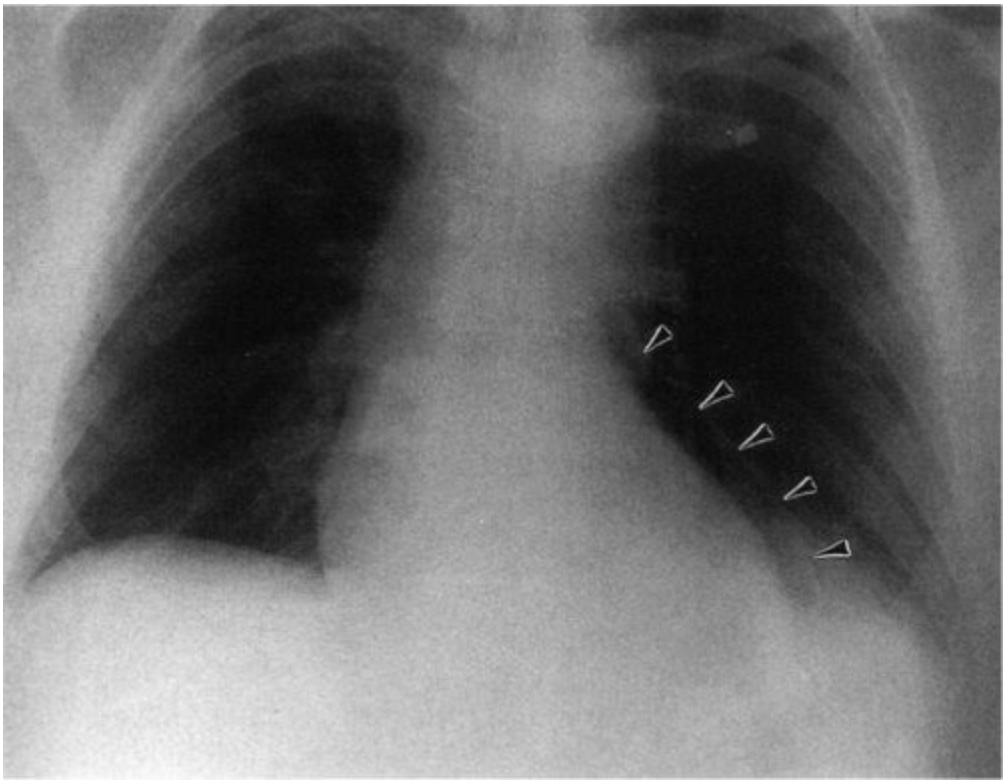

Figure 13.14 • (From Spodick DS. The Pericardium: A Comprehensive Textbook. New York: Marcel Dekker; 1997, with permission.)

23. A 59-year-old woman with a history of chronic renal insufficiency presents to the emergency department with anterior left-sided chest pain. She reports that the chest pain started after her last dialysis 7 days ago. She appears lethargic and in mild respiratory distress. The physical examination demonstrates a BP of 160/90 mmHg and an HR of 100 bpm. On cardiac auscultation, a loud friction rub is heard. An ECG is obtained (Fig. 13.15). What is the most important next step in this case?

a. Perform emergency dialysis.
b. Obtain an echocardiogram.
c. Prepare for pericardiocentesis.
d. Admit the patient to the cardiac care unit to rule out MI.

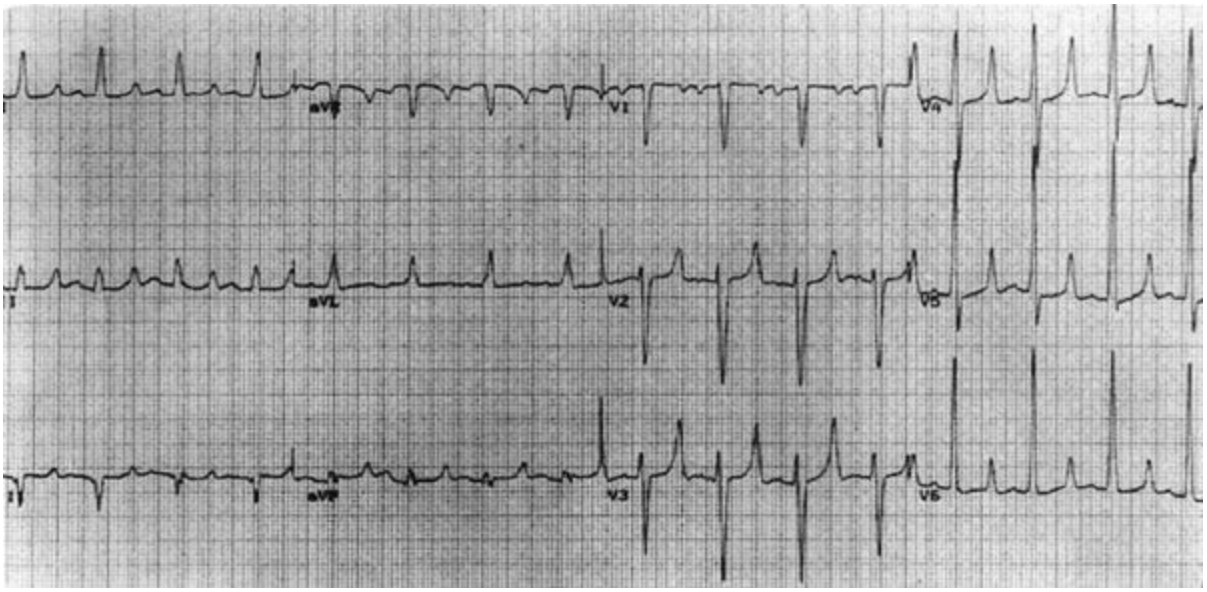

Figure 13.15 • (From Spodick DS. The Pericardium: A Comprehensive Textbook. New York: Marcel Dekker; 1997, with permission.)

24. A 29-year-old woman with known insulin-dependent diabetes mellitus was found unconscious 1 hour after an office party. Initial assessment by the emergency medical service team showed a BP of 90/60 mm Hg. Her pulse was 120, and her blood sugar was 870 mg/dL. She was given SC insulin and rushed to the emergency department. You are called to see her because of her abnormal ECG (Fig. 13.16). She is noted to be semiconscious. The emergency physician has already started her on IV insulin drip and hydration. What is your recommendation at this juncture?

a. She is having an acute MI, and immediate restoration of coronary flow is essential.
b. She has ECG evidence of hyperkalemia, and she needs IV calcium and, possibly, dialysis.
c. Continue the current management; the ECG will improve with the resolution of ketoacidosis.
d. Her ECG predicts high-degree atrioventricular block; a standby external pacemaker should be available.

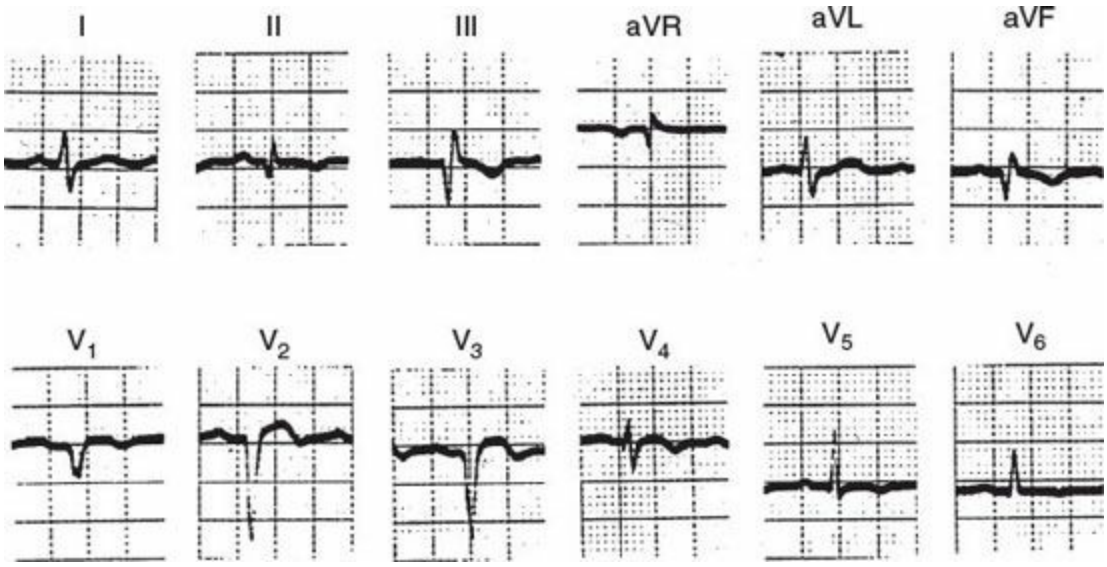

Figure 13.16 • (From Spodick DS. The Pericardium: A Comprehensive Textbook. New York: Marcel Dekker; 1997, with permission.)

25. Which of the following is the most common neoplastic pericardial tumor in adults?

a. Neuroma
b. Hemangioma
c. Mesothelioma
d. Teratoma

ANSWERS

1. **a.** Presence of an ASD. The presence of the iatrogenic ASD after the transseptal puncture for the radiofrequency ablation/pulmonary vein isolation procedure equates right atrial (RA) and left atrial (LA) pressures with inspiration. The predicted decrease in LV filling during inspiration due to interventricular dependence and exaggerated RV filling and septal shift toward the LV is mitigated by the presence of an ASD. With inspiration, the decrease in intrathoracic pressure is transmitted to both atria and thus preload to the LV is maintained and interventricular dependence is not as pronounced. Thus, the variation in systolic blood pressure is not as prominent, resulting in minimal to no pulsus paradoxus. Administration of excess fluid would stave off circulatory collapse in tamponade; however, it would not diminish the pulsus. Answer b is incorrect as with severe LV dysfunction, patients can have a pulsus alternans (variation in peak systolic pressure with every other beat) and Answer c is incorrect as obstructive lung disease can lead to the presence of a pulsus due to exaggerated inspiratory effort and negative intrathoracic pressure.

2. **a.** Ibuprofen 600 TID for 2 weeks followed by taper and colchicine 0.5 mg BID for 3 months. The patient presents with an initial attack of acute pericarditis without any high-risk features (small effusion, negative troponin, no fever/trauma, or anticoagulant use). The appropriate regimen in this case would be an NSAID (ibuprofen 600 to 800 mg TID or indomethacin 50 mg TID) for a course of 1 to 2 weeks with physician follow-up. In addition, the use of colchicine has been studied in two trials with improvement in symptom resolution and maintenance of remission at a dose of 0.5 mg (daily for <70 kg; BID for >70 kg) for a fixed period of 3 months.

   Aspirin and colchicine can be used together; however, the dosing is incorrect for Answer b (650 to 1,000 mg TID) and the colchicine should still be continued for 3 months. Prophylactic Proton-pump inhibitor (PPI) should be utilized during the high-dose NSAID use to prevent gastric ulcer. Answer c is incorrect (dosing of ibuprofen is incorrect). Answer d is incorrect since steroid therapy is only reserved for patients with NSAID or acetylsalicylic acid (ASA) contraindication or patients having relapsing pericarditis that is refractory to NSAID/ASA therapy.

3. **a.** Aspirin 650 TID for 2 weeks with taper to 81 mg daily + colchicine 0.5 mg BID for 3 months. The patient has postinfarction pericarditis with a typical presentation after reperfusion for late-presenting MI. Although not as frequent, postinfarction pericarditis (Dressler syndrome) is still seen in a small percentage of patients after large MI, and cardiac/pericardial trauma. The regimen used in these patients is modified to include aspirin (instead of NSAIDs) for two reasons: (a) aspirin is required for patients with CAD, with or without recent stenting; and (b) NSAIDs are postulated to impair scar formation and wound healing after an MI. Colchicine is still part of the regimen despite the recent MI and helps with symptom resolution. Correct answer is a—with high-dose aspirin initially with gradual taper once symptoms improve. The clopidogrel is continued despite high doses of aspirin, due to the placement of a recent intracoronary stent.

4. **a.** Initiate steroid therapy (0.25 to 0.5 mg/kg/day) along with colchicine, and initiate PO diuretic. The patient had acute pericarditis, which transformed into a chronic effusive constrictive pericarditis. There is evidence of therapy failure (persistent symptoms and elevated biomarkers) and ongoing inflammation, leading to symptomatic constrictive pericarditis with increasing hemodynamic significance (as demonstrated by symptoms/physical examination and echo findings). The next step would be to escalate anti-inflammatory therapy to include glucocorticoids (prednisone) to help abate the ongoing symptoms and pericardial inflammation. Glucocorticoids are generally not first-line therapy since patients who receive them early in the course of the disease process are more likely to have relapsing

pericarditis and eventually develop constrictive pericarditis. In the case of this patient, he does not have any other treatment options due to his NSAID allergy, so steroids should be initiated at a low dose and maintained with very gradual taper (weeks to months) that involves assessment of his symptoms, biomarker trend (ESR/hsCRP), as well as MRI findings to assess for inflammation/edema within the pericardium to help quell the disease process.

Admission for IV diuresis is not necessary as the patient has not proven resistance to PO diuretics and although a cardiac catheterization may be required alternative noninvasive diagnostic modalities should be performed prior to catheterization to make the diagnosis. Answer c is incorrect since the patient has demonstrated treatment failure with progression of symptoms in the interim. Answer d is incorrect as medical therapy options (steroids, diuresis) are still available. Pericardiectomy is generally reserved in medically refractory cases.

5. **a.** Tuberculous pericarditis. The patient presents with acute tuberculous pericarditis with large exudative effusion. Indolence of the effusion is likely over months; however, the salient findings in the fluid analysis are the elevated interferon gamma, ADA, and normal peripheral white blood cell count with pericardial lymphocyte predominance. The presence of interferon gamma elevation had a 92% sensitivity, 100% specificity, and 100% positive predictive value for tuberculous pericarditis. ADA was also linked to tuberculous pericarditis; however, it was not as sensitive or specific (87%/92%).

Although Answers b and c are epidemiologically possible, the fluid analysis is not suggestive of either. Pericardial biopsy (Answer d) is incorrect as tuberculous pericarditis can be defined by the interferon gamma and ADA elevation. Also Acid-Fast Bacilli (AFB) staining will reveal AFB + organisms confirming diagnosis. Biopsy should be reserved for patients with unrevealing fluid analysis who are still symptomatic and require further diagnostic testing to make a diagnosis.

6. **a.** Annulus reversus refers to reversal of septal and lateral mitral tissue Doppler velocities (E' septal > E' lateral) and annulus paradoxus refers to inverse correlation of E/E' and LV end-diastolic pressure. The annulus reversus phenomenon describes a reversal of mitral lateral and septal tissue Doppler velocity. Normally, E' lateral > E' septal; however, in constrictive pericarditis it is postulated that tethering of the free wall prevents longitudinal motion of the annulus at the lateral border, thus decreasing the lateral E' and the septal E' concurrently is mildly exaggerated.

The annulus paradoxus phenomenon was initially described after data looking at the correlation between the E/E' ratio and pulmonary capillary wedge pressure

were established. In a small subset of patients with constrictive pericarditis, inversion of the correlation between E/E' and PCWP was noted, and named annulus paradoxus.

7. **a.** Lack of preload due to overdiuresis. Volume loading is required to elucidate the diagnostic findings described above. Constrictive pericarditis is a preload-dependent condition and with overdiuresis and low central venous pressure, the hemodynamic findings of elevated and equal end-diastolic ventricular pressure waveforms as well as respiratory discordance of the LV/RV waveforms are not seen. Often in these cases, the patient is given a bolus of 1 to 2 L of normal saline to increase the RA pressure >12 to 15 mmHg and the study is performed once they are adequately volume loaded. Of note, in cases of atrial fibrillation, the patient may require a temporary venous pacemaker to regularize the rhythm for analysis purposes.

8. **c.** Reassure the patient and observe him over the next 3 months for worsening of symptoms. The natural history of acute viral or idiopathic pericarditis is usually short and self-limited. Occasionally, mild forms of constriction may develop weeks after the initial event, but they usually resolve without any specific treatment. No further treatment is indicated unless he becomes more symptomatic or develops signs of cardiac tamponade.

9. **c.** Give a nonsteroidal anti-inflammatory medication. The clinical presentation of a few days of severe chest pain does not favor an acute MI. Furthermore, the ECG tracing supports the diagnosis of pericarditis. Therefore, cardiac catheterization and thrombolytics are not appropriate. The only reasonable answer is to start the patient on anti-inflammatory medications and obtain a TTE to rule out pericardial effusion.

10. **a.** Constrictive pericardial disease. This patient did not have evidence of ischemia on a recent stress test. Furthermore, there is no evidence of obstructive disease in his coronaries or grafts. His tracings mostly support the diagnosis of constriction, given the diastolic equalization of pressures in the cardiac chambers and the typical square root sign. Amyloidosis would typically show signs of restrictive hemodynamics with no respiratory variation. Echocardiography typically shows increased LV wall thickness. Additionally, a diagnosis of tamponade should have been evident by echocardiography, which the patient had before heart catheterization. Otherwise, hemodynamic tracings of cardiac tamponade would look exactly the same as for constriction.

11. **b.** This patient has significant diastolic dysfunction, and his prognosis is guarded. He has evidence of restrictive LV filling (advanced diastolic dysfunction) in the absence of CAD. The differential diagnosis in his age group includes amyloidosis (especially considering concomitant renal dysfunction), hemochromatosis, and other infiltrative processes.

12. **c.** His symptoms are related to impairment of RV filling and pericardial disease. This patient with the main presentation of dyspnea has an increased cardiac silhouette. The nuclear image provided shows a circumferential echolucency surrounding the heart. This is consistent with a large pericardial effusion, and he most likely has RA and RV diastolic compromise. There is no evidence of a perfusion defect to suggest ischemia.

13. **c.** He is showing signs of early postinfarction pericarditis, and a nonsteroidal anti-inflammatory medication should be started. This patient had an MI 72 hours ago that was successfully treated with thrombolytics. The ECG shows diffuse ST elevation with PR depression. These findings support the diagnosis of post-MI pericarditis. The ECG changes are new and nonlocalizing. Most patients improve with nonsteroidal anti-inflammatory medications.

14. **a.** He has a pericardial cyst that is benign; no further treatment should be offered. The TTE and CXR show a pericardial cyst. Pericardial cysts are usually smooth structures containing transudative fluid. They are frequently only 2 or 3 cm in diameter, often located at the right cardiodiaphragmatic angle, and clinically silent. However, cysts can be associated with chest pain, dyspnea, cough, and arrhythmias likely caused by compression of adjacent tissues. They can also become secondarily infected. In this patient, whose nonspecific symptoms appear to be resolving, no further treatment is needed.

15. **a.** The patient should have immediate surgical intervention. This patient has evidence of acute type A aortic dissection with extension to the pericardium, as evidenced by the pericardial effusion on the TEE. He should be immediately referred for surgical repair. If the diagnosis were not certain based on the TEE, then CT, MRI, or aortic angiography would be needed to better define the anatomy. The safest and most efficient management of patients with aortic dissection is to carry out all diagnostic procedures in the operating room. Pericardial drainage often gives only temporary relief or no relief of the tamponade, and the subsequent increase in BP disrupts sealing clots, accelerating intrapericardial leakage.

16. **a.** Immediate surgical exploration of the pericardium. The TTE and TEE

demonstrate a pericardial hematoma compromising RA and RV filling. This is an indication for surgical exploration and evacuation of the hematoma.

17. **b.** IV hydration. This patient has evidence of pericarditis likely related to uremia, as he is close to requiring dialysis. Although his TTE shows signs of tamponade (RA collapse, moderate-sized effusion, and respiratory variation across the mitral inflow), there is no jugular venous distention, and the inferior vena cava is small sized, indicating that this patient has been overdiuresed. His hypotension and tachycardia are related to dehydration. He should, therefore, be treated with IV hydration.

18. **b.** Admit the patient for observation on telemetry with a follow-up TTE. The ECG shows findings consistent with an anterior wall injury, and the TTE shows a small pericardial effusion. Given this patient's history, he most likely has a cardiac contusion. Although the prognosis for recovery is generally excellent, these patients require careful monitoring and follow-up for late complications, which range from ventricular arrhythmias to cardiac rupture. Hence, the most logical answer to this question is to admit the patient to a telemetry bed with follow-up TTE.

19. **d.** Proceeding with chemotherapy without further cardiac evaluation. This patient's MRI shows congenital absence of the pericardium. This is a benign condition usually found incidentally. No specific cardiac treatment is needed unless there is entrapment of one of the cardiac chambers.

20. **d.** A surgical evaluation for pericardiectomy is necessary because the findings on his TTE indicate that he will develop problems in the future if this is not taken care of soon. The patient is currently symptomatic with edema of the lower extremities. Furthermore, he has a pericardial friction rub suggestive of an active pericardial process likely related to his rheumatologic disease process. He is already on methotrexate and prednisone as anti-inflammatory medications. Pericardial effusions related to rheumatoid arthritis often progress to constriction despite anti-inflammatory therapy, and early management consisting of pericardial stripping is recommended.

21. **b.** Immediate pericardiocentesis. The next step is an immediate pericardiocentesis. This patient has signs of early sepsis. Furthermore, the CXR shows pneumopericardium that likely developed secondary to gastric perforation from the esophagogastroduodenoscopy and cauterization of the ulcer. This patient needs immediate referral to surgery for repair.

22. **c.** He has an iatrogenic pneumohydropericardium; immediate drainage and surgical attention are needed. This patient had a TEE that most likely resulted in an esophageal tear with communication to the pericardial sac. On the CXR, there is a lucent triangle outlining the pericardium with pericardial passage over the aortic arch.

23. **a.** Perform emergency dialysis. This patient has missed her dialysis session and is now presenting with hyperkalemia (note peaked T waves on ECG) and uremic pericarditis. The most essential step is to start dialysis to treat the hyperkalemia.

24. **c.** Continue the current management; the ECG will improve with the resolution of ketoacidosis. Patients presenting with diabetic ketoacidosis can have ECG features that are typical of stage I pericarditis and hypokalemia. The treatment is usually that of ketoacidosis. The ECG returns to normal after resolution of the acidosis.

25. **c.** Mesothelioma. Teratoma is the most common pericardial tumor in infancy and childhood. Neuroma and hemangioma are uncommon enough to be considered curiosities.

SUGGESTED READINGS

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Cardiac Imaging

Ellen Mayer Sabik • Brian P. Griffin

QUESTIONS

1. The three-dimensional (3D) transesophageal echocardiographic (TEE) image in Figure 14.1 demonstrates a patient with
   a. normally functioning bioprosthetic mitral valve replacement (MVR).
   b. normally functioning bileaflet mechanical MVR.
   c. mitral valve (MV) endocarditis with a vegetation.
   d. abnormal mechanical MVR.
   e. abnormal bioprosthetic MVR.

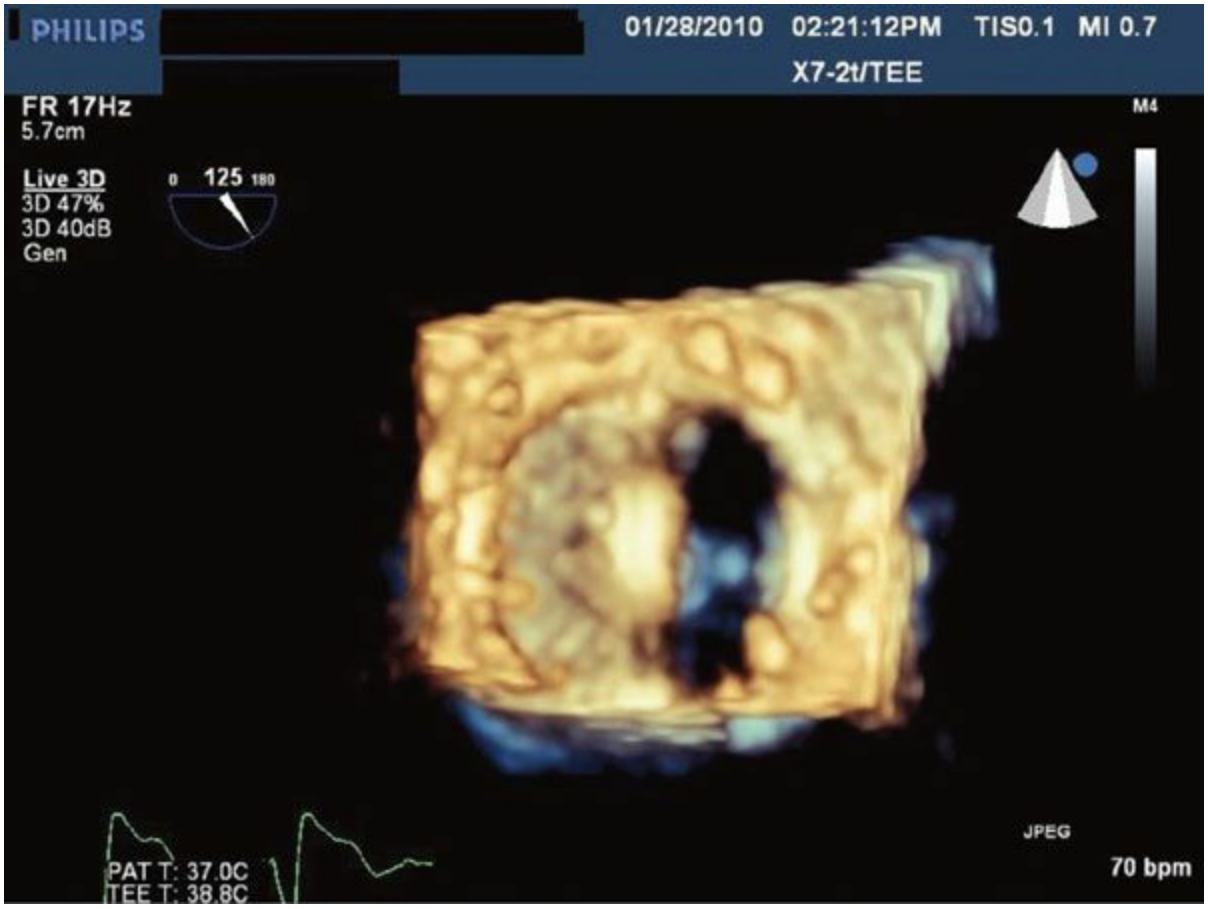
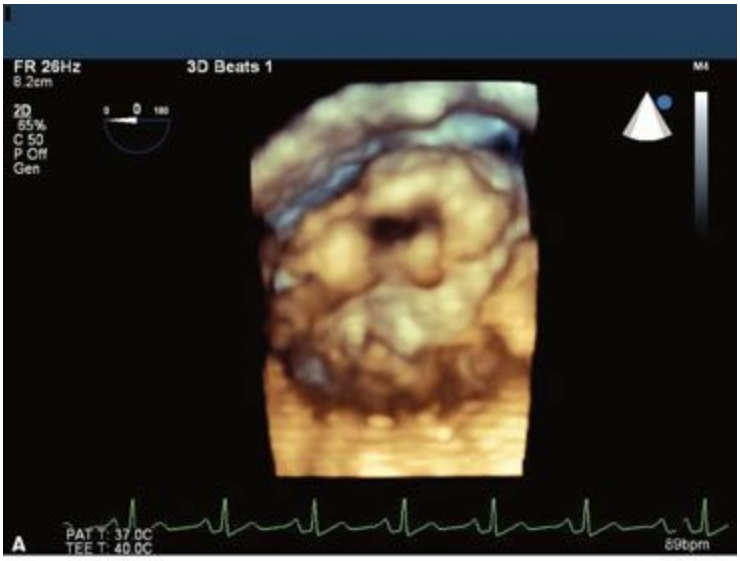


Figure 14.1

2. The images in Figure 14.2A–E come from an 18-year-old young man with marked shortness of breath (SOB). The most appropriate course of action would be

   a. closed mitral commissurotomy because he has a split score of 0 to 4 and minimal mitral regurgitation (MR).
   b. percutaneous mitral valvuloplasty (PMV) because he has a split score of 4 to 8 and minimal MR.
   c. surgical MVR because he has a split score of 8 to 12 and minimal MR.
   d. surgical MVR because he has a split score of 0 to 4 with significant MR.
   e. surgical MVR because he has a split score of 4 to 8 and significant MR.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M4
2D
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C 50
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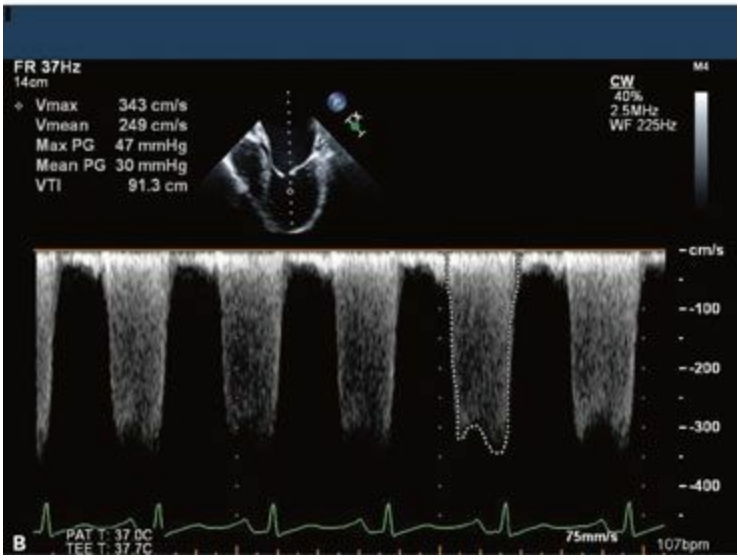
Gen
PAT T: 37.0C
TEE T: 40.0C
89bpm
A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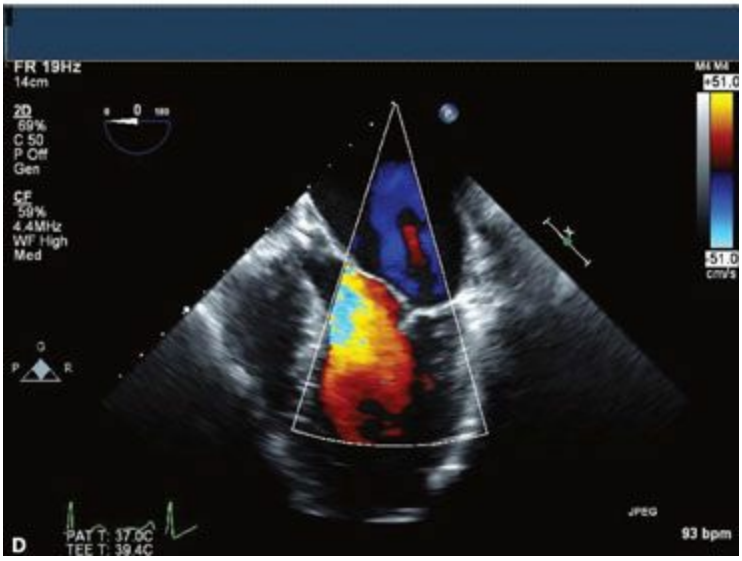
Vmean 249 cm/s
Max PG 47 mmHg
Mean PG 30 mmHg
VTI 91.3 cm
CW
40%
2.5MHz
WF 225Hz
cm/s
-100
-200
-300
-400
PAT T: 37.0C
TEE T: 37.7C
75mm/s
107bpm
B

FR 37Hz
14cm
2D
66%
C 50
P Off
Gen
M4
JPEG
115 bpm
C
PAT T: 37.0C
TEE T< 37.0C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C 50
P Off
Gen
CF
59%
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PAT T: 37.0C
TEE T: 39.4C

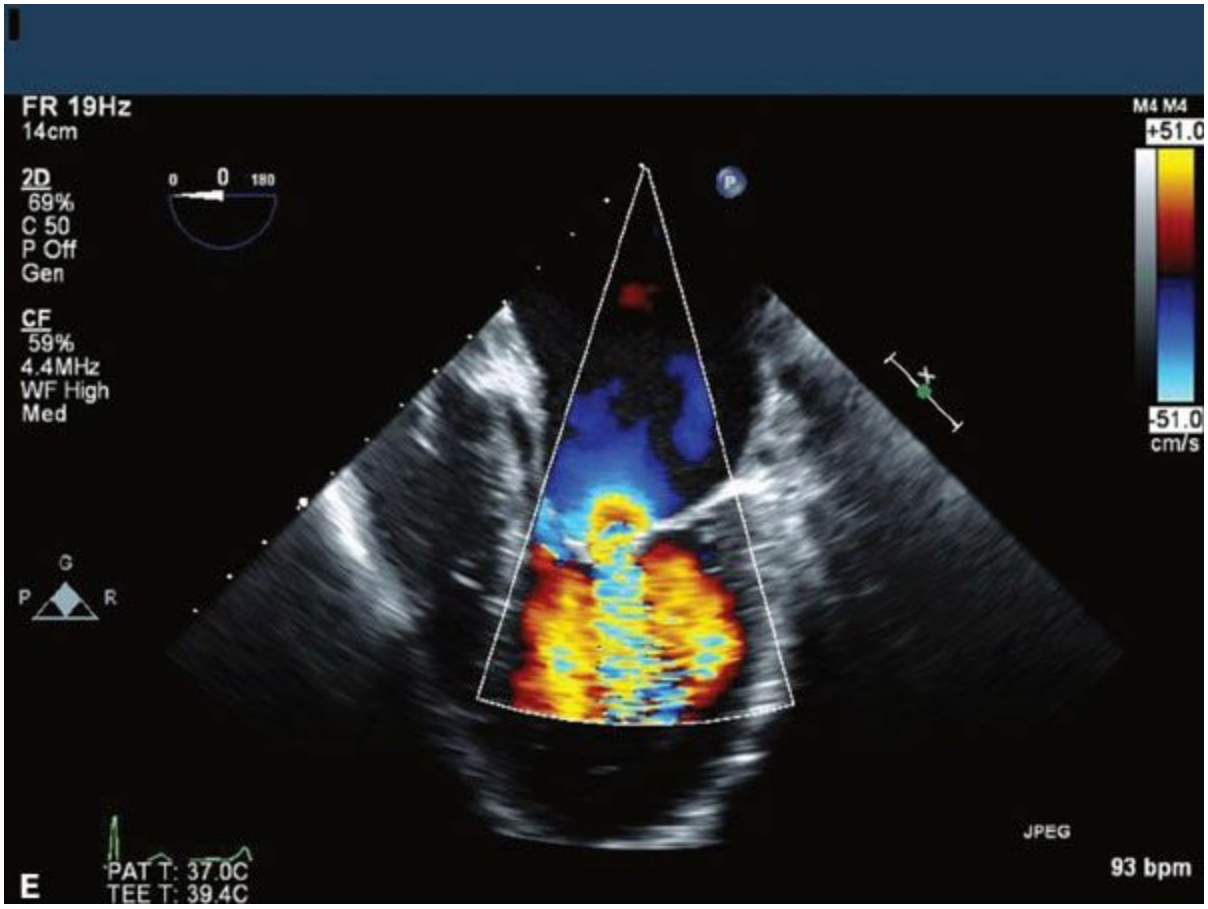


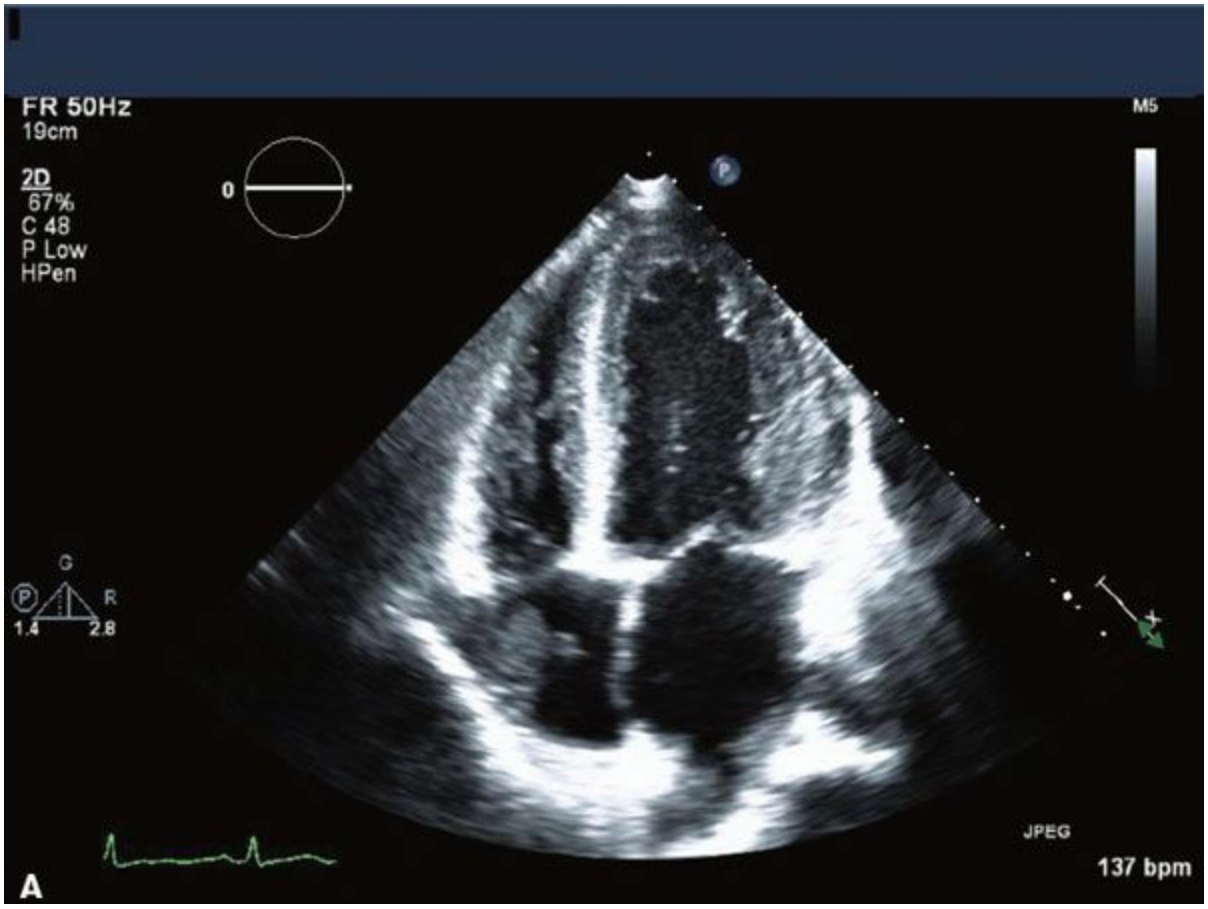
Figure 14.2

3. The images in Figure 14.3A–C belong to a 65-year-old woman with lung cancer and a central venous catheter for chemotherapy. The structure seen on these images is most likely to be

   a. prominent Chiari network.
   b. implantable cardioverter-defibrillator (ICD) wire.
   c. right atrial (RA) thrombus or thrombus on central venous catheter.
   d. RA myxoma.

4. The images in Figure 14.4A and B are associated with which of the following?

   a. Moderate risk of endocarditis
   b. No risk of heart failure
   c. Large jugular venous v waves
   d. Radiofemoral delay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2D
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C 48
P Low
HPen
0
M5
G
P
R
1.4
2.8
JPEG
137 bpm
A

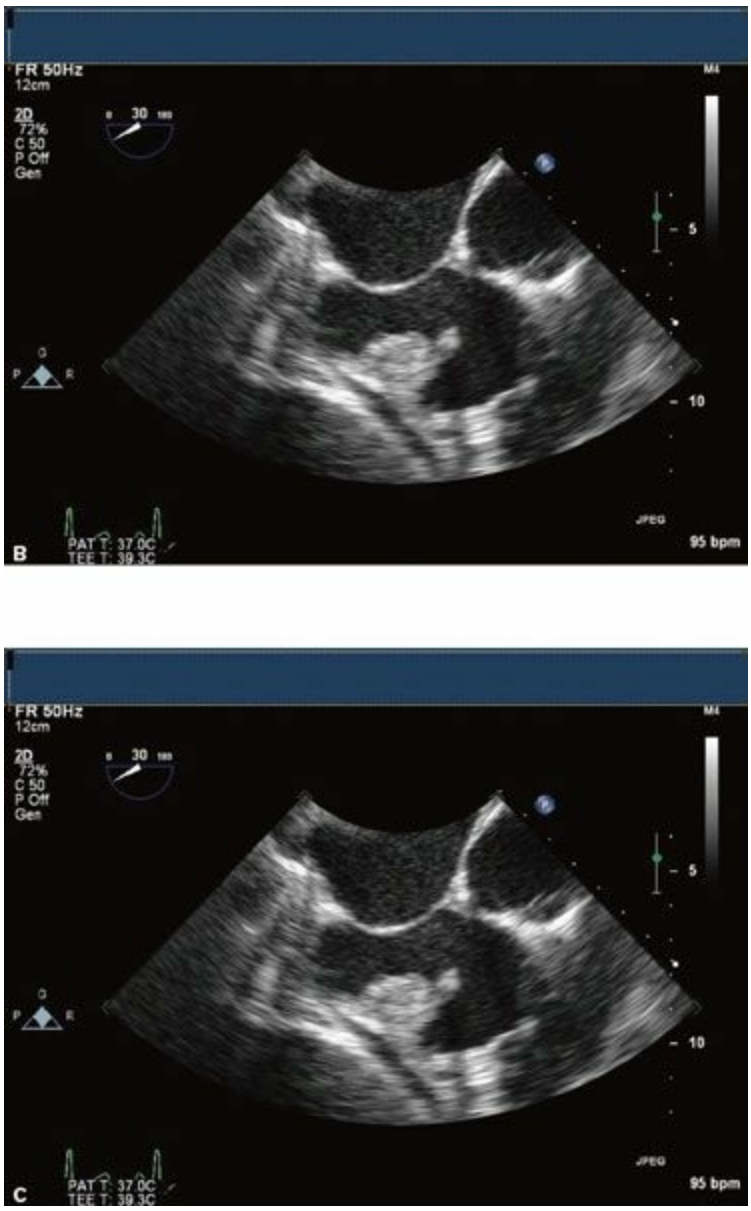


Figure 14.3

5. The images in Figure 14.5A–C are from a 43-year-old s/p carpentier edwards aortic valve replacement (CE AVR) with fevers and night sweats. These images demonstrate all of the following except

   a. paravalvular abscess.
   b. fistula.
   c. aortic stenosis (AS).
   d. aortic insufficiency (AI).
   e. vegetations.

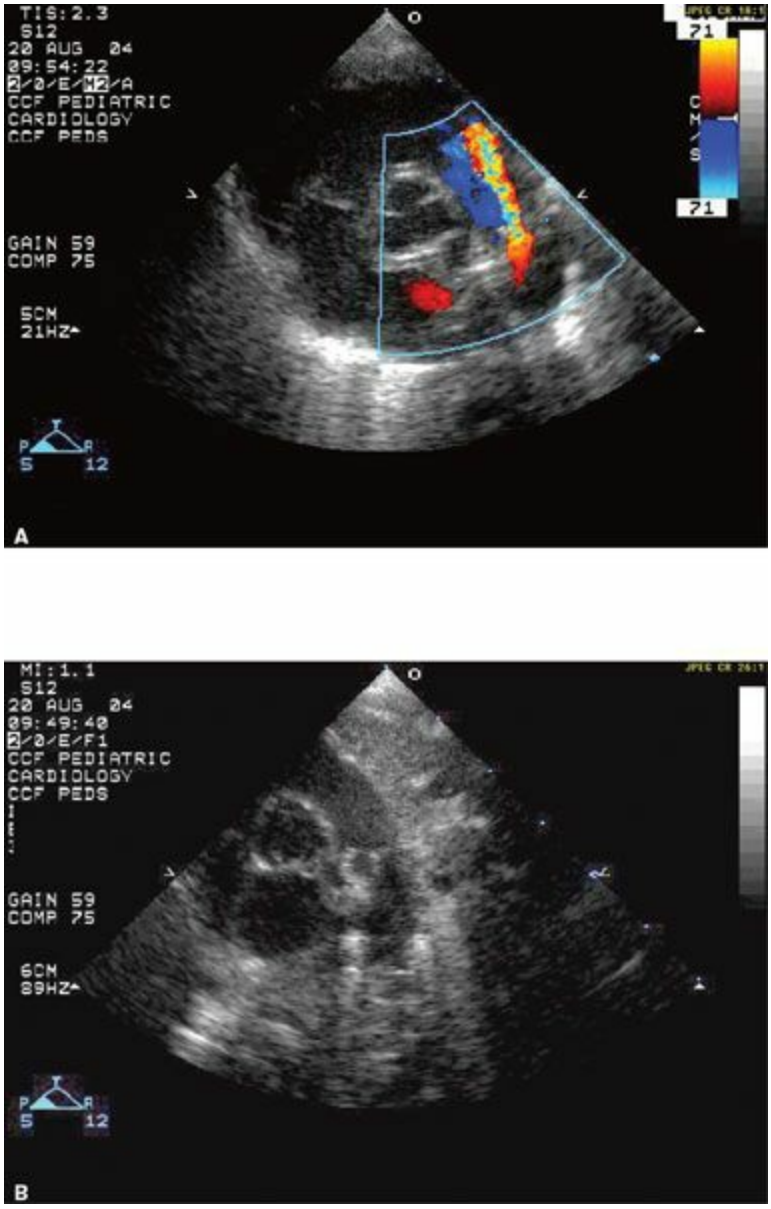
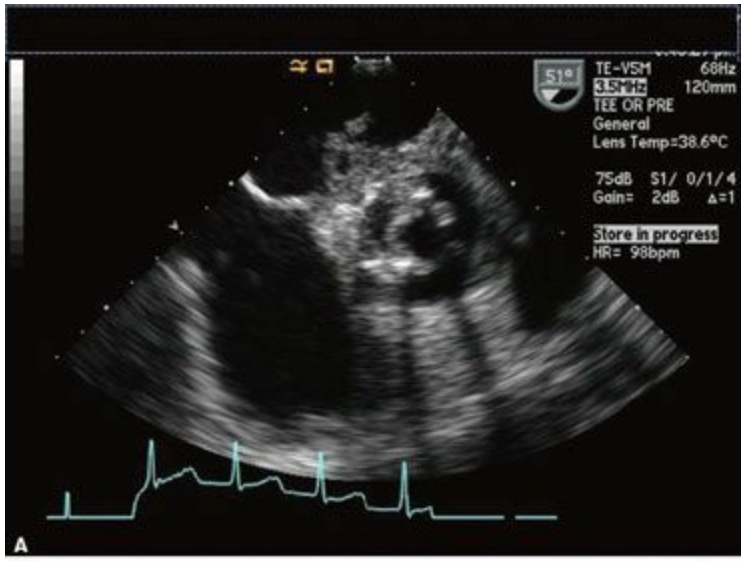


Figure 14.4

6. The images in Figure 14.6A and B are from a transthoracic echocardiogram (TTE) from a patient who is a 57-year-old woman with lung cancer who presents with chest pain (CP) and SOB. The most likely cause of her CP and SOB based on these images is

   a. myocardial infarction (MI).
   b. aortic dissection.
   c. pericardial effusion with pericarditis/tamponade.
   d. pulmonary embolus.
   e. pneumonia.


51°
TE-V5M 68Hz
3.5MHz 120mm
TEE OR PRE
General
Lens Temp=38.6°C
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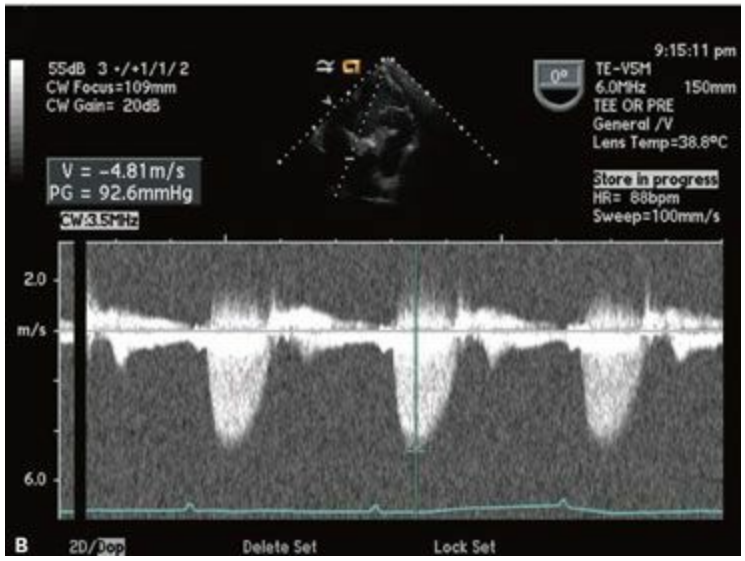
Gain= 2dB Δ=1
Store in progress
HR= 98bpm
A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PG = 92.6mmHg
CW:3.5MHz
9:15:11 pm
0°
TE-V5M
6.0MHz 150mm
TEE OR PRE
General /V
Lens Temp=38.8°C
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2.0
m/s
6.0
B
2D/Dop
Delete Set
Lock Set

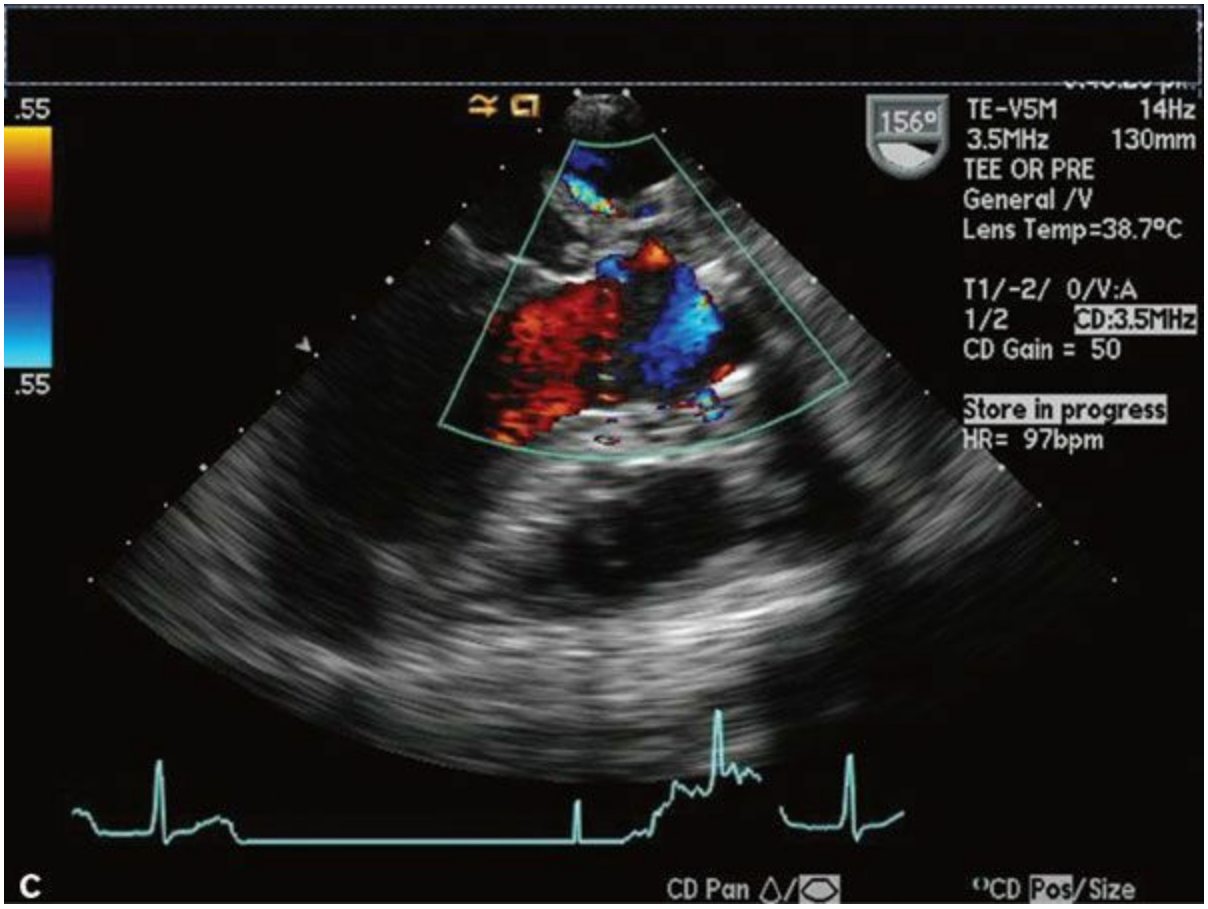
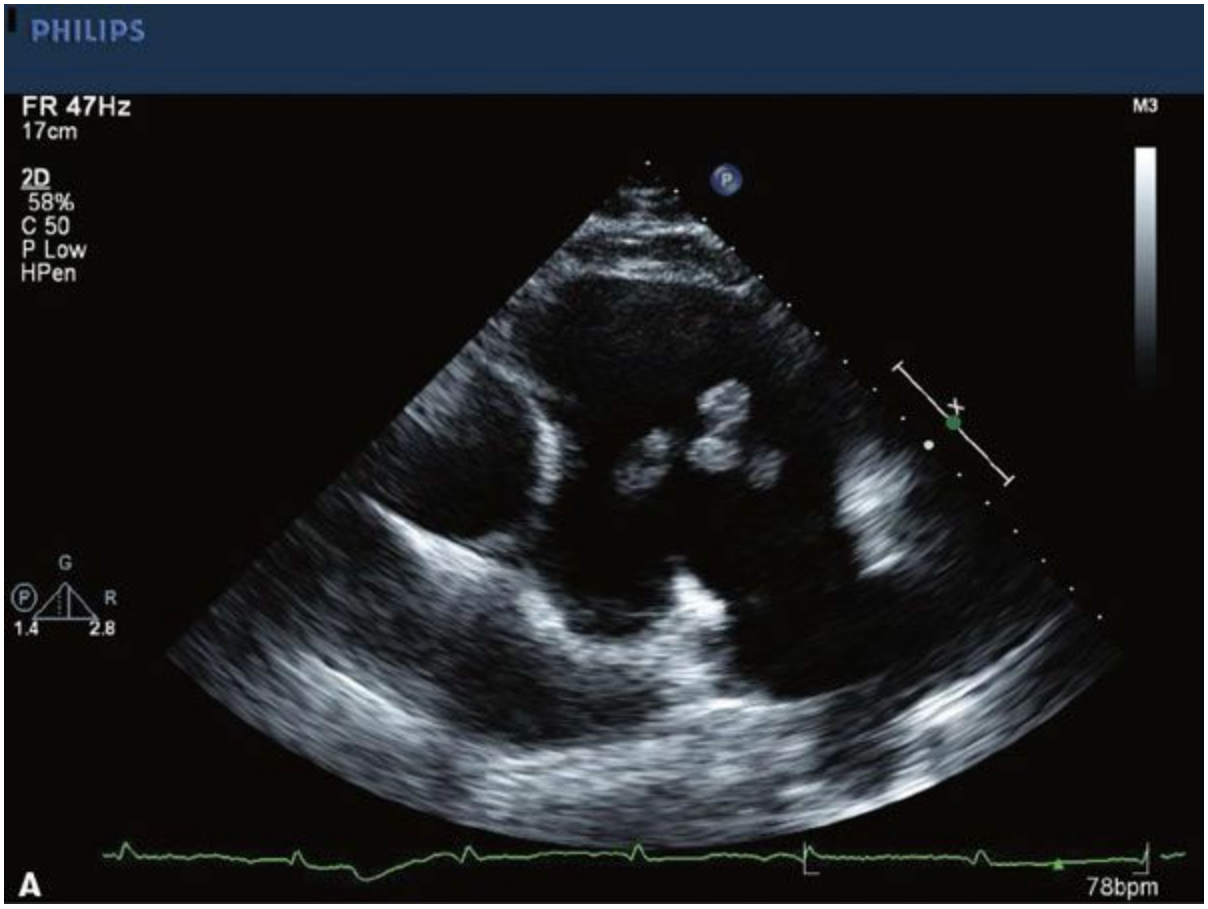


Figure 14.5

7. The patient is a 70-year-old woman with a history of hypertension, but no prior cardiac history, who comes in with sudden onset of CP, which later migrates to her back. She is diagnosed with a computed tomography (CT) of her chest to have a type I aortic dissection. Her blood pressure is 100/70 mmHg and her heart rate is 115 bpm. Images from her TTE are in Figures 14.7A–C. The next step in her care would be

   a. aortic stent graft.
   b. coronary angiography.
   c. intraaortic balloon pump placement.
   d. pericardiocentesis.
   e. emergent cardiac surgery.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FR 47Hz
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2D
58%
C 50
P Low
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G
R
1.4
2.8
78bpm
A

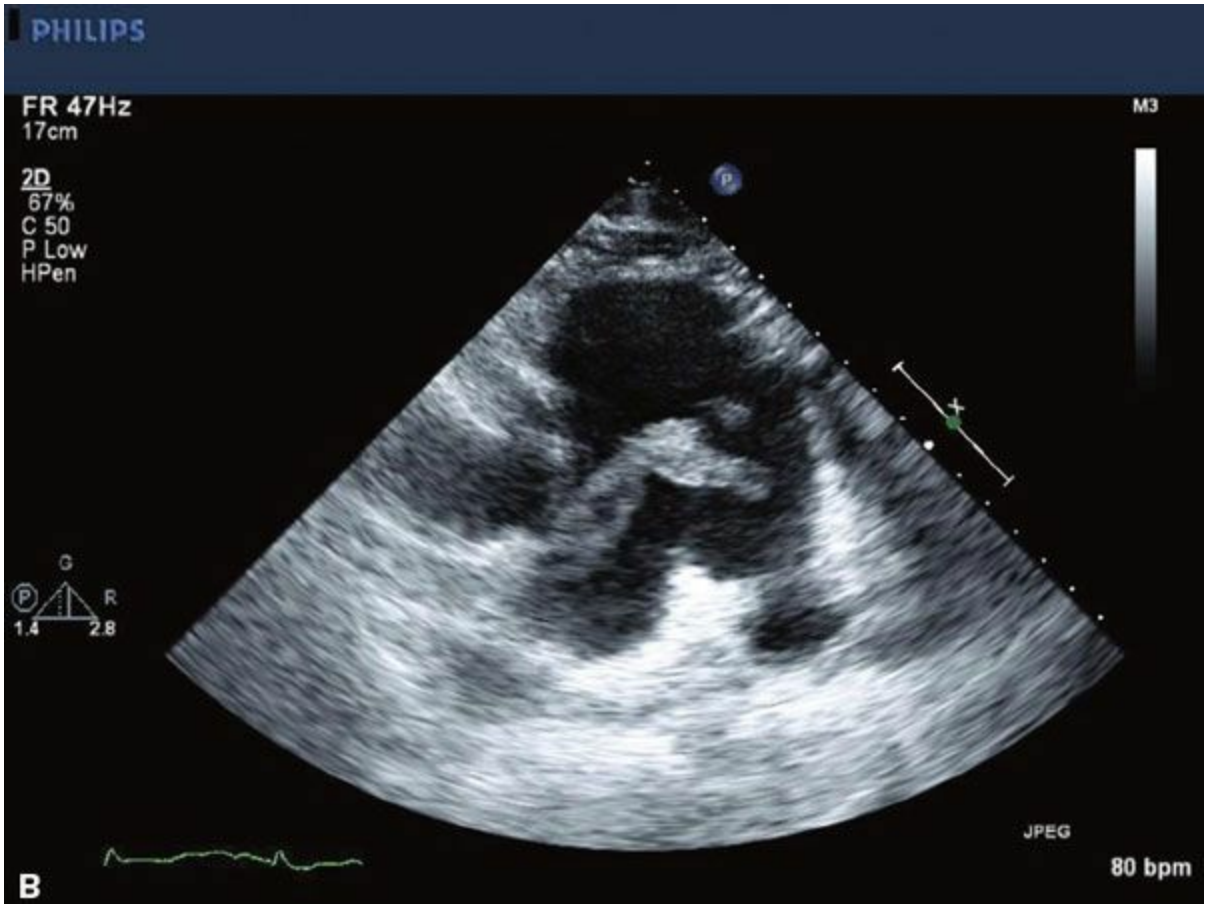

PHILIPS
FR 47Hz
17cm
2D
67%
C 50
P Low
HPen
M3
G
R
1.4
2.8
JPEG
80 bpm
B

Figure 14.6

8. The finding in the transthoracic images in Figure 14.8A and B is commonly associated with which of the following lesions?

   a. Congenitally corrected transposition
   b. Cleft MV
   c. Coarctation of the aorta
   d. Right ventricular (RV) infarction
   e. Bicuspid aortic valve (AV)

9. A 36-year-old man with a history of hypertension on medications for 5 years presents to your office with complaints of dyspnea on exertion and is found by his internist to have a heart murmur. Below are some representative views from his TTE (Fig. 14.9A–E). What is the diagnosis?

   a. Patent ductus arteriosus (PDA)
   b. Rheumatic AV with AI
   c. Rheumatic AS
   d. Coarctation of the aorta with bicuspid AV with AI
   e. Marfan's with aortic dissection

10. A 37-year-old patient presents with fever, weight loss, and blood cultures that are positive for Pseudomonas and the transthoracic echo finding in Figure 14.10. The patient's most likely demographic for this clinical scenario is

   a. patient with hypertrophic obstructive cardiomyopathy (HOCM) who had a dental procedure 3 weeks ago.
   b. patient with myxomatous MV disease with mitral valve prolapse (MVP).
   c. patient with subaortic stenosis after dental procedure 3 weeks ago.
   d. patient with a patent ductus.
   e. intravenous (IV) drug abuser.

11. This M-mode tracing (Fig. 14.11) demonstrates a patient with

   a. HOCM with systolic anterior motion (SAM) of the MV leaflets.
   b. MVP.
   c. AS.
   d. rheumatic mitral stenosis (MS).
   e. severe left ventricular (LV) dysfunction.

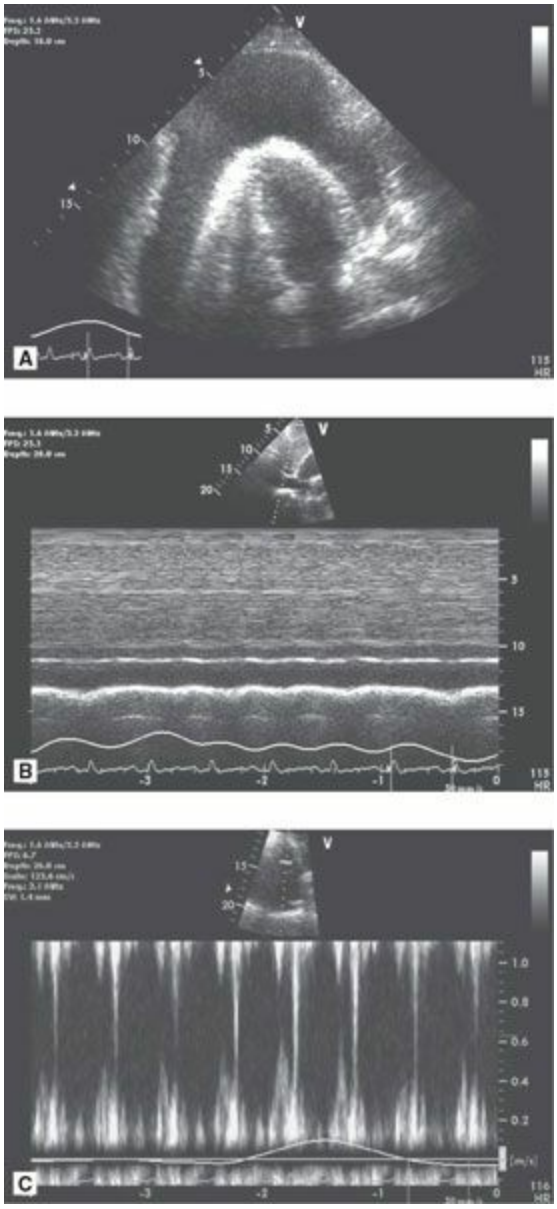


Figure 14.7 • **A.** Apical four-chamber view (TTE). **B.** M-mode through the IVC in the subcostal view (TTE). **C.** Continuous-wave Doppler through the mitral valve showing mitral valve inflow pattern.

12. The following TEE image (Fig. 14.12) demonstrates a patient with

a. trileaflet AV.
b. bicuspid AV with fusion of right coronary cusp (RCC) and noncoronary cusp (NCC).
c. bicuspid AV with fusion of RCC and LCC.
d. bicuspid AV with fusion of left coronary cusp (LCC) and NCC.
e. unicuspid AV.

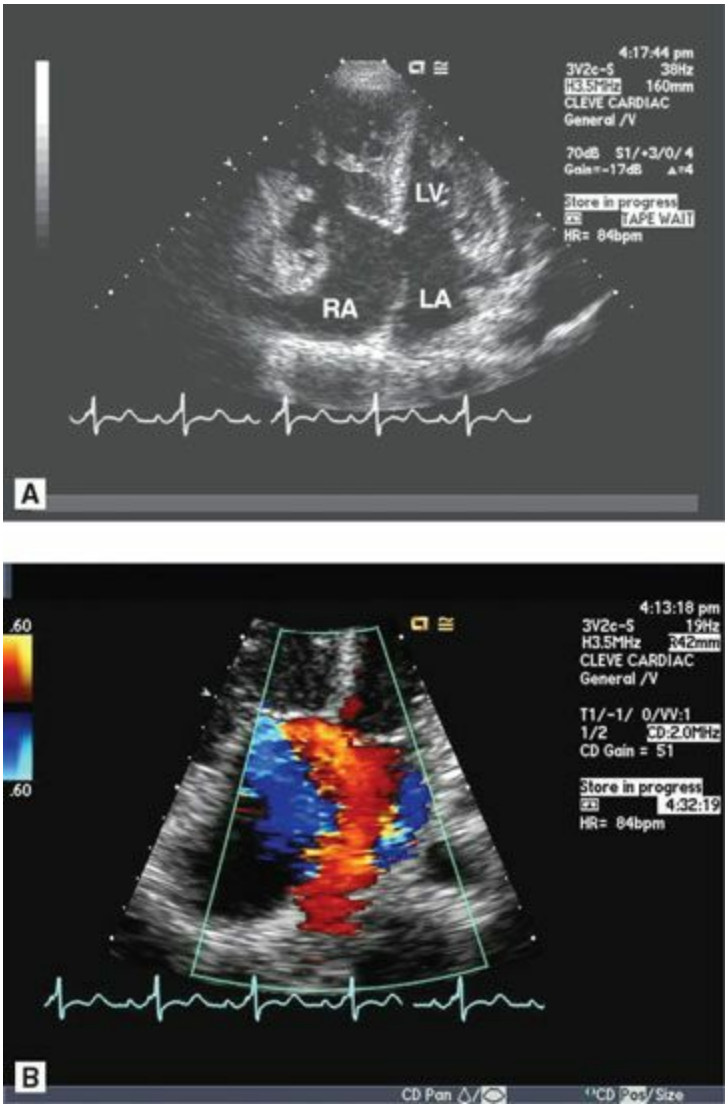
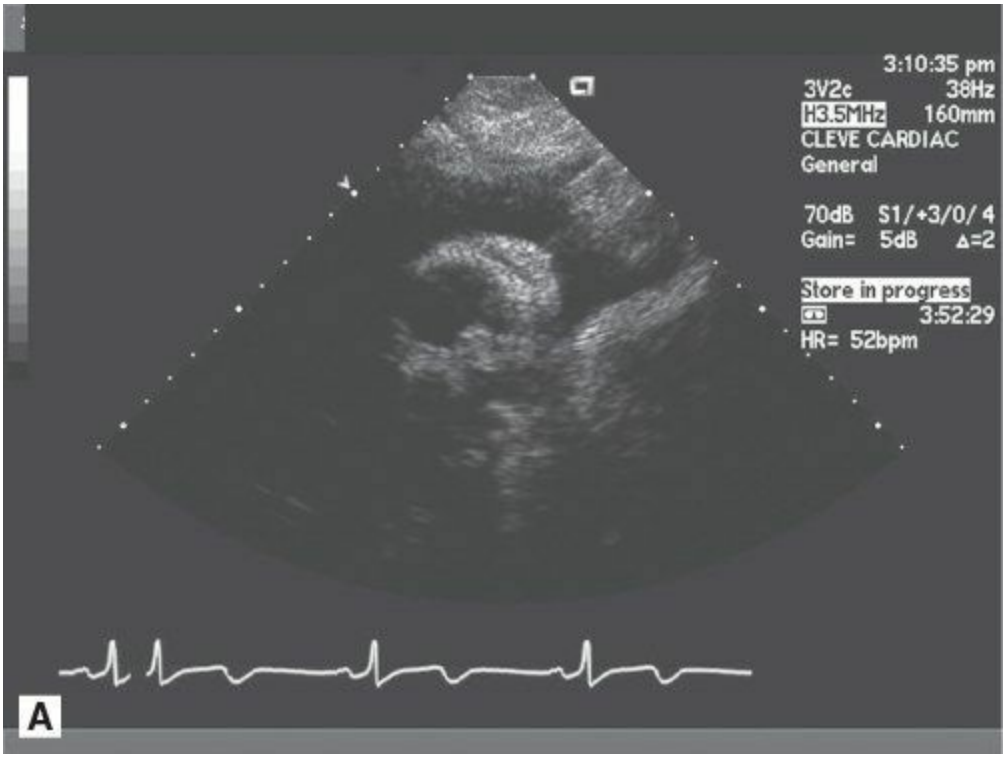
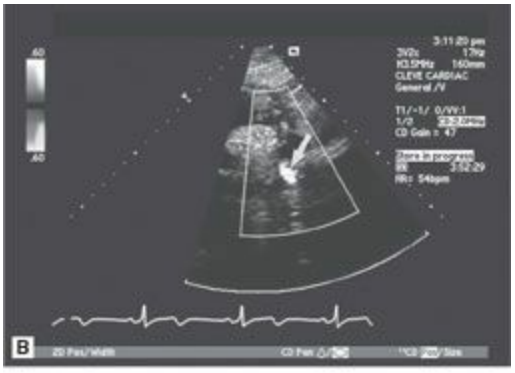


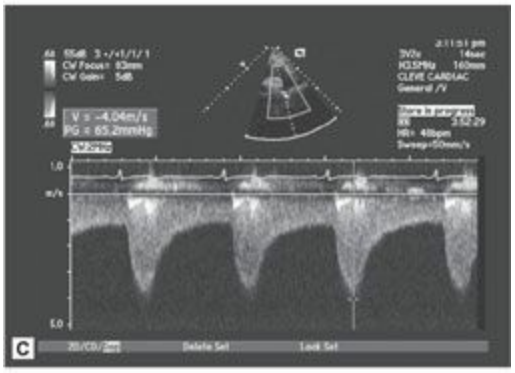
Figure 14.8 • **A.** Apical four-chamber view (TTE). **B.** Apical four-chamber view with color Doppler.

13. The patient is a 22-year-old with a systolic and diastolic murmur with the following echo images (Fig. 14.13A and B). These images demonstrate

- **a.** membranous ventricular septal defect (VSD).
- **b.** supracristal VSD.
- **c.** Ebstein anomaly.
- **d.** pulmonic stenosis (PS)/pulmonic insufficiency.
- **e.** PDA.


3:10:35 pm
3V2c
38Hz
H3.5MHz
160mm
CLEVE CARDIAC
General
70dB S1/+3/0/ 4
Gain= 5dB Δ=2
Store in progress
3:52:29
HR= 52bpm
A


B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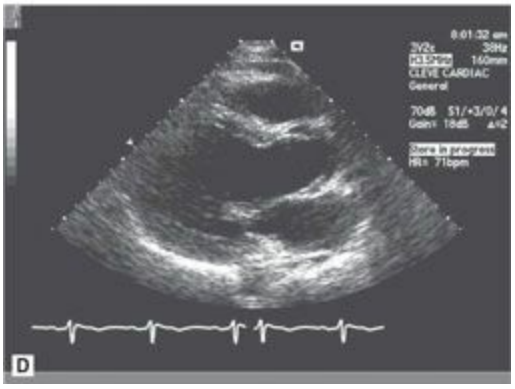
PG = 65.2mmHg
C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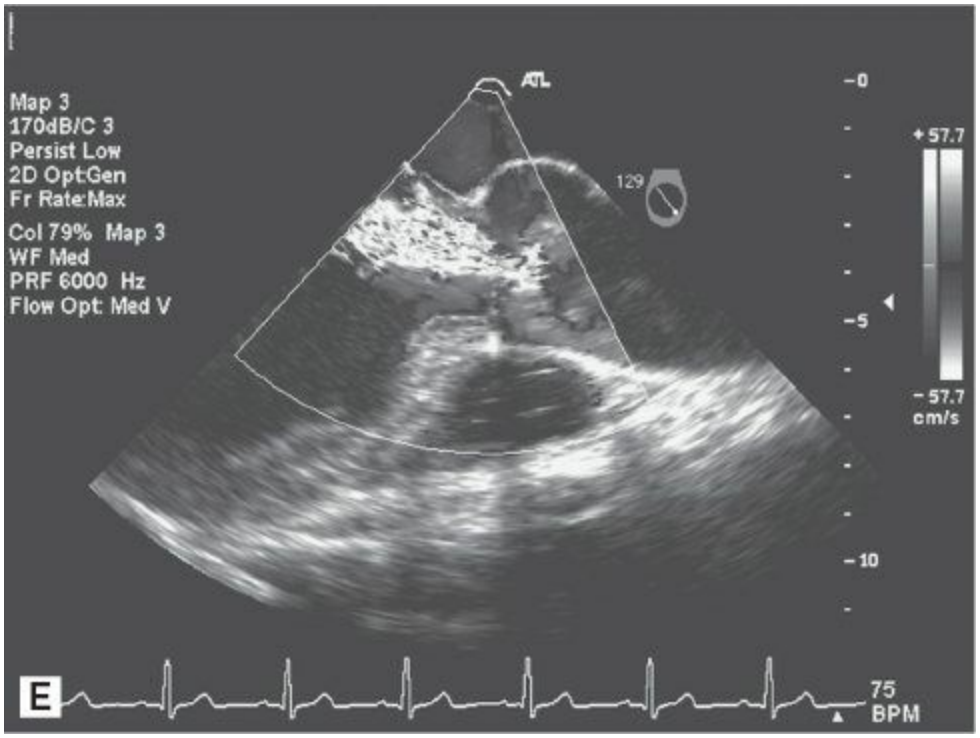


Figure 14.9 • **A.** Suprasternal notch view in 2D (TTE). **B.** Suprasternal notch with color Doppler. **C.** Continuous-wave Doppler in the descending aorta from the suprasternal notch. **D.** Parasternal long-axis view in systole. **E.** Parasternal long-axis view with color Doppler.

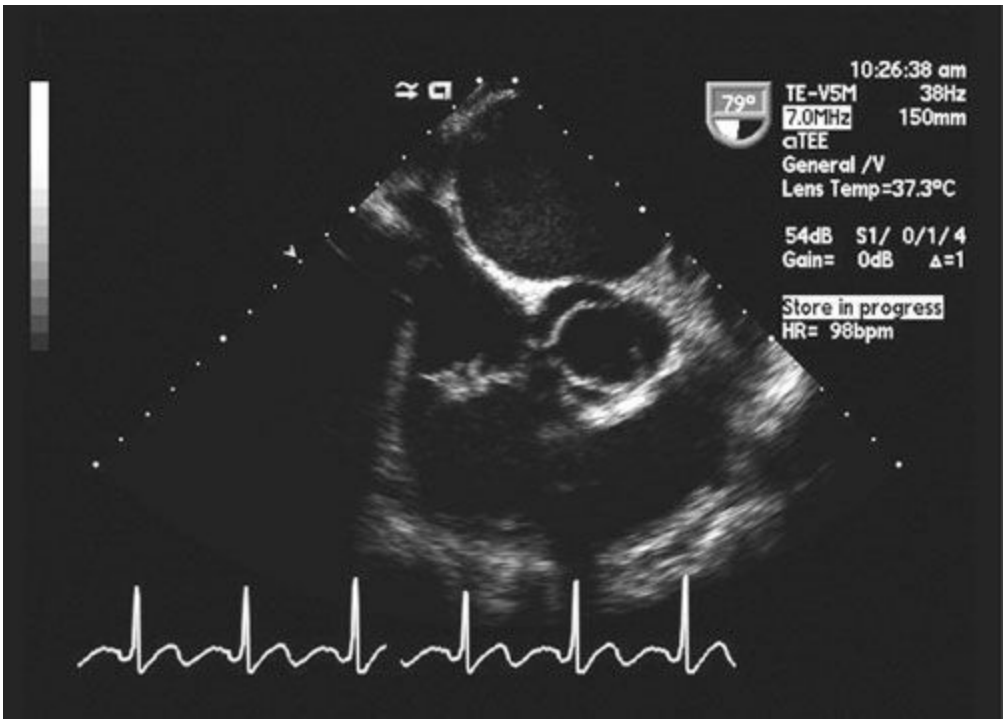


Figure 14.10 • Mid-esophageal short-axis view of the aortic valve (TEE).

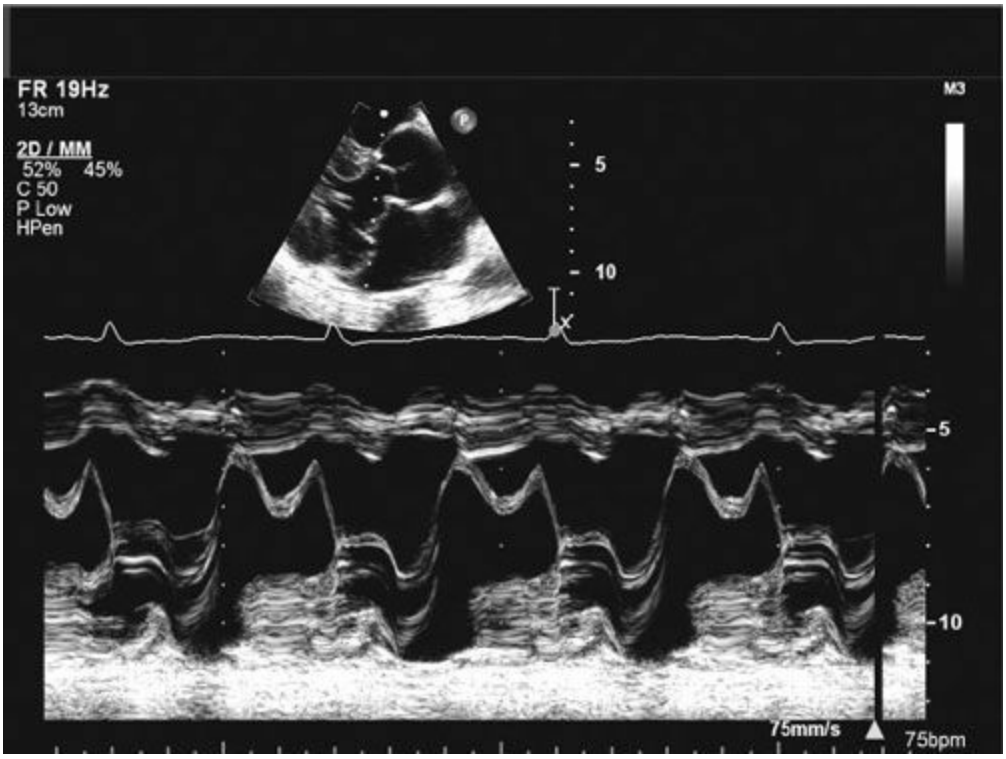


Figure 14.11 • M-mode through the mitral valve.

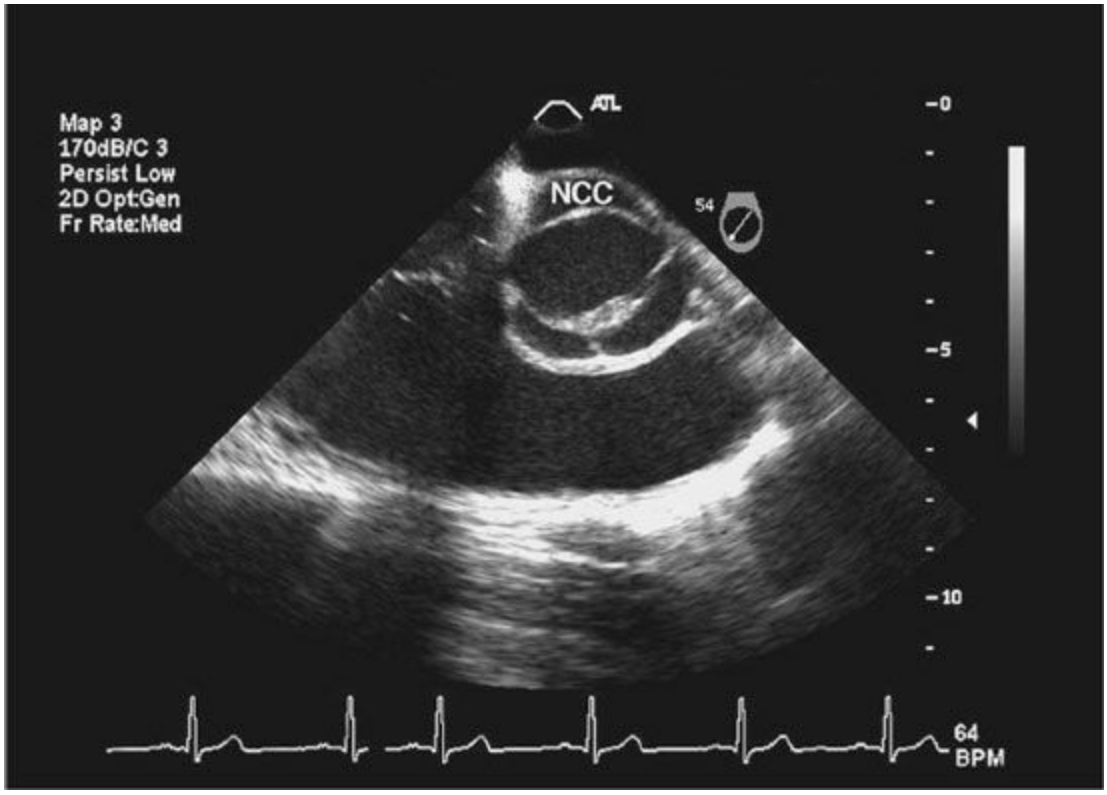


Figure 14.12 • Mid-esophageal short-axis view of the aortic valve (systole).

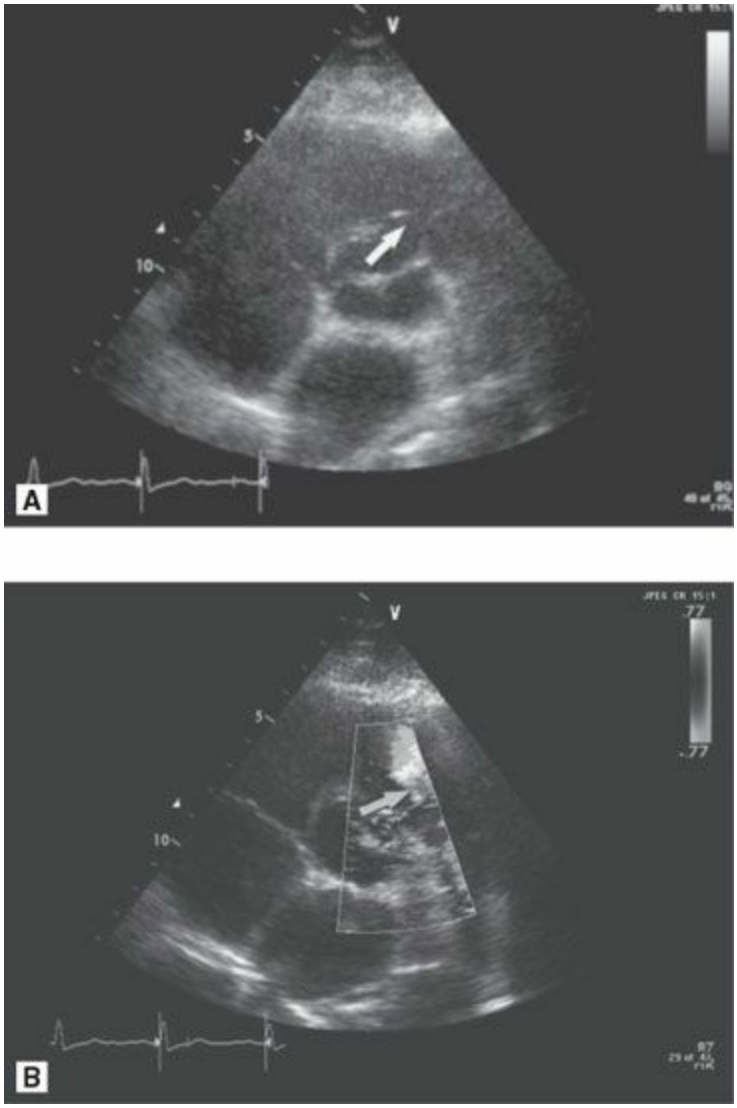


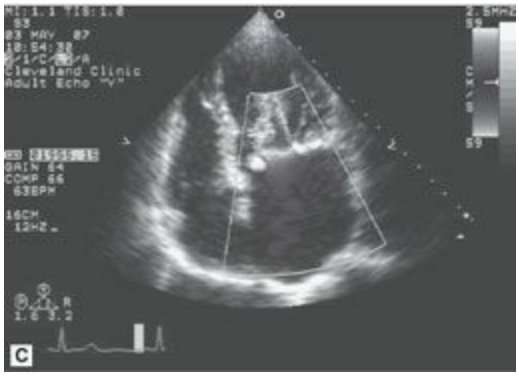
Figure 14.13 • **A.** Parasternal short-axis view. **B.** Parasternal short-axis view with color Doppler.

14. A 46-year-old woman with dyspnea on exertion with occasional palpitations has the following surface echo images (Fig. 14.14A–D). Her dyspnea on exertion can be explained by

a. myxomatous MV disease with MR.
b. rheumatic MV disease with MS and MR.
c. endocarditis with vegetation causing MR.
d. severe mitral annular calcification.
e. cleft mitral leaflet.

Cleveland Clinic
Adult Echo "V"
A

Cleveland Clinic
Adult Echo "V"
B


Cleveland Clinic
Adult Echo "V"
C

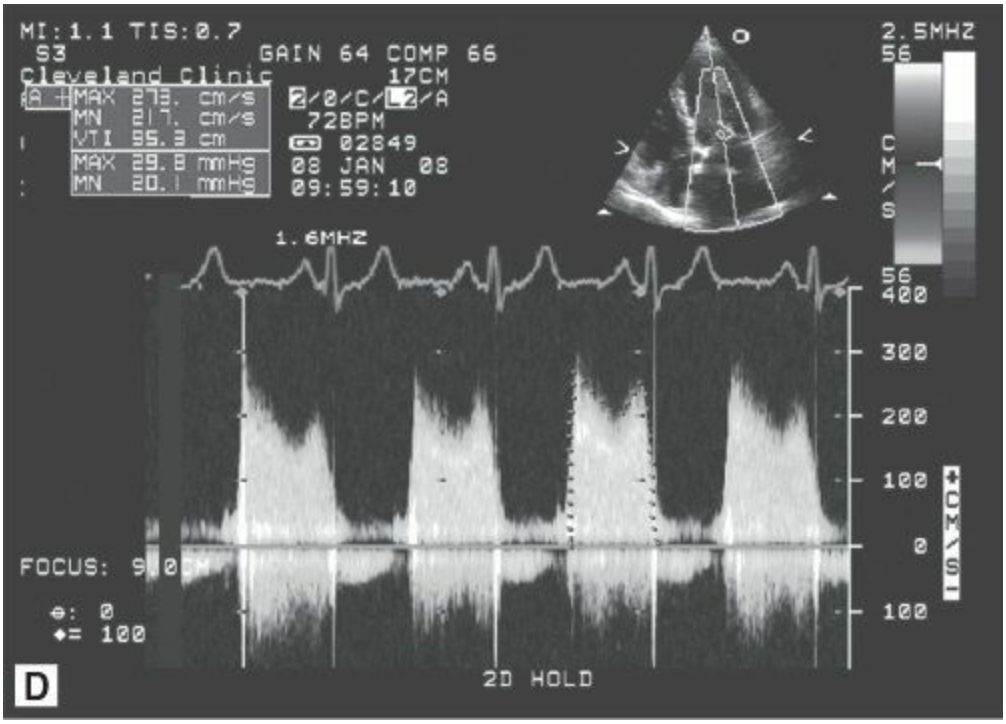


Figure 14.14 • **A.** Parasternal long-axis view. **B.** Parasternal long-axis view with color Doppler. **C.** Apical four-chamber view with color Doppler of the mitral valve. **D.** Continuous-wave Doppler through the mitral valve.

15. This parasternal short-axis view (Fig. 14.15) would be most consistent with which of the following patients?

a. Patient with severe MR
b. Patient with severe AI
c. Patient with severe tricuspid regurgitation (TR)
d. Patient with severe LV systolic dysfunction
e. Patient with a subaortic membrane

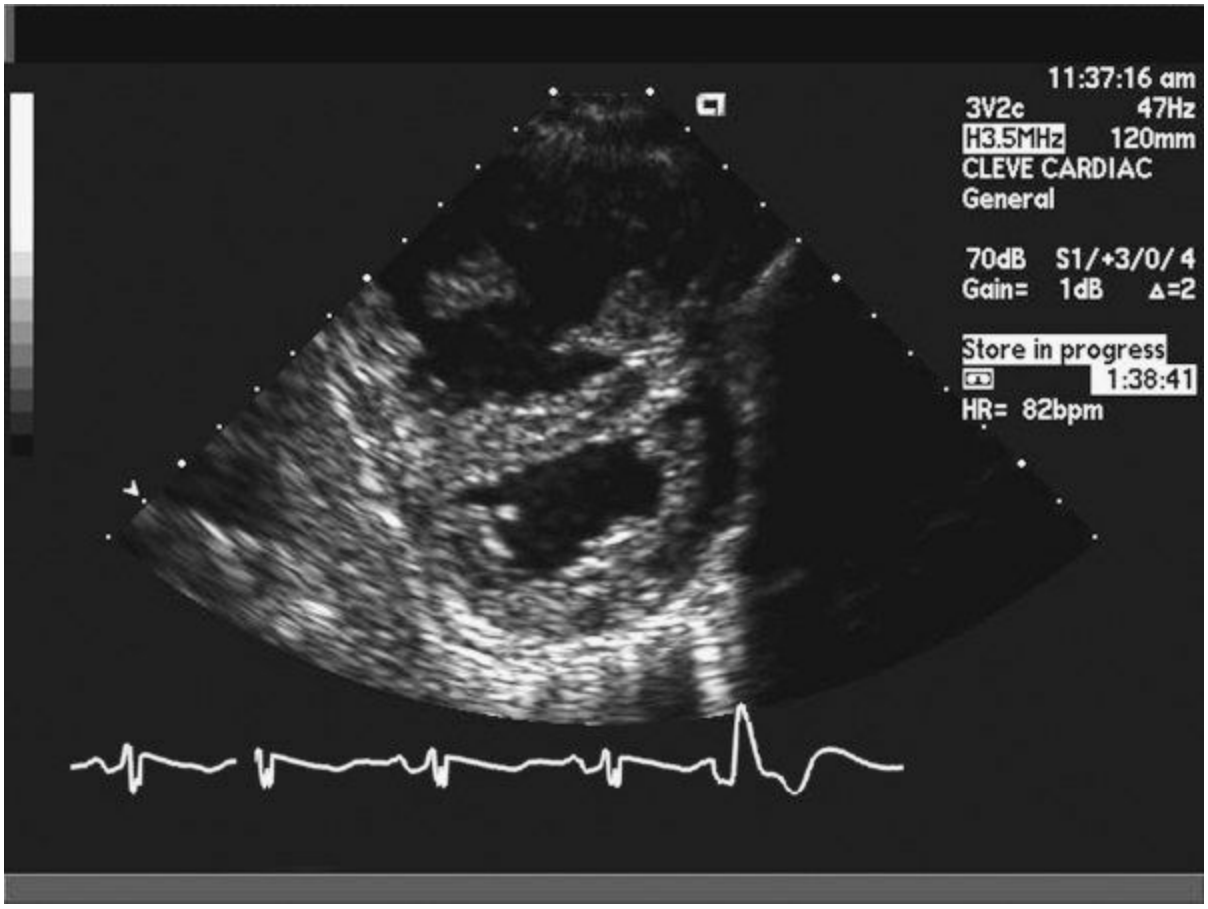


Figure 14.15 • Parasternal short-axis view (diastole).

16. The TEE images below are from a patient who has marked dyspnea on exertion and one episode of presyncope (Fig. 14.16A–C). The patient is now in the operating room for a procedure. The most appropriate operation for this patient would be

a. MV repair.
b. septal myectomy.
c. MVR.
d. coronary artery bypass grafting (CABG).
e. ascending aortic conduit.

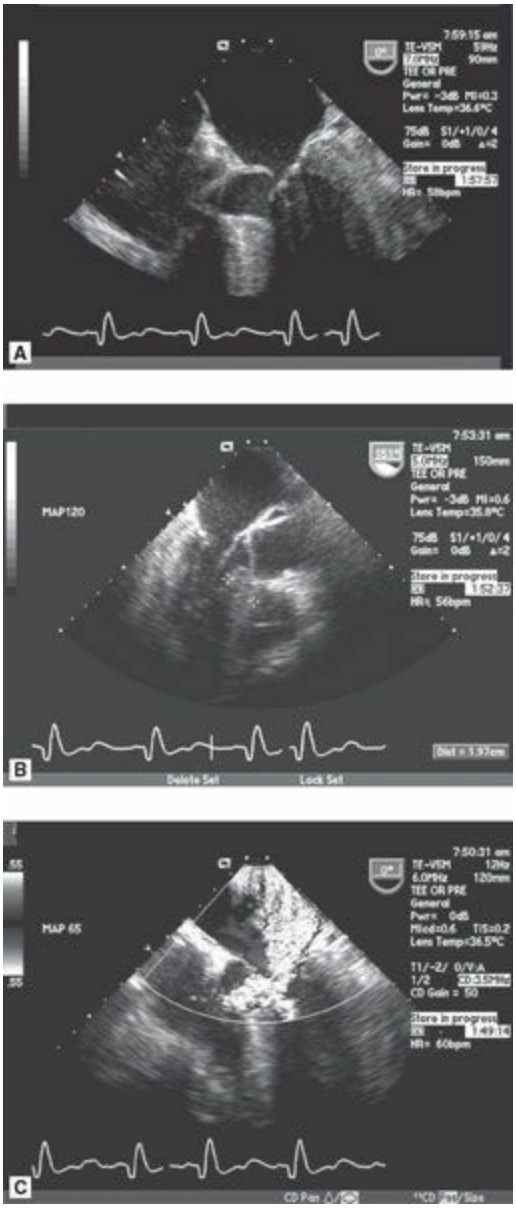


Figure 14.16 • **A.** Mid-esophageal four-chamber view (TEE). **B.** Mid-esophageal long-axis view (TEE). **C.** Mid-esophageal four-chamber view with color Doppler.

17. The following TEE images (Fig. 14.17A and B) demonstrate a large mass noted in the LV apex. This mass is located in a region of myocardial thinning and akinesis in a dilated LV. Although there is some mobility there does not appear to be a stalk. This mass is most likely which of the following possibilities?

a. Teratoma
b. Myosarcoma
c. Fibroelastoma
d. Thrombus
e. Adenocarcinoma

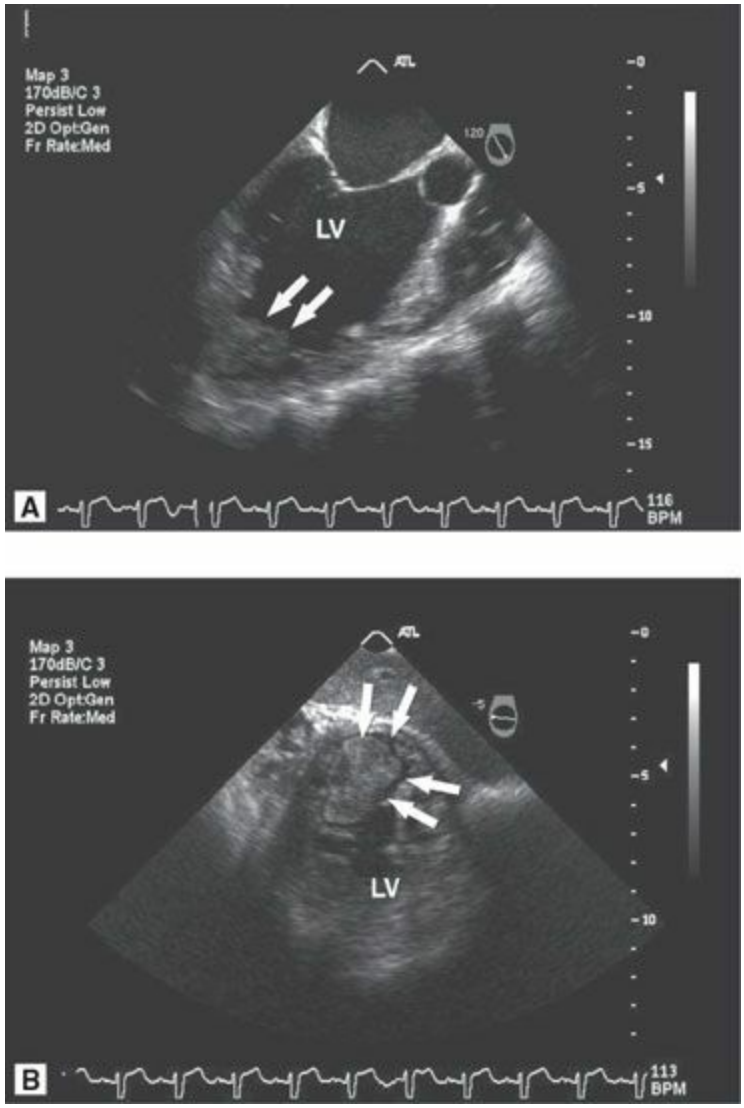


Figure 14.17 • **A.** Mid-esophageal long-axis view (TEE). **B.** Transgastric short-axis view of the LV (TEE).

18. The patient is a 56-year-old man with hypertension, diabetes, and obesity who was admitted 6 months ago to an outside hospital with a late presentation of an anterior MI. He presented approximately 3 days post MI and underwent cardiac catheterization at 1 week, which showed a total occlusion in the mid-left anterior descending artery (LAD), severe stenoses of the first and second diagonals, and no significant disease in either the right coronary artery (RCA) or left circumflex artery (LCx). The patient was then referred to your hospital for revascularization. The patient, however, failed to show for his appointment and finally presented 8 months later with CP and SOB. Prior to revascularization you order a positron emission tomography (PET) rubidium (Rb)/fluorodeoxyglucose (FDG) using $Rubidium^{82}/F18_A$ (flourine-18–labeled deoxyglucose) to determine the degree of inducible ischemia and viability. The images obtained are in Figure 14.18. The images from the PET scan demonstrate

a. scar in the LAD territory.
b. inducible ischemia in the LAD territory.
c. hibernating myocardium in the LAD territory.
d. a combination of inducible ischemia and hibernation in the LAD territory.
e. scar in the RCA territory.

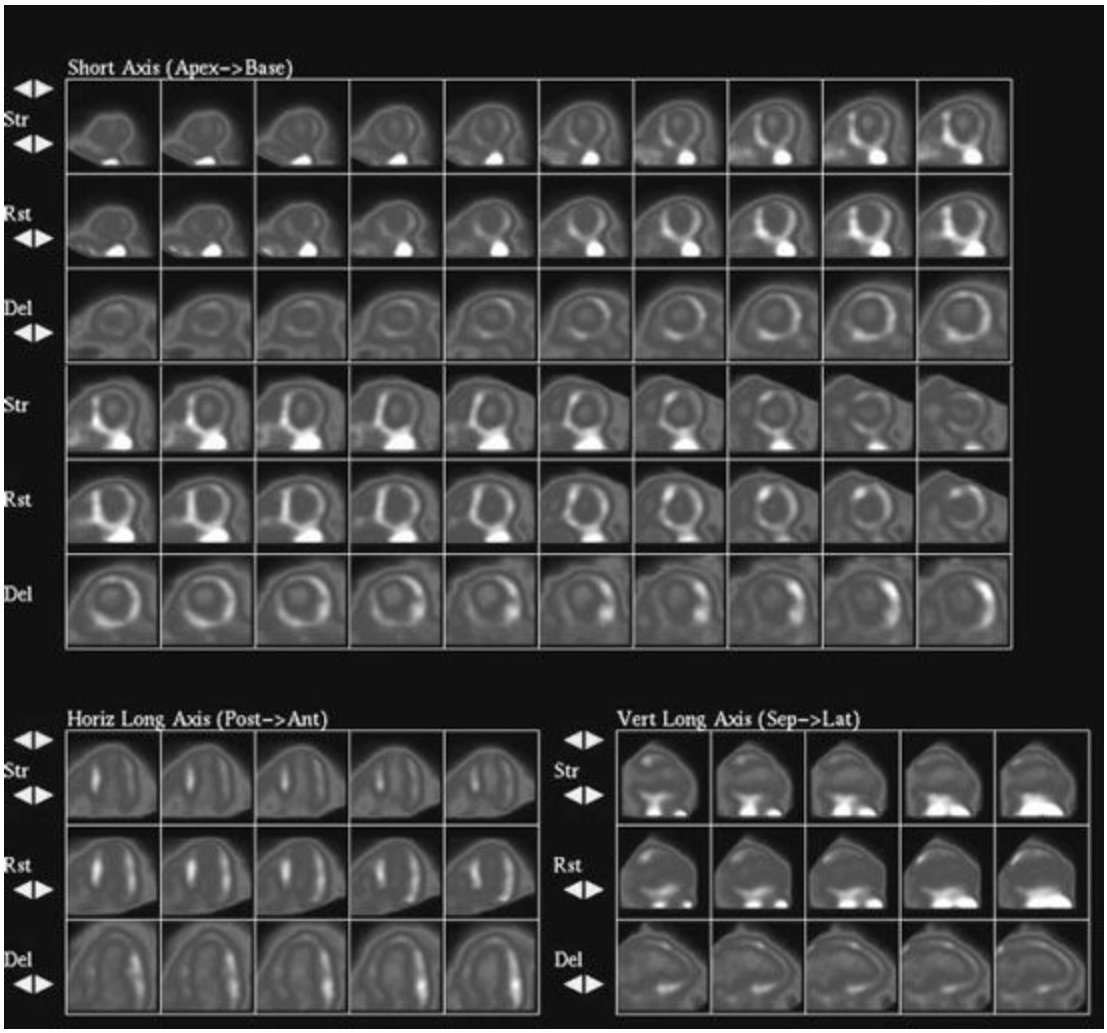


Figure 14.18 • Rubidium/FDG PET scan with the stress images displayed on top, the rest images next, and the delayed metabolic FDG images displayed on the bottom.

19. The patient is a 75-year-old man with hypertension, diabetes, hypercholesterolemia, and coronary artery disease (CAD) who is 10 years s/p CABG: left internal mammary artery to LAD, saphenous vein graft (SVG) to RCA, and SVG to first obtuse marginal. He is asymptomatic on a good medical regimen, although he is relatively sedentary. TTE demonstrated normal LV systolic function with left ventricular ejection fraction (LVEF) 60%, moderately severe left ventricular hypertrophy (LVH), and no significant valvular disease. The patient is now sent for cardiac evaluation prior to surgery on his dilated abdominal aorta (7.5 cm in diameter). An adenosine nuclear stress test is ordered for preoperative risk

assessment. During the adenosine stress he remained asymptomatic although he developed 2-mm ST depressions in I, L, and V_2–V_6. There were no significant changes in blood pressure. Figure 14.19 shows the scan. The scan demonstrates

a. marked attenuation.
b. multivessel ischemia.
c. infarct but no ischemia.
d. mixture of infarct and ischemia.
e. motion artifact.

20. The patient is a 62-year-old man with CAD risk factors including diabetes (16 years), hypertension, family history of CAD, and obesity. The patient had a silent inferior MI 2 years earlier detected by ECG. The patient is now sent for preoperative evaluation for bilateral knee surgery. The patient has no CP with exertion; however, his exercise capacity is limited by knee pain. He does occasionally have mild post-prandial dyspnea. His medications include insulin, a statin, an angiotensin-converting enzyme inhibitor, a β-blocker, and an aspirin. A pharmacologic dual-isotope (Thal/Tc) scan was performed and is shown in Figure 14.20. The gated images showed an LVEF of 42% with a wall motion abnormality in the inferolateral wall. There were no ECG changes or symptoms during the adenosine infusion. The rest and post-stress images demonstrate

a. scarred RCA/LCx territory.
b. scarred LAD territory.
c. normal test with artifacts.
d. scar and ischemia in the LCx/RCA territory.
e. scar and ischemia in the LAD territory.

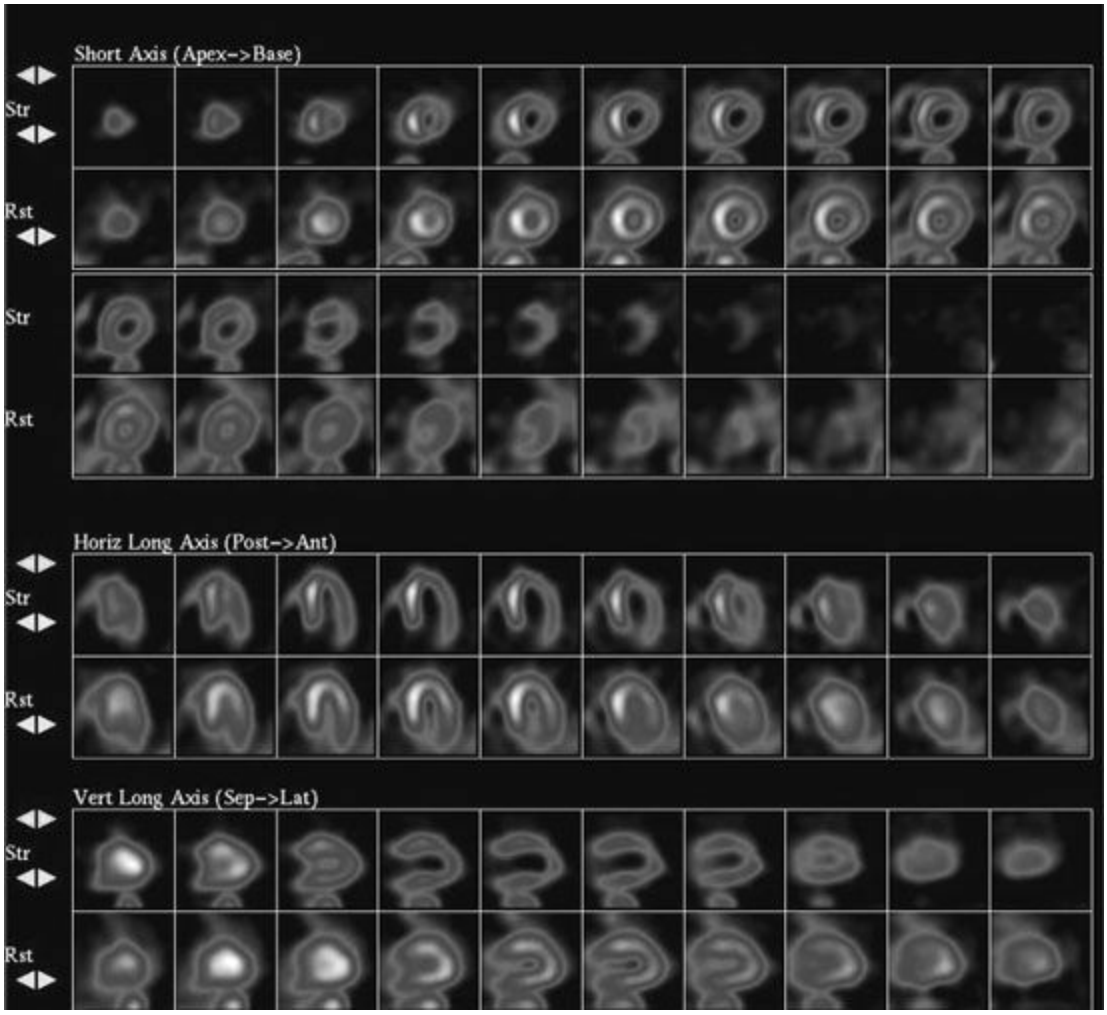


Figure 14.19 • Adenosine technetium-99m nuclear stress test with the stress images on top and the resting images below.

21. The patient is a 60-year-old man with hypertension, diabetes (newly diagnosed), and CAD (s/p percutaneous coronary intervention with drug-eluting stent in his mid-LAD 5 years ago, and bare metal stent to distal RCA, and a posteroventricular branch 7 years ago). The patient is now sent for symptom evaluation. The patient notes the onset of CPs with exertion while playing squash approximately 2 months ago. The pain occurs only with activity and resolves within a few minutes with rest. He denies other associated symptoms or discomfort at rest. A treadmill nuclear stress test was performed. The patient exercised using a standard Bruce protocol having completed eight metabolic equivalents and reached 98% maximum predicted heart rate (MPHR). There was a normal ST-segment response to stress, and there was no CP with exercise. He did, however, develop new ST depressions in recovery and new atrial fibrillation in recovery, requiring treatment with β-blockers. The scan images are shown in Figure 14.21. The appropriate interpretation of this scan is

a. RCA territory infarct.
b. LAD territory infarct.
c. RCA territory ischemia.
d. LAD infarct with peri-infarct ischemia.
e. LAD and LCx versus left main ischemia.

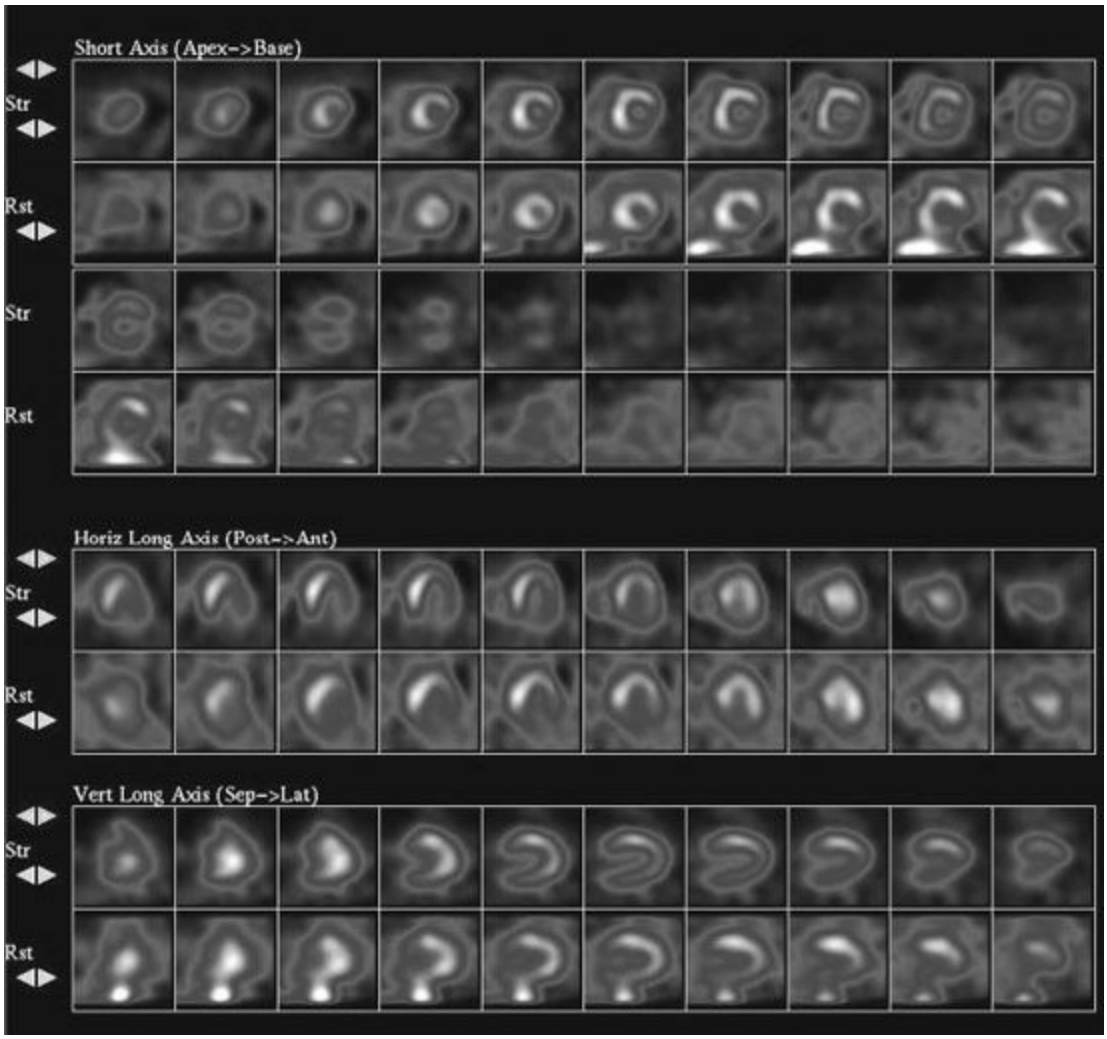


Figure 14.20 • A pharmacologic (adenosine) dual-isotope (Thal/Tc) scan with the stress images displayed on top with the resting images below.

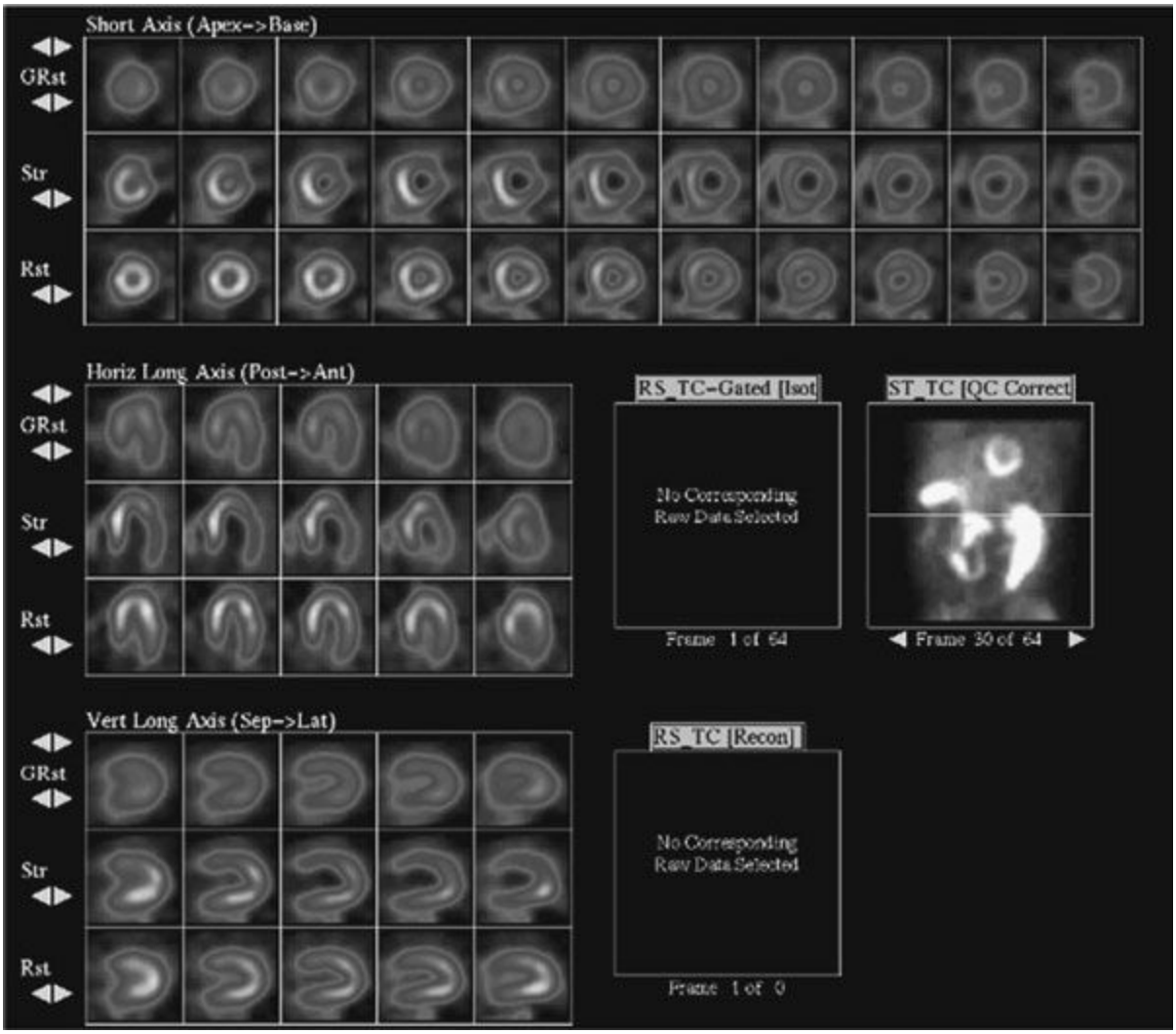


Figure 14.21 • An exercise technetium-99m nuclear stress test with the stress images with the gated images (currently still) on top, the post-stress images next, and the resting images on the bottom.

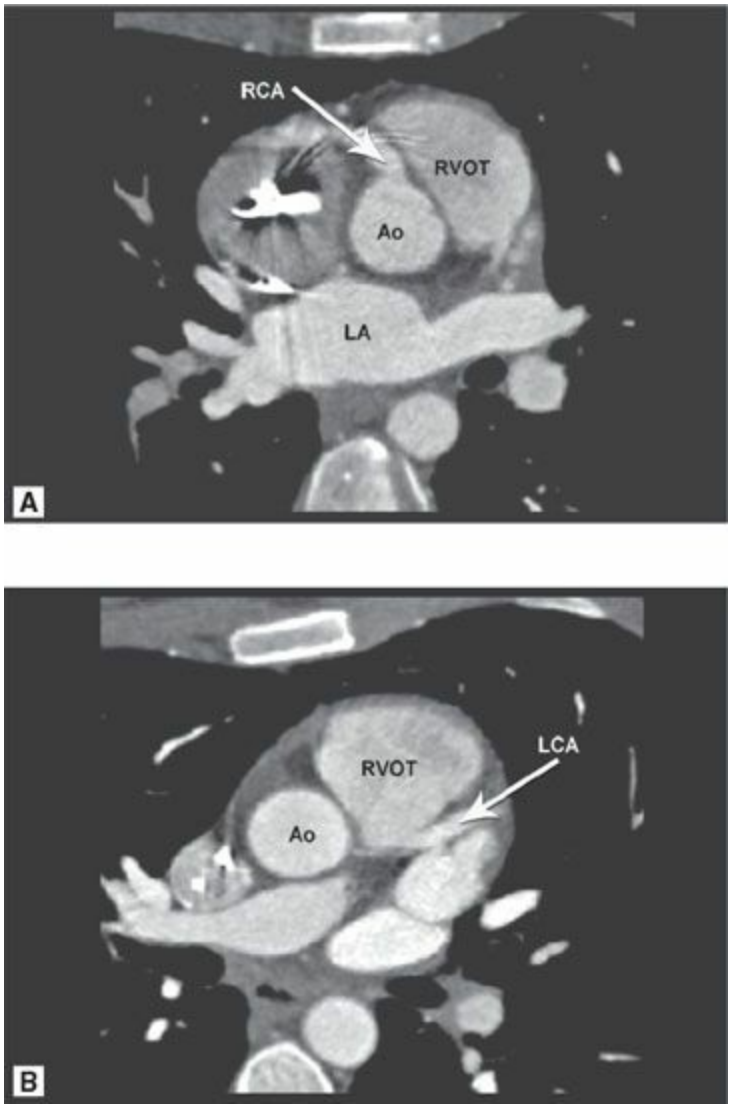


Figure 14.22 • **A.** Double-oblique image of the aortic root at the level of the right and left sinuses of Valsalva. Ao, aorta; LA, left atrium; RCA, right coronary artery; RVOT, right ventricular outflow tract. **B.** Oblique axial image at the level of the left coronary artery origin. LCA, left coronary artery.

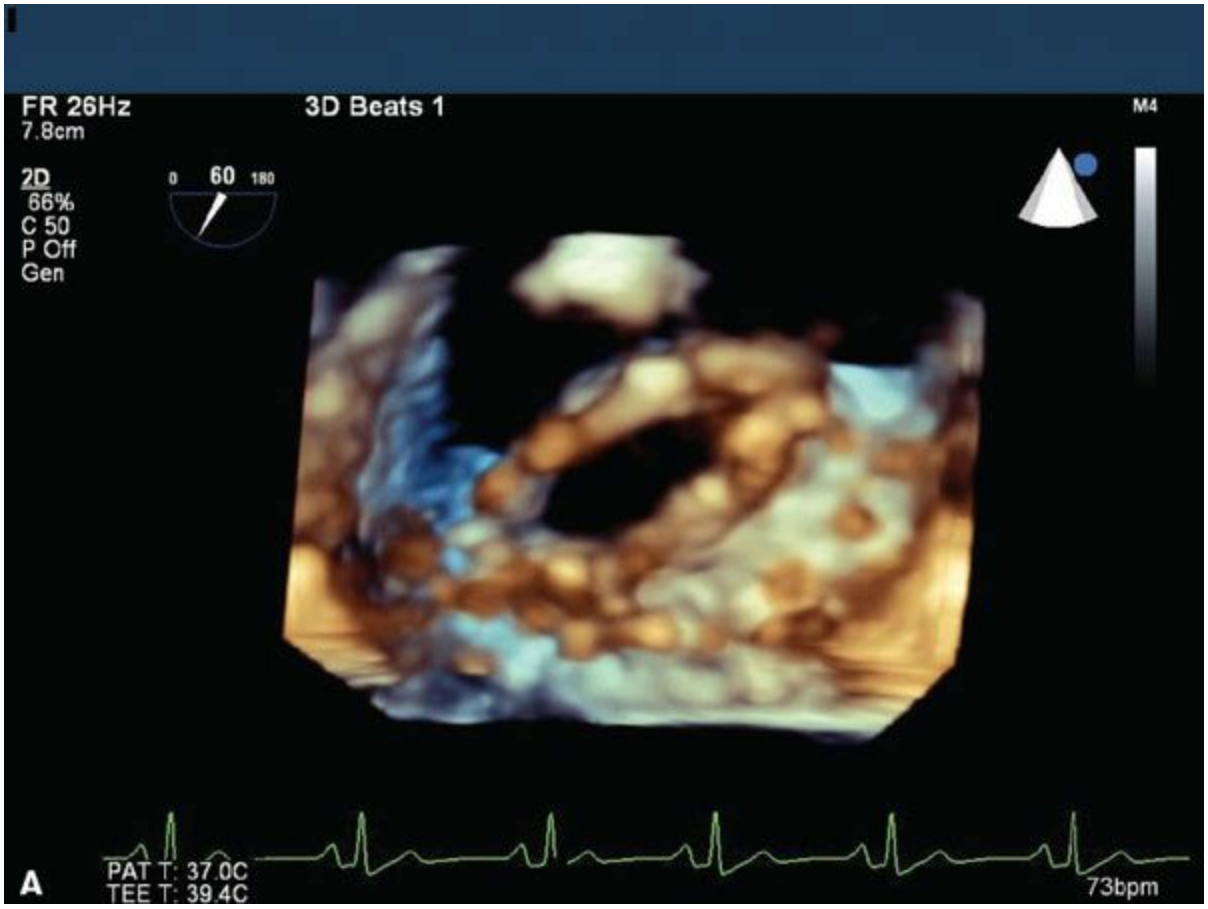
22. A 19-year-old young woman is referred to your office for evaluation of congestive heart failure (CHF) and MR. She has a history of complete heart block and has previously undergone pacemaker implantation. On physical examination, her heart rate is 85 bpm, respiratory rate of 16, and blood pressure 108/65 mmHg. Her jugular venous pulse is visible 6 cm above the sternal angle at 45 degrees. The point of maximum impulse is sustained but normal in location. She has a grade II/VI holosystolic murmur at the apex that radiates to the axilla. There is trivial bilateral pedal edema. A posterior–anterior and lateral chest X-ray demonstrates mild cardiomegaly. A TTE reveals moderately reduced LV systolic function with an EF of 35%. There is 2+ to 3+ posteriorly directed MR. A cardiac CT with contrast is obtained to evaluate the coronary arteries (Fig. 14.22A and B). Which of the following is true regarding this patient's condition?

a. This condition is a common cause of sudden cardiac death in athletes.
b. The anomaly shown represents origin of the left coronary artery from the right coronary ostium.
c. Surgical reimplantation of the anomalous coronary artery is indicated.
d. Patients with this condition who survive past childhood often present with varying degrees of heart failure, myocardial ischemia, and MR, depending on the development of collateral circulation.
e. This condition is usually inoperable and best left alone.

ANSWERS

1. **d.** Abnormal mechanical MVR. Figure 14.1 is a 3D echo image showing a malfunctioning bileaflet mechanical MVR. This image demonstrates one leaflet that is open (to the right of the image), while the other remains shut. You can see the sewing ring of the prosthesis well. This is most likely due to thrombus although impingement by a chord or piece of valve could do this as well.

2. **b.** Percutaneous mitral valvuloplasty (PMV) because he has a split score of 4 to 8 and minimal MR. The MV "split score" as it pertains to " splittability" of a rheumatic MV with MS is derived by grading four features of the stenotic valve. The features, which are graded on a scale of 1 to 4, include leaflet thickening, leaflet calcification, leaflet mobility, and involvement of the subvalvular apparatus. Grade 1 denotes the least abnormality while 4 denotes the most severe abnormality. Because each feature is graded on a scale of 1 to 4, the total score can range from 4 (more splittable) to 16 (least splittable). A valve with a score of ≤8 is considered amenable to PMV as long as there is no significant MR. Of note, the degree of MR typically increases by 1 grade when a patient undergoes balloon mitral valvuloplasty. A score of >8 denotes a valve that would not be amenable to PMV and if the patient is symptomatic or has significant pulmonary hypertension or other indication for an intervention (other than maximizing medical therapy), the patient would undergo a surgical valve replacement as long as they were considered a surgical candidate. The images presented for this example show a patient with severe MS due to rheumatic disease with minimal leaflet thickening or calcification, and no subvalvular involvement with preserved mobility. The stenosis is due almost entirely to commissural fusion and as such has a split score of 4. In addition, the color Doppler still frame in systole showed only trivial MR. For these reasons, the patient is an ideal candidate for PMV. The images in Figure 14.23A and B were taken following the balloon inflations during the PMV.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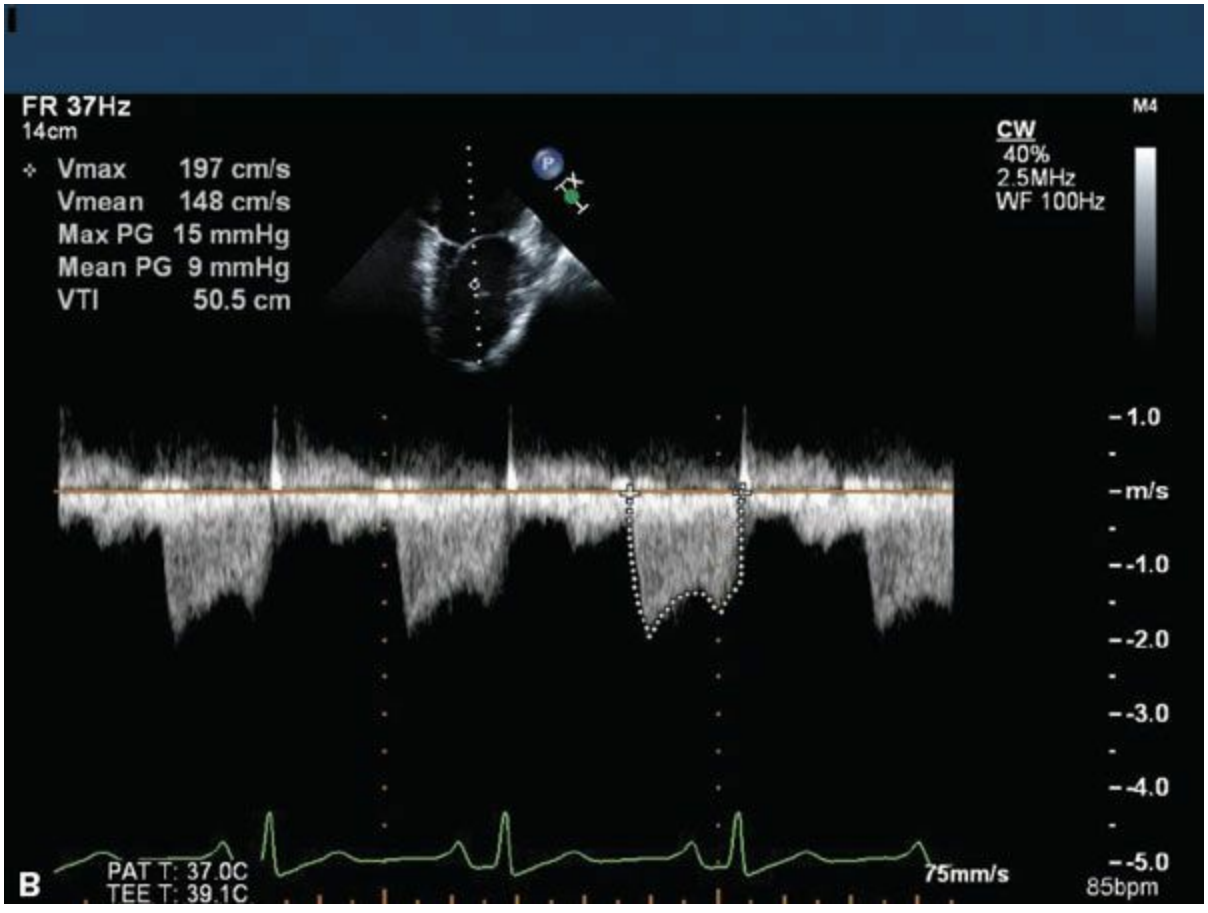
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CW
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Vmean 148 cm/s
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-4.0
-5.0
PAT T: 37.0C
TEE T: 39.1C
75mm/s
85bpm
B

Figure 14.23 • **A.** Three-dimensional images of the mitral valve showing a larger orifice and the split commissures compared with the pre-PMV image. **B.** The transmitral gradient post balloon inflation. The mean mitral gradient has decreased from 30 to 9 mmHg.

3. **C.** Right atrial (RA) thrombus or thrombus on central venous catheter. The patient discussed in this question has a malignancy and is likely in a hypercoagulable state. The mass noted within the RA appears to be broad based and may be in association with her central venous catheter. In this situation, this is most likely to be an RA thrombus. The prosthetic appearing structure within the RA appears to be the central venous catheter and does not go through the tricuspid valve (TV) into the RV, and therefore is not an ICD. An RA myxoma typically has a thin stalk and is most often associated with the interatrial septum. It can be seen within the RA or left atrium (LA). Figure 14.24A and B demonstrates a classic myxoma, one showing surgical pathology and the other showing an echo image of a myxoma. A Chiari network is a more fenestrated mobile structure seen at the junction of the vena cava and RA.

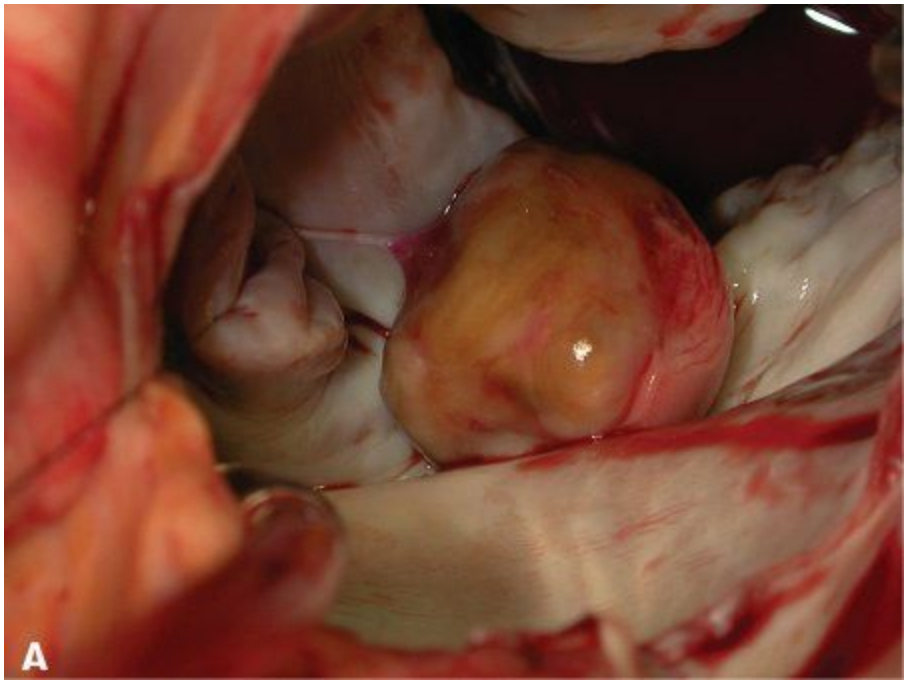


Figure 14.24

4. **a.** Moderate risk of endocarditis. The images in Figure 14.4 demonstrate a PDA. This is seen as the color flow into the pulmonary artery (PA). In this example, the PDA is large and its orifice can be seen in the two-dimensional (2D) images opening into the PA. The complications that can be associated with a PDA include the development of CHF and a moderate risk of endocarditis (although antibiotic prophylaxis is not recommended unless the unrepaired PDA is complicated by pulmonary hypertension/Eisenmenger syndrome causing cyanosis). The clinical manifestations of the PDA depend on the size of the left-to-right shunt. The larger the shunt, the worse the clinical manifestations. The murmur associated with a PDA is a continuous murmur (since the left-sided pressures are higher than the right side throughout the cardiac cycle), not a systolic murmur.

5. **d.** Aortic insufficiency (AI). Although all of the answers are possible complications of infective endocarditis, the images displayed in Figure 14.5 do not show any significant AI. Figure 14.5A shows the short axis of a bioprosthetic AV with a paravalvular abscess with vegetations. It also shows the valve during systole which although it is open, the opening is restricted suggestive of AS which is confirmed by the peak AV gradient of 92.6 mmHg shown in Figure 14.5B. Figure 14.5C shows

the long-axis TEE view of the AV with a small fistula into the LA (seen at the top of the image).

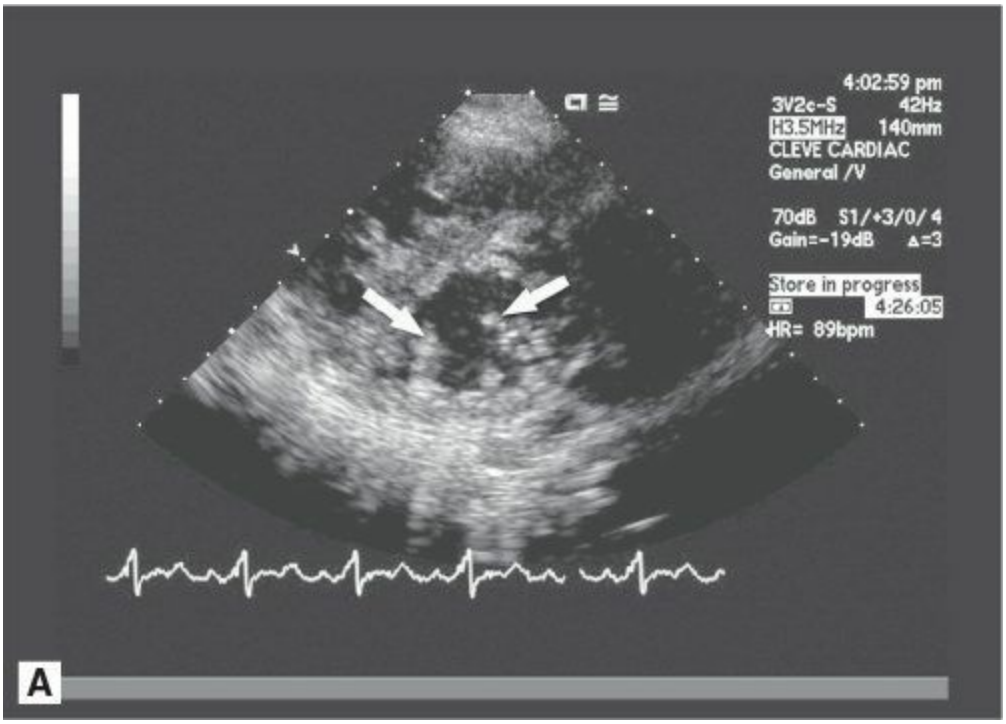
6. **d.** Pulmonary embolus. The images in Figure 14.6 show the parasternal short axis showing specifically the main PA/PA bifurcation. Both images show a large multilobulated echodensity or mass within the main PA which represents a clot in transit. The patient is hypercoagulable due to her malignancy and has developed a deep venous thrombosis which has embolized and is on its way to the lungs. The multilobular appearance shows that this mass is a cast from a deep vein in the leg. The remaining answers are causes of CP; however, these answers do not describe the situation found on TTE. Patients with malignancy can present with tamponade from a pericardial effusion but no effusion is seen on these images.

7. **e.** Emergent cardiac surgery. The images demonstrate a patient with cardiac tamponade. Findings include significant respiratory variation of MV inflows (>25%) and RV diastolic collapse, RA inversion, and inferior vena cava plethora (dilated >2 cm and does not collapse normally with inspiration). A patient with a type I dissection and cardiac tamponade needs to go to emergent cardiac surgery as soon as possible for drainage of the pericardium and repair of the aorta. Pericardiocentesis could potentially cause complete rupture of the flap into the pericardium, causing cardiac arrest and death. An aortic stent graft is currently not the treatment of choice for a type I dissection and could certainly not address the problem of tamponade. Coronary angiography in this patient would only delay the definitive therapy (surgery) as well as possibly further propagate the dissection flap. Recall that delay of surgery in a patient with a type I dissection is associated with a 1% per hour increase in mortality in the first 48 hours of the process. (Note that this patient has not had prior cardiac surgery—if the person had prior cardiac surgery, that would likely change the need for cardiac catheterization prior to surgery, although in this patient emergent surgical drainage of the pericardium would be needed.)

8. **b.** Cleft MV. The image displays an apical four-chamber view of a patient with a primum ASD. (Note Fig. 14.8B with color Doppler shows left-to-right shunting through the ASD.) This is part of either a partial or complete AV canal defect. A complete AV canal defect includes a primum ASD, a cleft anterior mitral leaflet, and a widened anteroseptal tricuspid commissure. A partial AV canal defect is as above but without the VSD. Note that because of the long-term, significant right-to-left shunt through the ASD in this patient the right side is dilated and there is right ventricular hypertrophy from pulmonary hypertension. The short-axis view of the MV (Fig. 14.25A) demonstrates the cleft anterior mitral leaflet, which “splits” in

the center, as opposed to opening like a fish mouth as is seen with normal MVs. Figure 14.25B is a drawing showing normal short axis of MV versus cleft MV.

9. **d.** Coarctation of the aorta with bicuspid AV with AI. The patient is a young man with hypertension beginning in his late 20s or early 30s. Secondary hypertension must be considered and ruled out in this patient. When he was initially diagnosed he should have had his blood pressure checked in both arms and legs in consideration of a coarctation of the aorta. Note: Someone may also notice rib notching on a chest X-ray. Other etiologies that should have been excluded include renal artery stenosis (more commonly seen in women if caused by fibromuscular dysplasia), pheochromocytoma, Cushing syndrome, or primary aldosteronism. This patient's heart murmur was a diastolic murmur from AI caused by prolapse of a bicuspid AV. At least 50% of patients with a coarctation have a bicuspid AV. Fewer patients with bicuspid AV have a coarctation. Note that bicuspid AVs dome (doming aortic leaflets are seen in Fig. 14.9D) and could be mistaken on initial glance in long axis with a rheumatic AV. However, in addition to doming there is prolapse of the conjoined cusp (which would not be seen in a rheumatic valve) and the anatomic situation could be clarified with a good short-axis view.



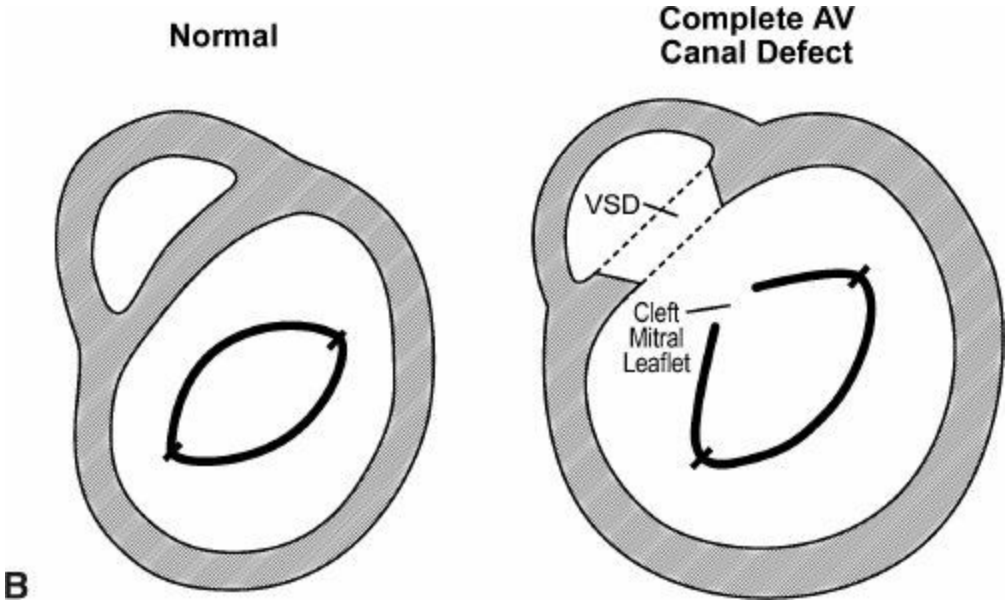


Figure 14.25 • **A.** Parasternal short-axis view of the mitral valve (TTE). **B.** Drawing comparing the parasternal short-axis view of a normal mitral valve to the opening of a cleft anterior mitral leaflet.

10. **e.** Intravenous (IV) drug abuser. Right-sided endocarditis is less common than left-sided endocarditis. The TEE image (Fig. 14.26) shown demonstrates a patient with a vegetation on the tricuspid valve, and the organism identified by culture is Pseudomonas. This is associated with IV drug use with contamination at the time of injection. Although the other clinical situations listed are at increased risk for endocarditis (typically left sided), Pseudomonas would be a very unusual pathogen in those situations.

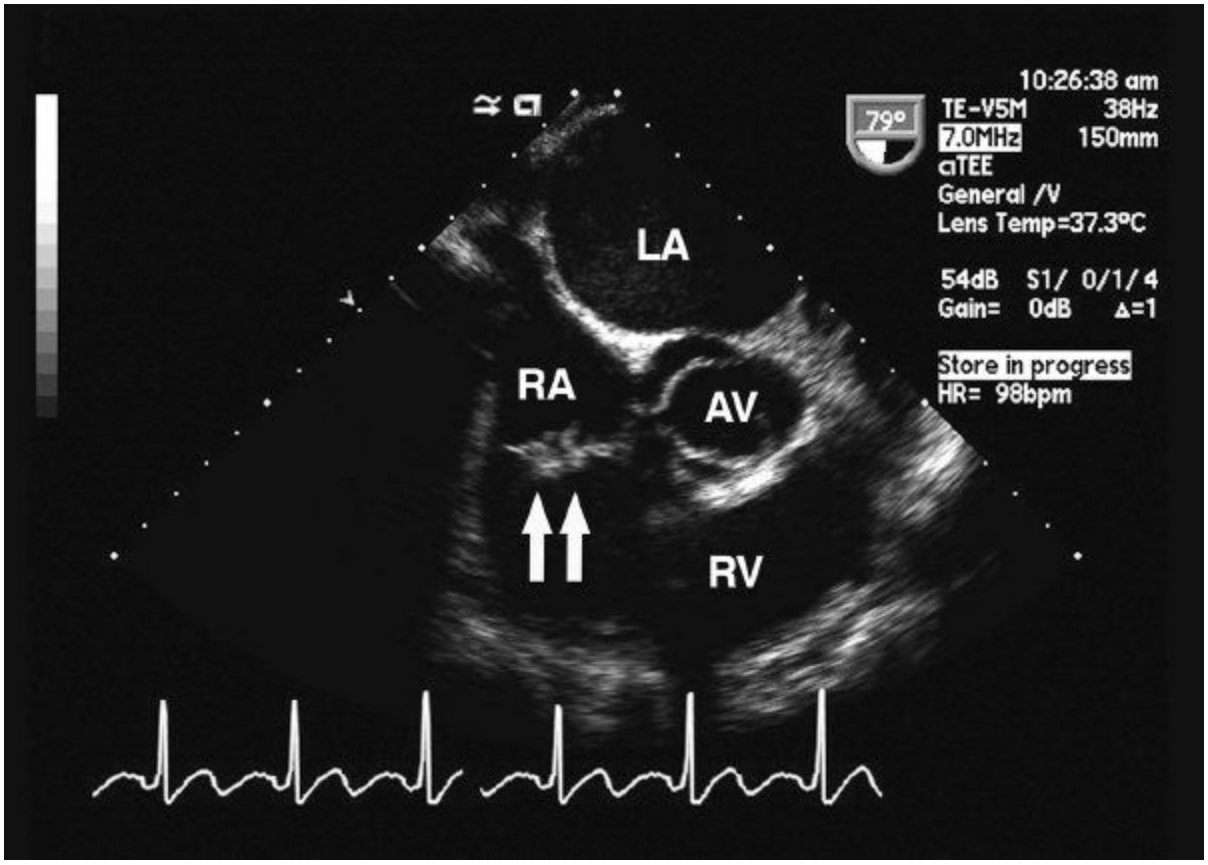

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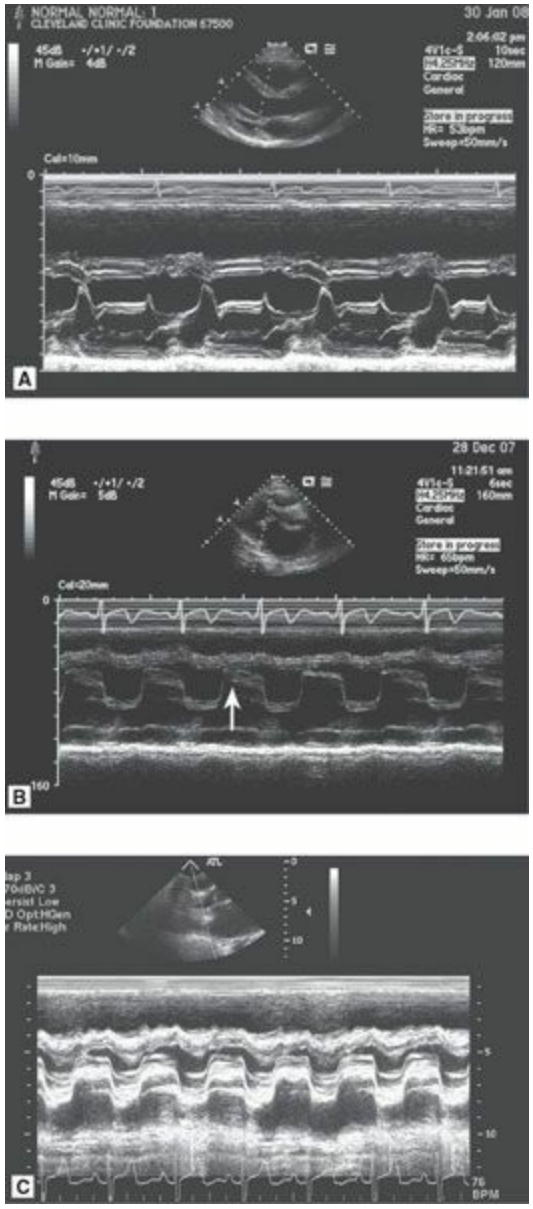
Figure 14.26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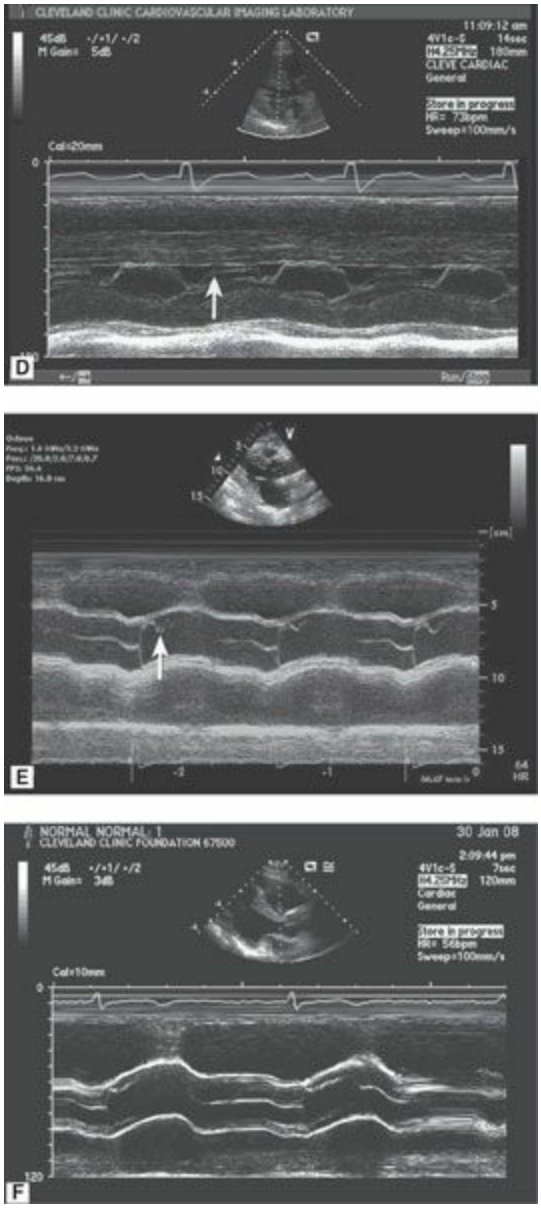
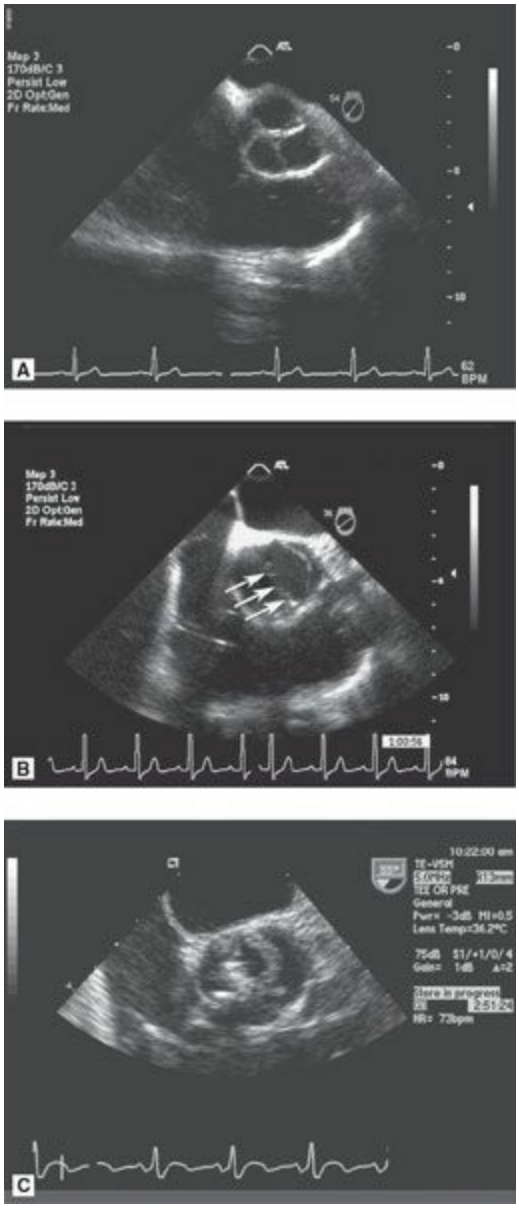


Figure 14.27 • **A.** M-mode through the mitral valve. **B.** M-mode through the mitral valve. **C.** M-mode through the mitral valve. **D.** M-mode through the mitral valve. **E.** M-mode through the aortic valve. **F.** M-mode through the aortic valve.

11. **b.** MVP. The M-mode trace is performed through the MV in a patient with myxomatous MV disease with bileaflet prolapse. Note the marked dip backward of the MV leaflets after the closure point (see Fig. 14.11). Note that there is full systolic range of motion creating the "M" trace of the anterior mitral leaflet and the normal "W" trace of the posterior leaflet. This is in contrast with a normal MV M-mode, which would not have the systolic dip (Fig. 14.27A). Thus, there is no rheumatic MS, which would look like Figure 14.27B in which there are still pliable but tethered leaflets causing a loss of the normal "M" and "W" appearance of the mitral leaflets. More advanced MS with thickened and calcified leaflets would have thicker and brighter appearance of the leaflets together with more restriction

of the leaflet motion (Fig. 14.27C). M-mode for a patient with HOCM and SAM would appear like the images in Figure 14.27D and E. Note the SAM of the mitral leaflets in Figure 14.27D and the early closure of the AV in Figure 14.27E (compared with the M-mode of a normal AV [Fig. 14.27F]).



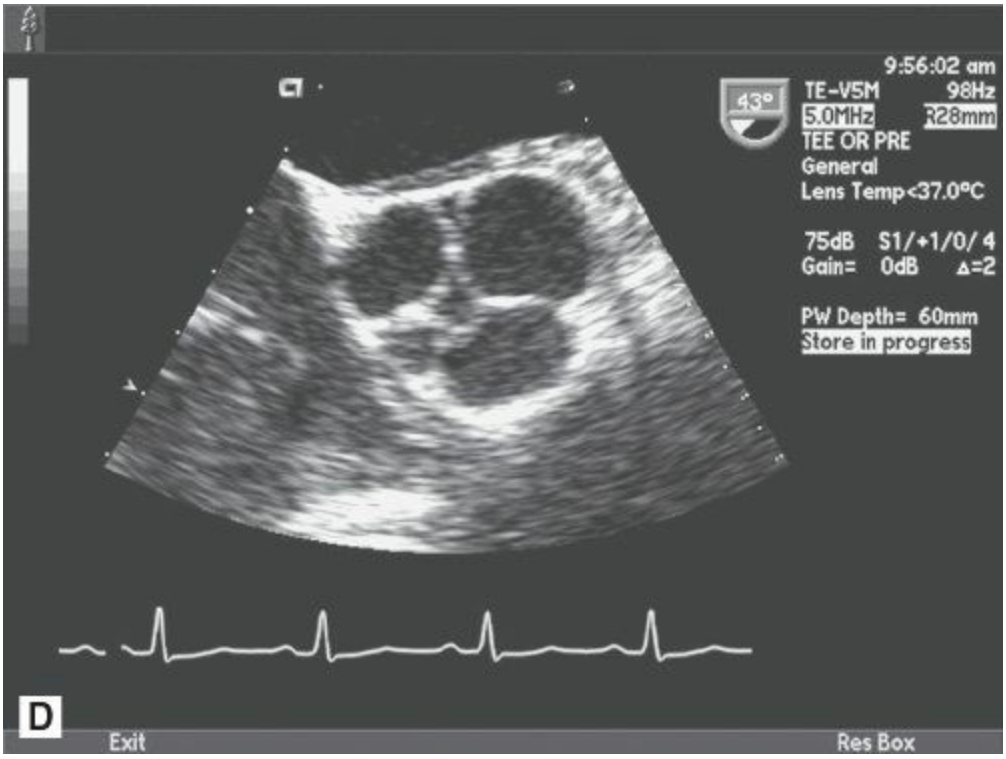


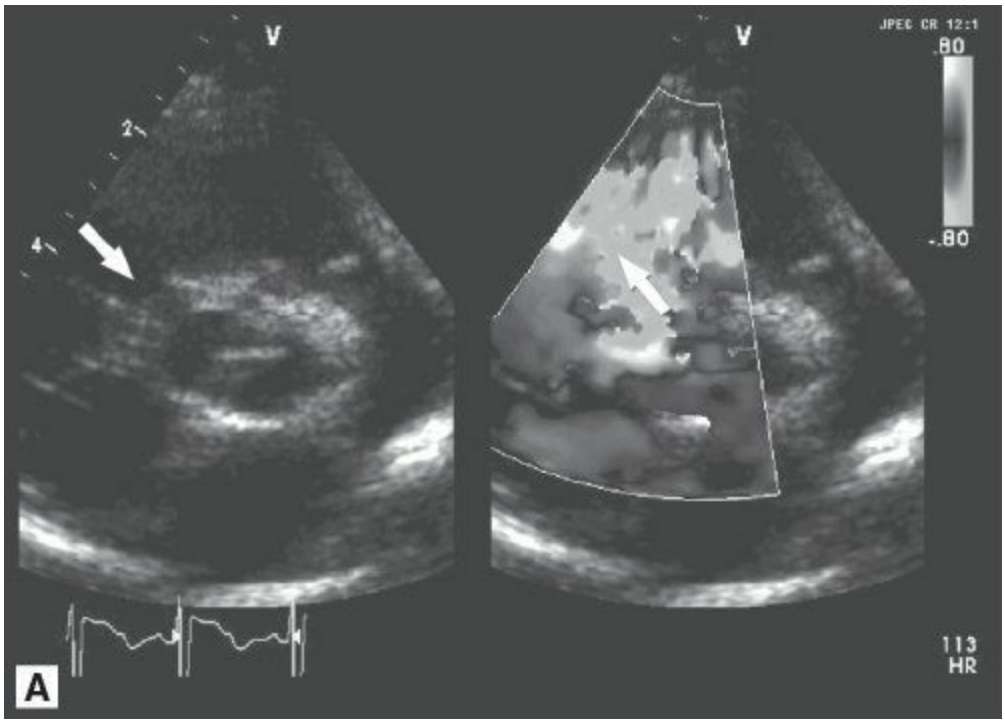
Figure 14.28 • **A.** Mid-esophageal short-axis view of the aortic valve (diastole). **B.** Mid-esophageal short-axis view of a bicuspid aortic valve with fusion of the RCC and NCC. **C.** Mid-esophageal short-axis view of a unicuspid aortic valve. **D.** Mid-esophageal short-axis view of a quadricuspid aortic valve.

12. **c.** Bicuspid AV with fusion of the RCC and LCC. The 2D TEE mid-esophageal view (see Fig. 14.12) demonstrates a bicuspid AV in short axis. To determine cusp anatomy one must view the AV in systole. If one looks for a "Mercedes Benz" image of the valve in short axis during diastole (Fig. 14.28A), one may mistake a bicuspid valve for a tricuspid valve, not realizing that one of the arms in the Mercedes Benz sign is actually a calcified raphe between two fixed cusps. Thus, it is important to look at the valve in systole to determine the true cusp anatomy. The most common form of bicuspid AV is fusion of the RCC and LCC. Bicuspid AVs are also associated with a dilated aorta with an aortopathy involving cystic medial necrosis. Another form of bicuspid AV is fusion of the RCC and NCC (Fig. 14.28B). There are other congenitally abnormal AVs, including unicuspid valves (Fig. 14.28C) and quadricuspid valves (Fig. 14.28D). The unicuspid and quadricuspid valves are much less common than bicuspid valves.

13. **b.** Supracristal VSD. This image demonstrates a supracristal VSD. The VSD is located just under the pulmonic valve, best seen in the parasternal short-axis view (seen at 1 o'clock). A membranous VSD would be seen at 10 or 11 o'clock in short-axis view (Fig. 14.29A). Ebstein anomaly involves apical displacement of the tricuspid valve with atrialization of some of the RV (Fig. 14.29B). Patent ductus can also be seen in the parasternal short-axis view seen best by color Doppler

showing a flow entering the PA (from the aorta) (Fig. 14.29C). PS is seen on 2D in the parasternal short-axis view with doming pulmonic valve leaflets with color acceleration across the valve. In diastole there may also be some PI as the leaflets may have restricted closing.

14. **b.** Rheumatic MV disease with MS and MR. The images shown demonstrate a doming anterior mitral leaflet and a fixed posterior leaflet. There is color acceleration across the MV, suggestive of MS, which is supported by the high gradients found by continuous-wave Doppler through the MV. There is also significant MR (posteriorly directed) seen in the systolic frame with color Doppler. The mechanism of MR in this case is restricted leaflet motion. Myxomatous MV disease (Fig. 14.30), in contrast, is characterized by markedly redundant, prolapsing leaflets, which prolapse back into the LA, occasionally with a torn chord causing a flail leaflet. Typically, the jet of MR is very eccentric if only one leaflet is involved (the jet is in the opposite direction from the most involved leaflet). If there is balanced bileaflet prolapse, the jet is usually centrally directed.



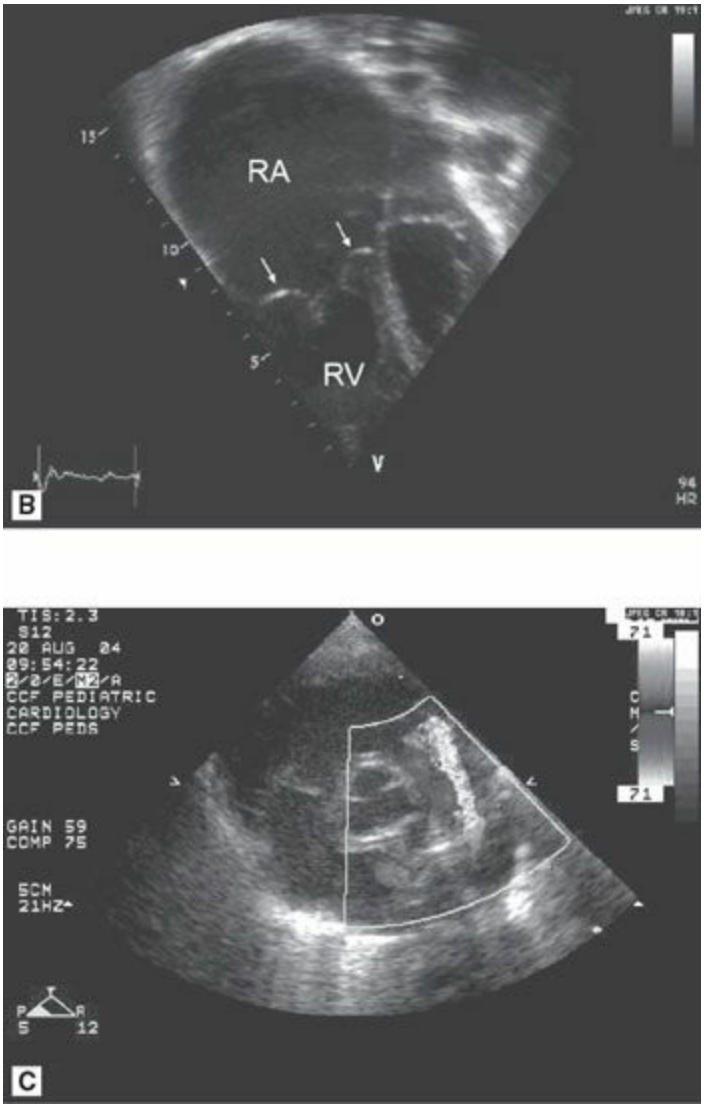


Figure 14.29 • **A.** Parasternal short-axis view (both 2D and with color Doppler). **B.** Apical four-chamber view (pediatric display with atria at the top of the screen). **C.** Parasternal short-axis view.

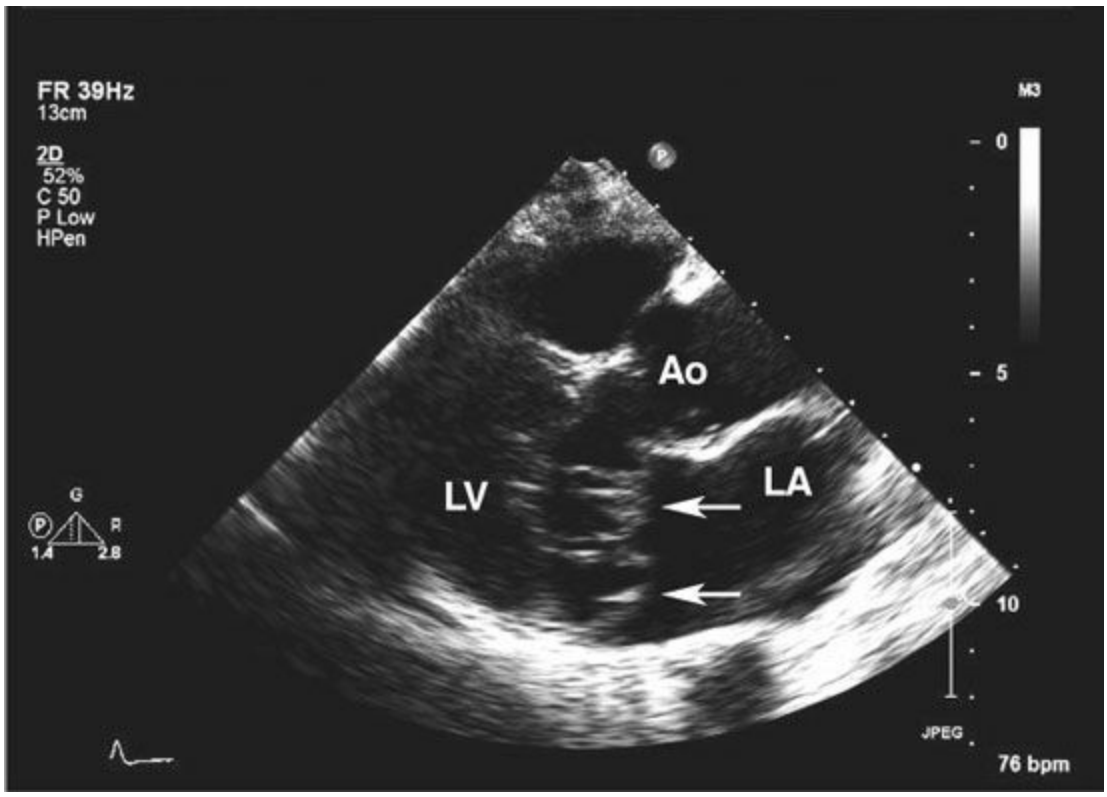


Figure 14.30 • Parasternal long-axis view of a patient with mitral valve prolapse.

15. **c.** Patient with severe tricuspid regurgitation (TR). The parasternal short-axis still frame in diastole demonstrates a patient with diastolic septal flattening. This is found in a patient with right-sided volume overload. You can also see patients with systolic septal flattening, which is consistent with right-sided pressure overload. The patient with severe TR has right-sided volume overload and would have diastolic septal flattening as shown. Patients often have both diastolic and systolic septal flattening if they have both volume and pressure overload on the right side, for example, in a patient with chronic pulmonary embolisms who has developed pulmonary hypertension and also developed significant TR. The lesions of MR and AI are volume loads for the LV, and the subaortic membrane is a pressure load on the LV.

16. **b.** Septal myectomy. The TEE images demonstrate a patient with HOCM. There is septal hypertrophy and the systolic frame demonstrates SAM, which is SAM of the mitral leaflets (Fig. 14.31). The color Doppler images for this patient demonstrate severe MR that is posteriorly directed, which is classic for MR caused by SAM of the mitral leaflets. SAM can involve either the anterior or posterior leaflet alone, or a patient may have bileaflet SAM. Typically, if the mitral leaflet has not been too damaged by years of contact with the septum, performing a septal myectomy can fix the severe MR by eliminating the left ventricular outflow tract (LVOT) obstruction

and eliminating the SAM. This type of MR is often hemodynamically labile depending on the loading conditions of the LV. The SAM can be brought out or accentuated by giving the patient amyl nitrite or isuprel. The SAM is decreased by volume loading the ventricle or increasing the systemic pressure. If the mitral leaflets, however, have been scarred by years of contact with the septum, a simultaneous MV repair or replacement may need to be performed. If the MV has to be replaced, often the surgeon has to use a lower-profile valve (typically a bileaflet mechanical valve) because of the narrowed LVOT. Neither a CABG nor an ascending aortic conduit would help this patient unless he had concomitant CAD or an ascending aortic aneurysm, in which case these procedures would have to be performed in addition to the myectomy.

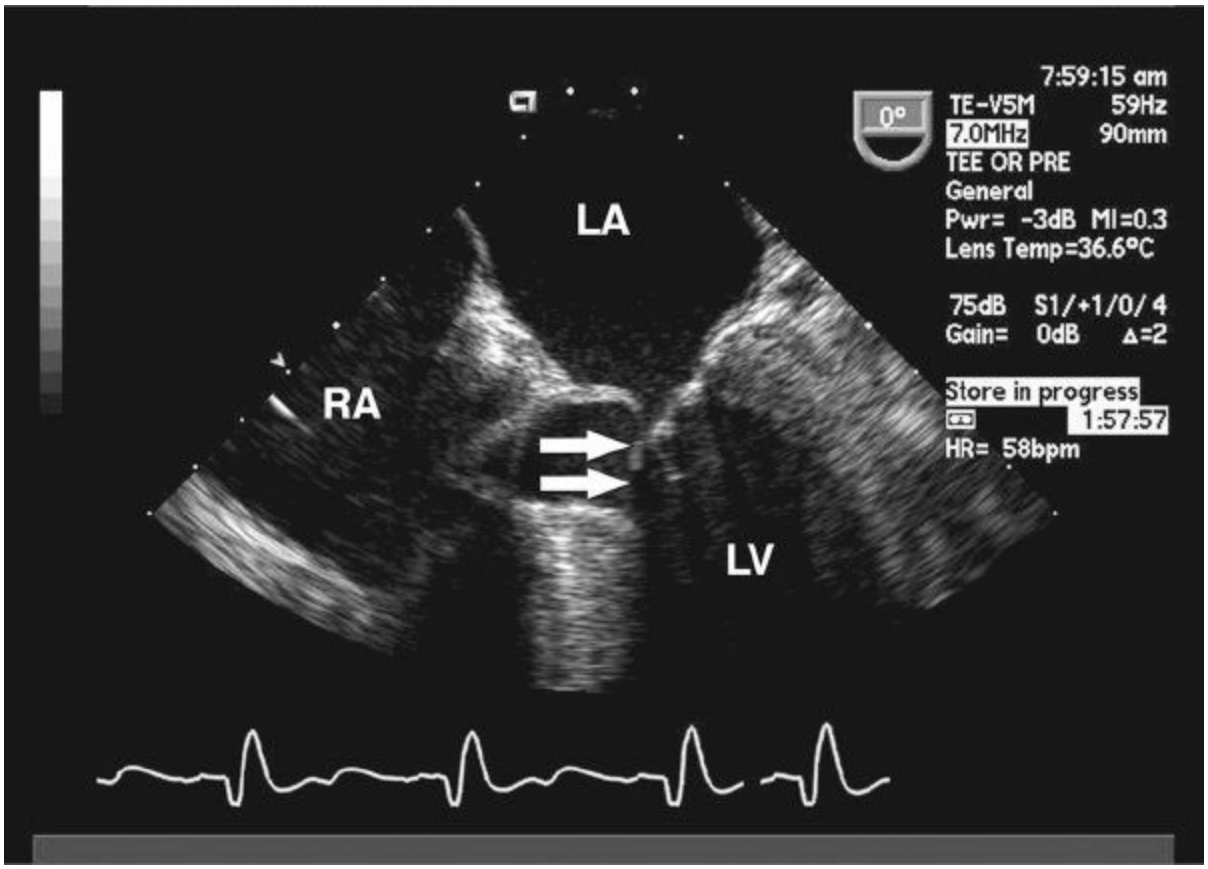


Figure 14.31

17. **d.** Thrombus. This patient had a very large anterior MI and has significant thinning and akinesis of the anterior wall and LV apex. Because of this significant wall motion abnormality, there is stasis of the blood and the patient is at risk for forming a thrombus, which this patient has done. The homogeneous nature of the mass with an echogenicity similar to that of the myocardium (or slightly less echogenic than the myocardium) suggests that the thrombus is relatively fresh. As this heals or organizes over time, calcium may be deposited, and old, organized thrombi in the

heart are often quite echogenic. A sarcoma, on the other hand, would be an invasive mass and would not respect the boundaries of the myocardium, but rather would infiltrate the myocardium. Teratomas if found in the heart arise from the pericardium, not within the LV cavity. These are typically benign although may compress the heart. A teratoma would also have a more heterogeneous appearance on echo. Myxomas are the most common benign tumor of the heart and 80% of those are located in the LA, and most of the remaining ones are found in the RA. Papillary fibroelastomas are the second most common benign cardiac tumors and are typically pedunculated (with a stalk) and mobile. Most (>80%) are located on heart valves.

18. **c.** Hibernating myocardium in the LAD territory. There is a matched defect in the LAD territory seen on the resting and post-stress images involving the apex and four periapical segments as well as the mid-anterior and anteroapical segments. This is consistent with a large LAD territory infarct without any inducible ischemia. The metabolic FDG images show a perfusion/metabolism mismatch with FDG uptake seen in the previously mentioned LAD segments, suggesting a large region of hibernation in the LAD territory without any significant scar. (Note that there is significant gastrointestinal [GI] uptake near the inferior wall.) The degree of hibernation involved 40% of the myocardium (6% for each involved segment except for the apex, which represents 4% of the myocardium). A study by Hachamovitch et al.[1] in 2003 showed that revascularization was superior to medical therapy if the amount of myocardium at risk (ischemic and hibernating) exceeded 20%. Since the above patient demonstrated a large area of hibernating myocardium in the LAD territory, the patient would benefit from revascularization of the LAD territory as well as the diagonals. This patient underwent surgical revascularization of all three vessels.

19. **b.** Multivessel ischemia. The resting scan showed GI activity, but overall normal tracer uptake. There was increased septal uptake caused by the moderately severe LVH. Post stress there is severely reduced tracer uptake involving the mid- and apical anterior, entire anteroseptal, and inferolateral walls and inferior wall and apex. There was also cavity dilation post stress. This is known as transient ischemic dilation (TID). The gated images that accompanied this study demonstrated hypokinesis of the above segments. Note that the post-stress gated images are acquired post stress, but at rest. That is to say that there is a delay between stress and imaging, which may allow for some recovery of function. This scan is of high risk in that there is ischemia in all three vascular territories with TID and extensive wall motion abnormalities. Although the patient was asymptomatic under his baseline conditions, it was appropriate to order the

adenosine nuclear stress test since the patient is diabetic with prior revascularization and with a questionable functional status who was going to undergo a high-risk surgical procedure (aortic aneurysm repair).

20. **d.** Scar and ischemia in the LCx/RCA territory. The full interpretation of the study was that there was marked GI activity in the rest images, but there was also a severe resting perfusion defect involving the basal and mid-inferolateral segments. Although GI activity can make the basal and mid-inferior segments difficult to interpret at rest, the post-stress images clearly show that the defect now involves the entire inferolateral and inferior walls, showing infarct with peri-infarct ischemia in the LCx/RCA territory. Cardiac catheterization demonstrated a total obstruction of the proximal LCx (a dominant LCx) with collaterals from the RCA and LAD. There were no obstructions in the RCA and LAD. Important points from this case include that diabetics are at high risk for CAD and clinical parameters do not predict ischemia (from the detection of ischemia in asymptomatic diabetes (DIAD) trial). Myocardial perfusion imaging can be performed safely post MI to assess infarct size and the amount of myocardium at risk. It is also a good test to assess the adequacy of collateral blood flow.

21. **e.** LAD and LCx versus left main ischemia. The resting images demonstrate normal perfusion. Post stress, however, there are significant perfusion defects in the anterior, anterolateral, and inferolateral walls. There is also cavity dilatation, which is consistent with either left main disease or multivessel ischemia. The gated images showed new wall motion abnormalities in the LAD and LCx territories. The presence of stress-induced perfusion defects in multiple vascular territories as well as TID and new wall motion abnormalities on the gated images are all findings associated with high-risk scans. The cardiac catheterization in this patient demonstrated 70% stenosis in the proximal LAD, while the stent in the mid-LAD was patent. There was a large obtuse marginal with a 90% proximal stenosis. There was mild disease in the proximal RCA, and the stents in posterior descending artery and posteroventricular branch were patent.

22. **d.** Patients with this condition who survive past childhood often present with varying degrees of heart failure, myocardial ischemia, and MR, depending on the development of collateral circulation. This CT demonstrates an anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). Also known as Bland-White-Garland syndrome, ALCAPA is a rare but serious congenital anomaly. It is caused by either (a) abnormal septation of the conotruncus into the aorta and PA or (b) persistence of the pulmonary buds together with involution of the aortic buds that eventually form the coronary arteries. Occurrence is similar

between men and women and is not considered an inheritable congenital cardiac defect. Because of the low pulmonary vascular resistance, left coronary artery flow reverses and enters the pulmonic trunk (coronary steal phenomena). As a result, the LV myocardium remains underperfused, leading to infarction of the anterolateral LV wall. This often causes anterolateral papillary muscle dysfunction and variable degrees of mitral insufficiency. Consequently, the combination of LV dysfunction and significant MV insufficiency leads to CHF symptoms (e.g., tachypnea, poor feeding, irritability, and diaphoresis) in the young infant. Collateral circulation between the right and left coronary systems eventually develops. Approximately 85% of patients present with clinical symptoms of CHF within the first 1 to 2 months of life. Left untreated, the mortality rate in the first year of life is 90% secondary to myocardial ischemia or infarction and MV insufficiency leading to CHF. In unusual cases, the clinical presentation with symptoms of myocardial ischemia may be delayed into early childhood. Rarely, a patient may stabilize following infarction and may present with MV regurgitation, periodic dyspnea, angina pectoris, syncope, or sudden death later in childhood or even adulthood, as in this patient. Treatment consists of surgical ligation of the anomalous coronary artery origin and bypass grafting to the left coronary artery. Reimplantation onto the native aortic root is typically not possible because of the friable quality of the anomalous left coronary artery ostium.

REFERENCE

1. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. Circulation. 2003;107(23):2900–2907.

Electrocardiographic Interpretation

Donald A. Underwood

CODING SHEET

General Features

1. Normal electrocardiogram (ECG)
2. Borderline ECG or normal variant (specify in other section)
3. Incorrect electrode placement

P-Wave Abnormalities

4. Right atrial abnormality
5. Left atrial abnormality
6. Nonspecific atrial abnormality
7. Sinoventricular condition with absent P wave

Supraventricular Rhythms

8. Normal sinus rhythm (without other abnormalities of rhythm or atrioventricular (AV) conduction)
9. Sinus rhythm (in presence of abnormality of rhythm or AV conduction)
10. Sinus arrhythmia
11. Sinus bradycardia
12. Sinus tachycardia

13. Sinus pause or arrest
14. Sinoatrial exit block
15. Ectopic atrial or junctional rhythm
16. Wandering atrial pacemaker
17. Atrial premature beats, normally conducted
18. Atrial premature beats, nonconducted
19. Atrial premature beats with aberrant intraventricular conduction
20. Atrial tachycardia (regular, sustained, 1:1 conduction)
21. Atrial tachycardia, repetitive (short paroxysms)
22. Atrial tachycardia, multifocal (chaotic atrial tachycardia)
23. Atrial tachycardia with AV block
24. Atrial flutter
25. Atrial fibrillation
26. Retrograde atrial activation
27. Supraventricular tachycardia, unspecified

Atrioventricular Junctional Rhythms

28. AV junctional premature beats
29. AV junctional escape beats or escape rhythm
30. AV junctional rhythm, accelerated rhythm (nonparoxysmal junctional tachycardia)
31. AV junctional tachycardia

Ventricular Rhythms

32. Ventricular premature beat(s), uniform, fixed coupled
33. Ventricular premature beats, R on T phenomenon

34. Premature ventricular contractions, in pairs

35. Ventricular parasystole

36. Ventricular tachycardia

37. Accelerated idioventricular rhythm

38. Ventricular escape beats or rhythm

39. Ventricular fibrillation

Atrioventricular Conduction Abnormalities

(Also see items 48 to 53)

40. AV block, primary

41. AV block, secondary—Mobitz type I (Wenkenbach)

42. AV block secondary—Mobitz type II

43. AV block, 2;1, 3:1, 4:1

44. AV block, complete

45. AV block, varying

46. Short PR interval (with sinus rhythm and normal QRS duration)

47. Preexcitation (Wolff-Parkinson-White) syndrome(s)

Atrial Ventricular Interactions in Arrhythmias

(Also see items 40 to 47)

48. Fusion beats

49. Reciprocal (echo) beats

50. Ventricular capture beats

51. AV dissociation (without complete AV block)

52. Isorhythmic AV dissociation

53. Ventriculophasic sinus arrhythmia

Abnormalities of QRS Voltage or Axis

54. Low voltage, limb leads only

55. Low voltage, limb and precordial leads

56. Left axis deviation (>30 degrees)

57. Right axis deviation (>+100 degrees)

58. Electrical alternans

Ventricular Hypertrophy

59. Left ventricular hypertrophy by voltage only

60. Left ventricular hypertrophy by left ventricular hypertrophy by voltage and ST-T segment (secondary repolarization changes)

61. Right ventricular hypertrophy

62. Combined ventricular hypertrophy

Intraventricular Conduction Disturbances

63. Right bundle branch block (RBBB), incomplete

64. RBBB, complete

65. Left anterior fascicular block

66. Left posterior fascicular block

67. Left bundle branch block (LBBB), complete with ST-T waves suggestive of acute myocardial injury or infarction

68. LBBB, complete

69. Intraventricular conduction disturbance, nonspecific type

70. Aberrant intraventricular conduction with supraventricular arrhythmia (specify rhythm)

Transmural Myocardial Infarction

(Also see items 88 and 89)

	Age Recent or Probably Acute	Age Indeterminate or Probably Old
Anterolateral	71	72
Anterior	73	74
Anteroseptal	75	76
Lateral or high lateral	77	78
Inferior (diaphragmatic)	79	80
Posterior	81	82

83. Probable ventricular aneurysm

ST-, T-, and U-Wave Changes

84. Subendocardial or subepicardial nontransmural infarction

85. Normal variant, early repolarization

86. Normal variant, juvenile T wave

87. Nonspecific ST- and/or T-wave changes

88. ST- and/or T-wave changes suggesting myocardial ischemia

89. ST- and/or T-wave changes suggesting myocardial injury

90. ST- and/or T-wave changes suggesting acute pericarditis

91. ST-T segment changes secondary to intraventricular conduction distribution or hypertrophy

92. Post extrasystolic T waves

93. Isolated J-point depression

94. Peaked T waves

95. Prolonged QT interval

96. Prominent U waves

Suggested Probable Clinical Disorder

97. Digitalis effect

98. Digitalis toxicity

99. Hyperkalemia

100. Hypokalemia

101. Hypercalcemia

102. Hypocalcemia

103. Atrial septal defect, secundum

104. Atrial septal defect, primum

105. Dextrocardial, mirror image

106. Mitral valve disease

107. Chronic lung disease

108. Acute cor pulmonale including pulmonary embolus

109. Pericardial effusion

110. Acute pericarditis

111. Hypertrophic obstructive cardiomyopathy (idiopathic hypertrophic subaortic stenosis)

112. Hypertrophic obstructive cardiomyopathy; apical

113. Coronary artery disease

114. Central nervous system (CNS) disorder

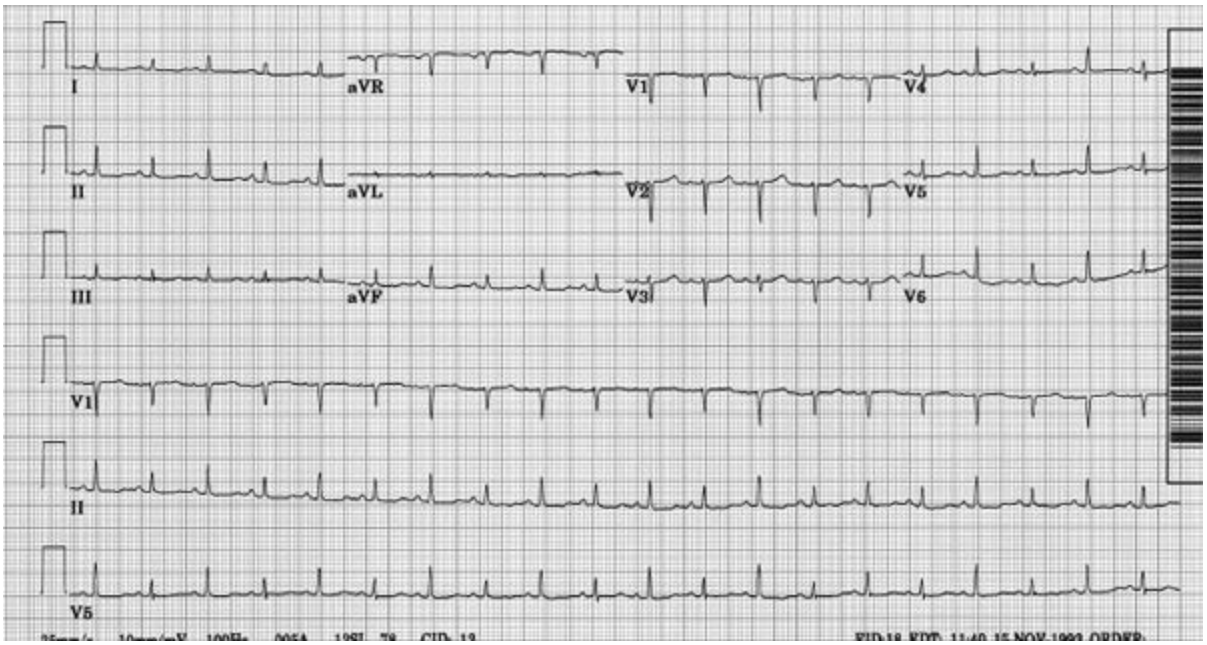
115. Myxedema

116. Hypothermia

117. Sick sinus syndrome

118. Cardiac transplant

ECG INTERPRETATION AND CODING



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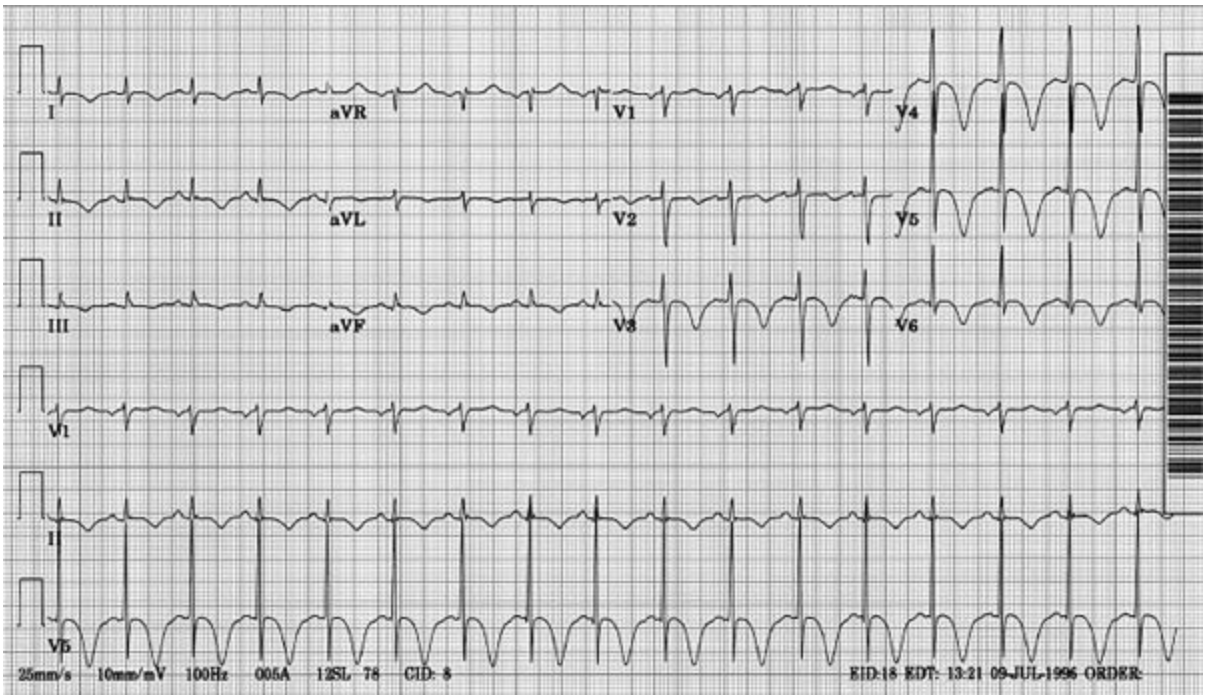

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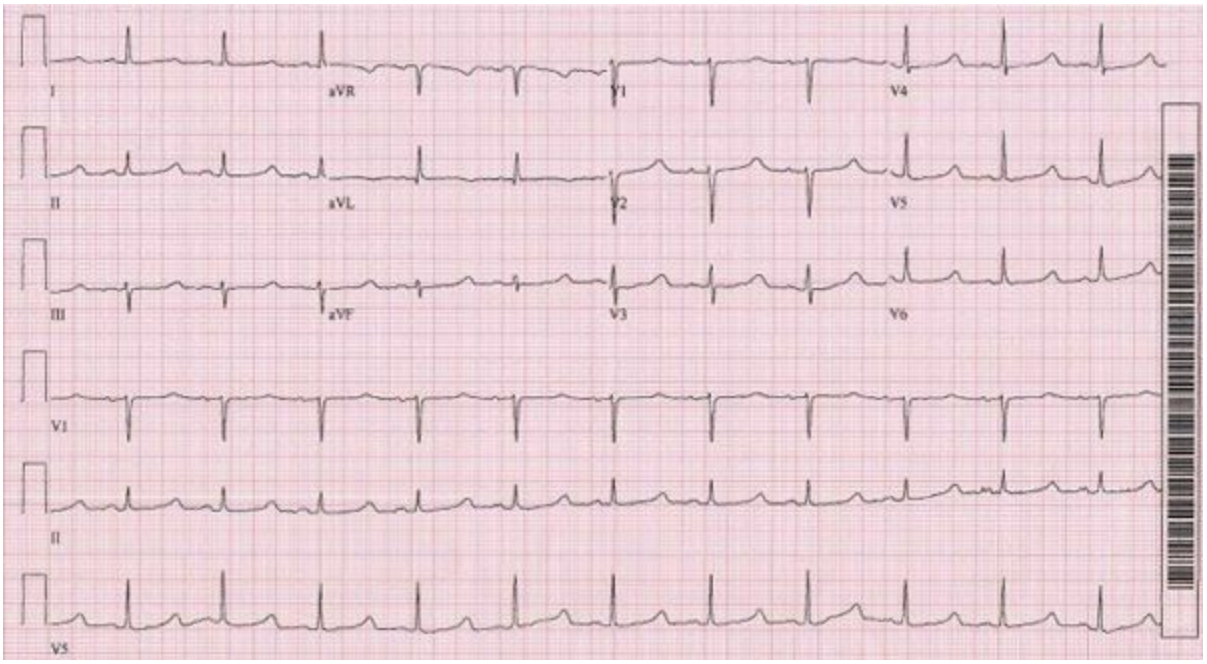

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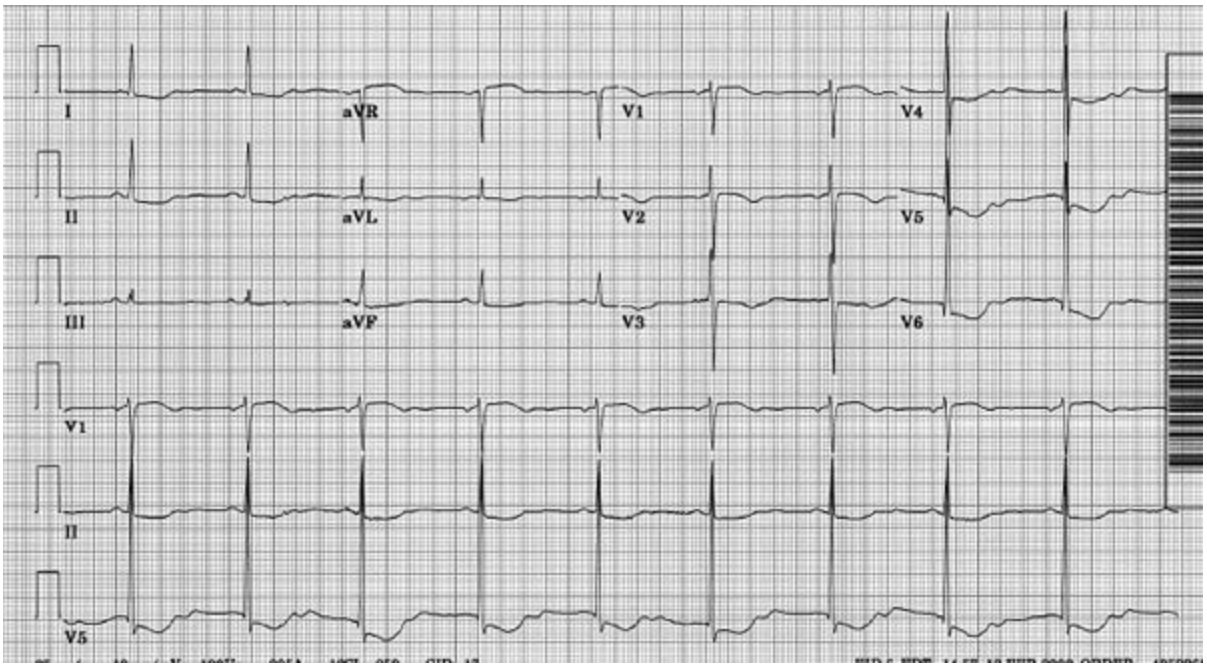

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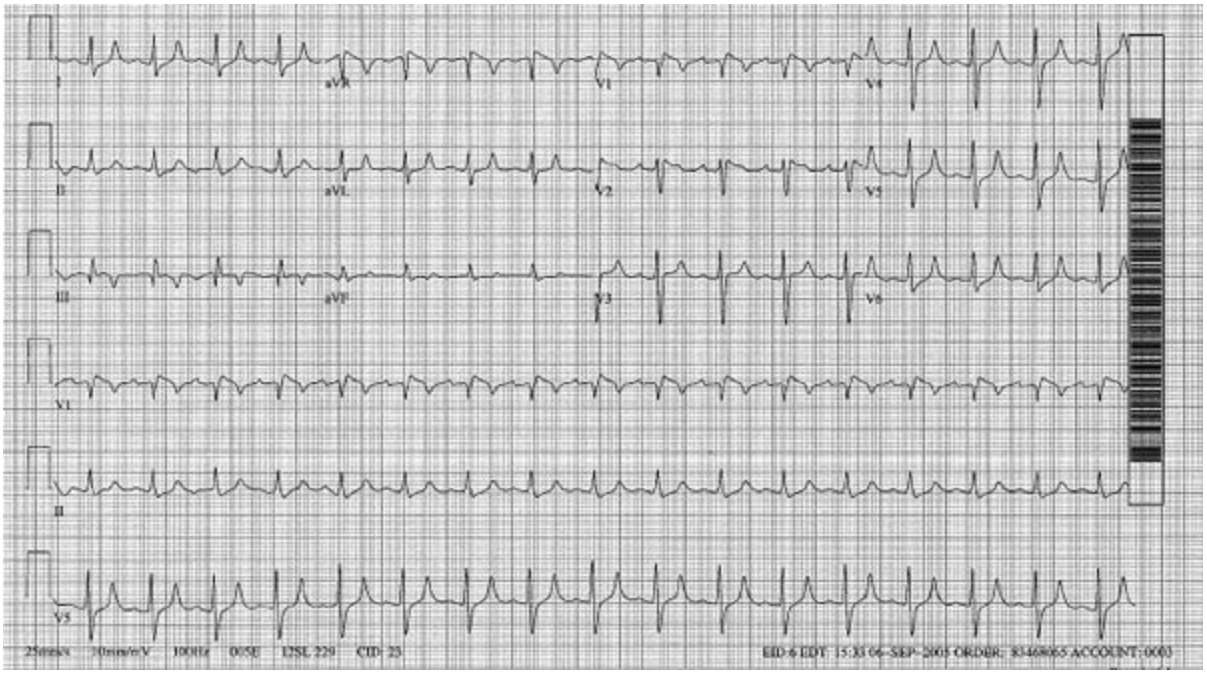

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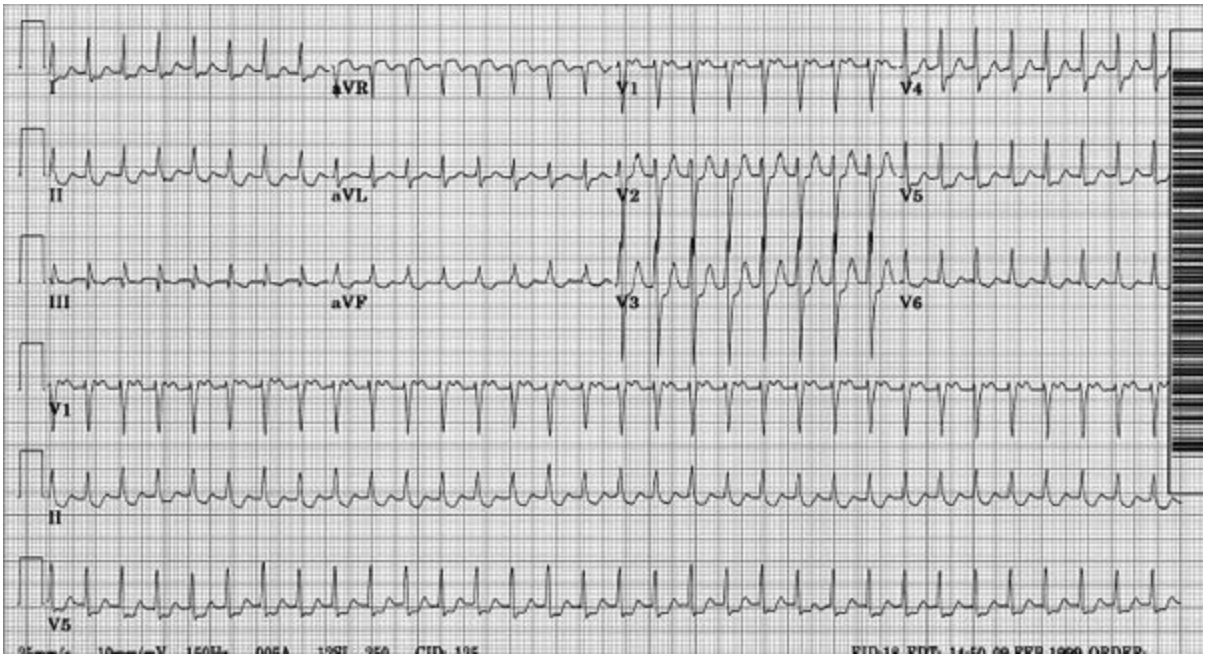

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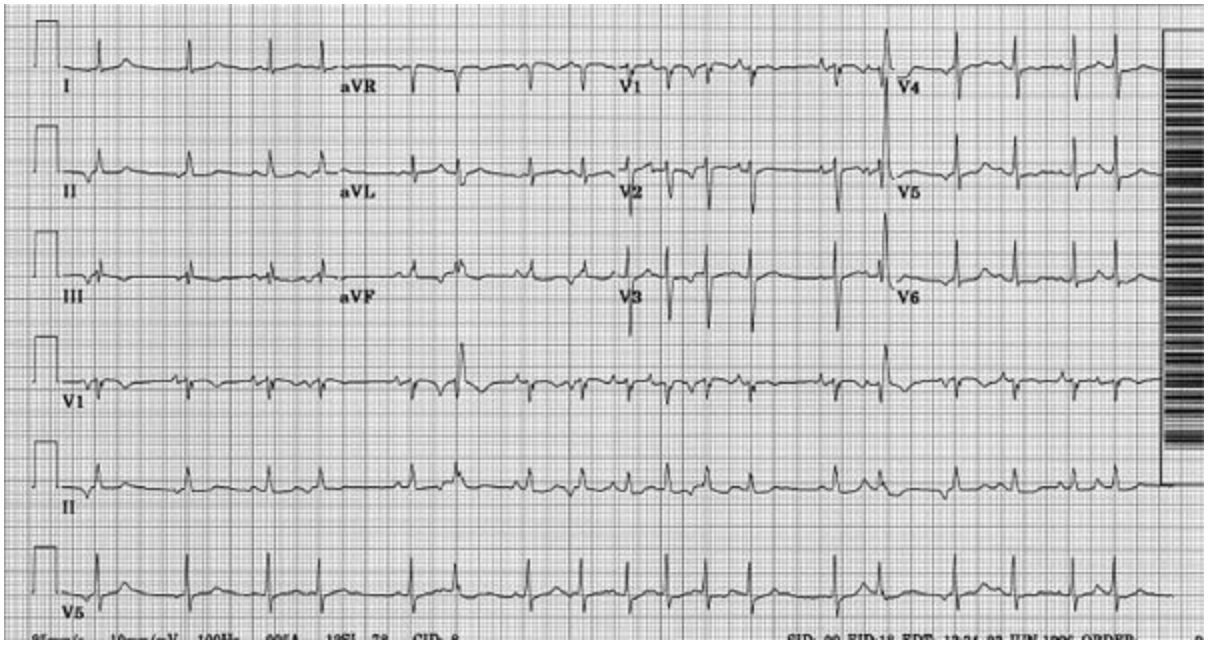

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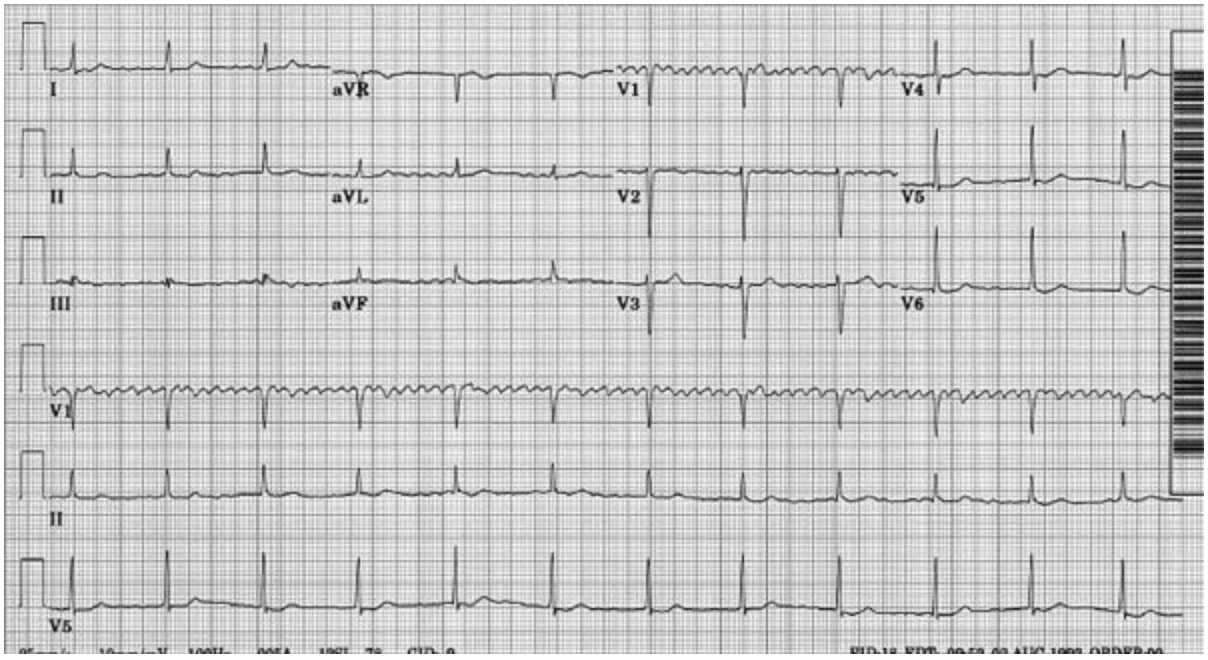

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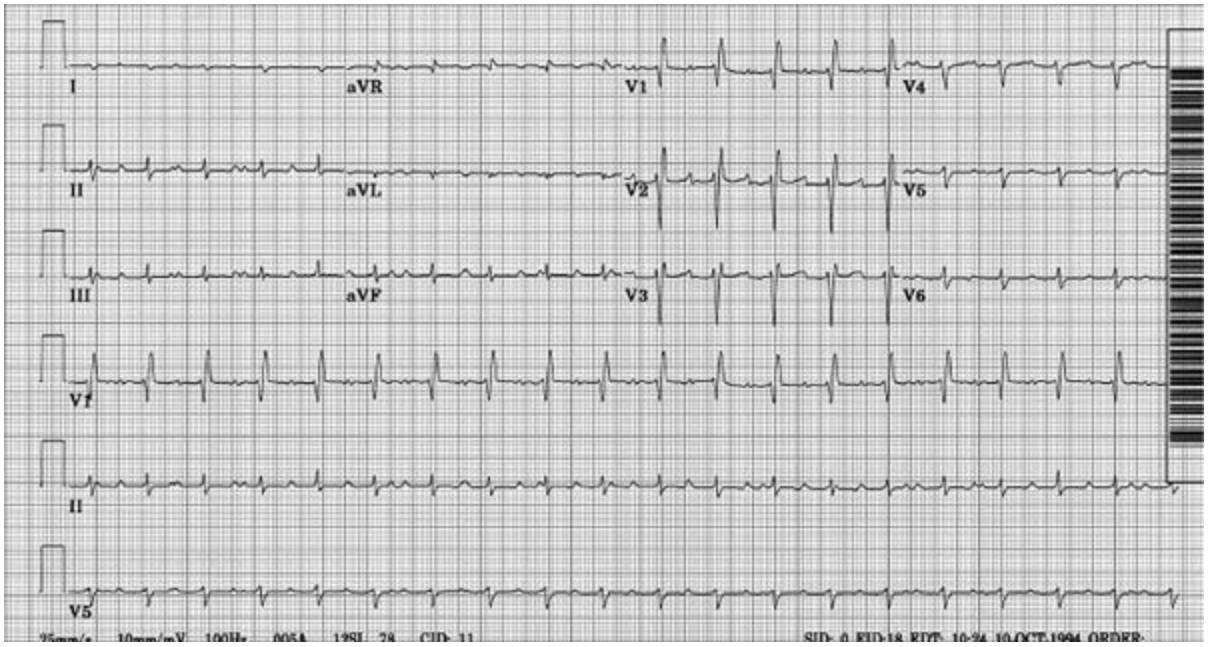

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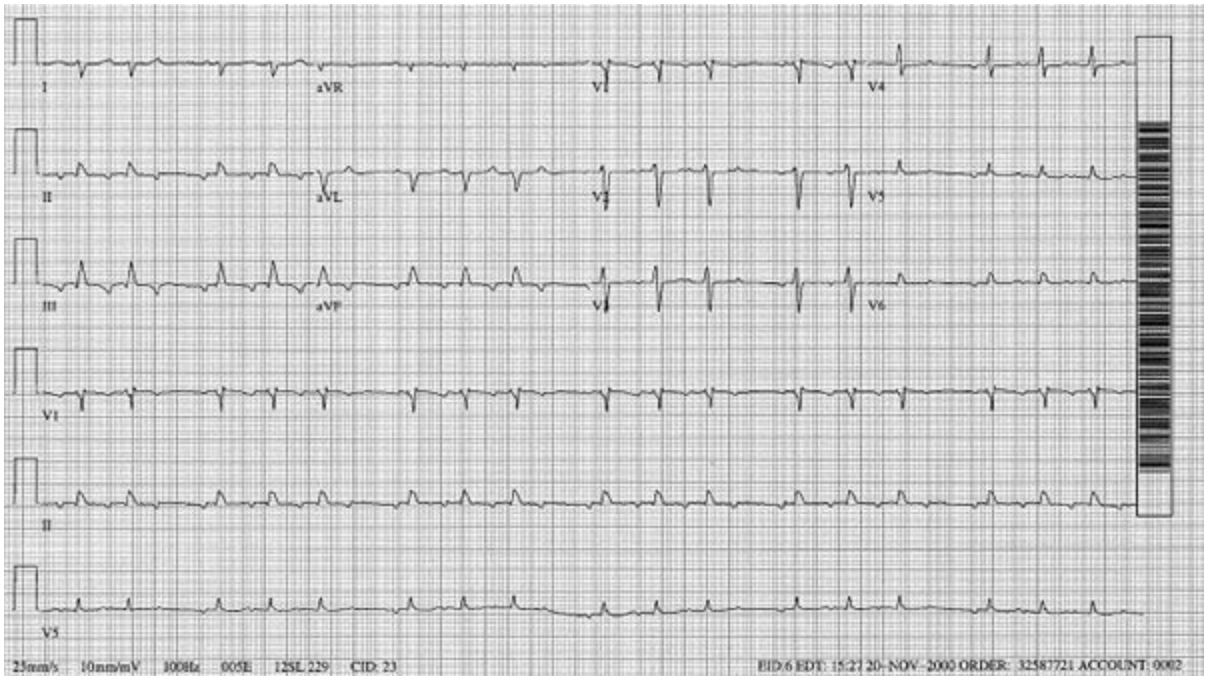

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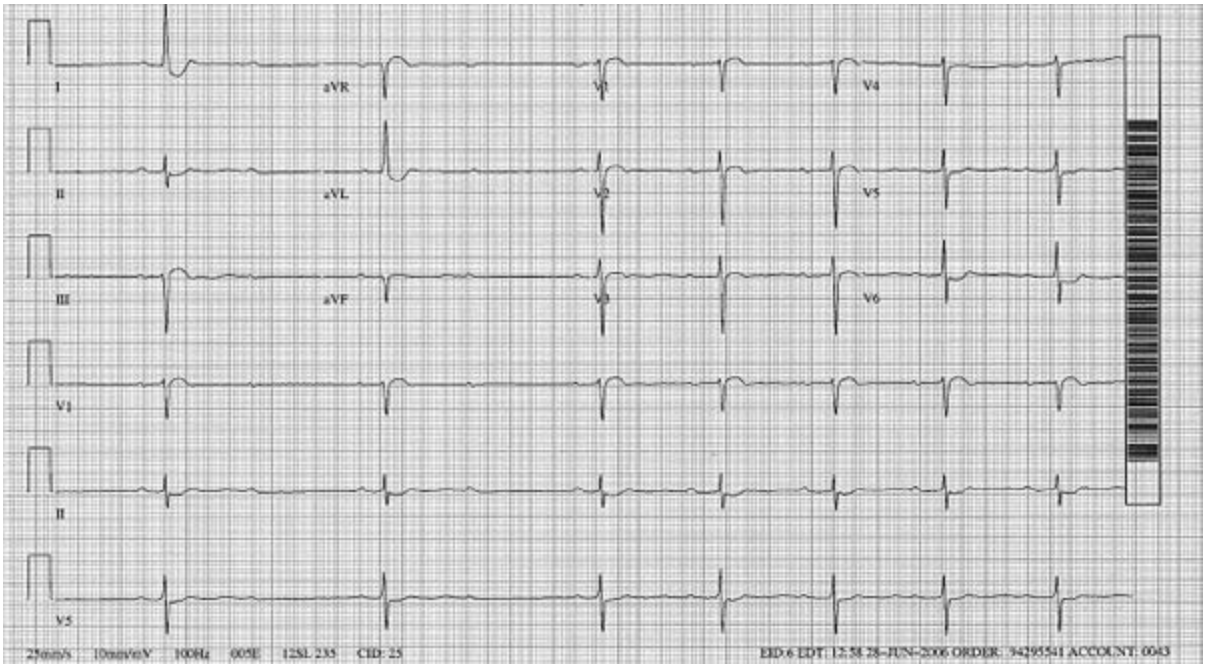

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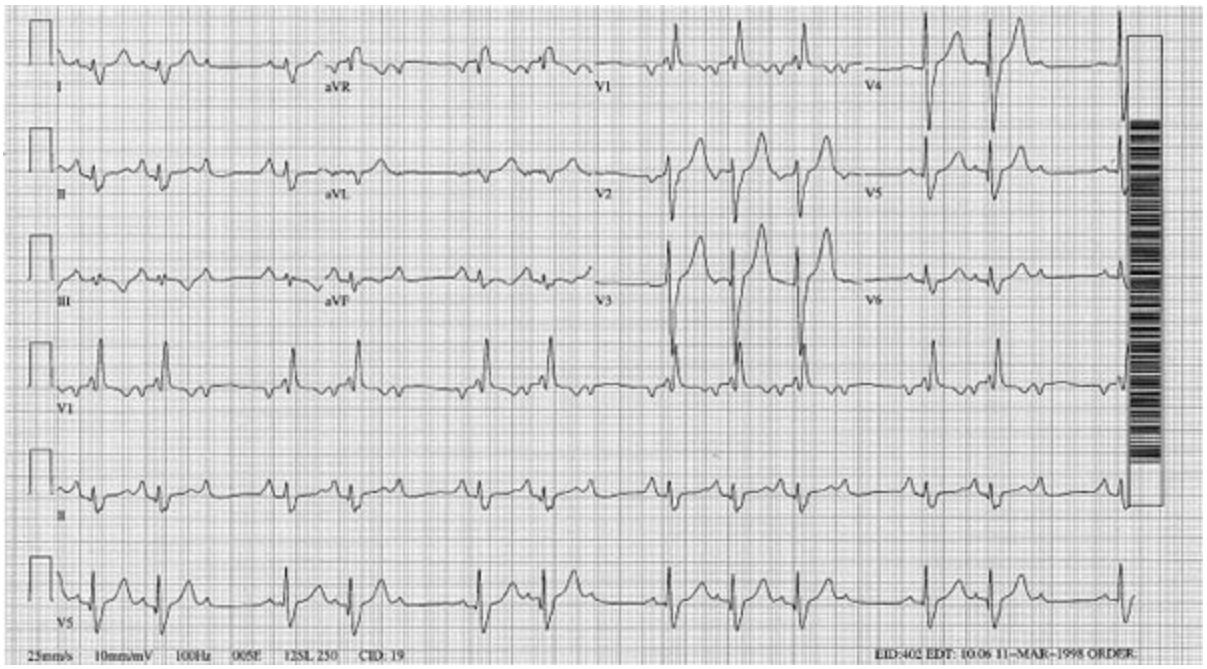

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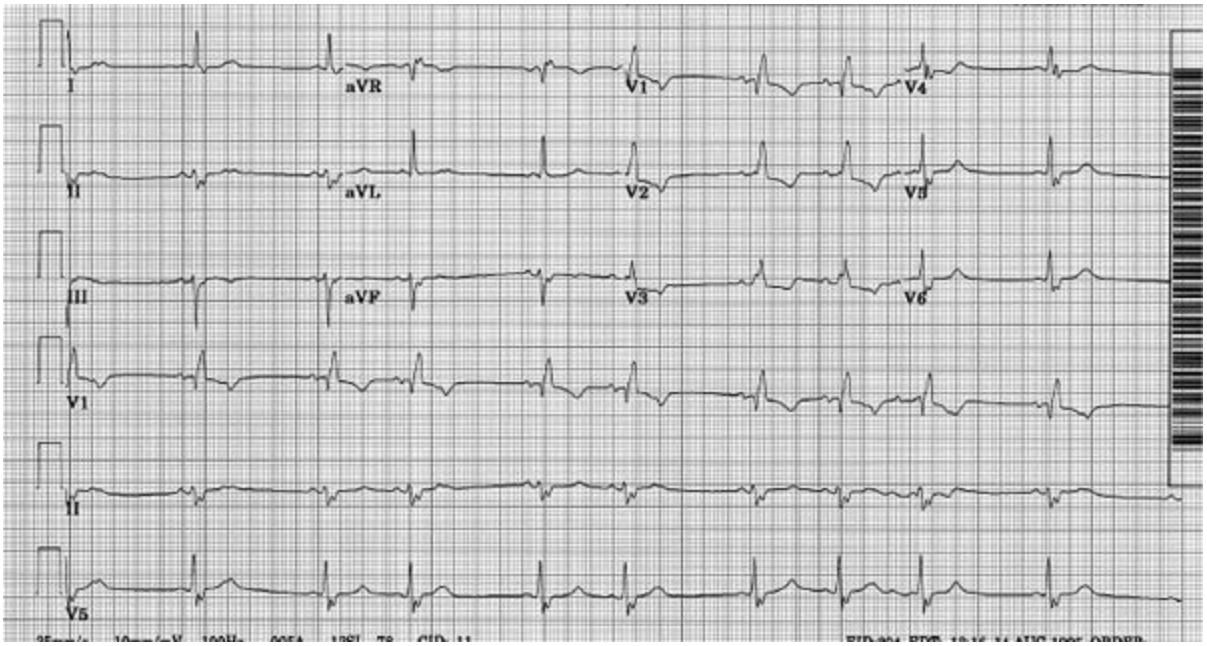

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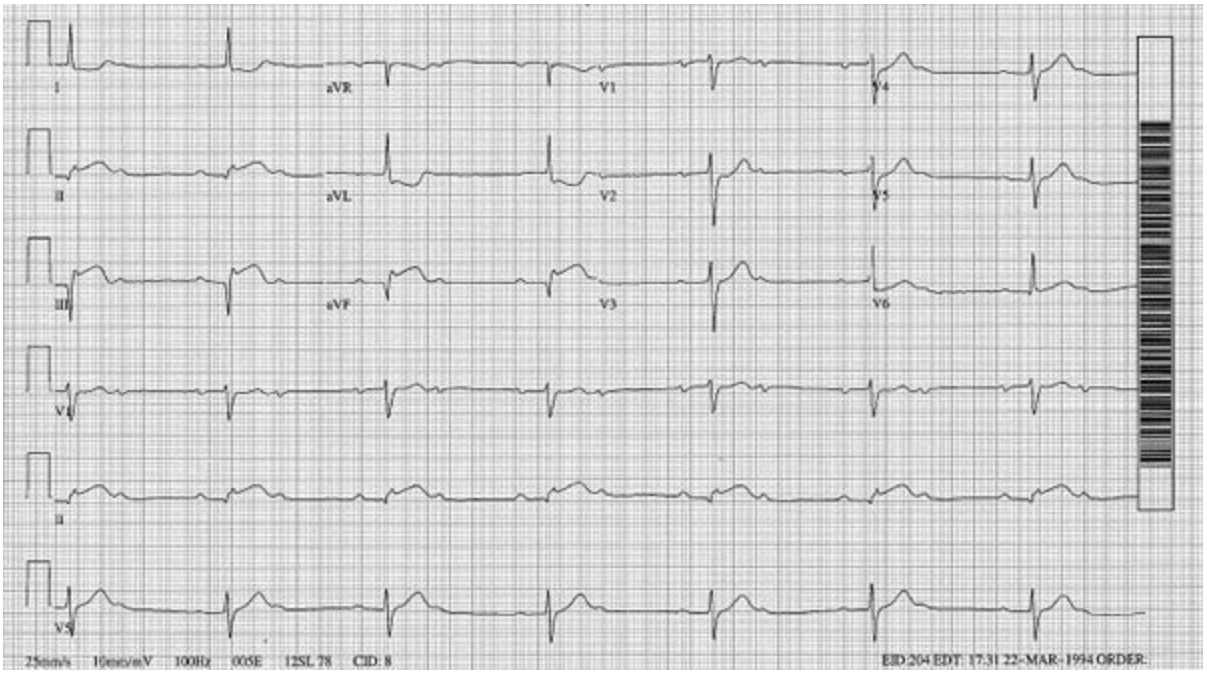

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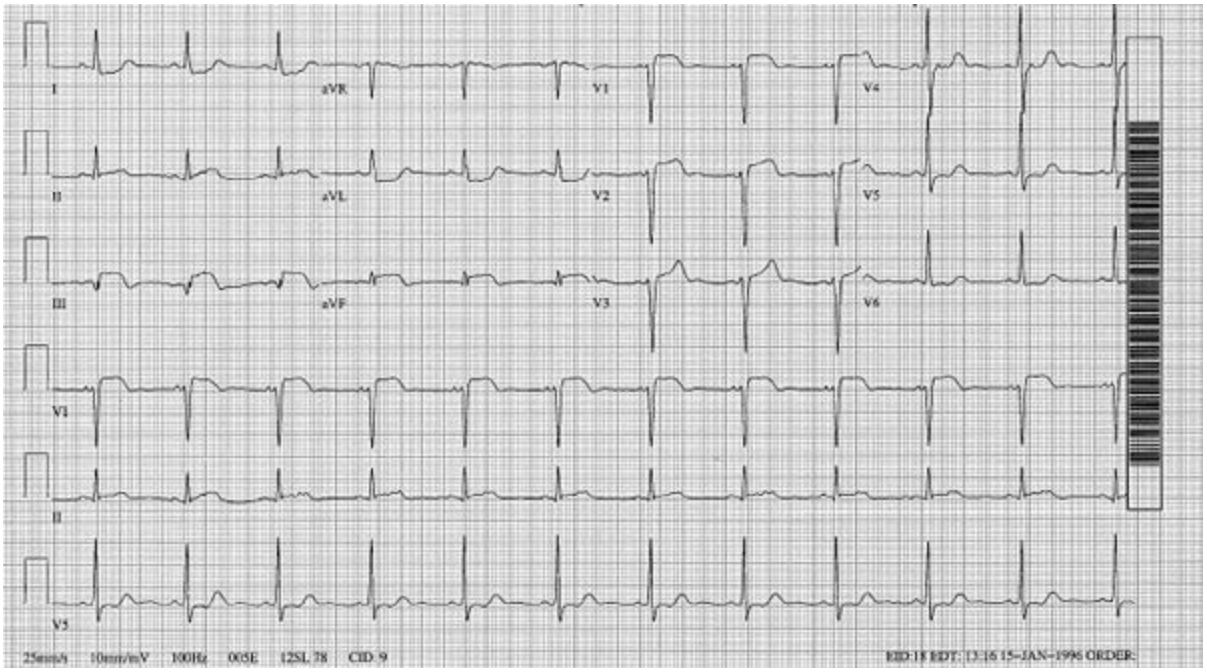

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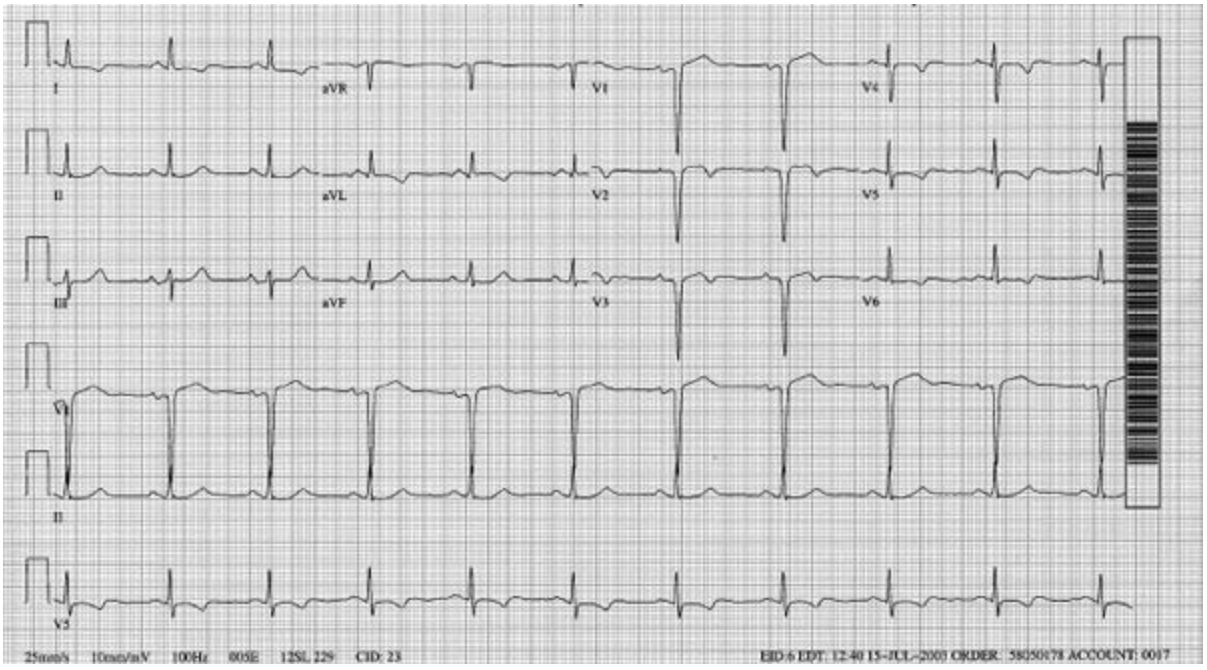

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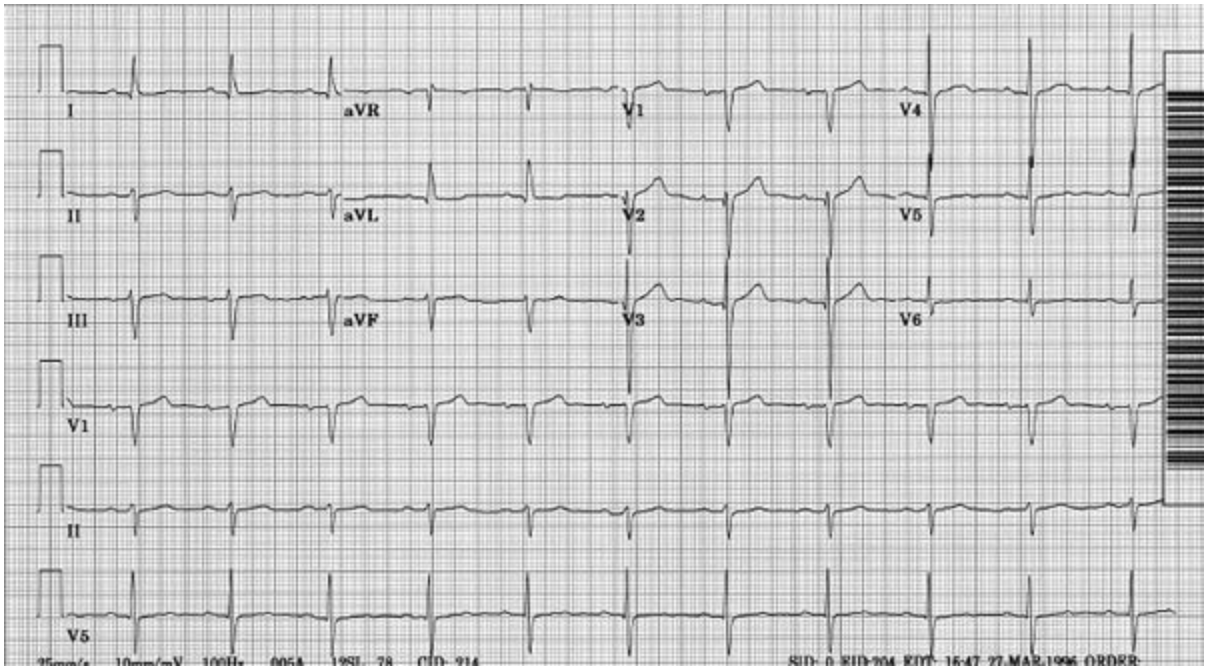

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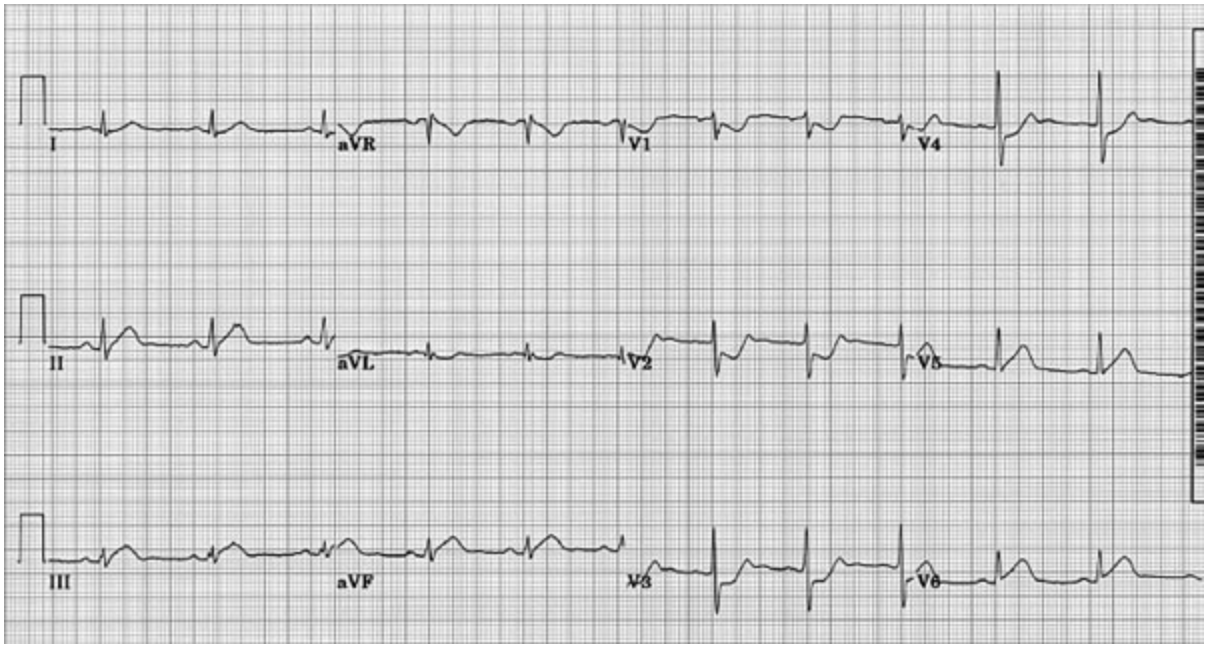

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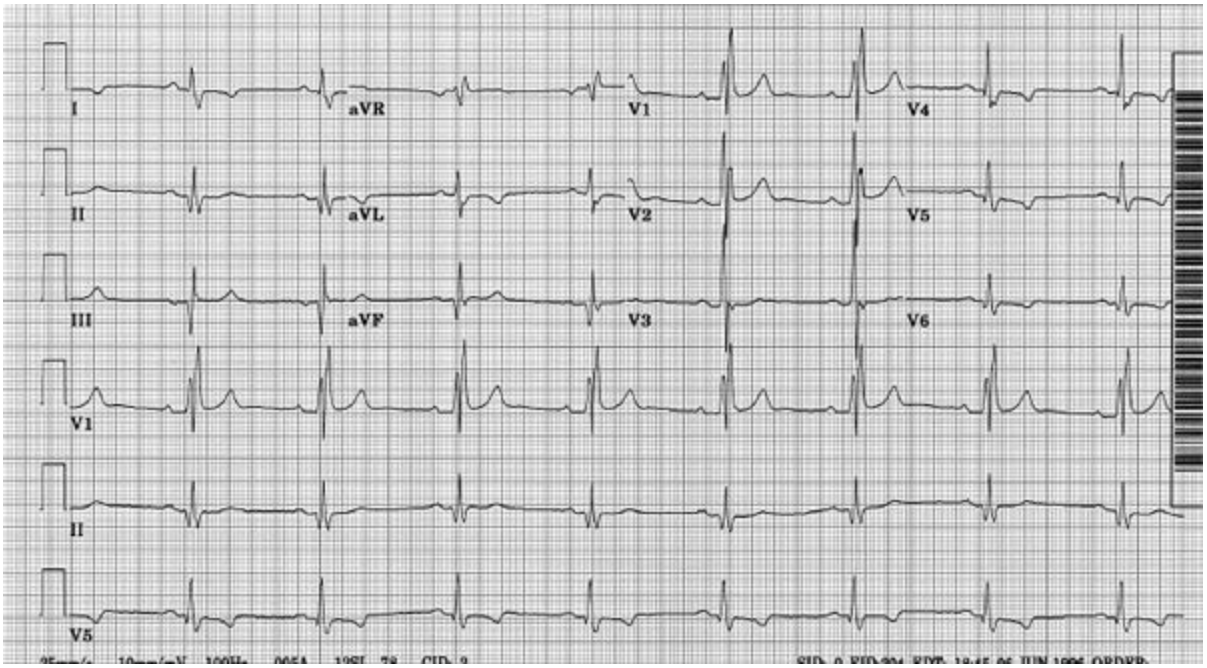

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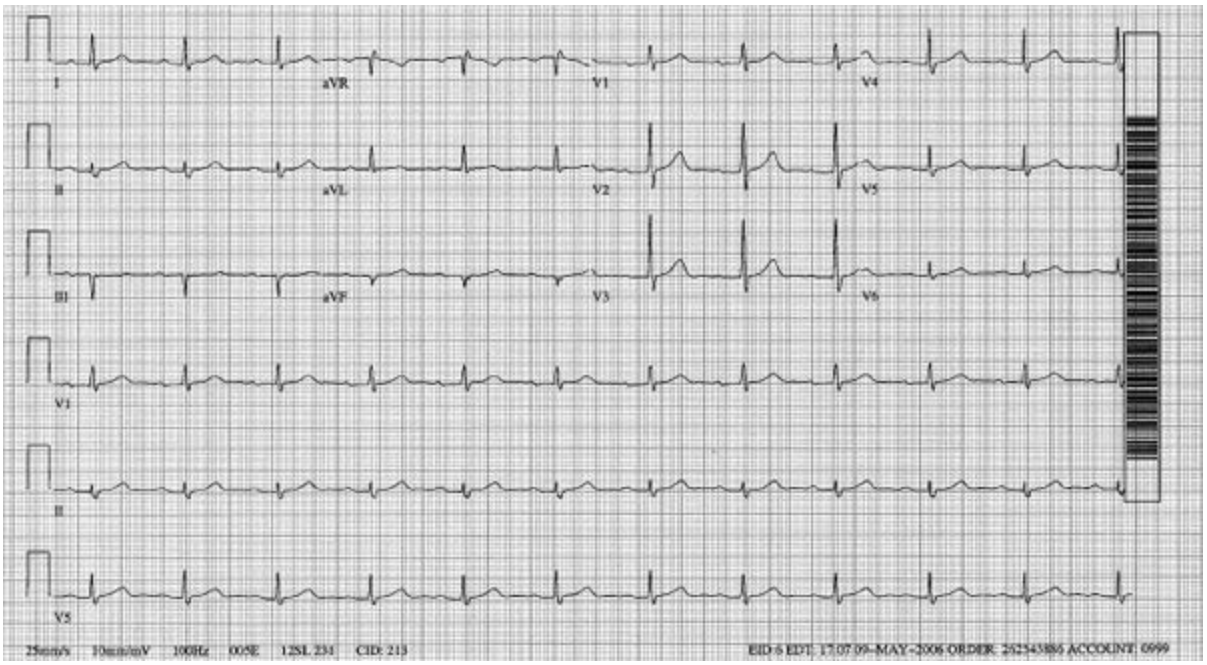

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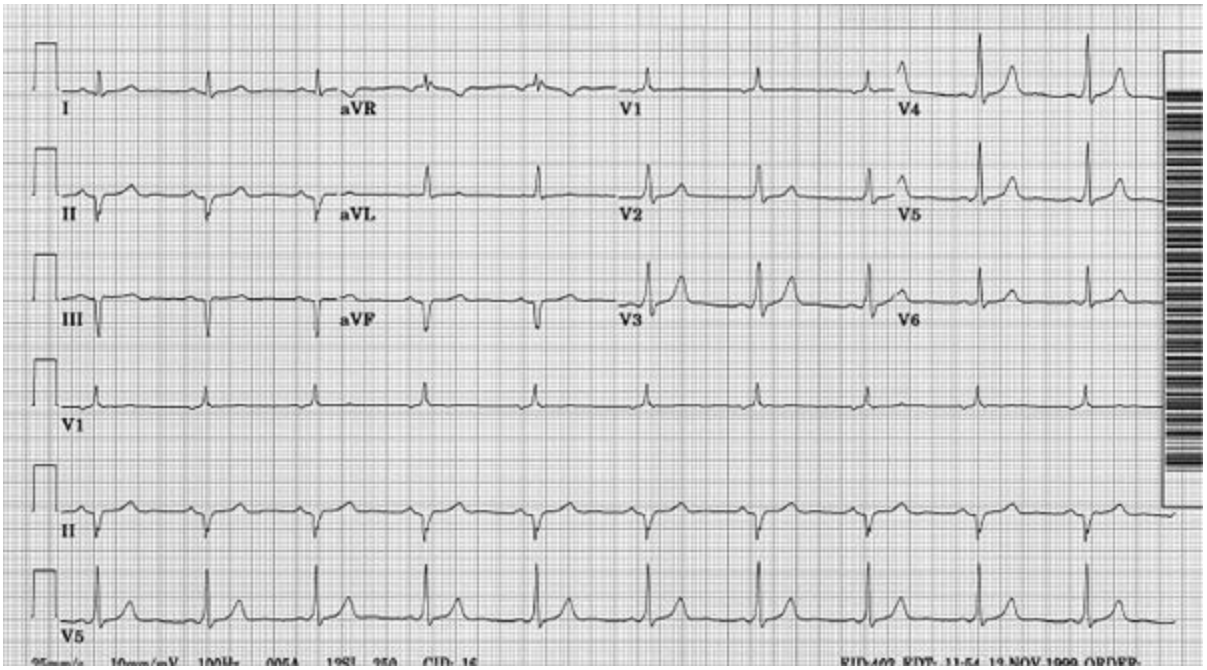

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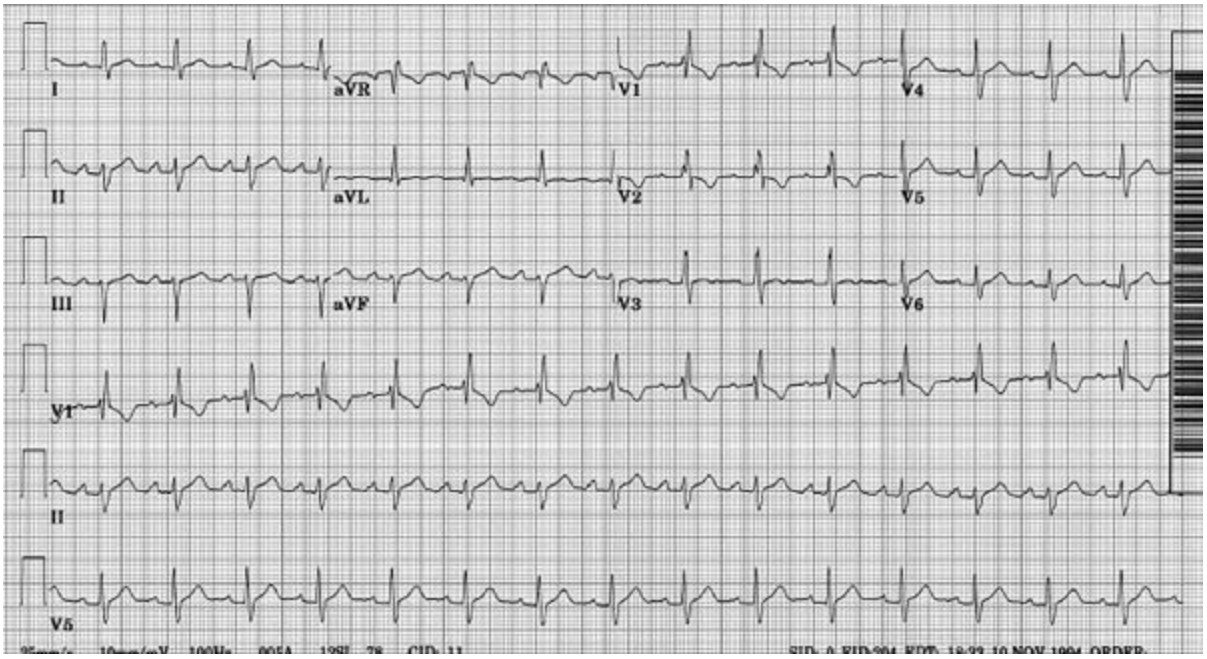

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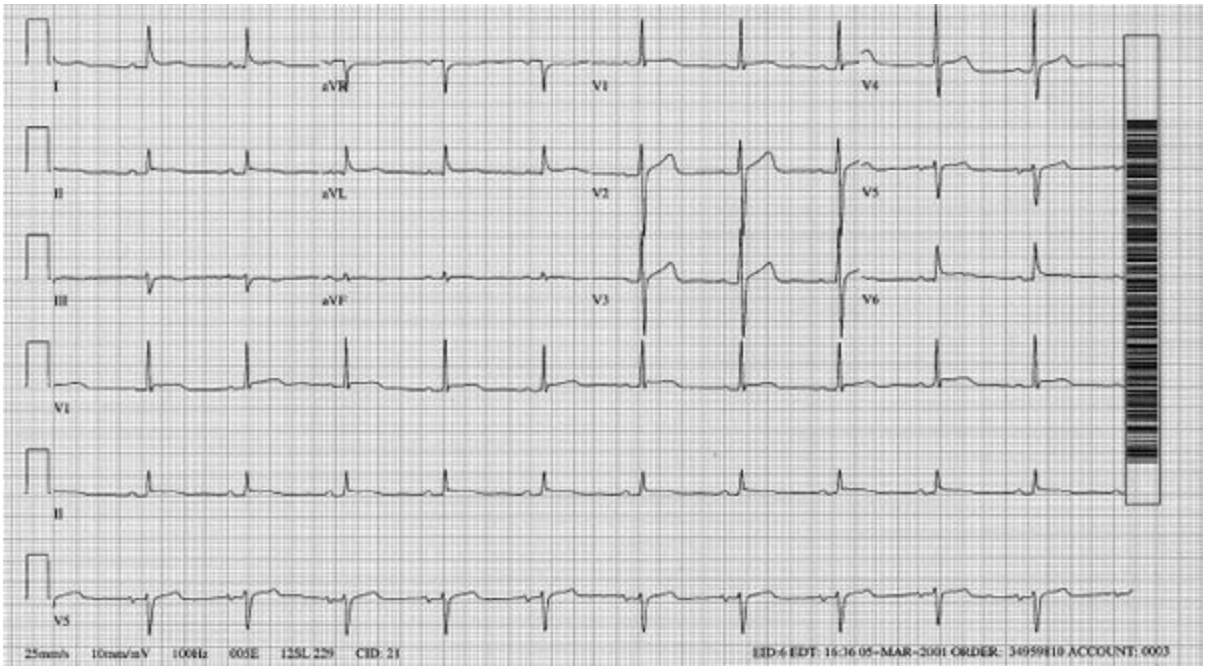

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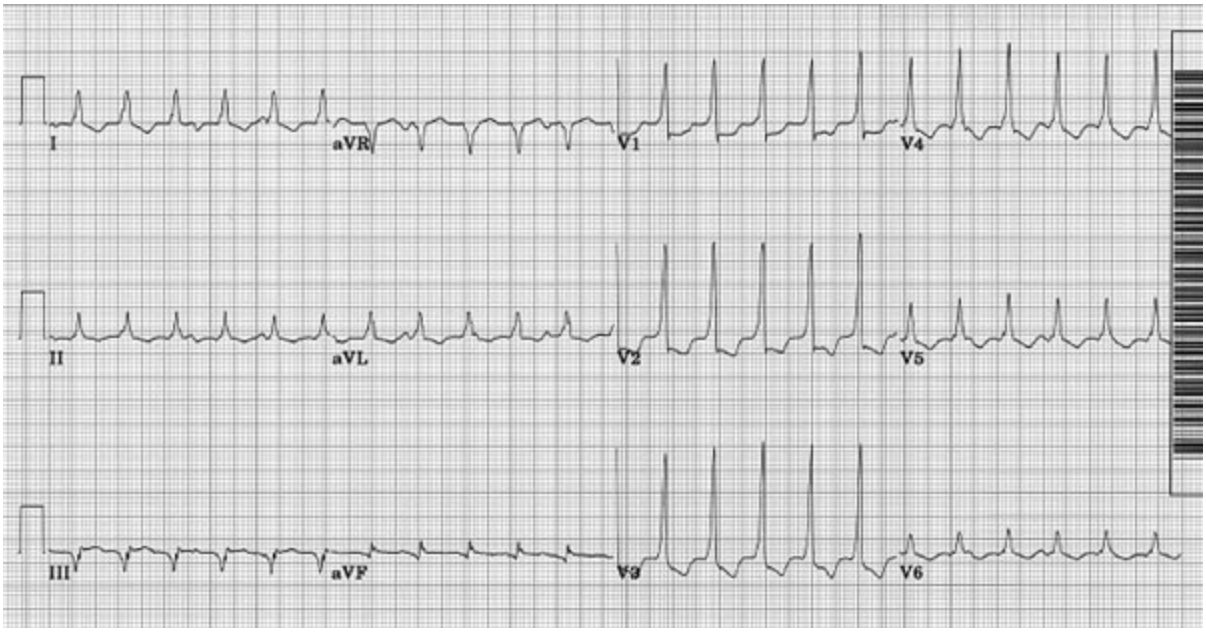

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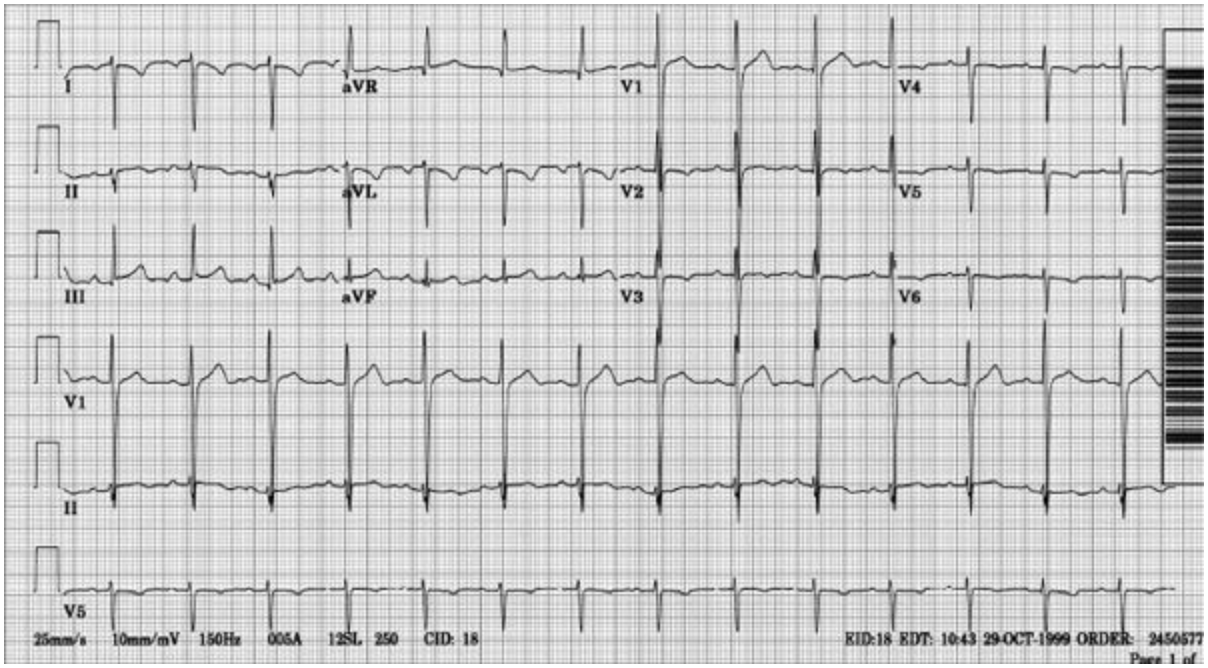

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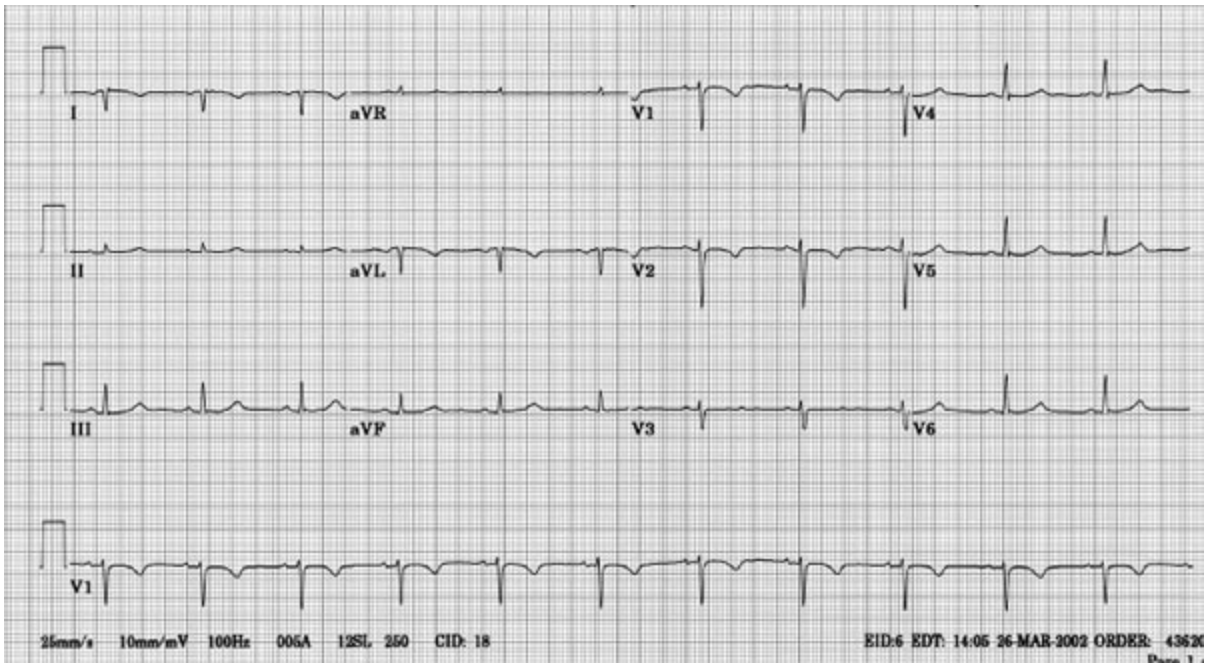

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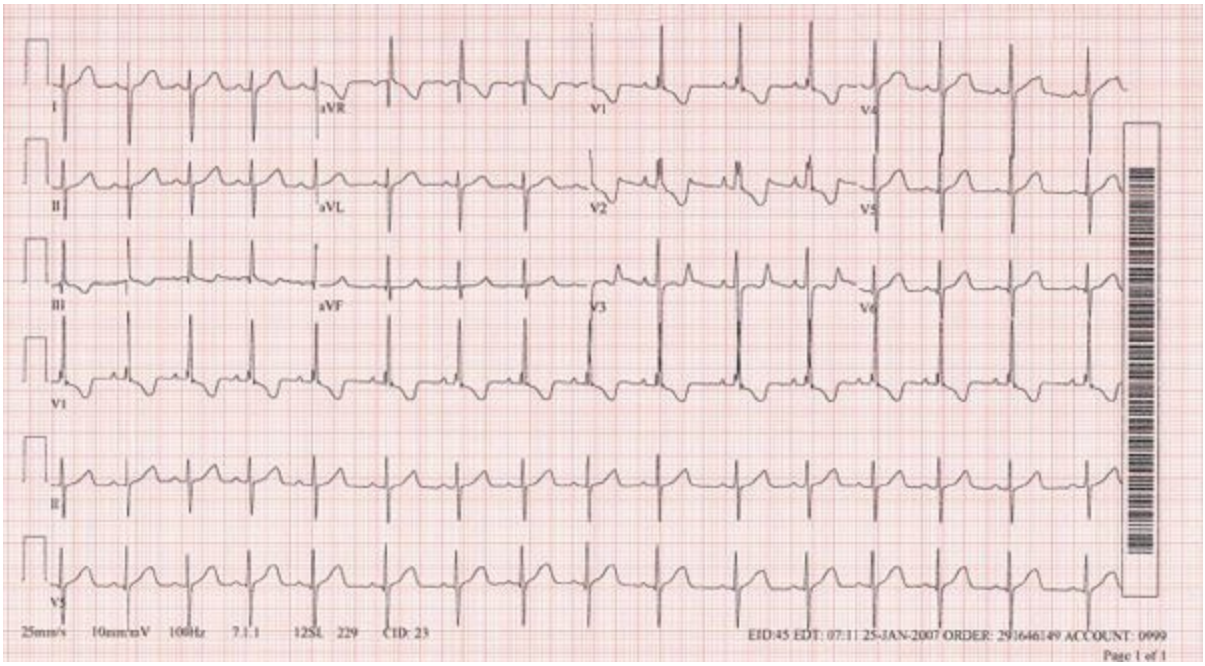

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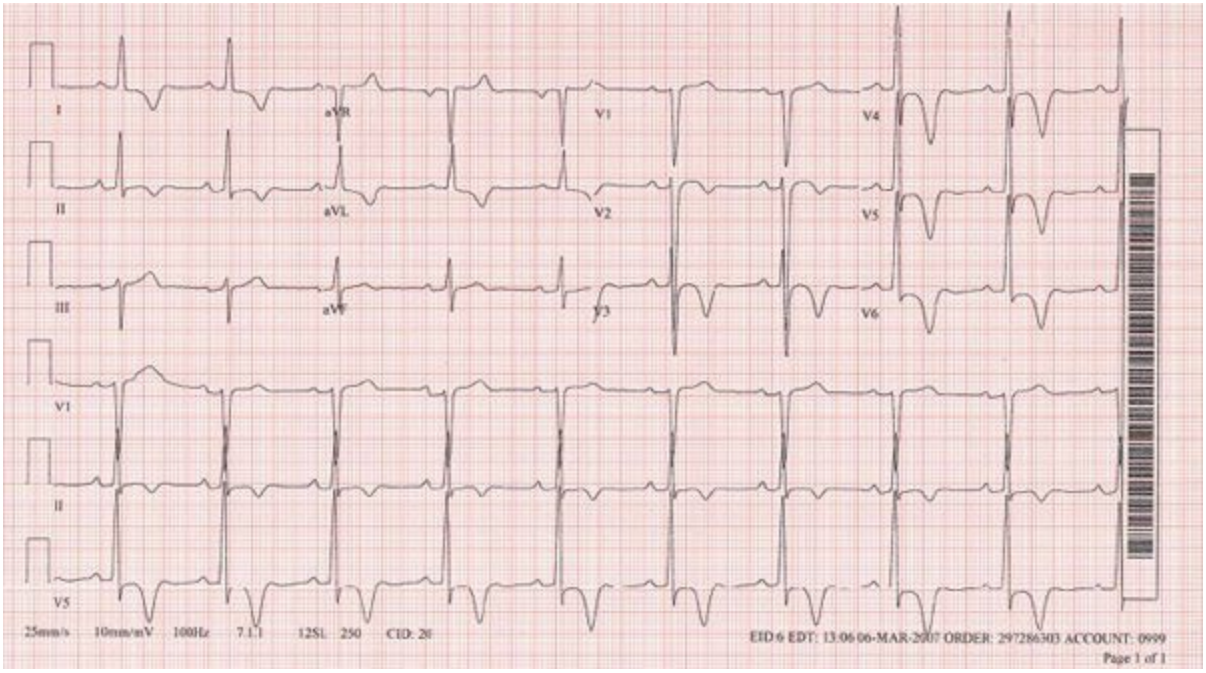

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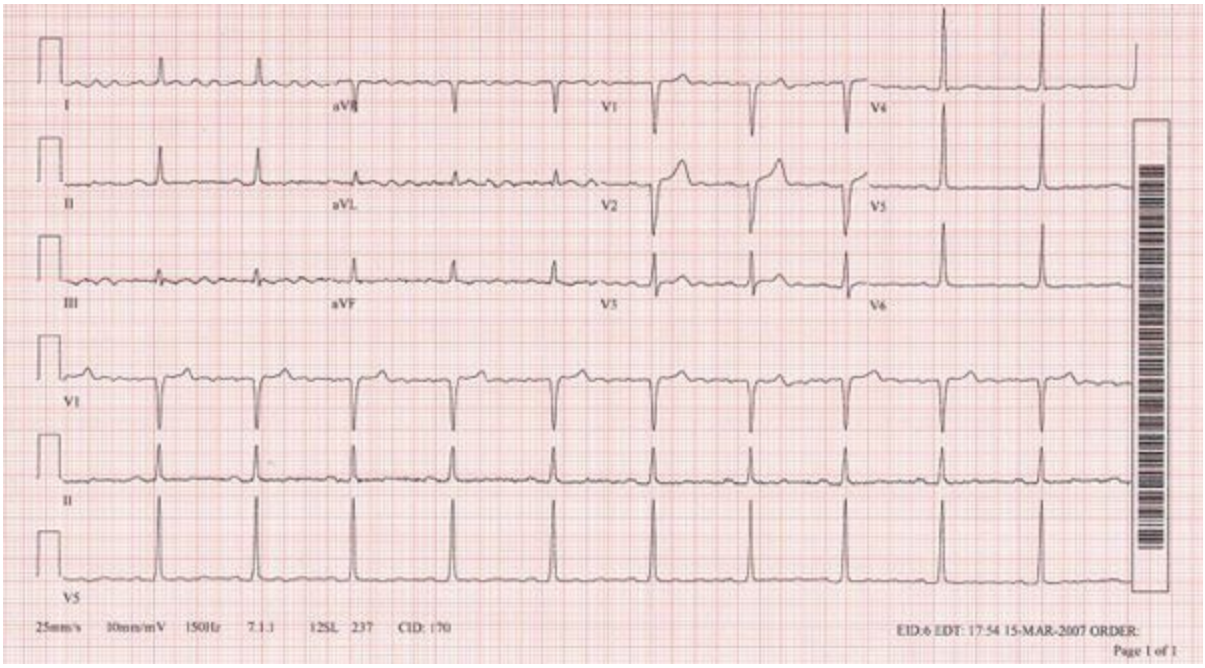

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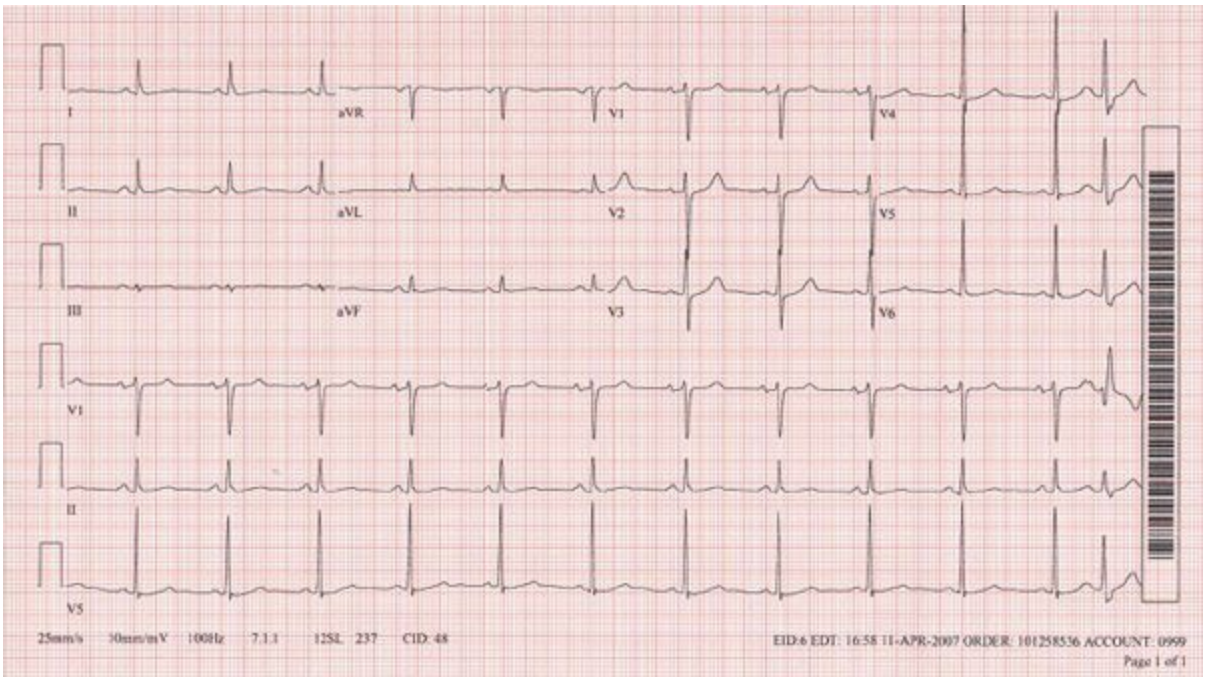

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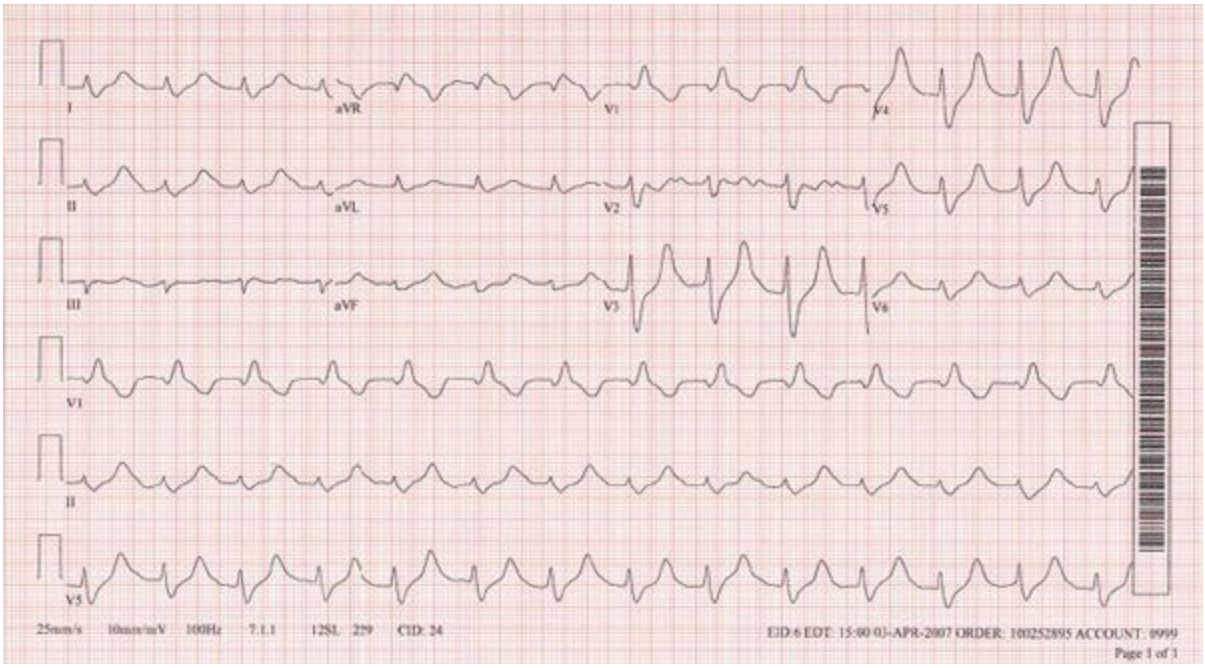

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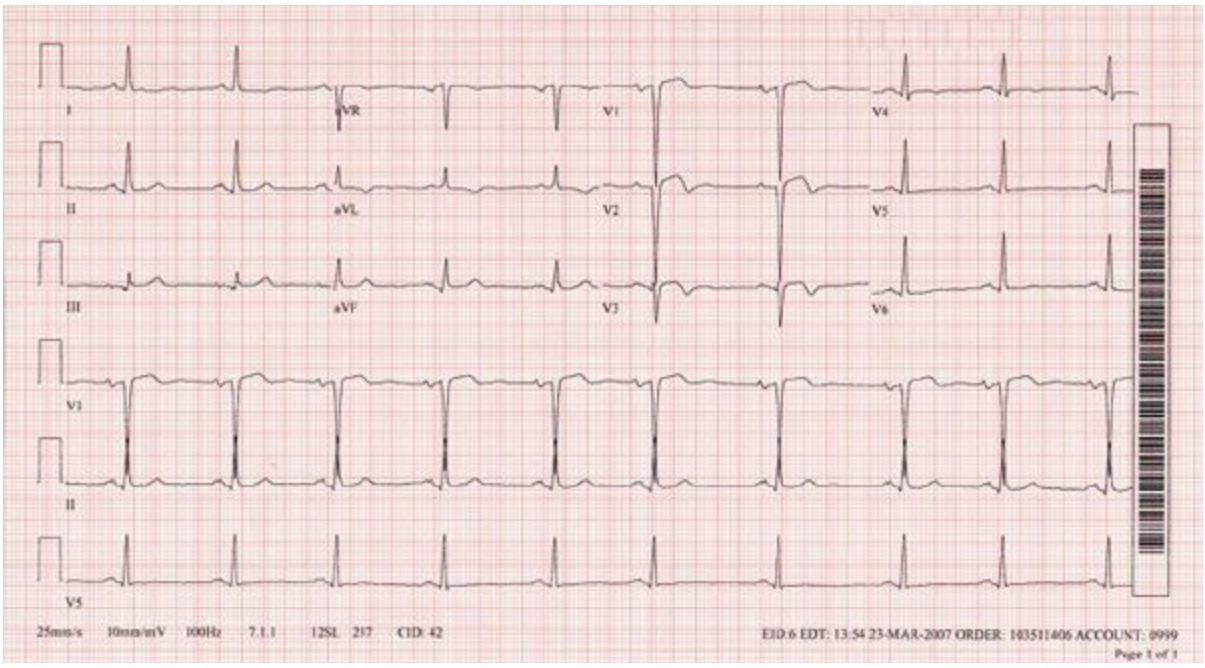

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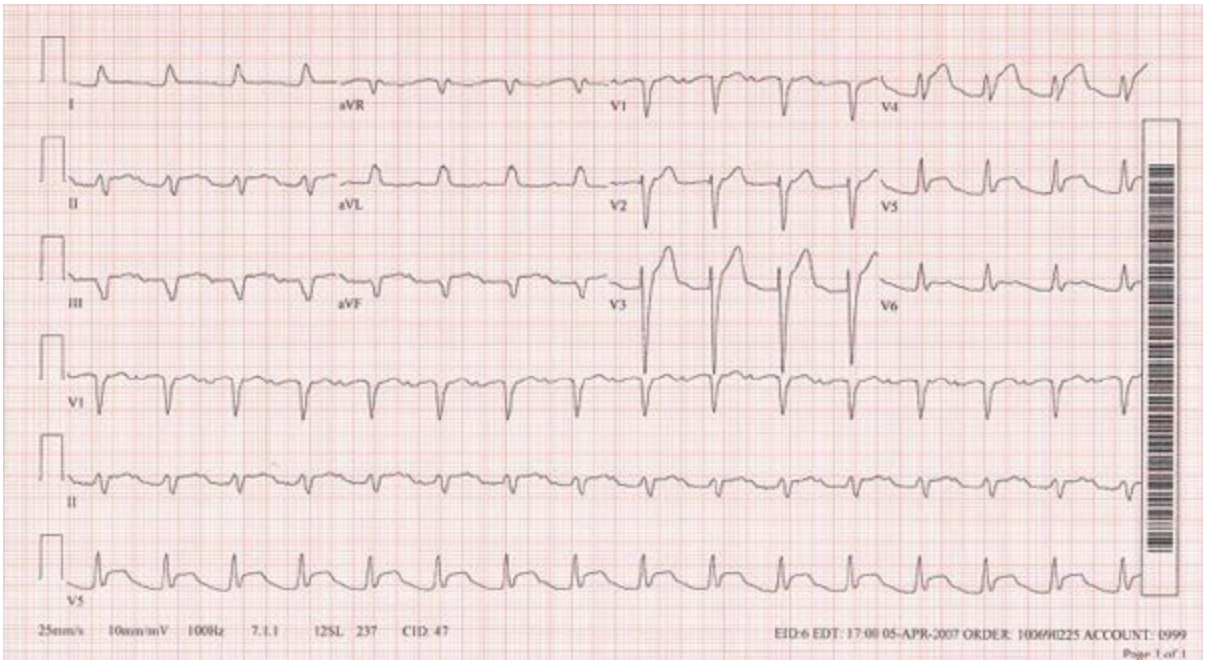

Figure 15.33

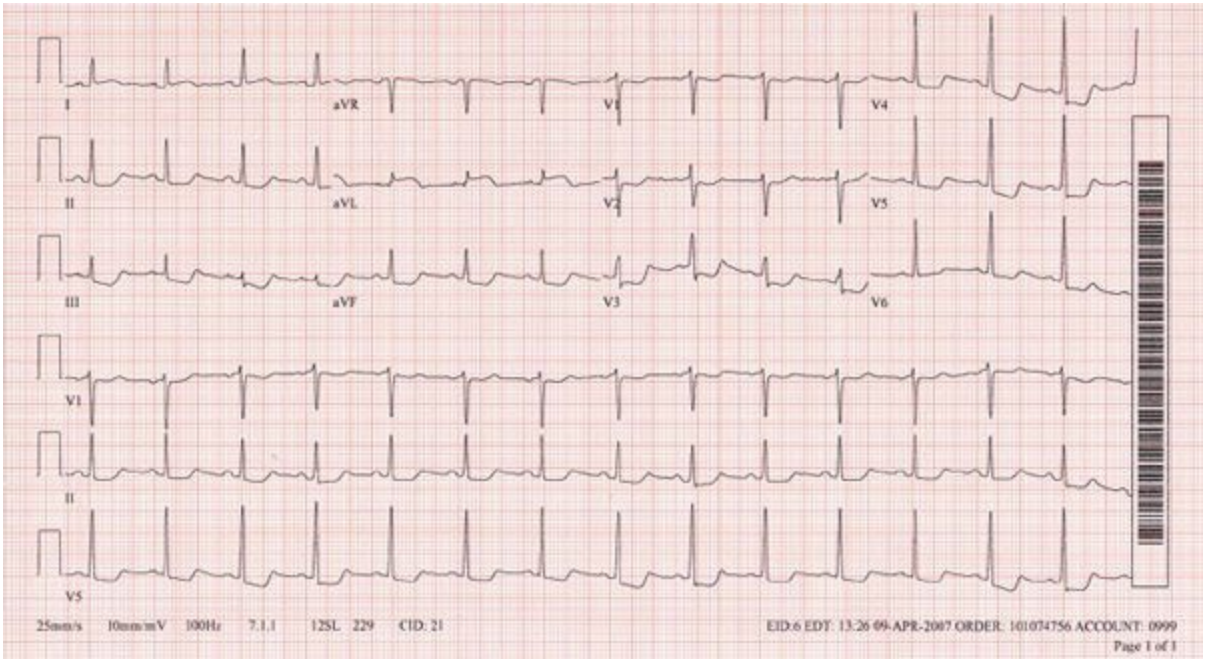

Figure 15.34

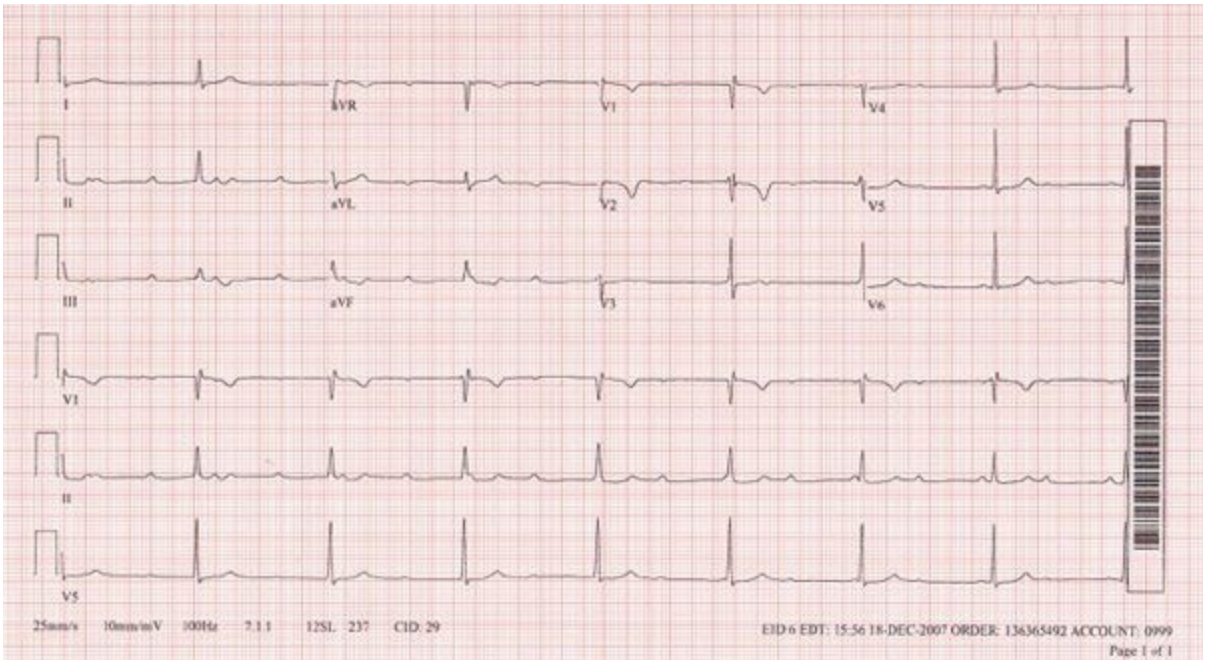

Figure 15.35

1. FIGURE 15.1: On this electrocardiogram, there is a sinus tachycardia. The voltage is low and in the V_1 and II rhythm strips, electrical alternans can be seen. This is an ECG from a patient with cardiac tamponade. Electrocardiographic coding is 12, 58, and 109.

2. FIGURE 15.2: This electrocardiogram shows a sinus tachycardia. There is a generalized T-wave inversion. The T waves are symmetric, deep, and have a long QT interval. This is an electrocardiogram from a patient with a major CNS event such as a subarachnoid or intraventricular hemorrhage. Electrocardiographic coding would be 12, 95, and 114.

3. FIGURE 15.3: This electrocardiogram shows a sinus rhythm. There is prolongation of the QT interval. The T wave has a fairly normal duration and contour, however. This is an example of hypocalcemia. (Type III congenital long QT syndrome also has this appearance.) Electrocardiographic coding would be 8, 95, and 102.

4. FIGURE 15.4: On this electrocardiogram, there is a sinus rhythm. It is sinus bradycardia. There is a prolongation of the QT interval. In this case, there is ST-segment depression, T-wave flattening, and TU fusion with prominent U waves in the lateral precordial leads. This should suggest hypokalemia. Another possibility is digitalis plus an antiarrhythmic drug's effects (such as quinidine or procainamide). Electrocardiographic coding would be 11, 96, and 100.

5. Figure 15.5: This patient has a sinus tachycardia. There is symmetry of the T waves

and there is a degree of QT prolongation. This is an example of a mixed electrolyte abnormality, hyperkalemia, and hypocalcemia. Values at the time were potassium of 7.2 and calcium of 80. This would be coded 12, 94, 95, 99, and 102.

6. FIGURE 15.6: On this electrocardiogram, there is a narrow complex tachycardia. The complexes are regular. In lead V_1, there is an atrial wave that has a short RP, long PR relationship. This is an example of supraventricular tachycardia or AV nodal reentrant tachycardia (AVNRT). If the atrial wave seen in V_1 extends to 70 or 80 milliseconds out into the ST segment, then this type of tracing could be an example of AV reentrant tachycardia (AVRT), which usually involves a larger reentrant loop and a bypass tract. Electrocardiographic coding is 27.

7. FIGURE 15.7: Here there is a narrow complex tachycardia. It is chaotically irregular and there are multiple P-wave vectors. This is not atrial fibrillation, which also is chaotic, but instead is a multifocal atrial tachycardia. This patient also shows aberrancy in the 6th and 14th beats. Electrocardiographic interpretation is 22, 87, 70, and 107.

8. FIGURE 15.8: This patient has a regular rhythm, but the baseline as seen in lead V_1 is chaotic. It is an example of atrial fibrillation with a regular ventricular response. This is actually an accelerated junctional rhythm most likely caused by digitalis excess. In lead V_6 there is ST-segment sagging that is smooth and associated with QT interval shortening. This suggests digitalis "effect." Digitalis effect is seen in the repolarization changes with ST-segment scooping. Digitalis "excess" is usually suggested by arrhythmias and in this case the accelerated junctional rhythm. The coding would be 25, 30, 97, and 98.

9. FIGURE 15.9: This patient shows an rSR′ pattern in lead V_1 that might suggest a volume-overload right ventricular hypertrophy (RVH). That is supported in part by the right axis deviation. However, in looking at the rhythm strip in lead II, there is a basic sinus rhythm with a first-degree AV block and in addition there is a second atrial rhythm that is dissociated from the basic PQRS sequence. This is accessory atrial activity related to cardiac transplantation. This would be coded 9, 40, 57, 63, and 118.

10. FIGURE 15.10: On this electrocardiogram, there is a regular atrial activity, but the P waves are inverted in the inferior leads, suggesting an ectopic atrial tachycardia. This conducts with group beating and gradual PR prolongation. This is an example of atrial tachycardia with Mobitz type I AV block. This would be coded 23 and 41.

11. FIGURE 15.11: This electrocardiogram shows a sinus rhythm. There is a first-degree AV block and intermittent 2:1 block. In addition, there is ST-segment depression that is scooping in quality in the lateral leads. This is an example of digitalis excess with intermittent second-degree AV block and digitalis effect. It would be coded 11, 41 or 42, 97, and 98.

12. FIGURE 15.12: This patient has a right bundle branch block and left axis deviation. He also has pauses. In this case, the P waves are regular and the PR intervals do not change. This is an example of a Mobitz type II second-degree AV block. The P-wave vectors are prominent in both leads II and V_1, suggesting left atrial enlargement. This would be coded 8, 42, 5, 56, and 64.

13. FIGURE 15.13: This patient has a right bundle branch block. There is also left axis deviation which probably is enough to qualify as an anterior hemiblock. There are occasional pauses. In this case, the pauses are preceded by P waves, which are within the preceding T waves, and so this is an example of blocked PACs and not an example of more advanced AV block associated with bifascicular block. This would be coded 11, 18, 56, 64, and 65.

14. FIGURE 15.14: This patient shows a sinus rhythm with a 2:1 AV block. This can either be a Mobitz type I or II AV block. It is impossible to tell which. This also shows ST-segment elevation with Q waves in the inferior leads with reciprocal changes in leads I and aVL and is an example of an acute inferior infarction with 2:1 AV block. This would be coded 8, 43, and 79.

15. FIGURE 15.15: This patient shows a sinus rhythm. There is ST elevation in the inferior leads, especially leads III and aVF. There are reciprocal depressions in leads I and aVL. In leads V_1 and V_2, there is also ST elevation. This is an acute inferior infarction plus acute right ventricular infarct. This would be coded 8 and 79. At least on this code sheet, the ability to call right ventricular infarction would not be available to you.

16. FIGURE 15.16: This electrocardiogram has a sinus rhythm. There are lateral T-wave changes that are not specific, and there are QS waves in leads V_1 through V_3. This is an anteroseptal infarction of uncertain age. It would be coded 8, 76, and 87.

17. FIGURE 15.17: Here, there is a normal sinus rhythm and marked left axis deviation. There are small Q waves in leads I and aVL with a slight activation delay in aVL. This is anterior hemiblock. Anterior hemiblock produces small Q waves in the right precordial leads. The QRS pattern seen in V_2 is often very suggestive of

anteroseptal infarction, but the specificity is much less in the presence of anterior fascicular block. This would be coded 8 and 65.

18. FIGURE 15.18: In this patient, there are symmetric, prominent T waves that are upright. These are seen in the inferolateral leads and are associated with ST depression in leads V_1, V_2, and V_3. There are no Q waves so this is not an acute infarct, but it is an acute current of injury. The rhythm is sinus. Electrocardiographic coding would be 8 and 89.

19. FIGURE 15.19: On this electrocardiogram, there is a sinus rhythm. It is slow so sinus bradycardia. There are significant inferior Q waves and also Q waves in leads V_5 and V_6. There is also a prominent R-wave vector in lead V_1, and the T waves are upright despite the presence of a right bundle branch block. Usually with a right bundle branch block, ST-segment and T-wave inversion are expected. In this case, the upright T wave is an example of a "primary" T wave. A prominent initial vector and upright T wave in V_1, associated with inferior and lateral Q waves, are interpreted as an inferoposterior and lateral infarct. Electrocardiographic coding is 11, 80, 82, 78, and 64.

20. FIGURE 15.20: This electrocardiogram has a sinus rhythm. There is a prominent initial vector in lead V_1 that is greater than the S wave. T wave is upright. This is compatible with posterior infarct. That is supported by the presence of pathologic Q waves in leads III and aVF. Electrocardiographic coding would be 8, 80, and 82.

21. Figure 15.21: This electrocardiogram shows a sinus rhythm. There are inferior Q waves and prominent R vector in leads V_1 and V_2. This might suggest inferoposterior infarction, but in leads V_3 and V_4, especially there is a short PR interval and a delta wave suggesting that this is preexcitation or Wolff-Parkinson-White syndrome. Electrocardiographic coding would be 8 and 47.

22. FIGURE 15.22: This patient has a sinus rhythm. Lead II does suggest left atrial enlargement with a P wave that is broad and notched. There is an rSR′ pattern in lead V_1 with T-wave inversion and R′ greater than S. This type of pattern is commonly seen in volume-overload-type RVH. Volume-overload RVH and left axis should suggest ostium primum ASD. Usually an ASD will not affect P waves greatly, at least in the early phases of the process. Ostium primum ASDs, however, very often have mitral valve and notable mitral insufficiency plus left atrial enlargement. Electrocardiographic coding would be 8, 5, 63, 61, 56, and 104.

23. FIGURE 15.23: This electrocardiogram shows a sinus rhythm. There was a very

prominent vector in lead V_1 associated with upright T waves. This drops down to a more typical appearance in lead V_2. This is not an example of posterior infarction but instead is an example of switched leads, V_1 and V_5 having been transposed. There is also ST-segment elevation throughout and perhaps some PR-segment elevation in aVR. This suggests acute pericarditis. Electrocardiographic coding would be 8, 3, and 90.

24. FIGURE 15.24: This patient has a wide complex tachycardia. There is AV dissociation and there is anterior, positive concordance in the chest leads. This is ventricular tachycardia. Electrocardiographic coding would be 9, 51, and 36.

25. FIGURE 15.25: This patient has marked right axis deviation and loss of voltage across the precordium. The P waves are inverted in leads I and aVL. Inverted P waves in leads I and aVL (if it is not an ectopic atrial rhythm) are caused by either dextrocardial or switched arm wires. Loss of voltage across the precordium suggests that this is dextrocardia. Electrocardiographic coding would be 8 and 105.

26. FIGURE 15.26: This patient has a sinus rhythm and right axis deviation. The vectors in leads I and aVL are incompatible with those seen in the other lateral leads, V_5 and V_6. The discrepancies are explained by the inverted P waves in leads I and aVL, which suggest switched arm wires. This is a normal ECG with a technical error. This would be coded 8 and 3.

27. FIGURE 15.27: The patient is a 6-year-old with an outflow tract murmur. Rhythm is sinus with a narrow complex. V_1 shows small rSR′ with a large R′. There is right axis deviation. This is right ventricular hypertrophy. It is a volume-overload-type pattern. Most likely an ostium secundum ASD. Coded 8, 57, 61, and 103.

28. FIGURE 15.28: Here there is sinus bradycardia with left ventricular hypertrophy (voltage) and secondary T-wave changes extending into the right precordium. Most likely this is a hypertrophic cardiomyopathy with apical hypertrophy. This is occasionally called Yamaguchi syndrome after the initial describer of the variant. Coded 11, 60, and 112.

29. FIGURE 15.29: Although leads I, aVL, and III might suggest an atrial tachycardia, other leads clearly show a sinus rhythm. This is a motion artifact due to unilateral tremor and Parkinson disease. Coded 8 and 87.

30. FIGURE 15.30: Here is a sinus rhythm with minor lateral T-wave flattening. The last beat is premature and is an aberrant PAC. Characteristics of aberrancy are

preceding atrial activity (seen in the T wave) and initial narrow vector with broadening toward the end of the complex and often a right bundle branch block type of pattern. Coded 8, 19, and 87.

31. FIGURE 15.31: This shows a sinus rhythm with first-degree AV block, generalized broadening of the QRS (with a right bundle branch block-like pattern), and symmetric broadening of the T wave. This is hyperkalemia. Potassium at the time was 6.2 mEq/L. Coded 8, 64, and 99.

32. FIGURE 15.32: Here is a sinus bradycardia with a sinus arrhythmia. There is terminally a symmetric T-wave inversion in leads V_2 and V_3 plus a qrS pattern in V_3. This is an anteroseptal infarct of uncertain age. Also there are lateral T-wave changes that are not specific. Coded 11, 76, 87, and 113.

33. FIGURE 15.33: Rhythm is sinus with a first-degree AV block. There was a wide complex without septal Q waves in leads I and V_6 (a left bundle branch block pattern) and left axis deviation. ST and T waves are "discordant" in the anterolateral leads (and also generally). There is also PR-segment elevation in lead aVR. This could be anterior "injury," but more suggests acute pericarditis. Coded 8, 40, 56, 68, and 90.

34. FIGURE 15.34: There is a sinus rhythm with ST-segment elevation in lead aVL and reciprocal changes in the inferior and lateral leads. This is an acute high lateral infarct. Coded 8, 77, and 113.

35. FIGURE 15.35: A sinus rhythm with AV dissociation (complete heart block) and junctional escape. V_1 shows an incomplete right bundle branch block pattern. T waves are not entirely normal in V_3. Coded 12, 44, 63, and 87.

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